TEXTBOOK OF VETERINARY INTERNAL MEDICINE

EIGHTH EDITION

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ELSEVIER

Textbook of Veterinary Internal Medicine

DISEASES OF THE DOG AND THE CAT

EIGHTH EDITION

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Contributions from Around the World

This new edition of *Textbook of Veterinary Internal Medicine* is globally diverse and we are excited to share content from experiences gained throughout the world. These flags represent the countries that our authors call home.

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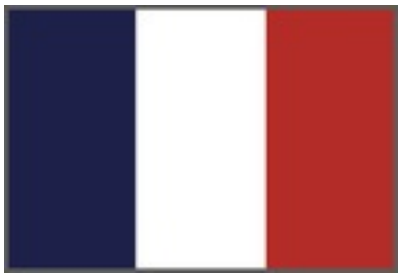

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Dedication

He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all.

Sir William Osler

With love to my wife Pat and my children Ricky, Robbie, Michael, Andrew and Nicole. You remain my inspiration for all that I do.

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Love to Shawn, Rhonda, Shaina, and Rowan who provided me with the time and unconditional support to follow my dreams.

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To Jen and Hélène, with love and gratitude.

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The Physical Examination
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"Ain't Doing Right": The Nonspecific Chief Concern of Ill Thrift
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Urine Collection
Management of Urinary Catheters
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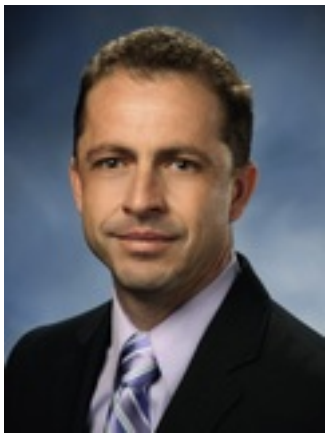
Diseases of the Pulmonary Parenchyma



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Reproductive Disorders in the Neutered Male or Female Dog

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Cachexia and Sarcopenia
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Intoxication versus Acute, Nontoxicologic Illness: Differentiating the Two
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Antibacterial Drug Therapy
Antifungal and Antiviral Therapy

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PANCREATIC DISEASE

Laboratory Evaluation of the Gastrointestinal Tract
Canine Pancreatitis: Diagnosis and Treatment
Exocrine Pancreatic Insufficiency

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Coccidioidomycosis

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Clinical Approach and Laboratory Evaluation of Renal Disease

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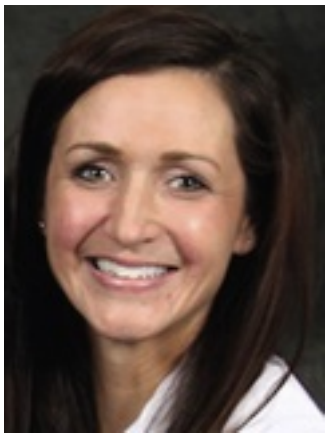
Immunologic and Hematologic Diseases: Introduction and Drug Therapy



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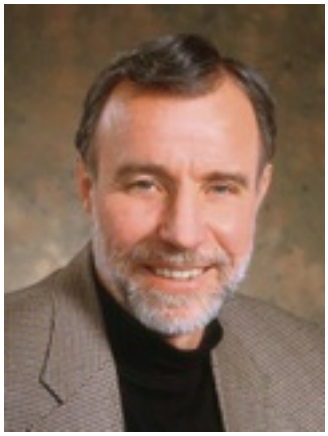
Royal (Dick) School of Veterinary Studies
The University of Edinburgh Hospital for Small Animals
Edinburgh, Scotland, United Kingdom

Nonneoplastic Diseases of the Spleen



Clarke Atkins DVM, DACVIM (Small Animal Internal Medicine and Cardiology)
Jane Lewis Seaks Distinguished Professor of Companion Animal Medicine, Emeritus
College of Veterinary Medicine
North Caroline State University
Raleigh, North Carolina

Canine and Feline Heartworm Disease
Heart Disease and Kidney Disease

Eva Agneta Axnér, DVM, PhD, DECAR
Professor
Department of Clinical Sciences
Swedish University of Agricultural Sciences
Uppsala, Sweden

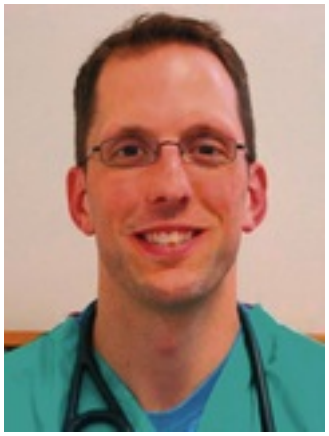
Clinical Feline Reproduction

Kerry Smith Bailey DVM, DACVIM (Neurology)
Staff Neurologist
Neurology
Oradell Animal Hospital
Ramsey, New Jersey

Muscle and Nerve Biopsy

Elizabeth A. Ballegeer BS, DVM, DACVR
Assistant Professor, Diagnostic Imaging
College of Veterinary Medicine
Michigan State University
East Lansing, Michigan;
IDEXX Telemedicine Consultants
Westbrook, Maine

Congenital Diseases of the Lower Urinary Tract



Matthew W. Beal DVM, DACVECC
Professor
Emergency & Critical Care Medicine
Department of Small Animal Clinical Sciences
College of Veterinary Medicine
Michigan State University
East Lansing, Michigan

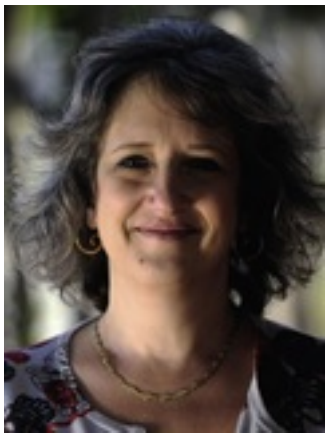
Respiratory Interventional Therapies

Julia A. Beatty BSc (Hons), BVetMed, PhD, FANZCVSc (Feline Medicine)
Professor of Feline Medicine
Faculty of Veterinary Science
University of Sydney
Sydney, NSW, Australia

Feline Immunodeficiency Virus Infection

David P. Beehan MVB (Hons), MS, DACT
Veterinary Inspector
Irish Department of Agriculture, Food and the Marine
Dublin, Ireland

Brucellosis



Ellen N. Behrend VMD, PhD, DACVIM (Small Animal Internal Medicine)
Joezy Griffin Professor
Department of Clinical Sciences
Auburn University
Auburn, Alabama

Non-Cortisol-Secreting Adrenocortical Tumors and Incidentalomas

Niek J. Beijerink DVM, PhD, DECVIM (Cardiology)
Senior Lecturer
School of Life and Environment Sciences, Faculty of Veterinary Science
University of Sydney
Sydney, NSW, Australia

Congenital Heart Disease

Marie-Claude Bélanger DMV, MSc, DACVIM (Small Animal Internal Medicine)
Professor of Small Animal Internal Medicine and Cardiology
Clinical Sciences
University of Montreal
St-Hyacinthe, Quebec, Canada

Echocardiography

Elsa Beltran Ldo Vet, DECVN, MRCVS
Lecturer in Veterinary Neurology and Neurosurgery
Department of Clinical Science and Services
The Royal Veterinary College, University of London
North Mymms, Hatfield, United Kingdom

Unique Feline Neurologic Disorders

Peter Bennett BVSc, FANZCVS, DACVIM (Oncology, Small Animal Internal Medicine)
Clinical Specialist in Oncology and Small Animal Medicine
Veterinary Teaching Hospital Sydney
University of Sydney
Sydney, NSW, Australia

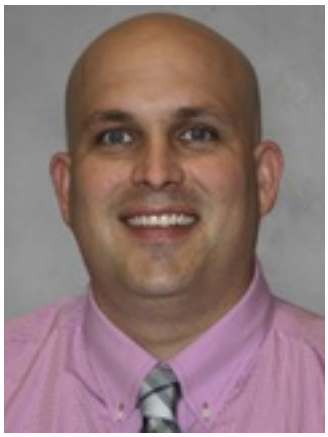
Exocrine Pancreatic Neoplasia

Emmanuel Bensignor DVM, DECVD, DESV (Dermatology)
Dermatology
Clinique La Boulais
Rennes-Cesson, France;
Dermatology
Veterinary Clinic Paris 3
Paris, France;
Dermatology
Veterinary Hospital Atlantia
Nantes, France

Diseases of the Ear

Allyson C. Berent DVM, DACVIM (Small Animal Internal Medicine)
Staff Veterinarian, Interventional Radiology/Medicine
Director of Interventional Endoscopy
The Animal Medical Center
New York, New York

Gastrointestinal Interventional Therapies
Urologic Interventional Therapies
Hepatic Vascular Anomalies



Darren Berger DVM, DACVD
Assistant Professor of Dermatology
Veterinary Clinical Sciences
Iowa State University
Ames, Iowa

Body Odors

Annika Bergström DVM, PhD, DECVS
Senior Lecturer
Department of Clinical Sciences
Faculty of Veterinary Medicine and Animal Sciences
Uppsala, Sweden

Pyometra and Cystic Endometrial Hyperplasia

Alexa M.E. Bersenas DVM, MS, DACVECC
Associate Professor
Department of Clinical Studies
Ontario Veterinary College, University of Guelph
Guelph, Ontario, Canada

Peritoneal Dialysis

Sonya V. Bettenay BVSc (Hons), DEd, FANZCVS, DECVD
Dermatologie Department
Fachklinik Haas & Link
Germering, Germany

Scrapings, Fine-Needle Aspiration, and Biopsy of Skin and Subcutaneous Tissues

Nick Bexfield BVetMed, PhD, DSAM, DECVIM-CA (Internal Medicine), FRSB, AFHEA, MRCVS
Clinical Associate Professor in Small Animal Medicine and Oncology
School of Veterinary Medicine and Science
University of Nottingham
Sutton Bonington, Leicestershire, United Kingdom

Neoplasms of the Liver

Frédéric Billen DVM, MSc, PhD, DECVIM-CA (Internal Medicine)
Senior Lecturer in Internal Medicine of Companion Animals
Department of Clinical Sciences of Companion Animals and Equine
Faculty of Veterinary Medicine, University of Liege
Liege, Belgium

Aspergillosis—Canine

Barbara J. Biller DVM, PhD, DACVIM (Oncology)
Associate Professor of Oncology
Clinical Sciences
Colorado State University
College of Veterinary Medicine and Biomedical Sciences
James L. Voss Veterinary Teaching Hospital
Flint Animal Cancer Center
Fort Collins, Colorado

Cancer Immunotherapy

David S. Biller DVM, DACVR
Professor
Department of Clinical Sciences
College of Veterinary Medicine
Kansas State University
Manhattan, Kansas

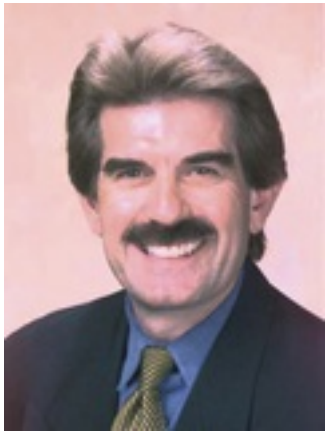
Diseases of the Mediastinum, Chest Wall, and Diaphragm

Vincent C. Biourge DVM, PhD, DACVN, DECVCN
Health and Nutrition Scientific Director
R&D
Royal Canin
Aimargues, France

Nutritional Management of Lower Urinary Tract Disease

Petra Bizikova MVDr, PhD, DECVD, DACVD
Assistant Professor of Dermatology
Department of Clinical Sciences
North Carolina State University
Raleigh, North Carolina

Immune-Mediated Dermatologic Disorders



Byron L. Blagburn MS, PhD
Distinguished University Professor
Department of Pathobiology
College of Veterinary Medicine
Auburn University
Auburn, Alabama

Fecal Examination
Antiparasitic Therapy

Shauna Blois DVM, DVSc, DACVIM (Small Animal Internal Medicine)
Associate Professor
Clinical Sciences
Ontario Veterinary College, University of Guelph
Guelph, Ontario, Canada

Petechiae and Ecchymoses
Blood Transfusions, Component Therapy, and Oxygen-Carrying Solutions
Anti-inflammatory Therapy
Hyper- and Hypocoagulable States

Amanda K. Boag MA, VetMB, DECVECC, DACVECC, DACVIM (Small Animal Internal Medicine), FHEA, MRCVS
Clinical Director
Vets Now
Dunfermline, Fife, United Kingdom

Hepatic and Splenic Emergencies

Manuel Boller Dr.med.vet., MTR, DACVECC
Senior Lecturer, Veterinary Emergency and Critical Care
Faculty of Veterinary and Agricultural Sciences
University of Melbourne
Melbourne, Victoria, Australia;
Veterinary Emergency and Critical Care Service
UVet Werribee Hospital
Werribee, Victoria, Australia

Cardiopulmonary Arrest and CPR
Cardiac Emergencies

John D. Bonagura DVM, MS, DACVIM (Cardiology, Small Animal Internal Medicine)
Professor Emeritus
Department of Veterinary Clinical Sciences
The Ohio State University
Attending Cardiologist
Cardiology and Interventional Medicine
The Ohio State University Veterinary Medical Center
Columbus, Ohio

Congenital Heart Disease
Venous and Lymphatic Disorders

Juan F. Borrego DVM, DACVIM (Oncology)
Head of the Oncology Department
Hospital Aúna Especialidades Veterinarias
Director
Instituto Veterinario de Oncología Comparada
Valencia, Spain

Urogenital and Mammary Gland Tumors

Adrian Boswood MA, VetMB, DVC, DECVIM-CA (Cardiology), MRCVS
Professor of Veterinary Cardiology
Clinical Science and Services
The Royal Veterinary College
London, United Kingdom

Heart Failure: Clinical Management

Søren Boysen DVM, DACVECC
Professor
Veterinary Clinical and Diagnostic Sciences
University of Calgary, Faculty of Veterinary Medicine
Calgary, Alberta, Canada

Acute Abdomen

Christina Alanna Bradbury DVM, MS, DACVIM (Small Animal Internal Medicine)
Staff Internist
Vista Veterinary Specialists
Sacramento, California

Jaundice

Allison Bradley DVM, DACVIM (Small Animal Internal Medicine)
Small Animal Internal Medicine
VCA Veterinary Specialists of Northern Colorado
Loveland, Colorado

Ammonia

Fred C. Brewer IV, DVM, DACVIM (Cardiology)
Owner
California Pet Cardiology
Long Beach, California

Weakness

Marjory B. Brooks DVM, DACVIM (Small Animal Internal Medicine)
Director, Comparative Coagulation Section
Population Medicine & Diagnostic Sciences
Animal Health Diagnostic Center, Cornell University
Ithaca, New York

Thrombocytopenia, Thrombocytosis

Ahna G. Brutlag DVM, MS, DABT, DABVT
Associate Director of Veterinary Services & Senior Veterinary Toxicologist
Pet Poison Helpline & SafetyCall International, PLLC
Minneapolis, Minnesota;
Adjunct Assistant Professor
Department of Veterinary and Biomedical Sciences
College of Veterinary Medicine, University of Minnesota
St. Paul, Minnesota

Prescription and Over-the-Counter Drug Toxicoses

Steven C. Budsberg DVM, MS, DACVS
Director of Clinical Research
Professor
Small Animal Medicine and Surgery
College of Veterinary Medicine, University of Georgia
Athens, Georgia

Evidence-Based Medicine

C.A. Tony Buffington DVM, PhD, DACVN
Emeritus Professor
Veterinary Clinical Sciences
The Ohio State University
Columbus, Ohio

Feline Idiopathic Cystitis

Shelley Burton DVM, MSc, DACVP
Professor of Clinical Pathology
Department of Pathology and Microbiology
Atlantic Veterinary College, University of Prince Edward Island
Charlottetown, PE, Canada

Hypoproteinemia, Hyperproteinemia

Christopher G. Byers DVM, DACVECC, DACVIM (Small Animal Internal Medicine), CVJ
Medical Director
VCA Midwest Veterinary Specialists of Omaha
Omaha, Nebraska

Crystalloid and Colloid Fluid Therapy

Julie K. Byron DVM, MS, DACVIM (Small Animal Internal Medicine)
Associate Professor-Clinical
Veterinary Clinical Sciences
The Ohio State University
Columbus, Ohio

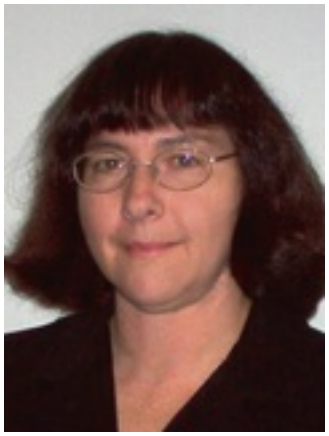
Cystoscopy and Urethroscopy
Diseases of Abnormal Micturition

Mary Beth Callan VMD, DACVIM (Small Animal Internal Medicine)
Professor of Medicine
Department of Clinical Studies
School of Veterinary Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Immune-Mediated Thrombocytopenia, von Willebrand Disease, and Other Platelet Disorders

Amanda Callens BS, LVT
Veterinary Technician
BluePearl Veterinary Partners Seattle
Seattle, Washington

Urine Collection
Management of Urinary Catheters



Karen L. Campbell DVM, MS, DACVIM (Small Animal Internal Medicine), DACVD
Adjunct Clinical Professor and Dermatology Section Head
MU Veterinary Health Center at Wentzville
University of Missouri College of Veterinary Medicine
Columbia, Missouri;
Professor Emerita
Department of Veterinary Clinical Medicine
University of Illinois College of Veterinary Medicine
Urbana, Illinois

Dermatologic Manifestations of Systemic Disease

Stephan Anthony Carey DVM, PhD, DACVIM (Small Animal Internal Medicine)
Assistant Professor
Department of Small Animal Clinical Sciences, College of Veterinary Medicine
Veterinary Medical Center
Michigan State University
East Lansing, Michigan

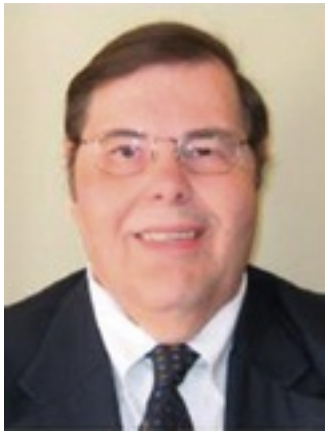
Clinical Evaluation of the Respiratory Tract

Didier-Noël Carlotti Doct-Vét, DECVD †
Clinique Vétérinaire Aquivet, Parc d'Activités
Mermoz, Eysines
Bordeaux, France

Diseases of the Ear

Margret L. Casal Dr.med.vet., PhD, DECAR
Associate Professor of Medical Genetics
School of Veterinary Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Pediatric Care during the Postpartum Period



James L. Catalfamo MS, PhD
Department of Population Medicine and Diagnostic Sciences
College of Veterinary Medicine
Cornell University
Ithaca, New York

Immune-Mediated Thrombocytopenia, von Willebrand Disease, and Platelet Disorders

Nick John Cave BVSc, MVSc, MANZCVS, PhD, DACVN
Senior Lecturer in Small Animal Medicine and Nutrition
Institute of Veterinary, Animal and Biomedical Sciences
Te Kunenga Ki Pūrehuroa
Massey University
Palmerston North, New Zealand

Immunology and Nutrition

Serge Chalhoub DVM, DACVIM (Small Animal Internal Medicine)
Instructor
Veterinary Clinical and Diagnostic Sciences
Faculty of Veterinary Medicine, University of Calgary
Calgary, Alberta, Canada

Pathophysiology and Clinical Manifestations of Systemic Hypertension

Daniel L. Chan DVM, DACVECC, DECVECC, DACVN, FHEA, MRCVS
Professor of Emergency and Critical Care Medicine and Clinical Nutrition
Clinical Science and Services
The Royal Veterinary College, University of London
North Mymms, Hertfordshire, United Kingdom

Critical Care Nutrition

Marjorie Chandler DVM, MS, MANZCVS, DACVN, DACVIM (Small Animal Internal Medicine), DECVIM-CA, MRCVS
Honorary Senior Lecturer in Small Animal Medicine and Clinical Nutrition
Internal Medicine
University of Edinburgh
Edinburgh, Scotland, United Kingdom;
Clinical Nutritionist
Clinical Nutrition
Vets Now Referrals
Glasgow, Scotland, United Kingdom

Nutritional Management of Exocrine Pancreatic Disease

Valérie Chetboul DVM, PhD, DECVIM-CA (Cardiology)
Professor of Cardiology
Alfort Cardiology Unit (UCA)
Centre Hospitalier Universitaire Vétérinaire d'Alfort (CHUVA)
Ecole Nationale Vétérinaire d'Alfort
Maisons-Alfort, France

Feline Myocardial Diseases

Cécile Clercx DVM, PhD, DECVIM-CA (Internal Medicine)
Professor
Internal Medicine of Companion Animals
Department of Clinical Sciences of Companion Animals and Equids
CVU, Companion Animals Pôle
University of Liège
Liege, Belgium

Diseases of the Trachea and Small Airways

Craig A. Clifford DVM, MS, DACVIM (Oncology)
Director of Clinical Studies
Oncology
Hope Veterinary Specialists
Malvern, Pennsylvania

Complications of Anticancer Therapy
Hemangiosarcoma

Martha G. Cline DVM, DACVN
Clinical Veterinary Nutritionist
Department of Clinical Nutrition
Red Bank Veterinary Hospital
Tinton Falls, New Jersey

Nutrition for Healthy Adult Dogs

Joan R. Coates BS, DVM, MS, DACVIM (Neurology)
Full Professor
Department of Veterinary Medicine and Surgery
Service Leader
Neurology and Neurosurgery Service
Veterinary Health Center (Small Animal Hospital), College of Veterinary Medicine
University of Missouri
Columbia, Missouri

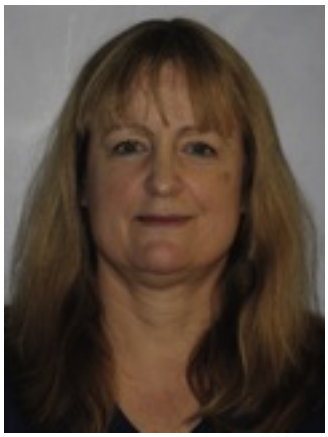
Neurophysiology
Brain Diseases: Degenerative, Anomalous, Metabolic, Neoplasia, Idiopathic Epilepsy, and Vascular

Sarah Cocker DVM
Internal Medicine Resident
Internal Medicine
The Veterinary Specialty Hospital
San Diego, California

Diagnostic Evaluation of the Liver

Ronald Jan Corbee DVM, PhD, DECVCN
Assistant Professor
Clinical Sciences of Companion Animals
Utrecht University, Faculty of Veterinary Medicine
Utrecht, The Netherlands

Nutritional-Related Skeletal Disorders

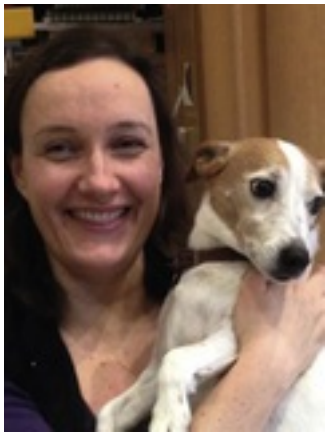


Susan Cox RVT, VTS (Small Animal Internal Medicine)
Small Animal Internal Medicine Technician
Small Animal Internal Medicine Service
William R. Pritchard Veterinary Medical Teaching Hospital
University of California, Davis
Davis, California

Care of Endoscopic Equipment

Sylvie Daminet DVM, PhD, MSc, DECVIM-CA (Internal Medicine), DACVIM (Small Animal Internal Medicine)
Professor
Department of Companion Animals
Faculty of Veterinary Medicine
Ghent University
Merelbeke, Belgium

Polyphagia
Feline Hypothyroidism

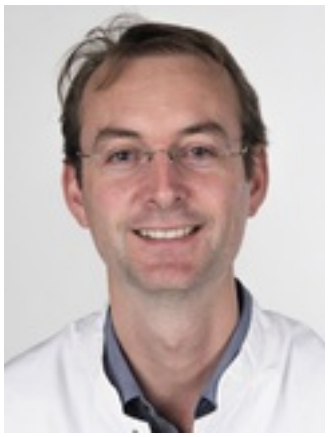


Lucy J. Davison MA, VetMB, PhD, DSAM, DECVIM-CA (Internal Medicine), MRCVS
University Lecturer in Genetics and Small Animal Medicine
Department of Veterinary Medicine
The Queen's Veterinary School Hospital
University of Cambridge
Cambridge, United Kingdom;
Wellcome Trust Veterinary Postdoctoral Fellow
Wellcome Trust Centre for Human Genetics
University of Oxford
Oxford, United Kingdom

Diabetes Mellitus and Corticosteroid-Responsive Disease

Michael J. Day BSc, BVMs (Hons), PhD, DSc, DECVP, FASM, FRCPath, FRCVS
Professor of Veterinary Pathology
School of Veterinary Sciences
University of Bristol
Langford, North Somerset, United Kingdom

Companion Animal Vaccinations
Disease of the Small Intestine

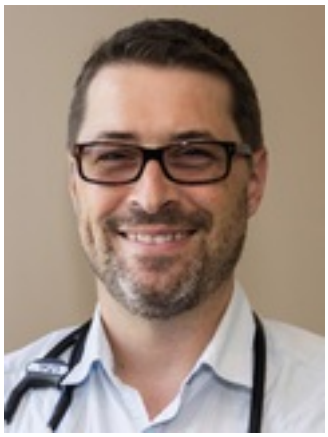


Jeffrey de Gier DVM, PhD, DECAR-CA
Assistant Professor
Department of Clinical Sciences of Companion Animals
Faculty of Veterinary Medicine, Utrecht University
Utrecht, The Netherlands

Vulvar and Preputial Discharge

Armelle de Laforcade DVM, DACVECC
Associate Professor
Department of Clinical Sciences
Tufts Cummings School of Veterinary Medicine
North Grafton, Massachusetts

Hemorrhage



Louis-Philippe de Lorimier DVM, DACVIM (Oncology)
Staff Medical Oncologist
Oncology Service
Centre Vétérinaire Rive-Sud
Brossard, Quebec, Canada

Complications of Anticancer Therapy
Hemangiosarcoma

Luisa De Risio DMV, MRCVS, PhD, DECVN, European and RCVS Recognized Veterinary Specialist in Neurology
Head of Neurology/Neurosurgery
Head of Research-Clinics
Neurology/Neurosurgery Service, Center for Small Animal Studies
Animal Health Trust
Newmarket, Suffolk, United Kingdom

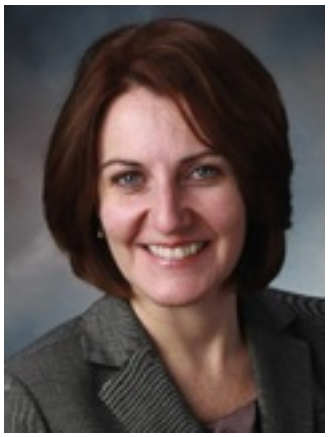
Unique Feline Neurologic Disorders

Hilde de Rooster DVM, MVM, PhD, DECVS
Professor Doctor
Small Animal Medicine and Clinical Biology
Faculty of Veterinary Medicine, Ghent University
Merelbeke, Belgium

Effect of Spay or Castration on Long-Term Health of Dogs and Cats

Jonathan D. Dear DVM, DACVIM (Small Animal Internal Medicine)
Assistant Professor of Clinical Internal Medicine
Medicine & Epidemiology
University of California, Davis
Davis, California

Swollen Joints and Joint Pain
Arthrocentesis and Arthroscopy



Camille DeClementi VMD, DABT, DABVT
Adjunct Instructor
Department of Veterinary Biosciences
University of Illinois, College of Veterinary Medicine
Urbana, Illinois;
Senior Director
Animal Health Sciences
American Society for the Prevention of Animal Cruelty (ASPCA)
New York, New York

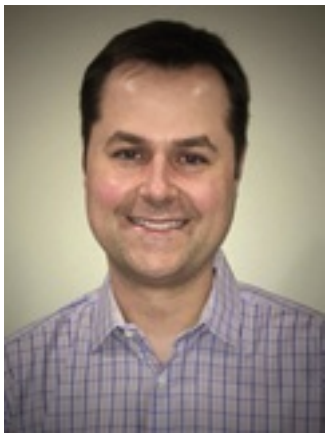
Toxin Exposure Therapy/Decontamination

Amy E. DeClue DVM, MS, DACVIM (Small Animal Internal Medicine)
Associate Professor
College of Veterinary Medicine
University of Missouri
Columbia, Missouri

Leukopenia, Leukocytosis
Sepsis and the Systemic Inflammatory Response Syndrome

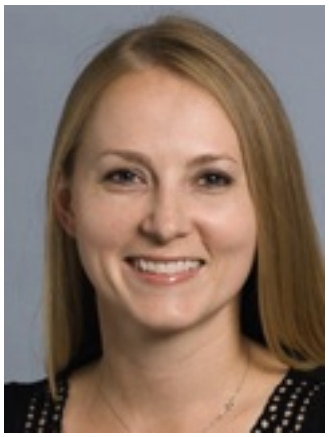
Andrea Dedeaux DVM
Internal Medicine Resident
Department of Veterinary Clinical Sciences
Louisiana State University
Baton Rouge, Louisiana

Blastomycosis and Histoplasmosis



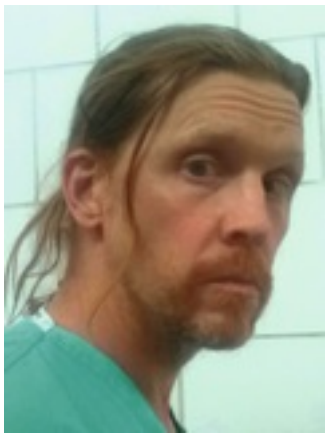
Sean J. Delaney DVM, MS, DACVN
Founder
Balance IT, A DBA of DVM Consulting, Inc.
Davis, California

Unconventional Diets (Homemade, Vegetarian, and Raw)



Ann-Marie Della Maggiore DVM, DACVIM (Small Animal Internal Medicine)
Assistant Professor of Clinical Internal Medicine
School of Veterinary Medicine, Department of Medicine and Epidemiology
University of California, Davis
Davis, California

Potassium, Magnesium



Curtis W. Dewey DVM, MS, DACVIM (Neurology), DACVS
Associate Professor and Section Chief, Neurology/Neurosurgery
Department of Clinical Sciences
Cornell University
Ithaca, New York

Inflammatory, Infectious, and Other Multifocal Brain Diseases

Ryan M. Dickinson BA, DVM, DACVP
Assistant Professor
Department of Veterinary Pathology
Western College of Veterinary Medicine, University of Saskatchewan
Saskatoon, SK, Canada

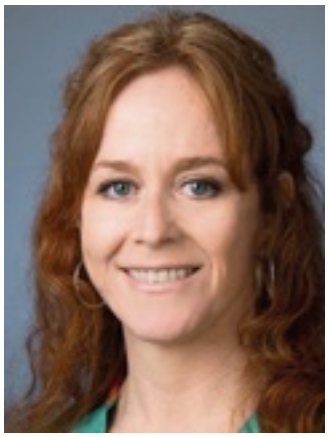
Cytology of the Skin and Subcutaneous Tissues

Pedro Paulo V.P. Diniz DVM, PhD
Associate Professor of Small Animal Internal Medicine
College of Veterinary Medicine
Western University of Health Sciences
Pomona, California

Bartonella—Canine

David C. Dorman DVM, PhD
Professor of Toxicology
Department of Molecular Biomedical Sciences
North Carolina State University
Raleigh, North Carolina

Plant Intoxications



Katie Douthitt RVT
Small Animal Clinic Medicine Services
Veterinary Medicine Teaching Hospital
University of California, Davis
Davis, California

Care of Endoscopic Equipment

Kenneth J. Drobatz DVM, MSCE, DACVIM (Small Animal Internal Medicine), DACVECC
Professor and Section Chief, Critical Care
School of Veterinary Medicine
Director, Emergency Services
Matthew J. Ryan Veterinary Hospital
University of Pennsylvania
Philadelphia, Pennsylvania

Global Approach to the Trauma Patient

Marilyn E. Dunn DMV, MVSc, DACVIM (Small Animal Internal Medicine)
Professor
Department of Clinical Sciences
University of Montreal
St-Hyacinthe, Quebec, Canada

Urologic Interventional Therapies

David A. Dzanis DVM, PhD, DACVN
Chief Executive Officer
Regulatory Discretion, Inc.
Santa Clarita, California

Pet Food Safety and Regulatory Aspects of Pet Food

Melissa L. Edwards DVM, DACVECC, Douglas, Alaska

Hyperbaric Medicine

Laura Eirmann DVM, DACVN
Clinical Nutritionist
Nutrition
Oradell Animal Hospital
Paramus, New Jersey;
Veterinary Communications Manager
Nestlé Purina PetCare
St. Louis, Missouri

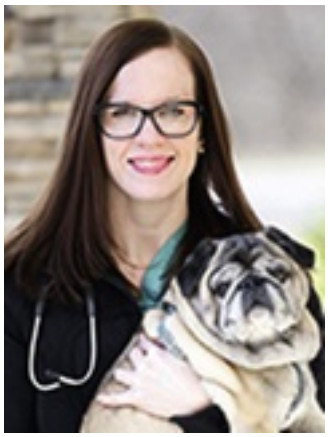
Antioxidants, Nutraceuticals, Probiotics, and Nutritional Supplements

Gary C.W. England BVetMed, PhD, DVetMed, DVR, DVRep, DECAR, DACT, FHEA, FRCVS
Foundation Dean & Professor of Comparative Veterinary Reproduction
School of Veterinary Medicine & Science
University of Nottingham
Loughborough, Leicestershire, United Kingdom

Breeding Soundness Examination and Disorders of Reproduction in Male Dogs

Steven Epstein DVM, DACVECC
Assistant Professor of Clinical Small Animal Emergency and Critical Care
Department of Surgical and Radiological Sciences
University of California, Davis
Davis, California

Urinary Electrolyte Concentrations
Pulse Oximetry

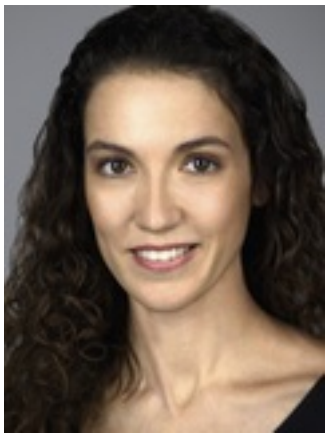


Chelsie Estey MSc, DVM, DACVIM (Neurology)
Neurology/Neurosurgery Service
Upstate Veterinary Specialties
Latham, New York

Inflammatory, Infectious, and Other Multifocal Brian Diseases

Amara H. Estrada DVM, DACVIM (Cardiology)
Associate Professor and Associate Chair for Instruction
Department of Small Animal Clinical Sciences
Director of Teaching Academy
College of Veterinary Medicine
University of Florida
Gainesville, Florida

Cardiac Pacing



Amy Farcas DVM, MS, DACVN
Owner, Veterinary Nutritionist
Veterinary Nutrition Care
San Carlos, California

Nutritional Uses of Fiber

Luca Ferasin DVM, PhD, CertVC, PGCert(HE), DECVIM-CA (Cardiology), GPCert(B&PS), MRCVS
European & RCVS Specialist in Cardiology
CVS Referrals
Cardiology
Lumbry Park Veterinary Specialists
Alton, Hampshire, United Kingdom

Coughing

Deborah M. Fine-Ferreira DVM, MS, DACVIM (Cardiology)
Cardiologist
Ali'i Veterinary Hospital
Kailua-Kona, Hawaii;
Cardiologist
Veterinary Emergency and Referral Center
Honolulu, Hawaii

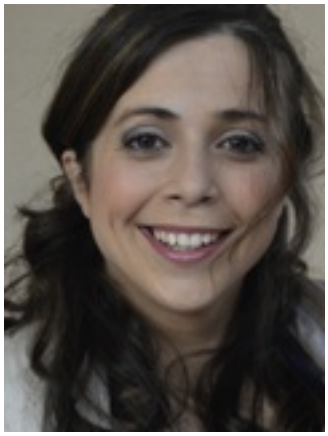
Peripheral Edema

Daniel John Fletcher PhD, DVM, DACVECC
Associate Professor of Emergency and Critical Care
Clinical Sciences
Cornell University College of Veterinary Medicine
Ithaca, New York

Cardiopulmonary Arrest and CPR

Peter Foley MSc, DVM, DACVIM (Small Animal Internal Medicine)
Assistant Professor
Department of Companion Animals
Atlantic Veterinary College
University of Prince Edward Island
Charlottetown, PE, Canada

Constipation, Tenesmus, Dyschezia, and Fecal Incontinence



Yaiza Forcada DVM, PhD, DECVIM-CA (Internal Medicine)
Lecturer in Small Animal Internal Medicine
Clinical Sciences and Services
The Royal Veterinary College
North Mymms, Hertfordshire, United Kingdom

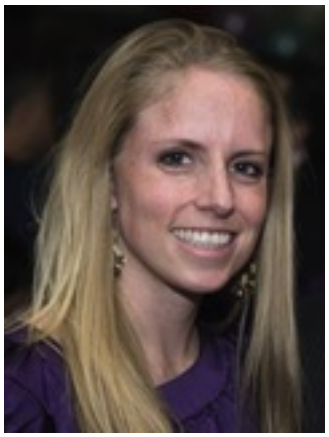
Hypoglycemia, Hyperglycemia

Marnin A. Forman DVM, DACVIM (Small Animal Internal Medicine)
Head of Internal Medicine, Staff Internist
Internal Medicine
Cornell University Veterinary Specialists
Stamford, Connecticut

Anorexia
Feline Inflammatory/Infectious Hepatic Disease

Catharina Linde Forsberg DVM, PhD, DECAR
Professor Emeritus of Small Animal Reproduction
Department of Clinical Sciences, Division of Reproduction
Swedish University of Agricultural Sciences
Private Company
Uppsala, Sweden

Artificial Insemination in the Dog



Amanda Foskett DVM
Resident, Medical Oncology
The Oncology Service, LLCWashington, DC

The Hallmarks/Origin of Cancer

Federico Fracassi DVM, PhD, DECVIM-CA (Internal Medicine)
Professor
Department of Veterinary Medical Sciences
School of Agriculture and Veterinary Medicine
Bologna, Italy

Canine Diabetes Mellitus

Thierry Francey DVM, DACVIM (Small Animal Internal Medicine), DECVIM-CA (Internal Medicine)
Department of Clinical Veterinary Medicine
University of Bern
Bern, Switzerland

Hematuria and Other Conditions Causing Discolored Urine

Diane Frank DVM, DACVB
Professor (Behavioral Medicine)
Clinical Sciences
Université de Montréal
St-Hyacinthe, Quebec, Canada

Distinguishing Behavioral Disorders from Medical Disorders

Angela E. Frimberger BS, VMD, DACVIM (Oncology), MACVSc
Director
Veterinary Oncology Consultants
Wauchope, NSW, Australia

Principles and Practice of Chemotherapy

Jason W. Gagné DVM, DACVN
Senior Manager, Veterinary Technical Marketing
Nestlé Purina PetCare
St. Louis, Missouri

Adverse Reactions to Foods: Allergies versus Intolerance

Sara Galac DVM, PhD
Assistant Professor
Clinical Sciences of Companion Animals
Faculty of Veterinary Medicine, Utrecht University
Utrecht, The Netherlands

Pheochromocytoma

Alex Gallagher DVM, MS, DACVIM (Small Animal Internal Medicine)
Clinical Assistant Professor
Small Animal Clinical Sciences
University of Florida College of Veterinary Medicine
Gainesville, Florida

Vomiting and Regurgitation

Rosalind M. Gaskell BVSc, PhD, MRCVS
Professor (Emeritus) and Honorary Fellow
School of Veterinary Science
University of Liverpool, Leahurst Campus
Neston, Cheshire, United Kingdom

Feline Upper Respiratory Infections
Other Feline Viral Infections

Olivier Gauthier DVM, MSc, PhD
Professor of Small Animal Surgery and Dentistry
Small Animal Surgery
Oniris Nantes-Atlantic College of Veterinary Medicine, Food Science and Engineering
Nantes, France

Diseases of the Ear

James S. Gaynor DVM, MS, DACVAA, DAAPM
Medical Director
Peak Performance Veterinary Group
Breckenridge, Colorado;
Medical Director
Animal Emergency Care Centers
Colorado Springs, Colorado

Sedation and Anesthesia in Critical Care

Alexander James German BVSc, PhD, CertSAM, DECVIM-CA (Internal Medicine), MRCVS
Reader in Small Animal Medicine
Institute of Ageing and Chronic Disease
School of Veterinary Science
University of Liverpool
Neston, Merseyside, United Kingdom

Flatulence

Alireza A. Gorgi DVM, DACVIM (Neurology)
Department Head, Neurology/Neurosurgery
VCA West Coast Specialty & Emergency Animal Hospital
Fountain Valley, California;
Associate Clinical Professor
Western University of Health Sciences College of Veterinary Medicine
Pomona, California

Status Epilepticus

Susan A. Gottlieb BVSc (Hons), BSc(vet), BAppSc, MANZCVS
Veterinarian
The Cat Clinic
Brisbane, Queensland, Australia

Feline Diabetes Mellitus

Peter A. Graham BVMS, PhD, CertVR, DECVCP, MRCVS
Clinical Associate Professor
School of Veterinary Medicine and Science
University of Nottingham
Sutton Bonington, Leicestershire, United Kingdom

Urinalysis

Thomas K. Graves DVM, PhD, DACVIM (Small Animal Internal Medicine)
Dean and Professor
College of Veterinary Medicine
Midwestern University
Glendale, Arizona

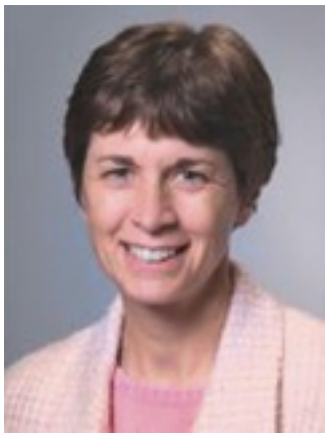
Feline Hyperthyroidism

Amy M. Grooters DVM, DACVIM (Small Animal Internal Medicine)
Professor
Companion Animal Medicine
Louisiana State University
Baton Rouge, Louisiana

Miscellaneous Fungal Infections

Sophie Alexandra Grundy BVSc (Hons), MANZCVS, DACVIM (Small Animal Internal Medicine)
Internal Medicine Consultant
IDEXX Laboratories, Inc.
Westbrook, Maine

Other Infectious Causes of Infertility and Subfertility in Dogs and Cats



Lynn F. Guptill DVM, PhD, DACVIM (Small Animal Internal Medicine)
Associate Professor
Department of Veterinary Clinical Services
Purdue University
West Lafayette, Indiana

Bartonella—Feline

Tim B. Hackett DVM, MS, DACVECC
Professor of Emergency and Critical Care Medicine
Department of Clinical Sciences
Colorado State University
Fort Collins, Colorado

Epistaxis and Hemoptysis
Chest Tube Placement

Jens Häggström DVM, PhD, DECVIM-CA (Cardiology)
Professor
Department of Clinical Sciences
Faculty of Veterinary Medicine and Animal Science
The Swedish University of Agricultural Sciences
Uppsala, Sweden

Adult-Onset Valvular Heart Disease

Edward James Hall MA, VetMB, PhD
Professor of Small Animal Medicine
School of Veterinary Sciences
University of Bristol
Langford, Bristol, United Kingdom

Diseases of the Small Intestine
Diseases of the Large Intestine

Meri F. Hall RVT, LVT, CVT, LATG, VTS (Small Animal Internal Medicine)
Veterinary Technician
Internal Medicine
Veterinary Specialty Hospital
Palm Beach Gardens, Florida

Jugular Catheterization and Central Venous Pressure Measurement

Cathleen A. Hanlon VMD, PhD, DACVPM
Team Lead, Rabies; WHO Collaborating Center Head; OIE Expert (Retired)
Division of High Consequence Pathogens and Pathology
Centers for Disease Control and Prevention
Atlanta, Georgia

Rabies

Katrin Hartmann Dr.med.vet., Dr.habil., DECVIM-CA (Internal Medicine)
Professor
Head of Clinic of Small Animal Medicine
Director of Centre of Clinical Veterinary Medicine
Ludwig-Maximilian-Universitaet
Munich, Germany

Feline Leukemia Virus Infection
Coronavirus Infections (Canine and Feline), Including Feline Infectious Peritonitis

Camilla Heinze DVM, RHD
Dyrlaege Camilla Heinze ApS
Karlslunde, Denmark

Ptyalism and Halitosis

Eric J. Herrgesell DVM, DACVR
Partner
Veterinary Medical Imaging
Sacramento, California

Abdominal Ultrasound: Aspirations and Biopsies

Michael E. Herrtage MA, BVSc, DVSc, DVR, DVD, DSAM, DECVIM-CA (Internal Medicine), DECVDI, MRCVS
Professor of Small Animal Medicine
Department of Veterinary Medicine
University of Cambridge
Cambridge, Cambridgeshire, United Kingdom

Feline Hyperadrenocorticism

Rebecka S. Hess DVM, DACVIM (Small Animal Internal Medicine)
Professor of Internal Medicine
Chief, Section of Medicine
Department of Clinical Studies, Philadelphia
School of Veterinary Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

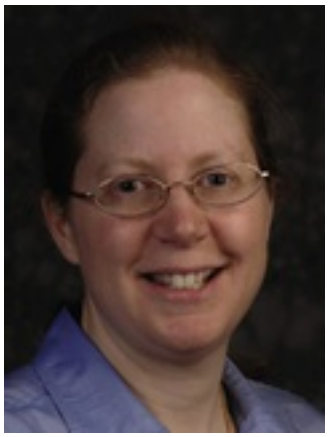
Hypoadrenocorticism

Richard C. Hill MA, VetMB, PhD, DACVIM (Small Animal Internal Medicine), DACVN, MRCVS
Associate Professor
Department of Small Animal Clinical Sciences
University of Florida, College of Veterinary Medicine
Gainesville, Florida

Dietary and Medical Considerations in Hyperlipidemia

Daniel F. Hogan DVM, DACVIM (Cardiology)
Professor, Cardiology
Veterinary Clinical Sciences
College of Veterinary Medicine, Purdue University
West Lafayette, Indiana

Arterial Thromboembolic Disease



Kate Hopper BVSc, PhD, DACVECC
Associate Professor of Small Animal Emergency & Critical Care
Veterinary Surgical and Radiological Sciences
University of California, Davis
Davis, California

Oxygen Therapy

Takuo Ishida DVM, PhD, DJCVP
Medical Director
Akasaka Animal Hospital
Minatoku, Tokyo, Japan;
President
Japanese Board of Veterinary Practitioners
Shibuyaku, Tokyo, Japan

Lymph Node Aspiration and Biopsy

Nicholas Jeffery BVSc, PhD, MSc, DECVN, DECVS, DSAS, FRCVS
Professor, Neurology and Neurosurgery
Veterinary Clinical Sciences
Texas A&M University
College Station, Texas

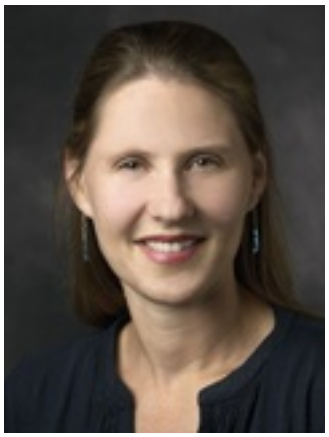
Spinal Cord Diseases: Traumatic, Vascular, and Neoplastic Disorders

Rosanne Jepson BVSc, MVetMed, PhD, DACVIM (Small Animal Internal Medicine), DECVIM-CA (Internal Medicine), FHEA, MRCVS
Lecturer in Small Animal Internal Medicine
Clinical Sciences and Services
Royal Veterinary College
London, United Kingdom

Clinical Approach and Laboratory Evaluation of Renal Disease

Albert Earl Jergens DVM, PhD, DACVIM (Small Animal Internal Medicine)
Professor
Department of Veterinary Clinical Sciences
College of Veterinary Medicine
Iowa State University
Ames, Iowa

Host-Microbiota Interactions in Gastrointestinal Health and Disease



Jennifer L. Johns DVM, PhD, DACVP (Clinical Pathology)
Assistant Professor
Comparative Medicine
Stanford University School of Medicine
Stanford, California

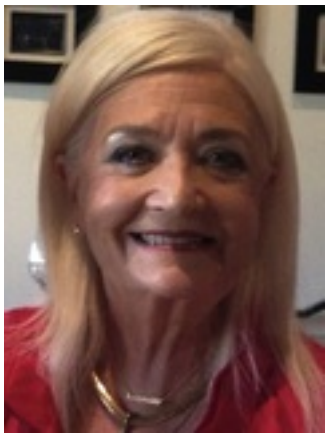
Immune-Mediated and Other Nonneoplastic White Blood Cell Disorders

Andrea N. Johnston DVM, DACVIM (Small Animal Internal Medicine)
Molecular Biology
University of Texas Southwestern Medical Center
Dallas, Texas

Liver Enzymes

Ron Johnson DVM, PhD, DACVCP
Associate Professor
Biomedical Sciences
University of Guelph
Guelph, Ontario, Canada

Compounding Drugs



Dinah G. Jordan BSPh, RPh, PharmD, DICVP
Chief of Pharmacy Services and Clinical Professor, Retired
College of Veterinary Medicine
Mississippi State University
Starkville, Mississippi

Compounding Drugs

Philip H. Kass DVM, MPVM, MS (Statistics), PhD (Epidemiology), DACVPM (Specialty in Epidemiology)
Professor of Analytic Epidemiology
Population Health and Reproduction, School of Veterinary Medicine
University of California, Davis
Davis, California

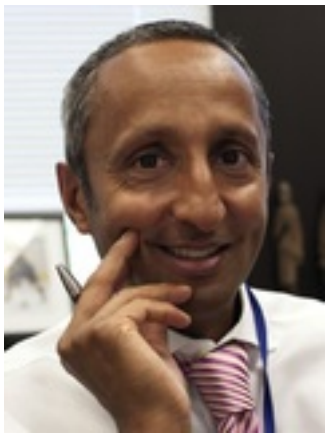
Biomedical Statistics: Selected Topics

Eileen Kenney DVM, DACVECC
Criticalist
Emergency/Critical Care
VCA West Los Angeles Animal Hospital
Los Angeles, California

Head Trauma

Marie E. Kerl DVM, MPH, DACVIM (Small Animal Internal Medicine), DACVECC
Teaching Professor
Veterinary Medicine and Surgery
University of Missouri
Columbia, Missouri

Acid-Base, Oximetry, and Blood Gas Analysis
Renal Tubular Diseases



Chand Khanna DVM, PhD, DACVIM (Oncology), DACVP (Hon)
Chief Science Officer
Ethos Veterinary Health
Woburn, Massachusetts;
The Oncology Service
President
Ethos Discovery
Washington, DC

The Hallmarks/Origin of Cancer

Peter P. Kintzer DVM, DACVIM (Small Animal Internal Medicine)
Field Medical Specialist Manager
CAG Medical Organization
IDEXX Laboratories
Westbrook, Maine

Weight Gain

Karen Lynne Kline DVM, MS, DACVIM (Neurology)
Staff Neurologist
Department of Neurology
VCA Veterinary Specialty Center of Seattle
Lynnwood, Washington

Stupor and Coma

Amie Koenig DVM, DACVIM (Small Animal Internal Medicine), DACVECC
Associate Professor of Emergency and Critical Care
Department of Small Animal Medicine and Surgery
College of Veterinary Medicine, University of Georgia
Athens, Georgia

Gastrointestinal Emergencies

Amy M. Koenigshof DVM, MS, DACVECC
Assistant Professor, Emergency and Critical Care Medicine
Small Animal Clinical Sciences
Michigan State University
East Lansing, Michigan

Urinary Tract Trauma

Hans S. Kooistra DVM, PhD, DECVIM-CA (Internal Medicine)
Associate Professor
Department of Clinical Sciences of Companion Animals
University of Utrecht
Utrecht, The Netherlands

Failure to Grow
Canine Growth Hormone Disorders

Peter Hendrik Kook PD, Dr.med.vet., DACVIM (Small Animal Internal Medicine), DECVIM-CA (Internal Medicine)
Privatdozent
Clinic for Small Animal Internal Medicine
Vetsuisse Faculty, University of Zurich
Zurich, Switzerland

Gagging
Amylase, Lipase

John M. Kruger DVM, PhD, DACVIM (Small Animal Internal Medicine)
Professor, Internal Medicine
Small Animal Clinical Sciences
Michigan State University
East Lansing, Michigan

Congenital Diseases of the Lower Urinary Tract

Butch KuKanich DVM, PhD, DACVCP
Professor of Pharmacology
Department of Anatomy and Physiology
Kansas State University
Manhattan, Kansas

Principles of Drug Disposition and Pharmacokinetics

W. Douglas Kunz MS, DVM
Medical Director
VCA Desert Animal Medical Hospital
Palm Springs, California

Euthanasia

Michelle Anne Kutzler DVM, PhD, DACT
Associate Professor of Companion Animal Industries
Animal and Rangeland Sciences
Oregon State University
Corvallis, Oregon

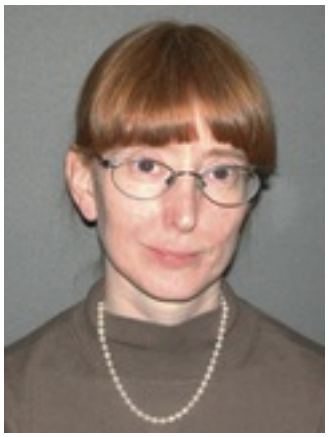
Prostatic Diagnostic Techniques
Prostatic Diseases

Mary Anna Labato DVM, DACVIM (Small Animal Internal Medicine)
Clinical Professor
Section Head, Small Animal Medicine
Department of Clinical Sciences
Staff Veterinarian
Foster Hospital
Cummings School of Veterinary Medicine
Tufts University
North Grafton, Massachusetts

Pollakiuria, Stranguria, and Urinary Incontinence
Continuous Renal Replacement Therapy/Hemodialysis
Lower Urinary Tract Urolithiasis—Feline

Gary Landsberg DVM, DACVB, DECAWBM (Companion Animals)
Veterinary Behaviourist
North Toronto Veterinary Behavior Specialty Clinic
Thornhill, Ontario, Canada;
Vice President, Veterinary Affairs
CanCog Technologies
Toronto, Ontario, Canada

Cognitive Dysfunction in Aged Dogs and Cats



Cathy E. Langston DVM, DACVIM (Small Animal Internal Medicine)
Associate Professor
Veterinary Clinical Sciences
College of Veterinary Medicine
The Ohio State University
Columbus, Ohio

Acute Kidney Injury

Michael R. Lappin DVM, PhD, DACVIM (Small Animal Internal Medicine)
Professor
Department of Clinical Science
College of Veterinary Medicine and Biomedical Sciences
Colorado State University
Fort Collins, Colorado

Laboratory Diagnosis of Infectious Disease
Zoonoses
Protozoal Infections

Jennifer Larsen DVM, PhD, DACVN
Veterinary Medicine, Molecular Biosciences
School of Veterinary Medicine
University of California, Davis
Davis, California

Nutrition for Healthy Adult Cats
Nutritional Management of Endocrine and Metabolic Diseases

Martha Moon Larson DVM, MS, DACVR
Professor
Department of Small Animal Clinical Sciences
Virginia-Maryland College of Veterinary Medicine
Virginia Polytechnic Institute and State University
Blacksburg, Virginia

Diseases of the Mediastinum, Chest Wall, and Diaphragm

Patty Lathan VMD, MS, DACVIM (Small Animal Internal Medicine)
Associate Professor, Small Animal Internal Medicine
Department of Clinical Sciences
Mississippi State University College of Veterinary Medicine
Mississippi State, Mississippi

Hypoparathyroidism

Jessica Lawrence DVM, DACVIM (Oncology), DACVR (Radiation Oncology), MRCVS
Head of Oncology and Senior Lecturer in Oncology
Royal (Dick) School of Veterinary Studies
Easter Bush Campus, University of Edinburgh
Edinburgh, Scotland, United Kingdom;
Associate Professor of Radiation Oncology
Department of Veterinary Clinical Sciences
University of Minnesota, College of Veterinary Medicine
St. Paul, Minnesota

Principles and Practice of Radiation Oncology

Justine A. Lee DACVECC, DABT
VETgirl, LLC
St. Paul, Minnesota

Hypothermia
Chemical Toxicoses

Tekla M. Lee-Fowler DVM, MS, DACVIM (Small Animal Internal Medicine)
Assistant Professor
College of Veterinary Medicine
Auburn University
Auburn, Alabama

Transtracheal Wash and Bronchoscopy

Andrew Lambert Leisewitz BVSc, MMedVet(Med), PhD, DECVIM-CA (Internal Medicine)
Professor
Companion Animal Clinical Studies
University of Pretoria
Pretoria, Gauteng, South Africa

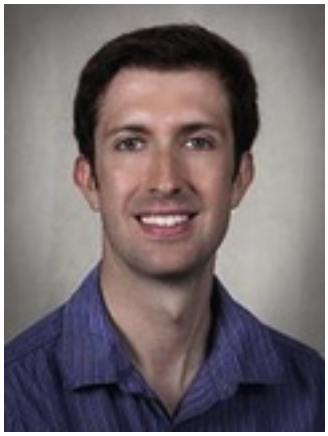
Canine and Feline Parvovirus Infection

David Levine PT, PhD, DPT, DABPTS (Orthopedics), CCRP, Cert. DN
Professor and Walter M. Cline Chair of Excellence in Physical Therapy
Physical Therapy
The University of Tennessee at Chattanooga
Chattanooga, Tennessee

Physical Therapy and Rehabilitation

Julie K. Levy DVM, PhD, DACVIM (Small Animal Internal Medicine)
Professor
Maddie's Shelter Medicine Program
College of Veterinary Medicine
University of Florida
Gainesville, Florida

Feline Leukemia Virus Infection



Jonathan Andrew Lidbury BVMS, MRCVS, PhD, DACVIM (Small Animal Internal Medicine), DECVIM-CA (Internal Medicine)
Assistant Professor of Small Animal Internal Medicine
Gastrointestinal Laboratory Associate Director of Clinical Services
Veterinary Small Animal Clinical Sciences
Texas A&M University
College Station, Texas

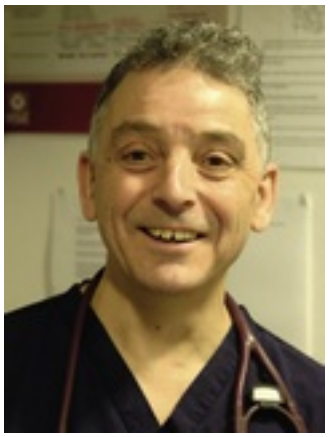
General Principles in the Treatment of Liver Disease

David Lipsitz DVM, DACVIM (Neurology)
Staff Neurologist
Neurology
Veterinary Specialty Hospital of San Diego
San Diego, California

Electromyography and Nerve Conduction Velocity

Julius M. Liptak BVSc, MVetClinStud, FACVSc, DACVS, DECVS
Small Animal Surgeon and Surgical Oncologist
Alta Vista Animal Hospital
Ottawa, Ontario, Canada

Bone and Joint Tumors



Christopher Little BVMS, PhD, DVC, MRCVS
Veterinarian
Barton Veterinary Hospital
Canterbury, Kent, United Kingdom

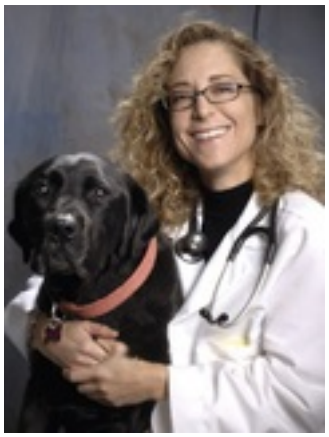
Pulse Alterations

Meryl P. Littman VMD, DACVIM (Small Animal Internal Medicine)
Professor of Medicine
Clinical Studies—Philadelphia
University of Pennsylvania School of Veterinary Medicine
Philadelphia, Pennsylvania

Lyme Disease

Ingrid Ljungvall DVM, PhD
Associate Professor
Department of Clinical Sciences
Swedish University of Agricultural Sciences
Uppsala, Sweden

Adult-Onset Valvular Heart Disease

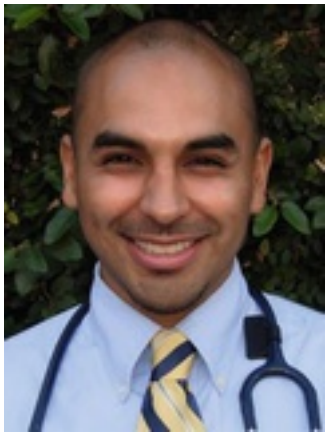


Cheryl London DVM, PhD, DACVIM (Oncology)
Research Professor
Molecular Research Institute, Tufts Medical Center
Cummings School of Veterinary Medicine, Tufts University
Associate Faculty Professor
College of Veterinary Medicine
The Ohio State University
Columbus, Ohio

Molecular Targeted Therapy

Cheryl Lopate MS, DVM, DACT
Co-Owner and Clinical Veterinarian
Reproductive Revolutions
Aurora, Oregon;
Co-Owner and Clinical Veterinarian
Wilsonville Veterinary Clinic
Wilsonville, Oregon

Vaginoscopy and Vaginal Cytology in Dogs
Reproductive Endocrinology and Breeding Husbandry of the Bitch



Julio López DVM, DACVIM (Small Animal Internal Medicine)
Staff Internist
Studio City Animal Hospital
Los Angeles, California

Sneezing and Nasal Discharge
Dysphagia

Jody P. Lulich DVM, PhD, DACVIM (Small Animal Internal Medicine)
Professor
Minnesota Urolith Center
University of Minnesota
St. Paul, Minnesota

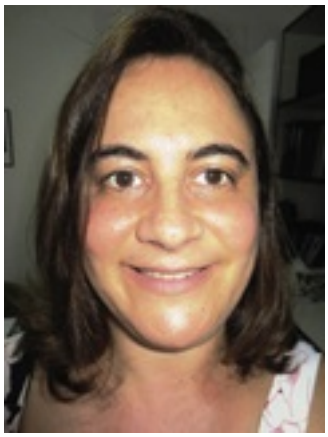
Unblocking of the Urethra
Lower Urinary Tract Urolithiasis in Dogs

Kristin MacDonald DVM, PhD, DACVIM (Cardiology)
Veterinary Cardiologist
VCA Animal Care Center of Sonoma
Rohnert Park, California

Pericardial Diseases

Valerie MacDonald BSc, DVM, DACVIM (Oncology)
Associate Professor
Department of Small Animal Clinical Sciences
Western College of Veterinary Medicine, University of Saskatchewan
Saskatoon, SK, Canada

Bone Marrow Aspiration and Biopsy



Lúcia Daniel Machado da Silva DVM, PhD
Professor
Laboratory of Carnivores Reproduction
Veterinary Faculty
State University of Ceará
Fortaleza, Ceará, Brazil

Breeding Soundness Examination and Disorders of Reproduction in Male Dogs

Catriona M. MacPhail DVM, PhD, DACVS
Associate Professor, Small Animal Surgery
Department of Clinical Sciences
Small Animal Chief Medical Officer
Veterinary Teaching Hospital
Colorado State University
Fort Collins, Colorado

Diseases of the Larynx

Denis J. Marcellin-Little DEDV, DACVS, DECVS
Professor, Orthopedic Surgery
Department of Clinical Sciences
College of Veterinary Medicine, North Carolina State University
Raleigh, North Carolina

Skeletal Disorders in Companion Animals

Christopher L. Mariani DVM, PhD, DACVIM (Neurology)
Associate Professor of Neurology and Neurosurgery
Clinical Sciences
Director, Comparative Neuroimmunology and Neurooncology Laboratory
North Carolina State University
Raleigh, North Carolina

Peripheral Neuropathies
Neuromuscular Junction Disorders

Stanley Leon Marks BVSc, PhD, DACVIM (Small Animal Internal Medicine, Oncology), DACVN
Professor
Department of Medicine and Epidemiology
School of Veterinary Medicine
University of California, Davis
Davis, California

Nasoesophageal, Esophagostomy, Gastrostomy, and Jejunal Tube Placement Techniques
Enteric Bacterial Diseases
Diseases of the Pharynx and Esophagus

Steven L. Marks BVSc, MS, MRCVS, DACVIM (Small Animal Internal Medicine)
Associate Dean and Director of Veterinary Medical Services
North Carolina State University
Raleigh, North Carolina

Constant Rate Infusions

Mike Martin MVB, DVC, MRCVS
Specialist Veterinary Cardiologist
Willows Referral Centre and Referral Service
Shirley, Solihull, West Midlands, United Kingdom

Syncope

Ana Martins-Bessa DVM, PhD
Professor
Department of Veterinary Sciences
Veterinary Teaching Hospital
University of Tras-os-Montes e Alto Douro, UTAD
Vila Real, Portugal

Reproductive Emergencies

Karol A. Mathews DVM, DVSc, DACVECC
Professor Emerita, Emergency & Critical Care Medicine
Department of Clinical Studies
Ontario Veterinary College
University of Guelph
Guelph, Ontario, Canada

Anti-inflammatory Therapy

Glenna E. Mauldin DVM, MS, DACVIM (Oncology), DACVN
Staff Veterinarian in Oncology and Nutrition
Cancer Centre for Animals
Western Veterinary Specialist and Emergency Centre
Clinical Instructor, Distributed Veterinary Learning Community
Faculty of Veterinary Medicine
University of Calgary
Calgary, Alberta, Canada

Nutritional Management of Cancer

Elisa M. Mazzaferro MS, DVM, PhD, DACVECC
Staff Criticalist
Cornell University Veterinary Specialists
Stamford, Connecticut

Heatstroke

Margaret C. McEntee DVM, DACVIM (Oncology), DACVR(RO)
Alexander de Lahunta Chair of Clinical Sciences, Professor of Oncology
Department of Clinical Sciences
College of Veterinary Medicine
Cornell University
Ithaca, New York

Soft-Tissue Sarcomas

Maureen McMichael DVM, DACVECC
Professor
Veterinary Clinical Medicine
University of Illinois
Urbana, Illinois

Coagulation Testing

Carlos Melián DVM, PhD
Director
Department of Veterinary Teaching Hospital
Universidad de Las Palmas de Gran Canaria
Clinica Veterinaria Atlantico
Las Palmas de Gran Canaria, Spain

Hyperadrenocorticism in Dogs

Richard John Mellanby BSc, BVMS, PhD, DSAM, DECVIM-CA (Internal Medicine), MRCVS
Head of Small Animal Medicine
Royal (Dick) School of Veterinary Studies and The Roslin Institute
Hospital for Small Animals
The University of Edinburgh
Easter Bush Veterinary Centre
Midlothian, United Kingdom

Calcium, Phosphorus

Linda Merrill LVT, VTS (AIMVT-Small Animal Internal Medicine & AVTCP-Canine/Feline)
Executive Director
Academy of Internal Medicine for Veterinary Technicians
Seattle Veterinary Associates
Green Lake Animal Hospital
Seattle, Washington

Venous and Arterial Puncture

Kristen Messenger DVM, DACVAA, DACVCP
Assistant Professor of Anesthesiology
Molecular Biomedical Science
North Carolina State University College of Veterinary Medicine
Raleigh, North Carolina

Analgesic Therapy

Kathryn M. Meurs DVM, PhD, DACVIM (Cardiology)
Professor, Clinical Sciences
Associate Dean, Research and Graduate Studies
North Carolina State University College of Veterinary Medicine
Raleigh, North Carolina

Basic Genetics
Clinical Genomics
Myocardial Disease: Canine

Kathryn E. Michel DVM, MS, MSED, DACVN
Professor of Nutrition
Department of Clinical Studies
School of Veterinary Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Nutritional Assessment

Darryl L. Millis MS, DVM, DACVS, CCRP, DACVSMSR
Professor of Orthopedic Surgery
Small Animal Clinical Sciences
University of Tennessee College of Veterinary Medicine
Knoxville, Tennessee

Physical Therapy and Rehabilitation

Luis Miguel Fonte Montenegro Master's Degree
Clinical Director, Doctor
Surgery
Hospital Veterinário Montenegro
Porto, Portugal

Reproductive Emergencies

Carmel T. Mooney MVB, MPhil, PhD, DECVIM-CA (Internal Medicine), MRCVS
Associate Professor
University Veterinary Hospital
University College Dublin
Belfield, Dublin, Ireland

Canine Hypothyroidism

Antony S. Moore BVSc, MVSc, DACVIM (Oncology)
Veterinary Oncology Consultants
Wauchope, NSW, Australia

Principles and Practice of Chemotherapy

Sarah A. Moore DVM, DACVIM (Neurology)
Associate Professor, Neurology and Neurosurgery
Department of Veterinary Clinical Sciences
The Ohio State University
Columbus, Ohio

Neuromuscular Junction Disorders

Lisa Moses VMD, DACVIM (Small Animal Internal Medicine)
Pain Medicine Service
Angell Animal Medical Center
Fellow in Medical Ethics
Center for Bioethics
Harvard Medical School
Boston, Massachusetts

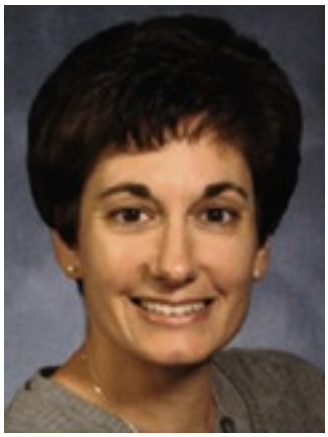
Chronic Pain: Pathophysiology, Identification, and General Management
Pain Physiology, Identification, and Management in the Acute Care Setting

Jane D. Mount MS, PhD
Research Fellow
Pathobiology
Auburn University
Auburn, Alabama

Fecal Examination
Antiparasitic Therapy

Ralf S. Mueller Dr.med.vet., Dr.habil., DACVD, FANZCVSc, DECVD
Professor
Center of Clinical Veterinary Medicine
Clinic of Small Animal Medicine
Ludwig Maximilian University of Munich
Munich, Germany

Scrapings, Fine-Needle Aspiration, and Biopsy of Skin and Subcutaneous Tissues



Karen R. Muñana DVM, MS, DACVIM (Neurology)
Professor, Neurology
Department of Clinical Sciences
North Carolina State University College of Veterinary Medicine
Raleigh, North Carolina

Seizures

Laura A. Nafe DVM, MS, DACVIM (Small Animal Internal Medicine)
Assistant Professor, Small Animal Internal Medicine
Veterinary Clinical Sciences
Oklahoma State University
Stillwater, Oklahoma

Respiratory and Inhalant Therapy

Thandeka Roseann Ngwenyama DVM, DACVECC
Clinical Assistant Professor of Emergency and Critical Care
Veterinary Clinical Sciences
Washington State University
Pullman, Washington

Peritonitis

Brook A. Niemiec DAVDC, DEVDC, Fellow AVD
Chief of Staff
Dentistry
Southern California Veterinarian Dental Specialties & Oral Surgery
Founding Consultant, VetDentalRad.com
President, Practical Veterinary Publishing
Lead Instructor, San Diego Veterinary Dental Training Center
San Diego, California

Ptyalism and Halitosis

Stijn J.M. Niessen DVM, PhD, DECVIM-CA (Internal Medicine), PGCVIM, PGCVetEd, FHEA, MRCVS
Senior Lecturer and Co-Head, Small Animal Internal Medicine
Clinical Science and Services
Director, Feline Diabetic Remission Clinic
Royal Veterinary College
London, United Kingdom;
Research Associate
Diabetes Research Group
Newcastle Medical School
Newcastle-upon-Tyne, Tyne and Wear, United Kingdom;
Consultant, Endocrinology
Veterinary Information Network
Davis, California

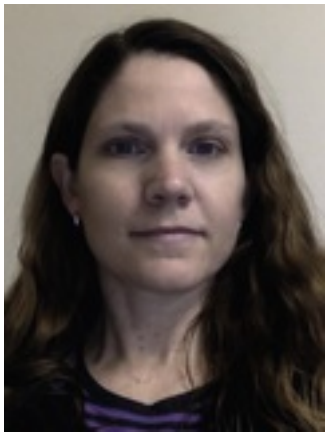
Feline Growth Hormone Disorders

Carolyn R. O'Brien BVSc, MVetClinStud, FANZCVS (Feline Medicine)
PhD Candidate
Faculty of Veterinary and Agricultural Sciences
University of Melbourne
Registered Specialist in Feline Medicine
Melbourne Cat Vets
Parkville, Victoria, Australia

Mycobacterial Infections, Actinomycosis and Nocardiosis

Dennis P. O'Brien DVM, PhD, DACVIM (Neurology)
Chancellor's Chair in Comparative Neurology
Department of Veterinary Medicine & Surgery
University of Missouri
Neurology & Neurosurgery Service
Veterinary Health Center
Columbia, Missouri

Neurophysiology
Brain Diseases: Degenerative, Anomalous, Metabolic, Neoplasia, Idiopathic Epilepsy, and Vascular



Mauria O'Brien DVM, DACVECC
Clinical Associate Professor
Veterinary Clinical Medicine
University of Illinois
Urbana, Illinois

Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome

Robert T. O'Brien DVM, MS, ACVR
Department of Veterinary Clinical Medicine
Director of Imaging, Epica Medical Innovations
Staff Radiologist, Oncura Partners Diagnostics, LLC
Nobleboro, Maine

Nonneoplastic Diseases of the Spleen

Gerhard Ulrich Oechtering Dr.med.vet.habil., DECVAA
Professor
Small Animal Department—Ear, Nose and Throat Unit
University of Leipzig
Leipzig, Saxony, Germany

Diseases of the Nose, Sinuses, and Nasopharynx

Dan G. Ohad DVM, PhD, DACVIM (Cardiology), DECVIM-CA (Cardiology)
Clinical Senior Lecturer in Cardiology
Koret School of Veterinary Medicine
Robert H. Smith Faculty of Agriculture, Food and Environment
Hebrew University of Jerusalem
Rehovot, Israel

Pallor
Treatment of Systemic Hypertension

Carl A. Osborne DVM, PhD, DACVIM
Veterinary Clinical Sciences Department
College of Veterinary Medicine
University of Minnesota
St. Paul, Minnesota

Unblocking of the Urethra
Lower Urinary Urolithiasis in Dogs

M. Lynne O'Sullivan DVM, DVSc, DACVIM (Cardiology)
Associate Professor
Department of Clinical Studies
Ontario Veterinary College, University of Guelph
Guelph, Ontario, Canada

Tachypnea, Dyspnea, and Respiratory Distress

Mark A. Oyama DVM, MSCE, DACVIM (Cardiology)
Professor and Chief, Section of Cardiology
Department of Clinical Studies
University of Pennsylvania
Philadelphia, Pennsylvania

Congenital Heart Disease
Heart Disease and Kidney Disease

Caroline Page BA, VetMB, DACVIM (Small Animal Internal Medicine)
Page Veterinary Consulting
Huntington Beach, California

Rhinoscopy, Nasal Flush, and Nasal Flushing

Carrie A. Palm DVM, DACVIM (Small Animal Internal Medicine)
Assistant Professor
Medicine and Epidemiology
University of California, Davis
Davis, California

Blood Urea Nitrogen and Creatinine

Douglas Palma DVM, DACVIM (Small Animal Internal Medicine)
Staff Internist
Small Animal Internal Medicine
The Animal Medical Center
New York, New York

Pathophysiology and Clinical Manifestations of Systemic Hypertension

Manon Paradis DVM, MVSc, DACVD
Professor of Dermatology
Department of Clinical Sciences
Faculté de Médecine Vétérinaire, University of Montreal
St-Hyacinthe, Québec, Canada

Nutritional Management of Dermatologic Disease

Dominique Peeters DVM, PhD, DECVIM-CA (Internal Medicine)
Professor in Companion Animal Internal Medicine
Equine and Companion Animal Clinical Sciences
University of Liege
Liege, Belgium

Aspergillosis—Canine

Sally C. Perea DVM, MS, DACVN
Clinical Veterinary Nutritionist
Research and Development
Royal Canin, A Division of MARS, Inc.
Lewisburg, Ohio

Unconventional Diets (Homemade, Vegetarian, and Raw)

Dolores Pérez-Alenza DVM, PhD
Professor
Animal Medicine and Surgery
Veterinary School, Complutense University of Madrid
Head of Service
Small Animal Internal Medicine Service, Veterinary Teaching Hospital Complutense
General Secretary, Board Member
AVEPA
Madrid, Spain

Hyperadrenocorticism in Dogs

Michael Peterson DVM, MS
Staff Veterinarian
Reid Veterinary Hospital
Albany, Oregon;
Associate Investigator
Viper Institute
University of Arizona
Tucson, Arizona

Venomous Bites and Stings (Zootoxicosis)

Christine Piek DVM, PhD, DECVIM-CA (Internal Medicine)
Department of Clinical Sciences and Companion Animals
Faculty of Veterinary Medicine, Utrecht University
Utrecht, The Netherlands

Immune-Mediated Hemolytic Anemias and Other Regenerative Anemias

Simon R. Platt BVM&S, MRCVS, DACVIM (Neurology), DECVN
Professor, Neurology and Neurosurgery
Small Animal Medicine and Surgery
College of Veterinary Medicine, University of Georgia
Athens, Georgia

Tetanus and Botulism
Spinal Cord Diseases: Congenital (Developmental), Inflammatory, and Degenerative Disorders

Rachel E. Pollard DVM, PhD, DACVR
Department of Surgical and Radiological Sciences
School of Veterinary Medicine
University of California, Davis
Davis, California

Abdominal Ultrasonography

David James Polzin DVM, PhD, DACVIM (Small Animal Internal Medicine)
Professor and Chief of Internal Medicine
Department of Veterinary Clinical Sciences
College of Veterinary Medicine
University of Minnesota
St. Paul, Minnesota

Chronic Kidney Disease

Nathalie Porters DVM, MVM, PhD, DECVS
Professor Doctor
Small Animal Medicine and Clinical Biology
Faculty of Veterinary Medicine, Ghent University
Merelbeke, Belgium

Effect of Spay or Castration on Long-Term Health of Dogs and Cats

Simon Lawrence Priestnall BSc (Hons), BVSc, PhD, PGCert(VetEd), FHEA, DACVP, FRCPath, MRCVS
Associate Professor of Veterinary Anatomic Pathology
Department of Pathology and Pathogen Biology
The Royal Veterinary College
Hatfield, Hertfordshire, United Kingdom

Canine Infectious Respiratory Disease

Robert Prošek DVM, MS, DACVIM (Cardiology), DECVIM-CA (Cardiology)
Adjunct Professor of Cardiology
University of Florida
Gainesville, Florida;
President
Cardiopulmonary Medicine and Interventional Therapy
Florida Veterinary Cardiology
Miami, Florida

Abnormal Heart Sounds and Heart Murmurs
Thoracocentesis/Pericardiocentesis

Yann Queau DVM, DACVN
Research and Clinical Nutritionist
Research and Development Center
Royal Canin
Aimargues, France

Nutritional Management of Lower Urinary Tract Disease

Oriana Raab DVM, MVSc, DACVIM (Small Animal Internal Medicine)
Staff Internist
Internal Medicine
Tufts Veterinary Emergency Treatment and Specialties
Walpole, Massachusetts

Abdominocentesis and Diagnostic Peritoneal Lavage

Alan Radford BVSc, PhD, MRCVS
Reader in Infection Biology
Institute of Infection and Global Health
University of Liverpool
Neston, Cheshire, United Kingdom

Feline Upper Respiratory Infections
Other Feline Viral Infections

Juan José Ramos-Plá DVM, PhD
Associate Professor
Medicine and Surgery
Cardenal Herrera CEU University
Clínica Veterinaria Vinaroz
Valencia, Spain

Obesity

Ian K. Ramsey BVSc, PhD, DSAM, DECVIM-CA (Internal Medicine), FHEA, MRCVS
Professor of Small Animal Medicine
University of Glasgow
Glasgow, Scotland, United Kingdom

Fever
Feline Hyperadrenocorticism

Jacquie Rand BVSc (Hons), DVSc (Guelph), DACVIM (Internal Medicine)
Emeritus Professor
School of Veterinary Science
The University of Queensland
Executive Director and Chief Scientist
Australian Pet Welfare Foundation
Brisbane, Queensland, Australia

Feline Diabetes Mellitus

Kenneth M. Rassnick DVM, DACVIM (Oncology)
Director, Oncology Consultation Service
Veterinary Medical Center of Central New York
Syracuse, New York;
Director, Oncology Consultation Service
Colonial Veterinary Hospital
Ithaca, New York

Tumors of the Skin

Carol R. Reinero DVM, DACVIM (Small Animal Internal Medicine), PhD
Associate Professor
University of Missouri
Columbia, Missouri

Initial Evaluation of Respiratory Emergencies

Alexander M. Reiter Dipl. Tzt, Dr.med.vet., DAVDC, EVDC
Associate Professor of Dentistry and Oral Surgery
Department of Clinical Studies, Philadelphia
School of Veterinary Medicine, University of Pennsylvania
Philadelphia, Pennsylvania

Oral and Salivary Gland Disorders

Keith Richter DVM, MSEL, DACVIM (Small Animal Internal Medicine)
Chief Medical Officer
Ethos Veterinary Health
Staff Internist
Internal Medicine
Veterinary Specialty Hospital of San Diego
San Diego, California

Laparoscopy
Diagnostic Evaluation of the Liver

Teresa M. Rieser VMD, DACVECC
Staff Criticalist
Department of Emergency and Critical Care
VCA West Los Angeles Animal Hospital
Los Angeles, California

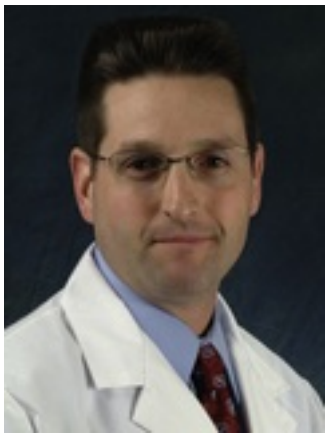
Shock

Stefano Romagnoli DVM, MS, PhD, DECAR
Professor
Animal Medicine, Production and Health
University of Padova
Legnaro, Padova (Veneto), Italy

Reproductive Endocrinology and Breeding Husbandry of the Bitch

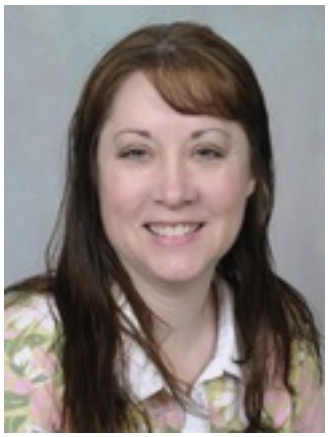
Dan Rosenberg DVM, PhD
Internal Medicine Unit
MICEN VET
Créteil, France

Sodium, Chloride



John Henry Rossmeisl Jr., DVM, MS, DACVIM (Small Animal Internal Medicine and Neurology)
Professor, Neurology and Neurosurgery
Small Animal Clinical Sciences, VA-MD College of Veterinary Medicine
Virginia Tech
Blacksburg, Virginia

Cerebrospinal Fluid Collection, Analysis, and Myelography
Cranial Neuropathies



Elizabeth Rozanski DVM, DACVIM (Small Animal Internal Medicine), DACVECC
Associate Professor of Critical Care
Cummings School of Veterinary Medicine
Tufts University
North Grafton, Massachusetts

Thoracic Trauma
Diseases of the Pleural Space

Craig G. Ruaux BVSc, PhD, MACVSc, DACVIM (Small Animal Internal Medicine)
Associate Professor, Small Animal Medicine
Department of Clinical Sciences
Oregon State University
Corvallis, Oregon

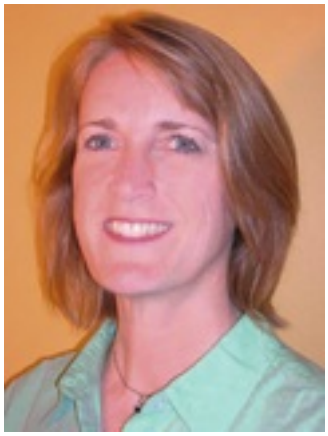
Nutritional Management of Hepatobiliary Disease
Feline Pancreatitis: Diagnosis and Treatment

Clare Rusbridge BVMS, PhD, DECVN, FRCVS
Chief of Neurology
Fitzpatrick Referrals
Eashing, Surrey, United Kingdom;
Reader in Veterinary Neurology
School of Veterinary Medicine
University of Surrey
Guildford, Surrey, United Kingdom

Tremors

John E. Rush DVM, MS, DACVIM (Cardiology), DACVECC
Tufts Cummings School of Veterinary Medicine
North Grafton, Massachusetts

Nutritional Management of Heart Disease



Helena Rylander DVM, DACVIM (Neurology)
Clinical Associate Professor
Department of Medical Sciences
School of Veterinary Medicine
University of Wisconsin
Madison, Wisconsin

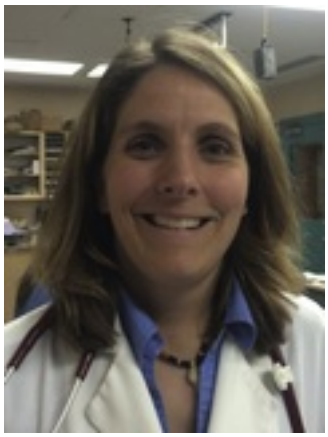
Neurologic Manifestations of Systemic Disease

Veronique Sammut DVM, MS, DACVIM (Neurology)
VCA West Los Angeles
Los Angeles, California

Vestibular Disease

Kari Santoro Beer DVM, DACVECC
Assistant Professor, Emergency and Critical Care Medicine
Department of Small Animal Clinical Sciences
Michigan State University
East Lansing, Michigan

Lactate

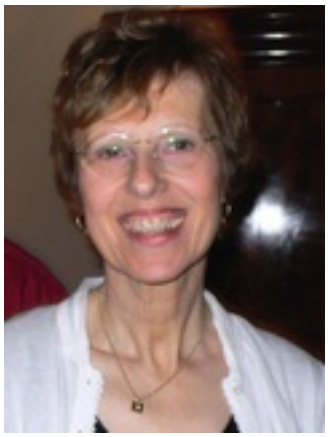


Christine Savidge DVM, DACVIM (Small Animal Internal Medicine)
Assistant Professor, Small Animal Internal Medicine
Department of Companion Animals
University of Prince Edward Island, Atlantic Veterinary College
Charlottetown, PE, Canada

Buccal Mucosal Bleeding Time

Brian A. Scansen DVM, MS, DACVIM (Cardiology)
Associate Professor
Clinical Sciences
Colorado State University
Fort Collins, Colorado

Cardiovascular Interventional Therapies
Venous and Lymphatic Disorders



Auke C. Schaefers-Okkens DVM, PhD, DECAR
Department of Clinical Sciences of Companion Animals (retired)
Faculty of Veterinary Medicine, University of Utrecht
Utrecht, The Netherlands

Vulvar and Preputial Discharge

Michael Schaer DVM, DACVIM (Small Animal Internal Medicine), DCVECC
Emeritus Professor
Adjunct Professor, Emergency and Critical Care Medicine
College of Veterinary Medicine
University of Florida
Gainesville, Florida

The Medical History

Scott J. Schatzberg DVM, PhD, DACVIM (Neurology)
Director of Neurology/Neurosurgery
The Animal Neurology and Imaging Center
Algodones, New Mexico

Neurologic Examination and Neuroanatomic Diagnosis

Thomas Schermerhorn VMD, DACVIM (Small Animal Internal Medicine)
Professor
Department of Clinical Sciences
Kansas State University
Manhattan, Kansas

Weight Loss as a Chief Complaint
Gastrointestinal Endocrinology

Chad W. Schmiedt DVM, DACVS
Associate Professor
Department of Small Animal Medicine and Surgery
University of Georgia
Athens, Georgia

Renal Transplantation

Johan P. Schoeman BVSc, MMedVet, PhD, DSAM, DECVIM-CA (Internal Medicine)
Professor and Head of Department
Department of Companion Animal Clinical Studies
Faculty of Veterinary Science, University of Pretoria
Onderstepoort, Pretoria, South Africa

The Endocrine Response to Critical Illness
Insulin-Secreting Tumors

Simone Schuller Dr.med.vet., DECVIM-CA (Internal Medicine), PhD
Professor
Department of Clinical Veterinary Medicine
Internal Medicine
Small Animal Hospital
Vetsuisse Faculty Bern
Bern, Switzerland

Leptospirosis

Wayne Stanley Schwark DVM, MSc, PhD
Emeritus Professor of Pharmacology
Molecular Medicine
College of Veterinary Medicine, Cornell University
Ithaca, New York

Adverse Drug Reactions

Katherine F. Scollan DVM, DACVIM (Cardiology)
Assistant Professor
College of Veterinary Medicine
Oregon State University
Corvallis, Oregon

Pathophysiology of Heart Failure

Gilad Segev DVM, DECVIM-CA (Internal Medicine)
Senior Lecturer
Koret School of Veterinary Medicine
Hebrew University of Jerusalem
Rehovot, Israel

Familial and Congenital Renal Diseases of Cats and Dogs

Rance K. Sellon DVM, PhD, DACVIM (Small Animal Internal Medicine, Oncology)
Associate Professor
Department of Veterinary Clinical Sciences
College of Veterinary Medicine
Washington State University
Pullman, Washington

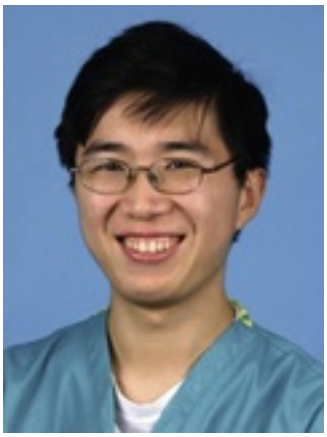
Peritonitis

G. Diane Shelton DVM, PhD, DACVIM (Small Animal Internal Medicine)
Professor
Department of Pathology, School of Medicine
Director, Comparative Neuromuscular Laboratory
University of California, San Diego
La Jolla, California

Muscular Disorders

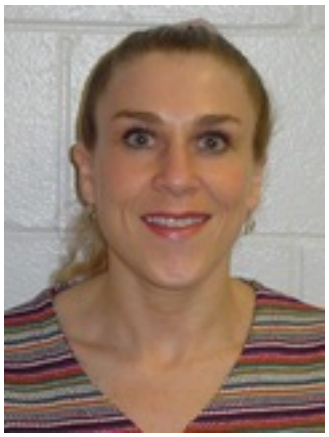
Robert E. Shiel MVB, PhD, DECVIM-CA (Internal Medicine)
Lecturer
Small Animal Medicine Section, School of Veterinary Medicine
University College Dublin
Dublin, Ireland

Polyuria and Polydipsia
Diabetes Insipidus



Andre C. Shih DVM, DACVAA, DACVECC
Associate Professor
Large Animal Clinical Sciences
University of Florida College Veterinary Medicine Anesthesia Service
Gainesville, Florida

Intraosseous Catheters



Deborah C. Silverstein DVM, DACVECC
Associate Professor of Critical Care
University of Pennsylvania
Philadelphia, Pennsylvania

Gastric Intubation and Lavage

Kenneth W. Simpson BVM&S, PhD, DACVIM (Small Animal Internal Medicine), DECVIM-CA (Internal Medicine)
College of Veterinary Medicine
Cornell University
Ithaca, New York

Diseases of the Stomach

D. David Sisson DVM, DACVIM (Cardiology)
Professor Emeritus
Veterinary Clinical Sciences
Oregon State University
Corvallis, Oregon

Pathophysiology of Heart Failure

Barbara J. Skelly MA, VetMB, PhD, CertSAM, DACVIM (Small Animal Internal Medicine), DECVIM-CA (Internal Medicine), MRCVS
University Senior Lecturer in Small Animal Medicine
Department of Veterinary Medicine

Queen's Veterinary School Hospital
University of Cambridge
Cambridge, Cambridgeshire, United Kingdom

Primary Hyperparathyroidism

Stephanie A. Smith DVM, MS
Research Assistant Professor
Department of Biochemistry, School of Molecular and Cellular Biology
Adjunct Clinical Assistant Professor
Department of Veterinary Clinical Medicine, College of Veterinary Medicine
University of Illinois
Urbana, Illinois

Coagulation Testing

David Stephen Sobel DVM, MRCVS
Director of Medicine
Metropolitan Veterinary Consultants
Hanover, New Hampshire;
Clinical Consultant
Elands Veterinary Clinic
Dunton Green, Sevenoaks, United Kingdom

Otoscopy, Ear Flushing, and Myringotomy

Maria M. Soltero-Rivera DVM, DAVDC
Adjunct Assistant Professor
Dentistry and Oral Surgery
Penn Vet—Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania;
Veterinary Specialist
Dentistry and Oral Surgery
VCA San Francisco Veterinary Specialists
San Francisco, California

Oral and Salivary Gland Disorders

Dennis R. Spann DVM, DACVIM (Small Animal Internal Medicine)
Staff Internist
Internal Medicine Department
Sacramento Area Veterinary Internal Medicine
Roseville, California

Leukopenia, Leukocytosis

Thomas Spillmann Dipl.med.vet, Dr.med.vet., DECVIM-CA (Internal Medicine)
Professor of Small Animal Internal Medicine
Department of Equine and Small Animal Medicine
Faculty of Veterinary Medicine, University of Helsinki
Helsinki, Finland

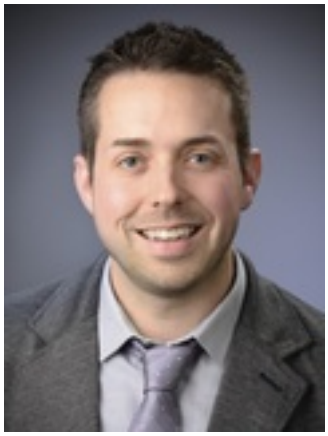
Pancreatitis: Etiology and Pathophysiology

Timothy J. Stein DVM, PhD, DACVIM (Oncology)
Medical Oncologist
Oncology
Austin Veterinary Emergency & Specialty Center
Austin, Texas

Paraneoplastic Syndromes

Rebecca L. Stepien DVM, MS, DACVIM (Cardiology)
Clinical Professor of Cardiology
Department of Medical Sciences
School of Veterinary Medicine
University of Wisconsin—Madison
Madison, Wisconsin

Blood Pressure Measurement



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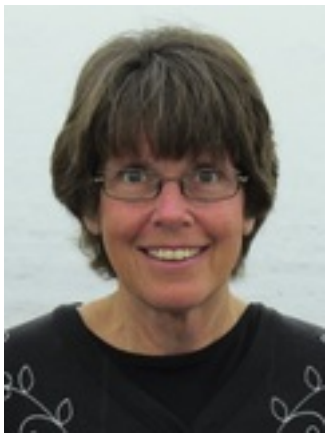
Fever
Hemotropic Mycoplasmas



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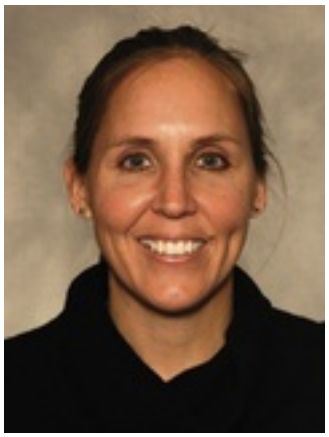
Cyanosis



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Rectoanal Disease

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Mycobacterial Infections, Actinomycosis and Nocardiosis

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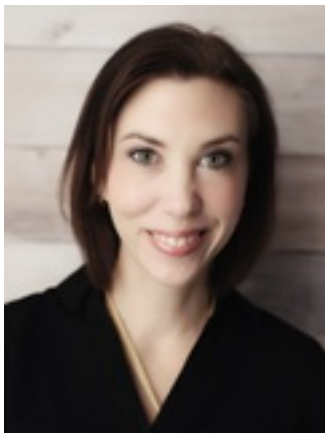
Nonregenerative Anemia



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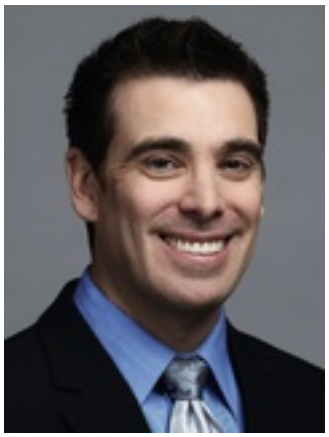
Cholesterol, Triglycerides



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Nutritional Management of Gastrointestinal Disease

†Deceased.

Preface

We began the preface to the 7th edition by acknowledging that we had already begun to work on the 8th edition. Little did we realize how this 8th edition was going to evolve, how the publishing field was to change and how the preferences of “junior” and “senior” readers would develop during this relatively brief period. Who would have imagined in 1975 when the first edition came out that at least 7 editions would follow, that figures would have color, that there would be algorithms in almost every chapter, that more than 500 videos would each be available at the click of a mouse (in 1975 a mouse was still a small rodent), and that there would be 360 succinct but complete chapters contributed by 348 authors? More comprehensive internal medicine has been compressed into two volumes that are not significantly different in size from that first edition in 1975. Think of the advances since then! This edition is so different from those that came before that it is truly unique. Now it is a given that the entire textbook is produced both in traditional typeset and in digital format. The reader may choose his/her own preferred format(s). This resource is compatible with desktops/laptops, tablets, and smartphones.

Perhaps the biggest change was adding a third co-editor to assist with every aspect of developing this edition. Etienne Côté has been a friend, a trainee and now a mentor. He has truly helped Ed and Steve bring forth new ideas, enhance the editing process and be part of obtaining new contacts, additional literary input and guidance with digitizing information essential to the intent of the textbook. We thank Etienne for his time, expertise, diligence and never-ending enthusiasm.

The 8th edition brings on major changes. Our greatest pride could be the more than 300 authors who agreed to contribute; or maybe it is the more than 20 countries that our authors call home; or perhaps it rests in the hundreds of original videos and innumerable additional diagrams and other digital media that make this a vibrant book. It could be the true skill of authors, which is revealed in their ability to capture the most important, newest, relevant material for the reader of this textbook—sorting out what matters, and presenting it clearly, without fluff or embellishment. As all will appreciate, it is all these and more.

Previously the book was set up by clinical medicine and then chapters of disease conditions specific to that one system. While this has not changed, what we have emphasized is the cohesion and thoroughness of the material among the sections. Rather than reviewing the table of contents here, we invite the reader to thoroughly peruse the table of contents to see how easy it will be to search the book and how it has been presented so as to mimic the clinical thought process of the reader-practitioner.

The textbook is presented in a manner that reflects clinical veterinary medicine. The very first chapters present the true fundamentals of our professional work. Sections follow on the differential diagnosis for clients' chief concerns and reasons for seeking veterinary care, physical examination abnormalities, and clinicopathologic abnormalities. The latter section is entirely new and it integrates laboratory testing with clinical medicine through detailed differential diagnoses, and explanations of the physiology of different analytes. These are followed by a section that includes virtually all the procedures needed to further clarify or confirm a diagnosis: the core techniques that define veterinary internal medicine, ranging from feeding tube placement and cerebrospinal fluid collection to electromyography and hyperbaric medicine. Another new section consists of 6 chapters on interventional therapies; these urologic, cardiovascular, gastrointestinal, and other procedures are at the forefront of small animal therapeutics today. Disease-specific chapters have been comprehensively updated or rewritten altogether. The book concludes with a new section that acknowledges that diseases do not always exist in isolation. This Comorbidities section identifies pairs of diseases that involve diametrically opposing treatment requirements and make some complex internal medicine cases especially challenging.

All chapters and sections are set up for easy cross-referencing to specific conditions and easy movement from one chapter to another. Figures are set so that the reader can go from one chapter easily to the next, further strengthened by the search function in the digital version of the book. The cross-references in chapters

(which refer the reader to other, pertinent chapters) were implemented by the editors, given their view "from the crow's nest" over the entire book. They are not meant to imply that the chapter's author shares the same viewpoint as that presented in a cross-referenced chapter, but rather to help the reader quickly navigate to relevant, additional information.

Good videos say in a few seconds what would take multiple paragraphs to express less effectively. This edition has an entire library of original, high-quality video clips that embody the notion that ***seeing is believing.*** Each and every video has been carefully chosen by the authors, adapted for learning and teaching and set up with titles and legends that we believe make internal medicine come to life.

Many of the authors have provided client information sheets, which can be found in a subsection of the electronic edition of the book. These are short, easy-to-understand, clinical commentaries describing a condition, diagnostics, and/or treatment options specifically for a disease or procedure. They are available to print out for any client, to supplement discussions regarding a pet's health concern. These aim to help educate a client when there are serious decisions to be made. Then, when clients do go home to consult family, friends or Dr. Google, they will have a reasonable place to begin their search and will have a spelled-out set of information from which further legitimate reading can be accessed.

As a bridge between the print and digital formats, each chapter ends with a QR code for the reference section. Opened, this takes the reader instantly to a separate reference website where each reference is listed for that chapter. Many are linked directly to PubMed, providing the reader access to original source material. In this way, readers can access references quickly and effectively, without having to carry a printed reference section for citations.

The astute reader will note that in the written book there are references to figures and videos that may not appear to be sequentially numbered. This is because all videos and some digital material are presented exclusively in the electronic version, whose numbering is sequential. Some prefer the print edition only but in today's rapidly evolving digital world we believe that the reader should have access, in a digital format, to most every process seen clinically. The saying that "a picture is worth a thousand words" is never more true than it is here. Each reader can view additional photographs and diagrams that can positively impact the management of their own patients. If one hears about a disease once, it is likely to be forgotten, but to see it reinforced with images, videos, and additional graphics provides a greater likelihood for the condition to be remembered and understood.

Because this is a worldwide production, involving authors from 23 countries, we also know that different countries and laboratories utilize upper and lower limits differently or even in different terms for reference ranges. We prefer that laboratory results typical of any condition be reviewed in generalities, suggesting that values may be above, below, or within reference ranges. It is no longer appropriate to provide specific results since each laboratory likely uses different assays and protocols, which invariably cause each reference range to be specific to the laboratory where a test is performed. This approach reflects our desire to meet the needs of readers from around the world.

Traditionally, we provide pictures of the authors in the front matter. The reader, through the author's picture, can recognize anyone who has contributed a chapter to the book. How nice too to see that our authors continue to be thrilled to be part of this effort. We cannot thank them enough for holding to such a short schedule and for keeping their chapters up to date and current, often as close as one month before deadline. Contributing a chapter with a strict page limitation is likely one of the most difficult chores one can impose on an author(s). Condensing scientific material to an advanced level takes a special expertise and our goals have been such that we continue to meet the needs of today's veterinary students, young graduates and practicing veterinarians wanting an encyclopedic effort in small animal medicine. We also thank past authors who contributed content to previous editions and thus added an original layer to the first versions of current chapters.

We are proud of our effort to incorporate outstanding colleagues from so many countries. This book has evolved quickly into an international textbook, published in at least five languages and read in most of the world by veterinarians and students alike. It is with honor, pleasure and a distinct sense of pride that we can offer the reader many of the finest veterinary writers and observers throughout the world. We honor these colleagues and their countries on the inside cover of the book, to signify our belief that this is a one-world, one profession book. In a letter to us about his chapter, one of our contributors, Adrian Boswood, related something that energized us to keep working, when he said, "It is an honor to be able to contribute to your textbook. The book has a reputation that precedes my career and will no doubt also outlive it!" Thank you all

for your well-needed support at such crucial points in the preparation process.

In the past we have not had section editors for this textbook and we have continued this approach into the 8th edition. However, we recognized that there are a growing number of outstanding experts in the profession today. As editors, we cannot know all of these individuals. Thus, we have called upon some of our friends and colleagues to help provide names of potential authors for their specific areas of expertise, and to review the proposed chapter titles as representative of the field. We are most grateful to these colleagues who spent time and effort helping us this way. In some cases, new authors were veterinarians that we knew, but in others we were offered an extensive list of new names, and we are delighted to have been able to call upon them as well to contribute to the book. To our section advisors, we are most appreciative for your assistance. Specifically, we would like to thank Drs. Vanessa Barrs, Joe Bartges, Leah Cohn, Ronaldo da Costa, Autumn Davidson, Lisa Freeman, Ann Hohenhaus, Safdar Khan, Mark Papich, Jörg Steiner, Harriett Syme, Jane Sykes, David Twedt, and David Vail.

As always, the staff at Elsevier has been most helpful in building this new edition of the book from the ground up. We had so many new ideas, so much new material to work with and a huge list of audio-video material, that alone we were overwhelmed. The execution of all this could not have been done without the continued support of Rhoda Howell, Jolynn Gower, Catherine Jackson, David Dipazo, and of course, Penny Rudolph. Thank you so much for your patience and regular input.

To our wives and children, we once again feel the overwhelming desire to remind you how important you are to us. Your support, compassion, and willingness to share this effort means so much to us. We love you so!!! To our colleagues who have been ever so supportive over the years, thank you for your constructive comments as well as your passion for what we have attempted to provide. Your warm welcome, both here at home and wherever we travel, has always been a real joy to us and makes us realize just how much we all communicate in our expanding world of one veterinary medicine.

Sincerely,

Steve Ettinger

Ed Feldman

Etienne Côté

October 2016

About the Cover

Bastet was an Egyptian goddess, and in Greek mythology she is also known as Alluros. She is a protector figure, including protection against illness. To the editors of this textbook her likeness, as shown on this cover, embodies the dignity of the animal.

Bronze statuette, Egypt, Macedonian-Ptolemaic Period (332-330 B.C.E.).

Courtesy of the Metropolitan Museum of Art, New York, NY.

Client Information Sheets

The following client information sheets can be found at ExpertConsult.com.

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The Physical Examination

Chapter 3

Veterinary Genetics: Modes of Inheritance

Chapter 4

Guidelines for Baseline Recommendations for Genetic Diseases

Chapter 9

Distinguishing Behavioral Disorders from Medical Disorders

Chapter 10

Dermatologic Manifestations of Systemic Disease

Chapter 11

Topical Ophthalmic Corticosteroid Medication
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Brain Disorders
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Ataxia, Paresis, Paralysis

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Halitosis: Bad Breath in Dogs and Cats
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Pleural Effusion
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SECTION I

The Real Basics of Veterinary Medicine

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CHAPTER 1

The Medical History

Michael Schaer

Overview

The art of practicing medicine will always begin with two essential components: the history and physical examination. The history is certainly the most important diagnostic aid in medicine and the physical examination is easily second. The history is frequently key in determining cause of an illness, its significance, treatment options and even prognosis. Any clinician who fails to appreciate the value of a thorough history, who does not develop expertise in being able to obtain an owners' complete account of their concerns, or who takes "short cuts," will create an environment for misdiagnosis or errors in therapy. As is true for any individual with *expertise,* practice is critically important. Repetition can improve history-taking skills if coupled with frequent self-assessments. This is an excellent method to avoid repeating errors. One can ask after any difficult diagnosis is confirmed, what questions should have been asked that were not? What did the owner know but was never asked? Could I have changed the formulation of a question to gain better insight? The excellent clinician is an excellent historian and excellent listener. The excellent clinician continuously works to improve his or her skill set.

Obtaining a history is a "process" which should be approached in a methodical manner. This "process" should ensure that no valuable question is forgotten. Thus, the successful clinician has a group of questions consistently asked of every owner. Each question can be expanded or altered as dictated by answers given about the patient by the historian (usually the owner). In some cases, the order of questions may be changed. In other cases, answers provided may stimulate a subsequent set of questions. The clinician should always strive to be an approachable and compassionate listener. One will be well served by having the pet owner calm in order for her or him to provide clear and thoughtful responses. The medical history is a "story" about the patient. The following guidelines should assist with successful procurement of the patient's medical history.

The Approach to the Pet Owner

1. Meeting a client for the first time forms the foundation for any relationship. The adage is true: "You only have one chance to create a first impression." In this scenario, the "you" includes the primary clinician plus all hospital employees, because "the relationship" often begins before the veterinarian ever meets a client. As a client enters your facility and meets the receptionist or any other employee, opinions are formed and trust may or may not begin to be established. Successfully placing a client at ease is much easier when all hospital employees are respected members of the veterinary team with the same goal of providing the best care for a pet and the owner.[1] Owner and pet "needs" must be perceived as having highest priority.
2. Having every client completely comfortable in your presence is desirable but not easily achieved. Remember that with you being a complete stranger, a client may be insecure regarding your trustworthiness in caring for their pet. Many but not all owners prefer a warm, friendly, understanding, patient, and compassionate veterinarian. If an animal arrives in a life-threatening situation, the clinician may speak quickly and even go so far as to remove the pet from the owner in order to provide treatment. Once the patient is stable, the clinician should return to an examination room to obtain the detailed history and begin to build a client-doctor relationship.
3. Your greeting should inform the client who you are and in what capacity you function at the veterinary facility. Every clinician should be well groomed, speak clearly and use an understandable vocabulary.
4. Verify that the owner can understand what is being said or asked. Clearing any form of obstruction between you and the pet owner's ability to understand your questions is extremely important.

5. Verify the patient's age, gender, neuter status, and breed (signalment), even if this information has previously been entered into the medical record. Incorrect data can be misleading and could cause disastrous outcomes in case management. Also, verify vaccination history, routine use of anti-parasite products, as well as all previously and currently used medications.
6. The clinician should determine the relationship between the person to whom one is speaking and the pet. The more familiar an individual is with an animal, the more valuable their information. Next, one can inquire how long the person has "known" this pet. Have they lived in the same home for 12 years or have they been together for 12 days?
7. When seeing an ill pet, the clinician will benefit from knowing when the animal was last "normal." It also may be quite important to understand the owner's definition of "normal."
8. Owners of ill pets may be fearful and anxious. Stress can impair an ability to recall essential historical information. Remember that your patience should be a virtue. It might require you to repeat questions several times. Alternatively, one may inquire about a subject using more than one perspective or more than one question.

Requirements for a Thorough History

Box 1-1 lists the criteria necessary for obtaining a complete history. This box has been modified from a document created for physicians by the American Board of Internal Medicine.[2] It seems obvious for the clinician to always try to ask the key questions pertinent to a specific primary concern or "owner chief concern." However, typical issues caused by one disease will almost always overlap with observations associated with another. Although initial differential diagnoses based on signalment or another factor might steer the examining clinician to a correct diagnosis, it behooves the clinician to avoid "tunnel vision" in situations where another disease process might actually be responsible for the illness (Box 1-2). Owner concerns or initial clinician suspicions are, therefore, always subject to misinterpretation. One objective of the medical history is to obtain an actual "feel" for what is clinically wrong with the animal based on owner-perceived issues. Some clinical signs are difficult to fully understand until either the owner or clinician actually imitates what is being seen or heard. One example is trying to determine if an owner is observing coughing, retching, reversed sneezing, regurgitation, or vomiting. It may be quite valuable to have an owner make a video record of an actual worrisome "event."

Box 1-1

Competence in History-Taking[2]

1. Develop the habit of recording a complete history.
2. Pursue with appropriate thoroughness all historical clues.
3. Establish rapport with the historian in order to obtain accurate information.
4. Adapt language appropriately to ensure communication with the person available.
5. Patiently adapt to clients who provide a disorganized history.
6. Develop a depth of knowledge that permits a thorough exploration of signs related to the patient's problems.
7. Have a depth of knowledge that permits consideration of the various causes that might explain the patient's signs.
8. Understand signs in terms of altered structure and function of the body systems.
9. Approach the history in a logical, directed way to ensure completeness.
10. Follow up medical clues in a directed logical pattern.
11. Organize and record the history completely in a fashion that will be understandable.
12. Be able to integrate signs into a diagnostic hypothesis while obtaining the history.
13. Assess the reliability of the history obtained.
14. Separate irrelevant from relevant information appropriately.

Box 1-2

Essentials for the Complete History

Signalment (age, breed, sex)
Geographic origin and places visited
Prior ownership and location (adopted from pound, found as stray, quality of previous care)
Current environment (indoor or outdoor pet; rural or urban environment; exposure to other animals and potential sources of intoxication)
Diet (raw meat, milk products, fish, commercially prepared, disease-specific or organ-specific diet, ingestion of wild animals)
Prior medical problems (describe illness, medications used, and outcome)
Vaccination and parasite prevention status (history of prior worm infections; prior worming treatments)
Current or "chief" concern or "complaint"
  Last known period of normalcy
  Disease onset—acute or gradual
  Progression and duration
  Intervening signs
  Previous treatments for the current illness and the animal's response
  Present status (weight loss or weight gain, attitude, activity level, appetite status, urination and defecation characteristics, amounts of water intake)

In addition to questions integral to every history, specific clinical abnormalities may have a set of questions designed to help clarify the nature of a medical disorder. The reader is referred to each appropriate section in this text for a more detailed description of the diagnostic approach recommended for various "owner chief concerns" (Section II), "physical examination abnormalities" (Section III), and various "clinicopathologic abnormalities" (Section IV). The focus of this chapter is not to develop a "history" for each condition or concern, but to review the art of asking the right questions.

The Elements of the History

1. *Obtaining the facts.* You will likely obtain the most information by reviewing the history with the person who spends the most time with the patient. Their familiarity with the animal may provide valuable insights. It is the care-giver who has had the best opportunity to have made key observations regarding a concern or illness, i.e., the "chief concern." Sometimes the individual who has brought the pet to the facility is not able to convey the necessary information because of language, handicap, or another issue. This will direct you to attempt identification of the next most knowledgeable source of information. Always verify the patient's signalment as an easy means of beginning a conversation while avoiding misplaced diagnostic and therapeutic pursuits. There are many examples of diagnoses being made after a mistake in the record is identified. It is "best not to assume anything."
2. *Diet and appetite.* Animals with normal appetites are rarely critically ill. Changes in appetite, up or down, are easily and often observed. This reality is the reason that appetite is frequently a cause for concern and may be one of the first observed signs of illness. It may be important to know how much of an increase or decrease in appetite has taken place and over what period of time. Has the change progressively worsened or has it reached some plateau? Changes in appetite often parallel duration of illness. Dietary information is especially important in patients who are cachectic, obese, or who have chronic digestive system complaints. When possible, determine the current diet, duration of providing that food, and all other sources of oral intake. It may be critically important to know if a diet is homemade or a commercially available food. Supplements and "chew toys" may be important.
3. *Drinking, urination, and defecation patterns.* These are 3 daily activities typically observed by owners. As such, they are common areas of concern and frequently represent an "owner chief complaint." Even if an owner's chief concern appears unrelated to water intake, urine output, stool quality, or defecation frequency, having an understanding of the current status of these physical traits will be of general value and may help explain a primary concern. Answers to questions about these matters may provide the clinician with insight regarding the care-giver's observational skills.
   As examples, **polydipsia** can be associated with numerous syndromes while **adipsia** will sometimes be a reason for an animal becoming severely hypernatremic. **Polyuria** can accompany the same syndromes associated with polydipsia while **stranguria** and **dysuria** will usually be associated with lower urinary outflow concerns. Stool quality and frequency of production could provide important information about the pancreas and intestines. High volume, greasy stools in a polyphagic pet who has experienced weight loss or difficulty gaining weight are typical of exocrine pancreatic insufficiency. Frequent watery stools

are associated with small bowel dysfunction. Colonic disease is often characterized by a pet with stable body weight but who has straining (tenesmus), frequency, and the stool may be small in volume while containing blood and/or mucus.

4. *Geographic history.* Knowing the geographic background can provide important information because certain diseases are endemic to specific geographic areas. Clinical diagnosis can escape the clinician who fails to understand the importance of where the pet has traveled or lived.
5. *Describe home environment.* Knowing the conditions of the animal's home is essential. A dog or cat that is allowed to be unattended outdoors might be subjected to various forms of trauma or be exposed to one of several of nature's maladies such as venomous snake encounters, toxic plant ingestion, etc. Behavioral problems can sometimes be traced to changes in the home environment. The addition or loss of a person or another animal from the home may be significant. Remember that pets may be exposed to or consume medications prescribed for people in the home.
6. *The chronology of the sequence of events.* Knowing when the animal was last normal and then being able to trace subsequent events in chronological order may help in understanding a concern. In some cases, this may help categorize the disorder as being either acute (occurring over the past hours or days) or chronic (occurring over a period of two weeks or more). The duration of subacute illnesses lies somewhere in-between.
7. *The initial abnormal signs and their progression.* This information provides the opportunity for the clinician to perceive not only how the illness began, but it furthers the understanding of the disorder by providing important information for how the illness progressed and its effects on the animal. As mentioned, it may allow the clinician to actually get a "feel" for the disease. This can be illustrated in a dog that is examined for initially vomiting a clear watery fluid. If the vomitus then progressed to being bile-colored and if the patient then begins to produce profuse watery brown diarrhea with or without hematochezia, it may be interpreted as gastritis that has progressed to involve the proximal and distal small intestine. The presence of bile provides evidence that the pylorus is probably patent.
8. *Changes in body weight.* Acute disease rarely causes significant weight loss. When weight loss is present in the acute setting, it is usually reflected in dehydration caused by water loss through vomiting and/or diarrhea. Polyuria, if present, will cause dehydration to develop quickly if the animal is not drinking. It is possible for an animal to lose as much as 12 percent of its body weight via water lost through vomiting and diarrhea while retaining muscle mass.
   The chronically ill pet may be brought to the veterinary facility with a "chief concern" of weight gain or weight loss. The hydrated pet with weight loss will have often lost both fat and muscle mass. These more chronic concerns have usually developed over a period of at least 1-2 weeks. Changes in body weight should trigger a number of questions directed at determining duration, changes in environment, diet, appetite, presence of intestinal signs, travel history, water intake and urine output, etc.
9. *Vaccinations and medications.* The owner of every pet should be asked about current, recent and previous medications given. Knowing what vaccinations have been given, when, and where may become valuable. Responses by the pet, positive or negative, to any medications should be noted. This information is not only important to help diagnose the disease, but might also help with its subsequent treatment management. A young dog may have been successfully treated at another hospital with glucocorticoids and parenteral fluids. Later, the dog relapses with the same symptoms after the effects of the treatment dissipated. This treatment history would be classic for adrenocortical insufficiency.
10. *The animal's present condition.* After all of the above information has been obtained, it is helpful to know if the previous treatment(s) has helped. The basic question is whether the animal is doing better, remaining the same, or getting worse.

All of the above information will help the clinician accomplish the clinical mandate of "knowing thy patient."

Questions for the Vague Clinical Complaint

There are occasions when the clinician is presented with a patient where there is virtually no accompanying medical history. Herein lies the formidable challenge of trying to solve the unknown (see ch. 8). The circumstances surrounding this particular situation might involve a stray animal, a pet that is mostly kept out of doors, the person knows little about the pet, or a pet owner is unable to communicate. The recommended approach is to attempt identification of the chief complaint(s) and then to obtain as much as possible of the information described above. If the person accompanying the animal cannot provide this important information, ask to speak with someone who might be able to provide more information. If not possible,

diagnosis will depend on the results of a physical examination, any imaging and/or laboratory test results, and the experience of the clinician.

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CHAPTER 2

The Physical Examination

Stephen J. Ettinger, Edward C. Feldman, Etienne Côté

Client Information Sheet: The Physical Examination

The physical examination begins before the veterinarian ever touches the animal. The traditional teachings of look, smell, and listen are as important as ever. Excellent veterinarians avoid making diagnostic decisions driven by laboratory-derived data that bypass the physical examination. This chapter is founded on the concept that veterinarians must bring together data from the history, physical examination, and diagnostic tests to care for an animal in the context of its life—including the expectations the owner envisions for the pet. Algorithms by themselves are of limited value without an excellent history and physical examination.

When possible, the animal's temperature and weight should be recorded before the veterinarian enters the examination room. This provides the nursing staff the chance to communicate with the animal's caretaker, gather pertinent information, note changes in weight, and identify the owner's primary concerns or requests. The veterinarian may review these findings with the owner if there are questions about the history or why the pet is being presented for examination. Unskilled staff should not be doing "TPRs" since mistakes can be made and the veterinarian may lose valuable information such as the anal tone, skin around the perianal region, incorrect weight, etc. Also, skilled technicians know how to talk to the owner and the animal and help to relax rather than frighten the pet.

This is a good time for the staff to record current medications and dosages being administered, prophylactic agents being utilized (e.g., for heartworm, ectoparasites, internal parasites), and herbal or other supplements being administered. The animal's vaccination and reproductive status (i.e., spayed, neutered, or last heat cycle) should be identified in the record. Knowing the current diet being fed can save valuable doctor time and should be recorded. Notation of medications should always be accompanied by the owner's perception of their efficacy, since this information may influence future treatment and prognosis. Nursing staff may also utilize this time to provide valuable client information on subjects the veterinarian may have limited time to discuss. Examples include new vaccine programs, wellness programs, microchipping information, behavior and products to aid in training and health as well as office financial policies.

Always attempt to provide the client with an on-time, efficient examination. Reading material (magazines of interest to a wide variety of clients and their children) should be available if there is a likelihood of the pet's caretaker having to wait. Pet owners should be given an indication of the doctor's schedule and the length of a delay, if any is anticipated. Providing the client with this information can offset frustration, anger, or anxiety. If the hospital has new client brochures or information about hospital services, this is a good time to deliver these and to allow the client to browse through the material. Likewise, appropriate video recordings may be of interest to the client.

Observing the Pet and Meeting the Caretaker

Every veterinarian approaches a pet in his or her own way. With time, it becomes second nature. It is important to develop proper animal handling skills. Clients observe a great deal during this process and may determine long before any recommendations are made just how trusting they will be. Gentle care, compassion, concern, and attention cannot be overemphasized. While already discussed in ch. 1, it is good for the veterinarian to restate the client's concerns because this allows the pet's caretaker to know that you have been listening and are being attentive to them.

The process begins as the veterinarian enters the examination area (Figure 2-1) where the owner and pet are waiting. A friendly greeting and a small but appropriate amount of banter are often appreciated. An occasional client makes it clear that the veterinarian should get down to business. People appreciate being

greeted and particularly like being acknowledged (Figure 2-2). Asking about something unique to an owner assures them that the veterinarian knows who they are and provides a sense of identity. If the case is a referral, noting the distance traveled or offering a kind word about the trip and the referring veterinarian acknowledges the client in an important way. It is not a technique easily taught, and it is not difficult to see whether the veterinarian "gets it" quickly and learns to communicate or simply turns away from such contact.

FIGURE 2-1 When Dr. Ettinger enters the exam room he greets the client and pet. When both are provided the opportunity to feel relaxed, the balance of the examination is likely to be more successful.

FIGURE 2-2 Patient and client in exam room. Comments about the pet or the owner help to break the silence and relieve some of the owner anxiety that likely is associated with the veterinary hospital visit. “That's a nice little comb, where did you get it?”

The importance of letting each client know that the veterinarian cares about him or her and the pet cannot be overemphasized. This must be done in a genuine way, reflected in dialog, attention, body language, and actions. Such a sense of “community” is far more likely to be appreciated and will be recognized as more genuine than superficial attempts like having “We Care” or some other logo stamped on hospital leashes or stationery. Clients value compassion as much as (and often much more than) possession of knowledge. Every successful veterinarian can relate tales about brilliant doctors whom clients dislike! The smartest veterinarian may never have the opportunity to demonstrate his or her skills if concern and caring are not expressed in a way that is meaningful to the client. In fact, clients are likely to be antagonistic toward veterinarians who fail to express compassion. Complaints are likely to be made much more frequently about an arrogant veterinarian than about one who is poorly trained or medically inadequate but friendly and compassionate. Ultimately, an excellent veterinarian approaches the case with both medical skill (which benefits the patient) and personal empathy (which benefits both the patient and the client). Professionals with a disproportionately higher number of malpractice claims may be readily separated from those with fewer claims by evaluation of their examination room attitude.

If there has been a delay, it is paramount that the doctor acknowledges this upon entering the room. The veterinarian should show clients the courtesy of recognizing that they have been waiting. Unnecessary interruptions should be minimized and every hospital should have a policy in this regard. In a large critical care setting, delays and interruptions do occur, but these must be limited. Phone calls should be restricted to those that are professionally relevant or urgent. When such calls interrupt me (SJE) with new clients, I explain that I need to speak with another owner about their hospitalized pet; yet I do try to make it clear that I am focusing on their pet's problems.

A skilled veterinarian understands that no part of the examination is as important as carefully listening to the client. Therefore, adequate time must be allowed for this interaction in an environment that enhances the

process. Examination rooms should be comfortable and inviting. Privacy for clients is necessary, because the situation may be a difficult one for them. Remember, the owner may perceive diagnoses or recommendations that may seem routine or minor to the practicing veterinarian as quite serious and worrisome.

It is important to get the owners' version of the history and not one that has been "dictated" to them. For example, when questioned, the owners may acknowledge that a friend, family member or referring DVM told them about the supposed problem. Further questioning may determine that the owners themselves have not noted any clinical signs that warrant concern (see ch. 1).

Computers today are commonly used for making notations during the history and examination process. Whether the physical exam findings are entered electronically or on paper, it is important to maintain eye contact with the owner as much as possible while recording information. If the owner feels that your computer takes precedence over their impressions, an important component of the examination and history may be lost. Worse, the owner may feel disregarded and dissatisfied. Benefits of computer tablets include their being portable and easily managed in front of the client (Figure 2-3).

FIGURE 2-3 Computer tablets allow the client and the veterinarian to face each other while inputting information. A 2015 paper reports that over 50% of human patients feel neglected while their physician is looking at the computer rather than the patient.

There is no single technique for the examination process. Because this chapter is intended to explain my method of examination, I (SJE) will delineate the regimen I follow, a process learned over decades of experience. When possible, I try to make eye and physical contact with the pet. First, I make a brief attempt at greeting the animal by extending the back of my hand toward its face. For this, cats and smaller dogs can be placed on the examination room table (Figure 2-4, *A* and *B*). Usually, with medium to large dogs, I kneel down on the examination room floor to greet the animal (I [SJE] use a gardener's pad to protect my knees) (Figure 2-5). Of course, some dogs and cats (those that are aggressive [Figure 2-6, *A* and *B*], in cages, or tightly held by the owner) let me know beforehand whether or not they are ready for such a greeting. If not, I bypass the greeting and make a light comment to the owners about the pet not wishing me well ("After all," I say, "who likes going to the doctor?"). This begins a conversation with the owner that acknowledges the

possibility of the pet being fearful and allows the owner(s) to let me know how they feel about the process or about previous veterinary experiences. Frequently it is easier to do the initial examination of the cat while he or she is still in the carrying case if it opens from the top or side (Figure 2-7, *A* and *B*). While not as thorough, it avoids difficulty handling a fractious cat or dog, something the owner does not like to view. Another useful technique is to examine the cat in a blanket-covered basket. This often settles the anxious cat nicely (see Figure 2-7, *C*).

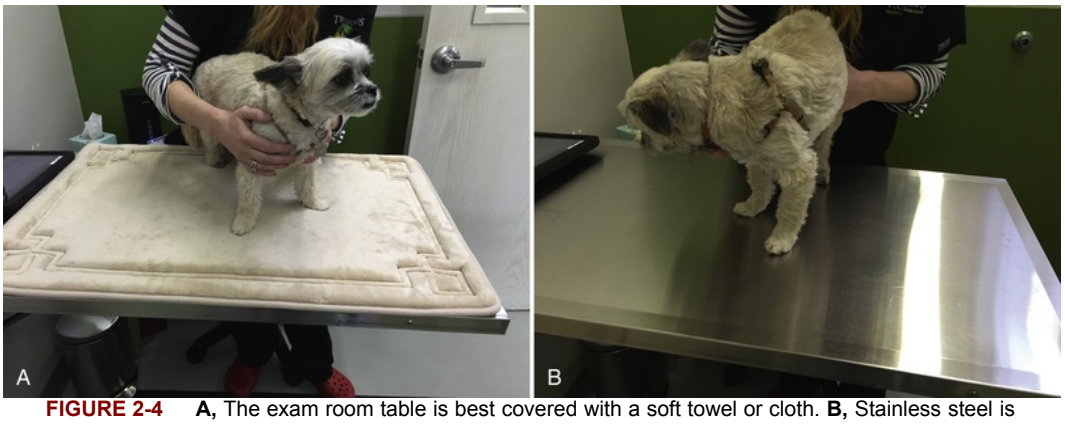

FIGURE 2-4 **A,** The exam room table is best covered with a soft towel or cloth. **B,** Stainless steel is very intimidating, slippery, cold, and unfriendly.

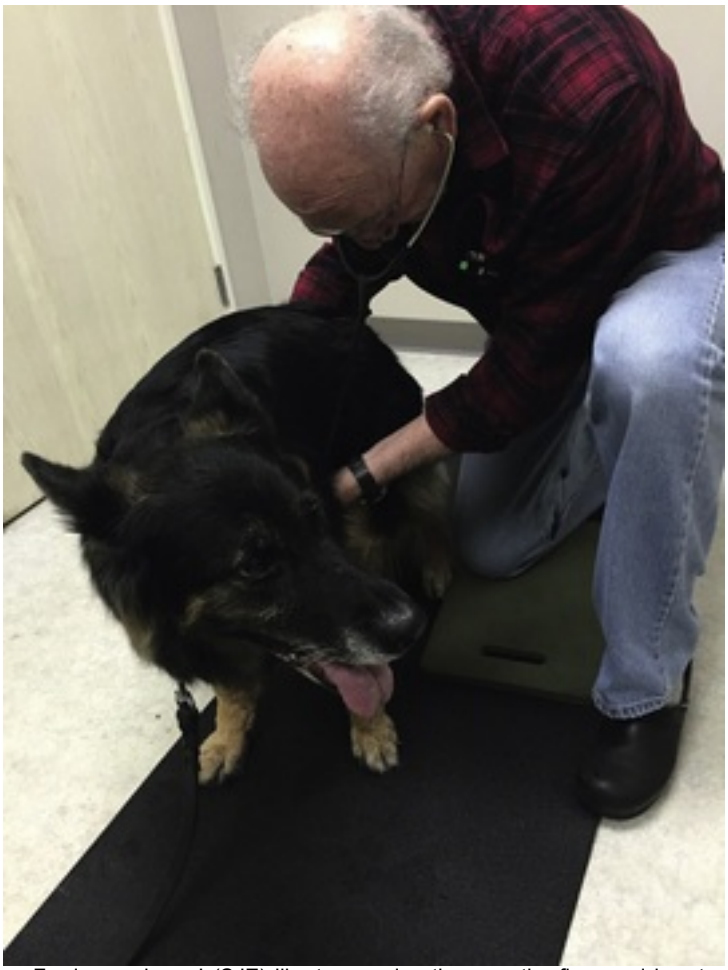

FIGURE 2-5 For larger dogs, I (SJE) like to examine them on the floor and be at eye level with them. I often kneel on a gardener's pad to be more comfortable.

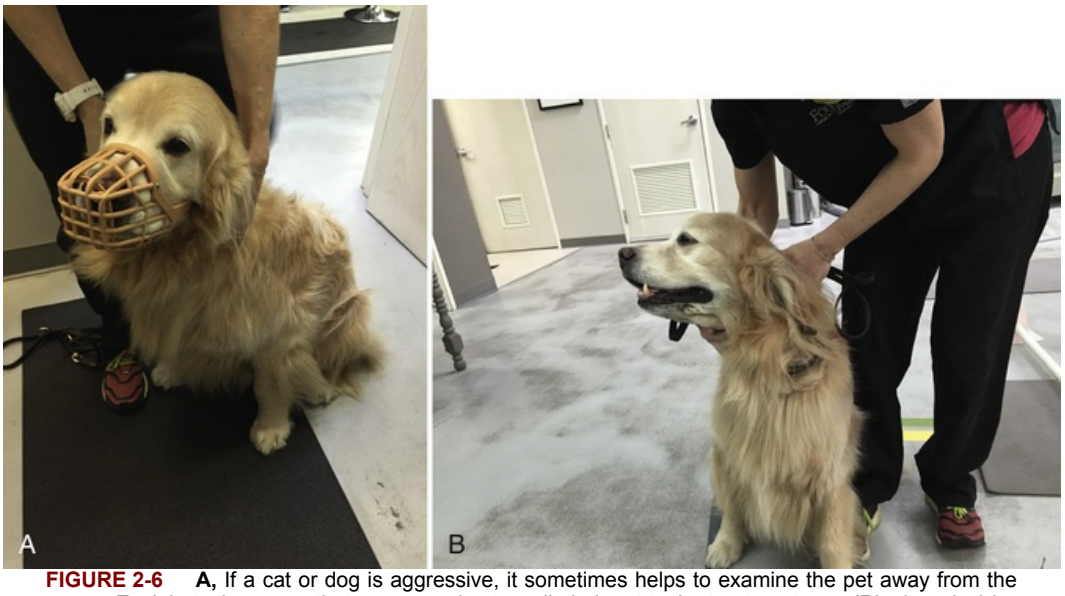

FIGURE 2-6 **A,** If a cat or dog is aggressive, it sometimes helps to examine the pet away from the owner. Explain to the owner that you are going to walk their pet to the treatment area **(B)** where he/she is likely to experience less fear as the animal need not feel that it must protect its owner.

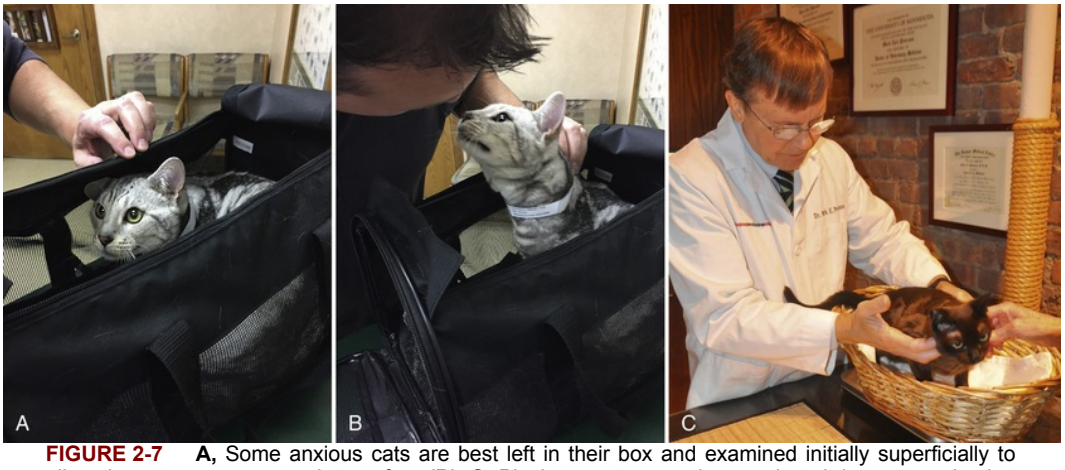

FIGURE 2-7 **A,** Some anxious cats are best left in their box and examined initially superficially to allow them to overcome anxiety or fear **(B). C,** Placing a cat, even those agitated, in an open basket such as this provides enough calming effect that a physical examination can then be completed. (**C** courtesy Mark E. Peterson, DVM, New York.)

Clients often wish to share what they know, think, or understand about their pet's problems. Regardless of how clearly and confidently clients relate their interpretation of their companion's issues, it is essential for the examiner to "go back to square one" in order to provide an objective assessment. Thus, the client's opinion and the veterinarian's analysis may run in parallel. Enough confidence must be placed in the client's story to solidify the trust being developed during this important part of the examination, but the veterinarian must also think independently enough to avoid being led down an incorrect path of deduction. I like to give clients a few minutes to express themselves, regardless of relevance, because what they have to say is likely to be important to the ultimate outcome. For example, clients may refuse to acknowledge how sick the pet is, or they may be worried about "cancer" or may focus on something that may not be pertinent ("can we also clean the anal sacs or trim the toe nails?"). Clients' comments provide valuable insight into their personality, their understanding of veterinary medicine, as well as their concerns and goals. There are different levels of owner commitment to their pet, and this will influence choices they make regarding the pet's care.

Clients may offer information obtained from friends, breeders, or other sources, such as the Internet. They

may wish to have the veterinarian go over this material. A reasonable technique that precludes taking time away from the office call is to acknowledge the request and inform the caretaker that material will be reviewed once the examination and early decision-making processes have been completed. Dr. Google has become a regular but silent partner in the examination room. Dr. Google often will be consulted immediately upon the owner's having access to him/her/it following your examination. If an owner implies: "OK, you are the doctor, so you tell me what is wrong," a different tack then becomes necessary to deal with owners that are more assertive or blunt like this. The approach changes from "tell me what you have observed" to "it appears that your dog (or cat) has been losing weight; tell me, has this been a recent occurrence?" Or, "have you always been able to feel your dog's spine this clearly?" Comments or questions like this may be all that is necessary to have the owners begin talking about their pet.

Not every owner-veterinarian experience is informative. All valuable and relevant acquired facts should be noted in the record. If a client refuses to provide information or begins to verbally attack another individual, the record should be so-noted. The record provides not only a potential legal defense but also a guide to further owner communication.

Clients, who have been dissatisfied with the results of prior care, reasonably object when you prescribe the same medication as the prior DVM did. This suggests that you have not been listening or reading the reports from prior care. This requires careful explanation directly with the owner. See ch. 1 regarding the history concerning drugs given, diet, travel, vaccine history, and other pets in the household, etc.

Inquiring in an unobtrusive manner about the owners' needs and expectations helps define their wishes and permits the veterinarian to provide options from which the owners can choose.

The history and the owner's story are important. These convey to the examiner the owner's perceptions during this initial period of acquaintance or contact. I find that this can be the most useful time of the examination process. I can touch the pet, gently stroke it, observe the quality of the hair coat and skin, determine the hydration status, and generally gain an impression of the animal's health status (e.g., debilitated or well-conditioned, obese or thin, growths or masses) (Videos 2-1A and 2-1B and Figures 2-8 and 2-9). This is also a convenient time to gently examine some pets without the animal being fearful, because a pet may be more aware of its owner's talking than of the veterinarian's gentle palpation. This practice also offers an opportunity to assess the animal's behavior while assuring the client that I am becoming acquainted or reacquainted with their pet. Pets generally seem less fearful while I am at their eye level and when I refer to them by name. Thus, the physical examination begins when the pet enters the examination room and while the history is still being taken.

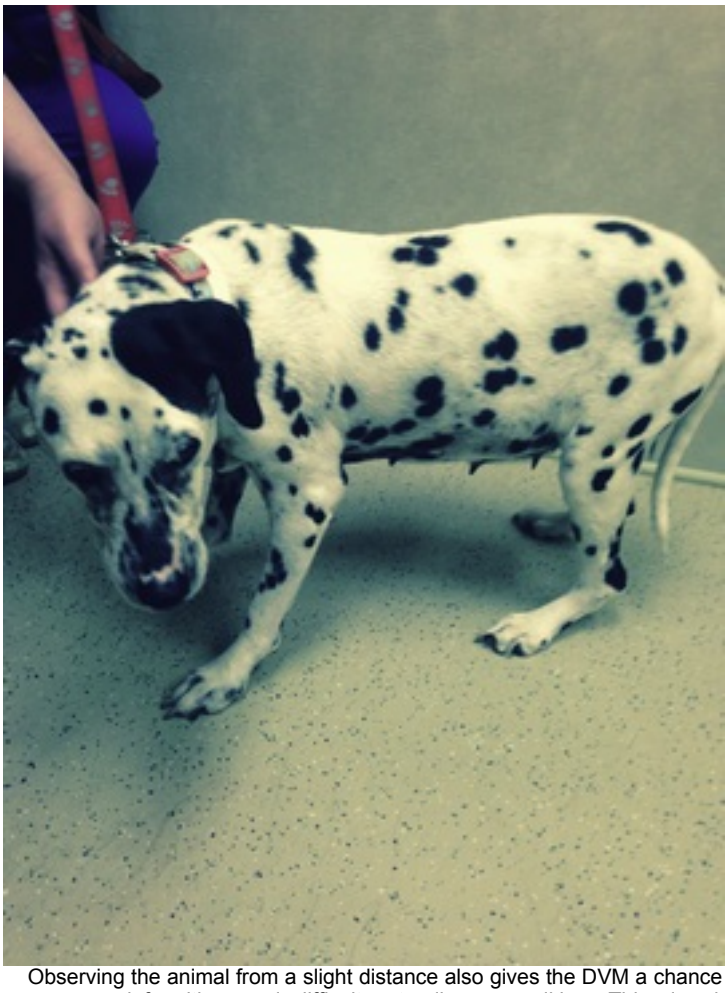

FIGURE 2-8 Observing the animal from a slight distance also gives the DVM a chance to note other abnormalities—masses, deformities, and difficulty standing or walking. This dog is weak, has plantigrade stance in the rear legs and is uncomfortable standing or walking.

FIGURE 2-9 Observing the dog or cat from a distance allows the DVM to note evidence of an enlarged abdomen (in this case due to ascites) and heavy breathing, which would allow your questioning and examination to move along in a more specific direction.

It is not always possible to begin the examination process during the previously described situation, and I (SJE) do not make a distinct effort to perform every examination this way. If the dog or cat is sitting anxiously (i.e., protectively or in a frightened manner) in the client's lap, I avoid contact and dwell on the pet and the owner's story. Pets often relax during this period and are less fearful of me as time goes by. A truly frightened or fractious animal presents a different situation, which may require use of a muzzle. Before muzzling any dog, it is strongly recommended to attempt an examination away from the owner (see Figure 2-6, *A* and *B*)—for example, while taking a dog to a scale outside the examination room or to an environment that no longer requires the pet to feel protective of the owner. It is important to remember that owners should not be allowed to hold their pets during any examination process that entails a likelihood of injury to anyone, as could occur with a frightened or injured pet. This remains a chronically differing point of view amongst veterinarians (but not insurance companies). Many clients wish to hold their own pet, yet the veterinarian is liable for examination room injuries. Too, the pet is often more likely to be irritable and protective while being so-held. On the other hand, many owners feel uncomfortable not holding their pet. Thus, the examining doctor must use caution, experience, and the cues provided by the owner and the animal to determine the best approach. Most importantly, one must always work to avoid situations likely to result in a bite wound injury to the owner, the veterinarian, or anyone else. When a dog or cat reacts adversely to the veterinarian, it is important to back off slowly, reassess the process, and move forward in a manner that is safe for all involved. Usually the client recognizes the need for this. When the client insists on holding a fractious animal, the veterinarian must step up and identify the need for a safe process to continue, often with the client out of direct sight.

The Physical Examination Process

As previously discussed, the physical examination commences when the veterinarian first sees, smells, and hears the patient. Usually, this takes place in the examination room, where the pet's general appearance, odor, and any irregularities are noted (see Figure 2-8). A severely sick or crisis presentation requires an entirely different approach from that used for a dog or cat presented for a wellness examination or those with a mild or chronic issue. Clients must also be observed and evaluated, since many people are understandably anxious in severe or acute life-threatening situations. Owner anxiety, however, may manifest in a spectrum of

responses (ranging from a quiet, stunned composure to near-hysteria). Skilled veterinarians assess these factors when beginning to talk with an owner. In these and less emotionally charged situations, the veterinarian should assess the owner's state when first approaching the pet. Intense questioning may be inappropriate if the owner feels that the pet needs immediate medical attention. In such situations, it may be wise to advise the client that you are taking the pet to the treatment area so that a more thorough examination may be completed and medications initiated. It is imperative to advise the client that either you or your assistant will be back shortly to brief them on the pet's condition.

While observing the patient, the veterinarian should listen for abnormal breathing sounds or labored respirations, suggesting either respiratory or systemic disorders (see ch. 28 and Video 2-2). The animal's body size and posture also should be observed: for example a plantigrade stance could suggest a neuropathy (Figure 2-10) or a tendon injury (see ch. 354); neck ventroflexion in cats may indicate hypokalemia (see ch. 68) or thiamine deficiency; overweight pets (Figure 2-11) may be overfed, rarely hypothyroid (see ch. 176), or inactive (see ch. 176); thin pets may be sarcopenic, systemically ill, or underfed (Figure 2-12) (see ch. 177). It is true that owners may point out these concerns, but they may misinterpret such changes or may simply not be cognizant of their significance. Dogs and cats with ascites may appear to have gained weight to the owner while in fact they have become rather wasted instead (Figure 2-13 and Video 2-3). In a desire to "wish well" for the pet, the owner sometimes can fail to provide information for fear of its significance. The veterinarian has the responsibility to seek out this information. Examples of owner concerns and signs the veterinarian may observe are presented in ch. 8 through 47 of this textbook. The examination process must not be so quick or expedient as to result in an obvious underlying condition being overlooked. Likewise, an acutely ill patient may require immediate intervention (such as fluids and an IV catheter). This should not be delayed but rather identified in the record as requiring immediate attention and that the balance of the examination will be completed once the pet is stable. This is an early manifestation of triage management being practiced.

FIGURE 2-10 Dog plantigrade in stance (R>L) associated with weakness and pain due to multijoint

osteoarthritis. Right carpal flexion makes the dog ambulate awkwardly and with a limp, suggesting pain.

FIGURE 2-11 Obese dog **(A)** (19.5 kg [42.5 lb]) and cat **(B)** (15.5 kg [34.5 lb]) require an appropriate medical diagnosis first and then nutritional discussion based upon the cause (medical or dietary) of the weight gain. **(C)** 1.6 kg (3.5 lb) weight loss brought this overweight pug down to a healthy weight and resolved most of his respiratory distress without medication and helped him regain a normal walking pattern.

FIGURE 2-12 Cachexia requires a thorough history and medical evaluation to determine if age, disease, or malnutrition is primary to the weight loss. In this case, cardiac cachexia, ascites and chronic dilated cardiomyopathy have been assessed.

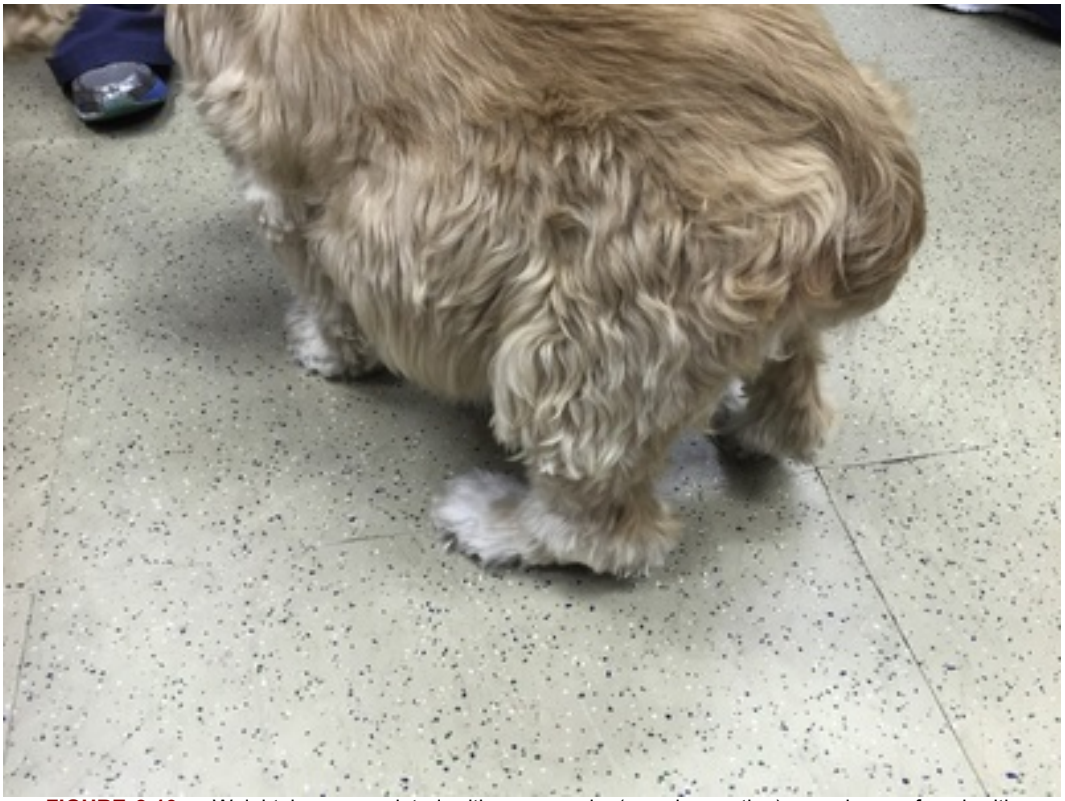

FIGURE 2-13 Weight loss associated with sarcopenia (muscle wasting) may be confused with weight gain by the owner, if ascites is present.

If the animal is ambulatory and has a history of a lameness, a neurologic deficit, or weakness, it is essential that the veterinarian watch the animal move (Figure 2-14 and Video 2-4). This may be done before or after the hands-on physical examination process. At some point during this initial phase of the examination, the veterinarian must observe the pet's gait. For dogs, this may require having the pet walk on a surface with adequate traction, preferably with the owner as the handler. Lameness, signs of neurologic deficits, or irregularity in gait and appearance may become critically important to the ultimate diagnosis (Figure 2-15 and Video 2-5). As the physical examination continues, the clinician should attempt to carefully evaluate any specific lameness or suggestion of a localized abnormality (e.g., patella luxation, stifle cranial drawer sign, elbow pain or mass).

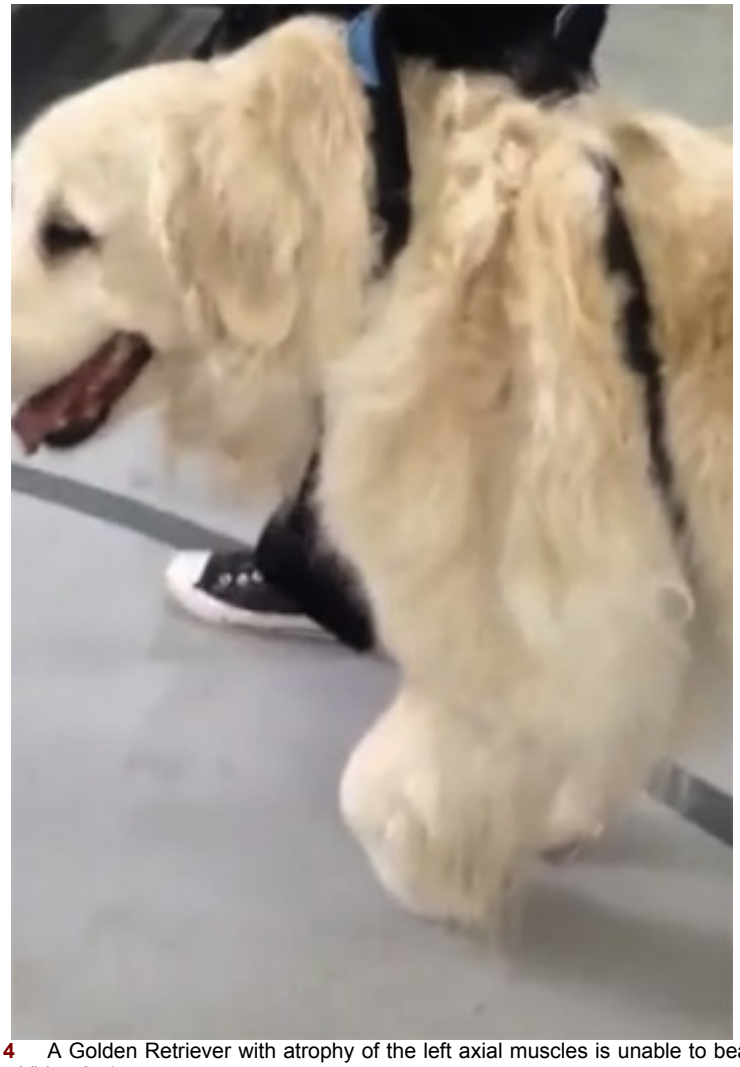

FIGURE 2-14 A Golden Retriever with atrophy of the left axial muscles is unable to bear weight on that limb (see Video 2-4).

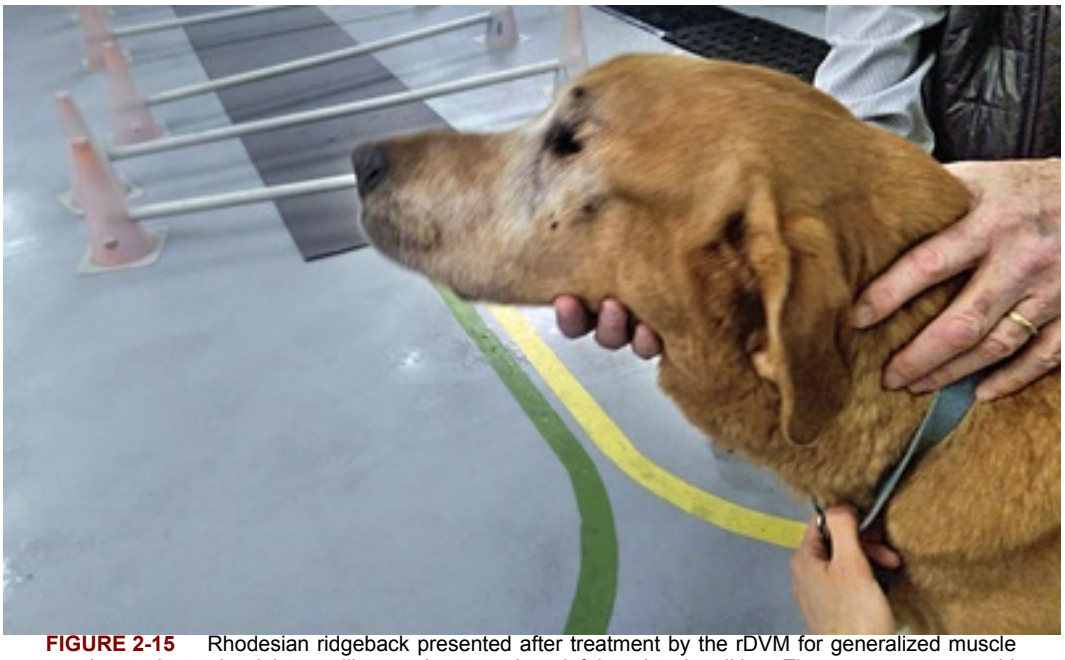

FIGURE 2-15 Rhodesian ridgeback presented after treatment by the rDVM for generalized muscle wasting and atrophy, joint swelling, and extremely painful assisted walking. The response to steroid and antibiotic therapy and physical rehabilitation provided this dog with an additional two excellent years of life with only intermittent bouts of lameness. Immune-mediated muscle disease and polyarthritis were assumed to be the cause of this dog's recumbent position at the time of entry to the hospital.

A review of previous examination notes or itemized assessments from the SOAP (Subjective, Objective, Assessment, and Plan—i.e., the entries in the medical record) regarding prior issues can aid in the clinical assessment. For example, comparing the size of a mass with previous findings is something clients appreciate, particularly if the record clearly identifies prior dimensions, appearance, and location. Measurement of lesions with calipers or a ruler is good for review and trend purposes (Figure 2-16). The availability of digital photography makes good use of these tools for the clinician and the client, particularly if digital images can be attached to the medical record (Figure 2-17).

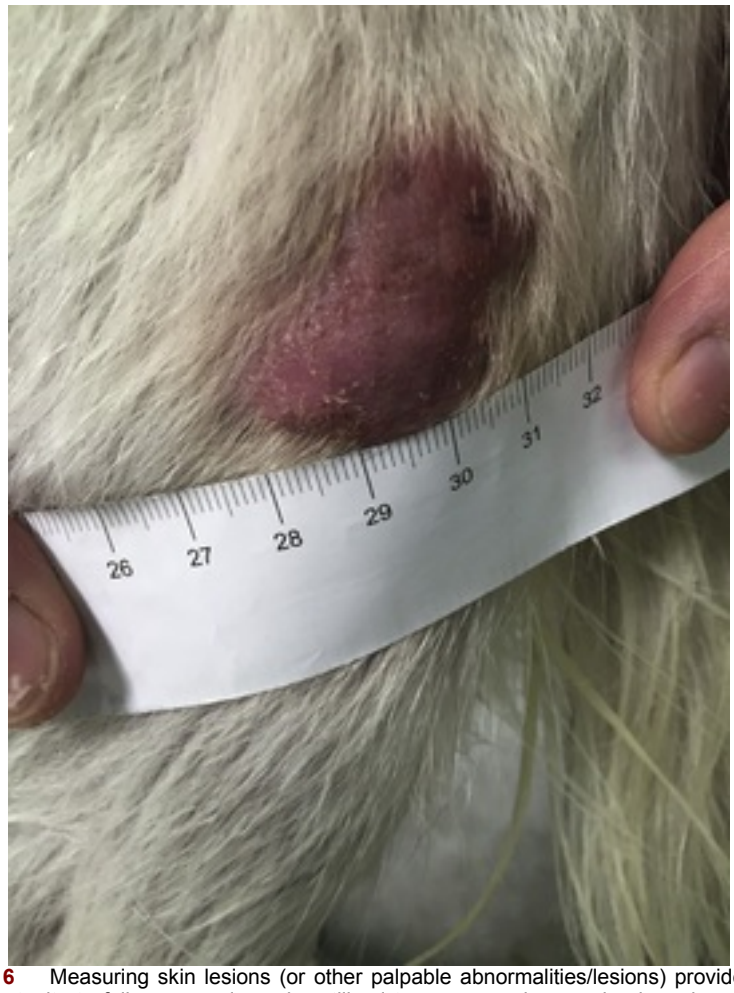

FIGURE 2-16 Measuring skin lesions (or other palpable abnormalities/lesions) provides the client with an opportunity to follow up and can be utilized to compare changes in size, shape, or color to previous examinations. Utilizing handheld devices to photograph such lesions and include them in the medical record is advisable.

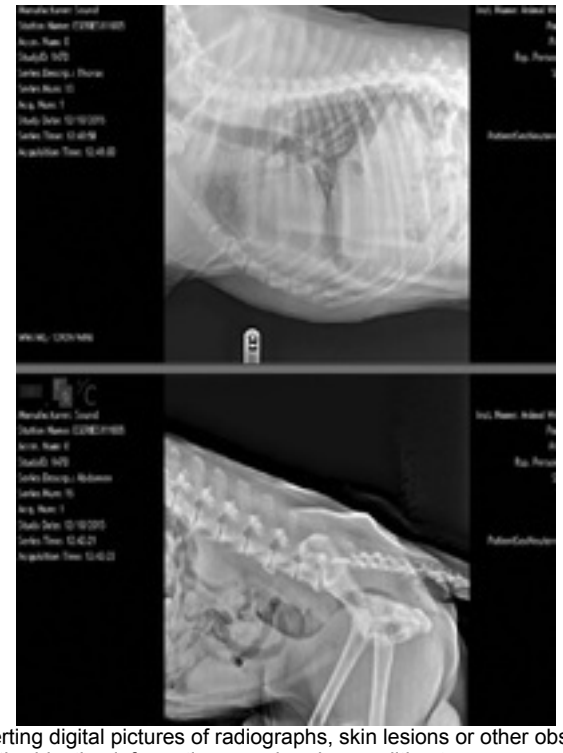

FIGURE 2-17 Inserting digital pictures of radiographs, skin lesions or other observable abnormalities provides the DVM with objective information on prior abnormalities to compare with those observed at the next examination.

Neurologic signs, such as diminished conscious proprioception, diminished muscle tone, limb dragging, or unusual evidence of pain during compression of the muscles or lumbosacral compression, are noted and could require further investigation to point to a diagnosis (Figure 2-18) (see ch. 259). Something can be said for performing the distant or "stand back" examination at this time, which allows the veterinarian to observe breathing patterns or abdominal changes. Note any area that appears extremely painful, since it will provide important clues to the veterinarian and the owner will appreciate your recognition of the nature of the problem.

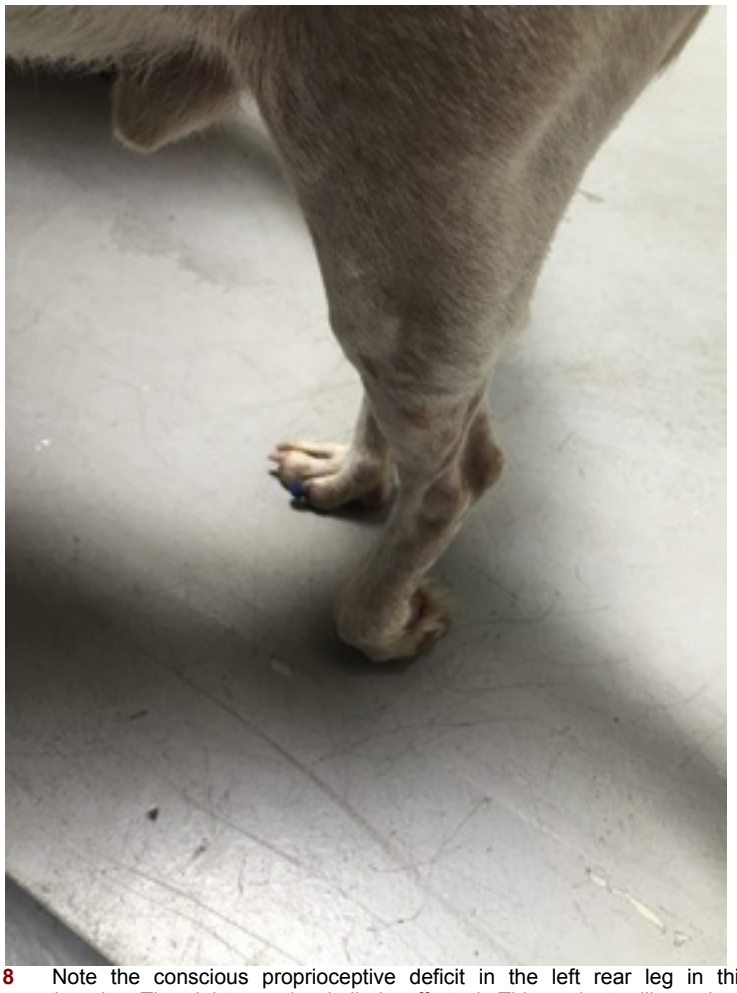

FIGURE 2-18 Note the conscious proprioceptive deficit in the left rear leg in this dog with degenerative myelopathy. The right rear is similarly affected. This patient will require a thorough orthopedic and neurologic examination to determine the etiology of the proprioceptive deficits.

Every seasoned veterinarian has developed his or her own method of performing the hands-on portion of the physical examination, derived from experience. For example, animals are frightened by a large figure looming overhead and are less anxious when approached at eye level. As stated above (Figure 2-5) I (SJE) prefer to kneel on the examination room floor to perform the physical examination (except for cats and small-medium sized dogs). I find I am better able to perform thoracic auscultation in large breed dogs completely and more thoroughly in this manner (Figure 2-19). Medium-, large-, and giant-breed dogs standing on the floor, rather than the examination table, are almost always more relaxed, making it easier to palpate thoroughly while having a good presence with the pet. Whenever possible, animals should be in the same position (table or floor; standing) each time they are examined.

FIGURE 2-19 Examination of the heart and lungs in my hands (SJE) in a medium- to large-sized dog is best done on the floor, where the animal remains less active and provides a better setting for this critical examination. Others may prefer to do this exam on a table but whatever you choose, use the same technique each time.

After the initial greeting, I (SJE) prefer to stroke the pet to gain a more general knowledge of the overall body status (Videos 2-6 and 2-7). The body condition score is assessed (Figures 2-20 and 2-21), as are hydration status, physical appearance, and hair coat. Cutaneous and subcutaneous masses or areas of concern (size, shape, and appearance) are noted. I then examine the entire torso by touch, gaining a general impression of any specific or general concern. Concerns may include lymph node enlargement, abdominal swelling (fluid, masses, fat, distention, pain), discomfort, and skin or musculoskeletal abnormalities (changes in the hair coat, open wounds, fleas, dirt, ticks, or other abnormalities). Looking for bumps, lumps, or irregularities, I am able to distinguish lymph node changes, evidence of pain or swelling in the joints or limbs (see ch. 15), physical deformities (see ch. 353), and the nature of the femoral pulse. I evaluate the pulse, including its rate, quality, and character (see ch. 56), and listen for irregularities in cardiac sounds while auscultating the heart simultaneously (see ch. 55 and Video 2-12).

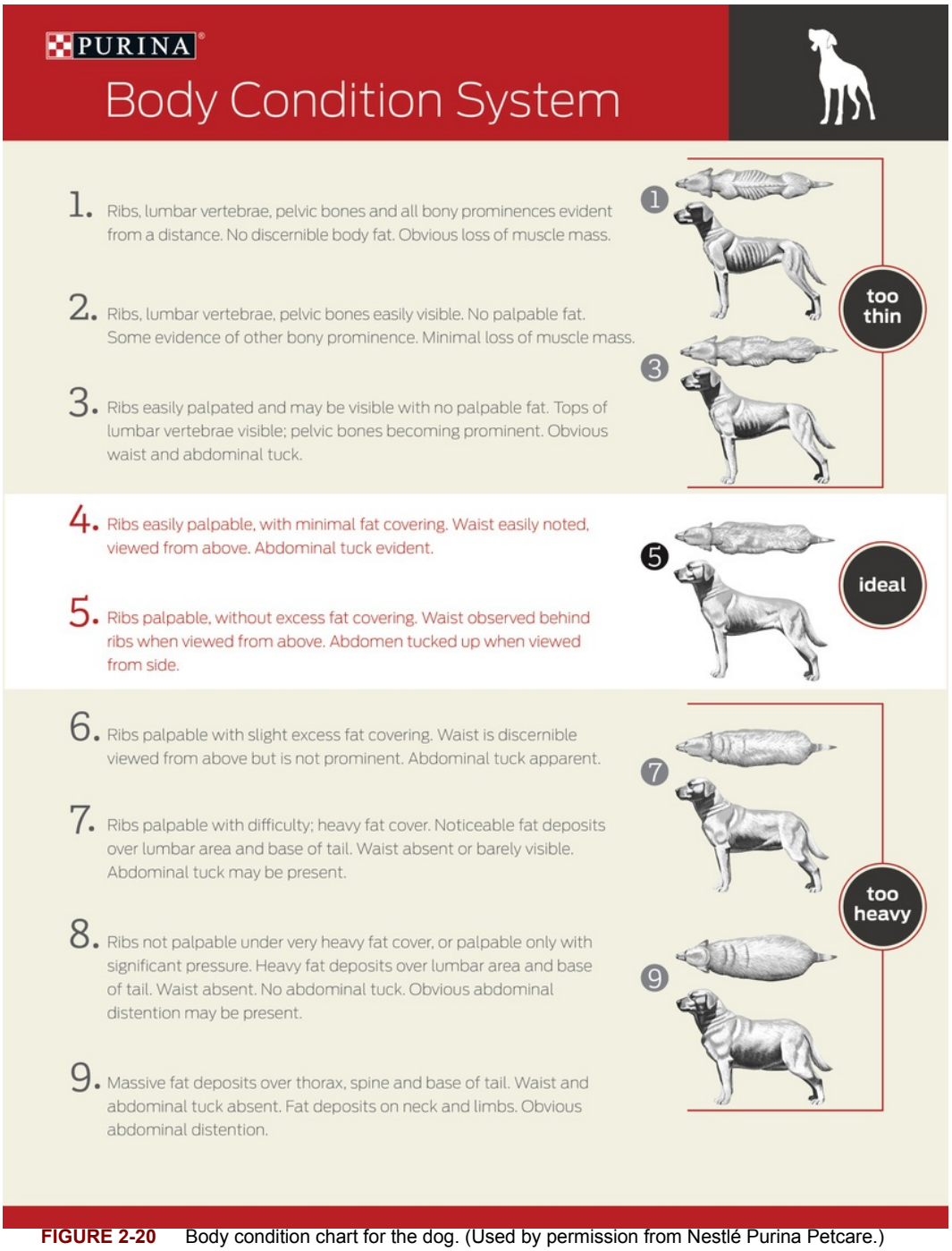

FIGURE 2-20 Body condition chart for the dog. (Used by permission from Nestlé Purina Petcare.)

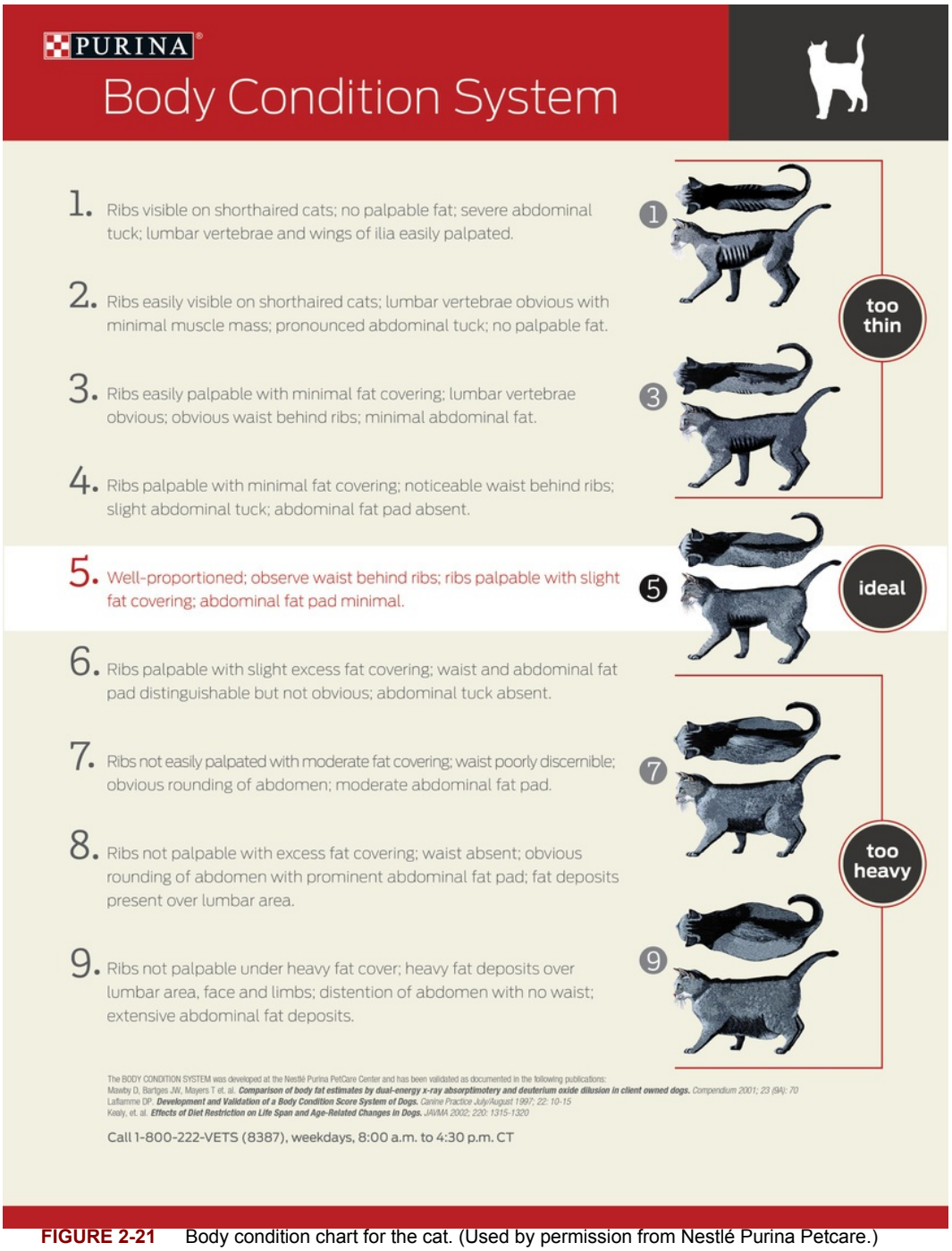

FIGURE 2-21 Body condition chart for the cat. (Used by permission from Nestlé Purina Petcare.)

Swellings in the form of edema or fluid collections are correlated with other changes. Edema is identified as being generalized, localized to one limb or region (ventral thorax, for example), or associated with abdominal fluid. It should be described as: painful, pitting, cold, warm, or oozing (see ch. 15, 17, and 18; Video 2-8).

Specific lameness associated with trauma is identified and may provide an obvious explanation for an owner's concern. However, the veterinarian should not make that assumption without giving reasonable consideration to other possibilities (e.g., a pathologic fracture in a dog with osteosarcoma). I like to run both hands down the animal's body to check for asymmetry in body form.

Skin and coat changes must be evaluated in light of the animal's living arrangements, as established in conversation with the caretaker. Indoor pets should not have foreign body material in their coat (unless some other pets in the household are both indoor and outdoor pets); fleas, flea dirt, ticks, and other ectoparasites should not be present. Hair loss or thinning is a clue to cutaneous or systemic disease and should be noted. Hair loss should be assessed as unilateral or bilateral, patchy or generalized and its full significance should be

identified in the record. Coat changes must also be correlated with other changes that may indicate a systemic illness, such as Cushing's syndrome (see ch. 306 and 307). Areas of skin change should be evaluated and comments made with respect to the potential benefit of skin or hair culture, skin scraping, skin biopsy or allergy testing. Pets that live outdoors are more likely to have ectoparasites, weather-related hair coat changes, or bite wounds. As with the indoor pet, an attempt can be made to find correlations in a skin condition with the owner's concerns or other issues. Recommendations can then be made accordingly. Hair coats with a strong odor of perfume, skunk, oil or smoke could suggest to the examiner possible problems with regard to allergic, skin or lung disease, highly reactive lungs, or an animal that has been in or around a fire with subsequent smoke inhalation (see ch. 25).

My preference (SJE) is to progress during the physical examination from the head toward the tail. First, a generalized evaluation of the hair coat (above) is ascertained. Hydration status, mucous membrane color and capillary venous return should be identified. Pain on dorsiflexion or ventroflexion or lateral movement of the head and neck may be indicative of local discomfort such as cervical disc disease, shoulder muscle spasm or a more distant issue (see ch. 259). The head first should be examined superficially for hair loss, muscle wasting, swelling, or asymmetry. Pay specific attention to the appearance of the mucous membranes (see ch. 50 through 54) (e.g., pallor gives reason to suspect anemia, hypoperfusion, or hypoxemia; muddy in heart failure, pulmonary hypertension and age related primary lung disease; cyanotic with A-V shunting, hypoxemia, intoxication, etc.) (Figures 2-22, 2-23, and 2-24). Note the appearance of the oral cavity, pharynx, lips, gums and teeth (Figures 2-25 and 2-26). Drooling, oral discharge (see ch. 36) or malodor (see ch. 25) should be apparent (see ch. 272). It is important for the veterinarian to speak to the owner about the condition of the pet's teeth and gums; it also is important for the owner to see, if possible, any area of concern in the oral cavity (Figure 2-27).

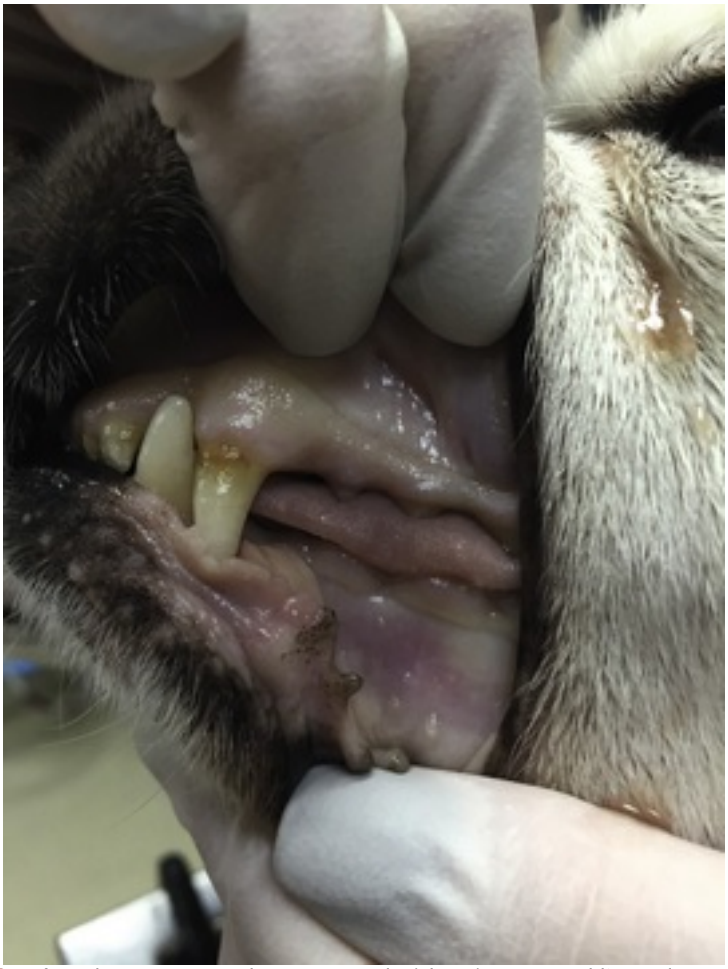

FIGURE 2-22 Anemic mucous membranes are pale (above) or even white, and associated with a BB-shot or water hammer-like pulse that may also be described as quick to rise and quick to fall.

FIGURE 2-23 Cyanosis in a cat. The blue color of the tongue (and mucous membranes) in this case is associated with a right-to-left–shunting cardiac defect.

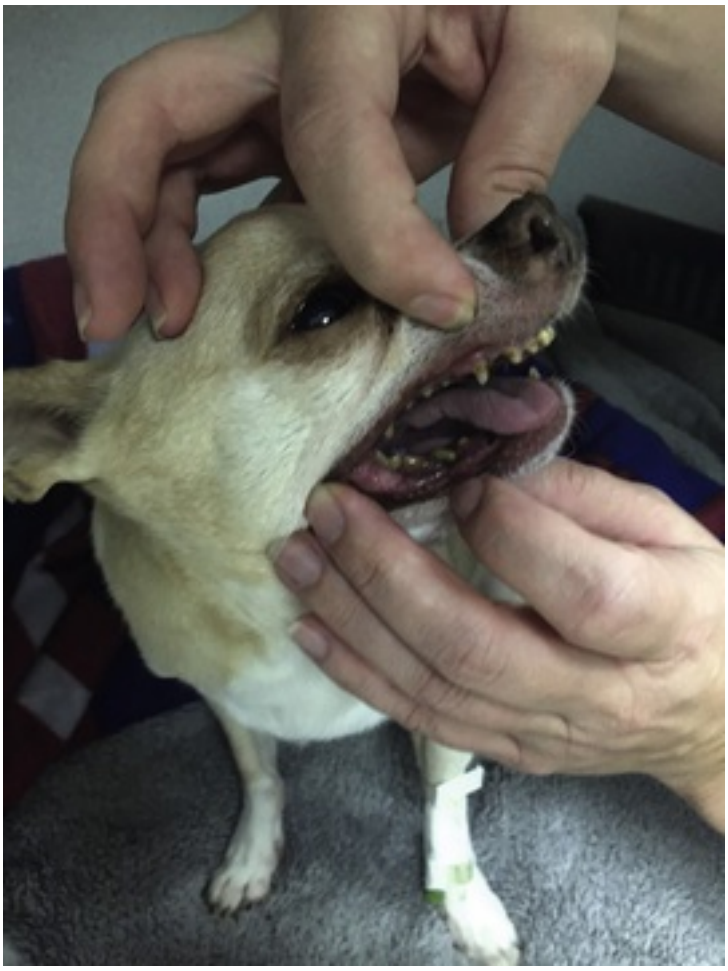

FIGURE 2-24 Ashen (muddy) colored gums and tongue are often associated with heart failure. This pet has long-standing chronic mitral valve disease and is experiencing an episode of recurrent heart failure.

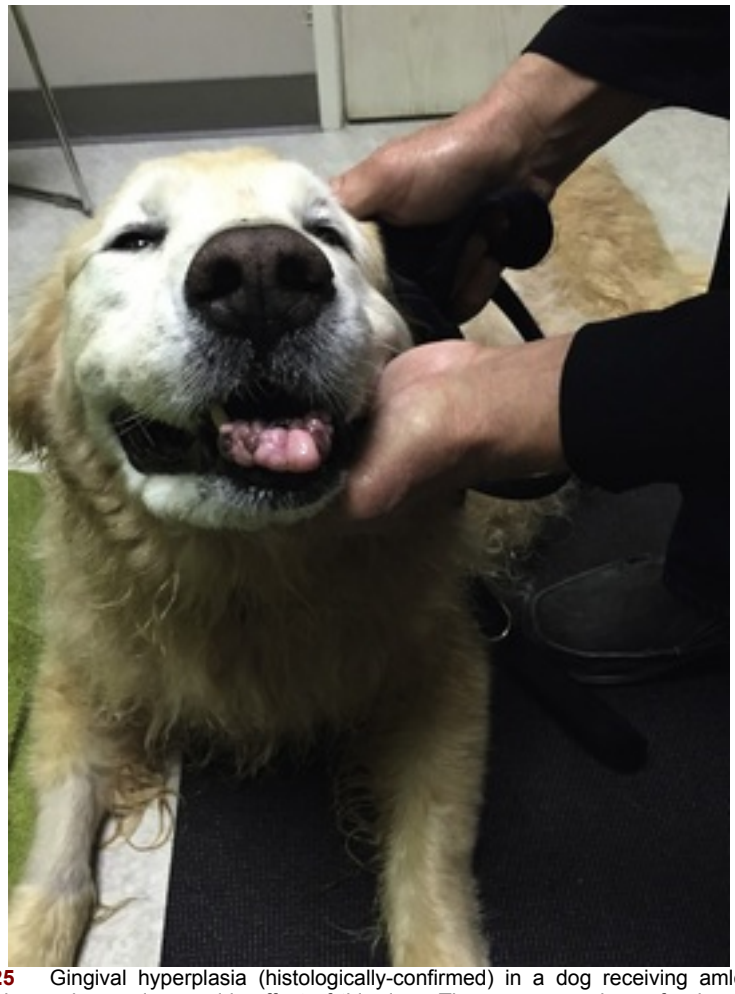

FIGURE 2-25 Gingival hyperplasia (histologically-confirmed) in a dog receiving amlodipine; this change has been observed as a side-effect of this drug. There were no signs of pain or difficulty in prehension of food over many years.

FIGURE 2-26 Chronic dental tartar and gingivitis is common in middle-aged to older dogs and cats and should be identified as a treatable problem. Chronic periodontal disease leads to other medical problems as dogs and cats age and should not be neglected.

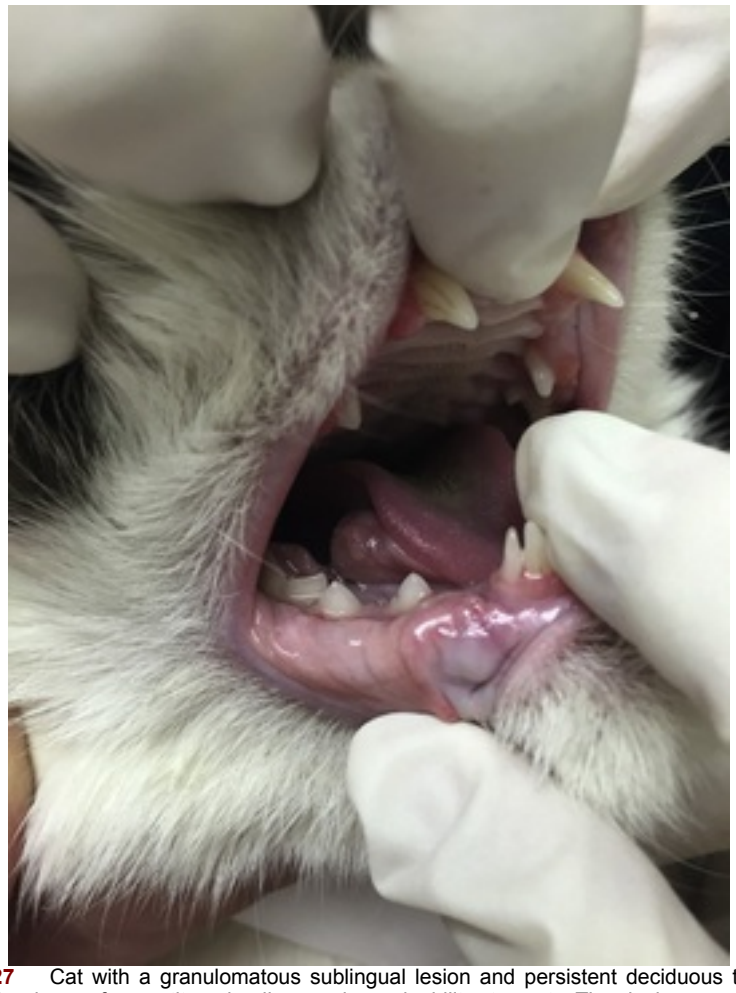

FIGURE 2-27 Cat with a granulomatous sublingual lesion and persistent deciduous teeth initially presented for loss of appetite, drooling and an inability to eat. The lesions were biopsied (pyogranuloma) and the lesions began to regress after removal of much of the affected tissue. One month later the condition extended to the large and small intestines.

Thorough neurologic examinations are not usually a component of the routine physical examination. However, a brief cranial nerve examination should be included during this portion of the examination process. The posture of the head (e.g., head tilt, Figure 2-28), masticatory muscle mass and tone, and the appearance of the eyes may be relevant. Monitoring for superficial and deep changes within the globes and the periorbital region should be assessed. Ophthalmic sensitivity (Figure 2-29), squinting/blepharospasm, or any other evidence of photophobia is noted. Lip and facial skin folds, especially in brachycephalic breeds, may result in inflammation, moist exudate, and a foul odor (Figure 2-30). Any ocular discharge should be described as to color, composition, volume, and whether the discharge is unilateral or bilateral. Tear production is recorded (Schirmer tear testing), as is nasolacrimal duct patency (e.g., note dry, cracked nasal tissue). If nystagmus (Video 2-9), strabismus (Figure 2-31) or other deviations of one or both globes are noted this suggests the need for a more thorough neuro-ophthalmic examination (see ch. 259). Continue the examination while looking for signs of conjunctival color changes or inflammation. Pupillary size, symmetry, and integrity are noted, as is the pupillary light response, both direct and consensual. Sensation in the eyelids and the surrounding tissue is observed as are masses involving the eyelids, noting their size and whether they are irritating the cornea. Corneal lesions should be noted in the record for future comparison, particularly the size, shape and depth of corneal ulcerations.

FIGURE 2-28 Head tilt (right-sided) in a dog with idiopathic vestibular disease, chronic pulmonary hypertension, and mitral valve disease.

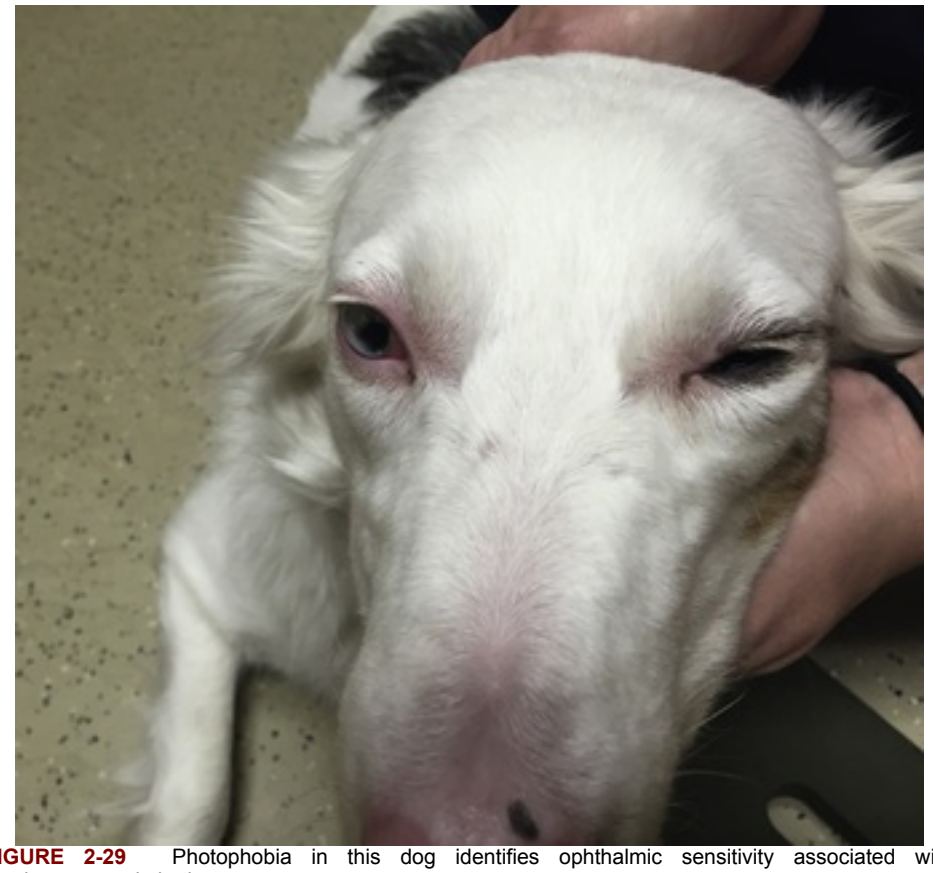

FIGURE 2-29 Photophobia in this dog identifies ophthalmic sensitivity associated with blepharospasm in both eyes.

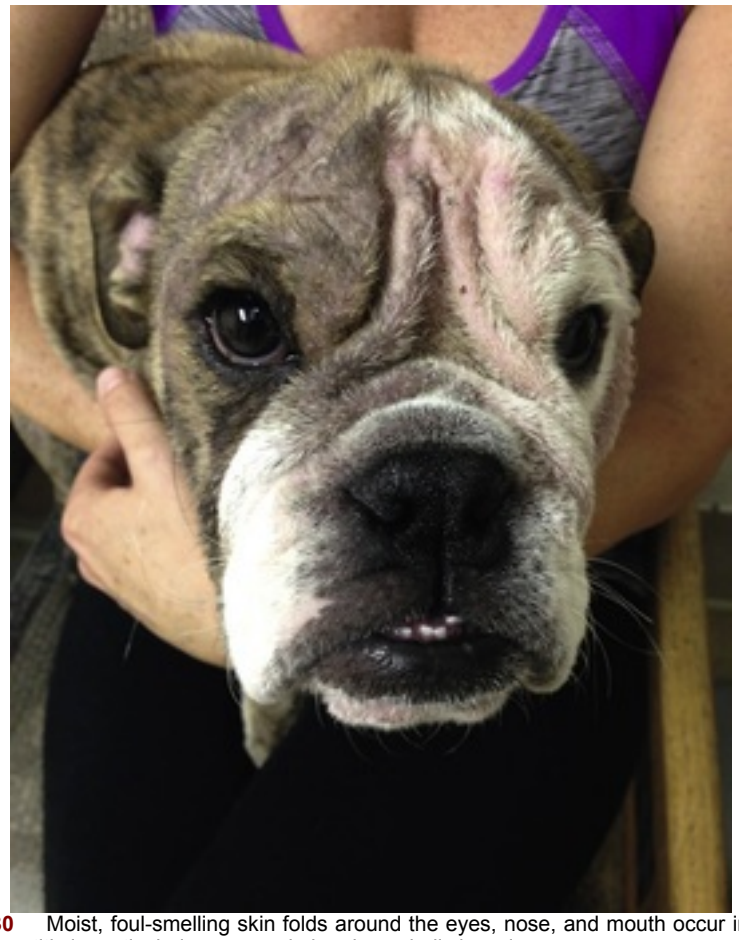

FIGURE 2-30 Moist, foul-smelling skin folds around the eyes, nose, and mouth occur in all breeds. Skin fold dermatitis is particularly common in brachycephalic breeds.

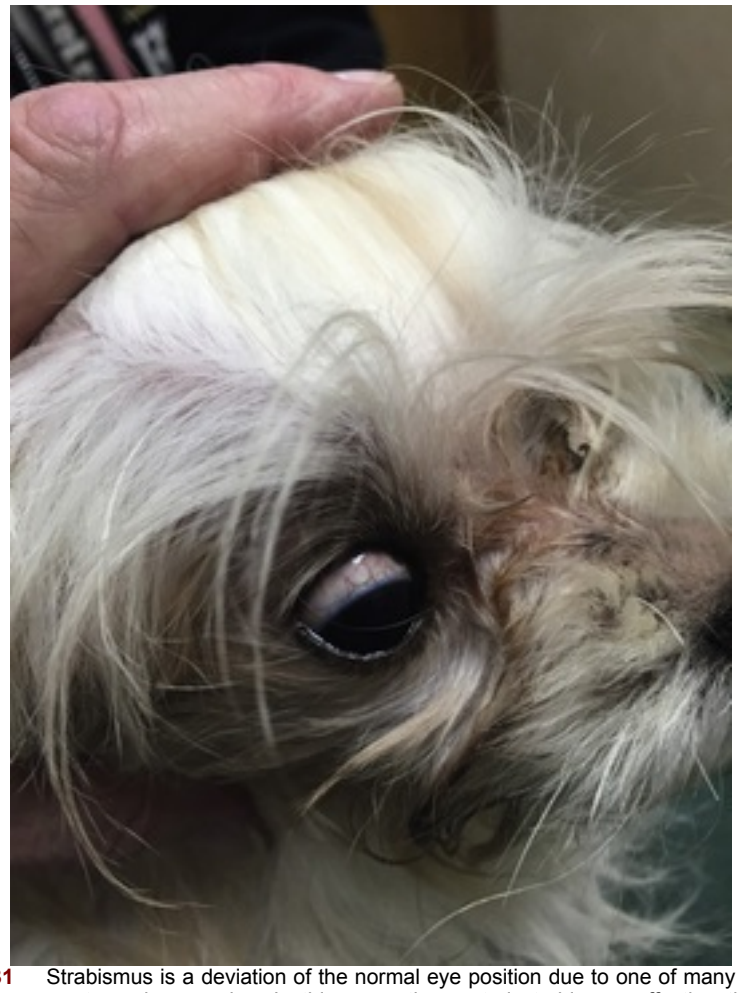

FIGURE 2-31 Strabismus is a deviation of the normal eye position due to one of many disorders of cranial nerves or extraocular muscles. In this case, the ventral strabismus affecting the right eye requires further neuro-ophthalmic examination to identify the etiology.

The appearance of the skull, the muscles of mastication, and the muscles around the head are noted (Figure 2-32). Clients frequently suggest that a mass has developed on the skull, which is in fact the occipital protuberance. This is associated with weight loss as the temporal muscles atrophy, making the external occipital protuberance very obvious (Figure 2-33). In puppies, particularly those with unusually large heads, examination of the fontanelles for hydrocephalus should be part of the examination (Figure 2-34). Enophthalmos can be a sign of periorbital fat loss and may relate to myositis, weight loss, cachexia, or a primary ophthalmic process. Pain, swelling, or heat is identified. More detailed examination of the eyes, including direct and/or indirect ophthalmoscopy, may be completed at this time; or, complete the rest of the physical and then perform a thorough ophthalmic examination. See ch. 11.

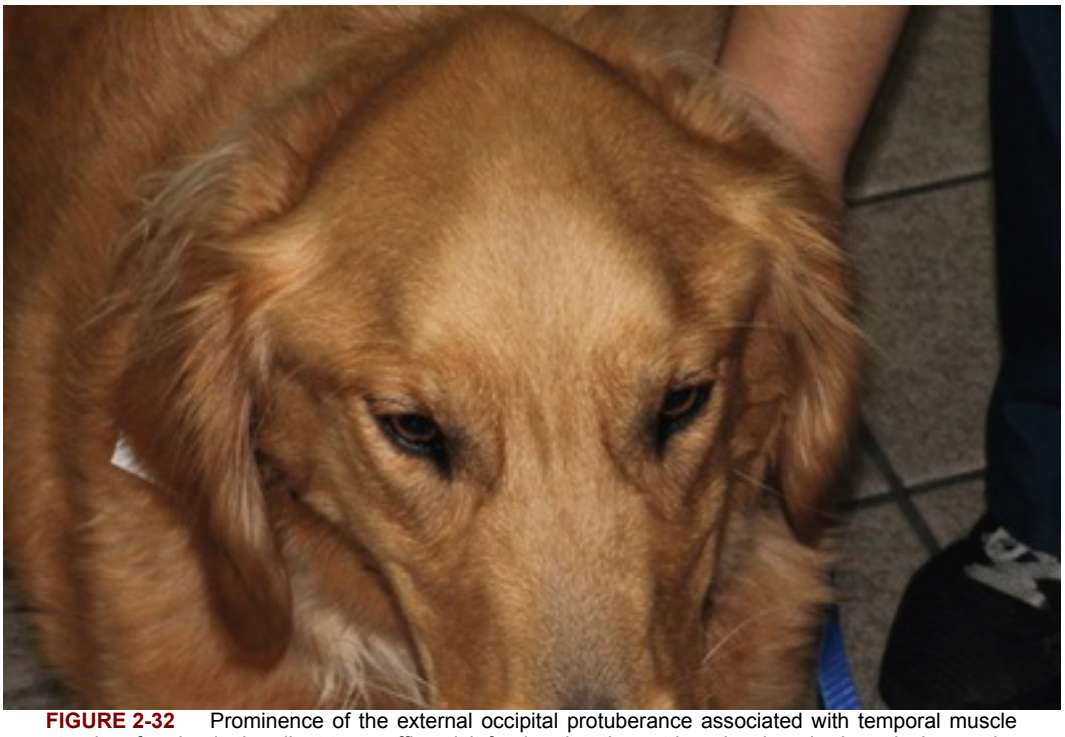

FIGURE 2-32 Prominence of the external occipital protuberance associated with temporal muscle atrophy often leads the client to an office visit fearing that the pet has developed a bony lesion on the top of the skull.

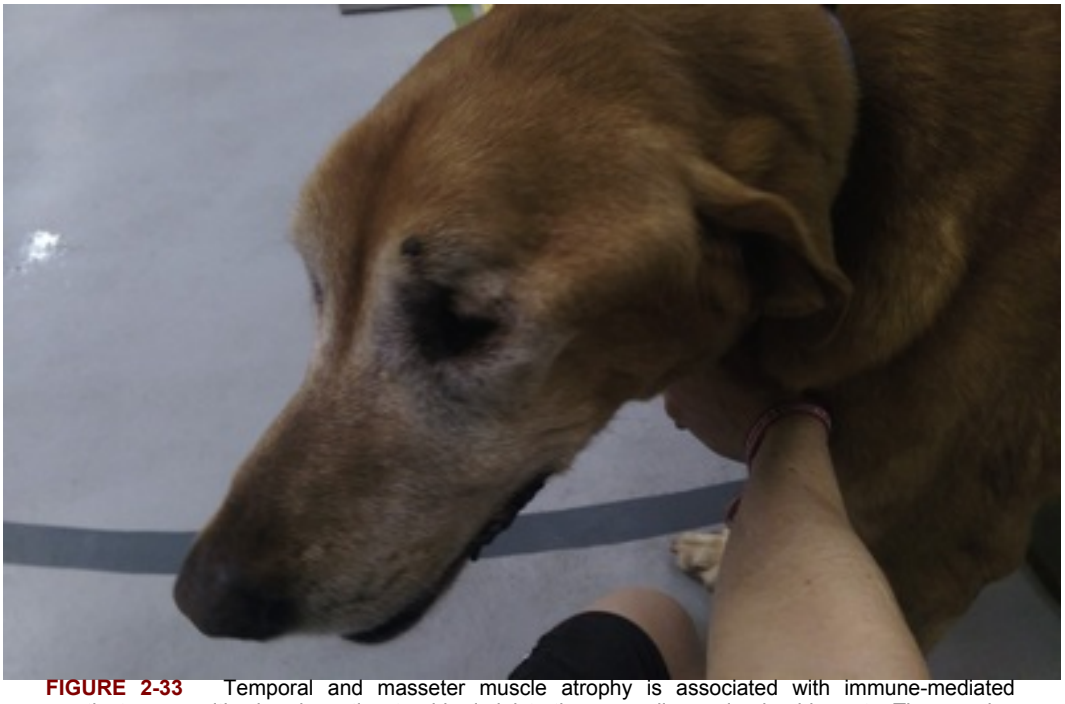

FIGURE 2-33 Temporal and masseter muscle atrophy is associated with immune-mediated masticatory myositis chronic corticosteroid administration, as well as aging in older pets. The muscles of mastication and the temporal muscles atrophy. This may cause difficulty chewing, opening the mouth, pain, and enophthalmos. It is important to differentiate the causes of this problem (see ch. 354).

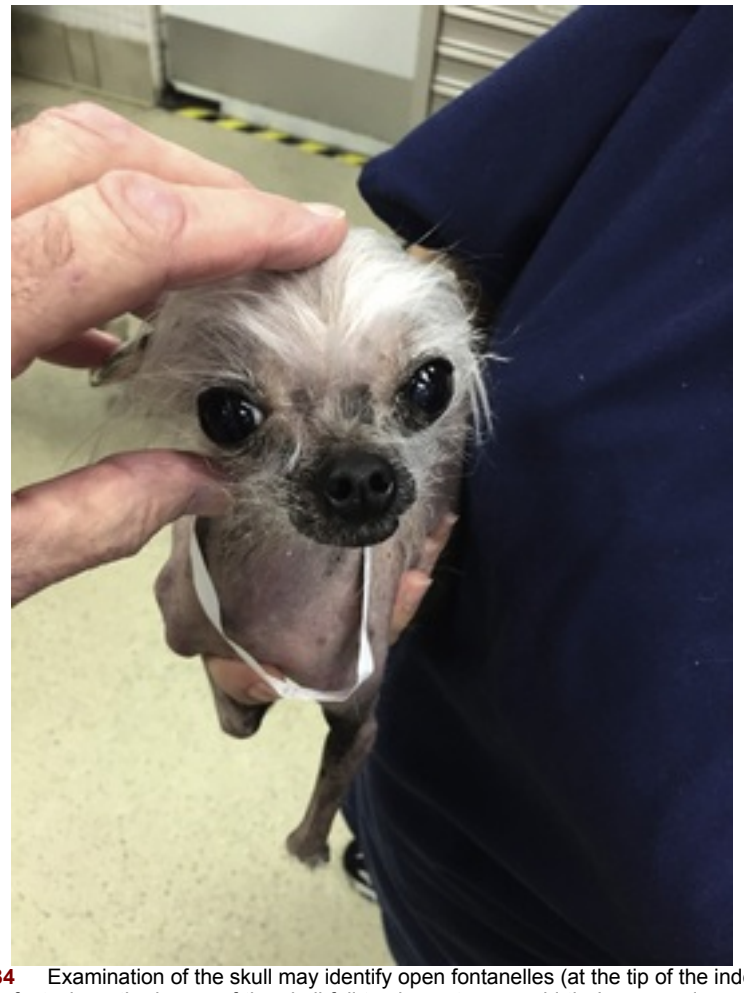

FIGURE 2-34 Examination of the skull may identify open fontanelles (at the tip of the index finger), a congenital defect where the bones of the skull fail to close at or near birth. In young dogs, this may be associated with clinical signs of hydrocephalus. In this 12-year-old Chinese Crested Dog, there were no problems during her lifetime associated with the open fontanelles. She did present for signs of unrelated mitral valvular cardiac disease at a younger age than would normally be expected.

Airflow through the nostrils can be assessed quickly using a stethoscope and contralateral compression of the nares. One may utilize a wisp of cotton in front of each nostril to assess airflow or have the pet breathe onto a metal surface (e.g., a counter top in most examination rooms) or glass microscope slide and observe for fogging as evidence of nostril patency. While seemingly basic, the results of such examinations can be challenging.

Examination of the ears (pinnae and ear canals) is expected by the client and is an important part of every veterinary physical examination (see ch. 237 and Figure 2-35). Presence of ear mites, inflammation, discharge, or abnormal odor is particularly relevant in the new puppy or kitten. In adult dogs, it is more common but by no means absolute to see ear disease in those with long floppy pinnae that cover the ear canal. An owner may report that a pet has difficulty eating or chewing, but the problem may in fact be caused by pain from one or both ear canals (see ch. 237). Discharge, unusual "yeasty" odor, or discoloration of the canal tissue may be noted (Figure 2-36). Owners are likely to notice abnormal conditions of the pinnae (e.g., aural hematoma). Superficial examination of the ear canal can usually be accomplished in the examination room without difficulty, allowing the veterinarian to discuss chronic ear disease with the owners while showing them any abnormality. Otoscopic examination is indicated if there is significant head-shaking or buildup of debris within the ear canal. Video otoscopy is a preferred technique by some veterinarians to show the caregiver changes in the ear canal (see ch. 85 and Video 2-10). Cats likewise are prone to ear disease, particularly when they are outdoor cats or in a household with many cats. Scratching at the ear is likely to leave them with crusts and excoriations at the base of the pinna. Swabs taken from the external ear canal and observed microscopically best identify ear mites and *Malassezia*. Aural hematomas occur in cats but less frequently than in dogs. Careful cleaning of a dirty ear canal is warranted; however, if it is too aggressive, the tympanic

membrane may be affected, leaving the cat with a short-term head tilt. In either dogs or cats presenting with significant disease of the ear canal, sedation may be required to properly clean and evaluate the external ear canal and the tympanic membrane.

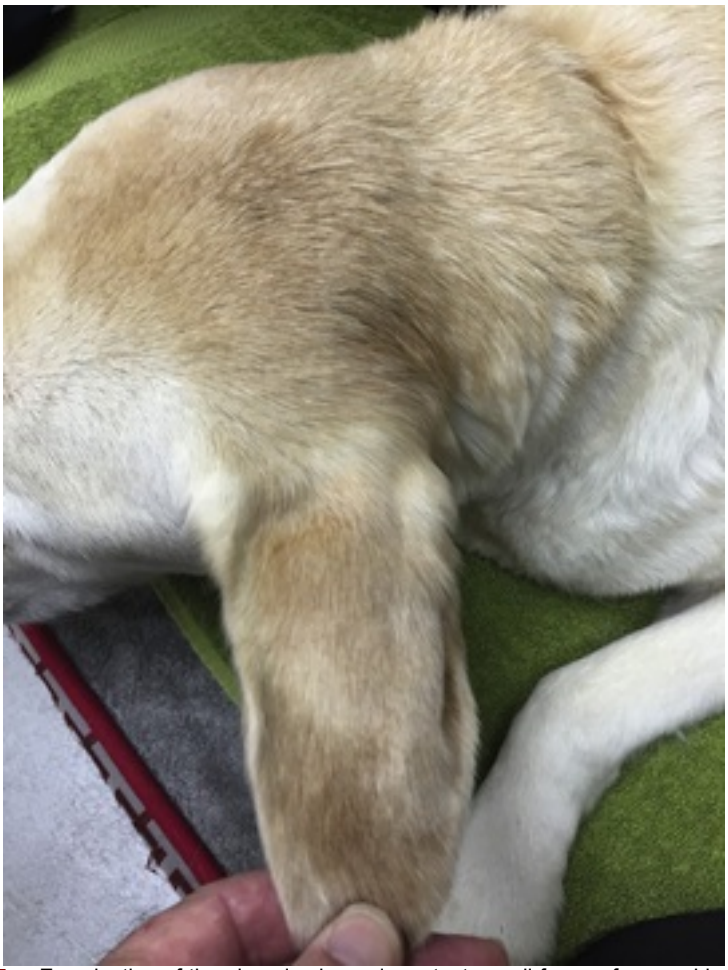

FIGURE 2-35 Examination of the pinna is always important, as all forms of ear problems represent a large percentage of daily clinical practice. This is a normal pinna but slightly dirty due to external otitis that required attention (see Figure 2-36).

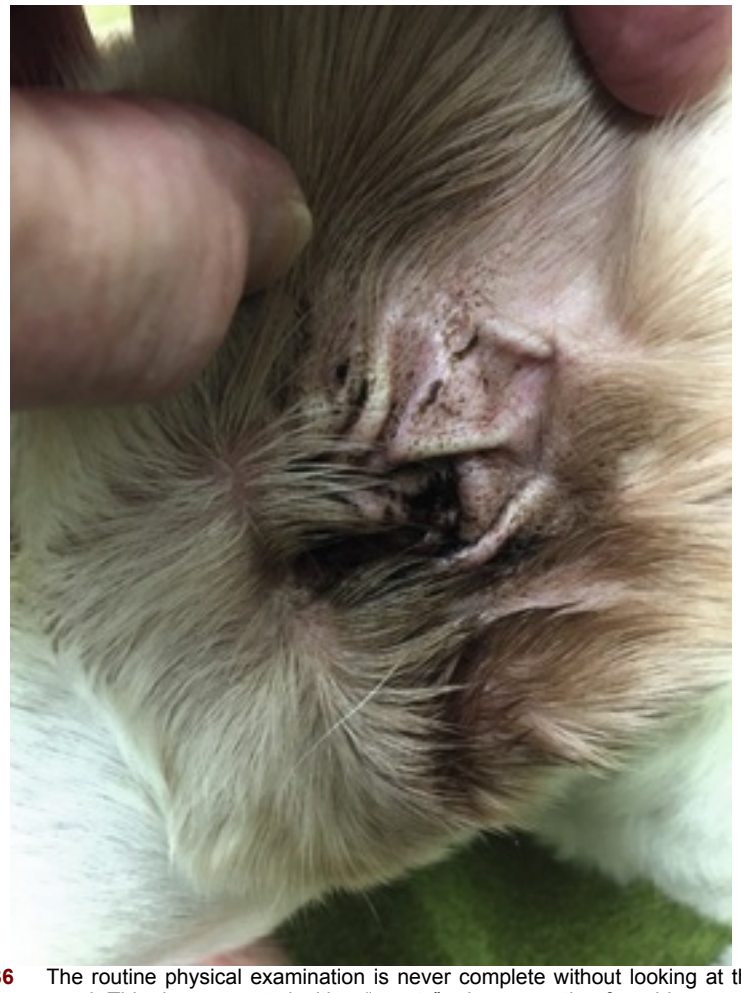

FIGURE 2-36 The routine physical examination is never complete without looking at the ears and the external ear canal. This dog presented with a "yeasty" odor emanating from his ear canals, along with a waxy moist debris suggesting *Malassezia*, which was confirmed on microscopic examination of a slide swabbed with the debris from the ear canal.

Alignment of the jaw bite (Figure 2-37, *A* and *B*), teeth, and gums should be assessed (see ch. 36). Mucous membrane color, capillary refill time, presence of ulcers, or any discoloration in the oral cavity should be checked. The teeth are examined for calculus, fractures, displacement, or discoloration. Abnormalities, including missing or persistent deciduous teeth, are recorded and mentioned to the owner. Drooping of the tongue to one side suggests a loss of teeth in that part of the mouth (Figure 2-38). Signs of dental wear due to fence biting or rock chewing should be noted, as well as any resulting sensitivity. Gingival hyperplasia, masses, gingivitis, foreign bodies or ulcers may correlate with clinical signs. During the first-time puppy or kitten examination, evaluation for cleft palate or other congenital defects is required. With an uncooperative or fractious animal, examination of the oral cavity can be a daunting procedure. When the pet resists such an examination, removing the pet from the owner often allows a more complete examination without difficulty. Special care is required for aggressive dogs and may require sedation. If drooling or a behavioral change is mentioned, *concern for a rabid patient is always paramount.*

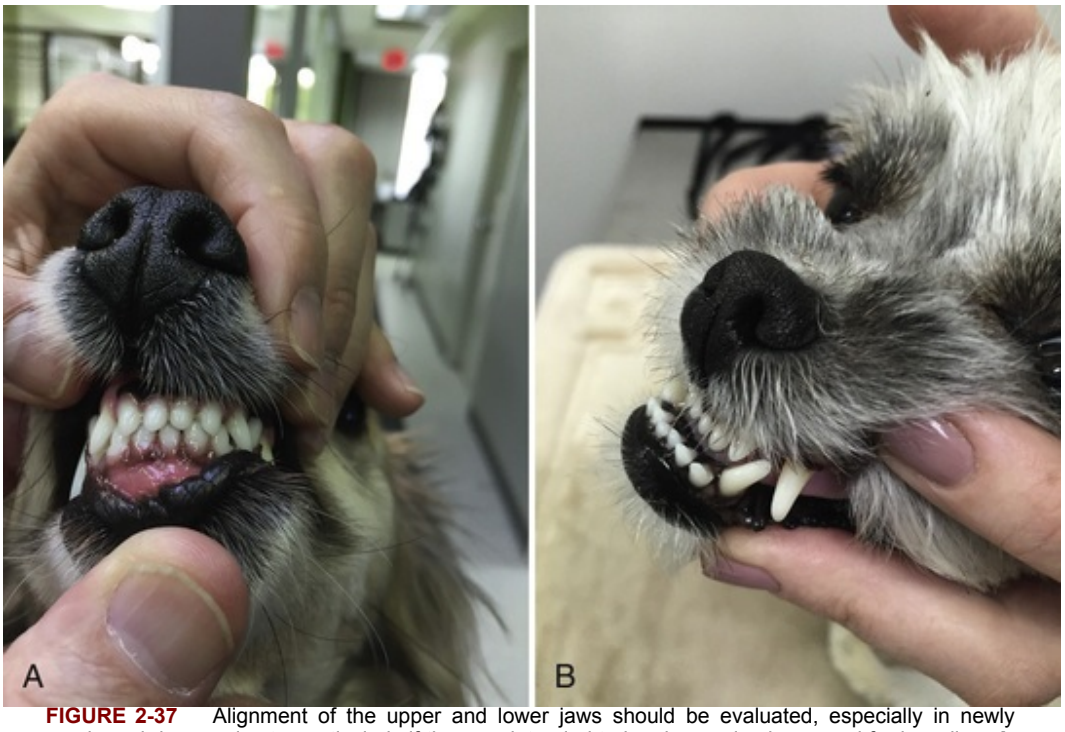

FIGURE 2-37 Alignment of the upper and lower jaws should be evaluated, especially in newly purchased dogs and cats, particularly if they are intended to be show animals or used for breeding. **A,** A normal bite is shown in this young dog, whereas **(B)** this dog has a maxillary brachycephalic bite (prognathism) that is already impeding bone growth and formation. The owner should be made aware of such abnormalities at this time, since in many breeds of dogs and cats, such a condition would eliminate them from being shown.

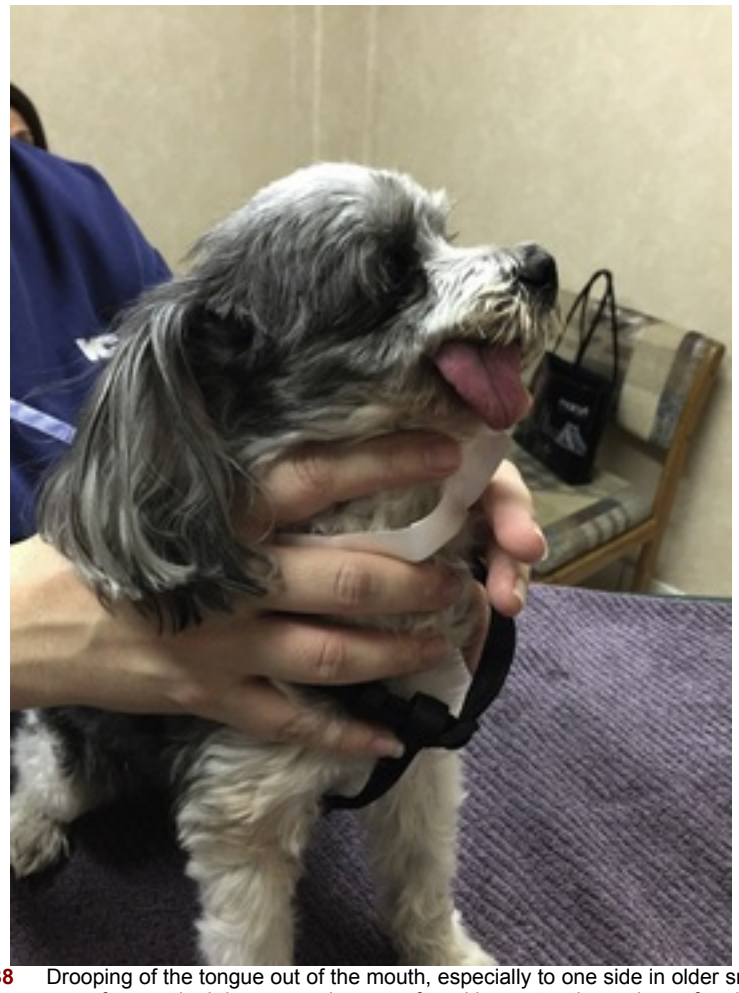

FIGURE 2-38 Drooping of the tongue out of the mouth, especially to one side in older smaller breed dogs and cats, occurs frequently. It is commonly seen after either extraction or loss of major teeth that hold the tongue in place.

Evaluation of the pharyngeal region is limited to external palpation during the physical examination. In some dogs and rarely cats, pressing down on the base of the tongue with an index finger when the animal's mouth is open allows visualization of the tonsils and oropharynx. However, complete visualization is rarely possible. If there is indication of an abnormality in the pharyngeal or laryngeal region, a more thorough examination under sedation may be indicated. The tongue should be elevated (using dorsally directed pressure with the thumb externally, between the mandibles) to assess the sublingual region, such as for masses (see Figure 2-27) in dogs and cats and linear foreign bodies in cats. This type of visualization and assessment of the sublingual area should be a component of every physical examination. The laryngeal region should be checked for sensitivity, pain, or masses or institution of the gag reflex. Detection of visible or palpable deformities and monitoring of the laryngeal apparatus may yet be possible without sedation. Palpation for changes in the salivary glands and the submandibular lymph nodes is important and it is equally important to distinguish between these two organs. Enlargement of the submandibular or sublingual salivary glands is particularly important when there are signs of localized pain or chronic drooling.

Continuing to the ventral cervical region, the veterinarian evaluates for masses, tracheal sensitivity, lymph nodes and the thyroid gland (normal thyroid glands are not usually palpable in dogs and cats). In the cat, noting a "thyroid slip" as the examiner gently moves his/her finger along the trachea just caudal to the thyroid cartilage best identifies an enlarged thyroid. At the thoracic inlet, the clinician palpates for pre-scapular lymph node enlargement, crepitus (subcutaneous air leakage), or masses. Gently palpating the trachea at this time often allows the veterinarian to incite a cough (Video 2-11), which may be the cause for the pet being brought in for an examination (see ch. 241). Asymmetry of the thorax (scapulae, muscles, rib cage, masses, or fat accumulation) should be correlated with signs, as should kyphosis or sternal deformities. Breathing difficulty can be associated with changes in the appearance of the rib cage. Fluid accumulation in the thoracic cavity (see ch. 244), significant pleural or pulmonary disease, and some muscle disturbances may

cause the rib cage to feel or appear abnormal. Congenital thoracic deformities may cause respiratory signs. Peritoneopericardial diaphragmatic hernia (PPDH) (see ch. 254) may be associated with deformities of the xiphoid region of the sternum, such that the examiner can insert a finger into the thoracic cavity and sometimes actually touch the heart (Figure 2-39).

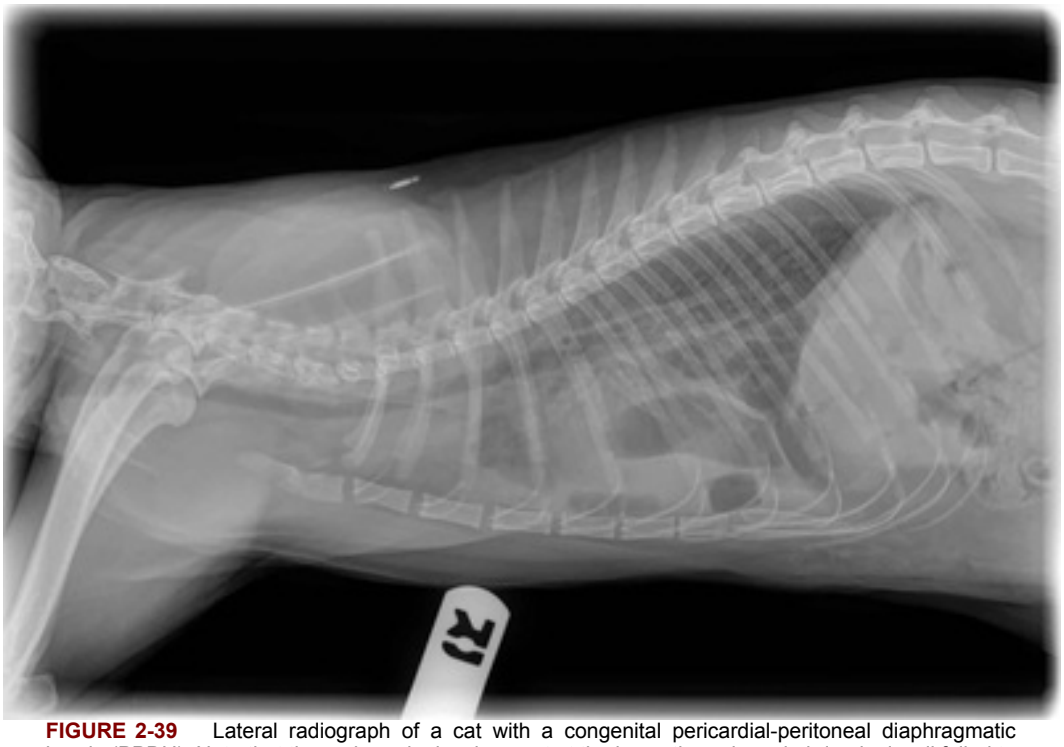

FIGURE 2-39 Lateral radiograph of a cat with a congenital pericardial-peritoneal diaphragmatic hernia (PPDH). Note that the embryonic development at the lower thoracic and abdominal wall failed to close, leaving an opening at the xiphoid where the abdominal contents slip through and into the thoracic cavity. In some cases the examining veterinarian can insert a finger from the caudal ventral xiphoid and push it forward into the thoracic cavity and actually touch the beating heart under the skin.

My preference (SJE) is usually to complete the entire physical examination before auscultating lung and heart sounds (Video 2-12). These portions of the physical examination are described in ch. 55 and 246. When palpating the thorax, the examiner should notice the location of the apex beat of the heart (point of maximal intensity [PMI]). Normally this is over the left fourth to sixth intercostal space at the level of the costochondral junction. Deviations are consistent with cardiac or thoracic cavity issues. Similarly, palpation of a cardiac "thrill" is indicative of an extremely loud heart murmur (higher than grade 4/6). Cardiac thrills should be identified and correlated with the heart sounds and clinical signs. Heart sounds should be identified in terms of rate, rhythm and presence or absence of a murmur, in addition to other abnormal sounds including whoops, clicks, ejection sounds, gallop sounds and splitting of the first and/or second heart sounds (see ch. 55).

Normal lung sounds vary from breed to breed depending upon conformation of the head, neck and thorax of the pet. Normal lung sounds are quiet, non-wheezing, non-crackly inspiratory sounds that are soft, smooth and pure, equal in intensity across the right and left thorax. They are devoid of obstructive sounds, wheezing, or noisy and of unequal sounds of air being pulled into the lungs. Forced open-mouth breathing is not normal except in brachycephalic breeds where they can be very noisy, yet still normal. To some degree it would be correct to say that normal inspiration is usually associated with comfortable inspiratory sounds without tachypnea or dyspnea unless the animal is anxious, hot or excited. They are followed by smooth expiration without undue crackles, wheezing or distinct grunting. Harsh, open-mouth breathing with lower-airway inspiratory stridor, upper airway inspiratory stridor (upper airway obstruction [UAO]) may be typical of chronic lung disease, brachycephalic breathing (Videos 2-13A, 2-13B, and 2-13C) or laryngeal paralysis, especially in larger breeds of dogs (Videos 2-14A and 2-14B). This frightening sound is usually more pronounced with excitement and diminishes as the dog relaxes and quiets down. It can, however, progress to a more advanced state requiring aggressive therapy (see ch. 238, 239, and 241). There are significant

differential diagnoses for UAO (see ch. 238 and 239). Unless laryngeal paralysis is associated with an advanced state, this abnormal respiratory sound is associated with normal gingival mucous membrane and tongue color. Laryngeal paralysis in cats has a very different appearance and sound unique to this species and not at all similar to that of larger breed dogs. It often is not associated with dyspnea but the sounds do bring the client to the veterinarian because of their odd nature.

Progressing caudally to the abdomen, the examiner first should note whether the abdominal wall is pumping rapidly, a possible sign of anxiety, tachypnea, or dyspnea. Tachypnea, dyspnea or abdominal breathing should be observed while standing back from the pet, rather than via auscultation (see ch. 28).

The general appearance of the abdomen should first be assessed. Distended, tucked up, muscular and firm, painful, tense, soft and doughy are all terms used for describing findings from abdominal palpation. Apparent pain should be characterized regarding location and severity. This portion of the examination requires gentle but firm pressure using both hands and moving from dorsal to ventral and cranial to caudal. Adequate palpation includes utilizing ipsilateral fingers in line or touching with thumbs aligned as the abdomen is carefully traversed. This recommendation is important in order to avoid attempting to "hold" a pet in place with thumbs on the spine, where accidental compression in a dog with back pain may be misinterpreted as being abdominal. Some pets do not appreciate abdominal palpation, and may display their displeasure by tensing the abdomen or otherwise avoiding palpation and this should not be mistaken for a pathologic process (Video 2-15).

Examination of the abdomen, as with all other parts of the body, should be performed systematically (Video 2-16). Examine both the abdomen and spinal column independently, before progressing with deeper palpation. This allows the clinician to avoid being misled by apparent sensitivity in one area that is, in fact, derived from another. Assessing the mammary glands and surrounding tissue can be completed during the introductory portion of the physical examination, as noted above, or immediately prior to deeper abdominal palpation. Mammary masses are usually easily palpated but can be confused or mistaken for subcutaneous lesions. Small masses may not be noted unless one dedicates a few moments to carefully assess the area. Moving fingertips up and down the mammary chain on both sides permits the examiner to note discrepancies in the tissue. Likewise, significant enlargement of the sublumbar lymph nodes may be noted. In the male, changes in and around the prepuce may be identified. Preputial discharge (smegma), a small amount of a thin yellowish color that is normal, might not be readily seen unless the pet is placed in lateral recumbency (Figure 2-40). Extruding the penis to appreciate changes in the mucosa or sheath of the penis (Video 2-17) may explain abnormal findings or a history of chronic licking or discharge that the owner may be concerned about and that is normal in most adult male dogs. The presence of the os penis in dogs should allow the penis to be easily and painlessly extruded and evaluated. In the male cat (Video 2-18), evaluation of the penis and its surrounding area is important, particularly in cases of suspected feline lower urinary tract disease. Neutered tomcats have small to no "spines" present on the penis, in contrast to the obvious spines seen in intact tomcats (Figure 2-41).

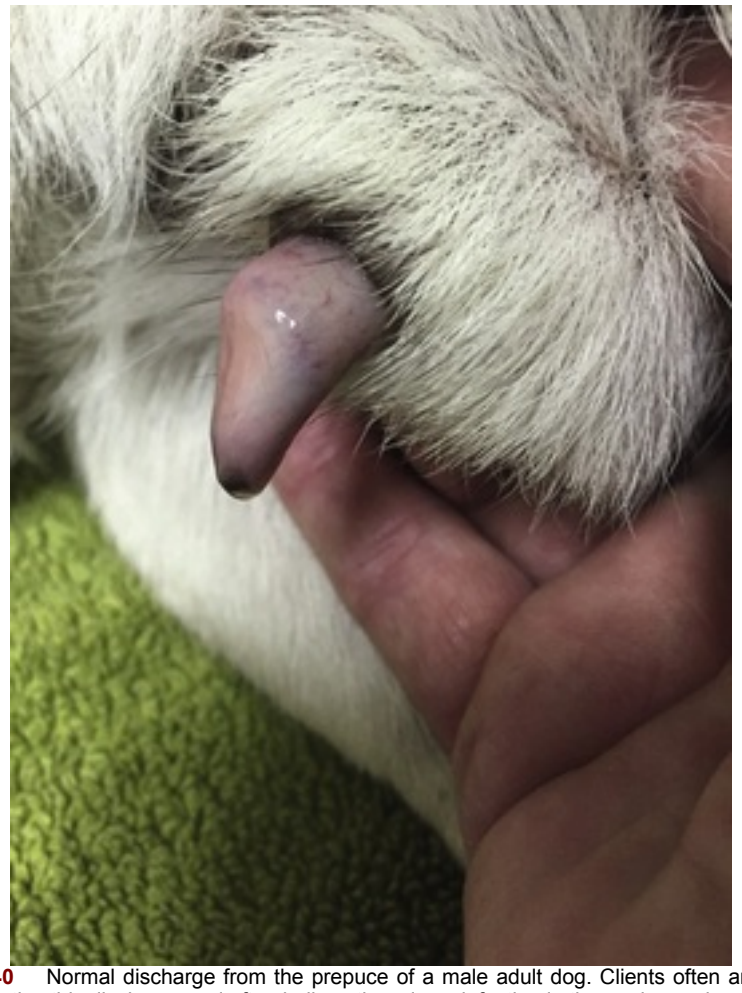

FIGURE 2-40 Normal discharge from the prepuce of a male adult dog. Clients often are disturbed when they notice this discharge and often believe there is an infection in the penis or urinary system.

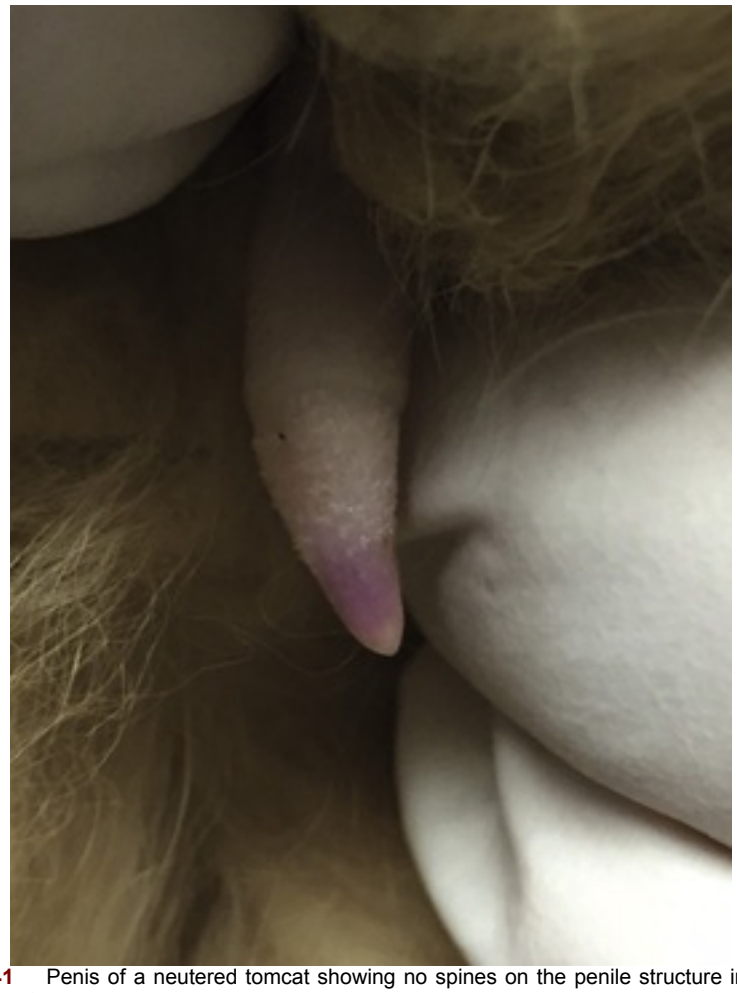

FIGURE 2-41 Penis of a neutered tomcat showing no spines on the penile structure in contrast to an intact tomcat.

Palpation of the abdomen is an individually determined technique. I (SJE) like to examine animals both from behind and from the side. When examining the abdomen from behind, I am able to palpate symmetry, one or both kidneys, and identify mid-abdominal masses (normal or abnormal). Lateral palpation provides another perspective regarding any structure: liver, spleen, bowel, bladder, prostate, etc. Occasionally it is helpful to have an assistant pick up the pet (Figure 2-42) and allow it to stand on the hind legs so that the abdominal viscera or free fluid falls caudally, permitting yet another perspective.

FIGURE 2-42 Lifting the pet up so that the abdominal organs slide to the caudal aspect of the abdomen sometimes allows the examiner to be more thorough in palpation of the abdominal organs or identifying the presence of free abdominal fluid that has collected at the most ventral level.

Distention of the abdominal cavity (see ch. 17) requires attention. In general, there are four major causes of abdominal enlargement: fluid, fat accumulation, muscle laxity, and abdominal organ enlargement (see Figure 2-9). The examination begins with gentle ballottement to determine whether enlargement is likely to be associated with obesity, pregnancy, fluid accumulation, one or more masses, intestinal obstruction, muscle weakness, or poor muscle condition (Cushing's disease, see ch. 306). Correlating the findings of this examination with other history and laboratory tests allows the veterinarian to consider potential causes. It is generally easier to perform a complete abdominal palpation on cats and smaller dogs than on large dogs. In cats, it is frequently possible to palpate the intestines, spleen, both kidneys, and bladder. In larger companion animals this may not be as easily accomplished, but enlargement of abdominal organs, masses, and fluid collection should still be apparent. In cats, palpation of an enlarged spleen often is a sign suggesting mast cell disease, lymphoma, or another neoplastic process. In dogs, a large, irregular splenic margin strongly suggests hemangiosarcoma or hematoma, although other causes of splenomegaly must be considered (see ch. 206 and 347). Differentiation from other abdominal masses can be done initially through the physical examination and later via imaging.

Pain on palpation of the abdomen is a significant finding. Pain requires the clinician to distinguish tensing of the abdomen in a normal frightened patient from referred spinal pain, abdominal pain or generalized pain and discomfort. Pain correlated with abdominal palpation may in fact be referred spinal pain and should not be misinterpreted, which may lead to a misdiagnosis. The acute abdomen needs correlation with laboratory testing and clinical signs. Pain should be localized, if possible, as cranial, mid-abdominal, caudal, or generalized. Palpation for masses and the detection of enlarged viscera comprise an art that is not replaced by more sophisticated, expensive, and complicated tests. Pain in the abdomen is a clear indicator for further testing, such as radiography, sonographic imaging, and laboratory analyses. It also must be correlated with the clinical history. Malaise, failure to move or change position, belching, fever, and nausea may be explained

by abdominal or back pain. In contrast, a fractious cat whose ears are back and whose pupils are dilated, and who seems agitated on palpation may simply be displeased with being examined (Figure 2-43).

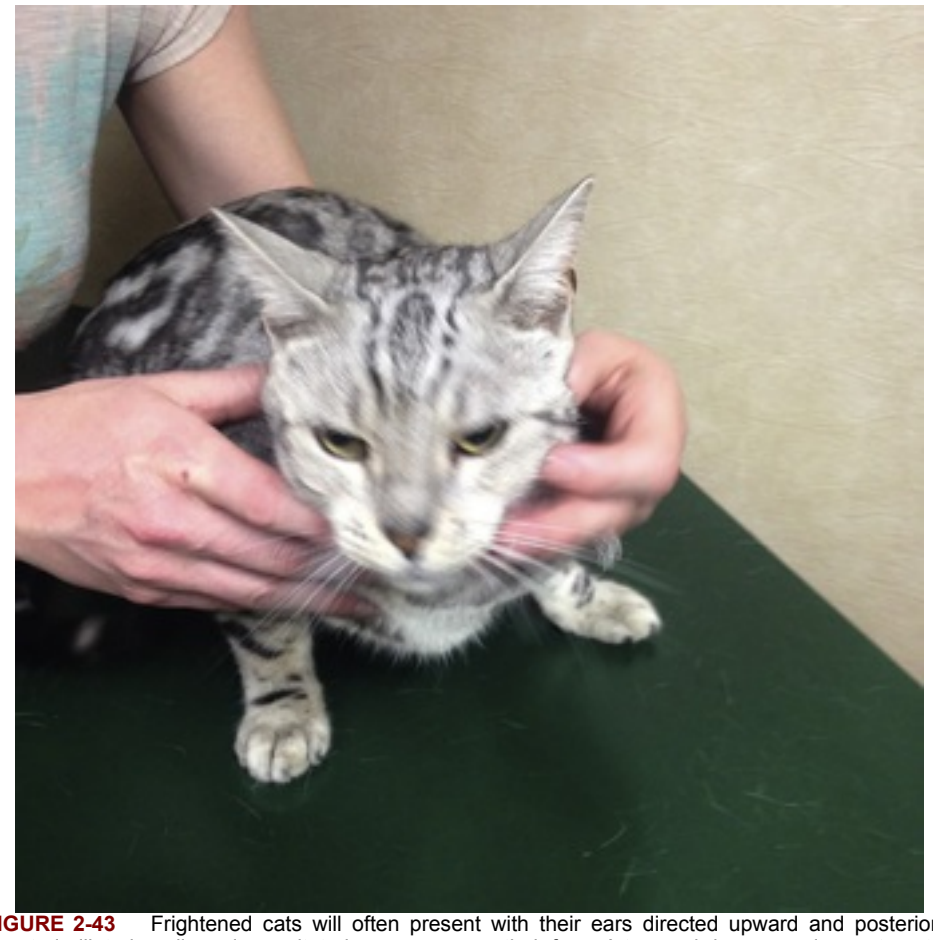

FIGURE 2-43 Frightened cats will often present with their ears directed upward and posteriorly directed, dilated pupils and an agitated appearance on their face. A tense abdomen, and resentment of palpation, should not automatically be interpreted as evidence of abdominal pain in these cases.

Distention of the abdomen must be assessed in the context of owner observations and additional factors. These factors include, but are not limited to: age, breed, gender, neuter status, clinical signs, palpable (balloting) fluid collection, pregnancy, neurologic status, obesity and the presence of masses. Urinary bladder distention should be palpable and defined as normal or distention from abdominal disease or neurological distention (i.e., upper or lower motor neuron). Both kidneys are not always palpable in healthy dogs. Their left kidney is easiest to feel while the right might only be palpable caudally or when it is enlarged or displaced. When bilaterally enlarged, both kidneys in dogs may be palpated. When an otherwise healthy dog is obese, one may not feel either kidney. Both kidneys are usually palpable in cats. The presence of a large or painful prostate in a dog should be noted and correlated with clinical signs. Symmetric enlargement of the fat pads and muscles of the lumbar region ("love handles") are commonly seen in an older pet, particularly if it is gaining weight. The "love handles" are often of concern to the owner in an otherwise normal adult aging dog (Figure 2-44).

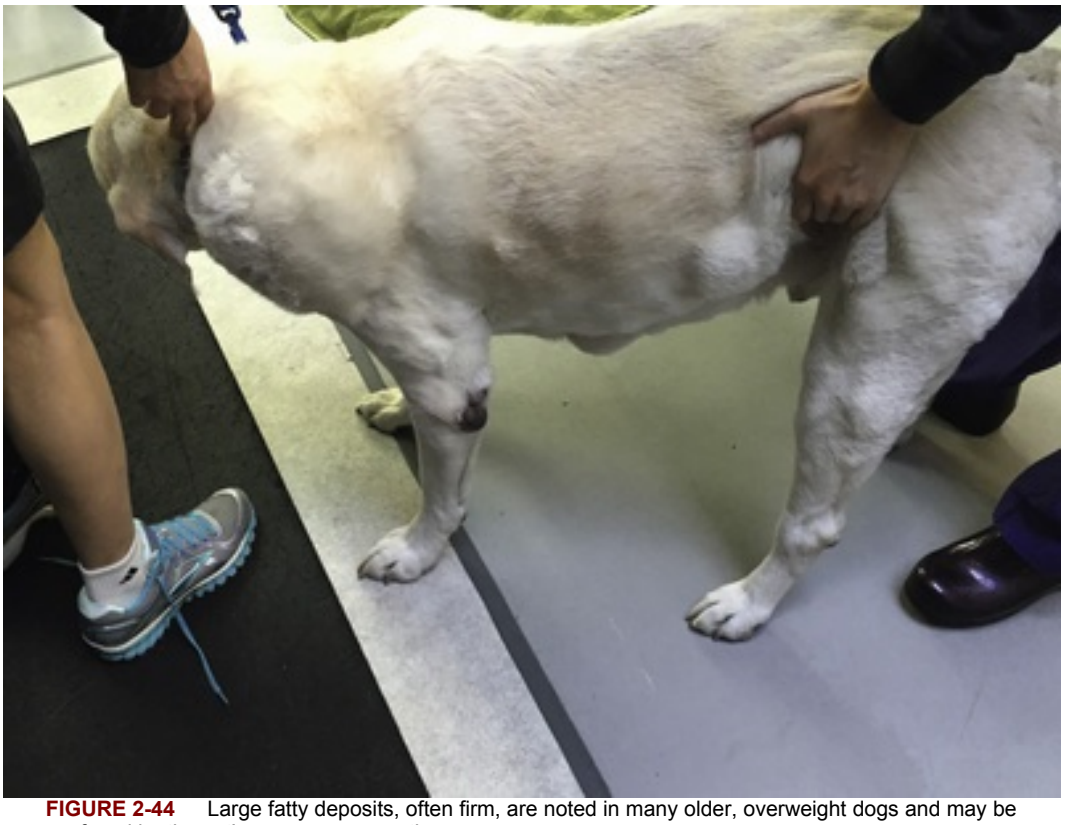

FIGURE 2-44 Large fatty deposits, often firm, are noted in many older, overweight dogs and may be confused by the pet's owner as a growth or mass.

Rectal examination is a component of palpating the caudal abdomen and should be part of every physical examination in medium- and large-breed dogs (Figure 2-45). While examining the rectal region and tissue, the clinician should check the animal for evidence of constipation, obstipation, or generally dry, hard stools (see ch. 42). Such problems lead to difficulty defecating. The perianal region should be examined for fecal staining, anal sphincter integrity, masses and, particularly when straining to defecate occurs, for perineal hernia, either unilateral or bilateral. Perineal hernias (Videos 2-19A and 2-19B) are detected by lateral deflection of the index finger immediately after entering the rectum (i.e., no farther than the first or second joint of the inserted finger). If the examiner probes too deeply past that point, this important lesion will be missed. Rectal prolapse must be differentiated from ileocolic intussusception because of different etiologies and treatments. Prolapse is associated with the inability to pass a blunt instrument or digit alongside the everted viscus per rectum beyond the level of the pelvic inlet. Perianal fistulas are readily identified on the physical examination; however, they are often so painful that examination of this area is made difficult without sedation. Perianal masses (Figure 2-46) should be evaluated for changes in size, and appearance. During this portion of the examination, the tail is checked for skin lesions and for pain on rotation and extension/dorsiflexion. Animals experiencing tail pain, and occasionally urinary and/or anal sphincter problems, should be examined with injury to the tail region in mind. Tails that have been caught in doors or pulled aggressively (more common in the cat) can be associated with neurologic problems involving the urinary bladder, anal sphincter, and/or the ability to move the tail.

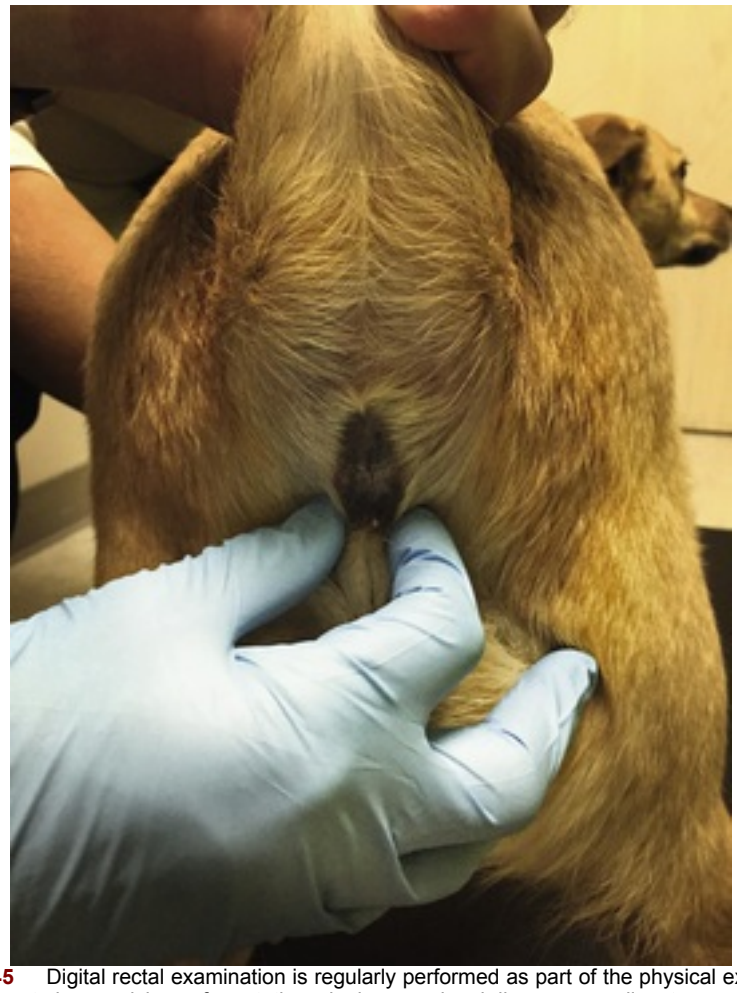

FIGURE 2-45 Digital rectal examination is regularly performed as part of the physical examination if there is reason to be suspicious of prostatic, colonic, or perianal disease as well as to examine the anal sacs and sphincter. Initial insertion of a gloved, lubricated finger should be gentle and limited to a short insertion to evaluate the anal sacs, rectum and the perianal tissue. Deeper palpation after that is useful for evaluating the colon, prostate gland and occasionally the aortic bifurcation.

FIGURE 2-46 Perianal masses are likely to be painful, irritated and often covered with stool, making them difficult to examine without being gently but well cleaned. This cat presents with an ulcerated mass just ventral and to the right of the anal sphincter.

In older male dogs or when signs suggest lower bowel dysfunction, lower urinary tract problems, prostate concerns, or hind end disorders of an orthopedic or neurologic nature, the findings on rectal palpation gain even greater importance. With the increased use of abdominal sonography, palpation gains value because lesions within the pelvic canal often do not image well. Prostatic abnormalities are likely to be palpated per rectum in all but larger male dogs. Correct palpation of the prostate is done with the index finger of one hand in the rectum while the other hand, externally, is providing dorsocaudal upward pressure at the level of the caudal abdomen to elevate the prostate gland toward the palpating finger. This is especially useful for larger dogs and/or the palpator with a short index finger. A normal rectal examination (see ch. 278) identifies a symmetric, bilobed, nonpainful, rubbery-textured prostate with a median raphe that clearly separates two lobes. Palpation of the surrounding tissue should evoke no pain or irregularity along the canal wall or the bony pelvic structure surrounding the gland. The urethra is a thin, flat tube usually palpable above the pelvic symphysis. A thickened, ropy urethra may be felt in cases of urethritis or transitional cell carcinoma. Rotation of the hand so the palm points dorsally then allows the examiner to palpate the aortic trifurcation and aortic pulse, and may rarely allow the palpation of sacral (sublumbar) lymph nodes if very enlarged. Rotation of the wrist in the other direction (45-90 degrees past midline) is warranted, to identify masses or other abnormalities within the pelvic canal.

With the index finger in the rectum, the examiner palpates the anal sacs at the 4 and 8 o'clock positions to determine whether they are enlarged and if they can be readily expressed. The ease with which these sacs can be expressed and the type of fluid released aids the evaluation for anal sac disease. Many clients worry considerably about “full” anal sacs, and it is important to identify problems if they exist. It could be necessary to alter a diet's fiber content in some dogs to improve natural anal sac compression and expression with each bowel movement. Serious anal sac disease does occur in cats, albeit uncommonly, and expression from outside the anus and rectum is appropriate in small dogs and cats (see Figure 2-45). The rectal tissue should

be neither rough nor painful and no blood should be noted on the examination finger when removed from the anus. Note the presence of mucus or blood specks (red or black) particularly if there are complaints regarding stool appearance at home.

The testicles and scrotum should be examined in the intact male for pain, skin lesions, and variability in testicle size and shape. The scrotum of a neutered male should be examined for masses or ulcerations. The presence of one or no testicles in an intact male is an important diagnostic finding. Retention and/or neoplasia of one or both testicles may correlate with the presenting clinical signs. In the puppy examination, the presence or absence of testicles may indicate a congenital defect and must be identified to the pet owner because the purchase agreement may need to be reviewed. It is important to note the presence of an inguinal (flanker) testicle because showing and breeding would not be allowed and the pet may be infertile. Explanation of such a finding for the new puppy owner is relevant, particularly if the pet was purchased for breeding purposes.

In females, examination of the vulvar region is important in determining the presence of a discharge, the state of estrus, or the presence of skin conditions that may be responsible for licking or irritability of the hind region. Asking questions that relate to the timing of the last or latest heat cycle may elicit insightful information relevant to pseudopregnancy or pyometra. (Remember that not every spayed female has been completely spayed and estrous cycles or stump pyometra remain in the differential diagnosis until proven otherwise.) Vaginal swabs taken to evaluate the state of the mucosa are a quick, easy way to determine the presence of pus or red cells in the canal as well as the hormonal status of the bitch. Examination of the hood region (Video 2-20) may provide a cause for odors and irritation due to the accumulation of mucus or pus. Females usually tolerate gentle digital vaginal palpation, regardless of neuter status or stage of estrous cycle. However, in healthy spayed dogs, vaginal palpation is not a routine component of the physical examination. Some disorders are quite painful, requiring additional restraint or sedation for digital examination. Examination of the mammary glands (Video 2-21) should be thorough, moving up and down both right and left chains probing for masses, irregularities and evidence of enlarged glands. Enlarged glands producing small amounts of fluid may be an indication of a false pregnancy, a near term pregnancy or an infection in that gland. Masses should be noted as to size, shape and texture (Figure 2-47) so that they may be re-examined on the next visit. Hot, ulcerated or rapidly growing masses should be considered for surgical removal.

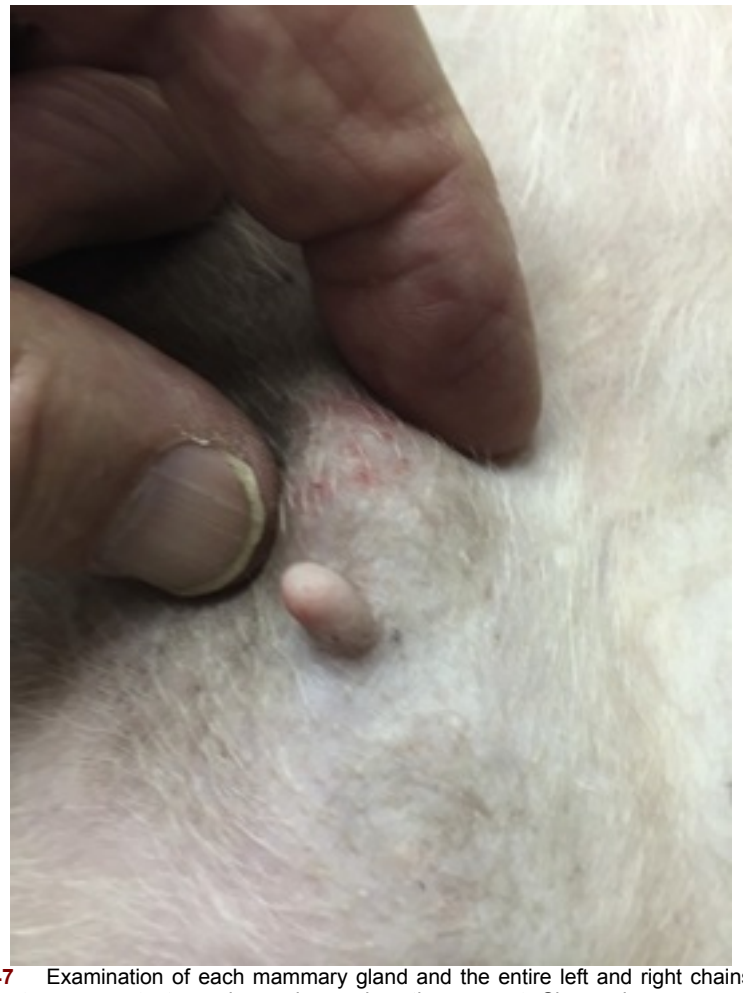

FIGURE 2-47 Examination of each mammary gland and the entire left and right chains should be completed; note masses, texture, size and any ulceration present. Size and appearance should be noted in the record for comparison at the next health care visit. This firm irregular nodule is measured and noted in the record.

Prior to examining the limbs, particularly in cases of lameness, the examining veterinarian evaluates the mobility and flexibility of the head and neck (see ch. 259 and Videos 2-22A and 2-22B). Particularly in larger breeds of dogs, cervical conditions can cause neck-guarding, failure to thrive, with nondescript signs of acute painful crying, lameness, and malaise. Intermittent or recurrent problems may not be immediately obvious on the physical examination. Dogs that are difficult to examine or animals with acutely painful conditions may be better evaluated utilizing conscious sedation.

Rear leg pain, weakness, and wobbliness may be signs of a musculoskeletal or neurologic disorder, such as cervical disease, thoracolumbar disease, and/or lumbosacral disease. The physical examination should include compression of the tissues along the spinal column and the lumbosacral region (Videos 2-23A, 2-23B, 2-23C, and 2-23D). Sensitivity alone may be inadequate grounds for making a diagnosis and may only point to one of several conditions in the differential diagnosis. Neurologic changes, including postural tone, conscious proprioception deficits, or muscle atrophy, assist the process of evaluating disease states (see ch. 259 and Figure 2-48; see also Video 2-23).

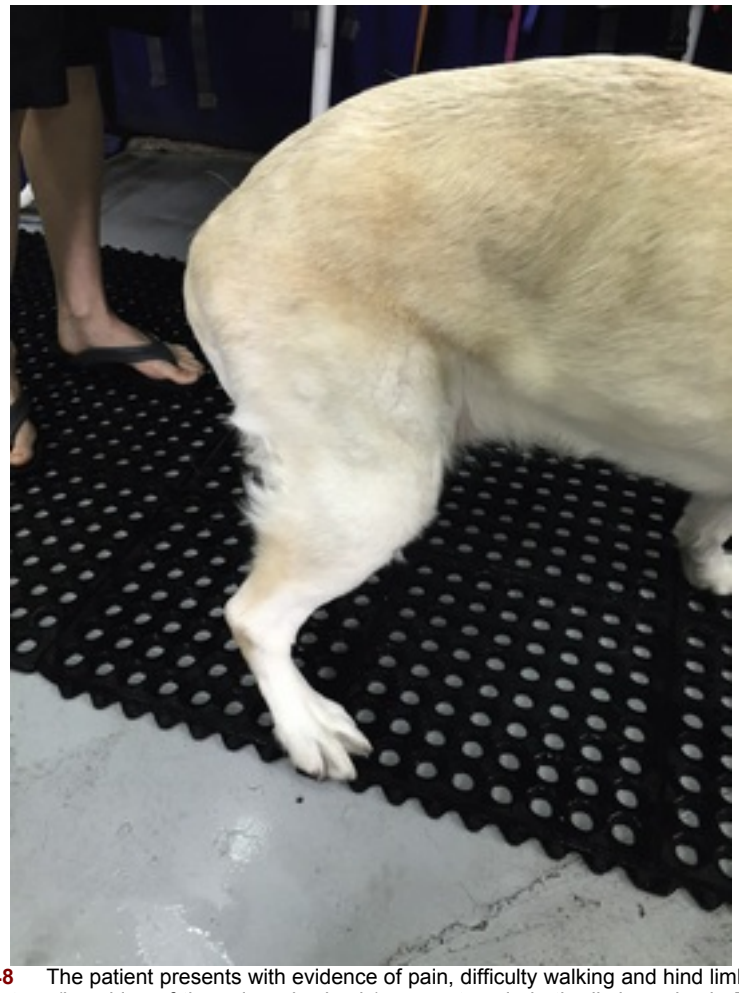

FIGURE 2-48 The patient presents with evidence of pain, difficulty walking and hind limb weakness. His body posture (hunching of the spine—kyphosis) suggests pain in the limbs or back. Deep pain is present, as are patella and toe pad withdrawal reflexes. He is a candidate for a complete neurological and orthopedic examination to establish a differential diagnosis.

Evaluation and examination of the limbs, including bilateral femoral pulses, lymph nodes, joints, footpads, and interdigital regions, can reveal important clues to the presence of medical problems. Joint disease, often silent or less than immediately obvious, is easily overlooked unless specific attention is paid to joint swelling (Figures 2-49 and 2-50) or discomfort. Ch. 353 provides a summary of the orthopedic examination along with figures that demonstrate most common skeletal deformities of concern to the internist. The examiner should flex each of the patient's carpi with moderate pressure to assess for signs of joint pain that would otherwise not be recognized; animals with nonspecific signs, especially suggesting intermittent neck or back pain, may in fact be found to have polyarthritis (see ch. 15 and 203). It is important to observe symptomatic cats out of their carrier, on the floor in a safe, escape-proof room. Many cats will not ambulate in the veterinary clinic and it is good to suggest that the owner video such abnormalities at home when the cat is less inclined to remain static (Video 2-24). Swelling, heat, and pain in one or more joints can explain many signs, including lameness, malaise, and fever. Swelling of the adjacent peripheral subcutaneous tissues provides reason for further evaluation. Claudication, painful or non-weight-bearing lameness directs the examiner to the affected limb. Thorough examination of the limbs for differentiation of warmth, pulses, or swellings may yield a direct clue to the cause of lameness. Embolization is usually associated with pain when the embolism is arterial in contrast to acute paresis with a fibrocartilagenous embolism (FCE). Noting a disparity in the circumference of the joints, muscles of the hindlimb or the presence of atrophy in the shoulders or muscles of the scapula may more readily help to identify the source of the lameness (Figure 2-51).

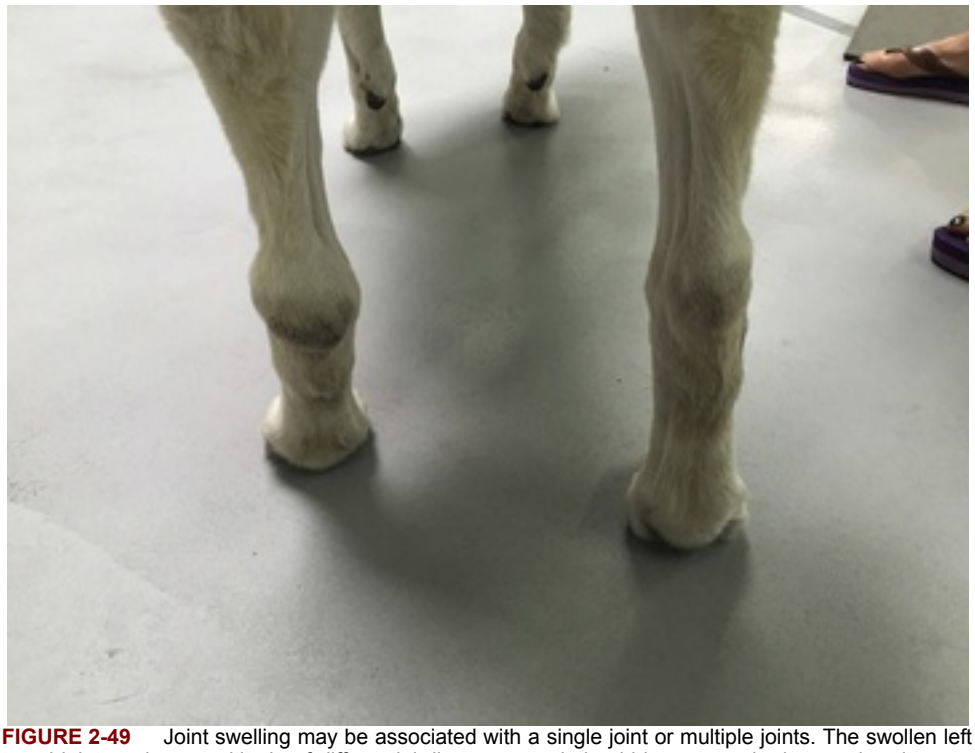

FIGURE 2-49 Joint swelling may be associated with a single joint or multiple joints. The swollen left tarsal joint carries a multitude of differential diagnoses and should be approached as such unless an obvious cause is identified at the time of the physical examination (see ch. 15). This enlarged joint was firm, cool and only minimally painful on palpation and was associated with chronic arthritis with degenerative joint disease. The discoloration of the hair implies that the dog is chronically licking at his enlarged joint suggesting that sensory discomfort is present.

FIGURE 2-50 Measuring an enlarged joint to compare with the opposite limb may assist in following progression of the disease and also helps to identify to the client the initial disproportionate size of the joint. Client follow-up is more likely to be successful if they recognize the difference in joint size themselves.

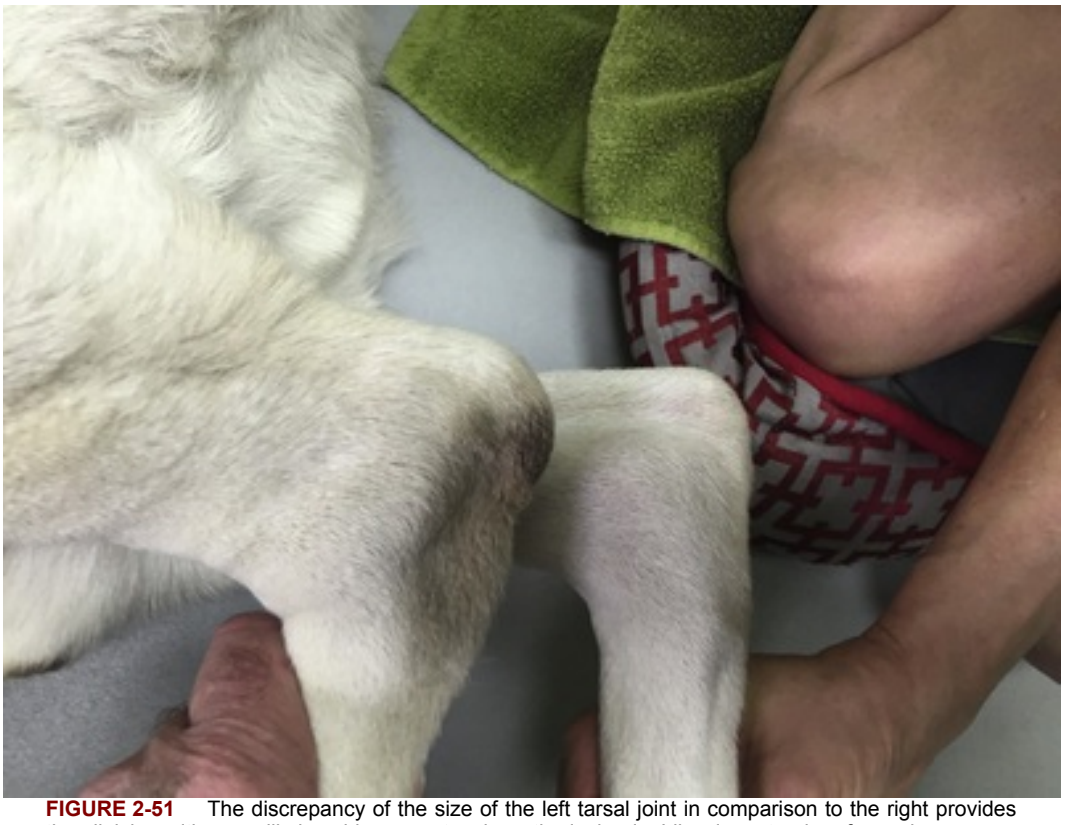

FIGURE 2-51 The discrepancy of the size of the left tarsal joint in comparison to the right provides the clinician with more likely evidence as to where the lesion is. Likewise, atrophy of muscle mass on one side of the body compared to the other may be an indication of disuse or underuse because of pain, nerve damage or discomfort.

Deep palpation of the bony tissue provides information relevant to both medical and orthopedic problems. Taking into account the age and health of the animal is relevant, because some diseases are specific to young, growing dogs (panosteitis), whereas others would be expected in older, overweight dogs (cranial cruciate rupture, osteoarthritis, bone cancer) (see ch. 353). Although a general evaluation of the joints is required whenever lameness is present, joint palpation is always performed with the realization that problems may not be recognized without use of conscious sedation or general anesthesia. Cats are usually easier to palpate than dogs, and larger-breed dogs may be difficult to examine without sedation. Prior to sedation and clinical studies it is important to gait the animal to evaluate pain, lameness or proprioceptive deficits at a walk and a trot (see Video 2-5). It may be advantageous to discuss the benefits of sedation or anesthesia with the client for a more thorough physical examination, radiographs or joint tap (arthrocentesis) (see ch. 15 and 94). Palpation of the hips and evaluation for coxofemoral disease must distinguish this from lumbosacral and stifle disorders. Stifle drawer sign and clicking are indications of internal stifle disorders such as cruciate ligament tears, sprains and meniscal tears. The opportunity to evaluate these findings in greater detail may need to be conducted with sedation. When radiographs of a limb are to be taken, the examiner should exercise the benefit of evaluating both limbs to evaluate the significance of the changes noted by comparing symmetry. Some orthopedic problems, including patellar disease in small to mid-size dogs, are usually identified without sedation (see Video 2-22).

No lameness examination is complete without evaluation of the footpads and interdigital regions. It is of paramount importance to examine these tissues carefully for infiltrating problems, foreign bodies, interdigital cysts, tumors, or footpad lesions (Figure 2-52). Lengthy toe nails, sometimes so long that they curl around and re-enter the skin, can be a cause of significant lameness, easily treated by observation and then toe nail trimming.

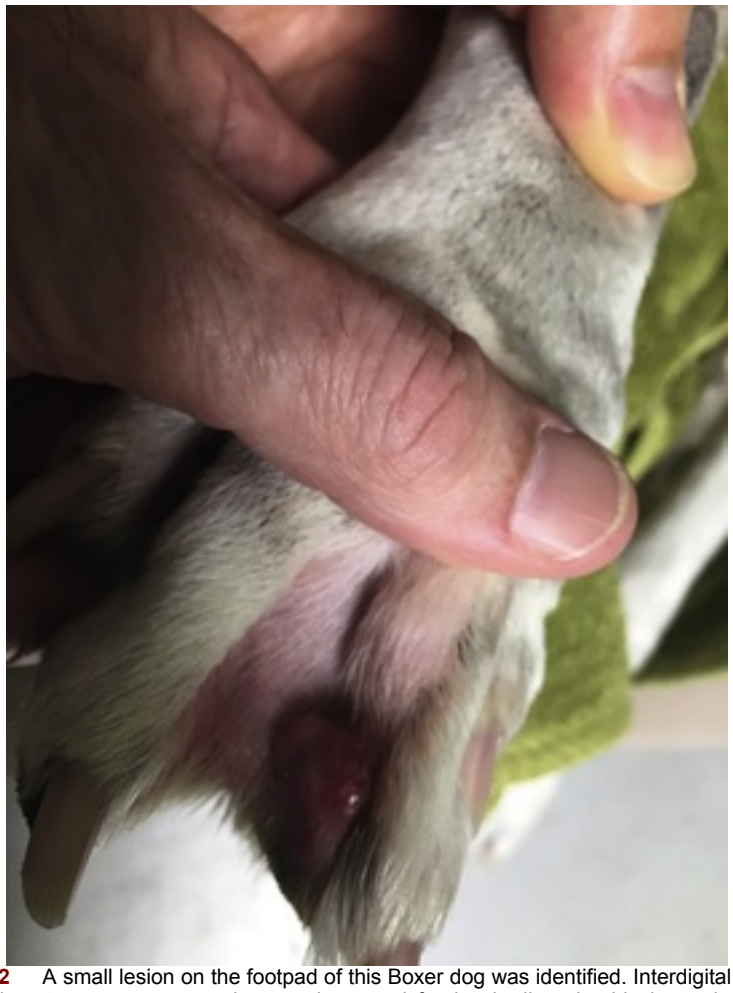

FIGURE 2-52 A small lesion on the footpad of this Boxer dog was identified. Interdigital and footpad cysts, granulomatous masses, neoplasms, ulcers and foreign bodies should always be considered when unidentified lameness is noted.

Completing the Physical Examination

Every hospital has its own set of digital or paper records. This is the time to complete a well-written medical record. The traditional "SOAP" (subjective, objective, assessment and plan) method provides the entire hospital and others with a record of the physical examination, history, findings and the plan for moving forward with the pet's care.

No physical examination is complete until the results are listed in the examination report and an assessment is made of the findings. The veterinarian should identify in the records his or her recommendations for proceeding with the case. It is here that the client or caregiver can once again participate. The veterinarian needs to summarize the findings, note the pertinent points, and identify how care might proceed. Noting the findings alone without recommending a course of action does not complete the process. The examiner should also note in the record, in addition to the subjective and objective findings, the likely rule-outs and tentative clinical assessment. A definitive diagnosis need not be made at this time, but identifying the rule-outs helps to portray a thought process in progress. The owner must be informed of the possible courses of action, the advantages and drawbacks of each, and the estimated cost of such work. If the prognosis is potentially poor or guarded, the examining veterinarian should discuss this with the owner at this point. Clients who fail to "hear" bad news may be very surprised to see that the veterinarian had written the discussion about it in the record one or more times in the course of recordkeeping. From the outset, regularly discussing serious findings with the client ensures better practitioner-client communication. In the plan, the veterinarian should identify the course of action to be followed so that he/she or another DVM may continue the examination process one step at a time if that is how the owner wishes to proceed. From a medical-legal point of view, keeping the client informed and up to date is necessary for maintaining good

doctor-client relations and communication.

CHAPTER 3

Basic Genetics

Kathryn M. Meurs, Joshua A. Stern

Client Information Sheet: Veterinary Genetics: Modes of Inheritance

Canine and feline medical genetics is a rapidly growing field. Both the canine and feline genomes are readily accessible resources and other genetic tools such as DNA extraction, polymerase chain reaction, genome-wide association and whole genome sequencing are now routinely performed for studying both canine and feline genetic diseases. The focus of this chapter will be to provide relevant basic genetic knowledge for the small animal practitioner.

Important Genetic Terminology

Understanding and fully utilizing genetics in veterinary medicine requires knowledge of a few common genetics terms.

Allele—one of a number of different forms of the same gene.
Genotype—the genetic makeup of an individual.
Heterozygous—having two different copies (alleles) of a gene for a specific trait or disease. One of the two is usually the wild type (normal).
Homozygous—having two identical copies of a gene for a specific trait or disease.
Phenotype—the observable characteristics of an animal that result from the interaction of the animal's genetic makeup and the environment. In veterinary medicine we may think of it as an affected or normal phenotype.
Polygenic—a disease or trait caused by the interaction of two or more genes.
Transcription—first step in gene expression when the DNA gets transcribed to RNA.
Translation—second step in gene expression in which RNA becomes decoded to form amino acids.

Dna to Protein

The double helix of DNA is composed of specific sequences of four nucleotides, adenine (A), guanine (G), cytosine (C) and thymine (T), that are arranged to make up both coding and noncoding regions of the genome. The processes that move that sequence of DNA all the way to gene expression include transcription of DNA to RNA and then translation of RNA to the generation of polypeptides and proteins. The processes are complex and transcription and translation errors do occur although there are systems in place that catch and correct many of the errors before an abnormal protein is produced.

Genes are the regions of DNA that code for the production of polypeptides. They contain both coding region (exons) and noncoding regions (introns, untranslated regions). There are also regions that serve to regulate the transcription process. The exons are separated by non-coding intronic regions, which can include areas of regulation called enhancers and silencers. One of the most important areas of regulation is the promoter region, a region at the 5′ end of the gene that helps initiate the transcription process. In the dog and cat, the promoter region of many genes has not yet been fully defined and only a general region can be assumed. Although promoters, introns and untranslated regions all have important functions, at this time, most of the medically relevant DNA variants (mutations) in the genome have been identified in exonic regions. It is very likely that increasingly, disease causative variants will be found in these other regions.

Translation from the RNA to the protein product is aided by ribosomes, which read the RNA (mRNA) as a three-nucleotide codon. Each three-nucleotide codon then codes for the production of a specific amino acid, which is then added into a polypeptide chain to form the protein. The first amino acid that is translated by a ribosome is called the “start” codon and in eukaryotes this almost always produces the amino acid

methionine. The "stop" codon is the codon that signals the end of translation and is typically one of the following codons: TAG, TAA or TGA.

As mentioned above, the DNA replication and transcription system is quite intricate but errors do occur. Many of them are identified and repaired; however, if they are not fixed, an incorrect DNA nucleotide (or in some cases a deletion or insertion) may occur and may result in the translation to an incorrect amino acid. Although the amino acid sequence of a protein is quite specific, some regions of the protein may allow for more variability and the placement of an amino acid of similar size and polarity to the correct amino acid may be very well tolerated. Thus, many DNA errors that result in DNA variant production and a change in the amino acid produced will not impact the individual. However, a DNA variant that codes for an amino acid of a very different size, polarity or other characteristic may greatly alter the protein product produced, impact the cells within the organ of interest and change the phenotype of the animal to that of a genetic disease or disorder. DNA variants that change the amino acid to one of a very different structure, size, or polarity or that result in the development or loss of a stop or start codon are most likely to be of clinical relevance.

Canine Genome

The dog has 38 autosomal chromosome pairs and one pair of sex chromosomes. The sequence of the canine genome was derived from a single female Boxer dog and was first sequenced in 2005.[1] It has coverage of 7.5X plus, meaning that each nucleotide was sequenced 7.5 times on average to determine its identity. The deeper the coverage (higher the number), the more likely the accuracy of the sequence will be. The canine genome is an excellent resource for studying canine genetics; however, since its sequence is based on a single female dog with relatively low coverage (7.5X), additional samples are always evaluated as normal controls when performing genetic studies. The most current version of the canine genome is available for evaluation through searchable websites including the UCSC Genome Browser[2] and the Ensembl Genome Browser.[3]

Feline Genome

The cat has 18 autosomal chromosome pairs and one pair of sex chromosomes. The sequence of the feline genome was derived from an Abyssinian cat from the University of Missouri in 2006.[4] The most recent version is called felcat5 with a 2X coverage.[5] The lower degree of coverage in the cat is indicative of the weaker state of development of the feline genome. The genomic resources for feline studies still lag behind those available for canine genetic research. The most current version of the feline genome is also available for evaluation through searchable websites including the UCSC Genome Browser[5] and the Ensembl Genome Browser.[3]

A unique aspect of the feline genome is its naming system. While canine and human chromosomes are numbered consecutively starting at 1, the feline chromosome numbering system is numbered from A-F as follows: A1, A2, A3, B1, B2, B3, B4, C1, C2, D1, D2, D3, D4, F1 and F2.

Modes of Inheritance

Understanding the mode of inheritance of familial diseases in dogs and cats can provide important clinical information and be used to guide breeding decisions even if a genetic mutation has not yet been identified for a particular disease. Of the identified disorders in which the mode of inheritance is known, the majority are reported to be an autosomal recessive trait.[3] Autosomal recessive traits are not evident unless the individual carries two copies of the disease variant (homozygous). They are often not observed within a family unless two silent carrier parents are inadvertently bred to each other. The high frequency of autosomal recessive traits in companion animal populations likely represents a conscious attempt by pet enthusiasts to breed away from obvious disease traits and demonstrates the complications associated with using this mechanism to attempt to reduce disease in which silent carriers exist.[2]

Determining the mode of inheritance of a disease is ideally performed by prospectively planning breeding experiments and breeding known affected to unaffected animals of known genetic background to study the results of the breeding. However, this type of breeding study is rarely practical since it results in the intentional production of animals with known disease. A simpler approach, which can often give a very good general idea of the mode of inheritance within a particular line of animals, can often be done by careful evaluation of pedigrees as long as the disease status (phenotype) has been accurately determined.

If the mode of inheritance is understood for a disease, a well thought out breeding plan may be developed

which may actually help reduce the frequency of the familial disease even before a mutation has been identified. The most common modes of inheritance in companion animals include autosomal dominant, autosomal recessive, X-linked recessive and polygenic.

Autosomal Recessive

Autosomal recessive traits are carried on autosomal chromosomes and are not evident unless the individual carries two copies of the disease variant (homozygous). Pedigrees of animals with an autosomal recessive trait generally show a pattern where the disease appears to "skip" a generation since the parents can carry the trait but not show the trait if they only have one copy of the disease variant (heterozygous). Males and females should be fairly equally affected (Figure 3-1). Frequently, there will be an example where the mating of two individuals that appear to be clinically normal produces affected offspring. Generally the proportion of affected offspring from the mating of two normal parents (silent carriers) should only equal approximately 25% of all offspring produced. Finally, if two affected animals are bred to each other, all offspring should show the trait.

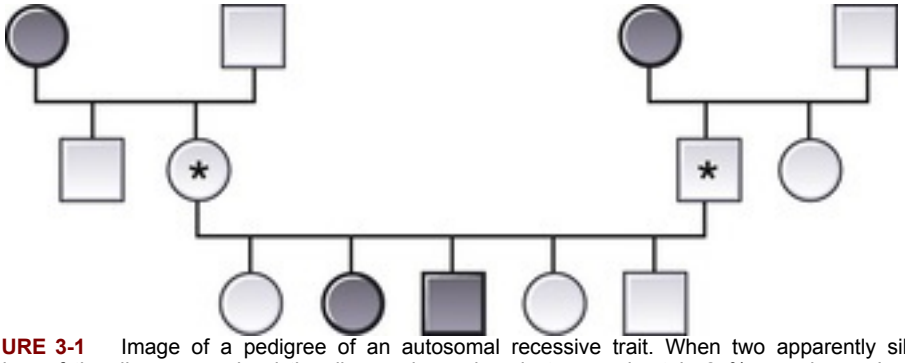

FIGURE 3-1 Image of a pedigree of an autosomal recessive trait. When two apparently silent carriers of the disease are bred the disease is produced at approximately 25% prevalence. In this diagram, circles are females, squares are males. White symbols are unaffected, black are affected. *Indicates a silent carrier of this disease.

They often become clinically apparent within inbred families since the risk of inadvertently breeding two silent carriers of the same trait is increased. If there is a potential likelihood of an autosomal recessive trait within a line, outbreeding to an unrelated family should decrease the risk of breeding to a silent carrier and producing more affected animals.

Autosomal recessive is the most common mode of inheritance identified in cats and dogs.[3] Examples of diseases and disorders that are inherited as autosomal recessive traits in veterinary medicine include nephritis (Alport syndrome) in English Cocker Spaniels, exercise induced collapse in Labrador Retrievers and spinal muscular atrophy in cats.[6-9] Canine cystinuria can be inherited as both an autosomal recessive (Labrador Retriever) and autosomal dominant (Australian Cattle Dog) trait depending on the breed.[10]

Autosomal Dominant

Autosomal dominant traits are also carried on autosomal chromosomes and are clinically evident even when one gene copy possesses the disease variant (heterozygous). Evaluation of pedigrees from affected animals should identify a fairly equal number of affected males and females. Additionally, every affected individual should have at least one affected parent since there are no silent carriers. Animals that show the trait could be either heterozygous or homozygous for the disease variant although generally one cannot tell which one they are by looking at the pedigree (Figure 3-2).

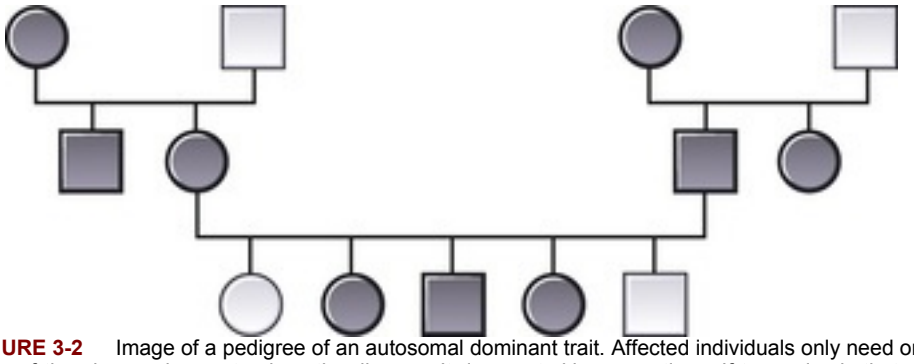

FIGURE 3-2 Image of a pedigree of an autosomal dominant trait. Affected individuals only need one copy of the abnormal gene to show the disease. It does not skip generations. If two animals that are heterozygous for the trait are bred, both affected and unaffected individuals can be produced. In this diagram, circles are females, squares are males. White symbols are unaffected, black are affected.

Examples of diseases and disorders that are inherited as autosomal dominant traits in veterinary medicine include polycystic kidney disease, retinal dystrophy in Abyssinian cats and dilated cardiomyopathy in Doberman Pinschers.[11-13] As mentioned above, canine cystinuria can be inherited as both an autosomal recessive (Labrador Retriever) and autosomal dominant (Australian Cattle Dog) trait depending on the breed.[10]

X-Linked

X-linked traits are carried on the X chromosome. Although X-linked traits can be dominant and demonstrate the trait even if the variant is only carried on one X chromosome, they are almost always recessive in veterinary medicine. X-linked recessive traits are only apparent in females if the disease variant is carried on both X chromosomes. Since the male only has one X chromosome, males will show the trait even if it is on their single X chromosome. Therefore, pedigrees of X-linked recessive traits generally show a predominance of affected males since they only have to have the trait on their single X chromosome. Females are more often silent carriers of disease since they frequently have the abnormal variant on only one of their X chromosomes. Pedigrees of animals with X-linked traits generally show many more affected males than females. Additionally, an affected male crossed with a normal female could produce unaffected females that are silent carriers. Affected males can never pass the disease to their sons since males cannot pass the X chromosome to their sons (Figure 3-3).

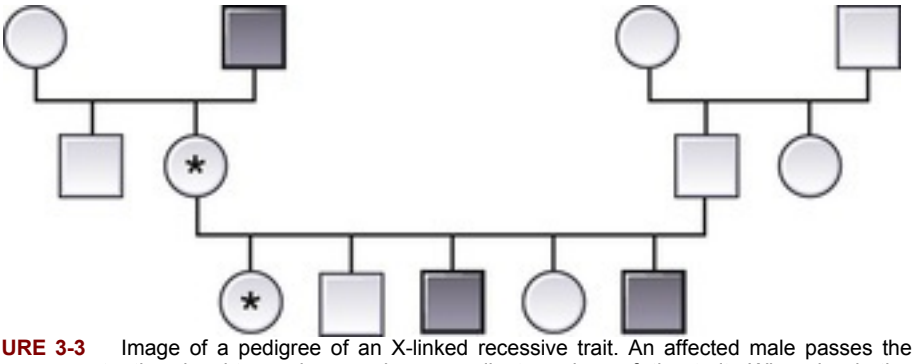

FIGURE 3-3 Image of a pedigree of an X-linked recessive trait. An affected male passes the X chromosome to the daughters who can become silent carriers of the trait. When bred, the X chromosome with the abnormal gene can be passed to some of the male offspring who will show the trait. In this diagram, circles are females, squares are males. White symbols are unaffected, black are affected. *Indicates a silent carrier of this disease.

X-linked traits are much less common in veterinary medicine but an example would include X-linked myotubular myopathy in Rottweilers.[14]

Polygenic

The modes of inheritance described above are generally used to describe diseases, which are thought to be caused by the effect of a single gene (monogenic). However, there are many familial diseases and disorders in veterinary medicine that have been characterized as polygenic, which suggests the impact of at least two genes working together to create the clinical presentation. Polygenic traits are particularly frustrating for both clinicians and geneticists since it is difficult to identify the specific genes of importance and to understand how they work together to create the disease. It is equally complicated to advise breed enthusiasts how they might breed away from a trait that is multifactorial without the risk of breeding away from other positive factors within the breed. The lack of knowledge of the individual genes involved in polygenic diseases makes it very difficult to develop specific breeding recommendations.

An example of a polygenic trait in the dog would be canine hip dysplasia.[15]

Dna Evaluation

Modern technology and increased genetic resources now allow the veterinarian to go beyond the study of pedigrees to that of actual chromosomal and DNA evaluation for their patients. Chromosomal and DNA evaluation of genetic traits can be obtained from a variety of sources including hair, buccal swabs, blood samples (EDTA, heparin), semen straws and tissue samples among others. The sample chosen should be selected based on the clinical evaluation needed. For example, a sample needed for chromosomal evaluation of an animal with infertility issues should include blood samples in heparin and EDTA tubes. A DNA sample needed to test for paternity or for a specific genetic mutation to identify the animal's genotype for a trait generally only requires a small amount of DNA and can come from a hair or buccal sample. DNA samples needed for an individual to participate in a research study for mutation identification requires a large amount of DNA and is best obtained from a blood sample.

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CHAPTER 4

Clinical Genomics

Kathryn M. Meurs, Joshua A. Stern

Client Information Sheet: Guidelines for Baseline Recommendations for Genetic Diseases

Canine and feline medical genetics is a rapidly growing field. The first description of a disease-causing mutation in the dog was the identification of a single base pair mutation in the Factor IX gene which resulted in the development of hemophilia in the Cairn Terrier.[1,2] This discovery was made by Evans et al in 1989. In the past 26 years, key mutations have been identified for 186 canine diseases and 49 feline diseases.[3] An additional 104 mendelian diseases have been identified in cats and dogs although the causative mutation(s) have yet to be discovered. Dr. Don Patterson, one of the true fathers of veterinary genetics, suggested that the rapid growth in the importance of clinical genetics in veterinary medicine over the past 20 years was not because of a sudden increase in the development of genetic diseases. Instead, he suggested that the development of antibiotics, anthelmintics, more effective vaccines and improved diets over the past 50 years resulted in a marked reduction in diseases associated with environmental causes.[2] This in association with the increased accessibility of the canine and feline genome and genetic resources for studying genetics in these species has allowed us to begin to utilize clinical genetics as an important part of veterinary medicine. The focus of this chapter will be to provide relevant genetic knowledge for the small animal practitioner.

Important Genetic Terminology

Understanding and fully utilizing genetics in veterinary medicine requires knowledge of basic medical genetic vocabulary.

Allele—one of a number of different forms of the same gene.

Cytogenetics—the study of normal and abnormal chromosomes. Most frequently an assessment of the number or shape of the chromosomes.

Expression—variation in the clinical features of the genetic disorder. Genetic diseases with variable expression may present with variability in severity of disease, even with individuals with the same disease variant.

Genotype—the genetic makeup of an individual.

Heterozygous—having two different copies (alleles) of a gene for a specific trait or disease. One of the two is usually the wild type (normal), but not always.

Homozygous—having two identical copies of a gene for a specific trait or disease.

Karyotyping—evaluation of the number and appearance of chromosomes (Figure 4-1).

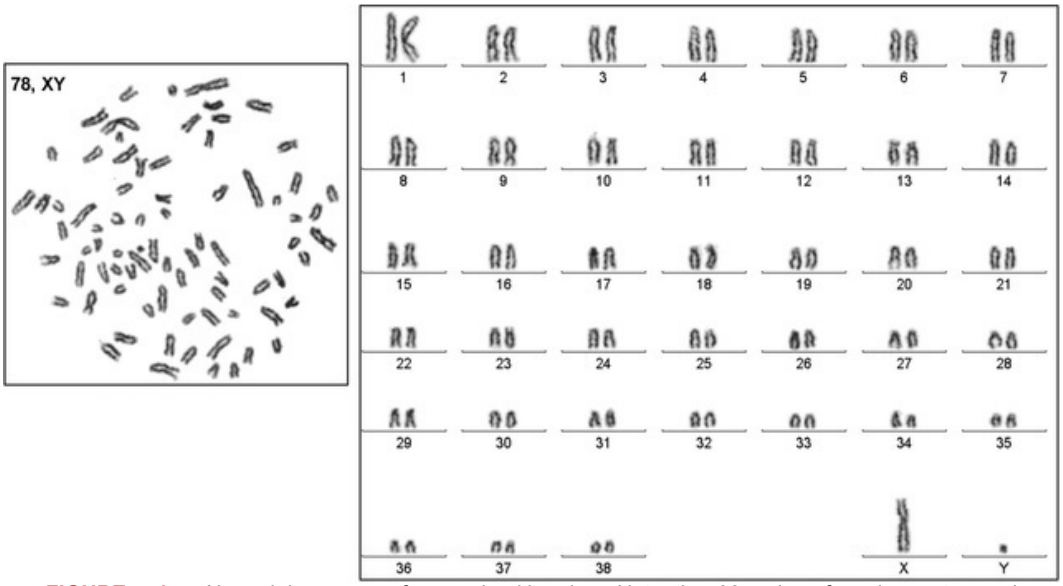

FIGURE 4-1 Normal karyogram from a healthy dog. Note the 38 pairs of canine autosomal chromosomes and the X and Y chromosome.

Missense mutation—a single nucleotide change that results in the formation of a different amino acid than is typically observed.

Nonsense mutation—a single nucleotide change that results in the development of a stop codon, prematurely.

Penetrance—proportion of individuals with a disease gene variant that will develop the disease. If a disease has incomplete penetrance some individuals with the disease gene variant (mutant) will not develop the disease.

Phenotype—the observable characteristics of an animal that result from the interaction of the animal's genetic makeup and the environment. In veterinary medicine we may think of it as an affected or normal phenotype.

Polymorphism—naturally occurring single base pair variants in the DNA sequence that have no adverse effects in the animal and are generally observed in at least 5% of the population.

Wild type—the most common copy (allele) of the gene, typically that found in the normal individuals.

Clinical Genetics

Genetic developmental disorders and diseases typically occur either because of large changes in chromosomal structure (deletions; chromosomal rearrangements) or smaller DNA variants (DNA deletions, insertions or changes).

Cytogenetics

Cytogenetics is the study of normal and abnormal chromosomal number and shapes. A karyotype is number and structural appearance of the chromosomes in a cell. A karyogram is the image of the chromosomes in the cell that allows for the evaluation of the chromosomes to assess chromosomal abnormalities including chromosomal duplications and rearrangements (see Figure 4-1). In human beings, these types of chromosomal changes have been linked to medical issues including cardiac and neurologic birth defects, abnormal sexual development, infertility and miscarriages.[4] Karyotyping has also been used to study neoplastic cells for specific chromosomal abnormalities unique to some forms of cancer.

In veterinary medicine, cytogenetic analysis of the chromosomes has been fairly limited to date. Its widest use has included evaluation of animals with reproductive or neoplastic issues. Chromosomal abnormalities in both dogs and cats have been associated with infertility as well as the development of abnormal external genitalia.[4-6] Evaluation of the feline karyotype in a sterile male tortoise shell cat was performed to identify an extra X chromosome.[7]

Oncologic studies have been using cytogenetic analysis to evaluate neoplastic cells for aberrations in chromosomal number and structure that could be used to improve our understanding of the etiology, prognosis and likelihood of response to treatment in canine neoplasia.[8]

Cytogenetic analysis in canine and feline veterinary medicine at this time is most important for the evaluation of sexual development disorders and should be considered in cases of abnormal sexual development or infertility. However, in the future this technique is likely to have increasing importance in our overall understanding of oncologic issues as well as neurologic and cardiovascular disorders.

Cytogenetic analysis and interpretation can be routinely provided for veterinarians through a number of different diagnostic labs with a small blood sample for a cost of between three and five hundred dollars. Searching for laboratories that perform canine and feline cytogenetic analysis can identify diagnostic laboratories that provide this service.

DNA Variants

Familial diseases and developmental disorders can also develop from genetic variants that occur at the DNA level. This type of DNA variant might include a single base pair change or a small insertion or deletion. However, a significant amount of this type of genetic variation exists normally at the DNA level without causing any specific disease. Polymorphisms are naturally occurring single base pair variants in the DNA sequence that have no adverse effects in the animal and are generally observed in at least 5% of the population. Determining if a DNA variant is a polymorphism or actually causative for the development of a familial disease or disorder can be challenging. Newly discovered DNA variants are typically carefully scrutinized to determine if they have characteristics which could likely lead to an important change in gene function. These might include single base pair variants that lead to the development of a different amino acid (missense mutation) (Figure 4-2) particularly if the amino acid is highly conserved across species, or the creation of a premature stop codon (nonsense mutation). Additional DNA variants that are highly likely to have important functional consequences are the insertion or deletions of additional DNA nucleotides particularly if they are in exonic regions (Figure 4-3).

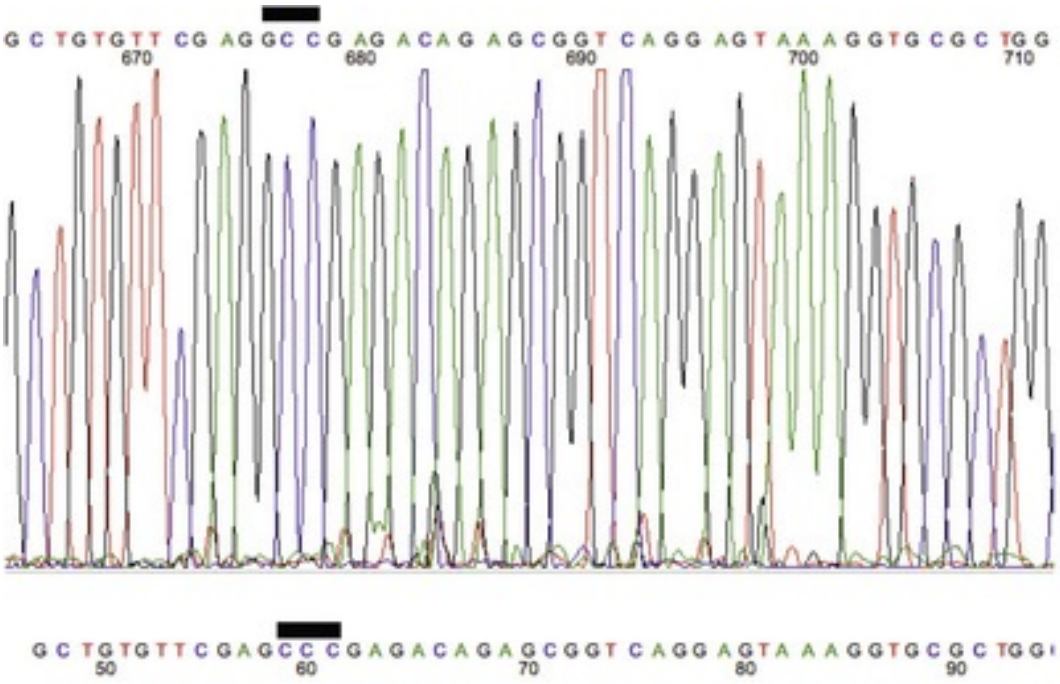

FIGURE 4-2 Missense mutation in a Maine Coon cat with hypertrophic cardiomyopathy. Note that the DNA sequence under the black bar in the top image is GCC, but the sequence under that black bar in the lower image shows the disease variant as CCC. The G has been replaced with a C. This will result in the production of a different amino acid.

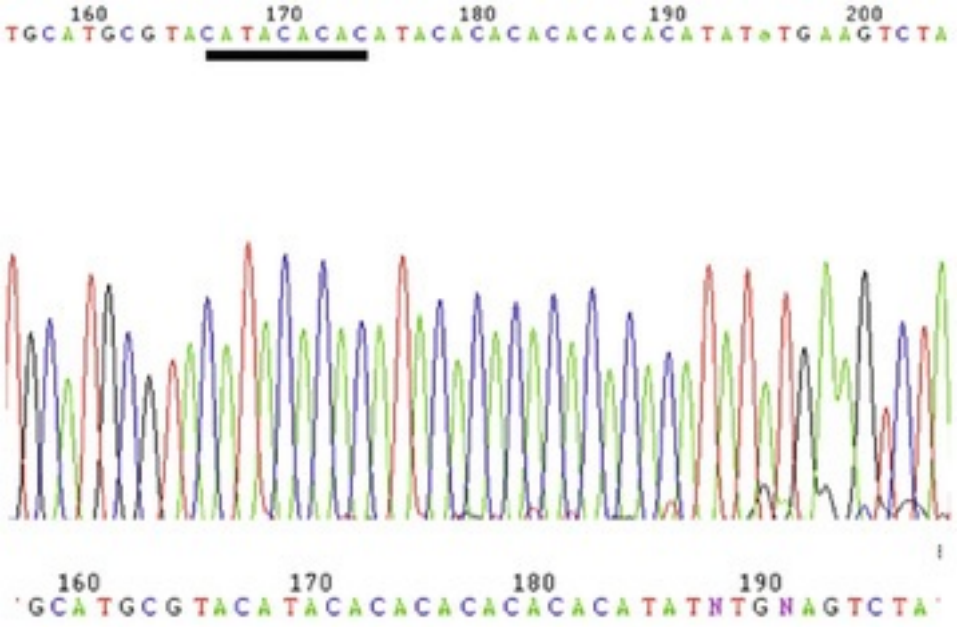

FIGURE 4-3 Deletion mutation in a Boxer dog. The sequence under the black bar in the top image represents a normal dog. In the lower image, the sequence under the bar has been removed and the rest of the DNA sequence has been shifted to the left.

The field of veterinary medical genetics is a rapidly changing field with new disease-causing variations being found on a frequent basis. As new DNA variants are discovered and linked to the development of clinical issues in the canine and feline populations, they are recorded in one or more of several electronic databases that are open-access. Clinicians counseling pet owners about familial diseases are encouraged to visit one of the following databases for the most current information on specific diseases.

1. *Online Mendelian Inheritance in Animals (OMIA)*[3]: The Online Mendelian Inheritance in Animals database is a comprehensive database that includes detailed information on genetic variants of cats, dogs, cattle, pigs, sheep, chickens, horses, goats and a few other species. Information on the DNA variant, evidence for its association to disease and availability of genetic testing are all provided. It serves as an excellent resource for veterinarians who need to do a quick search by disease or breed of dog or cat to identify current information on familial diseases.
2. *Canine Inherited Disorders Database*[9]: The Canine Inherited Disorder Database is more helpful for the pet owner than for veterinarians because it is generally directed at individuals with very little medical training. However, it still provides valuable genetic information on known inherited disease in dogs and it may be a useful resource for referring clients who need additional information on familial disease. This database provides lists of familial canine diseases as well as very brief clinical information on the

more common diseases for the layperson. It is searchable by both breed and disease process. Additionally, it provides general information on familial diseases including basic genetic definitions and recommendations for responsible breeding practices.

3. *Inherited Diseases in Dogs*[10]: This database is also a searchable database with an emphasis on the genetic aspects of the disease. It is intended for someone with a strong genetics background. The genetic data are carefully scrutinized for solid scientific evidence that links a DNA variant to disease.[11]

Factors That Impact Clinical Presentation of Familial Disease

Over 200 genetic mutations (variations, deletions, insertions) have now been associated with the development of clinical disease in the dog and cat.[3] However, it has become increasingly clear that medical genetics in the dog and cat is complicated. Not all individuals with a disease-causing mutation will develop the disease due to incomplete penetrance and not all individuals that develop disease due to a known DNA variant will develop the disease with the same disease severity due to variable expression. Many genetic diseases in animals are inherited with variability in penetrance and expressivity. A trait that is designated as having incomplete penetrance will be one in which less than 100% of individuals with the disease variant (mutation) demonstrate the trait. A trait designated as having variable expressivity is a disease or developmental disorder that has a spectrum of phenotypic expression with some individuals more severely affected than others. For example, some Maine Coon cats with the Maine Coon hypertrophic cardiomyopathy mutation (A31P) may have significant ventricular hypertrophy and develop congestive heart failure while littermates with the same mutation may not even ever show the disease. The Maine Coon mutation has been shown to exhibit incomplete penetrance and variable expressivity.[12] Another example of a disease where incomplete penetrance is thought to play a role in the development of the disease is canine epilepsy, although a genetic mutation has not yet been identified.[13] The mechanisms for the phenomena of variable expressivity and incomplete disease penetrance are poorly understood even in human genetics. It is likely that both environmental and genetic modifiers have an impact on the development of the trait associated with a particular mutation.

Penetrance and genetic expressivity are key concepts for veterinarians to understand and be able to explain to pet owners. They help explain why genetic testing rarely provides a black and white answer to the question of whether an animal should be used for breeding. In many genetic diseases, the presence of a causative mutation does not indicate that the animal will definitely get disease or the severity of the disease. It is very important that pet owners and pet breeders understand that not all individuals that carry a genetic mutation or are the offspring of affected parents will show the disease, or will show it with the same severity. Individuals with the disease variant are generally at increased risk of disease development (based on mode of inheritance), certainly, but are not guaranteed to develop disease. Understanding the limitations as well as the true value of genetic testing will help pet owners maintain confidence in genetic tools.

Genetic Counseling

With the increasing role of genetics in veterinary medicine there is also increasing desire to use this new genetic knowledge to reduce the prevalence of important familial diseases. Once a genetic mutation has been identified and genetic testing becomes available, counseling a pet owner or breeder on how to use the tests is imperative. Although genetic testing represents a great advancement for veterinary medicine, the improper use of genetic tests can be detrimental to the breeds involved. Once a genetic test has been developed, there is often a great desire to test for the causative mutation and remove any animals with the mutation immediately from the breeding pool (gene pool). This may seem initially to be a logical approach but it can have a significant negative impact on the breed overall. Cat and dog breeds are, by definition, closed gene pools. If the mutant gene is found to exist in 30% of a breed's population, which is not an uncommon scenario, a sudden reduction in 30% of the gene pool could dramatically alter the genetic makeup of the breed. Additionally, due to the incomplete penetrance and variable expression noted in many genetic diseases, it should be emphasized that not all animals that have the mutation will develop a clinical form of the disease. These concepts need to be carefully weighed against the ethics of continuing to produce animals that may carry a disease variant and could potentially suffer from the disease. Therefore, guidelines for counseling owners about the results of their genetic tests need to be carefully developed. For an individual animal this information can be used to guide decisions about increased clinical monitoring and could impact recommendations on diet, treatment and even exercise. For the breeding animal, recommendations to continue breeding animals that carry disease variants should be based on many factors including size of the

breed (gene pool), type of disease, risk that the animals produced will develop disease from the mutation (penetrance) and the likely severity (expressivity) of the disease. Finally the positive attributes of the animal that could be passed on and maintained within the gene pool should be considered.

Below are some guidelines for baseline recommendations for counseling owners about genetic diseases.

Genetic Test Results

Negative

This genotype status indicates that the individual animal does not carry any copies of the known disease genetic variant (mutation).

Considerations for the individual animal and breeding population: No special considerations are warranted as this individual should neither develop disease nor have the ability to propagate disease within the population.

Positive Heterozygous

This genotype status indicates that the animal has one copy of the normal gene (wild type) and one copy of the disease genetic variant.

Considerations for the individual animal: If the disease is autosomal recessive, this animal should never develop the disease, and no special considerations are needed. If the disease is autosomal dominant, this animal is at risk of developing disease. In some diseases, heterozygous animals have a more mild form of the disease than do homozygous animals and in some cases (variable penetrance) may never develop disease.[14] However, since this animal carries the disease variant and is at risk of disease development, a patient management strategy that includes annual monitoring for signs of disease and considers dietary, medical or other options that might help prolong the disease free state should be discussed. If the disease is X-linked recessive, a male with the disease variant on his X chromosome is likely to develop disease, but a female with the disease variant on one X chromosome is likely to be a silent carrier of disease.

Considerations for breeding animals: If the disease is autosomal recessive, this animal will not develop disease and can be safely bred to an animal that is negative for the disease variant. This strategy will likely produce both genotype negative and positive heterozygous animals but neither will develop disease. Ideally, a mutation-negative offspring with the desirable traits of the parents could be selected to replace the positive heterozygous parent for future breeding. This would ensure maintenance of genetic diversity within the breed. However, this individual should never be bred to another positive heterozygous animal since they will likely produce positive homozygous animals that will develop the disease.

If the disease is autosomal dominant, a similar strategy for breeding could be considered and one could breed a positive heterozygous animal to a genotype-negative animal. The offspring of this mating (positive heterozygous to a negative) will ideally produce at least some genotype-negative offspring and one of these with the desirable traits of the parents could be selected to replace the positive heterozygous parent in future breedings. This will help maintain the positive attributes of the breed and gradually reduce the prevalence of the disease variant in the breed over a few generations while maintaining breed diversity. However, this breeding will likely also produce a few positive heterozygous animals as well. As such, this strategy does risk producing animals that may eventually suffer from disease. Therefore, this strategy should be considered with regard to the type of disease that may develop in the offspring, the degree (if any) of disease in the positive heterozygous parents since in some diseases a parent with low penetrance of disease may produce low penetrance (healthy) offspring, and the importance of the positive heterozygous animal to the breed. If the animal is an exceptional animal due to personality, health, intelligence or other characteristics, one may be more likely to try this approach once or twice in hopes of producing a genotype-negative replacement animal.

If the disease is X-linked recessive, a male with a disease variant on his X chromosome could be safely bred to a negative female. This will produce both male and female dogs that are clear of disease. The male offspring of this mating will be clear of disease and not carry the disease variant since males cannot pass on their X chromosome to their sons. They will obtain their X chromosome from their genotype-negative mother. Female offspring will also be clear of disease as well since they will only have the disease variant on one chromosome and as a recessive trait, they would need to carry it on both X chromosomes to actually demonstrate the disease. However, importantly, females with a disease variant on one X chromosome will be silent carriers of the trait and can indeed produce clinically affected male dogs even if bred to a negative male. So female offspring resulting from this breeding strategy should not be bred even though they will be clear of disease.

Positive Homozygous

This indicates that the animal has two copies of the disease variant.

Considerations for the individual animal: In autosomal recessive, autosomal dominant and X-linked recessive diseases, positive homozygous animals have the highest risk of developing the disease. A patient management strategy should be developed that may include annual monitoring for signs of disease and consideration to dietary, medical or other options that might help prolong the disease-free state.

Recommendations for breeding animals: Since positive homozygous animals carry two copies of the disease variant, they will certainly pass on the variant even when bred to a genotype-negative animal. This will result in continued presence of the disease variant in the breed. Additionally, since the individual breeding animal is more likely to show the disease, using these animals for breeding may put increased stress on their possible disease states. In general, positive homozygous animals should not be used for breeding.

Types of Genetic Tests

A large number of diagnostic testing laboratories now offer genetic tests for a number of canine and feline diseases. Samples may be submitted in a variety of forms including buccal swabs, blood samples in EDTA, and semen straws, among others. Some labs prefer to send a specific kit for sample collection and others allow samples to be sent directly from the veterinary clinic in a standard EDTA tube. It is important to understand the type of testing performed and its respective sensitivity and specificity. PCR-based sequencing continues to be one of the most accurate methods for testing because it allows the laboratory to actually visualize the animal's DNA sequence and identify the variant. It continues to be slightly more expensive and takes a bit longer than assays that simply amplify the region of the variant and predict the presence or absence of the variant or normal (wild type) sequence based on color or fluorescence.

Importantly, since these canine and feline familial diseases are complicated with issues that include incomplete penetrance, variable expression, closed gene pools and variable phenotypes, it is ideal to use a testing service which is closely linked with the investigators that studied and discovered the disease variants and can provide the most expertise in genetic counseling for pet owners. A reasonable consideration is to identify the report of mutation discovery and contact the corresponding author's laboratory to identify the testing facility of choice.

Pharmacogenetics

Pharmacogenetics is the study of the impact of genetic variation on drug pharmacokinetics and pharmacodynamics, and how the actions and reactions to drugs vary with a patient's genes.[15,16] Pharmacogenetics is frequently viewed as a component of personalized medicine and indicates the personalization of pharmacological therapy to an individual based on their genetic background. A patient's genomic background can influence both a patient's ability to respond to medications as well as the ability to tolerate them without significant side effects. In veterinary medicine, breed-related genetic differences can impact both pharmacokinetics and pharmacodynamics and may suggest the need to alter doses for breed or individual animal variations.[17] Although this is still a fairly new area of clinical genetics, a few well known examples can be discussed.

Cytochrome P450

Cytochrome P450 (CYP) is responsible for the metabolism of a large number of drugs.[16] In human beings, the Cytochrome P450 2D6 (CYP2D6) gene has genetic variations (polymorphisms) that are associated with alterations in drug metabolism. Individuals with a specific genetic variant are considered to be poor metabolizers in comparison to those with the normal (wild type) sequence. Variants have also been identified in the Cytochrome P450 2D15 (CYP2D15) gene in the dog and some dogs have different rates in drug metabolism.[18,19] A genetic deletion in the CYP2D15 gene has been identified and may be associated with the variation in metabolism although this relationship has not yet been well studied.[16] The genetic variation might also be expected to be associated with metabolism of other drugs including propranolol and dextromethorphan.[16]

Thiopurine Methyltransferase

Thiopurine methyltransferase (TPMT) is important for metabolizing a number of cancer and

immunosuppressive agents including azathioprine and 6-mercaptopurine.[20,21] In human beings, genetic variants in this gene are associated with low enzyme activity and can lead to increased toxicoses including bone marrow supression.[16] Genetic variants in this gene have also been identified in both the canine and feline genes.[16,21] In both species, variation of red blood cell TPMT activity was associated with different genetic variants although a specific link to any single variant was not identified. Although the association is not clear enough for a specific clinical application at this time, in the future screening for these variants could possibly be used to determine an individual's activity level of TPMT to determine appropriate dosing.

P-Glycoprotein

For many drugs, plasma and tissue concentrations are very dependent on the activity of a drug transporter.[22] The ABC protein superfamily contains proteins that use ATP to transport substrates across biological membranes.[23] The ABC transporter superfamily transports drug molecules as their substrates. Two examples of this are the P-glycoprotein (P-gp) (encoded by the ABCB1, formerly MDR1, gene) and the breast cancer resistance protein (BCRP) (encoded by the ABCG2 gene).

In 2001, a four base pair deletion was identified in the collie ABCB1 gene that resulted in increased sensitivity to ivermectin.[24] The deletion causes a frame shift mutation that results in the development of a premature stop codon and produces a truncated, non-functional protein. This variant has been estimated to be in approximately 75% of Collies in the United States and 50% of Australian Shepherds. Traditionally thought of as a Collie issue, the mutation has been identified in a wide variety of other breeds including Australian Shepherds, Border Collies, English Shepherds, German Shepherds and Long Haired Whippets.[25] ABCB1 mutant dogs that are homozygous can suffer adverse neurologic signs after even one dose of ivermectin. Variability of ABCB1 expression can also influence pharmacokinetic characteristics of P-gp substrates and many other drugs including digoxin, cyclosporine A, dexamethasone, opioids, fluoroquinolones, beta-adrenergic agonists, loperamide and certain antivirals.[15,16] P-glycoprotein is also known for its role in mediating many chemotherapeutics.[26] Therefore, testing of at-risk breeds for the mutation should be considered before administration of chemotherapeutics including vincristine, doxorubicin and vinblastine.

Pharmacogenetics remains a rapidly growing field with current investigations into the influence of a patient's genetic makeup on response to cardiac medication (ACEI and PDE5a gene reports), chemotherapeutics, anesthetics and anticoagulants.

Clinical genetics is a rapidly growing field of veterinary medicine. It includes both the identification of causative disease mutations as well as the field of pharmacogenetics. The tools and information provided through canine and feline genetics provide exciting new aspects of veterinary medicine.

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CHAPTER 5

Evidence-Based Medicine

Steven C. Budsberg

One of the biggest challenges facing today's primary-care veterinary clinicians is staying current in a vast and ever-changing knowledge base and then trying to incorporate this new information into their daily practice routines. Evidence-based veterinary medicine (EBVM) offers a perspective and a set of tools that veterinarians can employ to manage information, facilitate better clinical decision-making, and improve patient care. EBVM represents a shift from opinion-based clinical decision-making to one that is data-based. The critical appraisal of all available information is at the core of EBVM. Modern EBVM is composed of five main elements (Box 5-1)[1] and is defined as *the conscientious, explicit, and judicious use of current best evidence, combined with individual clinical expertise and client/patient preferences and needs, in making decisions about the care of individual patients.*[2]

Box 5-1

The Five Basic Steps of Evidence-Based Veterinary Medicine

1. Converting the need for information (e.g., about prevention, diagnosis, prognosis, therapy, causation) into an answerable question.
2. Tracking down the best evidence with which to answer that question.
3. Critically appraising that evidence for its validity, impact, and applicability.
4. Integrating the critical appraisal with the clinician's expertise and each client/patient's circumstances.
5. Evaluating effectiveness and efficiency in executing steps 1-4 and seeking ways to improve for next time.

As stated above, EBVM has the great potential to improve patient care. Past experience has shown that better outcomes can be achieved with better knowledge. However, as we embark on this new journey, we must be cautious. We must be mindful that the information on which we base our decisions is not always created equal and that misinformation can certainly be worse than no information. It must be constantly remembered that the evidence obtained while practicing the methodologies of EBVM, by itself, does not make a decision, but it can help support decisions regarding patient care (Figure 5-1).

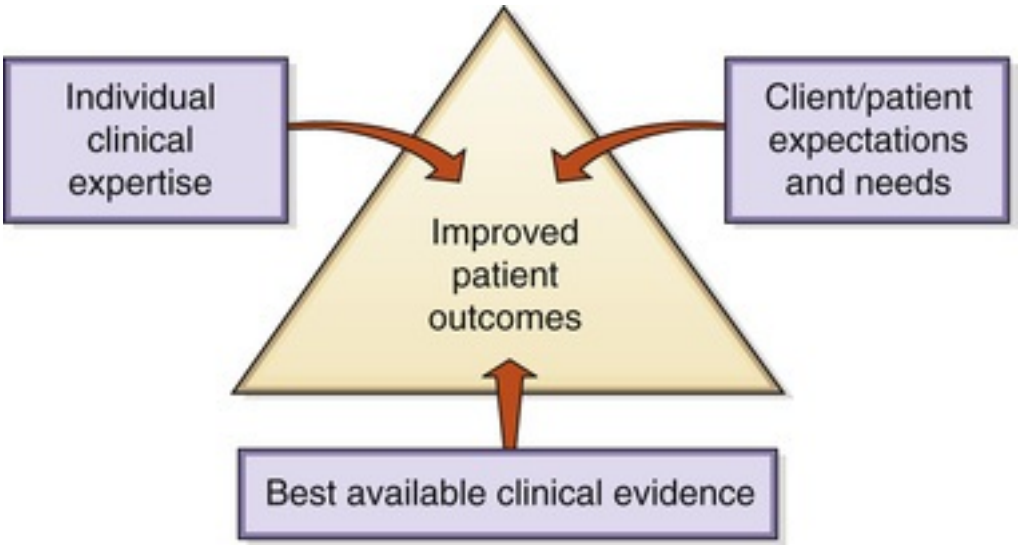

FIGURE 5-1 The optimal decision-making process of EBVM. The best outcome depends on the expertise of the clinician, the best available evidence, and client/patient expectations and needs.[2]

Evidence-based veterinary medicine requires specific skills of the clinician, including efficient literature-searching, and the application of formal rules of evidence in evaluating the clinical literature.[3-5] Let us review the process and show examples of how one begins the practice of EBVM. There are five basic steps employed when teaching or practicing EBVM, as outlined in Box 5-1. However, another popular algorithm is called the five "A." One must **Ask** a question, **Acquire** the evidence, **Appraise** the evidence, **Apply** the evidence to the patient, and finally **Assess** the outcome. This algorithm follows the same fundamental steps described here, presented in a different format, and it has been highlighted in the following example to show how both systems strive for the same information. Remember, EBVM always starts with the patient and thus the process starts as follows:

1. The clinician has a problem/question that arises out of the care of the patient. Next, the clinician must construct a well-developed question derived from the aforementioned problem/question. The question to be asked must be specific to the patient, precise in scope and answerable. Therefore, the first stage of any evidence-based practice process is to **ask** an answerable question. This question forms the foundation for the appropriate searching of the literature and then ultimately the evidence incorporated into the care of that specific patient. A well-formulated question will facilitate the search for evidence and will assist in determining whether the evidence is relevant to the question. An answerable question often takes the format that follows the PICO concept. The acronym translates to:

   P—Populations/Patient/Problem
   How would you describe a group of patients similar to your patient? What are the most important characteristics of the patient? This may include the primary problem, disease, or co-existing conditions.

   I—Intervention(s)
   Which main intervention, prognostic factor, or diagnostic test are you considering? What do you want to do for the patient? Prescribe a drug? Order a test? Recommend a surgical procedure? Which factors may influence the prognosis of the patient? Age? Breed? Sex? Or metabolic status?

   C—Comparison
   What is the main alternative to compare with the intervention you are proposing? Are you trying to decide between two drugs, a drug and no medication, or two diagnostic tests? Remember, your clinical question does not always need a specific comparison.

   O—Outcome
   What are you trying to do for the patient? Relieve or eliminate the signs? Reduce the number of adverse events? Improve function or test scores?

2. Once an answerable question has been created, one must select the appropriate available resource(s) to conduct the search to **acquire** evidence to answer the clinical question. Certainly when starting to search and acquire information, one often turns to the Internet. The most common sites to start with are PubMed (Medline) (www.ncbi.nlm.nih.gov/PubMed) and CAB Direct (www.cabdirect.org or www.cabi.org/publishing-products/online-information-resources/cab-abstracts). However, recently, two newer sites, specific to clinical veterinary medicine, have been developed and are now available and

searchable. BestBETs for Vets (www.bestbetsforvets.org) and VetSRev (www.nottingham.ac.uk/cevm/vetsrev) may vastly improve search capabilities for acquiring the desired information. Other sources of information would include hard copy journals available to the clinician as well as appropriate textbooks and of course information gleaned from lectures, presentations or colleague discussions.[6]

3. With the evidence located and acquired, one must **appraise** that evidence for its validity (strength of data) and applicability (usefulness in clinical practice). This next step involves evaluating the evidence that has been acquired. In essence, one is trying to determine what is the "best evidence" among all the information that has been gathered in the search to use to treat the patient.[7-10] Although the randomized controlled trial is touted as the be-all and end-all of clinical evidence, one can still practice evidence-based medicine without such information. In fact, evidence-based medicine involves using the best available evidence at the time, and what qualifies as "best evidence" differs by clinical question. Therefore, various types of evidence can be used to develop the best treatment plan for a patient, and this evidence is ranked by its strength or level of evidence; the more rigorous the study design, the higher the level of evidence (Figure 5-2). Moreover, this evidence can be synthesized into practice recommendations that are graded according to the strength of the supporting evidence. There are several scales for rating levels of evidence and grading recommendations.[11-16]

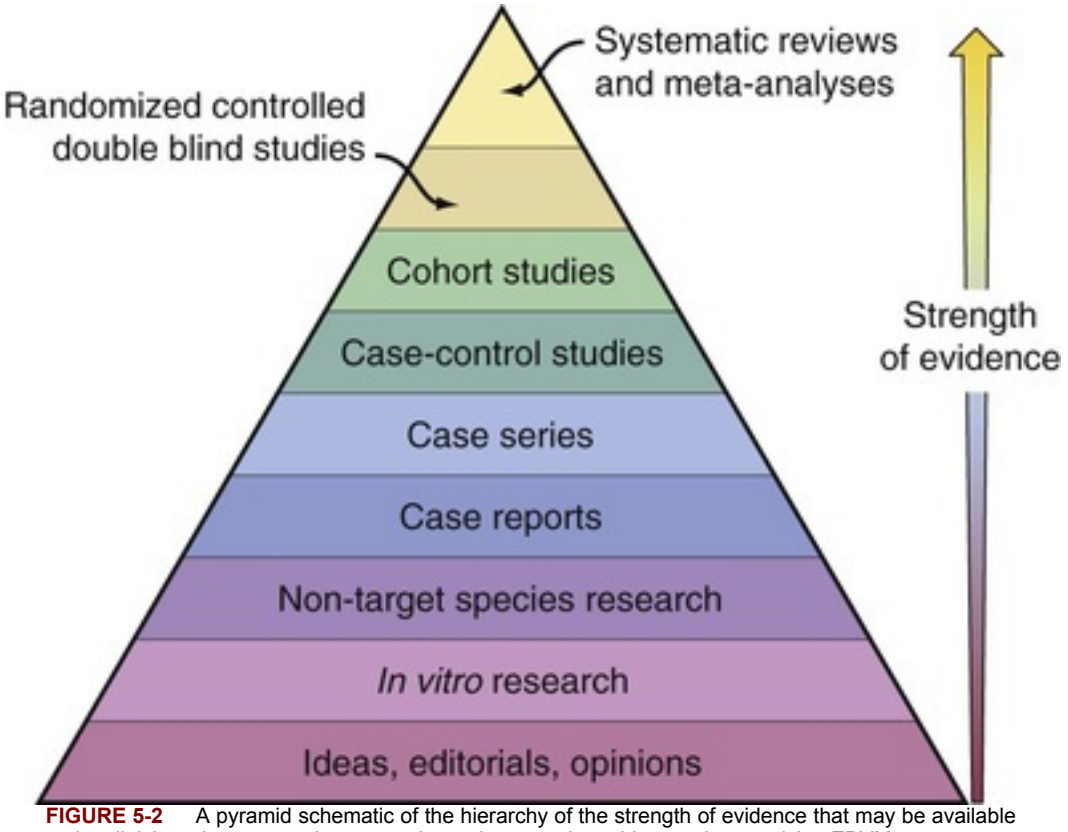

FIGURE 5-2 A pyramid schematic of the hierarchy of the strength of evidence that may be available to the clinician when attempting to acquire and assess the evidence when applying EBVM.

4. Return to the patient—Integrate that evidence with clinical expertise, client/patient needs and **apply** it to that patient in practice.
5. Evaluate your performance with this patient—Critically **assess** the outcome of that decision and the overall benefits to the client/patient.

The goal of EBVM is not to remove the experience of the clinician in treating his or her patients, but to improve clinical decision-making with stronger data. It provides a formal method to generate information that has less bias or error and it can greatly facilitate better clinical decision-making. However, EBVM takes effort and commitment from the clinician. One must learn and be vested in the process as well as the effort needed to complete the search for evidence. Despite the success of EBVM over the last two decades, there

remains wide variation in the implementation of EBVM among clinicians. Additionally, confusion about what EBVM is has led to disagreement, disillusion, and dissent among veterinarians.[5] Many references discuss and reflect on this discord and Table 5-1 outlines some of the misunderstandings and controversies about EBVM.[17-19] Certainly, there are several issues that have slowed the expansion of EBVM, including education on its use by clinicians and the limited student exposure at teaching institutions.[17,20] Yet as progress is made and client/patient outcomes improve through the systematic collation, synthesis, and application of the highest quality evidence available, EBVM will become a potent tool for the primary care veterinarian.

TABLE 5-1

Evidence-Based Veterinary Medicine Issues

OPPONENTS	PROPONENTS
EBVM is "old hat." Clinicians have been using the literature to guide their decisions for a long time. Only the label is new.	The new focus on EBVM "formalizes" that "old hat" process and filters the literature so that decisions are made based on "strongest" evidence available.
EBVM is "cook book medicine." It suggests that decisions are based solely on the evidence, removing or down playing sound clinical judgment.	EBVM should be one part of the process. Decisions must be blended with individual clinical expertise, client/patient needs and when available good evidence.
EBVM is the mindless application of population studies to the treatment of the individual. It takes the results of studies of large groups of animals and tries to apply them to individuals who may have unique circumstances or characteristics, not found in the study groups.	The last step in the EBVM process is to decide whether or not the information and results are applicable to your patient and to discuss the results with the client.
Often there is no randomized controlled trial or "gold standard" in the literature to address the clinical question.	Clinicians might consider the "evidence pyramid" and look for the next best level of evidence. Clinicians need to understand that there may be no good evidence to support clinical judgment.
There is often great difficulty in getting access to the evidence and in conducting effective searches to identify the best evidence.	Tools and information exist to teach clinicians effective searching skills. Additionally there are now reference sites that have already conducted much of the research to give clinicians the information they desire.

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CHAPTER 6

Biomedical Statistics

Selected Topics

Philip H. Kass

Science exists as a disciplined, systematic methodology for investigating and understanding the complex world in which we live. The scientific method is, in turn, the series of progressions used for generating knowledge through experimental and nonexperimental inquiries. Central to this method is the postulation of scientific hypotheses for formulating predictions about populations, although they must be falsifiable to be testable. Null hypotheses are examples of falsifiable hypotheses: they typically (but not always) specify the absence of differences, effects, or relationships between comparison groups. Studies in turn generate empirical findings used for testing null hypotheses under certain model assumptions: evidence (data) contravening the veracity of the null hypothesis may be persuasive enough to convince an investigator to seek an alternative explanation and advance a new hypothesis, again subject to later potential refutation.

Hypothesis Testing

Statistical inference is a formalization of the process by which data are reconciled with hypotheses. Under a specified probabilistic model (sampling distribution) framework, it becomes possible to estimate the probability (*P*-value) of obtaining findings that are as much, or more, in conflict with the null hypothesis than findings that would be expected under it. It is important to understand that although ubiquitously reported, the *P*-value is only correct insofar as the model assumptions are correct as well. One common assumption is that population data arise from a normal distribution; another is that individuals are randomized to distinct treatment groups. Small *P*-values therefore do not necessarily correspond to an improbable null hypothesis—they can instead result from one or more erroneous model assumptions, or arise even by chance. Conversely, large *P*-values do not necessarily provide affirmative support for a null hypothesis: the study sample size could have been inadequate for a given contrast (e.g., a difference or effect) between groups, the measure contrasting the groups could have been too small given the sample size, or the model assumptions may be fallacious. Just as important to recognize is that low *P*-values may have no relationship with practical or medical importance, and high *P*-values may mask potentially important findings.

It is sufficient when hypothesis testing to report the model-generated *P*-value. However, it has become common, although far less desirable, to present findings as either $P > 0.05$ or $P \leq 0.05$. The similarly ubiquitous use of statistical "significance" as a proxy for employing $P = 0.05$ as a bright line of demarcation for decision-making is equally undesirable because it reduces a continuous probability distribution from {0 to 1} into two mutually exclusive categories, and attaches a meaning almost effortlessly misconstrued: that "significance" refers to "important" or "real difference," and that "non-significance" corresponds to "unimportant" or "no difference." While firmly ensconced perhaps by no more than habit and rote teaching in the medical literature, its extirpation would come as no loss to readers.

Variability

Intrinsic to hypothesis testing is the measurement of variability in data. The most commonly used (and taught) method of measuring dispersion of observed data is the calculation of sample variance or its square root, the standard deviation. Of the two, the latter is typically preferred for reporting in descriptive studies because it is in the same measurement unit as the reported center of the data distribution (typically the sample mean). A related measure of dispersion, but on an actual calculated statistic instead of observed data, is the standard error. This quantifies the precision surrounding a statistic, such as a sample mean, a

proportion, an odds ratio, and so on (it is, in reality, the standard deviation of the sampling distribution of the statistic). Because the standard error is inversely related to sample size, then usually the larger the study, the more precisely statistics from it can be estimated. Variability of a statistic that cannot be explained by known factors influencing it is known as "random error." While massively large studies have been promoted as scientifically definitive because of their extreme statistical precision, in isolation this is illogical because of another important source of study error.

Validity

When a statistic from a study fails to capture what an investigator is trying to estimate in a population, the statistic is designated as biased. This can arise from a myriad of causes: comparing groups that, if treated exactly the same, would nevertheless have different outcome measurements (confounding bias); selecting or retaining individuals for a study in a way that renders comparisons invalid (selection bias); using incorrect diagnostic or measurement instruments (information bias); and performing improper statistical analyses (specification bias). Such biases, also known as systematic errors, can be present in any sized study; importantly, a large study is no guarantee of the absence of bias, even when random error is negligible or ignorable. Sometimes, the biases introduced in study design or implementation can be rectified in statistical analyses, although these normally require complicated multivariate techniques.

Sample Size and Power

Every inferential study is designed to test one or more hypotheses; with the intent of trying to reject the null form of at least one considered of primary importance, an investigator must enroll a requisite number of individuals to have a reasonable probability of accomplishing this goal. It is a common error for investigators to believe that there is a universal minimum sample size for clinical studies; in reality, every hypothesis test requires a dedicated sample size calculation. Because many studies investigate multiple, and perhaps many, hypotheses (especially those studying potential causal associations between putative risk factors and health outcomes), it is common for an investigator to focus on one or a few key hypotheses, and design a study around testing those. Sample size calculations are intimately related to the principles of hypothesis testing, and are essential in grant and internal review board applications to justify the number of individuals sufficient to find contrasts statistically "significant." Invariably, a sample size calculation requires the specification of a level of significance (alpha), which is the chosen *P*-value below which significance is found (conventionally, if not reflexively, $P = 0.05$ is used), and a level of statistical power (1-beta) that corresponds to the probability of rejecting the null hypothesis when it does not accurately reflect the truth. Ancillary information required for a sample size calculation depends on the statistical test to be used for hypothesis testing. For example, comparing differences in proportions between two groups requires specifying the two proportions the investigator deems worthy of finding significantly different (Figure 6-1). Web-based interactive sample size software is readily available for many kinds of hypothesis tests (e.g., http://www.epibiostat.ucsf.edu/biostat/sampsize.html and http://powerandsamplesize.com).

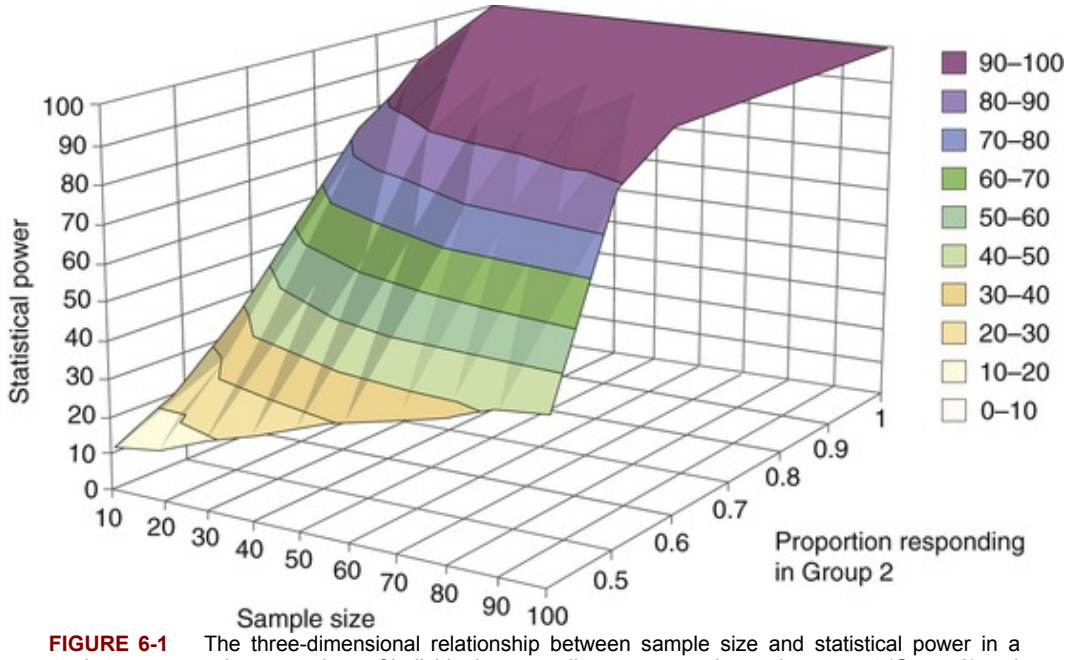

FIGURE 6-1 The three-dimensional relationship between sample size and statistical power in a study to compare the proportions of individuals responding to an experimental treatment (Group 2) and a control treatment (Group 1). The example assumes the proportion of individuals responding to a control treatment in Group 1 is 0.3, and the Type I error probability is 0.05. As the difference in proportions gets larger, statistical power increases because it becomes easier, for a fixed sample size, to find larger differences significant than smaller differences. As the sample size gets larger, statistical power also increases for any fixed difference in proportions.

Another common misunderstanding arises when a study fails to find a statistically significant contrast, and an author is asked to provide the "study power." Such a request is unjustified on two counts. First, as noted above, there is no single "study power"—every null hypothesis has a unique probability of being rejected or not, depending on the factors noted earlier (including sample size). Second, there is no logical reason to perform post-study power calculations because if a hypothesis test was not rejected, by definition the study had insufficient power to reject it, rendering the request tautologous. At best, it could be argued in response that given the magnitude of the contrasts found in a study, a more relevant question would be what sample size should be required in future studies to find such contrasts statistically significant.

Experimental Studies

Controlled clinical research can be broadly divided into experimental and nonexperimental studies, which are distinguished by whether factors of interest, such as treatments, are under the control of the investigator. Both kinds of studies have distinctive advantages (and disadvantages), but it is generally accepted that controlled studies of risk factors of diseases in companion animals are usually nonexperimental, and studies of the effects of interventions or treatments on physiologic responses (including recovery or survival) ideally are experimental. Exceptions to these rules are controversial and should be avoided.

Crossover studies are the most common controlled experimental studies performed in healthy animals, and frequently are used for comparing responses to different treatments (and sometimes dosages within treatments). By doing such studies within rather than between subjects, validity issues arising from endogenous factors that could affect study outcome are obviated because the factors are held constant. This advantage over randomized studies comes at a cost, however, as two critical assumptions must be met. First, the effect of successive treatments must be independent of the effect(s) of earlier treatment(s); i.e., absence of a "carryover" effect. This is often addressed by allowing an appropriate time ("washout") interval between treatments that allows an individual's response to return to a baseline state, and the assumption can be evaluated (though not proven) by comparing baseline (prior to treatment administration) outcome measurements prior to introducing each new treatment. Implicit in this assumption is that the order of treatments should have no effect on outcome. Second, there must be no effect of time on the outcome measurement that operates independently of treatment. Therefore, this study design is best suited to experimental interventions that have rapid onset of effects with transient durations.

The most common controlled experimental studies in companion animal patients are randomized clinical

trials, in which individuals are randomly assigned to different treatments. These studies have superior properties with respect to prevention of confounding bias compared to non-experimental studies because the probability of non-comparability between groups becomes smaller as the number of enrolled individuals increases. Randomization is a constellation of allocation approaches designed to ensure that individuals have equal probabilities of being assigned to a treatment or intervention. The most common approach utilizes random number generation to determine individual-level allocation, and can be modified through stratification (e.g., done separately for females and males or within age categories) and blocking (e.g., performed within non-overlapping sub-intervals of time under study) to ensure that an adequate number of individuals within all covariate categories receive all treatments. However, randomization itself does not guarantee the absence of confounding, especially in small studies prone to random group imbalances in factors affecting outcomes. Although it is common to see groups statistically compared for reassurance of the "success" of randomization with respect to equal distribution of baseline characteristics (age, breed, sex, weight, etc.) or physiologic values, such tests are misleading because of their dependence on sample sizes, and so should not be used for making conclusions about comparability (which can later be addressed as part of a multivariate data analysis). That said, an important advantage of such experimental studies is that the statistical methods used for analyzing them assume randomization of treatment (and other factors, including those unmeasured or unmeasurable), which allows correct estimation of standard deviations, standard errors, and *P*-values even in the presence of confounding.

Intention-to-Treat

The practice of conducting clinical research on patients, especially longitudinally, can be fraught with problems that almost invariably arise, as experienced investigators will attest. Foremost among these is missing data, which transpires for design deviations that include failure of collection, sample mishandling or loss, measurement instrument failure, patient loss to follow-up, and noncompliance (non-adherence) with study protocols. A steadfast design rule prescribing analysis of clinical trial data and recognized by governmental grant agencies is the "intention-to-treat" (ITT) principle: that all randomized study subjects remain members of the treatment group to which they were assigned regardless of what transpires following commencement of the study. All data (regardless of integrity) are retained for analysis, and all individuals are included regardless of whether they successfully complete the study or not (regardless of reason for withdrawal). Underlying this conservative approach is the recognition that violations of study design and protocol that arise in a controlled experimental setting are also likely to arise in clinical (i.e., non-experimental) settings.

An additional analytic strategy that can be used in a supportive role to ITT analyses is the "per-protocol" (PP) or "efficacy subset" approach, which involves willfully excluding patients and observable patient information from the analysis because of flawed or incomplete information obtained during study implementation or after completion. This leads to including only the subset of the original ITT patients to whom the intervention is effectively administered and who remain compliant with protocols. Although this less conservative approach has intuitive appeal, it involves restricting the population eligible for analysis only after study commencement, so the validity advantages intrinsic to randomization are therefore lost with this approach. Concordant results between ITT and PP analyses provide supportive evidence that the protocol violations were unlikely to meaningfully affect the study conclusions.

Confounding by Indication

While randomized clinical trials remain the standard of practice for comparing treatments in patients, nonrandomized approaches (particularly retrospective cohort studies) have been used with hospital-based data to accomplish the same objective. This practice should be strongly discouraged because a clinician's deliberate choice of a treatment can never be assumed to be unrelated to disease severity or patient prognosis. The bias arising from the almost certain differences between groups of patients receiving optional treatments in the absence of random allocation is known as "confounding by indication." Although such retrospective studies may have some value for hypothesis generation, potentially leading to future experimental studies of treatment efficacy, even with statistical control of prognostic indicators their conclusions must be regarded as suspect until confirmed (or refuted) by more appropriate study designs.

Statistical Methods

Scientific hypotheses not only guide the choice of study design, but also the election of the type of data

collected for analysis. Measurements can take on one of several forms that help determine the appropriate analytic approach. These include categorical data that can be subdivided into nominal categories (no natural ordering), ordinal categories (naturally ordered but unequally spaced), interval categories (naturally ordered and equally spaced), and quantitative data that exist on a continuum. Causal hypotheses further allow the dichotomization of "causes" and "effects," which have a direct correspondence with explanatory variables (also called predictors, covariates, and independent variables), and outcome variables (also called dependent variables), respectively. The type of explanatory and outcome data will in turn determine the appropriate statistical test to use. A non-exhaustive assemblage of the most common statistical approaches used in biomedical research is contained in Table 6-1. Software to perform these tests is readily available without requiring programming experience. However, there are several recurrent issues that arise in statistical testing that are important to understand prior to undertaking the actual analyses.

TABLE 6-1

Recommended Statistical Test for Data Commonly Arising in Clinical Settings

OUTCOME DATA TYPE	OUTCOME GROUPING (IF APPLICABLE)	EXPLANATORY VARIABLES	NULL HYPOTHESIS (H_O)	RECOMMENDED STATISTICAL TEST
Continuous (independent data)		Two groups	Means are equal	Student's two-group T-test
			Distributions of data are equal	Wilcoxon-Mann-Whitney test*
		Three or more nominal groups	Means are equal	Analysis of variance
			Distributions of data are equal	Kruskal-Wallis test*
		Three or more ordinal groups	No monotonic relationship	Spearman correlation*
			No ordinal (dose-response) relationship	Jonckheere-Terpstra test*
			No ordinal (dose-response) relationship	Nonparametric trend test*
		Continuous	No linear relationship	Pearson correlation
			No linear relationship	Linear regression
Continuous (time to outcome)	If outcome occurred or not (censored)	Groups	Times to event are equal	Kaplan-Meier survival analysis
		Continuous and/or groups	Times to event are equal	Cox proportional hazards regression
Continuous (correlated data)		Two groups	Paired differences are zero	Paired T-test
			Distributions of paired differences are equal	Wilcoxon signed-rank test*
		Three or more groups	Means are equal	Repeated measures analysis of variance
			Means are equal	Mixed effects analysis of variance
			Distributions of data in matched groups are equal	Friedman test*
		Continuous	No linear relationship	Mixed effects linear regression
Categorical (independent data)	Two groups	Two groups	Proportions are equal	Fisher's exact test*
		Three or more nominal groups	Row and column variables are independent	Pearson chi-square test*
			Row and column variables are independent	Fisher-Freeman-Halton test*

		Three or more ordinal groups	Distributions of data are equal	Kruskal-Wallis test*
		Continuous and/or groups	No association with binary outcome	Logistic regression
	Three or more nominal groups	Two or more nominal groups	Row and column variables are independent	Pearson chi-square test*
		Three or more ordinal groups	Distributions of data are equal	Kruskal-Wallis test*
	Three or more ordinal groups	Two groups	Distributions of data are equal	Wilcoxon-Mann-Whitney test*
		Three or more nominal groups	Distributions of data are equal	Kruskal-Wallis test*
		Three or more ordinal groups	No ordinal (dose-response) relationship	Jonckheere-Terpstra test*

*Indicates a distribution-free test.

Multiple Comparison Adjustment

In every instance where a hypothesis test is performed, an investigator risks making a mistake when calling a finding "statistically significant" and rejecting a correct null hypothesis. When the null hypothesis is in fact correct, this error will occur approximately one out of 20 times when the level of significance is conventionally set to 0.05. Each time a test is performed, however, another opportunity to make mistakes arises, and when many tests are performed, making at least one mistake becomes probable (note that there is an analogy to defining multiple test results as abnormal in chemistry and hematology panels). To lessen the frequency of such errors, the level of significance (alpha) may be divided by the number of tests performed (n), making rejection of a single null hypothesis less likely. This correction, where alpha* = alpha/n, is known as a *Bonferroni adjustment*. For example, if five tests are performed, in order to keep the overall error percent at 0.05, each test should have its own alpha* of 0.01.

Assumption of a Normal Distribution

Many familiar tests assume that data from discrete populations arise from a normal distribution. This holds, for example, within groups compared using Student's two-group T-test and on the differences within pairs using paired T-tests, and can be assessed using normality tests found in software (e.g., Shapiro-Wilk test). For more complex methods, such as analysis of variance and linear regression, the normality assumption applies to model-based "residuals" (observed minus predicted values), and not the dependent variable. Regression diagnostics on the residuals are also available in software to assess this assumption and goodness of statistical model fit.

Small Sample Sizes

When the number of observations is small, tests for normality have low power to detect non-normal distributions, so non-significance should not be interpreted as verification of normality. If investigators either have no *a priori* knowledge that population-based data follow a normal distribution, or have *a priori* belief that the data are non-normal, then analyses relying on statistical tests that do not assume an underlying distributional structure should be employed instead. Such distribution-free tests are collectively called "non-parametric tests" and are noted in Table 6-1. These tests perform nearly as well as other tests that assume normality when sample data arise from a population with normally distributed data, and have superior properties when data are not normally distributed. They are also the methods of choice for analysis of categorical outcome and contingency table data.

CHAPTER 7

Euthanasia

W. Douglas Kunz, Stephen J. Ettinger

As veterinarians, we are very fortunate to be advocates for the well-being of our patients from their first visit to the end-of-life considerations. When we recommend a diagnostic procedure, a surgery, or medication, we are acting for the well-being of the animal under our care. At times, we also must be advocates for the humane demise of our patients. This is a unique position for practitioners of the healing arts. It provides us with certain rights and obligations that no other health care professional has. This is something we as veterinarians deal with daily. Euthanasia takes a toll on our staff and us. This should not be ignored nor should the responsibility of making appropriate decisions regarding euthanasia be dealt with lightly.

We are presented with the request to euthanize a beloved pet for a variety of reasons. These reasons can vary from deterioration of the quality of life to the point that euthanasia is a kind relief from suffering to the cast off pet whose owner is unwilling or unable to find another home for it. Whereas the former is a much easier process for the practice team, as all know that a compassionate service is being performed, the latter can be very difficult because we are in fact being asked to kill a healthy pet. Of course, there are numerous other reasons for euthanasia, such as a severely injured or ill pet whose owner does not have the financial resources for treatment, the pet that has severe, irresolvable behavioral problems, or a puppy born with birth defects that the owner is unwilling to treat or which may not be amenable to intervention. Some veterinarians are asked to provide euthanasia services to a local animal shelter,[1] resulting in a situation that poses other unique considerations.

We also do not know all of the circumstances leading up to the decision on the part of the owner to ask that their pet be put to sleep. Occasionally, the difficult task of euthanasia is requested because the pet is a burden to the owner, affecting the mental and/or physical health of that person or because the owner may have passed away and there is no one to care for the pet that may have some very special needs. The number of excuses, reasons, and simply requests made of the veterinarian for such services seems to grow exponentially daily.

In the course of treating pets, it sometimes becomes necessary to gently suggest to an owner that the time has come for them to consider releasing their beloved pet from a circumstance that no longer provides significant quality of life. Not infrequently, the client will acknowledge this suggestion and indicate that he/she too was thinking this might be appropriate but was afraid the veterinarian would not agree. This has important repercussions upon the ongoing doctor-client relationship. Before such a step is undertaken, it is important to consider the situation. We must be certain that the care the veterinarian is providing is in fact all that is available or requested. Under such circumstances, a second opinion consultation or a referral to a specialist may be in order. It is clearly important to recognize this in advance because the decision to euthanize is not one easily taken and one that is often not forgotten by the client, but rather dwelled upon in some detail. If the client feels that the veterinarian did not judiciously use all of the available resources in his/her community to help this pet, very negative feelings may develop. This could affect the client and the client's decision to return at a later date with another pet. Further, making such a recommendation without consideration of other options also leaves the veterinarian open to question by the client. Should the client decide that this is not the right course and then seek independent review of the case, there can be more serious problems if the animal is subsequently successfully treated after the first veterinarian recommends euthanasia. The veterinarian must recognize, too, what is considered the standard of care for such a problem in that area.

The discussion of euthanasia involves four key factors[2]:

1. Clear communication of the pet's conditions.
2. Assessing the client's feelings and desires, and empathizing with them.
3. Explanation of the process and options associated with euthanasia.

4. Giving grief support and providing outside support resources.

If a pet's condition has deteriorated to the point where the quality of life is poor, how can we best communicate this to the owner? Honest communication describing the professional assessment helps provide the basis for client decision-making. Such a conversation may go as follows: "Robert, Fluffy's heart failure has progressed to a point that medication is no longer effective in maintaining his quality of life. His lungs are being compressed by fluid so that he can't obtain sufficient oxygen for the body to function properly. This is why he is reluctant to lie down." A similar discussion could take place with any medical condition that has impaired the quality of life to the point of suggesting euthanasia. There are schemes[2] to assess the quality of life, but it always is a judgment call based on our knowledge and experience as practitioners of veterinary medicine. Some clients respond immediately and clearly that such an option is not something to be considered. If so, note this directly in the record and proceed with caring for the patient as the owner requests. Decision-making, especially when the veterinarian differs in opinion from the owner, is very difficult. However, it is the choice of the owner and not the veterinarian. Assuming all professional efforts are made to help the pet, then the veterinarian has the responsibility to provide humane care and comfort as best as possible for the pet and the owner. Second opinion referral may also be advisable.

Every client has a different thought process about his or her pet's quality of life. Part of our job is to support the owner's choice.

Reassurance to the client at this point is helpful. Often, agreeing with the client will help. Many clients suggest that the pet is going to heaven, to be with another past pet, to go where things are better. This is not the time or place to differ with the hopes and desires of the owner. It is their pet, their belief system, and their decision. The veterinarian should not be the decision-maker. Often, even suggesting a time period for treatment, say "another day or two to see if this medication will help before we make this difficult choice," may be enough. At times, the client will then ask if it really will make any difference and this can be a time for the veterinarian to offer his/her opinion. Another request that may occur in the office or on the telephone is requesting that euthanasia services be provided at the client's home (see below for a discussion on home euthanasia).

The process of euthanasia in the clinic should be explained along with the option for the client to be present or not. The discussion should include how the client wishes the pet's remains to be handled. Private cremation or burial is an option. In many larger cities, when disposal is requested, it may mean rendering of the body. While this is not something pleasant to discuss, the owner should not be told a lie but rather the facts must be presented. Fees for euthanasia (which can be substantial) and for the disposal of the body should be discussed. Client complaints in this area are not unusual, in part because this occurs during the grieving process and at this stage of the process the client may be angry at what is perceived to be high fees for something that is so unpleasant. It is here that one hears complaints about inappropriate fees, price gouging, or simply, "You are supposed to love pets, but you charged me so much more money than it should have been." Much of this is resolved by advanced discussion and payment. This also allows the client to leave the hospital without having to deal with payment when the bereavement process is so acute.

One area for discussion prior to euthanasia is whether children should participate or be in the room when this is taking place. Of course, ultimately it is the owner's choice; however, often owners will request the opinion of the veterinarian. Generally, our belief is that anyone who cares for the pet and wishes to view the procedure should be there. Occasionally, one of the adults will stay and one will leave, again a personal option. Sometimes the client will ask only to see the pet momentarily after the euthanasia is completed. With respect to the children, we recommend that children too young to really understand the process not be permitted to view the procedure because it may frighten them or make them leery of anything given to them by injection at some later date. On the other hand, young children who love and know their pet, who understand what is happening, and who wish to be with their pet and their parents should be acknowledged and given the privilege of viewing the process and being with their pet. Lying to children about this process is not recommended, and we as veterinarians should not participate in extending an untruth told to them. We want them to understand suffering, humane care, and the role the veterinarian plays in the important human-animal bond process.

If the pet is to be euthanized during the office visit, dealing with the charges and payment should be handled with sensitivity. A possible scenario might be, "While we take Fluffy away for a few minutes to place a catheter in his vein, my nurse has a form for you to sign and she will take care of your bill with you so that you won't have to stop at the desk after we put Fluffy to sleep." If euthanasia will take place at a future visit, fees should be collected prior to entering the exam room on the day of euthanasia. Some[2] have suggested that a dedicated room with soft lighting, candles, and flowers be used for euthanasia. The reality is that in many clinics cramped for space this is not possible. Some method should be in place for alerting staff that a

euthanasia is taking place so that a solemn and sensitive environment is created toward not only the pet's owner and family, but also toward other clients who may be aware of what is to take place. Try to have the staff prepared for the euthanasia and avoid loud noises or laughter on the part of the other hospital personnel when such a serious procedure is being attended to. Often, this simple process is not recognized and causes discontent on the part of the pet's owner. More often, the soft, compassionate staff expressing their true feelings to the client helps to assuage guilt and sadness and allows the process to move along smoothly. If at all possible, set aside a more quiet time of the day for the client to come for this service. It provides the client with a quieter atmosphere and one that is less hectic. If this is anticipated to be a difficult and long, drawn-out process, do not schedule it for the end of the day, when closing the clinic interferes with the client remaining with the patient. Some clients will stay for significant periods of time, causing havoc with the hospital's staff.

The process of the euthanasia itself can be very moving and comforting to the owner if properly prepared. In virtually every case where the client wishes to see and be with the pet, an intravenous catheter should be placed first. Always have saline-filled syringes to check on the patency of the catheter even if it was just placed. Explain to the owner the actual process that you choose to use. Some veterinarians prefer only to use euthanasia solution, others administer the solution after a short acting anesthetic is given, and others prefer to give diazepam or another tranquilizer first to lessen any impact that the pentobarbital solution will have on the central nervous system. The important thing is to explain in detail what will happen, to have an assistant in the room to help hold the pet, and, if the owner wishes to hold the pet as well, to allow them to do so without hampering the process of injecting the euthanasia solution. Infusions, given slowly and efficiently, help the process. Often the pet relaxes quickly, but the veterinarian should continue to administer all of the drugs and should not withhold medication assuming that the pet has died. Not at all unusual is for the pet to continue to breathe for another few moments or for the heart to continue beating. These bodily processes disturb the client and can make them feel distrustful. Some clients believe that veterinarians want to experiment on their pets, and they must be assured that the pet is really dead: that the heart has stopped beating, and that the respirations have ceased. Some clients (rarely) ask to listen with the stethoscope to assure themselves that the pet is dead, and if they do, it certainly behooves the veterinarian to allow that to happen without comment. We prefer at this time to speak softly to those in the room, offer them the opportunity for alone time with their pet, and to quietly leave the room.

Home euthanasia may be requested by the client and should be offered to the client if that is their preference. The veterinarian may not provide this service outside of the hospital and the regular veterinarian may refer the client to someone who does do house call services including euthanasia. Regardless, the consent of the owner should be obtained before any work has commenced. This allows the client to pay full attention to his or her pet and permits the veterinarian to proceed in a professional manner. Arrangements for euthanasia, handling of the remains of the body and other final considerations should be determined prior to taking any activity regarding the procedure. Explanation of what is the plan and how the pet will respond should be undertaken before beginning any drug administration. Collection of fees should be done prior to proceeding, since the owner may be too upset after euthanasia has occurred to consider or discuss fees. Papers that need to be signed should also be completed before proceeding with drug administration.

If the pet is a cat or smaller animal, it is best for the doctor to hold the animal for the initial subcutaneous injection so that the animal will not bite the owner who is likely to be hovering over the pet. Explain to the owner that they will have all the time they need to cuddle or stroke their pet once the sedative takes effect. Usually this occurs after 5-10 minutes and then the animal is in a deep plane of sedation and ready for the final injections. These are given SC, IV or via the intraperitoneal or intrathoracic route depending upon the drugs used, whether there is help available to the veterinarian and the patient's condition. If intravenous drugs are to be used, it is best to shave a small amount of hair at the site of the venous injection. Use of a good quick-release tourniquet is important if the final injection is to be given IV if there is no assistant to help hold off the vein. Every housecall veterinarian has his or her own special combination of drugs used for euthanasia. Frequently dexmedetomidine (Dexdomitor) at 3-5 mcg/kg or tiletamine-zolazepam (Telazol) at 3-5 mg/kg are utilized. Butorphanol may also be administered to provide deep sedation. After 5-10 minutes, when the pet is deeply unconscious, pentobarbital is administered to euthanize the pet.

After the procedure is completed, it is appropriate to express support and sympathy to the client. Ask if they would like a few moments alone with their deceased pet and, if so, withdraw. Explain once again that there may be some muscle twitching which is normal, a deep breath or final expiratory effort may be made, and as the muscles begin to relax the pet might even urinate. Explain that these are normal signs. Also, many owners expect the veterinarian to listen for heart sounds with a stethoscope—they see it daily on TV and in the movies and such a step may be comforting despite the fact that you know the pet died moments ago during the injection process. Some clients express concern that the eyes are not closed; they should be told

that this usually does not occur in people either (again, the TV and movie expectation). Everything should be done with respect for the client. A phone call a few days later to ask how the client is doing is appropriate, as is a sympathy card or a donation to any of the many foundations that accept donations on behalf of a deceased pet. One of our clinics (SE) has sent personalized letters to clients, always with a hand-written note on the letter. Clients return with another pet years later, often expressing the importance of the written note that was personalized.

If, on the follow-up phone call, the client is struggling to cope with the loss, it would be appropriate to refer the client to a grief counsellor. Be prepared by consulting with a local mental health care professional to know what resources are available in your community. If you have mental health care professionals whom you work with, be prepared to offer names to the client. We like to have both psychologists and psychiatrists on our lists and both men and women so that the client may also find comfort in choosing a health care professional. Lengthy discussions regarding the final days, health condition, or laboratory tests often occur with the client who remains unwilling to accept the loss of the pet. While it is more than appropriate to discuss these with the client, record such discussions in the medical record, and be prepared to assist the client in understanding the process. It is also important to recognize when the process goes beyond normal grief and requires professional help. Part of this process is offering to discuss the situation with the client. In the majority of cases this is all that is required. If more is required, be prepared to offer some help but do not allow lengthy discussions to occur if they remain unfruitful and offensive. Offering to continue discussions at a later date, providing written material on the disease process, or even allowing the client to come and review the radiographs and discuss the problem in the office can be helpful. One good method of helping the client is to offer to see them in the office on a no-charge appointment. Have the records, lab tests, and radiographs prepared. Ascertain that the client understands the time limit set for the appointment. Often explaining that your time has elapsed and that you do have another client waiting can make a good ending. Advise the client that if he/she feels that another appointment is necessary, your staff would assist them in making another appointment. Usually there should be a consultation fee for further visits.

Euthanasia can be a difficult time for the pet owner. If the veterinarian and staff are sensitive and caring throughout the process, long-term relationships through multiple pets' lives are often the result. It is of particular importance to help the client not feel guilty over their decision.[3] By implementing and practicing dialogs such as those described above and establishing procedures to empathetically deal with euthanasia, the client and the staff benefit. Role-playing at staff development meetings can be an aid to teach the skill needed for this difficult task. If the staff has been prepared and trained to provide this important service, the process will flow with compassion and professionalism.

One critical component of euthanasia is the method by which the office handles the disposition of the body. More clients are lost to other hospitals here than at any point in the process, other than the lack of professionalism and sensitivity on the part of the veterinarian and staff to the client. It is essential for the hospital to have a well-organized system for determining how the body is to be disposed of. Carefully identifying the body, the pet's name spelled properly, the owner's name spelled properly, and the choices of the owner are incredibly important. Methods for holding the body must also be considered. A hospital should have a time limit during which bodies can be held and the client must be informed of this. Have a limited number of options available to the client, carefully and repeatedly make certain that this is understood, and have the staff do the same with the owner. Then be certain that there is a hospital policy for who handles the body, how it is handled, and what is to become of it. Lost bodies that were intended for private burial and/or cremation cause untold havoc, anxiety, displeasure, and the loss of a client. Such problems simply should not occur when all of the arrangements for euthanasia have been made correctly, fees are discussed and received, and papers requesting euthanasia and handling of the remains of the body are completed in a well-organized facility. Every aspect of this process should also be clearly noted in the medical record and signed by the person acknowledging the decisions being made by the owner. Requests for euthanasia over the phone should be heard by a second member of the staff at the time the phone call occurs and both members of the staff should note this in the record and sign their names for legal purposes.

The process of euthanasia also impacts the veterinary staff. Patients that we have cared for over the years become special to us as well, and we may suffer their loss. Encourage the staff to discuss their feelings and express themselves. This can ward off burnout or compassion fatigue and build the regard for each other as well as team relationships.[4] Staff who have been especially close to the client, the pet, or the medical process may express personal feelings about being present at the time of euthanasia and if possible these feelings should be acknowledged. Similarly, allowing the staff to express their feelings to clients is a wonderful way to let the client know how much everyone cares. A condolence letter or card written by the doctor and the staff is a very important part of closure for all.

Euthanasia represents the end of what may have been a long relationship with a client and his or her pet. During this period, much has been shared in the lives of the family and the veterinary hospital. A good closure is really important to the client and the veterinarian. We were fortunate to have taken care of an important member of the family and to have shared in many experiences. Closure is helpful to all involved and often represents not only closure but also a new beginning. This may be veterinary medicine at its very best!

Selected Web site links for those seeking additional sources of information on euthanasia or pet loss:

- http://csu-cvmbs.colostate.edu/vth/diagnostic-and-support/argus/Pages/default.aspx
- http://www.pet-loss.net
- https://www.aspca.org/pet-care; then go to end of life care
- http://www.vetmed.wsu.edu/PLHL/
- http://www.pethospice.org/NHFP%20FRAME.htm

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SECTION II

Differential Diagnosis for Chief Concerns

OUTLINE

General
Cardiorespiratory
Neurologic
Gastrointestinal
Urogenital

General

OUTLINE

Chapter 8 “Ain't Doing Right”: The Nonspecific Chief Concern of Ill Thrift
Chapter 9 Distinguishing Behavioral Disorders from Medical Disorders
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CHAPTER 8

"Ain't Doing Right": The Nonspecific Chief Concern of Ill Thrift

Stephen J. Ettinger, Edward C. Feldman, Etienne Côté

Ill thrift refers to a vague change in activity level, mental arousal, behavior, or some combination thereof. Often, it is difficult for clients (pet owners, caretakers, family members) to describe it clearly, and they simply can characterize the situation as "He's not himself" or "Ain't doing right" (ADR). Subjectively, it is a common reason for veterinary consultations and it can be caused by a disorder of essentially any organ system.

The hallmark of ill thrift is its nonspecific nature: instead of a discrete clinical sign like coughing or inappetence, ill thrift connotes a poorly defined decrease in vitality. A second characteristic is the wide variability in severity of the underlying cause. Ill thrift can be associated with trivial disorders requiring minimal treatment, or it can be the first manifestation of disorders that progress to life-threatening states. In some cases, it is further complicated by the nature of the concern, the client voicing his or her concern, and the reality of the situation. Usually, these are real concerns, but in other situations they are totally benign processes misidentified by a client with a heightened sense of anxiety. Regardless of the veterinarian's feelings about the concern, it should always be taken seriously and investigated in such a way that the patient's health concern is addressed correctly and the client is guided appropriately.

Virtually any disorder in veterinary internal medicine can cause ill thrift as its clinical expression. The goal of evaluating the patient with ill thrift is foremost to determine severity. When the underlying cause is benign and self-resolving, efforts can focus on exclusion of more serious disorders, on client reassurance, and on monitoring parameters and milestones. When the underlying cause seems likely to be persistently harmful to the patient, the veterinarian's efforts should focus on defining the extent of the problem and on more intensive and immediate intervention.

Since the range of possible diagnoses for ill thrift is vast, the first step necessarily should be a review of the patient's signalment and medical history.

Signalment

Signalment is an important general guide, beginning with the patient's *age*. Young animals are more likely to have ill thrift due to congenital malformations, parasitoses, or ingested foreign bodies or substances, for example. Conversely, mature dogs and cats have a higher prevalence of degenerative diseases and neoplasia. A patient's *somatotype* is important: large-breed dogs have a higher prevalence of osteosarcoma, splenic and cardiac neoplasia, and many other disorders. Small-breed dogs are overrepresented with respect to degenerative/myxomatous mitral valve disease, chronic pancreatitis, and others. Chondrodystrophic breeds have a higher prevalence of intervertebral disc disease, which can manifest with nonspecific signs that a client interprets as not feeling normal. *Gender* has an obvious link to the prevalence of reproductive disorders like pyometra and acute prostatitis, but also to certain disorders like immune-mediated polyarthritis, which has a higher prevalence in females. Any of these disorders first can manifest with vague signs of ill thrift. Importantly, these broad generalizations are nonspecific, and conclusions drawn from a patient's signalment must be kept loose and amenable to change because these guidelines, like the clinical algorithms included in most chapters of this textbook, offer the clinician a starting point and preliminary orientation.

Medical History

A detailed review of the medical history is the next important step. Experience suggests that ill thrift notoriously can trigger suspicions in a client's mind that can be unfounded, such as poisoning by a neighbor, or concerns about infectious disease outbreaks triggered by news headlines. These represent a client's

rationalization of observed signs within the limits of his or her understanding: the immediate environment, the animal's typical behavior, and increasingly, the most readily available information on the Internet. Such interpretations can be useful, or can be misleading, and a skilled veterinarian should consider the client's insistence and convictions with a suitable degree of internal skepticism. Just as importantly, key items of the history could be overlooked by the client and only become apparent on careful questioning. Therefore, the medical history should be explored in a way that is not leading or suggestive, to avoid miscommunication with clients, but in a way that also is thorough and insightful. See ch. 1.

Key aspects of the medical history in patients with ill thrift include:

- Frame of reference. A first-time pet owner might not be familiar with normal interindividual variations in energy and stamina among dogs or cats, whereas an experienced and astute client can identify important, subtle signs that are not even apparent to the veterinarian initially.
- Duration and course. The client should be asked when the pet last was normal, and how the general malaise evolved over time. Medically important ill thrift can be of any duration. If the condition seems to have continued without change for days to weeks or more, two important possibilities should be considered. A chronic disorder could be present, which could be producing obvious physical abnormalities (e.g., morbid obesity, severe osteoarthritis) that might not be as obvious to the client as to the veterinarian and the owner simply feels that the pet "ain't doing right." Alternatively, the client might be misinterpreting the animal's normal state as being abnormal. The latter possibility is more challenging to confirm and generally emerges as a diagnosis of exclusion after completion of diagnostic testing. An important third possibility is a disease that follows a waxing-waning course, and this information must be elicited during the collection of the medical history.
- Exposure, environment, and habits. An adult dog that has never been inquisitive and does not like to mouth objects is unlikely to have ill thrift from intestinal obstruction due to ingestion of a foreign body, for example. Similarly, an indoor cat is unlikely to be exposed to toxic substances that are found outdoors. The client's habits can be informative: dropped (human) medication tablets, missing sewing needles or thread, remodeling of an older home (lead poisoning), the possibility of outdoor exposures (spider bites, plant foreign bodies, encounters with wildlife), use or misuse of nutritional supplements and nontraditional diets and remedies, and a home with a garage (where the animal can have ingested ethylene glycol antifreeze) are examples of important clues.
- Vital functions. The veterinarian should ask about the pet's appetite, and ability to prehend and swallow food; about any changes in elimination of feces and urine; and about change in diet, including dietary indiscretion.

Physical Examination

Together, the findings from the signalment and medical history can allow the clinician to create an initial, often general, differential diagnosis list. In all cases, this information then is refined through interpretation of physical examination findings. The physical exam, which always begins with a hands-off observation of the animal's mentation and gait, is described in detail in ch. 2. The process, and the application of physical examination findings, is as relevant to patients with ill thrift as to patients with any general presenting concern, including a wellness examination.

Diagnostic Tests

Often, a conclusive diagnosis is not reached with signalment, history, and physical exam findings alone. Additional, objective information is available in the form of diagnostic test results. Diagnostic tests provide information on two levels: abnormal results suggest—or conclusively identify—the causative problem, whereas normal results increase the level of reassurance that a serious problem is less likely.

Test selection for patients with ill thrift can be considered according to whether the patient is considered a serious case or a nonserious case. *Serious cases* have one or more of the following characteristics: presence of overt systemic signs that suggest hypovolemia or hemodynamic instability (e.g., poor perfusion, weak/absent pulse, severe cardiac arrhythmia, evidence of dehydration), neurologic compromise (e.g., depressed mentation, locomotor deficits, generalized weakness), respiratory difficulty (e.g., dyspnea, inappropriate tachypnea), or persistent pain (e.g., change in mentation, subdued behavior, guarding). Obvious, externally visible abnormalities such as wounds or spontaneous hemorrhage of course can be evidence of serious disorders, but these specific findings lie outside the realm of ill thrift as a poorly defined, general state of malaise. *Nonserious cases* have none of the characteristics listed above. Specifically, nonserious cases have

normal (or, in the veterinarian's opinion, insignificantly abnormal) physical exam findings for all body systems, notably the cardiovascular, neurologic, and respiratory systems. When the distinction is unclear as to whether a patient is a serious or nonserious case, both the veterinarian's concern and the client's concern (and the client's logistical, financial, and emotional factors) are used for guiding the degree of diagnostic testing to be pursued.

In nonserious cases, basic tests are implemented according to the information obtained in the history and physical examination. A first tier of tests that applies to many situations includes a packed cell volume and total solids, blood glucose, estimation of blood urea nitrogen (e.g., Azostix), urine specific gravity, and a urine dipstick profile. Often, this information and much more can be obtained with the same blood and urine samples, and only a marginally higher cost to the client, via a complete blood count, serum biochemical profile, and complete urinalysis. Clients who make an appointment for their pet to be evaluated for nonspecific malaise should be encouraged to bring a sample of the pet's urine, collected at home in a clean and sealed container. Simple analysis can be performed prior to meeting the client and seeing the patient, which immediately informs the clinician of some important diagnoses (e.g., diabetes mellitus, renal concentrating capacity, various causes of discolored urine). A serum total thyroxine level can be considered for adult cats, and retroviral testing for all cats. A serologic titer for heartworm disease is warranted in endemic areas. Thoracic and/or abdominal radiographs have value if the signalment, history, and physical exam suggest a structural lesion in the thorax or abdomen as the leading differential diagnosis.

In serious cases, these same tests are indicated, and often are followed by a second tier of tests. These additional tests can investigate abnormalities found on the first tier of tests, or they can explore the most likely remaining differential diagnoses given the disorders that have been ruled out by normal results on the first tests. Importantly, serious cases are more likely to produce diagnostic test abnormalities that give a clear direction to the treatment that is necessary.

Depending on the context, including the client's ability and desire to monitor the animal at home, perceived importance of hospitalization for observation, cost of testing, and the client's history of similar situations with other pets, the client may wish to forgo any diagnostic testing and monitor the animal at home. In nonserious cases, such an approach is acceptable, and monitoring typically should involve client assessments of mentation, appetite, ambulation, respiration, digestion, water intake (which the client can measure at home if there is a concern about polydipsia; normal is <100 mL/kg/24 hours in dogs and cats, and usually <80 mL/kg/24 hours), and general responsiveness. Persistent abnormality or worsening of any of these parameters warrants reevaluation and diagnostic testing. The veterinarian should explain to the client both the advantages and the drawbacks of not pursuing testing initially if this direction is chosen. The explanation should be informative without eliciting a sense of guilt in the client, nor the perception of the veterinarian trying to force the client to commit to testing. Importantly, the veterinarian needs to outline how he or she expects the patient's situation to evolve if the problem is self-resolving versus how it is expected to evolve if the problem is worsening. This type of explanation helps the client feel the veterinarian cares, and it empowers the client to pursue tests and treatment with the veterinarian if deterioration occurs, rather than being left with the impression that the veterinarian lost interest because the full array of tests was not pursued. A useful option is to give the client a sheet of paper on hospital letterhead and a broad, written plan, e.g., (1) Exam and history; (2) Blood panel; (3) If not better in 7 days or worse anytime, radiographs (X-rays); (4) If no answers and the problem persists, ultrasound/referral/other; etc. This gives the client a continuum of what could be necessary and the client may then ask for all of it to be done or none of it. A copy in the medical record is useful for continuity if colleagues care for the animal later, and for medicolegal purposes. A follow-up phone call from a staff member in 24-48 hours helps the client understand that the veterinarian cares, and provides early troubleshooting if the problem is worsening.

In serious cases, if the client declines diagnostic testing, the veterinarian needs to provide monitoring guidelines that include indicators of suffering; describe risks that could be posed to the client, including zoonosis, bite wound injuries, and the like, where applicable; and provide recommendations for supportive care.

Treatment

Treatment of patients with ill thrift depends on the inciting cause. When none is found, supportive care can be provided, either by the veterinarian and his or her staff in the hospital or by the client at home. Treatment might need to be implemented sooner, or the patient might be more likely to require hospitalization, in serious compared to nonserious cases.

Ill Thrift That is Not a Sign of Disease

An important element that helps differentiate medically serious from medically nonserious cases of ill thrift is background information that could be affecting the client's perception of the animal's quality of life. The recent loss of another pet or other member of the family, recent illness in the family, forthcoming travel where the pet is being left behind, and other sources of anxiety, tension, and guilt can trigger a heightened level of concern and unjustly raise the perception of ill thrift. This is a common situation in small animal practice and it must neither be overapplied nor discounted too quickly. Without being intrusive, the veterinarian should be mindful of the critical role of these types of circumstances and assess whether the intensity of the client's response might place "overinterpretation of normal signs" on the differential diagnosis, rather than a true medical disorder. "Client overinterpretation," then, becomes a diagnosis of exclusion. A complete physical examination and evaluation according to the serious/nonserious approach described above can identify important problems when they are present, or can be reassuring to the client when results are within normal limits. Follow-up, both to identify emerging disease and to create an atmosphere of support for a concerned client, becomes especially important in this context.

Another example of "relative" ill thrift that can reflect normal variation is the natural decrease in spontaneous activity often associated with aging in an animal with no historical or physical abnormalities to indicate cognitive dysfunction, neurologic disease, or other internal disorder. Often, a client compares a pet to its former self, or to a fellow animal, and identifies "ill thrift" not associated with any existing or emerging disease. Such situations simply can reflect normal maturation and its associated behavioral and physical changes that remain within normal limits. If no abnormalities are present on physical exam or diagnostic tests, or if abnormalities emerge that are considered too mild to explain the client's concern, then having the client videorecord the clinical signs when they occur can be valuable, as can specific laboratory testing guided by the features of the history and physical exam.

Resolution

Follow-through for patients who "ain't doing right" is important. Nonserious cases that fully respond to nonspecific treatment or whose clinical signs simply normalize with time still should be addressed. Veterinarians should request that the client communicate an update to the veterinary hospital staff. Such feedback then needs to be entered in the animal's medical record. This way, the client understands that the veterinarian cares about the patient's outcome and the client bears some of the responsibility for communicating with the veterinary hospital after discharge. Cases that worsen at home instead of improving, or serious cases that are discharged, should be followed more closely, with telephone updates and return visits for reevaluation as dictated by the patient's signs, response to treatment, and perceived severity of the underlying problem. Typically, such deterioration also triggers the emergence of new physical signs that can be more specific, leading to additional diagnostic testing, treatment, and/or referral to a specialist.

Suggested Readings

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CHAPTER 9

Distinguishing Behavioral Disorders from Medical Disorders

Diane Frank

Client Information Sheet: Distinguishing Behavioral Disorders from Medical Disorders

Introduction

Distinguishing behavioral disorders from medical disorders can be challenging. Owners will often report that their animal is ill because of behavioral changes.[1] Behavioral "problems" of animals can be subdivided into undesirable normal behaviors (species-appropriate behaviors that humans dislike) or undesirable abnormal behaviors (behavioral disorder, behavioral illness) (Figure 9-1). *Behavioral disorders* typically have one or several of the following characteristics: (1) the behavior is inappropriate for the context (i.e., one cannot justify the behavior in that situation); (2) the behavioral sequence is altered; (3) the frequency is excessive for the context; (4) the severity and/or duration is excessive for the context; (5) the animal exhibits signs compatible with anxiety in one or several contexts.

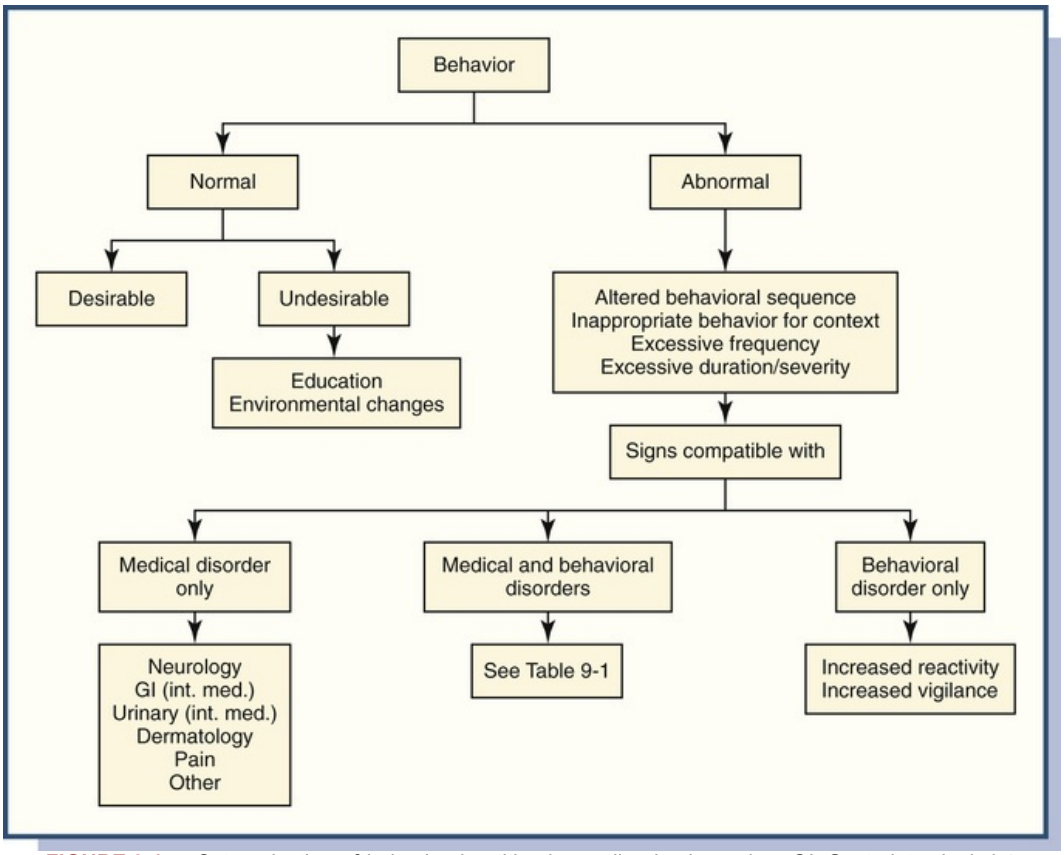

FIGURE 9-1 Categorization of behavioral entities in small animal practice. *GI,* Gastrointestinal; *int. med.,* internal medicine.

Medical disorders or *painful conditions* can have one or several of the following: inappropriate behaviors for the context, altered behavioral sequences, increased frequency and/or duration of behaviors. For example, a dog with a brain tumor could be presented for veterinary care due to sudden-onset aggressive behavior that is not appropriate for the context; a dog or cat that self-mutilates because of pain will have an altered behavior sequence because the animal does not stop the chewing/biting behavior and eventually causes self-injury; and a pruritic cat or dog will lick or groom itself more frequently or for longer periods than normal.

Therefore, certain changes in behavior are nonspecific. Other behavioral changes that can be associated with either medical or behavioral disorders could include appearance of a new behavior (e.g., hiding) or disappearance of a normal behavior (e.g., no longer playing), inappropriate behavior (e.g., aggression "out of the blue"), and changes in frequency and/or duration of normal behaviors.

Truly behavioral disorders ("mental illness") could therefore be defined as behaviors that are inappropriate for the context, have an altered sequence, are excessive in duration and/or frequency, occur in the absence of other identifiable medical disorders, or some combination of these features. It is important to remember that comorbidity of medical and behavioral disorders also occurs, perhaps more often than recognized.

In addition to this overlap of signs for medical and behavioral disorders, many terms used in behavioral medicine as diagnoses are in fact nonspecific signs. Examples could include urine marking, inappropriate elimination, and all of the repetitive behaviors (also called "obsessive compulsive disorders" or "compulsive disorders"), including but not limited to pica, fly-biting, circling, and tail chasing. And finally, signs compatible with anxiety overlap with signs of pain, discomfort or medical conditions.[2] Some examples (Table 9-1) could include restlessness, pacing, vocalizing, panting, licking lips, and repetitive swallowing.

TABLE 9-1

Anxiety Signs Compatible with Behavioral Disorders, Medical Disorders, or Concurrent Medical and Behavioral Disorders

SIGNS	MEDICAL (± PAIN) DISORDER ONLY	BEHAVIORAL DISORDER ONLY	CONCURRENT MEDICAL (± PAIN) AND BEHAVIORAL DISORDER	EXAMPLES OF MEDICAL CAUSES OTHER THAN ANXIETY DISORDERS
Aggression	✓	✓	✓	Neuro
Agitation	✓	✓	✓	GI (abd pain); Neuro; Pain
Air licking	✓		✓	GI; Neuro
Avoidance	✓	✓	✓	Pain
Attention-seeking		✓		
Checking (rear end)	✓		✓	GI; Pain
Circling	✓	✓	✓	Neuro
Destruction		✓		
Dilated pupils	✓	✓	✓	Ophtho; Neuro
Ears pulled back		✓	✓	Pain/discomfort
Elimination	✓	✓	✓	Urinary; Neuro; Endocrine; GI
Excessive activity	✓	✓	✓	GI; Neuro; Pain
Excessive licking of surfaces	✓		✓	GI; Neuro
Flank sucking	✓		✓	GI; Derm; Neuro
Fly-biting	✓		✓	GI; Neuro; Ophth
Hiding	✓	✓	✓	Pain/discomfort
Immobility/freezing	✓	✓	✓	Pain/discomfort
Increased reactivity*		✓		

Increased vigilance†		✓		
Lip licking	✓	✓	✓	GI
Lowered body posture	✓	✓	✓	Pain/discomfort
Lowered tail	✓	✓	✓	Pain/discomfort
Pacing	✓	✓	✓	Pain/discomfort; GI
Panting	✓	✓	✓	Pain; Cardio; Resp; etc.
Paw lifting (forelimb)	✓	✓	✓	Pain/discomfort; Neuro
Pica	✓		✓	GI; Neuro
Repeated swallowing	✓	✓	✓	GI
Repeated yawning		✓	✓	
Restlessness	✓	✓	✓	Pain; Neuro; GI (abd. pain)
Salivation/drooling	✓	✓	✓	GI; Dental; Neuro
Self-mutilation	✓		✓	Pain; Derm; Neuro; etc.
Shaking/trembling	✓	✓	✓	Pain/discomfort; Neuro
Star-gazing	✓		✓	GI; Neuro; Pain
Tail chasing	✓		✓	Neuro
Vocalization	✓	✓	✓	Pain
Wandering	✓	✓	✓	Neuro

*Increased reactivity includes signs such as piloerection; long recovery time after an event; propensity to startle easily; appearance of a dog that seems "unable to hear" owner instructions during undesirable behavior (aggression) as opposed to a dog that does not want to obey. See Video 9-5.

†Increased vigilance includes signs such as constant visual scanning; inability to relax; keeping eyes half closed (i.e., the dog is exhausted; different from eyes half closed due to pain/globe retraction). See Video 9-1.

Abd, Abdominal; *Der,* dermatologic disorder; *GI,* gastrointestinal disorder; *Neuro,* neurologic disorder; *Ophtho,* ophthalmic disorder; *Resp,* respiratory disorder.

Behavioral Disorders

Anxiety is a dominant feature of many behavioral disorders and can be an important characteristic for differentiating behavioral from medical disorders. Anxiety is defined as an emotional state associated with adaptive physiological and behavioral responses. Anxiety becomes a disorder when it is exhibited in contextually inappropriate situations or in natural ones but at a level that impairs adaptive responses.[3] Anxiety disorders in companion animals generally are characterized by increased reactivity (heightened arousal)[4] and increased vigilance. The normal dog spends most of its time in a calm, non-vigilant, non-reactive state. The reactive/anxious dog spends most of its time being vigilant (unable to relax even though, in some cases, the dog is totally exhausted) and overly reactive (Video 9-1). An affected dog might startle more easily even at the sound of day-to-day "regular" noises. This dog in specific situations could exhibit piloerection more rapidly and more frequently, could be difficult to interrupt (e.g., the dog "seems unable to hear" the owner), and requires more time to return to "normal" baseline behaviors after an event of inappropriate or undesirable behavior.

Age of Onset of Signs

Behavioral disorders generally are observed in young animals,[5,6] although some exceptions occur. In dogs, behavioral disorders such as redirected aggression, interdog aggression, and impulse-control aggression (formerly called dominance aggression) are reported to commonly occur at social maturity (18-24 months).[7,8] In dogs, anxiety disorders other than aggression often develop in young individuals (e.g., 6 to 18 months) or

at the onset of social maturity.[6] Similarly, in cats, anxiety-related disorders such as intercat aggression or status-related aggression typically appear when the cat reaches social maturity (2-4 years of age).[9] This prevalence by age group can help to raise or lower the likelihood of a behavioral disorder as the cause of clinical signs in an individual patient.

Two studies[10,11] showed that the behaviors of approximately 10% of puppies were significantly different from the behaviors of their peers. One study described puppy behavior in the veterinary clinic.[10] One hundred and two 8- to 16-week-old puppies (46 males, 56 females) that had been adopted at least 1 week prior to evaluation were observed and videorecorded. The evaluation was divided into three different parts: (1) free-floor assessment; (2) physical examination; and (3) specific manipulations. Most puppies (free on the floor) behaved in a similar fashion. They were very active and oriented to the environment (exploring), silent, and not panting. They interacted little with the veterinarian. However, about 10% of puppies were outliers that did not explore, were panting, were vocal (whining or barking), and sought active interaction (jumping up and barking) with the veterinarian.

During the physical examination with pups placed on a table, the "outliers" actively tried to avoid the physical examination, panted, and held their ears drawn back. These "outliers" also licked their lips and yawned during both the physical examination and manipulations on the floor. Many behaviors expressed by the "outliers" were compatible with recognized signs of anxiety such as panting, excessive motor activity (pacing), active avoidance, vocalization, decreased exploration, flattened ear position, lip licking and yawning. This study illustrated that some individuals behave very differently at a young age.

In another study,[11] 32 puppies (16 males and 16 females), ranging in age from 50 to 118 days (mean 82.1 days) were videorecorded at home alone for 60 minutes. The recording process was repeated after 1 and 2 months, yielding a total of 3 recordings per puppy. Puppies were mainly inactive, resting, or sleeping. Vocalization, lip licking, and oral behaviors (chewing, biting, destroying items), which are signs compatible with stress-related/anxious behaviors and tended to cluster together in the dogs of this study, were apparent in 3/32 (10%) of puppies. Although this study did not follow up on all puppies' future behaviors, one of the 3 "anxious" puppies did exhibit separation anxiety as an adult and required treatment. Overall, these findings support the clinical experience of an early-age onset of behavioral disorders. They suggest that careful history-taking can detect signs compatible with anxiety at an early age in puppies, and that such elements in a thorough medical history can be valuable in helping to differentiate behavioral from medical causes of clinical signs.

Potential Medical Disorders in Dogs

Oral Repetitive Behaviors Including Pica, Surface Licking, Fly-Biting, Air Licking, Flank Sucking, and Self-Mutilation

In general, these oral repetitive behaviors are most likely signs of medical disorders in isolation, or possibly with concomitant behavioral conditions. Historically, oral repetitive behaviors were considered almost universally to be of primary behavioral origin, but newer investigations have identified direct causal associations between some of these signs and primary gastrointestinal (GI) and other abdominal disorders. These signs could be heightened by anxiety and coexisting behavioral disorders, but in general, oral repetitive behaviors should carry a broader differential diagnosis than primary behavioral disorders alone.

Pica is defined as the ingestion of non-food items. Owners generally do not distinguish between destruction and pica. If destruction occurs during the owner's absence, the dog should be filmed home alone before diagnosing separation anxiety. One destructive dog tentatively diagnosed with separation anxiety was filmed home alone and slept during the entire duration of the owner's absence. The destruction was associated with pica and the dog also had a history of intermittent diarrhea. Following medical investigation, the dog was diagnosed with inflammatory bowel disease (IBD). With a change in diet and treatment with prednisone, both the diarrhea and pica improved. Whenever the prednisone dosage was decreased, the dog resumed pica. This case illustrates the importance of obtaining GI biopsies when performing surgery for GI foreign body removal in dogs (see ch. 275 and 276), particularly in cases of "repeat offenders," because the foreign body ingestion may be the consequence of primary GI disease; in turn, such GI disease may be escaping detection if it is manifesting through clinical signs that are misinterpreted as being purely behavioral in origin.

Based on preliminary studies and case reports, GI disease can manifest with unusual behavioral signs including excessive licking of surfaces,[12] fly-biting,[13] and star-gazing.[14] In general, there are also other subtle signs of GI disease, such as presence of flatulence, borborygmus, eructation, lip licking, repetitive swallowing,

or drooling, although not always (Videos 9-1, 9-2, 9-3A, 9-3B, 9-4A, 9-4B, 9-4C, 9-5, 9-6A, and 9-6B). Owners will not necessarily report these subtle GI signs unless asked about them specifically.

In a study of dogs licking surfaces (floors, walls, blankets, sofas, etc.) excessively,[12] where patients received concurrent evaluations by a behavioral medicine service and an internal medicine service, 14/19 dogs (74%) had GI disorders including eosinophilic or lymphoplasmatic GI infiltration, delayed gastric emptying, irritable bowel syndrome, chronic pancreatitis, giardiasis, and a gastric foreign body. Mean duration of the "behavior" problem (e.g., how long the dog had been licking surfaces) was 32 months (range 0.08 to 82). Sixteen of the 19 dogs licked surfaces daily. Following treatment for the underlying condition, complete resolution of signs was achieved at 90 days in 53% (9/17) and in 59% (10/17) at 180 days (unpublished results). Three dogs showed both a decrease (more than 50%) in duration and in frequency of licking bouts at 180 days. Therefore, 76% of dogs (13/17) improved significantly clinically over the 6 month follow-up. Of the 5 dogs without GI abnormalities and treated non-specifically (hydrolysed protein diet), two dogs stopped licking by day 90. One of the surface-licking dogs was also air licking (repetitive horizontal tongue movement in and out of the mouth), retching, and closing his eyes partially; endoscopy revealed a 12-inch (30 cm) piece of rope in the stomach, which had been present for an estimated 6 months prior to presentation. Treatment included endoscopic removal of the foreign body and a switch to a hydrolysed protein diet, and both the GI signs (air licking, surface licking, and retching) and the pain-related sign (eyes partially closed)[15] ceased once this treatment was implemented (see Videos 9-6A and 9-6B).

Fly-biting is defined as an activity where the dog appears to be snapping at imaginary flies.[16] In one case series, medical investigation of seven fly-biting dogs[13] revealed that the onset of fly-biting occurred within the wide age range of 6 months to 10 years. At the time of presentation, dogs had exhibited fly-biting from six days to four years. Frequency of bouts varied from once daily to once hourly. Duration of a single bout varied from seconds to one hour. At home, fly-biting was more frequent following feeding in three dogs. The most significant finding was the occurrence of head-raising and neck extension preceding jaw snapping in all dogs. Clinical presentation was similar for all seven dogs. In two cases raising the head and extending the neck occurred more frequently than snapping. Underlying medical abnormalities included gastric and/or duodenal eosinophilic or lymphoplasmacytic infiltration, and delayed gastric emptying. Two dogs had gastroesophageal reflux during endoscopy. One dog had no histological abnormalities but presented a very flaccid and distended stomach on ultrasonographic and endoscopic examination. Medical treatment of the underlying GI disease resulted in complete resolution of fly-biting in 5/6 dogs (within 30 days for 4 dogs, including one dog that had been fly-biting for 2 years). Four dogs also presented behavioral changes compatible with anxiety (pacing, panting, hiding, increased attention seeking) along with the fly-biting episodes. These signs disappeared once the underlying GI disease was treated (see Videos 9-3, 9-4A, and 9-4B).

Some of the repetitive behaviors also labelled as obsessive-compulsive disorders, such as "flank sucking," "self-mutilation," and "checking," could in fact be secondary to somatic or visceral neuropathic pain. Inflammatory bowel disease could, in some cases, be causing anal sac disease.[17] Therefore "checking behaviors" reported in Miniature Schnauzers and "flank sucking" in Dobermans should include GI disease in the differential. These dogs could be experiencing pain or discomfort and are therefore looking repeatedly ("checking") at the hind end or sucking the flank. Similarly, in cats, one case series identified that a majority (16/21 cats; 76%) suspected of having psychogenic alopecia in fact had an underlying medical cause.[18]

Self-mutilation should always alert the veterinarian to the possibility of pain. Pain can be local or neurogenic (see ch. 126 and 356). However, animals should still be assessed for behavioral disorders when pain is suspected. Neuropathic pain often is worsened by stimuli that evoke a sympathetic response, such as the startle response and emotional arousal.[19] Therefore, arousal (increased reactivity often seen in anxiety disorders) can contribute to neuropathic pain.

Summary

- Typically, behavioral disorders are seen in young animals. Dogs suffering from anxiety disorders tend to be more vigilant and reactive.
- For oral repetitive behaviors, owners should always be questioned about more subtle GI signs such as flatulence, borborygmi, eructation, neck extension and stretching, lip licking, tongue flicking, repetitive swallowing, or drooling in addition to more obvious signs such as vomiting, diarrhea, or tenesmus.
- Gastrointestinal biopsies should always be taken when performing surgery for GI foreign body removal in dogs, particularly in cases of "repeat offenders."

- Medical and behavioral disorders may occur concomitantly, and probably more so than is currently recognized. A thorough history of all signs will help to identify these patients as well as address both the medical and behavioral conditions.

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CHAPTER 10

Dermatologic Manifestations of Systemic Disease

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Client Information Sheet: Dermatologic Manifestations of Systemic Disease

While not always thought of as "an organ," the skin is, in fact, the body's largest and most visible organ. With an epidermal turnover time of approximately 22 days in dogs, it is also quite "dynamic."[1] Cutaneous markers of internal diseases are common and often indicative of or consistent with specific systemic diseases (E-Table 10-1). Cutaneous signs may be the result of the same etiologic agent or pathogenic process as the systemic condition (bacteria, protozoa, fungal, immune-mediated and neoplastic disorders). Alternatively, signs may be due to hormonal changes, genetic links, or other factors. Recognizing typical cutaneous signs may facilitate diagnosis of an underlying disease process. Skin is easily the most accessible organ for obtaining samples used in cytology, biopsy for histology, culture, and other tests.

E-Table 10-1

Summary of Cutaneous Manifestations of Systemic Diseases

CUTANEOUS LESION(S)	ASSOCIATED SYSTEMIC DISEASE(S)	OTHER FINDINGS	DIAGNOSTIC TESTS
Hypotrichosis/generalized alopecia	Hypercortisolism	Polyuria/polydipsia, hepatomegaly, thin skin, bruising, muscle wasting	Skin scrapings (rule out *Demodex*), DTM culture (rule out dermatophytes), trichogram (rule out color dilute alopecia), hormonal assays (cortisol, ACTH stimulation test, dexamethasone suppression test, ACTH, thyroid hormones, TSH, estradiol, insulin-like growth factor)
	Hypothyroidism	Brittle, faded hairs, pinnal margin alopecia, alopecia of bridge of nose, thickened skin (mucinosis), bradycardia, lethargy	
	Hyperestrogenism	Feminization (gynecomastia, pendulous prepuce), linear preputial erythema	
	Pituitary dwarfism	Small stature, retained deciduous teeth	
Diffuse hypotrichosis with scales and crusts	Feline thymoma-associated exfoliative dermatitis	Waxy debris between digits and in clawfolds	Skin biopsy, thoracic ultrasound, radiograph, CT or MRI
	Cutaneous T-cell lymphoma	± cutaneous plaques or nodules, footpads may also be affected	Skin biopsy, immunohistochemistry
Facial + dorsal alopecia, erythema, scaling,	Leishmaniasis	Weight loss, lethargy, polyarthritis, anemia,	Cytology, skin biopsy, PCR assay, serology

crusting		renal disease, onychogryposis, depigmentation	
	Lupus erythematosus	Polyarthritis, fever, protein-losing enteropathy, anemia, thrombocytopenia	Antinuclear antibody test, Coombs test, skin biopsy
	Exfoliative cutaneous lupus erythematosus (German Shorthaired Pointers)	Polyarthritis, pain, hunched back	Skin biopsy, rule out other differentials
Alopecia, erythema, scaling, crusts affecting face, legs, tail	Dermatomyositis (Collies, Shetland Sheepdogs, others)	Variable dysphagia, abnormal gait and/or megaesophagus	Skin biopsy, muscle biopsy, EMG
Alopecia with shiny skin involving periocular region, ventral neck, ventrum and legs (cat)	Feline paraneoplastic alopecia (pancreatic adenocarcinoma, biliary cholangiocarcinoma, hepatic carcinoma)	Rapid onset, may be pruritic if secondary *Malassezia* dermatitis; Skin is shiny but not fragile	Skin biopsy, abdominal ultrasound, CT, or MRI
Cutaneous erythema, alopecia, scales, crusts of mucocutaneous junctions, ± footpads	Zinc-responsive dermatosis	Most common in Arctic breeds (Alaskan Malamutes, Siberian Huskies), also reported in Pharaoh Hounds	Skin biopsy (parakeratotic hyperkeratosis)
	Lethal acrodermatitis (Bull Terriers)	Autosomal recessive in Bull Terriers, other signs include splayed digits, dysphagia, small stature, secondary infections	Skin biopsy (parakeratotic hyperkeratosis)
	Canine distemper	Also commonly have nasal hyperkeratosis, history of respiratory or neurologic signs	Skin biopsy, immunohistochemistry
	Superficial necrolytic dermatitis (concurrent hepatic disease, diabetes mellitus or pancreatic tumor, e.g., glucagonoma)	Skin lesions may be result of hypoaminoacidemia as consequence of elevated levels of glucagon or hepatic insufficiency	Skin biopsy, serum biochemical profile, serum amino acid levels, abdominal ultrasound
	Erythema multiforme (trigger may be an adverse drug reaction, systemic infection or neoplasia)	Skin lesions are a result of T-cell mediated apoptosis of keratinocytes	Skin biopsy, evaluate history for clues of adverse drug reaction, infection or neoplasia
	Paraneoplastic pemphigus	May also have stomatitis and other lesions; canine cases have been associated with splenic lymphoma and thymoma	Skin biopsy, abdominal ultrasound, thoracic radiographs
	Cutaneous T-cell lymphoma	Wide variety of clinical presentations	Skin biopsy and immunohistochemistry
Cutaneous plaques	Calcinosis cutis—	PU/PD, history of	Skin biopsy, serum biochemical profile,

	hypercortisolism, renal disease, systemic granulomatous disease (blastomycosis)	exogenous or endogenous corticosteroids or progesterone administration; concurrent granulomatous disease or renal disease	review treatment history, history of blastomycosis or other systemic fungal disease
	Xanthomas—hyperlipidemias (familial, diabetes mellitus, hypercortisolism, hyperprogesteronism)	Familial hyperlipidemia has been associated with xanthomas in cats, most cases are secondary to diabetes mellitus, hypercortisolism or hyperprogesteronism	Skin biopsy, serum biochemical profile, serum lipid profile, review history of previous treatments
	Hyperpigmented—papillomavirus associated	May progress to squamous cell carcinomas	Skin biopsy, immunohistochemistry, PCR for papillomavirus
	Eosinophilic—hypersensitivity associated	Cats—associated with flea, food or environmental allergies	Skin biopsy, allergy workup
	Cutaneous T-cell lymphoma	May also have generalized scaling and/or mucocutaneous lesions	Skin biopsy, immunohistochemistry
Cutaneous nodules	Collagenous—nodular dermatofibrosis	Most common in German Shepherd Dogs, concurrent renal cystadenocarcinoma or cystadenoma, also uterine leiomyoma or leiomyosarcoma	Skin biopsy, abdominal ultrasound, CT, MRI
	Sterile nodular panniculitis (SNP)—pancreatic panniculitis	SNP can be associated with pancreatitis or pancreatic neoplasia; cutaneous lesions may ulcerate	Deep skin biopsies (include subcutaneous fat), rule out infectious causes of panniculitis; abdominal ultrasound, pancreatic lipase immunoreactivity
	Infectious—pyogranulomatous nodules may develop in association with blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis and aspergillosis	Infectious pyogranulomas usually occur secondary to dissemination of a systemic fungal infection to the skin, less commonly from direct cutaneous inoculation	Cytology and/or biopsy of the skin nodules often results in identification of the organism responsible for the lesions
Skin fragility	Cutaneous asthenia due to abnormal collagen fibril formation	May be associated with joint laxity or hernias	Skin biopsies for histopathology, ultrastructural and/or biochemical evaluation
	Feline acquired skin fragility may develop secondary to hypercortisolism, FIP, or hepatic disease	Skin is fragile and tears easily	Skin biopsy, serum biochemical profile, abdominal ultrasonography

Thick skin	Excessive mucin accumulation results in thickening of the dermis in dogs with hypothyroidism, acromegaly, and is a breed characteristic of Chinese Shar-Pei dogs	Clinical signs of hypothyroidism are highly variable; those of acromegaly include inspiratory stridor and thickening of interdental arcade and thick, hard claws	Thyroid hormones, TSH, evaluation for other diseases, measurement of IGF-1 levels and history are helpful in diagnosis

ACTH, Adrenocorticotropic hormone; *CT*, computed tomography; *DTM*, dermatophyte test medium; *EMG*, electromyography; *FIP*, feline infectious peritonitis; *IGF-1*, insulin-like growth factor-1; *MRI*, magnetic resonance imaging; *PCR*, polymerase chain reaction; *PU/PD*, polyuria/polydipsia; *TSH*, thyroid-stimulating hormone.

Systemic Diseases Associated with Alopecia

Overview

There are numerous differential diagnoses for diffuse hair loss. The classic systemic diseases associated with generalized alopecia are the endocrinopathies: hypothyroidism, hyperadrenocorticism, hyperestrogenism, and pituitary dwarfism. It is always important to rule out other potential causes, including demodicosis, dermatophytosis, bacterial folliculitis, pattern baldness, follicular dysplasias, congenital hypotrichosis, telogen effluvium, color dilution alopecia, sebaceous adenitis, and epitheliotrophic lymphoma.[2]

Hypothyroidism (see ch. 299)

Thyroid hormone is necessary for hair follicles to cycle into the anagen phase. In a hypothyroid animal, hairs remain "in telogen" until shed, resulting in a dull hair coat composed of mature hairs that are not replaced following shedding or shaving. Hair loss commonly first develops over the bridge of the nose, ear pinnae, tail and elbows. The skin may become thickened due to an accumulation of hyaluronic acid in the dermis (mucinosis). Secondary bacterial skin and ear infections are common in hypothyroid dogs.[2]

Hypercortisolism (Hyperadrenocorticism) (see ch. 306 and 307)

The skin is a sensitive indicator of hypercortisolism in dogs with both non-specific (alopecia, secondary infections, poor wound healing) and specific findings (thinning of skin, calcinosis cutis). Early changes include a dull hair coat and alopecia. Over time, many affected dogs develop thin skin. In some, the skin may demonstrate hyperpigmentation, easy bruisability, phlebectasias (dilated blood vessels), striae (pigmented stretch marks), poor wound healing, secondary infections and/or calcinosis cutis.[2]

Hyperestrogenism (see ch. 319)

Hyperestrogenism may develop in female dogs as a result of an estrogen-secreting ovarian neoplasm or follicular cysts. Ovarian cysts in most dogs are clinically silent, being either non-functional or progesterone-secreting. Cutaneous signs of estrogen excess include bilaterally symmetric alopecia, enlarged vulva and nipples, and a history of abnormal estrous cycles. Male dogs may develop hyperestrogenism as a result of an estrogen-secreting testicular tumor, most commonly a Sertoli cell tumor (particularly common in cryptorchid testes). Clinical signs include nipple enlargement, pendulous prepuce, ventral hyperpigmentation, attracting male dogs, and atrophy of the non-neoplastic testicle. Any dog is at risk for iatrogenic hyperestrogenism including a small percentage of the dogs being given estrogen-containing compounds for urinary incontinence. Additionally, iatrogenic estrogenism can occur after contact with or consumption of creams or patches intended for human use. A unique cutaneous manifestation of hyperestrogenism in male dogs is linear preputial dermatosis—a linear, erythematous or hyperpigmented narrow band of skin located between the preputial orifice and the scrotum.[3] A tentative diagnosis may be made based on clinical signs, physical examination, serum estrogen concentrations (variable depending upon which estrogen metabolite is measured), and abdominal or testicular ultrasonography.

Pituitary Dwarfism

Pituitary dwarfism (see ch. 295) has been reported as an autosomal recessive disorder in the German

Shepherd Dog and Karelian Bear Dog. Affected dogs develop a bilaterally symmetric alopecia (E-Figure 10-1), proportionate dwarfism, and delayed eruption of permanent teeth. Clinical signs and low circulating IGF-1 concentrations are consistent with this disorder.[2]

E-FIGURE 10-1 German Shepherd Dog with pituitary dwarfism exhibiting generalized thinning of the hair coat.

Systemic Diseases With Diffuse Hypotrichosis, Scales and Crusts

Feline Thymoma-Associated Exfoliative Dermatitis (see ch. 245)

Skin lesions of erythema, crusting and scaling with alopecia may be the first sign of disease in cats with a thymoma. Secondary infections with *Malassezia* may cause pruritus. Affected cats may later develop coughing, dyspnea, anorexia and/or weight loss. Skin biopsies demonstrate hydropic interface dermatitis with apoptotic keratinocytes. Imaging may demonstrate a mediastinal mass. Surgical removal may be curative.[4,5]

Epitheliotropic/Cutaneous T-Cell Lymphoma (see ch. 344)

Epitheliotropic cutaneous lymphoma can cause erythroderma, alopecia, variable pruritus, scales, crusts, plaques, nodules, leukoderma, mucocutaneous ulcers, and/or depigmented, ulcerated or hyperkeratotic footpads. A few affected animals also have neoplastic lymphocytes in circulation (Sezary syndrome). Diagnosis can usually be confirmed with skin biopsy and immunohistochemistry.[2]

Systemic Diseases With Facial and Dorsal Erythema, Alopecia, Scaling and Crusting

Leishmaniasis (see ch. 221)

Skin lesions have been observed in > 80% of dogs with visceral leishmaniasis, most commonly, silvery white scales over the head, pinnae and limbs and periocular alopecia. Nasodigital hyperkeratosis, onychogryposis

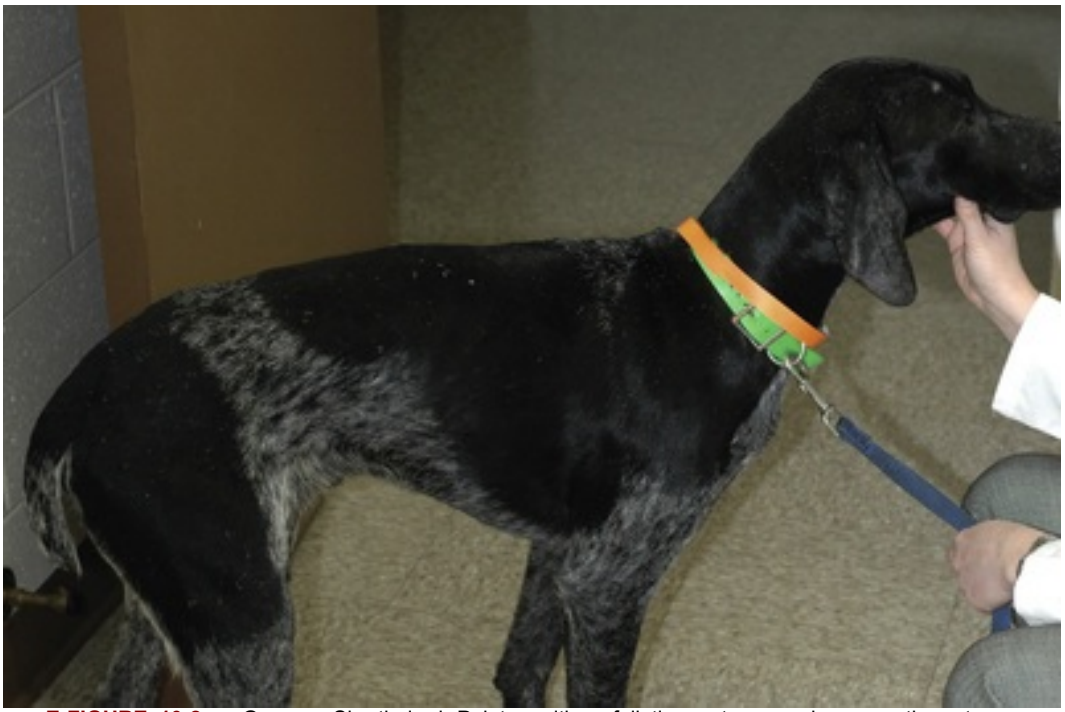
(deformed overgrowth of the nails), paronychia, nasal depigmentation and nodular dermatitis may be present. Systemic signs include lethargy, weight loss, generalized lymphadenopathy, hepatosplenomegaly, muscle wasting, cachexia, fever, epistaxis and lameness. Kidney disease may lead to polyuria and polydipsia. Diagnosis may be confirmed by finding the organism on skin biopsy, polymerase chain reaction (PCR) assay, cultures or serology.[2]

Lupus Erythematosus

Lupus erythematosus is an autoimmune, inflammatory, multisystemic disorder of complex etiologies that may have clinical manifestations restricted to the skin or involve multiple organs (see ch. 205). Discoid lupus erythematosus (DLE) causes skin lesions which are usually restricted to the face, particularly the planum nasale and dorsal surface of the nose. However, severe DLE may involve the nasal turbinates causing epistaxis and the potential for secondary infections.[6] Systemic lupus erythematosus (SLE) is a multisystem disease with variable clinical presentations. Skin lesions are present in 40% to 50% of cases.[7] Skin lesions are usually symmetrical and vary from mild scaling and/or alopecia of the face and dorsum to severe ulcerations. Various other signs may be present depending upon the organ systems affected. Skin biopsy from an affected area should demonstrate hyperkeratosis, epidermal atrophy, basal cell vacuolar degeneration, basement membrane zone thickening and mononuclear cell infiltration at the dermoepidermal interface.[2]

Exfoliative Cutaneous Lupus Erythematosus (ECLE)

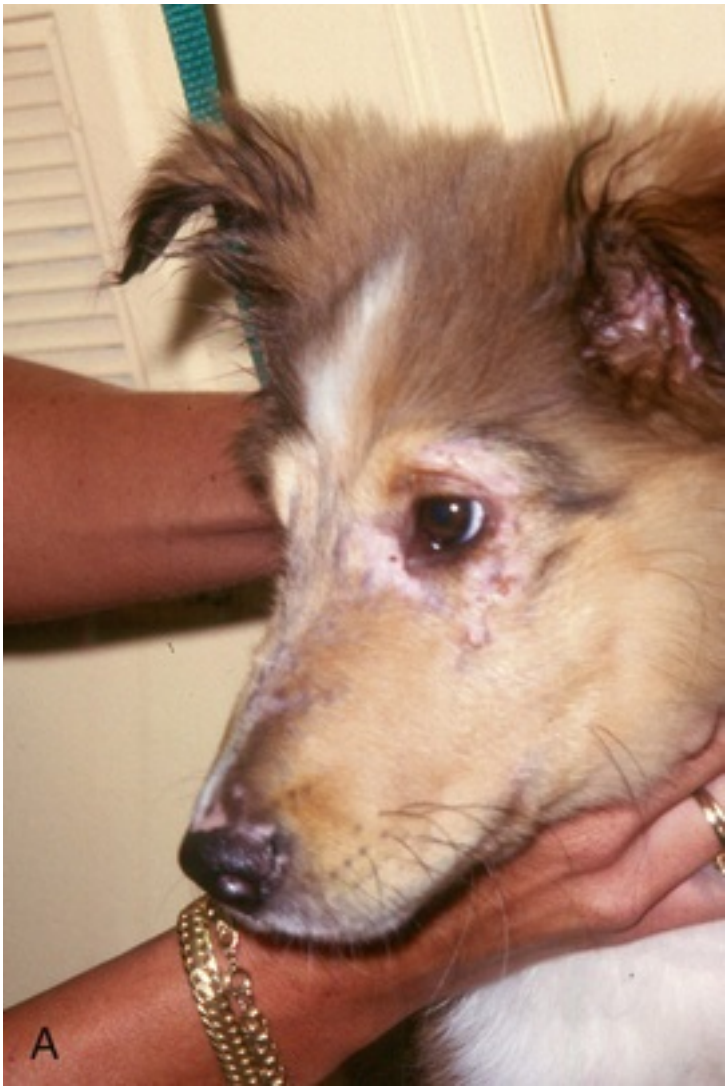
ECLE is a familial form of lupus affecting German Shorthaired Pointer dogs.[8,9] Skin lesions are often the first abnormality observed and include excessive scaling and crusting of the muzzle, pinnae and dorsum (E-Figure 10-2). As the disease progresses, some dogs become severely lame and/or develop renal disease. Diagnosis is made on clinical signs and compatible skin biopsy results: hyperkeratosis, epidermal atrophy, basal cell vacuolar degeneration, basement membrane zone thickening and mononuclear cell infiltration at the dermoepidermal interface. Most affected dogs are euthanized before 4 years of age.[8,9] A genome-wide association study identified a SNP allele on canine chromosome 18 that "segregated with the disease."[10]

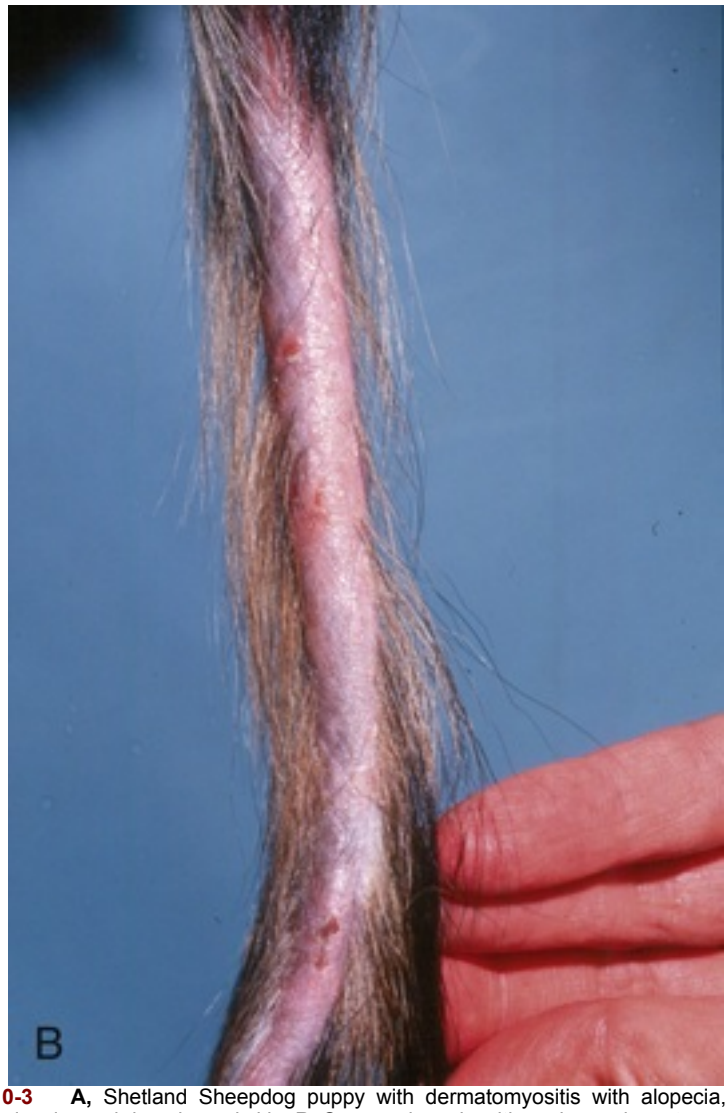


E-FIGURE 10-2 German Shorthaired Pointer with exfoliative cutaneous lupus erythematosus exhibiting generalized cutaneous scaling.

Systemic Diseases With Alopecia, Erythema, Scales and Crusts Affecting Face, Legs and Tail; Dermatomyositis (DM)

DM is an inflammatory disease affecting skin and/or muscle. In dogs, DM occurs most often in Collies and Shetland Sheepdogs. Skin lesions vary from mild to severe, starting with small focal areas of crusting, scaling and alopecia. The condition most commonly affects the face, lower extremities and tail (E-Figure 10-3). Over time, their skin becomes atrophic. Concurrent muscle involvement may result in dysphagia and gait abnormalities. Affected dogs may develop megaesophagus. The disease is thought to be autosomal dominant with incomplete penetrance in Collies.[11] A study of linkage disequilibrium (LD) mapping in Shelties had evidence of LD linkage to microsatellite marker FH3570 on canine chromosome 35.[12] Gene expression profiles failed to detect any disease-specific autoantibodies.[13] This disorder has also been classified as an ischemic dermatopathy.[14] Diagnosis can be confirmed histologically from affected skin tissue, which usually demonstrates scattered hydropic degeneration of cells in the stratum basale, follicular atrophy, perifollicular fibrosis, mild perivascular to interstitial dermatitis and vasculitis. Histopathology of muscle may demonstrate fiber necrosis and atrophy.[15]





E-FIGURE 10-3 **A,** Shetland Sheepdog puppy with dermatomyositis with alopecia, scaling and crusting of periocular and dorsal nasal skin. **B,** Severe alopecia with scales and crusts on the tail of the Shetland Sheepdog puppy in **A.**

Systemic Diseases With Alopecia and Shiny Skin of Periocular Region, Ventral Neck, Ventral Abdomen and Legs; Feline Paraneoplastic Alopecia (see ch. 352)

Rapid development of extensive alopecia in an older cat may be the first sign of underlying pancreatic or hepatic neoplasia.[16] Hair loss often begins around the eyes and may rapidly progress to the ventral neck, abdomen and legs (Figure 10-4). Hairs epilate easily and the alopecic skin appears shiny but not fragile. Secondary *Malassezia* infections may result in excessive grooming. Some cats also have dry, scaly footpads. Histopathology should demonstrate miniaturization of hair follicles and adnexa with epidermal hyperplasia. Pancreatic adenocarcinoma is most commonly associated with this syndrome. Less frequently, hepatic carcinoma or biliary cholangiocarcinoma has been diagnosed. Pancreatic or hepatic tumors may be identified with imaging or exploratory laparotomy. The prognosis is grave. One cat who improved following surgical removal of a pancreatic adenocarcinoma, relapsed due to metastatic disease.[17]

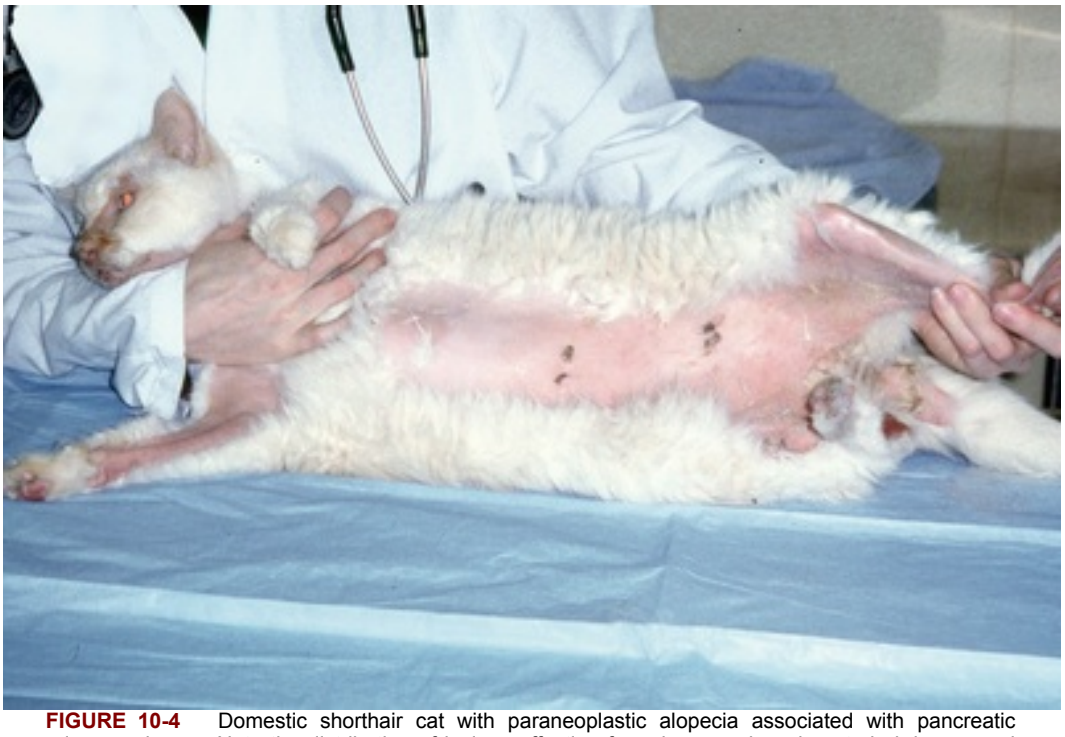


FIGURE 10-4 Domestic shorthair cat with paraneoplastic alopecia associated with pancreatic adenocarcinoma. Note the distribution of lesions affecting face, legs, neck and ventral abdomen and the shiny texture of the skin.

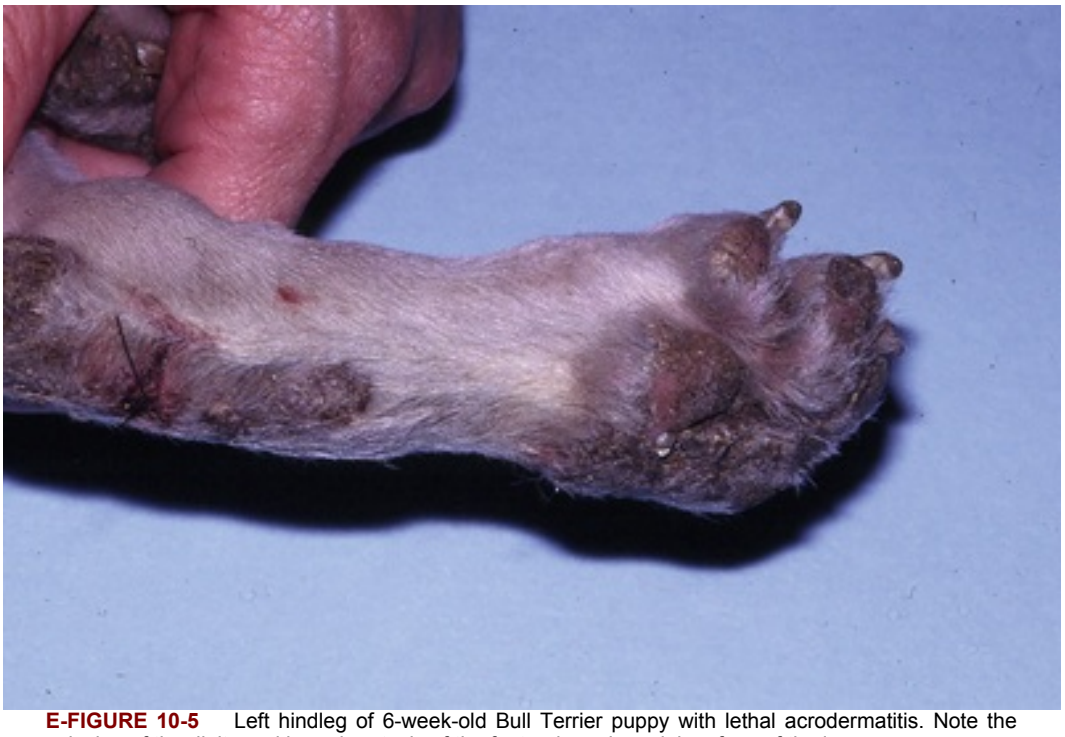
Systemic Diseases With Cutaneous Erythema, Alopecia, Scales and Crusts of Mucocutaneous Junctions and Footpads

Zinc-Responsive Dermatitis

Skin lesions associated with zinc deficiency or zinc-responsive dermatitis include areas of erythema, alopecia, scales and crusts starting on the face, mucocutaneous junctions, feet and footpads. Other findings may include decreased appetite, weight loss, impaired wound healing and increased susceptibility to secondary infections. Alaskan Malamutes and Siberian Huskies are most often affected, perhaps due to decreased intestinal absorption of zinc.[18,19] Pharaoh Hounds have also been reported to have a severe form of the disease.[20] Diagnosis may be confirmed with histopathology that demonstrates parakeratotic hyperkeratosis in a dog with low serum zinc concentrations and improvement following oral and/or intravenous zinc supplementation.

Lethal Acral Dermatitis/Acrodermatitis

Bull Terriers may be affected by an autosomal recessive condition associated with defective zinc and copper metabolism and altered production of liver proteins. Affected puppies have lighter than normal skin pigmentation and often have difficulty chewing and swallowing. They develop splayed digits in addition to crusting and cracking of their footpads (E-Figure 10-5) and ulcerated crusted lesions on their ear pinnae and mucocutaneous junctions. Foot lesions may progress to onychodystrophy, paronychia and interdigital pyoderma. Systemic signs may include diarrhea and respiratory infections. Most affected dogs succumb to secondary infection before 7 months of age. Diagnosis is tentatively made based on signalment, clinical signs, decreased serum and liver zinc concentrations, and parakeratotic hyperkeratosis on skin histopathology.[21-23]



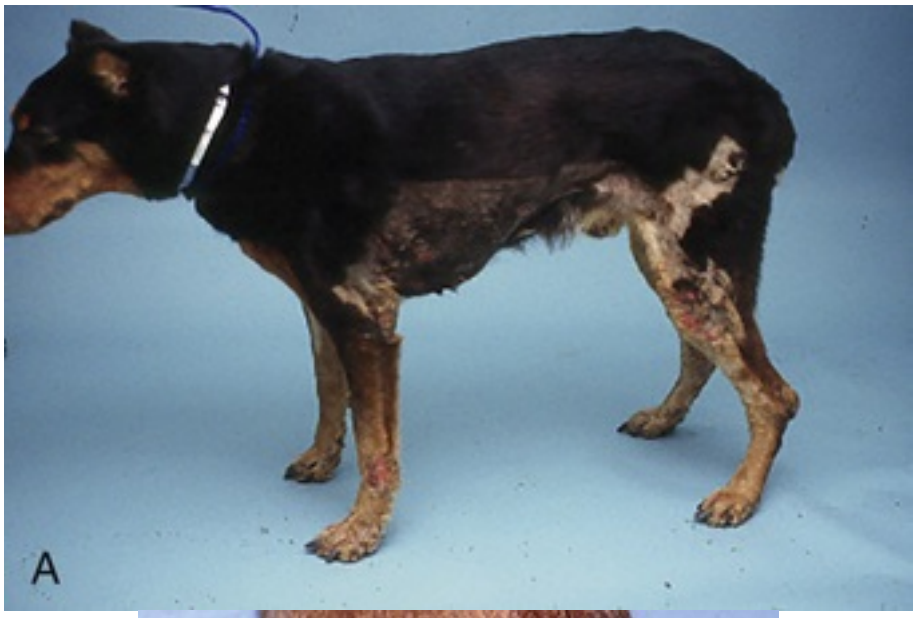
E-FIGURE 10-5 Left hindleg of 6-week-old Bull Terrier puppy with lethal acrodermatitis. Note the splaying of the digits and hyperkeratosis of the footpads and caudal surface of the leg.

Canine Distemper (see ch. 228)

The classical skin manifestation of canine distemper is "hard pad disease" due to hyperkeratosis of the footpads (and planum nasale). Early in the disease, some affected dogs develop superficial pustules (impetigo). Skin biopsies may show the presence of intracytoplasmic inclusion bodies in keratinocytes. Immunohistochemistry (IHC) may be used to detect canine distemper virus.

Superficial Necrolytic Dermatitis (SND), Metabolic Epidermal Necrosis (MEN), Hepatocutaneous Disease, Necrolytic Migratory Erythema (NME) (see ch. 285)

In people, this condition represents a cutaneous marker for alpha$_2$-glucagon-producing pancreatic islet cell tumors. Skin lesions are caused by degeneration of keratinocytes, resulting in epidermal edema and necrosis. Only a small proportion of dogs with classical lesions of SND, however, have underlying glucagonoma, the majority having had liver disease.[24-26] Degeneration of keratinocytes is believed due to hypoaminoacidemia resulting in inadequate nutrients to maintain a viable epidermis. Lesions begin in areas of high cell turnover including mucocutaneous junctions, face, footpads and pressure points (Figure 10-6). The lesions include crusts and ulcerations with perilesional erythema. Most affected dogs also have a non-regenerative anemia, mild hyperglycemia, increased serum liver enzyme activities and a "honeycomb-appearing" liver on abdominal ultrasonography. Serum amino acid concentrations are decreased. Dogs with pancreatic tumors usually have increased circulating glucagon concentrations.[27] The disease in cats has been associated with pancreatic tumors and chronic liver disease.[28,29] Skin biopsy findings are unique for this syndrome and consist of basal cell hyperplasia, vacuolar degeneration of the stratum spinosum and parakeratotic hyperkeratosis ("blue," "white" and "red" zones). Prognosis is grave, although surgical removal of a pancreatic tumor may be curative in the unlikely scenario that metastasis has not occurred.[30]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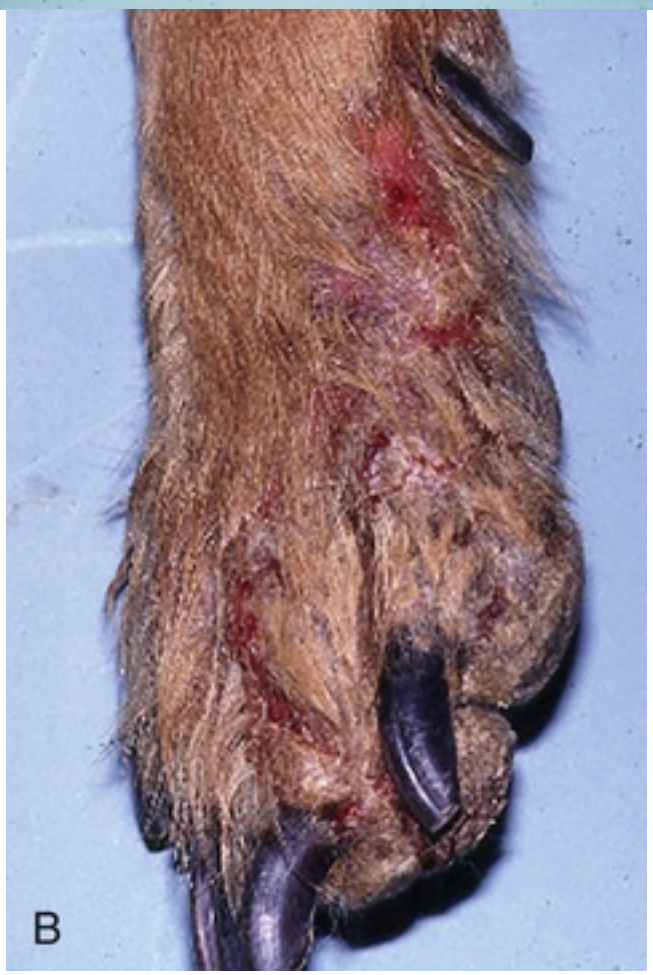
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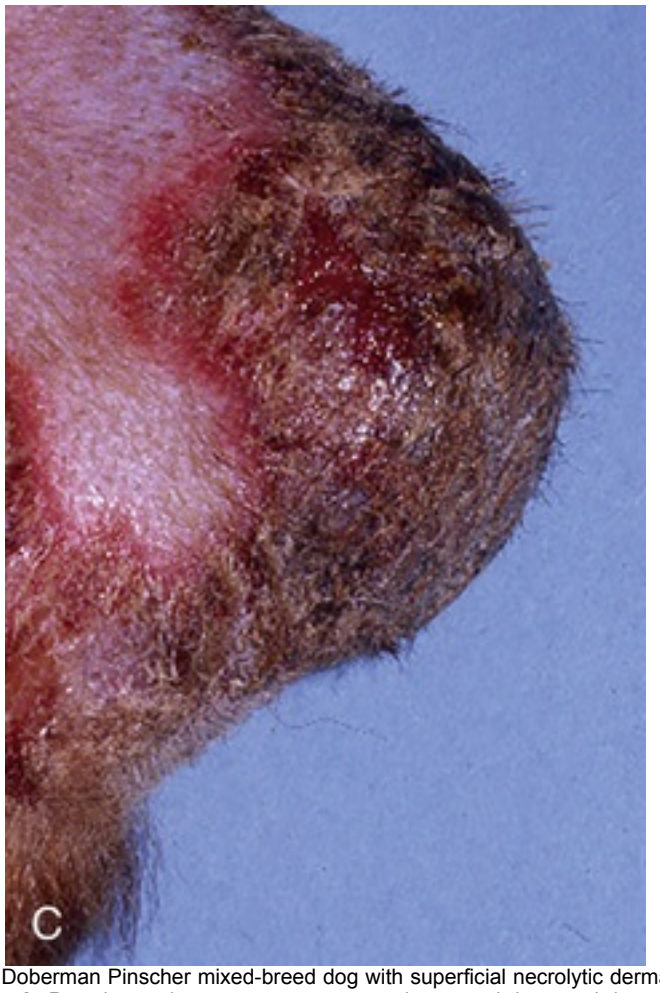


FIGURE 10-6 Doberman Pinscher mixed-breed dog with superficial necrolytic dermatitis associated with liver disease. **A,** Pustules and crusts are present on the ventral thorax, abdomen and limbs. **B,** Ulcerations and crusts of lower leg and footpads of dog in **A. C,** Ulceration and crusting over hock of dog in **A.** Note the intense erythema of the skin adjacent to the crusts.

Paraneoplastic Pemphigus

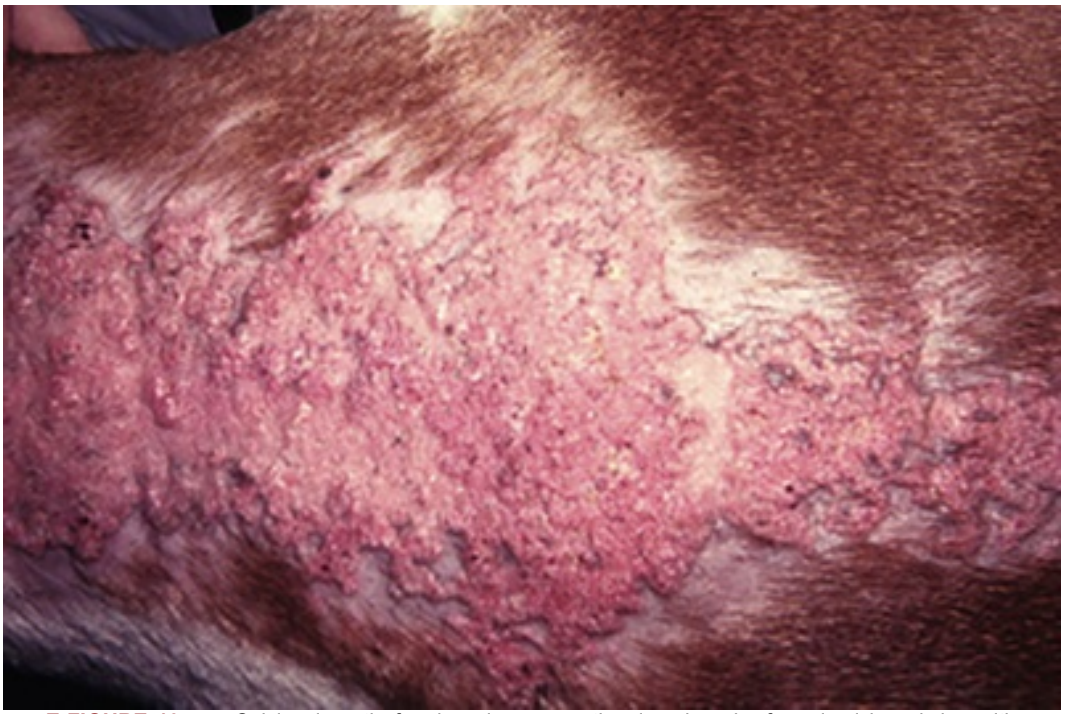
Paraneoplastic pemphigus has been reported in dogs with either thymic lymphoma or splenic sarcoma (see ch. 204 and 352). Autoantibodies in affected dogs have targeted desmoplakin, envoplakin, periplakin, desmoglein 1 and desmoglein 3. Histologically, lesions have features of pemphigus foliaceus (intraepidermal pustules with acantholysis), pemphigus vulgaris (suprabasilar clefts) and erythema multiforme (apoptotic keratinocytes). Prognosis is grave.[31,32]

Systemic Diseases With Cutaneous Plaques

Calcinosis Cutis (see ch. 298 and 306)

Calcinosis cutis appears as granular plaques in the skin (E-Figure 10-7), most commonly over the dorsum or inguinal regions. Microscopically, dermal deposits of apatite crystals are usually identified in association with collagen or elastin fibers. This "metastatic calcification" occurs as a result of excesses in circulating calcium and/or phosphorus in dogs with chronic kidney disease or systemic blastomycosis or paecilomycosis. Dystrophic calcification is thought to occur as a result of alterations to collagen fibers in dogs with hyperadrenocorticism or as a result of inflammatory conditions such as leptospirosis, follicular cysts, foreign body granulomas, interdigital pyoderma, demodicosis or pilomatrixomas. Iatrogenic calcinosis cutis has been associated with percutaneous absorption or injection of calcium-containing products. Calcinosis circumscripta lesions occasionally develop over pressure points or areas of trauma (including the tongue and footpads) of juvenile dogs when serum levels of phosphorus and calcium are increased. Diagnosis is made with

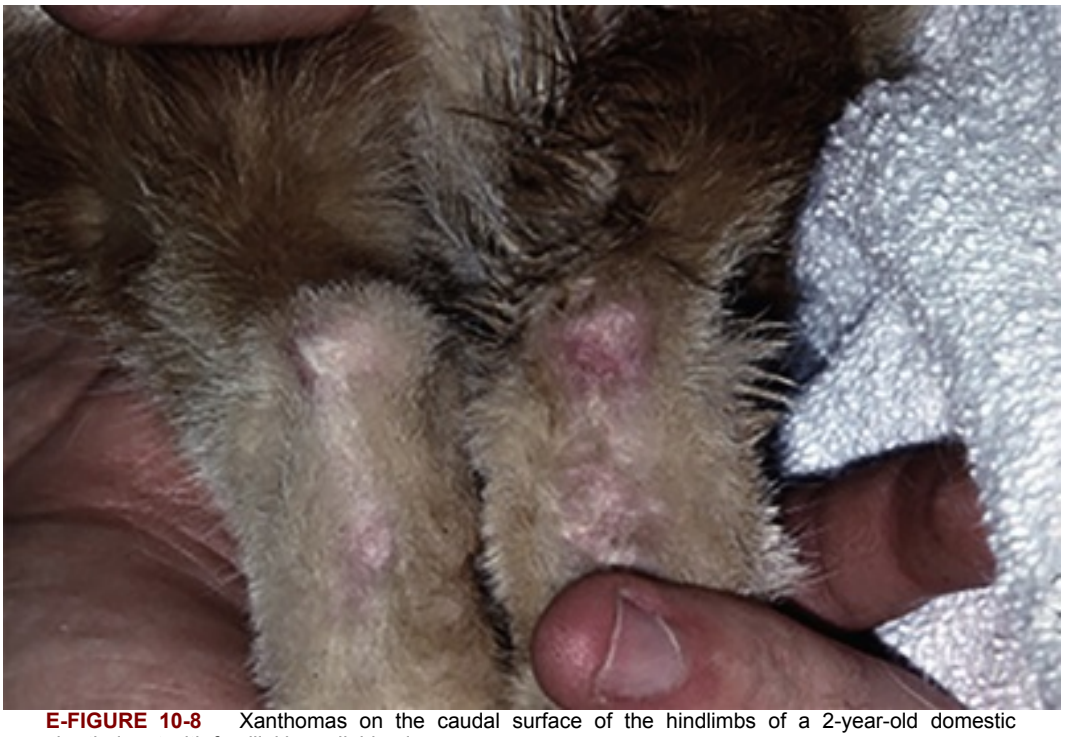
histopathology or after confirming an underlying disorder.[33]



E-FIGURE 10-7 Calcinosis cutis forming plaques on the dorsal neck of a mixed breed dog with iatrogenic hypercortisolism.

Xanthomas

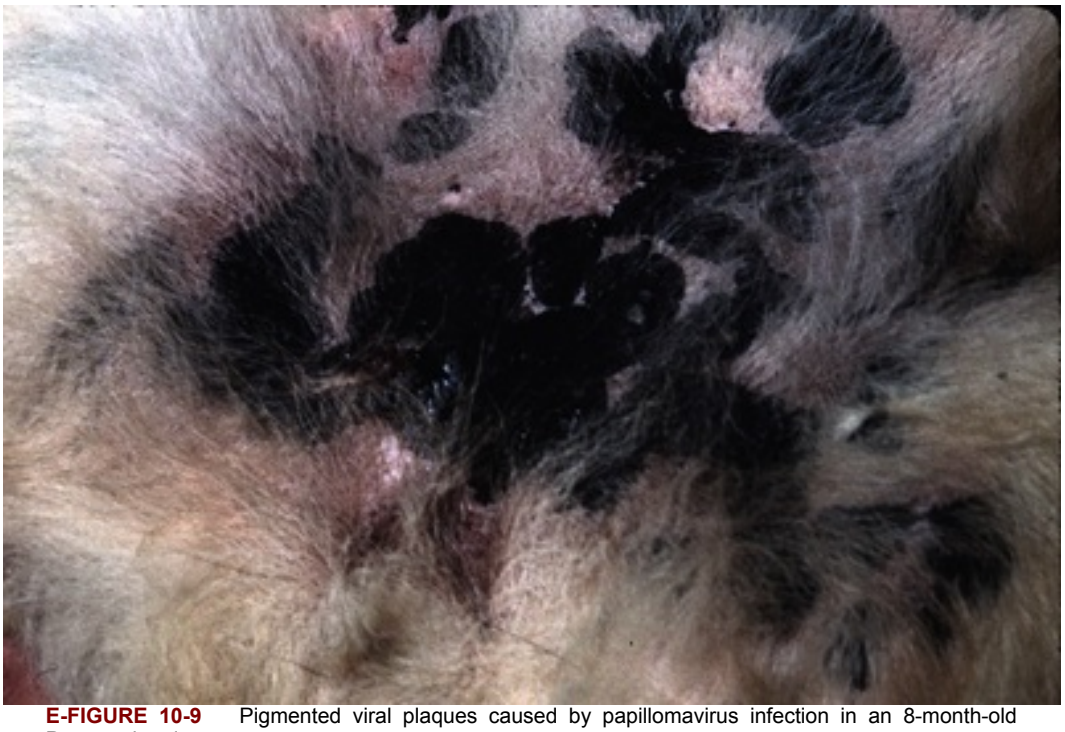
Xanthomas appear as yellow-white papules, nodules or plaques located on the head, limbs, feet or over bony prominences (E-Figure 10-8). The lesions may ulcerate and are often surrounded by erythema. Xanthomas are composed of foamy macrophages and giant cells surrounding deposits of lipid in the dermis. These lesions are cutaneous manifestations of abnormalities in lipid metabolism or may be associated with diets extremely high in fat. Xanthomas develop in cats with hereditary hyperlipoproteinemia and in a small percentage of those with diabetes mellitus, Cushing's syndrome, treated with progestational compounds or fed high-fat foods and treats.[34-37] Diagnosis is based on histopathology or confirmation of an underlying cause of hyperlipidemia.



E-FIGURE 10-8 Xanthomas on the caudal surface of the hindlimbs of a 2-year-old domestic shorthair cat with familial hyperlipidemia.

Hyperpigmented Viral Plaques

Canine viral plaques are an uncommon manifestation of papillomaviral infection in dogs. In contrast to the more common papillomas, viral plaques do not spontaneously resolve. However, most viral plaques remain as small pigmented lesions on the ventral abdomen (E-Figure 10-9) or in the axillary region. The major differential for pigmented viral plaques is canine seborrheic keratosis (SK) which also appear as raised, variably pigmented plaques on the skin of dogs. On occasion, papillomavirus-associated viral plaques progress to squamous cell carcinomas. Histopathology of skin and IHC or PCR for papillomaviruses can be used to distinguish viral plaques from SK.[38,39]



E-FIGURE 10-9 Pigmented viral plaques caused by papillomavirus infection in an 8-month-old Pomeranian dog.

Eosinophilic Plaques

Eosinophilic plaques develop in cats in association with underlying allergies (parasitic, dietary or environmental). Differential diagnoses include mast cell tumor, squamous cell carcinoma, lymphoma and metastatic mammary adenocarcinoma.[2]

Cutaneous Lymphoma—Plaque Form

See previous discussion.

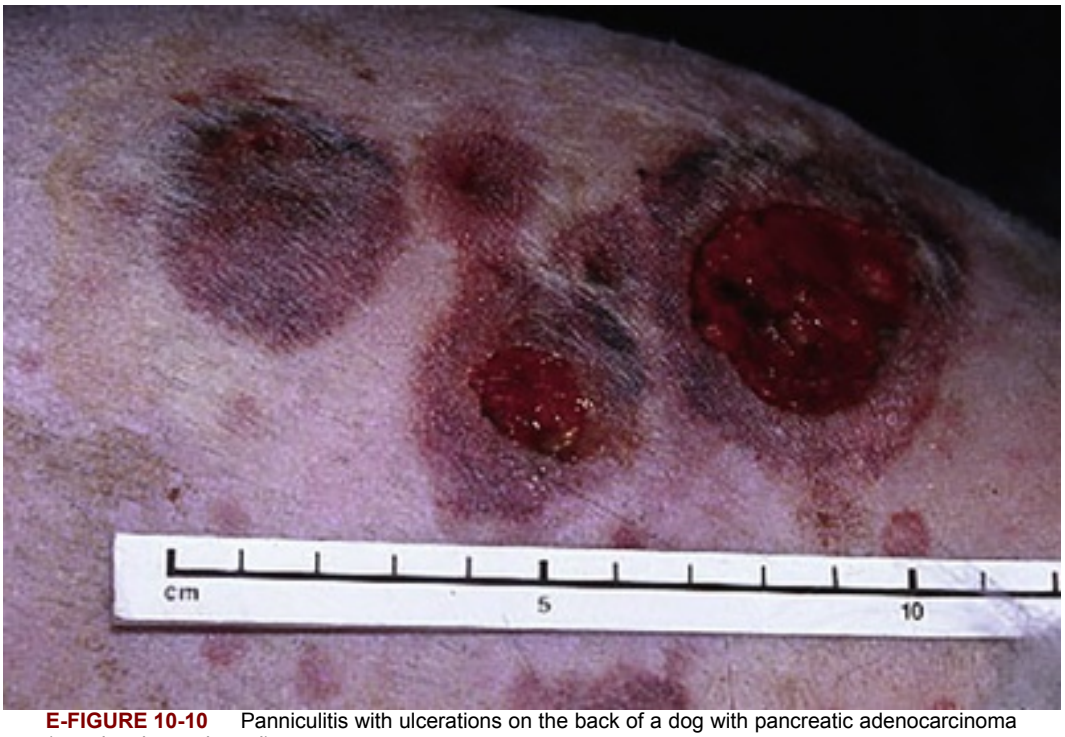
Systemic Diseases With Cutaneous Nodules

Nodular Dermatofibromas

German Shepherds and related dogs have an autosomal dominant genetic disease caused by mutations in the folliculin gene (FLCN) that results in the development of multiple cutaneous nodules as well as multiple renal cysts and cystadenocarcinomas.[40,41] Females may develop uterine leiomyomas and leiomyosarcomas. Skin lesions may develop months or years before renal lesions, although renal cysts or tumors may be identified with imaging by 4 to 5 years of age.

Sterile Nodular Panniculitis (SNP)—Pancreatic Panniculitis Variant

Sterile nodular panniculitis is characterized by sterile subcutaneous inflammatory nodules that may ulcerate and drain a purulent or oily exudate. Lesions often develop in the absence of any concurrent disease or infection; however, pancreatitis and pancreatic tumors have been associated with panniculitis (E-Figure 10-10). Dogs and cats with panniculitis should be evaluated for pancreatic disease.[42-46] Other differential diagnoses for causing nodular panniculitis include foreign bodies, immune-mediated reactions, infection, vitamin E deficiency, serum alpha-1-antitrypsin deficiency, injection reaction, burns and trauma.[47] Minimum database evaluation should include a complete blood count, biochemical profile, pancreatic lipase immunoreactivity screening, abdominal ultrasonography as well as deep cutaneous biopsies for histopathology, culture and PCR evaluations to rule out other causes.



E-FIGURE 10-10 Panniculitis with ulcerations on the back of a dog with pancreatic adenocarcinoma (area has been shaved).

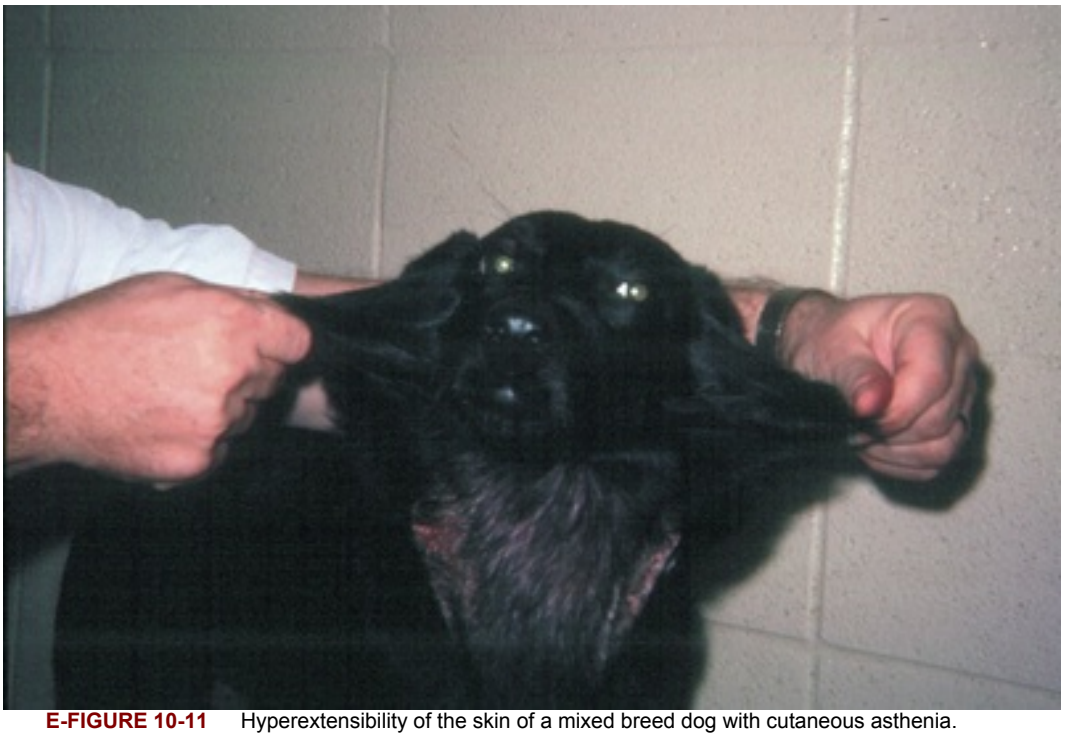
Infectious/Pyogranulomatous Nodules

Cutaneous nodules can develop in animals with blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis or aspergillosis. These nodules usually develop as a consequence of hematogenous dissemination of the organism from another site (pulmonary, nasal, gastrointestinal). Less commonly, skin lesions may develop following direct inoculation of fungal organism into the skin. Cytology from impression smears or fine needle aspirates or skin biopsies represent a readily accessible source for organism identification.[2]

Systemic Diseases With Skin Fragility

Cutaneous Asthenia (Ehlers Danlos Syndrome, Dermatosporaxis)

Cutaneous asthenia is a hereditary disease caused by defective connective tissue formation resulting in skin fragility and, in some cases, excess joint laxity, hernias and vascular complications. Several forms occur in animals and humans. The condition in cats is associated with reduced quantities of dermal connective tissue that has shortened and fragmented collagen fibers.[48,50] Clinical signs include hyperextensible skin (E-Figure 10-11) that may tear with minor trauma.[48-50] Dyspnea may occur secondary to diaphragmatic hernia. One affected cat had a perineal hernia.[50] A defect in procollagen peptidase was identified in one cat.[51] Affected dogs have exhibited skin hyperextensibility and fragility, vessel fragility, coxofemoral joint dislocation, medial patellar luxation, subcutaneous hematomas and periodontal disease.[52] Presumptive diagnosis is based on presence of hyperextensible, easily torn skin. Microscopic evaluation of skin biopsies may demonstrate fragmented, shortened, disoriented, eosinophilic collagen fibers. In some cases, ultrastructural or biochemical evaluation is needed to document the collagen abnormalities.[48,51]



E-FIGURE 10-11 Hyperextensibility of the skin of a mixed breed dog with cutaneous asthenia.

Feline Skin Fragility

Acquired skin fragility in cats is most often associated with hyperadrenocorticism, either due to cortisol or sex hormone excess secreted from an adrenal tumor, excess cortisol secretion in pituitary dependent hyperadrenocorticism, or after administration of glucocorticoids or progestational compounds.[53] Affected cats have thin, fragile skin that tears easily (see ch. 307). Skin fragility has been reported in a few cats with feline infectious peritonitis, hepatic lipidosis or hepatic neoplasia.[54-56]

Systemic Diseases With Thick Skin

Mucinosis

The skin may be thicker than normal due to excessive amounts of mucin in the dermis as a breed-associated characteristic of Chinese Shar-Pei dogs or as a result of hypothyroidism.

Acromegaly

Cutaneous changes associated with acromegaly include thickened myxedematous skin with excessive skin folds, hypertrichosis and thick, hard claws. Acromegaly is caused by excessive secretion of growth hormone by a pituitary tumor or is secondary to hyperprogesteronism (see ch. 294-295).

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CHAPTER 11

Ophthalmic Manifestations of Systemic Disease

Alexandra van der Woerdt

Client Information Sheets:
Topical Ophthalmic Corticosteroid Medication
Anterior Uveitis/Chorioretinitis
Cataract

Introduction

A thorough ophthalmic examination is an important part of a physical examination in every patient. The clinician has the unique opportunity to directly visualize blood vessels as well as neurologic tissue (the optic nerve) in the fundus of the eye. Abundant blood supply to the iris and choroid make these tissues susceptible to spread of infectious organisms or neoplastic cells to these tissues with inflammation of the iris, ciliary body and choroid as a result. Other parts of the eye may be affected by various systemic diseases as well. This chapter will first describe ophthalmic examination techniques, followed by ocular manifestations of systemic disease in the various parts of the eye.

Ophthalmic Examination

Examination of the anterior segment of the eye is best performed in a clinical setting using a bright light source. A slit lamp biomicroscope is ideal for examination of the anterior segment, as it provides illumination and magnification at the same time (Figure 11-1). The slit lamp function allows further localization of lesions by providing optical cross sections of the anterior segment of the eye. Most penlights are not bright enough for a thorough examination. A Finoff transilluminator will provide a focal bright light beam. Magnification and illumination can be obtained at the same time by using an otoscope. The eyelids are evaluated for function, anatomy and the presence of abnormal ciliae. Normal conjunctiva is thin and has scant blood vessels. Hyperemia and swelling of the conjunctiva (chemosis) are commonly seen abnormalities. A normal cornea has a glossy appearance and is transparent. The anterior chamber is best evaluated for the presence of aqueous flare by focusing a small light beam on the cornea and observing light scattering on proteins and cells in the anterior chamber if present. A normal lens is transparent and located between the iris and the vitreous cavity. The fundus can be examined by either direct or indirect ophthalmoscopy. Direct ophthalmoscopy is easy to learn and the equipment is often readily available (Figure 11-2). It provides high magnification of a small portion of the fundus. Because of the limited size of the area observed in the fundus, relatively large lesions may be easily missed. Indirect ophthalmoscopy is the preferred choice for evaluating a large part of the retina at one time at a relatively low magnification. Equipment needed includes a focal bright light source (such as a Finoff transilluminator) and an indirect viewing lens (see Figure 11-2). Popular lenses include the panretinal 2.2 lens, as well as a 20 or 28 diopter lens. Indirect ophthalmoscopy is a technique that does require practice to master, but the advantages outweigh the disadvantages when compared with direct ophthalmoscopy. The Welch Allyn Panoptic ophthalmoscope combines the ease of use of a direct ophthalmoscope with a relatively large area of the fundus evaluated at one time (Figure 11-3).

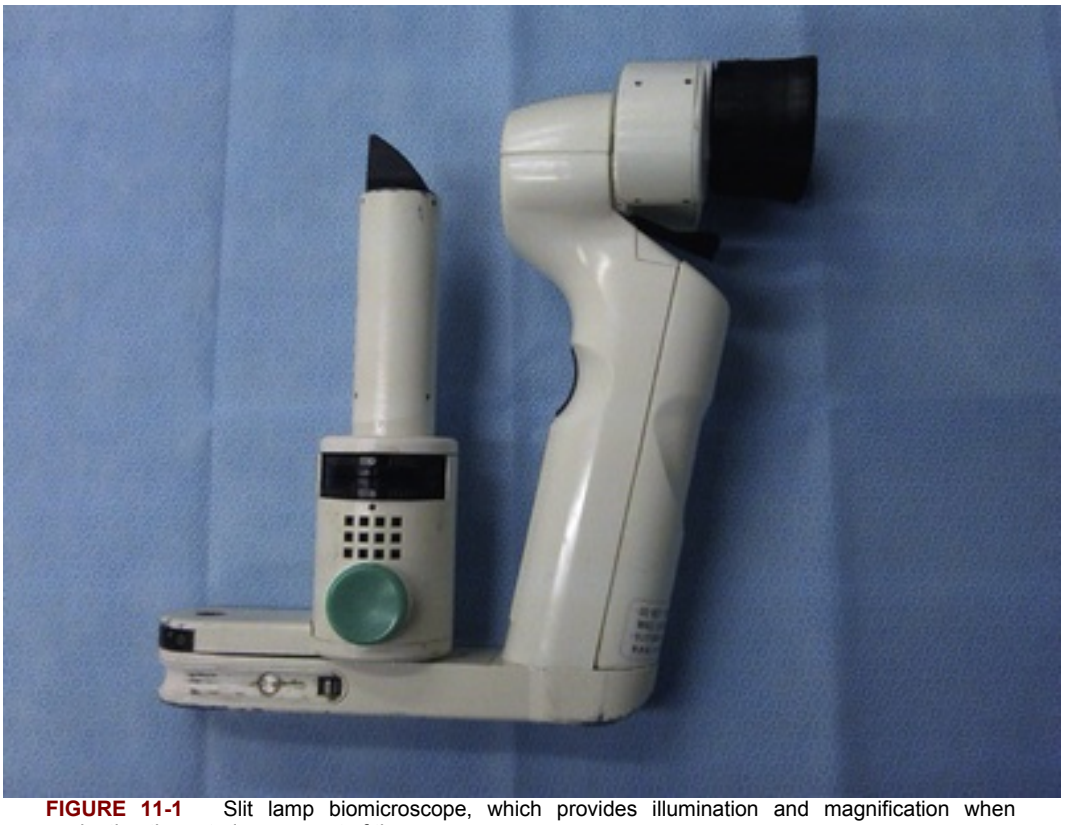

FIGURE 11-1 Slit lamp biomicroscope, which provides illumination and magnification when evaluating the anterior segment of the eye.

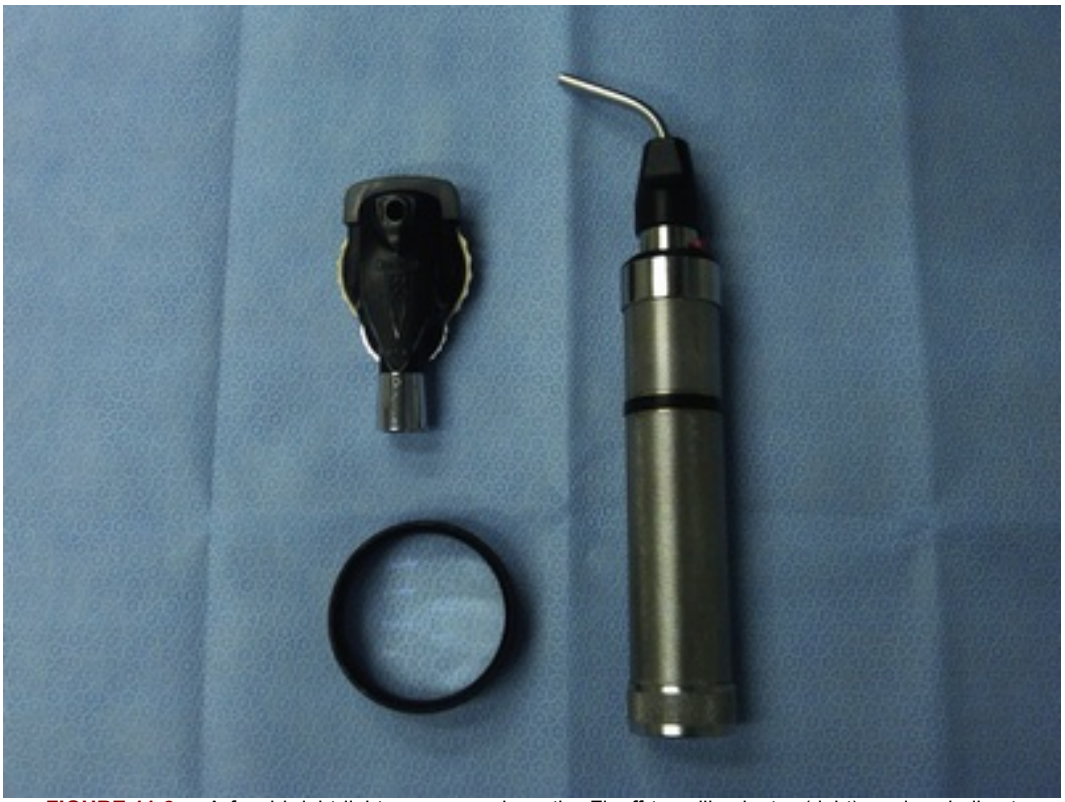

FIGURE 11-2 A focal bright light source, such as the Finoff transilluminator (right), and an indirect viewing lens (lower left) are used for indirect ophthalmoscopy. The ophthalmoscope head (upper left) is used for direct ophthalmoscopy.

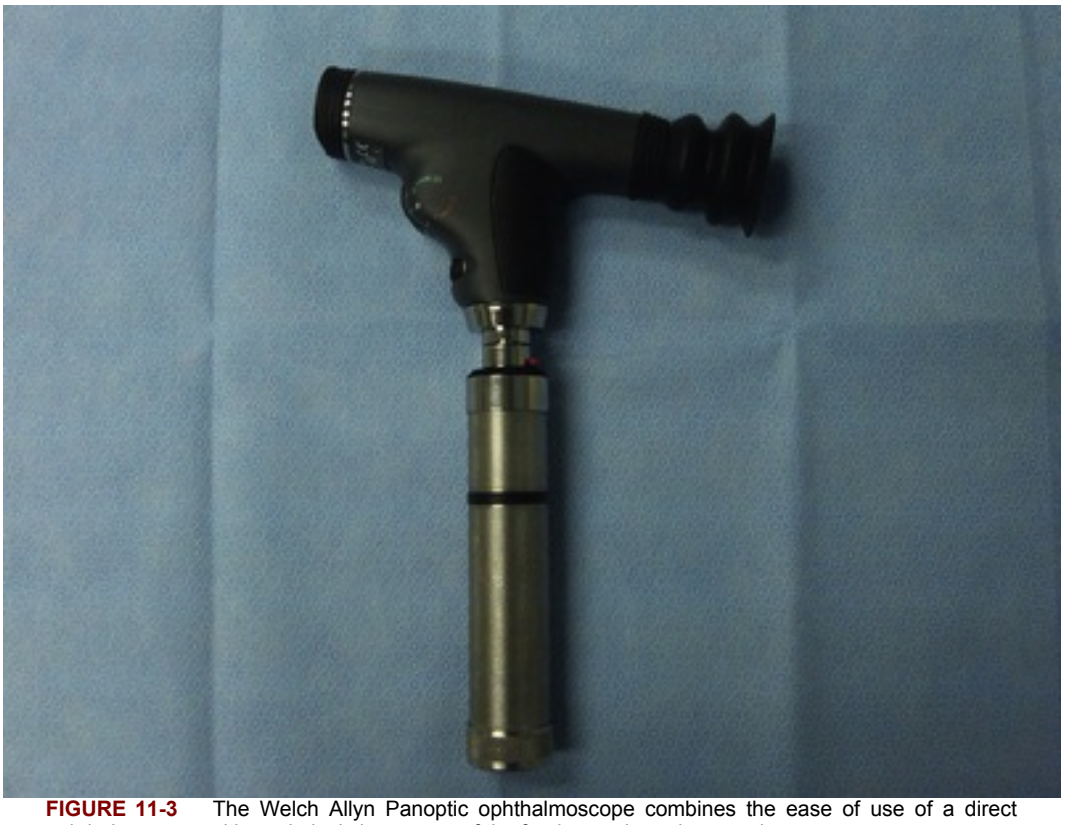

FIGURE 11-3 The Welch Allyn Panoptic ophthalmoscope combines the ease of use of a direct ophthalmoscope with a relatively large area of the fundus evaluated at one time.

Interpretation of Fundus Lesions

One of the most important questions to ask when observing a lesion in the fundus is whether it is an active lesion or an inactive lesion (scar). Inactive lesions are common incidental findings that have little clinical significance. The presence of active fundus lesions may help determine diagnostic plans for current diseases in the patient. Evaluating the color and reflectivity of a lesion in the tapetal area of the fundus can help determine whether a lesion is active or inactive. Focal areas of chorioretinitis over time will result in thinning of the retina, exposing the reflective tapetum to a greater degree than normal. The result is a focal hyperreflective area in the tapetum. If a tapetal lesion involves the retinal pigment epithelium in the deepest part of the retina, focal hyperpigmentation is a common result (Figure 11-4). Clinically this is seen as a hyperreflective lesion with a dark center. When evaluating for the presence of hyperreflectivity, one needs to bear in mind that hyperreflectivity is only seen if the light hits the scar at a perfect angle. If not, the lesion will appear dull and may give the impression of being an active lesion. If the color of the underlying tapetum in an active lesion appears to have changed little compared to the surrounding tapetum, clear fluid is present in the lesion. This can be seen with (early) hypertension and secondary retinal edema. If the color of the underlying tapetum has changed, this indicates the presence of cells in the lesion. This could be either hemorrhage or other cellular infiltrates such as white blood cells or neoplastic cells. Figure 11-5 is a flowchart for evaluating tapetal fundus lesions.

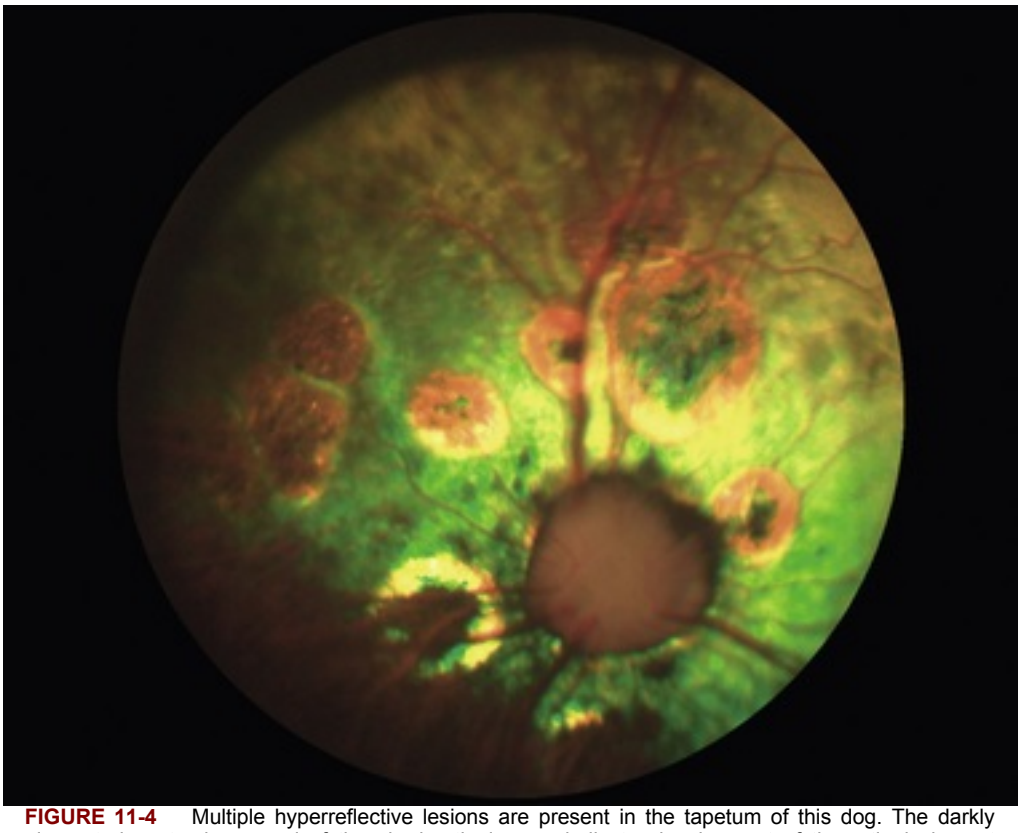

FIGURE 11-4 Multiple hyperreflective lesions are present in the tapetum of this dog. The darkly pigmented center in several of the chorioretinal scars indicates involvement of the retinal pigment epithelium.

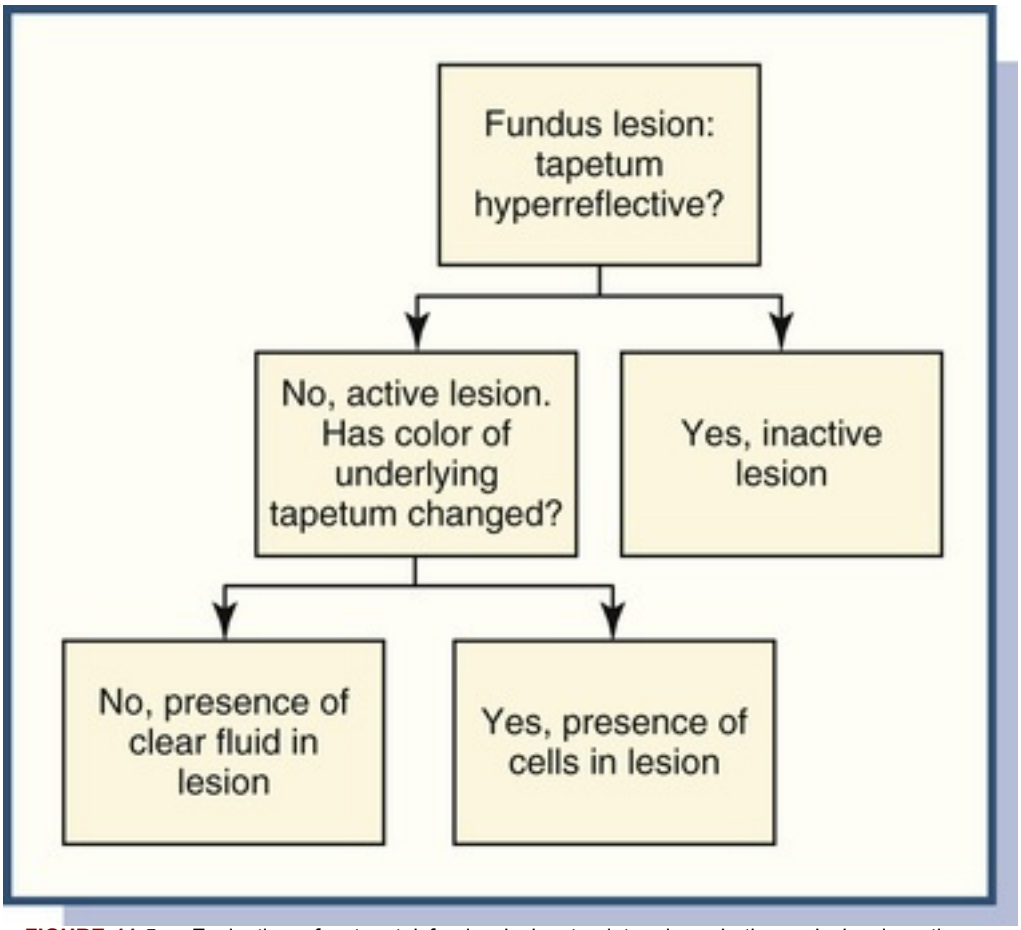

FIGURE 11-5 Evaluation of a tapetal fundus lesion to determine whether a lesion is active or inactive.

Eyelids and Conjunctiva

Blepharitis, inflammation of the eyelids, can be a disease in itself, or be part of a generalized dermatologic problem. The eyelids have numerous meibomian glands, which are an important part of the tear film as they secrete the oily surface part of the tear film. These glands can become impacted and secondary infection with *Staphylococcus* spp. may result in painful, swollen eyelids. Infection with *Demodex* spp. may result in alopecia of the eyelids. Immune-mediated diseases such as uveodermatologic syndrome or pemphigoid diseases may affect the eyelids and the mucocutaneous junctions of the eyelids (ch. 204).[1] Infectious diseases can manifest themselves in the eyelids as well. An example of this is leishmaniasis.[2]

Inflammation of the conjunctiva (conjunctivitis) is common in cats. Hyperemia of the conjunctiva, chemosis, blepharospasm and epiphora are common signs. Infection with feline herpesvirus 1 (FHV-1) is a common cause of conjunctivitis in cats and is often self-limiting in nature. Primary infections with this virus are often associated with upper respiratory signs. Recrudescent infections often involve the eye(s) only. Supportive care with a topical antibiotic ointment three to four times a day is indicated to prevent secondary bacterial infections. In cats with a weak immune system, such as very young cats, older or sick cats, antiviral therapy is often needed to help resolve the clinical signs. This can be either topical (0.5% cidofovir twice a day, or idoxuridine four times a day) or systemic by using famciclovir. The recommended dosage for famciclovir has a broad range from 62.5 mg twice daily by mouth per cat to 90 mg/kg by mouth three times a day. Recent research suggests that a dosage of 40 mg/kg by mouth three times a day may be recommended to treat FHV-1 infections.[3] *Chlamydia felis* is another conjunctival pathogen in cats although less common than FHV-1. Conjunctivitis in dogs is often secondary to a decrease in tear production (keratoconjunctivitis sicca) or systemic allergies. Infectious causes of conjunctivitis such as canine herpesvirus are rare in dogs. Conjunctivitis is a disease in itself without significant other ocular diseases present. This should not be confused with conjunctival hyperemia, which is often a sign of more significant ocular diseases present.

Keratoconjunctivitis Sicca (KCS)

A decrease in tear production is a very common cause of redness, irritation and discharge in dogs. An immune-mediated destruction of the tear gland is the most common cause for KCS in dogs. Many breeds are predisposed, including the English Bulldog, American Cocker Spaniel, Shih Tzu, Lhasa Apso, Cavalier King Charles Spaniel and Pug. Clinical signs include redness and (mucoid) discharge, especially in the morning. In acute KCS, corneal ulceration is common. Measurement of the tear production using a Schirmer tear test is indicated in any dog with a corneal ulcer. The results of the Schirmer tear test should be interpreted with the clinical signs in mind. Tear production in a normal dog's eye is at least 15 mm/min. Surface disease of the eye, such as a corneal ulcer, stimulates tear production and tear production should be much greater than 15 mm/min in an affected eye. Medications can also be a cause of KCS in dogs. Oral sulfonamides have been associated with KCS in dogs, as has the non-steroidal anti-inflammatory drug etodolac.[4,5] Oral antihistamines commonly used in management of atopy in dogs can cause a decrease in tear production as well. Careful monitoring of clinical signs (discharge/redness) and Schirmer tear test results in dogs treated with these medications is indicated.

Special consideration needs to be given to dogs that are sick enough to be hospitalized. A recent study evaluating tear production in dogs admitted to an intensive care unit found a significant decrease in tear production in these dogs.[6] This may predispose to the development of painful corneal ulcerations. Application of lubricating artificial tear ointment several times a day may help prevent surface ocular disease in sick dogs.

KCS is rare in cats and clinical signs are different in cats than in dogs. A transient decrease in tear production is often seen in FHV-1 infection. This decrease may become permanent in some cats. The most common clinical sign of KCS in the author's experience is blepharospasm that is fairly mild but persistent. Mucoid discharge as seen in dogs is not usually present and conjunctival hyperemia is often subtle. Corneal changes such as fibrosis/pigmentation/vascularization are not usually present in KCS in cats. Diagnosis of KCS in cats can be challenging as normal cats can have a low STT reading secondary to stress. Presence of clinical signs in combination with response to therapy (viscous artificial tear solution two to three times a day) often confirms the diagnosis of KCS in cats.

Cornea

A normal cornea is transparent, devoid of blood vessels and pigment, and is in a constant state of dehydration. The cornea receives its nutrition from the aqueous humor and the tear film. The cornea consists of several layers: the epithelium, stroma, Descemet's membrane and endothelium. The corneal endothelium maintains the dehydrated state of the cornea. The stroma is the thickest layer of the cornea. Descemet's membrane has elastic properties and may be seen bulging forward if a corneal ulcer has progressed through the corneal stroma. Multiple different abnormalities can be seen within the cornea. Table 11-1 lists corneal changes and their characteristic appearance. The most common causes of corneal edema include glaucoma, anterior uveitis, corneal ulceration, (anterior) lens luxation, and corneal endothelial cell degeneration. Additional clinical signs of glaucoma include conjunctival and sclera hyperemia, loss of vision, elevated intraocular pressure, and mydriasis. Additional clinical signs of anterior uveitis include conjunctival and scleral hyperemia, presence of aqueous flare and/or cells in the anterior chamber, low intraocular pressure, and miosis. If corneal edema is present, the intraocular pressure should be measured to rule out glaucoma, fluorescein should be applied to the eye to rule out the presence of a corneal ulcer, and careful examination of the anterior segment should be performed to rule out anterior uveitis or lens luxation. The diagnosis of endothelial cell degeneration is made by excluding all other causes of corneal edema.

TABLE 11-1

Corneal Abnormalities and Characteristic Appearance of the Abnormalities

COLOR	LESION	CHARACTERISTICS
White	Fibrosis	Scar tissue. This is usually in the shape and size of the original injury to the cornea. The appearance is smooth, and varies from light grey to a dense grey area. The eye is comfortable.
	Corneal edema	Honeycomb appearance. Corneal edema may be diffuse or focal. Whether or not discomfort is present is determined by the cause of the edema.

	Crystalline infiltrate	Cholesterol/lipid infiltrate: corneal dystrophy is a genetic disorder in some breeds. Lesions are often paracentral in the cornea and may be bilateral. The infiltrate is often well-circumscribed and densely white. The eye is comfortable. This often appears within the first few years of life.
		Cholesterol/lipid infiltrate secondary to systemic disease: This is often located adjacent to the limbus in the periphery of the cornea (arcus lipoides). The eye is comfortable.
		Calcium infiltrate: Corneal degeneration. This is a degenerative disease in older dogs. Calcium spicules are located within the cornea. Their distribution is uneven. The eye is often uncomfortable. Affected areas of the cornea may slough, resulting in corneal ulceration.
	Cellular infiltrate	Abscess formation within the cornea. Significant discomfort is often present as well as vascularization towards the affected area. The affected area may have a yellow-white appearance.
Red	Superficial corneal vessels	Superficial corneal vessels have a branching pattern and are often seen to cross the limbus into the conjunctival vessels. They indicate the presence of superficial corneal disease.
	Deep corneal vessels	Deep corneal vessels originate at the limbus and are straight. They may be 360 degrees around the limbus or in a focal area of the cornea. Deep corneal vessels indicate deep corneal disease or intraocular disease.
	Intrastromal corneal hemorrhage	An intrastromal corneal hemorrhage is a focal bleed between the lamellae of the cornea. It requires the presence of pre-existing corneal vessels. Intrastromal corneal hemorrhages can persist within the cornea for an extended period of time.
Brown	Pigmentation	Secondary to chronic irritation from any source. Examples include chronic entropion, KCS, and abnormal ciliae.
	Pigmentation	Pigmentary keratitis in Pugs. This is a hereditary, progressive pigmentation of the cornea in this breed.
	Corneal sequestrum	Focal brown pigmented spot in the cornea of cats. Brachycephalic breeds are predisposed.

Healing of a corneal ulcer is a rapid process in a young healthy animal with a normal tear production and normal eyelid function and position. It is delayed in older animals, in dogs with KCS and if abnormal eyelid function or position is present. In addition, corneal sensitivity is decreased and wound healing delayed in diabetic dogs.[7]

Iris

The anterior uvea of the eye consists of the iris and ciliary body. Both structures are usually inflamed in anterior uveitis. The ciliary body is continuous with the choroid and inflammation of the anterior uvea is often associated with inflammation of the choroid as well. The uveal tract is a highly vascular area and is often affected by systemic diseases. Inflammation of the uveal tract results in a breakdown of the blood-aqueous barrier. This is clinically visible as aqueous flare when proteins and/or cells enter the aqueous humor. A decrease in production of aqueous humor by the ciliary body in combination with increased resorption through the inflamed uveal tract results in a decrease in intraocular pressure. Spasm of the ciliary body muscles may result in a painful miosis. Other clinical signs seen in anterior uveitis include conjunctival and scleral hyperemia and a decrease in vision or loss of vision if inflammation is severe.

Anterior uveitis has many causes in both dogs and cats.[8] The most common causes in cats include infection with feline leukemia virus, feline immunodeficiency virus, feline infectious peritonitis, *Toxoplasma gondii*, and the various fungal diseases. The role of *Bartonella henselae* in anterior uveitis in cats is still debated. Numerous etiologies exist in dogs and include infectious organisms such as bacterial, fungal, rickettsial, protozoal, parasitic or viral diseases.[9-11] Uveodermatologic disease is an immune-mediated destruction of pigment in the eye and the skin resulting in uveitis and loss of pigmentation in skin and hair.[1] Trauma to the eye may result in uveitis and uveitis can also be the result of ocular diseases such as lens-induced uveitis. A cause may not always be found for anterior uveitis in dogs and cats and symptomatic treatment is indicated in these animals. Treatment of uveitis consists of treatment of the underlying disease if possible as well as treatment of the uveitis itself. Treatment of anterior uveitis consists of topical corticosteroids such as 1% prednisolone acetate or 0.1% dexamethasone solution. The frequency of application depends on severity of the disease. A painful miosis is often present and is best treated with application of topical 1% atropine solution or ointment. The author prefers to avoid using atropine solution in cats, as drainage through the nasolacrimal system may result in profuse salivation. Topical non-steroidal anti-inflammatory medications such as 0.03% flurbiprofen

or 0.1% diclofenac are especially useful if the presence of a corneal ulceration precludes the use of topical corticosteroids. Systemic corticosteroids or other immunosuppressive medications are indicated in treatment of severe anterior uveitis or if the choroid is involved in the disease process as well. Careful monitoring of the intraocular pressure is indicated, as secondary glaucoma may occur in anterior uveitis. This is especially the case if atropine or non-steroidal anti-inflammatory eye medications are used.

Lens

The lens is an avascular structure and abnormalities of the lens are limited to cataract formation and lens luxation. The most common reason for cataract formation in the dog is a hereditary abnormality. The second most common cause is diabetes mellitus in the dog[12] (Figure 11-6). The onset of diabetic cataracts is often very sudden and affected dogs may lose their vision within days to weeks.[13] The high concentration of glucose in the lens is metabolized through aldose reductase into sorbitol which accumulates in the lens. This results in an accumulation of water in the lens with subsequent lens fiber damage and cataract formation. The lens can become much larger than normal (intumescent cataract) and secondary spontaneous lens capsule rupture has been reported in diabetic dogs. The window of opportunity for successful cataract surgery is much shorter in diabetic dogs than in dogs with genetic cataracts and surgery should be performed soon after the onset of cataract formation if possible. Focal cataract formation in the lens can be seen in dogs with hypocalcemia. The most common cause for cataract formation in cats is chronic anterior uveitis. Diabetes mellitus does not cause cataract formation in cats.

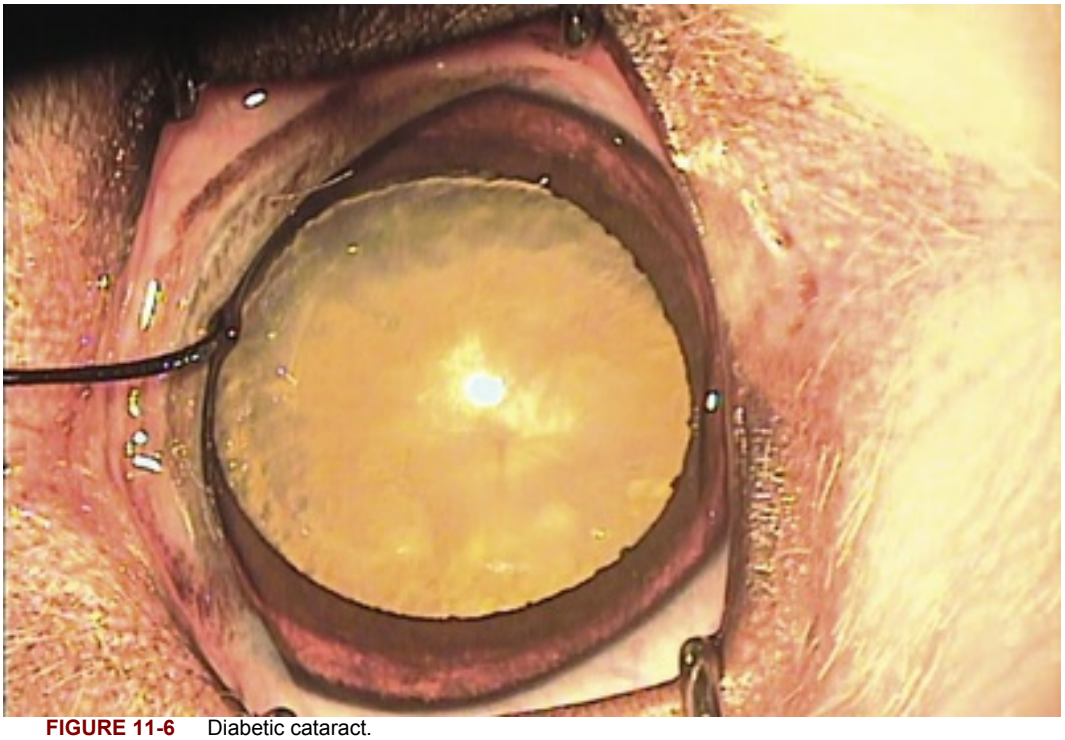

FIGURE 11-6 Diabetic cataract.

Choroid and Retina

It is uncommon for diseases to affect the choroid and/or retina without affecting the anterior uvea as well. The causes for choroiditis, retinitis, and chorioretinitis are similar to the causes for anterior uveitis in dogs and cats. Clinical signs of chorioretinitis may include retinal edema, retinal vascular changes such as tortuosity or vasculitis, intraretinal, preretinal or vitreal hemorrhages, and retinal detachment. Vision may be impaired if changes are severe. Diagnosis and treatment of chorioretinitis is similar to the diagnosis and treatment of anterior uveitis. Topically applied medications, however, are not effective in treating chorioretinitis and systemic treatment is indicated if chorioretinitis is present.

The optic nerve is the only part of the central nervous system that can be observed and evaluated directly.

A normal optic nerve in a dog is variable in size and shape, depending on the amount of myelin present (Figure 11-7). Although there is a large variation in optic nerve size and shape between dogs, the optic nerves in one dog are usually fairly similar in size and shape making comparison between the two eyes a reasonable thing to do. A normal optic nerve in dogs is a combination of white myelin and red blood vessels, resulting in a light pink appearance in most dogs. The edges of a normal optic nerve are well-defined. Edema of the optic nerve and inflammation of the optic nerve can have a similar appearance. The optic nerve is swollen, protruding into the vitreous cavity, the edges are hazy and indistinct, and there may be edema present in the area immediately adjacent to the optic nerve (Figure 11-8). The color of the optic nerve may be much more red than normal. Optic nerve edema may be associated with an increase in intracranial pressure. Evaluation of the optic nerve prior to collection of cerebrospinal fluid is indicated. Vision may not be affected when optic nerve edema is present. Inflammation of the optic nerve (optic neuritis) is usually associated with a mydriatic pupil and loss of vision. Optic neuritis should be considered part of a neurologic disease and appropriate diagnostic workup for neurologic disease is indicated (see ch. 12 and 259).

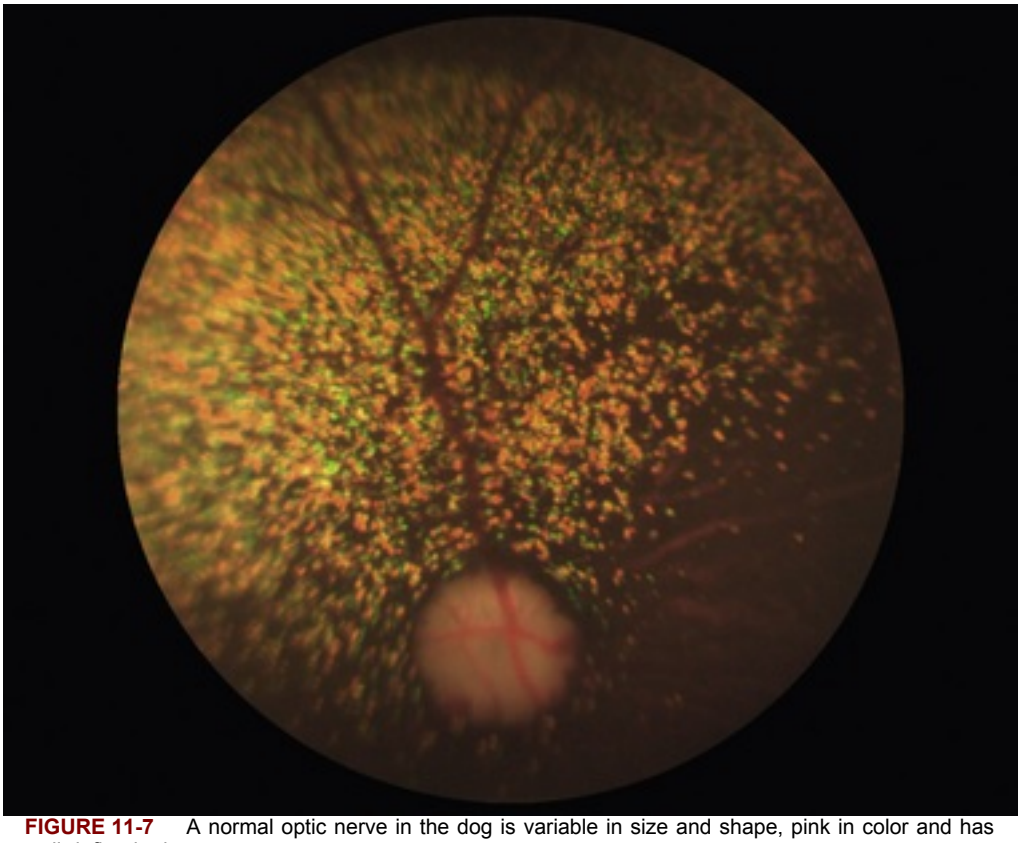

FIGURE 11-7 A normal optic nerve in the dog is variable in size and shape, pink in color and has well-defined edges.

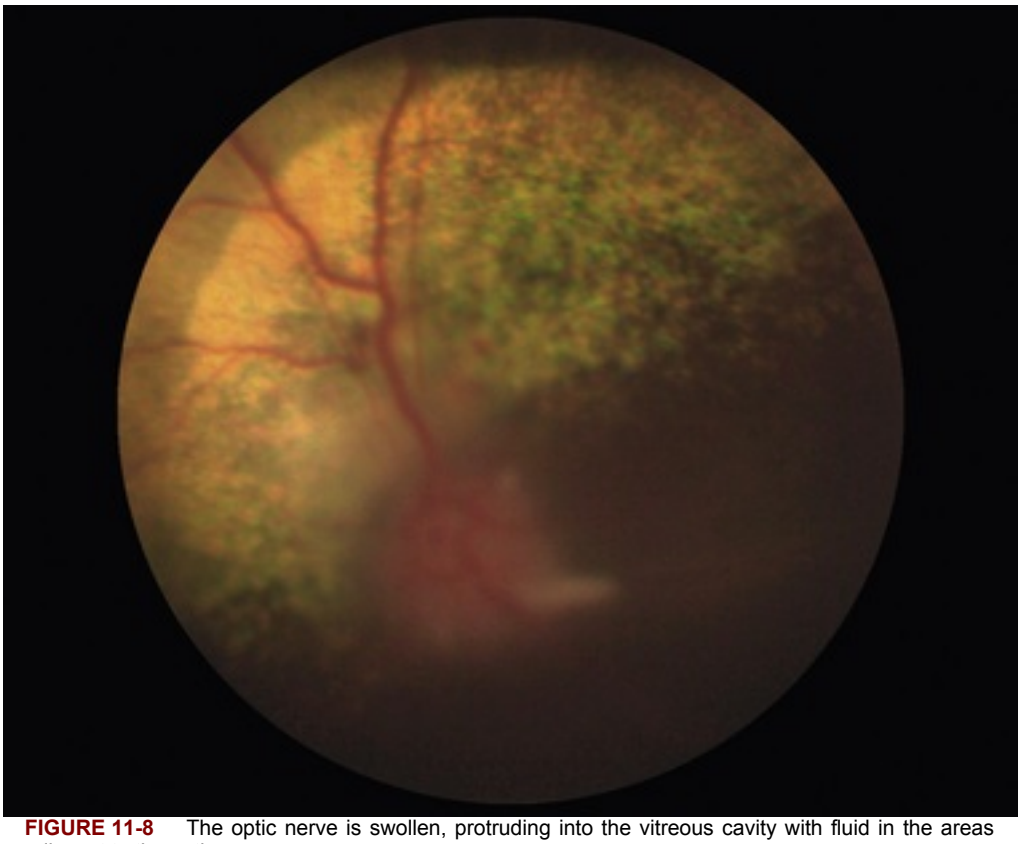

FIGURE 11-8 The optic nerve is swollen, protruding into the vitreous cavity with fluid in the areas adjacent to the optic nerve.

Orbital Disease

Inflammatory or neoplastic diseases of the orbit are often local diseases and not associated with systemic disease. Signs of orbital disease may include exophthalmos, protrusion of the third eyelid, decreased retropulsion of the globe into the orbit, loss of vision and pain upon opening of the mouth. Abscess formation in the orbit of dogs may be associated with dental disease, foreign body penetration through the mouth or conjunctival surfaces, or rarely be a consequence of abscess formation elsewhere in the body. Orbital inflammatory disease often has an acute onset, is very painful, and general malaise is usually present. Masticatory myositis is an immune-mediated inflammation of the masticatory muscles and may result in bilateral painful orbital disease.[14] Diagnosis is confirmed by testing for type 2M fiber specific autoantibodies against masticatory muscle myosin heavy and light chains (see ch. 354). Treatment is aimed at immune suppression and should be long-term to avoid relapse of the disease. Extraocular polymyositis is a disease that is most commonly seen in young Golden Retrievers. Swelling of all extraocular muscles results in bilateral exophthalmos; however, retropulsion in the orbit is normal. The sclera is visible 360 degrees which gives these dogs a distinct look. Diagnosis is confirmed by the presence of enlarged extraocular muscles on computed tomography scan or magnetic resonance imaging. Treatment is aimed at immune suppression.

Orbital neoplasia can be primary orbital neoplasia or secondary from extension from adjacent tissues (most commonly the nasal cavity) or metastatic spread from elsewhere. Orbital neoplasia is usually malignant in both dogs and cats.

Systemic Hypertension

Systemic hypertension may go unnoticed in cats and dogs until loss of vision prompts the owners to bring their cat or dog in for evaluation and treatment. Ocular manifestations of systemic hypertension include hyphema, vitreal hemorrhage, retinal hemorrhage, retinal vascular tortuosity, retinal edema, retinal detachment, and loss of vision[15,16] (Figures 11-9 and 11-10). Secondary to the loss of retinal function, the pupil becomes mydriatic, which is often noted by the owner. Similar clinical signs can be seen in dogs with hyperviscosity syndrome.[17] The reader is referred to ch. 99 and 157-159 for diagnosis and treatment of

systemic hypertension. Multiple blood pressure measurements are sometimes needed to diagnose hypertension. On the other hand, acquiring a single high blood pressure in a stressed cat with a completely normal ocular fundus is unlikely to represent persistent systemic hypertension. Treatment of hypertensive retinopathy consists of treatment of the hypertension. If hyphema is present, use of topical corticosteroids such as 1% prednisolone acetate or 0.1% dexamethasone is indicated two to four times a day. The prognosis for return of vision depends on the ease with which the hypertension can be managed as well as the severity of the ocular abnormalities present. In the author's experience, the presence of significant vitreal or retinal hemorrhages carries a poor prognosis for return of vision. The prognosis for return of vision is much better if retinal edema or detachment is present without the presence of hemorrhages.

FIGURE 11-9 Hypertensive retinopathy in a cat. Focal areas of retinal edema are present.

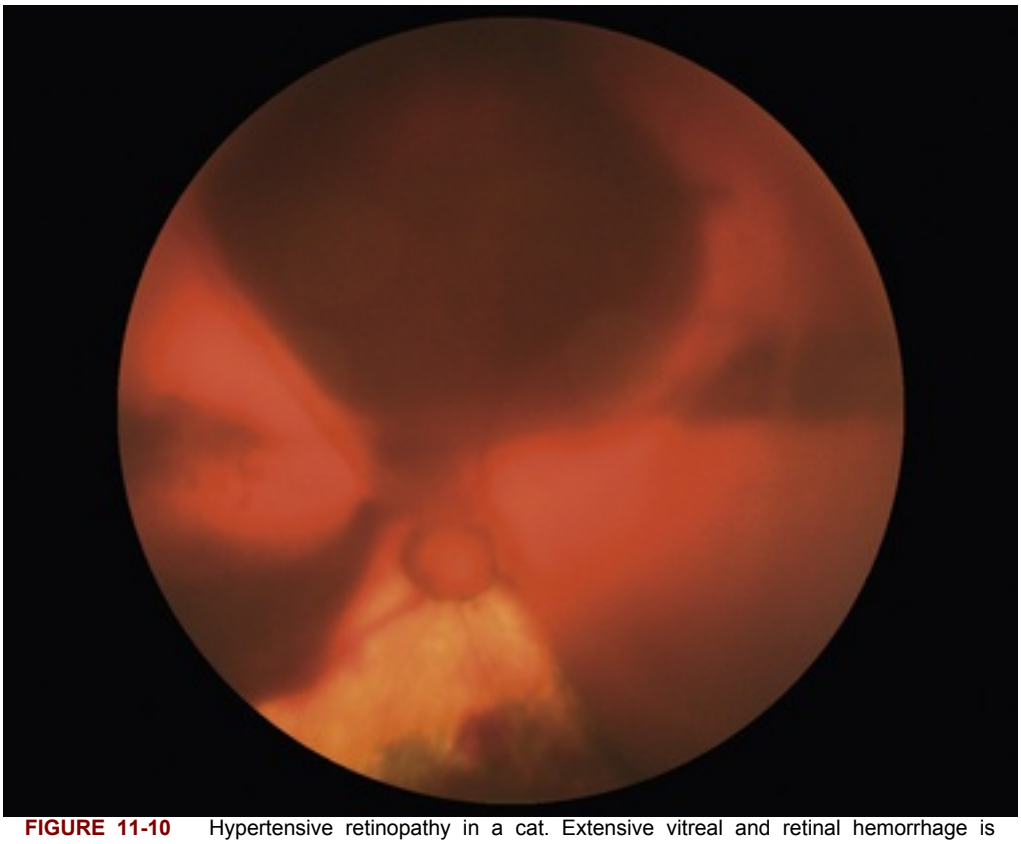

FIGURE 11-10 Hypertensive retinopathy in a cat. Extensive vitreal and retinal hemorrhage is present.

Metastatic Neoplasia

The uvea is a highly vascular structure within the eye that acts as a filter for pathogens and neoplastic cells in the body. Metastatic neoplasia can be seen in the iris and choroid of dogs and cats. The most common metastatic neoplasia found in the iris is lymphoma.[18] Lymphoma (see ch. 344) in the iris of cats is usually a focal pink raised lesion in the iris. Performing an aqueocentesis and submitting the aqueous humor sample for cytospin and cytology may help aid in the diagnosis of lymphoma in cats. Lymphoma in the iris in dogs more commonly manifests itself as an anterior uveitis with or without focal nodules in the iris. Involvement of the uveal tract indicates systemic involvement, especially in dogs. Debate still exists as to whether primary ocular lymphoma without systemic involvement exists in dogs and cats or not.[19] Treatment of ocular lymphoma consists of systemic treatment of the lymphoma. The iris lesions can resolve completely in response to chemotherapeutic agents. Topical corticosteroids are indicated if systemic disease cannot be adequately controlled with chemotherapeutic agents.

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CHAPTER 12

Neurologic Manifestations of Systemic Disease

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Client Information Sheets:
Brain Disorders
Neuromuscular Disorders

A variety of systemic diseases can cause neurologic signs. Findings on history and physical examination may reveal abnormalities that can be associated with a specific systemic disease causing neurologic signs. Neurologic signs may be the only manifestation of systemic disease. The cerebral cortex and the peripheral nervous system (PNS) are areas of the nervous system most susceptible to systemic disease. In addition, white matter, brainstem, and cerebellar signs have been documented secondary to systemic conditions. Specific neurologic signs and lesion localization are discussed in ch. 259.

Diseases Causing CNS Signs

Diseases causing central nervous system (CNS) signs are presented in Table 12-1.

TABLE 12-1

Neurologic Manifestation of Systemic Disease

CENTRAL NERVOUS SYSTEM	PERIPHERAL NERVOUS SYSTEM
Energy Deprivation	**Hypoxemia: Aortic Thromboembolism**
1. Hypoxemia a. Pulmonary disease b. Cardiac failure i. Infarcts ii. Hypoxia iii. Hypertension c. Anesthetic accident d. Vascular i. Hypertension ii. Coagulopathies iii. Vasculitis iv. Hyaline arteriopathy 2. Hypoglycemia a. Insulin-producing neoplasia b. Insulin overdose c. Sepsis 3. Nutritional a. Thiamine deficiency b. Irradiated diet	a. Cardiovascular b. Renal disease c. Hyperadrenocorticism d. Hypothyroidism e. Neoplasia f. Disseminated intravascular coagulation (DIC) g. Sepsis
Metabolic	**Metabolic**
a. Hepatic-encephalopathy b. Uremic encephalopathy c. Hypothyroidism	a. Kidney failure b. Hypothyroidism c. Hyperthyroidism

d. Hyperthyroidism e. Hyperadrenocorticism f. Hypoadrenocorticism	d. Hyperadrenocorticism e. Hypoadrenocorticism f. Diabetes mellitus
Electrolyte Abnormalities	**Electrolyte Abnormalities**
a. Hypercalcemia b. Hypocalcemia c. Hypernatremia d. Hyponatremia e. Hyperkalemia f. Hypokalemia	a. Hypokalemia
Neoplasia	**Neoplasia**
a. Primary b. Metastatic c. Infarcts d. Paraneoplastic syndrome	a. Paraneoplastic syndrome

Hypoxemia from Systemic Disease

Decreased arterial oxygen tension or reduced cerebral blood flow can result in hypoxic encephalopathy. Hypoxemia can occur secondary to an anesthetic accident, hematologic disorders (especially anemia), or cardiovascular and respiratory failure (see ch. 240 and 246). Autoregulatory mechanisms are responsible for providing relatively constant cerebral blood flow despite changes in systemic arterial pressure. Some areas of the brain are more susceptible to energy deprivation or may contain a higher concentration of *N*-methyl-D-aspartate (NMDA) membrane receptors.

Increased release of the excitatory neurotransmitter glutamate in cell injury leads to increased cellular influx of calcium and neuronal death. Global ischemia is associated with bilateral infarcts in the "watershed zones" between areas supplied by major arteries. Changes in blood flow to the brain may occur secondary to hyperviscosity from erythrocytosis (relative or absolute), hypercholesterolemia, hyperlipidemia (familial hyperlipidemia, hyperadrenocorticism, hypothyroidism), immune-mediated disease, sepsis, coagulopathies, and hyperglobulinemia. Hyperviscosity can result in emboli which then cause ischemic infarcts (see ch. 260).[1,2] Clinical signs reflect the area of the brain affected. Recent studies suggest that acute vision loss in cats after a cerebrovascular accident may be due to occlusion of the maxillary arteries and reduced blood flow to the brain, in particular when using a mouth gag.[3] Cytotoxic edema in the white matter can be detected on magnetic resonance imaging (MRI) scans.[4] Treatment consists of attempting to establish normal brain blood flow and oxygenation. Steroids are contraindicated and may cause further damage. Recovery is slow, taking weeks to months. Residual neurologic signs may persist after severe brain injury.

Systemic Hypertension

During a rapid and sustained rise in blood pressure, autoregulatory mechanisms for maintaining blood flow can fail, resulting in hypertensive encephalopathy (see ch. 157). Neurologic signs may occur at a lower blood pressure (170 mm Hg) if hypertension develops rapidly.[5] Common neurologic signs are seizures, ataxia, stupor, and blindness. Postmortem findings may include cerebral edema, caudal displacement of the vermis of the cerebellum, arteriolar hyalinosis, hyperplastic arteriosclerosis, ischemia, and necrosis. Cerebral microhemorrhages, possibly secondary to hypertension, have been reported on both MRI scans and necropsy in dogs.[6] Controlling hypertension in cats after renal transplantation reduces both incidence of seizures and neurologic complication–related deaths.[7] Hyaline arteriopathy in cats secondary to hypertension may result in thrombosis with signs of cervical myelopathy or encephalopathy.[8]

Endocrine/Metabolic Causes

Hepatic Encephalopathy

Hepatic encephalopathy (HE) can be caused by portosystemic shunt (PSS), microvascular dysplasia, idiopathic noncirrhotic portal hypertension, or other causes of liver failure (ch. 280, 281 and 284). Neurologic signs have been reported in about 95% of dogs with PSS.[9,10] The clinical signs may be more obvious after a

meal and tend to wax and wane. Neurologic signs are typical of diffuse cerebral disease and vary from mild (an inability to learn new things and behavioral changes) to more severe (head pressing, blindness, mentation changes and seizures). Brainstem and cerebellar signs have been described.[11] Neurologic signs were more common when the shunts inserted caudal to the liver.[12] One case report describes resolution of generalized neuromuscular weakness and regurgitation after surgical correction of a PSS.[13] MRI scans of dogs with PSS showed hyperintense, non–contrast-enhancing lesions in the lentiform nuclei and widened sulci.[14]

The pathogenesis of HE is not fully understood. Various endogenous toxins (amino acids, ammonia, mercaptans, gamma-aminobutyric acid [GABA], false neurotransmitters) normally cleared by the liver contribute to CNS signs. Hyperammonemia and inflammation predict the presence of hepatic encephalopathy in dogs with PSS.[15] Hyperammonemia, >120 mcmol/L due to urea cycle enzyme deficiency, has been documented in young Irish Wolfhounds without PSS.[16] Increased cerebrospinal fluid concentration of glutamine, quinolinic acid, tryptophan, and tryptophan metabolites have been found in dogs diagnosed with a PSS.[17,18] Activation of GABA receptors by increased levels of endogenous benzodiazepines may contribute to the clinical signs of HE, and a withdrawal effect may cause postsurgical seizures.[19] Hepatic encephalopathy has been successfully treated with flumazenil, a benzodiazepine-receptor antagonist. This also suggests that increased GABAergic tone has a role in the pathogenesis of HE.[20,21] Medically, production and absorption of toxins generated by bacteria in the gastrointestinal tract may be reduced with low-protein diets, antibiotics and/or lactulose.

Seizures may be controlled with potassium bromide (40 to 60 mg/kg PO q 24 h) or levetiracetam (20 mg/kg PO q 8 h) (see ch. 260). Sodium bromide, IV, can rapidly increase serum levels. Phenobarbital (3 to 5 mg/kg PO q 12 h) should be used with caution since it is protein-bound and metabolized by the liver. Benzodiazepine (0.5 mg/kg IV) may prevent postsurgical-withdrawal seizures.[22,23] Surgical correction of congenital PSS carries a better prognosis for postoperative survival and neurologic morbidity if done before 2 years of age according to some, whereas others suggest that the prognosis is similar in dogs >5 years of age.[24,25] Prophylactic antiepileptic therapy may reduce the incidence of postsurgical neurologic signs and seizures.[26-30]

Uremic Encephalopathy

Toxic substances not excreted due to acute kidney injury (AKI; ch. 322) or chronic kidney disease (CKD; ch. 324) can cause signs similar to those of hepatic encephalopathy. Increased concentrations of parathyroid hormone (PTH) and subsequent hypercalcemia may also contribute to uremic encephalopathy. A recent study did not show a significant reduction in serum PTH after treatment with calcitriol in normal cats or those with CKD.[31] Phosphate binders and low phosphate diets aid in minimizing uptake of phosphorus and treating high blood pressure can lower the risk for hypertensive encephalopathy.[31-35]

Hypothyroidism

The only clinical changes in some hypothyroid dogs may consist of acute or chronic progressive central vestibular signs (see ch. 299 and 300). The pathogenesis of hypothyroidism-associated abnormalities is likely multifactorial, and includes atherosclerosis with hypercholesterol-induced or hypertriglyceride-induced microthrombi causing infarcts or transient ischemic attacks, segmental demyelination, dysfunction of metabolic pathways within the brain, and metabolic derangement of neuronal or glial cell populations.[36,37] Intermittent vestibular signs may be seen with transient ischemic attacks. Typically, changes are not detected on MRI scan or on brain histology. Abnormalities may be noted on brain auditory-evoked response (BAER) or electroencephalogram (EEG). Increases in protein content of cerebrospinal fluid may be seen. Thyroid hormone supplementation usually resolves neurologic signs.

Myxedema coma is a rare but life-threatening manifestation of hypothyroidism. Clinical signs include mentation changes due to brain edema, hypothermia without shivering, non-pitting skin edema, and bradycardia. Hyponatremia and hypoventilatory hypoxemia can worsen neurologic status. Treatment consists of adequate ventilation, IV saline, passive correction of hypothermia, and levothyroxine (5 mcg/kg IV q 12 h). This should be followed by oral thyroid supplementation. Clinical improvement, when it occurs, is usually seen within 24 hours. Mortality, however, is high.[38,39]

Congenital hypothyroidism has been described in both dogs and cats. Clinical signs include disproportionate dwarfism, abnormal hair coat, lethargy, a stiff/stilted gait and abnormal mentation. Histologically, hypomyelination is seen in the corpus callosum, corona radiata, pons, pyramids, and the

lateral funiculi of the spinal cord.[40] Recently, a mutation causing congenital hypothyroidism in Tenterfield Terriers was described.[41]

Hyperthyroidism

Cats with hyperthyroidism may show mild CNS signs such as hyperactivity, change in sleep/wake cycle, aggression, or obtundation (ch. 301). Neurologic signs usually improve (and may completely resolve) with treatment.

Hyperadrenocorticism

Direct compression from a pituitary macroadenoma can cause mild to severe neurologic signs (ch. 306). Early clinical signs of macroadenoma include inappetence, mild obtundation, pacing, and disorientation (ch. 306). The condition may progress to more severe obtundation, circling, tetraparesis, ataxia, and seizures. Dogs with clinical signs usually have masses >1.0 to 1.5 cm in greatest diameter. Blindness rarely occurs in dogs and cats. Hyperlipidemia may result in infarcts. Ten of 13 dogs diagnosed with pituitary-dependent hyperadrenocorticism had a visible pituitary tumor at the time of or within a year of diagnosis, and 2 of these dogs developed neurologic signs within one year of diagnosis. Pituitary tumors cause neurologic signs in 15% to 30% of dogs before or after diagnosis and treatment for pituitary-dependent hyperadrenocorticism.[42,43]

Hypoglycemia

The brain neither synthesizes nor stores glucose. It is dependent on blood glucose for cellular metabolism. The brain utilizes ≈100 grams of glucose per day. Persistent hypoglycemia causes vascular constriction and hypoxia. Hypoglycemia can occur in dogs and cats secondary to a variety of conditions, including simple poor nutrition, insulinoma, liver failure, hypoadrenocorticism, nonislet cell tumors producing insulin-like growth factors, large metabolically active tumors (leiomyosarcoma), severe erythrocytosis, and sepsis (ch. 61). Hypoglycemia is a paraneoplastic syndrome (ch. 352).[44-48] It can also be associated with exogenous insulin overdose.

Neurologic signs secondary to hypoglycemia wax and wane with episodes of obtundation, weakness, disorientation, tremors, partial or generalized seizures, blindness, and/or coma. There is no correlation between the severity or frequency of clinical signs, degree of hypoglycemia, and survival time post-treatment. Symptomatic treatment with IV glucose (2 to 4 mL/kg of 50% glucose diluted to 25% concentration) usually quickly reverses neurologic signs. Medical management with prednisone is used to stimulate gluconeogenesis and glycogenolysis. Frequent small meals of high-protein, high-fat, and high–complex-carbohydrate diets can be helpful.

A serum insulin concentration within the midreference range or higher, with a serum glucose concentration <60 mg/dL, is consistent with a diagnosis of insulin-producing tumor (see ch. 303). Surgical removal of insulinoma is ideal, but this is a highly malignant form of cancer. Median survival time in one study of dogs with insulinoma was 196 days with only medical treatment, 785 days with only surgical treatment and 1316 days in dogs treated medically after relapse postsurgery.[46] Diazoxide inhibits insulin secretion, stimulates production of glucose by the liver, and inhibits glucose uptake by the cell. It has been successfully used in dogs but not in cats with insulin-producing tumors.[49] Permanent brain damage from neuronal death may persist despite normalization of blood glucose and insulin concentrations with treatment.[50,51]

Thiamine Deficiency

Thiamine is essential for decarboxylation of pyruvic acid and other alpha-keto acids. Thiamine deficiency causes decreased utilization of pyruvic acid and some amino acids, increased utilization of fats, and aciduria.[52] Thiamine deficiency occurs in cats and dogs fed meat preserved with sulfur dioxide, food low in thiamine due to processing, or thiaminase-containing fish. Histopathologic findings are those of polioencephalomalacia with bilateral symmetrical spongiosis, necrosis, and hemorrhage in the medial vestibular nuclei, caudal colliculi, cerebellar nodulus, and the subcortical grey matter.[53,54] Experimental thiamine deficiency in cats led to learning deficits likely related to lesions in the hippocampal formation.[55] Neurologic signs of thiamine deficiency reflect lesions in the cerebrum and vestibular nuclei. MRI scan lesions are hyperintense on T2-weighted and FLAIR sequences and contrast-enhance after IV gadolinium. Oral supplementation with thiamine (25 to 50 mg total dose q 12 h) usually resolves clinical signs after weeks to months.[54]

Irradiated Diet

Leukoencephalomyelopathy has been described in cat colonies fed irradiated diets in New Zealand and the UK. Cats became ataxic after several months on these diets. Histopathology demonstrated Wallerian degeneration in the brain and spinal cord. The cause of the encephalomyelopathy is unknown, but oxidative stress may play a role. The cats recover when returned to a normal diet.[56,57]

Electrolyte Abnormalities

Hypercalcemia

Hypercalcemia due to primary hyperparathyroidism or secondary to malignant neoplasm rarely has been related to seizures (ch. 69). The mechanism for seizures is poorly understood. Coagulopathies in hypercalcemic dogs have been documented.[58]

Hypocalcemia

Hypocalcemia can be due to any of several conditions, including AKI, CKD, primary hypoparathyroidism, and lactation (eclampsia). See ch. 69. Hypocalcemia causes increased membrane excitability in both muscle and the CNS. This leads to generalized stiffness, lameness, muscle twitching, nervousness, behavior changes, tetany, and seizures (see Video 298-1). Acute treatment consists of IV calcium (0.5 to 1.5 mL/kg 10% calcium gluconate) over 10 to 20 minutes while monitoring the heart rate. Calcium administered too quickly can result in arrhythmias. Long-term care is dependent on managing the underlying condition or administering vitamin D (see ch. 298).[59]

Hypernatremia/Hyponatremia

Severe *hyponatremia* can cause cerebral edema and life-threatening, diffuse encephalopathy.[60] Overaggressive correction of hyponatremia in dogs may also cause cerebral edema with central pontine myelinolysis and loss of oligodendroglial cells. These complications may occur 48 hours to several days after treatment.[61-63] MRI scans of these dogs has shown bilateral symmetrical hyperintense areas on T2-weighted images in the central thalamic nuclei. Correction of hyponatremia should not cause the rise in serum sodium concentration to exceed 10 mEq/L during any 24-hour period, to reduce the likelihood of such lesions. Aggressive IV saline treatment in symptomatic patients with hyponatremia of less than 24-hour duration may be successful without causing neurologic signs.

Hypernatremia, secondary to osmotic shifts in water from brain cells, leads to reduction of brain volume which, in turn, may cause vascular rupture and focal hemorrhage. Severity of neurologic signs appears related to rapid changes in sodium rather than magnitude of hypernatremia. In chronic hypernatremia the brain adapts to hypertonicity by producing idiogenic osmoles, which prevent cellular dehydration. Rapid correction of hypernatremia, however, results in movement of water into cells and subsequent cerebral edema. Mild hypernatremia can be corrected by offering water to animals willing to drink. More severe hypernatremia can be treated with IV hypotonic saline or 5% dextrose in water calculated using the following formula[64]:

$$\text{Free water deficit} = 0.6 \times \text{body weight (kg)} \times [(\text{plasma } Na^+ / 148) - 1]$$

Neoplasia

Neoplasia can cause neurologic signs secondary to direct invasion, metastasis, or ischemic and hemorrhagic infarcts. Diagnosis can be supported with an MRI scan, cerebrospinal fluid (CSF) analysis, or by identifying the primary neoplasia.[2,65] Paraneoplastic syndromes directly affect the CNS (ch. 352). These include hypoglycemia induced by an insulin-producing tumor or hypercalcemia secondary to lymphoma, thymoma, or apocrine adenocarcinoma.[66]

Hyperthermia

The canine brain has an intrinsic thermal resistance. The origin of neurologic dysfunction in dogs and cats with hyperthermia is usually not directly due to increased brain temperature, but from secondary changes such as hepatocellular degeneration, disseminated intravascular coagulation, respiratory alkalosis, or reduction in mean arterial blood pressure. Mentation changes, loss of pupillary light and oculocephalic reflexes, and tetraparesis have been described.[67]

Diseases Causing PNS Signs

Diseases causing peripheral nervous system (PNS) signs are listed in Table 12-1.

Hypoxia

Aortic thromboembolism, although uncommon in dogs and slightly more common in cats, usually occurs secondary to an underlying condition, such as cardiac disease, hyperadrenocorticism, neoplasia, disseminated intravascular coagulation, sepsis, renal disease, atherosclerosis (hypothyroidism et al), or autoimmune hemolytic anemia. Neurologic signs observed by owners may include progressive exercise intolerance with pelvic limb weakness, or more acute symmetric or asymmetric pelvic limb ataxia, paresis, or plegia. Such signs could follow an ischemic myopathy, neuropathy, or myelopathy.[68-70] Cats usually have peracute signs that include tachypnea, hypothermia, paraparesis, or plegia (ch. 256). Underlying causes are cardiomyopathy, hyperthyroidism, and neoplasia.[71]

Metabolic/Endocrine Disorders

Hypothyroidism

Thyroxine (T_4) stimulates mitochondrial respiratory activity, thus facilitating production of adenosine triphosphate (ATP). In hypothyroidism (ch. 299), the associated ATP deficiency impairs Na^+/K^+ pump activity that reduces axonal transport and causes axonal degeneration and demyelination. Myopathy has also been described secondary to hypothyroidism. In rare circumstances, neurologic signs may be the only manifestation of hypothyroidism. Signs include generalized weakness and muscle atrophy. Focal signs include laryngeal paralysis, megaesophagus, facial paralysis, or peripheral vestibular signs. Lameness as the sole clinical sign has been reported in four dogs.[72] Electrodiagnostic abnormalities and histopathologic abnormalities on muscle and nerve biopsies may be detected before clinical signs.[73] Neurologic signs may resolve after several months of thyroid hormone supplementation.[74]

Hyperthyroidism

Feline hyperthyroidism (ch. 301) has been associated with neuromuscular weakness: cervical ventroflexion, a plantigrade stance, and exercise intolerance. Clinical signs may reverse with treatment.

Hyperadrenocorticism

Hyperadrenocorticism (ch. 306) commonly causes muscle weakness. In rare cases, dogs have fibrotic myopathy or polyneuropathy. Clinical signs of fibrotic myopathy may include a stiff and stilted gait, generalized muscle atrophy, and difficulty flexing the limbs (Video 12-1). Clinical signs of polyneuropathy include generalized weakness and muscle atrophy. Diagnosis may be confirmed on electrodiagnostic testing (electromyogram [EMG] and nerve conduction, ch. 117) and biopsy of muscle and nerve (ch. 116). Type II myofiber atrophy is common. In dogs with fibrosis, stiffness may not change or only partially improve with months of treatment.[75,76] Steroid myopathy has also been described secondary to treatment with prednisone.[77,78]

Hypoadrenocorticism

Hypoadrenocorticism (ch. 309) results in episodes of lethargy, weakness, tremors, and collapse. Painful episodes of muscle cramps are extremely rare.[79] Secondary hypoglycemia may contribute to generalized weakness. Treatment with physiologic doses of glucocorticoids (e.g., prednisolone 0.1 mg/kg PO q 24 h) typically results in full clinical recovery.[80,81]

Diabetes Mellitus

Peripheral nerve metabolism is dependent on glucose. Sensorimotor polyneuropathy is a late complication of diabetes mellitus (DM; ch. 304 and 305). Two major theories of pathogenesis involve metabolic derangement and vascular changes.[82] Clinical signs are most prominent in the pelvic limbs with a plantigrade stance, difficulty jumping, postural reaction deficits, decreased tendon reflexes, and muscle atrophy (see ch. 305). Neuropathic signs are much more common in cats than in dogs (Video 12-2). Horner's syndrome has been reported secondary to DM.[83,84] Abnormalities in nerve conduction studies and EMG are found in both thoracic and pelvic limbs. Histopathologic abnormalities include demyelination, splitting and ballooning of the myelin sheath, and axonal injury. Myelin injury is likely associated with microvascular increase in capillary size, increase in capillary lumen diameter, and increased basement membrane thickness.[82,85-87] Permanent deficits, despite control of the DM, are common.

Kidney Disease

Dogs and cats with CKD may have weakness associated with renal secondary hyperparathyroidism, which causes peripheral neuropathy and myopathy. Inositol phosphates, protein kinase C, and cyclic adenosine monophosphate (AMP), among other regulatory enzymes and signal-transducing systems in muscle cells, are directly affected by calcitriol. PTH-mediated uremic myopathy may be reversible when treated with calcitriol. Excess PTH also partially affects motor nerve conduction velocity. Nerve excitability is modulated by calcitriol, which also affects the synthesis of nerve growth factors. Changes can be found on electromyography and nerve conduction studies (ch. 117).

Hypokalemia

Naturally-occurring hypokalemia is uncommon and may follow dietary restrictions (ch. 68). It is most frequently diagnosed in cats with CKD but seems less common in dogs similarly afflicted. Aside from CKD, it is a rare condition secondary to an adrenal tumor causing excess synthesis of aldosterone (primary hyperaldosteronism, Conn's syndrome) or adrenal-dependent hyperadrenocorticism.[88] Hypokalemia alters resting membrane potentials of muscle, resulting in weakness. Neurologic signs, cervical ventroflexion in cats and generalized weakness in both dogs and cats, are nonspecific. Initial treatment requires IV potassium supplementation if seriously ill. Chronic oral administration can alleviate or minimize the condition. However, IV fluids containing potassium may worsen hypokalemia due to increases in vascular volume and through renal losses associated with increased perfusion. Oral administration of 5 to 10 mEq of KCl per day is safe. Dopamine causes a shift of potassium from the intracellular to the extracellular fluid.[89]

Paraneoplastic Syndrome

Paraneoplastic syndromes can cause neurologic signs due to a remote effect of cancer (ch. 352). This may not be caused by direct neoplastic cell invasion of the nervous system. Nor is this condition caused by any other mechanism related to the presence of cancer: coagulopathy, vascular disorder, infection, or metabolic and nutritional deficits. The syndrome can affect both the CNS and the PNS. Neurologic signs can develop months to years before a tumor is detected. The lack of specific diagnostic tests makes the recognition of the syndrome difficult. Pathogenesis may be due to antibodies produced against cells of the nervous system. Removal of the tumor may result in resolution of the neurologic signs. Paraneoplastic syndromes have been documented secondary to insulinoma, adenocarcinoma, cholangiocellular carcinoma, lymphoma, melanoma, myeloma, and thymoma. Thymoma is a common cause of myasthenia gravis in humans and cats and less common in dogs (ch. 269). Neurologic signs can be focal (megaesophagus) or generalized. The myasthenia gravis may improve with removal of the mass; however, megaesophagus signals a poor prognosis.[90-93]

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CHAPTER 13

Intoxication versus Acute, Nontoxicologic Illness: Differentiating the Two

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Case History

Upon presentation of an acutely ill animal, a veterinary professional must consider poisoning as a potential cause among the differentials. A complete and thorough case history in this regard is essential for differentiating a poisoning situation from a naturally occurring disease (see ch. 1). Obtaining a clear recent history may sometimes be quite challenging, especially in situations where the pet was unsupervised before the initiation of clinical signs. History questions must include animal signalment (breed, sex, and age) and weight, previous medical history, vaccination history, dietary history (brand; home-made or commercial; if nutritional intoxication is suspected, obtain product label and lot number) and any medications the pet is taking. Initial information about any other animals present in the household, timeline of clinical signs, types of clinical signs reported by the owner, number of affected animals, pet's environment (indoor vs. outdoor; fenced or free roaming), location (urban vs. rural), time of the year (summer vs. winter), recent renovations/updates (construction material; lead in older farms/houses), recent visitors, availability of human medications in the pet's environment (antidepressants, pain killers, stimulants, nutritional supplements), presence or recent use of chemicals (insecticides, herbicides, rodenticides) in the house/yard, information about neighboring animals (outbreaks; illnesses; death) and information about indoor/outdoor plants may help provide clues to the clinician to narrow down the search for a possible cause for the pet's illness. A good case history can help speed up the process of narrowing down a potential cause, eliminate several unnecessary steps, and save time and money.

Stabilizing the Patient

Before obtaining a complete case history, the first goal should be to stabilize the patient and preserve the life of the acutely ill animal irrespective of the cause. Relying too much on specific antidotal treatment may be dangerous. A majority of clinical cases on presentation are treated supportively as only a very few specific antidotes are available or needed for treating specific poisonings. Therefore, on presentation, it is essential to make sure the animal has a patent airway and adequate, effective ventilation (see ch. 139). Heart rate, heart rhythm, and blood pressure should be monitored, and cardiac arrhythmias (see ch. 248) and systemic hypo- or hypertension should be treated as needed (see ch. 158 and 159). Hydration status, serum electrolyte concentrations, and acid-base balance should be checked and abnormalities corrected accordingly (see ch. 67-70 and 127). Central nervous system abnormalities (excitation, depression, seizures) should be identified and treated as required (see ch. 136 and 148), and hypothermia or hyperthermia should be identified and corrected if present (see ch. 48, 49, and 134).

After stabilizing these vital functions, obtain the medical history; then, provide other necessary treatments such as decontamination (administration of activated charcoal, gastric lavage, bathing, dilution; ch. 151), supportive care, and carrying out other diagnostics (e.g., complete blood count, serum biochemistry profile, urinalysis, radiographs, ultrasound) based on the information obtained and on the patient's progress. Collection of samples for toxicologic analyses can be important. Toxicology testing performed in a diagnostic laboratory can be expensive and time-consuming and in most instances, results are not available immediately. Therefore, to rule in or out a suspected cause, commonly used in-house diagnostic tests are likely to be of greater immediate benefit to the patient (whereas toxicologic analyses can be of superior value for group exposures or for cases involving litigation). For example, assessment of prothrombin time or clotting times can be pivotal in anticoagulant poisoning cases. Other samples for toxicologic testing in a diagnostic laboratory include whole blood for heavy metal analysis (lead), blood cholinesterases (organophosphate

poisoning), and presence of pesticides (anticoagulant rodenticides). Serum or plasma can be analyzed for levels of some metals (zinc), drugs, alkaloids, and electrolytes (useful in sodium chloride poisoning or water intoxication). Stomach contents (vomitus; freeze upon collection) can be used for detecting pesticides, metals, baits, alkaloids, and drugs. Urine (chilled or frozen) can be used for some metal analysis, drugs and their metabolites, and alkaloids (strychnine).

Toxicologic Versus Nontoxicologic

Table 13-1 outlines some important toxicologic versus nontoxicologic rule-outs based on clinical abnormalities one must consider in an acutely ill animal. It is important to note that an acutely ill animal with sudden onset of clinical effects may often have multiple major clinical signs/abnormalities present, and that toxicologic problems can trigger nontoxicologic complications (e.g., aspiration pneumonia). The purpose here is to provide an initial guideline for considering toxicologic versus nontoxicologic rule-out in a patient with an uncertain recent history.

TABLE 13-1

Toxicologic versus Nontoxicologic Rule-Outs

MAJOR CLINICAL ABNORMALITY	TOXICOLOGIC RULE-OUTS	NONTOXICOLOGIC RULE-OUTS
CNS abnormalities (excitation and seizures; see also ch. 35)	• Strychnine (rapid onset, rigidity, hyperesthesia, wooden-horse–like stance) • Metaldehyde (hyperthermia, tremors) • Amphetamines or cocaine (ingestion in dogs: sympathomimetic effects and hyperthermia) • Tremorgenic mycotoxins (penitrem A, roquefortine) from eating moldy foods (GI signs, hyperthermia, and tremors) • Cold medications: pseudoephedrine, ephedrine, some antihistamines (sympathomimetic effects, hyperthermia) • Organophosphate or carbamate pesticides (cholinergic crisis; SLUD signs) • Pyrethrin/pyrethroid-type pesticides (especially permethrin in cats: tremors, shaking, ataxia, seizures, GI signs) • Organochlorine pesticides (tremors, shaking, ataxia, seizures) • Chocolate: caffeine, theobromine, methylxanthines (polydipsia, polyuria, GI and CV effects) • Zinc phosphide: mole or gopher baits (GI signs, shaking, dyspnea due to pulmonary edema) • Bromethalin toxicosis: rat or mouse bait (paresis, weakness, ataxia, tremor) • Lead (GI signs, hematologic abnormalities [nucleated RBCs, basophilic stippling, anemia]) • Metronidazole toxicosis (in dogs with repeated use and/or high dosage: nystagmus, ataxia, weakness, paresis, seizures) • Nicotine: tobacco or cigarettes (ingestion in dogs: spontaneous vomiting, tremors, CV effects) • Tricyclic antidepressant toxicosis: amitriptyline, clomipramine, imipramine,	• Trauma/head trauma (outdoor animal, external or internal wounds/injuries) • Meningitis (fever, hyperesthesia, neck stiffness and pain; fundic lesions possible if optic nerve affected) • Hydrocephalus (large, rounded head; divergent strabismus; seizures; brain ultrasound exam possible if open fontanelle) • Intracranial neoplasia (primary or secondary brain tumor; typically older animals; neurologic deficits almost always asymmetrical) • Congenital portosystemic shunts (more common in certain breeds, <6 months of age, small liver) • Rabies (acute behavior changes, excitation, paralysis; endemic region) • Canine distemper (young dogs: history of fever, respiratory, and/or GI signs usually precede CNS signs) • Hypocalcemia or hypercalcemia (hypocalcemic tremor/tetany; hypercalcemia-induced kidney injury can cause uremic signs) • Hypoglycemia (disorientation, ataxia, seizures; serum glucose <60 mg/dL) • Idiopathic epilepsy (dogs 1-5 years of age: diagnosis of exclusion) • Primary or secondary erythrocytosis (causing hyperviscosity), PCV 65% to >80%, brick red mucous membranes • Uremia (secondary to AKI or CKD) • Endotoxemia/septic shock (hemorrhagic GI signs, progressive weakness, abdominal pain)

	nortriptyline (agitation, nervousness, ataxia, CV effects)	
CNS abnormalities (e.g., CNS depression and/or seizures; see also ch. 35)	• Ivermectin, moxidectin and other avermectin toxicosis (ataxia, weakness, depression, tremors, seizures, blindness) • Marijuana ingestion (ataxia, hypothermia, urinary incontinence) • Benzodiazepines ingestion: alprazolam, clonazepam, diazepam, lorazepam (hyporeflexia, ataxia, CNS excitation: paradoxical reaction) • Barbiturate overdose: short-acting or long-acting (coma, hypothermia, weakness, ataxia) • Ethylene glycol (see ch. 322) (ataxia, disorientation, GI signs) • Methanol or ethanol ingestion (GI signs, ataxia, weakness, depression) • Propylene glycol: antifreeze (depression, ataxia, GI signs) • Baclofen or other centrally acting muscle relaxant ingestion in dogs (vocalization, ataxia, disorientation, coma, hypothermia) • Amitraz insecticide exposure (depression, ataxia, CV effects, paralytic ileus)	• Thiamine deficiency in cats (cats fed mainly raw fish diet; ch. 12 and 192) • Polyradiculoneuritis/Coonhound paralysis (ascending flaccid paralysis; often, evidence of muscle pain; occasionally, raccoon exposure within preceding 2 weeks) • Feline infectious peritonitis (blepharospasm due to iritis, fever, weight loss, ataxia, seizures) • Feline leukemia (lymphadenopathy, nonregenerative anemia) • Feline panleukopenia (fever, GI signs, ataxia, neutropenia)
Muscle weakness, paresis, paralysis (see ch. 21 and 269)	• Black widow spider bite (cats: swelling, pain) • 2,4-D and other phenoxy herbicides (dogs: ataxia, weakness, GI signs) • Metronidazole; see Seizures, above • Bromethalin rodenticide; see Seizures, above • Coral snake envenomation (cats: local swelling, pain, puncture wound) • Macadamia nuts ingestion in dogs (weakness, ataxia) • Concentrated tea tree oil exposure: *Melaleuca* oil (both cats and dogs: weakness, ataxia, CNS depression)	• Polyradiculoneuritis/Coonhound paralysis, see above • Botulism (ascending paresis and paralysis; muscles of pharynx can be affected) • Tick paralysis (flaccid ascending paralysis; rapid improvement of signs [<24 hours] after tick removal if North American [*Dermacentor* spp.], longer if Australian [*Ixodes* spp.]) • Aortic thromboembolism (cold extremities, weakness, firm and painful gastrocnemius muscles [cats]) • Profound anemia (measure PCV) • Severe hypokalemia, hyponatremia, hypovolemia, hypo- or hyperthermia (measure parameter) • Degenerative spinal cord diseases (mentation, cranial nerve function intact)
Acute blindness (ch. 11)	• Lead; see Seizures, above • Ivermectin, moxidectin, and other avermectin toxicosis; see Seizures, above • Salt poisoning (in dogs: polydipsia, GI signs, tremors, ataxia, seizures; serum sodium >160 mEq/L is strongly supportive)	• Retinal detachment or hemorrhage (fundic exam; ocular ultrasound) • Glaucoma (measure intraocular pressure) • Trauma (penetrating injury of head, face) • Acute cataract (ophthalmic exam) • Optic neuritis (fundic exam) • Other visual pathway disorders (optic chiasm, optic radiation, occipital cortex) • Sudden acquired retinal degeneration (hyperadrenocorticism-like signs; electroretinogram to confirm)
Acute kidney injury, acute uremia (ch. 322)	• Ethylene glycol toxicosis (ataxia, altered mentation/depression, GI signs; urine may fluoresce with Wood's lamp; azotemia, calcium oxalate monohydrate crystalluria appear after kidney injury has occurred) • Easter lily *(Lilium longiflorum),* tiger lilies *(L. tigrinum, L. lancifolium),* rubrum or Japanese show lilies *(L. speciosum),* day lilies (*Hemerocallis* sp.) ingestion in cats	• Renal infiltration (lymphoma; usually symmetrical nephromegaly; CNS signs common due to brain metastases) • Renal thromboembolism (evidence of peripheral thromboembolism common) • Infectious (pyelonephritis, leptospirosis, Rocky Mountain spotted fever, borreliosis, feline infectious peritonitis: cats) • Urinary tract obstruction (bladder palpation;

	(initially GI signs, azotemia generally 24-72 hours after ingestion) • Cholecalciferol rodenticide and other vitamin D_3 analogs: calcipotriene, calcitriol (initial GI signs, then CV, CNS signs; azotemia; hypercalcemia with hyperphosphatemia differentiates from hypercalcemia of malignancy or hyperparathyroidism) • Grapes and raisins ingestion in dogs (initial GI signs, then azotemia in >24 hours, possible pancreatitis) • NSAIDs: ibuprofen, naproxen, nabumetone, piroxicam, carprofen, diclofenac, ketoprofen, indomethacin, ketorolac, oxaprozin, etodolac, flurbiprofen, sulindac (initially GI signs, azotemia in 24-72 hours after acute ingestions) • Zinc toxicosis; see Acute Hemoglobinemia, below • Melamine and cyanuric acid food contamination (2007 outbreak in the United States, contaminated dog and cat food: crystalluria, azotemia, GI signs)	abdominal ultrasound to evaluate kidneys, ureters) • Chronic kidney disease (end stage) • Ischemic kidney injury and uremia (hypotension, trauma, shock, anaphylaxis, myoglobinuria; urinalysis for renal casts, discoloration) • Amyloidosis (notably Shar-Pei dogs, Abyssinian cats) • Hypercalcemia (lymphadenopathy, hepatosplenomegaly possible with lymphoma, rectal palpation for anal sac mass with anal sac adenocarcinoma; malignancy and primary hyperparathyroidism typically cause concurrent hypophosphatemia) • Transfusion reactions (history)
Acute hepatic injury (ch. 286)	• Mushrooms: *Amanita*-type (delayed onset GI signs [12 hours after ingestion], acute liver injury in 1-3 days) • Blue-green algae: *Microcystis* sp. (exposure to stagnant body of water; acute onset GI signs, hypovolemic shock) • Iron: multivitamin ingestion (GI signs, hypovolemic shock, acute liver injury in 1-2 days) • Sago or cycad palm: *Cycas* sp. (ingestion: GI signs, liver injury in 1-3 days, seizures) • Acetaminophen toxicosis: cats > dogs (methemoglobinemia within a few hours, GI signs, increased liver enzymes in 1-3 days) • Aflatoxicosis (dogs: mostly from contaminated dog food, several outbreaks reported in the United States) • Xylitol; see Hypoglycemia, below • Other drugs (carprofen: GI signs, increased ALT days after starting treatment; corticosteroids: steroid hepatopathy after weeks/months of use; phenobarbital: chronic hepatopathy after months of use)	• Hepatic lipidosis (cats: period of stress, anorexia, obesity) • Hepatic neoplasia (primary or metastatic, acute or gradual; abdominal ultrasound and biopsy to confirm) • Infectious hepatitis (leptospirosis, infectious canine hepatitis, canine herpesvirus, feline cholangiohepatitis, liver abscess, histoplasmosis, coccidioidomycosis, babesiosis, toxoplasmosis, some rickettsial diseases, feline infectious peritonitis; identify other characteristic features of individual diseases) • Septicemia/endotoxemia (vomiting, diarrhea, hypothermia, collapse) • Copper storage (breed: Bedlington Terrier, others) • Heatstroke (high body temperature) • Shock (weak pulse, poor capillary refill time, progressive weakness)
Presence of acute oral lesions/ulcers (ch. 272)	• Acid ingestion (corrosive lesions on lips, gums, tongue, salivation, vomiting, fever) • Alkali ingestion (same as with acid, esophageal perforation more likely) • Cationic detergents: present in several disinfectants (oral burns, salivation, vomiting, fever) • Alkaline battery chewing/ingestion (oral burns, salivation, vomiting) • Potpourri ingestion (cats > dogs: oral burns, salivation, vomiting, tongue	• Uremic stomatitis (uremic halitosis, azotemia, GI signs) • Periodontal disease (associated with dental calculus; gingival lesions) • Trauma (presence of foreign body, recent tooth fracture) • Electrical cord chewing (sharply demarcated ulcers, dyspnea due to noncardiogenic pulmonary edema) • Systemic lupus erythematosus and other autoimmune diseases (lesions are characteristically at the mucocutaneous junction; joint pain, other

	protrusion, fever) • Bleaches: sodium or calcium hypochlorite (bleachlike smell, salivation, vomiting, wheezing, gagging) • Ingestion of phenolic compounds (especially in cats: oral ulcers/lesion may be present, Heinz body anemia and hemolysis may be seen)	systemic signs can be present) • Infectious (feline calicivirus infection, FeLV, FIV, nocardiasis, ulcerative necrotizing stomatitis, *Fusobacterium* spp. infection; identify other characteristic features of individual diseases)
Acute methemoglobinemia, Heinz body anemia, hemolysis or blood loss (anemia) (ch. 198)	• Acetaminophen (chocolate brown-colored mucous membrane within hours, dyspnea) • Naphthalene mothball ingestion (mothball-like odor in the breath, hemolysis) • Onions and garlic toxicosis (hemolysis in 2-3 days, anemia, coffee-colored urine) • Zinc toxicosis (metallic object in the GI tract, gastritis, pancreatitis, hemolysis, hemoglobinuria) • Iron; see Acute Hepatic Injury, above • Anticoagulant rodenticides: brodifacoum, bromadiolone, chlorophacinone, difethialone, diphacinone, pindone, warfarin (lethargy, dyspnea due to pulmonary hemorrhage, persistent bleeding at venipuncture site; increased PT +/- aPTT) • Rattlesnake envenomation (swelling, pain, +/- fang puncture marks in skin; endemic region) • Other drugs (local anesthetic toxicosis [lidocaine, benzocaine, tetracaine, dibucaine]: methemoglobinemia, CV and CNS effects; phenazopyridine and other azo dyes toxicosis [methemoglobinemia, hemoglobinuria])	• Trauma (overt blood loss) • Immune-mediated hemolytic anemia (spherocytosis +/- autoagglutination on blood smear) • Thrombocytopenia (immune-mediated or infectious, uncommonly drug-induced; platelet count) • Chronic kidney disease (smaller kidneys, azotemia, uremic halitosis, oral ulcers) • Infectious (ehrlichiosis, FeLV, hookworms, *Mycoplasma hemofelis*, babesiosis; serologic testing, fecal flotation, blood smear) • Disseminated intravascular coagulation (secondary to shock, neoplasia, septicemia, viral infections, pancreatitis) • Inherited bleeding disorders (von Willebrand disease, factor X deficiency, factor XI deficiency; specific factor analysis needed for confirmation) • Causes of epistaxis (trauma, infectious, nasal polyps, malignant neoplasm, systemic bleeding disorder, systemic hypertension)
Cardiac arrhythmias (ch. 248)	• Foxglove: *Digitalis* sp. (plant ingestion: GI signs, ventricular and/or supraventricular arrhythmias) • Lily of the valley: *Convallaria majalis* (plant ingestion, GI signs, ventricular and/or supraventricular arrhythmias) • Oleander: *Nerium oleander* (GI signs, ventricular and/or supraventricular arrhythmias) • Bufo toads: *Bufo* sp. (endemic region; GI signs, collapse, seizures, sinus tachycardia, ventricular arrhythmias) • Azalea and other *Rhododendron* plants (GI signs, possible cardiac arrhythmias) • Antidepressant toxicosis (CNS signs, anticholinergic effects)	• Automobile trauma (evidence of other injuries) • Gastric dilation and volvulus (abdominal distension, dyspnea, shock; radiographs confirmatory) • Severe anemia (due to any cause of anemia; packed cell volume to confirm) • Severe hypokalemia (due to any cause) • Acidosis (due to any cause) • Hypoxemia (due to any cause) • Primary heart disease (cardiomyopathy, valvular heart disease, congenital heart problems, heartworm infestation: heart murmur, cardiomegaly, and/or evidence of congestive heart failure)
Dyspnea due to pulmonary edema (ch. 242)	• Petroleum distillates: kerosene, gasoline and other hydrocarbons (hydrocarbon smell in the breath, salivation, vomiting, CNS depression, diarrhea, aspiration) • Zinc phosphide (exposure to gopher bait or similar; GI and CNS signs, dyspnea due to noncardiogenic pulmonary edema) • Smoke inhalation (dyspnea, collapse, panting, shock; smell of smoke on fur in	• Cardiogenic (multiple causes of left-sided congestive heart failure) • Noncardiogenic (seizures, head trauma, electrical shock, drowning and near-drowning)

	virtually every case) • Organophosphate or carbamate pesticides (cholinergic crisis, SLUD signs) • Paraquat herbicide (rare; progressive dyspnea, panting, delayed onset after exposure) • Some organic arsenicals (mainly injectable, melarsomine)	
Gastrointestinal signs (vomiting, diarrhea, abdominal pain, drooling) (ch. 36, 39, and 40)	• Garbage poisoning (vomiting, diarrhea, dehydration, abdominal pain) • Chocolate toxicosis (initial stages: polydipsia, polyuria, vomiting, hyperactivity, tachycardia) • Fertilizer ingestion (NPK: vomiting, diarrhea, polydipsia) • NSAID toxicosis (initial stages: GI signs with or without blood in vomitus, diarrhea) • Endotoxins and enterotoxins: staphylococcal, clostridial, *Escherichia coli, Salmonella* (severe GI signs, progressive lethargy, dehydration, hypothermia) • Zinc oxide (diaper rash ointment ingestion in dogs; mild to severe gastritis) • Iron toxicosis; see Acute Hepatic Injury, above • Arsenical herbicides (initial stages: vomiting, abdominal pain, watery diarrhea) • Castor beans: *Ricinus communis* (initial GI signs within several hours) • Insoluble calcium oxalate containing plants: elephant's ear (*Caladium* sp.), dumb cane (*Dieffenbachia* sp.), philodendron (*Philodendron* sp.), peace lily (*Spathiphyllum* sp.) (vomiting, diarrhea, oral swelling, salivation) • Zinc phosphide (GI and CNS signs, pulmonary edema; liver and kidney damage possible)	• Dietary discretion (recent change in diet) • Intestinal parasites (coccidia, roundworms, hookworms) • Foreign body (plastic, wood, metal, cloth, bones; partial or complete obstruction) • Infectious (feline panleukopenia, canine distemper, canine parvovirus, canine coronavirus, infectious canine hepatitis, leptospirosis, salmonellosis) • Gastric dilation/volvulus, intussusception (abdominal distension, pain, dyspnea, shock) • Liver diseases (secondary to gastric ulceration; evaluate serum liver parameters, pre- and postprandial bile acids) • Kidney diseases (uremia secondary to either intrinsic renal disease or post-renal obstruction) • Endocrine disorders (diabetic ketoacidosis, hypoadrenocorticism) • Sudden change in the environment (traveling, weather change, boarding, moving) • Inflammatory bowel disease
Hypernatremia (measured serum sodium >160 mEq/L in dogs and >165 mEq/L in cats)	• Paintball ingestion (dogs: history of paintball ingestion, polydipsia, vomiting, diarrhea, ataxia) • Salt toxicosis (history of inducing emesis with sodium chloride, ingestion of excessive amounts of salt-containing objects [play dough/plasticine] and foods) • Activated charcoal administration (can occur sporadically in some dogs, possibly due to fluid shift) • Sea water ingestion (history of visit to a beach, lack of access to fresh water, swimming)	• Due to pure water loss (nephrogenic diabetes insipidus, heatstroke, fever, burns, no access to water) • Due to hypotonic water loss (severe diarrhea, vomiting, diabetes mellitus, polyuric kidney disease, hypoadrenocorticism)
Hypoglycemia	• Ingestion of xylitol-containing products (dogs; sugar-free gum, sugar-free bakery products, etc.; hypoglycemia within 12 hours; seizures, acute hepatic damage and coagulopathy in 1-3 days) • Ingestion of oral diabetic/hypoglycemic agents (sulfonylureas)	• Insulinoma • Acute hepatic disease, portosystemic shunt • Functional hypoglycemia (idiopathic in neonates, insufficient caloric intake in young puppies and kittens, severe exercise) • Intestinal parasitism • Hypoadrenocorticism • Leiomyosarcoma/smooth muscle tumor

		• Endotoxemia

2,4-D, Dichlorophenoxyacetic acid; *AKI,* acute kidney injury; *ALT,* alanine aminotransferase; *aPTT,* activated partial thromboplastin time; *CKD,* chronic kidney disease; *CNS,* central nervous system; *CV,* cardiovascular; *FeLV,* feline leukemia virus; *FIV,* feline immunodeficiency virus; *GI,* gastrointestinal; *NPK,* nitrogen, phosphorus, potassium; *NSAID,* nonsteroidal antiinflammatory drug; *PCV,* packed cell volume; *PT,* prothrombin time; *RBC,* red blood cell; *SLUD,* salivation, lacrimation, urination, defecation.

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CHAPTER 14

Orthopedic Manifestations of Systemic Disease

Bing Yun Zhu

Client Information Sheet: Investigation of Mobility Problems

Dogs and cats of any age may present for lameness, abnormal gait, difficulty rising or more subtle signs such as unwillingness or reduced ability to jump up onto furniture or into a car. It is important to maintain an open mind regarding such signs. A primary orthopedic problem may or may not be the underlying cause of the presenting signs, as there can be many underlying systemic diseases that can cause orthopedic signs. Some medications empirically prescribed can be contraindicated, such as immunosuppressive drugs when there is an underlying infectious condition. Alternatively, some empirical therapies may delay response to later more appropriate treatment. Whenever possible, an accurate diagnosis should precede and direct management.

Diagnostic Approach to Orthopedic Manifestations of Systemic Disease (Figure 14-1)

Signalment

As with any presenting complaint, it is important to first consider patient signalment, as this will impact the likelihood of certain differential diagnoses. Although signalment and presenting complaint alone should not dictate subsequent treatment, this information may aid in listing likely diagnoses by probability. This, in turn, may help selecting tests in an attempt to establish a diagnosis, especially in circumstances where finances are limited. For example, large and giant breed dogs are predisposed to primary orthopedic conditions such as joint dysplasia and degenerative joint diseases. Alternatively, immune-mediated diseases occur more commonly in middle-aged female dogs as compared with cats, in whom primary immune-mediated polyarthropathies are rare.[1] Neoplasia is of higher concern in older pets, while crush injuries may be suspected in nursing puppies or kittens. Males are more likely to develop discospondylitis and any male dog with prostatic disease may appear lame.[2]

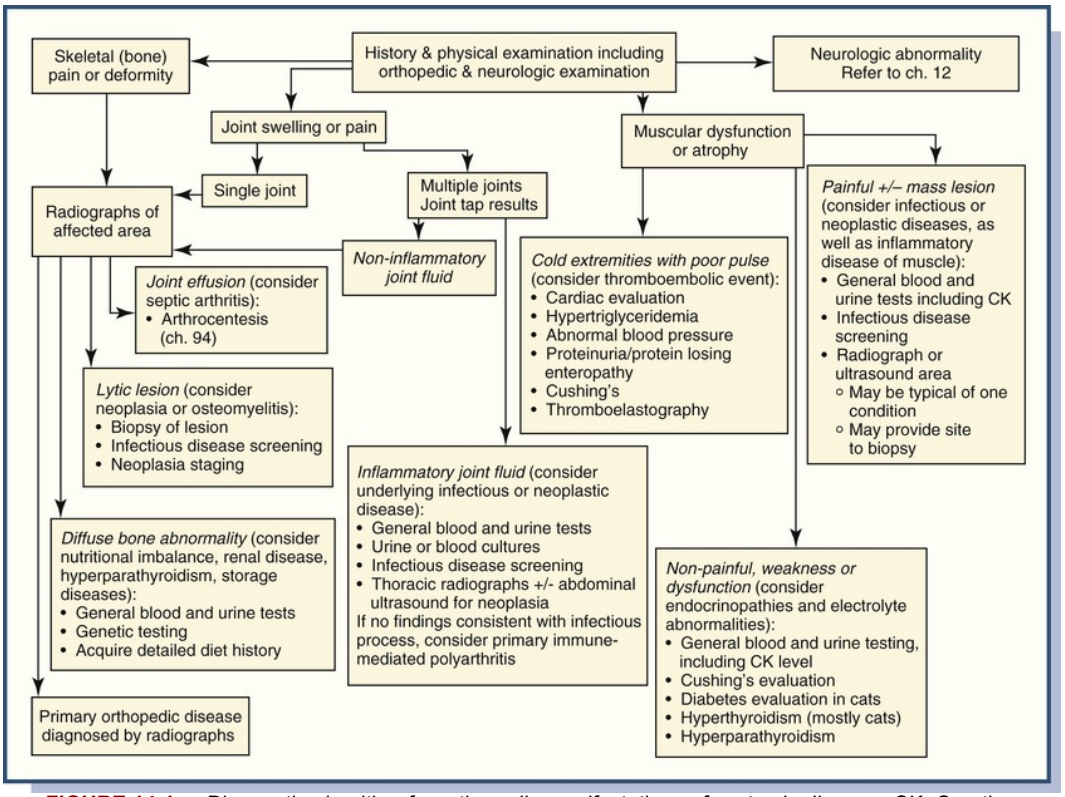

FIGURE 14-1 Diagnostic algorithm for orthopedic manifestations of systemic disease. *CK,* Creatine kinase.

History

Owner observations are extremely valuable. One may inquire about any earlier traumatic episode or ask about issues in littermates or related pets. Review all recent and previous travel because orthopedic signs may be associated with tick borne disease (rickettsial, protozoal, bacterial, spirochete), fungal disease (histoplasmosis, blastomycosis, coccidioidomycosis, cryptococcosis), or leishmaniasis. Seasonality and environment should be considered. Warm weather marks the onset of tick and snake activity. Bites from some can cause rapid-onset paresis and paralysis.

An enquiry into animals' general health should always be undertaken. Cats with recent onset polyuria and polydipsia, weight loss and a plantigrade stance with decreased ability to jump may have diabetic neuropathy. Certain medications may also "trigger" orthopedic signs. Muscle atrophy caused by corticosteroids can reduce a dog's ability to ambulate or jump. Antibiotics such as trimethoprim-sulfur may induce immune-mediated polyarthritis.

Physical Examination

In the scenario of an orthopedic issue, the physical examination should begin when first meeting the pet by carefully observing both ability to rise and gait. Ideally, veterinarians should assess walking and trotting gaits of dogs being led by their owners on a non-slip surface. Cats should be allowed out of their carrier to explore the examination room as the history is taken.

After a thorough general physical examination, a full orthopedic examination should be performed, focusing on palpation of long bones and the vertebral column, including lumbosacral palpation via digital rectal examination. All peripheral joints should be palpated for effusion and manipulated. The clinician should open the jaw to assess the temporomandibular joint. Stifles should be assessed for ligament laxity. Any muscle atrophy should be noted. It is wise to palpate and manipulate non-painful areas in order to gain some patient and owner trust. This also allows the veterinarian to gain insight into a pet's personality and possibly identify pain in areas not suspected as being painful.

Following thorough orthopedic evaluation, a neurological assessment should be performed. At minimum, this should include testing proprioceptive placement reflexes in all four limbs. Any abnormality in

proprioceptive placement, gait, or mentation is an indication for a full neurological examination (see ch. 259). Fundic examination (see ch. 11) may be suggestive of hypertension, fungal disease or another systemic inflammatory or infectious condition.

Differential Diagnoses

One method for remembering many of the possible differentials is to break them down into the main histopathological processes. While these categories are exclusive of other conditions, they provide a starting point in the quest for a diagnosis.

Diseases of Bone

Degeneration, Tissue Injury, and Death

Fractures can be due to trauma or an underlying condition causing weakened bone structure. Bone disease can be focal (such as with infection or neoplasia) or diffuse. Many systemic diseases can lead to diffuse changes in bone. One example is the increased osteoclastic activity associated with excess parathyroid hormone due to primary, nutritional secondary, or renal secondary hyperparathyroidism.[3-6] Disuse osteoporosis begins in a few weeks.[7,8] Osteoporosis has been associated with vitamin D deficiency, whether from inadequate dietary intake or malabsorptive conditions.[9,10]

Inflammation (Infectious or Sterile)

Pain associated with osteomyelitis commonly causes lameness. Severe disease can lead to pathological fractures. Bacterial osteomyelitis can follow hematogenous spread, direct trauma and inoculation, or surgical intervention.[11,12] Fungal causes of osteomyelitis include blastomycosis, systemic aspergillosis, cryptococcosis, histoplasmosis, and coccidioidomycosis.[13] Panosteitis is a disease of medullary adipocytes associated with eosinophilic granular degeneration that affects young, medium- to large- and giant-breed dogs. Clinical signs include lameness, difficulty rising, and pain on palpation of long bones.[14]

Disorders of Cell Growth (Abnormal Growth and Neoplasia)

Disorders of cell growth can be categorized as either deviations in normal growth or those secondary to some cancers. Abnormal growth of bone can cause discomfort when bearing weight or it could cause pain in surrounding tissues. If abnormal bone growth occurs in or near the vertebral column, spinal cord compression can cause paresis or paralysis. Neoplasia of bone can be primary (osteosarcoma, chondrosarcoma, fibrosarcoma, hemangiosarcoma, myeloma) or metastatic.[15] Common cancers that spread to bone include mammary carcinoma, urinary tract carcinomas (including prostate), lymphoma, melanoma and mast cell tumor.[16] Benign neoplasia of bone can also cause lameness. These include osteochondromas, bone cysts and multiple cartilaginous exostoses (see ch. 348).[15,17]

Systemic diseases that can cause abnormal skeletal development in growing dogs and cats include pituitary dwarfism, congenial hypothyroidism, and nutritional imbalances such as hypovitaminosis D (rickets in growing animals), copper deficiency, and calcium or phosphorus deficiencies.[6,17,18] Hypervitaminosis A, in cats fed liver diets, can cause multiple bone exostoses and enthesiophytes, joint laxity, and impingement on nerves causing spinal cord or peripheral nerve and plexus disorders (see ch. 187).[19]

Mucopolysaccharidoses are inherited storage diseases that can cause long bone and/or vertebral column malformations. These conditions can cause changes in gait that often include "crouching," paresis or paralysis.[17,20-22] Clues for the presence of mucopolysaccharidosis are seen in leukocytes as metachromic granules on peripheral blood smears.

Primary diseases of bone development (see ch. 353) include osteogenesis imperfecta and osteochondrodysplasia syndromes. Various skeletal structures are affected, causing signs of lameness and increasing susceptibility to fractures.[17,23] Physeal dysplasia in cats can lead to slipped capital femoral epiphyses.[24,25]

Hypertrophic osteodystrophy is a painful idiopathic disease of young, growing, large-breed dogs affecting the metaphyses of long bones.

Hypertrophic osteopathy may occur secondary to pulmonary neoplasias and systemic infections in adult dogs and cats.[17,26-28]

Vascular Disturbances

Avascular femoral head necrosis is well documented in young small breed dogs, although ischemic necrosis has also been reported in other locations.[29,30] Medullary bone infarcts can occur, but are usually associated with neoplasia or surgical intervention (see ch. 353).[31,32]

Diseases of Joints

Degeneration, Tissue Injury, and Death

Degenerative joint diseases that cause inflammation are common in dogs and cats. Combinations of conformational abnormalities and degenerative changes to ligamentous structures that provide joint stability, such as the cranial cruciate ligament or patella luxation, can precipitate degenerative joint disease. Degenerative arthropathies can also occur secondary to abnormal bone growth, such as in acromegaly.[6]

Inflammation (Infectious or Sterile)

Inflammation in joints may be sterile, or secondary to infectious causes. Septic (bacterial) arthritis is often a result of hematogenous spread or direct traumatic inoculation of bacteria.[33] Single joint effusion, especially of a proximal joint, should raise suspicion for septic arthritis. Other infectious organisms that have been identified in joints include systemic fungi (coccidioidomycosis, blastomycosis, cryptococcosis, sporotrichosis, and aspergillosis), rickettsiae (Rocky Mountain spotted fever, ehrlichiosis, anaplasmosis), spirochetes (Lyme disease), viral (feline calicivirus and coronavirus) and protozoal diseases (leishmaniasis, hepatozoonosis, babesiosis).[13,34] Confirming presence of infectious arthritis is difficult because infected joints often do not "culture positive" and too few organisms may be present for cytologic detection on joint fluid.[34] Blood cultures and serology may be helpful in detecting systemic infectious diseases. Intervertebral spaces can be infected and can cause bacterial or fungal discospondylitis.[2]

Sterile inflammatory joint disease is often immune-mediated, typically affecting multiple distal joints. These can either be erosive (rheumatoid) or the far more common non-erosive (see ch. 203 and 205). Non-erosive, immune-mediated polyarthritis may be an idiopathic, primary auto-immune disorder or it may occur secondary to infectious or neoplastic diseases.[35,36] Drugs such as trimethoprim-sulfur may induce inflammatory polyarthritis. For this reason, a thorough history and screening for underlying disease is important (see ch. 15 and 203).

Disorders of Cell Growth (Abnormal Growth and Neoplasia)

Abnormal growth and conformation of joints can lead to degenerative joint disease. These are described in detail in orthopedic textbooks and include conformational dysplasia of hips and elbows as well as abnormal cartilage development with osteochondrosis.[37] Primary joint tumors that can cause joint deformity include histiocytic sarcoma, synovial cell sarcoma, synovial myxomas as well as fibrosarcoma and chondrosarcoma.[38]

Vascular Disturbance

Primary ischemic joint disease is uncommon. However, secondary coagulopathies can lead to hemarthrosis, an accumulation of blood in the joint space (see ch. 197). This bleeding can be caused by genetic factor deficiencies (such as hemophilia) or acquired (such as by rodenticide intoxication).[39]

Pigmentation and Tissue Deposits

Joint swelling and pain can be associated with systemic amyloidosis, most commonly in Shar-Pei dogs.[40] Amyloid deposits have also been identified within joints.[41] Calcinosis circumscripta is an uncommon syndrome of calcium salt deposition in soft tissue that can affect the joints. This condition may appear idiopathic or secondary to systemic diseases (neoplasia and, rarely, chronic kidney disease [CKD]). In dogs and cats, CKD usually causes calcinosis of footpads, not joints.[42]

Diseases of Muscle

Degeneration, Atrophy or Dysfunction

Distinct from primary muscular dystrophy, muscle atrophy or weakness can be caused by decreased innervation or systemic conditions (see ch. 21). Excess glucocorticoids, whether naturally-occurring or

iatrogenic, often leads to muscle weakness.[6] Catabolism of muscle initiated by hyperthyroidism can cause weakness.[6] Hypokalemia can cause generalized muscle weakness due to altered electrical activity.[43] Hypocalcemia affects nerve and muscular function, leading to rigidity ("tetany") but the patient may be described as weak.[44] Hypercalcemia commonly causes mild weakness.[6] Myolysis can occur secondary to exertion (rhabdomyolysis) or can follow snake envenomation of myolysins. Primary muscular dystrophies have been reported rarely in dogs and cats (see ch. 354).[45,46]

Inflammation (Infectious or Sterile)

Many protozoal infections *(Toxoplasma gondii, Neospora caninum, Hepatozoon canis, Cytauxzoon felis* and *Leishmania)* can cause myositis. Blood tests are available to aid in identifying these infections (see the Infectious Disease section). Microscopic evaluation of muscle biopsy is required for the diagnosis of non-infectious myopathies. Diagnosis may require special analysis for neuromuscular junctionopathies and inflammatory myopathies (see ch. 116 and 354).

Disorders of Cell Growth (Neoplasia)

Muscle tumors that cause changes in mobility are usually large, painful or impacting nerves. Otherwise, muscular neoplasia may only be detected as a palpable non-painful mass. Types of neoplasia that can arise from muscle include varieties of soft tissue sarcoma, hemangiosarcoma, histiocytic sarcoma, and leiomyoma.

Vascular Disturbance

Thromboembolic disease can cause acute, extremely painful, ischemic muscle injury. This can occur in large vessels such as in cats with aortic thromboembolism, or at distal extremities of limbs. Affected limbs will be cold to touch on physical examination and exhibit reduced pulse quality. Search for the cause of hypercoagulability should be undertaken (see ch. 197 and 256).

Diseases of Nerves

It is difficult to break down the various nerve disorders into histopathological processes because many conditions are functional (see ch. 12). Of note, systemic conditions that manifest as changes in mobility include diabetic neuropathy in cats, hypothyroid-associated neuropathies, insulinoma or other neoplasia-induced neuropathy, hypo- and hyperkalemia and hypo- and hypercalcemia.

Other Causes of "Orthopedic Signs"

Conditions unrelated to the musculoskeletal system can cause lameness and/or difficulty rising. Both inflammation and cancer of the prostate can be painful and either can spread to the vertebral column causing discomfort and pain. Disease affecting paw pads such as superficial necrolytic dermatitis and plasma cell pododermatitis can cause lameness.

Diagnostic Testing

After completing a thorough history and physical examination, one should begin to consider most likely differential diagnoses. Clinicians may or may not be suspicious of a specific condition or lesion causing orthopedic signs. Bone and joint disease are often best assessed by radiography. Joint fluid can be obtained for cytology and culture (see ch. 94). If potentially nephrotoxic non-steroidal anti-inflammatory therapy is being considered, kidney function should first be assessed via urine specific gravity and blood for urea nitrogen and/or creatinine.

Complete blood cell count, serum biochemistry profile, urinalysis and urine culture are more strongly indicated in animals exhibiting not only orthopedic signs, but also systemic signs. Those non-specific systemic signs may include lethargy, decreased appetite, fever, lymph node enlargement, vomiting, diarrhea, weight loss, coughing, polyuria and polydipsia. Further diagnostics should be pursued as dictated by radiographic and laboratory findings. This may include specific infectious disease screening, congenital disease testing or investigation of coagulopathies.

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CHAPTER 15

Swollen Joints and Joint Pain

Jonathan D. Dear

Client Information Sheet: Swollen Joints and Joint Pain

Overview and Definitions

Lameness and gait abnormalities are common presenting complaints for small animals. In many, signs may be the result of traumatic or developmental orthopedic disease. Others may have neoplastic or infectious bone disease. This chapter focuses on atraumatic inflammatory joint diseases.

A pet with degenerative joint disease (DJD) may appear to an owner to have intermittent or shifting leg lameness. Pets with DJD are generally well and lack signs of systemic disease. Those with inflammatory joint disease, by contrast, are not thought to be lame. Rather, affected pets may be brought to their veterinarian for lethargy or decreased appetite. They often have a fever.[6] The practitioner may be the first individual to detect lameness or joint disease. Inflammatory joint diseases can be subdivided into septic and nonseptic etiologies. Furthermore, arthropathies are often characterized by the number of affected joints: monoarthropathies (single joint) or polyarthropathies (multiple joints).

Physical Examination

Before beginning to develop a differential diagnosis list, a comprehensive physical examination should be performed with particular attention paid to the orthopedic and neurologic examinations. The practitioner should casually observe the patient within the exam room in addition to evaluating gait from a distance (i.e., within a hallway). Different surfaces or speeds may reveal subtle ambulatory disturbances. Some pets who appear "stiff" in an examination room or hospital (particularly cats) may simply be reluctant to move.

Each appendicular joint should be palpated for warmth, effusion and sensitivity. One can progress to assessing flexion, extension and range of motion in those joints. Typically, DJD affects a few joints while immune-mediated and hematogenous arthropathies affect many joints.[10] Distal joints such as the carpus and tarsus are specifically targeted by immune-mediated diseases. The stifle and elbow are affected less commonly.

Pathophysiology

Joints are comprised of two or more articulating bones with articular cartilage, synovium and synovial fluid. Joints are found throughout the body, including along the appendicular skeleton (such as the carpus or stifle) or axial skeleton (such as the vertebral articulations or the temporomandibular joint). In most cases of joint pain or lameness, the appendicular skeleton is predominantly affected.

Due to their vascular anatomy, joints are particularly susceptible to emboli. Emboli to the synovium can be bacteria (as with septic arthritis) or antibody-antigen complexes (as in immune-mediated polyarthritis). Immune-mediated polyarthritis is the most common form of inflammatory joint disease and is generally considered to be a type III hypersensitivity reaction.

The diagnostic approach to joint swelling and pain uses clinical signs, the physical examination, blood tests, radiographs and joint fluid analyses as guides to confirming a diagnosis (Figure 15-1) (see ch. 94).

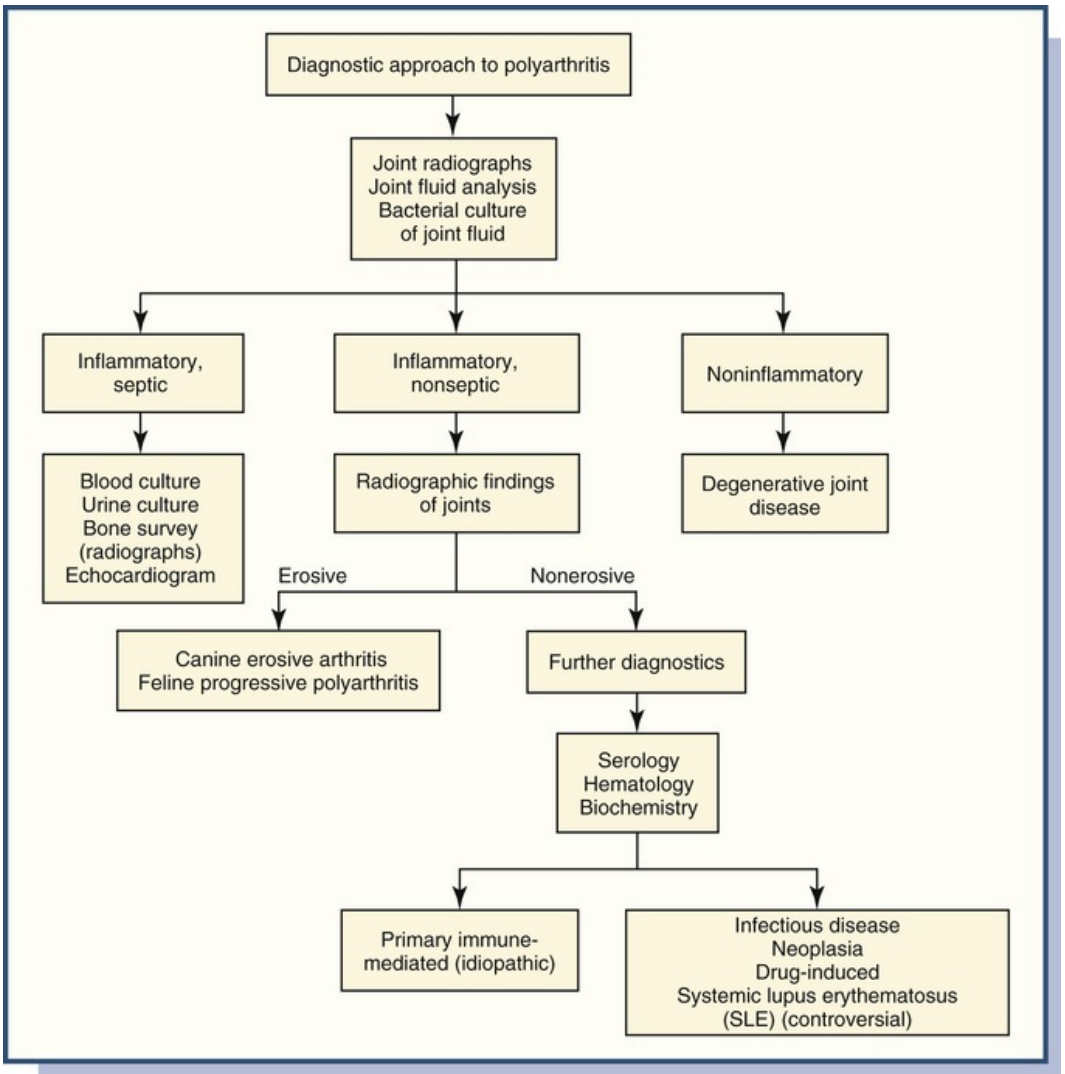


FIGURE 15-1 Algorithm for diagnostic approach to polyarthritis.

Septic Arthritis

Septic arthritis can affect single joints, as with post-operative joint infections, penetrating wounds or foreign bodies. Septic arthritis may affect multiple joints when caused by bacteremia. A septic process should be a top consideration when a single proximal joint is affected (stifle, elbow, shoulder or hip). Recent history of trauma or surgical intervention may lead to the diagnosis of septic inflammation. Neutrophilic inflammation is seen in both septic and immune-mediated arthritis, though degenerative neutrophils or presence of intracellular bacteria suggest infection. Joint culture should be performed when septic inflammation is suspected, though the sensitivity of joint cultures is disappointingly low.

Septic joints should be lavaged and the patient administered appropriate systemic antimicrobials while awaiting joint or other culture results.

Immune-Mediated Polyarthritis

Immune-mediated polyarthritis (IMPA) is the most common form of inflammatory joint disease encountered in small animal patients (see ch. 203 and 205). Patients with IMPA often present for cyclic lethargy (often associated with fever), anorexia, shifting leg lameness, or apparent hyperesthesia. Affected animals are frequently described as appearing to be "walking on eggshells." As with any immune-mediated disease, IMPA can be either primary (autoimmune) or secondary to either endogenous or exogenous triggers. The diagnostic evaluation for immune-mediated disease is discussed in the Additional Testing section, but notable triggers of secondary IMPA include vector-borne disease (specifically *Borrelia burgdorferi*) and

sulfonamide-containing medications (such as trimethoprim-sulfa administration to Doberman Pinschers) (see ch. 211).

Immune-mediated polyarthritides are classified radiographically as either erosive or non-erosive based on assessing bony and cartilaginous lytic and proliferative changes. These categories can be further subdivided based on other diagnostic criteria (see ch. 203 and 353).

Erosive Polyarthritis

Erosive polyarthritis is characterized by progressive osteolysis and proliferation of periarticular joint surfaces. Initially, mild soft tissue swelling and joint effusion may be the only radiographic markers of erosive disease. As the condition progresses, evidence of erosive disease can include decreased opacity of perichondral and subchondral bone, narrowing of the joint space and enthesiophytosis or osteophytosis. In dogs, both septic and rheumatoid arthritis can be erosive. Since radiographic changes are not specific, it is critical to perform joint fluid analysis and culture as aids in differentiating these disorders.

Rheumatoid Arthritis

Rheumatoid arthritis in either dogs or cats is catalyzed by antibody production directed at patient IgA, IgG and IgM—called rheumatoid factor (RF).[1] These antibody complexes circulate and are deposited within synovial tissue, leading to intense inflammatory reactions.[2] Progressive cartilage and bone destruction take place over months to years. In some, the chronic inflammation has been so destructive and poorly responsive to medical therapy that bone deformation and subluxations occur.[10] The underlying cause for development of these autoantibodies is not understood. Though the diagnosis of rheumatoid arthritis in humans follows a rigorous algorithm involving a host of criteria and factors, these criteria have not been established in veterinary medicine. Plasma rheumatoid factor can be measured but is neither sensitive nor specific for this diagnosis (see ch. 195, 203, 205, and 353).

Feline Periosteal Proliferative Polyarthritis

Erosive polyarthropathies are particularly uncommon in cats. Affected cats develop a progressive polyarthropathy and osteopathy that involves periosteal proliferation, subchondral osteolysis, and may progress to ankylosis.[3] Soft tissue edema and joint effusion are typical. This disease appears most frequently in males of any age. Joint fluid cytology reveals aseptic neutrophilic inflammation, though with chronicity, the inflammatory nature may become lymphoplasmacytic. Radiographic features of this disease include intense periosteal proliferation, which may develop a characteristic trabecular pattern, and subchondral bone destruction.[9]

Nonerosive Polyarthritis

Commonly, the inflammation caused by IMPA leads to joint pain and soft tissue swelling without notable or permanent articular destruction of the synovium or cartilaginous interface (see ch. 195, 203, 205, and 353). As a type III hypersensitivity reaction, the disease stems from antibody production directed at chronic antigenic stimulation.[8] However, it is not often possible to identify the source of this antigenic stimulation and the disease is termed *idiopathic polyarthritis*. When identified, inciting causes include neoplasia (particularly hemic neoplasia), chronic infection (such as deep mycoses, diskospondylitis or endocarditis), primary immune disease (such as systemic lupus erythematosus [SLE]) or administration of certain drugs and vaccines.[4]

Patients with nonerosive polyarthritis often are seen for an intermittent, shifting leg lameness or for generalized nonspecific systemic signs such as lethargy and anorexia. Physical exam often reveals fever as well as warmth and effusion involving multiple distal joints. The tissue around affected joints may appear edematous and local lymph nodes may be enlarged as a component of the systemic immune reaction. Though IMPA appears to favor distal joints, other joints such as the temporomandibular joint and vertebral articulations may be affected, leading to the clinical appearance of odynophagia, dysphagia, neck pain or back pain.

Vaccine-induced polyarthritis usually develops within 1-2 weeks of administration and almost always within a month (see ch. 208). This polyarthritis may develop following either initial or booster vaccines. Implicated vaccines include those directed against canine distemper and Lyme. Drug-induced polyarthritis has been reported to occur most often following the administration of sulfonamide-containing drugs (such as

trimethoprim-sulfonamide [TMS]) administered to Doberman Pinschers (see ch. 169).[5,7] The penicillins and cephalosporins have also been implicated. Other causes of nonerosive polyarthritis include juvenile-onset polyarthritis of Akitas and the familial swollen hock syndrome in Chinese Shar-Pei.

Other Causes of Mono- or Polyarthropathies

Hemarthrosis is an uncommon cause for single or multileg lameness. When seen, it may result from thrombocytopenia or other bleeding disorders. Most skeletal system malignancies spare joints, though neoplasia of the synovium or round cell tumors (such as lymphoma or histiocytic sarcoma) can affect the joint and its articulating bone and cartilage (see ch. 308).

Arthrocentesis

Arthrocentesis is the single most important diagnostic aid in patients suspected as having an inflammatory joint disease and can usually be easily performed in most small animals (see ch. 94). Joint aspiration should be performed under heavy sedation or anesthesia using aseptic technique. When immune-mediated disease is suspected, multiple distal joints (carpus and tarsus) should be aspirated and submitted individually for cytology. Remaining samples can be pooled for culture. In pets with suspected monoarthropathy, arthrocentesis of multiple joints can indicate whether single or multiple joints are involved. Synovial fluid viscosity and consistency can be assessed crudely by placing a small drop between the thumb or a glass slide and the index finger (Figure 15-2). Normal joint fluid should be transparent, colorless and string several centimeters when tested in this manner.

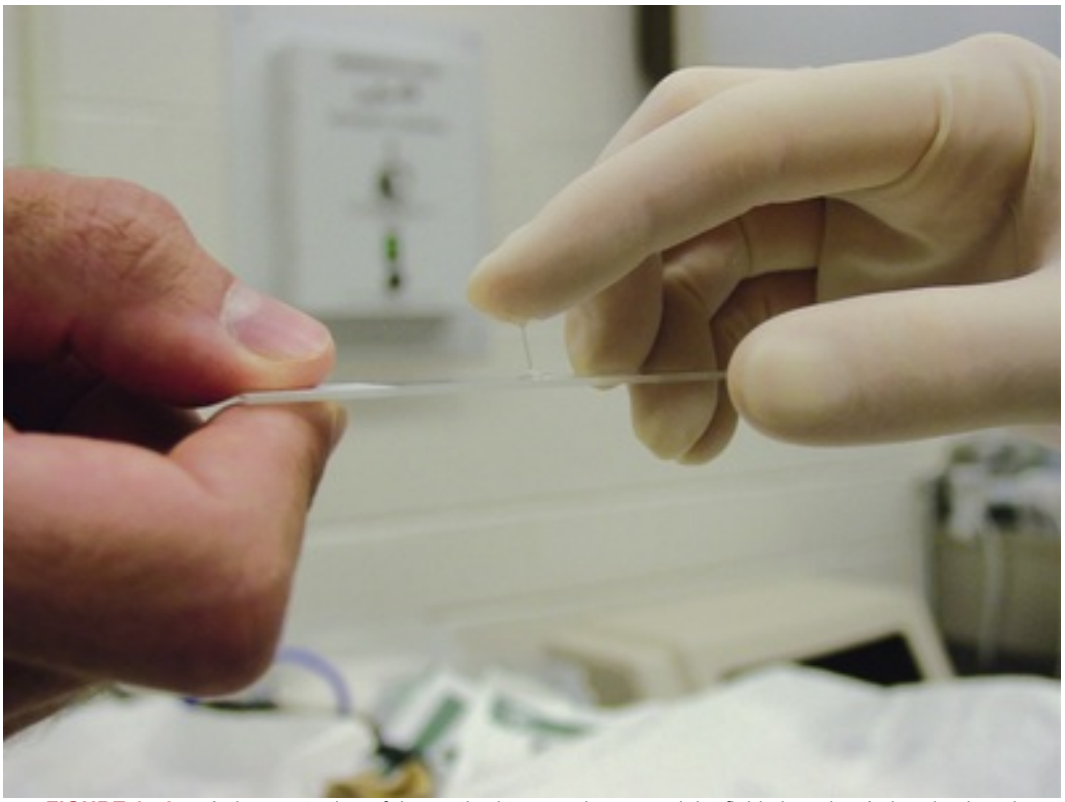


FIGURE 15-2 A demonstration of the method to grossly assess joint fluid viscosity. A drop is placed on a glass slide. It is gently touched with a fingertip that is then slowly moved away. The reader should note the strand of viscous fluid typical for normal joint viscosity.

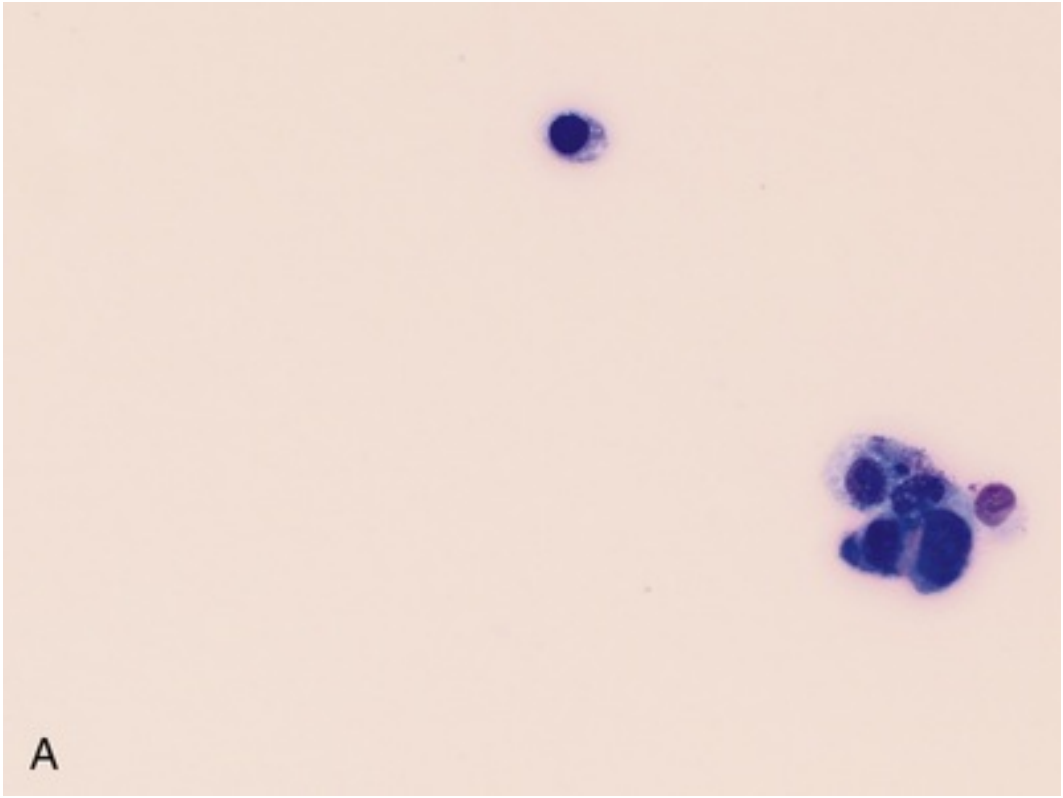
Joint Fluid Analysis

Normal synovial fluid is present in small volumes, clear, viscous, and of low cellularity. A crude test for viscosity can be performed by placing a small drop between the thumb and forefinger allowing the fluid to

string 4-5 cm, as the fingers are pulled apart (see Figure 15-2). Fluid from diseased joints often lacks viscosity and may be turbid or discolored. Samples contaminated with blood from superficial vessels, while entering or withdrawing the needle from the joint, have a small portion of red discoloration.

Normal joint fluid has a relatively small population of large mononuclear cells as "housekeepers." Normal cell counts are less than 3,000 cells per microliter. In IMPA, individual joint cell counts can exceed 50,000 cells per microliter and are primarily nondegenerate neutrophils. Septic joints may be similarly neutrophilic, although the joint fluid often has signs of septic inflammation: degenerate neutrophils, intracellular neutrophils and a positive bacterial culture. In addition to aerobic and anaerobic cultures, *Mycoplasma* culture should be requested for cats with polyarthritis since various species have been associated with a form of septic arthritis that causes nondegenerate joint inflammation (see ch. 219).[11] This organism is difficult to culture using conventional microbiology methods. Ancillary joint fluid testing provides little clinically useful information.

These photomicrographs (Figure 15-3) are of cytology specimens from normal *(A)* and sterile, inflammatory joint fluids *(B).* Normal joint fluid is a relatively acellular, thick, proteinaceous fluid with a small number of large, with rarer small, mononuclear cells (see Figure 15-3). Joint fluid from a dog with immune-mediated polyarthritis contains a larger number of nondegenerate neutrophils and may contain lupus erythematosus (LE) cells (indicated by the arrow in Figure 15-3) in cases of SLE.



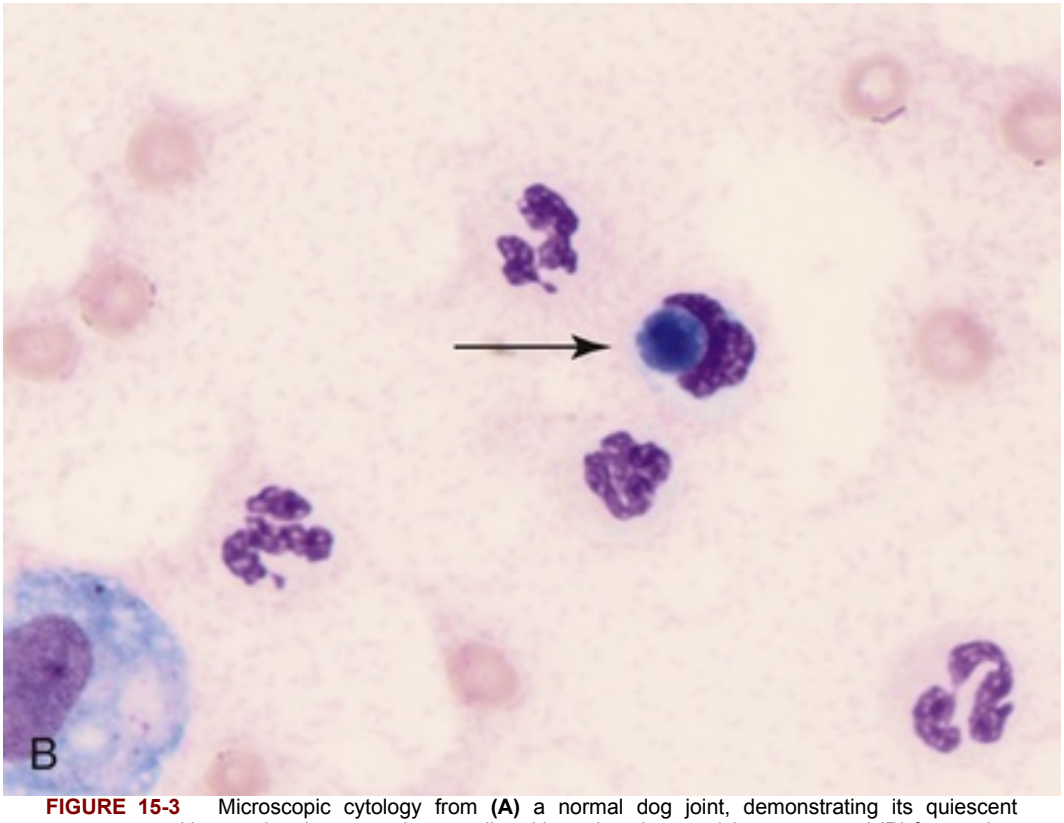


FIGURE 15-3 Microscopic cytology from **(A)** a normal dog joint, demonstrating its quiescent appearance with occasional mononuclear small and large lymphocytes/phagocytes and **(B)** from a dog joint that is sterile but inflamed, demonstrating the high cellularity and influx of neutrophils typical of this condition (arrow). (Courtesy A. Adedeji, DVM, William Pritchard Veterinary Medical Teaching Hospital, UC Davis.)

Additional Testing

Septic arthritis may be suspected in a joint despite there being no clear pathway for introduction of bacteria (i.e., recent orthopedic surgery, trauma or penetrating wound). In such a case, the clinician should investigate the possibility of hematogenous spread of bacteria to the synovium. Specific conditions associated with bacteremia include endocarditis (including *Bartonella* spp.), diskospondylitis, pyelonephritis or prostatitis. Diagnostic imaging and blood or urine cultures should be employed to confirm or deny the presence of these conditions.

Immune-mediated polyarthritis is thought to arise from chronic antigenic stimulation often stemming from chronic infection, inflammation, neoplasia or drug and vaccine exposures. Patients suspected of having immune-mediated polyarthritis should be evaluated for these triggers of immune system activity. This investigation starts with a detailed medical history, paying close attention to the patient's home environment as well as recent travel, medications or vaccination. A thorough physical examination should help identify comorbidities which may relate to current condition and help understand the number of joints involved. Particular attention should be paid to assessing the fundus (ch. 11), thoracic auscultation, axial skeleton palpation, rectal examination, and lymph node size.

A comprehensive medical evaluation helps identify any inciting disease and determine the overall health of the patient prior to initiation of therapy. A complete blood count, serum biochemistry profile, and urinalysis with culture should be performed in all patients. Serologic testing for endemic infectious diseases associated with polyarthritis (such as *Ehrlichia canis, Borrelia burgdorferi, Anaplasma phagocytophilum* or systemic mycoses) should be performed according to the geographic exposure of the patient. When erosive disease is suspected, radiographs of the affected and contralateral joints should be obtained to determine the extent of disease. In order to rule out neoplastic disease and other infectious disease, diagnostic imaging of the thorax and abdomen should be performed. Additional testing such as blood cultures, echocardiogram, vertebral radiographs or cerebrospinal fluid collection and analysis should be considered on a case by case basis.

All cats with polyarthritis should be tested for both feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV). Immunosuppression may play a role in disease development and FeLV has been

implicated in the pathogenesis of periosteal proliferative polyarthritis.

Markers of immune disease such as a Coombs' test, anti-nuclear antibody or rheumatoid factor can bolster the suspicion for immune disease, though both sensitivity and specificity of these tests are controversial. Positive results do not exclude the possibility of secondary disease.

In the absence of other disease inciting polyarthritis, a diagnosis of idiopathic or primary IMPA is reached (see ch. 203). This disease may affect patients individually or along with other immune diseases such as glomerulonephritis or systemic lupus erythematous (ch. 205).

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CHAPTER 16

Weight Gain

Peter P. Kintzer

Overview

In canine and feline patients, weight gain is common, both as an historical complaint or a physical examination finding. Generally, pets more than 10% above their ideal body weight are considered significantly overweight and obese when they exceed ideal by greater than 20%.[1] It is important to identify and treat, if possible, any underlying disease state responsible for weight gain. In many cases, however, weight gain is due to a combination of overeating and inadequate exercise. Caloric intake in excess of need leads to weight gain and often obesity. It has been suggested that at least 50% of dogs and cats in the United States can be classified as overweight or obese. It has been suggested that 37% more dogs and 90% more cats were overweight in 2013 as compared with five years earlier. This is important as obesity is not simply an excess amount of adipose tissue, but the condition can be associated with deleterious metabolic and hormonal changes and can affect both longevity and quality of life.[2-4] There are a few clinical conditions that can cause weight gain in dogs and cats. Disorders that result in ascites, pleural effusion and/or edema must be differentiated from those causing a true increase in body tissue mass. Several endocrinopathies may cause weight gain and obesity. Dogs with primary hyperlipidemias may manifest unexplained increases in body weight.

History

A thorough history, including a detailed investigation of diet and lifestyle, is critical in evaluating the patient with weight gain. One needs to determine if the appetite is normal, increased, or decreased. In the majority, weight gain and obesity results from caloric intake in excess of need. In other words, there is a combination of overfeeding and inadequate physical activity. Therefore, it is imperative to obtain a detailed account of caloric intake (including treats, table scraps, etc.), if more than one person in the household feeds the pet, and if there are additional animals whose food could be eaten by the pet in question (see ch. 170). Assessment of exercise level and presence of any orthopedic or neuromuscular disorders is needed. Calculation of the pet's caloric requirements relative to their physical activity allows identification of excess caloric intake as a reason for weight gain. Certain breeds may have a genetic predisposition to weight gain and obesity. Furthermore, individual patients may be more prone to weight gain than others. Lastly, older, less active pets and those with orthopedic problems generally require fewer calories and are at risk of weight gain (see ch. 176).

An increased appetite or polyphagia can lead to weight gain and varying degrees of obesity. Potential underlying factors include drug therapy, certain endocrine disorders and behavioral issues. Certain medications, including corticosteroids, phenobarbital and progestins, can result in polyphagia through stimulation of the appetite center. By stimulating food intake, promoting fat redistribution, and organomegaly, both acromegaly and hyperadrenocorticism usually cause weight gain (see ch. 294, 295, 306, and 307). Behavioral and husbandry issues may play a role (see ch. 176). The ready availability of highly palatable pet food can promote overeating. Boredom and lack of access to physical activity can exacerbate this tendency. Weight gain with a normal or decreased appetite can be seen in association with certain endocrine disorders, including hypothyroidism, as a result of a decreased metabolism (see ch. 299); other historical findings associated with the underlying endocrine disorder are often reported. A careful history to assess for the presence of other clinical signs such as polyuria, polydipsia, lethargy, exercise intolerance, excess panting and cold intolerance among others can provide the clinician with additional clues to an underlying disease condition.

Physical Examination

A complete physical examination is imperative. The clinician can assess a pet for weakness, neuromuscular abnormalities or orthopedic problems. Is such a condition resulting in decreased physical activity and contributing to weight gain? Assessing body weight using an accurate scale is vital, as is an objective determination of body condition using an accepted scoring system (see ch. 2 and 170). It should also be determined if weight gain is due to an increase in adipose tissue or muscle mass. Lean body mass gain can be caused by vigorous exercise as well as anabolic endocrine disorders such as insulinoma in dogs and acromegaly in cats.

There are several physical examination findings that may point the clinician to the underlying cause of the weight gain. Body temperature, capillary refill time, pulse rate and careful auscultation of the heart and lungs may provide clues. The patient should be carefully evaluated for the presence of ascites, pleural effusion and/or edema, which can be caused by cardiac disease, infectious or inflammatory conditions and hypoproteinemic states (such as protein-losing nephropathies and enteropathies). The weight gain associated with these conditions is due to the excess fluid and not a true increase in body mass (see ch. 17 and 18). The skin and hair coat should be carefully examined for abnormalities such as hair thinning or alopecia, seborrheic changes, myxedema, thin skin, hyperpigmentation and comedones, some of which are consistent with conditions like hyperadrenocorticism or hypothyroidism. The abdomen should be carefully palpated for the presence of abdominal masses, abdominal distension and organomegaly. Acromegalic cats frequently have weight gain and organomegaly. The presence of these clinical findings in a diabetic cat, particularly one poorly regulated and/or on higher than typical dosages of insulin, is consistent with concurrent acromegaly (see ch. 294). Patients with hyperadrenocorticism often exhibit hepatomegaly, as well as centripetal fat redistribution and abdominal muscle weakness which can result in a pot-bellied appearance (see ch. 306 and 307). Assessing whether the patient has been neutered is critical (see ch. 313). Neutering has been shown to reduce daily energy requirements (DER) of adult cats by 24-33%. Similar reductions in daily energy requirements have been documented in neutered dogs (see ch. 313 and 319).[5] Reduction in energy requirement is most likely due to a decrease in the basal metabolic rate. An increase in the drive for food and decreased energy expenditure predisposes the patient to weight gain and obesity.

Diagnostic Approach

Figure 16-1 shows an algorithm for a diagnostic approach to weight gain. The presence of fluid retention and large abdominal masses are excluded. Caloric intake in excess of energy requirements is ruled out. Assessment of appetite (polyphagia vs. normal or decreased) will further guide the clinician. A minimum database (complete blood count, serum electrolyte panel and urinalysis) should be performed. The typical laboratory abnormalities of certain endocrine disorders may be observed. The addition of a vector-borne disease screen would be appropriate in certain areas. Depending on the patient, imaging studies may be indicated. Lastly, endocrine testing (e.g., thyroid screening, insulin level, IGF-1 level, ACTH stimulation test, low-dose dexamethasone suppression test) may be appropriate to further assess the causes of weight gain.

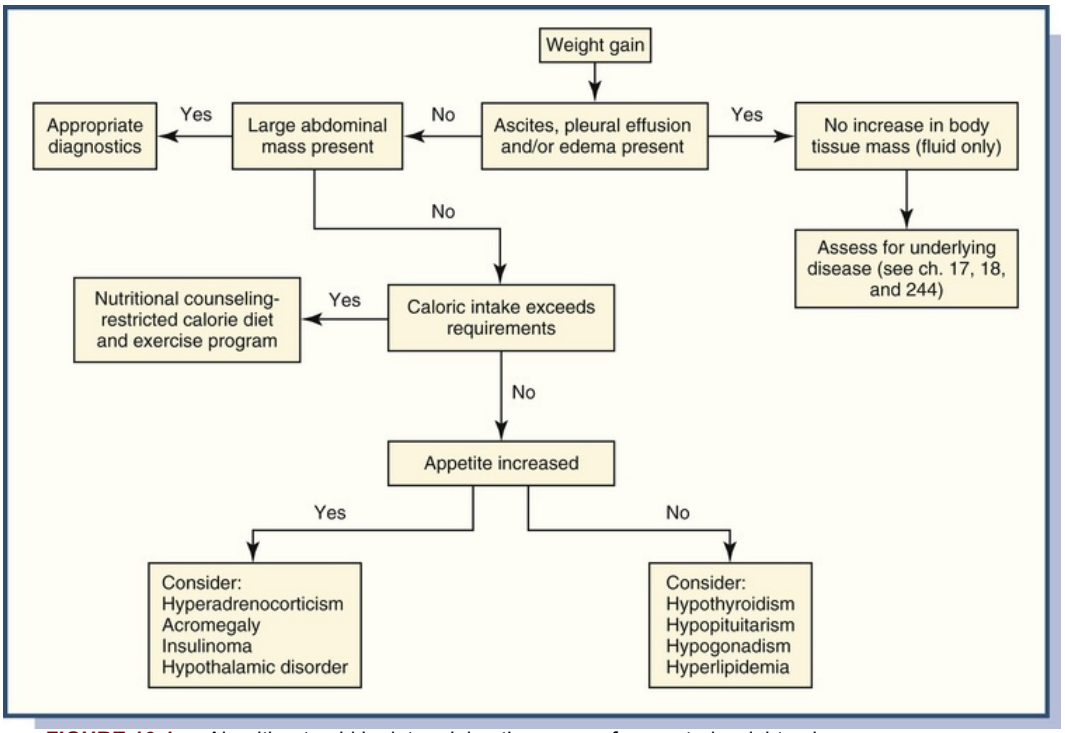

FIGURE 16-1 Algorithm to aid in determining the cause of unwanted weight gain.

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CHAPTER 17

Abdominal Enlargement

Julie Walter

Client Information Sheet: Abdominal Enlargement

Enlargement of the abdomen is a common presenting complaint and can be a component of many disease processes. An animal's owners may note abdominal distension or they may describe weight gain, lethargy, weakness, exercise intolerance, increased respiratory rate and effort, decreased appetite, or clinical signs specific to the underlying disease process (e.g., collapse with cardiac tamponade, or retching with gastric dilation/volvulus [GDV]). Some patients with abdominal enlargement require emergency intervention, particularly when it is associated with tachycardia, dyspnea, hypotension, abdominal pain, prolonged capillary refill time (CRT), fever, profound lethargy, and/or weakness (see ch. 143 for more information on the acute abdomen). A thorough history is vital for assessing the need for such emergent intervention and for developing a complete differential diagnosis list. The history should include, but is not limited to: description and duration of clinical signs, the pet's environment, travel history, drug administration and previous medical history. Physical examination findings will vary depending on the etiology and can include: abdominal pain, organomegaly, fluid wave on ballottement of the abdomen, gas distension of the abdomen or gastrointestinal tract, or palpation of a soft tissue mass. Causes of abdominal enlargement can be classified into the following five categories: soft tissue, fluid, gastrointestinal (GI) contents (fluid or feces), gas, and hypotonia of the abdominal musculature (Table 17-1).

TABLE 17-1

Differential Diagnoses for Abdominal Enlargement

SOFT TISSUE	FLUID	GI CONTENTS	GAS	ABDOMINAL MUSCLE HYPOTONIA
Organomegaly (infiltration, congestion, torsion) Fat deposition Neoplasia Granuloma Pregnancy	Effusion (pure transudate, modified transudate, exudate, neoplastic) Cyst Abscess Pyometra Urinary tract outflow obstruction (e.g., hydronephrosis) Ileus (functional or mechanical)	Constipation, obstipation Megacolon Ileus (functional or mechanical) Overeating Heavy intestinal parasite burden (puppies, kittens)	Gastric dilation/volvulus Intestinal or mesenteric torsion GI tract rupture Ileus (functional or mechanical) Iatrogenic (post-surgical) Emphysematous bacterial infections (liver, gallbladder, urinary bladder) Penetrating trauma	Hyperadrenocorticism

Differential Diagnoses[1]

Soft Tissue

Soft tissue structures in the abdomen can cause abdominal enlargement as a result of organomegaly, deposition of fatty tissue (e.g., obesity or lipoma formation), neoplasia, granuloma formation, or pregnancy.

Organomegaly, including hepatomegaly, splenomegaly, renomegaly, and prostatomegaly, can be present secondary to infiltration of the organ (neoplasia), congestion via vascular or lymphatic obstruction, or torsion of the organ (e.g., splenic torsion). Neoplastic processes are common and can be hepatic, splenic, urogenital (renal, urinary bladder, uterine, ovarian or prostatic), GI, adrenal, or pancreatic in origin. More diffuse neoplastic processes, such as lymphoma and carcinomatosis, can produce similar clinical signs. Granuloma formation has also been reported as a cause of abdominal distension and may be seen with parasitic disease (e.g., parasitic larval migrans), fungal infections, or pythiosis (see ch. 236).

Fluid

Fluid accumulation in the abdomen may be within organs, within abscesses or cystic structures, or free in the peritoneal or retroperitoneal spaces. Within organs, fluid accumulation can occur in the GI tract secondary to functional ileus or obstruction; the uterus (e.g., pyometra); the kidneys (e.g., hydronephrosis secondary to ureteral obstruction); and the urinary bladder (e.g., urethral obstruction, disruption of the micturition reflex). Fluid may also be present in abscesses or cystic structures within the kidneys, liver, pancreas or prostate, and cysts can be associated with polycystic kidney disease or liver disease.

Peritoneal and retroperitoneal effusions can be separated into several categories based on gross appearance, protein content, cell counts, and cytologic characteristics (Table 17-2).[2] Identifying effusions by specific gravity as measured with a standard refractometer is often described; however, this approach has not been validated for fluid types other than urine and is not recommended due to interlaboratory variation.[3]

TABLE 17-2

Characteristics of Common Abdominal Effusions

EFFUSION TYPE	GROSS APPEARANCE	TOTAL PROTEIN (g/dL)	NUCLEATED CELL COUNT (cells/mcL)	PREDOMINANT CELL TYPES/CYTOLOGIC FINDINGS
General				
Transudate	Clear; colorless	<2.5	1000-1500	Mesothelial cells (occasional)
Modified transudate	Slightly cloudy; straw-colored	2.5-5.0	>1000, <5000	Mesothelial cells, non-degenerate neutrophils, macrophages, lymphocytes
Exudate	Turbid to opaque; tan, may be blood-tinged	>2.5	>5000	Non-septic: mesothelial cells, non-degenerate neutrophils, macrophages, lymphocytes, occasionally neoplastic cells
				Septic: degenerate neutrophils, intracellular bacteria
Specific				
Blood	Cloudy to opaque; red (clear supernatant after centrifugation)	>3.0, may be = to peripheral blood	>1000, may be = to peripheral blood	Erythrocytes, leukocytes similar to peripheral blood, erythrophagocytosis
Chyle	Opaque; white to pink	>2.5	Variable, <10,000	Small lymphocytes (may be mixed if chronic); fluid [triglyceride] > serum [triglyceride]
Urine	Clear to slightly cloudy; pale yellow to yellow	Variable	>3000	May be septic; fluid [creatinine] > serum [creatinine]
Bile	Clear to cloudy; green to brown	>2.5	>5000	May be septic; presence of bilirubin crystals

Pure Transudates

Pure transudates are characterized by both low cellularity and low total solids, and most commonly occur secondary to decreased oncotic pressure; concurrently increased hydrostatic pressure, and vasculitis, can contribute to the presence of pure transudates. Protein is essential in maintaining appropriate oncotic pressure, with decreased oncotic pressure most commonly resulting from hypoproteinemia (see ch. 60), and

often more specifically hypoalbuminemia. Hypoalbuminemia may be due to loss, which is characteristic of protein-losing nephropathy (see ch. 325), protein-losing enteropathy (see ch. 276), or as a result of weeping of proteinaceous fluid from wounds (e.g., burns). Alternatively, hypoalbuminemia can be due to decreased production, most often as a result of hepatic failure (e.g., cirrhosis) or starvation.

Increased hydrostatic pressure most often leads to modified transudates, but can cause the formation of pure transudates, especially in patients with low-normal or low serum albumin concentrations. High hydrostatic pressure can result from pre-hepatic portal hypertension (e.g., congenital portal vein atresia, extraluminal obstruction such as neoplasia, or intraluminal obstruction such as portal vein thrombosis), intra-hepatic portal hypertension (e.g., pre-sinusoidal disorders such as chronic cholangitis, sinusoidal disorders such as lobular dissecting hepatitis, or post-sinusoidal disorders such as with veno-occlusive disease), or post-hepatic portal hypertension (e.g., right-sided heart failure, or Budd-Chiari syndrome).[4]

Modified Transudates

Modified transudates have nucleated cell counts and total solids concentrations that fall between those of pure transudates and exudates. They may be present due to a variety of causes and therefore can have a multitude of cell types. Decreases in oncotic pressure, increases in hydrostatic pressure, and vasculitis, as previously described with pure transudates, can also result in a modified transudate, typically when the fluid accumulation is chronic. A modified transudate can also be present secondary to neoplastic processes, granulomas, post-surgical or laparoscopic procedures, organ torsion (e.g., splenic, intestinal, or mesenteric), and/or infarction.

Exudates

Exudates are those effusions that have high cellularity and total solids concentrations, with the cellular component consisting primarily of neutrophils and macrophages. Exudates can be divided into non-septic and septic groupings (for peritonitis, see ch. 279). Non-septic exudates are seen in neoplastic processes, pancreatitis, or feline infectious peritonitis (FIP). Septic exudates are most commonly due to perforation of the GI tract, abscess rupture, penetrating injury, or foreign body migration. Rupture of the biliary tree or the urinary tract can result in either a non-septic or septic exudate.

Eosinophilic effusions can present as modified transudates or exudates with a cell population >10% eosinophils. These effusions are most often caused by lymphoma, systemic mast cell tumors, aberrant larval migrans, fungal disease, or disseminated eosinophilic granulomatosis.

Similarly, neoplastic effusions often are considered as a subtype of modified transudates or exudates that contain neoplastic cells. It is important to note that cytologically, normal mesothelial cells can display many criteria of malignancy and therefore can be misinterpreted as neoplastic. For this reason, it is essential that a clinical pathologist perform cytologic evaluations, and even so, definitively confirming or refuting mesothelial neoplasia cytologically can be impossible in some cases.

Blood

Hemorrhagic effusions typically are defined as having a packed cell volume >10%. Thus, cytology of hemorrhagic effusions should closely resemble that of the peripheral blood including red blood cells, neutrophils, and lymphocytes. Unless hemorrhage is peracute, platelets are not typically present and therefore the samples do not readily form a clot. Hemorrhagic effusions are seen most commonly secondary to trauma (e.g., organ rupture, arterial avulsion), neoplasia (e.g., hemangiosarcoma), coagulopathies (e.g., rodenticide intoxication), or in post-surgical patients.

Chyle

Chylous effusions are characterized by high triglyceride concentrations and lower cholesterol concentrations relative to the patient's serum, and variable cell counts. Small lymphocytes usually predominate, but a mixed cell population can be seen with chronicity. Chylous effusions most commonly are associated with disruption of lymphatics (e.g., extraluminal obstruction or rupture) by neoplasia or trauma, or right-sided heart failure. More rarely, lymphangiectasia can be the inciting cause.

Urine

Uroabdomen can result from rupture of one or more structures of the urinary tract (e.g., ureters, urinary bladder, and/or urethra). Urine may accumulate in both the peritoneal and retroperitoneal spaces secondary to trauma or obstruction (e.g., ureteroliths or neoplasia such as transitional cell carcinoma), and may result in

either a non-septic or a septic exudate. The characteristics of the resulting effusion are variable, but a creatinine concentration greater than that of the patient's serum is expected.

Bile

Bilious effusions can be either non-septic or septic exudates, and contain bilirubin crystals. It is worth noting that the concentration of bilirubin in the effusion will be higher than that found in the serum. Bilious effusions are associated with rupture at some level of the biliary system (i.e., the gallbladder, or bile ducts), which may occur secondary to trauma, cholelithiasis or mucocele with subsequent obstruction, neoplasia, or cholecystitis.

Gastrointestinal Contents

An increase in the volume of contents within the GI tract can result in abdominal enlargement. Possible etiologies include overeating, constipation or obstipation, heavy intestinal parasite load in puppies or kittens, functional or mechanical ileus, and megacolon.

Gas

Gas accumulation can cause abdominal distension and may occur within the GI tract, the liver and/or gallbladder, the urinary bladder, or freely in the peritoneal or retroperitoneal spaces. Distension of the GI tract with gas can be seen with gastric dilation, GDV, or mesenteric torsion. Gas accumulation in the GI tract can also be secondary to mechanical and/or functional ileus. Emphysematous bacterial infections can result in gas production within the gallbladder, liver, or urinary bladder. Lastly, free gas in the peritoneal and retroperitoneal spaces may be the result of GI perforation, secondary to gas-producing bacteria in bacterial peritonitis, perforating trauma, or can be iatrogenic in origin after surgical interventions (traditional or laparoscopic).

Abdominal Musculature Hypotonia

Laxity of the abdominal muscles can result in the appearance of abdominal distension, and is most commonly associated with hyperadrenocorticism (see ch. 306 and 307). Hepatomegaly secondary to steroid hepatopathy and redistribution of body fat also contribute to the abdominal enlargement in these patients.

Diagnostic Approach

Due to the number of etiologies causing abdominal enlargement, it is essential that the diagnostic approach be thorough and stepwise (Figure 17-1). It is also important to take into consideration the presentation of the patient, particularly when the clinical signs are consistent with shock (e.g., hypotension, prolonged CRT), which may alter the diagnostic course. After using a thorough history and physical examination to formulate an initial differential diagnosis list, a minimum database (including a complete blood cell count [CBC], serum biochemistry profile and urinalysis) should be obtained. The CBC may reveal changes such as those consistent with sepsis or a bleeding tendency, while the serum biochemistry profile and urinalysis can identify evidence of organ dysfunction that prompts further investigation of a particular body system (e.g., hepatobiliary or urinary tract). Imaging of both the abdominal and thoracic cavities is fundamental and can involve the use of multiple modalities, identifying several abnormalities such as an abdominal mass, cavitary effusions, or cardiomegaly. After the completion of such tests, diagnostic evaluations that are more specific can become necessary and could include abdomino- or thoracocentesis (see ch. 90 and 102, respectively) with fluid evaluation and cytologic examination, fine needle aspiration or biopsy of soft tissues with subsequent cytologic or histopathologic evaluation, echocardiography, or abdominal exploratory laparotomy for organ evaluation and collection of tissue biopsies.

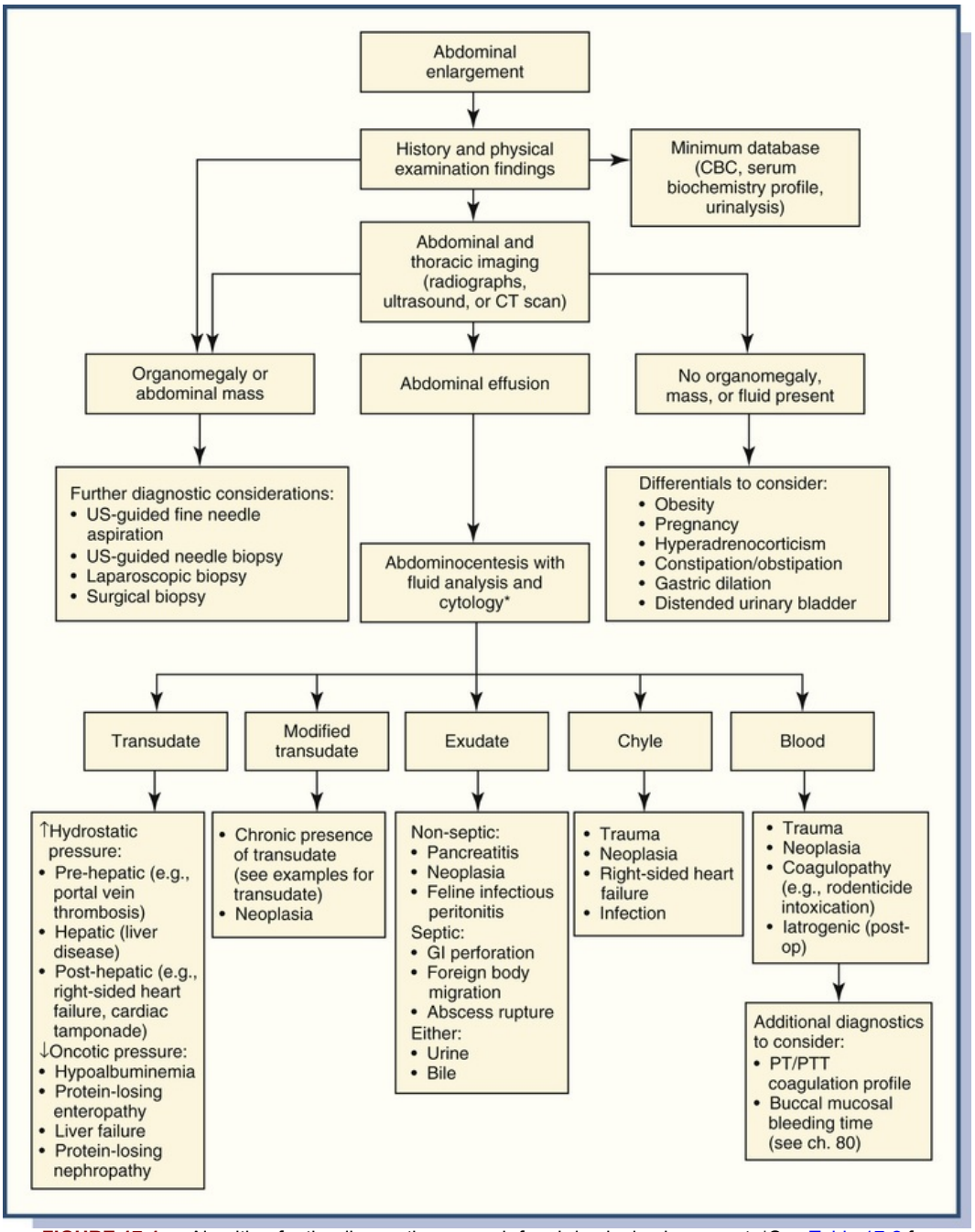

FIGURE 17-1 Algorithm for the diagnostic approach for abdominal enlargement. *See Table 17-2 for characteristics of common effusions. *CBC,* Complete blood count; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *US,* ultrasound.

Treatment

Treatment of abdominal enlargement should be targeted at the underlying cause. This may involve interventions specific to a disease process, such as medical management of hyperadrenocorticism or surgical correction of GDV, or may be palliative in nature, such as therapeutic abdominocentesis in patients with right-sided heart failure. Intra-abdominal pressure measurement may be appropriate in patients with acute increases in abdominal pressure that can result in inadequate regional blood flow and decreased tissue perfusion, culminating in systemic inflammatory response syndrome and multiple organ failure, which is commonly referred to as abdominal compartment syndrome.[5]

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CHAPTER 18

Peripheral Edema

Deborah M. Fine-Ferreira

Client Information Sheet: Peripheral Edema

Peripheral edema is the palpable accumulation of fluid within the subepithelial interstitium (Figure 18-1). The interstitial matrix is a dense meshwork composed of proteoglycan filaments, glycoproteins, hyaluronan, collagen, and elastin fibers creating a tissue that is flexible yet remarkably strong.[1,2] There is normally very little free fluid in this compartment, but in disease states, the interstitium is capable of containing a considerable amount of edema. Fluid homeostasis between the intravascular and extravascular compartments is maintained through interplay of the following forces: (1) intravascular hydrostatic pressure, (2) plasma oncotic pressure, (3) extravascular hydrostatic pressure, (4) interstitial oncotic pressure, (5) vascular permeability, and (6) lymphatic function.[3] Classically, Starling's equation describes the relationship between the first 4 of these: $Q = K[(P_{mv} - P_{pmv}) - (p_{mv} - p_{pmv})]$, where Q = net transvascular fluid flow, K = membrane permeability, Pmv = hydrostatic pressure in the microvessels, Ppmv = hydrostatic pressure in the perimicrovascular interstitium, pmv = plasma protein osmotic pressure in the circulation, and ppmv = protein osmotic pressure in the perimicrovascular interstitium. In the cutaneous capillaries, the normal balance of these forces slightly favors the translocation of fluid into the interstitium; however, reabsorption by post-capillary venules and lymphatics maintains normal interstitial fluid volume.[4] There are considerable safety factors built into this system such that a diminution in the function of one factor will be offset by a gain in the function of others, preventing any change in the early stages of disease.

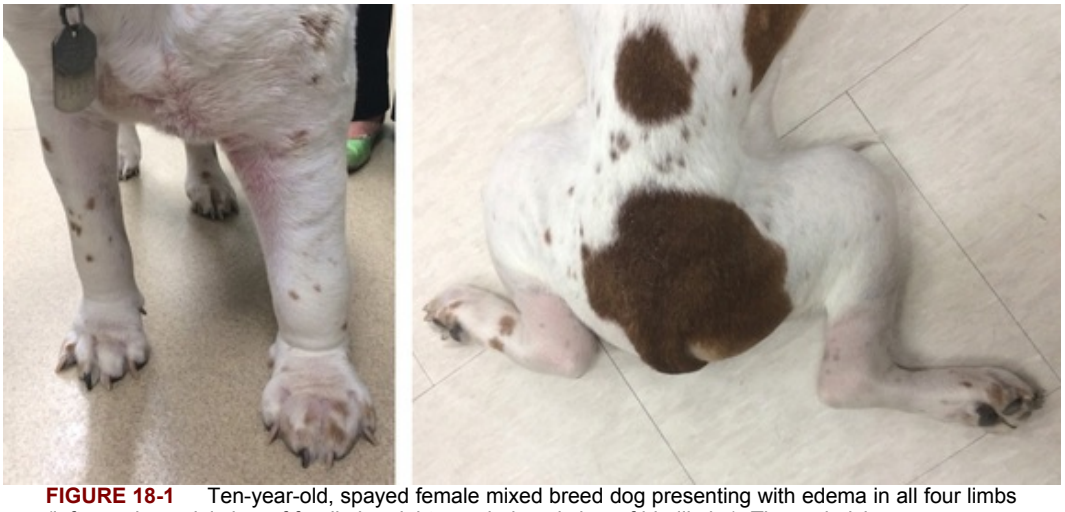

FIGURE 18-1 Ten-year-old, spayed female mixed breed dog presenting with edema in all four limbs (left panel, cranial view of forelimbs; right panel, dorsal view of hindlimbs). The underlying cause was a poorly differentiated widely spread carcinoma. Although all limbs were affected, the left fore- and hindlimbs were much more severely affected than the right. (Courtesy Amy DeClue, University of Missouri.)

Mechanisms of Edema Formation

There are many potential sources of peripheral edema in small animals and certain abnormalities can contribute to the development of edema through more than one mechanism (Box 18-1). Increased intravascular hydrostatic pressure may occur as a localized process, secondary to a mass or trauma to a vascular bed resulting in venous obstruction, or systemically as a generalized process in the setting of plasma volume expansion. Plasma volume expansion ensues from diseases that result in sodium retention via activation of the renin-angiotensin-aldosterone system (e.g., heart failure and chronic kidney disease).[5] In the early stages of these diseases, edema is prevented by a concomitant increase in lymphatic uptake and simultaneous increase in interstitial hydrostatic pressure, which decreases the gradient for fluid movement. However, as the lymphatics ultimately return fluid to the circulatory system, edema is inevitable if the underlying abnormalities progress. Physical examination findings that indicate the presence of plasma volume expansion include distension of the jugular veins and superficial vasculature. This latter finding is particularly obvious in the sparsely haired region of the caudal abdomen. Whereas peripheral edema is a very common manifestation of congestive heart failure in humans, it is rare in small animals. This may be due to differences in fluid homeostasis between species, or simply be a function of increased hydrostatic pressure in the lower limbs of humans (primarily vertically oriented) compared to small animal patients (horizontally oriented).

Box 18-1

General Mechanisms and Specific Causes of Peripheral Edema in Small Animals

Increased Hydrostatic Pressure

- Increased plasma volume
  - Arteriovenous fistula
  - Chronic kidney disease*
  - Right-sided heart failure*
- Venous obstruction
  - Cranial mediastinal mass
  - Caudal abdominal mass
  - Trauma
  - Surgery

Decreased Plasma Oncotic Pressure* (albumin <1.5 – 2.0 g/dL)

- Protein loss
  - Protein-losing enteropathy or glomerulopathy
- Reduced albumin synthesis
  - Liver disease
  - Malnutrition

Increased Capillary Permeability

- Allergic reactions including angioedema
- Inflammation secondary to neoplasia
- Septicemia
- Envenomation
- Burns
- Trauma
- Myxedema

Lymphatic Dysfunction

- Lymph node hypoplasia or aplasia
- Lymph node destruction due to malignancy
- Lymphangiosarcoma

*May cause ascites and/or peripheral edema.

Another potential source of peripheral edema is a decrease in plasma oncotic pressure from either loss of protein[6] (e.g., protein-losing enteropathy or glomerulopathy) or decreased protein synthesis (e.g., hepatic failure, malnutrition).[7,8] Initially, the development of edema in hypoproteinemic states is prevented by a parallel decline in the interstitial oncotic pressure due to decreased albumin entry into the interstitium. This decreases the oncotic gradient between the interstitium and vascular space. Additionally, fluid entry into the interstitium causes a concurrent increase in interstitial hydrostatic pressure, which also opposes the formation of edema. It is important to note that the degree of hypoproteinemia must be quite severe to cause overt edema. Edema is unlikely to develop until albumin falls below 2.0 g/dL unless another process is also occurring.[5] In small animals, hypoproteinemia more commonly manifests as peritoneal effusion (ascites) rather than peripheral edema.

Increased vascular permeability underlies the edematous response to inflammation. These processes include hypersensitivity reactions (e.g., urticaria, angioedema) and sepsis. Vascular permeability is influenced by a myriad of signaling chemicals including inflammatory cytokines, vasodilatory prostaglandins, nitric oxide, bradykinin, and histamine, among others.[5] Increased vascular permeability can also occur due to direct cell damage from mechanical or chemical trauma. Unfortunately, there are no practical clinical methods for measuring increased vascular permeability and thus it must be inferred by other abnormalities such as inflammatory changes on a complete blood count, hyperglobulinemia and hypoalbuminemia on a serum biochemistry panel, and hyper- or hypothermia on physical examination.

Lymphatic abnormalities are another important cause of peripheral edema in small animals.[9] Lymph fluid is high in protein and its presence increases the oncotic gradient within the interstitium, further increasing edema formation. Lymphatic abnormalities can be primary or secondary. Congenital lymphedema is uncommon in dogs and is very rare in cats.[9,10] Affected animals usually show evidence of edema at birth or within the first few weeks of age, though in some instances it may be many months before edema is manifested. The most common presentation in affected animals is hindlimb edema, with one limb usually being more severely affected than the other (Figure 18-2). However, in some instances, all limbs or even the head and ventrum are affected. Patients with congenital lymphedema have small or absent lymph nodes in the affected limbs. The diagnosis may be suspected from the clinical signs and age at presentation, but definitive diagnosis requires lymphatic imaging or biopsy.[11] There are many secondary causes of lymphatic disease, including obstruction or destruction secondary to neoplasia,[12,13] infection, filariasis, surgery, and trauma.

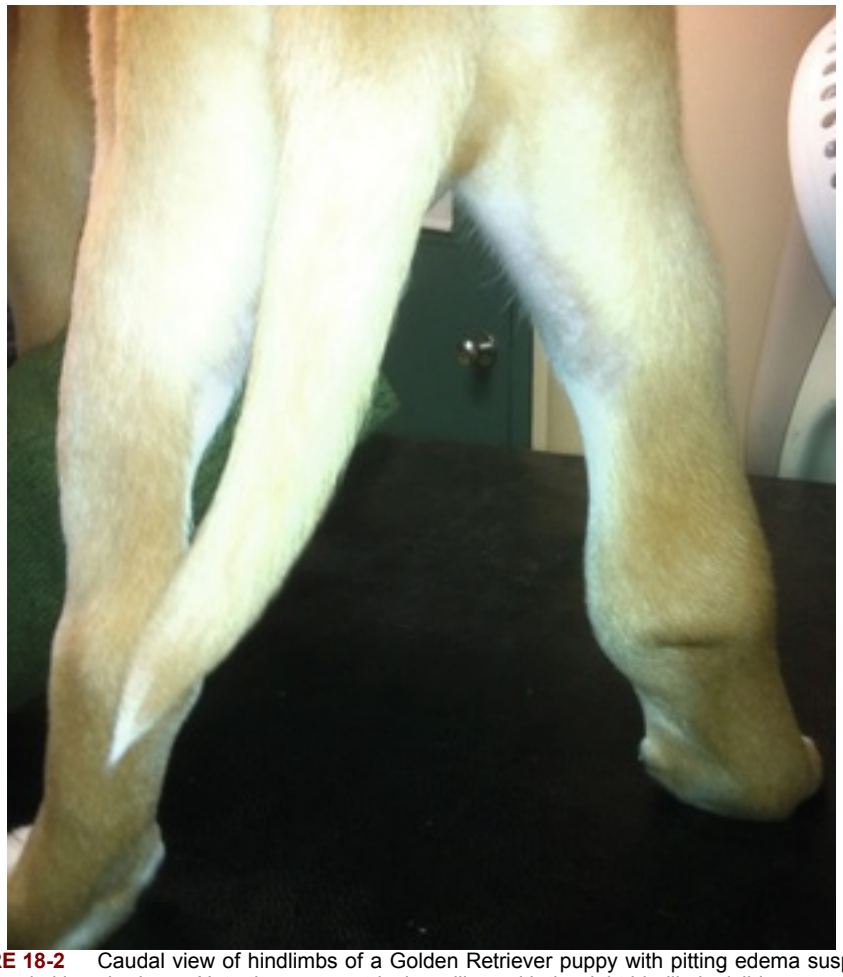

FIGURE 18-2 Caudal view of hindlimbs of a Golden Retriever puppy with pitting edema suspected of congenital lymphedema. Note the asymmetrical swelling, with the right hindlimb visibly more swollen than the left. No abnormalities were found on complete blood count, serum biochemistry panel, or abdominal ultrasonography. (Courtesy Leah Cohn, University of Missouri.)

Myxedema, a manifestation of profound hypothyroidism, results in edema through the combinations of increased capillary leakage of proteins and diminution in lymphatic uptake.[14] This results in non-pitting edema on physical examination, as well as hypothermia, respiratory depression, and bradycardia (see ch. 299).[15,16]

Diagnosis and Treatment of Edematous Diseases

Evaluating the distribution of edema and response to palpation are crucial diagnostic steps in helping to diagnose the underlying cause of the edema (Figure 18-3). Peripheral edema that is diffuse is more likely the result of a systemic inflammatory response (e.g., sepsis, angioedema) or increased plasma volume (e.g., nephrotic syndrome). In contrast, edema that is localized is more commonly the result of venous or lymphatic abnormalities, or possibly an envenomation. Generally, peripheral edema will be most severe in the dependent regions due to gravitational and hydrostatic forces.

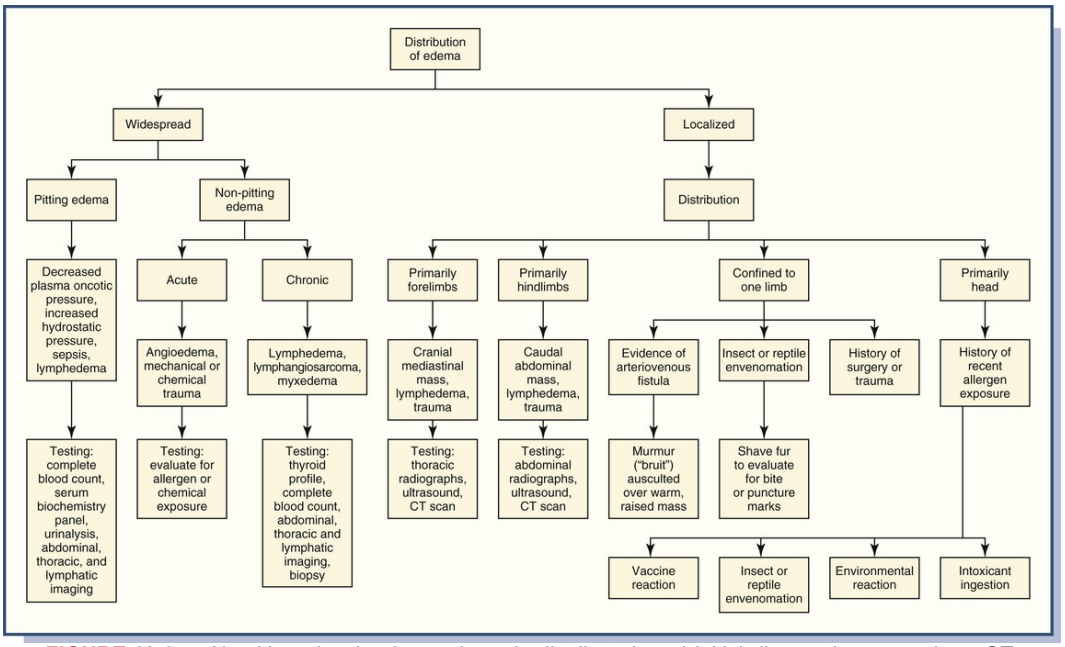

FIGURE 18-3 Algorithm showing how edema is distributed, and initial diagnostic approaches. *CT*, Computed tomography.

Determining if edema is pitting or non-pitting will also help diagnose the cause. Pitting edema is recognized by a persistent depression in the skin after firm pressure is applied (Video 18-1). Mechanistically, pitting edema indicates displacement of fluid within the interstitial space, whereas non-pitting edema indicates intracellular swelling, or interstitial fluid retention with clotted fibrinogen that prevents fluid shifts.[17] In small animal patients, pitting edema is most commonly a manifestation of increased vascular permeability (e.g., inflammation), venous obstruction (e.g., mass, trauma), or lymphatic abnormalities (e.g., obstruction, hypoplasia). Edematous states that are non-pitting include angioedema, post-surgical or traumatic swelling, chronic lymphedema, lymphangiosarcoma, and myxedema. Angioedema is non-pitting due to the process occurring in the deeper layers of the skin below the dermis. Chronic lymphedema will gradually transform into a non-pitting state due to collagen deposition and the development of fibrosis in the affected tissues.[9] Once fibrosis occurs, there is little that can be done therapeutically to resolve the edema.

The diagnostic approach to the edematous patient should be based on history and physical examination findings. Generalized edema warrants a systemic approach including complete blood count, serum biochemistry profile, serum thyroxine concentration, and urinalysis. Diagnostics performed in the presence of edema that is localized to the front or rear limbs should include radiography and ultrasound for ruling out obvious masses and determining if more advanced imaging is indicated.

Direct imaging of lymphatics and lymph nodes requires specialized techniques.[18,19] In the past, lymphangiography via direct lymphatic cannulation was the only method for evaluating lymphatic structure and function. This technique is technically challenging and is rarely performed anymore. Instead, it has been largely supplanted by non-invasive imaging techniques including scintigraphy, computed tomography (CT), magnetic resonance imaging, and positron emission tomography scanning. However, these modalities suffer from limited availability and being relatively expensive to perform.

Therapy for peripheral edema should always be directed at treating the underlying abnormality when possible (e.g., plasma transfusion, surgical removal of an obstructive mass, levothyroxine treatment of myxedema, etc.). In situations where a definitive treatment is not possible, then palliative care can be offered. Except in states of increased hydrostatic pressure, diuretics are relatively contraindicated in edematous states. Although they will initially help decrease the size of a limb in lymphedema, they ultimately increase the progression of disease by concentrating proteins in the interstitium and acting as a draw for further fluid translocation. These patients may benefit from chronic bandaging, surgical palliation, or therapy with rutin, though the latter has not been scientifically evaluated.[11] Efficacy of treatment may be monitored by measuring the circumference of the affected limb before and after performing an intervention in order to objectively assess therapeutic response.[20] In most instances, the finding of peripheral edema confers a

guarded prognosis and owners should be advised that palliation is usually a more realistic goal than a definitive cure.

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CHAPTER 19

Weight Loss as a Chief Complaint

Thomas Schermerhorn

Client Information Sheet: Weight Loss

Background

Weight loss may be intentional or unintentional. Intentional weight loss in animals occurs as a result of caloric restriction dictated by a voluntary (or prescribed) dieting program (see ch. 176). Unintentional weight loss, the focus of this chapter, is a frequent clinical complaint and can be associated with serious disease. Maintenance of body weight is a reflection of nutrient intake, absorption, and utilization. These factors may be impacted by age, health status, and environment (diet, food availability, etc.). In people, unintentional loss of ≥5% body weight over 6-12 months warrants investigation.[1] While clinically relevant weight loss has not been defined for dogs and cats, ≈5% is a reasonable benchmark.

The frequency of weight loss as an owner's chief complaint for dogs and cats is unknown. Weight loss is a well-recognized clinical sign in numerous disorders. Weight loss is also common in human illnesses; unintentional weight loss is reported in as many as 65% of geriatric patients.[2] The high prevalence of unintentional weight loss in clinical illness underscores the need to carefully monitor weight in dogs and cats as a part of their general health assessment.

History

Dogs and cats may be brought to a veterinarian with weight loss as a primary or sole complaint. More commonly, it accompanies other signs associated with an underlying condition. Careful history-taking should include questions about appetite, caloric intake, daily exercise, and environment (see ch. 170). Appetite is variable in animals with weight loss and may be reported as reduced, normal, or increased (see ch. 16 and 17). Appetite may be preserved or increased when malnutrition results from starvation, malabsorption, or maldigestion. However, appetite is reduced (hyporexia) or suppressed completely (anorexia) by many systemic illnesses, leading to unintentional weight loss (see ch. 16). When an owner mentions the possibility of weight loss, the dietary history should be carefully reviewed (see ch. 170). This review should include the type and quantity of food offered (including any dietary supplements provided), the possibility that other pets at home might be competing for food, and the pet's appetite. It is important to distinguish those animals that have an appetite but cannot prehend or swallow food from those who have no appetite but can chew and swallow normally (see ch. 272). Diagnostic considerations suggested by various patient history findings are presented in Box 19-1.

Box 19-1

Diagnostic Considerations for Patients with Marked Weight Loss

Dietary History—Inadequate

Starvation
Underfeeding
Poor quality food

Dietary History—Adequate

Environmental/housing factors

Competition for food from other pets
Limited access to food
Oral and dental disease
Impaired use of nutrients
Specific nutrient deficiency
Maldigestion of any cause
Malabsorption of any cause
Diabetes mellitus
Protein-losing disease
  Nephropathy
  Gastroenteropathy
Cardiac disease*
Elevated metabolism
Hyperthyroidism
Chronic fever of any cause*
End-stage renal disease*
Neoplasia*
Chronic infection*
Chronic inflammation of any cause (e.g., immunologic disease*)
  Note: Patients may present with or without a loss of appetite.

*Diseases typically associated with cachexia in humans and animals.

Common mechanisms leading to weight loss include decreased caloric intake, increased metabolic demand, accelerated energy loss, inability to utilize ingested calories, and inappetence. Specific etiologies usually cause weight loss through several mechanisms, each of which may need to be evaluated if weight loss is to be understood and treated. Some cancers can cause weight loss if the tumor mass interferes with food intake or nutrient processing. Some cancers cause severe weight loss via the production of humoral factors that impair metabolism. For example, oral cancer may impede mastication or swallowing while gastrointestinal neoplasia may interfere with digestion and absorption of nutrients or cause nausea, vomiting and/or diarrhea. Some cancers secrete substances that cause anorexia or induce cachexia (see ch. 177).

In humans, gastrointestinal disorders are the leading non-neoplastic cause of unintended weight loss; the same may be true for dogs and cats. Oral and dental diseases, megaesophagus, chronic gastroenteritis, inflammatory bowel disease (IBD), pancreatitis, dysmotility, and other disorders can produce weight loss through a variety of mechanisms that include induction of nausea, inappetence, protein loss, maldigestion and malabsorption.

Several endocrine disorders are associated with weight loss. Hyperthyroidism causes weight loss, in part, due to increases in metabolic rate. Diabetes mellitus, a condition associated with an absolute or relative deficiency of insulin, causes weight loss due to an inability to utilize nutrients. Both these conditions are usually associated with increases in appetite. Other endocrine conditions, such as hypoadrenocorticism and hyperparathyroidism, commonly cause weight loss and are associated with a reduction in appetite.

Chronic bacterial or fungal infection, especially those accompanied by persistent systemic inflammation, are associated with weight loss. Likewise, the persistent systemic inflammation of connective tissue disorders, such as systemic immune-mediated conditions, may cause weight loss through similar mechanisms. Both cardiac and respiratory disorders can lead to an increase in metabolic demands and induce cachexia. Indeed, heart failure caused by chronic valvular disease or cardiomyopathy is a frequent cause of cachexia (cardiac cachexia) in dogs.[3] Uremia secondary to chronic kidney disease (CKD) commonly leads to nausea, gastric ulceration, and vomiting that, in turn, decreases appetite and reduces caloric intake. Some neurological disorders reduce appetite that leads to weight loss. Other neurologic conditions decrease food intake by impairing mastication or swallowing. Some neurologic disorders that impair autonomic function or cause dysmotility may cause gastrointestinal dysfunction and weight loss. Cognitive dysfunction and psychiatric disorders are present in a substantial proportion of people with weight loss but the role of similar neurologic disorders in dogs and cats is unknown.

No standard definition for cachexia exists. In clinical practice, cachexia is the term used to describe the weight loss, loss of muscle, and anorexia that accompany many chronic disease conditions (see ch. 177).[3]

However, cachexia is not simply caused by inadequate nutrient intake. Cachexia and starvation are not equivalent physiologic processes. Two biochemical features distinguish malnutrition caused by cachexia from that caused by starvation.[4] First, unlike starvation, inflammation is a consistent feature of cachexia. Cachexia causes marked activation of the inflammatory cascade, characterized by a pronounced acute phase inflammatory response and excessive production of proinflammatory cytokines such as interleukins (IL-1 and IL-6, among others) and tumor necrosis factor alpha (TNF-alpha).[5] These cytokines stimulate the ubiquitin pathway, a central pathway in protein turnover.[6] Ubiquitin complexes with target cellular proteins and stimulates their metabolism via the proteasome system. Second, cachexia is associated with a rise in resting energy expenditure, which increases as a consequence of altered protein, fat, and carbohydrate metabolism. Loss of body muscle and adipose tissues is marked and an insulin-resistant state may develop. Despite a similar clinical appearance, activation of the ubiquitin-proteasome system and increased energy expenditure are not features of starvation. A diagnosis of cachexia should be considered for any dog or cat with marked weight loss, severe muscle loss, and decreased appetite in the setting of a chronic inflammatory response or cancer.[3] By this definition, cachexia is not a specific diagnosis but a state of disordered metabolism that can be caused by a variety of diseases.

Physical and Laboratory Findings

Weight loss is a clinical sign, not a specific diagnosis. Suspected weight loss should be verified, when possible, by comparing previously recorded body weights with the current status. Owner perception of weight loss may not be accurate. Suboptimal body weight, loss of subcutaneous fat with prominence of underlying skeletal structures, an emaciated appearance, and a low body condition score (BCS) support the suspicion of weight loss (see ch. 2). It must be borne in mind that substantial weight loss may occur without obvious physical changes. Some pets have a normal BCS, despite significant weight loss. Marked loss of body condition is a characteristic finding of severe cachexia in which muscle loss may be disproportionate to fat loss. In many cases, a diagnosis may be apparent after completion of the physical examination. Examples of a "physical examination diagnosis" or "physical examination suspicion" abound. These include, but are not limited to, identifying oral disease, a cervical mass (thyroid tumor?), cardiac arrhythmia, or abdominal mass. If the physical examination fails to identify a concern, a directed physical examination (e.g., detailed neurologic or orthopedic examination) or laboratory examination may be needed to confirm a diagnosis.

Laboratory findings in animals with unintended weight loss are neither specific nor consistent. Test results typically reflect the primary pathologic processes responsible for the weight loss. In cachexia, laboratory findings may show characteristic yet nonspecific changes.[5] Serum protein concentrations vary even in the presence of a systemic inflammatory response. For example, elevated fibrinogen concentrations (as a component of the acute phase response) in humans with neoplasia may be offset by reduced albumin synthesis. Increases in hormone concentrations, such as cortisol and insulin, may be observed in animals with cachexia; these changes may result from or be the cause of cachexia-induced alterations in metabolism. In general, as for other forms of unintended weight loss, the physical and laboratory findings of a patient with cachexia will be representative of the underlying disease rather than specific indicators of cachexia. No compelling reasons exist to perform specific laboratory tests to make a diagnosis of cachexia. Instead, cachexia is largely a clinical diagnosis that is made when appropriate physical findings are present in a dog or cat with a disease associated with a chronic inflammatory response.

Diagnostic Plan

A general algorithm for making a diagnosis of unintended weight loss is shown in Figure 19-1. Unintended weight loss of >5% over a period of less than 12 months in any patient should evoke concern about the possibility of underlying disease. A suitable and tailored diagnostic plan based on physical and laboratory findings should be developed for affected animals. It is important to recognize cachexia because animals with this condition may not respond as expected to therapeutic interventions and nutritional support. In people, a diagnostic work-up may fail to uncover an etiology in as many as 30% of patients with a complaint of unintended weight loss.[1] The proportion of dogs and cats with weight loss that have unrewarding diagnostic evaluations is not known but it is certain to occur.

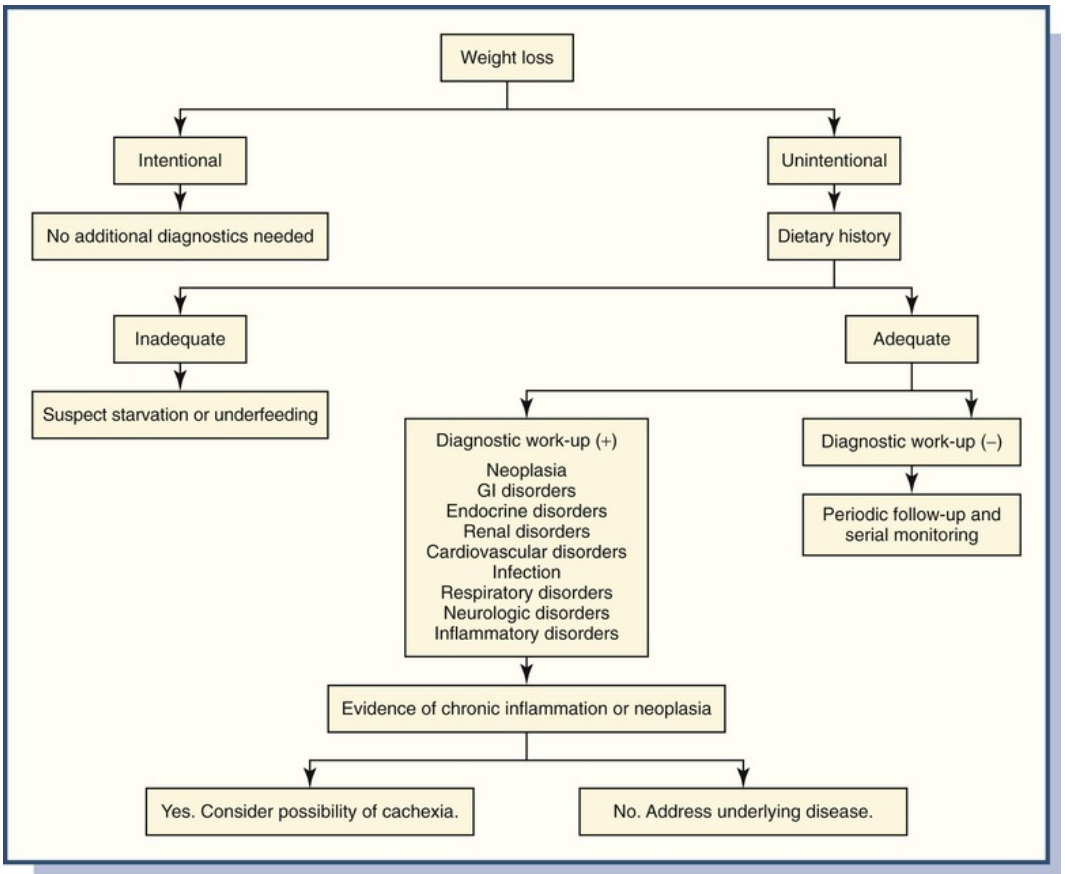

FIGURE 19-1 Algorithm for making a diagnosis of cachexia. +, Testing allowed; −, testing rejected; *GI*, gastrointestinal.

Therapy

Successful therapy or resolution of the primary disorder is the most efficacious means to address unintended weight loss. Therapy will ameliorate or reverse the underlying factors contributing to weight loss and body weight may be restored with nutritional support. When weight loss is due to cachexia, nutritional support remains the cornerstone of specific therapy; however, additional considerations must be given to designing the nutritional plan (see ch. 170). Hypercaloric feeding is intended to supply the dog or cat with sufficient calories to meet increased maintenance caloric needs (because of hypermetabolism), prevent additional weight loss, and promote weight gain. Unfortunately, hypercaloric feeding alone may not be sufficient therapy for animals with true cachexia. People with cachexia who receive hypercaloric feeding gain weight, but the increase in body weight is almost exclusively the result of an increase in adipose tissue without change in lean body mass. Thus, it appears that simple feeding therapy may not be sufficient in all situations to reverse the abnormal protein catabolism that accompanies cachexia. Pharmacologic therapies that have been used for cachexia in humans that may prove useful for the treatment of animals include nutritional supplements (including fish oils), appetite stimulants, anabolic agents, anti-inflammatory drugs, and cytokine inhibitors. Although some of these drugs have been extensively used for other indications in small animals, information is limited about their efficacy when used for cachexia. Specific inhibitors of the ubiquitin system, which inhibit the effects of cachexia at the molecular level, may eventually be developed.

It is less clear which steps should be taken when a patient with weight loss has a non-diagnostic work-up. Cancer is perhaps the most serious diagnosis that clinicians fear may have been missed under these circumstances. While specific information about dogs and cats is lacking, the number of occult neoplasms later diagnosed in humans with weight loss and an unremarkable initial work-up is surprisingly small (<5%). Given the information gleaned from studies of human patients and lacking concerning physical, laboratory or imaging findings, it may be prudent to adopt a wait-and-see strategy when a dog or cat that is presented for weight loss has a negative physical examination and lacks a specific diagnosis after blood, urine, blood pressure and imaging results. Wait-and-see takes a strategy of serial monitoring over time rather than

immediate continued non-directed efforts that might involve more expensive or invasive diagnostics or the pursuit of unlikely diagnoses.

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CHAPTER 20

Failure to Grow

Hans S. Kooistra

Client Information Sheet: Failure to Grow

Introduction

Linear growth is a complex process that can easily be disturbed. Young dogs and cats grow rapidly over a relatively short period of time. Linear (vertical) growth primarily occurs during the first 6 to 9 months of life, but can continue in some dogs until about 2 years of age. Growth in long bone length is limited to the growth plates and occurs via the process of endochondral ossification. Linear growth halts when the growth plates close. There is no other species with so much variation in body size as the dog, which may make it difficult to determine whether failure to grow is really a problem.

Failure to grow is defined as not growing at the anticipated rate or to a normal extent. Failure to grow may be an owner's chief concern or may be identified by a veterinarian during routine physical examination. Usually there is good correlation between parental height and that of their offspring. Thus, if possible, the size of the dog with supposed failure to grow should be compared with parental and sibling height. The possibility should be considered that an apparent dwarf may simply be a small individual whose size is within normal biological variation. Alternatively, the individual may be the offspring of an unexpected or unwanted mating with a small sire.

Pathophysiology

Genetic factors play a major role in linear growth, with numerous genes involved in its regulation. After domestication of the dog, selection of such genes by humans has resulted in breeds with a wide variety of body sizes and growth rates. The chondrodystrophic dog breeds are an example of selection by people for the genes that give rise to angular limb formation and short legs. As these breeds have been created intentionally, they are usually not considered as having a problem with failure to grow.

To meet its full genetic potential for growth, any animal must consume sufficient calories and nutrients. Following consumption, food must be digested, absorbed, and the nutrients transported to the necessary tissues and used for metabolic maintenance and growth. The causes of failure to grow can be subdivided into three major groups: (1) inadequate intake of calories and nutrients, (2) metabolic changes associated with increased use of energy, and (3) loss of energy. Because several hormones are important determinants of linear growth, it may be helpful to differentiate endocrine and non-endocrine causes of failure to grow.

Endocrine Causes of Failure to Grow

Growth Hormone and Insulin-Like Growth Factor-1 Deficiency

Growth hormone (GH), originating from the pituitary anterior lobe, plays a central role in the modulation of growth. Hypersecretion of GH at a young age, i.e. juvenile hypersomatotropism, is an important determinant of linear growth.[1] Serial measurements of plasma GH concentrations have revealed that the initial increases documented in Great Dane puppies decrease to adult concentrations by about 6 months of age.[2] In Beagles, GH secretion is increased only until about 7 weeks of age.[1] In Miniature Poodles, GH concentrations do not change significantly with time and values in young animals are within adult reference ranges.[3]

In the total absence of GH, linear growth occurs at about a third to a quarter of the normal rate. Growth hormone deficiency in a young animal affects the growth of almost all tissues, resulting in “proportionate

dwarfism." This means that all body components are equally small.

Although GH has a direct effect on several tissues, the majority of its growth-promoting actions are mediated by insulin-like growth factor-1 (IGF-1). Growth hormone stimulates the synthesis and secretion of IGF-1 by the liver. In the systemic circulation, IGF-1 is bound to carrier proteins, the IGF-binding proteins (IGF-BPs). This binding prolongs the half-life of IGF-1, consistent with its long-term growth-promoting action. This hepatic IGF-1 reaches the target cells via the circulation and stimulates anabolic processes, such as protein synthesis, chondrogenesis, and growth. In addition to its endocrine effects, GH also stimulates local production of IGF-1. Locally synthesized IGF-1 stimulates anabolic processes in a paracrine or autocrine manner. For example, linear growth is largely dependent on local production of IGF-1 in growth plates. In adult dogs, there is a strong correlation between plasma IGF-1 concentration and body size, while basal plasma GH concentrations are quite similar among various breeds. This implies that breed-specific reference ranges must be used to determine whether failure to grow is due to insufficient circulating concentrations of IGF-1.

Juvenile Hypothyroidism

Adequate circulating thyroid hormone concentrations appear to be an absolute prerequisite for normal growth. Total absence of thyroid hormones leads to an almost complete cessation of linear growth. Thyroid hormone exerts direct effects on cell metabolism. In addition, the actions of IGF-1 on cartilage cells are dependent on thyroid hormone. Because skeletal growth strongly depends on thyroid hormones that promote chondrogenesis, in synergy with GH and IGF-1, juvenile hypothyroidism is associated with delayed epiphyseal closure, retarded epiphyseal growth, reduced long bone growth, and disproportionate dwarfism.[4]

Insulin Deficiency (Juvenile Diabetes Mellitus)

Insulin has strong anabolic actions separate from its effects on carbohydrate metabolism. These actions include stimulation of protein synthesis and cell division. Consequently, insulin deficiency, i.e. juvenile diabetes mellitus, is associated with growth retardation. This failure of normal growth, typical of dogs and cats with juvenile diabetes mellitus, is also due to a decrease in insulin-dependent transportation of glucose and fatty acids into muscle and fat cells. Further, glucose is lost in urine.

Glucocorticoid Excess

The catabolic effects of the glucocorticoids are characterized by increased gluconeogenesis, decreased uptake of glucose by muscle and fat cells, increased protein breakdown, and lipolysis. In addition, glucocorticoid excess suppresses pituitary GH secretion. Consequently, long-term administration of glucocorticoids to young growing animals may result in growth retardation.

Gonadal Steroids Excess

Gonadal androgens and estrogens are contributors to linear growth. Prepubertal gonadectomy may result in taller individuals (see ch. 313).[5] Administration of androgens or estrogens at an early age may result in stunted growth due to premature closure of the growth plates.

Other Endocrine Hypofunctions

Hypoadrenocorticism may occur at any age. The Nova Scotia Duck Tolling Retriever is a breed recognized to occasionally develop primary hypoadrenocorticism at an early age. Hypoadrenocorticism is often associated with a decrease in appetite, vomiting and diarrhea. These problems result in reduced nutrient intake, which may give rise to a failure to grow. Hypoparathyroidism may also occur at a young age. Parathyroid hormone (PTH) has an important role in bone metabolism and its deficiency may result in growth retardation. Disorders associated with severe polydipsia, such as central diabetes insipidus, may result in impaired appetite and failure to grow normally.

Non-Endocrine Causes of Failure to Grow

In addition to genotype, another important factor affecting growth is intake of calories and nutrients. Nutritional deprivation severely impairs growth. Selective deficiencies in vitamins or minerals may also cause

abnormalities of growth. The quality and palatability of food should be taken into consideration.

A poor appetite, e.g., due to a systemic disease, may result in less food intake. Oropharyngeal disorders may cause anorexia. Regurgitation or vomiting could result in insufficient nutrients reaching the intestines. A vascular ring anomaly, due to a persistent right aortic arch, should be considered in puppies with stunted growth and chronic regurgitation, especially after weaning. Maldigestion, e.g., due to exocrine pancreatic insufficiency, and malabsorption, e.g., due to an intestinal wall disorder, can result in decreased uptake of nutrients. Intestinal parasites are a frequent cause of inadequate uptake of nutrients in puppies and kittens.

Catabolic processes, such as those associated with inflammatory processes and fever, will result in increased use of energy. Cardiac congenital anomalies and endocarditis may be associated with tachycardia which, in turn, utilizes excess energy, leaving fewer calories for growth. Disorders involving organs that play a central role in metabolism, i.e. the liver and the kidneys, may result in failure to grow. Both congenital renal disorders and acquired kidney disease, e.g., pyelonephritis, can result in stunted growth. Portosystemic shunting resulting in hepatic encephalopathy is the most common liver disorder associated with failure to grow. Hepatitis and glycogen storage diseases have been associated with growth failure. Growth failure in chronically anemic individuals may be associated with impaired oxygen delivery to tissues as well as increased cardiovascular effort. Failure to grow can be associated with glucosuria due to (juvenile) diabetes mellitus or it may follow abnormalities in renal proximal tubules. Persistent proteinuria and protein-losing enteropathies decrease growth potential.

Diagnostic Approach (Figure 20-1)

A detailed history should be obtained regarding the amount, quality and palatability of food consumed. A poor appetite, despite the feeding of a palatable, high-quality food suggests a disorder of the gastrointestinal tract or the presence of systemic disease. Stunted growth in pets with extremely good or ravenous appetites may point to maldigestion, malabsorption or loss of energy. History-taking may also reveal treatment with steroids for an unrelated problem.

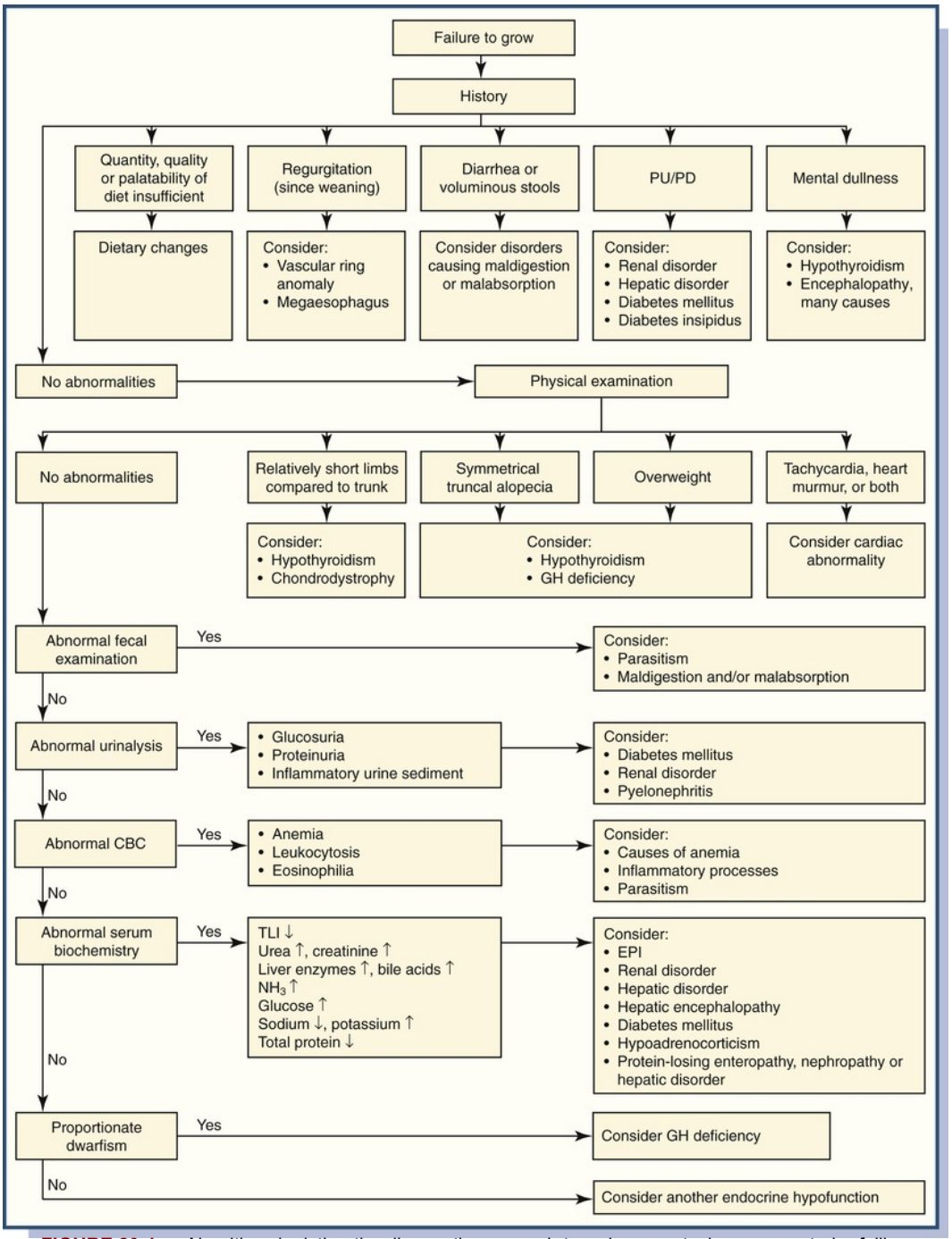

FIGURE 20-1 Algorithm depicting the diagnostic approach to a dog or cat who appears to be failing to grow as expected. *CBC,* Complete blood count; *EPI,* exocrine pancreatic insufficiency; *GH,* growth hormone; *PU/PD,* polyuria/polydipsia; *TLI,* trypsin-like immunoreactivity.

Concurrent clinical signs may help identify an underlying cause for failure to grow. Diarrhea or voluminous stools may point to maldigestion or malabsorption. Polyuria may point to renal disease, hepatic disease, diabetes mellitus, diabetes insipidus or other conditions. Mental dullness may point to hypothyroidism or (hepatic or renal) encephalopathy. Symmetrical truncal alopecia can be seen in dogs with GH deficiency or hypothyroidism. Regurgitation since weaning may point to vascular ring anomaly and megaesophagus.

Body proportions must be carefully evaluated in dogs or cats who fail to grow. Relatively short limbs compared to the trunk suggest either juvenile hypothyroidism or chondrodystrophy. Growth hormone deficiency, in contrast, causes proportionate dwarfism. It is also important to note the ratio of height to weight. An animal with stunted growth that is overweight for its height is more likely to have an endocrine

disorder such as GH deficiency or hypothyroidism. Malnutrition or systemic disorders are more likely to result in underweight animals with stunted growth.

A thorough physical examination is essential in animals with failure to grow, as specific physical findings may point to a specific disorder. For example, dogs with hypothyroidism usually will have a weak pulse or a heart murmur may disclose a cardiac abnormality.

Laboratory evaluations should include multiple fecal examinations for intestinal parasites, e.g., *Giardia*. Fecal examination may also provide information regarding digestion and absorption. Urinalysis may reveal proteinuria, glucosuria or hyposthenuria. Indications for pyelonephritis may be found in the urine sediment. A complete blood count (CBC) should be evaluated for anemia, inflammation or eosinophilia. Remember that puppies and kittens normally have lower red blood cell counts as compared with adults. Eosinophilia may point to parasitism or hypoadrenocorticism. Results of a routine serum biochemistry profile can help to identify renal disease, hepatic disease, diabetes mellitus or hypoadrenocorticism. Decreased serum protein concentrations may point to hepatic disease, protein-losing enteropathy or protein-losing nephropathy. Decreases in serum trypsin-like immunoreactivity (TLI) in a fasted dog confirms exocrine pancreatic insufficiency (EPI). Serum cobalamin and folate concentrations may suggest intestinal abnormalities causing maldigestion and malabsorption.

Specific tests may be required to diagnose endocrine disorders. Growth hormone deficiency can be diagnosed indirectly by measuring and finding low serum IGF-1 concentrations. Absence of a significant increase in circulating GH concentration after IV administration of GH-releasing hormone also implicates GH deficiency. Decreases in serum thyroxine concentration together with increases in thyroid stimulating hormone (TSH) concentration may confirm hypothyroidism. A TSH-stimulation test can be used to secure the diagnosis in dogs whose TSH concentrations are not increased. The diagnosis of hypoadrenocorticism should be based on the results of an adrenocorticotropic hormone (ACTH) stimulation test.

Diagnostic imaging may reveal skeletal abnormalities. Ultrasonography may be helpful to detect structural abnormalities of the internal organs or identify a portosystemic shunt. Biopsy may be needed if gastrointestinal, hepatic or renal disease is suspected.

Treatment

Treatment is dependent on the underlying disorder. Some disorders can be well managed medically, whereas others may require surgical correction. If the underlying disorder is diagnosed and treated early, "catch-up" in growth is usually seen.

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CHAPTER 21

Weakness

Fred C. Brewer IV

Weakness or asthenia (lack/loss of or reduced strength) is the clinical manifestation of many disease conditions and consequently, is a common clinical sign (Figure 21-1). In veterinary medicine, the term weakness is often used synonymously with fatigue, lethargy, and exercise intolerance. Weakness is the inability to initiate a task, while fatigue is the inability to continue to perform a task after it has begun. Lethargy is defined by a deficiency in mental or physical alertness or activity, and refers to drowsiness, sluggishness, dullness, or inactivity. Exercise intolerance is defined by the inability to sustain a level of physical exercise expected based on the patient's physical condition. For purposes of this discussion, the term weakness will be used interchangeably to include fatigue, lethargy, and exercise intolerance.

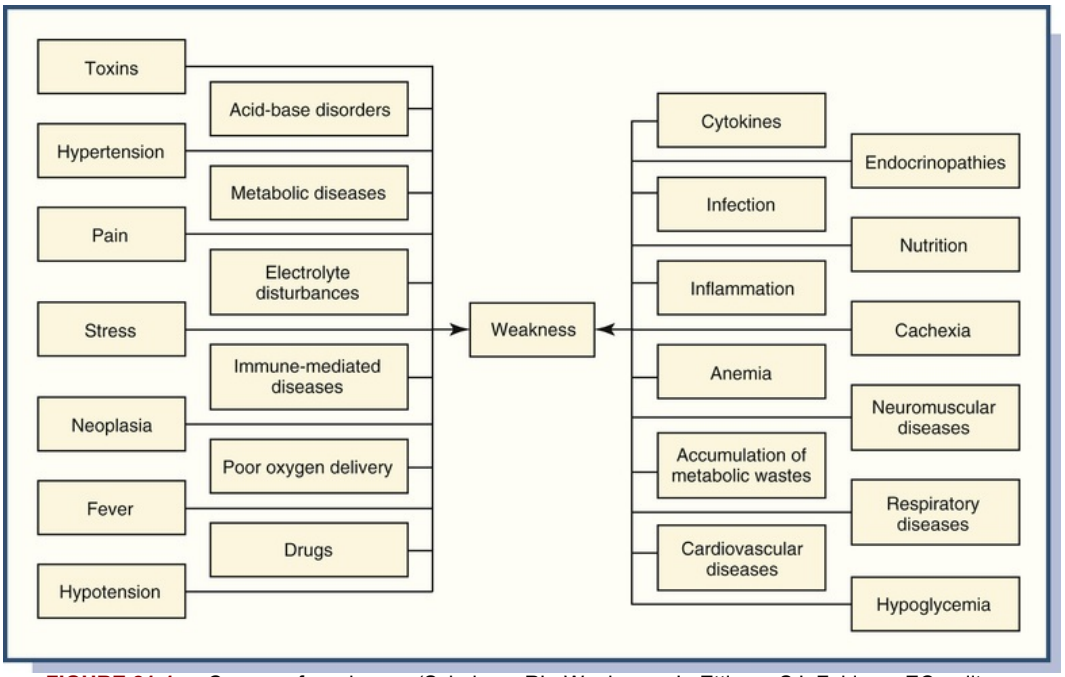
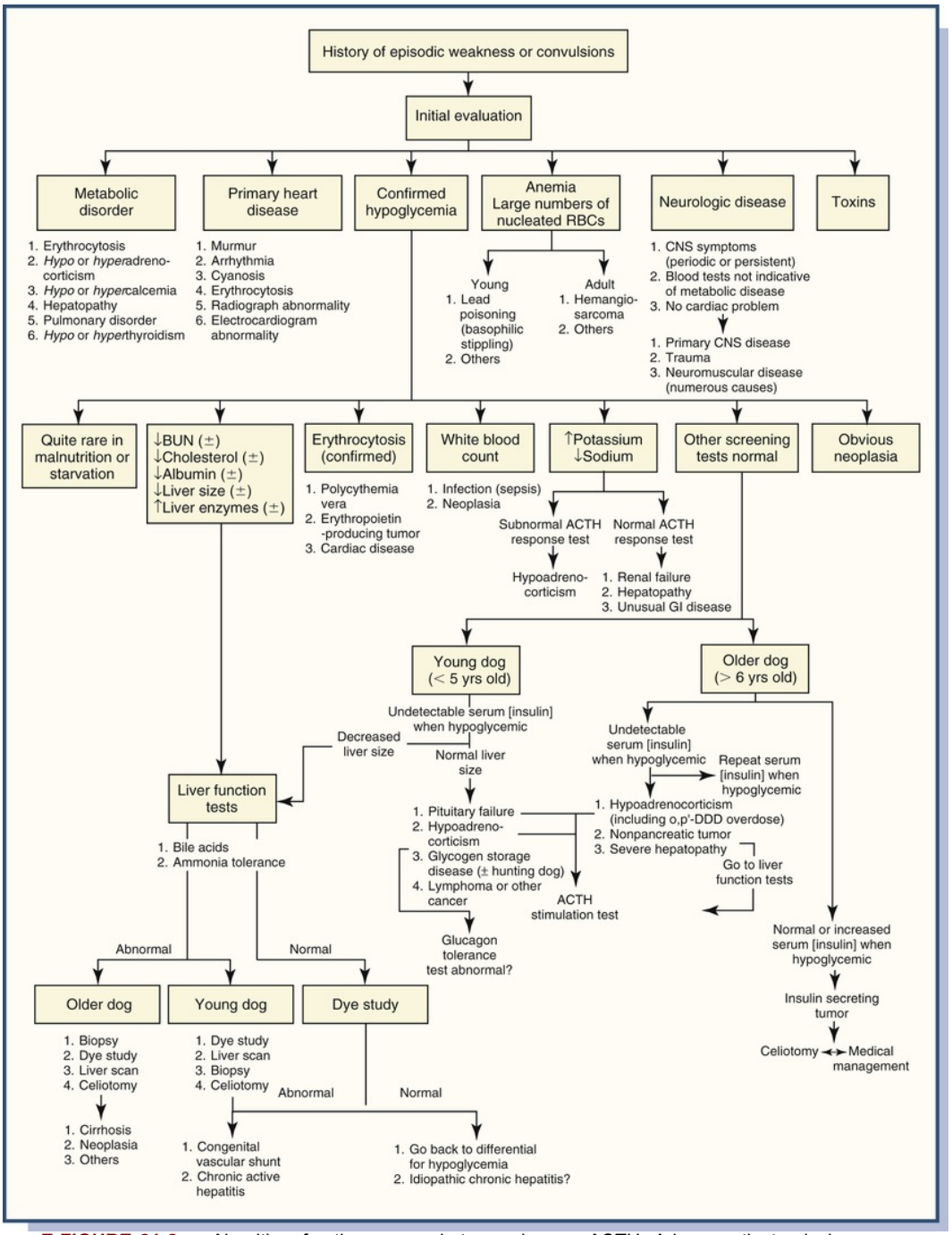


FIGURE 21-1 Causes of weakness. (Schulman RL: Weakness. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine*, ed 7, St Louis, 2010, Elsevier, pp 148-152.)

Various degrees of weakness may be difficult to appreciate or accurately quantify in veterinary patients. As a result, the patient presenting with a clinical sign of weakness poses a diagnostic challenge for many clinicians (Video 21-1). Signalment profiling, obtaining an exhaustive history, and performing a thorough physical examination may not result in a definitive diagnosis, but are important steps toward a diagnosis in patients presenting with weakness. Early use of basic diagnostics (blood pressure [BP], complete blood count [CBC], biochemistry) is also important in evaluating causes of weakness.

Evaluating the patient's signalment will aid in prioritizing the differential diagnosis list (E-Figure 21-2). Puppies and kittens are more likely to suffer from dietary indiscretion, toxin exposure, intestinal parasitism, congenital disease, hypoglycemia, or infectious diseases. Geriatric patients may be more likely to suffer from degenerative diseases of the cardiovascular, musculoskeletal, or neurological systems, in addition to endocrine disorders, or neoplastic conditions. In young to middle-aged female dogs, immune-mediated

diseases are more prevalent. Breed predilections for specific diseases must also be considered, some examples of which are arrhythmogenic right ventricular cardiomyopathy in Boxers, hypoadrenocorticism in Standard Poodles, and primary hyperparathyroidism in Keeshonds.



E-FIGURE 21-2 Algorithm for the approach to weakness. *ACTH,* Adrenocorticotropic hormone; *BUN,* blood urea nitrogen; *CBC,* complete blood count; *GI,* gastrointestinal.

Historical information about the pet will provide clues as to the cause of weakness. Questions regarding the time course, severity, associated triggers, concurrent medications, additional symptoms or illnesses, potential exposure to toxins, and travel history will further shorten the list of differentials. For example, a tachypneic and coughing dog with a loud murmur and recent and progressive onset of weakness or exercise intolerance may be in congestive heart failure.

The importance of a thorough physical examination (see ch. 2) cannot be overemphasized. It is the

foundation to all subsequent clinical steps and will determine the use of specific diagnostic tests. Auscultation of the heart and lungs for murmurs, arrhythmias, or abnormal lung sounds will assist in ruling in or out cardiovascular or respiratory disease as a cause for weakness. Pain on palpation and manipulation of joints and long bones may be secondary to underlying orthopedic diseases leading to weakness. A complete neurologic examination (see ch. 259) may reveal neurologic deficits and disorders responsible for weakness. Endocrine disorders may manifest with symmetrical alopecia, cachexia, peripheral neuropathies, or recurrent pyoderma.

Specific Mechanisms and Diseases

Metabolic Diseases

Metabolic disorders encompass a wide range of diseases and are among the most common causes of weakness. Metabolic diseases can cause weakness secondary to major organ failure or from electrolyte derangements, acid base disturbances, accumulation of metabolic wastes, excessive cytokine production, anemia of chronic disease, and nutritional imbalances. Failures of the hepatic or renal system are examples of metabolic diseases that lead to weakness from a multitude of mechanisms.

Electrolyte Disorders (see ch. 67, 68, and 69)

Derangements in electrolyte balances result from many diseases and are commonly the primary cause of weakness. Severe electrolyte disorders can cause muscle weakness and fatigue by affecting the central nervous system and at the cellular level by affecting myocyte membrane potentials. However, mild shifts in electrolyte balances typically do not cause weakness. Significant hypokalemia can occur secondary to many diseases including chronic kidney disease, unregulated diabetes mellitus, excessive diarrhea, endocrinopathies (hyperadrenocorticism), iatrogenic causes (diuretics), and internal shifts (metabolic alkalosis). Hyperkalemia is seen in anuric/oliguric renal failure, urethral obstructions, reperfusion injuries, and hypoadrenocorticism. Hyponatremia is seen in hypoadrenocorticism, diuretic use, gastrointestinal and urinary losses, congestive heart failure, and third spacing. Hypernatremia can be seen in free water loss (vomiting/diarrhea), salt poisoning, and hyperadrenocorticism. Hypocalcemia commonly causes restlessness and excitation, muscle tremors and fasciculations, and seizures. However, between episodes of tetany and seizures, dogs and cats are observed to be weak. Common causes of hypocalcemia include renal failure, primary hypoparathyroidism, eclampsia, and ethylene glycol intoxication. Hypercalcemia can be seen in neoplasia, particularly lymphoma, and also, primary hyperparathyroidism, renal failure, intoxications, and secondary to idiopathic causes (cats). Hypomagnesemia commonly occurs in critically ill pets and is usually secondary to excessive loss. Hypermagnesemia is less common but has been noted in endocrinopathies, renal failure, and iatrogenic causes.

Acid-Base Disorders

Dramatic shifts in acid-base balance can be the result of metabolic or respiratory diseases and result in weakness. Drugs and toxins can also cause acidosis or alkalosis. Most critically ill patients will have an acid-base imbalance (see ch. 128).

Inflammatory Conditions

Inflammatory conditions can be the result of infectious diseases, pancreatitis, neoplasia, hepatitis, burns, trauma, and immune-mediated conditions. Systemic inflammation causes the release of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and interferon-alpha, which can directly cause fatigue via central pathways and lead to cachexia. Other mediators, such as tumor necrosis factor (TNF)-alpha and nitric oxide, can depress myocardial contractility and reduce vascular tone, causing systemic hypotension and subsequently weakness. Chronic excessive cytokine production inhibits erythropoiesis leading to anemia and weakness.

Infectious Diseases

Infectious diseases may produce weakness by releasing toxins that lead to a cascade of events resulting in cytokine production, systemic inflammation, acid-base derangements, metabolic disorders, anemia, and a

negative energy balance, all of which worsen the signs of weakness. Bacterial, viral, rickettsial, fungal, parasitic, or protozoal agents can infect organs and body systems, directly and indirectly causing weakness.

Immune-Mediated Diseases

Immune-mediated diseases can affect specific organs or multiple body systems, leading to joint and muscle pain, anemia, renal or hepatic dysfunction, systemic inflammation, or cachexia, all of which lead to weakness, fatigue, or exercise intolerance (see ch. 198 and 201-203). The sole presenting complaint for a dog with immune-mediated polyarthritis may be generalized weakness, which may also be secondary to pain-induced reluctance to move.

Anemia

Anemia is a common laboratory test abnormality in dogs and cats and can cause generalized weakness secondary to poor oxygen delivery to tissues (see ch. 57, 198, and 199). Extensive investigation into the underlying cause for anemia is typically warranted, as multiple organ systems can be involved. Patients with anemia can present with severe clinical signs from shock (peracute blood loss) to more subtle signs of lethargy and weakness (chronic anemia).

Endocrine Disorders

Weakness can be appreciated in most endocrine disorders, including hypoadrenocorticism, hyperadrenocorticism, hypothyroidism, diabetes mellitus, and hyperparathyroidism. Weakness is not a common component of hyperthyroidism. Some endocrine disorders result in electrolyte derangements leading to weakness. Other endocrine disorders may cause muscle wasting, affect blood pressure, or trigger cardiac arrhythmias, all of which may lead to persistent or transient weakness. Neuropathies and myopathies causing weakness may be seen in hyperadrenocorticism, hypothyroidism, diabetes mellitus, and hypoglycemia.

Cardiovascular Disease

A hallmark symptom of cardiovascular disease is exercise intolerance. However, it is typically more apparent in severe stages of heart disease. In a patient with mild cardiovascular disease and weakness, further investigation into the underlying cause may be necessary. Cardiovascular disease can cause weakness from poor cardiac output resulting in reduced oxygen delivery to tissues. The muscle wasting and weakness associated with cardiac cachexia is observed in end-stage disease. Arrhythmias may cause transient weakness. Bacterial endocarditis may cause severe lethargy due to the concurrent septicemia present. Pericardial effusion from various causes may cause sudden and dramatic weakness and collapse.

Blood Pressure

Abnormalities in blood pressure can directly and indirectly cause significant weakness (see ch. 99 and 157-159). Hypotension can directly cause weakness secondary to reduced oxygen delivery to tissues. Hypotension can result from cardiovascular disease (poor cardiac output), decreased preload (hypovolemia, impaired venous return), and decreased vascular tone. Hypertension can indirectly cause weakness by affecting multiple organ systems (kidneys, heart, etc.). Hypertension can result from multiple disease processes such as renal disease, diabetes mellitus, hyperadrenocorticism, hypothyroidism, hepatic disease, and cardiovascular disease.

Respiratory Diseases

Lethargy, fatigue, and exercise intolerance are commonly associated with respiratory diseases and can result from hypoxemia-induced reduction in work capacity of the muscles. Important causes of respiratory disorders include infectious and inflammatory causes; however, neoplasia, toxins, trauma, and hemorrhage can also cause pulmonary disease.

Neurologic Diseases

Brain

Brain diseases can lead to persistent or transient weakness. A more generalized weakness is seen with more severe brain diseases and transient weakness can be observed, for example, after seizure episodes. Causes of brain disease include infectious (viral, bacterial, fungal, rickettsial, or protozoal meningoencephalitis), inflammatory (granulomatous meningoencephalitis), neoplastic (meningioma), congenital/hereditary (hydrocephalus, Chiari-like malformations), metabolic (organic aciduria), and vascular diseases (infarction).

Spinal Cord Disease

Diseases affecting the spinal cord can cause varying degrees of paresis or paralysis that may be interpreted as generalized weakness. Vague generalized signs of weakness are typically appreciated in more chronic and progressive spinal cord diseases. Degenerative diseases, inflammatory conditions, neoplasia, trauma, infectious diseases, and vascular accidents can cause spinal cord problems.

Neuropathies

Diseases that affect peripheral nerves and their neuromuscular transmission are commonly associated with hypotonia, muscle atrophy, and paresis—all of which can manifest as weakness (see ch. 268 and 269). Causes of neuropathies include metabolic disorders (diabetes mellitus), neoplastic disorders (nerve sheath tumors), paraneoplastic causes (insulinomas), infectious disorders *(Toxoplasma gondii),* inflammatory disorders (polyradiculoneuritis), trauma, toxic disorders and drugs (organophosphates, vincristine), autonomic disorders (dysautonomia), and idiopathic causes. Myasthenia gravis may present with constant or episodic weakness after activity that improves with rest.

Myopathies

Disorders of skeletal muscles commonly cause exercise intolerance and generalized weakness (see ch. 354). Causes for weakness with myopathies include generalized or focal muscle atrophy, muscle swelling, myotonia, and pain. Myopathies may result from inflammatory, infectious, metabolic, congenital, immune-mediated, neoplastic, and paraneoplastic causes.

Neoplasia

Many forms of neoplasia are associated with generalized weakness or lethargy. Some cancers cause weakness secondary to cachexia, induced by an overexpression of inflammatory cytokines such as TNF-alpha, which leads to muscle wasting, anorexia, and a negative energy balance. Some tumors may also release specific growth factors and hormones such as parathyroid hormone, insulin or insulin-like growth factors, erythropoietin, estrogen, and steroids that cause or worsen the signs of weakness. Some malignancies can lead to paraneoplastic syndromes that cause peripheral neuropathies causing episodic or constant weakness, as seen in myasthenia gravis (see ch. 269 and 352).

Physical and Psychological Stress

Acute and chronic physical or psychological stress can influence the release of pro-inflammatory cytokines, such as TNF-alpha, IL-1, and IL-6, through activation of both the hypothalamic-pituitary-adrenal axis and sympathetic nervous system with the subsequent release of glucocorticoids and catecholamines. The imbalance of pro-inflammatory and anti-inflammatory cytokines can lead to generalized weakness. Psychological stress in animals is difficult to appreciate but should not be overlooked. Both acute and limited stressors (fireworks, thunderstorms, travel, boarding) and chronic stressors (illness, pain, shift in social status, chronic abuse) can result in vague signs of weakness (see ch. 9). Excessive physical activity or activity beyond the physical or endurance capabilities of an animal may lead to exercise intolerance.

Pain

Acute or chronic pain can result in lethargy, exercise intolerance or weakness. Acute joint, spinal, or bone pain may result in the unwillingness of the animal to move, which may be interpreted as lethargy or weakness. Chronic progressive pain as a form of stress will lead to hyperactivity of the hypothalamic-pituitary-adrenal axis, which can lead to generalized weakness (see ch. 356). Animals experiencing chronic pain may have vague signs of weakness, lethargy, decreased appetite, and depression.

Nutritional Derangements

Nutritional deficiencies may cause generalized weakness and can occur as a primary problem (inadequate diet) or secondary to a chronic disease (malabsorption, decreased intake). Imbalances in nutrition can result in a negative energy balance, reduction in muscle mass and strength, reduction in caloric intake, vitamin and mineral deficiencies, altered glucose homeostasis, dyslipoproteinemias, and electrolyte derangements, all of which cause or exacerbate the signs of weakness (see ch. 170 and 177). Chronic diseases that cause nutritional disorders include neoplasia, endocrinopathies (diabetes mellitus), inherited diseases, and hepatic, renal, gastrointestinal, and pancreatic diseases.

Drugs and Toxins

Many drugs and toxins can cause varying degrees of weakness. An exhaustive history will help provide information regarding possible exposure to toxins or drugs. Medications and toxins that can result in weakness include beta-blockers, anticonvulsants, diuretics, narcotics, antihistamines, antibiotics, chemotherapeutic agents, glucocorticoids, tranquilizers, ethylene glycol, macadamia nuts, xylitol, grape/raisin toxicosis, and marijuana ingestion.

CHAPTER 22

Restlessness

Michael D. Willard

Client Information Sheet: Restlessness

While recognized as an important behavioral problem, restlessness has not received much focused attention by veterinary internists. Hence, this concern has not been as carefully defined or thoroughly discussed in internal medicine circles as have many other "owner chief concerns." Therefore, many veterinarians either do not recognize restlessness when it occurs in a patient, ignore it because they are unsure what to do when it is mentioned, or some may automatically relegate restlessness as a behavior issue (see ch. 9). Restlessness, however, may represent a sign of major, even life-threatening, disease. Thus, not considering medical causes of restlessness may place a patient at unnecessary risk. Granted, it can sometimes be difficult to diagnose the cause of restlessness. However, when uncertain of cause, it may be more appropriate to tell an owner that you have no doubt that the behavior they describe is real, but it can be difficult (and sometimes costly) to ascertain the cause.

History

The first step is to recognize that the patient is restless, and here history is key in detecting and determining its significance. While some clients will use the term "restless," many use words like "agitated," "anxious," "nervous," "pacing," or "uncomfortable." Sometimes owners state that their pet has been recently and constantly "seeking attention." Others indicate that the restlessness is episodic. For example, some dogs with congestive heart failure are described as restless at night, a reflection of respiratory difficulty that an owner may or may not appreciate. Dogs and cats with pleural effusion or pulmonary edema may be restless due to respiratory distress, underscoring the need for careful auscultation and for imaging of the thorax. Dogs with pheochromocytoma have been described as having unpredictable episodes of restlessness. Restlessness in animals who have been placed in a new environment (e.g., caged in a veterinary or boarding facility) is not generally worth pursuing because this is simply recognized as a result of being placed in an unfamiliar environment. Restlessness is much more likely to have medical significance when the owner reports "restlessness" while their pet is in more familiar surroundings.

If the pet has other problems that are both prominent and have more clearly defined rule-outs (e.g., cranial nerve deficits, muscular weakness, vomiting, diarrhea, weight loss, localized pain, etc.), these issues should be the focus of the diagnostic work-up, assuming the patient's restlessness can be readily attributed to the cause of the more typical concerns (Figure 22-1). Placing less significance on this one sign in such cases is likely appropriate, efficient, and cost-effective since restlessness has such a wide range of causes. An example would be restlessness in a cat who is considered a candidate for hyperthyroidism, a problem that is usually easy to diagnose by history (e.g., weight loss despite a ravenous appetite), physical examination (e.g., palpable thyroid nodule), and/or a serum thyroxine measurement.

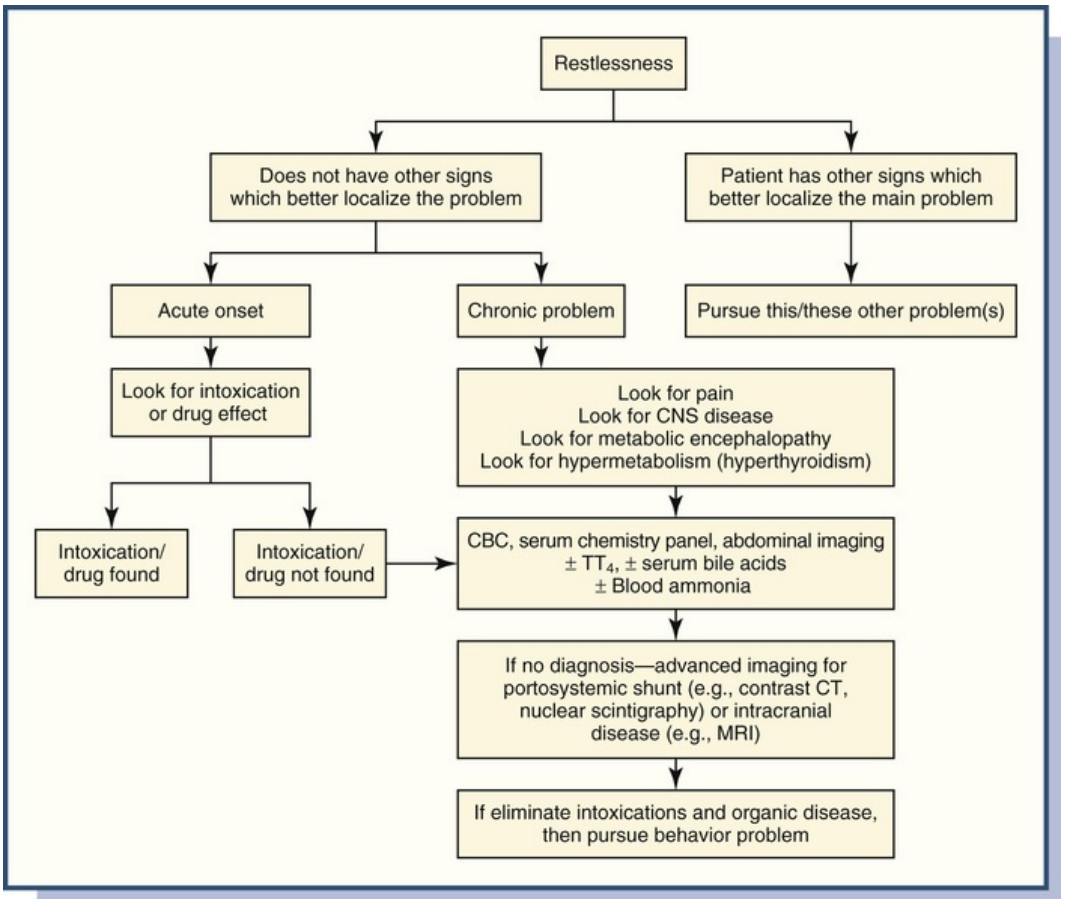


FIGURE 22-1 Suggested diagnostic approach to the problem of restlessness in the dog and cat. *CBC*, Complete blood count; *CNS*, central nervous system; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *TT_4*, total thyroxine.

If restlessness cannot be explained by an obvious "other problem," or if it is the only major complaint with no localizing findings on history or physical examination, then one must attempt to further characterize the observation. Quantify the degree of restlessness (i.e., mild, moderate, severe), how abruptly the restlessness began, how consistent it is (e.g., <10% of the time [episodic?], about half the time, >90% of the time) and whether the restlessness is static, getting better, or becoming worse over time. Are the owners aware of any stimulus that consistently results in the sign?

Intoxications and Drugs

Selected causes of restlessness are listed in Box 22-1 and the general approach to this concern is provided in Figure 22-1. Some causes (e.g., shock, dyspnea) may be identified from the history and/or physical examination because evidence of an underlying illness could be obvious and localizing; these causes will not be discussed further. If no cause is apparent on history and physical examination, then the abruptness of onset is particularly important. If the patient very suddenly became clearly restless, intoxications or drug-induced disease abnormalities are of major consideration. Restlessness can occur before more serious signs of intoxication are noticed.

Box 22-1

Causes of Behavior That Can Be Interpreted as "Restlessness" in the Dog or Cat

Intoxication

Iatrogenic (Drugs)*

Antipsychotics
Tricyclic antidepressants
Selective serotonin reuptake inhibitors
Methylxanthines
Sympathomimetics
Prostaglandins
Opioids
Metoclopramide
Antihistamines (especially cats)
Digoxin
Salicylates
Benzodiazepines (excitatory phase)
Dysphoria (drug-induced)

Various Other Toxic Substances*

Metaldehyde
Pyrethrins
Strychnine
Nicotine
Organophosphates/carbamates
Recreational drugs (cocaine, amphetamine)
Select mycotoxins (especially tremorgens)
Latrodectus envenomation
Bufo toad toxicosis

Normal Behavior

Estrous cycle/mating
Periparturient
Pseudopregnancy
Discomfort
  Pollakiuria
  Tenesmus

Altered Mentation/Encephalopathy

Primary CNS Disease

Epileptic aura (pre-ictal)
Tumors
Inflammation
Rabies/pseudorabies
Canine cognitive dysfunction

Metabolic Encephalopathies

Hepatic encephalopathy
Hypoglycemia
Hypocalcemia

Increased Metabolic Rate

Hyperthyroidism (iatrogenic or spontaneous)

Physiologic Distress

Shock
Transfusion reaction
Anaphylactic reaction
Overhydration (iatrogenic)
Dyspnea
Pheochromocytoma
Overheating
Fever
Pruritus

Emotional Distress

Fear
Stress from altered environment or blindness
Pending natural calamity such as earthquake

Pathologic Behavior

Various causes, including various types of anxiety and projection of the owner's personality on the pet
Pain

CNS, Central nervous system.

*These lists are not meant to be comprehensive; rather, they are lists of some of the more common examples.

Intoxication can result after a patient ingests and/or absorbs a toxic substance such as recreational drugs (e.g., amphetamines,[1] cocaine[2]), metaldehyde,[3] chocolate, tremorgens (i.e., mycotoxins from *Penicillium* spp.), zinc phosphide, being envenomated (e.g., black widow spider bite[4]), etc. (see ch. 152-156). Diagnosing one of these exposures requires some suspicion from the history, physical examination, and, in some cases, appropriate toxicological analysis. Intoxication can also refer to an adverse drug effect (see ch. 169). The classic drug-induced cause of restlessness, in small animal practice, is dogs receiving excess thyroid medication. Pets with diabetes mellitus being treated with excess insulin may exhibit restlessness as a sign of hypoglycemia. Sympathomimetics (e.g., ephedrine, phenylpropanolamine, albuterol), metoclopramide[5] (especially if given as a rapid IV bolus), methylxanthines (e.g., theophylline [especially if given with enrofloxacin, which results in higher blood levels], theobromine, aminophylline, caffeine), atropine, lidocaine (when given IV), and prostaglandins are recognized by most veterinarians as being able to cause restlessness. Drug-induced restlessness can be surprising or unexpected because the most common adverse effect of many drugs is drowsiness or sedation (e.g., antipsychotic drugs, analgesic drugs). However, such agents can have paradoxical effects if they "disinhibit" behaviors. Antihistamines, cyproheptadine, benzodiazepines, buspirone, mirtazapine, haloperidol, phenothiazines (especially perphenazine), amantadine, phenobarbital, levetiracetam, and selegiline can produce such unanticipated behavior. Glucocorticoids are recognized for altering behavior in people and this class of drug can occasionally cause restlessness in dogs. If a drug effect is suspected, the drug should be withdrawn and the patient observed for several days. The reader is directed to ch. 151-156, ch. 169, and to textbooks on toxicology and pharmacology for more information on specific toxins and drugs.

The "serotonin syndrome," in particular, is a potentially fatal intoxication in which restlessness is a prominent finding. Tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI) each can cause restlessness. If such drugs are combined with other medications that increase serotonin (e.g., monoamine oxidase inhibitors [MAOI], such as amitraz), restlessness can result.[6,7] Metoclopramide, s-adenosyl-L-methionine, 5-hydroxytryptophan (a nutritional supplement) and dextromethorphan should be used cautiously or better yet avoided in patients receiving a TCA or an SSRI. St. John's wort, which has been used extensively in complementary medicine, should not be used in conjunction with TCA or SSRI drugs. L-deprenyl, alone, is an MAOI that can cause restlessness.

Pain or Discomfort

Once intoxications and drugs are tentatively eliminated as a cause of restlessness, one should consider pain, discomfort, or encephalopathies as possible explanations. Pain can cause restlessness as an acute or gradual and subacute condition (see ch. 126 and 356). Detecting pain varies from being easy to quite difficult, depending upon cause, how stoic the patient is, and how adept the veterinarian is at physical examination (see ch. 2).[8] Diffuse abdominal pain and generalized muscular discomfort can both be especially difficult to localize. Be sure that the patient is not receiving analgesic or anti-inflammatory drugs that make it difficult to detect and localize pain. If the patient is receiving such drugs, they should be discontinued and the patient re-examined several hours or (in the case of anti-inflammatory drugs) days later. One may need to repeat the physical examination several times before deciding whether or not pain is present. The "feline hyperesthesia syndrome" has numerous causes and can be a diagnostic challenge.[9] A complete blood count (CBC) is indicated because inflammation can be responsible for pain. Readers are referred to ch. 126 and 356, and texts

on pain that deal with these problems in more detail.

Metabolic Encephalopathies

The restlessness associated with encephalopathies may be acute or insidious-and-chronic in onset. Metabolic encephalopathies (i.e., hepatic encephalopathy, hypoglycemia, hypocalcemia) may initially produce restlessness as the only discernable clinical sign to an owner. Hence, a serum biochemistry panel (with the blood preferably taken while the patient is displaying the restlessness) is important. As previously mentioned, hypoglycemia is common among diabetics receiving insulin. Restlessness due to hypoglycemia has been commonly described in patients with insulin-secreting tumors, hepatic failure, or hypoadrenocorticism. Measuring ionized calcium instead of total serum calcium may be advantageous. Abdominal imaging (radiographs ± ultrasound) is typically done at this time because such an evaluation will need to be obtained regardless of serum biochemistry findings. The incidental finding of an adrenal mass in a pet described as having episodic restlessness may be consistent with pheochromocytoma.

While hypoglycemia and hypocalcemia are relatively easy to detect, hepatic encephalopathy can sometimes be difficult to diagnose. Congenital portosystemic shunts (PSS), the major cause of hepatic encephalopathy in dogs and probably cats, can occasionally be a major diagnostic challenge (see ch. 284). Some dogs with congenital PSS may first show signs of encephalopathy when they are 7-12 years of age and have normal serum biochemistry profiles, urinalysis, fasting/post-prandial serum bile acids and resting blood ammonia concentrations. A substantial number of dogs with PSS have a normal-sized liver on abdominal imaging and the shunting vessel or vessels may not be identified even by highly experienced ultrasonographers. Therefore, it is sometimes worth re-measuring serum bile acid and blood ammonia concentrations in patients with undiagnosed restlessness. The ammonia tolerance test is thought by some to be more sensitive for congenital PSS than serum bile acids. Protein C determinations may reveal hepatic insufficiency in some patients who are otherwise not obviously hepatic insufficient. In select cases in which no reason for restlessness can be found after extensive testing, advanced imaging (e.g., contrast abdominal computed tomography [CT], nuclear scintigraphy) may be worth considering.

Primary Intracranial Conditions

Restlessness can be the only sign of primary central nervous system (CNS) disease (see ch. 258-268). Cranial nerve deficits, postural deficits, and seizure activity are absent in some animals afflicted with major CNS disease. Restlessness in these patients may have an acute onset or may develop and progress insidiously. In epileptic animals, restlessness can be a pre-ictal event or even the primary seizure event (see ch. 35 and 260). Advanced imaging with cranial magnetic resonance imaging (MRI) scans is preferred. However, contrast CT may be diagnostic. Cerebrospinal fluid (CSF) analysis may be necessary to aid in confirming a diagnosis in some of these patients. Because of cost, MRI and CSF analysis are often among the last diagnostic tests performed and are done when everything else has seemingly been eliminated.

Need for Behaviorist?

Intoxications, pain/discomfort and altered mentation/encephalopathy are particularly important because they may be caused by diseases that can progress rapidly and cause serious injury or death. Only after these have been considered and tentatively or definitively eliminated should restlessness be attributed to behavior and a behaviorist consulted.

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CHAPTER 23

Anorexia

Marnin A. Forman

Client Information Sheet: Loss of Appetite

Anorexia is a common owner concern encountered by veterinarians in small animal practice. Anorexia may be associated with numerous conditions or disease processes. This clinical sign can be both a diagnostic and therapeutic challenge (Figure 23-1), as well as a source of frustration for many owners.

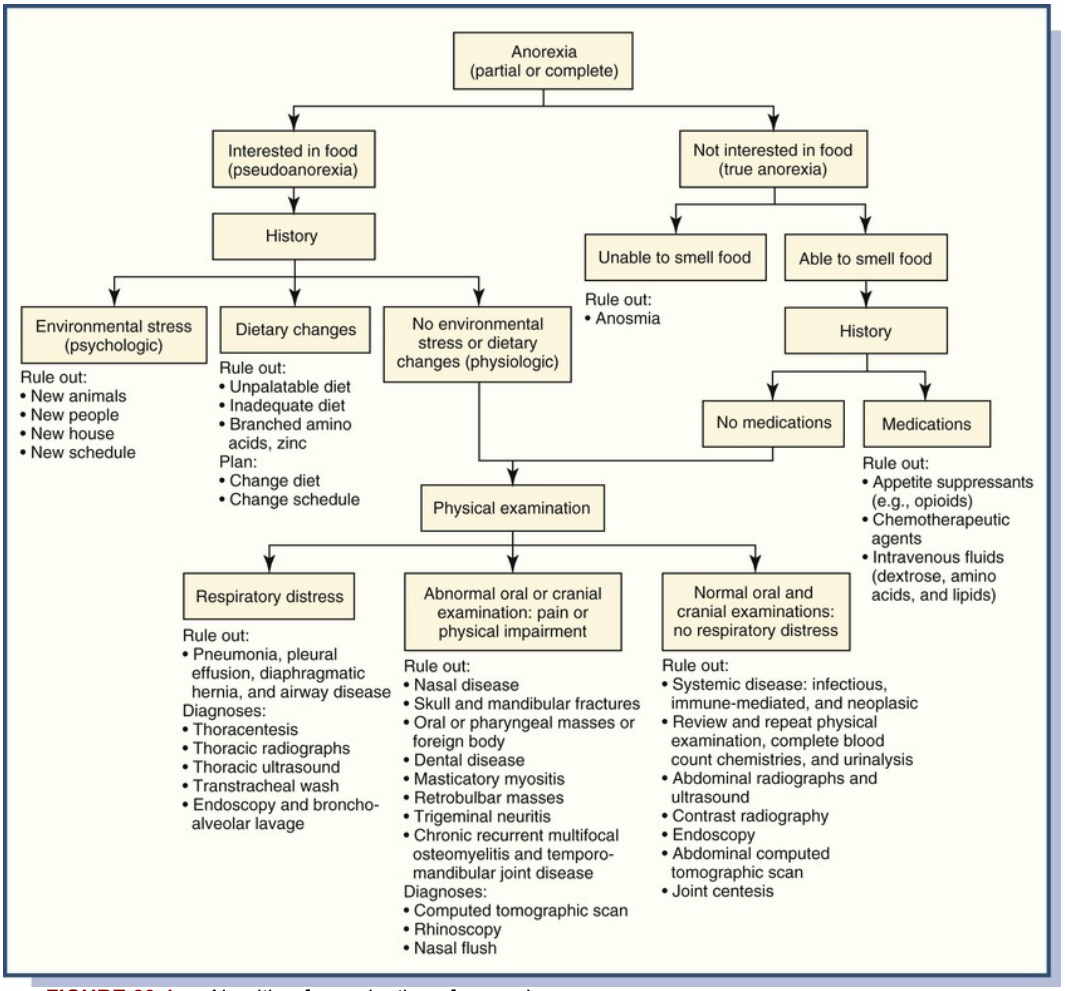


FIGURE 23-1 Algorithm for evaluation of anorexia.

Definitions and Consequences

Anorexia is defined as a lack or loss of appetite for food. The term *hyporexia* has been introduced and may be

a more accurate term to describe a reduction, rather than a complete loss, of appetite.[1] Complicating our understanding of this clinical sign, some disease processes that classically have been described as causing anorexia more accurately produce an inability to eat, rather than a lack of appetite for food. Examples include (there is a myriad of possibilities): (1) severe dental disease; (2) a foreign body in the mouth or pharyngeal area; and (3) an inability to open the mouth due to advanced masticatory myositis.

Considering the challenges in determining and communicating hyporexia vs. anorexia, client-based questionnaires have been evaluated. These questionnaires were evaluated in dogs and cats treated with chemotherapy and focused on two parameters: presence/absence of a normal appetite and the duration of a decreased appetite (1-2 days, 3-5 days, >6 days).[2] It is important to determine the duration of anorexia in an effort to prevent secondary complications. Carbohydrate reserves, such as glycogen, may be exhausted in 3-5 days, resulting in altered metabolism to generate glucose, primarily from fat and some protein, through gluconeogenesis.[1]

Complications of prolonged inadequate nutritional intake are numerous and, for certain disease processes (e.g., feline hepatic lipidosis), can be more serious than the underlying disorder (see ch. 177). Examples of these complications include immune system suppression (decreases in cell-mediated immunity, immunoglobulin synthesis, complement production, and phagocytic activity) and secondary organ dysfunction (decreased hepatic detoxification ability and intestinal alterations).

Causes

Since the causes of anorexia are multiple, an organized diagnostic approach is needed to determine quickly and accurately the causative disorder (Figures 23-1 and 23-2). Obtaining a complete medical, dietary, and environmental history is a critically important first step. Many medications produce anorexia, including antibiotics, antifungals, nonsteroidal anti-inflammatory drugs, narcotic analgesics, chemotherapeutic agents, cardiac glycosides, and diuretics. Identification of nausea, vomiting, labored breathing, or painful behaviors is important. Alterations in diet can lead to, but also can be helpful in treating, anorexia. These may include modifications in flavoring, moisture content, nutrient composition, or feeding location (including physical barriers to eating). Stressful environmental changes, including introduction of new pets and movement to a new household, may cause anorexia.[3]

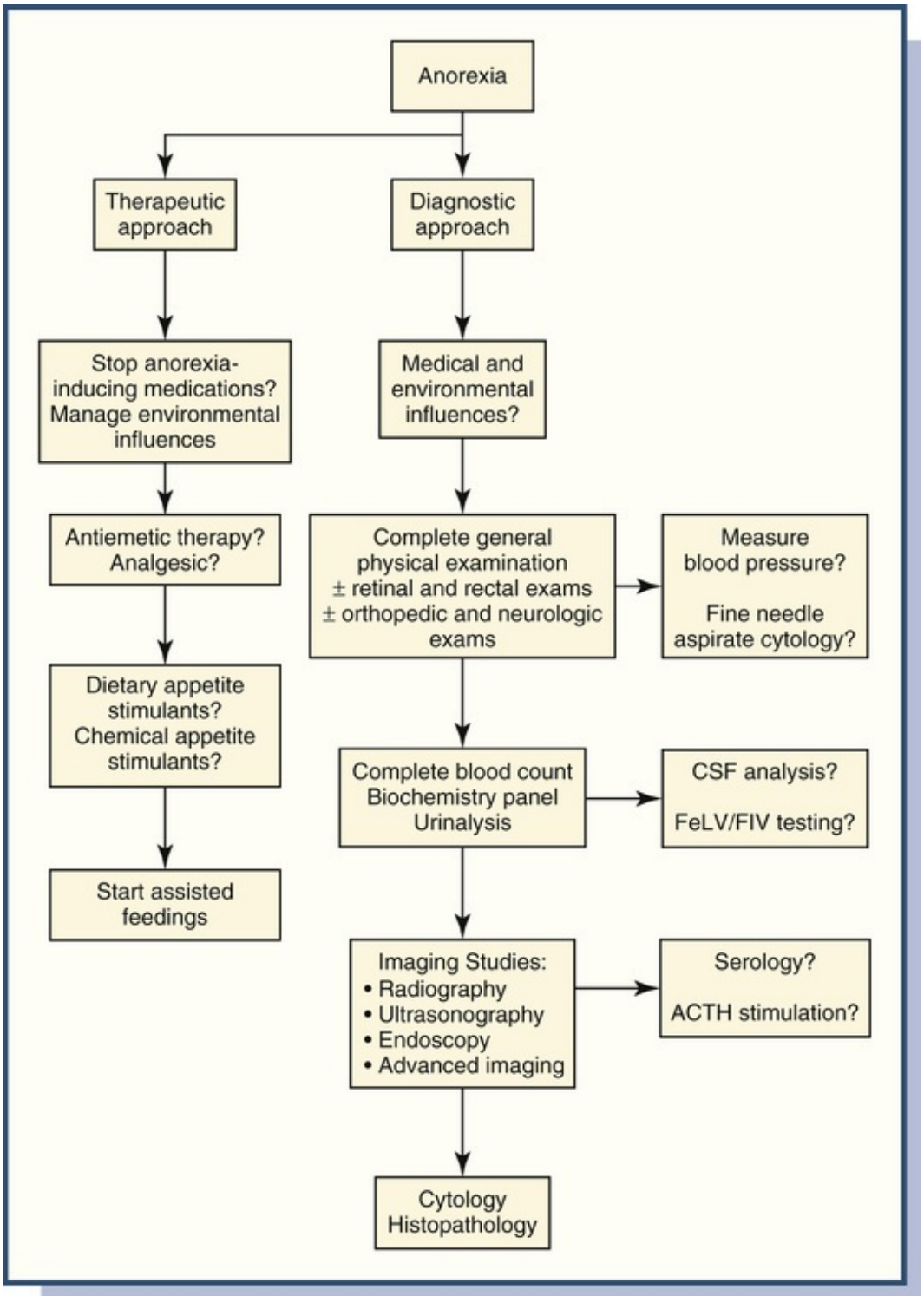


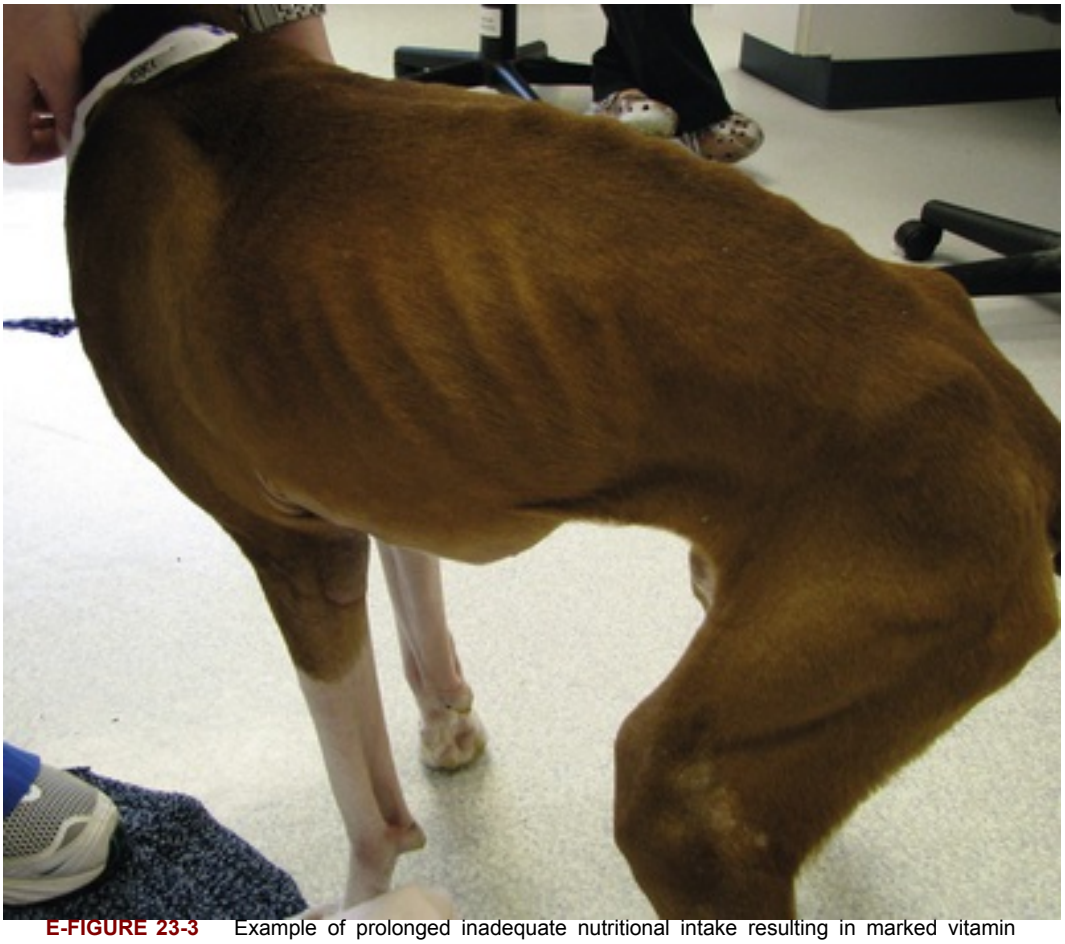
FIGURE 23-2 Therapeutic and diagnostic approach for feline and canine anorexia. *ACTH,* Adrenocorticotropic hormone; *CSF,* cerebrospinal fluid; *FeLV,* feline leukemia virus; *FIV,* feline immunodeficiency virus.

The next step in determining the cause of anorexia is a complete general physical examination, including thorough oral, thoracic, abdominal, rectal, and retinal examinations. In dogs and cats suspected of having anorexia secondary to chronic pain, an orthopedic and neurologic examination should be performed (see ch. 126, 259, 353, and 356). Following these examinations, and in addition to a minimum database (complete blood count [CBC], biochemistry panel, and urinalysis), certain cases require imaging studies (radiography or ultrasonography) or serology. Many causes of anorexia will be identified with these initial evaluations. Additional testing, such as cytology/histopathology, will occasionally be required. It should be understood

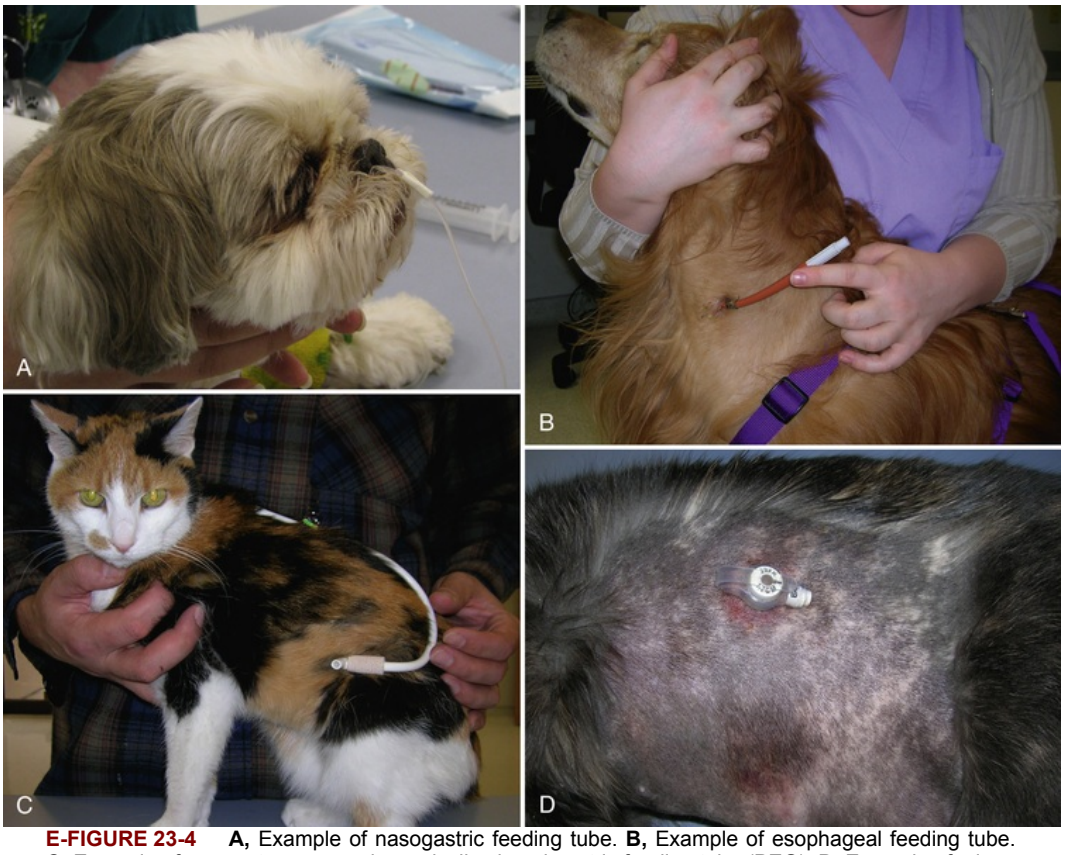
that the purpose of the complete history and physical examination is to identify causes of anorexia that would not be obvious from blood, urine, fecal, or imaging examinations. The dog or cat with heart, liver, kidney, or any other major organ dysfunction could develop anorexia acutely or it could progress over a period of time. Unfortunately, a dog or cat with an oral foreign body will likely have similar clinical problems.

Treatment

Therapy of the anorectic dog or cat should always be directed at understanding and treating the underlying cause. These measures may include modification of anorexia-inducing medications or environmental stressors, instituting definitive therapy (e.g., removal of an abscessed tooth), or appropriate utilization of anti-inflammatory, antiemetic or analgesic medications. During the diagnostic workup of an anorexic patient and prior to determination of the causative disorder, chemical and dietary appetite stimulants can be tried. Such stimulants provide only short-term benefit, if any. However, appetite stimulants are useful during the diagnostic workup or prior to implantation of an assisted feeding device, if one becomes necessary (E-Figures 23-3 and 23-4).



E-FIGURE 23-3 Example of prolonged inadequate nutritional intake resulting in marked vitamin deficiencies.



E-FIGURE 23-4 **A,** Example of nasogastric feeding tube. **B,** Example of esophageal feeding tube. **C,** Example of a percutaneous endoscopically placed gastric feeding tube (PEG). **D,** Example of a low-profile (MicKey Low-Profile Gastrostomy Feeding Tube) gastric feeding tube.

Numerous chemical appetite stimulants have been utilized including benzodiazepines (e.g., diazepam [Valium]), cyproheptadine (Periactin), low-dose propofol (Diprivan), mirtazapine (Remeron), and maropitant citrate (Cerenia). Compared to placebo, mirtazapine administration results in an increase in appetite and body weight in cats with chronic kidney disease.[4] Preliminary research suggests maropitant citrate does not significantly improve appetite or result in weight gain in cats with IRIS stage II and III chronic kidney disease.[5] In the author's practice, the most commonly used appetite stimulant is mirtazapine (feline: 1.875 to 3.75 mg total dose PO daily; canine: 3.75 to 30 mg PO daily).[6,7] Adverse side-effects have been detected at the 3.75 mg dosage in cats, including vocalization, agitation, vomiting, ataxia, and restlessness.[8]

Dietary appetite stimulation broadly involves modification of the environment or the type of food offered. Prior to discussing dietary modifications, it is important to consider learned food aversions. This condition involves the association of food with an adverse event (e.g., vomiting) and can lead to avoidance of potentially beneficial diets in the future. Warming, feeding multiple small meals, and the addition of non-nutritive flavors may help prevent the development of learned food aversions to a new diet. Offering a new diet(s) should be avoided in nauseated pets until the nausea is resolved.

A guideline on when to initiate assisted feeding has not been established and often is dependent on patient factors. It is generally indicated when nutritional intake is less than resting energy requirements (RER) = 70 × (body $\text{weight}_{kg}^{0.75}$) for 3 to 5 days. Even with identification of a causative disease process, assisted feeding can be needed during the recovery process for patient support (see ch. 82 and 170, and see E-Figure 23-4).

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CHAPTER 24

Polyphagia

Sylvie Daminet

Client Information Sheet: Polyphagia (Increased Appetite)

Polyphagia refers to excessive food consumption and can be classified as physiologic (i.e., increased appetite secondary to expected increased caloric use, such as occurs with lactation or a canine performance athlete [see ch. 171 and 173]), pathologic (i.e., secondary to disease) or drug-induced (e.g., glucocorticoid administration). Polyphagia is almost never the sole clinical sign of a disease. Knowing whether weight gain or weight loss has been observed during the period that the pet has been polyphagic should help in determining cause and in developing a diagnostic plan (see also ch. 16 and 19).

Physiology and Pathophysiology

Food intake is controlled by a variety of factors, including gastrointestinal, environmental, and central nervous system (CNS) phenomena. Within the CNS, key circuits regulating energy homeostasis and food intake originate in the hypothalamus and brainstem. The lateral hypothalamic nuclei represent the "feeding center"; their stimulation causes an animal to eat and their destruction usually results in severe, fatal anorexia. Conversely, the ventromedial hypothalamic nuclei are the "satiety center," as their stimulation causes a refusal to eat even highly appetizing food. Ablation of these cells usually leads to polyphagia and obesity. The feeding center is constantly active unless inhibited by the satiety center (e.g., postprandially). The brainstem serves a secondary coordinating role and the nucleus of the solitary tract and area postrema have minor roles.

In the brain, melanocortin peptides, such as alpha-melanocyte-stimulating hormone (alpha-MSH), and the melanocortin-4 receptor (MC4-R), for which alpha-MSH is the agonist, are extremely important in food intake. Neurons that express pro-opiomelanocortin or coexpress agouti-related protein and neuropeptide Y are also vital to food intake.

Gastrointestinal factors affecting consumption of food include degree of gastric distention, rate of gastric emptying, release of gastric hormones, and absorption of nutrients (fatty acids, glucose, and amino acids) (see ch. 170). Gut hormones may act locally on the gastrointestinal tract and on the CNS. Secretion of insulin, glucagon, cholecystokinin, PYY (a peptide related to neuropeptide Y), and pancreatic peptide causes a decrease in CNS-derived hunger signals. Leptin, a polypeptide released from adipose tissue, may also contribute to a sense of satiety. Ghrelin, a peptide secreted primarily by the stomach, stimulates eating. Serum ghrelin concentrations progressively decrease as a meal is consumed and then progressively increase prior to the next meal. Decreased serum concentrations of glucose, amino acids, or lipid metabolites may cause hunger by stimulating neural centers. Pathologic conditions that affect the CNS can increase hunger despite normal energy stores (primary polyphagia; Box 24-1).

Box 24-1

Differential Diagnosis of Primary Polyphagia

Destruction of satiety center
- Trauma
- Mass lesion (e.g., neoplasia)
- Infection/inflammation

Psychogenic

Stress
Introduction of a more palatable diet

Secondary polyphagia exists when hunger is stimulated by non-neural factors and can be caused by an increased metabolic rate, decreased nutrient supply or certain drugs (Box 24-2). An augmented metabolic rate can be physiologic (e.g., pregnancy) or pathologic (e.g., hyperthyroidism). An inability of cellular response to insulin or an absolute insulin deficiency (diabetes mellitus) results in an inability for cells to utilize glucose. Increasing hunger is the result of an inability for cells to "capture and absorb" this "hidden" sugar. The satiety center is insulin-dependent. In lay terms, the body believes it is dying of hunger despite the blood carrying excessive quantities. Certain diseases (e.g., hyperadrenocorticism and liver disease) lead to polyphagia by unknown mechanisms. Polyphagia can also be caused by certain drugs.

Box 24-2

Differential Diagnosis of Secondary Polyphagia

Physiologically Increased Metabolic Rate
- Cold temperature
- Lactation
- Pregnancy
- Growth
- Increased exercise

Pathologically Increased Metabolic Rate
- Hyperthyroidism
- Infection/neoplasia in early stage

Decreased Energy Supply
- Diabetes mellitus
- Malassimilation syndromes
  - Exocrine pancreatic insufficiency
  - Infiltrative bowel disease
  - Parasites
  - Lymphangiectasia

Decreased Intake
- Megaesophagus (congenital)
- Low-calorie diet
- Hypoglycemia

Unknown
- Hyperadrenocorticism
- Portosystemic shunt/hepatoencephalopathy
- Sudden acquired retinal degeneration syndrome (SARDS)

History

When seeing a pet for polyphagia, one of the clinician's objectives is to assess the possibilities of an owner overfeeding or simple gluttonous behavior. While seemingly straightforward, it is not always obvious. In this context, open questions such as "have you noticed a change in food consumption" will avoid leading the owner. Second, the clinician should establish if a change in body weight has occurred, as this has a major impact on differential diagnosis (Figure 24-1).

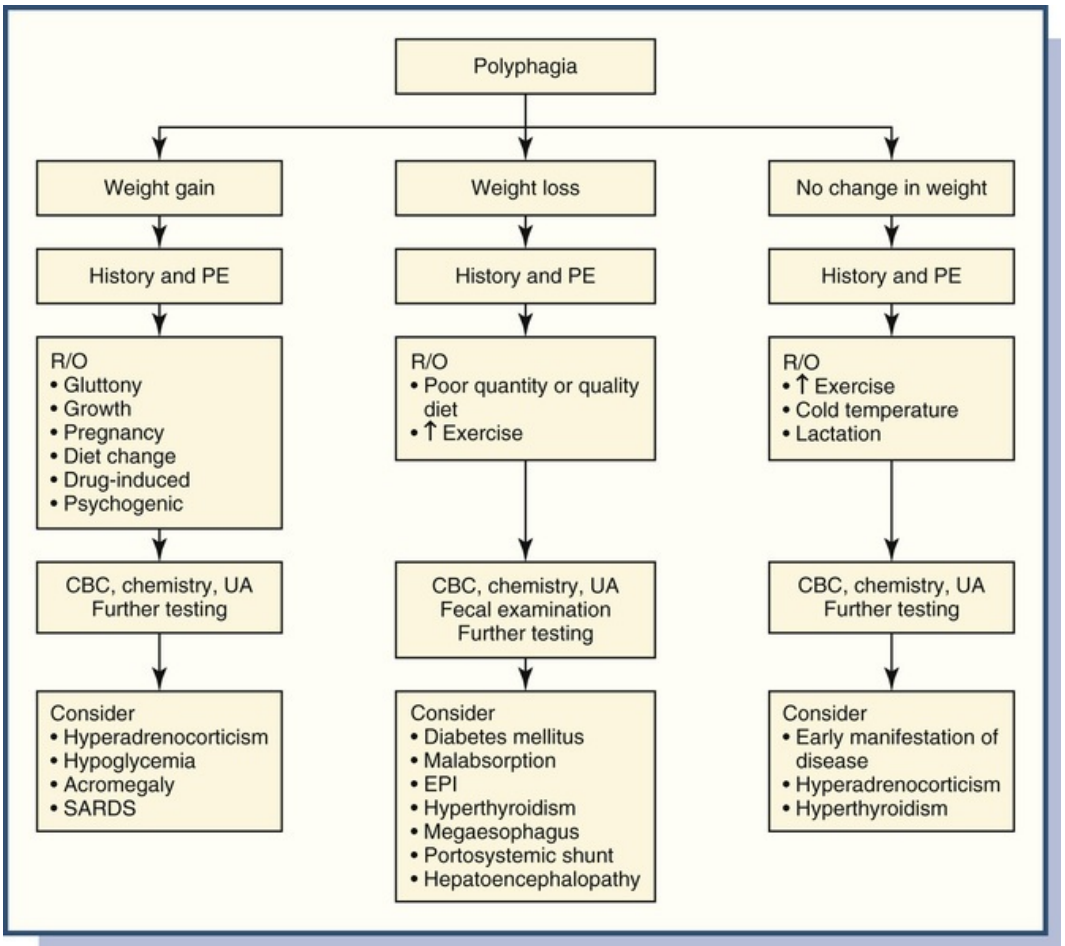

FIGURE 24-1 Algorithm for diagnostic approach to polyphagia. *CBC,* Complete blood count; *EPI,* exocrine pancreatic insufficiency; *PE,* physical examination; *R/O,* rule out; *SARDS,* sudden acquired retinal degeneration syndrome; *UA,* urinalysis.

Primary or drug-induced polyphagia typically results in weight gain. In this scenario, hunger is inappropriately increased and continues each meal despite the pet having consumed an adequate amount of nutrients. Pathologic secondary polyphagia is more commonly associated with weight loss, because the nutrient supply usually does not meet physiologic demands. However, some conditions, such as acromegaly, hypoglycemia caused by an insulinoma, sudden acquired retinal degeneration syndrome (SARDS), and hyperadrenocorticism (HAC), may lead to weight gain. Physiologic polyphagia can result in weight gain (e.g., pregnancy, growth) or weight loss (e.g., lactation, cold environment, increased exercise). Stable weight may be present in the early stages of any of these conditions.

Certain causes of polyphagia may be diagnosed on the basis of the history. Feeding a low-calorie diet, exposure to a cold environment, increased exercise and, for intact females, pregnancy and/or lactation should be ascertained. Polyphagia is commonly associated with phenobarbital or glucocorticoid therapy. Polyphagia has also been observed with other medications (Box 24-3). Psychogenic polyphagia has been noted after introduction of a more palatable diet. Similarly, increased appetite may be a response to a stress, such as introduction of a new pet or child into the household.

Box 24-3

Differential Diagnosis: Drug-Induced Polyphagia

Glucocorticoids
Phenobarbital
Antihistamines
Progestins
Benzodiazepines

Cyproheptadine
Mirtazapine

An animal with primary polyphagia caused by destruction of the satiety center may have a history of trauma or of clinical signs associated with CNS disease (see ch. 259). Depending on the extent of a hypothalamic lesion, upper motor neuron signs may be seen in all four limbs or unilaterally. A midbrain lesion often leads to incessant pacing, circling, and blindness; polyuria/polydipsia (PU/PD) may also be present. Disorders caused by diffuse or multifocal CNS disease may cause other neurological clinical signs.

Historical findings associated with secondary polyphagia can be highly varied. Animals with diabetes mellitus, acromegaly, SARDS, and hyperthyroidism usually have PU/PD. People and cats with HAC do not typically exhibit polyphagia or PU/PD, while these signs are extremely common in dogs with HAC (see ch. 306 and 307). Feline acromegaly is mainly seen in middle-aged to older males, and naturally occurring canine acromegaly is seen almost exclusively in intact bitches under the influence of progesterone (diestrus) (see ch. 294 and 295). In dogs of either sex, progestin administration can lead to acromegaly. Owners of acromegalic pets may note inspiratory stridor or a change in body conformation, such as increased interdental spaces, skin folds, or head size (see ch. 294 and 295). It should also be noted that progestin administration to dogs and cats can increase appetite without causing acromegaly. A multitude of historical details associated with HAC may include abdominal enlargement, persistent panting, failure to regrow hair after clipping, lethargy, and muscle weakness. Animals with SARDS typically have sudden-onset blindness, but PU/PD and polyphagia may precede the blindness. Hyperthyroidism commonly leads to increased activity (rarely depression and lethargy) and gastrointestinal signs (e.g., vomiting and diarrhea) (see ch. 301 and 302).

Hypoglycemia has a number of etiologies. Insulinoma is the most likely to lead to polyphagia, but a few other neoplasms and insulin overdose in any diabetic may also be associated with an increased appetite (see ch. 61 and 303). Dogs and cats with hypoglycemia may exhibit weakness, trembling, ataxia, disorientation and, possibly, grand mal seizures. Malassimilation can be due to a variety of problems, e.g., parasites, exocrine pancreatic insufficiency (EPI), infiltrative bowel disease, and lymphangiectasia (see ch. 276). Each of these conditions may cause large-volume, malodorous, soft stools. EPI is most commonly diagnosed in German Shepherd Dogs <2 years of age (see ch. 292). In older dogs and cats, EPI is rare. When seen, EPI is most commonly associated with chronic pancreatitis. “Infiltrative disease” encompasses processes such as inflammatory, infectious, or neoplastic bowel conditions. Historical details vary according to the underlying disease.

Animals with congenital megaesophagus are often polyphagic, re-eating their regurgitated food (see ch. 273). Although anorexia is more common in animals with a portosystemic shunt (PSS), polyphagia has been reported in as many as 10% of afflicted pets (see ch. 284). Obtundation, vomiting, weight loss, PU/PD, and neurologic signs may also be observed. Polyphagia has been reported rarely with hepatoencephalopathy. With hepatic failure not due to a PSS, icterus is often noticed.

Physical Examination

Physical examination findings in polyphagic animals vary and depend on the underlying condition. With primary polyphagia, neurologic abnormalities such as ataxia and proprioceptive deficits may be present. Complete neurologic and fundic examinations should be performed (see ch. 11 and 259). With acute causes of central blindness, however, the fundus may appear normal.

If unclear from the history, pregnancy may be diagnosed by abdominal palpation and lactation by inspection of the mammary glands. Approximately 80% of cats with hyperthyroidism have a palpable thyroid nodule, and approximately 50% have tachycardia or a gallop rhythm. Hyperthyroidism is much less common in dogs, and they usually have a large palpable cervical mass. Hyperadrenocorticism can have a variety of physical examination findings, including abdominal and hepatic enlargement, muscle wasting, bilaterally symmetric alopecia, cutaneous hyperpigmentation, areas of poor hair regrowth, or calcinosis cutis (see ch. 306). Although animals with HAC may not have weight change, abdominal enlargement may create the impression of weight gain. Physical changes associated with acromegaly include a prominent head, prognathia inferior, stridor, heart murmur and degenerative polyarthropathy. Some acromegalic cats have a normal appearance. In this scenario, assessing photographs of the cat from several years earlier may demonstrate facial changes not otherwise appreciated.

Physical examination in a dog with SARDS may be unremarkable because in the early stages of the disease, the retinas appear normal on examination. Dogs or cats with EPI, insulinoma, megaesophagus, hepatoencephalopathy, or a PSS may have no abnormal physical findings other than changes in weight. In

rare cases, polyneuropathies (especially of the rear legs) are associated with insulinoma. Aspiration pneumonia and chronic cough may accompany megaesophagus. Neurologic abnormalities may be detected in an animal with a PSS, while ascites is uncommon. Neurologic findings associated with hepatoencephalopathy are usually episodic and other examination findings vary with the cause of liver disease. Depending on the cause of malassimilation, the intestines may feel thickened. Lymphangiectasia may lead to ascites.

Other historical and clinical signs are dependent on the cause.

Diagnostic Plan

The first step in diagnosis is to ascertain if there has been a change in body weight (see Figure 24-1). After as many differential diagnoses as possible have been ruled out on the basis of the history and physical examination, further testing may be warranted: complete blood count (CBC), serum biochemistry profile, and urinalysis.

To diagnose primary polyphagia, a complete neurologic examination should be performed and any abnormalities localized (see ch. 259). A cerebrospinal fluid analysis or diagnostic imaging such as computed tomography (CT), or magnetic resonance imaging (MRI) scan, may be necessary. Insulinoma usually can be confirmed by paired blood glucose and insulin serum concentrations when the animal is hypoglycemic (see ch. 303). The diagnosis of SARDS can be made on the basis of appropriate history, physical examination findings, a CBC, biochemistry and urinalysis that rules out other causes, and, if necessary, an electroretinogram (ERG). For dogs or cats suspected of HAC, adrenal testing should aid in confirming or refuting a diagnosis (see ch. 306 and 307). Diagnosis of acromegaly can be difficult because of the lack of a commercial assay for growth hormone, but measurement of insulin-like growth factor-I (IGF-I) may be helpful (see ch. 294 and 295). The history, together with conformational changes if present, can provide evidence of the underlying disease. Most acromegalic cats have insulin-resistant diabetes mellitus, and imaging of the pituitary may reveal the growth hormone–secreting tumor.

Table 24-1 lists common causes of pathologic polyphagia in cats and dogs, including accompanying PU/PD, diarrhea and weight changes. Polyphagia, PU/PD, and weight loss are classic clinical signs for diabetes mellitus and any animal with these clinical signs should have urine and blood assessed for glucose concentrations. Diabetic dogs and cats have glycosuria and persistent hyperglycemia. Another cause of polyphagia, PU/PD, and weight loss is hyperthyroidism, a common condition in older cats but uncommon in dogs. Hyperthyroidism can usually be diagnosed with a single serum thyroxine measurement (see ch. 301 and 302).

TABLE 24-1

Common Causes of Pathologic Polyphagia in Cats and Dogs Including Accompanying PU/PD, Diarrhea and Weight Changes

DISEASE	SPECIES	EXPECTED ACCOMPANYING SIGNS
Diabetes mellitus	cats and dogs	PU/PD, weight loss
Hyperadrenocorticism	dogs > cats	PU/PD, weight gain possible
Hyperthyroidism	cats > dogs	PU/PD, weight loss
Acromegaly	cats > dogs	PU/PD, weight gain
Malabsorption syndromes	cats and dogs	Diarrhea, weight loss
Exocrine pancreatic insufficiency	dogs > cats	Diarrhea, weight loss
Insulinoma	dogs > cats (rare in cats)	Weight gain

PU/PD, Polyuria/polydipsia.

"Malassimilation syndromes" cover a myriad of differential diagnoses (see Box 24-2). Weight loss associated with polyphagia can be caused by intestinal parasitism. If parasites are suspected, fecal examinations and/or therapy with anthelmintics are recommended. If deworming does not resolve the problem, further investigation is needed. Protein-losing enteropathies can be associated with hypoalbuminemia and hypoglobulinemia. Depending on the suspected cause, measurement of serum for

folate, cobalamin or fecal alpha-1 protease inhibitor concentrations may be diagnostic. Abdominal radiography, ultrasonography, and/or biopsy either by endoscopy or exploratory surgery may also be considerations. For verification of EPI, fasted serum trypsin–like immunoreactivity (TLI) should be determined (see ch. 292).

Megaesophagus can be diagnosed with thoracic radiographs. Further testing is necessary to determine cause. Measurement of preprandial and postprandial serum bile acid concentrations can document hepatic dysfunction, but a biopsy may be required to identify the cause. Ultrasonography, CT or a radionuclide scan may be used to visualize a PSS.

If a disease is in the early stages, weight change may not yet have occurred and the list of differentials is more difficult to narrow down. However, a thorough history and physical examination combined with routine CBC, serum biochemistry, urinalysis and fecal parasitology can lead to a direct diagnosis in many conditions.

Management

The management of polyphagia depends on the cause. Physiologic causes of polyphagia are transient. If the condition is drug-induced, polyphagia may be temporary, as is usually seen with anticonvulsants. Psychogenic polyphagia may be corrected by removing the instigating element, if possible, and/or by behavioral therapy.

With pathologic polyphagia, treatment of the underlying disease will resolve the polyphagia in most cases. In some pets, weight management might be necessary, especially if the underlying disease leading to weight gain cannot be effectively treated or if the polyphagia is drug-induced. Small meals and use of low-calorie, high-protein and high-fiber foods can aid in obtaining satiety and prevent obesity. In cases of SARDS, polyphagia usually is self-limiting.

Suggested Readings

Laflamme D. Polyphagia and hyperphagia. Section II approach to clinical signs in gastrointestinal disease. Washabau R, Day MJ. *Canine and feline gastroenterology*. Elsevier: St Louis; 2012:148–150.

Stuckey JA, Pearce JW, Giuliano EA, et al. Long-term outcome of sudden acquired retinal degeneration syndrome in dogs. *J Am Vet Med Assoc*. 2013;243:1426–1431.

CHAPTER 25

Body Odors

Darren Berger

Client Information Sheet: Common Causes of Body Odor in Dogs and Cats

A classic definition of odor is a perceived sense through olfaction, which is stimulated via volatile chemical compounds and may be interpreted as pleasant or unpleasant. However, many people fail to take into consideration that the situation, a person's culture, and his or her experiences are important factors that determine individual perception of an odor.[1] Besides these contextual references, inter-individual variations in odor sensitivity or thresholds exist. These inter-individual variations have long been observed by olfactory researchers and are influenced by age, sex, personality, cognitive function, and health status.[2-4] These differences in odor threshold, sensitivity and perception are important to comprehend, as clinicians may not be able to detect the malodor that a client is describing or vice versa even when a medical condition is present. A relevant clinical example exists in patients with diabetic ketoacidosis, where only a percentage of people can detect the presence of ketones through olfaction, and those that do may describe the odor differently as either fruity or like nail polish remover. As a result of these differences in perception, many terms are used for describing odors, such as aroma, fragrance, scent, stink, stench, reek, malodor, or essence. Understanding these terms and their connotations can be useful to clinicians in picking up subtle clues from clients regarding possible concerns and in appropriately conveying messages to owners in a delicate or forthright manner.

Addressing the Body Odor Issue

Many factors contribute to the overall odor of an animal. It is important to be aware of the factors that can contribute to the complaint of a malodorous pet so that the clinician can determine if it is the result of a (1) normal pet, (2) a healthy pet with an obvious non-medical cause, or (3) the result of a pet with an underlying disease. Regardless, it is the clinician's duty to either correct the underlying disease process or make the pet's odor more acceptable to the owner. The first step in addressing a patient with a primary complaint of malodor is to obtain a thorough history. Most owners are familiar with the normal odors of their animal. This awareness of the scent of their pets was highlighted by a recent investigation that demonstrated that 89% of participants were able to distinguish their dog's odor from that of another dog.[5] Given this evidence, and clinical experience, many owners are aware of changes in the normal odor associated with their pets, when it occurred, and events that may have been associated with the change. This information is very helpful in differentiating between the various possibilities for a pet's presentation.

Once a thorough history has been acquired, all patients require a complete physical examination, which includes actually smelling the patient from snout to tail to identify if an abnormal odor is present. Many patients that present for abnormal odor will have *Malassezia* dermatitis or an active pyoderma. To help identify these patients, the clinician should pay particular attention to subtle clinical signs and body locations. Clinical signs suggesting a secondary infection is present include: erythema, alopecia, abnormal or excessive exudate, papules, pustules, epidermal collarettes, or excessive scale formation. Specific anatomic locations where meticulous attention should be directed include: the ear canals, skin and facial folds (Figure 25-1), mandibular lip folds (Figure 25-2), around collars, interdigital areas (Figure 25-3) and the perivulvar and perianal regions.

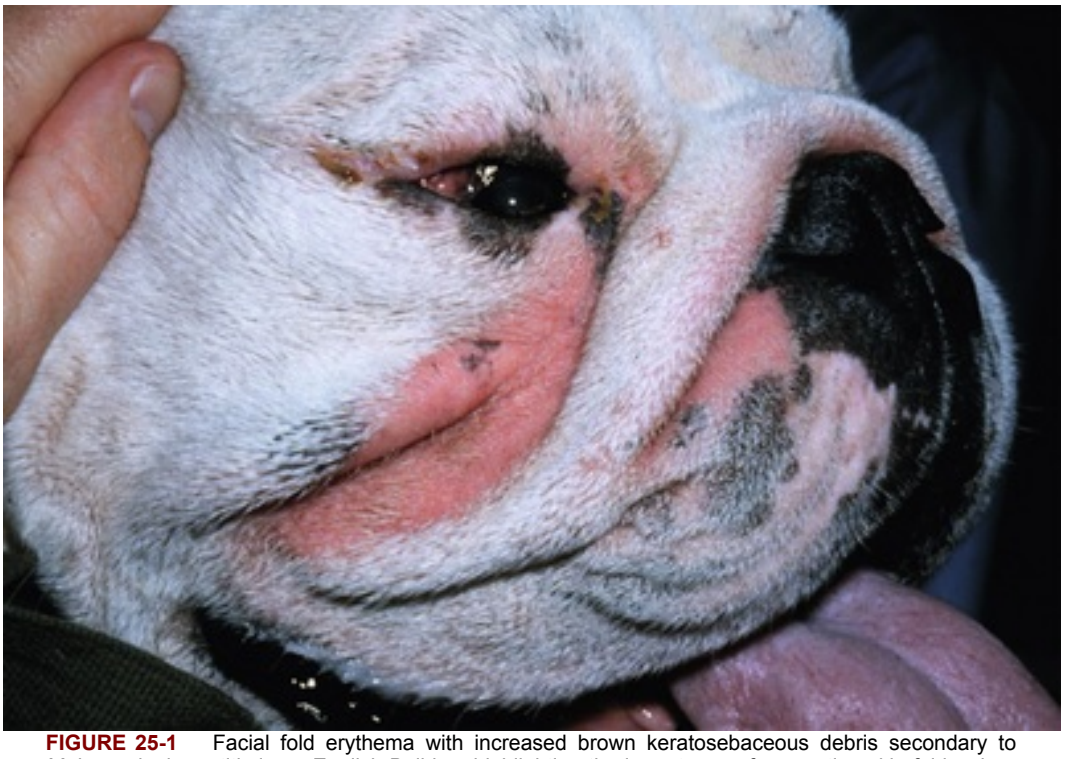

FIGURE 25-1 Facial fold erythema with increased brown keratosebaceous debris secondary to *Malassezia* dermatitis in an English Bulldog, highlighting the importance of separating skin folds when present in a patient who is presented for a complaint of malodor. (Photo courtesy James Noxon, Iowa State University, Ames, IA.)

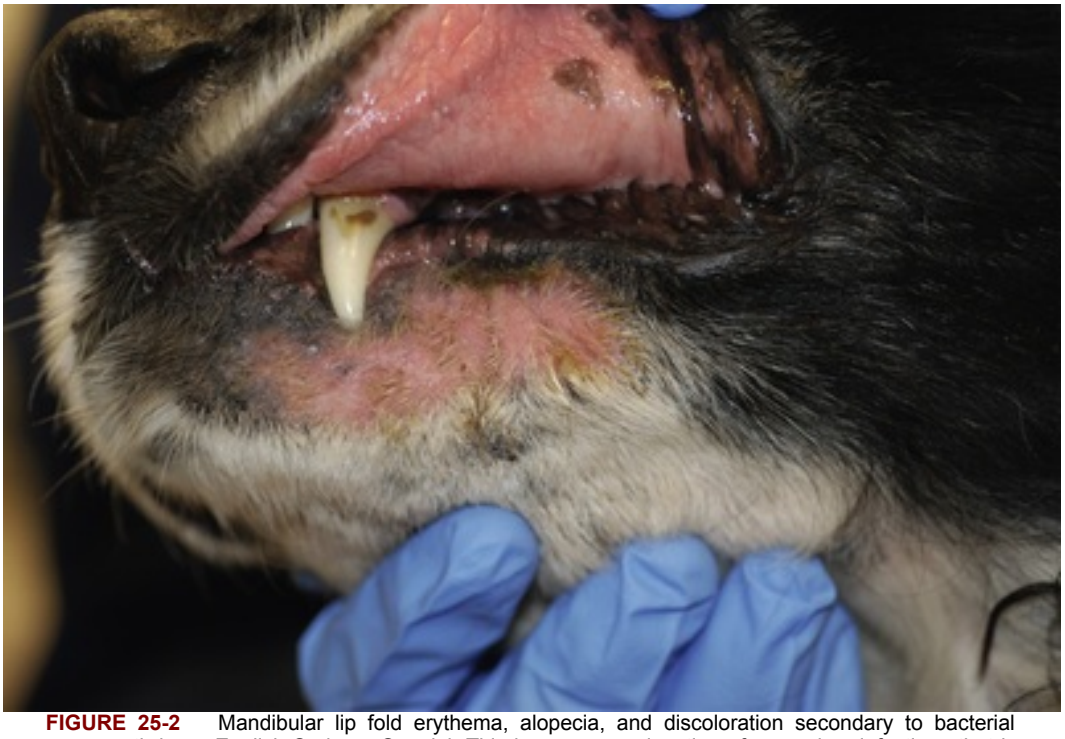

FIGURE 25-2 Mandibular lip fold erythema, alopecia, and discoloration secondary to bacterial overgrowth in an English Springer Spaniel. This is a common location of secondary infections that is easily overlooked, which results in facial pruritus and the misconception of odor originating from the oral cavity.

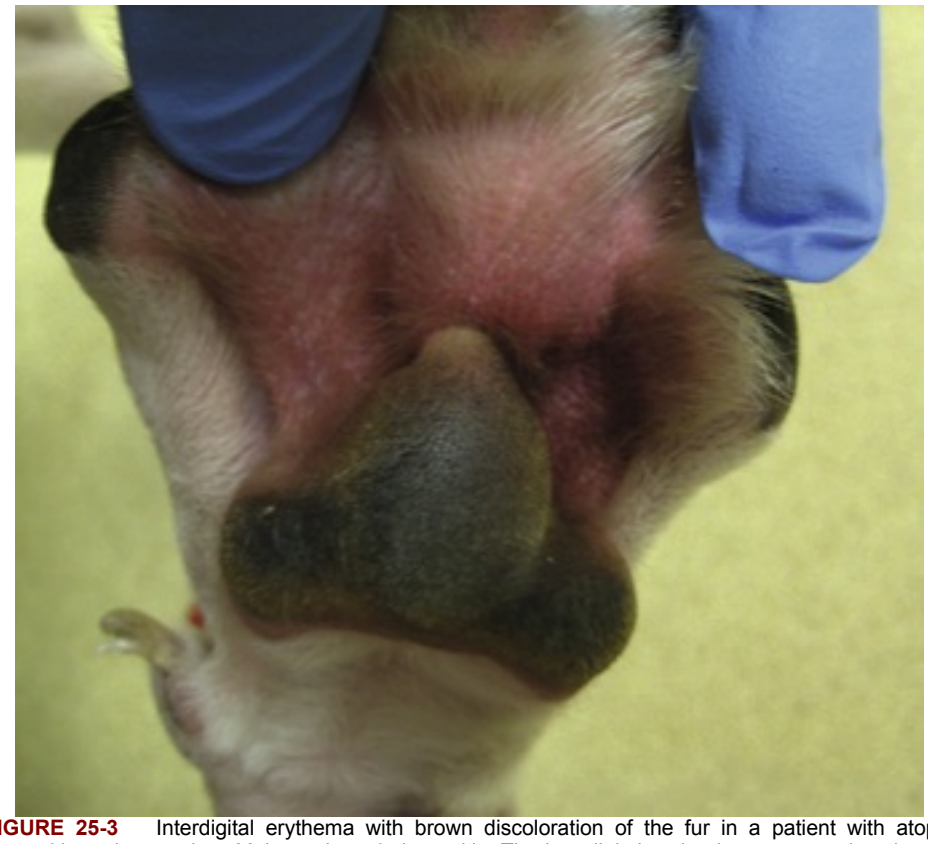

FIGURE 25-3 Interdigital erythema with brown discoloration of the fur in a patient with atopic dermatitis and secondary *Malassezia* pododermatitis. The interdigital region is a common location for secondary microbial overgrowth in patients with predisposing conditions that can result in patient malodor.

Normal Pet Odors

Natural body odor is the result of epidermal lipid production, gland secretions (sebaceous, epitrichial, atrichial, ceruminous, and anal sacs) and their decomposition by lipase-producing bacteria into unsaturated and aromatic fatty acids, which produce the perceived unpleasant scent.[6] Glandular density is highest near mucocutaneous junctions, paws, dorsal neck, rump, and specific portions of the tail and these are areas where normal odors predominate.[7] Natural pet odor also is dependent on the species, breed, age, sexual status, and overall health of the individual. Specific examples of a pet's signalment impacting its natural odor include: members of the hound family having a muskier odor; dogs with oilier coats (e.g., Labrador Retrievers) having increased odor; intact male cats compared to their castrated counterparts; animals with excessive skin folds (e.g., Mastiffs); or those that drool excessively, such as St. Bernards and Newfoundlands.[7]

If the pet is deemed healthy with no obvious abnormal odor, client education is required along with management strategies to improve or mask what the client finds offensive. This may require a change in grooming habits or frequencies, shampoo choice, use of conditioners, and fragrance sprays. This would be similar to the approach upon which the entire cosmetic industry is built, and in some cases, it is simply what the client wants. In other circumstances this may not be enough and a second choice of topical agents with different ingredients may be needed, as some owners will find the constituents of products noxious. Finally, diet has been suggested to influence a pet's odor, specifically by proponents of raw dog foods, although studies documenting this are lacking.[8] Despite this, the most common anecdotal report of diet contributing to body odor has been observed with dogs predominantly fed fish-based diets.[9] In cases where no cause can be determined, it may be worth changing the diet to investigate whether alternative ingredients improve the animal's odor.

Normal Pet with an Obvious Non-Medical Cause

The second category encountered is patients who lack a primary medical condition but an obvious cause for

the odor exists. One example would be in patients with long, dense, or corded hair coats that are not maintained or allowed to dry properly. This is seen with dogs that swim frequently, drool excessively, or in animals whose hair coat needs more intensive grooming (e.g., Old English Sheepdogs). In all of these circumstances, client education, improved grooming habits, or shaving the hair coat will eliminate the problem. However, it is important to keep in mind that shaving the hair coat may create a more significant cosmetic issue for some clients.

In other cases, an animal's behavior may be the source of the abnormal odor. This is particularly true with animals that roll in feces or decaying material. These patients require changes in grooming or more frequent bathing similar to that of normal patients without identifiable causes. Other pets may be easily frightened and liberally express their anal sacs. Dietary changes, behavior modification, or surgical excision may be required in these instances. Finally, pets may come across wildlife such as skunks, and as dogs and skunks do not mix, the dog may be sprayed during the encounter. It is important to note that it may take days to weeks to completely eliminate the skunk odor and commercial as well as home remedies are available to address this situation in these patients.[7,9]

Primary Medical Condition Resulting in Pet Malodor

The vast majority of patients presenting with a complaint of body odor are those with a primary medical condition or skin disease. These conditions are outlined in Figure 25-4 and Box 25-1. Thorough historical information, physical examination, and appropriate diagnostics should result in identification of the underlying condition and secondary problems. Detailed discussion and management of these causes are beyond the scope of this chapter. For specific management recommendations of these conditions, the author encourages the reader to refer to other chapters within this textbook, or if required, *Muller & Kirk's Small Animal Dermatology*. Regardless of the cause, targeted therapy against the primary condition and secondary infections present is required to resolve the issue and prevent recurrence.

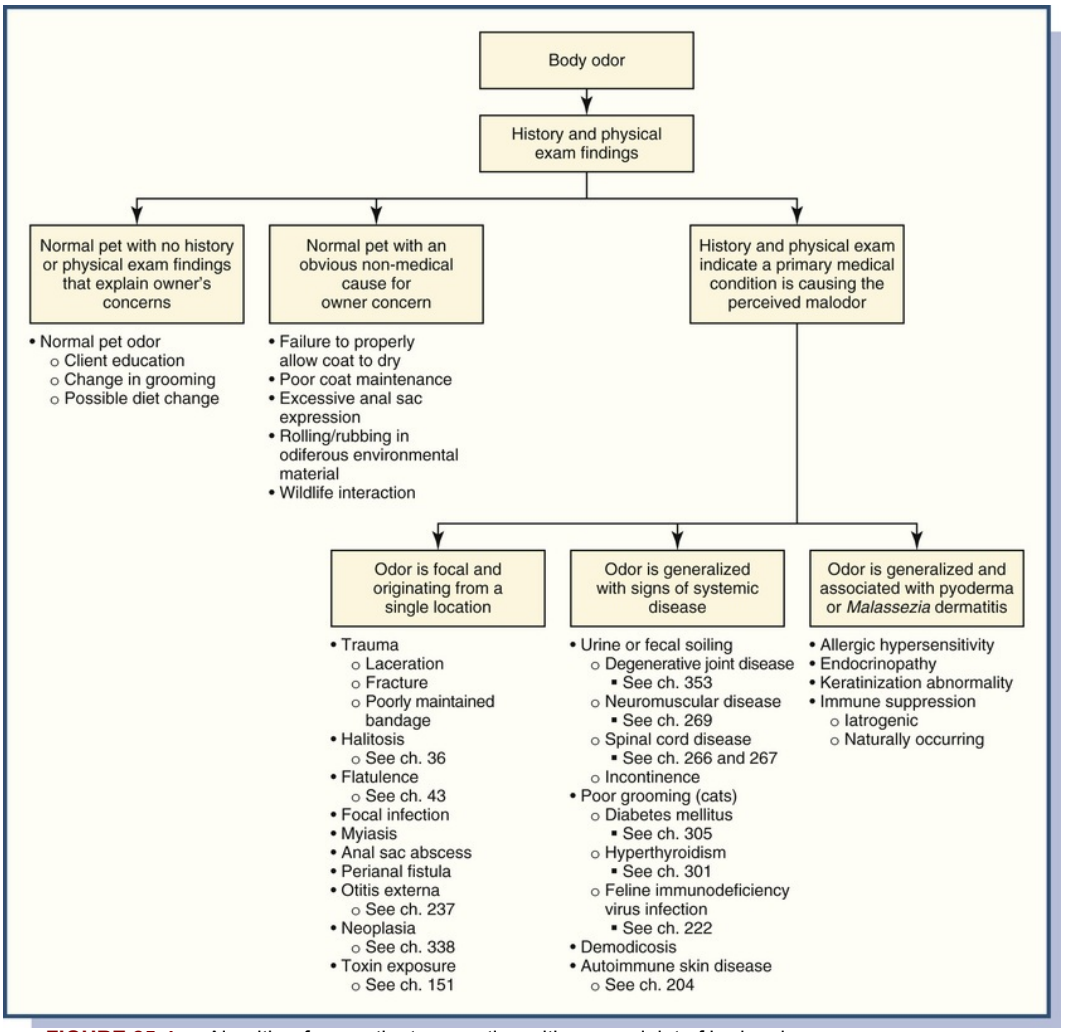

FIGURE 25-4 Algorithm for a patient presenting with a complaint of body odor.

Box 25-1

Common Conditions That Predispose to the Development of Recurrent Secondary Infections Such as Pyoderma, *Malassezia* Dermatitis, and Otitis Externa

Allergic Hypersensitivity

Atopic dermatitis
Cutaneous adverse food reaction
Parasitic hypersensitivity

Endocrinopathy

Hypothyroidism
Hyperadrenocorticism

Keratinization Abnormalities

Primary seborrhea
  American Cocker Spaniel
Feline acne
Ichthyosis
  Golden Retriever, American Bulldog

Miscellaneous Diseases

Sebaceous adenitis
  Standard Poodle, Akita, Vizsla
Feline idiopathic facial dermatitis
  Persian and Himalayan cats

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Cardiorespiratory

OUTLINE

Chapter 26 Coughing
Chapter 27 Sneezing and Nasal Discharge
Chapter 28 Tachypnea, Dyspnea, and Respiratory Distress
Chapter 29 Epistaxis and Hemoptysis
Chapter 30 Syncope

CHAPTER 26

Coughing

Luca Ferasin

Client Information Sheet: Cough

Cough is an important physiological function to preserve the normal health of the respiratory tract, which operates by rapidly expelling harmful substances, such as foreign bodies, excessive mucus, or debris, from the upper airways. However, cough is not only a defensive mechanism. It can also represent an important sign of an underlying disease or even a detrimental symptom when it becomes persistent.[1] Occasionally cough can cause syncope, urinary and fecal incontinence, muscle pain, and exhaustion.[2]

Coughing Mechanisms

The typical coughing reflex (CR) is characterized by an initial deep breath, followed by a rapid and powerful expiratory act against the closed glottis and finally opening of the glottis, closing of the nasopharynx and forceful expiration through the mouth, accompanied by a typical vocalization caused by the vibration of the vocal cords. Cough can be evoked by stimulation of coughing receptors localized in the larynx, trachea, or bronchi, whereas irritation of smaller bronchi, bronchioles, and alveoli does not elicit coughing.[3,4] A second important defensive mechanism, similar to cough, is the expiration reflex (ER). This is induced by stimulation of the vocal cords or trachea and consists of forced expiratory effort against a closed glottis, which is not preceded by a particularly deep inspiration.[4] This reflex is often observed in dogs and sounds like a "huff" sound. The distinction between CR and ER is important since their physiological functions are different. True cough will draw air into the lungs to augment the force of the subsequent expulsive phase, promoting clearance of mucus and foreign material from trachea and bronchi. Conversely, the ER from the larynx will prevent the entry of noxious material into the airways.[2] Therefore, the presence of CR should suggest lower airway disease, such as bronchial disease (Video 26-1), whereas ER is more commonly associated with upper airway irritation (Video 26-2). Finally, the sneezing reflex is also similar to coughing but it is evoked from the nasal mucosa and its expulsion phase occurs mostly through the nose, in order to eliminate the provoking stimulus (see ch. 27).[5,6] Hybrid responses are possible and are characterized by a mixture of coughing and sneezing features (Video 26-3). When these reflexes are ineffective, such as in muscle weakness, laryngeal paralysis, bronchomalacia, and chronic bronchitis, recurrent pneumonia can occur.[2]

History

History alone rarely provides sufficient information to determine the clinical reasons for coughing. Nevertheless, a careful history should include questioning of the duration, characteristics and timing of the cough. Pets' owners often fail to provide a correct terminology or accurate description of the symptom and therefore, audio-video recording of their coughing pet can be invaluable, even when obtained with a mobile phone camera. Very often, the notorious "nocturnal cough" is reported simply because the pet sleeps in the owner's bedroom, while the pet may be unsupervised during the day. Finally, severity of coughing may be perceived differently by different pets' owners, and therefore appropriate questions should be asked once the problem has been identified. Classification of cough based on its duration is rather arbitrary. A cough lasting less than 3 weeks is termed "acute." It usually results from viral upper respiratory tract infection (e.g., kennel cough) and often resolves spontaneously, although post-infective cough can sometimes persists for a longer period of time. A cough present for at least 8 weeks is defined as "chronic" and clinicians should also

recognize an overlap period of between 3 and 8 weeks.[7] Cough can be classified as "productive," "wet" or "chesty" when it is associated with expectoration of large amounts of sputum, often swallowed after coughing. Conversely, a "dry," "honking" or "hacking" cough is characterized by little or no production of phlegm. However, there are substantial overlaps between these two forms. Furthermore, character and timing of a cough are not diagnostically helpful since diagnostic approach and outcome are almost identical, whether the cough is productive or not. A history of hemoptysis (coughing up blood) should prompt urgent investigations since it could be the first clue to the presence of lung tumors, bleeding disorders, pulmonary thromboembolism, heartworm disease, or lungworms. Home environment and animals' habits may also provide useful elements for a successful diagnosis. Indoor pets can be exposed to compounds that could cause coughing, such as dust mites, molds, fireplace ash, dandruff, litter tray dust, sprays, deodorants, and cigarette smoke. Histological bronchial changes have been reported in several animal models following experimental chronic cigarette smoke inhalation, and biochemical evidence of exposure to passive cigarette smoke has been demonstrated both in privately owned dogs and cats.[7-10] History may reveal exposure to boarding kennels, grooming parlors, dog parks and general contact with other dogs in the few days preceding the onset of an acute cough suggesting infectious disease, especially in young unvaccinated animals. Coughing pets living in endemic areas for *Dirofilaria immitis* (heartworm disease), *Angiostrongylus vasorum* (French heartworm) or *Aelurostrongylus abstrusus* (cat lungworm) should be tested for these parasites. Geographical presence of these parasites changes rapidly and it is important to know their potential prevalence in different regions.[11]

Differential Diagnosis for Coughing

Cough is mostly induced by stimuli originating in the airways, with upper airways more frequently involved than lower airways. Dynamic and static airway collapse is one of the most common causes of coughing in dogs and this disorder can affect different portions of the trachea, as well as major bronchi. The condition is mostly associated with weakness of the tracheal or bronchial wall, in isolated tract or extended tracts (i.e., tracheomalacia, bronchomalacia, and tracheobronchomalacia). Dogs affected by airway collapse typically present with a persistent, dry, paroxysmal "honking" cough sometimes associated with varying degree of dyspnea[12,13] (see ch. 241). One of the most common causes of cough in cats is chronic lower airway inflammatory disease, which may originate from multiple etiologic causes. Affected cats commonly present with paroxysmal coughing, which resembles hacking up hairballs and can inadvertently lead to gastrointestinal investigations rather than respiratory workups. Clinical signs can often escalate into bronchospasm associated with severe dyspnea (asthmatic crisis)[14] (see ch. 131, 139, and 241).

Parenchymal conditions, such as pneumonia alone, may not induce cough unless the noxious process extends to the airways (e.g., bronchopneumonia and sputum production). Similarly, converse to inaccurate former reports and opinion, cardiogenic and non-cardiogenic pulmonary edema does not cause coughing.[15,16] This can be easily extrapolated by the fact that cough reflex is not present in the deeper respiratory tract. Patients with pulmonary edema will rather present with tachypnea/dyspnea, although they may occasionally cough if there is concomitant airway irritation or if the amount of fluid in the alveolar space is severe enough to reach higher airways and stimulate coughing receptors, as occasionally observed in large-breed dogs with fulminant pulmonary edema. Cardiomegaly, in particular left atrial enlargement (LAE), is associated with an increased risk of cough in dogs with chronic degenerative mitral valve disease (MMVD), and there is a ten-fold increased risk of coughing if LAE and airway disease coexist.[15] There seems to be a weak association between LAE and airway collapse in dogs with MMVD and therefore underlying airway inflammation might represent the major cause of coughing in such patients.[17]

Gastroesophageal reflux disease (GERD), postnasal drip syndrome (PNDS), and use of angiotensin-converting enzyme inhibitors (ACEi) or beta-blockers are common causes of coughing in people but are only occasionally reported in animals.[18-25] Risk factors for cough are listed in Table 26-1.

TABLE 26-1

Risk Factors for Inducing Cough in Dogs and Cats

ETIOLOGY	DOGS	CATS
Inflammatory		

Rhinitis	M	M
Sinusitis	M	M
Pharyngitis	L	L
Tonsillitis	L	L
Laryngitis	H	H
Tracheitis	H	H
Bronchitis	H	H
Pneumonia	L	L
Bronchopneumonia	H	H
Lung abscess	M	M
Allergic		
Asthma (with bronchospasm)	X	H
Eosinophilic bronchopneumopathy	H	H
Degenerative		
Laryngeal paralysis	M	M
Tracheal collapse	H	H
Bronchomalacia	H	H
Bronchiectasis	H	H
Traumatic		
Near-strangulation	H	H
Near-drowning	H	H
Inhaled foreign body	H	H
Chest contusion	M	M
Cardiovascular		
Non-cardiogenic pulmonary edema	L	L
Cardiogenic pulmonary edema	L	L
Cardiomegaly without concomitant airway dz	L	L
Cardiomegaly with concomitant airway dz	H	L
Pericardial effusion	M	L
Pleural effusion	M	M
Pulmonary embolism	M	M
Neoplastic		
Laryngeal tumor	H	H
Tracheal tumor	H	H
Lung tumor	M	M
Mediastinal tumor	H	H
Gastrointestinal		
Gastroesophageal reflux	M	L
Tracheoesophageal fistula	H	H
Bronchoesophageal fistula	H	H
Dysphagia	H	H
Parasitic Infections		
Larval migration of intestinal nematodes	M	M

Dirofilaria immitis	M	H
Angiostrongylus vasorum	H	X
Aelurostrongylus abstrusus	X	M
Other lungworms	M	M
Fungal Infections	M	M
Iatrogenic		
ACE-inhibitors	L	X
Beta-blockers	L	X

dz, Disease; *H*, high risk of inducing coughing; *L*, low risk of inducing coughing; *M*, moderate risk of inducing coughing; *X*, no risk of inducing coughing or condition not reported in this species.

Clinical Assessment

The physical examination of the patient with cough may reveal a potential underlying cause. Nasal and ocular discharge accompanied by frequent licking and swallowing could be an indication of PNDS associated with rhinitis and sinusitis. A cough easily elicited by gentle tracheal or thoracic palpation suggests that coughing receptors are already stimulated by an underlying condition where the pathologic stimulus is not sufficient to reach a threshold for continuous coughing (Videos 26-3 and 26-4). Therefore, the widely used concept of "positive tracheal pinch" is incorrect because this maneuver does not provide a "positive/negative" response.[2] Auscultation over the larynx and trachea can reveal stridors or clicks in coughing animals with laryngeal paralysis or tracheal collapse. Thoracic auscultation often reveals stridors, rhonchi, crackles and wheezes, which are suggestive of airway disease at different levels in the respiratory tract. Inspiratory crackles can be present in coughing dogs with chronic interstitial lung disease (ILD), especially in West Highland White Terriers and other terrier breeds.[26] An association between interstitial lung disease and coughing has also been reported in cats.[27] The exact mechanism of cough in ILD is elusive but may be related to up-regulation of lung airway sensory receptors, increased cough sensitivity, and chest wall vibration.[28] Although crackles are commonly reported in the veterinary literature as an indication of alveolar pulmonary edema, the most likely mechanism of crackle generation is sudden airway closing during expiration and sudden airway reopening during inspiration, as happens more commonly in pneumonia and ILD.[29,30] Furthermore, rhonchi associated with bronchial disease can be mistakenly described as crackles by some clinicians. Chest percussion can reveal a horizontal line of dullness consistent with pleural effusion, sometimes associated with cough both in dogs and in cats. Thoracic masses, often responsible for cough by mechanical compression, can sometimes be identified by chest percussion.

Clinical Investigations

Laboratory tests should include differential white cell count, which may reveal neutrophilia in inflammatory diseases or eosinophilia and basophilia in parasitic or fungal infections. Fecal Baermann test should be considered to attempt identification of lungworms. Serological tests are available for detection of *Dirofilaria immitis* and *Angiostrongylus vasorum* and their use is recommended in all coughing animals living in endemic areas. Thoracic radiographs are recommended at an early stage, as a significant abnormality will alter the diagnostic plan and avoid unnecessary investigations. Unfortunately, radiographic examination has a poor sensitivity in identifying dynamic airway collapse, infectious tracheobronchitis, or parasitic infections.[31-33] Bronchoscopy (see ch. 101) can be considered for further evaluation of coughing patients, although diagnostic yield from bronchoscopy in the routine evaluation of chronic cough tends to be low. Bronchoscopy may have a higher diagnostic potential in selected cases, such as inhaled foreign bodies, dynamic or static airway collapse, chronic bronchitis and lungworms. Furthermore, bronchoscopy provides the opportunity for airway sampling by either mucosal biopsy or bronchoalveolar lavage (BAL). Transtracheal wash (TTW) can be considered as an alternative sampling technique, although it provides a lower diagnostic yield. Thoracic computed tomography scanning is becoming widely available in veterinary medicine and this technology allows more accurate diagnoses of diffuse parenchymal lung disease, bronchial disease, and foreign bodies, which may have not been identified on thoracic radiographs. Additional diagnostic investigations may include fluoroscopy, gastrointestinal endoscopy, rhinoscopy, allergy testing, etc. An algorithm for clinical

approach is presented (Figure 26-1).

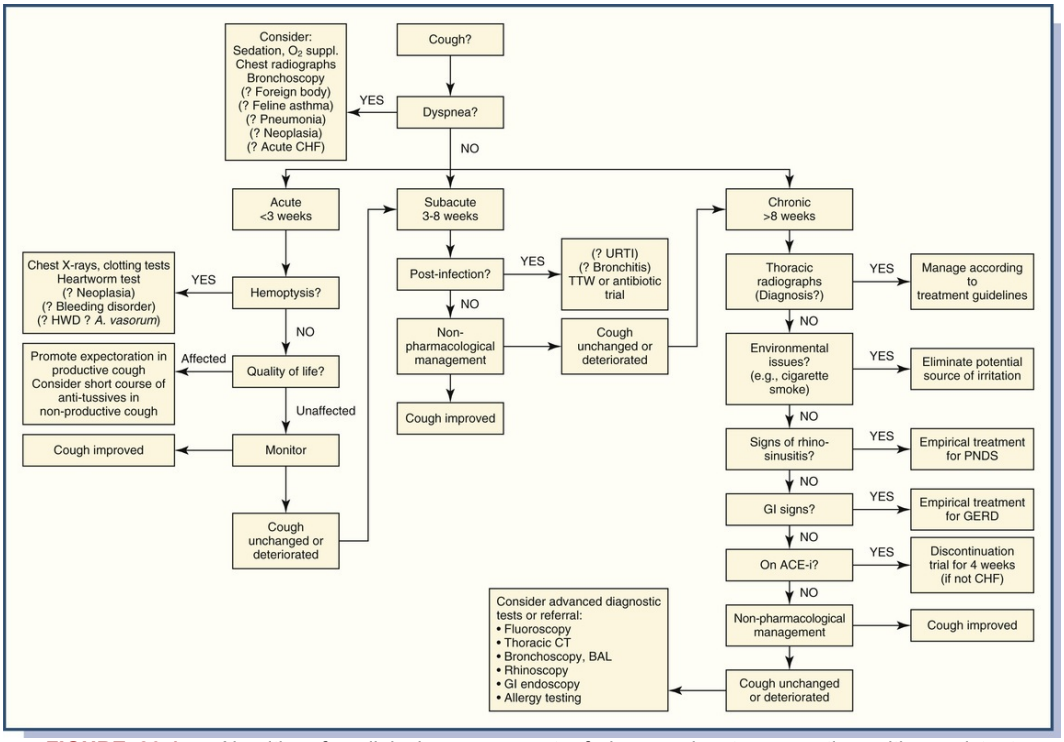

FIGURE 26-1 Algorithm for clinical management of dogs and cats presenting with persistent coughing. *ACE-i*, Angiotensin converting enzyme inhibitors; *BAL*, bronchoalveolar lavage; *CHF*, congestive heart failure; *CT*, computed tomography; *GERD*, gastroesophageal reflux disease; *GI*, gastrointestinal; *HWD*, heartworm disease; *O2 suppl*, oxygen supplementation; *PNDS*, postnasal drip syndrome; *TTW*, transtracheal wash; *URTI*, upper respiratory tract infection.

Clinical Management

Cough alone is seldom a life-threatening condition. However, when it occurs hyper-acutely, it may indicate a serious underlying problem (foreign body inhalation, severe airway obstruction, near-drowning, smoke inhalation, etc.). Cough is a protective mechanism and should not be suppressed. However, incessant coughing may affect the patient's quality of life when it interferes with respiration, eating, drinking, exercise and sleeping. The pet owner's sleeping pattern can also be affected if the dog sleeps in the same room. Cough can also spread infections and, by further irritating the airways, it may initiate a vicious circle of cough-induced cough. Cough suppression should be reserved for use only in the above situations.[2] Ideally, when a primary cause can be identified, removal of the underlying etiology should be considered first (removal of inhaled foreign body, antibiotic treatment in bacterial infections, etc.).

Non-Pharmacological Approach

The initial approach can be empirical and aimed at controlling cough, relieving airway obstruction and reducing the source of irritation, as indicated below:

1. Cigarette smoke, dust, spray cleaners and deodorants should be avoided. Carpets should be vacuumed frequently. Cleaned cotton sheets should be used to cover the pet's bed.
2. Gentle and long walks are more indicated than short intense runs. Light exercise can assist in dislodging bronchial mucus and may help opening small airways.
3. A harness should be worn instead of a collar when the dog is walked on a leash.
4. Weight reduction will improve respiration, exercise capacity, and cardiovascular functions with dramatic results (see ch. 176). Indeed, fat tends to accumulate in the chest and reduce the lung volume. This can cause compression of the airways and stimulate cough.
5. Nebulization favors expectoration from the deeper airways, bronchi, and trachea because it thins the

mucus and lubricates the irritated respiratory tract (see ch. 97). Ultrasound nebulizers are available in many health and beauty shops and they can be activated overnight in the room where the animal sleeps. Repeated coupage may help dislodge some of the deeper secretions.

Pharmacological Approach

If improvement is not observed following empiric interventions, an antitussive approach can be considered, although it should be noted that scientific evidence in dogs and cats is lacking.

Inhaled corticosteroids (ICS) (e.g., fluticasone, beclomethasone, budesonide) act directly on the airway mucosa, reducing local inflammation. Since ICS are minimally absorbed, negligible side effects are expected. ICS are administered using dedicated spacers with mask (see ch. 97).

1. Expectorants (e.g., guaifenesin) work by increasing the volume and reducing the viscosity of airway secretions, therefore improving the efficiency of cough to remove such secretions.
2. Mucolytics (e.g., acetylcysteine, guaifenesin, ambroxol, bromhexine) modify the structure of mucus glycoproteins and reduce mucus viscosity. Their use should be restricted to a few special instances, such as liquefying thick, tenacious, mucopurulent secretions.
3. Cough suppressants (e.g., butorphanol, codeine, hydrocodone, dextromethorphan) are centrally-acting antitussives, which inhibit the cough reflex by acting on the medullary cough center. Most cough suppressants have sedative effects, which might be desirable in painful, persistent cough. The clinical usefulness of dextromethorphan in coughing children has been recently questioned and little information is available about its efficacy in small animals.[34]
4. Bronchodilators (inhaled salbutamol/albuterol, theophylline, aminophylline and terbutaline) relax contracted airways smooth muscle. Therefore, they are only useful during bronchospasm, such as in feline asthma. Inhaled bronchodilators are preferred over systemic medications. Naturally-occurring bronchospasm has not been convincingly demonstrated in dogs.

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CHAPTER 27

Sneezing and Nasal Discharge

Julio López

Client Information Sheet: Sneezing and Nasal Discharge

Sneezing is an involuntary, protective reflex that expels air from the lungs through the nose and mouth in a sudden, explosive manner to clear the upper airways. It is triggered when chemical or physical irritants stimulate the subepithelial receptors in the nose. Sneezing or nasal discharge may occur in diseases of the nose, sinuses and nasopharynx (Box 27-1) or may be secondary to lower airway or systemic disease (Box 27-2).

Box 27-1

Nasal and Paranasal Causes of Sneezing and Nasal Discharge

Congenital

Cleft palate
Ciliary dyskinesia
Nasopharyngeal stenosis
Choanal atresia

Inflammatory

Idiopathic lymphocytic-plasmacytic rhinitis
Allergic rhinitis
Nasopharyngeal stenosis
Nasopharyngeal polyp (C)
Polypoid rhinitis
Foreign body

Infectious

Viral

Feline calicivirus (C)
Feline herpesvirus-1 (C)

Bacterial

Mycoplasma spp. (C)
Bordetella bronchiseptica (C)
Pasteurella multocida (D)

Fungal

Aspergillus (D, C)
Penicillium (D)
Rhinosporidium (D, C)
Cryptococcus (C)

Parasitic

Pneumonyssoides caninum (D)
Eucoleus [Capillaria] boehmi (D, C)
Cuterebra sp. (D, C)

Linguatula sp. (D, C)

Neoplastic

Adenocarcinoma
Squamous cell carcinoma
Chondrosarcoma
Osteosarcoma
Fibrosarcoma
Lymphoma
Transmissible venereal tumor
Neuroendocrine carcinoma

Trauma

Blunt or sharp force

Dental Disease

Tooth root abscess
Oronasal fistula

Vascular Malformation

C, Cats; *D,* dogs.

Box 27-2

Systemic Causes of Sneezing and Nasal Discharge

Hemostatic Disorder

Thrombocytopenia
Thrombocytopathia
von Willebrand disease
Coagulation factor deficiency
- Congenital (hemophilia A and B, others)
- Acquired (anticoagulant rodenticide intoxication, disseminated intravascular coagulation [DIC], liver failure)

Vasculitis

Toxic
Inflammatory
Immune-mediated
- Systemic lupus erythematosus

Neoplastic
Infectious
- Ehrlichiosis
- Feline infectious peritonitis
- Rocky Mountain spotted fever
- Leishmaniasis

Hyperviscosity

Multiple myeloma
IgM (Waldenstrom's) macroglobulinemia
Chronic lymphocytic leukemia
Lymphoma
Ehrlichia canis
Feline infectious peritonitis (rare)
Amyloidosis
Plasma cell leukemia

Hypertension

Primary or essential (rare)
Secondary
- Acute or chronic kidney disease
- Pheochromocytoma
- Hyperadrenocorticism
- Hyperthyroidism
- Hypothyroidism
- Acromegaly
- Polycythemia
- Diabetes mellitus
- Overhydration

Infections

Infectious tracheobronchitis
Distemper
Bacterial bronchopneumonia

Clinical Presentations

Most patients with nasal disease will present for evaluation of nasal discharge or sneezing. Signs of caudal nasal cavity disease include stertor, reverse sneezing, excessive swallowing, gagging, coughing, dysphagia, and changes in phonation. Clinical signs are not usually pathognomonic for a particular disease and various ancillary tests are required to reach a diagnosis.

Stertor

This term refers to a snorting/snoring respiratory sound indicating an obstruction to airflow at the nasopharynx that usually resolves with open-mouth breathing. Nasal discharge, mass lesions, and nasopharyngeal swelling can cause it and it is classically heard in brachycephalic breeds due to an elongated soft palate, excessive nasopharyngeal tissue, and airway stenosis (Video 27-5).

Reverse Sneezing

Reverse sneezing is a loud, sometimes violent, inspiratory snoring sound that occurs without warning. Lasting seconds to minutes, it may give clients the impression that respiratory distress is occurring. Irritation of the nasopharyngeal mucosa triggers spasms of the pharyngeal muscles, leading to obstruction of air passage to the larynx and transfer of secretions and foreign material to the oropharynx for swallowing. It is common, and usually of no consequence (Video 27-1). Nasopharyngeal disorders such as a foreign body, the nasal mite *(Pneumonyssoides caninum)*, viral infection, allergic rhinitis or epiglottic entrapment of the soft palate should be investigated when reverse sneezing is new or increases in occurrence.

Nasal Discharge

Location and character of nasal discharge may help formulate a list of differential diagnoses, keeping in mind the tremendous overlap amongst diseases that cause it.[1] Discharge is typically unilateral with foreign bodies, oronasal fistulas, aspergillosis, and neoplasia, and bilateral in inflammatory, infectious, or allergic disease. It is classified as: serous, mucoid, mucopurulent, purulent, sanguineous (containing blood), epistaxis (frank hemorrhage), or food-containing. Nasal discharge may not be noted in nasopharyngeal disease, as secretions tend to be swallowed.

Serous discharge is watery, clear, and can be a normal finding. If excessive, it may be a sign of noninfectious inflammatory disease or a viral upper respiratory tract infection in cats.

Mucopurulent discharge is more viscous and opaque, usually having a white, yellow, or green coloration. Any nasal disease that causes inflammation and secondary bacterial infection can present with this type of discharge, thus making it nonspecific (Video 27-2).

A sanguineous discharge occurs from damaged nasal mucosa and may be brought on by continuous sneezing alone. Significant nasal turbinate destruction or erosion of nasal vascular structures caused by

craniofacial trauma, mycotic infection, or neoplasia, can cause a sanguineous nasal discharge or epistaxis[1] (see Video 27-2). It can also be caused by systemic diseases (hypertension) or hemostatic disorders (thrombocytopenia, thrombocytopathia, vasculitides, or a coagulopathy).[2]

Food material in the nasal cavity suggests a congenital abnormality such as a cleft palate, a dysphagic condition in a young animal, or an oronasal fistula in an older animal.

Diagnostic Approach

Signalment

Young animals are more likely to have congenital or infectious causes of nasal discharge. Conversely, neoplasia and dental disease are more frequent occurrences in older animals. Animals housed together or stressed (shows, shelters, kennels, new home), or those exposed to regional outdoor environments (mycotic infection), are more susceptible to infectious diseases.

Brachycephalic dogs commonly have conformational causes of upper airway disease and less frequently nasal neoplasia, while brachycephalic cats are at increased risk of fungal rhinitis.[3,4] Dolichocephalic breeds are overrepresented with respect to nasal disease, likely related to the greater surface area of their mucous membranes increasing exposure to inhaled irritants and allergens. They also have a higher incidence of fungal rhinitis and nasal tumors.[3]

In cats, nonspecific inflammatory rhinosinusitis is likely the sequela of upper respiratory viruses. They alter normal nasal anatomy and defense mechanisms, causing a predisposition to secondary bacterial infections and an abnormal immune response. Cats with neoplasia are more likely to be older, have dyspnea, or hemorrhagic or unilateral nasal discharge.[5]

History

A thorough history may assist in prioritizing diagnostic tests and treatments. The pet owner should be questioned about attendance at shows/kennels, trauma, travel, outdoor activities (exposure to foxtails/grass awns, fungal organisms) and recent anesthetic procedures (nasopharyngeal gastric reflux, dental extractions) (Videos 27-3 and 27-4).

Another diagnostic aid is the onset of clinical signs (peracute, acute, chronic). Paroxysmal sneezing in a dog that was recently outdoors might indicate a plant-origin nasal foreign body, especially if accompanied by pawing at the face. In contrast, acute sneezing in cats is commonly from a viral etiology. It is less likely from foreign body inhalation due to the smaller opening of the external nares in cats. Nasopharyngeal foreign bodies may occur secondary to vomiting or regurgitation of grass or fur into the nasopharynx. Clients may report reverse sneezing, increased swallowing or gagging (postnasal drip), coughing, or audible breathing noises (stertor) in pets with caudal nasal cavity disease.

Physical Examination

Clinical suspicion of nasal disease can be confirmed by a thorough physical exam, although at times no abnormalities may be noted even though significant disease exists. The nose is examined for the presence of discharge, ulceration/crusting around the nares, depigmentation of the nares (nasal aspergillosis), asymmetry of the nose and/or face (nasal neoplasia, cryptococcosis), and pain over the dorsum of the nose (nasal aspergillosis/neoplasia). Placing a glass slide, a few hairs or a wisp of cotton in front of each nare and noting condensation or movement, respectively, assesses patency of the nasal passages. In a quiet area, listen for nasal stertor while keeping the patient's mouth closed.

A thorough oral exam, usually necessitating anesthesia, is performed as part of a complete evaluation. Mucosal ulceration (feline calicivirus), fractured teeth, oronasal fistula, cleft palate, inability to depress the soft palate or a ventral displacement (nasopharyngeal space-occupying lesion) may be noted. Halitosis may indicate dental disease, oronasal fistula, or a foreign body.

Exophthalmos, prolapse of the nictitans, deformity of the facial bones, or inability to retropulse the eye should lead to suspicion for a retrobulbar mass. Epiphora may be a sign of nasolacrimal duct occlusion. Fundic examination (see ch. 11) may reveal chorioretinitis (neoplastic or infectious diseases) or tortuous retinal vessels, retinal hemorrhages, or retinal detachment (systemic hypertension).

Nasal disease extending beyond the cribriform plate (neoplasia/aspergillosis) may affect the central nervous system and therefore a neurological exam should be performed (see ch. 259).

Primary thoracic diseases may cause secondary nasal signs from secretions coughed into the nasopharynx. Crusting of the nares with the absence of sneezing or nasal discharge suggests keratoconjunctivitis sicca (KCS) or primary dermatoses such as discoid lupus erythematosus.

Epistaxis (see ch. 29) is the most common clinical sign associated with thrombocytopenia. If petechiae, ecchymoses, or melena are noted, a hemostatic disorder should be the primary consideration.

Diagnostic Plan

Using the information gained from the clinical signs, signalment, history, and physical examination, an appropriate systematic diagnostic plan can be formulated (Figure 27-1). Despite thorough evaluation, 36.3% of cases of nasal disease in dogs remain undiagnosed and 23.7% of dogs and 64% of cats are diagnosed with nonspecific rhinitis.[6,7] Likely contributing to these numbers are cases of early neoplasia or foreign bodies, where repeated testing would probably lead to a diagnosis. Testing should also be repeated in patients with chronic rhinosinusitis that have worsening of clinical signs, to investigate the development of a second disease process.

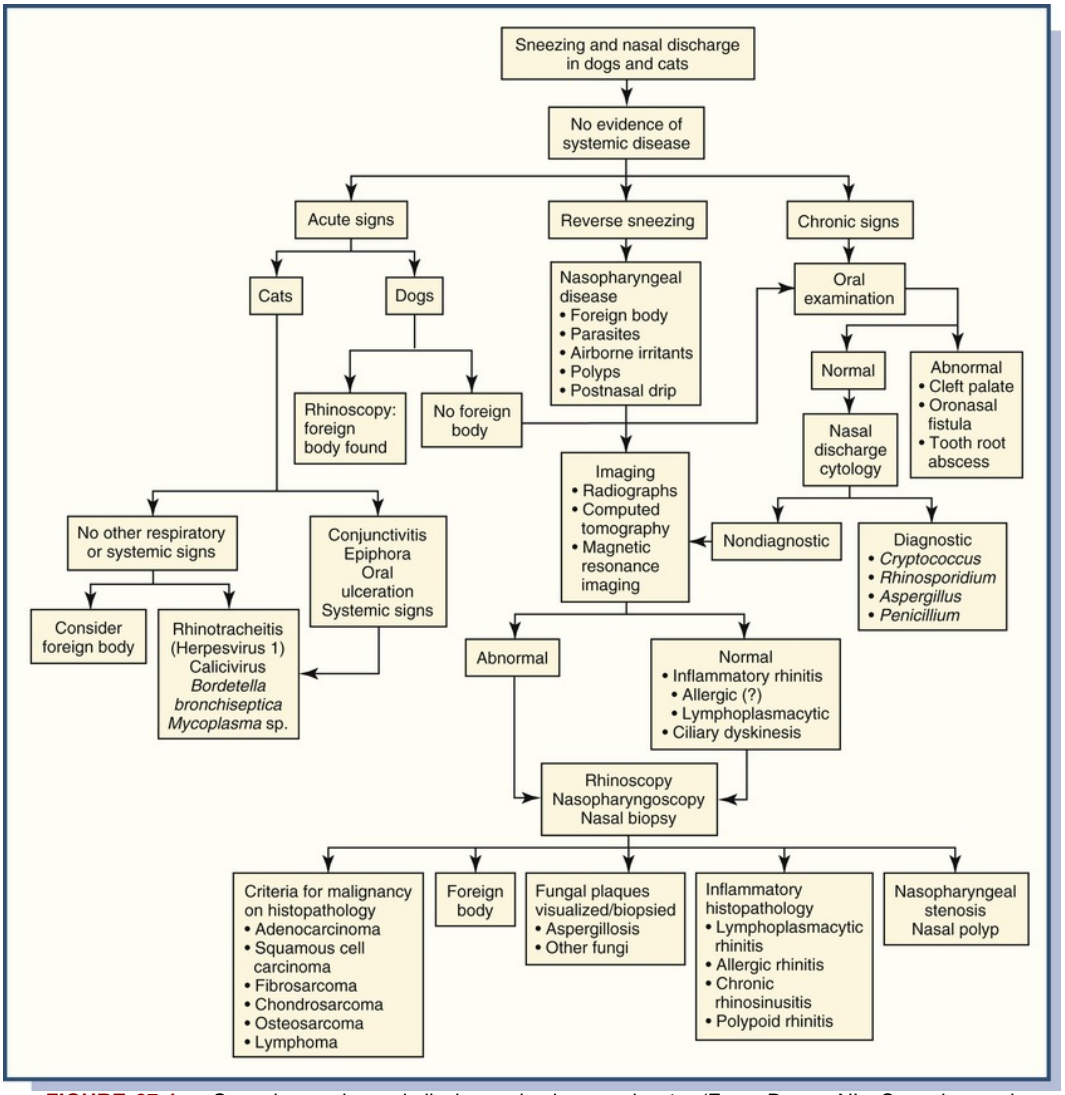

FIGURE 27-1 Sneezing and nasal discharge in dogs and cats. (From Brown NL: Sneezing and nasal discharge. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine*, ed 7, St Louis, 2010, Saunders Elsevier.)

In most cases of nasal disease, complete blood count and chemistry panels are not usually helpful in determining a diagnosis. Despite this, they must be performed to screen for systemic diseases manifesting

with nasal signs and before undergoing diagnostics that require general anesthesia. Cryptococcal serology should be performed in cats. *Aspergillus* serology by agar gel immunodiffusion test may support a diagnosis of fungal rhinitis, as it was shown to be highly specific (98%) but not sensitive (i.e., a negative result does not rule out the disease).[8] Fungal culture as a sole means of diagnosing fungal rhinitis is not recommended due to the possibility of nonclinical transient fungal organisms.[9] Testing for respiratory viruses (feline calicivirus, feline herpesvirus-1) by immunodiffusion, enzyme-linked immunosorbent assay, or polymerase chain reaction is of no use in most situations due to the high prevalence in healthy cats.[10] In cases of epistaxis, a platelet count, coagulation times (prothrombin time, activated partial thromboplastin time) or levels of proteins induced by the antagonism or absence of vitamin K, and blood pressure should be assessed, and, if indicated, a buccal mucosal bleeding time (BMBT) should be performed (see ch. 80 and 99).

Cytology of nasal secretions usually reveals nonspecific inflammation. Occasionally, fungal organisms (*Cryptococcus* sp.), parasitic ova *(Eucoleus boehmi)* or neoplastic cells are noted. Samples obtained by swabbing, brushing, flushing, or impression smears of tissue fragments can be used (see ch. 96 and 240). Facial or nasal swellings and enlarged lymph nodes should be sampled by fine needle aspiration or biopsy (needle core [Tru-Cut] or punch).

Bacterial culture of nasal discharge or the nasal cavity (deep swabbing or biopsy) is generally considered of little value as it commonly yields a mixed growth of normal commensal microflora. Although primary bacterial rhinitis is rare, notable exceptions include *Pasteurella multocida* (dogs), *Bordetella bronchiseptica* (dogs and cats) and *Mycoplasma* spp. (cats).[11,12]

Further assessment beyond these initial steps requires general anesthesia and should begin with an oral examination. If dental disease is suspected, dental radiographs should be acquired. Imaging studies should be obtained before performing dental probing or endoscopic procedures to avoid causing hemorrhage within the nose that will affect visualization. Regardless of the diagnostic method chosen, it cannot be stressed enough that bilateral examination and sampling of the nose should always occur even when unilateral disease is suspected.

Skull Radiographs

Although not the ideal imaging modality when investigating nasal disease, routine radiography may reveal the extent and character of the disease and help direct biopsy sampling. Advantages are that it is widely available and relatively inexpensive. Disadvantages include the need for general anesthesia for proper patient positioning and the inability to detect subtle changes within the nasal cavity. Superimposition of structures or accumulated fluid may obscure abnormalities and can be minimized by obtaining intraoral dorsoventral and/or open-mouth ventrodorsal views, the latter allowing assessment of the cribriform plate. Lateral oblique views and rostrocaudal views allow visualization of the dental arcade and frontal sinuses, respectively.

Rhinitis in dogs and cats, regardless of cause, can have a variable radiographic appearance depending on the chronicity and severity. Destruction of conchae can be a feature of both rhinitis (fungal/other) and neoplasia. This finding along with soft tissue swelling, bony invasion and ipsilateral sinus opacity are more commonly noted in nasal neoplasia.[13,14] In cats, *Cryptococcus neoformans* does not usually cause bony destruction. Radiopaque foreign bodies may be identified. Radiolucent foreign bodies can be localized by the appearance of a soft tissue opacity caused by secondary inflammation and discharge.

Computed Tomography (CT)

In contrast to skull radiographs, CT is much quicker to perform and provides vastly superior, detailed images without the problem of superimposition.[15,16] It also allows for visualization of areas inaccessible by endoscopy, provides guidance for biopsy procurement, and helps plan therapeutic strategies for fungal rhinitis (cribriform plate integrity) or neoplasia (radiation therapy). Disadvantages include availability and the need for general anesthesia, although it is becoming more accessible and, with newer units, sedation may be possible. While cost can be a factor, the superior images obtained may lead to an expedited, cost-effective diagnosis.

Although CT provides a reasonably accurate differentiation between neoplastic and nonneoplastic disease in dogs, confirmation via biopsy should always be performed. Neoplasia is typically associated with a soft tissue density and extensive turbinate destruction, whereas normal to moderate destruction, with or without soft tissue densities, is more typical of inflammatory rhinitis.[17] Fungal rhinitis is associated with extensive turbinate destruction and hyperlucency of the nasal passages.[16,18,19] In cats, features overlap between

nasal neoplasia and fungal rhinitis.[20] Contrast enhancement may differentiate fluid from vascularized soft tissue, although it cannot determine the nature of the lesion.

Magnetic Resonance Imaging (MRI)

Although studies show the ability of MRI to diagnose neoplastic versus inflammatory nasal disease, it is currently not the advanced imaging modality of choice. In dogs with nasal neoplasia or aspergillosis, studies have failed to demonstrate an advantage of MRI over CT.[19,21] The lack of a mass effect was significantly associated with inflammatory disease and a mass effect along with vomer bone lysis, cribriform plate erosion, paranasal bone destruction, and invasion of the mass into the sphenoid sinus or nasopharynx was significantly associated with neoplasia.[22] Disadvantages of MRI include prolonged anesthesia due to the time required to obtain images, the expense, and availability compared to CT. In cases of undiagnosed chronic nasal disease, MRI may be of value.

Rhinoscopy/Nasopharyngoscopy (see ch. 96)

The nasal cavities, nasopharynx, and, in some cases, the frontal sinuses can be directly visualized with endoscopic equipment. The procedures require expertise and moderately expensive equipment. Small rigid or flexible endoscopes provide adequate visualization of the nasal cavities. A flexible endoscope is required for access to the nasopharynx and frontal sinus, although sinuscopy may require trephination.[23] Rigid scopes have better optics and are easier to maneuver, while flexible scopes are associated with less mechanical trauma to the tissue. Nasopharyngoscopy should be performed first, as hemorrhage from rhinoscopy may pool in the nasopharynx and impair visualization.

The procedure can be diagnostic (visualization of fungal plaques, foreign bodies, nasal polyps, mass lesions, nasal mites, nasopharyngeal stenosis) as well as therapeutic (removal of foreign bodies, fungal plaques, flushing/suctioning excessive secretions). It allows for biopsy procurement under direct visualization. Endoscopy was superior to nasal radiographs in achieving a diagnosis in dogs with persistent nasal disease.[24] Evaluation of the choanae correctly identified nasal neoplasia in 26 of 34 animals where biopsies were obtained.[25]

Nasal Biopsy

Several biopsies from each nasal cavity should be procured from all dogs and cats with chronic nasal disease even if etiology appears to be unilateral, is obvious (foreign body), or no apparent lesion is noted. Rhinoscope-guided biopsies are preferred, as visualization ensures that specific lesions are sampled. Blind biopsy techniques can also be used, although in order to avoid inadvertent penetration of the cribriform plate, the clinician should measure the distance from the tip of the nose to the medial canthus of the eye and ensure the biopsy instrument does not pass this distance. A CT can determine the length the biopsy instrument must be advanced to reach the affected area. Biopsies may also be acquired via traumatic nasal flush or via rhinotomy.

Cytology of impression smears from biopsy samples may provide a fast tentative diagnosis.[26] If *Cryptococcus* spp. is detected, serologic testing should be obtained to determine asymptomatic carriage from true infection (positive result) and to help monitor treatment. Hemorrhage (which can be life-threatening) and aspiration of blood are complications that should be expected.

Treatment/Outcome

The diagnosis and treatment of nasal disease can be frustrating for both the veterinarian and pet owner. Despite a systematic and extensive investigation, an etiologic diagnosis remains elusive in many cases. More often, a descriptive diagnosis based on inflammatory infiltrates is provided (nonspecific rhinitis) with management based on symptomatic therapies to alleviate clinical signs. Specific treatments are available for neoplasia, fungal rhinitis, foreign bodies, most congenital abnormalities, parasites, and dental disease. Prior to undergoing an extensive and costly investigation, educating the client of possible outcomes and the potential for lifelong management will help minimize unrealistic expectations and frustration.

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CHAPTER 28

Tachypnea, Dyspnea, and Respiratory Distress

M. Lynne O'Sullivan

Client Information Sheet: Tachypnea, Dyspnea, and Respiratory Distress

Dyspnea is used clinically to refer to difficult or labored breathing, though it actually more precisely refers to the conscious sensation of shortness of breath or breathlessness.[1] Respiratory distress is therefore perhaps a more accurate term for what is observed clinically, and implies a certain severity to the situation. Tachypnea refers to increased rate of respiration, which may accompany dyspnea. This should be differentiated from panting, which is rapid breathing without evidence of respiratory distress and which is associated with thermoregulation, anxiety, or pain. Orthopnea refers to dyspnea that is positional, specifically present whenever the patient is not standing or sitting upright.

Pathophysiology

Control of breathing involves the integration of three main elements: 1. Sensors that gather data, and 2. Respiratory control center in the brain that coordinates the data and sends impulses to the 3. Effector muscles (diaphragm and intercostal muscles). The main sensors include central and peripheral chemoreceptors, which are sensitive to changes in arterial carbon dioxide levels and both arterial oxygen and carbon dioxide levels, respectively. Dyspnea is triggered by hypoxemia or hypercarbia (generally PaO_2 < 60 mm Hg or $PaCO_2$ > 50 mm Hg, respectively, depending on duration). Causes of hypoxemia include 1. Decreased fraction of inspired O_2, 2. Hypoventilation, 3. Diffusion impairment, 4. Right-to-left cardiovascular shunt, 5. Ventilation-perfusion (VQ) inequality, and 6. Abnormal hemoglobin. This discussion focuses on disorders resulting in 2, 3, 4, and/or 5. The main causes of hypercarbia include: 1. Hypoventilation, and 2. VQ inequality.[2,3]

Immediate Assessment and Management of the Dyspneic Patient (see also ch. 131 and 139)

Respiratory distress is a common presenting complaint that necessitates immediate evaluation and attention, as respiratory compromise can very rapidly deteriorate to respiratory failure. Since stress and anxiety can contribute to this deterioration, these patients should be handled minimally. Oxygen therapy should be immediately administered via face mask, flow-by, nasal prongs, nasal cannula, hood, or cage. The choice of delivery method necessitates balancing the invasiveness of the technique with the inspired oxygen levels achieved for the given patient's condition and temperament. While oxygen is being administered, much information can be gained from observing the patient at a distance (see ch. 2). It is important to note posture, mental alertness and behavior, and respiratory pattern, including rate, regularity, depth, and effort (degree and timing with the respiratory phase). This information is used for assessing severity and localizing the problem to the upper airways, lower airways, pleural space, or thoracic wall.[3] Breathing patterns may be described as obstructive (slower, deeper breaths) or restrictive (short, rapid, shallow breaths). Obstructive patterns can further be characterized as having more inspiratory effort (suggesting an upper airway disorder) (Video 28-1) or more expiratory effort (suggesting a lower airway disorder) (Figure 28-1; Video 28-2).

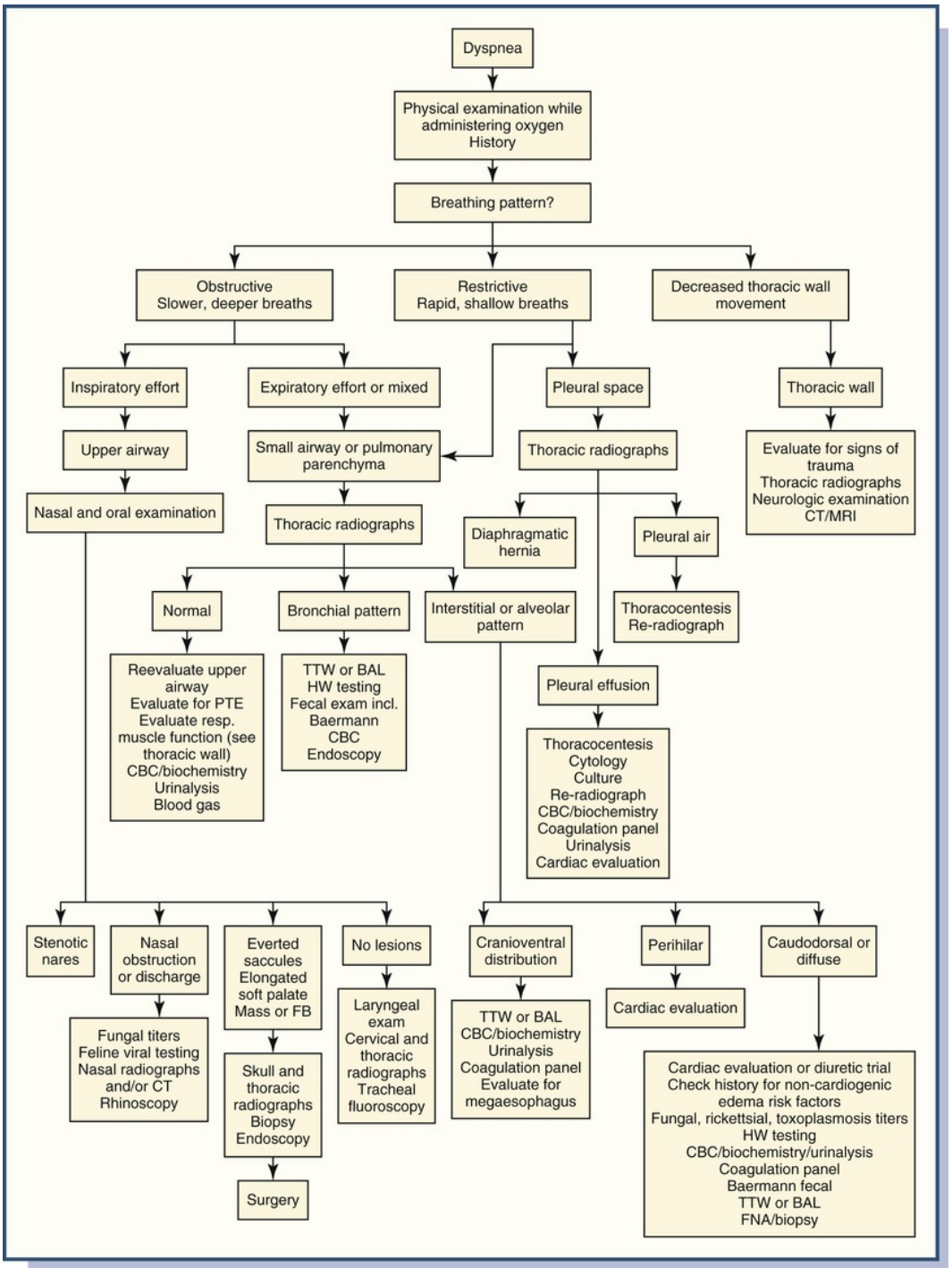

FIGURE 28-1 Algorithm for the approach to the dyspneic patient. *BAL,* Bronchoalveolar lavage; *FNA,* fine needle aspirate; *HW,* heartworm; *TTW,* transtracheal wash.

Markedly hypoxemic animals will appear panicked, often with elbows abducted, head and neck extended, nostrils flared, and with a glazed expression as they are focused on breathing. It is important to promptly recognize upper airway obstruction (exaggerated inspiratory effort with little to no air movement) as sedation and intubation are immediately necessary. Also important to recognize is the paradoxical breathing pattern, which indicates greatly increased work of breathing and respiratory muscle fatigue. During inspiration, the caudal intercostal muscles and ribs are noted to collapse inwards with diaphragmatic contraction and the abdomen is noted to move outward as the cranial abdominal contents are forced backwards (Video 28-3).[1] A thorax that is barrel-shaped or increased in size with expansion of the thoracic wall may indicate tension pneumothorax or marked pleural effusion. Two or more fractures of two or more adjacent ribs may result in flail chest, recognized as a segment of thoracic wall moving in during inspiration and out on expiration.

Some patients will require immediate therapy in addition to oxygen supplementation (see ch. 139). This may include sedation to reduce anxiety and work of breathing or to facilitate intubation. Opioids and benzodiazepines alone or in combination tend to be effective and have a good safety profile.[4] IV access is desirable as soon as safely possible. Cooling may be necessary as patients frequently become hyperthermic from the work of breathing. Techniques include using a fan, cool wet towels, cooled IV fluids, or ice packs in extreme cases. If airway obstruction or imminent respiratory arrest is anticipated, then endotracheal (ET) intubation should be performed. Suction of the ET tube can be helpful therapeutically and diagnostically. Manual or mechanical ventilation may then be instituted if necessary depending on blood gas analysis and work of breathing. If intubation cannot be achieved due to the presence of a physical obstruction, a tracheotomy may be necessary. A red rubber feeding tube or jugular catheter can sometimes be passed beyond the obstruction to deliver oxygen while preparing for a tracheotomy. If a restrictive breathing pattern is noted and either air or fluid is suspected in the pleural space based on auscultation, thoracocentesis should be performed and fluid samples saved for cytologic evaluation and microbial culture (see ch. 102). Readiness of the veterinary team with equipment, drug dosages, and personnel for all of the above are a key part of effective management.

Important Historical Information

Signalment can be very relevant for identifying breed and age predispositions. Examples include brachycephalic breeds like Bulldogs and brachycephalic syndrome (stenotic nares, hypoplastic trachea, elongated soft palate, everted laryngeal saccules), smaller breed dogs like Yorkshire Terriers and Pomeranians and collapsing trachea, older small breed dogs and congestive heart failure due to chronic mitral valve insufficiency (CMVI), older larger breed dogs and laryngeal paralysis, young patients and infectious diseases, West Highland White Terriers and pulmonary fibrosis, young to middle-aged cats and asthma, and middle-aged to older cats and pleural effusion.

Historical information of importance includes the duration and progression of clinical signs, and the presence of concurrent respiratory signs like coughing, wheezing, sneezing, snoring, nasal or ocular discharge, or change in bark or meow. Also of importance is the presence of other systemic signs that may point to involvement of other body systems (weakness, exercise intolerance, collapse, vomiting, regurgitation, seizures) or the presence of known pre-existing disorders (respiratory, cardiac, neuromuscular, metabolic, immune-mediated, inflammatory). Thorough questioning on possible exposure to trauma, toxins, allergens, smoke, other environmental conditions, other dogs, and ticks should be performed.

Complete Physical Examination

Complete and thorough physical examination remains the mainstay of accurate patient assessment and initial diagnosis. As mentioned above, of primary importance is noting the respiratory pattern, including rate, depth, and timing and degree of effort (see Figure 28-1).

During examination of the head, symmetry of the face and nose should be noted, because asymmetry may suggest space-occupying lesions or traumatic injuries. Ocular and nasal discharge may indicate an infectious process, and precautions to avoid spread to other patients +/- isolation protocols may be warranted. Stertor or stridor is indicative of upper airway obstruction (see below). Oral mucous membrane color provides an indication of oxygenation and crude perfusion (cyanosis, pallor). An oral exam for electrocution burn wounds, or obvious mass, foreign body (FB), or blood in the mouth or pharynx is warranted, though a complete exam may not be achievable until the patient is sedated. Light sedation is certainly necessary to properly examine laryngeal function (see Video 28-1). The neck should be palpated for signs of trauma or esophageal FB.

The thorax should be palpated for signs of trauma, rib fractures, or cardiac thrills. In cats, compressibility of the cranial thorax should be assessed, as lack thereof suggests the presence of a cranial thoracic or mediastinal mass. Thoracic auscultation is of central importance. The identification of murmurs, gallops, or arrhythmias on cardiac auscultation supports the presence of cardiac disease that may be responsible for respiratory distress. It is important to recognize, however, that the same geriatric small breed dogs that are predisposed to CMVI may also be predisposed to chronic bronchitis or collapsing trachea; therefore, the presence of a murmur does not automatically indicate the dyspnea is cardiac in origin. Displaced or muffled heart sounds may indicate the presence of a mass or diaphragmatic hernia. Pulmonary auscultation may reveal increased bronchovesicular (BV) sounds as a result of airway narrowing by constriction or secretions causing flow turbulence. Tracheal auscultation should be performed to determine whether the source of increased BV

sounds is indeed the lower airways or referred from the upper airway. Crackles or wheezes may be heard with lower airway disorders. Crackles or rales are discontinuous popping sounds resulting from air bubbling through fluid (not just cardiogenic edema) or from rapid opening of stiff airways. Wheezes are high-pitched continuous musical sounds indicating air movement through very narrowed airways. Decreased to absent lung sounds indicate the presence of something preventing transmission of lung sounds through the thoracic wall. If decreased ventrally, pleural effusion or a space-occupying mass may be present, whereas if decreased dorsally, pneumothorax may be present. Thoracic percussion would tend to yield dullness and increased resonance, respectively, with those two scenarios.

Abdominal palpation should be performed and may reveal discomfort or pain, ascites (suggesting cardiac disease or hypoproteinemia), or distension from aerophagia. Femoral pulse quality may reveal additional information referable to cardiovascular status.

It is important to recognize that in many cases, further diagnostics may not be immediately attainable for the safety of the patient. However, obtaining a good history and physical exam will go a long way in the diagnostic process. When procedures or diagnostics are eventually instituted, they are best done in an interrupted fashion to allow the patient to return to oxygen and to rest.

Localization

Upper Airway (see ch. 239 and 241)

The upper airway is composed of the nasal passages, pharynx, larynx, trachea, and mainstem bronchi. Patients with upper airway obstruction exhibit inspiratory dyspnea characterized by effort during a long inspiratory phase and slower respiratory rate. The exception is intrathoracic tracheal or bronchial collapse, which tends to cause expiratory dyspnea. Patients with upper airway disorders may have noisy stertor (snoring) if there is partial obstruction of the nasal passages or nasopharynx. Differential diagnoses in this case may include stenotic nares, nasal FB, neoplasia, rhinitis (infectious or inflammatory), or nasopharyngeal polyp. Dyspnea may be accompanied by stridor, a harsh high-pitched inspiratory sound, in the case of laryngeal or tracheal obstruction. Common differential diagnoses would include laryngeal paralysis, neoplasia, FB, brachycephalic syndrome, and tracheal collapse. Additional signs with upper respiratory obstruction may include choking, retching, pawing at the face, or a honking cough (in the case of tracheal collapse). Immediate therapeutic priorities in patients with upper airway obstruction include oxygen supplementation, sedation if anxious, ± cooling, ± intubation or tracheotomy, depending on severity. Occasionally, surgical intervention is needed urgently to address laryngeal paralysis, tracheal collapse, or other forms of upper airway obstruction.

Small Airway (see ch. 241)

The small airways include bronchi and bronchioles. Patients with small airway disease typically exhibit expiratory dyspnea, characterized by a shorter inspiratory phase and longer expiratory phase with effort or push, sometimes involving the abdomen. Increased BV sounds, wheezes, or crackles (inspiratory and/or expiratory) may be ausculted. Common differential diagnoses include feline asthma in cats, chronic bronchitis, allergic airway disease, smoke inhalation, and bronchopneumonia.

Pulmonary Parenchyma (see ch. 242)

Disease involving the alveolar ducts and alveoli, pulmonary interstitium, or pulmonary vasculature may result in mixed inspiratory or expiratory dyspnea. Alternatively, these patients may have a restrictive pattern with rapid and shallow breathing if the disease prevents the lungs from fully expanding. Increased BV sounds and often crackles are noted on auscultation. Differential diagnoses may include cardiogenic pulmonary edema, non-cardiogenic pulmonary edema (secondary to strangulation/upper airway obstruction, electrocution, head trauma, post-seizure, vasculitis), pneumonia (viral, bacterial, fungal), hemorrhage, neoplasia, parasitic disease, pulmonary thromboembolism, idiopathic pulmonary fibrosis, the acute respiratory distress syndrome, or pulmonary contusions (trauma). This extensive (yet still incomplete) list of differentials emphasizes the importance of identifying and considering other historical and physical exam data including history or evidence of cardiac disease, history of vomiting or regurgitation to suggest aspiration pneumonia, history of trauma, electrocution, heartworm status, and travel.

Pleural Space (see ch. 244)

Patients with pleural space disease typically have a restrictive breathing pattern characterized by rapid and shallow respirations due to an inability of the lungs to expand. As mentioned above, lung sounds tend to be muffled at least ventrally with pleural effusion and dorsally with pneumothorax. If air or fluid in the pleural spaced is suspected, thoracocentesis should be performed (see ch. 102). Differential diagnoses for pleural space disease include pneumothorax, pyothorax, hemothorax, chylothorax, masses, diaphragmatic hernia, and transudative pleural effusion due to a variety of causes including neoplastic disease, cardiac disease, lung lobe torsion, or hypoproteinemia. As mentioned above, a mass should be suspected in cats with a non-compressible cranial thorax.

Thoracic Wall (see ch. 245)

Patients with disorders of the thoracic wall tend to hypoventilate due to failure of the normal respiratory apparatus. They exhibit respiratory distress in the face of decreased thoracic wall movement, lacking intercostal, diaphragmatic, and abdominal assistance during respiration. They may or may not have signs of trauma. This pattern may be a result of neuromuscular disease (peripheral neuropathies, central disorders, spinal cord disease between C1-C4, phrenic innervation abnormalities) or trauma (rib fractures, flail chest, penetrating wounds). Therapy in these patients typically necessitates intubation and ventilation.

Further Diagnosis and Therapy

Appropriate diagnostic work-up based on this initial assessment is outlined in Figure 28-1. Diagnostics may include thoracic radiography, pleural fluid analysis and culture, oral and laryngeal exam, rhinoscopy, fluoroscopy for tracheal or bronchial collapse, transtracheal wash, bronchoscopy and lavage, computed tomography, and fine needle pulmonary or mass aspirates, among others. Therapy beyond that already described depends on physical examination and diagnostic results. If diagnostics are not available for some time due to stability of the patient, then empirical therapy for the common causes of respiratory distress is often administered, at least as single doses (furosemide for heart failure, bronchodilator and corticosteroid for feline asthma or chronic bronchitis), particularly when there is evidence to support these on history or physical exam.

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CHAPTER 29

Epistaxis and Hemoptysis

Tim B. Hackett

Epistaxis

Epistaxis is hemorrhage from the nose due to a variety of etiologies (E-Box 29-1 and Figure 29-1). Knowledge of the animal's environment and signalment can assist in recognition of the source of hemorrhage. Trauma, intranasal transmissible venereal tumors (TVT), and parasitic, rickettsial, and fungal infections are more often seen in dogs and cats allowed outside. Foreign bodies are generally inhaled grasses observed in dogs allowed to roam. While rodenticide ingestion is also associated with roaming, it can also occur in pets kept indoors. Purebred dogs are more commonly affected with immune-mediated diseases, von Willebrand disease (vWD), or congenital coagulation factor deficiencies. Nasal tumors in dogs are more common in older, dolichocephalic animals. Nasopharyngeal polyps occur more often in young cats, while brachycephalic felines are more susceptible to chronic viral respiratory infections.

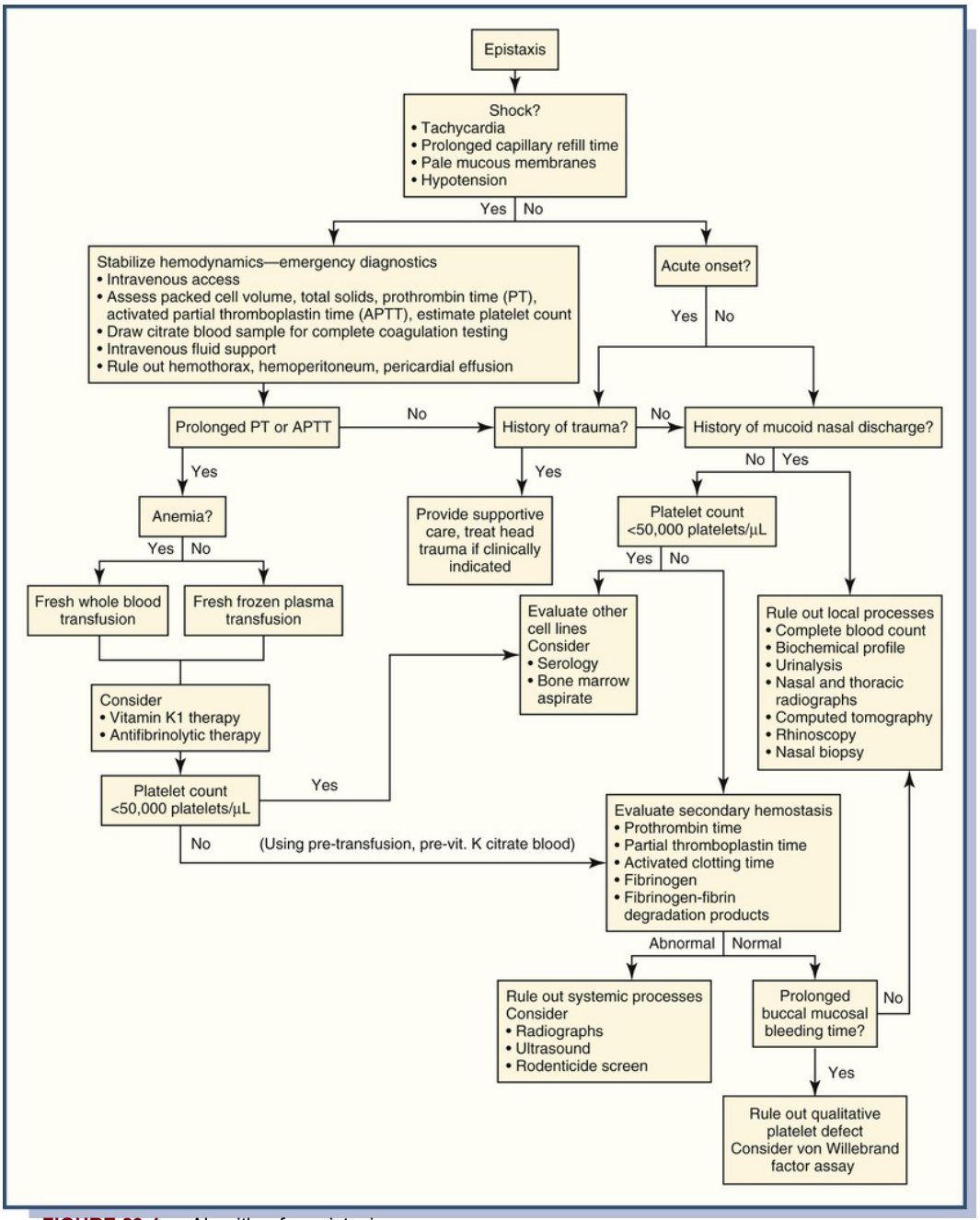

FIGURE 29-1 Algorithm for epistaxis.

E-Box 29-1

Causes of Epistaxis

Extranasal (Systemic) Causes of Epistaxis

Thrombocytopenia (quantitative platelet abnormality)

Decreased production

Infectious: Ehrlichiosis, feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), Rocky Mountain spotted fever, hepatozoonosis, septicemia, endotoxemia, leishmaniasis, *Bartonella* spp. infections

Drugs: Cytotoxic drugs, modified live virus vaccines, estrogens

Neoplasia: Myelophthisis secondary to myeloproliferative or lymphoproliferative diseases

Immune-mediated: Antibodies against megakaryocytes
Other: Bone marrow aplasia, cyclic thrombocytopenia, myelofibrosis, hyperestrogenism (secondary to Sertoli cell and granulosa cell tumors), myelodysplasia, toxins, osteosclerosis, idiopathic
Increased destruction
Immune-mediated: Idiopathic or secondary to drugs, neoplasia, infection
Microangiopathy: Shearing of platelets; associated with hemangiosarcoma
Sequestration
Neoplasia: Large vascular tumors
Splenomegaly or splenic torsion
Hepatomegaly
Increased consumption
Disseminated intravascular coagulopathy (DIC)
Vasculitis: Rocky Mountain spotted fever, endotoxemia, neoplasia, heartworm disease, bacteremia, *Bartonella* spp. infections
Hemorrhage-induced thrombocytopenia
Thrombocytopathia (qualitative platelet defect)
Congenital: von Willebrand disease (vWD), platelet procoagulant activity deficiency in German Shepherd Dogs, Glanzmann's thrombasthenia in Great Pyrenees, Basset Hound thrombopathia
Acquired: vWD (associated with hypothyroidism), uremia, dysproteinemia (associated with multiple myeloma, ehrlichiosis, leishmaniasis), drugs (NSAIDs)
Coagulation factor deficiency
Congenital: Hemophilia A and B, others
Acquired: Anticoagulant rodenticide intoxication, liver failure, DIC
Increased capillary fragility
Hypertension: Primary or secondary to chronic kidney disease, glomerulonephropathies, pheochromocytoma, hyperadrenocorticism, hyperthyroidism, heart disease
Hyperviscosity syndrome: Secondary to multiple myeloma, ehrlichiosis, erythrocytosis (primary or secondary to hypoxia or neoplasia), leukemias
Hyperlipidemia
Thromboembolic disease
Neoplasia invading blood vessels

Intranasal (Localized) Causes of Epistaxis

Trauma
Benign nasal polyps (cats)
Neoplasia
Epithelial: Adenocarcinoma, undifferentiated carcinoma, squamous cell carcinoma
Mesenchymal: Chondrosarcoma, fibrosarcoma, hemangiosarcoma, osteosarcoma, melanoma
Round cell: Lymphoma, transmissible venereal tumor, mast cell tumor
Infection
Fungal: *Cryptococcus, Aspergillus, Penicillium, Rhinosporidium, Exophiala jeanselmei*, phaeohyphomycosis
Parasitic: *Pneumonyssus, Eucoleus, Cuterebra, Linguatula, Capillaria*
Bacterial: Primary *(Bordetella, Pasteurella, Mycoplasma)* or secondary
Viral: Canine infectious tracheobronchitis, canine distemper, feline viral rhinotracheitis, calicivirus
Inflammation
Lymphoplasmacytic: Primary or secondary
Eosinophilic: Allergic rhinitis
Dental disease
Tooth root abscess
Oronasal fistula
Foreign body (FB)
Vascular malformation

A history of bleeding after elective neutering or minor trauma might indicate a congenital coagulation factor deficiency or platelet disorder. Epistaxis from foreign body inhalation is acute in onset and often accompanied by sneezing, agitation and pawing at the face. Foreign objects lodged in the nasal cavity for long periods of time are associated with a cellular and chronic nasal discharge. Patients on vitamin K antagonists

or platelet inhibitors should have those dosages reassessed, along with diet, and concurrent medications. Platelet dysfunction is seen with nonsteroidal anti-inflammatory drug (NSAID) administration. Immune-mediated platelet dysfunction is seen with vaccines and some drugs. Estrogens, phenylbutazone, and many cytotoxic chemotherapy agents can cause thrombocytopenia.

Nasal trauma results in acute-onset bleeding that resolves with supportive measures and does not recur. There are usually other signs of trauma and, due to the proximity of the brain, patients should be closely monitored for evidence of increased intracranial pressure or focal intracranial hemorrhage.

Seasonal epistaxis might be the result of allergic rhinitis. Low humidity, especially change from a humid to dry climate, can dry nasal mucous membranes and result in mild epistaxis. Recurring episodes of epistaxis are seen with oronasal fistulas, fungal and bacterial rhinitis, and nasal tumors. Travel to endemic areas for fungal and rickettsial organisms, such as ehrlichiosis, leishmaniasis, and hepatozoonosis, can help rank differential diagnoses and refine the diagnostic plan.

The initial physical examination should prioritize patient hemodynamics and tissue oxygenation. While emergency diagnostics are indicated to identify specific treatments, the possibility of significant hemorrhage should be assumed since it is difficult to know the volume of blood lost prior to presentation. The patient's heart rate, mucous membrane color, capillary refill time, pulse quality, and blood pressure should be assessed. Coagulopathic patients with epistaxis might also be bleeding into the lungs or other body cavities. Auscultation of the chest can identify intrapleural or intrapulmonary hemorrhage. Muffled heart sounds might indicate hemopericardium. Patients with petechiae, mucosal bleeding, melena, or fundic hemorrhage are likely to have a defect of primary hemostasis (platelets), whereas those with hemarthrosis, hematomas, or bleeding into the chest, lungs, or abdomen are likely to have a defect of secondary hemostasis (coagulation factors).

With any evidence of hypovolemia, vascular access should begin with a peripheral intravenous catheter or intraosseous system (see ch. 75-77). Before beginning fluids, blood samples should be collected for coagulation testing, packed cell volume, complete blood count, blood type, and biochemical profile. Rapid restoration of vascular volume should begin while awaiting results.

Anemic patients showing signs of shock should receive a transfusion of red blood cells. See ch. 130 and 198. Patients with prolonged clotting times should receive a unit of fresh frozen plasma or fresh whole blood. Plasma is always indicated in the presence of clinically significant hemorrhage and an abnormal coagulation profile. The decision to use whole blood should be guided by available component blood products and the need for red blood cells. Blood loss can be minimized by anesthetizing the patient, protecting the airway with a cuffed endotracheal tube, and occluding the nares and oropharynx with appropriately sized Foley catheters to create tamponade (Video 29-1). Arterial embolization with interventional radiology techniques is a viable treatment for intractable epistaxis.[1]

When the patient is stable, inspect the nares and regions above the nasal sinus. Holding a few strands of cotton or a glass slide in front of the nose can assess nasal patency and airflow. Many intranasal diseases, such as nasal tumors, begin with unilateral epistaxis that can become bilateral as the disease progresses and the nasal septum is disrupted. Although bilateral epistaxis might indicate "extranasal" causes such as coagulopathies, hypertension, thrombocytopenia, and thrombocytopathia (a defect in platelet function), this does not always occur.

Ulceration and depigmentation of the nasal planum can be seen with immune-mediated disease, fungal infections, or neoplasia. Asymmetry of the nose is most often associated with neoplasia. Cats with nasal cryptococcosis often have a convexity of the nose referred to as "Roman nose." Polypoid masses extending from the nares are seen with rhinosporidiosis and cryptococcosis.

Careful examination of the mouth for severe dental disease, oronasal fistulas, loose teeth, palate deformity, or masses should be performed. In addition to facial deformities, nasal tumors can extend in other directions, causing hard palate deformity. A fundic examination (see ch. 11) might reveal chorioretinitis with systemic inflammatory diseases, or signs of hypertensive retinopathy such as retinal hemorrhage or retinal edema and detachment (especially in cats). Nasal masses can make retropulsing the globe difficult and can cause epiphora. Regional lymph nodes should be examined and potentially aspirated looking for reactivity, infectious organisms, or metastatic neoplasia. Melena and hematemesis can occur when blood from the nasopharynx is swallowed. Central nervous system (CNS) dysfunction might occur with hyperviscosity syndromes or nasal tumors invading the brain.

Intranasal processes are the most common cause of epistaxis, with nasal tumors the most common cause of epistaxis in older pets. Animals with severe dental disease and/or oronasal fistulas can have nasal discharge or epistaxis. Much less commonly, arteriovenous malformations can rupture, causing severe, acute epistaxis. Primary bacterial rhinitis is uncommon, but usually involves agents ubiquitous to the respiratory tract like

Bordetella, Pasteurella, and *Mycoplasma* spp. Aspergillosis in dogs and nasal cryptococcosis in cats are the most common fungal causes of epistaxis. Cats with upper respiratory infections can develop sneezing, chronic nasal discharge, mucosal damage, and intermittent epistaxis.

Systemic causes of epistaxis most often involve clotting disorders. Primary hemostatic defects (platelet plug formation) include thrombocytopenia or thrombocytopathia. Decreased platelet production, abnormal destruction, sequestration, and increased consumption will lower platelet numbers. Mild, moderate and severe clinical hemorrhage is possible with platelet counts less than 25,000 platelets/mcL, 10,000 platelets/mcL, and 5,000 platelets/mcL, respectively.[2] Spontaneous bleeding is uncommon with platelet counts over 50,000/mcL. Decreased production of platelets occurs secondary to infections, myelophthisic neoplasia, drug reactions, or immune-mediated disorders. Increased destruction of platelets can be immune-mediated or related to microangiopathic changes observed with diseases such as hemangiosarcoma. Sequestration of platelets in the spleen, liver, large vascular tumors, or following rattlesnake envenomation results in a circulating thrombocytopenia. Increased platelet consumption is seen with disseminated intravascular coagulopathy (DIC), vasculitis, and hemorrhage. von Willebrand's disease is the most common cause of primary thrombocytopathia. Secondary thrombocyopathias are more common than hereditary diseases and can occur with NSAID administration, neoplasia, DIC, liver disease, and dysproteinemias such as those seen with ehrlichiosis. Thrombocytopathia can occur with end-stage renal disease due to uremic toxins.[3]

Hemophilia A and B are uncommon congenital coagulopathies that vary in severity. Acquired coagulopathies affecting clotting factors include anticoagulant rodenticide intoxication and decreased coagulation factor production secondary to hepatic failure. Another, less common, systemic cause of epistaxis is increased capillary fragility resulting from hypertension, invasive neoplasia, hyperviscosity syndromes, hyperlipidemia, and thromboembolic disease.

Regenerative anemia indicates a bone marrow response to blood loss. It can take a few days to complete the normal regenerative response to blood loss, making acute hemorrhage appear non-regenerative. A non-regenerative, iron deficiency anemia can also be seen with chronic epistaxis. Schistocytes can be observed with microangiopathic diseases such as hemangiosarcoma and DIC. Leukocytosis occurs with chronic inflammation, infection, or a regenerative marrow response to blood loss. Leukopenia is seen with chronic ehrlichiosis, cytotoxic drug administration, sepsis, and infections such as *Salmonella* and canine parvoviral enteritis. Thrombocytopenia is the result of increased destruction, decreased production, consumption, or sequestration of platelets. A blood smear can assess platelet numbers.

Thrombocytopathia should be investigated if platelet numbers are above 100,000/mcL. Buccal mucosal bleeding time (BMBT) is a useful in-hospital screening test of platelet function (see ch. 80). When abnormal, specific tests such as a von Willebrand's titer are indicated. Coagulation studies, such as partial thromboplastin time (PTT), prothrombin time (PT), and activated clotting time (ACT), should be performed in cases of epistaxis in which thrombocytopathia and severe thrombocytopenia (<10,000/mcL) have been ruled out. If abnormal, a factor-deficiency coagulopathy should be assumed (see ch. 196-197). Further investigation into the cause of the coagulation defect includes testing for anticoagulant rodenticides, evaluation of hepatic and post-hepatic conditions affecting vitamin K production, and testing for specific factor deficiencies. Additional tests for consumptive coagulopathies might include fibrinogen, fibrin degradation products (FDPs), and antithrombin III concentration. Thromboelastography evaluates the efficiency of blood coagulation and can assess factors, such as platelet function, clot strength, and fibrinolysis, that PT, APTT, and ACT tests cannot.[4]

Panhypoproteinemia might develop with chronic blood loss. Hyperglobulinemia is associated with neoplasia or chronic infections. Serum protein electrophoresis can assist in distinguishing between monoclonal or polyclonal gammopathy. Monoclonal gammopathies occur with multiple myeloma, chronic ehrlichiosis, lymphoma, leukemias, and macroglobulinemia. Azotemia is usually seen with uremia-associated vasculitis. Hepatic dysfunction can lead to decreased production of clotting factors and might be evidenced by increased bilirubin and hepatocellular enzymes, or decreased albumin and glucose.

Rickettsial causes of thrombocytopenia, such as ehrlichiosis and Rocky Mountain spotted fever, are diagnosed with serology. *Aspergillus* spp. titers indicate exposure, but correlate poorly with active infection. Latex agglutination tests for *Cryptococcus* spp. capsular antigen are useful for diagnosis and therapeutic monitoring. Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) tests are indicated in cats with systemic illness.

The goal of imaging in epistaxis is to localize the disease, determine the severity, and guide biopsy procedures. Imaging studies should be performed prior to rhinoscopy and probing bad teeth or oronasal fistulas. Anything causing iatrogenic hemorrhage might complicate interpretation of the images. Nasal

radiographs should include lateral, oblique, open-mouth, ventrodorsal, intraoral, and frontal sinus views. Computed tomography (CT) is superior to radiographs for nasal disease because it allows visualization of bony and soft tissue lesions and it images all areas including turbinates, nasal septum, cribriform plate, and sinuses. Imaging studies should be examined for asymmetry and bone lysis. Contrast enhancement can distinguish tumors from an abscess or mucus accumulation.

Rhinoscopy is performed after coagulopathy has been ruled out with the animal anesthetized and intubated with a cuffed endotracheal tube to prevent aspiration of blood. With the animal in sternal recumbency, the least-affected side is examined first. Thorough evaluation of the oropharynx and oral cavity should be performed. Rigid arthroscopes are the most useful for visualizing the rostral nasal passages. The distance from the medial canthus to the end of the nostril should be marked on the instrument prior to entry into the nose to avoid penetration of the cribriform plate. An otoscope could also be used to view the rostral nasal passages, especially in cases with a foreign body or large tumor. A flexible bronchoscope is best suited to visualize the caudal nasal cavity and nasopharynx. If a rigid scope is used, a spay hook can be employed to retract the soft palate so that structures in the nasopharynx can be viewed with a dental mirror and light source. The entire nasal cavity should be examined for masses, foreign bodies, polyps, and fungal or inflammatory plaques.

Nasal swabs are limited in their utility. The presence of bacteria and even fungal hyphae is not definitive evidence of a primary infectious process. Culture of rostral nasal secretions also has limited value. *Cryptococcus* infections can be diagnosed cytologically using standard stains or India ink because of their characteristic thick, non-staining capsule. Before flushing the nasal cavity or taking biopsies, the cuff of the endotracheal tube should be checked and the oropharynx packed with gauze sponges. Ventroflexing the head and neck and working from below the level of the nose, lavage fluid and blood will come out the nose and mouth protecting the airway. Saline can be flushed through the nares using the rigid scope, a feeding tube, or catheter attached to a large syringe. The liquid recovered should be collected and examined for foreign bodies, accumulations of cellular debris, and even abnormal tissue and parasitic ova. Fluids can also be flushed from the nasopharynx through the nasal passages with a flexible endoscope or large feeding tube. Multiple biopsies should be obtained from suspicious areas identified on rhinoscopy. Complications of rhinoscopy and nasal biopsy include severe hemorrhage, aspiration of blood, and neurologic signs if the rostral brain is damaged.

Primary bacterial rhinitis is rare, but secondary infection is common. Antibiotic treatment might improve clinical signs by resolving secondary infections. If the primary disease is not addressed, it will likely recur. Deep tissue cultures are the most likely to yield primary pathogens in cases with bacterial infection. If a foreign body is too large to remove or if rhinoscopy, flushing, and biopsies fail to aid in diagnosis, exploratory rhinotomy should be considered.

Hemoptysis

Hemoptysis (from Greek *hamia,* "blood" + *ptysis,* "spitting") is the expectoration of blood or bloody mucus from the respiratory tract at or below the larynx (E-Box 29-2). As with epistaxis, environment and signalment can indicate the source of hemorrhage. Animals that roam are susceptible to trauma, rodenticide intoxication, inhalation, and parasitic, rickettsial, and fungal infections. Young animals might be inclined to chew electric cords or play with small objects that could occlude their airway. Older pets are more likely to suffer from mitral insufficiency and primary lung or metastatic neoplasia. Furthermore, fungal and heartworm disease have endemic regions where animals are more likely to be affected.

E-Box 29-2

Causes of Hemoptysis

Pulmonary

Non-cardiogenic pulmonary edema or acute respiratory distress syndrome: Secondary to systemic inflammatory processes and multiple organ failure, airway obstruction, strangulation, electrocution, near drowning, or seizures.

Pulmonary thromboembolism: Secondary to neoplastic, endocrine, cardiac, metabolic disease

Pulmonary hypertension: Secondary to heartworm disease, congenital or acquired cardiac defects that result in shunting of blood

Chronic bronchitis/bronchiectasis
Bacterial and fungal pneumonia
Pulmonary abscess
Canine kennel cough complex:
Viral causes: Canine adenovirus 1 and 2; canine parainfluenza virus; canine respiratory coronavirus; canine reovirus; canine herpesvirus-1; canine influenza virus
Bacterial causes: *Bordetella bronchiseptica; Mycoplasma* spp.
Parasites: *Paragonimus kellicotti, Eucoleus aerophilus* (formerly *Capillaria aerophila*), *Aelurostrongylus abstrusus*
Pulmonary infiltrate with eosinophils (eosinophilic bronchopneumopathy)
Neoplasia: lung: Primary adenocarcinoma, undifferentiated carcinoma, squamous cell carcinoma, chondrosarcoma; metastatic; primary tracheal tumors
Lung lobe torsion

Cardiovascular

Cardiogenic pulmonary edema
Heartworm disease
Arteriovenous fistula
Bacterial endocarditis

Systemic

Coagulopathies: Primary (quantitative or qualitative platelet defects) or secondary hemostatic (factor deficiencies, anticoagulant rodenticide intoxication, disseminated intravascular coagulopathy), abnormalities
Trauma: Pulmonary contusion, tracheal rupture, foreign body
Iatrogenic: Endotracheal intubation, complication of lung biopsy/aspirate, transtracheal wash, or bronchoscopy

Information regarding cardiac and pulmonary abnormalities, medications (including heartworm preventative), toxin exposure, and travel history are essential. Owners should be questioned about the pet's history of exercise intolerance, dyspnea, syncope, and cough. They should be asked about recent trips to a groomer or other potentially stressful events that could trigger non-cardiogenic edema. Since hematemesis can be confused with hemoptysis, a careful history of gastrointestinal problems might be necessary. Recent surgery, trauma, or systemic disease can predispose patients to pulmonary thromboembolism. Prior bleeding episodes suggest coagulopathy. Animals with a history of cough prior to onset of hemoptysis might have chronic disease, such as bronchitis, neoplasia, heartworm disease, or left-sided heart failure. If blood is mixed with inflammatory sputum, more suppurative problems, such as bronchopneumonia or chronic bronchitis, are likely. Pulmonary edema fluid is usually bloody, with a more frothy character, while bright red blood is likely to be active arterial hemorrhage.

As with epistaxis, the initial physical examination should prioritize patient hemodynamics and oxygenation. Small amounts of blood in the lower airways can cause ventilation/perfusion mismatch and significant hypoxemia. Supplemental oxygen is usually indicated especially if mucous membrane color is pale, gray, or cyanotic. If oxygen by face mask, nasal cannula, oxygen hood, or oxygen cage is not sufficient, the patient can be intubated and mechanically ventilated. Hemoptysis secondary to thoracic trauma is indicative of pulmonary contusions. Contusions are best managed with cautious fluid therapy and attention to coagulation function. Auscultation of the airways might reveal fixed stridor over the region of an airway foreign body. Dynamic stridor over the larynx, more pronounced on inspiration, is common with severe laryngeal paralysis. Auscultation of the chest might reveal a regurgitant murmur with mitral insufficiency, moist crackles with pulmonary edema, or a fluid line with pleural effusion.

Vascular access should be established, though fluid therapy should approached cautiously. Pre-treatment blood samples should be collected for coagulation testing, packed cell volume, complete blood count, and biochemical profile. Specific treatment for left-sided heart failure should be instituted if the patient is severely volume overloaded. Diuretics should be used with caution in hypotensive or hypovolemic patients.

Pulmonary edema, secondary to either left heart failure or non-cardiogenic causes, can result in expectoration of blood and pink froth. Non-cardiogenic pulmonary edema is associated with a variety of acutely stressful events, including electrocution, near drowning, airway obstruction (inhaled foreign bodies, strangulation, laryngeal paralysis), and seizures.[5] Platelet defects are less likely to cause hemoptysis, though acquired coagulopathies, like anticoagulant rodenticide intoxication, can present with hemoptysis.

Heartworm disease can cause hemoptysis in dogs and cats. In dogs, exercise after adulticide therapy can result in worm embolization, inflammation of the pulmonary vasculature and parenchyma, and hemoptysis. Parasites, including *Capillaria, Aelurostrongylus,* and *Paragonimus* spp., cause pulmonary lesions that can bleed into airways. Chronic bronchitis (including feline asthma), bronchiectasis, and pulmonary infiltrate with eosinophils (PIE, eosinophilic bronchopneumopathy) can inflame the mucosa, causing bleeding during coughing. Infiltrative bacterial and fungal (*Blastomyces, Histoplasma, Coccidioides* spp.) pneumonia, lung abscesses and invasive neoplasia can all result in hemoptysis. Less common causes of hemoptysis include pulmonary thromboembolism, pulmonary hypertension, ruptured arteriovenous malformations, bacterial endocarditis, and lung lobe torsions.

In addition to the minimum database above, evaluation for systemic disease should include arterial blood gas analysis, urinalysis and three-view thoracic radiographs. The blood gas can help identify hypoxemia and hypoventilation that might require aggressive oxygen support and mechanical ventilation. Proteinuria or a fixed urine specific gravity could suggest renal or endocrine causes of pulmonary thromboembolism. Thoracic radiographs should be carefully evaluated for evidence of cardiac enlargement, pulmonary vascular congestion, pulmonary edema, traumatic rib fractures and contusions, pleural effusion, pneumonia, primary or metastatic neoplasia, foreign objects, and evidence of heartworm disease. If radiographs localize bleeding to one lobe, the patient should be positioned with that side dependent. A heartworm serology should be performed in dogs and cats from endemic areas. An echocardiogram can help characterize cardiogenic pulmonary edema and diagnose pulmonary hypertension. Parenchymal lesions in the lung can require the additional detail of a CT or MRI scan of the thorax.

Pulmonary edema, arterial hemorrhage from an invasive lesion, and traumatic pulmonary contusions are the most serious causes of hemoptysis. Sedation and supplemental oxygen after treating the cause of non-cardiogenic edema is usually sufficient. Cardiogenic edema can be managed with diuretics alone, though severe cases might require additional support (see ch. 242, 243, and 247). Traumatic pulmonary contusions present a therapeutic challenge, as aggressive fluid therapy might exacerbate bleeding. Careful attention to blood pressure, patient temperature, calcium, and pH will help identify other treatable causes of bleeding in the trauma patient. Fortunately, most other causes of hemoptysis are self-limiting with mild sedation and cage rest.

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CHAPTER 30

Syncope

Mike Martin

Client Information Sheet: Understanding the Causes of Faints and Fits in Animals

Collapse is a broad, generic term, defined as a sudden loss of postural tone, not necessarily with a loss of consciousness; it may be of any duration. *Syncope* is a subset of collapse that involves a transient loss of consciousness, resulting from insufficient blood flow to the brain. There is an associated reduction in delivery of oxygen and nutrients, which is of short duration and is followed by a recovery to normal.[1] A partial loss of consciousness can result in a brief period of ataxia or stumbling, which is termed *pre-syncope*. It is of paramount importance to differentiate syncope from non-syncopal causes of collapse, particularly neurological causes such as epileptic seizures (also see ch. 35).

The diagnostic rate for animals that present with collapse has been reported as 67% in one study of 743 dogs,[2] which is relatively high, as many animals have abnormalities on physical examination or diagnostic tests that lead to a diagnosis. In this study, there were 153 dogs with undiagnosed collapse of which 42% resolved, 23% continued to collapse, 24% died and 11% were subsequently diagnosed.[2]

If an animal presents in a state of collapse, the opportunity for a physical examination, with a logical approach, during the episode may allow the affected body system to be determined. However, when the animal presents with a history of syncope or non-syncopal collapse and walks into the clinic without clinical signs, then a diagnosis is challenging. In one study of human subjects, the mechanism of syncope remained unexplained in 40% of cases.[3] Additionally, differentiation from an epileptic seizure is difficult; it is estimated that 20% of human patients presenting to a neurology department are subsequently diagnosed with cardiogenic syncope,[4] which is likely to be similar in veterinary medicine.

Mechanisms and Causes of Syncope

It is important to understand the pathophysiological mechanism of syncope so that the relative significance of abnormalities on diagnostic findings is understood and used for directing appropriate treatment (Figure 30-1). Since syncope, by definition, is associated with a transient reduction in blood flow to the brain, then cardiogenic disorders dominate, as a consequence of hypotension associated with cardiac arrhythmias or neurocardiogenic reflexes. It is only by reaching a diagnosis that appropriate treatment can be provided. For example, it may be that patients with intermittent bradyarrhythmias might need pacemaker implantation or those with tachyarrhythmias may require antiarrhythmic therapy.[5]

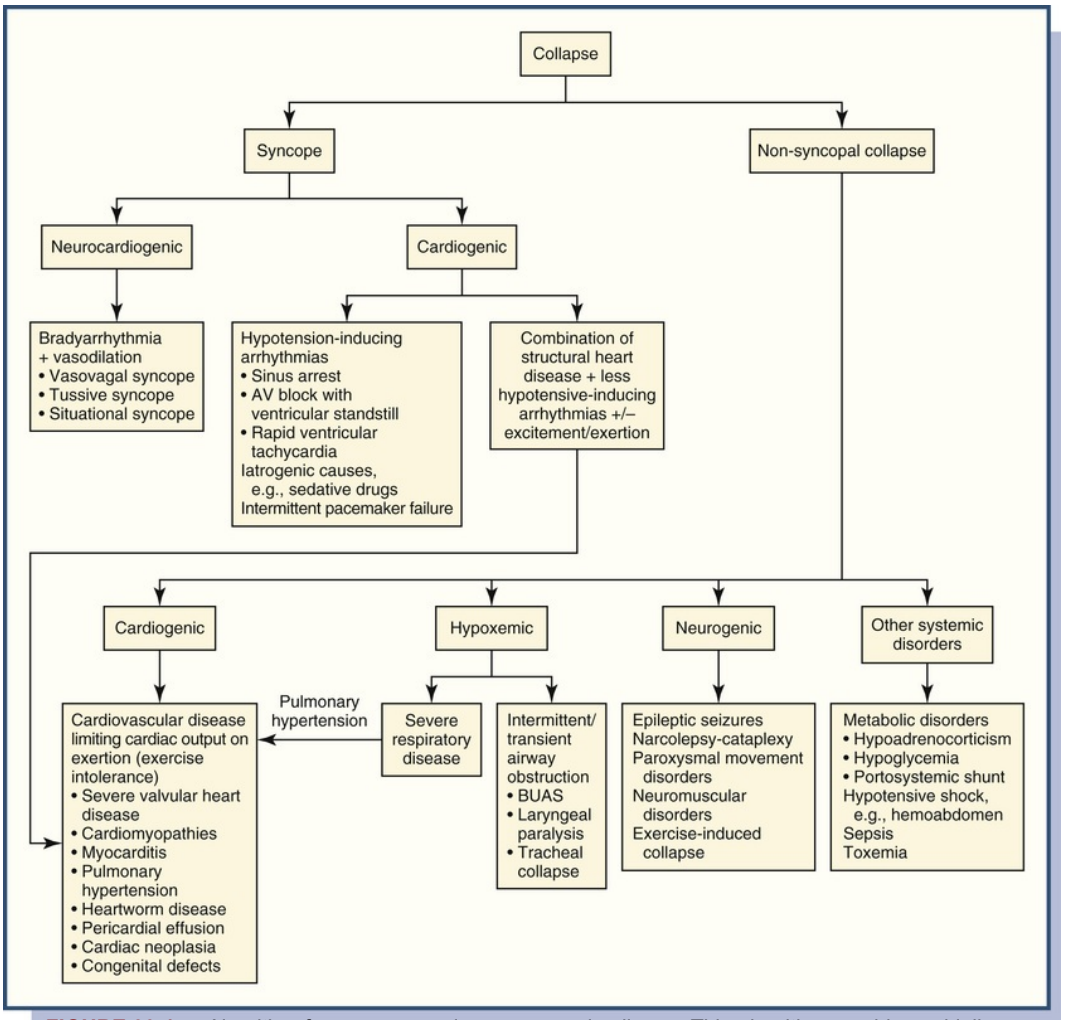

FIGURE 30-1 Algorithm for syncope and non-syncopal collapse. This algorithm provides guidelines for managing animals presenting with syncope and non-syncopal collapse, with the aims of assisting the veterinarian in how to approach this type of case. *BUAS*, Brachycephalic upper airway syndrome.

Cardiogenic Syncope

Cardiogenic syncope occurs when there is intermittent, profound hypotension that results in a marked reduction in blood flow to the brain. It is estimated that blood pressure has to fall by at least 50% before unconsciousness develops,[6] and blood pressure is usually much lower than this during syncope.[7] Therefore, for any arrhythmia to result in this degree of systemic arterial hypotension, it has to be profound and sustained. This requires an arrhythmia that results in asystole, such as sinus arrest or ventricular standstill, or a marked reduction in cardiac output, such as rapid ventricular tachycardia (VT). See ch. 248. Additionally, the duration of a sustained arrhythmia that causes sufficient hypotension to induce syncope has to be a minimum of 10-30 seconds, depending upon the activity level (metabolic demand) of the animal and the presence or absence of structural heart disease.

The most common arrhythmias that cause sufficient hypotension to result in syncope are bradyarrhythmias that result in asystole (for which a pacemaker might be indicated), such as sinus arrest (which might be part of sinus node dysfunction/sick sinus syndrome) or high-grade second-degree, or third-degree, atrioventricular block with periods of ventricular standstill; or tachyarrhythmias that have a marked effect on stroke volume, such as rapid VT (see ch. 248).[8-12] Atrioventricular block is usually evident at the time of examination, although rarely it can occur intermittently, particularly in cats with cardiomyopathy.[13] Sinus arrest or ventricular tachycardia can be intermittent and might only be detected on Holter or cardiac event recordings (Videos 30-1 and 30-3). Ventricular tachycardia does not always produce syncope, although at higher rates there will usually be a degree of hypotension, and it tends to be the more rapid VT that is

associated with syncope. If an arrhythmia is diagnosed, this should prompt further investigations to determine if there is an underlying cause of the arrhythmia such as cardiomyopathy, myocarditis, neoplasia, systemic or metabolic disorders, sepsis, toxemia, shock, or drug-related causes (see ch. 248). In animals fitted with pacemakers, checking for intermittent pacing failure such as lead displacement or high pacing thresholds needs consideration (see ch. 249).

Arrhythmias that produce a lesser degree of hypotension tend to result in episodic weakness rather than syncope. Such arrhythmias might include less-rapid VT or supraventricular tachycardia, or less profound bradyarrhythmias. However, the combination of structural heart disease or pulmonary hypertension (which is severe enough to limit cardiac output) with the addition of these arrhythmias, can result in syncope, particularly following excitement or exertion.[14] Importantly, there are several structural cardiac diseases that are known to be associated with a high incidence of arrhythmia, such as the various cardiomyopathies and myocarditis. Echocardiography is therefore always indicated in animals with syncope.

Neurocardiogenic Syncope

There are many synonyms that describe this type of disorder, including vasovagal syncope and vasodepressor syncope. Neurocardiogenic syncope occurs due to profound hypotension caused by the combination of a profound bradyarrhythmia and reflex vasodilation. It is characterized by sudden autonomic nervous system failure: there is withdrawal of sympathetic tone with abrupt increase in vagal tone,[15] although the exact mechanism remains unclear.[16] The triggering events are variable and determined by which afferent nerve or receptor is stimulated.[17]

Vasovagal syncope is probably the most well-known form of neurocardiogenic syncope in small animals, particularly in young Boxer dogs[2]; the trigger is usually intense excitement such as greeting the owner or play activity, resulting in triggering the neurocardiogenic reflex described above, and syncope. Vasovagal syncope also seems to be exacerbated by concurrent gastrointestinal or abdominal conditions, and syncope may resolve when the abdominal disorder resolves.[18] The presence of structural heart disease such as aortic stenosis or hypertrophic obstructive cardiomyopathy can exacerbate high left ventricular pressures, stimulating ventricular pressure receptors and triggering this neurocardiogenic reflex; this is termed the *Bezold-Jarisch reflex*.[19] This reflex originates in cardiac sensory receptors with non-myelinated vagal afferent C fibers in the left ventricle. When the receptors are stimulated by increased left ventricular pressure, the increased pressure is perceived as hypertension; reflex vasodilation, bradycardia, and syncope result. This reflex is also triggered in animals suffering rapid, severe hemorrhage; vigorous contraction of the left ventricle around a volume-depleted ventricular chamber produces a paradoxical increase in firing of these receptors, resulting in a reflex bradycardia and vasodilation.[19]

It is also well-known that some small breed dogs with degenerative mitral valve disease can present with syncope. The mechanism of the syncope in this setting remains unclear, but includes vasovagal syncope, arrhythmias, and pulmonary hypertension.[20] Situational syncope occurs when the neurocardiogenic reflex is triggered by activities such as coughing (tussive syncope),[21] vomiting, sneezing, micturition, defecating,[22] swallowing, or visceral pain.[1,23] Tussive syncope is common in dogs with either cardiac or respiratory disease; the mechanism remains unclear but may be associated with an increase in intrathoracic pressure during coughing inhibiting venous return or possibly a neurocardiogenic reflex vasodepressor-bradycardia response to cough.[21]

Non-Syncopal Collapse

It is difficult to differentiate syncope from the many causes of non-syncopal collapse that are not in association with a reduction in blood flow to the brain. Conditions to consider would include neurological conditions such as epileptic seizures (ch. 35), narcolepsy (ch. 262), paroxysmal movement disorders (ch. 31), neuromuscular disease (ch. 269) or exercise-induced collapse (EIC).[4,26] Animals with profound hypoxemia, such as those with severe respiratory disease, pulmonary hypertension, or transient upper airway obstructive conditions, can present with intermittent collapse particularly following excitement or exertion.[24-26] Coughing, common with respiratory conditions, can also lead to tussive syncope.[27]

History-Taking

When an animal is presented for evaluation of collapse, it can be very difficult to determine the type of collapse and to differentiate between cardiogenic syncope and seizures. Owners often will recall events in an array of descriptions, misleading analogies, or misunderstood terminology. It is critical that the clinician use analytical questioning to obtain as good an original description of the collapse as possible; this, therefore, also has to be from the person who witnessed the collapse. Differentiation between syncope and non-syncopal collapse is often difficult and therefore keeping an open mind to all causes of transient collapse is prudent. History-taking for collapse is a particularly difficult and challenging task for the clinician, which requires considerable time and experience. Obtaining movies of the animal during a collapse can be invaluable in these situations.

Determining if an animal was unconscious or not, from an owner, is difficult. Additionally, "unconscious" is a symptom, as opposed to a clinical sign. A client is usually unaware that the eyes often remain open when unconscious (or even dead) and this can be misinterpreted as being conscious (their pet was "staring at them"). It is more appropriate to ask questions around how responsive their animal was: did the pet react or move in response to touch or calling? Loss of bladder and/or bowel control with urination or defecation is not only seen with epileptic seizures but can also be seen with cardiogenic syncope (Video 30-2). Animals with cardiogenic syncope are often motionless (sleep-like) with flaccid limb and body tone. However, some that are partially unconscious can flail the limbs (as if struggling to get up), such that this can mimic epileptic seizures; detailed questioning is therefore needed to differentiate semi-conscious "leg-flailing" from repetitive paddling (swimming) movement of the limbs (more suggestive of epileptic seizures). Additionally, dogs with cardiogenic syncope that is prolonged or severe can develop profound cerebral hypoxia which results in a brief period of opisthotonos (forelimbs extended and stiff, with the head and neck extended dorsally), which seems to be uncommon with epileptic seizures (Videos 30-2 and 30-3). Epileptic seizures often are characterized by jaw chopping or chattering of the teeth, and salivation, followed by exhaustion on recovery due to the "exercise" that occurs with an epileptic seizure. Syncope may have a trigger event such as excitement or the onset of exercise, whereas epileptic seizures usually occur at rest or from sleep with no specific trigger, often have a pre-ictal period of anxiety or odd behavior, and also can be associated with facial muscle twitching. Cats can have cardiogenic syncope that mimics brief focal seizures.[28,29] Cardiogenic syncope typically is short in duration and the animal should generally return to normal within a few seconds to up to a minute, although it can be difficult for an owner to reliably recall the duration of time when in a panic. Epileptic seizures can be followed by a post-ictal period of up to hours where the animal may be confused, anxious, or display localizing neurologic signs.

Diagnostic Approach

If abnormalities are found on physical examination, these might identify the body system requiring further investigation. If there is no abnormality found on physical examination, then a meticulous history becomes the most important part of the assessment.

Comprehensive blood work is important (complete blood count and serum biochemistry profile including serum electrolyte and fasted glucose concentrations, and thyroid status); if hemorrhage is suspected, repeated blood tests may be necessary 12-24 hours later to reveal evidence of blood loss. If hypoadrenocorticism is suspected, an adrenocorticotropic hormone stimulation test should be performed.

An electrocardiogram (ECG) is usually indicated, certainly if an arrhythmia is present on physical examination. However, the ECG ideally needs to be performed when the syncopal event occurs, thus documenting if an intermittent arrhythmia was the cause of the syncope or not. Additionally, it is also important to rule out an arrhythmia prior to considering general anesthesia for additional diagnostic investigations such as magnetic resonance imaging of the brain. For these reasons, Holter monitoring has become a key diagnostic test in syncopal animals. It is important when using a Holter monitor that the timing of the event is accurately and reliably recorded, and this is really only reliably achieved by asking the client to press the "event button" on the Holter monitor. Pressing the button at both the start and end of the syncopal event can sometimes be useful (ch. 103). Many animals may not have a syncopal event while the Holter monitor is being worn, so attempts to induce syncope can be encouraged, in view of the importance of reaching a diagnosis so that the correct treatment can be chosen (provided such attempts do not pose undue risk to the patient). From the history, it should be determined if there is a trigger for the syncope, and while this may not be common, if there is, then this behavior or routine can be encouraged in moderation during the Holter recording, once the animal's owner understands the risk to benefit ratio of such an approach and provides informed consent. Holter monitoring typically continues for 24 hours for an arrhythmia count; however, in animals with syncope, the Holter ideally needs to be worn until there is an episode of collapse;

this can take several days, or potentially longer, depending upon the frequency of syncope. In such cases, an external cardiac event recorder also can be a viable option.[9] The limits of duration revolve around what the animal will tolerate, the capacity of the memory card, and battery life. For the majority of cases, the Holter monitor can be worn for 5-7 days. Even if the animal does not collapse within that time, there can be periods of arrhythmia that might be suggestive of the underlying mechanism of syncope.

Insertable loop recorders are implantable event devices that can be placed surgically.[30] Although they are not commonly used in veterinary practice, they provide an alternative option for animals that do not have a syncopal event during Holter monitoring but an arrhythmia is still suspected or important to rule out.

In the majority of cases, echocardiography is indicated to screen for structural heart disease, or for conditions that might be associated with arrhythmias, such as cardiomyopathy (ch. 104). Thoracic radiographs might reveal changes consistent with cardiac or respiratory disease; occasionally, they might be indicative of hypovolemic shock (microcardia, small caudal vena cava, hypovascular lung fields) warranting an investigation for underlying causes, including blood work and abdominal ultrasonography in search of abdominal disease such as hemoabdomen.

If the results of all of the above evaluations are still inconclusive, then the key step remains Holter recording to document if intermittent sustained arrhythmias are the cause of collapse or not; this may need to be repeated a few times, or an event recorder or implantable loop recorder may need to be considered. Alternative options include teaching the client to examine the mucosa for pallor (lips and gums are more reliable than the tongue), or palpating or even ausculting the heart during syncope, although this can be difficult if the duration of syncope is short. Instructing the owner to take a movie of the collapse is particularly useful in providing the opportunity for the clinician to observe the event and decide if this is syncopal or non-syncopal collapse and potentially the body system involved.

The prognosis for patients with syncope depends on the inciting cause. Syncope may indicate a worse prognosis when it is the presenting complaint in Dobermans with DCM[31] or Boxers with ARVC and syncope compared to Boxers with ARVC when the arrhythmia is an incidental finding. Conversely, a chief complaint of syncope is associated with a better prognosis than signs of CHF or ATE in cats with HCM.[32,33]

Summary

Collapse is a broad generic term, defined as a sudden loss of postural tone, but not necessarily with a loss of consciousness. Syncope is a subset of collapse that is characterized by unconsciousness, due to a transient reduction in blood flow to the brain, which is of short duration followed by a rapid recovery to normal. The common causes of syncope are classified as cardiogenic or neurocardiogenic. It is of paramount importance to differentiate syncope from the large number of non-syncopal causes of collapse, particularly epileptic seizures and paroxysmal movement disorders. Cardiovascular conditions dominate the differentials for syncope, most commonly as a consequence of hypotension associated with cardiac disease or neurocardiogenic reflexes. If no abnormality is found on physical examination, then a meticulous history becomes the most important part of the assessment. If diagnostic tests are inconclusive, then the key step is documenting an episode of collapse on Holter recording to rule in/out an intermittent arrhythmia, and this may need to be repeated in some animals. Once a diagnosis is reached, then causes need to be investigated in order to provide appropriate treatment.

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Neurologic

OUTLINE

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CHAPTER 31

Movement Disorders

William B. Thomas

"Movement disorders" are a group of heterogeneous neurologic conditions that result in slow movements (hypokinetic disorders) or abnormal involuntary movements (hyperkinesias). There is no classification system because neuroanatomic lesions or the pathophysiology is not always known. Clinical descriptions provide the best method for categorizing these diverse disorders.

Clinical Evaluation

Clinical evaluation requires a complete history as well as a description of the abnormal movement. The client's objective observations are generally more valuable than their subjective conclusions. For example, a complaint of "tremor" is less precise than reporting "the head suddenly jerks downward every second or so." Encourage clients to videotape episodes. For episodic abnormalities, ask about duration, frequency, progression, and any factor that might precipitate events, such as rest, excitement, or exercise. Is the patient conscious and responsive during episodes? Can the client stop the movement by distracting, petting, or feeding the pet? Past and current medical history, vaccination status, and previous illness, injury or toxin exposure can be important. Have any changes in behavior, gait, or other activity been observed between episodes? Perform a thorough neurologic examination to detect any persistent deficits that might help identify a neuroanatomic lesion (see ch. 259). Based on initial evaluation and differential diagnosis, imaging, electrodiagnostic testing (see ch. 117), or analysis of spinal fluid may be indicated.

Spasticity

Spasticity is an increase in muscle tone due to hyperexcitable muscle stretch (myotatic) reflexes (Video 31-1). Muscle tone is the velocity-dependent resistance of muscle to passive stretch, maintained by intrinsic muscle stiffness and myotatic reflexes mediated by lower motor neurons. Descending upper motor neuron pathways normally attenuate the myotatic reflex. Lesions of the upper motor neuron pathway cause changes in the excitability of motor neurons, interneuronal connections, and local reflex pathways that can lead to hyperexcitable myotatic reflexes and spasticity. The interval between injury and the appearance of spasticity varies from days to months. Once spasticity develops, chronic muscle shortening enhances intrinsic muscle, collagen tissue, and tendon stiffness that can lead to subclinical contractures and exacerbation of spasticity. Increased muscle tone predominates in the antigravity (extensor) muscles, causing a spastic gait characterized by decreased limb flexion. At rest, there is increased resistance to passive limb flexion, exaggerated myotatic reflexes and usually other signs of an upper motor neuron lesion such as paresis and ataxia.

Treatment of spasticity is directed at the underlying lesion, most commonly a chronic spinal cord disease. Physical therapy may be helpful (see ch. 355). It involves strengthening and stretching flexor muscles to maintain normal range of joint motion and minimize contracture. Benzodiazepines such as clorazepate (0.5 to 2 mg/kg PO q 12 h) sometimes help decrease muscle tone. In some patients, spasticity actually aids weight bearing by increasing extensor muscle tone. Thus, dosage should be titrated to avoid weakness.

Myotonia

Myotonia is prolonged contraction or delayed relaxation of a muscle after voluntary or stimulated contraction. Congenital myotonia is well characterized in the Chow Chow and Miniature Schnauzer and occurs sporadically in other dog breeds and domestic cats. Signs are evident by 3 weeks of age and include muscle rigidity (non–velocity-dependent resistance to stretch), difficulty rising, and a stilted gait that improves with movement. Patients may exhibit muscle hypertrophy, dysphagia, or a high-pitched bark. Tapping a muscle

with a reflex hammer causes a dimple. Diagnosis is based on clinical features (Video 31-2). Electromyography (EMG, see ch. 117) is used to confirm myotonia by finding complex repetitive discharges (Video 31-3). In the Miniature Schnauzer, congenital myotonia is caused by a chloride muscle channel mutation for which genetic testing is available. Extended-release procainamide (40 mg/kg PO q 8-12 h) or mexiletine (8.3 mg/kg PO q 8 h) improves the signs.[1]

Acquired myotonia is an uncommon complication of iatrogenic or naturally-occurring hyperadrenocorticism (see ch. 306). Affected dogs show a stilted gait with decreased limb flexion, increased muscle tone, enlargement of proximal limb muscles, percussion myotonia, and EMG evidence of myotonia. Treatment of hyperadrenocorticism partially improves the condition in only a minority, with most having persistent myotonia. Procainamide may be helpful. Myotonia is sometimes a component of other progressive myopathies.

Tetany

Tetany, sustained muscle contraction worsened by stimulation and lessened with relaxation, is a classic result of hypocalcemia (see ch. 69 and 298). Strychnine blocks the inhibitory neurotransmitter glycine causing tetany. A congenital syndrome due to stimulus-induced muscle contractions that resolve with rest has been described in a family of Labrador Retrievers.[2] Voluntary movement or stimulation induces extensor rigidity and apnea, but no alteration in consciousness. Although called "reflex myoclonus," the signs are more consistent with tetany and are similar to hyperexplexia or stiff baby syndrome in children, which is caused by a glycine receptor mutation.

Tetanus

Tetanus is sustained muscle contraction without relaxation. The most common cause is infection with *Clostridium tetani* (see ch. 214). Under anaerobic conditions, the organism produces the toxin tetanospasmin that interferes with release of inhibitory neurotransmitters glycine and gamma-aminobutyric acid. Patients with focal tetanus have sustained contractions in muscles close to the wound, usually the head or a limb. In generalized tetanus, patients suffer generalized muscle rigidity, trismus secondary to masticatory muscle contraction, dysphagia due to pharyngeal muscle involvement, and risus sardonicus resulting from facial muscle involvement (Figure 31-1).

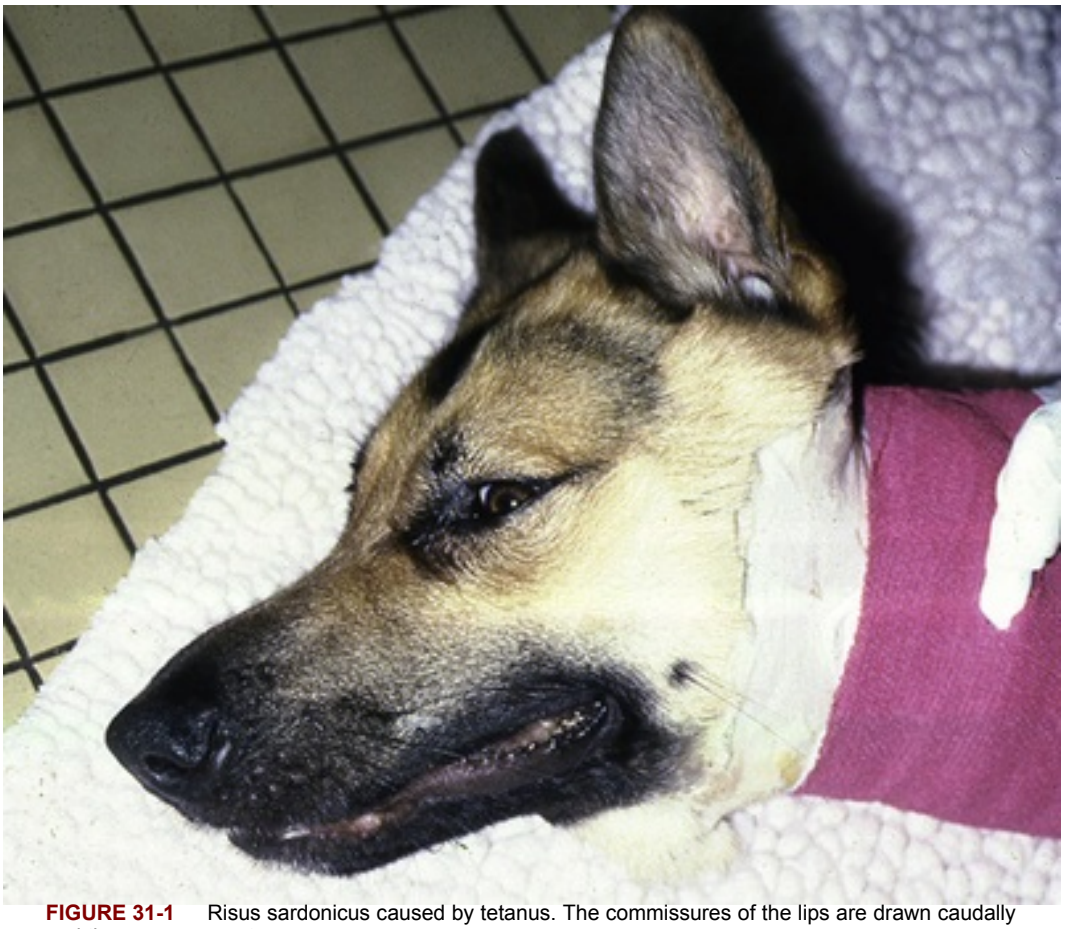

FIGURE 31-1 Risus sardonicus caused by tetanus. The commissures of the lips are drawn caudally and the ears are erect.

Paroxysmal Dyskinesia

Background

Dyskinesia is a general term for various forms of abnormal movement. Paroxysmal dyskinesia is characterized by episodes of abnormal movement in an individual who, between events, is normal in movement and behavior. Clinical manifestations vary and include: (1) dystonia: sustained muscle contractions resulting in twisting and abnormal posture of the face, trunk, or limbs, (2) chorea: rapid, irregular, non-repetitive movements of the face, trunk, or limbs, (3) athetosis: a slow form of chorea characterized by writhing movements that tend to overlap, and (4) ballism or ballismus: a severe form of chorea in which the movements have a violent, flinging quality.

Episodic Falling in Cavalier King Charles Spaniels

This disease is characterized by paroxysmal tetany or increased muscle tone diagnosed in dogs 3 months to 4 years of age. An autosomal recessive mutation in the gene *BCAN*, which encodes a proteoglycan called brevican found primarily in the central nervous system, is a likely cause.[3,4] Episodes are precipitated by excitement, stress, or variable periods of exercise and consist of sustained contraction of limb and trunk muscles, causing the dog to stand rigidly or fall. There is no loss of consciousness. Episodes last seconds to minutes, after which the patient recovers completely. Clients can sometimes interrupt an episode by interacting with the dog. Laboratory and electrodiagnostic testing are normal. Diagnosis is based on clinical features and DNA testing. Clonazepam (0.5 mg/kg PO q 8 h) is useful in minimizing frequency and severity of attacks in some dogs.[5]

Epileptoid Cramping in Border Terriers

The pathophysiology of this syndrome, initially called *Spike's disease,* is not understood. Age of onset varies from several months to 7 years of age. Affected dogs suffer paroxysmal episodes of difficulty walking, stretching, and licking, that progress to difficulty standing, tremor and dystonia of the limbs, head and neck. Episodes are sometimes associated with borborygmus, vomiting and diarrhea. Pets appear healthy between episodes. Since laboratory evaluation, brain magnetic resonance imaging (MRI), and spinal fluid analysis are normal, the diagnosis is based on clinical features. Anti-seizure medication is generally ineffective, but about 50% of afflicted dogs exhibit some improvement after being fed a hypoallergenic diet or a single protein and carbohydrate source diet.[6]

Paroxysmal Dyskinesia in Chinooks

This is an autosomal recessive inherited disorder. Signs generally start by 3 years of age. Episodes are characterized by kicking or flailing (ballism), limb flexion, repetitive limb movements and, occasionally, head tremor. There are neither autonomic signs nor loss of consciousness. Ictal electroencephalographic (EEG) monitoring is normal, suggesting a non-seizure condition.[7] Affected dogs are normal between episodes. Laboratory test results, brain MRI, and spinal fluid analysis are normal. The diagnosis is based on clinical features. Currently, there is no effective treatment.

Scottie Cramp

Scottie cramp is an inherited autosomal recessive condition in Scottish Terriers. An identical syndrome has been reported in related breeds (Cairn, Norwich, West Highland White and Cesky Terriers). Clinical signs become apparent by 6 weeks to 18 months of age. Excitement or exercise induces progressive increase in muscle tone causing lumbar kyphosis and decreased flexion of the pelvic limbs, sometimes severe enough to cause a fall. There is some evidence that the disease is caused by alteration in function of the neurotransmitter serotonin. Laboratory tests, electrodiagnostics, and muscle biopsies are normal. Treatment consists of lifestyle adjustments to avoid precipitating factors and acepromazine maleate (0.1 to 0.75 mg/kg PO q 12 h) or diazepam (0.5 mg/kg PO q 8 h). The disorder is nonprogressive and does not seriously compromise the dog's quality of life.[8]

Episodic Head Tremor

Episodic head tremor occurs in Doberman Pinschers, English Bulldogs, Boxers and, less commonly, other dog breeds.[9,10] The onset varies but is usually in adulthood. Dogs with this condition have paroxysmal vertical or horizontal head tremors. Episodes last from seconds to hours. Dogs are fully conscious and otherwise able to move normally during an episode. In many cases, the episode can be stopped momentarily by distracting the dog, such as by feeding a treat. The frequency of attacks varies from once every few months to multiple times daily. This syndrome is not fully understood, but it generally does not improve with antiseizure medication so it may be a paroxysmal dyskinesia. Diagnostic testing, including laboratory analysis, brain MRI, and spinal fluid analysis are normal. There is no effective treatment. The disorder does not adversely affect quality of life. The condition may naturally resolve. Clients should be assured that their pet does not have a more serious disorder.

Paroxysmal Dyskinesias in Other Breeds

Other paroxysmal dyskinesias have been reported in the Bichon Frise, Boxer, Springer Spaniel and Wheaten Terrier.[11]

Drug-Induced Dyskinesia

In people, dyskinesias are a side-effect of several drugs, most commonly those that antagonize dopamine. Other implicated drugs include metoclopramide, antiseizure drugs, anticholinergics, and antihistamines. Dyskinesia, characterized by contractions of facial, neck, and shoulder muscles, has been reported as an adverse phenobarbital effect in a dog.[12] Drug-induced dyskinesia should be considered in patients that develop movement disorders while taking medication. Signs typically resolve with withdrawal of the offending drug.

Myokymia and Spinocerebellar Ataxia

Myokymia is contraction of small groups of muscle fibers resulting in visible rolling, wormlike undulations. A complex neurologic disease characterized by ataxia, seizures, and episodes of myokymia occurs in Jack Russell, Parson Russell, and Russell Terriers. The cause is a mutation in the gene that encodes glial potassium channels that regulate neuronal excitability by buffering extracellular potassium and facilitating glutamate uptake.[13]

The age of onset is several months to several years. Episodes are often precipitated by excitement or exercise and are sometimes preceded by facial rubbing. There are visible undulating muscle contractions, often more obvious in the proximal limb. These muscle contractions often progress to generalized stiffness and collapse (neuromyotonia). Consciousness is maintained. Afflicted dogs are often anxious, restless, panting and hyperthermic during attacks. Episodes last from a few minutes to several hours. Severe attacks can be fatal. Affected dogs commonly have persistent generalized or pelvic limb ataxia and hypermetria starting at several months of age. Some also develop epilepsy. Laboratory analysis may show mild increases in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and creatine kinase results. Electromyography is normal or shows myokymic discharges (spontaneous activity consisting of regularly occurring high-frequency bursts of 2, 3, or more motor unit action potentials) in muscles showing visible contractions (see ch. 117). Procainamide (10 mg/kg PO q 12 h) or mexiletine (4 mg/kg PO q 12 h) may decrease severity and frequency of attacks. Sedation or general anesthesia is necessary to abort severe attacks.[14]

Myoclonus

Myoclonus is a brief, shock-like contraction of skeletal muscle (see Videos 31-1 and 31-4). Physiological myoclonus occurs in healthy animals and typically causes no disability. Familiar examples are hiccoughs (brief contractions of the diaphragm) and muscle jerks during sleep. The normal "startle response" is a stereotypical myoclonus response to an unexpected sudden stimulus, such as the eyelid blink and brief contraction of head, neck, and limb muscles in response to a loud noise. Epileptic myoclonus is a rare form of seizure that consists of focal or generalized myoclonic jerks. The cause may be idiopathic or underlying brain disease. A genetic disease similar to Lafora's disease in people has been described in several breeds of dog and cat that causes intermittent myoclonic jerks of the head, neck, and thoracic limbs, often in response to visual stimuli.[15] Drug- and toxin-induced myoclonus may follow exposure to chlorambucil, lead, or intrathecal morphine.[16-19] The myoclonus usually resolves after drug withdrawal or treatment of the intoxication.

Encephalomyelitis

Encephalomyelitis caused by canine distemper virus is the most common cause of myoclonus in dogs (see ch. 228; see Videos 31-4 and 31-5). This condition was once called *chorea*, but chorea is a more complex, nonrepetitive, irregularly-timed movement, not the brief, simple muscle jerk of myoclonus. Affected dogs often have other neurologic signs of distemper such as ataxia or weakness, but myoclonus can be the only sign. The muscle contractions are most obvious at rest and can persist during sleep or even general anesthesia, usually occurring rhythmically every 1 to 3 seconds. Rarely, myoclonus is generalized, but more commonly it is restricted to a muscle or a group of muscles innervated by adjacent regions of the spinal cord or brainstem. Limb or jaw muscles are commonly involved, but any skeletal muscle can be affected including the tongue and extraocular muscles. Distemper myoclonus is often refractory to treatment although focal myoclonus is usually not terribly disabling. Procainamide (10 to 20 mg/kg PO q 8 h) may be effective. Other inflammatory diseases of the nervous system can also cause myoclonus in dogs, including granulomatous meningoencephalomyelitis, bacterial encephalitis, protozoal encephalitis, and steroid-responsive meningitis-arteritis.[20]

Dancing Doberman

Dancing Doberman disease is initially characterized by flexion of one pelvic limb when standing (see Video 31-5). Within months, the other pelvic limb becomes affected such that the dog alternately flexes and extends each pelvic limb in a dancing motion. These dogs prefer to sit rather than stand.[21] This disorder is recognized in Doberman Pinschers 6 months to 7 years of age. They may develop an insidiously progressive paraparesis

with decreased proprioception and atrophy of the gastrocnemius muscle. Based on electrodiagnostic testing (see ch. 117) and nerve biopsy (see ch. 116), this may be a peripheral neuropathy with pelvic limb movements related to paresthesias in their paws.

Other Abnormal Movements

Muscle spasms caused by pain, especially intervertebral disk extrusion, can be confused with movement disorders such as myoclonus. Affected animals often suffer intermittent, painful contractions of their paraspinal muscles and may flex one limb. Movement often precipitates an attack. Palpation and manipulation of the spine usually identifies the painful region.

Tremor is a rhythmic oscillation of the body or body part due to alternating contractions of antagonistic muscles (see ch. 32). It occurs with a number of disorders.

Seizures can result in a variety of abnormal movements and are usually recognized by their stereotypic pattern and spontaneous onset (see ch. 35). Seizures are often accompanied by some alteration in consciousness. There may also be autonomic signs, such as urination or salivation. Postictal dysfunction, such as abnormal behavior and ataxia, has been reported.

Normal and abnormal movements can occur during sleep. Important features are that the movements only occur during sleep and the patient can be awakened normally during an episode with no postictal signs.

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CHAPTER 32

Tremors

Clare Rusbridge

Client Information Sheet: Idiopathic Generalized Tremor Syndrome (IGTS)/White Shakers

Definition

A tremor is a rhythmical, involuntary, oscillatory movement of a body part produced by alternating contractions of reciprocally innervated muscles.[1,2] Tremor is easy to see but more difficult to categorize and treat[3] and can be confused with other movement disorders such as dystonia (see ch. 31).[4]

Pathophysiology of Tremor

Achieving coordinated movement requires reciprocal innervation (Sherrington's Second Law), i.e., a premotor neuron sends excitatory projections to the motor neurons innervating the agonist muscle group (for example, the joint extensors) and to the inhibitory neuron innervating the motor neuron for the antagonist muscle group (for example, the joint flexors).[5] This reciprocal innervation is controlled by neural circuits in the thalamus, inferior olive nucleus, cerebrum, and cerebellum.[6] Of particular importance is the dentate-rubro-olivary tract, which links the dentate nucleus of the cerebellum with the contralateral red nucleus and the inferior olive nucleus.[7] These circuits with their complex feedback loops are inherently unstable. If neural membrane excitability increases or if inhibition is reduced, then the circuit begins to oscillate. These rhythmic oscillations manifest as tremor.[6]

Neurotransmitters and Tremorlytic Drugs

The cerebellar Purkinje neurons (or cells which synapse on them) are implicated in many tremor syndromes.[6,8] Purkinje cells are inhibitory and GABAergic and influence the outflow of the deep cerebellar nuclei such as the dentate nuclei. Other important neuron groups are the excitatory noradrenergic neurons of the locus coeruleus which synapse and influence the Purkinje cells.[9-11] It is suggested that decreased GABAergic inhibition of deep cerebellar neurons disinhibits their pacemaker activity, resulting in rhythmical activity of the thalamic and thalamocortical circuits.[12,13] Supporting this theory is the observation that many types of tremor respond to drugs that enhance postsynaptic GABA-mediated inhibition, such as phenobarbital and primidone, and/or drugs that have a membrane-stabilizing effect, such as propranolol, gabapentin, and topiramate.[6,8,14,15] Hence, these drugs are the mainstay for treatment of many human tremor conditions (such as essential tremor) and can be of benefit in some veterinary tremor syndromes.[16-18] Parkinsonian tremor is related to basal nuclei dopaminergic degeneration and abnormalities of striatal acetylcholine signaling.[19,20] The mainstay of treatment of human Parkinson's disease are drugs affecting dopaminergic neurotransmission such as L-dopa (increases striatal dopamine), dopamine agonists, and inhibitors of monoamine oxidase (block dopamine degradation).[15] In addition, symptoms are relieved by anticholinergics.[15,19] As conditions comparable to Parkinson's disease are not yet recognized in domestic small animals, use of these drugs for tremor syndromes has not been reported.

Classification

In human medicine, tremor is categorized according to topographical distribution, task- or position-dependence, frequency, and amplitude. Classification was simplified when the Movement Disorder Society

produced a consensus statement.[1] Typical diagnostic aids include tremor electromyographic (EMG) activity (see ch. 117) and computerized tremor analysis with accelerometers attached to body parts.[21] In veterinary medicine, there is no such consensus classification and "borrowing" from the human system has inherent problems because of the absence of diagnostic techniques, because dogs and cats are quadrupeds with weight-bearing forelimbs that cannot be asked to perform a task or hold a non-weight-bearing posture, and because a diagnosis often is made by the patient's subjective description.[1] In addition, it is rare for a tremor syndrome to be associated with a single type of tremor; for example, cerebellar disease is associated with more than an intention tremor. Consequently, it can be easier to consider each tremor syndrome separately. Nevertheless, different tremors have a different etiology and potential management, so it is useful to use a simple classification system. The basic tremor types are resting and action. As the name suggests, resting tremors occur in a body part that is completely supported against gravity without voluntary muscle contraction, whereas action tremors occur with voluntary muscle contraction. Action tremors are subdivided into postural, kinetic (simple, intention, and task) and isometric (Table 32-1).[1,22,23]

TABLE 32-1

Classification and Examples of Tremor Syndromes

TYPE OF TREMOR	FEATURES	EXAMPLE OF UNDERLYING DISORDER
Rest	Tremor when body segment (muscle) is at rest (see Videos 32-2 and 32-11). Demonstrated in a patient lying down and relaxed. More obvious in the distal limb. May be asymmetrical. Resting tremor is uncommon in veterinary medicine but in humans is one of the most important signs of Parkinson's disease and advanced stages of essential tremor.[60] Rule out dystonia where jerky movements may be seen at rest.	Mycotoxicosis
Action		
Postural	Occurs in a body part that assumes a posture against gravity (not standing). Holding the body part against gravity activates load-bearing muscles, which in turn activate tremor. In quadrupeds, most easily assessed in the head. Humans are assessed by being asked to maintain arm and finger posture.	Physiological Postural enhanced physiological (stress, metabolic disease, or intoxications) Cerebellar ataxias (only as part of other cerebellar signs) (see Videos 32-3 and 32-5) Idiopathic generalized tremor syndrome (see Video 32-1)
Kinetic—Simple	Tremor occurs during entire movement trajectory	Cerebellar ataxias Mycotoxicosis Harmaline neurotoxin (rodent model of essential tremor) Idiopathic generalized tremor syndrome (see Video 32-1)
Kinetic—Intention	Tremor progressively increases towards intended target	Cerebellar ataxia (see Videos 32-4 and 32-5)
Kinetic—Task-specific	Only during specific tasks, e.g., writing	No veterinary examples
Isometric	Tremor that occurs during isometric muscle contraction. An isometric muscle contraction, or static exercise, is one in which the muscle fires but there is no movement at a joint or change in length of the muscle. Occurs during voluntary	(senile) Isometric limb tremor (see Video 32-6) Orthostatic tremor in

	muscle contractions against a stationary resistance (e.g., standing).	Great Danes and Scottish Deerhounds (see Video 32-7)
Tremor-like Movement Disorders	Myokymia—rippling muscle contractions Myoclonus—brief, involuntary twitching of a muscle or a group of muscles Dystonia—a sustained involuntary contraction of a group of muscles characterized by a repetitive or patterned pulling or twisting movement	Myokymia—spinocerebellar ataxia with myokymia in the Jack Russell Terrier (see Video 32-9) Myoclonus—post distemper virus encephalitis Cortical myoclonus (cortical tremor) myoclonic jerks associated with epilepsy (see Video 32-8) Dystonia—idiopathic paroxysmal head tremor (see Video 32-10)

Acute Onset Generalized Tremor Syndromes

Physiological and Enhanced Physiological Tremor

Physiological tremor is a barely visible tremor that occurs in healthy individuals. Physiological tremor can be enhanced in certain situations such as loading (muscle fatigue), stress, some drugs and toxins (e.g., caffeine, theobromine, beta-adrenergic agonists), some metabolic diseases (e.g., thyrotoxicosis, hypoglycemia, hypocalcemia) and thermoregulatory shivering.[24]

Mycotoxicosis and Other Tremorgenic Intoxications

Ingestion of tremorgenic mycotoxins can result in acute-onset generalized tremor. Mycotoxins are toxic secondary metabolites produced by fungi and molds, and the most commonly ingested tremorgenic compounds are the *Penicillium* toxins, in particular penitrem A and roquefortine.[25] A whole-body tremor is present at rest and is exacerbated by effort and anxiety. Affected animals may also show mydriasis, vestibular signs, facial myoclonus, generalized seizures, hyperesthesia, hyperthermia, tachycardia and gastrointestinal signs (vomiting, diarrhea, flatulence).[25-27] The most important differential diagnoses are other intoxications including drugs (theobromine, cannabis/marijuana, lysergic acid diethylamide [LSD], cocaine, amphetamines, phenylpropanolamine, pseudoephedrine, cholinesterase inhibitors, ivermectin, methylxanthines) and poisons (permethrin, strychnine, metaldehyde, ethylene glycol, macadamia nuts).[25] In a rodent model, tremorgenic mycotoxins decreased GABAergic inhibitory outflow and increased release of glutamate (excitotoxicity).[26,28-30] Therefore, drugs affecting these targets would seem most appropriate for treatment. However, the tremors often are resistant to treatment with intravenous benzodiazepines,[25] possibly due to intracellular chloride ion accumulation secondary to excitotoxicity.[31] An outline of the management of tremorgenic intoxication is detailed in Figure 32-1. Drugs recommended vary between clinicians and use is often based on anecdotal and personal experience.[25,27,32] The author prefers dexmedetomidine as a first line agent followed, if necessary, by anticonvulsants.[32] Dexmedetomidine is a central alpha-2–adrenoreceptor agonist with a site of action at the locus coeruleus, influencing Purkinje cell and GABAergic output.[10,33,34] Use of the muscle relaxant methocarbamol in cases without seizures is described, but this concerns the intravenous preparation, which is not available in some countries.[35] Mycotoxins are highly lipid soluble, which explains their excellent ability to penetrate the brain,[25] and there is some evidence that using intravenous fat emulsion (i.e., Intralipid 20%) can be effective in management of nervous system toxicosis from lipophilic agents (see ch. 151).[36]

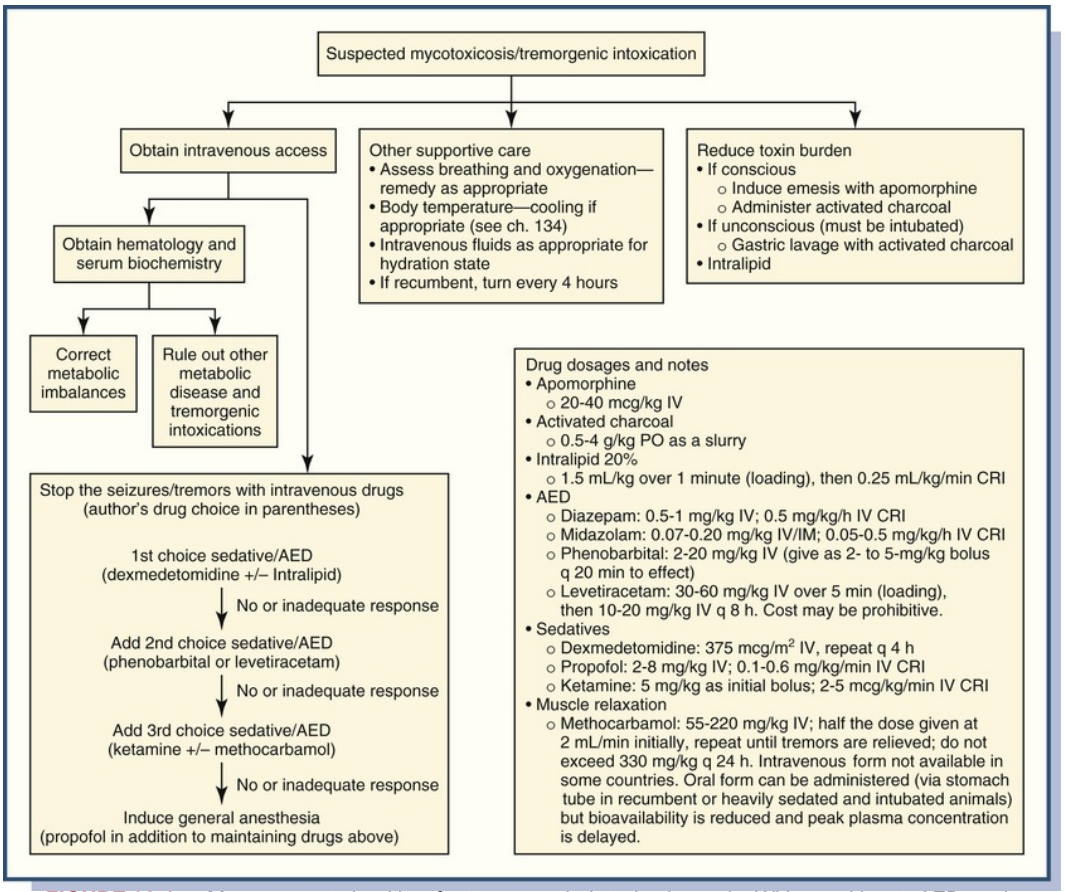

FIGURE 32-1 Management algorithm for tremorgenic intoxication. *+/−*, With or without; *AED,* antiepilepsy drug; *CRI,* constant rate infusion; *h,* hour; *IV,* intravenous; *min,* minute.

Idiopathic Generalized Tremor Syndrome (IGTS)

Patients with IGTS are also referred to as *white shakers*, because of a tendency for this disorder to occur in white breeds like West Highland White Terriers and Maltese dogs. However, IGTS may occur in any dog breed or cross (rarely in large breeds) and is also reported in cats.[37,38] It occurs in young adult dogs; other diseases are more likely in dogs aged 5 years and older. The etiology is undetermined, but histopathological studies and response to immunosuppressive doses of corticosteroids suggest that it is a non-infectious central nervous system (CNS) inflammatory disease. Affected dogs have a whole-body tremor that worsens with anxiety (Videos 32-1 and 32-2). Associated signs include elevated body temperature, hyperesthesia, opsoclonus (ocular tremor), and mild vestibular signs such as head tilt and ataxia. Results of magnetic resonance imaging and cerebrospinal fluid (CSF) analysis can be normal or suggest mild inflammatory change (mononuclear or lymphocytic pleocytosis on CSF analysis). Management is with immunosuppressive dosages of prednisolone starting at 1-2 mg/kg PO q 12-24 h. Some cases may require additional immunosuppressive therapy, such as leflunomide at a starting dosage of 4 mg/kg PO q 24 h. In most cases, the tremor improves in 3-10 days. After the tremor resolves, the corticosteroid dosage is tapered slowly, usually over 6 months or more. The prognosis is good, although relapses can occur and in some patients a low dosage of corticosteroids must be continued for many months. It is important to manage any comorbidities, especially inflammatory bowel disease. Treatment of the tremor with diazepam and/or propranolol in addition to prednisolone is reported.[18]

Other CNS Inflammatory Disease That May Present with Tremor

Any patient with CNS disease that involves the cerebellum or the neural circuits between thalamus, inferior olive nucleus, cerebrum, and cerebellum can present with tremor. However, unlike IGTS, where generalized tremor is the predominant sign, in other CNS inflammatory diseases the tremor occurs in addition to other

neurological signs, like postural deficits. If there is associated meningitis, then pain will be a predominant feature. The most important differential diagnoses for IGTS are granulomatous meningoencephalomyelitis (Video 32-3), necrotizing meningoencephalomyelitis, viral encephalitis (e.g., Aujeszky disease virus[39]) and protozoal encephalitis (Video 32-4).

Chronic Onset Generalized Tremor Syndromes

Cerebellar Tremor

The cerebellum regulates movement by adjusting the output of the descending motor system of the brain. It acts as a "comparator," compensating for errors of movement by comparing intended with actual performance.[40] The hallmark of cerebellar disease is the intention tremor, although many animals with cerebellar disease will also have postural tremor, particularly of the head, and a rhythmic postural sway (truncal tremor) (see Videos 32-3 and 32-5).[41] An intention tremor is an oscillation associated with visually guided movement. It appears during limb and head movement and increases in amplitude with approach of the target (Videos 32-4 and 32-5). In animals, this appears as bobbing action of the head as they go towards an object (e.g., towards food, to eat). There are many causes of cerebellar disease in domestic animals, including spinocerebellar ataxias and other (inherited) degenerative, metabolic, or inflammatory disorders (see ch. 260 and 261).

Disorders of Myelination (Shaker Pups)

Inherited developmental disorders of central myelination can result in the so-called shaker pup syndrome. Affected animals show a gross generalized tremor, particularly when aroused, from approximately 10 days old. Many affected dogs recover with time. The condition is recognized in the Springer Spaniel (autosomal recessive, sex-linked; males have a more severe and fatal phenotype),[42-45] Weimaraner,[46-48] Bernese Mountain Dog,[49] Samoyed,[50] and Siamese cats,[51] but other breeds may be affected. Magnetic resonance imaging of the brain may be useful to make a diagnosis in a non-invasive manner.[52] A differential is a leukoencephalopathy associated with parvovirus infection that has been reported in related Cretan Hound puppies.[53]

Isometric Limb Tremor

An isometric tremor is defined as an involuntary oscillation of one or more body parts during isometric muscle contraction, i.e., when the muscle fires but there is no movement at a joint or change in length of the muscle (e.g., standing).[40] A benign syndrome of pelvic limb tremor is recognized, particularly in older dogs, and has been referred to as a *senile tremor*.[18] Occasionally, the thoracic limbs may be affected. The tremor appears when the dog is standing and disappears during voluntary movement and when the dog is recumbent (Video 32-6). Although the tremor may become more pronounced with time, it does not appear to cause distress or interfere with function; consequently, treatment is not required.

Primary Orthostatic Tremor

A condition described as a primary orthostatic tremor has been detailed in young adult Great Danes and Scottish Deerhounds.[16,17] Tremor with a frequency of 13-16 Hz appears when the dog stands or when moving from one static posture to another (e.g., from standing to sitting, or when posturing to eat, drink or excrete) (Figure 32-2). The tremor disappears on walking and when the dog is recumbent. The condition is progressive over months and years. A distinguishing feature from benign isometric tremor is that the dog appears distressed, and function is compromised. The condition has been compared to primary orthostatic tremor in humans (shaky legs syndrome) which is also characterized by a high frequency tremor (13-18 Hz) predominantly in the limbs and trunk, and triggered during isometric contraction of the limb muscles or during standing.[54] However, there are several differences, most notably that the canine condition has a favorable prognosis as it responds completely or partially to phenobarbital (dosage: 2-3 mg/kg PO q 12 h), often at serum concentrations lower than those required to control seizures. By contrast, the human condition often is poorly responsive to medication.[55] In addition, in humans the tremor is described as fine amplitude rippling that may only be apparent on palpation, auscultation with a stethoscope, or EMG. The diagnosis is

dependent on a subjective feeling of unsteadiness when standing, which is relieved on sitting.[1,55,56] By comparison, in dogs the tremor is visible, gross, and severe (Video 32-7).

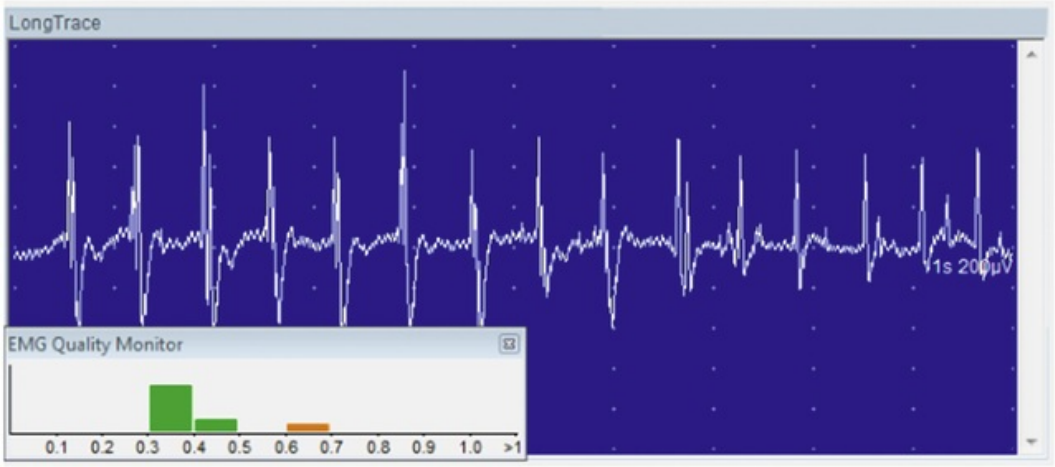

FIGURE 32-2 EMG recording from a 4-year-old male Great Dane with primary orthostatic tremor (see Video 32-7). The dog was conscious and fully weight bearing. The recording demonstrates rapid motor unit action potentials occurring at approximately 16 Hz. (Courtesy Dr. Colin Driver.)

Focal Tremor Disorders

There are many movement disorders that can result in brief, repetitive muscle contractions, which must be distinguished from tremor (see Table 32-1; Videos 32-8 and 32-9).

Idiopathic Paroxysmal Head Tremor

A syndrome characterized by paroxysmal rhythmic head movement is recognized in English Bulldogs (Video 32-10),[57] Dobermans,[58] Boxers, Staffordshire Bull Terriers and others. Affected dogs may have a yes-yes or no-no action. It is very unusual to see both no-no and yes-yes in an individual dog and the direction of movement does not change during an episode.[58] There may be a subtle head tilt (dystonia) and this syndrome may represent a dystonic tremor, i.e., a tremor of a body part affected by dystonia.[4] Paroxysmal episodes vary in duration from a few seconds to several hours and the movement has variable frequency (typical range 4-9 Hz) and amplitude. There is much variation in number of episodes per day and length of time between episodes.[58] Anxiety may be a trigger in some dogs and episodes are more likely (but not exclusively) to occur during rest or sleep.[57] The owners may be able to interrupt mild episodes. The dog remains aware, although may appear anxious, and able to move but may be described as more "stiff" or "floppy."[57] The dog may try to stop the action by pressing its head into an object or its paws. The first episode generally is noted when the dog is a young adult (in one study, the median age was 2 years[57]) and may resolve spontaneously in older animals.[57] Information on treatment is not available. As the condition is self-limiting and there can be many months between episodes, the majority of dogs are untreated.

Tremor Associated with Peripheral Neuropathy

An animal may present with a tremulous limb associated with weakness from a peripheral neuropathy or ventral horn cell (spinal cord) damage (Video 32-11).[10,18] Occasionally the tremor may be disproportionate to the weakness, and in humans it has been suggested that in some demyelinating neuropathies there may be a central component.[59]

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CHAPTER 33

Ataxia, Paresis, Paralysis

Ronaldo Casimiro da Costa

Client Information Sheet: Ataxia, Paresis, Paralysis

Ataxia, paresis, and paralysis are clinical signs commonly seen in various diseases of the brain, spine, and peripheral nerves. The main difference between ataxia and paresis is that ataxia affects coordination without affecting strength, while paresis affects only strength. These clinical signs provide fundamental information for lesion localization; it is therefore important to be familiar with their presentation, clinical significance, and main causes. The discussion that follows, combined with the videos and algorithms, aims at assisting the reader achieve this goal.

Ataxia

Ataxia means incoordination. It comes from the Greek word *a taxis,* which means without order or without coordination. It is one of the most important neurologic signs to recognize due to its importance in localizing lesions within the nervous system. Ataxia is an inability for the patient to coordinate the position of its head, trunk, and limbs into space. Ataxia is a sensory, not motor, dysfunction that can only be identified when the patient moves. The type of the ataxia is characterized through a complete neurologic examination (mental status, gait and posture, postural reactions, evaluation of cranial nerves and spinal reflexes, and pain perception). Special attention should be given to the gait and posture. Mild forms of ataxia may be difficult to recognize. The animal's gait should be carefully evaluated in a room large enough to allow the animal to move freely. The animal should also be walked, at a slow pace, toward and away from the examiner in an area with nonslippery floors. Ataxia is mainly a sign of a neurologic disturbance. It is often confused with weakness (discussed below) but they are quite distinct. Systemic conditions can cause ataxia, but more commonly cause weakness without ataxia. Examples of systemic conditions causing ataxia are hypocalcemia causing cerebellar ataxia and thiamine deficiency causing vestibular ataxia.

Types of Ataxia (Figure 33-1)

There are three types of ataxia, namely *proprioceptive, cerebellar,* and *vestibular.* Vestibular ataxia is the easiest to recognize. Vestibular ataxia is characterized predominantly by a head tilt. Usually the side of the head tilt indicates the side of the lesion. Other common signs of vestibular ataxia are leaning, falling, rolling, occasionally circling, strabismus, and nystagmus (see ch. 31 and 265). The severity of vestibular signs depends on a number of factors, but it is usually worse in the acute phase of the disease, while the patient still has spontaneous nystagmus. It is important to differentiate between central and peripheral vestibular disease because the differential diagnoses and prognoses differ greatly. Patients with central vestibular disease have changes in mental status (most commonly somnolence) and deficits in proprioceptive positioning and/or hopping. Nonambulatory tetraparesis is also commonly associated with central disease. Vertical nystagmus or positional nystagmus (one that changes direction when altering the head position) may also be seen. The proprioceptive positioning deficits are ipsilateral to the head tilt, except in cases of paradoxical vestibular syndrome, where proprioceptive deficits are contralateral to the head tilt. Central vestibular signs are associated with rostral medullary lesions (brainstem) or with lesions in the flocculonodular lobe of the cerebellum and are commonly caused by encephalitis or tumors. In peripheral vestibular disease, as the lesion involves the inner ear receptors located outside of the brain (petrosal part of temporal bone), the patient does not display changes in mental status or proprioceptive positioning deficits. The nystagmus is always in the same direction, either horizontal or rotatory, but not vertical. Both central (brainstem) and peripheral (inner ear) vestibular disease is common. It is important to emphasize that idiopathic vestibular disease is always

peripheral. If the patient has signs suggestive of central or paradoxical vestibular disease, further specific neurodiagnostic tests to investigate the brain are warranted. The most frequent causes of vestibular, cerebellar, and proprioceptive ataxias are presented in Box 33-1.

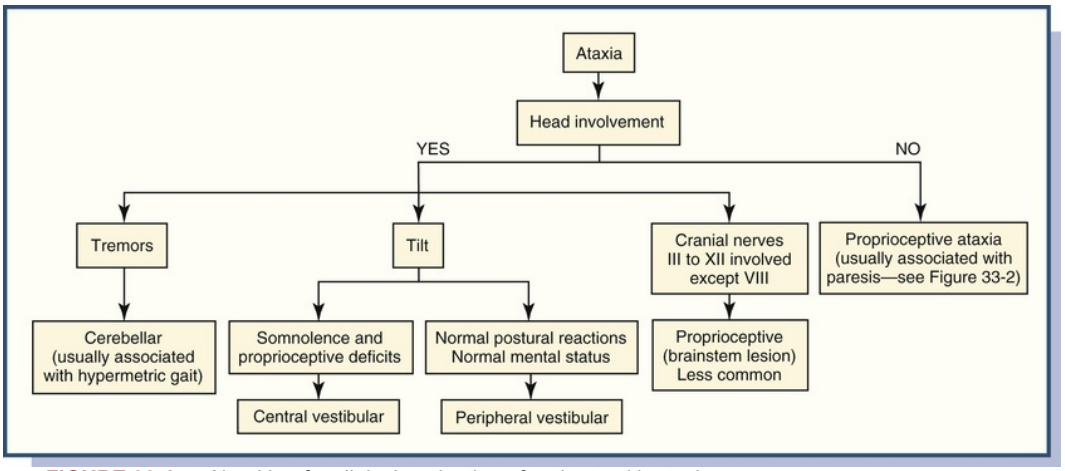

FIGURE 33-1 Algorithm for clinical evaluation of patients with ataxia.

Box 33-1

Frequent Diagnoses According to Type of Ataxia and Lesion Localization

Vestibular Ataxia—Peripheral

Otitis media–interna
Idiopathic vestibular disease
Neoplasia

Vestibular Ataxia—Central

Noninfectious meningoencephalitis
Infectious meningoencephalitis
Neoplasia

Cerebellar Ataxia

Noninfectious meningoencephalitis
Infectious meningoencephalitis
Cerebellar hypoplasia

Proprioceptive Ataxia

Intervertebral disk disease
Spinal trauma
Fibrocartilaginous embolism
Cervical spondylomyelopathy
Neoplasia
Atlantoaxial subluxation

Diffuse Lower Motor Neuron Signs

Acute polyradiculoneuritis (Coonhound paralysis)
Myasthenia gravis*
Botulism
Tick paralysis

C1-C5 Spinal Cord

Intervertebral disk disease
Atlantoaxial subluxation
Neoplasia

C6-T2 Spinal Cord

Intervertebral disk disease
Cervical spondylomyelopathy
Neoplasia

T3-L3 Spinal Cord

Intervertebral disk disease
Spinal trauma
Degenerative myelopathy
Neoplasia
Fibrocartilaginous embolism

L4-S3 Spinal Cord

Intervertebral disk disease
Fibrocartilaginous embolism
Spinal trauma
Neoplasia

Lumbosacral Region (Cauda Equina)

Cauda equina syndrome
Spinal trauma
Discospondylitis
Neoplasia

*Depending on the form of myasthenia gravis.

Cerebellar ataxia is characterized by dysmetria (inability to control the rate and range of stepping movements), which is usually manifested by hypermetria (exaggerated step). It is normally easier to recognize a hypermetric gait in the thoracic limbs. It is important to differentiate this sign from thoracic limb spasticity or hypertonicity, which often accompanies proprioceptive ataxia secondary to cervical myelopathies. Hypermetria is manifested by a prolonged flexion of the step (protraction), while spasticity causes the thoracic limbs to appear rigid or spastic. Other characteristics of cerebellar ataxia are head and whole body tremors, intentional tremors, and wide pelvic limb stance and gait (see ch. 31 and 32). Patients with pure cerebellar ataxia do not display weakness (paresis) or proprioceptive positioning deficits, as they have no involvement of the upper motor neurons or conscious proprioceptive tracts respectively. This can be very useful in distinguishing cerebellar from proprioceptive ataxia. Due to the close anatomic and functional relationships, occasionally patients present with a combination of vestibular and cerebellar ataxia, which indicates a central lesion (Video 33-2).

Proprioceptive ataxia is the type primarily related to spinal cord diseases. This ataxia can be differentiated from vestibular and cerebellar ataxia by the absence of head involvement (tremor or tilt) (Video 33-1).

Proprioceptive ataxia may be seen with brain lesions (brainstem, thalamus, basal nuclei, or cortex) but is much milder, and other brain signs are usually more obvious than the ataxia (somnolence, behavioral changes, cranial nerve involvement, circling, seizures). When evaluating an animal with proprioceptive ataxia, it is important to rule out the influence of any drug (e.g., sedatives) or metabolic disorder (e.g., severe anemia) that may be causing ataxia. As proprioceptive ataxia is commonly associated with spinal cord diseases, this discussion will focus on this aspect. Proprioceptive ataxia is a phenomenon of the spinal cord's white matter, reflecting a dysfunction of the sensory tracts carrying unconscious proprioception (dorsal, ventral, and cranial spinocerebellar tracts, as well as the cuneocerebellar tract). Clinical signs seen with proprioceptive ataxia are truncal sway (wobbliness) and abnormal limb stance and gait such as circumduction, abduction, or adduction with the limbs crossing with each other as the animal walks. Some animals also display a delay in initiating the protraction phase of the gait with a slight hyperflexion of the limb and a longer stride than normal. Proprioceptive ataxia is seen early in the course of compressive

myelopathies, and may or may not be accompanied by proprioceptive positioning deficits (conscious proprioception [CP] deficits or "knuckling"). Usually, patients with spinal cord disease have ataxia associated with proprioceptive deficits; however, dogs with chronic spinal cord disease display ataxia, without CP deficits. This can be explained by the fact that the tracts carrying conscious proprioception (fasciculus gracilis and cuneatus) are different from those involved in unconscious proprioception and responsible for ataxia. It is therefore the gait examination (presence or absence of proprioceptive ataxia) and not the evaluation of proprioception (knuckling) that conclusively defines the involvement of the spinal cord. As the spinal cord lesion worsens, paresis appears (Video 33-5).

Paresis and Paralysis

Paresis means partial loss of motor function, which is usually manifested as weakness. Paralysis (plegia) refers to the complete loss of motor function. The terms *plegia* or *paresis* can be used in association with a prefix to specify which limb(s) are involved. Tetra-, para-, hemi-, or mono-paresis/-plegia refers to involvement of all four limbs, pelvic limbs, ipsilateral limbs, or a single limb, respectively. It is important to make the distinction between ambulatory and nonambulatory paresis and plegia. A "down" dog can have nonambulatory paraparesis and if appropriate treatment is established, dogs with paresis will typically recover faster than those with paralysis (plegia). Paresis and proprioceptive ataxia are common signs in patients with spinal cord diseases (see ch. 266 and 267). The more severe the spinal cord involvement, the weaker the patient becomes, until the point of paralysis. Paresis can be seen with cortical or thalamic lesions, but it is usually mild and always contralateral to the lesion. More severe paresis can be seen with lesions caudal to the midbrain, and in these cases the involvement is ipsilateral. Paresis or paralysis can also be seen with involvement of the peripheral nerves, neuromuscular junction, and muscle. It is important to establish whether the patient has paresis with or without ataxia. Paresis without ataxia indicates that the lesion is located outside of the central nervous system and therefore not affecting the spinal cord. Clinical examples of this presentation are polyneuropathies and polymyopathies, where the patient shows variable degrees of weakness in all four limbs (tetraparesis) but does not have ataxia. A careful evaluation of cranial nerves, postural reactions, and spinal reflexes will assist to establish whether the problem is in the peripheral nerves, neuromuscular junction, or muscle. In a tetraparetic patient, if the reflexes are decreased or absent, a neuropathy or neuritis (e.g., Coonhound paralysis) is likely (Video 33-3). Myopathies cause only mild decrease in spinal reflexes. The clinical approach for a weak patient should first exclude systemic or metabolic causes of weakness. Several systemic conditions can cause weakness. Examples include anemia, metabolic diseases such as hypoadrenocorticism and hypothyroidism, electrolyte imbalances such as hypocalcemia and hypokalemia, cardiovascular diseases such as pericardial effusion or conditions associated with hypotension, and nutritional derangements such as thiamin deficiency. A thorough physical examination along with complete blood count and biochemistry profile may reveal evidence of metabolic or neoplastic diseases, which may cause either neuropathies (e.g., diabetes mellitus in cats [see ch. 305]) or myopathies (e.g., hyperadrenocorticism in dogs [see ch. 306]). Further tests such as a thyroid profile, and a complete cardiac work-up may also be recommended depending on the case.

If the patient is paralyzed, the lesion is within the spinal cord or somewhere along the peripheral nervous system. It is important to localize the spinal lesion as closely as possible to concentrate diagnostic efforts on the affected region. The principles of upper motor neuron (UMN) and lower motor neuron (LMN) are used to localize lesions within the spinal cord (see Figure 33-2). *Upper motor neuron* is a term used to designate a group of motor tracts originating from the brain and terminating within the spinal cord. The most important tracts forming the UMN are the corticospinal, rubrospinal, reticulospinal, and vestibulospinal tracts. Basically, the combined function of the UMN is to facilitate gait in animals, inhibiting extensor muscles of the limbs while facilitating flexor muscles. As such, when the animal has an UMN spinal cord lesion, there is paresis or paralysis with increased extensor tone of the limbs (due to the lack of UMN inhibition). The hallmarks of UMN signs are then paralysis or paresis with increased extensor tone (spasticity or hypertonus), normal to increased spinal reflexes (hyperreflexia), and slowly progressive muscle atrophy from disuse. On the other hand, LMN is formed by a group of neurons that originate in the ventral gray horn of the spinal cord or in a nuclei of the brainstem, to give origin to peripheral or cranial nerves that then innervate the target muscle(s). Lower motor neuron is also known as the final common pathway because any motor activity to be displayed has to go through the LMN. When the patient has a lesion somewhere along the LMN pathway, such as in the spinal cord enlargement (ventral gray horn), nerve roots, spinal nerve, peripheral nerve, or neuromuscular junction, LMN dysfunction occurs. Clinical signs of LMN dysfunction are basically the opposite of those seen with UMN lesions: paresis or paralysis with absent to decreased extensor tone (flaccidity or hypotonus),

decreased or absent spinal reflexes (hyporeflexia or areflexia, respectively), and rapid and severe (neurogenic) muscle atrophy. The presence of UMN or LMN signs dictates the location of the lesion within the spinal cord (Video 33-4).

Clinically, the spinal cord can be divided into four regions, cervical (C1-5), cervicothoracic (C6-T2), thoracolumbar (T3-L3), and lumbosacral (L4-S3). Involvement of all four limbs suggests a lesion at either C1-C5 or C6-T2. Assuming increased tone and reflexes in the pelvic limbs, normal to increased tone and reflexes (UMN signs) in the thoracic limbs indicate a lesion at C1-5, while decreased to absent tone and reflexes (LMN signs) suggest a lesion at C6-T2 (Figure 33-2).

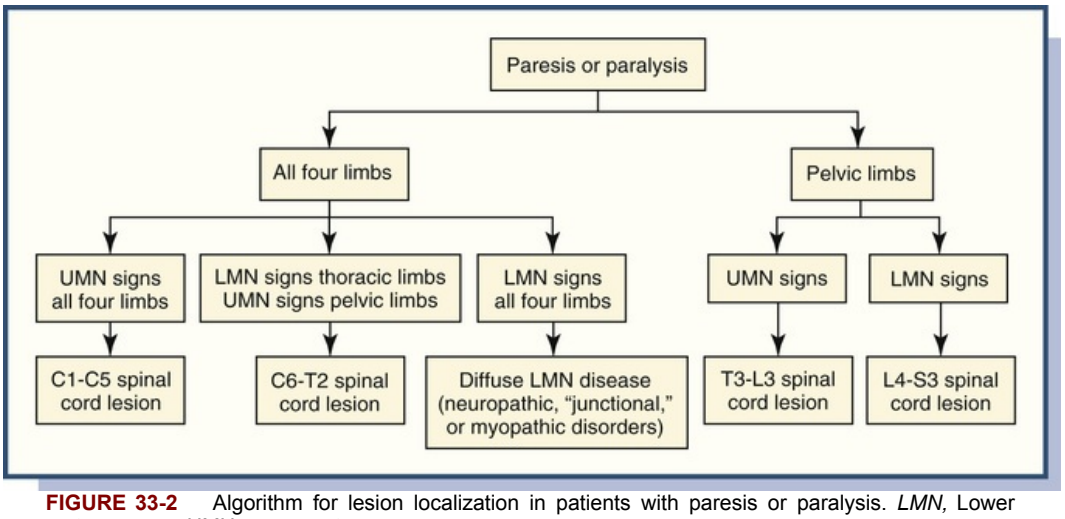

FIGURE 33-2 Algorithm for lesion localization in patients with paresis or paralysis. *LMN*, Lower motor neuron; *UMN*, upper motor neuron.

Paraplegia or paraparesis indicates a lesion caudal to T2. Normal to increased reflexes and muscle tone points to a T3-L3 lesion, the most common site for spinal lesions. More specific lesion localization within the segment T3-L3 can be achieved using the cutaneous trunci reflex and spinal palpation. Decreased tone and reflexes suggests a L4-S3 lesion (see Figure 33-2). It is important to note that the lumbosacral spinal cord segments do not match with their corresponding vertebrae. The entire lumbar enlargement (L4-S3) is located within the vertebrae L4-L5 in most dogs, and L5-L6 in cats. Lesions involving the vertebrae L6, L7, and S1 in dogs affect the nerve roots for the pelvic limbs, perineal region, sphincters and tail (reflecting involvement of sciatic, pudendal, pelvic and caudal nerves). As there is no spinal cord in this region, no proprioceptive ataxia is observed (although proprioceptive positioning deficits may be seen), but paraparesis and pain in the lumbosacral area are present. The flexor and perineal reflexes display signs of LMN. Box 33-1 presents common diagnoses according to lesion localization.

A notable exception exists to the lesion localization within the spinal cord based on the principles of UMN and LMN. It is the so-called Schiff-Sherrington phenomenon that occurs in patients with severe thoracolumbar lesions (T2-L7) damaging the propriospinal tract, which is inhibitory to the extensor muscles of the thoracic limbs. These patients are paraplegic with normal thoracic limb gait, but display, when laterally recumbent, thoracic limb spasticity.

In a paralyzed animal, it is important to establish whether or not nociception (pain perception) is intact. A noxious stimulus such as pinching at one of the toes or at the nail bed should elicit a withdrawal of the limb accompanied by a behavioral response, such as vocalization. If the patient flexes the limb but does not have conscious perception of the painful stimulus, this indicates a severe spinal cord lesion and carries a guarded to poor prognosis, particularly if the patient had an external spinal trauma, is paralyzed for many days, and displays LMN signs.

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CHAPTER 34

Stupor and Coma

Karen Lynne Kline

Client Information Sheet: Stupor and Coma

Definitions

Stupor and coma are pathologic abnormalities caused by an interruption in the structural, metabolic, and/or physiologic integrity of the brainstem or cerebral cortex. Stupor is characterized by a state in which the animal appears to be asleep or unconscious but can be aroused by a noxious stimulus. Once the stimulus is withdrawn, however, the animal may lapse back into the sleeplike state. Coma is characterized by a state of unconsciousness from which the animal cannot be aroused even by a noxious stimulus. A strong toe pinch, for example, can elicit a flexion reflex or increased extensor tone but does not cause a behavioral response, such as crying or biting. In either case, prompt action is required to attempt to reverse these signs and correct the underlying cause.

Pathophysiology

Consciousness is maintained by sensory stimuli that act through the ascending reticular activating system (ARAS) on the cerebral cortex. Decreasing levels of consciousness indicate abnormal cerebrocortical function or interference with cortical activation by the ARAS. The cerebral cortex controls the content of consciousness, whereas the brainstem controls the level of consciousness. In a sense, the cerebrum is the light bulb, and the brainstem is the rheostat that regulates its brightness. All sensory pathways have collateral input to the ARAS in the pons and the midbrain, and this information is projected diffusely to the cerebral cortex, where cholinergic synapses communicate constantly with cortical neurons. Balance is maintained between the ARAS and the adrenergic (sleep) system, which projects from the midbrain and diencephalon (thalamus). Signs ranging from hyperexcitability to coma can be observed if imbalance exists between the two systems.

The causes of stupor and coma are numerous. The three most important are (1) increased intracranial pressure, (2) cerebral edema, and (3) herniation of brain tissue. Increased intracranial pressure can occur secondary to an increase in the volume of tissue or fluid (e.g., cerebrospinal fluid, edema, or blood) within the cranial vault; even small shifts in these volumes can have dramatic consequences. Causes of increased intracranial pressure include encephalitis, meningitis, mass lesions (e.g., neoplasia, granulomas, or abscesses), vascular events, traumatic injury, or underlying metabolic disturbances, such as systemic hypertension.

Cerebral edema is an abnormal accumulation of fluid in the brain parenchyma. It is classified into three types: (1) vasogenic, which is most commonly associated with brain masses or stroke and is due to a breakdown in blood-brain barrier integrity; (2) cytotoxic, which is most commonly associated with metabolic disturbances, such as hypoxia and neuroglycopenia, that cause cell or neuronal death; and (3) interstitial, which is most likely associated with hydrocephalus. The end result of progressively increased intracranial pressure and/or cerebral edema is brain herniation.

There are four different types of herniation, two of which can induce stupor or coma: (1) caudal transtentorial herniation, in which portions of the temporal lobe shift ventral to the tentorium cerebelli and cause midbrain compression; and (2) foramen magnum herniation, the most common form, which occurs when the caudal cerebellar vermis moves through the foramen magnum, causing a compression of the displaced cerebellum and the medulla oblongata. In these cases, injury to the respiratory center, descending motor pathway tracts, and cardiovascular centers in the caudal brainstem can lead to irreversible midbrain and cerebral hypoxia and coma (Figure 34-1, *A* and *B*).

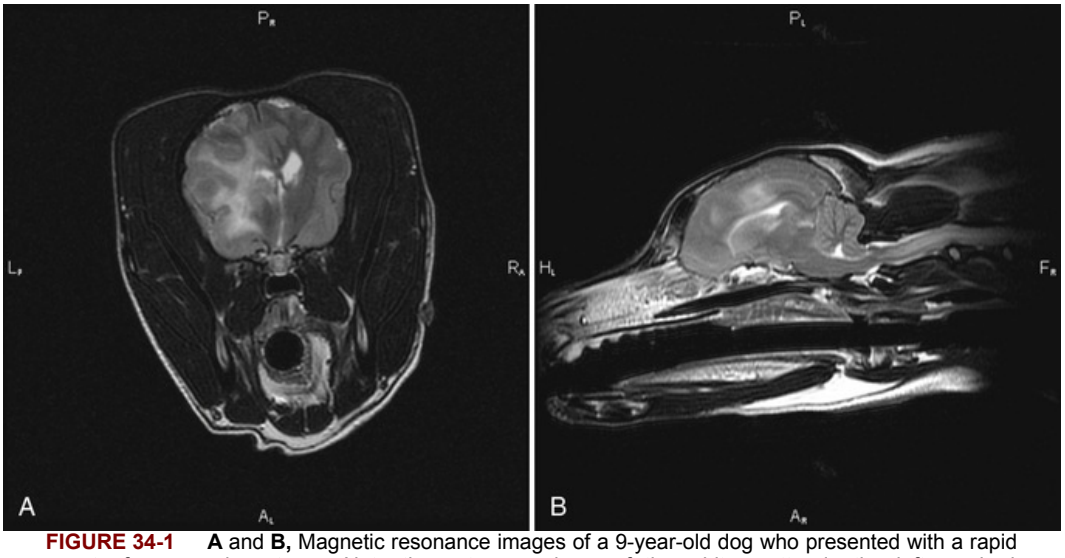

FIGURE 34-1 **A** and **B,** Magnetic resonance images of a 9-year-old dog who presented with a rapid onset of progressive stupor. Note the extreme edema of the white matter in the left cerebral hemisphere as well as the herniation of the cerebellum through the foramen magnum. The dog progressively developed an apneustic breathing pattern indicative of herniation of the brain through the foramen magnum and subsequent compression of the medulla of the brainstem resulting in damage to the respiratory centers. Despite aggressive resuscitation efforts, the dog did not regain consciousness and was euthanized.

Approach to the Patient with Stupor or Coma

After the pet's initial presentation, close attention must be paid to immediate life-threatening injuries and their sequelae, such as hemorrhage, hypoxemia, or shock. The ABCs of critical care medicine—airway, breathing, and cardiovascular status—are paramount. Concurrently, a thorough history, including onset and progression of signs, previous illness or injury, and drug use or toxin exposure, should be ascertained. Thorough physical (see ch. 2) and neurologic (see ch. 259) examinations should be performed, with emphasis placed on the respiratory pattern as well as on cardiac rate and rhythm. Simply observing the patient for a short time can yield considerable information. An anatomic diagnosis can be ascertained on the basis of the following: (1) content of consciousness or mental status and level of consciousness; (2) neuroophthalmic signs (vision, pupil size and symmetry, and ocular movements); (3) alterations in respiratory pattern; and (4) skeletal motor responses. The Modified Small Animal Coma Scale has been used to help distinguish prognostically the extent of the neurologic injury in our patients (see ch. 148). Neurologic function is assessed for each of the three categories (motor activity, brainstem reflexes and level of consciousness) and a grade of 1 to 6 is assigned according to the descriptions for each grade. The total score is the sum of the three category scores. A higher score indicates a better prognosis and a lower score indicates a grave prognosis. Following these trends can improve prognostication, aid the development of treatment protocols, and is essential for patient management (see ch. 148).

Mental Status and Level of Consciousness

Consciousness is maintained by the midbrain ARAS, which acts as a rheostat, projecting diffusely to the cerebral cortex. Consequently, diffuse cerebral disease or midbrain disease can result in stupor, coma, or other alterations in consciousness, such as dementia (see ch. 263). Differentiation between stupor and coma can be achieved with the application of a noxious stimulus, such as a hemostat or needle. Care must be taken to follow trends when evaluating the patient, and hasty prognostication should be avoided. In general, stupor has a better initial prognosis than coma, but exceptions can occur. Other factors include the patient's age, the underlying medical history, and the cause of the alteration in consciousness (Figures 34-2 and 34-3; Videos 34-1 and 34-2).

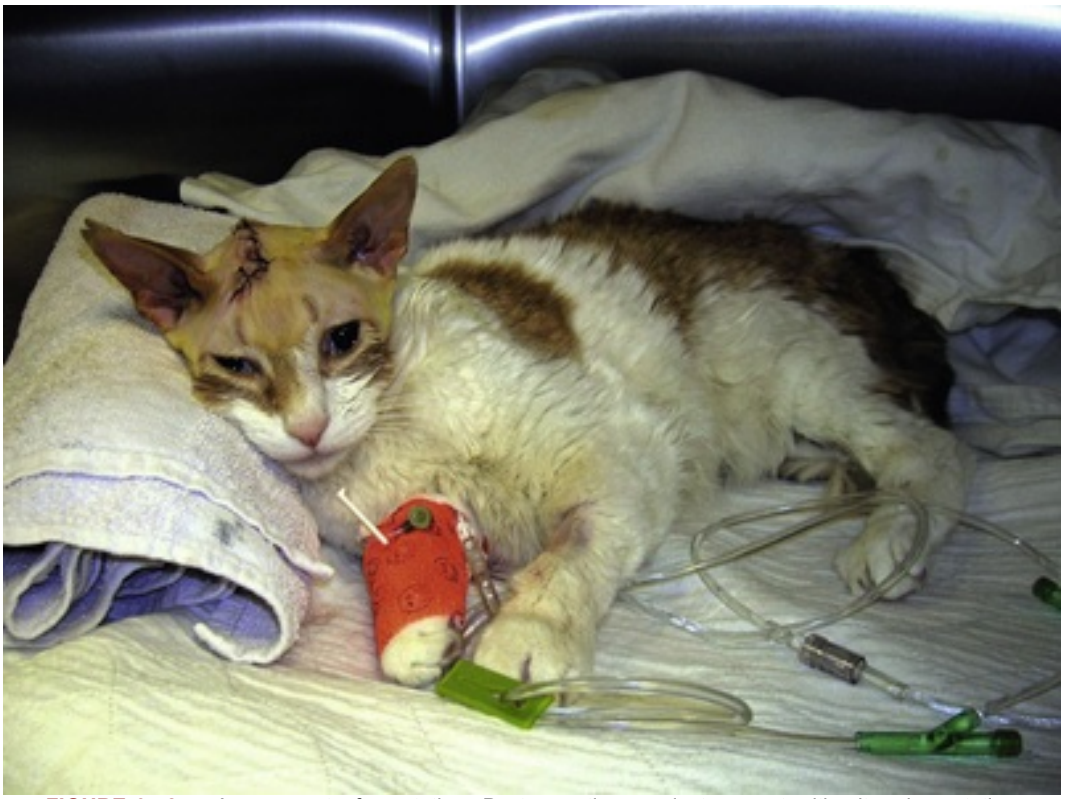

FIGURE 34-2 Assessment of mentation. Post-operative craniectomy cat with altered mentation secondary to meningioma. Evaluation of the patient for the doll's eye response and oculocephalic responses is imperative in the post-operative craniectomy patient. This cat also had its head elevated and had every-6-hour arterial blood pressure measurements to ensure adequate assessment of neurologic status. Physical therapy was instituted immediately post-operatively to help avoid contracture of the limbs and to aid in patient comfort.

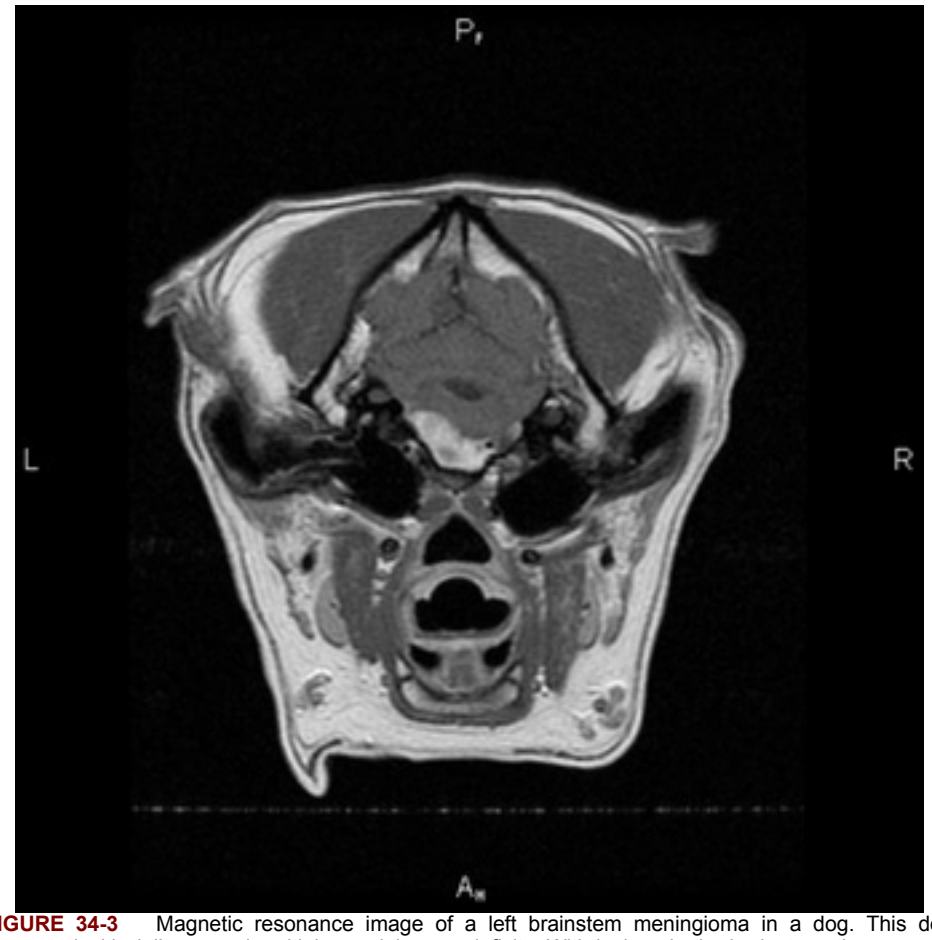

FIGURE 34-3 Magnetic resonance image of a left brainstem meningioma in a dog. This dog presented with dullness and multiple cranial nerve deficits. With lesions in the brainstem, the common presenting complaint will be a change in level of consciousness secondary to injury to the ascending reticular activating system or the rheostat of the central nervous system. The dog also had long tract signs to include hemiparesis and proprioceptive deficits on the same side as the lesion.

Neuroophthalmic Signs

Pupillary Reactions

Pupil size and reactivity to light can be normal in the comatose patient; alterations in these parameters can aid in neurolocalization and prognostication. Integrity of the retinae, optic nerves, and chiasm and of the rostral brainstem is consistent with pupils that are equal in size and that respond well to light and darkness. In general, lesions of the cerebral cortex and thalamus can result in normal or constricted pupils that respond to both darkness and light. Lesions in the brainstem can result in unilateral or bilateral pupillary constriction (pons) or dilation (midbrain), depending on the location. Peripheral lesions involving cranial nerve (CN) III usually result in dilated pupils with normal vision. Pupils that are bilaterally dilated (fixed) and unresponsive to light imply a lesion in the parasympathetic branch of CN III and carry a guarded to grave prognosis.

Ocular Movements

The pathways that mediate ocular movements lie adjacent to the brainstem regions responsible for consciousness, making it clinically useful to evaluate ocular movements in the stuporous or comatose patient. Physiologic nystagmus or conjugate eye movements (the oculocephalic and doll's eye reflexes) are normal and require integrity of CN VIII (vestibulocochlear nerve), the brainstem (vestibular nuclei, medial longitudinal fasciculus), the cerebellum (flocculonodular lobe), and the nuclei of CN III, IV, and VI. Any disruption in this pathway results in pathologic nystagmus (rotary, horizontal, or vertical downbeat). The doll's eye and oculocephalic reflexes are evaluated by moving the head back and forth in a horizontal plane (without moving the head dorsally or ventrally), either quickly, to evaluate the oculocephalic reflex, or slowly, to evaluate the doll's eye reflex. In the normal animal, this movement results in several beats of

horizontal nystagmus (with the fast component toward the direction of the head movement) that stop once the head movement stops. This is consistent with a normal oculocephalic reflex. If the nystagmus continues after the movement stops, if it occurs spontaneously, or if it changes with position, a lesion in the vestibular system is likely to exist. If there is absence of ocular movements in the comatose patient, severe brainstem injury should be suspected, and the prognosis for return to function is guarded to grave. It is important to emphasize that the changes in pupil size can occur suddenly, and an awareness of a sudden change may make the difference between life and death. This is also important to emphasize to the technical staff, as they are many times intimately involved in patient care and will be in charge of following trends. It is important to note that in a patient with seizure activity, the oculocephalic response (mediated through the cerebrum) may be diminished or absent, but the doll's eye reflex should be retained. If the doll's eye or slow phase of ocular movements is lost, this implies a more guarded prognosis and a more significant involvement of the brainstem. It is important to turn the patient on its back to make sure that the character of the nystagmus does not change, as this helps to discern between a central versus peripheral vestibular lesion (Video 34-3).

Alterations in Respiratory Pattern

Severe or progressive brain injury can result in changes in breathing patterns. Cheyne-Stokes respiration is characterized by hyperpnea alternating with apnea and can be an indication of a bilateral cerebral hemisphere or diencephalic lesion. Central neurogenic breathing or hyperventilation is associated with lesions in the midbrain pneumotaxic center, whereas lower pontine and medullary lesions result in apneustic or ataxic (gasping) respirations, respectively. Kussmaul respirations are deeper-than-normal breaths occurring in an otherwise normal pattern. These are typically associated with diabetic ketoacidosis, and the mechanism involves increased ventilation as respiratory compensation for severe metabolic acidosis. When a change in breathing patterns is noted in stuporous or comatose patients, aggressive therapy may need to be instituted to counteract brain herniation. Stimulation of the acupoint GV26 may be helpful in patients that are not breathing well and are in need of further ventilatory support and stimulation. This is done by placing a small-gauge needle at the ventral aspect of the philtrum of the nose and repetitively jabbing the nasal cartilaginous and bony tissue. Monitoring of arterial or venous CO_2 concentrations also is paramount in developing a long-term treatment strategy for the patient with stupor or coma. In cases where the respiratory pattern changes, poor ventilation can ensue and the patient may become hypercapneic and the respiratory drive may be altered. As mentioned previously, monitoring trends and following serial blood CO_2 concentrations is a vital component to patient outcome. It is important to emphasize that the changes in breathing patterns can occur rapidly and should be followed as trends. The importance of serial evaluations is paramount and this should be emphasized to the technical staff as commonly they are monitoring these patients very closely.

Skeletal Motor Responses

The examination of motor function in the stuporous or comatose patient provides valuable localizing information. Trends must be monitored in order to follow the disease course. Injury to the descending motor systems can result in either increased or decreased extensor and flexor tone, depending on where the injury occurs. Involuntary movements, such as twitching or paddling, may indicate seizure activity. Decerebrate posture (all four limbs extended) indicates a lesion in the midbrain or pons and can occur primarily or secondary to cerebrocortical herniation; decerebrate posture indicates that the motor pathways that aid in flexion are damaged and stupor or coma is present. Decerebellate posture (forelimbs extended with alternating hind limb flexion and extension) indicates a rostral cerebellar lesion, and the level of consciousness may not be impaired. Flaccid paralysis due to injury to the descending motor pathways implies a grave prognosis, especially when the patient is stuporous or comatose.

Diagnostic Plan

The causes of stupor and coma are numerous (Figure 34-4). Routine laboratory data (complete blood count [CBC], serum biochemistry profile, urinalysis) can aid in determining a metabolic cause of the alteration in consciousness. Inflammatory, infectious, or toxic agents may cause changes in the CBC, whereas metabolic or endocrine disorders may result in changes in the serum biochemistry results, which could suggest the need for other diagnostic tests, such as evaluation of blood ammonia levels and serum bile acids, adrenocorticotropic hormone (ACTH) stimulation, and thyroid profiles. Chest and abdominal diagnostic imaging (radiographs, ultrasonography) may also be indicated if metastatic, inflammatory, or infectious

disease is suspected. If minimal changes are noted in these parameters, a primary or intracranial cause of stupor or coma should be considered. Noninvasive methods used for determining the cause of intracranial disease include electroencephalography and brainstem auditory-evoked response (BAER). In addition, serial blood pressure monitoring (see ch. 99) is essential to assess for signs of a Cushing's reflex, which occurs when the heart rate decreases and the blood pressure rises to dangerous levels. This can be a sign of increasing intracranial pressure, cerebral edema formation, and herniation. Electroencephalography and BAER are useful for evaluating the integrity of the cerebral cortex and brainstem, respectively, and they can be performed without general anesthesia. Ophthalmic and retinal evaluation may help to determine whether high intracranial pressure or infectious disease is present. Computed tomography and magnetic resonance imaging of the brain are quite useful for confirming the presence and character of intracranial lesions, such as tumors, hydrocephalus, and vascular injuries (see ch. 260 and 261). If the dog or cat is comatose, general anesthesia may not be necessary. Cerebrospinal fluid analysis typically is useful for determining whether the animal has an inflammatory or a neoplastic intracranial process; general anesthesia is required and does carry some risk if high intracranial pressure exists.

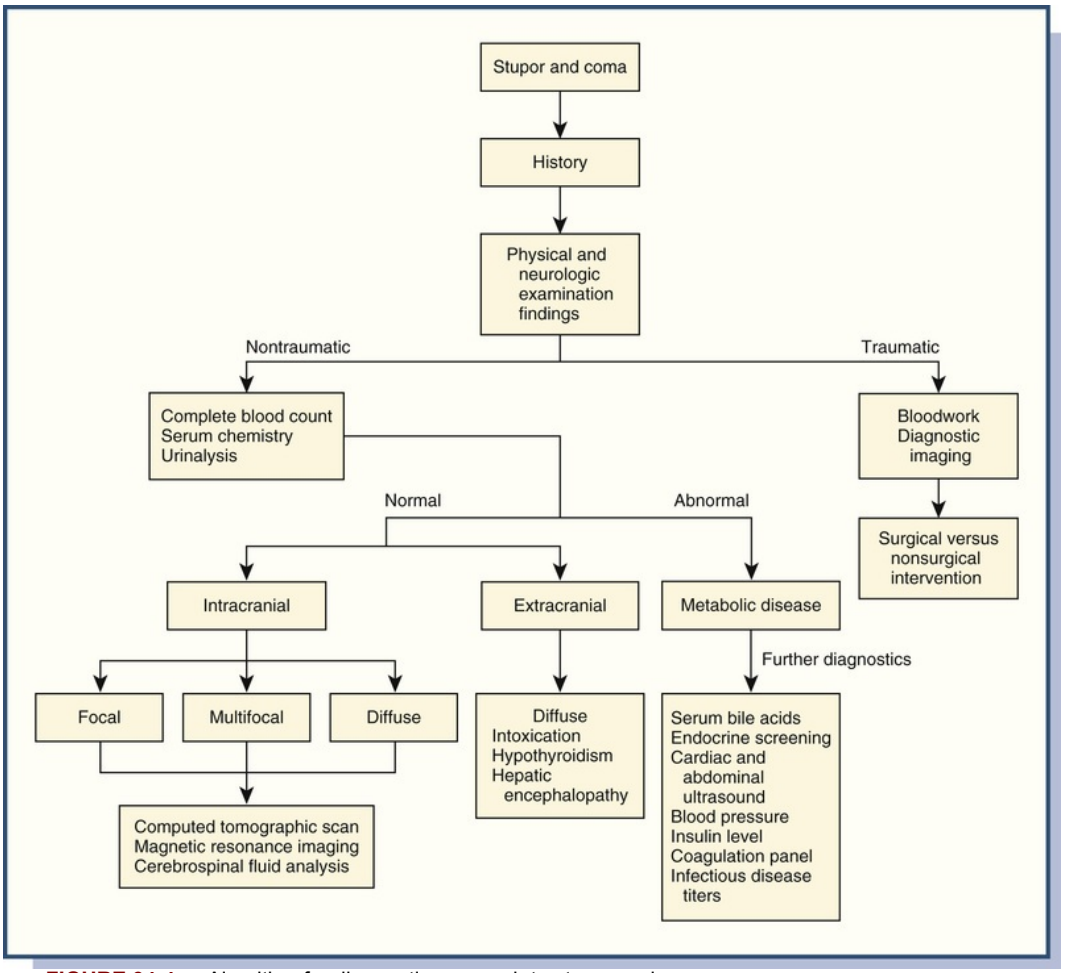

FIGURE 34-4 Algorithm for diagnostic approach to stupor and coma.

Treatment Goals

Most dogs and cats with stupor or coma have life-threatening injuries that require immediate attention. Establishing a patent airway and maintaining respirations and a stable hemodynamic status (in particular, blood pressure and blood CO_2 levels) are critical to stabilization, regardless of the underlying cause of the insult. Blood work should be evaluated, and intravenous administration of fluids, anticonvulsants, osmotic diuretics, and, in some cases, corticosteroids, can be instituted to aid patient stabilization. Elevation of the head may help reduce excessive cerebral blood flow, and body temperature should be monitored

continuously, especially in the case of seizures (see ch. 35). Cerebral edema can be treated using injectable corticosteroids (once the blood pressure has stabilized), osmotic and loop diuretics (mannitol and furosemide, respectively), and hyperventilation. Seizures can be controlled using injectable anticonvulsants such as diazepam, phenobarbital, and pentobarbital. These treatments are discussed in more detail in the chapters on specific brain diseases (see ch. 136, 148, and 260). Intensive nursing care is paramount, including frequent turning (to avoid hypostatic lung congestion), passive range of motion exercises of the limbs, and massage. Bladder evacuation, ocular lubrication, optimal nutrition, and proper bedding are imperative for continued support of the patient and optimization of outcome. Serial neurologic assessments and an assessment of positive and negative trends are essential for accurate prognostication.

Prognosis

The prognosis for animals with stupor or coma depends on the cause of the insult, other underlying disease processes, the location of the injury, the signalment, and the response to therapy. Serial neurologic evaluations that concentrate particularly on the level of consciousness, ocular movements, pupillary size, motor tone, and breathing patterns can guide the practitioner in terms of treatment options and prognostication. Patience is necessary, especially in cases of brain trauma, and trends in improvement or deterioration need to be followed. If the patient survives the immediate injury, sequelae such as seizures, permanent neurologic deficits, and long-term nursing care should be addressed with the client.

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CHAPTER 35

Seizures

Karen R. Muñana

Client Information Sheet: Seizures

Seizures are the most common neurologic condition encountered in small animal practice, with an estimated prevalence in a referral hospital population of 1-2% in dogs[1,2] and 2-3.5% in cats.[3,4] Seizures are transient paroxysmal disturbances in brain function that result from an imbalance between excitatory and inhibitory neurotransmission in the brain, and are characterized by hyperexcitability and hypersynchrony. The change in neuronal function can be identified by distinctive epileptiform activity on electroencephalography (EEG), and is typically accompanied by clinical manifestations. Clinical manifestations can be expressed as alterations in consciousness, behavioral changes, involuntary motor activity, and alterations in autonomic nervous system function such as mydriasis, salivation, vomiting, urination, and defecation. Seizures can be preceded by a preictal phase with atypical behavior such as restlessness, attention-seeking, or attempting to hide. The postictal phase immediately follows the seizure, during which an animal can show signs of fatigue, disorientation, restlessness, aggression, ataxia, or blindness. Postictal signs can persist from minutes to days, and the degree of postictal impairment does not necessarily correlate with the severity or duration of the seizure itself.

Seizure Classification

Seizures are classified as either generalized or focal, based on the EEG activity present at the onset of the seizure and the clinical signs that result from the neuronal disturbance. Generalized seizures are characterized by abnormal neuronal activity that originates from both cerebral hemispheres at the onset of the episode, and most often manifest in dogs and cats as symmetric tonic-clonic contractions of somatic muscles, loss of consciousness, and autonomic signs (Videos 35-1 and 35-2). Focal seizures originate within neuronal networks in a discrete region of the cerebrum or thalamus, and can manifest as focal motor activity or behavioral signs (Videos 35-3, 35-4, and 35-5). Focal seizures can secondarily generalize, in which case the seizure event spreads to involve both cerebral hemispheres. Focal seizures are associated with a higher incidence of underlying intracranial disease; therefore, it is important to attempt to discern the type of seizure an animal is having, as this will influence the differential diagnosis and diagnostic plan.

Diagnostic Approach

The general approach to the diagnostic evaluation of an animal with seizures is outlined in Figure 35-1.

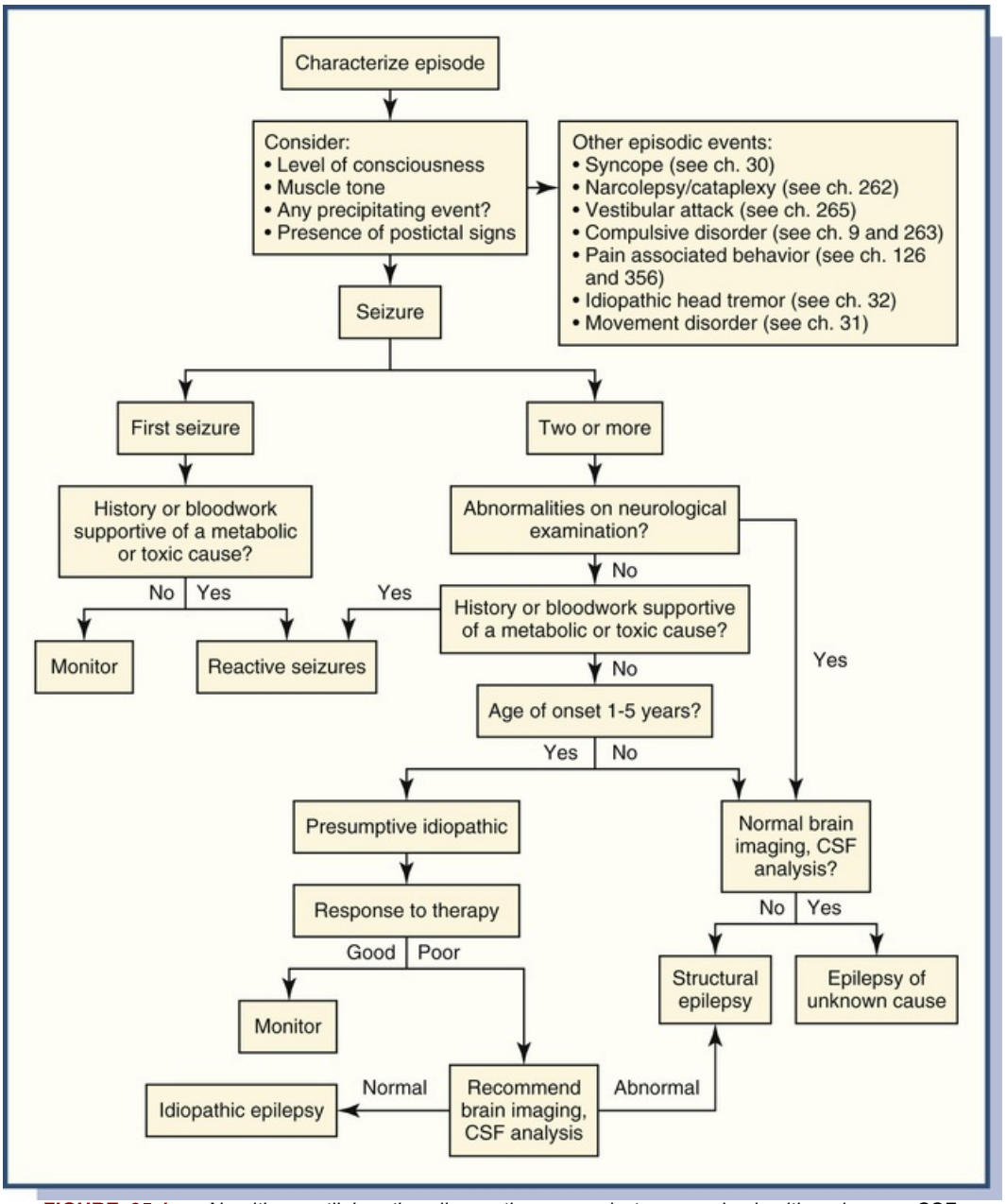

FIGURE 35-1 Algorithm outlining the diagnostic approach to an animal with seizures. *CSF*, Cerebrospinal fluid.

Historical Findings

Seizures, being episodic events, frequently are not witnessed by the veterinarian. Because of this, it is imperative that an accurate description of the episode be obtained from the pet owner to determine whether or not a seizure disorder is considered likely. Disorders that can be confused with seizures include syncope (see ch. 30), narcolepsy/cataplexy (see ch. 262), vestibular attacks (see ch. 265), behavioral disorders (see ch. 9), idiopathic head tremor (see ch. 32) and movement disorders (see ch. 31). If the episode proves difficult to characterize based on the description alone, it can be helpful to have the owner record an episode on video for review.

A thorough history also should be obtained to explore potential causes for the seizures. The owner should be questioned regarding the age of onset, duration and frequency of seizures, whether any events tend to precipitate seizures, any past history of illness or trauma, potential exposure to toxins, vaccination history, and any family history of seizures.

Examination Findings

A general physical examination is useful in evaluating for any evidence of cardiovascular or respiratory disease, as well as any signs of systemic disease that can provide clues as to the underlying cause of seizures. In addition, a complete neurological examination (see ch. 259) should be performed to assess for any signs of forebrain disease, such as changes in mentation or behavior, visual deficits, gait abnormalities, or postural reaction deficits.

Differential Diagnosis

Seizures often are categorized based on etiology (Table 35-1). Reactive seizures result from extracranial causes, in which metabolic (endogenous) or toxic (exogenous) disturbances secondarily impair normal brain function. The term *epilepsy* should be reserved to describe recurrent seizures due to a primary intracranial abnormality. The most common form of epilepsy in dogs is idiopathic epilepsy; this is a disorder characterized by recurrent seizures with no underlying cause other than a presumed genetic predisposition. The analogous condition in humans is now referred to as genetic epilepsy. Idiopathic epilepsy likely is the result of a functional defect at the molecular level, and occurs more frequently in certain breeds of dogs, with a typical onset at 1 to 5 years of age. Structural or symptomatic epilepsy refers to recurrent seizures associated with a congenital or acquired structural lesion in the brain, such as hydrocephalus, encephalitis, cerebrovascular disease, or neoplasia. Epilepsy of unknown cause refers to a condition of recurrent seizures in which genetic epilepsy is determined unlikely based on age of onset or examination findings, but a structural cause is not identified. This has also been referred to as cryptogenic epilepsy or probable symptomatic epilepsy.

TABLE 35-1

Classification and Differential Diagnosis for Seizures in Dogs and Cats

SEIZURE CLASSIFICATION	ETIOLOGICAL CATEGORY	SPECIFIC DISEASES
	Extracranial Causes	
Reactive seizures	Metabolic	Liver disease Renal disease Hypoglycemia Hypocalcemia Sodium imbalance Hyperlipoproteinemia Thiamine deficiency
	Toxic	Heavy metals Pesticides Ethylene glycol Caffeine/methylxanthines Mycotoxins Drugs
	Intracranial Causes	
Structural epilepsy	Degenerative	Neurodegenerative disorders Lysosomal storage disorders
	Anomalous	Hydrocephalus Lissencephaly Cortical malformations
	Neoplastic	Primary Metastatic
	Infectious	Viral Bacterial Protozoal Rickettsial Fungal

		Parasitic
	Inflammatory	Granulomatous meningoencephalitis Necrotizing encephalitis
	Traumatic	Brain trauma
	Vascular	Cerebrovascular disease Hypertension
Idiopathic epilepsy	Genetic	
Epilepsy of unknown cause	Undetermined	No structural cause identified

Diagnostic Plan

As a general rule, the initial diagnostic plan for an animal with seizures should focus on potential extracranial causes. Accordingly, any animal with seizures should have a complete blood count, serum biochemistry profile, urinalysis, and serum bile acid levels measured. If intoxication seems likely based on the history, then specific tests for toxin exposure are recommended (see ch. 152-155). Additional testing for systemic disease might be warranted based on examination and initial laboratory findings. Cats should be evaluated for serologic evidence of infectious disease, including feline immunodeficiency virus (see ch. 222), feline leukemia virus (see ch. 223), toxoplasmosis (see ch. 221), and cryptococcosis (see ch. 231).

If extracranial causes of seizures are excluded, then intracranial disease must be explored. When considering differential diagnoses for intracranial causes, it is often helpful to take into account the likelihood of diseases based on a dog's age at the onset of seizures. In dogs less than 1 year of age, anomalous conditions and infectious etiologies are identified most commonly. Ultrasound of the brain through an open fontanelle can often demonstrate the presence of ventriculomegaly in a patient with hydrocephalus (see ch. 260). Infectious disease testing, particularly in an unvaccinated animal, might lend support for the potential diagnosis of encephalitis. However, cerebrospinal fluid (CSF) analysis is necessary to exclude infectious causes, and advanced imaging of the brain is required to identify most structural abnormalities aside from hydrocephalus.

The most likely intracranial diagnosis in a dog with onset of seizures between 1 and 5 years of age is idiopathic epilepsy. Accordingly, if screening for extracranial causes produces negative results, and the signalment, history, and examination suggest that idiopathic epilepsy is likely, then further diagnostics are not necessary and a presumptive diagnosis can be made. However, if an owner desires a more definitive diagnosis, then brain imaging and CSF analysis are indicated (see ch. 115). In addition, animals in this age group with seizures that prove refractory to treatment should undergo further diagnostic testing to evaluate for structural brain disease.

In dogs with an onset of seizures at >5 years of age, intracranial disorders such as neoplasia and cerebrovascular disease assume a greater prevalence. Serial blood pressure measurements should be performed routinely in these cases (see ch. 99), and if normal, brain imaging and possibly CSF analysis should be recommended.

Since seizures in cats are more commonly associated with an underlying cause,[3,4] it is recommended that cats have advanced imaging and CSF analysis performed to evaluate for an intracranial cause for seizures, regardless of age.

Principles of Therapy

Guidelines for Initiating Treatment

Treatment should be directed at any underlying cause identified in the diagnostic evaluation. This is particularly important if a metabolic cause is identified, as seizures secondary to disorders such as hypoglycemia or hypocalcemia often are refractory to antiepileptic drug (AED) treatment if the primary cause is not addressed.

A decision on whether or not to initiate AED therapy for epilepsy should take into consideration the general health of the patient, as well as the owner's lifestyle, financial limitations and comfort with the proposed treatment plan. In general, the author recommends initiating AED treatment based on the following criteria: (1) seizure frequency of once a month or greater; (2) history of cluster seizures or status epilepticus; (3) seizure or postictal signs that are especially severe; and/or (4) strong desire by the owner to treat the

seizures regardless of the frequency or severity. The final decision on initiating AED therapy should be made on a case-by-case basis after careful consideration of these factors.

Client education is key to the successful management of an epileptic animal. The pet owner should have a clear understanding of the goals and expectations of treatment. The owner should realize that many animals do not become seizure-free with treatment, and adverse effects are common with AED therapy, such that the goal of therapy is to maximize seizure control while minimizing adverse effects to allow for the best quality of life. Furthermore, therapy is lifelong in most instances, and it is imperative that the AED be administered on a regular basis at established treatment intervals. Finally, animals with epilepsy require continuous care, and adjustments to the treatment regimen are likely to be required over time.

In general, therapy with a single AED rather than a combination of drugs is preferred in medical seizure management, as this avoids drug-drug interactions and provides a simpler regimen that may improve compliance.[5] A second drug should not be added until treatment failure has been demonstrated with the first drug, based on continued seizures in the face of maximum dosage or reference range serum concentrations being attained, or the presence of unacceptable adverse effects.

When choosing an AED, factors to consider include the mechanism of action, reported efficacy, potential for adverse effects and drug interactions, frequency of administration, and cost. Pharmacologic properties, dosage recommendations, and potential adverse effects for the AEDs used in dogs and cats are summarized in Table 35-2. A more extensive discussion of treatment options for seizures can be found elsewhere.[6]

TABLE 35-2

Oral Antiepileptic Drugs Used for Treating Seizures in Dogs and Cats

DRUG	SPECIES	RECOMMENDED STARTING DOSAGE	TIME TO STEADY-STATE CONCENTRATION (DAYS)	REPORTED ADVERSE EFFECTS
Phenobarbital	Dog	2.5-3 mg/kg q 12 h	10-14	Sedation, ataxia Polyphagia Polyuria/polydipsia Hepatotoxicosis Bone marrow suppression Hyperexcitability
	Cat	1.5-2.5 mg/kg q 12 h	16	Sedation, ataxia Weight gain Blood dyscrasias
Bromide	Dog	30 mg/kg q 24 h	100-200	Sedation, ataxia Vomiting Polyuria/polydipsia Polyphagia Pancreatitis
	Cat	Not recommended	37	Bronchial asthma Sedation Polydipsia Vomiting Weight gain
Gabapentin	Dog	10-20 mg/kg q 6-8 h	1	Sedation, ataxia
	Cat	5-10 mg/kg q 8-12 h	Not reported	Sedation, ataxia
Zonisamide	Dog	5-10 mg/kg q 12 h	3-4	Sedation, ataxia Loss of appetite
	Cat	5 mg/kg q 12-24 h	7	Sedation, ataxia Anorexia, vomiting, diarrhea
Levetiracetam	Dog/Cat	20 mg/kg q 8 h	1	Sedation, ataxia
Pregabalin	Dog	3-4 mg/kg q 8 h	1-2	Sedation, ataxia

	Cat	1-2 mg/kg q 12 h	Not reported	Sedation, ataxia

Monitoring Response to Therapy

Epilepsy is characteristically a chronic condition, and should be managed accordingly. Ideally, the goal of therapy is seizure remission; however, fewer than half of all epileptic dogs are able to maintain a seizure-free status without experiencing adverse effects associated with medical therapy.[7] Consequently, the primary focus of treatment is to optimize seizure control while minimizing drug-related adverse effects.

The monitoring of treatment response depends to a large extent on accurate owner observation, and owners should be instructed to maintain a calendar to record seizure activity and observed adverse effects and note any deviations in drug administration.

Therapeutic drug monitoring should routinely be performed for drugs such as phenobarbital and bromide that have a more narrow therapeutic index, and for which a reference range has been established. Drug concentrations should be measured once steady state has been achieved after initiation of treatment or dosage adjustment, when seizures persist despite an apparently adequate dosage, or when there are concerns about drug related toxicosis.[8] In addition, drug concentrations should be measured at 6-12 month intervals to screen for any changes in drug disposition over time, and aim to maintain levels within the reference range. Many of the newer AEDs approved for humans that are being utilized in veterinary patients, such as zonisamide and levetiracetam, have wide therapeutic indices such that drug monitoring is not routinely recommended. Furthermore, a reference range for serum concentrations of these drugs has not been established in dogs and cats. Nonetheless, the author finds it helpful to measure trough concentrations in instances where inadequate seizure control is reported, to determine whether a dosage increase might be warranted.

Outcome

The prognosis for an animal with seizures depends on the underlying cause and response to therapy. As would be expected, animals with idiopathic disease have a better prognosis than those with structural epilepsy.[4,9] Breed-related differences in seizure severity have been demonstrated among dogs with idiopathic epilepsy, with certain breeds such the Border Collie,[10,11] Australian Shepherd,[12] and German Shepherd Dog[11] less likely to have good seizure control. Furthermore, cluster seizures and status epilepticus have been shown to negatively influence survival.[9,13] However, many dogs with idiopathic epilepsy can expect a near-normal lifespan,[9,13] and a small percentage of dogs (13-15%) can undergo disease remission and become seizure-free.[9,14]

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Gastrointestinal

OUTLINE

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Chapter 37 Gagging
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CHAPTER 36

Ptyalism and Halitosis

Camilla Heinze, Brook A. Niemiec

Client Information Sheets:
Halitosis: Bad Breath in Dogs and Cats
Ptyalism: Drooling in Dogs and Cats

Ptyalism

Saliva is a viscous protein based fluid which flows throughout the mouth, playing an important role in support and maintenance of the health of the oral soft and hard tissues. Among the body's defense mechanisms, saliva works to lubricate and initiate breakdown of ingesta as well as to protect the oral soft tissues.[1] Ptyalism is defined as a pathologic overproduction of saliva, which may occur from a number of disease states.[2] Pseudoptyalism refers to drooling caused by an inability or reluctance to swallow a normal amount of saliva.[3] Excessive salivation, defined as saliva beyond the margin of the lips, is considered to be a normal finding in some breeds of dogs (e.g., Saint Bernard, Dogue de Bordeaux, and Mastiff).[4]

Etiology and Pathogenesis

Saliva is produced in and secreted by the salivary tissues, which are mostly in glands but also occur diffusely throughout the mouth. There are four major pairs of salivary glands in cats and dogs: parotid, zygomatic, mandibular, and sublingual[5] (Figure 36-1). The cat has, in addition, two small, circumscribed glands linguocaudally to each mandibular first molar tooth, which are called the lingual molar glands[6] (E-Figure 36-2).

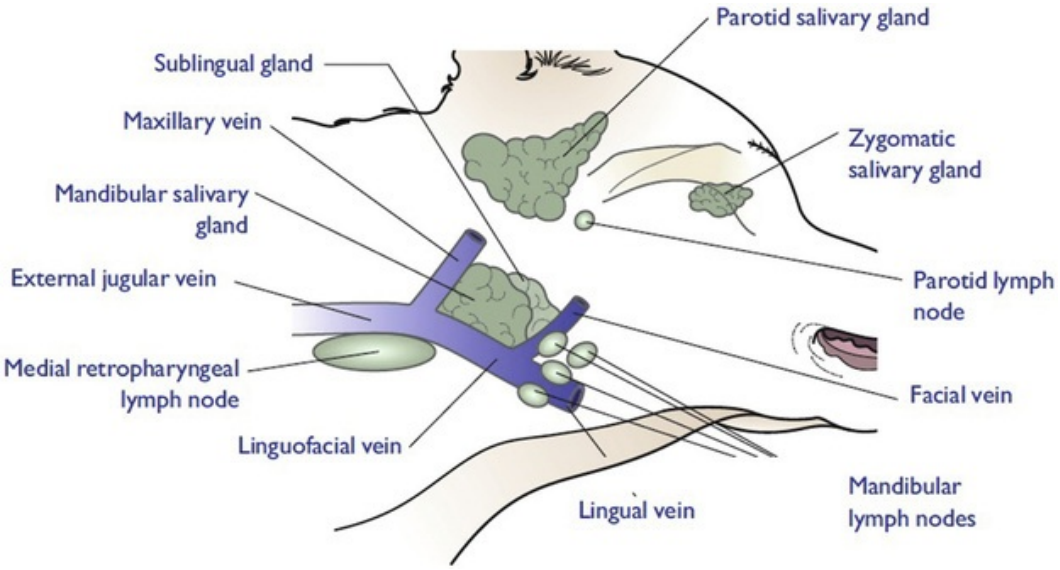
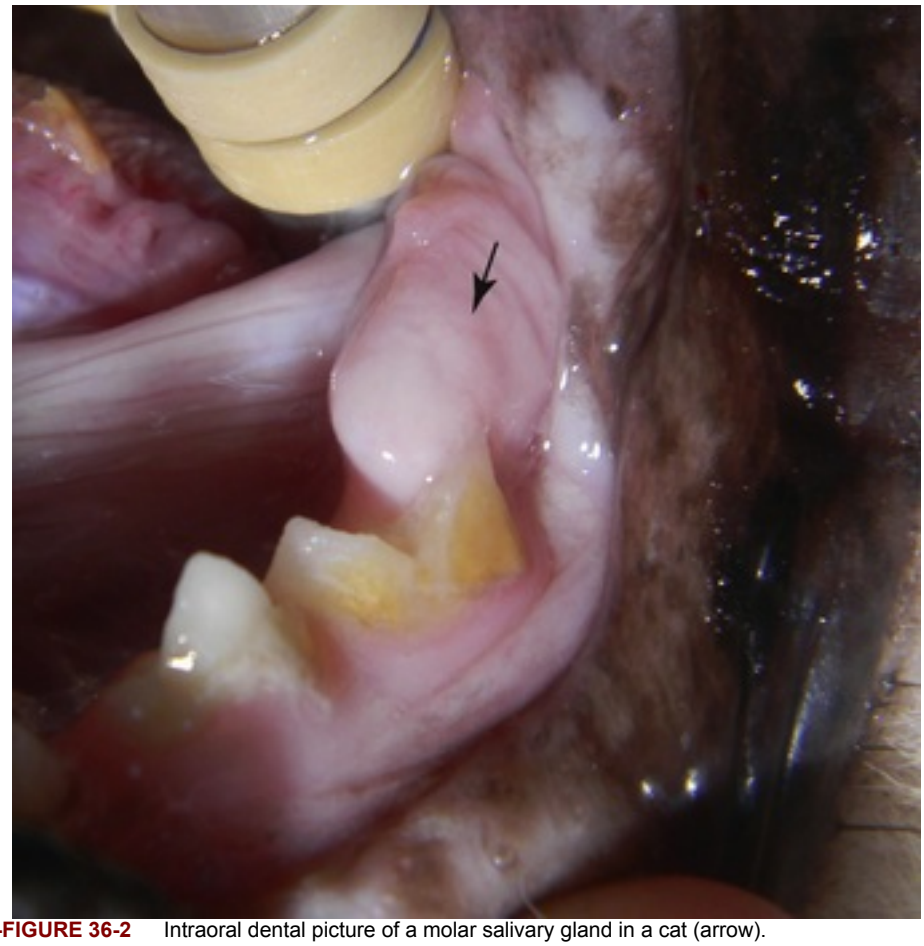


FIGURE 36-1 Scientific drawing of the anatomy of the feline and canine salivary glands. (Previously published in Niemiec BA: *Small animal dental, oral, and maxillofacial disease, a color handbook*, London, 2010, Manson.)



E-FIGURE 36-2 Intraoral dental picture of a molar salivary gland in a cat (arrow).

Parasympathetic postganglionic cholinergic nerve fibers control the rate of the salivary secretion, inducing the formation of large amounts of a low-protein, serous saliva. Sympathetic stimulation promotes saliva flow through muscle contractions at salivary ducts. In this regard, both parasympathetic and sympathetic stimuli result in an increase in salivary gland secretion. The sympathetic nervous system also affects salivary gland secretions indirectly by innervating the blood vessels that supply the glands.

Ptyalism results from an increase in production by one or all of the salivary glands. Pseudoptyalism results from some disruption of the swallowing mechanism, voluntary or involuntary. Often the voluntary disruption is pain-induced, whereas the involuntary is caused by obstruction.

There are numerous causes for hypersalivation, and numerous locations where the inciting cause may originate.[3,4] The inciting cause can originate from the oral cavity, esophagus or alimentary tract, or within the salivary glands themselves. Hypersalivation also can occur due to systemic or neurologic conditions.

Excessive salivation is a common clinical finding in patients with diseases of the oral cavity, and it is usually seen as a consequence of pain, inflammation or obstruction. Trauma patients, such as those with mandibular fractures, may have concurrent disruption in the normal mechanisms of swallowing.

Inability to retain saliva within the mouth due to poor head or lip control, a constantly open mouth, decreased or abnormal tongue mobility, decreased tactile sensation, macroglossia, dental malocclusion and nasal obstruction all lead to ptyalism.

Ingested toxins may have both direct noxious effects on the saliva production, and indirect effects through inflammation of the mucosal surfaces. Intoxicated patients can also be seen with ptyalism caused by the central nausea effect of the toxin.

Primary salivary gland disorders (e.g., necrosis, inflammation and cancer) usually provoke an increase in the secretion of saliva. However, other salivary gland diseases may actually result in a decrease in saliva production.

Neoplasia affecting structures of the oral cavity, oropharynx, or esophagus can disrupt the normal

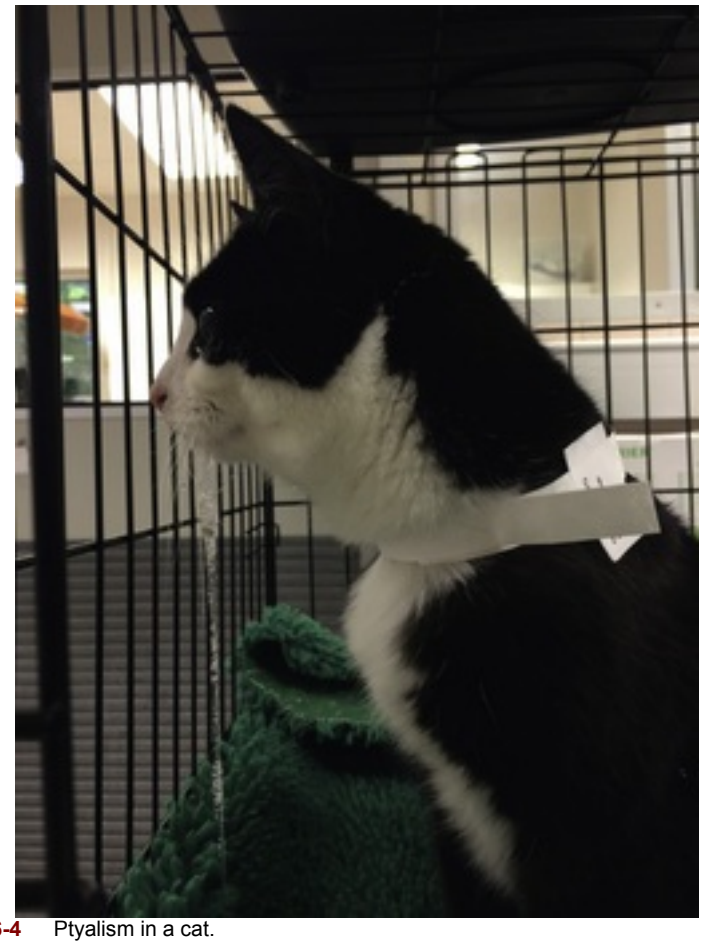
swallowing mechanism and cause pseudoptyalism.

True ptyalism is a common clinical sign with gastrointestinal, metabolic, and systemic diseases, and involves activation of the humoral and neural pathways for nausea and vomiting. Infectious diseases, including viral, bacterial, rickettsial, and protozoal infections, can have direct or indirect effects on saliva production. Central nervous system disorders can either increase salivation or interfere with normal swallowing function.

Clinical Signs[3,4]

The classic appearance is saliva dripping or pouring from the oral cavity (Figure 36-3 and E-Figure 36-4). The drooling may be categorized as mild to severe as well as intermittent to continuous. Clinical signs can occur acutely or be seen as gradual or chronic. The saliva may appear clear or it can be mixed with sanguineous or purulent exudates. Other potential clinical signs such as vomiting, regurgitation, anorexia, oral pain, and oral inflammatory lesions are related to the individual cause.

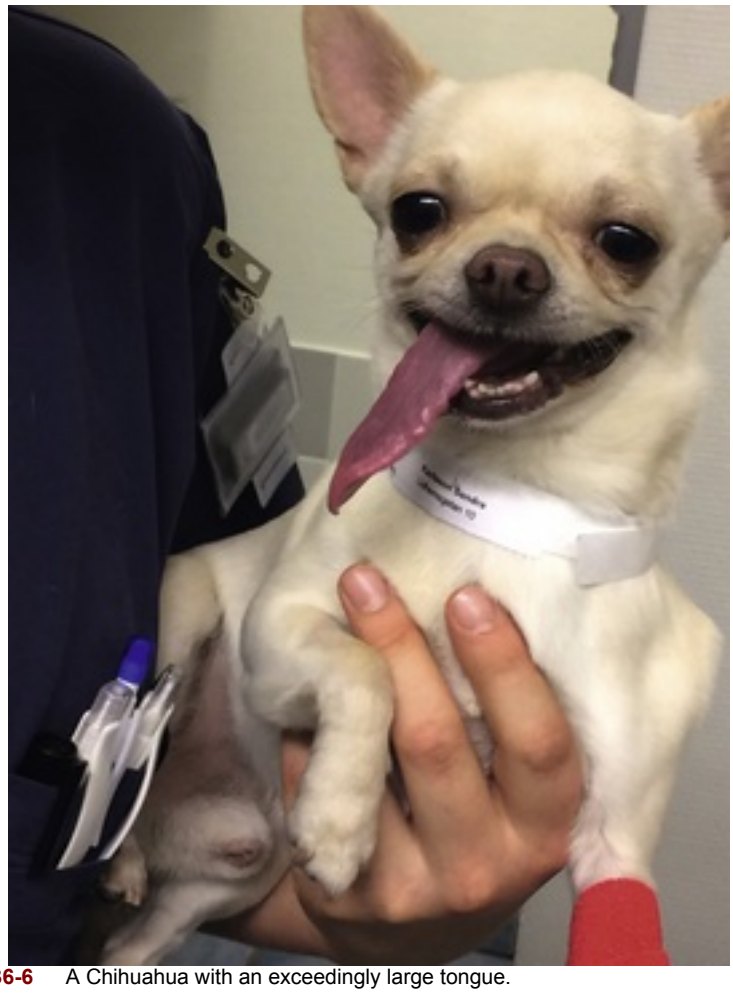
FIGURE 36-3 Ptyalism in a dog.



E-FIGURE 36-4 Ptyalism in a cat.

Differential Diagnoses[3,4] (Figure 36-5)

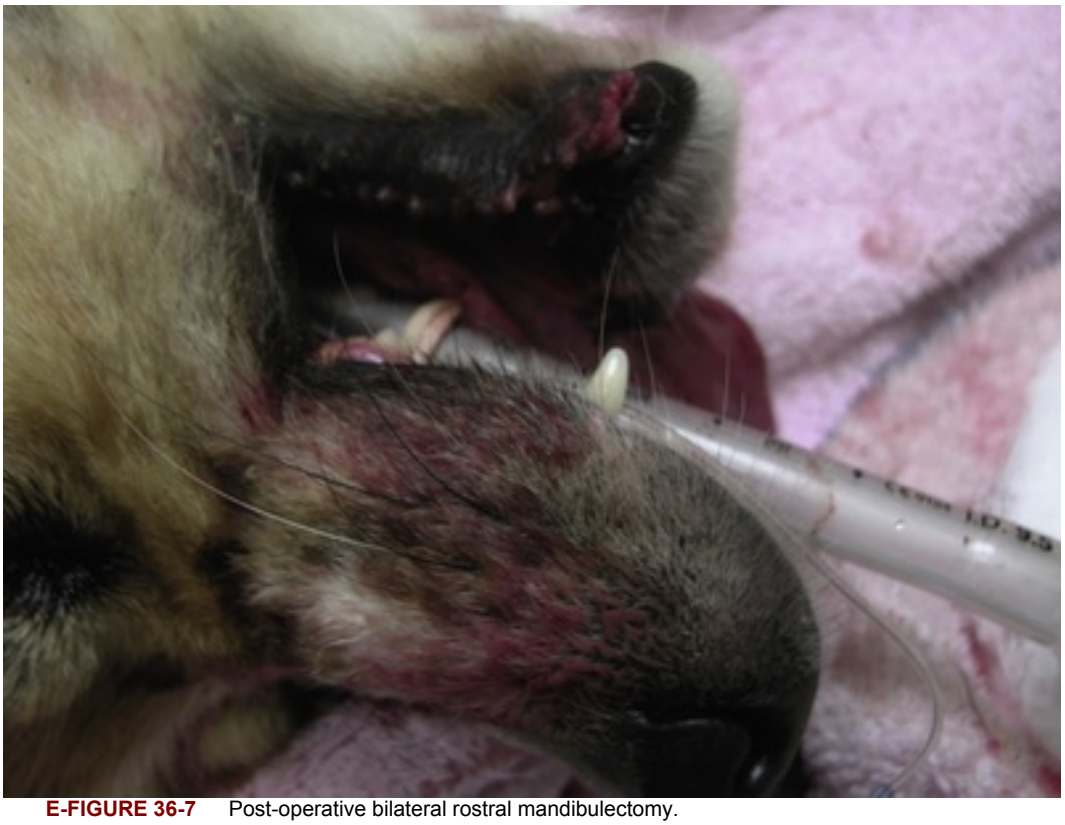
Neurologic: trigeminal neuropraxia, megaesophagus, facial paralysis, seizures, nausea from vestibular diseases; glossopharyngeal, hypoglossal or vagus nerve lesions that result in the inability to swallow.[7]
Developmental: severe brachygnathism, extensive lip fold, long tongue (E-Figure 36-6).



E-FIGURE 36-6 A Chihuahua with an exceedingly large tongue.

Trauma: soft tissue ulceration or laceration, electrical burn, temporomandibular joint (TMJ) luxation or fracture, mandibular fracture.[8-10]

Postsurgical: anesthesia, mandibulectomy (E-Figure 36-7) glossectomy, and mandibular canine tooth extraction.[11]



E-FIGURE 36-7 Post-operative bilateral rostral mandibulectomy.

Toxic: organophosphates, caustic ingestion, animal venom.[10,12-21]
Drug-induced: opiates, medications with a bitter or unpleasant taste.[22,23]
Behavioral: Pavlovian salivation associated with food, contentment/mood as in cats during purring, pain.
Obstructive: oral or esophageal foreign body, hematoma, seroma, or neoplasia.[8,10]
Metabolic: hepatic encephalopathy, uremia, exocrine pancreatic insufficiency, hyperthermia.[9,24-27]
Gastrointestinal: nausea, hiatal hernia, megaesophagus, gastric dilatation/volvulus, gastric ulcer, esophageal stricture, esophagitis, neoplasia, or foreign body.[28-30]
Infectious: acute calici- or herpesvirus infection, rabies, pseudorabies, tetanus, botulism, upper respiratory infection, candidiasis, severe periodontal disease, spirocercosis.[31-34]
Immune-mediated: chronic ulcerative paradental stomatitis (CUPS) in dogs, caudal stomatitis in cats, pemphigus, bullous pemphigoid, toxic epidermal necrolysis (TEN), masticatory muscle myositis, myasthenia gravis.[9,35-38]
Salivary: sialolith, foreign body, neoplasia, hyperplasia, infarction, sialocele, necrosis, idiopathic.[7,39,40]

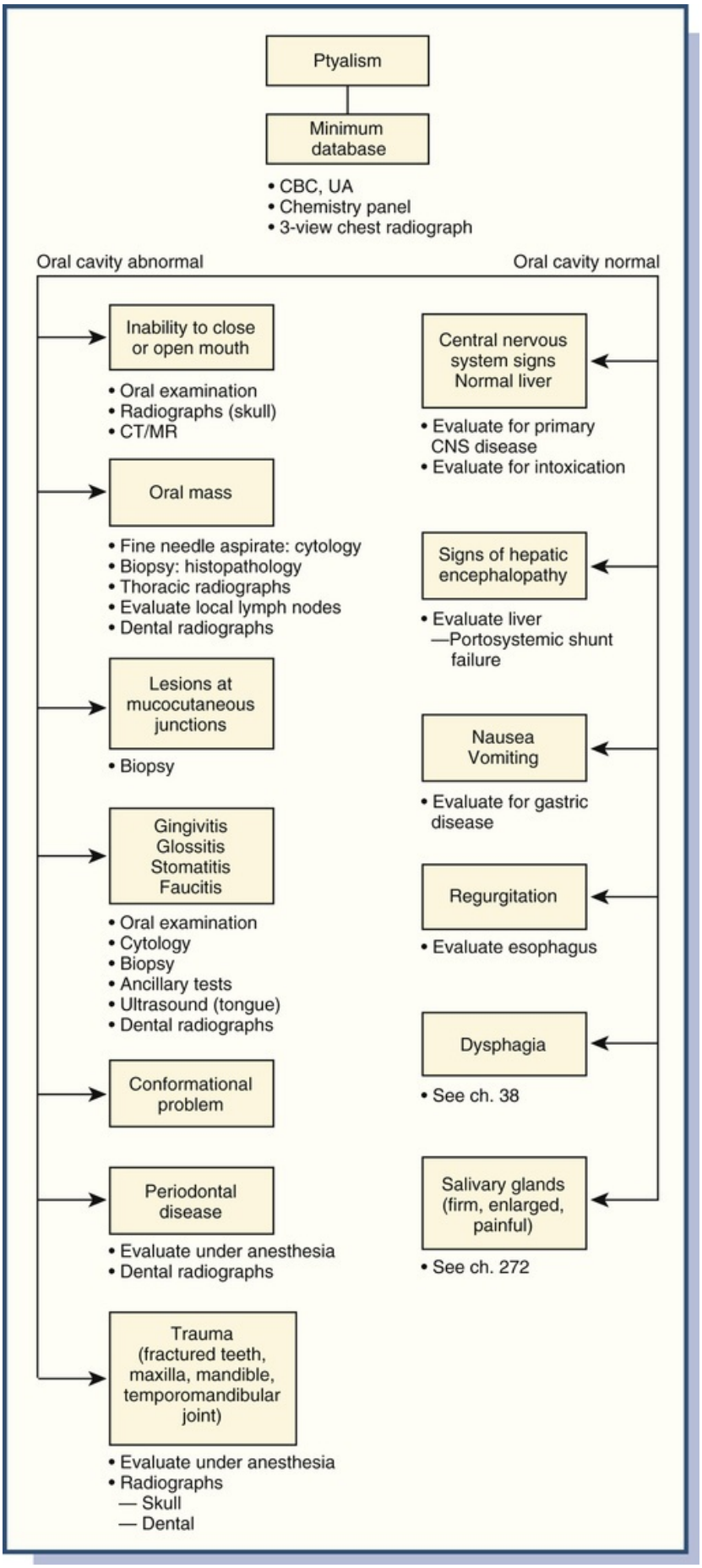

Ptyalism
Minimum database
• CBC, UA
• Chemistry panel
• 3-view chest radiograph
Oral cavity abnormal
Oral cavity normal
Inability to close or open mouth
• Oral examination
• Radiographs (skull)
• CT/MR
Oral mass
• Fine needle aspirate: cytology
• Biopsy: histopathology
• Thoracic radiographs
• Evaluate local lymph nodes
• Dental radiographs
Lesions at mucocutaneous junctions
• Biopsy
Gingivitis
Glossitis
Stomatitis
Faucitis
• Oral examination
• Cytology
• Biopsy
• Ancillary tests
• Ultrasound (tongue)
• Dental radiographs
Conformational problem
Periodontal disease
• Evaluate under anesthesia
• Dental radiographs
Trauma (fractured teeth, maxilla, mandible, temporomandibular joint)
• Evaluate under anesthesia
• Radiographs
— Skull
— Dental
Central nervous system signs
Normal liver
• Evaluate for primary CNS disease
• Evaluate for intoxication
Signs of hepatic encephalopathy
• Evaluate liver
—Portosystemic shunt failure
Nausea
Vomiting
• Evaluate for gastric disease
Regurgitation
• Evaluate esophagus
Dysphagia
• See ch. 38
Salivary glands (firm, enlarged, painful)
• See ch. 272

FIGURE 36-5 Algorithm for ptyalism. *CBC*, Complete blood count; *CNS*, central nervous system; *CT*, computed tomography; *MR*, magnetic resonance imaging; *UA*, urinalysis.

Diagnostic Steps

The most important initial step is to obtain a complete history and perform a thorough physical exam (see ch. 1 and 2).

History

Establish possible cause, severity, complications and progression of disease. Important areas of the history include: age and mental stage of the patient, chronicity of the condition, associated neurological signs, timing, provoking factors, and estimation of quantity of saliva. Historical questions should include: general history, age, acute vs. chronic clinical signs, other gastrointestinal (GI) signs (e.g., vomiting, diarrhea), toxic exposure, drug administration, or trauma.

Age of the Patient

Young patients are more likely to have toxic exposure, foreign body, acute viral infection, or portosystemic shunts (especially small breed such as Yorkshire Terriers and Maltese; see ch. 284).

Mature patients are more likely to be affected by metabolic, immune-mediated or neoplastic diseases.

Acute versus Gradual or Chronic

Acute onset of significant pseudo- or true ptyalism is most often associated with a virus, toxin, or oral trauma. *Gradual or chronic onset* is more likely to be associated with a metabolic or neoplastic process.

Gastrointestinal Signs

If ptyalism is associated with nausea or vomiting, a GI, systemic, or neurologic problem is more likely. Regurgitation should prompt an esophageal exam, as this is typically associated with an esophageal condition (e.g., megaesophagus) (see ch. 39 and 273). If ptyalism is noted in combination with difficulty eating or quidding, an oral problem should be suspected and a complete oral and maxillofacial exam performed.

Physical Exam

The most important part of the physical exam is a complete oral/maxillofacial/esophageal examination. A thorough oral exam evaluates for infection, neoplasia, fractured/abscessed teeth, periodontal status, trauma, inflammatory/ulcerative disease and foreign bodies.

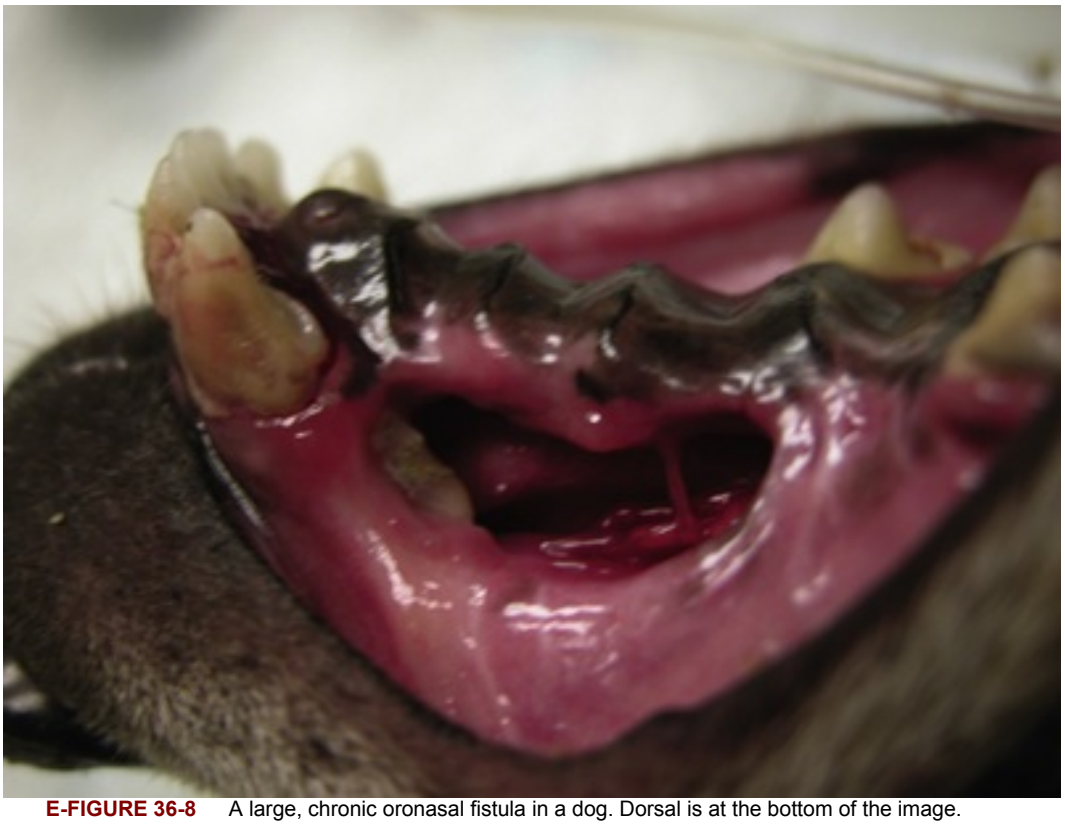
The clinician should check for sores on the lips or chin, tongue control, swallowing ability, nasal airway obstruction, decreased intraoral sensitivity, and anatomical closure of the mouth. The oral examination should include the sublingual area, as this is a common place for masses and string foreign bodies.

Oral ulcerative inflammatory diseases are typically in advanced stages before ptyalism is induced, and thus in these cases abnormal oral examination findings should be readily seen. These conditions include acute calici- or herpesvirus infection, immune-mediated diseases, caustic ingestion, and uremia.

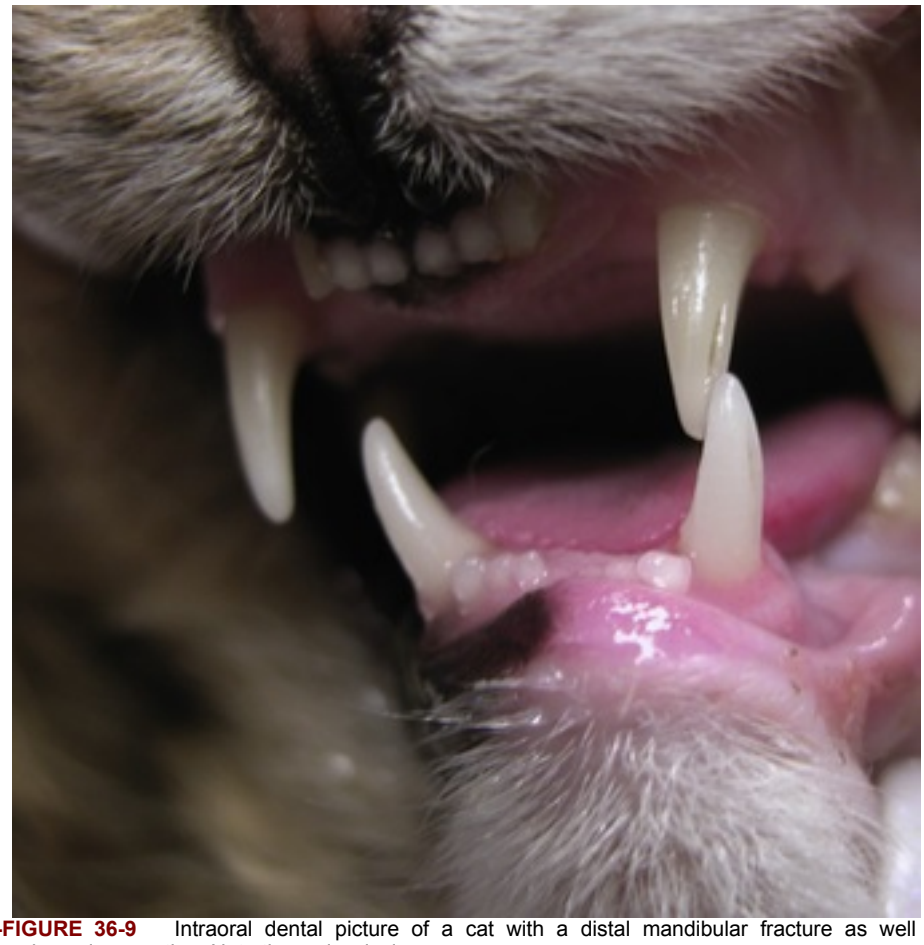
The saliva itself should be examined for consistency and any additional components (e.g., blood or pus). The severity and frequency of the drooling should be assessed. The hydration status and head posture of the patient should be evaluated.

It is important to note that a complete oral examination is not possible without general anesthesia, and that a minimum database should be obtained prior to the anesthetized exam.

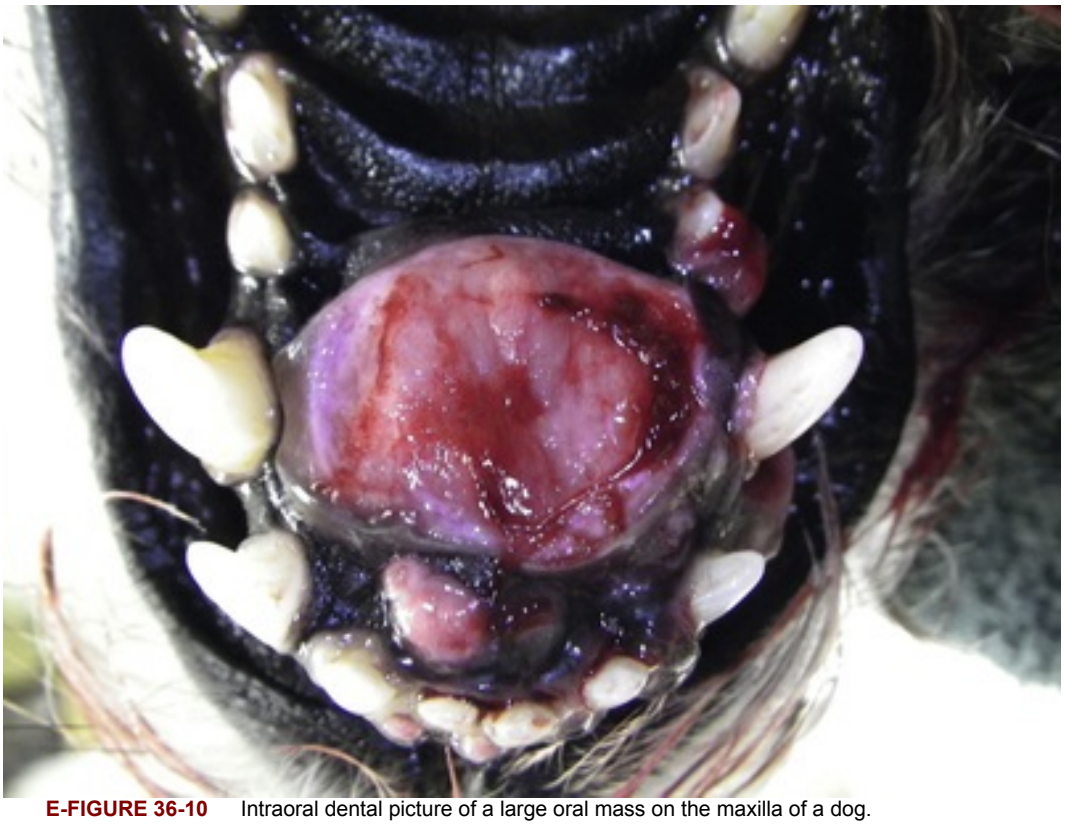
Saliva that has a sanguineous, purulent or fetid component is usually secondary to a problem within the oral cavity, such as: oral infections (such as oronasal fistula [E-Figure 36-8], trauma [E-Figure 36-9], neoplasia [E-Figure 36-10], inflammatory disease [E-Figure 36-11], or uremic ulcers [E-Figure 36-12]).



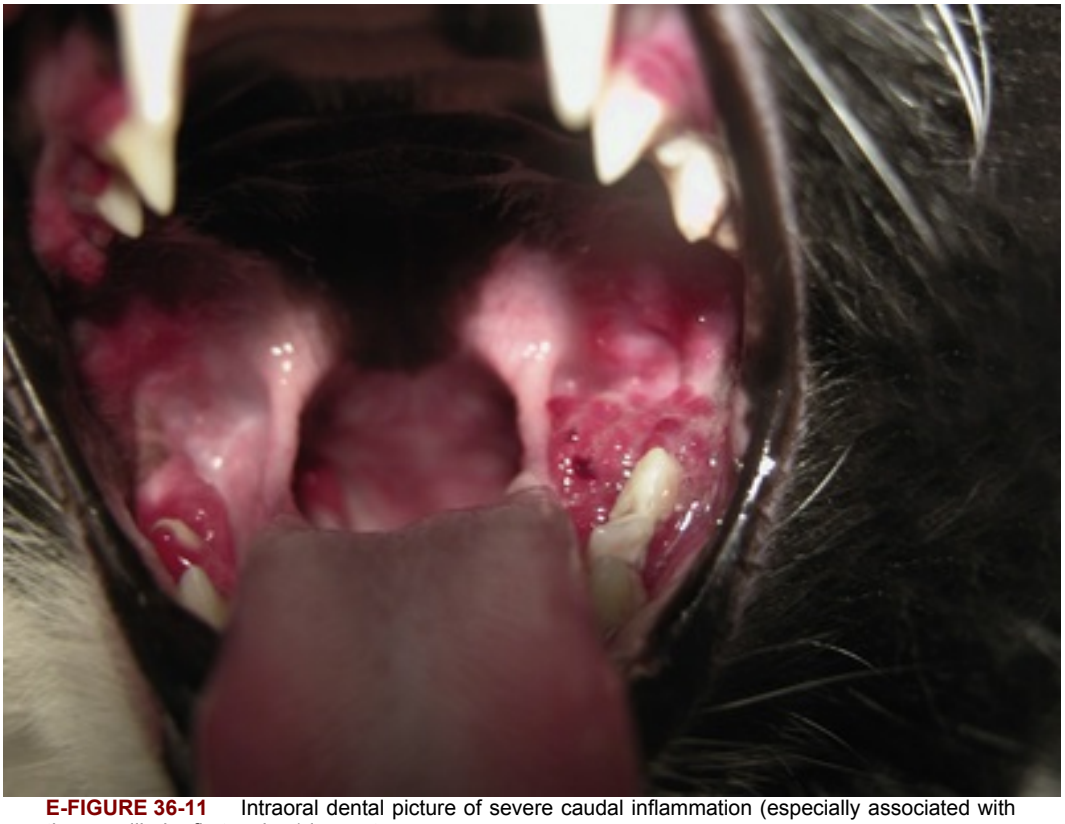
E-FIGURE 36-8 A large, chronic oronasal fistula in a dog. Dorsal is at the bottom of the image.



E-FIGURE 36-9 Intraoral dental picture of a cat with a distal mandibular fracture as well as symphyseal separation. Note the malocclusion.



E-FIGURE 36-10 Intraoral dental picture of a large oral mass on the maxilla of a dog.



E-FIGURE 36-11 Intraoral dental picture of severe caudal inflammation (especially associated with the mandibular first molars) in a cat.

E-FIGURE 36-12 Uremic ulcers in a cat with advanced renal disease.

A maxillofacial exam should include evaluation for swellings, asymmetry, TMJ luxation, trauma, cranial nerve function, and size and consistency of the salivary glands.

Inability to close the mouth indicates one of the following causes: traumatic (TMJ/mandibular fracture/luxation), neurologic (botulism or trigeminal neuropraxia), or obstructive (neoplastic or foreign body). **Inability to open the mouth** is most commonly associated with: tetanus, craniomandibular osteopathy, masticatory muscle myositis, neoplasia, or TMJ issues. The salivary glands should be systematically evaluated. Enlargement could indicate: infection, sialoliths, or neoplasia.

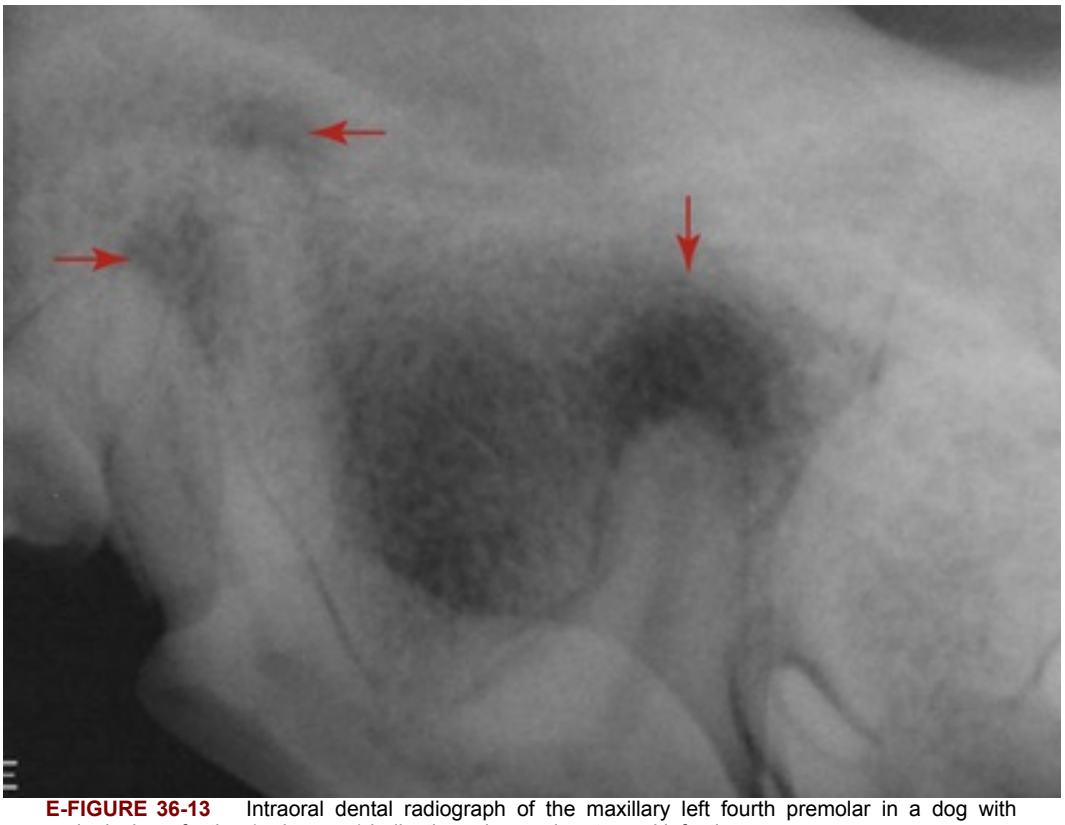
The physical examination of the esophagus is limited to external palpation for masses, pain or foreign bodies. Complete evaluation may require radiographs (+/− contrast), fluoroscopy, computed tomography (CT) scan, and/or endoscopy.

Diagnostic Tests[3,4]

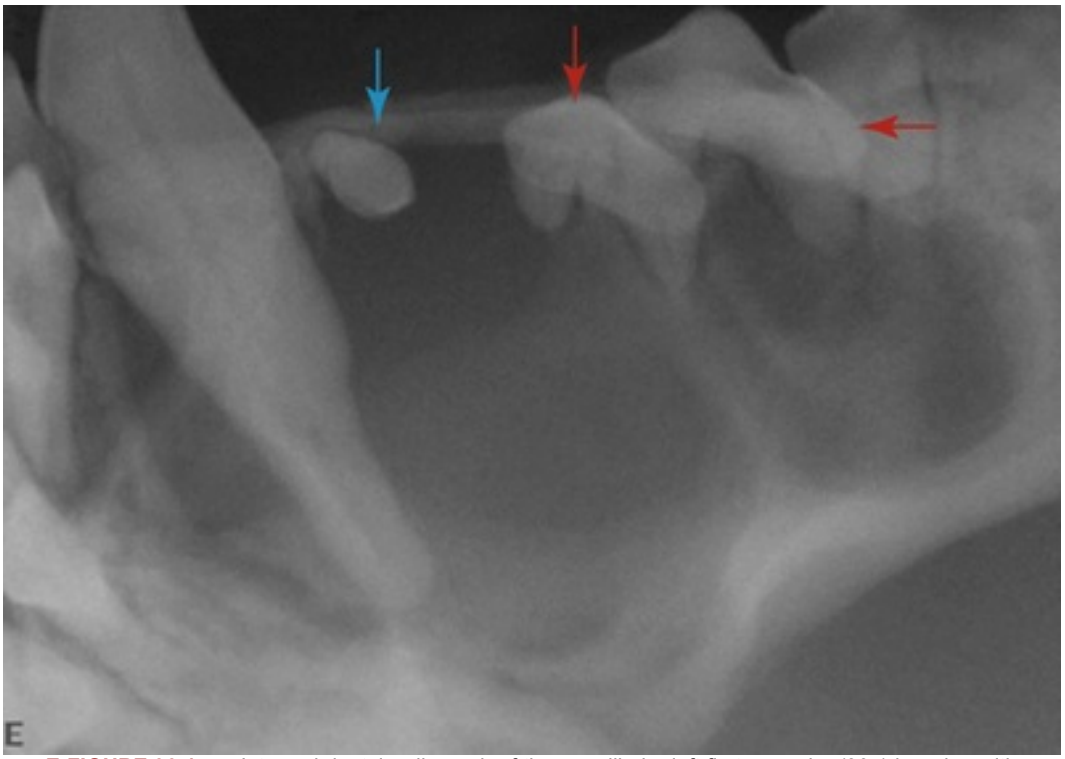
It is important to start initial diagnostic testing with a minimum database including complete blood count/chemistry panel/thyroid level, and urinalysis. This will rule out most of the metabolic causes as well as to verify that there are no blood count or blood chemical abnormalities that would preclude anesthesia for further evaluation.

For oral mucosal changes that are not obviously associated with a toxic or caustic cause or systemic disease (e.g., uremic ulcers), a surgical biopsy should be performed under general anesthesia and submitted for histopathology. When obtaining the tissue sample, ensure that it is representative of and of sufficient size for an accurate assessment. It is worthwhile to note that cytology as well as culture and sensitivity are often insufficient for an accurate assessment of disease processes in the oral cavity.[3,41]

In cases that clinically appear to have an oral cause but the problem cannot be readily identified on oral exam, dental radiographs should be performed. These radiographs may elucidate a subgingival cause such as a tooth root abscess or dentigerous/radicular cyst (E-Figures 36-13 and 36-14). Patients that present with derangements of jaw motion or maxillofacial swellings should be further evaluated with skull radiographs, nuclear scintigraphy, magnetic resonance imaging or CT scan. Finally, tests such as sialography can be of benefit.



E-FIGURE 36-13 Intraoral dental radiograph of the maxillary left fourth premolar in a dog with periapical rarefaction (red arrows) indicating advanced root canal infection.



E-FIGURE 36-14 Intraoral dental radiograph of the mandibular left first premolar (305) in a dog with a large dentigerous cyst. The cyst was created by the impacted first premolar (blue arrow). Note that the teeth are being moved by the cyst (red arrows).

Once oral and maxillofacial causes have been ruled out, further diagnostics are indicated, beginning with thoracic and abdominal radiographs. If the cause of the ptyalism has not been identified at this point, more specific testing should be performed, where indicated, such as upper GI studies, fluoroscopy, and endoscopy (see ch. 113). The clinician may also consider tests for botulism and rabies (see ch. 226 and 214).

Treatment

Treatment is directed at the underlying cause. Examples of treatments of ptyalism can be:

- **Direct toxic exposure** should be treated with dilutional therapy and supportive care.[9,10,42] Water or milk is considered the liquid of choice for dilution (see ch. 151).[43]
- Therapy for **oral inflammatory diseases** should be directed towards reducing the inflammation. This can be accomplished medically with immunosuppressive agents or surgically with periodontal treatment and/or extractions.[9,10,38,44]
- **Oral traumatic diseases** are best treated surgically.[8,10]
- **Portosystemic shunts** can be managed surgically or medically (see ch. 284).
- **Metabolic derangements** are treated as appropriate for the disease process.[9,10]

In case of idiopathic or incurable conditions such as structural or neurologic diseases, treatment is directed at decreasing the flow of saliva and protecting the epidermis in the chronically wet area. If one salivary gland is responsible for the increased production, surgical excision is the treatment of choice.[45,46] Cheiloplasty can be performed to help eliminate excessive drooling caused by lip malformation, mandibulectomy, glossectomy, or neurologic disorders of swallowing.[8] Finally, surgical repositioning of the parotid salivary duct may be effective in controlling the excess salvation.[47]

Decreasing the overall flow of the saliva can be attempted with atropine or glycopyrrolate.[48,49] In cases of idiopathic ptyalism, phenobarbital may be effective.[7] In these cases it is thought that the ptyalism is a form of epilepsy. In human dentistry, injections of biotoxin or ethanolamine oleate (EO) into the salivary glands, as well as radiotherapy, scopolamine via a transdermal patch, and even acupuncture have been investigated options for long-term salivary control.[50-54]

Halitosis

The origin of the term *halitosis* comes from the Latin word *halitus* meaning "breath or exhaled air."[55] Halitosis is defined as an offensive odor of the breath.[56] It is a common problem in companion animals and constitutes a significant psychosociological problem in the companion animal-owner relationship.[57] There is no sex or breed predilection, but the incidence increases with age.[55]

Classification of Halitosis

There is no universally accepted standardization in terminology and classification of halitosis.[58,59]

Genuine halitosis can be sub-classified as physiologic halitosis or pathologic halitosis. Pathologic halitosis means that the breath odor is a sign of a disease or a pathologic condition. Physiologic halitosis covers the situations where the patient has no disease but has a malodor because of putrefaction processes taking place in the oral cavity, most frequently caused by bacterial plaque. An example of physiologic halitosis is what is known in humans as "morning breath." In most cases, physiologic halitosis can be resolved with improved oral home care. This classification of bad breath is considered to be transient, in the sense that its presence comes and goes, as determined by temporary localized conditions in the mouth, and that it can be relatively easily resolved.

The best classification system for veterinary patients is based on etiology which divides halitosis into types based on where the offending molecules originate. This formula is broken into oral, airway, gastroesophageal, blood-borne, and subjective.

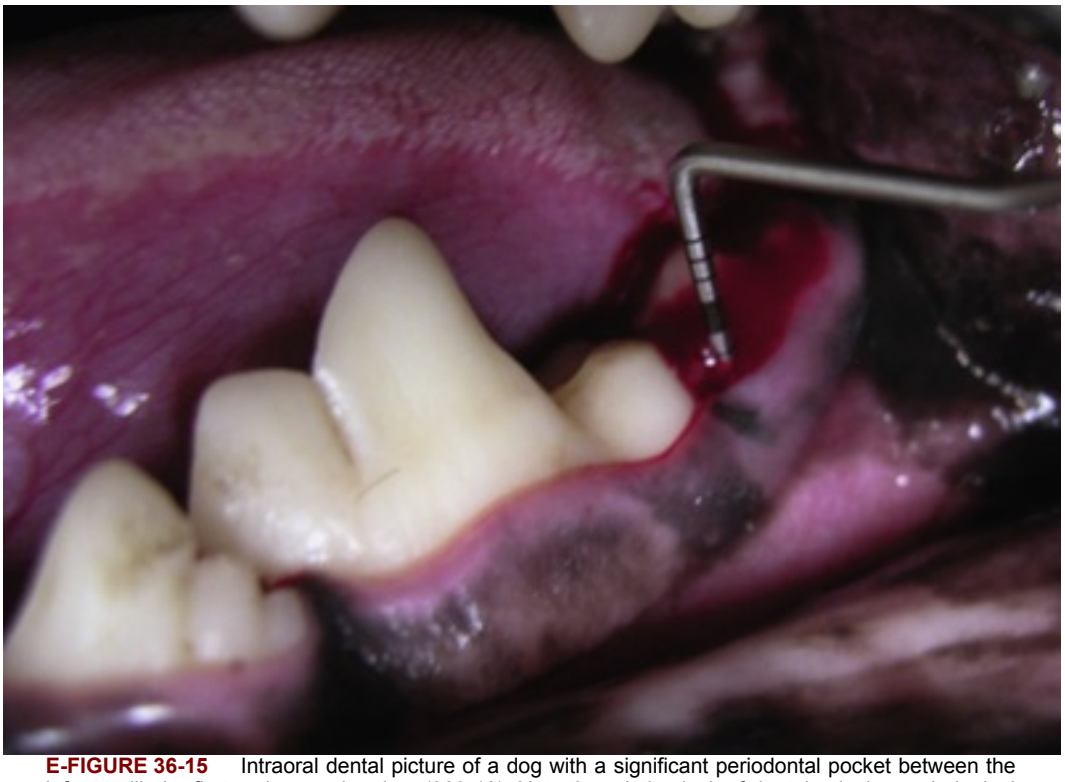
Halitosis can also be classified according to the character of the odor[60]: *Sulfurous* is caused by volatile sulfur compounds (VSCs): methyl mercaptan, hydrogen sulfide and dimethyl sulfide. *Fruity* is caused by acetone. *Urine* or *ammoniac* breath is caused by ammonia, dimethyl amine and trimethylamine. *Sweet* smelling breath is often associated with ketones. The degree of halitosis can be measured by a subjective scale from 0 to 3,[61] or

it can be objectively measured using a commercially available sulfide monitor.[62]

Causes of Halitosis

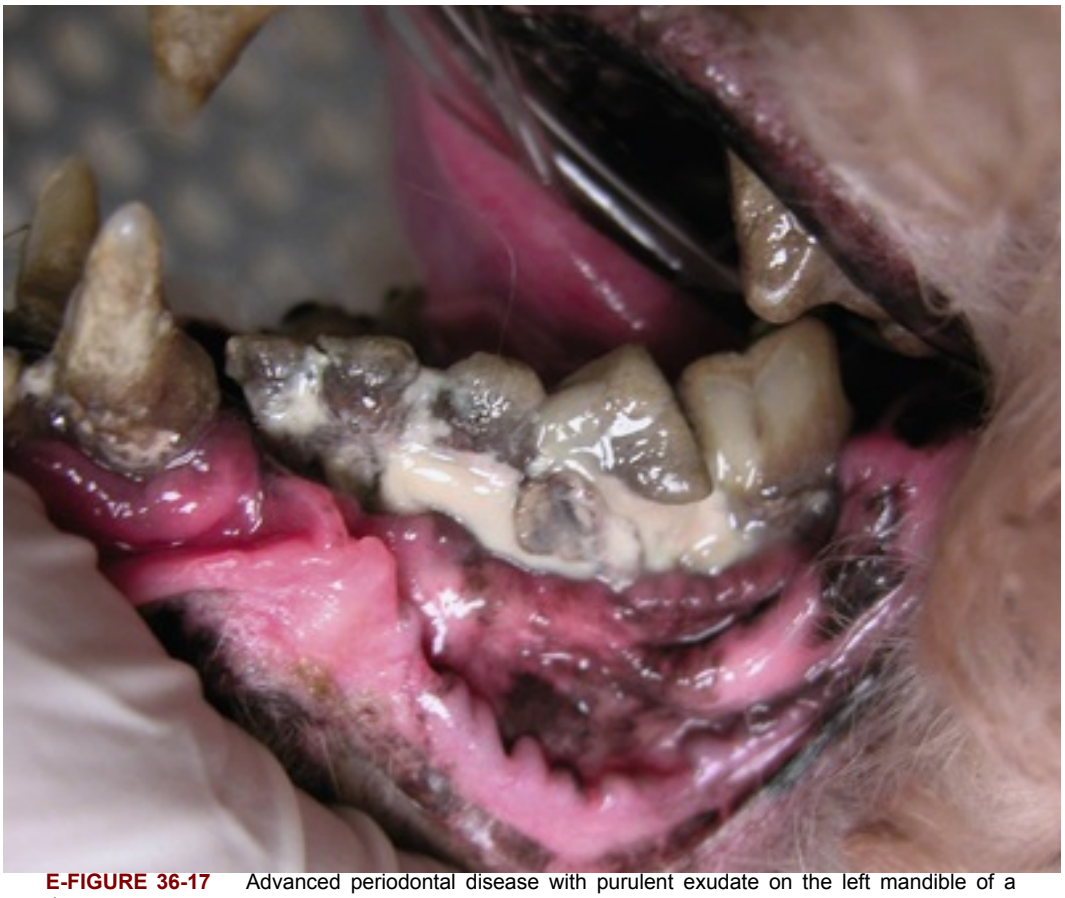
Oral Halitosis

In about 90% of human patients with halitosis, the origin of the problem is within the mouth itself.[63] The list of possible causes of halitosis originating from the oral cavity itself is long; however, by far the most prevalent cause is bacterial growth below the gum line in periodontal pockets created by periodontitis[64-67] (E-Figures 36-15 through 36-17).



E-FIGURE 36-15 Intraoral dental picture of a dog with a significant periodontal pocket between the left mandibular first and second molars (309-10). Note the relative lack of dental calculus and gingival inflammation. Therefore, do not assume that periodontal disease is not present just because the gums appear healthy. An exam under general anesthesia and dental radiographs are always necessary for proper periodontal evaluation.

E-FIGURE 36-16 Intraoral dental picture of a cat with a significant periodontal pocket on the palatal aspect of the left maxillary canine (204).



E-FIGURE 36-17 Advanced periodontal disease with purulent exudate on the left mandible of a dog.

Periodontal disease is generally described in two phases: gingivitis and periodontitis. Gingivitis is the initial, reversible stage of the disease, where the inflammation is confined to the gingiva.[68,69] At this point, there is no inflammation in the periodontal ligament or alveolar bone. The gingival infection is initiated by the plaque bacteria and can be reversed at this stage if a dental prophylaxis is performed and proper home-care maintained.[69] Periodontitis is the later stage of the disease process, which is defined as an inflammatory disease of the supporting structures of the teeth (the periodontal ligament and the alveolar bone) caused by microorganisms.[70] While it is initiated by plaque, the progression of disease is regulated by the patient's immune response.[71] In fact, it is actually the host response that often damages the periodontal tissues.[72-74]

Both gingivitis and periodontitis are initiated when oral bacteria adhere to the teeth in a substance called plaque.[64,65,75-77] Plaque is a biofilm almost entirely made up of oral bacteria contained in a matrix composed of salivary glycoproteins and extracellular polysaccharides.[68,69,73]

Plaque formation begins with the formation of the pellicle. The pellicle is a thin, saliva-derived layer including numerous proteins, enzymes and other molecules that can act as attachment sites for bacteria.[68] This starts forming nanoseconds after a prophylaxis.[15] Plaque is formed when bacteria attach to the pellicle.

Gingivitis is caused by an increase in the overall numbers of bacteria, which are primarily motile Gram-negative rods and anaerobic species.[76] The early colonizers are Gram-positive aerobic and generally minimally pathogenic. However, they promote the growth of the secondary and more periodontopathogenic colonizers, such as *Porphorymonas*. They accomplish this by using oxygen and making products such as lactate, formate, and succinate. The host provides nutrients to the pathogenic species in the form of blood and crevicular fluid.[78]

The whole process of plaque formation takes 24 hours if the plaque is not disturbed, which means that the teeth accumulate plaque **one day** following a complete dental prophylaxis.[68,79] After day 4, the plaque does not grow anymore, but the flora changes from Gram-positive to Gram-negative bacteria. This change in bacterial species is what initiates gingivitis.[80]

In dogs, anaerobes constitute only 25% of the culturable subgingival flora in healthy gingiva, but they become approximately 95% of the flora in dogs with periodontitis.[81] As the virulence of the bacteria increases, so does the effect of bacterial by-products, which elicit inflammation, including chemotoxins, mitogens, antigens, and enzymes such as hyaluronidase, chondroitin sulphate and proteolytic enzymes.[68]

Oral halitosis mainly originates from VSCs, especially hydrogen sulfide (H_2S), methylmercaptan (CH_3SH) and dimethyl sulfide ($(CH_3)_2S$).[82] These compounds typically result from the proteolytic degradation of peptides by oral microorganisms. These peptides are present in the saliva as well as gingival crevicular fluid, interdental plaque, and blood. In addition, they can come from shed epithelium, food debris, and discharge from the nasopharynx. It is interesting that only Gram-negative anaerobic bacteria possess such proteolytic activity. Wherever the location, the common pathophysiology is tissue destruction and putrefaction of amino acids by bacteria. The bacteria associated with gingivitis and periodontitis are almost all Gram-negative anaerobes and are all known to produce VSCs.[65,83-87]

The VSC levels in the mouth correlate positively with the depth of periodontal pocket(s).[67,82,88,89] This is likely due to the fact that deeper pockets will contain more bacteria, including a higher percentage of anaerobic species. The amount of VSCs in breath increases with the number, depth and bleeding tendency of the periodontal pockets.[82,88,89] The VSCs also directly aggravate the periodontitis process. They increase in the permeability of the pockets and mucosal epithelium and expose the underlying connective tissue of the periodontium to the bacterial metabolites.[90] Low oxygen tension in the deep periodontal pockets results in a low pH and activation of the decarboxylation of the amino acids (e.g., lysine, ornithine) to cadaverine and putrescine, both malodorous diamines. Thus, in the presence of gingivitis or periodontitis, VSCs play a prominent role in halitosis; but it is important to remember that not all patients with gingivitis or periodontitis have halitosis and vice versa.

The association between bad breath and periodontal disease in companion animals poses an important issue because halitosis is often the first clinical sign of periodontal disease noticed by the owner. However, it is important to note that halitosis is typically a sign of advanced periodontal disease. Clients should therefore be counselled that halitosis is not normal and that is an indication for professional dental therapy.

Treatment of Periodontal Diseases

There are numerous therapeutic options available for periodontal diseases; however, the basis of periodontal

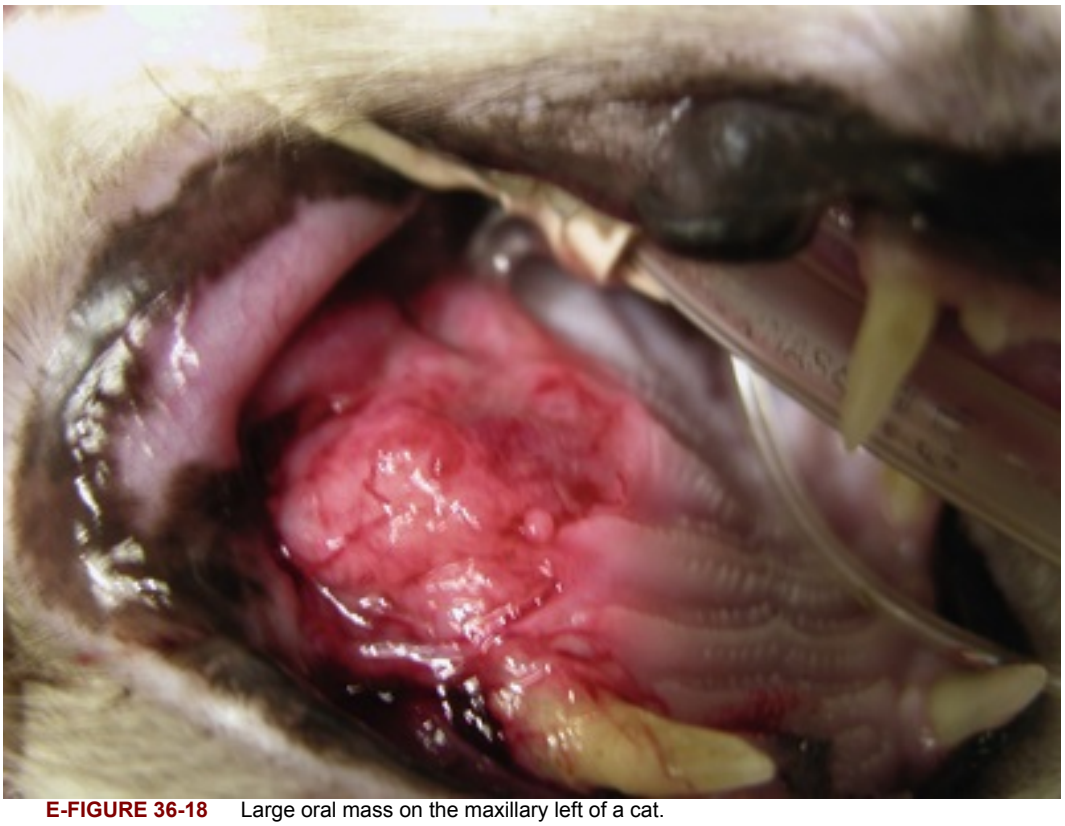
therapy remains plaque control.[91] The cornerstone of plaque control and the first step for any periodontal therapy is a thorough dental prophylaxis. A complete dental prophylaxis should include the following steps: pre-surgical exam, 0.12% chlorhexidine lavage, supra- and sub-gingival scaling, polishing, sulcal lavage, periodontal probing, oral evaluation, and dental charting, dental radiographs, treatment planning and surgery if necessary.[92]

Pockets with a depth of over 0.5 mm in cats and 3 mm in dogs are pathologic and require a deeper form of cleaning (+/− perioceutic). Teeth with pockets greater than 6 mm deep, furcation exposure level II or III, or mobility, require periodontal flap surgery or extraction to eradicate the infection.

Bacterial plaque colonizes clean tooth surfaces within 24 hours of cleaning.[68,79] Therefore, without a commitment to home care, gingival infection and inflammation quickly recurs.[70,93-96] In addition, with regards to established disease, a recent study found that periodontal pockets become reinfected within 2 weeks of a prophylaxis if home care is not performed.[94] This same study showed that pocket depth returns to pretreatment depths within 6 weeks of therapy. Furthermore, it was found in a human review that professional cleanings were of little value without home care.[97]

Other Oral Causes

There can be other intraoral courses of halitosis; however, these are all much less common than periodontal disease.[98-100] The list of differential diagnoses within the oral cavity is long but contains the following conditions: infections, ulcerations, tumors (E-Figure 36-18) and foreign bodies (E-Figure 36-19).



E-FIGURE 36-18 Large oral mass on the maxillary left of a cat.

E-FIGURE 36-19 Stick foreign body across the palate of a dog.

Owners often misdiagnose malodor caused by intertrigo or skin fold pyoderma as halitosis (see ch. 25).[101] Intertrigo arises from an overgrowth or colonization of skin folds by normal skin bacteria and sometimes yeast. Lip folds are common in brachycephalic breeds, spaniels, and many water dogs and these breeds are often presented due to the smell. The clinical signs are hair loss, redness, and accumulation of debris in the lip folds around the mouth (E-Figure 36-20).

E-FIGURE 36-20 Advanced intertrigo in a Poodle.

Airway

Nose and Sinuses

The nasal and sinus passages can also be the origin of halitosis. The smell typically has a stronger odor when coming from the nose compared to oral infection. Foreign bodies, neoplasia, or even chronic rhinosinusitis can cause nasal halitosis. Breath analysis techniques have not been applied to this condition, but theoretically there are several possible mechanisms of halitosis caused by infection in the nose or sinuses.[102-104]

Tonsils

In the human literature, there is disagreement as to the proportion of halitosis caused by tonsil pathology.[103] Tonsillar diseases which may be associated with halitosis include: chronic caseous tonsillitis, tonsillolithiasis and to a lesser extent peritonsillar abscess, actinomycosis, fungating malignancies and different kinds of tumors.[105]

Bronchi and Lungs

Pulmonary causes include chronic bronchitis and bronchiectasis.[106] Bronchiectasis is the result of chronic airway disease leading to a dilation of the bronchi and a collection of mucus and cell debris within the air passages. It is commonly found in those animals that have been suffering from chronic bronchitis or bronchopneumonia.

Gastroesophageal

Megaesophagus is a disorder of the esophagus characterized by dilation and decreased peristalsis (see ch. 273). Halitosis is a common clinical sign of megaesophagus along with regurgitation, weight loss, and coughing.[107] Halitosis resulting from other extraoral GI disorders is considered to be rare. However, it has been reported among the signs related to *Helicobacter pylori* infections and gastroesophageal reflux disease.[108]

Systemic conditions can also occasionally cause halitosis. The list of systemic differential diagnoses for halitosis includes: diabetes mellitus, renal infection and failure, liver disease, and carcinoma.[87,109] However,

patients suffering from such systemic diseases typically show additional and more diagnostically conclusive signs than halitosis alone.

Diabetes mellitus is a metabolic disorder characterized by a chronic hyperglycemic condition resulting from defects in insulin secretion, insulin action, or both (see ch. 304 and 305).[110,111] The deficiency in or the lack of action of insulin leads to uncontrolled lipolysis and elevated levels of free fatty acids in the plasma. This loss of proper regulation may result in the formation of ketones, used for energy production. A spontaneous breakdown product of the ketones (acetoacetate) is the acetone that is exhaled by the lungs, which gives a distinctive odor to the breath, which has been described as "rotten apples."[106]

Kidney insufficiency (uremia) will lead to increased uric acid levels in the blood, which is exhaled creating ammonium-like breath.[112] This is usually described as a "fish odor."[90] To fully investigate the underlying cause of kidney damage, imaging, blood tests and often renal biopsy are often used.

Liver insufficiency, such as with cirrhosis, will cause ammonium to accumulate in the blood and be exhaled.[113] *Foetor hepaticus* is a peculiar odor to the breath in people with severe liver disease, caused by volatile aromatic substances that accumulate in the blood and urine due to defective hepatic metabolism. It is a late sign in liver failure and is one of the clinical features of hepatic encephalopathy. Malodor caused by end-stage liver disease has a sweet odor, which some describe as that of "dead mice."[106]

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CHAPTER 37

Gagging

Peter Hendrik Kook

Client Information Sheet: Gagging

Anatomy and Physiology

The gag reflex is a normal defense mechanism that prevents foreign bodies from entering the trachea, pharynx, or larynx. Gagging comprises brisk and brief elevations of the soft palate together with bilateral contraction of the constrictor muscles of the pharynx resulting in ejection of unwanted, irritating, or toxic material. After intraoral stimulation, afferent fibers of the trigeminal, glossopharyngeal, and vagus nerves pass to the medulla oblongata. From there, efferent impulses give rise to the spasmodic and uncoordinated muscle movement characteristic of gagging. The corresponding center in the medulla oblongata is close to the vomiting, salivating, and cardiac centers, and these structures may be concurrently stimulated during gagging. Furthermore, neural pathways from the gagging center to the cerebral cortex allow the reflex to be modified by higher centers, illustrating why gagging may rarely also be elicited by nontactile sensations such as visual or olfactory stimuli. In small animals, the interpretation of a functioning gag reflex generally is that the neurologic pathways associated with gagging (the above-mentioned cranial nerves and their brainstem connections) are intact. However, in humans the gag reflex is not predictive of pharyngeal swallowing efficiency or aspiration risk because it can be absent in 20 to 40% of normal adults.[1] In dogs, central vagal stimulation can depress the onset of the gag reflex, possibly via blocking of impulses arising in response to pharyngeal stimulation by respiratory afferent impulses conducted through the vagal nerves.[2]

Gagging often occurs together with retching. Retching is an involuntary and futile attempt at vomiting associated with nausea. In retching, the direction of spasmodic and uncoordinated peristalsis is reversed and air is forced over the closed glottis producing a retching sound. It usually occurs post-swallowing and is suggestive of esophageal dysmotility. Ongoing retching usually culminates in the act of vomiting. Gagging, retching, and vomiting may occur separately or together. When they occur together, they are usually in sequence as manifestations of the different events that integrate the vomiting reflex. In contrast to vomiting, gagging and retching do not imply activation of the vomiting reflex. When gagging, retching or vomiting manifest as isolated clinical signs, their significance may differ from the stereotypical picture of vomiting. Gagging typically implies pharyngeal or retropharyngeal dysphagia and describes a patient that is trying to swallow in the presence of a dysfunctional pharyngeal phase of the swallowing process. This results in loss of the food bolus together with coughing or drooling. In addition, gagging tends to result in laryngospasm, particularly in cats. The act of swallowing comprises a series of sequential well-coordinated events that function to transport food and liquids from the oral cavity to the stomach. Deglutition has an oral, pharyngeal, and esophageal phase, and all three phases are involved in the transport of the bolus from the oral cavity to the stomach. The pharyngeal phase of swallowing involves the movement of the bolus from the pharynx to the esophagus. The required sequential contractions are initiated by stimulation of sensory receptors through touch, pressure, and similar action of food on the tongue, faucial pillars, soft palate, uvula, epiglottis, pharyngeal wall, and/or junction between the pharynx and esophagus. The corresponding nerve fibers belong to the maxillary branch of cranial nerves V and IX and to the cranial laryngeal nerve. These afferent pathways carry the information from peripheral receptors to the brainstem and thus evoke contraction of the buccal, tongue, pharyngeal, and esophageal muscles, propelling the food bolus aborally. Particular sensory patterns determine which pharyngeal motor responses will be evoked. Generally, solid boluses are more effective than liquids in stimulating pharyngeal receptors to initiate swallowing, whereas multiple swallowing attempts are sometimes necessary to stimulate deglutition of water, even in healthy animals. Finally, expectoration may be confused with gagging. Expectoration is defined as ejection of airway

and laryngopharyngeal mucus or other material and is not associated with nausea. It usually follows an episode of coughing, for instance in animals with inflammatory airway disease (Video 37-1). Gagging and retching under these circumstances is not associated with swallowing or gastrointestinal disease but rather is a consequence of cardiopulmonary disease usually following an episode of coughing.

History

There are a number of environmental and clinical factors that should be evaluated when a dog or cat is presented because of gagging. These include the occurrence of sneezing, coughing, vomiting, regurgitation, and salivation and changes in appetite, activity level, overall strength, and voice. In addition, environmental factors, the onset, duration, and progression of clinical signs, the potential for foreign body or toxin exposure, and the development of growing animals should be assessed. Vaccination history for rabies is also of interest because the inability to swallow saliva (and food) secondary to lyssavirus-associated laryngeal paralysis may also elicit gagging when intraoral areas known to be ''trigger zones'' such as the base of tongue or palate are stimulated (see ch. 226).

Clinical Evaluation

A physical examination must include thorough evaluation of the oral cavity and oropharynx, palpation of the pharynx, neck, and salivary glands, and assessment of airflow from the nares. Sedation or light anesthesia is usually required for complete examination of the oropharynx and larynx. Ear polyps may cause gagging and should be ruled out by means of an otoscopic examination, particularly in cats. Thoracic auscultation and routine thoracic radiography may also be part of the workup because severe respiratory disease can mimic gagging and retching. Gagging may occur as a sequel to oropharyngeal dysphagia and therefore a neurologic examination is indicated (see ch. 259). Neurologic diseases can damage the neural structures that are involved in the afferent or efferent limbs of the gag reflex; however, most neuromuscular diseases generally tend to weaken pharyngeal function rather than cause pharyngeal spasmodic contractions typically associated with gagging. On the other hand, decreased salivary clearance associated with impaired swallowing may stimulate the gag reflex, and functions mediated by adjacent neuronal structures can concurrently be involved. A complete blood cell count, biochemistry profile, including creatine kinase activity, and urinalysis may be considered to rule out systemic illness. In young breeds of dogs known to have hereditary cobalamin malabsorption, measurement of serum cobalamin concentration may be useful; intermittent impairment of swallowing secondary to stomatodynia and glossitis, which can trigger or mimic gagging, was recently described in canine Imerslund-Graesbeck syndrome.[3] Evaluation of the thyroid function may be helpful in single cases, because cricopharyngeal dysfunction has been reported as the presenting complaint in canine hypothyroidism and was fully reversible with thyroid supplementation.[4]

A list of causes of gagging accompanied by appropriate diagnostic tests is shown in Box 37-1. An algorithm (Figure 37-1) identifies how to workup a gagging dog or cat.

Box 37-1

Differential Diagnosis and Diagnostic Tests for Gagging in Dogs and Cats

I. Nasal sinus
- A. Cleft palate ⇒ oropharyngeal examination
- B. Nasal parasites (*Capillaria, Pneumonyssoides* spp.) ⇒ rostral and retrograde examination of nasal passage, rhinoscopy
- C. Nasal tumors ⇒ same as B plus CT scan/biopsy
- D. Nasal foreign body ⇒ same as B

II. Pharynx (morphologic)
- A. Neoplasia ⇒ oropharyngeal examination, possible CT/MRI scan, fine needle aspiration cytology, core-needle biopsy and histopathology
- B. Foreign body ⇒ oropharyngeal examination, fistulogram, CT/MRI scan
- C. Tonsillitis ⇒ tonsillectomy (rarely the only cause)
- D. Pharyngitis, pharyngeal abscess ⇒ same as A

E. Elongated soft palate ⇒ oropharyngeal examination
F. Nasopharyngeal polyps ⇒ oropharyngeal and nasopharyngeal examination
G. Pharyngeal mucocele ⇒ oropharyngeal examination, fine-needle aspiration cytology
H. Stylohyoid disarticulation ⇒ oropharyngeal examination, pharyngeal radiography or CT scan
I. Cricopharyngeal bar ⇒ videofluoroscopy, manometry

III. Pharynx (functional)

A. Cricopharyngeal achalasia ⇒ videofluoroscopy, manometry
B. Cricopharyngeal dyssynchrony ⇒ videofluoroscopy, manometry
C. Neuromuscular disease
1. Inflammatory ⇒ neurologic examination, EMG, muscle biopsy
2. Degenerative/idiopathic ⇒ same as 1 plus brain imaging
3. Neoplastic ⇒ neurologic examination, CT/MRI scan of brainstem
4. Infectious (rabies, pseudorabies) ⇒ history of exposure, vaccination history, clinical course, histopathology
5. Hypocalcemia ⇒ serum (ionized) calcium concentration

IV. Respiratory tract

A. Upper airway (morphologic)
1. Foreign body ⇒ pharyngeal/laryngeal examination, radiography, CT/MRI scan, endoscopy
2. Neoplasia ⇒ same as 1 plus cytology, histopathology
3. Tracheal collapse ⇒ radiography, fluoroscopy, endoscopy
B. Upper airway (functional)
1. Laryngeal paralysis ⇒ pharyngeal, laryngeal examination
2. Laryngitis ⇒ pharyngeal, laryngeal examination
3. Tracheobronchitis ⇒ radiography, transtracheal aspiration cytology/culture, bronchoscopy
C. Lower airway (functional)
1. Feline chronic bronchial disease ⇒ radiography, bronchoalveolar lavage
2. Canine tracheobronchitis ⇒ history, physical examination, tracheal cytology
3. Fungal pneumonitis ⇒ history, radiography, tracheal and bronchial cytology, fungal antigen testing

V. Esophagus

A. Morphologic
1. Stricture/stenosis ⇒ history, (contrast) radiography, (+/− fluoroscopy), endoscopy
2. Neoplasia ⇒ same as 1
B. Functional
1. Esophagitis ⇒ history, endoscopy, cytology/histopathology
2. Esophageal motility disorder ⇒ same as 1 plus ACh receptor Ab titer, edrophonium response test, EMG, thyroid profile, resting serum cortisol concentration/ACTH stimulation, muscle biopsy

VI. Miscellaneous

A. Salivary gland disease (hypersialosis) ⇒ salivary gland palpation, fine-needle aspiration, treatment trial with phenobarbital

AB, Antibody; *ACh,* acetylcholine; *ACTH,* adrenocorticotropic hormone; *CT,* computed tomography; *EMG,* electromyography; *MRI,* magnetic resonance imaging.

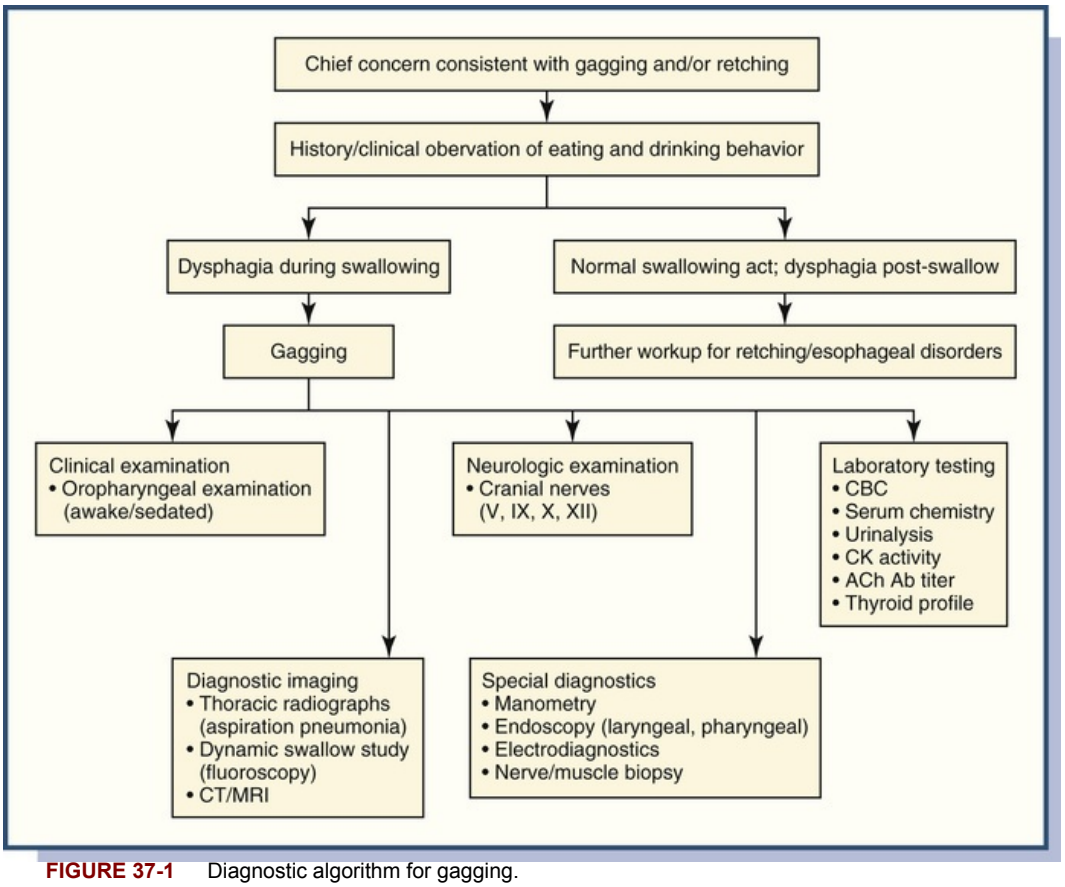

FIGURE 37-1 Diagnostic algorithm for gagging.

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CHAPTER 38

Dysphagia

Julio López

Client Information Sheet: Dysphagia

Dysphagia and regurgitation are clinical signs typically associated with disorders of the oropharynx or esophagus. Careful attention to the history and clinical signs assists the clinician in localizing the dysphagia and differentiating regurgitation from vomiting, which is necessary to formulate an appropriate diagnostic and treatment plan (Figures 38-1 and 38-2) (see ch. 39).

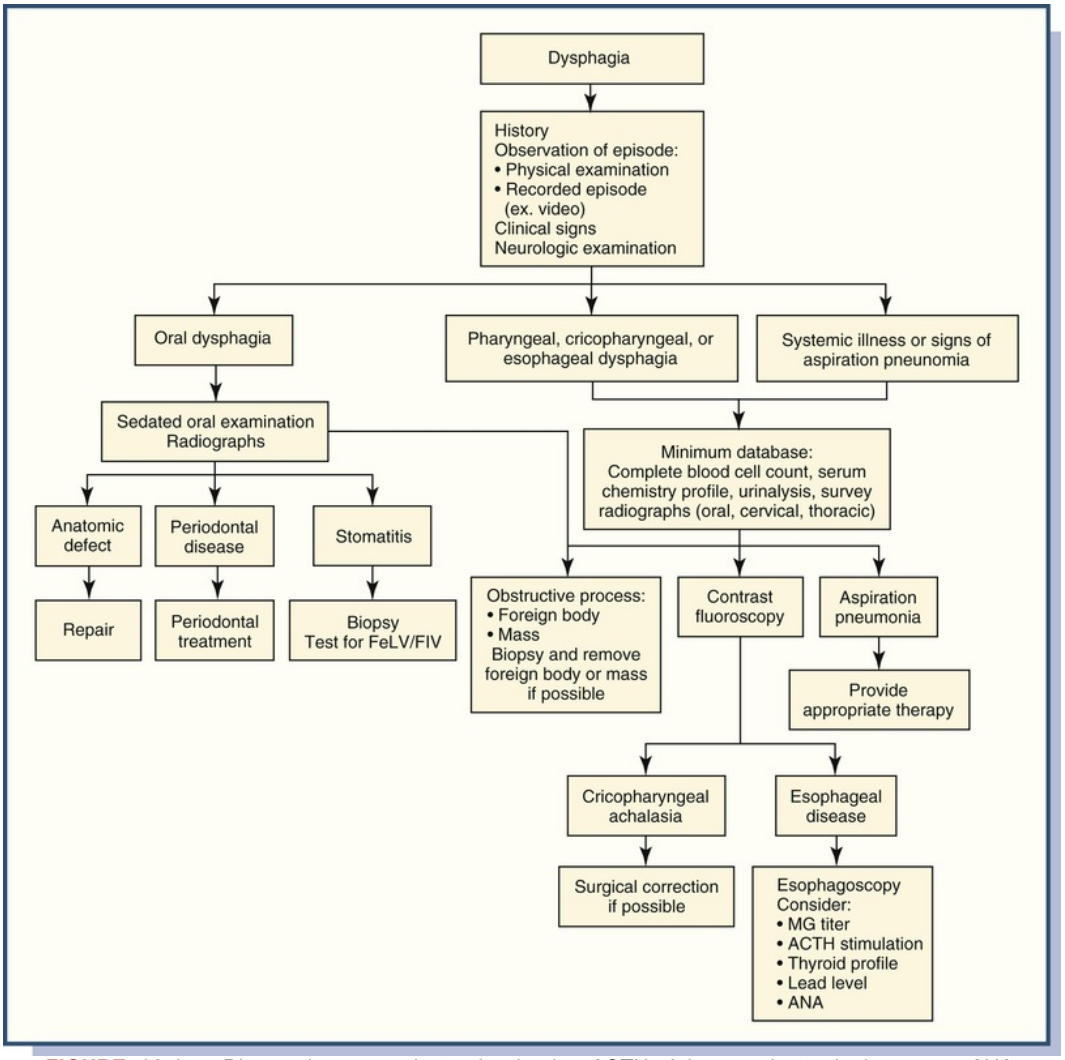

FIGURE 38-1 Diagnostic approach to dysphagia. *ACTH,* Adrenocorticotropic hormone; *ANA,* antinuclear antibody titer; *FeLV,* feline leukemia virus; *FIV,* feline immunodeficiency virus; *MG,* myasthenia gravis (acetylcholine receptor antibody). (From Schaefer Woolley C: Dysphagia and regurgitation. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine,* ed 7, St

Louis, 2010, Saunders Elsevier, pp 191-195.)

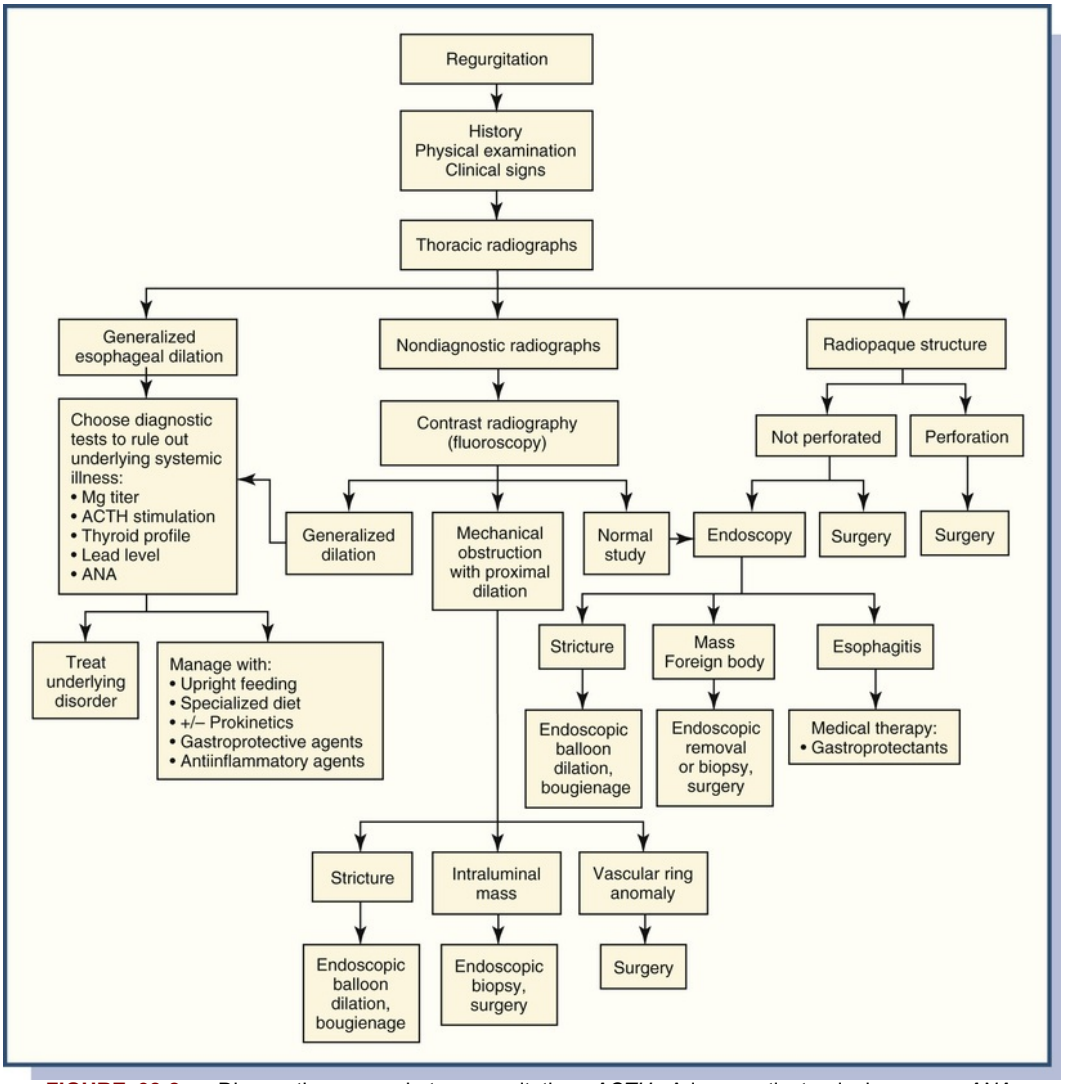

FIGURE 38-2 Diagnostic approach to regurgitation. *ACTH,* Adrenocorticotropic hormone; *ANA,* antinuclear antibody titer. (From Schaefer Woolley C: Dysphagia and regurgitation. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine,* ed 7, St Louis, 2010, Saunders Elsevier, pp 191-195.)

Dysphagia

Dysphagia is defined as difficulty swallowing. The process of swallowing consists of four phases: oral preparatory, oral, pharyngeal, and esophageal.[1] It is essential to observe the animal eating and drinking to assist in localization of the abnormal swallowing phase. The oral phases of dysphagia consist of abnormalities with prehension, mastication, lubrication, and transportation of food from the tongue to the pharynx. Pharyngeal dysphagia occurs when the food bolus cannot be propelled from the oropharynx, through the hypopharynx, and to the proximal esophagus. Cricopharyngeal dysphagia is the abnormal transportation of a bolus through the proximal esophageal sphincter. It is either due to an inadequate or complete lack of opening/relaxation of the upper esophageal sphincter (true cricopharyngeal achalasia) or from abnormal timing of its opening/relaxation (cricopharyngeal asynchrony). Esophageal dysphagia is difficulty in passing a bolus down the esophageal body.

Clinical Signs

Clinical signs are dependent on the location and severity of the swallowing disorder. Oral dysphagia manifests as difficulty prehending or masticating food, or an inability to transport it to the base of the tongue. Pharyngeal dysphagia may present with gagging or retching, and as with cricopharyngeal dysphagia may demonstrate repeated attempts to swallow, excessive head movements, and dropping food from the mouth. Regurgitation is associated with esophageal dysphagia. Coughing may occur in dysphagic animals, both in association with swallowing, or as a sign of aspiration pneumonia, a complication that can occur with any form of dysphagia (see ch. 242).

Signalment

A review of the signalment and age of onset of clinical signs may aid in formulating a differential diagnosis. Congenital defects, such as cricopharyngeal achalasia, are more likely noted in juvenile dogs and may be first observed at weaning. In Golden Retrievers, oropharyngeal dysphagia has been identified as a heritable trait.[2] Hypothyroidism may be considered as a differential diagnosis as well.[3] Mechanical obstruction (foreign bodies) or ingestion of a caustic substance is more likely in young to middle-aged pets. Geriatric pets, or those with chronic signs of disease (weight loss, anorexia), are more likely to have a systemic illness. When other neurologic deficits occur along with dysphagia, a nervous system disease such as a neuropathy, neuromuscular junction disorder, or myopathy is likely (Box 38-1).[4] Cats are less likely to have dysphagia compared to dogs, but when they do, it is usually secondary to a structural abnormality such as an oral tumor, ulcer or stomatitis.

Box 38-1

Causes of Dysphagia

Obstructive Lesion (Anatomic or Mechanical)

Foreign body
Neoplasia
Inflammatory (abscess, polyp, granuloma)
Lymphadenopathy
Sialocele
Lingual frenulum disorder
Cricopharyngeal achalasia/asynchrony
Cleft palate
TMJ disorder
Trauma (fracture, luxation)

Pain

Periodontal (tooth fracture/abscess, periodontitis)
Stomatitis/glossitis/pharyngitis (viral: FeLV/FIV, immune mediated, caustic ingestion)
Traumatic (electric cord burn)
Retrobulbar abscess

Neurologic Disorders

Rabies
CNS disease (brainstem)
Cranial nerve disease (V, VII, IX, X, XII)

Neuromuscular Disorders

Myasthenia gravis
Inflammatory myopathy (masticatory myositis, polymyositis)
Polyradiculitis
Botulism
Tick paralysis
TMJ disease

Endocrine
Hypothyroidism
CNS, Central nervous system; *FeLV*, feline leukemia virus; *FIV*, feline immunodeficiency virus; *TML*, temporomandibular joint.

From Schaefer Woolley C: Dysphagia and regurgitation. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine*, ed 7, St Louis, 2010, Saunders Elsevier, pp 191-195.

Diagnosis

Correctly localizing the source of the dysphagia will require combining observation of the abnormal swallowing along with the signalment, history, clinical signs, and physical exam. A neurological examination should also be performed as it may support a generalized neuromuscular disorder (see ch. 259). The gag reflex should be present in cases of cricopharyngeal dysphagia but may be diminished in pharyngeal dysphagia. As rabies is a differential diagnosis, caution should be taken in any case where there is an index of suspicion for this disease (see ch. 226). A complete oral and laryngeal examination under anesthesia is essential to identify obstructions (foreign body, mass), inflammatory processes (stomatitis, dental disease), or laryngeal paralysis (polyneuropathy).

Survey radiographs of the head, neck and thorax should be obtained, as well as a complete blood count, serum chemistry profile (including creatine kinase and electrolytes), urinalysis, thyroid testing, and acetylcholine receptor antibody titer for myasthenia gravis, which may present as an acquired focal disease.[5] Often, advanced diagnostics such as endoscopy and/or contrast videofluoroscopy motion studies (see Videos 271-1, 271-2, and 271-3) are needed to evaluate the structure and function, respectively, of the anatomic areas involved in the swallowing reflex and allow for a definitive diagnosis (see Figure 38-1).[6]

Treatment

An accurate diagnosis is the key to creating a treatment plan, as surgical intervention of a condition requiring medical treatment will lead to worsening of the dysphagia.[7] When the underlying cause cannot be treated, dietary modifications including changes in food consistency (liquid, solid), meal frequency (smaller, more frequent) and feeding positions (upright) should be attempted until the best fit for that patient is found. If these adjustments do not provide adequate caloric intake, placement of a feeding tube becomes necessary (see ch. 82). Complications, such as aspiration pneumonia, should also be addressed.

Regurgitation (also see ch. 39)

Regurgitation is the passive expulsion of food or fluid from the esophagus due to mechanical, obstructive disease or functional (motility) abnormalities. Clients may incorrectly report their pet is vomiting, a centrally mediated reflex in which gastric or duodenal contents are forcefully expelled, when in fact it is regurgitating. Therefore, careful questioning of the client is paramount in differentiating between the two.

Clinical Signs

With regurgitation, owners may notice the pet lower its head and produce material, or they may report finding fluid or food without having heard the pet. In contrast, vomiting involves retching and abdominal contractions and may be preceded by hypersalivation. Timing and the type or consistency of expelled contents does not help in differentiating regurgitation from vomiting. Regurgitation may occur immediately or hours after feeding, and the contents can vary from undigested to digested food, mucus or a clear, frothy liquid. Bilious material (yellowish-green coloration) is not associated with regurgitation. Sometimes odynophagia (painful swallowing) and ptyalism may be noted. Other systemic signs may include weight loss, polyphagia, weakness and other neurologic abnormalities. If aspiration pneumonia is present, dyspnea, fever and cough may be noted.

Signalment

Megaesophagus is the most commonly reported motility disorder to affect the canine esophagus and is the

most common cause of regurgitation in dogs.[7] There is an increased prevalence for congenital megaesophagus in Labrador Retrievers, Newfoundlands, Chinese Shar-Peis, and for both congenital and acquired forms in Great Danes, German Shepherds, and Irish Setters.[8] Other breeds such as Chinese Shar-Peis, Bouviers des Flandres and terrier breeds can have clinical and non-clinical esophageal motility disorders, without megaesophagus, that may improve or resolve as the esophagus completes maturation.[9] In young-adult, large-breed dogs living in endemic areas, spirocercosis may be a cause of esophageal dysphagia.[10] Recent anesthetic episodes (i.e., spay/neuter, dentistry) and oral medication administration (doxycycline, clindamycin) are the most common cause of esophageal stricture formation and they should not be overlooked as potential causes of regurgitation.[11] Besides stricture formation, anesthesia may also be associated with megaesophagus from esophageal muscle atony secondary to gastroesophageal reflux-induced esophagitis. Idiopathic laryngeal paralysis has also been associated with esophageal dysfunction.[12]

Diagnosis

Physical examination may reveal a thin body condition or a bulging of the neck due to esophageal dilation. Harsh or diminished lung sounds may be noted on thoracic auscultation if aspiration pneumonia is present. A complete neurological examination is necessary to reveal any abnormalities that may occur with diseases such as myasthenia gravis or other neuropathies or myopathies (see Figure 38-2, Box 38-2).

Box 38-2

Causes of Regurgitation

Esophageal Disorders
Megaesophagus (primary or secondary)
Esophagitis
Obstructive (stricture, foreign body, vascular ring anomaly)
Esophageal diverticula

Alimentary Disorder
Pyloric outflow obstruction
Hiatal hernia
Gastric dilatation volvulus

Neurologic Disorder
Central nervous system (brainstem lesion, neoplastic, trauma)
Peripheral neuropathy (lead, thallium, polyradiculitis, polyneuritis)
Dysautonomia

Neuromuscular Disorder
Myasthenia gravis
Botulism
Tetanus
Distemper
Acetylcholinesterase toxicity (organophosphates)

Infectious
Spirocercosis
Pythium insidiosum
Neosporosis

Plain cervical and thoracic radiography is the initial diagnostic step to evaluate for esophageal dilation (focal with stricture or vascular ring anomaly, generalized with megaesophagus), radiopaque structures (foreign body, mass), widening of the mediastinum (thymoma) and for evidence of aspiration pneumonia. A complete blood count, serum chemistry profile, urinalysis, total thyroxine and fecal analysis (see ch. 82) should be obtained. If plain radiographs are not diagnostic, contrast esophagrams, endoscopic examination,

or videofluoroscopic examination (see Videos 271-1, 271-2, and 271-3 and ch. 113) may be necessary. Esophageal retention of any contrast material is abnormal. Other specialized tests including adrenocorticotropic hormone (ACTH) stimulation test (hypoadrenocorticism), complete thyroid profile (hypothyroidism), acetylcholine receptor antibody test (myasthenia gravis), and lead level assay may be needed depending on suspicion for a specific underlying disease process (see Box 38-2).

Treatment

Although treatment of secondary complications such as aspiration pneumonia should be initiated, it is essential to address the underlying disease process for successful therapy. Management of regurgitation while providing adequate nutrition is the primary goal in cases of primary megaesophagus or esophageal dysmotility. Dietary and feeding modifications such as feeding small, frequent high-calorie meals must be made. Trial and error will help determine the right food consistency for each patient as it can vary from chunky food or meatballs to a liquefied diet. If there is difficulty drinking water, adding a tasteless thickening agent can be attempted. Keeping the pet upright during and after feedings, manually or with the aid of a Bailey chair, as well as gentle coupage may help the movement of food down the esophagus. Some patients will require gastrostomy feeding tube placement to achieve adequate caloric intake and reduce regurgitation episodes (see ch. 82). The use of prokinetic drugs (cisapride, metoclopramide) in dogs is controversial, as mechanistically they are likely to be ineffective on their striated esophageal muscle, and may make it more difficult for food to pass into the stomach as they enhance lower esophageal sphincter pressure. Bethanechol may be effective in some dogs.[13] In the cat, cisapride may be a more effective prokinetic agent as it works on the cholinergic neurons of the esophagus.[14] Gastroprotective therapy to decrease stomach acidity (proton pump inhibitors, H2-receptor antagonists), and mucosal protectants (sucralfate) should be instituted in all cases, with the addition of prokinetic agents to increase lower esophageal sphincter tone in cases of primary esophagitis.

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CHAPTER 39

Vomiting and Regurgitation

Alex Gallagher

Client Information Sheet: Vomiting and Regurgitation

Vomiting is a common presenting complaint in cats and dogs. While the majority of time the patient is truly vomiting, it may actually be regurgitation in some cases, as owners are often unaware of the difference. The clinician must distinguish between these two clinical signs as the differential diagnoses and diagnostic evaluation are quite different for each.

Differentiating Regurgitation From Vomiting

A complete history and thorough physical examination will usually allow differentiation of regurgitation from vomiting (Table 39-1; Video 39-1). Asking owners to describe the episodes is helpful, as a description of abdominal contractions (retching) or bile in the vomitus is specific for vomiting. In rare instances, bile may be present in regurgitation due to reflux of bile from the stomach into the esophagus prior to regurgitation. Additionally, vomiting is often associated with prodromal signs of nausea such as salivation or lip-smacking. With regurgitation, owners typically report that the animal simply lowers its head and material is expelled.

TABLE 39-1

Clinical Findings Used in the Differentiation of Regurgitation versus Vomiting

CLINICAL SIGN	REGURGITATION	VOMITING
Nausea or salivation	No	Common
Retching	No	Common
Presence of bile	Rare	+/−
Cervical esophageal distension	+/−	No
Amount of material	Any	Any
Time after eating	Variable	Variable
pH	Variable	Variable

Other factors such as timing of the episode in relation to feeding or the amount of material produced are not distinguishing factors. Animals may vomit undigested food or regurgitate digested-appearing food. The pH of the expulsed material has been considered a possible differentiating test. Vomited material is expected to have a low pH and regurgitated material to have a more neutral or high pH. However, some animals may regurgitate stomach contents (such as in reflux esophagitis) and some may vomit bicarbonate-rich fluid refluxed from the duodenum, making pH a poor indicator.

In some instances, the owner may not have witnessed the episode, but only report finding food or fluid on the floor. In other cases, the description of the episodes may not allow obvious distinction. In these cases, the rest of the history and physical examination should be used for determining if vomiting or regurgitation is more likely. As regurgitation is uncommon in cats, episodes can most often be assumed to be vomiting in this species. If possible, having the owner record an episode on video may be helpful. While rare, simultaneous vomiting and regurgitation may be present.

Regurgitation

Regurgitation is the passive expulsion of food, fluid, or other material from the pharynx or esophagus. It must be differentiated from expectoration, which is the expulsion of material from the respiratory tract associated with coughing. Regurgitation may be followed by a terminal retch or gag, which owners may confuse with cough, and regurgitation can lead to aspiration pneumonia resulting in a true cough.

Pathophysiology

The esophagus is a long tubular organ bordered proximally by the upper esophageal sphincter and distally by the lower esophageal sphincter. The muscular composition of the esophagus differs between dogs and cats. In dogs, the esophageal body is fully composed of striated muscle. In the cat, the distal ⅓ to ½ of the esophagus is composed of smooth muscle. In both species, during swallowing, the upper esophageal sphincter relaxes to allow passage of the food or liquid into the proximal esophagus. A primary peristaltic wave is initiated that moves food distally to the stomach. Secondary peristaltic waves are generated as a response to intraluminal distension to clear remaining material. The lower esophageal sphincter relaxes as the food bolus approaches, allowing passage into the stomach. Diseases that result in inflammation, obstruction, or hypomotility in the esophagus interrupt this normal process and can result in regurgitation.

Clinical Signs

The regurgitant may include undigested food, digested food, or clear, frothy fluid. Weight loss and polyphagia may occur due to inadequate nutrition. In some cases, dilation of the cervical esophagus may be apparent. Signs of aspiration pneumonia (see ch. 242) including lethargy, anorexia, cough, or dyspnea may be present. A neurological examination should be performed (see ch. 259) to evaluate for deficits consistent with generalized neuromuscular dysfunction.

Diagnosis

Initial evaluation consists of cervical and thoracic radiographs to assess for generalized (megaesophagus) or focal (vascular ring anomaly, stricture) esophageal dilation, foreign bodies, intra- or extraluminal masses, and aspiration pneumonia (Figure 39-1). Contrast radiography (esophagram) provides further assessment if survey radiographs are non-diagnostic. Use of video fluoroscopy is beneficial to better assess esophageal motility. Endoscopy (see ch. 113) can confirm radiographic findings, provide treatment for foreign bodies or strictures, allow biopsy of mass lesions, and identify esophagitis.

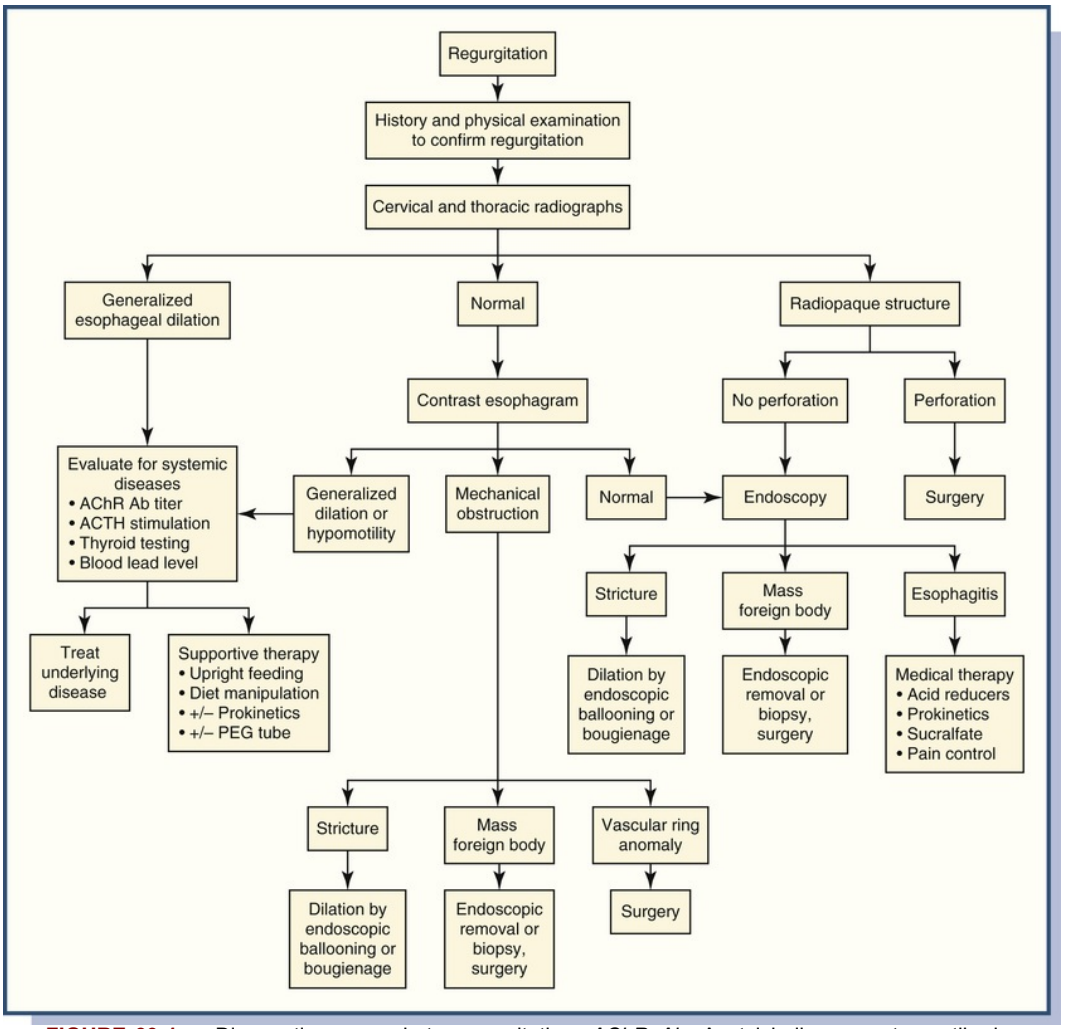

FIGURE 39-1 Diagnostic approach to regurgitation. *AChR Ab,* Acetylcholine receptor antibody; *ACTH,* adrenocorticotropic hormone; *PEG,* percutaneous endoscopic gastrostomy.

A minimum database including complete blood count, serum biochemistry profile, and urinalysis is warranted when systemic illness or megaesophagus is present. Adrenocorticotropic hormone (ACTH) stimulation, thyroid tests, acetylcholine receptor antibody test, and blood lead assay should be considered in cases with megaesophagus or esophageal hypomotility.

Treatment

Specific therapy should be used for any underlying disease as well as aspiration pneumonia if present. Management strategies to reduce frequency of regurgitation are used when primary disease is not identified or is unresponsive to therapy. Dietary management includes small, frequent meals and elevated feeding. Maintaining the patient in an upright position for 5-10 minutes after feeding may allow gravity to help esophageal transit. A Bailey chair can be used for this purpose. Owners should experiment with different food textures such as liquids, gruels, canned, or dry foods to determine which one works best for their pet. If gastroesophageal reflux disease is present, acid reducers and prokinetics may reduce the risk of esophagitis. Cisapride (cats) and bethanechol (dogs) may improve esophageal motility. Increasing the lower esophageal sphincter tone can exacerbate regurgitation in some cases.

Vomiting

Vomiting is one of the most common reasons dogs and cats are presented to a veterinarian for evaluation. It is an active expulsion of ingesta from the stomach and sometimes duodenum through the mouth. In contrast to regurgitation, vomiting involves a centrally mediated reflex with coordinated closure of the nasopharynx and glottis to protect the airway, reducing the risk of aspiration pneumonia. Like regurgitation, it must be

differentiated from expectoration.

Vomiting evolved as protection against the ingestion of toxic or noxious substances, which explains its activation by both neural and humoral stimuli. It is most often associated with primary gastrointestinal (GI) disorders, but may also occur due to non-GI diseases such as metabolic or neurological disorders. Severe or prolonged vomiting can have significant consequences including volume depletion (see ch. 127), acid-base and electrolyte derangements (see ch. 67-70 and 128), aspiration pneumonia (see ch. 242), and esophagitis (see ch. 273).

Pathophysiology

Vomiting is a complex reflex initiated by the emetic center, which is composed of a group of nuclei located in the medulla oblongata of the brainstem (Figure 39-2). Within this area are serotonergic ($5HT_1$) and adrenergic ($alpha_2$) receptors. In addition, neurokinergic (NK_1) receptors are located in the adjacent nucleus tractus solitarii, which can stimulate the emetic center. Activation of these receptors may occur indirectly by humoral pathways via the chemoreceptor trigger zone (CRTZ) or directly through neural pathways from the GI tract, cerebral cortex, or vestibular system.

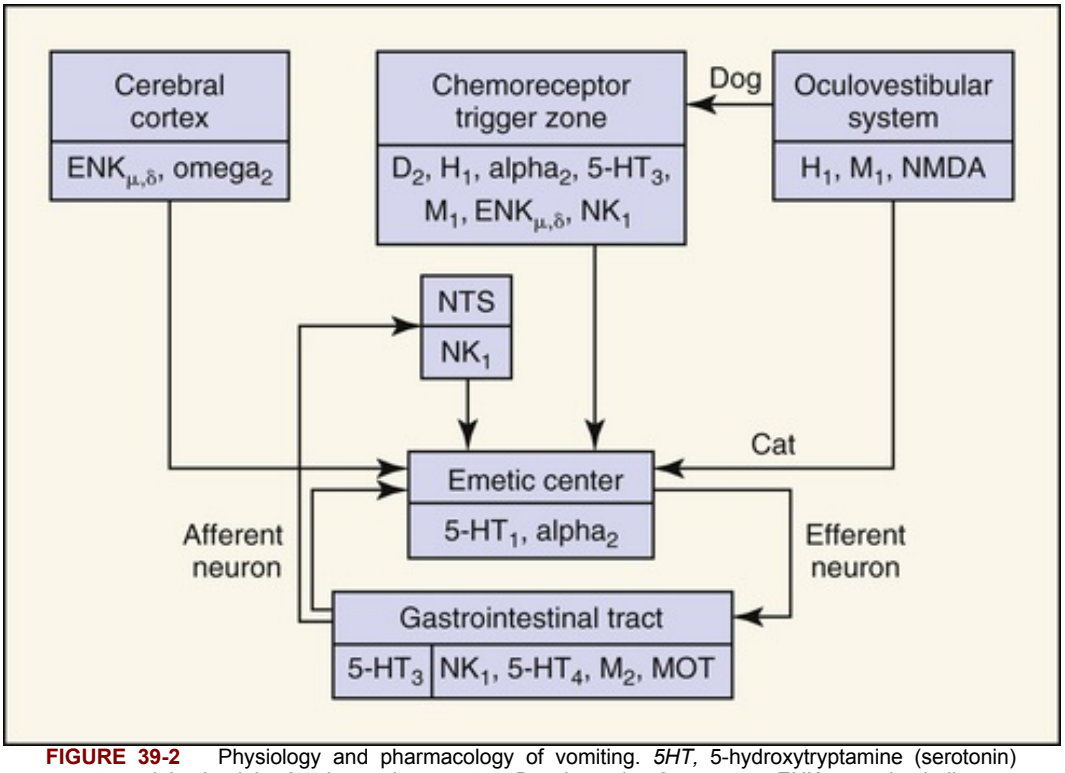

FIGURE 39-2 Physiology and pharmacology of vomiting. *5HT,* 5-hydroxytryptamine (serotonin) receptor; *alpha-2,* alpha-2 adrenergic receptor; *D_2,* dopamine-2 receptor; *$ENK_{\mu,\delta}$,* enkephalin mu, delta receptor; *gamma-2,* benzodiazepine gamma-2 receptor; *H_1,* histamine-1 receptor; *M,* muscarinic cholinergic receptor; *MOT,* motilin receptor; *NK_1,* neurokinin-1 receptor; *NMDA,* N-methyl d-aspartate; *NTS,* nucleus tractus solitarius. (From Washabau RJ, Day MJ: *Canine and feline gastroenterology,* St Louis, 2012, Elsevier, Figure 23-2, p 169.)

The CRTZ is located in the area postrema in the floor of the fourth ventricle and it lacks a blood-brain barrier, allowing it to sample chemical stimuli in the blood. Stimulants include endogenous (uremic or hepatoencephalopathic toxins) and exogenous substances (drugs, toxins). Dopaminergic (D_2), histaminergic (H_1), adrenergic ($alpha_2$), serotonergic ($5HT_3$), cholinergic (M_1), enkephalinergic ($ENK_{\mu,\delta}$), and neurokinergic (NK_1) receptors are present in the CRTZ, but there are species differences (see Figure 39-2). Apomorphine (D_1 and D_2 agonist) is a potent stimulator of emesis in dogs but it has little to no effect in cats, suggesting a lack of D_2 receptors in this species.[1] However, xylazine ($alpha_2$ agonist) is an effective emetic in cats, signifying that $alpha_2$ receptors may be more important.[2] Visceral rather than central $5HT_3$ receptors appear to be more

important in cisplatin-induced emesis in the dog.[3]

Neural stimulation of the emetic center occurs via afferent vagal, sympathetic, vestibular, and cerebrocortical pathways (see Figure 39-2). Gastrointestinal diseases can directly cause vomiting by stimulating release of serotonin from enterochromaffin cells that binds to $5HT_3$ receptors on afferent vagus nerves (dog) or the CRTZ (cat). Vestibular stimulation feeds into the CRTZ before activating the emetic center in the dog, but appears to act directly on the emetic center in the cat.

Clinical Approach

The initial approach starts with a thorough history. A description of the vomiting episodes is essential to differentiate them from coughing or regurgitation. The owner should be asked to describe the frequency, duration, relation to eating or drinking, and the character of the vomitus. Vomiting may be acute or chronic (>1-2 weeks in duration). In some cases, vomiting may be sporadic, making it difficult to determine if it is chronic versus intermittent acute disease. Vomiting food more than 8 hours after ingestion suggests delayed gastric emptying due to either gastric outflow obstruction or gastric hypomotility, while the presence of bile suggests patency of the gastric outflow tract. The presence of either fresh or digested blood ("coffee grounds") indicates GI erosions or ulcers.

A complete dietary history should be obtained, including past and current diets for planning possible diet trials (see ch. 178 and 191). Recent diet changes or opening a new bag or can of food may be the cause of vomiting. Medication history must include asking about drugs, supplements, nutraceuticals, and alternative therapies that could be associated with vomiting. The owner should also be questioned about the animal's possible exposure to toxins or foreign body ingestion. Vaccination status, travel history, and exposure to other animals are important for determining risk of infectious diseases, which are more common in young animals.

Physical examination should start with an overall assessment of patient demeanor (see ch. 2). Oral exam may reveal ulcers associated with uremia or toxin ingestion, or lingual linear foreign bodies (particularly in cats). Icteric mucous membranes suggest liver disease. Cardiac arrhythmias can indicate metabolic derangements or toxin ingestion. The abdomen should be palpated for evidence of pain (pancreatitis, obstruction), effusion (peritonitis), gas distension (obstruction, gastric dilation-volvulus), or organomegaly. Rectal exam may reveal evidence of melena, constipation, or material consistent with foreign body ingestion.

Diagnostic Approach

The diagnostic approach differs based on classification of the vomiting as acute or chronic (Figures 39-3 and 39-4). Acute vomiting with mild clinical signs is often self-resolving. As such, a minimalistic approach is usually appropriate. Fecal examination (see ch. 81) may identify parasitic causes of vomiting. Abdominal radiographs are performed if there is a clinical suspicion of surgical disease (e.g., suspected foreign body ingestion) or if vomiting does not resolve with initial therapy.

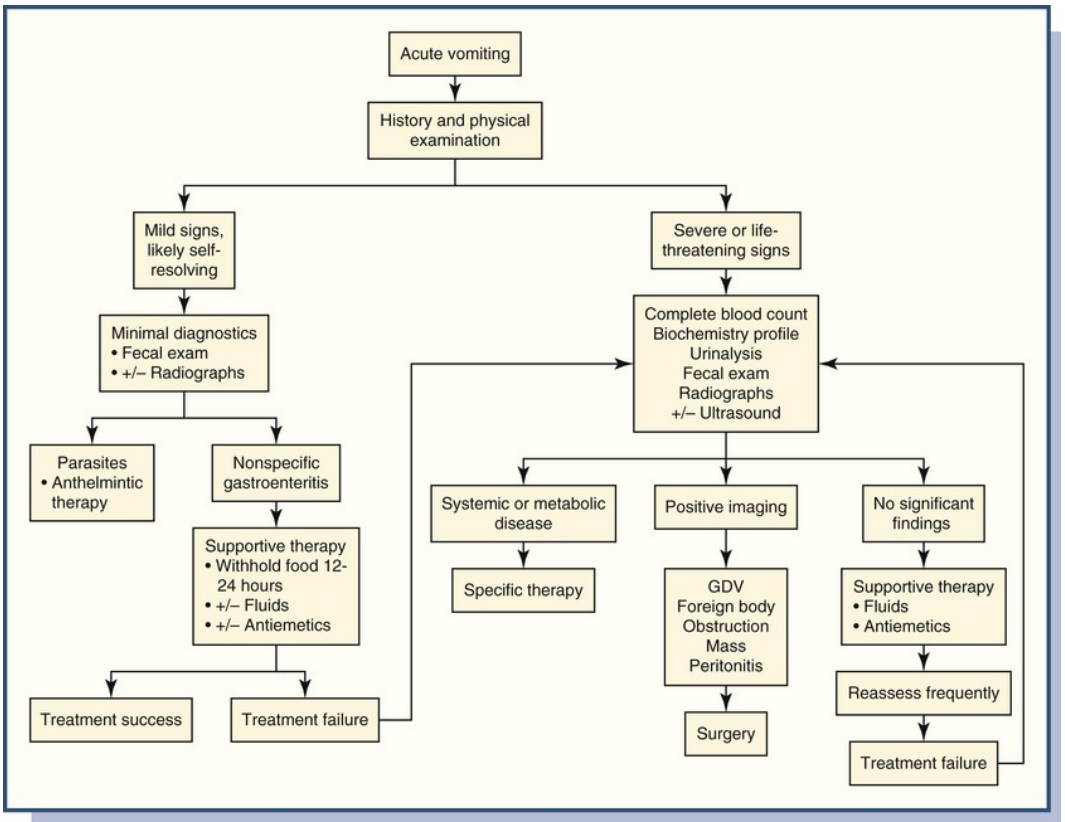

FIGURE 39-3 Algorithm for diagnosis of acute vomiting. *GDV,* Gastric dilation-volvulus.

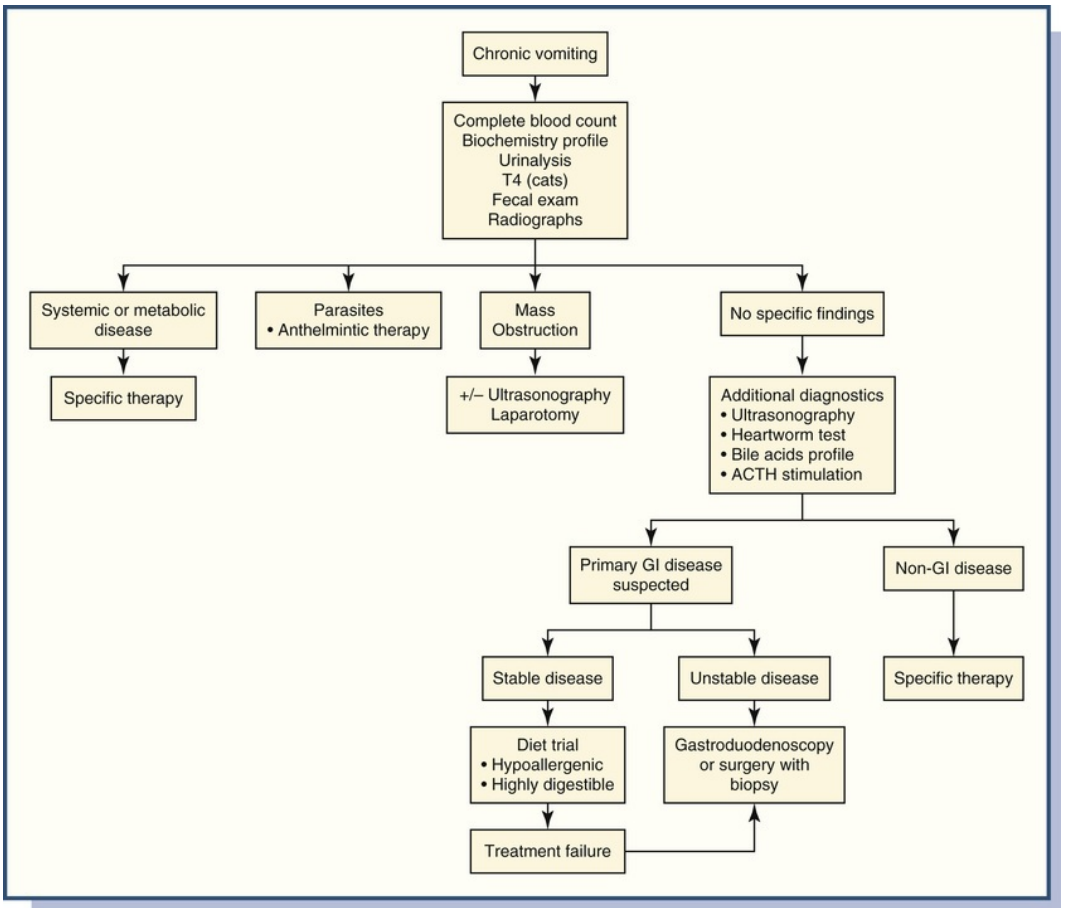

FIGURE 39-4 Algorithm for diagnosis of chronic vomiting. *ACTH*, Adrenocorticotropic hormone; *GI*, gastrointestinal; *T4*, serum thyroxine concentration.

Conversely, severe or life-threatening signs indicate a more thorough evaluation should be done. Complete blood count, serum biochemistry profile, and urinalysis allow identification of systemic or metabolic diseases. Metabolic alkalosis is suggestive of gastric outflow or proximal duodenal obstruction and is often associated with hyponatremia, hypokalemia, and hypochloremia. Abdominal radiographs +/− abdominal ultrasound are used for evaluating for surgical diseases such as foreign body, obstruction, gastric dilation-volvulus, or intussusception.

Chronic vomiting requires further investigation so definitive therapy can be prescribed. Complete blood count, serum biochemistry profile, and urinalysis should be performed. In addition, cats should be tested for feline leukemia and feline immunodeficiency viruses and those over 5 years of age should be evaluated for hyperthyroidism with a serum total T4 assay. If a cause is not found, additional diagnostic testing including ultrasonography, heartworm testing (cats), bile acids profile, pancreatic lipase testing, and ACTH stimulation testing should be considered. If a non-GI cause for the vomiting is not identified with such testing, further evaluation of the GI tract is needed. Contrast radiography may be helpful, particularly if ultrasonography is not available or the stomach is poorly visualized during ultrasonography due to intraluminal gas. Diet trials should be considered in stable animals to exclude diet-responsive disease prior to more invasive testing. Endoscopic or surgical biopsy is required to identify inflammatory disease such as chronic gastritis, *Helicobacter* gastritis, or inflammatory bowel disease (see ch. 113, 275, and 276).

Treatment

Initial treatment should be aimed at the primary disease, which often results in resolution of vomiting (Box 39-1). Acute, self-limiting vomiting usually resolves with fluid replacement and fasting for 12-24 hours. Acute cases with protracted or severe vomiting may benefit from antiemetic therapy (Table 39-2). Caution should be used, as antiemetics may mask underlying disease that has not yet been identified. Chronic cases are best treated by identifying the underlying cause. Antiemetic therapy can be considered for improving comfort and nutrition, and prevent excessive fluid losses.

Box 39-1

Common Causes of Vomiting

Metabolic Diseases

Renal disease
Hepatobiliary disease or failure
Electrolyte derangements
Acid-base derangements
Endotoxemia

Endocrine Diseases

Hypoadrenocorticism
Hyperthyroidism

Toxins/Drugs

Heavy metals
Ethylene glycol
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Antibiotics
Chemotherapy agents

Dietary Causes

Indiscretion
Allergy
Intolerance

Abdominal Diseases

Pancreatitis
Peritonitis
Neoplasia

Gastric Diseases

Gastritis
Parasites
Helicobacter
Foreign bodies
Obstruction
Gastric dilation-volvulus
Motility disorders
Neoplasia

Small Intestinal Diseases

Inflammatory bowel disease
Neoplasia
Obstruction
Parasites
Infections

Large Intestinal Diseases

Constipation
Colitis

TABLE 39-2

Common Antiemetics, Sites of Action, and Dosages

CLASSIFICATION	DRUGS	SITES OF ACTION	DOSAGES
Alpha$_2$ antagonists	Prochlorperazine	CRTZ, emetic center	0.1-0.5 mg/kg SC, IM q 6-8 h
	Chlorpromazine	CRTZ, emetic center	0.2-0.4 mg/kg SC q 8 h
D_2 antagonists	Metoclopramide	CRTZ, GI smooth muscle	0.2-0.4 mg/kg SC, IM q 8 h; 1-2 mg/kg/day CRI IV
	Domperidone	CRTZ, GI smooth muscle	0.1-0.3 mg/kg IM, IV q 12 h
	Prochlorperazine	CRTZ, emetic center	0.1-0.5 mg/kg SC, IM q 6-8 h
	Chlorpromazine	CRTZ, emetic center	0.2-0.4 mg/kg SC q 8 h
5HT$_3$ antagonists	Ondansetron	CRTZ, vagal afferents	0.5-1 mg/kg PO, IV q 12 h
	Dolasetron	CRTZ, vagal afferents	0.6-1 mg/kg PO, IV q 12-24 h
NK_1 antagonists	Maropitant	CRTZ, emetic center	1 mg/kg SC or IV q 24 h; 2 mg/kg PO q 24 h
$ENK_{\mu,\delta}$	Butorphanol	CRTZ	0.2-0.4 mg/kg IM, SC q 12 h
M_1 antagonists	Prochlorperazine	CRTZ, emetic center	0.1-0.5 mg/kg SC, IM q 6-8 h
	Chlorpromazine	CRTZ, emetic center	0.2-0.4 mg/kg SC q 8 h
H_1 antagonists	Diphenhydramine	CRTZ	2-4 mg/kg PO, IM q 8 h
	Prochlorperazine	CRTZ, emetic center	0.1-0.5 mg/kg SC, IM q 6-8 h
	Chlorpromazine	CRTZ, emetic center	0.2-0.4 mg/kg SC q 8 h

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CHAPTER 40

Diarrhea

Michael D. Willard

Client Information Sheet: Diarrhea

Diarrhea is caused by excess fecal water resulting from decreased intestinal absorption and/or increased intestinal secretion. Small intestinal disease causes diarrhea only if the material exiting the ileum exceeds the absorptive capacity of the colon or causes colonic secretion of water. Thus, while diarrhea means there is intestinal disease, lack of diarrhea does not eliminate substantive small intestinal disease. Many dogs and cats without diarrhea experience severe morbidity or die due to small intestinal disease. In contrast, large intestinal disease commonly causes diarrhea because there is nothing distal to it to absorb water. Patient activity also plays an important role in fecal consistency; active individuals are more likely to defecate more frequently than inactive ones (e.g., those confined to a cage or crate). Thus, a pet that has not had diarrhea while confined to a hospital cage may have diarrhea shortly after going home and resuming normal activity.

Routine Diagnostics

One must first decide if diarrhea is worth the cost or effort to diagnose or treat (Figure 40-1). Examples of diarrhea that should usually be attended to include diarrhea that (1) has a relatively small set of testable differentials, (2) is a predominant problem in the patient, or (3) is likely to cause morbidity or mortality. Diarrhea secondary to non-gastrointestinal (GI) disease is usually (but not invariably) relatively minor, and often there are historical, physical examination findings, laboratory, and/or imaging changes that are more pressing and/or more likely to quickly lead to a diagnosis. Examples of non-GI diseases causing diarrhea include acute pancreatitis, hepatic insufficiency, renal failure, and hypoadrenocorticism. Hyperthyroidism is an important non-GI cause of feline diarrhea.

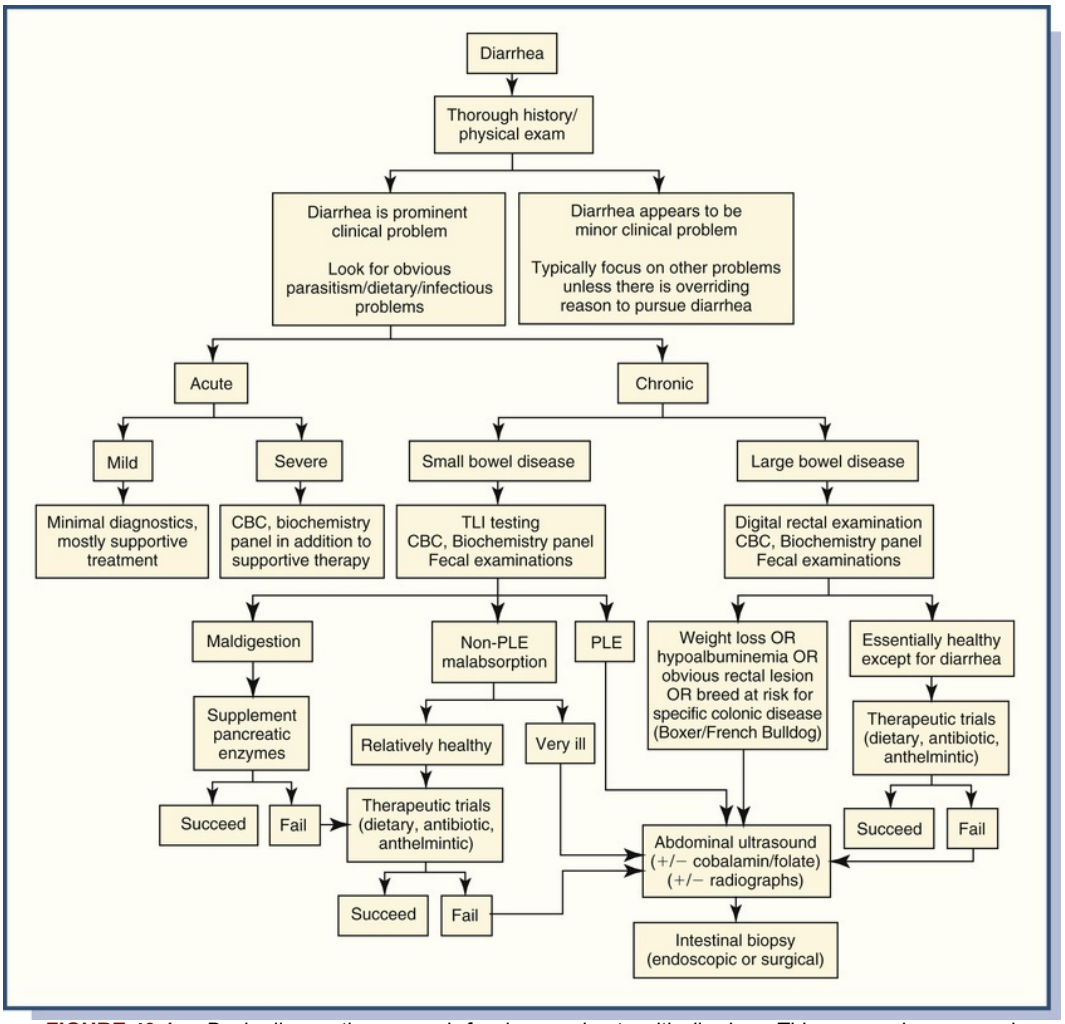

FIGURE 40-1 Basic diagnostic approach for dogs and cats with diarrhea. This approach may need to be modified, based upon specific situations. *CBC*, Complete blood count; *PLE*, protein-losing enteropathy; *TLI*, trypsinlike immunoreactivity.

The clinician should next look for and deal with "obvious" problems (e.g., substantial parasite burdens, poor-quality food, major dietary indiscretion, contagious disease) (ch. 170). Some parasites (e.g., giardiasis) can be difficult to diagnose. Next, one should determine whether diarrhea is acute or chronic. "Acute" means nonepisodic diarrhea occurring for less than 7 to 14 days. These dogs and cats may have diarrhea that is clinically nonthreatening or they may have severe diarrhea that places the patient at risk (e.g., hemorrhagic gastroenteritis; infectious, febrile gastroenteritis such as parvovirus). Most patients with acute, nonthreatening diarrhea spontaneously resolve with symptomatic/supportive therapy (e.g., anthelmintics, dietary change). Diagnostics in these patients are usually limited to fecal examinations and select laboratory tests (e.g., serum electrolytes, packed-cell volume [PCV]). Acute, severe diarrhea capable of causing morbidity/mortality is an indication for at least a complete blood count (CBC) and serum biochemistry panel.

Diarrhea not clearly improving within 14 days is considered chronic. Episodes of diarrhea that occur over 3-4 weeks may also be considered chronic. Chronic diarrhea should be subdivided into large or small bowel disease (ch. 276 and 277). Volume and frequency of bowel movements as well as vomiting are usually not helpful in making this distinction. Weight loss, hematochezia, and fecal mucus are more reliable criteria. Small intestines absorb nutrients; therefore, loss of body weight and/or condition are expected when it is chronically and substantially diseased. Steatorrhea is infrequent and melena distinctly rare in these patients. The large intestine absorbs water and acts as a reservoir for feces until defecation. Therefore, weight loss is unexpected in large bowel disease unless the disease is severe, in which case hematochezia and fecal mucus are typical. Hematochezia and fecal mucus are uncommon when colonic disease is mild to moderate. Tenesmus may occur if the rectal area is affected.

The next decision in patients with chronic small intestinal disease is whether maldigestion (e.g., exocrine pancreatic insufficiency [EPI]) or malabsorption exists. Uncommon in cats, EPI is an important consideration

in dogs (ch. 292). Serum trypsin–like immunoreactivity (TLI) is the most sensitive and specific test for EPI. Once EPI is eliminated, malabsorptive disease is diagnosed by exclusion.

Malabsorptive disease is divided into protein-losing enteropathy (PLE) and non-PLE. This distinction is important because severe hypoalbuminemia is associated with a poor prognosis more often than non-PLE: hence, PLE is usually an indication for a more aggressive diagnostic approach. Protein-losing enteropathy is typically only considered in hypoalbuminemic patients, but PLE is a concern whenever serum albumin concentrations progressively decrease. One must measure serum albumin (serum total protein is inadequate) and one should use the same laboratory for repeat samples so that one can meaningfully compare results. Panhypoproteinemia is neither sensitive nor specific for PLE, especially in areas where hyperglobulinemia is common. Serum albumin concentrations <2.0 g/dL are an indication for hepatic function testing and urinalysis. Eliminating hepatic insufficiency and protein-losing nephropathy in an individual without severe cutaneous disease (severe burns and secondary ulcerations, for example, can cause loss of protein) is consistent with a diagnosis of PLE by exclusion. Fecal alpha-1 protease inhibitor concentrations can be helpful when PLE is suspected but cannot be diagnosed by exclusion; however, there are nuances in performing/interpreting this test. Most PLE and hepatic insufficiency patients are hypocholesterolemic while many protein-losing nephropathy patients are hypercholesterolemic. Imaging, endoscopy, and biopsy are usually desirable in PLE patients, but therapeutic trials (e.g., ultra-low-fat diet for lymphangiectasia) are done if anesthetic risk is too great or client constraints dictate otherwise.

Any GI disease may cause PLE, but the most common causes in adult dogs are probably lymphangiectasia, lymphoma, fungal infections (regional), and inflammatory bowel disease (IBD) (see ch. 276). Lymphangiectasia can be difficult to diagnose unless one is aware of its subtleties. Occult parasitism and chronic intussusception are important in younger dogs. In cats, IBD and lymphoma are the main causes. Other causes include ulcers/erosions, antibiotic-responsive disease, and intestinal crypt lesions.

The major causes of non-PLE malabsorptive disease in dogs are dietary-responsive disease, antibiotic-responsive disease, and parasites (ch. 271, 276, and 277). IBD is often listed as an important cause. A full discussion is beyond the scope of this chapter, but IBD has been overdiagnosed in the past because IBD is not simply a histologic diagnosis. One must find inflammation and eliminate known causes (e.g., diet, parasites, bacteria). In cats, dietary-responsive disease, lymphoma, and IBD appear to be the most common causes, but hyperthyroidism closely mimics primary GI disease.

Advanced Diagnostics

The next step depends upon the patient's clinical condition. If a dog or cat is in relatively good health and not at major risk if a 2- to 3-week therapeutic trial fails, then one may elect to first treat for dietary-responsive, antibiotic-responsive, and/or parasitic disease. The first two diseases generally do not produce pathognomonic histologic lesions. If one cannot take a chance on investing 2 to 3 weeks in a therapeutic trial because of the advanced nature or rapid progression of disease, then aggressive diagnostics are reasonable. Abdominal ultrasound helps detect focal GI lesions that may be aspirated percutaneously (e.g., lymphoma, fungal infection) and may reveal whether GI disease is clearly diffuse or localized outside the reach of an endoscope. Ultrasound is specific but insensitive for GI lesions; absence of ultrasonographic changes does not eliminate serious GI disease.

Intestinal biopsy (surgical or endoscopic) is typically the next step after ultrasound. Faster, safer, and less expensive than surgery, endoscopy often allows one to find and biopsy focal mucosal lesions that cannot be seen from the serosal surface at surgery (see ch. 83 and 113). This ability to direct biopsies to affected areas of the intestinal mucosa enhances the chance to make a histologic diagnosis. Endoscopic biopsies of the ileum can be very important; some diseases (e.g., lymphoma, IBD, lymphangiectasia) may be diagnosed there when they cannot be diagnosed with duodenal samples (even when ultrasonography does not show any obvious difference between the two sites). Endoscopy is typically more than adequate to obtain diagnostic samples if the operator is skilled in taking and submitting biopsies. Endoscopic biopsies should routinely include the full thickness of the intestinal mucosa (with or without muscularis mucosa). If one is not trained in taking high-quality endoscopic samples, it may be better to perform surgical biopsies or refer the patient for endoscopy. Full-thickness intestinal biopsies will not help if they are taken where there is no lesion, a problem encountered if the intestinal disease (including severe intestinal disease) is patchy rather than diffuse. Diseased intestine outside the reach of the endoscope and intestines with dense submucosal infiltrates are indications for surgical biopsy. It is infrequent that diagnosis requires adequate submucosal tissue in small intestinal diseases. Remember, histology is not a good way to diagnose dietary-responsive or antibiotic-responsive enteropathies.

Chronic canine large bowel disease tends to be dietary-responsive, fiber-responsive, so called "clostridial" colitis (i.e., tylosin-responsive), and parasitic. Histoplasmosis, pythiosis and heterobilharziasis are regionally important. Cats tend to have dietary-responsive, clostridial, parasitic (e.g., *Tritrichomonas*), and IBD colitis. Digital rectal examination should be performed in dogs to assess for focal lesions (e.g., polyps) or mucosal thickening. Dogs from endemic areas should generally be treated for whipworms even if fecal examinations do not reveal ova. Giardiasis is a small bowel problem, but clinical signs sometimes mimic large bowel disease. Dogs and cats that are otherwise normal except for diarrhea, have no rectal lesions, and have normal serum albumin concentrations may often be successfully approached with therapeutic trials because: (1) the best way to diagnose dietary-responsive disease, fiber-responsive disease, and tylosin-responsive disease is by therapeutic trial; and (2) these animals are unlikely to worsen rapidly should the trial fail. Patients from areas endemic for histoplasmosis or schistosomiasis and those losing weight or becoming hypoalbuminemic should undergo testing (i.e., abdominal ultrasound, rectal scraping, colonoscopy/biopsy, antigen testing) because of their potential to suddenly become worse. Rectal scraping/cytology is an easy, quick, and specific (albeit insensitive) screening test for colonic histoplasmosis. Urinary antigen testing for histoplasmosis seems reasonably sensitive (see ch. 233). There is also a fecal polymerase chain reaction (PCR) test for *Heterobilharzia*. Colonic biopsy should be done endoscopically; full-thickness colonic incisions have substantial risk of dehiscence and peritonitis. Rigid biopsy forceps typically allow one to obtain large tissue samples with lots of submucosa (especially important in rectal lesions). It is recommended that Boxer dogs and French Bulldogs be biopsied earlier in the course of the workup than other breeds because of their predilection for histiocytic ulcerative colitis.

Abdominal radiographs do not commonly yield valuable information unless they detect an unsuspected radiopaque foreign body. Fecal cultures tend to be a low-yield procedure unless the history strongly suggests contagion. Simply finding "pathogenic" bacteria does not mean that they are responsible for clinical signs. It is critical to contact the laboratory for instructions on collection and submission relative to the specific pathogen(s) being sought. PCR analysis of feces for bacterial antigens can be difficult to interpret, just like fecal cultures.

Measuring serum cobalamin and folate concentrations can be helpful in select dogs and cats (ch. 276). Hypocobalaminemia is relatively specific for small intestinal disease in the dog; however, sensitivity is questionable. Cobalamin and folate determinations are insensitive and nonspecific for canine antibiotic-responsive disease (also called "dysbiosis"). Hypocobalaminemia in an animal with weight loss, but without diarrhea, is strong evidence of small intestinal disease; however, normal values are not helpful. Cobalamin supplementation often clinically benefits hypocobalaminemic cats, and hypocobalaminemia may be prognostic in dogs.

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CHAPTER 41

Melena and Hematochezia

Karen M. Tefft

Client Information Sheet: Melena and Hematochezia

Witnessing blood in the stool of their pets is distressing for many owners and can prompt an urgent visit to the veterinarian's office. The presence of blood in the stool may or may not indicate a life-threatening disorder, however. In addition, the source of the blood may not be gastrointestinal (GI) in origin. The veterinarian must localize the source and seriousness of the hemorrhage by careful evaluation of history, physical examination, and diagnostic test findings.

Melena

Definition

Melena refers to the passage of dark-colored to black, tarry stools due to the presence of hematin, which is oxidized hemoglobin (Figure 41-1). While classically this is thought to be due to hemorrhage originating from the small intestine or orad, the amount of time blood spends in the intestinal tract is more important than the site of bleeding. Colonic hemorrhage may present with melena if intestinal motility is decreased.

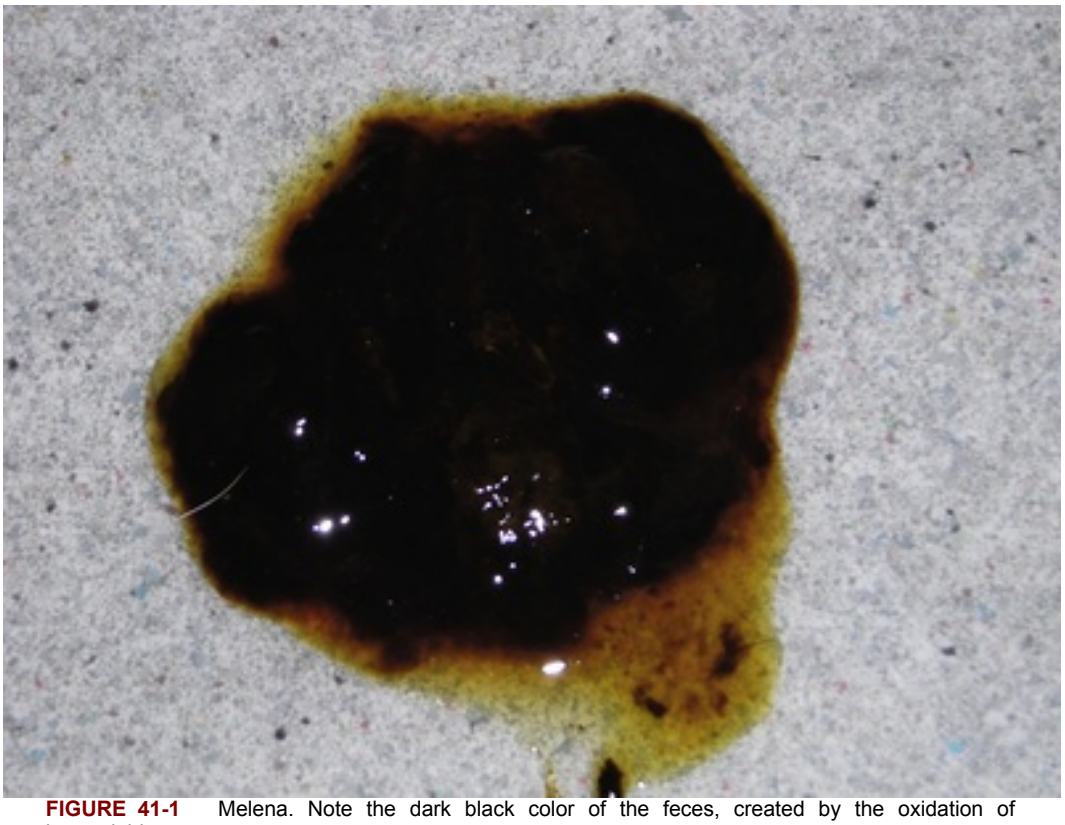

FIGURE 41-1 Melena. Note the dark black color of the feces, created by the oxidation of hemoglobin.

Causes

Sites of hemorrhage to consider in patients with melena include both the upper and lower respiratory tract, where blood from epistaxis or hemoptysis can be swallowed, and the GI tract, including the oral cavity, esophagus, stomach, and small intestine. Rarely, the cecum and colon can also be considered as a source for melena. Melena also can result from blood ingested as part of a raw diet. The absence of melena does not rule out GI bleeding. In humans, it has been experimentally determined that at least 50 to 100 mL of blood must be ingested before melenic stool is appreciated.[1-3] Important mimics of melena that can cause black stool include ingestion of activated charcoal, iron supplements, anti-diarrheal medications containing bismuth, or large quantities of blueberries.

Many diseases have the potential to cause melena (Box 41-1). The majority of these conditions result in GI hemorrhage by directly or indirectly disrupting mucosal barriers to injury.[4] Defense mechanisms utilized by the GI mucosa include an adherent mucus layer, hydrophobic nature of epithelial cells, epithelial secretion of bicarbonate, rapid repair of the epithelial layer by restitution, a high rate of mucosal blood flow, and prostaglandins (see ch. 274-277).

Box 41-1

Causes of Melena

- Ingestion of blood
  - Sinonasal lesions
  - Pulmonary lesions
  - Oral/Pharyngeal lesions
  - Diet
- Inflammatory
  - Esophagitis
  - Gastroenteritis
  - Eosinophilic gastritis
  - Inflammatory bowel disease
- Infectious
  - Bacterial: *Campylobacter, Clostridium, Mycobacterium, Neorickettsia helminthoeca, Salmonella*
  - Fungal/Algal: *Cryptococcus, Histoplasma, Pythium, Prototheca*
  - Parasitic: *Spirocerca, Physaloptera, Ancylostoma, Uncinaria*
  - Viral: parvovirus
- Ischemic/traumatic
  - Hypovolemic shock
  - Thrombosis/infarction
  - Intussusception
  - Volvulus
  - Foreign body
  - Racing sled dogs
- Post-surgical
  - Enterotomy
  - Gastric invagination post-correction of gastric dilation/volvulus
  - Percutaneous endoscopic gastrostomy tube placement
- Drug-induced
  - Corticosteroids
  - Non-steroidal anti-inflammatory drugs
- Neoplastic
  - Adenocarcinoma
  - Gastrointestinal stromal tumor
  - Leiomyoma/leiomyosarcoma
  - Lymphoma
  - Mast cell tumor

Gastrinoma
Vascular
Vascular ectasia/angiodysplasia
Arteriovenous fistula
Metabolic
Hypoadrenocorticism
Uremic kidney disease
Liver disease, particularly with portal hypertension or portosystemic shunt(s)
Pancreatitis
Hypereosinophilic syndrome
Bleeding disorder
Thrombocytopenia
Thrombocytopathia
Disseminated intravascular coagulation
Rodenticide intoxication
Specific factor deficiencies

Clinical Evaluation

History

A careful assessment of the history is the first step in the evaluation of a patient presenting with melena. The clinician should not ask leading questions about the patient's stool color, but instead let the owner use his or her own descriptors. Ideally, the owner can be shown a set of swatches from which to select which color best represents their pet's fecal color, as inconsistencies have been shown in subjective color reporting as compared to selecting a color off a scorecard.[5] The owner should be asked specific questions concerning diet, drug administration, and potential exposure to toxins; the veterinarian uses this information to determine immediately if the owner had administered a bismuth-containing medication or any other compound that can cause black stool. Determining the patient's diet, and specifically whether the animal eats a raw meat diet, or receives liver, spleen, or bones in the food, directly addresses this category of causes of melena.

After ruling out causes of black stool other than respiratory or digestive tract hemorrhage, the focus of the history collection can shift towards these pathologic causes. Clinical signs other than melena, notably exercise intolerance, stridor, coughing or dyspnea, raise the suspicion of respiratory tract disease. Anorexia, regurgitation, vomiting or diarrhea raise suspicion of GI tract disease. The owners should be asked about other instances of observed bleeding; epistaxis or hemoptysis can indicate primary respiratory tract disease and hematemesis can indicate primary GI tract disease. However, the clinician should remain mindful that a systemic bleeding disorder might alternatively be the cause, particularly if hematuria or ecchymosis is reported.

It is important to question the owners specifically about administration of corticosteroids and non-steroidal anti-inflammatory drugs. Both of these classes of drugs reduce the production of protective prostaglandins, leading to gastric mucosal injury. The history should address whether the patient had any opportunity to ingest anticoagulant rodenticides, corrosive compounds or foreign objects. The patient's travel history can suggest the possibility of specific infectious diseases.

Physical Examination

While particular attention should be paid to the respiratory and digestive systems, a thorough physical examination is necessary in the patient with melena (see ch. 2). Inspection of the skin, mucous membranes, and sclera can reveal petechiae or ecchymoses, which can indicate a bleeding disorder or icterus to suggest hepatobiliary disease. A fundic examination (see ch. 11) is important to identify retinal hemorrhages, which can indicate a bleeding disorder, hyperviscosity, or systemic hypertension. Examination of the skin, mucocutaneous junctions, and nail beds can reveal masses, which may indicate mast cell disease. A thorough examination of the nares and oral cavity is warranted, for active hemorrhage or lesions with the potential to bleed. Patients with moderate to severe blood loss can display mucous membrane pallor. Careful auscultation of the lung fields can reveal abnormal sounds supporting the presence of pulmonary disease. Thorough palpation of the abdomen can allow the veterinarian to identify signs of pain, organomegaly, or masses. A digital rectal exam must be included to confirm the presence of melena, to obtain a stool sample for fecal testing, and to assess for mucosal abnormalities and sublumbar lymph node enlargement.

Diagnostic Evaluation

After confirming the presence of melena, the clinician then should move to diagnostic testing to provide objective support for abnormalities detected on physical examination and to begin ruling in and out differential diagnoses (Figure 41-2). The initial diagnostic work-up at a minimum includes a complete blood count (CBC), serum biochemistry panel, urinalysis, prothrombin time, activated partial thromboplastin time, and fecal flotation. Anemia is the most common finding on the CBC of a patient with melena. The anemia can be mild to severe, and a regenerative response may be evident if sufficient time has elapsed since blood loss began and suitable regenerative capacity exists. Chronic, low-grade hemorrhage can result in iron deficiency that ultimately can cause a microcytic, hypochromic, non-regenerative anemia. Thrombocytopenia, if moderate to severe, can be the primary cause of melena. Mild thrombocytopenia likely is a secondary finding resulting from consumption of platelets at the site of acute hemorrhage. Thrombocytosis can be seen with chronic GI hemorrhage. Leukocytes may be decreased in number, within normal range, or increased based on the underlying disease, and a left shift may or may not be present. Eosinophilia can be caused by a variety of diseases that can result in GI hemorrhage, such as parasitism, systemic mycosis, mast cell tumor, eosinophilic gastritis, or hypereosinophilic syndrome. Common abnormalities on the serum biochemistry profile include disproportionately elevated blood urea nitrogen concentration compared to creatinine concentration, and hypoproteinemia. Elevated hepatic enzyme activities or azotemia should raise suspicions for liver or renal disease, respectively. Hyponatremia in conjunction with hyperkalemia should raise suspicion for hypoadrenocorticism, although salmonellosis and whipworm infections can occasionally cause pseudohypoadrenocorticism. A urinalysis is performed for evaluation of concurrent disease, including differentiating causes of azotemia. Prolonged coagulation times will aid in diagnosing cases of rodenticide intoxication or disseminated intravascular coagulation. A fecal flotation can identify parasite ova.

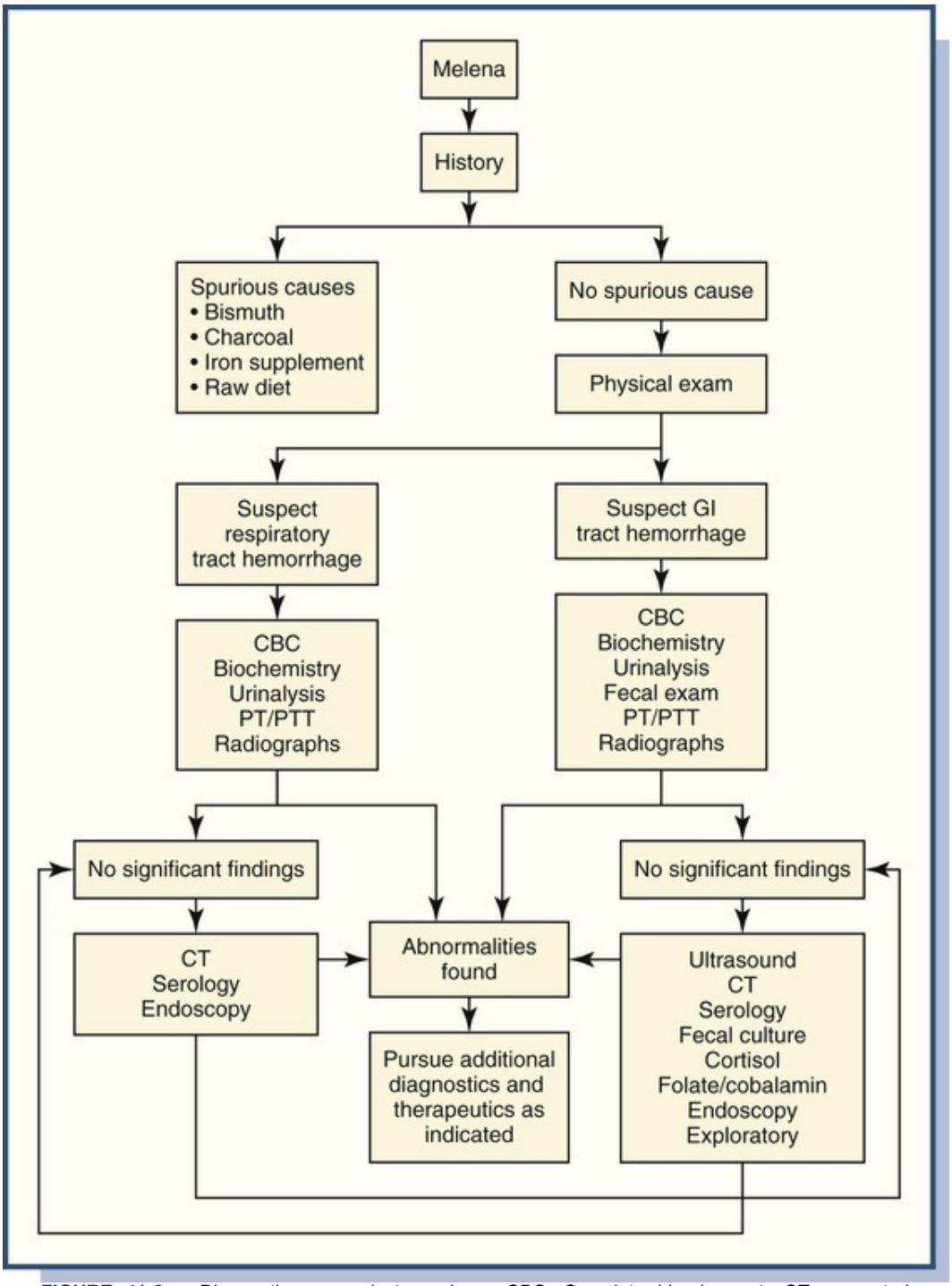

FIGURE 41-2 Diagnostic approach to melena. *CBC,* Complete blood count; *CT,* computed tomography; *PT/PTT,* prothrombin time/partial thromboplastin time.

The next phase of diagnostic testing, which can be performed concurrently with the previously described tests or subsequently, dependent on the owner's finances, includes fecal analysis and imaging. A fecal direct saline preparation and stained cytologic smear can assess for a variety of parasites, enterotoxigenic bacteria, and other organisms. Radiographic imaging of the thorax and abdomen can help further differentiate between respiratory and GI sources of melena. Clearly definable lung patterns likely will be present in cases with hemoptysis. Thoracic radiographs also are useful to screen for metastatic disease if a mass has been palpated in the abdomen. Abdominal radiographic abnormalities can include radiopaque foreign bodies, abnormal size or shape of abdominal organs, mass effects, and abnormal gas and fluid patterns in the GI tract. Abdominal ultrasound is complementary to radiography and can further evaluate for foreign bodies,

abnormal organ architecture, masses, lymphadenopathy, or intussusception.

Definitive diagnosis of the underlying cause of melena often requires advanced diagnostic techniques, which may include specific serologic testing, fecal cultures, computed tomography, rhinoscopy (see ch. 238 and 240), bronchoscopy (see ch. 101), GI endoscopy (see ch. 113), and exploratory laparotomy.

Treatment

Specific treatment for patients presenting with melena will vary dependent on the underlying cause. However, given that GI ulceration is the underlying etiology in most cases of melena, it is reasonable to start therapy that addresses ulceration while a definitive diagnosis is pursued. Pharmaceuticals used in the treatment of GI ulceration work by decreasing intraluminal acidity and promoting mucosal defense mechanisms. Proton-pump inhibitors, synthetic prostaglandin analogues, and sucralfate are commonly used in combination to treat GI ulceration (see ch. 275).

Hematochezia

Definition

Hematochezia refers to the passage of bright-red colored stools due to the presence of hemoglobin (Figure 41-3). While classically this is thought to be due to hemorrhage originating from the colon, the length of time blood spends in the intestinal tract is more important than the site of bleeding. Small intestinal hemorrhage may present with hematochezia if intestinal motility is increased.

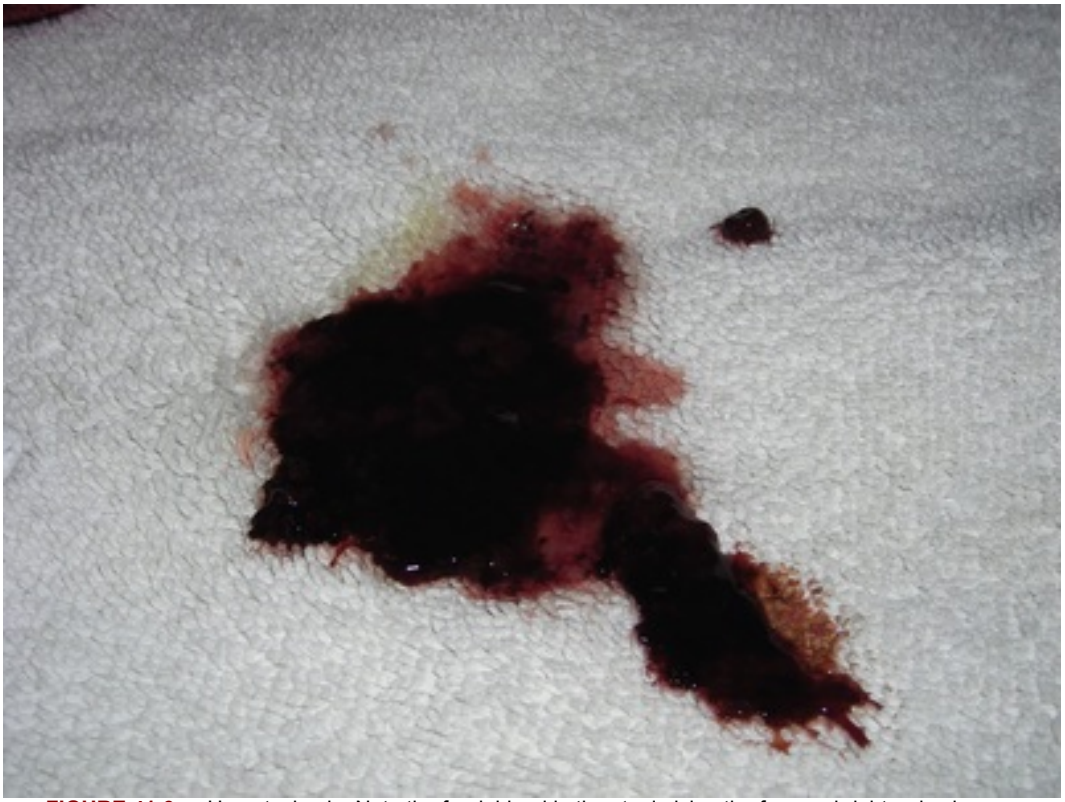

FIGURE 41-3 Hematochezia. Note the frank blood in the stool giving the feces a bright red color.

Causes

Some overlap exists between potential causes of melena and hematochezia; however, sites of hemorrhage to typically consider as causes of hematochezia include the cecum, colon, rectum, and anus. Mimics of hematochezia that can cause red stool include ingestion of foods or treats containing red food coloring or large amounts of beets. In addition, owners sometimes mistake bleeding from a perineal bite wound or anal

sac abscess as hematochezia. Many diseases have the potential to cause hematochezia (Box 41-2).

Box 41-2

Causes of Hematochezia

- Unclassified
  - Hemorrhagic gastroenteritis
- Inflammatory
  - Inflammatory bowel disease
  - Histiocytic ulcerative colitis
  - Idiopathic colitis
  - Perianal fistula
  - Mucocutaneous lupus erythematosus
- Infectious
  - Bacterial: *Campylobacter, Clostridium, Mycobacterium, Salmonella*
  - Fungal/Algal: *Cryptococcus, Histoplasma, Pythium, Prototheca*
  - Parasitic: *Ancylostoma, Uncinaria, Trichuris,* coccidia, *Tritrichomonas, Leishmania, Heterobilharzia americana, Entamoeba histolytica*
  - Viral: parvovirus
- Ischemic/traumatic
  - Hypovolemic shock
  - Thrombosis/infarction
  - Intussusception
  - Cecal inversion
  - Volvulus
  - Foreign body
  - Pelvic fracture
  - Rectoanal stricture
  - Racing sled dogs
- Drug-induced
  - Corticosteroids
  - Non-steroidal anti-inflammatory drugs
  - Cytotoxic chemotherapy drugs
- Neoplastic
  - Adenocarcinoma
  - Gastrointestinal stromal tumor
  - Leiomyoma/leiomyosarcoma
  - Lymphoma
  - Plasmacytoma
  - Colorectal polyp
- Vascular
  - Vascular ectasia/angiodysplasia
  - Arteriovenous fistula
- Metabolic
  - Hypoadrenocorticism
  - Uremic kidney disease
  - Liver disease, particularly with portal hypertension or portosystemic shunt(s)
  - Pancreatitis
- Bleeding disorder
  - Thrombocytopenia
  - Thrombocytopathia
  - Disseminated intravascular coagulation
  - Rodenticide intoxication
  - Specific factor deficiencies

Clinical Evaluation

History

The majority of questions for the owner of a patient with melena also apply for hematochezia, with the exception of questions pertaining to the respiratory tract. Additional questions specific to the lower GI tract include inquiring about the patient's bowel habits; i.e., is dyschezia, tenesmus, "scooting," or frequent attempts at defecation producing only small amounts of stool or mucus, present? It is useful to ask if the feces are entirely red or maroon-colored, suggesting a proximal colonic lesion or if they are otherwise normal in color with frank blood only on the surface, suggesting an anorectal lesion. Asking the owner if the patient may have experienced recent stress or an abrupt dietary change or indiscretion is useful, as these are frequent triggers for self-limiting colitis.

Physical Examination

While particular attention should be paid to abdominal and rectal palpation, a thorough physical examination is still necessary in the patient with hematochezia as described for the patient with melena. Thorough palpation of the abdomen is necessary for identifying signs of pain, organomegaly, or masses. A digital rectal exam must be included to confirm the presence of hematochezia, obtain a stool sample for fecal testing, and for assessment of mucosal abnormalities such as masses or strictures, sublumbar lymph node enlargement, pelvic fracture, or other perianal abnormalities such as fistulas or ulceration. The anal sacs should be palpated for the presence of nodules or cellulitis, and expressed for evaluation of their contents. The clinician should be cautious in performing rectal palpation as the underlying disorder may make it painful for the patient.

Diagnostic Evaluation

In a patient presenting with simple, acute hematochezia characterized by blood streaking on the surface of the feces and no other clinical signs or physical examination abnormalities, a fecal flotation and direct saline preparation are the only diagnostic tests initially indicated. Patients with severe hematochezia (i.e., feces that looks like "raspberry jam"), chronic hematochezia, and/or other clinical signs should have a diagnostic work-up as described for patients with melena.

Treatment

Specific treatment for patients presenting with hematochezia will vary dependent on the underlying cause. In a patient presenting with simple, acute hematochezia as described above, empiric treatment with a broad-spectrum anthelmintic, metronidazole, and a bland diet containing soluble fiber is often successful (see ch. 277 and 278).

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CHAPTER 42

Constipation, Tenesmus, Dyschezia, and Fecal Incontinence

Peter Foley

Client Information Sheet: Constipation and Straining to Defecate

Definitions

Constipation is defined as infrequent or difficult evacuation of dry, hard feces. *Obstipation* is a severe form of constipation where the feces are so dry and hard, or the constipation is so longstanding, that the animal is no longer able to defecate. Obstipation requires medical intervention. *Tenesmus* is ineffectual and painful straining at defecation or urination. *Dyschezia* is difficult or painful evacuation of feces from the rectum. In contrast to tenesmus, dyschezia is a result of disease of the anal and perianal tissues, whereas tenesmus is a result of disease of the large intestine or lower urinary tract. *Fecal incontinence* is defined as defecation without conscious control.

Physiology of the Large Intestine

The large intestine or colon serves two main functions in the dog and cat: absorption of water and electrolytes, and storage of feces. Absorption of water and electrolytes occurs primarily in the ascending and transverse colon, whereas the descending colon is mostly the site of storage of feces.

At rest, considerable mixing of colonic contents occurs as a result of segmental contractions of the colon. These *haustral contractions* are coordinated contractions of the circular and longitudinal smooth muscle of the colon that result in accumulation of colonic contents in unstimulated segments. This mixing of colonic contents increases exposure of contents to colonic mucosa for maximum water and electrolyte absorption, while slowly propelling the ingesta down the length of the colon.

In addition to haustral contractions, there are periods of intense propulsive activity down the entire length of the colon. These are called *mass movements,* and they serve to propel fecal matter toward the anus in preparation for defecation. Mass movements occur only a few times daily in contrast to the continuous haustral contractions. Mass movements are most common following a meal and are stimulated by the autonomic nervous system. See also ch. 277.

The anal sphincter is composed of two layers: an internal anal sphincter composed of smooth muscle, which is a direct extension of the circular smooth muscle of the rectum, and an external anal sphincter composed of striated muscle. The internal anal sphincter remains contracted most of the time and is the layer most responsible for fecal continence. The internal sphincter receives its parasympathetic nervous supply from the sacral spinal cord segments via the pelvic nerves. Its sympathetic innervation is from the lumbar spinal cord segments via the hypogastric nerves. Sympathetic stimulation results in contraction of the internal anal sphincter, whereas parasympathetic stimulation results in its relaxation. The external anal sphincter is under conscious control and allows the animal to resist and prevent defecation from occurring, but it is important to remember that it is the internal anal sphincter's continuous tone that is most responsible for anal continence. The external anal sphincter is innervated by somatic efferent nerve fibers originating in the cranial sacral spinal cord segments and coursing through the pudendal nerves. See also ch. 278.

As mass movements propel feces into the rectum, the internal anal sphincter is stimulated to relax. This usually results in defecation. The animal assumes a defecation posture, the diaphragm and abdominal muscles contract to increase the intraabdominal pressure, and the external anal sphincter relaxes. The animal has the ability to override the mass movements and relaxation of the internal anal sphincter by maintaining conscious constriction of the external anal sphincter. When defecation is voluntarily prevented, the mass

movements of the colon dissipate after 10 to 30 minutes, the rectum relaxes to accommodate the fecal material, the internal anal sphincter regains its tone, and the urge to defecate dissipates.

Constipation

There are several different disease states that can cause the feces to become dry, hard, and difficult to evacuate (Figure 42-1).

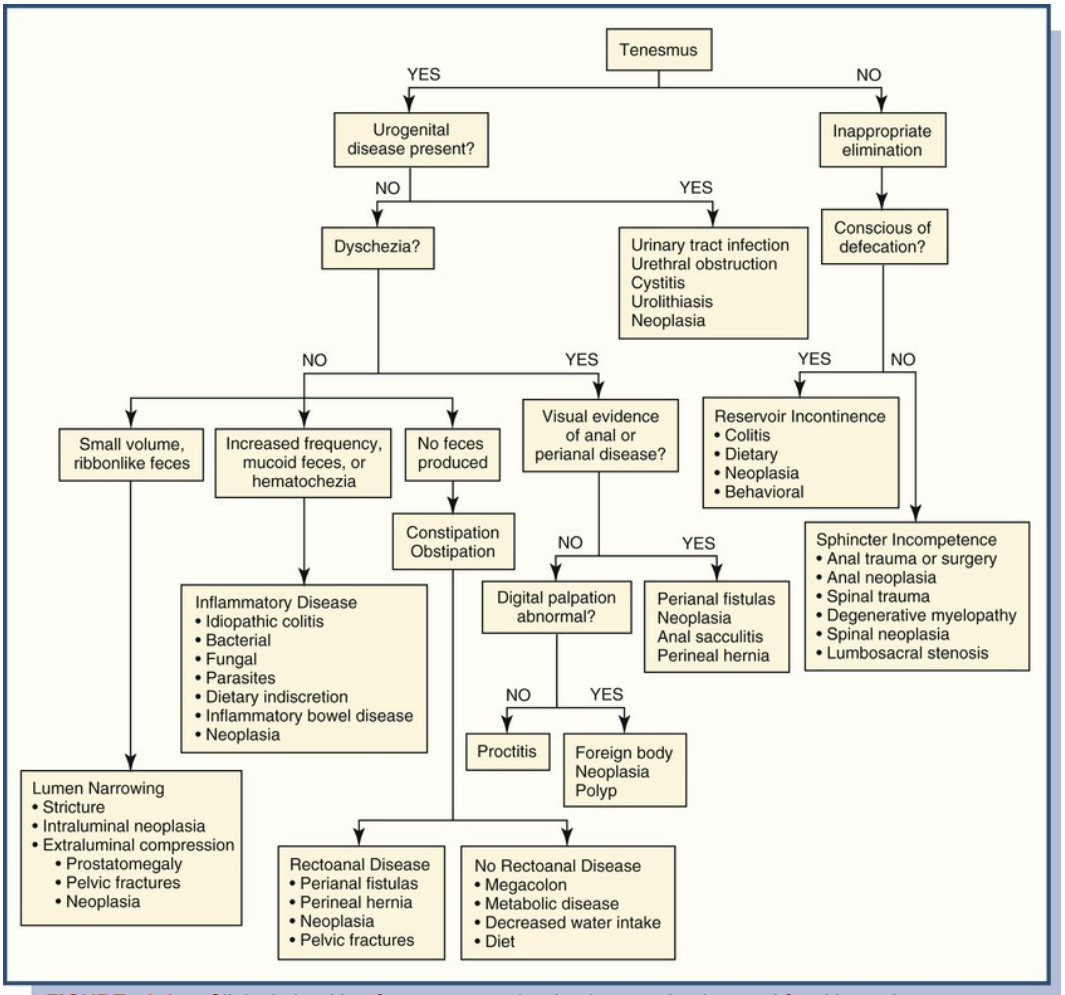

FIGURE 42-1 Clinical algorithm for tenesmus, dyschezia, constipation, and fecal incontinence.

Diets low in fiber or high in indigestible material such as hair or bones can contribute to constipation. Lack of exercise, and weakness, also can be contributing factors to constipation. Good hydration status is essential for normal defecation. Animals who have had restricted access to water or who otherwise experience decreased water intake (e.g., anorexia) commonly experience constipation. Similarly, increased water loss due to polyuria or vomiting also can lead to constipation if there is insufficient water intake to replace lost body water. Colonic or rectal obstruction, either intraluminal (masses or foreign bodies) or extraluminal (mass compressing the colon, pelvic fractures, perineal hernia, pseudocoprostasis [external obstruction from feces-matted hair, preventing defecation]), likewise can inhibit or prevent defecation and result in constipation. Similarly, neurologic abnormalities such as idiopathic megacolon or dysautonomia can result in constipation due to impaired colonic motility (Figure 42-2).

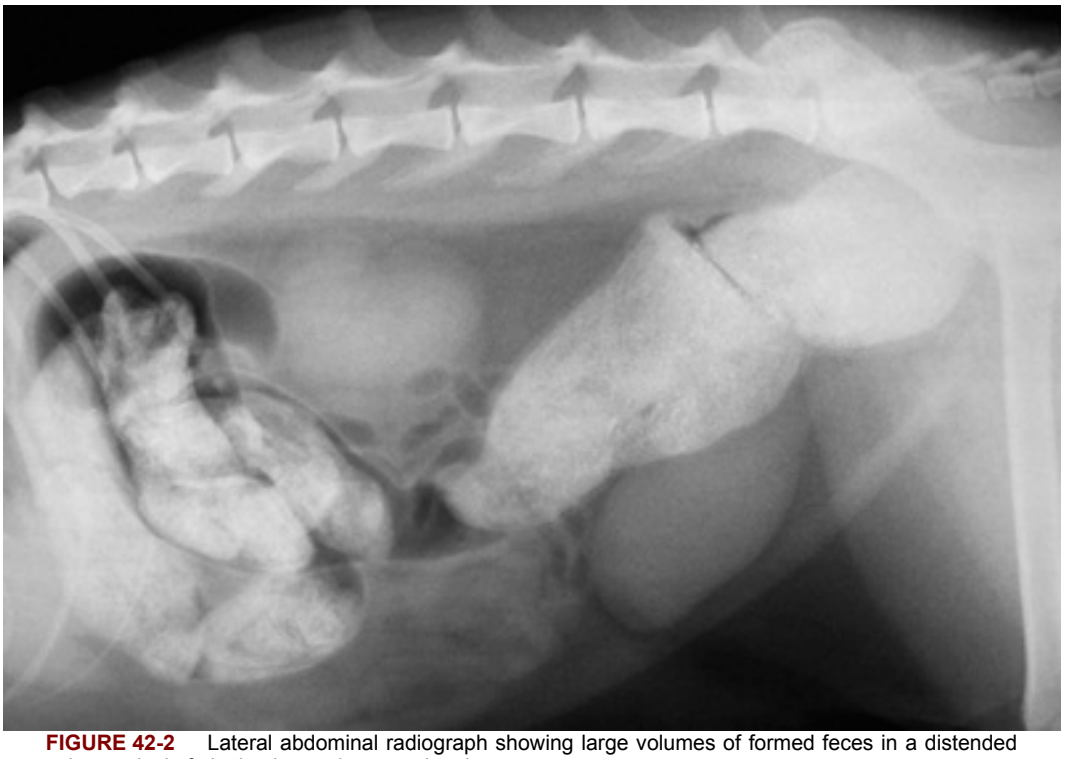

FIGURE 42-2 Lateral abdominal radiograph showing large volumes of formed feces in a distended colon, typical of obstipation and megacolon, in a cat.

History

Information should be gathered on the duration of the signs of constipation and how frequently the animal is attempting to defecate. Dietary details should be collected, including how much fiber is in the diet and whether the animal is consuming substantial quantities of indigestible material such as hair or bones. Anorexia or decreased access to food or water should be determined. A history of previous pelvic trauma or recent abdominal surgery is important because these can be additional contributing factors. Pets with a history of dyspnea can be reluctant to defecate, as straining may worsen their respiratory distress.

Signalment

Constipation can occur in any breed or either sex and at any age. English Bulldogs, Boston Terriers, and Manx cats tend to have an increased incidence of constipation due to possible malformations of the sacral spinal cord (see ch. 266). German Shepherd Dogs are predisposed to perianal fistulas that could result in dyschezia and constipation (see ch. 278). Megacolon tends to occur more commonly in middle-aged male cats. Intact male dogs should be examined closely for prostatomegaly (see ch. 337).

Physical Examination

The entire body should be examined closely for signs of underlying systemic disease that could be causing weakness, anorexia, or increased water loss (e.g., polyuria) that might be contributing to the constipation. Abdominal palpation can reveal a colon distended with hard feces. The anus should be visually inspected for fecal hair mats obstructing the anus (pseudocoprostasis), masses, and perianal fistulas. The rectum and distal colon should be carefully palpated digitally for evidence of hard, dry feces; colonic or rectal masses or foreign bodies; pelvic fractures; enlarged sublumbar lymph nodes; prostatomegaly in the male dog; perianal hernias; and evidence of anal sac disease.

Diagnostic Evaluation

A complete blood count, serum biochemistry profile, and urinalysis are useful in ruling out underlying systemic disease. Abdominal radiographs can confirm colonic distention with feces. In severe cases, the colon

is so distended with feces that the feces are not able to pass through the pelvic canal. Abdominal radiographs can also reveal evidence of colonic masses, foreign bodies, sublumbar lymph node enlargement, prostatomegaly, or pelvic fractures. Abdominal ultrasound may identify intraluminal or extraluminal masses, prostatomegaly, and enlarged lymph nodes. Once feces are evacuated from the colon and rectum, colonoscopy may reveal colonic neoplasia, perineal hernias, diverticula, and strictures.

Tenesmus and Dyschezia

It is important to localize the cause of straining to diseases of either the lower urinary tract or the lower gastrointestinal (GI) tract. Inflammatory and infectious diseases of the lower GI tract, such as inflammatory bowel disease, dietary indiscretion, intestinal parasitism, idiopathic colitis, pythiosis, and bacterial or fungal colitis, can cause irritation and straining at defecation. Obstructions, both intraluminal (colonic neoplasia, foreign bodies, strictures) and extraluminal (pelvic fractures, extraluminal masses, organomegaly), can make defecation difficult and result in tenesmus. Dyschezia results from diseases of the anus and perianal region including anal sacculitis, perianal fistulas, perineal hernia, anal/rectal neoplasia, and pseudocoprostasis.

History

Urination must be evaluated carefully to rule out lower urinary tract disease as a cause of tenesmus. Is the animal able to produce a normal stream of urine? Is there dripping of urine as the animal strains? Is the urine of normal appearance? Details of defecation are likewise important. Are normal feces being passed? Thin, ribbonlike feces, or small amounts of diarrhea, are common with intraluminal or extraluminal obstructions. Excessive grooming of the anal/perianal region is common with disease in that location (Figure 42-3). Sometimes the owners may report the animal turning around and looking at the hind end while attempting to defecate. There may be a history of trauma and pelvic fractures. Cats with tenesmus or dyschezia commonly vocalize or defecate outside the litter box. The timing of tenesmus in relation to defecation may help localize the problem: tenesmus prior to defecation suggests an obstruction, while tenesmus after defecation suggests irritation/inflammation.

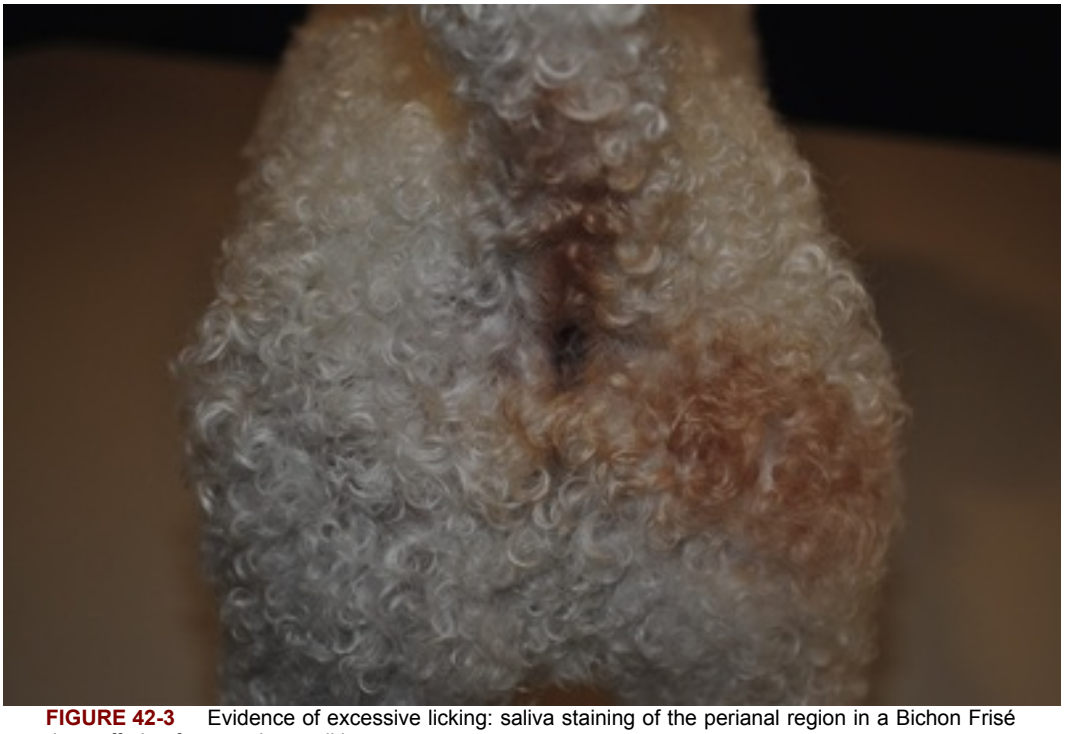

FIGURE 42-3 Evidence of excessive licking: saliva staining of the perianal region in a Bichon Frisé dog suffering from anal sacculitis.

Signalment

Inflammatory diseases are more common in young to middle-aged animals, while neoplasia is more common in older animals. German Shepherd Dogs are predisposed to perianal fistulas. Boxer dogs are predisposed to histiocytic colitis.

Physical Examination

The lower urinary tract should be examined by palpation of the bladder to rule out urethral obstruction (as evidenced by a distended and turgid bladder). The anus and perianal region are best inspected visually to rule out perianal fistulas, evidence of anal sac rupture, and fecal hair mats causing pseudocoprostasis. Digital rectal palpation may sometimes reveal uroliths in the urethra, or prostatomegaly in male dogs. It is also used for identifying rectal masses, perineal hernia, anal sacculitis, sublumbar lymph node enlargement, and pelvic fractures. Rectal palpation also allows for characterization of the feces; absent, scant, or bloody fecal material is consistent with inflammatory disease of the distal GI tract.

Diagnostic Evaluation

A complete blood count, serum biochemistry profile, and urinalysis are helpful in ruling out systemic disease. A fecal flotation can be performed to rule out GI parasites (see ch. 81). Abdominal radiographs and ultrasound are useful in ruling out extraluminal compression of the colon, foreign bodies, pelvic fractures, and colonic masses. Colonoscopy and proctoscopy are useful in identifying colonic masses, foreign bodies, and strictures, once fecal material is evacuated from the colon. Colonic biopsies may be necessary to evaluate the colonic wall for inflammation, infection, or neoplasia.

Fecal Incontinence

Fecal incontinence can be due to damage to the anal sphincter (nonneurogenic sphincter incompetence), disruption of the nervous supply to the anal sphincter (neurogenic incompetence), or reduced capacity or compliance of the rectum (reservoir incontinence). With reservoir incontinence, the animal is aware of the urge to defecate, but conscious control of defecation is overwhelmed by the presence of colorectal disease causing irritation, decreased storage capacity of the rectum, or overwhelming fecal volume. Diseases that can damage the anal sphincter and cause nonneurogenic sphincter incompetence include anal trauma or surgery, anal neoplasia, and damage to the levator ani and coccygeus muscles. Conditions that can result in neurogenic sphincter incompetence include cauda equina syndrome; damage to the pudendal nerve; sacral spinal cord trauma, neoplasia, or compressive lesions; and degenerative myelopathy (see Figure 42-1).

History

The first thing to establish is whether the animal is consciously aware of defecation and is assuming a normal posture to defecate. Conscious awareness of defecation, and the presence of diarrhea, increased frequency of defecation, and mucus or blood in the feces, suggest colorectal disease and reservoir incontinence. It is important to rule out behavioral problems when the animal is consciously defecating in inappropriate locations. With behavioral problems, there is normal posturing to defecate, normal frequency of defecation, and normal consistency of the feces. Often, the location of the defecation in the home is a clue to a behavioral problem. For example, if the dog has been punished previously when defecating inappropriately in the presence of the owner, the dog may seek out locations out of sight of the owner and away from the door outside. Animals with reservoir incontinence often attempt to get outside to defecate, but are unable to retain the feces, and defecate close to the door outside.

A history of recent trauma or perianal surgery may suggest damage to the anal sphincter. With neurogenic sphincter incompetence, other neurologic deficits may be detected, including loss of tail wagging, abnormal tail carriage, hind limb ataxia or weakness, decreased hind limb spinal reflexes, and concurrent urinary incontinence.

Physical Examination

Visual inspection of the anal sphincter may reveal evidence of trauma or mass lesions. Anal tone can be evaluated by the strength of constriction of the sphincter in response to a finger, thermometer, or hemostatic forceps stimulating the sphincter. A digital rectal exam may reveal masses disrupting the sphincter. Evidence of pain on palpating the sacrum or lumbosacral space rectally may occur with lumbosacral stenosis.

Abnormal fecal consistency, with mucus or blood, often is an indication of colorectal disease and reservoir incontinence. Neurologic examination (see ch. 259) can reveal decreased tail tone, hind limb ataxia, decreased hopping and wheelbarrowing, decreased hind limb spinal reflexes, decreased conscious proprioception of the hind limbs, evidence of lumbosacral pain, and loss of urinary bladder tone with many cases of neurogenic sphincter mechanism incompetence as a result of spinal cord disease or damage.

Diagnostic Evaluation

In addition to routine complete blood count, serum biochemistry profile, urinalysis, and caudal abdominal radiographs, additional diagnostic imaging of the caudal spinal cord (epidurogram, myelogram, computed tomography scan, or magnetic resonance imaging) may be required to characterize the nature of disease of the spinal cord if neurogenic causes of sphincter incompetence are suspected based on the history and physical examination.

CHAPTER 43

Flatulence

Alexander James German

Client Information Sheet: Flatulence

"Flatus" refers to gas generated within the gastrointestinal tract, and "flatulence is the act of expelling flatus through the anus." Flatulence is more common in dogs than cats, with a recent unpublished survey reporting an incidence of 10%, a quarter of which experienced daily signs.[1] However, in many instances owners are not concerned and do not seek veterinary attention.

Physiology and Pathophysiology of Flatulence

Passing flatus through the anus is a normal physiological phenomenon in mammalian species including cats and dogs, although volume, frequency, and smell vary. Most gas in flatus is derived from the gastrointestinal tract,[2] with some additional gas diffusing from the bloodstream. Aerophagia can also contribute to flatus, although its significance has been questioned.[3] Whilst rapid food consumption promotes aerophagia in dogs, excessive flatulence is not more frequently reported in dogs described as "greedy."[4] Aerophagia provokes more flatus in dogs with functional alimentary tract abnormalities, and examples include defects in gastro-esophageal sphincter function, eructation, or alimentary gas transit (see ch. 276 and 277).

Flatus comprises a mixture of gases, with >99% lacking odor. Typical gases include oxygen, nitrogen, carbon dioxide, hydrogen and methane. Most such gases are all produced within the gut, as a result of normal mammalian digestion (e.g., carbon dioxide) or microbial fermentation (e.g., methane), though some cases (e.g., nitrogen) arise from environmental air due to aerophagia.[5] A variable volume is produced, largely dependent upon diet composition (especially fermentable fiber), the presence of methane-producing bacteria, and concurrent disease.[6,7] In contrast, odor arises from the trace gas fraction, which is commonly <1% of total flatus volume. The odor-producing compounds in canine flatus include carboxylic acids, phenol, ammonia, hydrogen sulfide, indole, skatole, mercaptans, volatile amines, ketones, alcohols, and short-chain fatty acids.[8] Hydrogen sulfide is most important, but production is highly variable even amongst animals fed the same diet,[8] most probably due to differences in the presence of sulfur-reducing bacteria.[9] Possible sources of sulfur include intestinal mucin, nuts and vegetables, as well as carrageenan (a sulfated polysaccharide). Feeding a "high protein" diet can also increase volatile sulfur compounds and, therefore, odor.[5]

The propulsion of gas in the gastrointestinal tract is an active process which is separate from that of solid and liquid contents.[10,11] Dietary factors influence this process with protein, fat and fiber all slowing transit times, and simple sugars and dietary moisture having no effect.[12,13] Other factors that influence gas transit include physical activity, which increases the speed of gas transit and decreases retention.[11]

Pathophysiology

Since passage of flatus can be a normal physiological phenomenon, owners only present animals to a veterinarian when it is problematic (e.g., excessive volume or odor) or is associated with other clinical signs. Possible causes of excessive flatulence include aerophagia, alimentary tract disease, and diseases affecting other organs. Aerophagia commonly arises from disorders in gastro-esophageal sphincter function, eructation, and alimentary gas transit, with a key example being gastric dilatation volvulus (GDV).[14] Concurrent respiratory system disease might also be responsible, for example, brachycephalic airway syndrome.[15] Where excess flatus results from endogenous gases, it is usually either a byproduct of certain

foods or due to incomplete digestion. Foods commonly implicated are usually of vegetable origin, and contain large amounts of polysaccharides, which provide substrate for the large intestinal microbiota containing fermentable fiber or resistant starch, dairy products (if lactose intolerance is suspected), and other components (e.g., gelling agents such as carrageenan and guar gum in meat products). In humans, flatulence can result from carbohydrate malabsorption, and this is also a common feature in cats with gastrointestinal disease.[16] In a similar manner, dogs and cats that have hypersensitivity or intolerance to specific proteins might demonstrate flatulence, and other gastrointestinal signs if exposed to foods to which they are sensitive. Changes in protein content might alter the smell of flatus, whilst other dietary components can alter gas transit (e.g., dietary fat and fiber). Such changes can prompt an owner to present their dog for flatulence, even though the volume has not changed. Flatulence can occur with various diseases. In humans, a predominance of methane production can also occur in individuals with obesity, constipation, irritable bowel syndrome, and inflammatory bowel disease.[17,18] Lactose intolerance is an occasional cause of flatulence, as a result of gas production from intestinal bacteria utilizing lactose. Finally, certain enteric infections can cause flatulence, most notably infection with *Giardia* sp.,[19] and there is some suggestion that antimicrobial use can provoke flatulence, on account of effects on gastrointestinal microbiota.

Clinical Presentation and Differential Diagnosis

Clinical signs associated with flatulence include excessive flatus volume, unpleasant flatus odor, noise associated with episodes, and abdominal pain or abdominal distension ("bloating"). Patients with flatulence may also have excessive eructation or borborygmi, as well as other alimentary tract signs such as including vomiting, diarrhea, and weight loss.

Differential diagnoses for flatulence include excessive aerophagia, dietary factors, motility disorders, malabsorption, and microbial causes. As discussed above, aerophagia can result from swallowing disorders (e.g., esophageal dysmotility, and megaesophagus), respiratory tract disorders (e.g., those causing dyspnea), and problems relating to feeding behavior (e.g., rapid food ingestion, obsessive compulsive disorders). Dietary causes include excessive fermentation (e.g., due to excessive dietary fermentable fiber) and adverse reactions to food (e.g., hypersensitivity, intolerance, and dietary indiscretion). Motility disorders that cause flatulence include esophageal dysmotility, GDV, dysautonomia, ileus, obstructive intestinal disease (e.g., neoplasia, foreign body, stricture, and adhesions), and "irritable colon syndrome." The most likely causes of malabsorption are exocrine pancreatic insufficiency (EPI) and chronic enteropathies that affect the small intestine (e.g., inflammatory bowel disease, lymphoma). Since giardiasis and antibacterial use can cause flatulence in humans, they are also possible differential diagnoses in companion animals.

Investigation

As mentioned above, flatulence is a normal physiological phenomenon, and one aim of investigations is to determine whether the reported episodes are of significance. Therefore, the extent of the investigations and management should depend upon the individual case. Possible reasons for an owner presenting their dog include flatulence developing in a dog not previously affected, increasing severity of signs (in terms of volume, odor, sound), or concurrence of other clinical signs, perhaps suggesting a significant underlying gastrointestinal disease or disease in another organ. History and physical examination are first used to determine the likelihood of an underlying disease and whether there are any recent changes to diet or management (see ch. 1 and 2 and Figure 43-1). This will enable the clinician to determine if investigations are necessary. Appropriate treatments are used when an underlying disease is identified, while symptomatic therapy (diet, management, medical) can be used at any stage, if an underlying cause is neither suspected nor identified on investigations.

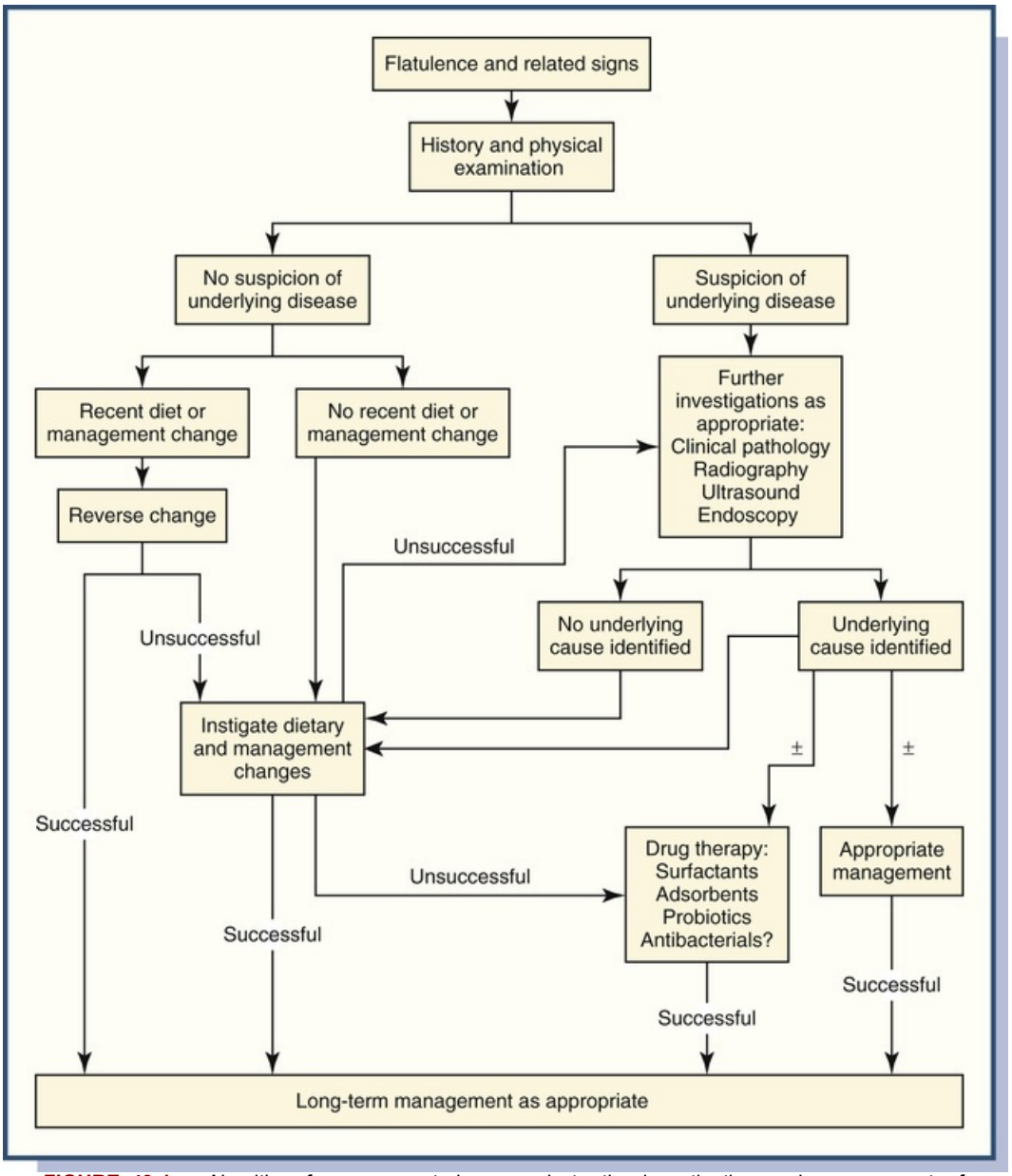

FIGURE 43-1 Algorithm for a suggested approach to the investigation and management of flatulence.

In addition to the medical history, diet history should be gathered, including all food given, timing, amount, and if recent changes have occurred. Both main meal and extras (e.g., supplements, table scraps, treats, or food scavenged) must be recorded. The clinician should also consider diet composition, since many components can cause flatulence (see above), and the possibility of an adverse reaction to food. On physical examination, flatulence, borborygmi, abdominal discomfort, and abdominal distension may be present. Since other signs would not be expected in simple flatulence cases, their presence can suggest an underlying disease (see ch. 178, 179, and 191).

Further investigations are required when underlying disease is suspected, with tests dependent upon the individual case. Routine hematological and serum biochemical analysis, coupled with urinalysis, can give information regarding general systemic health, whilst routine fecal examination may indicate an enteric infection. Measurement of folate and cobalamin can help to confirm malabsorption, whilst trypsin-like immunoreactivity (see ch. 292) can be used to identify EPI. Diagnostic imaging, especially thoracic and abdominal radiography, can show the presence and distribution of gas in the alimentary tract, as well as confirming problems such as megaesophagus or GDV. Finally, although gastrointestinal biopsy is rarely required, it is used when an underlying small intestinal malabsorption is suspected.

Management

Where there is evidence of an underlying disease, specific therapy should be implemented, and examples would include immunosuppressive medication for IBD with concurrent malabsorption, pancreatic enzyme supplementation for EPI, and antiparasitic medication for giardiasis. In such cases, the flatulence should resolve when the underlying disorder is treated, although symptomatic treatment may also be required. Examples of symptomatic therapies for flatulence include dietary management, altering feeding behavior, and medical therapies.

The goal of dietary management is to reduce (e.g., fat, fermentable fiber, gelling agents) or eliminate altogether (e.g., proteins suspected of causing hypersensitivity) the component of the food responsible for signs. The components in different foods should be compared relative to energy content of the food (i.e., g per 1000 kcal) rather than relative to dry matter. When it is not possible to determine the exact offending agent, a highly digestible diet should be chosen, which is reduced in fat and fermentable fiber. An empirical choice for a dog would be a food with less than 30 g/1000 kcal fat and 15 g/1000 kcal crude fiber (<25 g/1000 kcal total dietary fiber). Either a formulated therapeutic diet or a home-prepared diet can be used. The latter does not need to be balanced if fed for ≈7 days (i.e., as a diet challenge), but must be nutritionally balanced when fed long term, ideally by a board-certified clinical nutrition specialist. Generally, it is best to avoid vegetarian diets (given the potential for greater fermentable fiber content) and foods containing lactose. Further, some dry foods have an altered kibble shape and require more chewing, thereby slowing food intake. If an adverse reaction to food is suspected, it is advisable to consider conducting one, or more, exclusion diet trials using either a hydrolyzed or single source protein diet (see Section XI and ch. 191). Trials should last for at least 2 weeks since signs associated with adverse food reactions usually improve within 7-10 days.

Where flatulence is the result of aerophagia, changing the pattern, timing, and method of feeding can sometimes help. Animals that are group fed can be separated to avoid rapid eating through food competition. When rapid intake is a possible cause, interactive feeders (e.g., hollow toy "puzzle" feeders and modified feed bowls) can be used to slow the rate of food intake. Further, giving the daily food ration over a number of meals can help, though evidence of efficacy is mixed with one study suggesting twice daily feeding to be better than once daily,[20] and another study suggesting no effect of change in meal frequency.[4] Finally, increasing physical activity can also be considered since it can increase the rate of intestinal gas transit, and decrease gas retention[11]; indeed, dogs that are exercised frequently are less likely to bloat than sedentary dogs.

Various drugs can symptomatically reduce the volume and/or odor of flatulence, with options including surfactants, adsorbents, antibacterials, and probiotics. Simethicone is a surfactant that is used to treat flatulence in humans; it reduces surface tension causing gas bubbles within the stomach and intestine to coalescence, thereby reducing gas trapping and promoting its passage through the gastrointestinal tract.[21] Empirical use is thought to be safe in cats and dogs, using a scaled-down human dose (e.g., 25-200 mg q 6 h PO).[22] Plant saponins derived from *Yucca schidigera* has been shown to have effects on antimicrobial fermentation.[23] Indeed, extracts of *Yucca schidigera* reduce fecal odor when fed both to dogs and cats.[24-26] Other adsorbents used for symptomatic flatulence management include activated charcoal, bismuth subsalicylate, and zinc-containing compounds (e.g., zinc acetate, zinc sulfate). Bismuth and zinc are divalent cations that bind compounds with a sulfhydryl group (e.g., hydrogen sulfide), whilst activated charcoal has a large internal surface area binding molecules leading to flatulence. Whilst such products are effective,[27] they require frequent dosing, making compliance a possible challenge. Dietary activated charcoal reduces hydrogen sulfide concentrations and odor associated with flatus in dogs.[26] Combination products are also available for veterinary use, and the individual agents are synergistic. For example, a supplement containing *Yucca schidigera* extract, activated charcoal, and zinc acetate significantly decreased hydrogen sulfide content of flatus, when fed to dogs[26]; each component had independent effects, but the combination product was better overall.

In humans, antibacterials are used empirically to manage flatulence. Suitable drugs should be orally administered, effective against anaerobic bacteria, not be systemically absorbed, and be free from side effects. Examples include rifamixin, which is more effective than activated charcoal treating flatulence in humans.[28] Antibacterial therapy can also be considered for dogs with flatulence,[29] but caution is recommended with empirical use long term, given the potential for antimicrobial resistance. If necessary, nonabsorbed antibacterials are preferable, as in humans. Probiotics are a possible alternative given studies suggesting a reduction in severity of flatulence in humans with irritable bowel syndrome.[30] Recent work in dogs has also demonstrated possible efficacy of probiotics for treatment of flatulence in dogs, by decreasing number of

flatulence events, hydrogen sulfide concentration, and odor.[31]

Finally, whilst surgical procedures are not directly used for management of flatulence, prophylactic gastropexy may be required for dogs predisposed to gastric dilatation-volvulus. Rather than eliminating clinical signs, the main aim is to prevent torsion from developing in the future. Nonetheless, some cases of chronic partial torsion manifest with chronic low-grade signs of flatulence and borborygmi. In such cases, prophylactic surgery can also provide long-term relief from clinical signs.

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Urogenital

OUTLINE

Chapter 44 Vulvar and Preputial Discharge
Chapter 45 Polyuria and Polydipsia
Chapter 46 Pollakiuria, Stranguria, and Urinary Incontinence
Chapter 47 Hematuria and Other Conditions Causing Discolored Urine

CHAPTER 44

Vulvar and Preputial Discharge

Jeffrey de Gier, Auke C. Schaefers-Okkens

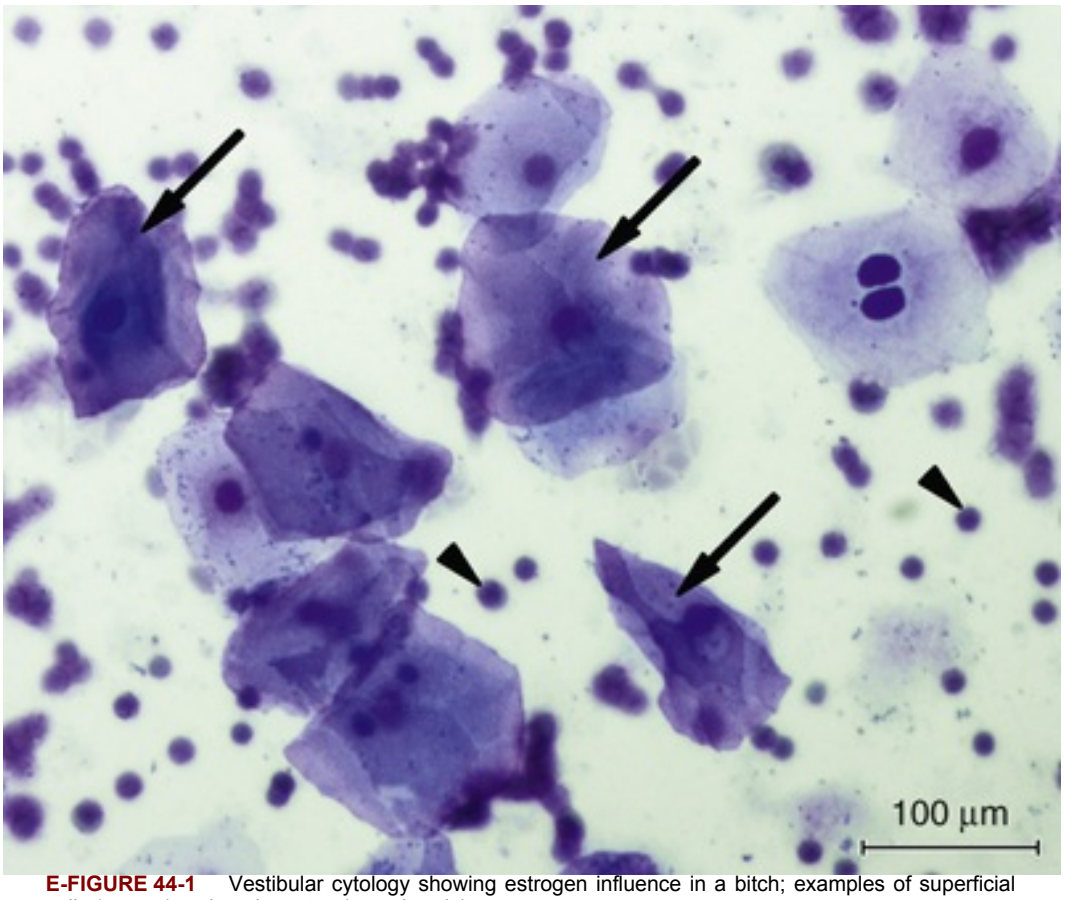
Client Information Sheet: Vulvar Discharge

Introduction

The content of this chapter is devoted to the causes of and clinical approach to non-physiological vaginal or preputial discharge. This discussion will not include disorders of the urological tract and/or perineal pathology, which may cause "pseudovaginal discharge," such as occurs with anal sac abscess or perivulvar dermatitis. Physiological vaginal discharge is commonly observed in the bitch during proestrus, estrus, pregnancy, parturition and the days to weeks following parturition. Discharge is normally seen in some cats during parturition and in the days thereafter. In male dogs, mucopurulent discharge from the prepuce without concomitant clinical signs is often considered physiological or of little consequence.

Vaginal Discharge

In order to make a proper diagnosis, one should begin with a complete history and then perform a thorough physical examination. The following information is important: (a) the pet's age; (b) the nature of the discharge: serosanguineous, mucoid, or mucopurulent? (c) is the animal intact or has an ovariectomy or ovariohysterectomy been previously performed? If intact, when was the last estrus? As the final component of the physical examination, the genital tract should be evaluated with abdominal palpation and, as indicated: digital palpation of the vaginal vault, vaginoscopy, and cytology of the vestibule to evaluate for estrogen influence (see ch. 119) (E-Figure 44-1). The more invasive examinations are usually not done or feasible in awake young animals or cats. Additionally, any of the following may be warranted: laboratory testing to assess for inflammation or bone marrow hypoplasia, endocrine testing of the pituitary-gonadal axis, ultrasonography of structures which are of concern, cytology of a fine needle aspirate or histologic assessment of a tissue sample.[1]



E-FIGURE 44-1 Vestibular cytology showing estrogen influence in a bitch; examples of superficial cells (arrows) and erythrocytes (arrowheads).

Serosanguineous Vaginal Discharge in Intact Bitches and Queens (Figure 44-2)

In young bitches during the first or second estrous period, prolonged estrogen influence or "split heats" are relatively common. Prolonged exposure to estrogen can result in a persistent sanguineous discharge and can be confirmed with vaginal cytology (see E-Figure 44-1) and/or vaginoscopy (Video 44-1) (see ch. 119). This condition is frequently caused by failure to ovulate, as can be demonstrated by persistently low plasma progesterone concentrations. Other causes of prolonged proestrus include cystic ovarian follicles, portosystemic shunt (see ch. 284), or exogenous estrogen influence. In middle-aged or older dogs, the most common cause for prolonged sanguineous discharge is ovarian neoplasia. Such neoplasia can usually be visualized with abdominal ultrasonography or more advanced imaging studies.

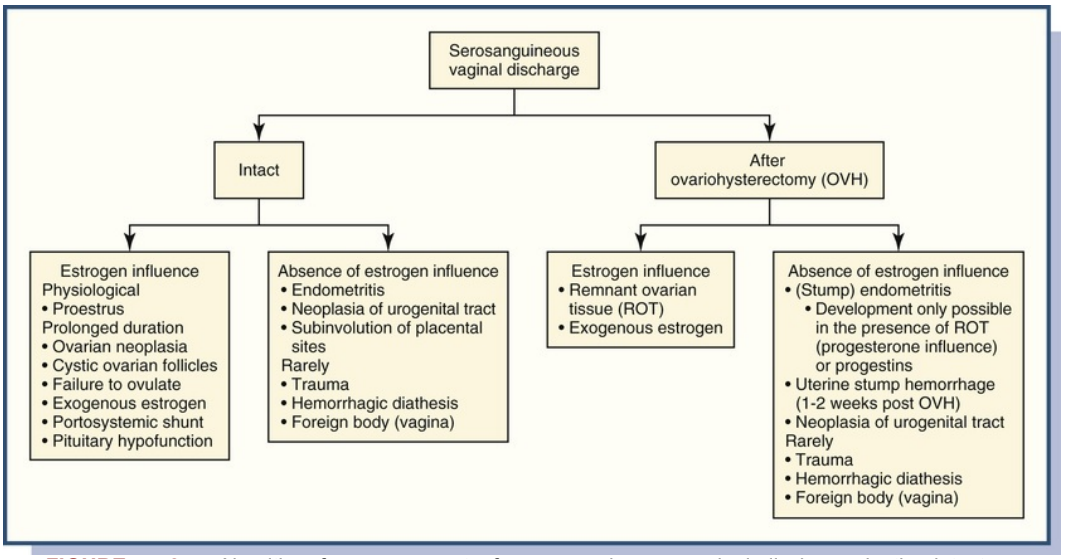
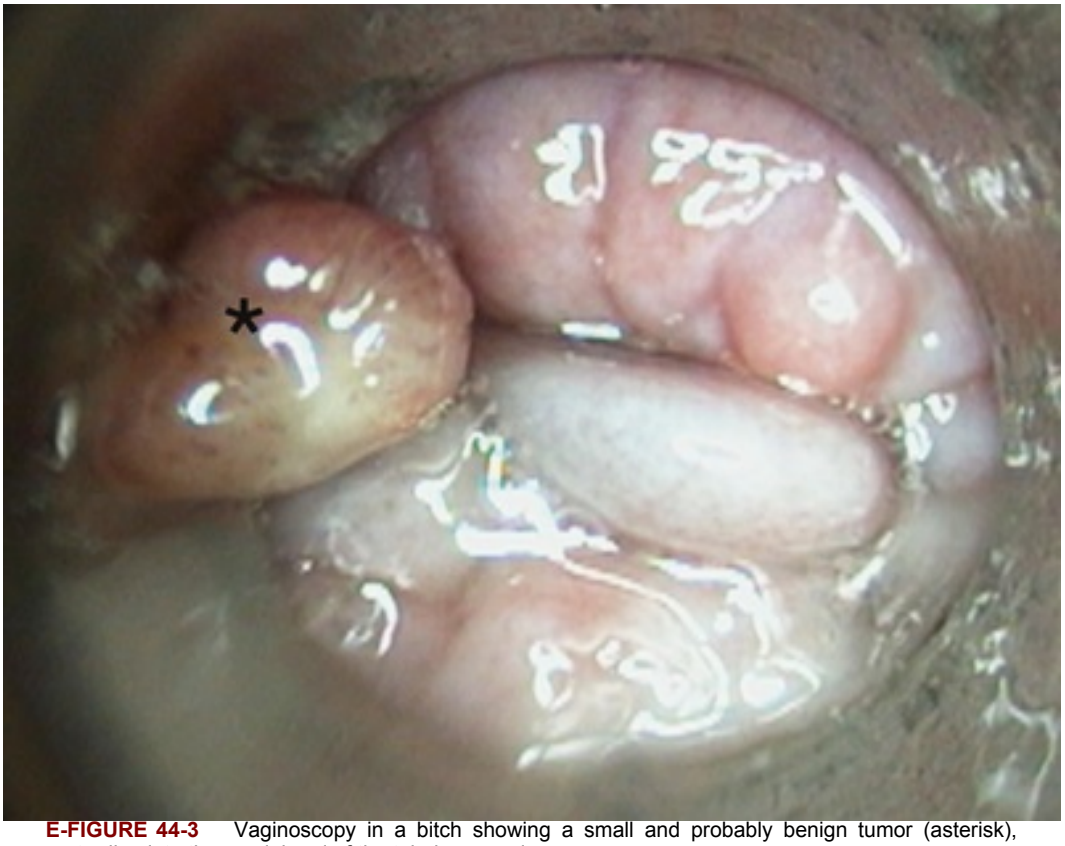


FIGURE 44-2 Algorithm for assessment of serosanguineous vaginal discharge in the intact or ovariectomized bitch based on the presence or absence of estrogen influence.

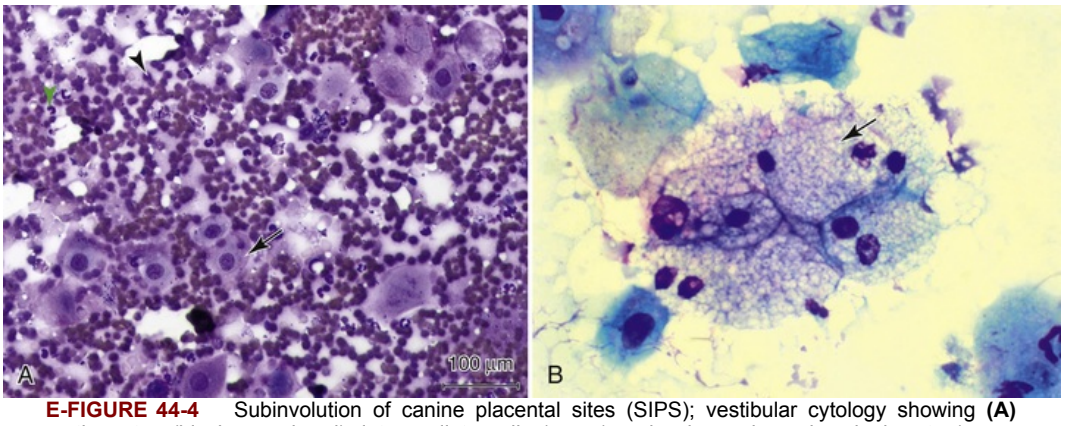
Bloody discharge in the absence of estrogen influence in middle-aged to older intact bitches is most frequently caused by endometritis or neoplasia of the urogenital tract (E-Figure 44-3; Video 44-2; see ch. 316 and 351). In intact bitches, vaginal tumors are often benign (e.g., leiomyoma, fibroma). Cytology or histopathology may be of value before surgical removal of the tumor(s) is attempted.



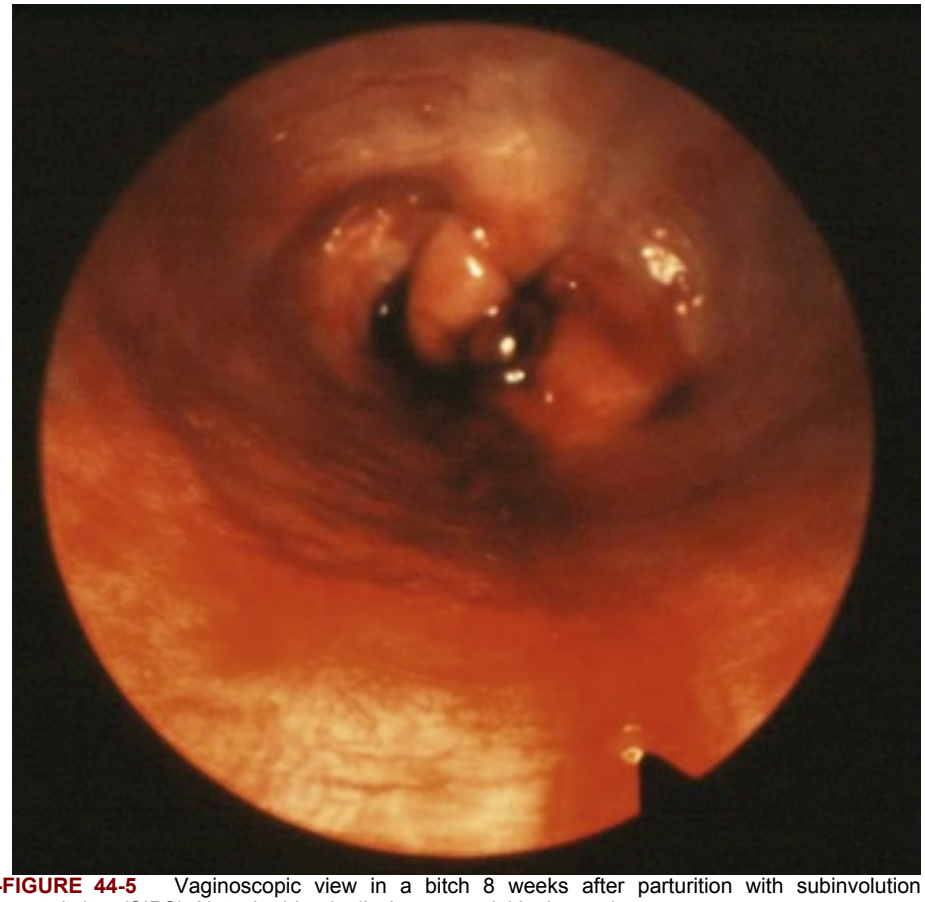
E-FIGURE 44-3 Vaginoscopy in a bitch showing a small and probably benign tumor (asterisk), protruding into the cranial end of the tubular speculum.

Subinvolution of placental sites (SIPS) is often the cause of prolonged bloody discharge (longer than 2-3 weeks) in bitches after parturition (see ch. 315). These bitches are otherwise healthy. The bloody discharge is

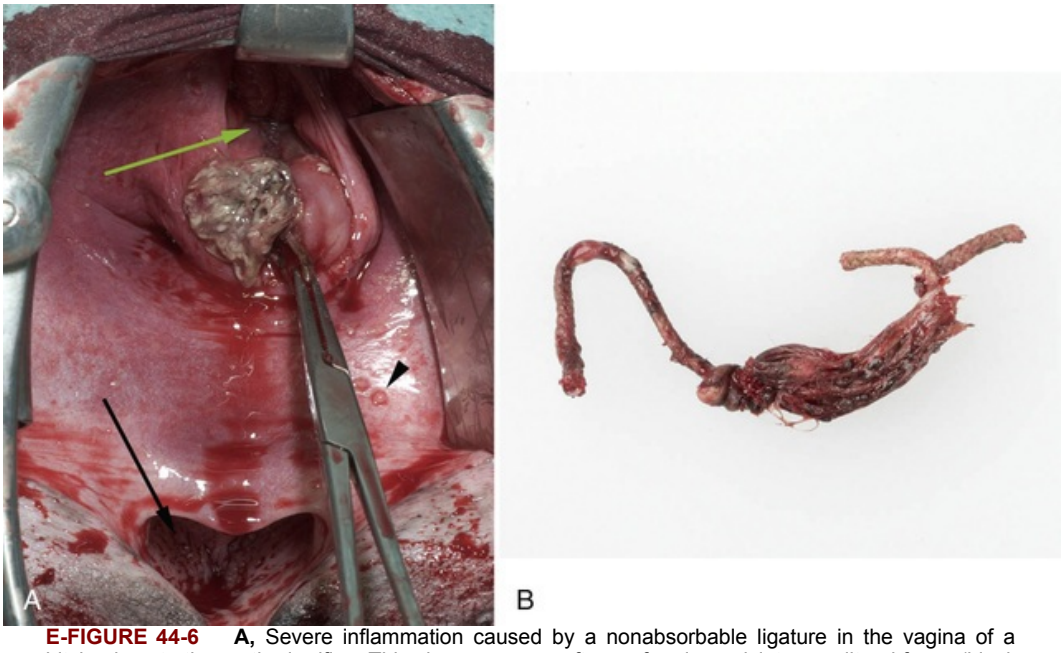
usually obvious on vaginoscopy. The cells seen on vaginal smears include erythrocytes, occasional neutrophils, and vacuolated giant cells (E-Figures 44-4 and 44-5). Placental sites visualized with ultrasonography may appear large. If left untreated the discharge may continue until the next estrus period.[2] In queens, bloody discharge may be caused by endometritis or (partial) abortion. Rarely, bloody discharge in bitches and queens may be due to trauma, hemorrhagic diathesis or a foreign body (E-Figure 44-6).



E-FIGURE 44-4 Subinvolution of canine placental sites (SIPS); vestibular cytology showing **(A)** erythrocytes (black arrowhead), intermediate cells (arrow) and polymorphonuclear leukocyte (green arrowhead) and **(B)** a polynucleated, vacuolated giant cell (arrow).



E-FIGURE 44-5 Vaginoscopic view in a bitch 8 weeks after parturition with subinvolution of placental sites (SIPS). Note the bloody discharge cranial in the vagina.



E-FIGURE 44-6 **A,** Severe inflammation caused by a nonabsorbable ligature in the vagina of a bitch, close to the urethral orifice. This view was seen after performing episiotomy; clitoral fossa (black arrow), possible lymphoid tissue (arrowhead), vagina (green arrow). **B,** Ligature after removal.

Serosanguineous Vaginal Discharge in Bitches and Queens after Ovariectomy (see Figure 44-2)

Serosanguineous discharge due to estrogen influence observed in a previously ovariectomized bitch is usually caused by functional remnant ovarian tissue. The diagnosis is easily made if estrogen influence is confirmed via vulvar swelling, vaginal cytology, vaginoscopy (Video 44-3; see ch. 119) and/or if the plasma progesterone concentration is >2 ng/mL. If no estrogen influence is observed and the plasma progesterone concentration is <2 ng/mL, then a gonadotropin-releasing hormone (GnRH) stimulation test or determination of anti-mullerian hormone concentrations may be necessary to confirm a diagnosis. Determination of basal plasma luteinizing hormone (LH) concentrations, alone, is not reliable due to changes in the hypothalamic-pituitary-ovarian axis after an incomplete ovariectomy.[3-5]

Serosanguineous discharge after ovariectomy may also be caused by long-term administration of estrogens, e.g., estriolum for urinary incontinence.[6] Further causes of bloody discharge after ovariectomy, without the presence of estrogen influence, include stump endometritis due to the administration of progestins, neoplasia of the urogenital tract (more frequently malignant than in intact bitches), or uterine stump hemorrhage in the 1-2 weeks after ovariohysterectomy. Rarely, trauma, hemorrhagic diathesis or a foreign body may cause bloody discharge.

Mucopurulent Vaginal Discharge in Intact Bitches and Queens (Figure 44-7)

Clear to opaque mucous vaginal discharge is sometimes observed physiologically around day 30 of normal pregnancy (E-Figure 44-8). Mucopurulent vaginal discharge in the intact bitch at the onset of diestrus may be physiological as well (E-Figure 44-9). The most common pathological cause of mucopurulent vaginal discharge in the intact bitch after estrus or parturition is endometritis (see ch. 316). The vaginal discharge in association with abortion is often dark green. Additionally, vestibulitis/vaginitis may cause mucopurulent discharge. Primary vaginitis is not seen in the cat.

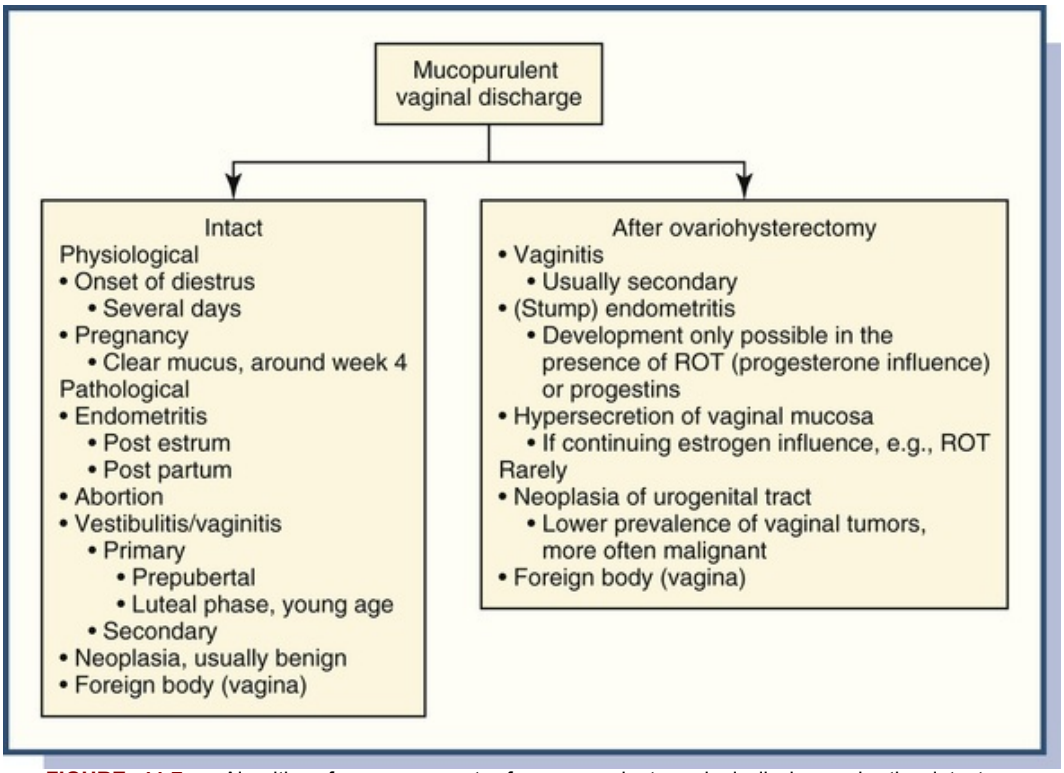
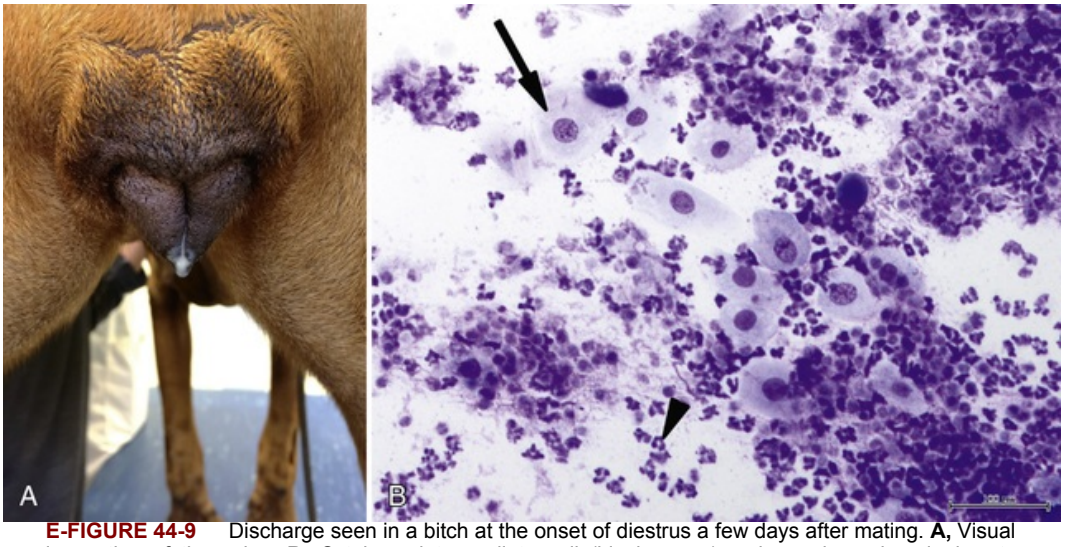


FIGURE 44-7 Algorithm for assessment of mucopurulent vaginal discharge in the intact or ovario(hyster)ectomized (OVH) bitch. *ROT,* Remnant ovarian tissue.

E-FIGURE 44-8 Clear and frequently seen physiological mucous discharge in the bitch around day 30 of pregnancy.



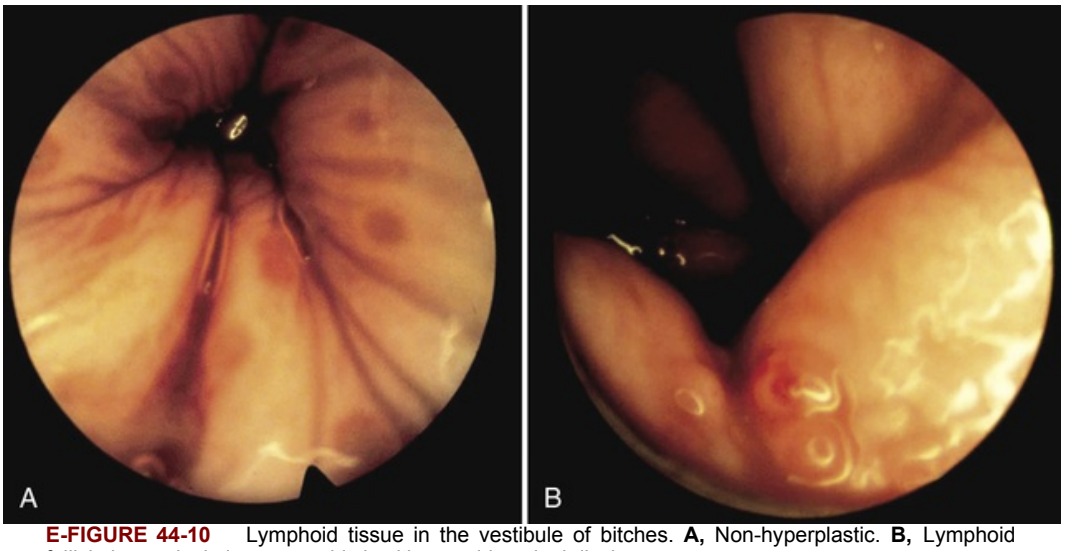
E-FIGURE 44-9 Discharge seen in a bitch at the onset of diestrus a few days after mating. **A,** Visual inspection of the vulva. **B,** Cytology, intermediate cell (black arrow), polymorphonuclear leukocyte (arrowhead).

The etiology of vaginitis and/or vestibulitis may be better understood by reviewing the embryologic development of this anatomic area. The area immediately proximal to the urethral opening is the caudal aspect of the internal genitalia, which fuses during development with the external genitalia. This "fusion"

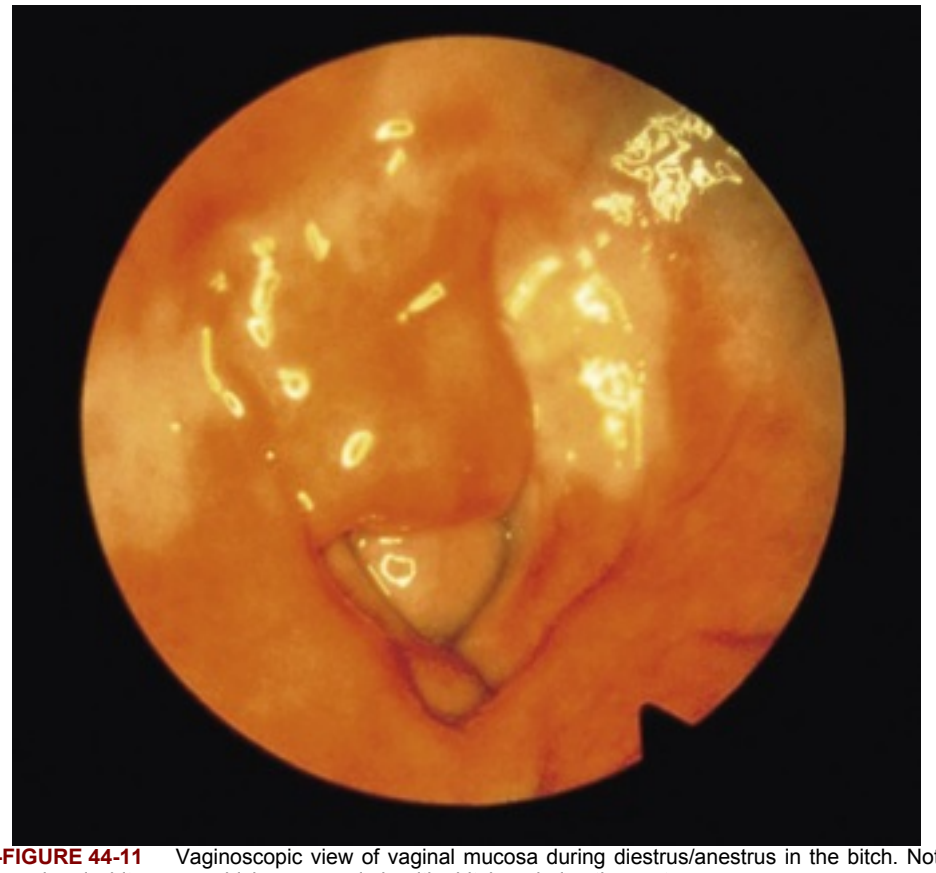
creates the entire vaginal vault.

Age and the stage of the estrous cycle may be important. Infrequently, inflammation within the vestibule may be due to an infection, e.g., with canine herpesvirus. Hormonal and immunological factors may play a major role in "vaginitis/vestibulitis" in young dogs, whose clinical signs are often restricted to mucous discharge and attractiveness to male dogs.

Prepubertal *"puppy vaginitis"* and *"vaginitis/vestibulitis" after the first or second estrus* are most commonly seen in large and brachycephalic breeds, sometimes as early as 3 months of age. This condition is characterized by a slightly swollen vulva, mucoid white or yellow discharge and/or attraction of male dogs. Vaginoscopy may reveal an exudate, mucosal lesions primarily in the vestibule and concomitant lymphoid follicle hyperplasia (E-Figure 44-10; see ch. 304). Vaginoscopy performed when a normal bitch is in diestrus shows a patchwork of white and red areas. Red areas in these dogs should not be mistaken for inflammation if mucosal lesions are not present (E-Figure 44-11; Video 44-4).



E-FIGURE 44-10 Lymphoid tissue in the vestibule of bitches. **A,** Non-hyperplastic. **B,** Lymphoid follicle hyperplasia in a young bitch with mucoid vaginal discharge.

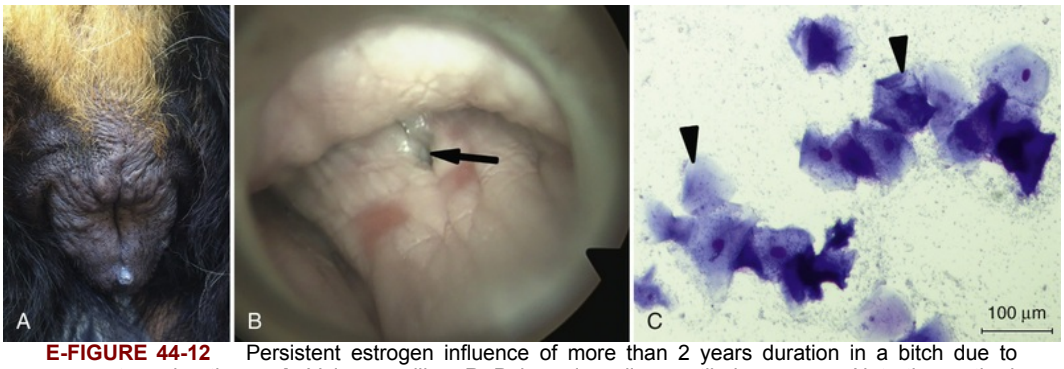


E-FIGURE 44-11 Vaginoscopic view of vaginal mucosa during diestrus/anestrus in the bitch. Note the red and white areas which are seen in healthy bitches during these stages.

Frequently, the signs in young dogs are self-limiting and disappear after the first estrous cycle or after the second or third luteal phase. Treatment of "puppy vaginitis" prior to the first estrus is not recommended for several reasons. Most drugs, such as local or parenteral antibiotics, will not alleviate signs. Application of locally active ointments or other medications are not well tolerated, especially in prepubertal bitches. Lastly, the general health and fertility of these patients is usually not affected by this condition.

"Vaginitis/vestibulitis" after the first or second estrus may be treated by local application of ointments containing glucocorticoids. If these agents are beneficial in alleviating the signs, it would support an underlying immunological etiology. If vaginal discharge is noted in a patient with concurrent urological problems (e.g., cystitis and/or pyelonephritis), more intensive therapy may be needed (see ch. 330 and 327). Bacterial culture of the vagina usually demonstrates normal flora and is not a test with significant value. However, if antibiotic treatment is being considered, culture and sensitivity testing should be performed. "Vestibulitis/vaginitis" may recur, but the problem is usually self-limiting with the end of the luteal phase or with advancing age.

"Vaginitis in the mature bitch" is usually secondary to other problems such as a foreign body or neoplasia in the vagina. Very rarely, anatomic deformities may lead to accumulation of secretions or urine, leading to inflammation and vaginal discharge. Vestibulitis with discharge may also be caused by urinary incontinence, e.g., after ovariectomy. In addition, vesicles may be temporarily observed along the mucosa of the vestibule if a bitch has a canine herpes infection. Remnant ovarian tissue in a bitch, after hysterectomy, may lead to non-bloody vaginal discharge, mostly of shed superficial cells (E-Figure 44-12; Video 44-5).



E-FIGURE 44-12 Persistent estrogen influence of more than 2 years duration in a bitch due to remnant ovarian tissue. **A,** Vulvar swelling. **B,** Pale and swollen vestibular mucosa. Note the urethral opening (arrow). **C,** Cytology showing erythrocytes and mainly superficial cells (arrowheads).

Mucopurulent Vaginal Discharge in Bitches and Queens after Ovariectomy (see Figure 44-2)

Mucopurulent discharge after ovariectomy without estrogen influence may be caused by neoplasia in the genital tract or it may be seen in dogs with "stump endometritis" due to progesterone secretion from remnant ovarian tissue (E-Figure 44-13) or may follow progestin administration. Progestin administration is always contraindicated after ovariectomy. If, after ovariectomy, cystic endometrial hyperplasia is present in the uterine tissue, and progestins have not been administered, then remnant ovarian tissue is present.

E-FIGURE 44-13 Surgically removed uterine stump showing pyometra due to progesterone influence in a bitch with remnant ovarian tissue.

Preputial Discharge

Preputial discharge may be composed of fluid and cells that originate from the urinary bladder, prostate gland, testicles and epididymides, urethra, and mucosa of the penis and penile sheath. Preputial discharge

may be present in either intact or castrated dogs but is extremely uncommon in tomcats. Rarely, generalized mucosal disease or hemorrhagic diathesis may cause preputial discharge.

Normal discharge in the intact male is characterized by a small amount of grayish-white to yellow mucopurulent material that may be seen at the preputial orifice as moist or dried exudate. Abnormal discharges may be mucopurulent (E-Figure 44-14) or serosanguineous (Figure 44-15).

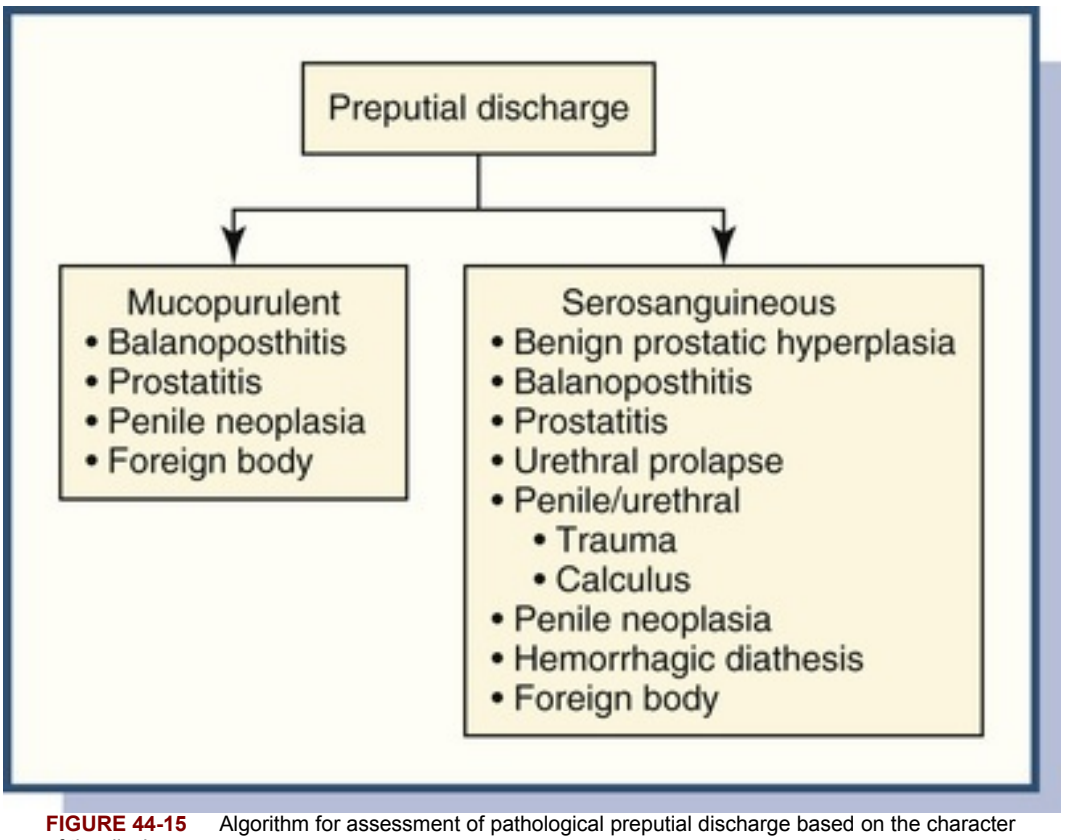
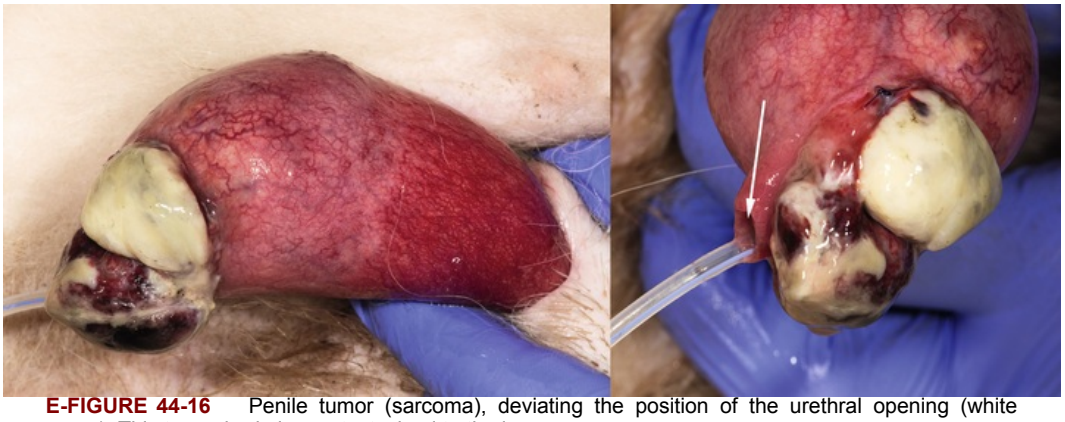


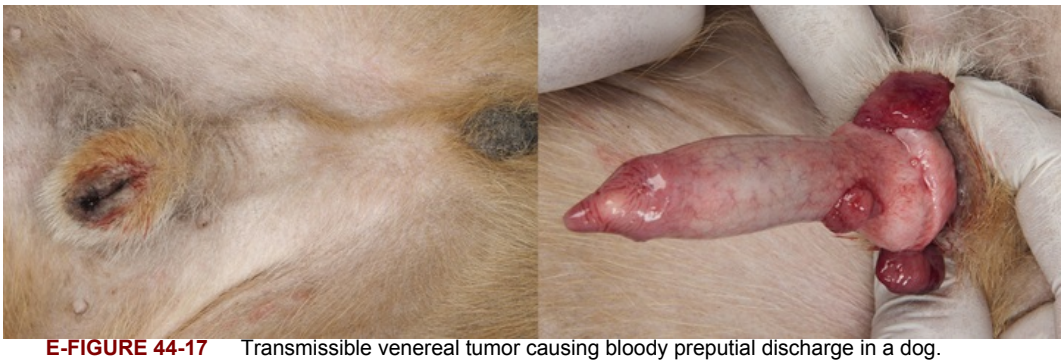
FIGURE 44-15 Algorithm for assessment of pathological preputial discharge based on the character of the discharge.

E-FIGURE 44-14 Mucopurulent preputial discharge in a castrated male dog.

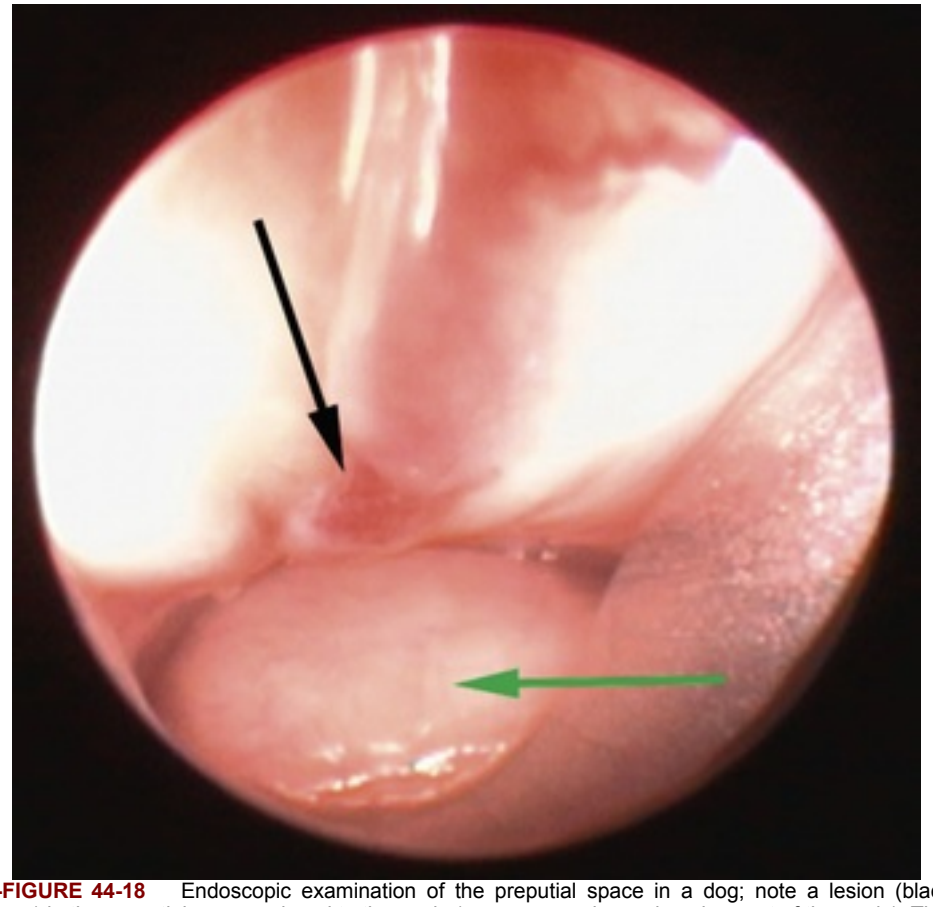
It is important to consider age, breed, and reproductive status of the pet. The duration and historical character of the discharge should also be noted. Systemic signs that precede or are associated with preputial discharge may accompany inflammatory conditions, infectious disease, neoplasia, trauma, or exposure to a toxin. Penile tumors are rare (E-Figure 44-16). The prevalence of transmissible venereal tumor varies with geographical location (E-Figure 44-17). A complete physical examination, including the male reproductive tract, should be performed.[7] Digital examination and visual inspection of the preputial space (preputioscopy) may be indicated to assess the entire mucosal surface (E-Figure 44-18).



E-FIGURE 44-16 Penile tumor (sarcoma), deviating the position of the urethral opening (white arrow). This tumor had also metastasized to the lungs.



E-FIGURE 44-17 Transmissible venereal tumor causing bloody preputial discharge in a dog.



E-FIGURE 44-18 Endoscopic examination of the preputial space in a dog; note a lesion (black arrow) in the preputial mucosa dorsal to the penis (green arrow shows dorsal aspect of the penis). This lesion was only visible using endoscopy and not upon extrusion of the penis.

In dogs and cats castrated prior to puberty, the penile tissue may appear less developed. Additionally, in cats it may be more difficult to completely extrude the penis for visualization. Based on the appearance of the preputial discharge, historical information, and physical examination findings, a list of possible diagnoses can be generated (see Figure 44-15).

Further evaluation might include a complete blood count, serum biochemical profile, and urinalysis, as well as imaging of the testicles, prostate, or urinary bladder with ultrasonography. Evaluation of testicular or prostatic secretions may be possible through semen collection or prostatic massage (see ch. 111). Additional diagnostics may include bacterial culture and sensitivity testing, fine needle aspiration, or biopsy.

Testing, as discussed, may lead to a definitive diagnosis. In the absence of definitive findings, the male should be re-evaluated at a later date. Comparison of subsequent findings with the original data may lead to a definitive diagnosis or management plan.

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CHAPTER 45

Polyuria and Polydipsia

Robert E. Shiel

Client Information Sheets:
How to Measure Your Pet's Water Intake
Polyuria and Polydipsia: Excess Urine Output and Water Intake

Introduction

Polyuria and polydipsia are common presenting complaints. Polydipsia is generally defined as a water intake greater than 90-100 mL/kg/day in dogs, and greater than 50 mL/kg/day in cats. However, water intake in healthy animals is variable and may be increased by high environmental temperature, exercise and feeding dry diets. Polyuria is defined in both species as urine output greater than 50 mL/kg/day.

Differential Diagnosis

The causes of polyuria and polydipsia are summarized in Box 45-1. Polyuria is caused by excessive intake of water (primary polydipsia) or decreased urinary concentrating ability (primary polyuria).

Box 45-1

Causes of Polyuria and Polydipsia in Dogs and Cats

- Central diabetes insipidus
- Primary nephrogenic diabetes insipidus
- Secondary nephrogenic diabetes insipidus
  - Hyperadrenocorticism
  - Hypoadrenocorticism
  - Hyperthyroidism
  - Hyperaldosteronism
  - Liver disease
  - Pyelonephritis
  - Pyometra/*Escherichia coli* endotoxemia
  - Hypokalemia
  - Hypercalcemia
  - Erythrocytosis
  - Leptospirosis
  - Acromegaly
  - Leiomyosarcoma
  - Drug administration, e.g., glucocorticoids, phenobarbital
- Osmotic
  - Diabetes mellitus
  - Chronic kidney disease
  - Primary renal glycosuria
  - Fanconi syndrome
  - Post-obstructive diuresis
  - Drug administration, e.g., osmotic diuretics

High salt diet
Low renal medullary tonicity
Renal medullary washout
Low protein diet
Other/unknown
Polyuric phase of acute kidney injury
Syndrome of inappropriate ADH secretion
Splenic hemangiosarcoma
Pheochromocytoma

Primary Polydipsia

Primary polydipsia represents a group of disorders in which increased thirst is the primary pathophysiological mechanism. In people, many cases are associated with psychiatric conditions, which have led to the term "psychogenic polydipsia." The cause of primary polydipsia in dogs and cats is not known (idiopathic). Behavioral disorders, altered hypothalamic thirst center function, or inappropriate stimulation of thirst centers by osmoregulatory, neural or hormonal abnormalities are often suspected, but difficult to confirm. Primary polydipsia is proposed to contribute to the polyuria reported in hyperthyroidism and with hepatic failure. An association between primary polydipsia and gastrointestinal disease has been reported in dogs.

Primary Polyuria

Diabetes Insipidus

Arginine vasopressin (AVP, antidiuretic hormone) is the primary hormone responsible for water homeostasis, acting within the renal collecting ducts to increase water permeability and absorption from the tubular lumen. A deficiency in production or lack of response to AVP is associated with an inability to concentrate urine. This results in polyuria and compensatory polydipsia. Central diabetes insipidus is a complete or partial lack of AVP production. It is most commonly idiopathic, but can be associated with neoplasia, inflammation, trauma or developmental structural defects (see ch. 296).

Nephrogenic diabetes insipidus is defined as a complete or partial lack of response to AVP. Primary nephrogenic diabetes insipidus is an extremely rare congenital disorder resulting in severe polyuria and polydipsia at an early age. Secondary nephrogenic diabetes insipidus is the most common cause of polyuria and polydipsia in small animals. Several diseases and some drugs have the capacity to decrease the responsiveness of renal tubules to vasopressin (see Box 45-1). Multiple additional mechanisms may be responsible for the development of polyuria and polydipsia. Interference with the action of AVP is important because it may lead to hyposthenuric, isosthenuric or minimally concentrated urine.

Osmotic Diuresis

The abnormal presence of osmotically active particles in urine impairs the ability of the kidney to reabsorb water. This mechanism is responsible for polyuria in diabetes mellitus, renal tubular disorders (such as primary renal glycosuria and Fanconi syndrome), chronic kidney disease (CKD), post-obstructive diuresis and following administration of some diuretics such as mannitol. In these conditions, solute abnormally present within tubules drives loss of water; therefore, hyposthenuria is not observed. When large quantities of solute are present, urine may be erroneously assessed as adequately concentrated.

Other Mechanisms

Increased intravascular volume and/or pressure reportedly contribute to polyuria observed during the polyuric phase of acute kidney injury (AKI), the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and in some dogs with pheochromocytoma.[1] Chronic polyuria or IV fluid administration can result in renal medullary solute washout and loss of the osmotic gradient necessary for water reabsorption. Similarly, low renal interstitial tonicity and polyuria can develop in dogs fed severely protein-restricted diets. Polyuria has also been described in dogs with splenic hemangiosarcoma, but the mechanism has not been well characterized.[2]

Diagnostic Approach

The investigation of polyuria and polydipsia is usually straightforward if a logical and sequential approach is used (Figure 45-1).

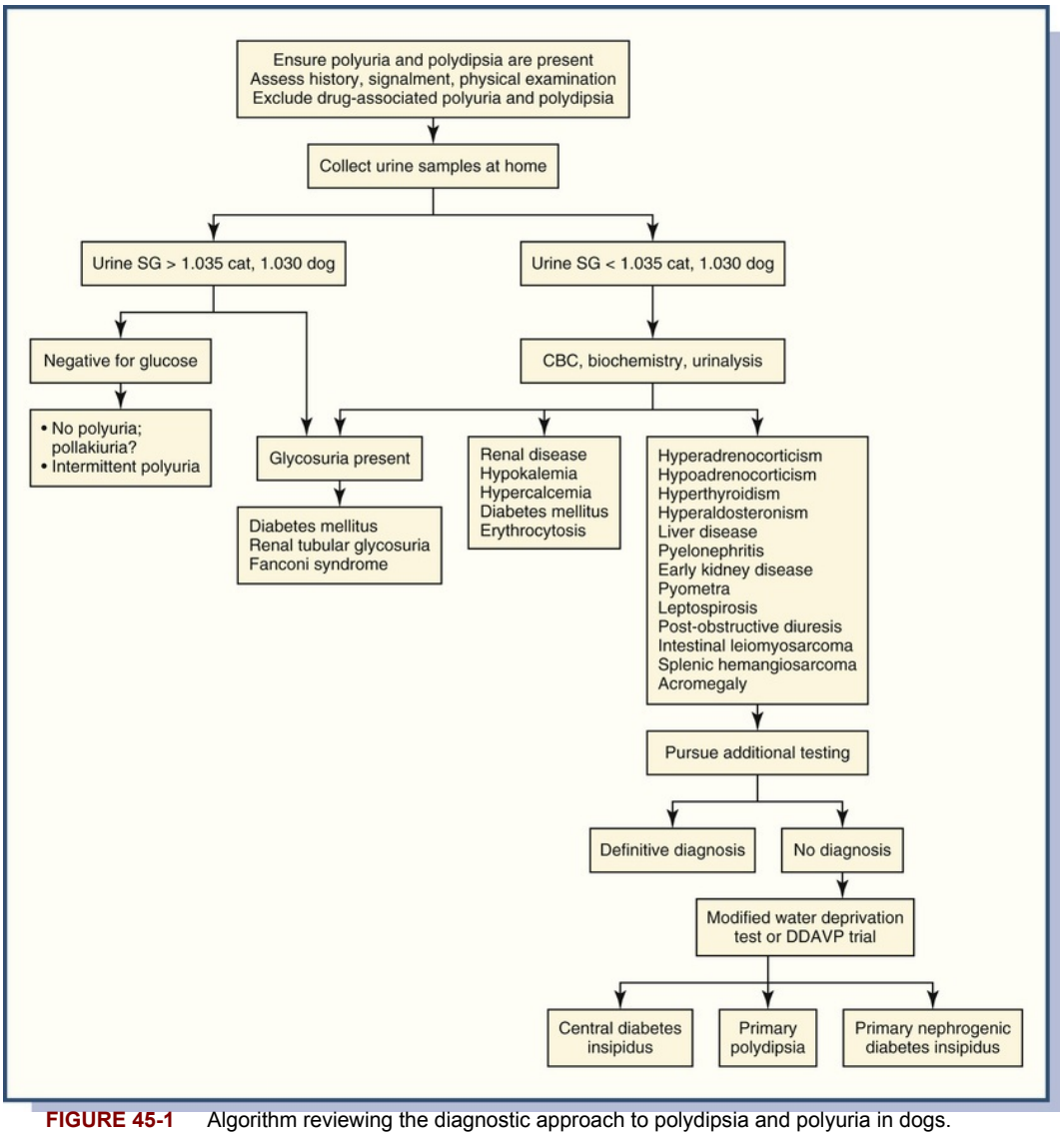

FIGURE 45-1 Algorithm reviewing the diagnostic approach to polydipsia and polyuria in dogs.

Step 1: Ensure Polyuria and Polydipsia Are Present

Before commencing a diagnostic investigation, it is necessary to ensure that polyuria and polydipsia are truly present. A thorough history should be undertaken to distinguish between polyuria, incontinence, nocturia and pollakiuria. Polydipsia without polyuria may be seen in animals with non-urinary water loss, such as diarrhea or excessive panting.

Calculation of water intake during hospitalization is unreliable because "home" drinking patterns may be altered. Measurement at home is possible, but can be difficult in multi-pet households. It is not usually possible to quantify urine volume, although it can be estimated by weighing cat litter in single cat households. Alternatively, the presence of dilute urine is suggestive of polyuria. Urine osmolality is the gold standard measure of concentration but is not widely available. The measurement of urine specific gravity by refractometry is more commonly used. In general, there is good agreement between the two techniques but there is considerable variation between individual refractometers.[3,4] Glycosuria can increase urine specific gravity by approximately 0.004 for each g/dL of glucose in urine. Animals with marked glycosuria may have

specific gravity values consistent with concentrated urine. When measuring osmolality or specific gravity it is essential to ensure free access to water because some animals may retain the ability to concentrate urine when water is withheld.

Unsurprisingly, urine specific gravity values in apparently healthy small animals vary markedly, ranging from 1.006 to 1.050 in dogs and 1.005 to 1.090 in cats.[5,6] In general, urine specific gravity is higher in healthy cats compared to dogs (mean 1.050 in cats versus 1.033 in dogs). In dogs, the specific gravity of morning samples is typically higher than evening samples.[5] One may recommend that an owner collect multiple urine samples at home over several days to determine the ranges of urine specific gravity. In most cases, maintenance of a urine specific gravity greater than 1.030 in dogs and greater than 1.035 in cats is not supportive of polyuria unless due to marked glycosuria, or intermittent polyuria (primary polydipsia or disorders of the regulation of AVP secretion).

Step 2: Signalment, History and Physical Examination

Although unlikely to lead to a definitive diagnosis, breed, age and sex may be useful to refine the differential list for polyuria and polydipsia. For example, hyperthyroidism is common in older cats and pyometra should always be considered in entire females. Primary nephrogenic diabetes insipidus can be excluded unless the animal is very young.

Recently administered drugs should be recorded. Drugs including glucocorticoids, diuretics and phenobarbital cause polyuria and polydipsia in a dose-dependent manner. However, the severity of polyuria in response to drugs can be variable. In particular, polydipsia can be observed at low doses and following topical administration of glucocorticoids. If possible, drugs should be discontinued or the dose reduced prior to additional investigations.

A complete physical examination is essential in all cases. Animals with diseases such as hyperadrenocorticism, hyperthyroidism, pyometra and liver disease may have additional findings that allow rapid refinement of the differential list.

Step 3: Complete Urinalysis

Although urine specific gravity may have been assessed to confirm the presence of polyuria, a complete urinalysis, complete blood count (CBC), and serum biochemistry profile should be performed. Marked hyposthenuria (SG < 1.006) is most commonly due to central diabetes insipidus, primary nephrogenic diabetes insipidus, hyperadrenocorticism, hypercalcemia, primary polydipsia or atypical leptospirosis. The presence of hyposthenuria allows exclusion of CKD and other osmotic causes of polyuria. Identification of glycosuria allows confirmation of diabetes mellitus or renal tubular disease, providing stress hyperglycemia is not present.

The value of performing urine bacterial culture in all animals with polyuria has been questioned.[7,8] However, the sensitivity of urine sediment examination for detection of urinary tract infection is low and the consequences of not identifying infection can be deleterious (see ch. 330).[8] As a result, urine bacterial culture is often recommended early in the investigation of polyuria. This is best performed on urine collected by cystocentesis (see ch. 105).[9,10] Pyelonephritis is a recognized cause of polyuria, and it is common to identify the same pathogen from cystocentesis samples (see ch. 330). Urinary tract infections are common in dogs with either diabetes mellitus or hyperadrenocorticism and in cats with diabetes mellitus, hyperthyroidism or CKD (see ch. 301, 304, 305, 306, and 324).[11,12]

Step 4: CBC, Biochemistry and Electrolyte Assessment

Most animals with hyperadrenocorticism, hyperthyroidism, hyperaldosteronism, liver disease, CKD or pyelonephritis have some changes on physical examination, CBC, serum biochemistry profile and/or serum electrolytes. Results of these blood tests may allow exclusion of erythrocytosis, hypokalemia, hypercalcemia, hypoadrenocorticism, diabetes mellitus and SIADH. CKD as a cause of polyuria can be challenging to confirm. Classically, isosthenuria or minimally concentrated urine is characteristic of renal azotemia and concentrated urine a feature of pre-renal azotemia. However, when polyuria is present, concentration of urine may not be possible despite severe hypovolemia and dehydration. Pre-renal azotemia with "low" urine specific gravity is common in animals with hypoadrenocorticism or hypercalcemia (see ch. 297 and 309). In addition, certain disorders, such as hypercalcemia, hyperthyroidism and hyperaldosteronism, can contribute to the development or progression of kidney disease. Finally, early CKD may be difficult to identify because

polyuria can precede the development of azotemia.

One of the main characteristics of primary polydipsia is the presence of decreased plasma osmolality, a dilutional effect of increased water intake. It is important to ensure free access to water until the time of sampling if plasma osmolality is to be measured. Osmolality is ideally determined from measures of freezing point or "vapor point depression," but this is rarely available in clinical practice. As an alternative, serum osmolality can be estimated based upon the concentrations of the major determinants. The following formula using common units has been shown to be reliable in both cats and dogs even when hyperglycemia or azotemia is present[13,14]:

$$\text{Osmolality (mOsm/kg)} = 2\,((\text{sodium [mEq/L]}) + (\text{glucose [mg/dL]}/18) + (\text{BUN [mg/dL]}/2.8))$$

The presence of low osmolality is supportive of primary polydipsia. Additional investigations are usually performed because primary polydipsia may contribute to the polyuria observed with several diseases including liver disease and hyperthyroidism.

Step 5: Additional Tests

If a definitive diagnosis has not been achieved, the selection of additional tests is largely dependent upon clinical suspicion. Abdominal ultrasonography is often performed because changes may be identified in dogs or cats with adrenal, liver or kidney diseases. It is sensitive for the diagnosis of pyometra, splenic hemangiosarcoma, and intestinal leiomyosarcoma. Although ammonia concentration is reported to be more sensitive than resting bile acid concentration for the diagnosis of a portosystemic shunt, the bile acid stimulation test has been evaluated in a larger range of hepatic diseases, is more widely available and requires less stringent sample handling (see ch. 284).[15]

Testing for hyperadrenocorticism may require ACTH response testing, low dose dexamethasone suppression testing or measurement of the urine cortisol to creatinine ratio. Assessment of thyroid function, initially by measurement of total thyroxine concentration, is indicated in older cats. Pyelocentesis can be performed if pyelonephritis is suspected based upon abdominal imaging or urinalysis results, but a presumptive diagnosis is usually made based upon abdominal imaging and urine culture results. Measurement of glomerular filtration rate is necessary to demonstrate decreased renal function in dogs or cats with early (non-azotemic) renal disease, although the symmetric dimethylarginine (SDMA) blood test may identify CKD earlier in the course of disease than BUN or serum creatinine. Leptospirosis can be confirmed by serum microscopic agglutination or urine polymerase chain reaction tests (see ch. 217). Acromegaly can be investigated by measurement of serum IGF-1 concentration (see ch. 294 and 295). Advanced imaging such as MRI is indicated if brain disease is suspected.

Step 6: Modified Water Deprivation Test or DDAVP Trial

The modified water deprivation test is performed to distinguish between primary polydipsia, central diabetes insipidus and primary nephrogenic diabetes insipidus. It is essential to ensure that all other differential diagnoses have been excluded prior to commencing a modified water deprivation test or DDAVP trial.

The modified water deprivation test is time consuming, labor intensive and associated with a risk of severe hypertonic dehydration, which can be fatal. For these reasons, some authors propose trial therapy with DDAVP as an alternative. Further details relating to these and additional tests are provided in ch. 296.

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CHAPTER 46

Pollakiuria, Stranguria, and Urinary Incontinence

Mary Anna Labato

Client Information Sheets:
Pollakiuria, Stranguria, and Urinary Incontinence: Dogs
Pollakiuria, Stranguria, and Urinary Incontinence: Cats

Disorders of urination are quite common and inappropriate urinations are a leading cause of a pet being presented for medical evaluation or worse, resulting in relinquishment of ownership or euthanasia. Differentiation must be made between pollakiuria, stranguria, and urinary incontinence and polyuria (an increased urine volume). The differential diagnosis for these three conditions is often the result of diseases of the lower urinary tract or genital tract.

Definitions

Incontinence is defined as an involuntary escape of urine during the storage phase of the urinary cycle. This can appear clinically in a variety of ways; however, the most common presentation is intermittent or continuous dribbling of urine combined with episodes of normal voiding. Causes of incontinence include urethral sphincter mechanism incompetence, an anatomic abnormality in the termination of the urethra, inability of the bladder to expand in capacity, spasms of the bladder, and nerve damage[1-4] (see ch. 333).

Urge incontinence or detrusor hyperspasticity or instability is defined as spontaneous and uninhibited detrusor contractions (an overactive bladder). It is characterized by involuntary bladder contractions resulting in the frequent voiding of small volumes of urine. This will result in urinary incontinence, although more commonly clinical signs resemble pollakiuria. Most often animals with detrusor hyperspasticity have an underlying cystitis that must be differentiated from a bacterial infection, inflammation, cystic calculi, polypoid cystitis, neoplasia or drugs and is referred to as urge incontinence. Cases in which no underlying cause is determined are referred to as idiopathic detrusor instability.[4,5] The syndrome is commonly seen in cats with cystitis or feline idiopathic cystitis (FIC) (see ch. 330-335).

Pollakiuria is defined as abnormally frequent passage of urine.[6] Common causes are urinary tract infection, inflammatory diseases of the bladder or urethra, polypoid cystitis, cystic calculi, neoplasia or drugs (see ch. 330-335).

Stranguria is defined as a slow and painful discharge of urine produced by spasmodic muscular contraction of the urethra and bladder.[6] This may be described as difficulty in micturition where the owner describes that urine is being passed only drop-by-drop with pain and even tenesmus. The common causes are similar to those of pollakiuria and include urinary tract infection, inflammatory diseases of the bladder or urethra, polypoid cystitis, cystic calculi, and neoplasia (see ch. 330-335).

Dysuria is defined as difficult or painful urinations and is often used as a "catch all" term to describe stranguria or pollakiuria. It is important in obtaining the history and through observation of the animal urinating to distinguish between these conditions.

Pathophysiology

Bladder function is primarily under the influence of smooth muscle. The body of the bladder contains smooth muscle, referred to as the detrusor muscle. The outlet conduit is comprised of the trigone and proximal urethra. The smooth muscle fibers of the detrusor continue into the proximal urethra, forming a functional internal urethral sphincter. The distal urethra is comprised of striated skeletal muscle and functions as an external sphincter.

During the storage phase of micturition, the bladder functions as a low-resistance, high-capacity vessel. The urethra functions as a high-resistance barrier. The reverse is true during the voiding phase. The bladder acts as a muscular pump and the urethra as a low-resistance vessel.

Nervous Control

Nervous control of the bladder and urethra is a combination of autonomic and somatic interactions.

Parasympathetic innervation is supplied to the detrusor by the pelvic nerve, which arises from sacral spinal cord segments S1-S3. Stimulation of the pelvic nerve results in detrusor contraction.

Sympathetic innervation is supplied via the hypogastric nerve, which is composed of preganglionic fibers exiting the lumbar spinal cord at L1-L4 and synapses in the caudal mesenteric ganglion. Sympathetic innervation is supplied to both the detrusor and urethral smooth muscles and characterizes the storage phase of micturition. Alpha-adrenergic fibers synapse in smooth muscle in both the trigone and urethra. Stimulation results in contraction of these muscles and forms a functional internal urethral sphincter. There are also alpha-adrenergic fibers that have a modulating effect on the external urethral sphincter. Beta-adrenergic fibers synapse in the detrusor muscle; stimulation results in relaxation. Somatic innervation is supplied via the pudendal nerve, which arises from sacral spinal cord segments S1-S3, providing stimulation to the striated urethral musculature.

For voluntary control of micturition to occur, there must be integration between the cerebral cortex, pons, and the spinoreticular tract. A second pathway from the cerebral cortex to the sacral nuclei coordinates voluntary sphincter control. Additionally, cerebellar neurons inhibit nervous transmission to the reticulospinal pathways in the pons.

Sensory receptors are located in the bladder mucosa and are numerous at the ureterovesicular junction and in the trigone. Inflammation of the mucosa or bladder contraction may cause pain, an urgency to urinate (even if the bladder volume is small), detrusor spasm, or a "burning" sensation. Sensory receptors in the urethra respond to flow, urethral sensation and traction on the trigone. Inflammation or irritation of the urethra causes pain, burning sensation and spasms of the urethral sphincter. In male dogs, prostatic disease (see ch. 337) usually involves the urethra and bladder, producing dysuria.[7]

Causes of Clinical Signs

Diseases of the lower urinary tract (urethra and bladder) or lower genital tract (prostate or vagina) may result in mucosal irritation or inflammation and result in frequent or painful urinations. Many of the causes of pollakiuria (Box 46-1) and stranguria (Box 46-2) are associated with pyuria, hematuria or both (see ch. 47). Many general disorders such as urolithiasis, urinary tract infections, urethral diseases, prostatic diseases and neoplasia are discussed in more detail in their respective chapters (see ch. 329-332 and 334-337). The main differential diagnosis for urge incontinence (Box 46-3) is cystitis or, in cats, feline idiopathic cystitis (see ch. 333 and 334). Once other causes are ruled out, a diagnosis of detrusor hyperspasticity may be established. This is confirmed by a urethral pressure profile demonstrating the presence of uninhibited detrusor contractions, or response to treatment with an antispasmodic if a urodynamic study is unavailable.

Box 46-1

Causes of Pollakiuria

Infection: bacterial, mycoplasma, viral, fungal, parasitic (bladder, prostate)
Inflammation: polypoid cystitis, pyogranulomatous cystitis, granulomatous urethritis, follicular vaginitis
Urocystolithiasis
Neoplasia (example: transitional cell carcinoma, prostatic adenocarcinoma, vaginal leiomyoma/sarcoma)
Detrusor atony (partial obstruction)
Urethral stricture
Feline idiopathic cystitis (FIC)
Chemical/drugs (example: cyclophosphamide)
Anatomic abnormalities (perineal hernia with retroflexed bladder, spay granuloma or uterine stump disease [infection, mass])
Iatrogenic: urethral irritation secondary to catheterization, palpation, voiding urohydropropulsion, overdistension of bladder secondary to flushing procedures

Box 46-2

Causes of Stranguria

Cystitis: infectious vs. inflammatory
Urethritis: infectious vs. inflammatory
Urocystolithiasis
Vaginitis: follicular (inflammatory) vs. infectious
Neoplasia (urethral: transitional cell carcinoma; prostatic: adenocarcinoma; vagina: leiomyoma/sarcoma)
Prostatic disease: prostatitis, prostatic abscess, neoplasia
Trauma, foreign body
Feline idiopathic cystitis
Ruptured bladder
Urethral stricture

Box 46-3

Causes of Urge Incontinence

Detrusor hyperspasticity (idiopathic)
Cystitis/urethritis: infectious vs. inflammatory
Anatomical abnormality such as ectopic ureter(s)
Pelvic bladder, urethral dysplasia
Neurological abnormality: upper motor neuron bladder
Urethral sphincter mechanism incompetence
Urethral stricture

Diagnostic Workup (Figure 46-1)

A complete history and physical examination are essential to the diagnostic workup for any patient presenting with pollakiuria, stranguria or urge incontinence. This should include the reproductive status; age at neutering; age at the onset of the problem; previous medical problems, especially those involving the urogenital system; previous history of trauma; and an accurate description of the abnormality. How frequent is urination? What is the volume of urine that is being passed? Pollakiuria may be associated with large or small volumes of urine. Is there stranguria, and if so, is any urine being passed? Stranguria is more frequently associated with voiding of small amounts of urine, or the owner may report that a normal volume is ultimately produced after multiple attempts to urinate with small volumes passed each time. If there is incontinence (Figure 46-2), is it continuous or intermittent? Is the animal aware of the incontinence? Does it occur only at rest/asleep or while the animal is awake and moving? Urge incontinence is most frequently associated with spontaneous voiding while the dog or cat is awake. Owners may report it as purposeful voiding.

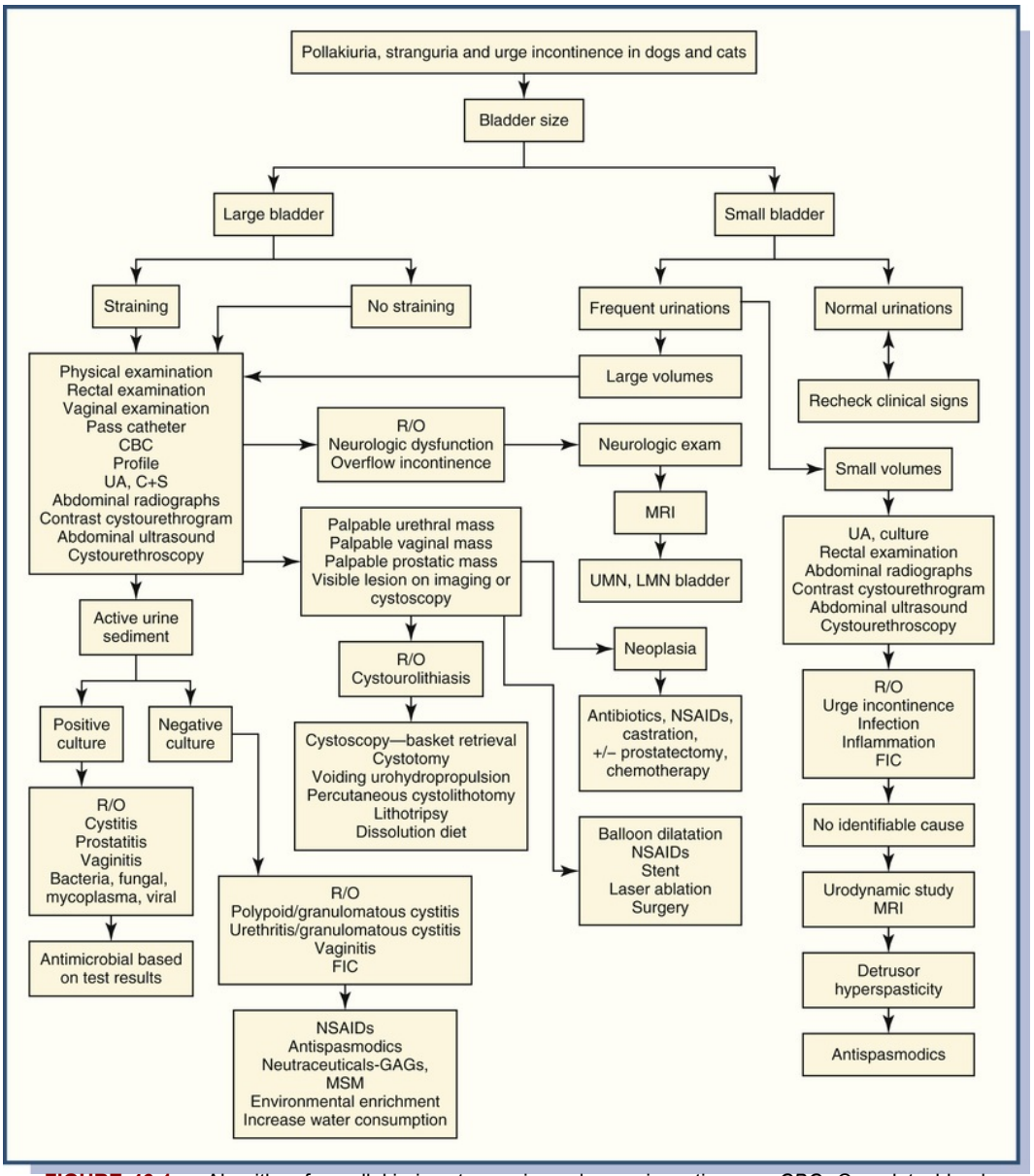

FIGURE 46-1 Algorithm for pollakiuria, stranguria and urge incontinence. *CBC,* Complete blood count; *C+S,* bacterial culture and sensitivity; *FIC,* feline interstitial cystitis; *GAG,* glycosaminoglycan; *LMN,* lower motor neuron; *MRI,* magnetic resonance imaging; *MSM,* methylsulfonylmethane; *NSAID,* nonsteroidal anti-inflammatory drug; *R/O,* rule out; *UA,* urinalysis; *UMN,* upper motor neuron.

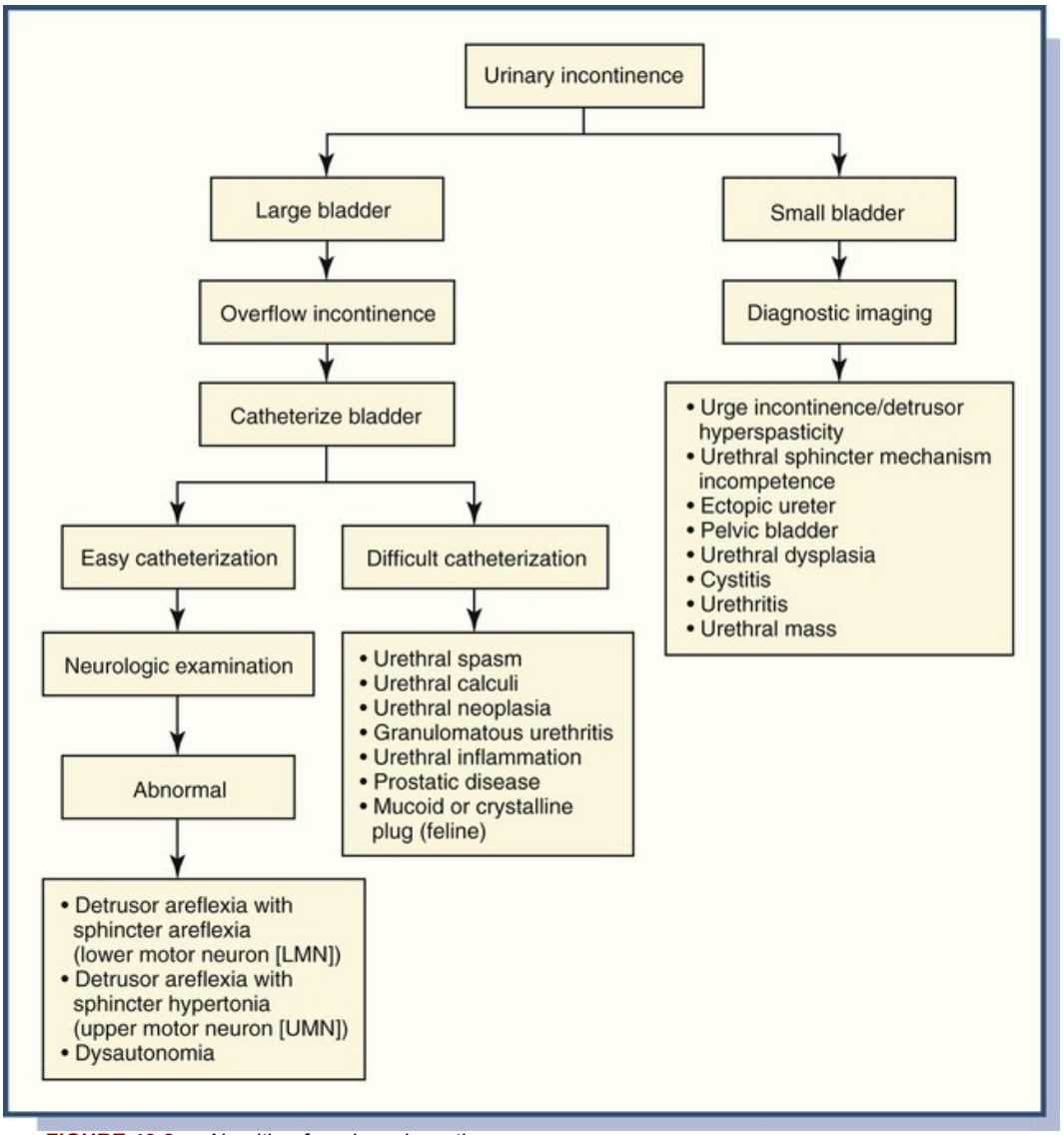

FIGURE 46-2 Algorithm for urinary incontinence.

Complete physical (see ch. 2) and neurologic (see ch. 259) examinations should be performed, with particular attention paid to the urogenital system. The bladder should be palpated carefully before and immediately after voiding to evaluate the extent of distension, tone, and the ease with which the bladder may be expressed manually. Lower motor neuron lesions generally are associated with easy manual expression and reduced sphincter tone. Upper motor neuron lesions generally are associated with difficult manual expression and increased sphincter tone. In the neurologic examination, the innervation of the urogenital system should be evaluated. The perineal reflex evaluates the pudendal nerve. The bulbospongiosus reflex evaluates the integrity of both the pudendal nerve and the sacral spinal segments. Pollakiuria is commonly associated with a moderate to small bladder and with normal to small amounts of urine being passed. Stranguria is commonly associated with a moderate to large bladder if there is a partial obstruction and normal, to moderate to small amounts of urine being passed if the stranguria is associated with infection or inflammation without an obstructive process. With urge incontinence, the bladder is often found to be small on palpation.

A rectal examination should be done to evaluate the prostate gland, pelvic diaphragm, and anal tone. Observe the animal urinating (Video 46-1) to verify the micturition abnormality. The residual urine volume should be measured. The animal is allowed to void until urine is no longer passed, the bladder is catheterized, and the volume of any remaining urine is measured. In a normal animal, the residual volume should not exceed 0.4 mL/kg. Catheterization of the bladder also assesses the patency of the urethra. This will help to rule in or rule out a complete or partial obstruction secondary to calculi, stricture or neoplasia.

Ultimately, a contrast cystourethrogram, ultrasound examination or cystoscopy may need to be performed to further characterize the lesion unless it is the result of a radiopaque calculus.

The diagnostic workup should include a complete blood count and serum chemistry profile to assess the patient's overall health status. Typically, the serum chemistry profile will be normal if there is infection or inflammation within the lower urinary tract. Obstructive lesions in the lower urinary tract may result in azotemia, hyperkalemia and hyperphosphatemia. If there is infection within the upper urinary tract, there may be a concurrent azotemia. A complete blood count may demonstrate a leukocytosis if upper tract infection is present, but not typically with lower tract infection except in cases of acute prostatitis or a prostatic abscess.

A urinalysis is one of the most important tests that can be performed (see ch. 72). Hematuria, pyuria and proteinuria indicate inflammation within the urinary tract. These are nonspecific findings, which may be associated with both infectious and noninfectious processes. It may be possible to visualize bacteria, fungal organisms or parasitic ova while examining the urine sediment. The presence of these organisms, however, may not represent infection. Quantitative urine culture and sensitivity are the definitive way of identifying actual infection. High bacterial numbers in a properly collected sample indicates true infection. Small numbers may indicate contamination.

Crystalluria may be seen in normal patients, those with urolithiasis, or those with disorders unassociated with the urinary tract such as with portosystemic shunts. The presence of crystals in urine sediment must be interpreted cautiously. Urine is best evaluated for the presence of crystals shortly after being obtained. In cats with feline idiopathic cystitis, crystalluria, hematuria and proteinuria occur, while pyuria of any significance is uncommon.[8]

The presence of neoplastic cells in urine sediment indicates the presence of urinary tract neoplasia. However, it may be difficult to diagnose neoplasia based solely on urine sediment examination. Atypical epithelial cells arising from inflammation or extremes in urine pH or osmolality are difficult to differentiate from neoplasia.[8] Cytological examination of prostatic fluid may be helpful in identifying prostatitis, abscess or neoplasia.

Imaging of the urinary tract is especially beneficial in differentiating the various causes of pollakiuria, stranguria and urge incontinence. Survey radiographs are helpful in identifying urocystolithiasis. Contrast radiographs, such as an intravenous pyelogram or double contrast cystourethrogram, may be helpful in determining the presence of calculi or a space-occupying mass, especially those causing a partial obstruction. Abdominal ultrasound is a helpful diagnostic tool, providing the ability to visualize wall thickness, presence or absence of cystouroliths, and soft tissue masses within the bladder or portions of the urethra (see ch. 88). Finally, cystoscopy (Figure 46-3, *A* and *B*) may be used to visualize the urethra, bladder and in females the vagina (see ch. 108). Biopsy and brush cytology may be performed via cystoscopy to help in identifying the underlying cause of the dysuria.

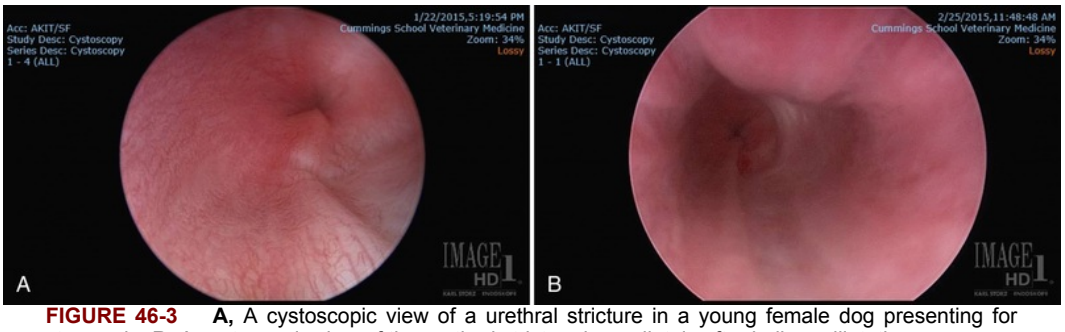

FIGURE 46-3 **A,** A cystoscopic view of a urethral stricture in a young female dog presenting for stranguria. **B,** A cystoscopic view of the urethral stricture immediately after balloon dilatation.

While causes of pollakiuria and stranguria are quite common and often are a relatively easy diagnosis based upon history, signalment, physical exam findings and diagnostic workup, urge incontinence is a diagnosis of exclusion. Urge incontinence may be diagnosed via a good history, observation of the animal urinating, imaging modalities, and urodynamic studies such as a cystometrogram and urethral pressure profile. Causes of an inflammatory cystitis or urethritis must be eliminated as the source of urgency. If it is possible to perform a urodynamic study, uninhibited contractions of the detrusor will confirm detrusor hyperspasticity. Otherwise, response to therapy will be the diagnostic test and treatment of choice.

Treatment

Treatment of pollakiuria, stranguria, and urge incontinence will be dictated by the underlying cause. Treatment in detail will be discussed in later chapters of this book that specifically deal with the underlying etiologies (see ch. 330-335).

Pollakiuria arising from a urinary tract infection is relatively easy to diagnose and treatment with an antibiotic should be based on culture and sensitivity results. If the underlying cause of the pollakiuria is from an inflammatory condition, treatment with anti-inflammatory agent such as a nonsteroidal anti-inflammatory drug and other analgesic agents, such as opioids, may be necessary if there is considerable pain associated with the stranguria. If urocystoliths are the source of the pollakiuria, then a variety of options is available with treatments incorporating antibiotics and dissolution diets, to minimally-invasive procedures such as voiding urohydropropulsion (see ch. 107), or cystoscopy and basket retrieval (see ch. 124), or lithotripsy or surgery. Neoplasia may be treated with chemotherapy, surgery, radiation therapy or a combination of modalities depending upon the type of cancer (see ch. 351). Diseases of the prostate or vagina may be treated with a range of modalities depending upon the underlying cause but may involve medical management (hormonal replacement therapy, hormonal limiting therapy), to medical management of prostatic infections or vaginitis, to surgical interventions (see ch. 44 and 337).

Treatment for the multiple causes of stranguria will range from medical management utilizing antibiotics, antispasmodics, and interventional therapy (laser lithotripsy/ablation, stent placement, cystostomy tubes; see ch. 124) to the management of cancer.

Identifying and then addressing the underlying cause best treats urge incontinence. If the problem is secondary to idiopathic detrusor hyperspasticity, then an antispasmodic agent such as flavoxate hydrochloride, or oxybutynin, tolterodine or dicyclomine is indicated. If the condition is recognized in cats with FIC, then treatments may range from administration of an antispasmodic for the bladder to a smooth muscle relaxant such as prazosin for the proximal urethra and diazepam for the skeletal muscle component of the distal urethra, to pain medication such as buprenorphine, dietary change to a canned food product, increased water consumption, glycosaminoglycans, to environmental enrichment.

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CHAPTER 47

Hematuria and Other Conditions Causing Discolored Urine

Thierry Francey

Client Information Sheet: Hematuria and Other Conditions Causing Discolored Urine

Overview

Visual inspection of urine is the first step in a standard urinalysis (see ch. 72) and it aims at evaluating color and turbidity. More than being just a leftover of uroscopy, macroscopic evaluation of urine can provide useful clinical information. Further, abnormal urine color is occasionally recognized by the pet owner and it may represent the only reason for a consultation, especially when the urine is overtly red. Abnormal urine color indicates presence of endogenous or exogenous pigments and is usually associated with a clinical problem. However, significant systemic or urinary tract disease may coexist with normal colored urine. Urine discoloration provides nonspecific information, but it should always prompt the clinician to pursue a thorough history, including questions related to diet, medications, environment, and collection technique. Physical examination is also critically important. We recommend examination of the urogenital areas last, in order to ensure completion of a thorough examination before approaching the "problem area." Laboratory testing is often warranted, including detailed urine sediment examination. Knowledge of urine color may also be important in interpreting dipstick colorimetric test results since discolored urine may interfere with the assays.

Normal Urine

Normal urine is typically transparent and light yellow, yellow, or amber in color. The intensity of the yellow color of normal urine varies primarily with degree of urine concentration or dilution (Figure 47-1, *A*). The yellow color is mainly associated with renal excretion of plasma urochrome, a yellow sulfur-containing oxidation product of a colorless urochromogen. The daily urinary excretion of urochrome is relatively constant and the intensity of urine color provides an estimate of the degree of urine concentration. Highly concentrated urine will thus be amber in color, while dilute urine may be light yellow or almost colorless. Production of urochrome does depend to some extent on the metabolic rate. Increased quantities of urochrome are excreted as a result of fever, catabolism, or starvation. Urochrome may further darken when exposed to light, giving a false impression of highly concentrated urine. Small quantities of the endogenous orange-brown heme degradation pigment urobilin may contribute further to the yellow color of urine. Urobilin is the oxidation product of its colorless precursor urobilinogen, a bacterial degradation product of intestinal bilirubin reabsorbed into the bloodstream. An increased bilirubin concentration in the urine may give it an intense yellow color, similar to that of concentrated urine (see Figure 47-1, *B*). When exposed to light, it may oxidize and turn brown to almost black.

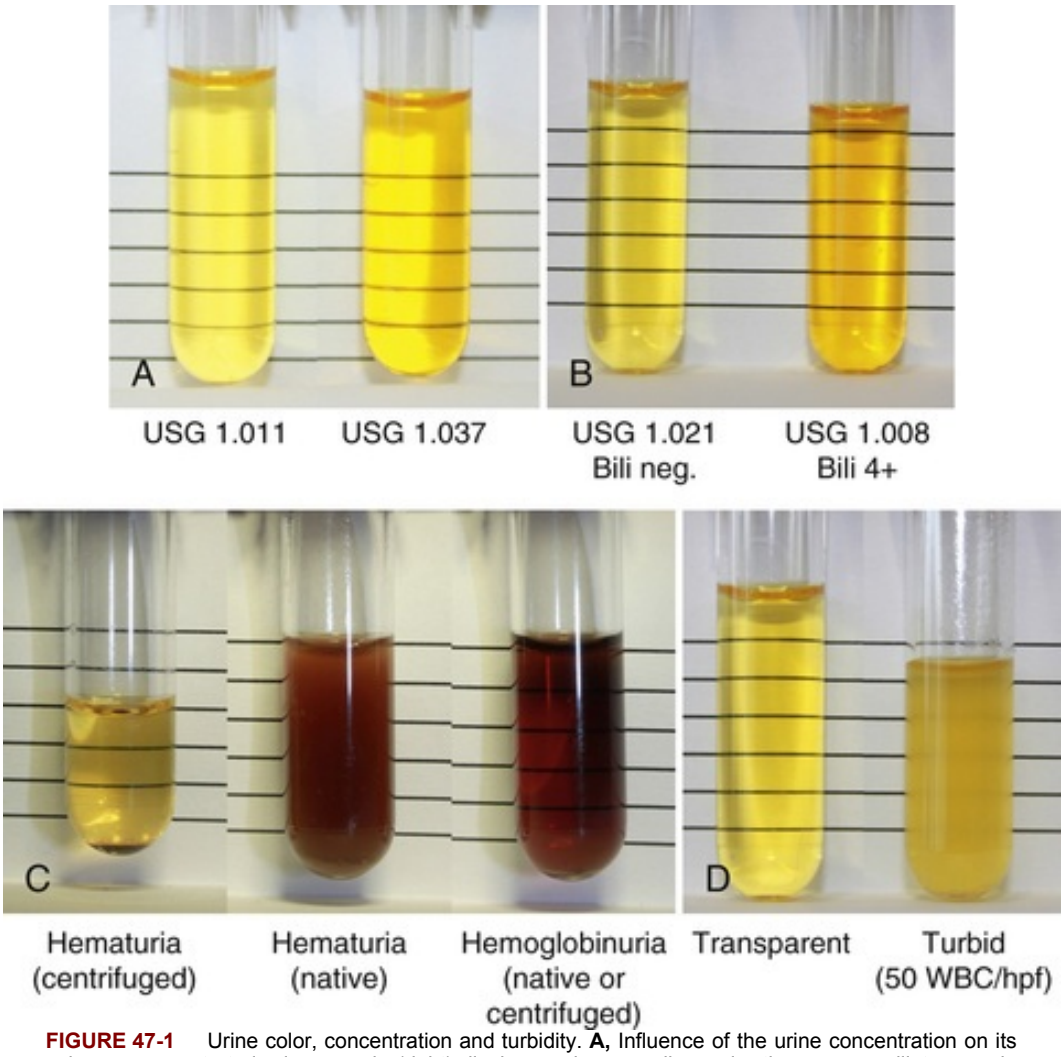

FIGURE 47-1 Urine color, concentration and turbidity. **A,** Influence of the urine concentration on its color—a concentrated urine sample (right) displays a deeper yellow color than a more dilute sample (left), due to different concentrations of the endogenous pigment urochrome. **B,** The presence of bilirubinuria (right) gives the urine sample a deep yellow to amber color and thus the wrong impression of concentrated urine. **C,** The visual inspection of a native red-brown urine sample often allows the distinction between hematuria (center, turbid) and hemoglobinuria (right, transparent). Centrifugation further indicates a clear supernatant on a red blood cell pellet in hematuria (left) and an unchanged sample in hemoglobinuria. **D,** Milky turbid appearance of a urine sample from a dog with urinary tract infection and pyuria (right) compared to a normal transparent urine sample with the same specific gravity (1.020). *Bili,* Bilirubin; *USG,* urine specific gravity; *WBC,* white blood cells.

Discolored Urine

Any urine color other than yellow or amber is abnormal. There are many potential causes of discolored urine (Table 47-1). The most common abnormal urine colors in dogs and cats are red, brown, or black. These colors may be caused by hematuria, hemoglobinuria, myoglobinuria, and possibly bilirubinuria (Figures 47-1, *C* and 47-2).[1-3]

TABLE 47-1

Potential Causes of Discolored Urine[1]

URINE COLOR	MOST RELEVANT CAUSES (DESCRIBED IN ANIMALS)	FURTHER CAUSES (DESCRIBED ONLY IN HUMANS)
Colorless	Very dilute urine (diuretics, diabetes	

	mellitus, diabetes insipidus, glucocorticoid excess, fluid therapy, overhydration)	
Yellow or amber	Urochrome, urobilin	
Deep yellow	Highly concentrated urine Phenolsulfonphthalein (in acidic urine)	Quinacrine, nitrofurantoin, phenacetin, riboflavin (large quantities)
Orange-yellow	Highly concentrated urine, bilirubinuria Excess urobilin, phenazopyridine	Orange food dye; 2, 4-D; acetazolamide; fluorescein sodium; flutamide; phenacetin; quinacrine; sulfasalazine
Yellow-brown or green-brown	Bile pigments	
Red, pink, red-brown, red-orange, or orange	Hematuria, hemoglobinuria, myoglobinuria, porphyrinuria Congo red, rifampicin, doxorubicin, phenolsulfonphthalein (in alkaline urine), neoprontosil	Chronic heavy metal poisoning (lead, mercury) Red food dye, food pigments (rhubarb, beets, blackberries), acetazolamide, bromsulphalein, carbon tetrachloride, phenytoin, emodin, eosin, phenazopyridine, phenindione, phenothiazine, rifabutin, warfarin
Brown	Methemoglobinuria, copper toxicosis, fecal contamination (rectal-urinary fistula) Melanin	Anthracin, bismuth, clofazimine, chloroquine, fava beans, furazolidone, mercury, methocarbamol, metronidazole, naphthalene, nitrofurantoin, phenacetin, primaquine, rhubarb, sorbitol, sulfasalazine, sulfonamides
Brown to black (brown or red-brown when viewed in bright light in thin layer)	Methemoglobinuria, hemoglobinuria, myoglobinuria, bile pigments Melanin	Aniline dyes, chlorinated hydrocarbons, homogentisic acid, naphthalene, nitrites, nitrofurantoin, phenolic compounds, thymol
Blue	Methylene blue, mitoxantrone	*Pseudomonas* infection Blue food dye, indigo carmine and indigo blue dyes Amitriptyline, anthraquinone, chlorophyll, indicans, rhubarb, toluidine blue, triamterene
Green	Bilirubinuria, biliverdin, urate crystalluria Methylene blue, dithiazanine	Green food dye, indigo blue, Evans blue Amitriptyline, anthraquinone, phenol, riboflavin, thymol, triamterene
Milky white	Lipiduria, pyuria, crystalluria	

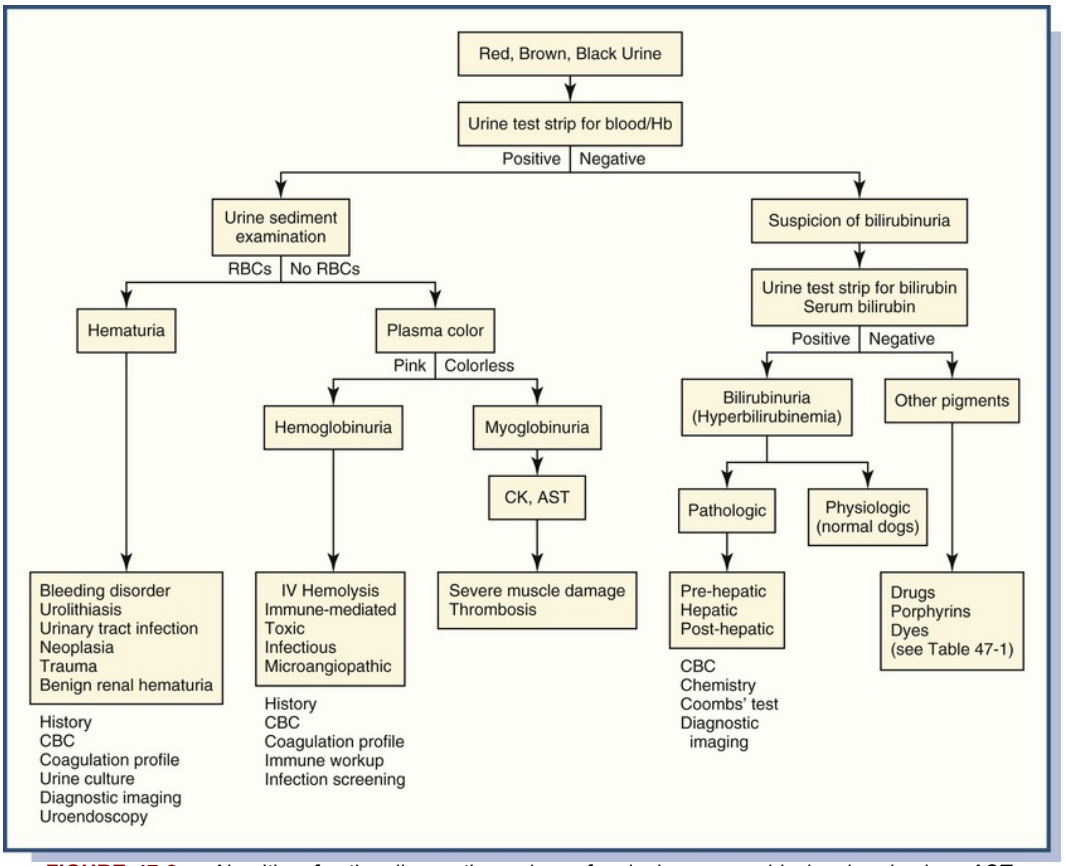

FIGURE 47-2 Algorithm for the diagnostic workup of red-, brown-, or black-colored urine. *AST,* Aspartate aminotransferase; *CBC,* complete blood count; *CK,* creatine kinase; *Hb,* hemoglobin; *RBCs,* red blood cells.

Pale Yellow Urine

Pale yellow or clear urine may be normal or indicative of polyuria (see Figure 47-1, *A*; ch. 45 and 72). Pale urine usually indicates a urine specific gravity of less than 1.015. Urine may be appropriately dilute if it is associated with recent consumption of water, administration of fluids, consumption of a low-protein or high-salt diet, or administration of diuretics, barbiturates, or glucocorticoids.[4] Urine would be considered inappropriately dilute in the presence of dehydration, indicating failure of physiological water-sparing mechanisms. Renal diseases, hyperthyroidism, diabetes insipidus, hyperadrenocorticism, hypoadrenocorticism, pyometra or other infections with lipopolysaccharide-producing bacteria, hypokalemia, and hypercalcemia may be associated with persistently dilute urine. However, dogs and cats with severe polyuria from uncomplicated diabetes mellitus usually have urine specific gravities of 1.025 to 1.035 due to the presence of glucose in the urine. Their urine often appears deeper yellow in color.

A simple test to determine whether polyuria is persistent is to determine the specific gravity of several owner-collected morning urine samples or to compare the specific gravity from different urine samples collected throughout the day. Based on dilute urine, the clinician may recommend a serum biochemical analysis and complete urinalysis. A complete blood count, abdominal imaging, measurement of serum thyroxine concentration, adrenal function testing, or monitoring urine specific gravity after several days of desmopressin administration may be warranted (see ch. 45 and 296).

Red, Brown, or Black Urine

Freshly collected urine that is red, brown, or black suggests the presence of blood, hemoglobin, myoglobin, or some of their degradation products (see Figure 47-1, *C*). Urine concentration, pH, and time in contact with blood can affect color. Red blood cells progressively disintegrate and release hemoglobin in urine. This may be oxidized to methemoglobin and result in a brown or black urine color. A thin layer of black urine viewed under a bright light usually appears brown or deep reddish-brown. Hematuria, hemoglobinuria, and

myoglobinuria cause the test for blood on reagent strips to read positive. "Blood" indicates presence of a globin with a heme group. Additional investigations are required to differentiate these possibilities (see Figure 47-2).[2,4]

A negative reagent strip test for blood in red, black or brown urine suggests presence of a chromogen other than hemoglobin or myoglobin.[1,5] Oxidized **bilirubin** should be ruled out first. An intense yellow coloration of plasma suggests hyperbilirubinemia, which can be quantified by measuring serum bilirubin concentration. Hyperbilirubinemia may result from pre-hepatic hemolysis, liver failure, or post-hepatic obstruction or rupture of the biliary tract (see ch. 53, 143, and 145).

A positive reagent strip test for blood should be followed by analysis of the urine sediment. If the discoloration is due to **hematuria,** there will be numerous red blood cells and increased turbidity. In contrast, urine remains transparent when color change is due to hemoglobinuria (see Figure 47-1, *C*). If no red blood cells are present on microscopic examination of the urine sediment, hemoglobin or myoglobin should be suspected. Examination of the plasma color may aid in differentiating these explanations. If the discolored urine is due to **myoglobin,** the plasma will usually be clear because myoglobin is not bound significantly to proteins and it is rapidly excreted. Myoglobinuria is indicative of severe muscle damage and serum creatine kinase (CK; see ch. 66) activity is usually markedly increased. Concentration of this muscle enzyme is typically used to confirm myoglobinuria rather than the more complex characterization of the urinary heme proteins using immunoassays. The serum CK activity offers the additional advantage of being cleared slowly from the blood which may allow a delayed diagnosis.

If plasma from a non-traumatic venipuncture sample is pink, it is suggestive of **hemoglobin.** When present in small quantities in the circulation, hemoglobin is bound to haptoglobin, hindering its glomerular filtration. When the binding capacity of haptoglobin is exceeded, however, free hemoglobin is filtered and appears in the urine. Hemoglobinemia and hemoglobinuria are therefore indicative of significant intravascular hemolysis, resulting from immune-, parasite-, or drug-mediated destruction of red blood cells or from fragmentation due to microangiopathic conditions. A marked red-brown discoloration of the urine may also cause false-positive reactions on other urine dipstick test pads and this should be taken in consideration in their interpretation (see ch. 72).

Milky White Urine

Milky white–colored urine may be due to presence of white blood cells (pyuria), lipid, or crystals. The more concentrated the urine, the more opaque it may appear. The presence of pyuria secondary to bacterial urinary tract infection is the most common cause of milky white urine (see Figure 47-1, *D*). However, pyuria may also occur due to non-infectious inflammations. The presence of lipid droplets in the urine of healthy animals is usually a microscopic observation. However, lipid droplets could contribute to urine turbidity. Lipiduria may be increased in cats with hepatic lipidosis. Crystalluria, if heavy and present in a concentrated urine sample, may also result in milky white urine color. Microscopic examination of urine sediment will aid in the differentiation of these causes.

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SECTION III

Differential Diagnosis for Physical Examination Abnormalities

OUTLINE

Chapter 48 Fever
Chapter 49 Hypothermia
Chapter 50 Pallor
Chapter 51 Hyperemia
Chapter 52 Cyanosis
Chapter 53 Jaundice
Chapter 54 Petechiae and Ecchymoses
Chapter 55 Abnormal Heart Sounds and Heart Murmurs
Chapter 56 Pulse Alterations

CHAPTER 48

Fever

Ian K. Ramsey, Séverine Tasker

"Fever is a mighty engine which Nature brings into the world for the conquest of her enemies."
Thomas Sydenham (1624-1689)

Client Information Sheet: Fever

Defining Fever, Hyperthermia, and Fever of Unknown Origin

Body temperature can be increased as a result of fever (pyrexia) or hyperthermia (Figure 48-1). For the purposes of this chapter, fever is defined as an increased body temperature associated with a raised (and often more variable) thermoregulatory set point in the anterior hypothalamus that is secondary to the release of pyrogens (fever-inducing substances). Hyperthermia, in contrast, is not associated with an alteration in the thermoregulatory set point. The hyperthermic animal will therefore make more efforts (physiologically and behaviorally) to cool itself at a given temperature when compared to a pyrexic animal at the same temperature. Hyperthermia most frequently arises from exposure to an increased environmental temperature, which is addressed in ch. 134. Hyperthermia also can arise due to exercise (especially in hot, humid environments by overweight dogs or those with respiratory impairment), seizures, hypermetabolic disorders (e.g., hyperthyroidism, hypocalcemia), certain medications (e.g., opioids and ketamine in cats, selective serotonin reuptake inhibitors in dogs and cats), intoxications (e.g., cocaine in dogs), malignant hyperthermia, and stress.[1-6]

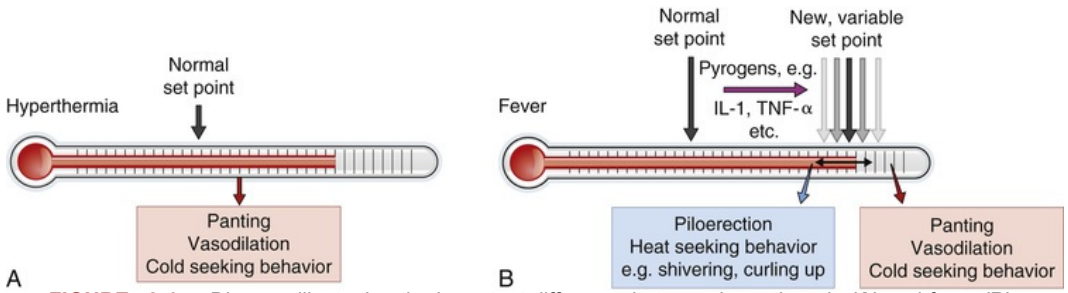


FIGURE 48-1 Diagram illustrating the important difference between hyperthermia **(A)** and fever **(B)**. Set point refers to thermoregulatory set point in the hypothalamus. *IL-1*, Interleukin-1; *TNF-α*, tumor necrosis factor-alpha.

Fever of unknown origin (FUO) is a term used relatively frequently in veterinary medicine[7,8] and definitions vary, as they have done in human medicine.[9,10] Extrapolating from the definition of classic FUO in humans,[9] FUO in dogs and cats could be defined as a temperature of >39.2° C (102.5° F) of at least 3 weeks' duration in which no obvious cause is apparent following at least 3 visits to the veterinarian and/or 3 days of hospitalization including a basic evaluation of history, clinical signs, clinical examination and minimal diagnostic testing (complete blood count, serum biochemistry profile, urine analysis). Additionally, FUO in dogs and cats often is only considered after a short (e.g., 7-10 days) course of an antibacterial agent to address possible bacterial infections has not resolved the fever.[5,11-13] In human medicine, over 200 diseases have been associated with FUO.[10] However, as a cause is found in many so called "FUO" cases, and as the causes of fever and FUO are not sufficiently different, it is suggested that cases of FUO should be considered within a

continuum of "fever." Perhaps, in the future, the term FUO should be reserved for those cases that truly remain unknown, despite the extensive investigations for fever outlined below. This chapter will focus on the pathophysiology, differential diagnoses, and approach to fever, including FUO, in dogs and cats.

Pathogenesis of Fever

Fever is an important part of the nonspecific adaptive response of the body to a disease process. The response has benefits and risks, the balance of which changes with time and the particular process and patient.[14] Similar to other adaptive processes, the animal usually gains short-term benefits from the process but in the long term, starts to develop unwanted complications.

Pyrogens may be classified into internal (endogenous) and external (exogenous) groups; however, exogenous pyrogens often exert most of their pyrogenic activity via endogenous routes.[15] Endogenous pyrogens, particularly the cytokines interleukin (IL)-1, IL-6 and tumor necrosis factor alpha (TNF-alpha), are released from neutrophils, monocytes, and many other cells, and they activate the arachidonic acid cascade.[16] This arachidonic acid cascade increases prostaglandin E2 concentrations, which acts on thermoregulatory neurons and raises the hypothalamic set point. More recent research has also suggested an important role for neural rather than humoral pathways for the initiation of the febrile response.[17]

Equally, the body produces endogenous antipyretics, including glucocorticoids, neuropeptides and certain cytokines (such as IL-10), to protect the body against the effects of fever.[18] It is even possible that at high temperatures, pyrogens (such as TNF-alpha) act as cryogens, limiting the severity of fever.[14] For these reasons, true fevers rarely exceed 41.1° C (106° F).

Benefits of Fever

In evolutionary terms, fever is a very old (at least 360 million years) response by the body to infection.[16] The conservation of this response suggests that possessing the ability to develop a fever confers significant evolutionary advantage. The proposed benefits of fever include the following:

- *Improved survival:* Several studies, both in human medicine and experimental, have shown that those patients that develop a fever are less likely to die and the higher the fever, up to a limit, the better the chances of survival.[19] A good veterinary example is the association between survival and the development of fever in rabbits with *Pasteurella* infections.[20] However, not all studies in human medicine have shown similar results, resulting in controversy.
- *Shorter length of illness:* Several studies have shown that fever reduces the symptomatic phase of illness and may reduce the time taken for viral and parasitic excretion.[21,22]
- *Improved immune system function:* Neutrophil mobility and phagocytic abilities initially are enhanced by fever, as are macrophage function and lymphocyte proliferation.[16] However, not all immune cell functions are improved by fever, and natural killer cells are less active at fever temperatures.[16] At temperatures higher than 41.1° C (106° F), neutrophil and monocyte functions are impaired.[16]
- *Production of heat shock and acute phase proteins:* These are important free-radical scavengers as well as preservers of cellular components.[23]

One widespread fallacy is that fever kills bacteria. In fact, the bacteria most commonly associated with infections continue to multiply and survive well above temperatures that would prove fatal to an animal.[20] Fever has evolved as a *response to* infection rather than occurring as a result of infection: the host is trying to improve its response to infection rather than the higher temperature itself directly killing the bacteria.

Costs of Fever

The proposed costs of fever include:

- *Increased number and severity of clinical signs,* leading to a reduction in animal welfare and increased owner concerns. However there is very little evidence that mild fever is actually harmful.[24]
- *Increased metabolic rate:* Typically the resting energy requirement is increased up to 1.3 times.[25,26] If this exceeds the energy intake of the host, energy deficits will occur in critical tissues, with increased oxygen demand and increased carbon dioxide production.

- *Reduction in some constitutive processes:* For example, hemoglobin's oxygen-binding affinity is reduced by fever, so at the very time that the peripheral tissues have an increased oxygen demand, the hemoglobin is less able to deliver oxygen.[27]

The published evidence to date suggests the benefits of fever often are limited to those with less severe disease, and in more severe diseases or more severe (or prolonged) fevers, the adverse effects start to outweigh these benefits.[19]

Measurement of Temperature

Invasive contact devices such as esophageal and pulmonary artery thermistors are considered the gold standard for assessing core body temperature,[28] but these are not suitable for conscious veterinary patients and are reserved for anesthetized or critical care cases.[29] Good agreement has been shown between rectal and core body temperatures in dogs.[29,30] Similar studies have not been performed in cats. However, it can be difficult to obtain rectal temperatures, particularly in fractious patients or in those with rectal or perianal disease. Rectal thermometers also are a potential source of cross-contamination and rectal injury. In addition, the accuracy and repeatability of rectal temperature measurements can be negatively affected by depth of measurement, the presence of feces, and conditions affecting local blood flow.[30,31]

There have been several studies examining the validity of measuring auricular or axillary temperatures as an alternative to rectal temperatures.[29-38] Auricular temperatures may be measured using dedicated thermometers, which use pyroelectric sensors to measure infrared radiation emanating from the tympanic membrane (TM). Auricular TM thermometers are quicker and better tolerated than rectal thermometers. However, they show greater variability between measurements than rectal temperatures.[31,35,36] Axillary temperatures may be measured with a standard rectal thermometer and are well tolerated but may be less reliable than rectal temperatures in overweight animals and dogs with thick coats.[32,33,35] Although the various studies have produced conflicting results, most authors agree that TM and axillary temperatures should not be used interchangeably with rectal temperatures. When rectal temperature measurement is not possible in dogs, then TM temperature is recommended over axillary temperature as it is better tolerated and significantly fewer dogs have clinically unacceptable differences of more than 0.5° C (0.9° F).[35] When rectal temperature measurement is not possible in cats, then axillary temperature is recommended over TM temperature as it is better tolerated and significantly fewer cats have clinically unacceptable differences of more than 0.5° C (0.9° F).[37,38]

Normal Temperature

Normal cats and dogs have a rectal temperature in the range of 38.0° C (100.5° F) to 39.2° C (102.5° F) but normal dogs and cats can reach as high as 39.7° C (103.5° F) in the consulting room.[39,40] Studies on the repeatability of these measurements have shown that rectal temperatures measured in the morning in hospitalized dogs can fluctuate about 0.7° C (1.26° F) day to day, due to spontaneous variation alone.[41] Exercise can increase the rectal temperature of a normal Labrador as high as 42.2° C (108.0° F), and most dogs can reach 41.1° C (106.0° F) immediately after exercise.[42,43]

Body temperatures that exceed 41.1° C (106° F) at rest are life-threatening, as they can result in neurological damage, disseminated intravascular coagulation (DIC), and metabolic abnormalities. Such levels are more likely to occur in hyperthermic patients (see ch. 134), and active cooling is required as immediate treatment.

Differential Diagnoses for Fever

Causes of fever, and especially FUO, can be divided broadly into infectious, immune-mediated, neoplastic, inflammatory, and miscellaneous categories.[13,44] In dogs, infectious, immune-mediated and neoplastic causes are important.[7,8,12,13] One study of 66 dogs with fever in a UK referral center described 33% of cases to be immune-mediated (including inflammatory conditions), 27% infectious, 8% neoplastic, 9% miscellaneous and 23% were undiagnosed,[7] whereas an earlier study, also from the UK, of 101 referred cases of canine FUO described 22% of cases to be immune-mediated, 16% infectious, 9.5% neoplastic 11.5% miscellaneous and 19% undiagnosed. In the latter study, 22% of cases were classified as having primary bone marrow diseases but these largely were of a neoplastic etiology; the higher overall prevalence of neoplasia in this study was

attributed to an oncology bias within that center at that time.[8] Another study of 50 dogs with fever that presented to a university veterinary hospital found that 48% of cases were due to so-called non-infectious inflammatory diseases (which included immune-mediated diseases), with only 18% of cases being infectious in origin and 6% neoplastic.[45] There have been no case series describing causes of fever and FUO in the cat, but it is believed that infectious causes are more common than primary immune-mediated diseases or neoplasia in this species.[5,11,13] The differences between the above 3 studies and the lack of studies from primary care clinics or cats illustrates the difficulties in quantifying the causes of fever.[46] Box 48-1 lists causes of fever in dogs and cats that have been identified in the peer-reviewed literature.

Box 48-1

Causes of Fever in Dogs and Cats

Infectious Diseases

Systemic Bacterial Infections

Bacteremia (from any source in the body)

Localized Bacterial Infections

Abscesses in any part of the body, e.g., subcutaneous tissues, liver, prostate, lung, tooth root ("periapical"). Septic (and infective) arthritis (D>C),[51] bacterial endocarditis (D>C),[52,53] cholangitis (C>D),[54] discospondylitis (D>C),[55,56] osteomyelitis (D>C),[57] prostatitis (D),[58] pyothorax,[59] pyometra (including stump) (D>C)[60,61]

Other Bacterial Infections

Anaplasmosis (D>C),[62,63] bartonellosis (C>D),[64,65] borreliosis (Lyme disease) (D),[66] ehrlichiosis (D>C),[67,68] tularemia—*Francisella tularensis* (C>D),[69,70] hemoplasmosis (C),[71] leptospirosis (D),[72] mycobacterial infections (C[73]>D), cutaneous nocardiosis (C),[74] plague (C>D)[75,76]

Viral Infections

Canine distemper virus (D),[77] adenovirus (D),[78] parvovirus (D>C),[79,80] influenza virus (D),[81] feline calicivirus (C),[82] feline herpesvirus (C),[83] feline infectious peritonitis (as a result of feline coronavirus infection) (C),[84] feline immunodeficiency virus (C),[85] feline leukemia virus (C),[86] poxvirus (C)[87]

Fungal Infections

Aspergillosis (disseminated, invasive or atypical) (D>C),[88,89] blastomycosis (D>C),[90] coccidioidomycosis (D>C),[91,92] histoplasmosis (D>C),[93,94] sporotrichosis (C>D)[95,96]

Protozoal Infections

Babesiosis (D>C),[97,98] hepatozoonosis (D>C),[99,100] toxoplasmosis (C>D)[101,102]

Inflammatory Diseases

Fat necrosis, steatitis and pansteatitis (C>D),[103-105] hypereosinophilic syndrome (C>D),[106-109] juvenile cellulitis (D),[110] myositis,[111] pancreatitis/sterile pancreatic abscesses (D>C)[112,113]

Immune-Mediated Diseases

Immune-mediated hemolytic anemia (D>C),[114,115] polyarthritis (including rheumatoid arthritis) (D>C),[7,116] polymyositis (D>C),[111] thrombocytopenia (D>C),[117,118] polysystemic immune-mediated diseases (e.g., systemic lupus erythematosus) (D>C)[119,120]; steroid-responsive meningitis arteritis (D[121]), vasculitis,[122] nodular panniculitis (D),[123] trapped neutrophil syndrome (D)[124]

Neoplastic Diseases

Lymphoproliferative diseases (D>C), e.g., leukemias,[125] lymphoma,[8,126] multiple myeloma (D)[8]; myeloproliferative diseases, e.g., histiocytic disease[127]; solid tumors, e.g., renal tumors,[128] Sertoli cell tumors,[129] lung tumors,[130] metastatic disease,[131] any necrotic or infected tumor

Miscellaneous Diseases

Idiosyncratic reactions to drugs (especially sulfonamides) or vaccines (D>C),[132,133] myelodysplasia (C>D),[134,135] metaphyseal (hypertrophic) osteopathy (D>C),[136,137] panosteitis (D)[138]

Examples of conditions in which fever, including FUO, is an important presenting sign (original references cited were possible and then list augmented from several sources[7,8,13]). Worldwide geographical variation in the prevalence of some of the diseases listed exists; those reported in the area in which the animal lives, or has travelled to, should be considered. *D* indicates dog, *C* indicates cat, with indications given as to any prevalence differences that may exist. If no species is stipulated, the disorder should be considered equally prevalent in both dogs and cats.

Note: Hypermetabolic diseases such as hyperthyroidism and pain can cause hyperthermia (not fever).

There is minimal evidence for portosystemic shunts or inflammatory bowel disease directly causing fever, but they can predispose animals to bacteremias. It is also worth noting that certain infections, e.g., leishmaniasis (dog or cat),[139,140] cryptococcosis (dog or cat)[141,142] and neosporosis (dog),[143] are not *usually* associated with fever.

Approach to a Fever

First, it is important to distinguish between fever and hyperthermia (Figure 48-2), as hyperthermia may require urgent therapy to reduce body temperature (see ch. 134). Fever is a common clinical finding in small animal practice but owners usually report non-specific signs such as lethargy, anorexia, depression, hyperpnea, and stiffness.

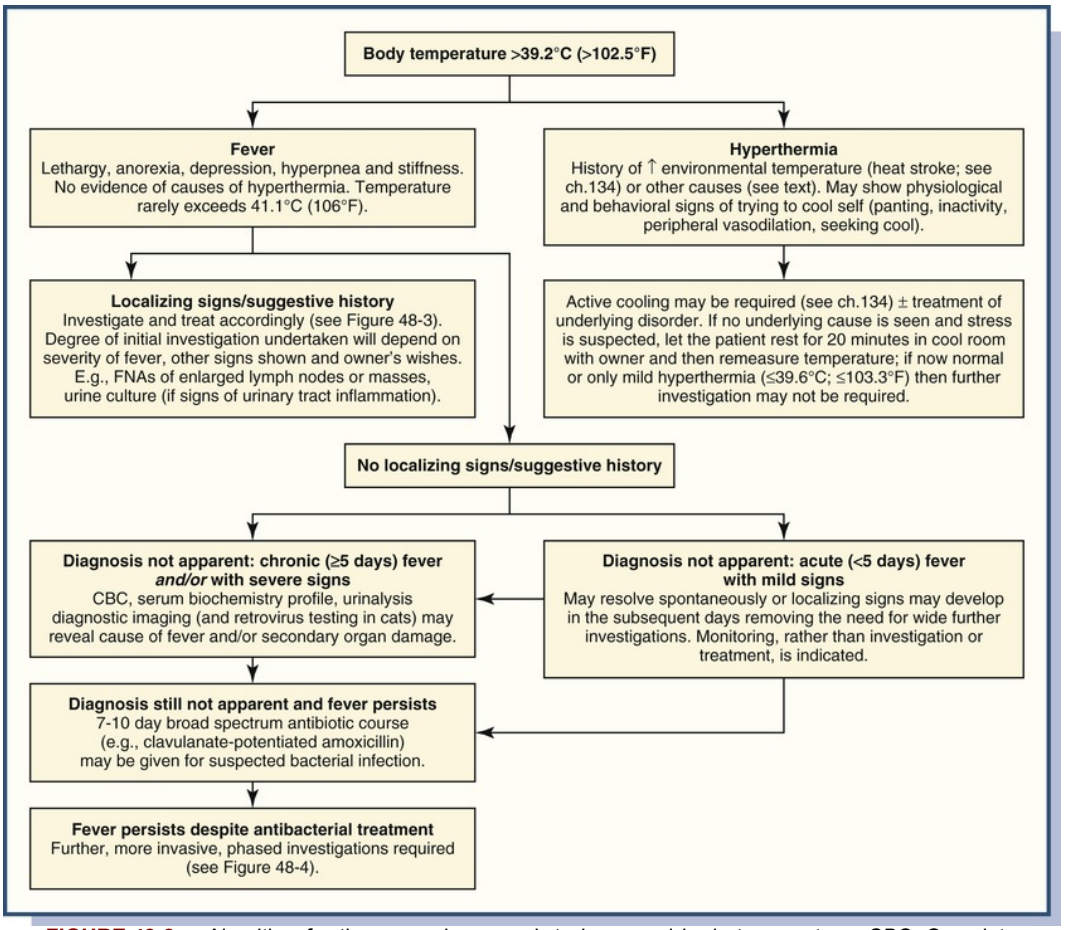
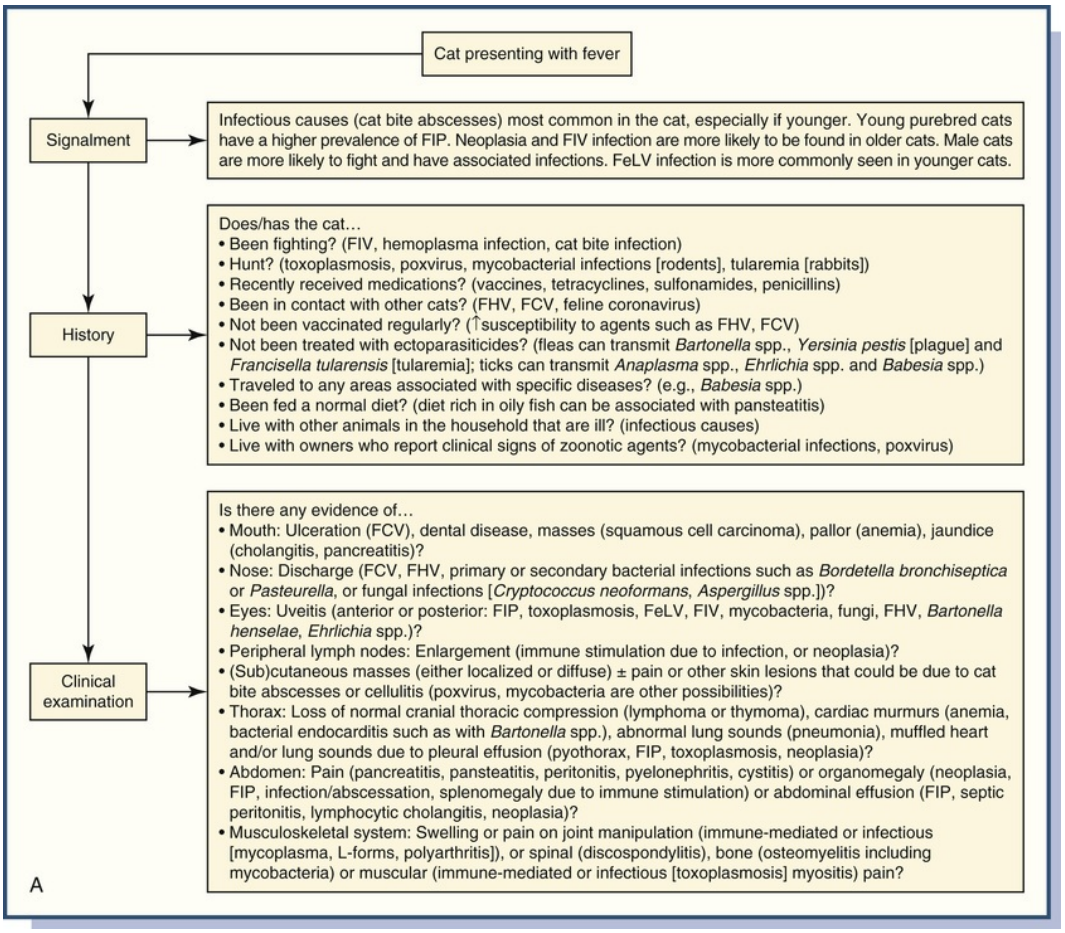


FIGURE 48-2 Algorithm for the general approach to increased body temperature. *CBC*, Complete blood count; *FNA*, fine needle aspirate.

The initial consultation can provide important clues as to the etiology of the fever, and these may either lead to a diagnosis themselves or point to diagnostic investigations that should help confirm a diagnosis.

Figure 48-3 shows algorithms depicting information based on signalment, history and clinical examination (including ophthalmic and neurological examinations) that can be important to consider when first presented with fever in a cat (see Figure 48-3, *A*) or a dog (see Figure 48-3, *B*). The first presentation of an animal with fever can usually be dealt with relatively easily. Many causes of fever can be identified during a thorough clinical examination, e.g., bite wound, upper respiratory tract infection, periapical dental abscess (see Box 48-1). These should be treated appropriately and further diagnostic investigations may not be required.



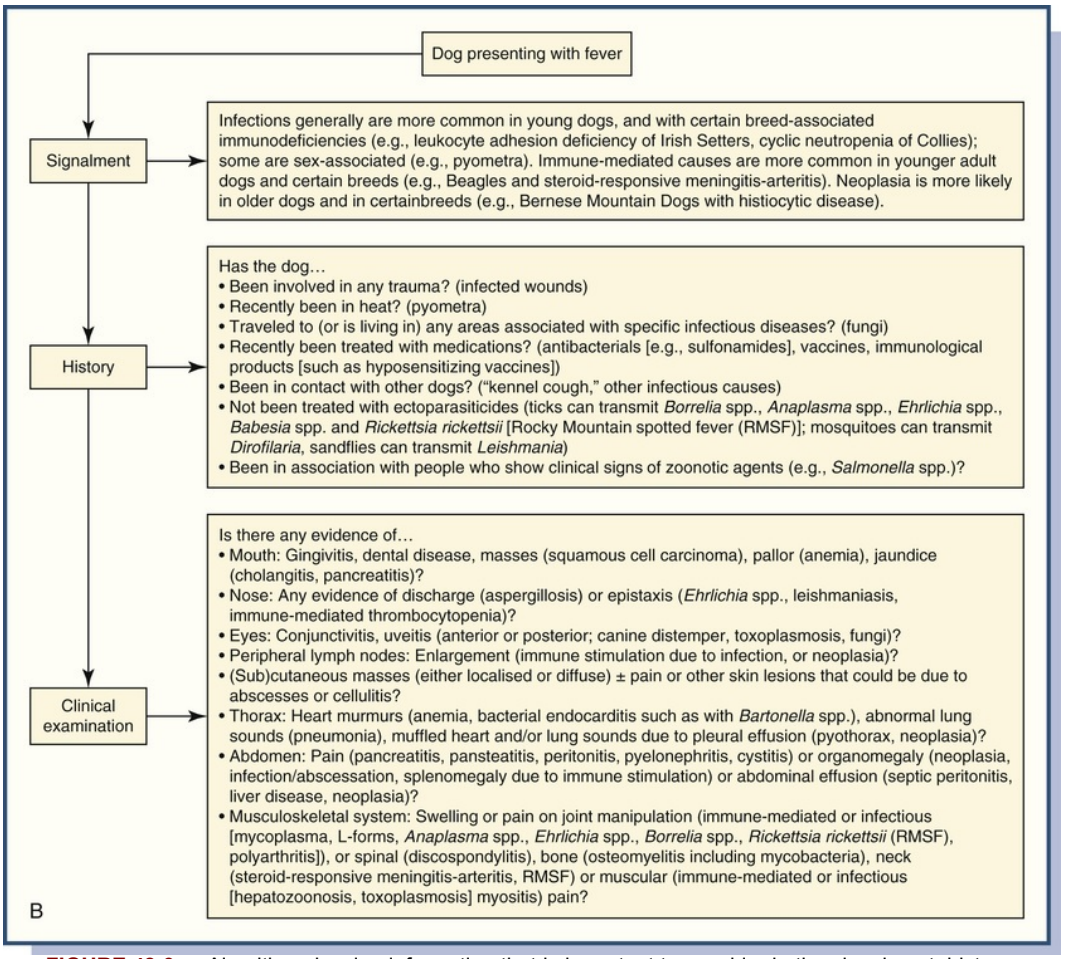


FIGURE 48-3 Algorithm showing information that is important to consider in the signalment, history, and clinical examination when investigating **(A)** cats and **(B)** dogs with fever. *FCV*, Feline calicivirus; *FeLV*, feline leukemia virus; *FHV*, feline herpesvirus; *FIP*, feline infectious peritonitis; *FIV*, feline immunodeficiency virus.

If localizing signs are not evident and the effects of the fever are relatively mild, and the temperature is below 41.1° C (106° F), then detailed diagnostic investigations may not be necessary as the underlying cause may become readily apparent. The fever should be monitored and the patient supported appropriately. A question that may arise at this stage is whether to give antipyretic and/or antibacterial therapy without a definitive diagnosis. Discussion of this is given in the Treatment section, below. However, if the fever causes severe side-effects, then early investigation may be warranted.

If the cause of the fever is not apparent on clinical examination within 5 days of initial presentation, and the fever persists, then a diagnostic plan is formulated. This will usually include a complete blood cell count, serum biochemistry panel, and urinalysis, with feline leukemia virus (FeLV) antigen and feline immunodeficiency virus (FIV) antibody testing in cats (Figure 48-4 and Table 48-1). While these tests are ongoing, 7 days of empirical antibacterial therapy can be a reasonable approach. Antipyretic therapy may also be *considered*, but depending on the severity of the clinical signs rather than the severity of the fever. If the fever persists despite this (and therefore has persisted for more than 12 days) then other diagnostic investigations can be planned according to the clinical findings or the results of initial diagnostic investigations, especially if the fever can be localized to a body system or region. Table 48-1 lists the diagnostic tests that can be used in the investigation of fever. It is important to repeat diagnostic investigations, particularly thorough clinical examinations, over time if the fever persists, as new abnormalities can develop that may provide important clues to the etiology or localization of the fever (see Figure 48-4). Subsequent examinations may reveal pain (e.g., in the neck or joints) or changes in ophthalmic or neurologic examinations (see ch. 11 and 259). In cases where the etiology of the fever remains elusive despite the above tests, then a sequential series of investigations which could include urine culture, blood culture, bacterial and fungal cultures of any discharges or lesions, arthrocentesis (see ch. 94), cerebrospinal fluid collection (see ch. 115), fine needle aspirates of any masses and some lymph nodes (even if normal on

palpation; see ch. 89), ultrasonography (see ch. 88), radiography (thoracic, abdominal, limbs and vertebrae), echocardiography (see ch. 104), serology and/or bone marrow samples (see ch. 92) should be started.[7,8] Cytology can be helpful in diagnosis, even in cases showing no clinical abnormalities of the body systems sampled.[7,8] Indeed, a recent study[45] found that cytology, or histopathology, were the most useful tests in determining the etiology of fever in a group of dogs, and other studies have similarly found cytology to be useful in enabling a diagnosis.[7,8] There may also be a role for magnetic resonance imaging in some cases. The exact order of diagnostic tests will depend on individual patient factors and consideration of regional variations in disease prevalence. As in human medicine, it is probable that there is no uniformly useful diagnostic algorithm for the further investigation of fever beyond the initial clinical examination.[10]

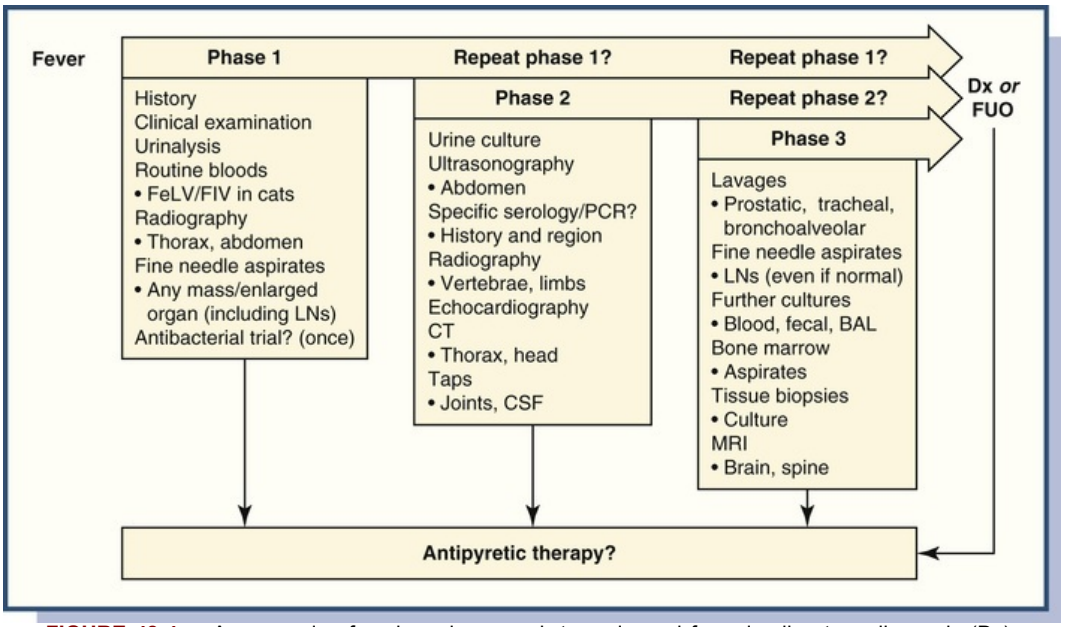


FIGURE 48-4 An example of a phased approach to prolonged fever leading to a diagnosis (Dx). *BAL,* Bronchoalveolar lavage; *CSF,* cerebrospinal fluid; *CT,* computed tomography; *Dx,* diagnosis; *FeLV,* feline leukemia virus; *FIV,* feline immunodeficiency virus; *FUO,* fever of unknown origin; *LNs,* lymph nodes; *MRI,* magnetic resonance imaging; *PCR,* polymerase chain reaction. The contents of each phase will vary with patient signalment, presenting signs, and local disease prevalence. Each phase may be spread over several consultations. Inherent in this diagram is the concept that the investigation of fever is a continuing and repetitive process and a patient cannot be said to have a "fever of unknown origin" until all of these tests have been performed and most of the ones in the earlier phases have been performed multiple times. Fever of unknown origin has to be truly unknown to be so described.

TABLE 48-1

Information That Can Be Obtained from Diagnostic Tests Used for Investigating Persistent Fever

TEST	DIAGNOSTIC INFORMATION
Urinalysis (including sediment examination) (1)	Urinary tract inflammation
Urine protein to creatinine ratio (2) (if urine sediment is inactive)	Assists assessment of renal function (urine specific gravity) Glomerular disease
Complete blood count (CBC) including blood smear examination (1)	Infection/inflammation* Hemoparasites, hematologic malignancy, and bone marrow disorders
Serum biochemistry profile (1)	Many metabolic organ diseases
Serum protein electrophoresis (2) if abnormal serum globulins are found	Systemic consequences of fever Monoclonal/polyclonal gammopathies
Acute phase proteins assay (2) (if neutrophil count	Acute phase proteins useful for monitoring response to therapy (not very

normal)	useful for diagnosis)
Culture & sensitivity—urine (2), fecal (2 or 3), and/or blood (3)	Urinary, enteric or blood-borne infections (bacteremia)
Fine-needle aspirates of any enlarged or abnormal lymph nodes or masses (1) or normal lymph nodes (3)	Lymphoma, lymphadenitis, metastatic disease, reactive lymphadenopathy
Thoracic radiography (2)	Pneumonia, mycobacterial infections, pleural effusion (pyothorax), intrathoracic masses
Abdominal radiography (2)	Organomegaly, abdominal effusions (peritonitis), lack of abdominal contrast (pancreatitis, pansteatitis), mass lesions
Abdominal ultrasonography with sampling of any abnormalities if appropriate (2). Examine, as far as possible, at least the liver, biliary tract, spleen, gastrointestinal tract, pancreas, urogenital tract, prostate, uterus, and lymph nodes.	General or localized changes in echotexture of organs or their size/shape. Opportunity to sample tissues or fluids (e.g., bile, abdominal effusions) by fine needle aspiration (2), core biopsy (3), or prostatic wash (2), for cytologic or histopathologic evaluation and/or Gram/acid-fast bacillary staining and/or culture and sensitivity.
Serology (2)	Evaluate for infectious causes (e.g., feline immunodeficiency virus, *Ehrlichia* spp., leptospirosis, toxoplasmosis) and/or immune-mediated diseases (e.g., Coombs' test, rheumatoid factor analysis, antinuclear antibody)
Polymerase chain reaction (PCR) test (2)	Alternative to culture to detect certain infectious agents in which culture is not possible or unreliable or slow (e.g., hemoplasmas)
Biopsies of abnormal tissues (3) (histopathology and culture) (e.g., lymph node, renal or liver)†	Lymphoma, lymphadenitis, metastatic disease, certain infectious agents (e.g., feline infectious peritonitis)
Skeletal radiography (including dental radiography) (3)	Discospondylitis, panosteitis, metaphyseal osteopathy, osteomyelitis, polyarthritis, bone metastases, multiple myeloma, mycobacterial infections, dental disease
Echocardiography—if murmur (2), if no murmur (3)	Valvular mass lesions (bacterial endocarditis) Myocarditis
Arthrocentesis—if stiff/lame/swelling (2), or if not (3). Samples submitted for cytology and/or Gram staining and/or culture.	Immune-mediated arthropathies or septic arthritis
Computed tomography (3), particularly of thorax and head	Pneumonia, intrathoracic masses, nasal disease, tooth root abscesses, skull osteomyelitis, temporomandibular joint abnormalities
Magnetic resonance imaging (3), particularly of brain and spinal cord before doing cerebrospinal fluid tap	Meningitis, encephalitis, discospondylitis
Cerebrospinal fluid tap—if head/neck pain (2), or if not (3). Submit samples for cytology and/or culture and sensitivity and/or PCR for infectious agents and/or antibody titers.	Steroid-responsive or septic meningitis Encephalitis Toxoplasmosis, neosporosis, feline coronavirus
Bone marrow aspirate and biopsy—if CBC abnormality (2), or if not (3)	Bone marrow disease (e.g., leukemia, multiple myeloma)
Bronchoscopy and bronchoalveolar lavage (or tracheal wash) (2 or 3). Samples can be submitted for cytology and/or culture and sensitivity and/or PCR.	Respiratory infections/inflammation (e.g., eosinophilic pulmonary disease, *Bordetella bronchiseptica* pneumonia)
Trial antibacterial treatment (1, 2, or 3)	Non-localizing or occult infections

*In fever, neutrophilia is more commonly seen with inflammatory and immune-mediated conditions (versus infectious causes).[45]

†The diagnostic value of exploratory laparotomy, laparoscopy, thoracoscopy without appropriate localizing signs is normally very limited.

(1) Tests often used early on in investigations, (2) tests that are usually employed based on the results of earlier tests, and (3) more advanced or invasive tests usually employed based on the results of tests in phases 1 and 2. Many of the tests can be sequentially repeated to enable detection of changes in the animal and provision of more clues to the etiology of the fever.

If all of these tests have been performed and the cause of the fever is still unknown, then it is reasonable to term this FUO but until then the distinction of fever and FUO in terms of differential diagnoses and

investigations is unclear and the two conditions should be regarded as a continuum. Assuming that only a small fraction of cases of fever are referred, then cases of true FUO are rare; out of 217 dogs referred to specialist centers, no diagnosis was achieved in 48 (22%) and some of these belonged to owners who did not wish to pursue all diagnostic options.[7,8,45] The majority of humans who develop true FUO will eventually recover spontaneously, and this may occur in dogs as well.[7,8,46]

Treatment

The treatment of fever assumes that fever is, at least in part, noxious, and that its suppression will reduce the noxious effects. Yet, despite many attempts, there is no evidence to suggest that specific treatment of fever actually improves survival or worsens the prognosis.[47] Furthermore, it has been shown that treatment of fever delays diagnosis of the inciting cause in dogs.[7] Patients treated with antipyretics undoubtedly look (and probably feel) better and are at less risk of fever-related complications ranging from the mild (e.g., inappetance) to the potentially life-threatening (e.g., DIC). However, such treatment prevents any of the benefits of fever described earlier. Many of the clinical improvements seen from antipyretic therapies could be due to the concomitant analgesic and/or anti-inflammatory actions of these drugs.

Therefore, antipyretic therapy ideally should be reserved for severe or prolonged fever. Mild acute fevers for which no cause has been identified are probably better left untreated. It may be more appropriate to educate clients that fever is often *good* for the animal and the use of medications might delay the development of important clinical signs that could help to identify the cause of the fever.

Physical Cooling

Active cooling of patients (as described in ch. 134) with fans, cool water, and other methods is not required unless the patient's temperature is greater than 41.1° C (106° F), when a degree of hyperthermia can be assumed. Obese patients or those with upper respiratory tract compromise are more prone to this situation and therefore should be monitored more closely.

Fluid Therapy

Fever increases insensible water losses and can reduce water consumption. Dehydration is therefore more common in febrile animals. Intravenous fluid therapy may be required, and at the very least, careful attention needs to be paid to monitoring the hydration status of an animal with fever.

Antibacterial Therapy

Antibiotics should be administered to all dogs and cats with fever and signs of bacterial infection, as well as all those with an unexplained fever of more than 5 days duration. The prevalence of systemic or unidentified bacterial infections in cases of fever is sufficiently high to warrant such treatment. Such therapy should use a single broad spectrum antibacterial with adequate penetration into most of the common sites of infection. As such, clavulanate-potentiated amoxicillin is a logical choice, though by no means exclusively so. In areas where vector-borne pathogens are common, then doxycycline may be a preferred alternative. Most authorities would regard fluoroquinolones, aminoglycosides, and later generations of the cephalosporins as being inappropriate first-line choices. The administration of multiple antibacterials in rapid succession over several days is unlikely to be successful and can increase antibacterial resistance (see ch. 209).

Nonsteroidal Therapy

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been at the forefront of antipyretic therapy for many years.[24] They act by reducing the synthesis of thromboxane and prostaglandins from arachidonic acid in the hypothalamus by directly inhibiting cyclooxygenase (COX) enzymes and downregulating their expression.[47] This returns the thermoregulatory set point to its normal level. There is also evidence that NSAIDs might exert a variety of non-COX-dependent actions on the pyrogenic cascade, such as by suppressing tissue inflammation, reducing pyrogenic cytokine production, or through enhanced expression of endogenous antipyretics.[47] They also have analgesic characteristics, such that they are capable of mollifying many clinical signs of illness and thereby improve patient welfare. However, NSAIDs are associated with a small number of undesirable side effects, including renal and hepatic impairment (which can in rare cases lead to kidney

and liver failure), gastrointestinal ulceration, vomiting, and blood dyscrasias. Repeated use of NSAIDs increases the risks of many of these undesirable side effects.[48]

Glucocorticoids

Glucocorticoids are potent antipyretic drugs that act in many different ways, including some of the same ways as NSAIDs. However, their use is associated with more side-effects than NSAIDs and, in addition, they reduce the chances of successful diagnosis and, for some conditions, successful treatment.[7] They are therefore indicated only once a diagnosis (such as an immune-mediated disease) has been established. However, on those occasions when it is difficult to differentiate primary immune-mediated from infectious causes of fever in cats (e.g., some arthropod-borne blood infections) that may also have a secondary immune-mediated disease, then glucocorticoid administration alongside an effective antibacterial (such as doxycycline) is unlikely to exacerbate such diseases, and will help control fever and other clinical manifestations of disease.[5] The concept of "relative adrenal insufficiency" has been largely and substantially discredited in human medicine and while equivalent evidence is not yet available in veterinary medicine, this concept should not be used as a generalized justification for the administration of steroids to a patient with fever, even if associated with sepsis (see ch. 133).[49,50]

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CHAPTER 49

Hypothermia

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Hypothermia, a subnormal body temperature in a homeothermic organism,[1] is defined as a core body temperature (CBT) <37° C (98.6° F).[2] Hypothermia is a result of the body's inability to maintain thermoregulatory homeostasis, and typically is due to excessive heat loss, decreased heat production, or a disruption of normal thermoregulatory functions.[2] Untreated, hypothermia can result in profound physiologic effects on the cardiovascular, respiratory, neurologic, and metabolic (including electrolyte, acid-base, and coagulation) systems, potentially increasing morbidity and mortality in the critically ill patient.[2,3]

Hypothermia can be primary or secondary. *Primary* hypothermia is defined as "accidental" hypothermia, and is a result of exposure to low environmental temperatures in the presence of normal heat production; an example is a dog living outside with poor shelter in a cold environment. *Secondary* hypothermia is more commonly observed in veterinary medicine, and is a sequela of disease (e.g., hypothyroidism, neoplasia, etc.), injury (e.g., with secondary hypoperfusion), surgery, or drug-induced alterations in thermoregulation and heat production (e.g., anesthetics, analgesics).[2-4]

Hypothermia is traditionally classified as the following[3,5]:

- Mild: 32° C to 37° C (90° F to 99° F)
- Moderate: 28° C to 32° C (82° F to 90° F)
- Severe: 20° C to 28° C (68° F to 82° F)
- Profound: <20° C (<68° F)

However, this grading scale is more accurate for primary hypothermia.[3] Some have proposed a newer classification of hypothermia based on the body temperature and clinical signs[2,3] (Table 49-1).

TABLE 49-1

Classification and Clinical Signs of Hypothermia[3]

CATEGORY	TEMPERATURE	CLINICAL SIGNS
Mild	36.7° C to 37.7° C (98° F to 99.9° F)	↑ HR, normal MAP, normal RR, normal LOC
Moderate	35.5° C to 36.7° C (96° F to 98° F)	↓ MAP, ↓ HR (cats), ↑ HR (dogs), mental dullness
Severe	33° C to 35.5° C (92° F to 96° F)	↓ HR, ↓ MAP, respiratory depression, severe CNS depression
Critical	33° C (<92° F)	Moribund, may appear dead, high mortality rate

CNS, Central nervous system; *HR*, heart rate; *LOC*, level of consciousness; *MAP*, mean arterial pressure; *RR*, respiratory rate.

Normally, complex mechanisms within the body help closely maintain CBT. The hypothalamus acts as the "thermostat" of the body, with temperature changes sensed by the preoptic and anterior hypothalamic nuclei, along with sensors throughout the body (within the skin, spinal cord, great veins, and abdominal viscera).[2] Both behavioral and physiologic changes occur when hypothermia develops, including curling up, heat-seeking behavior, piloerection, shivering, and peripheral vasoconstriction.

Causes for hypothermia occur due to heat loss, and are due to four main mechanisms:

- *Conduction:* transfer of heat occurs from the body surface to the air surrounding the body.[2] An example of this is the "wind chill factor," where circulated air results in heat transfer.[2]

- *Convection:* transfer of heat from the body surface to objects contacting the body. An example of this is an anesthetized patient on a stainless steel examination table.
- *Radiation:* loss of heat to surrounding structures that do not directly contact the body. Photons are emitted from any object that has a temperature above absolute zero, resulting in energy transfer.[2] An example of this is a marathon runner who wraps a reflective blanket around his or her body to minimize heat loss.
- *Evaporation:* transfer of heat from the respiratory tract or through moisture on the body surface to the environment. An example of this is an animal that has a large area of the body surface wet secondary to excessive surgery scrub.

In animals, heat loss generally occurs by convection and conduction.[6] Patients at risk for hypothermia include neonates (due to their ratio of body surface area to volume), geriatric patients, anesthetized patients, and those with underlying disease as their heat generation or temperature-regulating mechanisms may be impaired.

Cardiovascular Effects

Cardiovascular changes associated with hypothermia include an initial tachycardia followed by progressive bradycardia, arrhythmias,[7-9] conduction disturbances (e.g., lengthening of the PR, QRS, and QT intervals and the presence of pathognomonic Osborn waves, also known as J waves, in humans),[2,6] and changes in vasomotor tone (see ch. 103 and 248).[10] Potent constriction of the peripheral arteries can cause an increase in central venous pressure,[2,11] resulting in increased systemic vascular resistance.[2,12] As hypothermia and acidosis progress, there is a lack of responsiveness to catecholamines,[3] leading to progressive vasodilation and secondary hypotension.[2,3] With severe hypothermia (e.g., 28° C or 82.4° F), the heart rate can decrease by 50% as a result of decreased spontaneous depolarization of the cardiac pacemaker cells.[6] This profound bradycardia, which is often unresponsive to atropine,[6] can result in a progressive decrease in mean arterial pressure (MAP), peripheral vasoconstriction, and secondary fluid shifts. Increased blood viscosity, increased afterload, and capillary sludging can further develop, which reduce cardiac output.[6] As CBT approaches 23.5° C (74.3° F), death typically occurs due to the development of ventricular fibrillation and asystole.[2,6]

Respiratory Effects

Hypothermia can depress ventilation, resulting in reduced respiratory rate, minute ventilation, and tidal volume.[3] This can lead to secondary alveolar hypoventilation, hypercapnea, and respiratory acidosis. With increased blood viscosity, capillary blood flow is impaired and secondary hypoxemia can develop. Likewise, fluid shifts into the alveolar space can affect gas exchange, contributing to hypoxemia.[10] Finally, hypothermia causes an increased hemoglobin affinity (i.e., a left shift in the oxygen-hemoglobin dissociation curve) for oxygen, resulting in reduced oxyhemoglobin unloading at the tissue level,[10] further contributing to blood sludging.[3]

Neuromuscular Effects

Hypothermia results in disturbed cerebral autoregulation, decreased cerebral blood flow, and central nervous system depression as a result of decreased cerebral metabolism. For each Celsius degree decrease in CBT, there is a 6% to 10% drop in cerebral metabolism.[2,3,13] A flat electroencephalogram can occur with severe hypothermia (with CBT of 19° to 20° C or 66.2° to 68° F), and can potentially result in the misdiagnosis of death in a live patient.[6,14] At temperatures approaching 30° C (86° F), clinical signs of confusion, impaired judgment, decreased level of consciousness (LOC), and coma are reported in humans.[2] In veterinary patients, ataxia, hyporeflexia, and decreased LOC can be seen.[2]

Clinicopathologic Effects (Acid-Base, Coagulation, Electrolytes)

Hypothermia can result in increased catecholamine and cortisol production, resulting in hyperglycemia[3]; with severe hypothermia, this can progress to hypoglycemia due to impaired gluconeogenesis and glycogen depletion.[3] Acidosis also can be observed due to both a metabolic acidosis and respiratory acidosis (see ch.

128).[2,3] The presence of a metabolic acidosis can be due to poor perfusion with increased lactic acid production along with increased muscle activity (secondary to shivering).[2,3] Impairment of immune function also can occur with hypothermia due to impaired chemotaxis of, and phagocytosis by, granulocytes; impaired oxidative killing by neutrophils; and decreased mobility of macrophages.[2,3] Hemostasis also can be impaired by hypothermia with thrombocytopenia (due to sequestration of platelets in the liver and spleen),[2,3] coagulation factor dysfunction, reversible platelet dysfunction,[15] and a disruption of the fibrinolytic equilibrium.[2] Secondary hemostatic abnormalities also can be seen with hypothermia. Either a physiologic hypercoagulable state or disseminated intravascular coagulation (DIC) can occur (see ch. 197).[2] Evaluation of thromboelastography on hypothermic blood from dogs has demonstrated platelet dysfunction due to poor aggregation.[16]

Renal and Metabolic Effects

With hypothermia, a *cold diuresis* can be seen regardless of hydration state; this is due to the initial increase in blood volume caused by peripheral vasoconstriction.[2,3] Hypothermia can also cause a decreased production and responsiveness of the distal tubule to antidiuretic hormone, resulting in decreased resorption of water and electrolytes.[2] With moderate hypothermia, decreased glomerular filtration rate occurs due to decreased cardiac output and renal blood flow.[2,3] In humans, 40% of patients admitted into an intensive care unit due to accidental hypothermia had evidence of acute kidney injury.[2] Due to the reduction in tubular function, acidosis and hyperglycemia can develop as a result of decreased H^+ ion excretion and renal clearance of glucose.[2] The severity of hyperglycemia also can be worsened by decreased insulin sensitivity and reduced insulin secretion from the pancreas.[2] Electrolyte changes such as hypophosphatemia, hypomagnesemia, and hypokalemia may be seen secondary to hypothermia-induced intracellular shifts and renal tubular dysfunction.[2,3] Finally, decreased hepatic enzyme activity is associated with hypothermia, and is likely due to reduced perfusion of the liver.[2] This can potentially result in prolonged drug clearance and metabolism of substances commonly used for treating critically ill patients (e.g., opioids, benzodiazepines, anticonvulsants, propofol, etc.).[2]

Treatment

To minimize the physiologic dangers of hypothermia, the goals of therapy should include:

- Early detection and immediate correction of hypothermia (while providing safe rewarming rates)
- Prevention of further heat loss
- Support of vital cardiopulmonary and organ function (e.g., intravenous fluid therapy)
- Achievement of normothermia, and
- Reducing the risks of rewarming complications.

These goals can be addressed through passive and active warming techniques, and both should be implemented, as described below.

Passive Warming

Passive warming refers to minimizing loss of heat to the environment and augmenting the patient's own ability to generate heat.[2] This includes prevention of conduction losses by providing insulation from cold surfaces (e.g., stainless steel tables during anesthesia), wrapping the patient in insulated blankets, keeping the animal as dry as possible (e.g., using scrub only on the surgical site and removing excess scrub solution), and preventing evaporation of body fluids or liquids used for surgical preparation. Passive warming is effective for patients that are only minimally hypothermic.

Active Warming

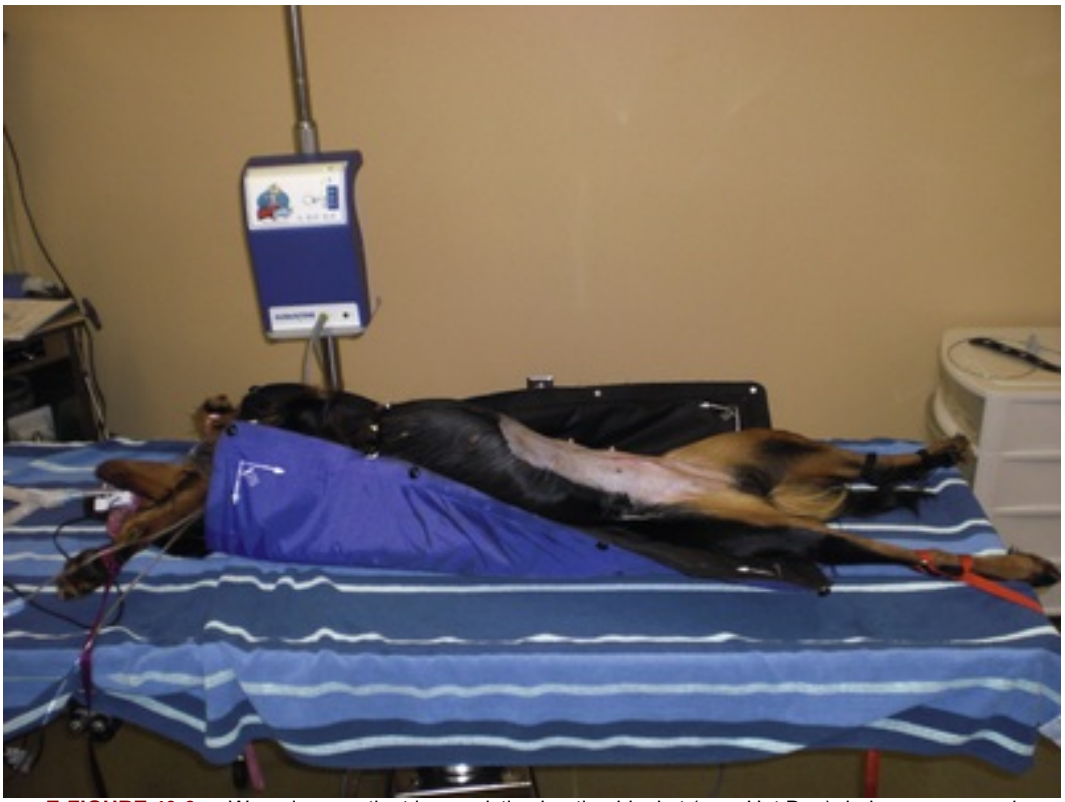
Active warming is the use of exogenous sources of heat, and is generally used for moderate to severe hypothermia; typically, the patient is unable to generate enough heat to be able to rewarm itself appropriately.[2] Examples of commonly used active external rewarming (AER) techniques used in veterinary

medicine include the following (Video 49-1):

- External warming devices (e.g., hot water blankets, heated pads, electric heating blankets, radiant heat, hot water bottles, warm rice packs, etc.); however, with some of these modalities, there is the risk for thermal injury from direct or indirect contact.
- Forced-air rewarming (e.g., 3M Bair Hugger), which provides forced air through disposable blankets to allow convective transfer of heat to patients (E-Figure 49-1).
- Resistive heating (e.g., Hot Dog warming blanket), which transfers heat to the patient using a non-disposable, semi-conductive polymeric fabric that warms by electrical resistance (e.g., low voltage electricity) (Figure 49-2 and E-Figure 49-3).

FIGURE 49-2 Use of a resistive heating blanket (e.g., Hot Dog) to prevent hypothermia in a patient undergoing a dental procedure. (Photo courtesy John Bayard.)

E-FIGURE 49-1 Forced air blanket used to treat hypothermia in a feline post-operative patient. (Photo courtesy Dr. Garret Pachtinger.)



E-FIGURE 49-3 Wrapping a patient in a resistive heating blanket (e.g., Hot Dog) during surgery and anesthesia to prevent hypothermia during ovariohysterectomy. (Photo courtesy John Bayard.)

Other methods of active warming include the use of warm saline to lavage the abdomen during surgery, warm fluids (typically by the intravenous route, although gastric, colonic, or peritoneal lavage can be considered), or warm inhaled air (if the patient is intubated). However, a recent study found that prewarming IV fluids might be minimally effective: even prewarming crystalloids to 60° C and administering them through a typical IV line at 300 mL/h produced a temperature at the point of delivery of only 24.2 +/− 1° C.[17] Goals of rewarming should be limited to an increase of 0.5° C to 2° C/hour.[2,3] General safe recommendations for rates of rewarming are found in Table 49-2.

TABLE 49-2

Rewarming Rates (Degrees Celsius Per Hour)[2]

	PASSIVE EXTERNAL REWARMING	ACTIVE EXTERNAL REWARMING	INHALATION OF WARM AIR	PERITONEAL LAVAGE (LESS COMMONLY DONE)
1st hour	1.4	1.5	1.0-2.5	1.5
2nd hour	1.4	2.4	2.0	2.5

Complications of Rewarming

Rarely, complications of rewarming can occur including rewarming shock, thermal injury, and overheating. Heat should be aimed at warming the trunk rather than the extremities; this helps minimize peripheral vasodilation and secondary pooling of blood, which can lead to *rewarming shock*. When superficial surfaces are rewarming, peripheral vasodilation can occur resulting in potential hypovolemia. Another complication includes the risk of thermal injury, which can be avoided by providing safer alternatives of heat support. Overheating should also be prevented. Active rewarming devices should always leave an area of the incubator or cage floor that is free of external heat, so the animal can move away from the heat source once normothermic if the heat is excessive. Clinicians should be aware of normal physiologic parameters when it comes to rewarming; this is especially important when providing heat support for neonates (e.g., normal rectal temperature of 36-37° C [96.8-98.6° F] at birth).

The Use of Hypothermia for Treatment

The use of therapeutic hypothermia (with a target temperature of 32° to 34° C or 89.6° to 93.2° F) has been investigated for its neuroprotective effect in patients with underlying cerebral injury, post-cardiac arrest, or secondary to hemorrhagic shock. Therapeutic hypothermia is thought to prevent cell death after cell injury, suppress free radical reactions, reduce cerebral oxygen demands, and retard destructive enzyme reactions.[2] Recently, the Reassessment Campaign on Veterinary Resuscitation (RECOVER) initiative suggested that the use of mild hypothermia might be beneficial when implemented as soon as possible and when maintained for longer than 12 hours after return to spontaneous circulation.[18] While limited studies have been investigated in veterinary medicine, preliminary evidence is promising; additional prospective studies are warranted.

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CHAPTER 50

Pallor

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Client Information Sheet: Pallor

Pallor is defined as the paleness of a tissue.[1] Assessing tissue color in animal patients is practical mostly by evaluating the color of mucous membranes, but can also involve areas of hairless skin. This simple but essential test is a component of the routine physical examination performed as a part of the overall assessment of each and every patient.

In normal animals the mucous membranes should be moist and pink, and they are considered pale when their color is subjectively judged to be too light. This is determined by the amount of oxygenated hemoglobin in the blood, and by the degree of tissue blood perfusion. It can be altered or even masked by the presence of other serum pigments, such as bilirubin or myoglobin. By the same token, pallor, if severe enough, can sometimes mask other conditions such as cyanosis, which should be considered when suspecting left-sided congestive heart failure, right-to-left shunting cardiovascular disease, or some intoxications (see ch. 52).

One should note that since hematocrit differs between species and between age groups within a given species, normal mucous membranes appear lighter in cats than they are in dogs, as they do in puppies or kittens relative to adult pets.

Pallor is most commonly sought by assessing non-pigmented areas of the inner side of the lips, the gums, and the conjunctiva. The tongue, nares and urogenital (penis and prepuce or vulva and vagina) mucous membranes can also be assessed, as can the rectoanal mucous membranes. Such membranes are rich with capillary vessels and are easily visible. Changes in perfusion or in their level of oxygenation, therefore, can be readily identified when examined appropriately. Such changes can occur due to either systemic or local pathological processes.

Pallor can result from anemia or from decreased tissue perfusion, or from a combination thereof. Any condition resulting in compromised capillary perfusion such as a decreased cardiac output, or a reduced red blood cell concentration can lead to the development of pallor.[2] Decreased cardiac output may result from extreme tachycardia or bradycardia, a highly irregularly irregular tachyarrhythmia, extreme systolic myocardial failure, cardiac tamponade, severe pulmonary arterial hypertension, shock of all kinds (hypovolemic, anaphylactic, distributive, cardiogenic or neurogenic), or systemic hypotension.

Systemic or localized arteriolar vasoconstriction, too, can trigger generalized or localized pallor, respectively.[3] This might depend on an elevation in sympathetic tone accompanying stressful conditions such as severe pain, fear, or heart failure.

While pallor is not necessarily present in every anemic patient, mucous membrane pallor is the most common clinical sign of all types of anemia, whether chronic or acute, regenerative or non-regenerative, regardless of tissue capillary perfusion. Acute hemorrhage can trigger pallor first via hypovolemia, and later via loss of hemoglobin, while chronic anemia triggers pallor mostly by the ongoing hemoglobin loss, typically when hematocrit is <25-30%. When blood loss is acute, pallor can already be identified at higher hematocrit levels.

Evaluation

An integrative, rapid, yet thorough assessment of a patient with pallor can sometimes be crucial and promote a life-saving decision, especially because some of the common etiologies can involve an emergency situation. Careful attention to the patient's signalment, history, and co-existing physical examination findings can provide important clues as to the underlying reason for pallor, and guide the clinician into prompt action such as fluid therapy for patients in shock, blood transfusion for patients with severe anemia, or intravenous

diuretic therapy for patients in congestive heart failure. Inadvertently choosing one modality when another is actually needed can sometimes be detrimental (if not catastrophic) for the patient, as some of the above mentioned conditions warrant an opposite approach from others. Nevertheless, whether pallor results from anemia or from decreased tissue perfusion (or both, when coexisting), other physical findings can sometimes guide the clinician towards the more likely reason for pallor. One should bear in mind however, that certain accompanying findings can sometimes result from several potential etiologies, which can be confusing. Possible examples include compensatory sinus tachycardia (when cardiac output and perfusion are too low, or when anemia-related hypoxemia has developed), compensatory tachypnea (when anemia-related hypoxemia is present), weakness, cool mucous membranes or extremities, or an abnormal demeanor. These are not always helpful in determining which of the two disorder categories is the one contributing the most to pallor. This is the reason why utmost efforts towards careful integration of all findings should be made prior to taking corrective action.

History and physical examination may both be consistent with external (e.g., melena or epistaxis) or internal blood loss: the combination of pallor and icterus (or the presence of pigmenturia) highly suggests anemia due to hemolysis.

One of the most informative parameters that can aid in differentiating decreased perfusion versus anemia is the capillary refill time (CRT). It is determined by lightly compressing a non-pigmented mucous membrane surface to blanch the mucosa by transiently arresting capillary flow and observing the time (in seconds) it takes for prior mucous membrane color to return. It will be longer than normal when capillary perfusion pressure is diminished. However, if the applied manual pressure is hard enough to actually compress arterial flow as well, CRT may become overly prolonged and lead to an overestimated severity of the true compromise. In contrast, CRT may remain unchanged even in the presence of severe anemia, especially when chronic. Normal CRT is 1.0 to 2.0 seconds; prolonged CRT is >2.0 seconds and is considered diagnostic for poor tissue perfusion.[2,4] However, this is a highly subjective and insensitive test, which can often appear normal in highly compromised patients, and vice versa, especially when not integrated into a panel of other tests and assessments.

While pets with decreased perfusion frequently present with rapid and weak peripheral pulsation and a prolonged CRT, those with chronic anemia (i.e., without concurrent hypovolemia resulting from acute blood loss along with its accompanying compensatory mechanisms) often present with rapid but bounding pulses, with a normal CRT. As both their intra- and extravascular volumes remain normal, their strong arterial pulsation results from a decreased blood viscosity combined with a compensatory increase in cardiac output. A simple blood test such as hematocrit or packed cell volume (PCV) measurement can supplement the physical examination findings in providing guidance as to which of these conditions is responsible for pallor.

Pulse quality may provide additional information regarding the underlying disease (see ch. 56). For example, when decreased during inspiration and increased during expiration (a "paradoxical pulse"), especially when accompanied by tachycardia, muffled heart sounds, and jugular venous congestion, cardiac tamponade should be suspected as the reason for pallor, and should be promptly treated, if confirmed (see ch. 254). When pulse pressure (the difference between arterial systolic and diastolic pressures), which dictates the palpable arterial pulse intensity, is abnormally high or low, this does not necessarily mean that tissue perfusion will follow the same pattern. A good example is severe bradycardia, which translates into an elevated systolic arterial pressure (due to longer diastolic filling of the left heart ventricle, and therefore an increased force of left ventricular contraction), in parallel to a decreased arterial diastolic pressure (resulting from the longer opportunity for diastolic pressure to drop to a lower value than usual). The combination of an elevated systolic and a decreased diastolic arterial blood pressure means the pulse pressure is increased for two different reasons, leading to a bounding palpable pulse (see ch. 56). This, however, should not give the wrong impression regarding capillary perfusion, which can still be highly compromised due to the overall decreased cardiac output, if bradycardia is severe enough. Pallor in this context can provide the astute clinician enough of a clue to keep this risk in mind, especially if combined with other physical examination findings such as core or regional hypothermia, or stupor.

Mucous membrane moisture might decrease with compromised hydration, which should not be expected in well-hydrated, anemic pets. Hydration status can also be evaluated non-invasively by testing skin turgor: if the inter-scapular skin promptly returns to its normal position after having been pulled dorsad and released, dehydration is less likely. When in doubt, however, selective blood tests (e.g., PCV, total solids) can supplement these subjective impressions.

Tachyarrhythmia with frequent premature cardiac cycles can explain a pulse deficit as a factor contributing to pallor, if severe and frequent enough (see ch. 248). A simple electrocardiographic rhythm strip can test this possibility (see ch. 103).

Figure 50-1 provides a suggested diagnostic test algorithm to be considered by clinicians and potentially follow integrated information gathered from the patient's signalment and history, when identifying pallor upon physical examination. It prioritizes physical examination tests and illustrates how the evaluation of a patient with pallor might help determine the cause, and how pallor may have more than one cause, all occurring at the same time.

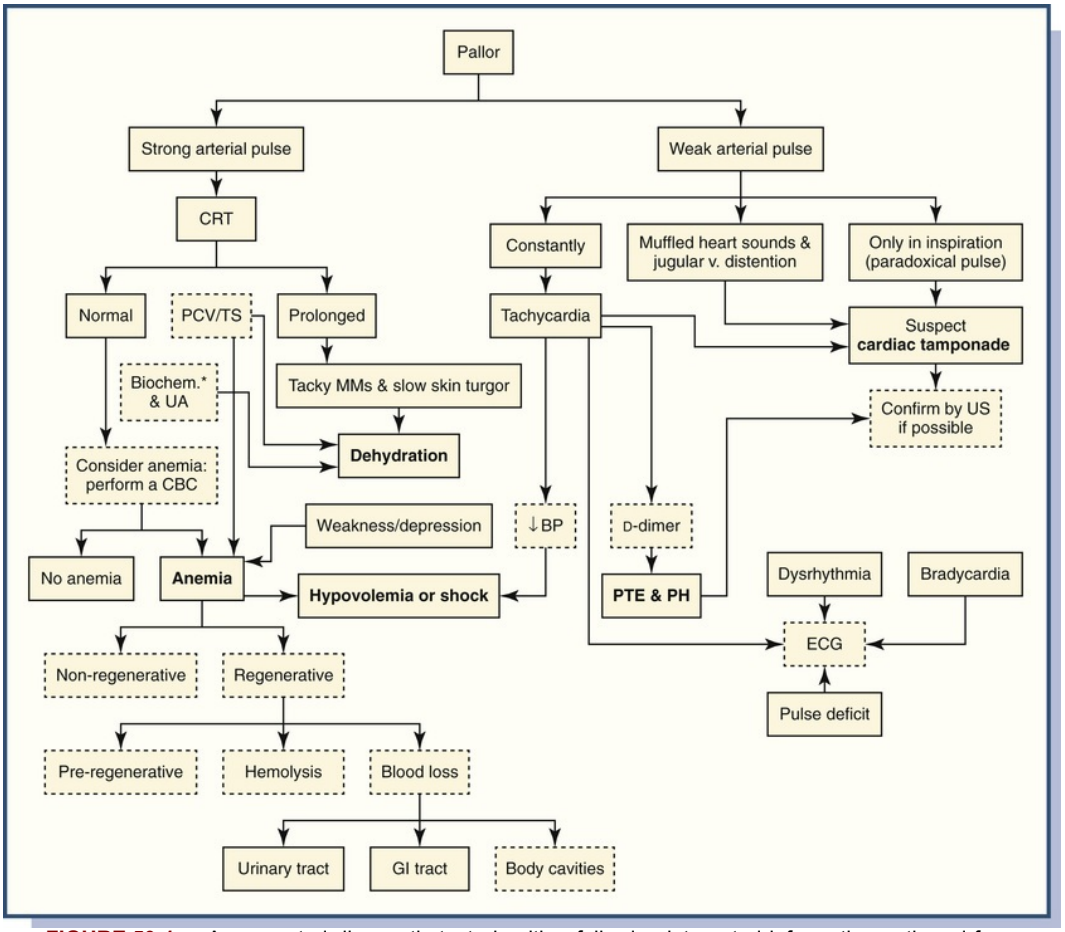

FIGURE 50-1 A suggested diagnostic test algorithm following integrated information gathered from the patient signalment and history, when identifying pallor upon physical examination. The flow chart illustrates how the evaluation of a patient with pallor might help determine the cause, and how pallor may have more than one cause at the same time. Physical examination findings are in solid boxes. Other, ancillary tests to be considered are in boxes defined by a broken line. Diagnoses are in bold font. *Biochem,* Serum biochemistry; *BP,* blood pressure measurement; *CBC,* complete blood count; *CRT,* capillary refill time; *ECG,* electrocardiography; *GI,* gastrointestinal; *MMs,* mucous membranes; *PCV,* packed cell volume; *PH,* pulmonary hypertension; *PTE,* pulmonary thromboembolism; *TS,* total solids; *UA,* urinalysis; *US,* ultrasound; *V,* venous. *At least glucose, electrolytes, lactate, creatinine, and urea or blood urea nitrogen.

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CHAPTER 51

Hyperemia

Anthony C.G. Abrams-Ogg

Client Information Sheet: Hyperemia

Hyperemia refers to increased arterial (pre-capillary) blood flow to a tissue. Active hyperemia is a normal physiologic response when there is increased metabolic activity in a tissue, as in exercising muscle, where the hyperemia delivers more oxygen and nutrients to the tissue.[1] Hyperemia is also a key pathophysiologic response as part of inflammation[2] (Figure 51-1). The main clinical sign associated with hyperemia is erythema, which will be less obvious in an anemic animal. Hyperemia is distinguished from congestion, which results from decreased removal of post-capillary blood, which does not cause erythema. This chapter addresses generalized hyperemia of peripheral mucous membranes, which are sentinel tissues for circulatory status because of rich vascular supply and ease of examination. Hyperemia is most likely to be initially recognized as gingival and conjunctival erythema during general physical examination. It is important to ensure that these are not caused by gingivitis or conjunctivitis. If gingivitis is present, the buccal mucosa should be examined. If pigmentation or patient behaviors preclude recognition of gingival, buccal mucosal or conjunctival hyperemia, and also to confirm generalized hyperemia, the vulva or penis and prepuce should be examined. In some cases, generalized cutaneous erythema may also be detected. The term "injected mucous membranes" is variably used by clinicians as a synonym for hyperemia or to refer to a subset of hyperemia characterized by brick-red mucous membranes, most often associated with sepsis, heat stroke, and hypoadrenocorticism.

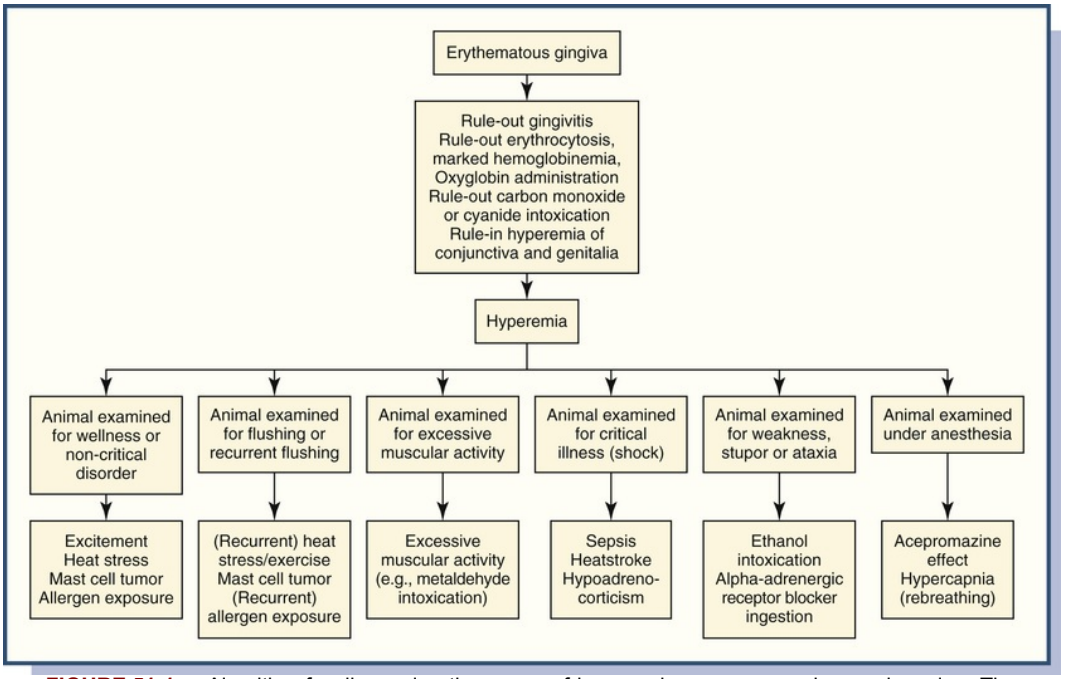

FIGURE 51-1 Algorithm for diagnosing the cause of hyperemic mucous membranes in a dog. The algorithm may also be used for cats but hyperemia is infrequently recognized.

Erythematous mucous membranes and skin may also be caused by erythrocytosis, hemoglobinemia, and treatment with Oxyglobin, which may be ruled out by history and a hemogram. The mucous membranes of neonatal pups and kittens are also relatively dark compared to their color at around 6 weeks of age due to high fetal mean corpuscular volume.[3] Experimentally, carbon monoxide and cyanide poisoning may cause bright red mucous membranes. In the former this is due to carboxyhemoglobin formation, in the latter it is because oxygen is not extracted from hemoglobin, and in both cases there is likely a hyperdynamic response.[4] Carbon monoxide and cyanide poisoning are most often encountered with smoke inhalation, where red mucous membranes are not commonly reported and other signs predominate.[5,6] These poisons may also be used for malicious poisoning and extended suicide.[7]

As with other tissues, blood flow through mucous membranes is predominantly determined by cardiac output and arteriolar vascular tone. Hyperemia cannot occur without vasodilation, and as such the causes of hyperemia will be causes of vasodilation, although not all causes of vasodilation will cause hyperemia. Vasomotor tone is under local (intrinsic) and extrinsic control. Local control signals include metabolic products, endothelin-1, nitric oxide (NO), thromboxane A2, prostacyclin, histamine, and bradykinin.[1] The main extrinsic control mechanisms are neurohormonal reflexes of the autonomic nervous system (e.g., secretion of acetylcholine).[1]

Capillary refill time (CRT) is typically determined while examining peripheral mucosa. It is a measure of gingival perfusion. The subjectivity and inconsistency of CRT has brought its utility into question in human medicine.[8] These factors likely affect judgment of CRT in animals as well, but it remains an important element of the physical examination. For hyperemic mucous membranes, the CRT will be normal (0.5-2 sec) to fast (<0.5 sec) if there is normal-to-increased cardiac output. Although seemingly paradoxical, prolonged CRT (>2-3 sec) may occur in hyperemic mucous membranes, and indicates severe vasodilation and risk for associated hypotension. When testing CRT, light pressure for 1-2 sec to blanch the tissue should be used. Excessive or prolonged pressure, and repeated testing in one area, may result in an exaggerated response from reactive hyperemia, the increase in above normal blood flow following transient vascular occlusion.

Hyperemia is infrequently recognized in cats compared to dogs, probably because of lower hematocrit, lower relative blood volume, and lower prevalence of disorders that cause hyperemia, and possibly because of high sympathetic tone in stressful conditions promoting vasoconstriction. Recognition of hyperemia in cats may also be complicated by the common occurrence of gingivitis and the lack of routine examination of genitalia except in cats with lower urinary tract signs.

The most common cause of hyperemia in the dog is the normal physiologic response to increased heat (Video 51-1). Increased heat may be internal or external. One function of the circulatory system is the transport of normal products of metabolism for elimination, and internal heat above what is needed to maintain normal body temperature is one of these products.[1] In the classical model of vasodilation, increased metabolism causes decreased oxygen concentration from consumption, and causes increased carbon dioxide, potassium, adenosine and lactic acid concentrations, all of which promote vasodilation. The classical model has been challenged by the "bang bang" model, where membrane NADPH oxidase is turned off and on based on the supply of oxygen and glucose relative to the demand. When NADP oxidase is turned on, there is release of superoxide anion into the interstitial space and subsequent neutralization of interstitial NO.[9] The increased blood flow to the skin will increase convective cooling in the dog to some extent, but panting is the main mechanism to increase evaporative cooling, which is facilitated by oral mucosal hyperemia. Increased physical activity and/or excitement will increase heat production from skeletal muscle. Increased activity is most often due to situation-related normal or abnormal behavior for an individual dog. One scenario of overheating unrelated to behavior is the work of breathing associated with Coonhound paralysis (see ch. 269). Pathologic muscular activity may also occur with metaldehyde poisoning.

Increased external heat comes from high ambient temperature or external warming sources, and external heat stress will exacerbate internal heat load. Increased ambient humidity will also exacerbate heat stress as it reduces the effectiveness of evaporative cooling. Cats that are overexcited and/or subjected to a high ambient temperature may also pant and have relatively hyperemic mucous membranes.

Initially, overheating will be associated with normal CRT, which will progress to rapid CRT with increasing heat stress, and then to heat stroke and eventual shock with pallor and prolonged CRT (see ch. 134).[10]

Fever is an adaptive response and does not in itself cause hyperemia (see ch. 48). However, fever is often due to sepsis, which is often associated with hyperemia. Unlike hyperthermia, where there is appropriate vasodilation, in sepsis the inflammatory mediators bradykinin, histamine, serotonin, and many others, cause inappropriate vasodilation[11] (Video 51-2). The hyperdynamic phase of septic shock is characterized by

fever, hyperemia, normal-to-increased CRT, and tachycardia. It may progress to hypodynamic septic shock characterized initially by prolonged CRT, followed by pallor and hypothermia. Hyperdynamic shock is infrequently recognized in cats.

Certain drugs and toxins may cause hyperemia. These include acepromazine, phenoxybenzamine, prazosin and other drugs that block alpha-adrenergic receptors; animals with hyperemia caused by these drugs will typically be sedated. Ethanol may cause peripheral vasodilation; the mechanism may be modulation of extrinsic vasomotor control mechanisms.[12] Animals with hyperemia will probably be ataxic. Ethanol ingestion may result from malicious/accidental poisoning, bread dough ingestion, or treatment of ethylene glycol poisoning (see ch. 152).[13] Hypercapnia caused by rebreathing during anesthesia may directly cause peripheral vasodilation. If blood pressure and oxygenation are adequate, the mucous membranes may be hyperemic. The animal may also be hyperventilating. It is emphasized that hypercapnia may occur without these signs.[14]

Some dogs with atypical and classical hypoadrenocorticism have presented with profound hyperemia with prolonged CRT, and in some cases have initially been misdiagnosed as septic (see ch. 309).[15] Cortisol is necessary for a normal response to adrenaline and inhibits NO synthesis; therefore, cortisol deficiency results in vasodilation. Dogs with hypoadrenocorticism may also present with pallor from volume contraction and peripheral vasoconstriction, and the variable circulatory findings are one more reason this disorder is "the great pretender." Low serum sodium : potassium ratio and/or absence of a stress leukogram will often be present, but protracted vomiting may lower the serum potassium concentration, and unrelated inflammation may mimic a stress leukogram. Hypoadrenocorticism may occasionally cause a fever.[16] An ACTH stimulation test should be considered in cases with unexplained hyperemia, but in interpreting an ACTH response test in this scenario, the possibility of critical illness-related corticosteroid insufficiency must also be considered (see ch. 133).[17]

Histamine is a potent vasodilator, and dogs with mast cell tumors will occasionally present with periodic self-limiting hyperemia not associated with increased activity or ambient temperatures (see ch. 349). Intermittent exposure to an allergen could also cause this sign. If history does not reveal repetitive allergen exposure and thorough examination of the skin does not reveal a mass, then imaging and/or aspiration of the spleen, liver and bone marrow should be considered (see ch. 89, 92, and 93).

Altered NO mechanisms are involved in menopausal vasomotor symptoms in humans. An animal model of vasodilation in the tail of forced exercise ovariectomized rats exists, but post-ovariohysterectomy vasomotor signs have not been recognized in dogs and cats.[18]

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CHAPTER 52

Cyanosis

Anna Tidholm

Client Information Sheet: Cyanosis

Cyanosis (*cyan* = blue, Greek) is defined as bluish discoloration of the mucous membranes and/or skin due to excessive amounts of deoxygenated (reduced) hemoglobin (Hb) in capillary blood. The presence of cyanosis is a subjective assessment, observed in different disease processes, and is typically categorized as *central* or *peripheral*.

Central cyanosis is caused by a systemic deoxygenation of arterial blood, most commonly due to cardiovascular or pulmonary disease, or the presence of increased amounts of non-oxygen carrying hemoglobin (e.g., methemoglobinemia). *Peripheral cyanosis* is caused by a localized reduction in oxygenated hemoglobin, secondary to obstructive causes (e.g., thromboembolism, tourniquet application, foreign body), vasoconstriction (e.g., shock, hypothermia, low output cardiac failure), decreased arterial supply, or any of the causes of central cyanosis. Central cyanosis is generally most evident in the oral mucous membranes, whereas peripheral cyanosis is most evident at the footpads and nail beds of the affected limb(s) (Figures 52-1 and 52-2).

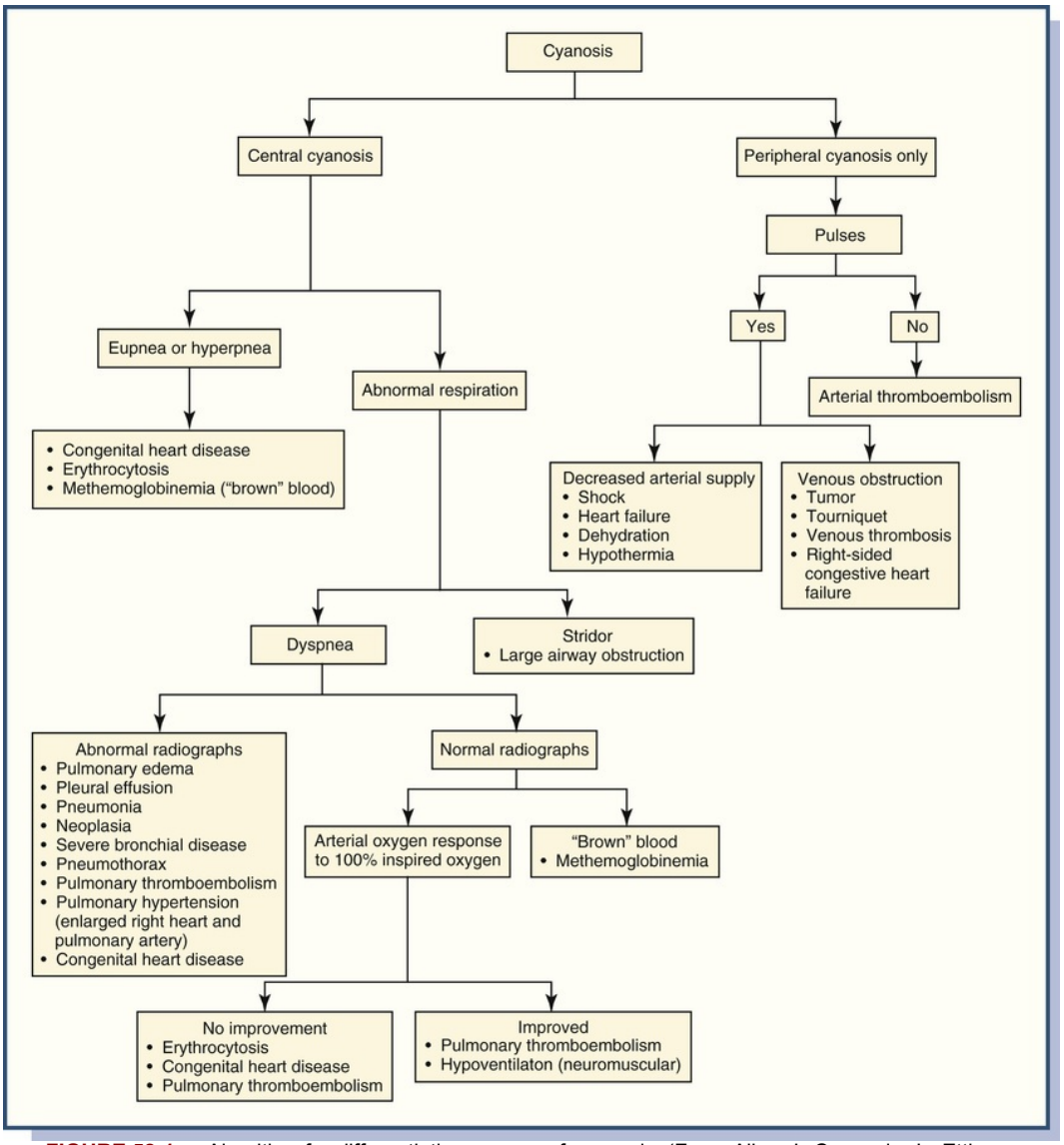


FIGURE 52-1 Algorithm for differentiating causes of cyanosis. (From Allen J: Cyanosis. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine,* ed 7, St Louis, 2010, Elsevier, pp 283-286.)

FIGURE 52-2 Central cyanosis (cat on right; cyanosis especially visible on the nasal planum) due to right-to-left shunting in a cat with a ventricular septal defect. The cat on the left is normal, for comparison. (Courtesy Dr. Etienne Côté.)

Physiology and Pathophysiology

Cyanosis is generally detected when deoxygenated Hb exceeds 5 g/100 mL blood within *capillary* beds. However, *arterial* deoxygenated Hb need only reach 3-3.5 g/100 mL blood to cause detectable cyanosis. The amount of deoxygenated Hb depends on the Hb concentration and percent saturation of Hb in arterial blood (SaO_2), which is related to arterial oxygen tension (PaO_2). The alveolar oxygen tension (PAO_2) is approximately 100 mm Hg when breathing room air and SaO_2 is approximately 97%, resulting in a PaO_2 of approximately 95 mm Hg. When decreased inspired oxygen concentration results in decreased SaO_2, arterial deoxygenated Hb increases and cyanosis becomes clinically detectable when the 3-3.5 g/100 mL threshold is reached. In animals with normal hemoglobin concentrations (approximately 10 to 20 g/100 mL blood), SaO_2 must decrease to concentrations below 73-78% (PaO_2 <39-44 mm Hg) to produce consistently visible cyanosis. As a result, cyanosis is an insensitive indicator of blood oxygen content, and detection of cyanosis in animals without cyanotic heart disease indicates severe arterial hypoxemia. *Erythrocytosis* is a condition characterized by an elevated red blood cell (RBC) concentration, which in dogs and cats most commonly is secondary to conditions resulting in chronic hypoxemia, but may also be primary (see ch. 57). Animals with erythrocytosis have higher total Hb concentrations, making it easier for reduced hemoglobin to accumulate. For example, in an animal with a hematocrit of 65%, 5 g of deoxygenated Hb/100 mL blood may be present if SaO_2 drops below 89%. Conversely, in anemic animals, cyanosis is rarely present as an absolute reduction in hemoglobin means that SaO_2 must decrease to concentrations incompatible with life to produce cyanosis.

Causes of Central and Peripheral Cyanosis (Box 52-1; see also Figure 52-1)

Central cyanosis is most commonly caused by cardiovascular or pulmonary diseases resulting in arterial deoxygenation (hypoxemia). Causes of hypoxemia can be categorized by the type of pathophysiology present (see ch. 128).

Box 52-1

Causes of Central and Peripheral Cyanosis

Central Cyanosis

Pulmonary

- Ventilation-perfusion mismatch
  - Pulmonary infiltration
    - Edema
    - Inflammation/infection
    - Neoplasia
    - Acute respiratory distress syndrome (ARDS)
    - Chronic obstructive pulmonary disease or pulmonary fibrosis
    - Pulmonary contusions/hemorrhage
  - Pulmonary thromboembolism
- Hypoventilation
  - Pleural effusion, pneumothorax
  - Respiratory muscle failure (e.g., fatigue, myopathy, or neurologic abnormalities)
  - Intoxication (e.g., sedative or anesthetic overdose)
  - Primary neurologic disease (e.g., neoplasia, inflammatory)
- Obstruction
  - Laryngeal paralysis
  - Foreign body (e.g., laryngeal, tracheal)
  - Mass lesion of large airways (e.g., neoplasia, parasitic, inflammatory)
  - Inadequate oxygen concentration of inspired gas (e.g., high-altitude, anesthetic complication)

Cardiac (Right-to-Left Shunting)

- Extracardiac
  - Reversed-shunting patent ductus arteriosus (PDA) (differential cyanosis)
  - Pulmonary arteriovenous fistulas
- Intracardiac
  - Tetralogy of Fallot
  - Atrial or ventricular septal defect with pulmonic stenosis or pulmonary hypertension
  - Endocardial cushion defect
  - Pulmonary artery atresia
  - Right ventricular hypoplasia
  - Double outlet right ventricle
  - Transposition of great vessels
  - Non–Oxygen Carrying Hemoglobin (Hg) (e.g., Methemoglobinemia)

Peripheral Cyanosis

- Central cyanosis (e.g., congestive heart failure)
- Arterial thromboembolism
- Peripheral vasoconstriction (e.g., hypothermia, shock)
- Decreased arterial supply
- Low cardiac output
- Obstruction of venous drainage
  - Tourniquet or foreign object (i.e., rubber band)
  - Venous thrombosis
  - Right-sided congestive heart failure

Ventilation-perfusion mismatch is probably the most common cause of hypoxemia encountered in clinical practice. In pulmonary thromboembolic disease and in diseases causing pulmonary infiltration (e.g., edema, pneumonia, neoplasia, hemorrhage, fibrosis) alveolar ventilation and oxygen exchange are impaired, so that blood flowing to those areas is inadequately oxygenated. This creates a "physiologic shunt," as the deoxygenated blood mixes with the oxygenated blood returning from better-ventilated areas of lung.

Hypoventilation is another potential cause of decreased PaO_2, where alveoli are not ventilated due to elevated pleural pressure (pleural effusion or pneumothorax), depressed respiratory drive (neurologic disease, drug overdose), or respiratory muscle failure. *Obstructive causes* of hypoxemia, such as laryngeal paralysis or tracheal foreign body, result in decreased oxygen availability. *Venous-to-arterial shunts* (right-to-left congenital cardiac or extracardiac shunts) cause deoxygenated venous blood to mix with oxygenated arterial blood, which can result in hypoxemia and cyanosis (see Figure 52-2). If cyanosis is present in a young animal, congenital heart disease must be suspected. A right-to-left shunting patent ductus arteriosus (PDA) results in *differential cyanosis* due to the location of the shunt. Deoxygenated blood from the pulmonary artery is shunted through the PDA to the aorta distal to the brachiocephalic trunk and subclavian artery, producing cyanosis of the caudal portion of the body whereas the cranial part of the body is supplied by adequately oxygenated blood. Other congenital heart defects should be considered in central cyanosis, such as tetralogy of Fallot, atrial or ventricular septal defects or endocardial cushion defects with concomitant pulmonary hypertension or pulmonary stenosis, pulmonary artery atresia, hypoplastic right ventricle, double outlet right ventricle and transposition of great vessels (see ch. 250).

Methemoglobin is a normal product of hemoglobin oxidation, which is maintained at low concentrations (≈1% of total Hb) by the enzyme methemoglobin reductase within the erythrocytes. The percentage of methemoglobin may increase due to exposure to oxidants or if erythrocyte methemoglobin reductase is deficient. Oxidants resulting in methemoglobinemia include acetaminophen (Tylenol), benzocaine, methylene blue, phenazopyridine, nitrates, and nitrites. As methemoglobin is incapable of carrying oxygen, hypoxemia may occur. When the concentration of methemoglobin exceeds 10% of total Hb, a brown discoloration of arterial blood may be grossly visible. Methemoglobinemia may be detected as brown or chocolate colored mucous membranes.

Peripheral cyanosis occurs when there is inadequate oxygenation of peripheral capillary blood. This may be caused by desaturation of Hb in the arterial blood supply, i.e., any of the conditions causing central cyanosis, or result from excessive desaturation of Hb in peripheral tissues due to an imbalance between oxygen supply and the metabolic need of the tissue, due to a variety of causes. Peripheral cyanosis is most commonly due to arterial thromboembolism (saddle thrombus) and/or shock, or other causes including occlusion to venous drainage (such as a tourniquet) and hypothermia.

Evaluation of the Cyanotic Animal

Clinical differentiation of cyanosis is based on history, physical examination findings, and diagnostic testing. History may include exposure to toxicants (such as acetaminophen) or sedatives that may have caused hypoventilation. Physical examination includes assessment of the patient's respiratory pattern (tachypnea, dyspnea, paradoxical breathing pattern), as well as assessment of airway patency (see ch. 28). Stridor, if noted, is indicative of upper airway obstruction, which may necessitate emergency tracheostomy or endotracheal intubation. It is essential to establish whether or not the cyanosis is central or peripheral. Both cranial (oral mucous membranes and tongue) and caudal (vagina or preputium) aspects of the body should be examined for evidence of differential cyanosis suggesting the presence of right-to-left shunting PDA. Differential cyanosis may be associated with hind limb weakness often worsening with exercise. The causes of central cyanosis are often associated with abnormal findings on physical examination reflecting the etiology. Peripheral cyanosis may present with signs of acute lameness or paresis of the affected limb(s). Physical examination of these patients may reveal signs of thromboembolism (pain, pulselessness, pallor, palpable coolness, and paresis) of the affected limb(s), a mass or foreign body (i.e., rubber band) causing venous occlusion, or generalized peripheral cyanosis due to vasoconstriction that may respond to warming or massage of the extremities.

Diagnostic Tests

Arterial blood gas (ABG) analysis is the gold standard for evaluating central cyanosis (see ch. 128). Although venous samples can contribute information, arterial samples provide definitive evidence of abnormalities in SaO_2, PaO_2 and $PaCO_2$, and response to oxygen. ABG can be evaluated when the animal is breathing room air, but for maximal diagnostic information, oxygenated ABG values must be obtained while the animal is receiving 100 percent oxygen. Unfortunately, the latter generally requires anesthesia, which may not be tolerated in many patients with cyanosis.

Pulse oximetry, which approximates SaO_2, is readily available in most clinics for evaluation of central cyanosis (see ch. 128). If a satisfactory signal can be recorded, there is reasonably good correlation between

pulse oximetry estimates and invasive measurements of SaO_2 in dogs. PaO_2 values are extrapolated from SaO_2 using the dissociation curve for oxygen. It should be noted that the use of pulse oximetry does not allow differentiation between oxygenated Hb, carboxy Hb, methemoglobin and cyanide toxicosis. Results of pulse oximetry registration may be influenced by hypovolemia, vasoconstriction and severe anemia. Although pulse oximetry has important limitations, it can be useful to evaluate baseline oxygenation and response to oxygen supplementation when ABG analysis is not available or practical.

Differentiating between deoxygenated Hb and methemoglobin in dogs with central cyanosis can be readily accomplished by exposing venous blood to air. Deoxygenated Hb quickly turns bright red on exposure to air, whereas methemoglobin remains dark brown.

Erythrocytosis may indicate congenital heart disease or chronic hypoxemia (see ch. 57). Evaluation of *lactate concentrations* in different limbs may help diagnose differential cyanosis or peripheral cyanosis caused by thromboembolism or other causes of decreased arterial supply or impaired venous drainage (see ch. 70). In cats and dogs with acute arterial thromboembolism, peripheral venous blood glucose concentrations in the affected limb(s) have been reported to be decreased compared to central venous blood glucose concentrations (see ch. 256). *Thoracocentesis* can be both diagnostic and therapeutic for pleural effusion and pneumothorax, and should be performed prior to other diagnostic tests if paradoxical breathing pattern suggests the presence of free fluid or air within the pleural space (see ch. 102). *Thoracic radiography* is essential to differentiate the many causes of cyanosis, such as pulmonary edema, pneumonia, pleural effusion, pneumothorax, or bronchial disease. The necessity of radiography must however be weighed against patient stability. *Echocardiography* may be extremely helpful in identifying cardiac disease, pulmonary hypertension, and pleural or pericardial effusion. Bubble studies can help determine if right-to-left shunting lesions are present (see ch. 104). *Computed tomography* may be needed to diagnose pulmonary thromboembolism and may help to diagnose right-to-left shunting intracardiac and extracardiac lesions.

Treatment

Central cyanosis is a potentially life-threatening condition that requires immediate attention. Presence of a patent airway is confirmed or established and oxygen is administered immediately while basic stabilization and evaluation are performed (see ch. 131). Most animals with central cyanosis will improve with oxygen therapy. Hypoxemia and cyanosis due to hypoventilation, diffusion impairment, and ventilation-perfusion mismatch (unless severe) will show the greatest improvement. Subsequent treatment greatly depends on the underlying etiology of cyanosis. Supplementing oxygen is not helpful when cyanosis is caused by right-to-left shunting congenital heart disease, because the amount of venous blood reaching the arterial blood is not diminished. Most animals with cyanotic congenital heart disease are relatively comfortable at rest and emergency intervention is not necessary. Therapy of methemoglobinemia involves elimination of the cause and attempt to limit tissue injury. Methylene blue and N-acetylcysteine are recommended for acute therapy of methemoglobinemia (see ch. 151-153). Oxygen supplementation is not useful as methemoglobin cannot bind oxygen. In all cases in which oxygen is administered, repeated evaluation of mucous membranes and measurements of oxygen saturation and ABG values are used to assess efficacy of therapy.

Peripheral cyanosis, although often indicative of serious disease conditions, is usually not life-threatening and therapy is directed toward resolution of the underlying disease process.

CHAPTER 53

Jaundice

Christina Alanna Bradbury

Client Information Sheet: Jaundice: What It Means, Why It Happens and What to Do About It

Jaundice is defined as yellow discoloration of the sclera, skin and mucous membranes due to deposition of the pigment bilirubin. Icterus is another term used interchangeably with jaundice. Hyperbilirubinemia, however, is applicable whenever the serum bilirubin exceeds normal. When bilirubin serum levels rise above 2.0 mg/dL in a dog or cat, one is typically able to discern the yellow hue. "Jaundice" is not a disease; rather, it is a clinical manifestation of an underlying disease process. There is a multitude of disease processes that can ultimately result in jaundice. A basic understanding of bilirubin metabolism and excretion is essential for a methodical and logical clinical assessment and diagnostic approach.

Pathophysiology

Bilirubin is the terminal product of heme metabolism. Heme is liberated from hemoglobin when senescent or damaged erythrocytes are removed from the blood via the mononuclear phagocytic system of the spleen, liver and bone marrow. Within the mononuclear cell (typically a macrophage), the red oxygen-carrying pigment, heme, is cleaved by heme oxygenase, forming the green pigment biliverdin. Biliverdin is reduced by biliverdin reductase to bilirubin, which is then excreted into the blood in its unconjugated lipophilic form and transported to the liver bound to albumin. Additionally, some aging red blood cells are destroyed intravascularly and hemoglobin is released directly into the blood. Free hemoglobin is bound to haptoglobin and delivered as a complex to the hepatic reticuloendothelial system for degradation to unconjugated bilirubin.

Bilirubin passes through the sinusoidal surface membranes of hepatocytes by both passive and facilitated diffusion. Once within hepatocytes, lipophilic bilirubin is processed and "conjugated" into a water soluble form via glucuronidation. The water soluble, conjugated bilirubin is excreted into bile canaliculi by an ATP-dependent active transporter. Conjugated bilirubin is incorporated into bile, stored in the gallbladder, and excreted into the duodenum via the common bile duct. Within the intestinal tract, bilirubin is converted by bacterial flora into urobilinogen (colorless), urobilin (orange-red), stercobilinogen, and, finally, stercobilin, the pigment that imparts the brown color to feces. In complete biliary obstruction, feces lack these pigments and are grey- or clay-colored, termed "acholic." In normal homeostasis, the liver and biliary system process and excrete all bilirubin produced via heme metabolism. If any aspect of this system becomes overwhelmed or deranged, jaundice may result.

Causes of Jaundice

Separating causes of jaundice into three primary conditions is logical when assessing a patient: moderate to severe hemolysis (pre-hepatic), inability of hepatocytes to properly process and transport bilirubin out of the hepatocyte (hepatic), and the inability to excrete bile into the duodenum due to an obstruction (post-hepatic) (Box 53-1). Pre-hepatic jaundice is usually due to extravascular hemolysis as intravascular hemolysis produces only small amounts of bilirubin. Excessive production of bilirubin overwhelms hepatic absorption, processing, and excretion. Bilirubin then accumulates in the blood. The most common cause of pre-hepatic jaundice in dogs is immune mediated hemolytic anemia (IMHA). Some infectious diseases and immune-mediated destruction of erythrocytes also cause hemolysis in cats. Feline red blood cells are particularly sensitive to oxidative damage and hemolysis may follow another disease, such as hepatic lipidosis. Therefore, careful evaluation of the entire patient and clinical picture is always indicated. In both dogs and cats, intoxications (zinc, onions, acetaminophen), genetic disorders (pyruvate kinase deficiency, osmotic fragility

syndrome, etc.) and hypophosphatemia are less common causes of hemolytic anemia.

Box 53-1

Causes of Jaundice

Pre-hepatic (Hemolysis)

Immune-mediated hemolytic anemia
Infectious
- *Mycoplasma* spp., *Babesia* spp., *Cytauxzoon felis*

Heinz body anemia
- Toxins/drugs (acetaminophen, onions, zinc)
- Hepatic lipidosis

Hypophosphatemia
Genetic disorders
- Osmotic fragility syndrome, phosphofructokinase deficiency, pyruvate kinase deficiency

Hepatic

Infectious
- Viral (feline infectious peritonitis, canine adenovirus-1)
- Bacterial (*Leptospira* spp., *Salmonella* spp., rickettsial disease)
- Protozoal (*Toxoplasma gondii, Neospora caninum*)
- Fungal (histoplasmosis, coccidioidomycosis)
- Parasitic (*Heterobilharzia americana*, visceral larval migrans)

Inflammatory/immune-mediated disease
Toxins
- *Amanita* spp., aflatoxin, Sago palm, cyanobacteria

Drugs
- Carprofen, acetaminophen, azathioprine, methimazole

Neoplasia
Copper-associated hepatopathy
Lysosomal storage disease

Post-hepatic

Intraluminal bile duct obstruction
- Mucocele, cholelith, inflammation, stricture, neoplasia

Extraluminal bile duct obstruction
- Pancreatitis, neoplasia, lymphadenopathy, duodenal foreign body

Hepatic hyperbilirubinemia in both dogs and cats is associated with hepatocellular dysfunction, due to toxins (drugs [carprofen], *Amanita* spp., blue green algae, aflatoxin, xylitol; see ch. 152), immune-mediated or inflammatory conditions (see ch. 282 and 283), infectious disease (bacterial, fungal, protozoal, viral), neoplasia, or genetic abnormalities in copper metabolism (copper-associated hepatitis; see ch. 285). Hepatic lipidosis is a common cause of jaundice in cats. Lipidosis follows rapid mobilization of peripheral fat to the liver where the hepatocytes become overwhelmed and cell function is compromised. Cats have also been shown to develop mild hyperbilirubinemia in response to significant systemic inflammatory disease, especially sepsis. However, these cats do not usually become clinically jaundiced as the serum bilirubin concentration is usually <2.0 mg/dL.

Post-hepatic jaundice, obstruction of the biliary system, can occur from abnormalities within the biliary system or secondary to diseases affecting organs surrounding the biliary tree (see ch. 288). Obstruction may be partial or complete. Common intraluminal causes of extrahepatic biliary duct obstruction (EHBDO) in dogs include biliary mucocele, cholelithiasis, infection or neoplasia. Infectious cholangitis causing partial obstruction is more common in cats than dogs, and biliary mucoceles are exceedingly rare in cats. Extraluminal causes of EHBDO include pancreatitis, neoplasia, enlarged regional lymph nodes, or an intestinal foreign body at the level of the papilla. Regardless of cause, complete obstruction of the biliary system is a medical and surgical emergency.

Clinical Approach (Figure 53-1)

Signalment and a thorough history are extremely valuable. Signalment may offer clues to explain the cause of jaundice since certain breeds are predisposed to genetic disorders such as pyruvate kinase deficiency or copper storage disease. Age is important because, for example, an adult dog is far less likely to have canine adenoviral hepatitis than is an unvaccinated puppy. A complete history should include travel, ectoparasite exposure, current medications, possible environmental toxins, and vaccination history. A variety of drugs may cause hemolytic anemia or liver toxicosis. Appetite, water intake, urination and defecation may further elucidate the nature of the underlying problem. Establishing duration and progression of clinical signs may prove to be important. For example, a dog who was clinically healthy and now has acute vomiting and sudden onset of jaundice is more likely to have a biliary obstruction or IMHA than copper-associated hepatitis.

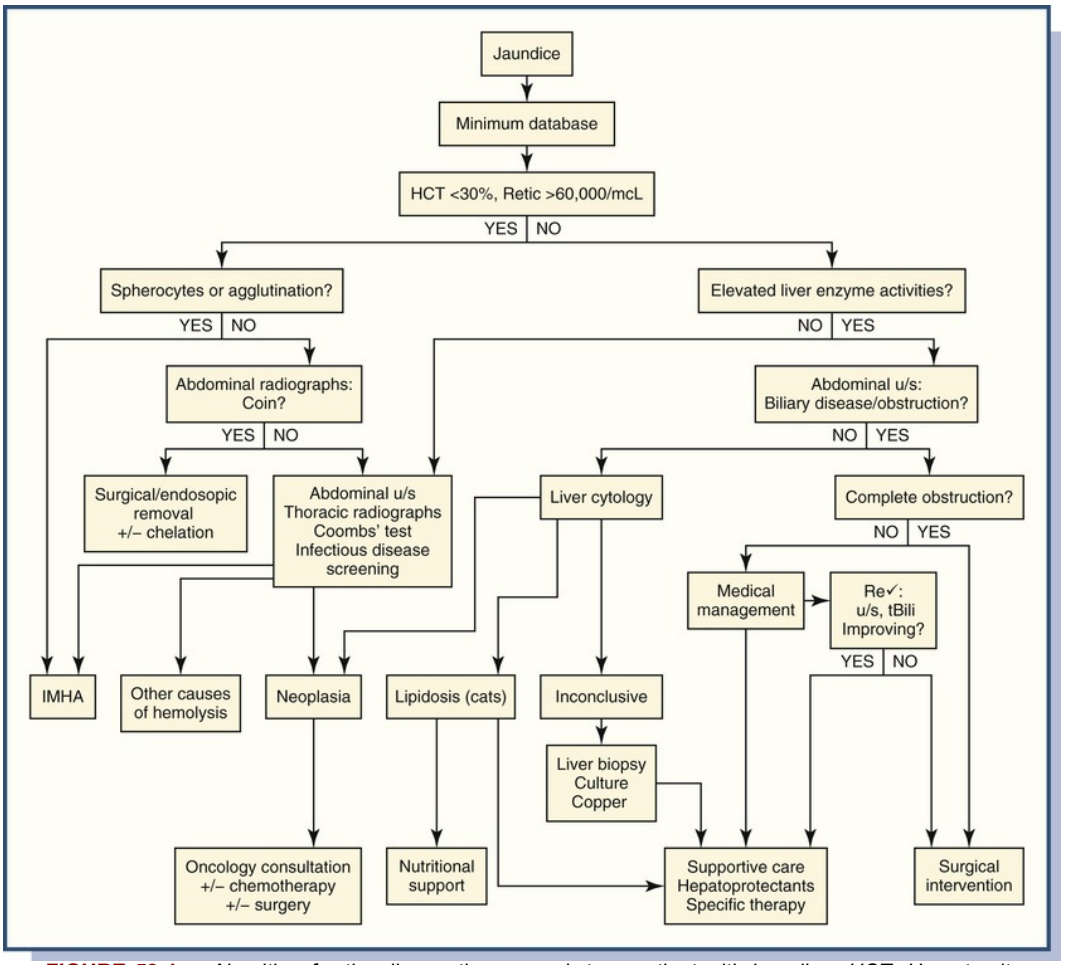


FIGURE 53-1 Algorithm for the diagnostic approach to a patient with jaundice. *HCT,* Hematocrit; *IMHA,* immune-mediated hemolytic anemia; *Retic,* reticulocyte; *tBili,* total bilirubin; *u/s,* ultrasound.

Results of a complete physical examination may further narrow the focus of the investigation. Careful attention to mucous membrane color, heart rate and pulse quality are essential in diagnosing anemia. Abdominal palpation may reveal hepatomegaly, cranial abdominal pain, masses or effusion. Fever is suggestive of an infectious or inflammatory process such as IMHA, pancreatitis, bacterial cholangitis or a ruptured gallbladder. Bleeding abnormalities can be associated with IMHA (Evans' syndrome, disseminated intravascular coagulation [DIC]), hepatic failure, and severe cholestasis; therefore, close inspection of the skin and mucous membranes may reveal petechiae or ecchymoses (see ch. 54). Rectal palpation may reveal melena or evidence of gastrointestinal (GI) bleeding secondary to drug exposure (for example, carprofen) and/or liver failure. A neurologic exam should be performed (see ch. 259), as hepatic encephalopathy may occur with hepatic lipidosis, acute liver failure and cirrhosis. In patients with hepatic encephalopathy, frequent neurologic exams should be performed, assessing response to therapy and progression of disease.

Information gathered from signalment, history and physical examination should aid in developing a prioritized list of differential diagnoses and the diagnostic approach. For example, pale mucous membranes, tachycardia, weakness, tachypnea and bounding pulses should lead the clinician to immediately assess the hematocrit in-hospital. Acute cranial abdominal pain, vomiting, fever, and dehydration are typical of biliary obstruction or pancreatitis and warrant aggressive diagnostic evaluation.

Diagnostic Plan

The classic "minimum data base" should be collected in any patient with jaundice. The complete blood count (CBC) should help identify and characterize the anemia, if present. Hemolysis typically causes a macrocytic, hypochromic, regenerative anemia while chronic liver disease may cause a microcytic, normochromic non-regenerative anemia. Microcytic hypochromic anemia is typically due to chronic blood loss, such as occurs with severe flea infestation or GI bleeding. Cats with hepatic lipidosis may develop a regenerative Heinz body anemia. Spherocytosis and autoagglutination confirm immune-mediated destruction of erythrocytes, and an inflammatory leukogram is often present. Thrombocytopenia may be noted with IMHA or DIC, which can develop secondary to liver failure or severe inflammatory states like pancreatitis or bile peritonitis.

The chemistry panel should include alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), cholesterol, blood urea nitrogen (BUN), albumin, glucose and bilirubin. Post-hepatic jaundice will generally reveal hyperbilirubinemia, marked cholestatic enzyme elevation (ALP, GGT), moderate to marked hypercholesterolemia, and moderate increases in "hepatocellular leakage enzymes" (ALT, AST). Liver function, as assessed with BUN, albumin and glucose are typically unremarkable unless other co-morbidities exist. In patients with hepatic jaundice, increases in serum ALT are similar to those in ALP, while BUN, albumin and glucose may be abnormal. IMHA may also cause increases in liver enzyme activity. An ALP > ALT coupled with a normal GGT in an obese, jaundiced cat is virtually pathognomonic for hepatic lipidosis. Bilirubinuria, proteinuria, glycosuria, or renal tubular casts may suggest multi-organ dysfunction requiring further investigation.

Abdominal imaging, with either radiographs or ultrasound, is valuable. Abdominal radiographs may show a penny or other foreign body causing zinc toxicosis, mass lesions or choleliths. Thoracic radiographs should be assessed for metastatic disease, pneumonia or other causes of secondary IMHA. Ultrasound is valuable for non-invasive evaluation of the biliary system and hepatic parenchyma. Splenomegaly is common in hemolytic anemia. Gallbladder content and wall thickness, liver morphology, the biliary tree, the pancreas, the surrounding mesentery and the surrounding lymph nodes should be carefully evaluated. Abdominal ultrasound may also identify incidental findings that alter recommendations and prognosis. Exploratory laparotomy is recommended when there is a persistently dilated common bile duct with increasing hyperbilirubinemia, biliary mucocele, gallbladder rupture, or cholelithiasis with evidence of obstruction. Without evidence of complete biliary obstruction, patients with suspected cholangitis or pancreatitis are treated medically. If cholangitis is suspected, ultrasound-guided fine-needle aspiration (FNA) of the gallbladder with culture of the bile is recommended to guide antimicrobial therapy. If cholangitis is suspected but culture is not possible, empirical antimicrobial therapy may be considered. If a partial obstruction is suspected, monitoring bilirubin and serial ultrasound exams may be useful indicators of response to therapy. If a hepatic cause of jaundice is suspected, cytology of an ultrasound-guided liver FNA is recommended (see ch. 89 and 93). Cytology is most useful in diagnosing diffuse infiltrative neoplasia and hepatic lipidosis. Liver biopsy may be recommended if cytology results are inconclusive.

Jaundice in any patient indicates a significant underlying pathologic process. Clearly, the etiologies are disparate. The veterinary clinician is encouraged to consider all aspects of the condition before recommending any tests. Often, with a logical approach and basic understanding of the underlying processes, it is possible to identify the cause and therefore make appropriate recommendations regarding treatment and prognosis.

CHAPTER 54

Petechiae and Ecchymoses

Shauna Blois

Client Information Sheet: Petechiae and Ecchymoses (Bruising)

Petechiae and *ecchymoses* are red to purple discolorations of the skin or mucosal surfaces, resulting from small blood vessel bleeding. Petechiae are typically <3 mm in diameter, resulting from capillary bleeding; ecchymoses are larger lesions caused by bleeding from small arterioles and venules. In human medicine, the term *purpura* is used for describing similar lesions (typically 3-10 mm in size). Signs of surface bleeding usually result from a platelet or blood vessel abnormality, but can be due to a more global bleeding disorder.

Pathophysiology

Blood vessel walls are lined by a single layer of endothelial cells, connected by tight junctions and anchored to a basal membrane. This selective barrier prevents the leakage of red blood cells from the circulation. The blood vessel has an active role in hemostasis. Under normal conditions, the endothelium expresses anticoagulant properties. Adequate numbers of circulating platelets help maintain endothelial structure and function. With vascular injury, the subendothelial matrix is exposed, allowing platelets to interact with collagen and other matrix molecules. Circulating platelets adhere to the site of the vascular defect, and recruit even more platelets to aggregate. Some of the major mediators of these processes include von Willebrand factor (vWF) and platelet integrin alpha-IIb–beta$_3$.[1] Coagulation proteins bind to and interact with phospholipids on activated platelet membranes of the platelet plug, accelerating and amplifying the coagulation reaction, eventually producing a fibrin clot.[2] The essential role of platelet-vascular interactions in maintaining hemostasis is illustrated when there is a quantitative or qualitative primary hemostatic disorder. Thrombocytopenia is the most common cause of petechiae and ecchymoses; thrombopathias and vascular diseases can also cause signs of surface bleeding.

Thrombocytopenia

Thrombocytopenia can be caused by increased platelet destruction, consumption, or sequestration, or can be secondary to decreased bone marrow production (see ch. 201). Immune-mediated thrombocytopenia (IMT) is the most common cause of severe thrombocytopenia in dogs. IMT is caused by antibodies directed against platelets (less commonly megakaryocytes), leading to platelet phagocytosis by the reticuloendothelial system. Primary IMT is idiopathic; secondary IMT can result from infectious, inflammatory, or neoplastic diseases, or drug therapy.[3] Primary IMT is rare in cats.[4] In addition to thrombocytopenia, IMT can cause platelet dysfunction.[5]

Disseminated intravascular coagulation (DIC) is a serious complication that can arise from various systemic diseases. Patients with DIC initially are hypercoagulable but the disorder can progress to a consumptive coagulopathy, resulting in thrombocytopenia and decreased circulating coagulation proteins. Clinical signs include petechiae, ecchymoses, and overt bleeding.[6] Other causes of platelet consumption include vasculitides.

Other causes of thrombocytopenia typically do not cause hemorrhage. Platelet sequestration can occur secondary to hepatomegaly, splenomegaly, hypotension, endotoxemia, and hypothermia. Moderate thrombocytopenia can result from hemorrhage.[7] Additional causes of thrombocytopenia include neoplasia and adverse drug reactions.[8]

Bone marrow diseases such as myelodysplasia can cause thrombocytopenia, as well other cytopenias.[9]

Bone marrow platelet production can be suppressed secondary to drugs, infections, and neoplasia.

In some conditions, thrombocytopenia can result from a combination of the factors stated above. For example, thrombocytopenia associated with rickettsial infections can be due to immune-mediated and non-immune-mediated platelet destruction, platelet consumption from vasculitis and DIC, splenic platelet sequestration, and decreased bone marrow platelet production.[10,11]

Thrombopathia

Platelet function defects can be inherited or acquired (see ch. 201). Inherited platelet dysfunctions have been reported in some dog breeds, including Glanzmann's thrombasthenia in Great Pyrenees Dogs and Otterhounds, thrombopathias of Basset Hounds and Spitz dogs, and delta-storage pool deficiency in American Cocker Spaniels.[12-16] Dogs with inherited platelet disorders can have a history of petechiae, ecchymoses, and other spontaneous bleeding, as well as increased hemorrhage after surgery or trauma. Inherited platelet dysfunction is rare in cats.

Platelet dysfunction can result secondary to infectious diseases such as rickettsial infections, hepatic disease, uremia, and neoplasia. Drugs such as aspirin and clopidogrel are used therapeutically to inhibit platelet function but petechiation, ecchymoses, and other signs of hemorrhage are rarely associated with therapy.[17,18] *In vitro* platelet dysfunction has been described secondary to various drugs and other agents including carprofen, hydroxyethyl starch solutions, and omega fatty acids, but clinical relevance is not known.[19-21]

Von Willebrand Disease

Von Willebrand disease (vWD; see ch. 201) is the most common inherited bleeding disorder in dogs, and is characterized by quantitative or qualitative defects in vWF. vWF molecules are essential for platelet adhesion to sites of vascular damage. Dogs with vWD form ineffective platelet plugs, leading to petechiae, ecchymoses, and other signs of mucosal and cutaneous bleeding.[22] vWD is rare in cats.[23]

Vascular Disorders

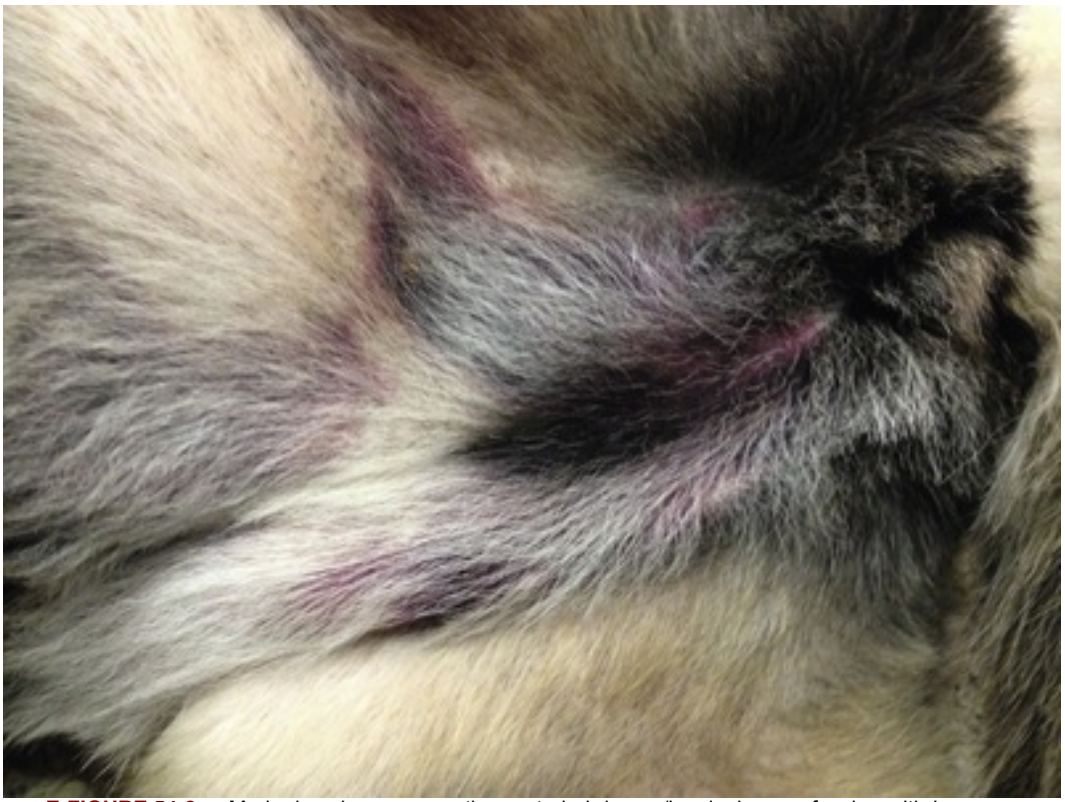
Signs of surface bleeding in patients with a normal platelet count and normal platelet function are suggestive of a vascular disorder. Immune-mediated vasculitis causes inflammatory changes to the blood vessel wall, and can result in edema, ecchymoses, and hemorrhage either spontaneously or after mild trauma. Progressive clinical signs include ulcerative and necrotic skin lesions, as well as pain. Vasculitis can be a primary immune-mediated event, or it can occur secondary to a variety of medications, infections, neoplastic conditions, and other diseases.[24]

Diagnostic Approach

A thorough patient history is essential in diagnosing primary hemostatic disorders. A patient or familial history of bleeding tendencies is suggestive of an inherited platelet disorder. A complete medication history is essential to rule out drug-associated thrombocytopenia, thrombopathia, and vascular disorders. Recent vaccination, tick exposure, travel history, and other current or previous medical history are relevant.

Platelet and vascular disorders can occur secondary to a wide spectrum of conditions. A detailed physical examination will help identify not only the extent of hemorrhage, but also signs of underlying disease. Petechiae are most commonly found on the inner pinnae, ventral abdominal and inguinal skin, and mucous membranes of the oral cavity and genitalia (E-Figure 54-1). Ecchymoses are most commonly found on ventral abdominal and inguinal skin, as well as over sites of recent venipuncture (E-Figure 54-2). Other clinical signs of primary hemostatic defects include gingival bleeding, gastrointestinal hemorrhage (hematemesis, melena, hematochezia), hematuria, epistaxis, ocular hemorrhage, and hematoma formation.[3,4] Excessive bleeding during or immediately after surgical procedures or minor trauma is observed in dogs with significant platelet disorders. Clinical signs unrelated to thrombocytopenia depend on the presence of an underlying disease, such as polyarthritis, hemolytic anemia, and proteinuria, suggestive of a systemic immune-mediated disorder.

E-FIGURE 54-1 Petechiation of the pinna of a dog with immune-mediated thrombocytopenia.



E-FIGURE 54-2 Marked ecchymoses on the ventral abdomen/inguinal area of a dog with immune-mediated thrombocytopenia.

The diagnostic approach to patients with petechiae and ecchymoses should begin with a platelet count (Figure 54-3). When thrombocytopenia is detected on a complete blood count, a blood smear should be reviewed to rule out analytical error (e.g., platelet clumping from suboptimal venipuncture), especially in cats.[25,26] In an emergency, a platelet count is estimated from the blood smear by multiplying the number of platelets per high powered field (1000× magnification) by 15-20,000/mcL.[27] The risk of spontaneous bleeding progressively increases as the platelet count declines below 30,000/mcL. Most IMT cases have platelet counts <10,000/mcL.[3,28]

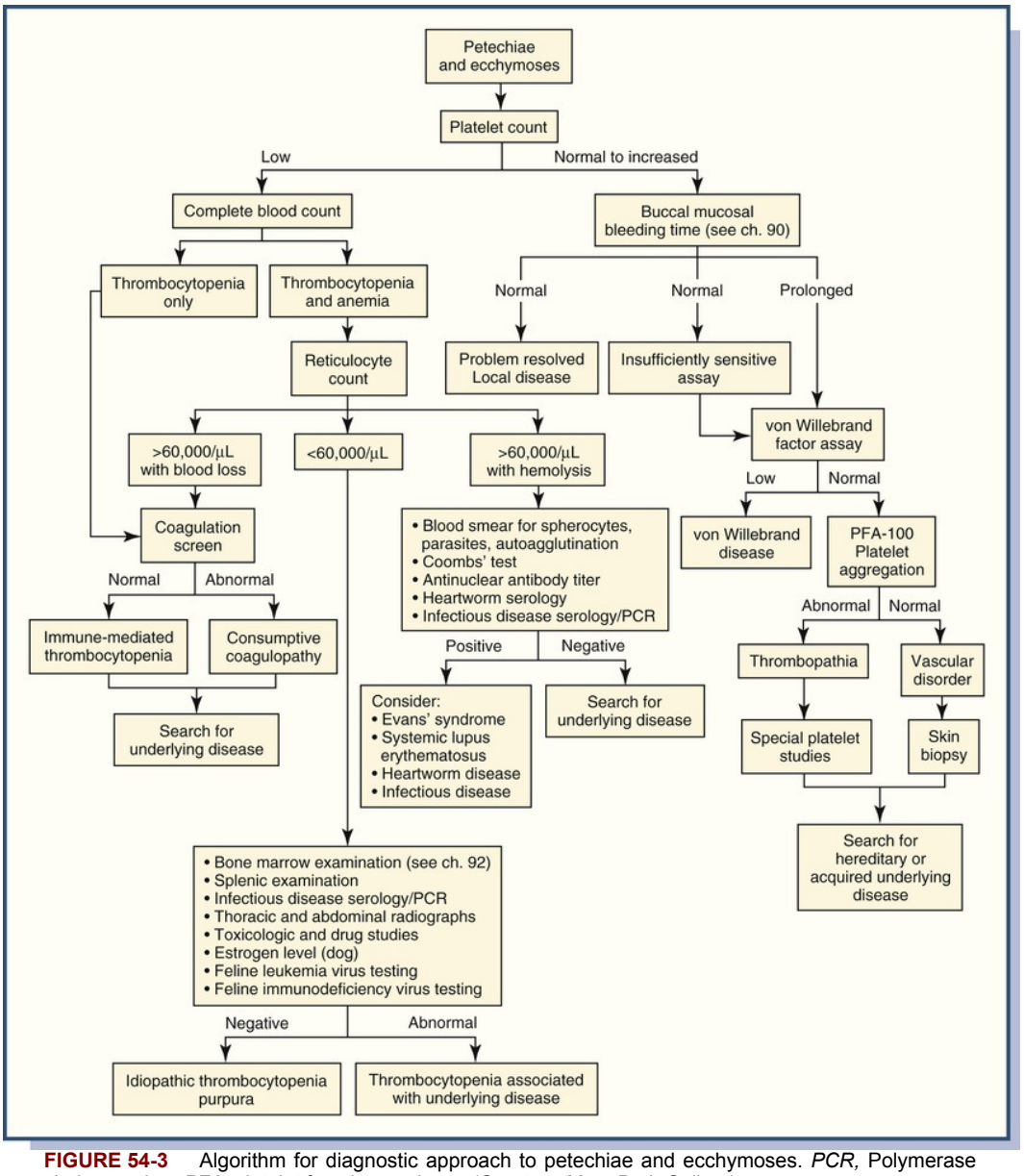


FIGURE 54-3 Algorithm for diagnostic approach to petechiae and ecchymoses. *PCR*, Polymerase chain reaction; *PFA*, platelet function analyzer. (Courtesy Mary Beth Callan.)

Other information from the blood smear and complete blood count may be suggestive of the cause of thrombocytopenia. Immune-mediated thrombocytopenia is diagnosed after ruling out other possible causes of thrombocytopenia. Increased mean platelet volume (MPV), platelet distribution width (PDW), or numbers of reticulated platelets could reflect increased megakaryopoiesis and release of large platelets into circulation of patients with IMT.[29,30] Concurrent anemia and thrombocytopenia can be due to blood loss, combined immune-mediated hemolytic anemia (IMHA) and IMT, or bone marrow disease. Presence of anemia plus red blood cell agglutination and/or spherocytosis is suggestive of concurrent IMHA. Presence of schistocytes on

the blood smear is suggestive of DIC. Pancytopenia is indicative of bone marrow disease, such as myelodysplasia or myelophthisis. When possible, jugular venipuncture should be avoided in patients with a suspected platelet defect or coagulopathy, due to the potential of large hematoma formation in an area that is not amendable to effective manual compression.

A coagulation profile (prothrombin and activated partial thromboplastin times; PT and aPTT, respectively) should be performed to rule out a combined coagulopathy (e.g., DIC) as the cause of bleeding. Prolongation of PT and/or aPTT in conjunction with thrombocytopenia and elevated fibrinogen degradation products or D-dimers is suggestive of DIC.[31] Activated clotting time (ACT) can be assessed to evaluate coagulation protein activity. Marked thrombocytopenia can prolong ACT due to decreased levels of phospholipid available to support clotting.

Bone marrow aspirate and biopsy (see ch. 92) can help rule out primary bone marrow disorders as the cause of thrombocytopenia, especially in patients with other cytopenias or atypical cells in circulation. Bone marrow aspirate and biopsy generally is unrewarding in patients with primary IMT, but should be considered in patients not responsive to therapy.[32] Marked thrombocytopenia is not a contraindication to bone marrow sampling, as excessive hemorrhage at the entry site is rare.

Platelet Function Tests

Platelet function should be evaluated when platelet count is normal in patients with petechiae and ecchymoses. Buccal mucosal bleeding time (BMBT) evaluates *in vivo* platelet-vascular interactions (see ch. 80). Normal BMBT is <4 minutes in dogs and <2 minutes in cats. Thrombopathias, vWD, and vascular disorders can prolong BMBT. BMBT will be prolonged in thrombocytopenic patients, and is contraindicated if platelet count is known to be low. Anemia alone can increase bleeding potential, and may influence BMBT results in the absence of primary hemostatic disorders.[33]

Because vWD is the most common inherited bleeding disorder in dogs, this disorder should be ruled out before additional platelet function testing is performed. The platelet function analyzer (PFA-100, PFA-200) is a point-of-care test that can be used for identifying platelet disorders and vWD.[34,35] Testing for vWD is necessary to differentiate an abnormal result from a primary platelet disorder. However, replacement of the patient's plasma with that from a normal dog will correct PFA results in cases of vWD but not in cases of a primary platelet disorder.[36] Anemia and thrombocytopenia prolong PFA results.[37]

Genetic testing is available for vWD and some other platelet defects. Other specialized tests (platelet aggregometry, flow cytometry) may be required to diagnose other platelet defects, but are not widely available.

Treatment

Treatment of platelet disorders is variable depending on the underlying cause. Dogs suspected to have IMT might initially be treated with doxycycline in addition to immunosuppressive therapy if they live in, or have traveled through, a region that has a high prevalence of rickettsial diseases causing thrombocytopenia. Medications that could cause thrombocytopenia (e.g., sulfa antibiotics, methimazole) should be discontinued.

Thrombocytopenic or thrombocytopathic patients uncommonly require blood transfusion support. Patients with critical hemorrhage may benefit from red blood cell transfusion (see ch. 130). Platelet transfusion usually is not indicated, due to the limited lifespan of transfused platelets, especially in IMT patients. However, if animals are showing signs of life-threatening hemorrhage (especially central nervous system hemorrhage or uncontrolled blood loss), platelet transfusion using fresh whole blood, platelet concentrate, or platelet-rich plasma can provide short term benefit while therapy directed at the underlying disorder is initiated (see ch. 130).[28]

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CHAPTER 55

Abnormal Heart Sounds and Heart Murmurs

Robert Prošek

Cardiac auscultation is an important tool in the clinician's armamentarium. Interpretation of heart and lung sounds is predicated on the clinician's understanding of their genesis in health and a variety of clinical disorders. Cardiovascular sounds of short duration are referred to as *transient heart sounds* and include the normally heard first heart sound (S_1) and second heart sound (S_2) (Audio 55-1). Heart murmurs are auditory vibrations of longer duration created when laminar flow is disrupted.

Implementing good technique with a quality stethoscope is fundamental. During auscultation the animal should be standing or sitting in a quiet environment. Both sides of the thorax should be carefully auscultated using the stethoscope's diaphragm and bell with special attention to the areas overlying the cardiac valves. The clinician should correlate the various heart sounds to the events of the cardiac cycle. A good orientation is palpation of the precordial impulse (left apex beat) that occurs just after S_1, and the arterial pulse that is felt between S_1 and S_2.

Transient Heart Sounds

The First (S_1) and Second (S_2) Heart Sounds

The first heart sound (Figure 55-1) is associated with closure and tensing of the atrioventricular valves (mitral and tricuspid) at the onset of systole coinciding with the QRS complex on the electrocardiogram. S_1 is longer, louder, and lower pitched than the second heart sound. Causes of increased intensity of S_1 include thin chest wall, tachycardia, high sympathetic tone, systemic arterial hypertension, and anemia. Diminished intensity of S_1 may be auscultated in animals with obesity, pleural or pericardial effusion, diaphragmatic hernia, dilated cardiomyopathy, hypovolemia, emphysema, or a prolonged P-R interval. Splitting of S_1 is occasionally auscultated at the cardiac apex in healthy, large-breed dogs or may result from electrical disturbances (ectopic beats, bundle branch blocks, cardiac pacing) or mechanical factors (tricuspid or mitral stenosis).

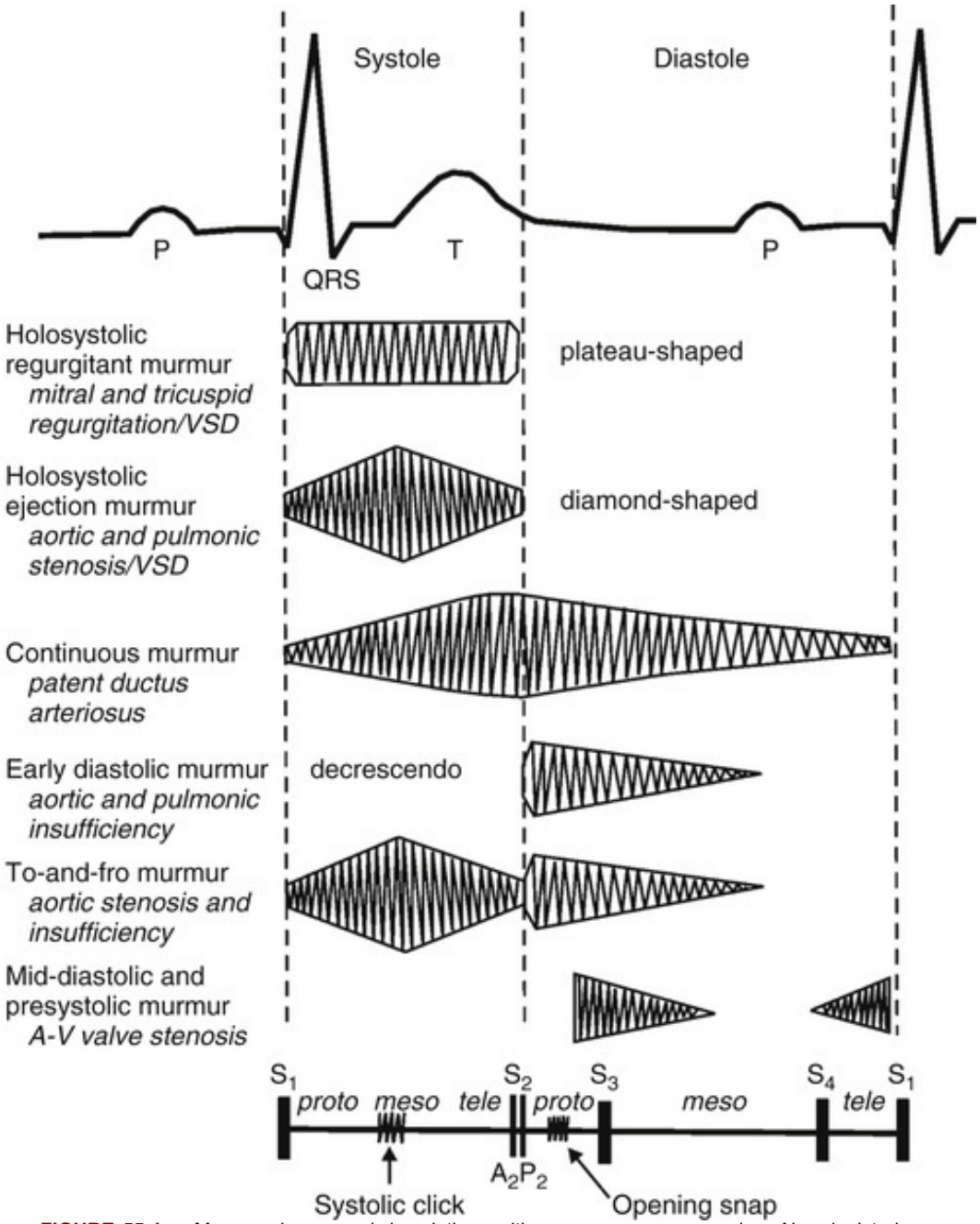

FIGURE 55-1 Murmur shapes and descriptions with some common examples. Also depicted are normal and abnormal transient heart sounds and their location within the cardiac cycle. *A_2,* Aortic valve closure; *A-V,* atrioventricular; *meso,* mid; *P_2,* pulmonic valve closure; *proto,* early; *S_1,* first heart sound; *S_2,* second heart sound; *S_3,* third heart sound; *S_4,* fourth heart sound; *tele,* late; *VSD,* ventricular septal defect.

The second heart sound (see Figure 55-1) is associated with closure of the semilunar valves (aortic and pulmonic) at the end of systole following the T wave on the electrocardiogram. In dogs and cats, pulmonic valve (P_2) closure follows aortic valve (A_2) closure by a very short interval, which causes S_2 to be heard as a single sound. On occasion an audible, split second heart sound may be seen in healthy, large-breed dogs during inspiration due to a longer right ventricular ejection period. Pathologic splitting of S_2 occurs with heartworm disease (Audio 55-2), primary pulmonary hypertension and right-to-left patent ductus arteriosus.

Delayed closure of P_2 also occurs with left-to-right intracardiac shunts (atrial septal defects), pulmonic stenosis, right bundle branch block, ectopic beats, and ventricular pacing. Premature A_2 closure can on

occasion be noted with mitral insufficiency and mitral stenosis. Paradoxical splitting of S_2 results from delayed closure of the aortic valve and is sometimes audible in dogs with aortic stenosis, left bundle branch block, ectopic beats, and systemic hypertension.

The Third (S_3) and Fourth (S_4) Heart Sounds

The third and fourth heart sounds occur during diastole and are not audible in normal dogs and cats. S_3 and S_4 heart sounds are of lower frequency than S_1 and S_2 and are usually best heard with the bell of the stethoscope. When heard, S_3 and S_4 may sound like the triple cadence of a galloping horse (Audio 55-3).

The term *gallop rhythm* should probably be avoided because the presence of an audible S_3 or S_4 has nothing to do with the heart's underlying electrical rhythm. Rapid ventricular filling generates the S_3 sound, also known as *S_3 gallop, protodiastolic gallop,* or *ventricular gallop*. An audible S_3 (Audio 55-4) is most commonly heard with diastolic volume overloading as in dilated cardiomyopathy, patent ductus arteriosus, and mitral insufficiency. In dogs with mitral insufficiency, the S_3 gallop may be mistaken for the second heart sound if a loud pansystolic (holosystolic) murmur extends through the second heart sound. Protodiastolic gallop sounds in cats are most commonly associated with dilated cardiomyopathy, anemia, and hyperthyroidism.

The presystolic gallop, also called *S_4 gallop* or *atrial gallop,* is heard just before S_1 and occurs just after the P wave on the electrocardiogram. This low-frequency sound is generated by blood flow into the ventricles during atrial contraction; hence the absence of S_4 gallops with atrial fibrillation. An audible S_4 (Audio 55-5) in the cat and dog is usually associated with increased ventricular hypertrophy and stiffness and is sometimes audible in animals with third-degree atrioventricular block.

At fast heart rates, rapid ventricular filling and atrial systole transpire very close together, which makes differentiation between S_3 and S_4 impossible. The resulting single accentuated sound is referred to as a summation gallop.

Ejection Sounds, Systolic Clicks, Opening Snaps, and Pericardial Knocks

Ejection sounds are left basilar high-frequency sounds generated by opening of the semilunar valves or dilatation of the great vessels during early systole. These sounds are occasionally noted in pulmonic stenosis, aortic stenosis, tetralogy of Fallot, and heartworm disease. Systolic clicks are mid to late high frequency sounds usually heard best over the mitral valve area (Audio 55-6). Systolic clicks are occasionally associated with degenerative valvular disease, mitral valve prolapse, and mitral dysplasia. The genesis of the sound in dogs is uncertain but is likely caused by the sudden tensing of redundant valve leaflets or elongated chordae tendineae as they buckle into the left atrium. A systolic click should be differentiated from a split (hear Audio 55-2) or gallop heart sound (hear Audio 55-3). Pericardial knocks are uncommon early diastolic sounds caused by restrictive pericardial disease. Timing of the sound is similar to S_3 and appears to be generated by abrupt restriction to ventricular filling by a diseased pericardium. See Figure 55-1 for timing of transient heart sounds and description of murmurs.

Cardiac Murmurs

Cardiac murmurs represent sounds of longer duration than the transient heart sounds. Cardiac murmurs are caused by turbulent blood flow in the heart or adjacent blood vessels created upon disruption of normal laminar flow. The development of turbulent blood flow can be created by high-velocity flow, flow from narrow restricted area into a larger area, or low blood viscosity. The relationship of cardiac murmurs and flow velocity, vessel size, and blood viscosity is defined by the Reynolds number. When the number reaches a critical high level, blood flow becomes turbulent.

$$\text{Reynolds number} = (\text{Radius})(\text{Velocity})(\text{Density}) \div \text{Viscosity}$$

Murmurs can be characterized and described by their timing within the cardiac cycle (systolic, diastolic, portions thereof), location (point of maximal intensity), radiation, intensity (loudness), shape, and frequency

(pitch).

Timing

Systolic murmurs may start immediately at the first (S_1) heart sound and last through the second (S_2) heart sound (pansystolic murmur), may start immediately after S_1 and last until S_2 (holosystolic), or may occur in early (protosystolic), mid (mesosystolic), or late (telesystolic) systole. Diastolic murmurs most commonly occur in early diastole (protodiastolic), throughout diastole (holodiastolic), or can occasionally be audible only at the end of diastole (presystolic).

Location and Radiation

The location of a murmur refers to the valve area at which the murmur is heard best (point of maximal intensity). Alternatively, location can be described simply by the terms *apex* or *base* (e.g., left apex or mitral valve area). Some murmurs may also radiate to other areas, yielding important clues as to the source of the murmur. For example, the murmur of subvalvular aortic stenosis (point of maximal intensity [PMI] at left heart base) may radiate to the ventral neck area due to turbulence in the carotid arteries and may also be heard on the right cranial thorax.

Intensity (Loudness)

The intensity of the murmur is commonly graded on a 1 to 6 scale, with grade 1 murmur the softest and grade 6 the loudest (Box 55-1).

Box 55-1

Grading of Cardiac Murmurs

Grade 1: Very soft, localized murmur detected in a quiet room after intently listening for a few minutes
Grade 2: Soft murmur but easily heard after a few seconds
Grade 3: Moderate-intensity murmur
Grade 4: Loud murmur but not accompanied by a palpable thrill (vibration)
Grade 5: Loud murmur accompanied by a palpable thrill
Grade 6: Very loud murmur that produces a palpable thrill still audible after stethoscope is removed from the chest

A grade 1 murmur is the faintest murmur and is heard in a quiet environment with particular effort, whereas grade 5 and 6 murmurs are associated with palpable vibrations on the chest wall (palpable thrill). The intensity of the murmur at its origin is determined by blood flow velocity and the rate of flow (velocity × flow = force). The intensity of the murmur at the body surface is affected by direction of the turbulent jet, character of tissue between auscultation area and the turbulent jet, and the frequency of the murmur. Often the intensity of a heart murmur is not directly correlated with the severity of a lesion. However, describing the loudness of a murmur is important for serial examinations, and in certain heart diseases at least a rough correlation exists.

Pitch (Frequency)

A murmur's quality and pitch relate to its frequency components, which may be high, medium, low, or of mixed frequency. Most murmurs consist of midrange mixed-frequency sounds. On occasion high-frequency musical tones or low-frequency “honks” are auscultated. Musical murmurs (whoops) are most commonly identified in dogs with modest mitral valve disease.

Shape

Heart murmurs are often described by their frequency profile within the cardiac cycle in relation to their shape on a phonocardiogram. Terms that are commonly used include *plateau-* or *band-shaped murmurs* for those murmurs of equal intensity throughout their duration; *decrescendo* for murmurs that gradually taper off

from an initial peak; and *crescendo decrescendo* (diamond-shaped, ejection murmur) for murmurs that build up to a peak intensity and then taper in intensity.

Systolic Heart Murmurs

Mitral Insufficiency

The murmur of mitral insufficiency is best heard at the left apex (mitral valve area) and commonly radiates dorsally and to the right thorax, making reliable diagnosis of tricuspid regurgitation difficult.

The characteristic murmur is plateau (band-shaped) and holosystolic; however, in its early stages the murmur may be protosystolic and with mitral valve prolapse the murmur may develop in mid- to late-systole. A mitral insufficiency murmur is typically of mixed frequency and harsh sounding (Audio 55-7), but it may be high-pitched or musical (whooping) in quality (Audio 55-8).

Mitral insufficiency can be caused by chronic degenerative valvular disease (endocardiosis), endocarditis, hypertrophic obstructive cardiomyopathy, congenital malformations, and diseases that cause left heart enlargement and dilation of the mitral annulus (e.g., patent ductus arteriosus, dilated cardiomyopathy).

Tricuspid Insufficiency

The murmur of tricuspid insufficiency sounds similar to that of mitral insufficiency but is loudest over the right apex (tricuspid valve area). It is often difficult to distinguish tricuspid insufficiency from a radiating murmur of mitral insufficiency. Tricuspid murmurs might be a different pitch compared with a radiating mitral murmur and can be accompanied by jugular pulsations. Tricuspid insufficiency can result from congenital malformations of the valve, chronic degenerative valve disease, or any disorders that cause marked right heart enlargement and valve annulus distention, such as pulmonary hypertension and arrhythmogenic right ventricular cardiomyopathy. Tricuspid valve endocarditis is extremely rare in dogs and cats.

Aortic Stenosis

Valvular and subvalvular aortic stenosis (SAS) produce a systolic ejection (crescendo-decrescendo) murmur that is usually best heard at the left heart base (Audio 55-11).

The murmur is usually of mixed frequency and harsh, and it sometimes radiates towards the right cranial thorax and up the neck along the carotid arteries. Mild obstructions cause soft murmurs that are difficult to distinguish from innocent or functional murmurs. Murmurs that vary dramatically in intensity with exercise or excitement should prompt consideration of a dynamic left ventricular outflow tract obstruction. Dynamic outflow tract obstruction is the most common type of ejection murmurs in cats with hypertrophic cardiomyopathy and its onset and duration coincide with systolic anterior motion of the mitral valve (Audio 55-9). Dynamic left ventricular outflow tract obstruction occurs uncommonly in dogs as an isolated abnormality or in association with mitral valve dysplasia or hypertrophy of the interventricular septum.

Pulmonic Stenosis

The pulmonic stenosis murmur is typically a high-frequency crescendo-decrescendo (ejection) holosystolic murmur, best heard at the left heart base over the pulmonic valve (Audio 55-10). The murmur can be very similar to the aortic stenosis murmur (hear Audio 55-8) described above but should not radiate along the carotid arteries. As the pressure gradient between the right ventricle and pulmonary artery increases, the murmur intensity becomes louder and peaks later in systole.

Ventricular Septal Defect

Ventricular septal defects (VSDs) produce murmurs that vary tremendously in shape and quality. Most often the murmur is a harsh, mid- to high-frequency holosystolic murmur best heard on the right cranial thorax (Audio 55-18).

Murmur intensity may be reduced when the VSD is large and as pulmonary hypertension develops. With severe pulmonary hypertension, the murmur may be entirely absent and splitting of the second heart sound is noted (hear Audio 55-2).

Atrial Septal Defect

Heart murmurs in dogs and cats with an atrial septal defect (ASD) result from increased flow across the pulmonic valve as a result of the left to right shunting. This murmur resembles that of mild pulmonic stenosis but is often accompanied by a fixed splitting of the second heart sound. Flow across the atrial septal defect is usually not audible.

Physiologic and Innocent Murmurs

Functional (physiologic) murmurs are usually caused by decreased blood viscosity or increased cardiac output. Physiologic murmurs are most often noted in animals with anemia, fever, pregnancy, hyperthyroidism, thin thoracic walls, and increased sympathetic tone. These murmurs usually are proto- to mesosystolic, soft to moderate intensity (grade 1/6 to 3/6), and loudest at the left heart base (Audio 55-12). They tend not to radiate extensively.

Innocent murmurs should disappear as the dog matures and appear to be the result of larger stroke volumes in puppies for the size of their great vessels in comparison with adult dogs.

In some cats, turbulent blood flow can be noted in the region of the right ventricular outflow tract, often causing a soft systolic apical sternal murmur ranging in grades from 1 to 3/6, with no evidence of structural heart disease and little clinical consequence (Audio 55-13).

Diastolic Heart Murmurs

Aortic Insufficiency

The murmur of isolated aortic insufficiency is typically a decrescendo murmur starting at the time of S_2 and extending variably into diastole (Audio 55-14).

In young dogs, aortic insufficiency can occur as an isolated defect or in combination with subaortic stenosis or a ventricular septal defect. Detection of aortic insufficiency in an adult dog or cat should prompt consideration of bacterial endocarditis.

When the regurgitant volume is large, the diastolic murmur is often accompanied by a soft mesosystolic ejection murmur, creating a distinct "to-and-fro" murmur (Audio 55-15).

The systolic ejection component tapers off in late systole and allows recognition of S_2 and differentiation from a continuous murmur. Other causes of "to-and-fro" murmurs include ventricular septal defects that cause loss of aortic root support and pulmonic valve stenosis and significant pulmonic insufficiency (rare). Occasionally massive aortic regurgitation causes premature closure of the mitral valve producing functional mitral stenosis and a diastolic murmur referred to as an *Austin Flint murmur*.

Pulmonic Insufficiency

The murmur of pulmonic insufficiency is similar to that of aortic insufficiency; however, clinically significant pulmonic insufficiency is uncommon. It is sometimes detected in animals with pulmonary hypertension, pulmonic valve dysplasia, or idiopathic dilation of the pulmonary artery.

Mitral Stenosis

The diastolic murmur of mitral stenosis is difficult to recognize in dogs and cats. This low-frequency murmur begins in mesodiastole and has presystolic accentuation due to atrial contraction (Audio 55-16). Mitral stenosis might be accompanied by other cardiac malformations, which cause murmurs such as valvular or subvalvular aortic stenosis. In dogs, mitral stenosis may be more common in breeds that are prone to congenital mitral valve malformations such as the Bull Terrier breed, in which it is often associated with aortic stenosis (see ch. 250).

Continuous Murmurs

The most common cause of a continuous murmur at the left heart base is patent ductus arteriosus (PDA). This classic "machinery-like" murmur of a PDA is usually audible throughout the cardiac cycle with peak intensity near S_2 (Audio 55-17).

The intensity of the murmur is diminished in late diastole in dogs with very slow heart rates and the diastolic component can also disappear with the development of pulmonary hypertension. Less common causes of continuous murmurs include aorticopulmonary windows, ruptured aneurysms of sinus of Valsalva, and coronary arteriovenous fistulas.

Auscultation and Beyond

Historical findings may suggest underlying heart disease; however, a thorough auscultation with identification and understanding of abnormal heart sounds and their genesis will permit recognition of the most likely cause (Figure 55-2).

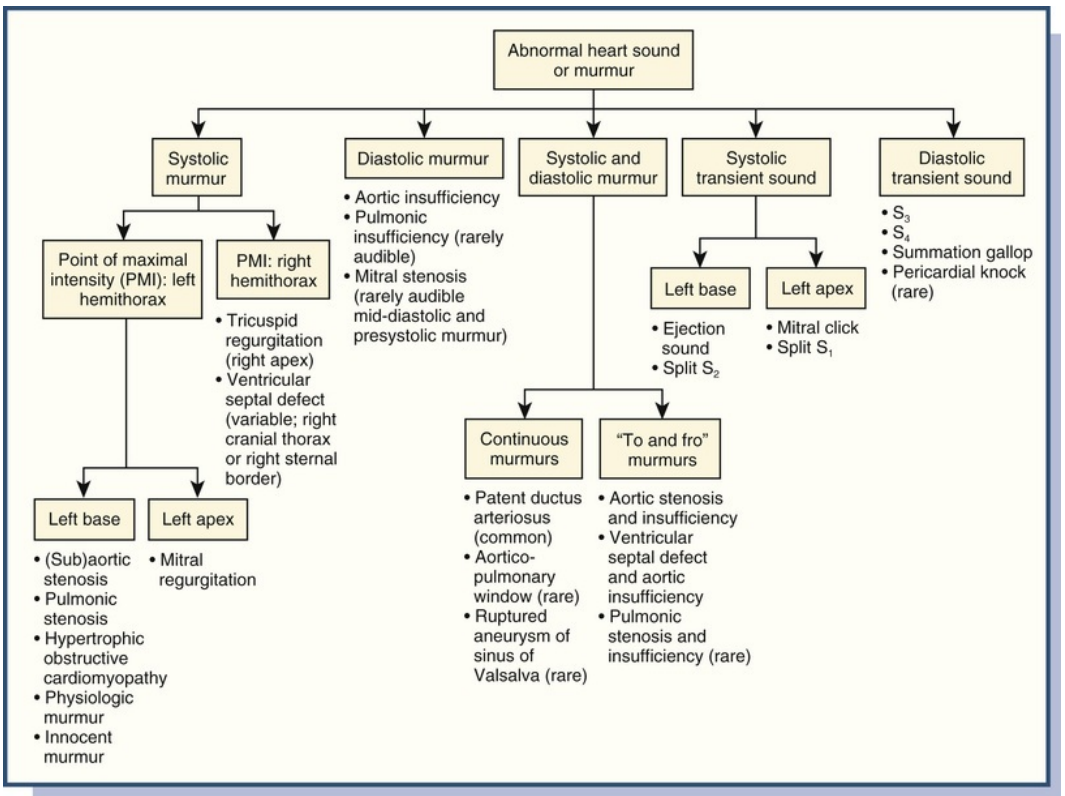

FIGURE 55-2 Algorithm for differentiating causes of abnormal heart sounds and murmurs.

As important a tool as cardiac auscultation is, it should be one part of a complete physical exam that integrates evaluation of lung fields, jugular veins, arterial pulses, and peripheral circulation. Increasingly the affordability and availability of next-generation electronic stethoscopes will allow the clinician to pick up difficult-to-hear heart sounds and other body sounds.

Additionally, other diagnostic tests might be needed to further classify and define the animal's abnormality, and in some cases differentiate a pathologic from a physiologic murmur (especially cats).

CHAPTER 56

Pulse Alterations

Christopher Little

Client Information Sheet: Pulse Alterations

Clinical examination of veterinary patients is grounded in tangible physical findings that we can appreciate with our senses. Evaluation of the rate, strength, and regularity of the pulse is the oldest, cheapest, quickest and easiest way to assess cardiac output.[1] The astute clinician will assess the pulse alongside the audible heart rate and rhythm while also assessing the color and refill of the capillaries. This chapter explores how and why pulse alterations occur.

The pulse usually is assessed by applying the tips of the fingers over one or both femoral arteries. Other sites, such as the dorsal pedal and median caudal arteries, can also be used. If the patient is restless, shivering, very hirsute, dirty, matted, or obese, these factors will hamper assessment of the pulse.

The pulse rate, under normal circumstances, will be identical to the heart rate. In the clinical setting, most dogs exhibit pulse rates between about 80 and 140 pulses per minute. There is a very weak relationship between body weight and heart rate in the dog, contrary to what was once believed.[2-5] Cats have faster heart/pulse rates than those of the dog, varying from about 130-240 per minute.[6-8]

The heart is the servant of the brain. Heart rate changes from instant to instant because of altering neural traffic from the brainstem.[9-14] During sinus rhythms, heart rate is determined by the sino-atrial node (SAN) where intrinsic heart rate is modified by the autonomic nervous system. The intrinsic rate of the canine SAN is about 150-180 beats per minute (bpm).[15-17] Sympathetic tone is sometimes described as the cardiac accelerator and parasympathetic tone the decelerator but this is an unhelpful and misleading description. A more accurate concept is that there are two autonomic oscillators which influence the SAN. Parasympathetic tone predominates in the healthy dog, especially at rest, so that the heart rate is usually much lower than the intrinsic rate of the SAN.[18-20] Varying parasympathetic tone adjusts heart rate by increasing the pulse interval (i.e., slowing the rate) to a variable degree. Changes in parasympathetic tone can, and do, occur extremely rapidly, within a period of less than one cardiac cycle.[11,21-23] Sympathetic tone, on the other hand, slowly changes heart rate over a time frame of many seconds; as sympathetic tone increases, the heart speeds up.[11,21,24,25] Thus, an increase in heart and pulse rate can occur by reduction in cardiac parasympathetic tone, or an increase in sympathetic tone, or both, whereas a reduction in heart/pulse rate may be brought about by an increase in parasympathetic tone, a reduction in sympathetic tone, or both. In healthy dogs at rest, sinus arrhythmia often is discernible, in which heart/pulse rate varies from beat to beat due to rapid oscillations of cardiac parasympathetic tone carried in the efferent fibers of the vagus nerve. Sinus arrhythmia is found in other species too, including horses and humans; it is fairly uncommon in cats during clinical examination, and is usually quite subtle in that species.

If the rhythm of the heart is regular, then usually the pulse strength will be regular too. Normally, each heartbeat causes ejection of blood into the systemic circulation. If the intervals between heartbeats vary substantially, preloading of the ventricles from beat to beat will change, and this will lead to variability in stroke volume from beat to beat. As each stroke volume is ejected into the aorta, the elastic tissue of the arteries is stretched and a pulse wave travels towards the periphery, which can be detected by a clinician feeling the pulse. The pulse pressure represents the difference in blood pressure from the end-diastolic arterial pressure to the maximum systolic arterial pressure. The pulse pressure is not related to absolute pressure (Figure 56-1). The rapidity of the increase in pulse pressure depends on the flexibility, or compliance, of the arteries as well as the inotropic behavior of the heart. If the heart beats very strongly, or the arteries are very stiff, or both, the pulse pressure will rise sharply. As blood runs off from the central arteries towards the periphery, the pressure within the arteries falls. The slope of this falling pressure curve is essentially an index

of total peripheral resistance; when peripheral resistance is high, the fall-off in arterial pressure will be shallow. On the other hand, if there is low peripheral resistance, run-off will be rapid and the slope of the falling pressure curve will be steep.[26] Unfortunately, the changing shape of the pulse pressure curve varies in too subtle a manner to be easily detected by the practicing clinician, but it is an arena where invasive monitoring, and more recently non-invasive electronic technologies, such as photoplethysmography, have provided useful insights.[27]

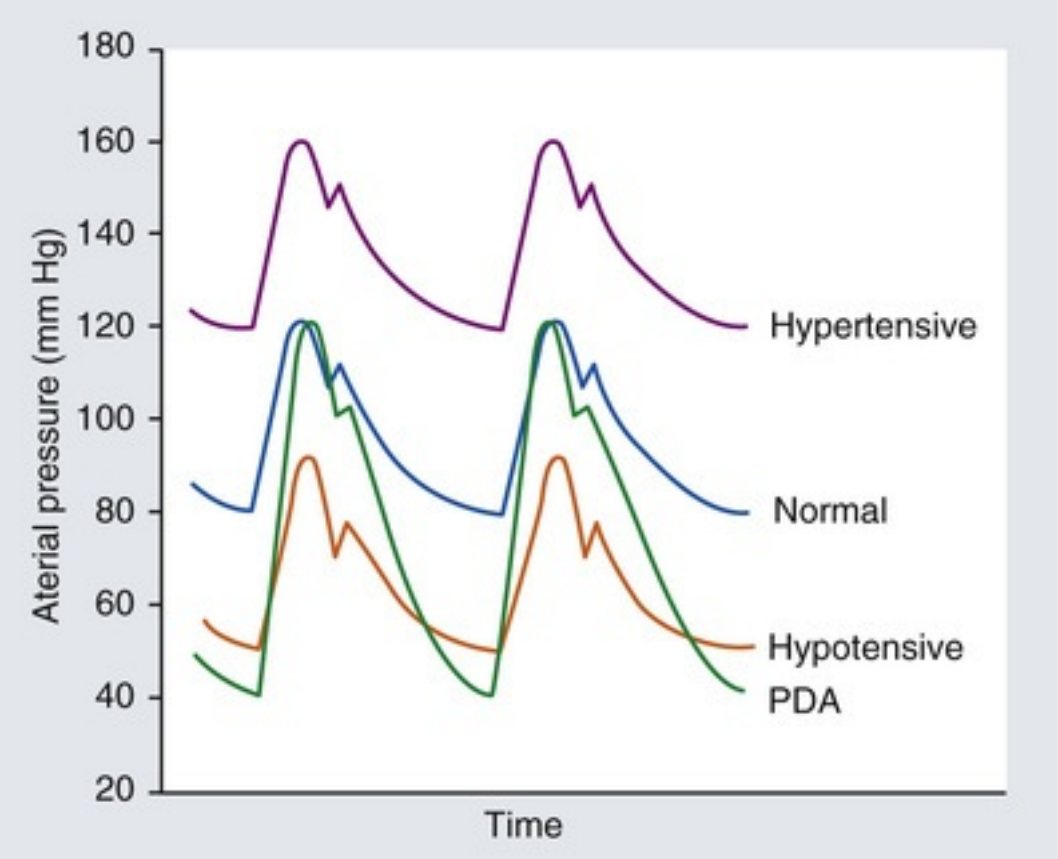

FIGURE 56-1 Normal and abnormal arterial pressure tracings. The strength of the palpable pulse depends on the *pulse pressure:* the difference between systolic and diastolic arterial pressures. *Blue:* in a normal individual, the peak systolic pressure may be 120 mm Hg and the lowest diastolic pressure 80 mm Hg. The normal pulse therefore reflects a pulse pressure of 120 − 80 = 40 mm Hg. *Purple:* in a hypertensive patient, the peak systolic pressure may be 160 mm Hg and the lowest diastolic pressure 120 mm Hg. The pulse pressure is still 40 mm Hg (160 − 120 mm Hg) so the pulse quality is normal. This example shows why systemic hypertension does not produce an unusually strong pulse. *Green:* in patent ductus arteriosus (PDA), diastolic runoff through the ductus greatly reduces diastolic pressures. The peak systolic pressure is 120 mm Hg, but the lowest diastolic pressure is 40 mm Hg. The pulse pressure is very high (120 − 40 = 80 mm Hg), which explains the bounding or "waterhammer" pulse that is characteristic of PDA. *Orange:* in moderate hypotension, both systolic and diastolic pressures can be low but again the pulse pressure may still be normal. If the pressures are very low a very weak or "thready" pulse will be felt, if any pulse is palpable at all. (Courtesy Dr. Etienne Côté.)

For any given peripheral resistance, end-diastolic pressure within the arteries will be lower when the inter-beat interval is prolonged and higher if the interval between beats is short. Thus, the perceived strength of the pulse can vary as a result of several factors. When the heart rate is slow, end-diastolic pressures will be lower because there is a long time for peripheral run-off of blood, and preloading of the left ventricle will tend to be enhanced, leading to a higher stroke volume, a stronger systolic impulse, and a higher maximum systolic pressure. On the other hand, fast heart rates tend to give a weaker pulse since stroke volume tends to be lower and end-diastolic pressure has less time to fall. When the heart rate varies widely from beat to beat, pulse pressure, too, will vary from beat to beat. This phenomenon is most frequently found in association with sinus arrhythmia in dogs, but any intermittent cardiac rhythm can lead to a variable pulse interval and strength or, if severe, the palpable pulse rate may be lower than the ausculted heart rate; this is known as a pulse deficit.

If the pulse pressure is high, the pulses are said to be hyperkinetic, whereas a low pulse pressure is designated hypokinetic (Figures 56-1 and 56-2). Aortic insufficiency and patent ductus arteriosus are forms of structural heart disease where the femoral pulses are hyperkinetic due to rapid diastolic run-off of blood from the aorta. Conversely, dogs with severe aortic stenosis may have a weak hypokinetic pulse, and/or may have a pulse pressure that has a later-than-normal peak in systole due to prolonged ejection time; this is sometimes termed *pulsus parvus et tardus*.

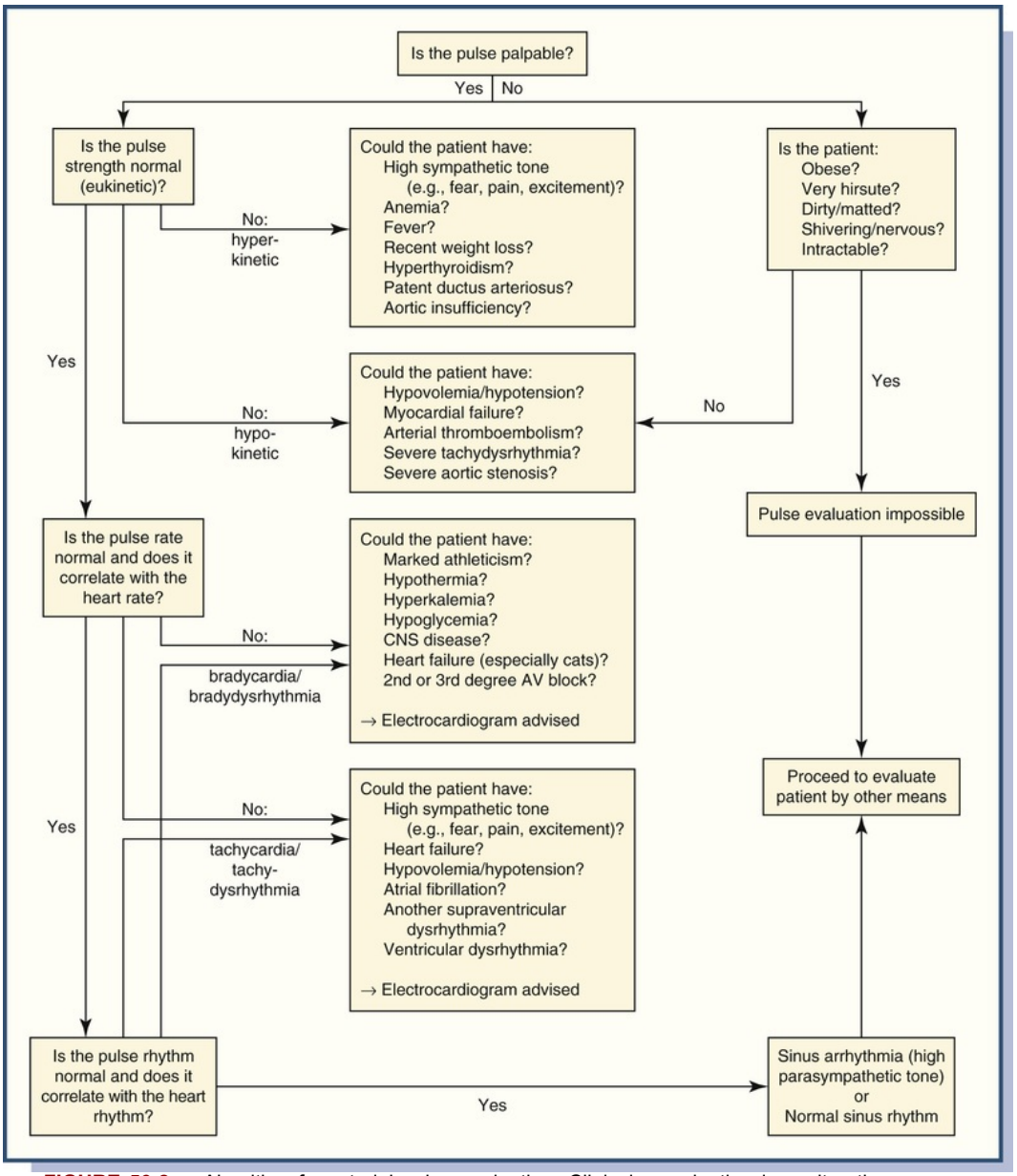

FIGURE 56-2 Algorithm for arterial pulse evaluation. Clinical examination is an iterative process which is informed and directed by the patient history. Pulse rate and rhythm should always be assessed in conjunction with other signs, especially the patient's level of arousal, body temperature, and auscultation findings. Pulse rate and rhythm should always resemble heart rate and rhythm; if they do not, then consider performing an electrocardiogram. *AV*, Atrioventricular; *CNS*, central nervous system.

Most changes in pulse rate and rhythm are due to altered cardiac autonomic tone. A fast, regular pulse can occur when an animal is exercising or excited, or is suffering from fear, anxiety, pain, fever, or anemia. These are situations in which parasympathetic tone is depressed and sympathetic tone tends to be elevated. Holter studies of dogs show peaks of tachycardia prior to and during exercise, or feeding, and whenever these animals are stimulated, such as when owners return from work.

Important disease states associated with tachycardia include hyperthyroidism and those conditions that are associated with hypovolemia, e.g., dehydration or recent blood loss. Animals that are febrile will often exhibit tachycardia together with a hyperdynamic pulse due to low peripheral resistance. Myocardial failure can produce a tachycardia with a weak (also called "thready") pulse. In this case, the low stroke volume occurs because of intrinsic cardiac disease. Atrial fibrillation, which is frequently found in dogs and cats with serious cardiac disease, may be recognized as a chaotic tachydysrhythmia that produces frequent pulse deficits (see ch. 248). When a patient has atrial or ventricular ectopic beats, the pulse pressure will often be variable too; again, pulse deficits can be recognized when the premature beat forces the ventricles to contract while inadequately filled, such that the heart sounds are ausculted but no pulse is felt.

In health, sinus bradycardia is seen mainly during rest and sleep when sympathetic tone is virtually absent and parasympathetic tone is dominant but varying. Bradycardias can be of major clinical significance, however; for instance, bradycardia may be found in patients with hypothyroidism, hypoglycemia, hypothermia, hyperkalemia (e.g., in acute hypoadrenocorticism), or central nervous system (CNS) disorders in which intracranial pressure is elevated ("Cushing's reflex").[28,29] In the author's experience, if a cat is presented in acute respiratory distress and with a heart rate of 140 beats/minute or less, it will frequently be found to be hypothermic and in heart failure.

There are a few pulse abnormalities which present very typical patterns that are said to be almost pathognomonic of certain diseases. Careful clinicians will be skeptical about such pattern recognition but *pulsus paradoxus* denotes an exaggerated decrease in systolic, mean, and pulse pressure on inspiration, and an exaggerated increase on expiration. This phenomenon in veterinary patients is particularly suggestive of cardiac tamponade due to a pericardial effusion (see ch. 254), although in human and experimental medicine it is found in other circumstances such as acute asthma, chronic obstructive pulmonary disease, bronchospasm and hypovolemic shock.[30-35] It can be difficult to recognize in many dogs because their panting creates very rapid fluctuations in intrathoracic pressure and venous return to the heart. *Pulsus alternans* refers to alternating strong and weak pulses that may occur sometimes when the left ventricle is severely dysfunctional, such as in dilated cardiomyopathy. Systemic thromboembolism, secondary to feline cardiomyopathy or hypercoagulable states, may result in a complete loss of arterial pulses (see ch. 256).

Venous Pulses

Venous pressures are always much lower than arterial pressures; this means that venous pulses, if they are perceived at all, are seen but not felt. This is impossible in hirsute patients. Jugular venous distension occurs when right atrial pressure is increased, as jugular venous pressures correlate with right atrial and ventricular pressures. Visible jugular venous pulsations sometimes occur when significant tricuspid regurgitation is present (large v waves). In normal animals, the jugular pulsations should not extend more than one third the distance up the neck from the thoracic inlet. Pulsations in the underlying carotid arteries may mimic jugular venous pulsations; occlusion of the jugular vein by manual compression will help differentiate venous pulsations from arterial pulsations. Performing the *hepatojugular* or *abdominojugular reflux test*, by applying abdominal pressure for about 30 seconds, may enhance jugular venous distension, as increased venous return in the presence of right-sided heart disease may elevate right atrial pressure.

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SECTION IV

Differential Diagnosis for Clinicopathologic Abnormalities

OUTLINE

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Chapter 58 Leukopenia, Leukocytosis
Chapter 59 Thrombocytopenia, Thrombocytosis
Chapter 60 Hypoproteinemia, Hyperproteinemia
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CHAPTER 57

Anemia, Erythrocytosis

Tracy Stokol

Anemia is defined as reduced red blood cell (RBC) mass and is recognized by a packed cell volume (PCV), hematocrit (HCT), hemoglobin concentration, or RBC count below established reference intervals for that species. Conversely, an increased RBC mass is called erythrocytosis and is recognized by values that are higher than the upper reference limit for these tests. Note that although "polycythemia" and "erythrocytosis" have been used interchangeably, they are not synonymous. Polycythemia is a more general term, referring to increases in any of the cells in blood (RBC, leukocyte, platelet) with polycythemia vera referring to a chronic myeloproliferative disorder specifically involving only the erythroid lineage. Erythrocytosis specifically refers to an *absolute* increase in RBCs (or a true increase in RBC mass) and will be used herein. The tradition in veterinary medicine is to use PCV or HCT (the default used herein) as the main indicator of RBC mass.

The first step in interpretation of HCT results is to decide whether the result is truly abnormal for that individual animal, i.e., interpret results in context of signalment (breed, age, sex, reproductive status). In this sense, the use of reference intervals can potentially be misleading because they are usually established from presumably healthy adult animals of various breeds and will be insensitive to breed- and age-specific changes. For instance, a HCT of 0.45 L/L (45%) is within established reference intervals for most laboratories, but this HCT would be compatible with anemia in a Greyhound, a breed which typically has higher HCTs than other breeds.[1] In addition, reference intervals can be broad and may be insensitive to changes in an individual animal. For this reason, the author considers it worthwhile to obtain baseline complete blood count and clinical chemistry results when a dog or cat has reached adulthood (generally 12 months of age in small or medium dog breeds and cats, and 2 years of age in large dog breeds), so that subsequent individual-specific abnormalities can be identified using a critical difference approach.[2] Unfortunately, critical differences are analyzer- and method-specific and have not been established for HCT (or other hematologic tests) in dogs and cats, so a subjective assessment of the degree of change in an individual animal must be made by the individual clinician. Once anemia or erythrocytosis has been conclusively identified, a systematic approach can be used to identify the pathophysiologic mechanisms and, hopefully, the underlying cause.

Anemia

Anemia is the most common hematologic abnormality encountered in veterinary clinical practice and can be the cause of disease (e.g., immune-mediated hemolytic anemia [IMHA]) or a marker of underlying disease (e.g., cancer, chronic kidney disease). There are three main pathophysiologic mechanisms for anemia: hemorrhage (loss), hemolysis (decreased lifespan), and decreased production. Distinguishing between these mechanisms is important for identifying the underlying disease or cause of anemia (Box 57-1) and is best accomplished by using a combination of signalment, historical information, clinical signs, imaging findings, and clinical pathologic results. Anemia can be multifactorial in origin, which can complicate discovery of the underlying cause and there are always going to be those challenging and potentially frustrating cases, where the mechanism and cause of the anemia remain ambiguous.

Box 57-1

Pathophysiologic Mechanisms for Anemia with Helpful Blood Smear Features (also see Box 57-3)

Hemorrhage: Acute or chronic
- Internal into body cavities, e.g., hemoperitoneum from splenic or hepatic trauma
- External via the skin or respiratory, genitourinary or gastrointestinal tracts, e.g., melena from an

ulcerated gastrointestinal tumor. Chronic external blood loss can result in a concurrent iron deficiency anemia, which may be regenerative or non-regenerative.

Hemolysis: Intravascular or extravascular

Immune-mediated*: Primary or secondary to infectious agents, blood group incompatibility (transfusions, neonates) or drugs. Uncommon in cats. Helpful smear features: Spherocytes, agglutination, ghost cells*.

Infectious agents: ***Babesia*** sp., ***Theileria*** sp., *Mycoplasma haemocanis* and *haemofelis, Leptospira* sp.[17-19] Only *Mycoplasma haemofelis* is a common cause of hemolytic anemia in cats. The other feline hemotropic mycoplasmas are not typically associated with an anemia.[20]

Oxidant-induced, e.g., zinc poisoning, onion ingestion, exposure to skunk musk in dogs,[21-23] acetaminophen toxicosis or accidental onion ingestion in cats. Helpful smear features: Heinz bodies, eccentrocytes, pyknocytes.

Fragmentation injury (microangiopathic hemolytic anemia), e.g., vasculitis, DIC. Helpful smear features: Acanthocytes, keratocytes, schistocytes. This type of anemia is frequently non-regenerative due to concurrent anemia of inflammatory disease.

Aberrant macrophage activity: Reactive or neoplastic histiocytic disorders, e.g., hemophagocytic histiocytic sarcoma[24]

Inherited defects of the RBC membrane (e.g., stomatocytosis in Alaskan Malamutes, spherocytosis in Golden Retrievers) or metabolic pathway enzymes (e.g., **phosphofructokinase deficiency** in dogs, pyruvate kinase deficiency in dogs and cats) (rare).[25-27] Helpful smear features: Stomatocytes, sphero-echinocytes (pyruvate kinase deficiency in dogs).

Miscellaneous: **Severe hypophosphatemia, snake** or **bee venoms.**[28,29] Helpful smear features: Echinocytes (certain snake venoms), ghost cells*.

Decreased production

Suppression from extramedullary disease (common)

Inflammatory disease ("chronic" disease): Inflammatory cytokines suppress erythropoiesis, erythropoietin release, and response to erythropoietin, and sequester iron via hepcidin. Can have an extravascular hemolytic component (particularly in cats).

Chronic kidney disease: Decreased erythropoietin (other factors may contribute, including hemorrhage from gastrointestinal ulcers, hemolysis from uremic toxins)

Endocrine disease: Hypothyroidism, hypoadrenocorticism

Bone marrow disease

Increased intramedullary cell death (ineffective erythropoiesis): Immune-mediated, i.e., non-regenerative immune-mediated anemia or precursor-directed immune-mediated anemia[30-33]; drugs or hormones (e.g., estrogen); toxins; infectious agents (e.g., *Ehrlichia canis*); histiocytic disorders (reactive or neoplastic)

Abnormal production with intramedullary cell death: Neoplasia (myelodysplastic syndrome or primary myelodysplasia; in cats, this is often secondary to feline leukemia virus infection)

Destruction or damage to erythroid progenitors: Immune-mediated (pure red cell aplasia), infectious agents including viruses (e.g., parvovirus) and bacteria (e.g., *Ehrlichia*), drugs (e.g., recombinant human erythropoietin[34,35]), toxins

Decreased hemoglobin production: Iron deficiency (chronic blood loss, functional deficiency secondary to portosystemic shunts), chronic lead toxicosis

Decreased or abnormal DNA production: vitamin B_{12} or folate deficiency (rare), feline leukemia virus infection

Primary (e.g., acute myeloid leukemia) or infiltrative (e.g., histiocytic sarcoma, multiple myeloma in cats, lymphoma in dogs) marrow neoplasia: Multiple mechanisms including myelophthisis, immune-mediated, inflammatory cytokines

DIC, Disseminated intravascular coagulation; *RBC,* red blood cell.

*Causes of intravascular hemolysis are highlighted in **boldface**. Ghost cells will only be seen when intravascular hemolysis is occurring. Be careful not to mistake "artifactual" ghost RBCs from ghost RBCs created by intravascular hemolysis (RBCs can lyse *in vitro* with stored blood samples or when the blood smear is prepared).

Mechanisms of Anemia

If an anemia is "adequately" regenerative, the underlying mechanism is hemorrhage or hemolysis. Distinguishing between these two mechanisms relies primarily on clinical signs, physical examination, imaging, and other laboratory tests, i.e., specifically identifying a source of hemorrhage or a cause for hemolysis on a blood smear examination (Figure 57-1). Note that in some diseases, the anemia may be due to a combination of hemorrhage and hemolysis.

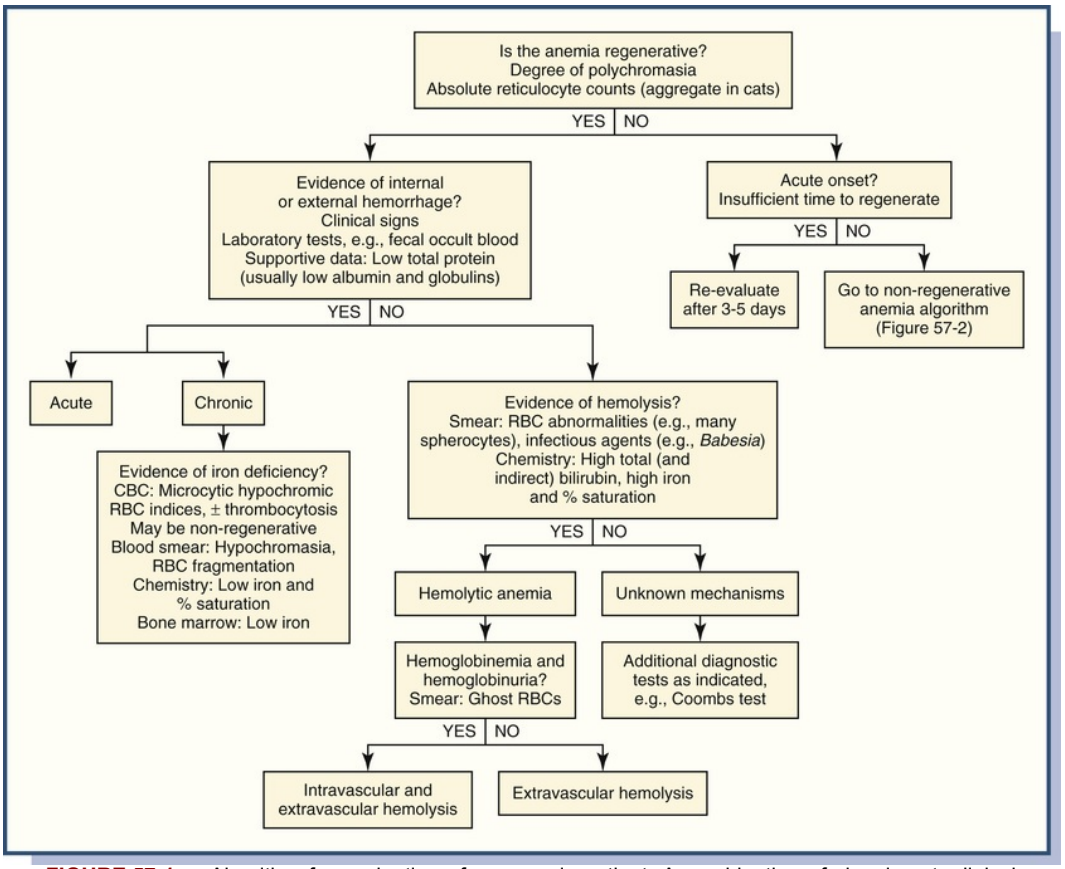

FIGURE 57-1 Algorithm for evaluation of an anemic patient. A combination of signalment, clinical signs, physical examination, imaging results and clinical pathologic testing results are used to determine whether the anemia is regenerative (due to hemorrhage or hemolysis) or non-regenerative (due to extramedullary or primary bone marrow disease). Hemolytic anemia can be extravascular or intravascular and extravascular, with specific disease entities causing intravascular hemolysis (see Box 57-1). *CBC*, Complete blood count; *RBC*, red blood cell. (Modified from eClinPath.com [section on anemia].)

Hemorrhage

This can be internal (into a body cavity) or external ("lost" from the body, e.g., from gastrointestinal hemorrhage) (see ch. 135). Low total protein (especially the combination of low albumin and globulins) would support the conclusion that an anemia is due to hemorrhage, but it is not specific for hemorrhage. A normal serum total protein concentration also does not rule out hemorrhage, since peracute hemorrhage, internal bleeding, or chronic intermittent external blood loss may not result in low protein concentrations. If external hemorrhage is chronic and occult, iron deficiency can ensue, which can be recognized by hypochromic RBCs and microcytic hypochromic RBC indices. Serum iron and percentage saturation of transferrin are usually quite low with iron deficiency anemia, but decreases in these test results are also seen with inflammatory disease. Newer diagnostic tests for iron content in reticulocytes can be helpful for confirming an iron deficiency anemia in dogs but these results are not generally available and are not specific for iron deficiency, being abnormal in dogs with inflammatory disease, portosystemic shunts or breed-associated microcytosis.[3]

Hemolysis

Decreased RBC lifespan can be due to extravascular (i.e., phagocytosis of RBCs by macrophages) or intravascular (i.e., rupture of RBCs in vessels) destruction of RBCs. Intravascular hemolysis is usually accompanied by extravascular hemolysis, but the latter can occur alone and is the most common mechanism of increased RBC destruction in a hemolytic anemia (see ch. 195 and 198). It is important to distinguish intravascular from extravascular hemolysis, because this helps narrow the differential diagnostic list (see Box 57-1). Intravascular hemolysis is characterized by hemoglobinemia and hemoglobinuria. Ghost RBCs and relevant RBC changes (e.g., oxidant injury) or pertinent infectious agents (e.g., *Babesia canis*) may also be seen on blood smears, but should not be relied upon for distinguishing intravascular from extravascular hemolysis. Ghost RBCs are RBCs on blood smears that have "lost" the bulk of their hemoglobin and look like faded RBCs; ghost RBC from intravascular hemolysis must be distinguished from *in vitro* hemolysis with ghost cell formation as an artifact of storage or blood smear preparation. Hemolytic anemia of any type is usually associated with a normal or high serum total protein concentration and can result in bilirubinemia, especially due to unconjugated (indirect) bilirubin. Note that conjugated (direct) bilirubin may increase and even dominate in dogs with IMHA and sick anorectic cats (due to bile sludging). Liver enzyme activities may be increased from hypoxic injury but can be normal. Serum iron and percentage saturation of transferrin are consistently increased in dogs and cats with hemolytic anemia, and siderocytes (RBCs with faint iron inclusions) may be seen on a blood smear in dogs. None of these results is specific for hemolytic anemia and they should be considered as supportive not confirmatory results. The lack of these findings does not rule out hemolysis either.

Decreased Production

If the anemia is non-regenerative or "inadequately" regenerative, this indicates a problem with RBC production in the bone marrow, of which there are many causes (see Box 57-1 and ch. 199). Clues as to the mechanism of a non-regenerative anemia can be gleaned from the severity of the anemia, RBC indices, and other hematologic findings, particularly concurrent cytopenias (specifically, neutropenia and thrombocytopenia) and abnormal (neoplastic) cells (Figure 57-2). A mild normocytic normochromic anemia is the most common form of non-regenerative anemia and is usually due to extramedullary disease, particularly anemia of inflammatory disease (also called anemia of chronic disease). The most common causes of a severe non-regenerative anemia, without other cytopenias, are immune-mediated conditions and feline leukemia virus infection in dogs and cats, respectively. Feline leukemia virus-associated hematologic disorders are far less frequent since vaccination was introduced.

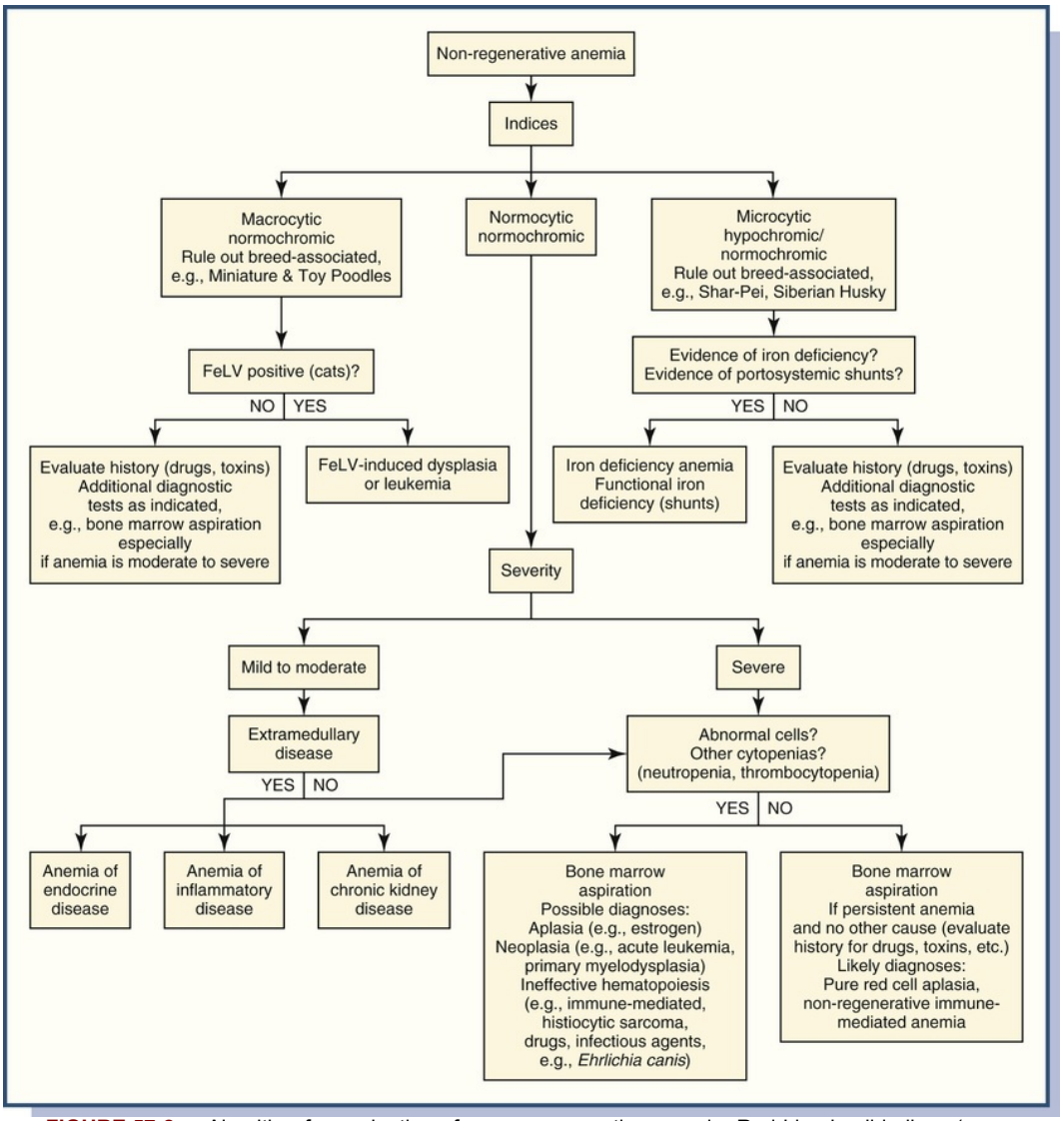

FIGURE 57-2 Algorithm for evaluation of a non-regenerative anemia. Red blood cell indices (mean corpuscular volume and mean corpuscular hemoglobin concentration) can be guides as to the potential underlying mechanism, as can the presence of other cytopenias or abnormal cells (e.g., leukemia). *FeLV,* Feline leukemia virus. (Modified from eClinPath.com [section on anemia].)

A Mechanistic Approach to Anemia

A stepwise approach can be used for distinguishing between mechanisms of anemia (see Figures 57-1 and 57-2) and is based on the following four questions (Box 57-2):

1. How acute is the anemia? This is important for assessing whether an anemia is regenerative (question 2 below). The bone marrow takes approximately 3-5 days to mount a regenerative response. An anemia of acute onset may appear "non-regenerative" if the bone marrow has had insufficient time to respond. Clinical signs and history can help with determining the duration of anemia, but this can be difficult because anemia frequently manifests with vague clinical signs that may be missed by the owner. Unless there has been a known traumatic event, a regenerative response should be manifest by the time of presentation in most affected patients. The expected marrow response will also depend on the degree of anemia. A robust regenerative response is expected in a moderate to severe anemia; however, a weaker response would be expected in a mild anemia.
2. Is the anemia regenerative? The bone marrow responds to an anemia by releasing immature anucleated RBCs, which are characterized by increased RNA content. These immature RBCs can be identified using intravital dyes that precipitate RNA and can be visualized on smears (e.g., new methylene blue) or fluorescent dyes that bind to RNA/DNA and can be detected with lasers in automated hematology

analyzers. When identified with these dyes, the immature anucleated RBCs are called reticulocytes and are quantified as a percentage of the RBC count (note that only aggregate reticulocytes or immature anucleated RBCs that contain aggregates or large amounts of RNA are quantified in cats). Due to their higher RNA content, immature anucleated RBCs can also be recognized as polychromatophilic (purple) RBCs on Romanowsky-stained blood smears (Diff-Quik, Wright's stain) and regeneration can be subjectively estimated from the degree of polychromasia in blood smears from both dogs and cats. As an example, in the monolayer of a blood smear there are approximately 100 RBCs per 100× oil immersion field. Counting 3 polychromatophilic RBCs per field (average the number in ten 100× oil immersion fields) would be roughly equivalent to 3% reticulocytes. However, there will be far fewer than 100 RBCs in the microscopic field in a severely anemic animal and this should be considered when estimating regeneration from a blood smear. A high reticulocyte percentage alone or the presence of small numbers of polychromatophilic RBCs in a smear does not necessarily mean that the bone marrow is responding appropriately to the anemia; therefore, various formulae are available to assess "adequacy" of regeneration by taking into account the severity of anemia, including the absolute reticulocyte count, corrected reticulocyte percentage (which is handy for practitioners because it is based on PCV and does not require an RBC count) and the reticulocyte maturation index. Which formula is used is a matter of personal preference; however, the author uses the absolute reticulocyte count (e.g., with our current reference intervals, an absolute reticulocyte count >95,000/mcL [dog] or >60,000/mcL [cat] generally indicates a regenerative response).[4] Note that nucleated RBCs (nRBCs) and Howell-Jolly bodies (nuclear fragments) may be seen in blood smears of animals with a regenerative anemia but are not used for evaluating the regenerative response because they can be seen in other conditions (e.g., heatstroke and bone marrow injury for nRBCs). Also, with newer hematology analyzers, the RBC indices (mean corpuscular volume and mean corpuscular hemoglobin concentration) are usually normal in a regenerative anemia (i.e., the anemia is not macrocytic and hypochromic) and should not be relied upon as an indicator of regeneration.[5] If an anemia is regenerative (i.e., absolute reticulocyte count above the reference interval), then the anemia is due to hemorrhage or hemolysis and decreased erythropoiesis can be ruled out. If the anemia is non-regenerative (i.e., absolute reticulocyte count is within reference intervals, even if the percentage of reticulocytes is high) and the bone marrow has had time to respond, mechanisms of decreased RBC production are operative and diagnostic testing should focus on identifying the underlying cause (see Box 57-1).

3. Is a cause for the anemia evident on a blood smear? Blood smear examination is an essential part of the assessment of an anemic patient and it provides a wealth of information. Changes in morphologic features of RBCs (and other cell lineages) and detection of infectious agents or neoplastic cells can provide clues to, or specifically identify, the cause of an anemia (Boxes 57-1 and 57-3). Finding abnormal RBC morphologic features in a blood smear does not necessarily mean they are of pathologic relevance. Relevance is subjective and depends on both the type and number of abnormalities and should always be determined in context of the patient. For example, a few schistocytes, keratocytes and acanthocytes may be seen as a consequence of mechanical fragility in iron deficiency anemia, whereas in a critically ill patient with thrombocytopenia, the same number of these RBC changes could reflect underlying disseminated intravascular coagulation (DIC) and should trigger additional testing for this hemostatic disorder. Naturally, the identification of these RBC abnormalities is highly dependent on the skill of the observer.
4. Which additional tests are indicated? Results of complete clinical pathologic testing (complete blood count, clinical chemistry, urinalysis) and imaging, combined with cytologic or histologic assessment of tissues, is essential in all anemic patients for identifying extramedullary disease that could be causing the anemia or suppressing the bone marrow's response. Testing for infectious diseases is worthwhile in animals with an unexplained regenerative or non-regenerative anemia, because blood smear examination can be insensitive for organism detection. Even if a cause of the anemia is identified on a blood smear, additional testing is frequently performed for confirmatory purposes, e.g., Coombs test for IMHA, antinuclear antibody testing for systemic lupus erythematosus, and genetic or serologic-based infectious disease tests. In general, bone marrow aspiration is not indicated in a regenerative anemia or a mild non-regenerative anemia, unless looking specifically for occult infectious agents or underlying neoplasms (e.g., *Leishmania* sp., multiple myeloma, lymphoma). Pancytopenia (defined as a non-regenerative anemia, thrombocytopenia, and neutropenia, regardless of severity of the anemia) and a severe non-regenerative anemia (alone or with other cytopenias) indicate a bone marrow problem, and bone marrow aspiration is warranted in affected patients. Similarly, bone marrow aspiration is worthwhile in animals with identifiable neoplastic cells in circulation (for staging lymphoma or

confirmatory diagnosis of leukemia). Bone marrow aspiration with Prussian blue staining for iron is also the gold standard test for confirmation of iron deficiency in dogs, but not in cats (stainable iron is absent in the bone marrow of healthy cats). However, marrow aspiration rarely is performed for the latter purpose.

Box 57-2

The Question-Based Approach to Anemia

1. How acute is the anemia?
2. Is the anemia regenerative?
3. Is a cause identifiable from a blood smear?
4. Which additional tests are indicated?

Box 57-3

Useful RBC Abnormalities in a Blood Smear

Acanthocytes: Fragmentation injury, iron deficiency anemia (mechanical fragility), vascular neoplasms (e.g., hemangiosarcoma), DIC. Usually seen with keratocytes and schistocytes. Can be a non-relevant finding (rarely seen in healthy young animals, potentially as a congenital or inherited disorder) or a finding of uncertain relevance in various diseases.[36]

Agglutination: IMHA, EDTA-dependent pseudo-agglutination.[37] Must be differentiated from rouleaux (usually by microscopic examination of a 1 : 4 to 1 : 10 dilution with saline). Macroscopic slide tests are less reliable.

Eccentrocytes: Oxidant injury. Low numbers may be seen in various diseases without indicating an oxidant-induced hemolytic anemia.[38]

Elliptocytes: Usually secondary to non-regenerative immune-mediated anemia or pure red cell aplasia in dogs (indicates myelofibrosis in these disorders[30]) and liver disease in cats (particularly lipidosis). Inherited in dogs[39] (rare).

Heinz bodies: Indicate oxidant injury. Small Heinz bodies can be normal in cats and do not result in anemia. Large or multiple Heinz bodies in cats or any size Heinz bodies in dogs are supportive of an oxidant-induced hemolytic anemia. Can be seen concurrently with eccentrocytes, ghost cells, pyknocytes (cells which resemble spherocytes)[40] and methemoglobinemia, depending on the oxidant.

Keratocytes: Fragmentation injury (vasculitis, DIC, iron deficiency; seen with acanthocytes and schistocytes) or oxidant injury (seen with eccentrocytes ± Heinz bodies). Low numbers may be normal in cats.

Poikilocytes: RBCs with various shapes can be seen in cats with liver disease, but may not result in anemia.

Rouleaux formation: Increased globulins secondary to antigenic stimulation (e.g., chronic liver disease), inflammation (e.g., feline infectious peritonitis) or B cell or plasma cell neoplasia (e.g., chronic lymphocytic leukemia, multiple myeloma). Serum protein electrophoresis is helpful.

Schistocytes: Fragmentation injury. Often concurrent with acanthocytes and keratocytes.

Siderocytes (particularly dogs): Hemolytic anemia, lead toxicosis, drugs (hydralazine), portosystemic shunts.

Spherocytes: Moderate to many spherocytes are usually diagnostic of IMHA. Can be seen concurrently with siderocytes (increased RBC turnover) and ghost cells (if intravascular hemolysis). Partial spherocytes (smaller RBCs with a small amount of central pallor) can be seen in dogs with non-regenerative variants of IMHA.[30] A few spherocytes can be seen in fragmentation injury and transfused RBCs can be sphered. Spherocytes are difficult to detect in cats (RBCs normally lack central pallor).

Erythrocytosis

An increased RBC count or HCT is occasionally seen in dogs and is quite rare in cats. A high HCT may be normal for specific breeds of dogs[1,6] and has been observed in individual animals of certain breeds (Jack

Russell Terriers and German Shepherd Dogs) by the author. Hence, breed-specific associations should be excluded before evaluating an animal for pathologic causes of a high RBC count or HCT. Similar to anemia, a sequential mechanistic approach can be used for diagnostic evaluation of an animal with a high HCT (Figure 57-3).

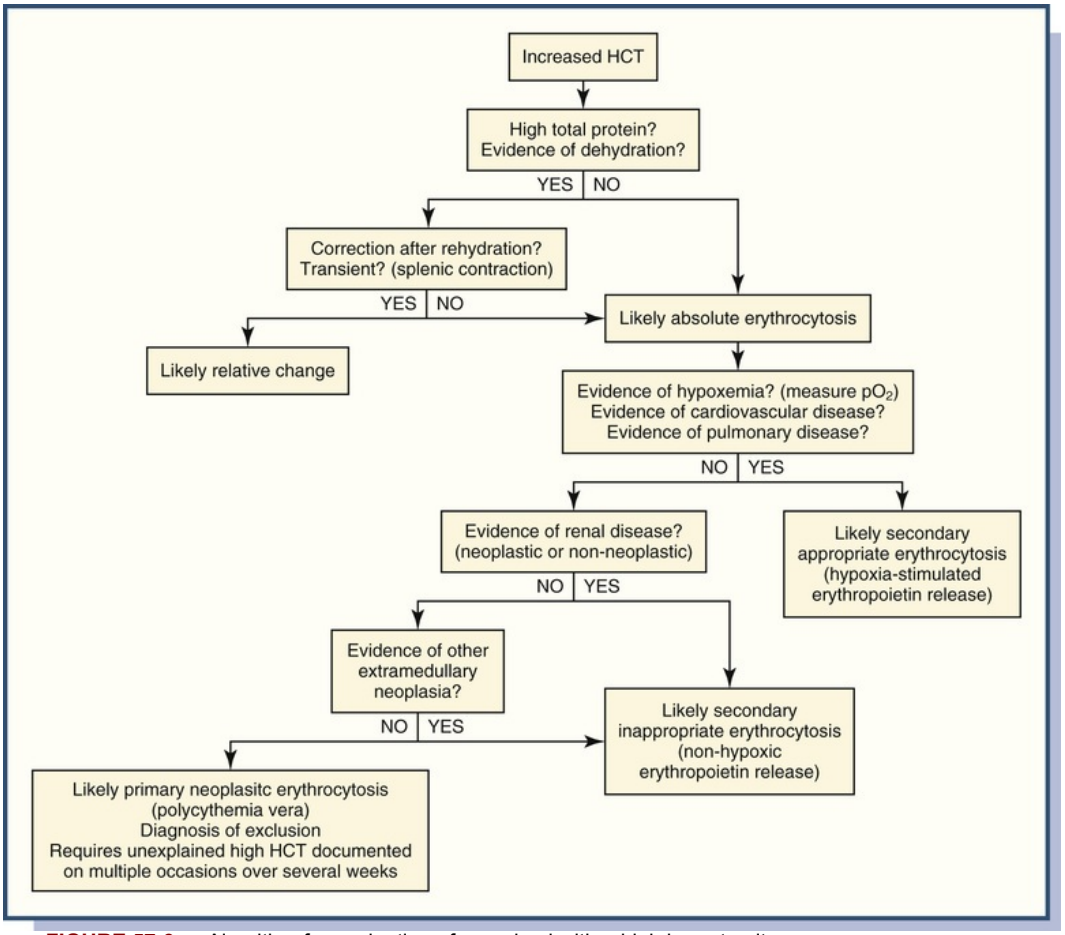

FIGURE 57-3 Algorithm for evaluation of an animal with a high hematocrit.

Mechanisms of Erythrocytosis

Erythrocytosis refers to an absolute or true increase in RBC mass and not just increased RBC numbers. High RBC numbers (or HCT) may be seen as a relative change, i.e., change in RBC numbers in relation to water content. A relative increase in HCT is due to a decrease in body water (e.g., dehydration) or release of RBCs from the spleen. Up to one third of RBCs are stored in the splenic red pulp and can be released with splenic contraction under the influence of epinephrine, although this is uncommon in dogs and cats. Measurement of total protein concentrations (high results expected) and rehydration of a dehydrated animal with sequential testing to confirm persistence of a high HCT are tools that can be used to rule out a relative from an absolute increase in HCT.

Erythrocytosis is a true increase in RBC mass due to increased RBC production (also called absolute increase in HCT). This can be separated into a primary or secondary erythrocytosis. Primary erythrocytosis can be inherited in some species (not dogs or cats) or can be an acquired neoplastic disorder, called polycythemia vera. The latter is a chronic myeloproliferative disorder that is quite rare in dogs and cats. Up to 90% of human patients with polycythemia vera have a mutation in the JAK2 non-receptor tyrosine kinase which is downstream of the erythropoietin receptor.[7] The mutation drives constitutive, usually erythropoietin-independent, stimulation of erythropoiesis. A mutation in JAK2 has been identified in a dog with polycythemia vera and may facilitate diagnosis of this rare disease (which is usually a diagnosis of exclusion; see Figure 57-3).[8] Secondary erythrocytosis due to increased erythropoietin is a far more common

cause of an increased HCT in both dogs and cats than polycythemia vera. Secondary erythrocytosis can be subclassified as appropriate or inappropriate, which refers to the stimulus for erythropoietin release. Appropriate release of erythropoietin occurs in hypoxemic conditions and can result in secondary erythrocytosis in dogs and cats with respiratory or cardiac conditions.[9] An inappropriate release of erythropoietin is most frequently seen in certain renal diseases but it also is seen as a paraneoplastic response with renal and non-renal neoplasia.[10-14] High erythropoietin concentrations support a diagnosis of secondary erythrocytosis but studies have shown an overlap in erythropoietin concentrations with different causes of erythrocytosis, limiting the usefulness of the test.[15,16] Bone marrow aspirates will not be informative because they will reveal an erythroid hyperplasia with any cause of erythrocytosis (whether primary or secondary). Thus, differentiating between causes of erythrocytosis requires other diagnostic tests (see Figure 57-3 and ch. 200).

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CHAPTER 58

Leukopenia, Leukocytosis

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Introduction

Peripheral blood leukocytes are primary components of the innate and adaptive immune systems. As such, their numbers are dynamic and affected by a large variety of stimuli. These stimuli include but are not limited to: infection, inflammation, autoimmune disease, tissue damage, parasitic infestation, and hormones. Leukocytes are produced continuously, in a series of steps, from hematopoietic stem cells in the bone marrow (see ch. 202). These initially pluripotent stem cells are self-renewing, but reproduce infrequently. They give rise to a variety of common lymphoid and myeloid cell lines after progression from hematopoietic stem cells to their respective progenitor cells, differentiating further to result in more determined and restricted cell lines. The bone marrow microenvironment of the precursor cells, essential for hematopoiesis, is composed of endothelial cells, stromal cells, adipocytes, osteoblasts, macrophages, lymphocytes, extracellular matrix and growth factors. The correct microenvironment, cell interactions, and extracellular matrix attachments are requisite to optimal proliferation, differentiation, and survival of hematopoietic stem cells. Alterations to the microenvironment can dramatically impact hematopoiesis.

Neutrophils in the bone marrow are included in two pools: a mitotic pool and a maturation and storage pool. Myeloblast maturation and release from the bone marrow generally take about 6-9 days, but maturation is expedited by certain inflammatory signals.[1-4] Interleukins (ILs)-1, 2, 3, 6 and 11, granulocyte-macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF) and stem cell factor (SCF) are inflammatory mediators that stimulate neutrophil production while GM-CSF, G-CSF, tumor necrosis factor (TNF) and C5a mediate release from the bone marrow. Monocytes originate from the granulocyte-monocyte progenitor cell under the influence of IL-3, IL-34, GM-CSF, and macrophage colony stimulating factor (M-CSF). Monocytes are produced more quickly than are granulocytes, and there is minimal reserve in the marrow; replication, rather than rapid release, is responsible for increases in monocyte numbers in the blood.[4-6] Eosinophils are derived from the eosinophil progenitor line under the influence of GM-CSF, IL-3 and IL-5 produced by activated Th2 lymphocytes.[7] Basophils are produced from the bipotential basophil-mast cell progenitor under the influence of IL-3, IL-5, GM-CSF, transforming growth factor beta (TGF-beta) and nerve growth factor.[8] In addition to microenvironment and cytokines, the role of microRNAs is under active study in regulation of inflammation and hematopoiesis.[9]

B lymphocytes, T lymphocytes and natural killer (NK) cells are derived from combined lymphocyte progenitor cells under the influence of SCF, Flt3L, insulin-like growth factor (IGF) and IL-7.[4] The Notch gene plays an important role in the B cell T cell lineage switch.[10] Lymphoblasts leave the marrow and migrate to the thymus where they develop into T lymphocytes because of stimulation from compounds in the thymic microenvironment, Notch gene product, and growth factors including Flt3L and IL-7.[10] NK cell production is thought to be stimulated by IL-2, IL-7, IL-15 and SCF. NK cells are produced in the bone marrow in approximately 7 days; NK cells also could arise from the lymph nodes, liver, and spleen.[4,11]

The peripheral white blood cell count is a function of the rate of production in the bone marrow, release from the bone marrow, the proportion of cells in the marginated versus circulating pools, and the rate of egress of white cells from the blood into the tissues. Peripheral blood leukocytes are divided into approximately equal circulating and marginated pools, although there is some species variation in the ratio. The marginated cells are found rolling along the endothelium, preparing to exit the circulation and migrate to target tissues. Marginated cells interact with the vascular endothelium through interactions between L-selectins on leukocytes and P- and E-selectins on endothelial cells as well as other cellular receptors. Marginated cells can return to the circulation during times of increased blood velocity or due to the effects of cortisol or epinephrine. Changes in the relative ratio of marginated to circulating pools of cells will alter the

white blood cell count, as only the central or circulating pool is evaluated in the complete blood count (CBC).

Leukocytosis

Because they are the most numerous and dynamic populations of white blood cells, neutrophils and to a lesser extent lymphocytes are the cell lines most commonly responsible for leukocytosis (see also ch. 202). Rarely, other cell lines expand sufficiently to result in a leukocytosis. Exercise, epinephrine, and cortisol are associated with a mild to moderate increase in neutrophils, largely due to shifts of cells from the marginal to the circulating pools with a rapid return to baseline cell counts. The neutrophil count should not be greater than twice the upper limit of the reference interval, nor should a left shift be present if the neutrophilia is the result of these physiologic effects alone.[4] Infection, inflammation, and neoplasia are associated with neutrophilia of varying magnitude with no clear cut-off that is discriminatory between each category of disease.

As an inflammatory process continues, increased demand for neutrophils triggers early release of neutrophils from the maturation pool, resulting in a *left shift* towards more immature forms of neutrophils. If the number of mature forms exceeds immature forms, the pattern is known as a *regenerative response*. When the demand for neutrophils exceeds the marrow's capacity to provide mature neutrophils, increasing ratios of immature forms are released resulting in a *degenerative left shift*. In both dogs and cats, a degenerative left shift most commonly is caused by infection and it is associated with a more guarded prognosis,[12-14] with a hazard ratio for the risk of death or euthanasia of 1.9 in affected dogs[12] and 1.75 in affected cats.[14]

Toxic changes are morphologic changes of neutrophils caused by accelerated maturation. They may include: cytoplasmic basophilia, Döhle bodies, increased vacuolization, decrease nuclear condensation and increased granules (Figure 58-1). Neutrophilic leukocytosis with a left shift and/or toxic changes should raise suspicion of infection such as peritonitis, pleuritis and pneumonia; however, the absence of a left shift or toxic changes does not exclude infection, and noninfectious inflammatory disease such as severe pancreatitis or hemolytic anemia and others can be associated with neutrophilia, left shift and toxic change.

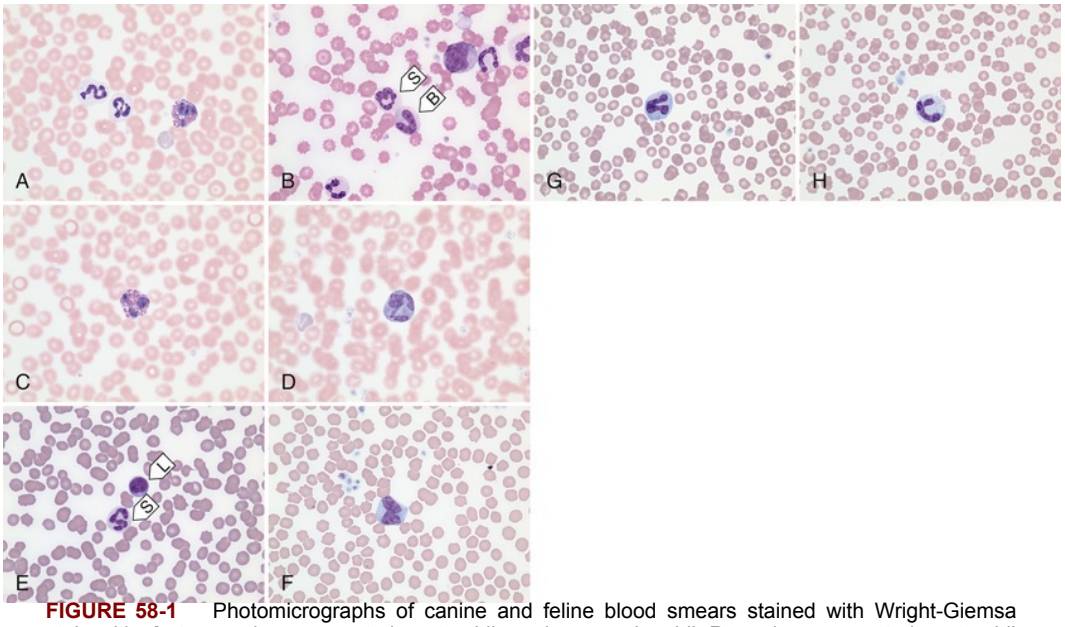


FIGURE 58-1 Photomicrographs of canine and feline blood smears stained with Wright-Giemsa stain with: **A,** two canine segmented neutrophils and one eosinophil; **B,** canine segmented neutrophil (S) and band neutrophil (B); **C,** canine eosinophil; **D,** canine basophil; **E,** feline segmented neutrophil (S) and lymphocyte (L); **F,** feline monocyte; **G** and **H,** toxic neutrophils. (Photos courtesy Dr. Angela B. Royal, Veterinary Medical Diagnostic Laboratory, University of Missouri.)

Severe leukocytosis (>35,000 cells/mcL) is often termed a *leukemoid response,* although this term generally has fallen out of favor.[15] Typically, neutrophils are the predominant cell type involved with severe leukocytosis, although other cells could be involved. The most common causes of severe neutrophilic leukocytosis include infection, tissue necrosis, neoplasia, and immune-mediated disease (Table 58-1).[13,15,16]

Other important differential diagnoses include leukocyte adhesion deficiency,[17] paraneoplastic leukocytosis,[18-20] *Babesia* infection,[21] *Hepatozoon canis* infection,[22,23] immune-mediated hemolytic anemia,[24] and bacterial prostatitis.[25]

TABLE 58-1

Causes of Severe Neutrophilic Leukocytosis (WBC > 50,000/mcL) in the Dog and Cat

CATEGORY	CANINE		FELINE
Study	Lucroy et al[13]	Weltan et al[15]	Lucroy et al[16]
Infection	40/115 (34%)	106/182 (58%)*	38/104 (37%)
Immune-mediated	38/115 (32%)	20/182 (11%)	23/104 (22%)
Neoplasia	24/115 (20%)	26/182 (14%)	24/104 (23%)
Tissue necrosis	12/115 (10%)	23/182 (13%)	19/104 (18%)

*Here we combined the infection group (56/182) and babesiosis group (50/182), which were listed as separate groups in the original paper.

Lymphocytosis sometimes can be profound enough to result in leukocytosis. Physiologic lymphocytosis usually is mild. Increased circulating concentration of epinephrine, but not cortisol, results in a lymphocytosis. Cats are more likely than are dogs to have reactive lymphocytosis in response to inflammation.[6,26,27] Lymphocytosis secondary to inflammation is usually mild, but it can be 2-3 times the upper limit of the reference interval.[26] Lymphocytosis occasionally can be associated with chronic infectious etiologies such as feline leukemia virus, feline immunodeficiency virus, toxoplasmosis, and *Ehrlichia canis*.[28] Hypoadrenocorticism is associated with lymphocytosis, but it rarely results in leukocytosis.[26] Lymphoma, chronic lymphocytic leukemia (CLL), and acute lymphocytic leukemia (ALL) can be associated with marked leukocytosis. Because the cells in CLL are mature, distinction between reactive lymphocytosis and CLL may require advanced techniques like immunophenotyping or clonality testing via polymerase chain reaction (PCR) for antigen receptor rearrangements (PARR). Leukemic lymphoma can be difficult to distinguish from ALL, though nodal infiltration is less common with ALL and the lymphocyte count associated with ALL tends to be greater.

Eosinophilia and monocytosis are uncommon causes of leukocytosis. The main categories of disease resulting in eosinophilia are parasitism, hypersensitivity reactions, mastocytic disease, hypoadrenocorticism, hypereosinophilic syndrome, and occasionally lymphoid neoplasia. Chronic granulomatous disease can cause moderate to severe monocytosis. Other causes of monocytosis include chronic infections and cellular and tissue damage. Myelomonocytic leukemia is a rare cause of leukocytosis and frequently is associated with concurrent neutropenia and thrombocytopenia.[29,30]

Leukopenia

Because neutrophils make up the largest fraction of the white blood cell count, leukopenias most commonly are secondary to neutropenia. Though reference ranges vary from one laboratory to another, neutropenia generally consists of a neutrophil count <3,000 cells/mcL (<3 × 10^9 cells/L, <3 × 10^6 cells/mL).[27] Neutropenia is classified as mild when the neutrophil count is 1,500-3,000 cells/mcL, moderate if it is 500-1,500 cells/mcL, and severe if it is <500 cells/mcL. Severe neutropenia often is associated with fever and opportunistic infection, since neutrophils are first-line defenders against a variety of pathogens and therefore, any animal with moderate to severe neutropenia and a fever should be treated emergently. Conversely, severe infections can cause neutropenia, making cause-and-effect sometimes challenging to discern. Increased demand of neutrophils secondary to pneumonia, peritonitis, ulcerative dermatitis, and viral and fungal infections all have been identified as causes of neutropenia in dogs and cats (Table 58-2).[31]

TABLE 58-2

Common Causes of Neutropenia in Dogs and Cats and Toxic Neutrophils in Cats

CATEGORY	CANINE AND FELINE NEUTROPENIA	FELINE TOXIC NEUTROPHILS
Study	Brown et al[31]	Segev et al[50]
Infectious disease	135/261 (52%)*	95/219 (43%)‡
Increased demand†	29/261 (11%)	NA
Drug-induced	30/261 (11%)	NA
Primary bone marrow disease	10/261 (4%)	NA
Metabolic	NA	20/219 (9%)

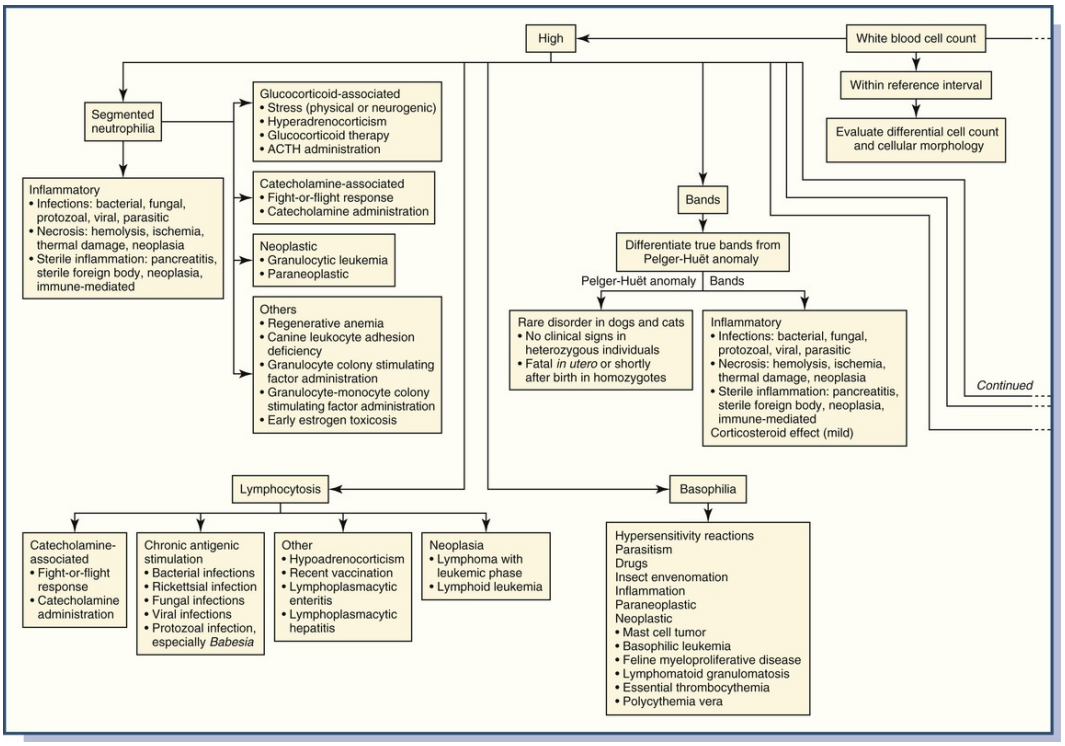
*Of these 123/124 dogs had parvovirus and 10/11 cats had either feline leukemia virus or feline immunodeficiency virus.

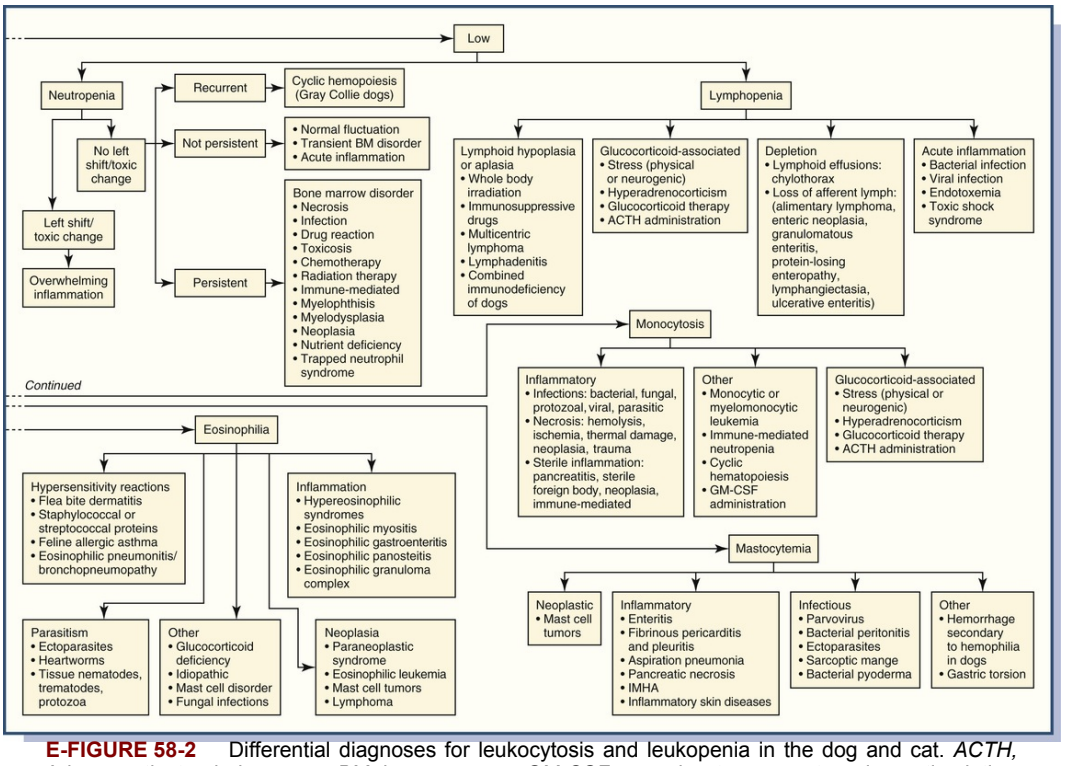
†Due to marked inflammation, bacterial sepsis or endotoxemia.

‡Bacterial or viral.

The number of affected cats, total number of cats in the study and then percentage of affected cats in study are noted.

General mechanistic causes of neutropenia include decreased marrow production, increased peripheral usage, vascular sequestration (anaphylaxis and sepsis), and immune-mediated destruction of either mature neutrophils (in the periphery or in marrow reserves), or immature precursors (E-Figure 58-2).[32] Causes of peripheral neutrophil usage include severe infections (bacterial, viral or fungal), and specifically, septic peritonitis, pyometra, pyothorax and enteric salmonellosis among others.[33,34] Inflammatory diseases like pancreatitis, bile peritonitis, organ torsion or tissue infarction also can cause neutrophil migration. Most of these conditions can result in neutrophilia; however, if demand exceeds production of neutrophils, neutropenia could result.[31] Neutrophils follow a cytokine and haptenic pathway composed of C5a, CXCL-8, leukotriene B4 and platelet activating factor among other signals to the site of inflammation.[35-37] Decreased bone marrow production of neutrophils or other cell lines occurs secondary to failure of the elements of the hematopoietic niche.[38] Pharmacologic agents like chloramphenicol, azathioprine, phenobarbital, phenylbutazone, methimazole, sulfa derivatives, and others have been linked to neutropenia and other cytopenias.[36,39-42] Additionally, chemotherapy or neoplastic infiltration of the bone marrow can result in marrow hematopoietic suppression or collapse.[43-46]





E-FIGURE 58-2 Differential diagnoses for leukocytosis and leukopenia in the dog and cat. *ACTH*, Adrenocorticotropic hormone; *BM*, bone marrow; *GM-CSF*, granulocyte-monocyte colony stimulating factor; *IMHA*, immune-mediated hemolytic anemia. (Adapted from Jackson ML: Leukocytes in health and disease. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine*, ed 7, St Louis, 2010, Saunders, p 809; Stockham SL, Scott MA: Leukocytes. In *Fundamentals of veterinary clinical pathology*, Ames, IA, 2002, Iowa State Press, pp 49-83; and Stockham SL, Keeton KS, Szladovits B: Clinical assessment of leukocytosis: distinguishing leukocytosis caused by inflammatory, glucocorticoid, physiologic and leukemic disorders or conditions. *Vet Clin North Am Small Anim Pract* 33(6):1335-1357, 2003.)

Lymphopenia rarely is a cause of leukopenia but it could contribute to a reduction in leukocyte count. Lymphopenia is most commonly due to viral infection, or the effect of glucocorticoids in ill animals. A decrease in circulating monocytes, eosinophils, or basophils rarely results in leukopenia because they account for a minor percentage of leukocytes.

Approach to Evaluation of Leukocytosis and Leukopenia

Leukocytosis and leukopenia are common findings on the CBC. Therefore, a systematic approach to assessing leukocytosis or leukopenia is essential. Changes in white blood cell counts generally are nonspecific findings and rarely are pathognomonic for a particular disease process. Rather, these changes help alert the clinician of possible disease. Additionally, a normal white blood cell count does not rule out infection, inflammation, autoimmune disease or neoplasia.

The first step in assessment of the peripheral blood white cell count should always include an overall absolute cell count, a differential cell count, and morphologic description of the cells. Machine-generated differential cell counts can be inaccurate; therefore, evaluation of the blood smear to determine a differential cell count and evaluate cellular morphology is an indispensable step in the diagnostic evaluation for any animal with leukocytosis or leukopenia. Often during the initiation of inflammation, a transient leukopenia develops, either due to a shift in the leukocyte pool or when, in cases of overwhelming inflammation, the demand for leukocytes transiently exceeds the supply. Care should be taken to identify if leukopenia is transient or persistent by serially evaluating the white blood cell count, the differential count, and morphology of the leukocytes. In general, transient leukopenia due to acute inflammation resolves within 4-24 hours.

Discriminating among the possible causes of leukocytosis and leukopenia (see E-Figure 58-2) requires identification of the specific pattern of cells affected, coupled with the clinical history and physical examination findings. A complete history (clinical signs, past or recent illnesses, exposure to toxins, medications, trauma, travel, vaccination, exposure to infectious agents) and performance of a thorough

physical examination allow the clinician to prioritize differential diagnoses. Exam findings of fever or hypothermia, scleral injection, lymphadenomegaly, organomegaly, effusions, abscesses, or heart murmurs are particularly important. A serum biochemical profile and urinalysis should be reviewed to look for clues not identified on physical examination. Based on the information gained, a list of likely differential diagnoses can be assembled and a logical approach can be planned for additional diagnostics. Testing may include imaging with modalities such as radiographs, ultrasound, computed tomography, or magnetic resonance imaging. Additional testing may include serologic titers, aspiration or biopsy of enlarged or morphologically altered organs or of effusions, cardiac ultrasound, and microbial cultures of blood, urine, effusions, or purulent material. Bone marrow aspiration or biopsy frequently is indicated in instances of suspected leukemia or when persistent leukopenia, bicytopenia, or pancytopenia is identified. Specialized tests like flow cytometry, PARR, and anti-neutrophil antibody testing can be employed to identify neoplasia or immune-mediated neutropenia if indicated.[47-49]

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CHAPTER 59

Thrombocytopenia, Thrombocytosis

Marjory B. Brooks

Platelets are small anucleate cell fragments that play a critical role in hemostatic and pathologic thrombus formation. Quantitative defects of platelet number are readily detected as increased or decreased platelet number in the complete blood count (CBC, hemogram). A consistent diagnostic strategy helps streamline the management of patients with thrombocytopenia or thrombocytosis.

Platelet Life Cycle

Platelets are produced from bone marrow megakaryocytes and they circulate for approximately 5-9 days in dogs and cats.[1] The cytokine thrombopoietin (TPO) is the major regulator of megakaryocyte maturation; however, additional non-TPO growth factors act synergistically with TPO. The liver is the primary site of TPO synthesis and, upon release, TPO binds to a ligand (c-Mpl) expressed on megakaryocytes and platelets. Free TPO levels maintain a constant platelet mass. As the platelet count falls, free TPO levels increase to stimulate thrombopoiesis. Conversely, as the platelet count rises, free TPO levels fall and thrombopoiesis slows. In addition to constitutive expression, senescent platelets, lacking sialic acid residues, bind to specific receptors on hepatocytes to induce upregulation of TPO production.[2]

Platelets in circulation undergo transient splenic sequestration, with approximately one third of total platelet mass compartmentalized within the spleen in healthy individuals.[3] Prothrombotic and inflammatory stimuli induce platelet activation and incorporation into a hemostatic plug, or egress into tissues from microvascular leakage. Non-activated platelets undergo gradual apoptotic death and subsequent clearance by hepatic and splenic macrophages.

Disease processes that upset the balance of platelet production, activation, and clearance result in an increase or decrease in platelet count. Thrombocytopenia is among the most common acquired bleeding disorders in small animal practice, whereas thrombocytosis more often is identified as an abnormal laboratory finding with no specific clinical signs. The reference intervals for platelet counts in dogs and cats are indicated in Table 59-1.

TABLE 59-1

Reference Intervals for Canine and Feline Platelet Count and Mean Platelet Volume*

	PLATELET COUNT ($\times 10^3$/mcL)	MEAN PLATELET VOLUME (fL)
Canine	186-545	8.4-14.1
Feline	195-624	9.1-24.3

*Advia 2120 Hematology System (Siemens Healthcare).

Values current 2014, Clinical Pathology Laboratory, Cornell University, Ithaca, NY.

Diagnosis of Thrombocytopenia (Figure 59-1)

Clinical Signs

The characteristic physical signs of thrombocytopenia include petechiae, ecchymoses, mucosal hemorrhage (e.g., epistaxis, hematemesis, hematuria, melena) and prolonged bleeding after injury (see ch. 201). The signs

can overlap with signs of acquired or hereditary platelet dysfunction, coagulopathies, von Willebrand disease, vasculopathies, or vascular injury. A platelet count is indicated as a quick assessment to confirm thrombocytopenia and guide subsequent testing. While the risk of bleeding is not strictly correlated with the platelet count, thrombocytopenia rarely is the sole cause of severe or spontaneous hemorrhage at counts >30,000/mcL. Hemorrhage can be exacerbated, however, in thrombocytopenic patients with concurrent coagulation disorders or vascular defects.

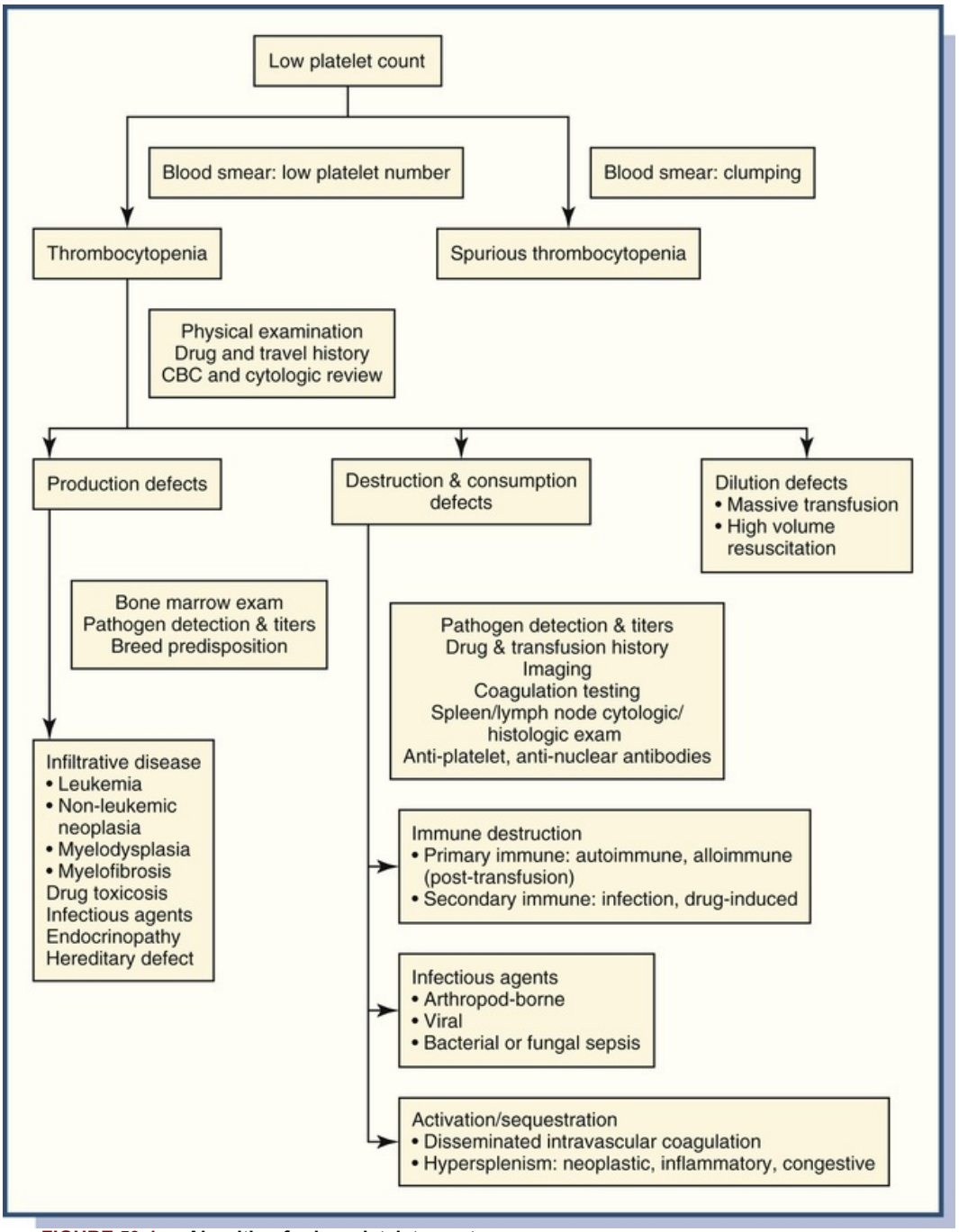

FIGURE 59-1 **Algorithm for low platelet count.**

Diagnostic Testing

Platelet Count and Blood Smear Examination

The platelet number for healthy dogs and cats ranges from approximately 200,000 to 500,000/mcL.[1,3,4] Hematology analyzers also measure mean platelet volume (MPV), an indicator of platelet size that could be useful in characterizing and monitoring thrombocytopenia. Species-specific reference intervals should be developed for in-house methods, or provided by each testing laboratory (see Table 59-1). Thrombocytopenia detected by manual or automated count should next prompt a careful blood smear examination.

Blood smear examination confirms a low platelet number and rules out spurious thrombocytopenia. Platelets are highly reactive and subject to activation and clumping in the process of blood collection or storage.[5] These artifacts are minimized by atraumatic venipuncture, blood collection directly into citrate anticoagulant, limited storage time, and avoidance of cold temperature. After review of the smear edges to detect platelet margination, platelet count is estimated from counting 10 oil immersion fields (100×) on the blood film monolayer as follows: Platelet count (per mcL) = average platelets/field × 15,000.

Additional Diagnostic Evaluation

A diagnosis of thrombocytopenia should prompt a CBC; detailed cytologic review of the blood smear; evaluation of drug and travel history; physical examination to include funduscopic examination; and careful evaluation of spleen, liver, and lymph nodes. Subsequent work-up can include bone marrow examination (see ch. 92), serologic or direct detection of pathogens, imaging with collection of cytologic or biopsy specimens, and coagulation testing (Table 59-2) (see ch. 196).

TABLE 59-2

Diagnostic Tests for Thrombocytopenia and Thrombocytosis

TESTS	SPECIFIC ASSESSMENTS
CBC (hemogram)	Platelet count, MPV, morphology, % reticulated platelets Abnormal cell morphology, cellular inclusion, infectious agents, neoplastic cells
Bone marrow cytology/biopsy	Megakaryocyte maturation, iron stores, infectious agents, lymphoid and myeloid neoplasia, myelodysplasia, myelofibrosis
Spleen/lymph node cytology/biopsy	Infectious agents, neoplastic cells, extramedullary hematopoiesis
Immunophenotyping	Expression of cell surface and cell-type specific markers on peripheral blood, bone marrow, lymph node or splenic cells
Imaging	Hepatosplenomegaly, lymphadenopathy, gastrointestinal and urinary tract integrity
Serologic assays	Detection of pathogen-associated antigens, antibodies directed against pathogens, or autoantibodies to nuclear antigens (ANA) or platelet antigens
Molecular assays	PCR, microarray, sequencing for specific pathogens
Isolation and culture	Pathogen detection
Coagulation assays	Coagulation screening tests (aPTT, PT), fibrinogen, antithrombin, D-dimer
Platelet associated antibody	Detection of immunoglobulin (IgG, IgM) bound to platelets
Mutation detection	*Beta1 tubulin* mutations in CKC Spaniels, Norfolk, Cairn Terriers

Classification of Thrombocytopenia (Figures 59-1 and 59-2; also see ch. 201)

Patients with a variety of systemic diseases can develop transient, mild to moderate thrombocytopenia (platelet count 100,000-150,000/mcL) that resolves as the patient recovers.[6,7] In contrast, persistent or progressive thrombocytopenia indicates an ongoing imbalance in platelet production or consumption, or more complex combined defects.

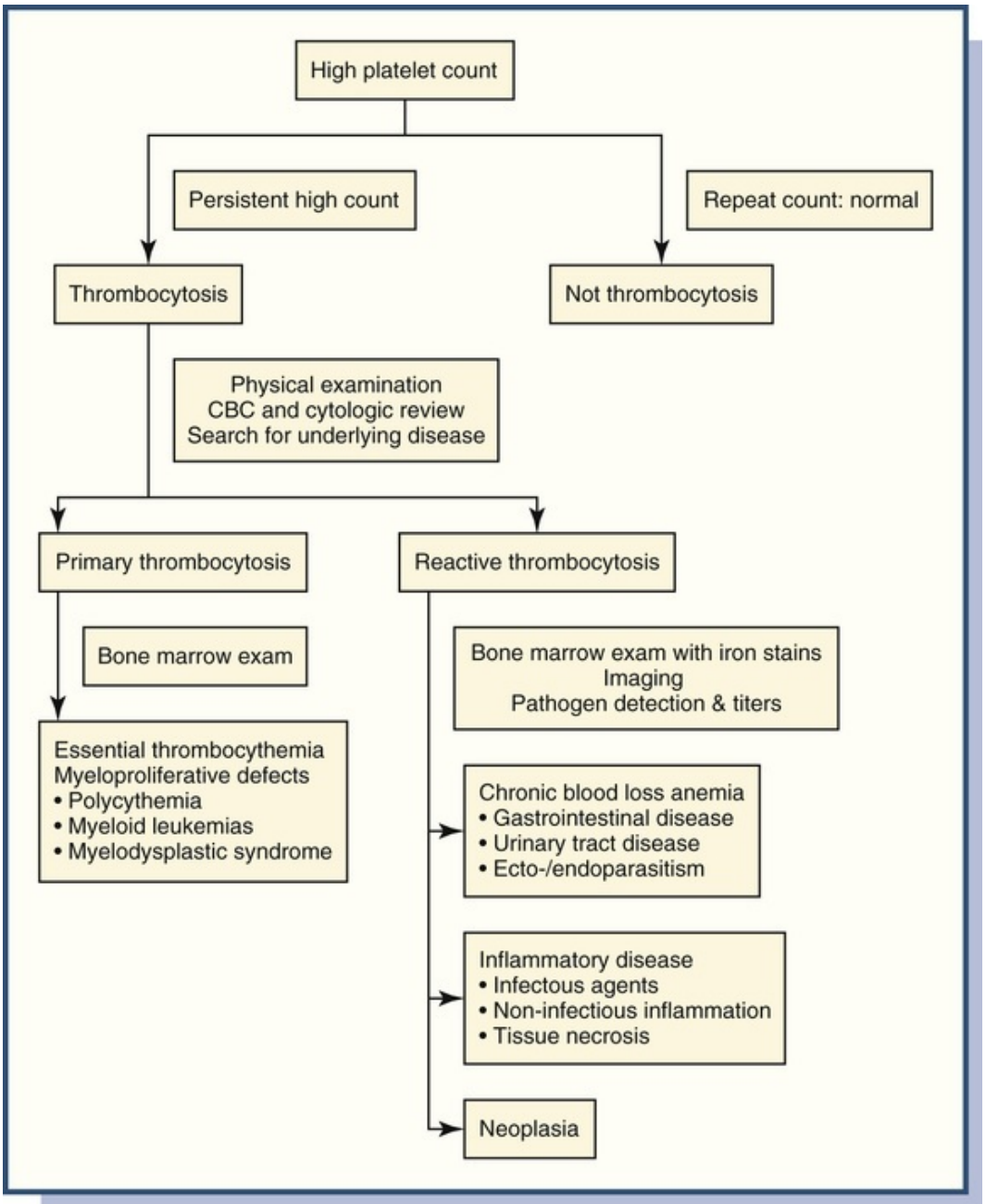

FIGURE 59-2 **Algorithm for high platelet count.**

Production Defects

Thrombocytopenia combined with leukopenia and/or anemia often is an indicator of defective hematopoiesis caused by an underlying bone marrow disorder.[4,6,8] High MPV and thiazole-orange-stained or "reticulated" platelets are characteristic of newly released platelets; however, direct examination of the bone marrow is the best means to evaluate thrombopoiesis (see ch. 92).

- Infiltrative disorders: Bone marrow infiltration by neoplastic cells typically results in hematopoietic failure, and systemic signs that include hemorrhage directly referable to thrombocytopenia. The clinical course, CBC, and bone marrow examination are used for classification of acute versus chronic leukemia and lymphoid versus myeloid leukemia (see ch. 344).[3,4,8] Beyond cell morphology, the most accurate classification includes immunophenotyping to characterize cell surface markers.[9] Bone marrow exam may reveal non-leukemic neoplastic infiltrates, e.g., lymphoma, multiple myeloma, mast cells, histiocytes, and metastatic carcinoma.[8,10] Clonal expansion of hematopoietic precursors (myelodysplasia) also causes

dysregulated cell maturation and cytopenias.[11] Myelofibrosis describes a non-cellular, fibrous matrix that replaces bone marrow stroma. Myelofibrosis results from excessive proliferation of bone marrow fibroblasts in response to injury. Inciting causes of myelofibrosis include chronic drug therapy, hemolytic anemia, bone marrow neoplasia, and prolonged inflammation.

- Drug toxicosis: Drug-induced thrombocytopenia can result from bone marrow suppression, in addition to immune-mediated destruction.[12] Drugs with stem cell toxicity cause pancytopenias, although signs of thrombocytopenia can develop first. Thrombocytopenia is a known side-effect of many chemotherapeutic agents, and a possible complication of the administration of drugs such as estrogen, chloramphenicol, methimazole, penicillin, procainamide, and sulfa antibiotics[13] (Box 59-1).

Box 59-1

Drugs Associated with Thrombocytopenia

Antibacterial and antifungal agents
  Cephalosporins, chloramphenicol, griseofulvin, penicillins, sulfonamides
Anti-inflammatory/analgesic drugs
  Acetaminophen, carprofen, ibuprofen, phenylbutazone
Cardiac and respiratory drugs
  Procainamide, quinidine, thiazide diuretics
Cytotoxic drugs
  Azathioprine, chlorambucil, cisplatin, cyclophosphamide, doxorubicin
Miscellaneous drugs
  Estrogen, phenobarbital, propylthiouracil, methimazole

- Infectious thrombocytopenias: Infectious agents can cause bone marrow suppression, peripheral platelet activation or sequestration, and immune-mediated platelet destruction. The apparent prevalence of infectious thrombocytopenias is increasing due to more advanced diagnostics and opportunities for exposure to infectious agents arising from pet-friendly travel, suburbanization, and climate change–induced vector range expansion[14-16] (Box 59-2). Point of care tests (ex. SNAP 4Dx, IDEXX Laboratories) are now available to rapidly screen for exposure to certain tick-borne agents. In addition to thrombocytopenia, infectious agents often cause systemic illness. Disease diagnosis is based on these physical exam and laboratory abnormalities and pathogen detection (e.g., immunologic assays, polymerase chain reaction [PCR] amplification, isolation and culture, direct visualization) and/or antibody assays that measure the host immune response to the infectious agent.

Box 59-2

Pathogens That Cause Infectious Thrombocytopenia

Viral agents
  Feline: Feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), panleukopenia virus, feline infectious peritonitis (FIP) coronavirus
  Canine: Distemper virus, herpesvirus, parvovirus, adenovirus
Arthropod-borne agents
  Anaplasma *(A. platys, A. phagocytophilum), Babesia, Bartonella, Cytauxzoon felis, Dirofilaria, Ehrlichia (E. canis, E. platys, E. ewingii), Leishmania, Mycoplasma haemofelis, Rickettsia rickettsii*
Fungal and bacterial agents
  Septicemia: Gram-negative and Gram-positive bacteria
  Histoplasma, Candida, Leptospira sp.

- Endocrine disorders: Estrogen causes bone marrow suppression in dogs and can cause severe thrombocytopenia or pancytopenia.[13] Functional ovarian granulosa cell tumors and Sertoli cell tumors are sources of endogenous estrogen excess that typically are diagnosed and treated through examination and surgical excision. Although such treatment is now uncommon, drug history could reveal exogenous

estrogen prescribed for pseudopregnancy, mismating, incontinence, or prostatic hypertrophy. Hypothyroidism is associated with general bone marrow depression; however, clinically severe thrombocytopenia due to thyroid insufficiency is unlikely.

- Hereditary thrombocytopenias: A large survey of Greyhounds revealed a mild, clinically silent reduction in platelet count.[17] Hereditary macrothrombocytopenia of Cavalier King Charles Spaniels is attributed to aberrant platelet microtubule assembly caused by a point mutation in the *beta1 tubulin* gene.[18] Homozygotes have high MPV and platelet counts from 25,000 to 75,000/mcL. A second, distinct *beta1 tubulin* mutation has been found in Norfolk and Cairn Terriers.[19] A *beta1 tubulin* structural variant unique to felids is also speculated to cause the relatively wide variation in platelet size and count in domestic cats.[20] Despite low counts, platelet mass is preserved in macrothrombocytopenic defects and the traits do not cause a bleeding tendency.

Destruction and Consumption Defects

Excessive platelet activation, sequestration, or targeted destruction can exceed the bone marrow's capacity to maintain platelet numbers. Among these mechanisms, immune-mediated destruction often is associated with the most severe thrombocytopenia (<20,000/mcL) (see ch. 201).[6,21,22]

- Immune-mediated destruction: Primary immune-mediated thrombocytopenia (ITP) is an autoimmune disorder characterized by production of antibodies directed against normal "self" platelet antigens.[21-23] Secondary immune thrombocytopenias are associated with an underlying disorder (e.g., infection, neoplasia, drug exposure, transfusion) that introduces neoantigens or upsets the host's immune balance. Anti-platelet antibody assays screen for antibodies bound to the patient's platelets (platelet surface immunoglobulin [PsAIg]) or circulating antibodies capable of binding platelets.[22] However, PsAIg or indirect antibody assays do not differentiate primary from secondary ITP, and non-specific platelet antibody binding further limits their clinical utility.
  Primary ITP is more common in dogs than in cats. Case series of canine ITP indicate a disease of middle-aged dogs, over-representation of females, and breed predispositions (Cocker Spaniels, Poodles, Old English Sheepdogs).[21,24] The diagnosis typically is based on combined clinical and laboratory criteria: exclusion of underlying disease, severe thrombocytopenia (<50,000/mcL), normal to increased megakaryopoiesis, and response to immunosuppressive therapy.
- Platelet activation and consumption defects: Platelet activation and depletion accompany infectious and non-infectious vasculitides through thrombus formation and egress from the vascular space. Thrombocytopenia is a common feature of endotheliotropic pathogens and is often present in cats with feline infectious peritonitis (FIP)–associated immune-complex vasculitis.[25,26] Certain snake venoms can directly activate platelets and indirectly result in activation and clearance due to tissue injury and vascular leakage.[27] Progressive platelet consumption is a feature of disseminated intravascular coagulation (DIC).[28,29] Diagnosis of activation and consumptive defects usually involves characterization of a DIC process through coagulation testing and screening for an underlying infectious agent, neoplastic disorder, or inflammatory syndrome. Cardiopulmonary bypass is uncommon in companion animals, but when it is performed, *ex vivo* platelet activation and thrombocytopenia can complicate pump circulation and associated drug therapy.[30,31]
- Sequestration defects: Diseases that cause splenic enlargement can result in platelet sequestration and clearance, or hypersplenism. Diagnostic efforts are based on the differentials for splenomegaly, such as infectious agents, neoplasia (often mast cell neoplasia, lymphoma, hemangiosarcoma), and congestion secondary to portal hypertension or heart failure (see ch. 206 and 344).

Dilutional Defects

Rapid administration of high volumes of crystalloid fluids or plasma expanders, and massive transfusion (replacement of >1 blood volume in 1 day, >50% blood volume in 4 hours) can result in a decreased platelet count.[32] Although uncommon, dilutional thrombocytopenia can be sufficiently severe to impair *in vivo* hemostasis.

Diagnosis of Thrombocytosis (see Figure 59-2)

Mild to moderate increases in the platelet count develop as a "reactive" bone marrow response to chronic

blood loss or inflammation. Reactive thrombocytosis requires no treatment beyond correction of an underlying disorder. Autonomous (primary) thrombocythemia is characterized by marked elevation in platelet count (>900,000/mcL) and is a feature of rare, potentially fatal myeloproliferative disease.[33]

Clinical Signs

Reported signs of primary thrombocythemia include fever, splenomegaly, anemia, evidence of thrombosis, and hemorrhage. Reactive thrombocytosis does not typically cause specific signs.

Diagnostic Testing

The presence of thrombocytosis should first be confirmed by repeating the CBC and reviewing the blood smear, followed by appropriate work-up to identify an underlying disorder.[33-36] Persistently high platelet counts also can occur after splenectomy. Primary thrombocythemia is diagnosed by bone marrow examination, often with assessment of iron stores to rule out iron deficiency.

Classification of Thrombocytosis

Primary (Essential) Thrombocythemia

Essential thrombocythemia refers to an isolated increase in platelet count. However, thrombocytosis can be a prominent feature of other myeloproliferative disorders, including myeloid leukemias, polycythemia, and myelodysplastic syndrome.[35]

Secondary (Reactive) Thrombocytosis

A general upregulation of cytokine growth factors, including TPO, is the presumed cause of reactive thrombocytosis. Chronic blood loss, infection, inflammation, malignancy, and tissue necrosis are among the disease processes associated with this response. Occult neoplasia and gastrointestinal or urinary blood loss can require concerted diagnostic efforts including careful imaging to identify the inciting cause of persistent thrombocytosis.

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CHAPTER 60

Hypoproteinemia, Hyperproteinemia

Shelley Burton

Measurement of Serum and Plasma Protein

On serum biochemical panels, protein concentrations determined by automated analyzers are reported as total protein, albumin, and globulin(s). The globulin concentration is obtained by subtracting the albumin concentration from the total protein concentration, so is comprised of all proteins which are not albumin. These are mainly antibodies, with acute phase proteins and numerous other proteins making up the rest. Compared to serum, plasma includes coagulation factors such as fibrinogen, which are absent from serum due to clot formation. Therefore, a plasma sample typically has a slightly higher protein concentration than a concurrently collected serum sample. Plasma protein concentrations obtained as part of a complete blood count are determined via refractometry, with total solids causing a proportional change in refractive index. The presumption that the refractive index is proportional only to protein assumes typical concentrations of other substances like glucose or lipids. However, high concentrations of these substances will increase the refractive index to result in falsely elevated protein readings. Because plasma contains coagulation proteins absent from serum, and refractometry and automated analysis are different methods, perfect numerical agreement in total protein concentrations is unreasonable. However, a good rule of thumb is that the two readings should generally agree within ≈0.5 g/dL (= 5 g/L). If the difference is beyond ≈1.0 g/dL, interfering substances or problems with the refractometer or analyzer should be investigated, but the reason is not always readily found.

Serum protein electrophoresis separates proteins via charge and weight within a gel or other substance to allow rough quantitation of protein groups and characterization of the migration pattern. Peaks on the resulting electrophoretogram correspond to gel areas to which proteins have migrated. Electrophoretograms are divided subjectively into sections, most typically alpha 1, alpha 2, beta and gamma. The alpha 1 and alpha 2 areas are where the majority of positive acute phase proteins migrate. IgM migrates to the beta region and IgA and IgG to the gamma region. Protein concentrations in each electrophoretic category are determined by multiplying area percentages by the total protein concentration. Minor changes in these are not significant and the overall electrophoretic pattern is much more useful. An increase in the gamma or sometimes beta region is termed a gammopathy; these are divided based on pattern shape into two types. Monoclonal gammopathies are characterized by a single narrow based peak and polyclonal gammopathies by a broad based smooth peak or series of peaks (Figure 60-1).

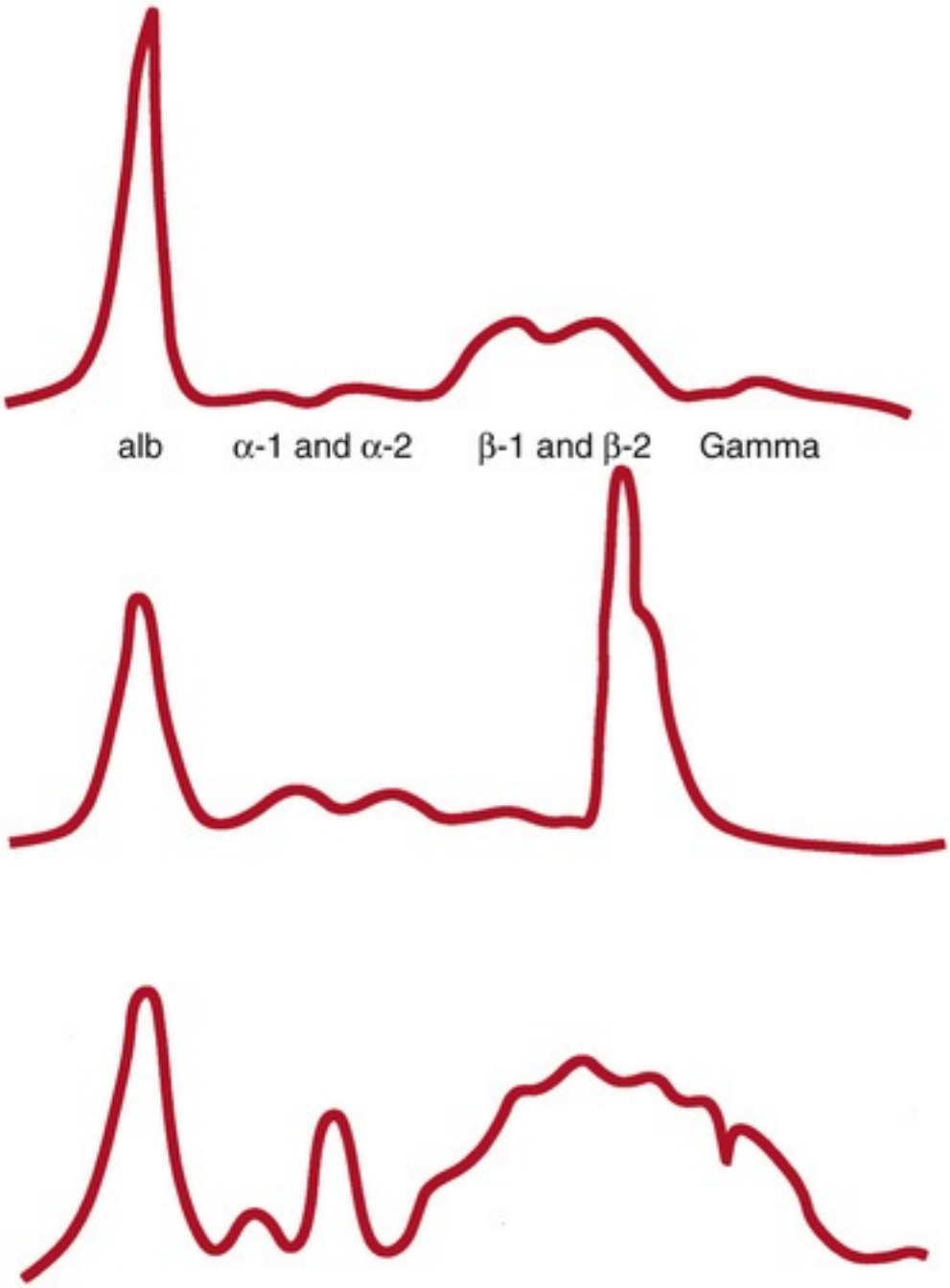

FIGURE 60-1 Serum protein electrophoretograms showing a normal pattern, a monoclonal gammopathy and a polyclonal gammopathy. *alb,* Albumin. (Courtesy Couto CG: Hyperproteinemia. In Nelson RW, Couto CG, editors: *Small animal internal medicine,* ed 5, St Louis, 2014, Elsevier, pp 1276-1278.)

Positive and Negative Acute Phase Proteins

Increased positive acute phase protein concentrations in serum or plasma support inflammation, but testing is not widely available. These are produced by the liver and include C-reactive protein, serum amyloid A, haptoglobin, and many others.[1] The degree of increase and the type of proteins produced vary between species. The acute term is a partial misnomer; although protein production does increase rapidly, it can also continue for many months if inflammation is ongoing. Aside from fibrinogen and haptoglobin, even marked increases in positive acute phase protein production do not increase total serum or plasma protein concentrations. Negative acute phase proteins are those with decreased serum or plasma concentrations in

inflammatory states. Cytokines such as interleukin (IL)-6 and IL-1 cause hepatocytes to decrease production of these proteins while increasing production of positive acute phase proteins.[2] Albumin is the main negative acute phase protein[2] and mild hypoalbuminemia is commonly found in patients experiencing inflammation.

Causes of Hypoproteinemia

Marked hypoproteinemia has serious consequences, especially if albumin concentrations are too low to maintain colloid osmotic pressure. Edema and effusions can result.[3] Hypoproteinemia can be due to a decrease in concentrations of albumin, globulin or both; this latter situation is termed panhypoproteinemia. A normal albumin : globulin (A : G) ratio is expected in panhypoproteinemia, a low ratio if only albumin is decreased and/or globulins are increased, and a high ratio if only globulins are decreased. A diagnostic pathway for hypoproteinemia is found in Figure 60-2.

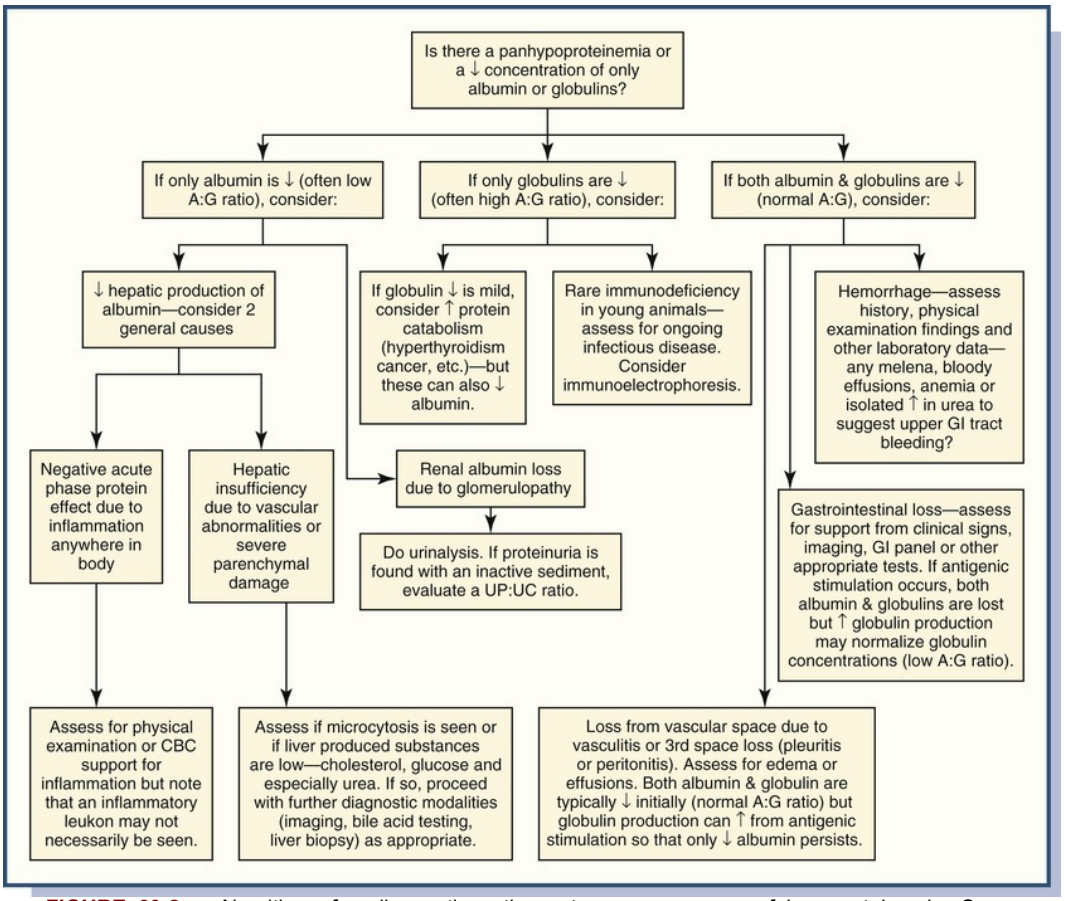

FIGURE 60-2 Algorithm of a diagnostic pathway to assess causes of hypoproteinemia. Some conditions overlap depending on severity and stage. *A : G,* Albumin : globulin; *CBC,* complete blood count; *GI,* gastrointestinal; *UP : UC,* urine protein : urine creatinine.

Panhypoproteinemia is seen in hemorrhage and is a typical feature of protein-losing dermatopathies and loss from the vascular space due to vasculitis, pleuritis, or peritonitis.[4] It also is common in protein-losing enteropathies,[5] but if sufficient antigenic stimulation occurs due to inflammatory bowel disease or other conditions, increased antibody production can offset globulin loss. This can instead result in normal or even high serum globulin concentrations (see ch. 276).[6] The same is true for chronic vasculitis, pleuritis, or peritonitis in which antigenic stimulation is occurring. Hypoalbuminemia with normal globulin concentrations should also prompt concern for decreased liver production and/or renal loss. Decreased hepatic production of albumin as a negative acute phase protein effect takes several days to occur, and clinical or hematologic support for inflammation can be found. The degree of albumin concentration decrease is typically mild (<30% from the patient's normal value)[4] so a more marked decrease should prompt

investigation into other causes. Decreased albumin production also occurs in hepatic insufficiency due to vascular anomalies such as portosystemic shunts[7] or from advanced hepatic parenchymal disease (see ch. 282, 284, and 285). The degree of hypoalbuminemia is typically more severe than that caused by inflammation. Serum concentrations of other liver-produced substances may be low, such as urea, cholesterol, and sometimes glucose. A diagnostic clue in some cases is microcytosis due to abnormal iron status.[8] Hepatic insufficiency is confirmed and characterized with bile acid testing, diagnostic imaging, and biopsy (see ch. 280). Another consideration for hypoalbuminemia is renal loss due to various glomerulopathies (see ch. 325).[9] Since albumin has a relatively low molecular weight,[3] it is lost more readily than the immunoglobulins making up the majority of the globulin component of serum or plasma. Finally, when marked hyperglobulinemia is seen, albumin concentrations tend to decrease. This could reflect decreased albumin requirement for oncotic pressure maintenance if the globulins are performing some of this role, but other disease-related causes might be contributory.[4]

Specific decreases in serum or plasma globulin concentration are not common, but considerations include rare inherited immunodeficiency syndromes or a decrease seen in racing sled dogs.[10] Mild hypoglobulinemia with or without mild hypoalbuminemia is a common finding in hyperthyroid cats in the author's diagnostic laboratory, presumably due to increased protein catabolism.

Breed differences must be considered when evaluating serum or plasma protein concentrations. Healthy Greyhounds have low total serum protein concentrations compared to canine reference intervals derived from other breeds[11]; this also occurs in other sighthounds but is less well documented. In Greyhounds, it is due to low concentrations of alpha and beta globulins, a consideration when interpreting electrophoretic patterns in this breed.[12]

Causes of Hyperproteinemia

Increased serum or plasma protein concentrations can be due to proportional or disproportional increases in the albumin and globulin components. In a proportional increase, the A : G ratio is normal; this is termed panhyperproteinemia or occasionally non-selective hyperproteinemia.[4] This is a relative hyperproteinemia resulting from hemoconcentration due to dehydration. Related findings can include erythrocytosis and pre-renal azotemia. In contrast, an absolute hyperproteinemia characterizes a high total protein concentration due to enhanced production of either albumin or globulin. This disproportional increase shifts the A : G ratio and is sometimes termed selective hyperproteinemia.[4]

It is rare for an appreciable increase in albumin concentration to occur without an increase in globulin concentration; this should prompt consideration of a laboratory error or rarely albumin production from a hepatic tumor.[13] In most cases, a disproportional increase in total protein concentration is due to increased globulin concentrations rather than a change in albumin. Increased globulin production is due to antigenic stimulation or, less commonly, due to production by a B-lymphoid or plasma cell neoplasm.

When marked hyperglobulinemia is detected, serum protein electrophoresis to classify the pattern as a polyclonal or monoclonal gammopathy is the next logical step. In antigenic stimulation due to infectious or immune-mediated disease, a polyclonal gammopathy pattern is expected. Increased production of antibodies that vary mainly in charge and weight by many clones of B-lymphocytes migrate widely to produce a smooth or jagged broad-based peak on the electrophoretogram. In contrast, the narrow peak of a monoclonal gammopathy pattern occurs due to restricted migration of many identical immunoglobulins or immunoglobulin fragments, both of which are termed paraproteins, or M proteins. A true monoclonal gammopathy reflects clonal proliferation of a single neoplastically transformed B-lymphocyte or plasma cell. This is seen in various cancers, including multiple myeloma, B-cell lymphoma or leukemia, or rarely Waldenstrom's macroglobulinemia (see ch. 344). Hyperviscosity due to high concentration of paraproteins in these conditions can cause signs such as bleeding,[14,15] ophthalmic disease,[16] or seizures (see ch. 352).[17]

Infectious or immune-mediated diseases occasionally can stimulate multiple clones of B-lymphocytes or plasma cells to produce antibodies which are so similar in charge and weight that they migrate similarly during electrophoresis. This results in a narrow peak which mimics a monoclonal gammopathy, and indeed is characterized as such on pattern evaluation. This has been more properly termed a restricted pattern oligoclonal gammopathy and is likely the explanation for monoclonal gammopathies reported in infectious or immune-mediated diseases such as pyoderma[18] or plasmacytic enteritis.[19] Awareness of this dictates that B-lymphoid or plasma cell neoplasia is never diagnosed solely on the presence of a monoclonal gammopathy. For example, other criteria needed to diagnose multiple myeloma in dogs include hypercalcemia, lytic bone

lesions, and marked marrow plasmacytosis.[20] The presence of immunoglobulin light chains in urine, termed Bence-Jones proteins, is also a supportive finding.[21] Detection of these is challenging but is supported by a thermal precipitation test or urine electrophoresis (see ch. 344).

Not all pathologic changes in protein components result in hyperproteinemia. While antigenic stimulation is a common cause of hyperglobulinemia, it does not necessarily increase total protein concentrations, especially if mild or early. In any situation of concurrent hypoalbuminemia and hyperglobulinemia, the A : G ratio will decrease but the total protein concentration may stay within the reference interval. There are also rare cases of increased production of paraproteins which cause a monoclonal pattern but do not result in hyperproteinemia[22] or those that cause Bence-Jones proteinuria without a detectable monoclonal gammopathy.[23]

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CHAPTER 61

Hypoglycemia, Hyperglycemia

Yaiza Forcada

Hypoglycemia

Definitions and Clinical Signs

Hypoglycemia in cats and dogs is defined as an inappropriately low blood glucose (BG), falling below the lower limit of the reference interval of the chosen measurement method. The exact number can vary, although <60 mg/dL is often quoted. Hypoglycemia should be repeatable (preferably by a standardized method). Clinicians should be aware of possible factors that could cause spurious hypoglycemia prior to embarking on further investigations. Such factors include a delay in separation of the plasma or serum which could lead to *in vitro* glycolysis in the cellular components of blood (most severe in pets with erythro- or leukocytosis), hemolysis, or the use of human-specific hand-held blood glucose devices.[1,2]

In most patients, clinical signs of hypoglycemia do not occur until the blood glucose is 10 to 20 mg/dL below laboratory reference intervals, although this can vary depending on chronicity and cause of hypoglycemia. Some of the most common clinical signs associated with hypoglycemia are associated with adrenaline-driven activation of the sympathetic nervous system: tremors, nervousness, anxiety, hunger and aggression. Clinical signs are also caused by neuroglycopenia, since the brain is dependent on blood glucose for cellular metabolism. Neuroglycopenia-related signs include weakness, ataxia, behavioral changes, seizures and coma. Clinical signs can be acute or progress over time, e.g., with insulin-producing tumors.

Causes of Hypoglycemia

The causes of hypoglycemia can broadly be divided into the following groups:

- **Decreased glucose production:** this is the most common cause of hypoglycemia seen in young cats or dogs (especially toy breeds). Hypoglycemia in puppies and kittens is most often related to inadequate food intake. Their glycogen stores are reduced when compared with healthy adults. Thus, hypoglycemia in fasting healthy adult animals is extremely rare. Additionally, pets with acute liver failure, end-stage chronic liver disease (see Section XIX) or cortisol deficiency (see ch. 309) can have a reduction in hepatic glycogen stores, as well as impaired gluconeogenesis and glycogenolysis. Hypoglycemia is relatively uncommon in pets with porto-systemic shunts (PSS; see ch. 284).
- **Increased glucose removal from the blood:** conditions in this category include over dosage of insulin or an oral hypoglycemic agent. Naturally occurring hypoglycemia can be caused by an insulin- or insulin-like-substance-producing tumor, usually in older pets (see ch. 303).[3-11] Toxins that induce inappropriate insulin release, such as xylitol, can cause hypoglycemia in dogs.[12,13] Primary renal glycosuria rarely leads to hypoglycemia.

Box 61-1 contains a more comprehensive list of the differential diagnoses to consider in both these groups. The list includes conditions that cause hypoglycemia due to a combination of factors or through unknown mechanisms.

Box 61-1

Causes of Hypoglycemia in the Dog and Cat, According to Pathophysiological Classification

Hypoglycemia Due to Reduced Glucose Production

Portosystemic hepatic vascular shunt
Acute liver failure
Chronic end-stage hepatopathy (mild hypoglycemia)
Hypoadrenocorticism (mild hypoglycemia)
Toxins: ethylene-glycol/ethanol
Medications/toxins: propranolol*
Growth hormone deficiency*
Glycogen storage disease*
Type I: von Gierke's disease
Type III: Cori's disease

Hypoglycemia Due to Increased Removal of Glucose

Insulin overdose
Oral hypoglycemic agents
Insulinoma
Insulin-like-substance-producing tumors: hepatoma, leiomyoma, leiomyosarcomas, carcinomas, melanomas, plasma cell tumors, etc.
Polycythemias: primary erythrocytosis, leukemias*
Toxins: xylitol, oleander[16,17]*
Renal glycosuria*
Infection: *Bartonella*[18]*

Other Causes: Combination of Factors/Unknown

Sepsis/systemic inflammation[19,20]
Babesia infection*
Cardio-pulmonary arrest/resuscitation[21]
Toxins: alpha-lipoic acid[22]*
Acute/chronic renal failure*
Hunting dog*

*Indicates a rare cause of hypoglycemia.

Diagnostic Approach (Figure 61-1)

When determining the cause of hypoglycemia in a pet, it is recommended to start by thoroughly reviewing history and a full physical examination. These may provide essential clues and help identify whether hypoglycemia is responsible for the patient's clinical signs. If a clinical suspicion of hypoglycemia is not supported on initial testing, it is recommended to repeat BG measurements following a closely monitored period of fasting or exercise. In general, puppies and kittens are at a higher risk of hypoglycemia after periods of anorexia, as are those pets with PSS, sepsis, growth hormone (GH) deficiency, glycogen storage diseases, or toxin ingestion. Adult younger dogs with hypoglycemia are candidates for having hypoadrenocorticism, PSS, liver failure, sepsis, systemic inflammatory disease or toxin ingestion. Older dogs are more likely to suffer from neoplastic disease producing insulin or insulin-like factors, hypoadrenocorticism, chronic end-stage liver failure, sepsis/systemic inflammatory disease or toxin ingestion.

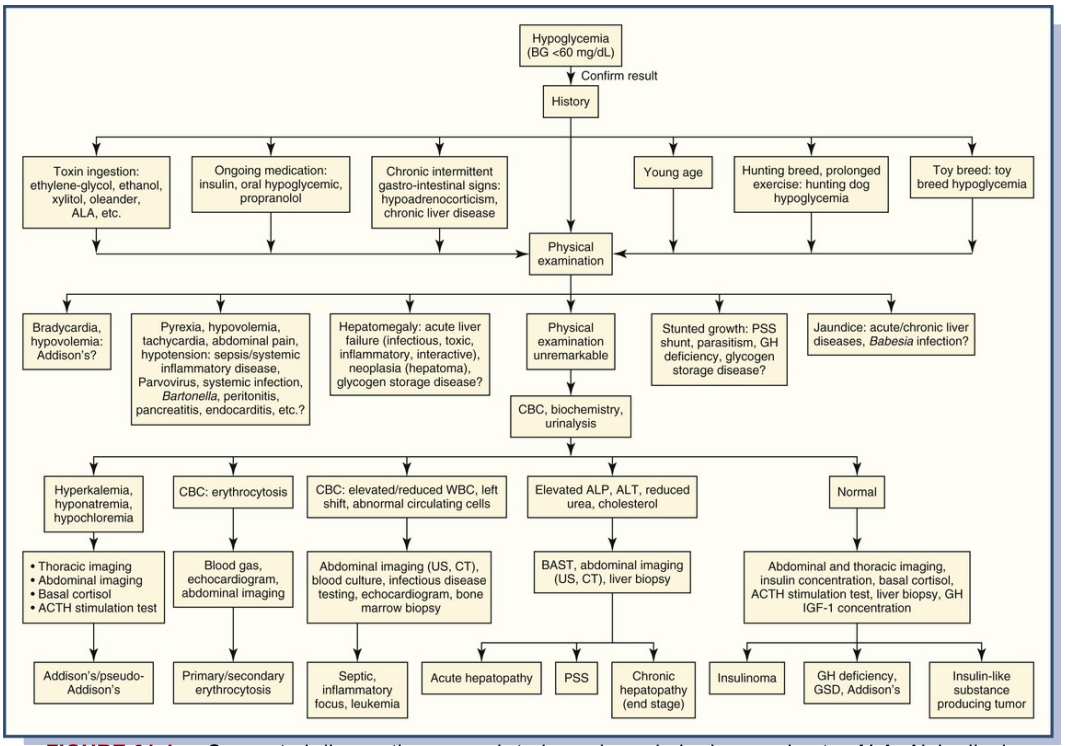

FIGURE 61-1 Suggested diagnostic approach to hypoglycemia in dogs and cats. *ALA,* Alpha-lipoic acid; *BAST,* bile acid stimulation test; *CBC,* complete blood count; *CT,* computed tomography; *GH,* growth hormone; *GSD,* glycogen storage disease; *IGF-1,* insulin-like growth factor-1; *PSS,* porto-systemic shunt; US, ultrasound.

A complete blood count (CBC), serum biochemistry panel and urinalysis can further assist in identifying the cause of hypoglycemia. CBC may reveal polycythemia, evidence of sepsis (leukocytosis/leukopenia, left shift) or the lack of a stress leukogram (hypoadrenocorticism). Patients with PSS or liver failure may have decreases in albumin, urea and/or cholesterol concentrations. Increased liver enzyme activities or serum bilirubin concentration may be observed in liver failure (not usually PSS). A bile acid stimulation test in these pets is likely to be abnormal. Animals with hypoadrenocorticism may have the typical electrolyte abnormalities of hyponatremia, hypochloremia and hyperkalemia. Absence of "classic" electrolyte changes does not, however, rule out hypoadrenocorticism. When hypoadrenocorticism is suspected, a basal cortisol or results of an adrenocorticotropic hormone (ACTH) stimulation test should be considered to confirm or exclude this diagnosis. The presence of glycosuria together with hypoglycemia may suggest possible primary renal loss as a cause for the hypoglycemia. Alternatively, the most common cause of hypoglycemia in an animal with glycosuria would be previous hyperglycemia exceeding renal threshold that decreased precipitously, as sometimes occurs in insulin-treated individuals. Pets with insulinoma or insulin-like factor–producing tumors do not usually have significant abnormalities in the minimum database.[14,15]

Survey diagnostic imaging of the thorax and abdomen (radiography, ultrasound or computed tomography) may prove helpful in identifying septic/inflammatory foci or neoplasia. For confirmation of an insulin-producing tumor, a blood sample should be taken strictly *at the time of hypoglycemia* (preferably when BG is below 50 mg/dL); a normal or high insulin concentration confirms pathological hyperinsulinemia.

Hyperglycemia

Definitions and Clinical Signs

Hyperglycemia in cats and dogs is defined as an inappropriately high BG concentration, exceeding the upper limit of the reference interval of the chosen measurement method. As with hypoglycemia, the exact number can vary, though is often quoted to be >130 mg/dL. Clinical signs of hyperglycemia appear when the blood glucose exceeds the renal threshold (this can be variable, though usually around 180-200 mg/dL in the dog and 200-280 mg/dL in the cat). Excess glucose in the renal tubules causes an osmotic diuresis which leads to polyuria (PU), secondary polydipsia (PD) and, if the water loss is not compensated by increased water intake, dehydration. Additional clinical signs of the primary disease can occur, e.g., weight loss in diabetes mellitus;

coat changes, excessive panting or abdominal enlargement with hyperadrenocorticism (see ch. 306 and 307).

"Stress-Induced" Hyperglycemia

Clinicians should remember that cats, far more commonly than dogs, can develop a physiological hyperglycemia thought to be "stress induced." Stress is associated with catecholamine, cortisol, glucagon and GH secretion, leading to an increase in blood glucose and interference with the actions of insulin. In addition, transformation of lactate generated through muscle activity in stressed animals has been implicated.[23] In suspected "stress hyperglycemia," a repeat BG measurement can be performed at a less stressful time (or at home) or urine can be screened for glycosuria since most of these pets do not have hyperglycemia that exceeds renal threshold (Figure 61-2). A small number, however, do have glycosuria. Alternatively, measurement of fructosamine concentration should help differentiate long-standing versus the brief stress hyperglycemia.[24]

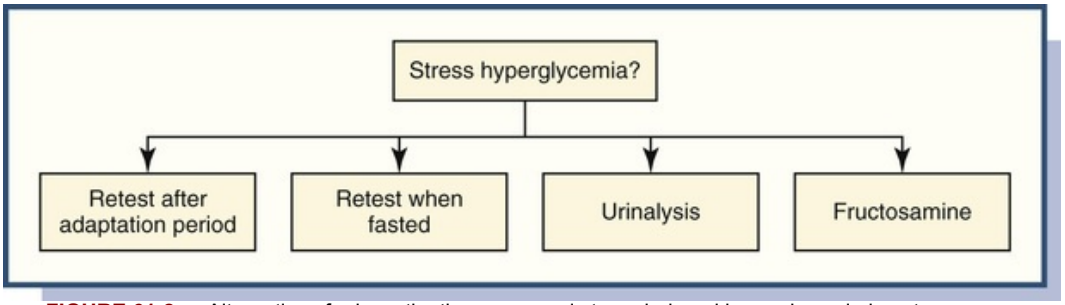

FIGURE 61-2 Alternatives for investigating presumed stress-induced hyperglycemia in cats.

Pathological Causes (Box 61-2)

Pathological causes of hyperglycemia include diabetes mellitus, diestrus diabetes, acromegaly, hyperadrenocorticism, pheochromocytoma, head trauma, pancreatitis, pancreatic neoplasia or iatrogenic (e.g., progestagens, glucocorticoids, megestrol acetate, glucose-containing fluids).

Box 61-2

Differential Diagnoses of Hyperglycemia in Cats and Dogs

Physiological Causes

Stress/excitement (cats)
Post-prandial
Diestrus

Endocrine Causes

Diabetes mellitus
Impaired glucose tolerance (pre-diabetes)
Acromegaly
  Cats: GH-producing pituitary tumor
  Dogs: GH produced in mammary glands during diestrus
Hyperadrenocorticism
Pheochromocytoma
Hyperthyroidism (common in cats, uncommon in dogs)

Problems Originating Initially from Exocrine Pancreas

Acute pancreatitis
Chronic pancreatitis (can be associated with EPI and/or diabetes mellitus)
Pancreatic neoplasia

Iatrogenic

Glucocorticoids
Progestagens
Alpha-2 agonists (medetomidine)
Beta-blockers
Glucose-containing fluids
Parenteral nutrition solutions

Miscellaneous

Toxins: Ethylene-glycol
Head trauma

EPI, Exocrine pancreatic insufficiency; *GH,* growth hormone.

Diagnostic Approach (Figure 61-3)

A thorough history and physical examination is extremely valuable. The clinician should determine if the patient has been receiving any medications that can account for the high BG. One should evaluate the displayed clinical signs and determine if they are related to hyperglycemia or if they give clues about a specific condition. A minimum database including CBC, biochemistry and urinalysis (including culture) is recommended in all cases to provide information about causes and possible consequences of the hyperglycemia. Abdominal imaging will be useful in patients with abdominal pain or to evaluate the adrenal glands. Further investigations such as thyroxine (T_4) concentration or endocrine testing can be considered as necessary.

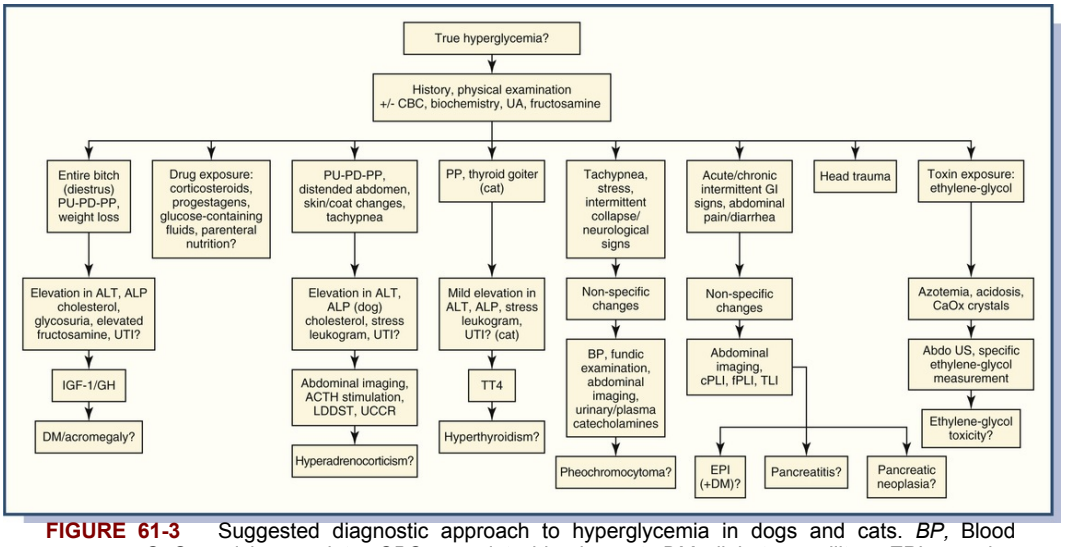

FIGURE 61-3 Suggested diagnostic approach to hyperglycemia in dogs and cats. *BP,* Blood pressure; *CaOx,* calcium oxalate; *CBC,* complete blood count; *DM,* diabetes mellitus; *EPI,* exocrine pancreatic insufficiency; *GH,* growth hormone; *GI,* gastrointestinal; *IGF-1,* insulin-like growth factor-1; *LDDST,* low-dose dexamethasone-suppression test; *PD,* polydipsia; *PP,* polyphagia; *PU,* polyuria; *UA,* urinalysis; *UCCR,* urine cortisol-to-creatinine ratio; *US,* ultrasound; *UTI,* urinary tract infection.

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CHAPTER 62

Blood Urea Nitrogen and Creatinine

Carrie A. Palm

Introduction and Definitions

Blood urea nitrogen (BUN) and serum creatinine concentrations are biomarkers commonly used in the health assessment of companion animals. While often evaluated together, each has unique value. Clinicians should appreciate how to utilize each in diagnosis and treatment monitoring. This chapter is dedicated to BUN and creatinine, with a focus on such factors as compound generation and excretion that should be considered in any interpretation.

Terms relating to BUN and creatinine must be defined in order to ensure understanding. Azotemia refers to an increase in concentration of nitrogen-containing substances in the blood, primarily BUN and creatinine. Since BUN and creatinine are both nitrogen-containing compounds, an increase in either compound is, by definition, "azotemia." Uremia or "uremic syndrome" refers to the significant accumulation of substances (uremic toxins) usually excreted in the urine under normal physiologic conditions in a healthy animal. The term uremia is used to describe more severe azotemia, when adverse clinical manifestations are present, while azotemia is defined by any increase in BUN and/or creatinine. BUN and creatinine are the most commonly measured uremic toxins. BUN and creatinine, themselves, are relatively benign and non-toxic, each acting as a marker for many unmeasured uremic toxins that are associated with development of "uremic syndrome."

Blood Urea Nitrogen

Urea is a nitrogen-containing compound excreted in urine, usually expressed in mmol/L. BUN is a measure of the amount of urea nitrogen in the blood and is expressed in mg/dL. These two values give similar information and BUN will be used for the majority of the following discussion. Urea represents a nitrogenous waste product excreted in urine. During protein catabolism, liberated amino acids are converted to ammonia, which is subsequently metabolized to urea through the urea cycle in the liver. Blood urea nitrogen is freely filtered at the glomerulus. BUN is an unreliable estimate of glomerular filtration rate (GFR), however, as urea can be passively reabsorbed in renal tubules. Therefore, the BUN concentration in urine is not necessarily equivalent to the amount filtered at the glomerulus. Understanding BUN production, filtration and reabsorption should help clinicians effectively apply this test result in any patient. For example, remembering that BUN is synthesized in the liver allows the clinician to conclude that a decrease in BUN concentration below the laboratory reference interval may indicate hepatic dysfunction.

Creatinine

Creatinine is generated from breakdown of phosphocreatinine in muscle and, therefore, muscle mass plays an important role in assessment of a patient's serum creatinine concentration. Like BUN, creatinine is freely filtered at the glomerulus. In contrast to BUN, creatinine can be used to provide an estimation of GFR, as there is no significant reabsorption or secretion of creatinine during transit through the nephron. There is, however, significant variation in "normal" serum creatinine concentrations associated with muscle mass and with breed size. Healthy small-breed dogs have creatinine values much lower than those of healthy giant-breed dogs. Serum creatinine concentrations increase from puppyhood through adulthood. Ideally, each patient would have at least one baseline serum creatinine concentration determined in conjunction with a urine specific gravity when they are a healthy young adult. It is critical to evaluate test results in the context of the individual patient.

Symmetric Dimethylarginine (Idexx SDMA)

Please see discussion under chronic kidney disease (CKD).

Causes of Azotemia (Increases in BUN and/or Serum Creatinine)

Background

Azotemia can be subcategorized into being caused by pre-renal (or volume-responsive), renal, or post-renal conditions. These subcategories all represent causes for a decrease in glomerular filtration rate with subsequent decreased excretion of the renal biomarkers, BUN and creatinine. While BUN and creatinine are the most commonly measured biomarkers, they represent only a fraction of the molecules that undergo decreased excretion in azotemia and then contribute to the "uremic syndrome." Azotemia, defined as BUN and creatinine concentrations above their defined reference intervals, requires that the function of approximately 75% of nephrons be impaired. Obviously, "abnormal" values are seen relatively late in a progressively worsening condition. Therefore, it underscores the importance of not simply looking for results above established reference intervals but understanding that small increases in BUN and/or creatinine concentration may indicate significant pathology. While discussed separately, it is important to note that these subcategories of azotemia may co-exist (Figure 62-1).

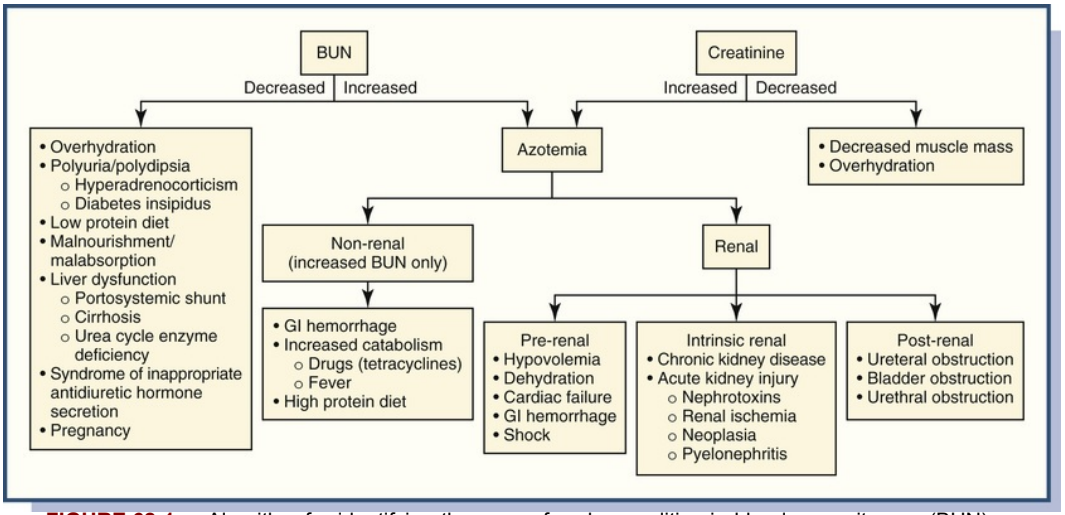

FIGURE 62-1 Algorithm for identifying the cause for abnormalities in blood urea nitrogen (BUN) or serum creatinine concentrations in dogs and cats. *GI*, Gastrointestinal.

Pre-Renal Azotemia

Pre-renal or volume-responsive azotemia is defined as a decrease in GFR secondary to hypoperfusion of structurally normal kidneys. In this condition, correction of hypoperfusion leads to rapid resolution of the azotemia, provided that secondary intrinsic renal injury has not developed. Hypovolemia due to dehydration, poor cardiac output secondary to cardiovascular dysfunction, and pathologic vasodilatory conditions (such as shock) are common causes for pre-renal azotemia. With pre-renal azotemia, the BUN to creatinine ratio often increases (greater than approximately 20:1) due to reabsorption of BUN in nephrons as physiologic mechanisms take place to re-establish a euvolemic state. Hypoadrenocorticism is an example of a condition commonly associated with pre-renal azotemia, sometimes mistaken for intrinsic renal disease (see ch. 309). Assessment of azotemia should include analysis of urine specific gravity. Suspicion for pre-renal azotemia increases when a corresponding urine sample is concentrated. However, in conditions where altered urinary concentrating ability is also present (i.e., hypoadrenocorticism), pre-renal azotemia can occur without the presence of concentrated urine.

Intrinsic Renal Azotemia

Definitions

Renal azotemia refers to abnormal decreases in the excretion of nitrogenous wastes due to intrinsic kidney dysfunction. This includes both acute kidney injury (AKI) and chronic kidney disease (CKD). With renal azotemia, careful evaluation of creatinine is crucial, as renal disease may be missed if only established reference ranges are used in decision making. Significant renal dysfunction can occur before serum creatinine concentrations increase above reference ranges. Familiarity with these concepts, and each patient, may allow identification of early kidney injury.

Acute Kidney Injury

The term AKI (see ch. 322) has replaced the various and ever-changing definitions for "acute renal failure" (ARF). AKI represents a spectrum of renal injury and disease severity, ranging from injury that is clinically non-detectable to severe damage resulting in fulminant ARF. When using traditional evaluation of BUN and creatinine based on laboratory reference ranges, many dogs and cats with intrinsic renal injury are not diagnosed until they have progressed to ARF, given that approximately 75% of renal function must be lost before BUN and creatinine values exceed their respective reference ranges. An entire kidney could theoretically cease functioning without a patient becoming azotemic. Application of the International Renal Interest Society (IRIS) AKI grading system allows a diagnosis of AKI to be made based on small changes in creatinine in non-azotemic patients (see ch. 322). Identification of more sensitive biomarkers for early diagnosis of AKI is being pursued.

Chronic Kidney Disease

CKD occurs when renal tissue is compromised secondary to a prolonged and irreversible disease process. The IRIS CKD staging system, based on creatinine concentration, defines early stages of non-azotemic kidney disease. Stage 1 CKD includes patients with creatinine concentrations <1.4 mg/dL (dogs) and <1.6 mg/dL (cats). Stage 2 includes creatinine concentrations of 1.4-2.0 mg/dL (dogs) and 1.6-2.8 mg/dL (cats). With these classifications, a dog or cat with a creatinine concentration within the laboratory reference range that has evidence of CKD on ultrasound should be classified as having CKD. Other factors that can affect creatinine, such as breed, hydration (i.e., ruling out pre-renal causes) and muscle mass must be considered to fully understand the clinical applications of BUN and creatinine results. Symmetric dimethylarginine (IDEXX SDMA) is a novel marker of GFR that is not affected by muscle mass and that detects CKD earlier than traditional evaluation of creatinine. Studies have shown SDMA to detect CKD an average of 9 months earlier in dogs and 17 months earlier in cats.[1,2]

Post-Renal Azotemia

Post-renal azotemia occurs secondary to obstruction of the urine drainage system (renal pelvis, ureter, bladder or urethra). When relief of obstruction is achieved, complete correction of azotemia should occur rapidly if there is no coexisting pre-renal or intrinsic renal disease. As discussed, unilateral ureteral obstruction may lead to non-azotemic kidney disease. Astute clinicians may observe and appreciate the importance of small but significant increases (i.e., >0.3 mg/dL) in serum creatinine concentrations that could aid early detection.

Non-Renal Effects on BUN and Creatinine

Increased BUN Concentration

Gastrointestinal hemorrhage and high protein intake can lead to azotemia through increased BUN generation; in this scenario a concurrent increase in serum creatinine may not occur. Catabolic states caused by prolonged fever, and less commonly tetracycline administration, can cause increased BUN concentrations.

Decreased BUN Concentration

The disease state most commonly associated with a decrease in BUN concentration is liver dysfunction, particularly cirrhosis and portosystemic shunting (see ch. 284). In both scenarios, the volume of functional liver is decreased, and subsequently, too few hepatocytes are available to convert ammonia into urea, resulting in decreased BUN concentrations. When portosystemic shunts are successfully treated, the BUN often increases. Urea cycle enzyme deficiencies, as seen in Irish Wolfhounds, can also lead to decreased synthesis of BUN. Iatrogenic overhydration and disease states preventing water removal or causing polyuria

and polydipsia, such as diabetes insipidus, the syndrome of inappropriate antidiuretic hormone secretion and hyperadrenocorticism can cause decreased BUN concentrations. Chronic feeding of a low protein diet or malabsorption can also lead to decreased BUN concentrations.

Decreased Creatinine Concentration

Decreases in muscle mass can cause associated decreases in serum creatinine concentration through decreased creatinine generation. This could lead to serum creatinine concentrations below established reference ranges in a puppy, whose "normal" reference range should be lower than those based on adult dogs. It could also cause a muscle-wasted patient to falsely have a serum creatinine concentration within the established reference range. In the latter case, because BUN generation is not affected by muscle mass, the BUN may be above the reference range and more representative of renal function than creatinine. Like BUN, creatinine values may decrease in fluid-overloaded patients and the measured results may under-represent the degree of renal compromise.

Understanding the intricacies of BUN and creatinine will allow a clinician to interpret these values beyond only using established reference ranges. With such critical evaluations and an understanding of how to evaluate these biomarkers in context of each individual patient, appropriate use of these tests is employed and accurate diagnoses can be made.

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CHAPTER 63

Cholesterol, Triglycerides

Panagiotis G. Xenoulis

Introduction and Terminology

Disorders of lipid metabolism are common in dogs but less so in cats. The term *hyperlipidemia* refers to an increased concentration of lipids (i.e., triglycerides, cholesterol, or both) in the blood (serum or plasma). Specifically, an increased blood concentration of triglycerides is referred to as *hypertriglyceridemia,* while an increased blood concentration of cholesterol is referred to as *hypercholesterolemia*. Because both triglycerides and cholesterol are transported in the blood combined with specific proteins called *apoproteins* or *apolipoproteins* (the lipid-protein complex is referred to as *lipoprotein*), the term *hyperlipoproteinemia* is often used interchangeably with the term hyperlipidemia. The term *lipemia* is used to describe a grossly visible turbid or lactescent appearance of serum or plasma. Lipemia is a result of moderate and severe hypertriglyceridemia (typically >200-300 mg/dL), but not hypercholesterolemia nor very mild hypertriglyceridemia. The terms *hypotriglyceridemia* and *hypocholesterolemia* refer to decreased concentrations of triglycerides or cholesterol in the blood, respectively. Finally, the term *dyslipidemia* is a more general term for describing any kind of disturbance in the quality and/or quantity of blood lipids and/or lipoproteins.

Canine and feline lipoproteins can be divided into four major classes based on their hydrated density after ultracentrifugation: chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). An intermediate-density lipoprotein (IDL) also likely exists in cats. Several subclasses of the above mentioned major classes of lipoproteins exist in dogs and cats, but their nature and clinical significance have not been fully elucidated.

Canine Hyperlipidemia

Major Causes of Canine Hyperlipidemia

Fasting Samples

A list of the most important causes of canine hyperlipidemia is shown in Table 63-1.[1] Postprandial hyperlipidemia is physiologic and typically resolves within 7-12 hours after a meal.[2,3] Therefore, determination of serum lipid concentrations should always follow a fast of at least 12 hours. However, recent evidence suggests that food might need to be withheld >12 hours when assessing fasting concentrations of serum triglycerides.[4]

TABLE 63-1

Main Causes of Hyperlipidemia in Dogs and Cats and Expected Lipid Abnormalities

	TYPE OF LIPID ABNORMALITY	COMMENTS
Postprandial Hyperlipidemia*†	HTG (rarely HCH)	Increases are typically mild and last <15 hours Most common cause of hyperlipidemia
High Fat Diets	HTG and/or HCH	Fat content must be very high (typically >50%) to cause fasting hyperlipidemia
Secondary Hyperlipidemia		
Disease		

Diabetes mellitus*†	HTG (mainly) and/or HCH	HTG and HCH can range from mild to marked; present in >50% of cases
Hypothyroidism*	HTG and/or HCH	HTG and HCH can range from mild to marked; present in >75% of cases
Hyperadrenocorticism*	HTG and/or HCH	HTG and HCH can range from mild to marked
Pancreatitis*	HTG and/or HCH	HTG and HCH are typically mild if other causes of hyperlipidemia are excluded; present in ~30% of cases
Obesity*†	HTG and/or HCH	HTG and HCH can range from mild to marked; present in ~25% of cases
Protein-losing nephropathy*	HCH	HCH is part of the nephrotic syndrome; HCH is usually mild
Cholestasis*	HTG and/or HCH	Increases are usually mild
Hepatic insufficiency*	HTG and/or HCH	Increases are usually mild
Lymphoma	HTG with or without HCH	Hyperlipidemia might persist despite treatment
Leishmania infantum infection	HTG and HCH	Increases are typically mild if present
Parvoviral enteritis	HTG	HTG is typically mild if present
Hypernatremia?	HTG and HCH	Based on a case report and evidence from human medicine
Hepatic lipidosis?		
Drugs*		
Glucocorticoids	HTG and/or HCH	Increases can range from mild to marked
Phenobarbital	HTG	HTG can range from mild to marked; present in ~30% of cases
Megestrol acetate	HTG and/or HCH	Mainly in cats
Primary Hyperlipidemia		
Miniature Schnauzer*	HTG with or without HCH	HTG can range from mild to marked; HCH may be mild to moderate; present in >30% of all Miniature Schnauzer dogs in the U.S.; prevalence increases with age
Beagle*	HTG and/or HCH	Increases are usually mild to moderate
Shetland Sheepdog*	HCH with or without HTG	HCH might be marked; HTG is typically mild; present in >40% of Shetland Sheepdogs in Japan
Doberman Pinscher	HCH	HCH is usually mild
Rottweiler	HCH	HCH is usually mild
Briard	HCH	HCH in Briards has only been reported in the UK
Rough-Coated Collie	HCH	Reported in a single family in the UK
Pyrénées Mountain Dogs	HCH	HCH is usually mild
Cats	HTG and/or HCH	Idiopathic hyperchylomicronemia
Cats	HCH	Idiopathic hypercholesterolemia

*Indicates common causes in dogs

†Indicates common causes in cats

HCH, Hypercholesterolemia; *HTG*, hypertriglyceridemia.

Secondary Hyperlipidemias

Persistent fasting hyperlipidemia is abnormal and can be either primary or secondary to other diseases or drug administration. Secondary hyperlipidemia is the most common form of hyperlipidemia in dogs. Most commonly, secondary canine hyperlipidemia is the result of an endocrine disorder, such as hypothyroidism, diabetes mellitus, or hyperadrenocorticism (see ch. 299, 304, and 306).[5-12] Hyperlipidemia has also been considered to be the result of naturally occurring pancreatitis in dogs (see ch. 289 and 290).[5,6,13,14] However,

results of a recent unpublished study in dogs with naturally occurring pancreatitis indicate that when concurrent diseases (e.g., diabetes mellitus, hypothyroidism) and use of certain drugs are excluded, hypertriglyceridemia and hypercholesterolemia occur infrequently (18% and 24%, respectively) as a result of pancreatitis and are typically mild.[15] Therefore, fasting hyperlipidemia (especially when severe) in dogs with pancreatitis likely reflects concurrent hyperlipidemia (primary or secondary to other causes, such as an endocrine disease), and warrants further diagnostic investigation. Several other causes of secondary hyperlipidemia have been reported in dogs and are discussed elsewhere.[1,3,16-30]

Primary Hyperlipidemias

Primary lipid abnormalities are usually, but not always, associated with certain breeds (see Table 63-1). Depending on the breed, the prevalence of a primary lipid abnormality can vary widely. Also, the geographic region of the canine population tested seems to play an important role due to genetic differences. Primary hyperlipidemia is very common in Miniature Schnauzers in the United States (>30% of Miniature Schnauzers are affected based on one study)[31-33] and has also been reported in Japan[34] and likely commonly exists in other countries as well. Based on anecdotal evidence, hyperlipidemia in this breed might be considerably less common in Europe. Primary hyperlipidemia in the Miniature Schnauzer is typically characterized by hypertriglyceridemia with or without hypercholesterolemia.[32,33,35] Primary hyperlipidemias have also been reported in Shetland Sheepdogs (in Japan and possibly other countries),[34,36,37] Beagles,[38] Briards,[39] a family of rough-coated Collies from the United Kingdom,[18] and anecdotally in Doberman Pinschers and Rottweilers.

Clinical Importance of Hyperlipidemia in Dogs

Canine hyperlipidemia has emerged as an important clinical condition that requires a systematic diagnostic approach and appropriate treatment (see ch. 182). Although hyperlipidemia itself does not seem to lead directly to the development of major clinical signs, it has been shown to be associated with the development of other diseases that are clinically important and potentially life-threatening (Table 63-2). Hyperlipidemia, and more specifically hypertriglyceridemia, has long been suspected as a risk factor for canine pancreatitis (see ch. 289 and 290), although this remained largely unproven.[1,13,14] The results of two recent clinical studies provided stronger evidence that hypertriglyceridemia, especially when severe (>900 mg/dL), is a risk factor for pancreatitis in Miniature Schnauzers.[40,41] In one of those studies, Miniature Schnauzers that developed pancreatitis were 5 times more likely to have hypertriglyceridemia before the development of pancreatitis than dogs of the same breed that did not develop pancreatitis.[41] Therefore, severe hypertriglyceridemia in Miniature Schnauzers should be treated even when clinical signs are not present, due to the risk of developing pancreatitis.

TABLE 63-2

Possible Consequences and Complications of Hyperlipidemia in Dogs and Cats

DISORDER	TYPE OF LIPID ABNORMALITY RESPONSIBLE
Dogs	
Pancreatitis	HTG
Hepatobiliary disease	
Vacuolar hepatopathy	HTG
Lipidosis	HTG
Biliary mucocele	HTG/HCH
Insulin resistance	HTG
Ocular disease	
Lipemia retinalis	HTG
Lipemic aqueous	HTG
Lipid keratopathy	HTG

Intraocular xanthogranuloma	HTG
Arcus lipoides corneae	HTG/HCH
Seizures	HTG
Lipomas	HTG
Atherosclerosis	HCH
Cats	
Xanthomata	HTG
Ocular disease	HTG/HCH
Other?	

HCH, Hypercholesterolemia; *HTG,* hypertriglyceridemia.

Clinical studies and anecdotal observations suggest that two hepatic disorders are associated with hypertriglyceridemia in dogs: diffuse vacuolar hepatopathy and gallbladder mucocele (see ch. 285 and 288).[1] Hyperlipidemia-associated vacuolar hepatopathy has been anecdotally reported and associated with primary hyperlipidemia in dogs. It is characterized by hepatocellular accumulation of triglycerides and glycogen, and it is often referred to as hepatic lipidosis or steatosis.[1] Gallbladder mucoceles have been commonly reported in dog breeds that are predisposed to primary hyperlipidemia (e.g., Miniature Schnauzers and Shetland Sheepdogs).[37] In a recent study, primary hypertriglyceridemia was found to be associated with increased serum hepatic enzyme activities in clinically healthy Miniature Schnauzers.[42] In that study, 60% and 45% of the Miniature Schnauzers with serum triglyceride concentrations ≥4.52 mmol/L (400 mg/dL) had increased serum alkaline phosphatase and alanine aminotransferase activities, respectively.

Another potential complication of hypertriglyceridemia in dogs is insulin resistance. In a recent study, almost 30% of Miniature Schnauzers with primary hypertriglyceridemia had evidence of insulin resistance as determined by serum insulin concentration.[43] However, the clinical importance of hypertriglyceridemia-associated insulin resistance remains to be determined. Other potential complications of hyperlipidemia in dogs include atherosclerosis (mainly as a result of secondary hypercholesterolemia due to endocrinopathies),[44-47] ocular disease (e.g., lipemia retinalis, lipemic aqueous, lipid keratopathy, solid intraocular xanthogranuloma in hyperlipidemic Miniature Schnauzers),[48,49] seizures and other neurologic signs,[50,51] and possibly cutaneous xanthomata and lipomas.

Diagnostic Approach to Dogs with Hyperlipidemia

Hyperlipidemia is typically diagnosed by measurement of fasting serum triglyceride and/or cholesterol concentrations. Because hyperlipidemia is most commonly the result of other diseases, it can serve as an important diagnostic clue. Hyperlipidemia is usually the only abnormality in dogs with primary hyperlipidemia. In order not to miss existing hyperlipidemia, the clinician should consider measurement of serum cholesterol and triglyceride concentrations as part of every "routine" chemistry profile. Measurement of the serum triglyceride concentration is often not included in a typical chemistry profile and has to be specifically requested by the clinician. Moderate and severe hypertriglyceridemia (but not hypercholesterolemia or mild hypertriglyceridemia) can be suspected based on inspection of serum or plasma that has a turbid or lactescent appearance. However, even in those cases, measurement of serum triglyceride and cholesterol concentrations is mandatory in order to reach an accurate assessment of the severity and spectrum of hyperlipidemia. In some cases, use of a meal challenge to diagnose postprandial hyperlipidemia might be necessary, although experience with such a test is limited.[4]

The general diagnostic approach when evaluating dogs with hyperlipidemia is presented in Figure 63-1. After hyperlipidemia has been diagnosed, the next step is to determine whether the patient has a primary or a secondary lipid disorder. If hyperlipidemia is secondary, the condition responsible for causing hyperlipidemia should be diagnosed and treated. Thus, specific diagnostic investigations should be performed in order to diagnose or rule out specific diseases that can cause secondary hyperlipidemia. If secondary hyperlipidemia is excluded, a tentative diagnosis of a primary lipid disorder can be made.

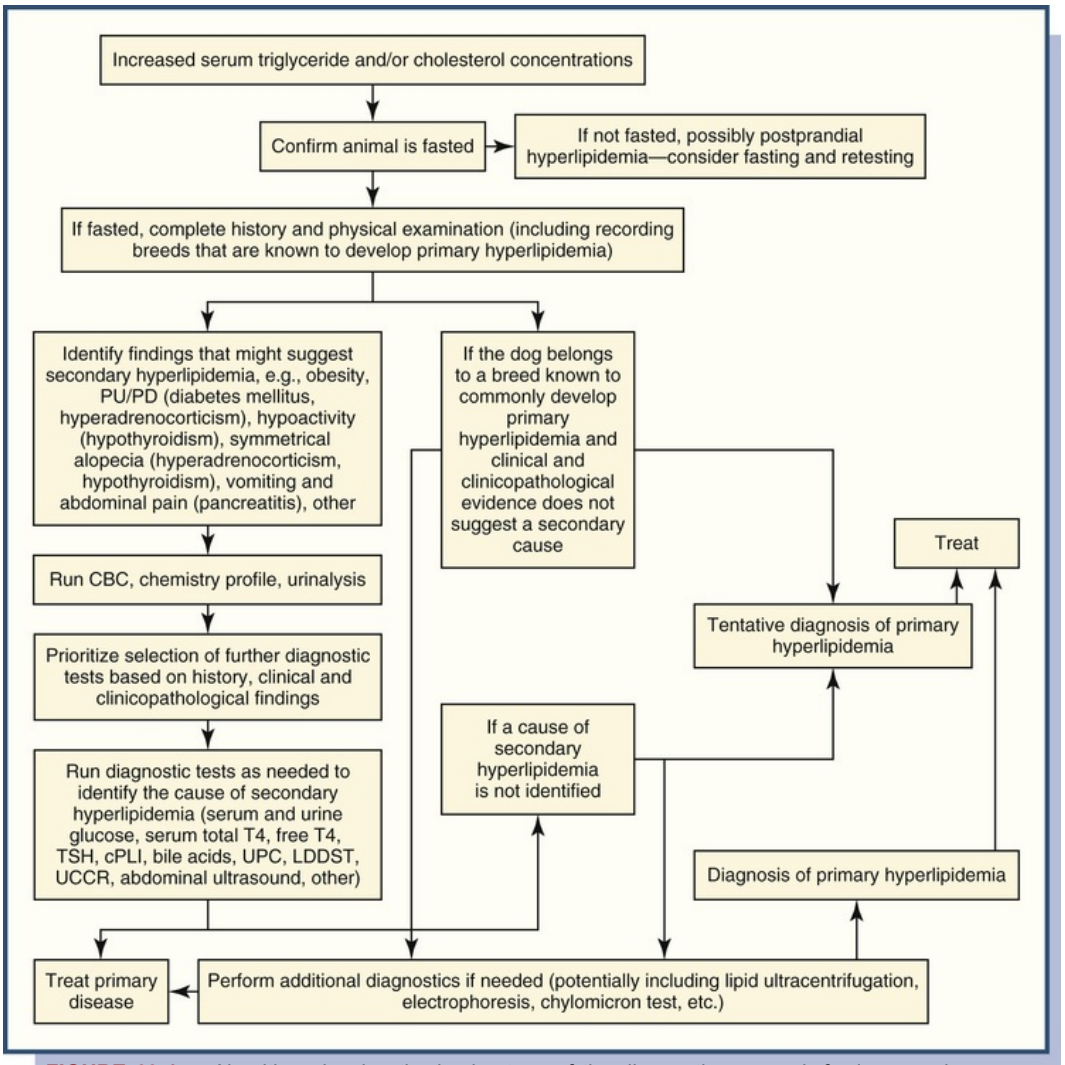

FIGURE 63-1 Algorithm showing the basic steps of the diagnostic approach for increased serum triglyceride and/or cholesterol concentrations in dogs and cats. *cPLI,* Canine pancreatic lipase immunoreactivity; *T4,* thyroxine; *TSH,* thyroid stimulating hormone; *UPC,* urine protein : creatinine ratio; *UCCR,* urine cortisol : creatinine ratio; *LDDST,* low dose dexamethasone screening test.

A detailed history should be obtained and physical examination performed. These are crucial because dogs with secondary hyperlipidemia typically show clinical signs of their primary disease (e.g., obesity, polyuria and polydipsia in dogs with diabetes mellitus or hyperadrenocorticism, hypoactivity and hair loss in dogs with hypothyroidism), which can help prioritize diagnostic tests and construct an appropriate diagnostic plan. Dogs with primary hyperlipidemia may or may not have clinical signs. Dogs with hyperlipidemia should have at least a complete blood count (CBC), chemistry panel, and urinalysis performed. Additional tests that may be useful for the diagnostic investigation of dogs with hyperlipidemia include measurement of serum total and free thyroxine concentrations, serum thyroid-stimulating hormone (TSH) concentration, serum glucose concentration and urine glucose (if not previously performed), serum pancreatic-lipase immunoreactivity concentration, serum bile acid concentrations, urine protein : creatinine ratio, and a "screening test" for hyperadrenocorticism.

Tests recommended after review of the history, physical examination, and routine laboratory test results should be tailored for each patient. A more general and wide selection of tests might be necessary for patients that have vague or no clinical signs. It should be noted that dogs with hyperlipidemia are often clinically healthy. It is likely that at least some of these dogs have some form of primary hyperlipidemia. If it is mild or moderate, there may be no need for detailed diagnostic investigations. Primary hyperlipidemia is common in Miniature Schnauzers from certain geographic regions. A detailed diagnostic investigation of hyperlipidemia may not be necessary in this breed in the absence of clinical signs suggesting an underlying cause. However, if hypercholesterolemia is the main abnormality (without or with only mild hypertriglyceridemia), then it is

more likely that the dog has some form of secondary hyperlipidemia, warranting recommendations for further diagnostic investigation.

To further characterize or investigate the cause of primary hyperlipidemia in dogs, one may employ the chylomicron test (i.e., lipemic serum is left for 12 hours undisturbed at 4° C; if chylomicrons are present, a cream layer will form; the remaining serum can be clear or turbid indicating an excess of VLDL), lipoprotein electrophoresis, ultracentrifugation, measurement of specific apoproteins, and indirect measurement of lipoprotein lipase activity with a heparin response test (i.e., measurement of serum triglyceride concentrations before and after IV administration of 90 IU/kg heparin; heparin activates lipoprotein lipase). None of these tests is used routinely in clinical cases and their availability is limited. Genetic testing for specific lipid disorders related to mutations of genes involved in lipid metabolism is currently not available.

Feline Hyperlipidemia—Species Differences[52-63]

Hyperlipidemia is encountered less frequently in cats than in dogs. In general, the same principles described above for dogs also apply for feline hyperlipidemia, which can be postprandial, primary or secondary. The conditions causing secondary hyperlipidemia in dogs likely also cause hyperlipidemia in cats, the most common and important being diabetes mellitus, obesity, nephrotic syndrome and possibly severe hepatic lipidosis (see Table 63-1; see ch. 176, 305, and 325). In addition, drug-induced hyperlipidemia may be encountered with administration of corticosteroids or megestrol acetate. The diagnostic approach for cats with hyperlipidemia does not differ from the one described for dogs (see above and Figure 63-1). Secondary causes should be excluded first using appropriate testing; if secondary hyperlipidemia is excluded, then a tentative diagnosis of primary hyperlipidemia is made. Use of more specific diagnostic tests (e.g., chylomicron test, ultracentrifugation) may be required at that stage to further characterize the type of hyperlipidemia. Primary hyperlipidemias in cats include an inherited hypertriglyceridemia (often called inherited hyperchylomicronemia) characterized by decreased lipoprotein lipase activity and idiopathic hypercholesterolemia (see Table 63-1). Cats with severe primary hyperlipidemia may develop cutaneous xanthomata, xanthomata in other tissues (e.g., liver, kidneys, heart), and ocular manifestations (e.g., lipemia retinalis). Complications of canine hyperlipidemia such as pancreatitis and atherosclerosis have not been proven to occur in cats.

Hypocholesterolemia and Hypotriglyceridemia

The main causes of hypocholesterolemia in dogs and cats include protein-losing enteropathy (e.g., severe inflammatory bowel disease, intestinal lymphoma, lymphangiectasia), hepatic insufficiency (e.g., cirrhosis, portosystemic shunts), and selected malignancies. History, physical and clinicopathological findings usually provide adequate information to identify the cause of hypocholesterolemia. In cases where it is unclear, additional diagnostics might be needed, including ultrasound, serum bile acids, fecal $alpha_1$-proteinase inhibitor, endoscopy or laparoscopy with biopsies, etc. Severe malnutrition may also lead to hypocholesterolemia. With the possible exception of severe malnutrition, hypotriglyceridemia is not known to be clearly associated with any disease.

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CHAPTER 64

Amylase, Lipase

Peter Hendrik Kook

Inflammatory diseases of the exocrine pancreas in dogs and cats occur relatively frequently, vary in severity and can be divided into acute and chronic forms based on histologic findings. Results of studies on the sensitivity and specificity of tests for the diagnosis of pancreatitis are controversial. Part of this confusion arises from the fact that there is no easily applied gold standard against which diagnostic methods can be evaluated. Clinically, nonspecific findings such as anorexia, vomiting, lethargy, diarrhea, abdominal pain, and weight loss may be seen, but this combination of clinical signs can also occur in other conditions. Because chronic pancreatitis is usually associated with decreased enzyme leakage due to fibrous pancreatic remodeling, the ability to clinically classify pancreatitis as acute or chronic would help in the interpretation of serum enzyme results. However, clinicopathologic assessment of the severity of pancreatitis can be very difficult in individual patients. The same holds true for the evaluation of disease chronicity when previous bouts of pancreatitis may have been clinically silent or simply misdiagnosed. The situation becomes even more complicated when one considers the results of 2 recent studies on the agreement of specific ultrasonographic pancreatic variables, generally regarded as useful diagnostic tools for pancreatitis, and concurrent serum lipase values (catalytic assay and immunoassay).[1,2,25] It was concluded that the results of pancreatic ultrasonography performed by radiologists using state-of-the-art equipment agreed only poorly with the results of serum lipase determinations in cats and dogs suspected of having pancreatitis.[1,2,25] However, these conclusions appear somewhat problematic because in previous clinical studies that evaluated the diagnostic accuracy of laboratory tests in the absence of histologic evaluation as the gold standard, the diagnosis relied on a combination of clinicopathologic and ultrasonographic findings.[3-5] Although a definitive diagnosis of pancreatitis requires histologic confirmation, histology *per se* does not represent the ideal gold standard because histologic evidence of mild forms of acute and chronic pancreatitis may not be associated with clinical disease, rendering the clinical significance of histologically mild pancreatitis questionable. Moreover, pancreatic biopsy is performed infrequently because of its inherent invasiveness, the possibility of highly localized disease that can be missed with a single biopsy,[6] and relatively few direct therapeutic consequences. Therefore, based on a review of the literature to date concerning the clinical utility of laboratory tests (e.g., serum amylase and lipase activities, results of immunoassays), it can be concluded that it is virtually impossible to reliably diagnose pancreatitis without a standardized pancreatic histologic examination, which is not practical in a clinical setting.

Dogs

Although pancreatitis is a relatively common disorder in dogs, its diagnosis can be clinically challenging. This is especially true with mild forms of the disease, which seem to prevail in dogs.

Serum Amylase Activity

An older study reported that a threefold increase in serum amylase activity supported a diagnosis of pancreatitis,[7] but this finding has never been clinically proven. Measurement of serum amylase activity was the least sensitive test for the diagnosis of mild or moderate to severe pancreatitis in 2 recent studies and should not be used as an initial screening test because of low sensitivity and specificity.[5,8] Exceptions are cases of pancreatitis secondary to organophosphate ingestion, which is usually accompanied by marked increases in serum amylase activity.

Serum Lipase Activity

Until recently, it was believed that catalytic assays for measuring serum lipase activity were less reliable for the diagnosis of pancreatitis because of unsatisfactory sensitivity and specificity. The conclusion that catalytic lipase assays were suboptimal tests for diagnosis of pancreatitis in dogs was based on studies that used assays that are no longer available[7-9] or the 1,2 diglyceride (1,2 DiG) assay,[5,8,10,11] which is still used by major commercial laboratories. However, a more recent prospective study that evaluated markers for pancreatitis in dogs with histologic evidence of pancreatitis found that the catalytic 1,2 DiG lipase assay had the overall highest sensitivity (54% for mild pancreatitis, 71% for moderate to severe pancreatitis), followed by pancreas-specific lipase measured by an immunoassay (Spec cPL cutoff >400 mcg/L; 21% for mild pancreatitis, 71% for moderate to severe pancreatitis); the reported specificity (for all forms of pancreatitis) of the 1,2 DiG lipase assay was poor at only 43% compared with 100% for the Spec cPL (cutoff >400 mcg/L).[8] In 2005, a novel catalytic assay, the 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6′-methylresorufin) ester (DGGR) assay, for colorimetric determination of serum lipase activity was validated for use in dogs.[3] We have used this more cost-effective DGGR lipase assay for about 10 years at our institution and believe it is useful in the investigation of pancreatitis. There was good agreement and a very strong correlation between the results of the DGGR lipase and Spec cPL assay in a recent investigation that evaluated 144 dogs suspected of having pancreatitis.[2] Similar conclusions were drawn by other veterinary teaching hospitals in North America and Europe.[12,13] Our current reference range for the DGGR lipase is 24-108 U/L. There may be intraindividual variability in serum lipase activity in healthy dogs with values outside the reference interval. In addition, it is virtually impossible to prove that transient mild pancreatitis does not occur in clinically healthy dogs. Therefore, we chose to integrate a twofold DGGR lipase "gray zone" (108-216 U/L) similar to what is currently used for interpretation of Spec cPL results. Presently it is not known which assay yields better diagnostic accuracy and further work is needed, especially considering the marked difference in cost and turnaround time between the two methods.

Cats

Chronic pancreatitis is much more common than acute pancreatitis in cats.[14-17] Unfortunately the available laboratory tests have poor sensitivity and specificity in chronic pancreatitis, presumably because there is little or no enzyme leakage from remodeled fibrous acinar cells, and this poses a diagnostic challenge for the clinician.

Serum Amylase Activity

Although extensive studies have not been done, serum amylase activity appears to be of no clinical value in the diagnosis of acute pancreatitis in cats.[18,19] Our own unpublished data show very poor agreement between elevated serum amylase activity and the results of DGGR lipase, Spec fPL, and pancreatic histology in cats suspected of having pancreatitis. Interestingly, experimentally induced acute pancreatic injury in cats resulted in rather low amylase activity,[20,21] but this finding has not been investigated in spontaneous acute feline pancreatitis. More recent work has shown that amylase activity may also be influenced by serum glucose concentration in cats,[22] and at this point in time, low amylase activity alone should not be considered a marker for pancreatitis. Even though studies on the usefulness of serum amylase activity in cats with chronic pancreatitis are lacking, it seems wise to assume that it offers no diagnostic benefit.

Serum Lipase Activity

Evidence for the poor performance of traditional catalytic lipase assays in cats is weak and based on only a few cases.[18,23,24] However, the type of lipase assay must be carefully considered because methodologies used for the determination of serum lipase vary and the 1,2 DiG lipase assay, which is the most commonly used commercial catalytic assay to date, has no doubt contributed to the general poor perception of traditional catalytic lipase assays for pancreatitis in cats. A newer catalytic serum lipase assay (DGGR lipase) was recently validated for use in cats and compared with the feline pancreas–specific lipase assay (Spec fPL) in larger scale studies of cats suspected of having pancreatitis.[1,12,16] There was substantial agreement and strong correlation between the results of the 2 lipase assays, and the DGGR assay seems to be a useful method compared with the feline pancreas–specific lipase test, particularly when cost is taken into consideration.[1] In the largest retrospective study on feline pancreatitis to date, pancreatic histopathology was available in 31 cases. Compared with the results of histologic evaluation, which was considered the gold standard, the

sensitivity of both lipase assays (DGGR lipase and Spec fPL) was 100% for acute pancreatitis and 47% (Spec fPL) and 37% (DGGR lipase) for chronic pancreatitis.[16] Intuitively, sensitivities in this range appear to be of little clinical value. It is important to critically assess these data because false-negative lipase results in cats with chronic pancreatitis may indicate a lack of active inflammation or be due to mild histologic changes, as recently demonstrated in dogs.[8] Unfortunately, the relevance of severity and type (acute versus chronic) of inflammation as well as its parenchymal distribution cannot be clarified without a standardized histologic examination of the entire pancreas. The same problem holds true for the assessment of the specificity of lipase results because the histologic diagnosis of pancreatitis may be missed during necropsy or surgery when focal disease is present. For this reason, we prospectively compared lipase measurements (DGGR lipase and Spec fPL) with a standardized histologic assessment of freshly procured pancreata (n = 60) where the entire pancreas was examined with serial sections every 0.5 cm.[17] Distribution of acute (15%) and chronic pancreatitis (64%) was similar to the findings of an earlier study.[15] The sensitivity of both lipase assays (DGGR lipase and Spec fPL) for detecting pancreatitis was calculated based on a pancreatitis activity index described earlier[6] and was 66.7% for DGGR lipase and 61.1% for Spec fPL. The specificity was 78.6% (DGGR lipase) and 69% (Spec fPL).[17] When the aforementioned pitfalls involved in the antemortem diagnosis of pancreatitis and the shortcomings of histologic evaluation as the gold standard are taken into consideration, the DGGR lipase assay appears to be as useful a method as the Spec fPL assay and more attractive in terms of cost.

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CHAPTER 65

Liver Enzymes

Andrea N. Johnston

Clinical Enzymology

Enzymes catalyze biochemical reactions in every cell in the body. Substrate specificity is manipulated to detect and quantify enzyme activity.[1] To be clinically relevant markers of disease, there must be correlation between changes in circulating enzyme concentrations and changes in the tissue of interest. Since many factors affect enzymatic activity *in vivo* and *in vitro* (pH, temperature, salt or protein concentration, ionic strength, cofactor concentration, inhibitors), interpretation also requires accurate assays. Serum or heparinized plasma samples are used in enzyme assays.[2] Citrate complexes divalent cations and EDTA inhibits activity of almost all enzymes; neither should be used for enzyme analysis.[1]

Liver Enzymology

Although numerous hepatic enzymes exist, only 4 are routinely used as biomarkers for hepatobiliary disease in dogs and cats: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma-glutamyl transferase or transpeptidase (GGT, GGTP).[1,3,4] These enzymes have relatively stable circulating concentrations due to normal and continuing cellular turnover. Concentrations may increase with membrane injury, whether reversible or irreversible (cell death). Concentrations may also rise with increased rates of synthesis (transcription and translation), decreased clearance, or, although not yet described in veterinary medicine, the presence of enzyme-autoantibody complexes (macroenzymes) which extend enzyme half-life.[1,5,6] Lactate dehydrogenase (LDH), commonly used with other species, is an oxidoreductase that catalyzes conversion of lactate to pyruvate. LDH resides in the cytoplasm of all cells and is of little value as a marker of canine or feline hepatic disease.

Serum liver enzyme activities aid in the identification, differentiation, and monitoring of liver disease but do not measure hepatic function. They are broadly classified as either "hepatocellular leakage enzymes" (ALT, AST) or "cholestatic enzymes" (ALP, GGT) based on their subcellular location and response to hepatocellular injury (Figure 65-1).[2,4,7] ALT and AST reside predominantly in cytosol, although a mitochondrial AST isoenzyme exists in humans and dogs. These enzymes are the first to leak into the peri-sinusoidal space and enter the systemic circulation secondary to hepatic necroinflammation that damages plasma membranes. ALP and GGT are associated with the hepatocyte canalicular membranes and, in the case of GGT, cholangiocytes. These enzymes are released as a result of bile acid membrane solubilization or cleavage of the membrane binding domain (GGT) during cholestatic injury.[2,4,7]

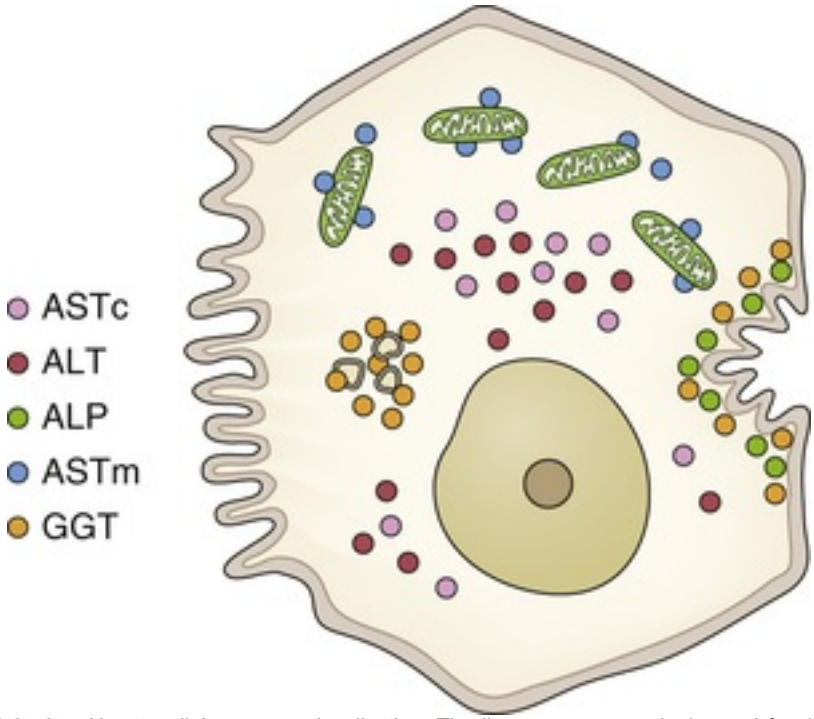


FIGURE 65-1 Hepatocellular enzyme localization. The liver enzymes routinely used for diagnosis are located in the cytosol, canalicular membrane (right), microsomes (SER; 3 beige rounded triangles at center-left), and the mitochondria (4 green ovals; top). Alanine aminotransferase (ALT) and cytoplasmic isoenzyme of aspartate aminotransferase (ASTc) are located in the cytosol. These leakage enzymes are released with plasma membrane damage. The canine mitochondrial AST (ASTm) is associated with the mitochondria. Both isoenzymes of alkaline phosphatase (ALP) are located at the canalicular membrane. Gamma-glutamyl transferase (GGT) is found at the canalicular membrane and in the microsome (SER), where it can respond to enzymatic induction. The latter 2 enzymes are released in cholestasis by bile acid membrane dissolution or cleavage of the plasma membrane binding domain. (Copyright Elsevier: Pincus MR, Tierno PM, Fenelus M, et al: Evaluation of liver function. In McPherson RA, Pincus MR, editors: *Henry's clinical diagnosis and management by laboratory methods*, ed 22, Philadelphia, 2011, Saunders, pp 296-311.)

Liver enzyme increases are commonly identified on biochemical screening tests, but do not definitively identify significant underlying liver disease (Table 65-1).[8] None of the aforementioned enzymes is entirely liver specific and isoenzymes exist. Further, the hepatic enzyme induction phenomenon may cause marked increases without histologic evidence of liver lesions.[3,8-13] Isoenzymes, or isozymes, have different amino acid sequences, varying subunit combinations (LDH), unique post-translational modifications (ALP), or protein structure (AST) but catalyze the same reactions. Enzymes modified by serum proteases to slightly different forms are called isoforms.[1] For example: the intestinal ALP isoenzyme has a different protein structure as compared with the tissue-nonspecific renal, liver, and bone isoenzymes, which have identical amino acid sequences but different carbohydrate composition.[1,10]

TABLE 65-1

Liver Enzyme Activities Not Associated with Primary Hepatic Disease

CONDITION	CAUSES OF INCREASED ENZYME ACTIVITY
Cardiovascular	Congestion, hypotension, ischemia
Endocrinopathies	Adrenal disease (cortisol and sex steroid abnormalities), diabetes mellitus, hyperthyroidism (cats), hypothyroidism (dogs)
Gastrointestinal disease	Diarrhea, constipation/obstipation, gastric dilatation volvulus, pancreatitis
Infectious disease	Abscessation, rickettsial disease, pyelonephritis, pyometra/prostatitis, septicemia, viral disease (parvovirus, coronavirus, feline respiratory disease)

Miscellaneous	Strenuous exercise, trauma, myopathies, severe anemia, malignant hyperthermia
Neoplasia	Bone, mammary, metastatic
Osseous	Growth, metabolic bone disease, osteomyelitis

Abnormal hepatic enzyme activities must be interpreted in the context of patient signalment, physical examination findings, and an owner history that includes previous and current medications, environmental exposure to hepatotoxins or infectious organisms, and comorbidities. Sequential monitoring of enzymes is needed to map the course of disease with particular attention to duration of elevation (acute, chronic), stability (increasing, decreasing, waxing and waning) and pattern (cholestatic, necroinflammatory, induced). For example, increased activities after an acute hepatic injury due to hepatotoxin exposure may rapidly return to reference limits (see ch. 285 and 286). However, activities that progressively increase or wax and wane may reflect chronic and/or progressive disease (necroinflammatory disease) (see ch. 280, 282, 283, 284, 287, and 288).[4,7,14-23]

The Leakage Enzymes: The Aminotransferases, ALT and AST

Overview

ALT and AST catalyze the transfer of the alpha-amino group of alanine or aspartic acid to alpha-ketoglutarate, resulting in the formation of glutamic acid and pyruvate or oxaloacetic acid, respectively.[3] These enzymes are integral components of the glucose alanine cycle. ALT and AST require pyridoxal 5′ phosphate (P_5P), the active metabolite of vitamin B_6, as a cofactor. Alanine reacts with P_5P to yield pyruvate plus pyridoxine. Pyridoxine reacts with alpha-ketoglutarate resulting in glutamate and regenerated P_5P. Decreased transaminase activities are associated with low systemic vitamin B_6 concentrations due to disease or drug administration (cephalosporin, cyclosporine, and isoniazid).[2,3] ALT and AST are cleared by adsorptive endocytosis in sinusoidal hepatocytes; therefore, clearance rates may be altered in severe liver disease and in cases of sinusoidal hypoperfusion (ischemia, portosystemic vascular anomalies).[4,24]

ALT and AST rise within 24 to 48 hours of acute hepatocellular injury, most markedly with necrosis. While there is a direct correlation between the degree of aminotransferase increase and the number of hepatocytes injured (mild, <5-fold high normal reference range value; moderate, 5- to 10-fold; severe, >10-fold), such values are not prognostic. Serial monitoring of enzyme activities and of serum albumin, cholesterol, coagulation factors, and bilirubin concentrations are needed.[3,4,9,15] Generally, following acute hepatic insult, transaminase activities decrease within 2 to 3 days and normalize in 2 to 3 weeks. Waxing and waning transaminase values are seen with chronic inflammatory conditions (see ch. 282 and 283).[4,18,19] Reducing values in chronic liver disease may be due to improvement in the disease process or diminished hepatocyte numbers.

Alanine Aminotransferase

ALT, while regarded as "liver-specific" in the cat and dog, is also present in lesser intracellular quantities in heart, kidney, and skeletal muscle. The half-life of ALT in dogs is 59 hours and is less than 24 hours in cats.[2,7] Mild to moderate increases may be seen with enzyme induction (anticonvulsants, glucocorticoids [dogs]), vacuolar hepatopathy, portosystemic vascular anomalies, and passive hepatic congestion (see ch. 284). Increases in canine serum ALT activity have the highest sensitivity (80% to 100%) for hepatic necrosis and hepatic failure but are less sensitive (50% to 80%) in cirrhosis, vacuolar hepatopathy, passive hepatic congestion, or portosystemic vascular anomalies.[4] In cats, ALT is sensitive for extrahepatic bile duct occlusion and cholangitis/cholangiohepatitis (80% to 100%).[4] ALT is non-specific for liver disease in both species (<25%). The largest ALT increases are seen in necroinflammatory diseases.[4,6,9,14,15] Acute necroinflammatory hepatic injury may be caused by drug-induced liver injury (Box 65-1; see also ch. 286), hepatic toxin ingestion (heavy metals, amanita toxin, cycads, xylitol), and infectious/inflammatory disease (leptospirosis, toxoplasmosis, copper associated hepatopathy, autoimmune disease; see also ch. 282, 283, and 285).[4,6,14,15,25,26] Not all cases of hepatic necrosis will result in transaminase elevation. Microcystin and aflatoxin B1 inhibit hepatic biosynthesis of ALT and AST, and therefore cannot be used as biomarkers of liver disease following intoxication.[15,27]

Box 65-1

Commonly Implicated Hepatotoxic Drugs in Cats and Dogs (see also ch. 286)

Acetaminophen
Amiodarone
Anabolic steroids
Carprofen
Cyclosporine
Diazepam
Diethylcarbamazine/oxibendazole
Fluoroquinolones
Griseofulvin
Halothane
Itraconazole
Ketoconazole
Mebendazole
Methimazole
Methoxyflurane
Mibolerone
Pennyroyal oil
Phenobarbital
Phenytoin
Primidone
Sulfonamides
Tetracyclines

Aspartate Aminotransferase

The greatest concentrations of AST are found in skeletal muscle, cardiac myocytes, and the kidneys. AST is also present in brain, small intestine, spleen, liver, and erythrocytes. A muscular isoenzyme may be considered as the source of increases in AST activity if there are concurrent increases in creatine kinase (CK) concentrations; however, in chronic myopathy the shorter half-life of CK may not allow differentiation.[2] AST is located in 2 canine hepatocyte subcellular sites: the cytosol (80%) and mitochondria (20%). Cytosolic AST is most important in veterinary medicine.[28,29] The half-life of AST in the dog is thought to be approximately 22 hours, but significantly longer periods have been reported.[2,4] In the cat, AST's half-life is 77 minutes. As a soluble cytosolic liver enzyme, serum AST activities mirror ALT activities. However, AST is the smaller moiety that diffuses into the sinusoidal circulation more rapidly following plasma membrane disruption. It may also become quiescent earlier than ALT due to its shorter half-life.[29] In the cat, AST is a more sensitive indicator of hepatocellular damage, particularly in hepatic necrosis, cholangiohepatitis, myeloproliferative diseases, infiltrative lymphomas, and chronic bile duct obstruction.[4,7,9]

The Cholestatic Enzymes: Alkaline Phosphatase and Gamma-Glutamyl Transferase or Transpeptidase

Alkaline Phosphatase

ALP is a membrane-bound glycoprotein that hydrolyzes phosphate esters.[1] In dogs and cats, ALP resides within cells of the renal cortices, placenta, intestine, bone, and liver.[2] Several ALP isoenzymes have been identified, usually from distinct organs or tissues.[10,13,30] In the dog, glucocorticoid-induced ALP (G-ALP) is believed to be a product of the intestinal ALP gene expressed in hepatocytes. Transcription of G-ALP is delayed approximately 10 days after beginning exogenous steroid administration. It may continue to rise with ongoing treatment.[10] The dog is unique in the expression of 2 hepatic canalicular membrane ALP isoenzymes.[4] The liver isoenzyme (L-ALP) is also inducible by glucocorticoids and is the first isoenzyme to be serologically detected.[10] Although transcription of L-ALP plateaus after approximately 10 days of prednisone

treatment, the enzyme continues to be translated, making differentiation of the 2 isoenzymes irrelevant.[10,28] The ALP induction phenomenon is not limited to glucocorticoids. G-ALP activity is also associated with inflammation and chronic disease (possibly secondary to increases in endogenous glucocorticoid secretion) and drugs: anticonvulsants (phenobarbital, phenytoin, primidone).[11,31,32] Therefore, ALP activities should not be used for confirming or suspecting a diagnosis of canine hyperadrenocorticism.

L-ALP and G-ALP isoenzymes have half-lives of approximately 70 hours.[2,4] Canine placental, renal, and intestinal ALP half-lives are less than 6 minutes. Feline intestinal ALP half-life is less than 2 minutes. In the cat, the placental isoenzyme can be detected in late term pregnancy.[4] The half-life of feline L-ALP is brief (6 hours). L-ALP, G-ALP and bone isoenzyme (B-ALP) are the 3 primary isozymes in the dog. Cats do not express G-ALP. B-ALP is present in growing dogs and cats up to 7 months of age. It is also seen in renal secondary hyperparathyroidism, bone tumors (negative prognostic indicator for osteosarcoma), osteomyelitis, and feline hyperthyroidism, partly due to increased parathyroid-hormone–induced bone mobilization.[7,12,33,34]

Increased serum ALP activity is one of the most commonly reported biochemical abnormalities in dogs.[8] ALP has a high sensitivity but low specificity for hepatobiliary disease. If a concurrent GGT elevation is identified, specificity for liver disease is significantly improved in both dogs and cats.[35,36] Canine serum ALP activity may increase with necroinflammatory, neoplastic, or cholestatic injury. The degree of ALP activity has not proven to be helpful in distinguishing between intra- and extrahepatic causes of cholestasis. Enzyme synthesis may be induced (secondary to inflammatory mediators or endogenous/exogenous glucocorticoids) or released from the hepatic canaliculi via bile acid solubilization. Vacuolar hepatopathy associated with mild to severely increased ALP activity and cytosolic glycogen accumulation was long considered a benign manifestation of steroidogenic hormones (cortisol and sex steroids) and a multitude of non-adrenal diseases. However, there is evidence that excess glycogen accumulation can become pathologic.[4,37] Many recent publications have highlighted a vacuolar hepatopathy breed-related disorder in Scottish Terriers. Increases may also be associated with development of hepatocellular carcinoma in some affected dogs.[9,38-41]

ALP elevation is less specific in cats but still clinically relevant, particularly in feline hepatic lipidosis wherein ALP elevations tend to predominate except in cases of underlying cholangitis/cholangiohepatitis.[4,7] Hepatocellular swelling, altered osmotic influx, and cholestasis due to cellular swelling likely cause the marked ALP increases associated with in feline hepatic lipidosis.[4,7,42]

Gamma-Glutamyltransferase or Transpeptidase

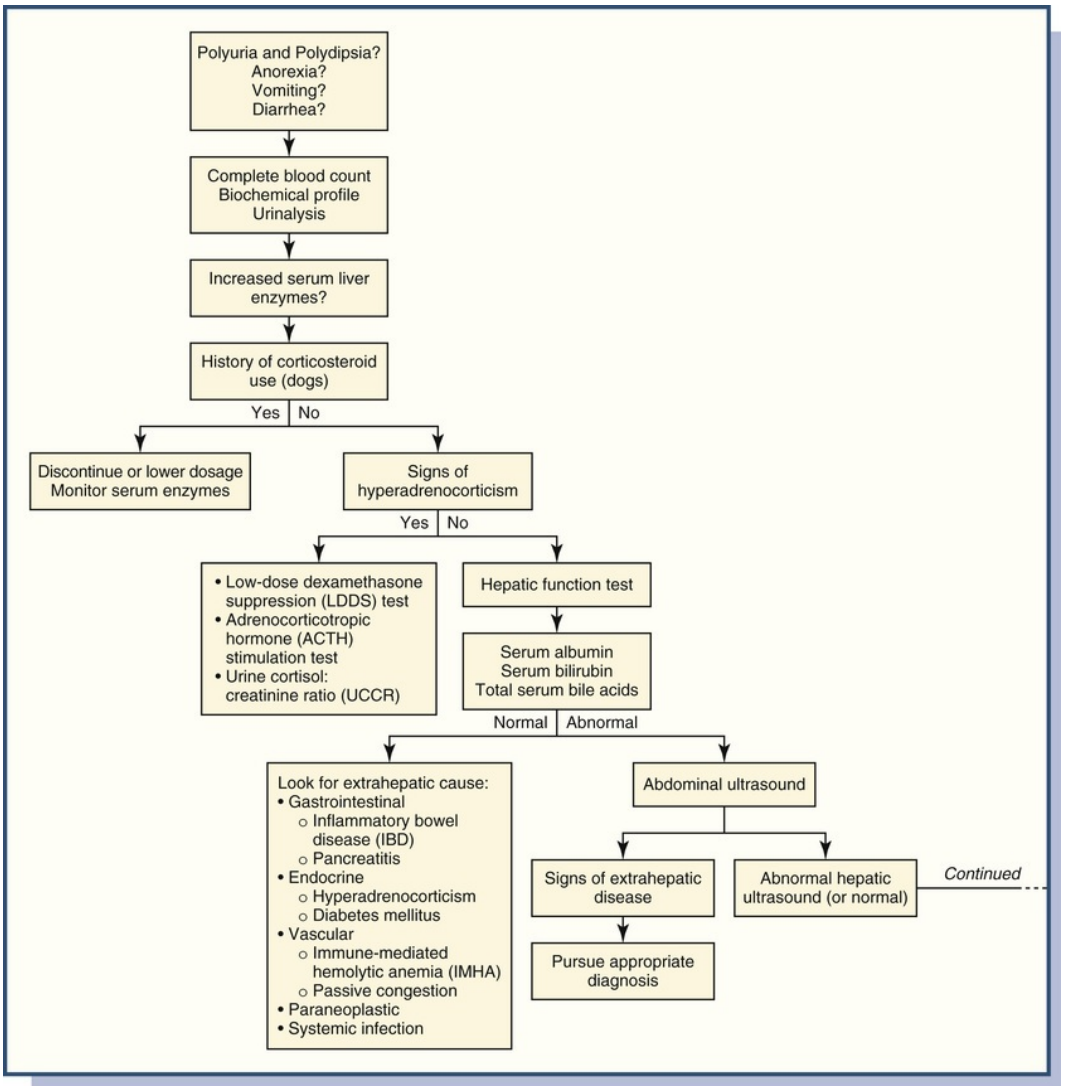
GGT catalyzes transfer of the gamma-glutamyl group from glutathione (GSH) to an acceptor, forming glutamate. This enzyme regulates amino acid transport across cell membranes and is critical for the cellular redox pathway. GGT is found in cell membranes of kidney, pancreas, biliary epithelium, hepatocytes (zone 1, periportal), intestine, spleen, heart, lungs, skeletal muscle and erythrocytes.[2,3] The half-life of GGT in dogs and cats remains undetermined.

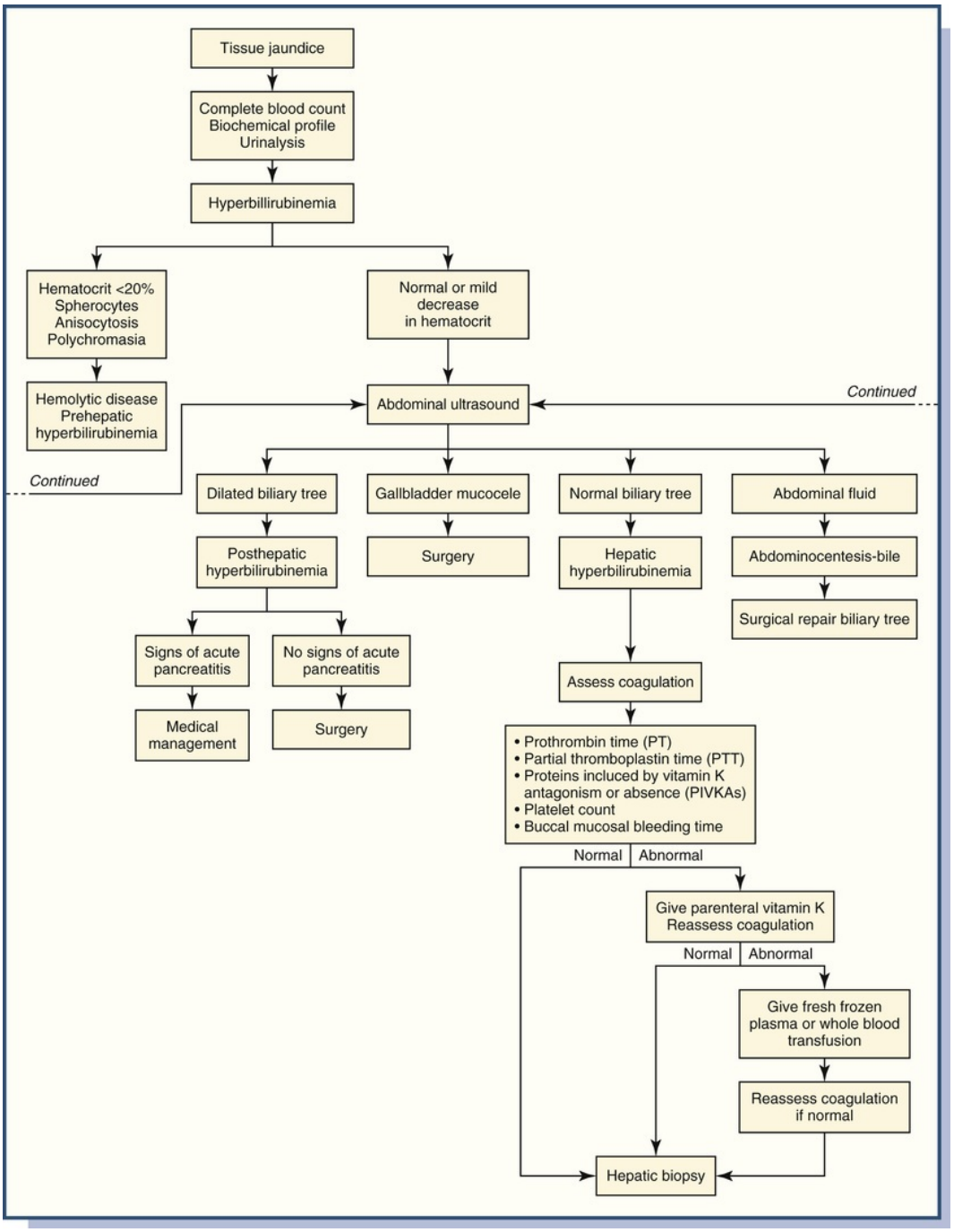
In dogs, GGT has its largest tissue concentration in the proximal renal tubules and pancreas. However, its epithelial location in these tissues results in loss into urine or pancreatic lumen, rather than into the circulation.[2,4] Microsomal enzyme induction occurs in dogs treated with glucocorticoids (up to 10-fold); this has not been proven in the cat. Mild increases may be seen with anticonvulsants (phenytoin, primidone) which increase further if hepatotoxicosis develops. Hepatobiliary and pancreatic carcinogenesis moderately increases GGT activity. Canine neonates exhibit markedly increased GGT activities during the first 1-3 days of life secondary to colostrum intake. This is not observed in kittens.[2,4]

GGT also increases expression in conditions of oxidative stress. GGT is a cholestatic liver enzyme and its activity increases when cleaved from its plasma membrane anchor by bile acid solubilization. GGT is not a sensitive marker of liver disease in the dog (40%) but it has a higher specificity than ALP.[4,35] In cats, sensitivity (55%) exceeds specificity of ALP for detecting inflammatory diseases and GGT activity is most markedly increased in necroinflammatory diseases of the portal triad, biliary tree, and pancreas.[4,36,43,44] GGT is minimally elevated in canine and feline hepatic necrosis affecting zones 2 and 3. Extrahepatic bile duct obstruction causes moderate to severe increases, typically greater in dogs than cats. Reportedly, cats with underlying necroinflammatory disease and bile duct obstruction or cholestasis may develop a higher-fold increase in GGT than ALP.[36,45-48]

Summary

Liver enzyme abnormalities are commonly encountered in practice. Interpretation of liver enzyme abnormalities requires a complementary approach including bilirubin, paired serum bile acids, arterial ammonia, and coagulation factors to determine the next step (Figure 65-2).[9,49-51] Imaging modalities may eliminate nonhepatic causes of liver enzyme activity (thoracic and abdominal radiographs) or increase suspicion for a specific diagnosis (abdominal ultrasound) prior to liver biopsy.[52,53]




Tissue jaundice
Complete blood count
Biochemical profile
Urinalysis
Hyperbillirubinemia
Hematocrit <20%
Spherocytes
Anisocytosis
Polychromasia
Normal or mild decrease in hematocrit
Hemolytic disease
Prehepatic hyperbilirubinemia
Continued
Abdominal ultrasound
Continued
Continued
Dilated biliary tree
Gallbladder mucocele
Normal biliary tree
Abdominal fluid
Posthepatic hyperbilirubinemia
Surgery
Hepatic hyperbilirubinemia
Abdominocentesis-bile
Surgical repair biliary tree
Signs of acute pancreatitis
No signs of acute pancreatitis
Assess coagulation
Medical management
Surgery
• Prothrombin time (PT)
• Partial thromboplastin time (PTT)
• Proteins incluced by vitamin K antagonism or absence (PIVKAs)
• Platelet count
• Buccal mucosal bleeding time
Normal
Abnormal
Give parenteral vitamin K
Reassess coagulation
Normal
Abnormal
Give fresh frozen plasma or whole blood transfusion
Reassess coagulation if normal
Hepatic biopsy

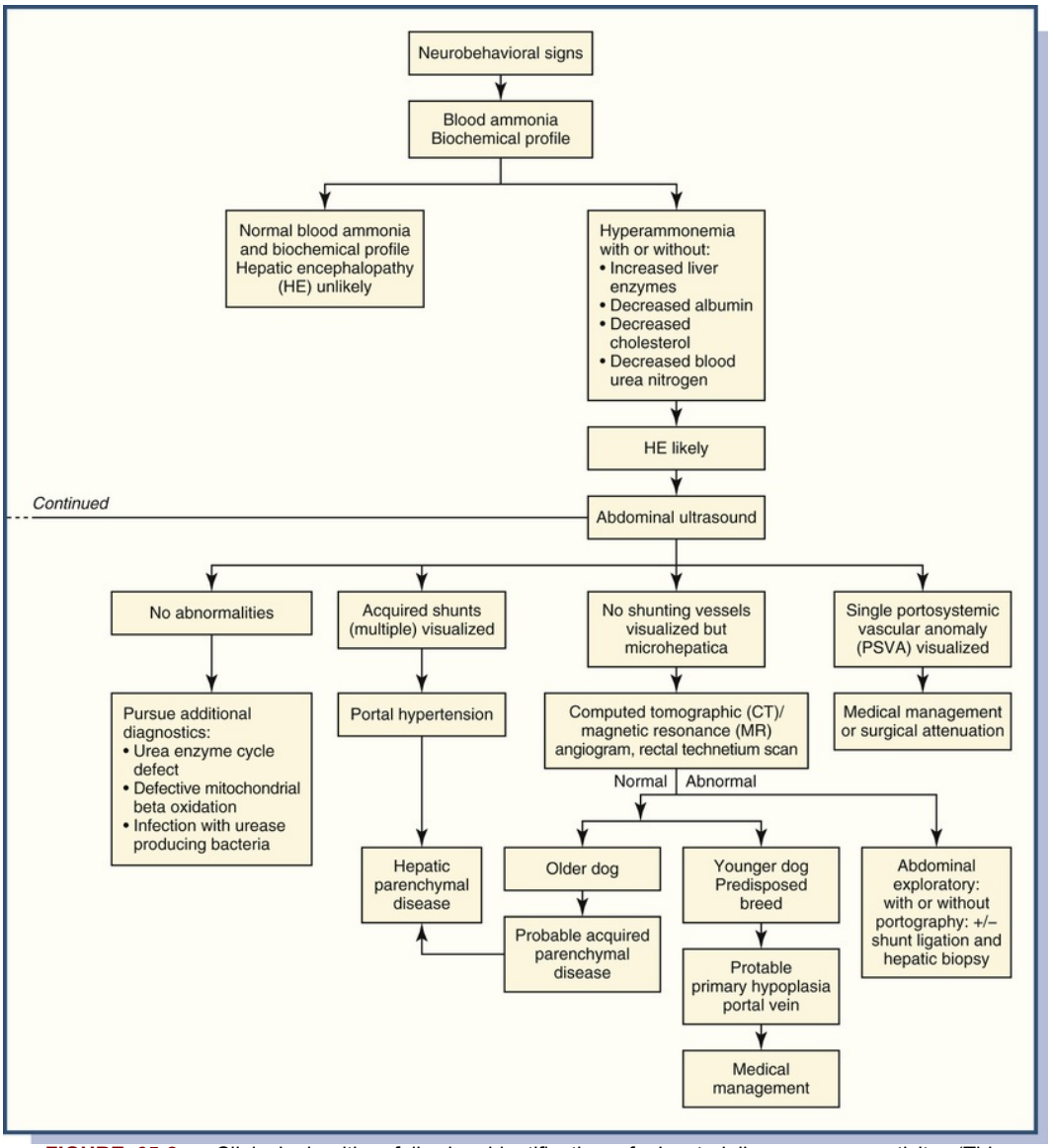


FIGURE 65-2 Clinical algorithm following identification of elevated liver enzyme activity. (This algorithm has been reproduced with permission from Webster CRL: History, clinical signs, and physical findings in hepatobiliary disease. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine: diseases of the dog and the cat,* ed 7, St Louis, 2010, Elsevier, pp 1612-1625.)

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CHAPTER 66

Creatine Kinase

Susan M. Taylor

Normal Activity and Tissue Distribution

Creatine kinase (CK) is an intracellular enzyme that catalyzes the reversible exchange of high energy phosphate bonds between phosphocreatine and ADP, generating ATP needed for muscle contraction. CK exists as three main dimeric isoenzymes (CK-MM, CK-MB, and CK-BB), a mitochondrial isoform (CK-MT) and two macroenzymes of uncertain significance. CK-MM accounts for 100% of CK activity in muscle, is the most common isoform found in serum, and is considered an important marker for muscle disease. Almost all CK activity in nervous system tissues is CK-BB and this isoenzyme may be increased in the serum of dogs and cats with neurologic disease. Cerebrospinal fluid CK-BB activity, for example, negatively correlates with prognosis for walking in dogs paralyzed due to intervertebral disk disease. Increased cerebrospinal fluid CK-BB concentrations may be associated with higher mortality in dogs with intracranial disease. CK-BB is also found in the small intestine and serum concentrations may be increased with intestinal necrosis or infarction. In people, the isoenzyme CK-MB predominates in cardiac muscle and is a reliable marker for myocardial infarction. However, in canine and feline myocardial tissue, most (97%) of the CK activity is CK-MM, rather than CK-MB. Total serum CK is often increased in dogs with ischemic, inflammatory and traumatic myocardial diseases and in dogs and cats with poor perfusion of skeletal muscles due to cardiac failure. The utility of measuring the activity of tissue specific isoforms of CK continues to be investigated, but total CK appears to be the most useful diagnostic test for dogs and cats.

Serum CK concentrations are usually slightly higher than plasma concentrations due to CK release from platelets during blood clotting. Serum CK activity is stable for 7 days at +4º C and for 1 month at −20º C, after which CK activity decreases. Hemolysis and hyperbilirubinemia increase measured CK but lipemia has no effect. The activity of CK in blood peaks 2 to 4 hours after muscle injury, and returns to reference concentrations within 24 to 48 hours if CK release has stopped. Puppies and kittens, less than 8 weeks of age, usually have higher CK concentrations than adult animals (1.5 to 2×). Greyhounds and other muscular breeds have been reported to have slightly higher (1.5 to 2×) CK activity than other dog breeds. Serum CK concentrations are not affected by site of sampling, but incorrect venipuncture technique can result in higher activity (2-3× normal) if underlying muscle has been penetrated.

Effect of Exercise on Serum CK Concentrations

An important factor in interpreting CK concentration results from normal individuals is their level of recent physical activity. Measured CK increases after physical activity, especially in untrained or poorly conditioned dogs. The increases seen with moderate activity for 60 minutes or strenuous activity for 10 minutes are generally not clinically significant (less than 5× increase), with CK activity peaking 2 to 4 hours after exercise and returning to baseline within 8 hours. More dramatic increases (5-15×) occur and persist for 24 to 48 hours in some dogs strenuously exercising for prolonged periods, such as sled dogs running in endurance races longer than 1000 km. These increases in CK activity suggest that mild muscle injury occurs whenever energy consumption within the muscle exceeds energy supply. Exercise past exhaustion can occasionally be a trigger for life-threatening exertional rhabdomyolysis, where intracellular calcium rises uncontrollably within myofibers, and release of calcium-dependent proteases results in myonecrosis. Individuals with rhabdomyolysis experience painful muscles (myalgia), weakness, marked elevations of CK (often >1000×) and myoglobinuria.

Disorders Causing Increased Serum CK Concentrations (Figure 66-1)

Increases in CK are considered to be diagnostically useful as a marker for myofiber damage (see ch. 354).

However, increases in CK also occur in association with many disorders that are not specifically muscle-related. Mild increases in CK (<5× reference range) occur commonly after physical restraint or moderate exercise. Prolonged recumbency, surgery, metabolic diseases causing acidosis and/or dehydration, pancreatitis, spinal cord or brain injury, dirofilariasis, endocarditis and myocarditis may each contribute to mild or moderate increases (usually <10×). Anorexia in cats has been associated with 10× to 100× increases in CK, presumably due to the breakdown of skeletal muscle for amino acids and energy. Muscle trauma (following injections, bite wounds or blunt trauma), severe dehydration, shock, disseminated intravascular coagulation, aortic thromboembolism, tissue hypoperfusion or infarction due to sepsis have been associated with moderate to severe increases in CK.

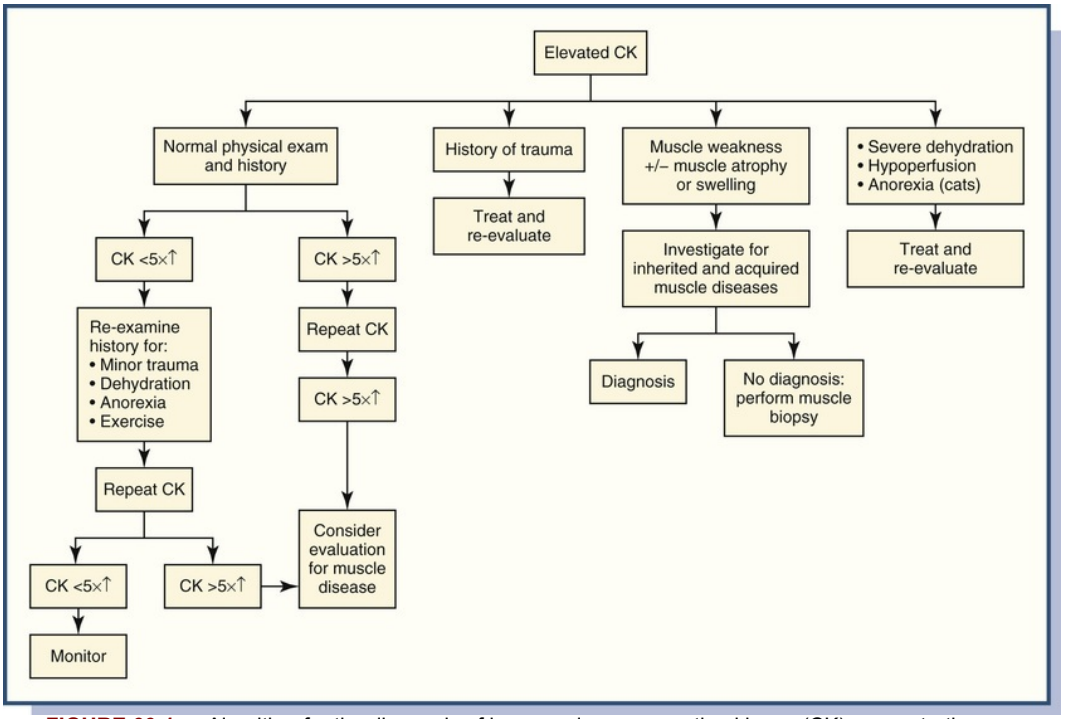

FIGURE 66-1 Algorithm for the diagnosis of increased serum creatine kinase (CK) concentrations.

In a well-hydrated, hemodynamically stable patient with no history of trauma, persistently increased serum CK concentrations should lead to a suspicion of muscle disease. The most marked increases in CK generally occur in dogs and cats with necrotizing, inflammatory and dystrophic myopathies (see ch. 354). Muscle necrosis (rhabdomyolysis) can be seen as a consequence of excessive exercise, hyperthermia, sepsis, drug reaction, crush injury, ischemia, or snake envenomation. Immune-mediated polymyositis and infectious myositides (neosporosis, toxoplasmosis, sarcocystosis, hepatozoonosis, babesiosis, etc.) typically cause moderate increases in CK, but occasionally muscle inflammation progresses to myonecrosis, resulting in marked increases. Dystrophin-deficient muscular dystrophies consistently have dramatic increases in CK (usually >100×) due to a loss of myofiber stability, leading to myonecrosis. Most other clinically severe congenital myopathies, including centronuclear/myotubular myopathies, central core myopathies, congenital nemaline rod myopathies, mitochondrial myopathies, and lipid storage myopathies have little (less than 5×) or no increase in CK. This distinction should allow clinicians to use serum CK activity in determining the likelihood of muscular dystrophy in symptomatic young dogs or cats. Metabolic testing and muscle biopsy are recommended in animals with muscle weakness even if CK results are normal or only mildly increased (see ch. 116). These tests should be considered in all animals with persistent moderate-to-severe increases in CK concentrations when a precipitating cause is not obvious.

CHAPTER 67

Sodium, Chloride

Dan Rosenberg

Overview

Sodium (Na) and chloride (Cl) are the primary cation and anion, respectively, in extracellular fluid (ECF). Both are crucial for maintaining osmolality and tonicity. Since their concentrations usually "parallel," clinicians focus more on Na concentration ([Na]) than on Cl concentration ([Cl]) when assessing water balance (see ch. 73). However, Cl and Na content are independently regulated, plus Cl is involved in acid-base regulation (see ch. 128). Thus, distinct differential diagnoses are needed, at times, for changes in [Na] versus changes in [Cl].

Hypernatremia (Figure 67-1)

Definitions

Body Sodium versus Water Content

The serum [Na] refers to the amount of Na relative to the amount of water in the ECF. Changes in serum [Na] often reflect changes in total body water stores rather than changes in total body Na content.[1,2] True hypernatremia always results in a hyperosmolar/hypertonic condition, indicating a deficit of water.[1,3] Not only mild measured hypernatremia but even subtle increases in serum [Na] within a reference interval initiate correction through thirst to increase body water and vasopressin (antidiuretic hormone [ADH]) secretion to decrease water loss.[3,4]

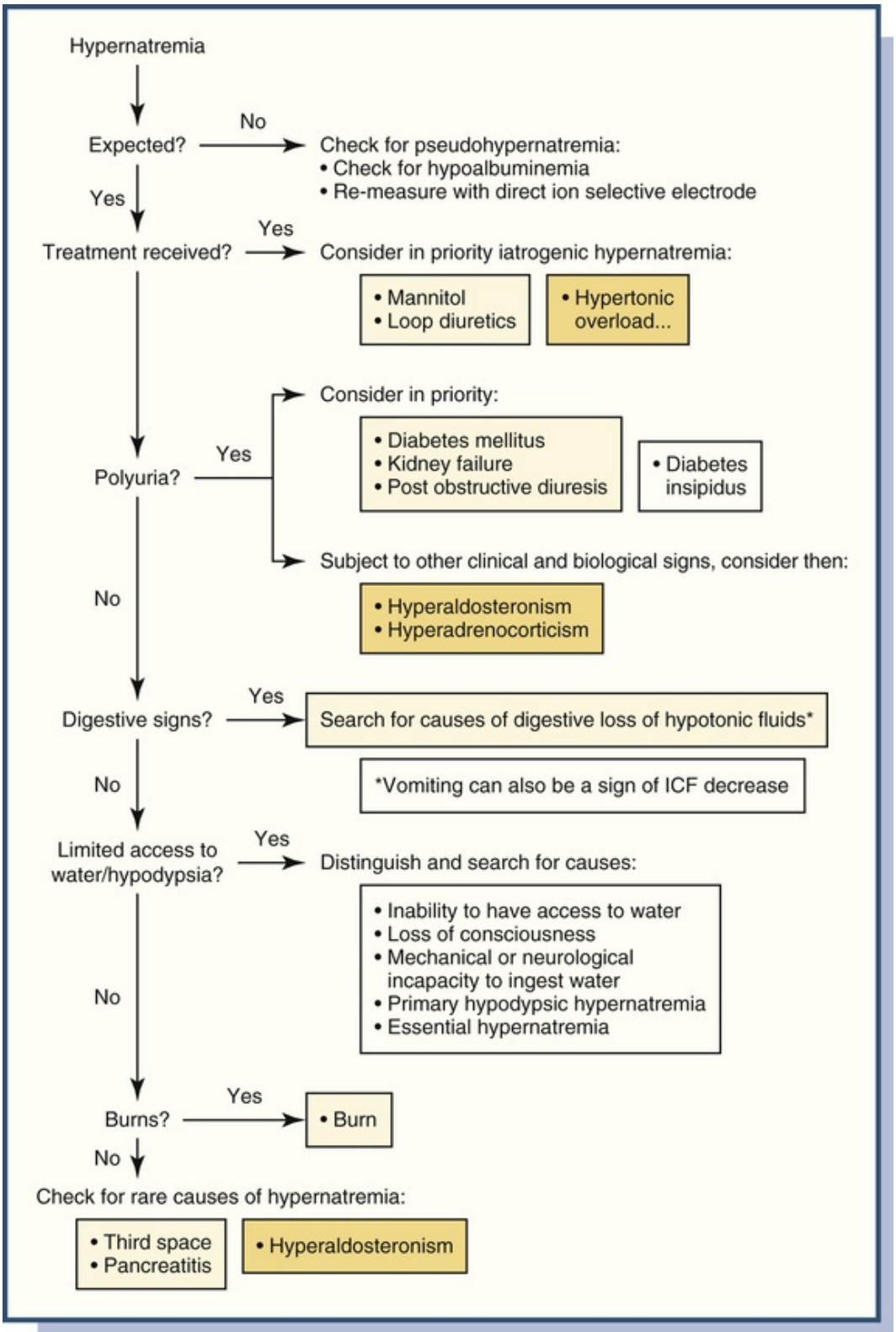

FIGURE 67-1 Diagnosis approach to hypernatremia in dogs and cats. For each diagnosis orientation, check for its clinical consistency by extracellular fluid assessment: unchanged or mildly decreased for causes of pure water deficit (non-shaded boxes), mildly to markedly decreased for causes of hypotonic losses (lightly-shaded boxes), increased for sodium overload causes (darkly-shaded boxes).

Osmolality and Osmolarity *(see ch. 296)*

Osmolality is a measure of solute concentration (osmotically active particles) in a liquid. Osmolality in healthy dogs ranges from about 290 to 310 and in cats from 300 to 330 mOsm/kg.[5-10] Although not absolutely equivalent, osmolarity (in mOsm/L) is used clinically because of availability and cost. Since all cell membranes display some degree of permeability to water (with the quasi-exception of some cells comprising the thick-ascending loop of Henle), the osmolality of the intracellular fluid (ICF) space and that of the ECF are similar.[11] Some solutes (e.g., urea) move freely across cell membranes. These so-called permeant solutes do not induce water movement or affect tonicity of either compartment. Compartmental tonicity is dependent on non-permeant solutes. ECF or plasma osmolality in dogs and cats can be estimated using the formula: plasma osmolarity (mOsm/L) = 2 [Na] + [BUN] + [Glu] when all concentrations are expressed in mmol/L or 2 × [Na] + [BUN in mg/dL]/2.8 + [Glu in mg/dL]/18.[8,9] Plasma tonicity is usually estimated using the equation: 2[Na] + [Glu] (in mmol/L). When insulin is absent or inactive, glucose is non-permeant while it is negligeable (averaging 5.6 mmol/L) and permeant in nondiabetic states. Thus it can be omitted except in pets with diabetes mellitus.[12]

Assays

Serum [Na] is reliably assayed in most veterinary situations.[13] Hyperlipidemia and hyperproteinemia can decrease measured [Na] *in vitro* when indirect methods requiring a dilution step are used and the opposite can cause [Na] to be incorrectly measured as increased.[14] Syndromes of pseudohypernatremia and pseudonormonatremia (sodium underestimation in a hypernatremic patient) should be given consideration when incidental hypernatremia is identified or when hypernatremia is suspected, though not confirmed, in a hyperproteinemic or hyperlipidemic dog or cat.[15-17] Na measurement using a direct selective electrode method is required if such concerns are present (see Figure 67-1). True hypernatremia can result from a deficit of pure water, a loss of hypotonic fluids, or an excessive Na gain (E-Box 67-1).

E-Box 67-1

Causes of Hypernatremia

Pseudohypernatremia

In theory, hypoproteinemia

Pure Water Deficit

Total body water ↓—Unchanged total body Na (ICF volume depletion—minimal change of ECF volume)

Isolated disturbance of water intake
- Inability to have access to water
- Loss of consciousness
- Inability to ingest water
- Primary hypodypsic hypernatremia and essential hypernatremia

Uncompensated loss of free water
- Diabetes insipidus with water restriction
- Heatstroke
- Fever with water consumption decrease

Uncompensated Hypotonic Loss

Total body water ↓—Total body sodium ↓ (signs of ECF volume depletion expected)

Renal loss
- Solute diuresis
  - Diabetes mellitus
  - Mannitol administration
  - Postobstructive diuresis
- Kidney dysfunction (except diabetes insipidus)
  - Chronic kidney disease
  - Polyuric intrinsic acute renal failure
  - Loop diuretics

Digestive loss
Vomiting
Diarrhea
Other loss
Peritonitis
Pancreatitis
Burns

Sodium Overload

Unchanged total body water—Total body sodium ↑ (signs of ICF volume depletion expected)

Excessive sodium intake
Salt poisoning
Iatrogenic
IV sodium-containing fluids (hypertonic saline, sodium bicarbonate)
Sodium-phosphate–containing enemas
Endocrine
Hyperaldosteronism and aldosterone precursor-secreting tumors
Hyperadrenocorticism

Causes

Isovolemic Hypernatremia

Simple water deficiency is an uncommon explanation for hypernatremia, usually caused by primary hypodipsia or an increased set point for secretion of ADH in association with diencephalic malformation, trauma, or neoplasia.[3,18-29] Decreases in intake can also be caused by lack of water for any reason. Pathologic conditions associated with free water loss (fever, diabetes insipidus) do not cause increased ECF tonicity if compensated by water intake. Failure to compensate with appropriate water intake would cause hypernatremia.[30,31] Compensation for pure water deficits is seen in both the ECF and ICF. Since the ICF volume is twice that of the ECF, most compensatory mechanisms initially involve the ICF.[3] Oncotic pressure also limits water movement from the ECF. Thus, pure water deficits are designated as causes of "isovolemic hypernatremia" with minimal, if any, signs of extracellular dehydration. Clinical signs associated with ICF volume depletion begin with the nervous system and are influenced by how quickly the ICF dehydration developed. Acute hypernatremia results in shrinkage of nervous system cells causing disorientation, ataxia, seizures, vomiting, anorexia or coma. Most animals with chronic hypernatremia are asymptomatic unless the [Na] is markedly increased and associated with increases in tonicity.[3]

Hypernatremia Secondary to Hypotonic Fluid Loss

Uncompensated losses of hypotonic fluids are the main causes of hypernatremia.[3] Unlike pure water loss, hypotonic fluid loss causes deficits in whole body Na content.[1] Renal hypotonic fluid losses (kidney disease, diabetes mellitus and diuretics) and digestive fluid losses (diarrhea and vomiting) account for most scenarios but hypotonic losses associated with third-space fluid accumulation (pancreatitis, burns) may be considered (see E-Box 67-1).[3,32-38] The impact of hypotonic losses on ECF volume depends on their tonicity. Loss of fluids with tonicity similar to that of the ECF compartment only affects the ECF volume as they do not induce osmotic changes. Hypernatremia develops if there is lack of compensation for the fluid loss.[3] Evidence of a depleted ECF volume can include loss of skin elasticity, delayed capillary refill time, weak pulse, and tachycardia.

Uncommon Causes of Hypernatremia

Na overload is a rare cause of hypernatremia in dogs and cats, salt poisoning having been described occasionally.[39-41] Over-administration of Na-containing fluids can generate hypernatremia, especially in cases of oliguria or marginal renal function (see ch. 129).[42-44] In rare cases, hyperaldosteronism, aldosterone precursor-secreting adrenocortical tumors and hyperadrenocorticism can be associated with mild hypernatremia (see ch. 306-308).[45-49] As these endocrinopathies often have obvious clinical manifestations plus expected clinicopathological abnormalities (e.g., hypokalemia for hyperaldosteronism and aldosterone

precursor-secreting tumors), the finding of this mild biochemical abnormality is rarely decisive in diagnosis.

Hyponatremia (Figure 67-2)

Physiologic Associations

Hyponatremia often, but not always, results in a hypotonic state.[3] Hypotonic hyponatremia, also termed dilutional hyponatremia, is a reflection of water retention (see E-Box 67-2).[50] Normotonic hyponatremia (pseudohyponatremia) refers to low Na concentrations measured in hyperproteinemic or hyperlipidemic patients who do not have hyponatremia (see previous discussion). Hypertonic hyponatremia refers to water translocation when osmoles other than sodium (glucose in diabetics) accumulate in one compartment because they do not cross cellular membranes, drawing water from the other space.[51-56] Incoming water dilutes concentration of all solutes in the ECF, including Na.[2] This hyponatremia is enhanced in ketoacidosis due to additional renal and gastrointestinal losses.

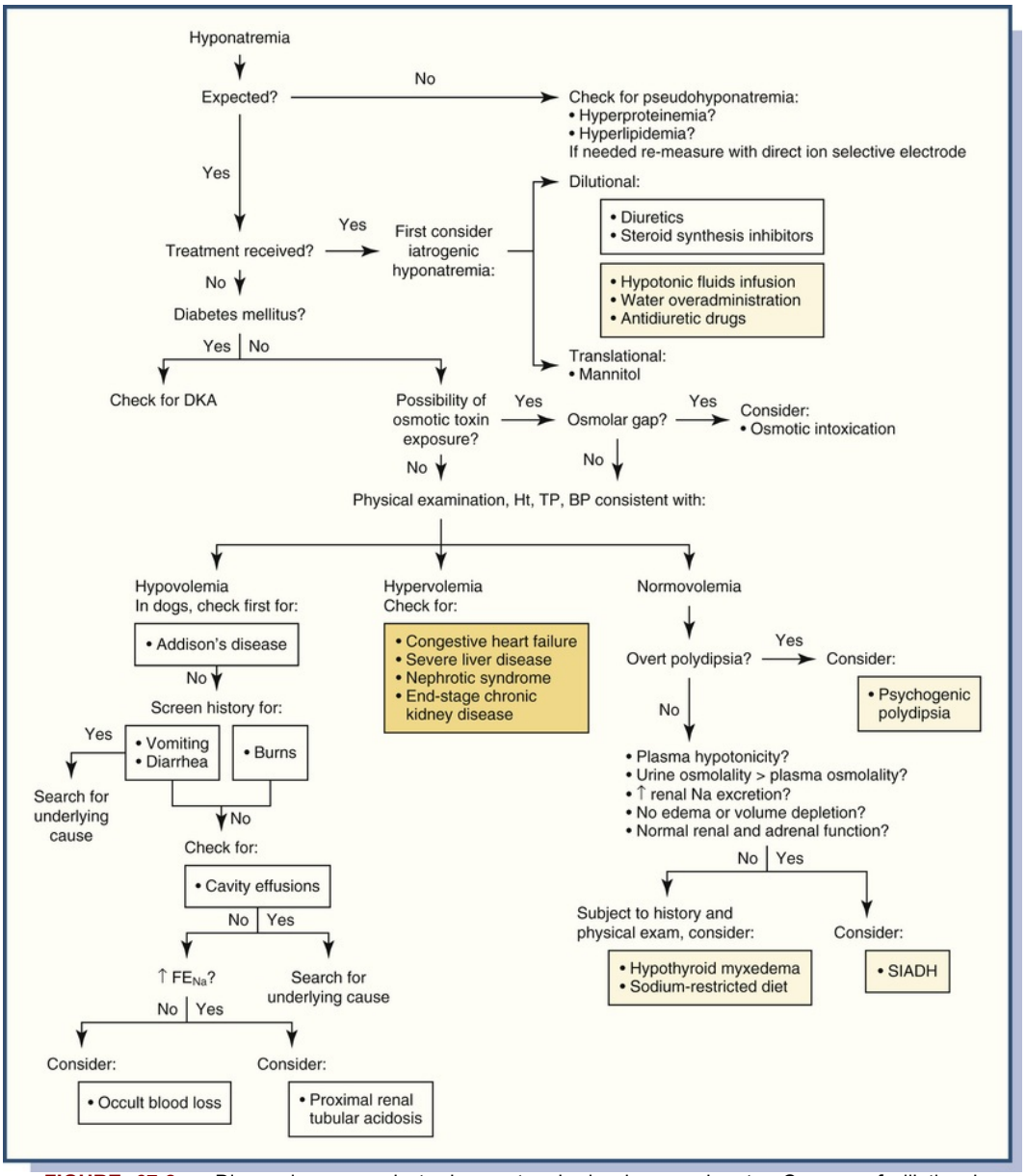

FIGURE 67-2 Diagnosis approach to hyponatremia in dogs and cats. Causes of dilutional hyponatremia are discriminated according to their corresponding extracellular volume: decreased (non-shaded boxes), unchanged (lightly-shaded boxes), increased (darkly-shaded boxes). *BP,* Systemic blood pressure; *DKA,* diabetic ketoacidosis; *FE_{Na},* fractional sodium excretion; *Ht,* hematocrit; *TP,*

serum total protein concentration.

E-Box 67-2

Causes of Hyponatremia

Non-Dilutional Hyponatremia

Pseudohyponatremia

Hyperlipidemia
Hyperproteinemia

Translocational (Hypertonic) Hyponatremia

Diabetes mellitus
Mannitol administration
Intoxication by other permeant molecules

Dilutional (Hypotonic) Hyponatremia

Loss of Sodium > Loss of Water

Total body water ↓—Total body Na ↓↓↓ (signs of ECF volume depletion expected)

Renal loss of sodium and water
- Hypoadrenocorticism
- Diuretic administration
- Proximal renal tubular acidosis

Non-renal loss of sodium and water
- Gastrointestinal loss
  - Vomiting
  - Diarrhea
- Third-space loss
  - Pancreatitis
  - Peritonitis
  - Uroabdomen
  - Other peritoneal effusion
  - Pleural effusion
  - Pericardial effusion
  - Uterine effusion
- Cutaneous loss
  - Burns
- Chronic blood loss

Pure Water Retention

Total body water ↑—Unchanged total body sodium (normal ECF volume)

Psychogenic polydipsia
Iatrogenic water retention
- Antidiuretic drugs
- Hypotonic fluids administration
- Uncontrolled enteral water administration

Sodium-restricted diet
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Hypothyroid myxedema coma
Exercise-associated hyponatremia

Low Effective Circulating Volume

Total body water ↑↑↑—Total body sodium ↑ (ECF volume expansion)

Congestive heart failure
Severe liver disease
Nephrotic syndrome
End-stage chronic kidney disease

Miscellaneous
Sepsis and systemic inflammatory response syndrome
Babesiosis
ECF, Extracellular fluid.

Causes

Hypertonic Hyponatremia

Hypertonic hyponatremia can follow mannitol administration or ingestion of other permeant molecules (e.g., ethylene glycol).[10,57-63] Identifying the cause of hypertonic hyponatremia is usually straightforward (see Figure 67-2). If the possibility of an alcohol intoxication is raised, measuring osmolality can help by identifying a "gap" between that which is measured and the lower calculated value. These solutes are not included in the formula used for osmolality calculation (discussed earlier).[64]

Hypotonic Hyponatremia

Dilutional (hypotonic) hyponatremia can be associated with decreased, normal, or increased Na stores and, thus, with decreased, normal or increased ECF volumes (see E-Box 67-2 and Figure 67-2).[2] Chronic hyponatremia tends to cause few signs.[2] When hypotonic hyponatremia takes place gradually, the brain adapts to ECF hypotonicity.[65] Treatment of chronic hyponatremia is beyond the scope of this chapter but rapid correction of electrolyte concentrations can have worrisome consequences (see ch. 129).[2,3,50,66] In acute hyponatremia, water moves from the dilute ECF space to the more concentrated ICF, including into brain cells (cerebral edema), which increases intracranial pressure and leads to signs that can appear vague but are serious: lethargy, nausea, vomiting, and depression, before incoordination, seizures and death.[3] Rapid correction of acute hyponatremia is not as worrisome.[66]

Dilutional Hyponatremia

Dilutional hyponatremia is associated with an appropriate non-osmotic stimulation of ADH secretion, or in rare cases, with a deregulated (inappropriate) secretion of ADH. In combination with other mechanisms, secretion of ADH explains why even hypotonic losses (e.g., gastrointestinal losses) result in hyponatremia through volume preservation at the price of decreased osmolality via thirst and enhanced renal preservation of water.[3] Exceptions include primary polydipsia, exercise-induced hyponatremia (see ch. 173) and advanced CKD in which ADH secretion is adequately suppressed (see ch. 324).

Hypovolemic Hyponatremia

Most hyponatremic patients are hypovolemic. Their sodium losses exceed water losses due to compensation via water intake. Thus, identifying clinical signs of ECF dehydration and perfusion deficits (e.g., loss of skin elasticity, dry mucous membranes, sunken eyes, delayed capillary refill time, rapid heart rate), or of third-space fluid (abdominal fluid wave, abdominal distension, dyspnea, muffled heart sounds, distended jugular veins) is critical. Measuring serum albumin, hematocrit and arterial or central venous blood pressure are cornerstones to understanding hyponatremia (see Figure 67-2).[67] Knowing the ECF volume constitutes only one piece of a larger puzzle that includes other historical and clinical data.[68] For example, only half of dogs with Addison's disease exhibit clinically perceptible dehydration.[69] Addison's disease (see ch. 309) is an obvious cause of renal NaCl loss and this condition should be considered, especially if the patient is hyperkalemic (see Figure 67-2). Although suggestive, concurrent hyperkalemia and hyponatremia are not pathognomonic for Addison's disease. This electrolyte pattern has been uncommonly observed with gastrointestinal diseases, whipworm parasitism, chylothorax, pregnancy, urethral obstruction, and other conditions.[70-74] Use of diuretics and proximal renal tubular acidosis are additional renal causes of hypovolemic hyponatremia.[3,32,75]

Extrarenal causes of hypovolemic hyponatremia include Na losses due to vomiting, diarrhea, third-space fluid accumulation, and chronic blood loss (combined with an inappropriate Na dietary intake in some cases; see E-Box 67-2).[34,70,71,76-83] Fractional renal Na excretion should be appropriately low (see ch. 73).[84] The pathophysiology of hyponatremia in third-space effusions is multifactorial and, in some cases, overlaps with hypervolemic hyponatremia. Conditions such as congestive heart failure, severe liver disease and the

nephrotic syndrome can lead to low effective arterial blood pressure. This, in turn, stimulates renin-angiotensin-aldosterone to retain Na and water while ADH secretion is stimulated to expand ECF volume through water reabsorption.[3] [Na] is diluted by the increase in ECF volume despite an increase in total body Na: hypervolemic hyponatremia (see E-Box 67-2). Na moving into fluid in a body cavity, into an edematous space, and the use of diuretics as treatment enhance the likelihood of hyponatremia.[81] Hypervolemic hyponatremia may also be seen in advanced CKD (see ch. 324) because of defective renal salt and water excretion capacities.[3] The recognition of clinical signs of hypervolemia (e.g., effusions, jugular distension, peripheral or pulmonary edema) is crucial for treatment.

Psychogenic polydipsia can overwhelm renal water excretion capacities leading to dilution.[2] The syndrome of inappropriate ADH secretion (SIADH) can cause normovolemic hyponatremia. Criteria for diagnosing SIADH include: hyponatremia with hypotonic plasma; urine osmolality above that of plasma; increased renal Na excretion; absence of edema or volume depletion; normal renal and adrenal function.[85-87] SIADH has been reported in dogs and cats secondary to dirofilariasis, hypothalamic neoplasia, Rathke's cleft cyst, *Acanthamoeba* meningitis, congenital hydrocephalus, liver disease, and vinblastine overdosage.[88-98] Increased ADH secretion may cause dilutional hyponatremia secondary to hypothyroid myxedema.[99-107] Parenteral hypotonic fluid administration, enteral water overload, and use of certain antidiuretic drugs (nitrous oxide, barbiturates and narcotics) can cause normovolemic hyponatremia.[3,108-110] Hyponatremia has been described in a puppy fed a Na deficient diet, in dogs with babesiosis or sepsis, a cat with toxoplasmosis, and as a syndrome of inadequate compensation for renal Na losses in Alaskan sled dogs (see E-Box 67-2).[111-118]

Hypochloremia (Figure 67-3)

Serum chloride (Cl) concentration assays are typically reliable, although hyperproteinemia, lipemia, and administration of bromides may alter results.[119-122] Cl ions constitute about two thirds of ECF anions; most of the balance is bicarbonate (bicarb).[123] Apart from maintaining ECF tonicity, Cl has an inverse relationship with bicarb with a key role in renal acid-base regulation.[124-127] Proportionality in these electrolytes can be demonstrated with the formula: [corrected Cl^-] = [measured Cl^-] × [mid-reference range Na^+]/[measured Na^+]. Measured hypochloremia with normal serum corrected Cl concentration is suggestive of increases in ECF water.[123] In this scenario, the differential diagnoses for hyponatremia and hypochloremia are similar (E-Box 67-3; see also Figure 67-3).[123] Corrected hypochloremia and a reference range measured serum Cl concentration is usually associated with hypernatremia.

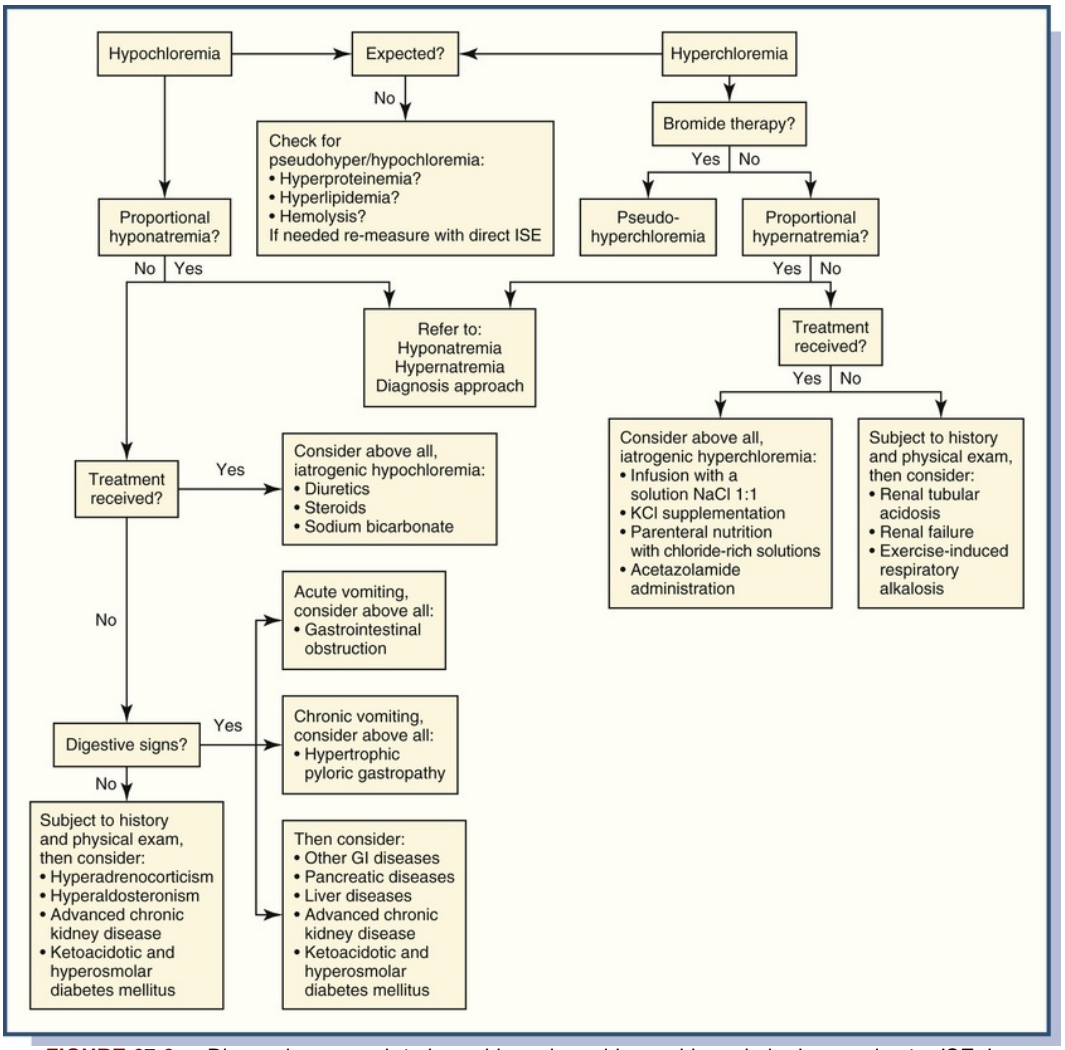

FIGURE 67-3 Diagnosis approach to hypochloremia and hyperchloremia in dogs and cats. *ISE,* Ion selective electrode.

E-Box 67-3

Causes of Hypochloremia and Hyperchloremia

Hypochloremia

Pseudohypochloremia

Hyperlipidemia
Hyperproteinemia

Hypochloremia with Proportional Hyponatremia (Measured Hypochloremia—Corrected Normochloremia)

Translocation hypochloremia and hyponatremia (refer to E-Box 67-2)
Dilutional hypochloremia and hyponatremia (refer to E-Box 67-2)

Hypochloremia without Proportional Hyponatremia (Corrected Hypochloremia)

Gastrointestinal Loss

Chronic hypertrophic pyloric gastropathy
Gastrointestinal foreign body
Other cause of digestive loss

Renal Loss
Diuretic (loop or thiazides) administration
Steroid administration
Hyperadrenocorticism
Hyperaldosteronism
Advanced CKD
Ketoacidotic and hyperosmolar diabetes mellitus
Babesiosis

Mixed (Dilution by Non-Chloride Solution and Serum Bicarbonate Concentration Increase)
Sodium bicarbonate administration

Hyperchloremia

Pseudohyperchloremia
Bromide therapy
Hyperlipidemia*
Hemolysis*
Hypoalbuminemia†

Hyperchloremia with Proportional Hypernatremia (Measured Hyperchloremia—Corrected Normochloremia)
Pure water deficit (refer to E-Box 67-1)
Uncompensated hypotonic loss (refer to E-Box 67-1)
Salt overload (refer to E-Box 67-1)

Hyperchloremia without Proportional Hypernatremia (Corrected Hyperchloremia)

Excessive Chloride Intake (Compared to Sodium)
Isotonic NaCl, hypertonic NaCl, or Ringer's solution infusion
KCl supplementation
Parenteral nutrition with chloride-rich solutions

Chloride Renal Retention
Renal tubular acidosis
Renal failure
Babesiosis
Acetazolamide administration
Exercise-induced respiratory alkalosis

*With colorimetric methods of chloride measurement.
†Described in humans.

Decreases (or increases) in serum Cl are not associated with clinical signs, but their identification may be of value in pursuing a diagnosis. Measured and corrected hypochloremia without parallel hyponatremia can be observed with gastrointestinal (GI) or renal losses and in mixed acid-base disturbances. When serum Cl concentrations decrease with GI or renal loss, bicarb reabsorption increases proportionally, resulting in metabolic alkalosis. Conversely, in chronic respiratory acidosis, the increase of bicarb reabsorption is assumed to be associated with increased urinary losses of Cl and hypochloremia.[128,129] Hypochloremia is common in pets with chronic hypertrophic pyloric gastropathy, those with GI obstruction, and some with other GI, liver and pancreatic conditions, usually secondary to vomiting and metabolic alkalosis.[77,130-138] In one study, dogs suspected but proven not to have hypoadrenocorticism had lower serum [Cl] than did dogs with hypoadrenocorticism.[69,139]

Renal Cl losses can be caused by administration of loop or thiazide diuretics and hypochloremia is enhanced if a pet is fed a salt-restricted diet.[123,140-143] Mild hypochloremia has been documented in naturally-occurring hyperadrenocorticism, hyperaldosteronism, and after receiving steroids.[45,144-148] About 33% of untreated diabetic cats and a larger percentage of dogs and cats with end stage CKD are hypochloremic, the severity of which is worse if hyperosmolar and/or ketoacidotic.[37,53,149-153] Hypochloremia has been

documented in dogs with early stages of babesiosis.[37,118] A decrease in serum Cl concentration may be observed after Na bicarb administration, due to simple dilution by a non-Cl Na salt solution and because an increase in serum bicarb will cause a reciprocal decrease in Cl.[10]

Hyperchloremia

Bromide therapy, hemolysis, and hyperlipidemia can cause pseudohyperchloremia (see E-Box 67-3; see also Figure 67-3).[121,122,154] Water deficits and loss of hypotonic fluids result in parallel increases in serum [Na] and [Cl]. When the serum corrected Cl concentration is within the reference range but serum [Cl] is measured high, the differential diagnosis for hypernatremia should receive priority (see E-Box 67-3 and Figure 67-3).[3] A similar approach is suggested with salt overload and in rare dogs with hyperadrenocorticism and hyperchloremia.[39-41,45] One may calculate hyperchloremia when the measured concentration is within the reference range with hyponatremia. Causes of calculated hyperchloremia without measured hyperchloremia are reviewed in the section on hyponatremia.

An excessive gain of Cl compared with Na can result in calculated hyperchloremia.[126] For example, an isotonic saline IV infusion or use of a parenteral nutrition formula rich in Cl can cause mild increases in serum Cl concentration without hypernatremia.[3,10,123,155] Hyperchloremia has been described in both proximal and distal tubular acidosis in dogs and in distal tubular acidosis in cats.[75,153,156-158] Compromised reabsorption of bicarb and altered secretion of hydrogen ions may have a role in development of proximal and distal tubular acidosis respectively. Similar inhibition of bicarb reabsorption within the proximal tubule by the carbonic anhydrase inhibitor acetazolamide results in a hyperchloremic metabolic acidosis.[159,160] Tubular dysfunction may have contributed to the hyperchloremia described in a few cases of cats and dogs with kidney disease and in dogs with babesiosis.[32,35,115,132,161] Hyperchloremia has been observed in dogs during exercise.[162-167] Increases in serum Cl concentration are likely multifactorial but respiratory alkalosis and subsequent Cl compensation of the renal bicarbonate loss may be involved.[162,165]

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CHAPTER 68

Potassium, Magnesium

Ann-Marie Della Maggiore

Potassium

Overview

Potassium (K^+), the body's primary intracellular cation, is essential for numerous physiologic processes including enzymatic action, neuromuscular and cardiac conduction, and routine cell function. Membrane permeability and the ratio of K^+ concentrations in the intracellular fluid (ICF) as compared with that in the extracellular fluid (ECF) are major determinants of resting cell membrane potentials. ICF K^+ (95% of total body K^+) has important roles in maintaining cell volume and growth. ECF K^+ concentrations (5% of total) are tightly regulated; serious increases or decreases in circulating K^+ concentrations are invariably worrisome and may be life-threatening. Reference intervals for serum or plasma K^+ concentrations should be determined by each laboratory, independently. Most reference intervals have a mean of approximately 4 to 4.5 mEq/L. Assays using serum or plasma are sensitive and specific for K^+ concentrations that usually, but not always, reflect total body K^+ status. An exception is inorganic acidosis (diabetic ketoacidosis, for example) in which extra- and intracellular K^+ concentrations become dissociated.

Dietary intake of K^+ is critical for normal homeostasis. K^+ is absorbed from the gastrointestinal tract (stomach and small intestine), distributed throughout the body, and excreted primarily by the kidneys (90-95%) and colon (5-10%).[1] Aldosterone has a critical role in determining the amount of K^+ excreted from the distal renal tubule and, thus, is a primary regulator of K^+ balance (see ch. 308, 309, and 326). Insulin and epinephrine are known to increase K^+ uptake by muscle and liver cells. Acute changes in pH will shift K^+ between fluid compartments.

Hypokalemia

Clinical Signs

Clinical signs due to hypokalemia in dogs and cats vary with severity and duration of the condition. Significant hypokalemia (< ≈3.0 mEq/L for most laboratories) usually results in vague-and-mild to profound muscle weakness. Hypokalemia may impair urinary concentrating ability, resulting in polyuria and secondary polydipsia. Severe deficiencies (< ≈2.0 mEq/L) have been associated with rhabdomyolysis and respiratory muscle paralysis.[2,3]

Differential Diagnosis and Approach (Figure 68-1)

Causes of hypokalemia include decreased intake, excessive or abnormal translocation between the ECF and ICF spaces, and/or excessive loss through the kidneys or gastrointestinal systems. Prolonged starvation as a cause of clinically significant hypokalemia is unlikely in otherwise healthy animals (i.e., no excessive K^+ losses) because aldosterone and the kidneys, within hours to days, adjust K^+ excretion to maintain serum concentrations. Administration of IV replacement fluids insufficiently supplemented with K^+, however, can lead to hypokalemia in anorectic patients, depending on duration and cause of their illness. Remember that the K^+ content of fluids such as Ringer's solution (4 mEq/L) is trivial and not adequate for long-term maintenance (saline contains no potassium). Ingestion of bentonite-containing clay cat litter can bind K^+ within the gastrointestinal tract.[4,5]

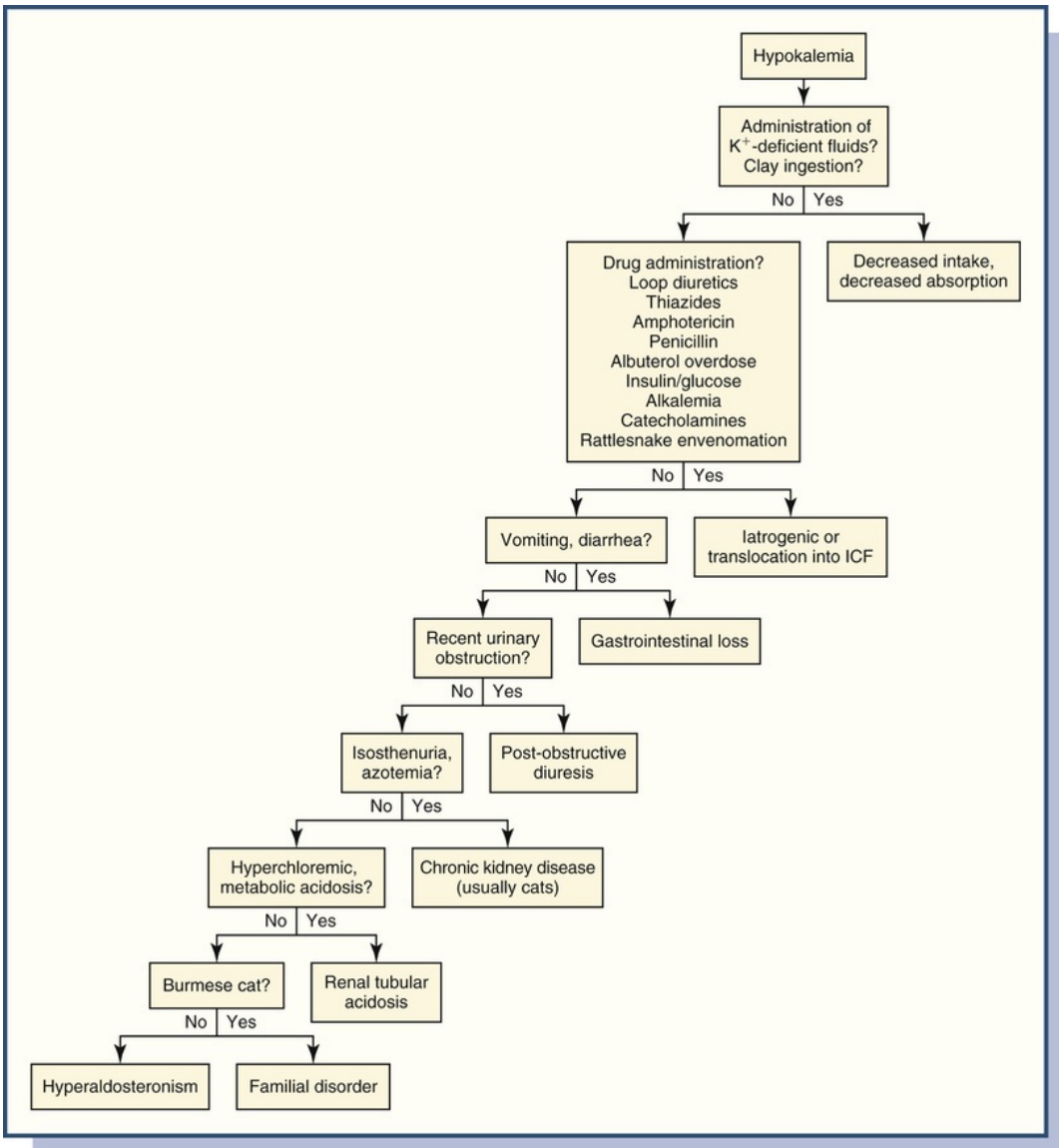

FIGURE 68-1 Algorithm for the evaluation of hypokalemia. *ICF,* Intracellular fluid compartment.

Dogs and cats severely ill with diabetic ketoacidosis are typically depleted in total body potassium stores following anorexia, vomiting, diarrhea, polyuria with and then without compensatory polydipsia (individuals decrease or stop drinking due to illness and become dehydrated). In these patients, excessive translocation of K^+ from the ECF to the ICF in response to administration of insulin, IV fluids, sodium bicarbonate, and glucose can be profound and life-threatening. Close monitoring to recognize and manage alterations in K^+ is critically important (see ch. 142). Catecholamine release, alkalemia, beta$_2$-adrenergic drug overdose, rattlesnake envenomation, and hypothermia may result in hypokalemia. There is a familial disorder of K^+ translocation in Burmese cats.[6-10]

Gastrointestinal losses of potassium, associated with vomiting and/or diarrhea, are one of the most common causes of hypokalemia. Although vomitus may not contain large quantities of K^+, loss of gastric secretions promotes increased renal losses. Urinary losses of potassium are also common, with as many as 20-30% of cats with chronic kidney disease (CKD) having hypokalemia.[11-13] It has been suggested that many cats thought to have primary kidney disease and secondary hypokalemia may indeed have primary hyperaldosteronism, which results primarily in hypokalemia and chronically leads to secondary CKD. Hypokalemia is less common in dogs with CKD. The incidence of primary hyperaldosteronism in dogs and cats is not known but likely underestimated in both species. Urinary potassium losses can be significant during post-obstructive diuresis, in some forms of renal tubular acidosis, and rarely following peritoneal dialysis.[14-16] Hypokalemia is uncommon in pets with polyuric disorders. Medications that lead to diuresis

and potential for hypokalemia include loop and thiazide diuretics, amphotericin B, and glucocorticoid excess (rare in hyperadrenocorticism).[17-19]

Hyperkalemia

Overview

Hyperkalemia is most frequently associated with acute kidney injury (AKI) or CKD because these conditions are common and failing kidneys may fail to excrete adequate quantities of potassium. Hyperkalemic dogs and cats may not show clinical signs until the condition becomes severe (>7.5-8 mEq/L) and even then the only typical observation is weakness (the same clinical sign associated with hypokalemia). Many severely hyperkalemic pets have bradycardia and the classic loss of P waves on electrocardiogram (ECG). The ECG from these patients may also reveal the less obvious and less specific "tented" T waves, shortened Q-T intervals, and prolonged P wave and P-R interval durations (prior to P wave disappearance).[20] ECG alterations do not consistently correlate with specific serum K^+ concentrations.

Differential Diagnoses and Approach (Figure 68-2)

Pseudohyperkalemia may occur with severe thrombocytosis (platelet numbers >1,000,000/mcL), severe leukocytosis (WBC >100,000/mcL), hemolysis in neonates and animals with high intracellular K^+ (e.g., Akitas, Shiba Inu, others?). If one of these issues is suspected, serum K^+ should be reevaluated. In breeds known to have high intracellular K^+ concentrations, attention must be paid to avoiding hemolysis and quickly separating red blood cells from serum or plasma.

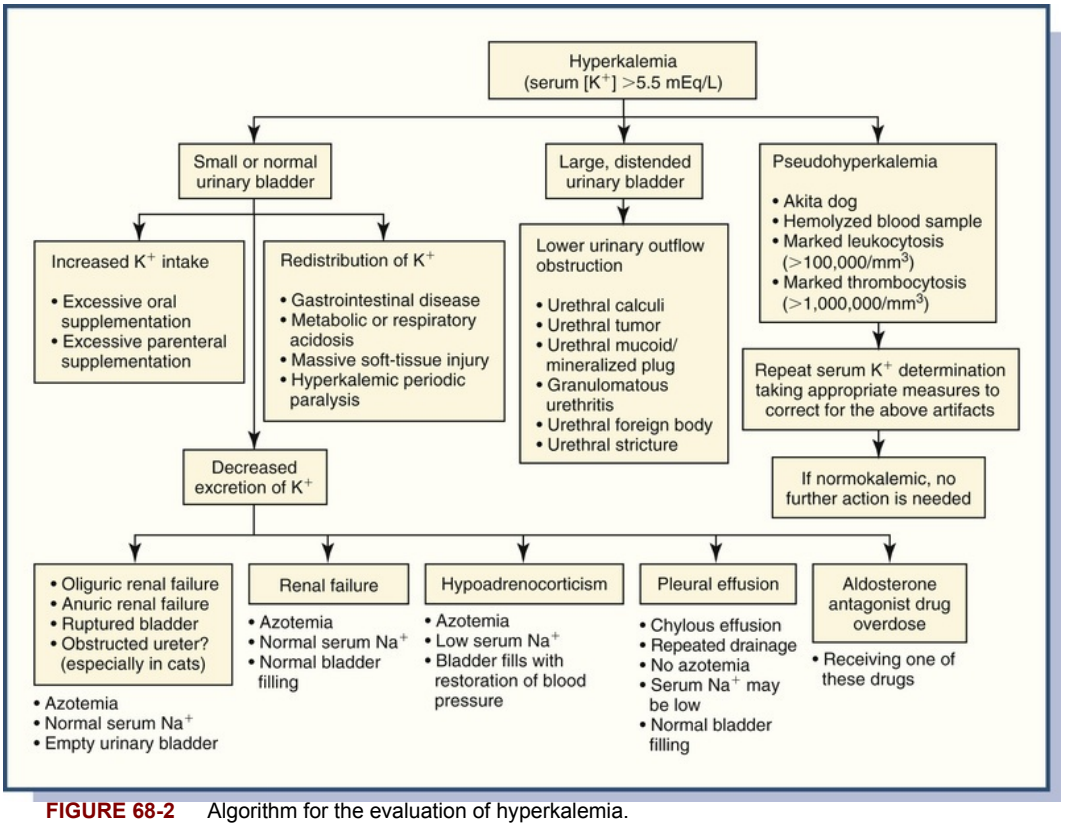

FIGURE 68-2 Algorithm for the evaluation of hyperkalemia.

As discussed, hyperkalemia is commonly associated with renal failure. Increased oral K^+ intake may contribute to hyperkalemia but is unlikely to be the sole cause. Hyperkalemia occurs when excessive amounts are administered IV. Several medications may contribute to hyperkalemia: ACE inhibitors, angiotensin receptor blockers, K^+-sparing diuretics (e.g., spironolactone), prostaglandin inhibitors (e.g., nonsteroidal anti-inflammatories), trimethoprim, cyclosporine, nonspecific beta-blockers (e.g., propranolol), and heparin.[21]

Serum potassium concentrations may transiently increase following oral potassium bromide administration, but sustained hyperkalemia is likely only in animals with compromised renal function. Tissue breakdown following severe exercise or due to rhabdomyolysis can cause hyperkalemia.

Hypoadrenocorticism, the classic cause of hyperkalemia and hyponatremia, is typically a condition resulting from mineralocorticoid and glucocorticoid deficiencies (some dogs with Addison's disease do not have serum electrolyte abnormalities; see ch. 309). Hyperkalemia and hyponatremia have been uncommonly reported in pets with chronic pleural or peritoneal effusion (see ch. 244) and with certain gastrointestinal diseases: parasitism (e.g., trichuriasis), infection (e.g., salmonellosis), or a perforating duodenal ulcer (see ch. 276).[22,23] Hyperkalemia and impaired renal K^+ excretion may occur despite increased aldosterone concentrations if rates of distal renal tubular flow markedly decrease (e.g., hypovolemia).

Urethral obstruction or bilateral ureteral obstructions prevent urine excretion. Urethral obstruction is a common cause of hyperkalemia. The hyperkalemic animal with a small or non-palpable bladder should be evaluated for oliguric or anuric renal failure (consistent with either AKI or end-stage CKD) or rupture. A history of trauma or urinary tract calculi and straining should make urinary rupture a consideration. Animals with hyperkalemia and urinary tract obstruction or rupture are usually severely ill, requiring rapid and thorough evaluation and treatment (see ch. 150).

Metabolic acidosis can result in K^+ translocation from the ICF to the ECF (e.g., lactic acidosis and ketoacidosis). Ill diabetics who have deficiency in total body K^+ may have normal or even increased circulating K^+ concentrations. It is important for the clinician to recognize that these animals are predisposed to life-threatening hypokalemia when treatment with insulin, IV fluids, sodium bicarbonate and glucose commences, each of which enhances K^+ movement from the ECF space to the ICF. The concern of over- or under-dosing potassium requires extremely close monitoring and appropriate responses (see ch. 142).

Magnesium

Overview

Magnesium (Mg), an abundant water-soluble intracellular divalent cation, plays critical roles in multiple cellular processes: stabilization of phosphorylation reactions, enabling glucose utilization and synthesis, supporting ion transport, and enhancing macromolecule synthesis (proteins, fats, and nucleic acids).[24] The study of magnesium-related disorders has been challenging simply because 99% of Mg is in the ICF space. We can only measure a portion of the ≈1% of total body Mg that is in the ECF. Approximately 67% of total body Mg is stored with calcium and phosphorus in bone. About 20% of total body Mg is found within muscle and about 10% in other soft tissues.[25,26] Extracellular Mg has been identified in three major forms: the biologically active free or unbound ionized Mg (≈55%); protein-bound (20-30%), and complexed (15-25%). The ICF distribution of Mg has made assessment of serum Mg concentrations of uncertain value. No gold standard test exists for determining total body Mg deficits or excesses. Serum total and ionized Mg concentrations are currently used to assess for hypomagnesemia but may not reflect total body stores. Studies, such as 24-hour urinary Mg excretion, Mg retention, ionized-to-total Mg ratios, and determining parenteral Mg tolerance are being evaluated.

Magnesium homeostasis is dependent on the interaction of three key organ functions: intestinal uptake, bone stores, and kidney filtration/excretion. The kidneys control Mg balance through glomerular filtration and reabsorption in the thick ascending loop of Henle and distal convoluted tubule. Gastrointestinal Mg absorption occurs primarily in the colon of dogs.[27]

Hypomagnesemia

Humans

Numerous causes of hypomagnesemia have been documented in human critical care patients. Hypomagnesemia is most common in hospitalized ill patients who have decreased Mg intake and increased loss through the gastrointestinal tract or altered kidney function. Causes of hypomagnesemia in veterinary patients are not as well documented, but general mechanisms of loss are believed to be similar between species.

Differential Diagnosis and Approach *(Figure 68-3)*

Causes of hypomagnesemia include decreased intake, alterations in cellular distribution, increased renal or

gastrointestinal loss, or any combination of these mechanisms. Gastrointestinal disorders that may cause hypomagnesemia include chronic diarrhea, malabsorption, short bowel syndrome, and colonic neoplasia. Drugs associated with hypomagnesemia in people include diuretics, gentamicin, cisplatin, cyclosporine, ticarcillin, carbenicillin, and proton pump inhibitors.[22] Renal losses of Mg may be seen secondary to diabetes mellitus, diabetic ketoacidosis, AKI, postobstructive diuresis, and renal tubular acidosis.[22]

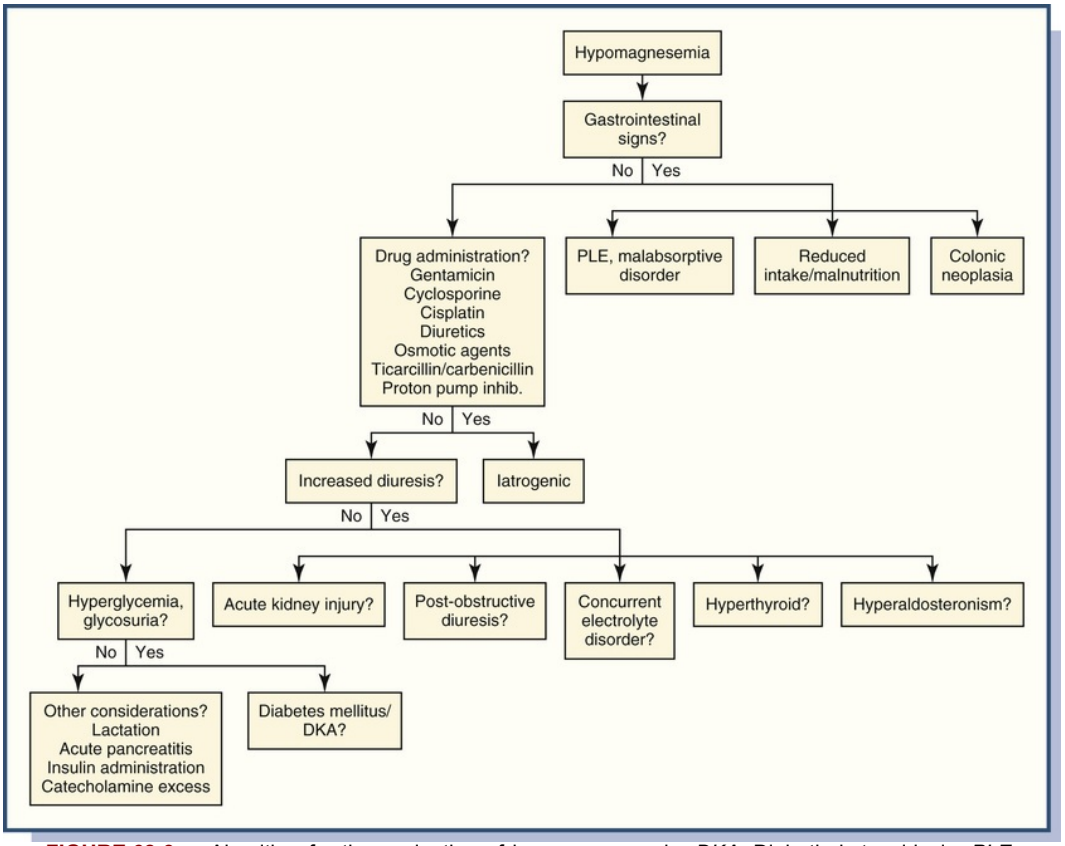

FIGURE 68-3 Algorithm for the evaluation of hypomagnesemia. *DKA*, Diabetic ketoacidosis; *PLE*, protein-losing enteropathy.

Hyperaldosteronism, hyperthyroidism, and primary hypoparathyroidism are endocrine conditions associated with hypomagnesemia. Hypomagnesemia is commonly seen with hypoparathyroidism (32% of dogs, 85% cats).[28] Magnesium depletion may impair parathyroid hormone (PTH) secretion and decrease sensitivity of receptors to ionized calcium. Thus, animals with hypoparathyroidism may appear refractory to calcium and calcitriol supplementation until their hypomagnesemia is treated.[22] Other causes of hypomagnesemia include excessive loss from lactation, myocardial infarction, acute pancreatitis, insulin administration or catecholamine excess.[26] Hypomagnesemia has been documented to occur with increased frequency in Bulldogs.[29]

Hypermagnesemia

Overview

Hypermagnesemia may be less clinically relevant in veterinary medicine than its counterpart. Hypermagnesemia has been observed in 18% of hospitalized cats and 13% of hospitalized dogs.[30,31] There is limited information in the veterinary literature documenting clinical signs of hypermagnesemia. Symptoms reported in humans include paresis, paralysis, impaired respiration, hypotension, nausea, vomiting, and electrophysiological derangements of cardiac conduction.[22] Significant cardiovascular effects, including arrhythmias, hypotension, and death have been noted in patients whose plasma concentrations were greater than 12 mEq/L.[32] Monitoring both blood pressure and ECG for irregularities is recommended during

parenteral Mg administration.

Differential Diagnosis and Approach (Figure 68-4)

Magnesium is predominantly excreted via the kidneys. Thus, renal insufficiency and post-renal azotemia are the most common causes of excess circulating concentrations of magnesium. Iatrogenic overdose through parenteral or oral administration has been documented in people but not dogs or cats. Hypermagnesemia has been associated with administration of methylpredacetate in cats and ACE inhibitors and spironolactone in dogs with degenerative valve disease.[28,33] While 35% of dogs with newly diagnosed hypoadrenocorticism had hypermagnesemia at the time of diagnosis in one study, it was not considered clinically significant.[34] Magnesium concentrations did not correlate with serum creatinine or pH.

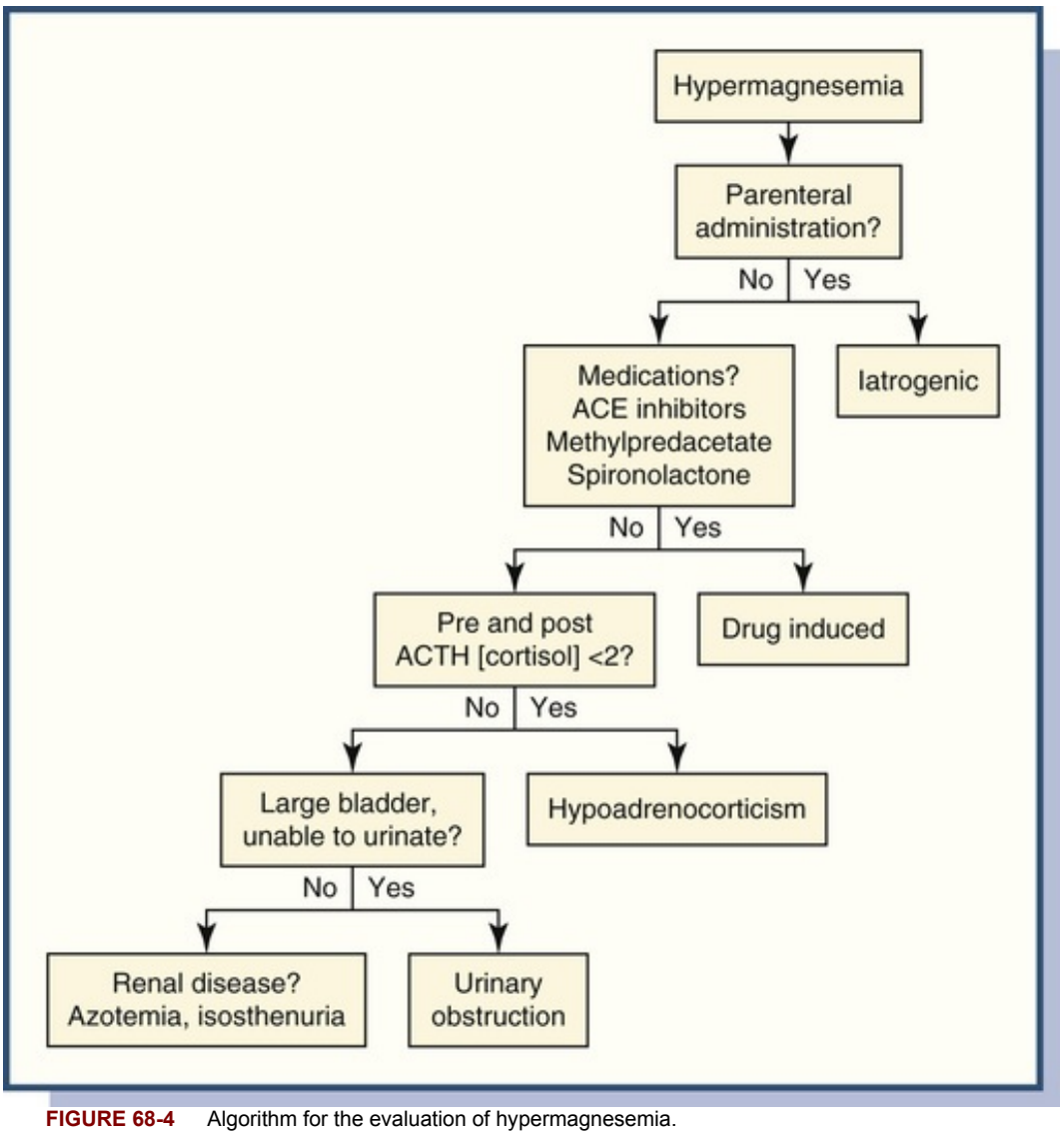

FIGURE 68-4 Algorithm for the evaluation of hypermagnesemia.

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CHAPTER 69

Calcium, Phosphorus

Richard John Mellanby

Calcium Overview

As well as causing clinical signs which may require urgent treatment, finding an altered serum calcium concentration is often of considerable assistance during the diagnostic evaluation of an animal showing vague clinical signs. Calcium is found in three forms in the circulation: the physiologically active ionized form which accounts for about 50%; the chelated form complexed with lactate, citrate and bicarbonate accounting for about 10%; and the protein-bound form accounting for about 40% of the total measured serum calcium concentration. The percentage of calcium in each form can vary depending on albumin and other protein concentrations, acid-base balance, and on the presence of potential chelators. An animal's serum total calcium concentration should always be interpreted together with the albumin concentration since hypoalbuminemia can result in spurious hypocalcemia or mask hypercalcemia. Changes in blood pH can lead to alterations in negative charges on protein molecules which in turn can alter the amount of calcium which is protein-bound. The primary hormones involved in regulating calcium metabolism in healthy animals are parathyroid hormone (PTH), 1,25 dihydroxyvitamin D (1,25$(OH)_2$D) and calcitonin (see ch. 297 and 298).[1-7]

Hypercalcemia in Dogs

Clinical Signs

Clinical signs associated with hypercalcemia vary depending on underlying cause. The neuromuscular, gastrointestinal, renal and cardiac systems are most commonly affected (Table 69-1). Hypercalcemia inhibits the action of antidiuretic hormone (ADH), leading to an inability to concentrate urine and polyuria and polydipsia. Urine specific gravities are commonly <1.012 and almost always <1.020 on home-caught samples of hypercalcemic dogs. Long-standing hypercalcemia, especially if accompanied by hyperphosphatemia, may result in renal tubular damage and intrinsic renal azotemia. Other common clinical signs include lethargy, muscle weakness, poor appetite, and weight loss. Vomiting, constipation, and diarrhea are uncommon and seizures are quite rare.

TABLE 69-1

Clinical Signs Noted in Hypercalcemic Dogs and Cats[17,27]

CLINICAL SIGN	FREQUENCY (%) IN HYPERCALCEMIC DOGS	FREQUENCY (%) IN HYPERCALCEMIC CATS
Anorexia	88	70
Polydipsia/ polyuria	68	24
Vomiting	53	18
Muscular weakness or twitching	23	0

Differential Diagnosis

Overview

The most common causes of hypercalcemia in dogs are malignancy, hypoadrenocorticism, primary hyperparathyroidism and chronic kidney disease (Box 69-1). Lymphoma and apocrine gland adenocarcinoma of the anal sac are the two most common causes of malignancy-related hypercalcemia. Less common causes of hypercalcemia include hypervitaminosis D (vitamin D toxicosis), granulomatous diseases, dehydration, healthy juvenile animals and laboratory error.

Box 69-1

Conditions Associated with Hypercalcemia

Common Causes

Malignancy
- Lymphoma
- Adenocarcinoma of the apocrine glands of the anal sac (rarely diagnosed in cats)
- Multiple myeloma

Primary hyperparathyroidism
Chronic kidney disease (CKD)
Hypoadrenocorticism (an infrequent cause of hypercalcemia in cats)
Some granulomatous diseases
Hypervitaminosis D
- Cholecalciferol rodenticide toxicosis
- Excessive dietary supplementation
- Ingestion of human medication containing calcitriol
- Oversupplementation for hypoparathyroidism

Less Common Causes

Idiopathic (cats)
Miscellaneous tumors (squamous cell carcinoma, lung carcinoma, malignant melanoma)
Hyperlipidemia
Juvenile dogs
Lab error
Hyperproteinemia

Rare Causes

Osteosarcoma
Metastatic bone tumors
Mammary carcinoma

Malignancy

Lymphoma is the most common cause of malignancy-related hypercalcemia. Hypercalcemic dogs with lymphoma frequently, but not invariably, have increased circulating concentrations of parathyroid hormone related peptide (PTHrP) synthesized by the cancer and suppressing PTH concentrations (see ch. 297). Normocalcemic dogs with lymphoma have low or undetectable concentrations of PTHrP.[1] Apocrine gland adenocarcinomas of the anal sac may also synthesize PTHrP, causing malignancy-related hypercalcemia.[8,9] A variety of other neoplasms have been associated with hypercalcemia, including thymoma, pulmonary carcinoma, nasal carcinoma, malignant melanoma, multiple myeloma and leukemia.[10-15] Since hypercalcemia of malignancy is typically driven by tumor PTHrP production, both total and ionized calcium concentrations are increased while serum phosphate is usually low or in the lower portion of the reference range (Table 69-2).

TABLE 69-2

Pertinent Circulating Serum Biochemistry and Hormone Results in Dogs with Conditions Associated with Hypercalcemia

	PRIMARY HYPERPARATHYROIDISM	MALIGNANCY	HYPERVITAMINOSIS D	CKD	HYPOADRENOCORTICISM
Total calcium	↑	↑	↑	↑ or N or ↓	↑
Ionized calcium	↑	↑	↑	N or ↓	↑
Phosphate	N or ↓	N or ↓	N or ↑	↑	N or ↑
Urea/creatinine	↓ N or ↑	N or ↑	N or ↑	↑	N or ↑
PTH	N or ↑	↓	↓	↑	N
PTHrP	-	↑	-	-	-
1,25(OH)2D	N or ↑	↑ or N or ↓	↑	N or ↓	N
25(OH)D	N or ↓	N or ↓	N or ↑	N or ↓	N

↑, Increased; ↓, decreased; -, negative; *CKD,* chronic kidney disease; *N,* normal.

Primary Hyperparathyroidism

Primary hyperparathyroidism is well recognized as a cause of moderate to marked hypercalcemia in dogs, most of whom have low or low normal serum phosphate concentrations (see Table 69-2).[16]

Chronic Kidney Disease (CKD)

Dogs and cats in later stages of CKD have phosphate retention and hyperphosphatemia. Mass law effects lead to decreases in circulating calcium concentrations, a condition enhanced by the kidney's reduced ability to synthesize vitamin D. Decreases in vitamin D lead to reduced calcium absorption from the intestine and increased PTH concentrations from the parathyroid gland. This sequence of physiologic events initially returns serum calcium concentrations toward "normal" (CKD patients are usually normocalcemic or less commonly hypocalcemic). If renal dysfunction progresses, these processes may become insufficient to support serum calcium concentrations and hypocalcemia develops. Thus, the hallmarks of CKD are azotemia, hyperphosphatemia, normocalcemia or mild hypocalcemia and isosthenuria. However, a small proportion of dogs and cats with CKD become hypercalcemic. The etiology of hypercalcemia in patients with CKD is poorly understood but may be due to autonomous secretion of PTH, a raised set point for calcium autoregulation or increased binding of calcium to retained anions (see Table 69-2).

Hypoadrenocorticism

Approximately 30% of dogs with hypoadrenocorticism are hypercalcemic when first examined.[17,18] Total and ionized hypercalcemia, when it occurs, tends to be mild. PTH, PTHrP and vitamin D metabolites are typically within reference ranges.[19,20] Hypercalcemia does tend to occur in patients with the highest potassium concentrations and usually quickly resolves with therapy. Unpublished data suggest that resolution of hypercalcemia in these patients follows fluid resuscitation together with glucocorticoid and mineralocorticoid replacement therapy.

Other Causes

Young healthy animals often have mild hypercalcemia and hyperphosphatemia when utilizing adult reference intervals. Hypercalcemia can follow ingestion of vitamin D–containing rodenticides, consumption of certain topical psoriasis preparations for people, overzealous dietary supplementation, or during vitamin D treatment of hypoparathyroidism.[6,21,22] Vitamin D increases gastrointestinal absorption of calcium and phosphate. Excessive vitamin D can lead to hypercalcemia, hyperphosphatemia, increased ionized calcium concentrations and suppressed PTH concentrations. Hypercalcemia is occasionally associated with granulomatous diseases such as blastomycosis, aspergillosis and schistosomiasis.[23-25] The cause of hypercalcemia associated with granulomatous diseases is likely an excessive production of $1,25(OH)_2D$ by

macrophages or via synthesis of PTHrP.[7,26]

Hypercalcemia in Cats

Review

Many causes of hypercalcemia in cats are the same as those discussed for dogs. There are also some important differences. The most common clinical signs in hypercalcemic cats are anorexia and lethargy, with polydipsia and polyuria less common (see Table 69-1). Malignancy and kidney disease are common causes of hypercalcemia in cats.[27] Squamous cell carcinoma was associated with hypercalcemia as frequently as was lymphoma.[17,27] Adenocarcinoma of the anal sac apocrine glands is rare and hypoadrenocorticism is uncommon in cats.[28,29]

Idiopathic hypercalcemia is an important differential in cats.[30] This diagnosis is reserved for cats where the underlying cause of the hypercalcemia cannot be identified despite extensive diagnostic evaluation and long-term follow-up. Both total and ionized calcium concentrations are moderately increased, PTH concentrations are normal-to-low, and PTHrP concentrations normal. It is important to rule out known causes of hypercalcemia in these cats prior to symptomatic treatment (see ch. 297).[30,31]

Diagnostic Approach to Hypercalcemia

A thorough history should be obtained and assessed followed by a careful physical examination in all hypercalcemic animals (Figure 69-1). Duration of any signs and the potential for access to toxins or medications containing vitamin D should be determined. Severity of illness may contribute to prioritizing potential causes. The peripheral lymph nodes should be assessed for size and the anal sac areas carefully palpated. Any enlarged lymph nodes should be fine-needle aspirated or biopsied. Consideration should be given to aspiration or biopsy of any other palpable mass, since malignancies and granulomatous lesions can cause hypercalcemia.

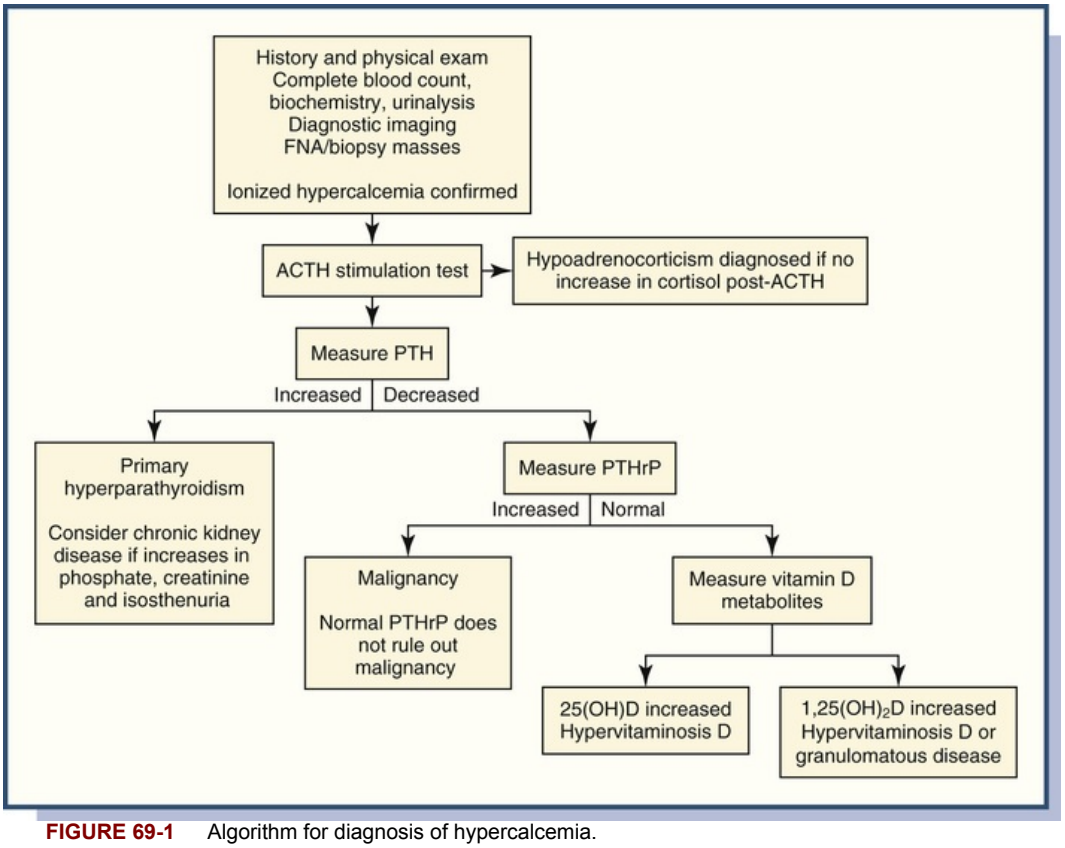

FIGURE 69-1 Algorithm for diagnosis of hypercalcemia.

Serum biochemistry results are invariably informative. Particular attention should be paid to electrolytes, albumin, urea (BUN), phosphate and creatinine concentrations. Evaluation of urine specific gravity is also valuable. However, urine specific gravity results from patients with CKD (usually isosthenuric) may not be different from those with hypoadrenocorticism or hypercalcemia due to PTH or PTHrP-driven conditions, who also may be isosthenuric (see ch. 324). Hypoadrenocorticism should be considered whenever hypercalcemia is documented in a dog or cat with hyperkalemia. An adrenocorticotropic hormone (ACTH) stimulation test should be considered when appropriate (see ch. 309).[18]

Thoracic imaging is of value since mediastinal cancers, such as lymphoma and thymoma, can be visualized and are the most common causes of hypercalcemia (see ch. 344 and 352). Abdominal ultrasonography may help to identify neoplastic or granulomatous lesions. Aspirates or biopsies of any abdominal masses may be helpful (see ch. 89). Ultrasonography of the ventral neck region may be helpful since a parathyroid nodule is frequently observed in cases of primary hyperparathyroidism (see ch. 297). Results of PTH and PTHrP assays may allow the clinician to understand the pathogenesis of hypercalcemia and may be necessary for confirming a diagnosis (see Figure 69-1). If available, reliable, and cost-effective, vitamin D metabolite assay results will also be of value.

Hypocalcemia

Overview and Clinical Signs

Hypocalcemia is caused by a relatively small number of conditions. Clinical signs may vary slightly depending on underlying cause. Some animals are asymptomatic despite low circulating calcium concentrations, but most exhibit signs directly attributable to hypocalcemia-induced increases in neuronal excitability. These signs include nervousness, behavioral changes, focal muscle twitching (especially ear and facial muscles), facial rubbing, chewing at the paws, muscle cramps, stiff gait, tetany and seizures (see ch. 298). Exercise, excitement and stress may induce or worsen clinical signs. Additional abnormalities include fever, cataracts and cardiac arrhythmias.

Causes of Hypocalcemia

Hypocalcemia has been reported in a variety of clinical conditions and occurs when there is either impaired PTH secretion or action, impaired vitamin D synthesis or action or in cases of calcium precipitation or chelation (Box 69-2).

Box 69-2

Conditions Associated with Hypocalcemia

Common Causes

Hypoalbuminemia
Acute and chronic renal failure
Hypoparathyroidism
Eclampsia
Protein-losing enteropathies
Pancreatitis
Exocrine pancreatic insufficiency
Trauma
Systemic inflammatory response syndrome

Uncommon Causes

Phosphate-containing enemas
Tumor lysis syndrome
Hypomagnesemia
Nutritional secondary hyperparathyroidism

Hypoalbuminemia

Hypoalbuminemia is a common cause of hypocalcemia which can occur secondary to protein-losing enteropathies, protein-losing nephropathies or liver disease. This hypocalcemia is not typically of clinical significance unless circulating ionized calcium concentrations are decreased, which can occur in dogs with a protein-losing enteropathy (see ch. 276).[32]

Impaired PTH Secretion

Naturally-occurring idiopathic primary hypoparathyroidism, rare in dogs and cats, can result in severe hypocalcemia.[33,34] Iatrogenic hypoparathyroidism may follow accidental damage or removal of parathyroid glands during cervical surgery, most commonly thyroid surgery in cats (see ch. 298).

Increased Calcium Loss

Eclampsia (lactation-induced hypocalcemia) occurs most commonly in young small dogs and is relatively rare in large dogs or in cats. Clinical signs are usually seen 2-5 weeks post-whelping, although it has been reported in a few dogs during late gestation and others >5 weeks post-whelp. Other potential causes include parathyroid gland atrophy and poor dietary supply of calcium.[35]

Vitamin D Deficiency

CKD in both dogs and cats may lead to mild decreases in ionized calcium concentrations but total calcium concentrations are typically within reference intervals (see ch. 324).[36] Reduced intestinal absorption of vitamin D in dogs and cats with protein-losing enteropathy or exocrine pancreatic insufficiency may lead to hypocalcemia.[32,37] Inadequate dietary vitamin D is a rare cause of hypocalcemia.

Precipitation or Chelation of Calcium

Ethylene glycol toxicosis results in calcium binding with oxalic acid in the renal tubules. This causes calcium oxalate crystalluria and increased renal loss of calcium. In acute kidney injury (AKI), rapidly rising phosphate complexes with calcium leading to hypocalcemia. Increased renal tubular loss of calcium exacerbates hypocalcemia. Urinary tract obstruction may cause mild-to-moderate hypocalcemia, likely due to increased binding of calcium with phosphate. Phosphate enemas have been reported to cause hypocalcemia in cats, again due to rapidly rising serum phosphate levels. In the acute tumor lysis syndrome, hypocalcemia may occur. In pancreatitis, hypocalcemia may result from sequestration of calcium in peripancreatic fat or soft tissues as a result of saponification (see ch. 289-291).[38] Hypocalcemia may follow citrated blood transfusion due to chelation of calcium.

Diagnostic Approach to Hypocalcemia

There are relatively few common causes for hypocalcemia. Findings on history, physical examination, hematology, biochemistry and urinalysis are often quite helpful or sufficient in establishing a diagnosis. Serum bile acids may be helpful in evaluating liver function and trypsin-like immunoreactivity and/or canine pancreatic lipase may be useful if pancreatic disease is suspected. Abdominal imaging may be helpful in evaluating anatomy of the gastrointestinal tract, liver, pancreas, and kidneys. A measurement of circulating parathyroid hormone concentration is required to definitively confirm primary hypoparathyroidism (see ch. 298).

Phosphorus

Overview

Phosphorus is essential for normal cellular function and is the body's major intracellular anion. The majority of total body phosphorus is found in bone. Although phosphorus is present in both organic and inorganic forms in the plasma, most clinical laboratories measure inorganic phosphate. Phosphorus absorption and excretion is regulated with calcium. PTH decreases phosphorus reabsorption in the kidney and $1,25(OH)_2D$ increases gastrointestinal absorption of phosphate.

Hyperphosphatemia

Hyperphosphatemia indicates the presence of an underlying disease and only rarely causes clinical signs by

itself unless associated with significant hypocalcemia. Hyperphosphatemia can occur due to increased intestinal phosphorus absorption, decreased phosphorus excretion via the kidneys into urine, or after a shift in phosphorus from the intracellular to extracellular compartment. CKD is the most common cause of hyperphosphatemia in dogs and cats (Box 69-3). Other causes of hyperphosphatemia include hypervitaminosis D, urinary tract obstruction, AKI, hypoparathyroidism and hyperthyroidism.

Box 69-3

Conditions Associated with Hyperphosphatemia

Common Causes

Young growing healthy animals
Hypervitaminosis D
AKI or CKD
Hypoparathyroidism

Uncommon Causes

Excessive dietary intake
Osteolytic bone lesions
Uroabdomen
Hyperthyroidism
Hyperadrenocorticism
Metabolic acidosis
Tumor cell lysis syndrome
Iatrogenic: e.g., phosphate-containing enemas, IV phosphorus administration
Lab error

Hypophosphatemia

Hypophosphatemia can occur due to decreased intestinal absorption, increased renal excretion or from transcellular shifts. Hypophosphatemia is commonly associated with excesses in circulating PTH or PTHrP, e.g., primary hyperparathyroidism and malignancy, respectively. Hypophosphatemia also occurs secondary to treatment of diabetic ketoacidosis (Box 69-4). Mild hypophosphatemia is not typically associated with clinical signs, although marked hypophosphatemia can be associated with hemolysis, respiratory distress and neurological abnormalities.

Box 69-4

Conditions Associated with Hypophosphatemia

Common Causes

Primary hyperparathyroidism
Malignancy-associated hypercalcemia
Diabetic ketoacidosis

Uncommon Causes

Vitamin D deficiency
Decreased dietary intake
Renal tubular disorders
Respiratory and metabolic acidosis
Iatrogenic: e.g., phosphate binders, parenteral glucose or sodium bicarbonate administration

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CHAPTER 70

Lactate

Kari Santoro Beer

Introduction

Lactate is the end-product of anaerobic metabolism, although small amounts are also produced during normal aerobic glycolysis. An elevated plasma lactate level in the absence of a metabolic acidosis is termed hyperlactatemia; lactic acidosis is characterized by an elevated plasma lactate concentration in conjunction with a decrease in systemic blood pH.[1-3] Hyperlactatemia and lactic acidosis are common in states of hypoperfusion and hypoxia, and have also been reported in association with other conditions (sepsis, neoplasia, drugs/toxins, mitochondrial dysfunction, inborn errors of metabolism).[4-6] Clinically, measurement of serum lactate has demonstrated utility in assessing tissue perfusion and oxygenation, as a risk stratification tool, and for predicting outcome or response to therapy in critically ill human patients.[7] Recent studies suggest that lactate measurement may have similar applications in veterinary medicine.[8-11]

Lactate Physiology and Metabolism

A small amount of lactate is produced under normal aerobic conditions, in which glucose is converted to pyruvate in the cell cytoplasm. Most of this pyruvate diffuses into the mitochondria, where it is eventually converted to CO_2 and H_2O via the Krebs cycle. The following net reaction summarizes aerobic oxidation of glucose: Glucose + 6 O_2 + 36 ADP → 6 CO_2 + 36 ATP + 42 H_2O.[5] However, in cells that do not contain mitochondria, such as red blood cells, pyruvate is converted to lactate by the enzyme lactate dehydrogenase (LDH). This reaction allows NADH to be oxidized back to NAD^+ so that glycolysis can continue: CH_3COCOO^- (pyruvate) + NADH + H^+ ↔ $CH_3CHOHCOO^-$ (lactate) + NAD^+.[8] Normal daily lactate production in humans is around 1300-1800 mmol/day, with the arterial lactate concentration reflective of net production and clearance, generally 0.5-1 mmol/L.[3,12,13] In dogs, the current reference range is 0.3-2.5 mmol/L; in cats, 0.5-2.0 mmol/L.[14,15]

During anaerobic conditions, glycolysis is much less efficient and total energy production is significantly reduced compared to aerobic metabolism. Anaerobic glycolysis of 1 mole of glucose occurs as follows: Glucose + 2 ADP → 2 $lactate^-$ ions + 2 ATP + 2 H_2O.[5] As lactate is produced from pyruvate in hypoxic cells, it crosses the cell membrane and diffuses into the blood. The formation of lactate with free hydrogen is favored at physiologic pH, and while hydrogen ions are initially titrated by body buffers, acidemia eventually occurs as lactate accumulates.[3,4,8]

The liver and kidneys are responsible for the majority of lactate metabolism and clearance. Other tissues such as skeletal muscle remove the remainder.[5] While lactate is freely filtered at the glomerulus, it is almost completely resorbed in the proximal tubule. Elevated blood lactate levels will increase urinary excretion of lactate, but this accounts for only 10-12% of lactate clearance in the kidneys and the remainder is metabolized to glucose during gluconeogenesis.[8] Renal and liver dysfunction have been associated with varying levels of reduced clearance.[12]

While all tissues in the body produce some lactate, the greatest producers are skeletal muscle, brain, heart, skin, intestine and red blood cells.[4,6,16] In critically ill patients, lactate production also occurs in the splanchnic organs, in the lungs during acute lung injury, and from leukocyte activation during sepsis.[7]

Two forms of lactate exist: L-lactate and D-lactate. The most commonly measured, L-lactate, is the levorotatory isomer and is produced by cellular metabolism in healthy monogastric animals. D-lactate, the dextrorotatory isomer, is produced during bacterial glucose metabolism or from alternate metabolic

pathways in some cases of intoxications or certain diseases.[7] While D-lactic acidosis is uncommon in monogastric animals, it has been reported in a cat with exocrine pancreatic insufficiency,[15] and in cases of diabetes mellitus, propylene glycol intoxication, and intestinal bacterial overgrowth.[8,17,18] While commercial lactate analyzers only measure L-lactate, total plasma lactate (including D- and L-lactate) can be measured using gas chromatography and mass spectrometry. In patients with an acidosis and gastrointestinal disturbance but normal L-lactate, increased D-lactate should be investigated.[8,18]

Lactic Acidosis: Types and Causes

Lactic acidosis occurs when production of lactate exceeds utilization and clearance, and results in an elevated plasma lactate concentration with a decrease in arterial pH to less than 7.35.[2,8,16] There are two major types of lactic acidosis: type A and type B. Common causes of each type are described in Table 70-1.

TABLE 70-1

Causes of Lactic Acidosis in Veterinary Medicine[1,8]

TYPE OF LACTIC ACIDOSIS	MECHANISM	CAUSES
Type A	Tissue hypoxia or hypoperfusion	Decreased O_2 delivery Anemia (PCV <10%) or severe hypoxemia (PO_2 <30 mm Hg) Shock: cardiogenic, hypovolemic, septic Regional hypoperfusion Global hypoperfusion Carbon monoxide toxicosis Increased O_2 demand Exercise Seizures Uncontrolled shivering
Type B1	Decreased lactate clearance	Liver disease Diabetes mellitus Sepsis, SIRS Renal failure Hyperthyroidism Neoplasia Alkalosis
Type B2	Drugs or toxins that interfere with oxidative phosphorylation	Ethylene glycol Propylene glycol Catecholamines Carbon monoxide Bicarbonate Salicylates Acetaminophen Others: cyanide, strychnine, nitroprusside, halothane, terbutaline, activated charcoal
Type B3	Mitochondrial defects	Mitochondrial myopathies Inborn Acquired
D-lactic acidosis	Production of D-lactate from bacterial glucose metabolism or alternate metabolic pathways	Diabetes mellitus Small intestinal bacterial overgrowth Exocrine pancreatic insufficiency Propylene glycol toxicosis

PCV, Packed cell volume; *SIRS*, systemic inflammatory response syndrome.

Type A lactic acidosis is the most common and is caused by tissue hypoxia and increased lactate

production due to anaerobic glycolysis. Common causes of tissue hypoxia include hypoperfusion from hypovolemia or decreased cardiac output, severe anemia and decreased blood oxygen content, or decreased ability of the tissues to move oxygen from the capillaries as with severe edema.[19]

Type B lactic acidosis is less common and occurs when oxygen delivery is adequate but there is altered mitochondrial function or carbohydrate metabolism. There are three subtypes of B lactic acidosis: B1 includes diseases that cause decreased lactate clearance; B2 includes drugs or toxins that interfere with oxidative phosphorylation; and B3 includes mitochondrial defects.[8]

While type A lactic acidosis is often the most common cause of hyperlactatemia in critically ill patients, both types likely exist together in many patients. A number of factors may contribute to both type A and type B lactic acidosis, including tissue hypoperfusion, increased metabolism due to inflammation, decreased lactate clearance and decreased entry of pyruvate into the Krebs cycle, and impaired mitochondrial function.[1,7,8]

Lactate Measurement

As lactate's use as a monitoring tool has increased, new point-of-care analyzers with improved speed, accuracy and ease of use have been developed. These tools may be useful clinically as a recent human study demonstrated improved clinical outcomes for critically ill patients when a more rapid turnaround time for lactate results was possible.[20]

There are two methods used to measure lactate: enzymatic colorimetry and enzymatic amperometry. In blood chemistry analyzers, enzymatic colorimetry is used, which measures NADH production when L-lactate is oxidized by NAD+ when catalyzed by LDH. The NADH is detected by spectrometric absorption at 340 nm and is proportional to the amount of lactate in the sample. Enzymatic amperometry is commonly used in most blood gas analyzers and it measures lactate based on the amount of hydrogen peroxide produced by the reaction of L-lactate with a lactate oxidase-containing membrane; an electrical potential is applied and the hydrogen peroxide is oxidized, creating an electron current that is proportional to the lactate level in the sample.[21,22]

A number of factors can affect blood lactate measurements. While sampling site (venous versus arterial) does not seem to result in clinical differences,[8,14,23-25] other factors including recent exercise, stress, seizures, excitement, food intake and prolonged venous stasis during collection can all increase lactate concentrations by 2.5-10 mmol/L.[1,26] In neonatal puppies (less than 28 days old), venous lactate concentrations may be significantly higher than in adult dogs, with values normalizing to adult reference ranges by 70 days of age. Increased lactate in puppies is hypothesized to be secondary to ischemia-reperfusion injury during birth, higher baseline levels to prevent hypoglycemia, and decreased hepatic clearance.[27] In cats, stress at the time of sampling may increase lactate levels, with one study demonstrating a 10-fold increase in healthy cats that were stressed before sample collection.[28] However, a more recent study showed that struggling during sampling did not cause statistically significant differences in lactate concentrations in cats.[29]

Ethylene glycol and propylene glycol can both increase lactate measurements. Ethylene glycol causes a false increase in lactate when measured using enzymatic amperometry because a major metabolite of ethylene glycol, glycolate, is chemically similar to lactate.[30] Propylene glycol is metabolized to L-lactate and D-lactate, and elevated lactate concentrations have been reported in dogs given activated charcoal containing propylene glycol.[17,31] Lactated Ringer's solution (LRS) is a balanced electrolyte solution commonly used in veterinary patients, and it contains a racemic mixture of D- and L-lactate.[32] The L-lactate in LRS is metabolized to glucose or oxidized to water and CO_2, both of which result in the consumption of hydrogen ions and an overall alkalinizing effect. Administration of LRS does not typically cause an increase in lactate,[1,33-35] although small amounts of LRS in catheters at the time of sample collection can result in increases in measured lactate.[8,24]

Clinical Utility and Applications in Veterinary Medicine

Lactate monitoring is commonly used in human patients to guide treatment and for prognostication purposes, based on the idea that severity of lactic acidosis is correlated with severity of disease, extent of tissue hypoperfusion and overall decrease in oxygen delivery.[16,36] In human patients, as blood lactate concentrations increase, the probability of survival decreases,[37-42] and patients with a lactic acidosis have a

higher mortality rate and are at a greater risk of developing multiple organ failure.[43,44] Because even mild lactate elevations have been correlated with worse outcomes in human patients, especially those with sepsis or septic shock, any elevation should be a cause for concern; the accepted threshold in human guidelines for early goal-directed therapy and care bundles is traditionally 4 mmol/L.[12,45-47]

More recently in human medicine, the emphasis has been placed on monitoring serial lactate concentrations. Studies in human patients have consistently demonstrated that patients who clear elevated lactate levels have improved outcomes compared to those who do not clear their lactate, and slower lactate clearance is associated with worse outcomes.[41,43,48-52] In one multicenter trial of septic human patients, those with a lactate clearance of ≥10% decrease from their initial measurement had a 41% decrease in mortality compared to those with lesser clearance.[49]

In veterinary medicine, the majority of lactate studies have been limited to dogs. Overall, measurement of lactate concentrations using venous samples has demonstrated that lactate in veterinary patients, similar to human patients, can be used to identify hypoperfusion and assess response to therapy.[9-11,14,53-55]

Elevated lactate levels have been documented and correlated with disease severity and survival in critically ill and injured dogs, including those with gastric dilatation-volvulus, babesiosis, and immune-mediated hemolytic anemia.[9-11,53,56,57] A number of these studies and several others have also supported monitoring of lactate over the course of treatment, with lactate clearance being associated with improved outcomes.[53,57-59]

Analysis of lactate in body fluids other than blood also has demonstrated diagnostic utility in veterinary medicine.[54,55] In dogs and cats with septic peritonitis, comparing peritoneal fluid and peripheral blood lactate and glucose measurements can aid in diagnosis. A blood-to-fluid glucose difference of >20 mg/dL was found to be 100% sensitive and specific for the diagnosis of septic effusion in dogs and 86% sensitive and 100% specific in cats. Septic peritoneal fluid also had higher lactate concentrations than peripheral blood, with a fluid-to-blood lactate difference of >2 mmol/L suggestive of septic peritonitis.[54] Comparisons of lactate levels have also been made in dogs with pericardial effusion, and while dogs with confirmed neoplasia had significantly higher pericardial effusion lactate levels, the difference was not helpful clinically due to overlap between the groups.[55]

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CHAPTER 71

Ammonia

Allison Bradley

Ammonia is produced in the gastrointestinal tract through bacterial degradation of nitrogenous compounds. It is carried up the portal circulation to hepatocytes, where the urea cycle detoxifies the ammonia, allowing for urea excretion by the kidneys. When this process cannot occur, either due to fulminant hepatic failure or, more commonly, due to portosystemic shunting (PSS), hyperammonemia results. Although many toxins have been implicated in the pathogenesis of hepatic encephalopathy (HE), ammonia is the only readily measured factor and is often regarded as one of the most important. However, not all patients with HE have hyperammonemia[1,2] and not all hyperammonemic patients exhibit overt HE.[1]

The most common indications for measuring ammonia are corroboration of suspicion of HE and to screen for PSS (Figure 71-1). Findings of different studies vary, but in general, resting ammonia is thought to be less sensitive than paired bile acids for identification of PSS.[3] Reported sensitivity of resting ammonia for detection of PSS is 62-100% compared to 79-100% for paired bile acids in dogs (80-100% for ammonia compared to 94-100% for bile acids in cats).[1,4-9] Ammonia measurement is, however, more specific for PSS than bile acids, because ammonia levels are not affected by cholestasis, which occurs to some extent in almost all hepatobiliary diseases.[10] Reported specificity of resting ammonia when screening for PSS is 86-89% (76% in the cat), whereas the specificity of bile acids in diagnosing PSS is 18-68% (71% in the cat).[4,8] Ammonia is less sensitive than bile acids for hepatobiliary disease not associated with PSS. Because the liver has a large reserve capacity for detoxifying ammonia, a majority of functional tissue must be lost before hyperammonemia results; therefore, ammonia measurement is an insensitive test for hepatic dysfunction.[10] Ammonia measurement may be useful in testing icteric animals (in which bile acids will be useless) for evidence of hepatic dysfunction or PSS and for confirming the benign bile acid elevations seen in some Maltese dogs and with portal vein hypoplasia.[11] Other causes of hyperammonemia are listed in Box 71-1.

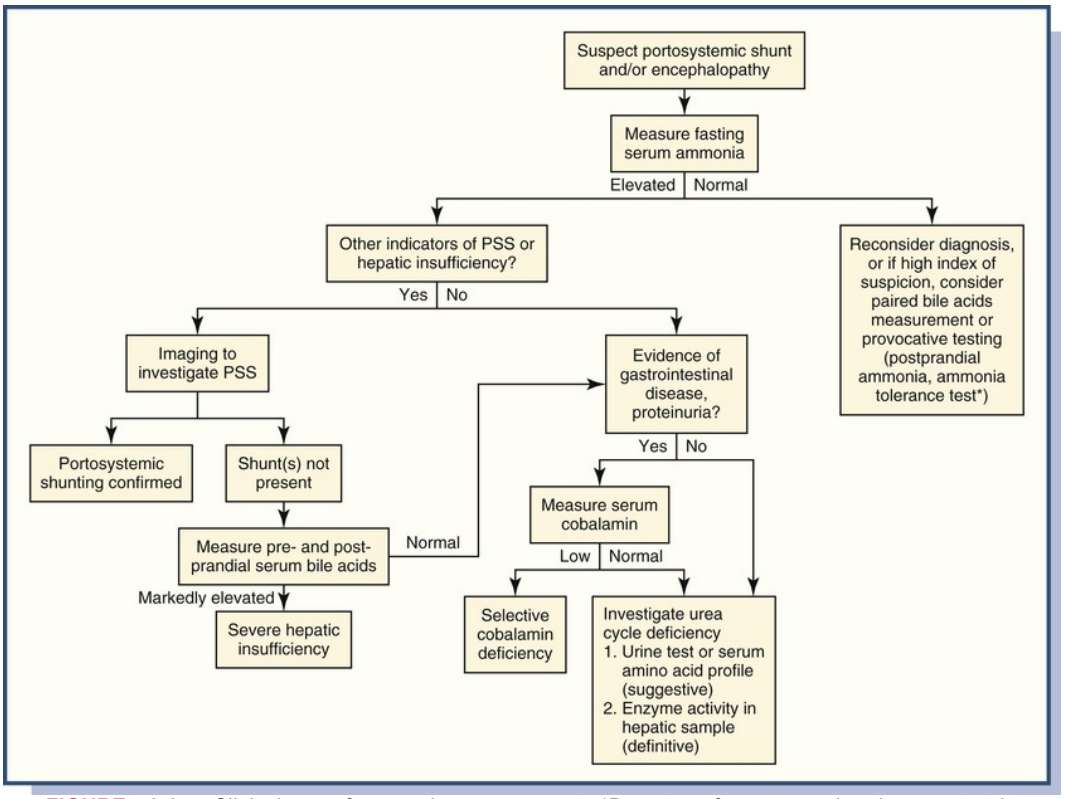

FIGURE 71-1 Clinical use of ammonia measurement. *Do not perform ammonia tolerance test in encephalopathic patients.

Box 71-1

Causes of Hyperammonemia

Portosystemic shunt—congenital or acquired
Fulminant hepatic failure
Urea cycle defect
- Transient and asymptomatic (e.g., Irish Wolfhound puppies)[12,13]
- Persistent enzyme deficiency[14,15]
- Selective cobalamin deficiency[16]
- Arginine deficiency (cats)[17]

Urinary tract obstruction especially in conjunction with urease-producing bacteria[18]
L-asparaginase therapy[19]

There is a variety of technical considerations for completing an ammonia measurement that limit its use in many settings. Although arterial blood contains higher concentrations of ammonia,[20] venous samples are more widely used. A 12-hour fast is typical prior to sample acquisition. The blood must be drawn into a tube containing anticoagulant (EDTA or heparin) and cooled immediately on ice (some authors advocate pre-chilling the tube as well). The blood must then be separated in a cooled centrifuge within 20-30 minutes. The assay should also be performed within 20-30 minutes. Sample storage and shipping is not advised.[21] Point-of-care analyzers available in some markets eliminate the need for complicated sample handling, but their quality is variable and only some yield accurate results.[22,23]

Pre-analytical and analytical errors reported to cause false positive results include: hemolysis, failure to adhere to rapid sample cooling and processing, ammonia or cigarette smoke in the air, and sweat or saliva contacting the sample tube stopper or reagent strips.[10] Patient factors reported to cause false positive results include: use of valproic acid, asparaginase, narcotics, and ammonium salts; hyperalimentation; a high protein

meal or gastrointestinal bleeding; strenuous exercise; hypokalemia; and alkalosis. Factors associated with false negative results include administration of antibiotics, probiotics, lactulose, enemas, and diphenhydramine.[3] Prolonged fasting has also been reported to result in false negative results.[24]

The sensitivity of the resting ammonia test can be improved by performing an ammonia tolerance test (ATT). Although this test is typically safe,[10] caution is advised, as it may result in vomiting (rectal administration of the ammonium chloride reduces this side effect[10]) as well as HE. An ATT should not be performed in a patient with HE or resting hyperammonemia. The details of performing an ATT have been described elsewhere.[1,3,10,25] Six-hour postprandial ammonia measurement has also been reported to increase the sensitivity of resting ammonia and may be safer[9] but less definitive than the ATT.[10]

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CHAPTER 72

Urinalysis

Peter A. Graham

Overview and Indications

The urinalysis (UA), inexpensive and easily performed, is a minimum database component that often provides crucial information to assist with diagnosis and/or patient management. Urine is the combined result of glomerular filtration plus renal tubular resorption and secretion and its analysis can provide insight to both urinary and systemic conditions. Since UA results cannot be predicted, it is reasonable to suggest that it should be included in routine screening and in any disease investigation. The most obvious need for UA is dogs and cats with polyuria and polydipsia (PU/PD); urinary tract signs (dysuria, hematuria, stranguria, pollakiuria); a history of urinary tract disease, infection, acute kidney injury (AKI), chronic kidney disease (CKD), current or previous urolithiasis; or systemic illness. Fanconi syndrome, urinary tract cancer and specific non-urinary conditions such as diabetes mellitus, diabetes insipidus, hemolytic disease and hepatic dysfunction may be better understood after reviewing UA results. When used for screening asymptomatic dogs or cats, dilute urine, proteinuria or crystalluria can indicate the need for a change in management or further investigation. UA results may be helpful in monitoring and in early detection of side-effects to medications that may impair renal function or damage renal tissue. Interpreting UA results in the context of serum biochemistry (SB) and complete blood count (CBC) results enhances value of each.

Collection and Care of Urine Samples

Reliable UA results require that the sample be collected and handled appropriately. Collection method may alter UA results or interpretation. For example, urine collected from a table-top may contain micro-organisms or chemical cleaning agents while cystocentesis samples are free from environmental and lower urinary tract contaminants, but small numbers of red blood cells (RBCs) from the needle causing bleeding may be seen (see ch. 105).

Urine should be analyzed within 30-120 minutes of collection. Delay in analysis of room temperature urine may cause changes in pH, allow growth of contaminating bacteria, cause loss of cellular detail, or result in disintegration or deterioration of casts. Refrigeration may promote precipitation of crystals. For chemical analyses only, urine may be frozen. Both refrigerated and frozen urine samples must be rewarmed to room temperature before analysis. Samples shipped to an external laboratory should contain suitable preservative, particularly if culture is to be requested. Tubes containing boric acid assist in preserving most aspects of UA, but not pH or specific gravity (USG).

Urine samples must be gently mixed before a standardized volume (allowing semi-quantitative comparisons) is centrifuged in a conical tube for sediment examination. Urine test dipsticks can be employed before centrifugation. A relative centrifugation force (RCF) of 400-450 for 5 minutes is recommended. Sometimes, dipstick results should be repeated on the supernatant, as with visibly turbid or bloody samples. The elements of a standard UA (physical, chemical, and microscopic properties), dipstick results and reference values are important aspects of urinalyses (E-Box 72-1; E-Tables 72-1 and 72-2).

E-Box 72-1

Elements of a Urinalysis

Physical

Visual examination (color and turbidity)
Specific gravity

Chemical

pH
Protein
Glucose
Ketones
Bilirubin
Blood

Microscopic

Sediment
- Blood
- White cells
- Epithelial cells
- Bacteria
- Casts
- Crystals

E-TABLE 72-1

Usefulness of Common Dipstick Reagent Pads

USEFUL	BETTER TECHNIQUE AVAILABLE	NOT USEFUL/UNRELIABLE
Glucose Bilirubin Ketones Blood pH Protein	Specific gravity—dipstick pads for urine specific gravity do not give reliable results for veterinary samples pH—a pH meter used at the time of sampling will give more accurate results than those from a dipstick pad or a meter used at a reference lab Blood and leukocytes—a more useful method to look for and quantitate hematuria and pyuria is microscopic sediment examination	Specific gravity Urobilinogen Nitrite Leukocytes

E-TABLE 72-2

Expected Findings in Healthy Canine and Feline Urine (Semi-Quantitative Sediment Values Will Vary by Lab Protocol)

EXPECTED FINDINGS	CANINE	FELINE
Color	Yellow to amber	Yellow to amber
Turbidity	Clear	Clear
Specific gravity	Typical: 1.015-1.050	Typical: 1.035-1.060
pH	Typical: 5.5-7.5	Typical: 5.5-7.5
Protein	Negative, 1+ in concentrated urine	Negative
	UPCR <0.2 Borderline: 0.2-0.4	UPCR <0.2 Borderline: 0.2-0.3
Glucose	Negative	Negative
Ketones	Negative	Negative
Bilirubin	0-1+	Negative
Blood	Negative	Negative
Sediment		
Erythrocytes	<5 catheter	<5 catheter

(/hpf)	<3 cystocentesis (more if needle trauma)	<3 cystocentesis (more if needle trauma)
Leukocytes (/hpf)	<5 catheter <3 cystocentesis	<5 catheter <3 cystocentesis
Other cells	Few transitional epithelial	Few transitional epithelial
Bacteria	None	None
Casts (/lpf)	<2 hyaline	<2 hyaline
Crystals	Variable but can include struvite and calcium oxalate (urate in Dalmatians)	Variable but can include struvite and calcium oxalate
Lipid	Uncommonly encountered	Commonly encountered

Physical Analysis

Visual Examination (Color, Turbidity, Odor)

Urine color is often related to hydration or renal status since it crudely correlates to concentration. In general, absence of color or pale urine is consistent with a dilute USG. Most concentrated samples are deep yellow or yellow-brown. Because bilirubinuria can appear as dark yellow urine, color should be interpreted in the context of USG and blood test results. The oxidation product of bilirubin, biliverdin, imparts a green color while hematuria, hemoglobinuria, myoglobinuria, and Oxyglobin cause urine to be red, pink, orange, dark brown or black. Urine pigments may interfere with dipstick test results (see ch. 47).

Urine transparency or turbidity should be reported semi-quantitatively. Turbidity can result from excessive white blood cells (WBCs), RBCs, epithelial cells, sperm, casts, mucus, crystals, bacteria, or lipid in urine. Lipiduria and pyuria occasionally appear milky, with lipid sometimes causing the surface of an unmixed sample to look cloudy. Turbidity may increase if analysis is delayed. Cooling and pH change can lead to crystal precipitation. Warming cooled samples may provide more accurate sediment examination. Fresh normal urine has a slight odor of ammonia, which increases with time or with some infections. An acetone smell is consistent with ketonuria.

Urine Specific Gravity (USG) and Osmolality

USG is the first and arguably most important test performed after initial visual inspection and is the only result that can provide information on renal function. Technically, USG is the ratio of urine weight to that of distilled water as estimated by its refractive index. The refractive index may be influenced by temperature and the number, type and size of solute molecules. Temperature effect is moderated in refractometers by mechanisms in the apparatus. Veterinary refractometers should have a separate scale for cat and dog urine, because their refractive indexes are distinct.[1]

Osmolality (see ch. 45 and 67) is the measurement of solute concentration independent of molecule type. USG and osmolality are closely related but osmolality, a more reliable indicator of renal concentrating ability, is recommended for estimating urine concentration in provocative tests.[2] One molecule of glucose and one molecule of albumin exert the same osmotic effects, but the higher weight of a protein results in greater effect on USG than does glucose. In the ratio of urine to plasma osmolality, >1 is consistent with renal concentrating and <1 renal diluting capability. If USG is above the refractometer's range, the sample may be diluted 50 : 50 with distilled water. This result can then be doubled, i.e., diluted 1.035 equals an undiluted result of 1.070. Dipstick USGs are not recommended.

No "reference range" exists for USG since healthy kidneys can produce extremely dilute or extremely concentrated urine ranging from 1.001 to >1.075. USG is influenced by hydration, electrolyte status, diet, and individual variation (E-Table 72-3).[3,4] Administration of fluids, glucocorticoids or diuretics lowers USG. Knowing hydration status, recent therapies, presence of protein or glucose in the urine, blood urea nitrogen and serum creatinine concentrations enhances the quality of any USG interpretation.

E-TABLE 72-3

Urine Specific Gravity Values

Typical values	1.015-1.050 Dog 1.035-1.060 Cat	Equivalent to 450 to 2000 mOsm (dogs), 1500 to 2000 mOsm (cats). These are estimated ranges only. Results can be affected by canned vs. dry diet, etc. Normal animals may have results outside these ranges.
Lowest to highest	1.001-1.070 Dog 1.001-1.080 Cat	Occasionally, higher USGs can be observed.
Isosthenuria	1.008-1.012	Approximately 300 mOsm. Urine and plasma osmolality are similar (urine is neither concentrated nor diluted). Normal animals may have a USG in this range but persistent findings in this range or if in combination with azotemia or dehydration indicate that failure of renal function is likely.
Hyposthenuria	<1.008	Urine is more dilute than plasma and therefore there must be renal tubular function. Central and nephrogenic diabetes insipidus are differentials as are conditions that interfere with the concentration of urine such as hypercalcemia, sepsis (e.g., pyometra, pyelonephritis), hepatic disorders, hypoadrenocorticism, hyperadrenocorticism and psychogenic polydipsia.
Evidence of adequate renal concentrating ability in azotemic or dehydrated animal	>1.040 Dog >1.045 Cat	Some authors suggest USG 1.030 for dog and 1.035 for cats; it would be prudent to consider USGs between these limits as questionable in terms of renal concentrating ability. When USG > 1.035 (dogs) or > 1.040 (cats) is present in combination with azotemia, the azotemia is classified as pre-renal.
Possible renal or extra-renal impairment of concentrating ability in azotemic or dehydrated animal	1.007-1.029 Dog 1.007-1.039 Cat	Primary renal failure is likely in azotemic patients but further investigation is warranted. When dehydration (or polyuria) is present in the absence of azotemia, extra-renal causes of polydipsia in addition to primary renal failure are possible differential diagnoses.

Chemical Analysis

pH

Urine pH usually reflects total body acid-base balance. It may be influenced by diet, time of day and disease (E-Table 72-4). High protein (e.g., meat) diets acidify while vegetable or cereal based diets alkalinize urine (see ch. 185). Urine obtained after a meal is often alkaline due to gastric acid secretion. Urine dipstick pH pads estimate to the nearest 0.5 or 1 unit, which is adequate for clinical use. A pH meter might provide more accurate results.[5,6] Results, regardless of instrument used, will be most accurate if performed on fresh urine. Struvite crystals form in alkaline urine while cystine and uric acid crystals tend to form in acid urine. The relatively uncommon urinary tract infections (UTI) due to urease producing bacteria (e.g., *Staphylococcus aureus*, *Proteus*) cause alkaline urine. The urine pH may indicate that other UA results may be unreliable (e.g., positive interference on protein test pad from alkaline urine). Interpretation of urine pH in the context of current blood gas, electrolyte and bicarbonate results assists in identifying renal tubular acidoses (see ch. 326).

E-TABLE 72-4

Causes of Acidic and Alkaline Urine pH

ACIDIC URINE	ALKALINE URINE
Meat based diet Protein catabolism Urinary acidifiers Acidosis (respiratory or metabolic)	Vegetable/Cereal diet Aged sample Alkalosis (respiratory or metabolic) Post-prandial

Paradoxical aciduria Metabolic alkalosis, hypochloremia, hypokalemia Loss of stomach acid (obstruction/severe vomiting)	Urease-positive urinary tract infection *(Staphylococcus, Proteus)* Urinary alkalinizers Renal tubular acidosis (relative alkalinuria in an acidotic animal)

Proteinuria (Figure 72-1)

Urine dipstick test pads assess protein content from their lowest detectable concentrations of 10-30 mg/dL ("trace") to their highest: 500 mg/dL − 2 g/dL ("+++"). There is higher sensitivity for albumin than globulin. Normal animals excrete negligible quantities of protein into urine and results must be placed in context of USG and pH. A "+" reading is unlikely to be significant if USG is high, but could be relevant if the USG is dilute. High pH or disinfectant contaminated urine may give false positive results whereas false negative results are seen with low pH or dilute urine. Quantitative protein analysis may be indicated to confirm dipstick proteinuria, if globulinuria is suspected, or with high pH. A ratio of urine protein to creatinine (UPC) is used to more accurately determine protein content. It is recommended to confirm all canine dipstick "++" and above results and all "+" results in samples <1.012 USG with UPC.[7] The sulphosalicylic acid (SSA) test is a semiquantitative alternative to UPC.

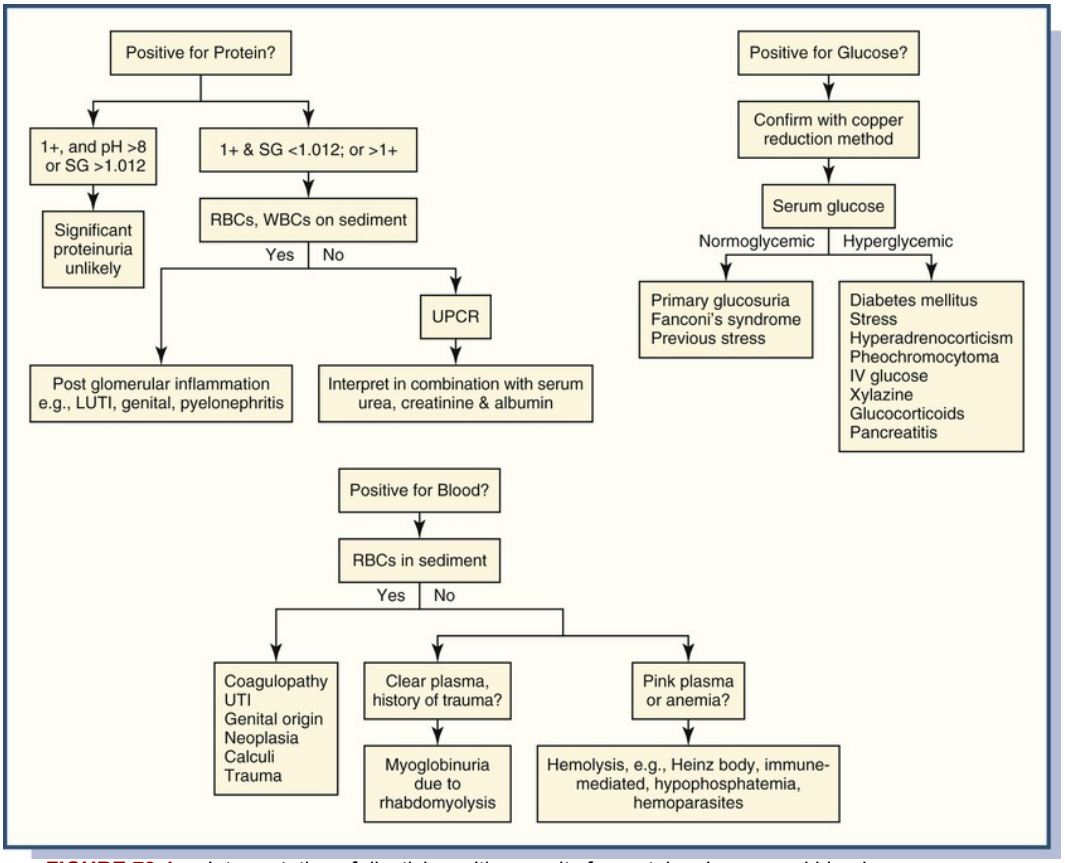

FIGURE 72-1 Interpretation of dipstick positive results for protein, glucose and blood.

Proteinuria is usually categorized as pre-renal/overflow, renal (glomerular or tubular), or post-renal. Interpretation of proteinuria should be made in the context of the sediment examination. Presence of RBCs and WBCs is indicative of renal or post-renal issues. Absence of RBCs or WBCs indicates a renal origin for proteinuria (glomerulonephritis, amyloidosis). Pathological pre-renal causes of proteinuria include hemolysis (hemoglobin), rhabdomyolysis (myoglobin) or plasma cell cancers (immunoglobulins). Functional pre-renal origins include strenuous exercise, fever and seizures.

Renal proteinuria may be functional and transient (e.g., inflammation) or persistent and pathological. Glomerular proteinuria is associated with loss of albumin, whose severity may cause hypoalbuminemia. Damaged or diseased renal tubules, whether due to congenital defects or an acquired AKI (e.g., Fanconi's

syndrome, gentamicin toxicosis), can interfere with resorption of filtered low molecular weight proteins and albumin (see ch. 60, 322, and 324-328).

Post-renal proteinuria can be associated with pathologic processes affecting the urinary tract from renal pelvis to urethra and the extra-urinary genital tract. Conditions include infection, inflammation, neoplasia or urolithiasis. Obtaining urine by cystocentesis avoids contamination by more distal areas. Quantitative analysis from post-centrifugation supernatant limits protein contribution from sediment. Presence of hematuria or pyuria does not necessarily interfere with usefulness of UPC, and proteinuria may not be detected in some pets with significant pyuria and bacteriuria.[8-10]

Glucose and Ketones (see Figure 72-1)

Glucose

Glucose passes through the glomerulus and is actively reabsorbed in proximal tubules. When capacity for reabsorption is exceeded (blood glucose concentrations >170-180 mg/dL in dogs and >260-310 mg/dL in cats) glucose appears in urine (see ch. 304 and 305). While glucosuria is usually due to hyperglycemia (diabetes mellitus, stress hyperglycemia, medication), normoglycemic glucosuria can occur (e.g., primary renal glucosuria, Fanconi syndrome; E-Table 72-5).

E-TABLE 72-5

Glucosuria

HYPERGLYCEMIC GLUCOSURIA	NORMOGLYCEMIC GLUCOSURIA
Diabetes mellitus Secondary diabetes mellitus Hyperadrenocorticism Pheochromocytoma Stress Excitement Exercise Certain conditions Intravenous fluids containing glucose Therapeutics Glucocorticoids Alpha$_2$ agonists	Renal tubular injury Nephrotoxic medications Severe renal hypoxia/hypovolemia Congenital Primary renal glucosuria Fanconi syndrome
FALSE POSITIVE GLUCOSURIA	**FALSE NEGATIVE GLUCOSURIA**
Oxidizing agents (dipstick) Peroxide/hypochlorite/bleach (e.g., floor/table samples) Non-glucose reducing sugars (Clinitest) Ascorbic acid (Clinitest) Minor/uncommon Formaldehyde (Clinitest) Medications (Clinitest) Salicylates, cephalosporins, nalidixic acid, penicillin, sulfonamides	Cold sample (dipstick) Marked bilirubinuria (dipstick) Marked ketonuria (dipstick) Formaldehyde (dipstick) Ascorbic acid (dipstick)

Urine dipsticks reliably measure glucose, provided the manufacturer's instructions are followed. Allow cooled urine to reach room temperature before testing and read the glucose result at the appropriate time after urine exposure. Dipstick technology is based on glucose oxidase; an alternative copper reduction test (Clinitest tablets) is useful if dipstick results need confirmation. Factors which can cause false results are listed in E-Table 72-5. Depending on manufacturer, urine glucose dipstick and tablet tests report in %, mg/dL or mmol/L: 1000 mg/dL (55 mmol/L; 1%), 500 mg/dL (28 mmol/L; 0.5 or 1/2%), 100 mg/dL (5.5 mmol/L; 0.1 or 1/10%). USG increases by 0.001 for each 270 mg/dL (15 mmol/L) of glucose.

Ketones

Ketones (acetone, acetoacetate and beta-hydroxybutyrate) accumulate when there is a shift from carbohydrate to fat metabolism, as occurs with untreated insulin-dependent diabetes mellitus (see ch. 142); they appear in urine when the renal threshold is exceeded. Dipstick test pads utilize nitroprusside, detecting acetone and acetoacetate but not beta-hydroxybutyrate. As diabetes is treated beta-hydroxybutyrate synthesis is reduced,

but its conversion to acetoacetate can result in the continuing presence or increasing concentration of measured urine ketones, which can create a false impression of continuing or worsening illness. False positives are not common but could occur with darkly pigmented urine, use of captopril or cysteine. Delay in analysis or in appropriate refrigerated storage may cause false negatives as acetone is volatile. UTI bacteria could degrade acetoacetate. Ketonuria is extremely rare in starvation, anorexia, vomiting, or low carbohydrate intake. It is also rare in lactating females and after extreme exercise.

Bilirubin

Bilirubin is a normal product of RBC turnover as heme is broken down within macrophages of the spleen and liver. Only conjugated ("direct") bilirubin is water soluble and therefore able to enter glomerular filtrate. Unconjugated ("indirect") bilirubin is protein bound and is not filtered. Urine dipstick pads for bilirubin are based on diazonium; a more sensitive confirmatory tablet test is available (Ictotest). Conjugated bilirubin is light- and (room) temperature-sensitive. Concentrations decrease when less soluble free bilirubin is liberated or bilirubin is converted to biliverdin. Dipstick tests for bilirubin should be performed on uncentrifuged urine, because bilirubin can adsorb to calcium precipitates. Test sensitivity is reduced if ascorbic acid is present. Chlorpromazine can cause false positives.

Bilirubinuria with hyperbilirubinemia is expected with RBC destruction (hemolysis), intrahepatic disease, cholestasis and biliary obstruction (see ch. 53). In dogs, since the renal threshold for bilirubin is low it may be detected in urine before hyperbilirubinemia is obvious. Canine kidneys synthesize bilirubin; thus, not all is derived from the blood. Low but detectable bilirubin concentrations may be found in concentrated samples from healthy male dogs. Bilirubinuria in cats is significant.

Blood (Hematuria, Hemoglobinuria, Myoglobinuria) (see Figure 72-1)

Dipstick methodology is based on the pseudoperoxide activity of heme reacting with organic peroxide. Detection of hematuria, hemoglobinuria or myoglobinuria occurs at levels not visually apparent; test pad sensitivity is 5-20 RBCs/mcL compared with 2,500 RBCs/mcL for visual recognition. Test strips detect intact RBCs (hematuria), hemoglobinuria and myoglobinuria. When RBCs exist without free hemoglobin, color changes on the pad are blotchy. Intact RBCs must be suspended for detection and unmixed urine can be falsely negative. False positives may occur in urine contaminated with cleaning agents (hypochlorite, bleach, peroxide). Dipstick assessment of blood must be made in the context of USG, sediment, the appearance of serum, and muscle enzyme concentrations. Hematuria is common, while hemoglobinuria is less common and myoglobinuria rare.

Hematuria may be present due to bleeding within the urinary tract due to trauma (cystocentesis), uroliths, inflammation, infection, neoplasia, or a coagulopathy (see ch. 47). Confirmation by sediment examination is recommended. Extraurinary (genital) sources of bleeding are possible. Hemoglobin may be present in urine either as a result of hemoglobinemia (intravascular hemolysis) or RBCs that have lysed in dilute or alkaline urine. Hemoglobin appears in urine when haptoglobin binding capacity in plasma is exceeded and renal tubular resorption mechanisms are overwhelmed. Myoglobinuria can occur if there is muscle trauma, ischemia or necrosis (see ch. 354).

Centrifugation of urine and comparison of uncentrifuged and supernatant can assist in confirming presence of intact RBCs to explain a positive result. Hemoglobinuria due to intravascular hemolysis is expected to result in pink-tinged plasma, whereas plasma would be clear with myoglobinuria. Peripheral blood smear evidence of parasites, spherocytes, ghost cells or Heinz bodies would support intravascular hemolysis as the origin of hemoglobinuria. When urine is discolored due to myoglobin, it may be described as red/brown rather than pink/red. Elevations in serum creatine kinase and/or aspartate aminotransferase activity would be expected with myoglobinuria (see ch. 65 and 66). Hemoglobinuria without icterus suggests acute hemolytic disease but when combined with hyperbilirubinemia is suggestive of chronic hemolysis. Discordant results in comparing dipstick results and sediment examination occur for several reasons (E-Table 72-6).

E-TABLE 72-6

Discordant Dipstick and Sediment Examination Results for Hematuria

POSITIVE TEST PAD & NEGATIVE SEDIMENT EXAMINATION	NEGATIVE TEST PAD & POSITIVE SEDIMENT EXAMINATION

Hemoglobinuria Myoglobinuria Lysis of hematuria cells by hyposthenuric or dilute urine Incorrect identification of red cells on sediment exam (e.g., bubbles) False positive test pad reaction (e.g., bleach)	Sample not mixed for dipstick test Low number of red cells that fail to lyse on surface of test pad Incorrect identification of, e.g., bubbles as red cells on sediment exam Inappropriately stored reagents False negative test pad reaction (e.g., formalin contamination)

Leukocytes (WBCs)

The leukocyte test pad is neither sensitive nor specific for WBCs in feline urine. Dipstick results on canine urine are specific but insensitive. Positive results have correlated well with canine bacteriuria (positive urine culture).[11]

Microscopic Sediment Examination

Overview

Urine sediment should be examined for RBCs, WBCs, epithelial cells, casts, crystals and organisms, each of which can settle to the bottom of a tube and be missed unless the sample is mixed before analysis. Sediment examination has added importance if macroscopic abnormalities are observed, but elements tend to deteriorate if UA is delayed.[12,13] Prompt evaluation is ideal (E-Table 72-7). Sediment assessment requires technical competence, appropriate instruments and standardized protocols (specific volume to be centrifuged, etc.) to provide consistent, reliable information.[11,14] Protocols vary between laboratories, and each should establish independent reference intervals. Consistently submitting 5 mL of urine is a compromise between providing sufficient volumes to identify elements in urine versus the practicalities of collecting urine from small animals. If 5 mL cannot be obtained, accurately recording the volume centrifuged and the re-suspended volume along with the microscope field number (low power [lpf] or high power [hpf]) and the volume under the coverslip will allow calculation of estimated sediment element concentration per mL (E-Box 72-2). Increasing centrifuged volumes with smaller resuspension volumes improves technique sensitivity. Casts are generally reported per lpf (although also viewed at high power for accurate identification) and cellular elements per hpf. Sediment stains can help identify some items but can dilute and alter semi-quantitative counts. One can place a drop of unstained and one of stained sediment on one slide for comparison.

E-TABLE 72-7

Factors Affecting Quality of Urine Sediment Examination

FACTOR	CONSEQUENCE
Inadequate sample mixing prior to transfer to centrifuge tube	Missed sediment elements
Volume of urine centrifuged not standardized	Variable quantitative results and difficulty in interpretation
Inadequate volume of urine examined	Missed sediment elements
Delay in analysis	Deterioration and loss of sediment elements. Refrigeration will assist in preservation but samples should be warmed prior to analysis—refrigeration will promote amorphous crystal formation
Volume of sediment examined	High volumes allow heavier elements (casts) to escape the edges of the coverslip
Centrifugation	Inconsistent speed/duration leads to inconsistent results Centrifuge braking disturbs the sediment
Voided sample	Higher numbers of red and white cells in normal samples
Urine concentration	Hyposthenuric urine will lyse cells Moderate numbers of cells/hpf in relatively dilute urine may be more significant than the same number in concentrated urine High concentration may result in crenated appearance to cells

pH	Highly alkaline urine will lyse cells and casts

E-Box 72-2

Example Standard Protocol for Urinalysis

1. Allow refrigerated sample to warm to room temperature.
2. Mix the sample well.
3. Transfer 5 mL well-mixed urine to a clean conical centrifuge tube. Record volume transferred.
4. Centrifuge for 5 minutes at 400 × g.
5. Decant supernatant leaving approx 0.5 mL urine and sediment.
6. Resuspend the sediment gently (flick the base of the tube with a finger).
7. Transfer a drop of the suspension by pipette onto a glass slide and place a coverslip gently over.
8. Adjust microscope for unstained examination.
9. Review at low magnification (×10 objective) for large elements (casts, crystals, parasites), count elements and report per low-power field (lpf).
10. Examine using ×40 objective to count red, white and epithelial cells, smaller crystals, count elements and report per high-power field (hpf) as average over at least 10 fields of view.
11. If desired, estimate concentrations as elements per mL by multiplying by "field conversion factor" specific to the microscope and the standardized slide/coverslip or commercial slide system being used.

Field Conversion Factor

1. Determine field of view (FOV = diameter of field in mm) for each of lpf and hpf
   a. Divide eyepiece field number by objective magnification (check microscope specifications), e.g., 20/40 = 0.5 mm
2. Determine $\text{"area of view"} = \pi\left[\frac{\text{FOV}}{2}\right]^2$,

e.g., $3.14 \times 0.25^2 = 0.196\ \text{mm}^2$

3. Calculate number of views per area possible by dividing area of coverslip or commercial urinalysis slide system by "area of view."
   a. E.g., 22 × 22 mm coverslip area possible = 484 mm^2; Kova System 32 mm^2
   b. E.g., 32 mm^2/0.196 mm^2 = 163 possible fields of view; 484 mm^2/0.196 mm^2 = 2470
4. Calculate "concentration factor" = volume urine centrifuged/volume of resuspended sediment examined;

e.g., 5 mL/0.5 mL = 10

5. Determine volume of urine sediment examined
   a. E.g., 22 mm × 22 mm coverslip holds approximately 0.02 mL sediment, Kova System holds 0.006 mL sediment
6. Calculate field conversion factor
   a. $$\frac{\text{Number of possible fields of view}}{\text{Volume of sediment examined} \times \text{concentration factor}}$$
   b. E.g., $$\frac{2470\ \text{possible fields of view}}{0.02\ \text{mL} \times 10} = \text{approx } 12{,}350\ \text{hpf/mL}$$
7. Using field conversion factor convert "per field" result into "per mL" by multiplication
   a. E.g., 4 RBCs/hpf × 12,350 hpf/mL = approx 49,400 RBCs/mL
   b. Field conversion factor need only be calculated once for each microscope/slide-system combination.

Hematuria (see Figure 72-1)

Small numbers of RBCs are commonly seen in the urine of normal dogs and cats. The fewest RBCs are seen in free catch samples. Cystocentesis samples from healthy dogs and cats often have fewer RBCs than samples obtained via catheterization. Manual expression of the bladder can be traumatic and a source of RBCs. One should assess dipstick results in the context of sediment analysis and USG. On sediment examination, unstained RBCs appear as pale yellow anucleate biconcave discs. RBCs may be shrunken and crenated in concentrated urine or swollen and lysed (therefore absent) in dilute or alkaline urine. RBCs can be distinguished from other round elements, yeast or lipid droplets, by their uniform size. Lipid droplets tend to float to the sample surface and remain at a different focal plane. Hematuria may be grossly visible or only seen microscopically. There are numerous causes for RBCs (see ch. 47).

Pyuria

Small numbers of WBCs are common in urine from healthy dogs and cats, with a ratio to RBCs of about 1 : 1. Neutrophils are the most common WBC, recognized by their size (1.5 − 2 × RBC), granular cytoplasm and distinctive lobed nuclei. Their morphology may vary depending on pH and USG, making it difficult at times to distinguish neutrophils from lymphocytes, monocytes or tubular epithelial cells. WBCs shrink in concentrated and swell or lyse in dilute or alkaline urine. Nuclear characteristics may be enhanced with sediment stains or by clearing with 2-10% glacial acetic acid. Numbers of WBCs/hpf may be slightly higher in normal samples obtained via catheterization or voiding as compared with cystocentesis.

Large numbers of WBCs are consistent with inflammation (infectious or non-infectious) and often accompanied by some degree of hematuria and/or proteinuria. Finding numerous bacteria with WBCs is consistent with active infection. Failure to see bacteria does not exclude infection, hence the recommendation to culture pyuric urine. Non-infectious causes of pyuria include neoplasias and uroliths. Recent antibiotic therapy can be expected to eliminate bacteria from sediment and result in a negative urine culture. Bacteria may be observed without WBCs in immunocompromised pets or as contaminants in inappropriately stored or transported samples.

Epithelial Cells

Renal Tubular Cells

Round with a round central nucleus and granular cytoplasm. Their size is from the same as to 4 times larger than WBCs. Unless embedded in casts, these cells can be difficult to identify. Columnar cells with a brush border originate in proximal tubules.

Transitional Epithelial Cells

Line the urinary tract from the renal pelvis to the urethra, have granular cytoplasm, and are present singly or in clumps. They are usually equal to or larger than WBCs, larger than renal tubular cells and smaller than squamous epithelial cells. They may be round, oval, caudate, spindle, or polyhedral. Large numbers are indicative of inflammation, although mechanical abrasions, neoplasia and other causes may be suspected.

Squamous Epithelial Cells

Common in low numbers in voided urine or that collected by catheterization. They are urethral or vaginal in origin, large, flat, thin polygonal cells with either no nucleus or a small dense eccentric nucleus. They may be present as individual cells or as sheets. Rolled up squamous epithelial cells should be carefully differentiated from casts.

Neoplastic Cells

It may be difficult to differentiate clumps of hyperplastic transitional epithelial cells from carcinoma. Cytological examination of stained fixed smears may help identify criteria of malignancy (see ch. 351). Catheterization, bladder lavage and urine cytospin may aid in harvesting neoplastic cells for cytological examination. However, histological examination of tissue biopsy is required to confirm neoplasia.

Bacteria

Both cocci and bacilli are observed in urine sediment; cocci in chains are relatively easy to identify. While normal urine is sterile, samples may contain bacteria from the distal urethra or genital tract in voided or

catheter samples. Small numbers of bacteria from the urethra or genital areas, in fresh catheterized or voided samples, are common. Delay in analysis or lack of preservative may result in a significant proliferation. Therefore, when large numbers of bacteria are seen without WBCs, contamination should be suspected. False positive results may occur if debris, lipid droplets or small amorphous crystals are misidentified as bacteria or if stain is contaminated.[15,16] Identification of bacteria in urine sediment may or may not be significant and failure to identify bacteria does not rule out their presence. Large bacterial numbers in cystocentesis, fresh or preserved catheterized samples are suggestive of UTI, particularly when accompanied by pyuria. Urine culture is indicated to confirm UTI. Bacteria seen on sediment but without growth on culture occurs with contaminated unpreserved stored urine, bacteria rendered non-viable by preservation method or recent antibiotic therapy.

Cylindruria (Casts)

Overview

Material concentrated in a tubule can be excreted in that shape, i.e., appearing as little tubes, called "casts" (cylinders). Casts are usually composed of cells and mucoprotein (Tamm-Horsfall) derived from the loop of Henle, distal tubules and collecting ducts. Casts from any of these areas are cylindrical, have parallel sides with rounded, square, irregular or tapered ends. Their width depends on the diameter of the tube in which they were formed; wider casts are usually formed in collecting ducts or dilated tubules. Any material trapped in mucoprotein, such as cells, and excreted within a cast and identified is the basis of cast classification. Time within a tubule may allow degeneration of trapped material, changing its structure and classification. Low numbers of hyaline or granular casts may be observed in healthy urine but not cellular casts (epithelial, WBCs).

Hyaline Casts

Hyaline casts are almost entirely composed of Tamm-Horsfall mucoprotein, colorless, homogenous, nearly transparent when unstained, and with rounded ends. Staining may help their identification. They are associated with renal or physiologic proteinuria. Small numbers of hyaline casts (e.g., up to 2/lpf) can be observed in normal moderately concentrated urine.

Epithelial Cell, Granular, Fatty, and Waxy Casts

Epithelial cell, fatty, granular and waxy casts may represent different stages of one process, the degradation of renal tubular epithelial cells within the cast. Epithelial cell casts contain tubular epithelial cells detached from their basement membrane. Their appearance is similar to that of free tubular epithelial cells. Since it is difficult to classify degenerated cells, reports may vaguely state "cellular casts." Casts containing granular material may contain cell degradation products rather than cells. This appearance may indicate duration rather than severity of tubular lesions. Epithelial cell casts indicate significant renal tubular injury/necrosis due to ischemia, inflammation or toxins.

Some casts are reported as "granular," because of their opaque granular content, and further categorized by granule size: coarse to fine. Granule size likely represents stages in cell degeneration and is not of significance. Necrotic debris of renal tubular epithelium origin may also be present. Low numbers of granular casts (e.g., 1 or 2/lpf) are occasionally seen in urine from healthy animals. Fatty casts, whose origin and importance are the same as other granular casts, contain refractive lipid droplets derived from degenerating cell cytoplasm. Waxy casts are colorless, homogenous, extremely refractive, look "waxy" with brittle jagged or sharply broken ends, may appear quite twisted, and are relatively stable in dilute or alkaline urine. Waxy casts are granular casts at an end stage of degeneration. Their presence suggests an extended period within tubules and prior tubular injury and/or urinary stasis. They are often seen in pets with CKD.

White Blood Cell Casts

WBC casts, composed of Tamm-Horsfall mucoprotein and WBCs, are indicative of tubular and interstitial inflammation. Since it is sometimes difficult to discriminate WBC from epithelial cell casts, they may simply be reported as "cellular casts." Staining may help identify neutrophil nuclei and one should distinguish WBC casts, most likely of renal origin, from mucus strands containing strings of free urinary WBCs, most likely from the lower urinary tract. After degeneration, WBC casts become granular. Tubular inflammation can exist without WBC casts. A mixture of WBC and epithelial cell casts may be observed following acute tubular necrosis.

Red Blood Cell Casts

RBC casts are rare, red-orange-yellow in color, and fragile. Their presence localizes bleeding to nephrons. When urine samples are bloody, RBC casts must be distinguished from clumped RBCs by visualization of the mucoprotein structure.

Broad Casts

Broad casts are much wider than other casts, but represent any of the described casts. Their wide diameter suggests formation during urinary stasis within collecting ducts or dilated tubules. They are often waxy. While broad casts imply a severe disorder, they may also imply recovery as urine begins to flow again following oliguria.

Pigmented Casts

Casts may be pigmented with golden-brown hemoglobin as RBC casts degenerate. The pigment may be yellow or golden brown bilirubin in pets with bilirubinuria.

Bacterial Casts

Bacterial casts are uncommon and challenging to distinguish from the more common granular casts. Cytological or Gram stain may help demonstrate bacteria-filled casts. Their presence would be consistent with severe tubular bacterial infection.

Crystalluria

Overview

Struvite, amorphous phosphate and oxalate crystals are commonly seen in urine of healthy animals. Urate, cysteine, or large quantities of calcium oxalate crystals are usually abnormal (see ch. 331 and 332). Some crystals are indicative of significant disease or a metabolic disorder and others may provide preliminary information concerning the structure of uroliths, if present. Crystals form in supersaturated urine. Factors that influence the detection of crystals in urine include USG, temperature, time to analysis, pH and diet.[17] Refrigeration promotes crystal formation and is not indicative of *in vivo* crystalluria. Urine samples for sediment examination should be rewarmed before analysis. The pH of urine is important because some crystals require a certain pH to form. Indeed, *in vitro* alteration of pH can make detection of certain crystals easier and may assist in identification of unusual crystals as will the medication history since some result from precipitation of drugs or their metabolites. Most common companion animal urinary crystals are easily recognized by shape, size, color and sample pH (E-Table 72-8).

E-TABLE 72-8

Characteristics of Urinary Crystals

TYPICAL PH RANGE	CRYSTAL	SHAPE	COLOR	INVESTIGATIONAL CHARACTERISTICS
<5-7	Uric acid	Variable including diamond or rhombic plates ± concentric rings, oval with pointed ends, occasional cystine-like hexagons	Yellow, yellow-brown	Dissolves in alkali
≤7	Amorphous urates (Na, K, Ca, Mg)	Amorphous, granular. Monosodium urate: slim pencil-like prism in small clusters	Yellow, yellow-brown	Dissolves in alkali and at 60° C. Convert to urate with acid.
	Bilirubin	Granules or needles, clustered or branching like twigs, granules	Amber to red-brown	
	Cholesterol	Large flat rectangular ± stacked plates with a notched corner	Colorless	Dissolves in organic solvent
	Leucine	Spheres with concentric circles/striations	Dark yellow/brown	Dissolves in alkali

	Tyrosine	Needle-like in sheaves or clusters. Similar to bilirubin crystals.	Colorless or yellow	Dissolves in alkali
	Radiographic contrast	Depending on agent used, flat cholesterol-like or needle sulfa-like	Colorless	Associated with high USG
	Ampicillin	Long thin needles or prisms. May form wheat-sheaf pattern like "sulfa" crystals.	Colorless	Lignin test negative
	Sulfonamide	Waisted "wheat-sheaves" or fans of fine needle-like crystal. Striated spheres.	Yellow-brown	Lignin test positive (equal drops of urine and dilute hydrochloric acid on newspaper—bright yellow-orange color is positive)
5-8	Calcium oxalate	Dihydrate (weddellite): 3-dimensional octahedral, dipyrimidal, "envelope" forms, squares with diagonal lines from corners. Monohydrate (whewellite): ovoid, dumbbell, "picket fence"/"stake" and "hemp seed" shapes (dumbbells are not likely to be calcium carbonate in canine and feline urine).	Colorless	Dissolves in dilute HCl
	Cystine	Thin hexagonal plates, layered, clumped or individual	Colorless	Enhance detection by acidifying and refrigeration of alkaline samples. Dissolves in alkali.
6-8	Calcium phosphate	Long, thin prisms often one tapered end, clumped into rosettes or as needles	Colorless	Dissolves in dilute acid
≥7	Amorphous calcium phosphate	Amorphous granular form similar to amorphous urates and xanthine	Colorless	Dissolves in acid (e.g., acetic). Insoluble at 60° C.
	Struvite	Orthorhombic, "coffin-like" prisms, plates with 3 to 6 sides and oblique ends	Colorless	Dissolves in acetic acid
	Ammonium biurate	May also be observed in neutral and slightly acidic urine. Spheres with irregular protrusions "thorny-apple."	Brown, yellow-brown	Dissolves in acetic acid and at 60° C. Convert to urate with concentrated acetic or acetic acid.

Bilirubin Crystals

Bilirubin crystals can be normal in concentrated urine and found in large numbers with significant bilirubinuria.

Calcium Oxalate Crystals

Calcium oxalate crystals are seen as either dihydrate or monohydrate. Dihydrate crystals may be seen in urine from healthy dogs, healthy cats, and pets with calcium oxalate uroliths. Monohydrate crystals form with hypercalciuria or hyperoxaluria (ethylene glycol intoxication, oxalate rich foods).[18]

Calcium Phosphate Crystals

Calcium phosphate crystals can be amorphous or needle-like. Amorphous calcium phosphate can be distinguished from similar-appearing amorphous urates or xanthine by pH, solubility in acid or alkali and susceptibility to heat. Calcium phosphate crystals are commonly seen, sometimes in large numbers, in urine from healthy pets. They may also be present in conjunction with calcium oxalate/calcium phosphate or struvite uroliths.

Cholesterol Crystals

Cholesterol crystals are non-specific, occasionally observed in healthy dogs, and likely originate from degenerating cell membranes. An association has been made with proteinuria and hypercholesterolemia (e.g., nephrotic syndrome).

Cystinuria

Cystinuria is an inherited defect reported in Scottish Deerhound, Newfoundland, English Bulldog, Chihuahua, Dachshund, Mastiff, Bullmastiff, American Staffordshire Terrier and mixed breeds. Dogs with cystine urolithiasis are far less common than dogs with crystals. Crystals resembling cystine may occasionally be formed by struvite or uric acid (see ch. 331).

Drugs

Drugs that are associated with crystal formation include sulfonamides, ampicillin and radiocontrast agents. Other drugs might initiate crystal formation.

Magnesium Ammonium Phosphate (Struvite) Crystals

Magnesium ammonium phosphate (struvite) crystals are common in healthy dogs and cats. They are also seen in pets with struvite urolithiasis, other uroliths and non-urolith urinary tract disease. UTI with urease-producing bacteria may provide a source of ammonia (see ch. 331 and 332).

Tyrosine Crystals

Tyrosine crystals are rarely seen in people with liver disease or aminoaciduria. They are rarely observed in canine and feline urine.

Urate Crystals

Urate crystals may be observed as amorphous urates or as biurate. Amorphous forms may be present in normal canine and feline urine. Biurate crystals may be seen in normal Dalmatians and English Bulldogs. They are also seen in hepatic failure, portosystemic shunting (hyperammonemia), and with ammonium urate uroliths.

Uric Acid Crystals

Uric acid crystals are seen under the same circumstances as amorphous urates and ammonium biurate.

Xanthine

Xanthine crystals are similar in appearance to amorphous urates and ammonium biurate. They are present in urine as a consequence of allopurinol therapy. They have also been rarely recognized along with xanthine urolithiasis in cats and as a consequence of an inherited disorder in Cavalier King Charles Spaniels.[19]

Lipids

Variably sized refractile lipid droplets may be present in urine. If left to sit before examination, lipid should float to underneath the coverslip, whereas other elements will sink to surface of the slide, meaning that they should be on a different focal plane from the other formed elements. Lipid droplets are more common in feline urine; it is believed that lipid may originate from degeneration or turnover of lipid-laden tubular epithelial cells. It is important that they are recognized so that they are not mistaken for other elements.

Other Elements

Spermatozoa may be present in the urine of intact males. Parasites including *Dirofilaria, Pearsonema (Capillaria), Dioctophyma* and contaminating fecal parasitic ova may be observed. Yeast and fungi are usually contaminants although occasionally urinary yeast infections (e.g., *Candida* spp.) or rarely polysystemic fungal infection (e.g., blastomycosis) may be identified.

Mucus strands are irregular in shape and longer allowing them to be differentiated from casts.

Other Routine Tests

Cytology

Examination of urine sediment on stained air-dried smears provides more detailed information on cell types, inflammatory cells, infectious agents and malignant characteristics.

Smears are prepared from urine sediment, spread on a slide by "blood smear" or preferably "line smear" technique to concentrate elements along a line at the end of the smear where the spreader slide has been abruptly lifted towards the end of the smear. Alternatively, cytospin preparations can be made. Bear in mind that urine is not an ideal medium for the preservation of cells; consequently, some cellular distortion and swelling is to be expected which should not be misinterpreted for a neoplastic appearance. Preferred stains include Papanicolaou's or Romanowsky-type (e.g., Wright's, Diff-Quik). This technique is also more sensitive for the detection of urine bacteria than unstained preparations.[15,20,21]

Indications for urine cytology include the presence of atypical cells on routine sediment examination in addition to the clinical presentations of hematuria, stranguria, suspicion or imaging evidence of a bladder mass or prostatomegaly. Transitional cell carcinoma is the most commonly recognized neoplasm and cytological criteria of malignancy should distinguish neoplastic from hyperplastic/reactive cells. However, the distinction is not always straightforward and fine-needle aspirate cytology or biopsy may be required.

Bacterial Culture

The observation of bacteria on urine sediment examination is not equivalent to a diagnosis of UTI (see ch. 327 and 330). However, if found on an aseptically obtained sample in combination with pyuria, UTI is more likely. That said, urine sediment examination is a relatively insensitive method to detect bacteria in urine and conversely, contaminating bacteria may be present in sediment. Bacterial culture is a much more sensitive method capable of detecting <10 bacteria/mL vs. 10,000 (rods) to 100,000 (cocci)/mL needed for visualization on sediment and has the advantages of being able to provide a quantitative result and to correctly identify the (predominant) species present and if required, the relevant antibiotic sensitivity. The number of bacteria (colony forming units; cfu)/mL that is considered significant and indicative of urinary tract infection varies according to collection methods[22] and differs between dogs and cats. Bacterial counts of $\geq 10^2$ cfu/mL are significant in canine and feline urine obtained by cystocentesis; counts of $\geq 10^3$ cfu/mL are significant in feline and male canine urine obtained by catheterization. Counts of $\geq 10^5$ cfu/mL are significant in female canine catheterized samples. Voided samples are generally unreliable for quantitative bacterial counts but $\geq 10^5$ cfu/mL in dogs and $\geq 10^4$ cfu/mL in cats has been considered significant. In cases of urolithiasis, culture of urolith or bladder mucosal biopsy may be necessary.[23] Reflex urine culture is not cost-effective in dogs with USG ≤1.013 in the absence of active urine sediment or high clinical suspicion for UTI.[24]

Creatinine

The measurement of urine creatinine allows for the calculation of creatinine clearance (CC) when urine production rate is known during timed collections and fractional excretion (FE) of electrolytes (see ch. 73), urine protein creatinine ratio (UPCR) and urine corticoid creatinine ratio (UCCR) in spot samples.

$$CC = \frac{\text{Creatinine}_{\text{Urine}} \times (\text{urine volume (mL)} / \text{collection interval (min)} / \text{bodyweight (kg)})}{\text{Creatinine}_{\text{Plasma}}}$$

$$FE_{\text{Analyte}}(\%) = \frac{100 \times \text{Analyte}_{\text{urine}} \times \text{Creatinine}_{\text{plasma}}}{\text{Analyte}_{\text{plasma}} \times \text{Creatinine}_{\text{urine}}}$$

UPCR

Urine-protein to creatinine ratio provides a good indication of quantitative proteinuria without the difficulties of obtaining a 24-hour urine collection (see ch. 325). UPCR quantification of proteinuria is recommend in samples with "2+" dipstick proteinuria and USG >1.012 and in samples with "1+" dipstick proteinuria and USG < 1.012. UPCR has been utilized to assist in the standardized classification of renal dysfunction.[25] Multiple samples collected at least 24 hours apart are recommended to mitigate the risk of overinterpretation of a single sample positive result.

UCCR

Urine corticoid creatinine ratio is used to screen for hyperadrenocorticism (see ch. 306 and 307). It is considered to be a highly sensitive but non-specific test for hyperadrenocorticism. Depending on the analytical process, this ratio may be reported as either urinary "corticoid" or "cortisol" creatinine ratio. The term corticoid implies no pre-analytical preparation and the analytical antibodies detecting all cross-reacting steroid and metabolites. Because there are several antibody types for the detection of cortisol, the results and consequently diagnostic cut-off values vary by laboratory. Much of the literature on UCCR is based on a particular detection antibody not commonly used in most international commercial laboratories. Consequently literature cut-off values are in the range of 10×10^6, whereas many commercial laboratories' cut-offs are in the range $24\text{-}30 \times 10^6$.

Non-Routine Tests

Bence-Jones and Urine Protein Electrophoresis

Bence-Jones proteins are light-chain immunoglobulins found in the urine of patients with plasma cell neoplasia (myeloma) (see ch. 344). They may not be detected by routine protein detection methods and should be requested when monoclonal gammopathy is suspected. Their identification is based on their precipitation at lower temperatures than other proteins (40° to 60° C). Urine protein electrophoresis may be helpful in further classifying proteinuria.

GGT, NAG

N-acetyl-beta-D-glucosaminidase (NAG) is a lysosomal enzyme and gamma-glutamyl-transferase (GGT) a membrane enzyme of the proximal tubular epithelium. Their presence in urine indicates renal tubular injury.[26] They are reported as a ratio with urine creatinine to provide a surrogate of 24-hour excretion[27] (see ch. 326 for further detail on urinary enzymes).

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CHAPTER 73

Urinary Electrolyte Concentrations

Steven Epstein

Introduction

Urine sodium (Na^+), potassium (K^+), and chloride (Cl^-) concentrations are infrequently utilized in veterinary medicine. Interpretation of *urine* electrolyte concentrations is based on what is "appropriate" given that patient's physiologic condition, as there is no normal range that applies to all patients. Knowing the urine electrolyte concentrations can aid in determining etiology of *serum* electrolyte abnormalities as well as some disorders of acid-base metabolism. Randomly obtained urine samples may be adequate. In certain disorders the utility of urine electrolyte concentrations is enhanced when interpreting results in the context of urine osmolality or creatinine.

Disorders of Sodium (Na^+)

Overview of Urinary Free Water Clearance and Urine Na^+

Abnormal serum Na^+ concentrations (dysnatremias) are associated with increased in-hospital mortality.[1,13] Severity of dysnatremia correlates with higher mortality rates, but whether it is the Na^+ concentration itself or the condition causing the disturbance is unknown.[1,13] Identifying the cause of dysnatremia can be extremely useful in patient care. Combining urinary free water clearance with urine Na^+ concentrations or fractional excretion of sodium (Fe_{Na}) can aid in determining the cause of hyponatremia or hypernatremia.

Urinary free water clearance, determined using urinary cations rather than osmolality, may provide a more accurate representation of water balance for dysnatremias.[2] When the urinary free water clearance is negative, the kidneys are conserving water and when positive, they are excreting free water.[3] Assessment of randomly obtained urine can provide a snapshot of how a patient's kidneys are regulating free water clearance during the time that urine was produced. If a urinary catheter has been placed, a sample drawn from the catheter can represent current renal free water regulation. A sample obtained from a closed collection system over a specified time period can provide an averaged assessment from the time the system was last emptied. Closed collection system urine volume can be multiplied by urinary free water clearance to provide a calculated volume of free water cleared or conserved by the kidneys. This volume can be integrated into the fluid plan for returning serum Na^+ concentrations toward normal.

Urinary free water clearance is determined primarily by the amount of water ingested and amount of antidiuretic hormone (ADH) released (Box 73-1).[4] The primary regulation for ADH release is an increased plasma tonicity with its major component being Na^+ concentration. As plasma tonicity increases, ADH is secreted and urinary free water clearance is negative. If plasma is hypotonic due to disease or ingestion of water, ADH secretion is inhibited and urinary water clearance is positive. ADH can also be secreted in response to low circulating blood volume or pressure. Large drops in blood pressure (10-15 mm Hg) stimulate ADH secretion, conserving free water to restore volume and pressure (non-osmotic ADH release). The result of this water conservation effort is to increase blood volume, and as a result the Na^+ concentration will decrease. These scenarios involving ADH release are physiologic and considered appropriate. However, ADH is sometimes secreted inappropriately. Examples of conditions associated with inappropriate ADH secretion include hypoadrenocorticism, hypothyroidism, and the "syndrome" of inappropriate ADH secretion (SIADH; Box 73-2). These conditions are associated with low serum Na^+ concentration and a negative free water clearance.

Box 73-1

Urinary Free Water Clearance Calculation

$$\text{Urinary free water clearance (\%)} = 1 - \frac{(\text{Urine [sodium]} + \text{Urine [potassium]})}{\text{Serum [sodium]}}$$

All three values should be in the same units.

Box 73-2

Potential Etiologies of SIADH

- Vascular event to the brain
  - Traumatic brain injury
  - Subarachnoid hemorrhage
  - Ischemic stroke
- Neoplastic production of ADH
- Pulmonary diseases
- Emotional state
  - Neuropsychiatric disorders
  - Pain
  - Nausea
- Medications
  - Amitriptyline
  - Carbamazepine
  - Cyclophosphamide
  - Oxytocin
  - Vasopressin

Apart from urinary free water clearance calculations, urine Na^+ concentrations can be of value in assessing blood volume status. The kidneys respond to decreased perfusion by conserving both Na^+ and water to expand the extracellular fluid (ECF) volume, in part by activation of the renin-angiotensin-aldosterone system. When aldosterone is secreted, the kidneys can conserve sodium such that in hypovolemic states, the urine Na^+ should be <20 mEq/L and may be as low as 1 mEq/L.[5] Values of 20-40 mEq/L are equivocal, while >40 mEq/L of Na^+ implies the kidneys are interpreting a normal blood volume. An exception would be conditions in which renal Na^+ handling is impaired, as with CKD or selective renal or glomerular hypoperfusion.[5] Determining the Fe_{Na} (Box 73-3) has been thought to help discriminate prerenal azotemia from acute kidney injury (AKI). A Fe_{Na} <1% is consistent with hypovolemia and >1% consistent with AKI.[6] Recent evidence suggests that this is not foolproof and a Fe_{Na} <1% has been associated with AKI, fluid therapy, and the use of vasoactive drugs or diuretics.[7]

Box 73-3

Fractional Excretion of Sodium Calculation

$$\text{Fractional excretion of sodium } (Fe_{Na})\ (\%) = 100 \times \frac{\text{Urine [sodium]} \times \text{Plasma [creatinine]}}{\text{Plasma [sodium]} \times \text{Urine [creatinine]}}$$

Hyponatremia

Overview and Definitions

Hyponatremia is common and, when documented, should be categorized as either true hyponatremia or pseudohyponatremia caused by hyperlipidemia, hyperproteinemia, hyperglycemia, or mannitol administration.[1,8] It is assumed in this discussion that pseudohyponatremia has been ruled out. Hyponatremia in association with a reduced free water clearance involves an abnormality in either the generation of free water in the loop of Henle/distal tubule or enhanced water conservation due to ADH secretion in the collecting ducts.[9]

Positive versus Negative Water Clearance

When constructing differential diagnoses for hyponatremia, free water clearance should be assessed. Positive free water clearance is considered appropriate handling. This excess water accumulation likely occurred via ingestion (voluntary, or via feeding tube) or IV hypotonic fluid therapy. Negative free water clearance may indicate inappropriate renal handling of water. To help determine if renal water handling is appropriate or inappropriate, the ECF volume should be assessed. Hyponatremia can be associated with hypovolemia, euvolemia, or hypervolemia and assessment of volume status is important in this context relative to urine Na^+ concentration and free water clearance (Figure 73-1).

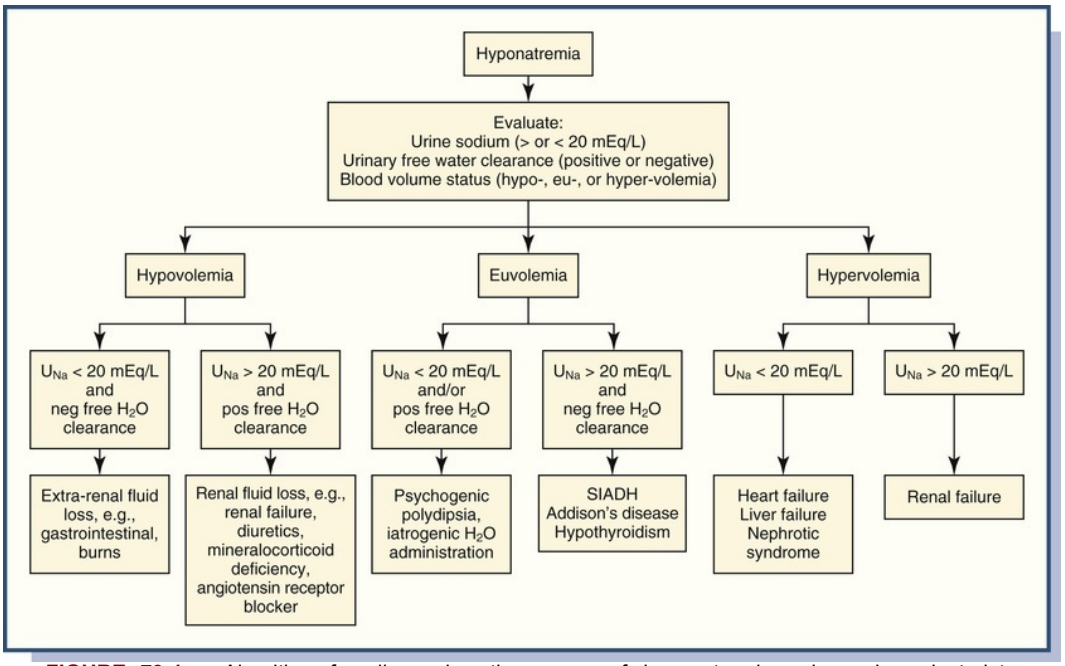

FIGURE 73-1 Algorithm for diagnosing the cause of hyponatremia using urine electrolyte concentrations. *Neg,* Negative; *Pos,* positive; *U,* urine.

Hypovolemia

A patient judged to be hypovolemic with appropriate kidney function should have increased aldosterone

concentration, negative free water clearance, and a urine Na^+ concentration <20 mEq/L. If present, this would indicate extrarenal fluid loss as the cause of hypovolemia. This is most likely associated with gastrointestinal loss or loss from the skin due to burns, and the associated nonosmotic release of ADH. If the urine Na^+ is >20 mEq/L, hypovolemia is likely to be secondary to renal losses from renal disease, diuretic administration, angiotensin receptor blocker administration, or mineralocorticoid deficiency (Addison's disease).

Euvolemia

When the patient is considered euvolemic with a urine sodium <20 mEq/L and a positive free water clearance, the history of the patient should be evaluated for polyuria/polydipsia which would indicate psychogenic polydipsia as the cause in the absence of any other iatrogenic water administration. Euvolemia, a urine sodium >20 mEq/L, and a negative free water clearance are compatible with SIADH, hypothyroidism, or glucocorticoid deficiency. Diagnosis of SIADH is based on the above findings and exclusion of hypothyroidism and Addison's disease.

Hypervolemia

Patients judged to be hypervolemic with an expanded ECF volume and urine Na^+ concentrations <20 mEq/L are most likely to have heart failure, liver failure, or nephrotic syndrome. If the urine sodium is >20 mEq/L, intrinsic renal disease is most likely.

Hypernatremia

Overview

Hypernatremia develops after increased consumption of Na^+ or most commonly after water loss. If hypernatremia is persistent, it is due to an inability to consume adequate amounts of water, whether due to failure to sense thirst or a failure to ingest water. Failure to drink may be due to metabolic illness, change in mental status, congenital adipsia, or lack of water (e.g., NPO status while hospitalized). As with hyponatremia, volume status, urine Na^+ concentration, and urinary free water clearance can help rule in or out conditions under consideration as causes for hypernatremia.

Hypervolemia

For patients that are deemed to be hypervolemic, it is usually a gain of sodium that is the factor that generates the hypernatremia. Urinary sodium concentrations are often >100 mEq/L and free water clearance is negative.[10] Causes include hyperaldosteronism, hyperadrenocorticism, administration of hypertonic solutions (sodium bicarbonate, total parenteral nutrition, 7.2% sodium chloride), dialysis, or excess ingestion of a hypertonic solution such as milk replacer. Patients with kidney failure receiving IV replacement fluids are at risk for developing hypernatremia due to their limited capacity for renal conservation of free water and the excess sodium being administered from fluid therapy.

Euvolemia or Hypovolemia

In these patients hypernatremia is most likely from water loss. Potential causes are listed in Box 73-4. To aid in distinguishing these disorders, free water clearance is evaluated together with urine volume. If free water clearance is negative and urine volume is low, extra-renal hypotonic fluid loss is likely (gastrointestinal or insensible losses). If free water clearance is negative, but urine volume is high, there is likely to be a renal source of hypotonic fluid loss (glucosuria, post-obstruction diuresis, mannitol administration). Positive free water clearance suggests a deficiency in ADH action on the kidneys, either from lack of secretion (central diabetes insipidus) or lack of renal sensitivity (nephrogenic diabetes insipidus).

Box 73-4

Etiologies of Water Loss

Insensible water loss
- Burns
- Respiratory tract

Renal loss

Diabetes insipidus (central or nephrogenic)
Osmotic diuretics (hyperglycemia, mannitol)
Gastrointestinal loss
Lactulose
Activated charcoal with sorbitol
Infectious diarrhea

Potassium (K^+) Disorders

Trans-Tubular Potassium Gradient (TTKG)

Urinary K^+ concentration can be helpful in determining cause of hypo- or hyperkalemia. Spot check urinary K^+ concentrations are not often useful, but TTKG determination can be helpful (Box 73-5). This formula is only useful when urinary Na^+ concentrations are >25 mEq/L, to ensure that renal Na^+ delivery is not rate limiting.[11] Healthy people usually have a TTKG ranging from 8 and 9; no values are established for dogs and cats.

Box 73-5

Transtubular Potassium Gradient Calculation

$$\text{Transtubular potassium gradient} = \frac{\text{Urine [potassium]} \times \text{Plasma osmolality}}{\text{Urine osmolality} \times \text{Plasma [potassium]}}$$

Hypokalemia

Hypokalemia is usually a result of inadequate intake, increased entry into cells, gastrointestinal loss or renal loss. The TTKG can help differentiate renal loss (TTKG >3) from other causes (TTKG <3).[12] Increased urinary losses are often associated with diuretic use, nasogastric tube suctioning, amphotericin B administration, mineralocorticoid excess, or hypomagnesemia.

Hyperkalemia

Hyperkalemic patients are often broken down into having one of three major causes: increased intake (oral or IV), transcellular movement, or decreased urinary excretion. Pets with non-renal causes of hyperkalemia have a TTKG <7, indicating defective renal secretion of K^+. Values >7 indicate excess intake or transcellular movement.[11] Decreased renal excretion of K^+ may be associated with renal failure, decreased distal renal tubular flow from decreased effective circulating blood volume, or hypoaldosteronism.

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CHAPTER 74

Fluid Analysis

Thoracic, Abdominal, Joint

Tracy Stokol

Thoracic and Abdominal Cavity Fluid

The thoracic and abdominal cavities are bathed in small amounts of fluid that cannot normally be aspirated. Therefore, any fluid accumulation is abnormal. Aspiration of fluid with subsequent cytologic analysis is a routine part of the diagnostic evaluation of patients with pleural or abdominal effusions. Aspiration is a relatively innocuous, minimally invasive, and inexpensive procedure that can yield clues as to the cause of the effusion and, in some cases, provide a definitive diagnosis of the underlying disease.

Fluid Analysis

Analysis starts at the moment of collection, with assessment of fluid color and ease of collection. If the fluid is clear initially and becomes bloody during collection, or vice versa, blood contamination is likely. If the fluid remains bloody throughout collection, then hemorrhage or red blood cell (RBC) diapedesis is likely occurring. If the fluid resembles peripheral blood, this could be due to severe hemorrhage or aspiration of a highly vascularized organ, such as the spleen. Differentiation between these possibilities can be accomplished by placing the bloody fluid into a non-anticoagulant (red top) tube. Because blood clots and lyses rapidly *in vivo*, the absence of a clot supports *in vivo* hemorrhage versus blood contamination. In contrast, clots in the fluid would support blood contamination, although peracute hemorrhage is possible. Visual inspection of fluid color and clarity after collection also yields other helpful information and can guide smear preparation and additional diagnostic testing (Box 74-1).

Box 74-1

Visual Characteristics of a Fluid Yield Clues as to the Mechanism and Potential Cause of an Effusion

Colorless, transparent: Likely low-protein transudate, low cellularity (sediment and direct smears recommended); assess patient for low albumin and protein-losing conditions and liver disease (portal hypertension).

Light to moderate yellow, transparent to slightly turbid: Likely transudative effusion (low- or high-protein); low to moderate cellularity (sediment and direct smears recommended). Various causes (see Table 74-1).

Light to moderate red to red-yellow, slightly to moderately turbid: Likely transudative effusion (high or low protein, but frequently high) with concurrent hemorrhage, RBC diapedesis, or blood contamination; low to moderate cellularity (sediment and direct smears recommended). Various causes (see Table 74-1).

Light to moderate yellow, transparent to lightly turbid, viscous, ± fibrin clot (cats only): Likely exudative effusion; moderate to high cellularity (direct smears likely sufficient); high total protein by refractometer (>2.5 g/dL); suspect feline infectious peritonitis.

Yellow to yellow-white, opaque to flocculent, may be lightly or moderately red, supernatant clears after centrifugation: Suspect exudative effusion; high cellularity (direct smears sufficient); culture or additional testing may be warranted, e.g., total bilirubin or creatinine concentrations if suspected biliary or urinary tract rupture or leakage.

White to pink to light red, opaque to opalescent with a cream layer on refrigeration, supernatant opaque after centrifugation: Suspect chylous effusion with concurrent hemorrhage, RBC diapedesis, or blood contamination (if red or pink); moderate to high cellularity (direct smears usually sufficient); additional testing may be warranted, e.g., triglyceride measurement.

Green to green-brown, moderately turbid to opaque: Likely high cellularity (direct smears sufficient); suspect bile peritonitis, enterocentesis, or ruptured GI tract (particularly if flocculent with food or particulate material); evaluate smear before accepting cell counts (bacteria, food debris counted as "cells").

Dark red (mimics blood), opaque, does not clot in a non-anticoagulant tube, measurable packed cell volume: Suspect hemorrhagic effusion (direct smears usually sufficient, although in laboratories buffy coats are prepared as well as direct smears).

Dark red (mimics blood), opaque, clots in a non-anticoagulant tube, measurable packed cell volume (EDTA): Aspiration of the spleen, peracute hemorrhage from large vessel, splenic or liver rupture.

Sample Handling, Storage and Submission

Fluid should be placed into an EDTA-anticoagulated (purple top) tube for cytologic examination. EDTA inhibits bacterial growth and preserves cellular features. Collection into a non-anticoagulant tube is helpful with bloody fluids and is always recommended (volume permitting) in the event biochemical tests or bacterial culture is desired, although submission of a culturette is preferred for the latter. Also, several smears should be made from fluids immediately after collection and rapidly air-dried (with a hair dryer on high aimed at the back of the slides) (see ch. 93). At the very least, a direct smear from unconcentrated fluid should be made; however, this can be paucicellular if the total nucleated cell count (TNCC) is low. Thus, sediment smears from centrifuged samples are recommended for fluids suspected to be of low cellularity (transparent to lightly turbid; see Box 74-1). Only a portion of the fluid should be centrifuged with the remainder left for cell counts and total protein estimation. Most laboratories also prefer to make their own cytologic smears. Smears and tubes should be labeled with the patient identification, date of collection, fluid (and smear) type, and a complete history provided. Submission of smears with fluid samples is critical to avoid storage-associated changes that impact cytologic interpretation and diagnostic accuracy of fluid analysis. These changes include:

- Deterioration of cells with storage: This affects cell counts and cell identification.
- Swelling of neutrophils: Mimics degenerative change.
- *In vitro* phagocytic activity: Phagocytosis of RBC and bacteria can occur within 30-120 minutes of sample collection, due to *in vitro* cellular activity.
- Bacterial proliferation: This can cause cellular lysis.

To minimize these storage-associated changes, fluid samples should be shipped promptly and kept refrigerated (on ice packs, avoiding direct contact with the pack to prevent freezing). Smears should be kept at 22° to 24° C and shipped in a break-proof container.

Cytologic Results

Most laboratories provide gross fluid characteristics, TNCC and RBC counts, a total protein estimate, and cytologic analysis on optimally concentrated smears (the smear type is dictated by the cell counts). Cytologic assessment can be done in-house using quick stains (e.g., Diff-Quik) and is worthwhile for rapid diagnosis and improving cytologic skills (e.g., comparing results to those of a clinical pathologist) (see ch. 86, 89, and 93).

- Cell counts: These can be done manually with a hemocytometer or with electronic counters. Point-of-care hematology analyzers should not be used for fluid analysis due to their poor sensitivity. Body cavity fluids also can plug or clog the analyzer. Not all nucleated cells are leukocytes (they could be mesothelial or cancer cells) and bacteria and particulate debris can be counted as "cells," falsely increasing the TNCC.
- Total protein: Estimates are obtained with a refractometer and are done on fluid supernatants after centrifugation if the fluid is turbid. A more accurate total protein measurement can be obtained from automated chemistry analyzers, but is more expensive and not usually required. Some laboratories provide specific gravity in lieu of total protein.
- Cytologic assessment: Smears are examined for the relative proportions of leukocytes, degenerate neutrophils (supporting bacterial sepsis), cytophagia (RBCs or other cells) and a potential cause; e.g.,

neoplastic cells, infectious agents. If RBCs are numerous, platelets would indicate blood contamination or peracute hemorrhage, whereas erythrophagia, hemosiderophages or hematoidin crystals support prior hemorrhage. If sample volume is insufficient for all tests, preference should be given to cytologic assessment, because cell counts can be estimated from direct smears. Cell counts and total protein measurement done in isolation may result in erroneous diagnoses.

- Other tests: Additional diagnostic tests may be desired, e.g., bilirubin, creatinine, pancreatic-specific lipase immunoreactivity or lipase,[1] lactate, pH, and glucose.[2,3] The latter 3 tests are best done in-house, because storage will yield erroneous values. Advanced cancer diagnostic tests, e.g., flow cytometric–based immunophenotyping[4,5] and clonality tests,[5] are best done on fresh samples (<3 days old).

Classification of Effusions

The author uses a mechanistic approach for fluid classification, which differs from the traditional classification scheme ("pure" transudate, "modified" transudate, exudate). Fluids accumulate in body cavities due to the following mechanisms: transudation, exudation, or viscus/vessel rupture (Table 74-1; Figure 74-1).

TABLE 74-1

Mechanistic Classification of Body Cavity Effusions*

TYPE OF EFFUSION	TOTAL PROTEIN (g/dL)	TOTAL NUCLEATED CELL COUNT ($\times 10^3$/mcL)	CYTOLOGIC FINDINGS	SOME CAUSES (NON-EXHAUSTIVE LIST, ITALICIZED ARE COMMON)
Transudative Effusions Venous or lymphatic hypertension, blockage, obstruction or dilatation (lymphangiectasia)				
Transudate (low-protein)†	<2.5	<5.0, usually <1.5	Mixture of macrophages and neutrophils, few lymphocytes and mesothelial cells (rare in cats), few RBCs	**Peritoneal:** *Chronic liver disease* (portal hypertension), hypoalbuminemia (<1.5 g/dL), non-exfoliating neoplasia, lymphangiectasia **Pleural** (uncommon): Neoplasia, cardiac disease, lung lobe torsion
Transudate (high-protein)†	>2.5	<5.0	Mixture of macrophages and neutrophils, few lymphocytes and mesothelial cells (rare in cats), variable RBC (diapedesis or hemorrhage, former more common)	**Peritoneal:** *Congestive heart failure* (dog), *chronic liver disease* (sinusoidal hypertension), *non-exfoliating neoplasia* **Pleural:** *Neoplasia, cardiac disease,* lung lobe torsion, etc.
Chylous effusion	>2.5 (can be falsely increased by lipid)	Variable, >3.0	High proportion of small lymphocytes, lipid vacuoles in macrophages; neutrophils may dominate if longstanding	**Peritoneal fluid** (rare): Neoplasia, lymphangiectasia, abdominal abscess, granuloma or adhesions **Pleural fluid:** *Cardiomyopathy* (cats), *idiopathic* (dogs, cats),

				neoplasia (e.g., thymoma), parasitic granuloma
Exudative Effusion Increased vascular permeability with or without leukocyte chemotaxis				
Classic exudate	>2.5	>5.0	Neutrophils dominate and may be degenerate or mixture of neutrophils and macrophages, cause may be identified	*Bacteria,* fungi, parasites (e.g., Mesocestoides), *neoplasia,* foreign body, *ruptured or leaking viscus, tissue/organ inflammation* (pancreatitis, pneumonia)
Feline infectious peritonitis	>2.5, often >5.0	<5.0, sometimes higher	Mixture of neutrophils (60-80%) and macrophages (20-40%), fibrin clots, proteinaceous background, few mesothelial cells and lymphocytes	
Vessel or Viscus Rupture May initially start out with transudative counts and low protein (biliary, urinary rupture) and become exudative with time				
Hemorrhage (usually >1 × 106/mcL RBC or a packed cell volume > 1%)	Usually >2.5	Depends on peripheral blood count	Many RBCs, no or very few platelets, erythrophagia and/or hemosiderin in macrophages and/or hematoidin crystals, leukocytes are blood-associated unless concurrent inflammation	**Both cavities:** *Trauma,* hemostatic disorder (e.g., anticoagulant rodenticide intoxication), neoplasia **Pleural cavity:** Angiostrongylus vasorum,[9] Streptococcus zooepidemicus[10] **Peritoneal cavity:** *Neoplasia* (e.g., hemangiosarcoma), ruptured liver (e.g., amyloidosis in cats)
Biliary rupture/leakage	Variable, often >3.0	Variable, often >5.0	If exudative, mixture of neutrophils (dominant) and macrophages, yellow-brown bile in background or in phagocytes, may see "white" bile (mucus), concurrent hemorrhage (erythrophages, hemosiderophages); patient may be icteric, confirm with bilirubin measurement of fluid (often >2× serum)	*Trauma, mucocele* (dogs), cholelithiasis, neoplasia, or severe necrotizing inflammation (cholecystitis)
Uroperitoneum	Variable	Variable	Initially low protein and cell count (dilution with urine if large rupture), becoming exudative with time; concurrent hemorrhage (see above); confirm with creatinine measurement of fluid (usually >2× serum)	*Trauma,* urolithiasis, neoplasia or severe necrotizing inflammation
Gastrointestinal rupture/leakage	Variable	Variable (often unreliable if interference from bacteria or intestinal contents)	Food material and/or phagocytized bacteria with peritoneal fluid cells (must be differentiated from a partial enterocentesis), may see concurrent hemorrhage	Trauma, severe inflammation, obstruction, torsion
Neoplasia Causes effusions through various mechanisms, including transudation, exudation and viscus rupture/leakage				
Neoplastic effusion	Variable,	Variable	Neoplastic cells in fluid (more common with round	*Lymphoma, carcinoma,*

	often >2.5		or epithelial cell tumors), usually fluid is transudative, but can be exudative (tumor necrosis, inflammatory cytokines, sepsis) with concurrent hemorrhage	mast cell tumor, mesothelioma, others

*This classification is based on a combination of total protein concentration, nucleated and red blood cell (RBC) count and cytologic findings, and is helpful for narrowing down the differential diagnostic list for the cause of the effusion.

†Differentiation of transudates into low- and high-protein effusions is only meaningful for peritoneal effusions.

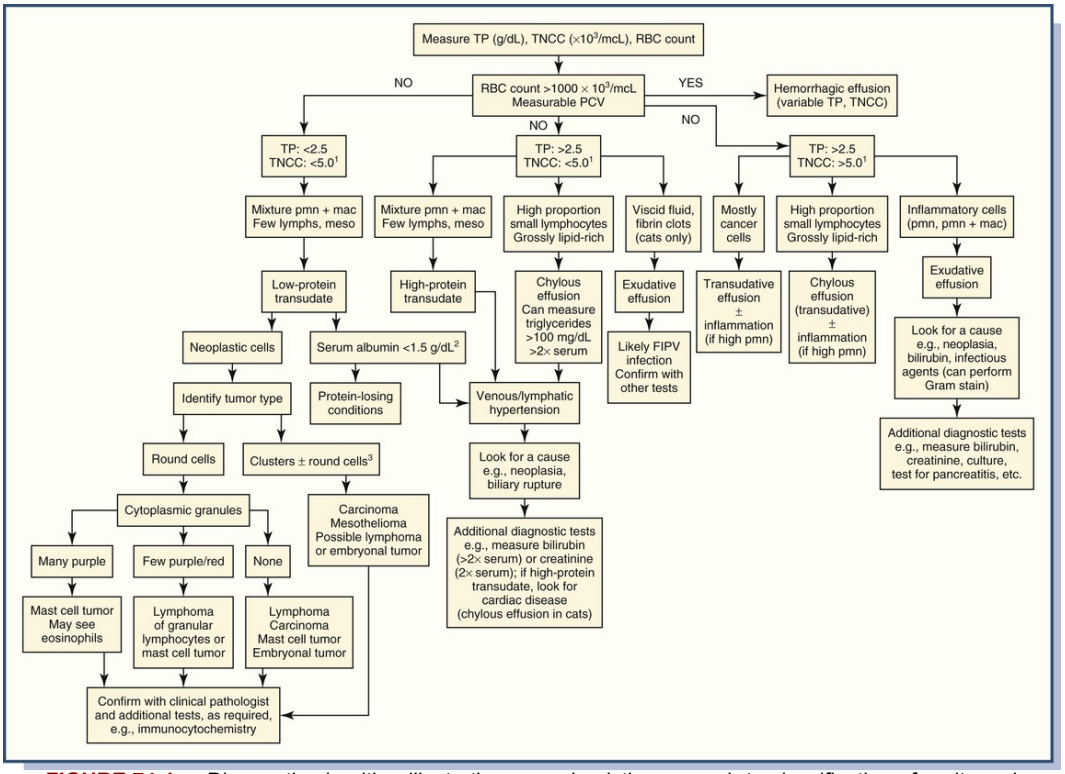

FIGURE 74-1 Diagnostic algorithm illustrating a mechanistic approach to classification of peritoneal and pleural cavity effusions in small animal patients. *FIPV,* Feline infectious peritonitis-associated coronavirus; *Lymphs,* lymphocytes; *Mac,* macrophages; *Meso,* mesothelial cells; *PCV,* Packed cell volume; *PMN,* neutrophils; *RBC,* red blood cell; *TNCC,* total nucleated count; *TP,* total protein by refractometer. [1]If RBC count is > 50 × 10^3/mcL and no overt contamination is noted during collection, there is likely concurrent diapedesis (transudates) or hemorrhage (exudates or less frequently, transudates). [2]Hypoalbuminemia is an uncommon solitary cause of transudative effusions, and usually other transudative mechanisms are concurrently at play, e.g., venous hypertension. [3]Tumor cells must be distinguished from reactive mesothelial cells, particularly in dogs. This distinction is based on cytologic criteria of malignancy but can be difficult in individual patients, necessitating additional diagnostic tests. (Adapted with permission from eClinPath.com.)

Transudation

This is the most common type of effusion and is due to alterations in hydrodynamic forces, typically venous or lymphatic hypertension or obstruction. A marked decrease in oncotic pressure from severe hypoalbuminemia (<1.5 g/dL, e.g., due to nephrotic syndrome) can also result in a transudative effusion, but is rarely the sole cause (usually accompanied by venous or lymphatic hypertension). Transudative effusions often are light to medium yellow, transparent to lightly cloudy, with TNCC <5,000/mcL and total protein usually <5.0 g/dL. RBC counts are variable. A mixture of non-degenerate neutrophils and macrophages, with fewer lymphocytes and mesothelial cells (rare in cats), is seen on cytologic smears. RBCs can be due to blood contamination, diapedesis (from the increased pressure) or less frequently, hemorrhage. Erythrophagia (and rarely hemosiderophages) will be seen with diapedesis and prior hemorrhage (unless peracute). Unfortunately, a cause frequently is not evident cytologically with transudative effusions. In peritoneal but

not pleural fluid, transudative effusions can be separated into "low-protein" and "high-protein" transudates. This distinction is useful because it identifies the location of the hypertension, which helps narrow down the list of causes (see Table 74-1).

- Low-protein (protein-poor or pure) transudates: Colorless to light yellow fluid with minimal blood. Prehepatic (mesenteric lymphatics) or hepatic presinusoidal (portal) or early sinusoidal hypertension causes leakage of low-protein intestinal lymph. The most common cause is liver disease, followed by protein-losing conditions.
- High-protein (protein-rich or modified) transudates: Light to moderately yellow fluid that is frequently blood-tinged from concurrent diapedesis. Hepatic sinusoidal or post-sinusoidal hypertension causes leakage of high protein hepatic lymph. Common causes are liver disease, cancer and congestive heart failure (dogs can develop pleural and peritoneal effusions, with the latter being more common, particularly with right-sided heart failure; in cats, pleural effusion can be seen with biventricular or right-sided heart failure).
- Chylous effusion: This transudative variant is more common in pleural fluid. The fluid is usually opaque and white and frequently blood-tinged (pink to light red). A fat layer can form on standing or refrigeration due to buoyant chylomicrons. The TNCC is variable (can be >5,000/mcL) and consists of high proportions of small lymphocytes, along with non-degenerate neutrophils and macrophages, which can contain cytoplasmic lipid droplets. In longer-standing chylous effusions, concurrent inflammation can be present from the irritating effects of chyle. In the latter fluids, neutrophils can dominate, but lymphocyte proportions are still high. A chylous effusion can be confirmed by high fluid triglyceride concentrations (usually >2× serum or >100 mg/dL). Chylous effusions from some anorectic animals may not be grossly chylous and may have low triglyceride concentrations. Chylous pleural effusions can be seen in cats with cardiomyopathy, presumably due to high hydrostatic pressure in the cranial vena cava. However, the absence of heart disease in many cases, and successful treatment using such techniques as thoracic duct ligation and pericardiectomy, suggest that other as yet unknown mechanisms (potentially associated with pericardial disease) may lead to the development of chylous effusions in cats with or without cardiac disease.[6] Chylous ascites is rare and is caused by lymphangiectasia or lymphatic blockage (neoplasia, adhesions, abscesses, etc.).

Exudation

Exudative effusions are caused by increased vascular permeability due to inflammation, with leakage of serum protein and inflammatory cell chemotaxis. Exudative effusions are usually yellow to white, lightly to moderately cloudy to opaque or flocculent, with TNCC >5,000/mcL and total protein >2.5 g/dL. The supernatant can clear after centrifugation (cells pellet). Variable proportions of neutrophils and macrophages with fewer lymphocytes are seen on cytologic smears, with clusters of reactive mesothelial cells (rare in cats). The dominant inflammatory cell will depend on the cause and duration of the effusion. Neutrophils usually comprise >80% of cells with acute bacterial infections and sterile peritonitis, whereas a more mixed inflammatory infiltrate (<80% neutrophils and >20% macrophages) occurs with longer duration effusions or specific causes, e.g., some fungal infections and cancer. Although degenerate neutrophils are considered evidence of bacterial sepsis, they can also be seen with sterile inflammation, e.g., bile peritonitis.

Culture of the fluid is indicated in animals with an exudative effusion, whether or not degenerate neutrophils or infectious causes are seen on smears. There are various causes of an exudative effusion, including infectious agents (bacteria, fungi, tapeworm, coronavirus causing feline infectious peritonitis [FIP]), foreign bodies (e.g., retained surgical sponge,[7] penetrating grass awn), viscus leakage or rupture, and tissue inflammation (e.g., pleuropneumonia, pancreatitis, steatitis). FIP deserves special mention due to the unique characteristics of the effusion. Although the effusion is exudative (from a vasculitis), leukocyte chemotaxis is not prominent, yielding a high-protein, light- to moderate-yellow viscid fluid, with fibrin clots, and a TNCC usually <5,000/mcL. Smears contain a mixture of slightly degenerate neutrophils with moderate macrophages and few lymphocytes or mesothelial cells, with protein crescents or precipitated protein in the background. In the author's experience, immunocytochemical staining for FIP coronaviral antigen[8] is unrewarding, and therefore, a confirmatory diagnosis still relies on the histopathologic finding of pyogranulomatous inflammation with positive histochemical staining for FIP-associated coronaviral antigen in macrophages (see ch. 224).

Vessel or Viscus Rupture or Leakage

These can be separated into hemorrhagic effusions, bile and uroperitoneum and gastrointestinal (GI) leakage or rupture (see Table 74-1) (see ch. 90 and 102).

- Hemorrhagic effusion: These effusions are bloody throughout collection, resemble peripheral blood, do not clot in a non-anticoagulant tube (see Box 74-1), and have a measurable packed cell volume (>1%). Direct and buffy coat smears (to concentrate nucleated cells) usually are prepared for examination. On smears, the fluid resembles blood with blood-associated leukocytes and variable numbers of mesothelial cells. There is evidence of chronic or prior hemorrhage (erythrophagia, hemosiderophages, hematoidin crystals) with no or few platelets. In peracute hemorrhage, platelets can be seen and the fluid can clot. Common causes of abdominal hemorrhage are trauma, neoplasia (hemangiosarcoma), and anticoagulant rodenticide intoxication. Hemorrhagic pleural effusions are uncommon and can be due to trauma, neoplasia, or parasitic or bacterial infection.[9,10] Any animal with an unexplained hemorrhagic effusion should be tested for an underlying hemostatic disorder, e.g., anticoagulant rodenticide intoxication.
- Bile peritonitis: Depending on the degree of leakage, the fluid can be transudative or exudative, although an exudative effusion with mixed non-degenerate neutrophils and macrophages is typical. Free or phagocytized green-brown to yellow bile pigment can be seen, but small amounts might be missed and can resemble other pigments, e.g., hemosiderin. In some patients, there are only aggregates of light blue mucus, so-called "white bile."[11] High bilirubin concentrations (usually >2× serum) in the effusion can confirm a bile peritonitis; however, low bilirubin concentrations can be seen in dogs with ruptured mucoceles, in which only "white bile" is present in the fluid. Note that mucus also can be seen with mucinous adenocarcinomas and myxosarcoma[12] and small amounts might be mistaken for fibrin (or vice versa).
- Uroabdomen: In an acute rupture, urine may flood the abdomen, yielding a low-protein transudate. However, with time, a sterile peritonitis will develop. There are no cytologic findings typical of uroabdomen, so confirmation requires finding high creatinine concentrations in the fluid compared to blood (usually >2×).[13]
- Gastrointestinal leakage or rupture: This results in a septic peritonitis with free and phagocytized mixed bacteria typical of gut flora, including Gram-positive cocci in pairs and various Gram-negative rods. If there is a yeast or bacterial overgrowth, offending organisms can also be seen. Bacterial phagocytosis is a key finding for differentiating a partial enterocentesis (with aspiration of abdominal fluid and GI contents) from an acute GI rupture. Intracellular bacteria are not expected with the former (in smears made from freshly collected fluid). If an aspirate only consists of intestinal contents (food debris and mixed bacteria), an enterocentesis is likely.

Neoplastic Effusions

Although neoplastic effusions are not part of the mechanistic classification scheme, identification of neoplastic cells can provide an immediate diagnosis. Neoplasia can yield effusions via all of the above mechanisms and more than one mechanism may be operative, e.g., hemorrhagic effusion with inflammation. Tumors of round (particularly lymphoma and mast cell tumor) and epithelial cell origin exfoliate readily, whereas neoplastic cells from sarcomas are rarely seen (unless the primary tumor is directly aspirated).

- Lymphoma: Lymphoma is diagnosed readily when there are many individual intermediate to large discrete cells with high nuclear to cytoplasmic ratios (see ch. 344). Low numbers of tumor cells or cells from a small-cell lymphoma are more difficult to distinguish from reactive and normal counterparts, respectively. Advanced diagnostic testing, such as flow cytometric or immunocytochemical-based immunophenotyping and clonality tests, can be performed on body cavity fluids but should only be done if there is a sufficient number of questionable tumor cells (to avoid misdiagnosis, e.g., pseudoclonality). Other tumors also can resemble lymphoma, including poorly granulated mast cell tumors, embryonal tumors (e.g., nephroblastoma), and carcinomas.
- Mast cell tumors: These also exfoliate as individual cells and can be distinguished from lymphoma by lower nuclear-to-cytoplasmic ratios and variable numbers of purple granules dispersed in the cytoplasm (see ch. 349). Accompanying eosinophilic inflammation can also be seen. Poorly granulated tumors can be difficult to distinguish from a lymphoma of granular lymphocytes[14,15] without other testing, e.g., tryptase or CD3 immunostaining.
- Carcinomas: These exfoliate as variably sized clusters of round to polygonal cells, with some individual cells. The tumor cells must be distinguished from reactive mesothelial cells (particularly in dogs; it is rare to find many reactive mesothelial cells in effusions in cats), and macrophages (which can be seen in small aggregates in some fluids). Distinction can be difficult unless the tumor cells are showing prominent cytologic criteria of malignancy, e.g., marked anisokaryosis and/or macronucleoli. Mesothelial cells can become quite reactive and demonstrate abnormal features (e.g., trinucleation) in effusions. Ultimately, the

diagnosis of carcinoma can rely on documentation of the tumor in internal organs, particularly if the cells are bland and mimic mesothelium.

- Mesothelioma: This tumor should not be diagnosed with certainty from an effusion. Neoplastic mesothelial cells can resemble reactive counterparts (can lack cytologic criteria of malignancy) and exfoliated carcinoma cells. Even if the cells resemble mesothelial cells (central nuclei, moderate cytoplasm with a fringe or "corona") and are displaying features of malignancy, a diagnosis of mesothelioma requires documentation of tissue invasion on histopathologic examination. Because mesothelioma is an uncommon neoplasm, if clusters of cells with prominent cytologic criteria of malignancy are seen in a fluid, an underlying carcinoma is far more likely. The presence of multiple body cavity effusions is not specific for mesothelioma.

Joint Fluid

Unlike thoracic and abdominal fluid, synovial fluid can be aspirated from normal joints (see ch. 94). Normal synovial fluid is light yellow and transparent, with no blood, and is quite viscous due to its hyaluronic acid content. The fluid should be collected into EDTA and handled as described above for other body cavity fluids, with emphasis placed on rapid drying of smears. This is because cells "ball up" in the viscous fluid and are difficult to identify, let alone find intracellular structures that may be informative, e.g., infectious agents. Cytologic analysis of joint fluid usually includes cell counts, measurement of total protein by refractometer, a viscosity estimate, and smear examination. Viscosity usually is measured subjectively as the length of a "strand" of fluid that forms between a needle tip and a slide or the edge of the collection tube and tip of a plastic pipette (a gloved fingertip can be used in place of the tip of a needle or plastic pipette; Figure 74-2). Joint fluid of normal viscosity should form a strand that is at least 2 cm long. As with other body cavity fluids, when a low-volume sample is obtained, preference should be given to cytologic assessment of well-made smears over cell counts or measurement of protein content.

FIGURE 74-2 Normal synovial fluid forms a strand between a gloved fingertip and the microscope slide on which it has been placed.

Normal TNCC in synovial fluid from dogs ranges from 500 to 3,000/mcL between different joints, with <3,000/mcL being used as a general "normal" upper limit, although most fluids have counts <1,000/mcL. Counts generally are <1,000/mcL in cats.[16] The normal total protein concentration by refractometer is

<2.5 g/dL. On smears, the fluid consists of mononuclear cells (mostly large, with <20% lymphocytes) with <10% neutrophils, and a stippled or stringy pink to purple background from the viscosity. It can be difficult to distinguish lymphocytes from non-reactive macrophages and macrophages from synoviocytes; therefore, many clinical pathologists use the term "small and large mononuclear" cells. The term "reactive" means that the macrophage has increased cytoplasm that appears foamy, and could contain vacuoles or phagocytic debris, versus a non-reactive macrophage, which has non-vacuolated cytoplasm and does not demonstrate phagocytic activity. Other biochemical analyses are not usually performed on joint fluid.

Cytologic Interpretation

Results of joint fluid analysis rarely are specific for a particular disorder and rather fall into two general categories: non-inflammatory and inflammatory disease. These can be distinguished by TNCC, total protein concentration, and proportion of cell types in smears (Figure 74-3).

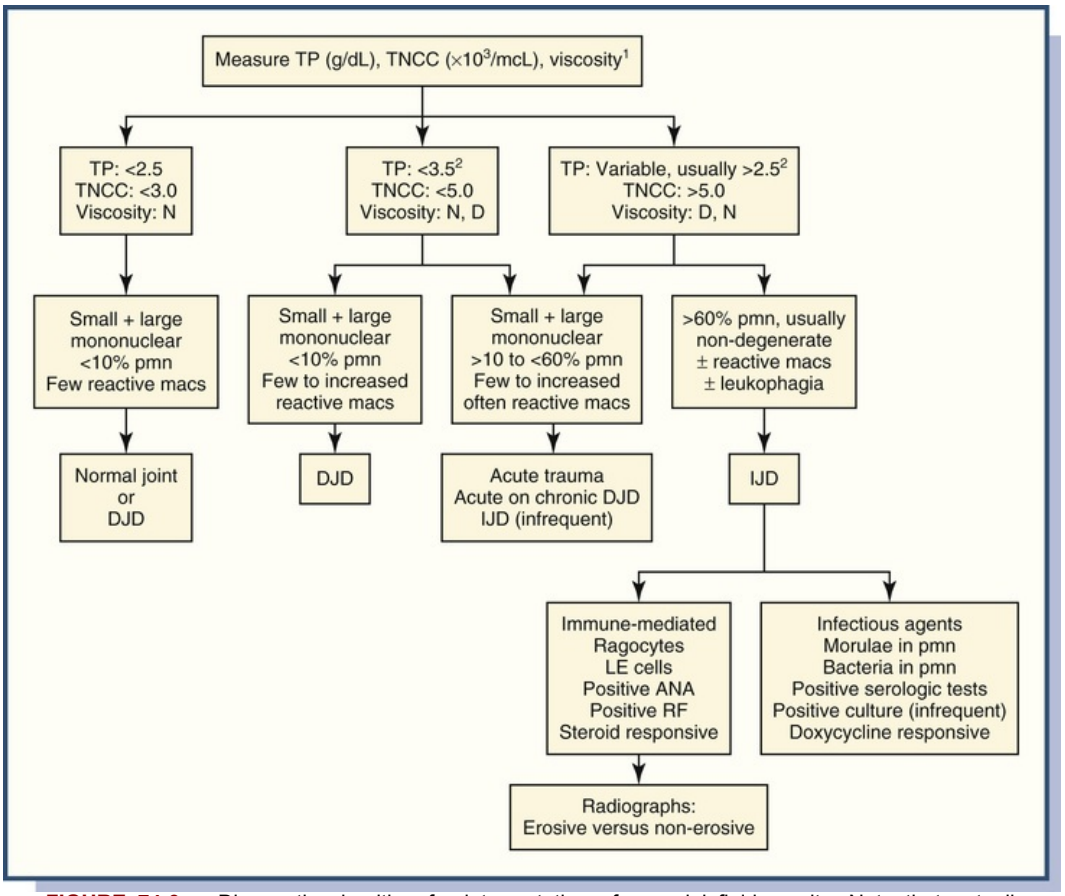

FIGURE 74-3 Diagnostic algorithm for interpretation of synovial fluid results. Note that not all scenarios are covered (e.g., neoplasia or hemarthrosis, but these are uncommon). *ANA,* Antinuclear antibody testing; *D,* decreased; *DJD,* degenerative joint disease; *IJD,* inflammatory joint disease; *macs,* macrophages; *N,* normal; *pmn,* neutrophils; *RF,* rheumatoid factor testing; *TNCC,* total nucleated cell count; *TP,* total protein. [1]A red blood cell (RBC) count should also be performed. Moderate to severe RBC contamination will increase the TNCC, total protein concentration, and proportion of neutrophils, which could hinder identification of an inflammatory arthropathy. Standard cytologic principles apply for differentiation of blood contamination and *in vivo* hemarthrosis (see text for abdominal and thoracic cavity effusions). [2]EDTA can falsely increase the refractive index in samples of small volume (<0.2 mL).[19] (Reproduced with permission from eClinPath.com.)

Non-Inflammatory Joint Disease

This term is used for joints with degenerative disease, due to musculoskeletal abnormalities (e.g., osteochondrosis) or trauma. The fluid lacks evidence of active inflammation (<10% neutrophils) and can be normal or show mild cytologic abnormalities, such as mildly increased total protein concentration, increased

proportions of reactive macrophages, mildly increased TNCC (usually <5,000/mcL) and decreased viscosity, alone or in various combinations. Some cases have evidence of synovial hyperplasia (multinucleated or aggregates of synoviocytes) or cartilage erosion (osteoclasts).

Inflammatory Joint Disease

This term applies to joints with active inflammation, specifically high TNCC (usually >5,000/mcL) with increased proportions of neutrophils (usually >20%).[17,18] There are two general causes: infectious agents and immune-mediated disease (primary, or secondary to vasculitis or infectious agents, e.g., borreliosis/Lyme disease). These causes are difficult to distinguish based on cytologic assessment alone, because neutrophils rarely are degenerate in septic joints and unique diagnostic features often are absent (see below). A single affected joint should raise suspicion for a bacterial infection (e.g., from a penetrating foreign body), whereas a polyarthropathy localized to carpi and tarsi is highly suspicious for immune-mediated disease. All animals presenting with signs of a monoarthropathy should be carefully examined for involvement of other joints so that a polyarthropathy is not missed. Note that acute joint trauma (e.g., cranial cruciate rupture) can result in mild inflammation (TNCC up to 12,000/mcL with up to 65% neutrophils); however, this abnormality should be localized to the affected stifle joint. Inflammatory joint disease of various causes usually affects dogs and is rare in cats.[19,20] The most common cause of an inflammatory polyarthropathy in dogs is immune-mediated disease,[17,18] although tick-borne infections (borreliosis, *Anaplasma phagocytophilum* or *Ehrlichia ewingii* infections) are becoming increasingly frequent. Neutrophils should be carefully examined for bacteria (e.g., *Anaplasma* morulae), protozoa (e.g., *Leishmania*[21]), and particulate (ragocytes) or homogenous nuclear material (lupus erythematosus cells), but these diagnostic findings are rarely observed. Cytologic analysis alone usually is not conclusive as to the cause of joint inflammation and other tests are required for a specific diagnosis, e.g., serologic tests. In some cases, diagnosis relies upon an appropriate response to therapy, e.g., doxycycline treatment for borreliosis.

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SECTION V

Techniques

OUTLINE

General
Skin
Abdomen
General Centesis and Biopsy
Respiratory/Cardiovascular
Renal/Urinary/Prostatic
Gastrointestinal
Neurologic
Reproductive

General

OUTLINE

Chapter 75 Venous and Arterial Puncture

Chapter 76 Jugular Catheterization and Central Venous Pressure Measurement

Chapter 77 Intraosseous Catheters

Chapter 78 Constant Rate Infusions

Chapter 79 Ear Vein Blood Glucose Monitoring

Chapter 80 Buccal Mucosal Bleeding Time

Chapter 81 Fecal Examination

Chapter 82 Nasoesophageal, Esophagostomy, Gastrostomy, and Jejunal Tube Placement Techniques

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CHAPTER 75

Venous and Arterial Puncture

Linda Merrill

Venipuncture is utilized for phlebotomy or intravenous injections. Patient and sample identification help avoid unnecessary venipuncture. A sampling catheter (see ch. 76) should be considered in patients requiring frequent assessment. The most commonly utilized veins include the cephalic, external jugular, femoral (cats), and lateral saphenous (dogs) (E-Table 75-1 and Video 75-1), but sublingual, pedal, auricular, and abdominal veins have been used. Hospital-acquired anemia is a concern in small animal medicine; it can be minimized by combining laboratory tests, utilizing microtainer vials, and using existing samples for additional tests. In humans it is of greatest importance when there is preexisting anemia and in cases that require frequent monitoring.[1] Ideally, blood samples should be collected at least 2 hours postprandially, but preferably after a >4-hour fast.[2]

E-TABLE 75-1

Venipuncture

Pull List—Materials and Equipment	
	Best practice—non-sterile gloves; accepted practice—washed or sanitized hands
	Clippers
	Isopropyl alcohol
	Skin preparation for blood culture—best practice >0.5% chlorhexidine with alcohol
	Tourniquet or manual occlusion
	Cotton ball, gauze square or Telfa pad
	Tape or wrap to use as an adhesive bandage if needed
	Tube holder and needle or syringe and needle or winged collection set
	Sample collection tubes as indicated by the prescribed tests
	Sharps container

Commonly Used Veins			
VEIN	**COMMONLY USED**	**LOCATION**	**COMMENTS**
Jugular	Dog/cat	Both sides of the neck, in furrow, beside trachea	Usually the largest, accessible vein, good for large samples
Cephalic	Dog/cat	Front leg veins	Don't use if scheduled for surgery or chemotherapy
Lateral saphenous (tarsal)	Dog	Lateral aspect of tarsal joint	Easy to visualize but very mobile vein
Medial saphenous/femoral	Cat	Medial aspect of thigh	Good choice for fractious cats

Checklist for Performing Venipuncture

	1. Hand hygiene—accepted practice; also put on non-sterile gloves—best practice
	2. Assemble needed equipment and materials, ensure they are within easy reach
	3. Confirm patient identity and samples needed
	4. Place tourniquet or manually occlude selected vein
	5. Clip hair if needed/required
	6. Use a small amount of alcohol if needed to visualize the vein
	7. Palpate vein—determine size, depth, direction and if suitable for venipuncture
	8. Release tourniquet or manually occlusion
	9. Cleanse the skin—surgical prep required for blood cultures
	10. Reapply tourniquet or manual occlusion
	11. Anchor vein with non-dominant hand—pull skin taut, flex joint, and/or stabilize
	12. Perform venipuncture—bevel up, angle of entry of 15-30°, under skin first if needed
	13. Using a tube holder, fill tubes in appropriate order OR Draw required amount blood
	14. Release tourniquet or manual occlusion
	15. Remove the needle and simultaneously cover venipuncture site
	16. Apply moderate pressure for 1-2 minutes
	17. Clean venipuncture site if needed
	18. Apply tape or wrap to use as an adhesive bandage if needed
	19. Place sharps into sharps container
	20. Label collection tubes
	21. Hand hygiene

Hand hygiene is essential; the use of non-sterile examination gloves is recommended. Palpation using gentle pressure allows for determination of the direction, size, and depth of the vein. Isopropyl alcohol can facilitate visualization of the vein but alcohol contamination of the sample may result in hemolysis. Clipping a small amount of hair is usually acceptable and can decrease the use of alcohol. The skin should be free of gross contaminants, cleansed, and dry. Surgical preparation is required prior to blood culture collection.

The vein should be stabilized with the non-dominant hand placed next to the vein, or pulling the skin taut, or flexing the limb. Venous occlusion should not last >1 minute, which can cause hemoconcentration and discomfort.[3] In dehydrated, thick- or loose-skinned patients, the needle may need to be placed through the skin first, before entering the vein. To enter the vein, the needle should be centered over the vein with the bevel facing up, then advanced using a swift, continuous motion until the entire bevel is within the lumen of the vein. The needle entry angle should be 15° (superficial veins) to 30° (deeper veins). A slight release in resistance may be detected when entering the vein. If no blood enters the syringe, it is appropriate to withdraw, slightly redirect, and advance the needle, minimizing the number of such changes to avoid tissue trauma. The negative pressure applied to the plunger should be slight and continuous. After collecting the sample, venous occlusion is released; then the needle is quickly withdrawn. Moderate pressure should be applied to the phlebotomy site with a cotton ball for 1-2 minutes to prevent bleeding. The phlebotomist must check the site before dismissing the patient. Hand hygiene should be performed post-procedure. Materials and a stepwise approach are listed in E-Table 75-1.

Complications are uncommon when phlebotomy is performed correctly. A hematoma may form if the needle is only partially inserted into the vein, if both the top and bottom walls are pierced, or if the patient moves during the procedure; if noted, stop immediately, withdraw the needle, and apply pressure to the site. Phlebitis can be minimized with aseptic technique and minimal movement of the needle tip. Referencing anatomic relationships of veins to nerves can minimize the chance of injury and nerve pain.[4] Vasovagal syncope during phlebotomy may be more likely to occur in patients with cardiac disease. A good maximum number of blood draw attempts is two, with reasonable certainty of accessing the vein on each attempt. Some test results may be altered by stress, anxiety or fear (E-Table 75-2) and multiple venipuncture attempts increase complications. A change in personnel, restraint, or technique, or the use of sedation, may resolve the problem.

E-TABLE 75-2

Effects of Hemolysis, Lipemia, and Stress on Laboratory Values

TEST	HEMOLYSIS EFFECT	LIPEMIA EFFECT	STRESS EFFECT
ALT	↑ Values	↑ Values	
Albumin	↑ Values	↑ Values	
Amylase	↑ Values	↓ Values	
Ammonia	↑ or ↓ Values		↑ or ↓ Values
AST	↑ Values	↑ or ↓ Values	
Bilirubin	↑ or ↓ Values	↑ Values	
Calcium	↓ Values	↑ Values	
Chloride	↑ or ↓ Values	↑ or ↓ Values	
Cholesterol	↑ Values		
Creatine kinase	↑ Values		Altered values
Creatinine			Altered values
Fructosamine	↑ Values		
GGT	↑ or ↓ Values		
Globulins	↑ Values	↑ Values	
Glucose			↑ Values
Lipase		↑ Values	
Lipids/triglycerides	↑ Values		
Magnesium	↑ Values	↓ Values	
Phosphorus	↑ Values		
Potassium	↑ or ↓ Values		
Sodium	↓ Values		
Total protein	↑ Values		

Commonly Used Blood Tubes, Their Draw Order, and Handling Instructions

COLOR	SIZES	ADDITIVE	ANTICOAGULANT?	SPECIAL DIRECTIONS	COMMON USES
NA	20 mL	Culture media		Sterile skin prep	Blood culture
Clear	3 mL	No	No	Sterile tube	Discard tube
Light blue (BTT)	1.8 mL	Sodium citrate	Yes	Invert 3-4 times, requires a full draw	Coagulation studies, minimum of 90% fill
Red (RTT)	3 mL	No (glass) coating (plastic)	No	Do not invert—glass Invert 5 times—plastic	Serum chemistry, therapeutic drug monitoring
Red/gray (SST)	3.5 mL	Gel separator and clot activator	No	Invert 5 times	Known as a serum separator or tiger top tube, used for serum chemistry
Yellow (gold)	Microtainer	Same as SST	No	Invert 5 times	Serum chemistry
Green	4 mL, microtainer	Heparin	Yes	Invert 8 times	Plasma chemistry

Lavender (LTT)	2 mL, microtainer	EDTA	Yes	Invert 8 times	Hematology
Gray	3 mL	Potassium oxalate, sodium fluoride	Yes	Invert 8-10 times	Glucose

Estridge BH, Reynolds AP: *Foundations of medical laboratory science,* ed 6, Mason, OH, 2012, Cengage Learning.

WHO: *WHO guidelines on drawing blood: best practices in phlebotomy,* Geneva, 2010, World Health Organization.

ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase; *BTT,* blue top tube; *GGT,* gamma-glutamyltransferase; *LTT,* lavender top tube; *NA,* does not apply; *RTT,* red top tube; *SST,* serum separator tube.

This table lists the most common blood collection tubes utilized. Tubes are listed in the recommended order of draw, first to last. Other options exist for specialized, rarely used tests. (Estridge & Reynolds, 2012) (WHO, 2010).

Placement of Peripheral Venous Catheters

A peripheral venous catheter is indicated when ongoing venous access is required. Selection of a vein for a catheter is dependent on the indication, expected duration of use (short/long term), and quantity and type of infusate. The first attempt at catheterization should be as distal on the limb as is practical if difficulties are expected, so repeat attempts can occur more proximally. In all but emergent situations, the smallest gauge catheter adequate for the prescribed therapy should be selected, for adequate blood flow around the catheter and lower risk of phlebitis. Central and jugular catheters are described in ch. 76.

Materials and a stepwise approach are listed in E-Table 75-3 and demonstrated in Videos 75-2 and 75-3. Prior to placement, the catheter should be pre-flushed with saline and spun on the stylet (to ease its advancement off the stylet). Topical anesthesia or local block may be indicated for patient comfort. To prevent intravascular catheter-related bloodstream infections (CRBSI), a complete, aseptic, surgical preparation of the skin using >0.5% chlorhexidine with isopropyl alcohol should be performed.[5] Aseptic technique must be maintained throughout. After successful venipuncture with the catheter and stylet, a blood flash occurs in the hub. Hypotensive patients may not show this indicator, requiring aspiration to confirm placement. The entire bevel of the stylet *and* 1-2 mm more must be entirely in the lumen of the vein. Then, the entry angle is reduced to make the catheter almost parallel to the skin, and the catheter is advanced off the stylet and into the vein. If resistance is felt, the catheter is repositioned until free blood flow is obtained, and then catheter advancement off the stylet is attempted again. The catheter is never pulled back over the stylet, which can cut the catheter tip causing embolization.[6] Digital pressure can be applied proximal to the catheter hub to prevent blood loss during port placement. If the catheter is in the vein lumen but will not advance farther, a "fluid stylet" can be used: the stylet is removed and replaced with a 3-5 mL saline syringe, aspiration confirms that the catheter tip is still in the vein, and then gentle saline infusion allows the catheter to be advanced and "floated" into place. This is demonstrated in Video 75-4. Tape and bandaging material are used for stabilizing, protecting connection points, and securing the catheter.

E-TABLE 75-3

Intravenous Catheter

Pull List—Equipment	
	Best practice—non-sterile gloves; accepted practice—washed or sanitized hands
	Clippers, skin preparation—best practice >0.5% chlorhexidine with alcohol
	Over-the-needle IV catheter—size appropriate to patient and vein
	Local anesthetic
	Injection port and optional T port—useful in small or short-legged patients
	Saline flush
	Tourniquet or manual occlusion
	Tape
	Band-aid or sterile nonadherent (Telfa) pad
	Bandaging material such as cast padding, stretch gauze, non-adhesive wrap

	Sharps container
Some IV Catheter Options for Consideration	
Shaving	Small rectangular shave provided the sterile field is adequate Complete circumferential shave may be indicated in long-haired animals
Asepsis	Cover hair just distal to field to protect catheter sterility during placement Place a Band-aid or sterile nonadherent (Telfa) pad over the venipuncture site
Tape	1-2 pieces with tabs for easy removal is adequate for short-term catheters Cross tape alters the direction of the pull Over/under taping isolates the port for easier injection
Wrap	Simple wrap helps to secure the catheter and ports to the limb Complete wrap of the limb may prevent distal edema
Checklist for IV Catheterization	
	1. Hand hygiene—accepted practice; also put on non-sterile gloves—best practice
	2. Assemble needed equipment and materials; ensure they are within easy reach
	3. Pre-flush catheter and ports with saline
	4. Place tourniquet or manually occlude selected vein
	5. Palpate vein—determine size, depth, direction, and if suitable for catheter
	6. Release tourniquet or manual occlusion
	7. Clip hair—area sufficient for sterile placement up to entire circumference of limb
	8. Surgical preparation of the skin—best practice >0.5% of chlorhexidine with alcohol
	9. Reapply tourniquet or manual occlusion
	10. Anchor vein with non-dominant hand—pull skin taut, flex joint, and/or stabilize
	11. Perform venipuncture—bevel up, angle entry of 15-30°, under skin first if needed
	12. Decrease angle, advance the catheter off the stylet, into the lumen of the vein
	13. Release tourniquet or manual occlusion
	14. Remove the stylet, ± manually occlude vein to minimize blood loss
	15. Place injection port, T-port or venoset into catheter
	16. Secure catheter to limb with tape
	17. Saline flush
	18. Cover venipuncture site with Band-aid or Telfa pad
	19. Apply additional tape and/or bandage material to further secure catheter
	20. Place sharps into sharps container
	21. Hand hygiene

Catheter maintenance should include the following[7]:

- Hand hygiene procedures before and after every catheter maintenance.
- Flushing of the catheter every 4 hours if continuous fluid therapy is not in use.
  - Use plain saline for flushes.[8,9] Aspirate and flush to check for patency.
- Evaluation of the site daily, including removal of the dressing if needed. Assessment for: (1) dampness of bandaging material; (2) tightness of the tape; (3) evidence of phlebitis (pain), thrombosis (palpable venous cord), or infection (warmth); (4) extravasation; and (5) limb swelling distal to the catheter.
- In humans, daily cleansing of the site with 2% chlorhexidine decreases CRBSI.[5]
- Swabbing needleless access ports with chlorhexidine before use (reduce contamination).

To minimize the risk of nosocomial infection, catheters should be replaced every 4 days,[5] if soiled, or if any problems are noted during catheter maintenance. The four recognized routes for contamination of catheters in human medicine are: migration of skin organisms at the insertion site to colonize the catheter tip (most

common), direct contamination of the catheter or catheter hub by contact (hands, fluids, devices), seeding of catheters from another focus of infection (less common), and infusate contamination (rare).[5]

When removing a catheter, material should be cut away or removed until the venipuncture site can be visualized. A cotton ball is placed on the venipuncture site and then the catheter is removed. Moderate pressure is applied for 1-2 minutes and then a wrap is placed for ≈30 minutes. The catheter should be inspected for signs of damage or infection.

Arteries: Arterial Puncture

Arterial puncture is used primarily for assessment of arterial blood gas (ABG) or acid base status (see ch. 128). The dorsal pedal and femoral arteries are used most commonly in dogs and cats (E-Table 75-4) but under certain circumstances, the sublingual, radial, brachial, or aural arteries can be utilized. The choice of artery also depends on adequate collateral circulation, which, in the rare event of arterial occlusion, ensures adequate perfusion to the limb. Arterial puncture is contraindicated in animals with severe bleeding disorders.

E-TABLE 75-4

Arterial Puncture

Pull List—Equipment	
	Best practice—non-sterile gloves; accepted practice—washed or sanitized hands
	Clippers
	Isopropyl alcohol
	Cotton ball or gauze square
	Tape or wrap to use as an adhesive bandage if needed
	Heparin-coated 1-3 mL syringe with a small gauge needle, or blood gas syringe
	Ice bath if collecting blood for blood gas analysis
	Cork or syringe cap
	Sharps container

Commonly Used Arteries		
ARTERY	**LOCATION**	**COMMENTS**
Dorsal metatarsal artery (pedal)	Dorsal aspect of the metatarsus	Smaller but easier access than other arteries
Femoral artery	Medial aspect of the thigh	Increased chance of hematoma formation

Checklist for Arterial Puncture	
	1. Hand hygiene—accepted practice; also put on non-sterile gloves—best practice
	2. Assemble needed equipment and materials, ensure they are within easy reach
	3. Confirm patient identity and sample needed
	4. Clip hair
	5. Palpate artery—determine size, depth, direction and if suitable for puncture
	6. Cleanse the skin
	7. Palpate artery with two fingers of the non-dominant hand
	8. Perform artery puncture—bevel up, angle entry of 45-60°, under skin first if needed
	9. Blood should spontaneously flow, aspirate if needed
	10. Remove the syringe/needle and immediately cap to prevent exposure to air
	11. Place sample in ice bath

	12. Simultaneously cover puncture site and apply moderate pressure for 5 minutes
	13. Clean patient if needed
	14. Apply tape or wrap to use as an adhesive bandage if needed
	15. Place sharps into sharps container
	16. Label syringe
	17. Hand hygiene

If utilizing a syringe, 1000 units (1 mL) of heparin should be drawn into the syringe to thoroughly coat the inside surface, then expelled. No air (falsely lowers $PaCO_2$, falsely elevates PaO_2) or heparin (falsely lowers $PaCO_2$) should be left in the syringe.[10] Use of an arterial blood gas syringe precludes the need for this preparation. Materials and a stepwise approach are listed in E-Table 75-4 and demonstrated in Video 75-5. Skin preparation is as for venipuncture. The preferred technique for arterial palpation is to place two fingers from the non-dominant hand proximal to the puncture site, to determine the location, direction, size, and depth of the artery. Use of Doppler ultrasound may aid localization. Some prefer to hold the syringe and needle like a dart and place the needle in one movement. Others prefer to first place the needle under the skin, then as with venipuncture, advance it into the arterial lumen. A sharper entry angle (45°-60°) minimizes vessel trauma and allows smooth muscle fibers to occlude the puncture site afterward.[10] Bevel-up and bevel-down positions are recognized; the current human recommendation is bevel up. Blood should spontaneously flow into the syringe, but hypotensive or small animals may require aspiration of the plunger. Afterward, manual pressure should be applied to the site for >1 minute, or longer if bleeding or a hematoma is seen. Frequent removal of the pressure should be avoided, but close monitoring of the site is indicated for at least 5 minutes.

Quality assurance techniques for arterial puncture are similar to venipuncture. In addition to residual air or heparin artifacts, the inadvertent submission of venous blood will produce erroneous results. If assessment of the patient breathing room air is needed, oxygen therapy should be discontinued 5-10 minutes before collecting an arterial sample when feasible.[2]

Placement of Arterial Catheters

Arterial catheters are placed for serial ABG assessment or monitoring of arterial blood pressure (see ch. 99). Indications and contraindications include those of arterial puncture and venous catheterization. Additionally, thrombotic risk factors identified in humans are: larger catheter size, hypotension, smaller arterial dimension, multiple arterial sticks, duration of cannulation, administration of vasopressor and inotropic agents, and the cannulation site.[11]

Catheters used for venous catheterization are used for arterial catheterization, although longer catheters are often selected. Material and a stepwise approach are listed in E-Table 75-5 and demonstrated in Videos 75-6 and 75-7. The approach is as described, above, for arterial puncture and venous catheter placement. Placement should be rapid to avoid arterial spasm. The bubble test for confirming arterial catheterization is demonstrated in Video 75-6.

E-TABLE 75-5

Arterial Catheter

Pull List—Equipment	
	Best practice—non-sterile gloves; accepted practice—washed or sanitized hands
	Clippers
	Skin preparation—best practice >0.5% chlorhexidine with alcohol
	Over-the-needle IV catheter—size appropriate to patient and artery
	Injection port
	Heparinized saline flush
	Tape

	Band-aid or sterile Telfa pad
	Bandaging material such as cast padding, stretch gauze, non-adhesive wrap
	Sharps container
Checklist for Arterial Catheterization	
	1. Hand hygiene—accepted practice; also put on non-sterile gloves—best practice
	2. Assemble needed equipment and materials, ensure they are within easy reach
	3. Pre-flush catheter and ports with heparinized saline
	4. Palpate artery—determine size, depth, direction and if suitable for catheter
	5. Clip hair—area sufficient for sterile placement up to entire circumference of limb
	6. Surgical preparation of the skin—best practice >0.5% chlorhexidine with alcohol
	7. Palpate artery with two fingers of the non-dominant hand
	8. Perform artery puncture—bevel up, angle entry of 45-60°, under skin first if needed
	9. Decrease angle, advance the catheter off the stylet, into the lumen of the artery
	10. Blood should spontaneously flow into the hub
	11. Remove the stylet, ± manually occlude artery to minimize blood loss
	12. Place injection port into catheter
	13. Secure catheter to limb with tape
	14. Heparinized saline flush
	15. Cover puncture site with Band-aid or nonadherent (Telfa) pad
	16. Apply additional tape and/or bandage material to further secure catheter
	17. Clearly label as "Arterial Catheter" as indicated by hospital's standard operating procedure
	18. Place sharps into sharps container
	19. Hand hygiene

The importance of catheter stabilization, secure connection points, and protective taping/wrapping is essential for arterial catheters, as substantial blood loss is possible if the catheter is dislodged, the connection leaks, or the catheter is removed prematurely. Arterial catheters must be clearly identified as such to prevent inadvertent administration of infusates. In addition to the venous catheter maintenance list, arterial catheters should be flushed hourly with heparinized saline.[12] Arterial catheters should be removed as soon as possible. When removing an arterial catheter, direct digital pressure should be applied for a minimum of 5 minutes and the limb should then be bandaged for at least 30 minutes.

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CHAPTER 76

Jugular Catheterization and Central Venous Pressure Measurement

Meri F. Hall

Jugular catheterization is useful for administration of intravenous fluids, drugs, hyperosmolar solutions, and parenteral nutrition, for blood sample collection, and for measurement of central venous pressure. Jugular catheters usually are well-tolerated, and are less likely to be contaminated in patients with vomiting or diarrhea than are peripheral catheters. Jugular catheters also are unlikely to be chewed out by a patient. Jugular catheters should be used with caution in patients with increased cranial pressure, which catheter placement can exacerbate, with coagulation abnormalities (risk of hemorrhage), or with an increased risk of thrombus formation, notably in patients with hyperadrenocorticism or immune-mediated hemolytic anemia (blood clots can form on the catheter surface).

When placing jugular catheters, it is important to use aseptic technique. This includes aseptic preparation of the skin, sterile draping, and use of sterile gloves. Prior to placing a jugular catheter, it is important to measure the distance from the point of insertion to the thoracic cavity just cranial to the right atrium (e.g., fourth rib), as this will indicate the length of the indwelling portion of the catheter. It is not required to sedate the patient, but sedation could be needed to aid in maintaining sterility due to patient movement. Placement of the jugular catheter can be achieved with the patient in dorsal recumbency, but it is best done with the patient in lateral recumbency. The patient's neck is extended and the forelimbs positioned caudally. A rolled towel can be placed under the neck to help with accessibility to the vessel. A wide area is clipped and prepared with aseptic scrub. The vein is located and visualized. Local anesthetic can be infiltrated, but is not required. The type of jugular catheter used will determine the steps to placement.

There are several types of catheters that can be placed in the external jugular vein: over-the-needle (structure is similar to a standard peripheral IV catheter) or through-the-needle, and single- or multilumen. Over-the-needle catheters are less expensive, but many are not long enough to reach the cranial vena cava except in very small patients, and cannot be used for central venous access in most dogs. For all catheter types, the insertion point into the skin and external jugular vein should be just cranial to the midpoint between the angle of the mandible and the point of the shoulder.

Through-the-needle catheters traditionally have been used in veterinary medicine; the catheter itself is passed inside the needle and into the jugular vein. These catheters are longer than most over-the-needle catheters, but can be problematic if the needle isn't placed in the guard and secured appropriately.

Multilumen catheters are available in double-, triple- or quadruple-lumen versions. They permit the administration of otherwise incompatible fluids, and concurrent fluid administration and central venous pressure measurement.

Placement: Seldinger Technique

Over-the-needle catheters are placed using the Seldinger guidewire technique or using a peel-off sheathed needle (Figure 76-1). The Seldinger technique uses a small introducer catheter and a guidewire to obtain venous access and position the jugular catheter in the vessel (Video 76-1). With the patient recumbent, the assistant holds the animal's forelimbs caudally and briefly occludes the external jugular vein with manual pressure at the thoracic inlet, to identify the vessel's location. The area around the venipuncture site is prepared first. The operator who will place the catheter locates and visualizes the vessel, then opens the catheter pack, keeping the contents sterile. The operator then puts on sterile gloves, flushes each port with sterile saline, and, using aseptic technique, drapes the site with sterile towels. The operator measures the appropriate distance for catheter insertion, as described above, and infiltrates the insertion site with local anesthetic if indicated. Pushing the skin dorsally, away from the jugular vein temporarily to avoid lacerating

it, the operator uses the scalpel blade to make a small (few mm) full-thickness skin incision, then allows the skin to return to its natural position so the incision lies directly over the vessel. The assistant occludes the vein and the operator advances the introducer catheter through the incision and under the skin. The operator directs the introducer catheter into the vein, confirming correct placement by observing blood flow. The operator removes the stylet and advances the guidewire into the vein (Figure 76-2). Many guidewires have a flexible J-tip at the distal end to prevent vessel puncture. The operator passes approximately two thirds the length of the guidewire, distal tip first, into the vein. Keeping hold of the guidewire, the operator removes the needle over the wire. The operator then passes the vascular dilator over the wire and, using a back-and-forth twisting motion, guides it into the vessel, keeping hold of the proximal end of the guidewire. The operator now withdraws the dilator, keeping the wire in place; bleeding is expected from the dilated venostomy site, and it can be controlled with direct pressure if needed. The operator now places the distal tip of the catheter onto the proximal tip of the wire and advances the catheter over the wire up to the venotomy site. The proximal tip of the guidewire will begin to emerge from the proximal port of the catheter. Holding this proximal tip of the guidewire securely, the operator now feeds the catheter farther over the wire and into the vein the desired distance. With the catheter in place, the operator withdraws the guidewire, withdraws any air from the port just vacated by the wire using a syringe, caps and flushes all ports of the catheter with sterile saline, and clamps them.

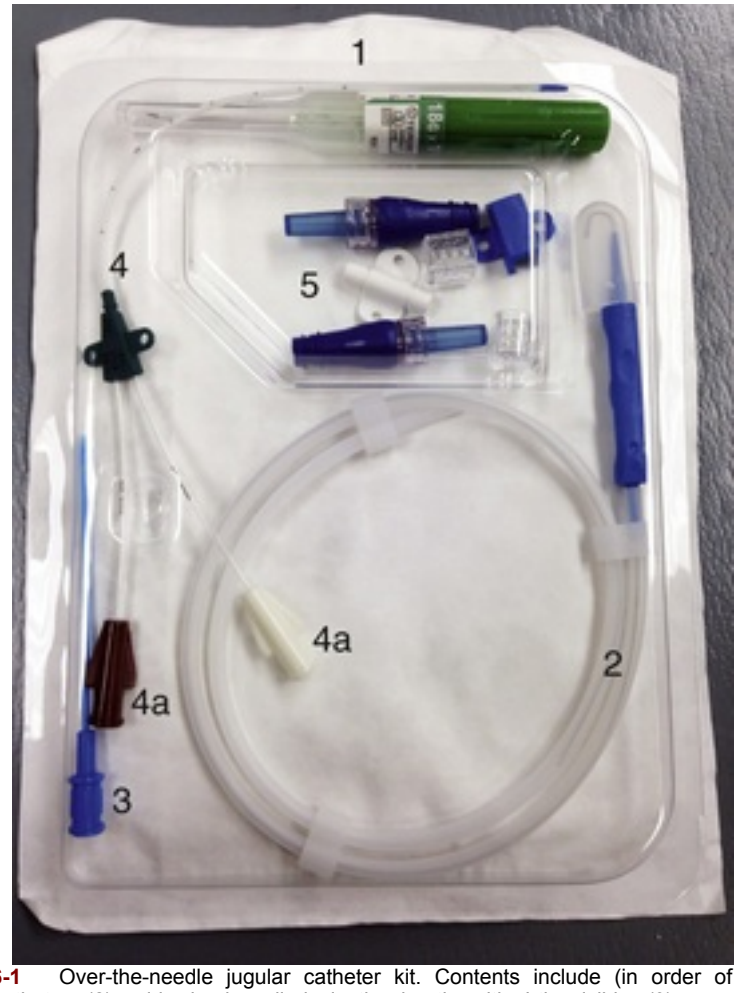


FIGURE 76-1 Over-the-needle jugular catheter kit. Contents include (in order of usage): (1) introducer catheter; (2) guidewire in coiled plastic sheath, with J-tip visible; (3) vessel dilator; (4) double-lumen jugular catheter, with 2 proximal ports (4a); (5) catheter caps and positioning adapters.

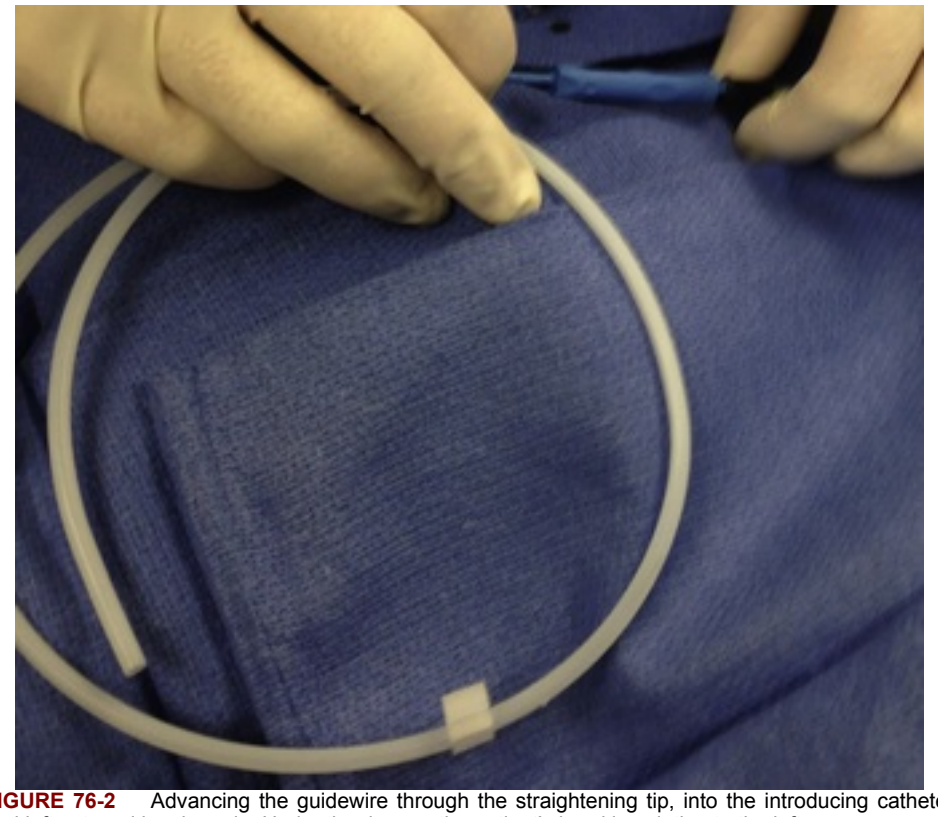


FIGURE 76-2 Advancing the guidewire through the straightening tip, into the introducing catheter and left external jugular vein. Under the drapes, the patient's head is pointing to the left.

The peel-away method uses a special introducer needle that is placed into the vessel like a peripheral catheter. The catheter is introduced through this needle. Once the catheter is in place, the introducer is peeled away and the lumen catheter is left in the vessel.

Once the catheter is in place with either method, it is sutured to the skin across the groove on the catheter base, and via the butterfly wings on the catheter or its positioning adapter (E-Figure 76-3). Special care is essential to not suture through the catheter itself. The area should be cleaned and the catheter bandaged in place. The operator should be sure to incorporate ports into the bandage to avoid contamination and tension when connected to IV tubing (Figure 76-4).

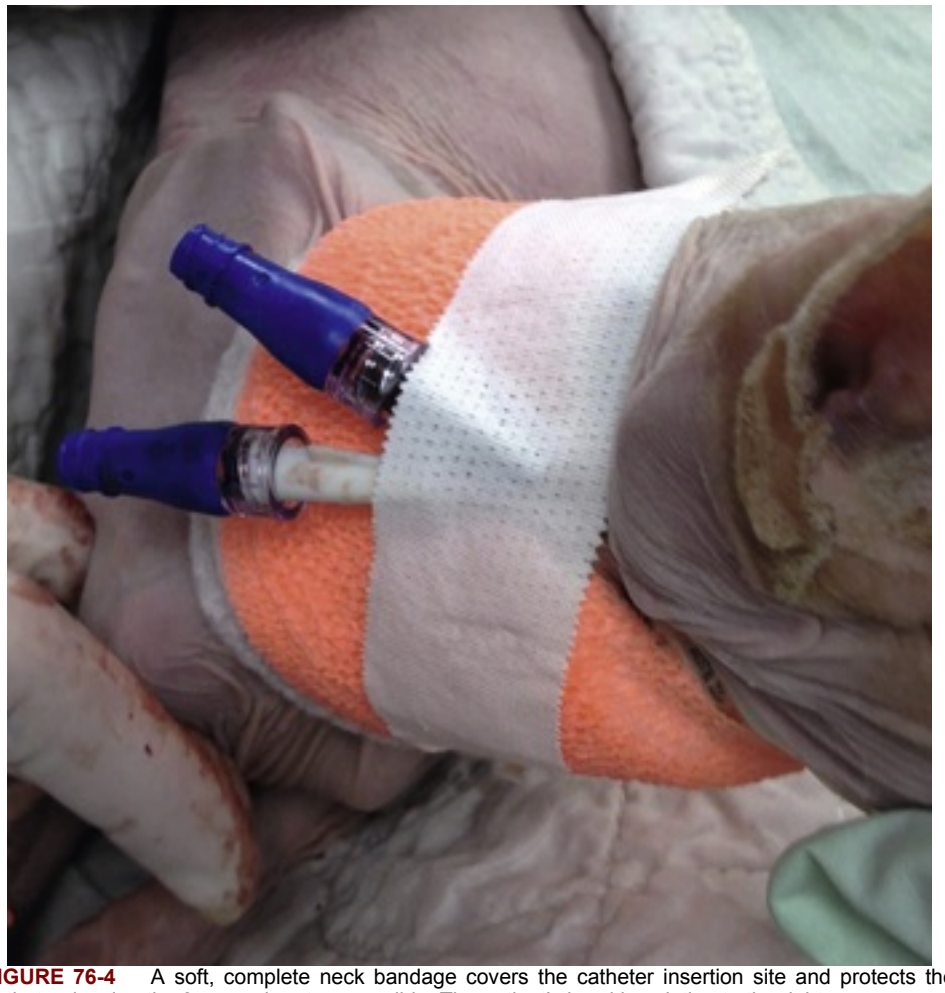
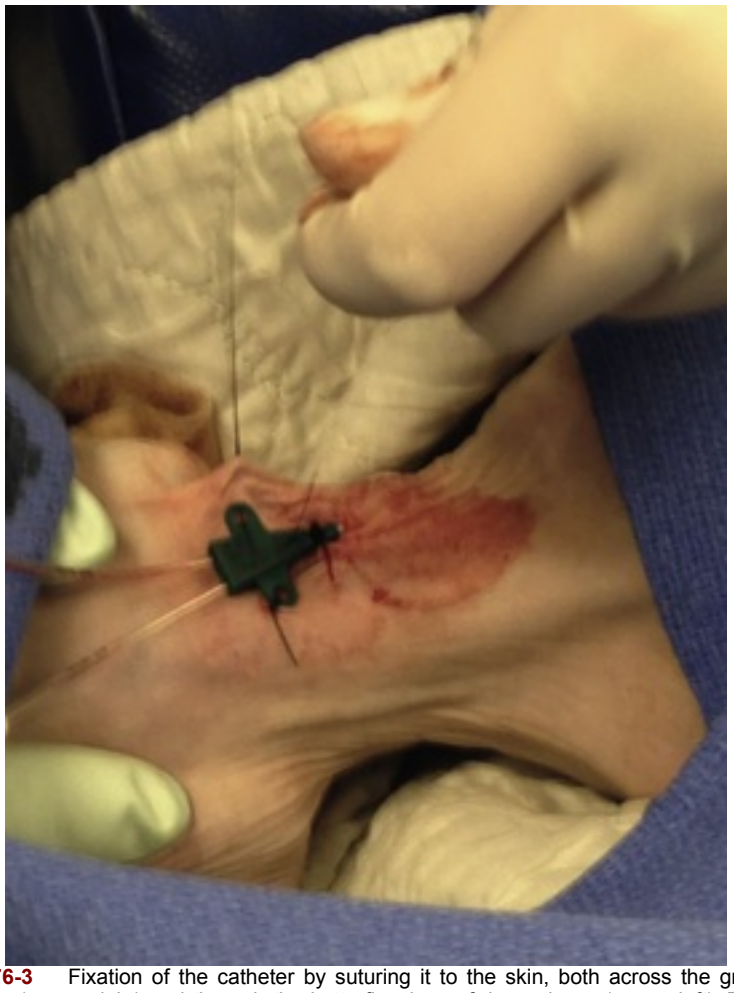


FIGURE 76-4 A soft, complete neck bandage covers the catheter insertion site and protects the catheter, leaving the 2 capped ports accessible. The patient's head is pointing to the right.



E-FIGURE 76-3 Fixation of the catheter by suturing it to the skin, both across the groove in the catheter base (center right) and through the butterfly wings of the catheter (center left). The patient's head is pointing to the left.

Peripherally Inserted Central Catheters

Peripherally inserted central catheters (PICCs) do not involve the jugular vein; therefore, they are useful in animals with head trauma or where there is a concern with increased intracranial pressure during placement. PICC lines are very long and are placed in either the medial or lateral saphenous vein (Video 76-2). Before placement, the distance from the insertion site to the vena cava is measured. They are placed using peel-away introducers and are sutured in place and bandaged to prevent the patient from chewing out the catheter and to keep them as clean as possible.

In small dogs and in cats, the use of a "long-through-short approach" works well. For this approach, an over-the-needle catheter is placed in the saphenous vein; then, the needle is removed from the through-the-needle catheter and the through-the-needle catheter is passed through the indwelling peripheral catheter. The hubs will seat together and a 20-gauge peripheral (over-the-needle) catheter will accommodate a 22-gauge long (through-the-needle) catheter. In small dogs and cats, the lateral or medial saphenous vein is used and the long catheter will be in the vena cava. If the long catheter needs to be replaced, it can be removed leaving the peripheral catheter in place and a new long catheter fed through the peripheral catheter.

After placing any central catheter, a confirmatory lateral radiograph should be taken to ensure proper placement prior to use (Figure 76-5). The bandages should be removed and the catheter site inspected as needed or at a minimum every 24 hours. There should be no clinical signs of thrombosis, infection or phlebitis. In very rare circumstances, a central venous catheter may need to be replaced. As long as the vessel is healthy this can be done by feeding a guidewire into the catheter, removing the current catheter and placing a new one over the guidewire.

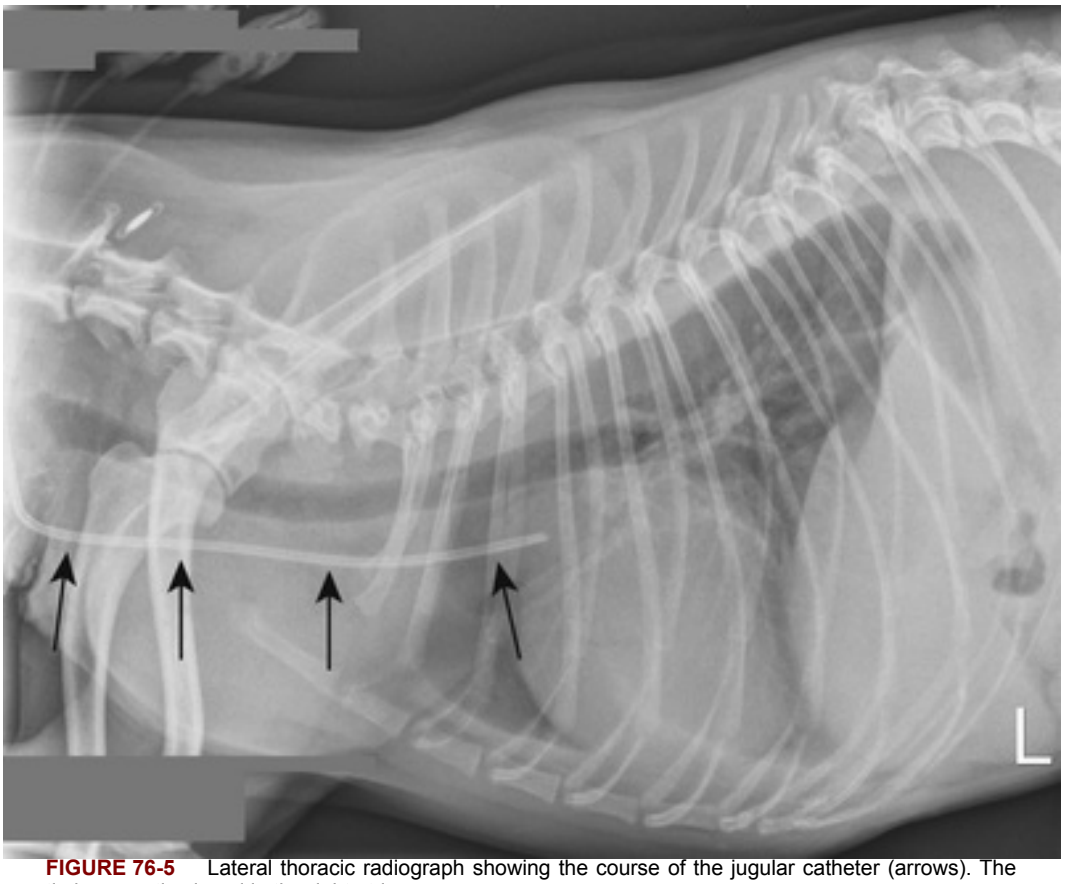


FIGURE 76-5 Lateral thoracic radiograph showing the course of the jugular catheter (arrows). The tip is correctly placed in the right atrium.

Central Venous Pressure Measurement

Central venous pressure (CVP) measurement is determined using either a jugular catheter ending at the point of the right atrium or a PICC line ending in the caudal vena cava. Measurement of CVP is useful in patients with pre-existing heart disease or in cases of high-volume intravenous fluid administration. CVP gives an estimate of the blood pressure entering the right atrium (Figure 76-6). The normal value of CVP is 0-10 cm H_2O. In optimally-perfused canine patients, CVP = 5-10 cm H_2O and in feline patients it is 2-5 cm H_2O. Repeated CVP measurements are very useful for identifying trends in individual patients. An increase in the value can indicate overperfusion, where a decrease in the value can indicate hypovolemia.

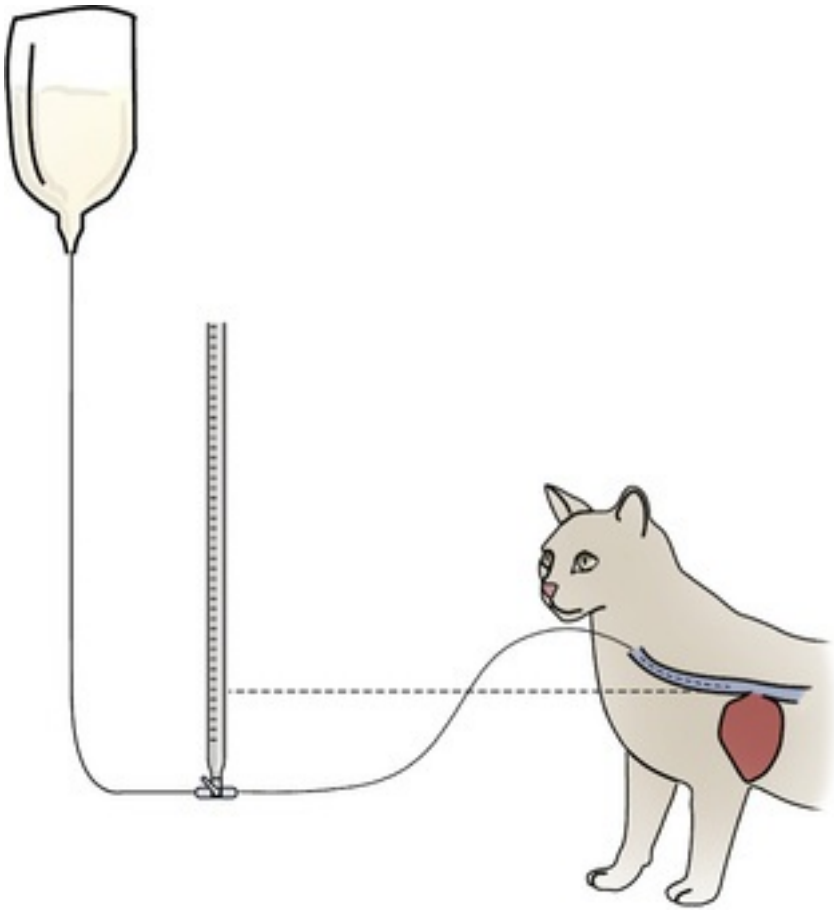


FIGURE 76-6 Correct positioning of the zero mark for manual measurement of CVP. Relative to the floor or bottom of the cage, the zero mark should be at the same height as the right atrium.

In critically ill patients, monitoring of the CVP is used as a guide for maintaining adequate organ perfusion. To obtain a CVP, a centimeter ruler, a manometer, or an electronic monitor will give equivalent results. The CVP can be measured hourly or continually depending on the method used. Confirmation of catheter placement in the cranial or caudal vena cava is required. The patient should be placed in right lateral recumbency, but sternal recumbency is also acceptable.

For manual measurement (ruler or manometer) the system is assembled using a bag of sterile 0.9% NaCl, a three-way stopcock, a measuring system, and extension lines. The "zero" of the ruler or manometer is placed at the level of the right atrium. The stopcock is turned off to the patient, and the manometer or the extension line is taped to the ruler and filled with 0.9% NaCl. The stopcock is then turned off to the fluid bag and in continuity with the patient. The level of the fluid in the manometer is permitted to settle, and this value is recorded as the CVP. Due to natural fluctuations in intrathoracic pressure, the level of the fluid in the manometer can change slightly with respiration.

For electronic monitors, the extension set is connected to a transducer that is attached to the monitor. The system is zeroed in the same manner as with the manometer. The stopcock is turned off to the fluid bag and the number on the monitor is the CVP (Figure 76-7).

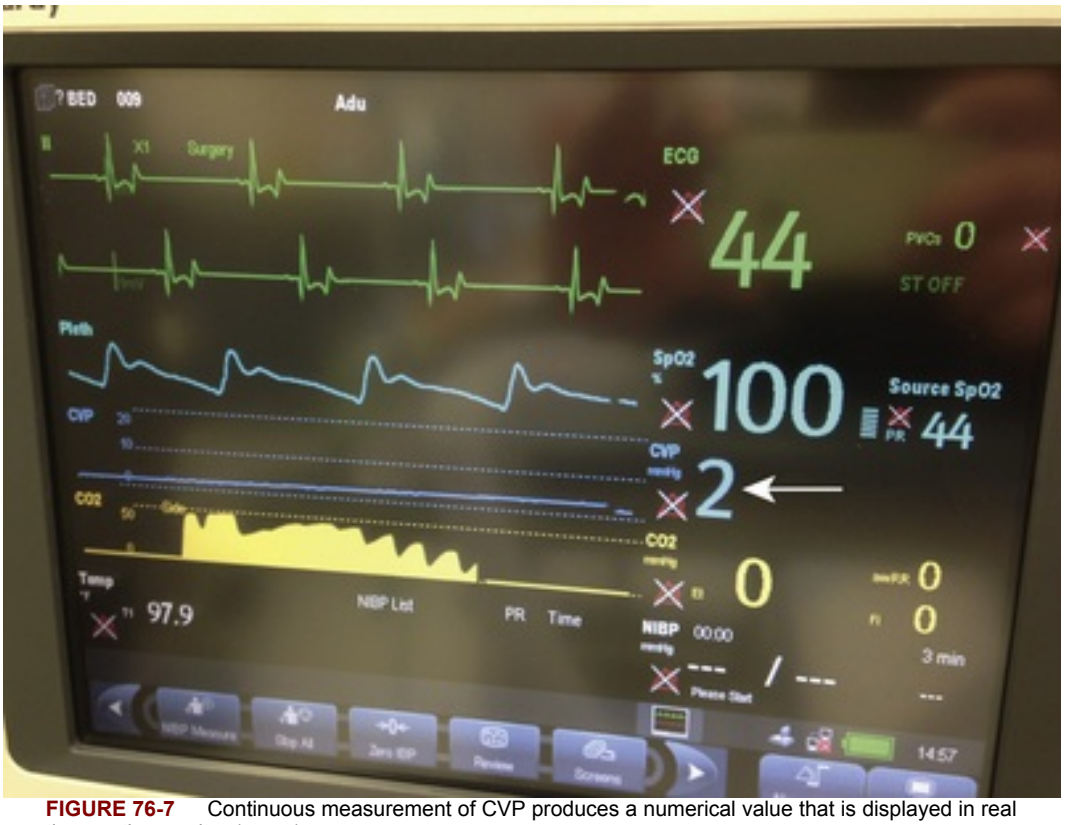


FIGURE 76-7 Continuous measurement of CVP produces a numerical value that is displayed in real time on the monitor (arrow).

CHAPTER 77

Intraosseous Catheters

Andre C. Shih

Introduction

Rapid vascular access can be a lifesaving event in many emergent situations encountered by the veterinary practitioner. Intravenous (IV) catheterization remains the gold standard for rapid vascular access and fluid and drug administration (see ch. 75 and 76). However, catheterization of central and peripheral veins can be technically challenging (if not impossible) in emergent situations including vascular collapse, catastrophic shock, and cardiopulmonary arrest.[1] In addition, small patient size, obesity, and venous thrombosis can further delay successful venous catheterization. Among the techniques available to the practicing veterinarian, the intraosseous (IO) route provides safe, rapid, and reliable vascular access for the administration of medications and fluids when IV catheterization is not possible.[1,2] In small animals, an IO catheter can be placed in <2 minutes.[3]

The IO route provides access to the systemic venous circulation via the bone marrow. The marrow is composed of several venous sinusoids that are drained by a venous canal that empties into the venous circulation. These vessels do not collapse even during severe hypovolemia or cardiac arrest.[1,2] Because the intramedullary vessel empties directly into the large central venous system, the time of onset of medications administered via the IO route is comparable to that of medications administered IV. In one study, Congo red administered IO was detected in the central circulation and heart within 10 seconds.[4] There was no difference in the hemodynamic variables between the IO and IV administration of hydroxyethyl starch (HES) in a hypovolemic animal model.[4] Administration of emergency drugs like epinephrine and atropine had faster onset of action by IO route when compared to endotracheal (ET) administration.[4]

Contraindications and Possible Complications

Overall, IO catheter placement appears to be a clinically safe and effective route of vascular access.[1] One large-scale human study examined 4,270 cases of pediatric IO cannulation and found an overall rate of morbidity of <1%.[4] There are, however, some risks to the use of IOs when compared to IV catheters (Table 77-1). Possible complications include fluid extravasation, skin infection, skin necrosis, bone fracture, osteomyelitis, fat embolization, compartment syndrome, and pain at the injection site.[3] In the author's opinion, the most common complication noticed in veterinary medicine is needle dislodgement with inadvertent subcutaneous drug/fluid administration. The IO catheter might be difficult to secure and maintain in place, leading to potential malfunction at a critical time.

TABLE 77-1

Comparison of Possible Complications with Intravenous (IV) Cut-Down Technique versus Intraosseous (IO) Catheterization

IV CUT-DOWN	IO CATHETER
Infection Need to stop chest compressions (CPR) during placement Proper training and surgical supplies required	Infection Dislodgement and fluid extravasation Risk of fracture, embolization, and infection Proper training required

The administration of hypertonic or strongly alkaline agents should be avoided. They have been associated with an increased incidence of local infection, transient medullary histologic changes, and myonecrosis in animal models.[4] Other potential complications include iatrogenic fracture or growth plate injury.[2,4] There is a theoretical risk of bone marrow or fat embolization to the lungs. Animal studies have revealed that high pressure and high volume of fluid administered IO increase the risk of embolism.[4] Despite these animal studies, there have been no documented cases of either fat or cortical bone emboli after IO infusions in veterinary medicine.

There are few absolute contraindications to IO placement. These include severe bone diseases, or the presence of a fracture. Sites that were used previously for IO access should not be used for >1–2 days and repeated attempts at the same site are discouraged.[4]

Techniques

Chemical Restraint and Anesthesia

Adequate sedation or general anesthesia is humane to the patient and will greatly facilitate the insertion of an IO catheter. If the animal is presented comatose, no sedation is usually necessary. Conversely, a conscious, wide-awake patient usually requires some sedation, such as an opioid (e.g., butorphanol 0.3-0.5 mg/kg IM). Patients also will benefit from a local anesthetic block (bupivacaine or lidocaine, 2 mg/kg) administered proximal to the IO site. Care is essential with neonates to avoid the toxic dosage of local anesthetic (the small volume to be injected can impede accurate dosing; do not exceed 4 mg/kg for either bupivacaine or lidocaine).

Equipment

Various needles and devices have been used for obtaining IO access.[3] A simple 20-22 gauge spinal needle can suffice for young kittens and puppies. At that age, bone is soft enough to permit easy placement. This has proven particularly useful in neonatal emergency cases with severe anemia/hypovolemia when presented for initial fluid resuscitation.[3] Hypodermic needles are not as successful: the lack of a handle makes it difficult to properly engage the needle tip in the dense cortical bone. The use of needles without stylets also cause higher incidence of obstruction by bony spicules. Spinal needles or bone marrow aspiration needles such as the Jamshidi needle (Baxter Healthcare, Deerfield, IL) have a stylet and handle for ease of insertion (Figure 77-1 and ch. 92).[5]

FIGURE 77-1 Cat with 15-gauge Jamshidi (Baxter Healthcare, Deerfield, IL) IO needle. Device has a handle to facilitate placement and a stylet to prevent obstruction by bone plug.

Beyond manual devices, there are several products available that have simplified the insertion of an IO needle, as they are not dependent on the manual process.[3,6-8]

The EZ-IO (Vidacare, San Antonio, TX) is a reusable, lithium—battery-powered device that is shaped and operates very much like a small drill (Figure 77-2). It uses a beveled, drill-tip 15 gauge needle that rotates into the IO space at a preset depth. Once the needle enters the IO space by the drilling motion, which is noted by a loss of resistance, the stylet is withdrawn and a metal catheter remains with a Luer-lock attachment left in place. A connection system (EZ-Connect) comes with each needle set and a 90° low-profile extension for delivery of medications and/or fluids (see Figure 77-2).[6-8]

FIGURE 77-2 EZ-IO (Vidacare, San Antonio, TX) battery-powered device used for drilling an IO catheter into position.

The Bone Injection Gun (B.I.G., WaisMed, Kansas City, MO) is a single-use disposable IO device. The "gun" is positioned 90° to the skin and pressed firmly against the skin to trigger a spring-loaded mechanism that actively drives the IO needle into the cortex (Figure 77-3). Once the IO space is penetrated, the device is removed, and the IO needle is left in place. A safety latch slides over the needle to keep it securely placed before taping.[6-8]

FIGURE 77-3 The pediatric version of the Bone Injection Gun (B.I.G., WaisMed, Kansas City, MO) is a single-use disposable IO device.

Both devices are being used in veterinary medicine. A study in dogs found the B.I.G. to provide more rapid

access than the manual insertion of the Jamshidi needle (JN) for fluid administration.[5] A follow-up study in cats demonstrated that all three IO access methods (EZ-IO, B.I.G., and manual JN IO needle) appear clinically acceptable.[3] The EZ-IO device, however, was significantly faster and easier to secure in cat cadavers[3] (Table 77-2).

TABLE 77-2

Success Rate, Insertion Time and Subjective Ease of Insertion for 3 IO Access Techniques in Cat Cadavers[3]

	EZ-IO	B.I.G.	JN
Success rate (%)	96	75	88
Insertion time (sec)	74.4 ± 15	113.0 ± 71	125.2 ± 39
Ease of insertion (quantitative score)	17.1 ± 20	45.5 ± 28	41.7 ± 23

B.I.G., Bone injection gun; *JN*, Jamshidi needle.

Inserting the Intraosseous Catheter

The use of adequate sedation or general anesthesia will greatly facilitate the insertion of IO catheter. Sites used for IO catheterization are the proximal humerus, the craniomedial aspect of the proximal tibia, the trochanteric fossa of the femur, and the iliac crest.

The proximal humerus is an easily accessible site in dogs and cats. The greater tubercle is easily palpated and the needle is placed in the flat area of the craniolateral aspect of the humerus, slightly distal to the greater tubercle. The dominant hand should remain sterile when securing the IO needle, while the other hand firmly holds the distal humerus and externally rotates the humerus to better expose the greater tubercle. The needle is inserted perpendicular to the long axis of the humerus (Videos 77-1 and 77-2).

Another site that is used frequently is the craniomedial surface of the proximal tibia. The flat surface of this portion of the tibia is covered by skin and subcutis but little or no muscle, making access to the bone easier. The dominant hand should remain sterile when securing the IO needle and the other hand firmly holds the distal tibia/fibula region and externally rotates the tibia to better reveal the medial surface of the proximal tibia. The needle is directed perpendicular to the bone and away from the physis (growth plate)[2] (Videos 77-3 and 77-4).

Other less-popular sites for IO catheterization include the trochanteric fossa of the proximal femur, and the iliac crest. The trochanteric fossa is medial to the greater trochanter femur and is best exposed with adduction and medial rotation of the limb. The needle is inserted parallel to the long axis of the femur. The iliac crest is the widest and most dorsal aspect of the wing of the ilium.[2] The crest can be used for bone marrow aspiration but is not commonly used for IO catheter placement because of the high chance of needle displacement during movement. It also can be difficult to palpate in large obese animals.

The selected site should be palpated and the area prepared using aseptic technique, including hair clipping and antiseptic scrub. The operator should put on sterile gloves, and then should make a small stab skin incision over the area using a scalpel blade (#11 or #12). The needle is placed through the stab incision down to the periosteum. The operator drives the needle through the cortex with a firm, back-and-forth rotating action along the long axis of the needle. Usually a decrease in resistance will occur when the needle tip enters the marrow cavity. Once the needle is properly positioned, it should feel firmly seated in the bone. Placement is confirmed by moving the limb: the needle should be firmly embedded in the bone and should move freely with the limb. The stylet can now be removed, a syringe with sterile heparinized saline attached, and the IO catheter flushed and capped (see Videos 77-1, 77-2, 77-3, and 77-4). The IO catheter should be secured using light bandage material and tape. It is important to avoid excessive movement of the limb. If not in use, the catheter should be flushed every 8 hours. Most of the time, IO catheters are removed once long-term IV catheterization is successful.

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CHAPTER 78

Constant Rate Infusions

Steven L. Marks

Client Information Sheet: Constant Rate Infusions

The intravenous administration of drugs is commonly utilized in veterinary medicine and allows for immediate and somewhat predictable effects. A constant rate infusion (CRI) is a technique for providing consistent serum, plasma or tissue concentrations of an intravenously administered compound. This method of administration can be utilized in lieu of intermittent bolus techniques.

CRIs can be delivered in parenteral fluids as a component of the patient's fluid therapy or can be delivered independent of the patient's fluid requirements.

After a constant rate infusion is started it takes approximately 5 drug half-lives to achieve steady state.[1] Drugs that are most suited for CRI are drugs with rapid onset and short half-life, which allows them to be titrated to effect. In cases where an immediate therapeutic effect is required, a loading dose of the agent may be administered and followed by the CRI.

In veterinary medicine there are specific indications for the use of CRI. These include but are not limited to time-dependent antibiotics, analgesic agents, antiarrhythmic agents, vasopressors, insulin and antiemetic agents.

See Table 78-1 for commonly used agents and dose protocols.[2,3]

TABLE 78-1

Commonly Used Agents and Dose Protocols

AGENT	CONCENTRATION	DOSAGE
Butorphanol	10 mg/mL	0.2-0.4 mg/kg IV then 0.1-0.2 mg/kg/h
Diazepam	5 mg/mL	0.2 mg/kg/h
Dobutamine	12.5 mg/mL	5-20 mcg/kg/min
Dopamine	40 mg/mL	1-3 mcg/kg/min
Epinephrine	1 mg/mL	0.025-0.3 mcg/kg/min
Fentanyl	0.05 mg/mL	0.003 mg/kg IV then 2-5 mcg/kg/h
Furosemide	50 mg/mL	3-8 mcg/kg/min
Insulin (regular)	100 U/mL	0.1 U/kg/h
Ketamine	100 mg/mL	0.3 mg/kg/h
Lidocaine	20 mg/mL	1-2 mg/kg bolus then 20-80 mcg/kg/min
Medetomidine	1 mg/mL	0.0015 mg/kg/h
Metoclopramide	5 mg/mL	1-2 mg/kg/24 h
Nitroprusside	10 mg/mL	1-10 mcg/kg/min
Norepinephrine	1 mg/mL	0.5-2 mcg/kg/min
Propofol	10 mg/mL	4-6 mg/kg slow bolus then 100-400 mcg/kg/min
Vasopressin	20 U/mL	0.001-0.004 U/kg/min

There are three devices which can be used to administer a CRI to a patient. These devices are volumetric fluid infusion pumps (Figure 78-1), syringe pumps (Figure 78-2) or buretrols (Figure 78-3).

FIGURE 78-1 Fluid infusion pump. (Courtesy Heska, Loveland, CO.)

FIGURE 78-2 Syringe pump. (Courtesy Medfusion, Smiths Medical, Dublin, OH.)

FIGURE 78-3 Buretrol (Pfizer, Inc., New York, NY).

Volumetric infusion pumps are used when adding drug to parenteral fluids. There are numerous manufacturers of these pumps and most are very accurate. When using this technique the clinician must know the dose of drug to be delivered, the fluid rate being administered and the total volume of fluid the drug is being added to. It will also be important to make sure the drug is compatible with the solution it is being added to.[4] As a general guide, the volume of drug being added to fluid bag should be removed from the bag prior to instillation. Overfill volume of fluid bags should also be considered. Multiple pumps can be used to infuse different agents.

Syringe pumps allow the clinician to provide very accurate infusions with minimal difficulty. There are numerous manufacturers. Most syringe pumps are able to be programmed with drug concentration and dose and the pump will deliver at a set rate. Syringe pumps can accommodate a varying size of syringes. The advantage of a syringe pump is that the compound can be delivered either undiluted or in a small volume of fluid.

Both types of infusion pumps have advanced safety features which can detect air in the line, occlusion and when an infusion is complete.

A buretrol is an infusion device which holds a limited amount of fluid to be infused. It is placed in line between a fluid bag and a volumetric infusion pump. This technique is very similar to using the volumetric pump alone but limits the amount of fluid to be administered.

In many cases, multiple IV access points must be used. This will require multiple lines and all lines and pumps should be labeled accurately. There are some multichannel pumps commercially available (Alaris, Carefusion, San Diego, CA) that can deliver multiple CRI agents simultaneously.

In order to calculate how much agent to add to fluids to administer a CRI there are several formulas which can be used.

Formula #1:

$$\text{Drug (mL/h)/Fluid rate (mL/h)} = \text{X mL of drug/total volume of fluid}$$

Example:

Metoclopramide (5 mg/mL) administered at 1 mg/kg/24 h
Patient body weight is 20 kg
Fluid rate is 50 mL/h
20 mg of metoclopramide must be delivered in 24 h, which is 0.83 mg/h
0.83 mg/5 mg/mL = 0.17 mL of metoclopramide/h
0.17 mL/h/50 mL/h = X mL of drug/1000 mL
3.4 mL of metoclopramide 5 mg/mL is added to the liter bag

Formula #2:

$$M = (D)\,(W)\,(V)/(R)\,(16.67)$$

or

$$R = (D)\,(W)\,(V)/(M)\,(16.67)$$

M = mg of drug to add to solution
D = dosage of drug in mcg/kg/min
W = patient body weight in kg
V = volume (mL) of solution
R = rate of delivery (mL/h)
16.67 = conversion constant

Example:

Metoclopramide (5 mg/mL) administered at 1 mg/kg/24 h
Patient body weight is 20 kg
Fluid rate is 50 mL/h
To calculate D: 1 mg/kg/24 h, or 1000 mcg/kg/24 h, or 41.7 mcg/kg/h, or 0.69 mcg/kg/min
D = 0.69 mcg/kg/min
W = 20 kg
V = 1000 mL
R = 50 mL/h
M = (0.69) (20) (1000)/(50) (16.67)
M = 16.6 mg
Metoclopramide is 5 mg/mL, so 16.6/5 = 3.3 mL added to 1 L bag

Formula #3

This is a quick technique for adding drug to a constant volume using a constant flow rate.

$$D \times W = \text{mg of drug to add to 250 mL bag of fluid infused at a rate of 15 mL/h}$$

D = drug dosage (mcg/kg/min)
W = body weight of patient (kg)

Example:

Lidocaine (2% or 20 mg/mL) to be infused at a dose of 50 mcg/kg/min
Patient body weight is 20 kg

50 × 20 = 1000 mg (50 mL) of lidocaine added to 250 mL of fluid run at a rate of 15 mL/h

In addition to these formulas there are web-based CRI calculators which can be used to minimize error (http://www.aucsoc.com/html/dosage_calculator.html).

When using CRI infusions it is important to double and triple check the calculations. Areas of confusion often involve dose (mg or mcg) or time of delivery (minutes, hours or days).

Whenever possible, make sure a second person reviews the calculations and make sure IV lines, fluid bags and syringes are clearly labeled, dated and initialed (Figure 78-4).

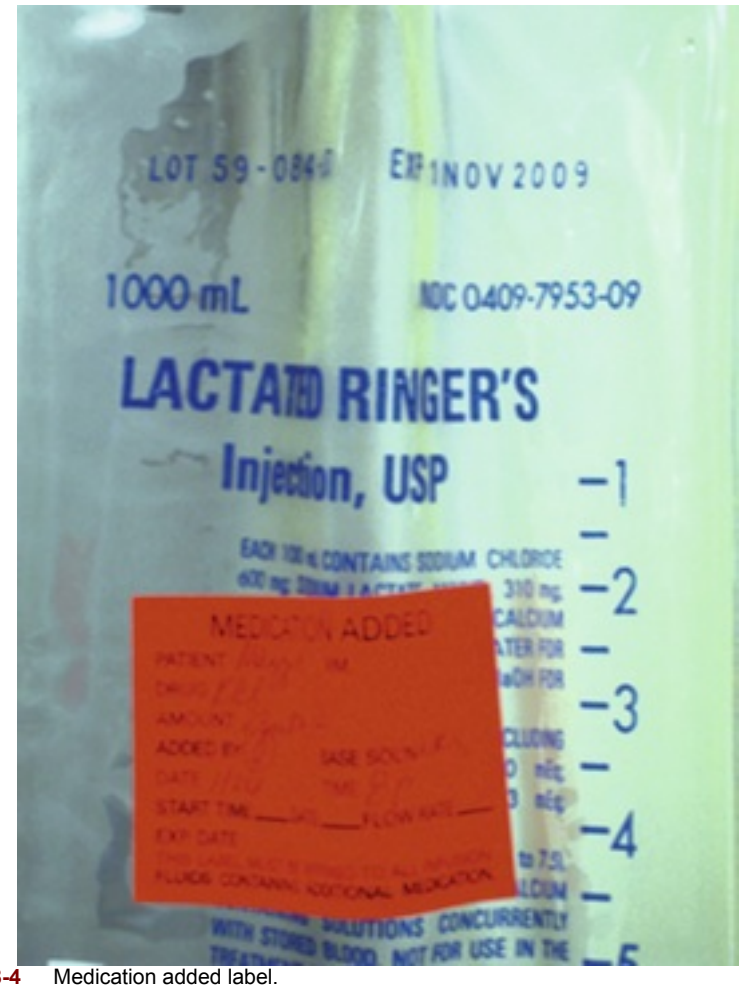

FIGURE 78-4 Medication added label.

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CHAPTER 79

Ear Vein Blood Glucose Monitoring

Melanie D. Thompson

Client Information Sheet: Home Blood Glucose Monitoring

In dogs and cats with diabetes mellitus, owner observation of clinical signs and in-hospital evaluation of serial blood glucose curves are common methods for assessing glycemic control. These parameters are also used as aids in determining insulin dose, the type of insulin to be used, and the frequency of injections needed (see ch. 304 and 305). Diabetic dogs and cats are typically hospitalized for glucose monitoring and blood samples are collected at 1- to 2-hour intervals by means of direct venipuncture of a peripheral vein.[1,2] Hospitalization, restraint for blood sample collection, and venipuncture have all been associated with stress hyperglycemia (especially in cats), and some hospitalized pets may not eat.[2] This can complicate interpretation of any blood glucose curve.

Most human diabetics perform self-monitoring of blood glucose concentrations using a portable blood glucose meter (PBGM) and capillary blood. Blood is obtained usually by pricking a fingertip with a lancet device. Such PBGMs are being used to generate serial blood glucose curves in diabetic dogs and cats. These meters are inexpensive, require only a single drop of blood for analysis, and provide results rapidly. In addition, the results obtained with these meters have been shown to be sufficiently accurate for use in clinical practice.[3-6] When only a small amount of blood is required for analysis; use of an ear vein for blood sampling can minimize patient discomfort, preserve the integrity of peripheral veins, and decrease need for physical restraint during sample collection. Studies have shown that the marginal ear vein (MEV) nick technique is a reasonable alternative to venous blood collection for serial measurement of blood glucose concentrations.[7] Two methods of blood sampling from the ear of dogs and cats are described here. Both methods are quick and easy to perform (Video 79-1).

Capillary Blood Sampling with Conventional Lancet Device

The first technique utilizes conventional lancet devices designed for pricking the fingertips of human diabetics. A device with a variable needle depth should be chosen. This allows the appropriate depth to be selected in order to provide an adequate amount of blood for the test (dogs usually require greater depth compared to cats). Although any portion of the inner pinna can be sampled for capillary blood, use of the MEV usually results in little discomfort, the site can be used repeatedly, and size of the drop of blood is usually excellent.

First the MEV is identified (Figure 79-1, *A*). A warm, damp gauze pad (or warm washcloth) can be applied to the MEV to increase perfusion as needed. A thin small film of petroleum jelly should be spread over the sampling site in longhaired pets. This allows the drop of blood to form without dissipating into the fur. The automatic lancing device is then placed over the vein (Figure 79-1, *B*); the ejected needle will nick the ear, causing a drop of blood to form (Figure 79-1, *C*). The person performing the test should place a folded gauze pad between the pinna and the individual's finger to avoid an inadvertent finger nick (the lancet rarely penetrates through the ear). The PBGM (AlphaTRAK2, Abbott Laboratories) with the test strip already inserted is then applied to the drop of blood to measure the blood glucose concentration (Figure 79-1, *D*).

FIGURE 79-1 **A,** The marginal ear vein is visualized. **B,** The automatic lancing device is placed over the ear vein. A folded gauze pad is placed so that the individual performing the test does not inadvertently get nicked. **C,** After the ejected needle nicks the ear, a drop of blood will form. **D,** The portable blood glucose meter with the test strip already inserted is applied to the drop of blood.

Capillary Blood Sampling with Vacuum Lancing Device

A second technique utilizes a vacuum lancing device (Microlet Vaculance, Bayer Diagnostics), to facilitate collection of an adequate drop of blood by creating negative pressure (Figure 79-2, *A*). The device was designed to allow blood collection from body sites other than the fingertips in people and is easily used for obtaining blood from the inner pinna in dogs and cats. It also has variable needle depth. The tip of the pinna is held between thumb and index finger. The surface of the pinna is laid flat by the remaining 3 fingers (Figure 79-2, *B*). The lancet device is then set on a non-haired area of the pinna. An airtight seal between the device and the ear is obtained by pushing the outer (haired surface) of the pinna against the device with the tip of one finger. The entire edge of the endcap must be in contact with the skin (Figure 79-2, *C*). The site is lanced by pressing the plunger cap down until it comes to a complete stop. While pressure is maintained between the endcap and the skin, the plunger is slowly released. This creates negative pressure which is maintained until an adequate drop of blood is obtained. The skin slightly bulges up into the endcap (Figure 79-2, *D*). The person performing the test should place a folded gauze pad or bandage roll between the ear and the individual's finger to avoid an inadvertent finger nick. When an adequate drop of blood has formed, the plunger is pressed three fourths of the way down to release the vacuum and remove the device. The PBGM with the test strip already inserted is then applied to the drop of blood to measure the blood glucose concentration.

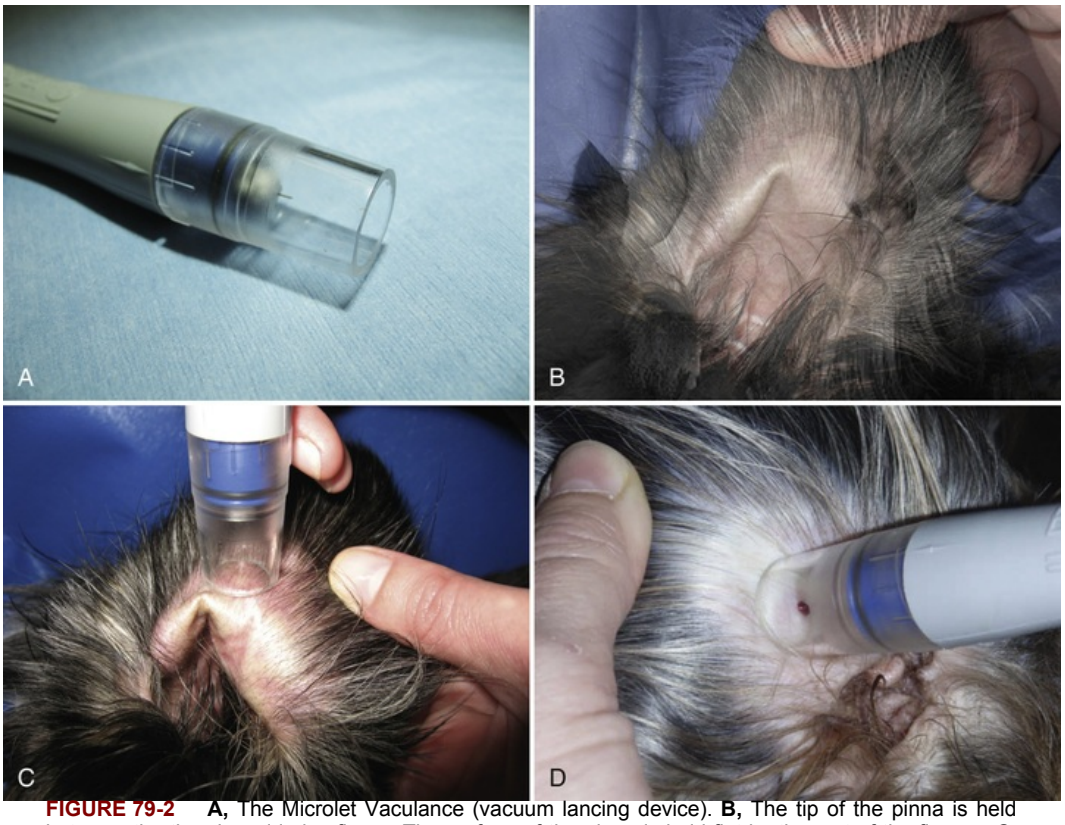

FIGURE 79-2 **A,** The Microlet Vaculance (vacuum lancing device). **B,** The tip of the pinna is held between the thumb and index finger. The surface of the pinna is held flat by the rest of the fingers. **C,** The lancet device is set on a non-haired area of the pinna. The outer surface of the pinna is pushed against the device to form an airtight seal. **D,** After lancing the pinna, pressure is maintained and the plunger is slowly released. Negative pressure causes the skin to bulge up into the endcap.

Other sites can be used for capillary blood sampling (see ch. 304 and 305). In dogs and cats, the carpal and metacarpal pads, respectively, have been validated as an alternative sampling site (Figure 79-3, *A*).[8,9] In dogs, the buccal mucosa has also been validated as an alternative sampling site (Figure 79-3, *B*).[10] Dry the buccal mucosa first with a dry gauze pad prior to sampling. Using the same site can help ensure consistent results. Many veterinarians and technicians who choose not to use the lancet device just hold the lancet or a small gauge needle for direct stick.

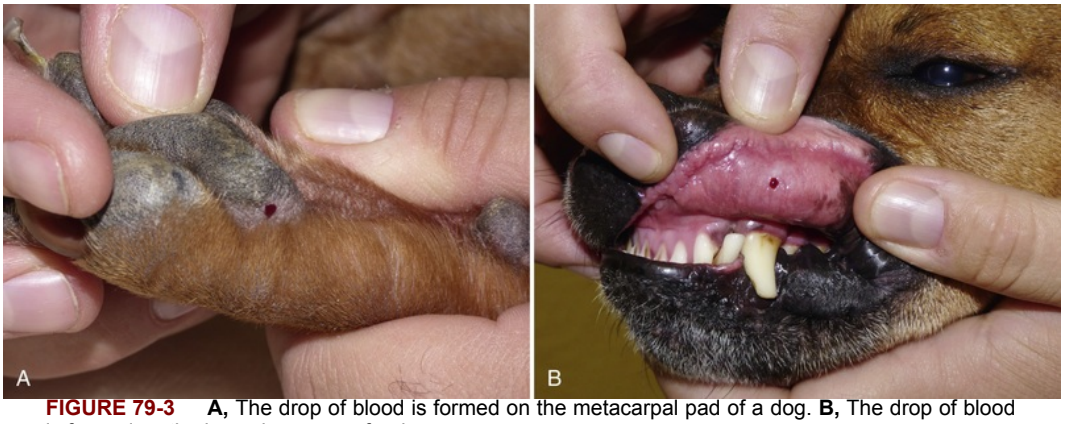

FIGURE 79-3 **A,** The drop of blood is formed on the metacarpal pad of a dog. **B,** The drop of blood is formed on the buccal mucosa of a dog.

Clinicians should be aware that there are limitations to the use of a PBGM. In particular, several factors can affect the accuracy of the blood glucose concentrations obtained with PBGM. These include the level of user training, whether the meter is properly maintained, whether appropriate quality control checks are

performed, whether the animal has any concurrent diseases, and the patient's hematocrit. Other factors that may affect results include altitude, environmental temperature and humidity, the triglyceride concentration, or presence of hypotension or hypoxia.

A PBGM that is simple to operate should be chosen. Portable blood glucose meters are constantly being improved; newer units offer greater precision, faster measurement, decreased blood volume, and decreased operator dependence. Blood glucose results from most PBGMs are lower than the results obtained by reference laboratories and the difference in test results typically increases as the severity of hyperglycemia worsens.[11] A veterinary glucometer (AlphaTRAK, Abbott Laboratories) has been introduced that has been shown to be superior to meters marketed for human use.[11,12] The meter is species-specific (calibrated and validated for use in dogs and cats), accurate, and easy to use. Glucose results obtained from the AlphaTRAK meter were significantly closer to corresponding reference results compared with other PBGMs. Importantly, glucose results should be taken "at face value" because results with this meter may be slightly higher or lower than laboratory results.[11] It is important to become familiar with the PBGM and perform routine maintenance. With practice, veterinarians, veterinary technicians, and veterinary students can become proficient in these techniques, minimizing errors. Capillary blood sampling can become the routine method of generating serial blood glucose curves in the hospital. These techniques can also be taught to clients for home monitoring of blood glucose concentrations. Owners also can be directed to Web sites dedicated to diabetic pets, which contain information on home monitoring of blood glucose. In the search field, type "home blood glucose monitoring of diabetic pets."

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CHAPTER 80

Buccal Mucosal Bleeding Time

Christine Savidge

Buccal mucosal bleeding time (BMBT) is an easy, readily available, diagnostic test used to screen for primary hemostatic abnormalities in cats and dogs. Primary hemostasis involves the interactions of functioning platelets, the vascular endothelium, and von Willebrand factor (vWf).[1] Diseases in cats and dogs known to affect primary hemostasis and platelet function include thrombocytopenia (see ch. 59); von Willebrand disease (vWD), thrombasthenia, congenital and acquired thrombocytopathies (see ch. 201); and vascular disorders.

Clinical signs consistent with an abnormality in primary hemostasis include superficial cutaneous bleeding (petechiae, ecchymoses, excessive bleeding at surgical or traumatic sites), mucosal bleeding (gingival bleeding, epistaxis, hematuria and gastrointestinal bleeding) and scleral hemorrhage. Petechiae and ecchymoses develop most commonly on the pinnae, gingiva, ventral abdomen, axillae and inguinal area.[2] See ch. 54 for differential diagnoses of petechiae and ecchymoses. By contrast, secondary hemostatic defects (i.e., disorders of the coagulation cascade) would typically cause hemorrhage into body cavities (e.g., hemothorax, hemoabdomen) or potential spaces (e.g., hemarthrosis).

Initial diagnostic steps to evaluate primary hemostasis in a bleeding or at-risk patient include a thorough history, physical exam, complete blood count, serum biochemistry profile and urinalysis. The history should include drug administration to screen for medications that can trigger thrombocytopenia or coagulation disorders. The complete blood count should focus on platelet parameters such as a platelet estimate on a blood smear, automated platelet count, and mean platelet volume. If quantitative platelet parameters are normal, a bleeding time can be used as a screening test for abnormal platelet function.[3]

The bleeding time is a measure of how long it takes for a small, standardized incision to stop bleeding, an indication of the effectiveness of initial platelet plug formation.[4] The BMBT is a point-of-care test that provides a reliable indicator of primary hemostatic abnormalities in cats and dogs.[1,5] A prolonged bleeding time can identify deficiencies in platelet number, deficient von Willebrand factor, abnormalities in vascular integrity, or abnormalities in platelet function. See ch. 197 and 201 for more information on diseases resulting in abnormal platelet adhesion and aggregation or vascular endothelial dysfunction. The BMBT is most useful in the presence of a normal platelet count. In a moderately to severely thrombocytopenic patient (<70,000 platelets/mcL), a BMBT provides no additional clinical information, as the bleeding time will be predictably prolonged. The magnitude of a prolongation of the bleeding time does not correlate with the clinical severity of abnormal primary hemostasis. Additionally, not all conditions that cause platelet dysfunction will result in an abnormal BMBT. Additional qualitative measures, such as vWf concentration, and *in vitro* platelet function tests, such as optical aggregometry, aperture closure time, and flow cytometry, can be used for complete evaluation of primary hemostasis.[1]

Performing a BMBT[2]

Materials (Figure 80-1):

- Adequate assistance for lateral or sternal recumbency or chemical restraint of the patient
- Fully automated spring-loaded device to make a standardized incision (5 mm long × 1 mm deep)
  - Surgicutt Adult template bleeding device (International Technidyne Corp., Edison, NJ)
  - Simplate II (Organon Teknika Corp., Durham, NC)
- 5 cm wide roll gauze
- Blotting paper/filter paper Whatman #1 filter disc (Fisher Scientific Co., Clifton NJ)
- Stopwatch

FIGURE 80-1 Material and equipment for performing a buccal mucosal bleeding time.

The BMBT test (Video 80-1) can be performed in conscious, sedated,[6] or anesthetized dogs and in sedated or anesthetized cats. With the patient in lateral or sternal recumbency, the maxillary lip is everted and held in place with a gauze strip tied around the muzzle. In a conscious dog, the gauze is not well tolerated around the maxilla alone, and as a result, tying the gauze around the entire muzzle (maxilla + mandible) will be necessary. The gauze is tied tightly enough to create venous congestion. In cats or brachycephalic dogs, the gauze is tied caudal to the ears.

It is important to use a standardized device that creates a 5 mm long and 1 mm deep incision, as devices that create smaller incisions, such as Surgicutt Junior or Newborn for people (Kitvia, Labarthe-Inard, France), or a scalpel blade, can result in different bleeding times,[7] thereby increasing the likelihood of an inaccurate result.

After removing the safety clip, the automated, spring-loaded blade device is gently and evenly placed against the labial mucosa at the level of the maxillary canine tooth, rostral to the gauze. It is important to avoid visible blood vessels and highly vascularized areas.[5] The incision is made either perpendicular or parallel to the lip margin.[2,5] The device is activated, and as an incision is made, the time is started on the stopwatch. The device is removed and discarded immediately after making the incision. With blotting paper, blood droplets are caught 2-4 mm below the incision. It is important that the incision remains clearly visible, because it is essential to not disrupt the forming clot by touching the incision. In an awake dog, any blood that reaches the patient's mouth or tongue can bother the patient, resulting in movement or attempted licking and disrupting the procedure. Blood droplets continue to be caught and absorbed on the filter paper, until the incision is not actively bleeding. At this time, the stopwatch is stopped. The bleeding time is defined as the length of time from the creation of the incision to the time when bleeding has stopped, indicating initial platelet plug formation.[4]

Published reference intervals for normal BMBT are 1.8-4.7 minutes in dogs[4,5,8] and 0.5-2.5 minutes in

cats.[9,10] For clinical purposes, BMBT <4 minutes is considered normal in dogs and BMBT <3 minutes is considered normal in cats.[9] Dogs with thrombopathia,[5] thrombasthenia,[11] type II or III vWD[5] and cats with Chédiak–Higashi syndrome[10] can have bleeding times >13 minutes.

For any given test there is operator variability, and with the BMBT even intra-operator repeatability can differ by more than a minute.[12]

There are many advantages of the BMBT in assessing primary hemostasis in cats and dogs. The BMBT is a simple test to perform. It is specific and fairly sensitive for both quantitative and qualitative primary hemostatic dysfunctions, though not specific for the type of abnormality.[8] The BMBT is considered to be essentially painless, non-invasive, and well tolerated in an easily restrained patient.[8] The required equipment is minimal (see Video 80-1), inexpensive, and readily available to practitioners. Limitations to the BMBT include that it is operator-dependent[12] and not sufficiently sensitive to detect mild bleeding disorders.[13] In humans, poor sensitivity is seen with mild type I vWD.[14] The BMBT is not helpful in identifying clotting factor disorders/coagulopathies and offers no additional information in a thrombocytopenic patient. The location and plane, as well as the vascularity and capillary density, of the chosen site of the incision and the extent of venocongestion can affect the BMBT.

In screening people for primary hemostatic disorders, bleeding times have been replaced by platelet function analyzers (e.g., PFA-100 assay) with increased reproducibility and improved sensitivity. While the PFA-100 assay may be superior to BMBT and is ideal when available, the PFA-100 assay is ideally run within 5 hours of sample collection[13] and equipment is not always accessible to many practitioners. The BMBT stands as a good screening test for abnormal primary hemostasis in small animal patients.

Causes of a Prolonged BMBT

See ch. 201 for a complete list of platelet disorders.

Inherited thrombocytopathies: intrinsic platelet function defects are rare.

- Impaired platelet adhesion and aggregation in vWD, a hereditary deficiency of vWF reported in various dog breeds and rarely in cats. vWD can result in a bleeding time more than three times normal.[5]
- Disorders of platelet membranes include Glanzmann's thrombasthenia in Otterhounds and Great Pyrénées dogs.[11]
- Disorders of platelet secretion are seen in Spitz[15] and Basset Hound thrombopathy[15] and platelet granule storage pool deficiency in American Cocker Spaniels[16] and feline Chédiak-Higashi syndrome.[10]

Acquired thrombocytopathies: platelet function is not consistently altered.

- Uremia, due to defective platelet adhesion[17]
- Hepatic disease, due to decreased platelet aggregation[18]
- Anemia[5,19]
- Dysproteinemias and disseminated intravascular coagulation are thought to result from platelet coating by paraproteins and fibrin degradation products.[5]
- Infectious causes that may prolong BMBT include: canine leishmaniasis,[20] ehrlichiosis, and anaplasmosis.[21]
- Myeloproliferative diseases and vasculopathies, e.g., vasculitis and inherited vascular defects[1]
- Intravenous infusion of dextran 70 in dogs[5]
- Nonsteroidal anti-inflammatory agents that inhibit cyclooxygenase 1 (COX-1) result in decreased thromboxane A_2, which will interfere with platelet function. Aspirin inconsistently prolongs the canine BMBT[22,23] while COX-1–sparing drugs, like carprofen and meloxicam,[24] do not.

Cutaneous bleeding times are described as an alternative to BMBT in dogs.[23,25] Results are not standardized, as there is great variation in skin thickness in different breeds. Cuticle bleeding times, performed by clipping a toe nail and determining the bleeding time, have been used for assessing coagulation. These are difficult to standardize, do not differentiate between primary and secondary hemostasis, and are painful unless performed under general anesthesia.[4,8] The cutaneous and cuticle bleeding times are not recommended by the author.

BMBT is a valuable diagnostic test when screening a patient for moderately to severely delayed primary hemostasis. The BMBT can be used prior to surgery when there is a concern for acquired or congenital

platelet dysfunction. The BMBT is an important part of the diagnostic workup for any bleeding patient with normal quantitative platelet parameters and normal prothrombin and activated partial thromboplastin times when specific platelet function tests are not immediately available.

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CHAPTER 81

Fecal Examination

Byron L. Blagburn, Jane D. Mount

Internal parasites are prevalent and important disease agents in companion animals, and a potential cause of zoonotic disease in pet owners (see ch. 40, 42, 210, 276, and 277).[1,2] Fecal detection of internal parasites is an important component of veterinary practice. Techniques include direct smear (wet mount), sedimentation, flotation (both centrifugal and standing), Baermann procedure, and fecal immunologic and molecular biologic techniques. Although the latter are not yet used commonly in the veterinary hospital, they are available at some diagnostic and reference laboratories, or can be requested from academic laboratories. Failure to employ "best practices" techniques when conducting fecal examination procedures can result in failure to detect parasite stages in fecal specimens.[3-7]

Collecting and Storing Fecal Specimens

For most procedures, we recommend the use of at least 2 grams of feces. Two grams of firm, normal feces will form a cube approximately ½ to ¾ of an inch on a side. Occasionally it is necessary to use a sample obtained with a fecal loop or a rectal thermometer. In these cases, a negative result can be meaningless; a positive result can imply a high level of parasitism. The specimen size should be increased as the amount of water in the sample increases. Ironically, diarrheic fecal specimens from animals with a large burden of parasites may contain fewer fecal parasite stages because of this dilution effect.

Collect fresh fecal specimens immediately after defecation, if possible. Specimens collected from the ground may contain eggs, larvae or other stages of free-living organisms. Feces should be stored in a container that will exclude air. A plastic bag or container with a tightly secured lid will suffice. Specimens should be held in a cool dry location, out of direct sunlight. Storage in a standard refrigerator would be ideal, although most clients are reluctant to do so. Samples can be refrigerated for several days to a week without affecting most parasites. Trophozoites of *Giardia* and *Tritrichomonas,* and certain nematode larvae, will not survive storage. When these parasites are suspected, the specimen must be examined immediately. It is best to examine specimens as soon as possible after submission. If fecal specimens are maintained at room temperature for more than a day or two prior to examination, many eggs and oocysts will begin to embryonate or sporulate. Recognition of partially embryonated or sporulated eggs or oocysts can be a challenge. Fecal specimens can be fixed in 5-10% buffered formalin if a sample is to be submitted to another laboratory. If molecular or immunologic techniques are to be used by the reference laboratory, it is always a good idea to inquire as to how best to fix and submit the specimen.

Gross Examination of the Fecal Specimen

Fecal specimens should be examined grossly for consistency (formed, semi-fluid or pulpy, fluid), and for the presence of fresh blood (hematochezia), mucus, or intact parasites. Parasite-induced damage to the small intestine often results in dark, tarry feces (melena), indicating the presence of partially digested blood (see ch. 41). Color, consistency and the presence of mucus or froth (air bubbles) are often indicators of gastrointestinal disease that may be caused by parasites (see ch. 40, 42, 276, and 277).

Fecal Smear

We have included a video and photographs depicting the following procedures (Figures 81-1 through 81-15; Video 81-1). The direct fecal smear or "wet mount" is used to detect motile protozoa such as *Giardia, Tritrichomonas, Pentatrichomonas,* amoeba, or larvae that may be damaged by flotation solution. Some presume

that if only a small amount of feces is available, the direct smear should be the procedure of choice. This is not true. Selection of techniques should not be dictated by the amount of feces. If an overall assessment for parasites were intended, the best technique would be centrifugal flotation. If the sample is fluid, it is probably best to examine the specimen using both a direct smear and centrifugal flotation even though the size of specimen may be small for each.

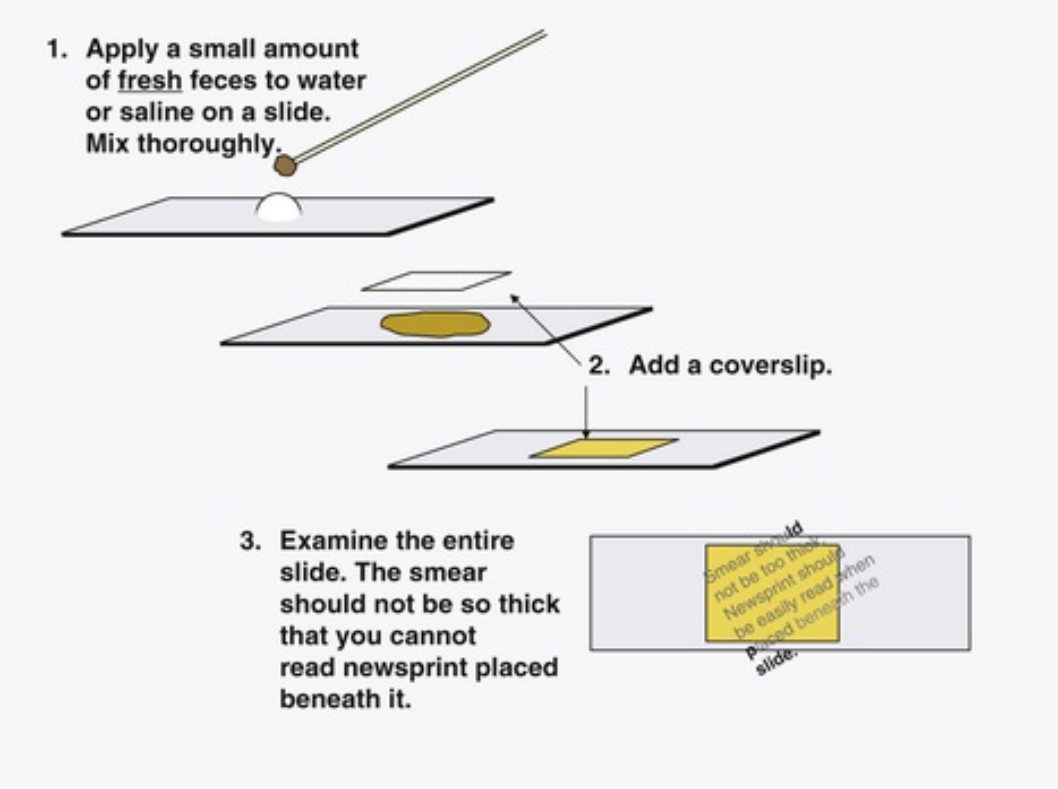

FIGURE 81-1 Procedure for performing a direct smear.

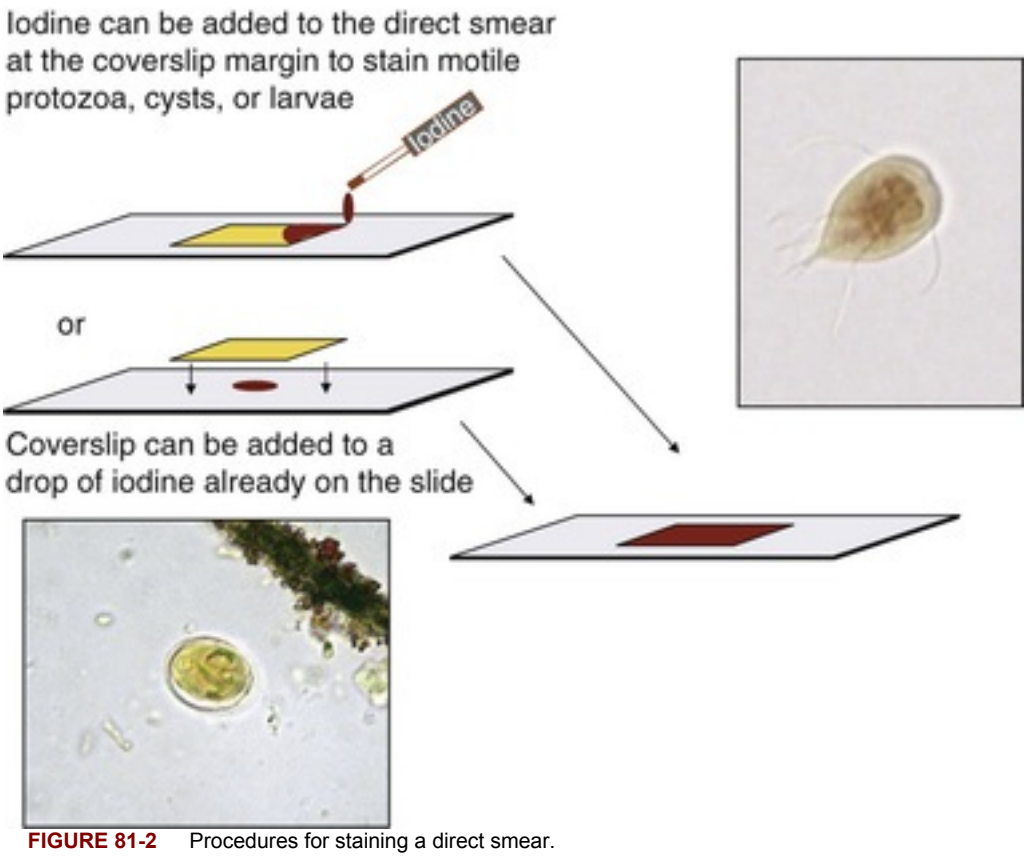

FIGURE 81-2 Procedures for staining a direct smear.

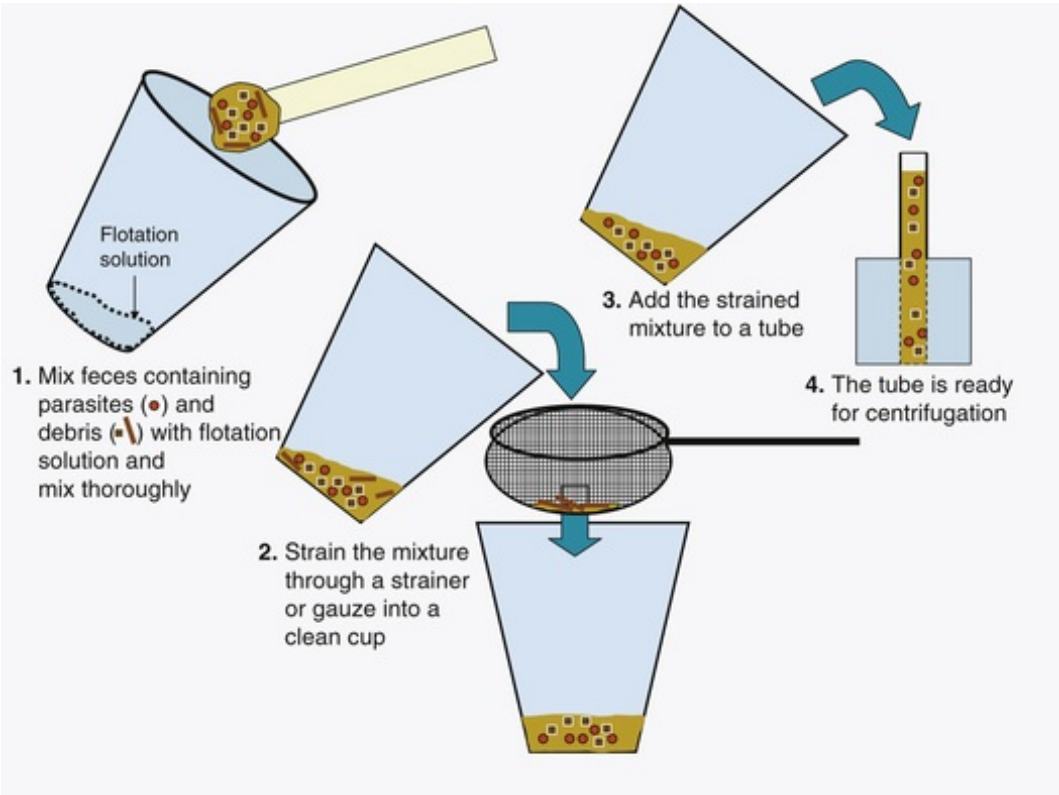

FIGURE 81-3 Preparing a fecal specimen for flotation

FIGURE 81-4 Add fecal specimen to flotation solution and mix thoroughly.

FIGURE 81-5 Pour mixed sample through a strainer to remove large debris.

FIGURE 81-6 Pour filtrate into a centrifuge tube.

FIGURE 81-7 Materials needed for fecal flotation.

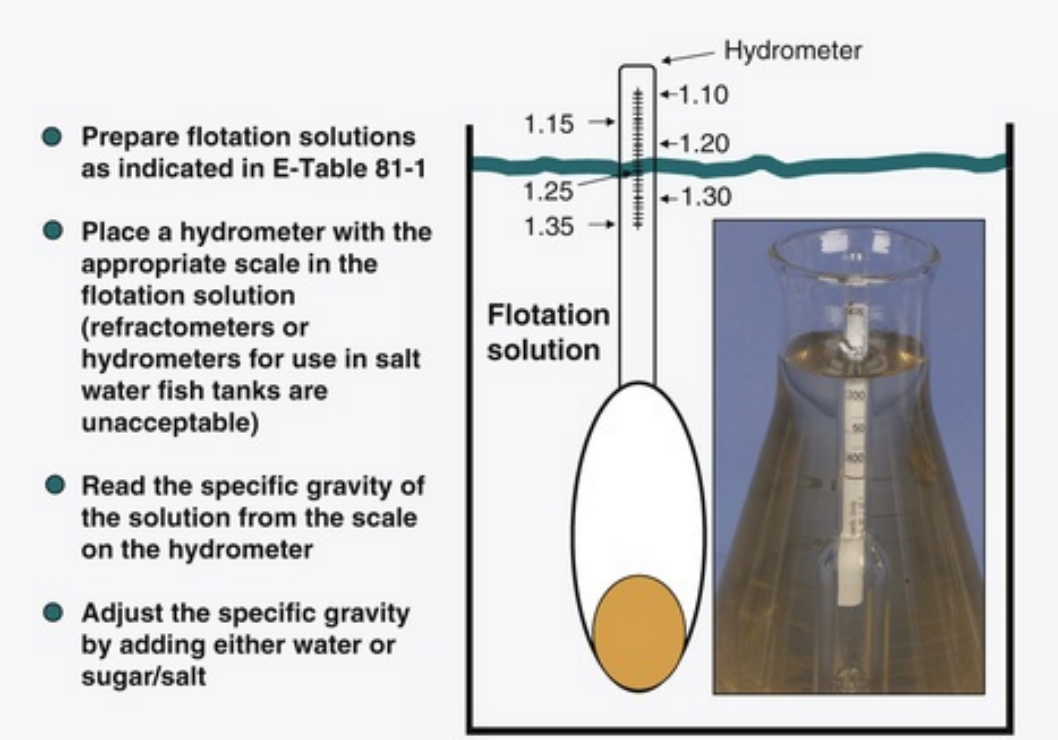

FIGURE 81-8 Measuring specific gravity of a flotation solution.

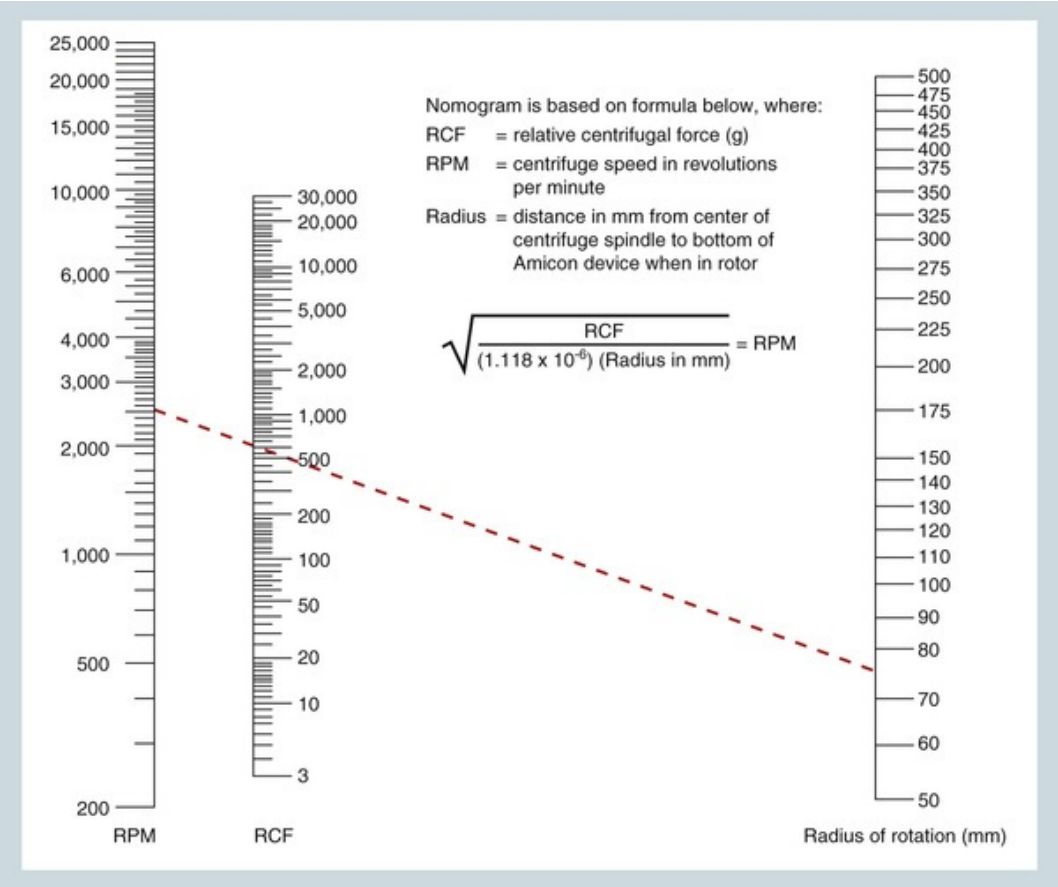

FIGURE 81-9 Nomogram for calculating relative centrifugal force.

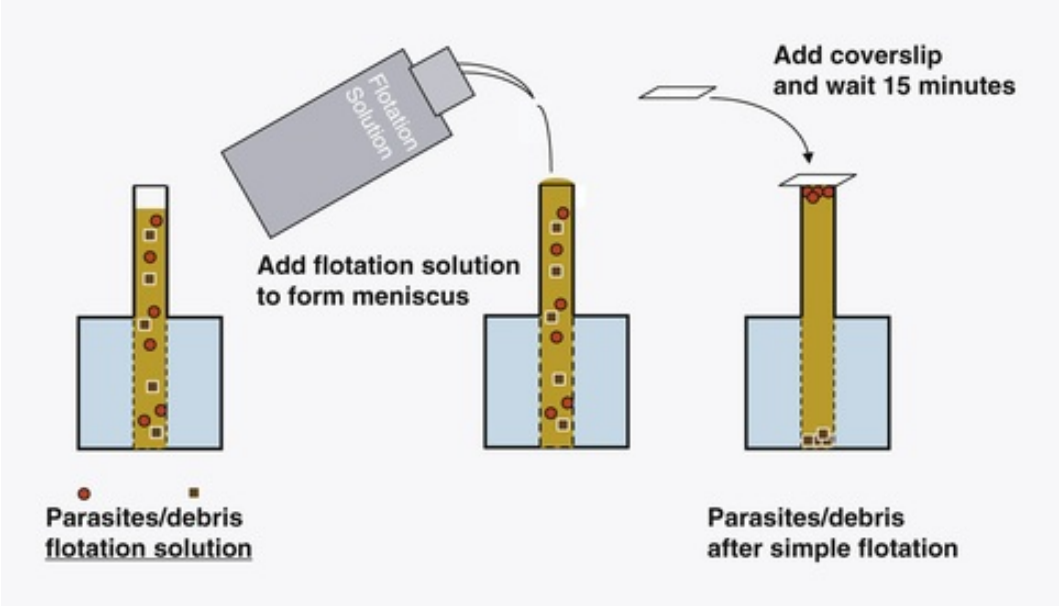

FIGURE 81-10 Procedure for performing a standing fecal flotation.

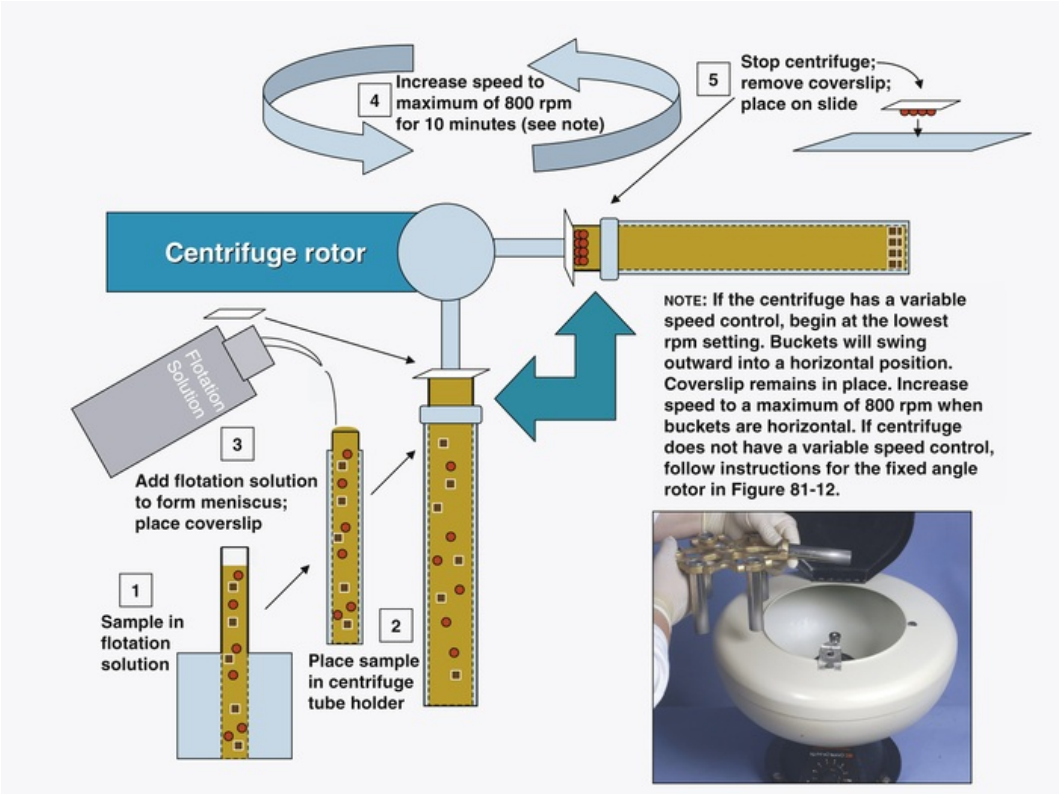

FIGURE 81-11 Centrifugal flotation using a swinging bucket rotor.

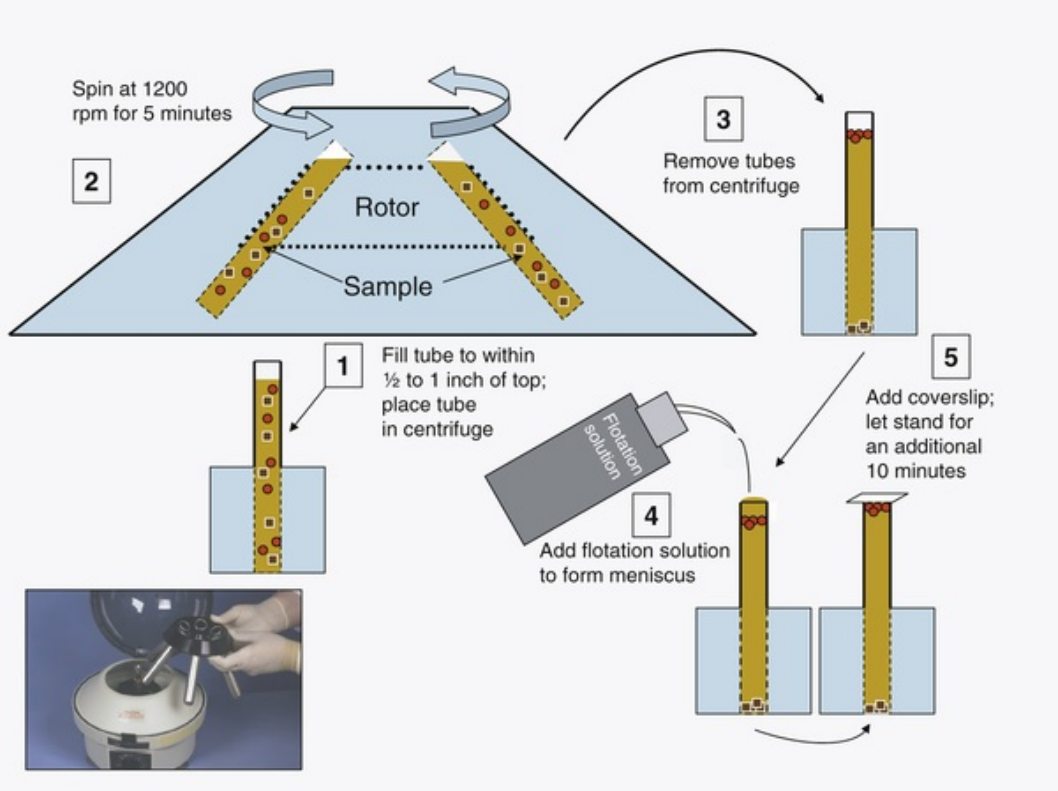

FIGURE 81-12 Centrifugal flotation using a fixed angle rotor.

FIGURE 81-13 Add flotation solution to form a meniscus.

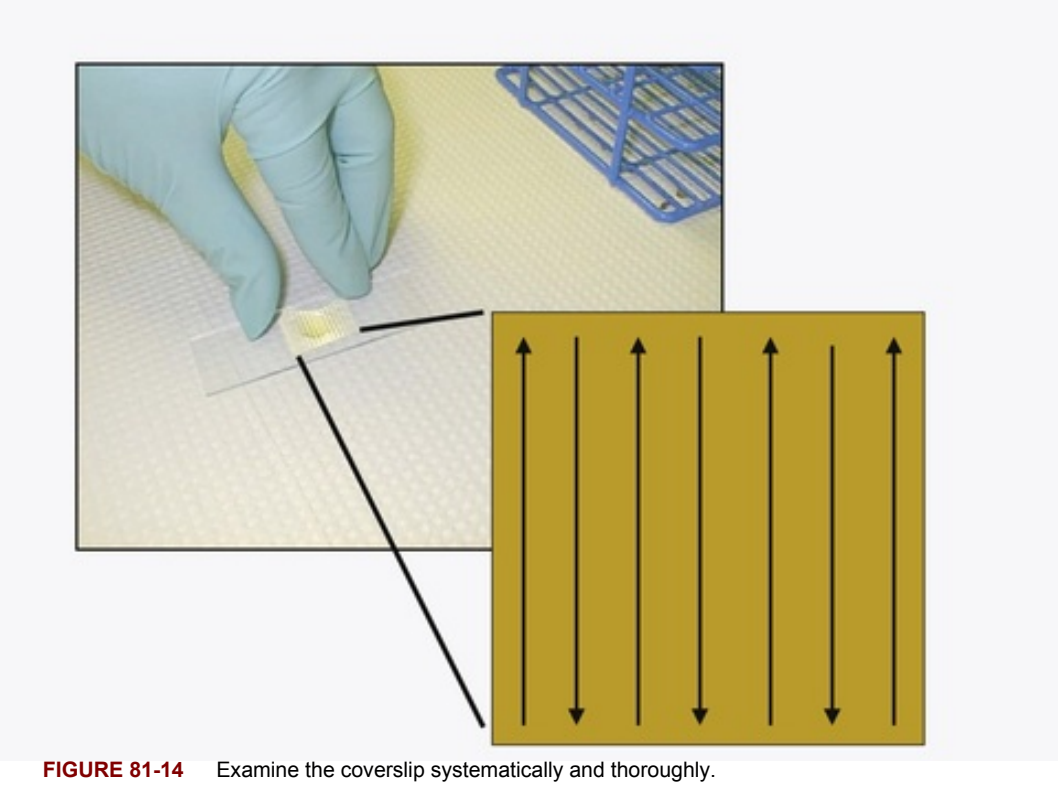

FIGURE 81-14 Examine the coverslip systematically and thoroughly.

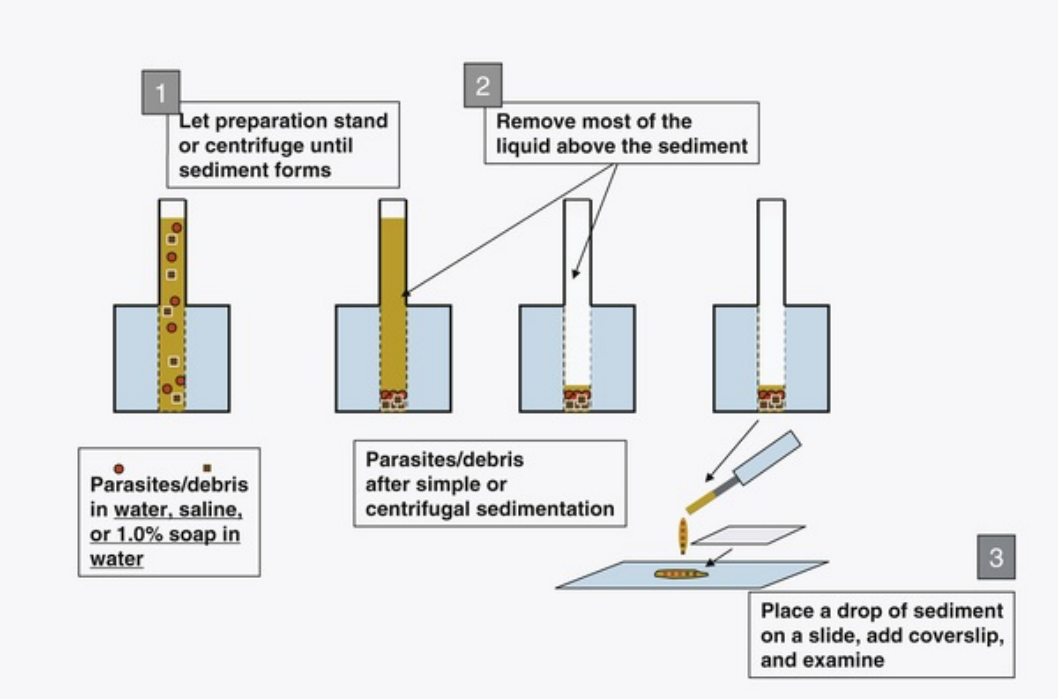

FIGURE 81-15 Performing a fecal sedimentation procedure.

The direct smear is performed by placing a small amount of feces (some say peppercorn size), using an applicator stick into a small amount of warm or room temperature 0.85-0.9% saline or lactated Ringer's solution (Figure 81-1). Do not use tap water because it will usually rupture fragile protozoa. We use 22 × 22 mm coverslips, but some parasitologists use 22 × 40 mm coverslips and claim that they make the specimen layer thinner and easier to read. The most common mistake in preparing a direct smear is using too much

fecal sample. Prepare specimens so that newsprint can be read when placed under the slide containing the preparation (see Figure 81-1). Always adjust the contrast on the microscope by rotating the sub-stage condenser to better see small parasites. Do not lower the sub-stage condenser because this will decrease the resolution of the microscope. We often add a drop of Lugol's or D'Antoni's iodine to the slide prior to adding the coverslip or we "wick" it under the edge of the applied cover slip (Figure 81-2). This will increase the detail of internal structures. Keep in mind that iodine will kill the organisms so that they are no longer motile. Other parasite stages, such as hookworm eggs and coccidial oocysts will also stain brown and may not be recognized. Smears may also be stained with methylene blue or other stains.

Fecal Flotation Techniques

Fecal flotation is the most common fecal procedure performed in veterinary clinics and laboratories. Fecal flotation is intended to separate parasites from other objects and debris based on their different densities.[3] Fecal flotation is based on the principle that when a fecal specimen is placed in a sugar or salt solution, parasites (and other objects) that are less dense than the flotation solution will move to the top; those that are more dense will eventually settle to the bottom. The densities of some common parasites and flotation solutions are given in E-Box 81-1 and E-Table 81-1.

E-Box 81-1

Common Fecal Flotation Solutions

Magnesium Sulfate

($MgSO_4$: SG = 1.20)
Add 450 g of $MgSO_4$ to 1,000 mL of warm tap water

Zinc Sulfate

($ZnSO_4$: SG = 1.18-1.20)
Add 331 g of $ZnSO_4$ to 1,000 mL of warm tap water

Sodium Nitrate

($NaNO_3$: SG = 1.18-1.20)
Add 338 g of $NaNO_3$ to 1,000 of warm tap water

Sodium Chloride

(NaCl: SG = 1.18-1.20)
Add 350 g of NaCl to 1,000 mL of warm tap water

Sheather's Sucrose Solution

(SG = 1.27)
454 g granulated sugar
355 mL tap water
6 mL formaldehyde

1. Heat the water to near boiling.
2. Add the granulated sugar and stir until it is dissolved.
3. Allow the mixture to cool to room temperature before adding the formaldehyde.
4. Check the specific gravity. Adjust to 1.27 using either tap water or sugar.

E-TABLE 81-1

Densities of Common Parasites and Flotation Solutions*

FLOTATION SOLUTION	DENSITY (SPECIFIC GRAVITY)	PARASITE EGG	DENSITY (SPECIFIC GRAVITY)

Sodium nitrate (338 g/L of water)	1.18-1.20	*Toxocara canis*	1.09
Zinc sulfate (331 g/L of water)	1.18-1.20	*Toxocara cati*	1.10
Sheather's sucrose[†] (454 g/355 mL of water, 6 mL of formaldehyde)	1.25-1.27	*Ancylostoma* spp.	1.06
Sodium chloride (350 g/L of water)	1.18-1.20	*Trichuris vulpis*	1.15
Magnesium sulfate (450 g/L of water)	1.20	*Taenia* spp.	1.23
		Physaloptera spp.	1.24

[*]Modified from references 4 and 6.

[†]Heat the water to near boiling. Add the granulated sugar and stir until it is dissolved. Allow the mixture to cool before adding the formaldehyde. Check the specific gravity and adjust to 1.27 by adding either water or sugar.

In preparing fecal specimens for flotation, it is desirable to eliminate large debris (Figures 81-3 through 81-6; see Video 81-1). First, the fecal specimen is added to flotation solution and the tube is filled to about 80% of its capacity. The mixture is stirred to distribute the fecal material. If sucrose is used, you can minimize air bubbles by stirring slowly. The mixture is poured through a strainer or 1 to 2 layers of gauze sponges into another clean container, and then into a centrifuge tube. In our laboratory, we use disposable paper cups, disposable tongue blades and washable tea strainers (Figure 81-7).

Flotation Solutions

Common densities of fecal flotation solutions and parasites are listed in E-Box 81-1 and E-Table 81-1. Notice that the densities of most of the solutions are between 1.18 and 1.20. Also notice that the densities of most of the common parasites in E-Table 81-1 are less than 1.18. We are often asked why flotation solutions are not prepared at the highest density possible. Couldn't we then recover the heavier parasite stages (i.e., *Taenia* and *Physaloptera;* see E-Table 81-1)? We could prepare the solutions at densities of 1.35. The problem with very dense flotation solutions is that they not only float the heavier parasites, they also float the heavier debris. Too much debris on the slide can make the preparation more difficult to read, or it can interfere with the flotation of parasites. High flotation densities also can damage or distort certain parasites. We recommend specific gravities between 1.18 and 1.27 for optimal recovery of parasites.[4] Sucrose solution prepared at a specific gravity of 1.27 and combined with centrifugal flotation results in the highest parasite recovery.[7] Check the density of the solution with a hydrometer when they are prepared and at weekly intervals (see E-Table 81-1; Figure 81-8). Instruments used to measure specific gravity of urine or salt-water fish should not be used to measure flotation solutions.

Centrifugal Flotation vs. Standing Flotation

Centrifugal flotation is more sensitive than standing flotation. The reason is simple; forces that we can apply to the parasites when we spin the tubes in a centrifuge are greater than the forces that we apply during standing flotation. Recovery is greatly improved for heavier eggs such as *Trichuris vulpis* (whipworms) and *Taenia* spp. (tapeworms), and substantially for *Eucoleus (Capillaria)* spp. and *Cystoisospora* (coccidia) spp. when centrifugal flotation was used.[4-7] Given that well-cared-for pets harbor fewer parasites than feral or stray animals, it is important to use centrifugation to increase parasite recovery rates.[4,5]

Contrary to presumption, swinging bucket and fixed angle centrifuges require little hospital bench space. Many are less than 16 inches in length. Most centrifuges are reasonably priced and can be used for decades with minimal service and little or no repair. Also, a variety of rotors is available to suit the needs of the busiest of practices. Examples of commercially available centrifuges are given in E-Tables 81-2 and 81-3, and Figure 81-9 (see Video 81-1).

E-TABLE 81-2

Examples of Commercially Available Hydrometers*

SUPPLIER	CONTACT INFORMATION	CATALOG #	DESCRIPTION	CURRENT PRICE
Fisher	1-800-766-7000 www.fishersci.com	11-522A	1.000-1.225 SG 186 mm long	$59.55 USD
Fisher	1-800-766-7000 www.fishersci.com	11-522B	1.200-1.425 SG 160 mm long	$59.55 USD
VWR	1-800-932-5000 www.vwrsp.com	34623-106	1.000-1.250 SG 165 mm long	$31.69 USD
VWR	1-800-932-5000 www.vwrsp.com	34623-150	1.200-1.450 SG 165 mm long	$31.69 USD
Cole-Parmer	1-800-323-4340 www.coleparmer.com	EW-08298-50	1.000-1.250 SG No length listed	$21.00 USD
Cole-Parmer	1-800-323-4340 www.coleparmer.com	EW-08298-52	1.200-1.450 SG No length listed	$21.50 USD

*These hydrometers are given as examples. Other suitable models are also available.

SG, Specific gravity.

E-TABLE 81-3

Examples of Commercially Available Centrifuges

WITH SWING-OUT ROTORS*							
MANUFACTURER	MODEL	SPEED (RPM)	DISTRIBUTOR	CATALOG#	SIZE (INCHES) L × W × H	ROTOR	TOTAL COST
LW Scientific	USA Universal 6-place Centrifuge	800-3400	LW Scientific 770-270-1394 http://www.lwscientific.com	UNC-06SD-15T3	14.5 × 14.5 × 10.65	6-place 3-15 mL swing-out, digital	$819.00 USI
Cole-Parmer	VS-3400 6-Place Variable Speed Small Benchtop Centrifuges	0 to 3400	Cole-Parmer 800-323-4340 http://www.coleparmer.com	EW-81058-30	13.75 × 15 × 11	6-place 3-15 mL swing-out	$1,795.(USI
VWR	Centrifuge Cell Culture Bundle (includes 4 × 100 mL Swing Out Rotor, Carriers for 15 mL and 50 mL Conical Tubes)	250-4,000 rpm	http://www.vwr.com	89176-490	14 × 18 × 13	Includes 4 × 100 mL swing-out rotor, carriers for 15 mL and 50 mL conical tubes	$6,286.: USI
*WITH FIXED ROTORS**							
LW Scientific	USA	800-3400	LW Scientific	UNC-	14.5 × 14.5 ×	8-place	$819.00

	Universal-8-place centrifuge		770-270-1394 LWScientific.com	08AD-15T3	10.65	3-15 mL angled, digital	USI
Cole-Parmer	VS-3400 6-Place Variable Speed Small Benchtop Centrifuge	0 to 3400	Cole-Parmer 800-323-4340 http://www.coleparmer.com	EW-81058-32	13.75 × 15 × 11	24-place fixed-angle rotor	$1,795.(USI

*These centrifuges are given as examples. Other models are also available. Other distributors may also carry these products.

Standing Flotation

Standing flotation (sometimes called "passive," "simple" or "table-top" flotation), depends on the force of gravity to move heavier objects (debris) to the bottom of the tube, and the buoyant force to move lighter objects (parasites) to the top. The procedure is detailed in Figure 81-10. Specimens are prepared as described above and in Figures 81-3 through 81-6. The fecal specimen is mixed with flotation solution and passed through a tea strainer or gauze sponge. The filtrate is added to a tube, a reverse meniscus is formed, and a coverslip is placed. The preparation is allowed to stand for a minimum of 15 minutes. The coverslip is then removed and examined for parasites.

Centrifugal Flotation

Centrifugal flotation is the procedure of choice for concentration of parasites from feces.[7,8] It is considered to be the gold standard for fecal examination.[8] The term used for characterizing the force applied to parasites in a centrifuge is relative centrifugal force (RCF). If the RCF is known, a centrifugal procedure can be reproduced using any centrifuge for which the rotor radius can be measured. A nomogram is used to determine the revolutions per minute that will achieve a comparable RCF on centrifuges with different rotor sizes (see Figure 81-10).[9] Centrifugal flotation can be performed using either a swinging bucket or fixed angle centrifuge. We prefer the swinging bucket centrifuge because it decreases the number of times that the specimen is handled (Figure 81-11). When using a swinging bucket centrifuge, place the specimen into a tube holder (bucket) in the centrifuge. Add flotation solution to form a reverse meniscus at the top of the tube. Gently place a coverslip on the tube. It is important to avoid trapping air bubbles under the slide. This can be prevented by placing one side of the coverslip in contact with the tube and then slowly "layering" the remainder of the coverslip over the meniscus of the specimen. The speed of the rotor should be increased gradually. This is only possible if the centrifuge is equipped with a dial, knob or digital entry button that will allow you to increase the speed incrementally. If the rotor speed is increased gradually to the target speed, the centrifuge bucket will move slowly to a horizontal position and the coverslip will remain in place. If the speed of the rotor is increased too rapidly, the coverslip may be dislodged from the specimen tube. If the centrifuge does not have variable speeds, follow the instructions below for the fixed angle centrifuge. After the required centrifuge time of 10 minutes, turn off the centrifuge and allow the rotor to come to a complete stop. Remove the coverslip in one upward motion and place it on a microscope slide. Place one side of the coverslip on the slide first and "layer" it onto the glass slide as described previously to prevent entrapped air bubbles.

Centrifugal flotation using a fixed angle centrifuge requires a change in procedures after spinning the sample (Figure 81-12). Because the specimen is placed in the centrifuge at an angle, it is not possible to form a meniscus at the top of the centrifuge tube or to place a coverslip on the tube. Also, since the tube is not topped with a coverslip, the final speed at which the specimen is centrifuged is not as important, nor is it necessary to start the centrifuge at a slower speed. However, faster centrifuge rates can be used without adversely affecting the result. We do not suggest reducing the centrifuge time to less than 5 minutes. Allow the centrifuge to stop as described above. Remove the centrifuge tube, place it in a holder and add flotation solution to form a reverse meniscus (Figure 81-13). Follow the same procedure for placing the coverslip as described previously. Allow the specimen to stand for a minimum of 10 minutes before removing the coverslip to a slide and examining it for parasite stages. If sucrose is used as a flotation solution, we have found that it may be necessary to allow the tube and coverslip to stand for 15-20 minutes to recover all of the parasites stages. It is not necessary to wait longer than 10 minutes when all other flotation solutions are used.

Proper Examination of the Coverslip

The coverslip should be examined thoroughly and systematically. A prepared fecal slide is three-dimensional, meaning that it has length, width and depth. The latter is the most important. Focus on dust on the top of the coverslip and then move downward. The smaller parasites (i.e., *Giardia, Cryptosporidium,* small coccidia) will be found in the top-most layer. The next layer down will contain the large eggs (roundworms, hookworms, whipworms), larger oocysts and larvae. Begin at one corner of the coverslip and move systematically through the specimen as shown in Figure 81-14. Focus up and down as you move through the specimen, unless a parasite of particular size is suspected. If this is the case, you may concentrate your efforts at the layer in which that parasite is found. The entire coverslip should be examined using the 10× objective (total magnification 100×). Small parasites or other objects should then be examined using the 40× objective (total magnification of 400×). The 100× (oil immersion) objective should not be used to examine fecal flotation slides. Some laboratories will "spot-check" 5-10 fields in the center of the slide using 400× magnification to ensure that very small parasites are not overlooked.

Fecal Sedimentation

Sedimentation is used to concentrate eggs or larvae that are too dense to float in flotation solutions or that might be distorted by the solutions. Sedimentation can be performed using either the standing or centrifugal procedure, but without flotation solution. We prefer to use a centrifuge because it results in faster movement of parasites to the bottom of the tube. To perform the procedure, mix the fecal specimen with either saline, water, or 0.1 to 1.0% soap in water solution and add the mixture to a centrifuge tube (Figure 81-15). Centrifuge the specimen or allow the tube to stand undisturbed for 30 minutes. Most of the supernatant is then removed and the entire sediment is examined microscopically. Some parasitologists recommend re-suspending the sediment a second time and then repeating the above steps.

Baermann Procedure

The Baermann procedure is used to recover larvae of parasites such as *Aelurostrongylus, Strongyloides* and *Filaroides* from fecal specimens. Larvae of these and similar parasites must be alive; therefore this procedure must be performed on fresh feces. The Baermann apparatus is a glass or plastic funnel with a piece of clamped flexible rubber or plastic tubing attached to the stem. Three to 10 grams of fresh feces is enclosed in two layers of gauze sponge or cheesecloth that is secured with rubber bands and placed on a wire mesh platform inside the funnel. Warm water (not hot water) is placed in the funnel until it covers the fecal specimen. The apparatus is allowed to stand undisturbed for approximately 6 hours (some allow the specimen to stand overnight). Any larvae that are present are collected by slowly opening the clamp and allowing 5-10 mL of liquid to flow into a centrifuge tube. The tube is centrifuged gently for a few minutes. The supernatant is removed and the sediment is examined for larvae.

Fecal Culture for Parasites

Numerous techniques have been used to culture parasites such as *Giardia, Tritrichomonas,* and *Pentatrichomonas* from canine or feline feces (see ch. 207, 211, and 276). Generally, these procedures require resources that are not readily available in the veterinary hospital. Samples should be submitted either to reference or academic laboratories if fecal culture is to be attempted. One exception might be *Tritrichomonas blagburni*. This agent causes large bowel diarrhea in cats and can be grown with relative ease in a commercially available culture system (Feline In Pouch™, Biomed Diagnostics, White City, OR). A very small amount of freshly voided feces (approximately 0.05 grams) or feces contained on a moistened cotton-tipped rectal swab can be added to the In Pouch. The In Pouch is incubated for 24 hours at 37°C and then held at room temperature and examined every 2 days for 10 days. Media in the In Pouch system allows the few organisms that may be present to reproduce, thus increasing the likelihood of recovering the motile protozoa. The In Pouch can be maintained at room temperature if an incubator is not available. However, organisms will appear in higher numbers sooner following preliminary incubation at 37°C.

Immunologic and Molecular Techniques

Several techniques have been developed to identify specific proteins or DNA from parasites in fecal specimens.[10-15] Immunologic techniques include enzyme-linked immunosorbent assays (ELISA) and

fluorescent antibody tests. ELISA is a technique used to detect the presence of either an antibody or an antigen in a fecal sample. An indirect ELISA is usually employed to detect antibodies to known antigens. The best known fecal ELISA procedure is SNAP *Giardia* (IDEXX Laboratories, Westbrook, ME) (see ch. 221 and 276). This test captures *Giardia* cyst wall proteins (CWP) present in the feces of *Giardia*-infected animals. To conduct the assay, a small sample of feces is mixed with an antibody/enzyme conjugate in a bulb. The bound antigen-antibody/enzyme mixture formed in the fecal/reagent emulsion is transferred to the SNAP device. Additional specific antibodies located on the solid substratum of the SNAP device trap the CWP/antibody/enzyme conjugate as they move over the antibody-containing spot. When the cassette is snapped, wash solutions and substrate are released. The wash solution eliminates non-bound CWP and the substrate is converted to a visible blue product by the enzyme. The SNAP *Giardia* test is an excellent method of confirming *Giardia*-induced cases of diarrhea in dogs and cats. The test is recommended only for testing samples from animals with clinical signs consistent with *Giardia* infection. Testing should not be conducted as a screening procedure on healthy animals. ELISA tests that detect antigens to canine intestinal worms have also been developed by commercial laboratories.[16] A direct fluorescent antibody assay is also commercially available for diagnosis of *Giardia* and *Cryptosporidium*. The Merifluor *Cryptosporidium*/*Giardia* assay (Meridian BioScience, Inc, Cincinnati, OH) contains a fluorescein isothiocyanate–labeled monoclonal antibody specific for cyst wall antigens. The Merifluor test requires the presence of cysts in feces for a positive result. Consequently, this test is not as sensitive as the SNAP *Giardia* assay. The Merifluor test also requires an epifluorescence microscope, which is usually not available in veterinary hospitals. An ELISA-based card that tests for *Giardia* and *Cryptosporidium* (ImmunoCard STAT!) is also available from Meridian.

There are many examples of the application of molecular techniques to fecal diagnosis of parasitic infections. Molecular techniques are particularly helpful for detection of parasites when present in low numbers. Fecal molecular diagnostic assays are usually available only in academic and reference laboratories. It is likely that commercialized, user-friendly versions of these tests will be available in the future.

Diagnostic Resources

Several diagnostic manuals can assist diagnosticians in identifying internal parasites.[17-20]

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CHAPTER 82

Nasoesophageal, Esophagostomy, Gastrostomy, and Jejunal Tube Placement Techniques

Stanley Leon Marks

Overview

Use of enteral feeding devices to deliver nutrients into the lower esophagus is indicated for animals who cannot ingest adequate calories on their own, but who have sufficient gastrointestinal (GI) function to allow digestion and absorption of liquid-diet formulas. The diet for each patient depends, in part, on the selected route of feeding, the functional status of the GI tract, and the animal's nutrient requirements. Other factors, such as cost, availability, and ease of use may be considered. Animals fed liquid formulas via nasoesophageal or jejunostomy feeding tubes are limited to receiving about 1.0-1.3 kcal per mL. When using human enteral formulas for longer than 2 weeks, particularly in cats, one should remember that many of these formulas contain <20% of calories as protein and lack the essential amino acids taurine and arginine. There are several techniques from which to choose for obtaining enteral access. The technique used depends on the anticipated duration of enteral support, aspiration risk, integrity of the GI tract, the pet's temperament, the clinician's expertise, and the animal's ability to tolerate anesthesia.

Enteral Feeding Tube Material and Access Devices

Most feeding tubes are made of red rubber, polyurethane or silicone elastomer. The main shortcoming of silicone is related to its stiffness and flexibility. Silicone feeding tubes require thick side walls to obtain tube wall integrity or stiffness; therefore, their internal diameter is smaller than the internal diameter of a similar sized polyurethane tube, which may lead to clogging.[1] Further, silicone is known for "notch sensitivity:" propagation of a defect after being nicked or torn.[1] Feeding tubes made of silicone and/or polyurethane co-polymers, or other polymer end groups, are being developed for the softness of silicone and durability/wall thickness of polyurethane. French (F) units measure the outer lumen diameter of a tube (each French unit is equal to 0.33 mm).

Nasoesophageal Tubes

Indications and Choices

Nasoesophageal tubes are a simple and efficient choice if nutritional support is planned for <10 days in a dog or cat with a normal nasal cavity, pharynx, esophagus, and stomach.[2] Nasoesophageal tube feeding is contraindicated in animals who are vomiting, comatose, or who lack a gag reflex. Polyvinylchloride (Infant Feeding Tube, Argyle Division of Sherwood Medical, St. Louis, MO) or red rubber tubes (Robinson catheter, Sherwood Medical, St. Louis, MO) are the least expensive, but polyvinylchloride tubes may harden within 2 weeks of insertion and cause irritation or ulceration of the pharynx or esophagus. Tubes made of polyurethane (MILA International, Inc., Erlanger, KY) or silicone (Global Veterinary Products, Inc., New Buffalo, MI) are more expensive, less irritating, longer lasting, and more resistant to gastric acid. An 8-French, 91 cm tube with or without a tungsten-weighted tip is suitable for dogs weighing >15 kg. 5-French tubes are more suitable for cats and smaller dogs.

Placement

Feeding tubes should terminate in the distal esophagus, reducing risk of reflux esophagitis. Placement is facilitated by ensuring that the tube is no longer than the length from nose tip to the seventh or eighth intercostal space.[3] Use tape to mark the appropriate length. Desensitize the nasal cavity with 0.5-1 mL of 0.5%

proparacaine hydrochloride and tilt the head up to allow it to coat the nasal mucosa. Lubricate the tip of the tube with 5% viscous lidocaine prior to passage. Maintaining the animal's head at a normal angle, avoiding hyperflexion or overextension, as the tube tip is gently directed caudoventrally. It should pass with minimal resistance through the ventral meatus, nasopharynx and into the esophagus. Nasoesophageal intubation is more difficult in dogs with long narrow nasal passages and extensive turbinate structures. The small ventral ridge at the proximal end of the canine nasal passage necessitates first directing the tip of the tube dorsally over that ridge and into the nasal vestibule (Figure 82-1; also see ch. 238).[2] The tube can then be directed in a caudoventral-medial direction while pushing the external nares dorsally.[4] This maneuver opens the ventral meatus and guides the tube into the oropharynx.

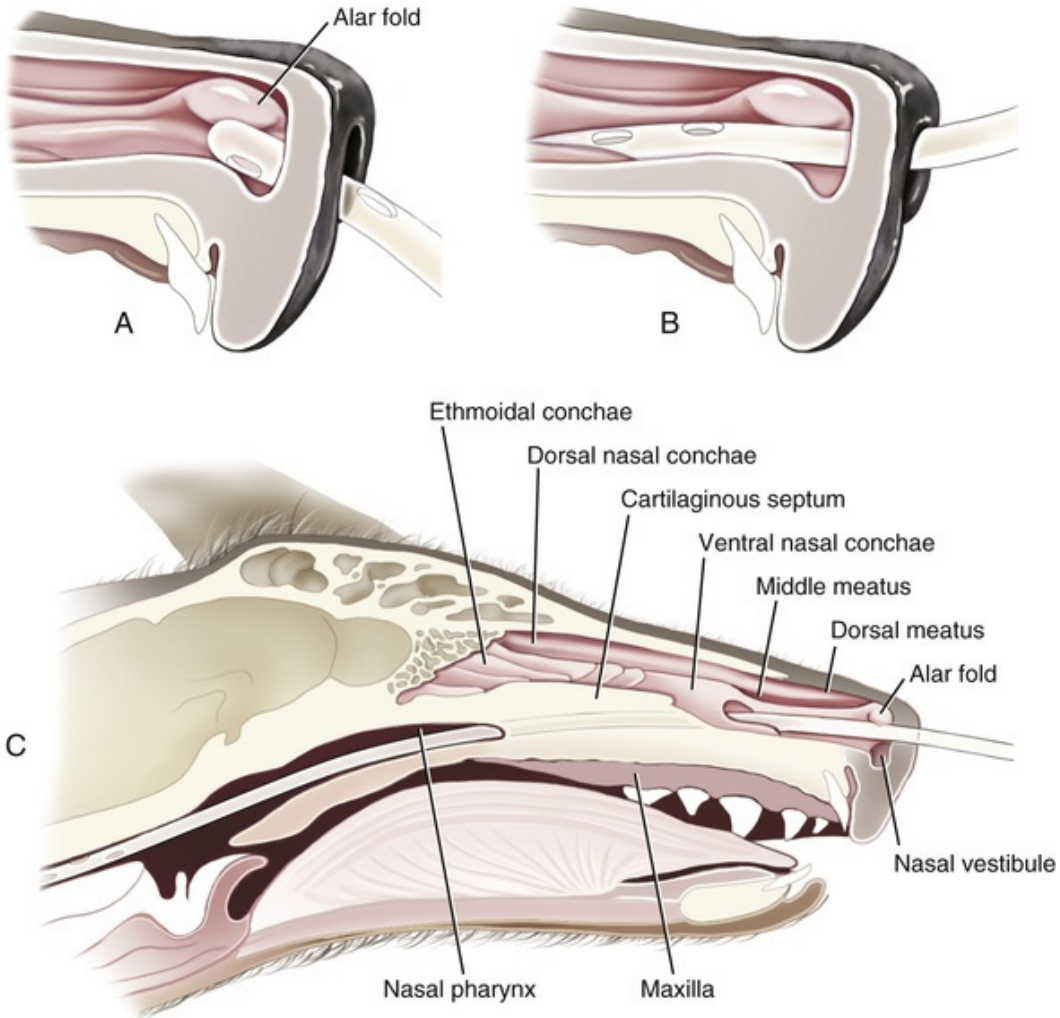

FIGURE 82-1 Parasagittal section showing step-wise insertion of a nasoesophageal tube through the ventral meatus of a dog. **A,** The presence of a small ventral ridge at the rostral end of the nasal passage necessitates directing the tip of the tube dorsally to clear the protuberance. **B,** Once past the protuberance, the tube is aimed medially and ventrally and advanced into the ventral meatus. **C,** Tube through ventral meatus and nasal pharynx. (Reprinted with permission from Crowe DT: Clinical use of an indwelling nasogastric tube for enteral nutrition and fluid therapy in the dog and cat. *J Am Anim Hosp Assoc* 22:675-682, 1986.)

If the tube does not pass with relative ease into the oropharynx, the tip may have gone through the middle meatus, reaching the ethmoid turbinate. The tube then should be withdrawn and re-directed. Once the tube has been passed correctly to the level of the marker, it should be sutured or glued as close to the nostril as possible (Figure 82-2, *A*; Superglue, Loctite Corp., Cleveland, OH). A second tape tab should be secured to the dorsal midline skin between the eyes (Figure 82-2, *B* and *C*). Tubes must not exit laterally nor come in contact with the whiskers of cats. An Elizabethan collar is usually required for dogs, not cats, to prevent inadvertent tube removal. Tube removal is facilitated by clipping hair attached to the glue.

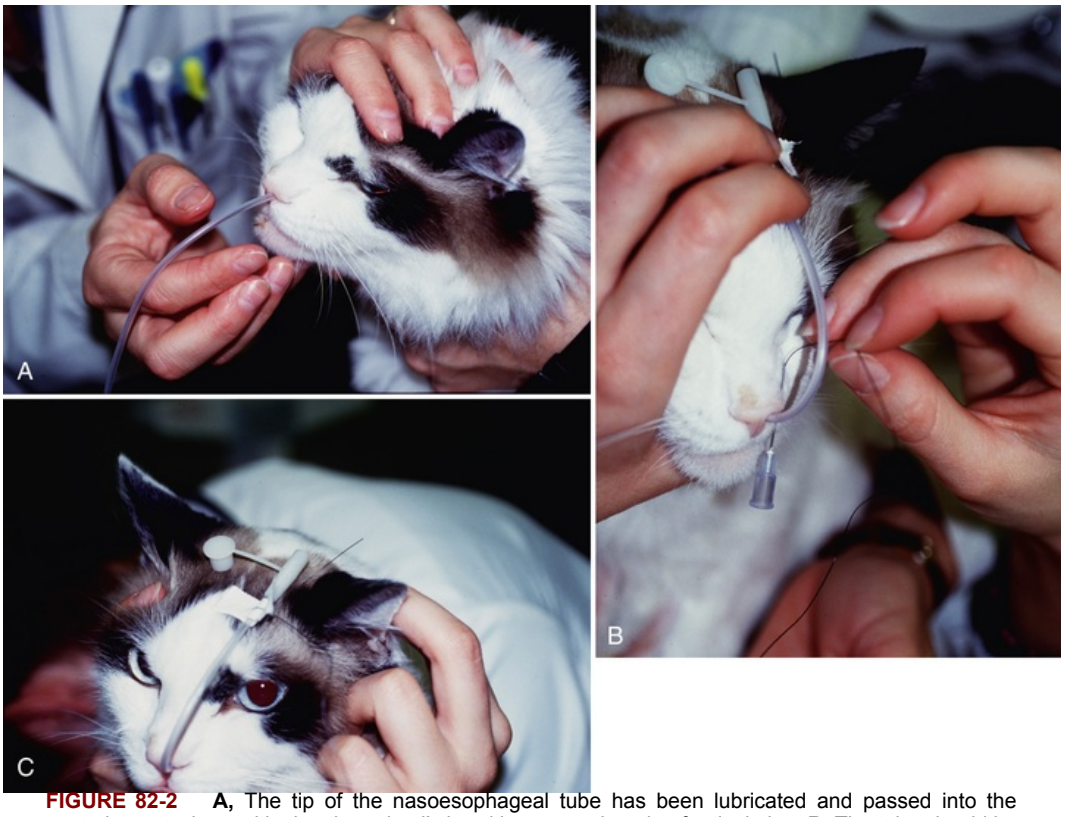

FIGURE 82-2 **A,** The tip of the nasoesophageal tube has been lubricated and passed into the ventral meatus by positioning the animal's head in a normal angle of articulation. **B,** The tube should be secured as close to the nostril as possible, with either suture material or glue. **C,** The nasoesophageal tube can be secured to the skin on the dorsal midline between the eyes with tape "butterflies."

After placement, tube position should be checked by injecting 5 to 10 mL of air while ausculting the cranial abdomen for borborygmus, by infusing 3 to 5 mL of sterile saline or water through the tube and observing for a cough response,[2] or by obtaining a lateral thoracic radiograph. Placement verification can also be accomplished with an end-tidal CO_2 monitor; tubes placed within the esophagus or stomach yield no CO_2. Diets are fed full strength on continuous (pump infusion) or bolus feeding schedules.

Complications and Disadvantages

The most common complications associated with the use of nasoesophageal tubes include epistaxis, dacrocystitis, rhinitis, tracheal intubation (pneumonia), and vomiting.[2] A major disadvantage of nasoesophageal feeding tubes is their small diameter, necessitating the use of liquid enteral formulas. Canned pet foods diluted with water invariably clog feeding tubes.

Esophagostomy Tubes

Overview and Material

Esophagostomy feeding tubes are easily inserted, requiring only heavy sedation or light general anesthesia and intubation with a cuffed endotracheal tube. Three basic techniques for placement of a midcervical esophagostomy tube have been described that are minimally invasive and require no specialized endoscopic equipment.[5-7] The patient should be placed in right lateral recumbency. Clip and aseptically prepare from the left mid-cervical region to the thoracic inlet.[5-7] The left side is preferred because the esophagus lies slightly left of midline. A 14- to 20-French red rubber catheter (Robinson catheter, Sherwood Medical, St. Louis, MO), silicone catheter (Global Veterinary Products, Inc., New Buffalo, MI) or polyurethane catheter (MILA International, Inc., Florence, KY) should be pre-measured from the mid-cervical esophagus to the seventh or eighth intercostal space and marked to ensure termination of the catheter in the distal esophagus.[3]

Technique Using Curved Carmalt, Mixter, or Schnidt Forceps

Advance the right-angle forceps into the midcervical esophagus from the oral cavity. Use the angle of the jaw and the point of the shoulder for landmarks to help ensure that the tip of the forceps can be palpated externally in the midcervical region. Push the curved tips of the forceps laterally at the mid-cervical esophagus, so they can be palpated below the skin. Use a No. 11 scalpel blade to make a stab incision through the skin only, exposing the SC tissue and the esophageal muscle layers. Be careful to avoid the jugular and maxillofacial veins. Exteriorize the tip of the forceps from the esophageal lumen through the skin incision. Guide the advancing forceps through the esophageal muscle layers, carefully dissect the esophageal mucosa off the tip of the forceps with a scalpel blade, use the forceps to grasp the distal end of the feeding tube, and draw the tube out of the oral cavity. Secure the distal end of the feeding tube using the forceps to ensure that the tube remains exteriorized while the proximal end of the tube is pulled out of the animal's mouth. Retroflex the proximal tip of the feeding tube and advance it in an aboral direction across the pharynx and down the esophagus, while slowly retracting on the external end of the tube 2 to 4 cm. A wire guide can be used to facilitate advancing the proximal tip of the feeding tube into the esophagus. The exteriorized portion of the tube will be observed to rotate in a cranial direction as the tube moves down the esophagus, indicating correct placement. Retention sutures (Chinese finger-trap suture), using 2-0 polypropylene, secure the tube's distal end to the skin. Another method of securing the tube involves passing heavy suture on a taper needle through the skin next to the tube and into the periosteum of the wing of the atlas. Antibiotic ointment and gauze dressing should cover the incision site, while the tube and entire site are loosely bandaged with gauze.

Correct tube placement (mid- to distal esophagus) should be confirmed with radiographs. Be certain that the tube does not extend beyond the lower esophageal sphincter and predispose the patient to gastroesophageal reflux. Feeding can begin after complete recovery from anesthesia. The tube esophagostomy-skin interface should be examined daily during the first week for evidence of infection or leakage of food or saliva. The stoma site can be kept clean with a topical antiseptic solution (1 : 100 Betadine solution in 0.9% saline). Once nutritional support is no longer needed, cut the Chinese finger-trap anchoring suture and remove the tube. The wound should be allowed to heal by second intention.

Percutaneous Feeding Tube Applicator Technique

An Eld percutaneous applicator is inserted into the midcervical esophagus via the oral cavity, the distal tip is palpated, and an incision is made through the skin and subcutaneous (SC) tissue over that tip.[8] Activate the spring-loaded instrument (Figure 82-3, *A*) to advance the trocar through the esophageal wall and incision (Figure 82-3, *B*). The distal end of the feeding tube is secured to the eyelet of the trocar with suture material. The Eld device and attached feeding tube are retracted into the esophagus and exteriorized via the oral cavity. The feeding tube is then redirected into the midcervical esophagus after inserting a wire stylet into the distal tip of the feeding tube. The tube is secured to the skin as described above.

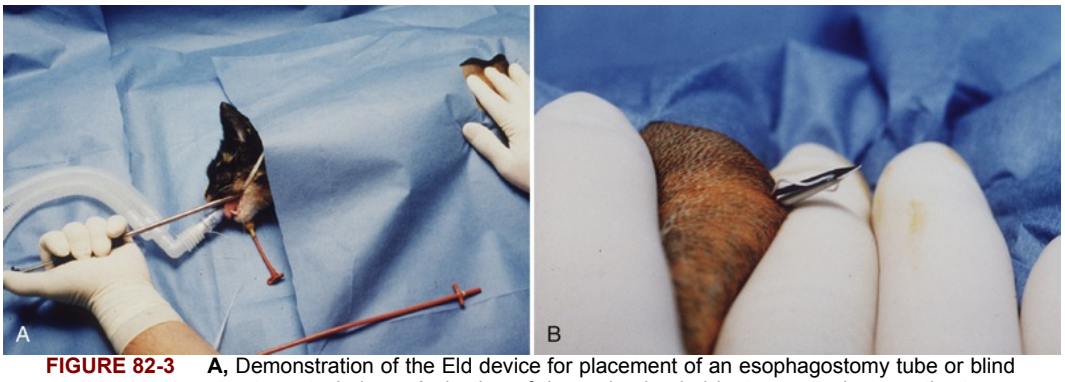

FIGURE 82-3 **A,** Demonstration of the Eld device for placement of an esophagostomy tube or blind percutaneous gastrostomy technique. Activation of the spring-loaded instrument advances the trocar through the esophageal or gastric wall. **B,** Suture material is attached to the exteriorized eyelet of the trocar which is retracted into the lumen of the instrument, and carefully removed out of the esophagus and out the mouth of the animal. The exteriorized suture material is attached to a feeding tube. (Courtesy Dr. Larry A. Eld.)

Percutaneous Needle Catheter Technique

With this method, an esophagostomy introduction tube (Van Noort esophagostomy tube set, Global

Veterinary Products, Inc., New Buffalo, MI) (Figure 82-4) is introduced into the midcervical esophageal area. The slot in the distal portion of the tube is palpated, and a Peel-Away sheath needle (Global Veterinary Products) is introduced into the distal portion of the tube. The needle is removed from the sheath and a 10-French catheter is introduced through the sheath to the distal third of the esophagus. The sheath is peeled away and the esophagostomy tube carefully removed. The feeding tube is secured as described. This technique is limited by the small diameter of the feeding tube (10 French), only allowing administration of water and liquid enteral formulas.

FIGURE 82-4 Photograph of the esophagostomy tube set, illustrating the esophagostomy introduction tube, 10-gauge, 5-cm long Peel-Away sheath needle, and a 10-French silicone catheter. (Courtesy Smiths Medical ASD, Inc., Minneapolis, MN.)

Complications

Despite potential for esophageal scarring, fistulas or strictures, none has been reported. A common minor complication is peristomal inflammation. Peristomal abscessation is infrequent.[5-7] Most inflammatory reactions are mild and responsive to cleaning and topical antibiotics. Less common complications include vomiting the tube into the oral cavity and tube obstruction.[5-7]

Gastrostomy Tubes

Indications and Contraindications

Gastrostomy tube feeding is indicated for long-term (weeks to months) nutritional support of anorectic or dysphagic animals with adequate GI function to allow digestion and absorption of feeding solutions. Gastrostomy tubes have a relatively large diameter (20 to 24 French), allowing use of blended pet food and medications. Gastrostomy tube feeding is contraindicated in animals with persistent vomiting, decreased consciousness, or GI obstruction. Caution should be exercised in conditions under which the stomach cannot

be apposed to the body wall (severe ascites, adhesions, space-occupying lesions).

Placement and Material

These can be placed using the percutaneous endoscopic gastrostomy (PEG) or blind percutaneous gastrostomy (BPG) techniques.[9-12] A variety of feeding tubes can be utilized for gastrostomy feeding: latex, polyurethane, and silicon tubes with French-Pezzer mushroom, balloon, bumper, or silicone dome tips (Figure 82-5). The silicone catheters can be purchased from Global Veterinary Inc., New Buffalo, KY or US Endoscopy, Mentor, OH; polyurethane from MILA International, Inc., Erlanger, KY; and latex catheters from BARD Urological Division, Murray Hill, NJ. One can modify the catheters by cutting off and discarding the flared open end and then cutting off two 2-cm pieces to be used as internal and external flanges from the same cut end. The end opposite the mushroom tip is trimmed to facilitate introduction into the larger opening of a disposable plastic micropipette. Make a small stab incision through the center of each flange and slide one flange over the cut end of the catheter until it rests against the mushroom tip. The other 2-cm piece of tubing will be used as an external flange that lies against the abdominal wall.

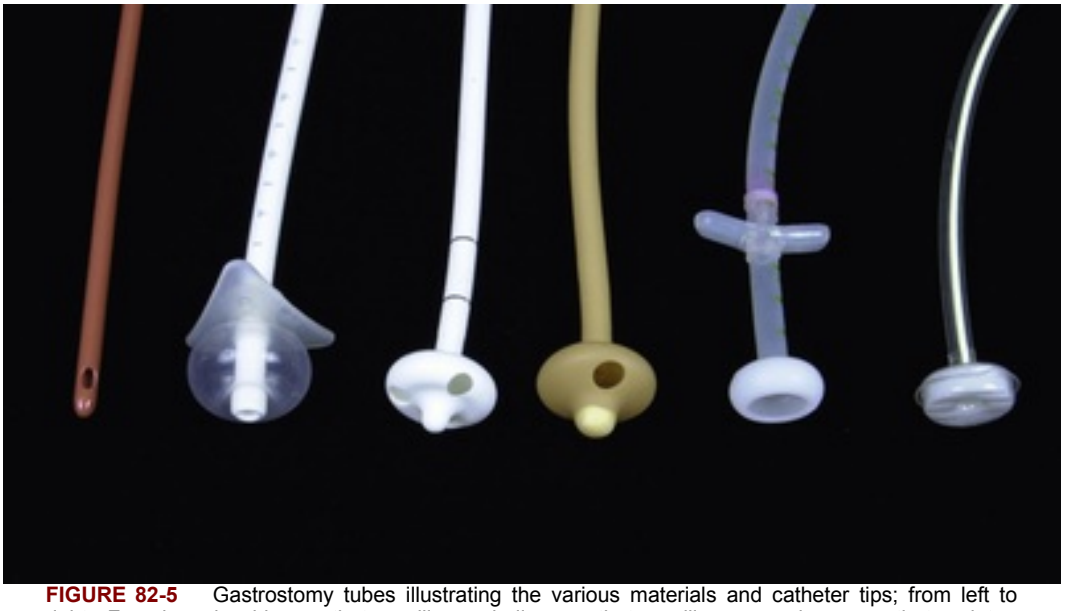

FIGURE 82-5 Gastrostomy tubes illustrating the various materials and catheter tips; from left to right, French red rubber catheter, silicone balloon catheter, silicone mushroom catheter, latex mushroom catheter, silicone catheter with dome, polyurethane catheter with bumper.

Percutaneous Endoscopic Gastrostomy Technique and Complications

Placement of gastrostomy tubes necessitates brief anesthesia. The animal should be placed in right lateral recumbency so that the stomach tube can be placed through the greater curvature of the stomach and the left body wall. Preparation for either percutaneous procedure involves surgical prep of the skin caudal to the left costal arch. The endoscope is introduced into the stomach and the stomach is carefully inflated until the abdomen is distended but not drum tight. The left body wall is transilluminated with the endoscope to ensure that the spleen is not positioned between the stomach and body wall. An appropriate site for insertion of the tube is determined by endoscopically monitoring digital palpation of the gastric wall. A small incision is made in the skin with a scalpel blade, and an IV catheter (16 to 18G, 1.5-2 inch long) is stabbed through the body wall into the lumen of the stomach (Figure 82-6, *A*). The stylet is removed and nylon or polyester suture is threaded through the catheter into the stomach lumen. The suture material is grasped with the endoscope biopsy forceps (Figure 82-6, *B*), and both endoscope and forceps are carefully withdrawn through the esophagus and out the mouth. The suture material is secured to the feeding tube and gentle traction is applied to the suture at its point of exit from the abdominal wall (Figure 82-6, *C*). The feeding tube is pulled out through the body wall, the mushroom end draws the stomach wall against the body wall (Figure 82-6, *D*), and the tube is anchored here by the external flange placed over the catheter at the skin surface (Figure 82-6, *E*). The endoscope is then reinserted into the stomach to verify the correct placement of the mushroom against

the gastric mucosa. If mucosal blanching is observed, tension applied to the tube should be reduced to avoid ischemia and necrosis. A plastic clamp is placed over the tube and the tube capped with a Y-port connector. A stockinette jacket (San Jose Surgical Supply, Inc., San Jose, CA) is fitted to protect the tube (Figure 82-6, *F*).

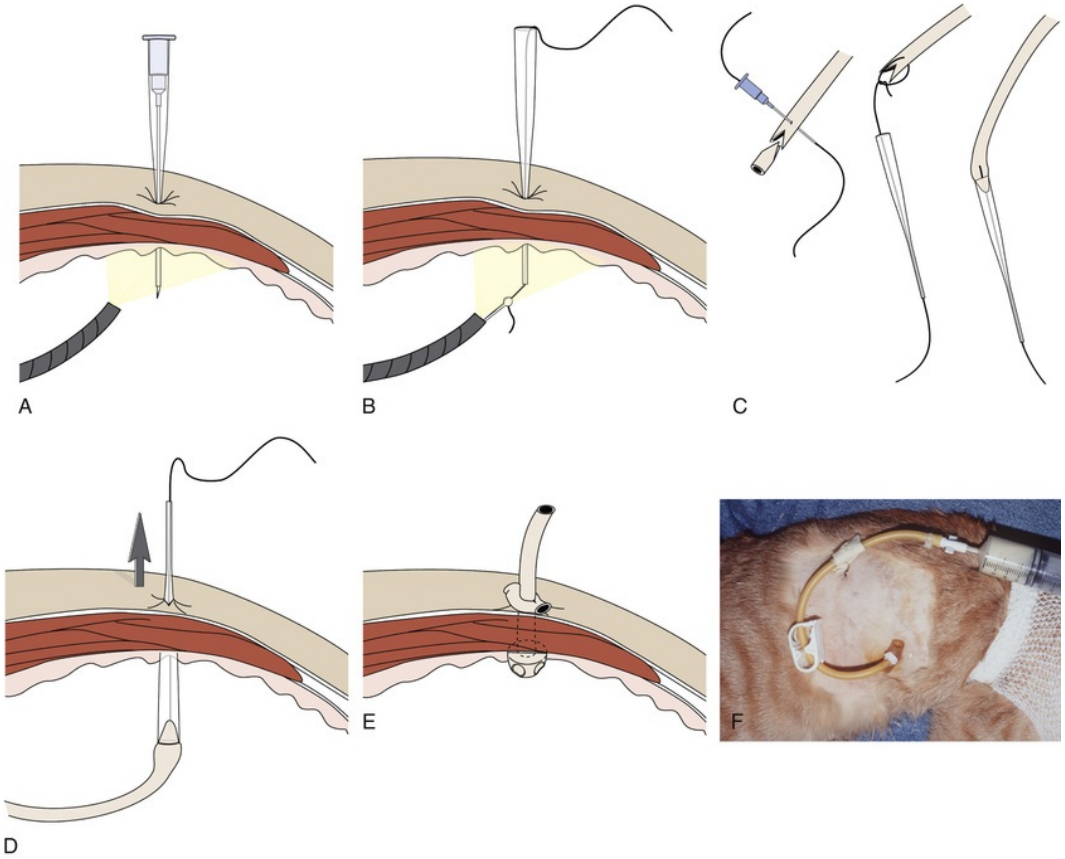

FIGURE 82-6 Percutaneous endoscopic gastrostomy (PEG) technique. **A,** With the animal in right lateral recumbency, the endoscope is introduced into the stomach, and the stomach is insufflated with air. The left body wall is transilluminated with the endoscope to ensure that the spleen is not between the stomach and the body wall. A 16-18G sheathed catheter pierces transabdominally into the insufflated stomach lumen. **B,** The catheter stylet is removed, and nylon suture is advanced through the catheter until it can be grasped with endoscopic retrieval forceps. The nylon suture is pulled out through the mouth as the endoscope is withdrawn. **C,** The suture material is secured to the feeding tube and water-soluble jelly is applied liberally to the catheter sheath and the mushroom-tip catheter. **D,** The lubricated catheter is drawn down the esophagus and into the stomach as the assistant applies traction on the suture exiting the abdominal wall. **E,** The catheter is advanced until the mushroom tip rests gently against the gastric mucosa. Endoscopy should be repeated to confirm the correct position of the mushroom tip. An external flange is fitted down the tube against the skin to prevent the tube from slipping into the stomach. **F,** Gastrostomy feeding tube in place in a cat, with the clamp in the open position. The stockinette jacket is pulled over the gastrostomy tube once feeding is completed. (Redrawn from Washabau R, Day MJ: *Canine and feline gastroenterology*, St Louis, 2013, Saunders. Drawings created by John Doval and Stanley Marks, UC Davis.)

PEG tube related complications caused by incorrect placement include splenic laceration, gastric hemorrhage, or pneumoperitoneum. PEG tubes may result in delayed complications of vomiting, aspiration pneumonia, tube extraction, tube migration, and stoma infection.[9,10,13] Minor complications include pressure necrosis at the stoma site and cellulitis.[9,10,13] Chances of splenic laceration are minimized by insufflating and trans-illuminating the stomach prior to needle or catheter placement into the abdominal wall. A discordant number of large-breed dogs have had the major complication of the stomach falling off the silicone dome end of the gastrostomy tube. The stoma has appeared normal in affected dogs and feeding may commence without knowledge of the detachment. Detachment has occurred despite placement of an internal flange between dome and gastric mucosa. Dogs heavier than 30 kg, particularly those that have delayed wound healing, should therefore have their gastropexy site reinforced with an Entuir secure GI suture anchor set (Cook Medical Inc., Bloomington, IN). This anchors the anterior stomach wall to the abdominal wall and

reduces risk of gastropexy site breakdown.

Blind Percutaneous Gastrostomy Technique and Complications

The non-endoscopic, non-surgical gastrostomy tube placement technique begins with a length of vinyl or stainless steel tubing (diameter 1.2 to 2.5 cm) purchased from a hardware store, or an Eld Gastrostomy Tube Applicator (Jorgensen Laboratories, Loveland, CO) or gastrostomy tube introduction set (Global Veterinary Inc., New Buffalo, KY).[11,12] The Eld Gastrostomy Tube Applicator is the only device with an internal trocar. The Cook gastrostomy tube introduction set contains a wire threaded through an introduction needle. The distal tip of a stainless steel tube can be flared and deflected 45 degrees from the long axis to help displace the lateral body wall. The lubricated tube is passed through the mouth, into the stomach and advanced until the end displaces the stomach and lateral abdominal wall. Positioning the patient's head beyond the table edge and lowering the proximal tube end facilitates identifying its tip through the body wall. For the Cook gastrostomy introduction set or similarly prepared device, a percutaneous needle is introduced into the lumen of the introduction tube while an assistant firmly holds the distal tube tip between two fingers. A skin nick is made over the end of the tube and a 14-gauge needle advanced into the introduction tube lumen (Figure 82-7, *A*). Proper positioning of the needle is confirmed by moving the hub from side to side and feeling the needle tip strike the inside of the tube. A guide wire included in the kit is threaded through the lumen of the needle, into the tube, and out the mouth of the patient. The introduction tube is removed and the threaded end of the guide wire secured to an adapter which fits snugly into the end of a feeding tube (Figure 82-7, *B* and *C*). Gentle traction is applied to the guide wire at its point of exit from the abdominal wall, facilitating placement of the mushroom end of the feeding tube against the gastric mucosa. The feeding tube is secured in an identical fashion to the PEG tube procedure described above.

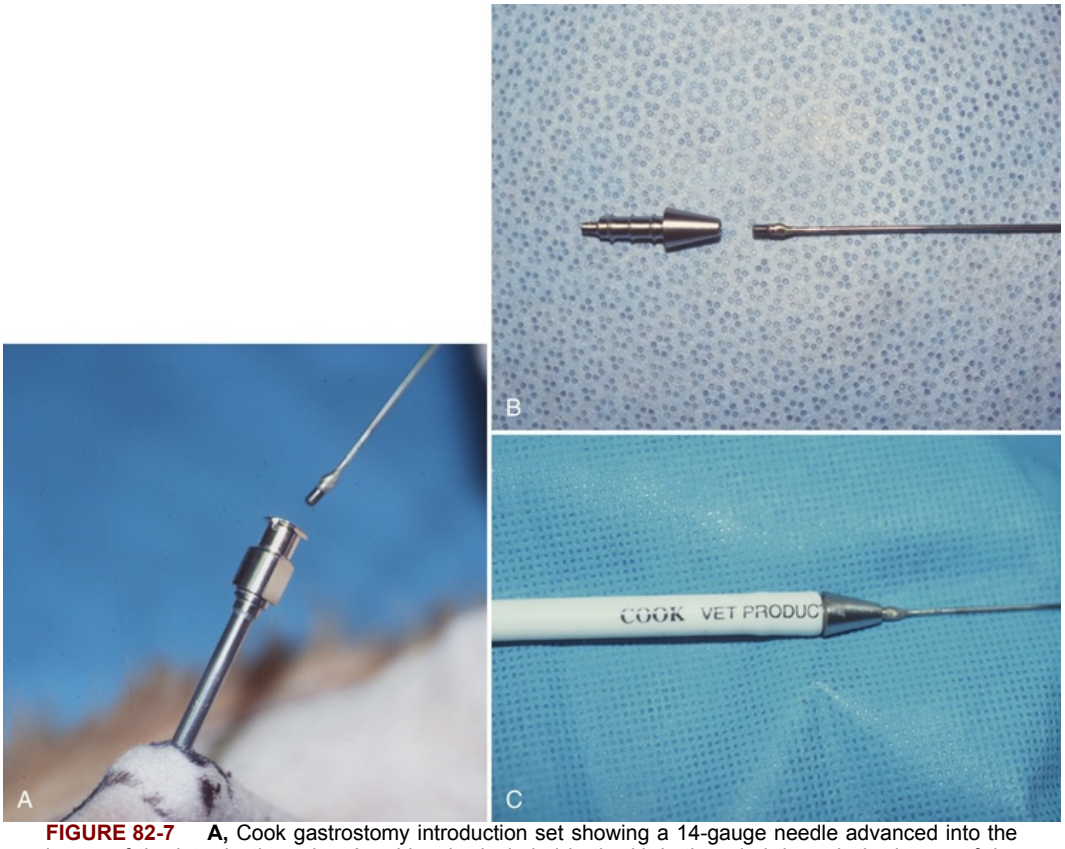

FIGURE 82-7 **A,** Cook gastrostomy introduction set showing a 14-gauge needle advanced into the lumen of the introduction tube. A guide wire included in the kit is threaded through the lumen of the needle, into the introduction tube, and out the mouth of the patient. **B** and **C,** Following the removal of the introduction tube from the animal, the threaded end of the guide wire is secured to an adapter that fits snugly into the end of the feeding tube. Gentle traction is applied to the guide wire at its point of exit from the abdominal wall to position the mushroom of the tube against the gastric mucosa.

Complication rates are similar for BPG and PEG. However, risk of penetrating spleen, stomach, or

omentum is greater if the stomach is not insufflated with air prior to positioning the tube against the lateral abdominal wall.[14] Contraindications to using the "blind" technique include esophageal disease and severe obesity, which precludes accurate palpation of the tube against the abdominal wall. In either case, gastrostomy tubes should be placed surgically.

Jejunostomy Tubes

Indications and Options

Dogs and cats unable to tolerate intragastric or intraduodenal feeding, but who have normally functioning distal small intestine and colon, are candidates for jejunostomy.[15] Specific indications for jejunostomy tube feeding include gastric outlet obstruction, gastroparesis, recurrent/potential aspiration, proximal small bowel obstruction, and partial gastrectomy. Jejunal tube feeding reduces stimulation of the pancreas and can be used for nutritional support of patients with severe pancreatitis.[15] Surgically placed jejunostomy tubes are commonly used for long-term feeding. An alternative to the surgical jejunostomy technique is placement percutaneously. These include percutaneous jejunostomy or gastrojejunostomy (PEG-J) tubes placed under fluoroscopic or endoscopic guidance. The advantage of the PEG-J technique is that it allows ready access to the stomach for aspiration of gastric luminal contents.

Placement and Complications

Four sequential steps must be followed to achieve successful PEG-J tube placement in dogs and cats: (1) routine PEG placement; (2) deep guide wire passage into the small intestine; (3) endoscope retraction leaving the guide wire in place; and (4) jejunostomy feeding tube placement over the guide wire.[16,17] Briefly, the animal is anesthetized and placed in right lateral recumbency. A PEG tube is routinely placed and the external portion of the tube trimmed to a length of 6 inches, maximizing the amount of jejunostomy tube that can be passed into the small intestine. Placement of a 65-cm jejunostomy tube (Gastro-Jejunal feeding tube, Wilson-Cook Medical Inc., Winston-Salem, NC) works well in cats, whereas a jejunostomy feeding tube ≥95 cm is recommended for most dogs. A standard loop snare is passed through the PEG tube into the stomach using an endoscope. The snare is opened and the endoscope advanced through it toward the pylorus. The animal is then positioned in left lateral recumbency, and the endoscope is advanced as far down the small intestine as possible. The accessory channel of the endoscope is flushed with water to facilitate rapid passage of a guide wire that is passed down the biopsy channel into the small intestine. As the endoscope is carefully retracted into the stomach, the tip of the endoscope is pulled past the open snare, which is then closed snugly on the guide wire. The endoscope is then removed from the animal with the resultant extension of the guide wire out the oral cavity. The closed snare is then pulled out through the gastrostomy tube, facilitating the exit of a portion of the guide wire from the opening of the gastrostomy tube. The snare is then released, an assistant gently pulls the proximal end of the guide wire through the gastrostomy tube, leaving the distal (aboral) end in the small intestine. The jejunostomy tube is flushed with water, activating lubricant on its inner surface. The jejunostomy tube is threaded over the guide wire under endoscopic guidance until its proximal end is seated in the gastrostomy tube. The guide wire is then removed from the PEG-J tube, and abdominal radiographs are taken to confirm adequate placement of the jejunostomy tube 40 to 60 cm distal to the pylorus. Passage of the jejunostomy tube far into the jejunum is critical for preventing the catheter from migrating retrograde into the stomach.

Endoscopically assisted placement of an esophagojejunostomy (EJ) feeding tube in 5 chronically anorexic dogs with pancreatitis was well tolerated in each. Tube occlusion, transient vomiting and loose stool were the most common complications.[18] Endoscopically assisted nasojejunal feeding tube placement has been used in dogs.[19,20] Facial irritation, sneezing, and the narrow 8-French tubes clogging limit use of this modality to patients anticipated to only need short-term nutritional support (<7 days).

Removal of Esophagostomy, Gastrostomy and PEG-J Tubes

Unlike gastrostomy tubes, an esophagostomy tube can be removed the same day it is placed without concern of leakage or development of secondary complications. The dressing and sutures are removed while the tube is held in place. The tube is then occluded by kinking and removed with gentle traction. The ostomy site should be cleaned, antibiotic ointment applied, covered with a light dressing for 24 hours which is then removed for ostomy site inspection. Skin sutures are not needed, as it should close within 24 to 36 hours.

For PEG tubes and PEG-J tubes, it is recommended that the PEG tube be left in place for a minimum of 3

weeks. Patients who are severely debilitated or receiving immunosuppressive therapy may require longer for formation of a peritoneal seal. The tube should be removed only when oral food intake is sufficient to meet the patient's caloric requirement (see ch. 172 and 174). One method of Pezzer PEG tube removal is to cut it at the body wall and push the mushroom tip into the stomach to be passed in the feces. This method is safe in medium- to large-size dogs because the mushroom and internal flange should easily pass in feces. A second method involves inserting a stylet into the tube to flatten the mushroom tip while exerting firm traction on the tube. This assumes the tip has not been cut with a scissors before placement. This second method is recommended for cats and small dogs because the mushroom can obstruct the intestine. Removal of the MILA catheter is accomplished by deflating the bumper, after removal of the Y-port adapter. Catheters with a dome (US Endoscopy) are removed by gentle but firm traction on the tube. The gastro-cutaneous tract should seal with minimal or no leakage within 24 hours.

Replacement of Gastrostomy and Esophagostomy Tubes

PEG tubes may malfunction or be prematurely removed by the patient, requiring replacement. If a gastrostomy tube is removed within 3 weeks of placement (before complete establishment of the gastrocutaneous tract), iodinated contrast material can be injected via the stoma site to determine if the gastrocutaneous tract is still intact, or a PEG procedure could be performed to evaluate the gastric mucosa and verify correct positioning of the replacement gastrostomy tube. If a tube is inadvertently removed once the gastrocutaneous tract is well healed, one can replace the original catheter with a balloon-type catheter (Flexiflo Gastrostomy tube, Ross Laboratories, Columbus, OH)[21] or a low-profile gastrostomy device (LPGD, Bard Interventional Products Division, Murray Hill, NJ) (Figure 82-8, *A*). Neither catheter type requires an endoscopic procedure or anesthesia for placement. The gastrostomy "button" is a small, flexible silicone device that has a mushroom-like dome at one end and two small wings at the other that lie flush with the outer abdominal wall (Figure 82-8, *B*). A one-way anti-reflux valve prevents reflux of gastric contents through the top of the tube. There are two types of LPGDs: obturated and non-obturated. The obturated device has an enlarged mushroom tip that must be stretched for placement in the stomach by using a special introducer[22] (Figure 82-8, *C*). The non-obturated tube works like a Foley catheter and does not require forceful entry into the gastrostomy stoma. The length of the gastrocutaneous fistula must be precisely determined to guide correct selection of the appropriate "button" shaft length. This is accomplished with a special stoma-measuring device provided with the kit. LPGD advantages include durability, decreased likelihood of inadvertent removal by the patient, and their aesthetically pleasing appearance for owners.[23]

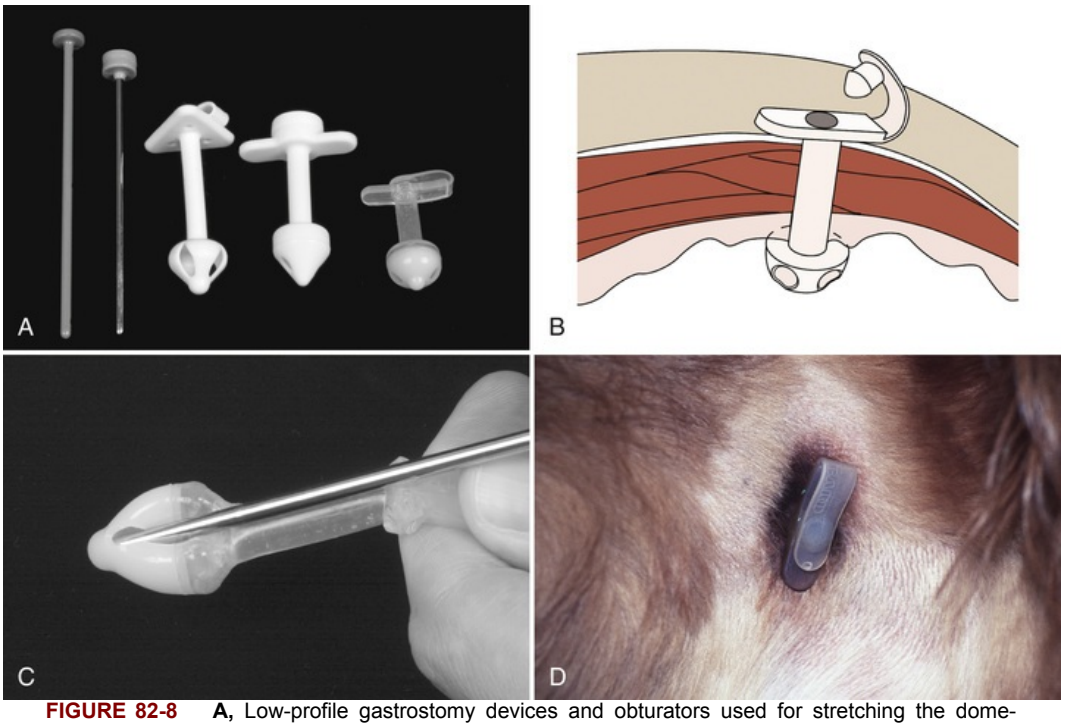

FIGURE 82-8 **A,** Low-profile gastrostomy devices and obturators used for stretching the dome-

shaped tip of the device. From left, The Ross Laboratories Stomate low-profile device, The Cook low-profile device, and the Bard "Button" low-profile device. **B,** Low-profile gastrostomy device with small outer wings of the device lying flush against the skin of the abdominal wall. For feedings, the small plastic plug is removed and a feeding adapter is connected to a syringe. **C,** Correct technique for stretching the dome-shaped tip of the low-profile gastrostomy device with an obturator. The dome should not be stretched by passing the obturator through the lumen of the device as it will compromise the integrity of the anti-reflux valve located adjacent to the dome. **D,** Low-profile gastrostomy device after placement in a dog showing the aesthetic appearance of the device that fits flush against the animal's skin.

An alternative low-profile device that can be used in lieu of a regular PEG tube or replacement low-profile device is a one-step or "initial placement" low-profile PEG tube (One Step Button, now renamed as EndoVive Low Profile Percutaneous Endoscopic Gastrostomy kit; Boston Scientific, Natick, MA) (Figure 82-9, *A* and *B*). The one-step avoids need for a second procedure to replace the original PEG tube. Tubes are available in 18 and 24 French diameters and range in stoma length from 1.2 to 4.4 cm. Use of silicon spacers supplied by the manufacturer (Figure 82-9, *C*) helps ensure that devices can be adapted to animals with different stoma tract length requirements. In a study evaluating complications and outcomes of one-step low-profile gastrostomy devices for long-term enteral feeding in dogs and cats, the devices were well tolerated and the most common complications were relatively minor: peristomal swelling and mucopurulent peristomal discharge.[24]

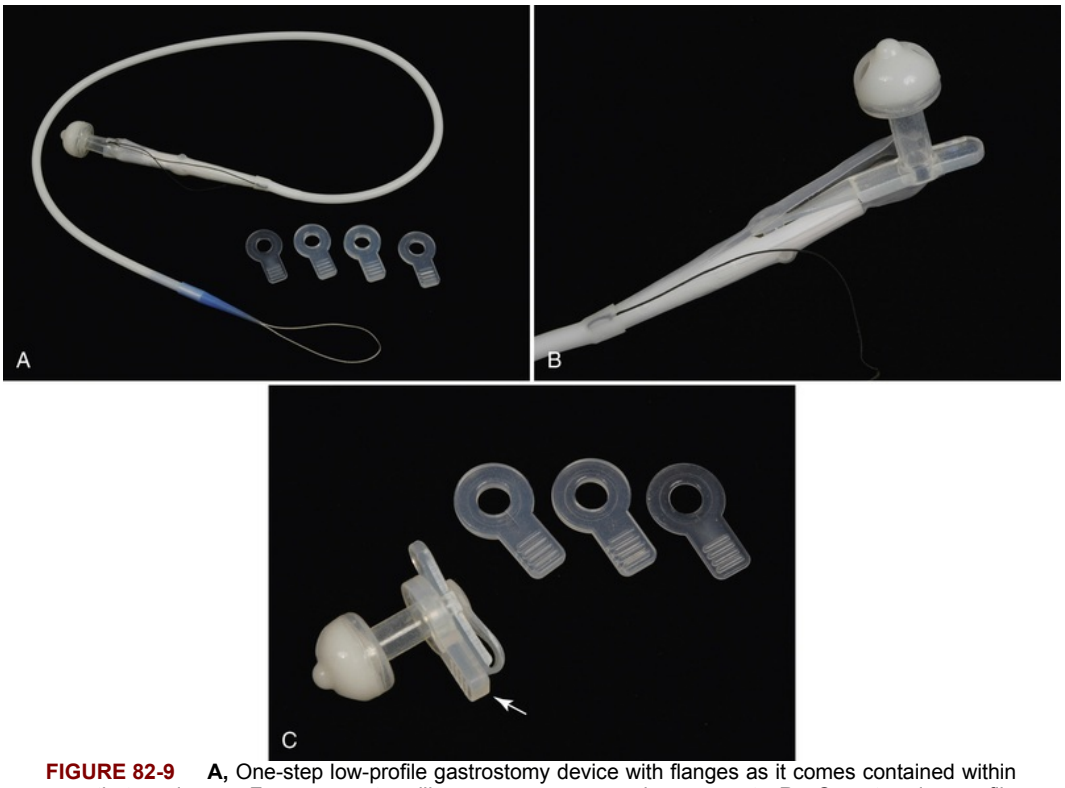

FIGURE 82-9 **A,** One-step low-profile gastrostomy device with flanges as it comes contained within a catheter sleeve. Four separate silicone spacers are also present. **B,** One-step low-profile gastrostomy device with flanges released after tearing the surrounding catheter sleeve open by pulling on the attached black suture material. **C,** One-step low-profile gastrostomy device separated from catheter sleeve, showing a single 5-mm silicone spacer (arrow) inserted over the shaft, and three other separate silicone spacers of varying thickness.

Complications of Enteral Feeding

Gastric Pressure Necrosis

Gastric pressure necrosis can occur from either the mushroom of the PEG tube or flange eroding the mucus layer of the stomach due to excessive tension being exerted on the PEG tube during placement. Overzealous PEG tube traction before placement of the external flange flush against the skin can also cause pressure necrosis, which appears red, swollen, and moist. To minimize these problems, be sure that the PEG tube can

be rotated following placement and leave a 1-cm space between the external flange or the bumper and the skin.

Feeding Tube Displacement

This is relatively common, particularly with nasoesophageal and PEG-J tubes. Displacement of the tube can lead to aspiration, diarrhea, or peritonitis in pets with a gastrostomy tube. Gastrostomy tubes should be marked with tape or a marking pen at the level of the skin to help verify tube position. Since stomach detachment from the abdominal wall, with subsequent intraperitoneal leakage, can occur in large-breed dogs, an internal flange or T-fasteners should be placed to minimize the chance of this complication.

Tube Obstruction

Obstruction of the feeding tube is one of the most common complications of enteral feeding.[25] Obstructions are usually caused by formula coagulation, although they can be caused by tablet fragments, kinks in the tubing, or precipitation of medications. Nasoesophageal tubes are prone to obstruction because of their small diameter. Obstructions may be three times more frequent in patients fed by continuous versus bolus feedings.[26] Sucralfate and acid suppressants have been reported to precipitate with enteral formulas, causing tube obstruction.[26] Warm water infused with gentle pressure and suction will relieve most obstructions. For more unyielding obstructions, carbonated water is instilled into the tube and allowed to remain for 1 hour before applying gentle pressure and suction. Pancreatic enzyme infusions and meat tenderizer have also been advocated to dissolve tube obstructions.[25] On rare occasions, passing an angiographic wire is needed to unclog the tube. Tube obstructions can be minimized by flushing with warm water before and after administering medications or feedings. Tubes should also be flushed after checking for gastric residuals because the acid pH will cause the formula to coagulate in the tube. Elixir forms of medication should be used rather than crushed tablets whenever possible. Tablets should be crushed and dissolved in water prior to administration through a feeding tube if no alternative form is available.

Leakage Through Ostomy Sites

Mild leakage at the stoma site can occur for the first few days following feeding tube placement. Persistent leakage may indicate tube dysfunction, peristomal infection, or a stoma that is too large for the tube. Signs of inflammation with or without discharge or fever may be indicative of stoma site infection which must be differentiated from fasciitis. If it is a simple wound infection, it can usually be treated topically with a dilute Betadine solution and more frequent dressing changes. Systemically administered antibiotics are usually reserved for patients with systemic signs of infection.

Aspiration

Pulmonary aspiration (see ch. 242) is a common complication of enteral feeding, although the actual incidence is difficult to determine. Risk factors for aspiration include impaired mental status, neurologic injury, absence of a cough or gag reflex, mechanical ventilation, and previous aspiration pneumonia.[27] The source of the aspirated material should be identified because withholding gastrostomy feedings or placing a jejunostomy feeding tube in a patient will have no benefit if the patient aspirated oropharyngeal secretions. Although controversial, most authors agree that post-pyloric feeding reduces risk of aspiration.[28] In addition, continuous feedings have been shown to induce less gastroesophageal reflux than bolus feedings.[29]

Diarrhea

Diarrhea is the most commonly cited complication associated with tube feeding in human and animal patients, with an incidence ranging from 2.3% to 63%.[30,31] The clinical implications of enteral feeding-related diarrhea are significant. Severe diarrhea leads to fluid, electrolyte, and nutrient loss, as well as considerable patient distress. Diarrhea in tube-fed patients occurs due to multiple factors, including hypoalbuminemia, hyperosmolar or high fat diets, infected diets, or antibiotic therapy.[30,31] The incidence of diarrhea in enterally fed patients taking antibiotics far exceeds the incidence in normally fed patients taking the same antibiotics. Antibiotic-associated diarrhea may arise from overgrowth of enterobacteria *(Klebsiella, Proteus, Pseudomonas)* or from proliferation of *Clostridium difficile*.

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CHAPTER 83

Care of Endoscopic Equipment

Valerie Walker, Susan Cox, Katie Douthitt

Overview

Endoscopes and the instruments which accompany them are a significant investment. Initial cost coupled with subsequent expenses for repairs can be sizeable. A great deal of frustration can be avoided and money can be saved if personnel understand the handling, cleaning and general care required of such equipment. In large busy practices, written policies and guidelines for cleaning, disinfecting (E-Box 83-1), handling, and conducting endoscopy procedures can help prolong the lifespan of this equipment. Disregarded or forgotten steps, especially in the cleaning process, can lead to losing an endoscope to repair for extended periods.

E-Box 83-1

Endoscope Cleaning Guidelines

A. Pre-cleaning performed immediately post-procedure to remove gross debris (also see Video 83-1).
   a. With clean water, wipe down insertion tube.
   b. Aspirate water then air through suction channel until water aspirated is clear.
   c. Attach air/water channel cleaning valve (if available).
   d. Flush water, then air through channels.
   e. For endoscopes containing an elevator channel or auxiliary water channel—flush with water, then air.
   f. Disconnect from unit.
   g. Place water resistant cap to protect electrodes (videoscopes).
   h. Move endoscope to reprocessing room.

B. Leak testing (also see Video 83-2)
   a. Inspect leak tester.
   b. Attach the leak tester to the venting connector.
   c. Immerse endoscope in clean water.
   d. Engage the leak tester and watch for air bubbles for 2 minutes.
      i. The A-rubber at the bending section will enlarge slightly; this is normal.
      ii. If there is a leak at the bending section, deflecting the distal tip under water can increase the success of finding smaller leaks.
      iii. Leaks from the biopsy channel will appear as bubbles emanating from the distal tip.
      iv. If a continuous flow of air bubbles is detected, or a continuous drop in pressure is visualized, stop the cleaning process and call your manufacturer or repair center.
      v. If a leak is detected and repairs must be made, the repair center may require you to continue the cleaning process to avoid cross contamination.
   e. If no bubbles or drop in pressure is seen, release pressure (hand-held) and leave attached to endoscope for 30 additional seconds, ensuring all air is removed.

C. Manual cleaning (also see Video 83-3)
   a. Remove all valves and biopsy port cover.
   b. Use a recommended enzymatic cleaner detergent solution. Dilute according to manufacturer's specifications.
   c. If using an endoscope basin, immerse the scope.
   d. Thoroughly wipe down all external surfaces. Use a soft brush to clean within the ridges of the control knobs and elevator channel opening if applicable. Clean the distal tip and remove any debris from the air/water nozzle.

e. Insert cleaning brush into suction valve port. Brush from valve port toward the light guide connector until the brush emerges from the suction adapter port. Repeat until clean.
f. Insert the brush from the suction valve port toward the insertion tube until you reach the biopsy port. Angle the brush to enter channel. Repeat until clean.
g. Insert a channel opening cleaning brush into the suction valve port and biopsy port. Care must be taken when inserting the brush into the air water valve port. Debris can be pushed into the channel and an obstruction may occur resulting in repairs.
h. Using clean enzymatic solution, attach the recommended suction cleaning adapter(s) and aspirate cleaning solution through all channels. Observe fluid streaming from all channels, including the air/water channel at the distal tip.
i. Repeat this process with clean water, then air until fluid is removed from endoscope. This prevents dilution or contamination of the high-level disinfectant.
j. Inspect and clean all valves and biopsy port.

D. High-level disinfecting (also see Video 83-4):

a. Use test strip or approved device to ensure the minimum recommended concentration specific to product is used.
b. If using an automated endoscope reprocessing (AER) unit, attach appropriate connections. Start unit as directed.
c. If using a large basin or tub, leave suction cleaning adapter in place to flush product into channels until no bubbles are observed.
d. The duration of contact time with endoscope will vary. Read label instructions for time and temperature variations.
e. Rinse endoscope with water and air. An AER will do this process for you.
f. Flush with 70% isopropyl alcohol to assist in the drying process.
g. Hang scope vertically to dry.
h. Place valves on clean surface to air dry.

Many organizations offer hands-on endoscope training sessions for veterinarians and technicians. For the remainder of this chapter, a gastroscope with 4-way deflection and air/water and suction capabilities will be used in describing care.

Nomenclature

Gastroscopes (Figure 83-1) start out as long hollow tubes. In order to visualize an object, thin filaments (light bundles) drive the light from the guide or terminal end, through the umbilical tube, control handle, insertion tube and finally to the distal tip of the tube. Image bundles travel from the eyepiece to the distal tip. This is the description of a fiberoptic endoscope, or fiberscope. A camera can be attached to the eyepiece allowing the image to be seen on a monitor for easier visualization and group participation. Videoscopes incorporate a video chip behind the objective lens, converting the image to a digital signal transmitted through connection wires to a monitor, eliminating the need for an eyepiece or camera head (indirect visualization) (see ch. 91, 96, 108, and 113).

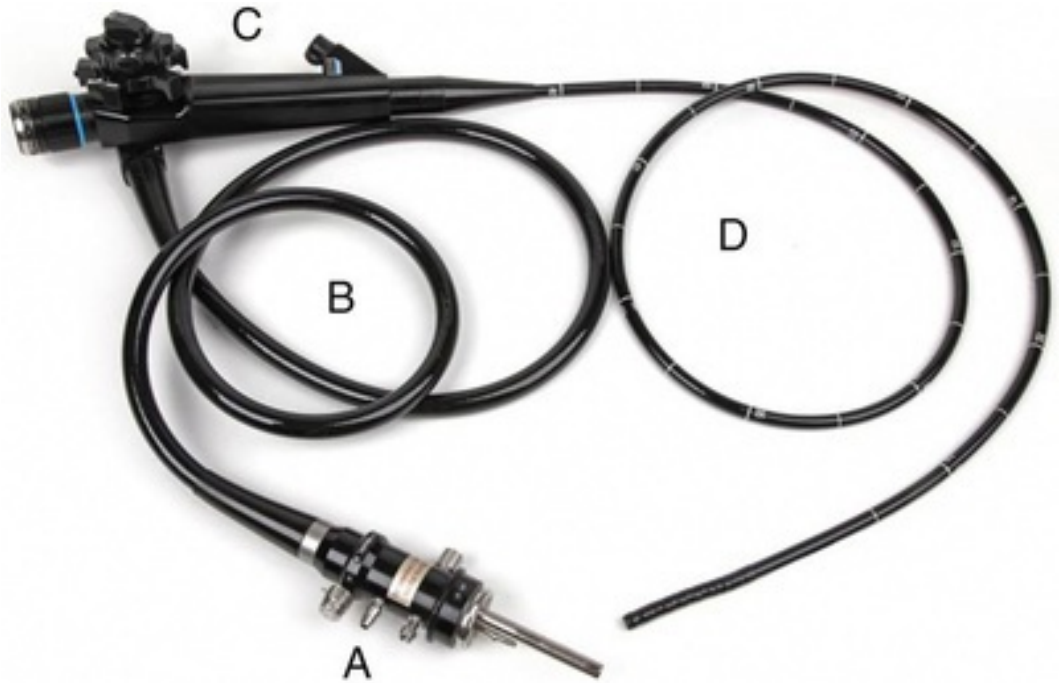

FIGURE 83-1 Sections of a videoscope. **A,** Light guide or terminal end. **B,** Umbilical tube. **C,** Control handle. **D,** Insertion tube.

Insufflation, suction and water capabilities are controlled by 2 valves housed in ports within the control handle. Depressing the top valve (suction) allows for fluid to be drawn into the biopsy-instrument channel and out the suction port at the light guide end. Insufflation from the distal tip occurs when the endoscopist lightly covers the hole at the top of the lower air/water valve (closest to the insertion tube). Water from the bottle attached at the light guide is controlled when the endoscopist depresses the lower valve. The water spray function acts as a clearing mechanism for the objective lens located at the distal tip. Angulation is controlled by thin wires attached to 2 dials on the control handle that connect to a mesh at the bending section (Figure 83-2). These wires act as a pulley system, allowing the distal tip to angulate when engaged. All channels of the endoscope are sealed at endpoints, keeping internal components dry. Water intrusion can cause fiberoptics to become brittle and break. Such breakage causes loss of light and an impaired image (Figure 83-3).

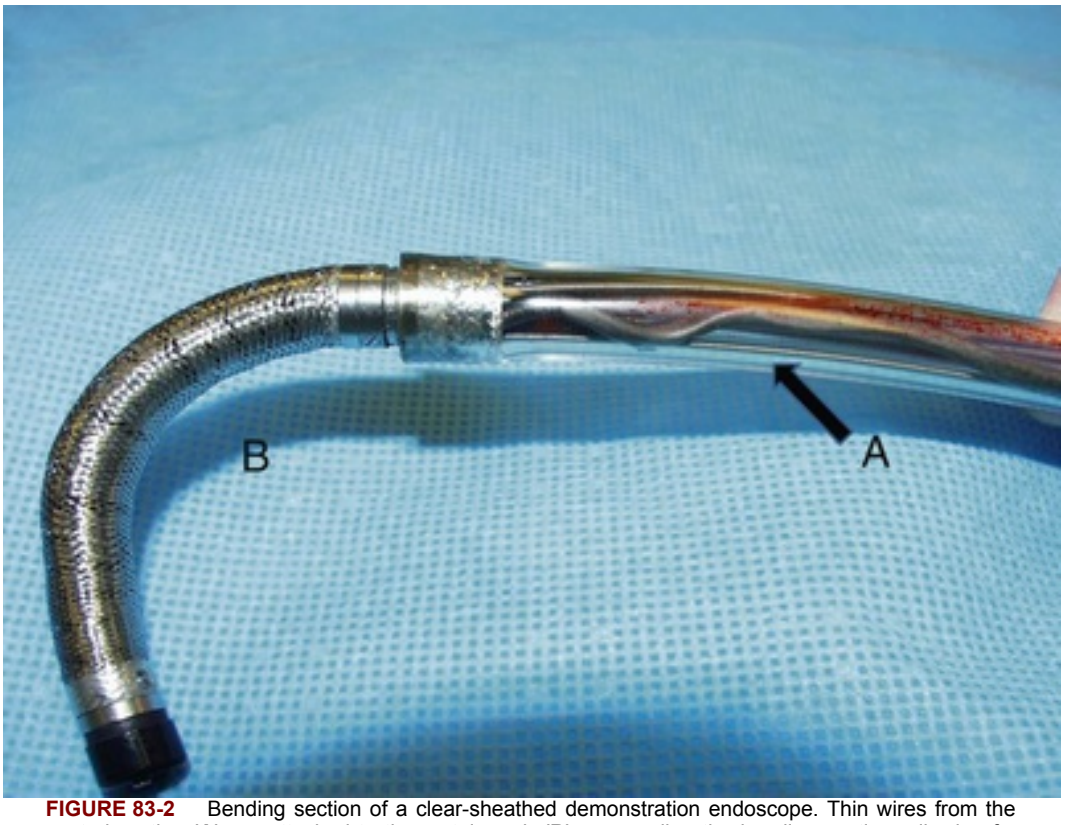

FIGURE 83-2 Bending section of a clear-sheathed demonstration endoscope. Thin wires from the control section **(A)** are attached to the metal mesh **(B)** surrounding the bending section, allowing for angulation of the distal tip.

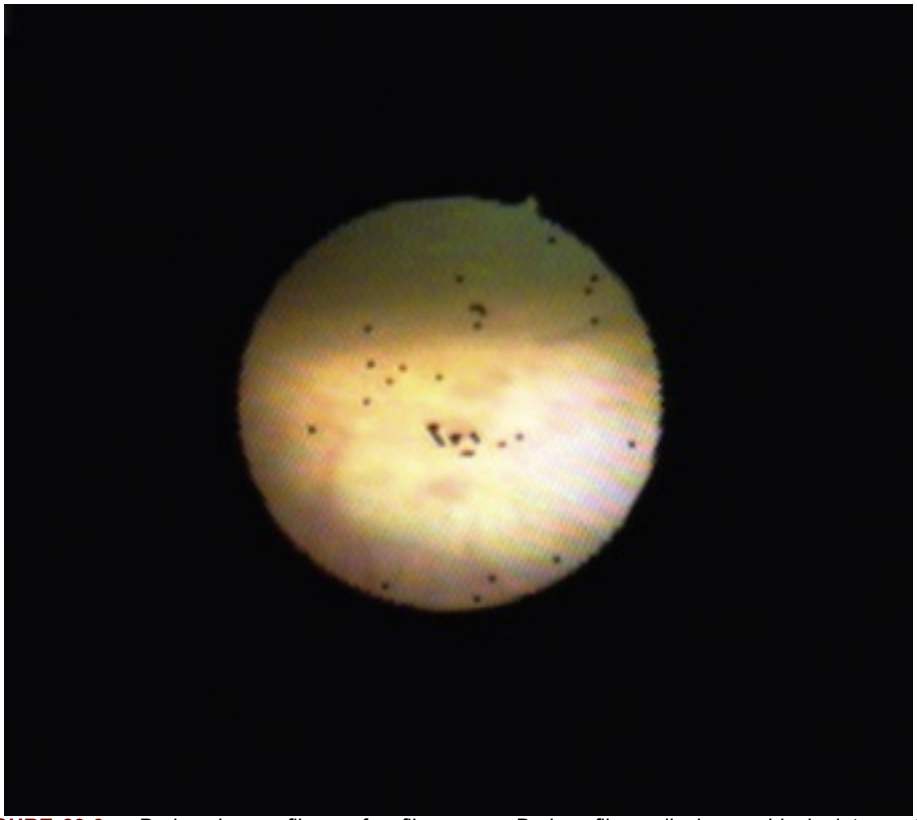

FIGURE 83-3 Broken image fibers of a fiberscope. Broken fibers display as black dots on the

image.

Handling

Endoscopes are typically designed for the control handle to be grasped in the left hand while the right hand continuously holds the insertion tube. The insertion tube should never be moved or twisted independent of the control handle ("torquing"). The "boot" of an endoscope is the junction between the control handle and the insertion tube. Scoping with the "boot" of the endoscope at a 90° angle could damage internal components of the scope. The insertion tube should never be dropped or dragged over sharp objects, such as teeth, when passing the endoscope through the oral cavity. When transporting an endoscope, it should be held with the terminal end and insertion tip in one hand and close to the body, on a cart with sides and sturdy wheels, or in a bin with a tight fitting lid. When not in use, valves should be removed for drying and endoscopes suspended from an endoscope hanger, away from traffic.

Instrumentation

A speculum must always be in place when passing an endoscope through the oral cavity. Use of small sections of cut-off 1 mL syringe barrels can be utilized as a speculum for small dogs and cats.[1] All forceps should be in the closed position before entering the instrument channel. Instrumentation should also be inspected for sharp edges that could damage the channel. Biopsy forceps "wings" should be visible to the endoscopist when extended outside the endoscope before being opened within the patient (Figure 83-4). The instrument channel size determines the outer diameter (OD) of the forceps. For example, endoscopes with a 2.0 mm diameter instrument channel require a 1.8 mm instrument. Length is also a factor. Instrumentation should be 13-15 cm longer than the insertion tube for ease of visualization and movement within the patient.

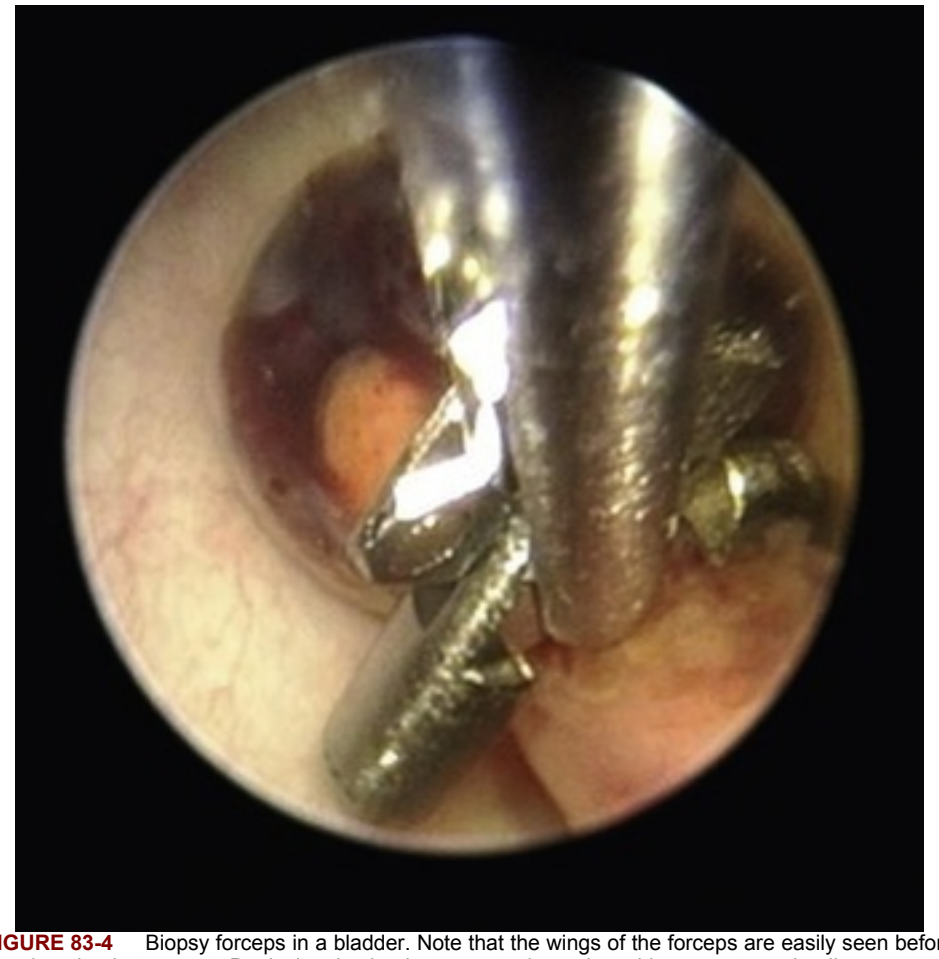

FIGURE 83-4 Biopsy forceps in a bladder. Note that the wings of the forceps are easily seen before opening the instrument. Deploying in the instrument channel could cause tears leading to water

intrusion.

“Bedside” Testing and Cleaning (Video 83-1)

Testing the endoscope's air, water and suction capabilities before each procedure is done to ensure that all features of the endoscope are functioning. Immediately following each procedure, those functions should be tested again. When flushing the channels, alternate between water and air using an all-channel irrigator valve which replaces the air/water valve.[2] This creates agitation within the channel. If a video endoscope is used, place a protective cap over the electrodes before exposing the endoscope to liquids. The outside of the endoscope, wiped clean of any debris, is transferred to a cleaning station for leak testing and manual cleaning.

Leak Testing (Video 83-2)

Leak testing ensures that the inside of the endoscope is free from water intrusion.[3,4] There are various leak testing devices available (hand-held manometers, automated units). The endoscope should be immersed in clear water for 2 minutes to check for leaks, which appear as air bubbles. The A-rubber (the thin sheath of rubber surrounding the distal tip) should appear slightly inflated when the leak tester is engaged. Bending the distal tip will stretch the A-rubber slightly, allowing for bubbles to appear if the endoscope is compromised. If an endoscope fails a leak test, cleaning should cease and the endoscope dried and sent for repair. Additional cleaning could introduce more fluid and further damage the endoscope.

Manual Cleaning (Video 83-3)

The purpose of manually cleaning endoscopes is to reduce the number of bacteria present before high level disinfection (HLD). Flushing with an enzymatic cleaning solution and brushing accessible channels removes protein-rich material, e.g., blood, tissue. Left in the endoscope, such debris can solidify when combined with HLD solutions, resulting in channel blockage. Manual cleaning should be initiated as soon after use as possible. Biofilm is defined as a group of bacteria that can adhere to endoscope channels and secrete a polysaccharide that cannot be removed with HLD.[4,5] Prompt attention to manual cleaning prevents biofilm formation. Fresh enzymatic cleaning solution should be prepared each time an endoscope is cleaned.[4] Dilution and temperature can alter effectiveness. It is therefore recommended that directions be carefully followed when diluting.

Brushing channels is the next step. Channel brushes must be in good condition, including intact bristles and rounded or covered tips. Some endoscope models have specific brushes for each channel; one should check the manufacturer's guidelines. Brushes should pass out through the channels and be cleaned before removal. Brushing should continue until the brush comes through clean. The brush should be passed straight through —back and forth movement could erode the channel.

The following channels should be brushed:

- Suction valve housing through the umbilical tube and out the suction port at the terminal end
- Suction valve housing through the suction/instrument channel and out the distal tip (angle brush to enter channel)
- Entrance to suction/instrument channel

When brushing is complete, attach the appropriate cleaning adapters and flush the enzymatic solution through channels. Pay particular attention to the appearance of the solution exiting the air/water channel at the distal tip. This channel is too small to brush and can become easily blocked. A forceful sideways stream should be observed. If specified by manufacturer guidelines, allow the endoscope to soak in the solution. Flush with water, then air. Fluid left in channels could dilute the HLD, decreasing its effectiveness. Wipe down the entire endoscope with a soft cloth, with particular attention around control handles and valve housings.

Valves, water bottles and biopsy ports should also be manually cleaned prior to HLD. Pipe cleaners or small brushes are used on the valve stem holes. The hole on the suction valve stem is revealed when depressed. Instrumentation (biopsy forceps, oral speculae) should be similarly cleaned. Wire coil-wrapped forceps should undergo ultrasonic cleaning and steam sterilization.

High-Level Disinfection (Video 83-4)

Overview

Endoscopes have been given a "semi-critical" designation on the Spaulding Classification of Medical Devices and Level of Disinfection. Therefore, endoscopes should receive high-level disinfection after every procedure.[6] A high-level disinfectant (HLD) is defined as a chemical germicide approved by the FDA capable of destroying all viruses, vegetative bacteria, fungi, mycobacteria and most bacterial spores.[3] One study demonstrated that all infections resulting from endoscopic procedures were the result of a breach in cleaning/disinfecting protocols.[7]

There are many types of HLDs on the market (see FDA approved list).[8] Check with the manufacturers' guidelines regarding which HLDs are compatible with their endoscopes. Some solutions are available with a 28-day efficacy. Although these solutions are more practical than the 14-day HLDs, they contain surfactants which can be difficult to rinse away. Temperature variations can also alter the effectiveness of the HDL solution and may require longer soaking times.[3] All solutions should be handled and diluted according to manufacturer recommendations. Test strips that measure maximum effective concentration should be used and logged daily.[3,9] HLDs should be changed if the test strip is negative, even if the end date has not been reached. Protective equipment, such as gloves and face shields, should be worn at all times when working with HLDs. Some HLDs have a noxious odor. Always use the HLDs in a well-ventilated area or under a fume hood.

HLDs can be used with endoscopes for manual disinfection or with an automated endoscope reprocessor (AER).

Manual Disinfection

Use a basin with a tight-fitting lid to prevent splashing. Immerse the entire endoscope in the HLD. Attach a 60 mL syringe filled with the HLD solution to the all-channel irrigator port(s); flush until all channels are in contact with the HLD solution, and no air bubbles are seen. Also include all accessory instrumentation, including mouth speculae, water bottles, cleaning brushes and valves. Cover the basin and allow the endoscope to remain in the HLD for the recommended exposure time. When the end of the soaking time has been reached, gently flush the endoscope with air to purge the HLD from the channels and remove. Flush the endoscope with water for the time period recommended by the manufacturer.

Drying the endoscope can be as important as manual cleaning and high-level disinfection.[10] Inadequately dried endoscopes can become a source of contamination. First, flush channels with 60 mL of 70% isopropyl alcohol to facilitate the drying process. Dry all endoscope channels with forced air or adapt the suction unit to fit the all-channel irrigator. Hang on an endoscope hanger with all ports open (Figure 83-5). Also remove, rinse and dry all accessory instrumentation.

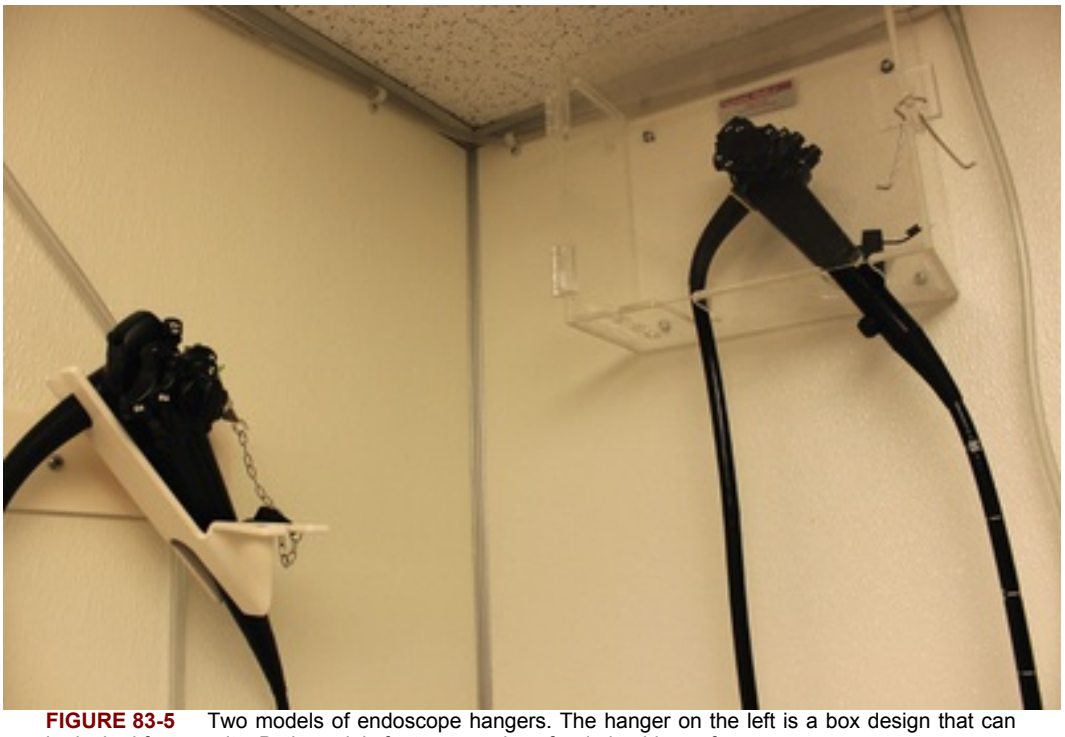

FIGURE 83-5 Two models of endoscope hangers. The hanger on the left is a box design that can be locked for security. Both models feature openings for drying biopsy forceps.

Automated Endoscope Reprocessor

For a busy practice that utilizes endoscopes on a daily basis, an automated reprocessor may be indicated. Advantages over manual disinfection include decreased personnel exposure time to HLDs, and consistent temperature and time controls. Reprocessors do not take the place of manual pre-cleaning.

The endoscope is connected to the reprocessor through the all-channel irrigator. A full cycle includes enzymatic solution flush, de-ionized (DI) water flush, HLD circulation, and final DI water flush. An air flush completes the process. An alcohol flush port is also included. Accessory instrumentation can be placed inside the unit as well. Sharp objects such as dental probes should be processed separately as they could shift in the basin and pierce the endoscope. The endoscope should be wiped off with a soft cloth, air-dried and placed on an endoscope hanger.

Endoscope Storage

Endoscopes should be stored vertically on endoscope hangers (see Figure 83-5). When stored in cases, moisture left in the channels can harbor bacteria. The exception to this are fragile ultrathin endoscopes, which are dried thoroughly and kept in cases. Endoscopes should be stored high enough so the distal tip does not touch the floor.

Documentation

Endoscopy reports often include a short history, the procedure performed, the endoscope used, and the features of interest (see ch. 113). A video/image log documents a brief description of each figure and endoscope used. A damage log may be kept for each endoscope in the inventory and include the personnel involved, procedure performed and date of repair and return. Damage logs can track trends and can pinpoint corrections that can be implemented to keep the endoscope in working order. Material Safety Data Sheets (MSDS) for HLDs and enzymatic solutions should be readily available.

E-Box 83-1 reviews the aforementioned techniques and provides a reference guide to cleaning and disinfecting a gastroscope.

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CHAPTER 84

Hyperbaric Medicine

Melissa L. Edwards

Client Information Sheet: Hyperbaric Oxygen Therapy

History

Hyperbaric medicine is the use of pressure (greater than 1 atmosphere absolute [ATA]) (Box 84-1) in the treatment of disease. It dates back to the mid 1600s. The discovery of oxygen in 1775 by John Priestly had a profound effect on hyperbaric medicine.[1] References to the use of hyperbaric oxygen in animals can be traced back to a study in rabbits in 1887.[2] The practice of modern hyperbaric medicine began around the mid 1950s[3] and typically involves the patient breathing >21% oxygen while under pressure, referred to as hyperbaric oxygen therapy (HBOT). This chapter will primarily discuss HBOT as the hyperbaric medical intervention most commonly practiced today.

Box 84-1

Pressure Conversions

1 atm = 101.3 kPa = 14.7 psi

Atmosphere absolute (ATA) = atmospheric pressure (atm) + gauge pressure (converted to atm)

atm, Atmospheres; *kPa,* kilopascals; *psi,* pounds per square inch.

Physiology

There are two primary effects of HBOT and several secondary effects. The first, primary mechanical effects of pressure, account for HBOT's effect on bubbles and gas-containing cavities within the body. As pressure increases the volume of gas decreases (Boyle's law) in addition to increasing solubility, which enhances resorption and elimination of gases (Henry's law) such as nitrogen. This is the primary reason for its use in conditions such as decompression sickness (bends),[4] and gas embolism as a procedural or surgical complication.[5] In cases such as bowel ileus with significant distention, where other treatment options have been unsuccessful, these effects would also be beneficial.[6] A recent study in humans suggested that in some conditions hyperbaric air may be just as effective as HBOT,[7] which would indicate an additional direct pressure effect. The mechanical effects are also responsible for barotrauma complications that can be associated with hyperbaric treatments discussed later.

The second primary effect of HBOT is increased oxygenation of plasma and ultimately tissues. The dissolved oxygen in plasma is the most bioavailable. Theoretically 100% oxygen delivered at 3 ATA can dissolve enough oxygen in plasma to meet normal resting oxygen requirements of the body without hemoglobin.[8] The increased concentration of oxygen in the plasma increases the driving force to help deliver oxygen to compromised tissues as it increases the rate and depth of diffusion (Fick's law). Oxygen is a necessary part of cellular function and its delivery can be compromised due to injury or illness. At the same time the oxygen demands of those tissues may be increased, further damaging the cells if sufficient oxygen cannot be obtained. The delivery of oxygen to cells can be affected by many factors including anemia, toxin exposure, decreased blood flow (hemorrhage, thromboembolism) and inflammation or edema since oxygen is more soluble in lipid than water. Blood and tissue oxygen tensions not only increase during HBOT but have

been shown to remain elevated for over an hour after.[9] Hyperoxygenation is the primary mechanism in the treatment of such conditions as severe anemia, carbon monoxide (CO) poisoning and compromised surgical grafts and flaps.[10] In CO poisoning, the increased oxygen tension helps dissociate CO from hemoglobin[11] as well as mitigating mitochondrial oxidative stress while this is occurring.[12]

Hyperbaric oxygen therapy has several secondary effects. These include vasoconstriction, antimicrobial effects, anti-inflammatory and immunomodulatory effects as well as neovascularization. In healthy tissue, vasoconstriction occurs to limit the effect of hyperoxia; however, oxygen delivery is maintained because of the higher plasma oxygen concentration. In compromised tissue, on the other hand, this vasoconstrictive effect is blunted, allowing increased oxygen delivery to compromised tissue. Cellular energy is preserved to inhibit swelling and edema formation[13] and may be due in part to HBOT's effect on nitric oxide production helping to maintain vascular responsiveness as noted in a septic shock model.[14,15] This can also decrease vasogenic edema and intracranial pressure (ICP) via decreased brain blood flow and blood-brain barrier permeability.[16,17]

Increased oxygen levels can have direct and indirect antimicrobial effects. Direct effects (both bactericidal and bacteriostatic) are not just seen in anaerobic infections,[18,19] they can also be effective in fungal infections as well as inhibiting some bacterial toxin formation.[20] Indirect antimicrobial effects arise from the maintenance of oxidative killing mechanisms in leukocytes and enhanced neutrophil phagocytic activity.[21] HBOT has also been shown to have synergistic effects with some antibiotics.[18]

It may seem counterintuitive, but many of the anti-inflammatory and immunomodulatory effects of HBOT are due in large part to the increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS).[22,23] The reactive species lead to increased growth factor production, stem and progenitor cell mobilization, decreased neutrophil adhesion and sequestration, modulation of chemokine production and enhanced reactive species scavenging.[22] Increased growth factor production and stem/progenitor cell mobilization lead to neovascularization and the effects HBOT has in many wound healing applications such as dermal wounds,[24] burns[25] and bone healing.[26] The neovascularization further improves oxygen delivery stimulating fibroblast proliferation and collagen production[27-32] which promotes ongoing wound repair. In ischemic, reperfusion and inflammatory conditions the modulation of macrophages and neutrophils can decrease further tissue damage and hypoxia locally as well as systemically. In addition to these anti-inflammatory effects, HBOT is also immunomodulatory via several mechanisms including major histocompatibility complex protein alterations,[33] interleukin 10^{11} and tumor necrosis factor alpha expression.[34]

Indications

Many of the same conditions exist in our veterinary patients as in humans so our veterinary use of HBOT is often based on the accepted human indications with the understanding that many of these were established from animal research models. HBOT use in human medicine can vary by organization and country but generally includes 14 well-accepted indications with decompression sickness and idiopathic sudden hearing loss being less relevant in veterinary medicine. Table 84-1 is a list of the remaining indications that are accepted by the Undersea and Hyperbaric Medical Society[35] and the mechanisms of action. As HBOT becomes more widely available in veterinary medicine pet insurance plans are beginning to cover it as a recognized primary and adjunctive therapeutic option similar to the insurance coverage in human medicine for these accepted conditions. As research continues, additional conditions may be found that benefit from HBOT. A list of some of these potential conditions is found in Table 84-2 along with the proposed mechanisms of action.

TABLE 84-1

Veterinary Applicable Indications from Accepted Human Sources[35]

ACCEPTED INDICATIONS	MECHANISM
Air or gas embolism	Hyperoxygenation Decreased gas bubble size

	Inflammatory modulation
Toxicities (carbon monoxide, cyanide)	Hyperoxygenation (carbon monoxide washout, ischemia) Inflammatory modulation
Clostridial myositis and myonecrosis	Antimicrobial Antibiotic synergy Toxin inhibition
Crush injury/compartment syndrome Acute traumatic ischemias	Hyperoxygenation Vasoconstriction Inflammatory modulation
Arterial insufficiencies (central retinal artery occlusion, select problem wounds)	Hyperoxygenation Angiogenesis Inflammatory modulation +/− Antimicrobial
Severe anemia	Hyperoxygenation Immunomodulation
Intracranial abscess	Antimicrobial Decreased edema Antimicrobial synergy
Necrotizing soft tissue infections	Antimicrobial Hyperoxygenation Inflammatory modulation Antimicrobial synergy
Osteomyelitis (refractory)	Hyperoxygenation Antimicrobial Antibiotic synergy Enhanced osteogenesis
Delayed radiation injury (soft tissue and bone)	Neovascularization Inflammatory modulation Stem cell mobilization
Compromised grafts/flaps	Hyperoxygenation Neovascularization Vasoconstriction/decreased edema
Acute thermal burn injury	Hyperoxygenation Vasoconstriction/decreased edema Neovascularization Inflammatory modulation Antimicrobial

TABLE 84-2

Other Potential Applications for HBOT

OTHER POTENTIAL CONDITIONS	PROPOSED MECHANISM
Envenomations (snake bite, brown recluse spider)	Hyperoxygenation Vasoconstriction/decreased edema
Other infections (aerobic, anaerobic, fungal, hepatic abscess, peritonitis, pyothorax)	Hyperoxygenation Antimicrobial Antimicrobial synergy
Sepsis	Hyperoxygenation Antimicrobial Inflammatory modulation

Tetanus	Antimicrobial Decreased toxin production
Lyme disease	Immunomodulatory +/− Antimicrobial (>2.4 ATA)
Asphyxia (birth, near hanging, near drowning)	Hyperoxygenation Vasoconstriction/decreased edema Inflammatory modulation
Bone healing (fracture, grafts)	Hyperoxygenation Neovascularization
Post cardiopulmonary arrest	Hyperoxygenation Vasoconstriction/decreased edema Inflammatory modulation
Ileus	Decreased gas bubble size and clearance
Pancreatitis	Hyperoxygenation Vasoconstriction/decreased edema Antimicrobial Inflammatory modulation
CNS injury (IVDD, traumatic brain injury, vascular events [stroke, FCE], degenerative myelopathy, vestibular disease)	Hyperoxygenation Vasoconstriction/decreased edema Inflammatory modulation
Immune-mediated disease (IBD, IMHA)	Immunomodulatory
Myocardial contusions	Hyperoxygenation Inflammatory modulation
Perianal fistulas	Hyperoxygenation Immunomodulatory Antimicrobial Neovascularization
Acute frostbite	Hyperoxygenation Vasoconstriction/decreased edema
Immediate post-operative swelling, compromised tissue (GDV, FB, wounds)	Hyperoxygenation Vasoconstriction/decreased edema
Thromboembolic disease	Hyperoxygenation Inflammatory modulation
Sports injuries	Hyperoxygenation Inflammatory modulation

ATA, Atmosphere absolute; *CNS*, central nervous system; *FB*, foreign body; *FCE*, fibrocartilaginous embolism; *GDV*, gastric dilation-volvulus; *IBD*, inflammatory bowel disease; *IMHA*, immune-mediated hemolytic anemia; *IVDD*, intervertebral disk disease.

Contraindications

Although the only absolute contraindication for HBOT is untreated pneumothorax, other conditions necessitate critical evaluation of the risks versus benefits before making a final treatment decision. Some of these relative contraindications include asthma, pulmonary bulla, history of thoracic or otic surgery, uncontrolled high fever (may potentiate oxygen induced seizures), poorly controlled seizure disorder, pregnancy (fetal effects are unknown), upper respiratory infection, pacemaker (ensure device has been pressure-tested and at what depth) and anxiety that may preclude treatment. These contraindications are primarily to limit known side effects of barotrauma and oxygen induced seizures. Medications or other

interventions may be able to mitigate some of these conditions allowing HBOT.

Complications

The complications associated with HBOT are generally related to barotrauma (middle ear, sinus, pulmonary), the toxic effects of oxygen (seizures, oxidative stress, pulmonary oxygen toxicity), and decompression sickness. These complications are infrequent and with careful patient evaluation prior to prescribing HBOT, monitoring during therapy and knowledge about the physiology and mechanisms of action of HBOT, veterinary practitioners can maintain HBOT as a relatively safe therapeutic option.

Equipment and Safety

There are 3 main types of chambers currently in use in hyperbaric medicine, low pressure (typical working pressure of 1.2-1.4 ATA) monoplace chambers, high pressure (typical working pressure of 2-2.5 ATA) monoplace chambers and high pressure multi-place chambers. The high pressure monoplace chambers are most often used in veterinary medicine at this time with veterinary specific models available. These chambers typically use oxygen as the compressive gas, unlike the low pressure and multi-place chambers that use air for compression, and have the patient breathe supplemental oxygen if prescribed. The low-pressure chambers are still relatively new by comparison and differences in therapeutic efficacy have not been studied.

There are some safety considerations when working with high-concentration oxygen in a pressurized environment including the risk of spontaneous combustion and explosion hazards. These situations are rare but certain safety precautions can help to mitigate them including patient and chamber grounding, ensuring that no exposed metal or high static fabrics are allowed in the chamber, and no electrical devices or flammable materials such as oil-based products are allowed in the chamber. In 2011 a veterinary certified hyperbaric technologist training and certification program was instituted through the National Board of Diving & Hyperbaric Medical Technology in conjunction with the Veterinary Hyperbaric Medical Society to further the safety and quality of veterinary hyperbaric medicine.[36]

Treatment Protocol (Dive)

There is currently no consensus on treatment protocols for HBOT. Typical recommendations in human and veterinary medicine are for 1-2 hour dive sessions (including compression and decompression) with 100% inspired oxygen at 1.5-3 ATA, 1-3 times daily, with a minimum of 4 hours between dive sessions to minimize the chance of oxygen toxicity. In acute conditions and toxicities, like gas embolism and carbon monoxide poisoning, timing may be very important and HBOT should be initiated as soon as possible. Treatment plans vary depending on the condition being treated and the tolerance of the patient, but in this author's experience begin with 1 hour treatments at 2 ATA twice daily in acute conditions until significant clinical improvement has been made, then decreased to once daily and 2-3 times weekly in more chronic conditions. Envenomation often only needs 1-2 treatments for clinical effect.

Treatments are generally well tolerated by veterinary patients based on their willingness to repeatedly enter the chamber and how relaxed they appear during the treatment. Anxious patients can be given a mild sedative including narcotics, benzodiazepines or acepromazine if needed to facilitate treatments. Discontinuation of a treatment may be necessary if distress is noted during a dive.

Summary

Hyperbaric oxygen chambers are increasing in availability in veterinary medicine. HBOT, as a primary therapy or adjunct to other standard therapies, should be considered in disease conditions where its use has been shown to be beneficial. Understanding the physiologic effects of HBOT will also guide treatment in non-accepted conditions and further research to aid in expanding the scope of indications for its use. Pursuit of the recently developed certified hyperbaric technologist–veterinary credential by those involved in administering HBOT will help increase the appropriate, efficacious and safe use of this treatment modality.

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Skin

OUTLINE

Chapter 85 Otoscopy, Ear Flushing, and Myringotomy
Chapter 86 Scraping, Fine-Needle Aspiration, and Biopsy of Skin and Subcutaneous Tissues
Chapter 87 Cytology of the Skin and Subcutaneous Tissues

CHAPTER 85

Otoscopy, Ear Flushing, and Myringotomy

David Stephen Sobel

When one considers the more common presentations by small animal patients to general practitioners, aural disease is at or near the top of the list. Clinical signs related to aural disease often are easy for owners to observe, frequently are dramatic in their presentation, often negatively impact the patient's quality of life, and can become chronic, with long-term adverse consequences. Fortunately, aural disease usually is readily diagnosed and, with appropriate and timely intervention, it is one of the more rewarding groups of diseases to treat in small animal practice (see ch. 237).[1-4]

To this end, minimally invasive surgery and diagnostic methods, especially otoendoscopy, have tremendous utility in both general practice and referral settings. Both diagnostic and therapeutic techniques are simple to learn and to perfect, and present the sort of utility that makes the associated time and financial investments tremendously worthwhile.[5]

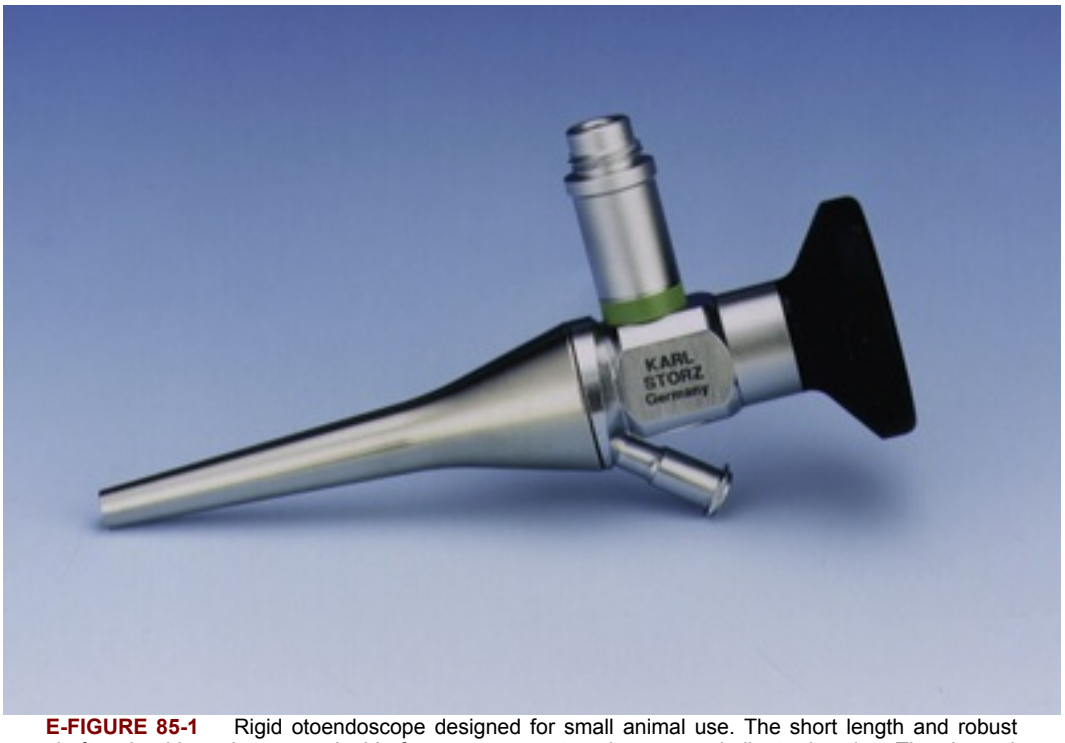
While small animal practitioners have been well accustomed to using hand-held otoscopes as a diagnostic tool for decades, modern endoscopic equipment and techniques enable the veterinarian to enjoy dramatically improved visualization of aural structures. Additionally, the modality offers the opportunity to document, monitor, and categorize a patient's disease and the progress made in management. Perhaps most importantly, the ability to intervene therapeutically is markedly enhanced with minimally invasive surgical (MIS) techniques.

Indications

Otoendoscopy is of great utility in differentiating diseases of the outer or external ear (e.g., otitis externa) and its adnexa, from diseases of the tympanum and middle ear (e.g., otitis media). Common clinical signs of aural disease include foul aural odor, head shaking, aural discharge, pain on palpation of the pinna and external aural structures, pawing at the head, and hearing loss. Less commonly, owners may observe anorexia or dysphagia, ataxia and balance problems, and the presence of abnormal resting nystagmus. Careful physical exam can reveal peripheral neurologic signs and cranial nerve anomalies (see ch. 259).

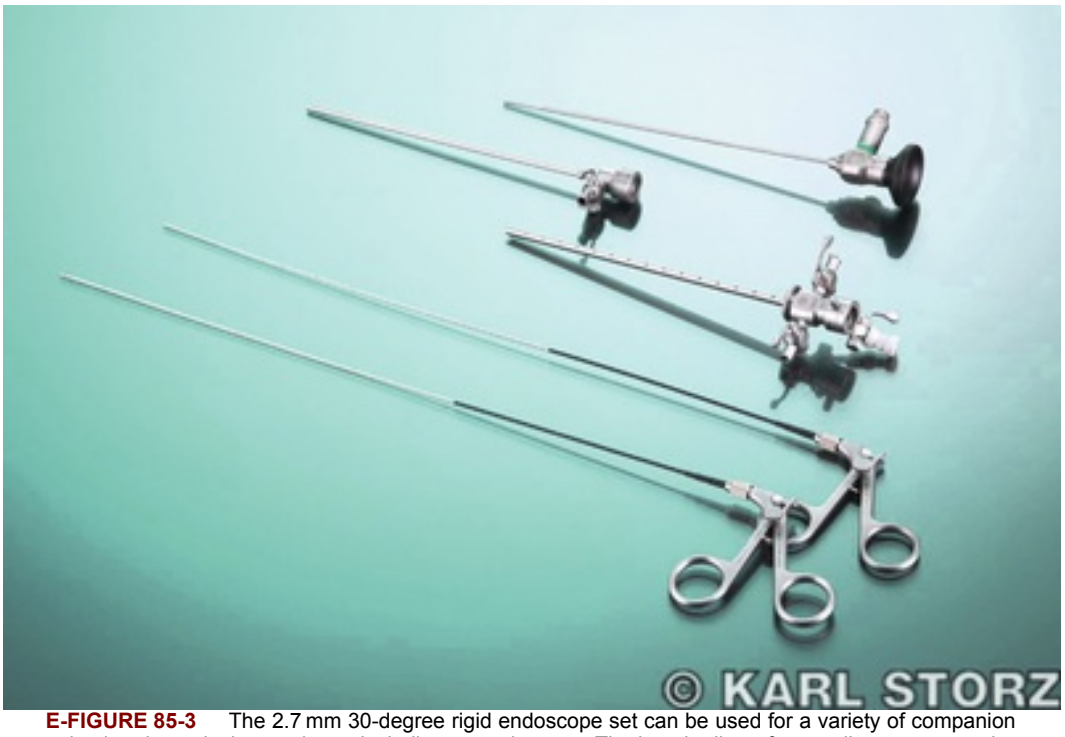
Equipment

Generally, equipment includes a video monitor, a medical-grade endoscopic video camera, an otoendoscope, a light source, and accessories. Most purpose-engineered single-piece otoendoscopes have a single portal to which a bridge can be attached to allow for irrigation and insertion of accessory instrumentation. Alternatively, a small-diameter, multipurpose rigid endoscope can be used; they generally are smaller in diameter and are housed in a removable protective sheath, with multiple ingress ports for fluids and instrumentation (E-Figures 85-1 to 85-3). Optionally, the kit includes mechanized irrigation/suction apparatus, devices to record procedure and store images, and a surgical energy source for electrosurgery, radiosurgery, and/or laser (E-Figures 85-4 and 85-5).

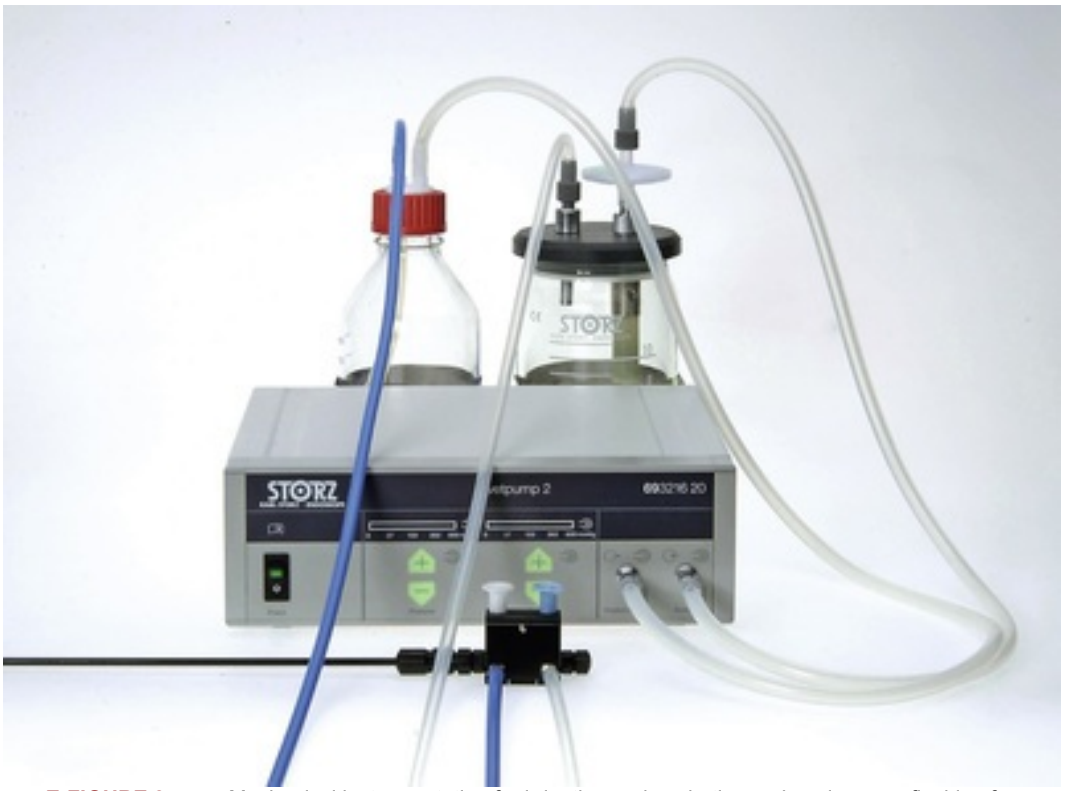


E-FIGURE 85-1 Rigid otoendoscope designed for small animal use. The short length and robust shaft make this endoscope valuable for exam room otoendoscopy and client education. The channel allows for introduction of instrumentation or irrigation/aspiration. (Image courtesy KARL STORZ GmbH & Co KG.)

E-FIGURE 85-2 Rigid otoendoscope and camera. The addition of a high quality endoscopic camera allows for improved ergonomics in otoendoscopy as well as improved visualization and magnification. (Image courtesy KARL STORZ GmbH & Co KG.)

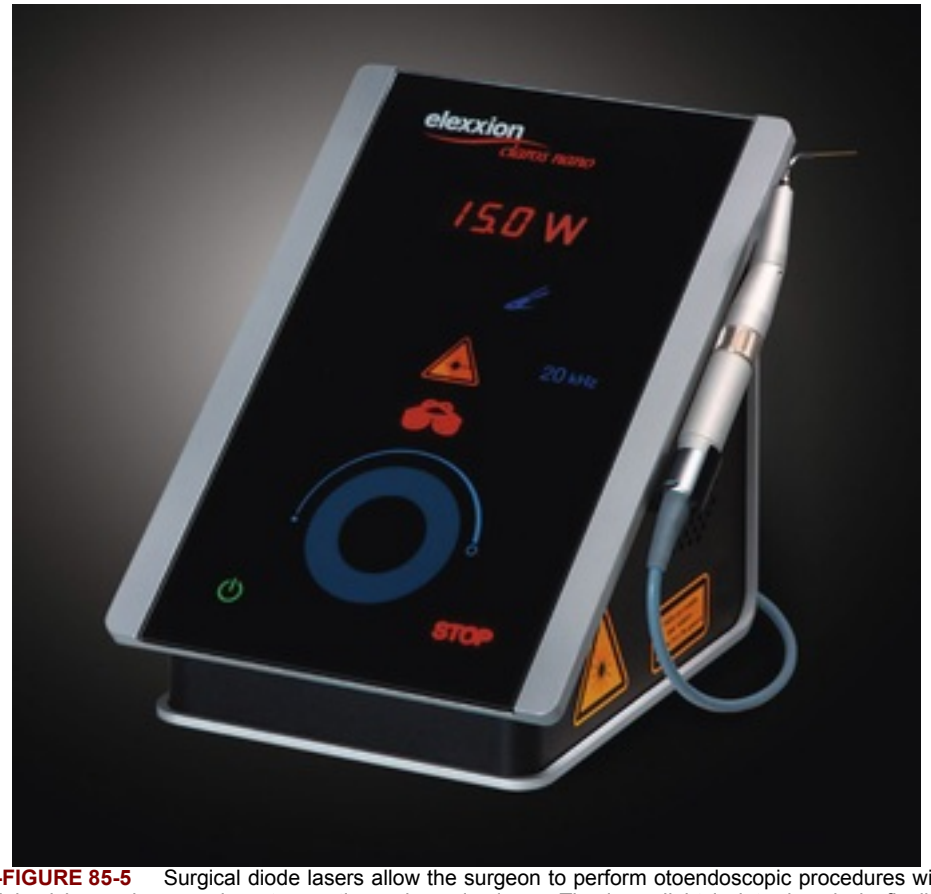


E-FIGURE 85-3 The 2.7 mm 30-degree rigid endoscope set can be used for a variety of companion animal endosurgical procedures, including otoendoscopy. The length allows for excellent access to the horizontal canal and tympanum in even the largest of patients with a variety of accessory instrumentation to facilitate therapeutic and diagnostic intervention. (Image courtesy KARL STORZ GmbH & Co KG.)



E-FIGURE 85-4 Mechanical instrumentation for irrigation and aspiration makes deep ear flushing far more efficient and expedient. This device combines a suction pump and an irrigation pump (with variable pressure). Using the bi-valved handpiece, the operator can perform the ear flushing through a small bore catheter or via the endoscope instrument channel. (Image courtesy KARL STORZ GmbH &

Co KG.)



E-FIGURE 85-5 Surgical diode lasers allow the surgeon to perform otoendoscopic procedures with minimal hemorrhage and post-operative pain and edema. The laser light is introduced via flexible quartz fibers available in a variety of diameters and shapes. Shown is a 15W 810 nm surgical diode. (Photo courtesy Elexxion AG.)

Clinical Anatomy

The external ear can be delineated by the external pinna, to and including the vertical canal. This includes the pinna, the cartilaginous support structures of the adnexa, and the vertical canal. By definition, the tympanum is considered the terminus of the external ear and the beginning of the middle ear. There are notable species and breed differences of the morphology of the external ear, which affect the length of the vertical canal and the angle of the junction of the vertical and horizontal canals. The beginning of the vertical canal generally is identified by the intertragic notch, separating the cranial and caudal cartilaginous ridges. The intertragic notch is a helpful anatomic landmark for the endoscopist in mapping out the presence of lesions in the vertical canal. The epithelial surface of the vertical canal is squamous and secretory, with an increase in ceruminous (modified sebaceous) glands as the vertical canal extends to the horizontal canal to the tympanum. Hair follicles generally are confined to the proximal portions of the vertical canal, but can exist to the level of the tympanum. The presence of hair is often related to breed or somatotype. A ridge of firm, minimally compliant cartilage can serve as a landmark between the vertical and horizontal canal, but depending on breed and somatotype, this landmark can be indistinct. Patients with an acute horizontal-vertical canal angle can prove a challenge to the beginning endoscopist. Patients with a less acute angle, including cats and brachycephalic dogs, have a horizontal canal that is easier to navigate and, as such, a tympanum that is more readily visualized.

The tympanum is a thin, glistening membrane at the terminus of the horizontal canal. In the normal ear, its pars flaccida is visualized dorsolaterally and, in most dogs, will account for approximately one third of the visible field. The pars tensa occupies the ventral two thirds of the visible tympanum. It tends to be the portion

of the tympanum most commonly observed as ruptured in cases of otitis media. In patients with a normal, lucent tympanum, a ventral bony ridge separating the tympanic cavity from the bulla can be seen. Caudodorsally, the manubrium of the malleus in the middle ear often can be seen through the tympanum. Frequently, when the tympanum is diseased, its opacity limits visualization of these landmarks. Severe middle ear disease can produce marked bulging of the tympanum, notable in the pars flaccidum, and demonstrative of fluid in the middle ear. Should the pressure compromise the integrity of the tympanum, it is most commonly the pas tensalis that is the first portion breached. However, in patients with tympanic rupture due to underlying middle ear disease, it often is difficult to differentiate the individual portions of the tympanum. When the tympanum is ruptured, either due to middle ear disease or iatrogenically, careful cleaning and suction/irrigation can reveal the middle ear structures (Figure 85-6).

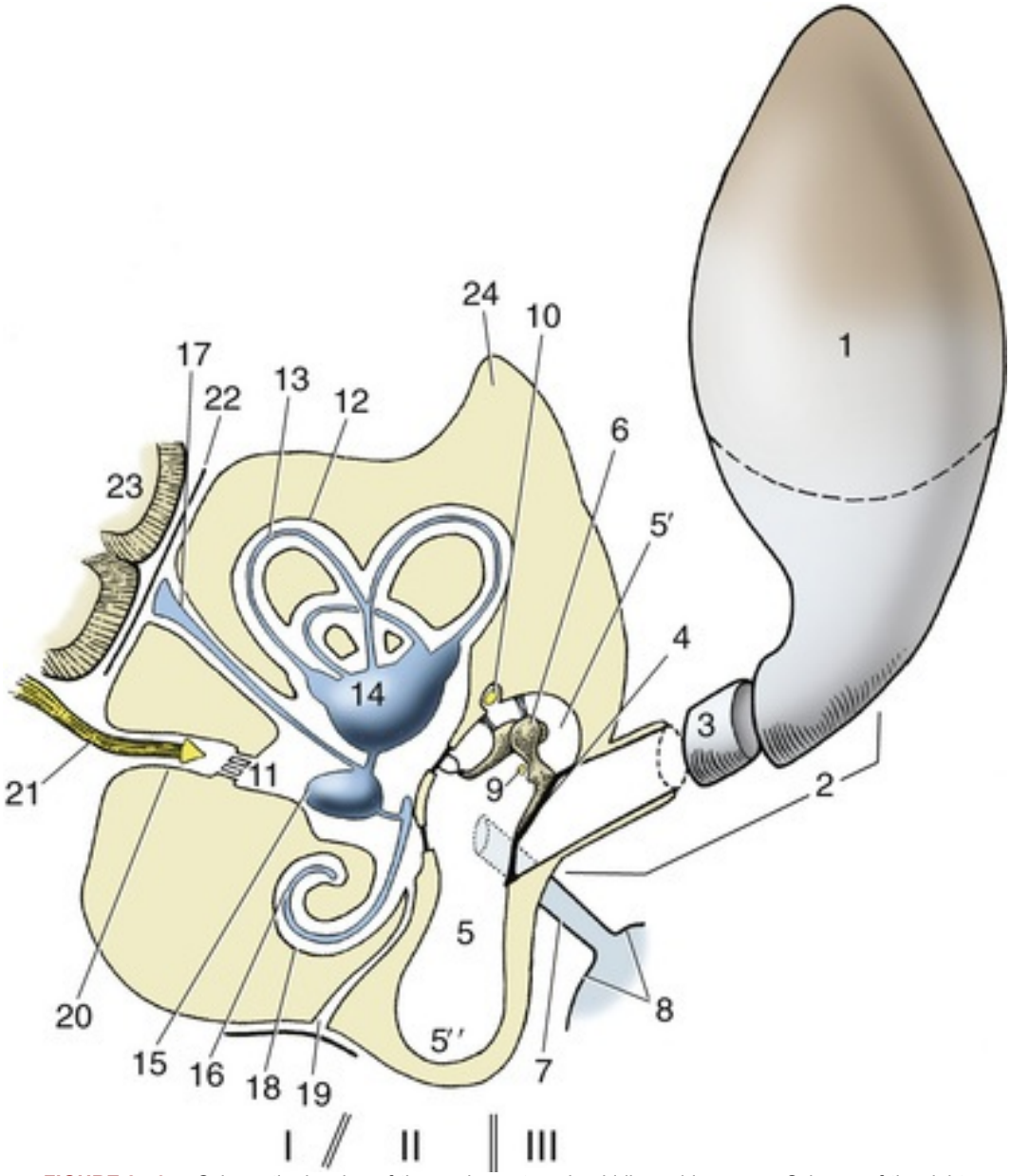


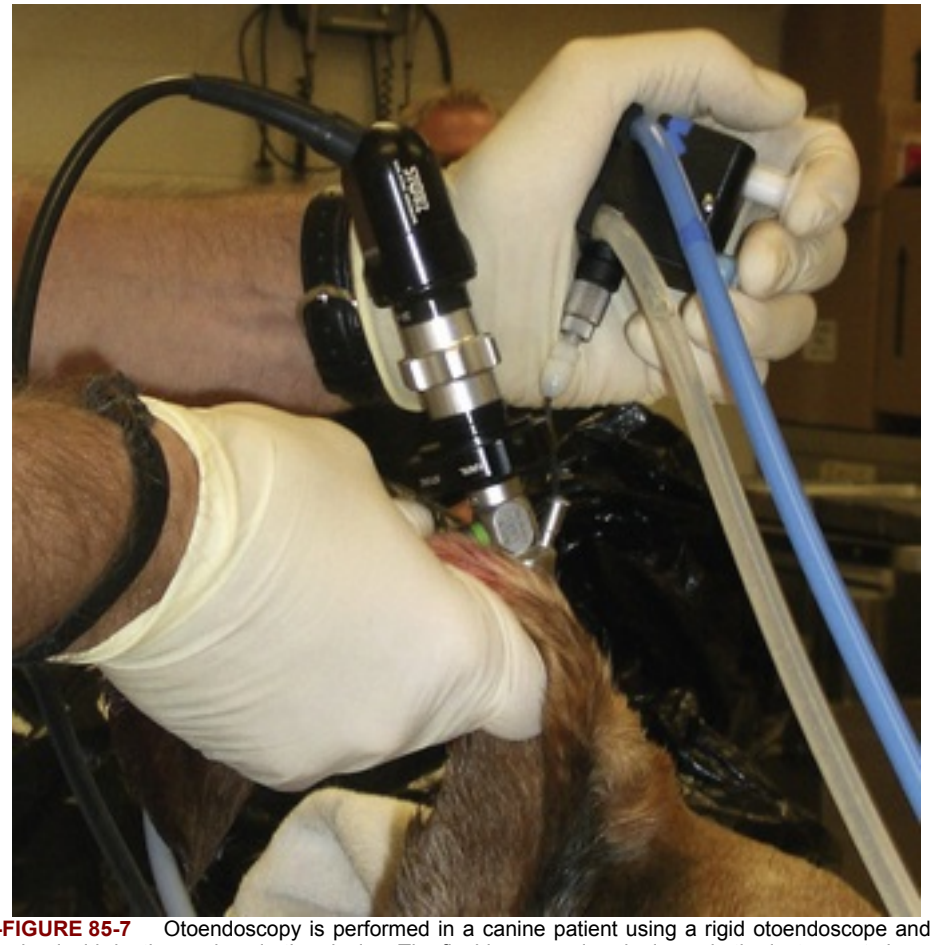
FIGURE 85-6 Schematic drawing of the canine external, middle and inner ear. Schema of the right ear, caudal view. Note that the sizes of the structures shown are out of proportion to each other. *I,* Internal ear; *II,* middle ear; *III,* external ear. 1, Auricle; 2, external acoustic meatus; 3, annular cartilage; 4, tympanic membrane; 5, tympanic cavity; 5′, epitympanic recess; 5″, tympanic bulla; 6, auditory ossicles; 6′, malleus; 6″, base of stapes in vestibular window; 7, auditory tube; 8, nasopharynx; 9, chorda tympani; 10, facial nerve; 11, vestibule; 12, semicircular canals; 13, semicircular ducts; 14, utriculus; 15, sacculus; 16, cochlear duct; 17, endolymphatic duct; 18, cochlea; 19, perilymphatic duct; 20, internal acoustic meatus; 21, vestibulocochlear nerve in internal acoustic meatus; 22, meninges; 23, brain; 24, petrous temporal bone. (From Dyce KM: *Textbook of veterinary anatomy,* St Louis, 2010,

Saunders.)

Otoendoscopic Exam

A complete history, physical examination, and preoperative diagnostic workup are essential first steps (see ch. 237). Premedication should include an opioid drug for analgesia. General anesthesia is induced via protocols based on patient risk profile, practitioner preference, and duration of the procedure. The patient is intubated and maintained under inhalant anesthesia.

Otoendoscopy is best performed on a "wet table" or surgical sink to reduce fluid pooling. Lateral recumbency, with the ear of interest on the nondependent side, is preferred to sternal recumbency for an easier, more complete examination. The endoscopic equipment cart is placed near the ventral aspect of the patient. The operator stands on the dorsal-facing side, near the patient's shoulder. The monitor is placed cranial to the patient, facing the operator. This allows the operator to hold the endoscope in a neutral position relative to the head, and for the monitor to display structures in an anatomically correct orientation (E-Figure 85-7).



E-FIGURE 85-7 Otoendoscopy is performed in a canine patient using a rigid otoendoscope and a mechanical irrigation and aspiration device. The flushing procedure is done via the instrument channel of the endoscope using a tomcat urinary catheter to accurately direct irrigation and aspiration.

For irrigation, an IV fluid bag and standard IV administration set are connected to the ingress port of the endoscope. Gravity flow is usually adequate, but manual pressure, a "squeeze bag," or a fluid pump can be used for increasing the rate and pressure of fluid flow. An irrigation/aspiration pump also is employed. The fluid should be non-ototoxic, and should be clear and free of dextrose. Appropriate choices include normal saline, lactated Ringer's solution, and other isotonic crystalloids (e.g., Normosol-R).[6,7]

For examinations on awake or sedated patients, clean, disinfected equipment can be used. However, if surgical intervention is planned, all equipment should be sterilized according to manufacturer's instructions.

Much endoscopic equipment is not safe for steam/heat sterilization methods, and either "cold soak" sterilizing fluids (such as glutaraldehyde-containing products) or ethylene oxide gas must be employed. Equipment sterilization is essential if the procedure involves obtaining samples for microbial culture.

For an otoendoscopic exam on an anesthetized patient, the procedure begins with a visual, open endoscopic examination of the visible portions of the pinna. If there is substantial ceruminous otic debris obscuring visualization, a standard ear cleaning is advised prior to attempting otoendoscopy. In all cases where culture samples are to be taken, sample collection should be performed prior to more invasive aural procedures. If bacterial cultures of the vertical or horizontal canals are to be taken, instrumentation must be prepared in strict aseptic manner to minimize the possibility of contamination of samples submitted to the laboratory. Culture of aural exudate should be taken as early as possible in the examination procedure, to minimize the risk of contamination from superficial flora being flushed into the ear canal. Samples for culture and for cytology can be retrieved via flush, directly with a culturette, or sampling the material with a grasping forceps.[8]

The operator assembles the endoscope, camera, light guide cable, irrigation fluid, and associated accessories and holds the endoscope in his or her dominant hand. The pinna is gently grasped in the nondominant hand and gently pulled laterally and very slightly caudodorsally. The endoscope is introduced into the vertical canal, slowly and gently, at an angle of ≈90° to the patient's skull. The flow of irrigant is begun, slowly and with minimal pressure at first, allowing for the gentle dislodging and evacuation of adherent ceruminous material. The bottom (medialmost aspect) of the vertical canal is visualized, and the otoendoscope is tilted to reveal the horizontal canal, with visualization of the tympanum in the far field. Care must be taken to avoid excessive torsion or bending of the shaft of the endoscope as the horizontal canal is entered, to avoid both iatrogenic injury and equipment damage.[9-12] If a biopsy is to be taken, a complete aural examination should be performed first because post-biopsy hemorrhage complicates visualization.

Deep Ear Cleaning/Aural Flushing

A deep cleaning is indicated if there is marked aural discharge that suggests disease of either the horizontal canal or middle ear. Essentially, a deep ear cleaning is a continuation of the irrigation performed with a standard otoscopic examination. If the volume of exudate necessitates a more aggressive cleaning, increased irrigation pressure will likely be needed, using pressure on the bag, or a pump (see Otoscopic Exam, above). Ideally, a mechanized suction/irrigation pump can be employed to allow for intermittent lavage followed by suction to expedite cleaning of the ear canal.[13,14] Purpose-made lavage catheters can be purchased, or a polypropylene tomcat catheter can be employed, cut to a manageable length. Purpose-made catheters are introduced via the instrument channel of the otoendoscope, offering the operator excellent visualization of the endoscopic field and an ability to monitor progress of the lavage. Lavage solutions should be the same as those used for the standard otoendoscopic exam. The use of ceruminolytic or ototoxic solutions should be avoided if the tympanum is compromised or its integrity is uncertain.

Excision of Aural Masses

Diode laser fibers in various diameters can be used via the instrument channels of otoendoscopes to ablate, debulk, vaporize, or resect aural masses (Video 85-1). This author favors the use of an 810 nm wavelength diode at powers ranging from 4-8 W. Each laser has unique properties necessitating effective and safe protocols for each device; this wavelength of laser light provides excellent tissue vaporization and cutting in a fluid medium, and is very effective in the presence of blood, providing excellent hemostasis and helping to maintain a continually visible surgical field. While it is unlikely that laser excision or vaporization provides clean surgical margins in aggressive neoplastic lesions, the device has significant utility in removing a variety of common mass lesions of the ear canal[15,16] (Figures 85-8 and 85-9). Ear masses and other diseases of the ear are discussed further in ch. 237.

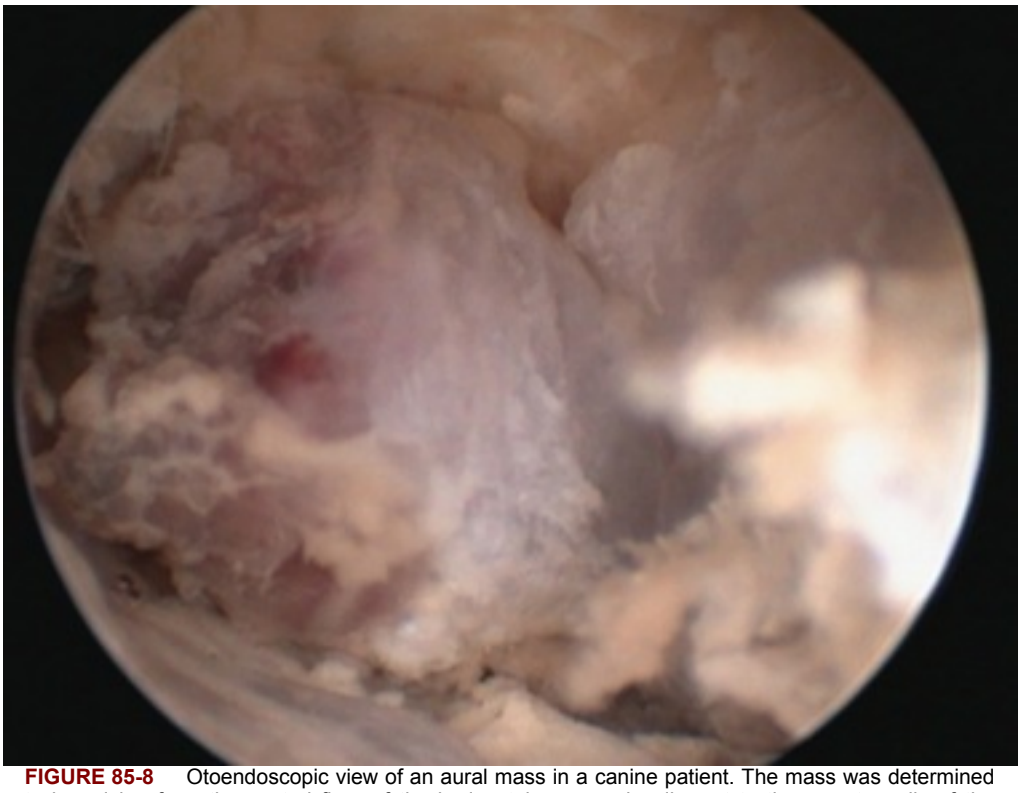


FIGURE 85-8 Otoendoscopic view of an aural mass in a canine patient. The mass was determined to be arising from the ventral floor of the horizontal ear canal, adherent to the pars tensalis of the tympanum. Removal necessitated a small myringotomy along the ventral edge of the pars tensalis. The mass was determined via histopathology to be a benign lymphoplasmacytic polyp.

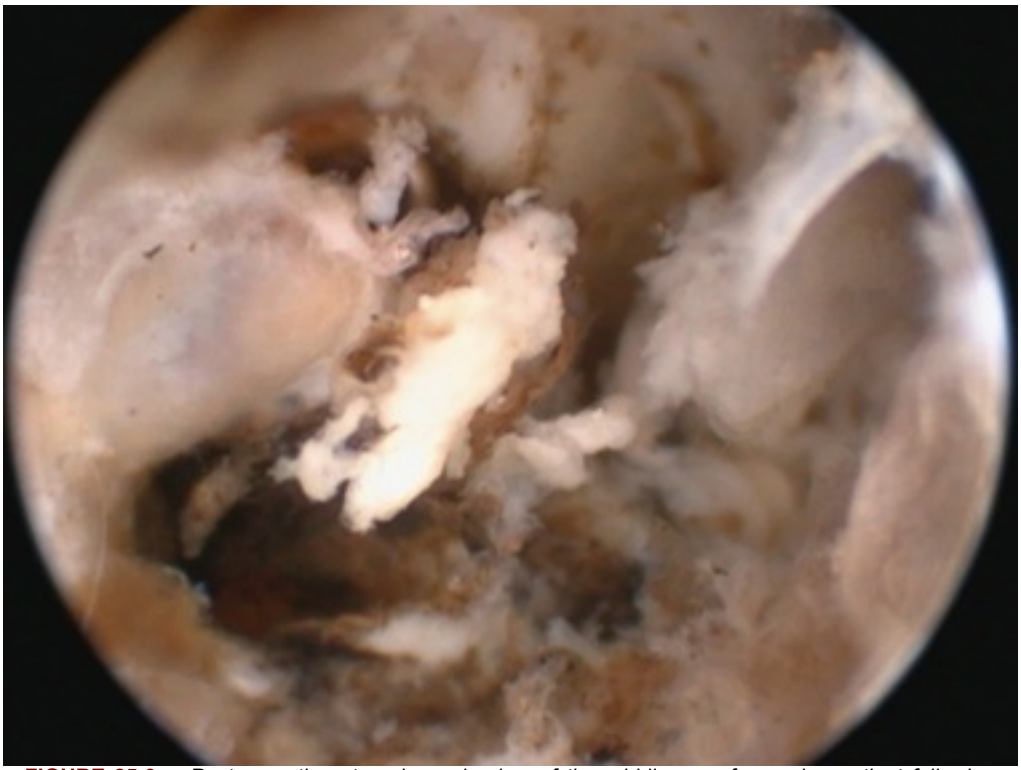


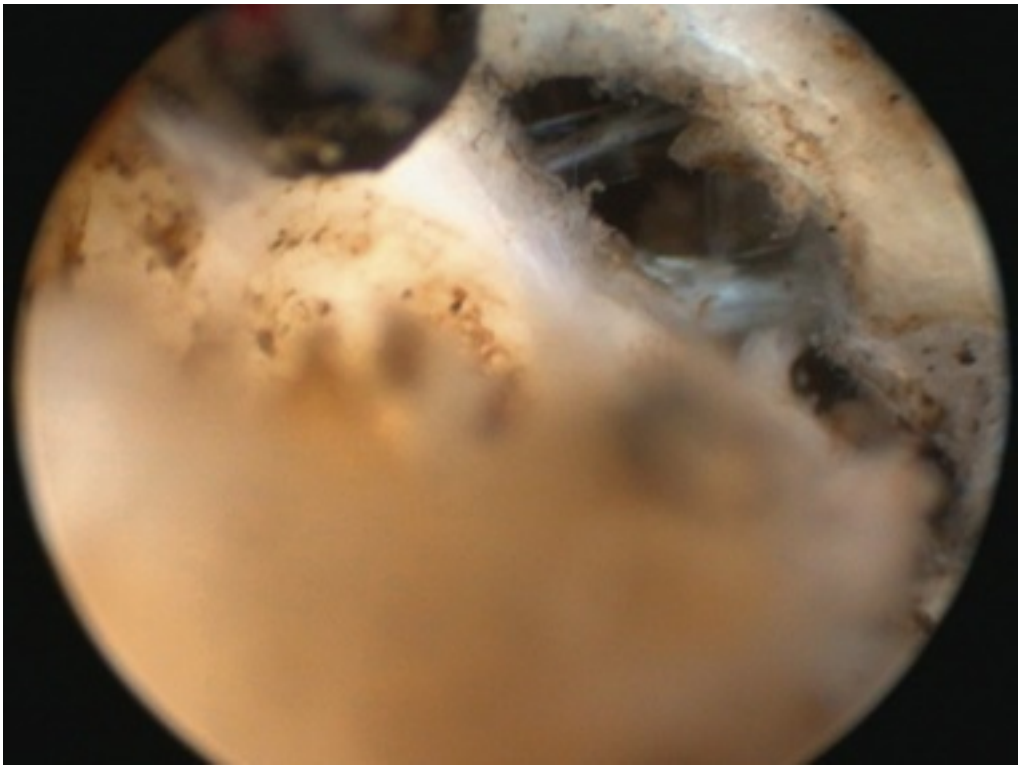
FIGURE 85-9 Post operative otoendoscopic view of the middle ear of a canine patient following laser endoscopic resection of an aural mass arising from the middle ear and extending into the tympanic bulla. A large portion of the tympanum was incised to allow for adequate exposure of the lesion, with evident damage to the ossicles. This lesion was determined via histopathology to be of

benign nature demonstrating the dramatic middle ear damage that can result from even benign disease.

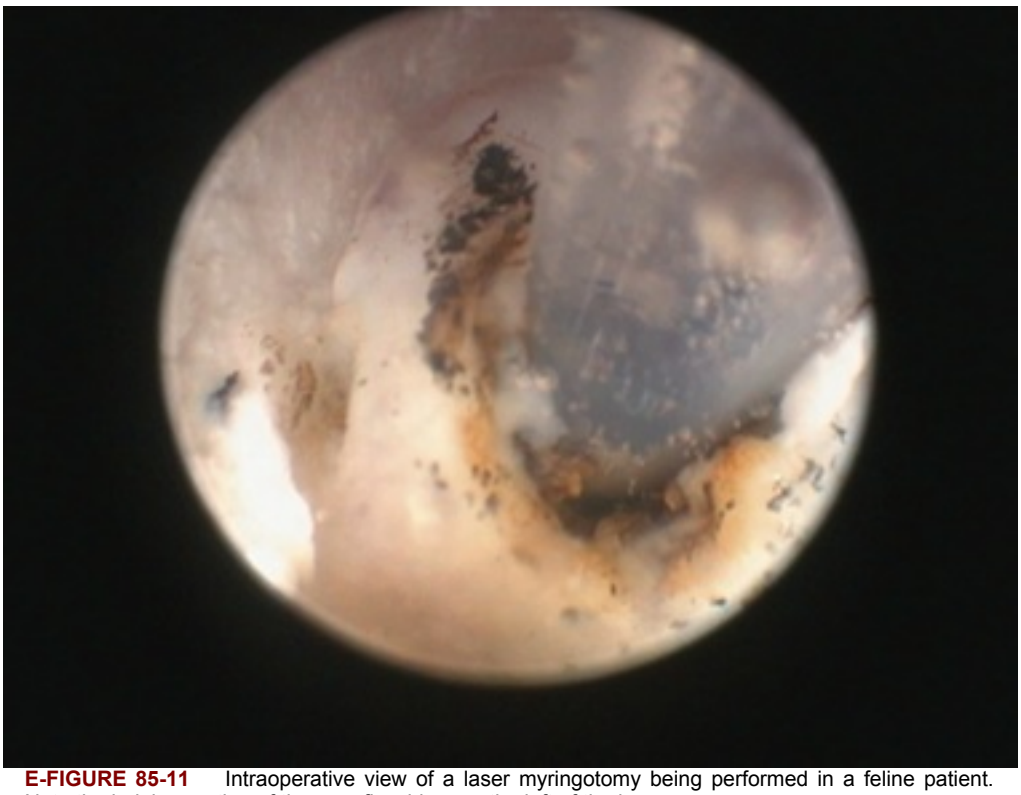
Myringotomy

Historically, veterinarians have been reticent to perform myringotomies. Indeed, iatrogenic myringotomy, when performed during otoendoscopic exam, has often been treated as a surgical crisis. Recent studies have demonstrated the previously underreported prevalence of otitis media in dogs (in particular) and the utility of myringotomy in the management of these diseases.[17,18]

Myringotomy is a simple and safe procedure that can be performed during a standard otoendoscopic exam in an appropriately anesthetized patient (Videos 85-2, 85-3, and 85-4). It should be considered in any patient with endoscopically visible evidence of disease of the tympanum and/or middle ear, typically manifesting as decreased opacity of the tympanum and abnormal anatomy of the tympanum. Bulging of the tympanum into the horizontal canal suggests clinically significant fluid accumulation in the middle ear that can benefit from drainage (see Video 85-2). Myringotomy can be performed via a simple perforation using a tomcat catheter with the end cut to a sharp bevel (see Video 85-3), or with a purpose-made myringotomy knife (see Video 85-4). One of the great frustrations to the practitioner performing a myringotomy is the rapidity with which the tympanum can heal: myringotomies can begin to heal within 72 hours, leading to chronic otitis media, whereas patency should last for at least 7-14 days to allow for adequate drainage of the middle ear. The use of diode lasers is an effective tool for performing myringotomy with the added feature of delayed tissue healing, as with any form of thermal energy used in surgery. The diode laser is set to very low power, a slender 400-600 micron fiber is used, and the pars flaccidum of the tympanum is identified. With empyema behind the tympanum, the most common region of bulging is the slightly more redundant pars flaccidum. The tympanum is cut in a cruciate fashion, centered in the pars flaccidum. The pars tensalis is to be avoided if possible, given its anatomic proximity to the manubrium of the malleus. However, chronic disease of the tympanum often makes it difficult to identify regions of the tympanum clearly. When the tympanum is incised, it is common to see a rush of dark or purulent fluid entering the horizontal canal from the middle ear, which should be collected directly for cytologic examination and bacterial culture and susceptibility testing (see Video 85-4). The pressure of irrigant inflow should be reduced at this point and gentle flushing will result in lavage of the middle ear[19-21] (E-Figures 85-10 and 85-11).



E-FIGURE 85-10 Intraoperative view of a laser myringotomy being performed in a canine patient. The incision is being made in the dorsal aspect of the pars tensalis. The incision is being made in a cruciate pattern extending from the dorso-rostral aspect proceeding caudo-ventrally. A second incision will be made in the opposite direction. This incisional pattern minimizes the likelihood of premature healing and recurrence of fluid or debris accumulation in the middle ear.



E-FIGURE 85-11 Intraoperative view of a laser myringotomy being performed in a feline patient. Note the bulging portion of the pars flaccidum on the left of the image.

Complications of Otoendoscopy

Even with a modest degree of experience, otoendoscopy is an extremely safe procedure associated with minimal surgical morbidity and rare surgical mortality. If otitis media is not adequately treated post-myringotomy, further delayed healing can occur. This can lead to a pattern of progressively worsening otitis media that can become refractory to common antimicrobial therapy. Aggressive topical and systemic antibiotic therapy is important for adequate and timely resolution of otitis media and healing of the tympanum. Rarely, patients experience a transient caloric- or pressure-induced head tilt or, more rarely, nystagmus, Horner's syndrome, or facial nerve paresis/paralysis. These complications, when noted, are usually mild and self-limiting.[21]

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CHAPTER 86

Scraping, Fine-Needle Aspiration, and Biopsy of Skin and Subcutaneous Tissues

Ralf S. Mueller, Sonya V. Bettenay

Skin Scrapings

Skin scrapings used as aids in diagnosing cutaneous ectoparasites are classified as either superficial or deep. These two types of scraping have distinct uses for identifying different parasites and differ substantially in their procedural approach.

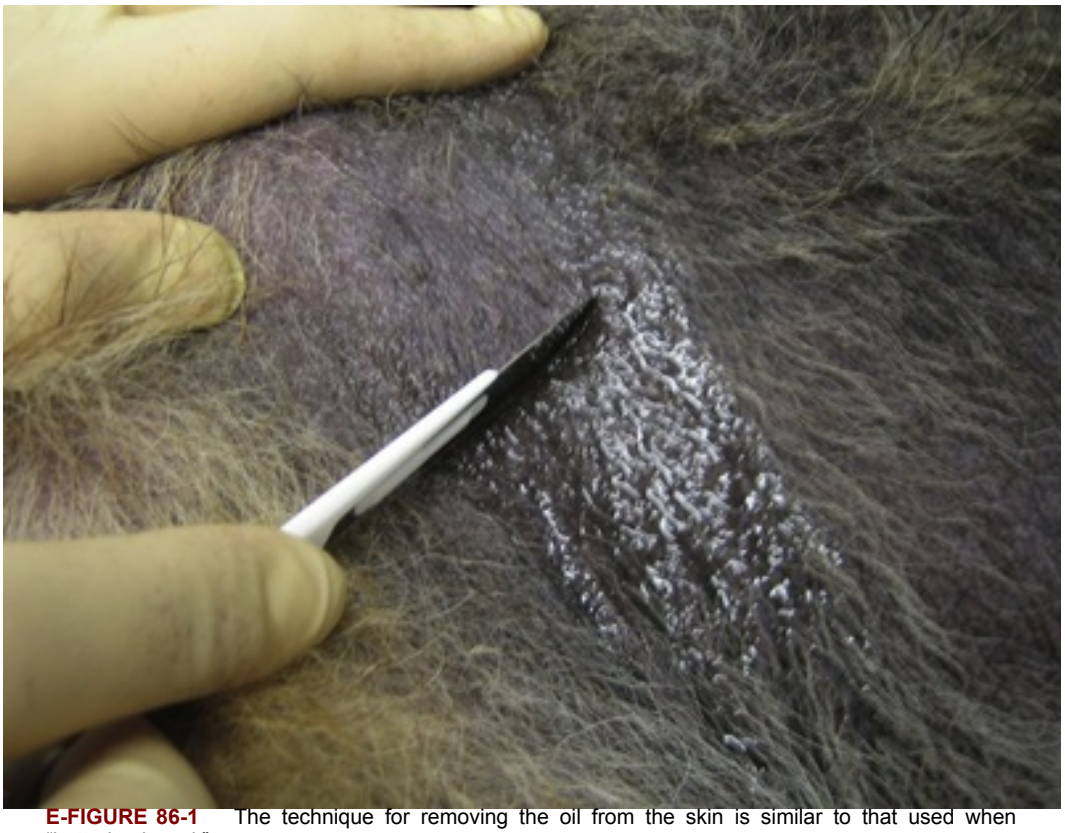
Superficial Skin Scrapings

Indication

Superficial skin scrapings are used to detect mites living on the skin surface or burrowing within the stratum corneum such as *Cheyletiella* spp., *Otodectes cynotis, Sarcoptes* spp. and *Notoedres cati*. Both *Cheyletiella* and *Sarcoptes* mites can be difficult to find; about 50-70% of pets with either of these parasites have positive scraping results.[1,2] Results may be <50% when there is an early infestation with fewer mites. Cats with *Notoedres cati* typically have abundant mites. Preferred anatomic sites for scraping vary. In the dog suspected of having scabies, the elbows, ear margins, lateral hocks, and ventrum are commonly affected. In cats, *Notoedres cati* affects the head. In both dogs and cats, *Cheyletiella* mites inhabit the dorsal trunk and typically cause scaling. *Otodectes cynotis* is most frequently associated with otitis externa, but may produce a head and neck pruritus and rarely a generalized dermatitis. Superficial skin scrapings should be performed in any scaly or pruritic dog or cat.[3]

Procedure

Mineral oil is applied to the affected skin in a thin film to facilitate the gathering of scale and surface debris and increase the chance of positive results.[1] Nonexcoriated scaly and/or papular sites are selected and a dulled, #10 scalpel blade is used to sample the surface of a large area (at least 5 × 5 cm). Hairy dogs with suspected scabies should be clipped first; use the clippers only in the direction of hair growth and leave 1-2 mm of hair—i.e., not a surgical clip—the aim being to keep the surface scale or crust that may be present. Clipping is not indicated in pets that might have cheyletiellosis. The oil is then gently scraped off the surface, as if "buttering bread" (E-Figure 86-1) in the direction of hair growth and transferred onto a glass microscope slide. This "large oil volume" technique provides multiple slides for examination, providing an excellent chance of success.



E-FIGURE 86-1 The technique for removing the oil from the skin is similar to that used when "buttering bread."

Microscopic Technique

A coverslip is applied to distribute the debris evenly—mites may be missed if covered by debris—and to speed microscopic evaluation by reducing need for continuous adjustment of focus. Scanning (4 × objective, 10 × ocular) power is used and the condenser of the microscope lowered to increase contrast. Skin scrapings for ectoparasites should be examined within a few hours of sample collection, because mites can actually walk off a slide if left too long.

Interpretation

One mite or egg is diagnostic and should be considered reason to initiate miticidal therapy. A negative scraping does not rule out presence of mites and diagnostic therapy may still be indicated.

Deep Skin Scrapings

Indication

Deep skin scrapings are performed to detect *Demodex* mites. In the dog, *Demodex canis* lives in the hair follicle; a longer-bodied *Demodex* mite *(Demodex injai)* is suspected to live in the sebaceous glands.[4-6] Canine demodicosis is characterized clinically by alopecia, comedones, papules, pustules, scales, and crusts and must be considered for almost any dog with inflammatory or non-inflammatory skin disease. Demodicosis in the cat is less common, typically secondary to systemic disease and affecting the head.[7,8] A ventral alopecia pattern has also been reported.[9]

Procedure

Ideally, follicular papules or pustules over an area of at least 1 × 1 cm should be sampled. Mite counts are higher when the skin is squeezed (prior to and during scraping) in an attempt to push the mites out from the depths of the follicles.[10] Using a mineral-oil-covered #10 blade, skin is scraped in the direction of hair growth until capillary bleeding is observed (Video 86-1). Trichograms (hair plucks, placed in mineral oil on a glass

slide for examination) provide an alternative test that is particularly useful in pets with periocular or pedal lesions. Trichograms are almost as reliable as deep skin scrapings, if sufficient hair shafts over the same 1 × 1 cm area are plucked.[10,11]

Interpretation

Demodex canis is a normal component of the cutaneous fauna and an occasional mite can be found on the skin scraping of normal dogs. If only one mite is found, but clinical signs are compatible, further scrapings, trichograms, or a biopsy are indicated.[3] It is important to note in the clinical record the site of scraping and the relative numbers of adults, larvae, nymphs, and eggs per low power field (LPF). Assessment of response to therapy is based on comparison of these numbers at subsequent monthly visits.

Fine-Needle Aspiration

Indication

Fine-needle aspiration is frequently performed on nodules in the skin or subcutis as the "first step" when attempting to differentiate neoplasia from inflammation or infection.

Procedure

The nodule should be firmly fixed between thumb and forefinger of one hand; a 20- or 22-gauge needle is then gently inserted into the nodule with the other hand and redirected several times without completely withdrawing it from the nodule. The needle is then withdrawn and the cells within the lumen of the needle are expelled by attaching an air-filled 5 mL syringe and blowing the content onto a glass slide. This method is particularly suitable for small nodules. Control of the needle tip is sufficient that even in lively dogs it is unlikely for a needle to penetrate through the nodule into normal underlying tissue possibly transferring neoplastic cells.

If no cells are obtained using the previously described technique, a "suction method" may be used. The needle is first attached to a 10 mL syringe before being inserted into the nodule and aspirated multiple times. Suction should be interrupted when the needle is redirected and particularly when being withdrawn, to avoid sucking cells into the syringe where they may not be retrievable. The needle is then separated from the syringe, the plunger drawn back, the syringe and needle reattached, and the contents blown onto a glass slide. The material is then spread as with blood smears, dried, stained with a modified Wright's stain (Diff-Quik), and examined.

Interpretation

If a uniform cell population is identified, then a neoplastic cause is likely. Characteristics of neoplastic cell populations are described elsewhere (see ch. 93). Histopathology is necessary to define tumor grade, enable a prognosis, and contribute to decisions regarding the next course of action. If inflammatory cells such as neutrophils and macrophages dominate, then infection is possible and the next step is a bacterial and/or fungal culture of the deep tissue to differentiate sterile inflammation from an infectious cause.

Getting the Most From a Skin Biopsy (E-Box 86-1)

E-Box 86-1

Ten Tips to Obtain a Better Skin Biopsy Result

1. Do not use aseptic technique to prepare the skin surface.
2. Before starting, spend 5 minutes looking for a representative range of lesions.
3. Select multiple (4-6) samples that represent the range of lesions from normal to most severely affected.
4. In inflammatory or alopecic skin disease, if possible, include a normal sample from the dorsum, not the ventrum.
5. Draw a follicle orientation line (on the trunk this is in the direction from the nose to the tail tip) in all samples.
6. Use 6- to 8-mm punches or an elliptical biopsy except on noses and paws.

7. Handle the biopsy specimen carefully; treat it like wet tissue paper even when excising.
8. Give the pathologist a succinct history, your physical findings and your differential diagnoses.
9. Use an incisional biopsy when a neoplasm is suspected, provided this can be followed by a second procedure for wide excision if indicated.
10. Ensure adequate formalin fixation through correct volume and/or partial incisional slicing of larger tumors.

Site selection and biopsy methodology can make the difference between success and failure to obtain a specific diagnosis.[3,12] Even "inconclusive results" can rule out some differential diagnoses.

Site Selection

A careful examination of the entire animal for the most representative range of lesions is the first step in biopsy site selection. Taking multiple samples from well-chosen sites helps to avoid inconclusive results. In a pustular disease, erythematous macules develop into papules, then pustules and finally crusts/erosions. Sampling each of these stages supplies the widest range of lesions, but wherever possible, multiple pustules should be sampled. Depigmenting lesions should be biopsied in an active area (i.e., gray color) rather than the final stage (i.e., white).

Alopecic areas should be sampled in the center of the most alopecic area as well as in junctional and normal areas. On submission, identifying sites biopsied can be achieved by placing samples in separate, carefully labeled, bottles of formalin, or through the use of tissue dyes marking different lesion types with a different color (E-Figure 86-2). When assessing alopecia, where possible, avoid the glabrous (nonhaired) areas of the body as they contain fewer hair follicle units and smaller sebaceous glands. A line drawn prior to biopsy on the skin in the direction of the hair growth, using a waterproof pen, indicates the direction needed for cutting the follicles longitudinally (Figure 86-3 and E-Figure 86-4).[13]

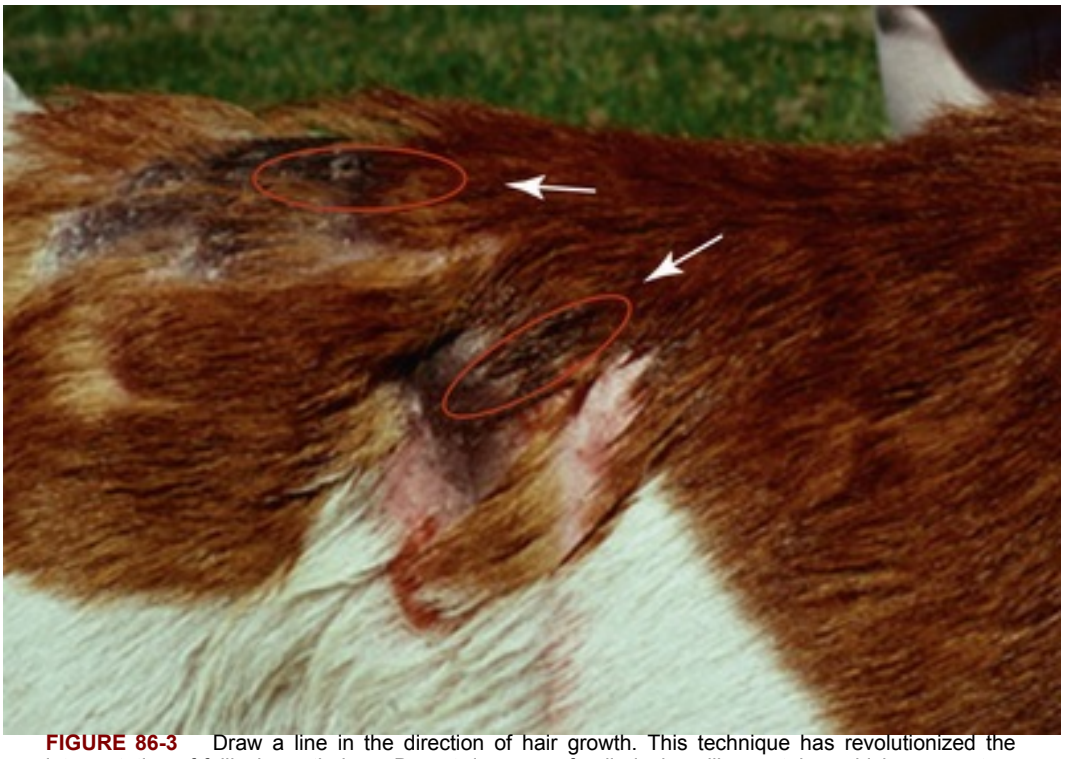
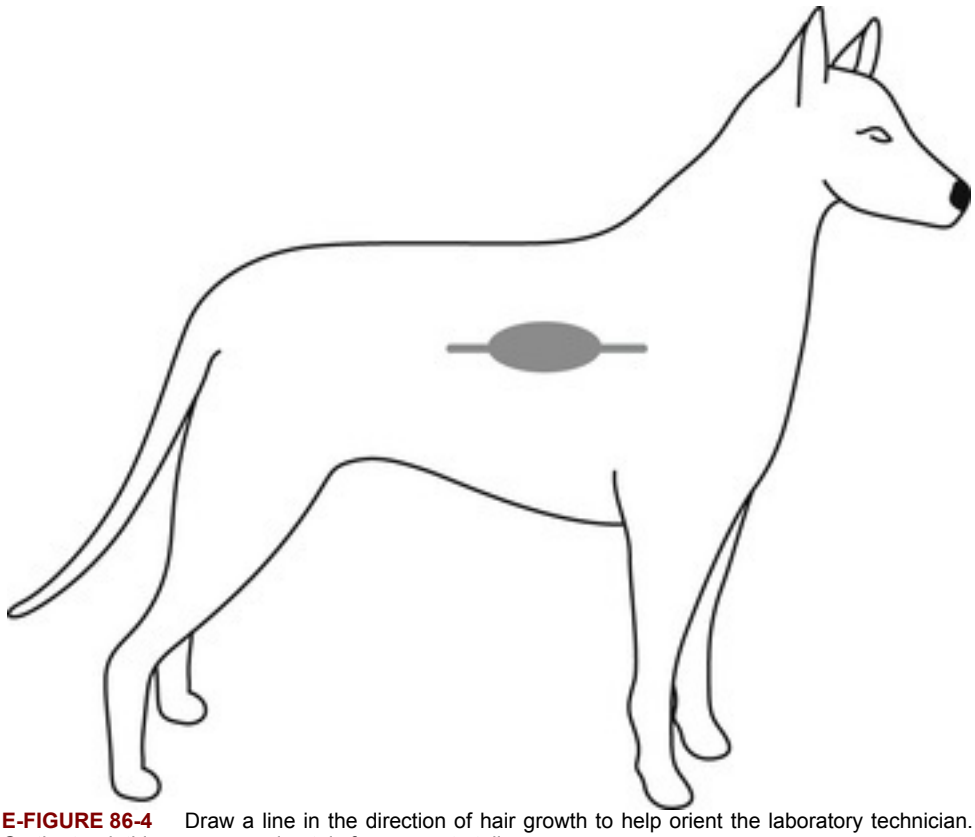


FIGURE 86-3 Draw a line in the direction of hair growth. This technique has revolutionized the interpretation of follicular pathology. Do not draw over fragile lesions like pustules, which may rupture with pressure.

E-FIGURE 86-2 Dye can be used to identify specific skin biopsies. It is spread thinly on the pannicular surface and *must* dry before the tissue is placed in the formalin (allow 1-2 minutes).



E-FIGURE 86-4 Draw a line in the direction of hair growth to help orient the laboratory technician. On the trunk this runs approximately from nose to tail.

In dogs and cats with severe inflammatory disease, clues with regard to the follicular growth characteristics may be present only in adjacent normal skin. Ulcerated areas should be avoided, unless deep dermal, vascular, or pannicular pathology is suspected. When sampling an ulcerated lesion, use an elliptical incision either to completely excise the ulcer with adjacent normal skin or oriented from the center of the lesion to include adjacent "normal or intact" skin.

Surgical Technique

Overlying hair should be clipped only in the direction of hair growth and gently removed to preserve any scale and crusts. Crusts should be left on the skin and included in the biopsy as they may contain microorganisms, inflammatory, or acantholytic cells that may help establish a diagnosis. Write "please cut in crusts" on the submission form. No aseptic preparation is performed, except when excising solitary nodules. Infection resulting from a lack of surgical preparation is almost never seen. General anesthesia is indicated for facial or paw biopsies and may also be necessary for larger excisional biopsies. Local anesthesia, with or without sedation, is a practical alternative for many pets with truncal biopsies. SC injection of 1 or 2 mL of xylocaine without adrenaline (lidocaine without epinephrine) usually provides adequate local anesthesia. The maximum amount of xylocaine used depends on body weight. The site is marked to enable easy relocation and the needle entry point should be outside the proposed biopsy area to avoid tissue disruption within the biopsy.[13]

Wedge/Ellipse versus Punch Biopsy

The punch biopsy is quick, relatively atraumatic, and often recommended when infectious, inflammatory, and endocrine dermatoses are suspected. Disposable, new, 8-mm punches are preferred. Four- and six-mm punches are reserved for biopsies of footpads, nasal planum, mucocutaneous junctions, or eyelids.

Punch Biopsy Sampling

Hold the punch at a 90° angle to the surface of the skin, firmly brace the surrounding skin, and rotate the punch in one direction with continuous, but relatively little, pressure. When the skin no longer "turns" with the punch rotation, sufficient depth has been reached to free the dermis from its underlying attachment. The punch is removed and any blood is carefully blotted. Grasp the tissue gently at the base and sever the SC attachments. Under no circumstance should the dermis or epidermis be squeezed as this leads to "crush artefact" and may result in a sample that is unreadable or misinterpreted as scarring. The use of ophthalmic instruments such as iris scissors and forceps is recommended.

Excisional/Incisional Sampling

The wedge or elliptical biopsy should be employed as an excisional technique when a deep dermal or panniculus lesion is suspected. This method should also be used when removing a solitary nodule or fragile lesion (such as vesicles). It is also used when there appears to be a range of changes radiating from the center to the edge of a lesion (e.g., central ulceration or alopecia and adjacent normal tissue can be included in the ellipse) (Figure 86-5, *A* and *B*).

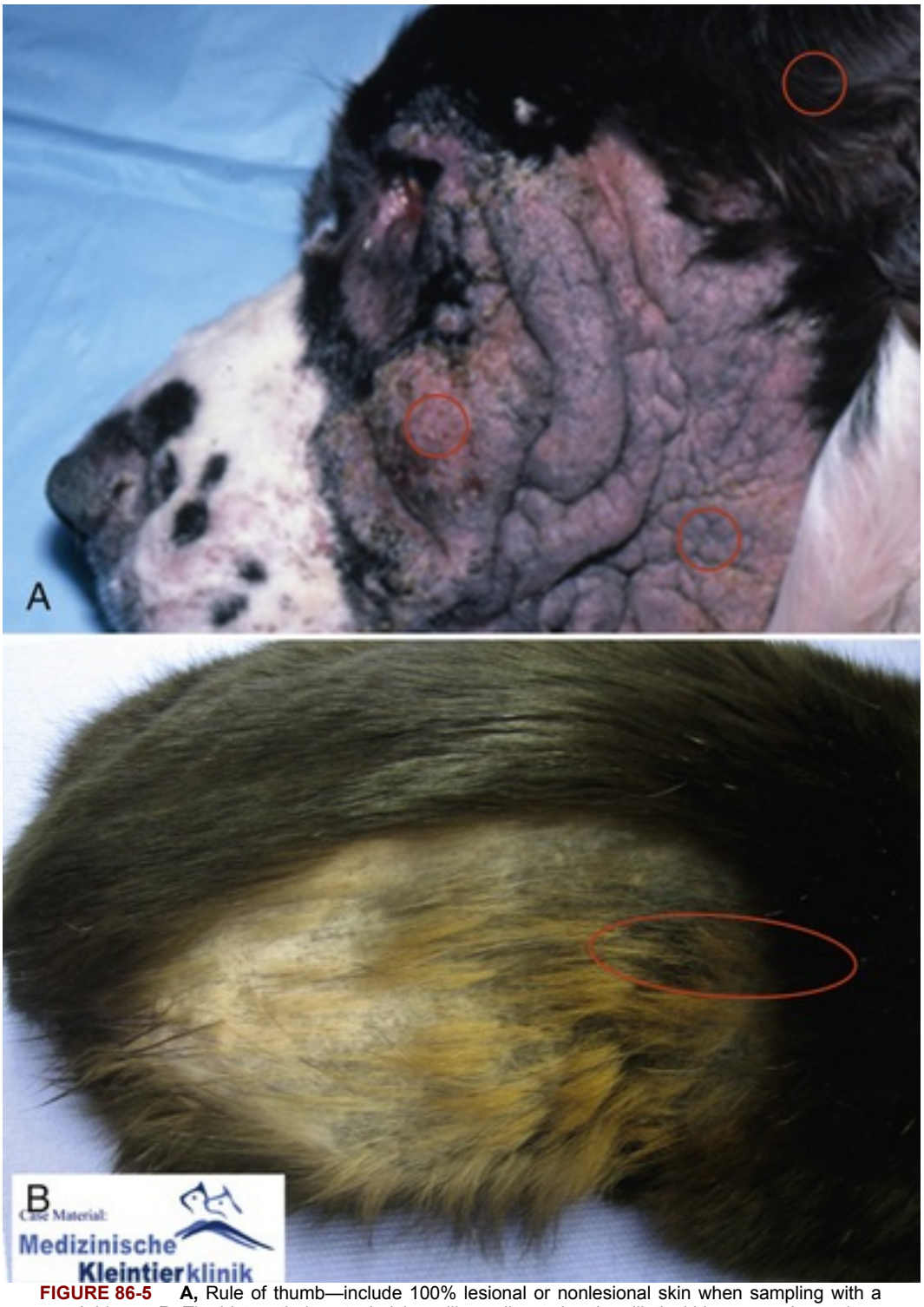


FIGURE 86-5 **A,** Rule of thumb—include 100% lesional or nonlesional skin when sampling with a punch biopsy. **B,** The histopathology technician will usually section the elliptical biopsy specimen along the midline of the long axis of the ellipse. Orientation of the ellipse across the junction between abnormal and normal tissues will allow the pathologist to view the skin from affected, through active, to nonaffected areas and so gain the best possible appreciation of the stages of the disease and hence the etiology. (Courtesy Medizinische Kleintierklinik.)

In the case of a suspected neoplasm, an incisional biopsy may be indicated. This allows an accurate diagnosis without concern of contaminating surrounding tissue or compromising any subsequent surgical intervention. Cytology may diagnose malignancy without the need for a biopsy, but it cannot replace the prognostic information obtained from the assessment of margins and vessels that histopathology allows.

Once the biopsy has been obtained, the wound is closed routinely.

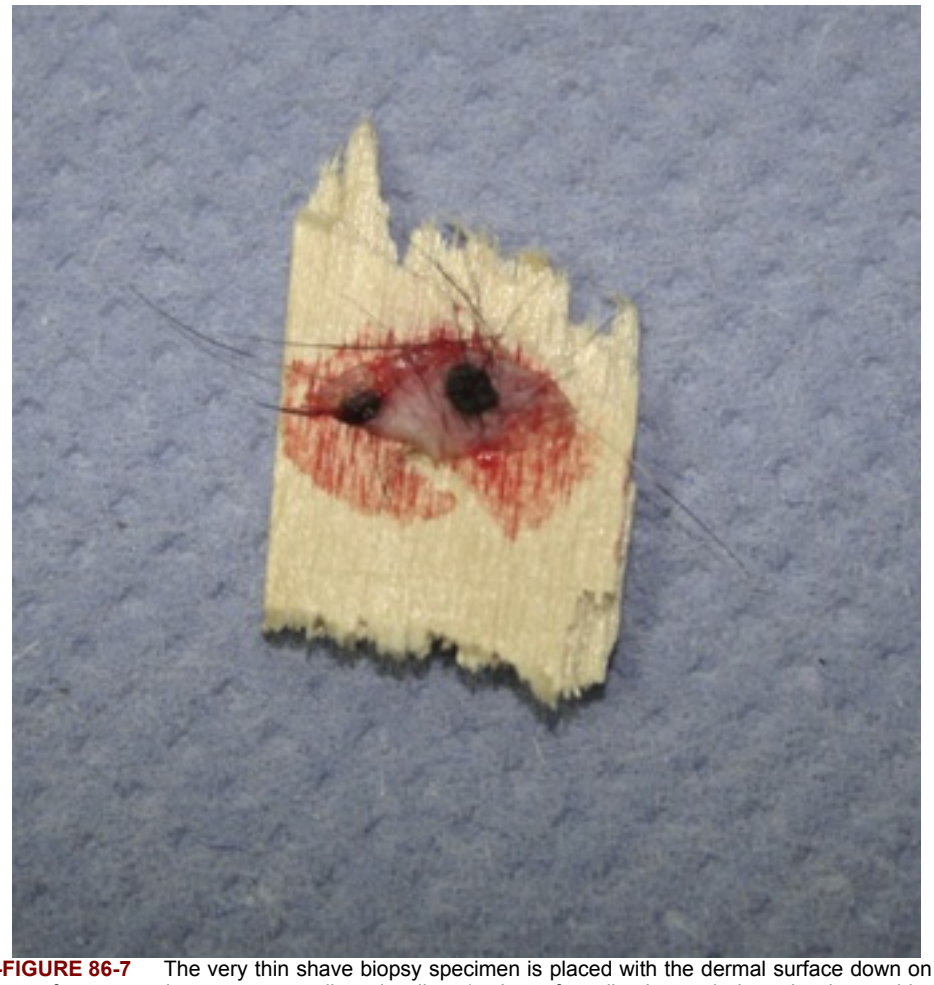
Fixation of Tissue

The biopsy sample surface should be gently blotted prior to placing it in formalin. A minimum volume of formalin, approximately 10 times the sample volume, is needed for adequate fixation. In cold climates, the addition of one part alcohol to nine parts formalin will prevent freezing during shipping. Large tissue pieces should be sectioned into 1-cm slices to allow adequate formalin penetration *without* sectioning through the nodule completely. To retain the original orientation for margin assessment leave the sections attached at the base (adipose tissue).

Shave Biopsies

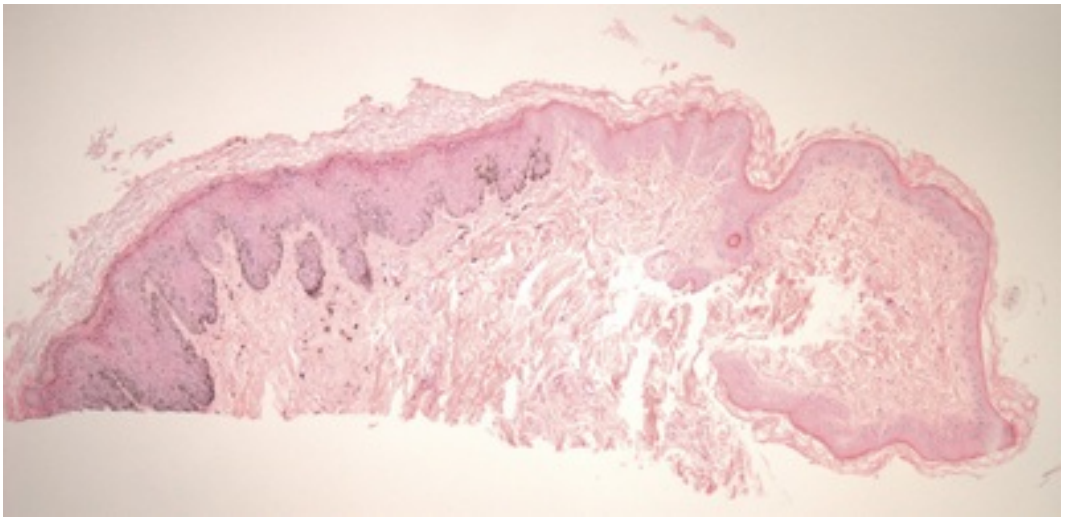
On the pinnae, cartilage is found directly under an extremely thin dermis and the panniculus is absent. With punch and wedge techniques, cartilage may inadvertently be damaged and a permanent change in the shape of the pinna may result. The shave biopsy is a fast technique to diagnose diseases of the epidermis or dermoepidermal junction (such as lupus or pemphigus), but which needs to be performed under general anesthesia. The outside of the ear needs to be clipped; the concave/inner pinna may not. A scalpel blade is held in one hand; the pinna is bent over the index finger of the other hand (E-Figure 86-6). On the stretched and bent convex surface, the scalpel blade enters the skin at an angle of approximately 20°, only to a depth where capillary bleeding is observed. At that depth, the incision is continued parallel to the surface of the skin until a specimen, approximately 5 × 5 mm (0.25 × 0.25 inches), is obtained. This sliced-out specimen is an extremely thin piece of skin that should be placed with the dermal surface down on a piece of a tongue depressor or cardboard to avoid distortion during fixation (E-Figure 86-7).

E-FIGURE 86-6 Shave biopsy. The pinna is bent over the index finger of one hand and a scalpel is used to obtain the biopsy specimen.



E-FIGURE 86-7 The very thin shave biopsy specimen is placed with the dermal surface down on a piece of a tongue depressor or cardboard—allow 1 minute for adhesion and place the tissue side in contact with the formalin.

Three minutes of firm digital pressure or use of a silver nitrate stick typically stops hemorrhage and suturing is not usually necessary. There is typically no scarring. Shave technique is only useful for diseases of the epidermis and upper dermis, as the depth of the specimen with proper technique will not reach below the midfollicular level (E-Figure 86-8) and deep dermal changes such as vasculitis and disorders of the cartilage cannot be evaluated.



E-FIGURE 86-8 Histopathology of a shave biopsy will reveal changes in the epidermis and upper dermis, as the depth of the specimen with proper technique will reach the midfollicular level.

Interpretation—Making a Diagnosis

One of the major reasons to perform a skin biopsy is to obtain a diagnosis. The second aim, even in the absence of a confirmed diagnosis, is to rule out differential diagnoses. In order for the pathologist to look for subtle clues and to interpret unusual changes, a list of clinical lesions and differential diagnoses must be included with the submission. Choose a pathologist with an active interest in dermatopathology or a dermatologist with advanced dermatopathology training.

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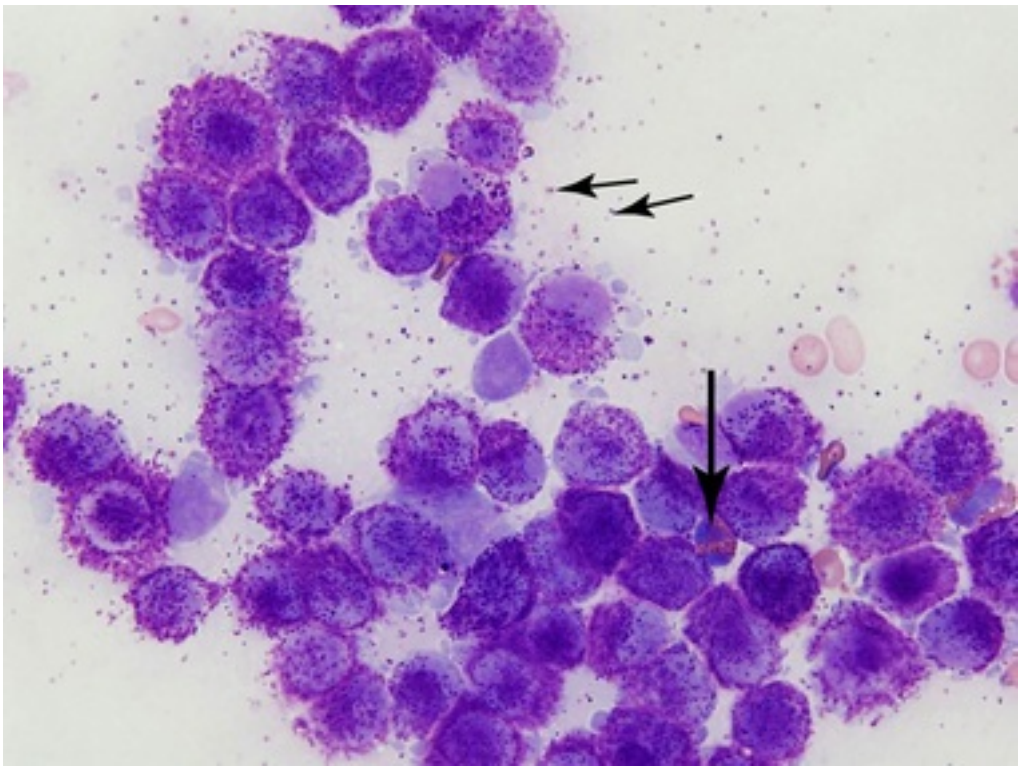
CHAPTER 87

Cytology of the Skin and Subcutaneous Tissues

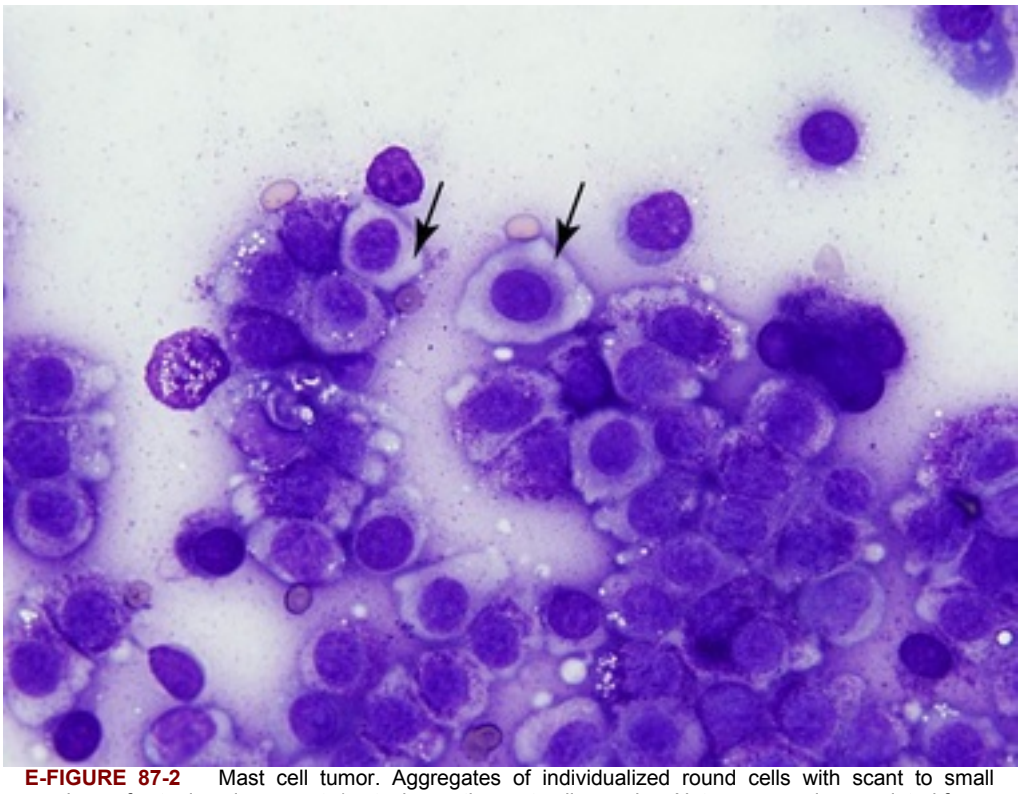
Ryan M. Dickinson

Evaluation of fine-needle aspirates (FNAs) or impression smears of skin lesions is a relatively inexpensive, fast, and accurate method of obtaining a diagnosis or providing a list of differential diagnoses when taking into account the patient's signalment, relevant clinical history, and other diagnostic information. Assessment of cytologic samples provides many advantages, including visualization of fine cellular detail (subtle, yet important nuclear and cytoplasmic features) and morphology of small organisms (e.g., bacteria [including mycobacteria] and protozoa). At the same time, interpretation of FNAs can be challenging and it requires distinguishing real from artifactual background material (e.g., stain precipitate). Thus, the diagnosis of many lesions requires the expertise of a formally trained clinical pathologist. However, clinicians with an interest in cytology may be able to make straightforward diagnoses or be able to categorize the disease process prior to submitting cytologic samples to a reference laboratory. Cytopathologic evaluation can help guide a clinician towards the appropriate therapy or pursuit of additional diagnostic testing, if required, to obtain a definitive diagnosis.

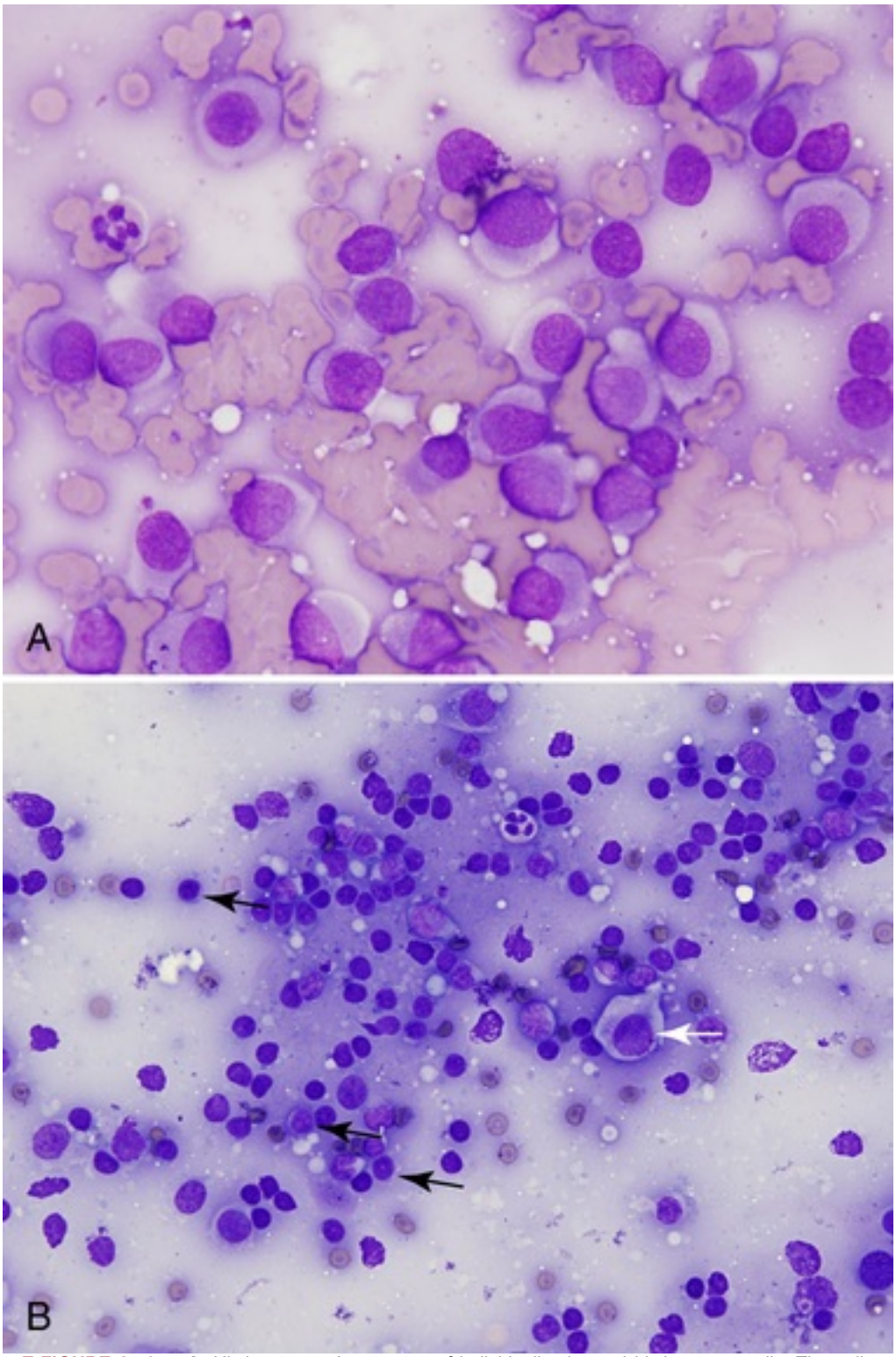
Important examples of cutaneous and subcutaneous masses where fine-needle aspiration can be useful for cytopathologic diagnosis include mast cell tumor (E-Figures 87-1 and 87-2), histiocytoma (E-Figure 87-3, *A* and *B*), lymphoma (E-Figure 87-4), plasmacytoma (E-Figure 87-5), hepatoid adenoma (E-Figure 87-6), keratin-filled cystic structures (E-Figure 87-7), sebaceous adenoma (E-Figure 87-8), squamous cell carcinoma (E-Figure 87-9), trichoblastoma (basal cell tumor; E-Figure 87-10), hemangiopericytoma/perivascular wall tumor (E-Figure 87-11), metastatic osteosarcoma (E-Figure 87-12), myxosarcoma (E-Figure 87-13), melanoma (E-Figure 87-14), abscesses (E-Figure 87-15), and systemic mycoses (blastomycosis: E-Figure 87-16).



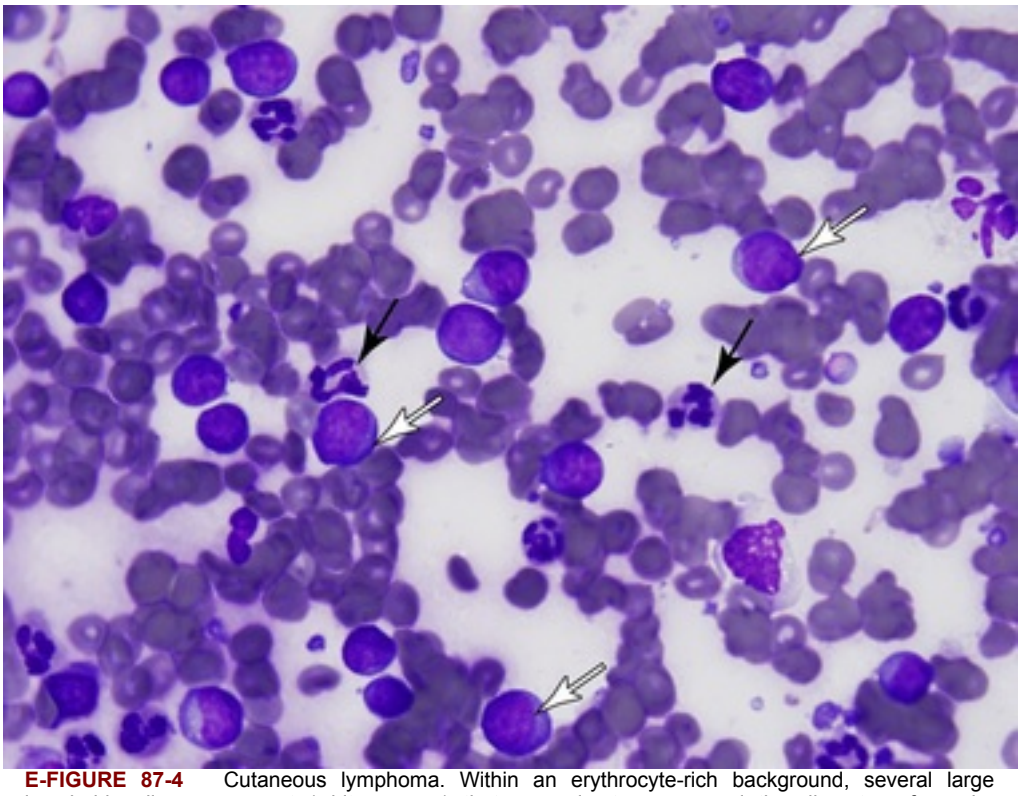
E-FIGURE 87-1 Mast cell tumor. Aggregated yet individualized round cells with many intracytoplasmic magenta/metachromatic granules. Note fewer extracellular mast cell granules as well (small arrows). Few eosinophils are present (large arrow). Modified Wright's stain ×1000.



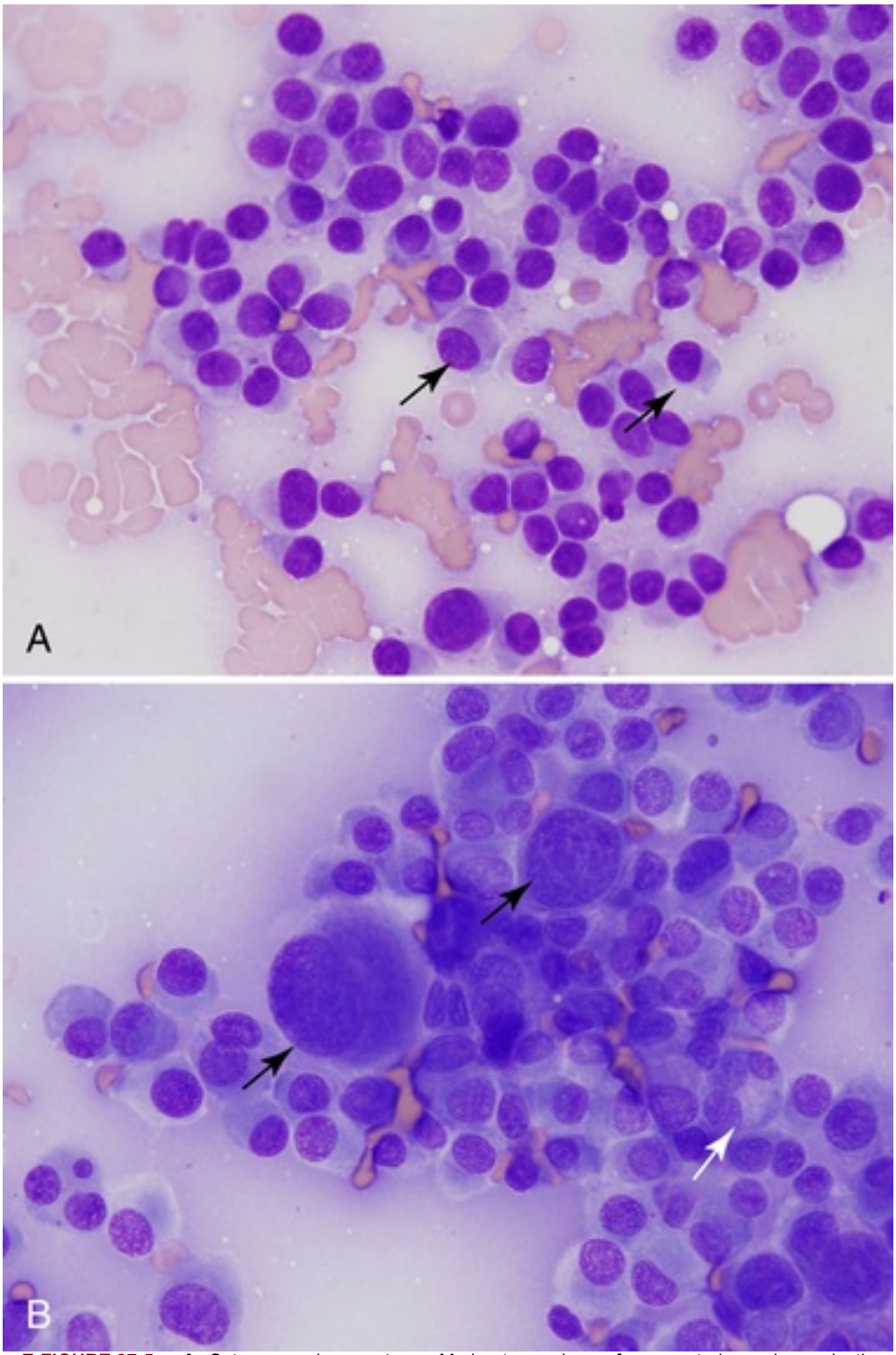
E-FIGURE 87-2 Mast cell tumor. Aggregates of individualized round cells with scant to small numbers of cytoplasmic magenta/metachromatic mast cell granules. Note very poorly granulated forms (arrows). In some cases, Diff-Quik stain may not stain mast cell granules very well, so the absence of striking staining patterns of granules should not be used as a basis for ruling out mast cell tumor. Modified Wright's stain ×1000.



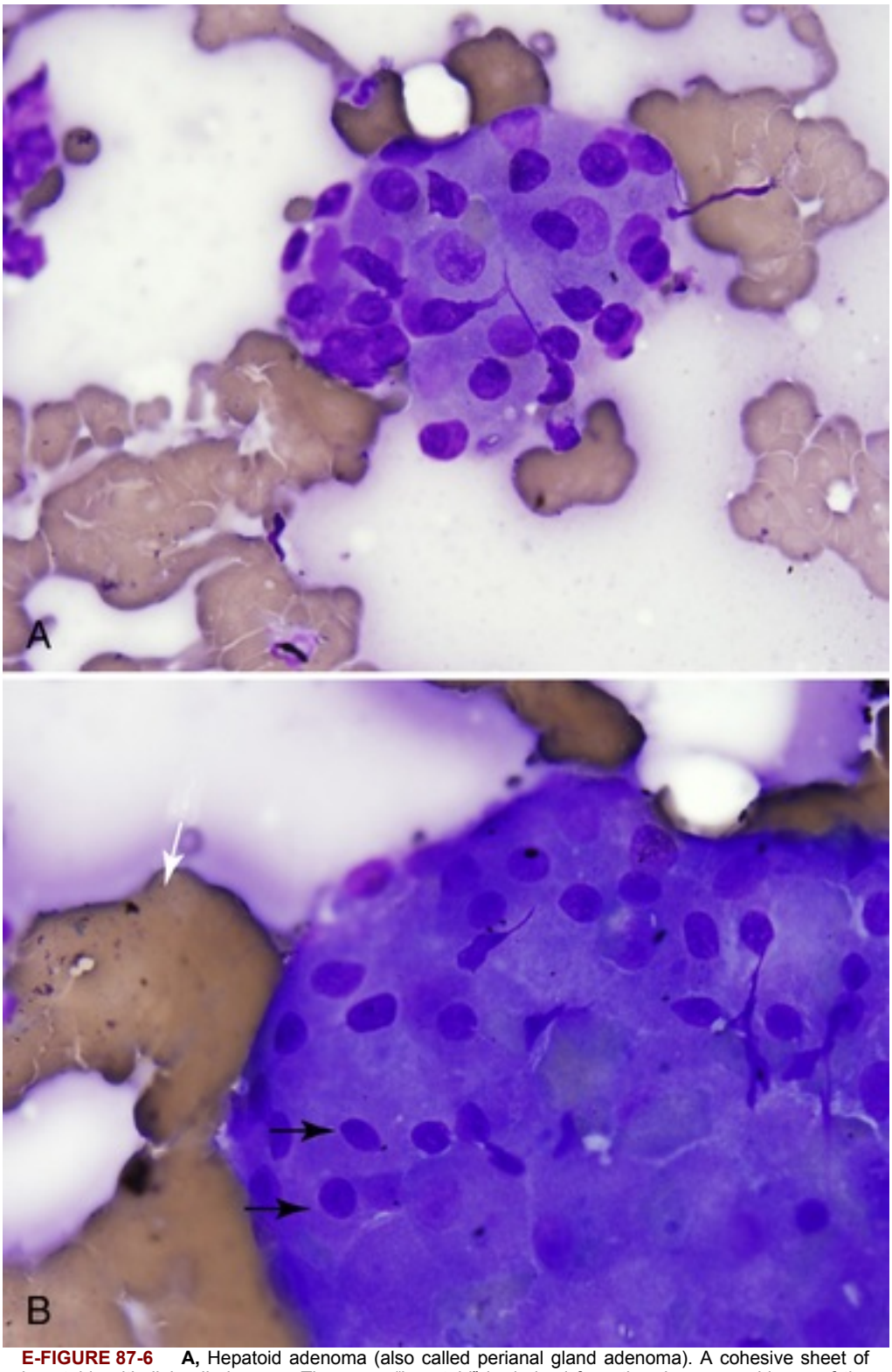
E-FIGURE 87-3 **A,** Histiocytoma. Aggregates of individualized round histiocytoma cells. The cells have moderate nuclear to cytoplasmic ratio with moderately abundant fine, amphophilic, scarcely vacuolated cytoplasm. Nuclei are round in this image, though they sometimes can appear indented or kidney-bean shaped. Modified Wright's stain ×1000. **B,** Regressing histiocytoma. A mixed population of cells is present. Small lymphocytes (black arrows) outnumber the fewer histiocytoma cells (white arrow). Infiltrates of small lymphocytes are “attacking” the neoplastic histiocytoma cells. Regression of cutaneous histiocytomas more often occurs in dogs <2 years of age. Modified Wright's stain ×500.



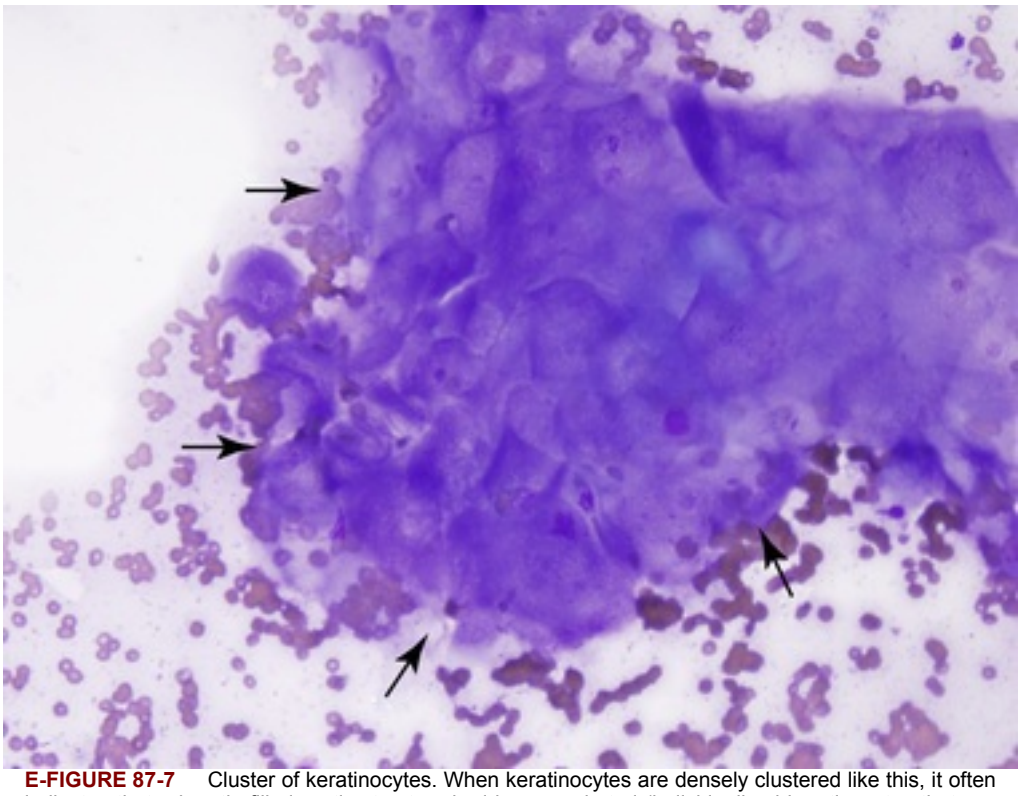
E-FIGURE 87-4 Cutaneous lymphoma. Within an erythrocyte-rich background, several large lymphoid cells are present (white arrows) that approximate or exceed the diameter of nearby neutrophils (black arrows). Note the high nuclear to cytoplasmic ratio of the lymphoid cells. Modified Wright's stain ×1000.



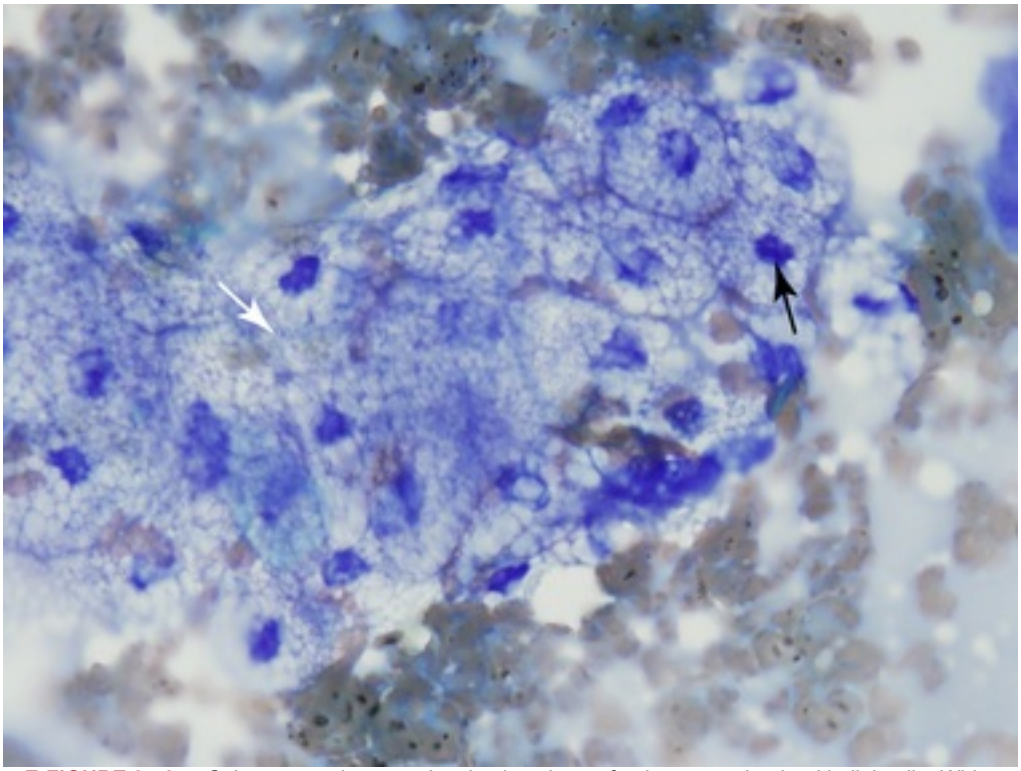
E-FIGURE 87-5 **A,** Cutaneous plasmacytoma. Moderate numbers of aggregated round, neoplastic plasma cells are present. Plasma cells often have an eccentrically placed nucleus within the cytoplasm (arrows). Mild pleomorphism in this population. The lesion was benign. Modified Wright's stain ×1000. **B,** Cutaneous plasmacytoma. There are moderate numbers of aggregated round, neoplastic plasma cells that are markedly pleomorphic. Note marked karyomegaly (black arrows) and presence of a trinucleate form (white arrow). This lesion was also benign. Modified Wright's stain ×1000.



E-FIGURE 87-6 **A,** Hepatoid adenoma (also called perianal gland adenoma). A cohesive sheet of hepatoid epithelial cells is seen. The name “hepatoid” is derived from the close resemblance of the epithelial cells of the perianal gland to hepatocytes. Modified Wright's stain ×600. **B,** Hepatoid adenoma. A dense cohesive sheet of hepatoid epithelial cells is surrounded by dense aggregates of erythrocytes (white arrow). Black arrows indicate small nuclei from basaloid reserve cells that often surround the larger hepatoid epithelial cells. Modified Wright's stain ×1000.

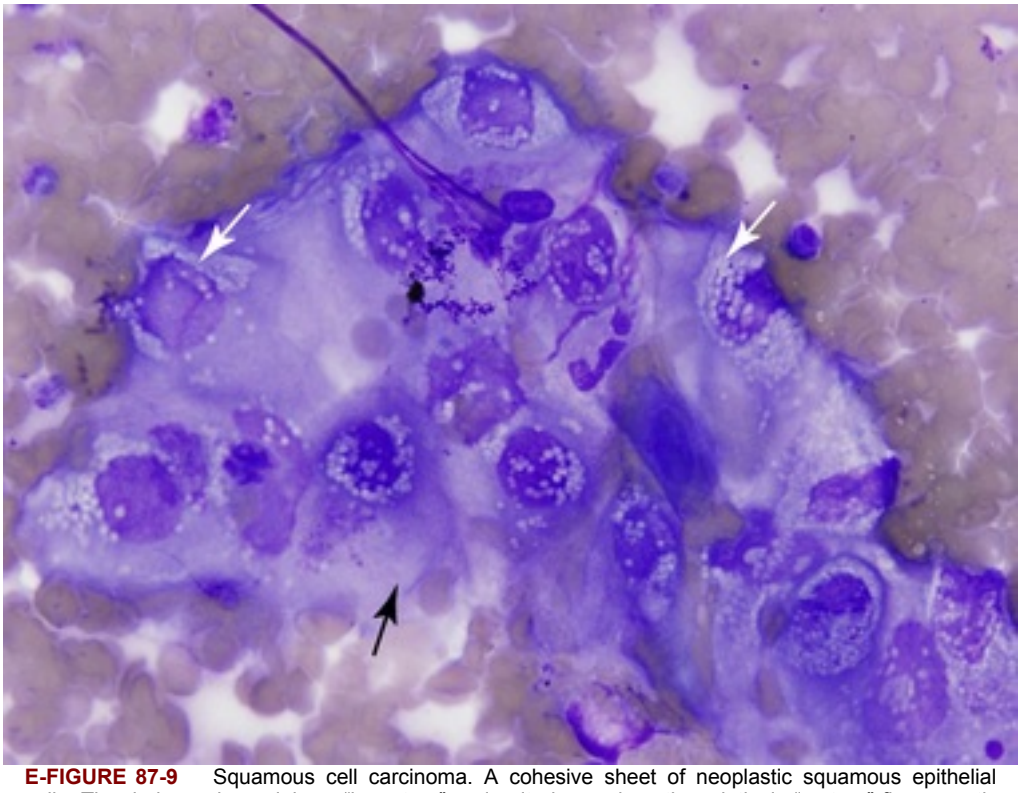


E-FIGURE 87-7 Cluster of keratinocytes. When keratinocytes are densely clustered like this, it often indicates that a keratin-filled cystic structure had been aspirated (individualized keratinocytes that are loosely scattered, by contrast, may reflect surface epidermal contamination). Arrows highlight the edge of the aggregate. Histologic evaluation of a biopsy often is indicated, to assess the wall of the cystic lesion to provide a definitive diagnosis. Modified Wright's stain ×400.

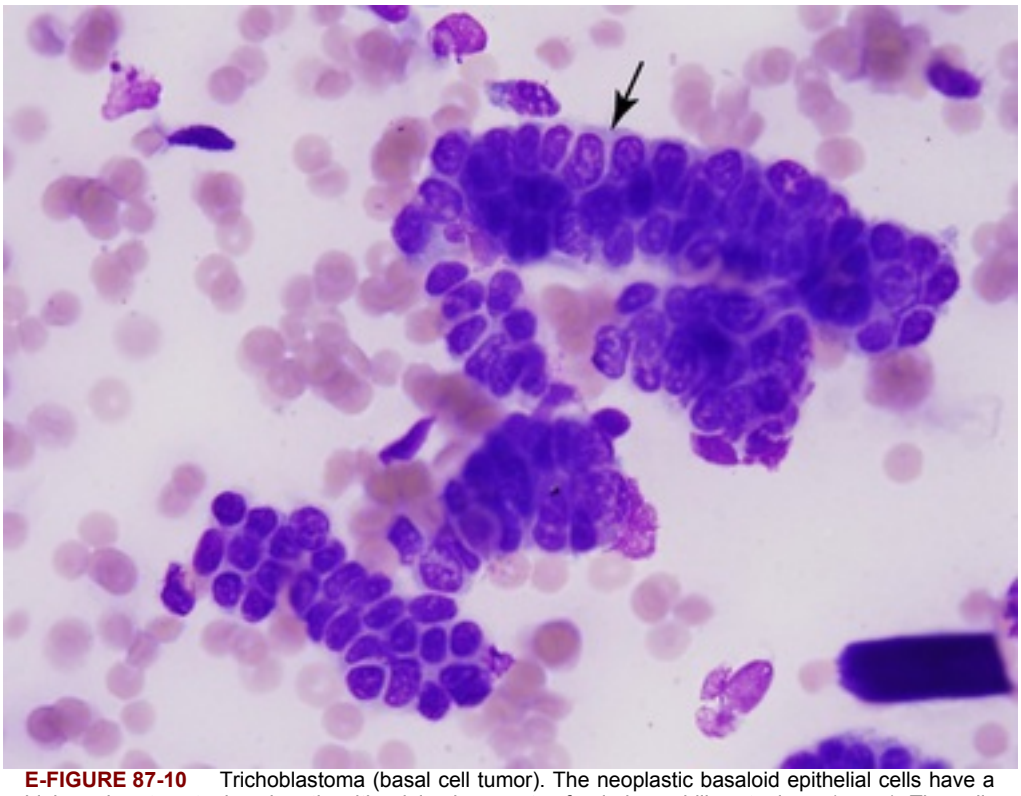


E-FIGURE 87-8 Sebaceous adenoma. A cohesive sheet of sebaceous gland epithelial cells. White arrow highlights the highly foamy cytoplasm. Black arrow highlights round nucleus with condensed

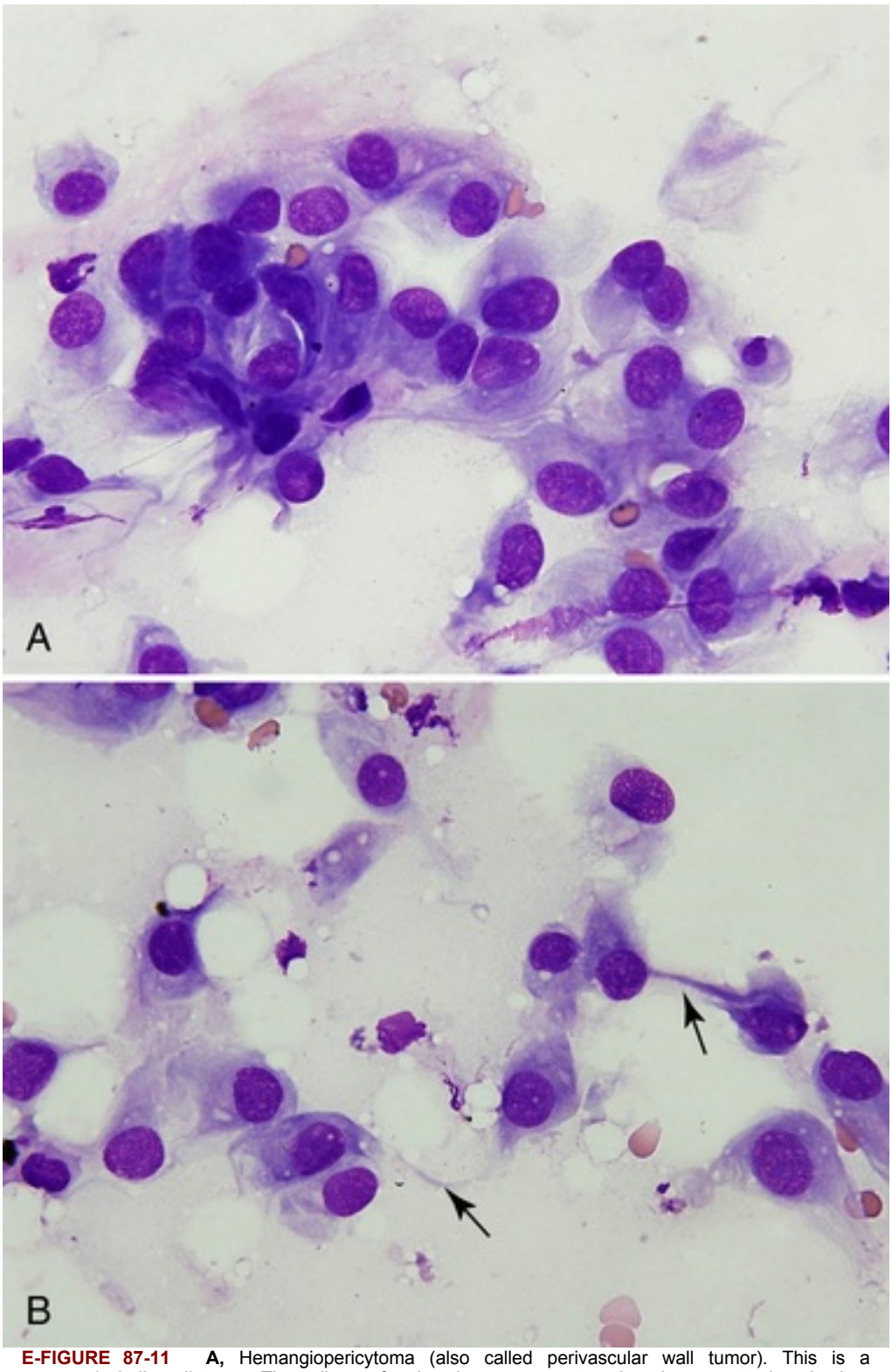
chromatin that is similar to neighboring nuclei. Modified Wright's stain ×600.



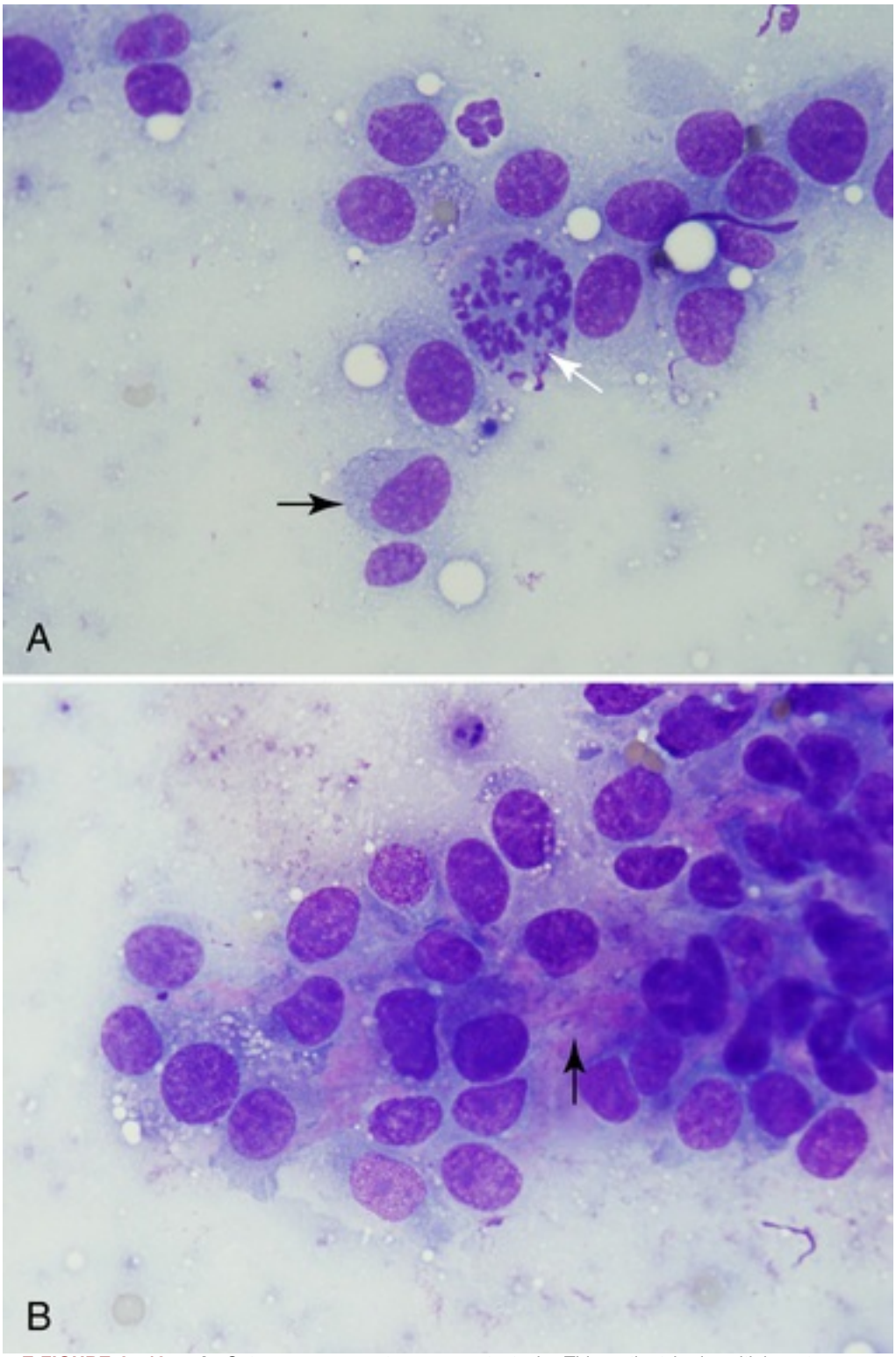
E-FIGURE 87-9 Squamous cell carcinoma. A cohesive sheet of neoplastic squamous epithelial cells. The dark purple nuclei are “immature” and quite large given the relatively “mature” fine smooth peripheral cytoplasm (black arrow). Perinuclear vacuolation (white arrows) often is found in neoplastic squamous cells. These cells can readily individualize and scatter loosely in the background. Modified Wright's ×1000.



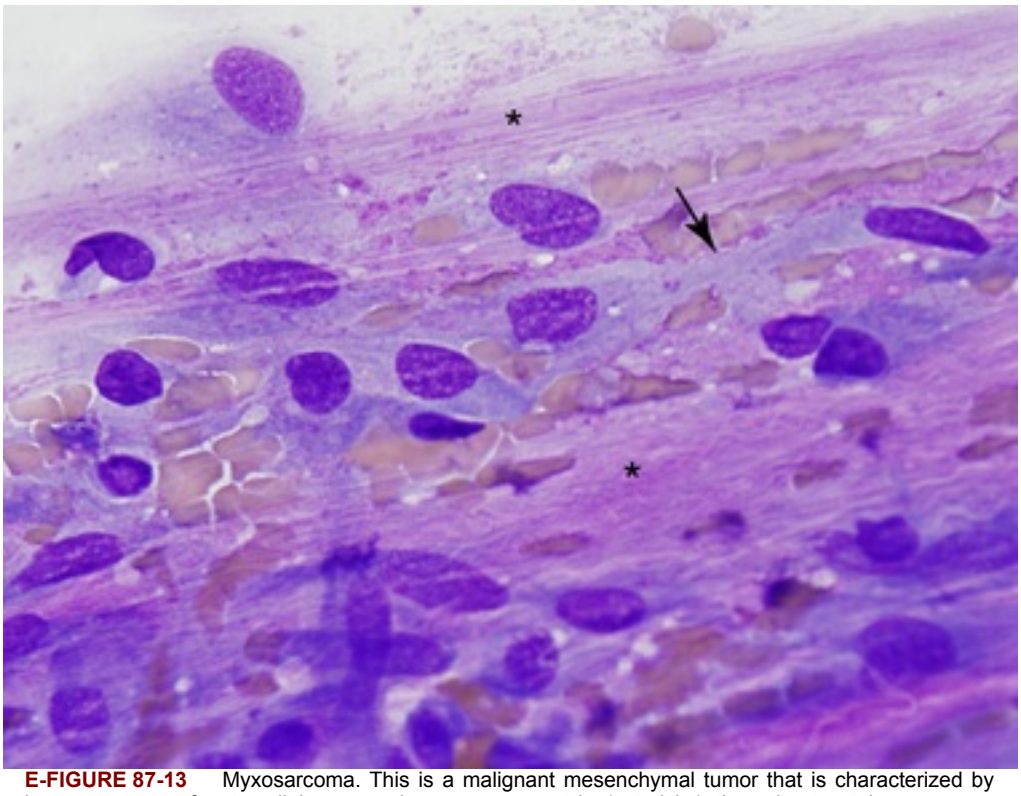
E-FIGURE 87-10 Trichoblastoma (basal cell tumor). The neoplastic basaloid epithelial cells have a high nuclear to cytoplasmic ratio with minimal amounts of pale basophilic cytoplasm (arrow). The cells form tightly cohesive sheets and often there is a “cobblestone” appearance to the sheets. Modified Wright's stain ×1000.



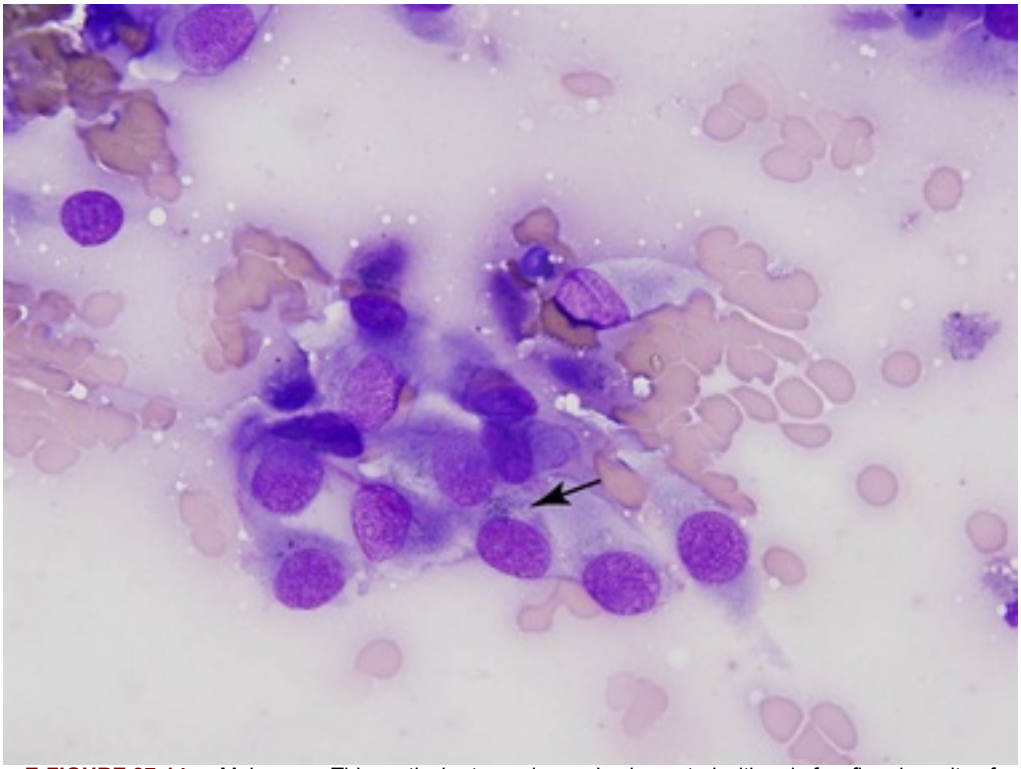
E-FIGURE 87-11 **A,** Hemangiopericytoma (also called perivascular wall tumor). This is a sarcoma/spindle cell tumor. The cells are forming dense aggregates, though are not truly cohesive. Modified Wright's stain ×1000. **B,** Hemangiopericytoma/perivascular wall tumor. Note the fine, tapering cytoplasmic terminations of the tumor cells (arrows). Modified Wright's stain ×1000.



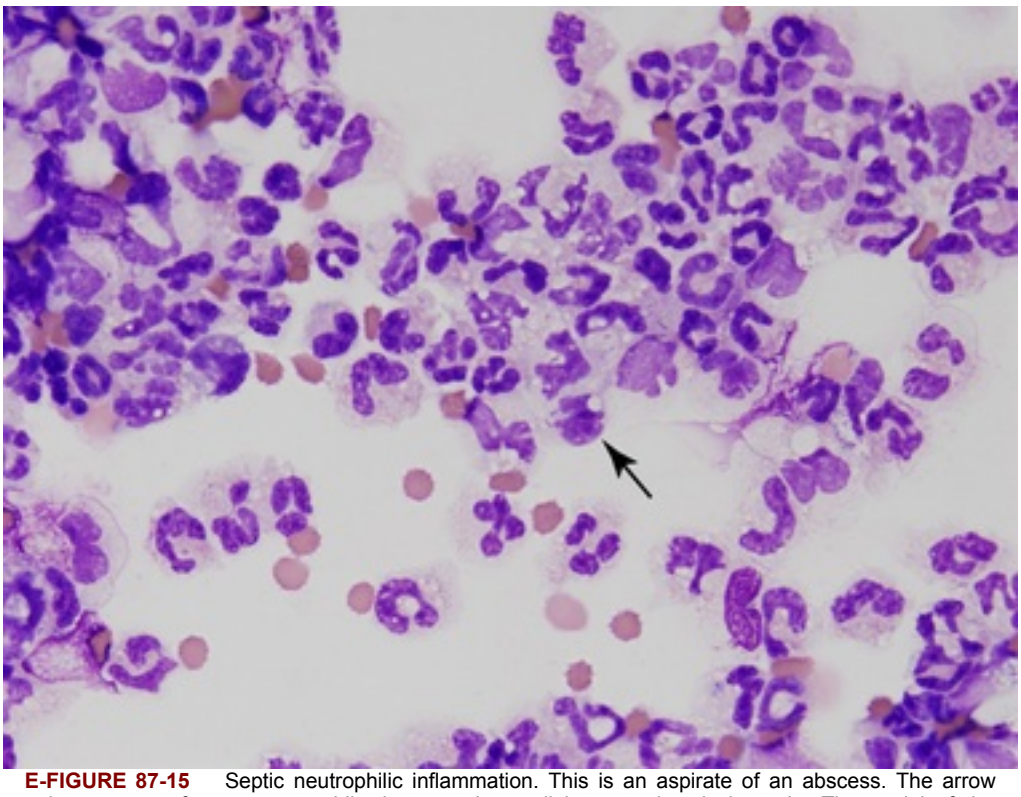
E-FIGURE 87-12 **A,** Osteosarcoma—cutaneous metastasis. This patient had multiple cutaneous metastases of osteosarcoma many months following amputation of a forelimb for previously diagnosed osteosarcoma of the proximal humerus. The tumor cells are round (black arrow) with no classic spindle shaped cells despite the fact that this is a mesenchymal tumor. The white arrow indicates a bizarre mitotic figure. Diff-Quik ×1000. **B,** Osteosarcoma. The arrow highlights magenta streaming extracellular matrix (osteoid) produced by the tumor cells. Diff-Quik ×1000.



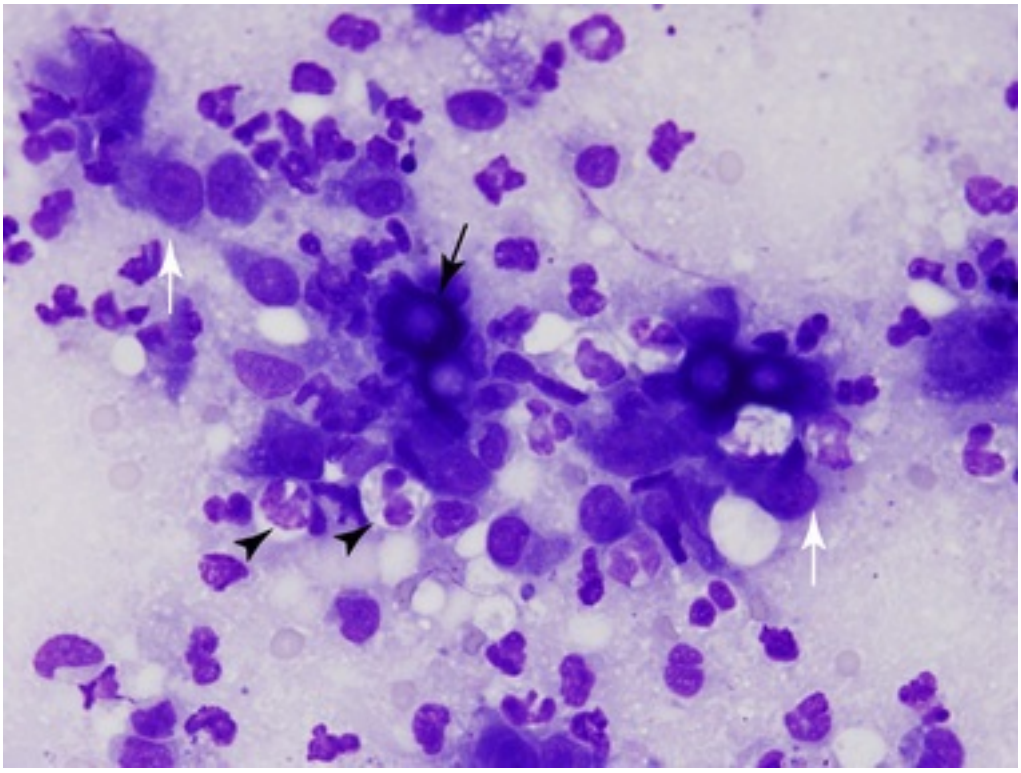
E-FIGURE 87-13 Myxosarcoma. This is a malignant mesenchymal tumor that is characterized by large amounts of extracellular streaming magenta matrix (asterisks) throughout cytology smears. During initial aspiration, the material can appear grossly mucoid. The arrow highlights tapering cytoplasmic terminations of the neoplastic spindle cells. Modified Wright's stain ×1000.



E-FIGURE 87-14 Melanoma. This particular tumor is poorly pigmented with only few fine deposits of intracytoplasmic melanin pigment (arrow). Neoplastic melanocytes often vary in shape, size, and degree of pigmentation. Modified Wright's stain ×1000.



E-FIGURE 87-15 Septic neutrophilic inflammation. This is an aspirate of an abscess. The arrow points to one of many neutrophils that contain small intracytoplasmic bacteria. The nuclei of the neutrophils are mildly swollen with relatively pale chromatin, suggesting degenerative change. Modified Wright's stain ×1000.



E-FIGURE 87-16 Cutaneous blastomycosis. White arrows highlight epithelioid macrophages (found in fungal infections and other chronic inflammatory processes such as with inflammation targeting foreign bodies). Black arrow highlights a *Blastomyces* sp. broad-based, budding yeast among clusters of neutrophils (arrowheads) and macrophages. Modified Wright's stain ×1000.

Many diseases and disorders can be diagnosed by cytopathologic evaluation of FNAs of skin lesions, and several excellent resources prepared by leaders in the field of veterinary cytopathology provide excellent descriptive detail and images of neoplasia, infectious and noninfectious inflammation, hyperplasia, and processes associated with tissue injury in domestic animals.[1,5,6] The reader is encouraged to refer to these resources for more detailed descriptions of specific diseases and conditions. This chapter focuses on optimization of sample preparation and on keys to deriving the best information from an FNA. Ch. 86 addresses technical aspects of collecting samples.

When evaluating a cytology smear, it is essential to view as many of the areas as possible to ensure the interpretation is made using representative cells from a lesion. This requires optimal smear preparation. The contents of a needle are discharged onto one edge of the slide, typically the edge closest to (but not touching) the frosted/labeled edge of the slide. Once the cellular contents are discharged onto the smear, very gentle pressure is all that is required during the smearing process. Overzealous application of pressure can cause cells to rupture, obscuring essential nuclear and cytoplasmic morphology and often precluding an interpretation. Smear the contents to within one-quarter of the opposite edge. The middle one-half of the slide should contain the majority of cells. Automated staining machines used by reference laboratories (modified Wright's stain or some other Romanowsky-type stains) often stain the middle half to two-thirds of the slide and any material outside this portion of the slide would be left unstained by such machines. Quick stains such as Diff-Quik will stain any portion of the slide that contacts the fixing/staining solutions. If a fluid sample is retrieved, a direct smear should be prepared immediately; the remaining fluid should be stored in a sterile tube if culture is desired, and an EDTA tube to prevent cell clotting so that additional smears can be made if needed. The feathered edge often contains large cells/clusters and organisms. Inadequate smearing leads to thick, three-dimensional, crowded clusters of cells, precluding assessment of individual cell morphology (Video 87-1). Appropriate smear technique more often yields excellent quality samples with highly cellular monolayers of intact cells, which increases diagnostic accuracy.

Impression smears of a biopsy specimen (or those made directly from a skin lesion) can provide important cytologic findings. Following collection of tissue, it is important to make a small incision in the superficial surface, avoiding the deep or lateral aspect of the lesion as this can obscure biopsy margins when the tissue is evaluated histologically. If it is possible to collect two tissue samples, one can be used for preparing imprints for cytologic evaluation and the other can be placed in buffered formalin for histologic processing. Impressions of ulcerated areas of a skin mass can yield many cells; however, often there are disproportionately large numbers of inflammatory cells, ruptured cells, and surface bacterial colonies that could mask the primary diagnosis. The impression smears should be kept away from the formalin container once it is opened as even trace amounts of formalin vapors can deleteriously affect the staining quality of the smears. Smears should be submitted in a tightly sealed container to protect the glass from breaking and also to protect from formalin vapors in case a concurrently shipped separate formalin container breaks during transit.

Keys to Consider When Submitting or Evaluating Cytologic Samples

1. When submitting smears to a reference laboratory, a brief yet complete clinical history should be included, as well as the exact anatomic location of the sampled lesion (e.g., clarify whether a site listed as "thoracic mass" indicates a skin mass on the thorax or an intrathoracic or mediastinal mass. If it is a skin mass, is it dermal? Subcuticular? Deeply attached?). This information allows a pathologist to provide the best answer possible.
2. Thorough evaluation of the smear(s). It is important to avoid making a premature diagnosis based on evaluation of only a few fields. Not all fields contain the exact same combinations of cells. Evaluation starts using a low-power objective. Many microscopes have a 4× lens (yielding 40× magnification when combined with the 10× ocular objectives) as the lowest setting. Using the lowest magnification to scan the whole slide allows the examiner to appreciate patterns of cellular arrangements; monolayers of cells can then be evaluated at higher magnification (400×-1000×) for cellular detail. It is important to avoid using high-power objectives initially, as important features on other areas of the slide can be missed.
3. Familiarity with the objective lenses. The 40× lens requires a glass coverslip unless it is an oil immersion lens. If the image is blurry or out of focus when using a dry lens, this could indicate that the objective

contains oil or that a coverslip is required. Glass coverslips can easily be placed over the sample by placing a drop of oil on the slide and then applying the coverslip.

4. Recognition of ruptured cells and avoidance of overinterpretation of their components. Following rupture, cytoplasmic details can become extensively altered and cytoplasmic fragments can sometimes be misconstrued as other elements, such as infectious organisms. Nuclei from ruptured cells can become markedly swollen, leading to spurious anisokaryosis that can be misinterpreted as a criterion of malignancy in an otherwise non-neoplastic population. Avoiding poorly stained areas also is important, as they may contain misleading features.
5. Recognizing artifacts in the background (e.g., stain precipitate, fabric fibers). Conversely, however, relevant "background" material should not be ignored. It could reflect a clinically significant finding (e.g., magenta deposits of extracellular secretory material or connective tissue matrix).
6. Recognizing that poorly cellular smears might not be fully representative of a lesion. Although less common, this also can be true of highly cellular smears.
7. Awareness that more than one type of process could be present.
8. Objectivity in the evaluation and interpretation. Using the essential clinical information that is available is crucial, but premature interpretation based on hasty presumptions also must be avoided.

Septic Versus Non-Septic Inflammation

When evaluating for infectious agents, it is best to become familiar with optimal magnifications to be used when searching for a given type of organism and whether the organism would be expected to be intracellular, extracellular, or possibly both. In general, it is best to follow the rule of evaluating the smear with a low-power objective for areas that contain monolayers containing inflammatory cells. It is helpful to recognize that some patterns of cell collections are more commonly found in certain situations. For instance, if *Blastomyces dermatitidis* infection is suspected, this organism often can be detected initially at 100-200× magnification and, if needed, confirmed at 400× magnification since it is a larger organism (7-15 micron diameter[1]) that is typically surrounded by dense clusters of neutrophils and epithelioid macrophages in variable proportions. The organism remains extracellular with few exceptions where the organism may be within the cytoplasm of a multinucleate giant macrophage. Bacterial organisms, by contrast, are much smaller than fungal organisms (1-4 micron, depending on the organism) and often are found within neutrophils and less often within a macrophage, although extracellular bacteria sometimes can be numerous in a smear. Bacterial organisms can be detected at 200-400× magnification; however, higher magnification (often requiring an oil immersion lens; 500×-1000× magnification) usually is required for detailed morphologic assessment of bacteria. Negative-staining mycobacterial organisms likewise can be both extracellular and intracellular within macrophages. It is worth remembering that in some septic lesions, bacteria are readily visible, whereas in others the organisms may be very few. It is not recommended to completely rule out an infectious component if infectious agents cannot be found in a smear, and appropriate microbial culture should be considered for cases where underlying infection is still a plausible consideration.

Neoplastic Versus Non-Neoplastic Lesions

Many continue to conceptualize lesions strictly as being "neoplastic versus inflammatory," possibly considering that either one process or the other is represented in a smear. In reality it is quite common that neoplastic cells are admixed with inflammatory cells due to a variety of reasons (e.g., necrosis within a tumor and cytokine production by tumor cells that attract inflammatory cells). Thorough evaluation of a smear is important since one may encounter a lesion that has exfoliated mainly inflammatory cells, but closer inspection reveals that smaller numbers of neoplastic cells are present among the inflammatory cells. Depending on whether the cellular yield is fully representative, it is certainly possible that only inflammatory cells exfoliate during an FNA of a neoplasm and that the main neoplastic component of a lesion was not directly sampled. In addition to strictly categorized neoplastic lesions, there is also a collection of less common *reactive* cell proliferations like reactive cutaneous histiocytosis, which is neither truly a clonal neoplastic proliferation nor an infectious process (see ch. 350).

Benign Versus Malignant Tumors

Many cytopathology textbooks list the cytologic "criteria of malignancy" one must consider when evaluating and interpreting neoplastic lesions in order that benign tumors might be differentiated from malignant

tumors. Terms such as *anisocytosis* (variation in cell size), *anisokaryosis* (variation in nuclear size), and *pleomorphism* (variation in overall cellular appearance) are terms that help describe the morphology of a cell population. Recognition of prominent and variably sized nuclei, variable nuclear chromatin pattern, variation in cytoplasmic composition, presence of binucleate/multinucleate cells, and presence of mitotic figures are additional features that provide important information about the expected biologic behavior of a tumor population. In many cases, these features are helpful in identifying a malignant lesion, but there are exceptions. For example, a benign cutaneous plasmacytoma may consist of well-differentiated, easily recognizable plasma cells (monomorphic morphology), but it is common that a benign cutaneous plasmacytoma is populated by very pleomorphic plasma cells that have frequent multinucleate forms and marked anisocytosis and anisokaryosis within the population. These cytomorphologic features can be quite striking, but they may not indicate that the biologic behavior of the tumor is any more aggressive than a plasmacytoma populated by monomorphic plasma cells. Conversely, a classic example of a malignant tumor that has a "benign" appearance is an apocrine adenocarcinoma of the anal sac. This tumor typically is populated by loosely cohesive epithelial cells that have minimal anisocytosis and anisokaryosis, and unremarkable chromatin features with rare mitotic figures; however, the tumor is aggressive, with strong potential for local invasion and distant metastasis. An experienced cytopathologist is aware of exceptions such as these and many others. For this reason, the best outcomes can be reached when clinicians and pathologists have solid working relationships and excellent communication when pursuing a cytopathologic diagnosis.

Types of Neoplastic Lesions

There is a large variety of cutaneous neoplastic lesions. As with any other organ system, the tumor types can be placed into large, general categories of round cell, epithelial, and mesenchymal, noting that within these broad categories, tremendous morphologic variation still exists.

More common canine and feline cutaneous round cell, epithelial, and mesenchymal tumors are listed here, with the respective approximate percentages of all skin tumors (data obtained from different sources), noting that there are other tumor types from these three general categories that occur less commonly and are not listed (Table 87-1).

TABLE 87-1

Prevalence of Canine and Feline Skin Tumors, by Category

	PERCENTAGE OF CUTANEOUS TUMORS	
NEOPLASM	**DOG**	**CAT**
Round Cell Tumors		
Mast cell tumor	16.8%2	16.5%2
Histiocytoma	8.4%2	
Plasmacytoma	1.5%3	Rare
Lymphoma	1%3	2.8%3
Epithelial Tumors		
Squamous cell carcinoma	6%2	10.4%2
Perianal gland adenoma or carcinoma	8-18%3	
Sebaceous adenoma	6.5%2	2.8%2
Basal cell tumor/trichoblastoma	2.6%4	2%4
Hair follicle tumors (trichoepithelioma and similar lesions)	6-7%3	1%3
Mesenchymal Tumors		
Lipoma	9%3	5%3

Fibrosarcoma	1.5%3	17.4%2
Melanocytoma/malignant melanoma	3-4%/0.8-2%3	1.3%/0.4-2.8%3
Hemangiopericytoma	4.4%2-7%3	

Round cell tumors typically are identified on smears by the presence of individualized round cells with round nuclei. Cytoplasmic and nuclear features vary between cell types. In some instances, tumors that are generally classified as "mesenchymal" will have a round-cell morphology. For example, melanoma cells can be found as round, polygonal, spindle and even in cohesive-appearing sheets. Also, there are rare cases of cutaneous metastasis of osteosarcoma and the neoplastic cells in primary and metastatic sites for osteosarcoma can mainly be round.

Epithelial tumors typically are identified by the presence of cohesive sheets, whereas individualized cells occur less frequently (e.g., with squamous cell carcinoma). The cytoplasm can vary in appearance and if the lesion is of glandular origin the cytoplasm may contain secretory vacuoles. With cystic hair follicle tumors and similar lesions, it is common that FNA might yield predominantly dense aggregates of mature anucleate keratinocytes with minimal or no representation of the wall of the cyst, making it difficult to arrive at a specific diagnosis. In such cases, it is important to consider performing a biopsy, as it will allow for architectural assessment of the cyst wall and for presence of additional features such as inflammation in foci where the cyst may have ruptured or even features that might suggest a less common malignancy.

Mesenchymal tumors are identified by the presence of individualized cells that often have spindle or polygonal shape (though round cell forms certainly are possible). The cytoplasmic margins of the cells often are tapered and occasionally indistinct. Nuclei may be round or oval and again, cytoplasmic and nuclear features can vary between lesions. The number of cells that exfoliate with mesenchymal lesions can vary, ranging from sparse to abundant. With high-yield smears, dense clusters of spindle cells can be found; scrutiny often allows the evaluator to realize that the clusters are not truly cohesive. Benign lipomas are included in the mesenchymal category and may be underrepresented in literature reports. Aspiration of adipocyte sheets is a common finding. Interpreting the significance of the adipocyte sheets in absence of a good clinical history is a challenge since aspiration of normal subcuticular fat can have identical cytomorphologic appearance as a lipoma. This is important because if a cutaneous lesion is targeted but the needle misses the mass and only the surrounding subcuticular fat is retrieved, an erroneous diagnosis of a lipoma could be made. If a lesion is clinically suspected to be something other than a lipoma and only adipocytes are retrieved during aspiration, re-collection of an aspirate (or biopsy of the lesion) may be indicated.

When to Biopsy

Since FNA typically can lead to a diagnosis quickly, clinicians often await the results of the FNA prior to deciding whether to collect a biopsy of a lesion. However, both types of samples can certainly be collected and submitted concurrently. If the samples are collected at the same time, the clinician also has the option of preserving the biopsy in formalin and deciding to submit it if the FNA results do not provide a definitive diagnosis. Cytopathologic evaluation has advantages, though a more complete "picture" of a process can be created when cytology smear results are combined with biopsy results. Histologic evaluation of a biopsy does not provide as much detail with respect to individual cell morphology. However, the major advantage is that architectural features can be assessed, which can be highly informative. For example, when pathologists evaluate mammary masses, histologic evaluation is critical since identification of features such as capsular invasion and lymphatic invasion (which cannot be assessed during cytopathologic evaluation of an FNA smear) will distinguish between a benign and malignant lesion if the tumor's cytomorphology is not convincingly definitive.

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Abdomen

OUTLINE

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CHAPTER 88

Abdominal Ultrasonography

Rachel E. Pollard

Abdominal ultrasound has become a common and valuable tool in the diagnostic arsenal for small animal practitioners (also see ch. 143). A fundamental understanding of ultrasound physics and imaging principles can allow the user to make basic diagnoses. Moreover, a consistent and repeatable methodology for performing an abdominal ultrasound examination will minimize errors, omissions, and missed lesions.

Ultrasound Physics

Medical ultrasound functions in a way similar to sonar. A sound beam of a specific frequency (megahertz [MHz]) is sent into the area of interest by the transducer. The transducer waits for the returned echoes and "listens" for their amplitude (intensity) and location (directly related to how long it takes for the echo to return). Once the ultrasound beam enters the area of interest, it can be absorbed, refracted, or reflected. If the beam is absorbed, no ultrasound waves will return to the transducer and, consequently, no information becomes available for generating an image. Similarly, if the ultrasound waves are refracted, their pathway is altered such that they do not return to the transducer. Thus, only ultrasound waves that enter the body, encounter an object (tissue), and are reflected directly back to the transducer are used to generate an image. Highly reflective structures will appear bright (gas, mineral), whereas parenchymal organs will be variable in their reflectivity and appear as shades of gray.

Tissue Characteristics

Most organs are described according to their size, shape, echogenicity (brightness) and echotexture (parenchymal pattern). Size and shape are self-explanatory terms and will not be further discussed. Echogenicity is assessed on a relative scale in comparison to other organs and to what is anticipated as normal. An object or tissue that is anechoic has no echogenicity and is black. An object that is bright in comparison to other objects or the anticipated norm is hyperechoic. An object that is dark in comparison to other objects or the anticipated norm is hypoechoic.

A relative scale of normal tissue echogenicity can be established (Table 88-1). It is essential to compare tissues to one another in order to establish true echogenicity since tissue brightness can also be affected by machine settings. However, using this scale of relative echogenicities, one can define pathologic changes. For example, a fibrotic or fat-infiltrated liver will become more hyperechoic than it should be in comparison to other organs because it has been infiltrated by more hyperechoic tissue. Similarly, an edematous or congested spleen will become more hypoechoic than it should be in comparison to other organs since it contains more fluid than it should.

TABLE 88-1

A List of Tissues in Order of Relative Echogenicity from Darkest (Fluid) to Brightest (Mineral, Gas)

TISSUE	ECHOGENICITY
Water/fluid	Anechoic
Renal medulla	Hypoechoic
Renal cortex	Medium echogenicity
Liver	Medium echogenicity

Spleen	High echogenicity
Prostate	Hyperechoic
Fibrous tissue, fat	Very hyperechoic
Mineral, gas	Most hyperechoic

The assessment of tissue echotexture is more subjective. Most normal organs have a smooth and homogenous echotexture. Changes in echotexture result in a heterogeneous appearance to the tissue, either focally or diffusely, and often accompany a change in echogenicity. Terms to describe diffuse changes in echotexture might include *coarse*, *mottled*, or *nodular* while focal lesions would be described as *complex*, *mixed echogenicity*, or *mass*.

Performing the Complete Abdominal Ultrasound Examination (Video 88-1)

Preparation

Before the ultrasound evaluation begins one must ensure that the animal is comfortable. It is recommended that the ultrasound exam be performed in a dimly lit room with as little traffic as possible. The ultrasound machine is placed adjacent to and to the right of the dorsally-recumbent dog's or cat's head, and the transducer is held in the right hand. Restraint of the pet is typically accomplished by having technicians hold the animal's legs and head while performing the exam. A foam pad cut into a wedge (V-trough) is used as a comfortable positioning device to hold an animal on its back during the examination. In the event that an animal is highly stressed or aggressive or that the ultrasound examination is lengthy, chemical restraint may be indicated.

For adequate ultrasound scanning, hair needs to be clipped from the ventral abdomen to reduce artifacts and provide better visualization of abdominal organs. The hair should be clipped from the xiphoid caudally to the inguinal region with the lateral margins of the clip following the costal arch and extending roughly half way up the flank. Alcohol or a water solution should then be applied to moisten the skin, displace air associated with the hair follicles, and remove the surface layer of grease, which can be present on the skin surface. The final preparation includes applying liberal amounts of coupling gel to the abdomen. This sonographic gel should be manually worked into the shaved skin surface for optimal acoustic coupling.

Getting Started

The image orientation dot or symbol on the screen should be positioned on the left side of the image display. This dot correlates to a mark, line, dot, or light on the transducer. This indicator should be directed toward the head of the animal for the longitudinal scan plane and directed toward the animal's right side (toward the machine and sonographer) for the transverse scan plane. When performing the ultrasound scan, the transducer should not be lifted from the skin when moving to another region; instead slide the transducer along the abdomen until the next area of interest is encountered.

Region 1: The Liver

To begin the scan, the transducer should be placed in a longitudinal orientation adjacent to the xiphoid process with the transducer angled craniodorsally at 60°. This position will give the sonographer a longitudinal image of the liver. Beginning the evaluation with the liver allows images of the liver to be obtained before the dog or cat has an opportunity to swallow air into the stomach. Air has the potential for blocking out some or all of the liver. Additionally, the liver resides in the deepest portion of the abdomen and is normally relatively homogenous. Machine depth, time gain compensation (TGC), and the overall gain can be set appropriately.

Once an adequate longitudinal image of the liver is obtained, the transducer should be angled back and forth from the left to the right to “interrogate” the liver. The gallbladder is best visualized by pointing the transducer toward the animal's right elbow with the transducer just to the right of the xiphoid process. For transverse scanning of the liver, the transducer is rotated counterclockwise so the indicator is toward the animal's right. As with the longitudinal plane, it is recommended to use a “fanning” motion to interrogate the liver instead of making large sliding movements with the transducer. The transducer should then be moved with a sliding motion toward the left to visualize the stomach. Complete evaluation of the stomach is usually

not attainable due to the variable amounts of gas present within the gastric lumen.

Region 2: Left Pancreatic Limb, Spleen, Left Kidney

With the transducer in the longitudinal orientation, the stomach is positioned to the left (cranial) of the display. The area on the caudalmost aspect of the stomach represents the greater curvature and fundic portion of the stomach and is one of the landmarks for the left pancreatic limb. Other landmarks include the splenic vein, spleen, and transverse colon. In the normal animal, the pancreas is not usually visualized.

As the transducer is moved to the animal's left across the abdomen in a caudal and lateral direction, the spleen should be visible in the "near" field. The dorsal extremity of the spleen lies adjacent to the lateral surface of the gastric fundus and can extend into the far field along the left lateral body wall (dorsally). After the dorsal aspect of the spleen is assessed, the display depth can be reduced so as to allow the sonographer to evaluate the more superficial body and tail of the spleen. Either the transverse or the longitudinal plane can be used to evaluate the spleen with equal effectiveness.

The transducer should then be moved caudally in the longitudinal imaging plane along the lateral surface of the abdomen until the left kidney is visualized. Once the left kidney is located, imaging the organ in the longitudinal plane initially is usually easiest and most informative. This plane allows the sonographer to evaluate kidney size and shape along with visualization of the corticomedullary definition. The transducer can then be rotated counterclockwise to produce a transverse kidney image. The transverse plane of the kidney is the most sensitive image for detecting renal pelvic dilation.

Region 3: The Left Adrenal

The landmarks used for the left adrenal are the medial aspect of the left kidney, the left renal vessels, and the abdominal aorta. To locate the adrenal, one must first locate the left kidney in a longitudinal plane and then aim medially to look for the aorta in the far field. By dropping or lowering the proximal portion of the transducer toward the table, the aorta will come into view. The normal adrenal gland lies in close proximity to the lateral wall of the aorta. The renal artery and vein are seen adjacent to the caudal surface of the adrenal and act as the most caudal landmark. When the abdominal aorta is identified in a longitudinal plane, the adrenal can be located by fanning the sound beam dorsally or ventrally. In most animals, it is necessary to increase the hand pressure placed on the transducer to obtain adequate visualization of the adrenal.

Region 4: Urinary Bladder, Prostate/Uterus, Sublumbar Lymph Nodes

The transition to this region requires the transducer to be drawn down the left side of the abdomen in a caudal and medial manner. The descending colon and multiple loops of small intestine (jejunum) are seen during the transition. The urinary bladder is usually easiest to identify in the longitudinal plane; however, in some animals with a small bladder, or a large, gas-filled descending colon, the transverse plane may be the easiest. The complete evaluation of the bladder requires both the longitudinal and transverse planes to be acquired because small bladder lesions such as polyps or early tumors can be easily missed. In the male dog, it is recommended to scan the bladder from both sides of the prepuce in both imaging planes for a complete evaluation. It is best to image the urethra in the longitudinal plane initially and then move to the transverse plane. Hand pressure should be increased slightly as compared to that used for the urinary bladder and the transducer should be kept as close to midline as possible. In most animals the transducer must be angled in the caudal direction 10° to 40° to obtain images dorsal to the pubis. In the intact male, the prostate is hyperechoic (see Table 88-1), symmetrical on either side of midline, oval in shape, with the urethra in its center. The prostate in neutered males is usually quite small and hypoechoic. The remnant of the prostate can be somewhat difficult to visualize in dogs that were neutered at an early age.

The body of the uterus, unlike the uterine horns, is usually visible adjacent to the urinary bladder. The location of the uterine body is somewhat variable but usually dorsal and lateral to the bladder. It is advantageous to locate the uterine body in the transverse plane and then rotate the scanhead to image the uterus in the longitudinal plane.

The iliac (sublumbar) lymph nodes are identified deep (dorsal) to the urinary bladder, where the abdominal aorta branches to become the external iliac vessels and terminal aorta. Visualization of these nodes is inconsistent in the normal animal and depends on technique and machine settings. It is easiest to find the nodes using the transverse plane because this gives the sonographer the best opportunity to visualize the aortic branches. The sublumbar lymph nodes can usually be visualized cranial to and between the vascular branches. The bifurcation of the caudal vena cava is also apparent in the caudal lumbar region on the right

side of the aorta and can be identified based on the ability to compress its lumen with increased transducer pressure.

Region 5: The Right Kidney, Duodenum/Right Pancreatic Limb

During the transition from the region of the bladder to the right kidney one is usually able to visualize more small intestine and the ascending colon. The small intestine lies medial to the region of the right kidney, as does the ileocolic junction. The right kidney lies in a more cranial and lateral location than one would expect. In the dog, the best way to visualize the right kidney is to place the transducer medial to the 13th rib and direct the sound beam cranially and perhaps a bit laterally. In the cat, the right kidney is usually easily seen and can be imaged directly from the right side without the interference of the ribs and the associated costal arch. Complete evaluation of the right kidney consists of both the longitudinal and transverse projections. Transducer pressure should be moderate for evaluation of the kidney, as the overlying small intestine needs to be displaced to limit imaging artifacts secondary to intestinal gas.

The descending duodenum and associated right pancreatic limb are in close proximity to the right kidney. Transducer pressure should be decreased from that used to image the right kidney and the depth of the display can often be decreased to increase resolution. The duodenum is located by fanning laterally from the kidney in the longitudinal plane. The right pancreatic limb is inconsistently visualized in the normal animal and lies adjacent to the medial aspect of the descending duodenum.

Region 6: The Right Adrenal

As with the left adrenal, in order to locate the right adrenal the sonographer must locate the kidney and the great vessels. Landmarks utilized in visualizing the right adrenal gland include the right kidney and the caudal vena cava. Adequate imaging of the adrenal requires the transducer to be directed in a dorsal and medial direction starting from a longitudinal view of the right kidney. This adrenal gland lies parallel to the vena cava and is often seen in the far field adjacent to the wall of the vessel.

Region 7: The Mid-Abdomen

Evaluation of the mid-abdomen includes the mesenteric lymph nodes and the small intestine along with the associated omentum. The technique for the mid-abdomen includes variations in transducer pressure and imaging planes. One should attempt to visualize loops of the small intestine in both a transverse and longitudinal plane.

The mesenteric or jejunal lymph nodes lie in clusters associated with the mesenteric vessels in the mid-abdomen. These nodes are inconsistently visualized in the normal dog but often can be seen in the cat. They are usually in close association with the cranial mesenteric artery adjacent to the body of the second lumbar vertebra. The lymph nodes can be either round or fusiform in shape and often will have the same echogenicity as the spleen. In the young animal, the mesenteric nodes are sometimes easily visualized and can appear prominent.

Summary

As with radiographic interpretation, a good abdominal ultrasound examination requires a solid knowledge of anatomy and a systematic approach. A basic knowledge of physics and tissue characteristics is also useful. The assessment of organ size, shape, echogenicity, and echotexture coupled with an understanding of what causes alterations in these four factors is the basis of all ultrasound diagnoses.

CHAPTER 89

Abdominal Ultrasound

Aspirations and Biopsies

Eric J. Herrgesell

Background

Ultrasound-guided tissue sampling has become a routine procedure in many small animal veterinary hospitals. Percutaneous ultrasound-guided procedures have gained popularity because precise needle placement is possible. This results in a safer collection procedure and a relatively high diagnostic yield. Not only peripheral lesions, but "deep-seated" tissues, can usually be sampled. Compared to blind procedures, ultrasound guidance has greater potential for more accurate diagnosis with less soft-tissue trauma. It is appreciated that ultrasound patterns are generally nonspecific regarding specific diagnoses and samples are required for a definitive diagnosis. In recent years, advancements in ultrasound machine quality and imaging potential have greatly improved the utilization of ultrasound-guided soft-tissue aspirate or biopsy.

One benefit of ultrasound-guided tissue sampling is that general anesthesia is not usually necessary, especially with fine-needle aspiration (FNA) procedures. Heavy sedation or anesthesia may be indicated for core biopsy procedures to minimize movement and pain perception. Decisions regarding use of sedatives or anesthetic agents should be made based on the nature of the patient and the lesion in question (see ch. 138). Usually, short-acting sedatives or anesthetic agents are utilized. One limitation of using ultrasound-guided tissue sampling is that some lesions cannot be adequately visualized. This is often due to superimposed gas or mineral density, either of which may cause significant ultrasound artifact. One should avoid passing a needle through any unrelated organ or tissue to limit hemorrhage or trauma.

In human medicine, a variety of specialized transducers has been developed. These include transesophageal and intracavitary transducers to facilitate diagnostic ultrasound and tissue sampling. When such transducers become more available for veterinary medicine, ultrasound-guided sampling will improve further. The standard transducers readily available in veterinary practice, either curvilinear or linear, are typically utilized for ultrasound-guided biopsy and cytology procedures. In general, curvilinear transducers are superior for deeper tissue sampling due to better orientation and imaging capabilities. Linear transducers are usually excellent for sampling superficial tissues or smaller lesions.

Indications

Evaluation of samples obtained via percutaneous ultrasound guidance can be beneficial in understanding the nature of diffuse parenchymal abnormalities or mass lesions involving one or multiple organs. Ultrasound-guided new methylene blue marking of a specific mass or soft tissue foreign body may be useful. Using ultrasound as "therapy" is mostly limited to drainage of fluid. Obtaining fluid from an abscess, cyst, pleural space, peritoneal cavity, or the pericardial sac can relieve pressure while also providing samples for cytological analysis (see ch. 74, 102, and 111). It is also somewhat common to utilize ultrasound-guided cytology samples to evaluate bone lesions.

Materials

Choosing an ultrasound transducer appropriate for a specific task depends on the type and location of a lesion and the preference of the sonographer. For lesions <2 cm in depth, a linear transducer may be chosen because of its higher resolution and spatial orientation. For lesions deeper than 2 cm, a curvilinear or sector transducer is most often indicated.

Of the cytology needles typically available in veterinary practice, either a 1.5 inch 22- or 25-gauge needle is utilized for tissue sampling. The range of needle size does vary and some practitioners favor 20-gauge needles. However, 25-gauge needles usually provide excellent samples for cytological analysis with less blood contamination. For deeper lesions, either a 2½ or 3½ inch 22-gauge spinal needle can be used.

Core biopsies are typically obtained with a needle containing a stylet and a biopsy port. These specialized needles are available in manual and automated configurations. The biopsy instrument is often a "Tru Cut" needle with numerous variations available. Typical core biopsy needles range from 14- to 20-gauge, providing tissue samples of 1 to 2 cm in length. Shorter core biopsy needles are easier to orient. Typical core biopsy needle sizes include 9 and 15 cm needle lengths, but these may vary. Automated needles, i.e., spring-loaded, usually provide excellent samples. Some ultrasound needles and ultrasound biopsy instruments have echogenic substances pre-attached to the shaft of the needle, providing better needle visualization during biopsy or aspiration procedures. Also, some ultrasound equipment manufacturers provide biopsy guides that attach to a specific transducer. These biopsy guides are not interchangeable. Biopsy guides help with needle placement by reducing motion. However, the biopsy guide may require use of longer needles as these guides are attached to the transducer approximately 2 cm from the patient transducer interface.

Techniques

Safe and successful collection of samples is reliant on placing the lesion within the focal zone of the transducer and on the ability to introduce the sampling device into the lesion. There are three factors of motion that must be considered: the patient, the transducer, and the needle. Patient motion is inevitable due to breathing and other minor movements. Patient movement can usually be limited with sedation or anesthesia. Once the lesion to be sampled is identified, one should place a hand on the patient with the transducer centered over the lesion to reduce some motion. The goal is to have the ultrasound transducer "attached" to the patient. This process is similar to resting the hand above an eye, with a tube in that hand, before applying ointment. Once the transducer is stabilized against the patient, the needle can be advanced into the lesion.

Orientation of both needle and transducer are critical factors in obtaining satisfactory samples with minimal tissue trauma. Transducers usually available for veterinary use have an "indicator." This is either a raised portion of the transducer housing or a light parallel to the crystals within the transducer. The indicator should be aligned with the imaging plane of the transducer. Basically, transducer and needle should form a V (Video 89-1). Advancing the needle in this plane facilitates visualizing most or all of the core biopsy needle length. The tip of the needle can also be visualized within the lesion in question. The goal is to have the lesion centered under the ultrasound transducer in order for the needle to extend through superficial tissues and terminate within the lesion without crossing a visceral structure.

There are numerous techniques recognized and utilized in veterinary practice to collect cytology samples (see ch. 93 and 95). One technique is to place the needle into the lesion and then advance and retract the needle approximately 1 to 1.5 cm, if possible, within the lesion while providing gentle suction. Spinal needles or standard hypodermic needles should be attached to a 3 mL syringe. Once blood or tissue is seen within the hub of the needle, the procedure should be terminated and the slide is prepared. Other methods for obtaining a sample are recognized, including using the needle without a syringe attached. Another procedure involves attaching an "extension set" to the needle, placement of the needle within the lesion, and then using the up-and-down sampling technique. The extension set creates mild negative pressure and can provide adequate cytological samples without employing as much negative pressure. When using a spinal needle, advance the needle into the lesion with the stylus in place. Once the needle is within the lesion, remove the stylus and obtain a sample either with an extension set or use a 3 mL syringe and gentle negative pressure or suction. One should always attempt to avoid passing the needle through multiple organs or viscera to obtain a tissue sample as this can result in unnecessary tissue trauma and complicate interpretation.

The procedure for ultrasound-guided drainage of fluid is similar to obtaining a tissue sample (see ch. 90 and 102). However, once the needle is placed into the fluid-filled space, there is no need for up-and-down manipulation. If a large amount of fluid is to be drained, the practitioner should consider using a three-way stopcock and an extension set (see Video 90-1). The stopcock allows the practitioner to repeatedly fill and empty the syringe by depositing the removed fluid into a container without moving the needle. This helps to avoid air contamination within the cavity/structure being drained while not losing the fluid location. Needle size is dependent, among many factors, on the condition of the patient, volume of fluid to be removed, and its viscosity.

Ultrasound-guided marking of either nodular lesions or, more commonly, foreign body abscess lesions using sterile dye with ultrasound guidance is popular. Soft-tissue foreign body lesions, especially those caused by grass awns, are recognized in various geographic regions. Identification of a lesion that appears compatible with a foreign body abscess or soft tissue granuloma is usually relatively straightforward. Surgical approach and evaluation of such lesions can be optimized with an ultrasound-guided "marker" placed on the lesion. One can inject about 0.1 mL of new methylene blue into the lesion immediately prior to surgical exploration. This technique results in a tissue blush that the surgeon can visualize during an exploratory surgery.

Ultrasound-Guided Procedures

Sedation and Positioning

Commonly, patients are sedated and placed in dorsal recumbency. For biopsy procedures, most clinicians use deep sedation or general anesthesia to reduce movement and pain. For ultrasound-guided core biopsy techniques, a clotting profile may be warranted because of enhanced chance of bleeding. For cytological sampling, the smaller needle causes less trauma and there is less concern about hemorrhage. Decisions regarding pre-procedure clotting profiles should be made on a case-by-case basis. The organs sampled most frequently include liver, spleen, kidney, and lymph nodes. Gastrointestinal mass lesions are also, but less commonly, sampled. The best position for the patient changes if, for example, a soft tissue structure on the lateral aspect of the abdomen is to be sampled.

Liver

Ultrasound-guided sampling from liver parenchyma is usually performed from the left side. The liver can be well visualized, there is adequate hepatic tissue, and one should be able to avoid the gallbladder and major vessels. Adequate visualization of the stomach is necessary via cranial angulation of the transducer and needle/biopsy device. Special attention should be paid to the diaphragm, a recognizable curvilinear echogenic structure cranial to the liver.

In some situations, collection of biliary fluid is warranted and would be performed from the right side of the patient. The approach to the gallbladder is from the ventral aspect of the animal with the needle then introduced into the ventral aspect of the gallbladder. While dependent on hepatic size, the gallbladder is usually cranial and slightly right of midline. If the gallbladder is quite cranial, it may become difficult to sample.

Spleen

Ultrasound-guided FNA of the spleen is commonly performed. Biopsy of the spleen, by contrast, is far less commonly indicated. Any aspect of the spleen can be sampled. Placing the needle is usually based on the spleen's ultrasonographic appearance. Most commonly, the spleen is located on the left and sampled from that side of the abdomen. Splenic vasculature resides on the dorsal, medial aspect of the spleen when the animal in dorsal recumbency. This location limits accidental perforation of the vasculature. An abnormal spleen is often enlarged, providing significant parenchyma for safe sampling.

Kidney

Renal cytology or biopsy may be indicated if there is significant enlargement, loss of parenchymal detail/echogenicity, or a mass. Core biopsy samples should be obtained from the caudal aspect of the kidney. Orientation of the biopsy should be from a medial to lateral approach to aid in avoiding penetration of the dorsal aspect of the kidney where the larger blood vessels are located. Renal cortical biopsies are usually most useful. Biopsy of the cortex and medullary junction can result in significant hemorrhage. Use of Doppler to identify vascular structures prior to biopsy can be valuable. Cytological samples can be obtained from any portion of the kidney. However, the cortex or region of interest should be sampled without extending the needle into the renal pelvis or medial aspect of the kidney to avoid hemorrhage.

Lymph Nodes

Lymph node sampling is common because lymphoma and other round cell neoplasias are frequently

encountered. Since lymphoma is highly exfoliative and because cytology can be confirmative, lymph nodes are usually sampled with FNA (see ch. 95). If a core biopsy sample is needed, Doppler should be employed first to identify the surrounding vasculature. Lymph nodes are usually poorly to moderately vascular. The technique used is similar to that used for obtaining samples from other visceral organs. The lymph node should be centered on the imaging field of the ultrasound transducer and the needle or biopsy instrument advanced to or slightly beyond the central portion of the structure. Transducer pressure can be critically important because lymph nodes are usually somewhat mobile within the abdomen.

Complications

Complications related to obtaining tissue samples via ultrasound guidance are fairly uncommon. Reduction of complications is reliant upon the skill and experience of the sonographer/clinician. The most common complication is hemorrhage. Less commonly, peritonitis may follow inadvertent perforation of the gastrointestinal tract. Neoplastic lesions involving the lower urinary tract, specifically transitional cell neoplasia, can be accidentally seeded into the abdomen. One should not use ultrasound guidance for sampling most lower urinary tract mass lesions.

CHAPTER 90

Abdominocentesis and Diagnostic Peritoneal Lavage

Oriana Raab

Abdominocentesis

Definition and Purpose

Abdominocentesis is the percutaneous removal of abdominal fluid using a needle or catheter. The procedure is routinely performed for diagnostic and therapeutic purposes.

Abdominocentesis can be carried out to obtain fluid for analysis if there is a high suspicion of effusion based on physical examination or if imaging indicates its presence. Analysis of abdominal fluid can aid in the diagnosis of abdominal hemorrhage, neoplasia, sterile or septic peritonitis, and hollow organ (gallbladder, gastrointestinal tract, uterine, or urinary tract) rupture (see ch. 74).[1] Abdominocentesis can also be performed to remove large amounts of fluid from patients that are experiencing effusion-related clinical signs such as dyspnea, inappetence, and signs of abdominal discomfort.

Contraindications and Considerations

Before performing abdominocentesis, the clinician should consider the benefits versus the risks of the procedure, particularly when a blind puncture is to be attempted. Abdominocentesis should be performed with caution in patients with hemostatic abnormalities. In these cases, percutaneous insertion of the needle or catheter along the avascular midline using ultrasound guidance can help to minimize bleeding. Close monitoring is recommended following the procedure.

Structural impediments to the safe introduction of a needle or catheter can include the gravid uterus, distended urinary bladder, distended intestine, or a large abdominal mass. Gentle manual expression or urethral catheterization should be performed prior to abdominocentesis in patients with extremely large urinary bladders. The intestine typically floats in abdominal fluid and will generally move safely out of the way of a slowly advancing catheter.

Abdominocentesis should be performed after radiographic and/or ultrasonographic evaluation has been completed. Without prior imaging, it can be difficult to determine whether free air present in the abdominal cavity was introduced iatrogenically during the procedure or whether it was caused by pathologic rupture of a hollow organ.[1,2]

Complications of Procedure

Complications including hemorrhage, local infection or peritonitis, and intestinal perforation, are uncommon; however, they can be minimized with the use of ultrasound guidance. The risk of a subcutaneous hematoma can be lessened by avoiding needle or catheter placement in the vicinity of the caudal superficial epigastric vessels, which lie paramedian and adjacent to a longitudinal line drawn between the nipples.[2] The use of an over-the-needle catheter rather than a hypodermic needle can also help to decrease the risk of penetration or laceration of an organ or blood vessel and minimize the chance of false-positive results[3]; however, the use of a catheter in thicker-skinned or obese patients, or those with extensive body wall movement (e.g., panting dogs) could lead to kinking of the catheter, making it ineffective.

Sedation/Analgesia

Abdominocentesis typically is performed in conscious animals using physical restraint. The use of a sedative could be warranted depending on the patient's temperament. The administration of an analgesic or

instillation of a local anesthetic in the region where the needle or catheter is to be placed should be considered, particularly when large-gauge catheters are utilized or when diagnostic peritoneal lavage is performed.

Sample Collection

Collection tubes that should be available during fluid sampling include EDTA (lavender top) tubes for cytologic analysis, total nucleated cell count, protein measurement and packed cell volume; and plain (red top) tubes and culturette swabs for biochemical analysis and bacterial culture and sensitivities. Additional tests can be performed depending on the clinical circumstances (see ch. 17).

Preparation, Equipment and Techniques

There are several acceptable methods for obtaining a sample of abdominal fluid. Ultrasound should be utilized whenever possible to confirm the presence of abdominal effusion and to guide needle placement for fluid aspiration (see ch. 143). If ultrasound is unavailable, a single blind puncture or four-quadrant technique can be performed. However, it is important to remember that blind abdominocentesis might be unsuccessful in patients with small volumes of abdominal fluid, or in patients with effusion confined to the retroperitoneal space.

Regardless of the technique chosen, patient preparation is the same. The ventral abdomen should be clipped free of fur and surgically prepared using antiseptic scrub and isopropyl alcohol. The individual performing the procedure should wear sterile gloves to ensure asepsis.

Depending on the size of the patient, a sterile 18- to 22-gauge, 1 to 1.5 inch (2.5-4 cm) needle or 16- to 22-gauge over-the-needle catheter may be utilized. If a catheter is utilized, prior to the procedure, 2 to 4 small fenestrations can be made in staggered positions at the distal third of the catheter using a sterile #10 or #11 scalpel blade (Video 90-1). Fenestrations should be no larger than one third of the catheter circumference and should be spaced far enough apart so that they do not weaken the shaft and lead to catheter breakage.[2] The creation of fenestrations lessens the chance of obstruction of the catheter by loose tissue such as omentum and increases the likelihood of obtaining a fluid sample.[3,4] Considerably lower false-negative results can be expected with the use of a dialysis catheter or fenestrated over-the-needle catheter, which have multiple side holes, rather than a hypodermic needle, which has a single end hole.[3,4] Additional equipment needed includes an appropriate sized syringe and collection tubes.

Simple Ultrasound-Guided Abdominocentesis

The patient may be placed in dorsal or lateral recumbency. The ultrasound transducer should be kept sterile via the use of a sterile sleeve or aseptic preparation. Using ultrasound guidance, a needle or over-the-needle catheter of appropriate size is directed percutaneously into a fluid pocket and the contents are gently aspirated.

Simple Blind Abdominocentesis

The patient may be placed in lateral recumbency or the procedure may be performed with the patient standing. A needle or over-the-needle catheter of appropriate size is percutaneously inserted on the ventral midline approximately 2 to 4 cm caudal to the umbilicus. Alternatively, the needle or catheter is inserted 1 to 2 cm to the right of the midline to avoid splenic penetration. A syringe of appropriate size is attached for gentle aspiration (closed method) or the needle or catheter is inserted, gentle abdominal compression is applied and fluid is collected from the hub without attaching a syringe (open method).[3]

Blind Four-Quadrant Abdominocentesis

If simple blind abdominocentesis is unsuccessful, a blind, four-quadrant technique may be attempted. The patient may be placed in dorsal or lateral recumbency, or with cooperative patients, some clinicians perform this technique with the animal standing, to increase fluid yield through gravitational draw of fluid ventrally. Using the umbilicus as the center point, a needle or over-the-needle catheter of appropriate size is inserted into the cranial dependent quadrant, the cranial nondependent quadrant, the caudal dependent quadrant and the caudal nondependent quadrant (or equivalent sequence if the patient is dorsally recumbent or standing).

Fluid may be collected via an open or closed method as described above. Placing needles (without attached syringes) in more than one quadrant at a time provides an air vent that may allow fluid to flow. Any positive tap in any quadrant completes the procedure.[2]

Large Volume Abdominocentesis

Patients who are hemodynamically stable but experiencing respiratory compromise or discomfort may have larger amounts of fluid removed to alleviate their clinical signs. The technique is identical to that of a simple abdominocentesis described previously except that a larger bore over-the-needle fenestrated catheter is used. Once the catheter is inserted, sterile extension tubing and a syringe with a 3-way stopcock are attached to permit aspiration and removal of abdominal fluid (Figure 90-1; see Video 90-1).

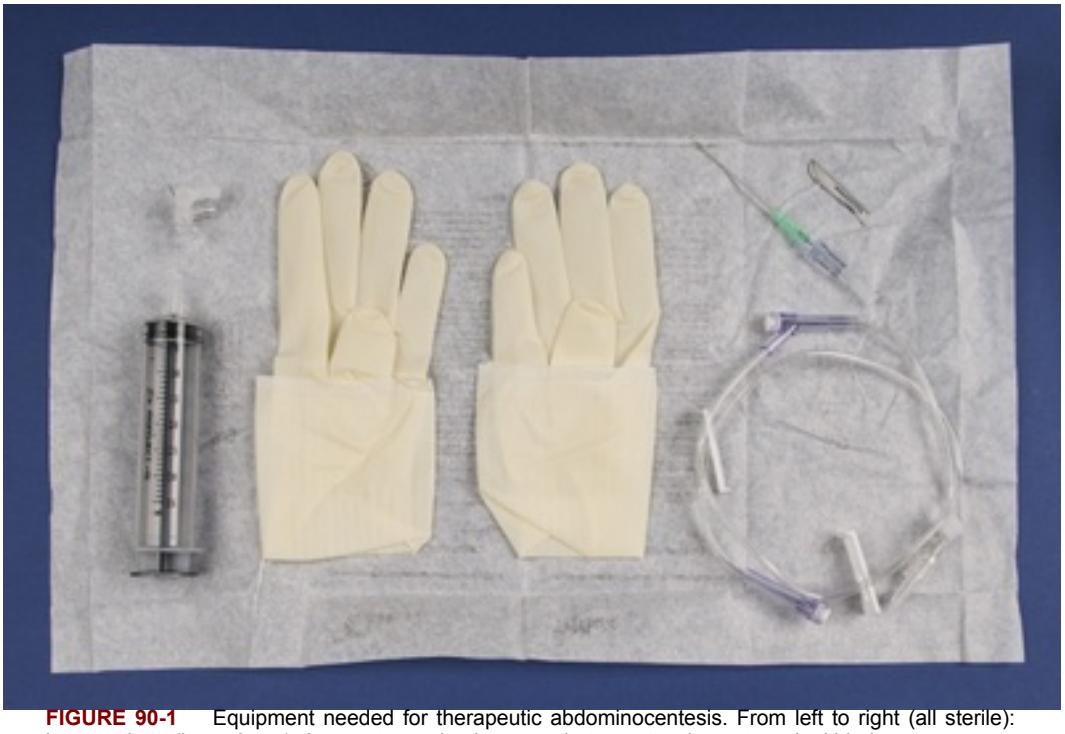

FIGURE 90-1 Equipment needed for therapeutic abdominocentesis. From left to right (all sterile): large syringe (here, 35 cc), 3-way stopcock, gloves, catheter, extension set, scalpel blade.

The main safety concern with large-volume abdominocentesis is hemodynamic changes; blood pressure initially falls as intra-abdominal pressure decreases.[5] However, relief of intra-abdominal hypertension can confer hemodynamic and constitutional benefits (e.g., improved appetite and demeanor) in patients with tense ascites. Although the procedure uncommonly leads to pronounced hypotension, blood pressure assessment (see ch. 99) may be performed following the procedure. There is no consensus with regards to fluid withdrawal rate.

Diagnostic Peritoneal Lavage

In cases in which the fluid pocket is too small or in a location that cannot be safely aspirated, or when peritonitis or other effusive disease is suspected, diagnostic peritoneal lavage (DPL) is an alternative to abdominocentesis. Historically, lavage (using a dialysis catheter or fenestrated over-the-needle catheter) was superior to blind abdominocentesis for detecting free intra-abdominal blood and other materials such as bile, urine, chyme, feces and exudate[6]; however, centesis techniques could yield superior results when performed with ultrasound guidance (see ch. 143). As with abdominocentesis, radiographs or ultrasound should be performed prior to DPL as the procedure can confound subsequent imaging by the iatrogenic introduction of fluid and possibly air into the abdominal cavity.[7] The urinary bladder should be emptied prior to the procedure to avoid inadvertent trauma to the bladder. If the patient cannot void on its own, gentle manual expression or urethral catheterization should be performed.

The patient is placed in lateral or dorsal recumbency. Conscious sedation and analgesia are provided. The ventral abdomen is clipped free of fur and aseptically prepared. Local anesthetic is then infiltrated into the midline skin and body wall, 2 to 3 cm caudal to the umbilicus. A small release incision is made in the skin with a #10 or #11 scalpel blade. Using aseptic technique, including sterile gloves, a commercial DPL catheter (or 14-gauge to 16-gauge fenestrated 2.5- to 5.5-inch [8-18 cm] over-the-needle catheter, or a fenestrated 18-gauge, 2-inch [5 cm] over-the-needle catheter in cats and very small dogs) is inserted percutaneously into the abdominal cavity.[6] After the peritoneum is penetrated, the catheter is carefully advanced in a dorsocaudal direction while the stylet is withdrawn. If the catheter does not advance easily, it could still be in the subcutaneous tissue or against an organ, and it should be repositioned. If fluid drains freely from the catheter, samples should be collected. If no fluid drains, once the catheter is seated to the hub, sterile extension tubing is connected and sterile, warmed physiologic saline (20 mL/kg) is infused into the abdominal cavity by holding the saline bag above the patient to counter intra-abdominal pressure. The catheter is then occluded with a sterile injection cap. After taking precautions to secure the catheter, the abdomen is massaged or the animal is gently rotated from side to side to distribute and mix the fluid in the peritoneal cavity. The patient is then turned on its side and a sterile collection system is attached to the catheter; the bag is placed at a level below the patient and the effluent is collected via gravity drainage. If no fluid is obtained, a syringe may be attached to the catheter for gentle aspiration. Samples of the obtained fluid are then submitted for cytologic, microbiologic and/or biochemical analysis. Complete removal of the infused fluid is not necessary and typically is not possible.

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CHAPTER 91

Laparoscopy

Keith Richter

Client Information Sheet: Laparoscopy

The use of laparoscopy for diagnostic and therapeutic purposes has increased tremendously in human and veterinary medicine during the last 15 years. This acceptance of laparoscopy stems from technologic advances in equipment, improved access and training, and superior results for many procedures achieved with this less invasive modality. Many of the procedures will gain acceptance due to their ease, effectiveness, and reduced morbidity. Advantages of laparoscopy over open surgery include less postoperative pain, a lower infection rate, improved visualization in many cases, and a shorter hospitalization time. Laparoscopy also has some advantages over other minimally invasive procedures, such as ultrasound and ultrasound-guided biopsy.

Equipment

Light is transmitted from a remote light source via a fiberoptic light cable to the rigid fiberoptic laparoscope (telescope). Size and viewing angles of laparoscopes vary. A forward-viewing (0°), 5.0-mm outer diameter, 35-cm long scope is preferred for most dogs and cats. Since most laparoscopic instruments are also 5 mm in diameter, this provides versatility by allowing the scope and instruments to be interchangeable with the same size cannula. Smaller scopes have a smaller image with less field of view. In addition, a greater light intensity is needed for smaller scopes. Scopes up to 10-mm diameter can also be used. Though these have slightly better image quality and allow more light than 5-mm diameter scopes, the difference is small and they only provide an advantage in quite large dogs. Scopes are available in various degrees of angulation of view, including 0° (direct forward viewing) up to 70°. The 0° angle is easier to use and generally preferred for most procedures. A 30°-angle scope can be used to view structures to the side of the tip, and through rotation, to expand the field of view. Angled scopes are more difficult for inexperienced operators with regards to spatial orientation. Most scopes have no biopsy channel. Operating scopes have a 5- or 6-mm channel, with an eyepiece extending from the proximal end. These scopes allow introduction of instruments through the same puncture as the scope. The disadvantage of operating scopes is the limited ability to manipulate instruments passing through the channel. Usually the accessory or secondary puncture technique is preferred (see below).

Video capabilities can be achieved with a handheld charged coupling device (CCD) video camera mounted on the eyepiece. These cameras have high resolution, magnify images 5 to 15 times, and provide a clear image. The use of video is essential for operative laparoscopy. A bright light source (usually 150 to 300 watts) is required to adequately illuminate the abdomen.

To visualize abdominal structures, a pneumoperitoneum must be created. This lifts the viscera away from the abdominal wall and is accomplished by insufflating gas through tubing attached to a Veress needle. The latter has a spring-loaded blunt inner portion and an outer cannula with a sharp point. The sharp point is used to penetrate the abdominal wall; then the inner blunt portion is protruded past the sharp point and left in that position to avoid traumatizing abdominal viscera. The abdomen can then be continually insufflated as needed to complete a procedure. Carbon dioxide (CO_2) is the gas recommended because it is rapidly absorbed, minimizing the risk of air embolism. The latter is a reported complication of laparoscopy using nitrogen, which is absorbed more slowly than CO_2.[1] Room air is the slowest gas to be absorbed. The disadvantage of CO_2 is that it is slightly more irritating to the peritoneal surface and therefore requires a slightly higher plane of anesthesia. Gas is infused with an automatic insufflator. These devices regulate flow rate and intra-abdominal pressure. Initial infusion of gas should be slow (1 L/min) to allow gradual accommodation to the increased intra-abdominal pressure. Once optimal insufflation pressure is reached, a higher flow rate can be used to maintain the desired pressure. Ideally, intra-abdominal pressure should not

exceed 10 mm Hg (cats and small dogs) to 15 mm Hg (large dogs). In most cases, arterial blood gas parameters remain within acceptable limits.[2] Excessive abdominal pressure decreases venous return to the heart and causes decreased ability to ventilate.

The laparoscope is introduced into the abdomen with the use of a trocar/cannula assembly. The cannula is a metal or hard plastic sleeve with a one-way valve that permits passage of instruments (such as the trocar, laparoscope, and accessory instruments) and prevents gas escape. The trocar is a sharp-pointed stylet that is used to penetrate the abdominal wall. It is removed, leaving the cannula in place so that the laparoscope can then be introduced. Accessory puncture sites are made for additional trocar/cannula assemblies, which allows introduction of blunt metal probes, suction tips, cautery instruments, grasping forceps, "spoon," or "clamshell" style (oval cup) biopsy forceps, and a wide variety of surgical instruments. These instruments are elongated, narrower versions of standard surgical instruments. Laparoscopy can guide the insertion of needle biopsy instruments for sampling kidney and other deep tissues. They are inserted directly through the abdominal wall without the need for a cannula. The use of stapling equipment has enabled surgeons to perform procedures such as vessel ligation and bowel resection.

Indications for Laparoscopy

Common indications for laparoscopy are for hepatobiliary evaluation. Laparoscopy allows procurement of large specimens (similar in size to surgical biopsies) using a 5-mm "spoon" or "clamshell" forceps. This approach yields tissue of superior diagnostic quality as compared with needle biopsies. The latter has an approximate 50% concordance with histologic findings from surgical biopsies.[3] Furthermore, the ability to visualize the liver gives the clinician a better feel for pathologic processes. Additional indications for laparoscopy are listed in Box 91-1.[4-29]

Box 91-1

Indications for Laparoscopy

- Biopsy of the liver, pancreas, kidney, spleen, prostate, intestine, mesentery, omentum, and the parietal peritoneum[4-13]
- Stage abdominal tumors
- Guide aspiration of the gallbladder, loculated ascites, abdominal cysts or abscesses[7]
- Guide transabdominal intrauterine artificial insemination[7]
- Evaluation of abdominal trauma
  - Hepatic and splenic laceration, diaphragmatic hernia, bladder rupture, renal rupture, abdominal hernia
- Variety of surgical procedures[14-29]
  - Ovariectomy/Ovariohysterectomy
  - Gastropexy
  - Cholecystectomy
  - Cystic calculi removal
  - Adrenalectomy
  - Splenectomy
  - Cryptorchid removal
  - Jejunal feeding tube placement
  - Bowel resection
  - Nephrectomy

Technique

It is preferred to perform laparoscopy with the animal under general anesthesia. The position of the dog or cat and location of the various puncture sites will depend on the procedure, size of patient, and organ being examined. Because the liver is the most common organ examined and biopsied, this procedure will be described in detail.

Laparoscopy-Guided Liver Biopsy (Video 91-1)

The main advantage of laparoscopy-guided biopsy is the ability to obtain large biopsy samples and to visualize the liver, biliary tree, and other abdominal organs. With experience, the gallbladder can be examined, palpated with a blunt probe, and the bile duct traced to its entry into the duodenum. In this manner it can be determined whether a common bile duct or cystic duct obstruction exists. In addition, because focal lesions of the liver can be directly visualized, an appropriate biopsy site can be selected while avoiding other intrahepatic structures (gallbladder and portal vessels). Hemorrhage can be observed and, when excessive, controlled with direct compression with a blunt probe over the biopsy site. Alternatively, electrocautery or application of a hemostatic material (Gel-Foam) can be used to control hemorrhage. Compared with laparotomy, much less anesthetic time is usually required. A complete laparoscopic examination can be completed and multiple hepatic biopsies obtained in 10 to 15 minutes. Because only a 0.5- to 1.0-cm incision is made, less risk exists for wound dehiscence and infection.

The animal is placed in left dorsal oblique recumbency at a 45° angle. This position allows visualization of both sides of the liver, gallbladder, bile duct, pancreas, duodenum, and much of the abdominal viscera. It avoids the falciform ligament which might be encountered with a midline approach. The puncture sites should be surgically prepared and draped. The Veress needle (for insufflation) is inserted through a small stab incision (using a No. 11 blade) on the midline just to the right of the umbilicus. Prior to insufflation, the Veress needle is aspirated to confirm that no viscus has been entered. Saline (6 to 8 mL) is then infused to ensure free flow into the abdominal cavity. The abdomen is then insufflated with gas to an appropriate pressure as determined by a pressure gauge on an automatic insufflator (see above) or when the abdominal wall is tympanic to the touch. Once the desired degree of pneumoperitoneum is attained, a 0.5- to 1-cm skin incision is made on the right lateral abdomen between the last rib and the flank. The incision is adjusted in a cranial direction for larger animals, in a caudal direction for smaller animals, and should take into account the size of the liver. The trocar and cannula assembly is then "popped" into the abdominal cavity with a twisting motion. Extending the forefinger down the shaft of the cannula or grasping the cannula ≈3 cm from the tip with the free hand will prevent inadvertent insertion of the assembly too far into the abdomen. The trocar is removed and laparoscope inserted into the abdominal cavity through the cannula. The remote light source is connected to the laparoscope with a fiberoptic cable and the liver examined. The insufflation line is then switched from the Veress needle to this cannula. The Veress needle is removed, its incision extended to 0.5 cm, and a second cannula is introduced under direct visualization. This allows introduction of a blunt probe, which can be used to palpate the liver and gallbladder. The probe should also be used to lift up each lobe of the liver to examine the dorsal surface and to move omentum aside in order to trace the bile duct to its duodenal entry point. The right limb of the pancreas should also be examined.

Once the abdomen has been examined, a suitable place on the liver is selected for a biopsy site. The author prefers using a laparoscopic "spoon" or "clamshell" type of biopsy instrument. This can be placed through the same accessory cannula as the blunt probe, thus avoiding an additional puncture site. This type of instrument results in less hemorrhage than biopsy needles and obtains much larger specimens. Repeated twisting of the shaft or retracting the closed jaws into the advanced cannula will prevent ripping of liver tissue and result in less bleeding. The number of biopsies obtained depends on the risk of bleeding and the anticipated need of adequate tissue. Multiple samples from various areas of the liver are recommended (observing for hemorrhage after each sample). Often, liver biopsy specimens are obtained for histopathologic examination, aerobic and anaerobic culture, and heavy metal (copper, zinc, iron) quantification. If excessive bleeding occurs, the blunt metal probe is used to put direct compression over the biopsy site. Suction can also be applied to clear the field if bleeding cannot be adequately assessed. If bleeding is not controlled, an electrocautery probe can be used to stop the bleeding. Alternatively, laparoscopic forceps can be used to place a piece of a hemostatic material (Gel-Foam) on the bleeding biopsy site. Once the biopsy samples are obtained, the clinician completes the procedure by removing all instruments, evacuating all the gas through opened cannula valves, and suturing the puncture sites. More detailed descriptions of laparoscopic liver biopsy techniques have been previously published.[4-8]

Potential complications of the procedure include those related to a general anesthetic, excessive bleeding, inadvertent organ damage during instrument introduction, over-distention of the abdomen with gas, air embolism, or tension pneumothorax if the diaphragm is inadvertently punctured (as abdominal gas enters the thoracic cavity). Meticulous attention to technique together with experience minimizes the incidence of complications. Postoperative pain should be anticipated, and this should be addressed with appropriate analgesics.

Laparoscopic Surgery

Many laparoscopic surgical procedures are currently being performed on dogs and cats (see Box 91-1).[14-29] Limitations of laparoscopic surgery include the two-dimensional image, restricted freedom of movement of the instruments, restricted sense of touch, limited opportunity to move the position of instruments once cannulae have been placed, and the need for extensive training. Controlled studies are necessary to substantiate the role of all laparoscopic procedures in veterinary medicine. As clinicians and equipment manufacturers address technical limitations, many surgical procedures performed within a body cavity should be amenable to laparoscopic surgery.

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General Centesis and Biopsy

OUTLINE

Chapter 92 Bone Marrow Aspiration and Biopsy
Chapter 93 Cytology of Internal Organs
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Chapter 95 Lymph Node Aspiration and Biopsy
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CHAPTER 92

Bone Marrow Aspiration and Biopsy

Valerie MacDonald

Overview

Abnormal complete blood count (CBC) results are typically the primary indication for bone marrow evaluation. Unexplained abnormalities such as non-regenerative anemia, neutropenia, thrombocytopenia, or markedly high blood cell counts should prompt bone marrow evaluation, as should the presence of immature blast cells or atypical mature cells on a blood smear. Other reasons include searching for organisms that cause systemic infections such as *Leishmania, Cytauxzoon,* and *Histoplasma* species, or looking for occult neoplasia when abnormalities are found on physical examination, diagnostic imaging, or a serum biochemistry profile. Certain cancers are definitively diagnosed through bone marrow evaluation, including multiple myeloma, lymphoma, and histiocytic sarcoma, and these procedures also are valuable for follow-up of patients undergoing treatment. Iron stores also can be subjectively evaluated by way of bone marrow aspiration or biopsy.[1]

There are very few contraindications to bone marrow aspiration, as the risk of bleeding from this procedure is very low. Thrombocytopenia is not a contraindication and in fact, bone marrow aspiration often is used for finding the underlying cause of thrombocytopenia. However, a severe coagulopathy involving deficiency or impairment of coagulation factors is a concern and marrow aspiration should be delayed until it is controlled. The risk of causing a bone fracture is low but it can occur if an inappropriately sized needle is used for a patient or if the bone is already compromised by disease.

Making the decision of whether to do an aspiration versus a biopsy, or both, can depend on the clinician's differential list and what exactly is being searched for. Many times, aspiration and core biopsy complement each other and both can be required. Individual cell morphology is best evaluated with cytopathologic examination of marrow aspirate smears that can highlight few or very small organisms or subtle cell features that can aid in identification of cell lineages. Bone marrow core biopsies give information on the architecture of the marrow, overall cellularity, and the presence of myelofibrosis, necrosis, and mass lesions within the marrow space.[2]

Materials and Equipment

To obtain high-quality samples, it is important to select appropriate materials and equipment. The size of the needle should be appropriate to the patient and the site being aspirated. A Rosenthal needle or Illinois sternal iliac needle is available for a bone marrow aspirate while the Jamshidi biopsy needle generally is reserved for bone marrow biopsies, although aspirates can also be obtained with this instrument (Figure 92-1). This author has used the Illinois needle for bone marrow biopsies as well as aspirates, especially in cats and small dogs. These needles are available in various sizes and lengths. A 15-gauge Illinois sternal iliac needle is most commonly used for dogs and an 18-gauge needle is available for cats and small dogs. A 1-inch (2.5 cm) needle can be sufficient for many animals, but a 1½-inch (4 cm) needle is required for large-breed dogs. Jamshidi biopsy needles are available in 13-gauge and the larger 8-gauge size, with the latter being reserved for larger dogs. All needles must be sterile, and all consist of two pieces—the hollow stainless steel needle and a solid stylet. The Illinois sternal iliac needle has a removable plastic cap and needle guard and can be re-sterilized for additional use, but the tip usually becomes dull quickly and one-time use is recommended. The Jamshidi needle does not have a needle guard and also can be re-sterilized, but it too might quickly become dull, making future use more difficult and potentially painful for the patient.[3]

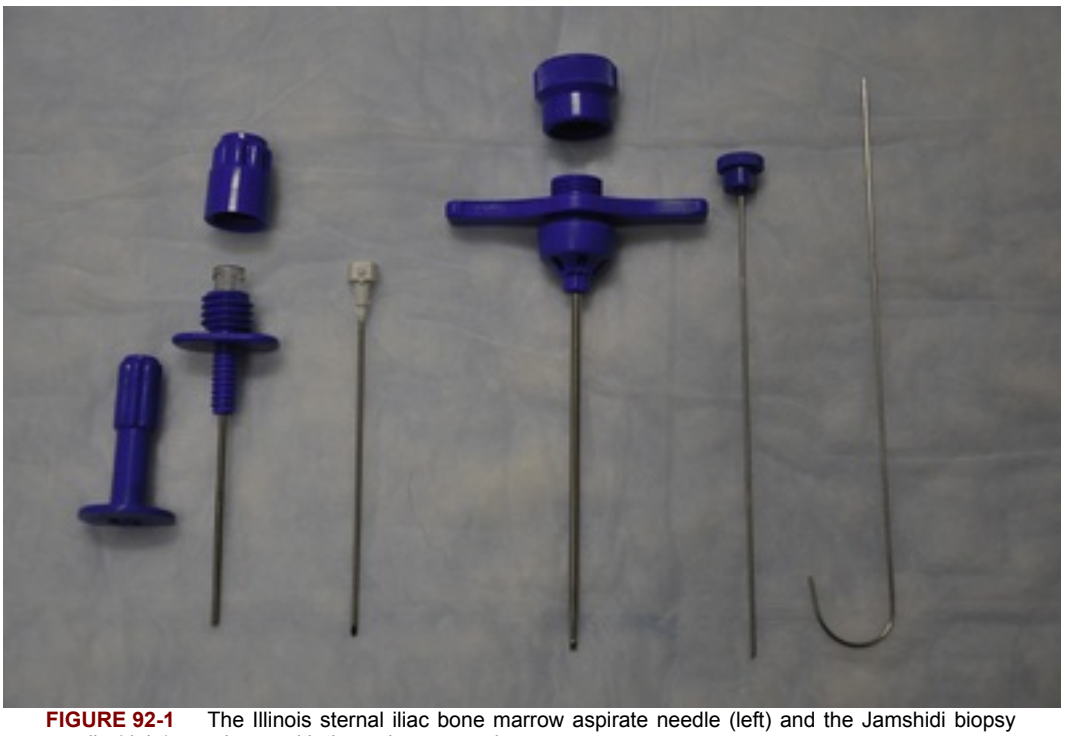

FIGURE 92-1 The Illinois sternal iliac bone marrow aspirate needle (left) and the Jamshidi biopsy needle (right) are shown with the stylet removed.

Recently, a battery-powered drill (OnControl Bone Marrow [OBM] Biopsy System, Vidacare) has been used for bone marrow aspiration and biopsy in humans and in healthy cats.[4] This device in humans is reported to yield better quality marrow biopsy cores, more quickly and with less patient pain when compared to the Jamshidi method.[5] In the cat study, the OBM was suitable for use in adult cats and the technique was easier and shorter in comparison to the manual method of collection. The drill does produce more heat than the manual collection method; however, the histologic thermal artifact did not significantly affect sample quality (Dickinson RM: personal communication, November 1, 2014). A different study evaluated the same device in both dogs and cats and found that good-quality aspirates could be obtained, marrow core samples were of increased size, and the core samples were judged to be of significantly better diagnostic quality.[6]

Because aspiration and biopsy are painful procedures, general anesthesia or heavy sedation with analgesia is recommended. The site should be shaved and surgically prepared, and a local anesthetic block performed, starting with the periosteum, subcutaneous tissues, and then the skin with 1% to 2% lidocaine. A nonsteroidal anti-inflammatory drug or tramadol should be provided for the patient if not contraindicated after the procedure is completed (see ch. 164).

Surgical gloves should be worn and all instruments and supplies kept within a sterile field. A small surgical drape could be used for helping to maintain a sterile field. A small stab incision is made in the skin with a #11 scalpel blade. Other required equipment includes microscope slides, 12-mL syringe, sterile anticoagulant (4% disodium- or dipotassium-EDTA), Petri dish or weigh boat, and forceps or pipette. An assistant should be available to help, and the slides should be laid out at an angle before starting the procedure, as noted below.

Preparation and Site Selection

Before starting the procedure, it is important to ensure that the stylet is properly aligned within the needle and, if the needle guard is being used, that all attachments are snug but not overtightened. A secure grip of the needle should be maintained by holding it in a modified pencil grip against the palm of the hand. The needle guard on the Illinois sternal iliac needle has a lip on the end where the finger and thumb can rest. This hold permits the application of firm pressure away from the operator (into the bone), and provides stability and precise control for placement of the instrument into the marrow. Some clinicians may find it helpful to keep their dominant forearm tucked in close to their hip, which may reduce shoulder strain and create a bracing effect if the needle tip slips off the bone.

The most common sites for obtaining a sample are the greater tubercle of the proximal humerus, the iliac crest of the pelvis, and the trochanteric fossa of the proximal femur. The humerus generally is the preferred

site but site selection can depend on the clinician's preference and the patient's condition and size. The trochanteric fossa may be used in cats or small dogs and the iliac crest is most easily accessed in thin dogs and large cats where the crest is easily palpable.[7] Sternal bone marrow aspiration in dogs is not commonly performed despite the fact that the sternum is easily accessible and associated with less pain from aspiration compared to other sites. One study evaluated samples taken from the sternum of clinically normal dogs and found that aspiration of marrow from this site was feasible, safe, and that sample quality was equivalent to that of samples from the humerus or ilium.[8]

Procedure: Bone Marrow Aspiration

For sampling the proximal humerus, the animal should be placed in lateral recumbency. It is easiest to sample the patient's humerus that is the same as the clinician's dominant hand. The right-handed clinician stands ventral to the patient and uses the left hand to grasp the patient's right forelimb distal to the elbow, slightly rotating it externally to stabilize it. The lateral aspect of the greater tubercle is the target site for aspiration: a flattened, roughened area of bone where muscle and fat coverage are minimal and the needle is least likely to slip off the bone. The needle should be placed through the stab incision and aligned along the long axis of the bone. Firm pressure is applied, with repetitive, back-and-forth twisting motions to advance the needle through the cortex (Figure 92-2).

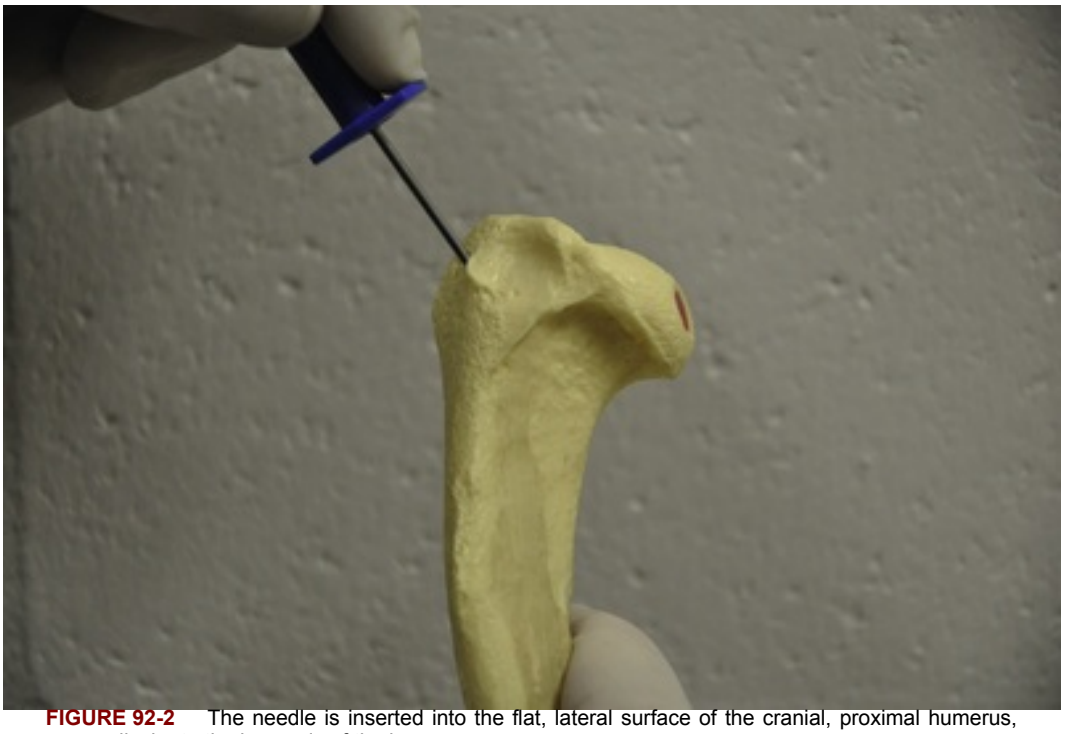

FIGURE 92-2 The needle is inserted into the flat, lateral surface of the cranial, proximal humerus, perpendicular to the long axis of the humerus.

For the proximal femur, the animal is placed in lateral recumbency. The trochanteric fossa is located by palpation of the greater trochanter. The fossa is located just medial to the trochanter. The limb should be adducted and rotated medially to minimize the risk of sciatic nerve damage. The needle is directed so it is parallel to the shaft to the femur, to allow placement within the marrow cavity (Figure 92-3).

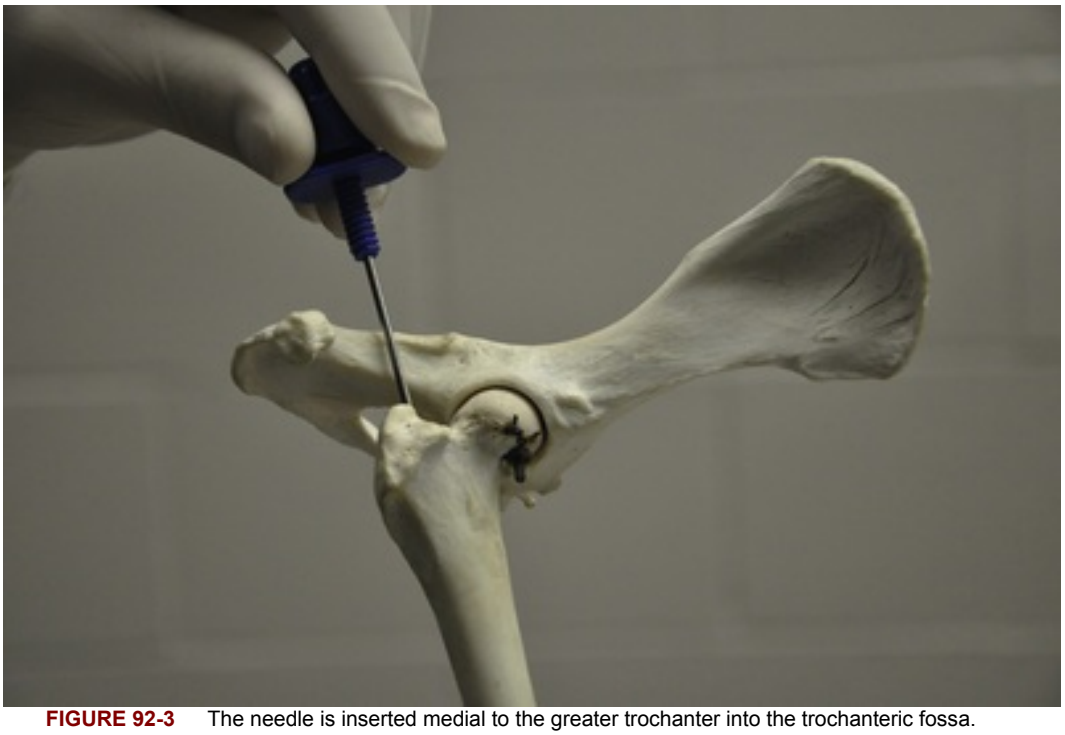

FIGURE 92-3 The needle is inserted medial to the greater trochanter into the trochanteric fossa.

For the iliac crest, the animal should be in sternal or lateral recumbency. The clinician should palpate the widest portion of the dorsal border of the iliac crest. The needle is advanced into the middle of the crest, aiming slightly caudal to the vertical line through the iliac crest (Figure 92-4).

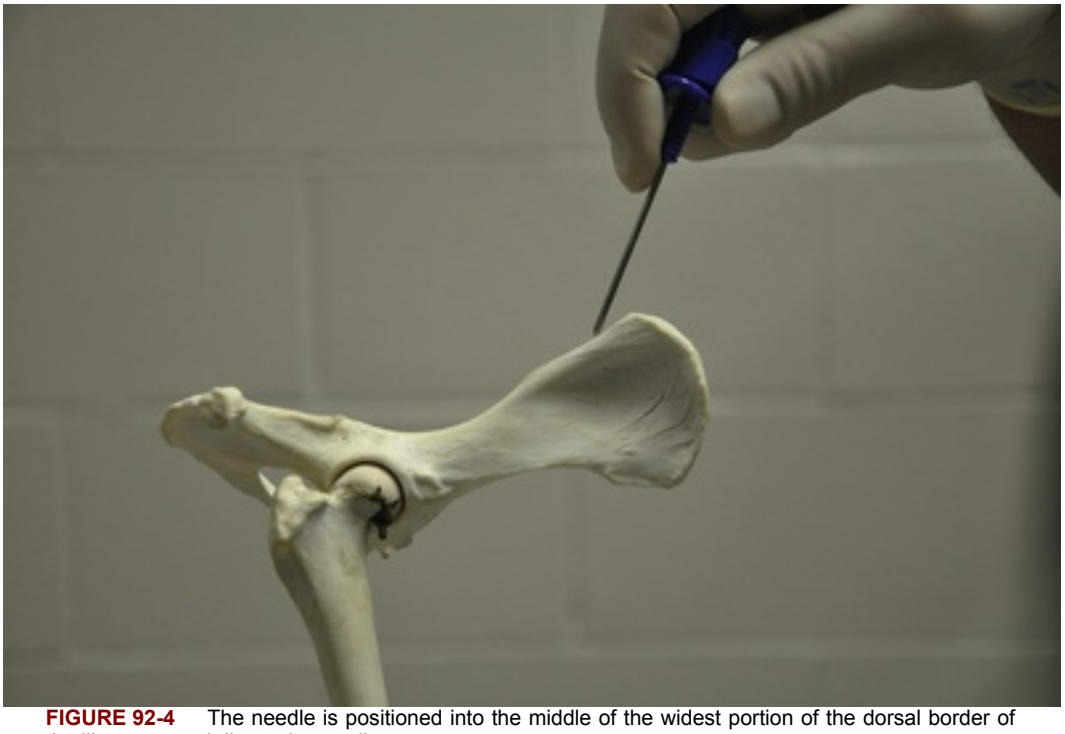

FIGURE 92-4 The needle is positioned into the middle of the widest portion of the dorsal border of the iliac crest and directed ventrally.

Regardless of the site chosen for aspiration, the procedure of aspiration is identical, as are the pitfalls. If the needle does not remain perpendicular to the cortex, it may be seated within it (or parallel to it) rather than through it. By maintaining a steady forward pressure from the palm of the hand combined with a twisting

rotation, the needle should penetrate the cortex and advance into the marrow space. It is important not to go too far through the cavity and come out through the opposite cortex. Some clinicians may sense a decrease in resistance that indicates they have entered the marrow cavity but others may not appreciate the sensation. If the needle is properly seated, it should not move on its own but rather should move in unison with the limb when the needle is manipulated.

Once the needle is firmly seated, the cap and stylet are removed. A 12 mL syringe is attached to the end of the needle. The clinician rapidly pulls back the plunger until the smallest flash of blood is seen, and then stops suctioning. It can be tempting to harvest as much marrow as possible in these situations but ongoing suction causes hemodilution, reducing sample quality.

The entire needle is removed (with the syringe attached) from the bone, and the contents of the syringe and needle are placed onto glass slides or into a collection dish. Alternatively, the syringe alone can be removed first and its contents expelled onto glass slides or into a dish containing EDTA; however, this author believes the best sample is actually contained within the needle.

If the marrow sample is placed onto glass slides, especially if there is no EDTA in the syringe, it is important to quickly prepare the slides to avoid sample clotting (see ch. 93 and 95). Therefore, having an assistant to smear the samples on the slides is best practice. The slides should be laid out at an angle prior to collection. The clinician should quickly place a drop of sample at the top of each slide while the assistant follows behind placing a second clean slide perpendicular to the first slide and gently spreading the marrow spicules across the slides, then rapidly air drying.

If using a Petri dish or weigh boat, the clinician should place the sample in the container, tilt the container to allow the blood to drain away, and gently pick up the marrow spicules with the end of a pipette or forceps. The spicules should be placed on a glass slide, and gently crushed with a second clean glass slide. The marrow and blood remaining in the container can be transferred to an EDTA vial in case additional slides need to be prepared.

To ensure an adequate sample has been obtained, the clinician should stain and examine one slide to look for evidence of cellularity (Figure 92-5, *A*). A cursory microscopic evaluation should reveal densely stained marrow particles populated by mixed hematopoietic cells with variable amounts of fat and hemorrhage (Figure 92-5, *B*). If cellularity is low or uncertain, a second attempt should be made to collect an adequately cellular sample. In some pathologic conditions like myelofibrosis or aplastic anemia, cellularity will be poor regardless of the best technique and in those cases a bone marrow biopsy should be collected. The slides should be submitted along with a recent CBC. It is preferable to have the CBC taken on the same day as the aspirate, as accurate interpretation of the bone marrow depends on the findings from the peripheral blood.

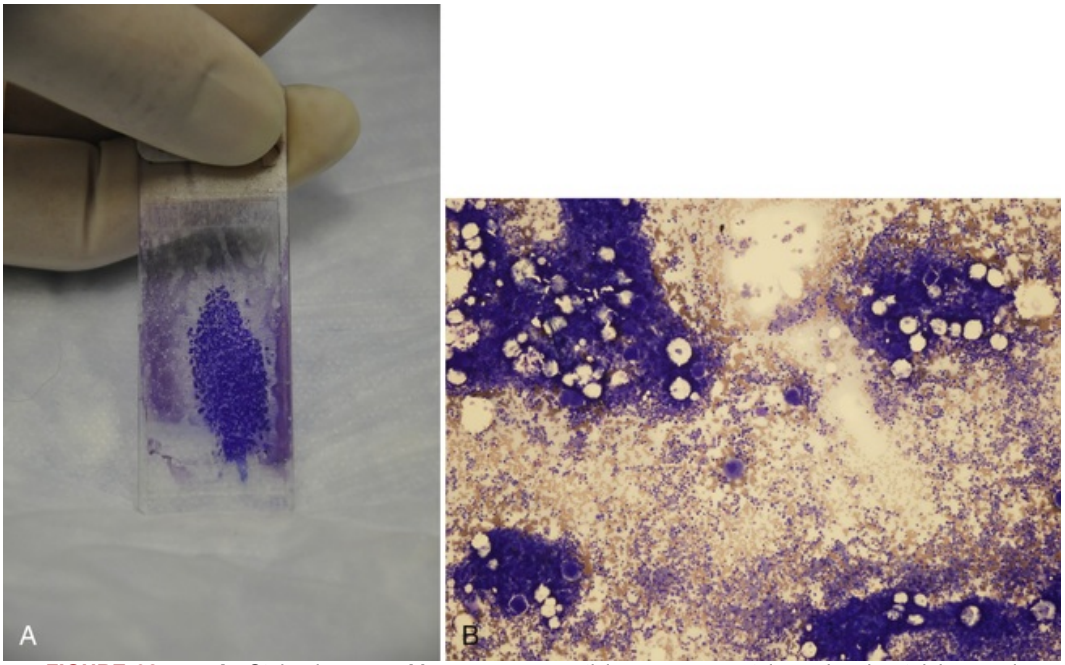

FIGURE 92-5 **A,** Stained smear. Many marrow particles are present in a deeply staining oval grouping surrounded by blood. The smear quality is excellent. **B,** Microscopic appearance of a bone marrow aspirate. Four densely cellular marrow particles are seen as “islands” with marked stain uptake

—one in each corner of the image—surrounded by looser monolayers of mixed hematopoietic cells.

Procedure: Bone Marrow Core Biopsy

A bone marrow core biopsy can be performed from the same site on the patient or from a completely different site. All of the sites for bone marrow aspiration are the same for marrow biopsy. One study evaluated a combined technique (using the same needle and site for the aspirate and biopsy) in comparison to obtaining a biopsy directly from the opposite humerus.[2] The authors found that the marrow length was shorter and hemorrhage artifact was more common using the combined technique. However, there were no differences in cellularity, megakaryocyte count, myeloid/erythroid ratio, iron stores, or diagnostic quality.

The needle should be inserted in the same way as for aspiration; however, once the needle has become embedded in the cortex, the stylet is removed. Then, the needle is advanced an additional centimeter, or slightly more in large dogs. Once the needle is deeply seated and secured, the clinician breaks the biopsy fragment loose of its deep attachments by slightly rocking the needle back and forth in a variety of directions. The clinician then removes the biopsy needle from the bone with outward traction and a continued twisting motion. The biopsy sample is removed from the needle by using a shepherd's hook to push it retrograde (out the handle end) with a Jamshidi needle, or using the needle's own stylet in the usual position to force the sample normograde and out the tip if using an Illinois needle.[9]

Before placing the sample in 10% buffered formalin, the clinician can roll it on a glass slide for cytological analysis. It is important to avoid placing cytology slides in the same package as formalin samples, as the formalin will fix the slides and deleteriously affect their staining.

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9. Dhumeaux MP. Bone marrow collection. *Veterinary Times*. 2014;37:5–8 [Available at] http://www.vetsonline.com [Accessed November 1, 2014].

CHAPTER 93

Cytology of Internal Organs

Lamberto Viadel Bau

Background

"Cytology," as a diagnostic tool, refers to the microscopic assessment of cells. Cytology samples can be obtained from practically any internal organ of small animals. Most often, cytology samples are obtained via fine needle aspiration (FNA) by placing the needle tip well into a target tissue. The plunger of the syringe, to which the needle is connected, allows for gentle aspiration after the needle is placed. Ideally, cells representative of that tissue are aspirated into the needle-syringe. Sometimes cytology samples are submitted after tissue has been gently pressed onto a glass slide (impression smear). These, and additional methods of collecting samples, are presented in Video 93-1. The most commonly submitted internal organ cytology samples are from liver, spleen, lymph nodes and thyroid glands.

Indications/Advantages

Overview: Inflammation versus Neoplasia

The primary objective of an internal organ cytological evaluation is to distinguish inflammation from neoplasia. Cytology, such as obtained with FNA, should be considered a "minor" procedure. It is often the first and least invasive diagnostic step in understanding the nature of suspicious or worrisome tissue. Biopsy assessment can be used to support a cytologic diagnosis or suspicion (submission of an actual "piece" of tissue). Biopsy can also be utilized if cytologic evaluation is inconclusive. In addition to being less expensive and less invasive, an advantage of cytology versus biopsy would include its immediate results. In contrast, biopsy samples usually require time for fixing and cutting the submitted tissue before slides can be stained and assessed.

Before or After Biopsy

Quick cytology of tissue obtained via biopsy, prior to submission, can be used to determine if a re-biopsy is indicated. Cytology may suggest that a biopsy specimen is likely to be representative, of good quality, and should be submitted. Cytology can be performed on slides after tissue impression or FNA. Some cancers can be reliably diagnosed via cytology (mastocytoma, transmissible venereal tumor, some lymphomas, carcinomas and melanomas). Other neoplasms (mesenchymal origin tumors, for example) exfoliate few cells and are more difficult to identify with cytology.

Multiple Masses, Recurrence, Metastasis

Fine needle aspiration of suspicious tissue is recommended when multiple masses or lesions are present, potentially indicating whether there are one or several processes present. Cytology of each (or more than one) may be of value in identifying an area to be selected for biopsy. Cytologic evaluation of tissue can be used to confirm the presence of metastases or to demonstrate local recurrence of a previously treated neoplasia. Such information can be useful when deciding the next step in care.

Cytology versus "Blind" Biopsy, Making the Most of Your Clinical Pathologist

Rather than "blind" surgical removal of a mass, a previously obtained cytological diagnosis enables the surgeon to better appreciate the tissue being extirpated. The clinical pathologist should be able to contribute

valuable insight, for example: by recommending margins to employ when excising a mass. Perhaps a non-surgical therapeutic modality should be considered prior to surgery. Intraoperative cytology of suspicious tissue can aid in deciding whether it should be removed, what the excision margins should be, or whether alternative sites should be considered for biopsy.

Disadvantages or Limitations

Even with the best techniques, cytology is not always informative. Some pathological processes cannot be detected or confirmed by cytology alone. Owners should be made aware of limitations and possible complications. Like any test, non-diagnostic results are common and frustrating. Cytology samples occasionally contain too few cells, non-representative cells, or are hemodiluted. Cytology results can provide false negatives, as might occur if necrosis seems obvious but the sample was obtained from the center of a large, rapidly growing tumor. Clinician-induced altered cell appearance, due to poor technique, can become diagnostic traps known as "malignancy imitating processes." Fine needle aspiration of tumors that do not readily exfoliate may not allow diagnosis, assessment of architecture, or invasion of the vasculature or lymphatics. Another complicating factor is benign tumors that imitate malignancies (histiocytomas, some parathyroid tumors) and some malignant tumors that appear benign (well-differentiated carcinomas, lymphocytic lymphomas). It can be challenging to distinguish normal tissue from hyperplastic tissue. It may be difficult to separate hyperplasia from dysplasia or neoplasia. Finally, cytologic diagnoses are usually nonspecific regarding tissue of origin, e.g., "carcinoma".

Complications and Contraindications

Serious complications secondary to obtaining a sample for cytology are quite uncommon. Complications do occur, including hemorrhage, release of bioactive substances (mastocytoma), organ rupture or laceration, pneumothorax, and sepsis or peritonitis (if an abscess ruptures, leaks, or drainage from a needle exiting an infected area occurs). Spread of tumor cells via the needle's exit path is extremely uncommon, but has been documented with splenic hemangiosarcoma, renal carcinoma, bladder transitional cell carcinoma, and ovarian tumors. FNA is contraindicated if there is high risk of hemorrhage or if anesthesia is both required but contraindicated.

Specimen Preparation (see Video 93-1)

The quality of the cytology specimen is of key importance for correct diagnosis. One should avoid using poor quality swabs, for example, because they often deposit "material artifacts" that could lead to diagnostic errors. After aspiration is complete and the needle removed from the patient, the plunger of the syringe should be advanced to expel needle and syringe content onto a labelled slide. The material should then be spread like a blood smear with the goal of creating a smooth single layer of cells. One needs to be quite gentle creating the smear to prevent cell distortion or lysis. Lysis, for example, may lead to unusual staining artifacts or large numbers of bare nuclei.

If only liquid is obtained on aspiration, it should be transferred to an EDTA tube, mixed, and centrifuged for 5 minutes at 1,000-1,500 rpm. Most of the supernatant can then be removed. A drop of supernatant can be mixed with a drop of sediment to create the cytology smear. No aspirated material should be discarded until it is demonstrated that there are adequate cells for submission. Imprints can be made of tissue, after which slides are dried, fixed and stained with Diff-Quik (Video 93-2).

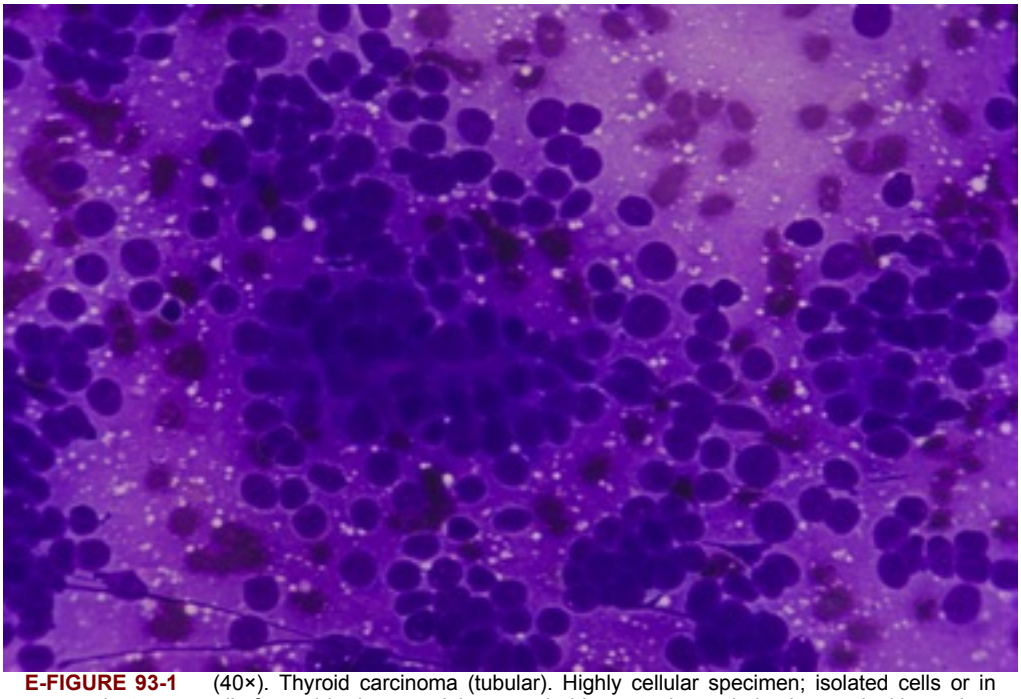
Sending Samples to a Laboratory

As some diseases are difficult to interpret, cytology specimens should be sent to a clinical pathologist for confirmation of any serious diagnosis. Clinical pathologists are trained to recognize artifacts or cell damage caused by poor sample preparation. Inadequately fixed or hemodiluted specimens are common. Other frequent issues include insufficient cells ("dry aspirates"), artifacts from contamination by ultrasound gel (purple-reddish amorphous material) or by cotton grains from surgical gloves. Formalin vapors can seriously alter cell morphology and staining quality (formalin and cytology samples should not be shipped in the same container). Adequate packaging is needed to prevent slides from breaking during transport. Every specimen should be clearly labelled and accompanied by a written review of the animal's clinical history, all test results, treatments employed, and their response. The more informed the clinical pathologist, the better the interpretations and recommendations. Difficult and complicated cases should be discussed.

Cytology of Different Internal Organs

Thyroids

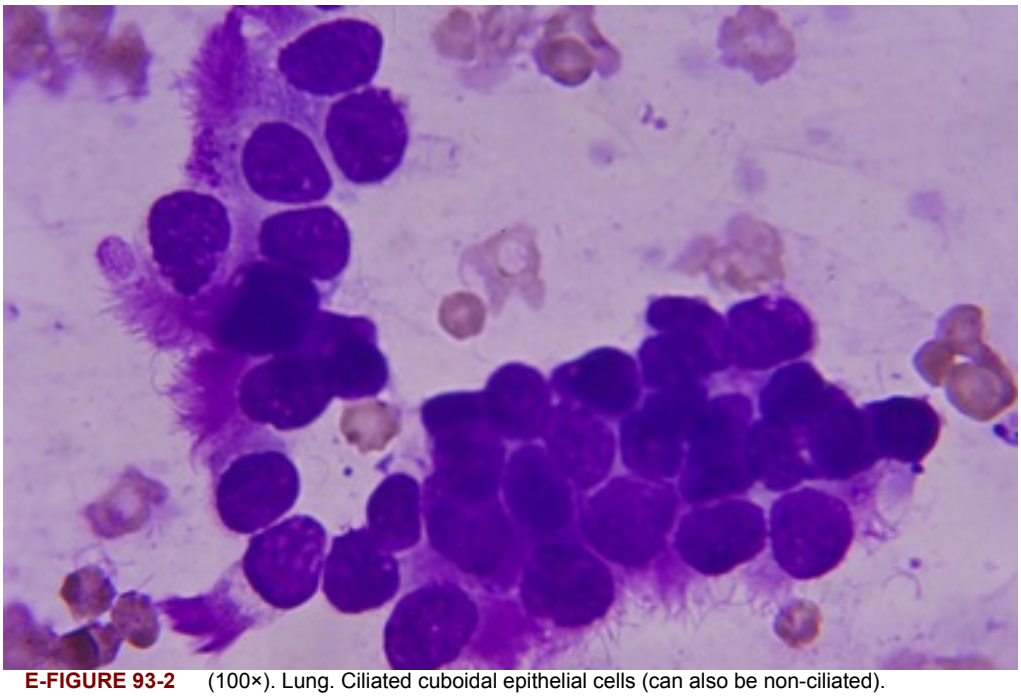
Blood contamination is usually significant and specimens are usually highly cellular, forming groups of bare nuclei on a pale blue cytoplasmatic background. Pink (colloid) amorphous material can be associated with some cell groups. Malignant thyroid carcinomas commonly invade surrounding cervical structures and commonly metastasize (E-Figure 93-1). Thyroid masses in cats are usually benign adenomas (uniform nuclei population without malignancy criteria) or adenomatous hyperplasia.



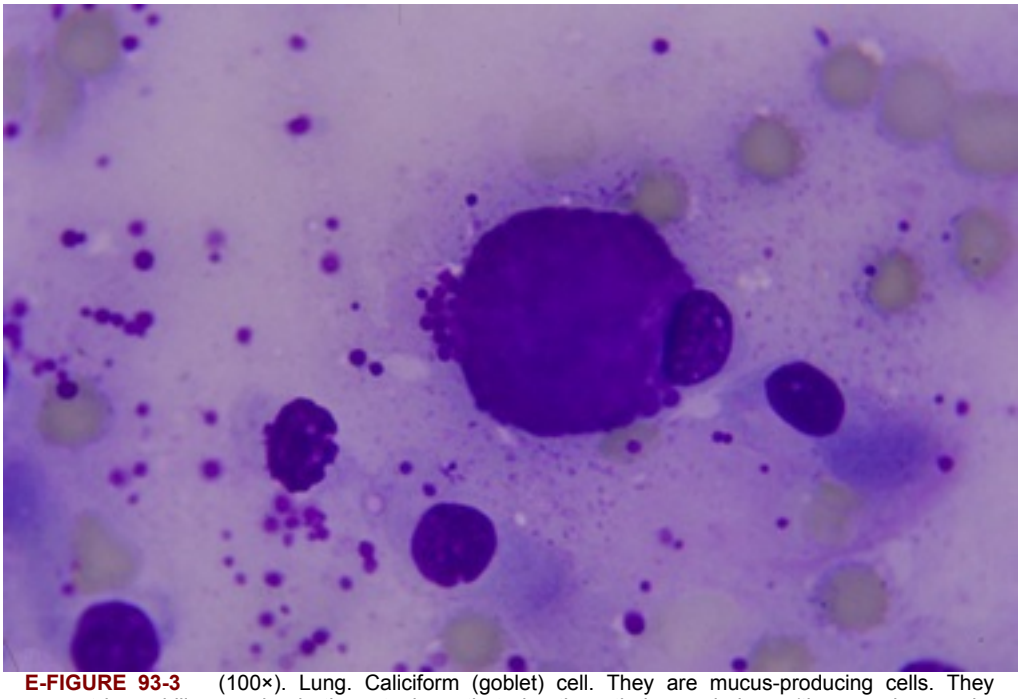
E-FIGURE 93-1 (40×). Thyroid carcinoma (tubular). Highly cellular specimen; isolated cells or in groups that are usually formed by bare nuclei on a pale blue cytoplasmatic background without clear limits. In the center of the image, there is an acinus with colloid substance inside.

Lung

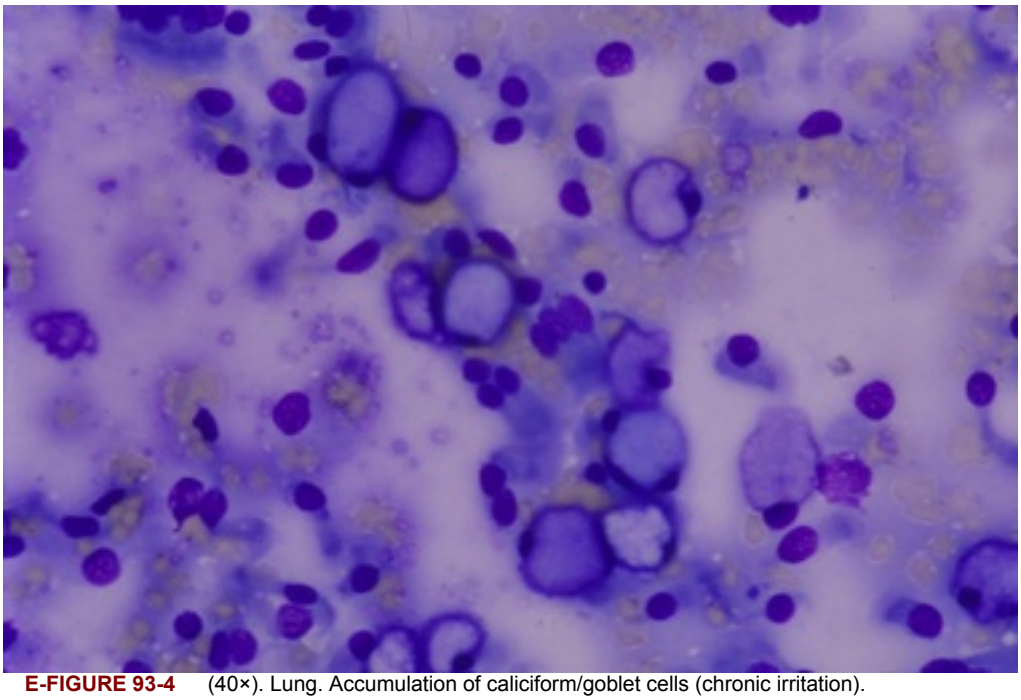
Normally, lung cytology consists of ciliated epithelial cells (E-Figure 93-2), mucus-producing cells (caliciform/goblet, E-Figures 93-3 and 93-4), and macrophages (common in bronchoalveolar lavage specimens and must be distinguished from neoplastic cells, E-Figures 93-5 and 93-6). Increased mucus is non-specific. Caution is required to not mistake groups of alveolar cells (round or cuboidal, E-Figure 93-7) as neoplastic cells. Blood contamination is common (erythrophagocytosis is indicative of pathological hemorrhage). Bacterial infection is usually associated with purulent inflammation. Pyogranulomatous inflammation is typical of mycotic infection and culture is advisable. Reactive hyperplasia is common (respiratory cells with a more cubic morphology). Squamous metaplasia due to chronic inflammation is difficult to distinguish from squamous neoplasia. Most pulmonary masses are neoplastic, but primary lung tumors (usually solitary carcinomas) are uncommon. Pleural fluid rarely includes tumor cells. Cytology cannot reliably distinguish primary (large number of epithelial cells in lamina) from metastatic carcinomas (E-Figures 93-8 through 93-10). Neoplasms of mesenchymal origin in the lung are often metastatic (E-Figures 93-11 and 93-12). Non-lung tissue may be aspirated by mistake. Accidentally obtained tissue is often lymph node, thymus, fat or abdominal organ tissue (hepatocytes and mesothelial cells). Care must to taken not to mistakenly believe these to be metastatic tumor cells of pulmonary origin.



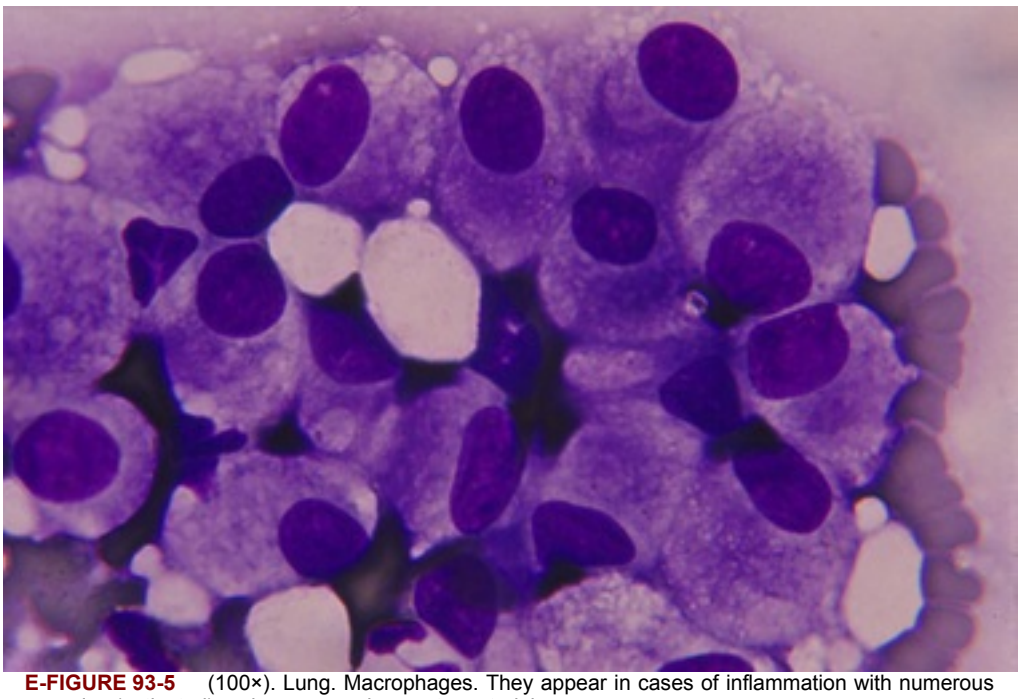
E-FIGURE 93-2 (100×). Lung. Ciliated cuboidal epithelial cells (can also be non-ciliated).



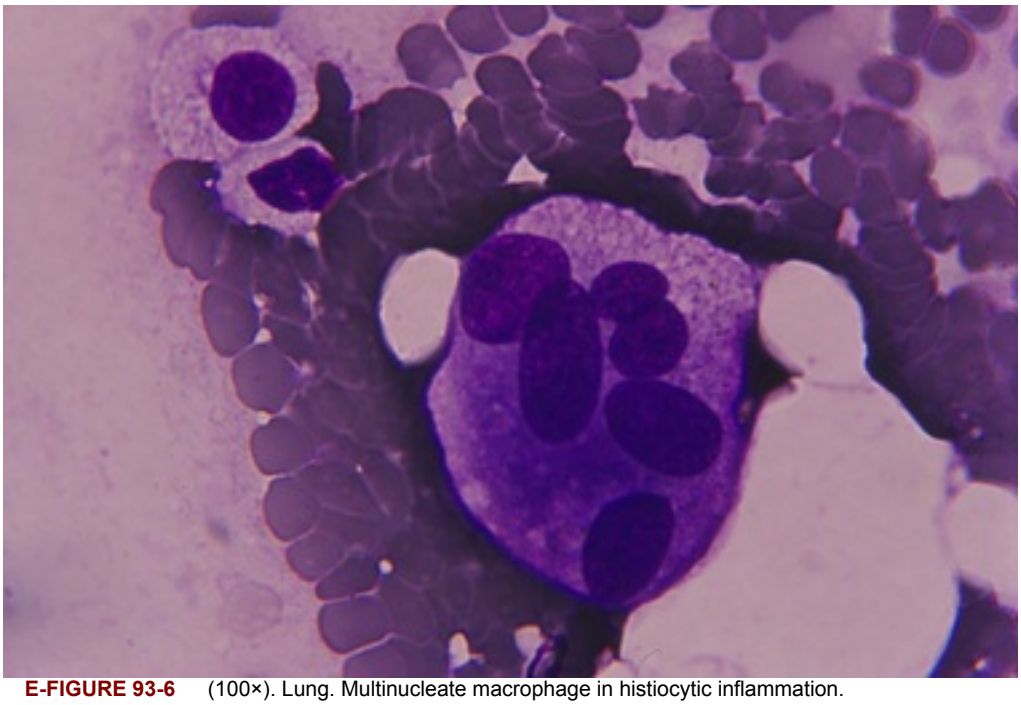
E-FIGURE 93-3 (100×). Lung. Caliciform (goblet) cell. They are mucus-producing cells. They present basophilic granules in the cytoplasm that give them their round shape (the granules can be spread throughout the specimen).



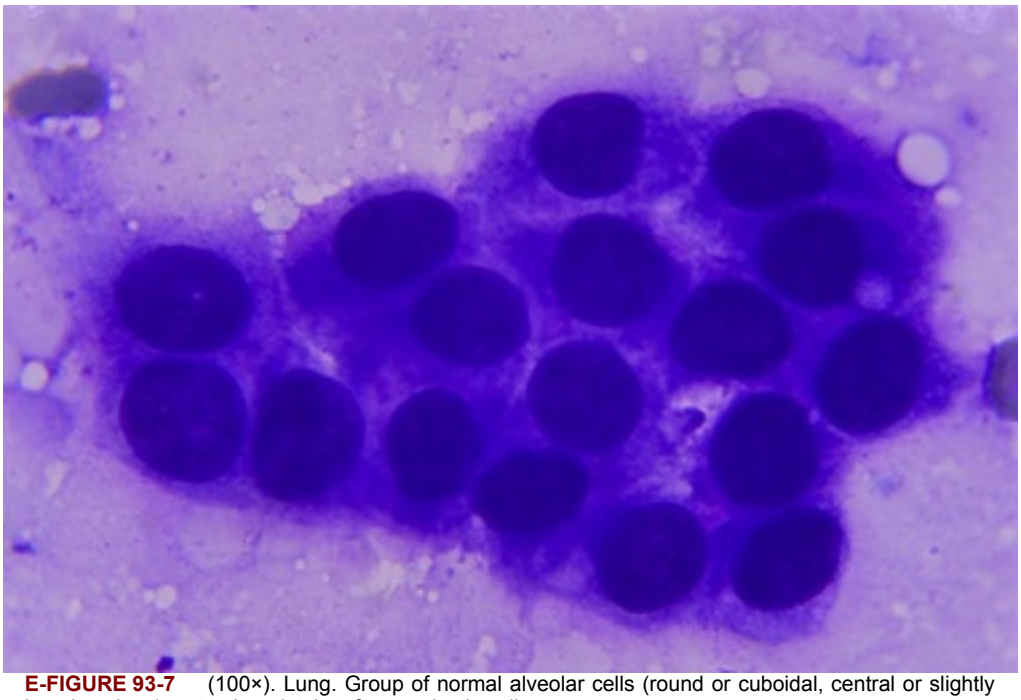
E-FIGURE 93-4 (40×). Lung. Accumulation of caliciform/goblet cells (chronic irritation).



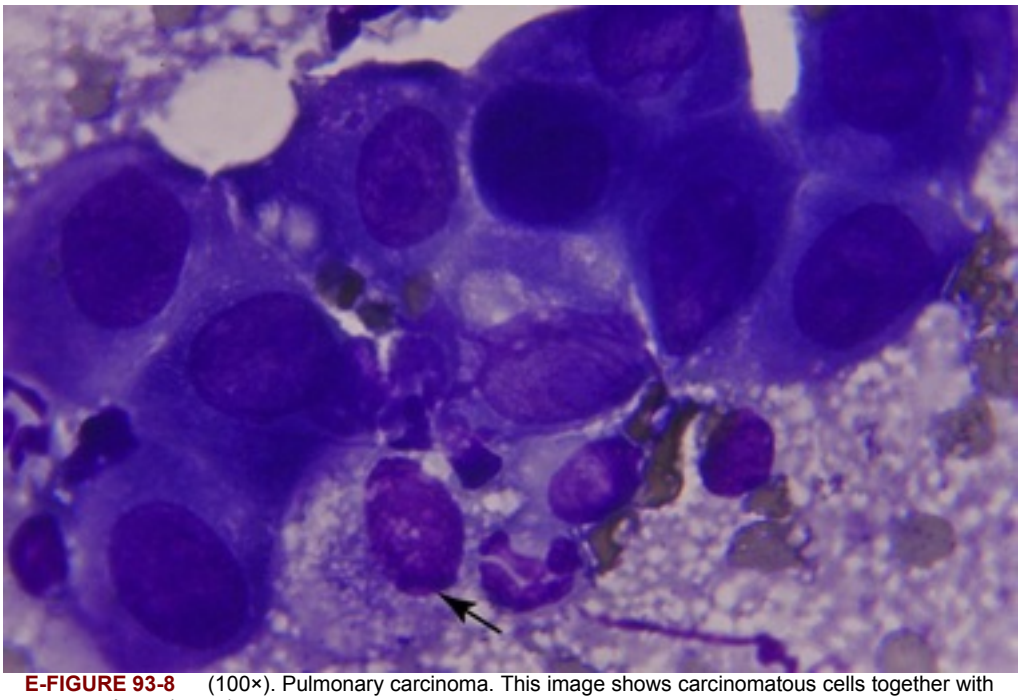
E-FIGURE 93-5 (100×). Lung. Macrophages. They appear in cases of inflammation with numerous vacuoles (activated) and can carry phagocyte material.



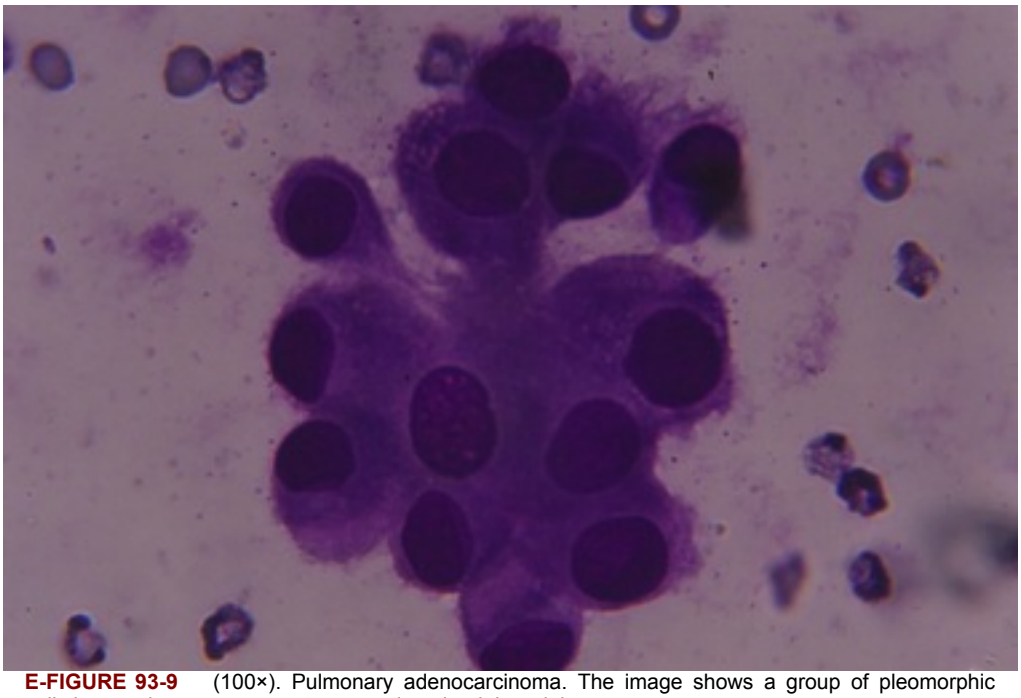
E-FIGURE 93-6 (100×). Lung. Multinucleate macrophage in histiocytic inflammation.



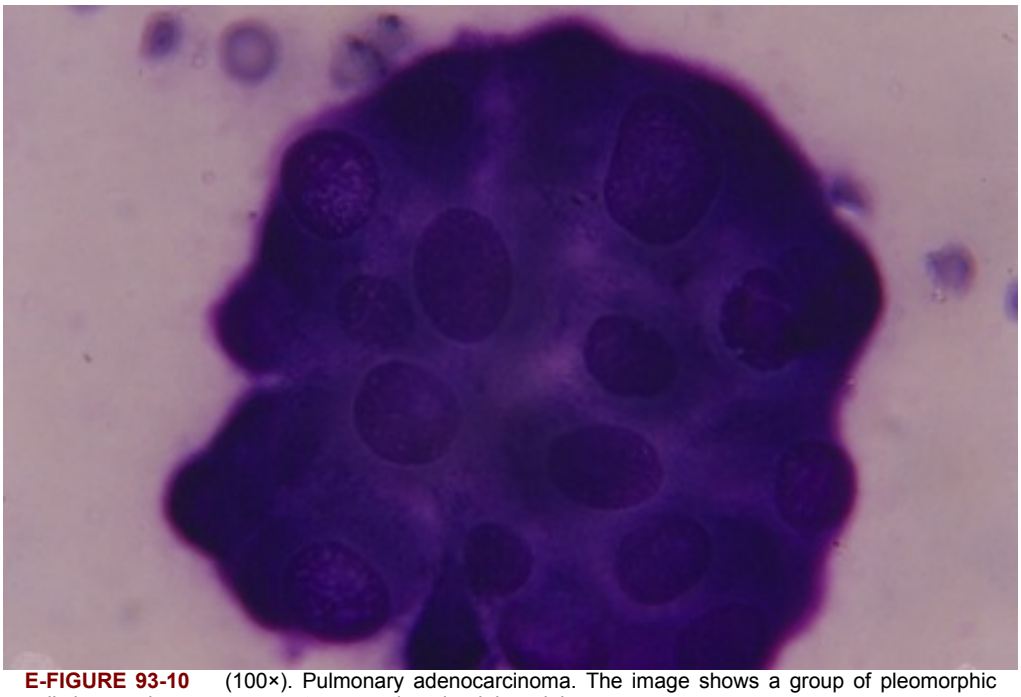
E-FIGURE 93-7 (100×). Lung. Group of normal alveolar cells (round or cuboidal, central or slightly basal nucleus), not to be mistaken for neoplastic cells.



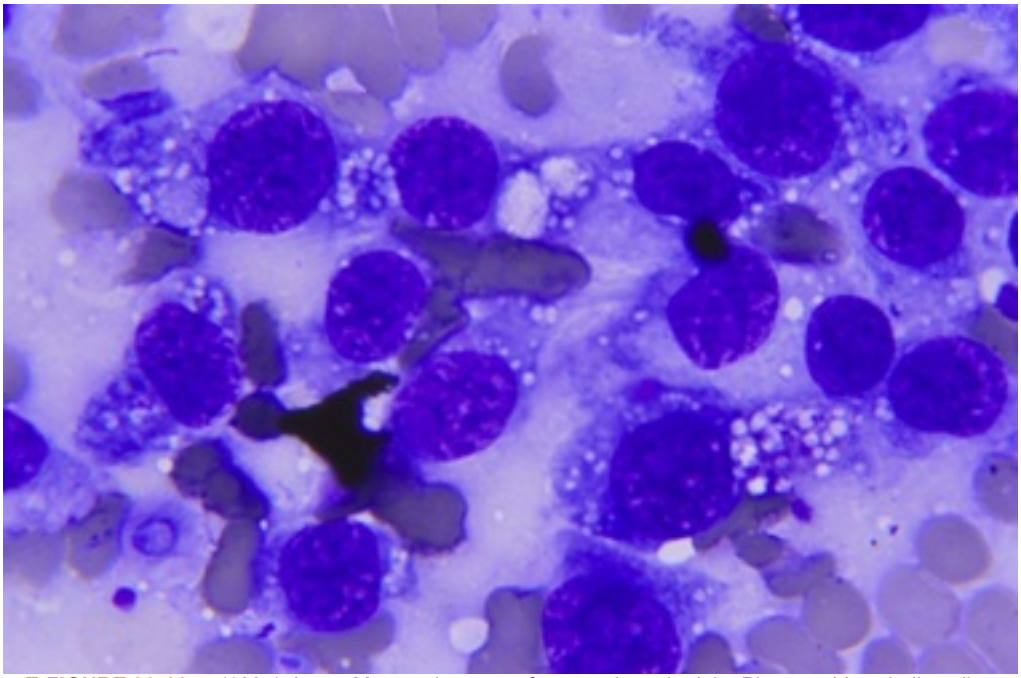
E-FIGURE 93-8 (100×). Pulmonary carcinoma. This image shows carcinomatous cells together with a macrophage (arrow).



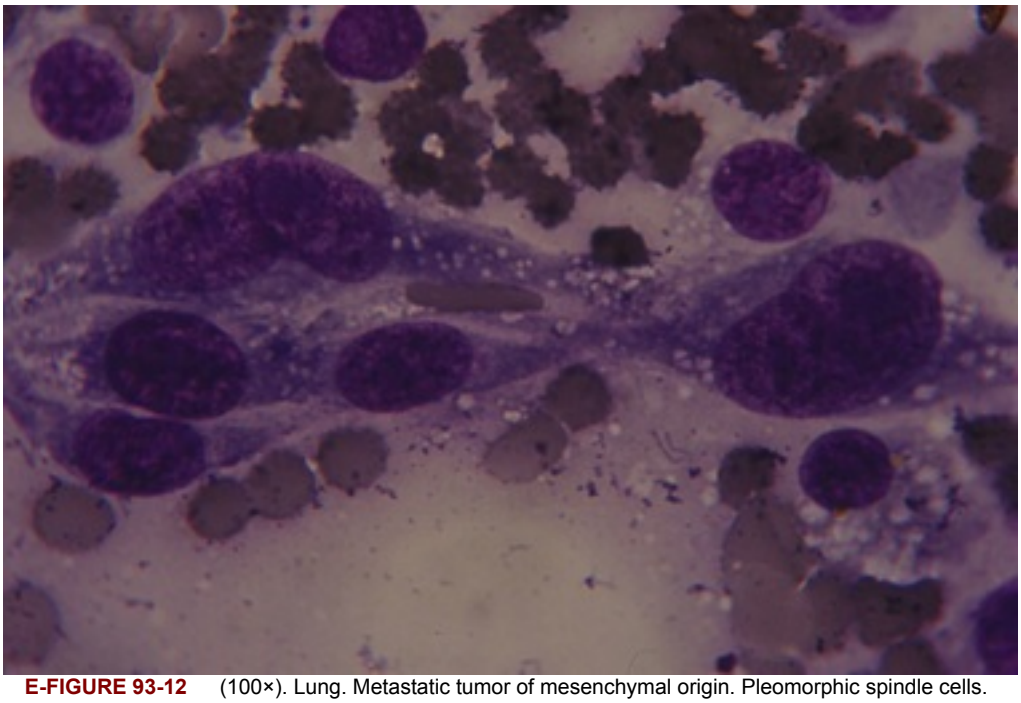
E-FIGURE 93-9 (100×). Pulmonary adenocarcinoma. The image shows a group of pleomorphic cells in an acinar arrangement, suggesting glandular origin.



E-FIGURE 93-10 (100×). Pulmonary adenocarcinoma. The image shows a group of pleomorphic cells in an acinar arrangement, suggesting glandular origin.



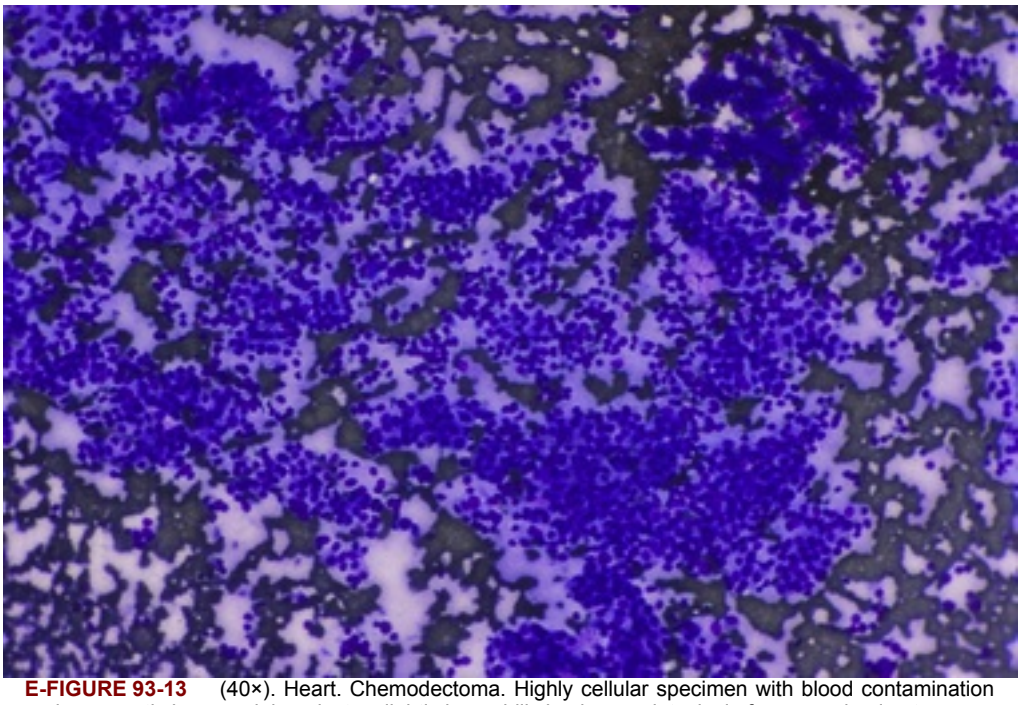
E-FIGURE 93-11 (100×). Lung. Metastatic tumor of mesenchymal origin. Pleomorphic spindle cells.



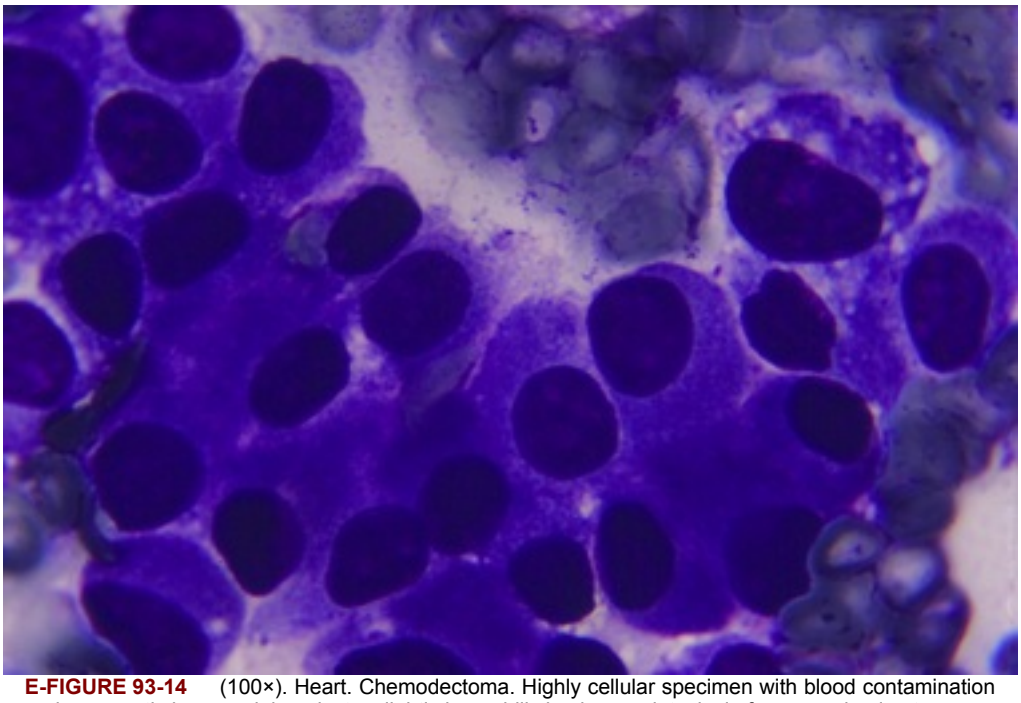
E-FIGURE 93-12 (100×). Lung. Metastatic tumor of mesenchymal origin. Pleomorphic spindle cells.

Heart

General anesthesia is usually required to obtain a specimen. Primary heart tumors are rare. The most often described cardiac tumor, hemangiosarcoma, is most often located in the right atrium, highly malignant, and often causes pericardial effusion. Heart base tumors and chemodectomas are less common (E-Figures 93-13 and 93-14).



E-FIGURE 93-13 (40×). Heart. Chemodectoma. Highly cellular specimen with blood contamination and apparently bare nuclei against a slightly basophilic background, typical of neuroendocrine tumors.



E-FIGURE 93-14 (100×). Heart. Chemodectoma. Highly cellular specimen with blood contamination and apparently bare nuclei against a slightly basophilic background, typical of neuroendocrine tumors.

Thymus

Cranial mediastinal masses are aspirated to distinguish between thymoma (uncommon) and thymic lymphoma. Thymomas are usually associated with large groups of large epithelial cells and small, medium, and large-sized lymphocytes. Thymic lymphoma is usually represented by a predominance of medium-sized and large lymphocytes.

Liver

Normal cytology consists of a moderate number of hepatocytes (in small groups, cells with abundant blue cytoplasm with a granular appearance, E-Figure 93-15), red blood cells due to blood contamination, and epithelial cells from the biliary tract (cuboidal, not to be mistaken for neoplastic cells, E-Figure 93-16). Vacuolar degeneration is due to accumulated fat (feline hepatic lipidosis, E-Figure 93-17) or accumulation of glycogen and water ("steroid hepatopathy" in dogs). Hepatic cytology is not sensitive for the diagnosis of inflammatory processes. It is important to be able to distinguish hyperplastic liver nodules (E-Figure 93-18) from cirrhosis or neoplasia. In dogs, hepatocellular neoplasia (E-Figures 93-19 and 93-20) is more common than cancer derived from the biliary system (cholangiocellular, E-Figure 93-21). Primary hepatic tumors are uncommon. Hepatocellular carcinoma (see E-Figure 93-19) is the most common liver tumor and is characterized by cell aggregates. Some well-differentiated carcinomas and adenomas are morphologically similar to normal hepatocytes and those of hyperplastic nodules. Non-epithelial tumors such as hemangiosarcoma are less common (Figure 93-22). The most common hemolymphatic hepatic neoplasia is lymphoma (E-Figure 93-23, generally formed by lymphoblasts).

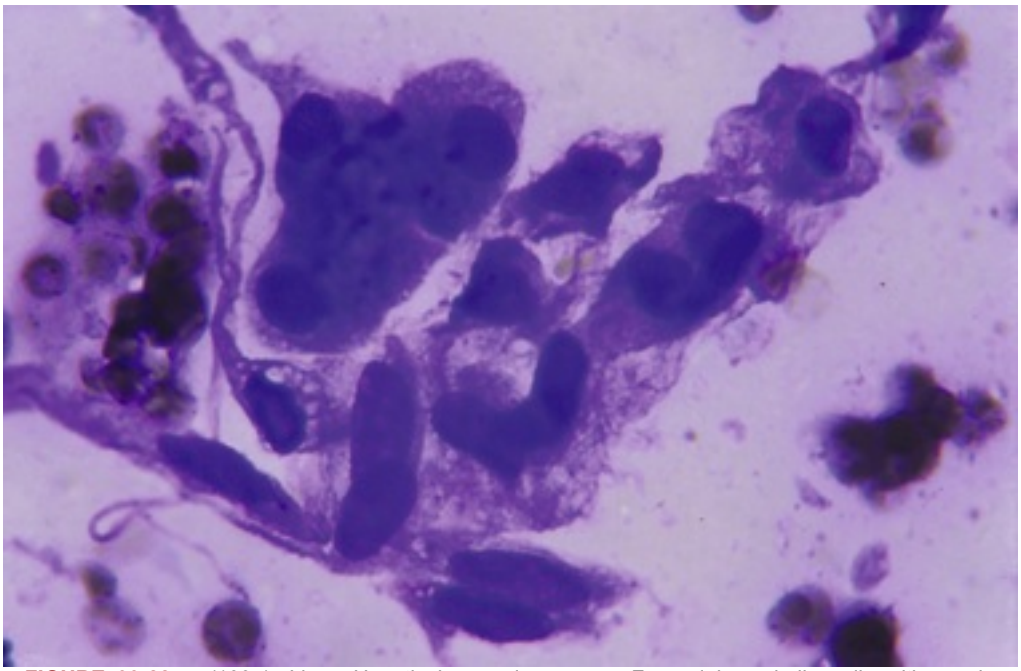
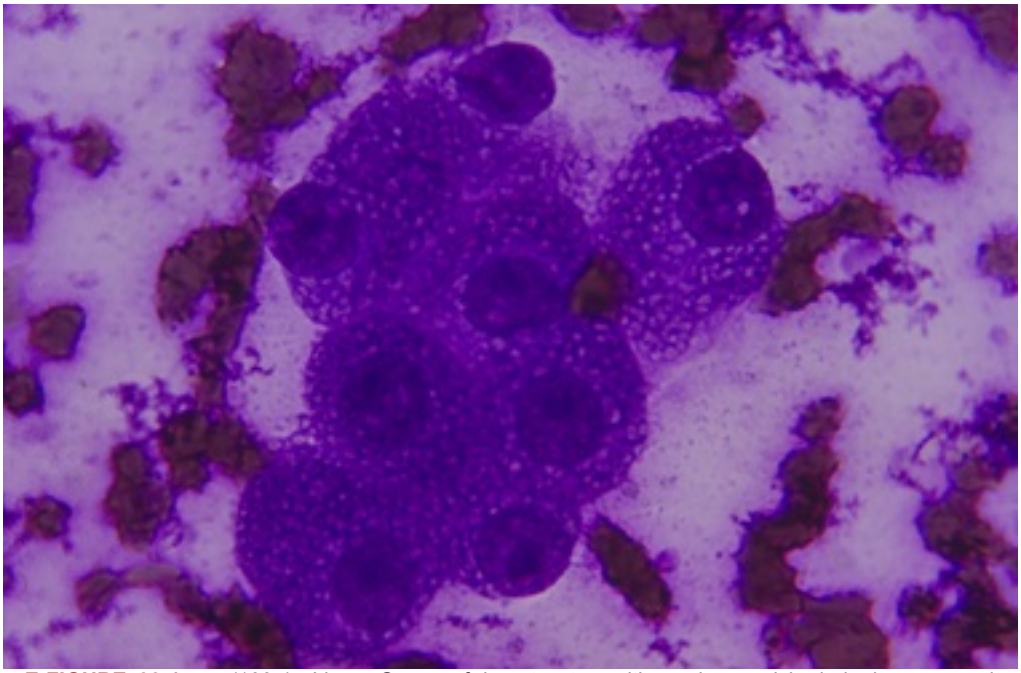
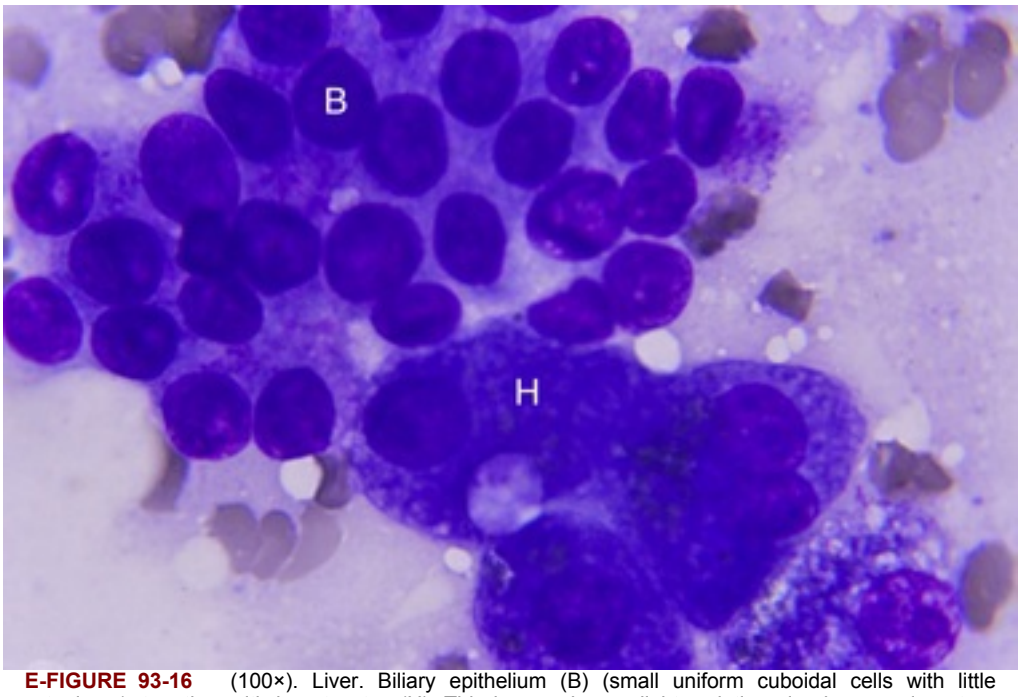


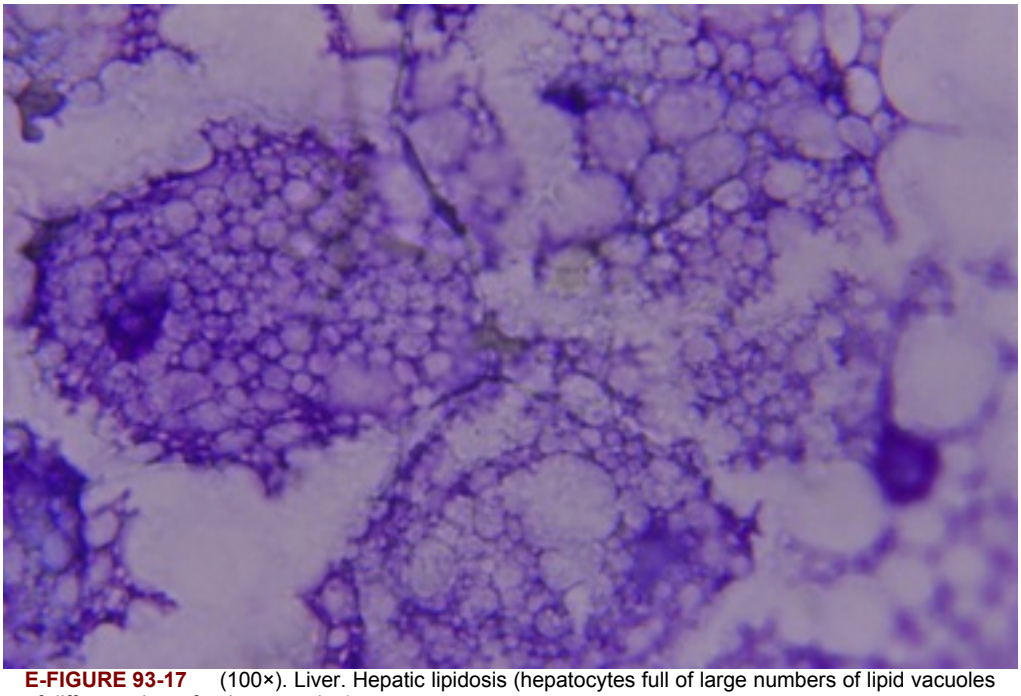
FIGURE 93-22 (100×). Liver. Hepatic hemangiosarcoma. Formed by spindle cells with poorly defined cell borders. Cell size varies from one sarcoma to another, from very uniform to marked anisocytosis and anisokaryosis.



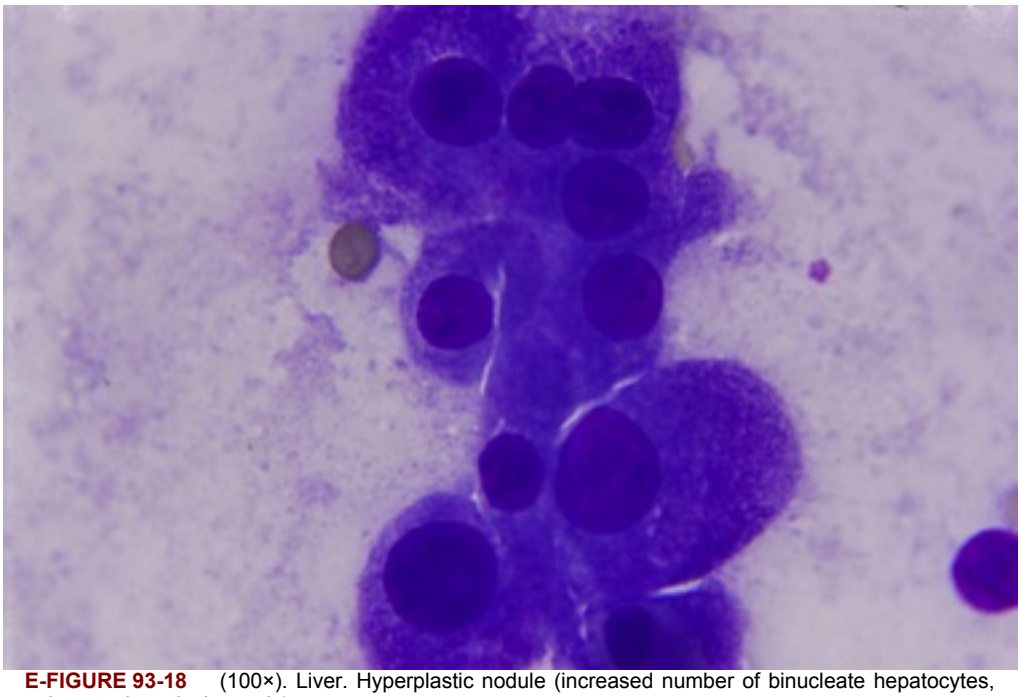
E-FIGURE 93-15 (100×). Liver. Group of hepatocytes with oval or polyhedral shape, round peripheral nucleus, abundant blue cytoplasm with little stained or pale pink organelles that normally give it a granular appearance.



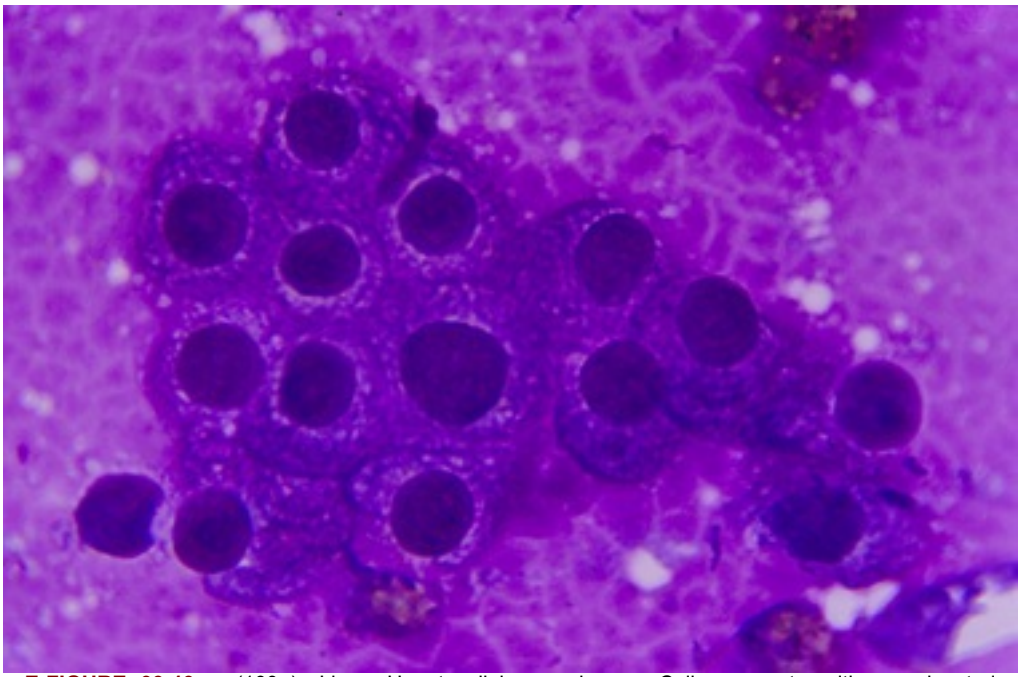
E-FIGURE 93-16 (100×). Liver. Biliary epithelium (B) (small uniform cuboidal cells with little cytoplasm), together with hepatocytes (H). This image shows slight variations in shape and contour suggesting reactivity status (hyperplasia).



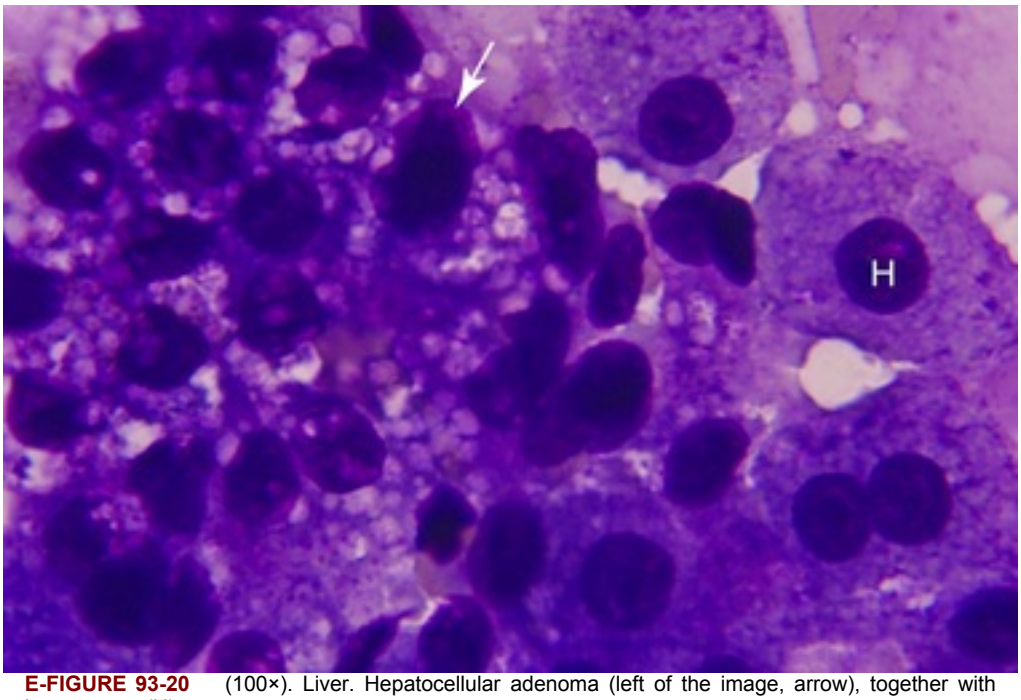
E-FIGURE 93-17 (100×). Liver. Hepatic lipidosis (hepatocytes full of large numbers of lipid vacuoles of different sizes, fat degeneration).



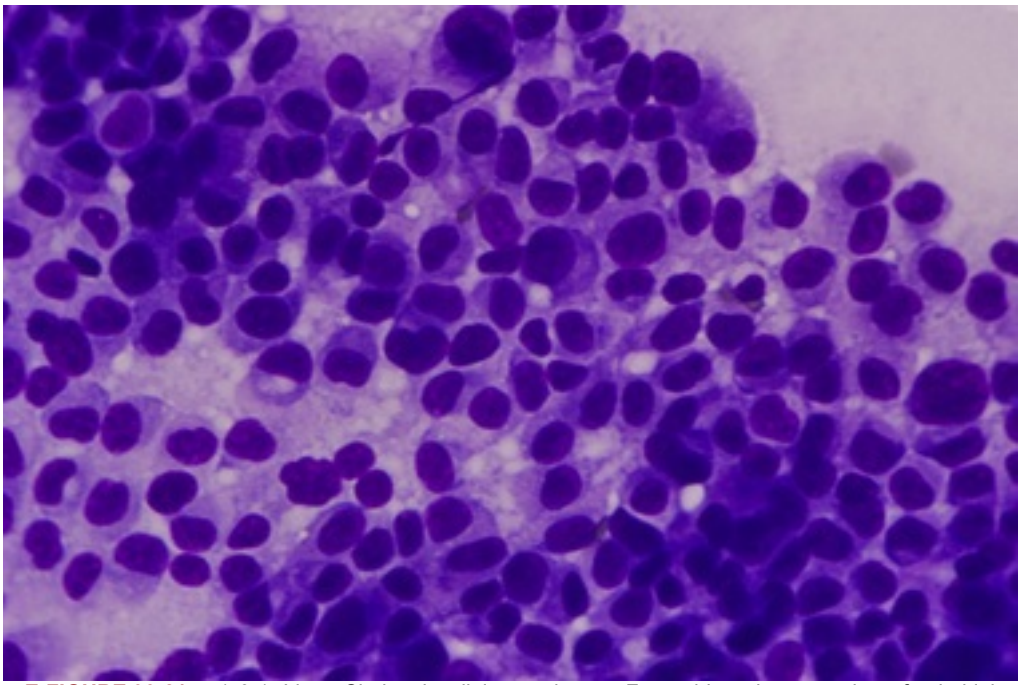
E-FIGURE 93-18 (100×). Liver. Hyperplastic nodule (increased number of binucleate hepatocytes, anisocytosis, anisokaryosis).



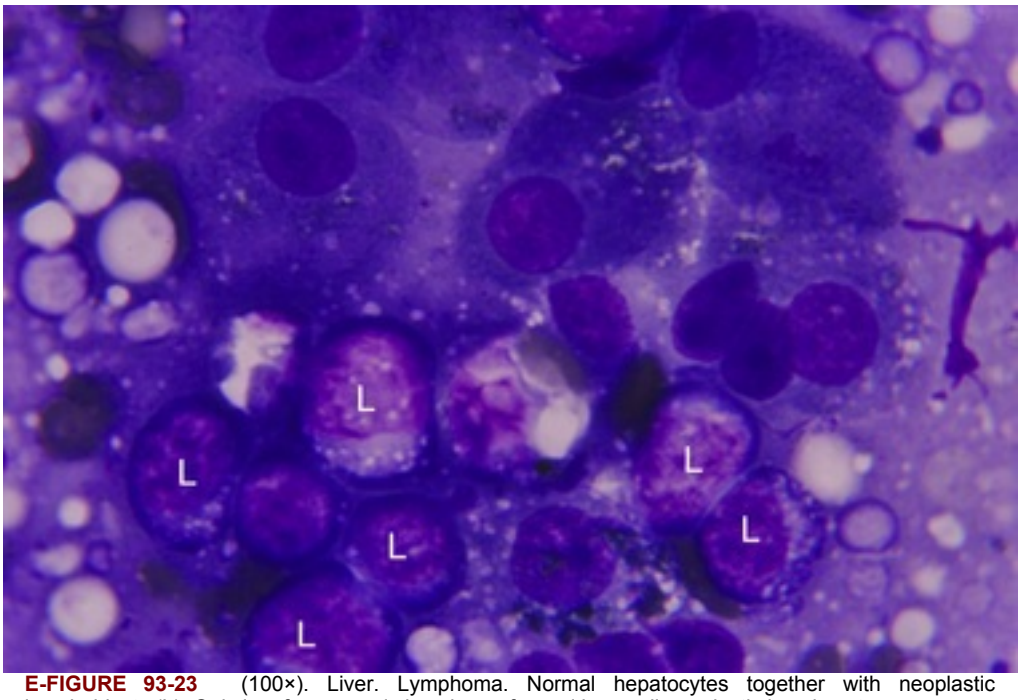
E-FIGURE 93-19 (100×). Liver. Hepatocellular carcinoma. Cell aggregate with an elevated nucleus/cytoplasm ratio. Cytological diagnosis is only possible in the presence of marked atypia. A histopathological evaluation is generally required.



E-FIGURE 93-20 (100×). Liver. Hepatocellular adenoma (left of the image, arrow), together with hepatocytes (H).



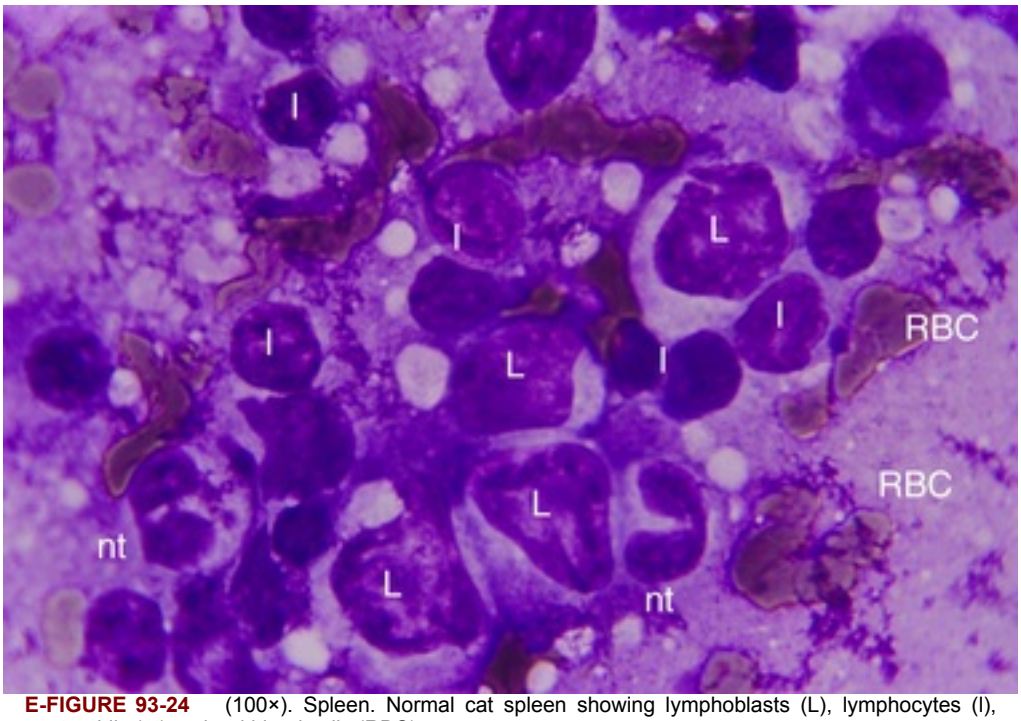
E-FIGURE 93-21 (40×). Liver. Cholangiocellular carcinoma. Formed by a large number of cuboidal cells with moderate anisokaryosis that does not show its malignancy. The nodular or diffuse form can be difficult to distinguish from nodular hyperplasia, cirrhosis or chronic hepatitis. A histopathological evaluation is required for its diagnosis.



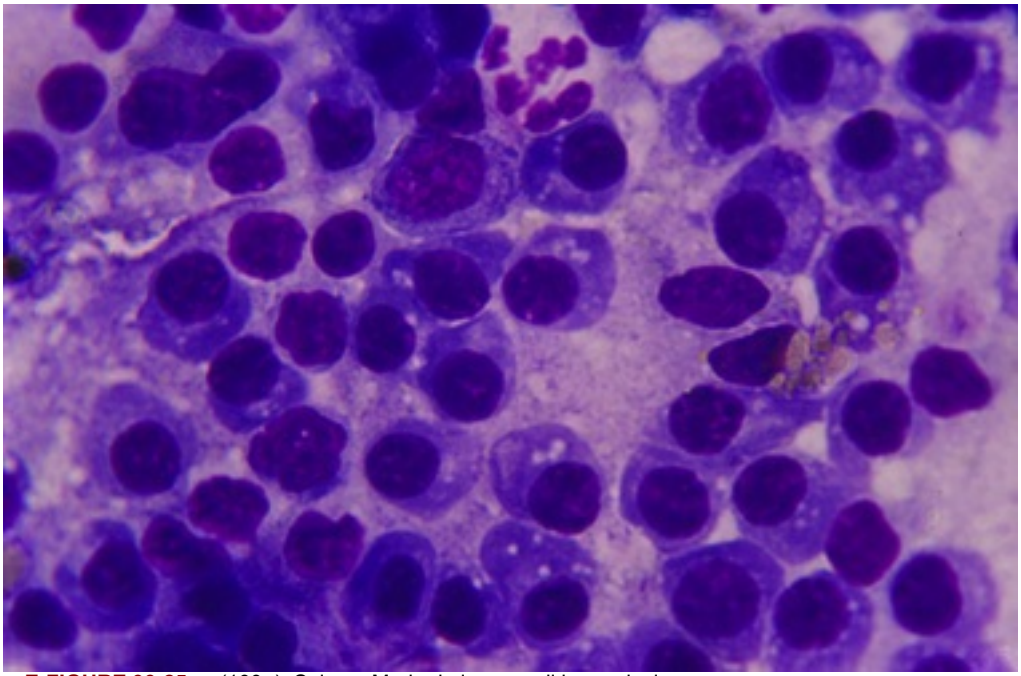
E-FIGURE 93-23 (100×). Liver. Lymphoma. Normal hepatocytes together with neoplastic lymphoblasts (L). Only in a few cases is lymphoma formed by small neoplastic lymphocytes.

Spleen

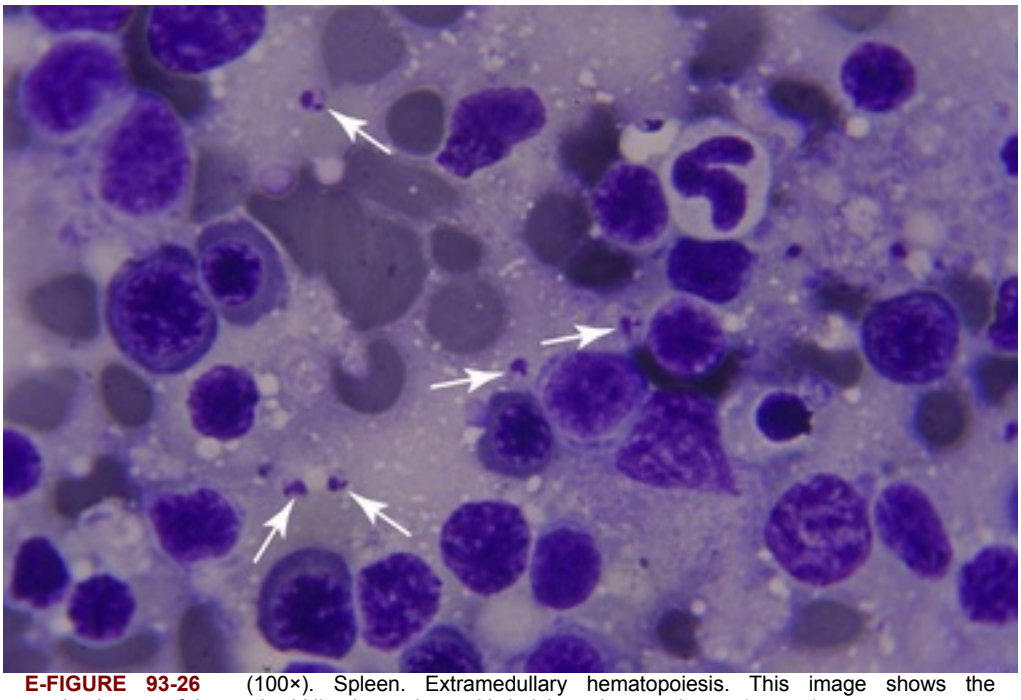
Normal splenic cytology includes hemodiluted small and medium-sized lymphocytes, lymphoblasts, plasma cells, stromal cells, and macrophages (E-Figure 93-24). Macroscopically, hyperplasia may appear nodular or diffuse. Microscopically, the cytology is consistent with chronicity (macrophages, plasma cells and lymphoblasts). Possible causal agents should be sought within macrophages (*Histoplasma* spp., *Leishmania* spp.) and red blood cells (*Mycoplasma, Babesia* and *Cytauxzoon* spp.). Heinz bodies could indicate toxic damage. Severe plasma cell hyperplasia (E-Figure 93-25) includes a differential diagnosis of ehrlichiosis, leishmaniasis, extramedullary plasmacytoma, or multiple myeloma. Lymphoid hyperplasia can be associated with some viral diseases. The presence of extramedullary hematopoiesis suggests increased erythroid precursors (E-Figure 93-26) and granulocyte and megakaryocyte precursors (E-Figure 93-27). Hematomas (relatively common) or extramedullary hematopoiesis can be associated with hyperplasia or neoplasia. The most common splenic tumors in dogs are hemangioma and hemangiosarcoma (E-Figures 93-28 and 93-29) and in cats are mastocytomas (E-Figure 93-30) and lymphoma. Lymphoma (E-Figures 93-31 and 93-32) or chronic lymphocytic leukemia can be a cytological diagnostic challenge because their cytological appearance is similar to that of a normal or hyperplastic spleen. In malignant histiocytosis, there is a predominance of abnormal and immature macrophages.



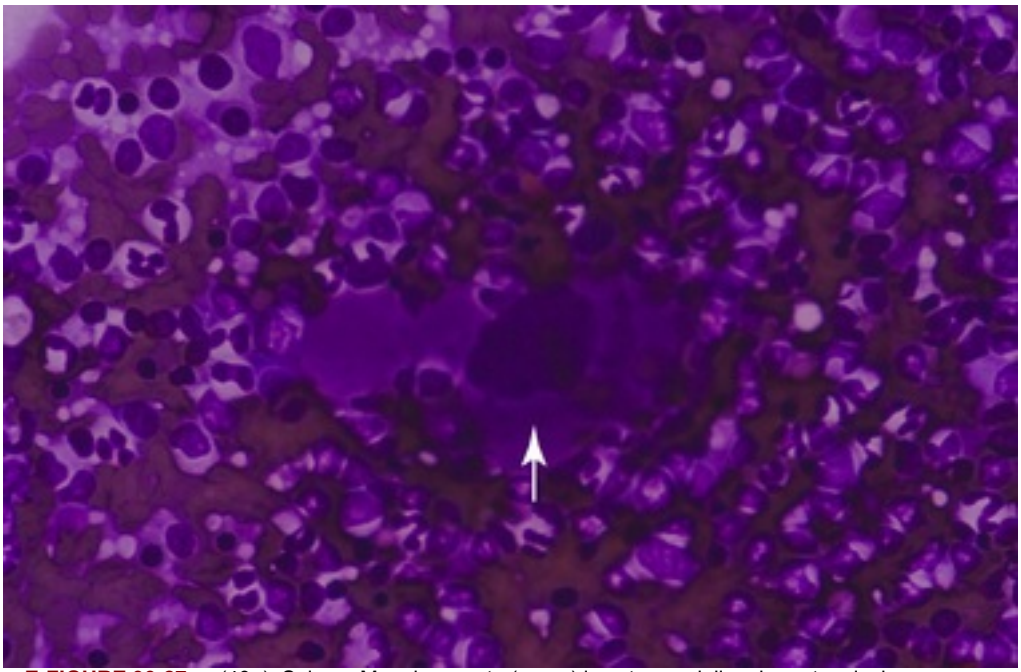
E-FIGURE 93-24 (100×). Spleen. Normal cat spleen showing lymphoblasts (L), lymphocytes (l), neutrophils (nt) and red blood cells (RBC).



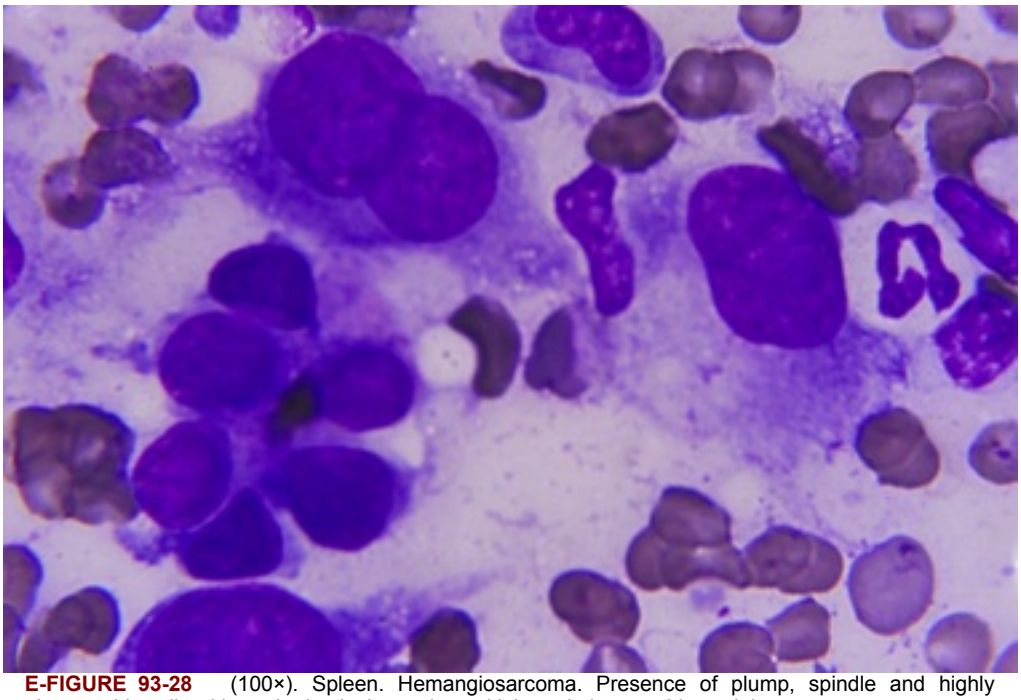
E-FIGURE 93-25 (100×). Spleen. Marked plasma cell hyperplasia.



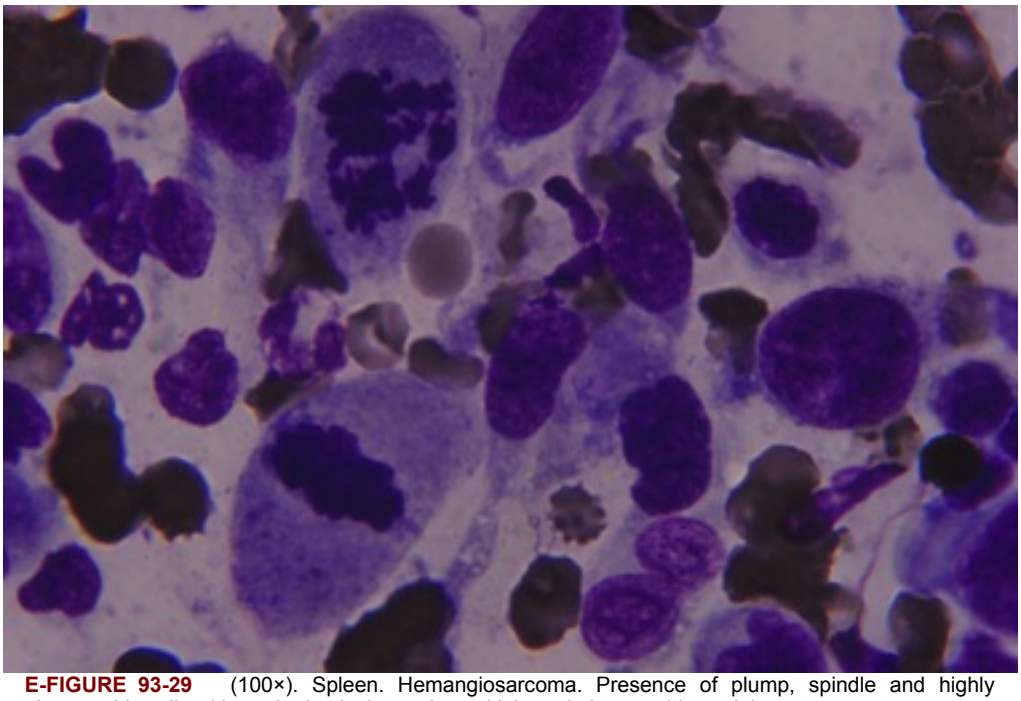
E-FIGURE 93-26 (100×). Spleen. Extramedullary hematopoiesis. This image shows the predominance of the erythroid line in a spleen with *Leishmania* amastigotes (arrows).



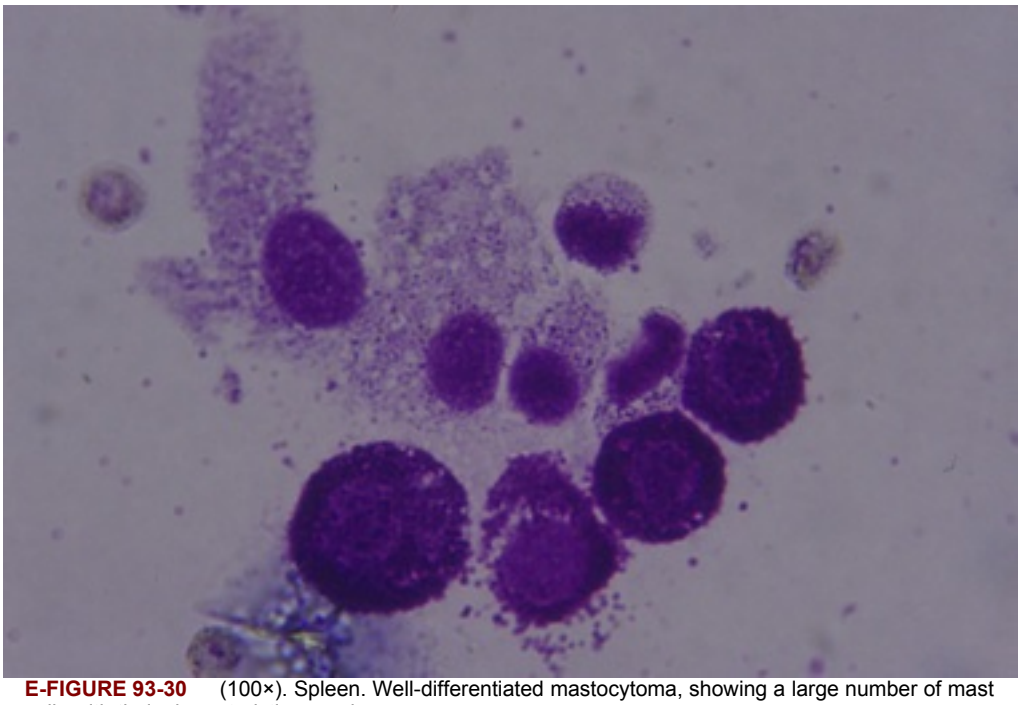
E-FIGURE 93-27 (40×). Spleen. Megakaryocyte (arrow) in extra-medullary hematopoiesis.



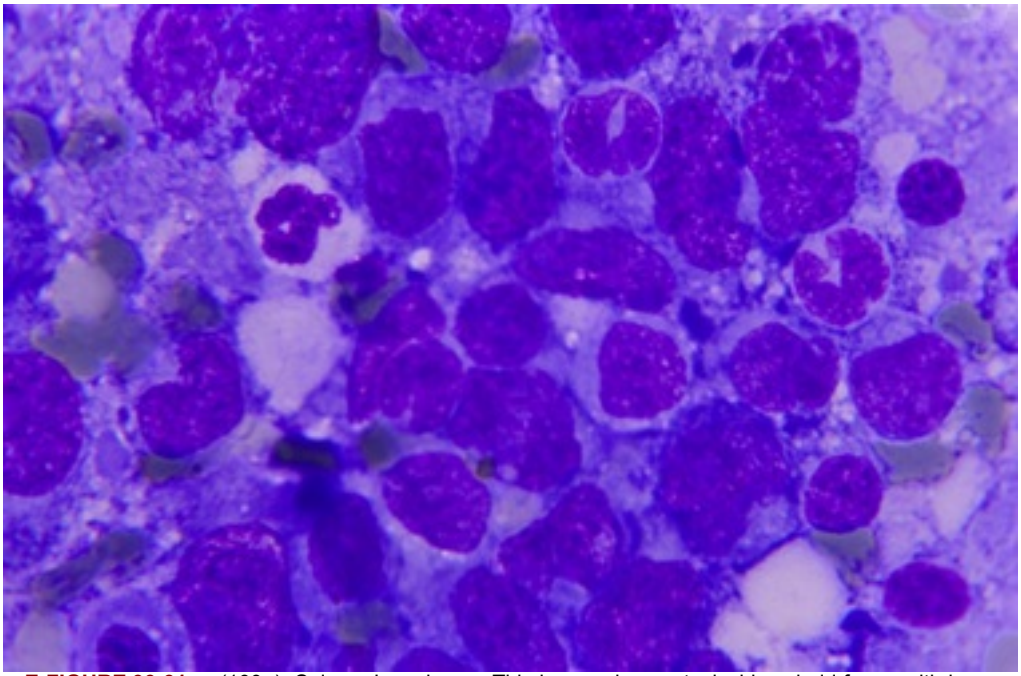
E-FIGURE 93-28 (100×). Spleen. Hemangiosarcoma. Presence of plump, spindle and highly pleomorphic cells with marked anisokaryosis, multiple and pleomorphic nuclei.



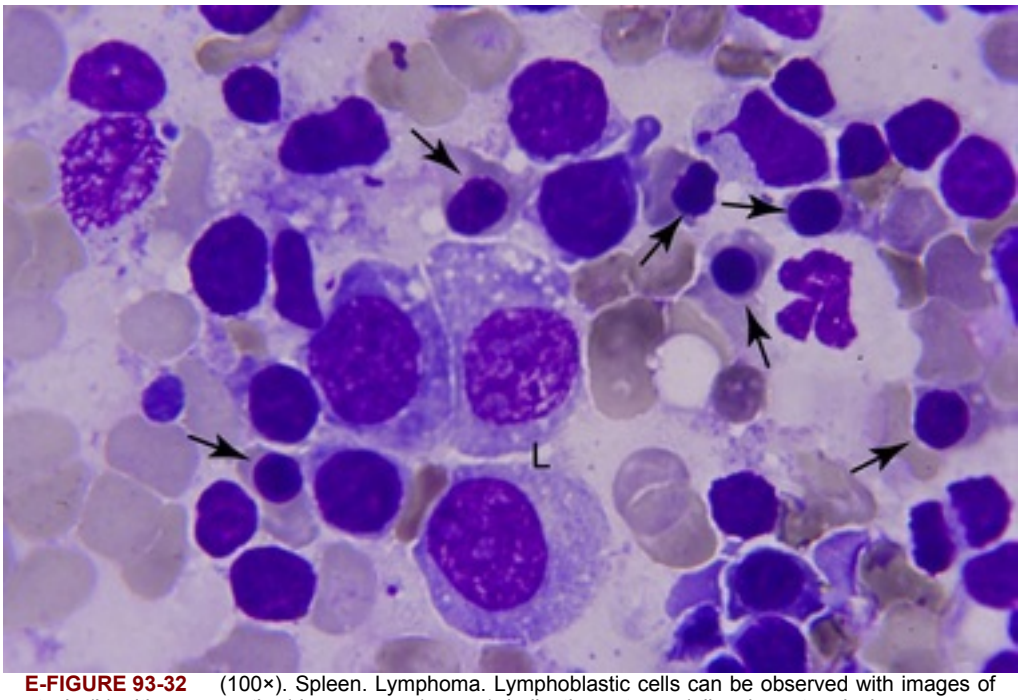
E-FIGURE 93-29 (100×). Spleen. Hemangiosarcoma. Presence of plump, spindle and highly pleomorphic cells with marked anisokaryosis, multiple and pleomorphic nuclei.



E-FIGURE 93-30 (100×). Spleen. Well-differentiated mastocytoma, showing a large number of mast cells with their characteristic granules.



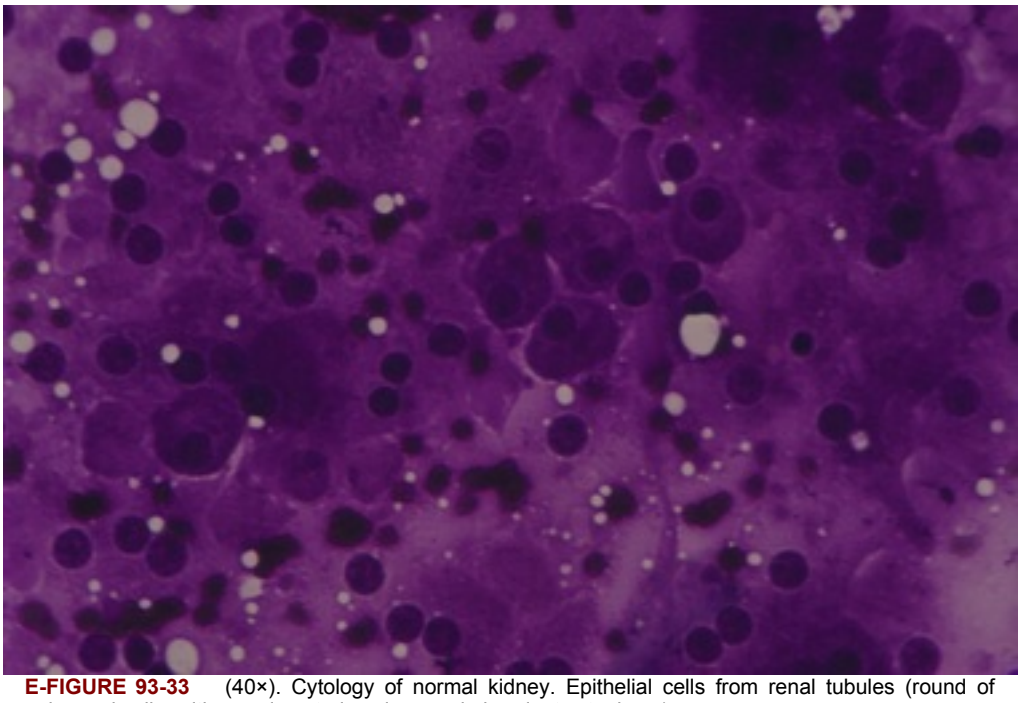
E-FIGURE 93-31 (100×). Spleen. Lymphoma. This image shows atypical lymphoid forms with large nuclei and irregular contours.



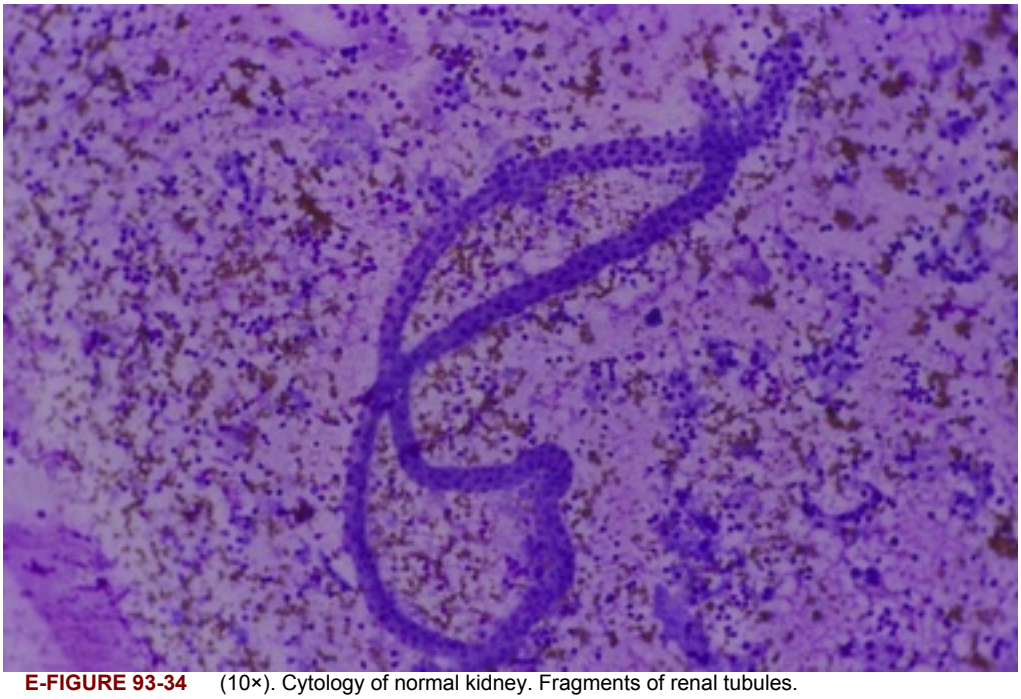
E-FIGURE 93-32 (100×). Spleen. Lymphoma. Lymphoblastic cells can be observed with images of atypia (L) with some erythroid precursors (arrows), indicating extramedullary hematopoiesis.

Kidney

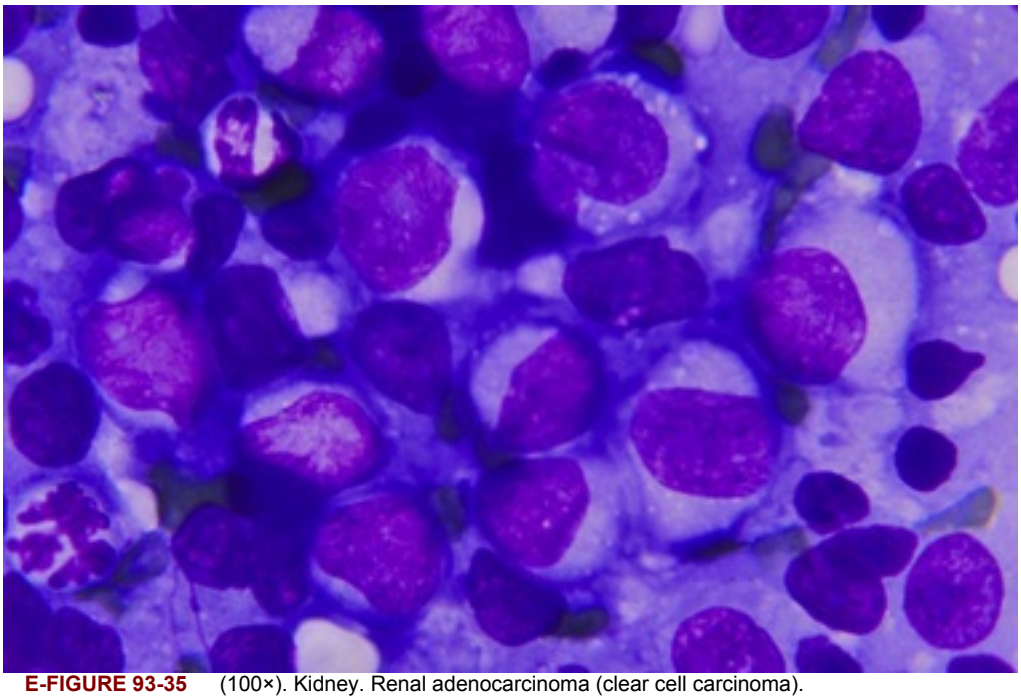
It is preferable to sedate or anesthetize dogs and cats for this procedure. Fine needle aspiration may be indicated if there is evidence of atypical renal enlargement or suspicion of a cyst, abscess or neoplasia. Little information is gained from aspirating atrophic kidneys. Complications are uncommon but excessive hemorrhage has been reported. Normal cytology includes round (E-Figure 93-33) or polygonal cells in cords (E-Figure 93-34), fragments of renal tubules, often with some blood contamination. Metastatic tumors are more common than primary tumors. Epithelial tumors are most common in older dogs (mostly carcinomas, E-Figures 93-35 and 93-36). Some tumors (adenocarcinoma and melanoma) may be bilateral. The most common renal tumor in cats is lymphoma.



E-FIGURE 93-33 (40×). Cytology of normal kidney. Epithelial cells from renal tubules (round of polygonal cells, with round central nucleus and abundant cytoplasm).



E-FIGURE 93-34 (10×). Cytology of normal kidney. Fragments of renal tubules.



E-FIGURE 93-35 (100×). Kidney. Renal adenocarcinoma (clear cell carcinoma).

Lymph Nodes

Aspiration is indicated when a node or nodes is/are enlarged or irregular. The purpose of cytology is to identify any neoplastic process. Cytology of normal lymph nodes includes small lymphocytes with lesser numbers of lymphoblasts (E-Figure 93-37) and immunoblasts. In hyperplasia (reactive lymphadenopathy), the enlarged node may have normal cytological characteristics but greater cell polymorphism and macrophage counts. Increased macrophage numbers are also seen in granulomatous lymphadenitis, but the macrophages tend to form groups (E-Figure 93-38) or may appear to blend into multinucleate cells. A predominance of plasma cells (plasmacytic hyperplasia, E-Figure 93-39) typically follows strong antigen stimulation. Attempts should always be made to detect parasites such as *Leishmania* spp. (E-Figure 93-40), but false negatives are common. As with cytology of the spleen or liver, there can be extramedullary hematopoiesis (E-Figure 93-41). Lymphoma (primary neoplasia) is cytologically divided into small- or large-cell lymphomas. Small-cell lymphoma (lymphocytic lymphoma) usually appears cytologically as a monotonous population of well-differentiated small lymphocytes which often fragment to produce varying sized cytoplasmatic pieces called lymphoglandular bodies (Figure 93-42). Medium- and large-cell lymphomas, called lymphoblastic lymphoma (E-Figures 93-43 and 93-44), typically include more than 50% lymphoblasts and abundant lymphoglandular bodies. Fewer lymphoglandular bodies may aid in distinguishing benign hyperplasia (E-Figure 93-45) from a malignant process. Morphological characteristics can be affected by the fixation and drying techniques used. The existence of lymphoma-imitating processes may interfere with establishing a definitive diagnosis. The most common neoplasms to metastasize to lymph nodes are carcinomas (E-Figure 93-46), mastocytomas, and malignant melanomas (E-Figure 93-47).

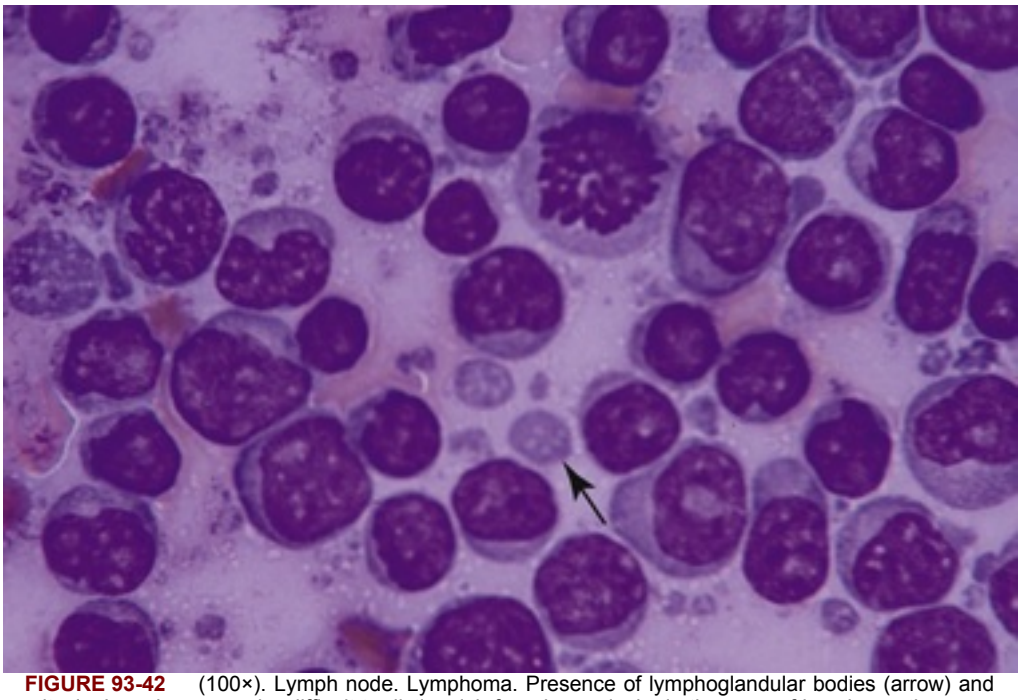
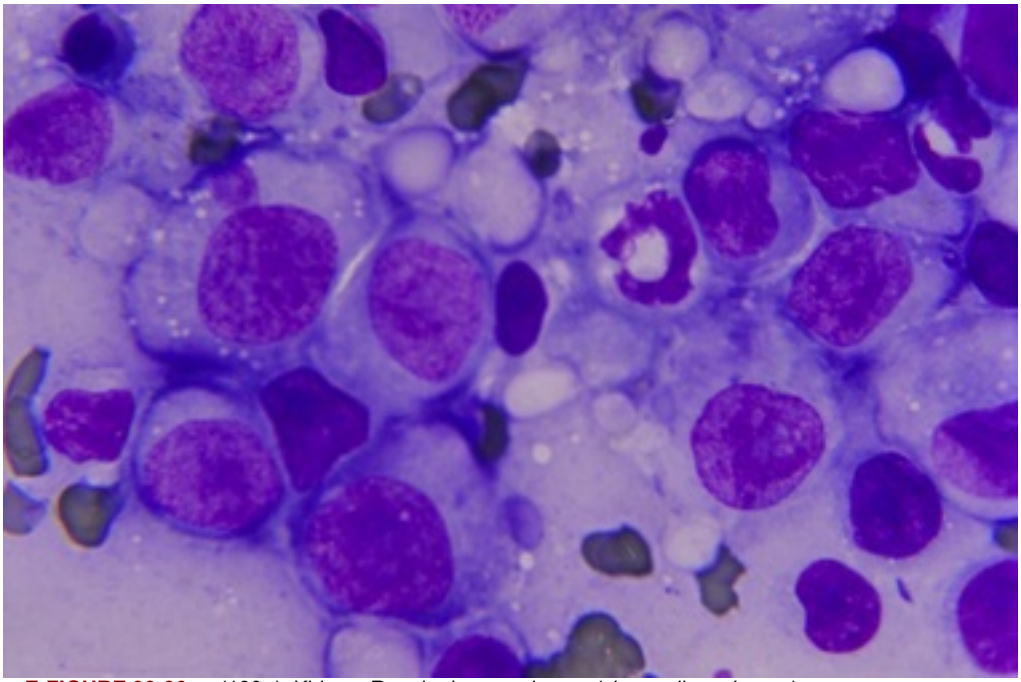
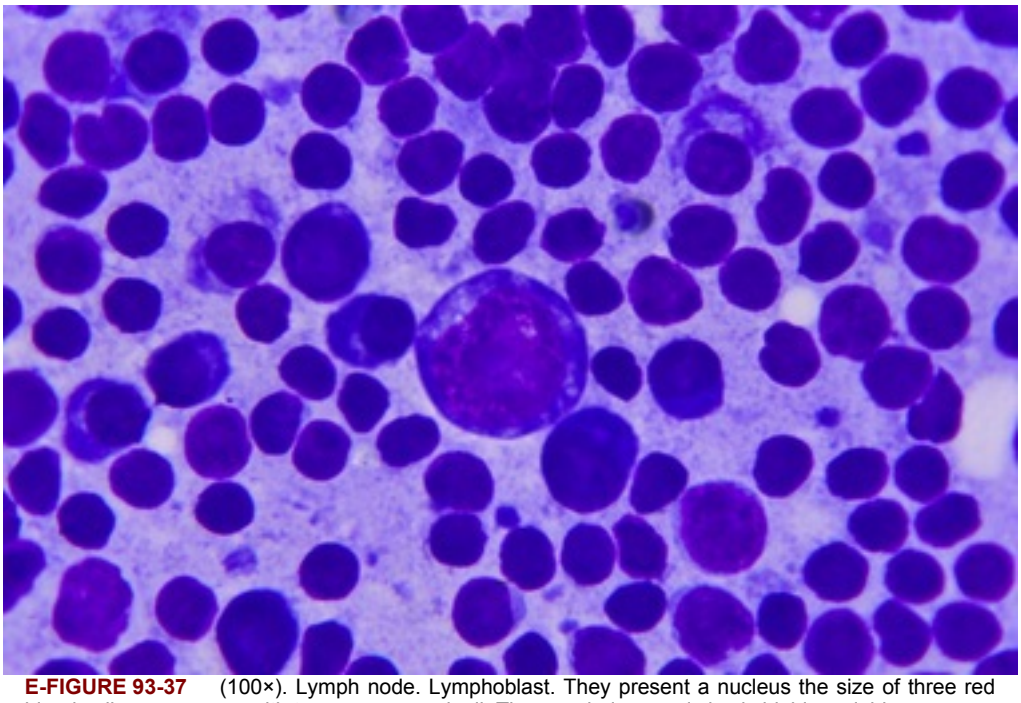


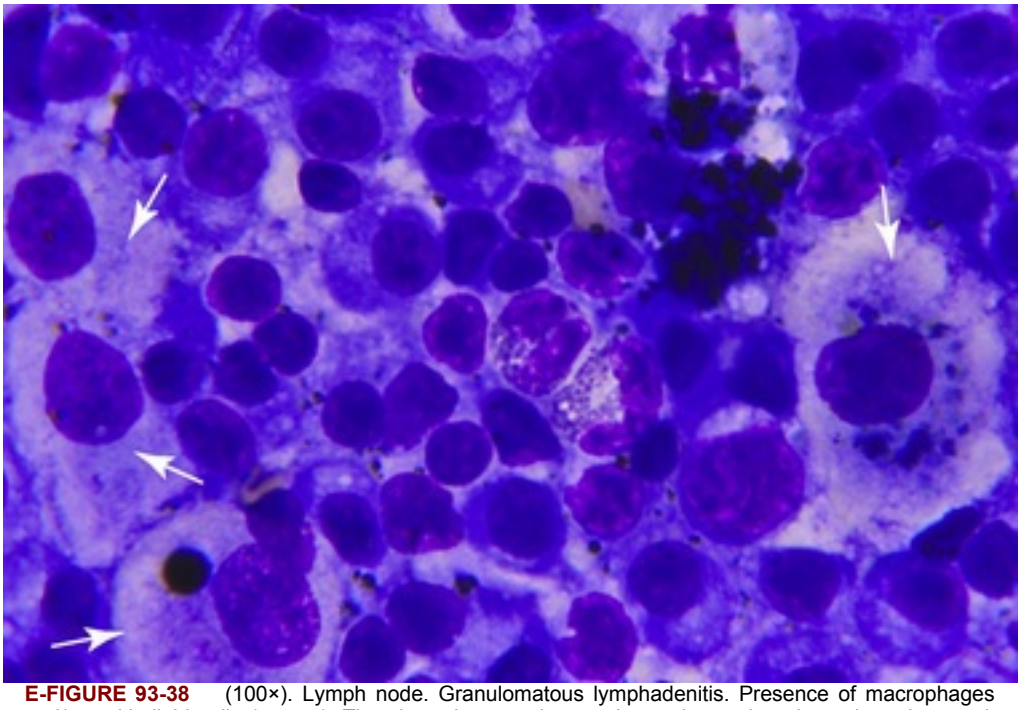
FIGURE 93-42 (100×). Lymph node. Lymphoma. Presence of lymphoglandular bodies (arrow) and mitosis. Lymphoma can be difficult to distinguish from hyperplasia; in the case of lymphoma there are generally more lymphoglandular bodies as a result of cell damage and the cell population is more homogeneous.



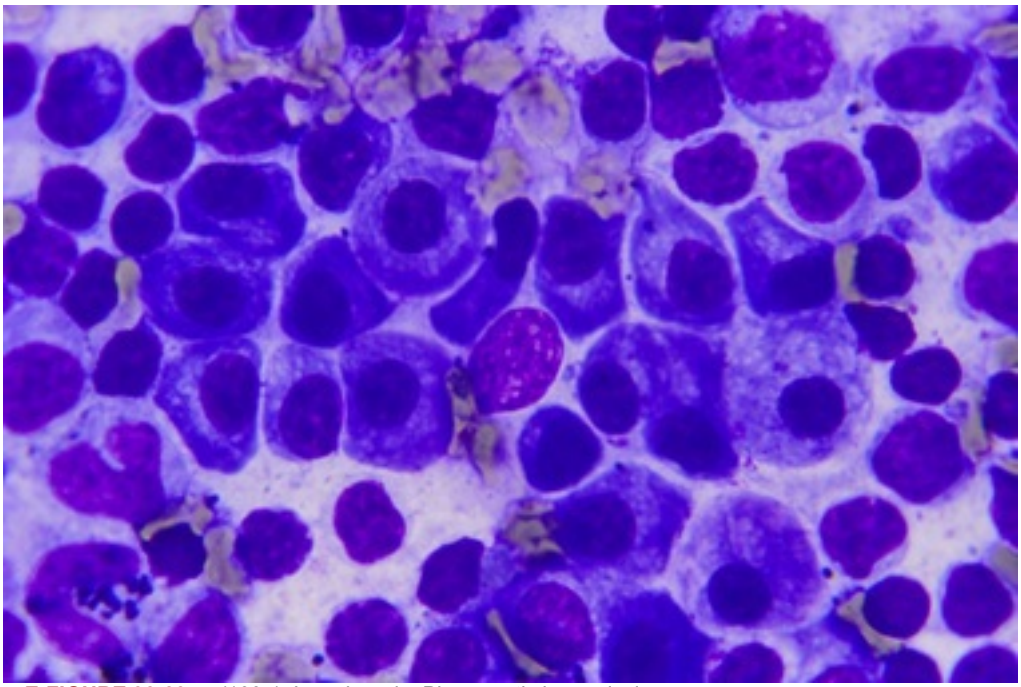
E-FIGURE 93-36 (100×). Kidney. Renal adenocarcinoma (clear cell carcinoma).



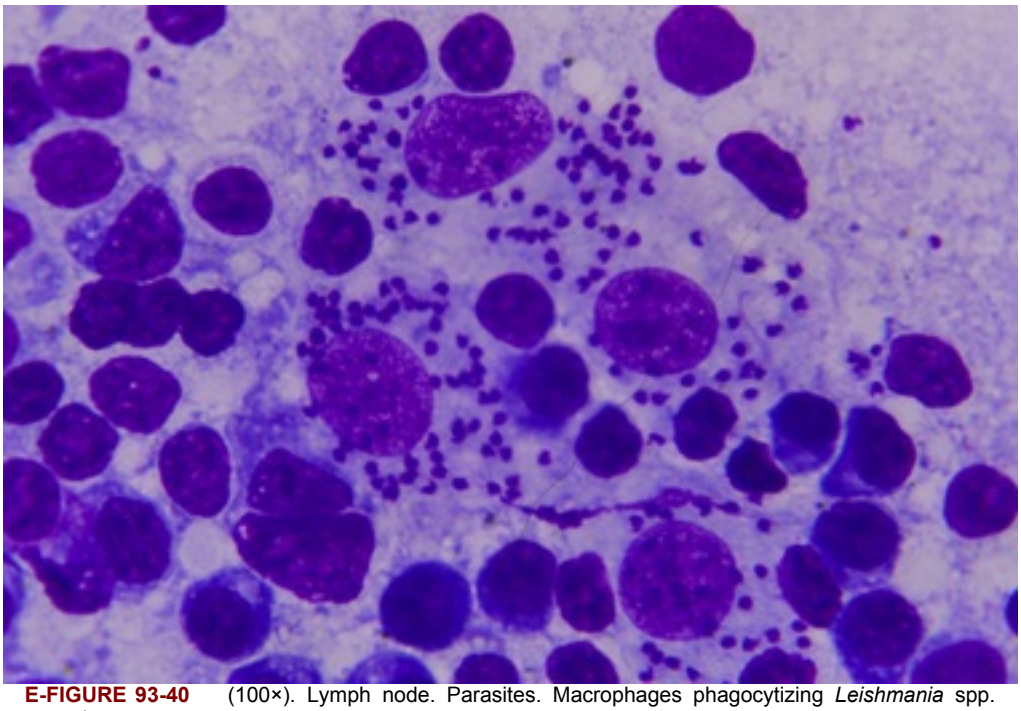
E-FIGURE 93-37 (100×). Lymph node. Lymphoblast. They present a nucleus the size of three red blood cells on average, with two or more nucleoli. The morphology and size is highly variable.



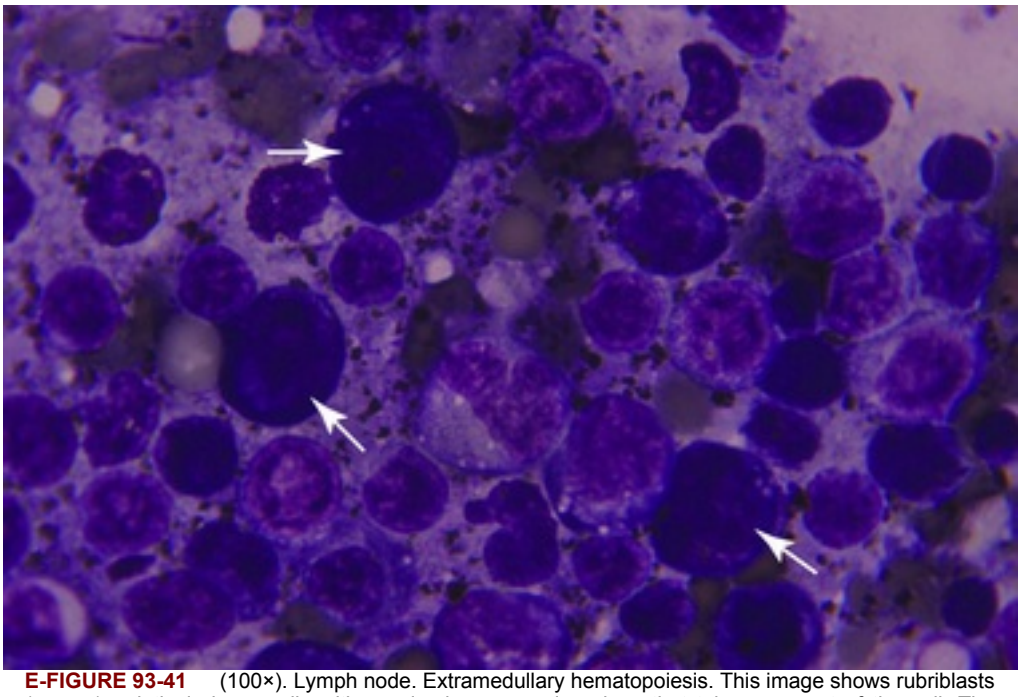
E-FIGURE 93-38 (100×). Lymph node. Granulomatous lymphadenitis. Presence of macrophages and/or epithelioid cells (arrows). They have large, pale cytoplasm; the nucleus is oval or elongated, with one or more visible nucleoli.



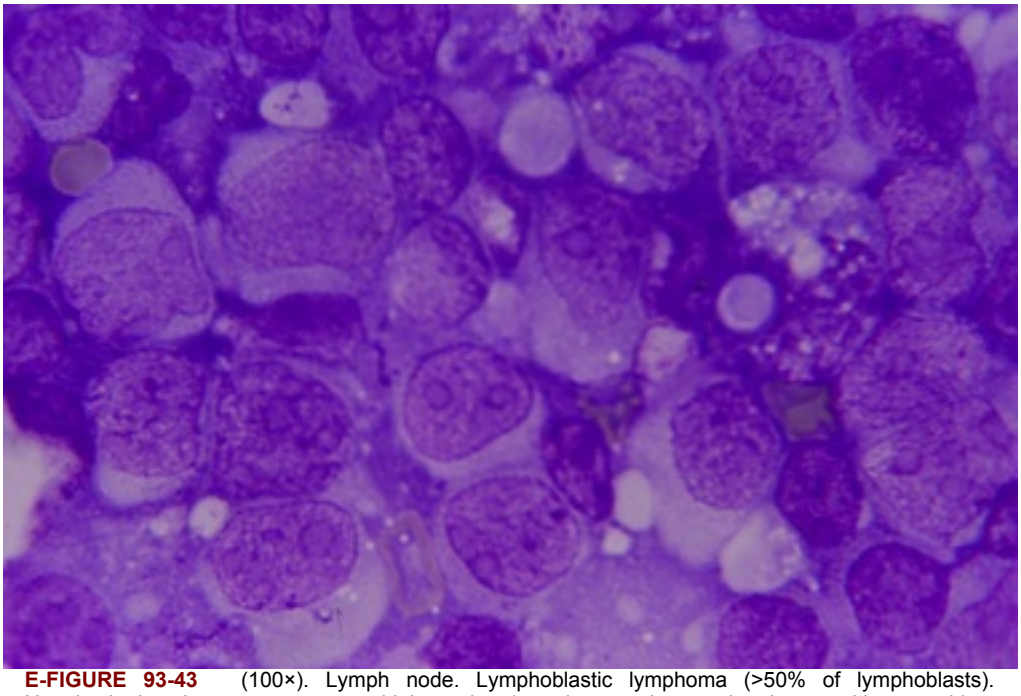
E-FIGURE 93-39 (100×). Lymph node. Plasmacytic hyperplasia.



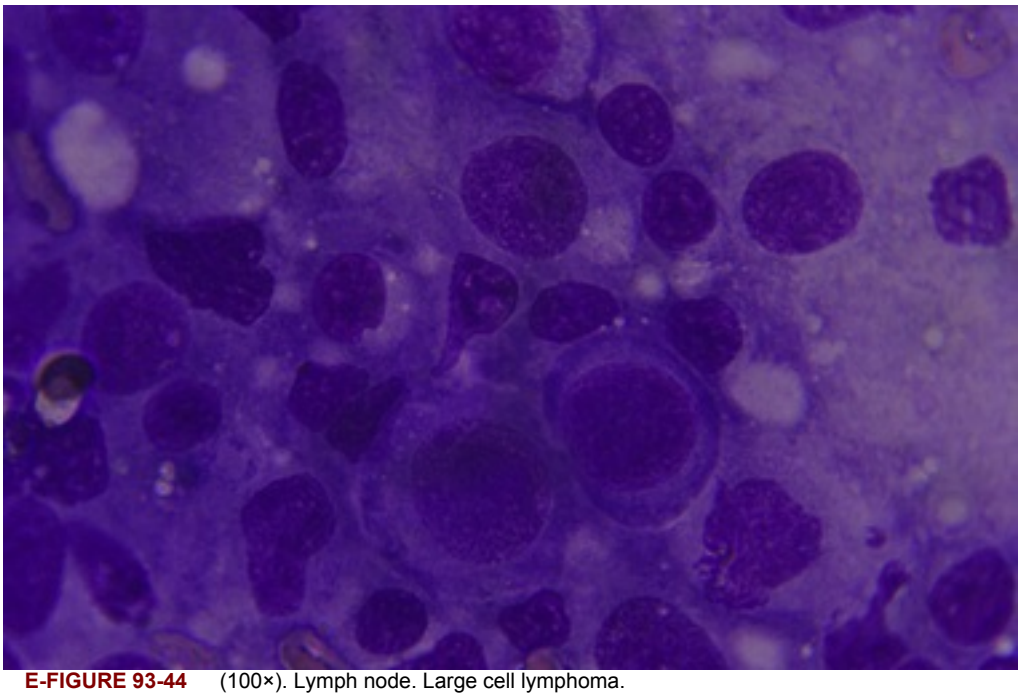
E-FIGURE 93-40 (100×). Lymph node. Parasites. Macrophages phagocytizing *Leishmania* spp. amastigotes.



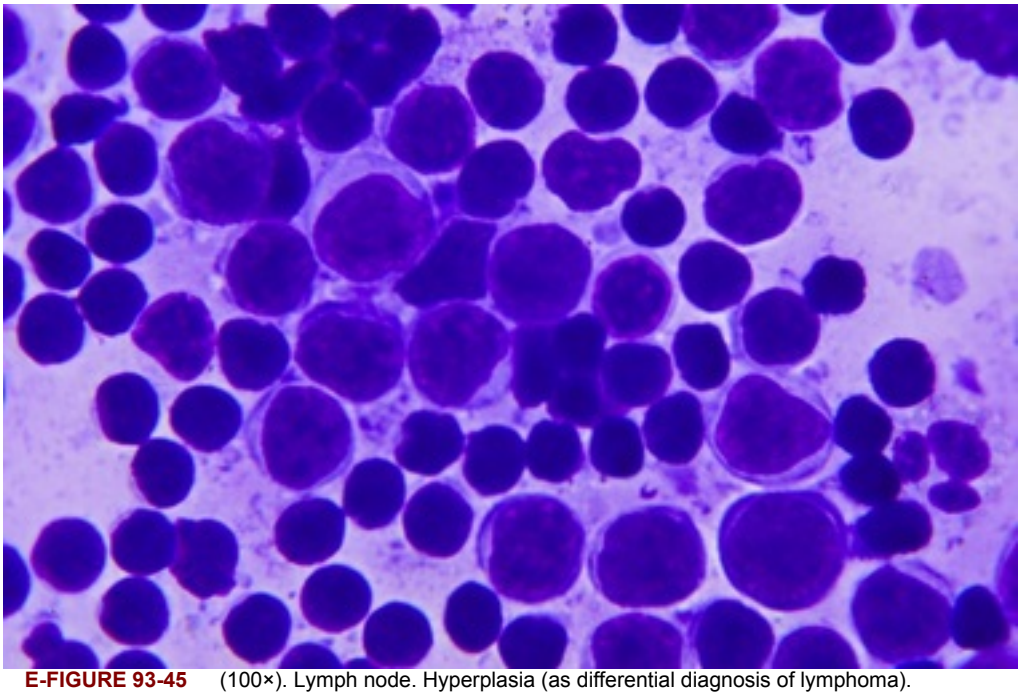
E-FIGURE 93-41 (100×). Lymph node. Extramedullary hematopoiesis. This image shows rubriblasts (arrows), relatively large cells with a voluminous round nucleus that takes up most of the cell. The small amount of cytoplasm is highly basophilic (very dark blue).



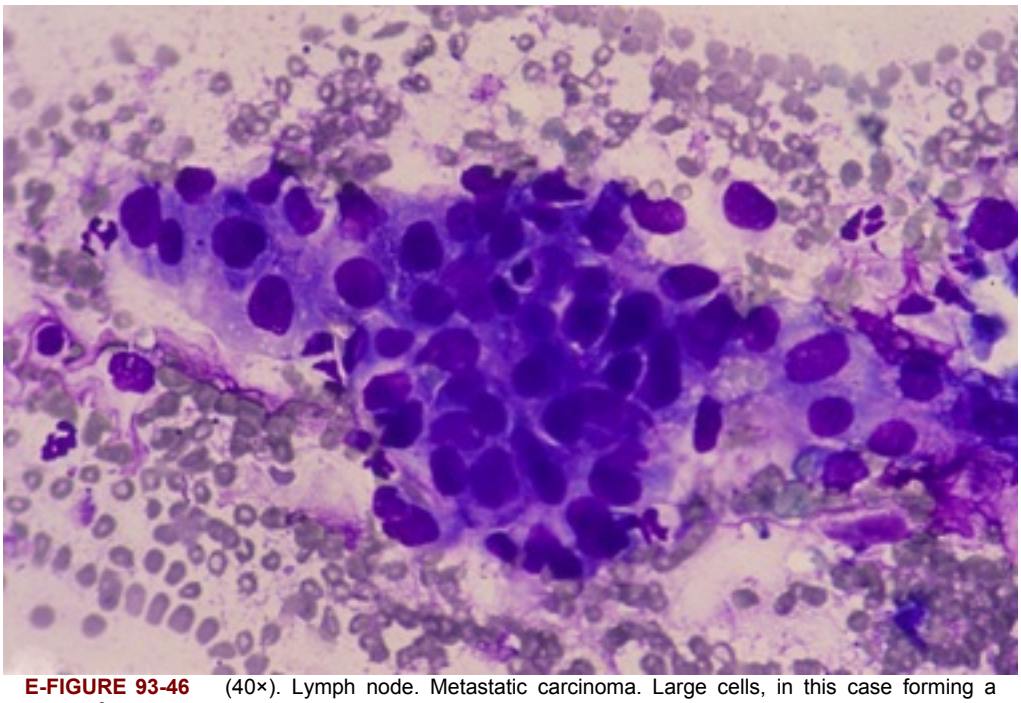
E-FIGURE 93-43 (100×). Lymph node. Lymphoblastic lymphoma (>50% of lymphoblasts). Neoplastic lymphocytes present a high nucleus/cytoplasm ratio, nearly always with an evident nucleolus. Lysate cells (bare nuclei) and cells with partial lysis present nucleolar tumefaction, imitating lymphoblasts.



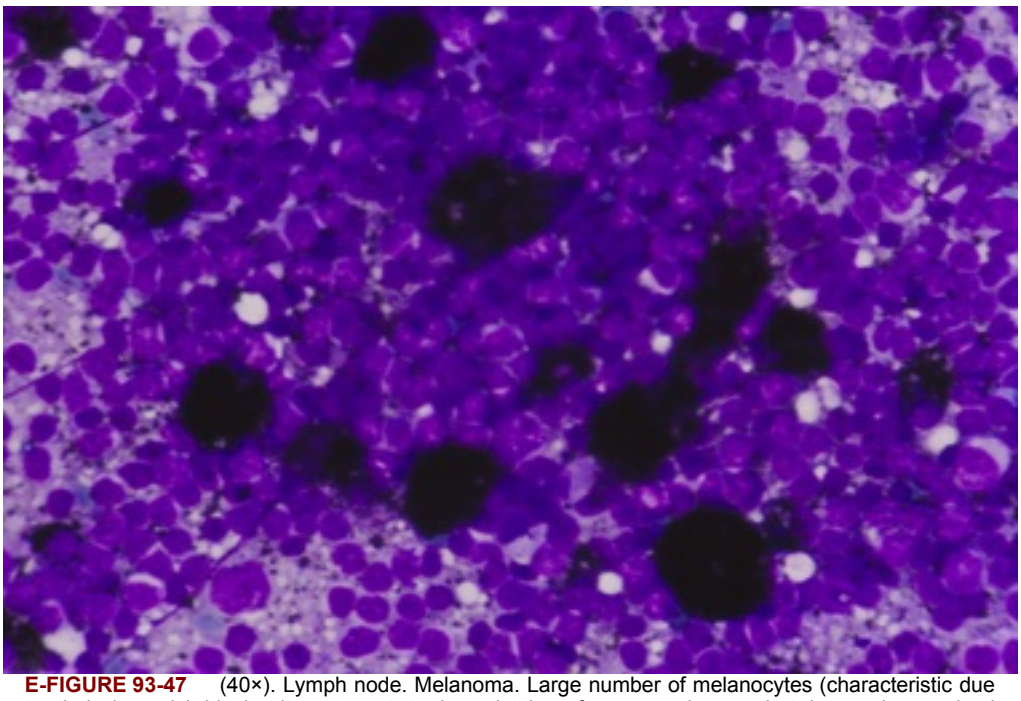
E-FIGURE 93-44 (100×). Lymph node. Large cell lymphoma.



E-FIGURE 93-45 (100×). Lymph node. Hyperplasia (as differential diagnosis of lymphoma).



E-FIGURE 93-46 (40×). Lymph node. Metastatic carcinoma. Large cells, in this case forming a group of squamous appearance.

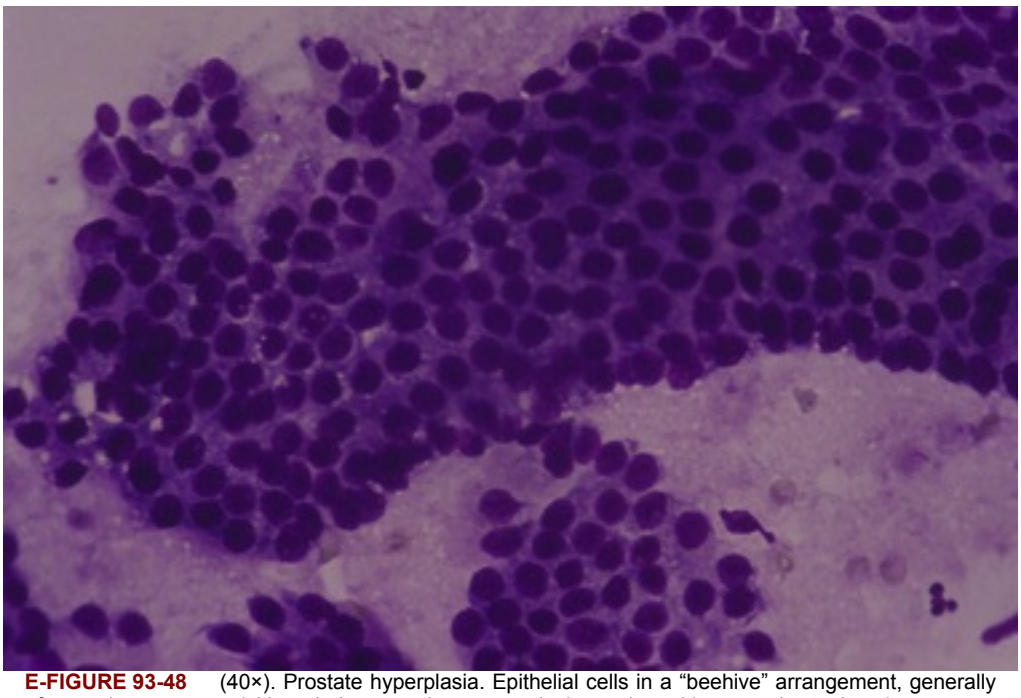


E-FIGURE 93-47 (40×). Lymph node. Melanoma. Large number of melanocytes (characteristic due to their brownish-black pigment, not to be mistaken for macrophages that have phagocytized pigments).

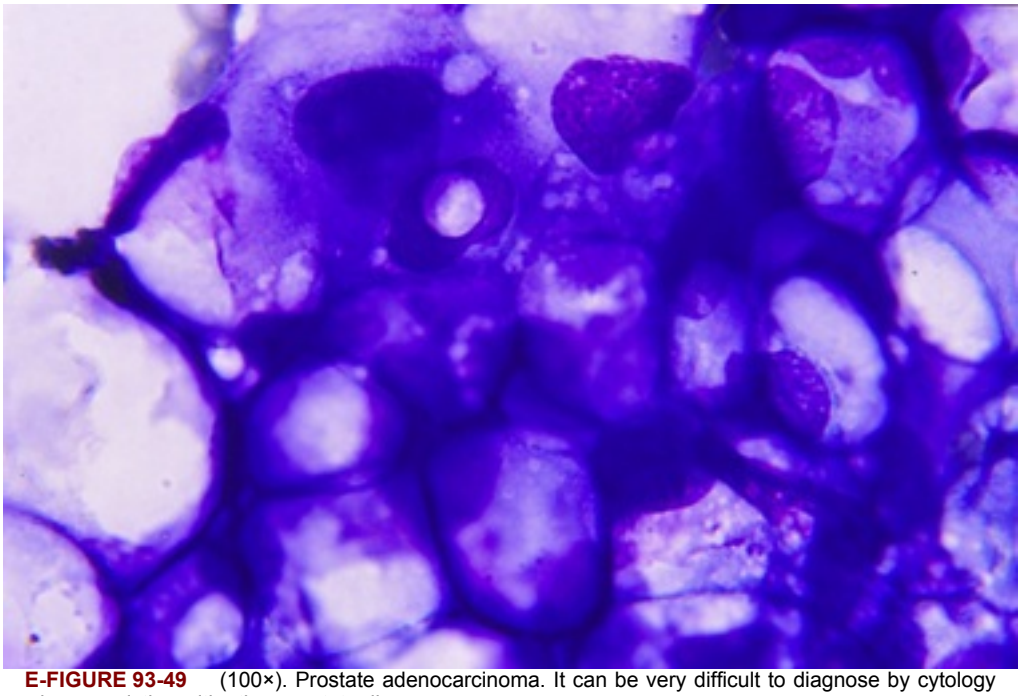
Prostate

Prostatic cytology is normally typified by groups of cubic or cylindrical cells in "beehive" arrangements. In benign prostate hyperplasia, cells appear normal but with a slightly increased nucleus/cytoplasm ratio (E-Figure 93-48). Prostate abscesses have large numbers of neutrophils, many of them degenerated. In squamous metaplasia, there are large numbers of squamous cells which may be difficult to distinguish from

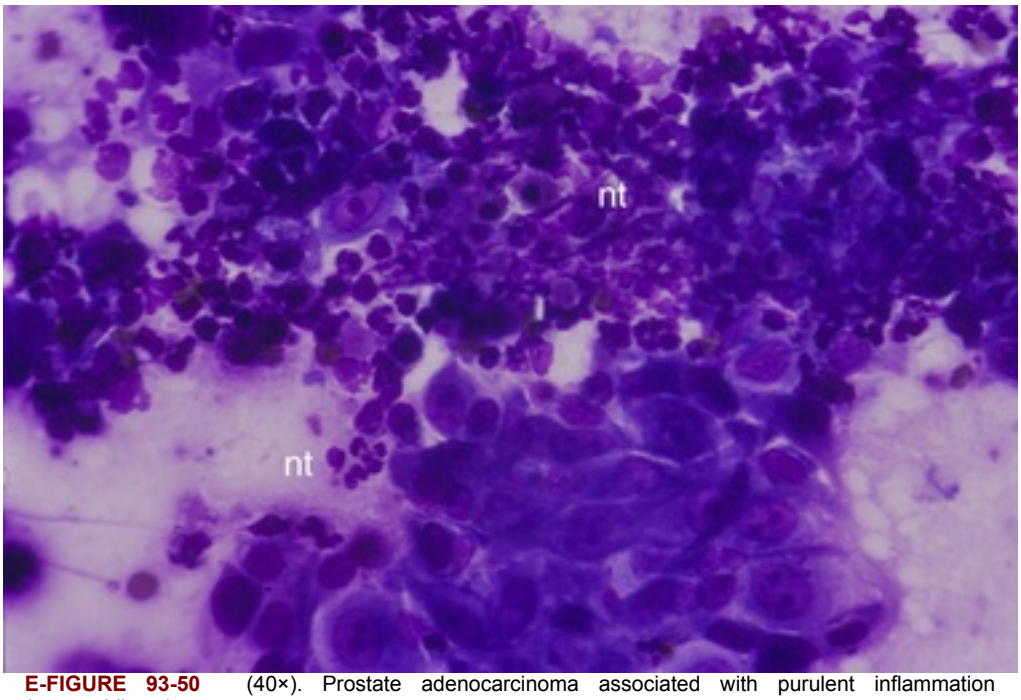
contamination with squamous cells of the distal urethra when samples are obtained by massage. Prostate neoplasias are uncommon and typically malignant. Adenocarcinoma, the most common tumor of the prostate, is difficult to diagnose with cytology (E-Figures 93-49 and 93-50). Transitional cell carcinoma is less common.



E-FIGURE 93-48 (40×). Prostate hyperplasia. Epithelial cells in a "beehive" arrangement, generally of normal appearance (although there can be some anisokaryosis and increased cytoplasm).



E-FIGURE 93-49 (100×). Prostate adenocarcinoma. It can be very difficult to diagnose by cytology when coexisting with other prostate diseases.



E-FIGURE 93-50 (40×). Prostate adenocarcinoma associated with purulent inflammation (neutrophils, nt).

Others

Urethral discharges (ch. 44), semen (ch. 111 and 318), urinary sediment (ch. 72), traumatic prostate or bladder aspirates (ch. 111), and transtracheal and bronchoalveolar lavage specimens (ch. 101) are each submitted to clinical pathologists on occasion. Such examinations can be of value.

CHAPTER 94

Arthrocentesis and Arthroscopy

Jonathan D. Dear

Client Information Sheet: Arthrocentesis and Arthroscopy

Anatomy and Physiology

Synovial joints are composed of two or more articulating bones with a superficial layer of articular cartilage, synovium and synovial fluid. Some joints may also contain intra-articular menisci, ligaments or fat pads. The synovium is a thin membrane of synoviocytes spanning the articulating bones to create an enclosed "compartment." Synoviocytes are characterized as either type A (phagocytic) or type B cells that secrete hyaluronan and other components into joint and surrounding extracellular fluid (ECF) spaces. Synovial fluid is a dialysate of plasma and is, in health, relatively acellular. Synovial fluid not only lubricates cartilage, but it also delivers nutrients to this tissue that has little direct blood supply. The elastic and thick viscosity of joint fluid accounts for its lubricating qualities. Any condition that causes joint inflammation may lead to abnormally porous synovial vessels and an accumulation of ECF, inflammatory mediators, and leukocytes in the joint space. This process decreases joint fluid viscosity, causes pain, and increased susceptibility to structural damage and development of arthritis.

Background and Indications

Arthrocentesis, joint fluid aspiration, is a technique for obtaining fluid from distal joints. Potentially valuable information, gained from gross and cytologic analysis of joint fluid, may aid in determining cause of swollen joints, lameness, fever, or polysystemic disease. While not technically challenging, there is a steep learning curve to these procedures. Once competent and confident, joint fluid analysis can be employed as a diagnostic aid in a variety of scenarios. It is particularly useful in evaluating dogs with obvious joint abnormalities, but also for dogs with fever of unknown origin (FUO) and those with vague signs of malaise. Indications for arthrocentesis are thoroughly reviewed (see ch. 14, 15, 31, 48, and 59). Joint fluid analysis is also reviewed (see ch. 74). The goals of this chapter are to review the techniques and approaches to acquiring samples for cytologic and microbiologic assessment.

Results of arthrocentesis can be helpful in differentiating osteoarthritis from immune-mediated, infectious or neoplastic processes. The joint fluid analysis should complement information acquired from the history, physical examination, orthopedic and neurologic evaluations, laboratory and imaging studies. When indicated, radiographs of affected joints and limbs should precede arthrocentesis as the development of hemarthrosis can lead to difficulty in radiograph interpretation.

Techniques

Overview

The decision regarding the joint or joints to aspirate should be determined using the information gathered from clinical history, physical exam and orthopedic evaluation. On physical examination, however, joints may not be obviously abnormal in patients with shifting leg lameness, systemic illness, fever, or suspected immune-mediated polyarthritis. In these pets, one may choose to aspirate multiple joints (usually carpus and tarsus) to increase diagnostic yield. Results of arthrocentesis should be interpreted in the context of the patient's overall condition. While results of joint fluid analysis may provide insight into a patient's disease, it rarely provides a definitive diagnosis.

Patient Preparation and Positioning

Since joint disease may be painful, adequate analgesia, sedation or anesthesia should be provided. Sedation, as a minimum, is not only imperative for fractious or excitable patients, but it also allows safe joint fluid aspiration from calm pets, minimizing risk of the needle causing intra-articular harm. After the patient is sedated or anesthetized, they should be positioned in lateral recumbency. Often the carpal joint is aspirated from the medial aspect of the leg, requiring access to the dependent thoracic limb. There is also a technique using a dorsal or anterior approach to the carpal joint. Elbow, stifle and tarsus joints are usually aspirated using a lateral approach, requiring access to the nondependent or upper limb. Prior to arthrocentesis, the joints should be clipped and prepped aseptically alternating chlorohexidine with alcohol. Sterile gloves, needles and syringes should be used. Draping is not necessary. To reduce chances of the procedure causing joint trauma, blood contamination or pain, first manipulate the joint to find the degree of flexion that allows the largest "window" into the synovial space. Flexing the leg can be done by the veterinarian performing the arthrocentesis or by a technician. Should the veterinarian prefer to manipulate the leg and joint, they must perform the joint aspirate with one sterile hand (usually the dominant hand) and one non-sterile hand (usually the nondominant hand).

Sample Acquisition (Video 94-1)

Small (22-25 gauge), short needles are usually used for arthrocentesis as they are less likely to cause joint damage. The needle should be attached to a small (typically 3 cc) syringe, ensuring a good seal between needle and syringe. Before introducing the needle into the joint space, break "the seal" in the syringe to allow for smooth movement of the plunger. The needle should be inserted slowly into the joint, perpendicular to the skin. The carpal joint is shallow, while the elbow, stifle and tarsus joints may require insertion of the entire needle to retrieve fluid. If bone or cartilage is encountered or no joint fluid aspirated, the needle should be withdrawn slightly and redirected.

Gentle and intermittent negative pressure should be applied with the plunger once the needle has passed through the skin and into joint space. While only a small amount of fluid is required for analysis, sometimes as much as 0.5-1 mL can be easily aspirated from abnormal joints. Avoid excessive negative pressure which may lead to hemorrhage, reducing the value of most samples. Negative pressure should be completely released prior to withdrawing the needle from the patient to avoid blood contamination from the skin or SC tissues. Discard any needle and syringe with blood contamination. One may not be able to withdraw more than 0.2 mL from a normal joint. Thus, apparent absence of fluid may be indicative of a healthy joint.

Anatomic Landmarks (Figure 94-1)

The carpus joint is sampled at the proximal radiocarpal joint either along its medial or dorsal aspect. When using the dorsal approach, care should be taken to avoid the cephalic vein which courses across the joint surface. The tibiotarsal joint is accessed from the lateral aspect along the talus; again, care should be taken to avoid the superficial blood vessels in the area. The needle should be advanced parallel to the axis of the metatarsals, perpendicular to the tibia. The stifle can be aspirated from either medial or lateral approach. From either approach a longer needle (often 1½ inch) is generally required as the synovial fluid tends to accumulate caudal to the patellar fat pat.

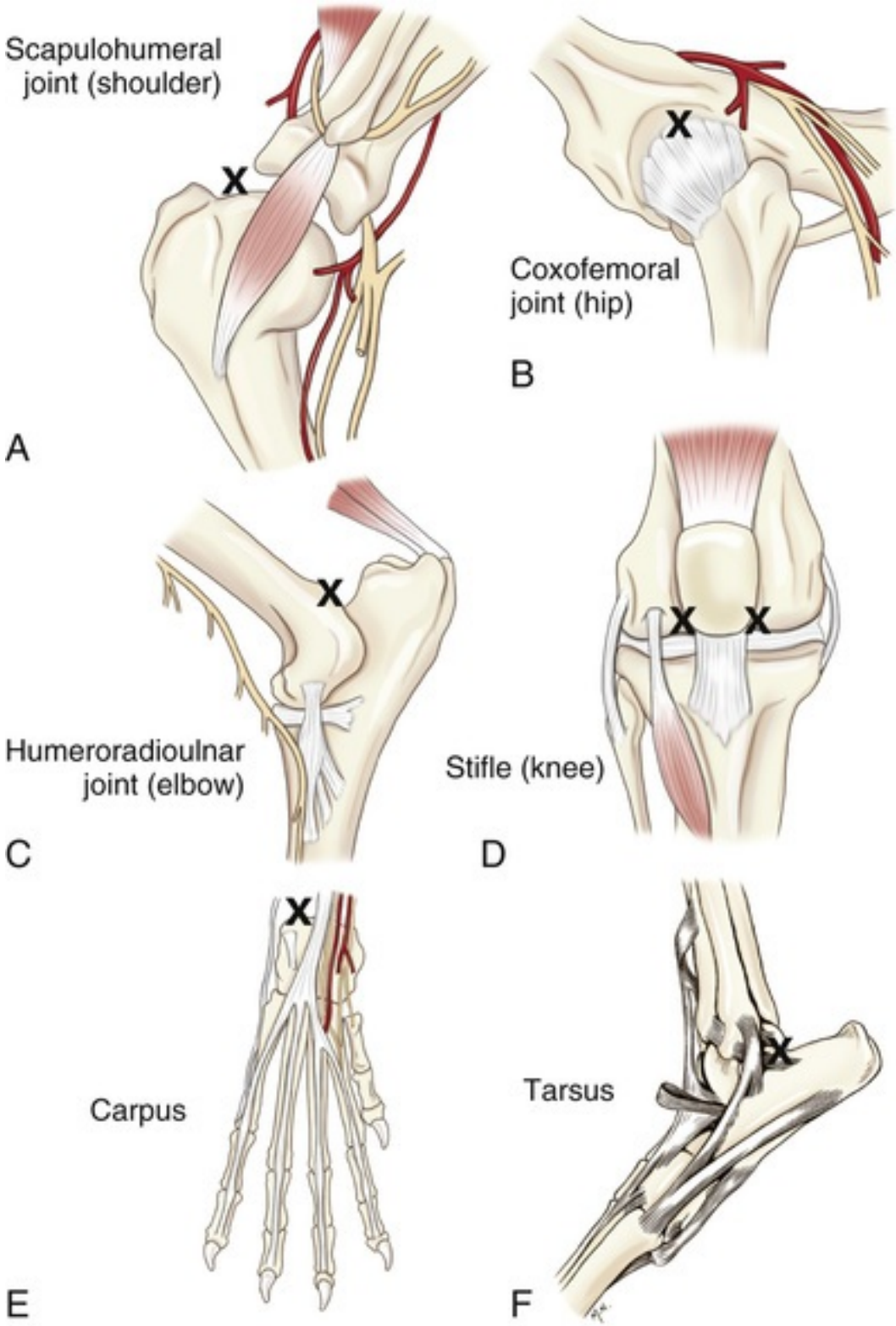


FIGURE 94-1 Sites of canine arthrocentesis (marked with an X). (**F,** From Evans HE, de Lahunta A: *Miller's anatomy of the dog,* ed 4, St Louis, 2013, Saunders.)

Fluid Handling

Synovial fluid should be submitted for cytologic analysis in an EDTA-containing tube and/or as prepared slides. This may depend on the volume of fluid aspirated. Slides can be prepared by dropping a small amount

of joint fluid onto a glass slide near the frosted edge and slowly spreading the sample across the slide using a second slide (see Video 95-1). Joint fluid and/or prepared slides should be evaluated by a clinical pathologist for color, turbidity, cellularity, differential cell count and cytologic inspection for infectious organisms or exfoliate neoplastic cells (E-Figures 94-2 through 94-5 and Table 94-1). A crude test of synovial fluid viscosity can be performed by stringing the sample between the thumb and index finger. Normal joint fluid should string 3-5 cm while joint fluid from affected joints will be less viscous and string shorter lengths. Lack of viscosity is due to lack of hyaluronan. It is recognized that assessing viscosity with one's fingers is subjective and may yield incorrect impressions.

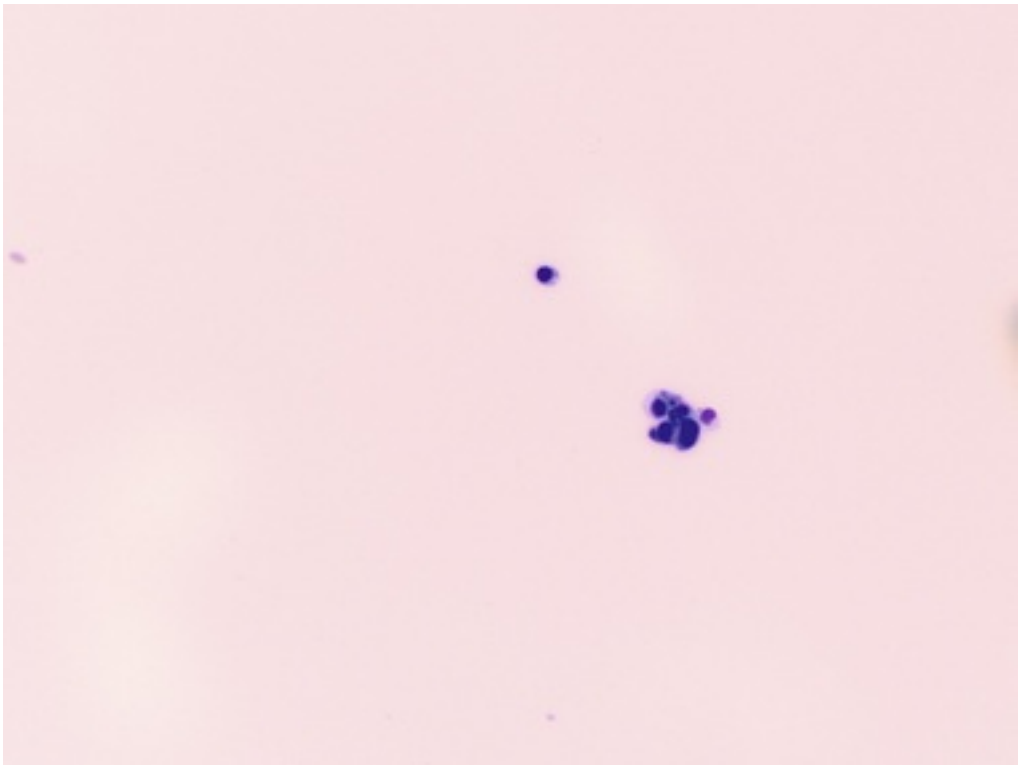
TABLE 94-1

Cytologic Characteristics of Synovial Fluid

CONDITION	COLOR	TURBIDITY	VISCOSITY	TOTAL PROTEIN (g/dL)	NUCLEATED CELLS (cells/mcL)	DIFFERENTIAL (%)	
						Mono	PMN
Normal	Colorless	Clear	High	<2.5	<3,000	>95	<5
Degenerative joint disease	Colorless	Clear	Variable	<2.5	<5,000	>90	<10
Trauma	Colorless to yellow	Hazy	Decreased	Variable	2,500-3,000	>75	<25
Infectious (e.g., bacterial, *Ehrlichia*)	Yellow to bloody	Cloudy	Decreased	>2.5	40,000-250,000	<10	>90
Immune-mediated (e.g., idiopathic, rheumatoid, erosive)	Yellow	Hazy	Decreased	>2.5	4,400-350,000	20-80	20-80

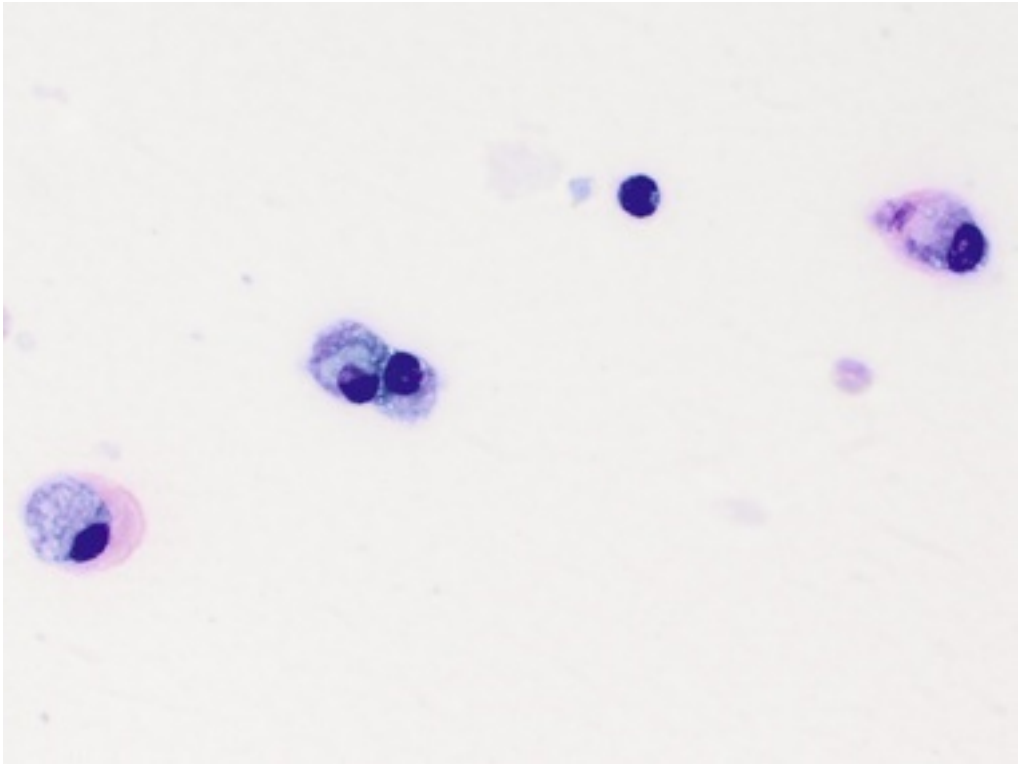
Mono, Monocytes; *PMN,* polymorphonuclear cells.

Adapted from MacWilliams PS, Friedrichs KR: Laboratory evaluation and interpretation of synovial fluid. *Vet Clin North Am Small Anim Pract* 33(1):153-178, 2003.

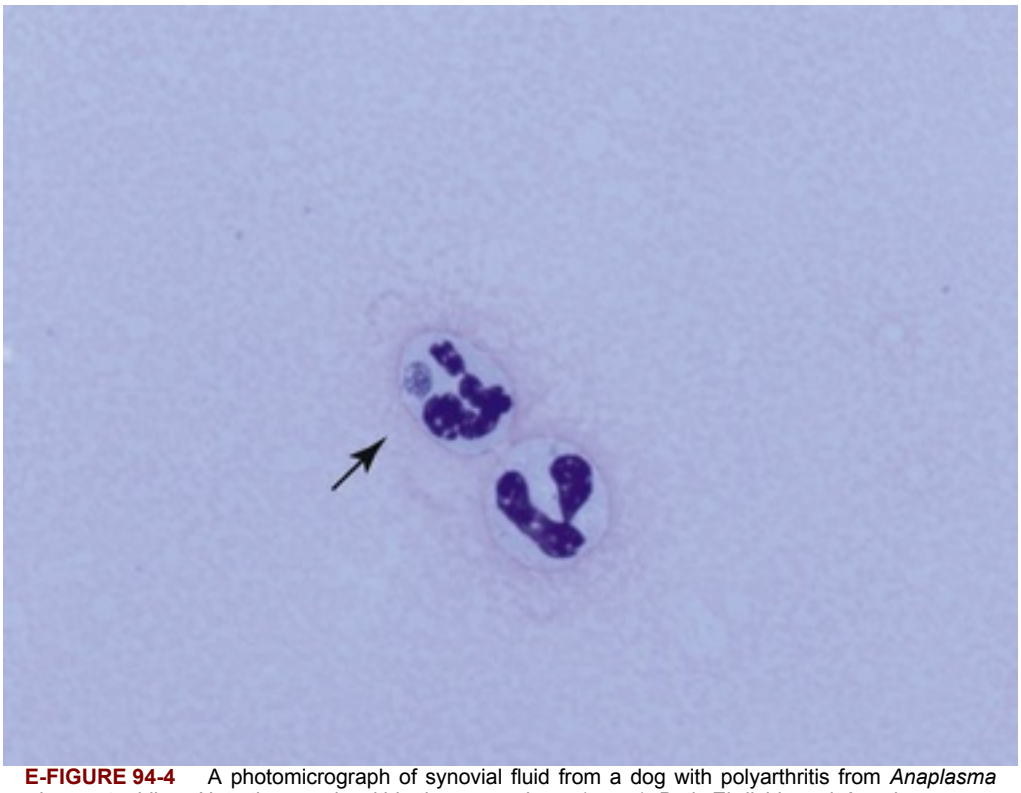


E-FIGURE 94-2 A photomicrograph of synovial fluid from a normal joint showing low cellularity and

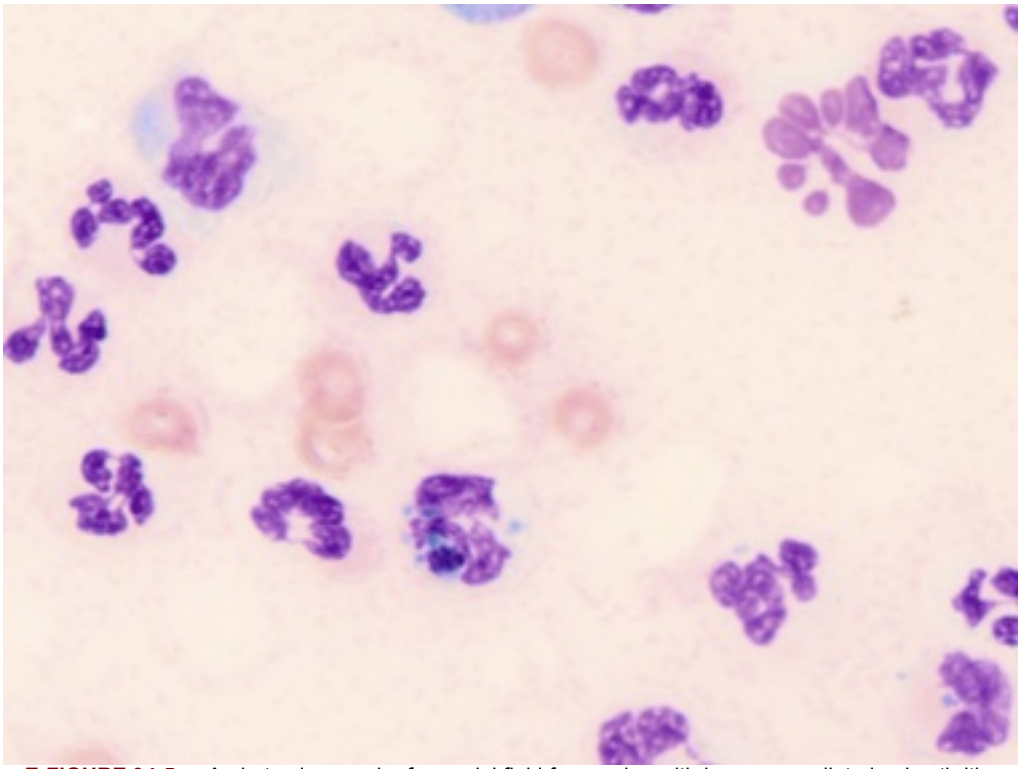
a pale pink hue in the background representative of hyaluronan. Cells within normal joint fluid should be primarily mononuclear. (Courtesy D. Schwartz, DVM, William Pritchard Veterinary Medical Teaching Hospital, UC Davis.)



E-FIGURE 94-3 A photomicrograph of synovial fluid from a dog with degenerative joint disease. Fluid from these joints may be slightly more cellular than that from a normal joint. Cells remain mononuclear, and may have an increased volume of vacuolated cytoplasm, as in this image. Increased numbers of small mononuclear cells can also be observed. (Courtesy D. Schwartz, DVM, William Pritchard Veterinary Medical Teaching Hospital, UC Davis.)



E-FIGURE 94-4 A photomicrograph of synovial fluid from a dog with polyarthritis from *Anaplasma phagocytophilum*. Note the morula within the macrophage (arrow). Both *Ehrlichia* and *Anaplasma* spp. can induce polyarthritis, but organisms are variably identified on cytology. (Courtesy D. Schwartz, DVM, William Pritchard Veterinary Medical Teaching Hospital, UC Davis.)



E-FIGURE 94-5 A photomicrograph of synovial fluid from a dog with immune-mediated polyarthritis. The cytologic features of IMPA include marked increased cellularity (mostly nondegenerate polymorphonuclear cells) with a notable absence of intra- or extracellular bacteria. (Courtesy A. Adedeji, DVM, William Pritchard Veterinary Medical Teaching Hospital, UC Davis.)

If the sample is of adequate volume and if clinically indicated, synovial fluid should be submitted for microbial culture and susceptibility testing in a sterile tube or culturette tube. If immediate results are needed, basic fluid analysis can be performed by assessing the total solids, color, turbidity, and microscopic appearance. The nucleated cell count can be roughly estimated by multiplying the number of nucleated cells per high power field by 1000. While the presence of intracellular bacteria is compelling evidence for a septic process, many cytologic features are subtle. Patients with septic arthritis often have non-degenerate neutrophils. Therefore, care must be used when interpreting in-house joint fluid evaluation. Full description of joint fluid analysis is available in ch. 74.

Suggested Readings

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CHAPTER 95

Lymph Node Aspiration and Biopsy

Takuo Ishida

Background

Lymphadenopathy (enlargement of the lymph node) is a concern because its differential diagnoses include a wide variety of worrisome pathologies. Enlarged lymph nodes are associated with neoplastic, infectious or immunologic conditions. Precise diagnosis, based on histologic evaluation of a biopsy, is mandatory to initiate appropriate treatment. The techniques usually utilized to obtain tissue from any enlarged peripheral or internal node are non-aspiration fine needle biopsy (FNB) or fine needle aspiration (FNA) for cytology. Cytology is both sensitive and specific in diagnosing neoplasia regardless of whether it is primary or metastatic.[1,2] Lymph node cytology, in combination with specific microbiologic techniques, is also of potential value for detecting evidence of infectious disease including leishmaniasis, ehrlichiosis, cryptococcosis, *Neorickettsia* infection, *Mycobacterium* infection, and others.[3-5]

It is advisable to sample more than one, if multiple nodes are enlarged. Biopsy or FNA of submandibular lymph nodes are usually avoided if others are available for sampling. Changes due to oral infection or from salivary gland cell contamination can make microscopic evaluation difficult. One should also try to avoid aspirating from the central area of severely enlarged nodes because of the possible sampling of necrotic tissue.[6] Superficial sampling may give inconclusive results due to central proliferation of indolent lymphoma cells in the node.[7]

The gold standard for trying to understand a cause for lymph node enlargement is to excise the entire node and have it submitted for histologic evaluation. Since the main purpose of histopathology is to obtain information on the tissue architecture, this method should always be considered if the patient can be safely anesthetized. Needle-core biopsies of lymph nodes can be attempted using manually-operated or automatic (Tru-Cut type) needles because the technique is straightforward and requires only sedation or light anesthesia. However, samples obtained in this manner often fail to provide proper and adequate samples for histopathology. The needle-core technique can be used when tissue architecture is not important for diagnosis, as in suspected infectious disease.

Lymph Node Cytology Techniques (Video 95-1)

Peripheral Nodes

Initially, one can attempt to obtain cells via non-aspiration FNB of the enlarged peripheral or intra-abdominal lymph node. A sterile 20- to 22-gauge (for large dogs) or 22- to 23-gauge (for small dogs and cats) needle is used. The skin over the peripheral lymph node should be gently cleaned with ethanol or isopropyl alcohol. The skin should be surgically prepared, if one is to biopsy an internal lymph node. While grasping the superficial node with one hand or with the ultrasound guide, the needle is held by the thumb and forefinger of the other hand. The needle is then inserted into the tissue, pulled back to the cortex without withdrawing, and redirected again deeper into the gland in a slightly different direction. Redirection of the needle and probing different areas is a procedure that should be repeated several times (5 times is excellent). Cells and fluid will collect within the needle lumen by capillary action (Figure 95-1, *A*). The needle is then removed from the node.

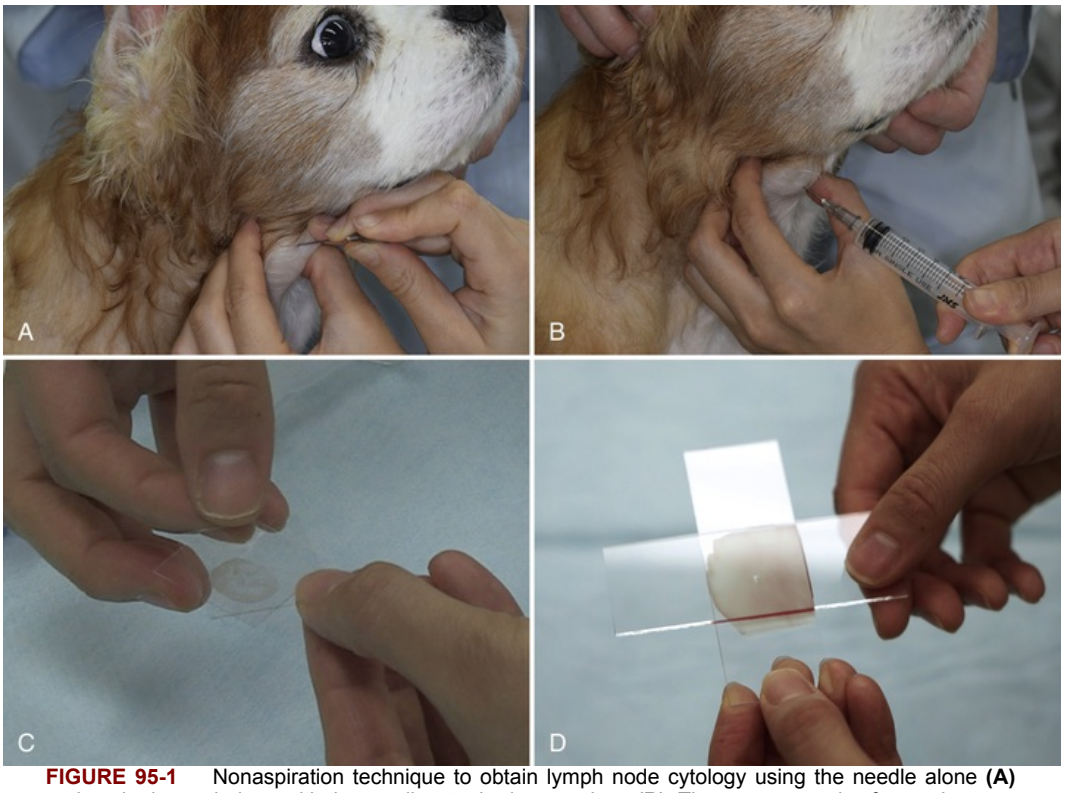

FIGURE 95-1 Nonaspiration technique to obtain lymph node cytology using the needle alone **(A)** and aspiration technique with the needle attached to a syringe **(B).** The smear samples for cytology are made either with two coverslips **(C)** or two glass slides **(D).**

Internal Nodes

If the tissue to be biopsied resides in the thoracic cavity, FNA should always be carried out with the needle attached to a 3- or 6-mL sterile syringe to avoid development of pneumothorax. The technique described here can also be used if an initial attempt at FNB failed to give adequate cells for an accurate cytologic diagnosis (Figure 95-1, *B*). Holding the lymph node or ultrasound guide with one hand, a sterile needle attached to a sterile syringe is inserted into the structure of interest. While pulling back on the plunger to generate a vacuum, the syringe held by the other hand should then be pulled back slightly. The needle tip should remain in the cortex area of the node. Then the vacuum pressure is released, and the needle should be advanced in a different direction before again applying vacuum. This needle redirection should be repeated more than once, 5 times whenever possible. When finished, the vacuum is again released and the needle gently withdrawn.

The needle should then be removed from the syringe and the syringe filled with air before being reattached to the needle. For both FNB and FNA, any material inside the needle should be gently expelled onto a clean coverslip or slide by gently pushing the plunger of the syringe down while the needle tip is positioned just above the slide. One should avoid ejecting a "jet" of material from the syringe. For the coverslip smear preparation, a second clean coverslip is placed on top of the first. The material between coverslips will naturally begin to spread after the weight of the upper coverslip is applied. The tip of each coverslip should be held separately and pulled apart horizontally just as the spreading sample material reaches the ends of each coverslip (Figure 95-1, *C*). Using this technique, fragile juvenile lymphocytes can be well preserved if 60% horizontal and 40% vertical motions are applied when separating the coverslips. The coverslips should be immediately air-dried or heat can be gently applied while holding the coverslip.

Similar high-quality smears can be made by using thin pre-cleaned glass slides. The sample is expelled gently on the first slide one-third of the distance from the top and a second slide is placed at right angles over the sample. The sample material will spread with the weight of the top slide and the top slide is then gently pulled away from the bottom (Figure 95-1, *D*). The smear on the bottom slide usually is best for evaluation. The slide should be immediately air-dried.

For "in-house" evaluation of cytology specimens, the air-dried coverslips or slides are fixed with fresh methanol for 2 to 5 minutes and stained with Wright-Giemsa stain. It is important that the methanol be fresh (>95%), that adequate fixation time be allowed, and that the stain solution is prepared fresh by using a proper

phosphate buffer of pH 6.2. A Diff-Quik type quick stain may be used for initial evaluation, but the final diagnosis should be made on the properly prepared Romanowsky-type stains such as Wright-Giemsa or May-Grünwald-Giemsa. When submitting the smear preparations to a reference veterinary laboratory, air-dried, unfixed samples can be mailed, but not with formalin-fixed histopathology specimens, as the formaldehyde gas fixes the specimen resulting in poor staining results with Romanowsky-type staining.

Lymph Node Cytology Interpretation

Cytologic evaluation of lymph nodes, in general, will provide one of the following findings: normal, hyperplasia (reactive), inflammation, lymphoma, metastatic neoplasm, or extramedullary hematopoiesis.[6] Normal lymph node cytology has approximately 90% well-differentiated small lymphocytes and up to 10% medium and large lymphocytes (Figure 95-2, *A*). Plasma cells, histiocytes (macrophages) and neutrophils are usually present in small numbers. A few mast cells per slide can also be identified.[8]

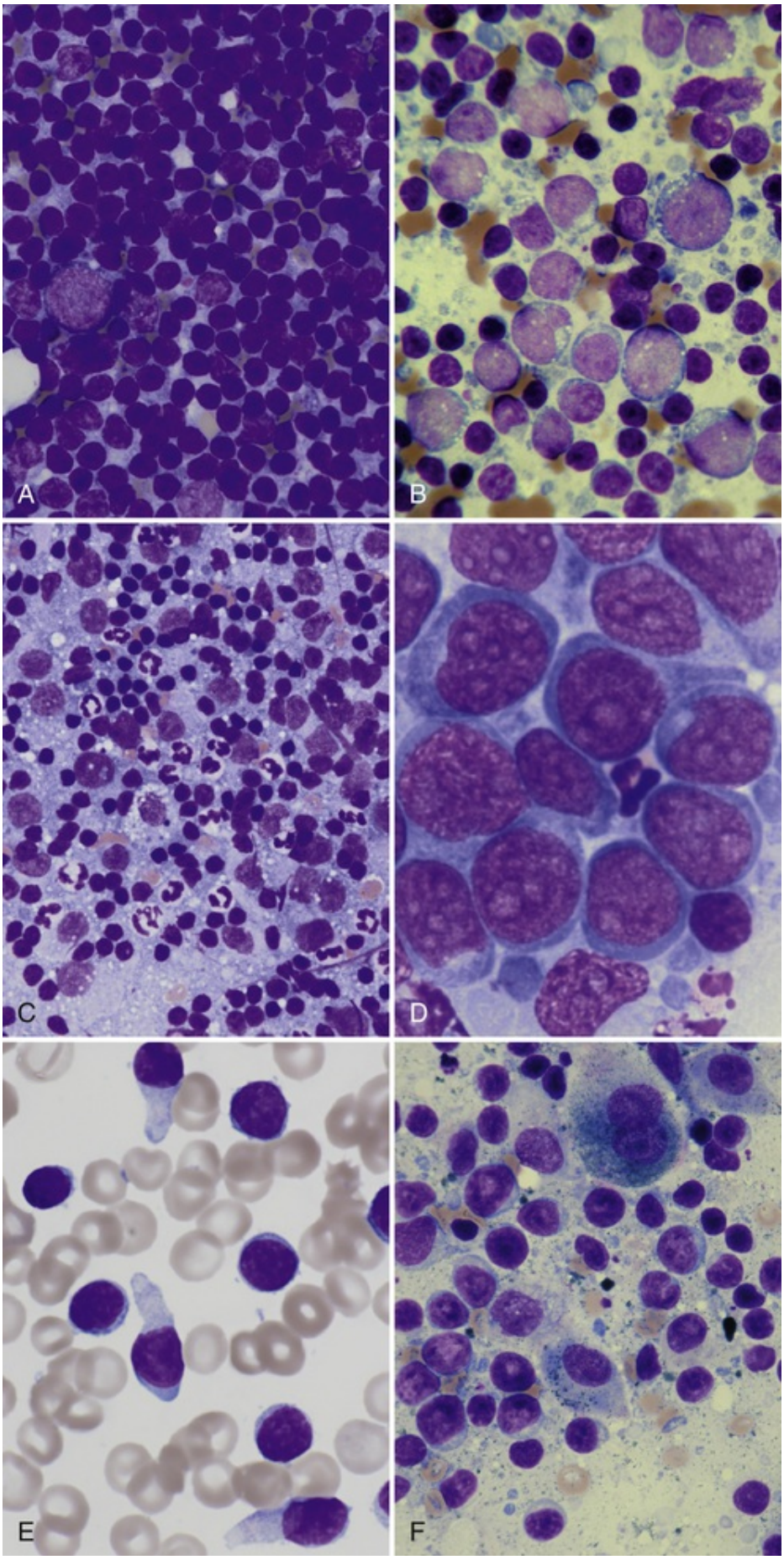
A
B
C
D
E
F

FIGURE 95-2 Cytologic appearances of lymph node samples. **(A)** Normal with >90% small lymphocytes, **(B)** hyperplasia with increased numbers (<30%) of medium and large lymphocytes, **(C)** inflammation with increased numbers of inflammatory cells (pyogranulomatous inflammation in this case), **(D)** high-grade lymphoma with an increased number of blast cells, **(E)** low-grade lymphoma suspected with a monotonous increase of small lymphocytes, and **(F)** metastatic neoplasm (malignant melanoma in this case).

Increased numbers (usually 15-30%) of medium and large lymphocytes are seen in the reactive or hyperplastic node. A majority of cells from hyperplastic nodes (>50%) are small lymphocytes (Figure 95-2, *B*). The percentage of the medium and large cells can be as high as 50% in some cytologic specimens. Examination of additional slides or histologic examination of a biopsy may be needed to differentiate hyperplasia and neoplasia.[9,10] In hyperplasia, the number of plasma cells is frequently increased and the number of other inflammatory cells mildly increased. Lymphoid hyperplasia is usually associated with antigenic stimulation due to one of several etiologies: infection, inflammation, immune-mediated disorders and neoplasia. Additional tests may be required to confirm a diagnosis.

Lymphadenitis is classified as suppurative, eosinophilic, histiocytic or pyogranulomatous on the basis of inflammatory cells.[11] Suppurative lymphadenitis is characterized by increased numbers of neutrophils (>5%). Neutrophil counts >20% of cells obtained are consistent with infection within the node or with secondary inflammation, perhaps from draining an infected area. Eosinophilic lymphadenitis is diagnosed if increased numbers of eosinophils (>3%) are noted. If histiocytes are >3-5% of the cells, histiocytic lymphadenitis is likely. Pyogranulomatous lymphadenitis has increases in both histiocytes and neutrophils (Figure 95-2, *C*). Pyogranulomatous lymphadenitis is often associated with fungal, *Leishmania*, *Neorickettsia* or *Prototheca* infections.

Cytologic diagnosis of high-grade lymphomas can be achieved by detecting >50% medium or large lymphocytes (Figure 95-2, *D*). However, additional examinations including histopathology, immunophenotyping and polymerase chain reaction assessment of clonality are usually used for establishing a diagnosis based on the latest World Health Organization (WHO) classification.[12] The histologic evaluation is best done with the largest section of a node possible. Nodes from pets with low-grade lymphoma, on the other hand, are usually composed of an almost uniform group of small lymphocytes, making diagnosis with cytology difficult (Figure 95-2, *E*). Again, histology and other diagnostic procedures are needed. The presence of cells not normally seen in the lymph node (e.g., epithelial cells or melanocytes) or the presence of normal component cells in excessive numbers (e.g., mast cells) confirms a diagnosis of metastatic neoplasia (Figure 95-2, *F*).

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CHAPTER 96

Rhinoscopy, Nasal Biopsy, and Nasal Flushing

Caroline Page

Rhinoscopy

Rhinoscopy is an integral component of the diagnostic investigation of nasal disease, and allows for the examination of the nasal cavity, nasopharynx, and in some circumstances the sinuses. It is indicated for evaluation of patients with nasal congestion, stertor, nasal discharge, epistaxis, sneezing and reverse sneezing. Rhinoscopy is contraindicated in patients with abnormal hemostasis, or if the cribriform plate is defective. It should be used with caution when there is hypertension, as severe bleeding could ensue. Before performing rhinoscopy, it is essential to have a basic understanding of nasal anatomy (see ch. 238). It is imperative to collect a complete history, to ascertain duration of signs, to note presence of nasal discharge, and whether the clinical signs are sudden or progressive, bilateral or unilateral. With physical examination, pay particular attention to nasal asymmetry, hypopigmentation, nature of any discharge, and identify signs of systemic illness, coagulation problems, or hypertension (see ch. 29, 157, and 197). Look for dental disease, which can result in nasal discharge secondary to fistula formation (see ch. 27 and 272). The greatest chance of diagnostic success in patients with nasal disease will be achieved by correlating clinical and anamnestic information with the rhinoscopy findings, advanced imaging and histopathology. Advanced imaging using computed tomography (CT) or magnetic resonance imaging (MRI) is a useful accompaniment to rhinoscopy, by providing detailed information about the extent and anatomic location of disease. These imaging techniques are far superior to radiographs in evaluation of nasal disease. Lesions identified on CT or MRI can be targeted with the scope for closer inspection and biopsy.[1] Imaging should always be performed prior to rhinoscopy, as disruption of the nasal mucosa or bleeding from scope trauma may affect imaging results. Pre-anesthetic screening for patients undergoing rhinoscopy should include complete blood count, biochemistry, coagulation parameters and chest radiographs. If there is epistaxis, blood pressure should be measured (see ch. 99), and systemic disease ruled out, e.g., tick borne disease (see ch. 218). The procedure can be painful, and pain-relieving drugs like opiates should be included in the anesthetic protocol. Nerve blockade, either infraorbital or maxillary, using bupivacaine and lidocaine (judiciously in cats) may be a useful adjunct to provide a reduction in the sneeze reflex and pain relief during the procedure.[2]

After imaging, the anesthetized patient is positioned in sternal recumbency with the muzzle directed ventrally. A double endoscopic examination using rigid and flexible endoscopes provides the most comprehensive evaluation of the nasal cavity and nasopharynx.[3] Rigid endoscopes are preferred by most clinicians for anterograde examination of the nasal cavity. Thirty-degree, angled visual field endoscopes allow for greater visibility with less movement of the scope than with 0-degree visual field scopes. For small dogs and cats a 1.9 mm scope is appropriate, and a 2.7 mm scope for those over 10 kg. Flexible endoscopes can be retroflexed to allow full assessment of the nasopharyngeal area. In patients with turbinate destruction (for example, with fungal rhinitis), a flexible scope can be maneuvered into the frontal sinus to aid diagnosis[4] and treatment. High-definition flexible video scopes allow good visualization of nasal tissue and some clinicians prefer these over rigid scopes for rhinoscopy.

The examination begins with evaluation of the nasopharynx. A mouth gag is placed to protect the scope and the endotracheal tube is fully cuffed to protect the airway. The nasopharynx is not packed as this interferes with drainage of liquid though the mouth. Culture samples can be taken (Video 96-1) at this point with a sterile swab inserted into the nostril. This can result in bleeding, which may interfere with visualization. Alternatively, tissue samples can be submitted for culture at the end of the procedure from biopsy specimens. The retroflexed flexible endoscope is inserted into the mouth and hooked over the soft palate to view the nasopharynx. Moving the scope rostrally allows full inspection of the nasopharynx. The nasopharynx, choanae and soft palate should be evaluated for polyps, stenosis, mucosal color and texture,

discharge, tumors or mites. The opening to the eustachian tubes may be visualized (see ch. 238). During this part of the procedure the patient may require deeper anesthesia due to the sensitivity of the area. Brush samples can be taken for cytology, and biopsies can be obtained from abnormal tissue using an endoscopic biopsy instrument.[5] Caution must be taken not to damage the scope by passing an instrument through the channel while the scope is in the retroflexed position. Instead, the biopsy instrument must be passed to the tip of the scope before the scope is flexed. Some clinicians use a rigid scope to examine the nasopharynx in an anterograde fashion; however, this can result in significant bleeding.

A rigid endoscope is then used to examine the nasal cavity in an anterograde approach. The scope is inserted initially at an angle, and then straightened to pass the alar cartilage. The scope is gently advanced and each meatus is examined. Continuous saline irrigation removes mucus and aids visualization. The nasal cavity is examined for presence of abnormal mucus, hyperemia, lysis, mucosal texture, and the presence of polyps, masses, and foreign bodies. Nasal turbinates have a varied appearance in different breeds and individuals.[6] Rostral turbinates are pink and smooth and the caudal ethmoid turbinates appear more tan in color with a corrugated texture. To avoid damage to the cribriform plate, measure the distance to eye level and do not pass this point with the scope. It is important to note that severe inflammatory changes can be found microscopically in macroscopically normal nasal cavities,[7] so biopsies should always be obtained[8] (see below). Patients must be monitored closely during recovery because if the mouth is closed and the nose is obstructed the pet may not be able to breathe. A mouth gag to hold the mouth open may be required until consciousness is regained. Extubation should be performed as late as possible, ideally when the gag reflex returns.

Nasal Biopsy

Before performing nasal biopsies, ensure the patient has adequate coagulation ability (see ch. 196) and a cuffed endotracheal tube. There are several techniques for obtaining a nasal biopsy. The goal of biopsy is to obtain tissue of adequate diagnostic quality. Biopsies can be procured using endoscopic biopsy forceps through the instrument channel of the scope. This provides accurate placing in the area of interest and great visibility, and is useful where there are focal lesions. However, with this method the sample size is very small and samples may be of poor quality for histopathological examination, especially if a small diameter scope or flexible scope is used. Alternatively, a larger biopsy instrument can be guided to the area of interest adjacent to the scope which allows a larger sample size to be taken (Figure 96-1). Maneuverability of the biopsy instrument can be difficult with this method, especially in a small nose. An effective way to obtain good quality sample sizes in most nasal diseases is blind biopsy. This involves passing the biopsy instrument into the nasal cavity and obtaining tissue without endoscopic guidance. The distance to the area of interest can be measured from imaging results and then marked on a biopsy instrument with tape before being passed into the nose (Figure 96-2). This technique produces comparable results to guided biopsies for nasal cancer diagnosis.[9] Several biopsies should be taken, more if the sample sizes are small. It is important to be aware of nasal anatomy when taking biopsies and not to pass the instrument further than eye level to avoid damage to the cribriform plate.

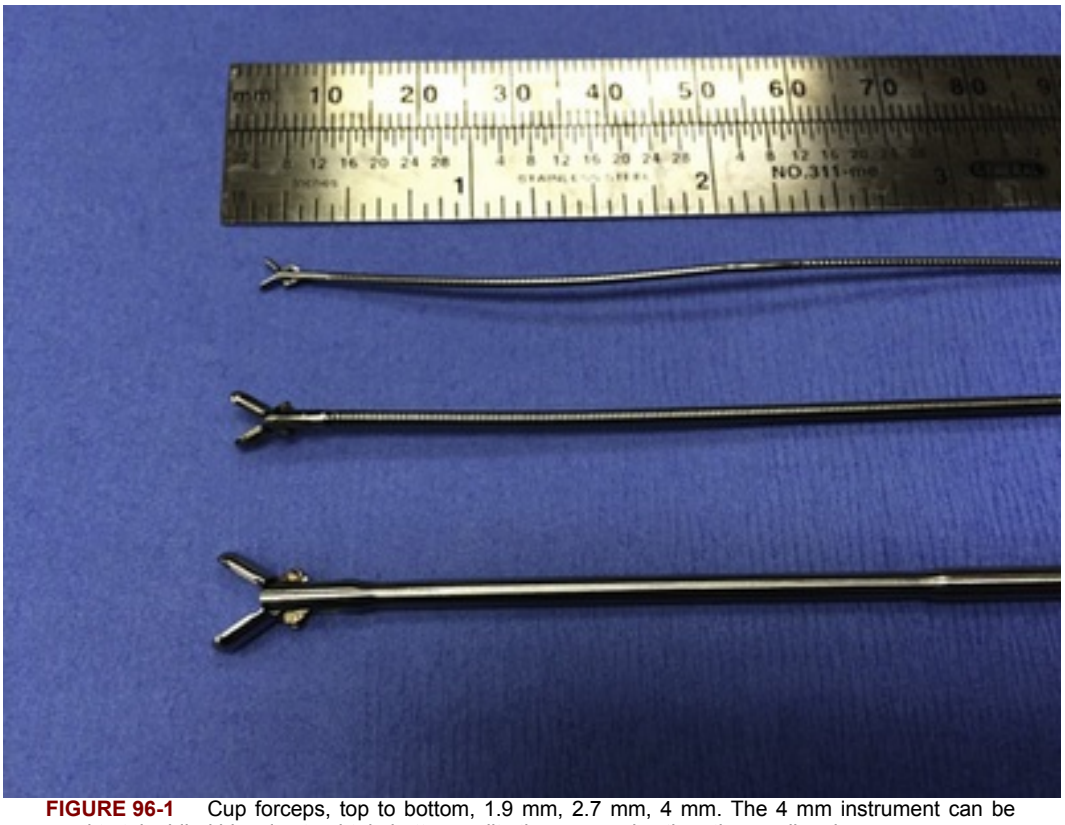

FIGURE 96-1 Cup forceps, top to bottom, 1.9 mm, 2.7 mm, 4 mm. The 4 mm instrument can be used to take blind biopsies to obtain better quality tissue samples than the smaller sizes.

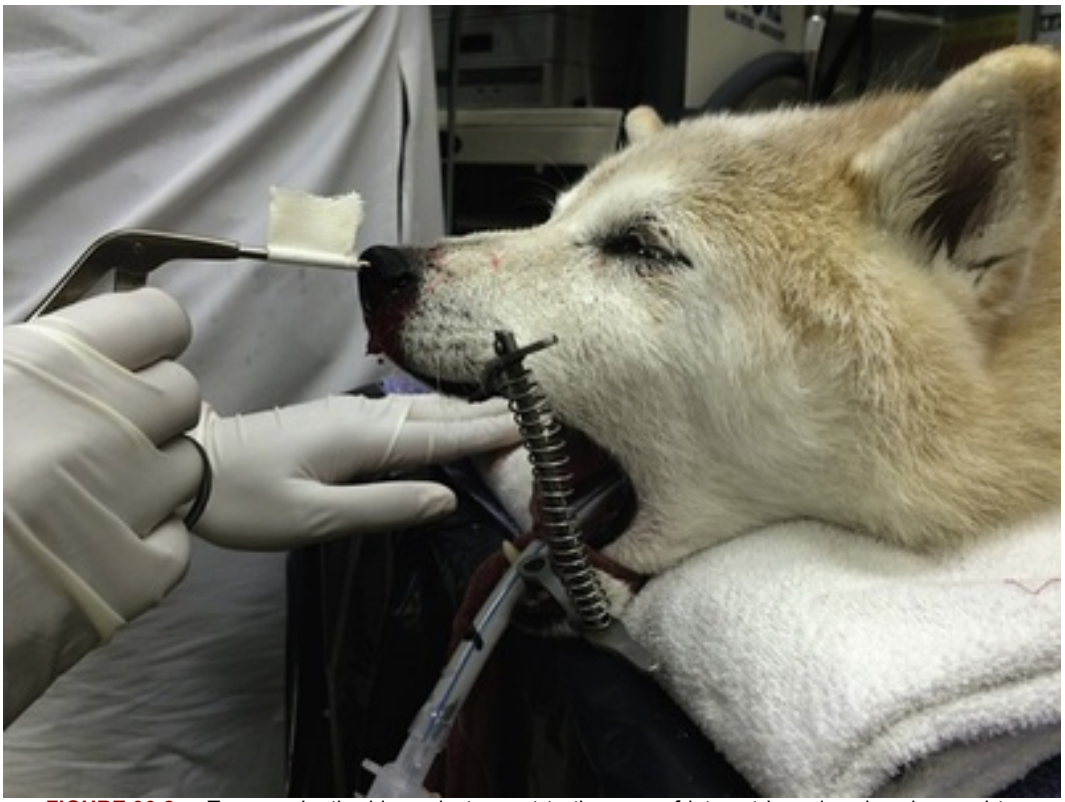

FIGURE 96-2 Tape marks the biopsy instrument to the area of interest based on imaging, and to prevent advancing the instrument past the level of the medial canthus to avoid cribriform plate damage.

Nasal biopsies usually result in moderate, self-limiting bleeding. Methods of post-biopsy hemostasis, if required, are instillation of phenylephrine, epinephrine, or several drops of the Chinese herb Yunnan Baiyao mixed in water. Cold packs applied to the bridge of the nose post-procedure can also be useful, as can flushing with cool saline into the nose which results in mucosal vasoconstriction.

Biopsy samples can be wrapped in saline soaked tissue (Kimwipes) or in a biopsy cassette and submitted in formalin.

Nasal Flushing

Nasal flushing (Video 96-2) is a useful procedure, which can remove mucus for palliation of chronic rhinitis, aid in foreign body removal, help to debulk some nasal tumors for palliative treatment or prior to radiation therapy, and prepare for topical treatments in fungal rhinitis. Nasal flushing is a suboptimal way of collecting quality diagnostic samples, and biopsy is preferred. Some lesions may not exfoliate well, or be located too caudally for flushing to collect a tissue sample.

There are various methods of nasal flushing depending on the purpose it is being performed for. Nasal flushing can be performed either forwards, through the nose into the nasopharynx, or backwards, from the nasopharynx out through the nostrils.

To remove mucus in patients with chronic rhinitis and to attempt to debulk tumors, the technique is as follows. The patient is positioned in sternal recumbency as described above, and a 12 or 35 cc syringe for smaller patients or 60 cc syringe for larger patients is filled with sterile saline, and flushed through the nose. The syringe tip can be directly inserted into the nose, or alternatively, a Christmas tree adapter can be used (Figure 96-3). The contralateral nostril is compressed to allow the flow to pass into the nasopharynx and out through the mouth. Vigorous force can be applied to produce a traumatic flush capable of debulking tumor tissue and removing fungal plaques. This technique can be combined with transnasal curettage for more effective tumor debulking.[10] Airflow restoration will be evident by low or no resistance to flushing with the fluid easily exiting through the mouth.

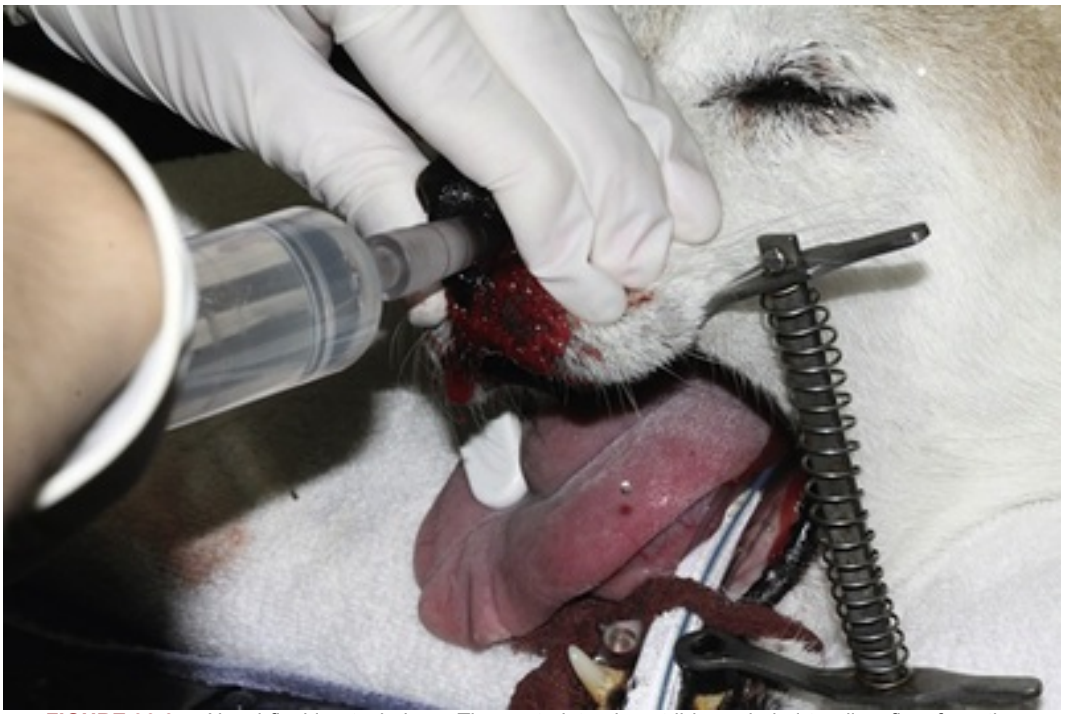

FIGURE 96-3 Nasal flushing technique. The contralateral nostril is occluded to allow flow from the nose into the mouth.

A retrograde flush may be useful if the cribriform plate has damage and a minimally invasive technique is needed to take samples from the rostral nasal cavity or in some foreign body situations. A long polypropylene catheter can be heated with a flame 1-2 cm from the tip for two seconds and molded to a hook shape to fit

easily into the nasopharynx. Saline can then be flushed as above. The patient often requires deeper anesthesia during this procedure due to the sensitivity of the nasopharynx.

Flushing the sinuses in patients with fungal rhinitis is a very effective way to debride fungal plaques prior to topical treatment, which aids in the success of therapy. Patience and several liters of saline are required. A red rubber catheter can be passed with a biopsy instrument at the end of a flexible endoscope and deposited into the sinus where flushing can be targeted. Alternatively, a forceful flush through the instrument channel of the flexible endoscope adjacent to the plaque is another useful technique in this situation as is vigorous anterograde flushing as above.

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Respiratory/Cardiovascular

OUTLINE

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CHAPTER 97

Respiratory and Inhalant Therapy

Laura A. Nafe

By definition, respiratory therapy is the administration of aerosolized therapy for management of acute or chronic respiratory conditions. In veterinary medicine, our ability to administer inhaled medications in this manner is limited due to the inability of dogs and cats to coordinate inspiration with activation of a metered dose inhaler (MDI) or nebulization device. Methods utilized in human pediatric respiratory therapy have been adopted in small animal veterinary medicine with success in appropriate patients.

Nebulization

Nebulization is the delivery of a substance via small droplets, facilitating delivery of sterile saline or a medication (usually diluted in saline to facilitate transport) to the respiratory tract directly. The particle size delivered varies depending on the type of nebulizer being used, with most devices delivering particles between 0.5 and 10 microns. Effective penetration of the lower airways is achieved in most patients with particles less than 3-5 microns in size.[1]

Types of Nebulizers

A variety of nebulizers is available for management of respiratory disorders. Although all nebulizers are capable of delivering saline or a medication, the power mechanism, portability, convenience, and particle size delivered vary. Most common nebulizers are either ultrasonic or gas-pressure-driven. Many veterinary hospitals and clinics may have a nebulizer to be used for inpatient care, but these nebulizers may be cumbersome for outpatient care due to large size. Particle size delivered is important when considering what region of the respiratory tract is being targeted. For example, larger particles (2-10 microns) will be deposited in the upper respiratory tract and are beneficial for upper airway (nasal, laryngeal, tracheal) inflammatory diseases.[1] Smaller particles will travel farther in the respiratory tract before being deposited, and are therefore more useful for lower airway diseases. In general, nebulizers that generate smaller particles and provide portability are more expensive, typically ranging from $150-250. For long term nebulization at home, the author prefers the Omron vibrating mesh nebulizer (Omron Healthcare, Inc., Lake Forest, IL) (Figure 97-1). In some geographical areas, there may be a respiratory pharmacy nearby that is willing to rent a nebulizer to a patient for a specified period of time.

FIGURE 97-1 Omron vibrating mesh nebulizer (Omron Healthcare) with facemask attached.

Benefit of Nebulization

Nebulization is an important aspect of respiratory therapy for patients with acute respiratory conditions, providing hydration or medication delivery directly to the affected area while minimizing systemic adverse effects. Of particular importance is the delivery of water droplets to help improve mucociliary clearance of respiratory secretions and mucus. Nebulization is not commonly performed chronically at-home, but for inpatient care, it plays an important role in management of common respiratory conditions.

Indications for Nebulization

In order to understand the indications for saline (0.9% NaCl) nebulization, one must understand the role of mucus present in the respiratory tract. Mucus is an adhesive gel consisting of water and glycoproteins mixed with serum, functioning to trap debris and bacteria to enhance removal from the respiratory tract.[2] Clearance of mucus is an important respiratory defense mechanism accomplished by an effective mucociliary apparatus and the cough reflex.[3] In order for the airway cilia to function appropriately, there must be a serous layer to facilitate movement of the cilia, and therefore mucus, in an upward motion.[3] In addition to rehydration of the mucociliary apparatus with intravenous fluid therapy, nebulization provides these patients with direct delivery of saline via droplets to the respiratory tract, thus hydrating the mucous layer to facilitate expulsion by the patient via mucociliary clearance and coughing. Saline nebulization is most commonly administered in patients with pneumonia, specifically aspiration pneumonia (see ch. 242).

Indications for nebulized medications include resistant bacterial infections, inflammatory airway diseases (see ch. 241), and treatment or prevention of bronchoconstriction with antimicrobials, glucocorticoids and bronchodilators being delivered for each condition, respectively.

How to Perform Nebulization

When providing saline nebulization, approximately 3-5 mL of normal saline (0.9% NaCl) is placed in the nebulization cup and when powered the nebulizer will convert this volume of liquid into saline droplets over a period of time (typically 10-20 minutes). There are multiple techniques that can be utilized to ensure the nebulized droplets are directed into the respiratory tract. Since most dogs and cats breathe through the nose, the nasal turbinates may trap some of the saline particles. In dogs that are panting, many of these particles may be trapped in the back of the mouth and/or swallowed due to the lack of deep inspiration. The author has found a facemask or small tent to be useful in facilitating delivery in patients that will tolerate these additions. In most cases, nebulization should be followed by coupage or light exercise (if tolerated by the patient) to further improve expulsion of respiratory secretions (Video 97-1). Contraindications to coupage include regurgitation, recent thoracic surgery, and recumbency. If the patient is recumbent, frequent repositioning to limit atelectasis and improve movement of airway secretions is an important aspect of patient care.

Nebulized Medications

There is minimal evidence to support the use of nebulized medications in small animal veterinary medicine. Although most medications that are water soluble can be administered via nebulization, the most commonly nebulized drug classes are antibiotics (e.g., gentamicin), anti-inflammatories (e.g., fluticasone propionate), and bronchodilators (e.g., albuterol). Other medications that have been evaluated for nebulization in a research setting include lidocaine, xylitol, and N-acetylcysteine.

A clinician may consider nebulized aminoglycoside treatment in canine patients with multi-drug resistant bacterial pneumonia (e.g., *Bordetella bronchiseptica, Pseudomonas* spp.), usually as an adjunct treatment to systemic antimicrobial therapy. The advantage of nebulized aminoglycoside therapy is the ability to administer an appropriate antibiotic with low risk of systemic adverse effects (e.g., nephrotoxicity).[4] Clinicians should keep in mind that aerosolized antibiotics may cause irritation to the airways and dosage calculation is often approximate, with it being impossible to estimate what percentage of the drug will reach the site of infection. The author doses gentamicin at 6-8 mg/kg diluted in 5-10 mL of saline administered once daily via facemask. Do not exceed 25 mg/mL concentrations as it may decrease drug delivery.

Glucocorticoid agents are more commonly delivered via metered dose inhaler to patients with inflammatory airway disease, and in a medium or large breed dog nebulization is likely more effective in targeting the lower airways. Budesonide has been evaluated for nebulization in humans, although no studies have evaluated nebulized glucocorticoids in dogs.[5] When considering this route of administration, the clinician must consider the limitations of nebulization, especially cost, as these patients will likely require lifelong therapy.

Like glucocorticoids, bronchodilator agents are most commonly delivered via metered dose inhaler. Nebulized albuterol (0.5% albuterol; 1.25 mg/cat diluted in 2 mL of saline repeated q 1-4 h PRN) is occasionally used as a one-time treatment for feline patients presenting with status asthmaticus (see ch. 241) or as pre-treatment for those undergoing a procedure that may induce or worsen bronchoconstriction (e.g., bronchoalveolar lavage; see ch. 101). If available, nebulized albuterol is preferred over MDI for emergency management of feline status asthmaticus, as patients in respiratory distress are often not taking adequate breaths, minimizing effective delivery to the lower airways with a spacer device. Although an injectable bronchodilator (e.g., terbutaline) is preferred in these situations, cats with significant heart disease may not be good candidates for parenteral beta-2 adrenergic receptor agonists or methylxanthine bronchodilator agents. Administration of beta-2 adrenergic receptor agonists is not typically recommended in dogs with respiratory disease, as bronchoconstriction is not a common feature of canine respiratory disease. Parenteral and oral administration of methylxanthine bronchodilator agents is used in feline and canine respiratory disease, but inhaled therapy has not been evaluated.

Nebulized lidocaine (4% without preservatives diluted to 2%; 2 mg/kg q 8 h for 2 weeks) was recently evaluated as a potential novel anti-inflammatory and bronchodilating agent for management of feline asthma.[6] Although no overt adverse effects were observed, lidocaine was only found to reduce airway hyperactivity and should not be used as monotherapy for management of asthma.[6] In specific cases, nebulized lidocaine may provide an alternative bronchodilator option in cats with heart disease.

Xylitol, a five-carbon sugar, is thought to hydrate the mucus layer and have potential antibacterial properties. As a result, this therapy has been investigated as a potential management strategy for cystic fibrosis in humans. A small safety study evaluated nebulized xylitol administration for 14 consecutive days in

research beagle dogs and found no adverse effects.[7] The use of nebulized xylitol in veterinary clinical medicine has not been evaluated and cannot be recommended until further safety and efficacy information is available.

N-acetylcysteine, an antioxidant and mucolytic, is occasionally administered parenterally, orally or via nebulization as a mucolytic agent. Evidence suggests that nebulized N-acetylcysteine may promote bronchoconstriction and resultant airflow limitation in cats with experimentally-induced asthma when delivered via endotracheal nebulization.[8] Diseases that result in excessive mucus production in dogs (e.g., pneumonia, ciliary dyskinesia) may benefit from N-acetylcysteine. However, the risk of bronchoconstriction during or after nebulized N-acetylcysteine is a concern, detouring the use of this treatment by most clinicians, and is not recommended by the author. Pre-treatment with a bronchodilator is recommended if this treatment is administered.

Limitations of Nebulization

Although nebulization of medications is an attractive option for many patients with respiratory disease, there are limitations that should be considered. First, there is concern for the amount of drug that is delivered to the affected area, with particle size playing an important role in the area being medicated. Second, the expense associated with purchasing or renting a nebulization device and the cost of the medication can be substantial. Third, the time required to deliver the medication appropriately may be labor-intensive for many caretakers, especially for patients with chronic conditions requiring multiple treatments per day indefinitely. Lastly, there is always potential for a medication to cause further irritation to the airways, in particular with antibiotics and bronchodilator agents. It is important to consider these limitations when recommending nebulized medications.

Metered Dose Inhaler

Delivery of medications via pressurized MDI is the standard of care for management of many human respiratory conditions and is gaining popularity in veterinary medicine. The main limitation of MDI therapy in dogs and cats is the inability to coordinate respiration with the release of the actuation. The use of a facemask and space chamber improves this limitation and makes delivery of medications via MDI a good option in small animal respiratory medicine.

Benefit of MDI

Like nebulization, delivery of medications via MDI allows treatment of a condition locally while minimizing systemic side effects of the medications being used. Unlike nebulization, administration of MDI is not labor-intensive and is well tolerated by most patients after appropriate acclimation to the facemask/chamber device. In fact, many cat owners find inhaled delivery of medications easier than oral administration.

Indications for MDI

Respiratory diseases that result in inflammation and/or bronchoconstriction can be managed with MDI therapy. In dogs, common diseases managed with glucocorticoids delivered via MDI include chronic bronchitis (see ch. 241), eosinophilic bronchopneumopathy (see ch. 242), and potentially tracheal collapse (see ch. 241) and lymphoplasmacytic rhinitis (see ch. 238). As mentioned earlier, dogs do not develop true smooth muscle bronchoconstriction, and therefore, do not benefit from beta-2 adrenergic receptor agonist medications (e.g., albuterol). In cats, common diseases managed with medications delivered via MDI include feline asthma (see ch. 241), chronic bronchitis (see ch. 241), and potentially lymphoplasmacytic rhinitis (see ch. 238).

How to Administer Medication via MDI

Cats and dogs cannot coordinate inspiration with release of the aerosolized medication from a MDI, making an aerosol-holding chamber or spacer device a necessary component of MDI therapy. A variety of spacer devices, all equipped with an exhalation valve, are available for purchase with most costing approximately $40-80/space chamber. The MDI fits on one end of the spacer, and the other end of the spacer has an attachment for the facemask. Shaking the MDI prior to delivery is necessary, as this opens an internal valve within the canister. The MDI should then be attached to the space chamber with facemask, and the space

chamber should be placed over the nose and mouth of the patient, ensuring a tight fit to maximize delivery of the aerosolized medication to the patient's airways (Figure 97-2; Video 97-2). With the actuation of the device, the MDI delivers a precise dose of the aerosol drug into the space chamber. The space chamber serves as a holding device for the aerosol so that the cat or dog can inhale it over a period of time. It is important to watch the patient take 7-10 adequate breaths, as it is natural for the dog or cat to stop breathing when the facemask is placed over the nose and mouth.

FIGURE 97-2 Administration of a medication via MDI, showing the entire inhalation device, equipped with facemask, space chamber, and MDI (Aerokat Trudell Medical International).

Medications Delivered by MDI

Glucocorticoids are the most commonly administered medications via MDI in small animal respiratory therapy, with fluticasone propionate being preferred because it is the most potent (18 times as potent as dexamethasone) and has the longest half-life.[9,10] In addition, the majority of inhaled medication (approximately 70% or more) will be deposited in the oropharynx after delivery and will be swallowed. Of the steroids available for inhalation, fluticasone is poorly absorbed in the gastrointestinal tract, and therefore, minimal systemic side effects will result.[9] Fluticasone (110 mcg q 12 h), budesonide (only available as dry powder MDI) (200 mcg q 12 h), and flunisolide (250 mcg q 12 h) have been investigated and found to be effective in management of feline inflammatory airway with minimal systemic adverse effects.[11-13] Although used often clinically, there is little evidence to support the use of inhaled glucocorticoids in canine inflammatory airway diseases.[14,15] Fluticasone is often preferred due to availability and efficacy; an alternative glucocorticoid may be chosen for particular patients based on ease of dosing, cost, and/or availability.

Beta-2 adrenergic receptor agonist medications (e.g., albuterol) are delivered via MDI in feline respiratory medicine, most commonly for management of acute respiratory distress secondary to bronchoconstriction. Racemic (R,S)-albuterol is not recommended for chronic management, as the S-enantiomer is associated with airway hyperactivity and promotes airway inflammation.[16] If chronic bronchodilator therapy via MDI is desired, daily treatment with levalbuterol, the R-enantiomer of albuterol, is recommended. The racemic

formulation of albuterol can be used for rescue therapy as needed for respiratory distress.

Limitations of MDI

As with nebulization, there are limitations that should be considered when recommending treatment with inhaled medications. There is always concern for the amount of drug that is actually delivered to the lower airway; this is especially true in any patient >7-10 kg. The expense associated with purchasing a MDI can be financially limiting for owners over time. In humans, inhaled glucocorticoids can increase the risk of respiratory infections, in particular oral *Candida* infections. Lastly, there is always potential for a medication to cause further irritation to the airways, in particular with bronchodilator agents (e.g., racemic albuterol).

Inhaled Chemotherapy and Immunotherapy

Treatment of pulmonary neoplasia, primary and metastatic, with inhaled chemotherapy has been minimally evaluated in small animal veterinary medicine. This technique offers a method of increasing exposure of the lung tumor to the chemotherapy agent, while minimizing systemic adverse effects. Delivery of cisplatin to a specific lung lobe via bronchoscopy with a specialized catheter has been described in normal, healthy dogs.[17] Aerosols of interleukin (IL)-2 liposomes have been evaluated in 9 dogs with pulmonary neoplasia with positive results and minimal toxicity, representing a promising potential therapy in specific cases.[18] Limitations of inhaled therapy for neoplasia are many, including need for specialized equipment, anesthesia, risk of human exposure, and expense. For specific cases (e.g., non-resectable primary lung tumor), inhaled chemotherapy may be a viable option for motivated clients.

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CHAPTER 98

Pulse Oximetry

Steven Epstein

Overview and Basic Principles

SpO_2 versus SaO_2

Pulse oximetry utilizes light to measure the amount of arterial blood hemoglobin saturated with oxygen. This diagnostic aid became available in the early 1980s for people and has since been employed in veterinary medicine. Pulse oximeters calculate the percent saturation of oxygen (SpO_2). The SpO_2 is used as surrogate for the arterial oxygen saturation value (SaO_2) that is directly measured by a CO-oximeter.

Pulse Oximetry Principles

Forms of Hemoglobin in Blood

An understanding of basic pulse oximeter principles allows recognition of situations in which a reading may incorrectly estimate SpO_2. The majority of hemoglobin in healthy adults exists in one of two forms: oxyhemoglobin with an oxygen molecule bound to its heme group or deoxyhemoglobin, also called "reduced hemoglobin," that has no bound oxygen. Methemoglobin and carboxyhemoglobin are two additional forms of hemoglobin with altered oxygen binding capabilities present in low concentrations. Methemoglobin has an oxidized iron component of the heme group. Carboxyhemoglobin has bound carbon monoxide molecules.

Light Absorptive Patterns

Pulse oximetry takes advantage of the different forms of hemoglobin absorbing unique spectra of red and infrared light (Figure 98-1). Most conventional pulse oximeters emit light at two wavelengths (660 nm and 940 nm) to exploit the light-spectral absorption qualities of oxyhemoglobin versus those of deoxyhemoglobin. Light from the unit either reflects back to the probe/sensor or is transmitted through the tissue to a sensor. These two forms of pulse oximetry are referred to as "reflectance" or "transmittance." The relative quantities of different light wavelengths passing through or absorbed by a tissue are measured by the pulse oximeter, determining the proportion of oxyhemoglobin to reduced hemoglobin and calculating the SpO_2. This calculated number is generated with an algorithm that evaluates a series of pulses, based on a calibration curve generated in humans. Results in cats and dogs have only minor differences that should not limit interpretation.[1] The algorithm utilized was generated from healthy people whose oxygen saturations were reduced from 100% to approximately 70%.[2] Thus, readings of <70% should not be used quantitatively, but only as a marker of severe hypoxemia.[3]

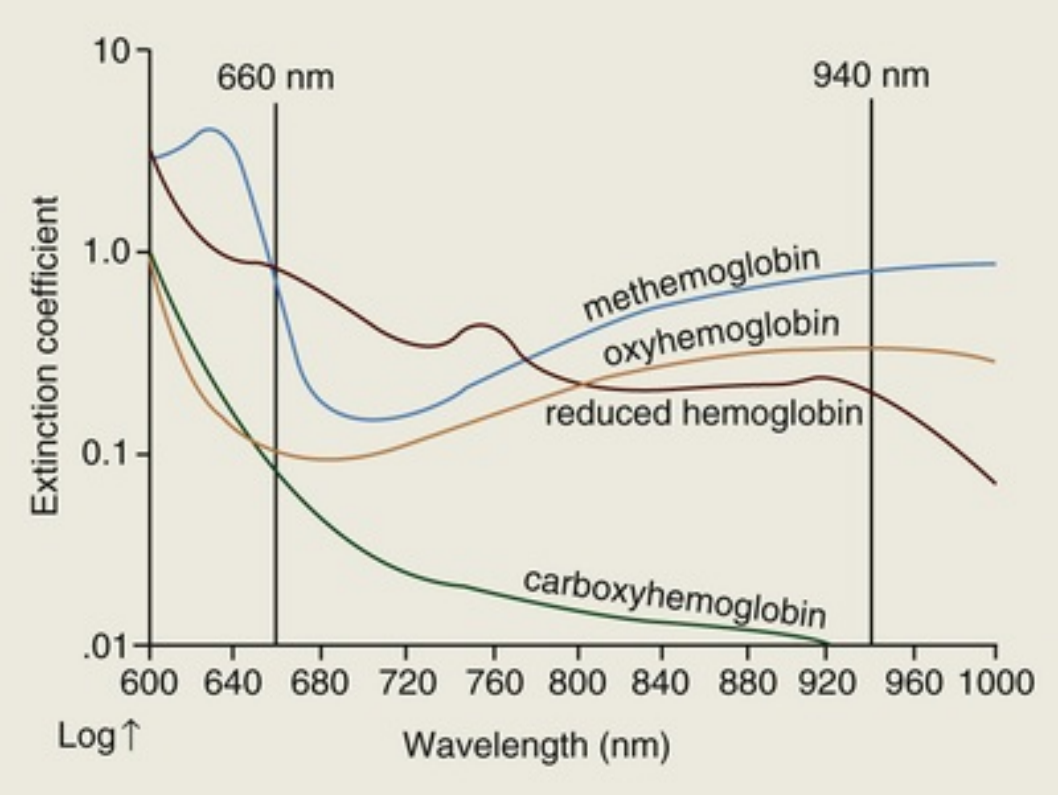

FIGURE 98-1 Extinction coefficients (absorption ratio) shown over a range of wavelengths for reduced hemoglobin, oxyhemoglobin, carboxyhemoglobin, and methemoglobin. The lines at 660 and 940 nm represent the red and infrared wavelengths, respectively, used by most pulse oximeters.

Pulsatile Nature of the Assessment

In addition to differences in light absorption, the second major principle of pulse oximetry is the need for pulsatile arterial blood flow. Light generated by pulse oximeters is inevitably transmitted through tissues that absorb some spectra of light: fat, capillary blood, venous blood, connective tissue. To exclude these patterns from the calculations, a complex filter is integrated into the unit to remove non-pulsatile segments of the signal (Figure 98-2). Thus, pulse oximeters function most reliably when placed over tissues with good pulsatile arterial blood flow. Modern pulse oximeters visually display a pulse intensity graphic to aid the operator in determining the ability of the machine to detect pulsatile flow. If the machine cannot detect an accurate pulse rate, the number generated should not be trusted.

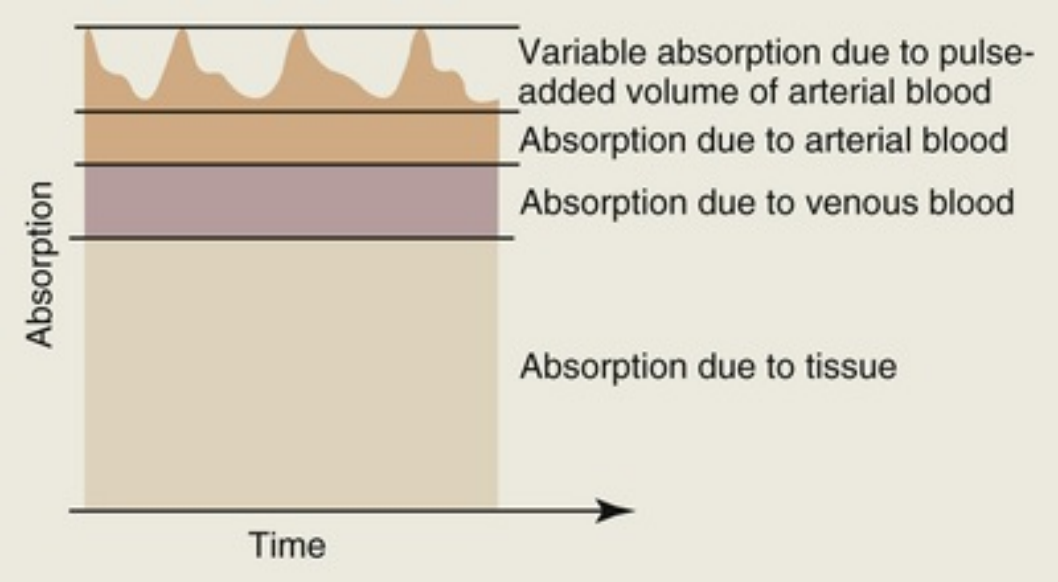

FIGURE 98-2 Sources of absorption of light as it passes through tissue. The pulse oximeter is able to recognize the change in absorption associated with a pulse and can then calculate the difference in absorption of red and infrared light at the peak of each pulse.

Technique of Obtaining a Pulse Oximeter Reading

Site Selection

As thick fur or pigmented skin can interfere with the pulse oximeter, such sites are avoided or a small patch of fur may be shaved. Common sites used in dogs are the tongue (if anesthetized), lips (Figure 98-3, *A*), pinna, vulva/prepuce, gastrocnemius tendon area, base of the tail, or occasionally a skin fold (Video 98-1). Common sites used in a cat are the tongue (if anesthetized), lips, pinna or across a digit (Figure 98-3, *B*). Results from several sites in both dogs and cats vary somewhat. Accuracy is better in dogs than cats.[4,5] If hypovolemia or hypothermia is suspected, the extremities should be avoided due to decreased peripheral perfusion.

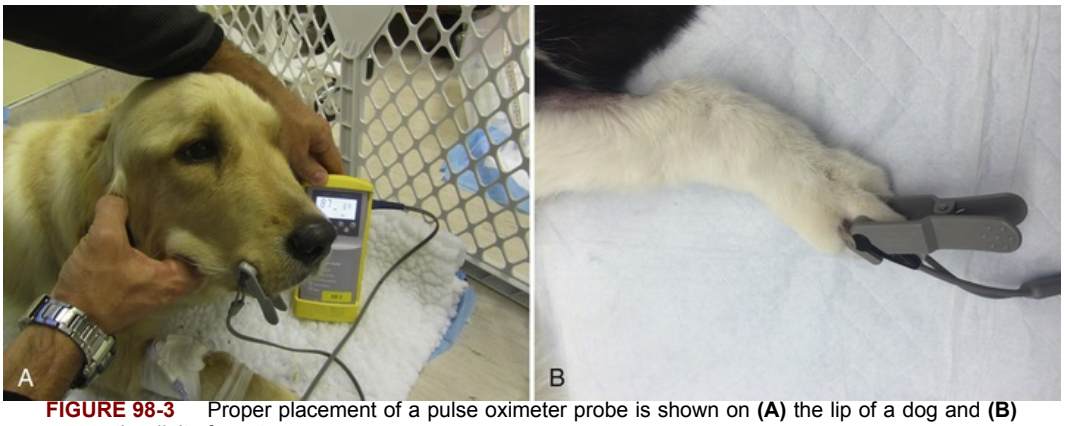

FIGURE 98-3 Proper placement of a pulse oximeter probe is shown on **(A)** the lip of a dog and **(B)** across the digit of a cat.

Obtaining a Reliable Reading

After the probe is placed on the patient, it should be held in place with the animal still to avoid motion artifact. Pulse oximetry units have been developed to function despite some patient movement, but are not more accurate in hypoxemia than older models.[6] After the unit displays a reading, the pulse rate displayed

should be verified manually. If the rates do not match, the oximetry reading is unlikely to be accurate. The probe should be moved to different sites until the unit reading matches the manually determined pulse rate with good signal strength. When the pulse oximeter displays a consistent reading, that number should be used. If the probe is to be left in place for continuous monitoring, the probe position may need to be changed every few hours as clip compression may cause a regional decrease in perfusion, creating inaccuracies.

Interpreting a Pulse Oximeter Reading

Oxygenation versus Ventilation

Pulse oximetry is a noninvasive method of continuously or intermittently monitoring oxygenation in either awake or anesthetized patients. Due to its ease of use, pulse oximetry is often the test first used to evaluate oxygenation status. Arterial blood gas analysis (see ch. 128) is technically more demanding but considered a more accurate assessment of pulmonary function. Pulmonary function is a combination of the lung's oxygenating and ventilating capacity, while pulse oximetry only assesses the oxygenation component. Ventilation is assessed by blood gas analysis (arterial or venous) or capnography, which can be combined with pulse oximetry to get a global view of pulmonary function.

Hypoxemia

The relationship between the SpO_2 and the partial pressure of oxygen dissolved in arterial blood (PaO_2) is dependent on the oxyhemoglobin dissociation curve. Hypoxemia is present when the PaO_2 is <80 mm Hg, corresponding to a pulse oximeter value of 93-95% under normal conditions. As the oxyhemoglobin dissociation curve can shift due to patient body temperature, pH and PCO_2, the cutoff value of 93% on a pulse oximeter for diagnosing hypoxemia must be used with caution as it will not reflect the same PaO_2 in all patients. Despite this limitation, pulse oximetry has been useful in monitoring critically ill small animals.[7,8] There is also the suggestion that routine use of pulse oximetry in anesthetized cats may reduce risk of anesthetic-related mortality by allowing recognition of problems earlier.[9]

For most animals breathing room air, a pulse oximeter reading of >95% would be considered normal and would correspond to a PaO_2 >80 mm Hg. Small decreases in oxygenating ability may lower pulse oximeter readings below reference ranges and may indicate mild decreases in oxygenation status. If a patient is placed on 100% inspired oxygen, such as under anesthesia, this should raise the PaO_2 to about 500 mm Hg, corresponding to a SpO_2 of 100%. A PaO_2 of 120-500 mm Hg gives the same 100% result on the pulse oximeter. In this scenario, a decrease in SpO_2 below the "reference range" indicates severe decrease in oxygenation status as the patient's PaO_2 had to decline from 500 mm Hg to <80 mm Hg before change is detected. Such a decrease should immediately be investigated.

Other Factors Affecting Pulse Oximetry

Apart from the above-mentioned limitation in the SpO_2 reflecting a patient's PaO_2, there are additional factors that may alter the ability of the SpO_2 to accurately reflect SaO_2. Thus, some find pulse oximeter readings as more random than reliable. One report documented a pulse oximeter reading of 99% with an appropriate plethysmography tracing despite the pulse oximeter having slipped off the patient.[10] Knowledge of pulse oximeter limitations can aid the clinician to trust a generated number or to look for a concurrent disease known to alter results.

Increases in the amounts of methemoglobin or carboxyhemoglobin can significantly alter pulse oximeter readings. Normal methemoglobin concentrations in dogs and cats are <1%.[11] Increases in methemoglobin can represent a congenital condition or are caused by any of a variety of drugs: benzocaine, nitrates, sulfa antibiotics, or acetaminophen. As methemoglobin levels increase, the patient's SpO_2 will change until a plateau is reached in the range of 82-86% regardless of oxygen concentrations inspired.[12] Pulse oximeter readings can markedly overestimate a patient's SaO_2, as methemoglobin values can reach 70% before being fatal.[11]

Carbon monoxide poisoning causes high concentrations of carboxyhemoglobin, most commonly encountered after being trapped in a house fire. At the spectra of light used by most pulse oximeters, oxyhemoglobin cannot be distinguished from carboxyhemoglobin. This causes the pulse oximeter to

overestimate blood oxyhemoglobin in both clinical and experimental settings. Even with carboxyhemoglobin levels reaching 70%, SpO_2 readings were still 90% or greater.[13,14]

A variety of pigments can also affect the ability of the pulse oximeter to accurately read. Vital dyes used in advanced clinical procedures or therapeutically may lower pulse oximeter readings. Lowered readings have been demonstrated with methylene blue used as in treating methemoglobinemia or as an ultrasound-deposited marker for surgery. Indocyanine green, used for measuring blood flow, also has lowered results.[15] Fluorescein, however, does not appear to affect pulse oximetry readings. Hyperbilirubinemia effects on pulse oximetry readings have not been consistent. Initial evidence suggesting that hyperbilirubinemia did not affect pulse oximeter readings based on studies done on patients with diseases associated with increases in carboxyhemoglobin. Newer evidence suggests severe hyperbilirubinemia can overestimate true oxygen saturation.[16,17] It seems unlikely that mild to moderate hyperbilirubinemia will interfere with pulse oximetry readings.

Severe anemia has been associated with inaccurate pulse oximetry readings. In one study, pulse oximetry readings in dogs were accurate with hematocrits as low as 10%. If the hematocrit is <10%, pulse oximeters overestimate true SaO_2.[18] Additionally, if anemia is treated with a hemoglobin-based oxygen carrier such as polymerized bovine hemoglobin (Oxyglobin), there can be a dose-dependent increase in the difference between SpO_2 and SaO_2.[19] Despite these limitations, pulse oximetry can be a valuable tool to the clinician in patient assessment.

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CHAPTER 99

Blood Pressure Measurement

Rebecca L. Stepien

Acute blood pressure (BP) measurement is required to diagnose hypertension or hypotension or to exclude these diagnoses as a cause for clinical signs in a patient. Multiple BP measurement techniques are available; each is associated with advantages and disadvantages.

Patient Selection

Blood pressure measurements are assessed as one part of a clinical evaluation that includes the patient history, physical examination findings, results of other diagnostic testing, and evaluation of concomitant medications, including anesthetics and sedatives. Many BP measurement techniques have test characteristics that require low diagnostic cutoff values for maximum sensitivity to hypertension (maximum opportunity to correctly identify an abnormally high value). Unfortunately, low diagnostic cutoff values also are associated with increased numbers of false-positive diagnoses. As a result, many BP measurement techniques are best able to correctly identify truly hypertensive patients as abnormal when the test is applied to patient populations with clinical signs or diseases likely to be associated with systemic hypertension. Routine "screening" BP measurements in clinically normal patients may assist the clinician in establishing a typical baseline BP value for an individual patient, but abnormally high BP values obtained from clinically normal patients must be viewed with caution due to the high incidence of false-positive readings in this patient population.

Indications for Blood Pressure Assessment

Blood pressure measurement should be part of the diagnostic evaluation for any feline or canine patient with clinical signs associated with systemic hypertension, known or suspected systemic diseases known to be associated with systemic hypertension, or both. Clinical signs of systemic hypertension occur when there is hypertensive damage to various organ systems ("target organ damage"). The organ systems most frequently affected include the eyes, kidney, brain, and heart. Damage to these systems may be overt (e.g., retinal detachment or seizures) or may be subtle, requiring the clinician to have a high index of suspicion for systemic hypertension when examining patients with subtle or vague clinical abnormalities.

Blood pressure assessment is indicated when any of the overt or subtle signs of end-organ damage are detected (Table 99-1). Conversely, if systemic hypertension is diagnosed, these body systems should be carefully evaluated for damage in conjunction with further diagnostic testing for causative diseases. In cases of renal disease, diagnostic testing for causative disease and target organ damage involve the same testing.

TABLE 99-1

Overt and Subtle Signs of Target Organ Damage with Recommended Testing Required to Assess Extent of Damage

ORGAN SYSTEM AFFECTED	OVERT CLINICAL SIGNS	SUBTLE CLINICAL SIGNS	RECOMMENDED TESTS
Eyes	• Acute blindness • Complete or near complete retinal detachment	• Behavior changes related to unrecognized vision loss • Bullous retinal detachment • Retinal hemorrhages	• Detailed direct or indirect funduscopic exam

	• Hyphema	• Tortuous retinal arteries • Periarterial subretinal infiltrates • Papilledema	
Kidneys	• Weight loss/inappetence • Polyuria/polydipsia • Palpable renal abnormalities • Azotemia • Increased urine protein/creatinine ratio	• Decreased urine-concentrating ability with normal creatinine/BUN • Increased urine protein/creatinine ratio with normal creatinine/BUN	• Assessment of creatinine and serum urea nitrogen concentrations • Urinalysis, with particular attention to urine specific gravity and protein content • Urine culture if required to rule out infection as a cause of proteinuria • Urine protein/creatinine ratio or other assessment of urine protein loss • Imaging, typically ultrasound, ± renal biopsy
Brain	• Seizures • Changes in mentation • Obtundation/coma	• Focal facial seizures • Depression • Photophobia • Behavioral changes (e.g., hiding)	• Detailed neurologic examination • Serum chemistry to rule out electrolyte and glucose abnormalities • Brain imaging (e.g., MRI)
Heart	• New murmur • New gallop heart sound	• Acute heart failure after fluid administration • Left ventricular hypertrophy on echocardiogram	• Echocardiographic examination

BUN, Blood urea nitrogen; *MRI*, magnetic resonance imaging.

Cats

The most common reason for clinical presentation of hypertensive cats is ophthalmic abnormalities. Although other causes of intraocular hemorrhage (e.g., coagulopathy) and retinal detachment (e.g., inflammatory disease) should be ruled out, immediate measurement of systemic BP guides the course of the diagnostic evaluation in these patients. For cats with neurologic signs (e.g., dull mentation or focal facial seizures) in addition to ophthalmic signs, diagnosis of critical levels of hypertension and immediate therapy can lead to rapid improvement in BP and relief of clinical signs.

Suspicion or diagnosis of diseases proven to be associated with systemic hypertension in cats (renal insufficiency or thyrotoxicosis) should lead to BP assessment. Other findings that may indicate BP assessment is warranted include palpable goiter or unexplained left ventricular hypertrophy. Systemic BP should be assessed in cats whenever auscultatory cardiac abnormalities (e.g., gallop heart sound, left-sided systolic murmurs), radiographic, electrocardiographic, or echocardiographic findings are consistent with hypertrophic myocardial disease involving the left side of the heart. Systemic hypertension (and hyperthyroidism in cats over 8 years of age) should be excluded by appropriate testing before a diagnosis of idiopathic hypertrophic cardiomyopathy is made. Early recognition of abnormal BP typically leads to evaluation for other systemic diseases, especially renal insufficiency.

Dogs

Although ophthalmic abnormalities, including retinal hemorrhage and detachment and hyphema, are as common in dogs with systemic hypertension as in cats, systemic hypertension in dogs is most often diagnosed when BP is evaluated as part of the clinical workup of dogs with systemic disease known to be associated with hypertension. In dogs, the diseases most frequently associated with elevations in BP are protein losing renal disease, acute or chronic renal failure of any etiology, hyperadrenocorticism, diabetes mellitus, and pheochromocytoma. In the case of renal disease, signs of renal dysfunction may be subtle (e.g., proteinuria without azotemia). Renal disease cannot be completely excluded based on a normal creatinine or serum urea nitrogen concentration, and a urinalysis should be performed to assess concentrating ability and protein loss. As with cats, systemic hypertension should be ruled out as a cause of left ventricular thickening of unknown etiology. Lastly, BP should be evaluated in dogs with any type of intracranial neurologic signs or ocular findings suggestive of systemic hypertension.

Hypotension

Dogs and cats that are presented with clinical signs of low cardiac output (e.g., weak peripheral pulses, cold extremities), shock, blood loss, or obtundation should be evaluated for hypotension. In some cases, hypotension is diagnosed clinically based on the constellation of history, presenting signs, and suspected clinical diagnosis (see ch. 127 and 159). Accurate measurement of BP is important in any hypotensive patient to confirm the diagnosis and to provide baseline data for monitoring the response to therapy. BP evaluation methods differ in their sensitivity to low BP. Automated noninvasive techniques (i.e., oscillometric techniques) may fail to detect a pulse when hypotension is present, and operator-reliant techniques for pulse detection (e.g., Doppler sphygmomanometry) can be unreliable if the pulse signal is difficult to discern. Of the methods typically used in acute BP measurement, arterial cannulation is the most accurate method of documenting and monitoring hypotension.

Choosing a Blood Pressure Measurement Technique

Acute Diagnostic Blood Pressure Measurement

Detection of systemic hypertension may prompt additional testing for an underlying disease condition. Therefore, it is often preferable to measure BP acutely (i.e., during a clinical examination or diagnostic evaluation), rather than hospitalizing patients and placing indwelling arterial catheters. When a technique to measure BP in a particular animal is chosen, specific issues to be considered include the availability of equipment, the availability of "normal" values to use for comparison, the skill and experience of the person making the measurement, and specific issues related to the animal (e.g., size, obesity, temperament).

Many studies have been performed in anesthetized and conscious dogs and cats and have rendered conflicting results regarding the accuracy of various noninvasive measurement methods to predict BP measured invasively via implanted telemetry devices or arterial catheters in peripheral arteries. Published validation studies, often performed on healthy young animals, have indicated that choice of measurement method (e.g., oscillometry, Doppler ultrasound, high definition oscillometry) and the specific technique details (e.g., position of patient during measurement, cuff position, anesthetized vs. conscious patient) have a large impact on the precision and accuracy of BP measurement in dogs and cats, but at this time, there is no consistent advantage or disadvantage to any of the noninvasive techniques to assess BP outlined below. Ultimately, the types of studies that are most helpful to the clinician are those that develop normal ranges of measured BP using specific devices in clinical patients (i.e., patients of varying ages, breeds and health status). Alternatively, a well-performed study using normal animals may be used to develop normal values for noninvasive methods if they are compared to a valid invasive method. Further, the technique used in a specific study must be accurately reproduced in the clinic for the suggested "normal values" to be valid. To date, few studies have addressed the ability of these techniques to discern "normal" from "abnormal" in a conscious clinical population. Therefore assessment of BP values obtained may involve comparisons with normal values or comparison with values known to be associated with clinical signs.

Continuous Blood Pressure Monitoring: Conscious Patients

The monitoring of BP over time requires either continuous measurement (arterial catheterization) or repeated measurements, recorded automatically (oscillometric or high definition oscillometric [HDO] methods) or manually (Doppler sphygmomanometric methods). Arterial catheterization has the greatest number of advantages in conscious patients. Blood pressure obtained via arterial cannulation is accurate when the technique is used correctly and the values obtained are objective and repeatable (no manual pulse detection is required). A particularly important advantage is that the system can be secured to continue BP measurement when the animal moves. The major disadvantages are the technical skills and equipment required to maintain an arterial catheter and transducer system. Noninvasive methods are commonly used to take serial BP measurements in conscious animals. Although noninvasive BP measurements appear to be technically simple to obtain, they are subject to marked inaccuracy with animal movement, poor pulse pressure, arrhythmia, or inconsistent technique. *When repeated BP measurements are obtained using these methods for monitoring, animal posture, limb position, cuff size and cuff position should be identical for the repeated recordings.*

Continuous Blood Pressure Monitoring: Anesthetized Patients

Blood pressure monitoring by most clinical methods is accurate and repeatable in anesthetized animals. The primary confounding problem of patient movement is absent in these patients, which renders them ideal subjects for BP measurement. Nonetheless, differences between values obtained by invasive methods (arterial

catheterization) and noninvasive methods have been documented in numerous studies of dogs and cats. These studies indicate that numeric values obtained by means of noninvasive methods often underestimate true BP. In the case of anesthetized animals, this may result in an erroneous diagnosis of hypotension, but it seldom leads to the more dangerous error of overestimating BP in these patients. In any case, the marked hypotensive effects of many anesthetic agents should be taken into account when assessing BP in an anesthetized patient.

Blood Pressure Measurement Techniques

Regardless of the technique chosen to assess BP in clinical patients, written records of the technique and results should be kept on a standard form, including cuff size and site, values obtained, rationale for excluding any values, the final (mean) result, and interpretation of the results by a veterinarian. It may be helpful to record assessment of patient demeanor during measurement (e.g., calm, agitated, panting, etc.) to help determine the need for confirmatory measurements.

Arterial Puncture or Arterial Cannulation ("Invasive" or "Direct" Technique)

Direct BP measurement involves advancing a needle attached to a pressure transducer directly into an artery to measure BP. This procedure may be performed acutely to obtain instantaneous BP readings, or BP can be measured over time through the use of an indwelling arterial catheter instead of a needle. Invasive BP measurements are typically used during anesthetic procedures, in critical care patients when ongoing BP information is desired, or to document or exclude hypertension acutely as a clinical diagnosis in dogs. Acute arterial puncture is seldom used for clinical diagnosis of hypertension in cats.

Direct BP measurement is usually performed by means of puncture of the femoral artery in dogs. Use of local anesthesia is strongly recommended for this procedure and when used, the procedure is well tolerated by most dogs. The patient is gently restrained in lateral recumbency. Approximately 5 minutes prior to arterial puncture, 1 to 2 mL of 2% lidocaine hydrochloride is injected subcutaneously over the area in which the femoral pulse is palpated in the dependent hind limb. A 22-gauge, 1-inch needle is attached to a transducer and flushed with heparinized saline, ensuring that no bubbles remain in the transducer. The transducer is zeroed at the level of the sternum in the laterally recumbent dog. The femoral pulse is palpated in the femoral triangle, and the needle is carefully advanced into the femoral artery (Figure 99-1) until a satisfactory pressure waveform is recorded on the monitor screen.

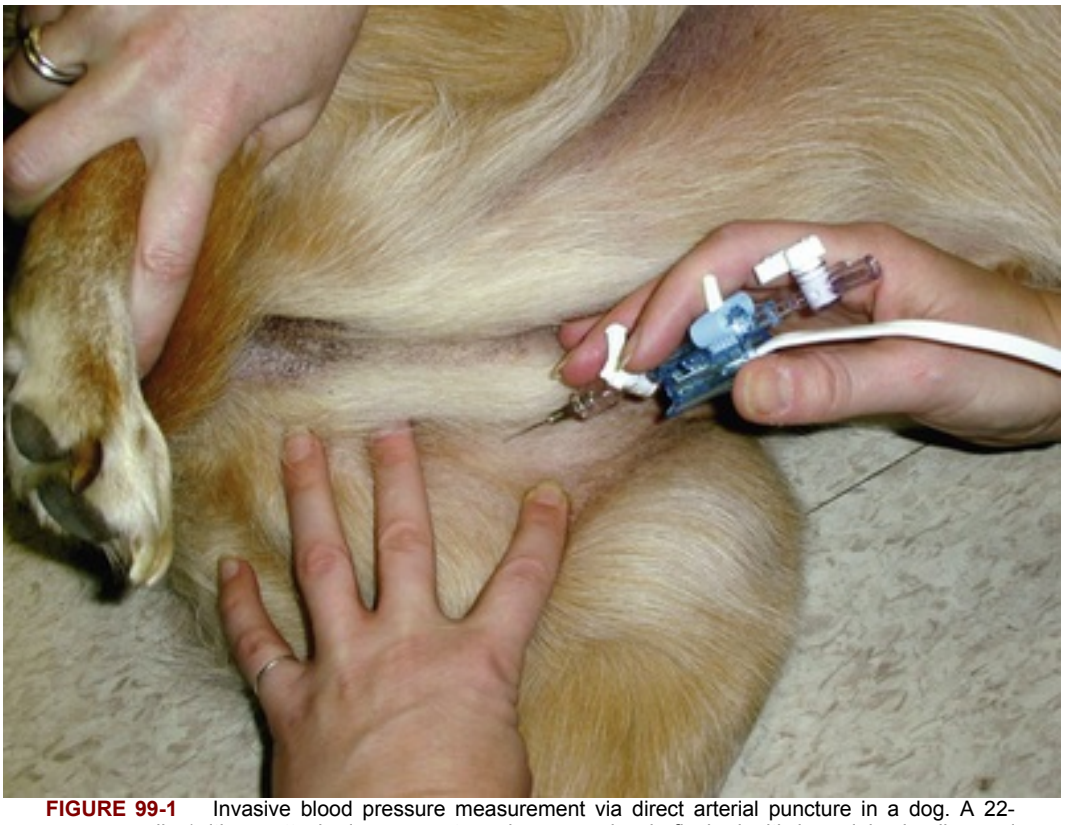

FIGURE 99-1 Invasive blood pressure measurement via direct arterial puncture in a dog. A 22-gauge needle (with an attached pressure transducer, previously flushed with heparinized saline and zeroed) is advanced into the femoral artery at the level of the palpable pulse in the femoral triangle after local anesthetic infiltration (see text).

A sample of the tracing is recorded, and the needle is withdrawn. Firm pressure is applied to the area of arterial puncture for a minimum of 5 minutes after measurement. The patient should be monitored closely for at least 1 hour after the procedure for any complications related to hematoma formation. Systolic, diastolic, and mean BP values from five consecutive cardiac cycles during normal sinus rhythm are averaged to obtain a representative value for the patient. When use of an arterial catheter is preferred, the catheter is usually inserted into the dorsal pedal artery. A local anesthetic may be used as described previously.

Oscillometric Technique

Oscillometric BP measurement involves the use of an automated detection system and a cuff that is wrapped around a limb or tail over an artery. The cuff is inflated automatically to a pressure that causes occlusion of the artery and then slowly deflated. The machine detects oscillations in the vessel wall as the occlusion is eased, and the pressure at which oscillations are maximal is recorded as the mean arterial pressure. The monitor using algorithms specific to the technique then calculates systolic and diastolic pressures. This technique uses data from many cardiac cycles to render a single reading and is therefore unsuitable for use in animals with rapidly changing BP.

Oscillometric BP measurement methods are more accurate in dogs than in cats. This measurement method may return inaccurate results if the patient is not motionless (e.g., trembling or panting), has a weak or irregular pulse, or has a small artery (i.e., most cats). Use of a cuff of appropriate size is extremely important to ensure accurate measurements. Cuff width should be approximately 40% of the circumference of the limb or tail in dogs and approximately 30% of the appendage circumference in cats. When used on the tail, the cuff is wrapped snugly high on the tail head with the dog in sternal or lateral recumbency. Although tail cuffs can be used in standing animals, animal movement often interferes with accurate measurement. Limb cuffs are wrapped around the forelimb distal to the elbow or around the mid metatarsus at the level of the superficial plantar arterial arch (Figure 99-2). In all cases, the center of the inflatable bladder on the cuff should be centered over the artery that will be compressed. The center of the inflatable bladder is often indicated on the cuff by a small arrow.

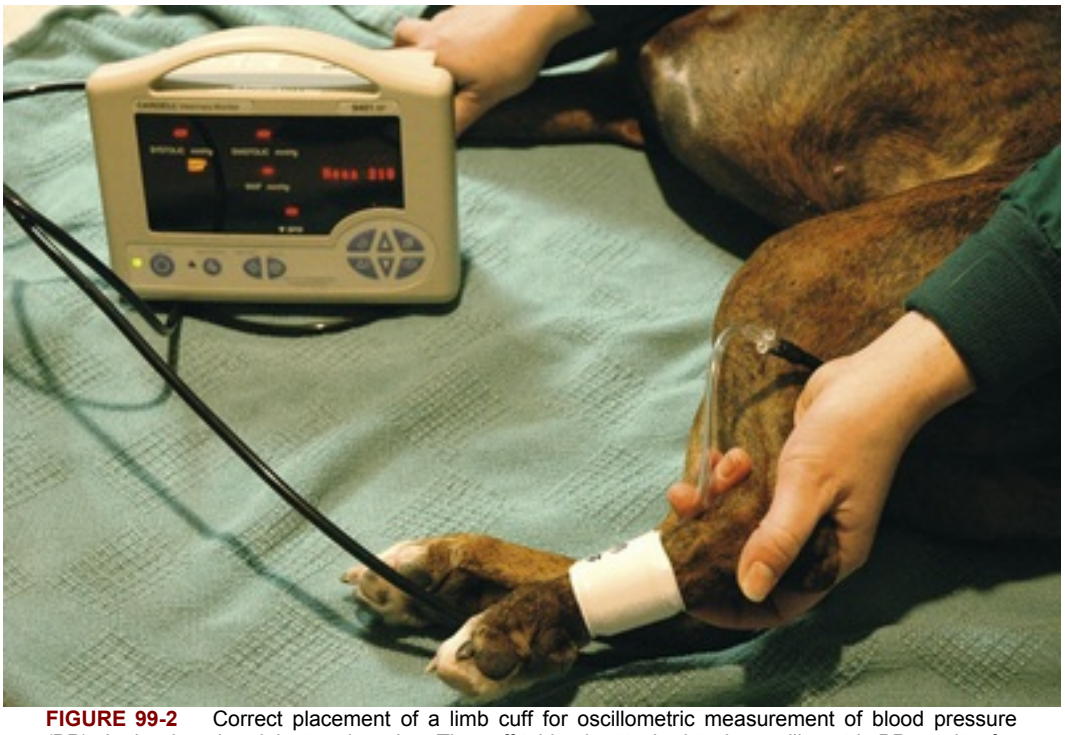

FIGURE 99-2 Correct placement of a limb cuff for oscillometric measurement of blood pressure (BP) via the dorsal pedal artery in a dog. The cuff tubing is attached to the oscillometric BP monitor for readings and the patient is gently restrained in lateral recumbency.

To maximize accuracy, the cuff should be at the level of the heart during readings; therefore lateral or sternal recumbency is preferred, and use of limb cuffs in standing patients should be avoided. In cats, tail cuffs return more repeatable measurements than limb cuffs. Typically, the cat rests in sternal recumbency during readings (Figure 99-3).

FIGURE 99-3 Correct placement of a tail cuff for oscillometric readings in a cat. The cat is relaxed and minimally restrained in sternal recumbency.

In all cases, best results are obtained when the patient is minimally restrained and soothed during the

procedure. A short acclimation period prior to measurement is recommended to allow patients to become calmer. A series of at least five readings are obtained at approximately 1-minute intervals. Any readings that are clearly erroneous are discarded. The multiple readings are then averaged to obtain a representative result (Video 99-1).

Oscillometric techniques are valuable in anesthetized dogs and cats to monitor trends in BP. Because the animal is immobilized and BP shows less variability over time, repeatable and accurate readings can be obtained over time in both dogs and cats.

High-Definition Oscillometric Technique

High-definition oscillometry is a variation of the conventional oscillometric method of BP measurement, but detects oscillations of the blood vessel in real time to measure pulse amplitude and is purported to have the ability to assess a wider range of BP values as well as the ability to detect arrhythmias. Cuff and limb positions are similar to those of conventional oscillometric devices, but cuff sizing is divided into two options based on weight of the dog. Attempts to validate and develop data for precision and accuracy of measurements using this technique in anesthetized and conscious dogs and cats have rendered variable results. Based on these evaluations, there is no consistent advantage to clinical use of this type of device vs. conventional oscillometry or Doppler sphygmomanometry. Regardless of device and technique used, body and limb position as well as cuff size and position should remain consistent for any individual dog and cat.

Doppler-Ultrasonic Technique (Doppler Sphygmomanometry)

Doppler ultrasonic flow detection through the use of a piezoelectric crystal allows detection of flow in a peripheral artery. Hair is clipped just proximal to the palmar metacarpal pad at the level of the superficial palmar arterial arch for forelimb measurement; over the dorsal pedal artery for hindlimb measurement; or on the ventral aspect of the tail for tail measurement (Videos 99-2 and 99-3). An occluding cuff (sized as outlined for oscillometric techniques) is placed proximal to the point of flow detection (midradius in the forelimb, proximal to the hock in the hindlimb, or proximal to transducer placement on the tail), and measurements are obtained with the cuff at the level of the heart. Ultrasonic coupling gel is placed on the concave surface of the Doppler transducer, and the transducer is held in position during measurements (Figure 99-4) or fixed in position using adhesive tape.

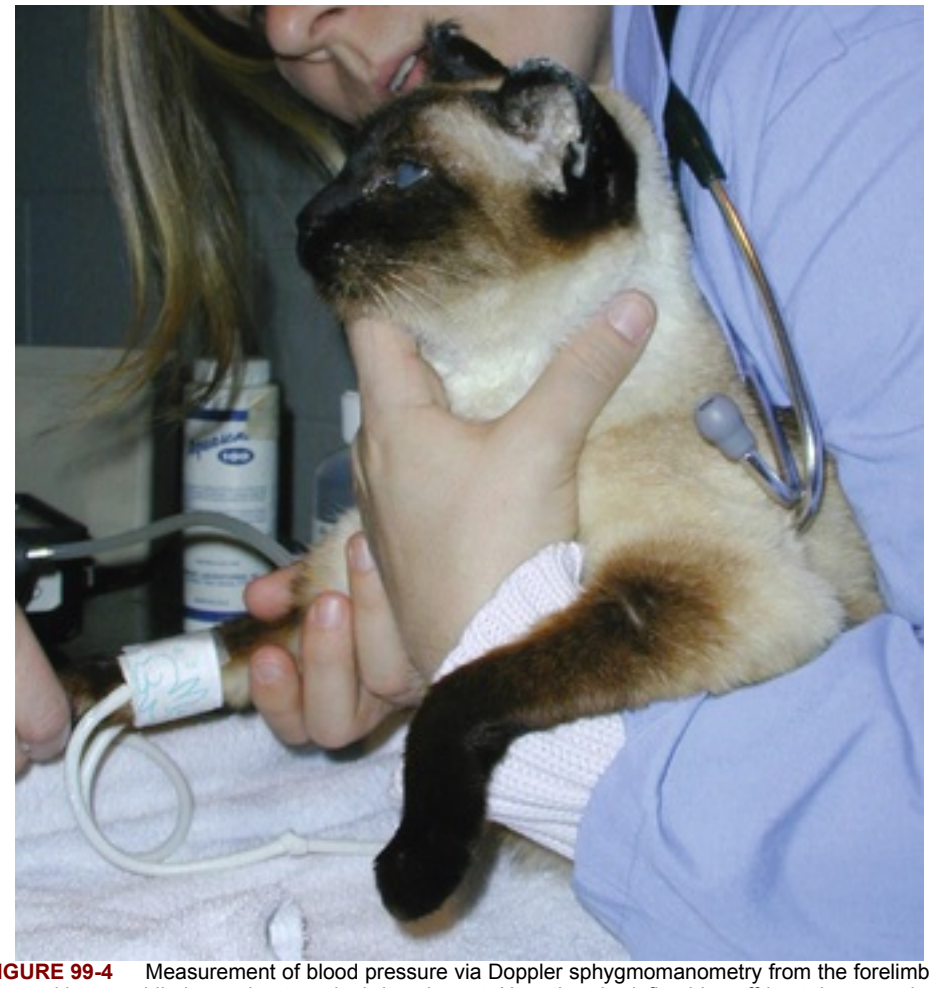

FIGURE 99-4 Measurement of blood pressure via Doppler sphygmomanometry from the forelimb of a cat with acute blindness due to retinal detachment. Note that the inflatable cuff is at the same level as the heart in the sitting and comfortably restrained animal.

An audible pulse signal is obtained, and the cuff is inflated with a bulb attached to a pressure gauge. The cuff is inflated to a pressure no less than 40 mm Hg above the audible cut-off point of the signal. The cuff is then slowly deflated, and the pressure at which the Doppler signal is again audible is recorded as the systolic pressure. The cuff is deflated further, and the pressure at which the audible signal abruptly changes in pitch or becomes muffled is recorded as the diastolic pressure.

The Doppler flow detection system of BP measurement is considered the most accurate and repeatable of studied noninvasive BP measurement techniques in conscious cats. It is frequently used in dogs but may provide spurious high readings in some individuals. When abnormal readings are obtained by this method from dogs, care should be taken to make sure the abnormal readings are repeatable over multiple measurement periods. The advantages of this technique include flexibility with regard to motion, low pressure, small vessels, or the presence of arrhythmias, as well as speed of measurement. The rapidity of the measurement techniques allows for prompt assessment of changing BP, but meticulous attention must be paid to obtaining strong, audible signals in order to obtain the most accurate BP readings. This technique is also the most operator dependent of the techniques discussed. Accurate identification of diastolic pressures improves with operator practice, and BP measurement using Doppler ultrasonic flow detection techniques is most accurate if a few well-trained individuals in a practice are responsible for this diagnostic test and perform the test frequently.

Suggested Readings

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CHAPTER 100

Chest Tube Placement

Tim B. Hackett

Space-occupying lesions in the pleural space reduce tidal volume, decrease lung compliance, and cause a restrictive breathing pattern. Restrictive breathing is characterized by rapid, shallow respirations and dull lung sounds (see ch. 139 and 244). In some cases, such as with tension pneumothorax, increased intrathoracic pressures can impair venous return to the heart, resulting in circulatory shock and further compromise of oxygen supply to vital organs. While radiographs are used to diagnose air and fluid in the pleural space, in emergency settings these conditions can be simultaneously diagnosed and treated by rapid thoracocentesis (see ch. 102). Once removed, fluid can be evaluated to determine the likely source (Table 100-1; ch. 74). Diaphragmatic hernia and intrathoracic masses may require additional imaging for a definitive diagnosis. Ultrasonographic examination is an excellent way to identify pleural fluid (see ch. 244).

TABLE 100-1

Common Causes of Pleural Effusion in Small Animals

TYPE OF EFFUSION	PROTEIN (g/dL)	CELL COUNT (/mcL)	ETIOLOGY
Modified transudate	<2.5	<500-1000	Right heart failure Pericardial disease Hypoalbuminemia Neoplasia Diaphragmatic hernia
Exudate	>3.0	>5000	Feline infectious peritonitis Neoplasia Diaphragmatic hernia Lung lobe torsion Pyothorax
Chylous	>2.5	>500	Idiopathic Cardiomyopathy Heartworm disease Neoplasia Lung lobe torsion Tuberculosis
Hemorrhage	>3.0	>1000	Trauma Coagulopathy Neoplasia Lung lobe torsion

Effusions are classified based on protein content and cell count.

Thoracostomy tubes are routinely placed in surgery following open thoracotomy to maintain negative intrapleural pressure. These short-term thoracostomy tubes allow normal expansion of the lungs as the visceral pleura of the lungs are brought back in contact with the parietal pleura of the chest wall. These tubes are not only useful to maintain negative intrapleural pressure, they also provide a means to administer repeated applications of intrapleural local anesthetics. With normal lung tissue and appropriate surgical closure, these tubes can usually be removed 6 to 12 hours postoperatively after several repeated negative aspirates. Inexpensive feeding tubes are often used for short-term postoperative thoracic drainage. The

surgeon will place these while the thorax is still open to confirm proper positioning. Thoracostomy tubes are also necessary in patients with intrathoracic disorders requiring repeated thoracocentesis to maintain negative intrapleural pressure and normal tidal volume. Examples of diseases requiring thoracostomy tubes include traumatic and idiopathic pneumothorax, pyothorax, chylothorax, and neoplastic pleural effusions. A variety of tubes is available and their selection is based on clinician preference and clinical use. Most conditions can be managed with a single tube, though cases of bilateral pyothorax usually require bilateral tube placement.

Basic Equipment and Types of Thoracostomy Tubes

To place a thoracostomy tube, the disposable materials needed include a chest tube, a tubing adapter to take the lumen of the tube down to a standard Luer connection, a three-way stopcock, 20 gauge orthopedic wire, extension tubing, large caliber suture to maintain tube position, and large volume syringes. Sterile instruments needed include curved forceps or hemostats, a scalpel handle and blade, towel clamps, and a surgical drape.

Commercially available chest tubes or red rubber catheters can be used (Figure 100-1). The red rubber catheter is the least expensive, and is often used for short-term, post-thoracotomy cases. These are flexible, can easily kink, and are more reactive than polyvinyl chloride commercial tubes making them undesirable for long-term use. Red rubber tubes are also nearly impossible to see radiographically without the use of contrast.

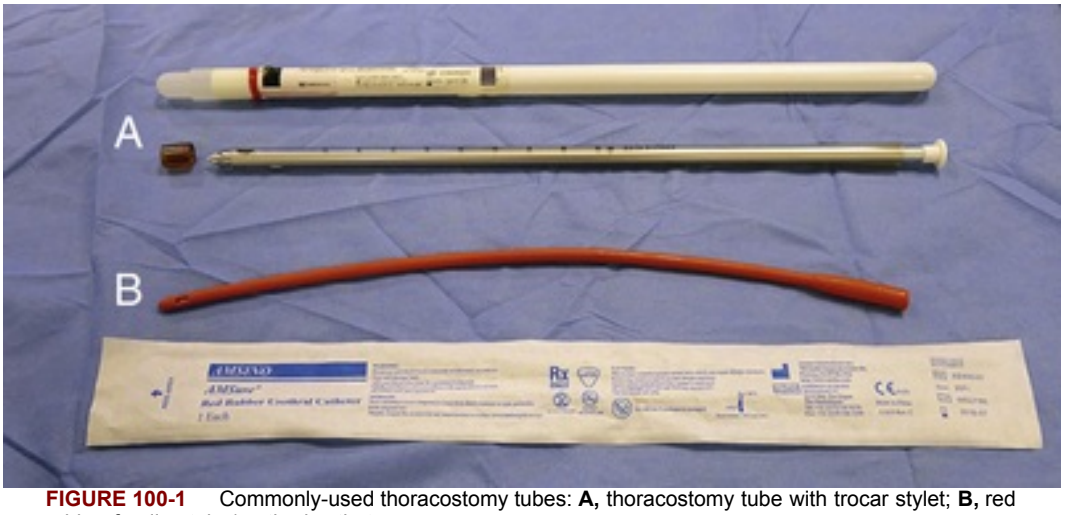

FIGURE 100-1 Commonly-used thoracostomy tubes: **A,** thoracostomy tube with trocar stylet; **B,** red rubber feeding tube/urethral catheter.

Commercial tubes are available in different sizes, ranging in diameter from 14 to 40 French. The commercial tubes are usually open at the end and have oval side holes. They also have a radiopaque line that runs the length of the tube to the side hole furthest from the tip of tube. This mark is important when evaluating tube placement radiographically. All holes should be within the thoracic cavity. If the side hole furthest from the tip is under the skin, air can be aspirated from outside the chest.

While sizes have traditionally been selected by matching the chest tube to the diameter of the mainstem bronchus, other factors should also be considered. Thoracostomy tubes are invasive and painful. If smaller tubes are sufficient, they might be better choices for chronic effusions and continuous, or mild, pneumothorax. Larger tubes should be considered with highly cellular effusions and large volume, continuous pneumothorax.

More recently, smaller products have become available, including over-wire kits and Veress needle style, spring-loaded catheter systems (Figure 100-2). The Veress systems have a blunt safety cannula housed within the sharp, beveled hollow needle and a safety color change indicator. These systems are potentially safer when there are concerns about pockets of fluid or concerns about the lung adhering to the parietal pleura. These systems usually contain small caliber tubes and can be indicated when palliative tubes are expected to be in place for long periods of time. The landmarks and technique described in the following section should be modified based on the localization of large fluid pockets, which are best assessed with ultrasonographic examination (see ch. 244).

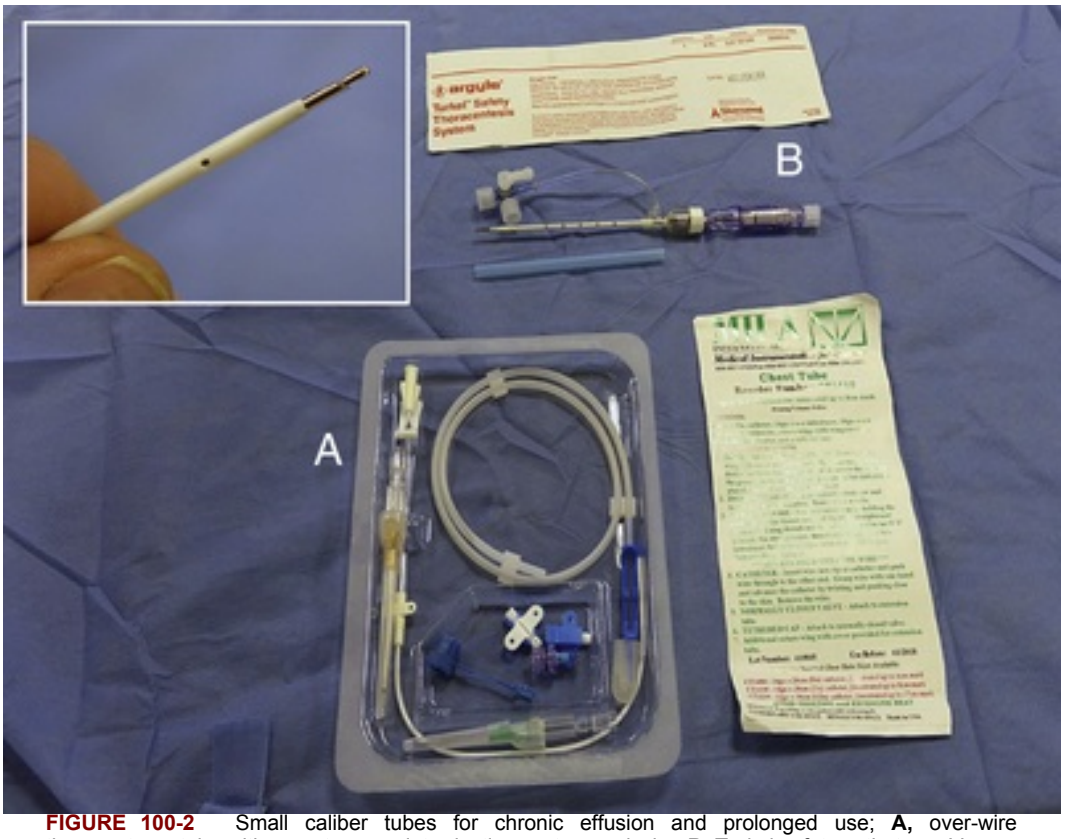

FIGURE 100-2 Small caliber tubes for chronic effusion and prolonged use; **A,** over-wire thoracostomy tube with percutaneous introduction system and wire; **B,** Turkel safety catheter: a Veress needle, with spring-loaded intraluminal cap to prevent iatrogenic laceration of the lung (inset).

Techniques

Several techniques have been described to place thoracostomy tubes. Whenever possible, the procedure is performed under general anesthesia. Usually the patient can be stabilized with thoracocentesis alone, though in some emergency cases tube placement might be necessary to establish normal tidal volume and minimize pleural air accumulation. In these cases, the clinician might place the tube with the patient under sedation and local anesthesia. In general, patients are held in lateral recumbency and the lateral chest wall is clipped and prepared aseptically (Videos 100-1 and 100-2). A skin incision is made over the ninth to eleventh intercostal space, and then the skin is pulled cranially to the site of tube entry at the level of the mid-thorax. The tip of the curved forceps is inserted into the skin incision and blunt dissection is used to separate the intercostal muscles, taking care to avoid the intercostal vessels and nerves caudal to the rib. If the patient is intubated and ventilated, there is little concern about air entering the pleural space during the procedure. Insertion of a tube with an internal stylet into the pleural space without prior chest wall dissection could put the patient at risk of iatrogenic injury to intrathoracic structures. Instead, the tube with internal stylet is gently manipulated through the hole created by blunt dissection. If a stylet is not used, the tip of the tube is grasped by the curved forceps and inserted into the hole created by blunt dissection. The thoracostomy tubes are placed into the chest with the tip barely reaching the cranioventral thorax. Over-insertion risks kinking the tube. When the skin is released and retracts caudally, a subcutaneous tunnel is formed from the skin incision to the point of entry into the thorax. This prevents air from entering the skin incision when the thoracostomy tube is removed. If the patient is intubated and ventilated, there is no reason to mechanically clamp the tube. Clamping the tube can create small punctures in the tube, potentially resulting in air leakage into the thoracic cavity. Making the necessary connections takes little time and insignificant quantities of air admitted during the procedure can then easily be removed. Once the connections are secured to the tube, evacuation of the pleural space can begin immediately. The chest tube should be attached to the skin with a self-tightening knot and all connections secured with cerclage wire. Chest tubes are painful and will result in a restrictive breathing pattern owing to the discomfort felt with normal respirations. Most patients with indwelling chest tubes should receive both systemic and local analgesia.

Intermittent Versus Continuous Suction

Following thoracostomy tube placement, intermittent or continuous suction techniques can be used. During the first few hours, the volume of air or fluid should be evaluated through intermittent aspiration. With small volume accumulation and appropriate monitoring, the intermittent technique can be manageable. Other advantages of the intermittent technique are that it is harder for the patient to accidentally remove the tube or traumatize it when a light bandage covers it.

Continuous suction is usually only indicated when there is rapid accumulation of air leading to repeat and frequent episodes of respiratory distress. Continuous suction requires a vacuum source and a closed system. It is important that the negative pressure is less than 20 cm H_2O and that the system does not allow air to enter the patient if the suction is turned off. Commercially available systems have replaced the three-bottle system with three separate chambers (Figure 100-3). The chamber closest to the patient is the largest and is used to quantitate fluids coming from the patient. The suction tube from the patient is connected to this chamber at an opening near the top. A tube from the top of the first chamber goes from the top of the chamber into the second chamber, opening approximately 1 centimeter under water. This is the water seal chamber and serves two functions. During continuous suction, any air seen bubbling into this chamber means air is coming from the patient (or a leak between the patient and this chamber). The other function is to prevent air being drawn into the patient if suction is discontinued. The third chamber, farthest from the patient and closest to the suction device, modulates the negative pressure. There is a tube from the top of this chamber open to outside air and terminated near the bottom. When water is added to this chamber and the suction turned up until air is drawn from the top to the bottom (as evidenced by bubbles coming from the tube), the pressure of the vacuum equals the depth of the tube. For a desired vacuum of 20 cm of H_2O, the chamber is filled to 19 cm (the additional 1 cm of water creates the water seal in the second chamber).

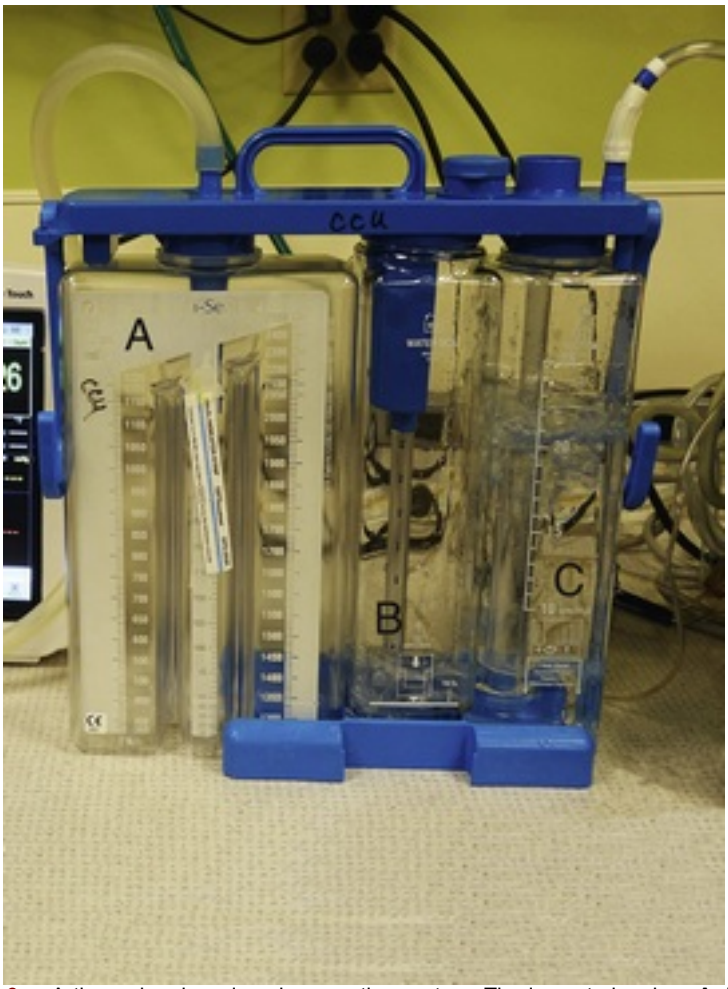

FIGURE 100-3 A three-chamber pleural evacuation system. The largest chamber, **A,** is connected to the patient's chest tube and can quantify the volume of liquid removed. The middle chamber, **B,**

creates a water seal that prevents air from being drawn back into the patient if suction is interrupted. Bubbling noted in this middle chamber indicates air production from the patient or connected tubing. The third chamber, **C,** is connected to the suction apparatus and moderates the negative pressure applied to the patient. When suction is applied and air is seen to bubble in this chamber, the negative pressure applied to the patient (cm H_2O) equals the depth of this tube.

Troubleshooting Continuous Air Production

Patients that continually produce air from a chest tube 12 to 24 hours after placement should be evaluated for leaks within the tubing or suction system. The system should be investigated between the pleural space (including radiographs to confirm all the tube side holes are within the thoracic cavity) and skin incision, and between the tube connections and the suction apparatus. The most common sites of leakage are the tube, from either a side hole just under the skin or a hole placed by a clamp, and the Christmas tree connection closest to the tube. A small amount of fluid placed in the tube at the Christmas tree might reveal a leakage site by bubbles drawn into the tube when negative pressure is applied (see Video 100-2).

The thoracostomy tube is removed when it is no longer indicated. Patients on continuous suction for a pneumothorax should be weaned by switching to intermittent aspiration at progressively longer intervals. Thoracic radiographs are recommended just prior to removal of the tube to ensure that the disorder has resolved. If stable, the animal is sedated with a combination sedative analgesic, holding sutures are removed, and the tube is withdrawn in a steady, rapid motion. The skin incision can be closed or left open and a light antiseptic bandage is placed over the hole.

Suggested Readings

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CHAPTER 101

Transtracheal Wash and Bronchoscopy

Tekla M. Lee-Fowler

Bronchoscopy and airway sampling techniques are useful tools for investigating airway disease. Tracheobronchoscopy allows visualization of the trachea and airways while providing access for sample collection. Airway wash techniques, independent of bronchoscopic guidance, include transtracheal wash, endotracheal wash, and bronchoalveolar lavage (blind technique). Procedure choice should be based on patient stability, whether the disease is focal or diffuse, goals of diagnostics and operator skill level.

Transtracheal Wash

Overview and Indications

A transtracheal wash can be performed to obtain samples from the proximal respiratory tract in medium- to large-size dogs. Results of this procedure can be quite informative in dogs with diffuse pulmonary disease. One major advantage of the transtracheal wash is that the patient is awake-to-minimally-sedated. Since they are not anesthetized, patients often cough during the procedure, increasing sample return and the likelihood of obtaining material from lower airways. Transtracheal wash is not suitable for aggressive or extremely anxious dogs. Hemostatic abnormalities, severe pyoderma of the neck, and respiratory distress could each be considered contraindications for this procedure.[1]

Procedure

The dog is placed in sternal recumbency and gently but firmly restrained by an assistant who is holding the head with the nose pointing upward. The ventral portion of the neck, beginning at the larynx and including the proximal portion of the trachea, is clipped and aseptically prepared. With sterile gloved hands, the target area can be palpated. Needle placement will be either through the cricothyroid ligament or on midline between two adjacent tracheal rings. An intradermal and SC injection of 2% lidocaine is administered over the target area. At least 10 minutes is required for local anesthesia to take effect. The cricothyroid ligament is located between the thyroid cartilages cranially and the cricoid cartilage distally. A 16- to 19-gauge through-the-needle IV catheter is inserted through the target area and into the tracheal lumen. Once the needle tip reaches the lumen, the needle should be angled downward (toward the thorax) and the catheter advanced into the airway and down the trachea. When the catheter is in place, the needle can be withdrawn from the trachea and covered with the attached needle guard. Warm sterile 0.9% saline (5-20 mL) is infused through the catheter using a syringe.[2] Suction is applied using the syringe plunger to retrieve as much of this fluid as possible. In the absence of coughing, coupage can facilitate return of sample. Generally, recovery of fluid is much less than with other techniques, with 10% or less of the instilled volume typically recovered.[1,2] It may be necessary to instill additional aliquots of saline until an adequate sample is retrieved; the total volume instilled will depend on the dog's size and respiratory stability. Although the recovered volume may be small, the amount should be adequate for cytology, culture and sensitivity.

Complications

Complications of transtracheal wash are uncommon. Transient SC emphysema is the most frequently described complication. Other complications include tracheal laceration, endotracheal hemorrhage, infection at the puncture site, and transient worsening of respiratory status.

Endotracheal Wash

An endotracheal wash can be utilized in dogs and cats, and is particularly useful in small dogs and cats for which a transtracheal wash is not suitable. This technique requires anesthesia, allows sampling of the proximal respiratory tract, and differs from a blind bronchoalveolar lavage in that the catheter is only advanced to the level of the carina. To prepare the sterile red rubber urinary catheter prior to the procedure, a sterile blade or scissors is used to create an open-ended catheter by removing the distal end of the catheter just above the lateral openings. A syringe adapter is attached to the proximal end of the catheter (Figure 101-1).

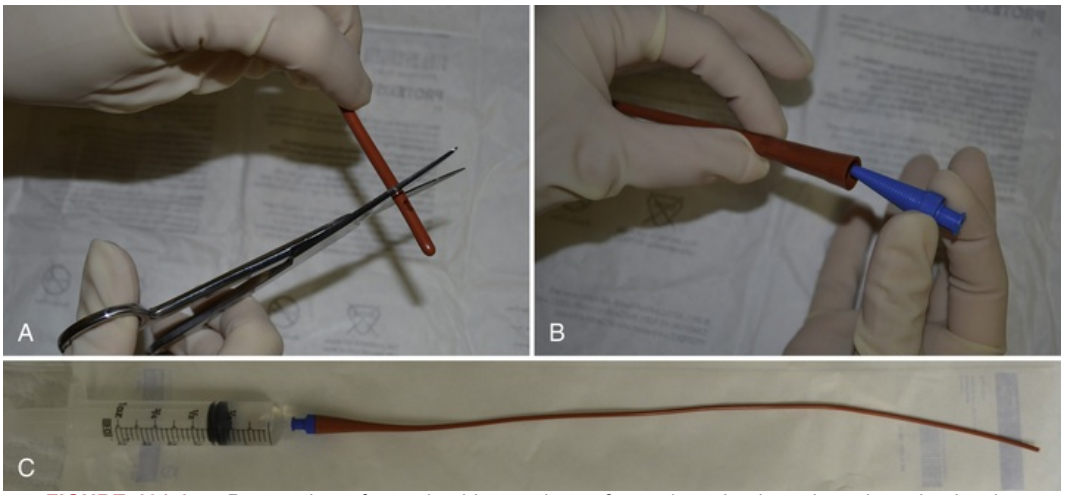

FIGURE 101-1 Preparation of a red rubber catheter for endotracheal wash or bronchoalveolar lavage blind technique. **A,** Sterile scissors are used to create an open-ended catheter by removing the distal end of the catheter just above the lateral openings. **B,** A syringe adapter is attached to the proximal end of the red rubber catheter. **C,** A prepared catheter with a preloaded syringe of sterile saline attached.

The patient is intubated with a sterile endotracheal tube, and the open-ended sterile red rubber urinary catheter is passed through the endotracheal tube lumen to the approximate level of the carina. 5-20 mL of warm sterile 0.9% saline is infused through the red rubber catheter, via the syringe, and negative pressure is applied to retrieve the sample. Coupage may be performed to facilitate sample collection. The volume of sample recovered is similar to that of the transtracheal wash. This process may need to be repeated to obtain adequate sample. Total volume of saline used is dependent upon the patient size and respiratory status.

Bronchoalveolar Lavage: Blind Technique

Bronchoalveolar lavage (BAL) can be performed without endoscopic guidance when diffuse disease is present. This sampling method differs from those described above by providing sample from the lower airways. This technique is most successful in small to medium-sized pets. Substitution of the red rubber catheter with a feeding tube has been described for larger dogs.[3] Preparation of the red rubber catheter prior to BAL involves using a sterile blade or scissors to produce an open-ended catheter by cutting the catheter just above the distal side openings. A syringe adapter is also attached to the proximal end of the red rubber catheter (see Figure 101-1).

The patient is anesthetized with a short-acting IV anesthetic, intubated with a sterile endotracheal tube, and placed in lateral recumbency. If the disease process is more marked on one side, the patient should be positioned with that side down. An open-ended sterile red rubber urinary catheter is passed through the endotracheal tube until it is gently wedged and cannot be advanced further. Withdrawing the catheter a few millimeters, rotating the catheter slightly and gently advancing again until wedged will help ensure that the catheter is wedged within an airway and not becoming lodged at an airway division. Once the catheter is in place, warmed sterile 0.9% saline is instilled through the catheter and immediately aspirated. The volume infused has not been standardized and recommendations vary from 5-30 mL aliquots to using 2-5 mL/kg. An additional aliquot may need to be infused to recover adequate volume. The volume of sample recovered should be 40-50% of the total volume instilled. After the sampling is complete, the patient is placed on 100% oxygen for about 5-10 minutes (see ch. 131).

Bronchoscopy

Overview

Tracheobronchoscopy, utilizing a flexible bronchoscope, is a tool for visually inspecting mucosal surfaces of the trachea and lobar bronchi. Additionally, specific sites for sample acquisition can be chosen for pets with focal disease. The patient is anesthetized with an IV anesthetic and maintained with either IV or gas anesthesia. With the latter option, the bronchoscope is passed through the endotracheal tube utilizing a T-adapter. However, internal endotracheal tube diameter becomes a limiting factor in small patients. In small dogs and cats, IV anesthesia and direct intubation with the bronchoscope is often necessary. It is helpful to intubate these patients with a small diameter (5-Fr), sterile, red rubber catheter alongside the bronchoscope to provide supplemental oxygen during bronchoscopy. Supplemental oxygen can also be supplied through the biopsy channel of the bronchoscope.

Initial Visual Evaluation

Inspection of the trachea should include assessing appearance of the mucosa, the amount of secretions present, and any evidence of collapse. The carina should then be identified and each lung lobe should be systematically examined (Figure 101-2 and Video 101-1). The endoscopist must note the presence of abnormalities such as mucus plugs, mucopurulent debris, hemorrhage, foreign bodies, static or dynamic collapse of airways, masses or nodules, and parasites (see ch. 241).

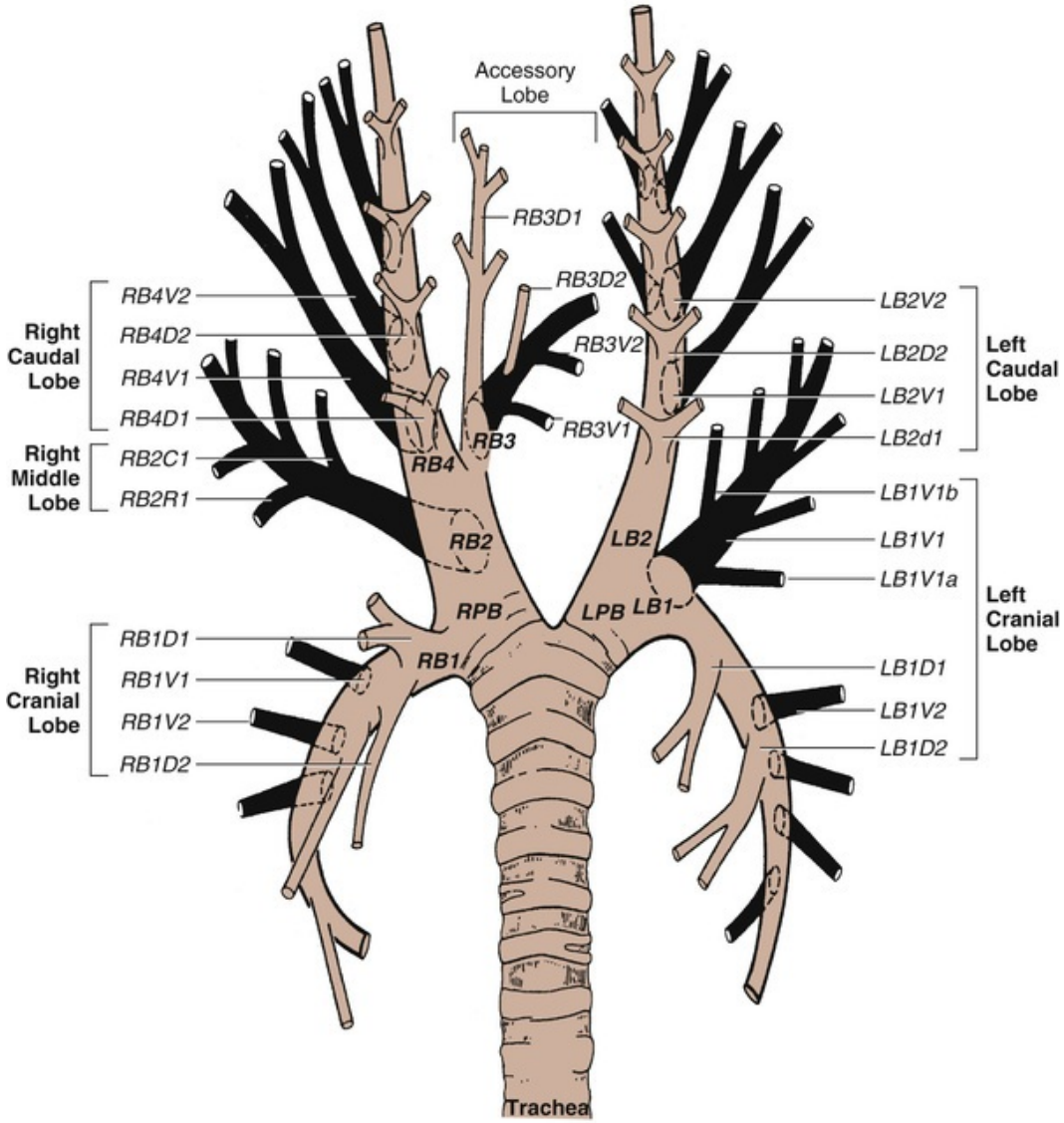

FIGURE 101-2 Diagram of normal bronchial anatomy in dogs. Each lobar bronchus is subdivided into segmental bronchi: *V1,* first ventral segmental bronchus; *V2,* second ventral segmental bronchus; *D1,* first dorsal segmental bronchus; *D2,* second dorsal segmental bronchus; *C1,* first caudal segmental bronchus; and *R1,* first rostral segmental bronchus. Segmental bronchi are subdivided into subsegmental bronchi: *V1a,* first subsegmental bronchus; *V1b,* second subsegmental bronchus. *LB1,* Lobar bronchus of left cranial lung lobe; *LB2,* lobar bronchus of left caudal lung lobe; *LPB,* left main stem bronchus; *RB1,* lobar bronchus of right cranial lung lobe; *RB2,* lobar bronchus of right middle lung lobe; *RB3,* lobar bronchus of accessory lobe; *RB4,* lobar bronchus of right caudal lung lobe; *RPB,* right main stem bronchus. (From Amis TC, McKiernan BC: Systematic identification of endobronchial anatomy during bronchoscopy in the dog. *Am J Vet Res* 47:2649, 1986.)

Brush Catheter

The airway mucosal surface can be sampled using a bronchoscope brush catheter. The brush is covered by a plastic sheath that can be pulled back once the brush is in its desired location. With the bronchoscope in the desired location, this small sampling brush is passed through the sampling channel. Once the brush catheter is visualized, it is uncovered, gently scraped against the mucosa, then retracted back into the sheath, and removed from the scope. The brush can be cultured and then gently rubbed on a glass slide for cytology.

Biopsy

In a similar method, the bronchoscope is placed in the desired location and the biopsy instrument is inserted into the sampling port (biopsy channel). The bronchoscope is then used to guide the instrument to the desired

location and the biopsy taken. Samples can be submitted for culture and histopathology. This technique is primarily indicated for sampling proliferative tissues or masses within the airways. A technique has been described for transbronchial biopsy of more peripheral tissue, particularly in the caudal lung lobes; however, complications such as bleeding, pneumothorax, small sample size and likelihood of sample crush artifact could outweigh benefits.[4]

Transbronchial Fine Needle Aspirate

This method is primarily indicated for obtaining samples from lymph nodes or masses impinging on the airways. While visualizing the compressed area with the bronchoscope, a transbronchial needle catheter is passed through the sampling channel. When the needle catheter is visualized, the needle is uncovered, advanced through the mucosa between the cartilage rings of the bronchus and into the impinging lymph node or mass (see ch. 95). A syringe is used to apply negative pressure to obtain an aspirate. The needle is withdrawn without suction, recovered, and retracted from the scope. Samples can be used for cytology slides. Possible complications are similar to biopsy, including hemorrhage and pneumothorax.

Bronchoalveolar Lavage: Endoscopic

This is a commonly used sampling technique to obtain lower airway cytology and culture sample and is performed after all lobes have been inspected. The bronchoscope is directed into the desired bronchus and then advanced until it is wedged or is occluding the airway. With the lumen of the airway centered in the image, warm sterile 0.9% saline is instilled into the sampling port and immediately aspirated. Aspiration can be performed by manual aspiration with a syringe or via suction pump aspiration.[5] The volume of saline to be infused has not been standardized in veterinary medicine. Aliquot volumes of 10-30 mL or a "dosage" of 2-5 mL/kg (small to medium-sized dogs and cats) have been recommended. About 40% to 50% of the sample should be retrievable. The lightly anesthetized animal may cough, producing a better sample. Coupage can also be performed during aspiration to facilitate sample recovery. This procedure can be repeated to obtain adequate samples depending on volume of saline used, patient size, and patient respiratory status. In cats, sampling two different lung segments may provide more accurate cytologic results.[6] Bronchoalveolar lavage fluid can be submitted for culture and sensitivity and cytological evaluation.

Possible complications of BAL include decline in oxygen saturation, bronchospasm, and pneumothorax. It is advised to provide supplementation with 100% oxygen to all animals immediately after BAL (see ch. 131). This can usually be discontinued shortly thereafter. Additionally, animals with significant respiratory disease may benefit from pre-BAL-oxygenation with 100% oxygen. Bronchospasm as a complication of bronchoscopy and BAL is most commonly seen in cats. Premedicating cats with suspected lower airway disease using a bronchodilator may reduce this complication.[7]

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CHAPTER 102

Thoracocentesis/Pericardiocentesis

Robert Prošek

Thoracocentesis

Thoracocentesis, also referred to as a chest tap or pleural tap, is both a diagnostic and often therapeutic (emergency) procedure to remove pleural air or fluid from the thoracic cavity. Indications for thoracocentesis are respiratory distress (increased respiratory rate and inspiratory effort) and dull lung sounds (often a fluid line can be identified with effusion) confirmed by thoracic radiographs (pleural effusion, pneumothorax) and/or ultrasound (effusions) (Figure 102-1, *A* and *B*; see ch. 149). Potential contraindications to thoracocentesis include severe coagulopathies and diaphragmatic hernias. Penetration of intestinal loops or liver should be avoided (ultrasound guidance will be needed) while potential complications of thoracocentesis include hemothorax, iatrogenic pneumothorax, laceration of intrathoracic organs, and acute death from the stress of over restraint.

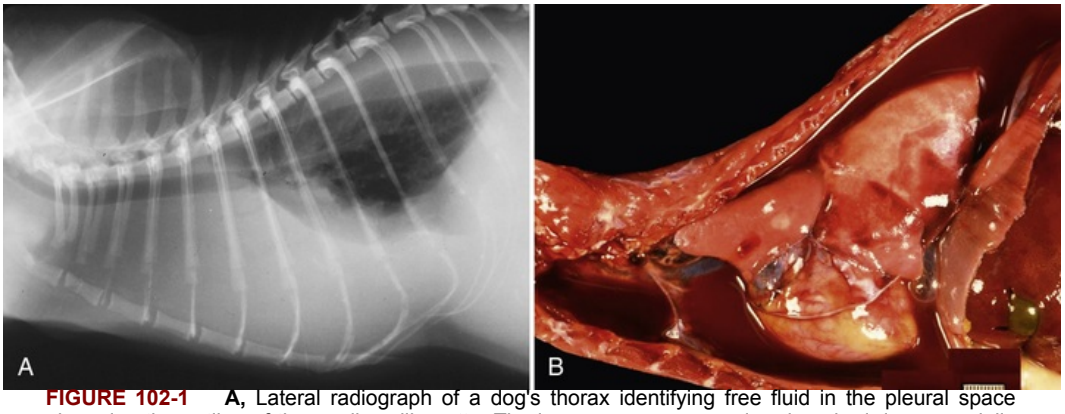

FIGURE 102-1 **A,** Lateral radiograph of a dog's thorax identifying free fluid in the pleural space obscuring the outline of the cardiac silhouette. The lungs are compressed and pushed dorso-caudally by the fluid. **B,** Necropsy view of an open thorax with free pleural fluid surrounding the lungs and compressing them.

With all the aforementioned considerations, thoracocentesis overall still is a simple procedure. The two most common techniques involve either the "butterfly" catheter or plastic catheter that has fenestrations. In cats and small dogs a ¾ to ⅞ inch (2 to 3.5 cm) butterfly needle or 22-23 gauge needle (author prefers butterfly), in medium dogs and large cats a 1 inch (2.5 cm) needle or 20-22 gauge over-the-needle catheter, and in large dogs a 1.5 inch (4 cm) needle or a longer 14-20 gauge over-the-needle catheter are the commonly preferred instruments to use for this procedure. The butterfly catheter, needle or fenestrated catheter is attached to an extension set (with a butterfly catheter, the extension set is usually not needed), a three-way stopcock and a syringe (10 to 60 mL depending on the size of the animal) to withdraw fluid or pleural air. If fluid is being removed, a graduated cylinder or bowl to collect and quantify the amount of fluid removed is needed (Figure 102-2).

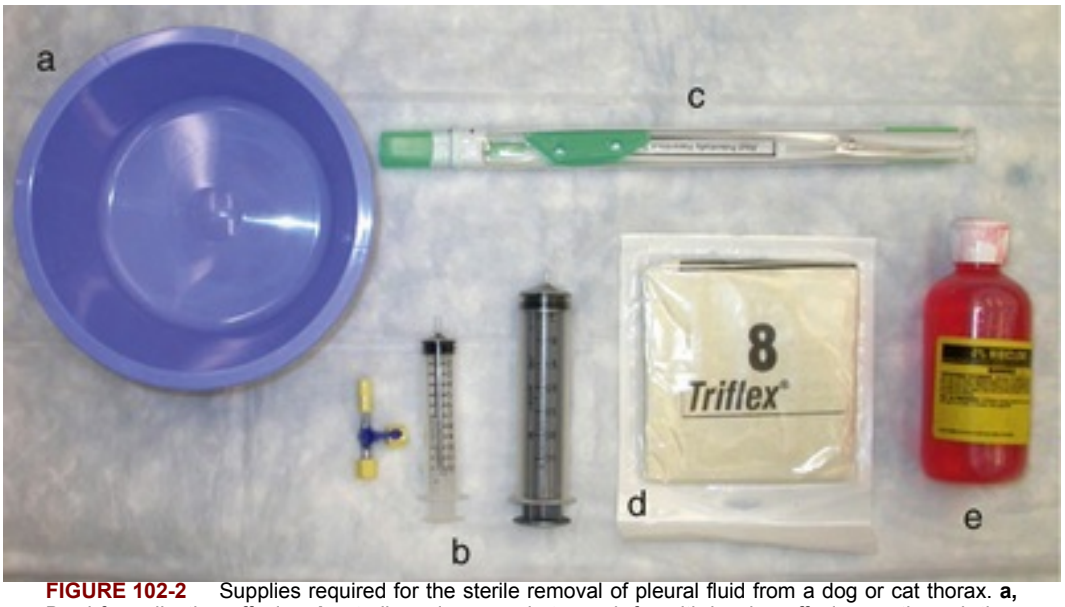

FIGURE 102-2 Supplies required for the sterile removal of pleural fluid from a dog or cat thorax. **a,** Bowl for collecting effusion; **b,** sterile syringes and stopcock for withdrawing effusion; **c,** through-the-needle central venous catheter for accessing the pericardial space; **d,** sterile gloves; **e,** aseptic scrub solution.

The patient is most commonly placed in sternal recumbency or standing for removing pleural effusion or a pneumothorax. If necessary, a lateral recumbent position can be used for tapping a pneumothorax. If the patient shows signs of severe respiratory distress and dull lung sounds, a thoracocentesis might need to be performed without further diagnostics. Otherwise radiographs will help to identify the location of the intercostal space for penetration. This is typically at the seventh or eighth intercostal space (ICS) at the level of the costochondral junction for fluid or the eighth or ninth ICS near the costochondral junction for air. Ultrasonography may be required to identify smaller pockets of fluid collection (see ch. 149). It may be advisable to pre-oxygenate the patient before the procedure and/or to provide a flow of oxygen during thoracocentesis. Clip and aseptically prepare the region to be tapped. Prepare a sterile environment for gloves, needles and syringes to be used (see Figure 102-2). A local anesthetic may be administered; however, it is often difficult to insert the needle into the same space that the centesis needle will be placed. Insert the needle just cranial to the rib (closed system as described above with three-way stopcock and syringe) to avoid the intercostal vessels and nerves that run caudal to the rib. Apply gentle suction on the syringe to generate negative pressure. Once the position of the needle is determined to be satisfactory, if fluid is obtained the needle should be oriented ventrally and if air is obtained the needle oriented dorsal to the body wall to reduce the risk of laceration of the adjacent lung lobe. The needle should be removed if frank blood is aspirated, if lungs can be felt rubbing against the needle or if the patient is moving excessively. Fluid initially removed is placed in sterile tubes for evaluation and cytology. If bloody fluid is removed and is thought to be whole blood, it will clot when placed in a red top tube. Blood from a hemothorax should not clot (minus bleeding disorders), whereas blood from the heart or blood vessels will clot. If an over-the-needle catheter technique is used, frequent kinking of the catheter may occur with patient movement or tachypnea due to pressure from the muscles of respiration. To help stabilize the catheter, the hand holding the catheter can be rested against the patient to try to prevent excessive movement or if all fails leave the stylet inside the catheter and be cautious about movement since the end of the catheter tip is a sharp point and can cause serious intrathoracic damage. Aspiration should continue until the fluid flow stops while aspiration of air should continue until negative pressure is reached (if negative pressure is never obtained, concern for tension pneumothorax exists and a chest tube with continuous suction might be needed; see ch. 100). Removing all the air from the thorax initially can be dangerous since the injured lung can re-expand and in doing so the rent in the lung tissue may reopen. Thus, removal of air should likely stop when the patient is seen to be breathing with less distress.

Samples of fluid extracted from the thorax should be submitted for fluid analysis, cytologic examination and culture/sensitivity as indicated. Chylous effusions are examined against whole blood for paired triglyceride levels. A portion of the fluid should be stored sterilely if future culture is anticipated. Post-centesis, the patient should be monitored for signs of respiratory distress suggesting accumulation of fluid or air or resulting from iatrogenic hemothorax or pneumothorax. Other than keeping the dog or cat at rest and warm and watching for recurrence of signs, no significant post-tap attention is usually required.

Pericardiocentesis

Pericardiocentesis also is referred to as a pericardial tap or pericardial drainage. This procedure involves inserting a catheter to remove a volume of pericardial effusate for diagnostic purposes and more often for the therapeutic relief of life-threatening pericardial tamponade associated with pericardial effusion. Prior to the procedure, if the patient is not critical, echocardiography is recommended to confirm the diagnosis. Cardiac neoplasia is a major cause of pericardial effusion and tumors are often easier to identify pre-centesis since the pericardial fluid often outlines the mass. Also, if inadvertent cardiac puncture occurs during pericardiocentesis, the diagnosis of the initial cause of the pericardial effusion increases the diagnostic challenge. Echocardiography can also yield information if pericardial effusion is due to an atrial tear, as a pericardial clot can often be visualized (Figure 102-3). Pericardiocentesis in this situation would be contraindicated as moving the clot can induce a reoccurrence of acute pericardial hemorrhage. Reviewing the echocardiogram, pericardial effusion is seen as an anechoic/hypoechoic space between the epicardium and the pericardium while pleural fluid also accumulates outside of the pericardial sac in the pleural space (Figure 102-4; Video 102-1) (see ch. 104 and 254). Pericardial effusion can increase intrapericardial pressures resulting in varying degrees of hemodynamic compromise. When intrapericardial pressure equals or exceeds the right ventricular diastolic filling pressure and right atrial pressure, cardiac tamponade occurs with clinical signs of right-sided heart failure and cardiogenic shock developing. Intravenous fluids may increase preload as the patient is prepared for pericardiocentesis if signs of cardiogenic shock are noted; however, significant intravenous fluid may also overwhelm the vascular system resulting in further extravasation of fluid, vascular overloading and heart failure. Supplemental oxygen may often help temporarily while the procedure is being performed.

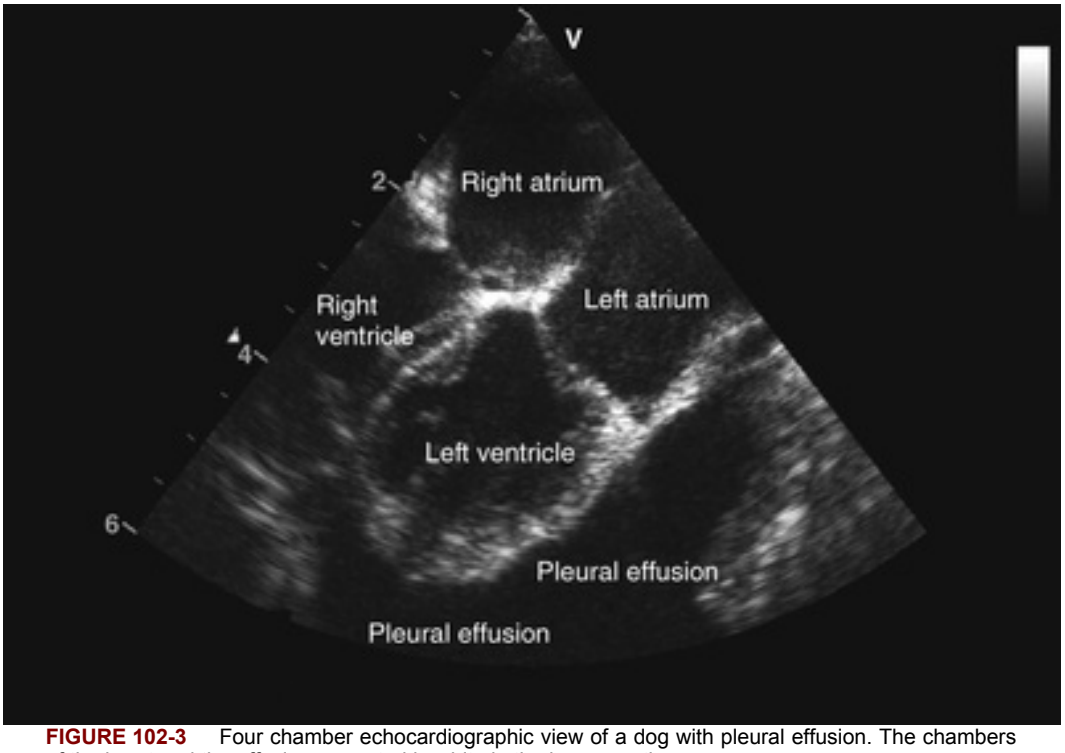

FIGURE 102-3 Four chamber echocardiographic view of a dog with pleural effusion. The chambers of the heart and the effusion are noted in white in the image on the screen.

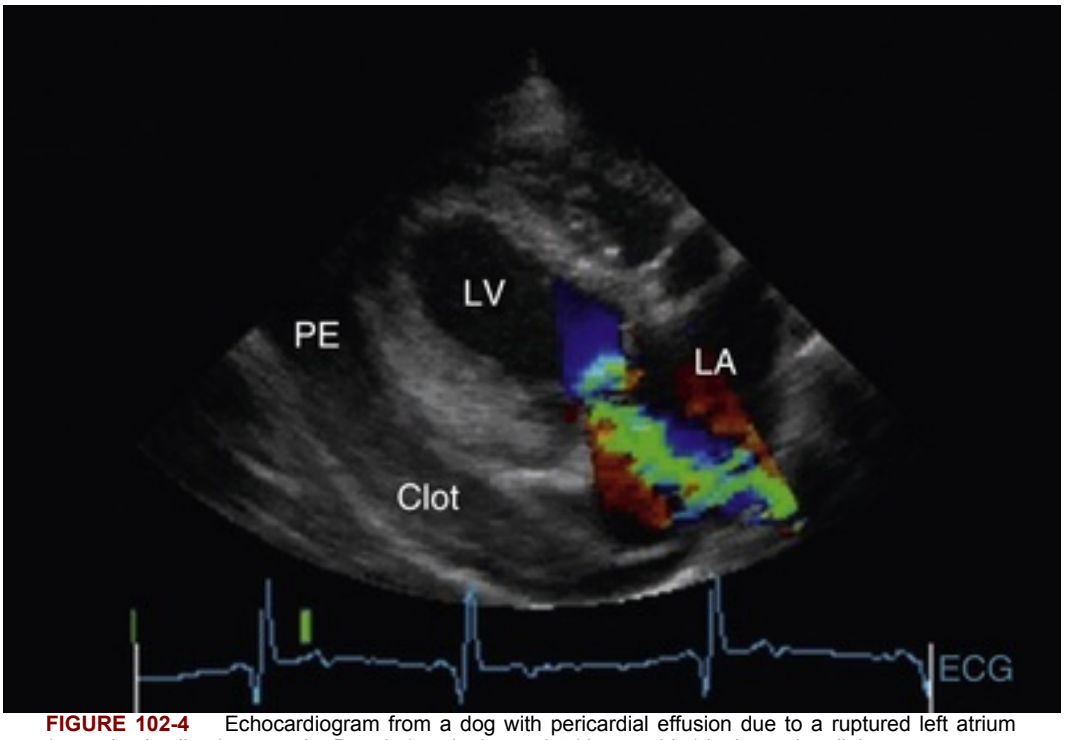

FIGURE 102-4 Echocardiogram from a dog with pericardial effusion due to a ruptured left atrium (see mixed yellow/green color Doppler) and a large clot (dense white) in the pericardial sac.

Pericardiocentesis (Video 102-2) is performed with the patient in left lateral recumbency, inserting the needle through the right hemithorax, typically at the costochondral junction of the right fourth or fifth intercostal space cranial to the rib. Ideally, the designated site for centesis is confirmed with ultrasound or if not available, by counting intercostal spaces on thoracic radiographs (see Figure 102-1). The right-sided approach is used to avoid laceration of a major coronary vessel and to a lesser degree to penetrate the larger cardiac notch, an area where the lungs do not cover the heart. The thoracic region to be tapped is widely clipped of hair and aseptically prepared.

Clip and surgically clean and prepare the region of the thorax to be approached. Prepare to have all of the following items immediately at hand to place on a sterile environment: a syringe for administering 2% lidocaine for local anesthesia (adding 0.1 to 0.2 mL of 8.4% sodium bicarbonate warmed to body temperature may decrease the initial discomfort of the lidocaine local anesthetic); sterile gloves; a #11 scalpel blade; a three-way stopcock; an extension set; a 14-gauge over-the-needle catheter or central venous catheter; several large sterile syringes; 6 mL syringes; a graduated cylinder or bowl to collect the fluid in; lavender and red top tubes for samples of the extracted fluid and possibly tissue glue (Figure 102-5).

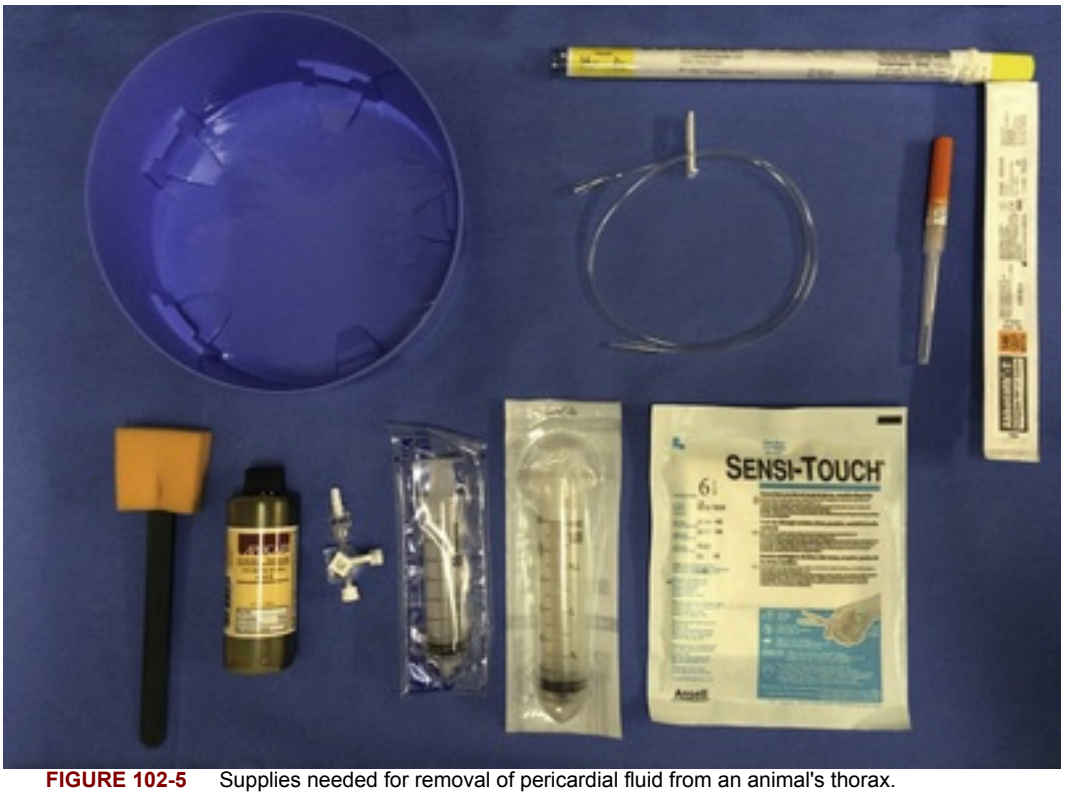

FIGURE 102-5 Supplies needed for removal of pericardial fluid from an animal's thorax.

The area for local anesthesia with 2% lidocaine is infused SC and IM in about a 2 cm^2 region (see Video 102-1). The patient's electrocardiogram should be monitored (reminder: pericardial effusion typically causes small QRS complexes). After sterile gloving, the catheter is attached to an extension set, which in turn is connected to a three-way stopcock and syringe. If needed, a scalpel blade can be used to make a small 2-3 mm skin incision. The needle or catheter-stylet combination is inserted through the skin (perpendicular to the thoracic wall into the thoracic cavity) while another person is drawing back on the syringe plunger to create negative pressure and the needle is slowly advanced towards the pericardium. Initially, a flash of serosanguineous fluid may be seen in the catheter when pleural effusion is present. Continue slowly advancing the needle until a flash of pericardial effusion is seen within the catheter (pericardial fluid is generally but not always hemorrhagic or "port wine" in color). This is usually confirmed by noting the fluid exits the needle in a soft pulsating manner as the heart beats and pushes the fluid to a lower pressure region. Once in the pericardial sac the catheter-stylet is advanced another 2-3 mm farther into the thorax, maintaining negative pressure as the catheter is advanced over the stylet to seat the catheter within the pericardial sac (monitor for arrhythmias throughout, repositioning the catheter as needed or removing it if life-threatening ventricular tachycardia develops). Remove the stylet and reconnect the extension set with the three-way stopcock attached to fill and drain the syringe into a bowl. The fluid removed should be quantified as to amount withdrawn, and if the etiology is not evident, it should be submitted for fluid analysis and cytology and culture as indicated.

Potential complications include arrhythmias (premature ventricular complexes and tachycardia), rapid reaccumulation of the effusion, cardiogenic shock (with malignancies such as hemangiosarcoma), atrial tearing and cardiac puncture. Cardiac puncture due to the catheter being advanced into the heart may not result in significant complications as long as the catheter is quickly withdrawn and repositioned. A coronary artery laceration complication is minimized using the right-sided approach. Withdrawn fluid that clots, either in the syringe or bowl, should alert the clinician that the catheter tip is in the heart, especially if flow is strongly pulsatile, or due to a rapidly bleeding pericardial effusion. Post-tap, the patient's comfort and body temperature are maintained and usually the animal rapidly becomes brighter and more mobile as the signs of cardiac tamponade regress. Radiographs and echocardiography post-tap are likely to be marred by pleural effusion as some of the fluid in the pericardial sac has leaked into the pleural space. Ultrasound examination helps to identify that the fluid has been successfully removed and the signs of cardiac tamponade have been relieved (see ch. 104, 149, and 254).

CHAPTER 103

Electrocardiography

Erin Anderson

Electrocardiography is a common, non-invasive diagnostic tool that records the electrical activity of the heart from the body surface. The resultant recordings, called electrocardiograms (ECGs, EKGs) provide valuable information about the heart rate, heart rhythm, function of the cardiac conduction system, and—with variable sensitivity and specificity—structural changes to the cardiac chambers.[1-6] Indications for obtaining an electrocardiogram include audible arrhythmias, clinical signs that could be caused by arrhythmias (such as lethargy, exercise intolerance, syncope), and assessment of antiarrhythmic therapy in patients with pathologic arrhythmias. Electrocardiograms also are commonly monitored in patients undergoing echocardiography or general anesthesia and in those with electrolyte abnormalities or critical morbidity who require intensive monitoring.

The Physics of Electrocardiography

What the ECG documents is the averaged voltage from the action potentials generated in the myocardium over time. At rest, myocytes have a negative internal charge with respect to the outside of the cell, where the charge is positive. As myocytes depolarize, the electrical charge becomes transiently positive inside the cells and negative outside the cells, creating a region of opposite charge (or polarity) compared to the adjacent non-depolarized cells.[7,8] This difference in polarity is called a dipole, and electrical currents flow readily between dipoles.[2] From the surface of the skin, negative and positive electrodes record the magnitude and orientation of the electrical wavefront; wavefronts are comprised of multiple dipoles between the electrodes (i.e., the net vector of electrical activity).[6-8] Each pair of one negative and one positive electrode constitutes a lead. Between one and 10 different leads may be used to record a surface ECG, with each lead offering a different "vantage point" from which to assess cardiac electrical activity. When the net vector of electricity moves parallel to the lead, a large amplitude deflection is recorded. When the net vector of electricity moves perpendicular to the lead, an isoelectric deflection is recorded: either flatline, or with equal amounts of the deflection existing above as below the baseline. In addition to the orientation of electricity in relation to the lead, the amplitude of the recorded deflection also depends on the voltage of the electrical wavefront, the distance of the lead from the source, and the conducting medium between the source of electricity and the electrodes.[2,6] The polarity of the deflection is determined by whether the net vector of electricity moves toward the positive or negative electrode.

Three standard leads (I, II, and III) and three augmented leads (aVF, aVL, and aVR) commonly are assessed in veterinary electrocardiography. These standard leads are generated by the combinations of electrodes on each forelimb and the left hindlimb, a configuration originally described by Willem Einthoven and still referred to as Einthoven's triangle (Figure 103-1).[9] Leads I, II, and III are bipolar, meaning that they are created by one positive and one negative electrode. In contrast, the augmented leads are unipolar, and they are created by one positive electrode and the average of the other two electrodes (a neutral reference point). The augmented leads create smaller deflections because they are unipolar, but the deflections are amplified by ECG machines (thus, the term "augmented"). Together, these six leads create a comprehensive assessment of cardiac electrical movement from various points along the frontal plane of the animal. Additionally, precordial chest leads are available for unipolar measurement of electrical activity from four different points along the dorsal and ventral planes. Recording these leads requires placement of one positive electrode at each of several specific points around the thorax (Table 103-1).[10] The leads are created by these positive electrodes and one "indifferent electrode" theoretically produced at the common junction of the three bipolar electrodes.[2,3] The nomenclature of the unipolar precordial leads originated in human cardiology but was

subsequently adapted for use in canines (see Table 103-1).[10,11]

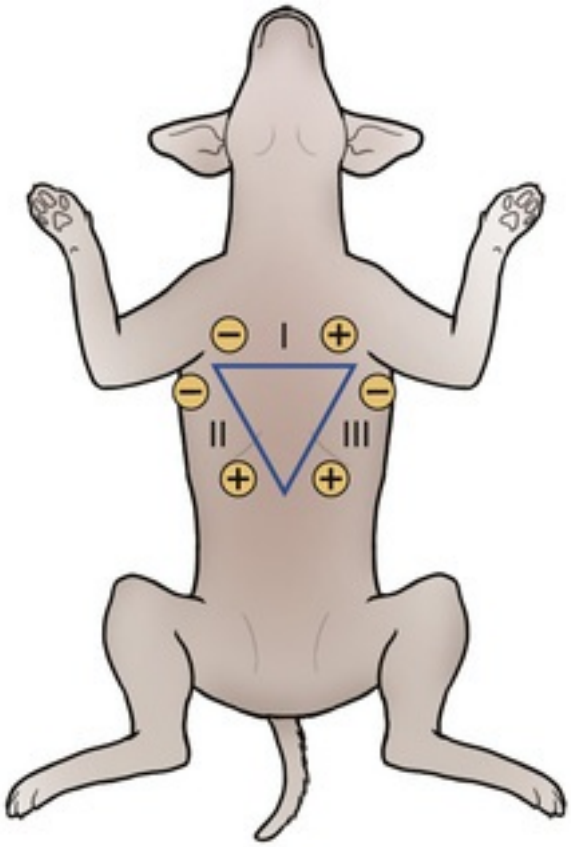

FIGURE 103-1 Einthoven's triangle is an equilateral triangle formed around the center of the heart. It is comprised of three electrodes, one on each of the forelimbs and one on the left hindlimb. Combinations of these three electrodes create three bipolar leads as follows: Lead I is created by a positive electrode on the left forelimb and negative electrode on the right forelimb. Lead II is created by a negative electrode on the right forelimb and positive electrode on the left hindlimb. Lead III is created by a negative electrode on the left forelimb and positive electrode on the left hindlimb. (Adapted from Ettinger SJ, Suter PF: *Canine cardiology,* Philadelphia, 1970, Saunders.)

TABLE 103-1

Electrode Position for Precordial Chest Leads

LEAD	CHEST LOCATION
V_1 (CV_5RL)	Fifth intercostal space, right parasternum
V_2 (CV_6LL)	Sixth intercostal space, left parasternum
V_4 (CV_6LU)	Sixth intercostal space, left costochondral junction
V_{10} (V_6)	Dorsal spinous process of T7

In whole, this creates 10 different recorded leads, all of which provide unique vantage points for "viewing," assessing, and measuring cardiac electrical activity. From these recordings, one can count the heart rate and identify the heart rhythm. There are also various reported criteria with variable degrees of sensitivity and specificity for identifying chamber enlargement and conduction disturbances (Table 103-2).[2,3,6,11-18]

TABLE 103-2

References Ranges for Normal Electrocardiograms in Dogs and Cats

	DOGS	CATS
Heart rate (beats per minute)	70-160 (adult dogs); 60-140 (giant breeds), 80-180 (toy breeds); up to 220 in puppies	140-240 in hospital setting (can be as low as 100-120 in home environment)
P wave amplitude (in millivolts [mV])	≤0.4	≤0.2
P wave duration (in milliseconds [msec])	<40 (up to 50 in giant breeds)	<40
P-R interval (in msec)	60-130 (varies inversely with heart rate)	50-90 (varies inversely with heart rate)
R wave amplitude (in mV)	0.5-2.5 or 3.0 in leads II, III, and aVF; <3 mV in V10 (V6); <5 mV in V2 and V4	<0.9
QRS duration (in msec)	<60	<40
Q-T interval (in msec)	150-250 (varies inversely with heart rate)	70-200 (varies inversely with heart rate)
ST segment (in mV)	<0.2 mV depression in limb leads and <0.25 mV depression in precordial leads; <0.15 mV elevation in leads II and III; coving or slurring of the ST segment may indicate abnormal repolarization.	No depression or elevation
T wave	Can be positive, negative, or biphasic; amplitude is <25% of R wave amplitude; positive in lead V1 and negative in V10(V4); positive in V10 in Chihuahuas	Can be positive, negative, or biphasic, but usually positive; amplitude should be <0.3 mV.
Mean electrical axis	+40° to +100°	0° to +/−180°

Recording the Electrocardiogram

Recording the ECG (Video 103-1) requires first restraining the patient in right lateral recumbency. This is the preferred patient position because the majority of published reference intervals for measurements of waves, complexes, and the mean electrical axis were obtained from animals in right lateral recumbency.[14-19] Recordings from sternal or left lateral recumbency or a standing position are often sufficient for interpreting the heart rate and rhythm, but the size and orientation of different deflections are altered to varying degrees.[1,19-22] Importantly, the patient should be restrained on the floor, a rubber or foam mat, or a non-metal table and not on a conductive surface. One or two assistants should be behind the patient with arms draped over the patient's neck and lateral left limbs, grasping the dependent (right) fore- and hindlimbs to maintain restraint. The patient's forelimbs should be drawn cranially and hindlimbs drawn caudally, such that the humerus and femur of each fore- and hindlimb, respectively, are perpendicular to the trunk (Figure 103-2). This avoids artifactual deviations in recorded parameters that have been reported in cats that spontaneously "tuck" their limbs.[20-22]

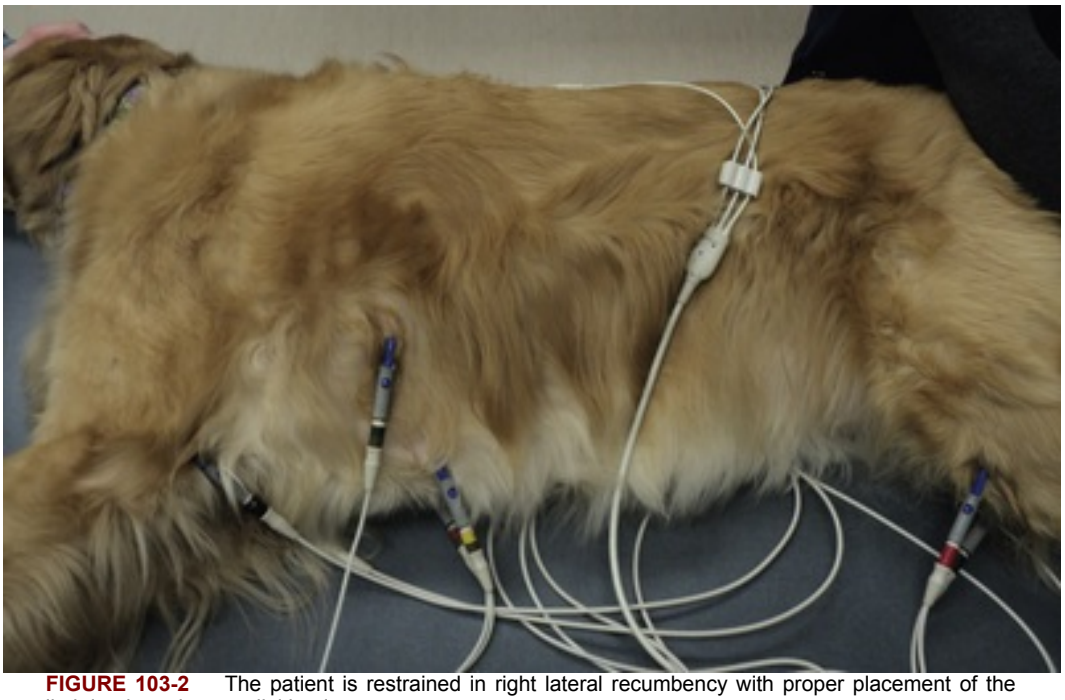

FIGURE 103-2 The patient is restrained in right lateral recumbency with proper placement of the limb leads and precordial leads.

The recording electrodes commonly are incorporated into alligator clips, small metal plates, or self-adhesive patches, any of which can be attached directly to the skin. The electrodes are color-coded: the white electrode is placed on the right forelimb, the black electrode on the left forelimb, the green electrode on the right hindlimb, and the red electrode on the left hindlimb. If alligator clips are used, the forelimb clips are affixed to the skin directly proximal to the elbows, the hindlimb clips directly over the stifles, and the precordial electrodes in their respective locations (see Table 103-1). When metal plates are used, the flat surface of the plate should make full contact with the caudal aspect of the metacarpus or metatarsus**.** Self-adhesive patches usually are affixed to the palmar (or plantar) surface of the paw, against the unhaired paw pads, so that removal of the patch is atraumatic. Contact between the skin and electrodes of the clips or plates should be optimized by moistening the skin with a conducting liquid or ECG paste, before or after affixing the electrodes in their appropriate position.[23] The patient should be encouraged to remain as calm and still as possible throughout recording in an effort to avoid the baseline artifact that comes from panting, purring, or muscle motion. Electrical interference (such as electrocautery or 60 Hz alternating current) should be avoided as much as possible by ensuring appropriate grounding via the use of a grounding electrode and adequate contact between electrode and skin.[3] Another tool for controlling artifactual electrical interference is the use of ECG filters, which filter out signals above a selected frequency. Filters can unintentionally distort the ECG signal and lead to an artifactually high frequency response, which reduces the R wave amplitude (the highest frequency component of the ECG spectrum) and/or dampens other subtle but clinically important high frequency features of the ECG (e.g., notching or ST slurring).[24,25] In order to maximize the use of filters in veterinary electrocardiography, 50 Hz filters are ideally used in dogs, and 150 Hz filters are ideally used in cats.[26]

The ECG can be recorded at various paper speeds, most commonly 25 and/or 50 millimeters/second on dedicated, calibrated paper. The amplitude calibration can be altered as necessary to produce complexes of various heights. Calibration should be optimized to produce complexes that are easily visible and measurable; 10 millimeters/millivolt is standard, but 20 mm/millivolt will make deflections larger (which can be particularly helpful in cats), and 5 mm/millivolt will make deflections smaller.

As many leads as possible should be recorded for several depolarizations or, ideally, for several minutes. Assessing more than one lead helps the clinician better understand the cardiac electrical activity (similar to the way thorough evaluation of thoracic radiography requires two orthogonal projections instead of a single lateral projection). Assessing the electrocardiographic recording requires interpreting the heart rate, rhythm, criteria for chamber enlargement, and mean electrical axis. This material is discussed further in ch. 248 (Cardiac Arrhythmias) with normal references ranges reported in Table 103-2.[1-6,13-18,27-32]

Ambulatory Monitoring

Extended ambulatory ECG monitoring can be achieved with an external cardiac event monitor, a Holter monitor, or an implantable loop recorder.[33-37] External cardiac event monitors and Holter monitors both feature surface electrodes adhered to the patient's skin and attached to a portable monitor, which is worn by the patient. Holter monitors continuously record the ECG for 24 or 48 consecutive hours. This is commonly pursued for one of several purposes: (1) to investigate intermittent clinical signs that are suspected of having an arrhythmic etiology; (2) to evaluate the extent and severity of a known arrhythmia; or (3) to investigate the need for, or efficacy of, antiarrhythmic therapy.[2,3,6,33,34] In contrast, an external cardiac event monitor will continuously monitor the ECG but only record it after physical depression of a "trigger" button on the device.[35] In this way, the monitor can be worn for the duration of battery life (usually 5-7 days); this longer monitoring period increases the likelihood of recording events that do not occur daily, potentially offering a higher diagnostic yield than a 24-hour Holter monitor.[6,35,36] Capturing the ECG during an episode of collapse can either implicate a cardiac arrhythmia as the inciting cause or acquit arrhythmogenic causes if the heart rate and rhythm are appropriate.

Internal events monitors like implantable loop recorders (ILRs, the Reveal monitor) are subcutaneously-implanted devices that can be programmed for manual and/or automatic recording of ECG in animals with very infrequent episodes of syncope, collapse, or weakness.[37,38] The recording device remains in the subcutaneous space on the thorax and can be activated via an owner-operated "remote control" device applied to the thorax when clinical signs arise. The data are retrieved with the use of software on a pacemaker interrogator, a device that is in common usage among veterinary cardiologists. These loop recorders are easy to implant, carry a low risk of complications, and can be left in place until an event is captured or the end of battery life (often several months). In veterinary medicine, ILRs have been reported to provide a diagnostic yield of 48-58% in dogs with intermittent weakness and/or syncope.[37,38]

Perhaps the newest device available for ECG recording is an application available on iPhones. The AliveCor Veterinary Heart Monitor incorporates wireless electrodes into a specialized smartphone case. Using this application and device, one must simply make contact between the case and the left side of the thorax of a patient restrained in right lateral recumbency. Comparison of the human-specific application (AliveCor Heart Monitor) to a standard diagnostic 6-lead ECG in 46 dogs and 23 cats showed identical instantaneous heart rate calculations, very accurate 15-second rhythm recordings, and high intra-observer agreement regarding rhythm diagnosis.[39] The AliveCor recordings produced different polarity complexes occasionally in dogs and frequently in cats.[39] This method of wireless ECG offers an innovative and widely available complement to standard electrocardiography.

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CHAPTER 104

Echocardiography

Marie-Claude Bélanger *

Echocardiography is a unique noninvasive tool that provides substantial information about cardiac size, structure, and function. Since its introduction by Edler and Hertz in Sweden in 1953,[1,2] clinical echocardiography has become an essential component of small animal cardiovascular diagnostic evaluations[3-10] (see ch. 250-255).

Principles of Ultrasound Physics[6-8]

Propagation of sound waves is favored by fluids and soft tissue and inhibited by bone, metal, and air. The basic idea of any ultrasound is that the probe emits a pulse of sound that penetrates the target tissue. A portion of that emitted ultrasound will go through the organ and will be lost, whereas another portion of the ultrasound will be reflected back to the probe. If much of the sound is reflected back, as from the myocardium, for example, the structure is said to be *hyperechoic* and will appear on the screen as a whiter image. When very little of the sound is captured back, as in blood or effusions, the structure is called *hypoechoic* and appears dark on the screen.

The echocardiographic ultrasound beam is generated by a phased-array transducer (probe) that consists of a series of small piezoelectric crystals that produce sound waves that travel in cycles. Sector scanning probes usually are preferred in echocardiography because of the necessity to use probes with small footprints that will allow imaging of the heart through the narrow intercostal spaces of small animals.

The frequency of a transducer is determined by the number of cycles it sends out per minute. High-frequency transducers (7.5-10 MHz) emit more cycles per time unit and thus have shorter wavelengths (low penetrating power). These transducers reflect sound from smaller structures and therefore produce a better image definition and resolution but less tissue penetration than low-frequency transducers. Low-frequency transducers have deeper penetration and produce superior Doppler signals but the resulting image has poorer resolution. In other words, the higher the frequency of the probe, the less tissue penetration is achieved. The choice of transducer therefore is determined by the size of the patient, since tissue penetration is inversely proportional to the frequency of the probe. Cats and small dogs usually require 7- to 10-MHz transducers. A 5-MHz probe is appropriate for most dogs. Very large dogs might require a 2.5- to 3.5-MHz transducer to obtain optimal tissue penetration. Some transducers have a frequency bandwidth allowing a single probe to operate at multiple frequencies. This useful feature allows the sonographer to adjust to the proper frequency on a given patient, without changing probes.

Equipment[5-8]

The quality of images obtained from echocardiographic studies depends on the sophistication and technology of the ultrasound machine, the skill and experience of the operator, as well as individual patient characteristics. Most veterinary sonographers position dogs and cats in lateral recumbency and approach the thorax from underneath. This position favors a larger acoustic window and better image quality since gravity improves the degree of contact between the cardiac structures and the chest wall. A special table (purchased or custom-made) with adjustable openings is used for creating a large and stable acoustic window (Figure 104-1). Echocardiograms also can be performed from a standing position, particularly in giant-breed dogs.

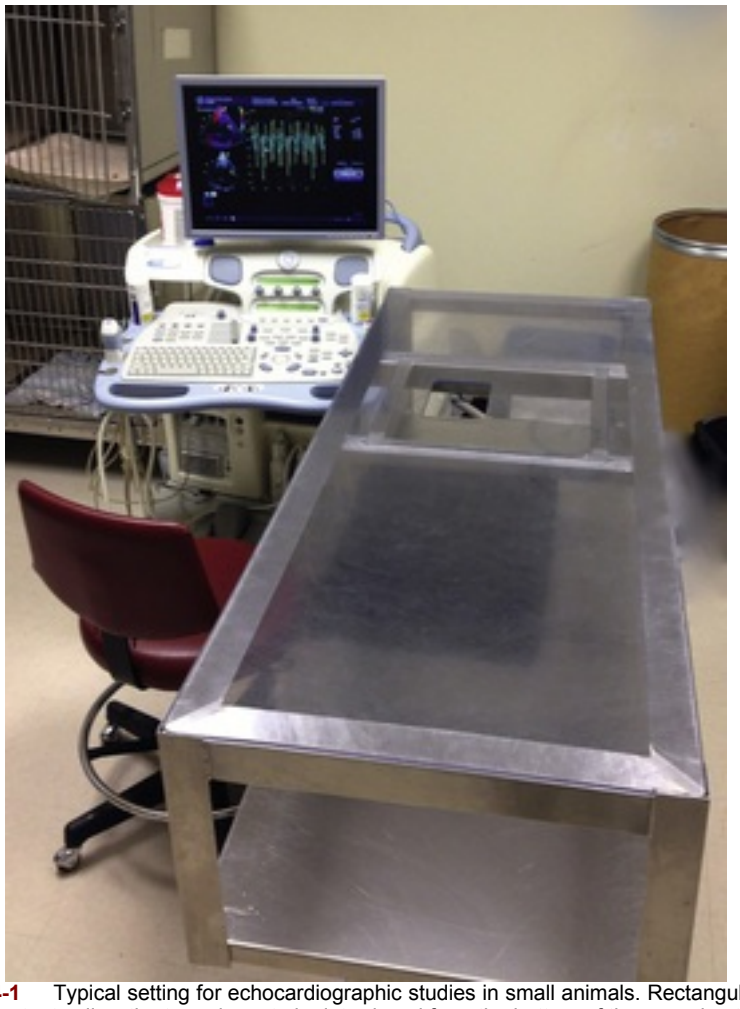
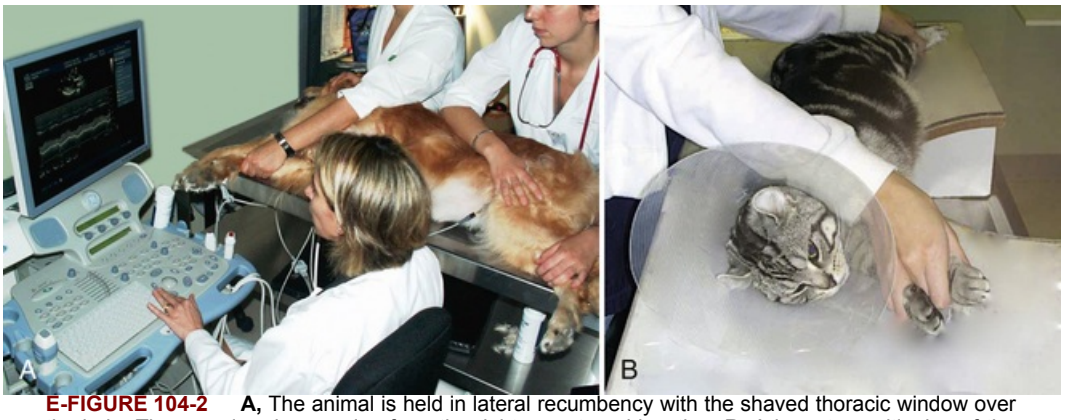


FIGURE 104-1 Typical setting for echocardiographic studies in small animals. Rectangular (here) or semicircular cutouts allow the transducer to be introduced from the bottom of the scanning table.

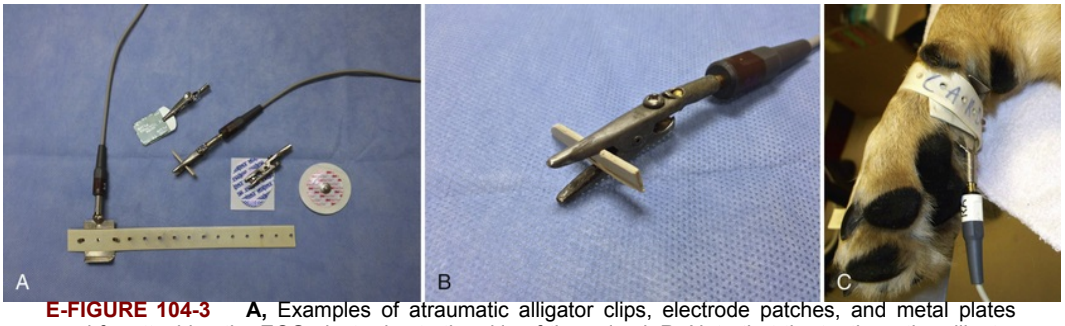
Technical Aspects[5-8,10]

In animals, the fur usually is clipped to improve transducer-skin contact and image quality, and coupling gel is applied over the right or left precordial thoraces. It is important to remember to obtain owners' and breeders' consent before clipping fur. Clipping sometimes is unnecessary in dogs with very short or sparse hair. The application of isopropyl alcohol or water can sometimes replace the coupling gel since it provides good but briefer contact. The animal is gently restrained in lateral recumbency on an echocardiographic table (see Figure 104-1 and E-Figure 104-2, *A* and *B*). One experienced restrainer is usually adequate. Sandbags also can be placed over the hindlimbs to limit the need for an additional restrainer. The patient's forelimbs should be pulled cranially in order to keep the elbows out of the area of interest. However, this position should not be exaggerated, as it can sometimes become uncomfortable in older animals with orthopedic diseases.



E-FIGURE 104-2 **A,** The animal is held in lateral recumbency with the shaved thoracic window over the hole. The examiner is scanning from the right parasternal location. **B,** Adequate positioning of the animal with only one restrainer. An Elizabethan collar can sometimes be useful in fractious cats as a means of protection for the restrainer. (**B,** Image reproduced with permission from Elsevier, Inc., and courtesy of Côté E: Echocardiography: common pitfalls and practical solutions. *Clin Tech Small Anim Pract* 20:156-163, 2005.)

Simultaneous ECG is obtained during the echocardiographic examination to allow accurate timing of measurements. Electrodes are attached to the skin (standard color code; see ch. 103) with atraumatic alligator clips, electrode patches, or metal plates held by bracelets (E-Figure 104-3, *A-C*).



E-FIGURE 104-3 **A,** Examples of atraumatic alligator clips, electrode patches, and metal plates used for attaching the ECG electrodes to the skin of the animal. **B,** Note that the teeth on the alligator clips have been sanded away and filled with solder to be more comfortable for the animal. **C,** Metal plates held by bracelets are particularly easy to use, comfortable for the patient, and reusable.

An echocardiogram usually can be performed in dogs and cats without chemical restraint since the procedure is painless, quiet, and peaceful. On the other hand, sedation has the advantage of minimizing stress, examination time, and poor image quality in squirmy patients (see ch. 138). An Elizabethan collar sometimes can be useful to protect technicians from cats that are fractious but are not good candidates for sedation (see E-Figure 104-2, *B*). Truly uncooperative, anxious, or aggressive animals in which an underlying cause of discomfort has not been found (e.g., painful joint disease, pulmonary edema, etc.) could require sedation. Table 104-1 lists sedation protocols used for echocardiography. Animals with overt clinical signs of congestive heart failure (CHF) should have such signs relieved with diuretics before the echocardiogram is performed, since the echocardiographic results will rarely change the immediate treatment plan (see ch. 247).

TABLE 104-1

Suggested Sedation Protocols for Echocardiography

SITUATIONS	DRUGS
Canine Sedation Protocols	
Most asymptomatic dogs needing sedation	Butorphanol 0.2 mg/kg ± midazolam 0.2 mg/kg IM or IV or if very uncooperative: butorphanol 0.2 mg/kg IM + acepromazine 0.025-0.05 mg/kg IM in the same syringe

Aggressive asymptomatic dog	Hydromorphone 0.1 mg/kg + midazolam 0.2 mg/kg IM in the same syringe
If sedation needed rapidly	Butorphanol 0.2-0.3 mg/kg IV
Puppies	Acepromazine 0.005 mg/kg + buprenorphine 0.01 mg/kg IV Or Butorphanol 0.2 mg/kg ± midazolam 0.2 mg/kg IM or IV
Dog with congestive heart failure or pathologic arrhythmia	Butorphanol 0.2 mg/kg ± midazolam 0.2 mg/kg IM or IV (treat with furosemide before ultrasound if dyspneic due to cardiogenic pulmonary edema)
Feline Sedation Protocols	
Most asymptomatic cats needing sedation	Butorphanol 0.2 mg/kg IM or IV or if very uncooperative: butorphanol 0.2 mg/kg IM + acepromazine 0.05 mg/kg IM in the same syringe
Aggressive asymptomatic cat	Acepromazine 0.05-0.1 mg/kg + hydromorphone 0.1 mg/kg SC or IM Or in very aggressive cats: dexmedetomidine 10 mcg/kg IM then reverse with atipamezole 100 mcg/kg IM when procedure is complete (inject same volume of atipamezole as used for dexmedetomidine)
Kittens	Butorphanol 0.2 mg/kg IM
Cat with congestive heart failure or pathologic arrhythmia	Butorphanol 0.2 mg/kg (+ acepromazine 0.025 mg/kg if uncooperative) IM (treat with furosemide before sedation if dyspneic due to cardiogenic pulmonary edema)

The Normal Echocardiogram: Image Acquisition, Standard Views, and Sequence[5-8,10,11]

A comprehensive echocardiographic study includes two-dimensional (2-D), M-mode, and finally, Doppler imaging. The examination always starts with the 2-D study, which provides orientation, reference, and diagnostic clues for M-mode and Doppler imaging (see E-Table 104-8). The most important information given by an echocardiogram often is not confined to the screen of the machine. It is essential to combine the echo findings with the observation of the patient itself. An accurate diagnosis combines a good physical examination and thorough history with an echocardiographic examination. Moreover, echocardiography should never replace thoracic radiographs since it does not give comparable information regarding the lungs such as the presence of cardiogenic pulmonary edema.

2-D Echocardiography

Two-dimensional echocardiography is used for evaluating the cardiac structural changes resulting from congenital defects or other cardiac diseases. It produces a real-time anatomic representation of the heart throughout the cardiac cycle. A complete 2-D study includes the imaging of all valves, proximal segments of great vessels, and relative sizes and wall thicknesses of the cardiac chambers (Video 104-1).

Two-dimensional echocardiography provides images of thin "slices" of the heart and blood flow. Each of these standard slices is conventionally defined by the position of the transducer on the animal (the transducer's *location* in the *acoustic window*) and the image plane of the heart (or *view*). Images are obtained from standard locations, which allow for specific portions of the heart to be visualized in detail. The right parasternal, left cranial parasternal, left apical, and subcostal positions are used most often, but a multitude of planes can be obtained to better visualize a distinct part of the heart.

Most of the heart is covered by sonographically impenetrable structures such as bones (ribs and sternum) and lungs. However, the right lung does not cover the heart completely (the cardiac notch), and there is an area just dorsal to the sternum at the fourth or fifth intercostal space where the pericardium lies directly beneath the chest wall. This region corresponds to the *right parasternal window*. For most patients, placement of the probe on the area of the right hemithorax where the heartbeat is palpable is generally the best starting point. For canine brachycephalic breeds, where the thoracic conformation is ventrodorsally compressed, the best acoustic window is obtained by placing the probe closer to the sternum or more ventrally than usual. The marker of the probe should be pointing toward the animal's shoulder in order to obtain a standard long-axis, four chamber view (Figure 104-4, *A* and *B*). The views that are routinely obtained at the right parasternal location are the long-axis four chamber view (see Figure 104-4), the long-axis left ventricular outflow view

(Figure 104-5), and the different short-axis views (Figure 104-6). The long-axis view is obtained with an imaging plane that transects the heart parallel to its long axis from apex to base, whereas a perpendicular imaging plane reveals the short-axis views (see Figures 104-4 and 104-6). Technically, this means that the short-axis views can be obtained from the long-axis views by a 90° rotation of the probe, but minor adjustments are necessary for each individual patient. The echocardiographer must always adjust the depth and gain settings to optimize the image on the monitor. By convention, the heart, on a 2-D view, should occupy two-thirds to three-fourths of the screen. The subcostal or subxiphoid position is used specifically to evaluate the left ventricular outflow tract (LVOT) in the dog (Figure 104-7). The image obtained from the subcostal view often can be improved by having the dog inhale after occluding its mouth and nostrils for 5 seconds. Inspiration shifts the diaphragm caudally and pushes the heart toward the transducer.

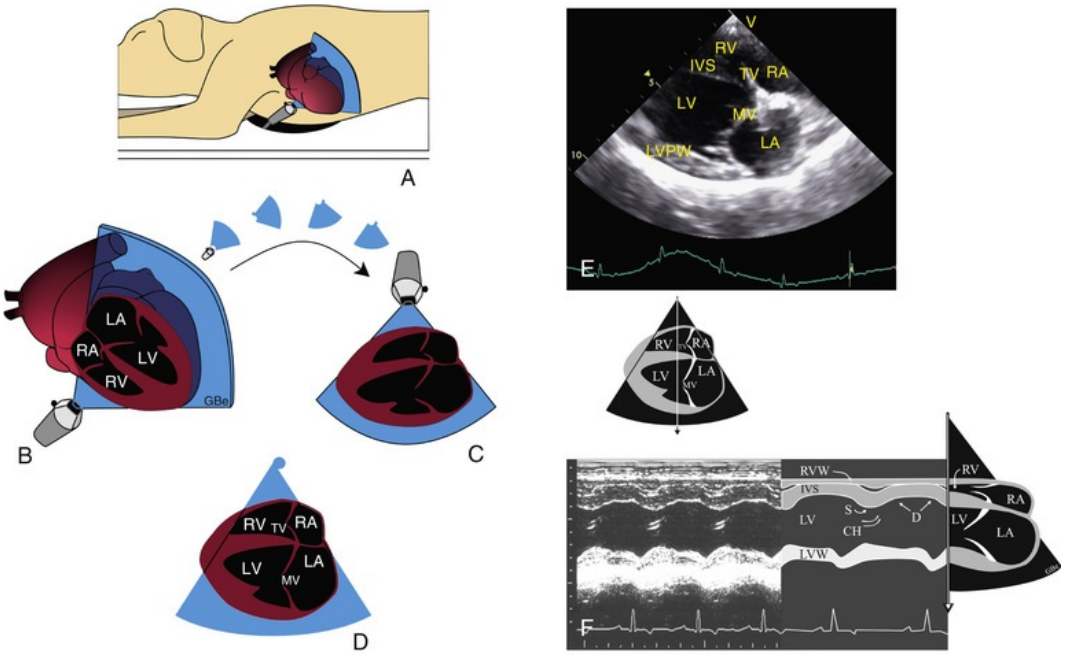


FIGURE 104-4 **A,** Typical positioning of the animal for visualization of the right parasternal long-axis view. In most dogs, the long axis of the heart is parallel to an imaginary line connecting the shoulder to the xiphoid. **B,** Spatial orientation of the right parasternal location, long-axis four-chamber view. **C,** Spatial orientation of the right parasternal location, long-axis four-chamber view as observed on the ultrasound monitor. **D,** Illustration of the different cardiac structures observed via this window. **E,** 2-D image of the right parasternal location, long-axis four-chamber view. **F,** Corresponding M-mode image obtained from this window. The ventricles are seen as they fill and empty (diastole [D] and systole [S]). *CH,* Chordae tendineae; *IVS,* interventricular septum; *LA,* left atrium; *LV,* left ventricle; *LVPW,* left ventricular wall; *MV,* mitral valve; *RA,* right atrium; *RV,* right ventricle; *RVW,* right ventricular wall; *TV,* tricuspid valve.

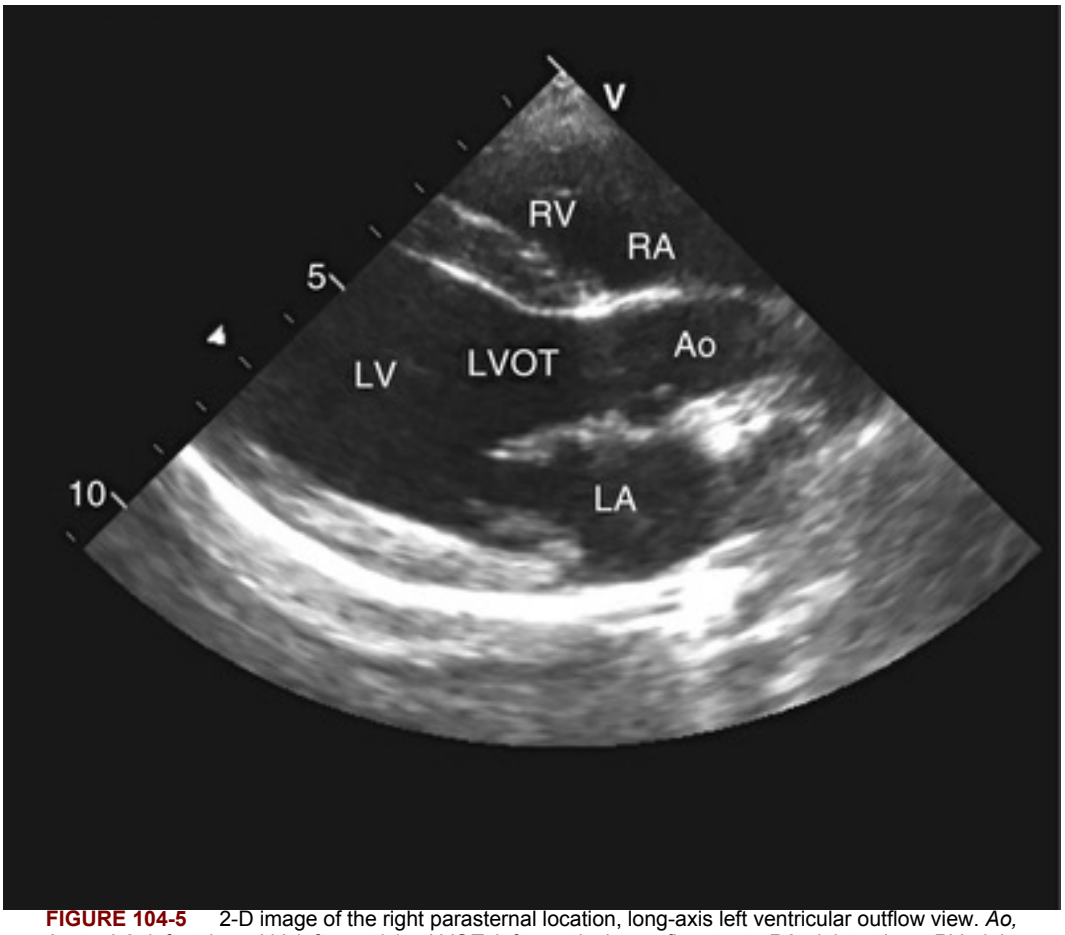


FIGURE 104-5 2-D image of the right parasternal location, long-axis left ventricular outflow view. *Ao,* Aorta, *LA,* left atrium; *LV,* left ventricle; *LVOT,* left ventricular outflow tract; *RA,* right atrium; *RV,* right ventricle.

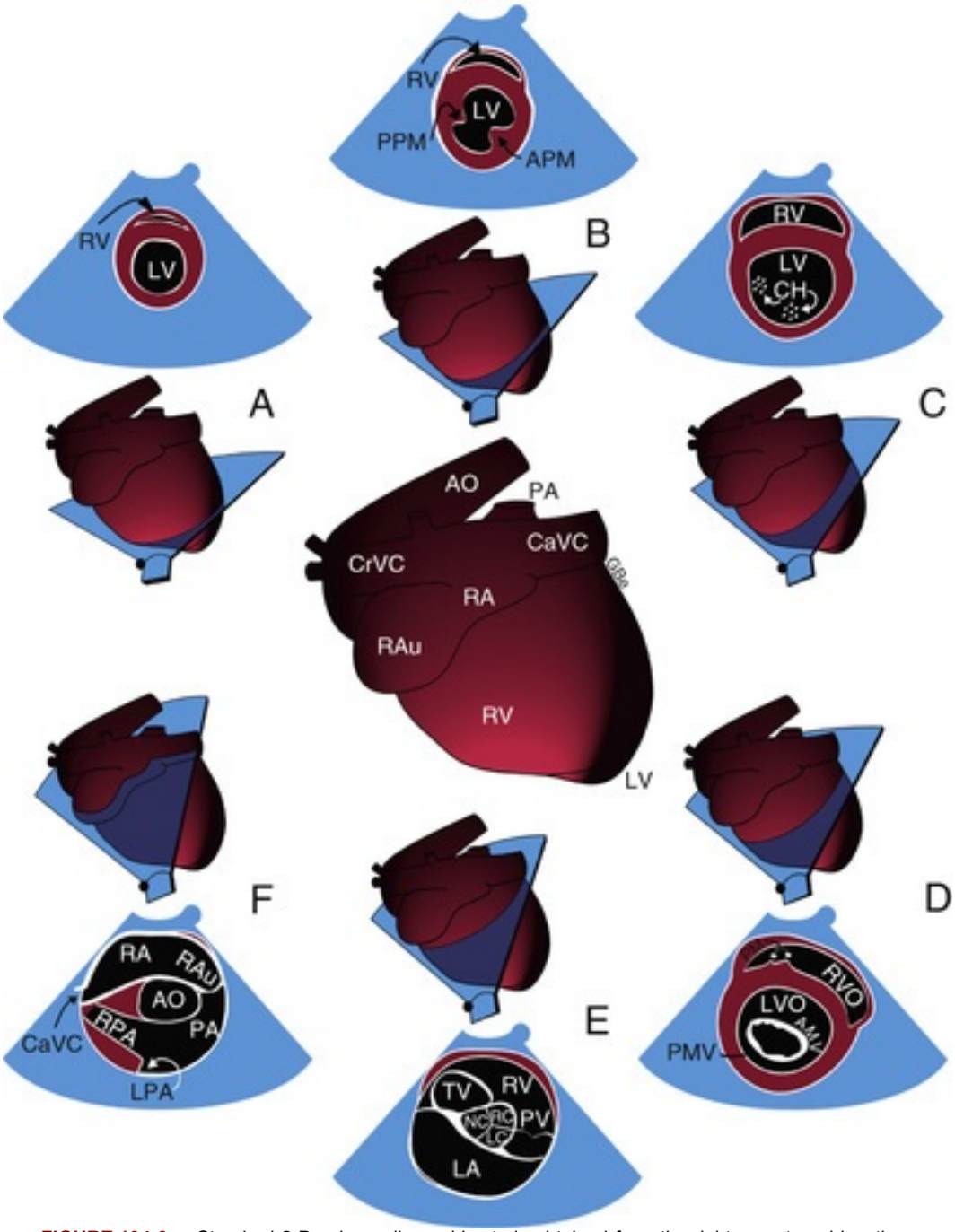


FIGURE 104-6 Standard 2-D echocardiographic study obtained from the right parasternal location, short-axis views at the level of **(A)** the apex, **(B)** the papillary muscles, **(C)** the chordae tendineae (CH), **(D)** the mitral valve, **(E)** the aorta, and **(F)** the pulmonary arteries. *AMV,* Anterior mitral valve leaflet; *APM,* anterior papillary muscle; *AS,* atrial septum; *CaVC,* caudal vena cava; *CrVC,* cranial vena cava; *IVS,* interventricular septum; *LA,* left atrium; *LC,* left coronary aortic cusp; *LPA,* left pulmonary artery; *LV,* left ventricle; *NC,* noncoronary aortic cusp; *PA,* pulmonary artery; *PMV,* posterior mitral valve leaflet; *PPM,* posterior papillary muscle; *PV,* pulmonary valve; *RA,* right atrium; *RAu,* right auricle; *RC,* right coronary aortic valve cusp; *RPA,* right pulmonary artery; *RV,* right ventricle; *RVO,* right ventricular outflow; *S,* systole; *TV,* tricuspid valve. (Modified from Thomas WP, Gaber CE, Jacobs GJ, et al: Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat. Echocardiography Committee of the Specialty of Cardiology, American College of Veterinary Internal Medicine. *J Vet Intern Med* 7:247-252, 1993.)

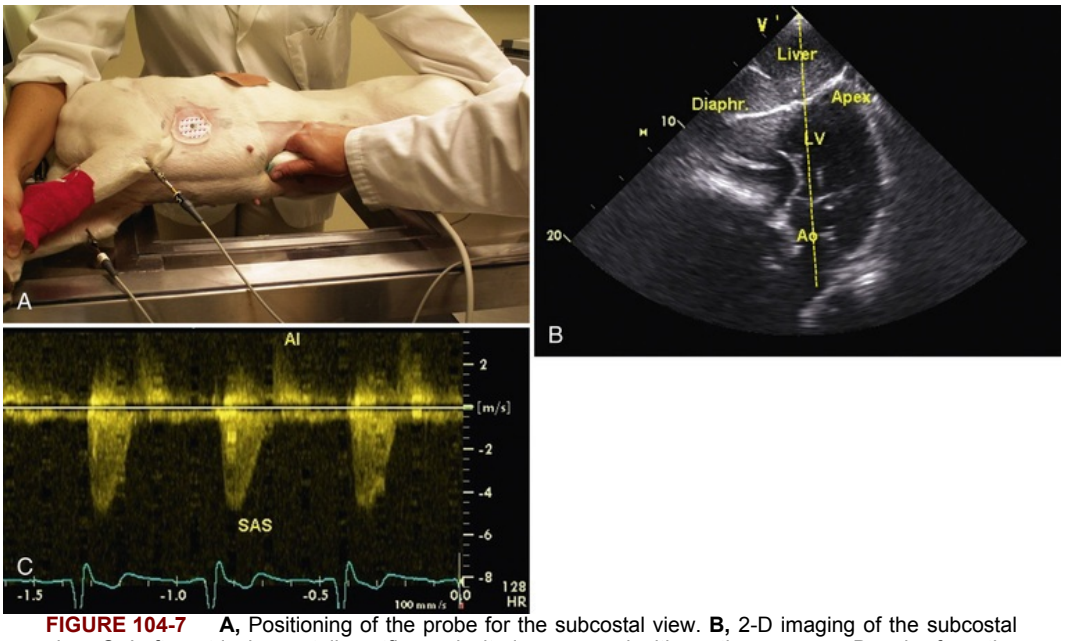


FIGURE 104-7 **A,** Positioning of the probe for the subcostal view. **B,** 2-D imaging of the subcostal view. **C,** Left ventricular systolic outflow velocity is measured with continuous-wave Doppler from the subcostal view, in a dog with severe subaortic stenosis. *AI,* Aortic insufficiency; *AO,* aorta; *LV,* left ventricle; *SAS,* high-velocity flow consistent with subaortic stenosis.

The second half of the echocardiographic study consists of the left-sided views. One should always perform the echocardiogram on both sides of the thorax. Evaluating only the right side is similar to the auscultation of only one lung: some information is gained but much information is missed. As opposed to the right parasternal location, there are two acoustic windows on the left side. The left cranial parasternal views are obtained at the level of the fourth intercostal space, whereas the left caudal (apical) parasternal views are best visualized through the animal's fifth to sixth intercostal spaces (Figure 104-8). These views can be obtained with the patient in left lateral recumbency. Alternatively, some sonographers obtain these views by keeping the patient on its right side and moving the transducer over the left side of the thorax.

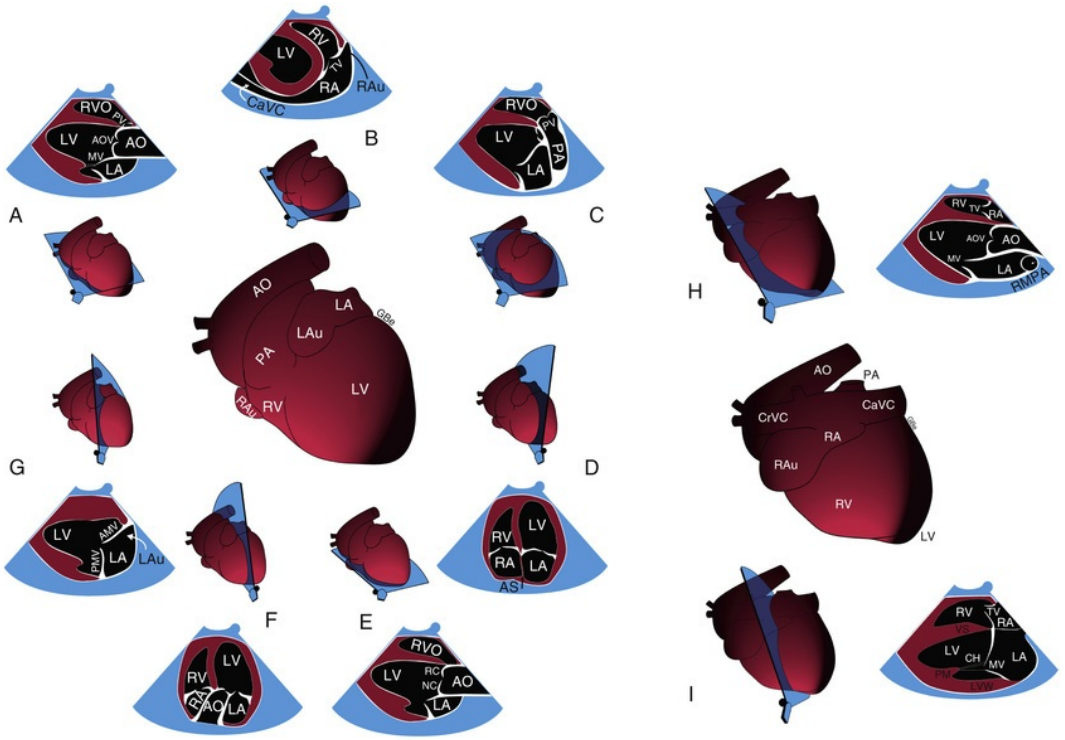


FIGURE 104-8 Standard 2-D long-axis views. **A,** Left cranial parasternal view optimized for the aortic root. **B,** Left cranial parasternal view optimized for right atrium and auricle. **C,** Left cranial parasternal view optimized for the right ventricular outflow tract and main pulmonary artery. **D,** Four-chamber inflow view from the left caudal (apical) parasternal position. **E,** Left caudal (apical) parasternal view optimized for visualization of the left ventricular outflow tract. **F,** Five-chamber left ventricular outflow view from the left caudal (apical) parasternal position. **G,** Left caudal (apical) parasternal location, two-chamber view optimized for visualization of the left ventricular inflow and left auricle. **H,** Left ventricular outflow view from the right parasternal position. **I,** Four-chamber right parasternal long-axis view. *AO,* Aorta; *AOV,* aortic valve; *AMV,* anterior mitral valve leaflet; *AS,* atrial septum; *CaVC,* caudal vena cava; *CH,* chordae tendineae; *LA,* left atrium; *LAu,* left auricle; *LV,* left ventricle; *LVW,* left ventricular wall; *MV,* mitral valve; *NC,* noncoronary aortic valve cusp; *PA,* pulmonary artery; *PM,* papillary muscle; *PMV,* posterior mitral valve leaflet; *PV,* pulmonary valve; *RA,* right atrium; *RAu,* right auricle; *RC,* right coronary aortic valve cusp; *RMPA,* right pulmonary artery; *RV,* right ventricle; *RVO,* right ventricular outflow; *TV,* tricuspid valve. (Modified from Thomas WP, Gaber CE, Jacobs GJ, et al: Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat. Echocardiography Committee of the Specialty of Cardiology, American College of Veterinary Internal Medicine. *J Vet Intern Med* 7:247-252, 1993.)

To obtain specific views of the cardiac structures or optimize the quality of images, the operator must always remember that the transducer can be moved in at least 3 different ways as illustrated in Figure 104-9:

- *Rotation* or *twisting:* rotation of the transducer in a single position to view the corresponding intersecting or perpendicular planes.
- *Tilting:* the transducer tip is repositioned in a rocking motion or angled to image different structures in the same plane.
- *Translation* or *sliding:* movement of the transducer to a different position on the patient's thorax to examine a specific cardiac structure from the best location; e.g., moving from one intercostal space to another.

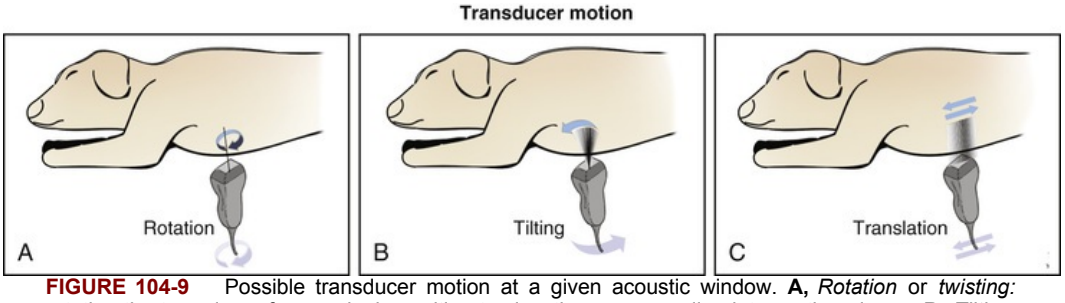


FIGURE 104-9 Possible transducer motion at a given acoustic window. **A,** *Rotation* or *twisting:* rotating the transducer from a single position to view the corresponding intersecting planes; **B,** *Tilting:* rocking the head of the probe to image different structures in the same plane or adjacent planes; and **C,** *Translation* or *sliding:* moving the transducer to a different position on the thorax to examine a specific cardiac structure from the best location.

M-Mode Echocardiography

M-mode refers to real-time *motion-mode*. M-mode echocardiography is used for evaluating the phasic motion of the cardiac structures during the cardiac cycle. M-mode echocardiography is complementary to the 2-D echocardiogram since it has a higher sampling rate (faster frame rate), allowing better resolution of rapidly moving structures. It is especially useful to record subtle changes in wall and valve motion and historically has been used for performing measurements of chamber diameters and wall thicknesses.[12-16] The M-mode image is viewed on a video screen, where depth of the structures is plotted on the Y axis and time is shown on the X axis. Only the structures transected by the cursor are seen on the M-mode images. The steerable cursor scrolls across the heart, and the associated changes in thickness or position of the structures are recorded on the screen as the cardiac chamber of interest fills and empties (Figure 104-10).

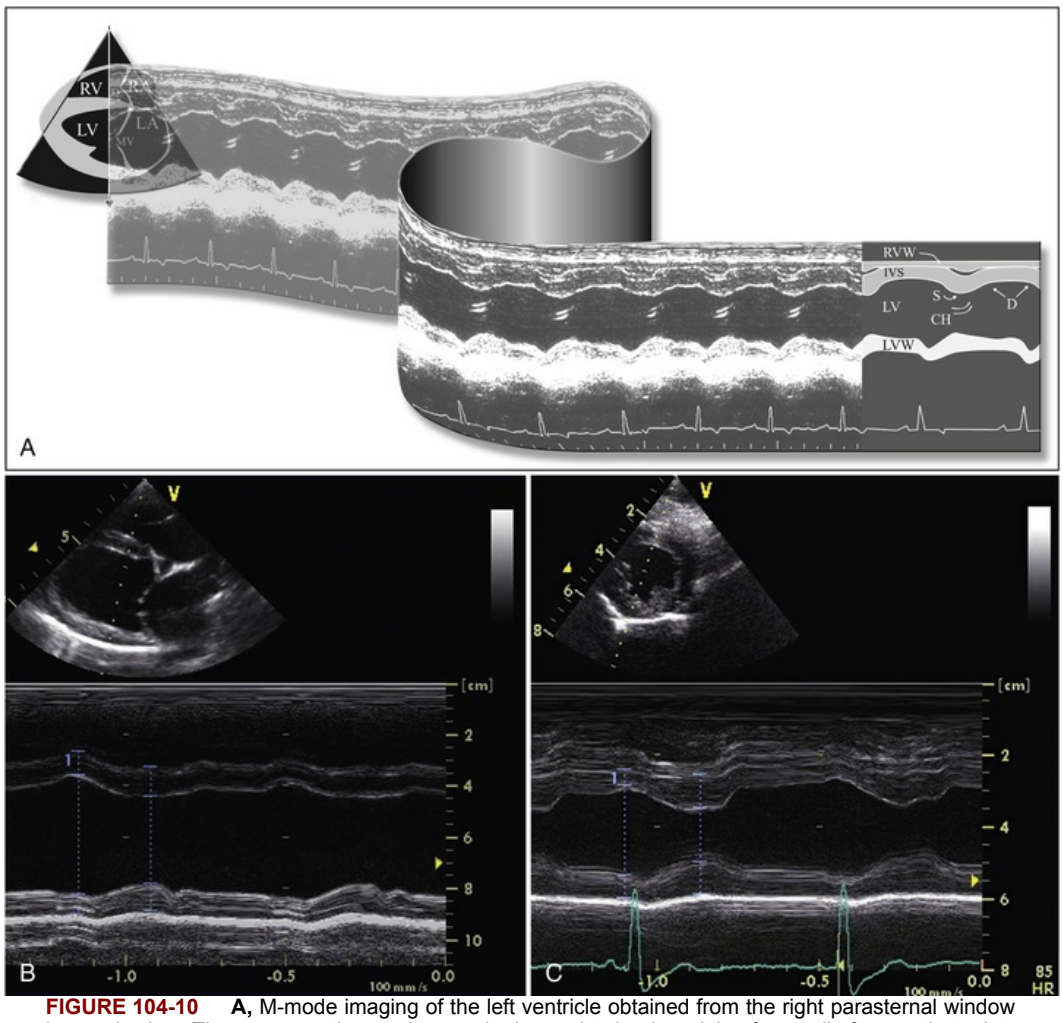


FIGURE 104-10 **A,** M-mode imaging of the left ventricle obtained from the right parasternal window long-axis view. The cursor on the monitor can be imaged to be the origin of a scroll of paper that prints as the ventricles fill and empty. **B,** M-mode right parasternal long-axis view and **(C)** right parasternal short-axis view.

In veterinary medicine, M-mode echocardiography generally is performed only from the right parasternal location (long- and/or short-axis views). The usual M-mode echocardiogram includes an evaluation of the left ventricle (LV; see Figure 104-10), mitral valve, and aortic root (Figure 104-11).

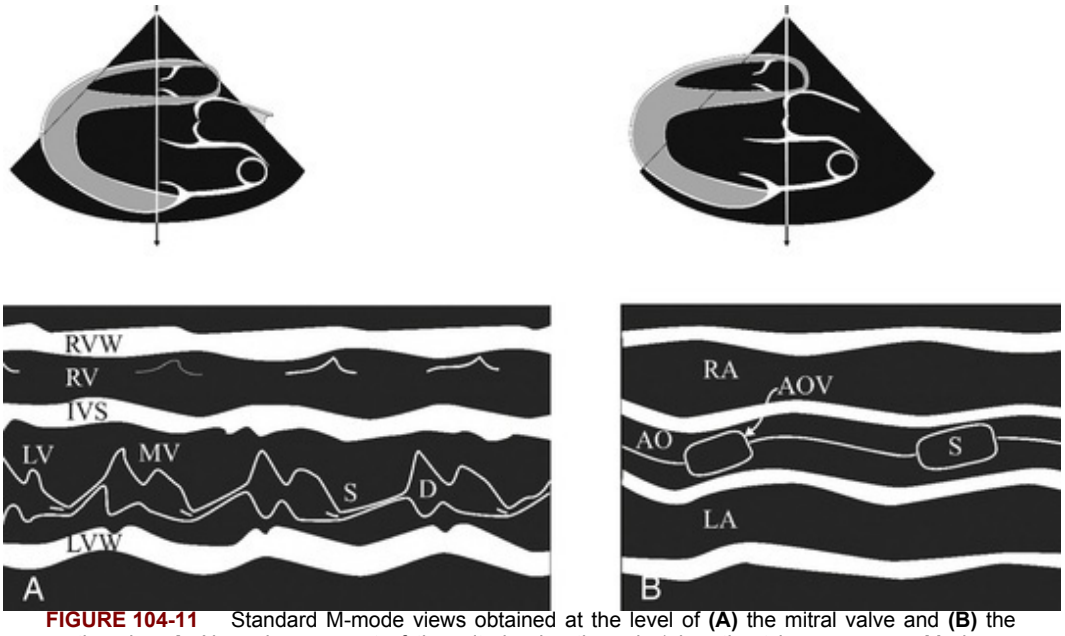


FIGURE 104-11 Standard M-mode views obtained at the level of **(A)** the mitral valve and **(B)** the aortic valve. **A,** Normal movement of the mitral valve through 1 heartbeat is seen as an M shape. During rapid ventricular filling (early diastole), the mitral valve is forced to open, with its leaflets moving toward the interventricular septum and LV free wall. As ventricular filling progresses, the pressure in the LA equalizes with the LV pressure and the mitral leaflets move toward each other. Finally, the mitral leaflets open again during atrial contraction. Closure of the mitral valve occurs after atrial systole. **B,** During diastole, the line in the middle of the aorta represents the closed aortic cusps. During systole, the aortic valve opens toward the walls of the aorta, remains open during the systolic ejection of blood, and then rapidly closes at the end of systole. *AO,* Aorta; *AOV,* aortic valve; *D,* diastole; *IVS,* interventricular septum; *LA,* left atrium; *LV,* left ventricle, *LVW,* left ventricular wall; *MV,* mitral valve (anterior leaflet); *RA,* right atrium; *RV,* right ventricle; *RVW,* right ventricular wall; *S,* systole.

As recommended by the American Society of Echocardiography (ASE), end-diastolic LV measurements are taken at the onset of the QRS complex (or the frame after mitral valve closure) and end-systolic measurements are made at the level of the maximum inward excursion of the interventricular septum.[17] The *leading edge* method is used (i.e., the measurements of each echo line are made beginning at the edge that is closest to the transducer). The sonographer should be aware that a tremendous potential exists for artifacts and error when the M-mode image is obtained in a suboptimal plane (e.g., tangential slices).

The LV M-mode study provides absolute measurements of the LV walls and chamber during systole and diastole (Tables 104-2 through 104-5). It can be performed using the right parasternal long-axis four chamber view or the right parasternal short-axis view at the level of the papillary muscles (see Figure 104-10). These M-mode measurements also are used for calculating the ejection phase indices described in the section on the evaluation of systolic function.

TABLE 104-2

Reference Intervals for M-Mode Long-Axis Values (cm) in Dogs

BW (kg)	$LVID_{ED}$	$LVID_{ES}$	LVW_{ED}	LVW_{ES}	IVS_{ED}	IVS_{ES}
1	1.3-1.9	0.7-1.3	0.3-0.6	0.5-0.9	0.3-0.6	0.4-0.8
3	1.8-2.6	1.0-1.8	0.4-0.8	0.6-1.1	0.4-0.8	0.6-1.0
4	1.9-2.8	1.1-1.9	0.4-0.8	0.7-1.2	0.4-0.8	0.6-1.1
6	2.2-3.1	1.2-2.2	0.4-0.9	0.7-1.3	0.4-0.9	0.7-1.2
9	2.4-3.4	1.4-2.5	0.5-1.0	0.8-1.4	0.5-1.0	0.7-1.3
11	2.6-3.7	1.5-2.7	0.5-1.0	0.8-1.5	0.5-1.1	0.8-1.4
15	2.8-4.1	1.7-3.0	0.5-1.1	0.9-1.6	0.6-1.1	0.8-1.5
20	3.1-4.5	1.8-3.2	0.6-1.2	0.9-1.7	0.6-1.2	0.9-1.6

25	3.3-4.8	2.0-3.5	0.6-1.3	1.0-1.8	0.6-1.3	0.9-1.7
30	3.5-5.0	2.1-3.7	0.6-1.3	1.0-1.9	0.7-1.3	1.0-1.8
35	3.6-5.3	2.2-3.9	0.7-1.4	1.1-1.9	0.7-1.4	1.0-1.9
40	3.8-5.5	2.3-4.0	0.7-1.4	1.1-2.0	0.7-1.4	1.0-1.9
50	4.0-5.8	2.4-4.3	0.7-1.5	1.1-2.1	0.7-1.5	1.1-2.0

BW, Body weight; *IVS_{ED},* interventricular septal thickness at the end of diastole; *$LVID_{ED}$,* left ventricular internal diameter at the end of diastole; *$LVID_{ES}$,* left ventricular internal diameter at the end of systole; *LVW_{ED},* left ventricular posterior wall thickness at the end of diastole.

TABLE 104-3

M-Mode Reference Intervals (cm) for Specific Canine Breeds

	MINIATURE POODLE[75]	BEAGLE[75a]	COCKER SPANIEL[77]	AFGHAN HOUND[75]	GOLDEN RETRIEVER[75]	DOBERMAN[84-87]	NEWFOUNDLAND[89]
$LVID_{ED}$	1.6-2.8	1.8-3.3	3.1-3.7	3.3-5.2	3.7-5.1	3.5-4.6	4.4-6.0
$LVID_{ES}$	0.8-1.6	0.8-2.7	1.9-2.5	2.0-3.7	1.8-3.5	2.6-3.7	2.9-4.4
IVS_{ED}	0.4-0.6	0.5-1.1	0.7-1.0	0.8-1.2	0.8-1.3	0.8-1.1	0.7-1.5
IVS_{ES}	0.6-1.0	0.6-1.2	—	0.8-1.8	1.0-1.7	1.3-1.6	1.1-2.0
LVW_{ED}	0.4-0.6	0.6-1.3	0.7-0.9	0.7-1.1	0.8-1.2	0.6-1.0	0.8-1.3
LVW_{ES}	0.6-1.0	0.7-1.7	—	0.9-1.8	1.0-1.9	0.8-1.4	1.1-1.6
EPSS	0-0.2	—	—	0-1.0	0.1-1.0	0-0.8	0.3-1.4
FS (%)	35-57	20-70	30-39	24-48	27-55	21-38	22-37
LA_S	0.8-1.8	—	—	1.8-3.5	1.6-3.2	2.4-3.0	2.4-3.3
Ao_D	0.8-1.3	—	—	2.0-3.4	1.4-2.7	2.5-3.5	2.6-3.3

Ao_D, Aortic root diameter in diastole; *EPSS,* E-point to septal separation; *FS,* fractional shortening; *IVS_{ED},* interventricular septal thickness at the end of diastole; *IVS_{ES},* interventricular septal thickness at the end of systole; *LA_S,* left atrial diameter in systole; *$LVID_{ED}$,* left ventricular internal diameter at the end of diastole; *$LVID_{ES}$,* left ventricular internal diameter at the end of systole; *LVW_{ED},* left ventricular posterior wall thickness at the end of diastole; *LVW_{ES},* left ventricular posterior wall thickness at the end of systole.

TABLE 104-4

Reference Intervals for M-Mode Long-Axis Values (mm) in Adult Cats[93-95]

$LVID_{ED}$	$LVID_{ES}$	LVW_{ED}	LVW_{ES}	IVS_{ED}	IVS_{ES}	LA_S	Ao_D	FS (%)	EPSS
11-20	4-11	3-6	5-9	3-6	4-9	7-13	7-11	33-66	≤4

Ao_D, Aortic root diameter in diastole; *EPSS,* E-point to septal separation; *FS,* fractional shortening; *IVS_{ED},* interventricular septal thickness at the end of diastole; *IVS_{ES},* interventricular septal thickness at the end of systole; *LA_S,* left atrial diameter in systole; *$LVID_{ED}$,* left ventricular internal diameter at the end of diastole; *$LVID_{ES}$,* left ventricular internal diameter at the end of systole; *LVW_{ED},* left ventricular posterior wall thickness at the end of diastole; *LVW_{ES},* left ventricular posterior wall thickness at the end of systole.

These measurement guidelines are based on the author's experience and published data.

TABLE 104-5

Reference Intervals for M-Mode Long-Axis Values (mm) in Kittens*

AGE (WEEKS)	$LVID_{ED}$	$LVID_{ES}$	LVW_{ED}	LVW_{ES}	IVS_{ED}	IVS_{ES}	LA_S	Ao_D	FS (%)
4	5.8-11.9	3.2-6.3	3-5	2.4-4.5	2-3.5	2.5-4.5	4.4-7.5	3.9-6.6	32-59
6	6-10	2.4-5.9	1.4-3.4	2.9-4.7	2-2.8	2.8-4.7	4.9-7.7	4-5.5	36-65
8	6-14	3-8	2-4	3-7	2.4-4	2.6-6.8	5.4-9.7	4.2-7.4	30-59

*Measurements made from the right parasternal long-axis view.

Ao_D, Aortic root diameter in diastole; *EPSS*, E-point to septal separation; *FS*, fractional shortening; *IVS_{ED}*, interventricular septal thickness at the end of diastole; *IVS_{ES}*, interventricular septal thickness at the end of systole; *LA_S*, left atrial diameter in systole; *$LVID_{ED}$*, left ventricular internal diameter at the end of diastole; *$LVID_{ES}$*, left ventricular internal diameter at the end of systole; *LVW_{ED}*, left ventricular posterior wall thickness at the end of diastole; *LVW_{ES}*, left ventricular posterior wall thickness at the end of systole.

These measurement guidelines are based on the author's experience and published data.

An important limitation of M-mode is the standardized position of samples, which means regional or focal lesions can be missed. It is for this reason that 2-D measurements of LV parameters are gaining favor, especially in cats being evaluated for hypertrophic cardiomyopathy.[18-21]

Doppler Echocardiography

Spectral and color flow Doppler imaging are used for evaluating blood flow velocity and direction within the heart and great vessels.[5,6,22,23] During the 19th century, Christian Doppler made the first description of the physical principles used in Doppler echocardiography when he noted through his observations of the light emitted by stars that the speed of a moving source of waves (light, sound) relative to the observer is responsible for the perceived frequency of that wave.[24] The change in frequency between sound transmitted by a structure and sound received by it is called the *Doppler shift*. One experiences the Doppler shift every day. For example, when standing on an overpass, we hear the sound of a car approaching toward us at a higher pitch than the sound we hear when the same car is moving away from the overpass. The engine is emitting the same sound when passing under the overpass, but we hear a change in pitch dependent upon the speed and the direction of the car (Figure 104-12).

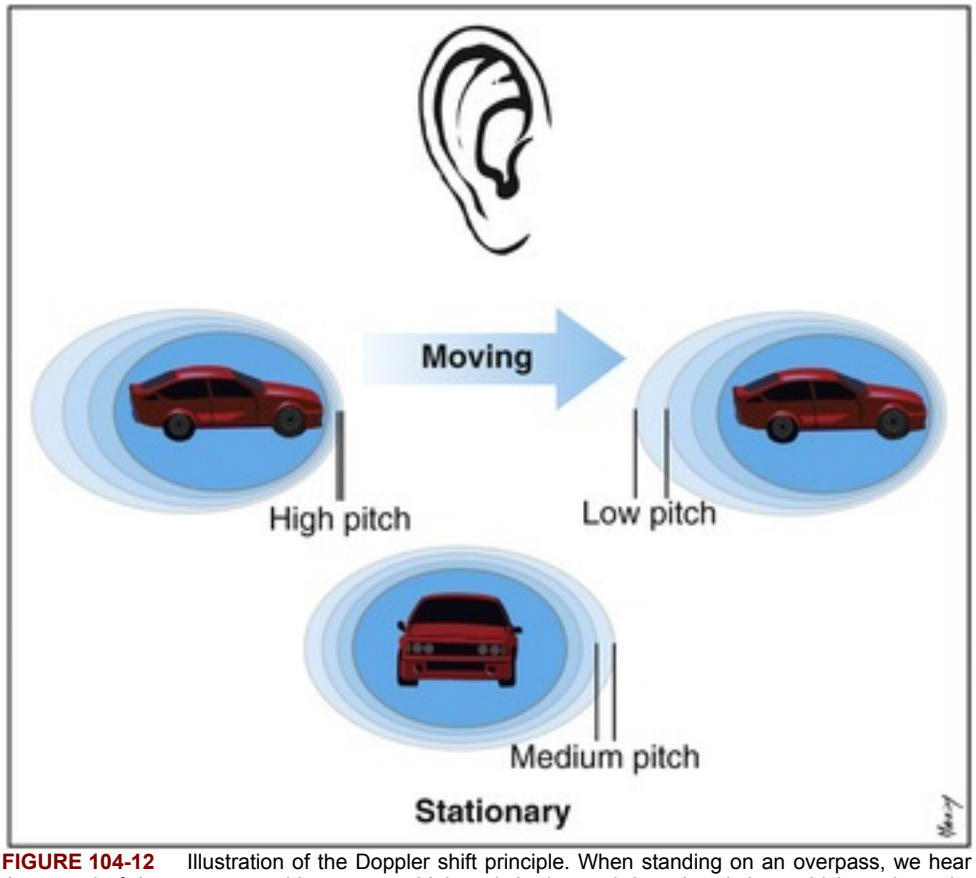


FIGURE 104-12 Illustration of the Doppler shift principle. When standing on an overpass, we hear the sound of the car approaching us as a higher-pitched sound than the pitch at which we hear the same car moving away from us. The engine is emitting the same sound, and the speed and direction of the car are responsible for the change in pitch that we hear.

In echocardiography, the Doppler principle relies on the fact that the transducer generates ultrasound waves that are reflected by red blood cells. The frequency of the reflected sound wave depends on the direction and velocity of the red blood cells and the transmitted frequency. Since the ultrasound frequency emitted from the transducer and the velocity of sound in blood are known, the velocity of red blood cells can be calculated and plotted in the form of curves called *envelopes*, that describe blood movement in a given area of the heart. These flow signals are displayed with time on the horizontal axis and velocity on the vertical axis (see Figure 104-7, *C*).

When the transmitted sound waves encounter red blood cells moving toward the transducer, they are reflected back at a frequency that is higher than that at which they were sent, producing a positive Doppler shift or positive deflection on the screen (Figure 104-13). The opposite effect occurs when the sound waves hit red blood cells moving away from the transducer, producing a negative Doppler shift. Thus, Doppler echocardiography assesses both the direction and the velocity of moving blood (or myocardium—see Tissue Doppler, below). Blood moving toward the transducer creates a positive frequency shift that is encoded red on color Doppler and is shown above the baseline of the spectral Doppler display. Blood flow moving away from the transducer is blue and, conversely then, is displayed as a negative flow profile under the baseline (see Figure 104-13).

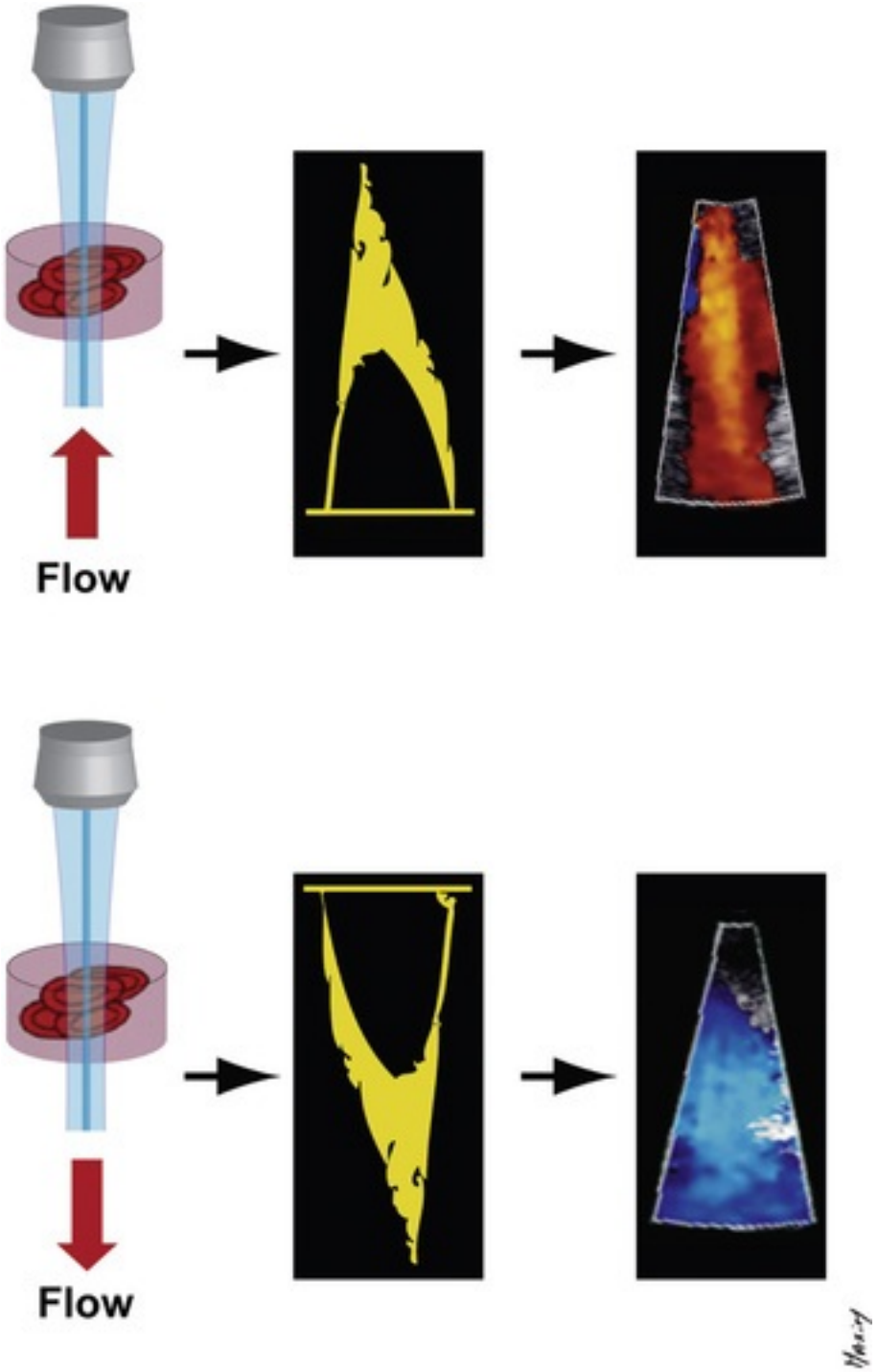


FIGURE 104-13 Doppler imaging of blood flow. When the ultrasound waves encounter blood moving toward the transducer, they produce a positive deflection on the monitor with spectral Doppler, and a red signal on color Doppler. The opposite effect occurs for red blood cells moving away from the transducer, producing a negative deflection on spectral Doppler and a blue signal on color Doppler.

Spectral Doppler

Cardiac spectral Doppler studies use imaging planes that align the sound beam to be parallel with the blood flow. A marker is represented on the cursor line that corresponds to the sampling volume or *gate* where the flow is interrogated (Figure 104-14). This parallel beam positioning is in contrast to M-mode, in which the beam is oriented in a perpendicular manner to visualize the cardiac structures. When performing Doppler studies, care should be taken to align the Doppler beam with the jet flow (intercept angle <20-25°) in order to minimize the underestimation of flow velocity. Parallel alignment of the ultrasound beam measures the true

or maximum velocity of the blood flow. In contrast, perpendicular alignment to flow will show a velocity of zero. Therefore, a wider angle of interrogation will result in a false reduction in the measured velocity as compared to the real velocity (Figure 104-15). Some ultrasound machines have a feature that corrects poor alignment of the beam with the jet flow (often called *angle correction*). However, this type of correction is inaccurate since correction of inappropriate angulation in one dimension or plane does not correct for the other two dimensions.

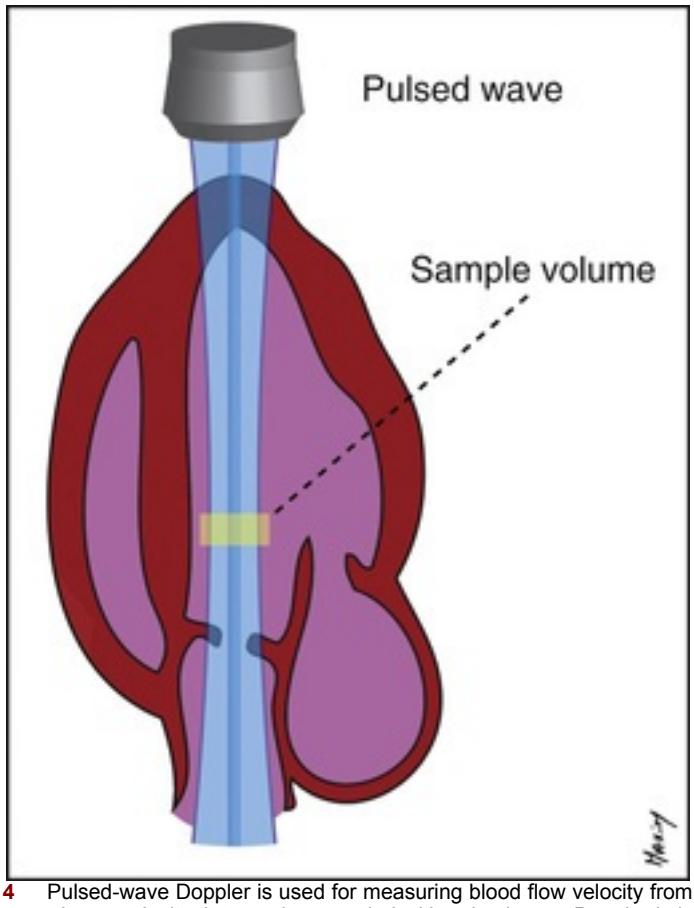


FIGURE 104-14 Pulsed-wave Doppler is used for measuring blood flow velocity from a distinct area of the heart; the maximum velocity that can be recorded with pulsed-wave Doppler is less than that of continuous-wave Doppler.

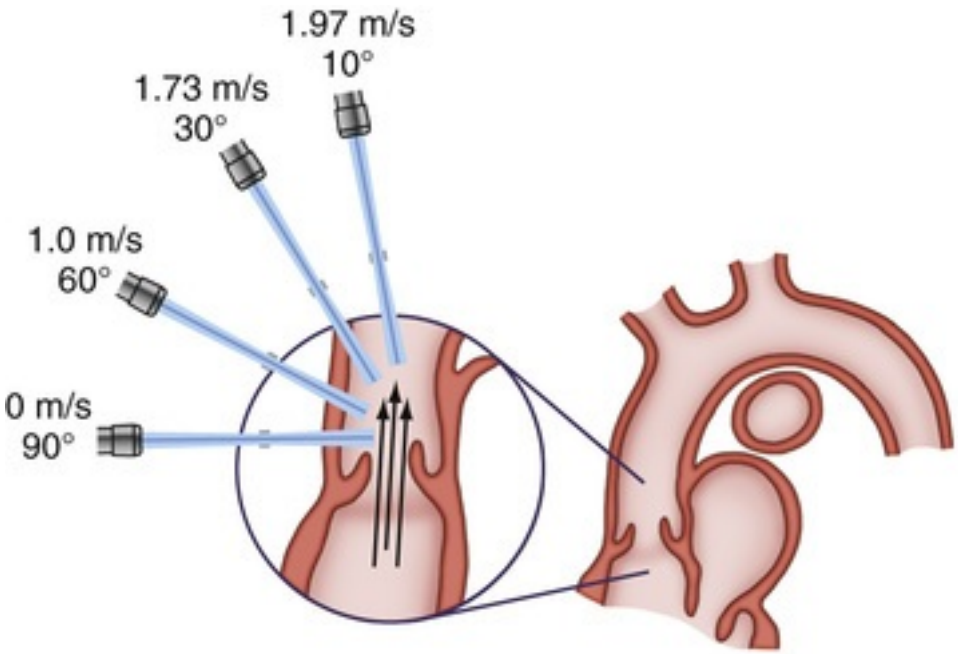


FIGURE 104-15 Effect of the angle of interrogation of flow on the obtained velocity.

Two types of spectral Doppler are used clinically: pulsed-wave Doppler (PW) and continuous-wave Doppler (CW). An intermediate between PW and CW Doppler, called *high pulse-repetition frequency* (HPRF), is another form of spectral Doppler that is used less frequently. It allows the operator to increase the pulse-repetition frequency above the Nyquist limit and thereby reduce aliasing (see PW Doppler section, below, for further explanation).

Spectral Doppler evaluations are helpful in the assessment of pressure gradients, intracardiac chamber pressures, regurgitant fractions, shunt ratios, valvular area/effective orifice area, and cardiac output. Spectral Doppler often is used for calculating *instantaneous pressure gradients* (ΔP, in mm Hg) across a stenotic area, regurgitant valve, or shunt. The maximum pressure gradient is calculated from the maximum flow jet velocity (v, in m/s) using the modified Bernoulli equation:

$$(\Delta P) = 4v^2$$

The peak pressure gradient is used in combination with the determination of the effective orifice area and other 2-D and M-mode echocardiographic findings in the clinical assessment of stenosis severity (see ch. 250).

Pulsed-Wave Doppler

Pulsed-wave (PW) Doppler uses a single crystal transducer that transmits and receives the Doppler signal. Short pulses of ultrasound are produced and the returning echoes from a small sample segment (called *sample volume* or *gate*) along the ultrasound beam are analyzed (see Figure 104-14).

The main advantage of PW Doppler is the possibility of interrogation of direction, velocity, and spectral characteristics (laminar versus turbulent) of the blood flow from a distinct anatomic region of the heart or blood vessels. Laminar flows are characterized by the similarity of the red blood cell velocities within the blood vessel or heart, which creates a Doppler signal with less disparity in velocity and little spectral broadening, as shown in Figures 104-16 and 104-17. Due to friction, normal blood flow is always slightly slower near the walls of a vessel, which gives the signal a typical parabolic profile. Flow across the cardiovascular system normally is laminar and its velocity rarely exceeds 2 m/s in healthy dogs and cats,[22,25-27] with a notable exception in some healthy Boxers.[28-30] Turbulence is observed when blood cell motion becomes disorganized and produces various eddies and whirls or different velocities and directions. It often is generated by an underlying structural lesion. Turbulent flow profiles are broad, and the area under the curve is filled in because the transducer is receiving many frequency shifts associated with variable velocities (Figure 104-17).

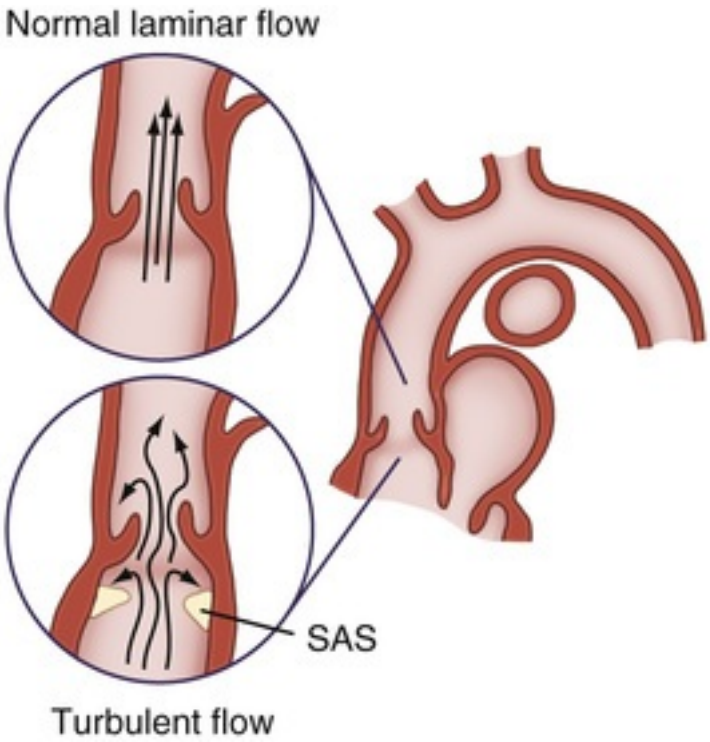


FIGURE 104-16 Laminar flows are characterized by the similarity of the red blood cells velocities. Due to friction, blood flow is always slightly slower near the walls of a vessel, which gives the signal a typical parabolic profile. Turbulent flow profiles are associated with variable velocities. *SAS,* Subaortic stenosis.

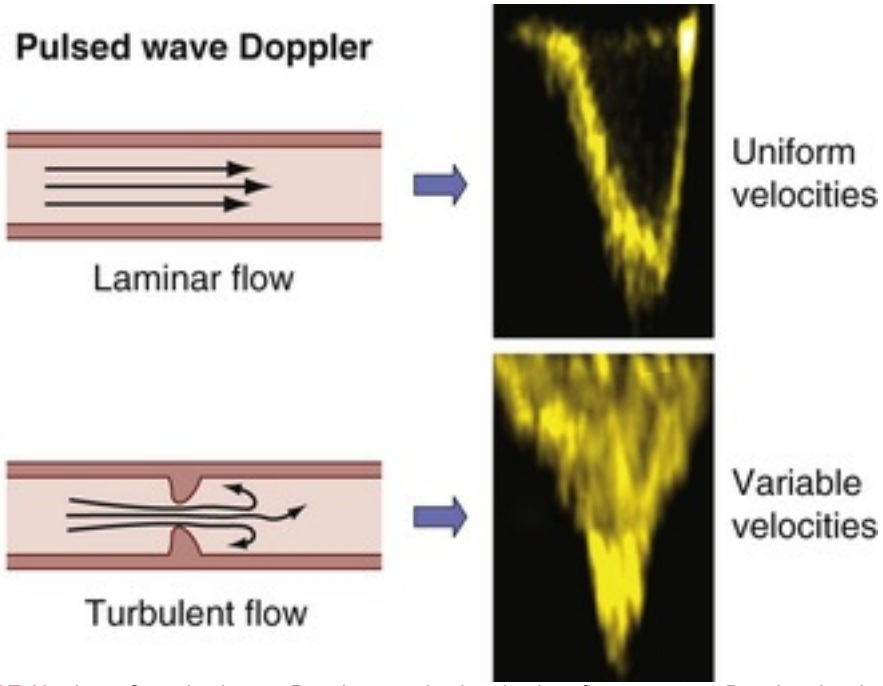


FIGURE 104-17 On pulsed-wave Doppler examination, laminar flows create a Doppler signal with less disparity in velocity and little spectral broadening. Turbulent flow profiles are broad, and the area under the curve is filled in because the transducer is receiving many frequency shifts associated with variable velocities.

The disadvantage of PW Doppler is that it relies on a maximum measurable velocity called the *Nyquist limit,* which cannot be exceeded because of a limited pulse repetition frequency. In other words, PW Doppler

is only accurate when measuring low, normal, or slightly elevated velocities. When the Nyquist limit is exceeded, a phenomenon called *aliasing* will be observed on the Doppler tracing (Figure 104-18). A simple change of probe can usually overcome this limitation since the Nyquist limit is determined by the frequency of the transducer used. A lower frequency probe increases the ability to record higher velocities at any given range. The main drawback of this trick is a reduction in the quality of the output. For these reasons, interrogation of a high velocity flow, as seen in stenotic valvular lesions, is usually achieved with continuous-wave (CW) Doppler.

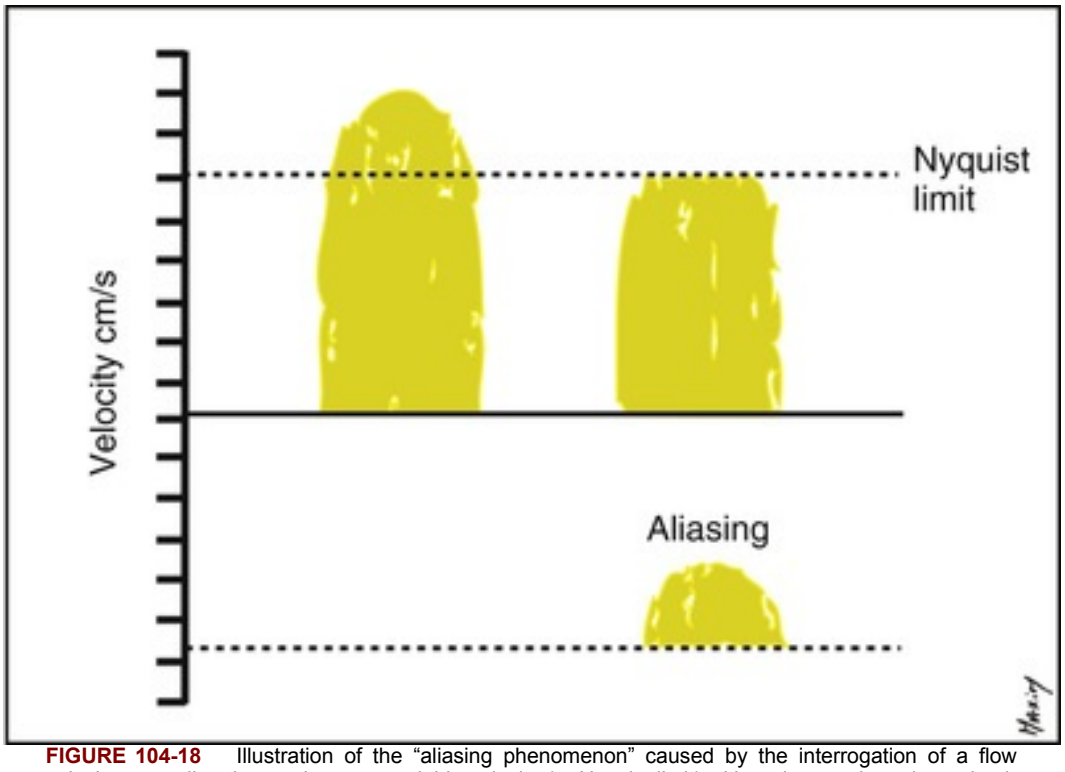


FIGURE 104-18 Illustration of the "aliasing phenomenon" caused by the interrogation of a flow velocity exceeding the maximum recordable velocity (or Nyquist limit) with a given probe using pulsed-wave Doppler.

PW Doppler is very useful in the evaluation of transvalvular blood flow patterns. Diastolic flow across the atrioventricular (AV) valves has similar patterns characterized by an initial high-velocity signal associated with rapid ventricular filling, called the *E wave,* followed by a smaller velocity signal produced by blood flow from atrial contraction, the *A wave* (Figure 104-19).

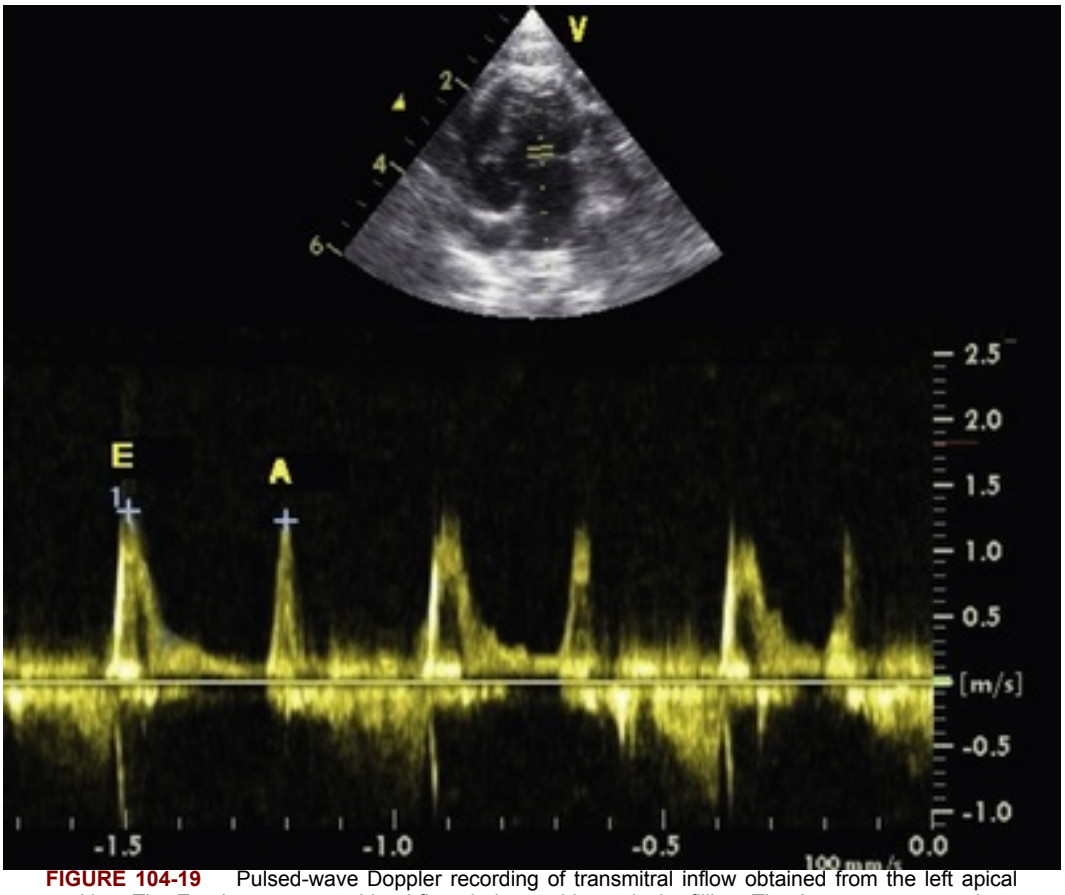


FIGURE 104-19 Pulsed-wave Doppler recording of transmitral inflow obtained from the left apical position. The E-point represents blood flow during rapid ventricular filling. The A wave corresponds to blood flow during atrial contraction. Simultaneous ECG display recorded but not shown.

The flow patterns across the semilunar valves are characterized by a rapid acceleration during ejection followed by a more gradual deceleration (Table 104-6). The variance of these valvular flow patterns, like the transmitral flow profile, is studied to identify different cardiac diseases (Figure 104-20).

TABLE 104-6

Reference Intervals for Spectral Doppler Velocities in Dogs and Cats (m/s)

	CANINE	FELINE
Mitral Valve		
Peak E wave	0.7-1.0	0.6-0.8
Peak A wave	0.4-0.7	0.4-0.6
Aortic Valve		
Peak systolic velocity	≤2.0	≤1.2
Pulmonic Valve		
Peak systolic velocity	≤1.5	≤1.2
Tricuspid Valve		
Peak E wave	0.8-0.9	—
Peak A wave	0.5-0.6	—

These values are based on the author's experience and published data.

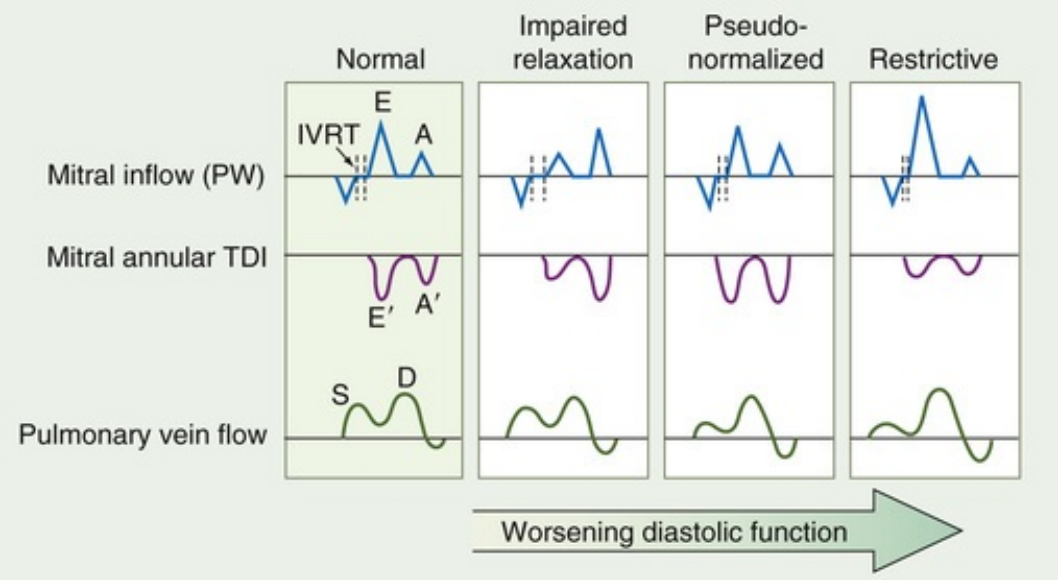


FIGURE 104-20 Schematic representation of various mitral inflow, mitral annular tissue Doppler imaging (TDI), and pulmonary vein flow profiles. *PW,* Pulsed wave.

Continuous-Wave Doppler

CW Doppler uses dual crystals for simultaneous transmission and reception of the Doppler signal. Very high velocity flows can be recorded with CW Doppler since there is no Nyquist limit; the continuous nature of the ultrasound beam in CW Doppler results in an essentially infinite pulse repetition frequency (PRF), and therefore there is no theoretical limit to the maximal velocity that could be recorded by CW Doppler techniques.[31] The disadvantage of CW Doppler is that the specific location and characteristic of flow cannot be documented since all velocities are measured along the cursor line (Figure 104-21).

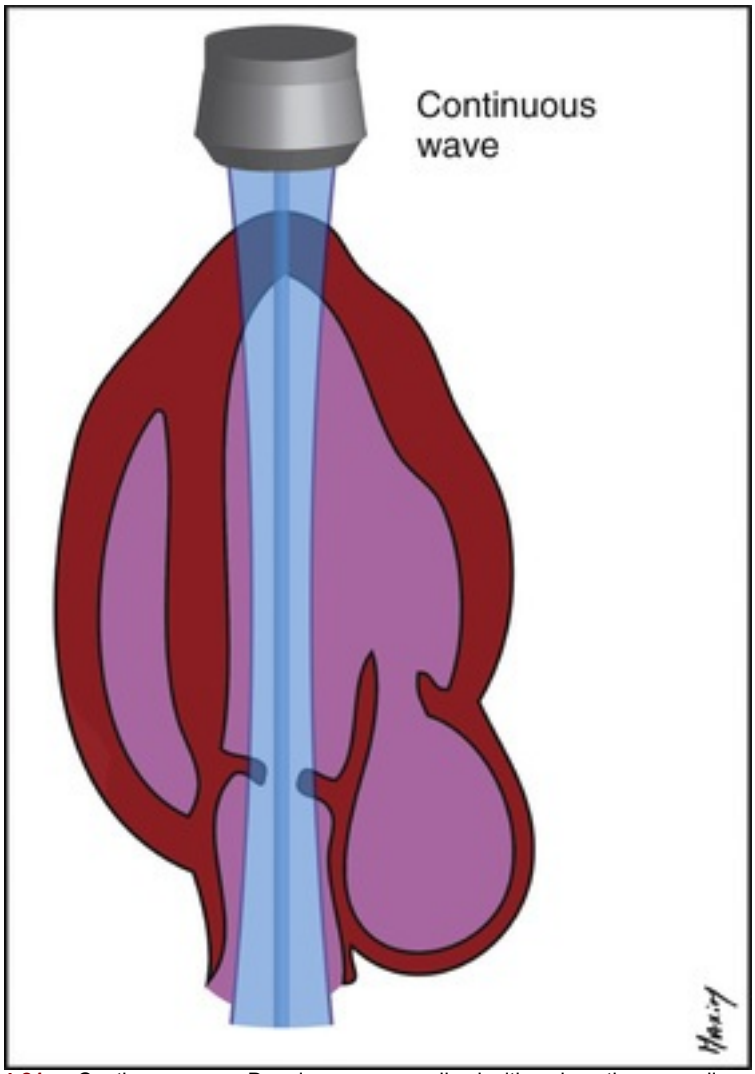


FIGURE 104-21 Continuous-wave Doppler measures all velocities along the cursor line.

PW and CW Doppler are complementary modalities; PW Doppler is indicated when the operator wants to know where a specific area of abnormal flow is located, whereas CW Doppler will document the maximal velocity across the abnormal flow.

Color-Flow Doppler

Color-flow Doppler is a form of PW Doppler that allows visual evaluation of direction and velocity of blood flow through the heart. Its primary clinical use is the detection of flow disturbances. The Doppler shift is encoded with a color map that usually uses red, blue, and green to produce other color shades such as cyan, yellow, and white. Conventionally, blood moving toward the probe is coded red, whereas blood moving away from the probe is coded blue. This color map configuration is called the BART display (Blue/Away and Red/Toward). Color Doppler is very helpful to appropriately align with flow jets, search for jets of insufficiency, describe the size and shape of regurgitant jets, identify other areas of turbulent flow, and confirm some cardiac shunts seen on 2-D echocardiograms (Figure 104-22). Turbulent flow is characterized by disparate velocities within the sampled area, which appear as disorganized flow with a typical mosaic pattern (see Figure 104-22; Video 104-2). Several transducer positions and planes are used for finding the optimal color-flow imaging of a specific cardiac structure.

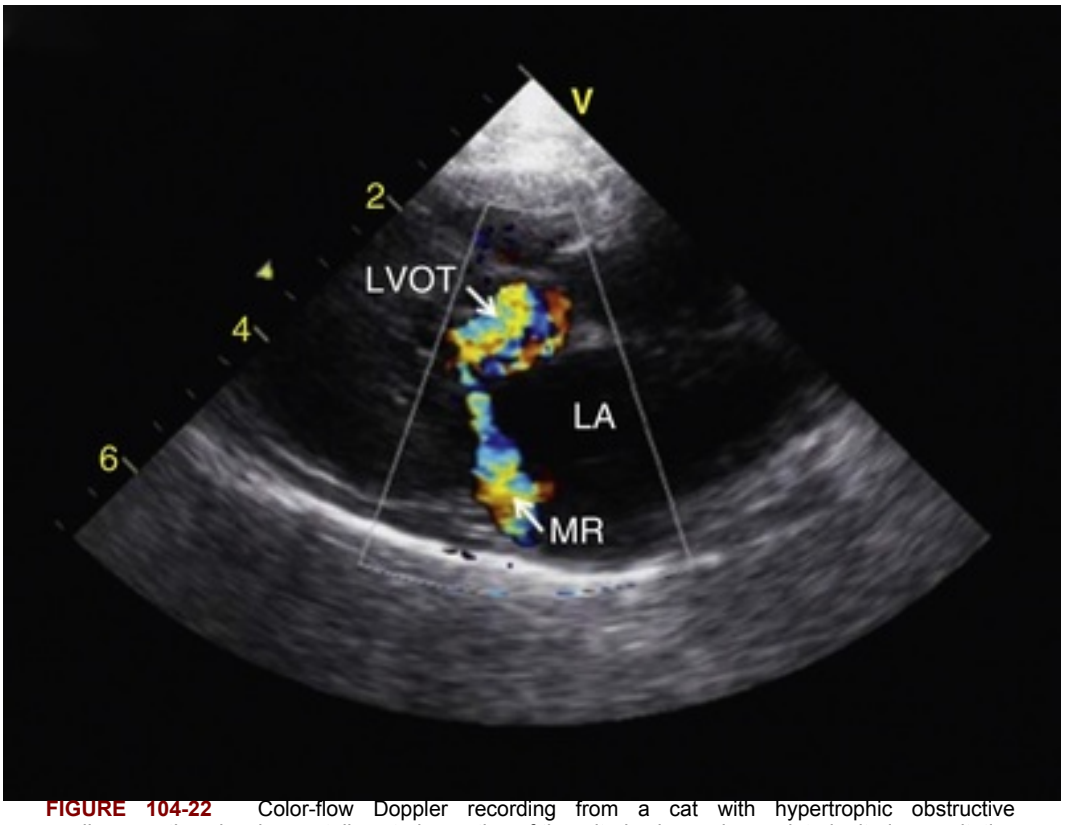


FIGURE 104-22 Color-flow Doppler recording from a cat with hypertrophic obstructive cardiomyopathy, showing systolic anterior motion of the mitral valve and associated mitral regurgitation (MR) and turbulence in the left ventricular outflow tract (LVOT). *LA*, Left atrium.

Artifacts

Image artifacts are unfortunately a common component of the echocardiogram. An inexperienced sonographer often is confronted with the possibility of missing a lesion (false-negative exam) or misdiagnosing a normal structure as a pathologic finding (false-positive exam). Oblique or tangential imaging of cardiac structures is a common pitfall of the echocardiographic study. Some artifactual images can be mistaken as masses or pseudomasses. A simple way to differentiate a real mass from an artifact is to examine the perpendicular plane where that mass is seen. If the mass cannot be confirmed in the perpendicular plane, then the most likely explanation is that it is artifactual. Again, the most common cause of a false-negative echocardiogram is failure to examine the heart completely (i.e., from multiple windows). Many publications describing common echocardiographic artifacts in animals are available elsewhere.[6-8,32]

Repeatability and Reproducibility in Veterinary Echocardiography

Quantitative echocardiography, especially involving serial echocardiographic measurements, often is used for evaluating the long-term outcome of cardiac diseases or drug efficacy. However, the small size of the canine and feline heart, stress and motion caused by restraint, duration of the procedure, and many other technical factors can result in suboptimal images or inaccuracies in measurement and interpretation of echocardiograms. Within-day and between-day coefficients of variation can be as high as 22% for routine M-mode measurements in cats.[33] Similarly in dogs, most coefficients of variation for these parameters are <20%.[34,35] These results suggest that differences >20% for parameters during serial echocardiograms should be considered to reflect genuine change. Also, variability and reproducibility are known to improve when a single experienced operator acquires and measures serial echocardiographic data.

Special Echocardiographic Techniques

Other echocardiographic techniques can provide useful information in the imaging of the canine and feline

heart. These techniques include tissue Doppler imaging[36-51] and its derivatives, tissue tracking, strain, and strain rate[52-56]; speckle tracking imaging[57-60]; contrast echocardiography[61-63]; transesophageal echocardiography (TEE)[64-69]; and three-dimensional echocardiography (3-DE).[70-74] Although very useful in the clinical setting, some of these imaging methods have a limited application in veterinary medicine since they require expensive equipment. Transesophageal echocardiography necessitates general anesthesia, which increases the time and cost (and a potential danger) of the procedure.

Transesophageal Echocardiography

TEE uses a specialized transducer mounted on a flexible, steerable endoscope tip (Figure 104-23).[64,65] The heart is imaged through the esophageal wall (Figure 104-24). The image quality is improved with TEE because of closer proximity of the cardiac structures to the transducer and the lack of intervening lung and bone structures. TEE is considered a complementary technique that especially allows better imaging of cardiac structures above the AV node such as the atria and pulmonary veins. TEE also is very helpful in assisting many interventional cardiology procedures (see ch. 122).[66,67,69]

FIGURE 104-23 A specialized flexible probe containing a steerable ultrasound transducer at its tip is used for performing transesophageal echocardiography.

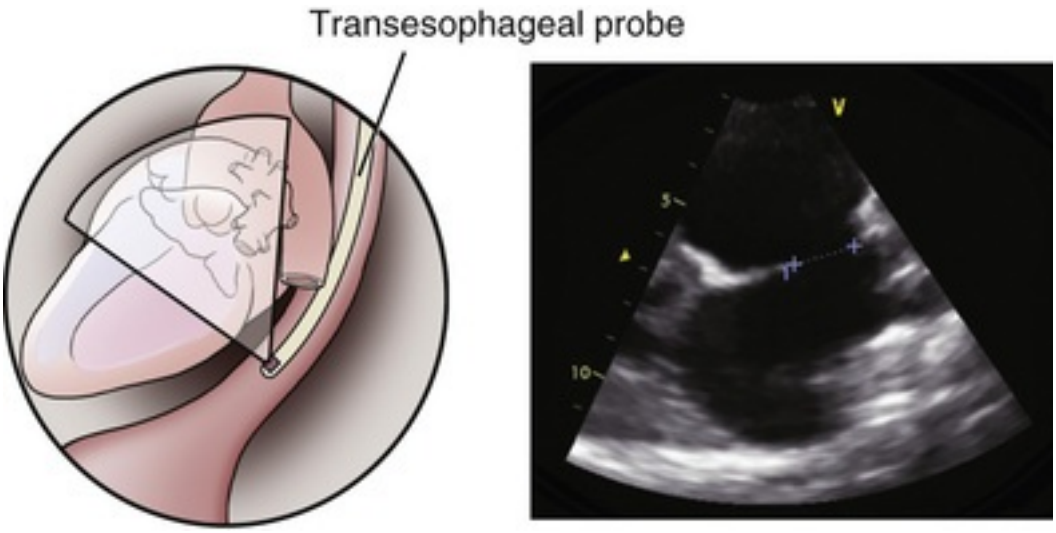


FIGURE 104-24 Illustration of transesophageal echocardiography with real-time 2-D imaging of a large atrial septal defect in a dog.

Three-Dimensional Echocardiography

3-DE is not yet a standard part of the routine clinical echocardiographic examination in animals and humans. It provides a more detailed anatomic description of cardiac defects and masses in all three spatial dimensions (Figure 104-25).[71] It is now also used in the quantification of chamber volumes (Video 104-3).[70,72-74] The ability to "slice" the heart in multiple planes and to reconstruct three-dimensional images of specific cardiac structures on the awake patient makes 3-DE echocardiography unique for characterizing the morphology of many congenital malformations (see ch. 250). Four-dimensional echocardiography refers to 3-DE performed in real-time display.

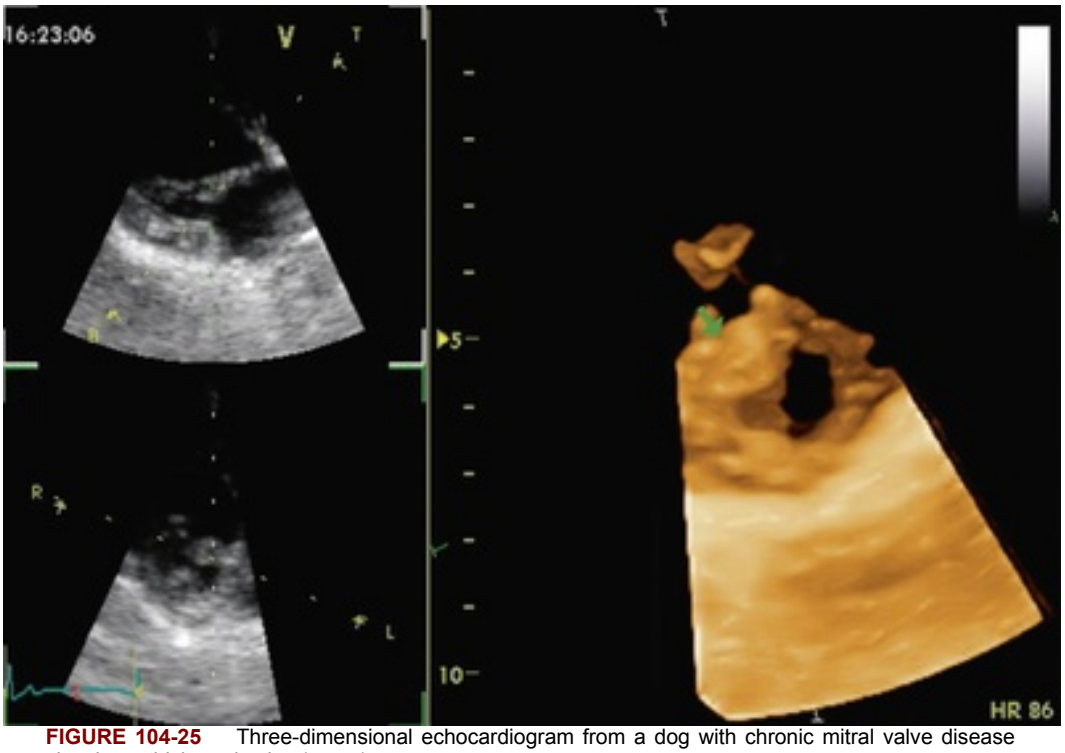


FIGURE 104-25 Three-dimensional echocardiogram from a dog with chronic mitral valve disease showing a thickened valve (arrow).

Contrast Echocardiography

Contrast echocardiography is another useful imaging method in the clinical evaluation of the cardiovascular system. It has four main applications: detection of shunts, enhancement of Doppler signals, left ventricular opacification, and demonstration of myocardial perfusion.

The microbubble technique was one of several contrast echocardiographic media to be used initially[61] and it remains the most widely utilized in small animal cardiology today. Microbubbles are created by back-and-forth injection of 3-10 mL of physiologic sterile saline through a 3-way stopcock, between 2 syringes (Figure 104-26). Injection in a peripheral vein can help to confirm right-to-left intracardiac shunting. Microbubbles reflect ultrasound and do not cross pulmonary or systemic capillaries; they dissolve and are reabsorbed in the pulmonary vasculature. Therefore, the microbubbles injected in the cephalic vein will stay on the right side of the heart in a normal patient. When right-to-left shunting is present, microbubbles will also be observed in the left side of the heart (Videos 104-4 and 104-5). In veterinary medicine, agitated saline (prepared as described above) is still the preferred contrast agent for the right side of the heart.

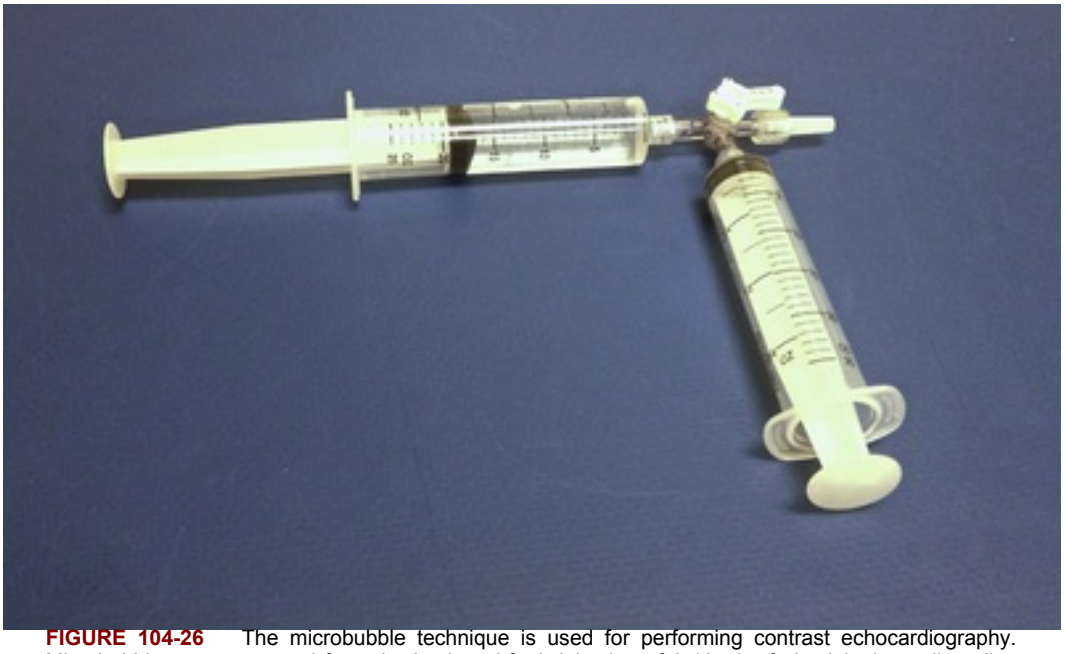


FIGURE 104-26 The microbubble technique is used for performing contrast echocardiography. Microbubbles are generated from the back-and-forth injection of 3-10 mL of physiologic sterile saline between 2 syringes connected by a three-way stopcock.

Commercially available contrast agents also can be used in echocardiography to improve diagnostic accuracy.[62,63] They consist of low-solubility fluorocarbon gas in stabilized microspheres encapsulated with denatured albumin. Contrast agents act by increasing ultrasound scattering and thereby enhancing the cardiac chambers, myocardial echogenicity, and Doppler signals. They are particularly useful for the assessment of intracardiac thrombi or masses in the heart.

Tissue Doppler Imaging (TDI) and "Derived Techniques" (Tissue Tracking, Strain, and Strain Rate)

TDI is the method of choice for non-invasive assessment of regional myocardial function in humans and is increasingly used in veterinary medicine.[36-56] TDI uses the same principles as conventional Doppler except that the target or reflector is the motion of the myocardial tissue rather than the flow of red blood cells. TDI is especially useful in evaluating diastolic function because the diastolic velocity of the myocardium is much less dependent on preload conditions than is transmitral blood flow. Pulsed-wave TDI can be performed in real time by placing a sample gate over a portion of the myocardium to record a positive or negative Doppler shift. The pattern of myocardial motion is similar to, but inverted and slower than, the transmitral flow (Figures 104-20 and 104-27).

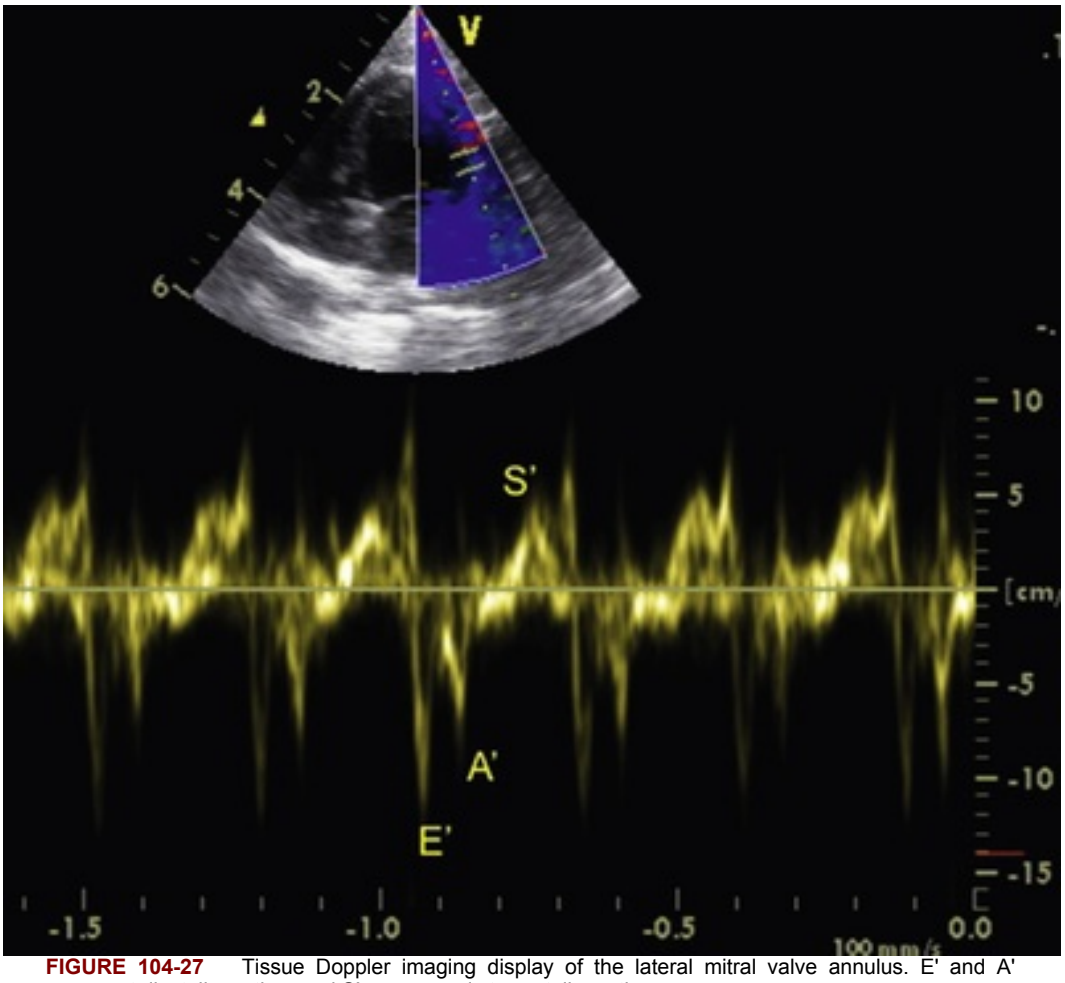


FIGURE 104-27 Tissue Doppler imaging display of the lateral mitral valve annulus. E' and A' represent diastolic motion, and S' corresponds to systolic motion.

Simultaneous color TDI of various areas of the heart can also be obtained by placing a sector of color over the myocardium and then saving the video loop for off-line analysis. A gate is then placed on a specific area of the myocardium, from the retrieved loop. The corresponding systolic and diastolic movements of the specific area are displayed (Figure 104-28). The advantage of this TDI modality is that motion from multiple areas of the myocardium under the color sector can be analyzed and compared offline from one stored loop. Color TDI can thereby reduce beat-to-beat variability.

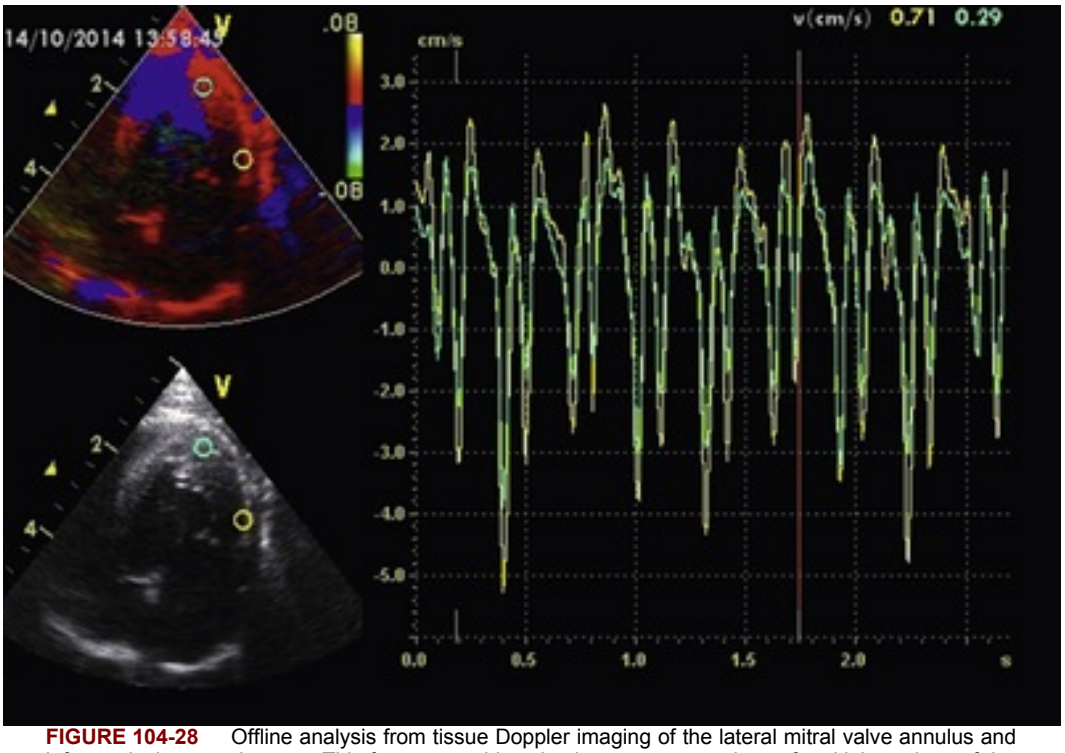


FIGURE 104-28 Offline analysis from tissue Doppler imaging of the lateral mitral valve annulus and left ventricular apex in a cat. This feature provides simultaneous comparison of multiple regions of the left ventricular myocardium.

LV myocardial tissue Doppler signals are recorded from the left apical four-chamber view using PW Doppler. The sample gate can be located at the levels of the mitral annulus, basal ventricular wall, and apex. TDI now is commonly used in veterinary cardiology, particularly in the evaluation of feline hypertrophic cardiomyopathy.

Tissue imaging technology also includes tissue tracking and strain rate imaging.[52-56] Tissue tracking allows the measurement and visualization of longitudinal motion in each myocardial segment during systole and diastole. Strain measures compression and distension of myocardial segments ("deformation magnitude") and strain rate imaging expresses strain changes per time interval. Myocardial strain and strain rate are measured using color TDI or more recently by speckle tracking imaging.

Speckle tracking is a new tissue imaging technology, which provides additional information on myocardial contractility and relaxation.[57-60] Speckle tracking determines myocardial deformation from continuous frame-by-frame tracking of a small image block of natural acoustic markers called "speckles." These markers are small areas of higher echogenicity that are caused by reflections, refraction, and scattering of echo beams. By tracking such speckles in the wall of the left ventricle throughout the cardiac cycle, it is possible to obtain information on the direction and velocity of myocardial motion. Comparing the motion of individual speckles to each other allows the analysis of the deformation of the myocardium or in other words the magnitude of myocardial fiber relaxation (diastole) or contraction (systole).

Evaluation of Cardiac Structure and Function

Cardiac Size and Chamber Dilation

Cardiac chamber dimensions traditionally have been determined by M-mode echocardiography, with reference intervals reported for several breeds of dogs[75-92] and for cats[11,93-97] and increasingly are obtained via 2-D echocardiography, especially in cats.[18-20] Tables 104-2 to 104-6 contain published reference intervals for dogs and cats; Table 104-7 summarizes the most common etiologies for anomalies in chamber size. M-mode measurements vary with body size, body surface area, breed, and sedative drugs. They also are modified by situations like fear and stress, which can significantly affect the heart rate and myocardial function of our patients. Therefore, reported reference intervals always should be regarded as approximate. The effect of breed can be minimized with specific calculations; in a post-hoc analysis, Cornell et al. logarithmically transformed LV M-mode values from 494 dogs weighing 2-95 kg and found a good

correlation to body weight using this approach.[15]

TABLE 104-7

Common Causes of Chamber Anomalies

	DILATION	REDUCTION IN VOLUME	WALL THICKENING
LV	Volume overload • Mitral regurgitation • Left-to-right shunting • Aortic insufficiency Dilated cardiomyopathy High-output state • Hyperthyroidism • Anemia	Volume depletion • Severe dehydration • Hypoadrenocorticism • Hypovolemic shock Inadequate blood return to the left heart • Dirofilariasis • Tetralogy of Fallot	Pressure overload • Aortic stenosis • Systemic hypertension Hypertrophic cardiomyopathy Infiltrative myocardial disease
RV	Volume overload • Tricuspid regurgitation • Atrial septal defect Dilated cardiomyopathy	Cardiac tamponade Volume depletion	Pressure overload • Pulmonic stenosis • Tetralogy of Fallot • Cor pulmonale • Pulmonary hypertension • Dirofilariasis Feline hypertrophic cardiomyopathy
LA	Mitral regurgitation/dysplasia Dilated cardiomyopathy Left-to-right shunting Mitral stenosis		
RA	Tricuspid regurgitation/dysplasia Dilated cardiomyopathy Right-to-left shunting Tricuspid stenosis Cor pulmonale • Dirofilariasis • Pulmonary hypertension		

LA, Left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle.

The *left atrial–to-aortic ratio* (LA : Ao ratio) is used for estimating the degree of left atrial enlargement. Multiple techniques have been described including 2-D (diameter, area, surface) and M-mode methods. The M-mode method compares the diameter of the left atrium in systole to the diameter of the aorta in diastole. This ratio is best obtained from the right parasternal short-axis view, but it may also be evaluated from the right parasternal long-axis view. The M-mode LA : Ao ratio is criticized because of the subjectivity of the cursor placement. This method underestimates the left atrial size when the cursor does not reach the body of the left atrium. Conversely, it overestimates the relative left atrial size when a tangential plane of the aorta is obtained. The reported reference interval for M-mode-derived LA : Ao ratio in normal dogs and cats is <1.3. Other 2-D echocardiographic methods have been described by Rishniw and Erb for estimation of left atrial size.[98] One method measures the LA : Ao ratio from the right parasternal short-axis view of the aorta and left atrium on the first frame that shows aortic valve closure. The internal diameter of the aorta is measured along the commissure between the closed noncoronary and right coronary aortic valve cusps (Figure 104-29). The left atrial internal diameter is measured from a line parallel to the commissure between the noncoronary and left coronary aortic valve cusps to the distant margin of the left atrium. A 2-D LA : Ao ratio >1.6 in dogs and >1.5 in cats suggests left atrial dilation, as does an absolute LA diameter >16 mm in cats.[99]

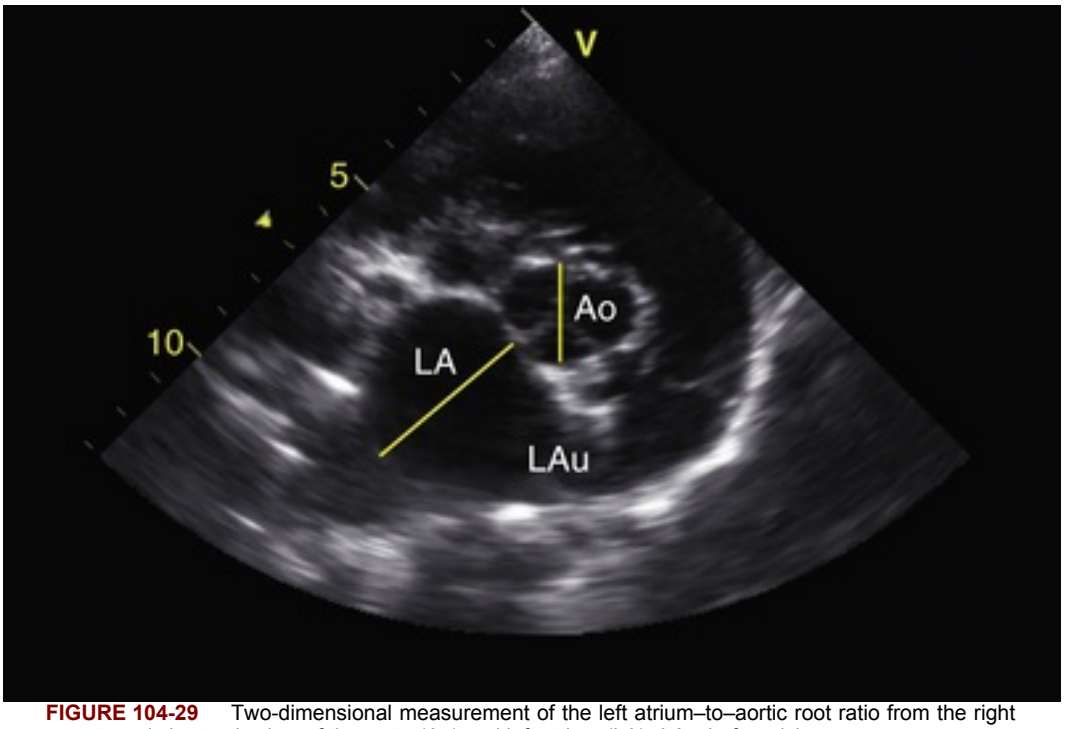


FIGURE 104-29 Two-dimensional measurement of the left atrium–to–aortic root ratio from the right parasternal short-axis view of the aorta (Ao) and left atrium (LA). *LAu,* Left auricle.

Systolic Function

Virtually all forms of cardiac disease can be associated with a certain degree of systolic and diastolic dysfunction. Evaluation of these dysfunctions can provide valuable prognostic information. Systolic dysfunction is characterized by impaired contractility and reduced ejection fraction. Many echocardiographic techniques to assess systolic dysfunction have been described.[5-8] The following parameters are those that are frequently used in clinical veterinary cardiology.

Ejection phase indices are used for quantifying LV systolic performance. They are calculated from linear M-mode measurements or more often nowadays from 2-D still images, and they include the *fractional shortening* (FS), the *stroke volume* (SV), and the *ejection fraction* (EF). The *end-systolic diameter* is also by itself a good indicator of LV performance and it is a more specific index of myocardial contractility than the fractional shortening. M-mode methods of volume determination have a limited correlation with more invasive methods, so these indices should rather be calculated from 2-D–specific echocardiographic methods. Also, the examiner should always remember that these indices all are significantly influenced by ventricular loading conditions (preload and afterload), such that changes could be due to heart rate, hydration status, or other variables, rather than intrinsic myocardial function.

Fractional Shortening

FS is the percent change in diameter of the ventricular cavity from diastole to systole. It provides a rough index of systolic function. Severe LV systolic dysfunction will usually be associated with a very low FS. Despite its many limitations, FS is the clinical index used most commonly in the evaluation of global LV systolic function in veterinary medicine, although improved methods for calculation of ejection fraction are gradually making FS obsolete. It is important to understand that FS is not a measure of contractility since it also depends on loading conditions. In other words, an abnormal FS can be caused by alterations of preload, afterload, or contractility. For example, a low FS can be observed because of hypovolemia (decreased preload), sedation with an alpha-2 agonist (increased afterload), or decreased systolic function (e.g., dilated cardiomyopathy). The reference interval for FS values in healthy dogs is 24-49%, with great variation among breeds (see Table 104-3).[75-92] The reference interval for FS values in healthy cats is 33-66%.[13,93-96] FS is calculated as follows:

$$FS\,(\%) = \frac{EDD - ESD}{EDD} \times 100$$

where *EDD* is the left ventricular internal diameter at the end of diastole (cm) and *ESD* is the left ventricular internal diameter at the end of systole (cm). Since the FS is calculated by M-mode, it is important that the measurements of the ventricular walls are made on an image that is a true transverse view of the LV (see Figure 104-10).

Left Ventricular Volume and Ejection Fraction

Determination of left ventricular volumes (LVV) and derived EF is essential to evaluate LV systolic function precisely. Many experimental models and formulas have been described in dogs to assess LVV by use of M-mode and 2-D echocardiography. Left ventricular end-diastolic volume (LVV_{ED}) and end-systolic volume (LVV_{ES}) can be estimated by the Teichholz method, the bullet method, and the disc summation method (i.e., Simpson's rule). The latter is considered the more accurate echocardiographic method in veterinary medicine.[99] As discussed above, the M-mode–derived Teichholz method, which is calculated automatically during M-mode measurements, is less accurate because it is calculated from only one dimension, which can introduce a level of error of up to 100% in a diseased heart. Consequently, the ASE recommends the use of 2-D methods involving fewer geometric assumptions, such as in the disc summation method (Figure 104-30).[17] This method is particularly more accurate when the heart has an irregular, enlarged, or asymmetrical shape, as in many of the canine and feline cardiomyopathies.

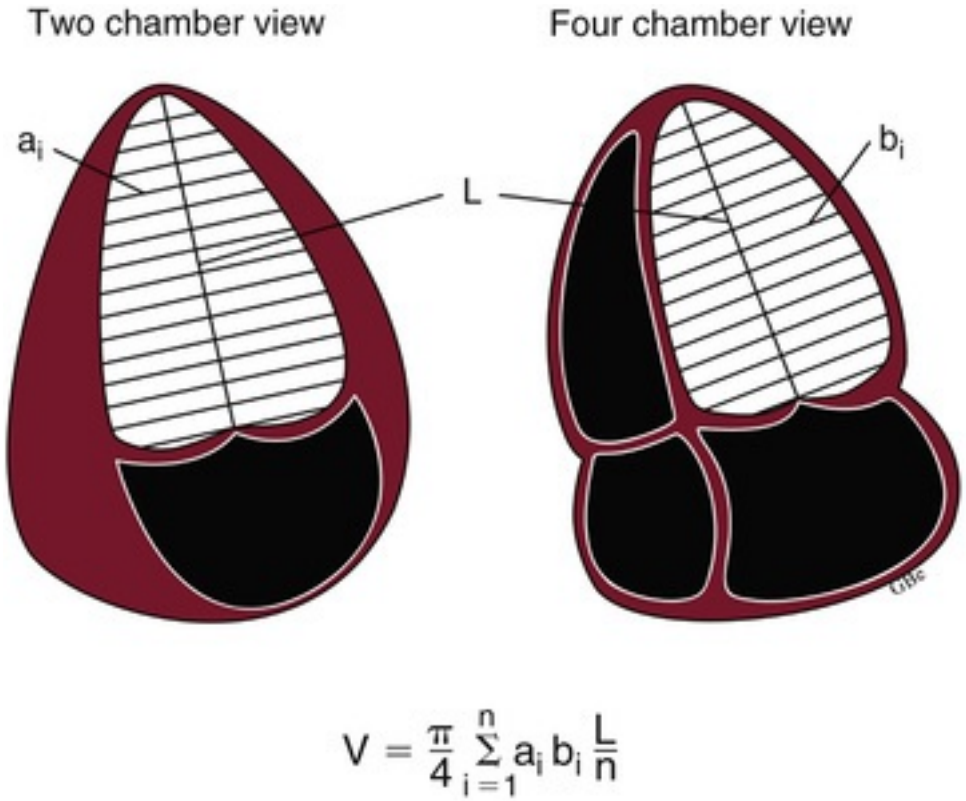


FIGURE 104-30 Disc summation (Simpson's method) to estimate left ventricular volumes.

In healthy dogs, the reference interval for LVV_{ED} indexed to body surface area (BSA) is 47.6 ± 8.4 mL/m^2 and for LVV_{ES} indexed to BSA it is 15.9 ± 3.9 mL/m^2.[5,6]

Stroke Volume

The SV and, ultimately, the cardiac output (CO) can be calculated from the LV end-systolic and end-diastolic volumes. SV is computed as follows:

$$SV\ (mL) = LVV_{ED} - LVV_{ES}$$

Cardiac Output

2-D and Doppler echocardiography can be used for calculating the CO, which ultimately reflects global LV performance. The *cardiac index* (CI) is the CO indexed for body surface area (BSA) in order to take into account body size variation between animals.

$$CI\ (mL/min/m^2) = CO/BSA$$

BSA is calculated from body weight using the formula:

$$BSA\ (m^2) = (10.1 \times w^{2/3}) \times 10^{-4}$$

where *w* is body weight in grams. CO is the product of HR and SV:

$$CO\ (mL/min) = HR \times SV$$

CO can be calculated from the SV determined by the assessment of LVV by Simpson's rule of summation of discs. Alternatively, the continuity equation can be used for evaluating the CO by use of Doppler. The continuity equation is based on the theory of conservation of mass applied to fluids, which specifies that flow through a given area of a conduit must equal flow through an adjacent area over a given time. Accordingly, SV ejected normograde through a valvular orifice during systole is equal to the flow that passes through the valve as expressed by this equation:

$$SV = A \times VTI$$

where *A* is the cross-sectional area of the orifice calculated from the diameter measured by 2-D echocardiography and *VTI* is the velocity-time integral of the pulsed-wave Doppler signal across the valvular orifice.

$$\text{Since } A = D^2 \times (\pi/4)$$

$$\text{therefore, } CO = HR \times D^2(\pi/4) \times VTI$$

Virtually any valve or area in the heart can be used for calculating the CO, but the left ventricular outflow tract and aortic valve are used most often.

Ejection Fraction

The EF is a rough index of LV cardiomyocyte shortening, since it is the percentage of the LVV_{ED} ejected with each heartbeat. It also corresponds to the LV stroke volume, and is the 3-D volumetric equivalent of the FS. The EF is the ratio of the left ventricular SV to the LVV_{ED} as calculated here:

$$EF\ (\%) = \frac{LVV_{ED} - LVV_{ES}}{LVV_{ED}} \times 100$$

In healthy dogs, the reference interval for the EF calculated from LVV assessed by Simpson's rule of discs is 66.5% ± 6.4.[5,6] It is generally accepted that an EF <40% indicates systolic dysfunction.

E-Point to Septal Separation

The *E-point to septal separation* (EPSS) is most useful for the assessment of left ventricular dilation and systolic dysfunction. EPSS measures the distance from the maximum opening of the mitral valve (E-point) to the adjacent endocardial aspect of the interventricular septum (Figure 104-31). In the normal heart, the mitral valve opens in diastole and its anterior leaflet almost contacts the interventricular septum. In dilated hearts, both decreased active filling in early diastole (due to myocardial diastolic dysfunction) and ventricular dilation/eccentric hypertrophy occur. As a result, the tip of the mitral valve does not reach the septum. In healthy dogs, the reference interval is EPSS <6 mm and in healthy cats it is <4 mm.[5,6] Reports in human medicine have shown that the size of the left ventricle alone does not alter the EPSS unless systolic dysfunction is present.

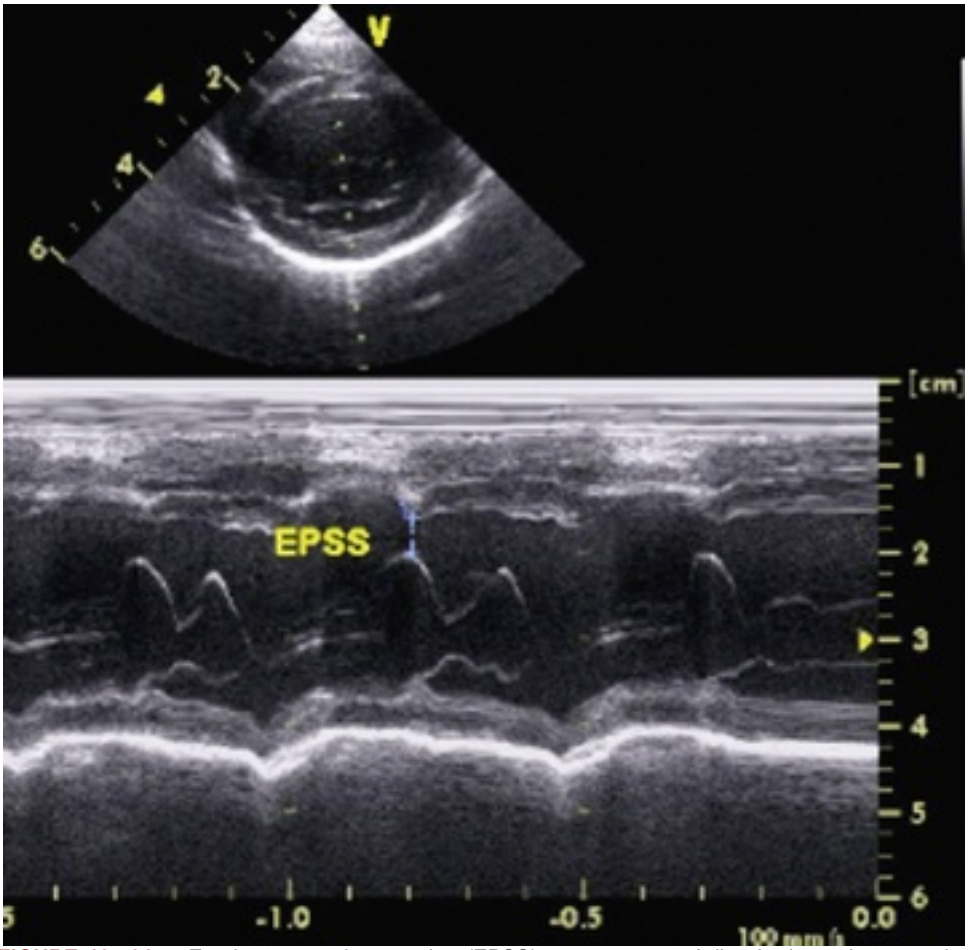


FIGURE 104-31 E-point to septal separation (EPSS) measurement. A line is drawn between the interventricular septum and the maximum initial opening of the mitral valve (E-point).

LV dP/dt

The calculation of LV change in pressure over a period of time *(dP/dt)* has proven to be a sensitive and accurate method to assess LV systolic function.[60,100] It represents the rate of increase in the LV pressure.

When measured during the period of isovolumetric contraction, it is a relatively load-independent measure of ventricular inotropy. Echocardiographically, LV dP/dt typically is calculated from the spectral display of a mitral regurgitation signal (Figure 104-32). To determine dP/dt, one calculates the time difference from the point at which the velocity is 1 m/s to when it is 3 m/s. The time between these two time points represents the period during which a known increase pressure (32 mm Hg, from the modified Bernoulli equation: $[4 \times 3^2] - [4 \times 1^2]$) occurs in the LV. A reduced dP/dt indicates a decreased LV systolic function. dP/dt is calculated as follows:

$$\text{dP/dt (mm Hg/s)} = 32 \text{ mm Hg} \div \text{time (seconds)}$$

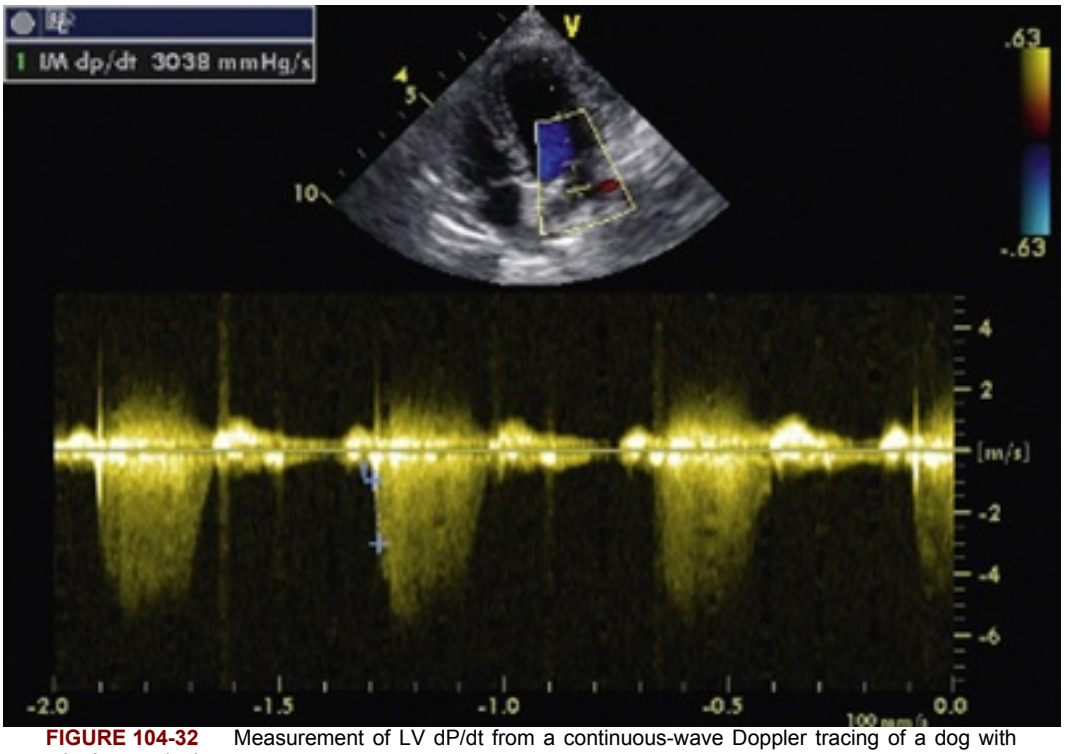


FIGURE 104-32 Measurement of LV dP/dt from a continuous-wave Doppler tracing of a dog with mitral regurgitation.

Diastolic Function

Normal diastolic function allows normal filling of the ventricles. Ventricular diastolic dysfunction implies an abnormality during one or more of the 4 phases of diastole: isovolumic relaxation, rapid ventricular filling, diastasis, and/or atrial contraction. Many echocardiographic techniques have been described to assess diastolic function. Currently in veterinary medicine, Doppler techniques evaluating transmitral flow profiles (E and A waves) and/or pulmonary vein flow profiles (S, D, A waves)[26,43,101-103]; isovolumic relaxation time (IVRT)[26,43,103]; and TDI of the mitral annulus (see above)[36-51] are the most useful in the clinical setting (see Figure 104-20).

Transmitral Flow

This parameter represents the instantaneous diastolic LA to LV pressure gradient (across the MV).[26,43,101-103] In normal animals, peak E wave velocity exceeds peak A wave velocity so E/A ratio >1. In general, when decreased ventricular compliance is present, the velocity during rapid ventricular filling, or E wave, is decreased and the active atrial contraction velocity, or A wave, is increased, making the E/A ratio less than 1—the typical delayed relaxation pattern. Unfortunately, interpretation of abnormal transmitral flow is

sometimes confusing because of a transient pattern called "pseudonormalization," where the E/A ratio seems to normalize while progressive diastolic dysfunction occurs (e.g., feline hypertrophic cardiomyopathy). With pseudonormalization, an increased LA pressure causes early opening of the MV and increased passive filling of the LV (E wave is tall because LA to LV pressure gradient is increased). Also, ventricular pressure rises more rapidly than normal causing the late diastolic LA to LV gradient to be lower than normal, resulting in a smaller A wave. This phenomenon is thought to be transient and occurs when increased LV stiffness has led to elevated LA pressure. However, as LV stiffness and LA pressure continue to rise even further, additional changes in the filling pattern occur, sometimes resulting in a restrictive transmitral flow pattern. Such a *restrictive pattern* is characterized by tall (often >1 m/s) and narrow E waves, and small A waves. Many animals have fast heart rates (>160 beats/min) that result in summation of the E and A waves precluding interpretation of the transmitral flow pattern, although this problem can be corrected in many cats by brief application of pressure to the nasal planum.[104] Pulmonary vein flow patterns and TDI can be used for resolving this limitation.

Pulmonary Vein Flow

Pulmonary vein flow reflects changes in LV compliance and LA and LV filling pressures.[26,43,101-103] Evaluation of pulmonary vein flow typically is performed via the left apical view. The sample volume of the cursor is placed in the pulmonary vein and the PW Doppler flow signal is recorded. Normal pulmonary vein flow profile consists of diastolic (D), systolic (S), and atrial reversal (A or AR) waves (see Figure 104-20).

Unlike conventionally measured transmitral or pulmonary venous flows, TDI is less dependent on preload and minimally affected by LA pressure, and is therefore very useful to further evaluate suspected pseudonormal patterns in particular. Evaluation of diastolic function with TDI often is achieved by placing the sample-gate at the level of the basalmost left ventricular free wall, just adjacent to the mitral annulus. The pattern of myocardial motion is similar, but inverted and lower in velocity, compared to conventional transmitral flow (see Figure 104-27).

Isovolumic Relaxation Time (IVRT)

IVRT is the time interval between aortic valve closure and mitral valve opening.[26,43,101-103] Impaired ventricular relaxation causes prolongation of IVRT, whereas decreased ventricular compliance and elevated ventricular filling pressures are associated with a shortened IVRT. IVRT is determined from a left apical four-chamber view. Using PW Doppler, a sample volume is positioned midway between the aortic and mitral valves to simultaneously record both the aortic outflow and mitral inflow (Figure 104-33). IVRT is the time (*x* axis) from the end of the aortic flow envelope to the beginning of the adjacent mitral flow envelope. It is known to increase with age and decrease with a faster heart rate. The reference interval for IVRT in healthy dogs and cats is 41-65 ms and 36-54 ms, respectively.

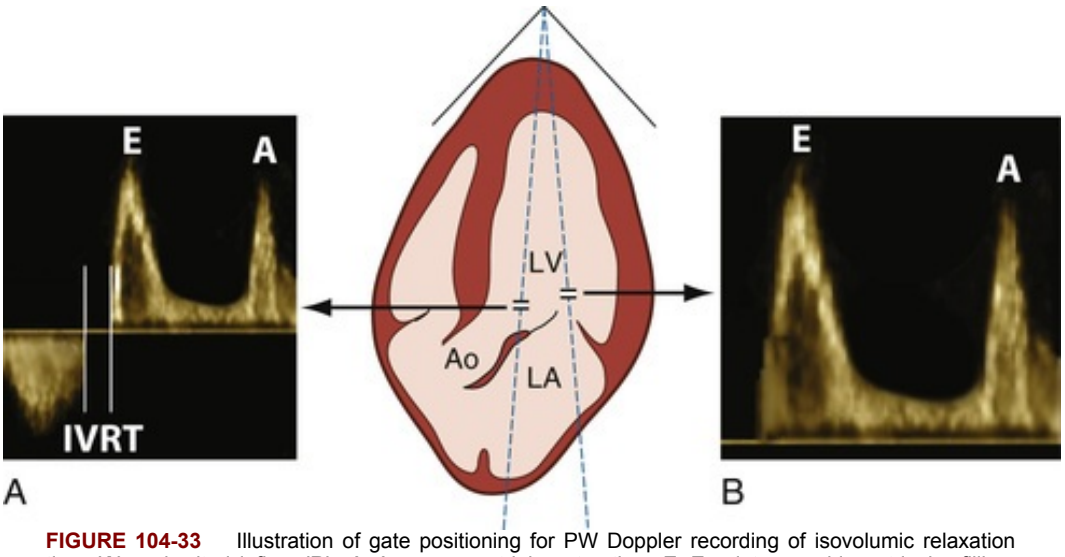


FIGURE 104-33 Illustration of gate positioning for PW Doppler recording of isovolumic relaxation time **(A)** and mitral inflow **(B).** *A,* A wave or atrial contraction; *E,* E-point or rapid ventricular filling; *IVRT,* isovolumic relaxation time.

Assessment of Global Cardiac Function

Myocardial Performance Index (MPI) or Tei Index

The MPI or Tei index reflects global myocardial function and includes both diastolic and systolic time intervals. It correlates well with both systolic and diastolic function of the right and left ventricles in dogs and is used for assessing overall cardiac function.[100,105,106] In animals, the Tei index can be used to identify subclinical dilated cardiomyopathy, or global dysfunction associated with valvular regurgitation and pulmonary hypertension. It can also be measured by TDI. The Tei index, a unitless value, is calculated as follows:

$$\text{MPI} = (\text{IVRT} + \text{IVCT})/\text{LVET} = (\text{MCO} - \text{LVET})/\text{LVET}$$

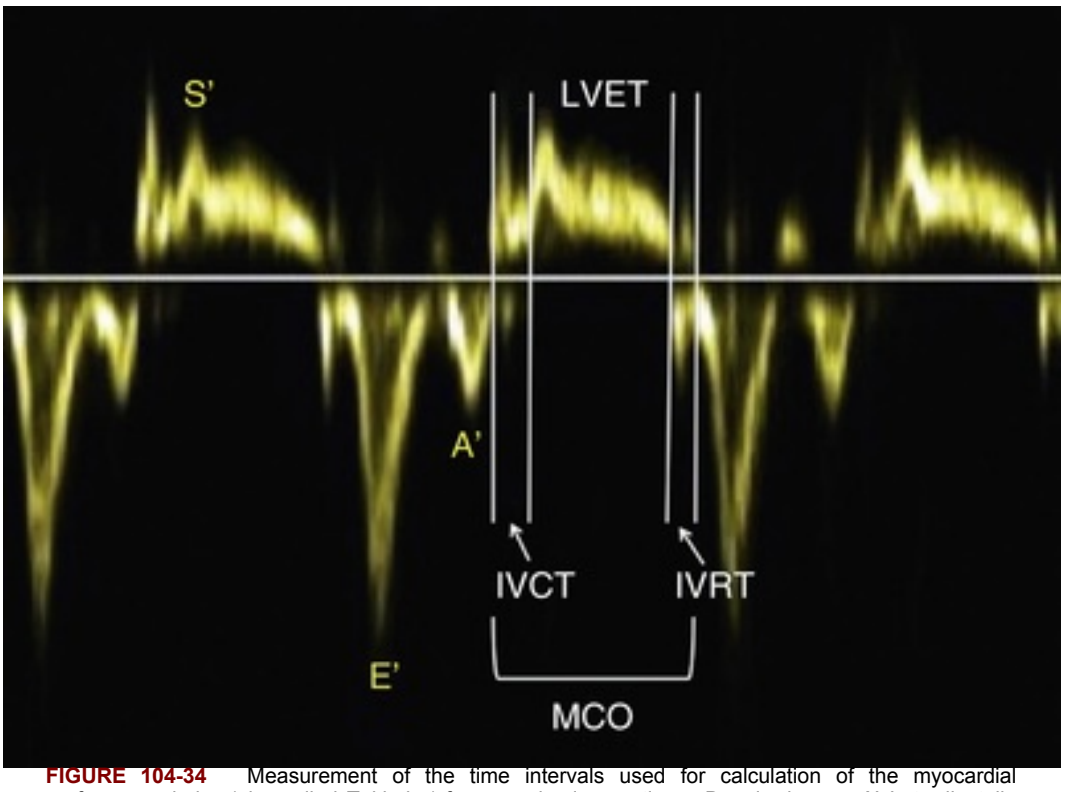


FIGURE 104-34 Measurement of the time intervals used for calculation of the myocardial performance index (also called *Tei index*) from a pulsed-wave tissue Doppler image. *A'*, Late diastolic myocardial motion; *E'*, early diastolic myocardial motion; *IVCT*, isovolumic contraction time; *IVRT*, isovolumic relaxation time; *LVET*, left ventricular ejection time; *MCO*, mitral closure to opening; *S'*, systolic myocardial motion.

where MCO is the time from mitral valve closure to reopening, i.e., from mitral valve closure in one heartbeat to mitral valve opening in the next heartbeat. Reference intervals for MPI are 0.38 ± 0.1 for dogs weighing 3-15 kg; 0.41 ± 0.1 for dogs weighing 15.1-35 kg; and 0.45 ± 0.1 for dogs weighing 35.1-55 kg.

E-TABLE 104-8

Tips to Optimize Echocardiographic Imaging in Small Animals

SITUATION	TIPS
To obtain the right parasternal long-axis view	The dot on the probe should point toward the shoulder of the animal

To obtain the right parasternal short-axis view	The dot on the probe should point toward the elbow of the animal
Structures from the right side of the heart are difficult to image	Image the right side of the heart from the left parasternal location
A specific cardiac structure is difficult to visualize	Remember the 3 ways to move the probe: sliding, tilting, and twisting
For the right parasternal location on brachycephalic breeds	The probe should be positioned closer to the sternum in comparison to other breeds
Unable to optimize the imaging of one extremity of the heart (apex or base)	Slide one intercostal space cranially or caudally
Horizontal lines with a hazy image are observed	Add some coupling gel to improve poor transducer contact
Decreased resolution of the structures in the lateral field	Decrease the overall gain
Poor near-field resolution/image quality in very small patients	Change to a higher frequency probe

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Renal/Urinary/Prostatic

OUTLINE

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CHAPTER 105

Urine Collection

Amanda Callens, Joseph W. Bartges

This chapter is enhanced with the following electronic assets at **ExpertConsult.com:** 4 Videos.

Background

Urinalysis is an integral component of a minimum database, along with complete blood cell counts and blood chemistry evaluation (see ch. 72). In some patients, urine culture is indicated in addition to or after review of the analysis. As with any sample evaluation, urine collection method can influence results.[1,2] It is imperative that urine samples be collected and handled properly for accurate results and to protect patients from traumatic complications or nosocomial infections by using good technique. There are several collection methods available to obtain urine from a patient including voiding, transurethral catheterization, and cystocentesis.

Collection Methods

Voiding

Methods and Containers

"Free catch" of naturally voided urine is commonly used to collect samples for analysis and is easy to do in most male dogs. A container lid is easy for most owners to use when collecting urine from female dogs: first slide the lid under the dog when she begins to urinate, collect 5-10 cc (1-2 teaspoons), pour the lid contents into the container and close. With these methods, one gains not only a urine sample for analysis, but one also has the opportunity to watch the patient urinate and determine if the process appears normal or abnormal. For indoor cats, one straightforward method is to place the cat in a room overnight that has a litter box with non-absorbable litter or a box from which most litter has been removed, leaving enough for scratching but not enough for absorption. The following morning, urine can be poured into a container. Disposable, sterile, inexpensive containers with tight fitting lids are available and help in good sample management. When an owner obtains a free catch sample from a dog or cat, use of improvised containers is discouraged as they may contain contaminants that alter results. Use of a sterile collection container does not ensure sterility as it is not a closed system. Use of transparent containers can be helpful in assessing color and turbidity.

Manual compression of the bladder also should result in urine flow, allowing easy collection. A consistent method is to palpate and isolate the bladder. Then, one should place moderate-but-firm pressure over as much of the bladder as possible. This is easiest when the bladder can be placed in one hand, as can be done with most cats. Both hands may be needed for either gender of either species. Hard pressure, intermittent or continuous, should be avoided.[3]

Advantages

The advantage of collecting naturally voided urine is that it is not associated with any patient risk. When free catch collection methods are used, urine flows through the distal urethra, genital tract, hair, and skin. These areas, however, can contaminate the sample with their bacterial populations. Ideally, the urine should be collected mid-stream to decrease these concerns. The risk of harming a dog or cat using manual collection is minimal, but exists as the urinary bladder may be traumatized if excessive pressure is used. Bladder palpation, much less compression, can be difficult to impossible if the bladder contains little or no urine.

Transurethral Urinary Catheter Procedure

Materials and Patient Preparation

A sterile, flexible, rubber urinary catheter similar to or smaller than the diameter of the patient's urethra should be used. In general, feline patients tend to be more difficult to catheterize than canine patients and females are more difficult than males. As veterinary patients vary greatly in size and cooperation, equipment and technique varies as well. The French (Fr) measurement scale is most commonly used in determining the diameter of catheters. Each unit in Fr is equal to $\frac{1}{3}$ mm. To convert the Fr size into millimeters divide the Fr size by three. In cats, a 3.5- or 5-Fr catheter is often used; in dogs, a 5- or 8-Fr catheter is usually appropriate. Catheters can have single or multiple fenestrations, or "eyes." These fenestrations are present to enable urine flow from the bladder. Flared-end catheters are preferred; otherwise, the catheter may migrate into the urethra.

Before placing any catheter through the urethra, cleanse the area around the catheter insertion site with water and germicidal soap. The soapy solution should be rinsed completely before catheterization, as it can alter analysis results. Soapy contamination may result in a cloudy appearance to the urine as well as causing cell lysis, bacterial inhibition, and enzymatic changes. If there are copious amounts of fur, clip the hair before cleaning.[4]

Catheter Placement

When placing the catheter, it is important to estimate the length of the urethra from the distal urethral orifice to the caudal aspect of the bladder. This length should be mentally noted on the catheter to avoid overinsertion. Overinsertion may cause damage to the bladder mucosa where the tip and/or body of the catheter rub on the bladder wall, causing abrasion. Rarely, catheters have tied a knot within the bladder after too much length was inserted, requiring surgical removal. The use of a stylet may be necessary with less rigid catheters, being inserted into the catheter lumen to increase rigidity. It is easier to insert a catheter with a stylet in place. Some catheters come with a stylet pre-placed and others require a separately sterilized stylet. The catheter should be coated with a sterile water-based lubricant before being inserted into the urethra. Proper lubrication improves patient comfort and compliance, and facilitates insertion by decreasing resistance from surrounding tissue while minimizing trauma.

It is important to maintain clean technique throughout the catheterization process. The catheter should not come in contact with any unsterile objects. Handling of the catheter should be done with sterile gloves after removing it from its sterile packaging, by manipulating the catheter within the sterile packaging (Figure 105-1), or by handling with sterile instruments. If resistance is met while passing a lubricated catheter, it should be removed or gently redirected. The catheter can be reinserted with a gentle rotating motion. Persistent, forceful pressure should not be used. If resistance persists, the diameter of the catheter should be re-evaluated and a smaller diameter catheter employed.

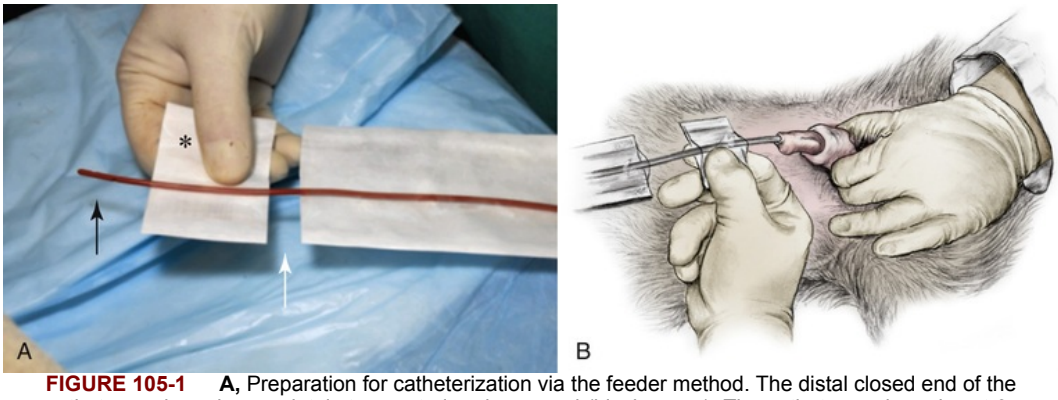

FIGURE 105-1 **A,** Preparation for catheterization via the feeder method. The distal closed end of the catheter package is completely transected and removed (black arrow). The catheter package is cut 3-5 cm from the cut end by making 2 cuts from both sides of the package without cutting the catheter (white arrow). The catheter package tab (asterisk) is then used to feed the catheter. **B,** Urethral catheterization of a male dog. A portion of the catheter's package is used to aseptically advance the catheter through the urethra.

Once the catheter is successfully passed through the urethra into the urinary bladder lumen, it is important to verify proper positioning. Ideally, the catheter should be passed until the "eye" of the catheter is just inside the bladder lumen. This positioning can be verified by passing the catheter while putting gentle negative pressure with a syringe attached to the distal end of the catheter. Once urine is obtained through the catheter and into the syringe, the fenestrated portion of the catheter has reached the bladder lumen.

Risk of Trauma

These methods carry the most risk of trauma and/or iatrogenic bacterial urinary tract infection. However, they are inexpensive and can be done without sedation or anesthesia in most dogs. Cats require sedation or anesthesia, unless obtunded. In this procedure, the catheter tip should always be well lubricated with sterile gel.

Male Dogs—Procedure

Male dogs are typically standing on the floor, standing on a table, or laterally recumbent for catheterization. The os penis in male dogs contains the urethra, which runs within the long axis of the shaft. This bone allows the penis to easily be exteriorized from the sheath and held during cleansing, lubricated catheter insertion and advancement. This procedure is well-tolerated and does not usually require sedation, especially if the clinician purposefully chooses a catheter diameter that is small.

Female Dogs—Procedure

There are numerous methods used for collecting urine from female dogs, two of which are presented here. With the female standing, one may place a gloved and lubricated finger, palm down, into the vaginal vault to gently palpate the urethral opening. Once the urethral papilla is felt, one can pass the catheter along the ventral aspect of the inserted finger using the other hand. As the catheter tip reaches the inserted fingertip, placing gentle downward pressure encourages the catheter to enter the urethra rather than continuing forward in the vaginal vault (Figure 105-2). One may choose to place a vaginal speculum into the vulvar opening to visualize the urethral opening and the catheter entering it (Figure 105-3). Use of a speculum often seems uncomfortable and may not be tolerated without sedation or anesthesia. Use of a speculum risks traumatizing the dog.

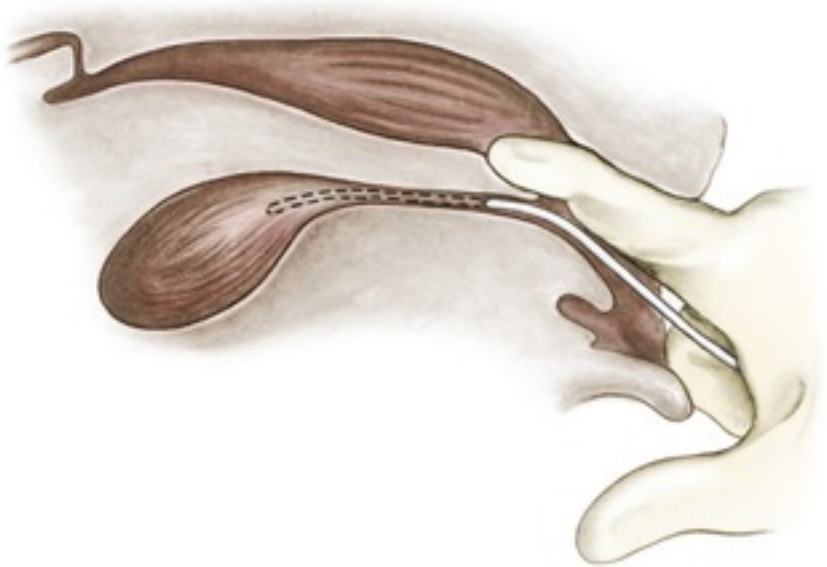

FIGURE 105-2 Urethral catheterization of a female dog. An index finger is placed over the urethral orifice to guide the catheter ventrally into the urethra.

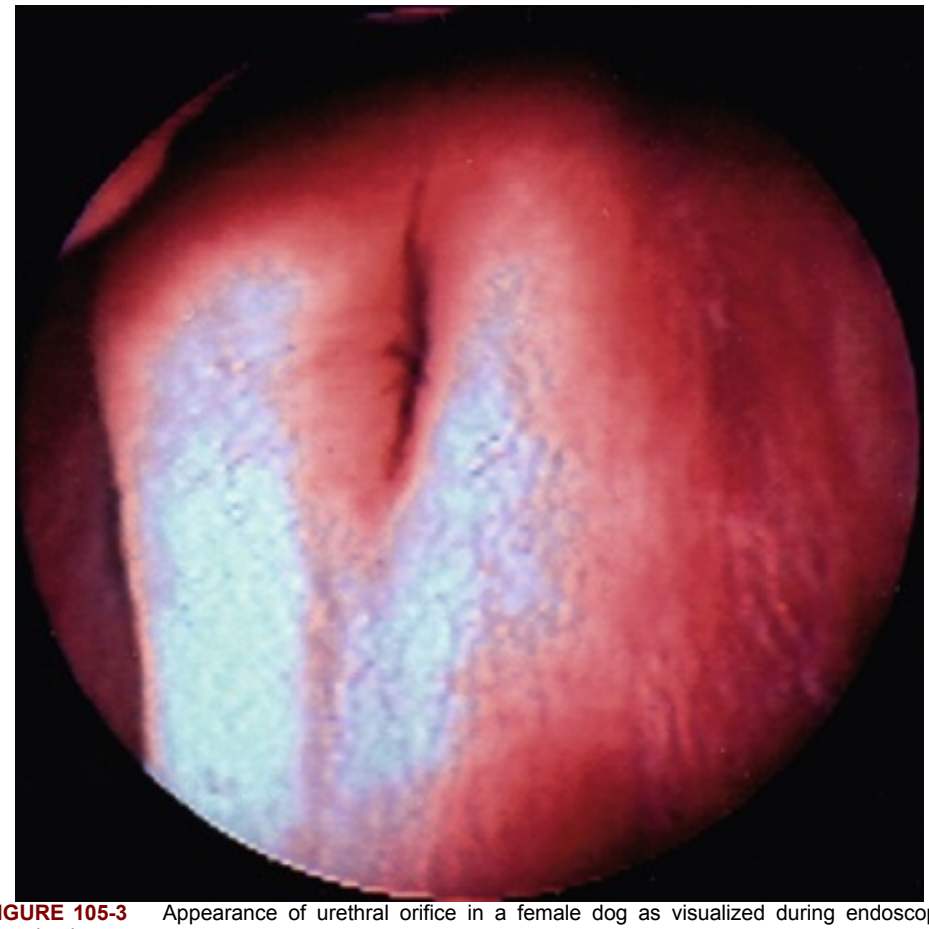

FIGURE 105-3 Appearance of urethral orifice in a female dog as visualized during endoscopic examination.

Cats—Procedure (Videos 105-1, 105-2, 105-3, and 105-4)

It is rare to pass a catheter into the bladder of cats for urinalysis. However, if the urethra is obstructed, knowing how to insert and pass a bladder catheter in cats can be vital (see Video 105-1). In obtunded or anesthetized males, the penis can usually be gently grasped between thumb and index finger, extended caudally to straighten the urethra, and the lubricated catheter gently inserted and advanced to the level of the obstruction or into the bladder (see ch. 107). Passing a catheter in female cats utilizes the same approach as with female dogs. However, cats are so small that this procedure is rarely employed.

Cystocentesis

Definition, Indications, Equipment

Cystocentesis involves percutaneous needle puncture of the urinary bladder for the purpose of removing urine directly via aspiration. Cystocentesis can be performed for diagnostic purposes, such as sample collection for urinalysis or urine culture. Cystocentesis can be employed for therapeutic uses by providing decompression of the urinary tract in cases of obstructive disease. Cystocentesis is usually associated with little risk of iatrogenic complications and is better tolerated than transurethral catheterization. Cystocentesis is the preferred collection method when a sterile urine sample is needed or preferred. The equipment usually employed is a sterile 3 or 6 mL syringe and 22-gauge, 1½ inch needle.

Technique in Cats and Small Dogs

Cystocentesis is best done with cats placed in dorsal recumbency but may be accomplished in lateral recumbency. In dogs it is most commonly performed with the patient in dorsal recumbency or standing (Figure 105-4). The urinary bladder should be localized and immobilized regardless of patient position. The

skin area to be penetrated by the needle should be cleaned with an antiseptic solution. A needle attached to the syringe is inserted through the ventral or lateral abdominal wall. When inserting the needle, it is important to angle the tip from cranial to caudal towards the trigone so that as urine is aspirated and the urinary bladder contracts, it contracts along the needle, minimizing risk of traumatizing the bladder mucosa with the needle tip. While the bladder and needle are immobilized, urine is aspirated into the syringe. Once the desired volume is obtained, aspiration ceases and then the needle is removed.

FIGURE 105-4 Cystocentesis may be performed with the patient in dorsal recumbency, particularly if the procedure is being done when the urinary bladder cannot be palpated. The site for needle insertion is generally at a point midway between the umbilicus and the pelvic brim. Normally, the clinician's left hand would be applying pressure to the abdomen to stabilize the bladder, but the hand is moved away here to improve visualization.

Technique in Large Dogs

In larger dogs, it can be difficult to palpate and immobilize the bladder for cystocentesis. If the bladder is not palpable due to patient size, one can use landmarks to guide the needle. One approach is to visualize the two most caudal pairs of mammary glands and draw lines between the last mammary gland on one side and the second to last gland on the other side and the last mammary gland on the contralateral side with the second to the last gland on the opposite side resulting in an "X." The needle is inserted where the two lines intersect. Ultrasound can be used to guide cystocentesis (see ch. 88 and 143). Ultrasound permits visualization of urinary bladder and needle during the procedure. The patient is positioned in dorsal recumbency and the needle is inserted under the transducer. It is essential to avoid puncturing the transducer. With ultrasound, it is not necessary to palpate the bladder or use landmarks to locate the bladder.

General Protocols

During cystocentesis, the needle should never be redirected when within the abdominal cavity, to avoid traumatizing any intra-abdominal organ. No negative pressure should be applied to the syringe with the plunger while inserting the needle or removing the needle from the abdomen. Constant suction potentiates contamination of the sample, the bladder, the peritoneal cavity, and organs as the needle passes through bowel loops and other abdominal, SC, or dermal structures.

The length of needle inserted varies as required by patient size. For larger patients, it may be necessary to insert the needle to the hub to achieve enough depth to reach the bladder. In smaller patients, it may only be

necessary to insert the needle a short distance. If the needle is inserted and no urine aspirated when negative pressure is applied, one may need to insert the needle further or retract it slightly, depending on patient size and bladder volume. If urine is not obtained on the first try, then the same technique can be used, either cranial or caudal to the first site, being conscious to stay on midline if the patient is in dorsal recumbency. A new sterile needle should be used with each attempt. If urine is not successfully retrieved, it may be necessary to visualize the bladder using ultrasound guidance.

Sample Management

If collected urine is not analyzed immediately, it should be refrigerated to slow degeneration of cells and inhibit bacterial growth (see ch. 72). The amount of time between collection and analysis, as well as refrigerating urine, increases likelihood of crystal formation; therefore, the clinician should take into account these factors when interpreting a urinalysis. If urine is obtained via cystocentesis, the needle must be changed before transferring the sample into a sterile submission vial or container. Failure to replace the used-contaminated needle with one that is new and clean can affect analysis results. If urine is collected for analysis only, a small amount should always be saved in a sterile container and refrigerated, in case the submitted sample demonstrates signs of active inflammation. If inflammatory cells are identified, the stored sample can be submitted for culture and sensitivity testing to rule in or out bacterial infection. Red blood cells may be observed on urinalysis with cystocentesis collection, but this blood is usually inconsequential and in quite small amounts. This blood is often caused by the needle puncturing the bladder and/or skin during collection. Resulting hematuria is usually microscopic and short-lived.

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CHAPTER 106

Management of Urinary Catheters

Amanda Callens, Joseph W. Bartges

Indications

Urethral catheterization may be used for ensuring urethral patency in patients with obstructive disease, for urine drainage away from recumbent dogs or cats, to know the urine volume produced in hospitalized patients, to collect diagnostic samples (see ch. 105), or to perform diagnostic radiographic procedures.[1] Urethral catheter placement in an intensive care setting is commonly used to monitor urine volumes (see section on "ins and outs," below). Closed system collection of urine is most accurate for measuring urine output and best for avoiding infection. Dogs or cats who have recently undergone bladder surgery may have catheters placed to avoid overdistention. In this scenario, the catheter is used to maintain low pressure in the bladder, reducing tension on the suture sites and providing optimal healing conditions. Similarly, patients with recent bladder trauma may benefit from an indwelling urinary catheter.

Urethral obstruction refers to any structural or functional abnormality that impairs normal urine outflow (see ch. 107). Obstruction of urine flow increases pressure within the lower urinary tract, which can damage mucosa and lead to inflammatory cell infiltrates. Prolonged excessive pressure can lead to nerve and detrusor muscle damage. Finally, pressure may extend to the upper urinary tract where glomerular filtration rates decrease and azotemia develops or worsens.[2]

Indwelling Urinary Catheter Care

Preparation and Instrumentation (Videos 106-1 and 106-2)

The goals of urinary catheter care are to maintain patency and decrease likelihood of inducing nosocomial infections.[3] Catheter care begins during placement with clean technique, where avoiding contamination is imperative (see ch. 105). The perivulvar or peripreputial area should be clipped and prepped with antiseptic, such as a 1 : 40 chlorhexidine solution. The area should be washed with diluted chlorhexidine scrub, the vulvar or preputial pouch flushed, and the area cleansed again. Any instruments that might be used for catheter placement should be gathered and, once sterile packets are opened, laid out on a sterile field. In addition to the catheter and a spare (that might be slightly larger or smaller in diameter), one usually needs sterile lubricating gel, a stylet (if need is anticipated), visualization tools, and a syringe containing sterile fluid for balloon inflation, if a Foley catheter is being placed.

Closed Collection Systems (Video 106-3)

Indwelling urinary catheters should be incorporated into a closed collection system. Required materials are catheters, adapters, sterile tubing, and a collection bag. Once the catheter is placed, an adapter should be tightly connected to collection tubing. A tight connection helps avoid leakage from the collection set and decreases likelihood of inadvertent detachment. Once all tubing is connected, a reservoir bag can be secured to the distal end of the system to hold urine until emptied. Sterile pre-packed single-use collection bags with one way valves to prevent urine from refluxing back into the line are available. These bags often contain a drain at the distal end with easy open/close valves. Alternatively, empty IV fluid bags can be used. Used IV bags, however, do not provide the safeguards of purpose-made bags nor should they be considered sterile, if not re-sterilized after use. If traditional IV fluid lines are used for collection tubing, their clamps should either be disabled or removed to avoid unintentional clamping of the line that will obstruct urine outflow.

Securing the System (Video 106-4)

Dogs and cats are likely to remove indwelling catheters if no preventative measures are taken, making it imperative that deterrents be used to prevent a patient from interfering with their indwelling catheter. Securing the catheter at multiple points is recommended through a combination of catheter balloon inflation, suturing, and stress loops on legs or tail to avoid inadvertent removal. The steps taken to secure a catheter in place and to keep the patient from self-removal cannot be overemphasized, as catheter removal often leads to a second round of sedation, additional time, need for a new catheter, unnecessary patient stress, and owner expense.

Personnel

Appropriate maintenance of the catheter and collection system is essential to maintain patency, decrease risk of infection, and prevent self-removal. Catheter care protocols should ensure constant appropriate monitoring and care. Personnel should be certified for being able to provide consistent appropriate care.

Monitoring and Care

It is important to always wash one's hands and don disposable gloves before handling urinary catheters and lines to protect patients and personnel from contamination during examination. Gloves should be changed if they become soiled. New gloves should be used with each patient. The collection bag and tubing should be placed at a level lower than the patient to encourage urine drainage. This decreases the likelihood of backflow or stagnant urine within lines. Urine pooling in collection lines can lead to sediment buildup and occlusion. Avoid placing the collection bag and/or tubing on floors.

All connections should be checked and secured frequently. When urethral diameter is larger than catheter diameter, leakage will be noted at the catheter insertion site. In this case, the catheter should be replaced with a larger size. If leakage is noted at a connection site, those sites should be cleaned and tightened. Catheter and collection system cleanliness must be maintained by periodically wiping down the lines with antiseptic solution. Skin around the catheter should be gently cleaned and monitored for signs of infection. Urine volumes should not be measured using marks on a reservoir, as this is unreliable. Instead, the urine should be poured into a measuring beaker for an accurate volume reading. Tracking volume of urine produced is imperative. Urine should be assessed for appearance every 2 to 4 hours. At this time, the collection bag should be emptied and volume recorded. Normal urine output is about 1-2 mL/kg/h or more depending on fluid rates and the cause for illness.

Complications

A patient with an indwelling urinary catheter should have an empty bladder that is flaccid. If a large bladder is palpated, it must be addressed immediately. Occlusion can result if flocculent material gathers in the catheter or collection system. To rule out an occluded system, the catheter can be flushed with 5-10 mL sterile saline. This volume should easily flow into the catheter and be easily retrieved. If the saline does not flow easily, then the catheter is kinked or occluded and must be removed. If urine flows easily into the catheter, but cannot be aspirated, then the catheter position is likely inappropriate; most commonly, the catheter has migrated caudally from the bladder into the urethral lumen. This will allow fluid to be flushed in but not retrieved.

An empty collection bag at the end of any checkpoint may be a serious concern, indicating either a problem with the collection system or failure to produce urine. Immediate attention should be given to such patients. If catheter location is in question, abdominal radiography or ultrasonography can help visualize the catheter and verify its location. A catheter that has migrated distally into the urethra should never be reinserted, as bacteria and debris may have accumulated at the catheter tip. Migrated catheters should be replaced. Occlusions distal to the catheter can be identified by flushing saline into the collection system, away from the patient. If saline cannot be flushed, then the collection system should be replaced. If lines are kinked, the occlusion must be resolved. If an area is likely to re-occlude (re-kink), that catheter and/or tubing should be replaced or repositioned. If lines become loose or disconnected, they should be re-secured and, if there is a defect, replaced.

Catheter-Associated Urinary Tract Infection

Catheter-induced bacterial urinary tract infections (UTI) are common (see ch. 330). Bacteria may migrate along the outside or through the lumen of any catheter. There is an increased risk of bacterial UTI with pre-

existing urinary tract disease or with urothelial damage. Bacterial UTI occurs in >50% of animals with an indwelling urethral catheter for 4 days.[3] Systemic antibiotic therapy, while an indwelling catheter is in place, decreases frequency of bacterial UTI; however, when bacterial UTI occurs, the organisms exhibit a greater degree of antimicrobial resistance. Therefore, prophylactic antibiotic therapy for patients with an indwelling urinary catheter is NOT recommended. Antibiotics should only be given in patients with indwelling urinary catheters if infection is present.

Infection monitoring includes temperature checks and submitting urine for culture and sensitivity testing, if indicated. Patients with indwelling urinary catheters should be observed closely for development of fever, pyuria, or discomfort. Catheters can remain in place as long as signs of infection (fever, purulent discharge, odor) are not observed. However, since urinary catheters are invasive and carry risk of infection, they should be removed as soon as indicated.

Urinary tract infection may occur if bacteria are introduced during catheterization. Risk of iatrogenic infection increases with various issues, including the following: if the urinary tract is traumatized, when aseptic technique is not used, in the presence of vaginal or preputial discharge, with immunosuppressed patients, and after repeated catheterizations. Trauma leading to infection can be induced if too much force is applied during catheterization, inadequate lubrication is applied, or urethral obstruction was present at time of catheterization.

Monitoring "Ins & Outs"

Monitoring fluid volumes, both intake and outflow, can be vital for critically ill patients, especially those with conditions associated with rapid dehydration or at risk for fluid overload. Fluid volumes "in" include IV fluids, parenteral nutrition, and enteral water intake. Fluid volumes "out" include urine output, vomitus, and estimates of loose or watery stool volumes. Together, these are known as the "ins and outs."

Patients with renal insufficiency represent an excellent example of a clinical condition in which knowing ins and outs is imperative because overhydration is common and consequences are worrisome. By measuring fluid losses, an appropriate volume can be replaced, avoiding over-hydration. In pets with polyuric renal failure, dehydration is a risk because of their inability to concentrate urine. One can match ins and outs by replacing the volume out in one time period with the volume "in" in the next (see ch. 129, 322, and 324). Any dog or cat receiving high fluid rates should have ins and outs monitored. These patients must be monitored closely for signs of fluid overload.

Urine output volume should never be zero. If no urine is noted the collection system and the bladder size should immediately be assessed. Possible issues leading to an empty urine collection bag include occlusion within the system, a leak between connections in the system, or a displaced catheter. If the urine output is in fact zero then oligoanuria may be occurring and should be addressed immediately (see ch. 322).

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CHAPTER 107

Unblocking of the Urethra

Jody P. Lulich, Carl A. Osborne

Overview

A variety of methods exists for unobstructing the urethra. However, safely restoring urine flow without causing trauma to the urinary tract requires stabilizing the patient, knowing the underlying cause, selecting anesthetic protocols that completely relax the urethra, employing a gentle and cautious technique, and incorporating appropriate aftercare.

Patient Management

Prior to unobstructing the urethra, it is important to ensure that the patient is sufficiently stable to undergo anesthesia. Complete urethral relaxation is usually essential to clear an obstruction. Most dogs and cats with a urethral obstruction are metabolically stable. However, about 15% of obstructed cats and fewer dogs require therapy for hyperkalemia, hypocalcemia, hypothermia, acidosis, dehydration, and/or azotemia (Table 107-1). An IV access line should be placed in all patients to administer fluids, anesthetics, electrolytes, etc.

TABLE 107-1

Minimizing Metabolic Consequences of Urethral Obstruction

CONSEQUENCE	INDICATIONS TO TREAT	THERAPY
Hypothermia (see ch. 49)	Core temperature <99° F (<37.2° C) or cardiac decompensation	Heating pad Heat lamps Infuse only warm saline into the bladder
Hypovolemia (see ch. 127 and 129)	Azotemia Cardiovascular collapse	Replace deficits in 2 to 12 hours with 0.9% saline Consider an initial bolus of fluids to rapidly correct hypovolemia if needed (10 to 30 mL/kg) Although saline has been recommended because patients are often hyperkalemic, any balanced replacement electrolyte solution will help
Azotemia	If serum creatinine is greater than 3 mg/dL	Replace fluid deficits with balanced electrolyte solutions Decompressive cystocentesis to promote renal excretion
Acidemia (see ch. 128)	If blood pH <7.1-7.2	Administer ⅓ to ½ of the dose of $NaHCO_3$ (0.3 × BW in kg × base deficit) administered over 15 min. Rapid or excessive administration of bicarbonate may exacerbate hypocalcemia. Fluid administration to correct hypovolemia Decompressive cystocentesis to promote renal excretion
Hyperkalemia (see ch. 68)	Weakness or shock due to cardiovascular depression	To promote potassium excretion: 1. Decompressive cystocentesis 2. Fluid administration with potassium-sparing fluids To promote intracellular translocation of potassium, consider one of the following: Correct metabolic acidosis with sodium bicarbonate (mmol = ⅓ [0.3 × BW in kg × base deficit]) or

		Administer 0.1 U/kg regular insulin IV with 1 gram of glucose per unit of insulin administered To antagonize adverse cardiac effects: 50 to 100 mg/kg calcium gluconate slow (2-5 min) IV Concomitant hypocalcemia and acidemia contribute to worsened heart function
Hypocalcemia (see ch. 69)	Hypocalcemic tetany or hyperkalemic cardiac decompensation	50 to 100 mg/kg calcium gluconate slow (2 to 5 min) IV with cardiac monitoring

Determining the Cause

Knowing the cause of an obstructed urethra is essential in planning to re-establish urine flow and prevent re-obstruction. For example, cats with calcium oxalate urethroliths should have the stone flushed into the urinary bladder immediately, followed by minimally-invasive or surgical removal (see ch. 124). To achieve this level of coordinated care, survey radiography prior to urethral clearance is essential. While urethroscopy is accurate for verifying, localizing and determining cause of an obstruction (see ch. 108), it can be technically challenging and cumbersome during an emergency.

Clinical signs of dysuria are similar, regardless of whether or not a patient has urethral obstruction. Therefore, one must verify an obstruction prior to urethral catheterization. Use of urethral catheterization to diagnose obstruction may not be reliable and carries the risk of iatrogenic perforation. Likewise, inability to manually express the urinary bladder can be misleading and dangerous (i.e., rupture). If feasible, evaluation of the urinary tract should include external palpation of perineum and distal urethra, rectal palpation of urethra and pelvic canal, and evaluation of perineal reflexes, tail reflex and hind limb proprioception. Consider observing attempts at voiding urine followed by assessment of bladder size (e.g., survey abdominal radiography, ultrasonography). Small bladders are consistent with pollakiuria. A large bladder is consistent with urethral obstruction. Survey abdominal radiographs provide a global assessment of the urinary tract, verify bladder size, and may allow visualization of radiodense objects within the entire urinary system, but specifically within the urethral lumen. In some scenarios, antegrade or retrograde contrast urethrography is indicated.

Anesthesia

Since the urethra is highly innervated, it can be one of the most difficult areas to successfully anesthetize. To avoid iatrogenic urethral trauma, complete urethral relaxation and analgesia are necessary. Type and degree of sedation/anesthesia vary depending on patient status and veterinarian preference, but for complete urethral relaxation a combination of systemic and local anesthetics (i.e., lumbar or caudal epidural) are recommended. On occasion, complete urethral relaxation will be sufficient for a urethral plug to pass. It has been suggested that unobstructing moribund cats be attempted without sedation, using only intraluminal instillation of a local anesthetic agent (e.g., lidocaine) or with an epidural. However, initial stabilization (e.g., decompressive cystocentesis, IV fluids) followed by a balanced anesthetic protocol is recommended. Adding local anesthetics to flushing solutions is not effective because there is not sufficient contact time nor drug concentration to anesthetize the urethral mucosa. Use of anesthetics that may increase urethral tone should be avoided; for example, dexmedetomidine, a relatively selective alpha 2-adrenergic agonist, may stimulate alpha-1 adrenergic receptors, induce constriction of the proximal urethra and impede urethral clearance.

Unobstructing the Feline Urethra

Overview

Several techniques can be employed for removing an intraluminal urethral obstruction. Technique selection should be based on underlying cause, need/willingness to perform decompressive cystocentesis, and severity of life-threatening metabolic abnormalities (Table 107-2). To minimize urethral trauma, one should never use a catheter to force or push luminal contents; rather, the catheter is the vehicle through which one can use flushes of fluid to dilate the urethra and propel luminal contents out. To do this, one should assemble an open-ended urethral catheter (e.g., olive tipped, tomcat), IV extension tubing, and a saline-filled syringe (Figure 107-1, Video 107-1). The IV tubing allows one person to extend the urethra and carefully advance the catheter while an assistant manages the syringe when flushing is indicated. Scenarios are invariably

encountered in which the clinician without assistance must attempt to unblock a urethra. We still recommend attaching IV extension tubing between the catheter and syringe. If the syringe and catheter are connected directly, it becomes difficult to empty the syringe without inadvertently forcing the catheter further into the urethra and sometimes through the urethral wall.[1] Remember that small syringes provide greater flushing force than larger ones. There are four techniques to unobstruct the feline urethra. We have the greatest success using retrograde flushing while occluding the distal urethral orifice (the second procedure listed below).

TABLE 107-2

Characteristics of Methods to Relieve Urethral Obstruction in Male Cats

PROCEDURE	RETROGRADE FLUSHING WITHOUT URETHRAL OCCLUSION	RETROGRADE FLUSHING WITH URETHRAL OCCLUSION	ANTEGRADE EXPULSION VIA URINARY BLADDER EXPRESSION	ANTEGRADE EXPULSION VIA PHARMACOLOGIC MANIPULATION
Indications	• Matrix crystalline plugs • Blood clots	• Matrix crystalline plugs • Urethroliths • Blood clots • Solid foreign material	• Matrix crystalline plugs • Blood clots • Mural edema or inflammation • Urethral spasm	• Matrix crystalline plugs • Blood clots • Mural edema or inflammation • Urethral spasm
Contraindications	Inadequate anesthesia	Inadequate anesthesia	• Urethroliths • Inadequate anesthesia • Solid foreign material	• Urethroliths • Solid foreign material
Analgesia or sedation	Consider	Consider	Consider	Yes
Anesthesia	Yes	Yes	Yes	Not applicable
Decompressive cystocentesis	Not necessary	Yes	No	Yes, multiple
Potential advantages	• No need for cystocentesis • Rapid reversal of azotemia	• Very successful • Rapid reversal of azotemia	• Avoid iatrogenic urethral trauma • Reduced cost • Plug is flushed out	• Avoid iatrogenic urethral trauma • Reduced cost
Potential disadvantages	Urethral trauma or inflammation	Urethral trauma or inflammation	• Bladder rupture, uroabdomen, or hemoabdomen • Poor success	• Bladder trauma, uroabdomen, or hemoabdomen • New technique, requiring further validation

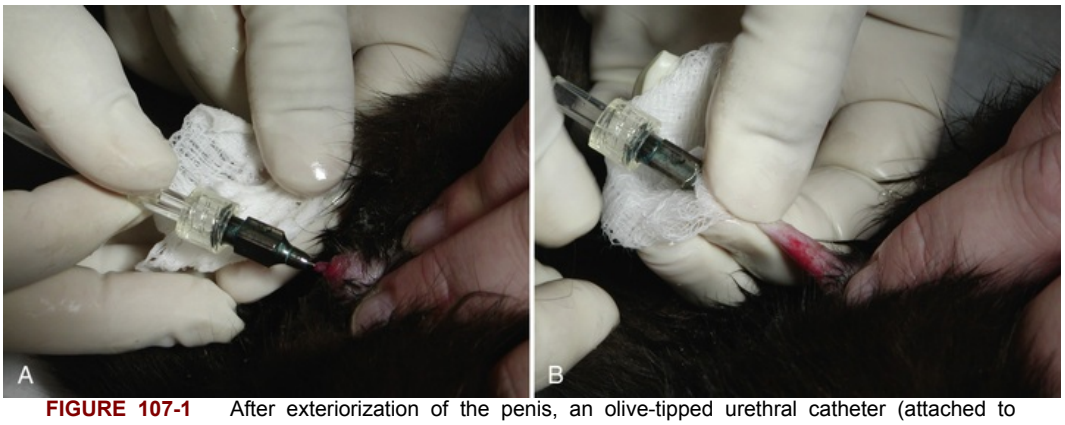

FIGURE 107-1 After exteriorization of the penis, an olive-tipped urethral catheter (attached to

intravenous extension tubing) is inserted into the distal urethral lumen (**A,** Video 107-1). Using a moistened gauze sponge, the distal urethral lumen is occluded around the shaft of the urinary catheter with the thumb and first finger; the urethra is pulled caudally to eliminate the urethral flexure **(B).** To clear the urethra, saline is flushed in a retrograde direction through the extension tubing, urethral catheter and urethral lumen into the urinary bladder.

Retrograde Flushing without Decompressive Cystocentesis or Occluding the Distal Urethra

1. Gently massage the distal urethra by rolling it between your thumb and forefinger with the goal of disrupting the continuity of any urethral plug. Exteriorizing the penis will facilitate this process.
2. Assemble the urethral catheter, IV extension tubing, and large (20 to 60 mL) saline-filled syringe. Evacuate air from the lines by flushing saline through the assembled apparatus.
3. Exteriorize the penis, pulling gently caudally and dorsally (i.e., parallel with the vertebral column).
4. Without excessive force, slowly insert the tip of the urinary catheter into the urethra and advance the catheter to the site of obstruction.
5. While keeping the penis exteriorized and extended caudally (usually accomplished by pulling the prepuce caudally), flush large quantities of physiologic saline into the urethral lumen, allowing it to reflux back out of the external urethral orifice with pieces of the plug. As the plug disrupts, advance the catheter slowly toward the urinary bladder.
6. When the tip of the catheter reaches the urinary bladder, empty the bladder through the catheter.

Retrograde Flushing with Occlusion of the Distal Urethral Orifice (see Video 107-1)

1. Perform decompressive cystocentesis, if needed, using a 22-gauge, 1.5-inch needle attached to IV extension tubing, 3-way stop-cock and syringe. Most but not all urine should be removed.
2. Select an olive-tip urethral catheter (or other suitable catheter) to flush fluid into the urethra. Assemble the urethral catheter, IV extension tubing, and small syringe (3 to 12 mL) filled with normal saline. Evacuate air from lines by flushing saline through the apparatus.
3. Exteriorize the penis caudally and dorsally (i.e., parallel with the vertebral column).
4. Without using excessive force, slowly insert the tip of the urinary catheter into the urethra and advance the catheter toward the site of obstruction.
5. With the catheter in place, occlude the urethra around the catheter shaft using your first finger and thumb. Placing a moistened gauze sponge or pad between the urethra and your fingers will minimize trauma to the surface of the urethra.
6. Extend the urethra caudally and dorsally while an assistant presses the syringe plunger to flush urethral contents into the urinary bladder. By preventing reflux of solutions out of the external urethral orifice, this maneuver dilates the urethra, releasing the plug, and allowing it to flow into the urinary bladder. Additional flushing may be needed to completely clear the urethra. To avoid overdistension of the urinary bladder, use small volumes (e.g., 6 mL) of saline to flush. Repeat the decompressive cystocentesis as needed.
7. Once the urethral lumen is cleared, advance a longer catheter slowly toward the urinary bladder. Empty the bladder.

Antegrade Evacuation via Bladder Compression

1. Massage the distal urethra by rolling it between your thumb and forefinger with the goal of disrupting the continuity of any urethral plug. Exteriorizing the penis will facilitate this process. The plug can also be disrupted by flushing large quantities of saline into the urethra (see retrograde flushing without occluding the distal urethra for this technique).
2. Ensure that the plane of anesthesia is deep and the urethra completely relaxed (see Video 107-1). Provide steady, but not excessive, manual pressure on the urinary bladder to evacuate the plug. Avoid excessive bladder pressure because it may result in trauma, reflux of potentially infected urine into the ureters, and/or rupture the bladder wall.

Antegrade Evacuation via Pharmacologic Relaxation of the Urethra[2]

1. Administer buprenorphine (0.01 mg/kg or 0.075 mg/cat) IM q 8 h and acepromazine (0.25 mg/cat) IM q 8 h. In one study, cats were also given 0.1 mg medetomidine IM q 24 h.
2. Some also advocate placing cats in a dark, quiet environment to minimize stimulation.
3. Perform decompressive cystocentesis as needed to keep bladder small (at least three times a day).
4. Cats are expected to begin urinating within 3 days. If unsuccessful, reassess the diagnosis and the need to select another method of clearing the urethra.

Unobstructing the Canine Urethra

Overview

Although urethral plugs have been reported in dogs, the most common cause for intraluminal urethral obstruction in male dogs is urethrolithiasis and in older females it is urethral neoplasia. Retrograde urohydropropulsion with urethral occlusion is recommended to clear the urethra of uroliths.[3] As with the cat, complete urethral anesthesia is essential for success without harming the urethral lining.

Technique

1. Perform decompressive cystocentesis, if needed, using a 22-gauge, 1.5-inch needle attached to IV extension tubing, 3-way stopcock and syringe. Most, but not all urine should be removed.
2. Fill one 6 mL syringe with 3 mL of saline and another 6 mL syringe with 3 mL of sterile water-soluble lubricant. Attach these two syringes with a 3-way stopcock. Mix the contents of both syringes together by emptying one syringe into the other several times. After inserting a urethral catheter into the tip of the dog's penis, inject 3 to 6 mL of the mixture to lubricate around the urethrolith(s).
3. To flush uroliths into the urinary bladder, insert a large bore flexible catheter into the distal end of the urethra.
4. Have an assistant insert his or her gloved finger into the rectum. Press ventrally on the pelvic floor to occlude the pelvic urethra between your finger and the floor of the pelvis.
5. Using your thumb and first finger, occlude the distal urethral orifice around the shaft of the flexible catheter. Placing a moistened gauze sponge between the urethra and your fingers will minimize trauma to the surface of the urethra and provide a more secure occlusion.
6. Fill a large syringe (e.g., 20 to 60 mL) with sterile isotonic solution (e.g., saline, LRS, etc.). Never flush more than 50% to 75% of the estimated bladder capacity (normal bladder capacity is about 8-10 mL/kg BW).
7. Firmly attach syringe and catheter; turn the syringe upside down so that the plunger is on top of the table. Hold the syringe by the barrel and empty the syringe forcefully by using your body weight to press the plunger down.
8. Once the pelvic urethra dilates, occlusion of the pelvic urethra is released while fluid is continually flushed through the urethra, propelling urethroliths into the urinary bladder.
9. In the majority of cases, uroliths can be successfully flushed into the bladder without intraurethral lubrication or pelvic urethral occlusion (steps 2, 4, and 8).

Post-Obstruction Care

After the urethra has been unblocked, additional care may be needed to prevent re-obstruction and further stabilize the patient (Table 107-3). If urethral clearance is not successful or perineal edema develops, consider contrast urethrocystography to determine the cause. If the urethra has been unobstructed recently (2 weeks to 2 months), urethral tear and subsequent strictures are common, often requiring repeated dilation (see ch. 124) or surgical intervention (e.g., urethrostomy).

TABLE 107-3

Patient Management Strategies Following Relief of a Urethral Obstruction

CONSEQUENCE	INDICATION TO TREAT	THERAPY
Urethral swelling	Poor urine stream, azotemia	Indwelling transurethral catheterization is commonly performed in cats When indicated, 3 to 5 Fr flexible urinary catheters composed of material that

		minimizes foreign body inflammatory reactions are preferred Catheters will need to be secured in place and preferably connected to a closed collection system In most cases catheters can be removed in 1 to 2 days
Residual plug precipitates and urine debris	Poor urine stream	Intravenous or subcutaneous fluid therapy can be used to increase urine output, dilute precipitate concentration, and increase their evacuation during voiding Using a transurethral catheter, gently fill and remove instilled saline. Be careful not to cause additional trauma or over-distend the bladder. Most urethral plugs in cats and dogs are composed of struvite. Consider foods to dissolve and prevent struvite as soon as severe metabolic consequences of obstruction (e.g., azotemia, acidemia, hyperkalemia) abate.[4]
Urethral spasm	Poor urine stream	Primarily a concern in cats The diagnosis is based on conjecture To relax the proximal urethra (smooth muscle): phenoxybenzamine 2.5 to 7.5 mg/cat PO q 12 to 24 h or prazosin 0.25 to 0.5 mg/cat PO q 12 to 24 h To relax the distal urethra (skeletal muscle): diazepam 1-2.5 mg/cat PO q 8 h or dantrolene 0.5 to 2 mg/kg PO q 12 h To relax proximal and distal urethra: Acepromazine 1.1 to 2.2 mg/kg PO q 12-24 h
Pain (see ch. 126)	Vocalization, excessive licking of genital area, irritable demeanor, difficult unobstruction	Consider pain medications that are unlikely to cause additional disease. Use of non-steroidal anti-inflammatory drugs in dehydrated (e.g., post-obstructive diuresis) and hypotensive (e.g., prazosin or acepromazine administration) conditions is contraindicated. Consider opioids and other safer drugs.
Post-obstructive diuresis	Anticipate post-obstructive diuresis in all patients that develop azotemia (e.g., creatinine >4 mg/dL)	The quantity of fluid lost is variable and sometimes profound Adjust fluid replacement rate based on clinical signs, perfusion parameters, body weight and/or urine output For every gram of body weight lost, consider replacing it with 1 mL of a balanced electrolyte solution
Detrusor atony	Should be anticipated in patients with extensive and prolonged bladder distension	Extended (2 to 5 days) transurethral indwelling catheterization is best Drugs to relax the urethra are listed above Drugs to promote bladder contraction: bethanechol 5 to 15 mg/dog PO q 8 h or 1.25 to 5 mg/cat PO q 8 h Manually express the urinary bladder 3 to 5 times a day. Do not express the bladder unless the cause of obstruction has been resolved and the patient is comfortable.
Urinary tract infection (see ch. 330)	Urinary instrumentation/catheterization	In patients without systemic or renal infection, consider prophylactic antimicrobials for 1 to 3 days after removal of short-term urinary catheters. Antimicrobials may need to be administered longer if the urinary tract is likely to remain damaged or take longer to recover. With confirmed infections, antimicrobial selection should be based on culture and susceptibility results and administered for a minimum of 7-10 days
Hypokalemia (see ch. 68)	Serum potassium levels below 3.0 mEq/L (3.0 mmol/L)	Supplement intravenous fluids with potassium chloride in those patients undergoing profound diuresis. Resume nutrition as soon as possible.
Anemia (see ch. 135)	The need for blood is rare. Hematocrits less than 13-15% or clinical signs of anemia (e.g., hyperpnea, depression, anorexia).	Consider packed red blood cells (see ch. 130)

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CHAPTER 108

Cystoscopy and Urethroscopy

Julie K. Byron

Overview

Uroendoscopy (cystoscopy and urethroscopy) is a minimally invasive technique which allows assessment of the lower urinary and distal reproductive tract that can be important for diagnosis and treatment of a variety of disease processes. Uroendoscopy allows visual evaluation of the vaginal vestibule, vagina, urethra, urinary bladder, and ureteral openings. In some cases, the endoscope may be passed into the ureters for luminal evaluation as well. Diagnostic and therapeutic procedures can also be performed via urinary endoscopy including biopsy, urolith retrieval or lithotripsy, and laser surgical procedures (see ch. 124 and 329-337). Uroendoscopy can be a valuable part of the diagnostic and therapeutic management of urinary tract diseases and can yield different information than that gained from other imaging modalities due to magnification of the luminal surfaces.

Equipment

The term "endoscope" is a general term that may be applied to both flexible and rigid cystourethroscopes. Both rigid and flexible endoscopes may be used. Rigid cystourethroscopes consist of three parts: the telescope, sheath, and bridge (Figure 108-1). These may be separate components or integrated by the manufacturer. The glass fiber telescope provides an angled view of 0°, 12°, 30°, or 70° from the tip of the scope. The author prefers a 30° view which allows for visualization of all areas of the bladder with less manipulation as well as good visualization of the working field when using instruments (Figure 108-2). The sheath contains the irrigation and operating channels and the bridge has the light-source and camera connections as well as the instrument port. Rigid endoscope systems come in a variety of diameters and lengths. For small animal cystourethroscopy, three sizes are generally recommended: 4.0 mm × 30 cm for medium to large female dogs, 2.7 mm × 18 cm for small and medium female dogs, and 1.9 mm × 18 cm for female cats and male cats with a perineal urethrostomy (Figure 108-3). Additionally, a flexible or semi-flexible 5 Fr endoscope may be used to examine male cats. Male dogs with urethras that will accommodate an 8 Fr diameter catheter can be examined using a flexible 7.5 Fr × 70 cm fiberoptic or digital scope human ureteroscope. A flexible endoscope may also be used to evaluate larger female dogs in absence of a rigid cystourethroscopy system.

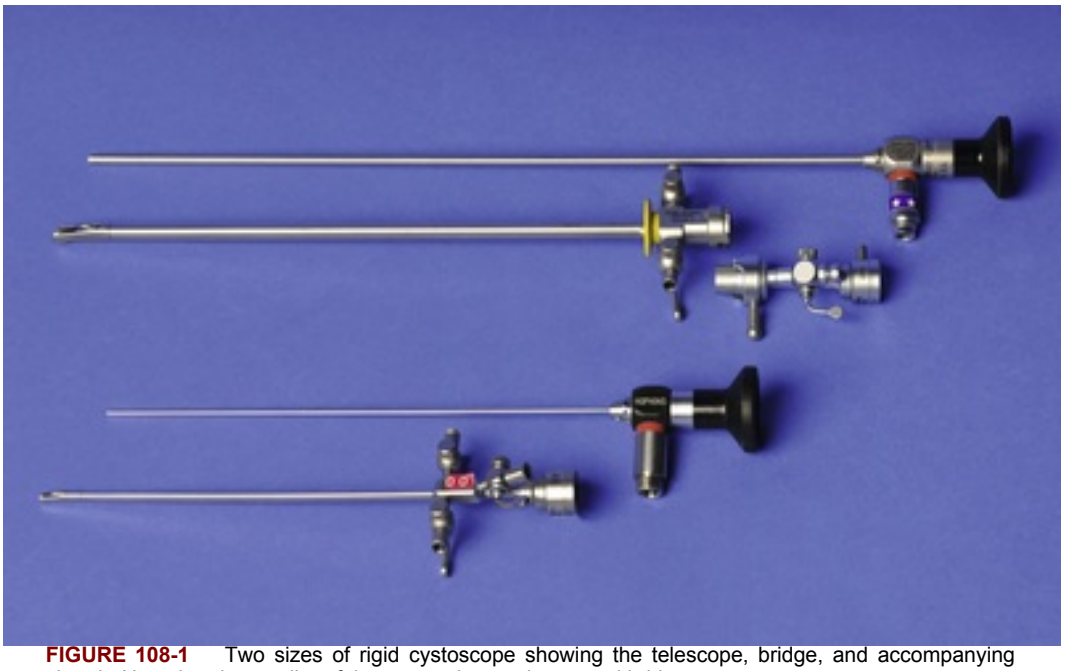

FIGURE 108-1 Two sizes of rigid cystoscope showing the telescope, bridge, and accompanying sheath. Note that the smaller of the scopes has an integrated bridge.

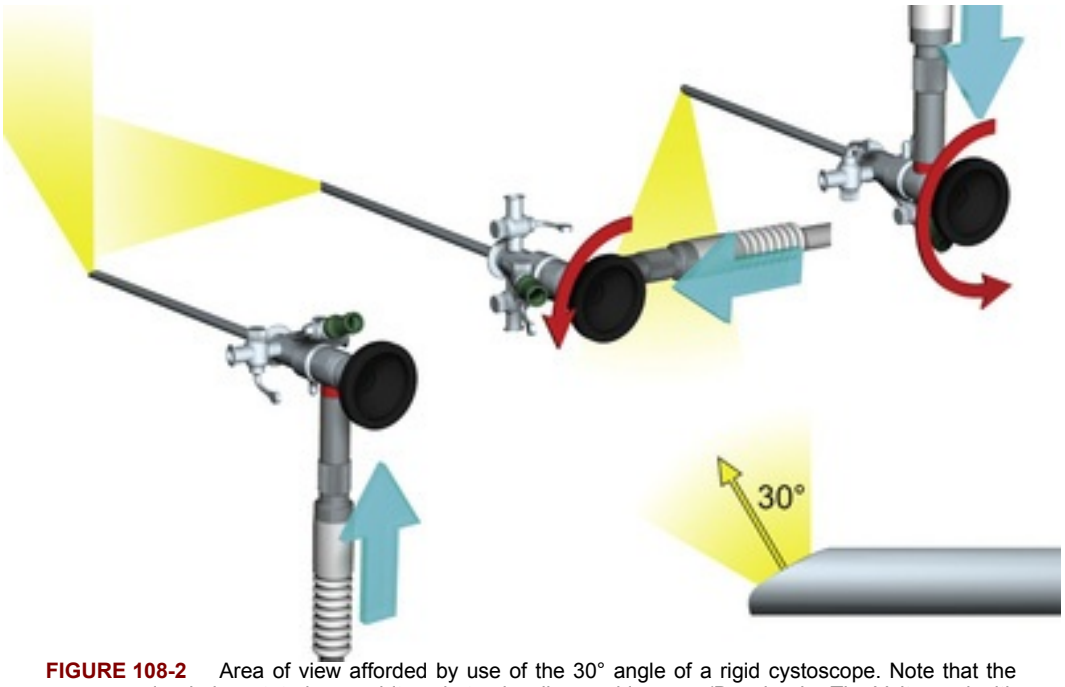

FIGURE 108-2 Area of view afforded by use of the 30° angle of a rigid cystoscope. Note that the scope need only be rotated around its axis to visualize a wide area. (Drawing by Tim Vojt, used with permission from The Ohio State University.)

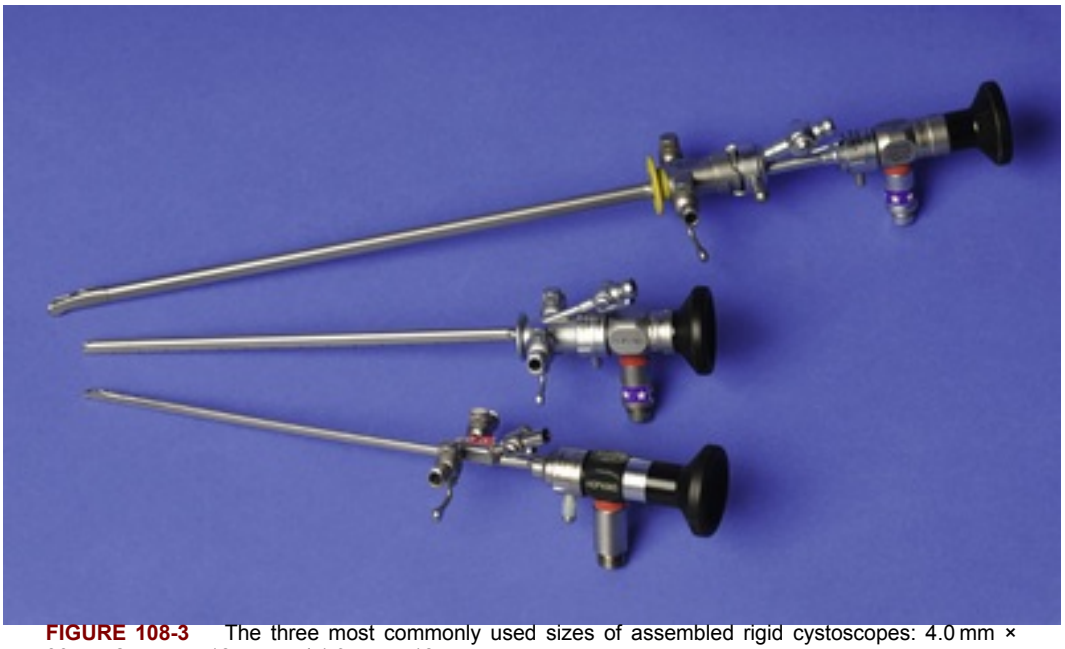

FIGURE 108-3 The three most commonly used sizes of assembled rigid cystoscopes: 4.0 mm × 30 cm, 2.7 mm × 18 cm, and 1.9 mm × 18 cm.

There is a variety of accessories and instruments available for rigid and flexible endoscopes. At least one good quality biopsy forceps that fits through the operating channel is required for obtaining tissue samples. In addition, stone retrieval baskets, grasping forceps, and cautery tips are available.

Rigid endoscope systems require a light source, camera, video monitor, and preferably an image capture system that allows for data storage onto CD or DVD. There are several manufacturers of these systems and they are often purchased as part of a package with the endoscopes. Some incompatibilities exist between systems, so it is best to use components from the same manufacturer or verify their compatibility prior to purchase.

The best light sources for video uroendoscopy are xenon with automatic intensity adjustment. Halogen light sources can be used as well, but have a lower intensity and image quality than xenon lights. Although many rigid and flexible endoscopes have eyepieces, a camera and video system are essential for proper detailed viewing and documentation of uroendoscopic studies. Cameras are generally available in one- or three-chip models. The three-chip has higher image quality due to 3-color capture and processing and produces better images in low-light conditions, although one-chip models are adequate for most applications. Ideally, the camera has a focusing system and image capture controls mounted on the operating head or via foot-pedal operation. A wide range of image capture systems is available from state-of-the-art high definition video to those that record only still images. Since dynamic imaging is desirable in uroendoscopy, a system that provides capture and recording of both still and video images is preferable.

Patient Preparation and Procedure

Female Dog and Cat

Uroendoscopy can be performed with the patient in dorsal or lateral recumbency. The use of sterile technique is important to minimize iatrogenic contamination of the urinary tract. The endoscope is either gas- or liquid-sterilized and sterile gloves are worn during the procedure. Some practitioners also don a sterile gown for the procedure, although this is not a universal practice in routine diagnostic uroendoscopy. The endoscopist is generally seated at the caudal end of the animal and the tail is secured out of the operating region. The external genitalia of the anesthetized patient is shaved and surgically prepared. The patient is aseptically draped and a small opening is cut in the drape to access the vulvar opening. The endoscopist assembles the scope and its components and attaches the light and camera cables. Appropriate white balancing and focusing are performed according to the system's requirements. The irrigation and efflux lines are attached and the scope is liberally coated with sterile water-based lubricant. Sterile 0.9% NaCl is passed through the irrigation channel to distend the anatomy and improve visualization. The scope is passed into the vaginal vestibule and the vulvar folds are gently grasped around the scope to allow for fluid distension of the

chamber.[1]

Normal Appearance in the Female

The mucosa of the vestibule is light pink in color and smooth (Video 108-1). The vaginal opening, surrounded by a ridge of tissue, the cingulum, is seen at the craniodorsal aspect of the vestibule. Ventral to this is the smaller urethral opening. There may be a thin band of tissue crossing the opening dorso-ventrally of the vagina, which has been called a hymenal membrane. A thicker band referred to as the mesonephric remnant is often associated with abnormalities of development of the urethra and ureter (Figure 108-4).[2] The urethral opening is often covered by a dorsal fold of tissue in the intact female dog and should not be interpreted as a mass lesion. This fold of tissue is not present in the spayed female dog. Lateral to the urethral opening are fossae, which may contain crypt-like areas. These can be normal findings and should not be mistaken for ectopic ureter openings.

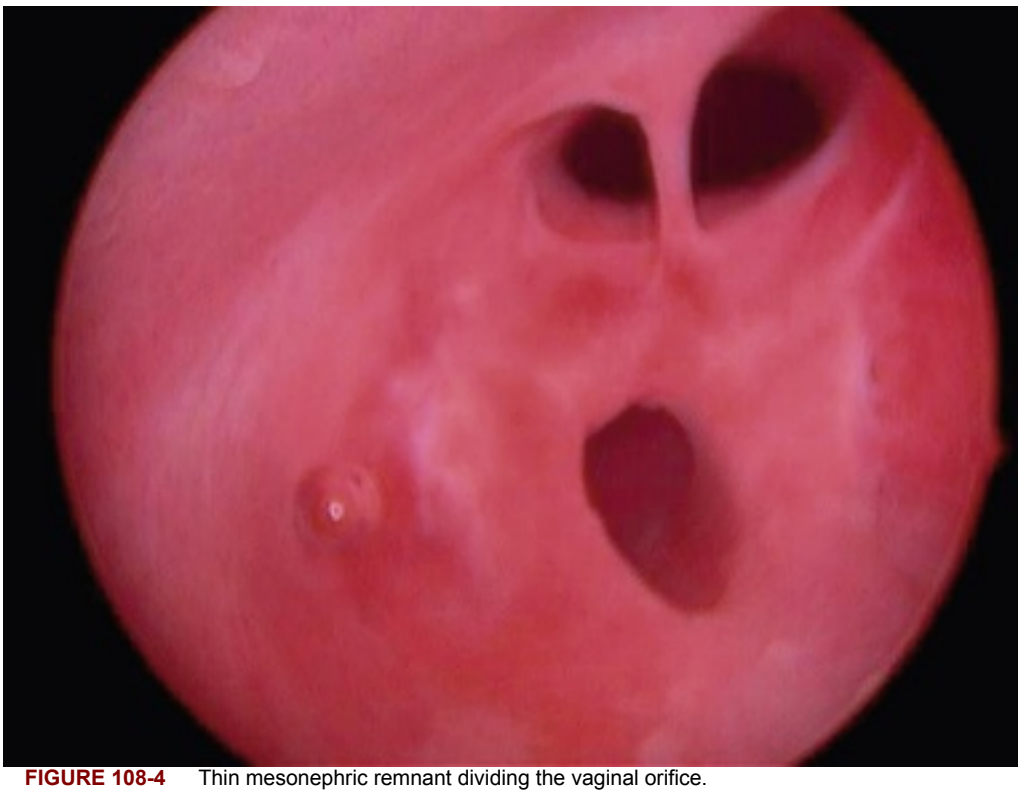

FIGURE 108-4 Thin mesonephric remnant dividing the vaginal orifice.

Evaluation of the vagina may occur before or after investigation of the urethra and bladder; however, if substantial vaginal mucus or discharge is present, the vagina should be viewed last. The vaginal mucosa is pink with a prominent longitudinal fold running along the dorsal wall. The scope is passed cranially until the caudal aspect of the cervix is reached. This has a folded appearance and passage of the scope beyond this point may be difficult and is rarely performed during routine urologic examinations.

The scope is redirected into the urethra and slowly passed cranially into the bladder. The urethra also has a dorsal fold, particularly prominent in the female cat, and generally has smooth, light pink mucosa. The length of the urethra may vary between normal dogs. Care must be taken to keep the scope centered in the lumen, a visual angle that will depend on the type of scope used. The author uses a 30° angled scope which requires keeping the lumen in the lower third of the visual field. Once the vesicourethral junction is reached, the bladder is drained of urine and re-distended with saline to provide a clear view. Distension of the bladder is essential to get an adequate evaluation of the ureters and bladder wall; however, over-distension will cause tearing of the urothelium and hemorrhage. To prevent this, the bladder should be manually palpated through the abdomen by an assistant and distension ceased when it is slightly firm. If bleeding occurs, the bladder can be drained of fluid and chilled saline infused to induce vasoconstriction and reduce the impact on visibility. The infusion of cold fluid may cause the patient's body temperature to drop, and this should be closely

monitored, especially when multiple cycles of chilled fluid are infused and drained.

When the bladder is fully distended, the trigone is examined. The ureters are located dorsolateral to midline as two crescent-shaped slits in the bladder wall that face each other as mirror images. An inverted V- or Y-shaped ridge may run cranially from the openings and join at midline. Verification of their patency should be made by observing the pulsatile urine flow from each ureter. The cystoscope is then passed cranially to the apex of the bladder and the entire bladder wall is examined. The bladder mucosa is light pink with a fine vascular pattern. Occasionally the bladder wall will be semi-transparent and abdominal organs may be faintly visualized from the lumen. It is important to examine all areas of the bladder interior in order not to miss small lesions or calculi, which may fall to its dependent aspect. Manual palpation and manipulation of the bladder through the abdomen can assist in a full evaluation, as can rotation of the scope around its axis. After completion of the exam, the efflux channel is opened and the fluid is drained from the bladder.

Male Dog and Cat

Uroendoscopy of the male is generally performed with a flexible endoscope. An assistant may be required to exteriorize the penis from the prepuce and atraumatic hemostats or stay sutures may be necessary to maintain retraction, particularly in the male cat. The endoscope is prepared and lubricated as with the female. The endoscopist gently introduces the flexible tip of the endoscope into the external urethral orifice (Figure 108-5). Infusion of saline facilitates distension of the urethra ahead of the scope. It is important not to use the scope tip itself to dilate the urethra as this can cause injury to the delicate urothelium that may be interpreted as a lesion. For this reason, the urethral mucosa must be evaluated both on insertion and withdrawal to differentiate iatrogenic lesions. Very small adjustments in scope angle and external manipulation of the penis and perineal region may facilitate maintaining the urethral lumen within the visual center of the scope (Video 108-2). As the scope is passed from the perineal urethra into the prostatic urethra of the dog, tiny prostatic duct openings may be noted in the mucosa. These indentations are generally not seen in the male cat. The colliculus seminalis is a dorsal mound of tissue that sits at the level of the openings of the ductus deferens. It should not be mistaken for a mass lesion; and the ductus openings should not be mistaken for ectopic ureters. Examination of the trigone, ureters, and bladder lumen is as with the female, but may be difficult due to the small size of the endoscope in relation to the size of the bladder lumen. Care must be taken to keep the tip of the scope close to the bladder wall to avoid missing lesions.

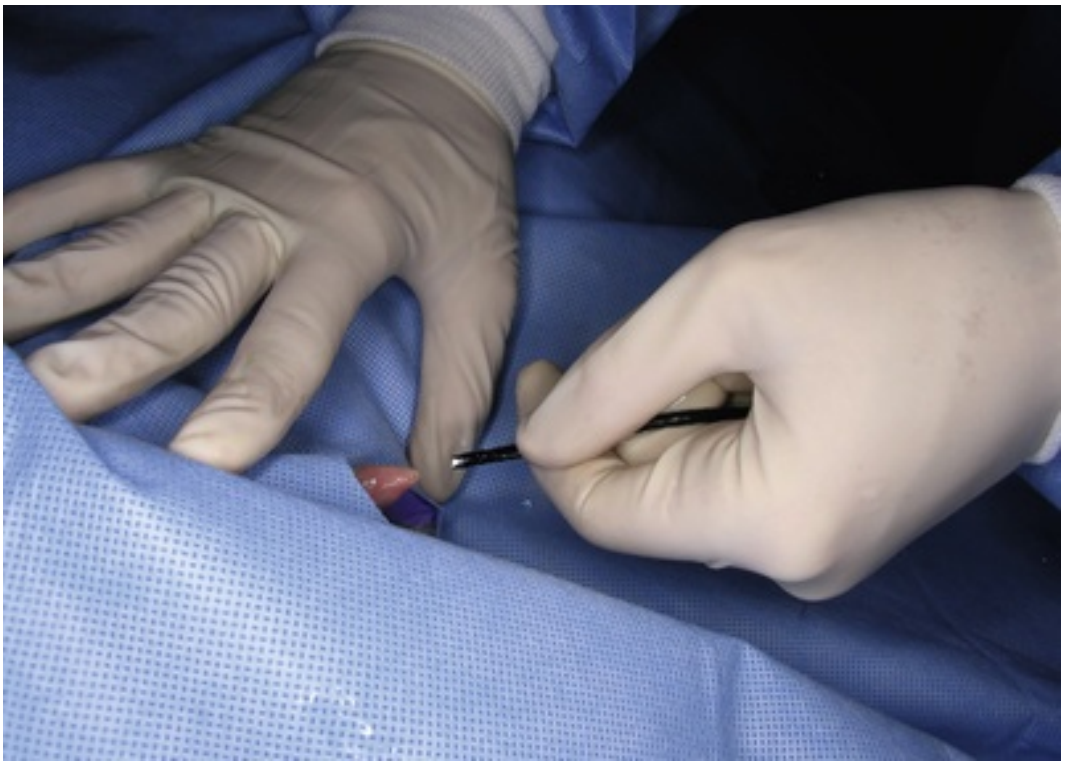

FIGURE 108-5 Careful insertion of the flexible tip of the urethroscope into the external urethral orifice.

Postoperative Management and Complications

Despite strict attention to asepsis, the mild to moderate trauma to the urinary tract and the proximity of the anus may increase the likelihood of iatrogenic contamination during uroendoscopy. It is therefore recommended to place patients on 5-7 days of broad-spectrum antibiotics after the procedure.[1,3] Alternatively, patients may receive an intraoperative intravenous injection of a broad-spectrum antibiotic.

Both dogs and cats may experience a moderate amount of discomfort and pollakiuria after uroendoscopic procedures. The author prefers to administer epidural analgesia with a combination of ropivacaine and morphine pre-operatively, which improves pain control and can facilitate relaxation of the urethra.[4] Additional pain medication such as a non-steroidal anti-inflammatory drug or mild opiate may be used for 2-3 days. Mild hematuria may also occur in patients after cystoscopy. This is generally short-lived and self-limiting but owners should be advised of its presence.

Several complications may arise during uroendoscopy. The most common complication is failure to be able to safely advance the cystoscope through the lumen of the urethra. Lodging of the endoscope in the urethra can be avoided by proper selection of scope size for the patient and appropriate lubrication. The endoscope, whether flexible or rigid, should never be forced through the urethra. This can lead to urethral damage or "hair-pinning" and lodging of a flexible scope in the urethra. Gentle pressure and, especially in the case of males, proper use of fluid to dilate the urethra ahead of the scope should be sufficient to allow for passage. If this is not successful, a smaller diameter scope should be used.

Perforation of the lower urinary tract is also a risk with uroendoscopy, particularly in patients with a severely diseased urethra or bladder wall.[5] The endoscopist must be attentive to the degree of fluid distention in the bladder and release any overfilling through the efflux channel. Depending on the size of the damage, surgical repair may be necessary to correct a bladder tear. Rupture of the urethra can also occur, but may not require surgical intervention. Placement of a urinary catheter for several days may be sufficient to allow for healing of the defect. The careful selection of an appropriately-sized scope and gentle technique will minimize these risks.

Cystoscopy and urethroscopy can be a valuable tool in the assessment of the lower urinary tract, and as noted elsewhere in this text, they allow for minimally invasive therapeutic as well as diagnostic procedures. Comfort with the normal appearance of the urinary tract and knowledge of possible complications can make its practice safe and practical in many circumstances.

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CHAPTER 109

Peritoneal Dialysis

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Client Information Sheet: Peritoneal Dialysis

Overview

Peritoneal dialysis (PD) is a form of dialysis that utilizes the surface area of the peritoneum for removal of uremic toxins. It requires repeat instillation of a biocompatible solution into the abdominal cavity, a dwell time for transfer of uremic solutes from the blood through the peritoneum and into the solution, and subsequent evacuation of the solution from the abdominal cavity. Advantages of PD are that it is a relatively simple procedure and does not require complex equipment. Compared to hemodialysis (see ch. 110), it can be a preferred option for patients who are hemodynamically unstable, or of very low body weight (as there is no extracorporeal circuit), or at risk of bleeding (avoids anticoagulation). Removal of uremic toxins is gradual, with less risk of dialysis disequilibrium syndrome.[1]

Peritoneal dialysis relies on the principles of diffusion, ultrafiltration, and convection for solute and fluid removal. Molecules in high concentration in the blood diffuse across the peritoneal membrane into the dialysate solution until equilibrium is reached. Dialysate solution contains dextrose, at variable concentrations, to provide an osmotic draw, which draws fluid from the patient's circulation into the peritoneum, termed ultrafiltration. This ultrafiltration, or movement of water, promotes the movement of solutes, referred to as solvent drag, which creates a route for elimination of solutes from the bloodstream. By providing ultrafiltration, PD can be an effective method for removing excess fluid from patients that are fluid-overloaded.

In veterinary medicine, PD principally is indicated for the management of potentially reversible acute kidney injury (AKI; see ch. 322). Other reported indications for PD include treatment of certain dialyzable intoxications (e.g., ethylene glycol, ethanol, barbiturates, sodium monofluoracetate, severe hepatic encephalopathy; see ch. 152 and 281) and for the management of hypo- or hyperthermia (see ch. 49 and 134), refractory congestive heart failure (see ch. 247), and for pre-surgical management of unstable patients with urinary tract obstruction/leakage (see ch. 150).[2,3]

Preparation

Selecting patients with AKI for PD relies on considering urine production and the metabolic condition of the patient. Anuria, or oliguria (urine production < 0.5 mL/kg/h), and/or an inability to regulate water homeostasis, hyperkalemia, or abnormal acid base status, warrants dialysis implementation.[4] More recently, in humans, an improved outcome appears to occur with early implementation of PD, such as when creatinine > 5 mg/dL (>442 micromol/L) or BUN > 75 mg/dL (>27 mmol/L), even in the absence of overt signs of uremia.[5,6] More than any numerical value, the progression of the disease and the patient's clinical condition and prognosis should be considered when deciding whether to initiate PD.

Peritoneal dialysis relies on obtaining peritoneal access using a multi-fenestrated catheter. Soft "permanent"-type catheters should be used; semi-rigid acute catheters are less ideal, short-term alternatives.[1] Both can be used immediately after insertion. Semi-rigid acute catheters are inserted using a sharp trocar device and are associated with increased risk of bowel perforation, dialysate leak, discomfort, and should not be left in place for more than 72 hours due to high risk of peritonitis.[1,2] Several different types of soft "permanent" PD catheters have been used; Tenckhoff PD catheters are the most frequently used in human medicine, although Swan neck catheters are gaining popularity.[1,7] Commercial PD catheters have 1-2 Dacron

cuffs. These serve to anchor the catheter by fibroblast ingrowth. Cuffs are positioned in the rectus abdominis muscle +/– the subcutaneous space prior to skin exit. Dacron cuffs decrease the risk of infection and dialysate leak; however, these advantages are delayed, which is not helpful in the acute PD setting. In veterinary medicine, alternative catheters that have been used successfully when PD catheters are not accessible include the Jackson Pratt surgical suction drain and the Blake silicon drain.[3,8]

Procedure

Catheters can be placed surgically, percutaneously, or laparoscopically using local anesthesia (with sedation if needed).[1,3,9] Surgical placement is recommended in human pediatric medicine, and appears to be associated with better success in veterinary medicine.[1,10] Regardless of insertion technique, strict aseptic technique is mandated. Prophylactic antibiotic administration using a first generation cephalosporin (e.g., cefazolin) is recommended prior to PD insertion.[1,11] In order to establish successful early use of the catheter, and decrease dialysate leak, placement of PD catheters off midline is preferred, through the rectus abdominis muscle.[7] Regardless of technique, a subcutaneous tunnel is recommended to exit the skin approximately 5 cm away from the abdominal access point[1] (Box 109-1).

Box 109-1

Key Points for Successful PD Catheter Placement and Early Function

- Ensure the urinary bladder is empty
- Provide prophylactic antibiotics (e.g., cefazolin) at the time of PD catheter insertion
- Use a paramedian approach
- Position the tip of the catheter in the caudal abdomen (pelvic cavity)
- Ensure good closure of the rectus sheath around the PD catheter
- Include a subcutaneous tunnel prior to catheter exit
- Confirm excellent flow of dialysate prior to securing the PD catheter

A mini-surgical approach for PD catheter placement (Videos 109-1 and 109-2) requires the patient to be in dorsal recumbency, with aseptic preparation of the ventral abdomen. A 2-3 cm para-umbilical incision is made to the right of midline, over the planned, locally anesthetized abdominal entry site, and extended through the rectus muscle (external sheath, muscle, and internal sheath). The parietal peritoneum is definitively identified and incised (it is discrete from the internal sheath of the rectus muscle off midline).[3] The catheter (with stylet, or aided by hemostats) is advanced through the incision into the caudal abdomen. At the abdominal entry site, the distal (external) end of the PD catheter is tunneled subcutaneously before exiting the skin. Prior to further closure, the catheter should be connected aseptically to (1) dialysate, and (2) a closed collection system (using a Y system), and the catheter should be tested. A small volume of dialysate (5-10 mL) should be easy to flush and retrieve; otherwise, catheter repositioning is warranted.[3] Subsequently, snug closure of the rectus sheath (e.g., pursestring suture) around the catheter is necessary for early catheter use with less risk of dialysate leakage.[12] Alternatively, with the use of a trocar, the PD catheter can be tunneled under the external sheath of the rectus abdominis muscle, to exit the skin 5 cm from the abdominal access point.[3,13] This method allows full closure of the external sheath of the rectus muscle overlying the PD catheter. Thereafter, final closure of the skin incision is performed. The catheter exit site should be covered with a sterile bandage. External suture fixation is not recommended at the skin exit site; however, catheter movement should be prevented, to allow healing and decrease the risk of inadvertent catheter removal and exit site infections.[11] If a laparotomy is warranted or preferred for PD catheter placement, an omentectomy is advised, to decrease the likelihood of obstruction to dialysate flow.[9,14]

For percutaneous PD catheter placement, the abdomen should be filled with prewarmed (to body temperature), sterile physiologic saline first, to decrease the likelihood of inadvertent organ penetration. In human medicine, PD catheter placement using a Seldinger technique with sequential dilations of the body wall has been reported to be fast and provide successful dialysis.[15,16] However, percutaneously placed

catheters have an increased incidence of dialysate retention in veterinary medicine.[10]

Once the catheter is in place, dialysis can begin, and everyone involved must always follow strict aseptic technique. Hand sanitizing and use of sterile gloves is indicated for any manipulation of the PD line or catheter. The circuit should be a closed system, preferably a Y system, with the three arms of the Y made up of (1) PD catheter from patient, (2) line from dialysate solution, and (3) line to closed collection bag. This type of 3-way system decreases the risk of infection. Every line connection should be covered with chlorhexidine-soaked dressings, and access ports (dialysate bags, drug vials, PD access) should be scrubbed with chlorhexidine and alcohol prior to penetration.[14,17] Spiking of new dialysate bags is the most frequent source of contamination; flushing the dialysis line before infusing ("flush before fill" technique) is advised.[11]

Commercial peritoneal dialysate solutions are buffered balanced electrolyte solutions (contain sodium, magnesium, calcium and chloride at varying concentrations); the majority use dextrose as the osmotic agent. Standard dextrose concentrations are 1.5%, 2.5% and 4.25%. Commercial dialysate solutions use lactate or bicarbonate as the buffer; both are well tolerated by the peritoneum.[18] Dialysis fluids can be prepared using intravenous fluids if commercial products are not available.[1,3,14] Lactated Ringers solution (LRS) is the most similar to commercial dialysate. The concentration of potassium in LRS is 4 mmol/L (4 mEq/L) which generally allows correction of mild to moderate hyperkalemia, and is ideal once the patient is normokalemic.[1] Alternatively, 0.9% NaCl can be utilized as a dialysate solution if a potassium-free solution is deemed necessary (severe clinical signs of hyperkalemia noted in the patient). In such instances, sodium bicarbonate should be added to the solution (30-45 mmol/L). If using non-commercial products, dextrose supplementation is needed. Using 50% dextrose solution added to a 1 L bag of dialysate, 30 mL, 50 mL, or 85 mL are added to make approximately 1.5%, 2.5% and 4.25% dextrose solutions, respectively.[3] Unfractionated heparin often is recommended as an additive to decrease the risk of clot formation and catheter occlusion. It is routinely added to the dialysate solution at 500 U heparin/L (range 250-1000 U heparin/L) at least for the initial PD exchanges and up to the first 5 days of therapy.[3] Heparin is minimally absorbed at this dosage range.[2] In the case of confirmed septic peritonitis, antibiotics as additives to dialysate solution are preferred.[2,19] Absolutely strict aseptic technique is required when mixing solutions. Any additives should be drawn from sterile, previously unused vials. Dialysate should be warmed to body temperature for improved tolerance.

Generally, a 2.5% dextrose-containing solution is used at the onset of dialysis to optimize ultrafiltration and solute removal. However, the concentration of dextrose is determined by the fluid status of the patient. A 4.25% dextrose solution is selected for fluid-overloaded patients. Once the patient is euvolemic, a 1.5% dextrose solution is used.

At initiation of PD, dialysate exchanges occur hourly, throughout the 24-hour day. Dialysate is instilled into the abdomen over 5-10 minutes. The inflow time should be kept to a minimum to maximize time on dialysis.[2] A 30-45 minute dwell time is allocated, to allow for diffusion and ultrafiltration to occur. Subsequently the abdomen is emptied, by gravity, over 15-20 minutes.[1-3] The ultrafiltration rate is maximal at the beginning of a PD exchange, when dextrose concentration is at its maximum. Intraperitoneal volume peaks at about 120-180 minutes of dwell time. A dwell time <30 minutes usually is not adequate.[2] Recommended dialysate volumes range from 10-40 mL/kg. At the onset of dialysis, 10 mL/kg should be attempted. If this is well-tolerated, increased volumes will improve uremic clearance, but will also predispose to dialysate leakage. Dialysate volumes can be increased over 2-3 days. During dialysate infusion, and dwell, the patient should be monitored for respiratory compromise and signs of abdominal discomfort. Exchanges should be continued at 1- to 2-hour cycles, until uremic control is achieved; subsequently, dwell times can be extended to 4-6 hours. Patients with oliguria or anuria will frequently require several (3-7) days of PD before a positive response in urine production can be noted or assessed.[3]

During PD, patient monitoring is paramount. Serial body weight measurements and re-assessment of hydration are mandatory, every 4-12 hours, with changes in PD orders reflecting changes in patient status. Patient's "ins" (IV fluids, medications, enteral feeds) and "outs" (urine production, dialysate retrieval, vomitus, etc.) should be tabulated every 4-12 hours (see ch. 106). Once the patient is euvolemic, "ins" should be matched to "outs." Other monitoring includes continuous ECG and blood pressure assessments (see ch. 103 and 99), serum electrolyte measurements (see ch. 67, 68, and 69), and blood gas monitoring (see ch. 75 and 128) along with packed cell volume, total solids and blood glucose determinations at least every 12-24 hours. Daily serum creatinine determination is ideal until improvement is well established.

Complications

Catheter malfunction, most often slow or incomplete outflow, is frequently encountered and may be associated with catheter migration, omental wrapping, or fibrin clot/occlusion.[2,3] Any retention of dialysate should be promptly noted. On occasion, a difference in dialysate retrieval is recuperated at the next exchange. Should this not be the case, patient repositioning, delivery of enema(s), or aseptic flushing of the PD catheter using a prefilled 20 mL syringe, can be attempted. Alternatively, PD catheter systems can be connected to active continuous suction devices (collection bulbs).[8] Other documented complications include dialysate leak, extravasation of fluid in tissue compartments (perineal/pelvic limb edema), lack of uremic control, unpredictable fluid removal rates, intra-abdominal hemorrhage, progressive hypoalbuminemia, pleuroperitoneal communications (pleural effusion), hyperglycemia, catheter exit-site infections, and peritonitis.[1,3]

Outcome

PD does not treat the renal insult, but allows time for renal recovery. PD can provide effective reduction in circulating concentrations of uremic toxins.[10] The available human literature, though limited, suggests that PD can provide uremic control similar to that which is achieved with extracorporeal methods.[20] Prognosis and renal recovery depend heavily on the underlying cause of renal injury. Overall mortality rate for AKI in dogs is 60%[21]; reports for survival after the initiation of PD range from 24-80%[10,22,23]; an improved response is noted in patients with AKI secondary to leptospirosis,[23] and urinary tract obstruction,[10] likely due at least in part to control of the inciting cause. Cats might also have a better outcome with PD than dogs, with reported survival rates of 45% and 83%.[8,10]

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CHAPTER 110

Continuous Renal Replacement Therapy/Hemodialysis

Mark J. Acierno, Mary Anna Labato

Overview

Extracorporeal blood purification therapies are a collection of modalities that employ the principles of diffusion, convection and adhesion to remove toxins, as well as correct a patient's fluid, electrolytes and acid/base balance. In veterinary medicine, these modalities have primarily been employed in the treatment of acute kidney injury (AKI; see ch. 322); however, they have also been successfully used for the management of chronic kidney disease (CKD; see ch. 324), and toxin exposures (see ch. 151 and 152). The most commonly employed extracorporeal therapies in dogs and cats include intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), and therapeutic plasma exchange (TPE).

The principles of extracorporeal blood purification were first described in 1914 when researchers anticoagulated a dog and directed its blood from an artery into an apparatus called "vividiffusion"[1] (Figure 110-1). This device divided blood into straw-like semi-permeable membranes, which were bathed in solution. It was noted that by changing the composition of the solution, the concentration of solutes in the patient's blood could be altered.[1] Although this vividiffusion apparatus, constructed from a glass cylinder and hand-made semi-permeable membranes seems rudimentary by today's standards, it has served as the prototype for all modern dialyzers. The dialyzer still functions as an "artificial kidney."

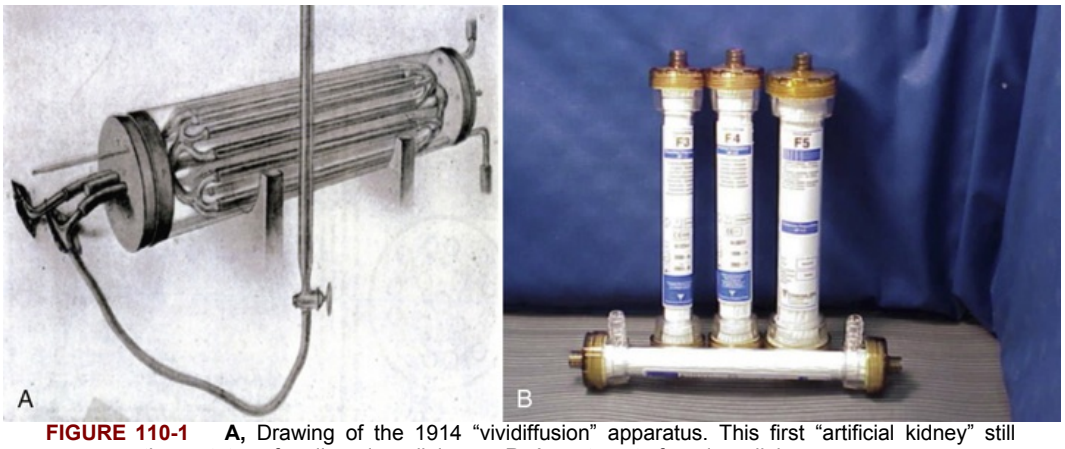

FIGURE 110-1 **A,** Drawing of the 1914 "vividiffusion" apparatus. This first "artificial kidney" still serves as the prototype for all modern dialyzers. **B,** Assortment of modern dialyzers.

Blood Purification

Diffusion is the tendency for molecules in solution to move from an area where they are in a high concentration to an area where they are in a lower concentration.[2] As patient blood enters the dialyzer, it is divided and travels inside thousands of straw-like semi-permeable membranes that are bathed in solution called dialysate.[3] Dialysate contains precisely measured concentrations of electrolytes and buffers.[3] Molecules can be made to diffuse out of the blood, across the membrane and into the dialysate by ensuring that their concentration in the dialysate is lower (e.g., creatinine). In addition, beneficial substances can be made to

move from the dialysate into the blood by increasing their concentration in the dialysate (e.g., bicarbonate).[4] After leaving the dialyzer, the exhausted dialysate is discarded and the purified blood is returned to the patient. The primary limitation of diffusion is the size of the molecule that will pass through the membrane. Generally, the likelihood that a molecule will pass across the membrane is inversely proportional to its size. Thus small molecules such as urea pass readily while larger molecules diffuse more slowly or not at all even if they physically could fit through the membrane. In addition, because the movement of molecules is guided by concentration gradients, a continuous supply of fresh dialysate is needed.

During convection, the patient's blood enters the dialyzer and is divided and travels inside thousands of straw-like semi-permeable membranes where it is subjected to a positive transmembrane pressure.[2] This causes fluid, called ultrafiltrate, to be forced out of the blood and across the membrane. The ultrafiltrate carries uremic toxins, electrolytes and other small molecules[2,5] which are discarded. A sterile balanced electrolyte solution is then added to the patient's blood to replace the ultrafiltrate. Unlike diffusion, it is the size of the pores in the semipermeable membrane that determines which solutes can be removed. All molecules small enough to fit through the pores of the membrane will pass at the same rate. Thus, convection can effectively remove an increased number of larger molecules than diffusion.[2,6] Convection can be used to quickly remove fluids in overhydrated patients. Nevertheless, convection is technically challenging, as the ultrafiltrate must be replaced with great accuracy or acid/base, electrolyte and fluid imbalances can occur.

Adsorption is the tendency of molecules in blood to stick to surfaces in the extracorporeal circuit and be removed from circulation. Studies have suggested that certain dialyzer membranes may remove cytokines associated with sepsis; however, at this time there is no clinically proven benefit.[5,7] Hemoperfusion involves the placing of an absorptive substance, often carbon or resins, in the extracorporeal blood path in order to trap and remove drugs and toxins. Although first described in the 1940s, it is only infrequently utilized in human or veterinary medicine.[8]

Intermittent Hemodialysis

For decades, IHD has remained the standard of care for patients needing treatment of AKI, CKD or for the removal of certain toxins (e.g., ethylene glycol).[9] This is the treatment commonly referred to as "dialysis." Patients are treated for finite periods of time, often 4-6 hours, after which they are cared for as typical hospital patients. In some cases, they can even be sent home. IHD is primarily a diffusive technology. Since significant changes in blood composition need to be made in relatively short periods of time, large amounts of dialysate need to be produced on-site. Since only a thin semipermeable membrane separates blood and dialysate, the dialysate must be relatively pure in order to prevent contaminants or endotoxins from being introduced into the patient's blood.[10] This requires a significant investment in both equipment and maintenance.[10]

Manufacturing dialysate requires that ordinary tap water be specially treated. Water is first passed through a sediment filter to remove gross contaminants. Then it is exposed to carbon, which extracts chlorine and chloramines. A reverse osmosis water filter removes remaining dissolved solutes. The water is then delivered to the dialysis machine, which heats the water and mixes it with bicarbonate and an electrolyte (acid) solution to produce dialysate. Since the entire fluid pathway is at risk for contamination, a proper maintenance program involving disinfection and bacterial surveillance is essential.

Continuous Renal Replacement Therapy

CRRT is a newer extracorporeal blood purification therapy, which combines the principles of diffusion and convection to produce four different treatment modalities: slow continuous ultrafiltration (SCUF), continuous veno-venous hemodialysis (CVVHD), continuous veno-venous hemofiltration (CVVH), and continuous veno-venous hemodiafiltration (CVVHDF).[11] Many CRRT systems can also perform therapeutic plasma exchange (TPE). As its name implies, CRRT is a continuous modality and once a patient begins treatment, therapy continues until renal function returns, the patient is transitioned to intermittent dialysis (IHD) or the patient is euthanized. Potential advantages of CRRT over IHD include better control of fluids, acid/base and electrolyte balance in hemodynamically unstable patients[12,13]; however, in veterinary medicine, much of the appeal is likely due to CRRT's reliance on pre-packaged fluids which do not require a significant investment in water purification facilities or the ongoing maintenance associated with producing dialysate. The obvious tradeoff is that patients receiving treatment require extensive 24 hour a day care and monitoring.

Slow continuous ultrafiltration (SCUF) (Figure 110-2) is a purely convective modality.[11] As the patient's blood enters the straw-like semipermeable membranes of the dialyzer, it is exposed to a positive

transmembrane pressure that forces fluid out of the blood. The hemoconcentrated blood is then returned to the patient. While SCUF has been used in the treatment of diuretic resistant congestive heart failure in people, its utility in veterinary medicine is unclear.[2]

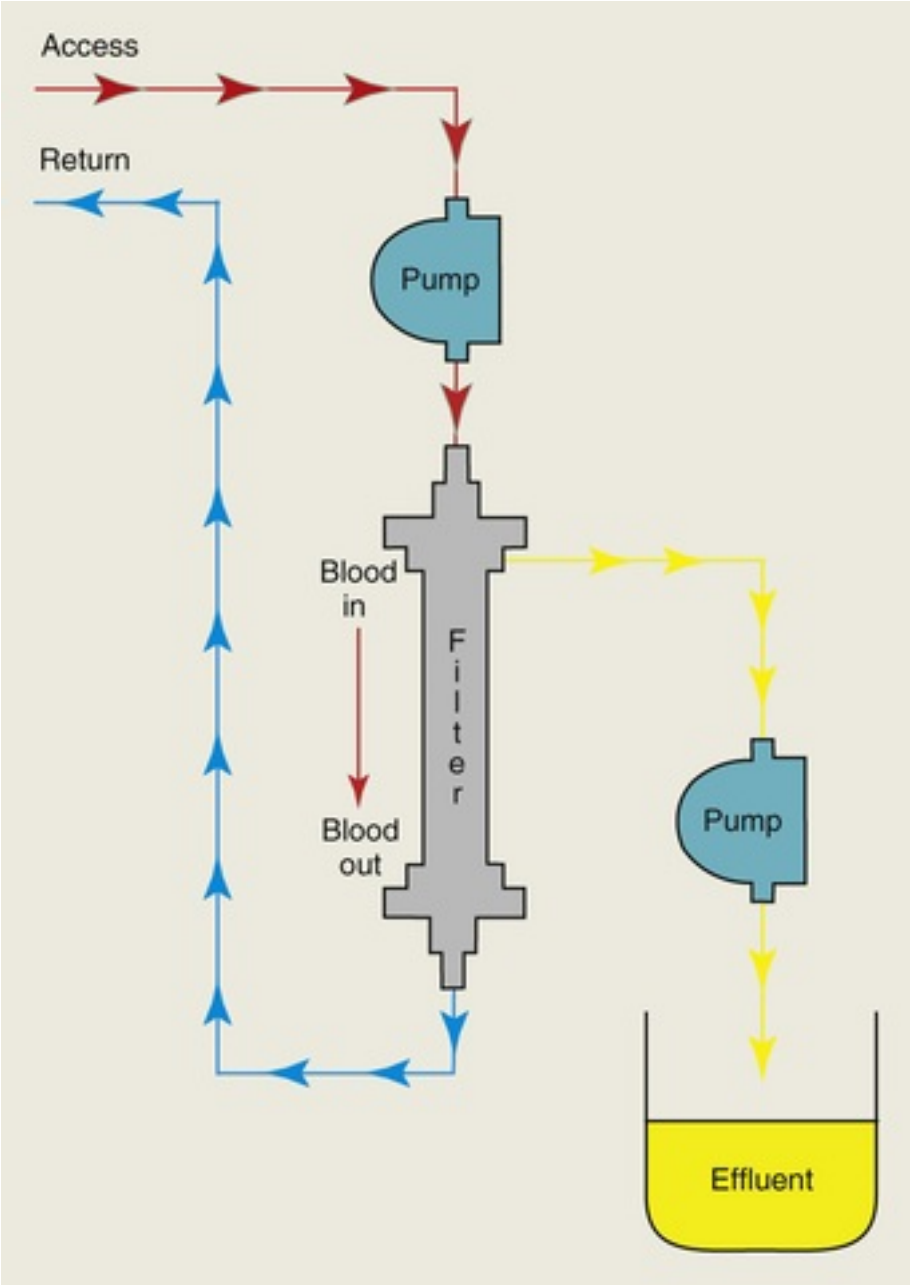

FIGURE 110-2 Slow continuous ultrafiltration (SCUF)—a purely convective modality which generates ultrafiltrate that is not replaced. (From Acierno MJ, Maeckelbergh V: Continous renal replacement therapy. *Compend Contin Educ Vet* 30:264-280, 2008.)

Continuous veno-venous hemofiltration (CVVH) (Figure 110-3) is also a convective modality; however, in CVVHD, the ultrafiltrate is replaced with a sterile balanced electrolyte solution.[2,14,15] The solution can be added to the blood before or after the dialyzer. When added after the dialyzer, a positive transmembrane pressure forces fluid out of the blood resulting in increasing hemoconcentration within the straw-like semipermeable membranes of the dialyzer.[2] Prior to returning the patient's blood, a sterile balanced electrolyte solution, called "replacement fluid," is added to restore the blood to a physiologic packed cell volume. Adding fluid after the dialyzer is an extremely efficient way to remove uremic toxins; however, as the blood becomes hemoconcentrated, there is a risk that the blood will sludge and clot. This limits the

amount of fluid that can be removed.[2] Alternatively, "replacement fluids" can be added to the blood before the dialyzer resulting in hemodilution. The excess fluid is then removed in the dialyzer by convection.[2] This is less likely to result in dialyzer clotting but is also significantly less efficient.[16]

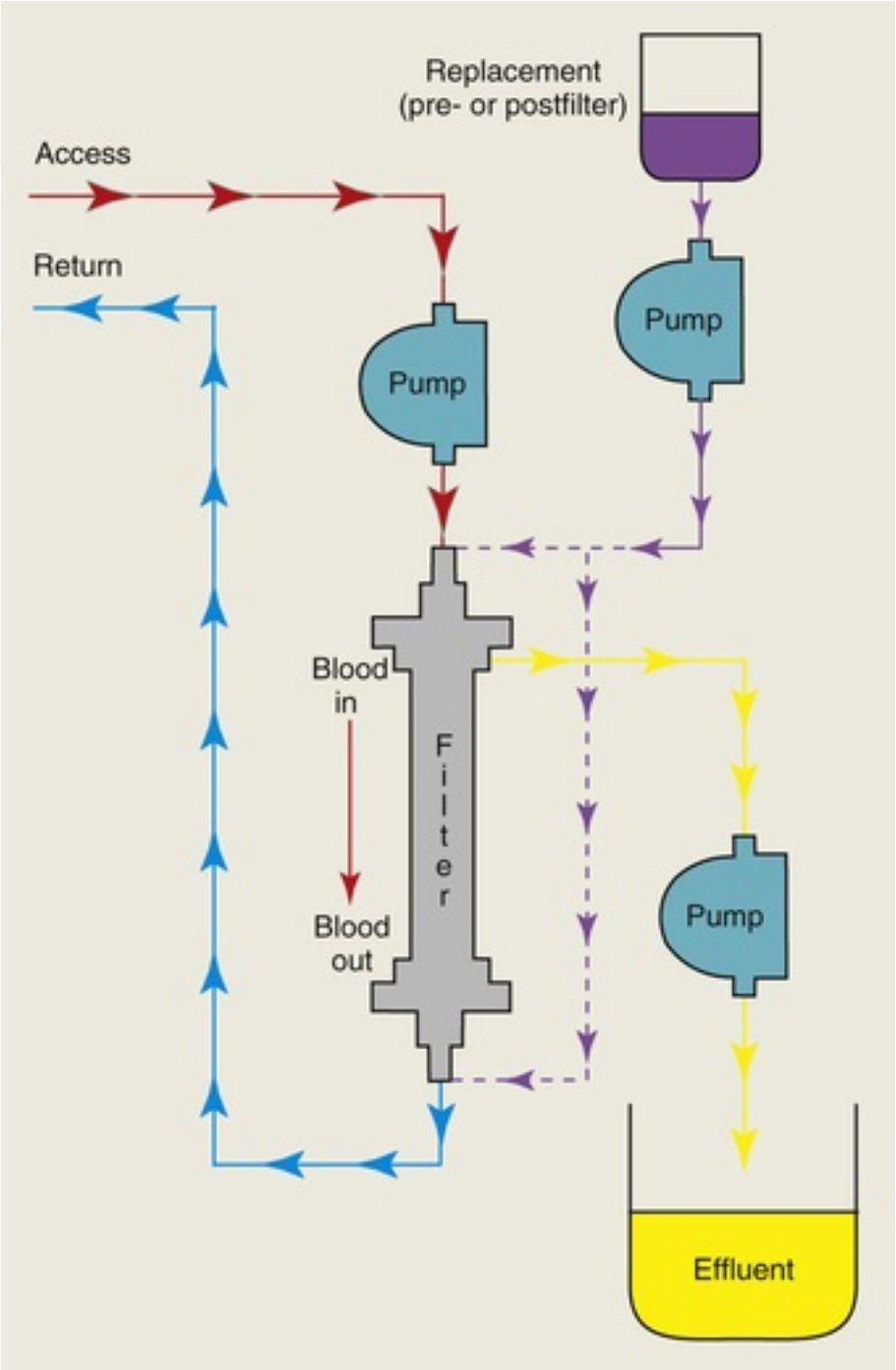

FIGURE 110-3 Continuous veno-venous hemofiltration (CVVH) is a convective modality that generates ultrafiltrate. Unlike SCUF, the ultrafiltrate is replaced with a sterile balanced electrolyte solution. This fluid can be added before or after the dialyzer. (From Acierno MJ, Maeckelbergh V: Continous renal replacement therapy. *Compend Contin Educ Vet* 30:264-280, 2008.)

Continuous veno-venous hemodialysis (CVVHD) is a diffusive therapy that closely resembles IHD (Figure 110-4).[11] Blood enters the dialyzer where it is divided and travels inside thousands of straw-like semipermeable membranes that are bathed in dialysate. Substances that are in relatively high concentration in

the blood leave the blood and enter the dialysate while substances whose concentration is higher in the dialysate enter the blood.[3]

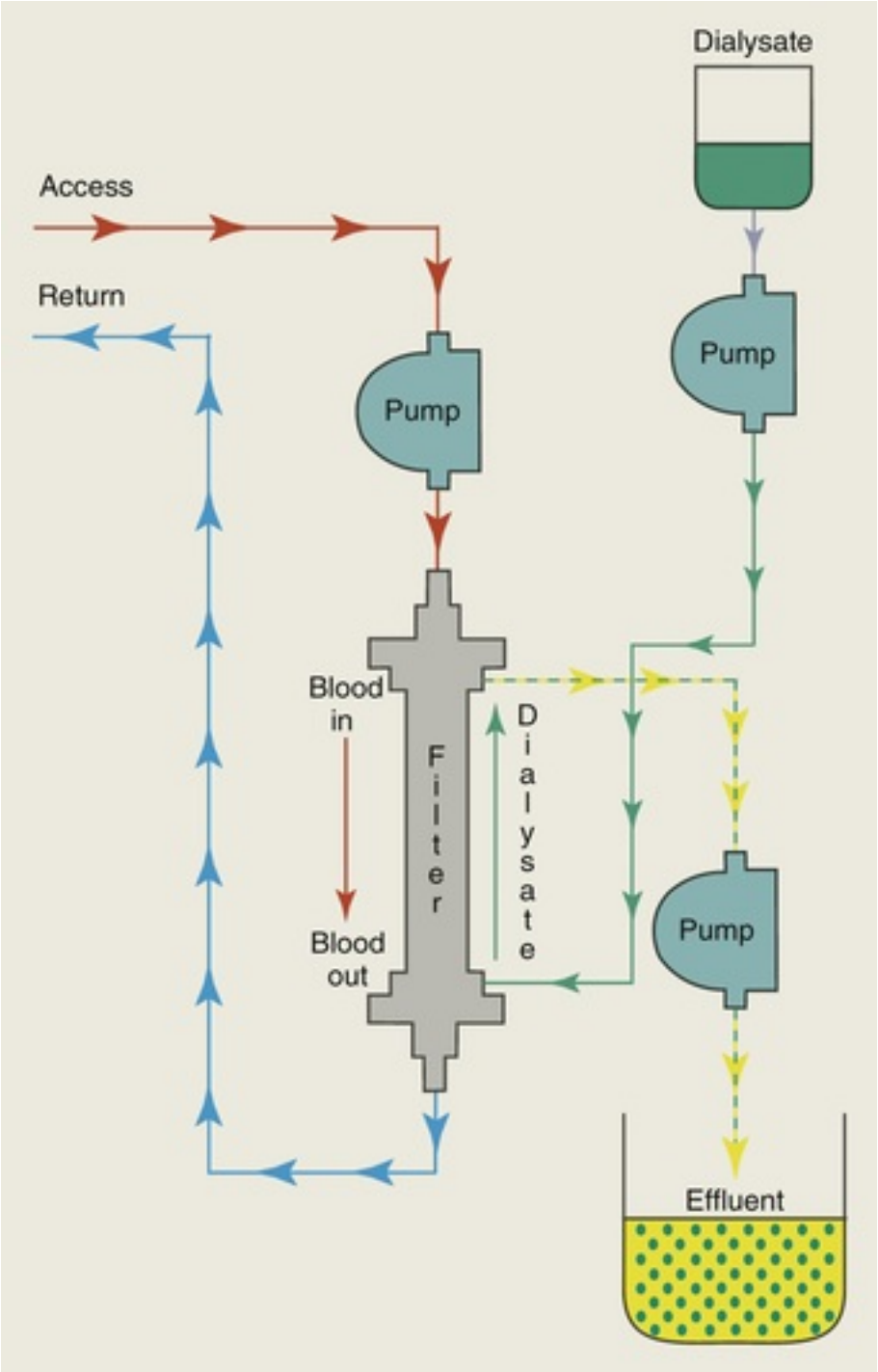

FIGURE 110-4 Continuous veno-venous hemodialysis (CVVHD) is a diffusive therapy in which the movement of small molecules is guided by their relative concentration in the dialysate. (From Acierno MJ, Maeckelbergh V: Continous renal replacement therapy. *Compend Contin Educ Vet* 30:264-280, 2008.)

Continuous veno-venous hemodiafiltration (CVVHDF) combines the diffusive aspects of CVVHD with the convective aspects of CVVH (Figure 110-5).[11] Blood flowing through the dialyzer's straw-like semipermeable membranes are bathed in dialysis solution and exposed to a positive transmembrane pressure so that both

diffusion and ultrafiltration guide the movement of solutes.[2] Because the operator can selected the amount of diffusion and ultrafiltration that takes place within the dialyzer, CVVHF gives the greatest control over the treatment administered.

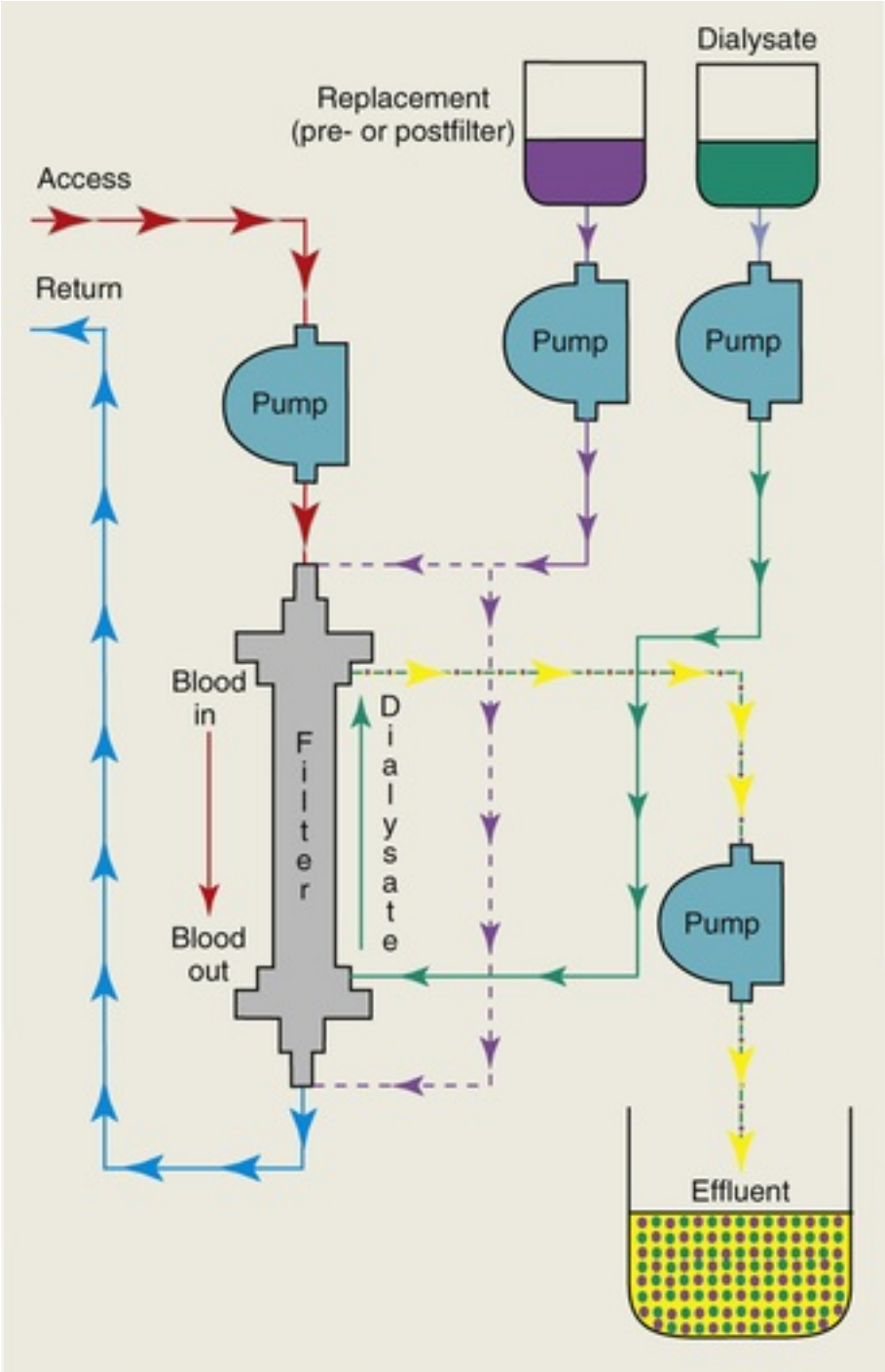

FIGURE 110-5 Continuous veno-venous hemodiafiltration (CVVHDF) combines the diffusive aspects of CVVHD with the convective properties of CVVH. Diffusion guides the movement of smaller uremic toxins and electrolytes while convection facilitates the movement of larger molecules and fluids. (From Acierno MJ, Maeckelbergh V: Continous renal replacement therapy. *Compend Contin Educ Vet* 30:264-280, 2008.)

For the treatment of AKI patients, it is unclear which CRRT modality is superior. Convective modalities (CVVH, CVVHDF) have the advantage of being able to remove larger "middle-sized" molecules and

therefore more closely mimic the function of the kidney.[17] Nevertheless, it is not clear what role these molecules play in the pathogenesis of AKI or uremia. Diffusive modalities (CVVHD) are equally effective in removing smaller molecules such as urea and creatinine and are associated with fewer dialyzer failures.[16,18]

Therapeutic Plasma Exchange

Therapeutic plasma exchange is a convective modality that utilizes a specialized dialyzer to separate plasma from the cellular components of blood. The patient's blood enters the dialyzer where it is divided into thousands of straw-like semipermeable membranes. The blood is then exposed to a positive transmembrane pressure that causes a plasma-like ultrafiltrate to be forced out. The ultrafiltrate, which includes albumin and globulins, is discarded while the cellular components are mixed with a colloid solution and returned to the patient.

In theory, any number of colloid solutions could be used including plasma, albumin, as well as synthetic colloids; however, in human studies, use of fresh frozen plasma has been associated with significant morbidity and mortality.[19] In veterinary medicine, hydroxyethylstarch (Hetastarch) has been used with no known adverse reactions. TPE is useful for the removal of autoantibodies, immune complexes, and highly-protein bound toxins.

In people, TPE is used to treat some autoimmune conditions (e.g., thrombotic thrombocytopenic purpura, myasthenia gravis, acute antibody-mediated renal allograft rejection, hyperviscosity syndrome), some intoxications (mushrooms) and some drug overdoses.[20] While the current veterinary literature includes case reports in which TPE was utilized in the treatment of a variety of immunological, infectious and neoplastic diseases,[21-24] it seems plausible that TPE would be efficacious in the treatment of some intoxications. Specifically, TPE is likely to be effective in the removal of toxins that demonstrate a low volume of distribution (V_d < 0.2 L/kg) and are highly protein bound (>80%).[20,25,26] Substances with a low volume of distribution remain primarily in the intravascular space where TPE can remove them. Many drugs are highly protein bound which results in long half-lives. While this makes them difficult to remove using IHD, TPE is ideally suited to remove protein-bound substances.

It's important to note that because TPE is a convective process, as the patient's plasma is removed, the blood traveling in the straw-like semipermeable membranes of the dialyzer becomes increasingly hemoconcentrated. As this occurs, the risk of clotting the dialyzer increases. Therefore, on each pass through the dialyzer, only a portion of the patient's plasma is actually removed by convection while the rest is mixed with a colloid and returned. Thus, removal of a substance by TPE is limited as the substance of interest is continuously being diluted by the colloid. While an estimated 63% of plasma solutes are removed on the first plasma volume exchange (PV = [(0.08 × wt/kg) × (1−HCT)]), an additional one half plasma volume exchange removes only an additional 15% of solutes and each subsequent exchange is increasingly less efficient.[27,28] Therefore, current treatment recommendations are for 1.5 plasma exchanges over 2-3 hours to remove approximately 78% of a substance of interest from the intravascular space.[20,28]

Anticoagulation

Despite being made of highly biocompatible materials, the catheter and extracorporeal circuit will activate the coagulation pathways.[29,30] This can lead to issues involving catheter blood flow, clotting of the dialyzer, and represents time that the patient cannot receive treatment. Also, the extracorporeal circuit can contain a significant portion of a patient's blood which will be lost if clotting occurs; therefore, appropriate anticoagulation is essential. There are two commonly employed methods of anticoagulation: heparin and citrate.

A constant rate infusion of heparin has historically been the most widely employed method of anticoagulation for extracorporeal procedures. Heparin binds to and causes a conformation change in antithromin.[31] This increases its activity by as much as 1,000 times. Antithrombin inactivates thrombin, factor X, and other proteases involved in blood clotting.[32] Heparin is effective and can be inexpensively monitored using an automated activated clotting timer.[33,34] Due to systemic anticoagulation, the primary risk in veterinary patients is uncontrolled hemorrhage. Monitoring activated clotting time and adjusting the heparin infusion rate can minimize this risk. In people, type II heparin induced thrombocytopenia (HIT) poses a serious risk. This can affect up to 5% of human patients and is the result of antibodies that activate platelets leading to thromboembolic events.[35] Type II HIT has not been documented to occur in cats and dogs.

Recently, there has been interest in regional anticoagulation using citrate to chelate calcium in the extracorporeal circuit.[36] Calcium is an important cofactor throughout the clotting cascade and blood cannot clot in its absence.[37] As blood enters the extracorporeal circuit, citrate is infused which chelates calcium, rendering the blood unable to clot.[37] Calcium chloride is then infused directly to the patient to maintain serum calcium at physiologic levels. The primary benefit of citrate is that the patient is not systemically anticoagulated. Significant risks of hypocalcemia and alkalosis occur,[37,38] necessitating frequent calcium and acid/base monitoring. Regional anticoagulation is popular in humans but its use in veterinary therapy is limited.

Blood Access

Extracorporeal therapies require significant blood flow rates; therefore, appropriate vascular access is essential. In most patients, the only vein large enough to provide this access is the jugular; therefore, these vessels should not be used for other purposes (e.g., blood draw). Dialysis catheters are made of highly biocompatible material such as polyurethane or silicone and designed so that there is minimal mixing of processed and unprocessed blood. While there are many variations, most catheters are either "catheter within a catheter" or "side by side" design (Figure 110-6). In all but the smallest patients, a dual-lumen dialysis catheter can be placed using the modified Seldinger technique. Typically, an 11-14 Fr catheter is placed in large dogs while smaller dogs and cats receive a 7 Fr catheter. In the smallest patients, one single lumen 5 Fr neonatal dialysis catheter can be placed in each jugular vein.

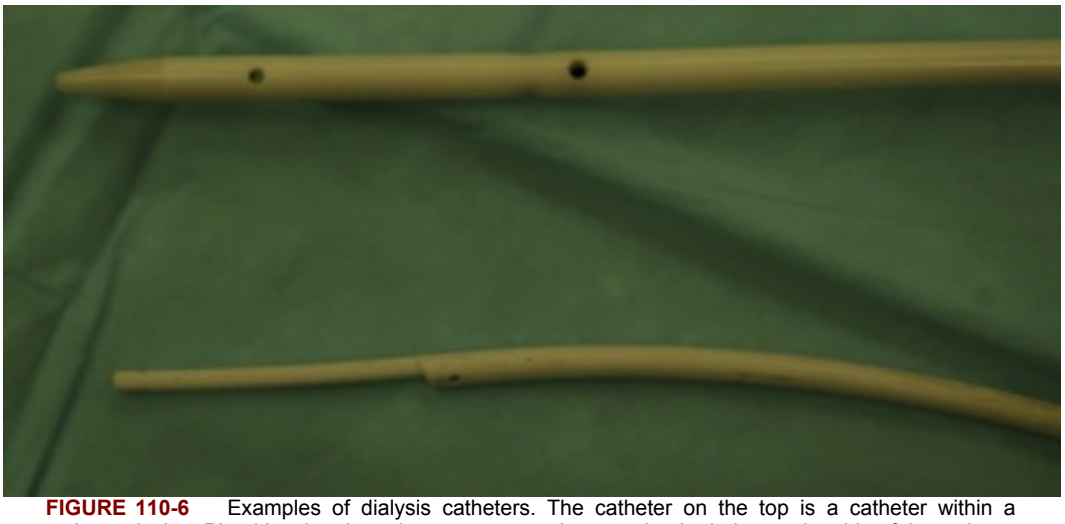

FIGURE 110-6 Examples of dialysis catheters. The catheter on the top is a catheter within a catheter design. Blood is taken in to the extracorporeal system by the holes on the side of the catheter and ejected at the tip. This minimizes recirculation, the mixing of purified and patient blood. The catheter on the bottom of the picture is an example of a "side by side" or double "D" catheter.

Complications

Problems associated with inappropriate anticoagulation and clotting are perhaps the most challenging aspect of providing extracorporeal therapies. Issues regarding clotting of the dialysis catheter and impaired blood flow are common.[39] With patients receiving CRRT over long periods of time, the entire circuit can become rendered inoperable because of blood clots in the extracorporeal circuit. Conversely, some patients develop bleeding at the catheter site after days of receiving heparin.

Hypotension is another potential complication. Although likely multifactorial, it is thought to be at least partly the result of the large amount of blood needed in the extracorporeal circuit.[40] In an attempt to address this problem in smaller patients, pediatric dialyzers and blood lines can be used and the blood pathway can be primed with colloids or blood.

Dialysis disequilibrium syndrome (DDS) can be a major concern when treating azotemic veterinary patients with IHD.[41,42] Although several theories have been proposed, it seems likely that DDS is related to

urea's role as an osmotically active particle.[43,44] As urea accumulates in the blood it diffuses into various tissues throughout the body. Each of these tissues can accept and lose urea at different rates. It is believed that as urea is rapidly removed from blood, there can exist a differential such that urea is higher in some tissues than in the blood.[44] The brain is one example of a tissue that loses urea more slowly than can be removed by IHD. In this case, urea acts as an osmotically active particle causing brain swelling resulting in mentation changes, seizures, coma or death.[44] Replacing urea in the blood with another osmotically active molecule such as mannitol is one strategy to help prevent DDS; another is to avoid rapid urea reductions. Because of its slow nature, dialysis disequilibrium syndrome has not been reported in CRRT.

Indications

The primary indication for CRRT is to control azotemia in cases of AKI where kidney function is likely to return in a relatively short period of time. This makes managing the injury significantly easier and provides time for the kidneys to heal. Anuria and oliguria are not the standards for treatment of AKI; rather, the decision to start therapy should be based on a patient's response to conventional therapy. Electrolyte imbalances, fluid overload and significant azotemia that does not respond to conventional therapy are all indications for treatment. CRRT has been used for treatment of AKI secondary to infectious diseases, heat stroke, and intoxications as well as for treating tumor lysis syndrome. CRRT can also be used in acute kidney injury cases where kidney function is not expected to quickly recover so these cases can be stabilized and transferred to a center offering IHD. In human medicine but not veterinary medicine, it has also been used for the treatment of diuretic resistant heart failure.

IHD is more flexible, offering opportunities to treat AKI as well as CKD patients and an array of intoxications. The ability of IHD to remove toxins is dependent on the substances' characteristics including: size, protein binding, and volume of distribution. The larger the molecule, the more tightly it binds to protein and the more widely it disperses throughout the body, the less likely IHD is to be helpful in treating an exposure. Listings of drugs and toxins that can be effectively removed by IHD and or CRRT are available and maintained by centers offering these modalities.

Measuring Efficacy

Calculations have been developed to help determine if the therapy delivered by a blood purification modality is adequate for patient treatment. Two of the more commonly utilized formulas are the urea reduction ratio (URR) and Kt/V. The URR represents the percent reduction in urea as a result of the therapy provided. It is simply calculated as [(pre-treatment urea − post treatment urea)/pretreatment urea] × 100. Its utility lies in its simplicity and its ability to predict clinical outcomes in people[45]; however, it does have limitations. The URR ignores urea being generated by the body during the procedure.[46] This might be a negligible factor during IHD, but during CRRT it can be significant. Indeed, after the initial CRRT treatment period when blood urea nitrogen (BUN) is reduced into the normal range and is no longer decreasing, the URR effectively becomes 0%. Clearly the body is producing urea and CRRT continues to remove it, but the URR is unable to account for it. In addition, URR does not account for urea that is convectively removed with excess bodily fluids.[46] This leads to an understatement in the urea removed from overhydrated patients.

Kt/V is closely related to the URR; however, it more accurately reflects urea removed by extracorporeal therapies.[46] Kt/V is a unitless number where K is a measurement of urea clearance expressed in mL/min.[47] Total solute removal per period of time is then defined as the product of K (mL/min) and time (minutes) that the patient receives treatment. Dividing Kt by the volume of urea distribution (mL) normalizes this product. Since urea is approximately equally distributed in all body water compartments V can be approximated as 60% of body weight in kilograms.[48] Kt/V calculations account for both urea being generated by the body and urea that is convectively removed with excess bodily fluids. For this reason, the Kidney Disease Outcomes Quality Initiative (KDOQI) group has adopted the Kt/V as the standard for dialysis adequacy determination in people.[49] In veterinary medicine, Kt/V is important for developing CRRT prescriptions as well as for comparing extracorporeal treatments between patients and modalities while the URR is invaluable for developing safe and effective IHD prescriptions.[52] The specifics of calculating Kt/V are discussed elsewhere.[50,51]

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CHAPTER 111

Prostatic Diagnostic Techniquess

Michelle Anne Kutzler

Before beginning any diagnostic techniques, a cursory examination of the prostate should be performed by concomitant rectal and abdominal palpation (see ch. 2). Rectal palpation permits examination of only the dorsal or dorsocaudal aspect of the prostate. Concomitant abdominal palpation not only allows for the cranial aspects of the prostate to be examined but also facilitates better palpation per rectum because the prostate can be pushed into or near the pelvic canal. During palpation, the prostate should be evaluated for size, symmetry, surface contour, mobility, and pain. The normal prostate is bilobed, symmetric, smooth, movable, and nonpainful. Based on history, clinical signs, general physical examination, and palpation findings, the clinician should then determine which combination of the following prostatic diagnostic techniques will most likely yield an accurate diagnosis.

Prostatic Imaging

Ultrasonography

Abdominal ultrasonography is the best imaging modality for evaluation of the prostate because it is a safe, noninvasive method that allows for precise measurements to be taken as well as evaluation of the prostatic parenchyma (see ch. 88). To image the prostate, the transducer is placed against the ventral abdominal wall cranial to the pubis. The prostate should be imaged in both longitudinal (sagittal) and transverse planes to ensure that all areas of the prostate are seen. The true longitudinal plane can be confirmed by observing the hypoechoic urethra. Prostate dimensions are measured on both the longitudinal and transverse planes (Figure 111-1). Prostate length and height are measured on longitudinal images. Length is defined as the maximum prostatic diameter along the urethral axis, while height is defined as the maximum prostatic diameter perpendicular to the axis of the length in the longitudinal view.[1] For a castrated dog, normal prostatic height is about 1 cm. The prostate width is determined from the transverse view, which is obtained by rotating the transducer 90°. The volume of each prostatic lobe can then be calculated using the formula for volume of an ellipse where V (cm^3) = (length × width × height) × 0.523.[2] The total prostatic volume can then be estimated by summing the measures for the left and right lobes. As both age and body weight influence the prostate volume in an intact dog, the expected volume of a normal prostate can be calculated from the formula V (cm^3) = (0.867 × body weight [in kg]) + (1.885 × age [years]) + 15.88.[3]

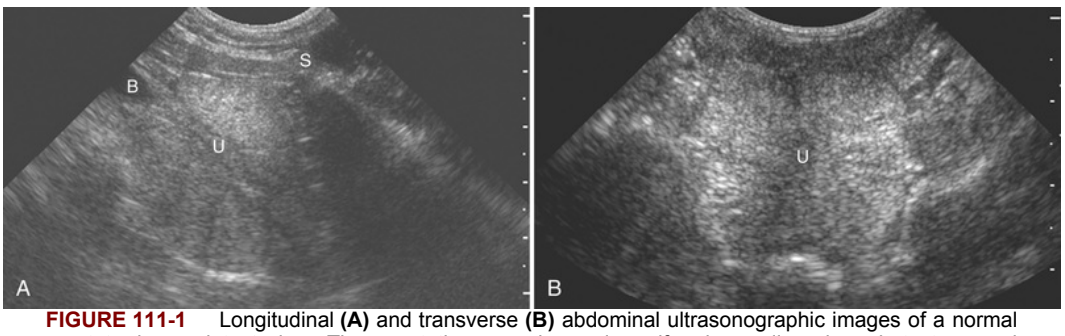

FIGURE 111-1 Longitudinal **(A)** and transverse **(B)** abdominal ultrasonographic images of a normal prostate in an intact dog. The prostatic parenchyma is uniformly medium in echotexture and moderately hyperechoic compared to surrounding structures, with a hypoechoic prostatic urethra (U). Note the anechoic bladder neck (B) and pubic bone shadow (S) on the longitudinal image.

The ultrasonographic appearance of a normal prostate from a intact dog is characteristic: there is a hypoechoic parenchyma with moderately echogenic stippling present in a uniform pattern throughout the gland, similar to that of the spleen, with a capsule that is echoic and has smooth margins.[4] The urethra generally is hypoechoic compared to the prostatic parenchyma, running lengthwise between the two lobes. In contrast, the ultrasonographic appearance of a prostate from a castrated dog is slightly hypoechoic compared to surrounding fat and adjacent structures, such that the urethra is more difficult to visualize. The echogenicity within the prostate should be assessed for focal, multifocal, or diffuse changes in texture. Increased echogenicity and coarse echotexture are associated with hyperplasia, inflammation, infection, and neoplasia (Video 111-1). Ultrasonography allows for determination of the presence or absence of cysts within the prostate. The size, number, and location of the cysts should be identified and noted. The luminal contents of the cysts should be characterized as hypoechoic or anechoic. Parenchymal mineralization also can be observed and it is frequently associated with neoplasia in neutered dogs.[5] However, mineralization occasionally can develop with chronic prostatitis in intact dogs.

Although ultrasound can detect enlargement and changes in the internal prostatic architecture, these features are not pathognomonic for a specific disease. Ultrasonographic appearance of the prostate does not correlate well with culture results, nor does the presence and number of cysts correlate with the presence of infection.[6,7] However, compared to radiography, ultrasonographic imaging is more sensitive in assessing focal or regional parenchymal disease.[8-10] Ultrasonography also has been proven to be a useful method for evaluating responses to pharmacologically-induced prostatic involution.[11,12]

Radiography

The location, size, and contour of the prostate also can be evaluated via caudal abdominal radiography. A normal prostate does not displace the colon or bladder from their normal positions. Radiographically, the prostate has a soft-tissue opacity and its identification is influenced by the differential subject opacity of surrounding tissues. In dogs, radiographic diagnosis of prostatomegaly can be made when the prostate dimensions exceed 70% of the pubic-promontory distance on a lateral radiograph[8] (Figure 111-2). However, prostatic size can vary from a slight enlargement to more than 20 times the normal size, and the severity of enlargement cannot be used to make a diagnosis or prognosis.[13] In addition, the exact dimensions of the prostate often cannot be determined due to superimposition of osseous structures or by lack of abdominal serosal detail from the absence of fat, the presence of ascites, or focal peritonitis associated with prostatitis.[13] The ability of radiography to identify parenchymal changes associated with disease is limited to mineralization, which can be indicative of neoplasia in neutered dogs or chronic inflammation in intact dogs.[5] With caudal abdominal radiography, evidence of sublumbar (medial iliac and hypogastric) lymph node enlargement may be observed from ventral displacement of the colon.[14] In addition, proliferative, lytic, or mixed bony lesions involving the lumbar vertebral bodies and pelvic bones can be identified.[14]

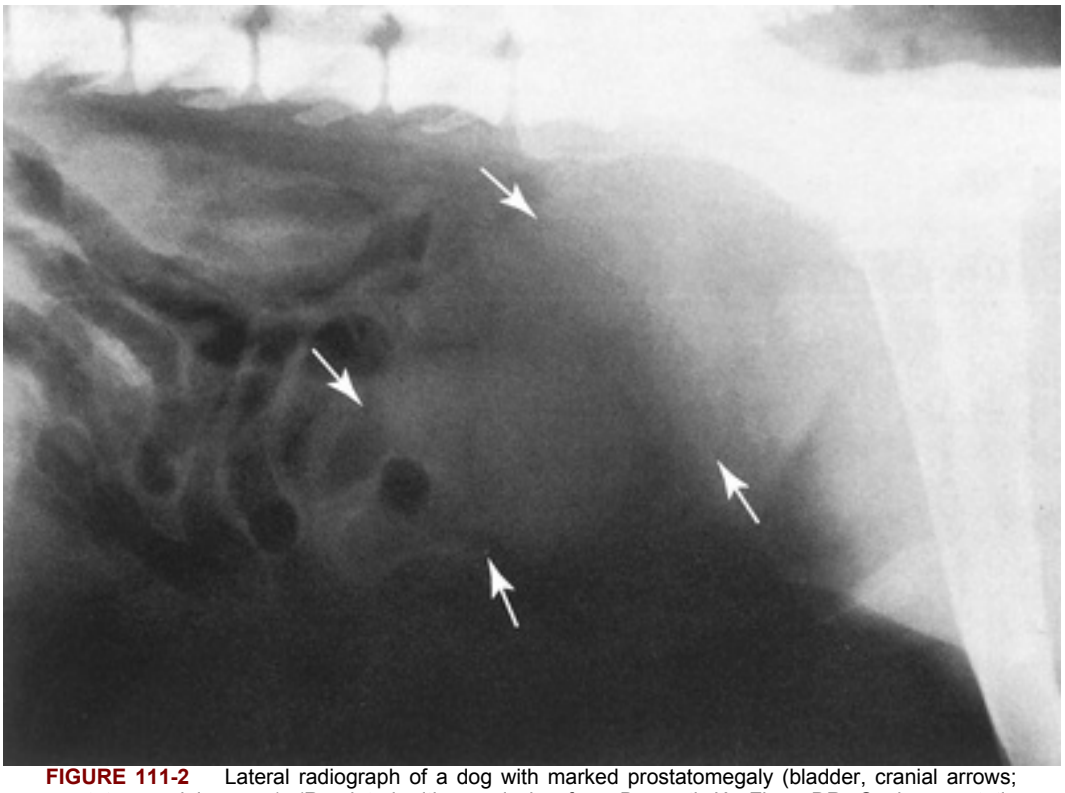

FIGURE 111-2 Lateral radiograph of a dog with marked prostatomegaly (bladder, cranial arrows; prostate, caudal arrows). (Reprinted with permission from Barsanti JA, Finco DR: Canine prostatic diseases. In Ettinger SJ, editor: *Textbook of veterinary internal medicine,* ed 3, Philadelphia, 1989, Saunders, p 1864.)

Distention retrograde contrast urethrocystography (DRCU) has been described as a method for determining prostatic integrity.[15] In a normal prostate, minimal positive contrast will be identified in the prostatic parenchyma near the urethra (urethroprostatic reflux). However, larger volumes of contrast material accumulating within the prostatic parenchyma (intraprostatic reflux) have been reported to occur with all types of prostate diseases.[16] Irregularity or an undulant pattern to the prostatic urethral surface has been associated with benign prostatic hyperplasia, chronic bacterial prostatitis, and neoplasia[15] (Figure 111-3). Narrowing of the prostatic urethral diameter during DRCU has been reported to occur in association with benign prostatic hyperplasia, prostatic abscessation, and neoplasia.[7] However, since the prostatic urethral diameter varies in dogs with normal prostates because of the degree of bladder distention, changes in prostatic diameter must be interpreted cautiously.[17] In addition, the absence of positive results on contrast studies does not rule out the presence of prostatic disease.[7]

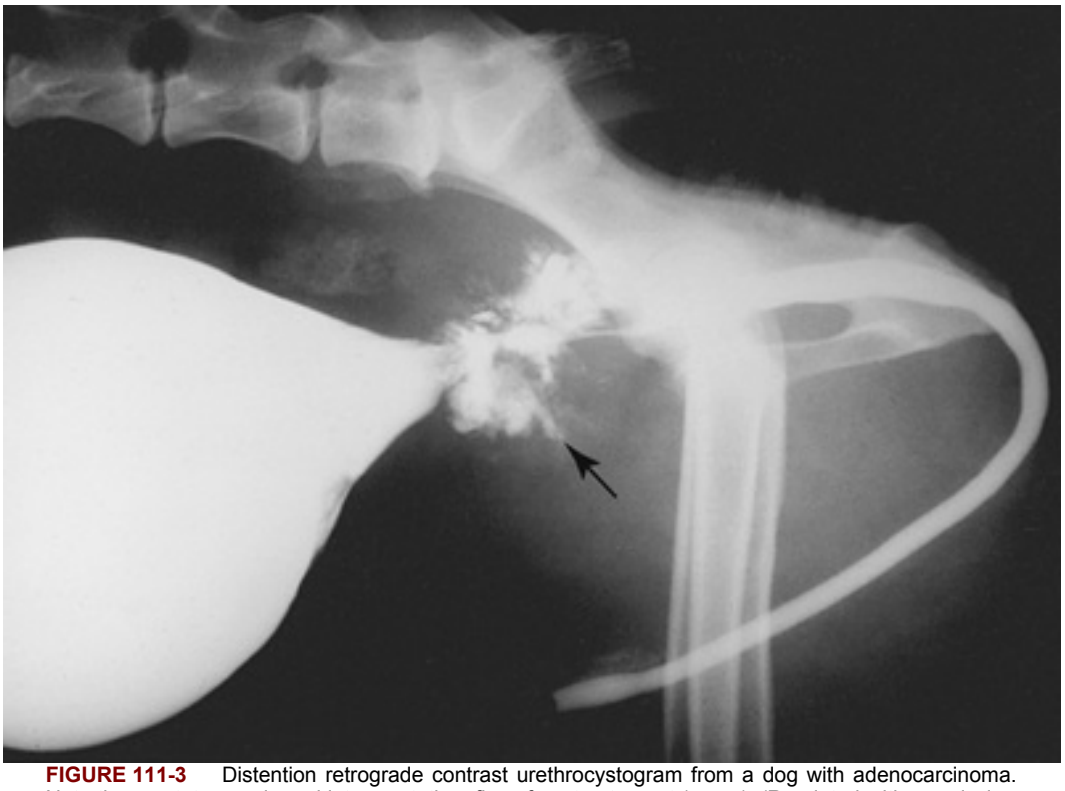

FIGURE 111-3 Distention retrograde contrast urethrocystogram from a dog with adenocarcinoma. Note the prostatomegaly and intraprostatic reflux of contrast agent (arrow). (Reprinted with permission from Root Kustritz MV, Klausner JS: Prostatic diseases. In Ettinger SJ, editor: *Textbook of veterinary internal medicine,* ed 5, Philadelphia, 2000, Saunders, p 1695.)

Other Imaging Modalities

Both computed tomography (Figure 111-4) and magnetic resonance imaging (Figure 111-5) are excellent methods for prostatic imaging as well as imaging of adjacent structures where metastasis could be a concern. Because dogs commonly are used as models for prostatic diseases in humans, there is abundant published information on the use of these techniques in dogs. Magnetic resonance imaging is an accurate modality to assess changes in canine prostatic volume: it is highly correlated with the weight of the excised prostates.[18] However, there is scarce information in the veterinary literature on the usefulness of these tools for diagnosing prostatic disease in the dog.[14,19,20] In veterinary practice, both technologies are expensive to perform, not uniformly available, and require immobilization with general anesthesia.

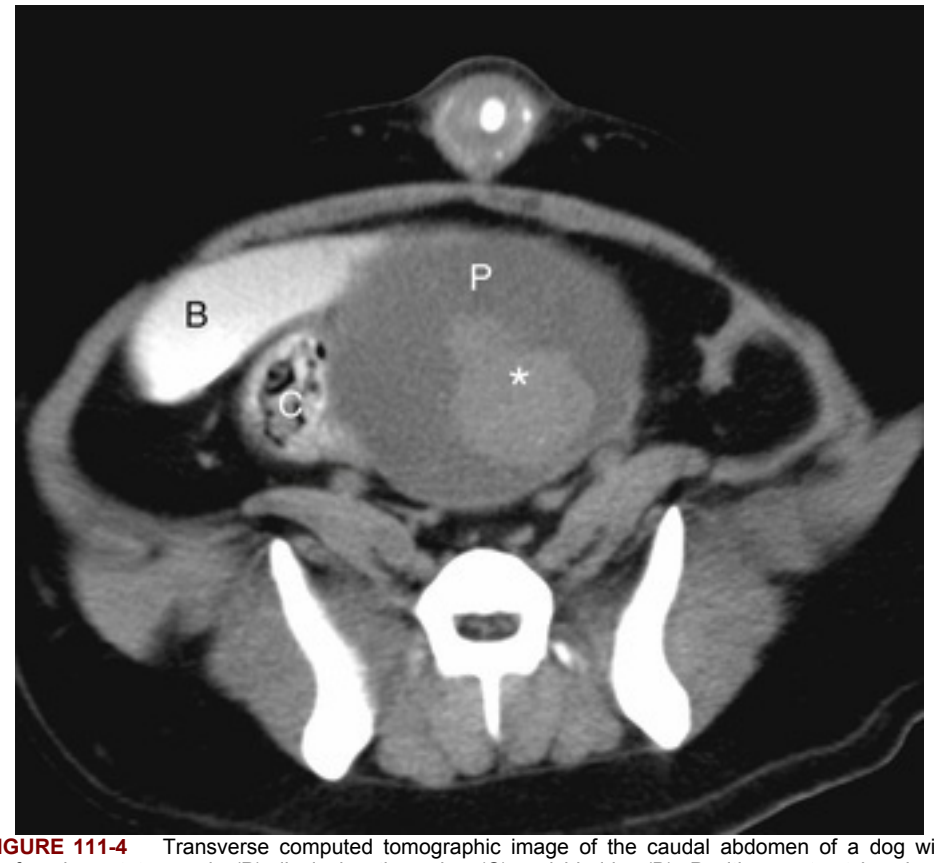

FIGURE 111-4 Transverse computed tomographic image of the caudal abdomen of a dog with profound prostatomegaly (P) displacing the colon (C) and bladder (B). Positive contrast has been placed into the bladder. Note the irregular, high attenuating mass within the prostate (asterisk).

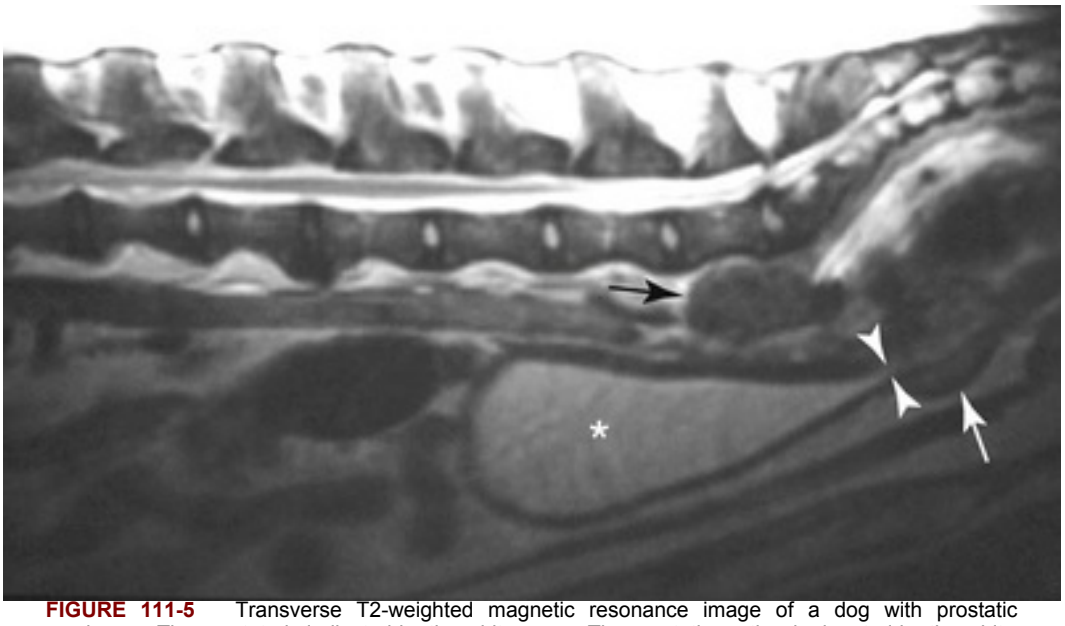

FIGURE 111-5 Transverse T2-weighted magnetic resonance image of a dog with prostatic carcinoma. The prostate is indicated by the white arrow. The prostatic urethra is denoted by the white arrowheads. Ventral to L7-S1 is an enlarged, metastatically infiltrated sacral lymph node (black arrow). The asterisk indicates the urinary bladder. (Reprinted with permission from LeRoy BE, Northrup N: Prostate cancer in dogs: comparative and clinical aspects. *Vet J* 180:149-162, 2009.)

Prostatic Sample Collection

Prostatic fluid should be assessed by cytologic evaluation and quantitative bacterial culture in any dog suspected to have prostate disease. Prostatic fluid can be obtained either by ejaculation or by prostatic massage and traumatic catheterization, where ejaculation is the preferred method of collection especially in cases of suspected bacterial infection and concomitant cystitis. For cystic conditions, fine-needle aspiration of the prostate with abdominal ultrasonographic guidance can yield the most diagnostic prostatic fluid samples (see ch. 89). Depending on the differential diagnoses, prostatic tissue samples might also need to be evaluated to confirm cytologic evaluation, determine appropriate treatment strategies, and provide the most accurate prognosis.

Ejaculation of Prostatic Fluid

The technique to collect prostatic fluid (collection of the third fraction) via ejaculation has been previously described[21] (Video 111-2). To ejaculate a dog, the prepuce is retracted caudally and digital pressure is applied to the base of the penis, proximal to the bulbus glandis. Intense pelvic thrusting occurs with ejaculation. Prostatic fluid (3rd fraction of the ejaculate) can be collected aseptically by ejaculation as long as the collection containers are changed after the combined 1st/2nd fractions are collected. The first two fractions flush out any normal flora colonizing the distal urethra so that the prostatic fluid sample is not contaminated with normal urethral flora. During collection of the third fraction, care must be taken to prevent the tip of the penis from touching the inside of the sterile collection container to avoid contamination of the sample with normal penile mucosal flora. The combined 1st/2nd fraction sample should be saved for semen evaluation if indicated. Cytologic evaluation of the prostatic fluid immediately after collection will aid in determining if an aseptic sample has been obtained. A sample that has been contaminated from the mucosal surface of the penis will contain squamous epithelial cells with Gram-positive cocci but lack neutrophils.[22] If there is concern that the prostatic fluid was contaminated during collection, a second ejaculate can be collected after a 1-2 hour rest period.

Prostatic Massage and Traumatic Catheterization

If the dog will not ejaculate, a prostatic massage and traumatic catheterization should be performed. If cystitis is known to be present, it is preferable to treat the dog with an appropriate antibiotic (e.g., ampicillin) that does not penetrate the prostate before doing the prostatic wash. After the cystitis has been treated successfully, the wash may be performed.

The technique for prostatic massage and traumatic catheterization has been previously described and must be executed carefully.[22] Briefly, using aseptic technique, the bladder is catheterized and all the urine is removed. The bladder is then flushed with sterile saline (5 mL) and this sample is withdrawn and saved (PM-1). The catheter is subsequently retracted so that the tip is distal to the prostate. The prostate is then massaged per rectum for about 1 minute to express a quantity of prostatic fluid into the urethra where it can be collected with a urinary catheter. Sterile saline (5 mL) is slowly infused into the catheter, while occluding the urethral orifice. Thus, the prostatic fluid is flushed into the bladder. The catheter is then advanced into the bladder as aspiration is performed and the sample (PM-2) is collected. The prostatic wash sample should be fixed on a glass slide, stained with hematoxylin and eosin, and evaluated for cellularity (Figure 111-6). By comparing the cytologic examination and quantitative bacterial culture results from both prostatic wash specimens (PM-1 and PM-2), the precise location of the problem can be determined[23]: evidence of infection in both samples is more consistent with cystitis, whereas evidence of infection only in PM-2 supports prostatitis. Prostatic massage is not without risks. In cases of acute prostatitis or prostatic abscess, there is a possibility of triggering septicemia by forcing bacterial organisms into the bloodstream or causing peritonitis.[24] Also, there is the uncertainty as to whether prostatic fluid has been obtained.

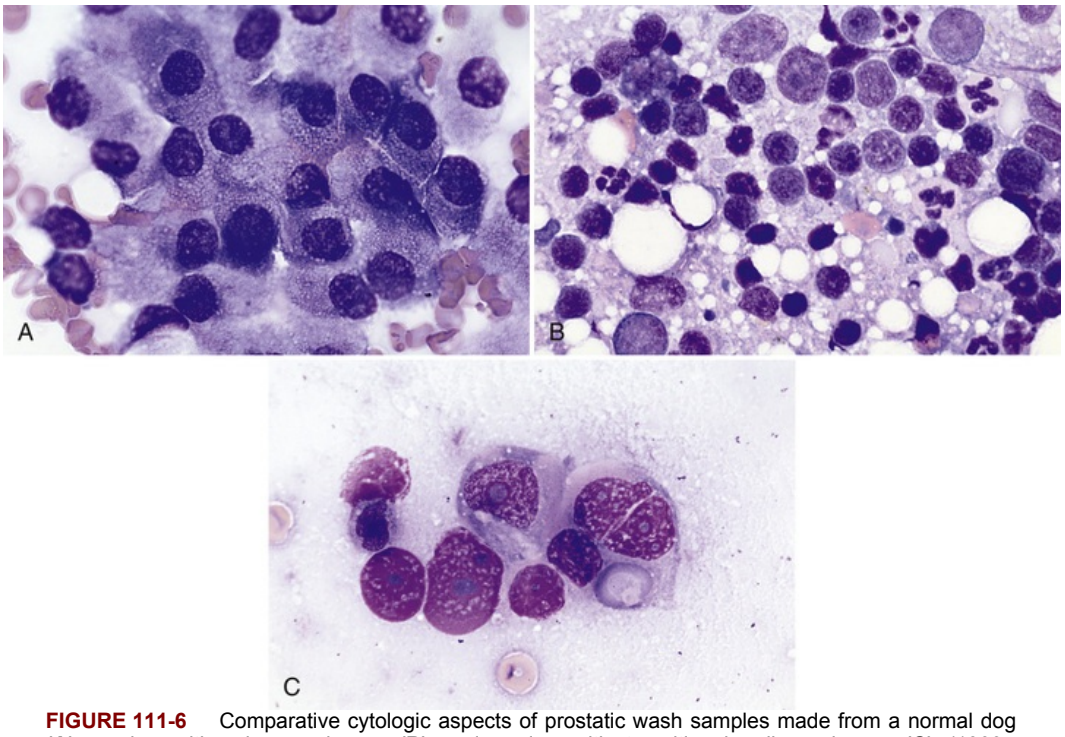

FIGURE 111-6 Comparative cytologic aspects of prostatic wash samples made from a normal dog **(A),** a dog with adenocarcinoma **(B)** and a dog with transitional cell carcinoma **(C)** (1000× magnification). The neoplastic prostatic epithelial cells **(B** and **C)** show multiple signs of malignancy, including anisocytosis, anisokaryosis, increased nuclear to cytoplasmic ratio, multiple nucleoli, and multiple nuclei.

Fine-Needle Aspiration

Fine-needle aspiration (FNA) techniques for collecting prostatic fluid samples have been reviewed.[22] If this technique is to be used, the skin surface through which the needle is inserted should be clipped and aseptically prepared. Once the needle enters the prostate, aspiration should be performed as the needle is redirected several times within the gland (see ch. 89 and 93). Negative pressure is then slowly released and the needle is withdrawn. About 17% of FNA samples are nondiagnostic due to low cellularity.[25] Diagnosis made by FNA could be discordant from a diagnosis made by histopathology if aspiration of fibrotic tissue results in low cellularity or if aspiration of inflamed or dysplastic tissue is misinterpreted as neoplasia.[25] Accuracy can be improved when the technique is combined with abdominal ultrasonography (Video 111-3). If prostatic neoplasia is suspected, a prostatic biopsy can give a greater diagnostic yield than FNA.[26] Complications associated with FNA have included hematuria and periprostatic hemorrhage.[22,26] In addition, aspiration of a sterile intraprostatitic cyst can result in the formation of a prostatic abscess.[27]

Prostatic Biopsy

Percutaneous prostatic biopsy techniques have been reviewed.[28] Careful selection and preparation of patients for biopsy are essential. Prostatic biopsies are not recommended if bacterial prostatitis is suspected unless neoplasia is also suspected or if existence of bacterial prostatitis cannot be confirmed by other tests.[29] Antibiotics should be started 48 hours before a prostatic biopsy is performed if bacterial infection is suspected. A fluid or air-filled urethral catheter can be passed before prostatic biopsy samples are taken to better define the prostatic urethra ultrasonographically and avoid damaging it. The biopsy site should be clipped and prepared aseptically. Ultrasound guidance should be used for performing a prostatic biopsy because it allows for accurate placement of the biopsy instrument. "Blind" prostatic biopsies are not recommended. Ultrasound guidance reduces the risk of post-biopsy complications (hematuria, dissemination of infection, laceration of major blood vessels, urethral fistulation, orchitis, inadvertent puncture of adjacent organs).[27] In addition, ultrasound guidance increases the diagnostic yield of the biopsy sample because

diseased tissue can be targeted. The ultrasound transducer should be covered with a sterile sleeve and sterile acoustic coupling gel should be used. The biopsy instrument (e.g., spring-loaded Tru-Cut type) should be directed tangentially to avoid the central prostatic urethra. The biopsy instrument can be introduced freehand or through a clip-on ultrasound guide. The clip-on guide ensures that the needle remains in the plane of the ultrasound beam. However, the guide limits the maneuverability of the biopsy instrument and can be awkward.

For additional information regarding the application and interpretation of these diagnostic techniques related to specific canine prostatic diseases, see ch. 337.

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Gastrointestinal

OUTLINE

Chapter 112 Gastric Intubation and Lavage
Chapter 113 Gastrointestinal Endoscopy
Chapter 114 Enemas and Deobstipation

CHAPTER 112

Gastric Intubation and Lavage

Deborah C. Silverstein

Gastric Intubation

Placement of a tube through the mouth into the stomach, also known as orogastric intubation, is performed for the purpose of removing gastric contents, decompressing a distended stomach (e.g., gastric dilation-volvulus), lavaging the stomach, and/or administering medications or diagnostic solutions (e.g., barium). Although the procedure itself is not difficult, the potential benefits and risks should be weighed prior to placement of an orogastric tube.

Indications and Complications

The primary indications for orogastric intubation include decompression of a dilated stomach (see ch. 275), toxin removal from the stomach with or without lavage (e.g., potentially lethal toxins, intoxicated patients with an altered level of consciousness requiring controlled decontamination, or those that may form a bezoar or obstruction within the stomach or bowel; see ch. 151), and medication or diagnostic solution administration into the stomach. Potential complications to consider include esophageal or gastric wall damage or perforation, regurgitation followed by aspiration of gastric contents, and adverse effects of general anesthesia. Animals that are critically ill or severely intoxicated could be at higher risk for anesthesia-related complications.

Procedure

Once the patient is identified as a candidate for orogastric intubation, the anesthetic protocol should be chosen according to the patient's systemic status. The main supplies necessary are shown in Figure 112-1 and include:

- Equipment and drugs for induction, maintenance, and monitoring of general anesthesia (not all shown); ensure cuff of endotracheal tube is functional and inflated during procedure
- Orogastric (stomach) tube
- Water-soluble lubricant
- Tape or permanent marker
- Gauze
- Mouth gag
- Receptacle for drainage
- Warm water or isotonic fluid for lavage
- Funnel, bilge pump or stomach pump (Figure 112-2)
- Stool or chair
- Charcoal if indicated
- Suction apparatus (precautionary)

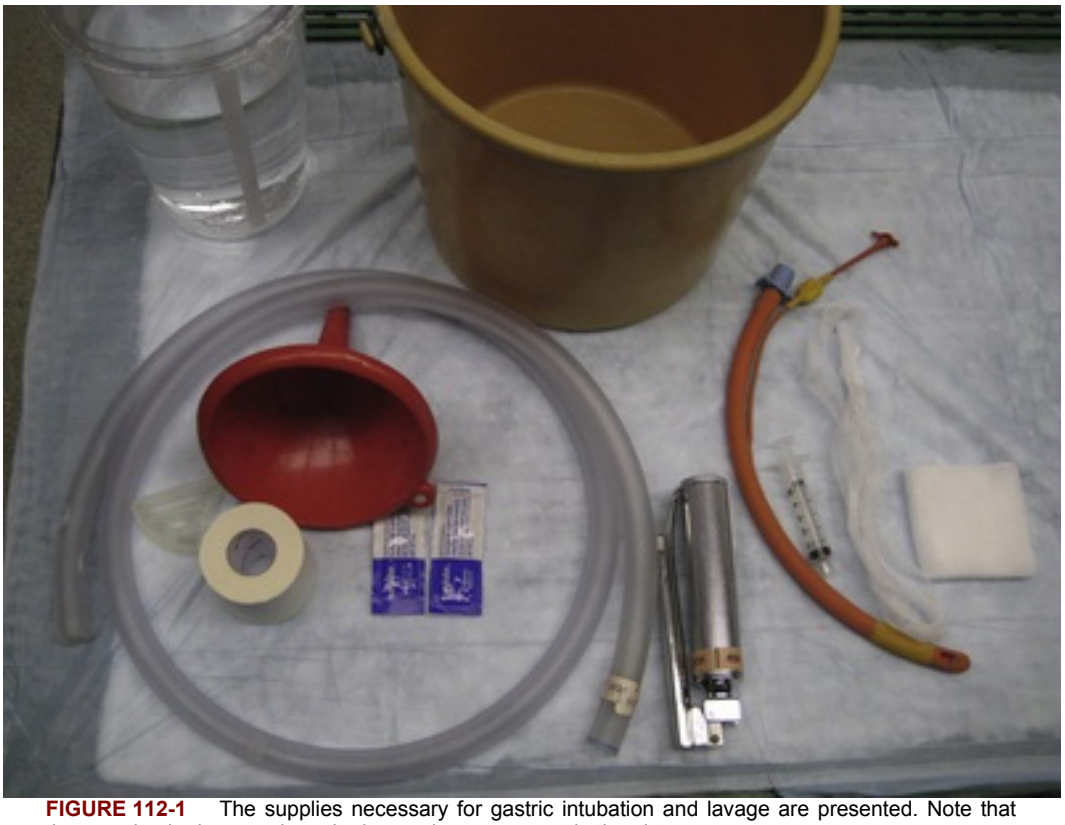

FIGURE 112-1 The supplies necessary for gastric intubation and lavage are presented. Note that the anesthesia drugs and monitoring equipment are not in the picture.

FIGURE 112-2 A JorVet Thirsty Stomach Pump (Jorgensen Laboratories, Inc., Loveland, CO) is pictured. This can be used in place of a funnel to pump through an orogastric tube and into the stomach quickly.

Once the endotracheal tube is in place, the cuff should be inflated prior to the procedure to help prevent aspiration of stomach contents or lavage fluid. The orogastric tube should be a single-lumen, semi-rigid tube with a smooth tip to avoid mucosal trauma. The clinician should choose a tube with the largest diameter possible for the patient's esophagus (approximately the same diameter as an endotracheal tube for the given animal). A 12 Fr red rubber catheter may be adequate for small puppies, whereas an 18 Fr red rubber catheter may be used in adults up to 15 kg, and a formal orogastric tube should be used in dogs weighing >15 kg. Measurement of the tube should be performed using the nares and the last rib as landmarks (Figure 112-3, *A*) and the tube should be marked with either a piece of white tape (Figure 112-3, *B*) or a permanent marker.

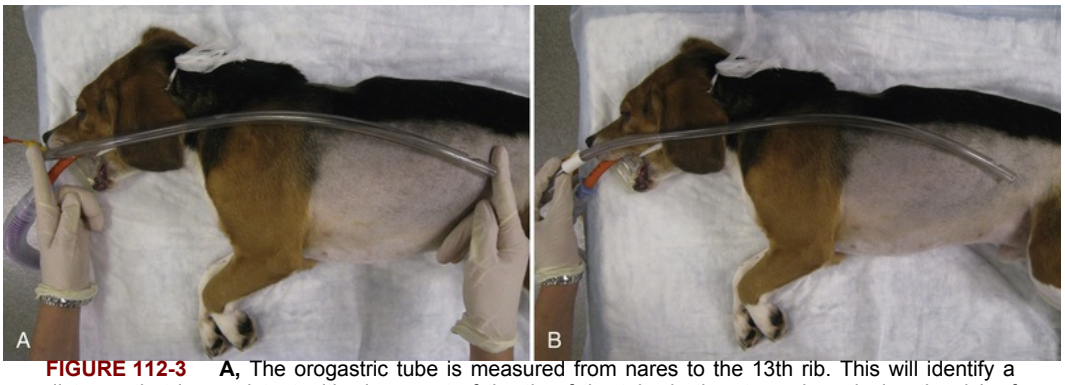

FIGURE 112-3 **A,** The orogastric tube is measured from nares to the 13th rib. This will identify a distance that is consistent with placement of the tip of the tube in the stomach, reducing the risk of over-insertion (gastric wall trauma), under-insertion (esophageal position of the tube tip), or, if the patient's trachea were not intubated with an endotracheal tube, misplacement (intra-tracheal). **B,** A piece of tape is placed on the tube to mark the distance from the tip of the nose to the 13th rib. Alternatively, the operator could use a permanent marker.

There is some controversy as to whether animals should be sedated or anesthetized prior to passing the orogastric tube. The author's preference is to anesthetize the patient and place an endotracheal tube with the cuff inflated to help protect the airway in case the animal regurgitates or vomits during the procedure. The exception may be neonates that are having an orogastric tube passed for a feeding and do not typically exhibit the gag reflex during the procedure (see ch. 171). Suction catheters and additional necessary equipment should always be available prior to starting the procedure so the oropharynx can be cleaned prior to extubation, or in the event of regurgitation or vomiting following orogastric extubation.

Once the patient is anesthetized and the endotracheal tube is placed, the mouth can be maintained in the open position using either a mouth gag or inner roll of tape, if necessary. Water-soluble lubricant should be applied to the end of the orogastric tube and the tube advanced slowly into the esophagus, located in the left dorsal aspect of the pharynx. The other end of the tube should always be lower than the dog (and inside a collection container) to allow for gravitational drainage. The tube is advanced gently to the predetermined length to reach the stomach. Dogs with gastric dilation-volvulus might require slight forward pressure with a twisting motion to aid with entry through the cardia into the stomach (Video 112-1). If there is continued resistance to passage of the tube, the operator can blow a small amount of air into the tube while gently advancing it (it is recommended that a piece of gauze be placed over the end prior to doing this to avoid contamination of the operator's mouth). Animals with severe distention of the stomach may require percutaneous trocarization of the stomach prior to successful passing of the orogastric tube. Once the tube is advanced to the premeasured length, there should be some fluid or gastric contents apparent in the collection container below the level of the patient; if not, careful ballottement of the abdomen may increase pressure and help increase flow through the tube (see ch. 17). If gastric contents are occluding the tube and preventing drainage, 10-30 mL of warm water can be flushed into the tube to dislodge the obstruction.

In order to prevent fluid from leaking out of the tube and into the esophagus or pharynx during removal, the tube should be tightly kinked ≈10 cm from the operator's end prior to removal. The kink should be maintained firmly until the tube is fully removed from the animal. The mouth and pharynx should be closely inspected for residual fluid or stomach contents and cleaned with gauze or suction as needed.

Gastric Lavage

Removal of gastric contents via orogastric intubation is referred to as gastric lavage. It is most commonly performed in an attempt to remove toxic material from the stomach or to empty the stomach prior to gastrotomy. It rarely has been used as a cooling technique or to confirm bleeding from the upper gastrointestinal (GI) tract.

The American Academy of Clinical Toxicology has concluded that the poisoned patient should not receive routine GI decontamination and clinical evidence in humans has shown no clear benefit of gastric lavage over activated charcoal for the treatment of toxin ingestion.[1,2] However, lavage currently is performed at many human hospitals and it still is a part of the current recommendation for the treatment of small animals in specific scenarios, despite limited evidence.[3-5] Before emesis or gastric lavage is performed, the clinician should always ensure that Bailey's "GI decontamination triangle" questions have been adequately answered[6]:

1. Is the ingested toxin likely to cause significant effects?
2. Is GI decontamination likely to change the outcome?
3. Do the risks of GI decontamination outweigh the potential benefits in this particular patient?

Patients that might benefit from gastric lavage include animals that have ingested a potentially harmful amount of toxin within 1 hour of presentation, but where induction of emesis is not deemed appropriate due to neurologic impairment (or emesis is not effective at removing gastric contents; also see ch. 151). If animals have ingested a very small amount of a toxin, or have already vomited prior to presentation, the potential risks and benefits of gastric lavage should be considered because the procedure is not benign, and activated charcoal administration may prove to be a safer option. There are exceptions, especially when very large amounts of a dangerous substance have been ingested. Gastric lavage is not indicated for the treatment of food bloat (without torsion) or ingestion of material that solidifies in the stomach, such as polyurethane adhesive (e.g., Gorilla Glue); the latter requires gastrotomy for removal. Gastric lavage is contraindicated in animals that have ingested caustic or volatile substances since esophageal reflux, mucosal damage, and aspiration pneumonia could result. Three canine studies have evaluated the effectiveness of gastric lavage for reducing the bioavailability of different markers (sodium salicylate or barium sulfate).[7-9] As expected, gastric lavage at 15 minutes recovered a much greater amount of the marker than at 30 or 60 minutes. All three studies showed <15% recovery at 1 hour post-administration of marker. Another study examined dogs that were given 500 mg/kg of aspirin, then lavaged and given activated charcoal (1.5 g/kg) 30 minutes after drug administration.[10] There was a 37% reduction in peak plasma salicylate concentration in the treated group compared to the control group, confirming the fact that early lavage (and charcoal therapy) may be worthwhile. It is not known how this treatment compares to induction of emesis in neurologically intact animals that have ingested non-corrosive toxins.

The primary risks of gastric lavage include anesthesia-related complications, aspiration of stomach contents, and trauma to (or perforation of) the esophagus or stomach. The incidence of GI tract perforation is very low in people,[2] and is assumed to be low in small animals, but there are no definitive data to prove or disprove this assumption in veterinary medicine. Excessive absorption of hypotonic lavage fluid could lead to water intoxication with hyponatremia and hypochloremia, but this is unlikely if a majority of the fluid is drained following administration. It is helpful to record the volume of fluid that is infused and retrieved to avoid excessive water administration. In order to perform gastric lavage, a single- or double-lumen orogastric tube should be placed as described above, the animal positioned in lateral recumbency, and the endotracheal tube cuff checked for inflation. Approximately 10-30 mL/kg of warm lavage fluid (e.g., isotonic saline or water) is infused into the stomach using a stomach pump, bilge pump, or gravity flow through a funnel (note: never use a hose). Once the fluid has been infused, the operator's end of the orogastric tube should be directed into the designated container and the effluent passively drains via gravity flow (Video 112-2). While fluid is infused, and when it is being drained, the stomach should be palpated to monitor for overdistention and gently balloted to assist with emptying of the lavage fluid, respectively. Suction should never be used for emptying the stomach as this may cause mucosal trauma. The retrieved stomach contents should be examined for foreign material or toxins and submitted for toxicologic analysis, if indicated. The infuse-drain cycle should be repeated several times (typically 5-10 times) in order to effectively clean out the stomach. The animal can be turned to the opposite recumbency for additional gastric lavages, as indicated, but it is important to check the endotracheal tube position and cuff inflation after repositioning. Following the final lavage cycle, activated charcoal (1-5 g/kg), with or without a cathartic, can be administered through the orogastric tube and into the stomach (and flushed in with water), if indicated. It is important that the stomach not be distended prior to recovery and extubation, in order to minimize the chance of vomiting and aspiration. There is no proven advantage to the use of pre-lavage activated charcoal administration in human medicine. This was previously thought to decrease intestinal absorption of toxin that could be advanced into the duodenum during the lavage.[2]

Following gastric intubation +/− lavage, the animal should remain endotracheally intubated with the cuff inflated until sternal and swallowing. Extubation should not be delayed in cats, however, due to risk of laryngospasm. Therefore, cats should either have a reduced dose of activated charcoal administered, or it can be given after recovery. Supplies for oropharyngeal suction should be readily available during recovery in case there is fluid in the mouth or pharynx that can be removed easily prior to extubation. The patient should be monitored closely for evidence of nausea or regurgitation and treated accordingly.

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CHAPTER 113

Gastrointestinal Endoscopy

M. Katherine Tolbert

Overview

Standard upper (esophagogastroduodenoscopy, EGD) and lower (colonoscopy, proctoscopy) gastrointestinal (GI) endoscopy are techniques that allow for visualization of the lumen and mucosal lining of the oropharynx, esophagus, stomach, proximal duodenum, ileum, colon and rectum. Advanced endoscopy procedures, including video capsule endoscopy (see ch. 276) and interventional endoscopy (see ch. 123), allow for assessment of additional sections of the GI tract. With proper equipment and operator training, GI endoscopy is a minimally invasive technique that can be used for a variety of diagnostic and therapeutic interventions. Diagnostic procedures include biopsy and collection of tissue or fluid for histopathologic examination, cytology, culture and/or infectious disease testing. Therapeutic GI endoscopic procedures include retrieval of ingested foreign bodies, dilation of esophageal and rectal strictures, polypectomy, and placement of enteral feeding tubes and stents. Unlike for human patients, no guidelines have been established to identify animals most likely to benefit from GI endoscopy; however, the indications for GI endoscopy are similar. Common indications for pursuit of GI endoscopy in companion animals include the presence of chronic GI signs (vomiting, diarrhea, weight loss) that persist despite trial therapies, signs compatible with active or chronic GI bleeding (hematemesis, melena, hematochezia, unexplained chronic iron deficiency anemia), dysphagia and/or regurgitation, and/or for therapeutic indications mentioned above. First-line diagnostic tests and empirical therapy (e.g., diet trial, anthelmintics) should be considered prior to pursuit of endoscopy as a diagnostic tool.

Equipment

Endoscope cost, frequency of use, and versatility guide the type of endoscope and endoscopic equipment purchased. The characteristics of standard endoscopic equipment used for canine and feline GI endoscopy are listed in Table 113-1.

TABLE 113-1

Characteristics of Endoscopes and Associated Equipment Commonly Used for Canine and Feline GI Endoscopy

ENDOSCOPE TYPE	FLEXIBLE VIDEOENDOSCOPE PREFERRED FOR MOST APPLICATIONS
Insertion tube diameter and length	5.9*-11 mm; 100-160 cm
Instrument channel	2.0-2.8 mm
Endoscope characteristics	4-way deflection of at least 180° in one plane × 90° in 3 planes; forward viewing
Tower	Monitor, image capture system
Endoscopy performance equipment	Portable or wall suction, irrigation instrumentation, biopsy forceps, retrieval instrumentation (baskets, snares, etc.), cytology brushes, injection needles, cautery
Additional equipment	Cassettes with sponges, glass slides, formalin jars, endoscopy cleansing solutions, endoscope cleaning adaptors, pressure (leak) tester

Light source	Xenon light source and cable

*Smaller diameter endoscopes might be preferred for exclusively feline practices.[1]

Flexible video endoscopes with an image capture system are preferred for most GI endoscopic procedures. Video endoscopy is more expensive and requires the use of a video monitor; however, this technology provides superior resolution and is a better diagnostic tool compared to fiberoptic endoscopes. Rigid endoscopes can be used for esophagoscopy and proctoscopy, and can be useful in the dilation of strictures, retrieval of foreign bodies, and biopsy of tumors in the proximal esophagus, distal colon, and rectum. However, rigid endoscopes are limited in their diagnostic capabilities because of inadequate reach and inflexibility. Smaller diameter flexible endoscopes can be preferred for intubation of the duodenum of small patients, but they sacrifice the diameter of the instrument channel, which restricts the size of biopsy samples. Smaller diameter endoscopes also result in less effective simultaneous suction while an instrument is in the instrument channel. Endoscopes ≤100 cm in length might not reach the duodenum or ileocecocolic junction in large- to giant-breed dogs. Therefore, if practice finances only allow for the purchase of one endoscope for both canine and feline GI endoscopy, a mid-size diameter flexible endoscope (5.0-6.0 mm) with the largest instrument channel possible (≥2.2 mm) and an insertion tube length of at least 120 cm is recommended.

The quality of endoscopic GI biopsy samples has a major impact on the consistency and accuracy of the histopathologic exam in both dogs and cats. When gastric and duodenal tissue samples are of a lower quality, a larger number of them will be needed to identify lesions.[2] Therefore, much attention should be paid to both the quality of the biopsy technique as well as biopsy instrumentation. Endoscopic biopsy forceps are available in a myriad of sizes (large, standard, pediatric cup), shapes (round, oval) and styles (spikes, alligator teeth). A recent study performed in healthy dogs demonstrated that size but not biopsy cup shape or presence of a spike had a significant influence on adequacy of histologic assessment.[3] Large capacity forceps were superior to small capacity forceps in providing specimens with less crush artifact and of higher quality and adequacy for histopathologic exam. Additional studies will need to be performed to determine if these findings translate to dogs and cats with gastrointestinal disease; however, using the largest cup biopsy forceps to obtain GI tissue samples is recommended.

Patient Preparation

Endoscopy often is useful to further characterize an abnormality (e.g., filling defect, stricture) identified on barium contrast radiography. However, unless the severity of signs dictates immediate examination, endoscopy should be delayed at least 24 hours following administration of barium because barium can hinder visualization of the GI mucosa and can obstruct the endoscope instrument channel if aspirated (Figure 113-1).

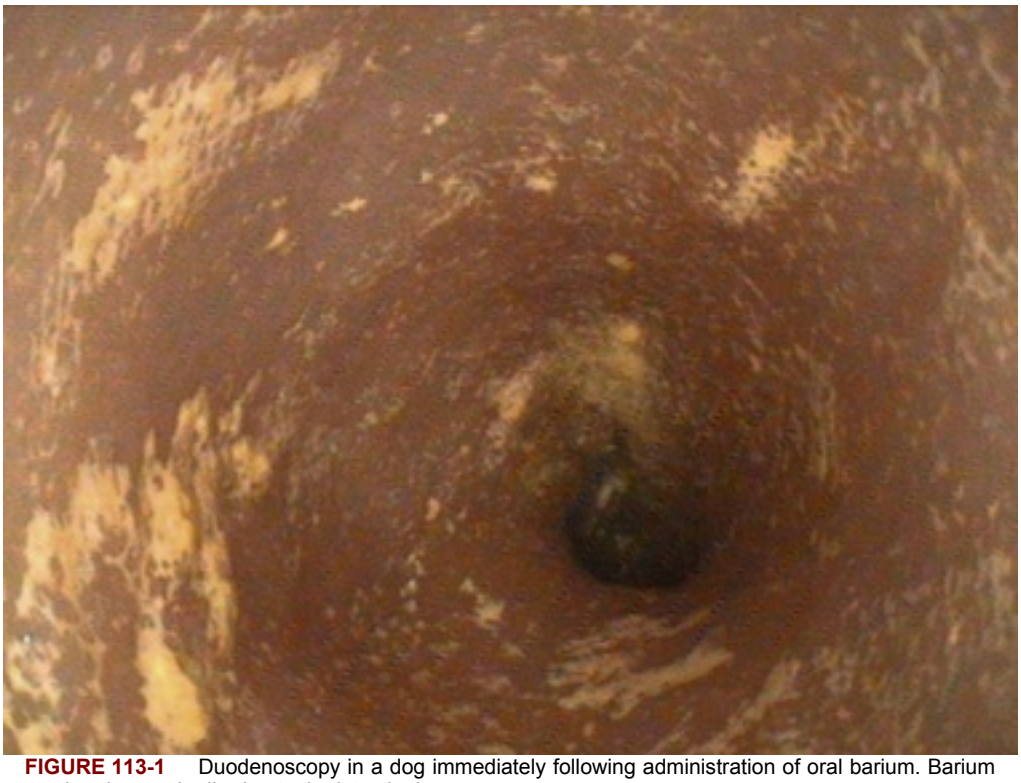


FIGURE 113-1 Duodenoscopy in a dog immediately following administration of oral barium. Barium can be observed adhering to the intestinal mucosa.

A fasting period of 12-24 hours and 24-48 hours is recommended for EGD and lower GI endoscopy, respectively. Water should be restricted up to 2-4 hours before the procedure; however, intravenous fluids should continue to be administered to prevent dehydration in animals with severe vomiting and/or diarrhea. Unless concern exists for vomiting and aspiration, a GI lavage solution (e.g., polyethylene glycol [GoLytely]) should be administered 12-18 hours prior in addition to multiple warm water enemas in preparation for colonoscopy.[4] The total dosage is 60-120 mL/kg (higher dosage recommended, barring nausea) in dogs and 60 mL/kg in cats. The solution should be divided into 2 fractions, administered 2-4 hours apart (2 or 3 fractions, 2 or more hours apart in cats), and administered slowly via an oro- or nasogastric tube to reduce the chance of vomiting and aspiration (see ch. 112); administration should be stopped if there is evidence of nausea (e.g., ptyalism) or vomiting.[5] Enemas, which should be administered well before or after administration of GI lavage solutions to further minimize the risk of vomiting the lavage solution, are given until the colonic fluid is clear (see ch. 114). Precautions against triggering nausea are warranted with gastric lavage solutions because their aspiration can be catastrophic. If possible, drugs affecting GI motility or sphincter tone should be withheld prior to GI endoscopy. Although there often is concern regarding premedication with opioids and alpha-2 agonists prior to GI endoscopy, hydromorphone with or without glycopyrrolate, butorphanol, and medetomidine have been demonstrated not to have a significant effect on the intubation of the feline pylorus by an experienced endoscopist. Therefore, these drugs can be reasonable choices to premedicate cats prior to EGD,[6] and the same approach has been extrapolated to dogs.

GI endoscopy often is performed in dedicated endoscopy suites, with the dog or cat under general anesthesia to reduce stress and anxiety associated with the procedure. A cuffed endotracheal tube is used for preventing complications such as aspiration pneumonia. The animal is positioned in left lateral recumbency for flexible GI endoscopy (to suspend the right-sided pylorus) unless a percutaneous endoscopic gastrostomy (PEG) feeding tube is being placed, in which case the animal is positioned in right lateral recumbency to allow percutaneous access to the gastric fundus. A mouth gag is recommended to prevent trauma to the endoscope; however, spring-loaded mouth gags should not be used in cats as cats lack an internal carotid artery and therefore are susceptible to post-anesthetic blindness secondary to mouth gag–associated compression of the maxillary artery.[7]

Esophagogastroduodenoscopy

Esophagogastroduodenoscopy always should be performed systematically and with the same approach, to ensure a comprehensive examination. With the animal's neck in extension, the flexible endoscope is passed along midline into the caudal oropharynx and through the pharyngoesophageal sphincter, which lies dorsal to the larynx (Video 113-1). When the tip of the endoscope has entered the proximal esophagus, air is insufflated to open the collapsed lumen. Manual compression of the proximal esophagus by an assistant can be necessary to maintain esophageal insufflation for visualization throughout the cervical and thoracic esophagus. The esophageal lumen is kept in the middle of the viewing field. The esophageal mucosa is pale-pink and, in cats, submucosal vessels often are visualized. The trachea can be observed to slightly compress the proximal esophagus extraluminally, and the heartbeat can be seen transmitted through the wall of the thoracic esophagus. Unlike the canine esophagus, which is comprised entirely of striated muscle, the distal third of the feline esophagus has a herringbone appearance due to its composition of smooth muscle in this area. The gastroesophageal sphincter generally is closed. The endoscope might need to be angled slightly dorsally, with air insufflation, to pass through the sphincter and into the gastric cardia. The stomach of healthy dogs and cats is darker in color than is the esophagus, and the gastric mucosa is arranged into rugal folds in the fundus and body. The endoscopist should minimally distend the stomach with air to allow for separation of the rugal folds and performance of a cursory examination. Inspection of the mucosal lining and luminal contents (e.g., presence of bile, food) of the gastric cardia, fundus, body, incisura angularis, and pyloric antrum is performed to ensure that endoscopic artifacts are not mistaken for lesions during later examination. A full examination should be postponed until after inspection and biopsy of the duodenum, to avoid paradoxic motion of the endoscope and difficulty in crossing the pyloric sphincter secondary to gastric distension. Following the cursory exam of the stomach, the endoscope is advanced in the minimally-distended stomach along the greater curvature towards the pyloric antrum and through the pyloric sphincter. The endoscope tip should be kept in line with the center of the pyloric orifice. Light to moderate force applied by the endoscope tip against the pyloric sphincter with intermittent insufflation of air can be necessary to advance through a closed pyloric sphincter. A smaller diameter endoscope (<9 mm) is needed to traverse the pyloric canal of small cats. Occasionally, a “fold” may be present over the pyloric sphincter, making access more difficult in some animals. Temporarily positioning the animal into right lateral recumbency can rectify this problem. Following intubation of the pyloric sphincter, a brief “red out” occurs as the walls of the pylorus close around the tip of the endoscope. The endoscope tip is directed ventromedially (typically, downward and to the right on the screen) to enter into the lumen of the proximal duodenum. With gentle force, the endoscope tip is advanced slowly, away from the wall of the proximal duodenum, through the cranial duodenal flexure, and into the descending duodenum. If substantial resistance is felt, the endoscope tip should be retracted and minor adjustments should be made. The healthy small intestinal mucosa is pale-pink with a shag carpet appearance created by the villi. The major duodenal papilla (and occasionally the minor duodenal papilla in dogs) can be visualized following entry into the descending duodenum (see ch. 274). Peyer's patches can be identified in the canine descending duodenum. Care should be taken to examine the mucosa when the endoscope first is being passed through the descending duodenum, because the duodenum is more friable than the esophagus and stomach, and iatrogenic endoscopic trauma could result in the appearance of mucosal lesions upon retraction of the endoscope (Figure 113-2). After advancing through the descending duodenum, the endoscope is passed through the caudal duodenal flexure into the transverse and ascending duodenum. Generally, the jejunum can be reached in small dogs and cats when using a moderate-length endoscope. Duodenal biopsies then are taken as the endoscope is retracted towards the pyloric sphincter.

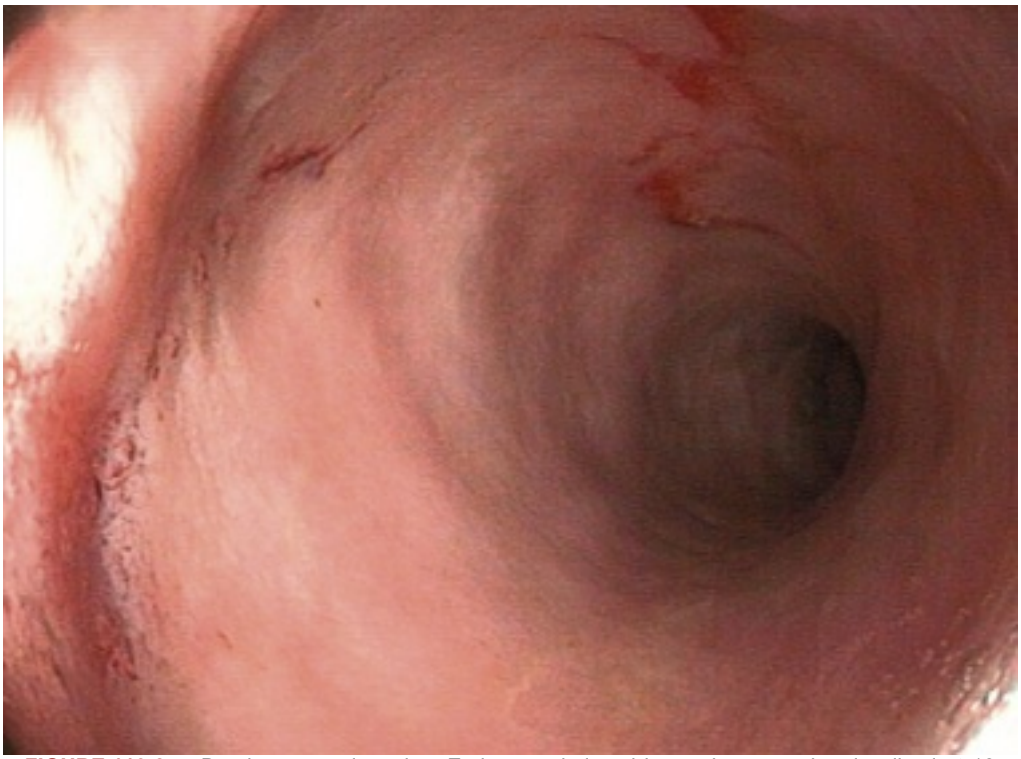


FIGURE 113-2 Duodenoscopy in a dog. Endoscope-induced hemorrhage can be visualized at 12 o'clock.

The pyloric antrum can be examined fully following retraction of the endoscope from the pyloric sphincter. As the insertion tube (endoscope body) continues to be retracted, the rugal folds of the greater curvature should be inspected prior to fully distending the stomach to complete the examination. When insufflating, care should be taken to avoid overinflating the stomach because this can alter the appearance of the gastric mucosa, result in respiratory depression from diaphragm impairment, and cause vagally-mediated bradycardia. Retroversion of the endoscope ("J maneuver") is performed to visualize the incisura, cardia, and fundus. With the endoscope along the greater curvature in the moderately distended stomach, the endoscope tip is deflected 180° so that the shape of the endoscope resembles the letter J. The endoscope then can be retracted towards the gastroesophageal sphincter to obtain a close-up view of the cardia and fundus. Following examination, biopsies should be collected from each region of the stomach.

After completion of the EGD exam and collection of biopsy samples, air and liquid should be completely evacuated from the stomach and esophagus with suction to reduce the risk of bloat, reflux and aspiration.[1,8,9]

Lower GI Endoscopy

Colonoscopy is an easier technique to perform for beginners compared to an EGD procedure. Following a digital rectal examination to evaluate for the presence of a perineal hernia and rectal masses and/or strictures, a well-lubricated endoscope is inserted past the anal sphincter into the rectum (Video 113-2). An assistant aids in air insufflation of the rectal lumen by closing the perianal tissue manually around the endoscope. The endoscope is advanced into the descending colon with the colonic lumen maintained in the center of the viewing field at all times, except when traversing flexures. If the colon has been adequately prepped, the healthy colonic mucosa appears to be pale-pink to slightly orange, shiny, and smooth. When the splenic flexure is encountered, the endoscope tip is directed dorsally while the endoscope is gently advanced against the colonic mucosa. With some minor adjustments, the endoscope generally glides easily into the transverse colon. The hepatic flexure follows the fairly short segment of the transverse colon. The endoscope is advanced gradually into the ascending colon, where the ileocecocolic junction can be viewed.

Biopsy of the ileum is recommended in all cats and dogs with signs of small intestinal disease, unless there is concern for perforation. The jejunum and ileum are the most common segments of bowel affected with inflammatory bowel disease and alimentary lymphoma in cats.[10] Thus, if endoscopy is pursued rather than exploratory laparotomy, colonoscopy and ileal biopsy should be included with EGD. Visualization of the ileal

mucosa often is not possible nor recommended in small dogs and cats, especially when a pediatric endoscope is not available; therefore, unless concern for perforation exists, blind ileal biopsy must be performed (Figure 113-3). In medium- to large-breed dogs, the ileocolic valve can be traversed but doing this might require the assistance of biopsy forceps to serve the function of a stylet. Once the closed biopsy forceps are gently advanced beyond the valve, the endoscope is passed over the forceps into the ileal lumen. If necessary to rectify difficulty in traversing the ileocolic valve because of an oblique valve angle, the animal can be temporarily placed in right lateral recumbency. Following biopsy of the ileum, the cecum can be inspected with the endoscope tip sitting at the cecocolic orifice. As with EGD, complete examination and biopsy of the colonic wall is performed as the endoscope is retracted towards the rectum.[1,8,9]

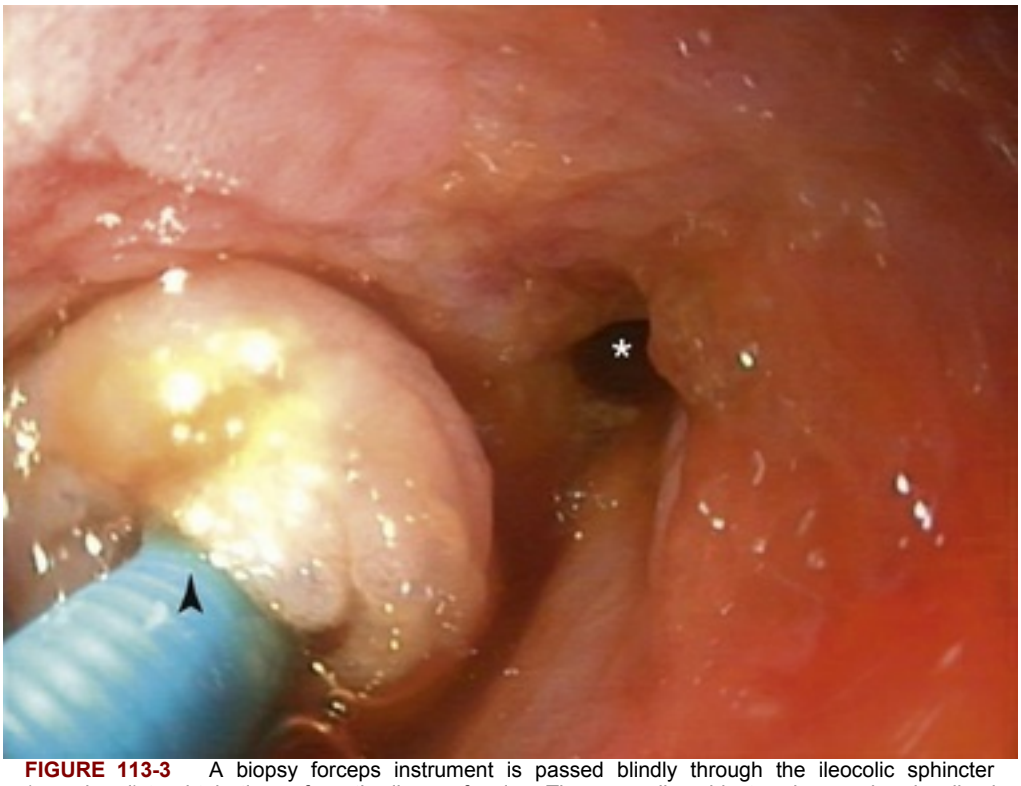


FIGURE 113-3 A biopsy forceps instrument is passed blindly through the ileocolic sphincter (arrowhead) to obtain tissue from the ileum of a dog. The cecocolic sphincter also can be visualized (asterisk).

Endoscopic Examination and Biopsy

During GI endoscopic procedures, the endoscopist should evaluate the GI mucosa for the presence of hyperemia, vascularity, edema, discoloration, hemorrhage, erosions and/or ulcerations, friability and other mucosal lesions. Luminal contents including food, bile, and other fluid should be noted. A standardized endoscopy report, such as that supplied by the World Small Animal Veterinary Association (WSAVA) International GI Standardization Group, should be used for documenting and standardizing GI endoscopic examinations: duodenal mucosa, colonic mucosa, the complete EGD procedure, and the complete colonoscopy procedure each can be recorded in detail with such forms[11] (E-Figures 113-4 and 113-5).

ENDOSCOPIC EXAMINATION REPORT: UPPER GI ENDOSCOPY

Date of procedure: ..... **Case Number:** .....

Patient and client information:
(card or stamp)

PROCEDURE(S): _____
Indication(s) for procedure: _____
Endoscope(s) used: _____
Forceps/retrieval device(s) used: _____

PROBLEMS/COMPLICATIONS: None ☐
Perforation ☐ Excessive bleeding ☐ Anesthetic complications ☐ Excessive time ☐ Other ☐
Comments: _____
☐ Unable to complete full examination: why? _____
☐ Unable to obtain adequate biopsies: why? _____
☐ Unable to retrieve foreign object: why? _____
☐ Visualization obscured why? _____

SAMPLING: Biopsy ☐ Brush cytology ☐ Washing ☐ Aspiration ☐ Foreign body retrieved ☐

DOCUMENTATION: Video ☐ Photographs ☐

ESOPHAGUS Normal ☐ Foreign body ☐ Mass ☐ Stricture ☐ Hiatal hernia ☐

Lesion	Code	Comments (include location)
Hyperemia/vascularity		
Discoloration		
Friability		
Hemorrhage		
Erosion/ulcer		
Contents (mucus/bile/food)		
Dilation		
Gastroesophageal sphincter		
Other		

Code: Normal = 0 Mild = 1 Moderate = 2 Severe = 3

STOMACH Normal ☐ Foreign body ☐ Mass ☐ Polyp(s) ☐ Parasite(s) ☐

Site(s) of lesions: Fundus ☐ Body ☐ Incisura ☐ Antrum ☐ Pylorus ☐

Site(s) of biopsies: Fundus ☐ Body ☐ Incisura ☐ Antrum ☐ Pylorus ☐

Lesion	Code	Comments (include location)
Can't inflate lumen		
Hyperemia/vascularity		
Edema		
Discoloration		
Friability		
Hemorrhage		
Erosion/ulcer		
Contents (mucus/bile/food)		
Gastroesophageal sphincter		
Passing scope through pylorus		
Other		

DUODENUM/JEJUNUM Normal ☐ Foreign body ☐ Mass ☐ Polyp ☐ Parasite(s) ☐

How far was the tip of the scope advanced? _____

Was/were the papilla(e) seen? Yes ☐ (which? _____) No ☐

Lesion	Code	Comments (include location)
Can't inflate lumen		
Hyperemia/vascularity		
Edema		
Discoloration		
Friability		
Texture		
Hemorrhage		
Erosion/ulcer		
Lacteal dilatation		
Contents (mucus/bile/food)		
Other		

Code: Normal = 0 Mild = 1 Moderate = 2 Severe = 3

Comments and Recommendations: _____

_____

_____

Endoscopist signature _____

WSAVA Global Veterinary Community

Hill's

This standard form was developed by the WSAVA Gastrointestinal Standardization Group (Drs Washabau, Willard, Hall, Jergens, Day, Mansell, Wilcox, Minami, Guilford, and Biltzer) with sponsorship from Hill's Pet Nutrition

E-FIGURE 113-4 Standardized form for upper gastrointestinal endoscopy.

ENDOSCOPIC EXAMINATION REPORT: LOWER GI ENDOSCOPY

Date of procedure: ..... **Case Number:** .....

Patient and client information:
(card or stamp)

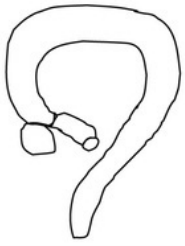
PROCEDURE(S): _____
Indication(s) for procedure: _____
Endoscope(s) used: _____
Forceps used: _____
Method of preparing colon: _____

PROBLEMS/COMPLICATIONS: None ☐ Colonic preparation inadequate ☐
Perforation ☐ Excessive bleeding ☐ Anesthetic complications ☐ Excessive time ☐ Other ☐
Comments: _____
☐ Unable to complete full examination: why? _____
☐ Unable to obtain adequate biopsies: why? _____
☐ Visualization obscured why? _____

SAMPLING: Biopsy ☐ Brush cytology ☐ Washing ☐ Aspiration ☐
DOCUMENTATION: Video ☐ Photographs ☐

COLON Normal ☐ Foreign body ☐ Parasite(s) ☐ Mass ☐ Polyp ☐
Visualized: ileo-colic valve ☐ ceco-colic valve (dog) ☐ cecum (cat) ☐
If did not see ileo-colic valve area, how far was the scope advanced ? _____

Lesion	Code	Comments (include location)
Hyperemia/vascularity		
Discoloration		
Friability/Hemorrhage		
Erosion/ulcer		
Intussusception		
Stricture		
Artifact		
Other		



Code: Normal = 0 Mild = 1 Moderate = 2 Severe = 3

ILEUM **NOT EXAMINED** ☐

☐ Tried to pass scope through ileocolic valve: Successful ☐ Unsuccessful ☐

☐ Tried to biopsy the ileum: Successful ☐ Unsuccessful ☐

Biopsies taken by: Direct visualization ☐ Blindly passing forceps through ileocolic valve ☐

Normal ☐ Foreign body ☐ Parasite(s) ☐ Mass ☐

Lesion	Code	Comments (include location)
Can't inflate lumen		
Hyperemia/vascularity		
Edema		
Discoloration		
Friability/Hemorrhage		
Erosion/ulcer		
Lacteal dilatation		
Texture of mucosa		
Mass		
Other		

CECUM **NOT EXAMINED** ☐

☐ Tried to intubate the cecum (dogs): Successful ☐ Unsuccessful ☐

Normal ☐ Foreign body ☐ Parasite(s) ☐ Mass ☐

Lesion	Code	Comments (include location)
Can't inflate lumen		
Hyperemia/vascularity		
Edema		
Discoloration		
Friability/Hemorrhage		
Texture		
Erosion/ulcer		
Other		

Code: Normal = 0 Mild = 1 Moderate = 2 Severe = 3

Comments and Recommendations: _____

_____

_____

_____

_____

Endoscopist signature _____

WSAVA Global Veterinary Community

Hill's

This standard form was developed by the WSAVA Gastrointestinal Standardization Group (Drs Washabau, Willard, Hall, Jergens, Day, Mansell, Wilcox, Minami, Guilford, and Biltzer) with sponsorship from Hill's Pet Nutrition

E-FIGURE 113-5 Standardized form for lower gastrointestinal endoscopy.

Whether the endoscopist or the endoscopy assistant obtains the biopsies is based on personal preference and the experience of the endoscopist. In order to obtain GI biopsies, the biopsy instrument is advanced through the instrument channel just beyond the tip of the endoscope. Depending on the desired biopsy location in the GI tract, the forceps are opened and either advanced straight ahead (more often with blind biopsies) or directed perpendicular to the mucosal wall. Once resistance is appreciated, the forceps are closed and retracted towards the endoscope. The number of biopsies needed from each region of the GI tract for histologic examination depends on the quality of the biopsied tissue and the specific disease process involved.[2] Approximately 6-28 samples typically can be required.[12] At the author's institution, at least 10-12 biopsies are taken in each region of the GI tract. More biopsies are taken from areas containing lesions than presumably normal areas. Biopsies thought to be poor in quality are discarded and not included in the count. Great care should be taken when removing tissue from biopsy forceps and unfolding it so as not to damage

the sample. The endoscopy team should have an open line of communication with the diagnostic laboratory to ensure that tissue is oriented and prepared according to the specific laboratory's requirements.[12] A review of basic principles for orienting and mounting GI tissue can be found in a consensus statement published by the WSAVA GI Standardization Group.[11] Gastrointestinal biopsy tissue should be evaluated and critiqued by the histopathologic laboratory according to the standardized classification system developed by the WSAVA GI group.[11,13] Additional biopsy samples also can be obtained for cytologic impression smears and/or infectious disease testing.

Endoscope Cleaning and Storage

To increase instrument shelf life and decrease the likelihood for transmission of infectious diseases between patients, endoscopes and instrumentation should be thoroughly cleaned and disinfected immediately following each procedure in accordance with manufacturer recommendations.[14,15] This process is described in ch. 83.

Complications

Complications from GI endoscopy are infrequent but can include aspiration pneumonia (see ch. 242), reflux esophagitis (see ch. 273), GI perforation (see ch. 279), and excessive hemorrhage (see ch. 135).[5] Sinus bradycardia and respiratory compromise also can occur secondary to overdistension of the stomach, although these signs generally are temporary if distension is corrected immediately by deflation of the stomach. Sudden blindness and neurologic deficits are also possible in cats if a spring-loaded mouth gag is used.[7]

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CHAPTER 114

Enemas and Deobstipation

Stefan Unterer

Constipation is retention of feces within the colon or rectum associated with infrequent bowel movements (i.e., <3-4 defecations per week) and/or dyschezia (i.e., straining to defecate). It is a major concern in cats[1] and is observed occasionally in dogs.[2-5] Early recognition of constipation helps prevent progression to obstipation (impaction), a severe form of constipation, which cannot be resolved without medical intervention. If obstipation occurs, enemas are required, and manual extraction of impacted feces followed by dietary modification,[6] laxatives, and prokinetics can be necessary.[1] Obstipated cats with megacolon characterized by irreversible smooth muscle dysfunction are often refractory to medical treatment and might require a colectomy.[7-9] Colonic impaction can be suspected from the history and is confirmed by abdominal palpation, digital rectal examination, and imaging studies (Box 114-1, Figure 114-1). See also ch. 277.

Box 114-1

Clinical and Radiographic Parameters Indicating Constipation

History

- Tenesmus ani
- Dyschezia
- Passing hard feces
- Absence of defecation for >2 days
- Recurrent episodes of constipation

Physical Examination

- Hardened feces in colon
- Distention of the colon
- Colorectal narrowing/stenosis on digital exam
- Painful lesion in peri- or rectoanal area

Radiographic Changes

- Colonic size
  - Maximal diameter of the colon/L5 length ratio >1.5 (cats)
  - Maximal diameter of the colon/L7 length ratio >1.5 (dogs)
- Fecal opacity
  - > Fluid or soft tissue density
  - Foreign material/bone chips

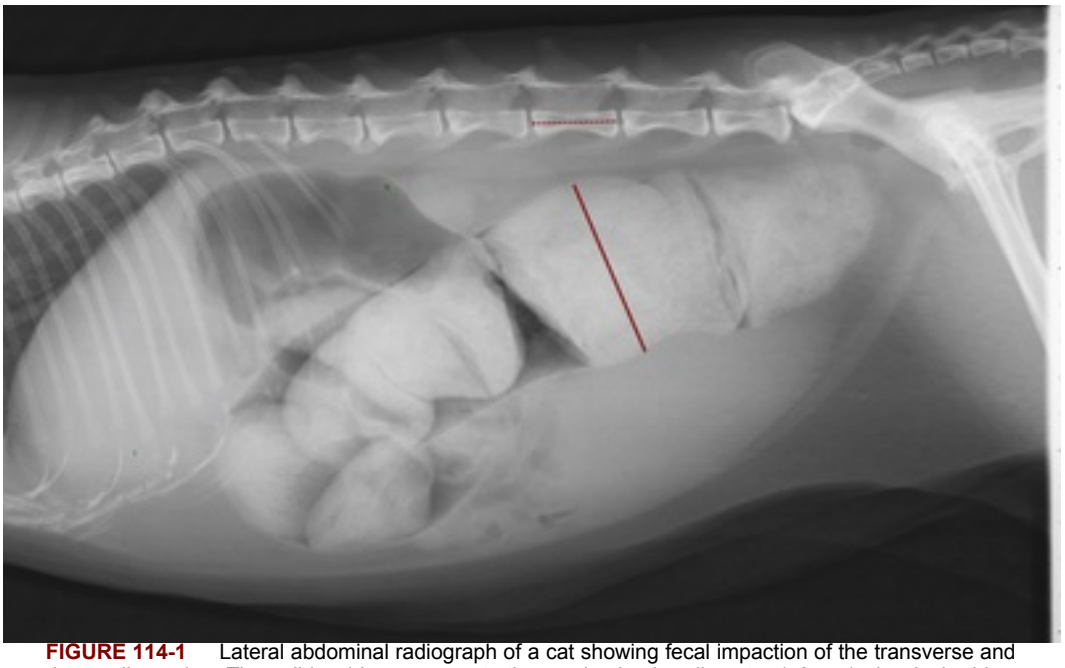

FIGURE 114-1 Lateral abdominal radiograph of a cat showing fecal impaction of the transverse and descending colon. The solid red bar represents the maximal colon diameter (48 mm); the dashed bar indicates the vertebral length of L5 (21 mm). The ratio of maximal colon diameter to L5 length is 2.3, which suggests the diagnosis of a megacolon. The high opacity of the feces (nearly bone dense) indicates dehydration and hardening of the feces. Note: In less severe radiographic changes, the diagnosis of constipation can only be made in association with information from history and physical examination.

Enemas and Manual Extraction: When to Use What

The efficacy of enemas and manual extraction of impacted feces is influenced by the cause and severity of the problem (Box 114-2). Mild constipation frequently can be managed with rectal suppositories or microenemas (low volume enemas with osmotic and stimulant activity on the colon and rectum such as Microlax 5 mL tubes) (Box 114-3), with or without oral lactulose and psyllium-/fiber-enriched diets as needed. Moderate constipation in a cooperative patient can generally be managed with macroenemas (large volume enemas to soften hard feces and to distend and stimulate colon and rectum, such as 10 mL/kg isotonic saline mixed with 5-10 mL lactulose and 5-10 mL mineral oil) without sedation. Patients with severe constipation may require enemas plus manual evacuation of feces performed under general anesthesia.

Box 114-2

Guidelines to Assess the Degree of Constipation

Mild Constipation

- First episode of constipation
- Absence of defecation for >2 days, but <4 days
- Straining with defecation
- Passing hard feces
- Hardened feces in colon
- Normal colonic size

Moderate Constipation

- Recurrent episodes of constipation (not always present)
- Absence of defecation for >2 days
- Straining without defecation (not always present)
- Hardened feces in colon

- Moderately enlarged colon
- Increased fecal density

Severe Constipation/Obstipation

- Recurrent episodes of constipation refractory to medical treatment
- Absence of defecation for >2 days
- Straining without defecation (not always present)
- Hardened feces in colon
- Significantly enlarged colon
  - Maximal diameter of the colon/L5 length ratio >1.5 (cats)
  - Maximal diameter of the colon/L7 length ratio >1.5 (dogs)
- Increased radiographic fecal density

Box 114-3

Useful Drugs for Deobstipation

Enemas and Suppositories

• Rectal suppositories		
• Docusate sodium	emollient laxative	1-3 tubes
• Bisacodyl	stimulant laxative	1-3 tubes
• Glycerin	osmotic laxative	1-3 tubes
• Microenema combining		1-3 tubes
• Sodium citrate	osmotic laxative	
• Sorbitol	osmotic laxative	
• Sodium lauryl sulfoacetate	lubricant laxative	
• Macroenema combining		
• Isotonic saline solution	softening feces	5-10 mL/kg
• Lactulose	osmotic laxative	5 mL per cat
		10 mL per dog
• Mineral oil	lubricant laxative	5 mL per cat
		10 mL per dog

Note: Docusate sodium should not be combined with mineral oil!

Pain Management with Minimal Influence on Colonic Motility

• Metamizole	20-50 mg/kg IV diluted	q 8-24 h
• Butorphanol	0.1-0.3 mg/kg IV, IM, SC	q 1-4 h
• Buprenorphine	10-20 mcg/kg IV, IM, SC	q 6-8 h

Anesthesia Protocol

• Premedication		
• Midazolam	0.1-0.3 mg/kg IV	*and*
• Butorphanol	0.1-0.3 mg/kg IV	
• Induction		

• Propofol	2-6 mg/kg IV	*or*
• Alfaxalone	1-2 mg/kg IV	
• Intubation (mandatory to prevent aspiration) and oxygen supply		
• Maintenance		
• Propofol	1-2 mg/kg IV	q 10-20 min *or*
• Alfaxalone	0.5-1 mg/kg IV	q 10-20 min *or*
• Inhalational anesthetics	(isoflurane, sevoflurane)	

Enemas and Manual Extraction: How to Do It (Figure 114-2)

Patient Preparation

General anesthesia is necessary to manually extract feces, but is not needed for simple enemas unless the patient is so painful that it is difficult to insert the enema tube. If anesthesia/sedation will be performed, an orthopedic examination (to rule out pain during positioning; see ch. 353 and 355) and a neurologic examination (to rule out neuromuscular disorders; see ch. 259) should be performed first. The patient should be rehydrated and metabolic abnormalities corrected before sedation or anesthesia (see ch. 128 and 129). Antibiotic treatment (e.g., amoxicillin/clavulanic acid 20 mg/kg IV q 8 h) could be indicated if there are signs of sepsis (i.e., hypo- or hyperthermia, tachycardia, tachypnea, leukopenia, leukocytosis, left shift). Medications that slow intestinal transit (e.g., diphenoxylate, atropine, loperamide) should be avoided.[10] Anesthetized patients must be intubated to prevent aspiration.

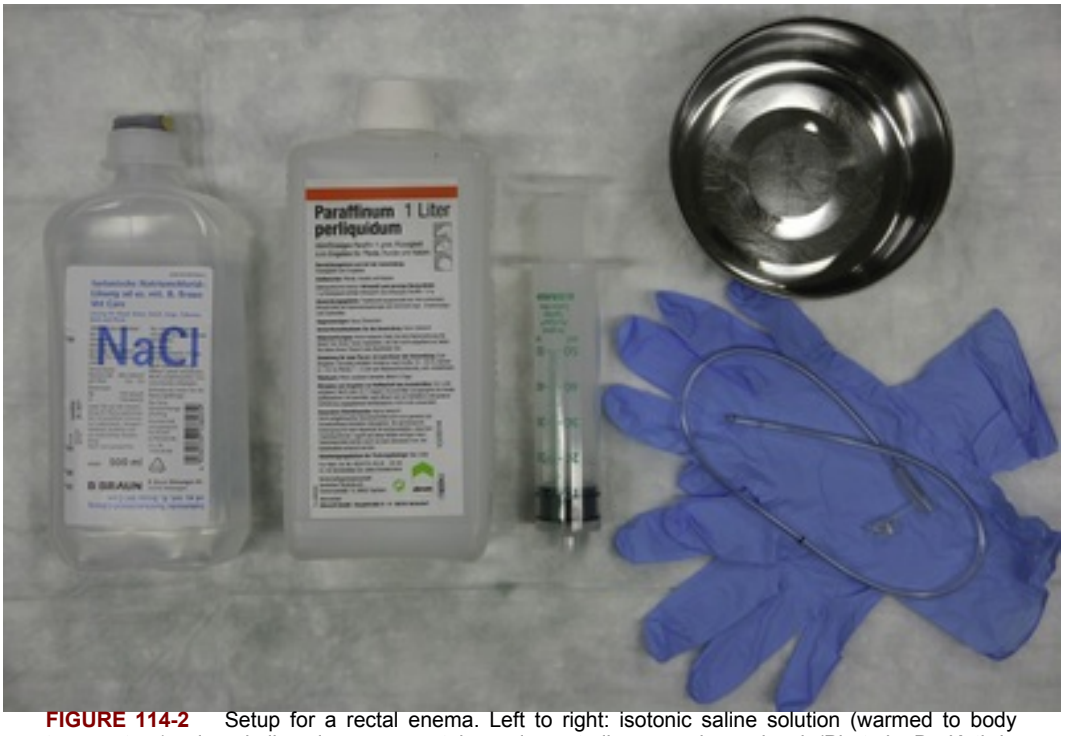

FIGURE 114-2 Setup for a rectal enema. Left to right: isotonic saline solution (warmed to body temperature), mineral oil, syringe, enema tube and nonsterile exam gloves, bowl. (Photo by Dr. Kathrin Busch.)

A thorough examination of the anus and the rectum is paramount in evaluating patients before attempting manual extraction of feces. The perianal area should be evaluated for painful conditions (e.g., perianal fistulas, anal sacculitis), obstructive lesions (e.g., anal sac and perianal neoplasia), and swelling or excessive laxity due to perineal hernia. A digital rectal examination should be performed to identify fecal impaction, anorectal stricture, pelvic canal stenosis, rectal mass, or outpouching of the rectal wall (i.e., perineal hernia). If

an underlying cause is identified, it should be treated as early as possible after deobstipating the patient to prevent further episodes of constipation and loss of colonic dysfunction by overdistention.

Materials and Setup

The procedure should be done in an easily cleanable environment (e.g., dental table, dog bath) without the danger of contaminating clean areas. Copious amounts of lubricant and a big bowl with about 50-100 mL/kg of warm (37° C) tap water (or isotonic fluid in cats and small dogs) should be available. The person performing the procedure as well as any assistant should wear waterproof aprons. Enema tube size depends on the patient's size and ranges from feeding tubes for cats and small dogs (i.e., 4 mm [12 French] tubes) to larger diameter tubes for big dogs (i.e., 7 mm [22 French] for 10-20 kg and 10 mm [30 French] for >20 kg). A 1-2 liter bag attached to the enema tube is an easy way of allowing gravity flow to infuse the fluid into the colon. A fluid pressure bag or rubber ball pump can facilitate instillation of fluids, but care must be taken to not instill fluids too fast or to distend the colon to the point of causing pain, vomiting, or perforation.

Contraindicated Types of Enemas

Rarely, administration of large volumes of tap water can produce water intoxication (i.e., acute hyponatremia) if the enema is retained.[11] Hypertonic sodium phosphate (e.g., Fleet) enemas can cause life-threatening hypernatremia, hypocalcemia, and hyperphosphatemia in cats and in dogs if the enema fluid is retained.[12,13] The safest option is an enema consisting of warm isotonic saline solution to soften impacted feces, sometimes with mineral oil as a lubricant (see Figure 114-2 and Box 114-3).

Technique

Under digital control, a well-lubricated tube (see above) is introduced into the colon. The length of insertion of the tube in the proximal part of the descending colon is determined by measuring the distance from the anus to the last rib. Stiff catheters/tubes should not be used. While slowly administering large volumes (10-20 mL/kg) of fluid, the tube should be gently inserted as far as possible into the colon, up to this limit. If resistance occurs while advancing the tube, the tube should not be forced further orad; rather, the clinician should try to reposition the tube by gently twisting it, while advancing it, so as to avoid causing trauma to the colorectal mucosa. Catheters should be introduced very gently into the large intestine to prevent perforation of the overly distended and fragile colonic wall. An attempt to carefully pass a very small catheter (feeding tube) alongside the impaction can be made in order to deliver fluid past the site of initial obstruction and lubricate the more proximal (orad) parts of the obstruction. The fluid should be instilled over 2-5 minutes. If vomiting or abdominal discomfort is noted, then the fluid was likely administered too quickly and is causing inappropriate colonic distention. Cats and small dogs are especially prone to such problems. After instillation of the enema and waiting for 5-15 minutes (depending upon how hard the feces are), with the anal orifice held closed by an assistant, the fecal mass should be broken down by gentle abdominal massage and compression of the colon over 10-15 minutes. This is supposed to manually propel small fecal pieces into the rectum, which can then be evacuated by digital manipulation. In severely impacted animals, this procedure will have to be repeated several times. Abdominal massage might not be sufficient to break down severely impacted material. The consistency of the impaction can be almost cement-like, in which case the surgeon/veterinarian will have to manually "chip away" small pieces from the distal end of the impaction via the rectum. Sometimes bone shards are embedded in the impaction, which have to be evacuated carefully with the distal end of the shard inside the palm of the surgeon's hand and the proximal end guarded behind the tip of the index or middle finger to avoid trauma to the mucosa. In severe cases of fecal impaction, sponge forceps can be introduced rectally to gently break down the fecal mass. To avoid damage to the colorectal mucosa, it is safer to introduce the forceps through a rigid colonoscope and remove the impacted feces under visual control. To improve patient recovery and avoid severe stress to the colonic wall, the whole procedure should not extend longer than 60 minutes.

Endpoint and Further Management

Complete removal of the impacted material can be an unrealistic goal, especially in larger dogs. A balance should be struck between removing as much material as possible and not endangering the integrity of the colon wall or prolonging general anesthesia in an unstable patient (e.g., elderly cats with underlying renal and/or cardiac disease). A young, healthy dog that has ingested bones can tolerate a longer procedure, both in

terms of fragility of the colon wall and adverse anesthetic effects, than can an elderly cat with megacolon that has chronic kidney disease. Even if removal of the impacted feces has only been partially successful, most patients will pass the remainder of the feces over the next 24 hours (especially if promotility drugs and topical lubricants are administered). Hospitalization could be necessary to ensure optimum hydration and analgesia in severe cases. Pain management can be necessary, but it is important to avoid narcotics, which slow intestinal transit (see Box 114-3). Nonsteroidal anti-inflammatory analgesics should be avoided due to potential gastrointestinal side effects.[14] Antibiotic treatment should be considered in immunocompromised patients with significant colonic mucosal trauma predisposing to bacterial translocation.

Evaluation of Treatment Success and Long-Term Managment

Repeating abdominal radiographs after deobstipating the patient might help assess treatment success and could reveal signs of colonic perforation (e.g., loss of serosal detail, free intra-abdominal air) if such a complication has occurred. After the patient has recovered from anesthesia, oral lactulose (0.5-1 mL/kg PO q 8-12 h), dietary modification (i.e., psyllium-/fiber-enriched diets) and colonic prokinetic medication (e.g., bisacodyl PO q 24 h: 5 mg for cats and dogs <10 kg; 10 mg for dogs 10-20 kg, 15 mg for dogs 20-30 kg and 20 mg for dogs >30 kg; or tegaserod 0.05-0.1 mg/kg q 24 h) are indicated. Analgesics and antiemetics can be used as needed. On the following day, the degree of constipation should be reevaluated radiographically. If hard feces are still present in the colon, enemas and/or manual extraction should be repeated. Continuation of medical treatment is recommended for at least 1-3 weeks and may need to be pursued long-term. Normal bowel function and defecation should be evaluated 1 and 3 weeks after removal of impacted feces and every week after changing medical treatment (e.g., discontinuation of prokinetics and lactulose) by history (i.e., daily defecation, no tenesmus, no dry/hardened feces in litterbox), physical examination (i.e., no enlarged impacted colon) and abdominal radiographs (i.e., normal-size colon, normal fecal density).

Summary

Recurrent episodes of prolonged, severe constipation can produce permanent loss of colonic smooth muscle function. It is important to identify patients with a predisposition for constipation early in the course of the disease, to eliminate underlying causes of constipation, and to prevent recurrences using dietary modification, laxatives, and/or promotility agents as needed.

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Neurologic

OUTLINE

Chapter 115 Cerebrospinal Fluid Collection, Analysis, and Myelography
Chapter 116 Muscle and Nerve Biopsy
Chapter 117 Electromyography and Nerve Conduction Velocity

CHAPTER 115

Cerebrospinal Fluid Collection, Analysis, and Myelography

John Henry Rossmeisl Jr.

Indications and Contraindications for Cerebrospinal Fluid Collection

Cerebrospinal fluid (CSF) collection and analysis are important aspects of the diagnostic evaluation of animals with disease of the nervous system (see ch. 259).[1-3] Collection of CSF is also indicated prior to the subarachnoid injection of contrast media (myelography), or intrathecal delivery of therapeutics. Although there are no absolute contraindications to CSF collection, the relative risks of the procedure require careful consideration in patients with intracranial hypertension, brain herniations, vertebral column trauma, thrombocytopenia or other bleeding disorders, and in cases of known or suspected epidural or paravertebral infections.[2,3] Patients with these conditions can be identified by performance of appropriate laboratory investigations and diagnostic imaging techniques, such as magnetic resonance imaging (MRI), prior to CSF collection.

Equipment, Techniques, and General Considerations

Standard equipment required for collection of CSF includes electric shears, sterile gloves, 20- to 22-gauge, 38 mm (1.5 in) to 63.5 mm (2.5 in) spinal needles with stylets, surgical scrub solutions, and sterile glass (red top) collection tubes without anticoagulant.[1-3] There are two sites from which CSF may be collected: the cerebellomedullary cistern (cisternal tap) and the lumbar region (lumbar tap). As net CSF flow occurs from a rostral to caudal direction, it is preferred to collect CSF caudal to the anatomic level of the disease process being investigated.[2,3] Thus, cisternal taps are typically performed in patients with intracranial disease, and lumbar taps in those with spinal cord lesions. Cisternal CSF taps are less likely to be iatrogenically contaminated with peripheral blood compared to lumbar taps.[3] Regardless of the sampling site, CSF collection is performed with the patient in a surgical plane of anesthesia, and the hair overlying the region should be clipped and the skin aseptically prepared. Approximately 1 mL of CSF per 5 kg of body weight may be safely removed during CSF collection.[2,3]

Cerebellomedullary Cisternal CSF Collection

The anesthetized patient should be intubated, with ventilatory support available. The optimal length and diameter of the spinal needle used is dictated by the size of the patient. As the cistern can lie only a few millimeters below the skin surface in neonates, cats, and small dogs, some clinicians use small (25 or 27 gauge) hypodermic or butterfly needles to collect CSF from these patients. The animal should be positioned in lateral recumbency, so that the dependent side is identical to the dominant hand of the person collecting the fluid, with the dorsal aspect of vertebral column and skull facing the operator and close to the edge of the table. An assistant should hold the head in a 90° flexed position with the nose parallel to the table top (Video 115-1).[1,3]

The desired position for placement of the spinal needle can be accomplished by palpation of several landmarks. To identify midline, a right-handed operator palpates the caudal aspect of the occipital protuberance with the index finger of the left hand and moves the finger caudally while applying firm digital pressure to identify the cranial aspect of the spinous process of the axis. If the dorsal arch of the atlas can be palpated along this line, the needle should be placed just cranial to it, perpendicular along the line between the axis and occipital protuberance. If the dorsal arch of atlas cannot be located, as is often the case, the wings

of the atlas are palpated, and a line coursing perpendicular to the long axis of the vertebral column immediately cranial to and connecting the cranialmost aspects of the two wings of the atlas is visualized (Figure 115-1, *A*; see Video 115-1). The needle should be inserted perpendicularly to the skin at the point where this line intersects with the line connecting the external occipital protuberance to the spinous process of the axis along the dorsal midline.

FIGURE 115-1 Procedure for collecting cerebrospinal fluid (CSF) from the cerebellomedullary cistern of a dog. **A,** The operator palpates the desired landmarks for needle insertion (white lines superimposed on the patient) with the non-dominant hand. **B,** Once the spinal needle is in place, as confirmed by CSF flow, it is digitally stabilized by the operator and CSF collected into sterile red top tubes.

Once inserted, the needle should be directed parallel to the table top and advanced in 1-2 mm increments in order to penetrate the muscle and fascia. Some operators prefer to stop advancing after an insertion of several millimeters, remove the stylet, and check for CSF flow. To remove the stylet, a right-handed operator would place the hypothenar aspect of the palmar surface of the left hand on the dorsal aspect of the cervical region and skull for support and immobilize the needle with the left thumb and index finger. The stylet is then removed with the thumb and index finger of the right hand (see Video 115-1). If no CSF flow is observed, the stylet is reinserted into the needle, the needle is advanced another 1-2 mm, and the operator checks again for CSF, with this procedure being repeated until CSF is obtained. If the needle tip hits bone, the needle is withdrawn 1-2 mm and redirected slightly cranially or caudally to the original trajectory. In some instances, penetration of the dura will result in a distinct loss of resistance or tactile "pop" that is transferred through the needle to the operator.[1,3] Once CSF flow is observed, the CSF opening pressure can be measured, if desired; otherwise collection of CSF should proceed by allowing the fluid to passively drop from the needle hub into the sterile glass collection tubes (Figure 115-1, *B*; see Video 115-1) until the desired volume is obtained, and then the needle is withdrawn. Temporary manual occlusion of the jugular veins can be performed to increase CSF flow. When possible based on the patient size, the author prefers to collect CSF into separate 0.75 to 1 mL aliquots to allow for dedication of samples for routine biochemical and cytological analyses, as well as ancillary serological, biomarker, or genetic assays, as indicated.[2,3]

If whole blood is observed in the needle, the needle should be withdrawn and the procedure repeated using a new needle, as this usually indicates that the vertebral venous plexus has been penetrated.[1] If the CSF is observed to have a blood-tinged appearance, iatrogenic bleeding from puncture of a meningeal vessel will often clear as CSF drips from the needle, and the cleared CSF may be collected into a second sterile container. Rotating the needle may also help to clear iatrogenic hemorrhage. Mild to moderate amounts of blood contamination do not prohibit interpretation of CSF results.[4,5]

Lumbar CSF Collection

Depending on the operator's preference, the patient may be placed in sternal or lateral recumbency. Recently, ultrasound- and electrostimulation-guided approaches to lumbar puncture have been described for dogs.[6,7] The pelvic limbs should be extended toward the head in order to facilitate opening the interarcuate space. This procedure may require the use of long (88 mm [3.5 in]) spinal needles in large-breed dogs. The L5-L6 space is the most common site for lumbar CSF collection, although L4-L5 can be used in dogs, and L6-L7 in

cats.[3]

The author prefers to perform lumbar taps using a paramedian approach (Video 115-2). The cranial aspects of the iliac wings are palpated using the left index finger, which then is moved craniad to palpate the spinous process of L6. The needle is positioned just lateral to the midline alongside the caudal edge of the L6 spinous process, and directed cranioventrally through the ligamentum flavum into the vertebral canal. Advancement of the needle should occur with the proximal aspect of the needle angled approximately 45° caudally relative to the desired needle insertion point into the ligamentum flavum. If the needle strikes bone, it may be "walked off" the edge of the dorsal lamina into the interarcuate space. As the needle penetrates the dura, it is possible, but difficult, to collect CSF from the dorsal subarachnoid space. Thus, many clinicians elect to further advance the needle to the floor of the vertebral canal and then retract the needle 1-2 mm into the ventral subarachnoid space, at which time the stylet is removed and CSF flow evaluated. Mechanical stimulation of the spinal cord and nerve roots in this area may result in a visible or palpable twitch of the pelvic limbs or tail. If this is observed, the needle should be advanced 1-2 mm, and the stylet removed to evaluate CSF flow.[1,3]

CSF typically flows more slowly in lumbar collection compared to the cisternal collection. As such, some clinicians advocate connection of a 2.5-3 mL syringe with a short extension set to the spinal needle and to allow for gentle aspiration of CSF from the lumbar region. If lumbar CSF collection using these techniques is unsuccessful, the procedure may be attempted at the L4-L5 site.

CSF Sample Processing and Analysis

CSF samples ideally are processed for analysis within 4 hours of collection.[3,8,9] If rapid processing is not possible, the addition of autologous serum (100 mcL serum/1 mL of CSF) or 6% hydroxyethyl starch (1 : 1; vol : vol) may improve the stability of the sample for up to 48 hours.[8,9]

Routine analyses performed on CSF include gross inspection for color and turbidity, assessments of a total protein and glucose concentrations, total nucleated and red blood cell counts, white blood differential count, and cytopathological review of cellular constituents typically made following cytocentrifugation procedure.[2,3,10] It should be noted that while abnormalities of CSF are sensitive for the detection of CNS disease, the results are extremely non-specific, and with a few exceptions, rarely provide a definitive diagnosis. Thus, CSF analysis should be integrated with the history, physical and neurologic examinations, diagnostic imaging findings, and other diagnostic tests in order to be maximally useful. The analytical techniques and principles of CSF interpretation have been reviewed elsewhere, and descriptions of CSF abnormalities associated with specific diseases are reviewed in the sections of this textbook covering neurological disorders (see ch. 33-35, 260-261, 265-267, and 270).[1-3,10]

Complications of CSF Collection

Risks associated with cerebellomedullary cisternal collection include rapid shifts in intracranial contents (brain herniations) associated with needle placement into the subarachnoid space in patients with intracranial hypertension. Most other potential complications are related to technical errors, or risks associated with anesthetizing patients with neurological disease.[3,11] Inadvertent advancement of the needle into the neural parenchyma may result in fatal brainstem dysfunction, but may also be associated with no observable adverse effects.[11] Complications of lumbar CSF collection include failure to obtain a diagnostic CSF sample due to significant iatrogenic blood contamination, and failure to obtain CSF ("dry tap").[3] Hematomyelia resulting in neurological deterioration has also been rarely reported following lumbar CSF collection.[12]

Myelography

Myelography, which is the radiographic study of the vertebral column and spinal cord following subarachnoid injection of contrast media, can be performed by either cisternal or lumbar (Video 115-3) injection, with the anesthetized patient in lateral recumbency.[13] Needle placement occurs as described above for CSF collection, although fluoroscopic guidance may be used to facilitate needle positioning, and CSF should be obtained for analysis prior to the injection of contrast material. Non-ionic contrast agents (iohexol or iopamidol, 180 to 300 mg iodine/mL) are typically used for veterinary applications.[13] The volume of contrast injected ranges from 0.3 mL/kg to 0.45 mL/kg body weight, and is dependent on both the site of

injection and the anticipated location of the lesion based on the neurological examination. For example, when performing a cervical myelogram via a lumbar injection, a higher contrast dosage is often necessary.

Once the desired needle position is obtained, a test injection is performed by connecting the contrast–dose-containing syringe and primed extension set to the spinal needle and infusing approximately 0.5 mL of contrast, after which subarachnoid contrast injection is confirmed with radiography or fluoroscopy. Once subarachnoid administration is confirmed, the remainder of the calculated contrast dose can be administered, the needle removed, and a series of lateral, ventrodorsal, and if necessary, additional (oblique, traction, flexion, extension, opposing lateral) radiographic views obtained of the region of interest of the vertebral column.[13,14] The goals of interpretation require recognition of abnormal myelographic patterns (extradural, intradural-extramedullary, intramedullary) in order to specifically describe the neuroanatomic location of any observed lesions and subsequently generate a refined set of differential diagnoses based on the imaging features present.

Although cervical injection is technically easier, it is more likely to be associated with intracranial contrast media accumulation, which increases the risk for post-myelographic seizures.[13,15] Tilting the patient 30° by lifting the head may help mitigate intracranial contrast accumulation. With cervical injections, the bevel of the needle should be directed caudally prior to injection. Lumbar injections should be performed with the bevel of the needle facing cranially, and can be performed by applying more pressure on the plunger of the syringe, which may facilitate the flow of contrast past an obstructive lesion.

Complications of Myelography

Obtaining a diagnostic myelogram is heavily dependent on the technical expertise and experience of the operator. Failure to obtain a diagnostic study can often be attributed to operator errors such as inadvertent epidural, intraparenchymal, or subdural contrast injection, or patient-inherent factors, such as obesity or degenerative vertebral column disease, that complicate ideal injection technique.[13,16] In addition, particularly with cervical injections, severe spinal cord swelling or compression may inhibit the flow of contrast caudal to the lesion, which may necessitate subsequent performance of a lumbar myelogram, although obstruction to contrast flow can sometimes be overcome by tilting, flipping, or rolling the patient carefully.[17]

Seizures are a common complication of myelography, and have been reported to occur in 3-21% of dogs undergoing the procedure.[15,17,18] Significant risk factors for post-myelographic seizures include large-breed dogs, cervical spinal cord lesion location, cerebellomedullary cisternal injection technique, and use of large volumes of contrast media.[17,18] Myelography can be associated with transient or permanent decline in neurologic status, which may occur as a result of the transient chemical meningomyelitis induced by the contrast injection, or following accidental injection of contrast into the spinal cord parenchyma or central canal.[19] The risk for a decline in neurologic function following myelography may be higher in patients affected by inflammatory myelopathies, chronic spinal cord compression, or neurodegenerative diseases. Rare but potentially fatal complications associated with myelography include cardiac arrhythmias and arrest, contrast medium infusion into the brainstem parenchyma with cisternal injection, and intracranial subarachnoid hemorrhage induced by lumbar myelography.[20,21]

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CHAPTER 116

Muscle and Nerve Biopsy

Kerry Smith Bailey

Neuromuscular diseases encompass diseases of muscles (myopathies; see ch. 354), nerves (neuropathies; see ch. 264 and 268), and the point at which the two meet (junctionopathies; see ch. 269). Diagnosis is based on interpretation of the neurologic examination, electrodiagnostic procedures including electromyogram (EMG) and nerve conduction studies (see ch. 117), and histopathologic evaluation of muscle and nerve. Examination of specific components of the motor unit, including intrafascicular nerve branches, neuromuscular junctions, myofibers and supportive connective and vascular tissues, and peripheral nerves, allows for more definitive classification of the pathologic process and helps target therapy.

Muscle Biopsy

Preparation for Performing Muscle Biopsy

Once it is determined a patient has neuromuscular disease that necessitates a muscle biopsy, several preparatory steps must be taken. Conventional formalin fixation techniques alone are not appropriate for muscle specimens because they greatly limit the information obtained. Muscles are metabolically very active tissues, and evaluation of specific enzyme localization and storage products can be important to a diagnosis. Fresh frozen sections are needed for these histochemical stains and enzyme reactions. Because of the unique handling and processing of the specimen, routine submission to most commercial pathology laboratories is not recommended. Additionally, the destination laboratory's specific instructions for selection, handling, and transportation of the specimen should always be obtained prior to sample collection. Specimens should be shipped to arrive at the laboratory within 24 to 48 hours and should not arrive at the laboratory during a weekend or holiday. Hence, the procedure needs to be planned accordingly.

Selection of Muscle

The muscle selected for biopsy should be affected by the disease process, as evidenced by clinical signs (atrophy, hypertrophy, myalgia, or weakness) or abnormal EMG results. Ideally, an affected but functional muscle should be selected. In acute disease, a more severely affected muscle should be selected, while in chronic end-stage disease, a less-affected muscle may be selected to avoid the atrophy and replacement of myofibers with connective tissue and fat that coincides with end-stage disease.

The biopsy procedure should be associated with low morbidity so an easily identified muscle with a minimal surgical approach is recommended. The muscle fibers should be oriented in a single direction and the specimen should be obtained from a site devoid of tendinous insertions and aponeuroses. The site should be free of artifacts induced by EMG needle insertion or intramuscular injections. Insertion of needles can induce localized necrosis and phagocytosis, "needle myositis," and could interfere with interpretation.

Commonly used muscles include the lateral head of the triceps brachii (distal third), vastus lateralis (distal third), cranial tibial (proximal third) and temporalis muscles. Diagnosis of generalized neuromuscular disease necessitates biopsy specimens from both thoracic and pelvic limb muscles. If a nerve biopsy is planned, biopsy of the cranial tibial muscle combined with a common peroneal nerve biopsy allows one surgical approach.

Some disease processes require specific muscles to be harvested. For example, the temporalis muscle is biopsied to diagnose masticatory myositis. A common mistake to avoid when performing a biopsy of the temporalis muscle is sampling the frontalis muscle, which is a thin muscle located directly under the skin, overlying the temporalis muscle. This muscle is not affected in masticatory myositis and will not give the information needed to make that diagnosis. In addition, diagnosis of congenital myasthenia gravis is based on the demonstration of decreased numbers of acetylcholine receptors in biopsies of external intercostal muscles.

Muscle Biopsy Procedure

Open muscle biopsy procedures performed under general anesthesia are recommended. Punch biopsies obtained under sedation provide too small a sample, with poor orientation of the muscle fibers. Typically, the procedure is performed following electrodiagnostic testing. To avoid EMG needle insertion artifacts, EMG is typically performed on one side of the body and the muscle biopsy is performed on the other.

Routine surgical preparation is required (Video 116-1). Then the skin and fascia overlying the muscle are incised, allowing visualization of myofiber orientation. Two parallel incisions are made with a #11 scalpel blade, parallel to the direction of the myofibers and approximately 1 to 2 cm long, 0.5 cm apart and 0.5 cm deep. The isolated muscle is removed from the surrounding muscle with a scalpel blade or scissors. Care must be taken to avoid excessive tissue handling and trauma. The tissue is then wrapped in a saline-dampened sterile gauze sponge and then placed in a dry, water-tight contained such as a 10 mL red top tube. This tissue must be refrigerated and then shipped on ice. Another smaller piece of muscle tissue is then collected adjacent to the original site and placed in 10% buffered formalin.

Wound closure is routine and it is recommended to apply a cold compress to the site postoperatively to minimize swelling and to aid in comfort. Complications (infection and hematoma) are uncommon and usually are the result of the animal interfering with the surgical site.

Transport

The quality of the information obtained from the biopsy depends on the quality of the specimen that arrives at the laboratory. Fresh muscle biopsy samples must arrive at the laboratory within 24 to 48 hours of collection. They need to be shipped under refrigeration. Many laboratories request that 5 mL of the animal's serum be shipped along with the muscle biopsy specimen.

Muscle Biopsy Interpretation

The following muscle features are assessed for variation from normal: fiber size (atrophy, hypertrophy, hypotrophy) and profile (polygonal, round, angular); fiber type proportions and distribution patterns (fiber type grouping); numbers and position of nuclei (peripheral vs. random and central); myonecrosis and regeneration; cellular infiltration; connective and vascular tissue morphology; intramuscular nerve morphology; and muscle fiber type selectivity or prevalence for the pathologic changes observed.

Nerve Biopsy

Selection of Nerve

As with muscle specimen selection, the nerve should be affected by the disease process as evidenced by abnormal electrophysiologic findings or clinical neurologic abnormalities in areas innervated by the nerve (atrophy, hypotonia, hyporeflexia, paresis, and/or sensory deficits). When possible (as with generalized neuromuscular disease) the nerve selected should be easily harvested with low morbidity, have established normal electrophysiology and morphometric data available, and innervate a muscle that is routinely biopsied. The common peroneal nerve typically is selected when generalized disease is present as it meets the above criteria and because of its flat anatomy and easily identified fascicles. It is a mixed nerve containing motor, sensory and autonomic nerve fibers. Other mixed nerves that can be biopsied readily are the tibial nerve and the ulnar nerve. When a predominantly sensory neuropathy is suspected, biopsy of the cutaneous sensory nerves, such as the caudal cutaneous antebrachial nerve in the thoracic limb or the caudal cutaneous sural nerve in the pelvic limb, is recommended.

Nerve Biopsy Procedure (Common Peroneal Nerve)

Biopsies are performed with the patient under general anesthesia, and they often follow biopsy of the ipsilateral cranial tibial muscle (Video 116-2). The common peroneal nerve is palpable on the lateral aspect of the distal femur and it extends caudally to the proximal tibia. A 6- to 8-cm incision is made over the region, following standard surgical preparation of the site. The fascia of the biceps femoris muscle is exposed and the nerve can be palpated through the fascia. A small incision (4 to 5 cm) is made in the fascia, taking care to elevate the fascia to avoid inadvertent damage to the nerve. The nerve can be seen as it passes over the lateral head of the gastrocnemius muscle. Careful blunt dissection of the fat and fascia from around the nerve helps

to isolate it. A 5-0 or 6-0 silk suture is placed through the caudal one-fourth to one-half of the nerve at the proximal end of the biopsy site, allowing minimal gentle traction as a 3- to 4-cm fascicular biopsy is excised using fine iris scissors. If individual fascicles of nerve are difficult to visualize, gently spreading the nerve with a scalpel handle may allow better definition of fascicles. The initial incision may then be accurately made with a #11 scalpel blade.

The incision is closed routinely. Complications can include temporary proprioceptive deficits, lameness, and knuckling of the distal pelvic limb on the side of the biopsy that typically resolve within 3 to 4 days.

Nerve Specimen Processing

The sample should be placed in 10% formalin or glutaraldehyde (based on the preference of the laboratory). To minimize artifact formation during fixation, the biopsy must be prevented from contracting (to maintain length); methods include pinning the nerve at either end with 25-gauge needles to a tongue depressor, or suturing around the nerve at either end onto the wooden stem of a cotton-tipped applicator. A nerve specimen also may be frozen in liquid nitrogen if specialized biochemical analysis is required.

Nerve Specimen Interpretation

Examples of pathologic changes seen in nerve biopsies include axonal degeneration, axonal dystrophies, and primary demyelination. Knowledge of the variations that might be seen in apparently normal animals is essential to interpreting peripheral nerve biopsy specimen pathologic findings. In older animals, axonal degeneration and demyelination can be a normal finding and should not be interpreted as pathologic. Similarly, lack of use of a limb can result in loss and abnormalities of myelinated nerve fibers that should not be interpreted as a primary disease process.

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CHAPTER 117

Electromyography and Nerve Conduction Velocity

David Lipsitz, D. Colette Williams

Overview

Disorders involving any component of the neuromuscular system (peripheral nerve, muscle, neuromuscular junction) cause identical clinical signs. A thorough neurological examination may not demonstrate the component affected (see ch. 259). Electrodiagnostic testing (EDX, Video 117-1) aids in localizing lesions within the neuromuscular system and is useful in selection of nerve and muscle biopsy sites (see ch. 116). To eliminate patient discomfort and movement, EDX is usually performed with the dog or cat under general anesthesia.[1-3]

Electromyography (EMG)

Background

Electromyography (EMG) is a method for detection and display of insertional, spontaneous and voluntary electrical activities in skeletal muscle. Veterinary EMG focuses on the electrical activity of single muscle fibers or small groups of myofibers. Use of EMG is based on the inherent electrical state of healthy skeletal muscle and changes in excitability patterns associated with disease. With few exceptions, normal resting muscle is electrically and mechanically silent. Denervated muscle fibers and fibers damaged by primary muscle disease may spontaneously depolarize, resulting in readily detectable abnormal activity.

Uses, Electrodes, Limitations

EMG may aid in defining mononeuropathies (see ch. 268), polyneuropathies (see ch. 268), myopathies (see ch. 354), and in differentiating neurogenic disease from disuse atrophy. EMG findings are not specific, but distinctions can be made on review of neurological examination results, distribution of affected muscles, and results of nerve conduction studies. EMG can be used to select an affected muscle for biopsy in diseases where only specific muscles are involved, such as masticatory muscle myositis. Disuse atrophy, diseases of neuromuscular transmission, and disease restricted to myelin or sensory neurons, fail to induce EMG abnormalities.

The most commonly used EMG electrodes are concentric (coaxial) needle electrodes. In addition to visual inspection of EMG waveforms, characteristic sounds assist interpretation. The sensitivity of the EMG examination can be enhanced by performing multiple insertions into a specific muscle and by sampling a number of different muscles. EMG abnormalities may be patchy in their distribution within a muscle (often seen in myositis) or limited to particular groups of muscles (i.e., those with the same innervation).

EMG Normal Event Definitions

Although normal muscles at rest are electrically silent, activity can be detected in normal skeletal muscle.

- *Insertional activity* is caused by the mechanical stimulation of muscle fibers and disruption of membranes by placement of the EMG needle; it should subside soon after electrode movement stops (within a few hundred milliseconds).
- *Miniature end-plate potentials (MEPP)* result from the spontaneous release of single quanta of acetylcholine from nerve terminals inducing partial depolarization of postsynaptic myofiber membranes. This activity is focal and can only be detected with the electrode positioned near the motor point of the muscle. The sound resembles that of the "seashore."

- *End-plate spikes* are associated with MEPPs and occur when enough acetylcholine is released to completely depolarize a single muscle fiber. This activity should not be confused with fibrillation potentials. Random high-pitched "popping" sounds are typical of this event.
- *Motor unit action potentials (MUAP)* result from summation of individual myofiber action potentials associated with activity in a single motor unit within the electrode's recording range. They are present during muscle contraction and have a regular clicking sound, similar to a "wind-up toy." Multiple overlapping MUAPs can be seen when several motor units are activated. These events are not routinely evaluated in veterinary EDX.

EMG Abnormal Event Definitions

These EMG activities are not necessarily spontaneous but are abnormal.

- *Increased insertional activity* is prolonged firing of muscle fibers due to mechanical irritation induced by the electrode.
- *Decreased insertional activity* is diminished activity secondary to loss of muscle fibers (adipose and connective tissue do not react to electrode placement).
- *Giant MUAPs* are large, often polyphasic potentials, which suggest reinnervation of muscle fibers. Collateral branching of healthy axons results in a greater number of myofibers being innervated by a given motor neuron (the histological correlate is fiber type grouping).

EMG Spontaneous Activity

This is the collective term for the following events; they are rated from 0 (normal) to 4+ based on their distribution within the muscle and the number present:

- *Fibrillation potentials* and *positive sharp waves* arise from depolarization of the T-tubular system or the surface sarcolemma. They result from similar pathological processes but have different morphology due to their orientation with respect to the electrode. These often occur together and the sound can be described as "bacon frying" or "rain on a tin roof."
- *Myotonic discharges* result from delayed relaxation of single muscle fibers due to ion channel defects; the discharges have a distinct pattern of waxing and waning in amplitude and firing rate. They produce the classic "dive bomber" sound.
- *Complex repetitive discharges* are the result of spontaneous firing in a single myofiber which induces firing in adjacent muscle fibers; they do not wax and wane like myotonic discharges but maintain the same amplitude and frequency throughout, ending abruptly. This sound has been described as similar to "machine gun fire." Previously used terms included pseudomyotonic or bizarre high frequency discharges.

Single Fiber EMG

Single fiber EMG (SFEMG) is a sensitive test of neuromuscular transmission. Techniques for recording SFEMG have been described in both cats and dogs. In SFEMG, individual myofiber action potentials are recorded by specialized needle electrodes. Minute latency variations occur between consecutive action potentials of the normal muscle fiber. Jitter is the term for this phenomenon. It is a measure of the safety factor of neuromuscular transmission. Excessive jitter is associated with disorders of the neuromuscular junction, whereby the safety factor is reduced.

Motor and Sensory Nerve Conduction

Overview

Nerve conduction testing is necessary for nerve function determination. Methods have been developed for independently examining both motor and sensory components. The nerves commonly tested are the peroneal, tibial, radial and ulnar. Motor nerves may be examined by stimulating a peripheral nerve and recording the compound muscle action potentials (CMAP) generated by a muscle innervated by that nerve.

Motor Nerve Conduction Velocities (MNCV)

MNCV are calculated by measuring the latency difference between the CMAP responses after stimulating at a

minimum of two sites along the nerve and by measuring the distance between these sites, using the formula: MNCV (m/s) = Distance (mm) / $Latency_{proximal}$ − $Latency_{distal}$(ms). This calculation is necessary as it takes neuromuscular junction transmission time and myofiber depolarization time out of the equation. Additional stimulus sites provide segmental information, helpful in assessing the distribution of the nerve disorder. Variations of this technique can be used to examine the integrity of the neuromuscular junction (repetitive stimulation) or the proximal nerve segment and nerve roots (late waves [f-wave and H-reflex]).

Sensory Nerve Conduction

Background

Sensory nerve conduction is evaluated by stimulating a cutaneous nerve (that lacks motor axons) and recording the sensory nerve action potential (SNAP) at sites along the nerve. Sensory nerve action potentials are recorded directly from the nerve itself; thus, only one stimulation site is required to calculate the conduction velocity but simultaneous recordings can be obtained from multiple sites along the nerve and spinal column. SNAPs are more temporally dispersed and are quite small when compared to CMAPs (microvolt versus millivolt range). Signal averaging a large number of individual responses is necessary to obtain interpretable recordings. Most background noise is random with respect to the stimulus and tends to average out, whereas the signal of interest is time-locked and enhanced.

Abnormalities

Abnormalities of nerve conduction studies include the following:

- Slowing of conduction
- Excessive temporal dispersion
- Decreased amplitudes of CMAP (can be neuropathic or myopathic) or SNAP. Diminished responses may occur at all sites or be more pronounced with increased distances (conduction block)
- Severely affected nerves may require the use of very high stimulus intensities to induce a response

A comprehensive EDX examination involves the use of all of the tests described here, often in multiples nerves. These are crucial in determining the functional integrity of the neuromuscular system in patients with neuromuscular disorders (see ch. 269).

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Reproductive

OUTLINE

Chapter 118 Artificial Insemination in the Dog
Chapter 119 Vaginoscopy and Vaginal Cytology in Dogs

CHAPTER 118

Artificial Insemination in the Dog

Catharina Linde Forsberg

Overview

Factors Affecting Vaginal or Intrauterine Artificial Insemination (AI)

AI success in dogs is dependent on a number of factors: breed, age, health, fertility, timing of insemination in relation to ovulation, one versus two inseminations, location of semen deposition (cranial vagina or into the uterus), quality of the freshly ejaculated semen (number of live, normal, motile spermatozoa), and handling of semen. Methods for AI in bitches include vaginal deposition of semen using a rigid plastic catheter or a catheter with an inflatable cuff (the Mavic or Osiris catheters). Semen can also be deposited using a transcervical intrauterine (TCI) technique with the Scandinavian/Norwegian catheter or endoscopic equipment. Semen can also be deposited via surgical or laparoscopic intrauterine insemination. Use of surgery to perform AI or embryo transfer in an animal is not considered ethical and may be illegal in some countries.

An international survey among small animal reproduction veterinarians indicated that surgical AI, although controversial, currently still is the most commonly used technique in dogs, especially with frozen-thawed semen, with low numbers of spermatozoa, or if semen is otherwise of inferior quality.[1] The number of veterinarians becoming competent with TCI is increasing. Use of the Scandinavian/Norwegian catheter is straightforward. The development of better-adapted endoscopic equipment has made TCI more broadly available. Owner interest has also increased use of TCI. Use of camera-equipped endoscopes is appreciated by breeders who can watch on the monitor as semen is injected into the uterus.

Timing the Insemination

AI timing (see ch. 119) is crucial, especially when using frozen semen whose sperm have a reduced survival time after thawing. Measuring serum progesterone [P] concentrations is commonly used for determining optimal days for breeding or AI. Luteinizing hormone testing to identify the preovulatory surge requires more frequent blood samplings. The bitch should be inseminated 2-5 days after ovulation, coinciding with the completion of maturation of the released oocytes. [P] at this stage is usually 10-20 ng/mL (30-60 nmol/L), but daily results may vary as much as 30-40% among healthy bitches. There is no evidence of diurnal secretory patterns.[2]

Semen Dose/AI

In the United States, a single AI with about 100×10^6 progressively motile spermatozoa (≥50%) has been considered adequate. In Europe, 150 to 200×10^6 live, normal, motile spermatozoa per breeding unit are used and two AIs are preferred per estrous cycle.[3-7] In a study of surgical AI using fresh or frozen-thawed semen, a dose of $>200 \times 10^6$ progressively motile sperm was more likely to result in whelping as compared with results using sperm counts of $100\text{-}200 \times 10^6$ or $75\text{-}125 \times 10^6$.[8] Another study comparing pregnancy success after endoscopic TCI and surgical AI of frozen-thawed semen found that pregnancy rates were greater ($P \leq 0.06$) when $>100 \times 10^6$ live, motile, normal sperm were inseminated, regardless of method.[9] Pregnancies have, however, been achieved with as few as 20×10^6 fresh spermatozoa deposited surgically at the tip of the uterine horn and with two doses of 50×10^6 frozen-thawed spermatozoa deposited into the uterus through the cervix with the aid of an endoscope.[10,11]

Vaginal deposition of fresh or frozen-thawed semen requires approximately 10 times as many spermatozoa to obtain the same whelping rates and litter size as by intrauterine deposition.[10,12] Pregnancy rates after endoscopic TCI of frozen-thawed semen (65%) were significantly higher than rates after surgical AI (45%).[9] To limit the volume of semen lost via backflow from the vagina, extended semen volumes should not exceed 1-3 mL for intrauterine AIs and 3-5 mL in vaginal AIs, depending on the size of the bitch.[1,4-6,13-16] Anecdotally, it has been suggested that inseminating slowly over 10-20 minutes allows administration of three to four times more semen, improving pregnancy rates and litter size. This is clearly an area where the veterinary community will benefit from research and experience.

How Many Times Should the Bitch Be Inseminated?

Theoretically, a single AI performed at the optimum time during estrus into the uterus of a healthy fertile bitch with semen of good quality should be adequate for maximizing pregnancy rates and litter size. However, clinical data indicate that two AIs, 24-48 hours apart, result in significantly higher pregnancy rates and litter sizes.[6,12,13,17,18] If only one insemination is possible, emphasis should be placed on determining the "optimum time" for AI, i.e., 2-5 days following the beginning of ovulation.

Results after AI in the Dog

Pregnancy rates range from 85-90% in dogs after natural matings under optimal conditions. Results with AI can be similar. When semen of good quality, even frozen-thawed, is inseminated via TCI at the appropriate time into the uterus of healthy bitches, whelping rates have been as high as 87.5%.[6,9,16,19] Whelping rates after intrauterine AI in dogs are significantly higher than those after vaginal AI. This is true for frozen-thawed (51% better), chilled (44%), and fresh (30%) semen.[1,18] Litter size using intrauterine AI of frozen-thawed semen is also significantly larger than by vaginal AI. Litter sizes are estimated to be 25-30% smaller in bitches receiving frozen semen compared to fresh and chilled.[12-14,16,18] Results also depend on breed, size, age, fertility of the dog and bitch, season of the year and numerous other factors.[8,16,20,21]

AI Techniques in the Dog

Palpation of the Canine Cervix and Uterus

One must be consistently able to abdominally palpate the cervix in order to develop competence in transcervical AI. This concept is emphasized when using the Scandinavian/Norwegian catheter technique to deposit semen into the uterus without injuring the patient. When using an endoscope to visualize and then catheterize the cervix, manual manipulation of the cervix and uterus can be useful. The anatomy of the caudal genital tract of the bitch is shown in Figure 118-1. The bitch should have an empty bowel and bladder to facilitate palpation. In order to palpate the cervix, a rigid canine AI catheter (Figure 118-2) is introduced into the vagina. This is facilitated when the vulva is raised to just below the anus, similar to the posture taken when a bitch stands for a male dog during breeding.

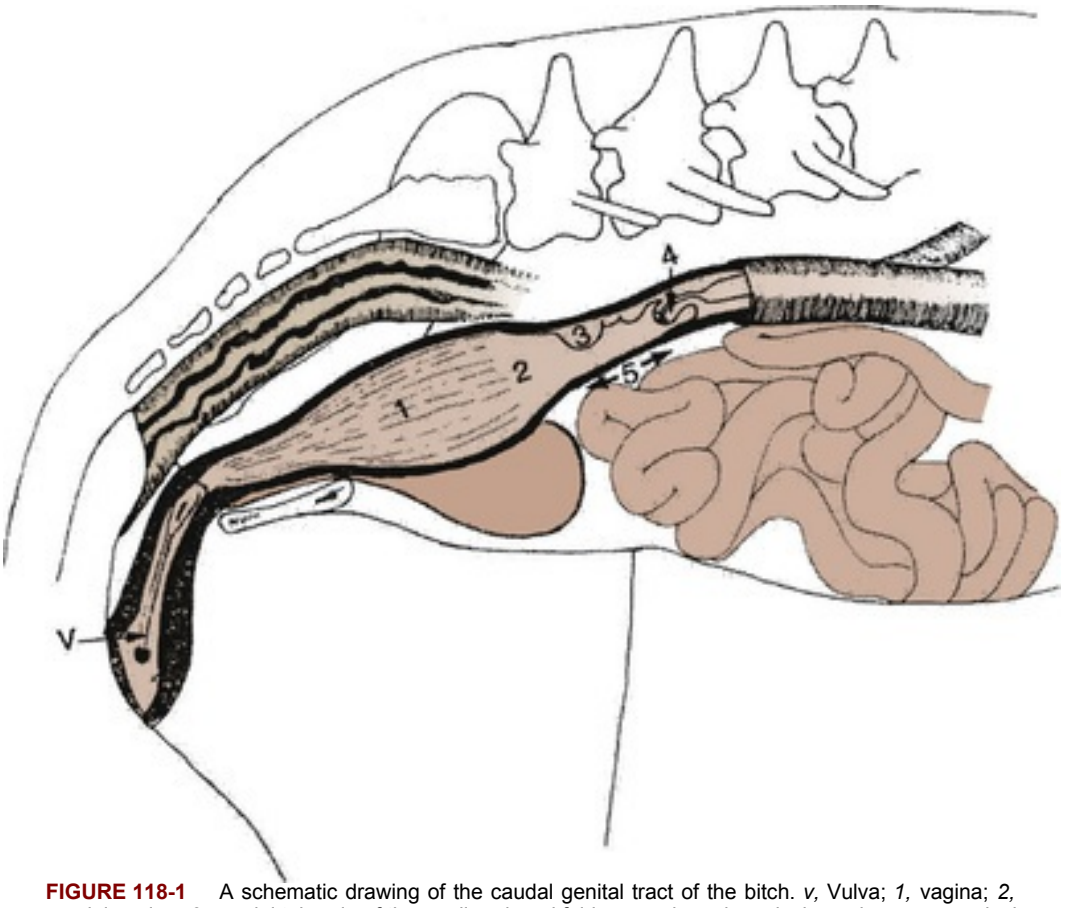

FIGURE 118-1 A schematic drawing of the caudal genital tract of the bitch. *v,* Vulva; *1,* vagina; *2,* cranial vagina; *3,* caudal tubercle of the median dorsal fold; *4,* cervix and cervical canal; *5,* paracervical region. (From Lindsay F: The normal endoscopic appearance of the caudal reproductive tract of the cyclic and non-cyclic bitch: post-uterine endoscopy. *J Small Anim Pract* 24(1):1-15, 1983.)

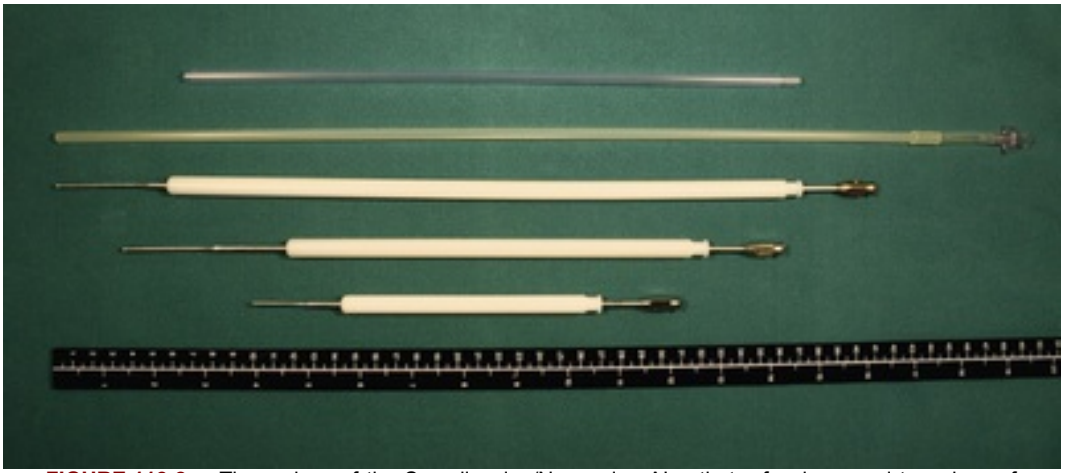

FIGURE 118-2 Three sizes of the Scandinavian/Norwegian AI catheter for dogs, and two sizes of rigid plastic single-use vaginal AI catheters.

By inserting the catheter along the left or right side of the vestibule of the vagina, accidental insertion into the centrally located urethral opening can be avoided. Because the urethral opening of the bitch is located at the pelvic brim, it is surprisingly easy for the plastic AI catheter, or a thin, rigid endoscope, to be unintentionally introduced into the urinary bladder. Apart from the hazards of perforating the bladder with the catheter, it is obvious that no pregnancy would follow after an AI when this occurs. Thus, the position of the catheter should always be checked by palpation before depositing semen. If the catheter is in the urinary

bladder, the cranial part of the vagina and the cervix can be palpated above the catheter and will not move in synchrony when the tip of the catheter is moved up and down. The walls of the urinary bladder usually are thinner than those of the vagina and the tip of the catheter stands out more distinctly than if it were in the vagina.

When the tip of the catheter has been advanced to a position immediately cranial to the pelvic brim, its position should be checked by palpation. Cranially, the vagina in most bitches slopes slightly downward. However, in some breeds (especially the sight hounds, many of which have an arched loin), the vagina may have a more dorsal direction (see Figure 118-1). The cranial end of the catheter should now be lowered closer to the abdominal wall to make it more accessible to palpation. When the catheter tip can be palpated and its correct position in the vagina thus checked, it is carefully advanced while continuously being palpated, until it reaches the paracervical area. This is the narrow, cranial portion of the vagina created by the dorsal, median postcervical fold and can be palpated as a 1- to 2-cm long, usually somewhat firm structure. It ends at the cervix, which in a bitch in estrus is a 0.5- to 1.5-cm, hard, rounded to ovoid, freely movable structure (see Figure 118-1).

The rigid plastic AI catheters, which have a diameter of 5 mm, may be too wide to be introduced into the paracervical area in some bitches, especially those of the smaller breeds or those that have not given birth to a litter of pups. Consequently, it is hardly ever possible to pass the outer protecting sheath of the Scandinavian/Norwegian catheter, which has a diameter of 10 mm, into the paracervical area. Once the cervix has been identified, the corpus uteri and the uterine horns can be palpated in front of this structure. This can be achieved by lowering the tip of the catheter and closing the tip of the thumb against that of the index finger above the catheter, then lifting the cranial end of the catheter in such a way that the cervix and the uterine horns are pulled upward between the fingers. Their size and consistency then become evident. (This method of palpating the uterus is also useful for early pregnancy detection and to examine bitches with suspected endometritis or pyometra.)

Vaginal Insemination

Vaginal AI is usually performed with a rigid plastic single-use catheter (20 to 45 cm long and 5 mm in diameter) (see Figure 118-2), which is introduced into the cranial vagina, as previously described, as close to the cervix as possible. With the catheter in place in the cranial vagina, a syringe containing the semen is attached and the hindquarters of the bitch then elevated before infusing the semen. After deposition of the semen dose, the catheter is withdrawn and the bitch is held with elevated hindquarters for 5 to 10 minutes to facilitate the transport of spermatozoa toward the oviducts. The bitch should also be "feathered" around the vulva and perineal region to stimulate uterine contractions. Spermatozoa may reach the tip of the uterine horn within 30 seconds to 1 minute during a natural mating and within about 30 seconds to 2 minutes after a vaginal AI if the bitch is held with elevated hindquarters. If the bitch is standing normally, transport of sperm into the uterus and oviducts is less efficient. One can also use either a Mavic or an Osiris catheter for vaginal AI. These have an inflatable cuff that occludes the distal vagina, preventing backflow of semen. It is intended to mimic the copulatory tie. These catheters usually are left in the vagina for 10 minutes after the AI while the bitch is free to move around (Figure 118-3).

FIGURE 118-3 The Mavic catheter for vaginal AI in dogs has an inflatable cuff and comes in three sizes. (Copyright MOFA Global 2014.)

Intrauterine Insemination Using the Scandinavian Catheter

The Scandinavian/Norwegian catheter (see Figure 118-2) is a 1- to 2-mm-wide steel catheter with a 0.75- to 1-mm diameter tip that comes in four different lengths: 20, 30, 40 or 45 cm. It is used with a 10-mm diameter outer nylon sheath to protect the bitch during placement. The medium-sized, 30 cm catheter fits most small, medium-sized, and large bitches. Giant breeds may require longer catheters. However, vaginal length varies more with breed than with size. Some large-breed bitches, sight hounds for example, have a relatively short vaginal vault.

Intrauterine AI with the Scandinavian/Norwegian catheter is performed with the non-sedated bitch standing. Most bitches in estrus readily accept this type of handling. In case light sedation should be required (in a large, obese, or nervous bitch), 1 to 3 mg/kg xylazine IM or IV can be used. The nylon sheath is first introduced into the vagina as far as possible. If lubrication is necessary, a small amount of Vaseline (or other non-spermicidal lubricant) can be used. If the nylon sheath is introduced together with the inner steel catheter, the tip of the steel catheter must be completely covered by the nylon sheath. The cranial end of the nylon sheath should be palpated cranial to the pelvic brim as previously described. If the tip of the sheath is lowered toward the abdominal wall, the cervix usually can be palpated a few centimeters in front and above the catheter. The steel catheter then is advanced through the sheath until its tip reaches the ventral fornix. To achieve this, the cranial vagina and cervix are manipulated to create an alignment between the catheter and the cervix.

The cervix is then fixed between the thumb and the index finger, taking care not to squeeze the canal closed, and by applying a slightly downward traction at the corpus uteri, it is tilted so that the angle of the cervical canal becomes more horizontal. The tip of the steel catheter is then carefully withdrawn while pushing it repeatedly against the surface of the cervix in search of the cervical canal opening. Touching the opening has been described as similar to touching cartilage (i.e., “crispy”). Once the opening is found, the catheter is held in place and the cervix is gradually worked over the catheter. The cervical canal is 5 to 10 mm long and not always completely straight (see Figure 118-1). Thus, slight pressure may be needed while rotating the catheter to ease it through. In most bitches, the tip of the catheter easily can be felt in front of the cervix in the corpus uteri, but sometimes this sensation is not distinct. In a few bitches, the catheter can only be introduced halfway through the cervix. This partial advancement, however, is often sufficient for depositing semen successfully.

The syringe containing semen is firmly connected to the catheter. Semen should be slowly infused into the uterus while gentle pressure is applied with thumb and index finger around the cervix to prevent backflow. Sometimes there is resistance to infusion if the opening of the catheter is pressed too hard against the endometrial mucosa. A slight downward traction at the corpus uteri or of the cervix usually alleviates the compression, allowing infusion. To be assured that the catheter tip is in the uterus, 1 to 2 mL of physiologic saline can be infused. If the catheter is in the correct uterine body position, the fluid can easily be infused. If the catheter is in the paracervical region of the vagina, however, there will be an almost immediate backflow of saline between the catheter and the nylon sheath. After intrauterine deposition of the semen, the catheter is withdrawn. To minimize backflow of semen and to facilitate uterine transport of spermatozoa toward the oviducts, the bitch may be held with elevated hindquarters for 5 to 10 minutes after the AI while being feathered around the vulva and perineal region to stimulate uterine contractions and sperm transport.

Learning this technique requires practice, but once learned it is a quick procedure requiring only a few minutes. At least 95% of attempts are successful. It is recommended that, initially, organ specimens be obtained for training purposes and anatomic study. First attempts, whenever possible, should be made in medium-sized, calm, non-obese bitches that have previously whelped litters, as they are usually easier to catheterize. Perforations may occur if the catheter is introduced blindly or with force, but when catheterization is performed carefully and correctly, the technique is safe. (This technique can be used for other infusions—for instance, for intrauterine infusion of contrast medium for hysterographic examinations of the bitch with suspected uterine lesions.)

Intrauterine Insemination Using Endoscopic Visualization of the Cervix (Video 118-1)

Transcervical intrauterine insemination can be performed on standing, non-sedated bitches using a fiberoptic endoscope. Although the use of a flexible endoscope has been found useful in Beagles, most practitioners use rigid endoscopes.[11,22,23] Various rigid endoscopes developed for humans have been used for AI in the bitch. Currently, the most commonly used endoscope for insemination is the Storz human uretero-renoscope, with a working length of 42.5 cm and a diameter of 3.15 mm at the tip (Karl Storz Veterinary Endoscopy, or MOFA Global). The endoscope can be used together with a camera and monitor (Figures 118-4 and 118-5).

FIGURE 118-4 The Storz uretero-renoscope with a working length of 42.5 cm and a diameter of 3.15 mm at the tip. (Copyright MOFA Global 2014.)

FIGURE 118-5 Transcervical intrauterine AI using a Storz uretero-renoscope with a working length of 42.5 cm and a diameter of 3.15 mm at the tip, here equipped with an insufflator, and a camera and monitor. (Courtesy Dr. Stuart Mason.)

MOFA Global has developed a set of three endoscopes of different lengths (Figures 118-6 and 118-7). Both medium (35 cm) and large (50 cm) length endoscopes accommodate up to 8 Fr sized catheters or two smaller catheters for advanced procedures. The small TCI endoscope is designed for toy breeds and cats and is 15 cm in length. These endoscopes (Storz, as well) also come with a special device, the TCI shunt (Figure 118-8), available in 16- and 21-cm lengths. The shunt is used by introducing it into the vestibule of the vagina and then advancing the tip past the urethral opening. Then, its cuff is inflated to create an airtight seal and fixed position in the caudal vaginal vault. The endoscope can then be introduced through the shunt. This shunt system acts as a stabilizing platform for the endoscope during the TCI procedure. This may be especially useful in the early stages of endoscopic TCI training. It does, however, restrict the mobility of the scope. Thus, if a bitch makes a sudden move, the endoscope cannot be quickly withdrawn, increasing risk for vaginal perforation.

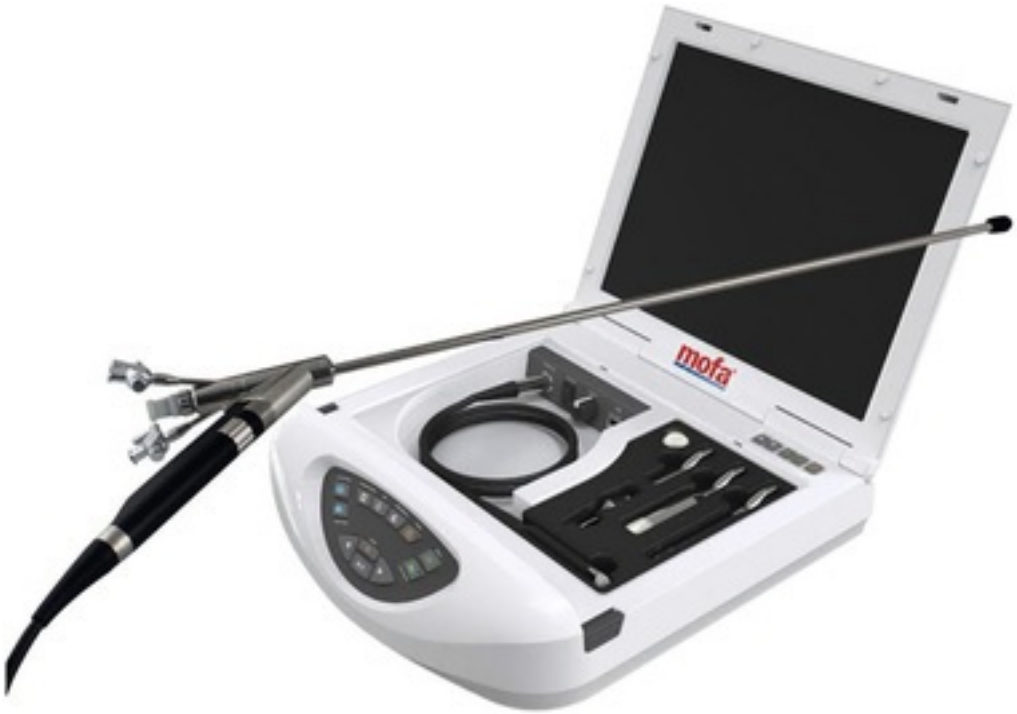

FIGURE 118-6 Equipment for transcervical intrauterine AI. (Copyright MOFA Global 2014.)

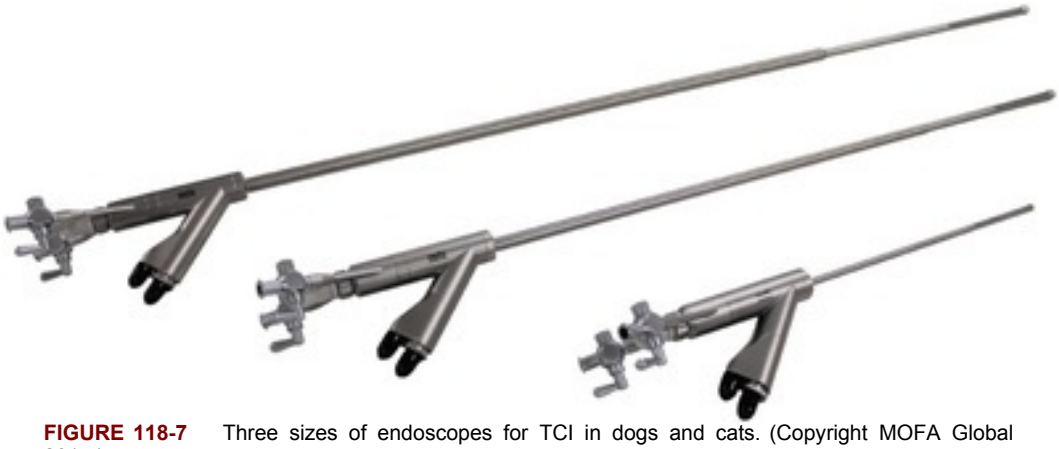

FIGURE 118-7 Three sizes of endoscopes for TCI in dogs and cats. (Copyright MOFA Global 2014.)

FIGURE 118-8 The so-called TCI shunt, which comes in two lengths, has an inflatable cuff and can be used with the Storz uretero-renoscope and the three sizes of endoscopes developed by MOFA Global. (Copyright MOFA Global 2014.)

A 6-8 Fr dog urinary catheter, or a custom-made longer and thinner (3-5 Fr) catheter, is passed through the operating channel of the sheath. The endoscope is introduced into the vagina and advanced until the external os of the cervix can be visualized. The urinary catheter is then manipulated into the cervical opening and further into the uterus. Insufflation of air distends the vagina and improves the field of vision. To guide the endoscope through the often tortuous vaginal vault, it can be quite helpful to let the urinary catheter lead the way by 1 or 2 cm, thus indicating the correct direction. If the opening of the cervical canal is directed away from the endoscope and thus out of sight, the cervix can be manipulated by pushing or lifting it with the tip of the endoscope, or with the catheter, while moving the instrument from side to side below the cervix. Similar to when using the Scandinavian/Norwegian catheter, correct positioning of the endoscope tip in relation to the cervix can be established with abdominal palpation. Palpation may also be used to change the cervix's position when needed for better alignment. After semen has been deposited into the uterus, the catheter and the endoscope are removed and the bitch may be held with elevated hindquarters for 5 to 10 minutes to prevent backflow of semen, as previously described.

The advantage of this technique is direct visualization of the cervical opening and intrauterine infusion of the semen. However, it requires skilled manipulation of the scope and catheter. Although equipment may be expensive, practitioners specializing in canine reproduction and AI should obtain at least one endoscope of a size that fits most breeds. The equipment can also be used for diagnostic procedures, such as endometrial biopsy and intrauterine culture and cytology.

Intrauterine Insemination Using Surgery (Video 118-2)

Surgical intrauterine insemination is still used in many countries, despite ethical concerns. To improve chances of a pregnancy and litter size, surgical AI may be combined with TCI or vaginal AI, at a 24-48 hour interval. For surgery, the bitch is placed under general anesthesia and in dorsal recumbency. The ventral abdomen is clipped and sterilized and a 4- to 6-cm incision made midway between the pubis and the umbilicus, through the linea alba. The uterus is elevated through the incision and the needle of the syringe containing the semen is inserted either into the lumen of the uterine body or into the cranial area of each horn at a 45° angle with the bevel of the needle up. The semen is slowly injected into the uterus. It should flow easily with obvious distention of the uterine horns or the needle may be repositioned. A saline-moistened gauze should be held over the injection site after the needle is withdrawn to prevent backflow of semen. After 1 minute the gauze is removed, the uterus replaced into the abdomen, and the wound closed using routine methodology. To avoid backflow of semen through the cervical canal, the bitch should be positioned with her rear elevated while she recovers from anesthesia. The risks associated with surgery and anesthesia, in general, and the limited number of surgical AIs that can be performed in a bitch are obvious disadvantages. Surgical AI can be more costly, more time consuming, and is less successful when compared with TCI.[9]

Intrauterine Insemination Using Laparoscopy

Techniques for laparoscopic AI in dogs are well-described, but this approach is not yet commonly used.[24] Concerns regarding equipment cost and the need for general anesthesia have slowed the use of laparoscopy.

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CHAPTER 119

Vaginoscopy and Vaginal Cytology in Dogs

Cheryl Lopate

Client Information Sheet: Vaginoscopy and Vaginal Cytology Examination

Indications

Vaginal cytology and vaginoscopy can be used to determine the stage of the bitch's estrous cycle, the presence of inflammation in caudal reproductive tract or to help elucidate the source of bloody vulvar discharge in the spayed or intact bitch.[1-7] The vaginal epithelium changes in response to circulating estrogen concentrations, be they endogenous or exogenous.[1-5,8,9] Vaginal cytology and vaginoscopy may be used to help in determining the optimal time to breed a bitch (in combination with progesterone and/or luteinizing hormone [LH] testing), to assess for the presence of infection or inflammation within the genitourinary tract, to elucidate the influence of estrogen on the patient, and to search for malignant cells.[1,2,5-9] There are various cell types that may be seen on vaginal cytology including epithelial cells, white blood cells (WBC), red blood cells (RBC), bacteria, and macrophages.[1-5,10]

Procedure for Obtaining a Sample

Vaginal cytology smears are best obtained using some type of guarded technique so the tip of the swab is not contaminated with skin, clitoral, vestibular or urinary tract secretions. A guarded or double guarded cytology swab or the use of a vaginal speculum (otoscope cone, short proctoscope, or small dual-bladed speculum) is useful in this regard. Either a clean cotton-tipped applicator or a cytobrush may be used. Acrylic tipped swabs cause more cellular damage and do not provide as high quality a specimen as cotton. A drop or two of physiologic saline (0.9%) may be added to the cotton applicator tip to minimize cell injury while the swab is obtained, particularly in bitches that are suspected to be in anestrus, since basal cells are particularly fragile. Initially, the speculum or guarded swab is passed at an angle about 45-70 degrees from horizontal, starting at the dorsal commissure of the vulva and maintaining the swab dorsally in the vestibule to avoid the urethral meatus (Figure 119-1, *A-F*; Video 119-1). Once the pelvic rim is reached the speculum or guarded swab is slid cranially within the vaginal canal. The swab, once fully seated, should be twirled back and forth for 10 to 15 seconds to exfoliate cells from the vaginal wall and then the swab is pulled out through the speculum or guarded outer sheath. After the swab is removed a light source may be attached to the speculum device and the color, texture and nature of the vaginal epithelium assessed visually; air insufflation with a hand bulb may be necessary in some cases. Once the swab is obtained, it should immediately be rolled gently onto a clean microscope slide, air-dried and stained with Wright-Giemsa stain. Alternatively, trichrome or Papanicolaou stains may be used.

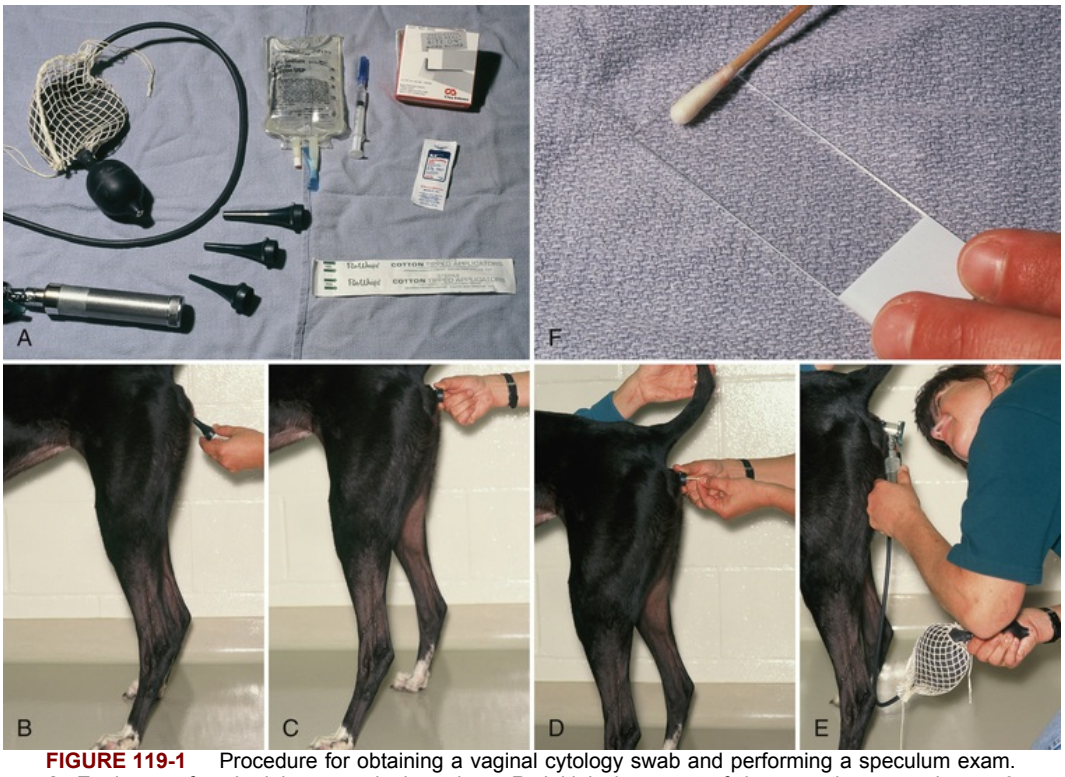

FIGURE 119-1 Procedure for obtaining a vaginal cytology swab and performing a speculum exam. **A,** Equipment for obtaining a vaginal cytology. **B,** Initial placement of the speculum cone is 45-70 degrees from horizontal. **C,** Once the rim of the pelvis is reached, the tip of the speculum is rotated to horizontal or a slight downward direction to allow full seating of the speculum in the vestibulum. **D,** The cytology swab or brush is slid cranially as far as possible and then rotated back and forth for 10-15 seconds. **E,** After removing the swab, a light source is attached to the speculum to allow visualization of the vaginal mucosa—air insufflation may be necessary to get adequate visualization. **F,** The cytology swab is gently rolled on a microscope slide and air dried before staining.

Cell Types Present on Cytology

Epithelial Cells

The epithelial cell types that may be present on a vaginal cytology slide include basal, parabasal, intermediate, nucleated superficial and anucleated superficial cells (Figure 119-2, *A* and *B*). Variations of these cells include metestrual cells, which are epithelial cells (typically parabasal and intermediate cells) that have engulfed a WBC (macrophages), and foam cells which are parabasal or intermediate epithelial cells that contain unstained cytoplasmic granules (Figure 119-2, *C* and *D*). Basal cells are the smallest of all the epithelial cell types and are round, with a large, centrally located nucleus and deeply basophilic cytoplasm when stained with Wright-Giemsa stain, which is readily available in almost any veterinary clinic. Parabasal cells are larger than basal cells with a round, smaller nucleus, that may be slightly eccentric in location, and less basophilic cytoplasm than basal cells. Intermediate cells are larger still, with smaller nuclei, that may be central to slightly eccentric in location. Small intermediate cells have cellular margins that are still round and cytoplasm is clear to very lightly basophilic, while large intermediate cells (sometimes called nucleated superficial cells) have a normal appearing nucleus. The edge of these cells have angled borders. Nucleated and anucleated superficial cells are the largest of the epithelial cells, with angled borders and either a smaller, pyknotic centrally located nucleus and lightly stained cytoplasm or are completely anucleated. Superficial cells are also sometimes called cornified cells.[1-5,10]

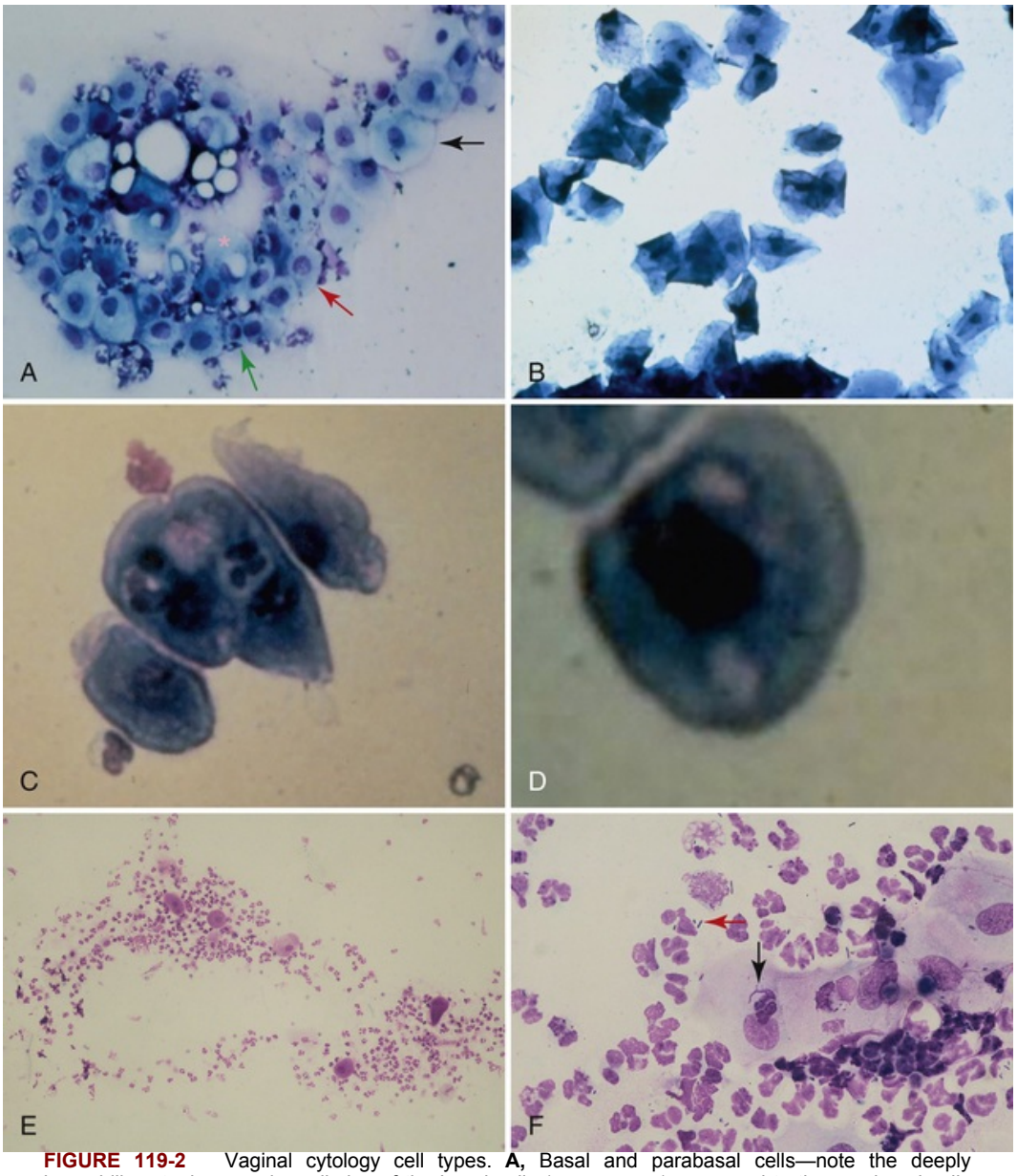

FIGURE 119-2 Vaginal cytology cell types. **A,** Basal and parabasal cells—note the deeply basophilic cytoplasm and small size of the basal cells (green arrow) compared to the parabasal cells (red arrow); intermediate cells (black arrow)—note the larger size, round cell margins, lightly stained cytoplasm; and foam (pink star). **B,** Superficial cells—nucleated and anucleated—note the angled cell border, large cell size. Some anucleated cells have pyknotic nuclei while others are completely anucleated. **C,** Metestrual cell—note the neutrophil being engulfed by the intermediate cell. **D,** Foam cell—note the clear granules in the cytoplasm of the parabasal cell. **E** and **F,** Vaginitis—note the large numbers of neutrophils with intracellular (red arrow) and extracellular bacteria and metestrual cells (black arrow).

White Blood Cells (Figure 119-2, *E*)

Neutrophils, typically non-degenerate are the predominant type of WBC present although occasional lymphocytes or eosinophils may be noted (particularly post abortion). In cases of vaginitis, endometritis, metritis and pyometra, degenerate neutrophils may predominate.[1-7]

Red Blood Cells

During proestrus, estrus and occasionally diestrus, red blood cells may be noted. They emanate from the endometrial capillaries that become leaky under the influence of estrogen and diapedesis ensues. As the bitch

progresses through the estrous cycle, the number of RBC typically declines.[1-5]

Bacteria (Figure 119-2, *F*; Video 119-2)

Bacteria are normally found on vaginal cytology smears. There are numerous species of bacteria that are found as part of the normal flora of bitches. They may be found in very high numbers early in proestrus and tend to decrease during estrus and are minimal during mid-late diestrus. Normally, there is a mixed population of cocci and rods, although often, cocci predominate.[5,11-17]

Metestrual and Foam Cells (see Figure 119-2, *C* and *D*)

During diestrus epithelial cells are known to be phagocytic and are seen in the form of metestrual cells. Foam cells are also present during diestrus—their function is not known.[1-5]

Contaminants and Other Cell Types

Fungal spores and yeast as well as urine crystals or talc crystals from exam gloves may be noted. Spermatozoa may be seen on vaginal cytologies.[1,2]

Neoplastic Cells

Cells from transmissible venereal tumors, squamous cell carcinomas, transitional cell carcinomas, leiomyosarcomas, lymphosarcoma, and metastatic mammary adenocarcinoma may be noted on cytology smears.[1,2,6,7]

Cyclic Changes during the Estrous Cycle[1-5,18] (Table 119-1; Video 119-3)

Anestrus

During anestrus the vaginal mucosa is not under any significant hormonal influence and is very thin. Cytologically, basal cells predominate, although occasional parabasal cells may also be noted. Often when cytologies are obtained during anestrus, the cytoplasm may be stripped from these fragile cells resulting in only nuclei being visible on the smear. Usually there are very few, if any bacteria or neutrophils during this stage of the cycle. There is often heavy mucus present. Speculum exam may reveal a dark red, streaky pattern to a dark, blotchy pink color. The mucosa is flattened with no crenulation or edema present.

TABLE 119-1

Cell Types Present on Vaginal Cytology Slides during the Estrous Cycle of the Bitch

	BASAL CELLS	PARABASAL CELLS	INTERMEDIATE CELLS	NUCLEATED SUPERFICIAL CELLS	ANUCLEATED SUPERFICIAL CELLS	RBC	WBC	FOAM AND METESTRU/ CELLS
Early proestrus	++	++	++	+/−	−	+++	+	−
Mid proestrus	−	+/−	+	+	+/−	++	−	−
Late proestrus	−	−	+/−	++	++	+	−	−
Estrus	−	−	−	+/−	+++	+/−	−	−
Diestrus	+	++	++	+/−	−	+/−	+	+
Anestrus	++	+	+	+/−	−	−	+/−	−

Vaginitis*	+/−	+/−	+/−	+/−	+/−	+/−	+ - ++ +	+

*The types of epithelial cells present and the presence or lack of RBC will depend on the stage of the cycle the vaginitis is noted.

Proestrus Cytology

During early proestrus, the vaginal epithelium begins to proliferate under the influence of estrogen. Initially, dark blood may be first noted and then quickly changes to a bright red, often voluminous, discharge. Cytologically basal and parabasal cells, along with intermediate cells are noted in early proestrus. There may be low to moderate numbers of neutrophils and heavy bacterial contamination during early proestrus, with the neutrophils disappearing by mid-proestrus, and bacterial numbers decreasing through proestrus and into early estrus, until there are far less bacteria visible. The numbers of RBC decrease as proestrus continues. As mid-proestrus approaches the numbers of superficial cells are increasing as the cells of the vaginal wall differentiate under the influence of estrogen. By mid to late proestrus, cytology reveals predominantly superficial cells, with some nucleated, some pyknotic and some anucleated. As proestrus proceeds through late proestrus to early estrus, the numbers of anucleated superficial cells increase and the numbers of nucleated superficial cells decrease.

Proestrus Vaginoscopy (see Video 119-1)

In early proestrus the mucosa is pink and edematous (Figure 119-3, *A*). As estrogen concentrations increase and the vaginal wall thickens, the mucosa begins to blanch and progresses from pink to light-pink and finally to white in color. The edema in the vaginal walls starts to diminish and the mucosa begins to crenulate, or wrinkle, resulting in the development of many folds (Figure 119-3, *B*).

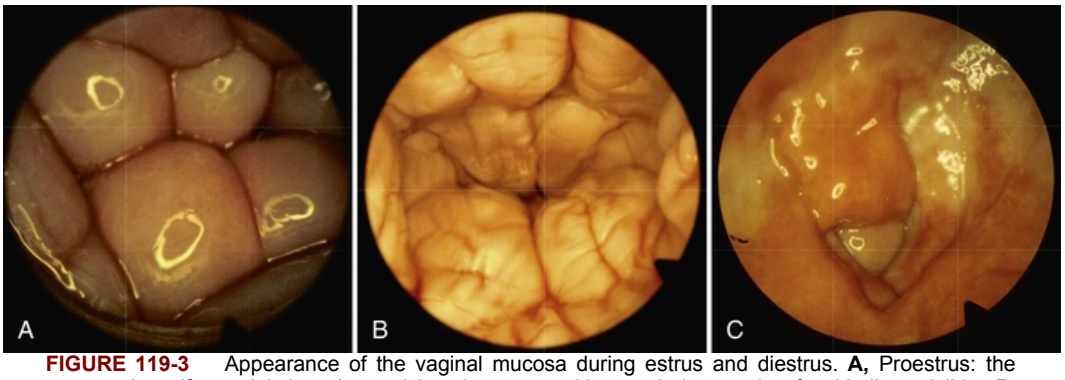

FIGURE 119-3 Appearance of the vaginal mucosa during estrus and diestrus. **A,** Proestrus: the mucosa is uniform pink in color and is edematous with rounded mounds of epithelium visible. **B,** Estrus: the mucosa is light pink–white with prominent folds or wrinkles; note the uniform color. **C,** Diestrus: mucosa is blotchy pink. Early in diestrus folds may still be visible, but very quickly the folds begin to flatten out; note the different shades of pink present.

Estrus Cytology and Vaginoscopy

As estrogen concentrations decline and ovulation occurs, all cells are superficial epithelial cells, primarily anucleated, although in some bitches, there may still be a large percentage of nucleated superficial cells present. There are decreasing numbers of RBC in most bitches but some may still have significant numbers through estrus. There are no WBCs. There can be minimal to moderate bacterial presence but this should be considered normal as long as there are no WBCs noted. The background is typically clear of debris and mucus. The cytology remains this way throughout the fertile period. Towards the end of the fertile period heavy exfoliation of superficial cells begins and clumping of superficial cells may be noted on cytology. It is not possible to directly correlate a specific cytology with ovulation but in many bitches ovulation occurs in correlation with maximal cornification (70-90% anucleated superficial cells).[8,9] Speculum examination reveals a white and crenulated mucosa throughout estrus and the number of folds and cross-folds increases as the fertile period progresses (see Figure 119-3, *B*).

Diestrus Cytology

There is a dramatic change in cellular characteristics at the onset of diestrus. The numbers of superficial cells decrease precipitously and the numbers of intermediate and parabasal cells increase. Within 24 hours of the onset of diestrus, neutrophils return. There may or may not be RBC in early diestrus but within a few days of the onset of diestrus, RBC presence ceases. Metestrual cells and foam cells appear within the first few days of diestrus. Bacterial numbers may be low to numerous (especially if breeding occurs). Early proestrus and early diestrus may be difficult to differentiate cytologically. Speculum examination reveals a blotchy (two-tone), pink–dark pink or red color with rapid flattening of the vaginal folds. Touching the mucosa with the end of a speculum or an endoscope results in rosette formation (first blanching of the mucosa with immediate refilling with blood) (Figure 119-3, *C*).

Other Reproductive Disorders That Vaginal Cytology May Be Helpful in Elucidating

Infection

Vaginal cytology may be used to diagnose infection within the genitourinary tract, including vaginitis, endometritis, pyometra, urethritis, cystitis, vestibulitis, clitoritis or vulvitis. Further diagnostics must be performed to elucidate the site of infection.[1,2,6,7,16,17,19]

Neoplasia

Transmissible venereal tumors, squamous cell carcinomas, transitional cell carcinomas, leiomyosarcomas, lymphosarcoma, and metastatic mammary adenocarcinoma may exfoliate cells into the vaginal canal that may be visible on cytology. Further diagnostics must be performed to determine the location and type of neoplasia present.[1,2,6,7]

Other Causes of Vulvar Hemorrhagic Discharge

Trauma, vaginal angiomatous neoformation, vascular ectasia or coagulopathy may also cause bloody vulvar discharge and need to be differentiated from proestrus hemorrhagic discharge through additional diagnostic procedures.[1,2,6,7,20,21]

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SECTION VI

Minimally Invasive Interventional Therapies

OUTLINE

Chapter 120 Overview of Interventional Medicine
Chapter 121 Respiratory Interventional Therapies
Chapter 122 Cardiovascular Interventional Therapies
Chapter 123 Gastrointestinal Interventional Therapies
Chapter 124 Urologic Interventional Therapies
Chapter 125 Neoplastic Interventional Therapies

CHAPTER 120

Overview of Interventional Medicine

Chick Weisse

Introduction

Minimally invasive surgical procedures are playing an important and growing role in veterinary medicine. As these therapies have developed over the years in human surgery, the benefits in terms of reduced morbidity, mortality, analgesia, time to recovery, hospitalization times, and even cost in some circumstances are beyond dispute. In addition, these therapies have provided the means to treat underlying conditions not amenable to more traditional approaches. These same arguments can be made in favor of the use of these procedures in veterinary patients; however, the science has not yet caught up to the practice in our profession. The background on specific diseases is covered elsewhere within the textbook.

Interventional Radiology/Interventional Endoscopy

Following the description of percutaneous arterial catheterization by Sven Ivar Seldinger in 1953, angiography developed into a widely-utilized and essential medical diagnostic tool.[1] Technological advances in imaging and medical devices have since helped transform this once diagnostic modality into a sub-specialization with enormous therapeutic potential. Interventional radiology (IR) involves the use of contemporary imaging techniques such as fluoroscopy and ultrasonography to selectively access vessels and other structures in order to deliver different materials for therapeutic reasons. Interventional endoscopy (IE) utilizes the recent advances in endoscopy to perform image-guided therapy alone or in conjunction with fluoroscopy. Endourology and interventional gastroenterology are some of the more common combined uses in which the operator(s) uses endoscopy to access an orifice such as the ureterovesical junction within the urinary bladder or the major duodenal papilla to subsequently use IR techniques under fluoroscopic guidance to access the upper urinary tract or biliary tract, respectively. Both IR and IE techniques provide therapeutic options for diseases once deemed untreatable—often now the standard of care for a variety of human conditions.

Advantages and Disadvantages

The use of IR and IE techniques in veterinary patients has the potential to provide a number of advantages compared to more traditional therapies. These procedures are minimally invasive and can therefore theoretically lead to reduced peri-operative morbidity and mortality, shorter anesthesia times, and shorter hospital stays. Examples of such procedures with reported advantages over traditional open surgical procedures might include treatment for feline ureteral obstructions or canine intrahepatic shunts.[2,3] Some less equipment-intensive procedures can result in reduced costs as well. While the equipment necessary to perform these techniques can often be expensive in terms of disposables and initial capital investment, the high (and rising) costs of hospitalization in tertiary referral and specialty hospitals can be dramatically reduced with these often outpatient or single night stay procedures. The more traditional “invasive” surgical therapies may be less expensive to perform; however, the prolonged intensive care unit (ICU) stays, postoperative care, transfusions, etc. can often add up to even higher veterinary bills. The majority of the IR/IE procedures performed at the author's institution are similar in cost to the comparative surgical therapy. The exceptions would be a variety of laparoscopic-assisted procedures (ovariohysterectomy, bladder stone removal, gastropexy, gastrointestinal biopsies). Perhaps the greatest advantage of these procedures is the ability to treat conditions for which more traditional therapies are contraindicated, associated with excessive morbidity, or unavailable to veterinary patients. Examples include sclerotherapy for renal hematuria, embolization or chemoembolization of nonresectable tumors or vascular anomalies, etc.

The primary disadvantages of IR/IE include the required technical expertise which is not currently available at most veterinary advanced training institutions, the specialized equipment necessary (wide range of endoscopes, fluoroscopy with or without digital subtraction capabilities), and the initial capital investment necessary to provide a suitable inventory of catheters, guide wires, balloons, stents and coils. Training labs and courses available at the major specialty college symposia as well as privately-run training labs are now commonplace.

Equipment

Operating Rooms/Angiography Suites

As most of these procedures are minimally invasive (performed through natural orifices or small holes in the skin), traditional sterile operating rooms (ORs) are not required, but recommended. During the learning process, and even for experienced interventionalists, open surgical conversion may be necessary. Performing these procedures within a sterile environment so open surgical conversions can be performed quickly and efficiently facilitates this. Additionally, hybrid approaches are often used in which small surgical approaches are performed to facilitate access for interventional therapies. In both circumstances, the pet owners should consent to open procedures prior to the procedure and the patient should be clipped and prepared for full surgical access if necessary. More standard, predictable endoscopy and interventional procedures can be performed in endoscopy or clean angiography suites, respectively.

Additional equipment needs require larger OR environments. Aside from common needs such as anesthesia machines, OR tables, and surgical equipment, the ideal room should provide ample space for a "crash cart," equipment cabinets, lasers, vessel sealing devices, lithotripters, and movement of the C-arm away from the table for additional surgical space. A control room station in the OR is recommended for fully integrated ORs; these are currently rare in veterinary medicine but growing in number due to flexibility to perform multiple different therapeutic modalities within the same space.

For many of the more commonly performed IR procedures, a traditional fluoroscopy unit is sufficient. Operators wear full lead (or similar) gowns, thyroid shields, caps, gowns, and masks. The more common fluoroscopy units currently available in veterinary hospitals are often "multi-purpose units," a combination digital radiography and fluoroscopy unit built into one system. While these are suitable for general fluoroscopy needs, the relative immobility of these units to rotate, the non-sterile environments in which they are standardly installed, and the inability to permit surgeons standing on both sides of the patient concurrently make them poor choices for many of the currently performed IR/IE procedures except the more standard cardiac interventions, or tracheal and urethral stenting.

Alternatively, mobile C-arm units may already be available in the OR in many larger referral veterinary hospital settings. Often these units are suitable for the more basic, non-vascular IR procedures and most endourological procedures. A C-arm fluoroscopy unit has the advantage of mobility of the image intensifier (or more recently digital flat panel detector), permitting multiple tangential views without moving the patient. In addition, many of these units may be able to receive software upgrades such as cardiovascular packages in order to improve performance according to the desired technique. Compared to the more expensive, larger, fixed (ceiling or floor-mounted) units which provide superior image resolution, the mobile C-arms are easily moved from room to room, have fewer radiation regulations (leaded walls not necessary but may vary by state), and can be purchased, leased or even rented at a fraction of the cost. Often overlooked during purchasing of this equipment is the OR table. While some standard OR tables are sufficiently thin to permit fluoroscopy when the patients are small and placed at the end of the table, specially designated "fluoroscopy surgery tables" are available in a variety of designs. These more expensive fluoroscopy tables are often equipped with a "floating" tabletop configuration to facilitate patient positioning without moving the more bulky C-arm.

As these procedures are often performed by surgeons or internists without recent training in radiation safety, it is important to refresh one's knowledge on the rather substantial radiation exposure that can occur during some of the more prolonged interventional procedures. The operator is encouraged to review radiation safety guidelines and reduce exposure as much as possible, minimize exposure time and beam size, and maximize shielding and distance from the beam. Non-essential people should not be in the suite during fluoroscopy, particularly when "runs" are performed as the radiation exposure levels are often increased. Radiation dosimetry badges should be worn and regularly evaluated to monitor for increased exposure.

Standard fluoroscopy, available on most veterinary multi-purpose and mobile C-arm units, is acceptable for the more common respiratory, urinary, and gastrointestinal procedures. Digital subtraction angiography (DSA) is highly recommended (and some might say required) for the vascular procedures, particularly when

performed in small caliber vessels with overlying boney and/or gas-filled structures that might otherwise interfere with image resolution. DSA is a computer software–processing program that takes an initial non-contrast fluoroscopic image (the "mask") and subtracts it from subsequent images during a "run" (or series of recorded images). This permits improved vascular imaging and resolution without overlying structures obscuring the view, allows the operator to access smaller structures more reliably, and requires much less contrast than would be necessary otherwise (Figure 120-1). DSA is required for super-selective angiograms of small caliber vessels and those vessels in the head (or where there is substantial bone which makes angiogram visualization difficult), particularly when delivering toxic (chemotherapy) or embolic substances that could reflux into, or enter, non-target vessels leading to vital structures. "Road-mapping" capabilities on some systems permit saving these contrast studies and placing them over real-time fluoroscopy images to provide a "vascular map" for guide wire, catheter, embolic, or stent manipulations.

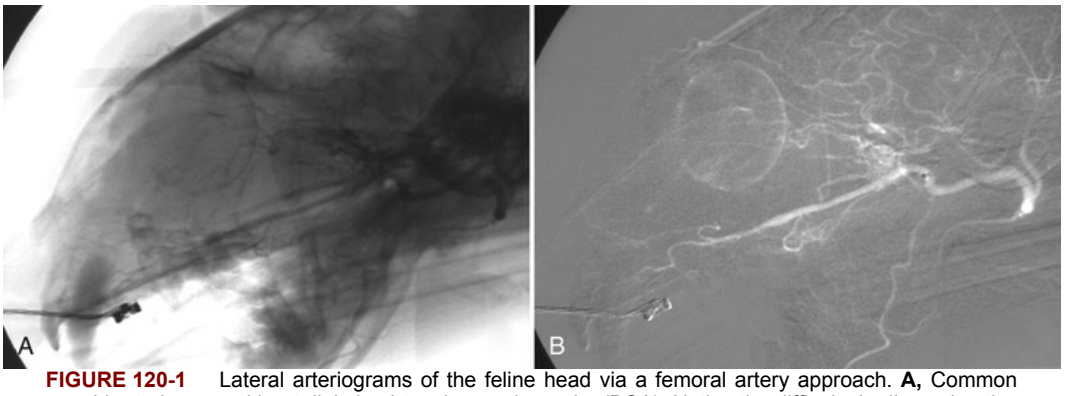

FIGURE 120-1 Lateral arteriograms of the feline head via a femoral artery approach. **A,** Common carotid arteriogram without digital-subtraction angiography (DSA). Notice the difficulty in discerning the small, complex vasculature. **B,** The same common carotid arteriogram using DSA to remove the underlying boney structure of the skull. Notice the clearly defined vascular anatomy now evident. (From Weisse C, Mayhew P: Basics of minimally invasive surgery. In Tobias KM, Johnston SA, editors: *Veterinary surgery: small animal*, St Louis, 2012, Elsevier.)

Endoscopy

The most common endoscopes used during IE procedures are rigid rod-lens cystoscopes and flexible fiberoptic ureteroscopes. Rigid cystoscopy using telescope diameters ranging from 1.9 to 6.5 mm is commonly performed in female animals to aid in urethral, urinary bladder, and ureteral access (see ch. 124). Similar scopes are used for antegrade rhinoscopy (see ch. 96). The scope sheath provides a smooth rounded edge to protect the mucosa and the telescope, as well as provides three separate ports for fluid irrigation, fluid drainage and a working channel for passage of a wide variety of interventional devices (biopsy forceps, needles, baskets, laser fibers, guide wires, stents, etc.). The 30° angle of view is the most commonly used cystoscope/rhinoscope allowing excellent visualization of the nasal cavity and bladder wall, as well as the ureteral orifices. Flexible ureteroscopes (2.5-2.8 mm diameter with a 1 mm working channel) are used for lower urinary tract access in male dogs and for ureteral access in dogs >18 kg. These scopes tend to have considerably diminished image resolution (compared to the rod-lens technology of rigid scopes), smaller working channels limiting devices and irrigation, and weaker illumination.

Ancillary Imaging Equipment

Aside from the endoscopes, a "tower" will be a necessary capital investment. This is a multi-tiered cart comprised of the camera control box, light source, monitor, and often data recording devices. Light sources are typically halogen or xenon with the latter being preferred due to closest similarity to natural light. If possible, multiple monitors (or at least a single monitor on an articulating arm/platform) are recommended to facilitate observation from multiple locations around the surgical table as these patients vary in size, positioning, and entry site among the wide variety of procedures currently performed. Designing the interventional suite with as much flexibility as possible will maximize the usefulness of the room. It is much easier to move the monitor than to relocate the often-cumbersome endoscopy towers. Data recording devices have become routine components allowing storage of images and videos of the procedures, recommended to

be saved as part of the patient record and facilitating review at a later date if/when procedures need to be repeated. Endoscopes are typically gas- (or sometimes cold-) sterilized; sterilization is necessary prior to any endourological procedures. Occasionally, ultrasonography is useful for percutaneous needle access into vessels or other structures such as the renal pelvis or percutaneous urethral access.

IR/IE Instrumentation

Access

Prior to any interventional procedure, luminal access is first necessary. This is the first and perhaps one of the most important parts of any interventional procedure as the chosen access location can make a difficult procedure easy, or an easy procedure difficult. Venous access is often performed percutaneously, while vascular cut-down for access to the femoral artery (or branches) or carotid artery is performed to permit arterial ligation at procedural completion. Ligation of the femoral and carotid arteries is safely tolerated in dogs and prevents post-operative hemorrhage that can be significant in animals often discharged the same day. Although reported otherwise, ligation of both carotid arteries in dogs may not be universally tolerated.[4] Some cats have safely tolerated ligation of both carotid arteries. Standard intravenous catheters or entry needles can be used for vascular access. "Gauge" is defined as the number of needles or catheters that can be placed next to one another to sum up to 1 inch; therefore larger gauge needles have smaller lumens. For instance, a 22 gauge needle has a smaller lumen than an 18 gauge needle. Once more experienced in these procedures, the operator will soon memorize which catheters accommodate suitable guide wire diameters. A "single-wall puncture" or "modified Seldinger" technique is preferred for vascular access to avoid double wall vessel perforation, particularly in coagulopathic patients in whom additional vascular punctures could increase the risk of hematoma formation.

Guide Wires

Once vascular access is achieved, or a targeted orifice (e.g., the ureterovesical junction [UVJ]) is identified, guide wire access is obtained. Standard spring guide wires (polytetrafluoroethylene [PTFE/Teflon], stainless steel, nitinol, etc.) are available in a wide range of diameters, lengths, stiffness, tip configurations, and surface coatings (Figure 120-2). In general, the guide wires currently used in veterinary patients range from 0.014″ to 0.038″ diameter and lengths from 150 cm to 300 cm. For larger vessels or lumens, access is typically obtained with an 18 gauge catheter followed by 0.035″ or 0.038″ guide wire placement. In smaller vessels or lumens, access may be obtained more easily and safely with a 22 gauge catheter followed by a 0.018″ guide wire. Urethral and ureteral luminal access is often achieved using similar angled hydrophilic guide wires[a] in the 0.018 to 0.035″ diameter range depending upon patient size.

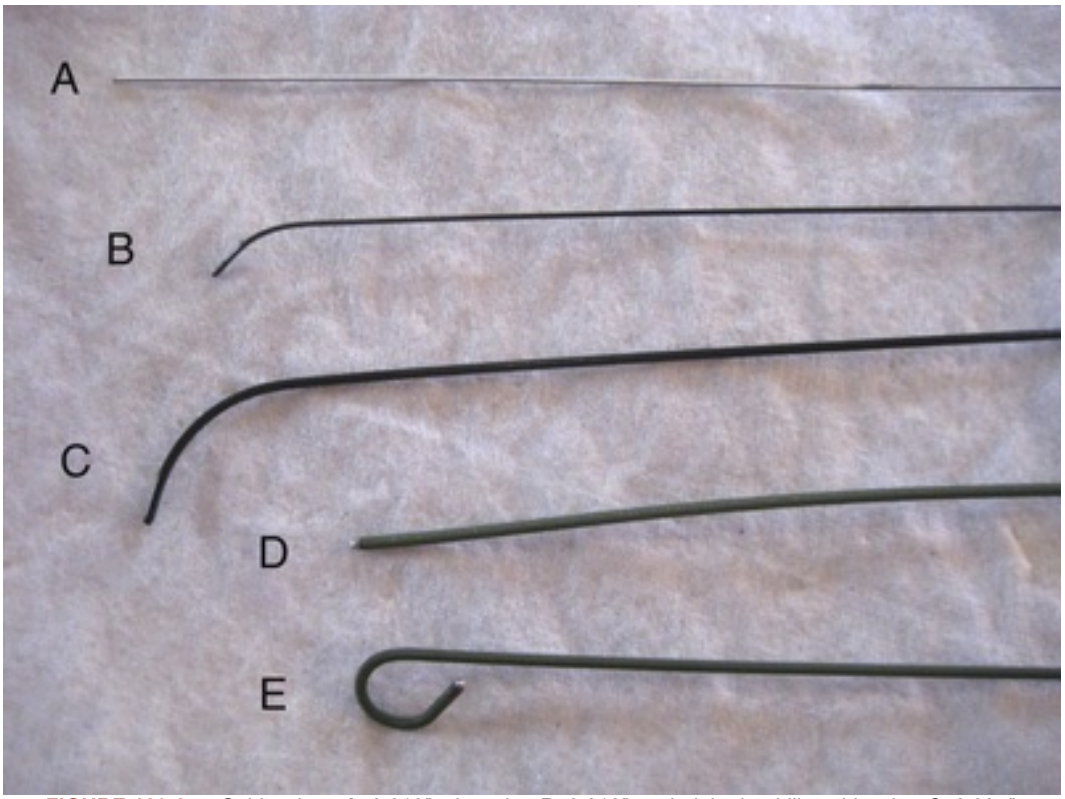

FIGURE 120-2 Guide wires. **A,** 0.018″ microwire. **B,** 0.018″ angled, hydrophilic guide wire. **C,** 0.035″ angled, hydrophilic guide wire. **D,** 0.035″ straight PTFE wire. **E,** 0.035″ Rosen PTFE wire.

Introducer Sheaths

Introducer sheaths[b] are composed of the sheath (basically a catheter), the associated dilator, a hemostasis valve, and a side port (Figure 120-3). They are used for almost all vascular procedures (see ch. 122), particularly those in which multiple devices may be exchanged, to permit safe, controlled, dilation of the entry vessel and subsequent protection from vascular damage or hemorrhage during the procedure. The side ports permit simultaneous flushing or sampling or contrast angiography if necessary. The check flow diaphragm prevents back-bleeding through the sheath while permitting placement of various sized catheters, balloons, stent delivery systems, or other devices that could otherwise result in trauma to the vessel or surrounding tissues. Sheaths are unique in that they are named for their inner diameters (ID) compared to all other devices that are named for their outer diameters (OD). This helps the operator choose what size sheath will be necessary for placement of a certain size stent delivery system, for instance. The typical sizes used range from 4-12 French (Fr). Three Fr is equal to 1 mm; therefore, a 6 Fr sheath has a 2 mm inner diameter but its outer diameter will be larger depending upon the thickness of the sheath. The author commonly uses introducer sheaths for endourological procedures as well, placing them in the urethra, up the ureter, and even percutaneously into the kidney, or into the urethra during perineal access (see ch. 124).

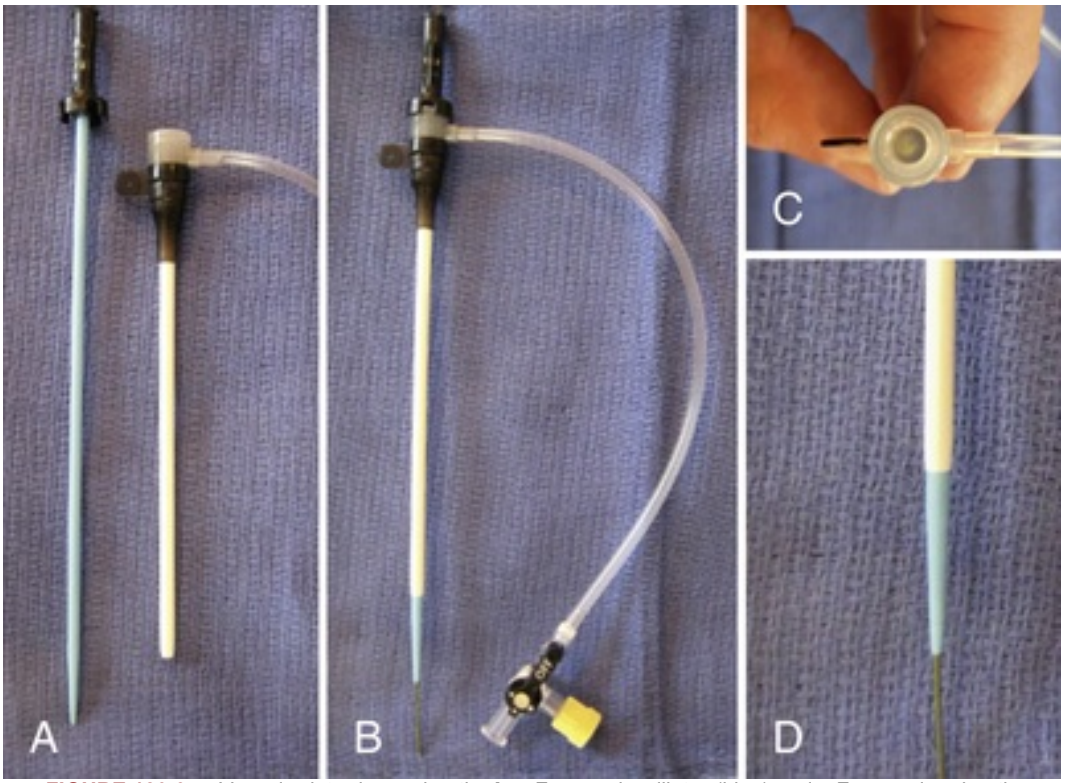

FIGURE 120-3 Vascular introducer sheath. **A,** 7 Fr vascular dilator (blue) and 7 Fr vascular sheath (white). **B,** Vascular sheath with vascular dilator and guide wire in place. **C,** Diaphragm of vascular sheath with dilator removed, demonstrating hemostasis valve. **D,** Tip of vascular sheath with dilator placed over guide wire. Notice the smooth transition from the sheath to the dilator and down to the diameter of the guide wire. (From Weisse C, Mayhew P: Basics of minimally invasive surgery. In Tobias KM, Johnston SA, editors: *Veterinary surgery: small animal*, St Louis, 2012, Elsevier.)

Selective Catheters

Selective catheters are used in combination with compatible guide wires to select different structures in order to perform contrast studies, obtain samples, or deliver materials (Figure 120-4). Pre-shaped angiography catheters are routinely 4 or 5 Fr and tapered to 0.035″ or 0.038″ guide wires. Most catheters are end-hole only (to prevent embolic delivery anywhere besides the tip of the catheter) but some have multiple side holes useful for power injection of contrast in high-flow vessels such as for cardiac angiography (pigtail catheters for instance; see ch. 122). The most commonly used catheter shapes include the hockey stick tip ("Berenstein")[c] and C-shaped or "Cobra"[d] tip. For access into vessels originating at very acute angles, reverse-curve catheters can be used in which the tips are angled backwards. Microcatheters[e,f] (typically 3 Fr or less) are used in combination with microwires[g,h] (typically 0.014″-0.018″) and passed coaxially through the pre-shaped catheter in order to access second- or third-generation vessels without causing vessel occlusion or spasm.

FIGURE 120-4 Selective catheters. **A,** Marker pigtail catheter. Note the radio-opaque markers on the shaft as well as the multiple fenestrations permitting rapid contrast injection without fear of damage to the vessel wall compared to an end-hole catheter. **B,** Rim (reverse-curve) catheter ideal for access from one external iliac artery to the ipsilateral internal iliac or contralateral external or internal iliac arteries. **C,** Cobra-type catheter with gentle bend facilitating access into first-order arterial branches off the aorta or vena cava. (From Weisse C, Mayhew P: Basics of minimally invasive surgery. In Tobias KM, Johnston SA, editors: *Veterinary surgery: small animal*, St Louis, 2012, Elsevier.)

Balloons

Occlusion balloons (low pressure, high compliance) are used for temporary occlusion of a vessel to facilitate angiography or redirect embolization materials away from a non-target organ. These balloons can also be used as flow-directed catheters to allow blood flow to direct the catheter towards difficult to access sites, particularly in cardiac interventions (see ch. 122). Balloon angioplasty catheters[i] (high pressure, low compliance) are typically filled with dilute contrast agent under pressure in order to dilate and efface strictures or stenoses of the blood vessels or other lumens such as the esophagus, rectum, nasopharynx, trachea, or urethra (see ch. 121, 123, and 124).

Drainage Catheters

Drainage catheters provide surgical or percutaneous removal of fluid collections (e.g., pleural fluid, peritonitis, abscess, etc.) or diversionary procedures (e.g., nephrostomy, cholecystostomy, gastric, etc.). Both locking- and non–locking-loop conformations are available and can be placed using a modified Seldinger technique (over the guide wire) or a trocar technique (direct puncture). The locking-loop catheters[j] are

typically preferred due to the suture locking mechanism that secures the catheter loop, minimizing premature catheter withdrawal (Figure 120-5). More recently, a subcutaneous ureteral bypass (SUB)[k] device has been described, composed of a locking-loop nephrostomy and cystostomy tube connected subcutaneously to divert urine around ureteral obstructions (Figure 120-6) (see ch. 124).[5,6]

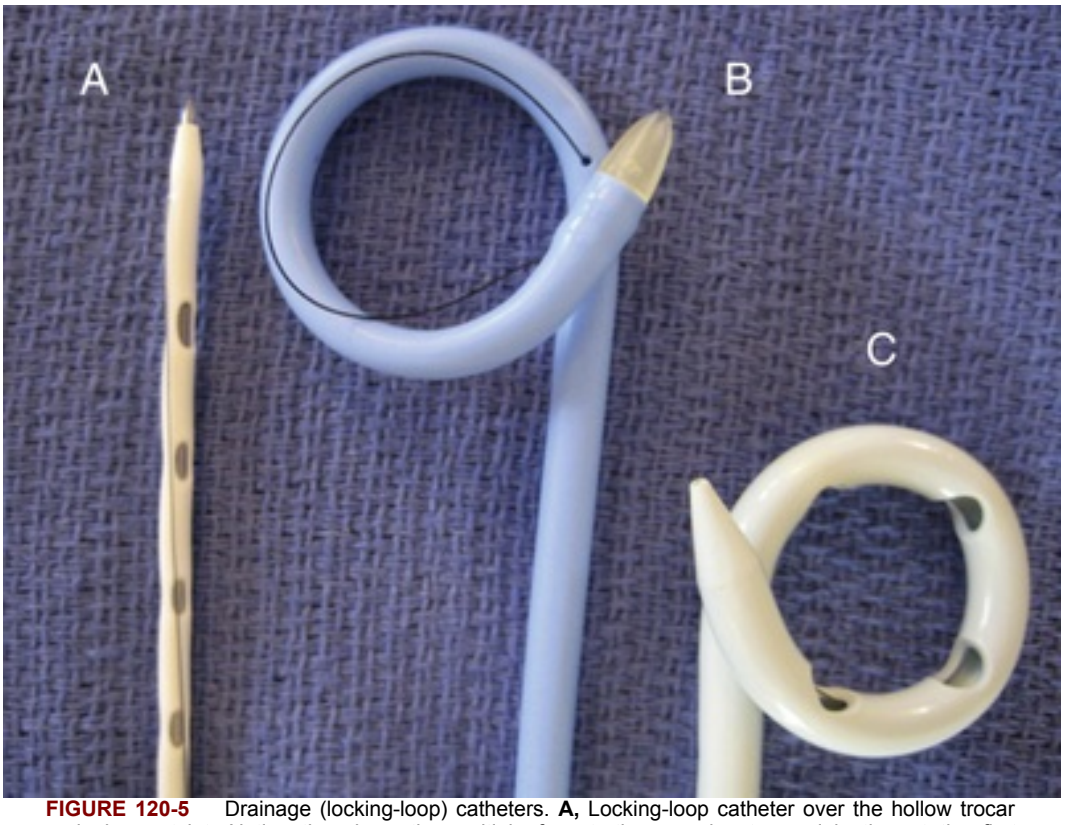

FIGURE 120-5 Drainage (locking-loop) catheters. **A,** Locking-loop catheter over the hollow trocar and sharp stylet. Notice the sharp tip, multiple fenestrations, and suture originating at the first fenestration and extending proximally to the most proximal fenestration. **B,** Similar locking-loop catheter with stylet and hollow trocar removed. Notice the retaining suture currently loose. **C,** Similar locking-loop catheter with retaining suture locked tight, drawing proximal and distal fenestrations together and forming a secure loop with internalized fenestrations to facilitate drainage. (From Weisse C, Mayhew P: Basics of minimally invasive surgery. In Tobias KM, Johnston SA, editors: *Veterinary surgery: small animal*, St Louis, 2012, Elsevier.)

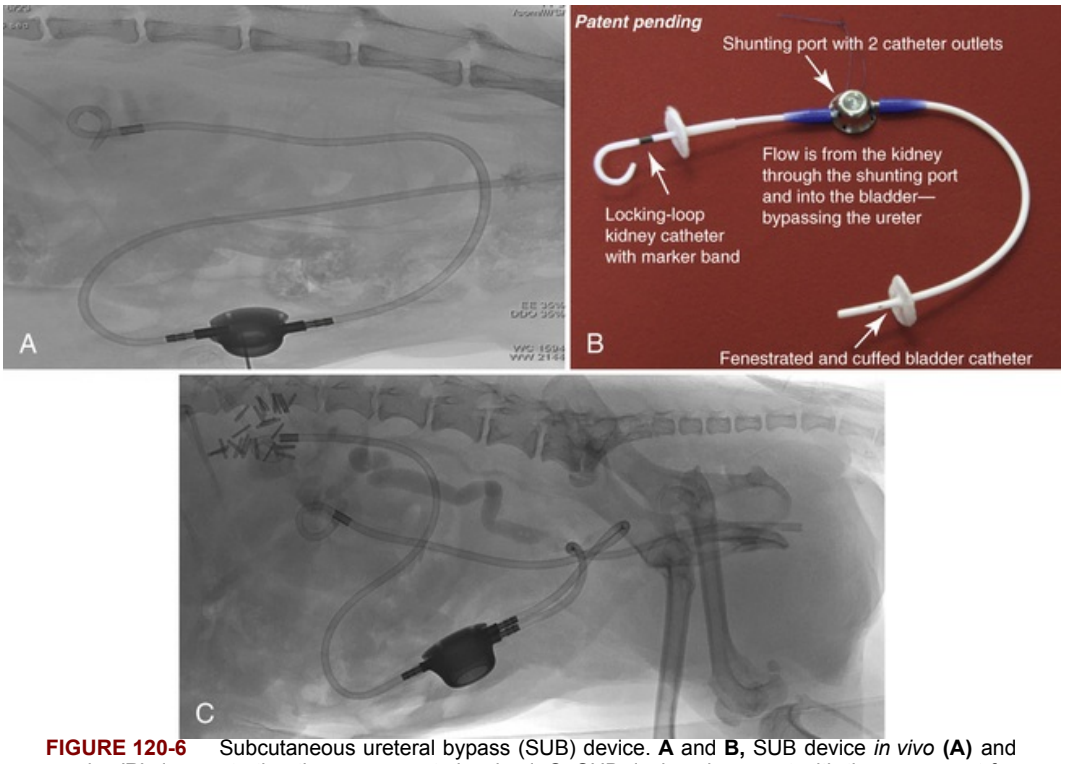

FIGURE 120-6 Subcutaneous ureteral bypass (SUB) device. **A** and **B,** SUB device *in vivo* **(A)** and *ex vivo* **(B)** demonstrating the components involved. **C,** SUB device placement with three-way port for canine patient with extensive transitional cell carcinoma. Two nephrostomies and a urethral catheter placed following radical excision of the urinary bladder, distal ureters and proximal urethra.

Stents

Stents are tubular structures designed to re-establish patency of a lumen that has become obstructed. They are available in a variety of materials, shapes, sizes, and designs that define their suitability for a particular structure or environment.

Stents can be most easily categorized by some of their properties including material (metallic versus non-metallic) and design (self-expanding versus balloon expandable and/or covered versus uncovered) (Figure 120-7). An individual stent is typically named for its diameter and length. Metallic (or similar) stents are typically supplied pre-mounted within a delivery system (self-expanding stents) or on a balloon catheter (balloon-expandable stents). Delivery systems are named for their outer diameters and can sometimes limit the ability to place the associated stent in our smaller veterinary patients.

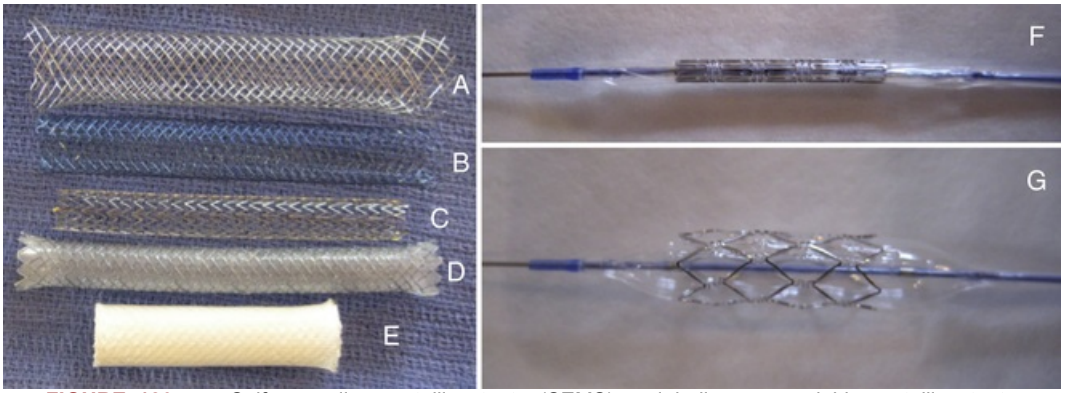

FIGURE 120-7 Self-expanding metallic stents (SEMS) and balloon-expandable metallic stents (BEMS). **A,** Stainless steel mesh SEMS (Wallstent, Boston Scientific Corporation). **B,** Nitinol mesh SEMS (Vet Stent-Trachea, Infiniti Medical, LLC). **C,** Nitinol laser-cut SEMS (Vet Stent-Urethra, Infiniti Medical, LLC). **D,** Silicone covered nitinol mesh stent graft (Vet Stent, Infiniti Medical, LLC). **E,** Polyester covered mesh stent graft (Wallgraft, Boston Scientific Corporation). **F,** BEMS compressed

onto percutaneous transluminal angioplasty balloon before dilation. **G,** Expanded BEMS subsequent to balloon dilation. (From Weisse C, Mayhew P: Basics of minimally invasive surgery. In Tobias KM, Johnston SA, editors: *Veterinary surgery: small animal*, St Louis, 2012, Elsevier.)

Self-expanding metallic stents (SEMS) are the most commonly used stents in veterinary medicine and their use has been described clinically (or experimentally) in the respiratory, cardiovascular, urinary, gastrointestinal, and hepatobiliary tracts of animals (see ch. 121-124). Mesh SEMS, composed of an interwoven strand (or strands) of fine wire, are most commonly used for tracheal stenting but can be used elsewhere in the body. In general (but not uniformly), mesh SEMS[l] are "reconstrainable," meaning at some defined point before complete deployment the stent can be recaptured within the delivery system and repositioned or removed. This functionality is particularly useful when imprecise positioning would be unacceptable. Unfortunately, these same stents typically undergo a variable degree of "foreshortening" encountered during stent deployment. As the stent expands during release from the delivery system it will shorten to assume its ultimate diameter and length. This shortening will depend upon the degree to which the stent ultimately expands within the lumen and can often be difficult to predict exactly, particularly by more novice operators. Reconstrainability and foreshortening must be understood and anticipated when mesh SEMS are being used. Woven or braided SEMS are also made from metallic wire but often of much thinner gauge to create a softer, almost fabric-like stent, and currently are not widely used in veterinary medicine; however, they have been used in the respiratory and gastrointestinal tracts of veterinary patients. Laser-cut SEMS[m,n] are produced from a narrow tube of metal in which a laser cuts the stent design that is later expanded to create the ultimate stent dimensions. Following a finishing and coating process, the stent is cooled and crimped onto a low-profile delivery system to permit placement through small entry sites. Upon reaching body temperature, the crimped nitinol (or similar shape-memory metal) stent changes properties and resumes its original stent diameter and length. These characteristics have revolutionized stent design and the laser-cut stents are one of the most commonly used SEMS in interventional radiology. These stents are rarely reconstrainable and have minimal foreshortening permitting precise placement across focal lesions, although once deployment from the delivery system begins the process cannot be reversed. In veterinary medicine, laser-cut SEMS are most commonly used in the urethra[7] or vasculature.[8,9] Grafts, or stent grafts, refer to stents with coatings or coverings (covered stents) such as silicone and various types of polytetrafluoroethylene (Teflon/PTFE) materials placed inside, outside, or surrounding the underlying metal structures. While these stents can be useful to prevent ingrowth of strictures or tumors through the stent interstices, disadvantages such as increased cost, larger delivery systems, and risk of occluding adjacent lumens particularly in the vascular systems generally limit their routine use.

Balloon-expandable metallic stents (BEMS)[o] are pre-mounted (compressed) onto a balloon catheter, positioned across the lesion, and as the balloon is inflated the stent expands. The balloon is then deflated and removed and the stent remains in place. BEMS are ideal for precise placement of short, rigid stents in areas that are not likely to be compressed externally. Disadvantages include the relatively short lengths available, poor flexibility, and static response to compression (i.e., if compressed the stent will remain compressed and not expand). BEMS are routinely used for nasopharyngeal stenoses (short strictures often surrounded mostly by bone) and occasionally elsewhere.[10]

Non-metallic stents (Figure 120-8) are primarily constructed of different polyurethane compounds for use in the urinary tract (e.g., ureteral stent) or bioabsorbable compounds (e.g., polydioxanone, etc.).[11] Ureteral stents[p] are available in a variety of sizes, lengths, configurations, and durometers (a measure of the material stiffness). These stents are placed over a guide wire and positioned with the use of a "pusher" catheter that advances over the guide wire behind the stent. Ureteral stents can be placed surgically, endoscopically, or percutaneously, and either temporarily (e.g., following shockwave lithotripsy of a nephrolith, or after ureteral reanastomosis) or permanently (e.g., for neoplastic obstruction or ureteroliths).[2,12]

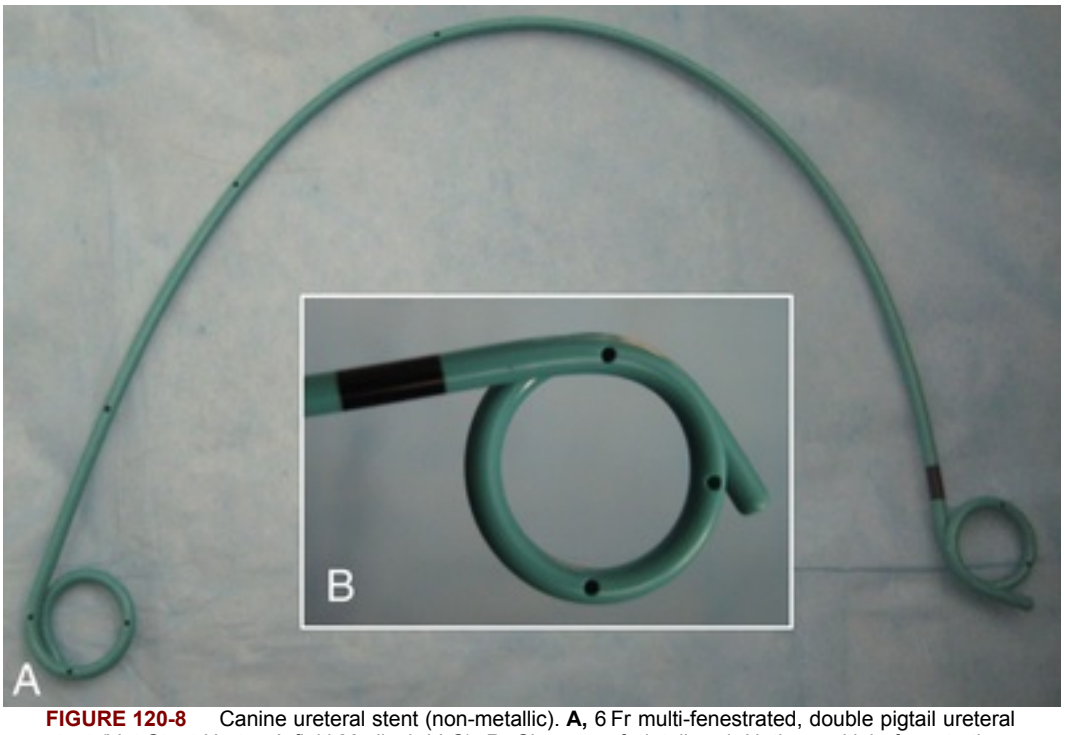

FIGURE 120-8 Canine ureteral stent (non-metallic). **A,** 6 Fr multi-fenestrated, double pigtail ureteral stent (Vet Stent-Ureter, Infiniti Medical, LLC). **B,** Close-up of pigtail end. Notice multiple fenestrations to facilitate urine drainage. (From Weisse C, Mayhew P: Basics of minimally invasive surgery. In Tobias KM, Johnston SA, editors: *Veterinary surgery: small animal*, St Louis, 2012, Elsevier.)

Embolics

Embolics are compounds or devices used to obstruct blood flow to a structure in order to reduce hemorrhage, attenuate blood supply, occlude vascular anomalies, or improve local concentrations of certain chemical or biological substances via prolonged elution or delivery. These agents are most commonly classified as mechanical or particulate, temporary/biodegradable or permanent, and solid or liquid (see ch. 125).

The most commonly used embolics in veterinary patients are the permanent mechanical devices used for relatively large vessel occlusion such as thrombogenic embolization coils[q] and custom woven nitinol vascular plugs and occluders[r] (Figure 120-9) (see ch. 122). These coils are now available in multiple sizes, wire diameters, coil conformations (e.g., straight, helical, complex), and detachable versions. A variety of more complex occlusion devices that are reconstrainable, repositionable and removable, are available for congenital cardiac malformations (e.g., patent ductus arteriosus, atrial septal defect, ventricular septal defect, etc.) but have also been used elsewhere in the cardiovascular systems of veterinary patients.[13-16] Particulate and liquid embolics are used to embolize the higher-order vessels and capillary beds when more distal embolization is preferred for tumor ablation or vascular malformations.[17] This ensures more definitive distal tissue ischemia (and reduced risk of revascularization) but increases the risk of tissue necrosis. The most commonly used permanent particulate agents include polyvinyl alcohol particles[s] and more recently hydrogel microspheres.[t] These are available in various particle sizes ranging from 45 to over 1000 microns and embolization results from initial mechanical vascular occlusion followed by permanent fibrin ingrowth. A variety of drug-eluting hydrogel microspheres is available and these have been demonstrated to provide a controlled release of doxorubicin for weeks to months.

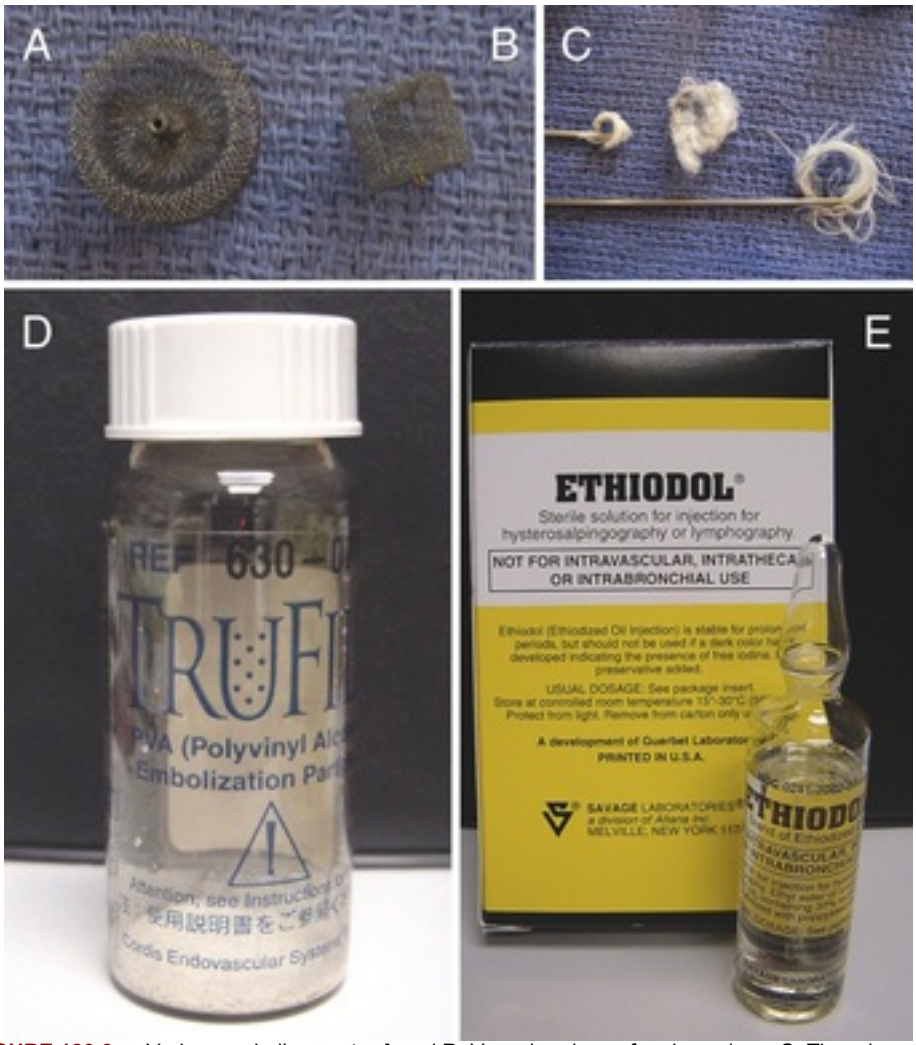

FIGURE 120-9 Various embolic agents. **A** and **B,** Vascular plugs of various sizes. **C,** Thrombogenic embolization coils in delivery catheter and deployed. **D,** Polyvinyl alcohol (PVA) embolic particles. **E,** Ethiodized oil liquid embolic.

Liquid embolics have the advantage of passing through the capillary beds of tumors and vascular malformations or lymphatics, permitting complete tissue destruction through to the venous circulation (see ch. 125). Glue (most commonly n-butyl cyanoacrylate)[u] has been used the most and has been reported for use in vascular arteriovenous fistulas, arteriovenous malformations, and thoracic duct embolizations[18] in veterinary patients. When mixed with ethiodized oil (Lipiodol)[v] in a 1 : 1 to 1 : 4 ratio, the polymerization rate can be slowed to mimic the speed of blood flow through the vascular bed; this is important to prevent embolization distal to the target site. The iodinated oil also lends radiopacity to the mixture. Care must be taken to avoid gluing the catheter into the vessel being embolized and additional training is recommended before attempting one of these procedures.

Laser

Lasers have become an increasingly important tool in veterinary surgery and interventional endoscopy for tissue ablation, coagulation, and stone management. The diode laser is a continuous laser that emits light at a wavelength of 980 nm. This type of laser energy has a high simultaneous absorption in water and hemoglobin making this a good laser for cutting and coagulating tissues such as during intramural ectopic ureter laser ablation or cutting the tissue of a persistent paramesonephric remnant (see ch. 124).[19] A holmium : YAG (Hol : YAG) pulsed laser falls in the near infrared portion of the electromagnetic spectrum (2100 nm) with the energy absorbed in <0.5 mm of fluid, making it an ideal surgical laser for endourologic applications like laser lithotripsy. The laser energy is delivered to the surface of the uroliths using flexible quartz fibers with

multiple different diameters (200, 365, 550 microns) guided through the working channel of small diameter flexible or rigid cystoscopes/ureteroscopes. The Hol : YAG laser combines tissue cutting and coagulation properties, as well as the ability to fragment stones upon contact.[20] Although the various commercial models of lithotripters vary slightly, the pulse duration, energy, and frequency chosen are based upon the particular application.

Contrast Agents

Low osmolarity, non-ionic iodinated contrast media such as iohexol[w] are most commonly used in interventional radiology. While ionic contrast agents are less expensive, the hypertonicity and associated cation (often sodium) can result in problems for those patients with concurrent renal or cardiac disease. Non-ionic contrast agents are not hypertonic and do not dissociate in solution and are therefore safer for compromised patients for intravascular use. The low osmolality of iohexol compared to ionic contrast media with similar iodine concentrations should result in fewer osmolality-related side effects. Iohexol is available with different iodine concentrations that should be reported when used; the author typically uses between 240 to 350 mgI/mL and often dilutes 1 : 1 or 2 : 1 saline : contrast. Complications associated with intravascular contrast media are typically mild and relatively uncommon but can include nausea, vomiting, pain, anaphylaxis, hemodynamic effects, and most notably nephrotoxicosis. Contrast-induced nephropathy remains incompletely understood but likely results from a combination of direct cytotoxicity and prolonged vasoconstriction and impaired renal vascular autoregulation.[21] For high-risk patients, alternatives to iodinated contrast media such as gadolinium or carbon dioxide can be considered. Patients should be well hydrated before use (Iohexol package insert)[22] and while a safe dosage has not been determined, the author tries to use less than 2-3 mL/kg during standard vascular interventional procedures.

Miscellaneous Devices

There are countless ancillary devices designed to facilitate minimally invasive procedures that are beyond the scope of this chapter. Examples include baskets and snares for retrieval of vascular or intraluminal foreign bodies or stones, biopsy devices, intra- and extracorporeal lithotripters, thrombectomy devices, and flow-switches or adapters to help perform coaxial procedures using microcatheters to name just a few.

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22. Iohexol package insert, GE Healthcare, Inc., Waukesha, WI.

[a]Weasel wire, Infiniti Medical, Menlo Park, CA.

[b]Vascular introducer sheath, Infiniti Medical, Menlo Park, CA.

[c]Berenstein Catheter, Infiniti Medical, Menlo Park, CA.

[d]Cobra Catheter, Infiniti Medical, Menlo Park, CA.

[e]Renegade or Tracker microcatheter, Boston Scientific, Natick, MA.

[f]Microcatheter, Infiniti Medical, Menlo Park, CA.

[g]0.018 Transend or V-18 microwire, Boston Scientific, Natick, MA.

[h]0.014 Microwire or 0.018 Weasel wire, Infiniti Medical, Menlo Park, CA.

[i]Vet balloons, Infiniti Medical, Menlo Park, CA.

[j]Locking loop drainage catheter, Infiniti Medical, Menlo Park, CA.

[k]Subcutaneous ureteral bypass device (SUB), Norfolk Vet, Skokie, IL.

[l]Vet Stent-Trachea, Infiniti Medical, Menlo Park, CA.

[m]Vet Stent-Urethra, Infiniti Medical, Menlo Park, CA.

[n]Vet Stent-Cava, Infiniti Medical, Menlo Park, CA.

[o]Vet stent-nasopharyngeal, Infiniti Medical, Menlo Park, CA.

[p]Vet stent-ureter, Infiniti Medical, Menlo Park, CA.

[q]Cook embolization coils, Cook Medical Inc., Bloomingdale, IN.

[r]Amplatz Canine Duct Occluder, Infiniti Medical, Menlo Park, CA.

[s]PVA particles, Cook Medical Inc., Bloomington, IN.

[t]Beadblock hydrogel microspheres, Biocompatibles UK Limited, Farnham, UK.

[u]TRUFILL n-BCA liquid embolic system, Cordis Neurovascular, Miami Lakes, FL.

[v]Lipiodol/Ethiodol, Guerbet LLC, Bloomington, IN.

[w]Omnipaque (iohexol) injection, Amersham Health Inc., Princeton, NJ.

CHAPTER 121

Respiratory Interventional Therapies

Matthew W. Beal

Client Information Sheet: Respiratory Interventional Therapies

Image-guided therapies have changed veterinary medicine in the past decade by providing alternatives to traditional surgical procedures in a minimally invasive fashion. These procedures often are performed through natural orifices, thus minimizing patient morbidity. Two of the most common respiratory interventions in veterinary medicine are tracheal stent placement for the management of tracheal collapse and nasopharyngeal balloon dilation with or without stent placement for the management of nasopharyngeal stenosis.

Tracheal Collapse

Introduction and Patient Selection

Tracheal collapse is a diffuse disease that affects the trachea, mainstem bronchi, and lobar bronchi. It is important to remember that all treatment of tracheal collapse is merely palliative, but that such palliation can be lifesaving when it dramatically improves the patient's clinical signs. Numerous approaches to treatment of tracheal collapse have been proposed, ranging from medical management to placement of extraluminal tracheal ring prostheses.[1] Recently, placement of intraluminal, self-expanding metallic stents (SEMS) has gained popularity and is currently the treatment of choice for management of tracheal collapse in dogs whose quality of life is compromised by manifestations of airway obstruction and cough or the medical management thereof (see ch. 241).[2-6]

There are four general phenotypes of the tracheal collapse syndrome that can present to veterinarians. One population of dogs presents with signs of airway obstruction. This is usually due to collapse of the cervical and thoracic inlet portions of the trachea. Stridorous breathing is most obvious during inspiration; however, stridor during both phases of respiration is common and suggests fixed airway obstruction. Airway obstruction in this population of dogs can be severe and can often lead to a vicious circle of dyspnea and worsening airway obstruction.[6] Severe episodes of airway obstruction can culminate in the need for emergency veterinary care including, but not limited to, sedation (acepromazine 0.02 mg/kg IV, butorphanol 0.3 mg/kg IV, or both), oxygen therapy (see ch. 131), cooling measures, and corticosteroids and/or antibiotics if needed. Some dogs will require emergency intubation to bypass the obstruction, and potentially require emergency tracheal stent placement. Although the phenotype of this population is airway obstruction, it is important to recognize that there is, very often, some degree of intrathoracic collapse and cough as well.[7] Despite the concurrent intrathoracic disease, intraluminal tracheal stent placement is highly effective at relieving airway obstruction and alleviating clinical signs of dyspnea. This population would also be amenable to extraluminal tracheal ring prostheses. Until a definitive work evaluating both acute and long-term outcomes is completed comparing similar populations of dogs managed with prosthetic rings versus those managed with intraluminal tracheal stent placement, we will not know the superiority of one procedure over the other.

A second population of dogs with tracheal collapse tends to be older and presents purely with cough and very little, if any, evidence of airway obstruction (no stridor). The phenotype of these dogs is intrathoracic collapse with cough. This population is least amenable to stent placement because the airways beyond the stent continue to collapse. This population is optimally managed medically (see ch. 124). Clinical signs usually can be controlled for many years in this population.

The third population of dogs is a combination of the first two populations. They manifest with both airway

obstruction and severe cough. In this patient population, tracheal stent placement will relieve the airway obstruction component of the disease, thus improving clinical signs, but it will not relieve the cough that is associated with collapse of the intrathoracic airways including the mainstem and lobar bronchi. However, persistent cough can be controlled through medical management.

A fourth and final population of dogs presents with inspiratory and expiratory dyspnea consistent with fixed airway obstruction resulting from tracheal ring malformation/inversion. In this condition, rather than collapsing dorsoventrally, dorsal collapse is accompanied by inversion of the ring ventrally, giving the entire ring a "w" shape cross-sectionally. Based on the author's experience, the Yorkshire Terrier appears to be the breed most affected by this condition. Dogs with this problem commonly present for evaluation of a "tracheal mass" due to a soft tissue density emanating from the ventral trachea as seen on lateral cervicothoracic radiographs (Figure 121-1, *A* and *B*). Tracheal stent placement in this condition is not recommended because it is difficult to evert the inverted segment of the ring even with substantial balloon dilation of the tracheal stent once in place. As a consequence, the stent might not contact the tracheal mucosa over the full 360° of its circumference, thus predisposing to recurrent infection and potentially inflammatory tissue formation. Prosthetic ring placement should be considered in this patient population.

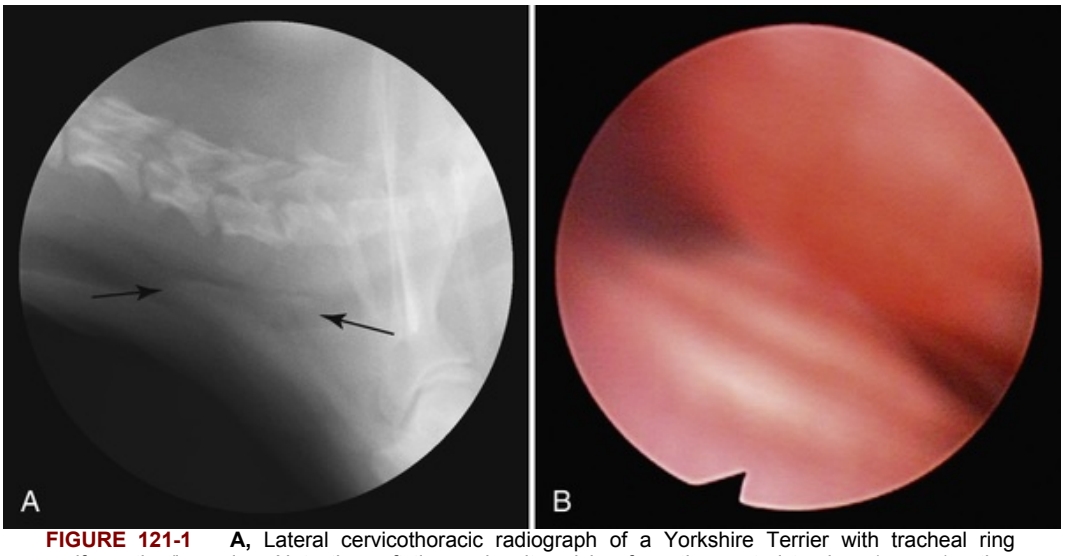

FIGURE 121-1 **A,** Lateral cervicothoracic radiograph of a Yorkshire Terrier with tracheal ring malformation/inversion. Note the soft tissue density arising from the ventral trachea (arrows) rather than the typical dorsoventral flattening seen in most dogs with tracheal collapse. **B,** Endoscopic view of the dog in **A.** Notice the ventral tracheal ring bulging dorsally into the lumen (5 to 9 o'clock positions).

Diagnostic Evaluation

Diagnostic evaluation is critical to select the ideal patient populations for tracheal stent placement. Thoracic radiography, fluoroscopy, oropharyngeal and laryngeal examination, and tracheobronchoscopy routinely allow for optimal characterization of the disease process affecting the large airways of dogs presenting with clinical signs consistent with, or a known complaint of, tracheal collapse.

Imaging performed using negative pressure ventilation has been described and is used by some for evaluation of the extent of tracheobronchial collapse, but fluoroscopic evaluation of the spontaneously breathing patient is of excellent diagnostic utility and is very physiologically useful to help assess the structural changes in the trachea during spontaneous breathing, stridor, and cough. Fluoroscopic studies should include a true lateral evaluation of the pharynx to rule out pharyngeal collapse, evaluation of the entire trachea, carina, and mainstem bronchi during all phases of respiration, during stridor (if present), and during cough. The region of collapse should be identified in reference to static anatomic landmarks such as vertebral bodies. During stent placement, these reference points can be utilized to ensure that the stent covers the most severely affected portion of the trachea.

Oropharyngeal and laryngeal examinations are performed to rule out concurrent laryngeal collapse, dysfunction, or other structural abnormalities. Additional upper airway abnormalities including, but not limited to elongation of the soft palate, upper airway neoplasia, and epiglottic retroversion, can be identified

concurrently.

Tracheobronchoscopy allows for detailed evaluation of the lumen of the trachea, grading of the severity of collapse in each anatomic region of the trachea and mainstem bronchi, as well as identification of other lesions including tracheal ring malformation/inversion and the presence of mass lesions due to neoplasia.

Treatment

A variety of different types of stents has been placed into the tracheal lumen of dogs with tracheal collapse.[2-6] The current recommendation is the utilization of a commercially-available mesh, self-expanding metallic stent made from nitinol.[a] Most of the stents utilized for the palliation of clinical signs of tracheal collapse in veterinary medicine come in a uniform diameter design or in a tapered design[b] in which the cervical portion of the stent is wider than the thoracic portion. The tracheal conformation of many dogs is tapered, and, as a result, a tapered design will allow the entire stent to expand closer to its nominal (relaxed) diameter. This can make the stent less susceptible to failure.

With the patient placed under routine general anesthesia using an endotracheal tube that includes a radiopaque marker to improve visualization, the patient should be placed in true lateral recumbency on a fluoroscopy table, with the neck extended such that the entire trachea is straight. The cricoid cartilage should be visualized fluoroscopically, as should the carina. An esophageal marker catheter[c] should be positioned over a hydrophilic guidewire[d] in the esophagus to serve as a reference for calibration of measuring tools (Figure 121-2, *A*). Use of an esophageal marker catheter is critical to obtaining appropriate measurements. The endotracheal tube should be repositioned just beyond the larynx (see Figure 121-2, *A*); often the cuff of the endotracheal tube resides within the larynx. Next, the anesthetist should deliver a positive pressure breath that is held at 20 cm H_2O and a static image should be acquired. This image will be used for identifying the maximum tracheal diameter in the cervical, thoracic inlet, and intrathoracic regions. Making multiple measurements from additional images will help ensure appropriate sizing (Figure 121-2, *B*). Computed tomography can also be utilized for optimal stent sizing, as radiographic measurements of tracheal stent size may underestimate true tracheal dimensions by approximately 1 mm.[8]

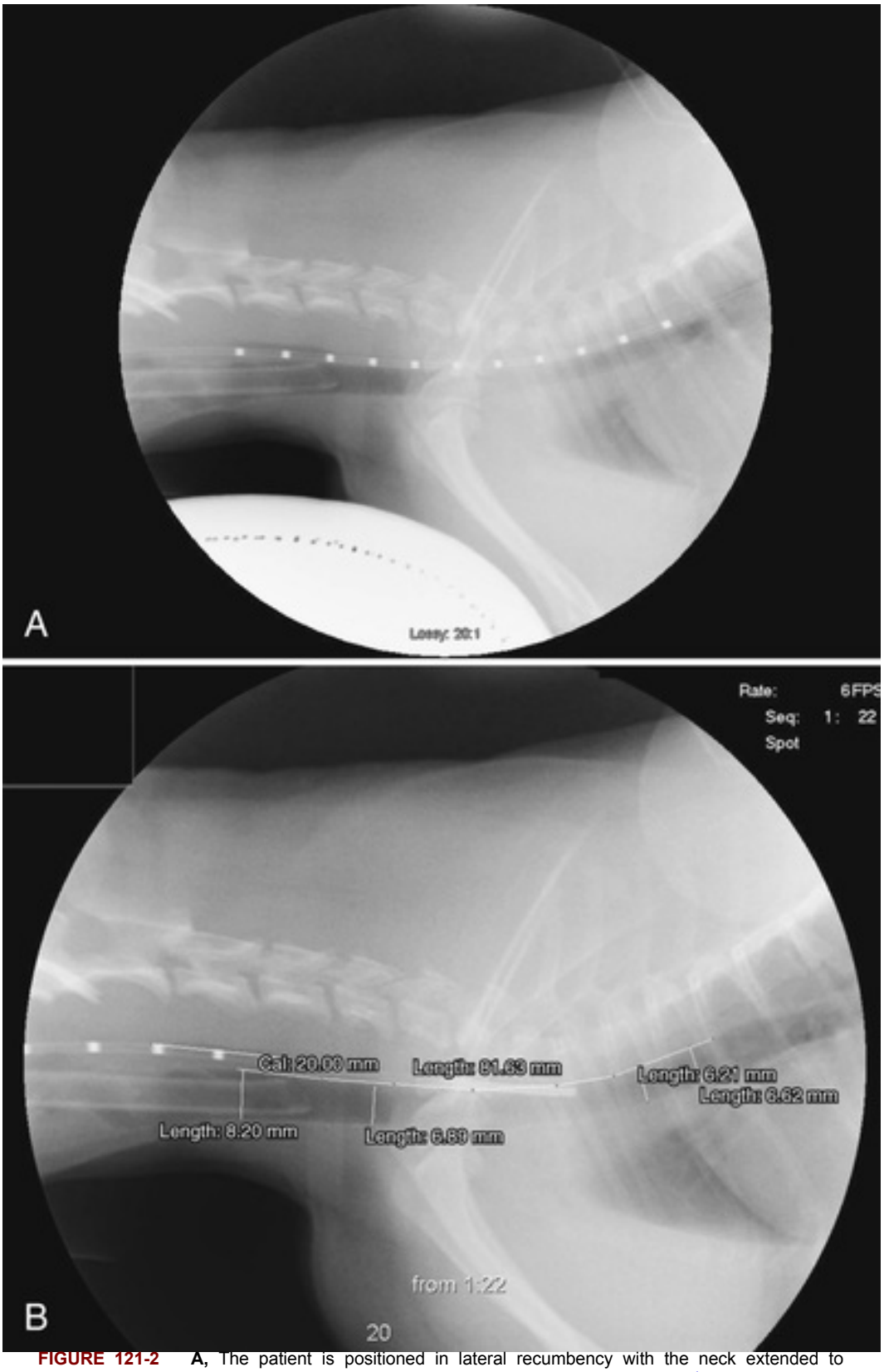

FIGURE 121-2 **A,** The patient is positioned in lateral recumbency with the neck extended to straighten the trachea. A 5 Fr marker catheter[c] has been placed over a guidewire[d] in the esophagus for calibration of measuring instruments. **B,** Measurements of the cervical, thoracic inlet, and intrathoracic tracheal diameters as well as length are made during a 20 cm H_2O positive-pressure breath.

When selecting a uniform diameter stent, a stent diameter should be chosen that is 10% to 20% greater than

the maximal tracheal dimension (usually the cervical measurement). A tapered stent may be considered when the difference in tracheal diameter is >2 mm between the cervical and intrathoracic trachea. A tapered stent may be selected that is 10% to 20% greater in diameter than both the cervical and intrathoracic measurements.

The primary goal when choosing stent length is to appropriately span the entire portion of the trachea that, based on diagnostic evaluation, shows significant collapse. Anatomic boundaries of the region(s) of collapse that were referenced during diagnostic evaluation are used for determining the boundaries of the length of the trachea that needs to be covered by the stent. Measurements of this length are determined (see Figure 121-2, *B*). Because the entire trachea is most often affected to some degree by tracheal collapse, the secondary goal is to span the entire trachea from approximately 1 cm caudal to the cricoid cartilage to approximately 1 cm cranial to the carina. Choosing stent length can be challenging because mesh self-expanding metallic stents foreshorten when deployed. This means that as the stent expands, it becomes shorter in length until it reaches its nominal diameter. For example, a 12 × 65 mm stent[a] is 12 × 65 mm when fully opened (nominal diameter); however, if it only opens to 10 mm, it will be 83 mm in length.[e] Because a stent size is chosen that is 10% to 20% greater in diameter than the maximal tracheal diameter, it should not expand completely, and, as a result, will be longer than the nominal length. When utilizing a tapered stent design, because the stent will more closely achieve its nominal diameter along its entire length, foreshortening is somewhat easier to predict. Shortening charts greatly aid the operator in choosing the appropriate stent length.[e]

Stent deployment most often is performed through a bronchoscope adapter placed between the endotracheal tube and the anesthesia circuit. This adapter allows for the maintenance of the connection to the anesthesia circuit during stent deployment. Tracheal stents most often are deployed using fluoroscopic guidance and according to manufacturer instructions (Video 121-1). Special caution must be exercised during deployment to ensure that the carina, cricoid cartilage, and the endotracheal tube locations are all visualized, such that the stent is deployed in the correct location. In most cases, the endotracheal tube is removed over the delivery system during the final stages of deployment and then very gently replaced using the delivery system as a stylet when the procedure is complete. Post-deployment radiographic imaging should be performed to ensure appropriate apposition of the stent to the tracheal mucosa (Figure 121-3). If there are obvious gaps, the stent can be gently "touched up" with the cuff of the endotracheal tube or using an appropriate diameter dilation balloon.

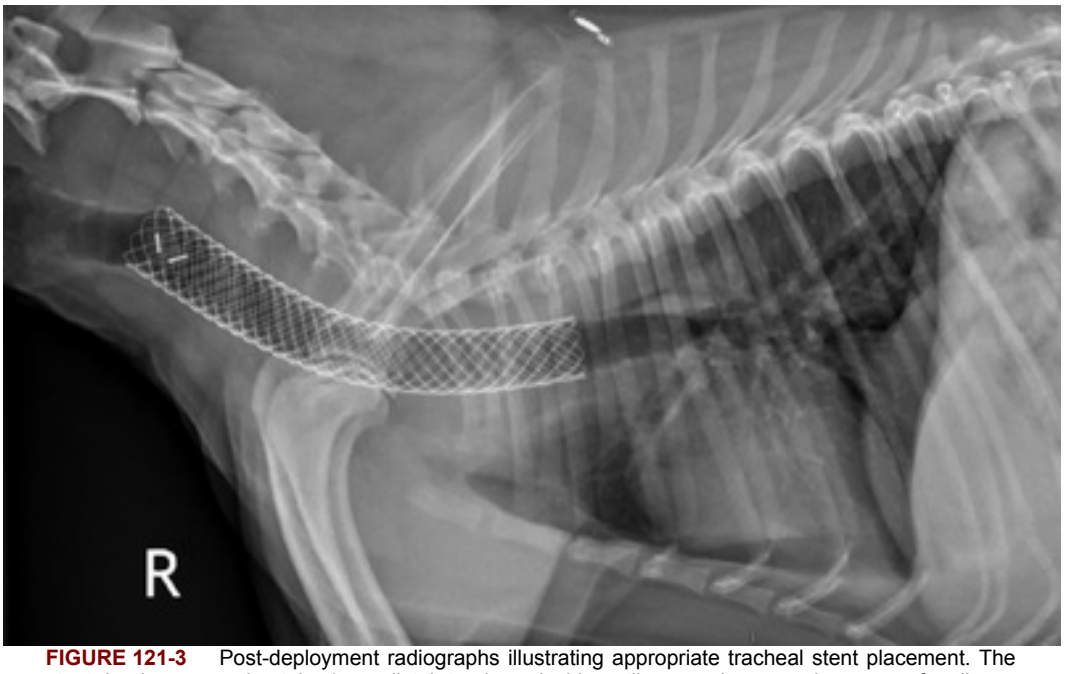

FIGURE 121-3 Post-deployment radiographs illustrating appropriate tracheal stent placement. The stent begins approximately 1 cm distal to the cricoid cartilage and spans the area of collapse determined through fluoroscopy.

When the tracheal stent is deployed in the appropriate location, the expected outcome is immediate and complete relief of airway obstruction. Because of the presence of a tracheal foreign body (stent) as well as

concurrent mainstem bronchial collapse in many dogs, coughing will occur or persist after stent placement. The author routinely administers hydrocodone (0.22 mg/kg PO q 6 h), a 2- to 4-week tapering course of prednisone (initiated at 0.5 mg/kg PO q 12 h), and a 10-14 day course of antibiotics with efficacy against *Mycoplasma* sp. Some degree of medical management may need to be continued to control coughing. Coughing can be a risk factor for stent fracture. Recheck examinations are generally performed at 1 and 3 months after the procedure to assess for stent shortening and to reassess clinical signs.

Complications

Complications after tracheal stent placement are well documented.[9,11-13] Acute complications (undersizing, malpositioning of the stent) are largely avoided through appropriate measuring, stent selection, and deployment and generally should not occur. Acute complications most often are dealt with by removing the stent and replacing it with an appropriately-sized and -positioned stent. Delayed complications that have been documented include stent shortening with collapse cranial to the stent, bacterial tracheitis, inflammatory tissue formation within the stent, and stent fracture.[5,10-13] Common manifestations of these signs are a recurrence of signs of airway obstruction or an acute or progressive worsening of cough. Owners should be warned at the time of discharge, and at each recheck examination, that evidence of these signs should immediately trigger reevaluation. Evaluation of return of airway obstruction or worsening of cough should include a thorough history and physical examination coupled with radiographic evaluation of the neck and thorax with the forelimbs positioned both cranially and caudally to allow for visualization of the tracheal lumen, which can help identify intraluminal inflammatory tissue formation or fracture (Figure 121-4). If the stent is not fractured, endoscopic evaluation of the tracheal lumen is performed to evaluate for inflammatory tissue formation and to acquire samples for aerobic and *Mycoplasma* sp. culture. Antibiotic therapy should be instituted based on results of this testing.

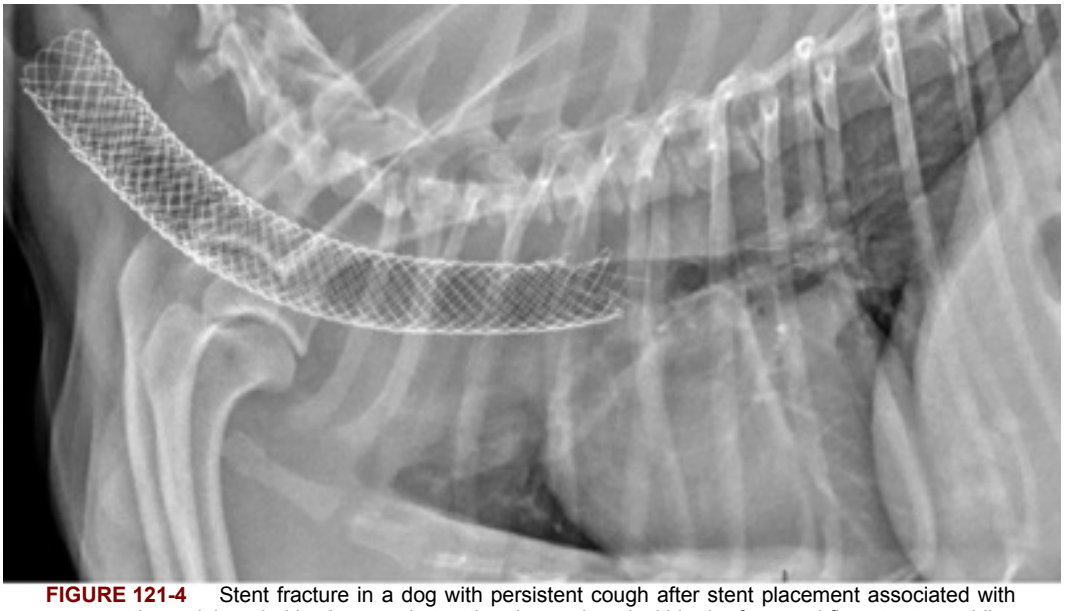

FIGURE 121-4 Stent fracture in a dog with persistent cough after stent placement associated with recurrent bacterial tracheitis. A second stent has been placed within the fractured first stent, providing an adequate tracheal lumen diameter.

Identification of inflammatory tissue formation (Figure 121-5) within the stent is most often treated with high-dosage corticosteroids coupled with treatment of bacterial processes based on culture and sensitivity testing (see above).[10] In some cases, regression is possible, whereas in others it is not. If inflammatory tissue formation is causing significant signs of airway obstruction, deployment of a new stent of the same diameter to marginalize the inflammatory tissue to the periphery of the lumen will be necessary (Figure 121-5, *C*). Secondary stent placement for inflammatory tissue formation should always be coupled with concurrent medical management of this condition.

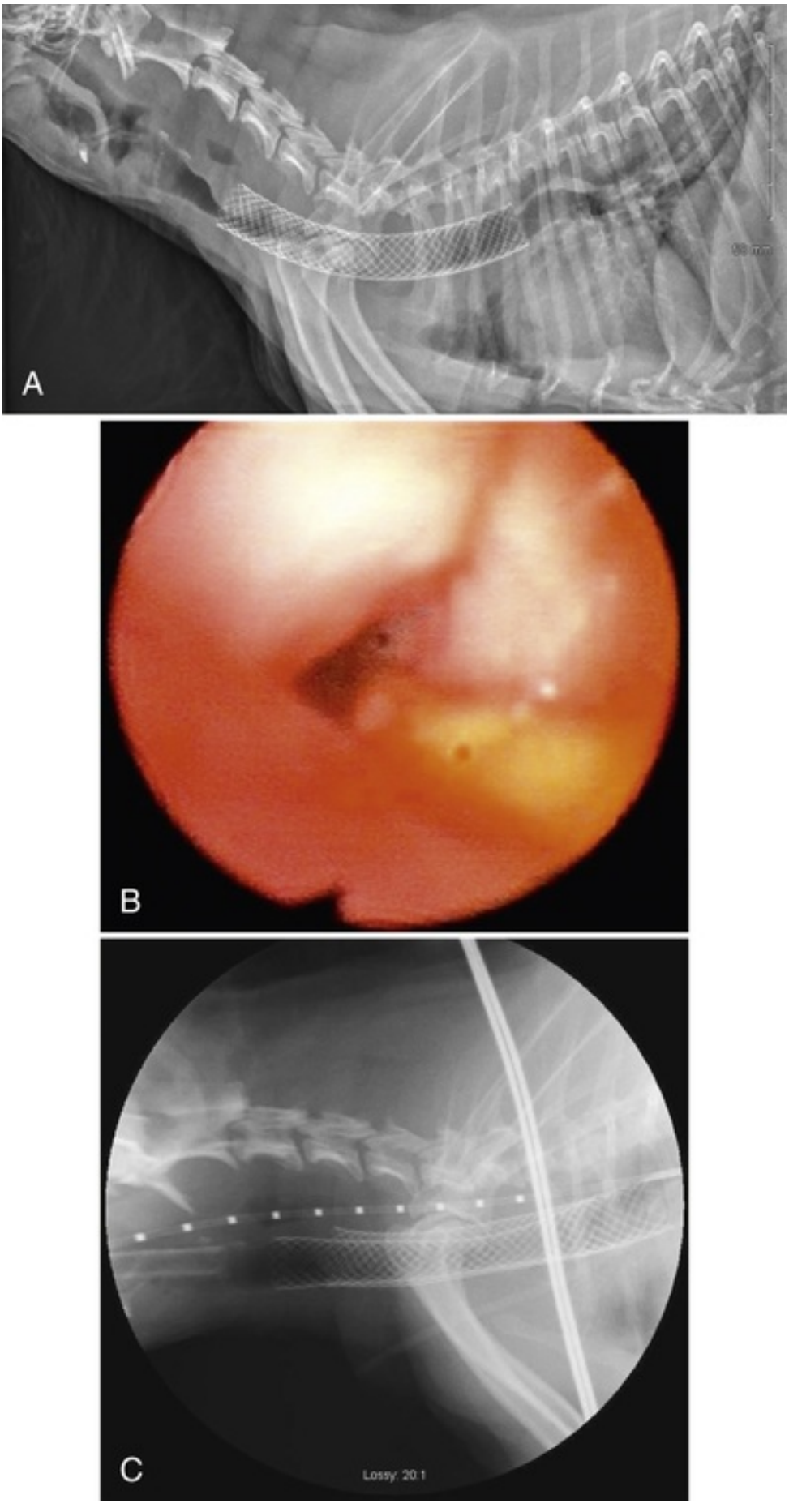
A
B
C
Lossy: 20:1

FIGURE 121-5 **A,** Lateral thoracic and cervical radiograph demonstrating a soft tissue opacity cranial to the stent, dorsally, and within the stent. **B,** Inflammatory tissue formation causing severe stenosis of the tracheal lumen in a dog with a tracheal stent placed 1 year prior. Note the ingrowth, especially in the right and left corners of the image, and very narrow lumen. Copious purulent material was also present in the lumen of the trachea. Cytologic examination was consistent with severe bacterial tracheitis. **C,** A second stent has been placed within the original stent and extends beyond the cranial edge of the original stent to marginalize the inflammatory tissue. Notice that the presence of inflammatory tissue within and cranial to the original stent prevents the second stent from opening completely and thus results in longer length.

Tracheal stent fracture is minimized through appropriate patient selection and stent sizing, and through improvements in stent design and manufacturing processes. In the event of stent fracture, the fractured stent can be stabilized by deployment of a stent of the same size within the original stent. It should be noted that the new stent will be slightly longer than the original because it will not achieve the same diameter as the original stent (Figure 121-5, *C*). In addition, when the new stent is placed, it must be placed through the true lumen of the original stent, rather than between the failed wires of the original stent.

Nasopharyngeal Stenosis

Etiology

Nasopharyngeal stenosis (NPS) is a narrowing or complete membranous occlusion of the nasopharynx (see ch. 238). Numerous etiologies have been reported, including upper airway infection, inflammation secondary to aspiration rhinitis (regurgitation or vomiting) or inflammation secondary to chronic rhinitis, trauma, surgery, expansile masses, or ulceration.[14] In one case series, 3/3 cats had concurrent lymphoplasmacytic rhinitis.[14] NPS can also be congenital, similar to choanal atresia. In dogs, regurgitation or vomiting with secondary aspiration rhinitis is the most likely etiology.[15]

Diagnostic Evaluation

NPS most often results in signs of stertor, gagging, inspiratory and expiratory difficulty (due to fixed airway obstruction), and nasal discharge. Inspiratory effort is often more severe than expiratory effort. These signs are coupled with the need to breathe through the mouth some or all of the time depending on the severity of the stenosis. When the mouth is opened manually, the stertorous breathing usually ceases. Signs are most often chronic.

Numerous diagnostic imaging modalities can aid in the diagnosis of NPS. Although lateral radiographic projections and positive contrast rhinography[16] may help, cross-sectional imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) coupled with retroflexed rhinoscopy is the gold standard for diagnosis. Cross-sectional imaging allows for multiplanar reconstruction, which will allow for determination of the location of the stenotic lesion, its length, and measurement of the dimensions of the normal nasopharynx rostral and caudal to the stenosis (Figures 121-6, *A-D*). These measurements will aid in treatment planning. The most common site for NPS appears to be just caudal to the junction of the hard and soft palate.[14]

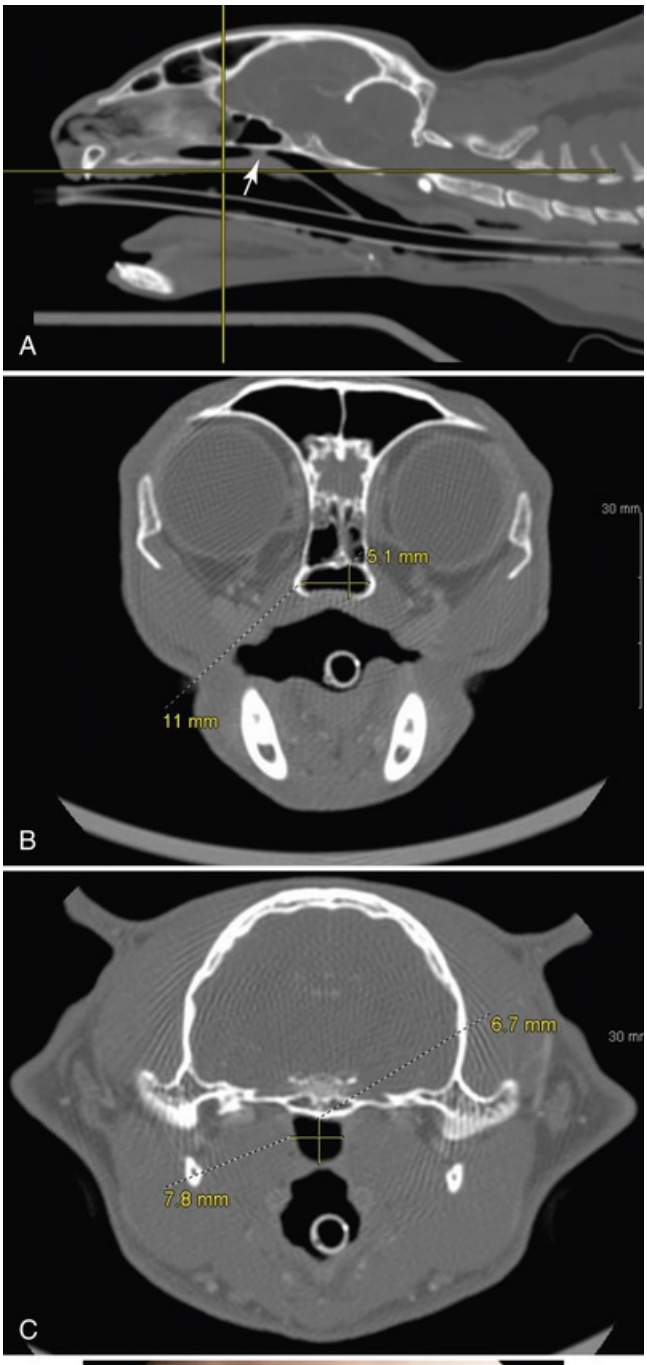
A
30 mm
5.1 mm
11 mm
B
30 mm
6.7 mm
7.8 mm
C
D

FIGURE 121-6 CT and retroflexed rhinoscopic images of a cat with nasopharyngeal stenosis. **A,** Sagittal midline section through the nasopharynx illustrating the stenotic lesion (arrow), approximately 1 cm caudal to the junction of the hard and soft palate. **B,** Axial section through the nasopharynx at the junction of the hard and soft palate to allow for measurements of the nasopharynx in two dimensions. **C,** Axial section through the nasopharynx approximately 1 cm caudal to the stenotic lesion to allow for measurements of the nasopharynx in two dimensions. **D,** Retroflexed rhinoscopic image from the same cat as in images **A-C.** A 0.035 in (0.88 mm) diameter hydrophilic guidewire has been passed through the stenosis.

Treatment

Surgery was the early treatment of choice for NPS, but it has largely been abandoned in favor of minimally-invasive treatment options due to concerns about recurrence of stenosis after surgical intervention. Currently, balloon dilation with or without placement of a nasopharyngeal stent is the treatment of choice.[14-18] Balloon dilation and nasopharyngeal stent placement are best performed using fluoroscopic and endoscopic guidance concurrently. Balloon dilation may be attempted in all patients prior to nasopharyngeal stent placement; however, most imperforate lesions and those that are >1-2 mm thick are probably optimally managed by nasopharyngeal stent placement.

Balloon dilation for the management of NPS using a multipurpose dilation balloon or angioplasty/valvuloplasty balloon has been reported with mixed success.[14-16,18] Repeat balloon dilation (rather than stent placement) is the treatment of choice for stenotic lesions that are located in the mid- to caudal soft palate. Measurements of the normal nasopharynx rostral and caudal to the NPS are utilized to plan for the size of balloon needed. In reported feline cases, balloon dilation of NPS most often is performed with a 10-15 mm balloon[16-18]; a 10-12 mm balloon usually will be effective, with the smallest risk of injury. A 2 cm balloon length usually is adequate, but a 4 cm balloon might be necessary in some dogs. Because passage of guidewires, catheters, and other devices through the nose stimulates the patient, utilization of local or regional anesthetic techniques in addition to general anesthesia is advisable.

Using fluoroscopy, the patient is positioned in true lateral recumbency. Retroflexed rhinoscopy is performed to achieve continuous visualization of the stenotic lesion. A 0.035 inch (0.88 mm) × 150 cm angled-tip, standard-stiffness hydrophilic guidewire[d] is advanced from the nostril through the ventral meatus and across the NPS (if patent) (see Figure 121-6, *D*). The guidewire is then advanced into the distal esophagus. If the stenotic lesion is imperforate, a catheter or vascular sheath is advanced retrograde through the ventral nasal meatus and against the central portion of the NPS. A sharp two-part trocar catheter[f] is advanced through it and centrally across the membrane to create an opening that allows for passage of a guidewire. Fluoroscopic guidance and concurrent retroflexed rhinoscopic guidance are critical to ensure that the direction of puncture is appropriate to avoid penetration of the cranial vault. Depending on the size of the stenotic lesion, a 6- to 8-French vascular dilator may be advanced over the guidewire to pre-dilate the lesion. The vascular dilator is removed and the balloon dilation catheter is advanced over the guidewire. Retroflexed rhinoscopy and fluoroscopy can be utilized to ensure that the balloon is across the lesion. Using a pressure inflator,[g] the balloon is inflated with diluted iodinated contrast medium in saline. Inflation will result in visualization of a "waist" in the balloon at the location of the stenosis. Further inflation will result in a "loss of waist" as the stenosis is broken down. Inflation generally is held for approximately 2 minutes and is repeated 2-3 times. The balloon is removed over the guidewire and the nasopharynx is examined using retroflexed rhinoscopy to ensure that the stenosis is resolved. Oropharyngeal examination is performed to evaluate the palate for injury. Local endoscopic injection of triamcinolone (0.2 mg/kg) has been utilized and a tapering dosage of corticosteroids (prednisone or prednisolone initiated at 0.5 mg/kg PO q 12 h) is recommended.[14,15] In some animals, balloon dilation might need to be repeated if restenosis occurs. Balloon dilation with local infusion of mitomycin C might also help minimize the chance of recurrent stenosis.[14] It should be noted that if the stenotic lesion is imperforate, simple balloon dilation, although initially effective, is unlikely to result in long-term resolution of clinical signs due to recurrence of stenosis. Instead, covered stent placement will most likely be necessary (see below).

Nasopharyngeal stent placement has been described as a treatment option for management of NPS in dogs and cats.[14,16-19] A stent simply prevents the re-formation of the NPS. Stents used for NPS are available in various forms including balloon-expandable metallic stents (BEMS),[h] covered BEMS which have a covering (often polytetrafluoroethylene [PTFE, Teflon]) to prevent tissue ingrowth and restenosis, and silicone stents constructed from tubular silicone medical devices.[14,16-19] Covered BEMS are most often utilized when the

lesion is imperforate. Non-covered BEMS are utilized in most other lesions and are less expensive; however, they still carry a risk of tissue ingrowth and restenosis.

Placement of BEMS and covered BEMS is performed using a technique that is similar to that described above for balloon dilation. However, BEMS sizing is critical to prevent migration. A stent size should be chosen that is 10% to 20% larger than the normal nasopharynx rostral and caudal to the lesion. The stent should not extend to within 1 cm of the caudal aspect of the soft palate.[14] After placement of a guidewire[d] across the lesion (see Figure 121-6, *D*), balloon dilation should be performed as described above to a diameter of 4-6 mm, or approximately half the diameter of the normal adjacent nasopharynx, to ensure that the BEMS delivery system can be passed across the stenosis. A recommended technique is to pre-dilate the stenosis (see above), which will allow for over-the-wire placement of a vascular sheath across the lesion. The BEMS can then be placed into the vascular sheath and positioned within the sheath across the lesion. The sheath protects the stent while it is being positioned. Once the stent is in position, the sheath is retracted and the stent remains in position for deployment (Figure 121-7, *A* and *B*). A pressure inflator[g] is utilized for BEMS and covered BEMS deployment and is inflated as described above. A loss of waist indicates that the stenosis has been broken down. Retrograde rhinoscopy is utilized to confirm that the stenosis has been relieved (Figure 121-7, *C* and *D*). If a non-covered BEMS is utilized, a tapering dosage of corticosteroids as described above is indicated. It is critically important to recognize that BEMS and covered BEMS undergo plastic deformation. Dorsal digital pressure on the soft palate will deform the stent and obstruct the nasopharynx. In the event this occurs, the stent can be opened via balloon dilation.

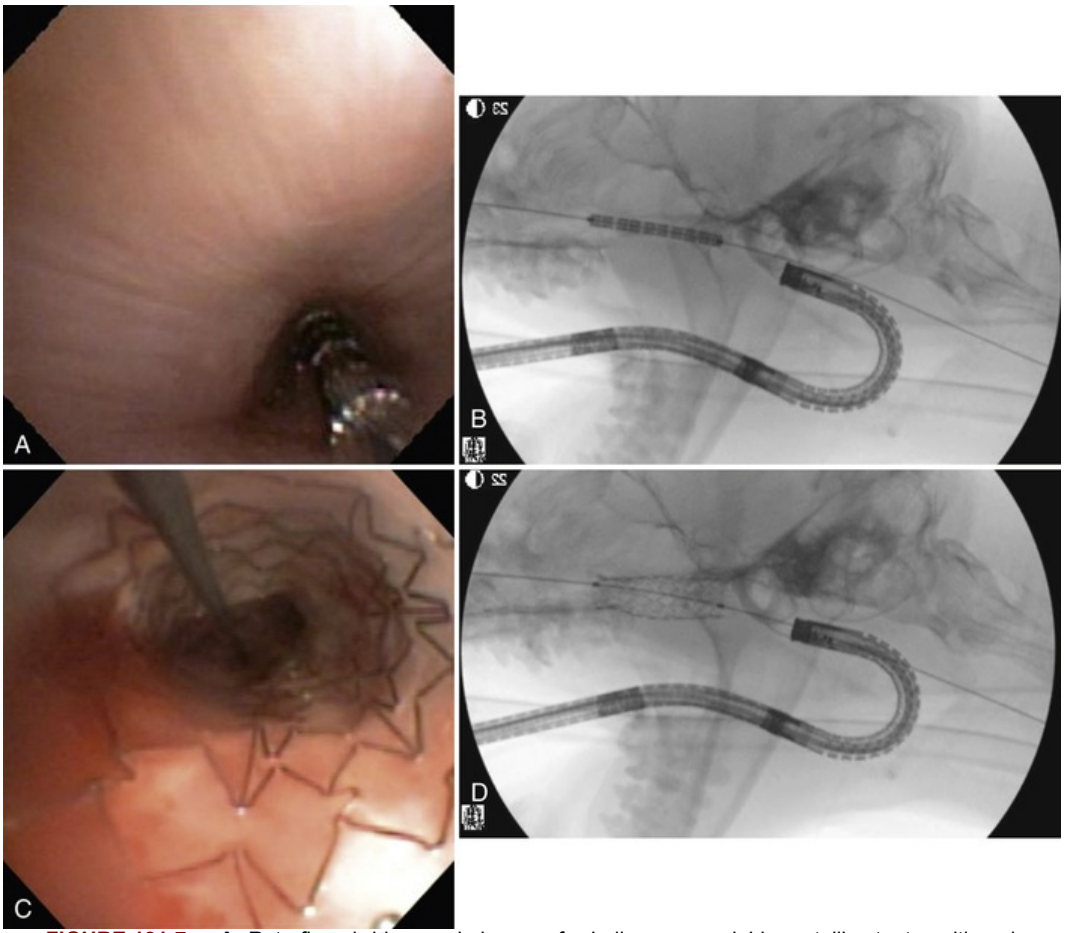

FIGURE 121-7 **A,** Retroflexed rhinoscopic image of a balloon-expandable metallic stent positioned across the stenotic lesion before deployment. **B,** Fluoroscopic image of a balloon-expandable metallic stent placed across the stenotic lesion before deployment. **C,** Retroflexed rhinoscopic image of a balloon-expandable metallic stent correctly deployed across the stenotic lesion. Notice that the choanae now are visible rostrally. The diameter of the lumen of the nasopharynx in relation to the guidewire in this image is dramatically larger than in Figure 121-6, *A*. **D,** Fluoroscopic image of a balloon-expandable metallic stent correctly deployed across the stenotic lesion.

An alternative stent placement technique recently has been described and used successfully in cats with NPS.[17] This technique involves balloon dilation or forceps dilation of the NPS followed by placement of a segment of 24-28 French (8-9.33 mm diameter) tubular silicone across the lesion (see ch. 238). This segment of tubing is left in place for approximately 3-4 weeks and is then removed. In this series, 14/15 cats had complete, long-term resolution of clinical signs and the remaining 1/15 demonstrated improvement.[17]

Expected Outcomes

Following recovery from general anesthesia for balloon dilation or stent placement for NPS, complete relief of airway obstruction is expected. Recurrence of clinical signs usually is indicative of restenosis. When present prior to intervention, clinical signs related to concurrent disease processes such as chronic rhinitis are expected and should be managed concurrently.

Complications

Complications of balloon dilation or BEMS placement for NPS are uncommon. Two cases of palatal erosion after BEMS placement have been documented but may have been related to patient factors or previous procedures.[19] In another study, recurrent obstruction of a BEMS with hair material was identified in a cat with a stent positioned in the caudal nasopharynx for management of NPS in that location.[14] Tissue ingrowth into non-covered BEMS has also been documented. If obstructive, placement of a covered BEMS within the non-covered BEMS will alleviate the problem.

Minor complications including minor bleeding and bradyarrhythmias are expected. Bradycardia has been documented during or immediately following (10-15 min) balloon dilation for the management of NPS. The exact mechanism is unknown; however, it is suspected to be related to stretching of the pharynx and/or compression of vagal afferents.[14,16] Anticholinergic responsiveness is expected and these medications can be given if needed or included preemptively as part of premedication.

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nasopharyngeal stenosis in dogs and cats: six cases (2005-2007). *J Am Vet Med Assoc*. 2008;233:1432–1440.
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[a]Vet Stent Trachea, Infiniti Medical LLC, Menlo Park, CA.

[b]Vet Stent Duality, Infiniti Medical LLC, Menlo Park, CA.

[c]Marker Catheter, Infiniti Medical LLC, Menlo Park, CA.

[d]Weasel Wire, Infiniti Medical LLC, Menlo Park, CA.

[e]Shortening Chart, Infiniti Medical LLC, Menlo Park, CA.

[f]Disposable Two-Part Trocar Needle, Cook Medical, Bloomington, IN.

[g]BasixCOMPAK Inflation Syringe, Merit Medical LLC, South Jordan, UT.

[h]Vet-Stent Nasopharyngeal, Infiniti Medical LLC, Menlo Park, CA.

CHAPTER 122

Cardiovascular Interventional Therapies

Brian A. Scansen

Angiography (angiocardiography) refers to the administration of contrast agents into the vascular system with imaging visualization, to outline and characterize vascular and cardiac structures. In the middle of the twentieth century and until the 1980s, angiography and cardiac catheterization were performed solely for diagnostic purposes.[1-3] However, the recognition that the veterinarian could intervene in cardiovascular diseases, guided by fluoroscopic imaging, became reality with the development of transvenous pacing systems,[4,5] balloon dilation catheters,[6,7] and coils/devices for vascular occlusion.[8,9] The breadth of small animal diseases that can now be treated by a minimally-invasive, transcatheter approach continues to expand. This chapter provides an overview of the equipment required for cardiovascular intervention, as well as the indications and therapeutic strategies currently employed in small animal cardiovascular medicine.

Preparation for Cardiovascular Catheterization

Performing diagnostic or interventional studies within the heart and vasculature requires detailed knowledge of the equipment used and the technical skills of catheterization, as well as an understanding of thoracic and cardiovascular anatomy. The catheterization laboratory should be a sterile space, with sufficient storage for a multitude of commonly used catheters, wires, and devices; high-quality fluoroscopic imaging, optimally with rotational capability or bi-plane; portable ultrasound for vascular access and transesophageal echocardiography; a power injector for rapid delivery of iodinated contrast; anesthetic and hemodynamic monitoring equipment for intravascular pressure recording; a sufficient number of monitors for visualization of live images and pertinent hemodynamic parameters; and a safety or crash cart for stocking of supplies required for emergent intervention, including a cardioverter-defibrillator (Figure 122-1).

FIGURE 122-1 Photograph of a catheterization laboratory. Optimally, such a space should contain: (1) ample storage for catheters, wires, and devices; (2) a crash cart with defibrillator and emergency medications; (3) a transesophageal echocardiography system; (4) a radiolucent table; (5) a fluoroscopic C-arm; (6) monitors that can be moved within comfortable sight for the operator; (7) hemodynamic recording equipment; and (8) a computer terminal for charting, access to the electronic record, and access to archived patient images. Not shown is a power injector, useful for controlled injections of contrast.

Prior to intervention, an understanding of thoracic anatomy and image interpretation is important for

appropriate diagnosis, planning, and equipment selection as well as during catheterization to verify the intervention is being performed at the correct site and to troubleshoot unexpected findings or complications. The thorax is a complex 3-dimensional shape with a wide variation in the radiographic opacity of thoracic structures; furthermore, the heart is a rapidly moving organ with a complex spatial relationship. These realities complicate interpretation of a 2-dimensional fluoroscopic image, which is made more challenging by the high rate of blood flow within the beating heart that results in a temporally brief period available for contrast and chamber visualization as contrast agents are quickly ejected and diluted following injection.

The difficulty in evaluating cardiovascular anatomy due to the complex structure of the thorax can be mitigated by review of multiple image planes, selective injection of iodinated contrast material in specific locations, use of a power injector, and by digital-subtraction angiography (DSA). Many human catheterization laboratories, particularly those that are used for the treatment of congenital heart disease, now employ biplane fluoroscopic systems that provide real-time imaging of two orthogonal views to improve anatomic guidance. There is also a new generation of fluoroscopic systems that perform rotational angiography to circumferentially record a single injection from all angles and create a 3-dimensional reconstruction of the anatomic structure. Alternatively, some systems have the capability of importing anatomic landmarks from cross-sectional imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) onto the 2-dimensional fluoroscopic image to improve guidance during the intervention. Few veterinary catheterization facilities have these capabilities, but most current veterinary interventions can be performed using a portable C-arm–mounted fluoroscope that easily rotates the field of view around the thorax to numerous projection angles. The fluoroscopic system chosen should provide high resolution (at least a 512 × 512 and optimally a 1024 × 1024 matrix), generate sufficient energy to penetrate the thorax of a large dog, and be capable of displaying and recording fast frame rates (25-30 frames per second or higher). The rapid heart rates of dogs and cats cause contrast filling of the structure of interest to be temporally brief and a frame-by-frame review of a recorded angiographic run often is needed to visualize the structures of interest and perform measurements. Fast frame rates prevent the operator from "missing" the lesion during contrast injection into a high-flow organ such as the heart.

Generally, it is not possible by hand injection to achieve a sufficiently tight bolus of contrast to optimally opacify a chamber of the heart in medium-sized and larger dogs. Automated power injectors overcome this limitation by allowing the operator to program the volume, flow rate, and pressure of an injection to maximize opacification of the heart or great vessels within 1-2 cardiac cycles. Importantly, angiographic catheters and high-pressure tubing should be in place if a power injector is used. An end-hole catheter is a poor choice for recording an angiographic study, particularly within the heart, as the full force of the injection is directed through the single end hole and catheter recoil is likely. Additionally, if the end hole is against a vessel wall or the endocardium, a high-pressure injection may damage the structure of interest. The preferred angiographic catheter is one with the largest diameter possible for the task, of the shortest feasible length, and with multiple side holes and a closed or tapered tip—all to maximize flow and minimize trauma. For intracardiac injections and angiographic studies in large vessels, the author prefers the Berman or pigtail catheter.

Contrast agents employed for angiocardiography are almost exclusively iodine-based (carbon dioxide gas rarely is used as a negative contrast agent). Iodine has a relatively high atomic weight, which equates to radiodensity, and the degree of opacity with this agent is directly proportional to the total amount of iodine in the image. Second-generation contrast agents (developed in the 1970s) are non-ionic monomers, which attach an amide group to an iodinated benzoic ring and prevent dissociation in solution. These agents cause far fewer adverse reactions than did early generation agents and are termed low-osmolar agents because the particles do not dissociate once in solution. These agents still have an osmolality 2-3 times that of the blood (e.g., 550-850 mOsm/kg for most agents); iohexol is an example of a second-generation contrast agent that is commonly used in veterinary medicine. The only commercially available third-generation agent is iodixanol, which is an iso-osmolar dimer made by combining two non-ionic tri-iodinated benzoic rings together. This arrangement does not dissociate in solution, has an iodine:particle ratio of 6:1, and has the same osmolality as blood (290 mOsm/kg). Although no studies are available in veterinary medicine, a meta-analysis of human patients at risk for contrast-induced nephropathy found a lower risk of adverse reaction for iodixanol compared to iohexol.[10] The viscosity of the contrast agent is also important as this affects the flow rate during injection. Warming the contrast can decrease viscosity and allow for more rapid injection rates. Last, iodinated contrast agents are available in various concentrations and smaller volumes are needed to create comparable degrees of radiopacity if highly concentrated solutions are used. Rare contrast reactions are reported in animals and both the agent used as well as the total amount of contrast given likely are important in the risk of this occurrence.[11,12] However, recommendations vary widely and no prospective studies are

available. In general, the author attempts to keep the cumulative dosage of contrast for a cardiovascular procedure to <720 mg iodine/kg, but has given animals as much as 2400 mg iodine/kg without apparent adverse effects. For animals with renal impairment, more conservative values and concurrent fluid diuresis should be employed.

Most contrast studies and interventions for cardiovascular disease are performed with the animal positioned in right or left lateral recumbency. Lateral positioning allows the operator to monitor dorsal-ventral and cranial-caudal motion of catheters and wires as they are advanced into the thorax. Right-to-left lateral deflection, however, is less clearly visualized. Although less commonly used than lateral imaging for cardiac intervention, the ventrodorsal projection allows visualization of left-to-right laterality and the cranial-caudal position of catheters introduced into the thorax. The location of catheters or wires in the dorsal-ventral plane, however, is challenging. Several additional imaging planes are used in human medicine to highlight and optimize imaging of cardiac structures. Variations from the traditional lateral or ventrodorsal projection are typically given by an angle, which refers to the position of the image intensifier in relation to the animal's thorax in a ventrodorsal position. Commonly used angulations in human medicine include the right and left anterior obliques (RAO and LAO, respectively) with variable cranial or caudal angulation. Typically, the image intensifier is rotated 30° to the animal's right (RAO) or left (LAO) and a variable 10° to 30° of cranial or caudal angulation may also be employed. Altering the angle of the C-arm can elongate structures (e.g., the left ventricular outflow tract in subaortic stenosis) or provide a more directly perpendicular visualization plane during device deployment (e.g., the atrial septum for closure of an atrial septal defect). These viewing angles have not been standardized in veterinary medicine and are largely operator- and case-dependent. In practice, adjusting the angle of the C-arm is most useful to optimize an angiogram for measurement, such as improving visualization of the minimal ductal diameter of a patent ductus arteriosus (PDA), or to compensate for suboptimal positioning of the animal on the table.

Right Heart Interventions

Cardiac Pacing

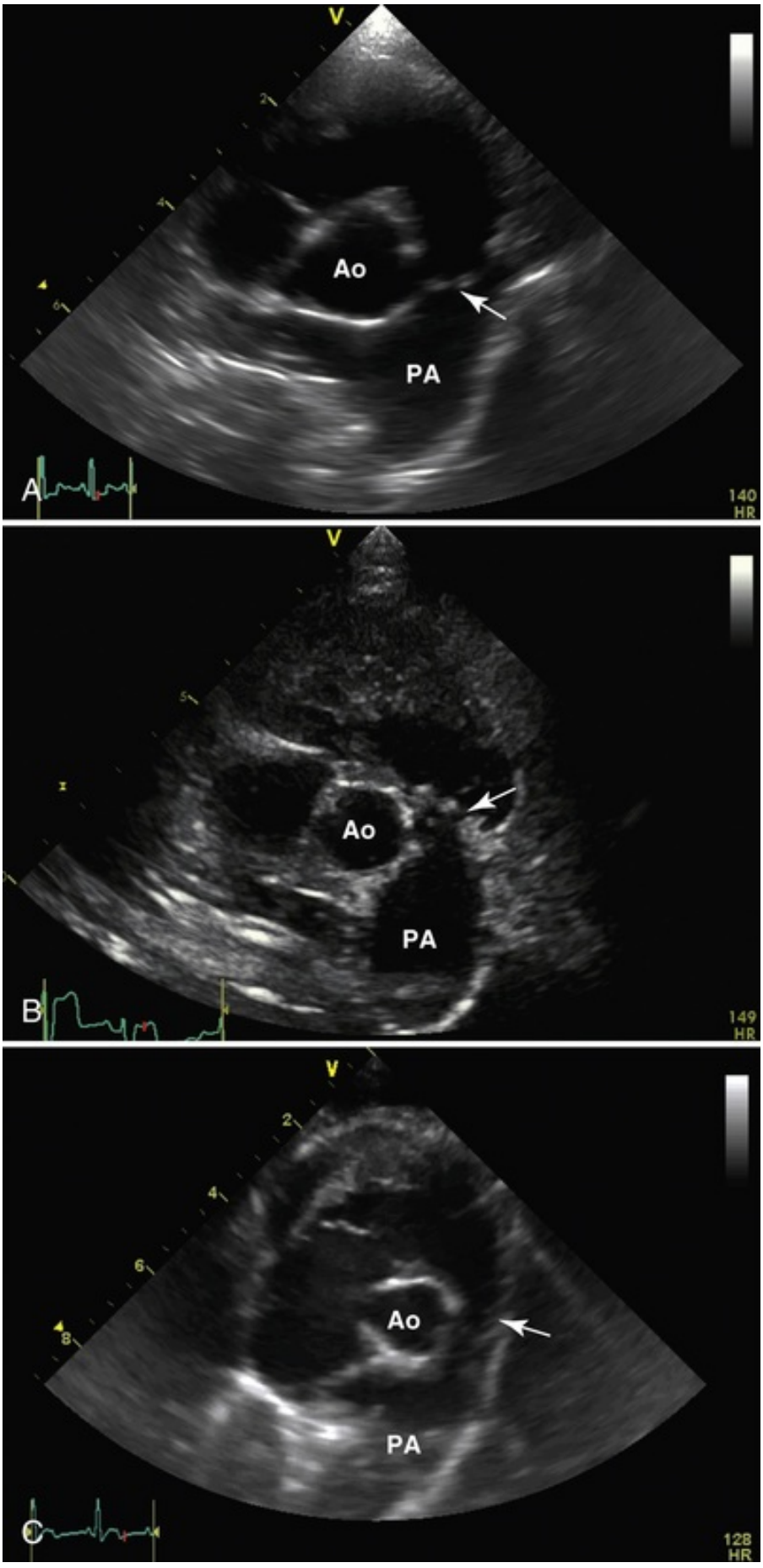
Permanent transvenous cardiac pacing is discussed in detail in ch. 248 and 249.

Balloon Pulmonary Valvuloplasty

Congenital pulmonary valve stenosis (PS) has been reported as the third most commonly diagnosed congenital heart defect of dogs in North America,[13] though more recent reports from Europe suggest it is the most common canine congenital heart defect.[14] Without therapy, dogs with valvular PS are at risk for clinical signs including exercise intolerance, syncope, sudden cardiac death, congestive heart failure, and cyanosis from a right-to-left shunt (see ch. 250).[15,16]

Balloon pulmonary valvuloplasty (BPV) was first performed in a dog in 1980[17] and reported in a child in 1982.[18] There is evidence that BPV improves the clinical outcome of human and canine patients with valvular PS, both with a reduction in clinical symptomatology and an improvement in survival.[15,19,20] The procedure now is routinely performed in clinical canine practice with low morbidity and mortality for those animals with a severe gradient or the presence of clinical signs referable to their disease.

Prior to intervention, an attempt should be made to characterize the valve morphology and to estimate the balloon size required. Transthoracic echocardiography with Doppler is the current standard of care in veterinary cardiology for evaluation of pulmonary valve morphology, annular size, and severity of stenosis (Figure 122-2). Valves that are severely dysplastic (redundant tissue, annular hypoplasia, or a subvalvular fibrous ring) are less likely to respond to BPV and clients should be so advised. The author still recommends BPV in such cases as it is difficult to quantify the degree of valvular fusion by echocardiography alone, and despite such fusion, BPV still can produce a partial response. The author has attempted stent implantation into the right ventricular (RV) outflow tract and across the annulus of such dogs with fair improvement in clinical signs and a reduction in pressure gradient.[21]


V
Ao
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V
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149
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HR

FIGURE 122-2 Echocardiographic images from dogs with pulmonary valve stenosis. Valve morphology may vary from a fused, doming valve in a Cavalier King Charles Spaniel **(A)** to a thickened and dysplastic valve in an English Bulldog **(B)** to a narrowed and hypoplastic pulmonary valve annulus in a Boxer dog **(C).** The best candidate for balloon pulmonary valvuloplasty is the fused, doming valve as shown in panel **A**. In all images the pulmonary valve is denoted by the arrow with the aorta (Ao) and pulmonary artery (PA) labeled.

An estimation of the pressure gradient across the stenotic valve is obtained by continuous wave spectral Doppler (see ch. 104), guided by color Doppler imaging to optimize alignment parallel to the direction of the turbulent jet. Most cardiologists consider the stenosis mild at a gradient of 10-49 mm Hg, moderate at 50-79 mm Hg, and severe when the gradient is ≥80 mm Hg. The decision to pursue BPV should be made with the pressure gradient in mind, with greater benefit from the procedure likely in dogs with severe stenosis. As with all Doppler estimates, the velocity measured is dependent not only on the orifice of the valve, but also on the flow across the valve at the time of measurement and the systolic function of the RV. Changes in the dog's sympathetic tone, intravascular volume status, or intrinsic RV function can alter the velocity measured.

There are many balloon dilation catheters available on the market, with varying profiles, materials, sizes, and maximal pressure. The most commonly used balloon dilation catheters in veterinary medicine are made by a human pediatric device company and include the TYSHAK and Z-MED lines of balloon dilation catheters. TYSHAK balloon dilation catheters are made of a thin, minimally-compliant thermoplastic elastomer and have a relatively low maximal burst pressure. They are, however, low profile and most sizes can accommodate a 0.035" guidewire making them a commonly selected catheter for BPV in dogs. Z-MED balloon dilation catheters are made from a thicker thermoplastic elastomer, which provides a greater maximal burst pressure, though requiring a larger introducer size. The author uses the Z-MED line of balloon dilation catheters for BPV in dogs with dysplastic valves (thick, redundant tissue or a subvalvular fibrous ridge) and the TYSHAK line of balloons for those with pure valve fusion or small dogs whose vasculature is too small for the required Z-MED introducer size. As discussed in the section below on subaortic stenosis, very high pressure ATLAS balloons also can be used for high pressure BPV with fair success in the author's experience.

The BPV procedure is performed from a transvenous approach, either via the external jugular vein or via the femoral vein. The jugular vein is preferred for small dogs as it affords a larger size vessel and therefore a larger introducer sheath can be used than otherwise would be possible if using the femoral vein. The femoral vein typically is used when an arterial study is desired concurrently given the close relationship of the femoral artery and vein. Percutaneous access with an appropriately-sized introducer is achieved with the animal in lateral (jugular vein) or dorsal (femoral vein) recumbency. A vascular sheath is selected that is at least one French (Fr) size larger than what is required by the anticipated balloon dilation catheter. The right heart is catheterized and intracardiac pressures are measured to evaluate starting right ventricular pressure and transpulmonary gradient. **Note:** *It is always preferable to cross cardiac valves antegrade with a flow-directed (balloon-tipped) catheter or one with a J-tip or pigtail. Theoretically, advancing an end-hold catheter across the valve can perforate a valve leaflet, ensnare chordae tendineae, or otherwise damage the valve apparatus. A balloon-tipped or pigtail catheter, however, will preferentially enter the true valve orifice and minimize trauma to the valve.* Right ventriculography is performed with an appropriate angiographic catheter (typically a Berman catheter) and the pulmonary annulus is measured to size the balloon (Figure 122-3 and Video 122-1). The angiographic measurement is compared to the echocardiographic measurement of pulmonary annulus diameter and a balloon is chosen with a diameter ≈1.3 times the annulus diameter.

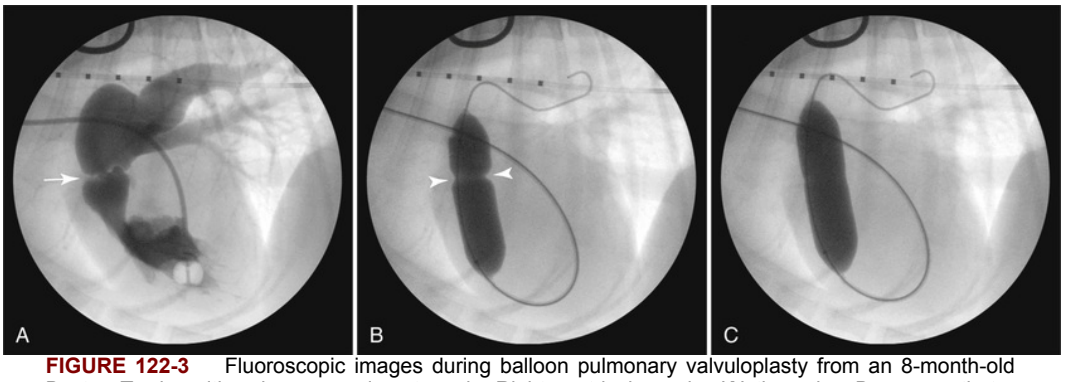

FIGURE 122-3 Fluoroscopic images during balloon pulmonary valvuloplasty from an 8-month-old Boston Terrier with pulmonary valve stenosis. Right ventriculography **(A)** through a Berman catheter highlights the right ventricular lumen and the fused, doming pulmonary valve (arrow). A balloon dilation

catheter is advanced over a guidewire and rapidly inflated, resulting in a stenotic waist (arrowheads) at the pulmonary annulus **(B).** With greater pressure generation in the balloon, the waist is torn and the valvuloplasty is complete **(C).**

A balloon wedge pressure catheter is floated across the pulmonary valve and out a distal branch pulmonary artery. The left pulmonary artery (the more dorsal branch pulmonary artery when viewed from a lateral image) is preferred, as it provides a smoother and more secure path for advancement of the balloon dilation catheter as compared to the right pulmonary artery. Next, a J-tipped exchange-length guidewire (typically >180 cm length) is selected and advanced through the wedge pressure catheter and its tip is placed within the distal branch pulmonary artery. The J-tip is preferred as it will be less traumatic to the distal pulmonary artery. The diameter and stiffness of the guidewire chosen will depend on the size of the dog and the stiffness of the balloon dilation catheter to be used. Guidewires of 0.035″ diameter in a standard stiffness or super-stiffness are preferred for BPV. In small dogs or those with severe RV hypertrophy, super-stiff guidewires place too much pressure on the tricuspid valve and the RV endocardium, particularly when they are advanced from a jugular venous approach. For larger dogs, the standard stiffness guidewires are overly flexible and do not maintain the balloon in a proper position during inflation; as such, super-stiff guidewires are preferred for large dogs or inflexible balloon dilation catheters. For very small dogs, the chosen balloon dilation catheter may not accept a 0.035″ guidewire. In such instances, a 0.018″ or 0.025″ guidewire can be used, but such wires provide even less stability during advancement and inflation of the balloon dilation catheter and stiffer varieties should be selected when possible.

The next step is balloon preparation. First, the protective plastic sheath around the balloon is removed. A three-way stopcock is attached to the catheter's balloon port, with a pressure inflation device connected to one of the stopcock's ports and a 12 mL Luer-lock syringe attached to the other. A mixture of iodinated contrast and isotonic saline (from 1:1 to 1:3, contrast to saline) is drawn into the inflation device and 3-4 mL of a similar mixture is drawn into the syringe. For larger balloons, a lesser proportion of contrast to saline should be used as the rate of balloon deflation is partially dependent on the viscosity of the fluid; contrast is necessary to visualize inflation, but results in a slower deflation rate. The balloon dilation catheter is then purged of air by drawing back with the syringe through the three-way stopcock opened to the balloon. The central lumen of the balloon dilation catheter is then flushed with heparinized saline and slowly advanced over the guidewire to a position spanning the pulmonary valve annulus. Projecting a reference image of the RV angiogram can aid in proper positioning of the balloon; platinum marker bands on the balloon dilation catheter allow the operator to adequately center the annulus, or site of stenosis, to the balloon. Many cardiologists place the balloon markers with one third of the balloon length past the site of stenosis and two thirds preceding the stenosis. Even so, the operator will need to hold traction on the balloon dilation catheter during balloon inflation to brace against the force of RV systolic contraction and blood flow. Rapid inflation of the balloon is performed under live fluoroscopy to visualize the development of a waist at the site of stenosis and to allow retraction/advancement of the catheter if the position changes (see Figure 122-3 and Video 122-2). The pressure generated by the inflation device should be monitored and increased to the nominal pressure of the balloon. Exceeding this nominal pressure (the pressure at which the balloon reaches its advertised diameter) can be done if the stenotic waist persists, but the burst pressure of the balloon should not be exceeded. Once the desired pressure is reached, or if the balloon migrates from the site of stenosis, rapid deflation of the balloon is performed. The duration of inflation should not exceed 5-6 seconds. A precipitous drop in systemic pressure is expected, with recovery rapid within the following 5-10 seconds. The desired outcome with BPV is resolution of the stenotic waist and the lack of waist on subsequent re-inflations. Typically, 2-4 inflations are performed to confirm the waist was engaged and has resolved. Right ventricular pressures and the transpulmonary gradient are again measured and, if the result is satisfactory, all equipment is removed. The vascular sheath is removed and hemostasis achieved with a purse-string suture around the access site as well as 5 minutes of direct manual pressure. A neck bandage is placed if the jugular vein was the point of access, to keep the site clean as the animal is recovered. The prognosis for BPV is generally good if a significant reduction in pressure gradient can be achieved.[15,19,22]

The coronary arterial anatomy is of particular importance in brachycephalic dogs; these dogs are reported to be at risk for anomalous coronary arterial circulations characterized by either a single right coronary ostium or single left coronary ostium (see ch. 250).[23-25] In such cases, the coronary artery that lacks a patent ostium arises from the contralateral coronary artery and passes adjacent and cranial to the pulmonary valve annulus or, rarely, in between the aortic and pulmonary valve annuli. Evaluation of coronary anatomy in brachycephalic dogs with PS should include imaging of the coronary ostia, either by aortic angiography during catheterization or cross-sectional imaging such as CT angiography prior to intervention (Figure 122-4).

Performing BPV with a standard size balloon (balloon-to-annulus ratio of 1.2 to 1.5) in a dog with a coronary artery anomaly can result in coronary artery avulsion, damage, and/or death.[26] BPV using a more conservative ratio of 0.9 to 1.0 in such dogs has been reported with some reduction in stenosis severity.[27] The long-term benefit of conservative ballooning in these dogs remains uncertain, but may be considered.

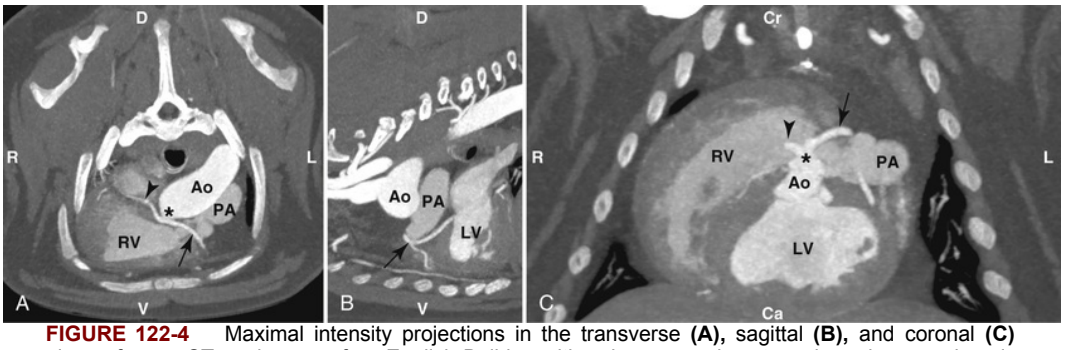

FIGURE 122-4 Maximal intensity projections in the transverse **(A),** sagittal **(B),** and coronal **(C)** planes from a CT angiogram of an English Bulldog with pulmonary valve stenosis and a prepulmonic left coronary artery. The single coronary ostium (asterisk) can be seen arising from the aortic root and giving off both the right (arrowhead) and left (arrow) coronary arteries. The left coronary artery takes a prepulmonic course, wrapping around the stenotic pulmonary valve; this is a relative contraindication to balloon pulmonary valvuloplasty. *Ao,* Aorta; *Ca,* caudal; *Cr,* cranial; *D,* dorsal; *L,* left; *LV,* left ventricle; *PA,* pulmonary artery; *R,* right; *RV,* right ventricle; *V,* ventral.

Heartworm Extraction

Dogs with caval syndrome from severe heartworm infection require emergent intervention to alleviate the mechanical obstruction to blood flow and halt ongoing hemolysis (Figure 122-5) (also see ch. 255). They are poor anesthetic candidates, but extraction of the worms is the only effective means to improve their clinical condition. In the most severely affected patients, extraction may be performed with light sedation and local analgesia to avoid further hemodynamic compromise from anesthetics. Stabilization of the patient should be performed during preparation for heartworm extraction, which can include fluid resuscitation, blood products to normalize bleeding disorders, and vasopressor medications.

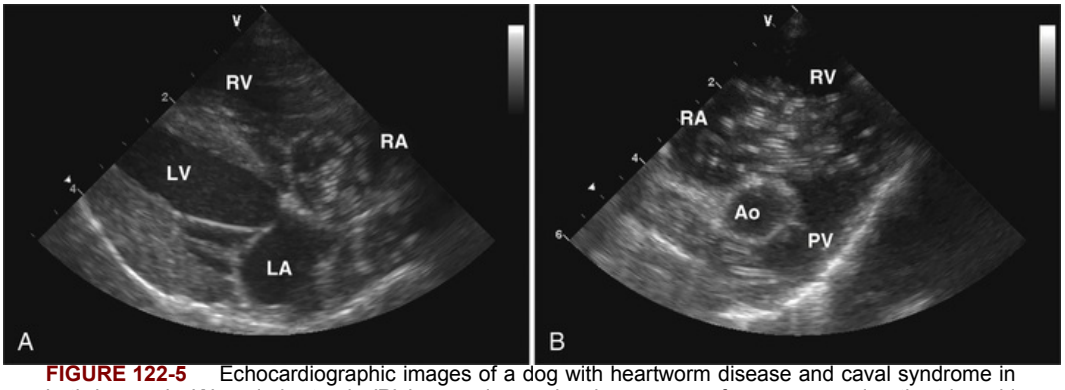

FIGURE 122-5 Echocardiographic images of a dog with heartworm disease and caval syndrome in both long axis **(A)** and short axis **(B)** image planes showing a mass of worms spanning the tricuspid valve and requiring worm extraction. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *PV,* pulmonary valve; *RA,* right atrium; *RV,* right ventricle.

To extract the worms, the dog is placed in left lateral recumbency and the skin over the right external jugular vein is clipped and surgically prepped. A 4-5 cm incision is made over the proximal right external jugular vein and the vein is isolated by blunt dissection. Suture or vessel loops are placed proximal and distal to the planned site of venous access to control the vein and limit hemorrhage. Tenotomy scissors are used for creating a 2-3 mm incision in the lateral wall of the jugular vein. The preferred extraction equipment is then advanced directly into the vein or through a vascular sheath to control hemostasis. Several techniques have

been reported, including passage of a snare catheter with a nitinol gooseneck snare.[28] Alternatively, an endoscopic retrieval basket,[29] alligator forceps,[30] or specially designed flexible forceps[31] may be used. A snare catheter comes in various sizes and is passed into the circulation through the vascular sheath to the level of the right atrium. The nitinol gooseneck snare is a loop set at a right angle to the end of a semi-stiff wire. The snare is passed through the catheter and advanced into the right heart. The loop is manipulated under fluoroscopic guidance with the goal of ensnaring the worms; echocardiographic guidance may be helpful. The loop is tightened as it is retracted back into the catheter and the worms are held firmly and withdrawn at the site of venous access in concert with the snare catheter. When using a snare catheter, it is important to apply gradual tension when tightening to avoid lacerating the worms, which would spill more dirofilarial debris and antigens into the circulation. Repeated passes into the right heart are performed until several negative passes have been achieved and/or brief cardiac ultrasound shows no more worms in the right heart or pulmonary trunk. The jugular vein is repaired or ligated at the end of the procedure and the skin incision closed routinely. On recovery, medical stabilization for hematologic and biochemical derangements is continued and adulticide treatment is scheduled over the following 1-2 months once the animal's clinical status has stabilized. Caval syndrome in the cat is much less common than in the dog and is associated with a lesser worm burden. However, similar interventional techniques have been reported in cats with caval syndrome and heartworm disease including use of alligator forceps,[32] endoscopic basket-type forceps,[33] a horsehair brush,[32] and a nitinol snare.[28] It is critically important to avoid damage to the worms during extraction in cats as severe anaphylactic-like reactions can occur, resulting in hypotension and death.[34]

The prognosis for caval syndrome historically has been guarded to poor. A review of 42 cases found that half of the dogs were euthanized or discharged with the intention of euthanasia at the time of diagnosis.[29] Of the 21 dogs in which heartworm extraction was attempted, 2 dogs died during the procedure, 4 dogs died in the postoperative period, 1 dog had no worms extracted due to distal migration, and 14 dogs had successful worm extraction and survived to discharge. Survival in the 14 dogs after successful extraction ranged from 2 to 56 months, with a mean of 24 months. Of the 21 dogs that underwent attempted extraction, 12 had disseminated intravascular coagulation and 9 of these dogs survived. As such, heartworm extraction should be considered for all dogs with caval syndrome and a successful outcome can be possible even for those with a severe bleeding disorder at the time of diagnosis.

Intracardiac Stenting for Central Venous Obstruction

In rare cases, intracardiac neoplasia can result in impaired venous return and obstruction of cranial or caudal vena caval flow, causing facial swelling or cavitary effusion.[35,36] Historically, medical therapy was the preferred therapeutic strategy for this condition, with variable results. However, deployment of intracardiac stents now has been reported for this condition and can palliate disease by restoring normal venous return. In a series of three cases, stent placement from caudal to cranial vena cava resulted in resolution or substantial reduction in clinical signs with survival of 5.5 to >22 months.[37]

Echocardiography is necessary to establish the diagnosis and evaluate the degree of venous obstruction (Video 122-3). Cross-sectional imaging with CT angiography or MR angiography can be useful to characterize the 3-dimensional extent of the tumor and the vena caval diameter, but is not mandatory. Stent selection is made with the intent to size 10-20% greater than the vena caval diameter to achieve sufficient purchase of the stent against the wall, and provide anchoring of the stent cranial and caudal to the right atrium. Both woven and laser-cut self-expanding stents have been used for this indication and there are advantages to each. The woven stent allows for reconstrainment, but suffers from foreshortening, while the laser-cut stent must be deployed at one time, but remains the length at which it resides in the delivery system.

The dog typically is placed in dorsal recumbency to allow access to both the neck and inguinal region and the right external jugular vein and left femoral vein regions are clipped, aseptically prepped, and draped. Vascular access is achieved through either jugular or femoral vein, depending on the site of obstruction, and a large introducer sheath (10 Fr) is advanced and sutured in place. For cranial vena caval obstruction, femoral venous access may be preferable due to swelling in the head and neck. Angiography, often DSA, is performed proximal and distal to the obstruction and vena caval measurements are made using a calibrated marker catheter. A guidewire is advanced across the right atrium, which may require a snare catheter to facilitate passage to the distal cava. Hemodynamic measurements may be taken above and below the obstruction to document a pressure gradient; collateral venous pathways are likely to have developed in this condition and absence of a pressure gradient suggests sufficient collaterals are present and stent placement may not improve clinical signs. The stent is deployed over the guidewire, with care taken to engage 4-5 cm or more in

both venae cavae (Figure 122-6). Transatrial placement helps to avoid stent migration across the tricuspid valve by securing its position in both the cranial and caudal venae cavae. It also can prevent excessively large tumor thrombi from dislodging and migrating to the pulmonary circulation. Following stent deployment, repeat angiography and pressure gradients should be performed. Tumors of the right atrium that lead to obstruction might release vasoactive substances and the anesthesiologist or anesthetist should be prepared for marked changes in blood pressure or heart rate as the tumor is compressed by the stent.[36] The venous access site is closed routinely, often by placement of a superficial pursestring suture. Follow-up depends on the nature of the disease, though repeat stent implantation has been performed if cavitary effusion recurs.[37] The prognosis is fair, with all reported cases showing improvement in clinical signs after transatrial stenting. However, this procedure is merely palliative and progressive disease from the primary tumor is likely. Survival of several years after stent implantation is possible.

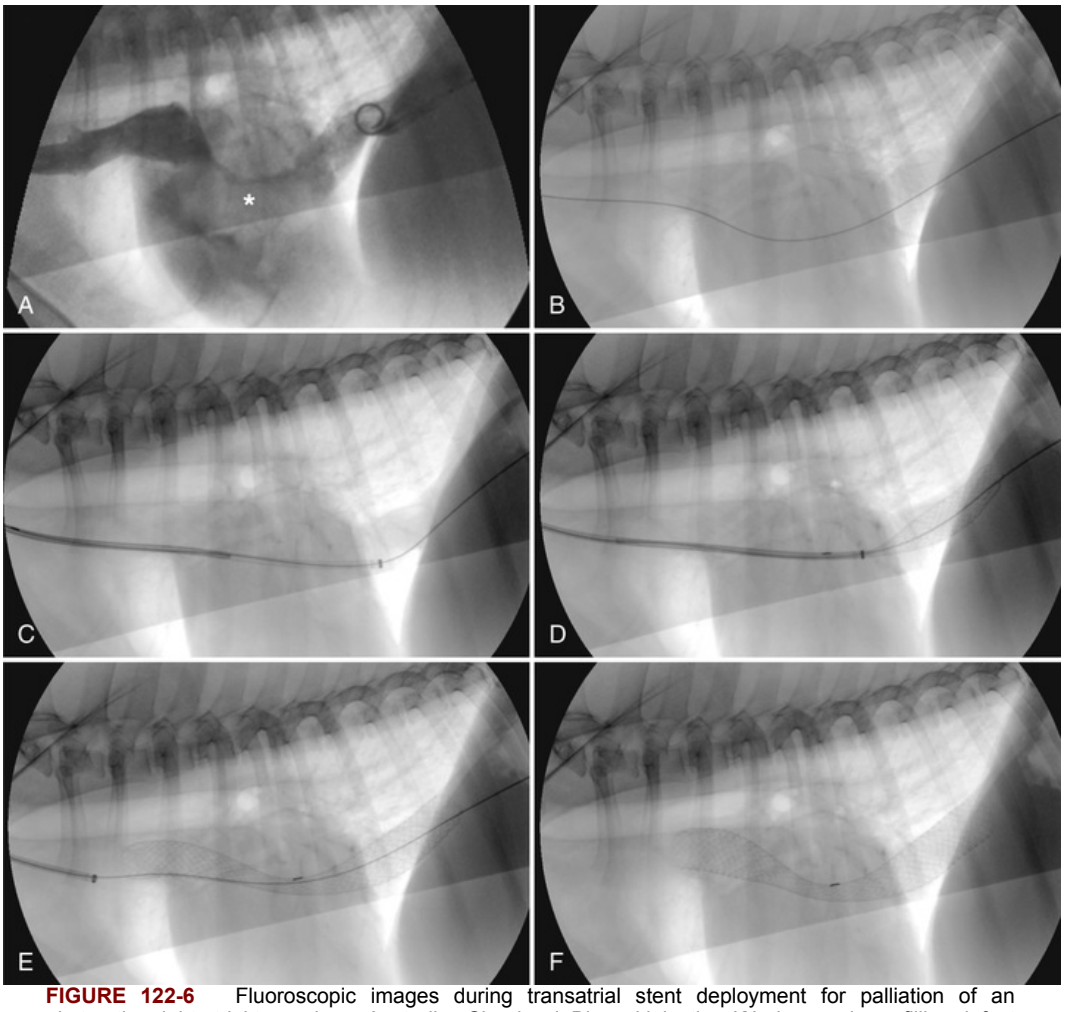

FIGURE 122-6 Fluoroscopic images during transatrial stent deployment for palliation of an obstructive right atrial tumor in an Australian Shepherd. Bicaval injection **(A)** shows a large filling defect in the body of the right atrium (asterisk). A guidewire is advanced across the right atrium from cranial vena cava to caudal vena cava **(B).** Over the guidewire, a delivery sheath is advanced **(C).** The stent is deployed from the caudal vena cava and through the body of the right atrium **(D).** The cranial aspect of the stent is deployed into the cranial vena cava **(E).** Once the wire and sheath are removed, the stent remains to push the tumor away and restore patency of caudal vena caval inflow **(F).**

Left Heart Interventions

Patent Ductus Arteriosus

Patent ductus arteriosus (PDA) is a common congenital heart defect in dogs, reported as the most common defect in some surveys (see ch. 250).[13,38] It also occurs in cats, albeit with less frequency.[38] Without therapy,

the prognosis is poor and therefore, closure of the ductus, either by surgical ligation or interventional occlusion, is necessary.[39,40]

Transcatheter therapy for PDA in dogs was first reported in 1994.[41] In the initial decade of transcatheter PDA therapy, transarterial or transvenous coil delivery was the predominant method used for ductal closure. Thereafter, human implants of variable design[42-48] were reported for PDA occlusion in dogs and in 2007, a device designed and optimized for canine anatomy came on the market.[49,50] The canine-specific device, the Amplatz Canine Duct Occluder (ACDO), is now the preferred transcatheter device for PDA occlusion in dogs due to an excellent safety and efficacy record and ease of deployment.[51] There remains a subset of small dogs, however, for which vascular access of sufficient size to deliver an ACDO is not possible; in these small dogs, coils remain a useful technique to achieve ductal closure. A nitinol device for small canine PDAs has been evaluated with good results, but is not yet commercially available.[52]

The technique for nearly all cases of transcatheter PDA occlusion begins with the animal in dorsal recumbency and access to the femoral triangle (typically the right side is chosen). Dorsal recumbency is used for ease of access and catheter advancement in the inguinal region; once access is achieved, the animal or fluoroscope can be turned to visualize the procedure from a lateral imaging plane. For the ACDO and transarterial coil delivery, the femoral artery is isolated by surgical cut-down and a combination of blunt and sharp dissection (Figure 122-7). Percutaneous access can be used for transvenous coil delivery through the femoral vein; percutaneous access also is feasible for a transarterial approach, although hemorrhage is a greater concern postoperatively for femoral arterial access. The author has used vascular closure devices[53] successfully in dogs to close percutaneous femoral arterial access, specifically the Mynx closure device; however, the thin subcutaneous tissue of puppies makes vascular closure devices more of a challenge in young dogs undergoing PDA intervention and typically a surgical approach with either repair or ligation of the femoral artery is employed. Arterial access first is achieved with a 22-gauge over-the-needle catheter and a 4-Fr micropuncture set with a 0.018″ wire. The micropuncture set is exchanged over a 0.035″ angled hydrophilic guidewire for a long vascular sheath of sufficient internal diameter to deliver the desired ACDO (Table 122-1). The long sheath is advanced to the aortic isthmus over the guidewire, after which the guidewire and dilator are removed. Angiography is performed through the long sheath and delineates ductal anatomy and minimal ductal diameter in most dogs (Figure 122-8, *A* and Video 122-4). If sufficient contrast flow cannot be provided through the sheath, a pigtail catheter is advanced through the vascular sheath and a power injection is performed in the ascending aorta; in the author's experience, this rarely is necessary. A measurement of the minimal ductal diameter at the pulmonary ostium is made from the angiographic image and compared to transesophageal measurements of minimal ductal diameter. An appropriate ACDO is chosen with a central waist that is 1.5 to 2.0 times the minimal ductal diameter. The hydrophilic guidewire and sheath dilator are then placed back into the vascular sheath and directed across the PDA into the pulmonary trunk under fluoroscopic guidance, taking care to not engage the pulmonary valve with the stiff dilator or sheath. The dilator and guidewire are removed and the device prepared for implantation. The screw-tip connection of the delivery cable to the ACDO should be tested by removing the device and screwing it back onto the delivery cable. The device must screw on and off easily or it should not be implanted in the animal. When tightening, the device should be turned until it stops (fully tight) and then turned back one-half turn; it should not be over-tightened. While on the delivery cable, the ACDO is vigorously flushed and purged of all air bubbles by extruding and reconstraining the device under saline. The ACDO is then advanced into the long sheath and passed out into the pulmonary trunk, taking care to extrude only the pulmonary artery disc. The entire system (sheath, delivery cable) is then withdrawn until the open pulmonary artery disc engages with the pulmonary ostium of the PDA (Figure 122-8, *B*). Slight tension is placed on the system to ensure the disc is flush with the PDA and this tension is maintained as the sheath is slowly retracted over the delivery cable to expand the ductal disc within the PDA ampulla (Figure 122-8, *C* and Video 122-5). It is common to require a slight forward advancement of the delivery cable after the ductal disc is deployed to allow it to regain its cupped shape. The position of the device on the fluoroscopic image should be compared to the prior angiogram to confirm it is in the correct location of the PDA. Gentle pushing/pulling on the delivery cable helps to confirm the device is appropriately seated; however, even an optimally positioned device can be pushed out or pulled out of the PDA if too great a force is exerted. The author typically waits 5 minutes after deployment and performs an angiogram through the long vascular sheath to confirm ductal closure (see Video 122-5). If a small amount of central flow is still observed, it will likely close without further intervention (Figures 122-8, *D* and *E*; see also Video 122-5). If contrast flow is noted cranial or caudal to the waist, around the device, the device is improperly positioned and should be re-

deployed. A similar effect, or failure of the ACDO to adopt the correct shape, can be caused by an ACDO with a proximal disc that is too large for the animal's ductal ampulla. If satisfactorily implanted, the device is deployed by counterclockwise rotation of the delivery cable, using either the supplied pin or a hemostat, and the cable and sheath removed (Figure 122-8, *F*; see also Video 122-5). The femoral artery is repaired, ligated, or otherwise controlled and the skin closed. The animal is kept sedated and quiet overnight and echocardiography performed the next day to confirm persistent ductal occlusion.

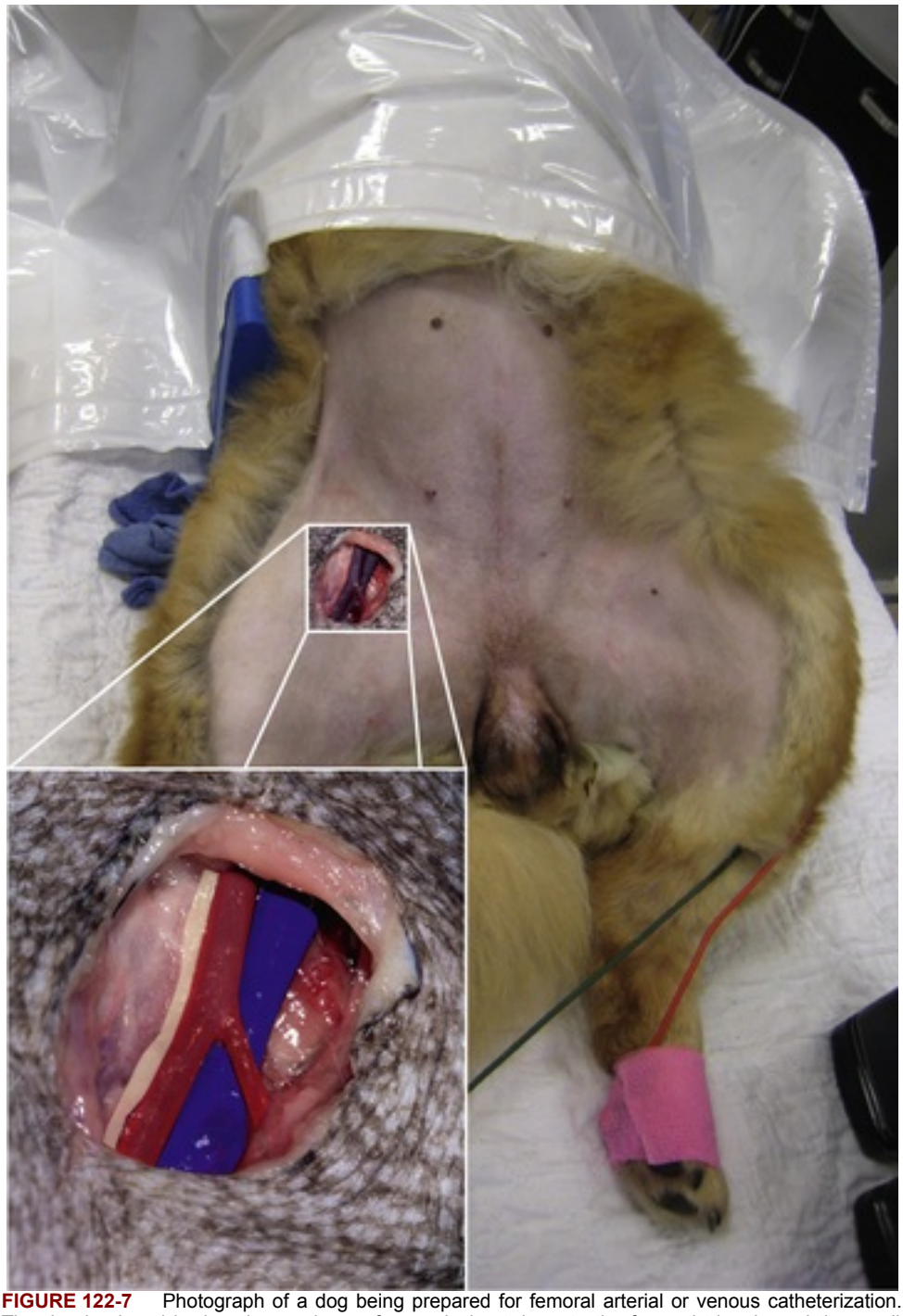

FIGURE 122-7 Photograph of a dog being prepared for femoral arterial or venous catheterization. The dog is placed in dorsal recumbency for surgical cut-down to the femoral triangle and the small inset represents this location within the limb. The enlarged inset shows the relationship of the femoral nerve (off-white overlay), common femoral artery (red overlay), and common femoral vein (blue overlay) as they lie in a cranial to caudal direction, respectively.

TABLE 122-1

List of Amplatz Canine Duct Occluder Device Sizes and Requirements for Delivery System Internal Diameter in Both Inches and Millimeters (mm)

DEVICE SIZE (central waist in mm)	MINIMUM INTERNAL DIAMETER OF DELIVERY SYSTEM (inches/mm)	RECOMMENDED DELIVERY SHEATH SIZE (French)
3	0.056″/1.42	4
4	0.060″/1.52	5
5	0.060″/1.52	5
6	0.060″/1.52	5
7	0.073″/1.85	5
8	0.073″/1.85	5
9	0.086″/2.18	6
10	0.099″/2.51	7
12	0.099″/2.51	7
14	0.099″/2.51	7

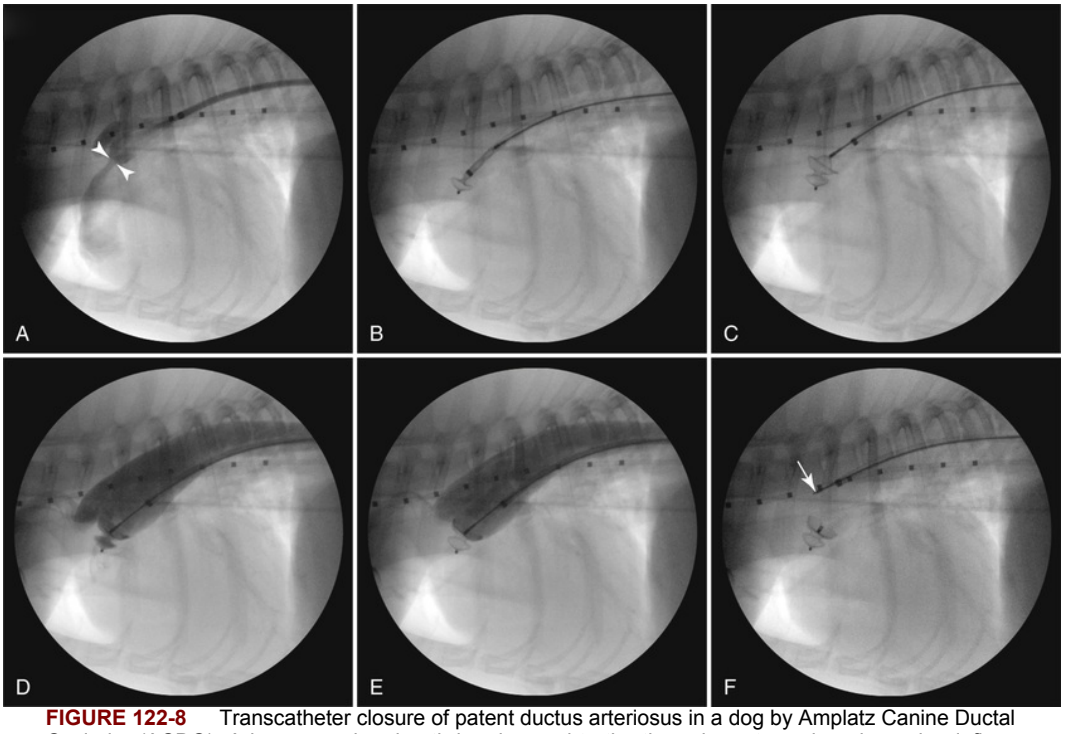

FIGURE 122-8 Transcatheter closure of patent ductus arteriosus in a dog by Amplatz Canine Ductal Occluder (ACDO). A long vascular sheath is advanced to the thoracic aorta and angiography defines the ductal location **(A)**, anatomy, and minimal ductal diameter (between arrowheads). The pulmonary disc is then deployed in the pulmonary trunk **(B)** and brought back against the pulmonary ostium before deployment of the ductal disc **(C).** Initial angiography shows mild flow through the center of the device **(D),** with complete closure noted at 10 minutes post-deployment **(E).** Counterclockwise rotation of the delivery cable results in release of the device **(F)** from the cable screw (arrow).

The procedure for transarterial coil delivery is comparable to that described for ACDO deployment, except a 4-Fr or 5-Fr catheter is used for vascular access either alone or through an introducer sheath. As most cases undergoing transarterial coil delivery relate to insufficient vascular size, the catheter is placed directly into the vessel with a hemostatic valve or Tuohy-Borst adapter placed on the catheter hub to control hemorrhage

rather than through a sheath. Angiography is as described above, through the catheter rather than a sheath. Coil selection is also based on the minimal ductal diameter, with a coil loop diameter chosen that is twice the minimal angiographic ductal diameter; typically 0.038″ or 0.035″ coils are chosen for small dogs. The catheter is positioned in the ductus, the position is verified by hand contrast injections, and the coil is carefully advanced through the catheter to the ductal ampulla (Figure 122-9). If detachable coils are used, they are mounted on the delivery cable and advanced into the catheter. The catheter is retracted to expose the coil and, once positioning is appropriate, the coil is released by counterclockwise rotation of the delivery cable. If non-detachable coils are used, they are advanced with a straight-tipped guidewire of the same thickness as the coil. The drawback to non-detachable coils is that reconstraint or repositioning is not possible; as such, confirmation of appropriate size and location of deployment is paramount to success. The author reserves transarterial coil delivery for dogs of small size (typically 2.0 to 3.5 kg) and with a narrow ductal ostium on the pulmonary side, as these cases appear most amenable to coil occlusion. Reports of smaller coils being deployed in even smaller dogs (1-2 kg), either from a carotid or femoral arterial approach, exist in the literature.[54,55] If the dog weighs <2.5 kg, the author typically recommends surgical ligation.

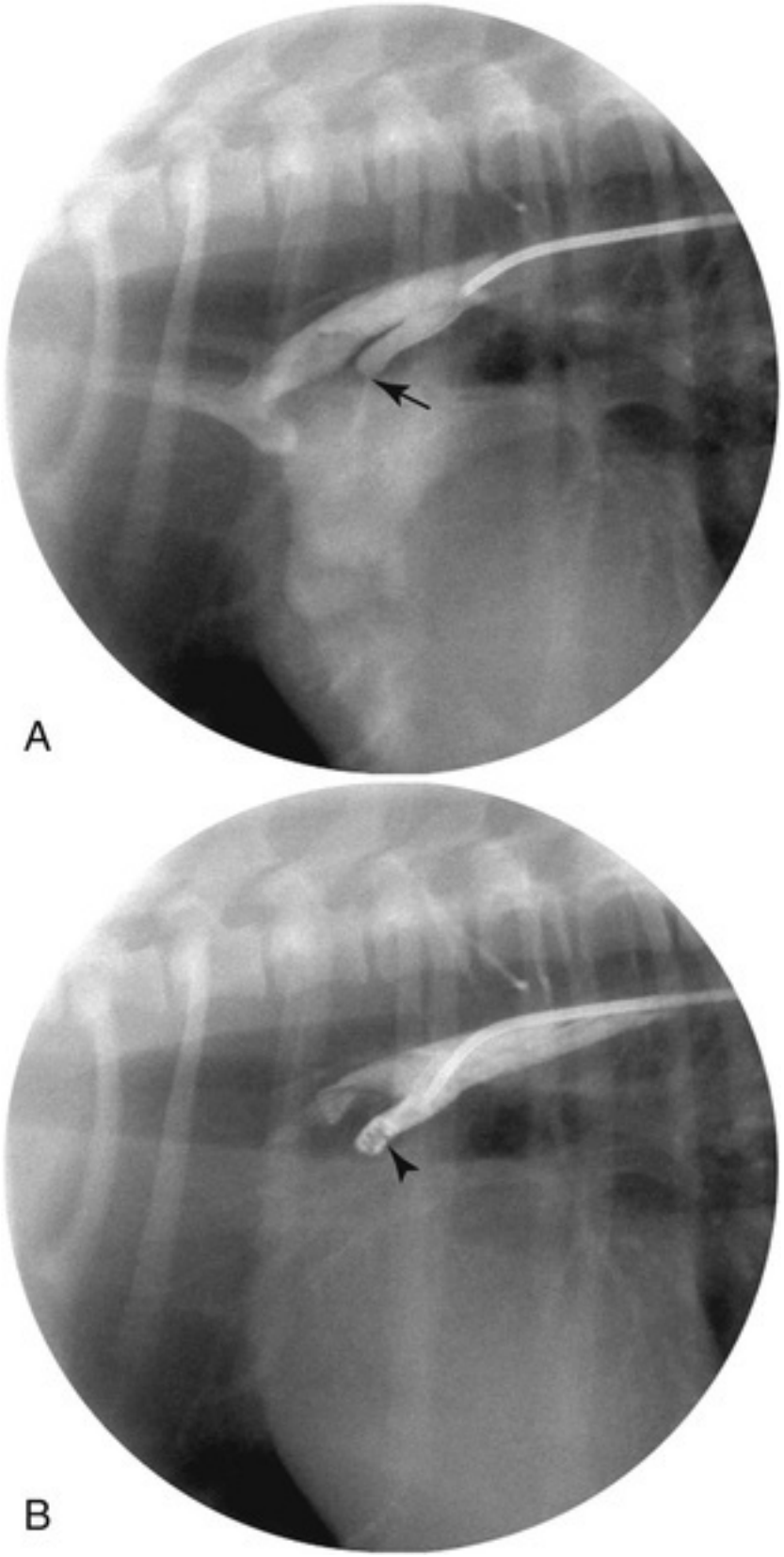

FIGURE 122-9 Fluoroscopic images during transarterial occlusion of patent ductus arteriosus (PDA) in a small dog. An angled (KMP) catheter is advanced to the aortic isthmus and an angiogram **(A)** highlights the location and minimal ductal diameter (arrow) of the PDA. The coil is delivered to the ductal ampulla and extruded via a guidewire. Upon delivery, a repeat angiogram **(B)** confirms the coil location (arrowhead) and cessation of ductal flow.

Transvenous coil delivery is also possible in small dogs or cats via retrograde cannulation of the ductus.[9,48,56] This technique allows for easier vascular access in small patients as the jugular or femoral vein are larger and more pliable than is the femoral artery. Catheterization of the PDA from venous access requires placement of an end-hole catheter into the pulmonary trunk with a straight-tipped flexible guidewire advanced across the ductus to the descending aorta. The delivery is comparable to that described for transarterial coil delivery, though the detachable coil system is preferred to allow the coil to be exposed in the descending aorta and then withdrawn into the ductal ampulla prior to release and then the delivery cable retracted to the pulmonary trunk, leaving a small segment of coil spanning the ductal ostium (Figure 122-10).

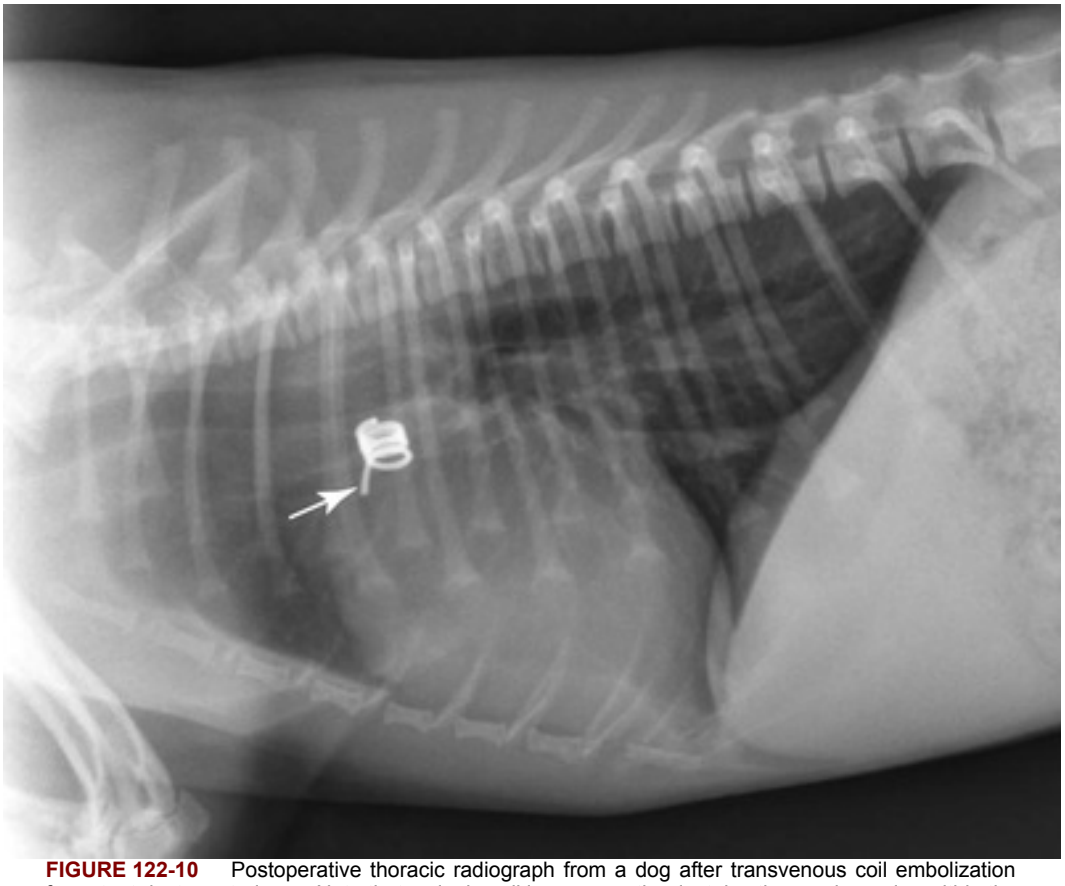

FIGURE 122-10 Postoperative thoracic radiograph from a dog after transvenous coil embolization for patent ductus arteriosus. Note that a single coil loop spans the ductal ostium and remains within the pulmonary trunk (arrow). (Image courtesy Jason Arndt, DVM, DACVIM [Cardiology]; ACCESS Specialty Animal Hospital, Los Angeles, California.)

The prognosis of transcatheter PDA occlusion is very good, with perioperative survival rates of 90-100% and median survival of >11.5 years.[47,51,57,58] Factors reported to have a negative effect on survival time include the preoperative presence of clinical signs, concurrent congenital heart disease, large breed, older age, increased weight, and severe mitral regurgitation documented within 24 hours of ductal closure.[40]

Balloon Aortic Valvuloplasty

Subaortic stenosis (SAS) is a common congenital defect of large-breed dogs; valvular aortic stenosis is more rarely encountered (see ch. 250).[14,59] Interventional therapy for SAS remains controversial, with a prospective case-control study showing no survival benefit for balloon aortic valvuloplasty (BAV) compared to medical therapy (atenolol) alone.[60] New developments in interventional treatment options, including cutting balloon (CB) and high pressure balloon (HPB) valvuloplasty, have been attempted in dogs with SAS with reasonable short and mid-term results.[61-63] However, long-term results remain unknown and no comparison to medical therapy or the natural history of the disease has been made. Currently, the author advises CB and HPB BAV for SAS in dogs that display clinical signs (syncope, weakness, congestive heart failure) or for very severe

stenotic gradients (e.g., >150 mm Hg instantaneous pressure gradient) given the uncertain benefit of therapy.

The approach for BAV is typically via a carotid artery cut-down. The dog is positioned in either dorsal or lateral recumbency and the ventral and lateral neck (either right or left) are clipped, aseptically prepped, and draped. A 3-4 cm incision is made along the lateral border of the trachea and blunt and sharp dissection used for exposing the common carotid artery, which must be carefully separated from the vagosympathetic trunk. Suture or vessel loops are passed around the carotid artery, cranial and caudal to the proposed access site, to stabilize the vessel during access. Arterial puncture is performed with an 18-gauge over-the-needle catheter or arterial access needle, and a vascular sheath of 1 to 2 Fr sizes larger than required by the desired HPB is advanced into the vessel. The left heart is catheterized with a marker pigtail catheter and left ventriculography is performed to delineate the site of subaortic obstruction as well as left ventricular size and function, presence of mitral regurgitation, coronary arterial anatomy, and other concurrent defects (Figure 122-11 and Video 122-6). The greatest challenge is crossing the aortic valve in these dogs as aortic valve excursion is limited by reduced forward flow, and extensive poststenotic dilation allows the catheter to wander in the ascending aorta. Rarely, the pigtail catheter will advance alone through the valve orifice. Alternatively, a guidewire with a long and floppy tip can be used for *gently* probing the aortic orifice and with repeated attempts will cross in most cases. Following angiography, the angiographic catheter is removed over a 0.018" guidewire that is pre-shaped with a 540 to 720 degree curve at the end, which will enable it to seat in the left ventricular apex. Over this wire the CB is advanced to the level of the subaortic ridge and rapidly inflated. Size selection of CB is based upon the minimal stenotic diameter of the left ventricular outflow tract, with a balloon chosen at a roughly 1 : 1 ratio to the stenotic diameter. Currently, the largest size of commercially available CB is 8 mm in diameter, which is large enough to engage the subaortic ridge of most dogs, though not all. After 2-3 inflations, the CB is deflated and removed from the animal, with the pigtail catheter placed again over the 0.018" guidewire. The guidewire is exchanged for an ultrastiff 0.035" guidewire with a long floppy tip. The end of the 0.035" guidewire is also pre-shaped with a 540 to 720 degree curve and placed in the left ventricular apex. A HPB is then chosen—typically the ATLAS or ATLAS GOLD line of HPBs—as these develop pressures of 12 to 18 atmospheres. Both of these balloon designs work well, but it is important to understand the differences between the two lines of balloon dilation catheters. The primary difference is the length of the shoulders, that portion of the balloon that tapers at each end. The original ATLAS HPB has long shoulders; as such, the 2 cm length balloons in the ATLAS HPB line are best for most BAV in dogs. In the ATLAS GOLD HPB line, the shoulders are more comparable to standard balloons and 4 cm length balloons work well for most dogs. The diameter of HPB chosen is based on the true aortic valve annulus and sized 0.9-1:1 for balloon to aortic valve diameter. For smaller dogs in which the smallest ATLAS HPB (12 mm diameter) is too large, the CONQUEST HPB can be selected, which also has very high burst pressures (up to 30 atm) and comes in appropriate lengths. The HPB is advanced over the 0.035" guidewire to the level of the subaortic lesion and rapidly inflated. As with BPV, successful inflation involves the appearance of a stenotic waist, which resolves with increased pressure and is not apparent on subsequent inflations (Figure 122-12 and Video 122-7). Following 2 to 3 inflations across the outflow tract, the HPB is removed and an aortic root injection is typically performed to evaluate the degree of aortic insufficiency. Pressures are again measured and the change in gradient evaluated compared to preoperative values. Once satisfactory results are achieved, the balloon dilation catheter is removed, often requiring constant negative pressure during retrieval to allow passage through the sheath, or the sheath and catheter are removed as a unit if excess tension is encountered during retrieval through the sheath due to the large profile common to deflated HPBs. The carotid artery is repaired with 5-0 or 6-0 monofilament suture and the surgical exposure closed routinely in three layers. Care should be taken to allow the carotid access site to bleed temporarily prior to repair, to be certain any thrombus around the introducer sheath is removed through the access site prior to closure. The neck is bandaged routinely and the dog recovered with monitoring of the cardiac rhythm and administration of analgesia, sedation, and prophylactic antibiotics.

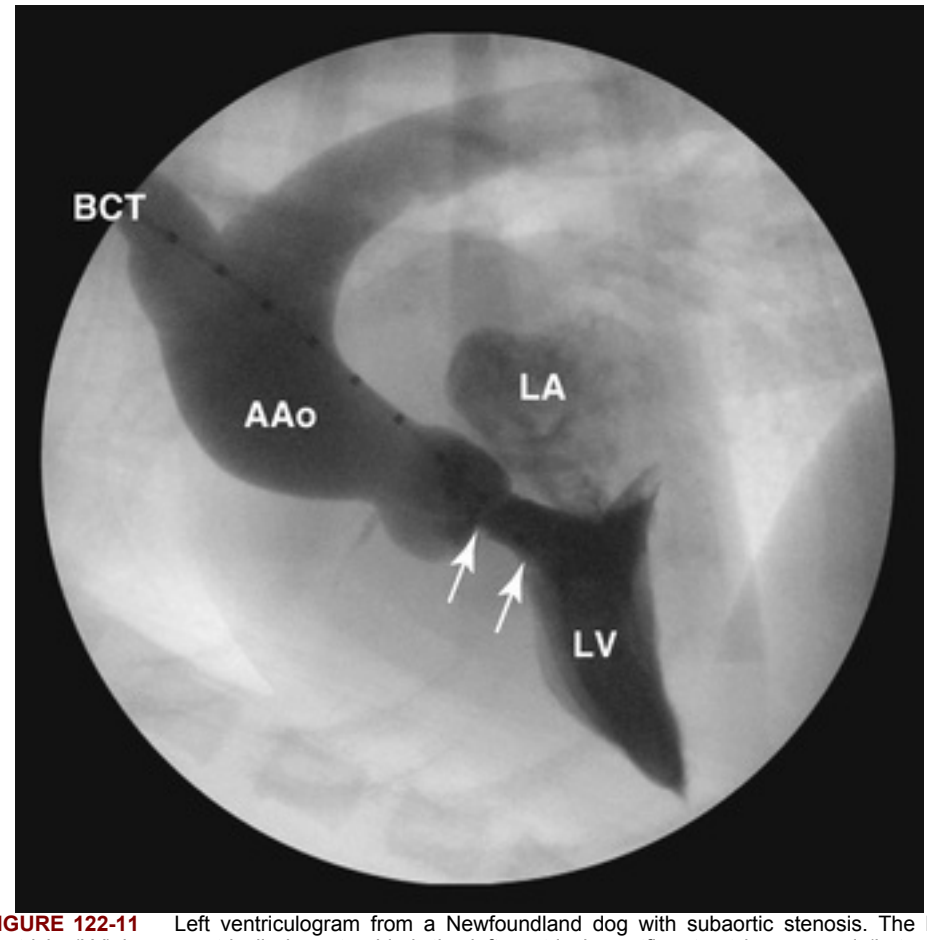

FIGURE 122-11 Left ventriculogram from a Newfoundland dog with subaortic stenosis. The left ventricle (LV) is concentrically hypertrophied, the left ventricular outflow tract is narrowed (between arrows), there is mild mitral regurgitation back into the left atrium (LA), and there is post-stenotic dilation of the ascending aorta (AAo) and brachycephalic trunk (BCT).

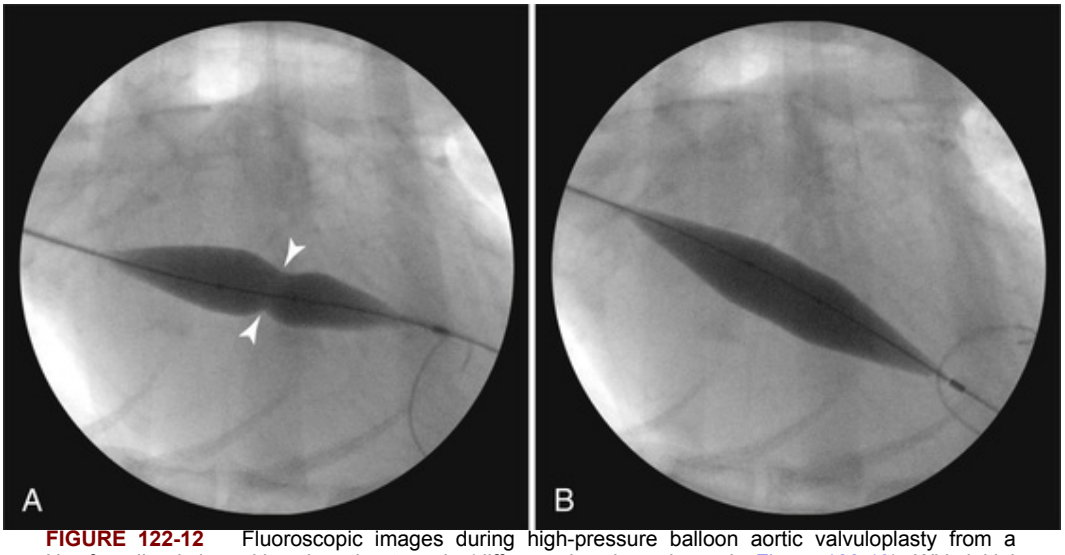

FIGURE 122-12 Fluoroscopic images during high-pressure balloon aortic valvuloplasty from a Newfoundland dog with subaortic stenosis (different dog than shown in Figure 122-13). With initial inflation **(A),** the indentation from the subaortic lesion creates a waist (arrowheads). With higher pressure **(B),** the waist is abolished as the subaortic ring is torn.

A similar approach to BAV can be undertaken for dogs with valvular aortic stenosis. However, the CB is

not used; rather the TYSHAK and Z-MED lines of balloon dilation catheters are utilized as described for BPV if these dogs have fusion of apparently normal aortic valve cusps because they do not require scoring and high pressure tearing of the fibrous tissue that is present in SAS. For aortic valvular stenosis with valve dysplasia (thickened, hypoplastic leaflets), BAV with the ATLAS or ATLAS GOLD line of HPBs may be required to achieve sufficient radial force on the valve. The ratio of balloon diameter to aortic valve annulus for conventional BAV in the setting of valvular aortic stenosis is chosen as 0.9-1:1 to limit the risk of postoperative aortic insufficiency.

The prognosis for CB and HPB BAV is unclear, though an interim analysis of 28 dogs that underwent this procedure for SAS found a decrease in peak systolic pressure gradient from a mean of 143 mm Hg to 78 mm Hg at 1 day after BAV, 84 mm Hg at 1 month, 89 mm Hg at 3 months, 92 mm Hg at 6 months, and 116 mm Hg at 12 months post-BAV.[63] Six dogs had died after BAV, including three dogs euthanized for progressive myocardial failure, one dog euthanized for syncope, and two dogs that died suddenly.[63] In the author's experience, a reduction in gradient is achievable and clients report improved exercise capacity. However, the gradient typically is reduced to the high moderate range (70-80 mm Hg) and substantial obstruction persists. As the procedure is costly and involves arrhythmic and anesthetic risk, it is of uncertain benefit though a randomized prospective study is required to answer this question. In the absence of such a study, the author reserves this procedure for cases that display clinical signs or that are at high risk for clinical signs based on the severity of cardiac remodeling and peak systolic pressure gradient as described above.

Septal Defect Occlusion

Large defects in the atrial or ventricular septum lead to left-to-right shunting of blood, pulmonary overcirculation, and either pulmonary vascular disease or left-sided congestive heart failure (see ch. 250). Closure of such defects is not common in veterinary medicine due to the scarcity and cost of open-heart surgery. However, transcatheter options have been described that allow for closure of both atrial septal defects[64, 65] (ASD) and ventricular septal defects[66-68] (VSD) by minimally invasive methods and without cardiopulmonary bypass.

Transcatheter closure of ASD is performed by a transvenous approach—either jugular or femoral venous access (Figure 122-13). Transcatheter techniques can only be applied to ASDs of the ostium secundum type at this time, as sufficient tissue around the defect is required to seat and hold the device in place; optimally, the defect should have septal tissue around 75% of the circumference to consider transcatheter closure.[65] All cases reported in dogs have used the Amplatzer septal occluder (ASO), though other devices are commercially available. The center with the largest case experience advises a jugular venous approach for canine ASD closure,[65] though the author has successfully performed the technique from a femoral venous approach and this was the approach used in the first reported canine case.[64] The defect is sized by transthoracic and transesophageal echocardiography and this size is confirmed in the catheterization laboratory using a balloon sizing catheter (Amplatzer sizing balloon II). The device is selected to match or be minimally larger (0.5-1 mm) than the largest diameter measured. The optimal imaging planes to determine maximal dimension by echocardiography have not been determined in animals; therefore, use of a sizing balloon is advised to determine the device required. The device is attached to the delivery cable and carefully purged of air by immersion in saline and repeated retraction into the delivery system followed by saline flush through the delivery system.

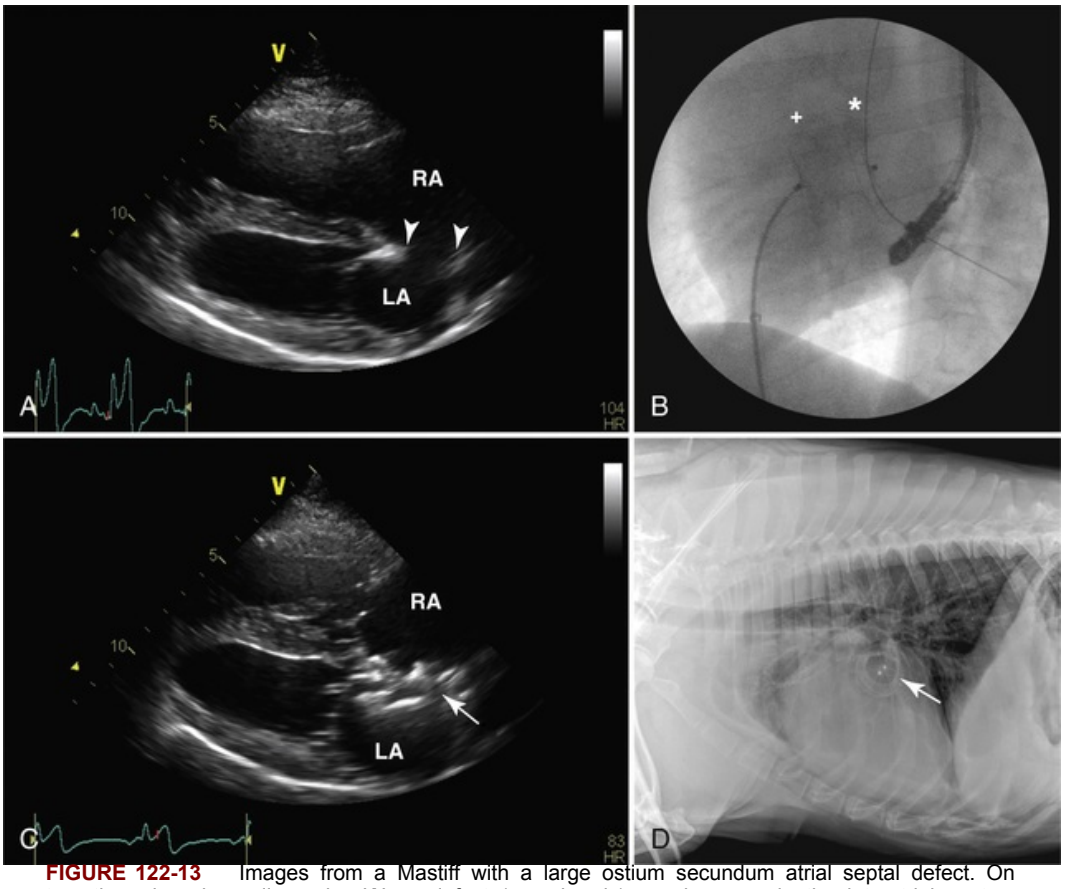

FIGURE 122-13 Images from a Mastiff with a large ostium secundum atrial septal defect. On transthoracic echocardiography **(A),** a defect (arrowheads) can be seen in the interatrial septum between the left atrium (LA) and right atrium (RA). Fluoroscopic delivery **(B)** of an Amplatzer septal occluder requires deployment of the distal retention disc (asterisk) on the left atrial side and the proximal retention disc (plus sign) on the right atrial side of the septum. A transesophageal echocardiography probe can also be seen in this image. After closure, the device (arrow) can be seen spanning the defect on both echocardiography **(C)** and thoracic radiography **(D).**

A delivery sheath, the Amplatzer TorqVue 45° Delivery System supplied by the manufacturer of the ASO, is advanced over a guidewire, across the atrial septum and into the left atrium. Once the left heart is catheterized, the animal is heparinized with 100 U/kg unfractionated heparin IV to limit thrombotic risk. The prepared device is advanced into the delivery sheath, allowing for some back-bleeding through the device to confirm all air has been removed. The device is then advanced to the left atrium and the distal retention disc (left atrial disc) deployed (see Figure 122-13). Careful tension is then placed on the entire delivery system as the distal retention disc is retracted against the atrial septum and the central waist is deployed by retracting the delivery sheath over the delivery cable. In animals with minimal rim tissue, it is very easy to pull the device through the ASD, so gentle traction and transesophageal guidance are mandatory. If the waist is appropriately seated in the ostium of the ASD, the proximal retention disc (right atrial disc) is then deployed (Video 122-8). All planes of the device are investigated by transesophageal echocardiography to confirm the device is appropriately positioned and that the distal and proximal discs are on the appropriate side of the septum (left and right, respectively) in all planes. Minimal manipulation of the delivery cable can be performed to assess the stability of the ASO, though as noted above it is easy to dislodge even an appropriately deployed device. If it is determined that the device is appropriately positioned and stable, the ASO is released from the screw tip of the delivery cable by counterclockwise rotation of the cable, either with the supplied pin or a hemostat, and the cable and sheath are removed (see Video 122-8). The femoral access site is repaired, ligated, or otherwise controlled and the skin closed. The animal is kept sedated and quiet overnight and echocardiography is performed the next day to confirm device position and assess ASD closure.

The technique for transcatheter VSD closure is comparable to that described for transcatheter ASD closure. The type of VSD most amenable to transcatheter closure is the muscular-type defect, surrounded entirely by muscular septum on all sides.[68] However, transcatheter closure of membranous-type defects has also been

reported in the dog with specific, asymmetric devices available.[67]

The outcome of transcatheter ASD and VSD closure appears good, with case reports and case series describing event-free survival in several dogs.[65,68] However, embolization of these devices is a risk and can be devastating as surgical retrieval may be required via advanced surgical techniques that are not available at all veterinary centers.[65,69] Additionally, thrombosis of the device is a risk and therapy with clopidogrel (2 mg/kg PO q 24 h) is advised for 6 months post-implantation.

Hybrid Interventions

A hybrid procedure refers to a procedure that utilizes a surgical approach combined with image-guided intervention.[70-72] Examples in veterinary medicine include delivery of balloon dilation catheters directly through the left atrium via echocardiographic guidance for treatment of mitral stenosis[73] or cor triatriatum sinister[74] as well as perventricular VSD occlusion[75] and transatrial ASD occlusion.[69] Future options for mitral valve repair or replacement also are likely to use a hybrid approach given the complexities of left heart access and the large delivery systems required of these techniques.[76]

Perventricular Ventricular Septal Defect Occlusion

As an example of the hybrid approach to cardiac disease, devices used for closing VSDs described above via a transcatheter approach can also be delivered directly through the right ventricular wall and guided by echocardiography.[75,77] The indication for such a technique is dictated by animal size; the transcatheter devices often require delivery systems of 9 Fr diameter and larger, which may be too large for vascular access in small dogs or cats. In such cases, a right lateral thoracotomy can be performed to expose the right ventricular free wall and beating heart. A pursestring suture is placed around the proposed access site prior to myocardial puncture to control hemorrhage. A vascular access needle is inserted directly across the right ventricular free wall, guided by echocardiography, through which a guidewire is placed and the desired delivery system advanced (Figure 122-14 and Video 122-9). Echocardiographic and fluoroscopic guidance can then proceed as is done with the transcatheter delivery of the same device. A hybrid approach such as this not only overcomes the challenge of vascular access in a small dog, it also allows for a more direct path to the defect, which can make deployment of the device more straightforward than a conventional, percutaneous approach. The drawback to hybrid techniques is an increased morbidity associated with the approach, but such morbidity is typically low in dogs.

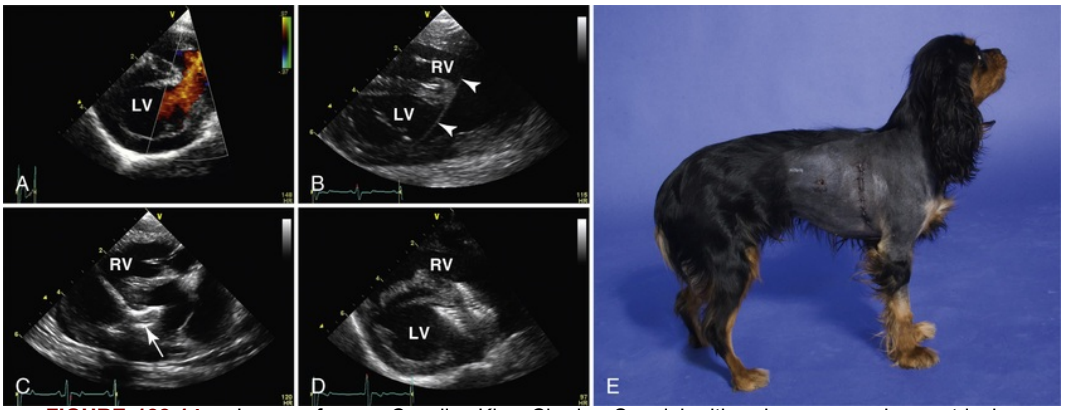

FIGURE 122-14 Images from a Cavalier King Charles Spaniel with a large muscular ventricular septal defect (VSD) undergoing hybrid perventricular VSD closure. **A,** The defect on preoperative transthoracic echocardiography. **B,** An epicardial echocardiographic image showing the guidewire (arrowheads) traversing the right ventricular (RV) free wall and crossing the VSD into the left ventricle (LV). **C,** The sheath across VSD with deployment of the distal retention disc (arrow) in the LV. **D,** The postoperative transthoracic echocardiogram with the device in place and spanning the interventricular septum. **E,** A photograph of the dog 2 days after surgery showing the site of right lateral thoracotomy that provided access to the beating heart for perventricular delivery of the Amplatzer muscular ventricular septal occluder. Caudal to the surgical incision is a small incision from the postoperative thoracostomy tube placement.

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CHAPTER 123

Gastrointestinal Interventional Therapies

Allyson C. Berent

Esophageal Balloon Dilation, Bougienage, and Stenting

Indications and Background

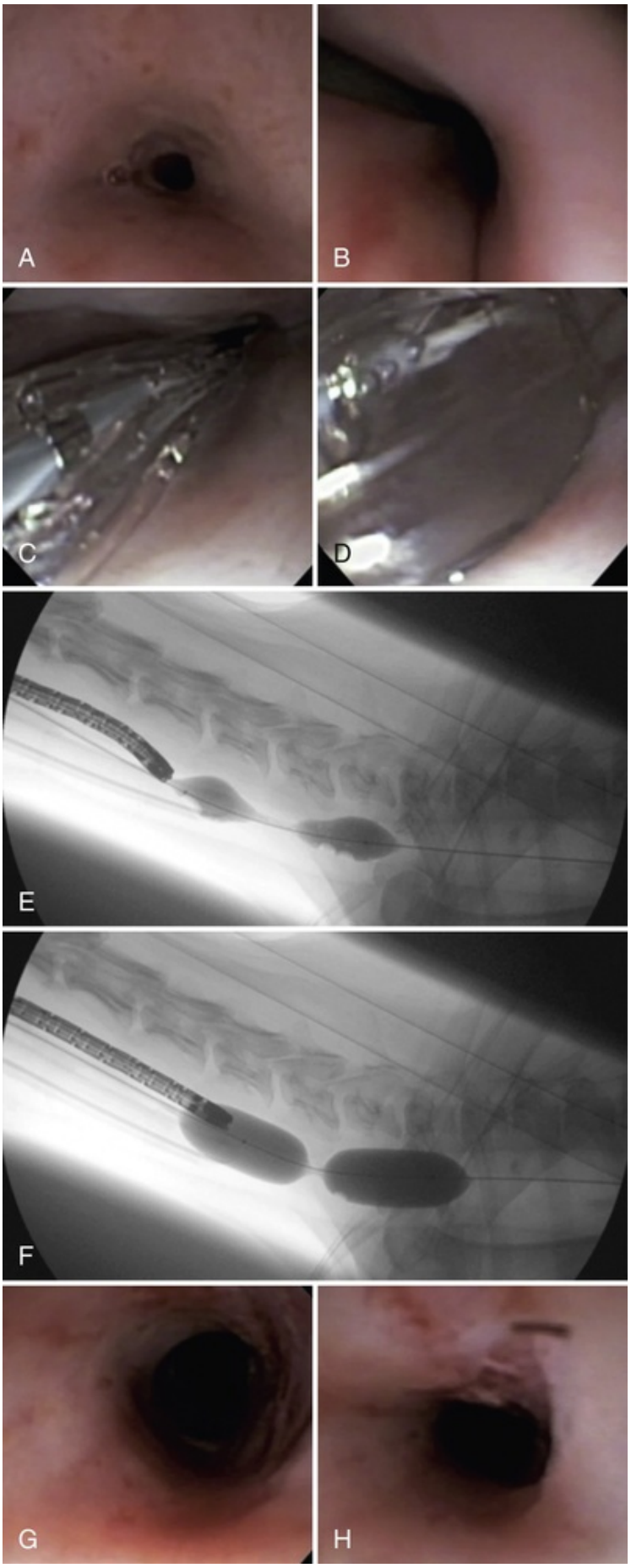
Esophageal obstructions in dogs and cats are most commonly associated with a foreign body or an acquired esophageal stricture. Other causes include esophageal neoplasia and extraluminal compressions from vascular ring anomalies (see ch. 273).[1-3] Strictures occur secondary to mucosal injury and this is commonly the result of severe gastroesophageal reflux, caustic mucosal damage, or trauma.[2-25] Since the esophageal mucosa is lined by non-keratinized, stratified squamous epithelial cells, the acidity and enzymes in gastric fluid can result in severe mucosal and muscular injury, leading to circumferential narrowing and an esophageal stricture.[16]

Various treatments for esophageal strictures have been reported including bougienage, balloon dilation, esophageal resection and anastomosis, and salvage esophageal stenting.[1-22,26] Esophageal strictures are notoriously a frustrating condition for veterinarians to treat because they are difficult to cure, are typically recurrent, and can be highly refractory to dilation.[26] Treatments using topical therapies to decrease stricture recurrence like triamcinolone injections[12,16] or mitomycin C[22] have been used. Previous retrospective studies evaluating esophageal balloon dilation suggest a good outcome in up to 75% of cases where a gruel diet is tolerated,[2,4-9] and only 14-25% of patients are reported to return to eating normal dry food. In humans, refractory strictures are those that fail to resolve despite more than three dilation procedures,[13-15] and this is commonly seen in veterinary patients as well.

Balloon dilation and bougienage are the most commonly considered treatment options in dogs and cats with esophageal strictures.[2-9] Esophageal stents (Video 123-3) are reserved for those cases where balloon dilation or bougienage fails.[18-21,26] The use of various types of stents was recently retrospectively reported[26] in a group of nine dogs: biodegradable, self-expanding plastic stents (SEPS), self-expanding metallic stents (SEMS), as well as covered and uncovered stents. These stents were found to ultimately improve the dysphagia, but were met with a common complication of discomfort when swallowing, profound chronic nausea, hypersalivation, and migration. Due to the high likelihood of poor tolerance, this procedure is reserved for those pets that have failed serial balloon dilation, and should be considered a salvage procedure. A covered stent is typically recommended so that if the stent is poorly tolerated it can be endoscopically removed. Stents seem to be far better tolerated for malignancy than benign strictures.[1,23]

Equipment

For evaluation of an esophageal obstruction, a standard flexible gastrointestinal endoscope is used (see ch. 83 and 113). Ideally, all bougie or balloon dilation procedures should be done under concurrent fluoroscopic guidance. This allows the operator to see when the entire stricture is effaced, which is not possible with endoscopic imaging alone (E-Figure 123-1). Many strictures result in esophageal muscular fibrosis, as well as mucosal, and if the fibrous band of the mucosa is sufficiently effaced, the muscular component may remain intact, resulting in recurrence.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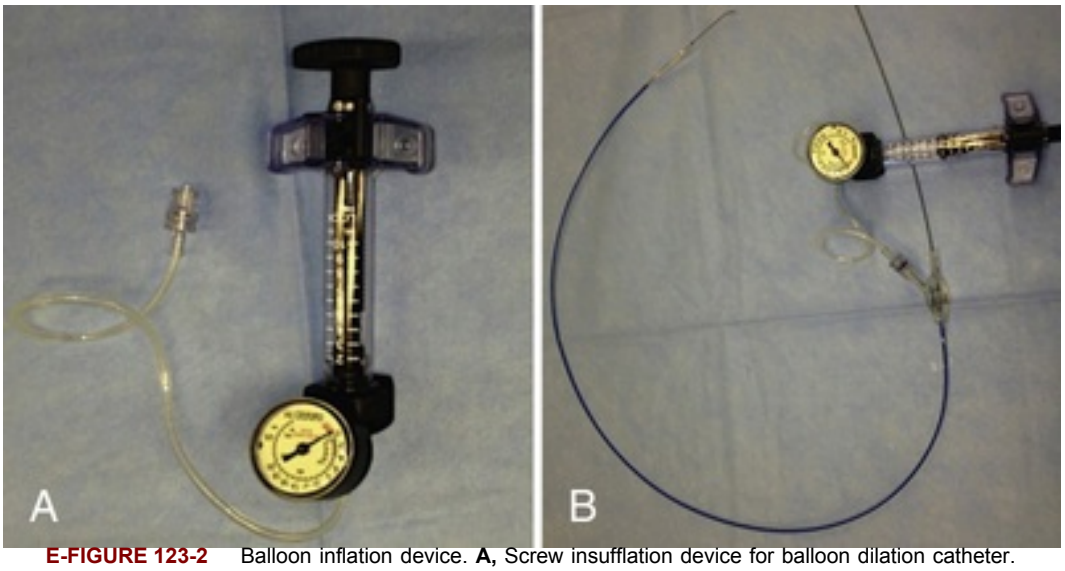
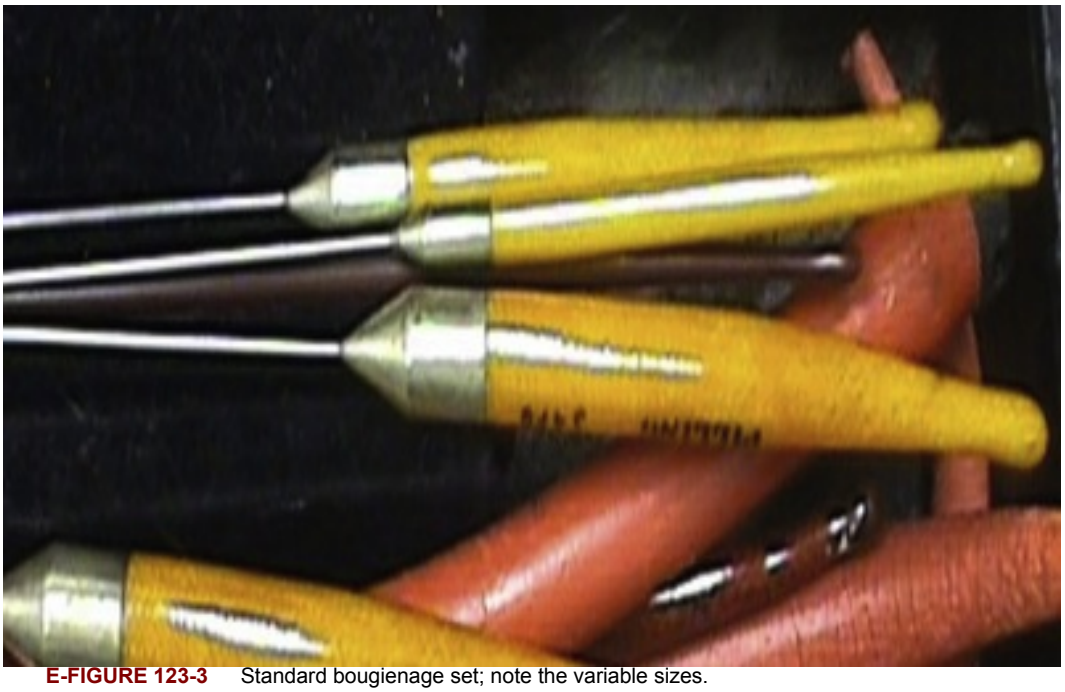
E-FIGURE 123-1 Endoscopic and fluoroscopic images during balloon dilation of an esophageal stricture in a dog. **A,** Endoscopic image of a stricture in the esophageal lumen. **B,** Guide wire passed through the stenosis. **C,** Deflated balloon passed over the guide wire, through the stenosis. **D,** Inflation of the balloon within the stricture. **E,** Fluoroscopic image of the dog in lateral recumbency during balloon dilation of the stricture. Notice the narrowing in the center of the balloon and the endoscope sitting in front of the balloon. **F,** Fluoroscopic image of the stricture during balloon dilation showing the severe narrowing of the esophagus, which is a muscular stenosis that is very difficult to break. **G,** Endoscopic image of the dog after balloon inflation when a waist was still present during fluoroscopy supporting that endoscopic visualization alone may underestimate the degree of stricture defacement. **H,** Endoscopic image after the stricture was effaced on fluoroscopic imaging showing the desired longitudinal mucosal tear (top of image).

Balloon dilation catheters can be variable or fixed in diameter, and some are placed over a guide wire, while others have a soft tip and closed end. For proper dilation, an insufflation device is required. The amount of force required to properly efface a fibrous band can be upward of 6-12 ATM of pressure, where digital hand inflation reaches only 1-4 ATM of pressure (E-Figure 123-2). A wide variety of balloon sizes should be available (6 mm to 30 mm diameter). Bougienage dilator sets (E-Figure 123-3) are recommended to be placed under fluoroscopic guidance.



E-FIGURE 123-2 Balloon inflation device. **A,** Screw insufflation device for balloon dilation catheter. **B,** Balloon dilation catheter with two ports on the end, one for a guide wire and the other for a balloon dilation device.

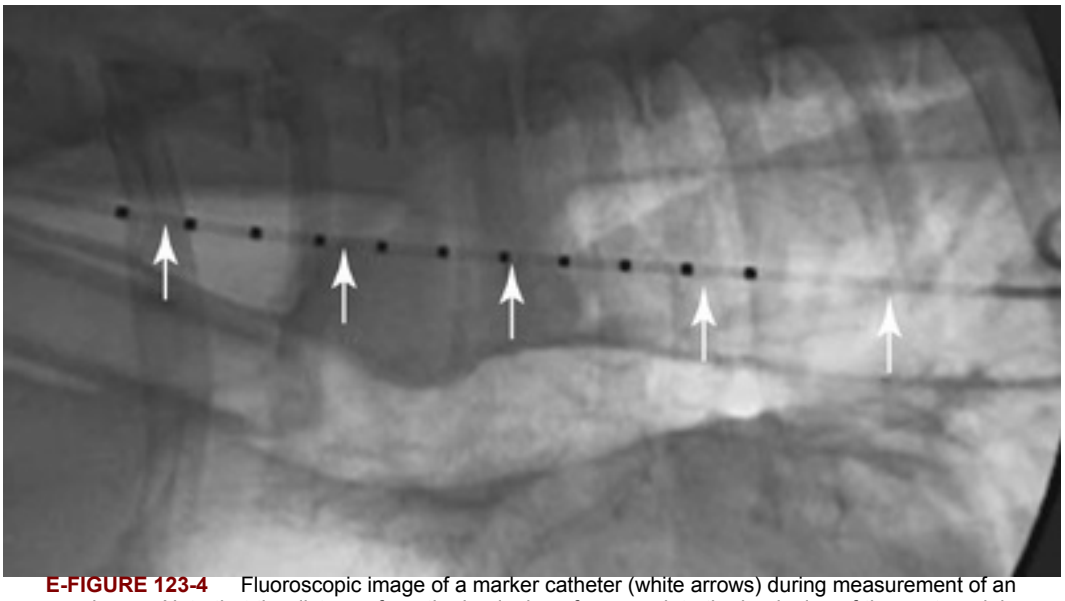


E-FIGURE 123-3 Standard bougienage set; note the variable sizes.

Techniques

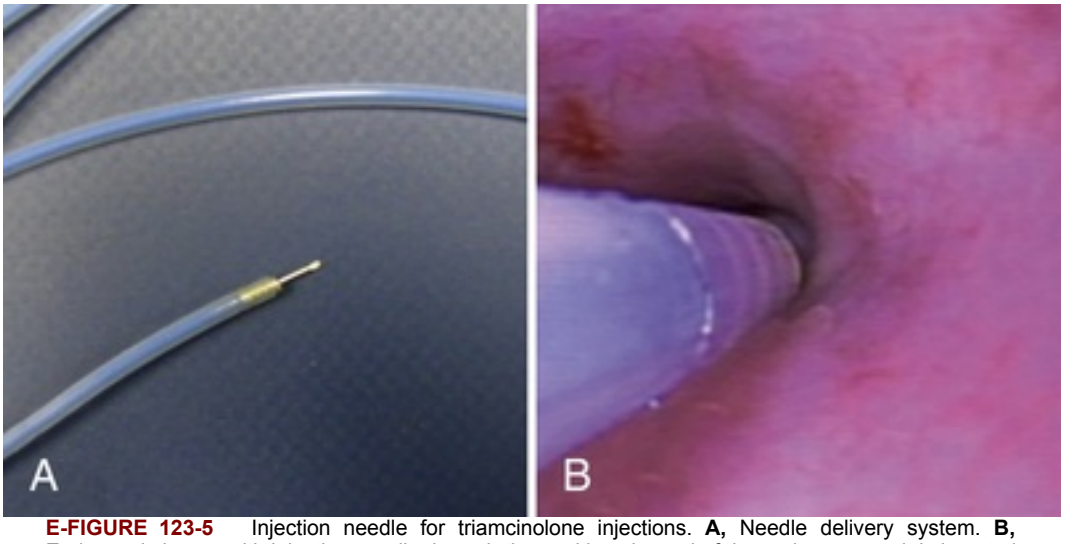
Balloon Dilation Procedure

Using endoscopic guidance, a balloon size is chosen based on the length of the stricture and the diameter of the normal esophagus. This can be estimated during endoscopy; however, a more accurate determination is typically done using a marker catheter, contrast/air, and fluoroscopic imaging (E-Figure 123-4). Once a balloon size is chosen, then this is advanced through the lumen of the stricture watching with endoscopic visualization. Using a guide wire helps to prevent iatrogenic trauma or esophageal perforation. A balloon is chosen that is 2 cm or more longer than the stenosis, and the diameter of the balloon should be equivalent to the diameter of the esophagus measured using fluoroscopy caudal to the stenosis. If fluoroscopy is not used, then an estimated diameter is chosen using the outer diameter of the endoscope for a reference. In this case, it is typically recommended to start small (≈6 mm) and work up in 2 mm increments until the lesion is visually torn and good apposition of the balloon is against the esophageal mucosal wall when inflated. Since endoscopic visualization is only confirming mucosal effacement of a stricture, fluoroscopy is used to confirm muscular effacement as well (see E-Figure 123-1).



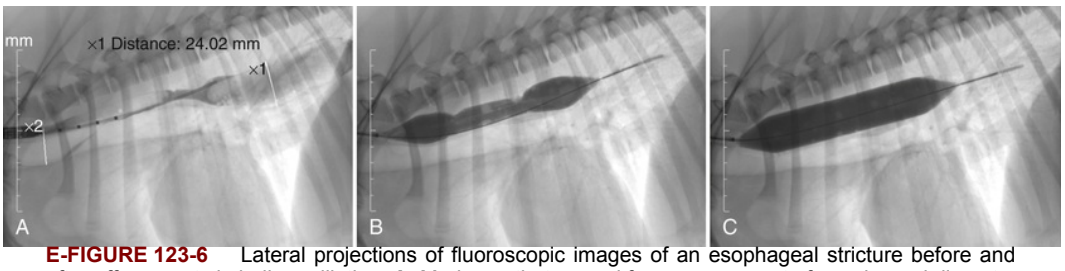
E-FIGURE 123-4 Fluoroscopic image of a marker catheter (white arrows) during measurement of an esophagus. Note that the distance from the beginning of one mark to the beginning of the next mark is 10 mm.

Prior to balloon dilation, superficial injections of local steroids (triamcinolone) may be utilized to help reduce stricture re-formation. Triamcinolone injections are done using a 23- to 25-gauge, 4- to 5-mm length endoscopic injection needle, preloaded with the appropriate dose of triamcinolone (6-8 mg/patient in 0.5 mL aliquots per quadrant up to 0.3 mg/kg). After injection, a bleb of fluid should be visualized under the mucosal tissue (E-Figure 123-5).

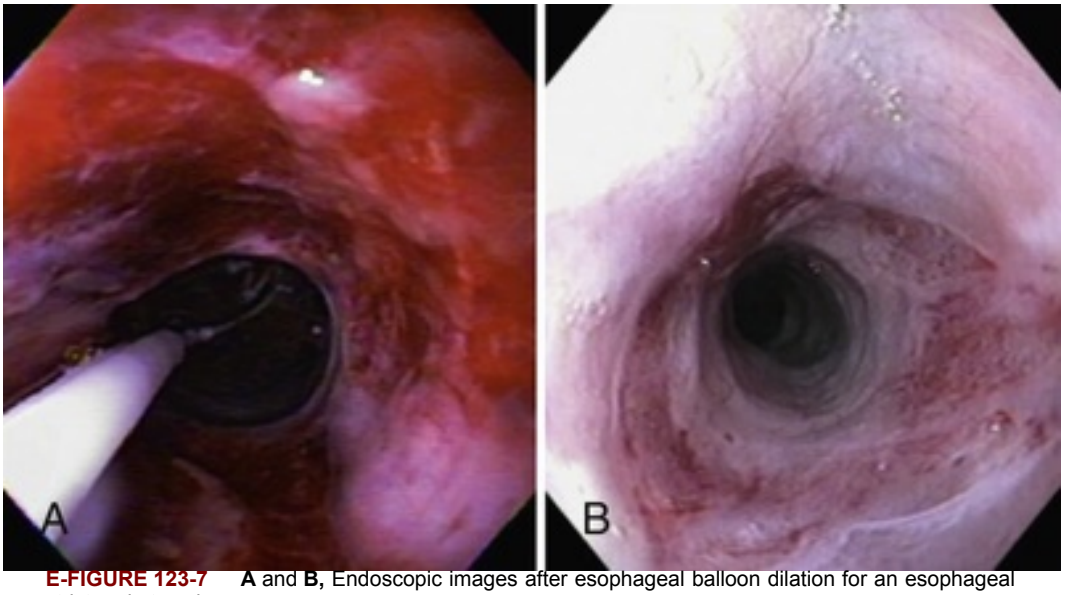


E-FIGURE 123-5 Injection needle for triamcinolone injections. **A,** Needle delivery system. **B,** Endoscopic image with injection needle through the working channel of the endoscope as it is inserted under the esophageal mucosa for injection.

If balloon dilation is being done under fluoroscopic guidance, the inflation device is filled with a 50% contrast solution so that the dilation can be visualized. If no fluoroscopy is being used, then saline infusion is acceptable. Once across the stenosis and the stricture is engaged, the inflation device is used to inflate the balloon to the recommended pressure while the balloon is tightly held in place at the mouth. Some degree of superficial mucosal tearing and bleeding is expected. In general, the procedure is complete when the stricture is effaced based on fluoroscopy (E-Figure 123-6), or the mucosal tearing seen endoscopically extends linearly beyond the stricture, deep into the submucosa, or excessive bleeding is seen (E-Figure 123-7).



E-FIGURE 123-6 Lateral projections of fluoroscopic images of an esophageal stricture before and after effacement via balloon dilation. **A,** Marker catheter used for measurement of esophageal diameter and stricture length. **B,** Balloon dilation showing the waist of the esophageal stricture. **C,** Effacement of the stricture when the balloon is fully inflated. (Courtesy Dr. Chick Weisse.)



E-FIGURE 123-7 **A** and **B,** Endoscopic images after esophageal balloon dilation for an esophageal stricture in two dogs.

A recommended interval between balloon dilation varies per clinician and institution. No consensus or standard has been established in either human or veterinary medicine.[13-15] There is very little data to support that frequent, small intervals of balloon dilation is better.[2-9]

Bougienage Procedure[3]

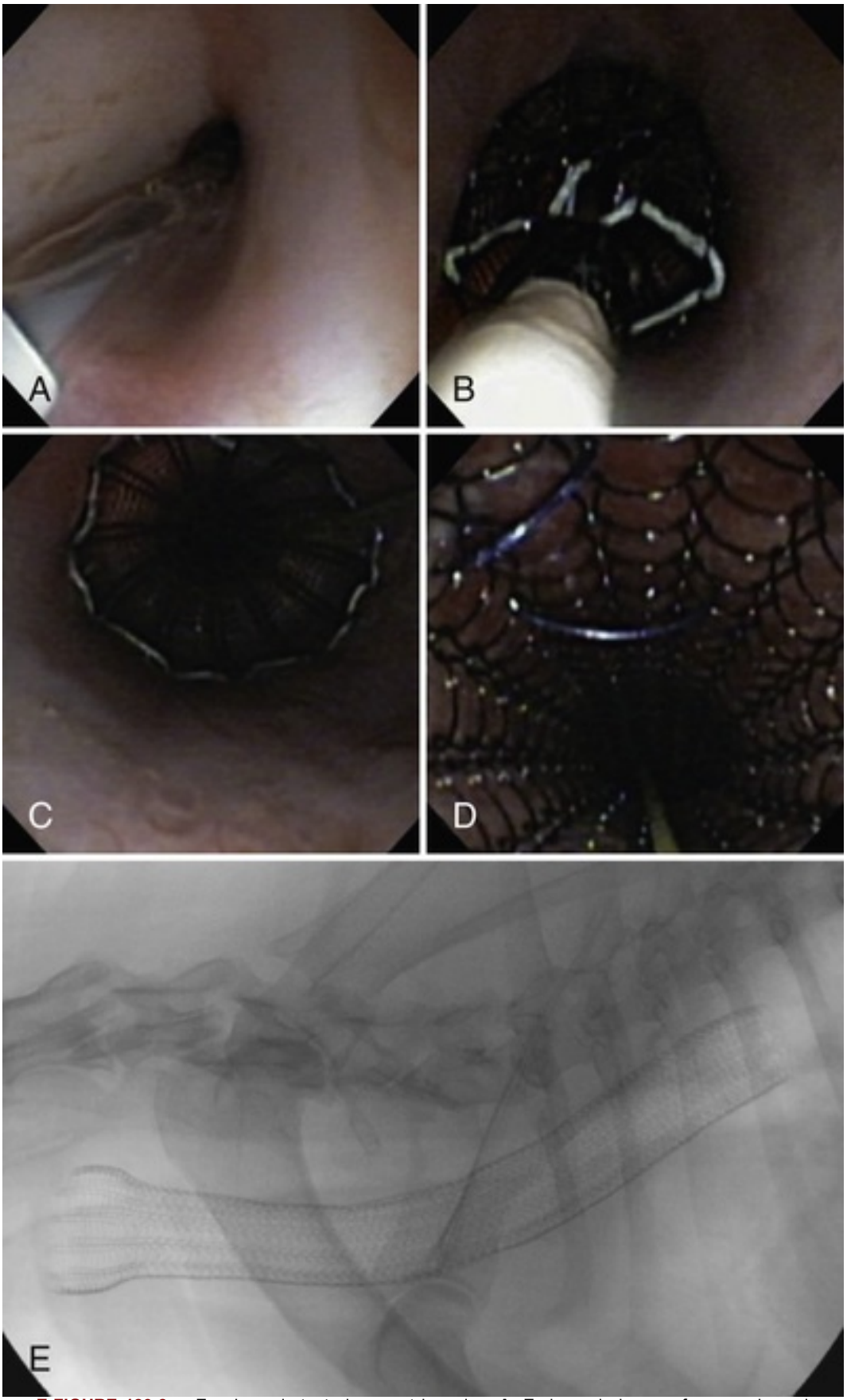
The bougie size is selected based on estimations of stricture diameter, as discussed above for balloon dilation. The initial bougie is typically 1-2 mm larger than the stricture meatus, and is subsequently increased in 1-2 mm increments until the lesion is similar in size to the normal esophagus.

Topical mitomycin C (MMC) infusions have been performed in cases of refractory strictures.[22] Mitomycin C is an antibiotic and antineoplastic drug that is produced by *Streptomyces caespitosus* resulting in inhibition of fibroblast proliferation. This has been shown in children with esophageal strictures to hold benefit in preventing recurrence.[22] In veterinary medicine, the author typically uses 2.5-5.0 mL of a 0.1% solution soaked on a gauze sponge and placed endoscopically over the stricture site topically for 5 minutes and then the site is flushed with saline. Gloves should be worn when using this material.

Esophageal Stenting

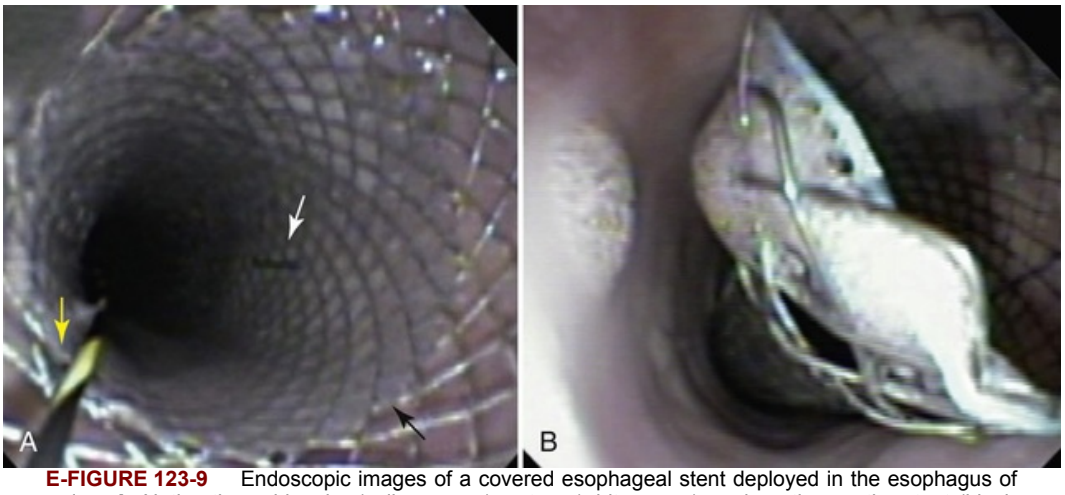
For esophageal stent placement, dogs are placed in lateral recumbency and the entire esophagus is visualized using fluoroscopic and endoscopic guidance. The ventral cervical region of the dog is clipped and aseptically prepared in order to place tacking sutures on the cranial aspect of the stent to prevent stent migration. Once the stricture is visualized, the esophagus and stricture are measured using a guide wire and marker catheter combination. The stricture is pre-ballooned partially, to permit safe passage of the endoscope through the

lumen to visualize the most caudal aspect of the abnormal tissue. Length is typically measured to ensure at least 1-2 cm of esophagus is stented both cranial and caudal to the location of the stricture. The patient is placed in dorsal recumbency and the C-arm is rotated so that a lateral image is projected during stent placement to accurately see stent deployment. If possible, the cranial aspect of the stent is extended to cross the level of the thoracic inlet so that it can be safely and easily sutured in place through the esophageal wall to prevent migration. Sutures can also be placed endoluminally using a double lumen endoscope. This procedure should not be done unless the operator is very comfortable understanding various types of stent deployment (E-Figures 123-8 and 123-9). Based on limited data[26] the author recommends a covered stent (see E-Figure 123-9) that is sutured in place, and then it can be removed if it is poorly tolerated.



E-FIGURE 123-8 Esophageal stent placement in a dog. **A,** Endoscopic image of an esophageal stent delivery system being placed over a guide wire through an esophageal stricture. **B,** Stent deployment using endoscopic imaging. **C,** Image of the rostral aspect of the esophageal stent after

deployment. **D,** Two sutures seen through the interstices of the esophageal stent. **E,** Endoscopic image of the esophageal stent after deployment.



E-FIGURE 123-9 Endoscopic images of a covered esophageal stent deployed in the esophagus of a dog. **A,** Notice the guide wire (yellow arrow), suture (white arrow), and coating on the stent (black arrow). **B,** Notice the endoscopic image of the dog-bone shape of the stent.

Follow-up

Patients are typically discharged the same day as the procedure and treated with a proton pump inhibitor and sucralfate. Repeat balloon dilation can be performed as needed based on clinical signs of recurrence.

Complications

The most severe complication seen with treatment of esophageal strictures is esophageal tearing, resulting in a pneumomediastinum, pneumothorax, and potentially pyothorax. Most tears do not require surgical correction and will heal by second intention, but require the placement of a percutaneous endoscopic gastrostomy (PEG) tube. Esophageal stricture recurrence post-dilation is also seen in a majority of dogs.[3-9]

Outcome

Success rates vary depending on the outcome measures. Balloon dilation is reported to have a success rate of 77-88%,[2-9] but the definition of success can be persistent regurgitation <50% of the original presentation, or the tolerance of any dietary consistency, including those dogs that can only be fed liquid or gruel. A study evaluating the use of bougienage in dogs and cats found a "good" outcome, with tolerance of solid food and minimal regurgitation, in 70% of dogs and 75% of cats.[3]

In the author's experience, a greater success has been achieved since using the combination of endoscopy and fluoroscopy to break each stricture, as a false sense of effacement is commonly seen if endoscopy alone is utilized.

Special Considerations

Esophageal stents should only be considered when traditional dilation attempts have failed.

Alternatives

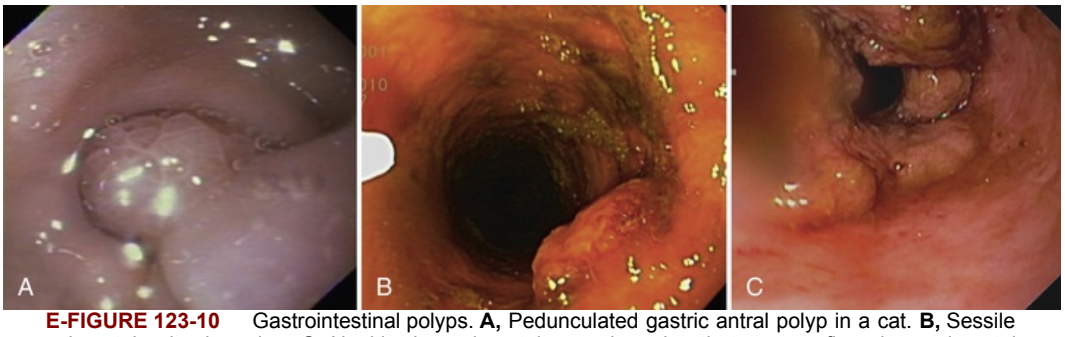
The author has placed an esophageal feeding tube through the lumen of a stricture after balloon dilation to prevent the edges of the stricture from coaptating, in hopes of maintaining a lumen and allowing a mechanism for feeding if the stricture recurs, without the need for a gastrostomy tube. This has been met with good preliminary success, but these data are not published. Another alternative is the use of an experimental device that is currently being investigated using serial balloon dilations daily.

GI Polypectomy/Electrocautery

Indications and Background

Gastrointestinal (GI) polyps are rare findings in veterinary medicine, and are most commonly in the stomach or at the colorectal junction.[24,25,27] In human medicine, malignant transformation of polyps is a major concern, necessitating screening and removal.[28] In dogs, colorectal masses are rare, and when diagnosed are either adenocarcinoma (≈60%), adenomatous polyps (≈20%), or carcinoma *in situ* (≈15%).[24,25] Approximately 18% of diffuse/multiple polyps and 7% of solitary polyps are documented to undergo a malignant transformation in dogs,[24] making timely removal ideal. If the mass is single, sessile or pedunculated, and the biopsy is suggestive of a benign condition like adenomatous polyp or carcinoma *in situ,* then endoscopic polypectomy, with or without endoscopic mucosal resection (EMR), can be recommended. Alternatively, if the mass is atypical (a "napkin ring" or "apple core shape"), poorly marginated, progressing in size and shape, or the histopathology is malignant and invasive, then surgical resection should be recommended.

A polypectomy procedure is one in which you can endoscopically remove a mass lesion with an electrosurgical snare. EMR is used when the polypoid mass is more broad-based and flattened, or sessile, and a "lift" is required in which fluid is injected into the submucosa to separate the mucosa from the muscular layer of the luminal wall, making full resection more effective and safe. Gastrointestinal polyps are typically superficial pedunculated masses with a narrow stalk. Sessile or flattened polyps are more commonly seen in the colon (E-Figure 123-10).



E-FIGURE 123-10 Gastrointestinal polyps. **A,** Pedunculated gastric antral polyp in a cat. **B,** Sessile colorectal polyp in a dog. **C,** Napkin ring colorectal mass in a dog that was confirmed as colorectal adenocarcinoma.

Equipment

Snare polypectomy requires the use of a standard gastrointestinal endoscope with a working channel large enough to accommodate the proper size snare device. This is typically 2.0 or 2.8 mm in diameter. Video gastroduodenoscopy improves visibility and is recommended. For electrocautery, a cautery pad should be placed on the exterior of the patient for grounding. A routine cautery unit with a proper adaptor and foot pedal is required (E-Figure 123-11). A standard endoscopic basket retrieval device is used to remove the polyp. If EMR is to be performed, an injection needle is required, and either saline or methylene blue should be used for the infusion (Figure 123-12 and E-Figure 123-13).

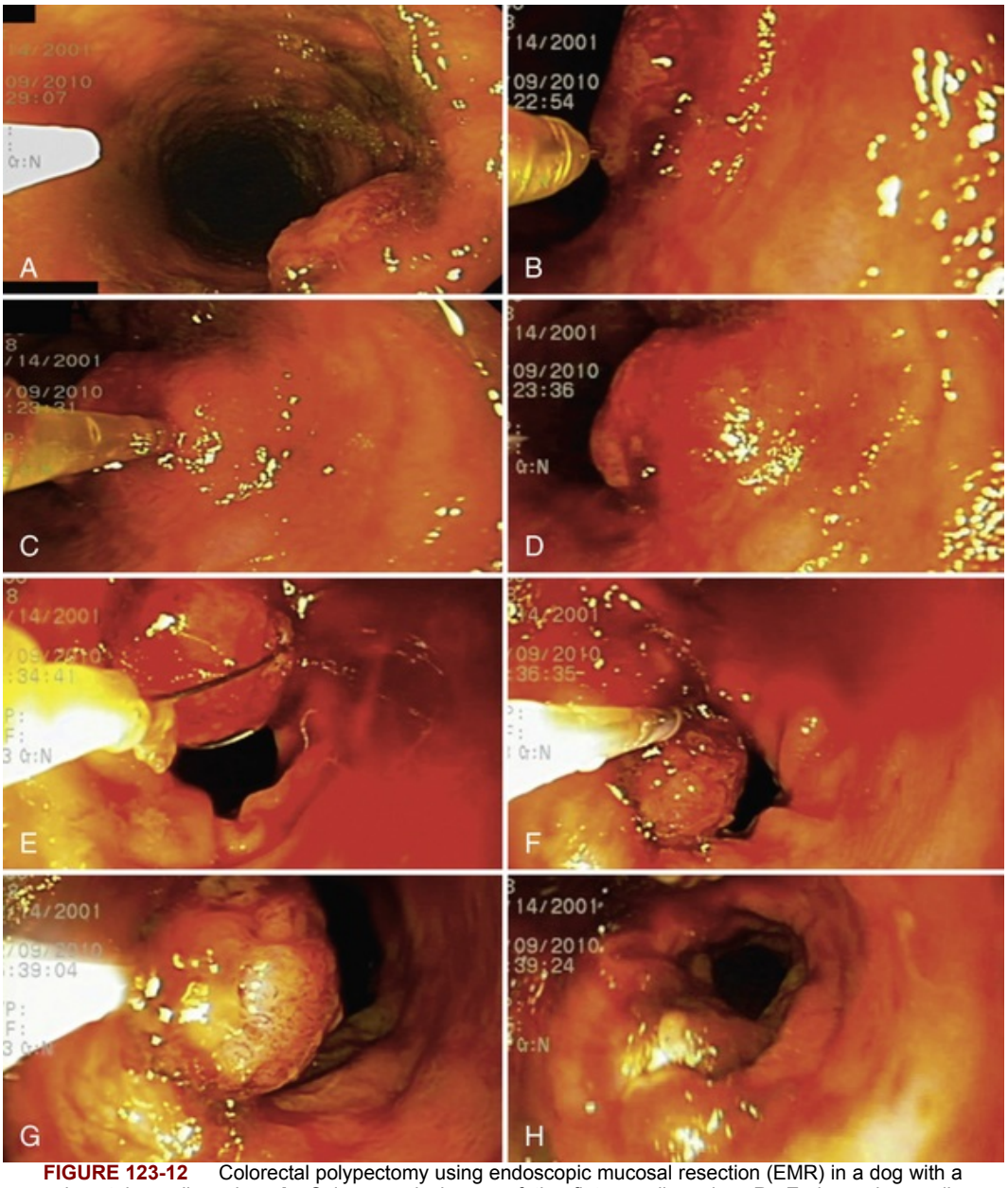
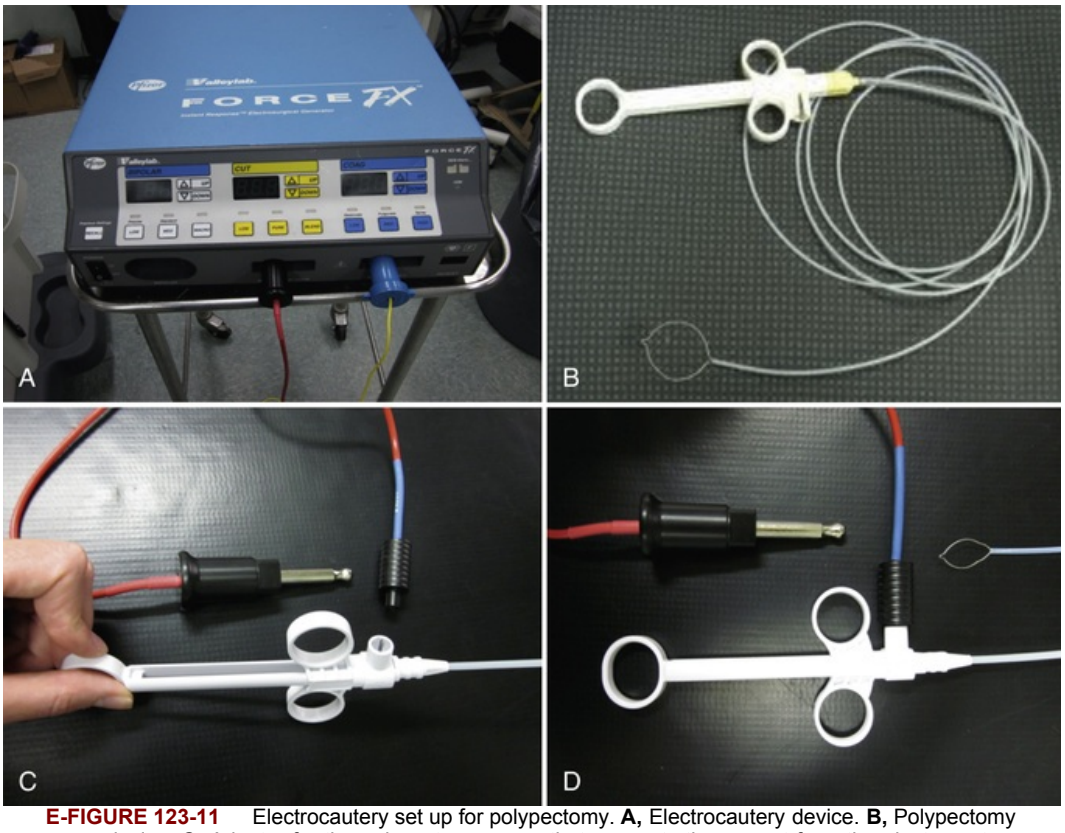
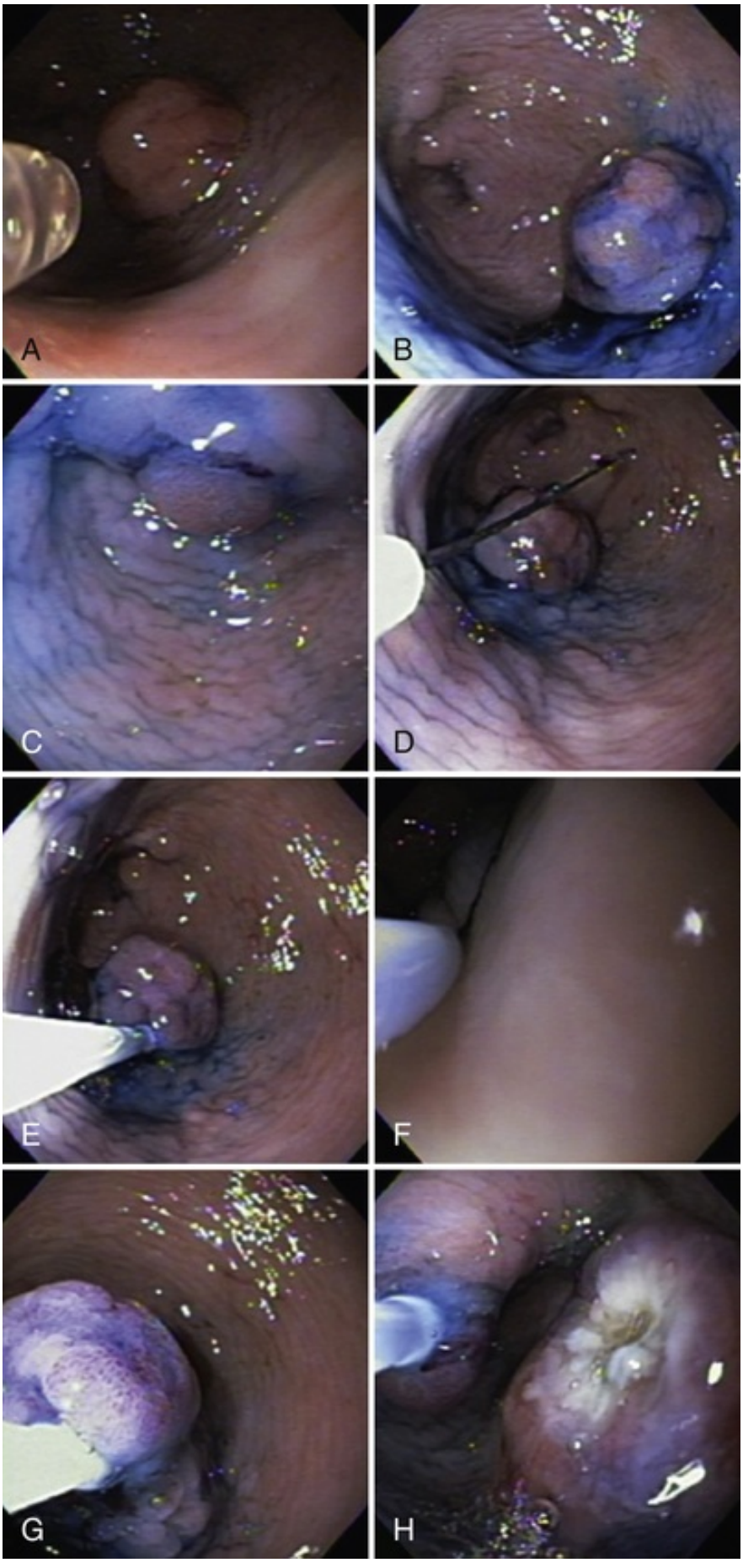


FIGURE 123-12 Colorectal polypectomy using endoscopic mucosal resection (EMR) in a dog with a colorectal sessile polyp. **A,** Colonoscopic image of the flat, sessile polyp. **B,** Endoscopic needle through the working channel of the endoscope as it approaches the base of the polyp. **C,** The needle inserted under the base of the polyp in the submucosal tissue as saline is injected between the tissue planes. **D,** A lift is performed creating a more pedunculated mass. **E,** Endoscopic polypectomy snare being placed around the polyp. **F,** The snare is engaging the base of the polyp at the lift site. **G,** Electrocautery is activated at the base. **H,** A clean base after polypectomy showing a mucosal defect with minimal hemorrhage. (From Weisse C, Berent A: *Veterinary image-guided interventions*, Hoboken, NJ, 2015, John Wiley & Sons, Inc.)



E-FIGURE 123-11 Electrocautery set up for polypectomy. **A,** Electrocautery device. **B,** Polypectomy snare device. **C,** Adaptor for the polypectomy snare that connects the current from the electrocautery unit to the metallic wire of the snare. **D,** Adaptor connected to the polypectomy snare.


A
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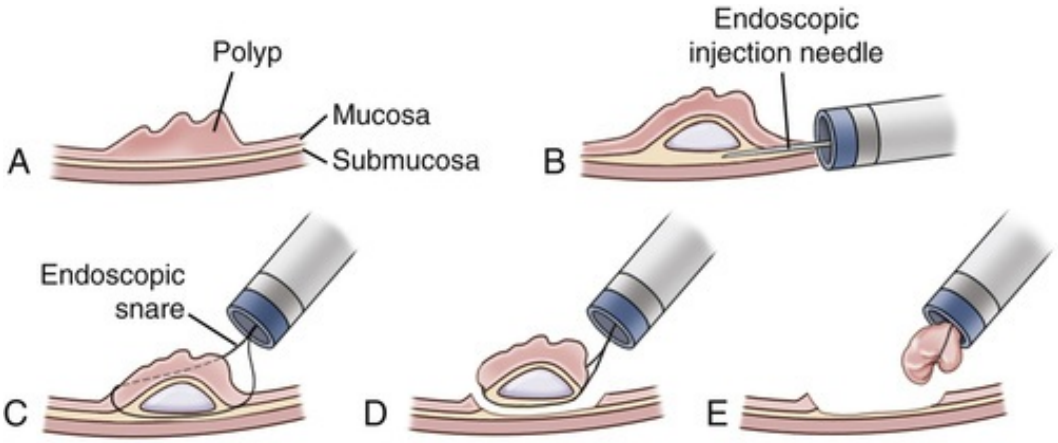
E-FIGURE 123-13 Gastric polypectomy using endoscopic mucosal resection and methylene blue injection. **A,** Polypoid mass in the stomach of a cat. **B,** Saline and methylene blue is injected at the base of the mass. **C,** Lift of the lesion. **D** and **E,** The snare encircles the lesion and is closed down at the base. **F,** Perpendicular positioning of the snare helps to encompass the base of the lesion. **G,** Cautery is applied and discoloration of the polyp can be observed before removal. **H,** Removal of the polyp from the surface of the stomach with the lesion free within the gastric lumen. (From Weisse C, Berent A: *Veterinary image-guided interventions*, Hoboken, NJ, 2015, John Wiley & Sons, Inc.)

Sessile polyps may require the use of an over-the-scope EMR cap. These allow suction to be applied to a lesion to more successfully perform the EMR and submucosal infusion during electrocautery (E-Figure 123-14).



E-FIGURE 123-14 **A-E,** Endoscopic mucosal resection with a plastic cap (EMRC).

Techniques

Each patient should be treated with broad-spectrum antibiotics, covering for intestinal microflora, and the patient should be prepared for a standard gastroscopy or colonoscopy. A thorough gastroscopy or colonoscopy should be performed to identify the location, size, shape and appearance of each polyp. If a flat or sessile polyp is seen, then a saline lift is done to see if it easily moves away from the submucosa. If it does, this is often a sign that the lesion is superficial and a polypectomy is indicated[29-31] (Video 123-2).

For sessile or flattened lesions, a "fluid" lift can be done using either saline, 5% dextrose in water (D5W), or a mixture of D5W and epinephrine and/or methylene blue. A 1 : 9 solution of epinephrine (0.1 mg/mL): D5W and then 1-2 drops of methylene blue is useful.[29] The blue color is often not taken up by the polypoid lesion, only the submucosal tissue, making a clear demarcation between the normal and abnormal tissues during resection.

The mass is manipulated to assess the base and determine if a lift is needed (see Figure 123-12).[27] If a lift is necessary then an endoscopic injection needle is inserted under the base, into the submucosal layer, and a fluid pocket is created. A "bleb" should be clearly visualized (see Figure 123-12, *C* and *D*). Then the snare device is placed around the base of the mass, including the bleb. This bleb allows a deeper cauterization while protecting the muscular layers from thermal burn and perforation. The snare device is attached to the electrocautery unit. The unit is set to monopolar coagulation at a power of 15-20 watts. Caudal traction is placed on the mass to protect the distal cranial wall. Once removed, the site is thoroughly evaluated with endoscopic visualization, insufflation, +/− contrast, to ensure there is no perforation. If any questionable areas are seen, and tissue integrity is lost, then endoscopic clips can be used to secure any defects. This technique is similarly done in the stomach for gastric lesions (see E-Figure 123-13).[32-34] It is harder to perforate the stomach than the colon during a polypectomy due to the relative thickness of the tissue. If a lesion is sessile, then an EMR can be done using a transparent plastic cap (EMRC, see E-Figure 123-14), allowing suction to pull the lesion away from the wall for a deeper cauterization.

Follow-up

After polypectomy, patients are typically discharged the same day. After colorectal polypectomy, metronidazole is recommended along with a high fiber diet. Rectal examinations to examine the location of polypectomy can be considered every 3-6 months. For gastric polyps, a proton pump inhibitor and canned food are recommended for a few days.

Complications

Perforation of the GI tract, hemorrhage, recurrence and incomplete resection are possible but rare. A post-polypectomy syndrome is reported in human medicine[29-34] resulting from transmural burning and late perforation. With experience, and the availability of EMR, the incidence of these complications has reduced dramatically.[30,31]

Outcome

Once complete excision for a benign mass is accomplished, the prognosis for recovery and resolution of hematemesis, vomiting, hematochezia or tenesmus is excellent.[29-34]

GI Stenting

Indications and Background

Obstructions of the GI tract secondary to strictures or tumors occur most commonly in the descending colon at the colorectal junction (see ch. 277 and 278).[25,35-38] Tumors have also been seen at the gastric cardia, pyloric antrum, and proximal duodenum.[39,40] In humans, stenting of GI malignant obstructions is commonly reported, and is typically considered as a palliative treatment for nonresectable neoplasia, or as a "bridge" to a more definitive surgery, providing immediate endoluminal decompression and improved quality of life.[37-40] If surgery is contraindicated, or not possible, stenting is considered a good long-term solution, with clinical success rates approaching 90%, and technical success rates as high as 92-100%.[37-40]

Gastroduodenal stenting of the stomach or duodenum is not commonly performed in veterinary medicine. It has been done for malignant obstruction of the gastric cardia, pyloric outflow tract, and duodenum in the author's practice. Stenting should be reserved for cases where traditional surgical resection is not recommended. The location of the major and minor duodenal papillae should be appreciated prior to duodenal stenting as compression of a tumor in this region could result in a biliary or pancreatic duct obstruction. If the lesion is obstructive, resulting in vomiting and malnutrition, then stents are the most useful.

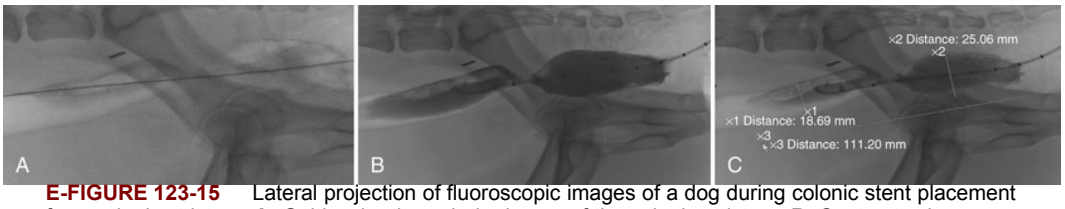
Feline GI adenocarcinoma is an aggressive form of GI neoplasia, most commonly found at the colorectal junction (see ch. 278). It is associated with distal metastasis 75% of the time, making partial colectomy a difficult treatment option. If a colectomy is performed, cats with metastasis had a much lower median survival time (MST) than those without (49 and 259 days, respectively).[41,42] Outcomes in dogs after partial colectomy had a longer MST (22 months) than those that did not have surgery (15 months).[25]

In both dogs and cats palliative stenting[35,36] can be considered, and is often chosen over more aggressive surgeries due to the outpatient nature, minimal morbidity, and low complication rates. Stenting will only be useful to treat obstipation caused by the obstructive lesion.

Colonic strictures have been treated with stents as well.[37,38] For strictures, covered stents are typically used due to the high risk of ingrowth of tissue. Migration is the biggest problem with covered, retrievable stents (>60%), and stricture recurrence can be seen after stent removal in approximately 50%.[37,38]

Equipment

Standard flexible GI endoscopes are needed. If the stent is to be placed through the working channel of the endoscope, then an appropriately sized delivery system must be used. The scope is used to evaluate and biopsy the lesion, and pass a guide wire (0.035" hydrophilic angle-tipped 260 to 400 cm long) through the lumen of the obstruction, and then standard fluoroscopy is used to monitor the guide wire and accurately deploy the stent. A marker catheter is used to estimate the luminal diameter and obstruction length so an appropriate stent size can be chosen (E-Figure 123-15).



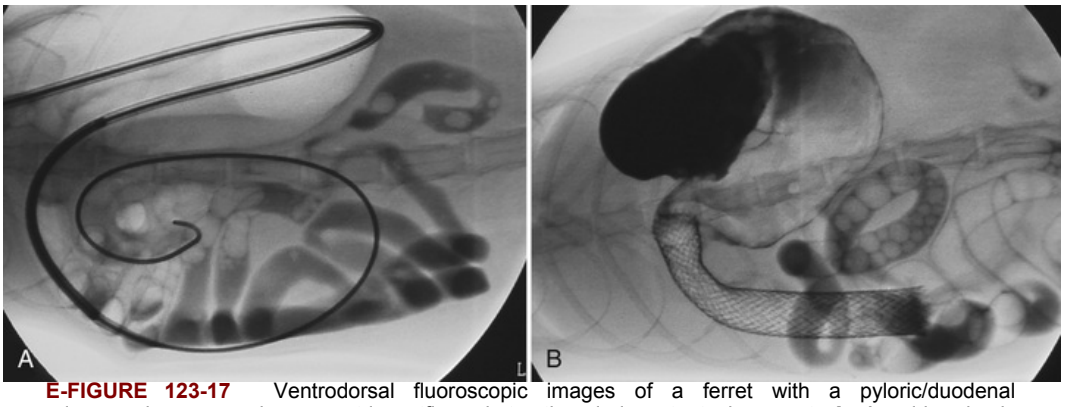
E-FIGURE 123-15 Lateral projection of fluoroscopic images of a dog during colonic stent placement for a colonic stricture. **A,** Guide wire through the lumen of the colonic stricture. **B,** Contrast colonogram using a marker catheter across the stenosis for measurement of the colonic lumen. **C,** Using the marker catheter for magnification, the diameter and length of the colon and stent location are measured.

Gastrointestinal stents are typically woven, metallic, and self-expanding. Some stents are covered and others uncovered. The uncovered stents are typically used for malignant obstructions, whereas a covered stent is for strictures. Colonic stents have a flare at the distal end to prevent aboral migration (E-Figure 123-16). Covered stents have a string at one end to endoscopically retrieve the stent.

E-FIGURE 123-16 A covered gastrointestinal stent. Notice the dog-bone shape to the stent to prevent migration and the string on the end of the stent for removal.

Techniques

Gastroduodenal stenting (E-Figure 123-17) is performed by gaining access across the obstructive lesion using fluoroscopy and gastroduodenoscopy (see also ch. 113). A guide wire is advanced through the working channel of the endoscope, in the GI lumen, and through the lumen of the tumor. Using fluoroscopic guidance, the wire is advanced aborad beyond the obstruction. Next, the endoscope is removed over the wire, as the wire is monitored under fluoroscopic visualization to ensure it remains across the obstruction. A marker catheter is advanced over the guide wire and a contrast study is done to measure the diameter of the lumen and the length of the obstruction for appropriate stent sizing. Once the stent is chosen, it is deployed under fluoroscopic guidance. In some instances for upper GI stenting it is deployed through the working channel of the endoscope for stent positioning. The endoscope is then used to assess stent location and contrast can be used to confirm luminal patency.



E-FIGURE 123-17 Ventrodorsal fluoroscopic images of a ferret with a pyloric/duodenal adenocarcinoma causing a gastric outflow obstruction during stent placement. **A,** A guide wire is advanced from the mouth, into the stomach, across the pylorus and duodenum and into the proximal jejunum. Over the wire is the delivery system with a non-deployed self-expanding woven metallic stent placed across the obstruction. **B,** The SEMS after deployment documenting patency of the proximal duodenum and pylorus. (From Weisse C, Berent A: *Veterinary image-guided interventions*, Hoboken, NJ, 2015, John Wiley & Sons, Inc.)

Colonic stenting (Figure 123-18 and E-Figure 123-19) is performed using colonoscopic guidance similar to that described above. Using a marker catheter, a colonogram is performed and an appropriate stent size is chosen. The stent is then deployed, being careful to prevent it from being more caudal than the rectoanal junction (see Figure 123-18 and E-Figure 123-19). Once the stent is deployed, the endoscope is advanced into the colon to ensure proper placement. If the stent is covered, the distal end can be sutured to the rectal mucosa to prevent stent migration.

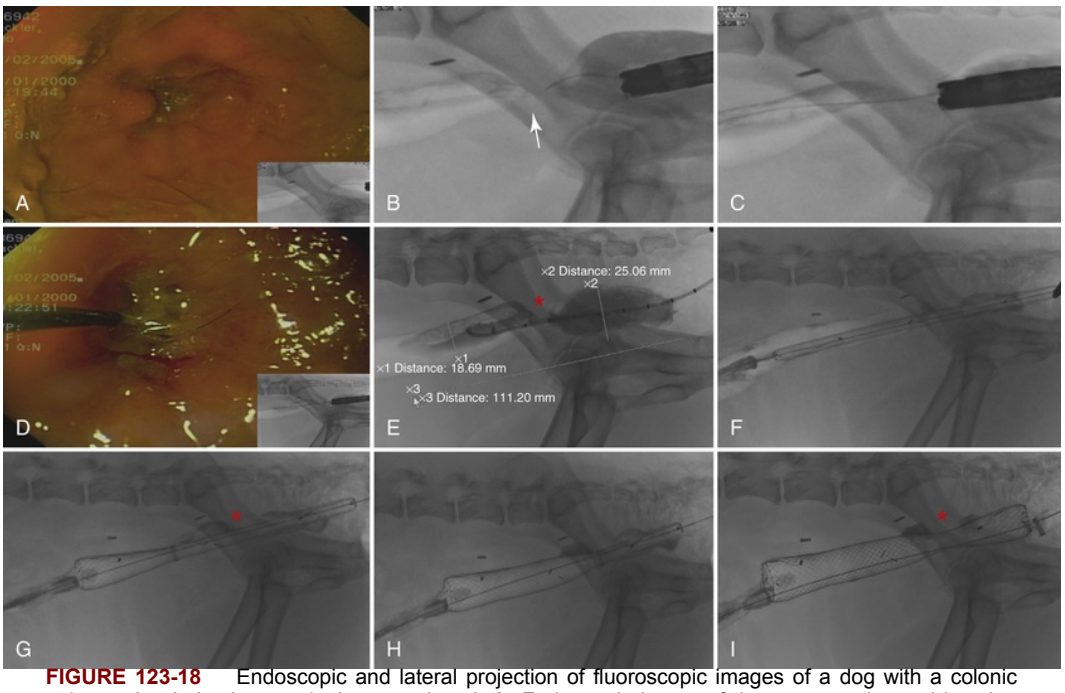
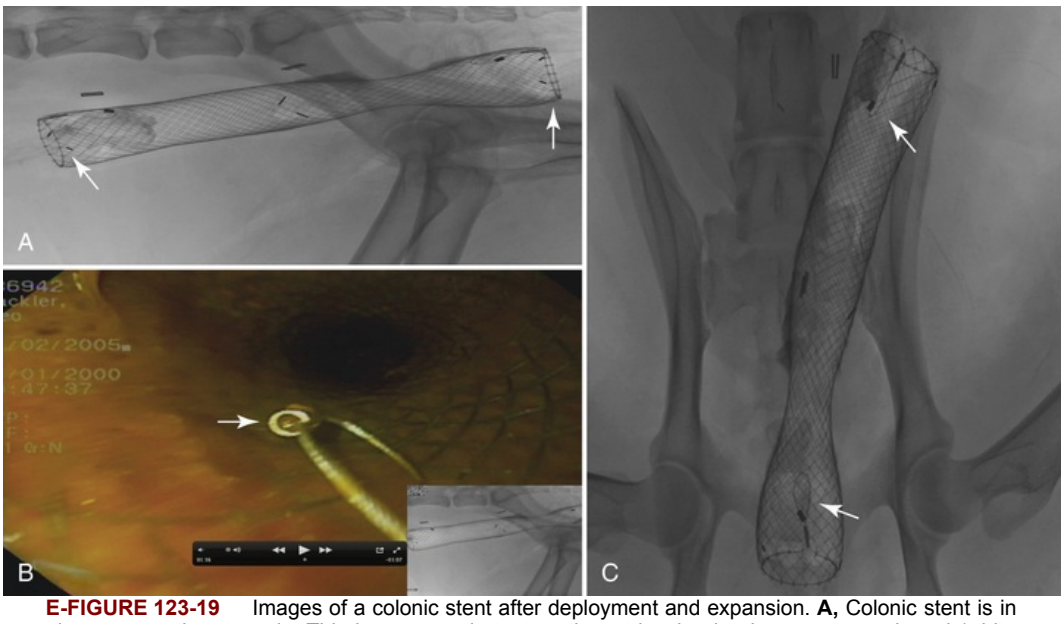


FIGURE 123-18 Endoscopic and lateral projection of fluoroscopic images of a dog with a colonic stricture that is having a colonic stent placed. **A,** Endoscopic image of the severe colorectal junction stricture. **B,** Fluoroscopic image of a guide wire entering the lumen of the stricture (white arrow) during colonoscopy. **C,** Wire through the lumen of the stricture. **D,** Endoscopic image of the wire entering the lumen of the stricture. **E,** Marker catheter through the lumen of the stricture (red asterisk) as contrast is injected to measure the colonic diameter. **F,** Stent in the delivery system placed over a guide wire imaged on a lateral projection during fluoroscopy. **G,** Deployment of the stent across the stenosis (red asterisk) under fluoroscopic guidance. **H,** Stent as it is being deployed across the stricture. **I,** Fluoroscopic image of the stent after it is fully deployed. Red asterisk is the location of the stricture.



E-FIGURE 123-19 Images of a colonic stent after deployment and expansion. **A,** Colonic stent is in place across the stenosis. This is a covered stent so the retrieval string is seen on each end (white arrows). **B,** Endoscopic image of colonic stent after deployment. Notice the retrieval string (white arrow) at the distal end. You can see the colon is now patent. **C,** A ventrodorsal image of the colonic stent after deployment with the retrieval strings (white arrows).

Follow-up

Patients with gastroduodenal stents should be fed small meals often for the first few days. For gastric cardia stents, antacid therapy and antiemetics should be continued aggressively. Patients with colonic stents are treated with a low residue diet, stool softeners, and broad-spectrum antibiotics.

Complications

Tissue ingrowth into an uncovered stent and migration of a covered stent are the most common complications seen in both human and veterinary medicine. Fecal incontinence of colorectal stenting can occur, but is rarely seen if the stent is positioned in front of the anus. For colonic tumors, tenesmus can be associated with infiltration of the pelvic nerves, and despite de-obstipation being successful with the stent, continued straining and discomfort may be seen.

Other potential complications, that have not yet been seen in the author's experience, include GI perforation, irritation, intractable tenesmus, persistent vomiting, stent shortening and associated re-obstruction, and hemorrhage.

Outcome

Only a small number of dogs and cats have had stents placed in both the upper and lower GI tract. For colonic stenting, the MST for malignancy in our cases was approximately 6 months (range, 19-274 days). Patients with malignancy died of distant tumor effects.

Special Considerations

Stents placed for GI obstructions will benefit the patient, but if the patient is straining or vomiting due to the presence of the disease and the local effects on the nerves, rather than a physical obstruction, then a stent will likely not help.

Endoscopic Retrograde Cholangiography and Biliary Stenting (ERC/BS)

Indications and Background

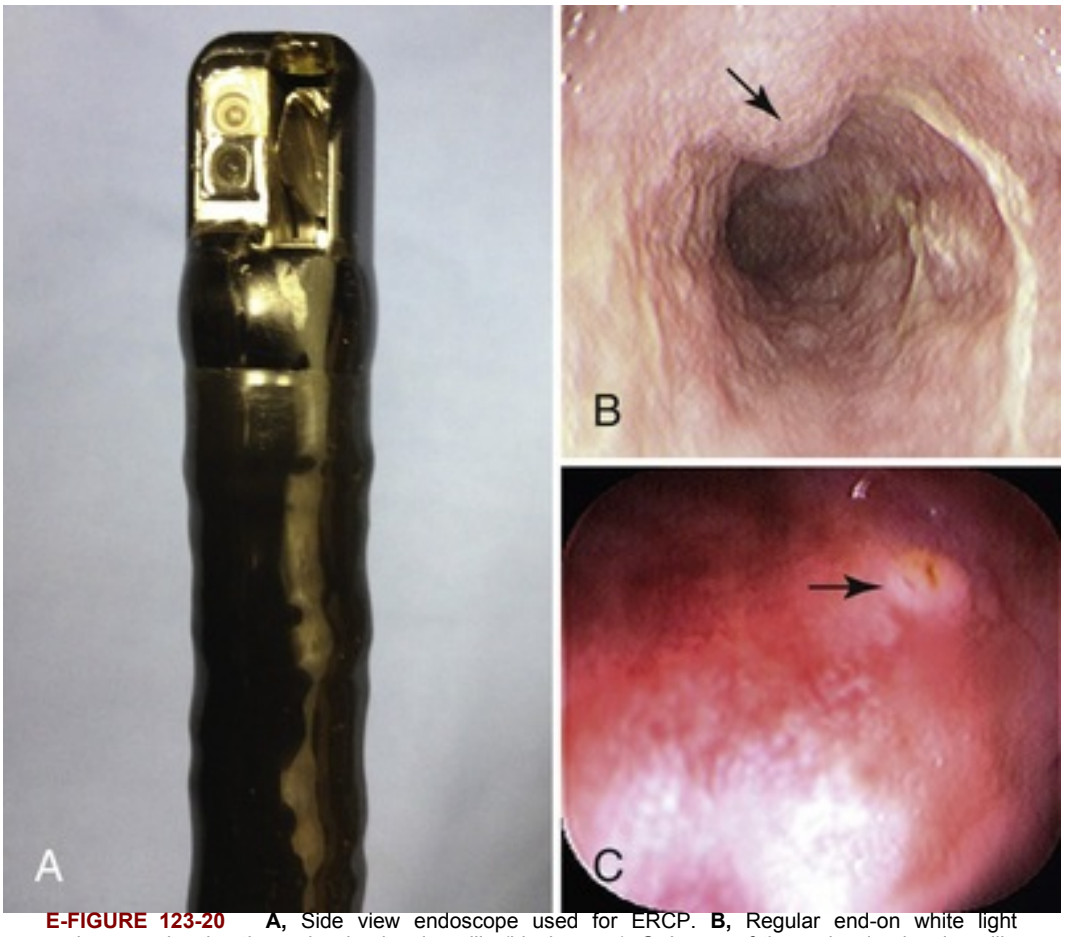
Diagnostic imaging using endoscopic retrograde cholangiopancreatography (ERCP) was first reported in

veterinary patients in 2005.[43-46] This series reported on diagnostic ERCP in 30 clinical dogs with vague GI signs, showing success to be associated with the size of the patient.[43] Then, in 2014 the same group reported on diagnostic ERCP in 4 research cats.[46] The first report of the use of endoscope retrograde cholangiography (ERC) with decompressive biliary stenting (ERC/BS) for the treatment of an extrahepatic biliary duct obstruction (EHBDO) was more recent.[47] ERCP is a minimally invasive technique that combines endoscopy and fluoroscopy to image the extrahepatic biliary system and pancreatic ducts. In the last few decades ERCP has been considered the best option for improving the diagnosis, and simultaneous treatment, of biliary and exocrine pancreatic diseases in humans.[48,49] Traditional surgical treatment options in veterinary medicine have been met with high surgical mortality rates in dogs and cats, ranging between 25-73% and 50-75%, respectively, and are discussed in more detail in ch. 280, 281, and 288.[50-53] In humans, similar problems have encouraged less invasive treatments like ERCP and biliary stenting.[48,49]

Cannulation of the duodenum was possible in 8 of 9 dogs, ERC was successful in 6 of 9 dogs, and stent placement was possible in 5 of 6 dogs recently.[47] This study was performed prior to using the pediatric ERCP scope, which improves duodenal cannulation, making procedure success higher for the smaller patients. None of these procedures were met with any major complications. This procedure is considered very difficult and should ideally be done in stable patients by someone well experienced with pediatric ERCP.

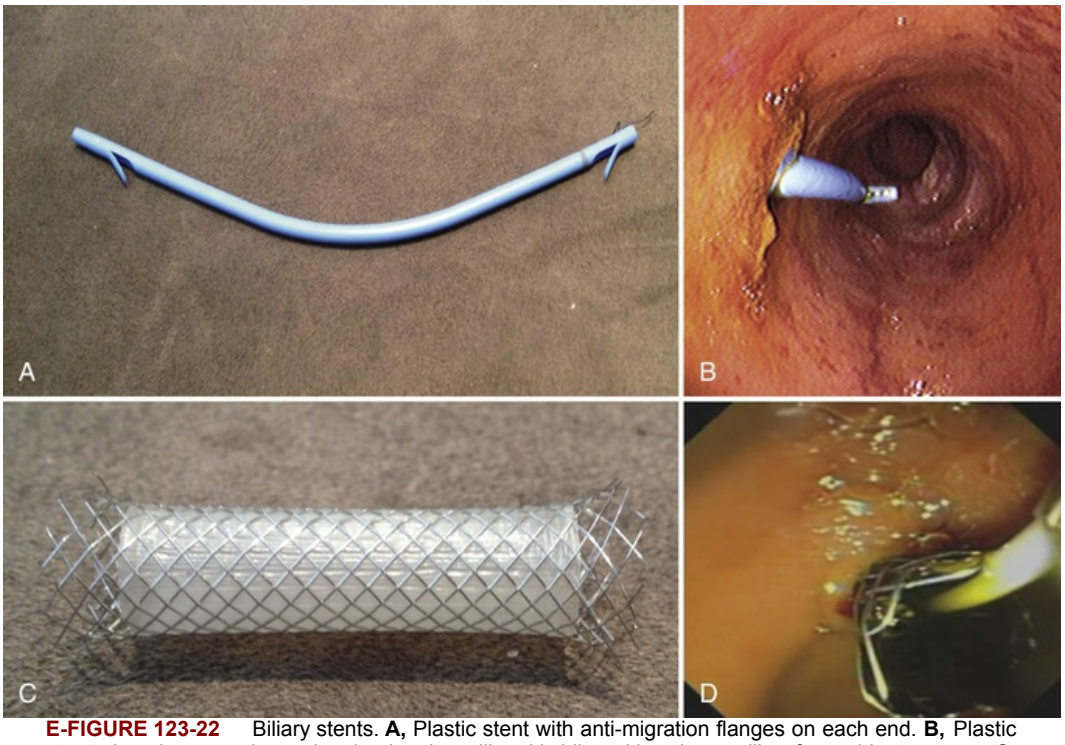
Equipment

A side-view duodenoscope (E-Figure 123-20) is required to perform this procedure and it is available in two sizes, 11.3 mm and 7.5 mm. The smaller pediatric scope has a smaller working channel (2.0 versus 3.2 mm), only accommodating smaller instruments (wires, catheters, and stents). A fluoroscopic C-arm is needed for visualization of the common bile duct (CBD) and gallbladder during the ERC/BS. A sphincterotome catheter appropriately sized for the endoscope is needed for cannulation of the major duodenal papilla (MDP). An exchange length soft-tipped guide wire is needed (typically 480 cm long). An electrocautery unit, with foot pedal and hand adaptor, is needed if sphincterotomy is to be performed (E-Figures 123-11 and 123-21). Various types of biliary stents are available, including both plastic and metallic (E-Figure 123-22). The polyurethane plastic stents have antimigration flanges to prevent migration. These stents are considered temporary and can be removed endoscopically with gentle traction. The metallic stents are self-expanding in design and typically permanent (if uncovered). The stent must fit through the working channel of the endoscope (3.2 mm in the larger scope and 2.0 mm for the smaller scope) and be long enough for the endoscopic deployment (typically a delivery system of 180 cm).



E-FIGURE 123-20 **A,** Side view endoscope used for ERCP. **B,** Regular end-on white light endoscopy showing the major duodenal papilla (black arrow). **C,** Image of the major duodenal papilla (black arrow) using side-view duodenoscope.

E-FIGURE 123-21 **A,** Sphincterotome used for ERC. The black arrow indicates the electrocautery wire. **B,** Guide wire used for ERC with the tigerstripe coloring to help monitor the wire for migration during cannulation, exchange and stent placement.



E-FIGURE 123-22 Biliary stents. **A,** Plastic stent with anti-migration flanges on each end. **B,** Plastic stent placed across the major duodenal papilla with bile exiting the papilla after sphincterotomy. **C,** Covered metallic stent. **D,** Metallic stent across the major duodenal papilla after stent deployment with bile exiting the lumen of the common bile duct.

Techniques

The differing anatomy of dogs and cats should be appreciated before considering this procedure (E-Figure 123-24). The patient is placed under general anesthesia in left lateral recumbency. Previous reports recommend *dorsal recumbency for cats*[46] and *sternal recumbency for dogs*,[43-45] but the author has found left lateral recumbency to work well. The side-view duodenoscope is placed into the stomach and the duodenum is entered. In cats, it has been recommended to use diluted topical methylene blue for better visualization of the MDP.[46]

Once the MDP is visualized (Figure 123-23), the sphincterotome catheter is angled to cannulate the CBD using the working channel lever and the sphincterotome wire. Once the catheter is positioned into the opening of the MDP, the guide wire is used to advance up the duct to document proper placement and ensure the CBD is entered. Once the wire is seen going up the CBD on fluoroscopy, the catheter is advanced and a bile sample is taken for culture and cytology. Then, a retrograde contrast study is done using a 50% mixture of iohexol : saline. The CBD can accommodate 5-10 mL of contrast, but the pancreatic duct should not be injected with more than 1-2 mL. Once the CBD is visualized, the guide wire is readvanced through the sphincterotome into the CBD until it is beyond the obstructive lesion, and into an intrahepatic duct or the gallbladder. Then the appropriately-sized biliary stent is advanced over the wire, through the working channel of the endoscope, and into the CBD, traversing the opening of the CBD at the MDP into the duodenum (see E-Figure 123-22 and Figure 123-23). Typically, feline patients accommodate a 5 French (Fr) plastic stent, and canine patients vary depending on their size (6-8.5 Fr plastic or 6-8 mm SEMS). In the author's experience, the length of the stents required in cats has been 3-5 cm long, and in dogs is 4-12 cm long. The length is measured fluoroscopically using the sphincterotome or the endoscope to adjust for magnification. Plastic stents are deployed using a pushing catheter through the endoscope, over the guide wire. The delivery system of the metallic stent is ensheathed using endoscopic and fluoroscopic guidance over the guide wire, ensuring the distal end of the stent crosses the MDP and approximately 5 mm of the stent is within the duodenal lumen (Video 123-1).

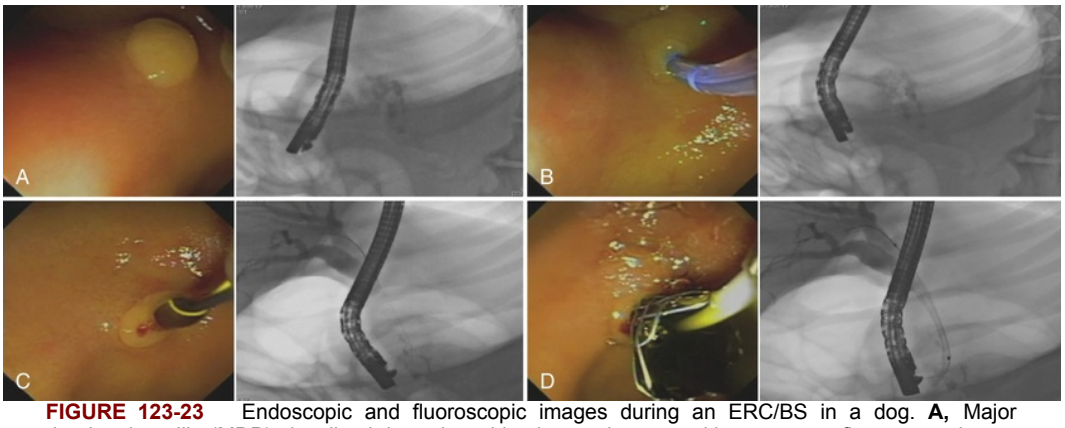


FIGURE 123-23 Endoscopic and fluoroscopic images during an ERC/BS in a dog. **A,** Major duodenal papilla (MDP) visualized through a side-view endoscope with concurrent fluoroscopy image being used simultaneously. **B,** Cannulation of the MDP with a sphincterotome visualized under endoscopy and fluoroscopy simultaneously. **C,** Guide wire cannulating the MDP and up the CBD visualized in both endoscopic and fluoroscopic images. Notice the contrast material in the severely dilated intrahepatic ducts. **D,** Stent deployed in the CBD and exiting the MDP visualized on both endoscopy and fluoroscopy simultaneously.

For benign and temporary conditions like pancreatitis, a plastic stent is recommended as it can be easily removed endoscopically.[48,49] If a tumor or stricture is present, then a covered metallic stent is recommended in humans.[48,49] In veterinary medicine, uncovered metallic stents have been used in 2 dogs and 2 cats with success, all of which were for biliary strictures of the CBD. Sphincterotomy is recommended by some physicians for distal MDP strictures, but this is not routinely used in veterinary medicine.

Follow-up

After successful biliary stenting, most patients will need standard supportive therapy for pancreatitis, perioperative antibiotics, and ursodeoxycholic acid (UDCA; ursodiol) supplementation. Once the patient is discharged broad-spectrum antibiotics are continued for 6 weeks. Serial hepatobiliary ultrasound and blood work is recommended (1 week, 1 month, then every 3 months for 1 year, then every 6 months thereafter). For permanent stents, the author continues UDCA and metronidazole therapy for life.

Complications

During ERCP, pancreatitis can be induced by infusing the pancreatic duct with contrast material, and care should be taken before any contrast study is done, knowing the anatomy of which papilla is being cannulated (major or minor duodenal papilla), and knowing the direction of the wire for the common bile duct versus the pancreatic duct at the orifice of the major duodenal papilla (E-Figure 123-24). Pancreatitis is induced in 5-20% of people during ERCP.[48,49] Additionally, perforation of the duodenum, CBD or pancreatic duct, bleeding, and biliary reflux into the intrahepatic ducts is possible with cannulation, sphincterotomy, and retrograde infusions, respectively.

Outcome

To date, few clinical cases in veterinary medicine have had ERC/BS performed, with only 7 research dogs and 2 canine patients reported.[47] In the author's practice, 8 patients (5 dogs and 3 cats) have had ERC/BS attempted. Four of 5 dogs and 1 of 3 cats were successful endoscopically and the liver biochemical parameters returned to baseline following decompression over the long term. The one failed canine patient had a large mass at the MDP, making cannulation not possible. The size of these patients ranged from 2.7 kg up to 41 kg. All patients survived to discharge and the first dog that had ERC/BS performed survived for over 2 years.

Alternatives

The author has been investigating the use of a subcutaneous intestinal biliary bypass device (SIBB) for bypass of the biliary tract using a cholecystostomy tube connected subcutaneously to a duodenostomy tube using a shunting port. To date, the experience with this device is still elementary and is currently under clinical

investigation. Externalized cholecystostomy tubes are also a temporary option (see Figure 123-27).[54]

PT(C)E: Percutaneous Transvenous (Coil) Embolization

Indications and Background

Portosystemic shunts (PSS) are vascular anomalies connecting the portal vein to the systemic circulation, resulting in a gamut of clinical signs. Intrahepatic portosystemic shunts (IHPSS) represent a much more complex correction than that of extrahepatic portosystemic shunts (EHPSS) due to their large size, and intrahepatic location.[55,56]

Pre-operative imaging including CT angiography can be very useful to help plan the surgical or interventional procedure. Various surgical options[55-61] have been described (see ch. 284) but this section will focus on percutaneous transvenous (coil) embolization (PT(C)E) via the jugular vein for the treatment of both IHPSS and specific types of EHPSS. Some techniques for PTE use various other devices for embolization, like vascular plugs, but coils are the most common device used.[62]

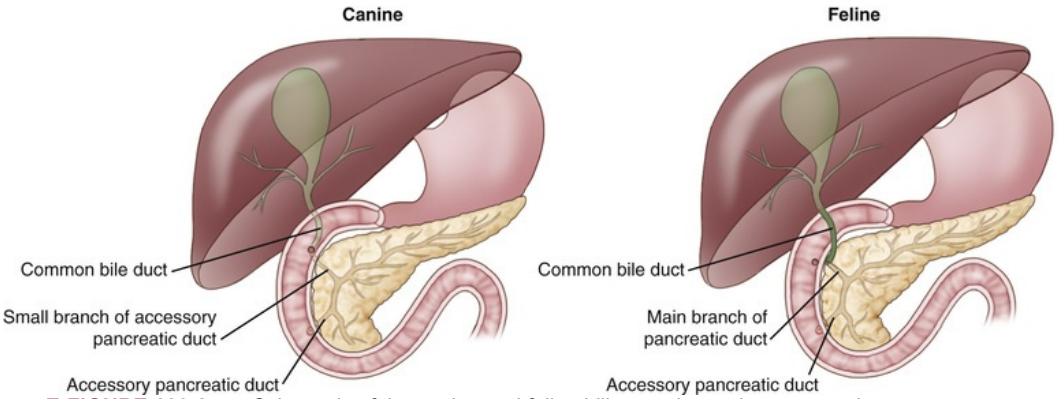
Interventional treatment has become far more common for the treatment of IHPSS in the last decade due to the higher complication rates seen with surgical treatment of IHPSS (29-77%)[57,58,60,61] compared to EHPSS (0-23%).[58-60,63] Percutaneous transvenous (coil) embolization (PT(C)E) has been described from various institutions within the past decade, with the largest series most recently reporting 100 dogs.[62] Similar intravascular techniques have been described for treatment of both IHPSS and EHPSS, in both dogs and cats, and for both partial and complete attenuation.[62,64] The peri-operative complications rates were much lower with the PT(C)E procedure, with similar long-term clinical results as that previously reported with surgical correction for those dogs that survived the surgery.

Equipment

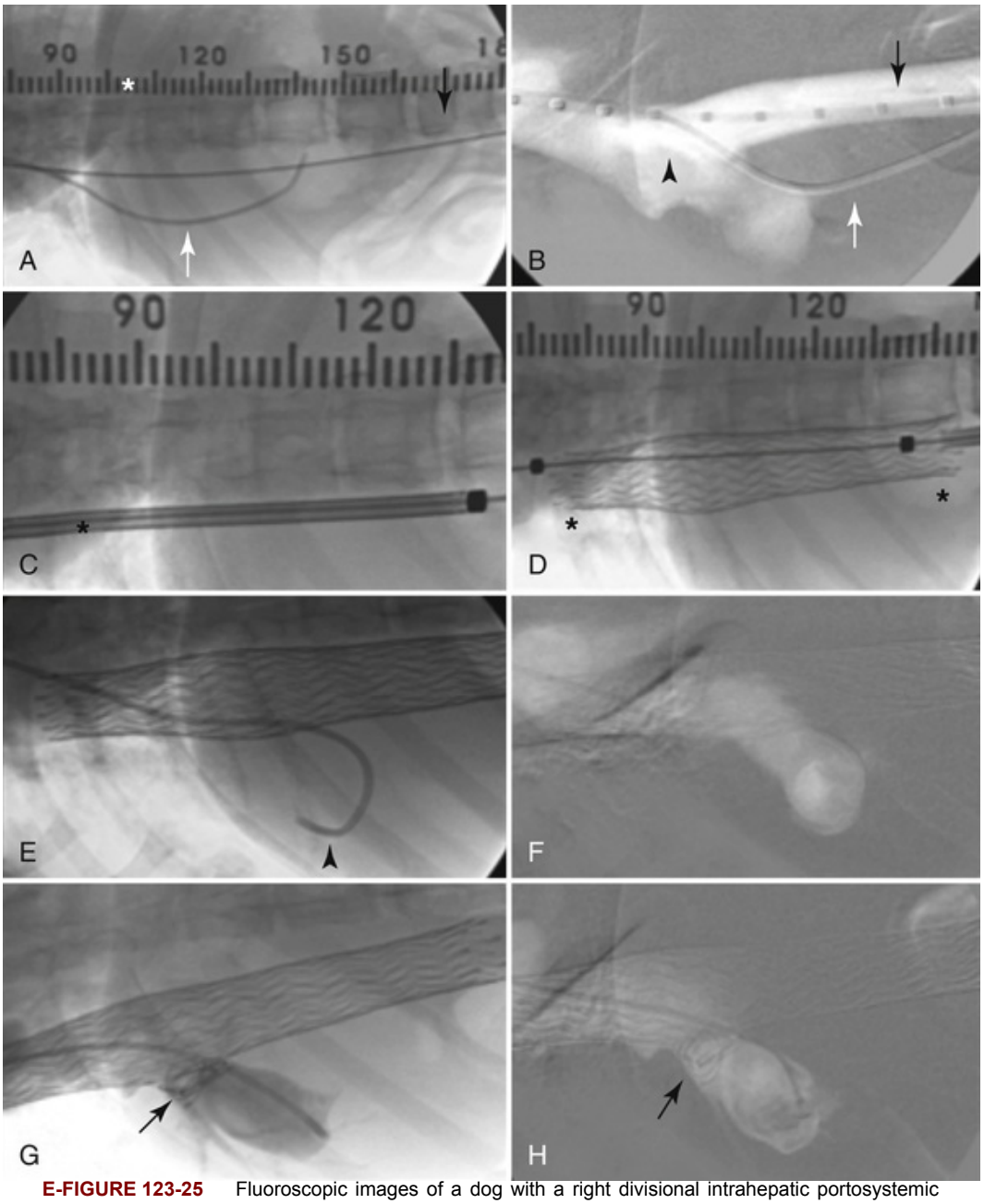
Equipment needed for PT(C)E includes a high-quality fluoroscopy unit that allows digital subtraction angiography (DSA). Various angiographic catheters (Cobra catheter, Berenstein catheter, marker catheter for measuring, various guide wires, embolic coils, and laser cut caval stents) are needed for this procedure. For cases where complete vascular occlusion is possible, then a vascular plug might be used. The standard coil used is a 0.035″ 8 mm diameter and 5 cm length stainless steel coil. Contrast is typically used at a dosage of 2-4 mL/kg and is diluted to a 50% mixture with sterile saline.

Techniques

Patients are placed under general anesthesia using drugs safe for liver dysfunction. Perioperative antibiotics are used before and during the procedure, and broad-spectrum antibiotics are continued for 2 weeks following the procedure. Patients are placed in dorsal recumbency and jugular access is obtained, through the right jugular vein. A radiopaque stent guide is placed under the dog on the fluoroscopy table to aid in stent deployment (E-Figure 123-25). The neck is clipped, aseptically prepared, and sterilely draped. Percutaneous jugular access is obtained through the placement of a vascular access sheath. A hydrophilic guide wire is advanced through the catheter, into the cranial vena cava, through the right atrium and then into the caudal vena cava. Next, the angiographic Cobra catheter is advanced over the wire and the shunting vessel is carefully selected until the portal vein is cannulated. Digital subtraction venography is performed to confirm the location and anatomy of the portal vein and shunting vessel. Then, a positive pressure caudal cavagram under positive pressure ventilation and a simultaneous caudal vena cavagram and portogram is performed using a marker catheter to measure for stent size. Portal venous pressures are obtained and compared to the central venous pressures in the caudal vena cava. If the resting portal pressure is greater than 16 mm Hg (21 cm H_2O) or the portal vein and CVP gradient is greater than 8 cm H_2O, then the procedure is not performed. If these pressures are under these parameters, then the portal vein catheter is removed and the marker catheter is removed over a polytetrafluoroethylene (PTFE, Teflon) guide wire for stent placement.



E-FIGURE 123-24 Schematic of the canine and feline biliary and exocrine pancreatic tracts.



E-FIGURE 123-25 Fluoroscopic images of a dog with a right divisional intrahepatic portosystemic

shunt during percutaneous transvenous coil embolization. **A,** Guide wire is down the caudal vena cava (black arrow) and a catheter is in the shunt (white arrow) through the right hepatic vein. A stent guide is under the dog (white asterisk). **B,** A dual angiogram using digital subtraction angiography (DSA) of the caudal vena cava (black arrow) and the shunt (white arrow). Notice where they come together at the caudal vena cava (black arrowhead). **C,** Stent on the delivery system in the caudal vena cava (black asterisk). **D,** Stent after deployment (black asterisks). **E,** Catheter (black arrowhead) placed through the interstices of the stent to place coils in the right hepatic vein. **F,** Angiogram showing the mouth of the shunt is covered by the stent. **G,** Coils (black arrow) inside the right hepatic vein being caged off by the stent. **H,** DSA study after coils are deployed (black arrow).

Next, the stent is deployed under fluoroscopic guidance in the caudal vena cava, using the stent guide to mark the appropriate location. Once the stent is deployed, the Cobra catheter is placed into the portal vein through the stent for a repeat portovenogram ensuring proper stent placement across the mouth of the shunt. Then portal pressures are obtained and if appropriate another catheter is advanced into the mouth of the shunt through the interstices of the stent for coil deployment, as the portal catheter measures continuous pressures. Coils are added until the shunt mouth is covered or the shunt pressures increase by approximately 6-7 mm Hg (≈8-9 cm H_2O) or maximal pressures approach 16 mm Hg (≈21 cm H_2O). Repeat angiography is performed at the completion of the procedure.

Follow-up

Patients are typically discharged 2 days after the procedure and are continued on all liver dysfunction medications for the following month. A proton pump inhibitor is continued for life. After 1 month, the liver medications are slowly weaned over the following 1-2 months, and the diet is transitioned to a normal adult maintenance diet. Blood work profiles are monitored regularly. If clinical signs return, or evidence of liver dysfunction persists on blood work, then medications can be reinstituted and evaluation for the need of additional coils is recommended.

Complications

Most of the complications reported are those pertaining to IHPSS, as there is little data on PT(C)E of EHPSS. In a recent study of 100 dogs with IHPSS,[62] the perioperative mortality rate was 5%, with a 13% perioperative complication rate. During the PT(C)E procedure, coil migration into the pulmonary circulation is possible; however, this has been substantially reduced with the addition of a caudal vena cava stent prior to coil deployment. Additionally, portal hypertension during embolization is possible, but this too is uncommon clinically after PT(C)E.

Postoperative seizures were approximately 6%, similar to that reported previously.[62,63] Portal hypertension, which has been commonly reported for surgical correction of IHPSS, was very uncommon with PT(C)E.[62] This is likely due to the location of the attenuation. In this study, 20% of dogs required additional coils to improve shunt attenuation over time, and at some point, before or after PT(C)E, 20% of dogs demonstrated signs of GI bleeding.[62] Severe GI bleeding is the most common complication seen in dogs with IHPSS, regardless of the treatment modality, and this has decreased to under 3% since the advent of life-long proton pump inhibitor therapy.[62] There are many theories as to why gastric ulceration occurs so commonly in dogs with IHPSS (hypergastrinemia, hypoprostaglandinemia, abnormal intestinal blood flow, poor mucosal integrity, abnormal mucus production, abnormal cell turnover). In the preliminary evaluation of serum gastrin levels, hypergastrinemia does not seem to be the cause.

Outcome

PT(C)E should be considered a safe, fast, and effective therapy for canine intrahepatic portosystemic shunts when performed by an operator well trained in interventional techniques.[62] PT(C)E resulted in a fair to excellent outcome in over 80% of patients and a median survival time of over 6 years. The perioperative mortality rate was 5%, far lower than that reported with traditional surgery.[62]

Special Considerations

Pet owners should be aware that approximately 5% of dogs have sufficient portal vein perfusion found during angiography to allow complete IHPSS occlusion, which can be done with various devices like vascular

plugs, vascular coils, or a covered stent.[62] Additionally, 10% of dogs have multiple intrahepatic shunts at the time of angiography, and about 5% have pre-existing elevated portal vein pressures, precluding the procedure from safely being performed.[62]

HAVM

Indications and Background

Hepatic arteriovenous fistulae/malformations (HAVM) are rare vascular anomalies involving multiple arterial communications to the portal vein (E-Figure 123-26) (see ch. 284). Since they usually involve multiple, rather than single communications the term malformation, rather than fistula, is more appropriate. These communications are usually from the hepatic artery, but have also been seen to involve the gastroduodenal artery (GDA), left gastric artery (GA), and phrenic artery. Due to the high pressure arterial blood shunting to the portal vein, there is severe chronic portal hypertension (often with subsequent massive ascites) that results in multiple EHPSS to decompress the portal vein.

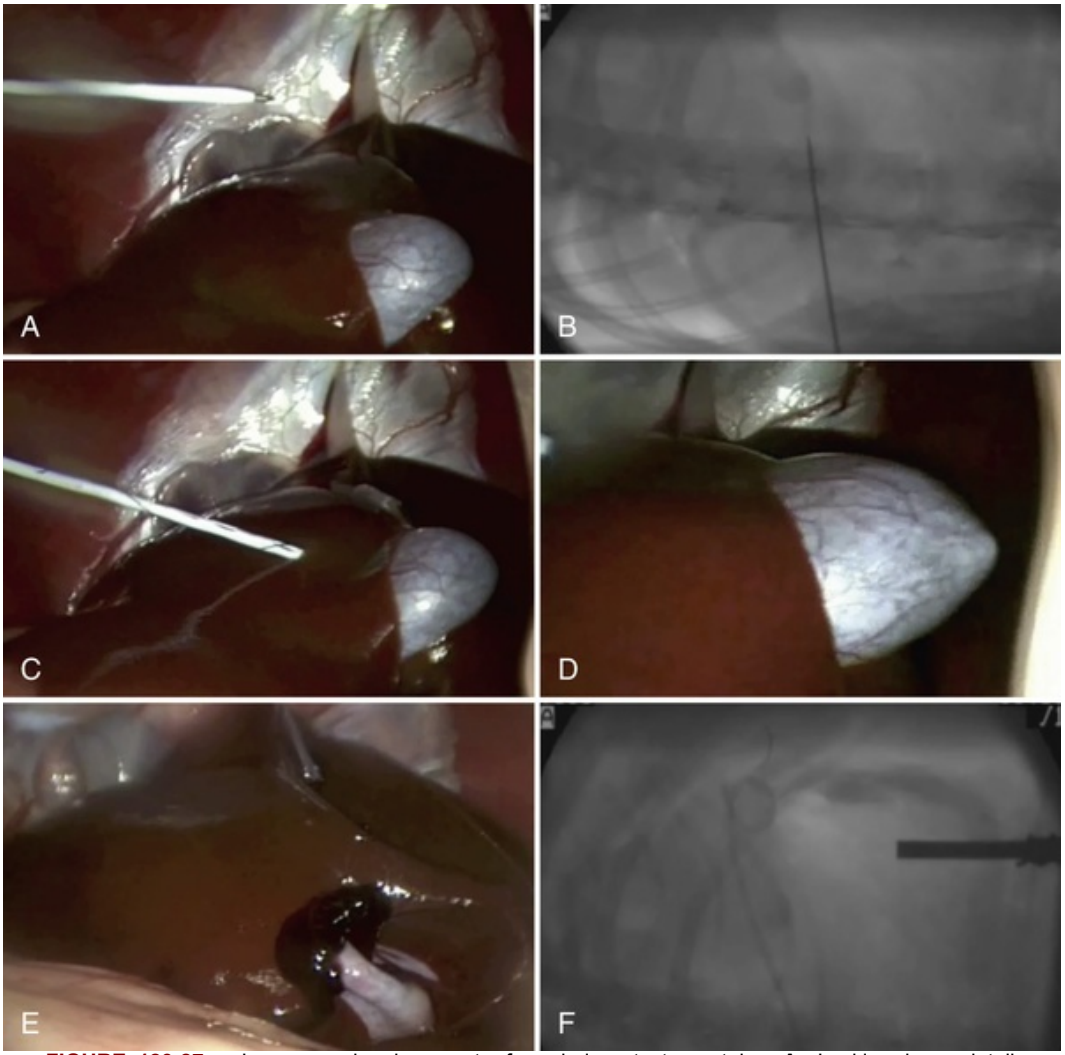
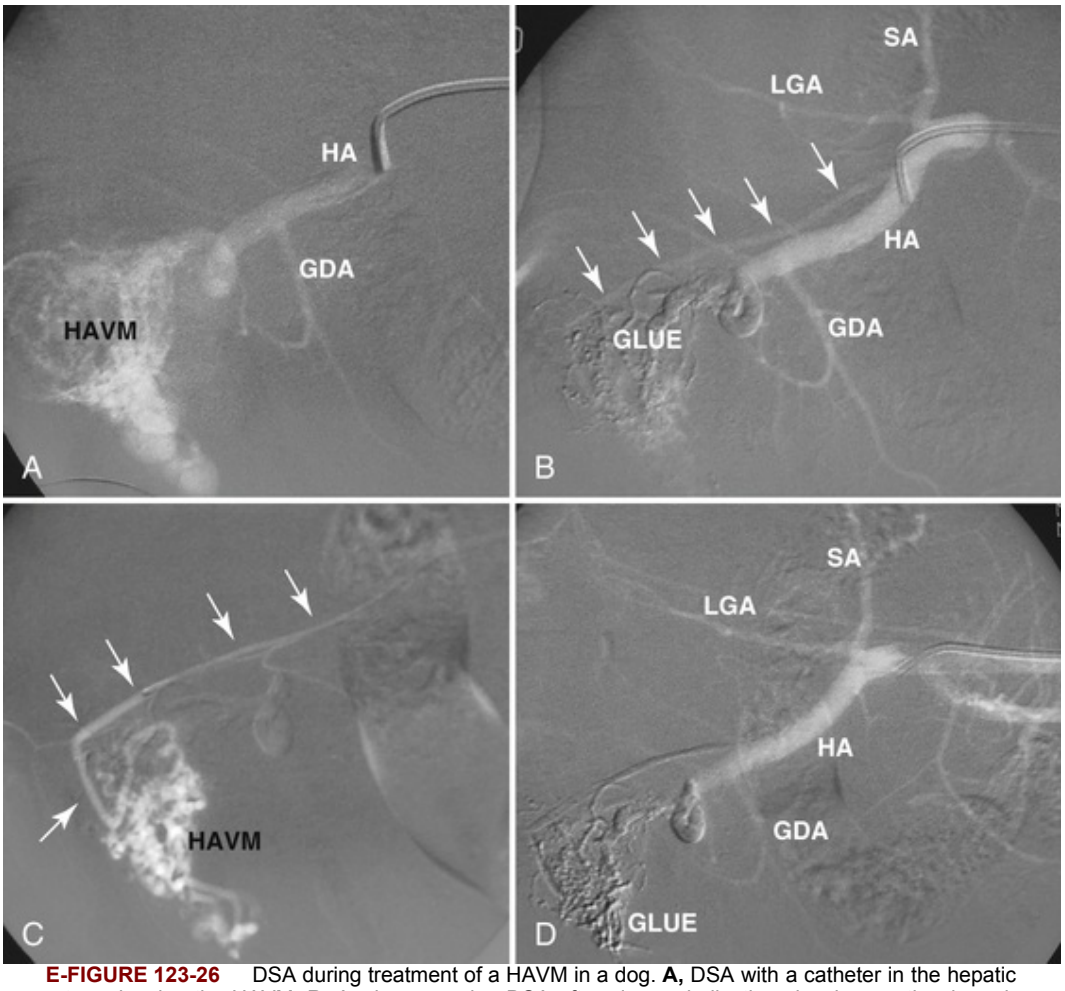


FIGURE 123-27 Laparoscopic placement of a cholecystostomy tube. **A,** Locking loop pigtail catheter (LLPC) passed through the body wall. **B,** Fluoroscopic image showing the needle in the abdomen. **C,** LLPC through the liver lobe prior to entry into the gallbladder. **D,** LLPC entering and coiling inside the gallbladder. **E,** Drainage of the bile after the catheter is in the gallbladder. **F,** Fluoroscopic image of the pigtail inside the gallbladder after the pigtail is coiled and locked in place.



E-FIGURE 123-26 DSA during treatment of a HAVM in a dog. **A,** DSA with a catheter in the hepatic artery showing the HAVM. **B,** Angiogram using DSA after glue embolization showing another branch (white arrows) feeding the HAVM. **C,** Glue embolization of that new branch (white arrows). **D,** Final angiogram after glue is polymerized. *GDA,* Gastroduodenal artery; *HA,* hepatic artery; *HAVM,* hepatic arteriovenous malformation; *LGA,* left gastric artery; *SA,* splenic artery.

Treatment options for HAVM include liver lobectomy, ligation of the nutrient artery, or fluoroscopically guided HAVM glue embolization (HAVM-GE) of abnormal arterial vessels.[65,66] Regardless of the therapy chosen for this condition, 75% of dogs will continue to require dietary or medical therapy due to the persistent portosystemic shunting that occurs through the multiple acquired EHPSS.[65]

Equipment

A good quality fluoroscopy unit that has DSA, and the ability to obtain orthogonal views, is necessary to avoid non-target embolization and ensure all contributing vessels are embolized. Femoral arterial access is needed. Protective eyewear is required when handling the glue material. The glue should only be handled on a special embolization table to ensure that no saline or blood is in contact with the glue to avoid premature polymerization. Supplies needed include a vascular access sheath (4 Fr), a micropuncture set, a 4 Fr Cobra catheter, a hydrophilic angle-tipped guide wire (0.035”), contrast material (iohexol), a Tuohy-Borst adapter, a flow switch, a few microcatheter-microwire combinations, four to six 1 mL polycarbonate syringes, cyanoacrylate glue (1-5 mL), ionized poppyseed oil (Ethiodol), and tantalum.

Techniques

For glue embolization of HAVM, access is obtained via the femoral artery. Under fluoroscopic guidance, access is obtained into the hepatic artery. Hepatic arteriography is performed to demonstrate the location, anatomy, and extent of the HAVM. Then, super-selective microcatheter access is obtained into each contributing branch of the HAVM (see E-Figure 123-26). Hepatofugal blood flow is seen as the contrast

material enters the portal vein traveling caudally until it reaches the multiple EHPSS where it travels through the caudal vena cava cranially. Glue embolization is performed with cyanoacrylate mixed (typically in a 1 : 1 to 2 : 1 ratio) with Ethiodol, an iodized poppyseed oil that is radiopaque and slows polymerization of the glue. Powdered tantalum can be added to lend additional radiopacity to the mixture. The glue polymerizes and occludes the small communications of the malformation. This is done until the HAVM is completely (or nearly completely) occluded. Once the nidus of the HAVM is embolized, the femoral artery is ligated at the access point and the incision is closed.

Follow-up

After HAVM-GE, improvement in the ascites should be seen due to the decrease in portal hypertension. Blood work is repeated the day after the procedure and then again at 1, 3, and 6 months and then every 6 months thereafter. Repeat procedures are recommended if the ascites persists or liver function worsens.

Complications

Complications associated with glue embolization include non-target embolization (glue entering unintended vessels such as the portal system, the extrahepatic shunts or pulmonary circulation). Other locations of non-target embolization include occlusion of proximal arterial vessels like the common hepatic artery, the gastroduodenal artery, and/or the splenic/left gastric artery. Additionally, polymerization of the catheter tip into the vessel wall is possible. Portal vein thrombosis is possible due to the stagnancy of the blood flow in the portal vein after decreasing the arterial flow into the HAVM.

Outcome

Perioperative survival was 100% in dogs undergoing HAVM-GE, with or without partial hepatectomy, compared to 75% to 91% of dogs undergoing surgery alone, but only 4 dogs had HAVM-GE in this study.[65] Recurrence of arteriovenous communications can occur and recurrence of clinical signs has been seen requiring additional embolization procedures, and this is seen in approximately 30% of cases. Long-term survival is considered fair to good with this interventional technique.

All patients have persistent acquired EHPSS due to portal hypertension, and these do not regress, resulting in the need for lifelong medical and dietary management.

Special Considerations

Glue embolization is considered one of the more complicated interventional procedures in human medicine, and human interventionalists undergo specialty training in the use of glue prior to performing this type of procedure. This should be considered the case in veterinary medicine as well.

Miscellaneous Hepatobiliary Interventions

Other diseases of the hepatobiliary system that can be treated with interventional radiology/endoscopy techniques include *chemoembolization* for benign or malignant nonresectable liver tumors, *arterial embolization for severe intractable GI bleeding,* and *cholecystotomy tube placement* (see above and Video 123-4).

Chemoembolization is described in ch. 125. Arterial embolization for GI bleeding is rarely needed, and is done using fluoroscopic guidance via the femoral artery through the cranial mesenteric artery, gastroduodenal artery, and/or caudal mesenteric artery. If a lesion is seen, then coil embolization or gel foam embolization can be considered.

Cholecystostomy tubes can be placed using either laparoscopic guidance, ultrasound guidance, or surgically assisted (Figure 123-27). Ideally, this is done with laparoscopic and fluoroscopic assistance. The liver is punctured with the sharp trocar of the locking-loop pigtail catheter, which is advanced through the liver parenchyma and into the fundus of the gallbladder. The catheter is then advanced off the stylet once the sharp trocar is removed and the tube is then locked in place and gravity drainage is used for biliary decompression. Using a feeding tube, the bile should be given back to the patient enterally for protection of the GI immunogenic barrier (see Video 123-4).

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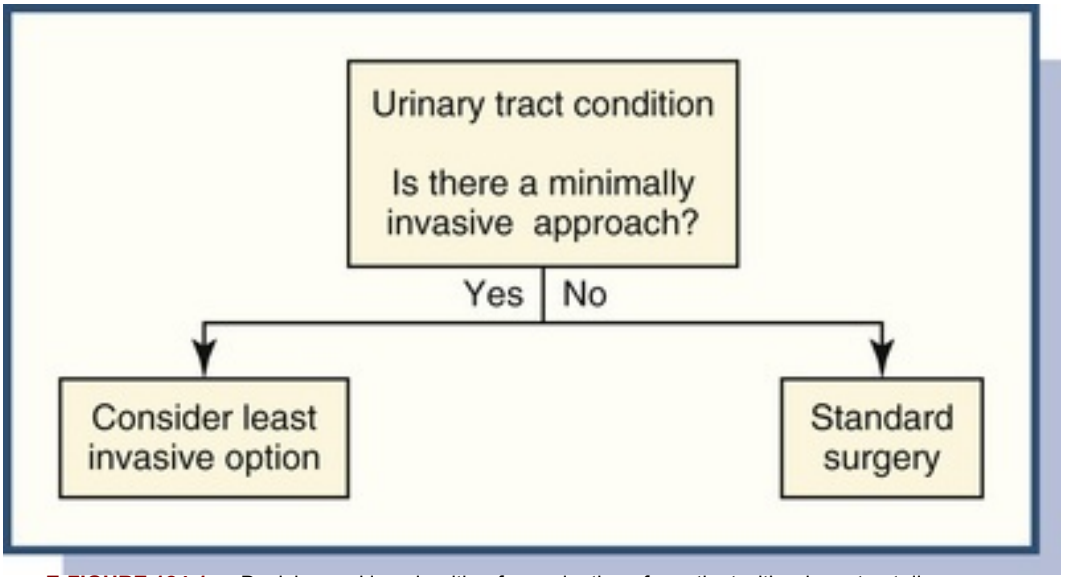
CHAPTER 124

Urologic Interventional Therapies

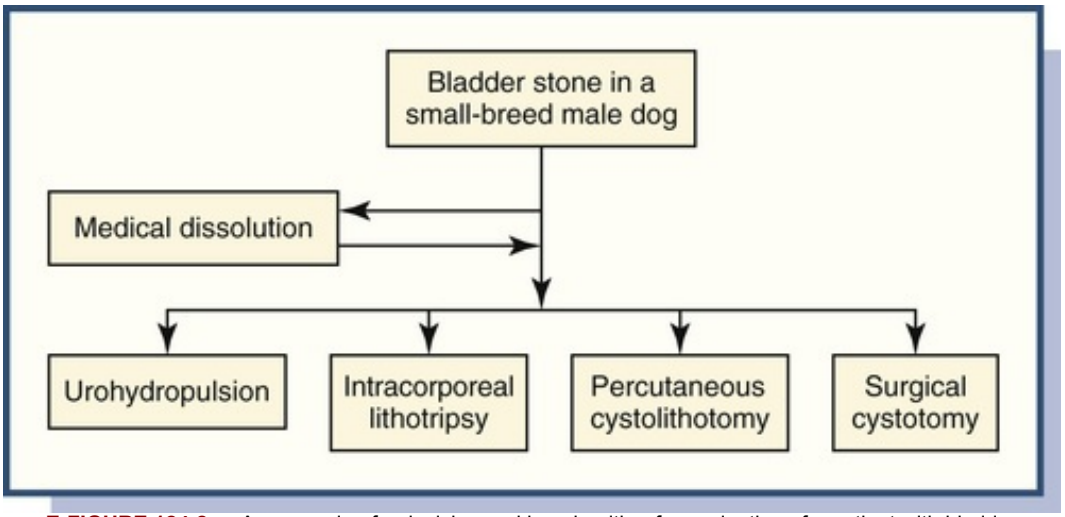
Marilyn E. Dunn, Allyson C. Berent

Client Information Sheet: Urologic Interventional Therapies

Interventional urology (also known as endourology) refers to the specialty of urology in which endoscopes, fluoroscopy, and other instruments are used for accessing, under direct visualization, structures inside the urinary tract. As opposed to traditional surgery, access most commonly is achieved through natural orifices and the procedures are done internally either without, or with few, external incisions. Minimally invasive approaches have a multitude of advantages over standard surgery, such as shorter hospitalization times, little to no recovery time, and less discomfort. Another application of endourology is for patients in whom traditional therapies are not available, are associated with poor outcomes, are contraindicated, or have failed. The authors feel that minimally invasive procedures should be considered and discussed with owners of pets suffering from urinary tract disorders. Algorithms can be used for aiding in the decision-making process (E-Figures 124-1 and 124-2). The entire urogenital system can be accessed from the vulva/penis, through the urethra, into the bladder, up the ureter and into the renal pelvis. While at times appearing technically simple, these procedures have been associated with serious complications when performed by inadequately trained personnel and should be referred to a formally trained and experienced specialist. There is a learning curve associated with these procedures and experience is critical in obtaining the best outcomes.



E-FIGURE 124-1 Decision-making algorithm for evaluation of a patient with urinary tract disease.



E-FIGURE 124-2 An example of a decision-making algorithm for evaluation of a patient with bladder stones. Procedures are considered in order from least to most invasive.

Equipment

Sterility and Drapes

Although the prepuce, vagina and distal urethra have a normal bacterial flora, the authors use sterile drapes and equipment, and thoroughly disinfect the material used between patients. Sterile waterproof drapes are available that preserve sterility while working with continuous saline flush.

Endoscopes

Rigid or flexible cystoscopes are indicated for specific procedures, as described below (see ch. 83 and 108).

Imaging

Fluoroscopy is used in a variety of these procedures and precautions must be taken to ensure safety of all personnel involved. Operators must wear appropriate radiation protection equipment and an effort should be made to minimize exposure time and beam size and maximize shielding and distance. A radiation monitoring badge should be worn at all times. The two most commonly used fluoroscopy units in veterinary medicine are the mobile C-arm and the fixed multipurpose unit. Digital radiography allows rapid serial image acquisition, allowing some interventional urologic procedures to be performed in hospitals without access to fluoroscopy. The most commonly used contrast agents in veterinary endourology are low-osmolarity, nonionic contrast media such as iohexol.

Guidewires, Catheters, Sheaths

The materials needed for the various procedures described in this chapter are detailed in the specific sections, below (see E-Table 124-1). In order to gain access to the urinary tract, hydrophilic guidewires generally are used. These guidewires have nitinol cores and are coated with hydromers to produce wires that are extremely lubricious and slippery when moistened. Once wire access has been achieved, an introducer sheath often is placed next, to facilitate entry into the lumen over the guidewire. Sheaths are named for their *inner* diameter, whereas catheters, delivery systems, and dilators are named for their *outer* diameter; for example, an 8 Fr catheter will fit into an 8 Fr sheath because the outer diameter of the catheter is 8 Fr, and the inner diameter of the sheath is 8 Fr.

E-TABLE 124-1

Commonly Used Equipment in Interventional Urologic Procedures

ITEM	SIZES	DOG	CAT	USES	PROCEDURES
Hydrophilic angled guidewire	0.035 inch 0.018 inch	0.035 inch 0.018 inch	0.035 inch (bladder, urethra) 0.018 inch (ureter, urethra)	Gain access to the upper and lower urinary tract	Various
Open-ended ureteral catheter	3 Fr 4 Fr 5 Fr	3 Fr (0.018 inch guidewire 4 Fr (0.025 or 0.018 inch guidewire) 5 Fr (0.035 inch guidewire)	3 Fr (0.018 inch guidewire)	Ureter: ureteral contrast study	Ectopic ureters, ureteral stricture
Locking loop pigtail drainage catheter	8.5 Fr 12 Fr	8.5, 10.2, 12, 14 Fr	8.5 Fr	Draining the bladder, renal pelvis	Nephrostomy tube, cystostomy tube
Berenstein catheter	4 Fr (0.035 inch guidewire, 5 Fr and > introducer sheath)	4 Fr	4 Fr	Contrast cystourethrogram	Urethral stenting
Introducer sheath	4, 5, 6, 7, 8, 9, 10 Fr	6, 7, 8, 9, 10 Fr (standard 8 Fr will accommodate the majority of stent delivery systems)	4, 5, 6, 7, 8 Fr (females, males with PU)	Maintain access to the urethra or renal pelvis	Urethral stenting
Marker catheter	5 Fr	5 Fr	5 Fr	Accepts guidewire up to 0.038 inch	Radiopaque metallic markers at 1 cm intervals allow sizing
Urethral stent	5-12 mm in diameter, 30-80 mm in length	Sized for the patient	Sized for the patient	Delivery system ≥6 Fr, accepts 0.035 inch guidewire	Urethral stenting
Diode laser	400 and 600 micron fiber			Cut tissue in the case of CLA-EU	CLA-EU
Ho : YAG laser	200, 400 and 600 micron fiber			Stone fragmentation (contact mode) and tissue cutting (non-contact mode)	Laser lithotripsy and CLA-EU
Endotip screw trocar	6 mm and 10 mm trocar			Accepts 1.9 and 2.7 mm cystoscope for stone removal	PCCL
Ureteral stents	2.5, 3.7, 4.7 and 6 Fr	3.7, 4.7, and 6 Fr diameter by 12-32 cm lengths depending on patient	2.5 Fr diameter by 12, 14, 16 cm length		
UPJ balloon	5 Fr and 6 Fr	Patient dependent	Not used in cats	Ureteral occlusion for intraluminal infusion	Sclerotherapy For IRH
Peel-away sheath	14 or 16 Fr	Patient dependent		Urethral access sheath for rigid male cystoscopy	Perineal urethral access
Ultrasonic/pneumatic	22 Fr	22 Fr in a 24 Fr sheath		Intracorporeal	ENL (PCNL or

lithotripsy*				lithotripsy for nephrolithiasis	SENL)
Subcutaneous ureteral bypass (SUB)	SUB1001K SUB2001K	SUB1001K SUB2001K	SUB1001K	Condition necessitating ureteral bypass	Placement of a subcutaneous ureteral bypass for ureteral obstruction
Artificial urethral sphincter	Lumen diameter: 4, 6, 8, 10, 12, 14 and 16 mm Width: 11 mm for 4 and 6, 14 mm for 8-14	8, 10, 12, 14, 16 mm × 14 mm width	4, 6 mm × 11 mm width	Treatment of sphincter mechanism incompetence	Placement of an artificial urethral sphincter for urinary incontinence

*Cyberwand Dual Ultrasonic Lithotriptor, Olympus, Gyrus/ACMI, Southborough, MA.

The items listed in the equipment section are recommended for individuals to have on site prior to performing these procedures. As size of catheters and guidewires vary greatly from one patient to another, it is essential to have a reasonable inventory to ensure the use of appropriately-sized material tailored to each patient.

CLA, Cystoscopic laser ablation; *ENL*, endoscopic nephrolithotomy; *EU*, ectopic ureters; *IRH*, idiopathic renal hematuria; *PCCL*, percutaneous cystolithotomy; *PCNL*, percutaneous nephrolithotomy; *PU*, perineal urethrostomy; *SENL*, surgically-assisted nephrolithotomy.

Stents

Stents are designed to establish patency of a lumen and are available in a variety of materials, shapes, and designs. Stents can be classified as metallic versus nonmetallic, self-expanding versus balloon-expandable, and uncovered or covered. The most commonly used stents in veterinary medicine are metallic, composed of nitinol, a nickel-titanium alloy. Nonmetallic stents, such as urethane double-pigtail stents, most often are placed in the ureter. Laser-cut stents are used primarily in the urethra and blood vessels (see ch. 122).[1]

Percutaneous Antegrade Urethral Catheterization

Indication

Urethral obstruction when standard retrograde urethral catheterization cannot be achieved. It is most commonly done in male cats with urethral tears secondary to trauma from serial attempts to catheterize (see ch. 107 and 335).

Equipment

0.035-inch hydrophilic angled wire, 5 Fr urinary catheter (cats), 18 gauge IV catheter, 3-way stopcock, iodinated contrast medium, fluoroscopy or digital radiography.

Procedure

The patient is placed under general anesthesia in lateral recumbency and the ventrolateral abdomen and the perineum are clipped, aseptically prepped, and draped. An 18 ga IV catheter is inserted transcutaneously into the apex of the urinary bladder, directing the catheter tip toward the trigone. The stylet is removed and an extension set with a 3-way stopcock is attached to an empty syringe and a syringe containing a 50 : 50 mixture of saline and contrast. Contrast is injected under fluoroscopic guidance until the bladder is distended and the proximal urethra is visible. The stopcock is removed, and a guidewire is inserted through the catheter and manipulated towards and down the urethra and advanced until it exits through the penis or vulva. A urinary catheter with the tip cut off is advanced in a retrograde manner over the wire and into the urinary bladder. The guidewire is removed by pulling it through the urinary catheter and the IV catheter is removed from the bladder[2,3] (Figure 124-3).

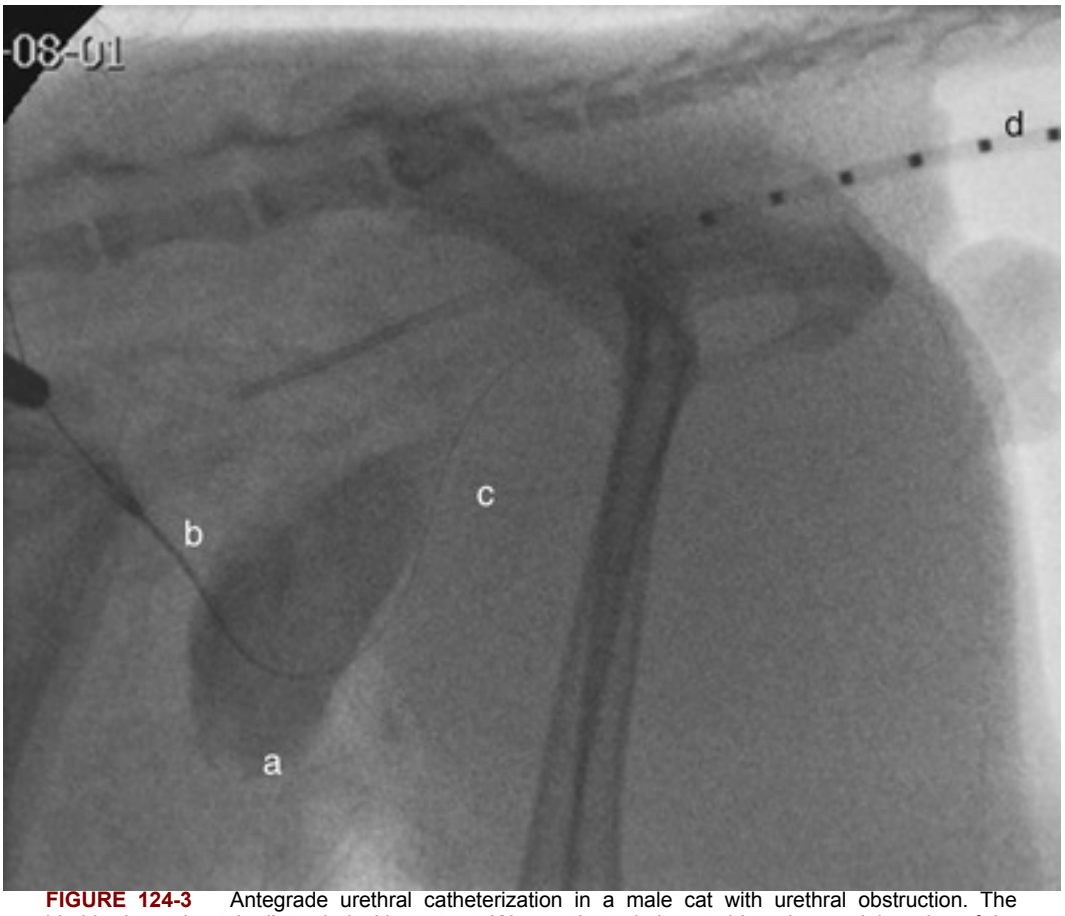


FIGURE 124-3 Antegrade urethral catheterization in a male cat with urethral obstruction. The bladder is moderately distended with contrast **(A),** a catheter is inserted into the cranial portion of the bladder **(B)** and a guidewire is passed through the catheter and can be seen in the urethra **(C).** A marker catheter **(D)** is in the colon to take measurements for a urethral stent.

Special Considerations

For urethral tears, the urinary catheter should be left in place for 5-10 days to allow complete healing.

Outcome and Follow-up

In a small study, percutaneous antegrade urethral catheterization was successful in 7/9 male cats. Within 6 weeks, all of these cats underwent perineal urethrostomy for recurrence of urethral obstruction.[2]

Complications

Inability to achieve access and, rarely, bladder rupture and leakage of urine and contrast into the peritoneal cavity.

Alternatives

Perineal urethrostomy, intermittent cystocentesis, cystostomy tube or urinary catheter placed by cystotomy.[4,5]

Percutaneous Cystostomy Tube Placement

Indications

Functional or mechanical urethral obstruction not amenable to medical therapy (see ch. 107 and 335). A cystostomy tube can be used as a temporary or permanent implant in conditions such as urethral, trigonal, and prostatic neoplasia; granulomatous urethritis; urethral stricture; dyssynergia; neurologic disease; and

urethral/bladder trauma.[3]

Equipment

Locking loop pigtail drainage catheter, hydrophilic angled guidewire, urinary catheter, 3-way stopcock, extension set, iodinated contrast medium, fluoroscopy or digital radiography.

Procedure

The patient is placed under general anesthesia and in right or left lateral recumbency. The abdomen is clipped, ensuring to clip laterally on the side the tube will be placed, and aseptically prepped. The caudal portion of the bladder is palpated and held in position as the craniolateral aspect of the bladder is accessed with a needle attached to an extension with a 3-way stopcock and 2 syringes. One syringe contains contrast and the other is used for withdrawing urine. Contrast is injected into the bladder, the extension set is disconnected, and a guidewire is passed quickly through the needle. The guidewire is looped in the bladder or can exit through the urethra. The needle is withdrawn over the guidewire and the locking loop pigtail catheter is passed over the wire and into the bladder under fluoroscopic guidance. The locking loop pigtail catheter is advanced into the bladder so that all fenestrations are well within the bladder, and then the guidewire is withdrawn. The loop is locked by pulling on the string and secured through the locking mechanism. The catheter is gently pulled so that the bladder wall is against the abdominal wall, and the catheter is secured using a finger trap suture.

Tube withdrawal: The tube should have been in place 10-14 days prior to removal.[6] A guidewire is inserted through the tube under fluoroscopic guidance to ensure that the loop is fully undone and the locking loop catheter is straight. The catheter is withdrawn with the guidewire, and an occlusive bandage is left in place for 24 hours. Urine leakage through the stoma is normal for 2-3 days following tube removal.[3,6]

Special Considerations

When placed for neoplastic urinary tract disease, there have been concerns regarding seeding of the abdominal cavity and skin.

Outcome

Effective means to provide long-term bladder emptying.

Follow-up

Bacterial infections only should be treated if the patient shows associated clinical signs, and targeted antimicrobial therapy based on culture and sensitivity is recommended.

Complications

Recurrent bacterial infections are common and occurred in up to 86% of patients in one study.[6] Slipping of the tube out of the bladder can result in uroperitoneum. Obstruction of the tube is possible; however, flushing the system or passing a guidewire through the tube can help relieve the obstruction.

Alternatives

Urethral stenting or surgically placed cystostomy tubes.

Cystoscopic Basket Retrieval of Lower Urinary Tract Stones

Indications

Removal of urethral and bladder stones not amenable to medical dissolution and too large to be evacuated with voiding urohydropulsion (see ch. 107, 331, and 332). Basket retrieval can be considered in female dogs with stones <5 mm in diameter, male dogs with stones <4 mm in diameter, and female cats with stones <3 mm in diameter.[3,7]

Equipment

Rigid or flexible cystoscope, stone basket that can be passed through the channel of the cystoscope.

Procedure

The patient is anesthetized and placed in dorsal (females) or lateral (males) recumbency. The vulva/prepuce and surrounding area are clipped, prepped, and draped. Cystoscopy is used for visualizing the stone(s). A stone basket is passed through the channel of the scope and the stone is grasped. Under continuous saline flush, the basket is pulled towards the tip of the scope and the scope along with the basket are withdrawn. If resistance is felt, the flush pressure can be increased in order to help dilate the urethral lumen and the basket can be gently rotated. If resistance is still felt, the basket should be opened to release the stone and another technique used in order to avoid damage to, or perforation of, the urethra.

Special Considerations

In the presence of urethral stricture/inflammation, the clinician should be prepared to remove the stone using another technique.

Follow-up

Stone recurrence is a concern.

Complications

Urethral stricture or perforation is possible during retrieval of embedded or sharp-edged stones.

Alternatives

Lithotripsy, percutaneous cystolithotomy, or cystotomy.

Intracorporeal Lithotripsy of the Lower Urinary Tract

Indications

Removal of urethral and bladder stones not amenable to medical dissolution and too large to be removed by cystoscopic-guided basket retrieval (see ch. 331 and 332).[7-10]

Equipment

Rigid or flexible cystoscope, holmium : yttrium aluminium garnet (Ho : YAG) laser with a fiber that can be passed through the scope channel/electrohydraulic lithotriptor, stone basket (optional).

Procedure

The patient is anesthetized and placed in dorsal (females) or lateral (males) recumbency. The vulva/prepuce and surrounding area are clipped, prepped, and draped. Cystoscopy is used for visualizing the stone. The tip of the laser fiber is placed in direct contact with, and perpendicular to, the surface of the urolith. The stone is fragmented by the laser's energy transmitted directly to the stone, creating a shock wave that induces fragmentation. Stones are fragmented until the pieces are small enough to be voided using urohydropulsion or removed with a stone retrieval basket (Figure 124-4, *A-C*).

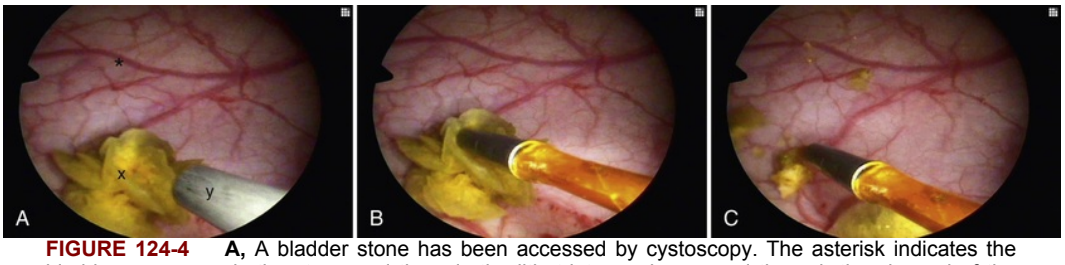


FIGURE 124-4 **A,** A bladder stone has been accessed by cystoscopy. The asterisk indicates the bladder mucosa, x is the stone and the y is the lithotriptor probe passed through the channel of the endoscope. **B,** The lithotriptor probe has come into contact with the stone. **C,** The stone has been fragmented.

Special Considerations

The major challenge is removal of stone fragments from the urinary tract, especially in male dogs. Success depends on careful patient selection (Table 124-2).

TABLE 124-2

Selection Criteria for Intracorporeal Lithotripsy

Patient characteristics	Size	Any female dog or female cat Male dogs >7 kg*
	Sex	Females are easier than males (easier to remove fragments by voiding urohydropulsion in females)
	Location	Urethral stones easier than bladder stones (easier evacuation of stone fragments)
Stone characteristics	Diameter	<2-3 cm females* <1 cm in males*
	Number	<5 stones in females*

*Patients with stones that do not satisfy these criteria are good candidates for minimally invasive stone removal by percutaneous cystolithotomy (PCCL).

Outcome

The Ho : YAG is effective on all stone types.[11] Complete urolith removal is achieved in 100% of dogs with urethroliths, 83-96% of female dogs with cystoliths, and 68-81% of male dogs with cystoliths.[7-10]

Follow-up

Stone recurrence is a concern.

Complications

Self-limiting urethral edema, and mild hematuria. Bladder perforation by the laser is a rare occurrence and can be treated by leaving a urinary catheter in place for 24-48 hours.[7-10]

Alternatives

Percutaneous cystolithotomy, surgical cystotomy and/or urethrotomy.

Transvesicular Percutaneous Cystolithotomy (PCCL)

Indications

Removal of urethral and bladder stones not amenable to medical dissolution and too large or too numerous to be removed by voiding urohydropulsion, cystoscopy-guided basket retrieval, or lithotripsy (see ch. 331 and

332). This antegrade approach through the bladder apex can also be used for gaining access to the urethra, bladder, and ureters.[3,12]

Equipment

Urinary catheter, standard surgical instruments, laparoscopic threaded cannula with diaphragm, rigid and flexible cystoscopes, stone basket.

Procedure

The patient is anesthetized and placed in dorsal recumbency. The ventral aspect of the abdomen and prepuce/vulva are clipped, prepped, and draped. A urinary catheter is placed and sterile saline infused until the bladder apex is palpable. A 2 cm ventral midline skin incision is made over the bladder apex. The incision is extended into the abdominal cavity, the bladder apex is identified, and is grasped with tissue forceps. Stay sutures are placed and a stab incision is made at the bladder apex. The laparoscopic cannula is screwed in place and directed toward the urethral lumen. A rigid cystoscope is advanced through the cannula into the bladder and the stones are identified and removed with the stone basket. To remove sediment/small stones, the diaphragm of the cannula is removed and the bladder is flushed while applying suction to the lumen of the cannula. Once all bladder stones are removed, the urethra is examined through anterograde passage (through the cannula) of the flexible scope in male dogs and cats and the rigid scope in female dogs. Stones in the urethra can be removed with a stone basket or flushed into the bladder and removed. The cannula is withdrawn and the bladder incision and abdomen are closed[12] (Figure 124-5, *A* and *B*).

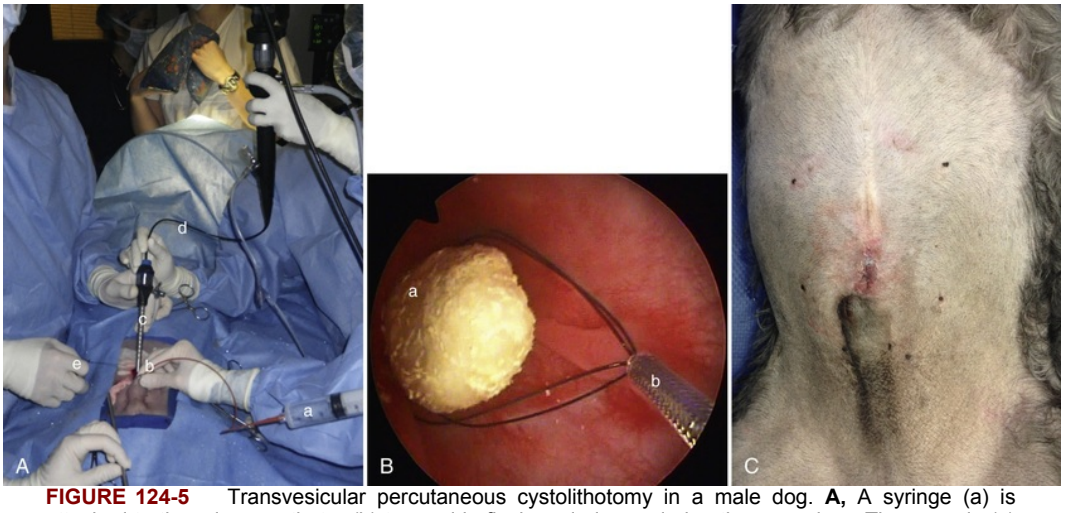


FIGURE 124-5 Transvesicular percutaneous cystolithotomy in a male dog. **A,** A syringe (a) is attached to the urinary catheter (b) to provide flush or drainage during the procedure. The cannula (c) is inserted into the apex of the bladder and a flexible scope (d) is inserted through the diaphragm of the cannula then into the bladder and urethra. The entire system is closed, preventing leakage and providing bladder and urethral distension. Stay sutures (e) help retract the bladder during the procedure. **B,** A stone (a) is being grasped by a 4 pronged stone basket (b) passed through the working channel of a rigid cystoscope inserted through a laparoscopic cannula. **C,** A very small (1.5 cm) skin wound caudal to the umbilicus and cranial to the prepuce is visible following the procedure.

Outcome

Complete stone removal is achieved in 96% of patients.[12]

Follow-up

Stone recurrence is a concern. Skin sutures can be removed in 10-14 days.

Complications

Wound infection, dehiscence, and uroabdomen are rare potential complications associated with the transabdominal approach.

Alternatives

Surgical cystotomy and/or urethrotomy.

Urethral Stenting

Indications

Relief of urethral obstruction and restoration of a urine stream in a patient with partial or complete urethral obstruction (see ch. 335). A urethral stent is a permanent implant and therefore careful consideration of the underlying condition is important. Urethral stents most commonly are placed to relieve obstruction caused by urethral, trigonal, and/or prostatic neoplasia.[13-17]

Equipment

Hydrophilic angled weasel wire, marker catheter, 14 Fr red rubber urinary catheter, appropriately sized self-expanding laser-cut nitinol urethral stent, Berenstein catheter (males), introducer sheath, iodinated contrast, fluoroscopy or digital radiography.

Procedure

The patient is placed under general anesthesia and in lateral recumbency. The prepuce or vulvar region is prepped and draped. A marker catheter inserted in a urinary catheter is advanced into the terminal portion of the colon under fluoroscopic guidance. The marker catheter is essential for accurate selection of stent size. A 0.035 inch guidewire is introduced into the urethra under fluoroscopic guidance and advanced until it curls into the bladder. An introducer sheath (usually 8 Fr) is slid along the guidewire into the distal urethra in males and up to and advanced gently past the obstruction in females. A contrast cystourethrogram is performed, using the sheath in females or a Berenstein catheter advanced over the guidewire and through the sheath in males. A 50 : 50 mixture of iodinated contrast and sterile saline is injected to ensure full bladder distension, creating a clear distinction between the urethra, trigone, and bladder. Contrast is injected continuously while withdrawing the catheter into the distal urethra under fluoroscopic guidance. The size and length of the obstruction can be determined along with measurement of the maximal urethral diameter. A voiding cystourethrogram (manual compression of the bladder under fluoroscopic guidance) can further assist in visualizing the obstruction.

Stent selection: A stent with a diameter 10-15% greater than the maximum diameter of the urethra near the obstruction is selected. The length of the obstruction is calculated and the stent length is chosen in order to ensure coverage of the entire obstruction along with 0.5-1 cm additional stent length cranial and caudal to the obstruction. Under fluoroscopic guidance, the stent is passed over the guidewire, into position, and deployed. The stent is not reconstrainable and once deployment has been initiated, it cannot be stopped. Once patency is confirmed, the stent delivery system, sheath, guidewire, and marker catheter are withdrawn[13,15] (Figure 124-6, *A-C*).

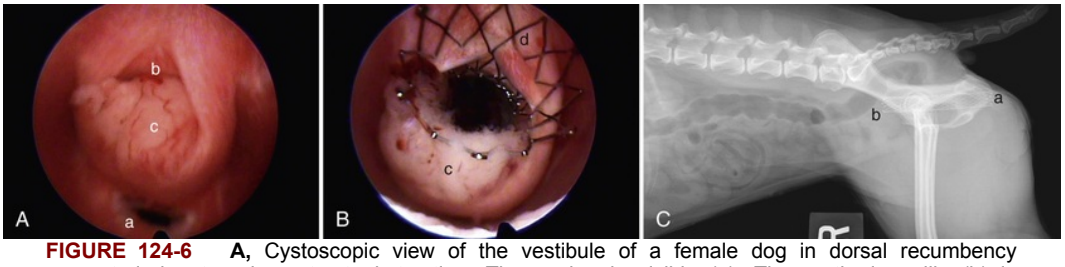


FIGURE 124-6 **A,** Cystoscopic view of the vestibule of a female dog in dorsal recumbency presented due to urinary tract obstruction. The vagina is visible (a). The urethral papilla (b) is completely filled by a mass (c) determined to be a transitional cell carcinoma. **B,** A urethral stent has been placed and is seen slightly protruding from the urethral papilla (d) into the vestibule and compressing the mass (c) that had previously obstructed the urethral lumen. **C,** Lateral radiograph of the same patient showing a urethral stent placed in the mid and distal urethra. The most distal end of

the stent terminates at the urethral papilla (a) and the proximal end in the proximal urethra (b).

Special Considerations

Unlike in tracheal stenting (see ch. 121), where the carina and larynx must be avoided, a urethral stent can extend to the trigone cranially and can "bird beak" out of the papilla and into the vestibule caudally if the obstruction involves the trigonal outflow tract or urethral papilla, respectively. Placing an inappropriately small stent will increase the risk of migration. Some patients with chronic obstructions can have concurrent bladder atony. Care must be taken when performing rectal palpation, administering an enema, or taking a rectal temperature, as the stent could become damaged or dislodged.

Outcome

Urethral stenting has a success rate of 97.5%-100% for relief of both benign and neoplastic obstructions. Survival times are variable and are a function of the underlying disease.[13-15]

Follow-up

Regular urinalysis with culture is recommended, as one third of dogs develop a urinary tract infection following stent placement.[13-15]

Complications

Urinary incontinence rates of 12.5% are reported in patients undergoing urethral stenting for benign obstruction and 26%-41% in patients with neoplastic obstruction. Neither stent length, diameter, location nor sex were predictors of incontinence.[13-15] Recurrence of obstruction due to tissue growth (more common with benign strictures) occurs in 12.8%-17%, stent migration in 12%, and persistent dysuria and stranguria in 19% of patients.[13-15] Cats are at risk of ureteral obstruction with placement of a proximal urethral stent given the location of their ureteral orifices.[17]

Alternatives

A urinary catheter, urethral resection and anastomosis, urethrostomy, or placement of a percutaneous cystostomy tube. Patients with obstructive neoplasia can undergo ultrasound-guided endoscopic diode laser ablation. Benign urethral strictures can be balloon dilated.

Ultrasound-Guided Endoscopic Laser Ablation of Transitional Cell Carcinoma of the Lower Urinary Tract

Indications

Debulking of bladder and urethral transitional cell carcinoma in dogs (see ch. 351). This technique also can be used for establishing a urine stream in patients with obstructive neoplastic disease caused by other neoplasms. A similar technique can be used to laser-ablate benign tumors and polyps from the urinary tract.[18,19]

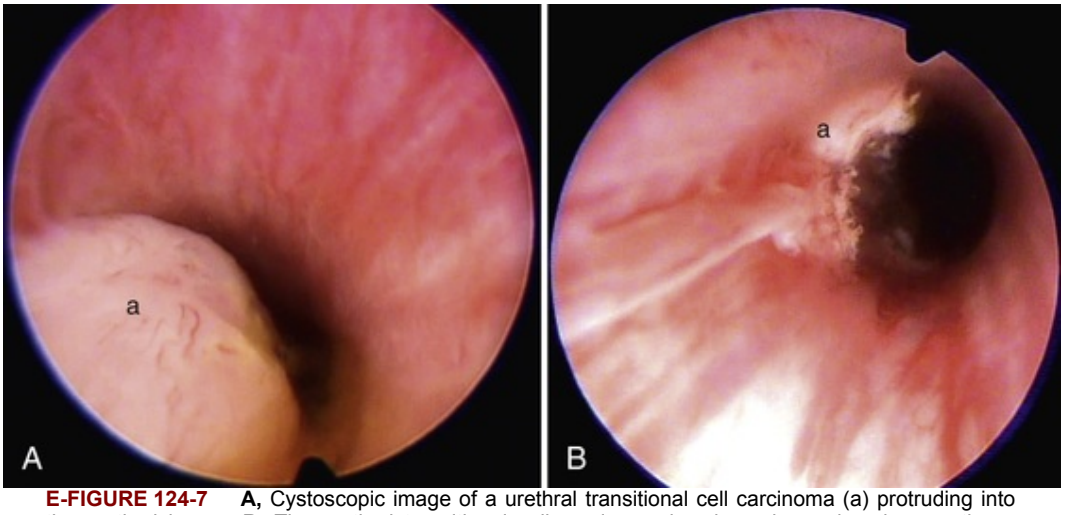
Equipment

Rigid cystoscope, Foley urinary catheter, diode laser with laser fiber that can be passed through the scope channel, ultrasound, and experienced ultrasonographer.

Procedure

The patient is anesthetized and placed in dorsal recumbency. The vulva/prepuce and surrounding area are clipped, prepped, and draped. The cystoscope is advanced to within 2-5 mm of the tumor and the region is simultaneously observed by abdominal ultrasound. Laser energy absorbed by the tumor increases tissue temperature, resulting in protein denaturation and making the tissue more hyperechoic on ultrasound.

Monitoring allows tumor ablation without penetration of the bladder wall. The resulting denatured, avascular tissue will slough within several days. At the end of the procedure, a Foley urinary catheter is placed in dogs with tumor in the urethra and trigone to avoid urethral obstruction while waiting for devitalized tissue to slough[18] (E-Figure 124-7, *A* and *B*).



E-FIGURE 124-7 **A,** Cystoscopic image of a urethral transitional cell carcinoma (a) protruding into the urethral lumen. **B,** The urethral transitional cell carcinoma has been lasered and some tissue remains adhered to the urethra (a).

Special Considerations

This procedure has a steep learning curve for both endoscopist and ultrasonographer. It is considered palliative, and chemotherapy should be maintained to improve outcome.

Outcome

Rapid resolution of urethral obstruction and improvement in clinical signs are reported, with a mean survival time of 380 days.[18]

Follow-up

The urinary catheter is left in place 3-7 days with urethral lesions, and 1-2 days with lesions of the trigone. 50% of patients develop bacterial cystitis postoperatively.[18] Bacterial cystitis or tumor regrowth/spread should be considered if lower urinary tract signs recur. Patients may undergo multiple laser treatments and follow-up ultrasound or cystoscopic examinations can aid in early identification of tumor recurrence.[18]

Complications

Despite relief of urethral obstruction, many dogs remain persistently dysuric and pollakiuric, which can improve over time. 34% of dogs demonstrate gross hematuria lasting 1-2 days, and 5% develop scar tissue at the cystourethral junction, necessitating subsequent laser treatments. Rarely, seeding of the tumor to other previously unaffected areas of the urinary tract has been reported. Urethral and bladder perforation are possible, with subsequent seeding of the abdomen with tumor cells.[18]

Alternatives

Urethral catheterization, urethral stent placement, urethral resection and anastomosis, urethrostomy, or placement of a percutaneous cystostomy tube.

Treatment with Urethral Bulking Agents for Sphincter Mechanism

Incompetence

Indications

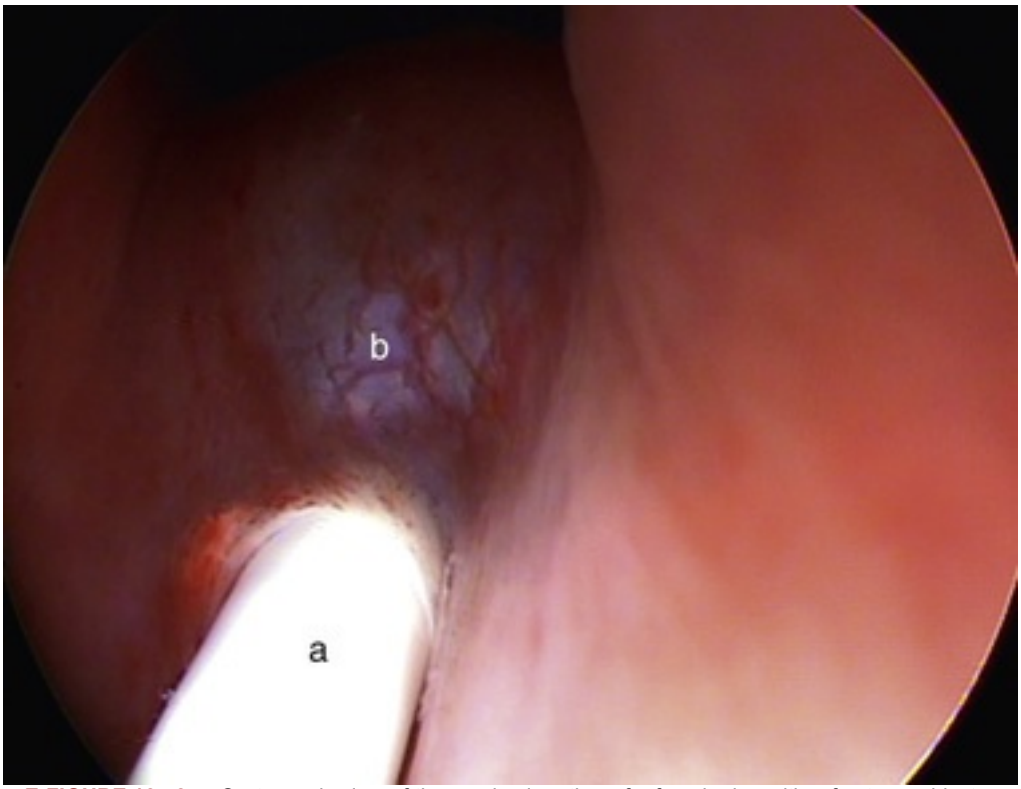
Treatment of urinary incontinence in dogs and cats with sphincter mechanism incompetence refractory to standard medical therapy (see ch. 46 and 333).

Equipment

Rigid cystoscope, injection needle furnished by the manufacturer of the bulking agent, cross-linked bovine collagen (limited availability) (injection needle: 5 Fr 23 ga) or polydimethylsiloxane (injection needle: 5 Fr 20 ga) with injection device.

Procedure

The patient is anesthetized and placed in dorsal recumbency. The vulva/prepuce and surrounding area are clipped, prepped, and draped. The ureterovesicular orifices, trigone, and proximal urethra are identified by cystoscopy. The cystoscope is withdrawn to the level of the proximal urethra, approximately 1-1.5 cm caudal to the bladder neck or at the location of the proximal urethra where the lumen appears to be the smallest. The urethral bulking agent is injected submucosally in 3 locations: at the 2, 6, and 10 o'clock positions, approximately. The needle is inserted so that its bevel is pointed towards the lumen and inserted superficially into the submucosa. The bulking agent is injected until a bleb is visualized that approaches midline (E-Figure 124-8). Once the volume has been administered, the needle is held in place for 60 seconds to allow the compound to congeal, as premature withdrawal of the needle will result in product leakage into the lumen. At the end of the procedure, the urethral lumen should be closed by the blebs. In males, a perineal or percutaneous cystolithotomy approach can be used for gaining access to the proximal urethra.[20-22]



E-FIGURE 124-8 Cystoscopic view of the proximal urethra of a female dog with refractory sphincter mechanism incompetence. An injection needle (a) is inserted into the submucosa and a bulking agent is injected. The submucosal bleb (b) significantly reduces the urethral lumen.

Special Considerations

The major drawbacks are lack of sustained efficacy and therefore, the need for repeated injections. The author will choose injection of a bulking agent in older female dogs with urethral sphincter mechanism incompetence refractory to medical therapy given the ease and minimal invasiveness of the technique. An artificial urethral sphincter is chosen in younger dogs as it can be placed at the time of spaying and has better long-term results.

Outcome

Continence rates using collagen in female dogs vary from 53-68%, with a mean duration of 17-21 months. Improved continence rates of 75% have been reported in dogs having undergone collagen injections and treated with an alpha-agonist.[21-23] A study using polydimethylsiloxane in female dogs reported continence rates of 86% 1 month after injection; however, long-term outcome was not available.[20]

Follow-up

If patients remain incontinent, a second injection of bulking agent can be done. Medical therapy consisting of estrogen and/or the use of alpha-agonists improves response to therapy.

Complications

Persistent incontinence is the main complication. Inability to urinate is infrequent and if it occurs, it can be treated with placement of an indwelling urethral catheter for 24-48 hours. No hypersensitivity reactions to collagen have been reported in cats and dogs; however, 3 dogs treated with polydimethylsiloxane experienced an acute allergic reaction (blepharedema and urticaria) managed successfully with diphenhydramine.[21]

Alternatives

Diapers, confinement, and limiting the patient to areas that are easy to clean; placement of an artificial urethral sphincter; colposuspension with or without urethroplasty.[24]

Artificial Urethral Sphincter (AUS) Placement

Indications

Treatment of urinary incontinence in dogs and cats with sphincter mechanism incompetence refractory to standard medical therapy (see ch. 46 and 333).

Equipment

Standard surgical instruments, artificial urethral sphincter with injectable access port, Huber needle, Penrose drain, ruler.

Procedure

The patient is anesthetized and placed in dorsal recumbency. The ventral abdomen is clipped, prepped, and draped. A median caudal ventral celiotomy is performed to expose the bladder and urethra. Using blunt dissection of the periurethral connective tissue, a 1.5 cm space is created circumferentially around the urethra. In females, the urethra is dissected away from the vagina; in males the bladder is retracted cranially to expose the urethra caudal to the prostate. The urethral circumference is measured using a Penrose drain placed loosely around the urethra. The length of the drain provides a measurement of the outer urethral circumference. The circumference measurement is divided by 50%, indicating the size of the AUS. The tubing is primed by retrograde infusion of sterile saline using a polyurethane catheter inserted down the tubing to remove air. The saline is withdrawn and its volume is noted prior to placement. The cuff is placed around the urethra and the ring is closed using suture placed through the eyelets. In a typical, medium-size female dog, the cuff is placed 3 cm caudal to the bladder neck whereas in a typical, medium-size male dog it is placed 2 cm caudal to the prostate. In smaller dogs and cats, the cuff should be placed as far caudal from the trigone

as possible to prevent cranial migration and kinking of the cuff during micturition. The cuff is left empty and is inflated 6 weeks post-operatively if incontinence persists. The right or left ventral body wall lateral to the incision is dissected between the subcutaneous tissue and ventral rectus muscle sheath, creating a pocket for the access port. The tubing is passed through the ventral body wall and inserted onto the male adaptor of the access port and the plastic boot is advanced to cover the junction. The port is sutured to the ventral rectus sheath, lateral to the midline incision. The bladder is inflated with saline and manually expressed to ensure urethral patency. The abdomen is lavaged and the celiotomy incision closed routinely[25-27] (Figure 124-9, *A* and *B*).

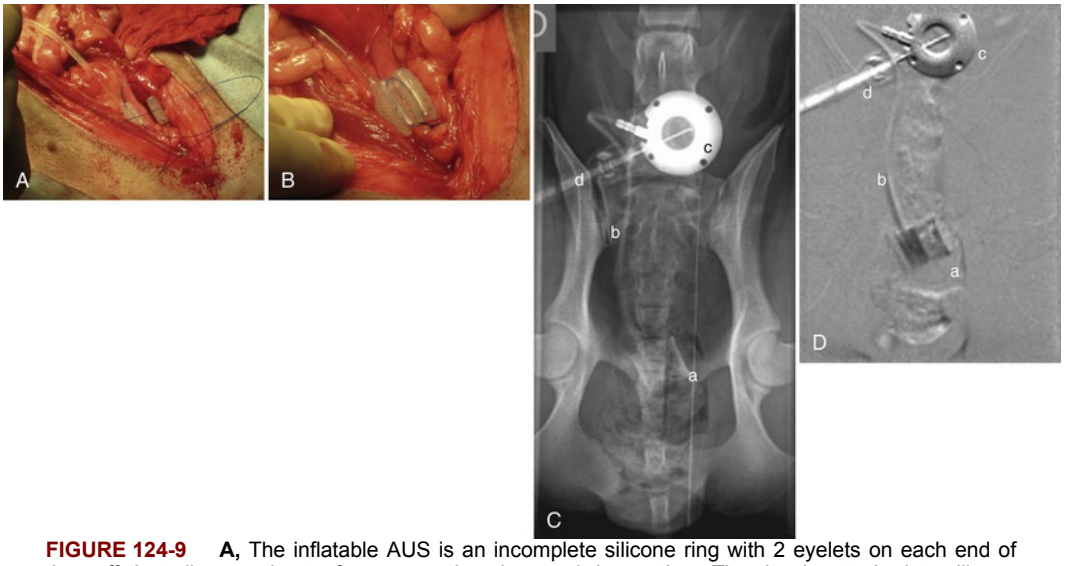


FIGURE 124-9 **A,** The inflatable AUS is an incomplete silicone ring with 2 eyelets on each end of the cuff that allows a ring to form once placed around the urethra. The ring is attached to silicone tubing that is attached to a subcutaneous access port. The cuff has been placed loosely around the urethra and suture has been passed through each eyelet. **B,** The eyelet sutures have now been attached and the cuff is in place around the urethra. The tubing leading from the cuff is visible. **C,** Ventrodorsal radiograph of a female dog with an AUS undergoing a contrast study. The cuff around the urethra filled with contrast is visible (a), the tubing leading towards the port is also filled with contrast (b). The access port is visible (c) along with the inserted Huber injection needle (d). **D,** The same image is seen under digital subtraction allowing better visualization of contrast material within the system.

Special Considerations

Only Huber needles should be used with the access port. Inflating the cuff before the periurethral tissue has healed could interfere with urethral vascularization. The AUS can be palpated transrectally and verified to ensure it has not slipped. If a leak in the system is suspected, patency can be checked by injecting contrast into the access port[28] (Figure 124-9, *C* and *D*). In dogs with pelvic bladders, a cystopexy can be performed at the same time as placement of the AUS to facilitate cuff placement and avoid entrapment of the ureters. Cystoscopy and urinary catheter placement should be avoided peri- and postoperatively as they could induce mucosal lesions, increasing the chance of intraluminal stricture formation.

Outcome

92% of dogs have shown marked improvement in continence, with 33%-45% of patients not needing cuff inflation.[25,26]

Follow-up

The patient should wear an Elizabethan collar until the skin sutures are removed. If incontinence persists, estrogen and/or an alpha-agonist can be administered.

Cuff inflation 6 weeks post-op: The area over the access port is clipped and prepped, and 0.1-0.2 mL of sterile

saline is injected into the port using a Huber needle. Patients then should be observed to urinate, before discharge, to ensure inflation has not resulted in urethral obstruction. If the patient is unable to urinate, 20% of the injected volume is withdrawn from the port. AUS inflation is repeated until continence is improved or signs of urethral obstruction occur. The volume injected each time should be noted to ensure that the maximal filling volume is not exceeded.

Complications

Minor complications include temporary worsening of incontinence during the first 14 days after surgery (19%), mild stranguria (7%) and seroma formation over the access port (11%). Urinary tract infections are observed in 61% of female dogs during long-term follow-up. In reported case series, major complications have occurred in 7-17% of dogs, with urethral obstruction at 1.5-23 months after surgery. Causes were intraluminal webbing in 1 dog that had undergone concurrent cystoscopy, and 4 cases of extraluminal stricture; 2 of these were treated by removal of the AUS (which resolved the obstruction in 1 case), and the other 2 underwent placement of urethral stents, which also resolved the obstruction.[25-27]

Alternatives

Diapers, confinement, and limiting the patient to areas that are easy to clean. Cystoscopic injection of a urethral bulking agent. Colposuspension with or without urethroplasty.[24]

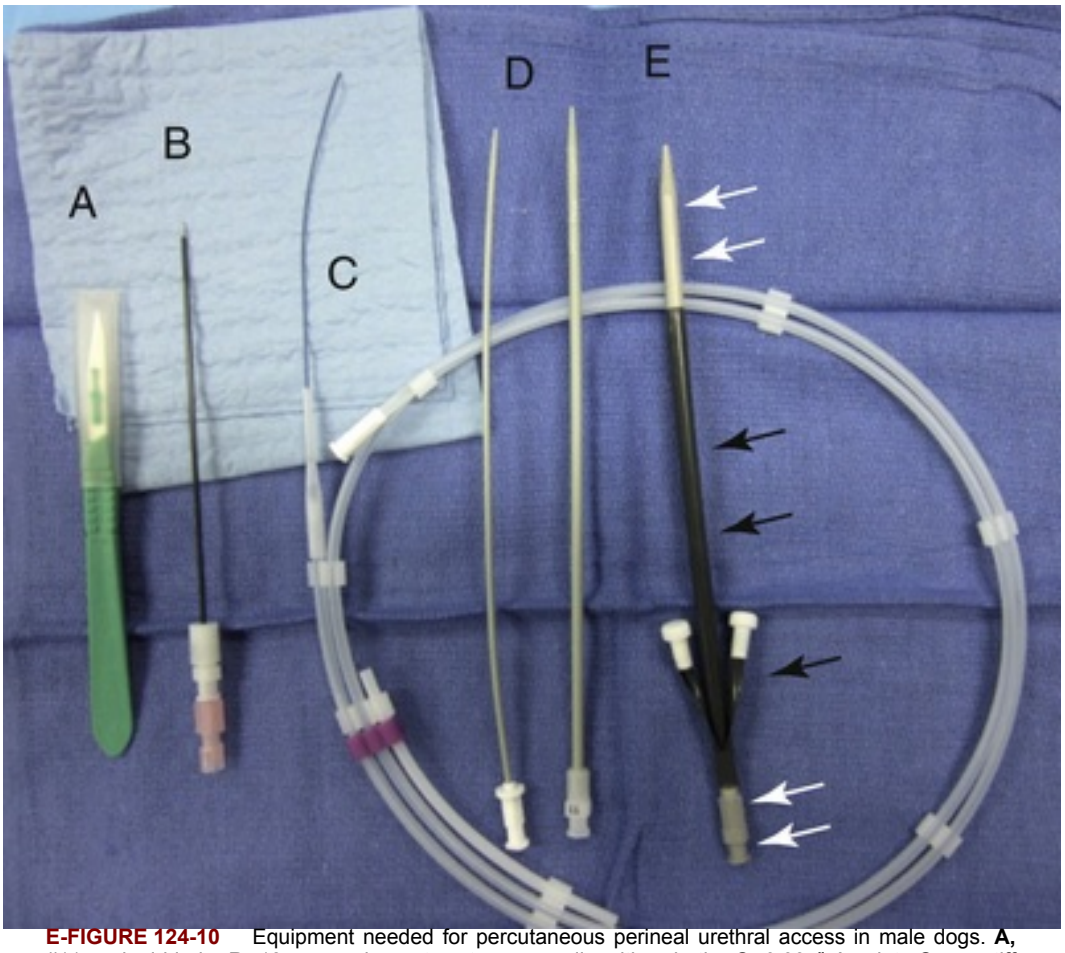
Percutaneous Perineal Access for Canine Rigid Male Cystourethroscopy

Indications

Perineal access into the urethra makes rigid cystourethroscopy possible in male dogs, resulting in dramatically improved visualization. This approach is particularly useful for endoscopic ureteral interventions in male dogs (e.g., laser ablation of ectopic ureters, sclerotherapy or ureteroscopy for idiopathic renal hemorrhage, ureteral stenting).

Equipment

A 2.7 mm rigid cystoscope, C-arm fluoroscope, 18-ga trocar needle, 0.035" Amplatz super-stiff guidewire, 0.035" angle-tipped hydrophilic guidewire, 8 Fr Foley urinary catheter, 14 Fr peel-away sheath, contrast material, and serial vascular dilators (8 Fr, 10 Fr, 12 Fr, 14 Fr) (E-Figure 124-10).



E-FIGURE 124-10 Equipment needed for percutaneous perineal urethral access in male dogs. **A,** #11 scalpel blade. **B,** 18-ga renal puncture trocar needle with echotip. **C,** 0.035" Amplatz Super-stiff guidewire. **D,** Vascular dilators. **E,** Peel-away sheath (black arrows) with dilator (white arrows).

Procedure

The perineal approach is performed with the patient placed in dorsal recumbency and the hindlimbs pulled cranially (Figure 124-11). The prepuce and perineal areas are clipped and prepared aseptically. A pursestring suture is placed in the anus. This positioning allows access for both retrograde flexible urethroscopy and perineal urethral access. Following flexible urethroscopy, an 8 Fr Foley catheter is placed and the urinary bladder is filled with diluted iohexol (50%). The C-arm fluoroscopy unit is positioned transversely across the dog in order to project a lateral image (see Figure 124-11). The catheter is pulled back into the ischial urethra and the balloon is filled with a 50% mixture of contrast. A 4-5 mm midline perineal skin incision is made into the pelvic urethra at the level of the ischium. An 18-ga trocar needle is placed, under fluoroscopic and ultrasound guidance, into the urethral lumen (see Figure 124-11). The needle is aimed such that it penetrates the balloon on the Foley catheter. The sharp stylet is removed and the hollow trocar is then advanced further, into the pelvic urethra, and a urine sample is collected to confirm proper location. Then the 0.035" Amplatz super-stiff guidewire is advanced and coiled into the urinary bladder under fluoroscopic guidance. The C-arm is rotated into a dorsoventral projection. The 18-ga catheter is removed over the wire and serial dilators (8 Fr, 10 Fr, 12 Fr, 14 Fr) are used for dilating the tract (see Figure 124-11) to accept a 14 or 16 Fr peel-away sheath. Once the 14 or 16 Fr sheath is within the mid-pelvic urethra, the dilator is removed and the 2.7 mm rigid cystoscope is placed through the sheath and rigid urethrocystoscopy is performed (Figure 124-12). Upon completion of the intervention, the sheath is removed. The puncture heals by second intention, and the patient is discharged the same day.

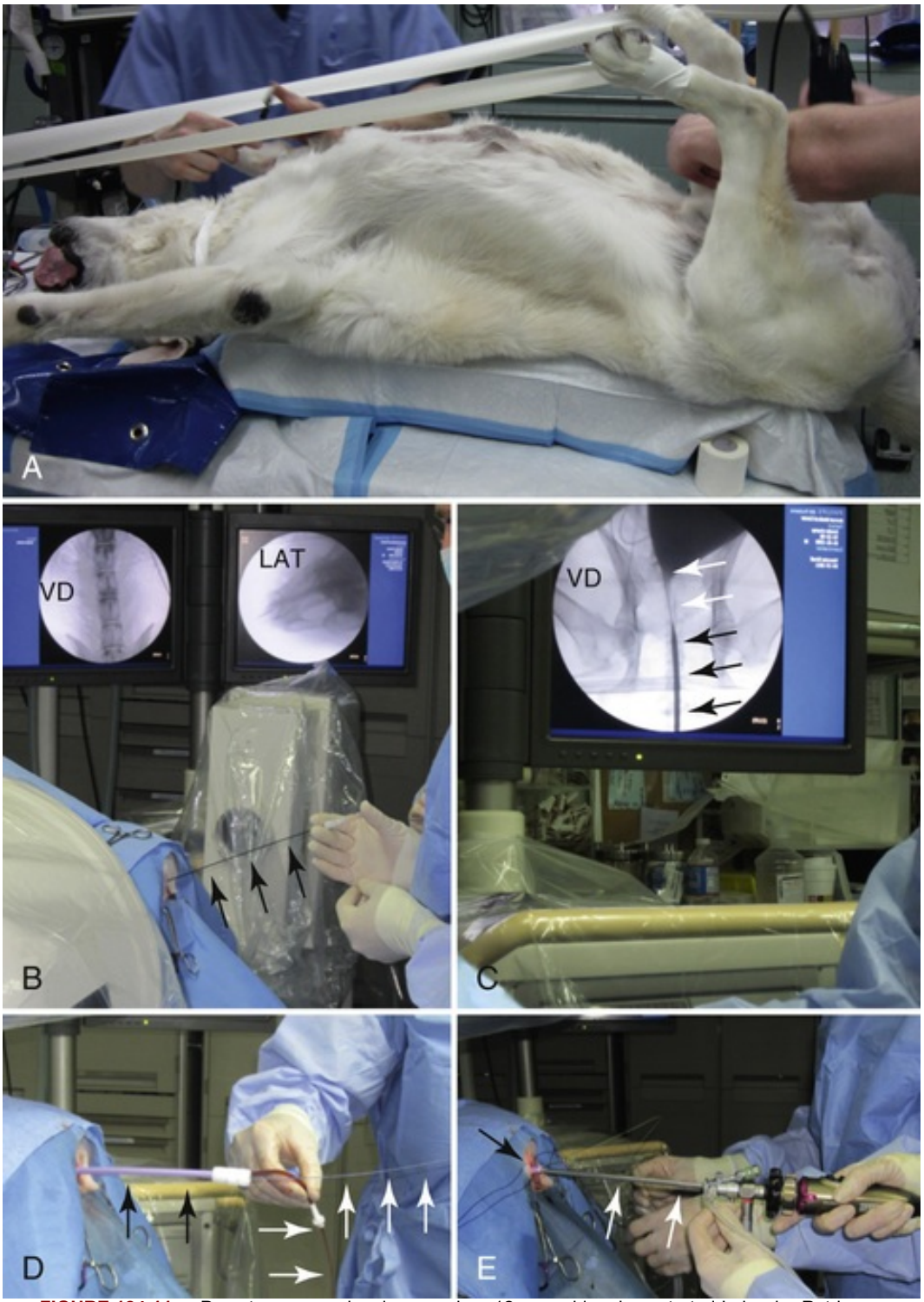


FIGURE 124-11 Percutaneous perineal access in a 12-year-old male castrated Labrador Retriever. **A,** Dorsal positioning of the dog with the tail off the end of the table. **B,** Fluoroscopy C-arm angled to image through the dog in a lateral projection. Notice the needle (black arrows) during percutaneous puncture, and the fluoroscopy images showing the ventrodorsal (VD) and lateral (LAT) projection. **C,** Fluoroscopic imaging showing the sheath (black arrows) over the guidewire (white arrows) on the fluoroscopy monitor once urethral access was obtained. **D,** Serial dilation (black arrows) over the guidewire (white arrows). **E,** Rigid endoscope (white arrows) entering the sheath for rigid cystoscopy. (Photo courtesy Dr. Chick Weisse.)

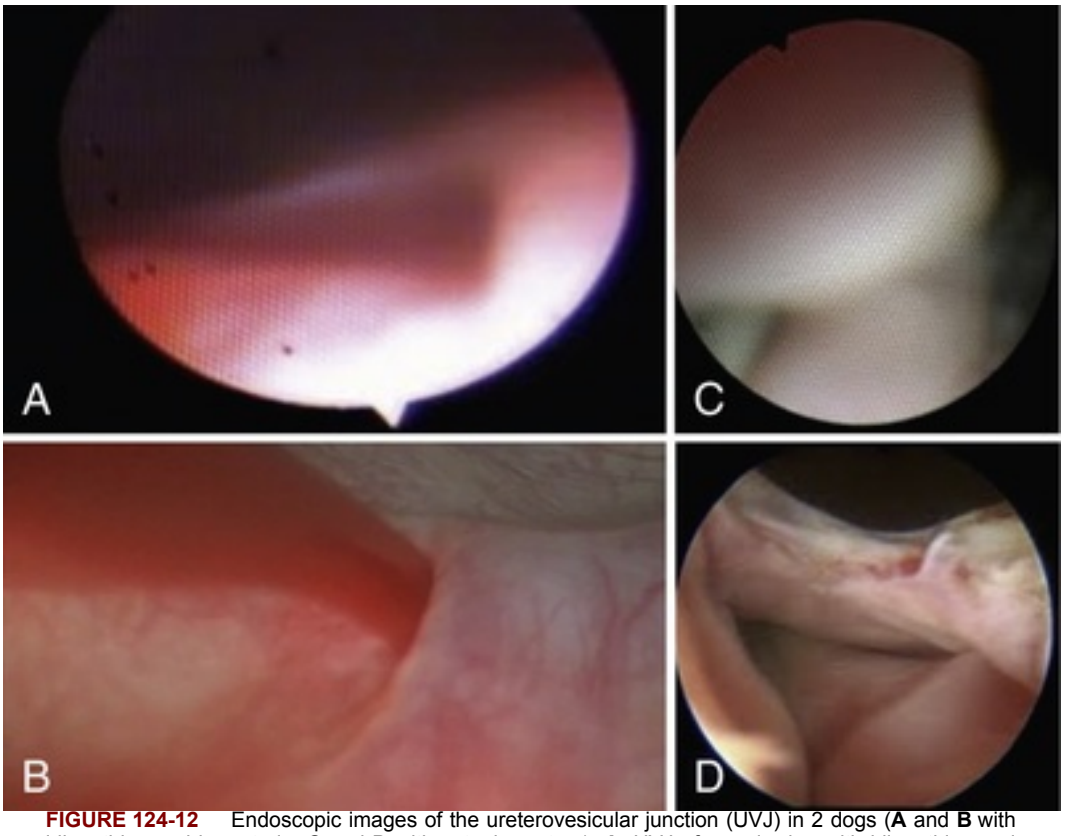


FIGURE 124-12 Endoscopic images of the ureterovesicular junction (UVJ) in 2 dogs (**A** and **B** with idiopathic renal hematuria; **C** and **D** with ectopic ureters). **A,** UVJ of a male dog with idiopathic renal hematuria showing blood jetting out of the orifice during flexible cystoscopy. **B,** Same dog as in image **A** using the rigid endoscope after perineal access. **C,** Male dog with a guidewire in his ectopic ureteral orifice during flexible cystoscopy. **D,** Same dog as image **C** after laser ablation of the ectopic ureteral orifice using the rigid cystoscope after perineal access is obtained.

Outcome

In a report of 10 dogs,[29] access time typically was <30 minutes, half the cases went home the same day as the procedure, and the only complication encountered was one dog leaking urine through the perineal incision 6 hours postoperatively, which did not recur. No long-term complications were identified in any of the dogs with a median follow-up time of ≈7 months and some >3 years.

Follow-up

The patient is recovered with no special treatments for the perineal approach, as treatments are based on the underlying condition that was treated (e.g., ureteral stent, ectopic ureter, renal hematuria).

Complications

The most concerning potential complications from the percutaneous perineal approach are hemorrhage from the vascular cavernous tissues of the ischial urethra and stricture formation.[29,30] Hemorrhage has not been a problem to date, likely due to the stretching (dilation) of the tissues rather than tearing or cutting that occurs during surgical urethral exposure/access. Strictures also are unlikely to occur with longitudinal incisions, rather than circumferential ones, as has been demonstrated experimentally in the urethra.[31,32]

Endoscopic Laser Ablation of Vestibulovaginal Remnants (ELA-VR)

Indications

Dogs affected by vestibulovaginal remnants, including persistent paramesonephric remnant (PPMR), vaginal septum (VS), or dual vaginas (DV), are suggested to display various signs like natural breeding difficulties,

persistent urinary incontinence, vaginal pooling of urine, chronic recurrent urinary tract infections, dysuria, vaginitis, dystocia, and vulvar dermatitis.[33-35] In a recent study,[34] endoscopic laser ablation of vestibulovaginal septal remnants (ELA-VR) was shown to improve continence scores and decrease urinary tract infections in affected dogs. However, the small number of dogs with isolated, single malformations limited the significance of correcting these lesions. As the current implications of these malformations remain unknown, having an effective, minimally invasive treatment option such as endoscopically-guided laser ablation is ideal.

Equipment

Typically, rigid cystoscopes with a 30° lens are used. Saline infusion is used for maintaining visibility, and this is ideally run on a pressure system to keep the vaginal vault distended. A guidewire and open-ended ureteral catheter are used for evaluating the length and location of the remnant. A laser used for ablating the membrane is either a diode or an Ho : YAG laser.

Procedure

The patient is placed in dorsal recumbency and the vulva is clipped and aseptically prepared. The cystoscope is advanced into the vestibule using saline irrigation on a pressure irrigation system. The vaginal opening is identified and each compartment is evaluated with the scope. The guidewire and ureteral catheter are advanced into one of the vaginal compartments, either using the working channel of the cystoscope or guided alongside the cystoscope. Next, the scope is removed over the wire/catheter combination and re-advanced into the vestibule next to the catheter (Figure 124-13). The scope can be advanced into the contralateral compartment to evaluate the length of the septum. Each malformation is classified as either a PPMR (<1 cm), VS (>1 cm) or DV (entire vagina to the cervix) based on measurements of the septum with the open ended ureteral catheter (1 cm marks throughout its length).

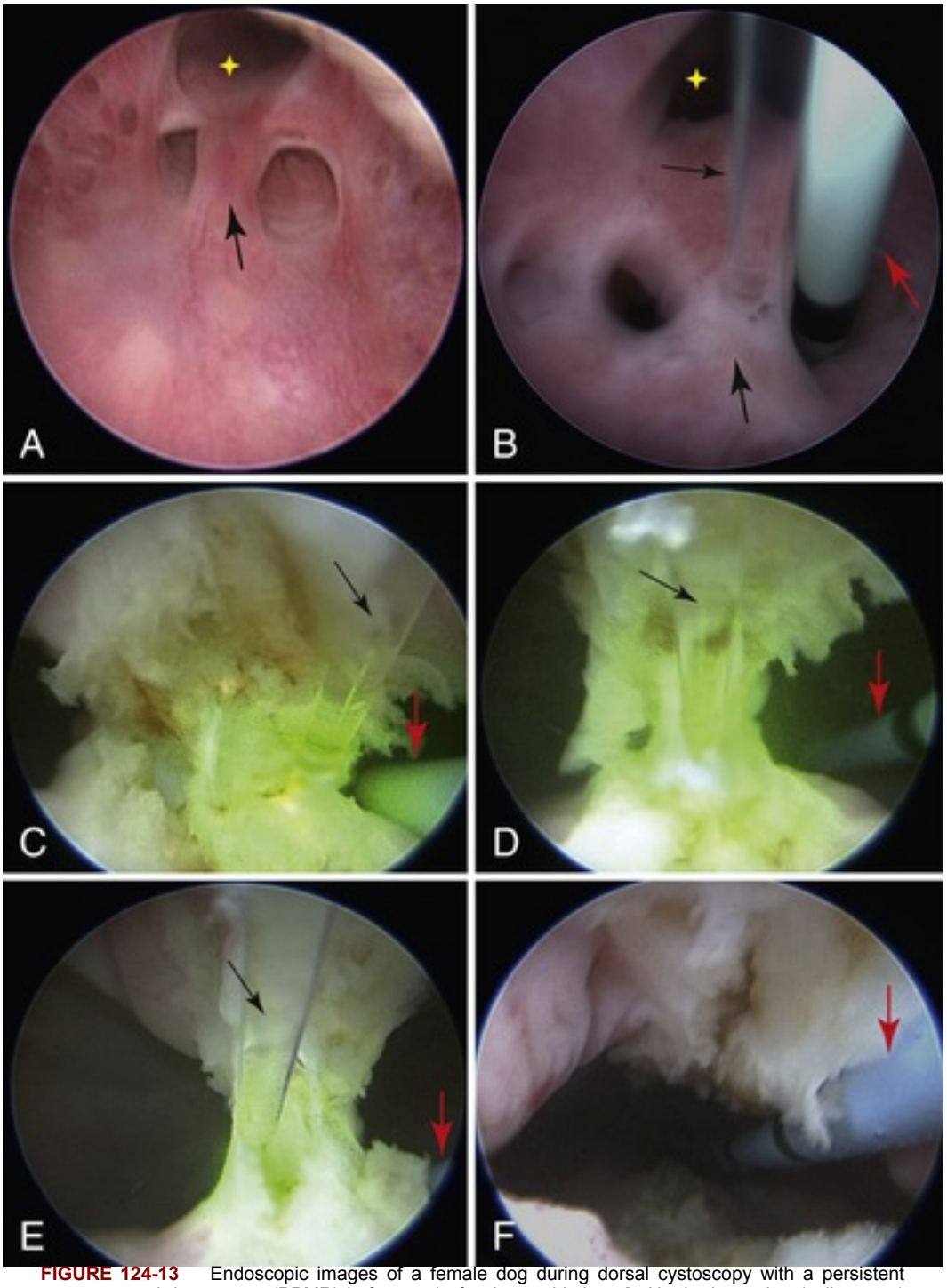


FIGURE 124-13 Endoscopic images of a female dog during dorsal cystoscopy with a persistent paramesonephric remnant (PPMR) before and after laser ablation. **A,** Urethral opening (yellow star) sitting just above (ventral to) the vaginal opening. The vaginal opening is covered by a dorsoventral band of tissue (black arrow), which is the PPMR. **B,** An open-ended ureteral catheter (red arrow) through one compartment of the vaginal opening while a laser (small black arrow) is directed onto the band of tissue (black arrow) through the working channel of the cystoscope. **C-E,** The laser (thin black arrow) progressively cutting the band of tissue while monitoring both compartments of the vagina with the ureteral catheter (red arrow). **F,** The entire remnant is cut showing one vaginal compartment.

A laser fiber is then placed inside the working channel of the endoscope (diode laser at 18-22 watts) and the malformation is laser-ablated from the caudal aspect to the most cranial aspect. The catheter is used for marking the contralateral vaginal compartment until the vagina is one open tube with one opening (see Figure 124-13). The vestibule is infused topically with a 1 : 1 mixture of bupivacaine (0.3 mg/kg) and sterile isotonic saline mixture for local transurethral analgesia.

Outcome

In a recent study, continence scores, vaginitis, and urinary tract infections all were improved after endoscopic guided laser ablation.[34] This finding is difficult to attribute to the correction of the VVSR, as most dogs underwent treatment of other congenital malformations, like ectopic ureters, concurrently. In 30 dogs in which this procedure was performed, no dog had re-formation of the VVSR.[34]

Follow-up

The patients are discharged the same day as the procedure. Owners are provided with an analgesic to be administered for signs of discomfort as needed. Bacterial culture of urine is performed 2-4 weeks after antibiotic therapy in all patients, and recommended at 8 weeks, 3 months, 6 months, and then every 6 months thereafter if the patient has had chronic urinary tract infections.

Complications

Complications with this procedure are possible and can include urethral tears, vaginal tears, and mucosal trauma. In a recent study evaluating ELA-VR, 5/36 dogs (14%) had immediate, mild, postoperative dysuria that resolved within the first 24-72 hours post-endoscopy.[34] Laser perforation of the vaginal wall occurred in one dog, without clinically significant consequences.

Alternatives

The alternative is open surgical resection of the lesion.

Cystoscopic-Guided Laser Ablation of Canine Intramural Ectopic Ureters

Indications

Correction of intramural ectopic ureters in females and males (see ch. 336). The diagnosis can be made/confirmed by cystoscopy and laser ablation can be performed at the same time.[36,37]

Equipment

Rigid or flexible cystoscope, hydrophilic angled guidewire, open-ended ureteral catheter, iodinated contrast medium, fluoroscopy or digital radiography, diode or Ho : YAG laser with a fiber that can be passed through the scope channel.

Procedure

The patient is anesthetized and placed in dorsal recumbency. The vulva/prepuce and surrounding area are clipped, prepped, and draped. Complete cystoscopy and vaginoscopy are performed to identify the site of the ectopia and identify concurrent anomalies. Once the ectopic ureteral orifice is identified, an angled hydrophilic guidewire is advanced through the working channel of the scope and passed into the ureter under fluoroscopic guidance. An open-ended ureteral catheter is advanced over the guidewire into the distal ureter. The guidewire is then removed and a retrograde ureteropyelogram is performed using iodinated contrast medium diluted 50 : 50 with sterile saline. The intramural path of the ureter can be confirmed and other anomalies of the renal pelvis and ureter can be assessed. The medial wall of the ectopic ureter is lasered until the ureteral orifice is situated within the trigone (Video 124-1). Retrograde contrast urethrocystography confirms correct positioning and ensures that no perforation of the urinary tract has occurred[36,37] (Figure 124-14, *A-C*).

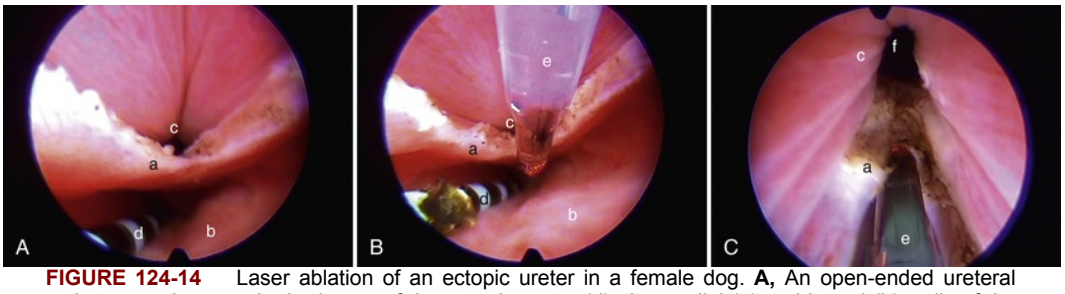


FIGURE 124-14 Laser ablation of an ectopic ureter in a female dog. **A,** An open-ended ureteral catheter can be seen in the lumen of the ectopic ureter (d), the medial (a) and lateral (b) walls of the ectopic ureter are visible along with the lateral wall of the urethra (c). **B,** The laser probe (e) is seen ablating the medial wall (a) of the ureter. **C,** The ectopic ureter has been lasered into the proximal urethra, the trigone along with the bladder lumen (f) are visible.

Special Considerations

Dogs with ectopic ureters can have various other anomalies of the genitourinary tract, including vestibulovaginal remnants, urethral sphincter mechanism incompetence, hypoplastic bladder, pelvic bladder, renal agenesis, renal dysplasia, and ureteral strictures. 93% of dogs with ureteral ectopia can have a vestibulovaginal remnant, which can be laser-ablated at the time of correction of the ectopia. Treatment of lower urinary tract infections is recommended prior to cystoscopic laser ablation if such infections are causing clinical signs.[36,37] Laser ablation of ectopic ureters in male dogs is best accomplished by fluoroscopic-assisted perineal urethral access allowing passage of a rigid scope into the pelvic urethra.[38]

Outcome

Cystoscopic laser ablation results in continence rates of 47% in female dogs 6 months following the procedure. Continence rates increase to 77% with the addition of therapy for urethral sphincter mechanism incompetence (see ch. 336).[29] Success rates are higher in male dogs.[31] Persistent incontinence is secondary to other concurrent urinary tract anomalies, such as urethral sphincter mechanism incompetence, which is reported in 75-89% of female dogs with ectopic ureters.[39,40]

Follow-up

Treatment of sphincter mechanism incompetence as needed. Regular urine cultures, as 30% of dogs are diagnosed with a urinary tract infection within 6 months following the procedure.[36]

Complications

Neither recurrence of the ectopia nor stricture at the ureterovesicular orifice has been reported. Perforation of the lower urinary tract is a rare occurrence and can be treated by leaving a urinary catheter in place for 24-48 hours. Patients can present with self-limiting mild dysuria and pollakiuria.

Alternatives

Surgical correction of ectopic ureters. The authors consider cystoscopic ablation as the standard of care for the correction of intramural ectopic ureters.

Treatment of Nephrolithiasis

Indications

Removal of nephroliths in canine and feline patients is only indicated if they are considered complex and problematic. The criteria for a complicated nephrolith and need for removal would be the following: if there is a partial or complete ureteropelvic junction (UPJ) obstruction resulting in progressive hydronephrosis; renal parenchymal loss is occurring due to stone growth; severe chronic hematuria; signs of renal pain are appreciated; or if recurrent urinary tract infections are occurring despite appropriate medical management of

an infected nephrolith. The main indication for removal of upper tract uroliths in cats is when the nephrolith moves into the ureter and becomes an obstructive ureterolith. If this occurs, then ureteral decompression with a subcutaneous ureteral bypass device (SUB, see below) is recommended over nephrolithotomy. Options for interventional removal of nephroliths are extracorporeal shockwave lithotripsy (ESWL) (dogs only)[41-43] and endoscopic nephrolithotomy (ENL; percutaneous or surgically-assisted endoscopic nephrolithotomy [PCNL or SENL] can be performed in both dogs and cats).[44,45]

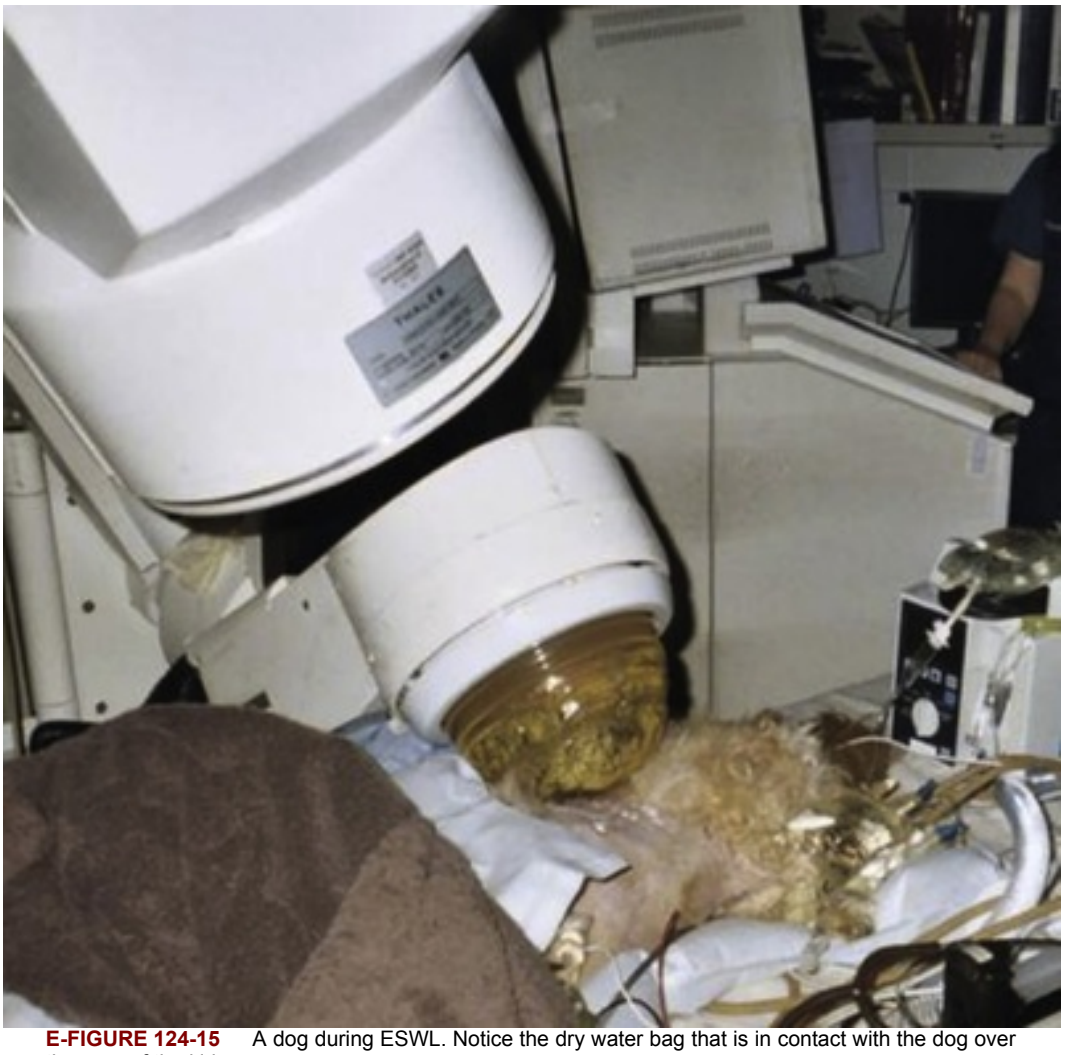
Equipment

There are many machines available for *ESWL*, with the most common being a dry lithotriptor. These units are mobile. The *ENL* procedure requires a puncture needle for renal access (18 ga), an angle-tipped hydrophilic guidewire, and a dilation set for endoscopic renal access (18, 24, or 30 Fr). A nephroscope of appropriate size (22 Fr) is necessary for the lithotrite to fit within the working channel. The author prefers the dual-probe ultrasonic lithotrite.* If a smaller nephroscope is needed, then the Ho : YAG laser, as mentioned above, can be used for laser lithotripsy. If the procedure is done percutaneously, then a 6 Fr locking-loop pigtail catheter is needed. All patients have an appropriate sized ureteral stent placed after completion of the procedure.

Procedure

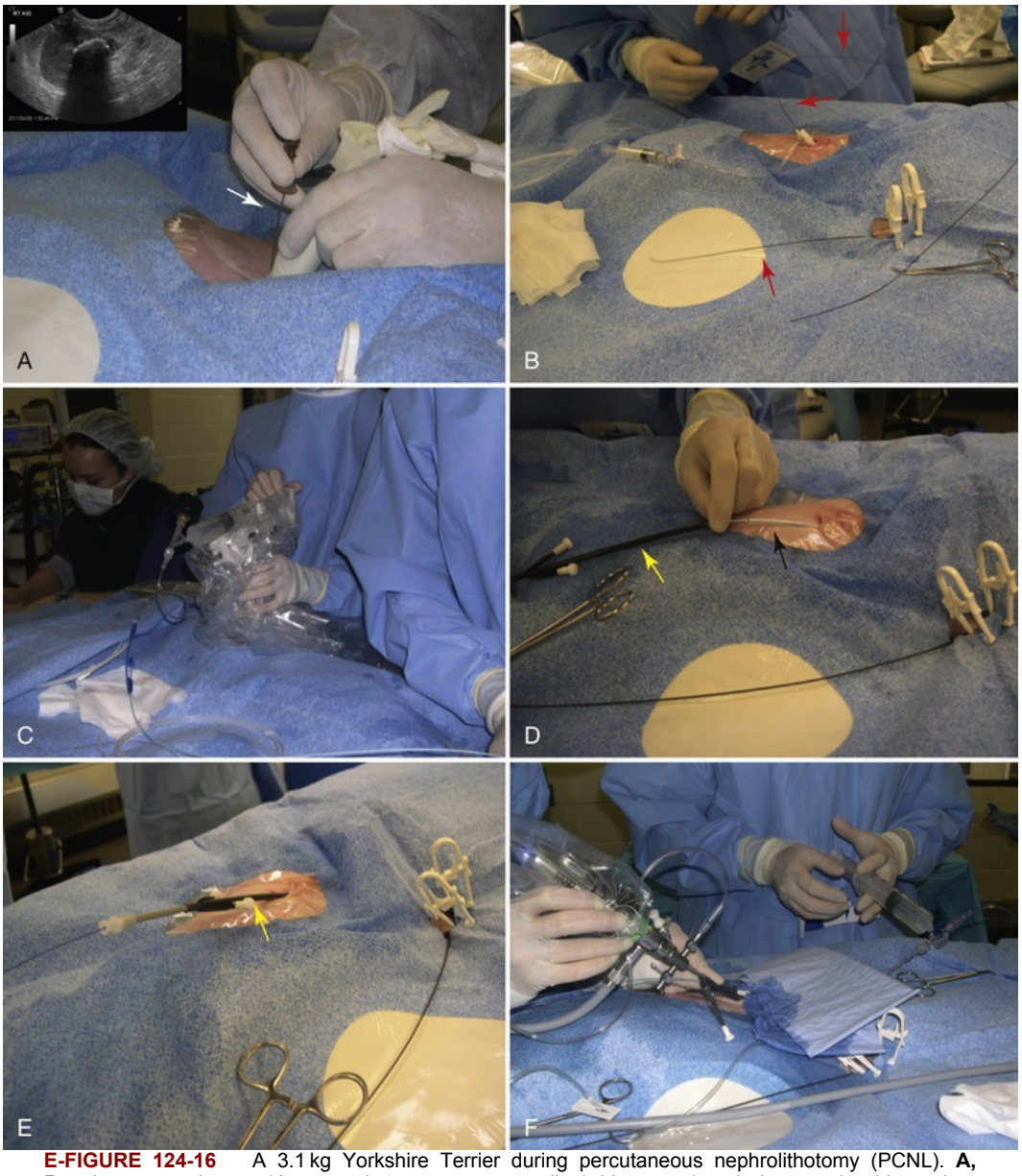
Extracorporeal Shockwave Lithotripsy

Once a patient is placed under general anesthesia, ESWL (E-Figure 124-15) can be performed by placing the patient in various oblique positions, using fluoroscopic guidance, so that accurate targeting via the lithotriptor is possible. The hair overlying the entry point of the shock waves is clipped and coupling gel is used for ensuring transmission of the shockwaves into the body and onto the stone and avoiding air bubbles from attenuating the shock waves at the skin surface. The urolith is placed in the focal spot on fluoroscopy using the machine's integrated targeting system. Shock waves then are delivered to induce urolith fragmentation and this is gated to the heart rate and rhythm to avoid fatal arrhythmias.



E-FIGURE 124-15 A dog during ESWL. Notice the dry water bag that is in contact with the dog over the area of the kidney.

Endoscopic Nephrolithotomy *(E-Figure 124-16 and Figure 124-17)*



E-FIGURE 124-16 A 3.1 kg Yorkshire Terrier during percutaneous nephrolithotomy (PCNL). **A,** Renal access using an 18-ga renal access trocar needle (white arrow) and ultrasound guidance into the renal pelvis. **B,** Guidewire access (red arrows) into the renal pelvis, down the ureter, into the urinary bladder and out the urethra. **C,** Inflation of the balloon/sheath combination, creating a tract into the renal pelvis. **D,** Sheath (yellow arrow) passing over the balloon (black arrow). **E,** Sheath inside the kidney. **F,** Scope inside the sheath for nephroscopy.

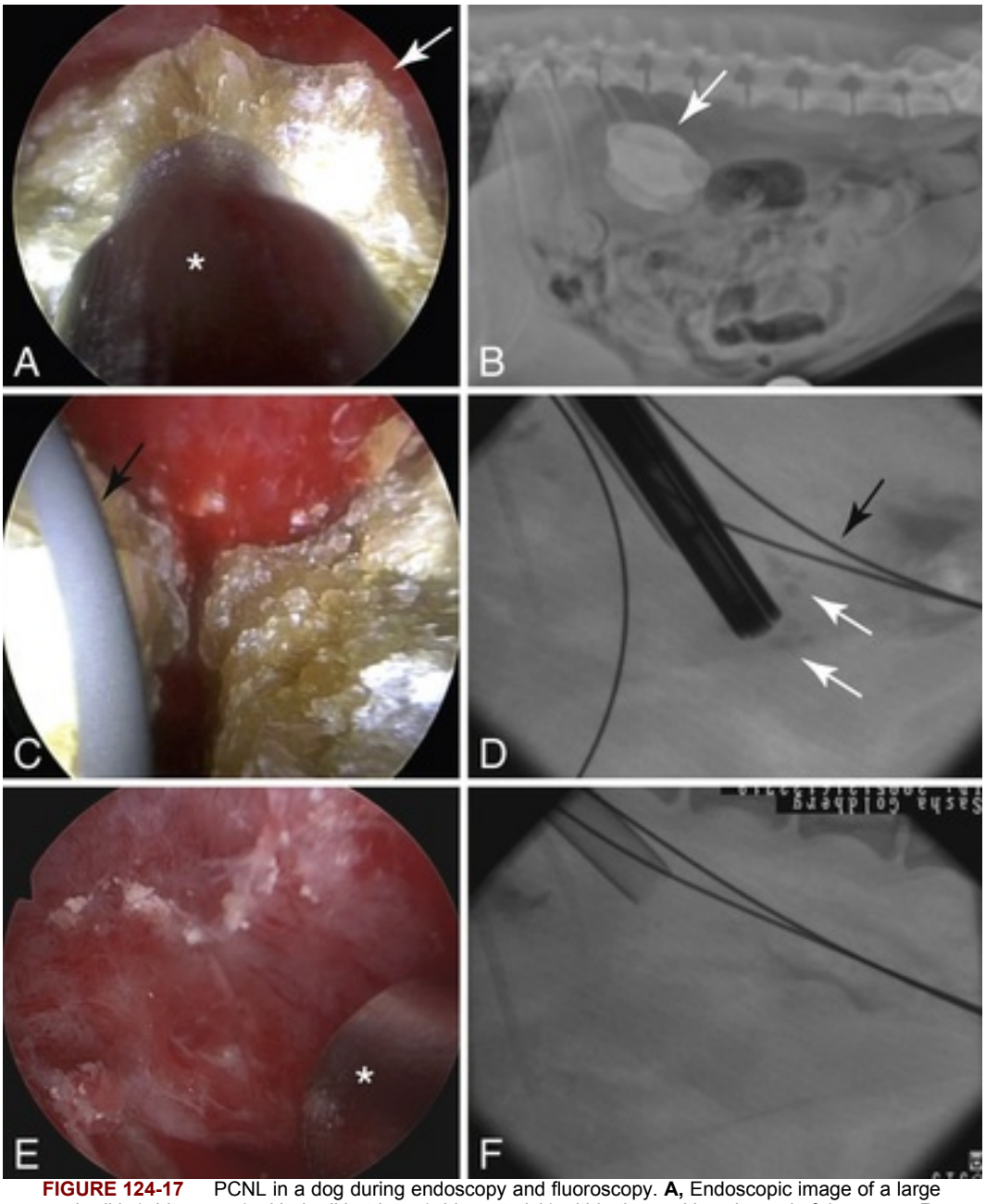


FIGURE 124-17 PCNL in a dog during endoscopy and fluoroscopy. **A,** Endoscopic image of a large nephrolith (white arrow) with the lithotripter (white asterisk) within the working channel of the scope. **B,** Lateral radiograph of a dog with large bilateral nephroliths (white arrow). **C,** Nephroscopic image after the stone is broken with a guidewire (black arrow) within the lumen of the renal pelvis. **D,** Fluoroscopic image of the nephroscope within the renal pelvis monitoring the location of all stone fragments (white arrows). Note the guidewires maintaining through and through access (black arrow). **E,** Renal pelvis after removal of the entire nephrolith. **F,** Fluoroscopic image showing all stone fragments after being removed.

ENL is done either percutaneously (PCNL) or surgically assisted (SENL). For PCNL, the patient is placed in lateral recumbency and the area of the kidney and the vulva/prepuce are clipped of hair and aseptically prepared. Using ultrasound guidance, an 18 ga renal access needle is used for puncturing the renal pelvis through the greater curvature of the kidney. Using fluoroscopic imaging, a ureteropyelogram is performed, and then a guidewire is placed antegrade into the renal pelvis, down the ureter, and into the urinary bladder, where it is then passed out the urethra to obtain through-and-through access. A tract is then dilated over the guidewire into the renal pelvis, using a balloon/sheath combination so that rigid nephroscopy can be performed to get intracorporeal access to the nephrolith. Then, the nephroscope and lithotriptor are used for breaking up the large stone and removing the fragments until the renal pelvis is clear of stone material, guided by endoscopy and fluoroscopy. Finally, once complete, a ureteral stent is placed to ensure post-

operative ureteral patency. If this is done percutaneously, then a locking-loop pigtail nephrostomy tube is placed to ensure a nephropexy is made. If this procedure is done surgically assisted (SENL), the same approach is used, but on completion of the procedure, the access point is closed using a mattress suture, which avoids the need for a nephrostomy tube.

Special Considerations

Most kidney stones in dogs and cats are not considered complex, meaning that they should not be removed. Careful consideration should be used prior to deciding to remove kidney stones, as the potential renal damage done, particularly with a surgical nephrotomy, typically does not justify removal. Prior to choosing the best procedure for nephrolith removal, stone size, patient size, and stone type should be considered. Exchanging a non-obstructive nephrolith for an obstructive ureterolith is contraindicated and concurrent ureteral stenting may be necessary to prevent this from occurring. Cystine stones are ESWL-resistant, and ENL should be considered when needed. Stone recurrence also is common, so medical management should be implemented appropriately to reduce the likelihood of this complication (see ch. 331 and 332). All of the procedures described above, like the other procedures in this chapter, should only be performed by trained operators.

Outcome

ESWL and ENL are safe, minimally invasive procedures, and can be highly effective when performed correctly.[46,47] Endoscopic nephrolithotomy (ENL) typically is more effective (90-100%)[46,48] than ESWL (50-80%)[47] when a single treatment is desired, and has been shown in people to have minimal effect on kidney function when compared to all other options.[48] However, it is important to realize that ENL is more difficult to perform and is more invasive than ESWL. In a recent report of 9 dogs and 1 cat (12 renal units) in which ENL was performed, the median stone size was 2 cm (0.7-5 cm) and the median pre- and 3-month post-operative serum creatinine concentration were 1.3 mg/dL (0.8-9.1 mg/dL) and 1.1 mg/dL (0.6-6.1 mg/dL), respectively.[45] Successful removal of all stones was documented in 92% of renal units with one procedure, and no patient died from the ENL procedure, similar to results reported in humans.[45,46,48] In a series of 140 dogs with nephroliths or ureteroliths treated by ESWL, the most common complication was the development of ureteral obstruction, occurring in approximately 10% of dogs.[41] The risk of ureteral obstruction has declined with the use of concurrent endoscopic ureteral stent placement.

Follow-up

After ESWL, dogs are treated with intravenous fluid therapy for 12-36 hours. Abdominal radiographs are taken at 24 hours to evaluate nephrolith fragmentation, and ultrasound is performed to confirm no ureteral obstruction has developed. If a ureteral stent is placed concurrently, dogs often are discharged the same day as the procedure. After ENL, pain medication is administered for 24 hours, while the patient is hospitalized and receiving IV fluids. Patients are discharged within 24-36 hours, and follow-up imaging and bloodwork are performed 2 weeks later. Once all stone fragments are confirmed to have been eliminated, the ureteral stent is removed either endoscopically or using fluoroscopic guidance. The renal pelvis can remain dilated for a few weeks/months, depending on the size of the stone that was removed and the length of time the stone was present. For PCNL, the nephrostomy tube is assessed with a urine culture in 5-7 days, and at 1 month it is removed. This should be done over a guidewire and can be done at the same time as ureteral stent removal.

Complications

The most common complication with ESWL is ureteral obstruction (10%).[41] Additional complications that can occur include pancreatitis, cardiac arrhythmias, transient hemorrhage, and the need for more than one procedure (15-30%).[41] ESWL is not recommended for treatment of nephroliths in cats because the feline ureter is only 0.3 mm in diameter, whereas a typical nephrolith fragment after ESWL has a diameter of ≈1 mm. Therefore, fragmentation of nephroliths in cats is prohibitively likely to result in ureteral obstruction. In addition, feline kidneys can have a tendency to hemorrhage more with ESWL compared to canine kidneys.

For ENL, the main risks are hemorrhage, ureteral perforation, and urine leakage from the renal access point. If the procedure is done percutaneously (PCNL), then a nephrostomy tube remains indwelling for a minimum of 4 weeks to create a nephropexy; otherwise, urine leakage can occur while the nephrostomy site

heals. Nephrostomy tube dislodgement and urinary tract infections should be considered and careful monitoring should be implemented. With SENL the access point is closed with a suture once the procedure is complete.

Regardless of which procedure is performed, the biggest risk is stone recurrence; this warrants monitoring and appropriate preventive measures.

Alternatives

The alternative to ESWL or ENL is a surgical nephrotomy, nephrectomy, or leaving the stone within the kidney. <5% of all stones require removal and care should be taken when deciding the best approach for each patient.

Treatment of Benign Ureteral Obstructions

Indications

Benign ureteral obstructions are a clinical problem seen with greater frequency in dogs and cats over the past decade (see ch. 329).[49-61] This condition most commonly is associated with ureterolithiasis and/or ureteral strictures. Interventional options have become a common treatment modality due to the lower morbidity and mortality rates reported when compared to traditional surgical techniques[52,54,56,57,60,61] (Table 124-3). To date, the recommended interventional treatments for ureteral obstructions are endoscopic ureteral stent placement for dogs and placement of a subcutaneous ureteral bypass (SUB) device in cats.

TABLE 124-3

Reported Outcomes for Small Animal Veterinary Ureteral Obstruction Treatment Options

Potential Outcomes of Various Ureteral Interventions

PROCEDURE	OPERATIVE	POST-OPERATIVE (<1 WEEK)	SHORT-WEEK MON
Medical management **Feline** Ureteral obstructions[49,73] (diuresis, mannitol, alpha-adrenergic blockade, data on stones only; will not help for the ≈20% of strictures[5])		• MORTALITY: 33% died or were euthanized prior to discharge[49]	• Fa rer fu im (87
Traditional ureteral surgery **Feline** (n = 153,[49,73] n = 47[51]) (ureterotomy/reimplantation/ureteronephrectomy/renal trans-plantation;[49,73] ureterotomy/re-implantation[51]; data on ureteroliths only)	• Uroabdomen leakage (6%[3]-15%[49]) • Presence of abdominal effusion post-op (34%)[51]	• Persistent ureteral obstruction (7%)[49] due to stricture, edema, persistent stones • Failure of renal function improvement (17%)[49] • Require second surgery during hospitalization (13%)[49,51] • Other[49]: fluid overload (3%), septic peritonitis (2%), pancreatitis (1%), • MORTALITY (to discharge): 21%[49,51] (25% with ureterotomy/reimplantation; 18% if include	• Fa im rer fu (17 • M((w mc 25

		transplantation and ureteronephrectomy)[49]	
Traditional ureteral surgery **Canine** (n = 16)[50] (ureterotomy/pyelotomy, ureteronephrectomy; data on ureteroliths only)	• Uroabdomen leakage • Stricture	• Persistent ureteral obstruction • Failure of renal function improvement (21%)[50] • Worsening renal function (15%)[50] • MORTALITY (to discharge): 6.25%	• Re ob • St su str • Pe rer dy (43
Ureteral stent[52,54,56,57] **Feline** (n = 79,[54] n = 92[56]) (data on 71-79% ureteroliths, 21-28% strictures, 1% obstructive pyelonephritis)	• Ureteral penetration/perforation with guidewire (17%) (little clinical consequence; no uroabdomen) • Leakage if concurrent ureterotomy needed (6.7%) • Eversion of ureteral mucosa during stent passage • Ureteral tear during stent passage (3.8%)	• Fluid overload during postobstructive diuresis (17%) • Concurrent pancreatitis (6%) • Failure of creatinine to improve (5%) • MORTALITY (to discharge): 7.5%[54] • Due to non-urinary causes (pancreatitis or CHF)	• In (te (25 • Dy (se 7-1 <1 • St mi (3%
Ureteral stent	• Endoscopic failure	• Hematuria (<5%)	• Dy

Canine (n = 84,[52] n = 14,[60,74] n = 57[61]) (Data on 55% ureteroliths, 40% tumors, and 5% strictures)	(≈10% female; 30% male) • Ureteral perforation (<1%) • Leakage (<1%) • Ureteral tear (<1%)	• Dysuria (<2%) • Migration (0%) • Occlusion with debris (0%) • MORTALITY (to discharge): <2%[61]	• Pe ob (<2 • He (20
SUB device[53,56,57] **Feline** (n = 61,[53] n = 71[56]) (Data on 20% strictures [+/− ureteroliths] 76% ureteroliths, 4% obstructive ureteritis)	• Kinking of catheters (3.5%) • Inability to place SUB device (<1%)	• Leakage (5%)[56] • Resolved with new device • Fluid overload (<5%)[53,56] • Blockage of system (2%)[53,56] (blood clot, purulent material, device failure) • Failure of creatinine to improve (3%)[53,56] • MORTALITY (to discharge): 5.8%[56]	• Dy <2 • Ina ≈2 (te • Se 1%

CHF, Congestive heart failure; *MST*, median survival time; *SUB*, subcutaneous ureteral bypass; *UTI*, urinary tract infection; *UVJ*, ureterovesicular junction.

Equipment

Various rigid and flexible endoscopes are needed for retrograde ureteral stent placement in dogs. This is possible in any size female dog and male dogs weighing >6 kg. Guidewires and catheters are needed for each procedure, and size depends on the size of the stent and catheter that ultimately are used (E-Table 124-4). The SUB device[†] is a specialized 6.5 Fr nephrostomy tube that is connected to a cystostomy tube through a shunting port that is placed subcutaneously, creating an artificial ureter.

E-TABLE 124-4

Guidelines for Equipment Used for Ureteral Stenting in Dogs and Cats

URETERAL STENT SIZE (FRENCH)	GUIDEWIRE SIZE	OPEN-ENDED URETERAL CATHETER SIZE	RIGID CYSTOSCOPE LENS SIZE (WORKING CHANNEL DIAMETER)	OVER-THE-NEEDLE CATHETER SIZE (GAUGE)
2.5-feline	0.018″	3 Fr or 0.032-0.034″ ureteral dilator	1.9 mm (3 Fr)	21 or 22
3.7-small dog	0.025″	4 Fr	2.7 mm (5 Fr)	20
4.7-medium/large dog	0.035″	5 Fr	2.7 mm (5 Fr)	18
6.0-large dog/cancer stent	0.035″	5 Fr	4 mm (6 Fr)	18

Procedure

Ureteral Stents

Ureteral stents are most commonly placed cystoscopically in dogs. This is performed in a retrograde manner through the ureterovesicular junction (UVJ). This is not possible when the obstruction is due to a trigonal tumor covering the UVJ (see below). For endoscopic ureteral stent placement, the patient is placed in dorsal recumbency and the vulva or prepuce is clipped and aseptically prepared. In a female dog, a 30° cystoscope is used for routine cystoscopy, and an appropriately sized, angle-tipped, hydrophilic guidewire/ureteral catheter combination is used for cannulating the ureter. Once the catheter is in the distal third of the ureter, the wire is removed, and under fluoroscopic guidance, a retrograde ureteropyelogram is performed. Then the wire is re-advanced through the catheter, up the ureter, around the obstruction, and into the renal pelvis (Figure 124-18). The wire is removed from the catheter and contrast is injected into the renal pelvis. The wire is re-advanced and coiled within the renal pelvis, and the catheter is removed over the guidewire, monitoring with fluoroscopic guidance to ensure the wire remains coiled within the renal pelvis. During this withdrawal, the ureteral length is measured using the catheter and monitoring the UVJ through the endoscope. Then an appropriate-size stent is chosen based on the ureteral diameter and ureteral length. This double pigtail ureteral stent then is placed over the guidewire, through the working channel of the endoscope, up the ureter, and is coiled on the wire into the renal pelvis. Once a curl is seen in the renal pelvis, then the wire is withdrawn into the cystoscope and a pusher catheter is used for pushing the distal end of the stent into the urinary bladder.

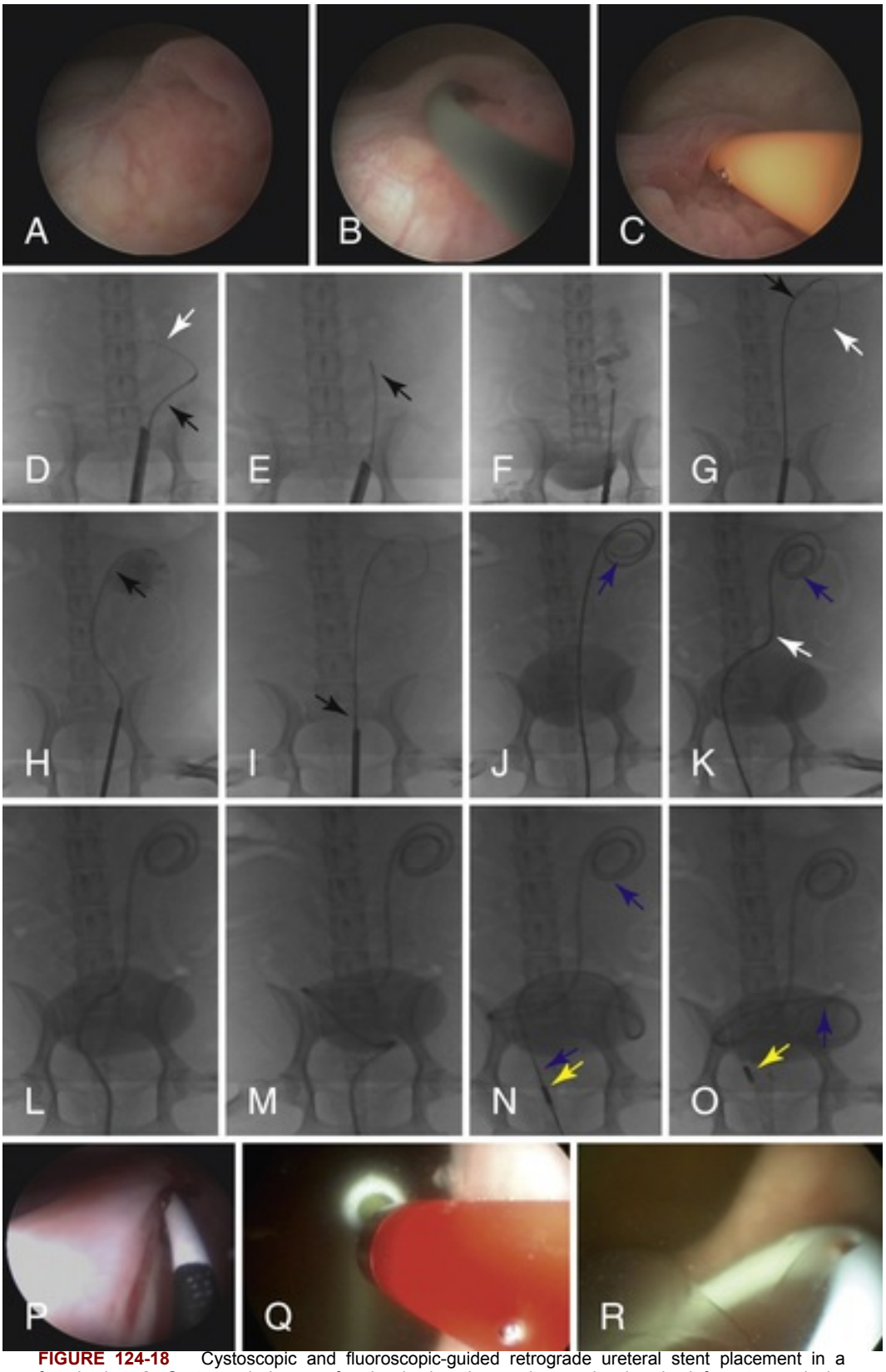


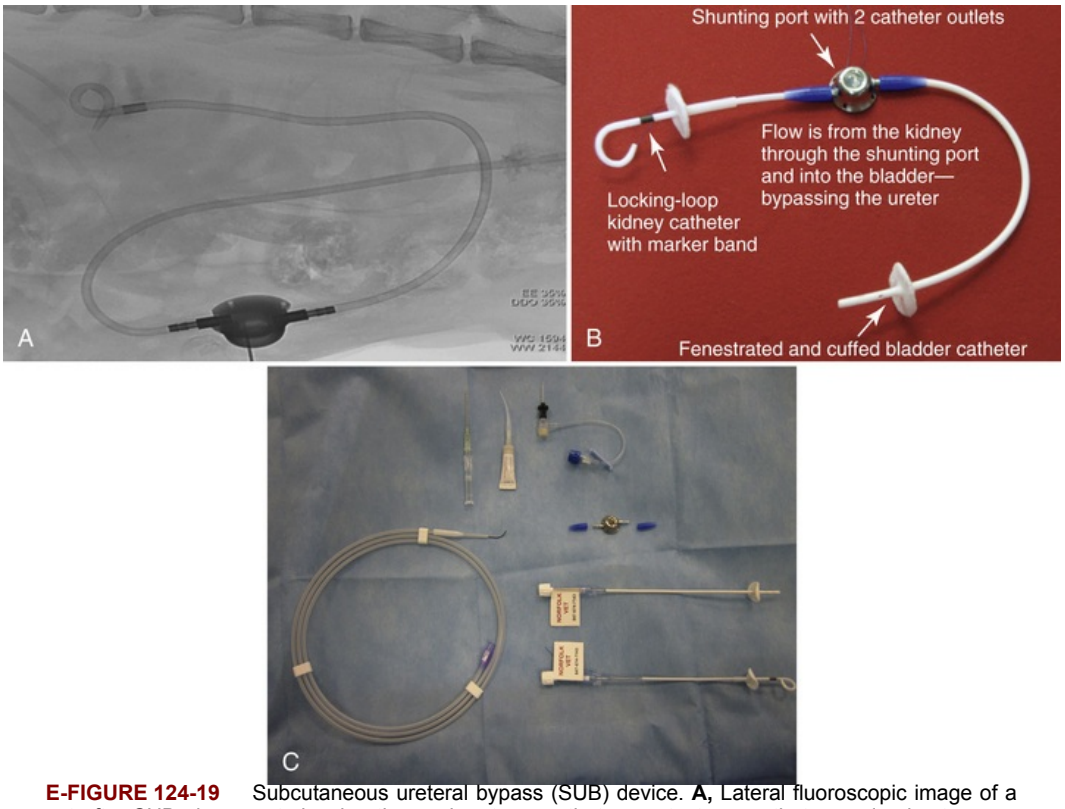
FIGURE 124-18 Cystoscopic and fluoroscopic-guided retrograde ureteral stent placement in a female dog. **A,** Cystoscopic image of a dog in dorsal recumbency showing the left ureterovesicular junction (UVJ). **B,** Guidewire being advanced into the ureteral lumen from the UVJ. **C,** Open-ended ureteral catheter being advanced over the guidewire into the ureteral lumen. **D,** Fluoroscopic image of the guidewire (white arrow) and open-ended ureteral catheter (black arrow) being advanced retrograde up the ureter. **E,** The wire is removed and the catheter remains in the ureter for a retrograde ureteropyelogram. **F,** Retrograde ureteropyelogram being performed, outlining the ureteral obstruction. **G,** Guidewire (white arrow) advanced back into the catheter and curled within the renal pelvis with the ureteral catheter (black arrow) advanced to the renal pelvis. **H,** Contrast seen within the renal pelvis

after a pyelogram was performed through the ureteral catheter (black arrow). **I,** The ureteral catheter (black arrow) is pulled back over a guidewire from the UPJ in image **(H)** to the UVJ in image **(I)** allowing for measurement of the ureteral length for stent sizing. **J,** The ureteral stent (blue arrow) is advanced over the guidewire and curled within the renal pelvis. The bladder is filled with contrast to be able to mark the UVJ under fluoroscopy. **K,** Once the proximal loop of the stent (blue arrow) is within the renal pelvis the guidewire is retracted (white arrow). **L,** The guidewire is pulled back to the distal end of the stent within the urethra. Notice the distal end of the stent is folding into the bladder once the wire is not within the lumen. **M,** The distal end of the stent is being pushed into the urinary bladder. **N,** The pusher catheter (yellow arrow) has a radiopaque mark to mark the distal end of the stent. Notice the wire is crossing the junction between the stent (blue arrows) and pusher. The stent is coiling within the urinary bladder. **O,** The entire distal end of the ureteral stent is coiled within the urinary bladder (blue arrow) and the pusher catheter is in the urethra (yellow arrow). **P,** Endoscopic image of the ureteral stent as it exits the UVJ. The black mark seen is an endoscopic marker to alert the endoscopist when the distal loop of the pigtail is beginning. **Q,** Endoscopic image of the junction of the ureteral stent and the pusher catheter as they both exit the working channel of the endoscope. Notice the guidewire is through the lumen of both catheters. **R,** Once the stent is within the bladder the pusher catheter and wire are completely removed and fluid is seen draining through the fenestrations of the stent ensuring patency.

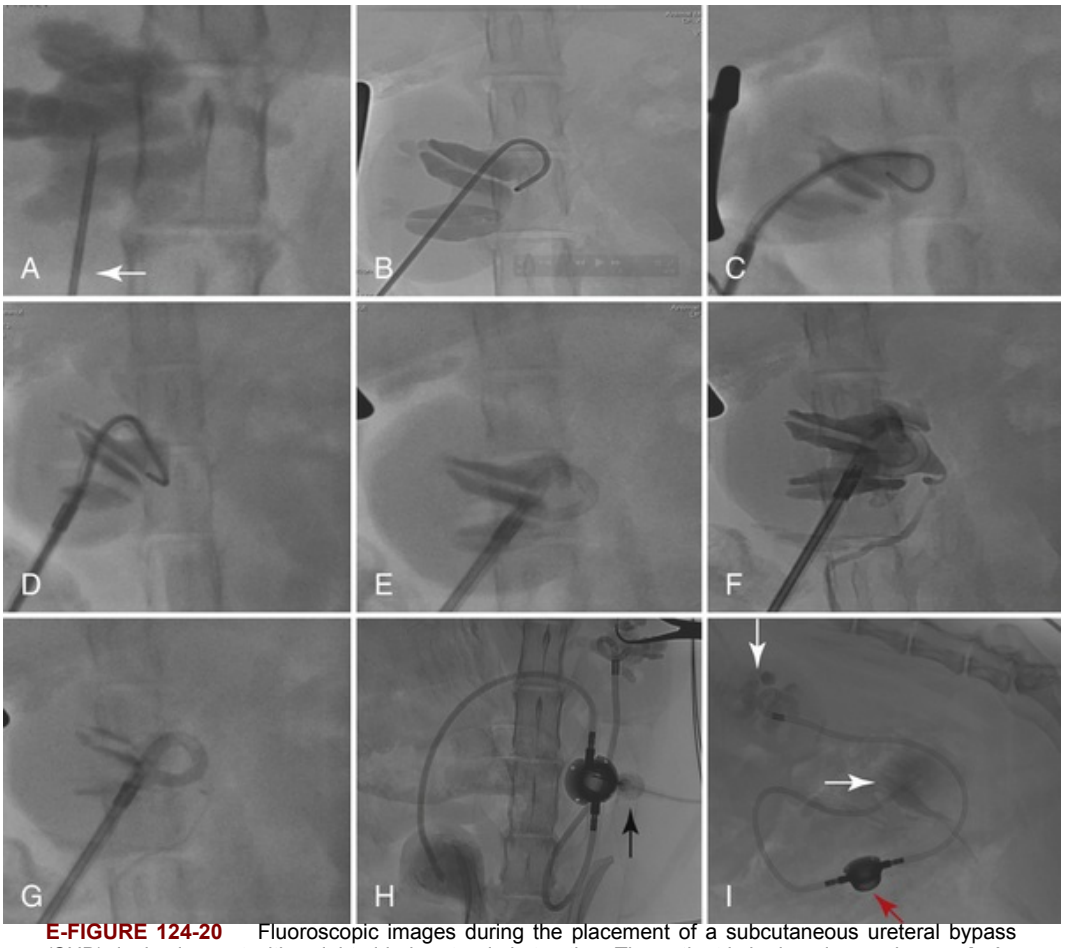
If pyonephrosis is present, as it has been in ≈25-30% of dogs with ureteral obstruction in the authors' practice, then once the renal pelvis is catheterized with the open-ended ureteral catheter, this pelvis should be flushed and drained to provide adequate pelvic lavage prior to placing the ureteral stent. Care is taken to remove as much of the purulent debris as possible.

SUB Device

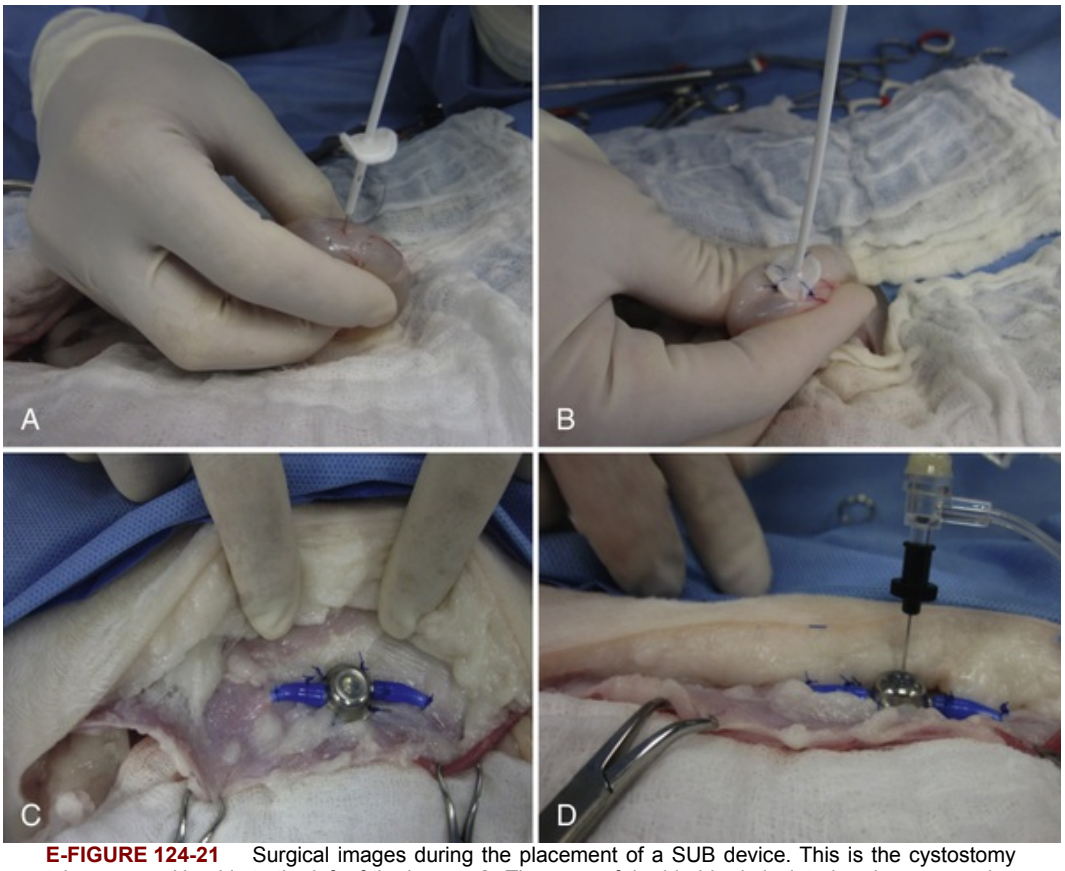
The SUB device (E-Figure 124-19) typically is used for all causes of ureteral obstructions in cats, but is used only rarely in dogs. This device has simplified the treatment of ureteral obstructions. The bladder apex and affected kidney are exposed through a ventral midline celiotomy. Using the modified Seldinger technique, an 18 ga catheter is advanced through the caudal pole of the kidney and into the renal pelvis. An antegrade pyelogram is performed and then a J-tipped 0.035" guidewire is advanced through the catheter and coiled within the renal pelvis (E-Figure 124-20). The 18 ga catheter is removed over the wire while monitoring under fluoroscopic guidance, and the locking-loop nephrostomy tube is advanced over the wire, so that it can be coiled within the renal pelvis. The string is then locked. Next, the urinary bladder apex is isolated and a pursestring suture is placed using 3-0 monocryl suture (E-Figure 124-21). A #11 scalpel blade is used for making a small stab incision in the bladder (in the center of the pursestring suture) and the cystostomy catheter is advanced into the bladder lumen using the hollow trocar. The sharp stylet is removed and the pursestring is tightened. Then, suture is used for securing the Dacron/silicone cuff to the bladder wall (full thickness), using 3 interrupted sutures. After the first suture, sterile cyanoacrylate glue is used for gluing the Dacron cuff to the bladder serosa. Then the final 2 sutures are placed so that the catheter is secure. Finally, the nephrostomy and cystoscopy tubes are connected to the subcutaneous shunting port (E-Figures 124-21 and 124-22). The skin and subcutaneous tissues lateral to the incision are dissected down to the abdominal musculature and the catheters are passed through the body wall, leaving enough room for the shunting port and some tubing to connect to the male-to-male adaptor (≈6 cm). The nephrostomy catheter is passed caudally and the cystostomy catheter cranially, which helps to prevent kinking. The blue cuff is advanced over the nephrostomy catheter and the port is attached. The pin of the port is used for securing the locking string so that the pigtail of the catheter is locked (see E-Figure 124-22). The locking string is cut using a #11 blade, ensuring that none of it protrudes from the catheter once it is advanced over the barbs of the port. This is a site of potential leakage. The same procedure is done for the bladder catheter, cranial to the port. Once the system is closed, both catheters are clamped off using digital pressure and the port is injected with saline to ensure there is no leakage. Care should be taken to ensure that no fluid is flushed up into the kidney catheter using digital pressure on the tubing, as that could over-distend the pelvis. Then, the port is secured to the body wall using permanent suture material. Finally, the system is drained of fluid using a non-coring Huber needle and the system is flushed with contrast under fluoroscopic guidance. Digital subtraction radiology is recommended to monitor for leakage at the kidney, bladder, and port, as well as any kinking of the device. Once patency is confirmed, the subcutaneous tissue is closed and topical bupivacaine is infused into the pocket. Then, the abdomen is flushed copiously with warm saline and closed routinely. A final fluoroscopic image is taken to ensure no kinking of the catheters is seen prior to complete closure.



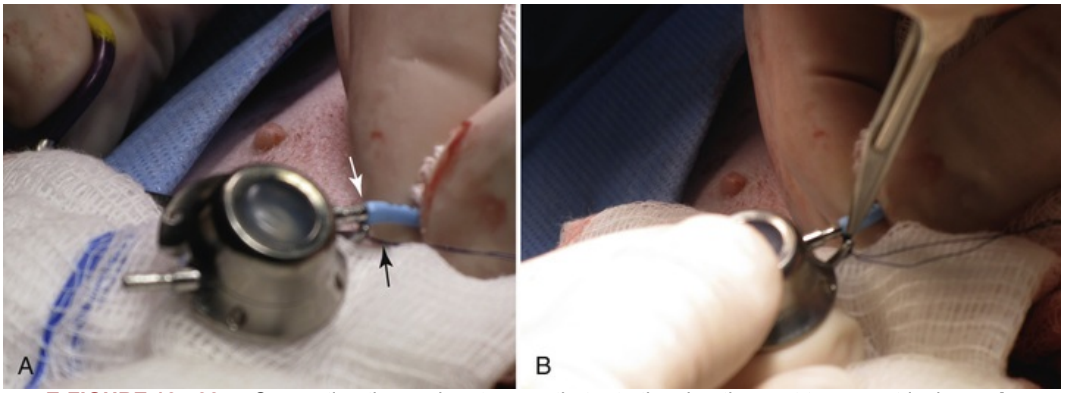
E-FIGURE 124-19 Subcutaneous ureteral bypass (SUB) device. **A,** Lateral fluoroscopic image of a cat after SUB placement showing the nephrostomy catheter, cystostomy catheter, and subcutaneous shunting injection port. **B,** The device assembled outside of the patient. **C,** Each piece of the device and the equipment needed for SUB placement: an 18 gauge over-the-needle catheter, a 0.035" angle-tipped hydrophilic guidewire or "J-tipped" guidewire, the nephrostomy and cystostomy catheter, sterile tissue glue (cyanoacrylate), the shunting injection port with the cuffs that secure the junction on the catheters and a Huber needle used to flush and inject the access port, connected to a T-port connector.



E-FIGURE 124-20 Fluoroscopic images during the placement of a subcutaneous ureteral bypass (SUB) device in a cat with a right-sided ureteral obstruction. The patient is in dorsal recumbency. **A,** An 18-gauge catheter (white arrow) is advanced into the renal pelvis from the caudal pole of the kidney. This is usually how the initial pyelogram is done unless the renal pelvis is < ≈6-7 mm. **B,** The "J"-tipped wire is passed through the renal catheter, and allowed to bend within the renal pelvis. **C,** The locking-loop nephrostomy catheter is being advanced over the "J"-tipped wire as it is making the bend along the renal pelvis. **D,** The coil of the nephrostomy catheter over the wire. **E,** The wire removed as the pigtail is made by locking the loop of the nephrostomy catheter. **F,** Ureteropyelogram performed showing the dilated renal pelvis and proximal tortuous ureter, which is obstructed mid-ureter by stones. Notice there is no leakage at the entry point of the nephrostomy tube at the caudal pole of the kidney. **G,** Draining of the renal pelvis through the nephrostomy tube showing patency. **H,** The SUB device is flushed with a 22-ga non-coring Huber needle (black arrow) prior to closing the abdomen. Notice the pyelogram, cystogram, and no leakage of contrast is seen from any junction of the system (port, kidney, bladder). **I,** Lateral fluoroscopic image of the SUB device. The white arrows are the nephrostomy and cystostomy tube and the red arrow is the shunting port.



E-FIGURE 124-21 Surgical images during the placement of a SUB device. This is the cystostomy tube access. Head is to the left of the image. **A,** The apex of the bladder is isolated and a purse-string suture is made. Then a stab incision is made through the center and into the lumen for the cystostomy catheter to be advanced into the bladder lumen using the sharp stylette. **B,** Once the catheter is within the bladder lumen, the pursestring is tightened around the catheter and the Dacron cuff is sutured using 3 interrupted sutures to the bladder wall. **C,** The subcutaneous tissue is dissected off the ventral abdominal wall on the ipsilateral side of the obstruction just lateral to the incision and the nephrostomy catheter and cystostomy catheter are passed through the body wall and connected to the shunting port. **D,** The shunting port is gently sutured to the ventral body wall musculature to avoid tissue necrosis and port loosening and a Huber needle inserted into the shunting port to test the SUB device prior to closing the abdomen and to ensure there is no leakage.



E-FIGURE 124-22 Connecting the nephrostomy catheter to the shunting port to prevent leakage. **A,** The locking-loop nephrostomy catheter being connected to the pin of the shunting port (white arrow), with the locking string (black arrow) being pulled until it is entrapped. **B,** The string is entrapped on the first rung of the pin and then cut flush with the pin using a #11 blade.

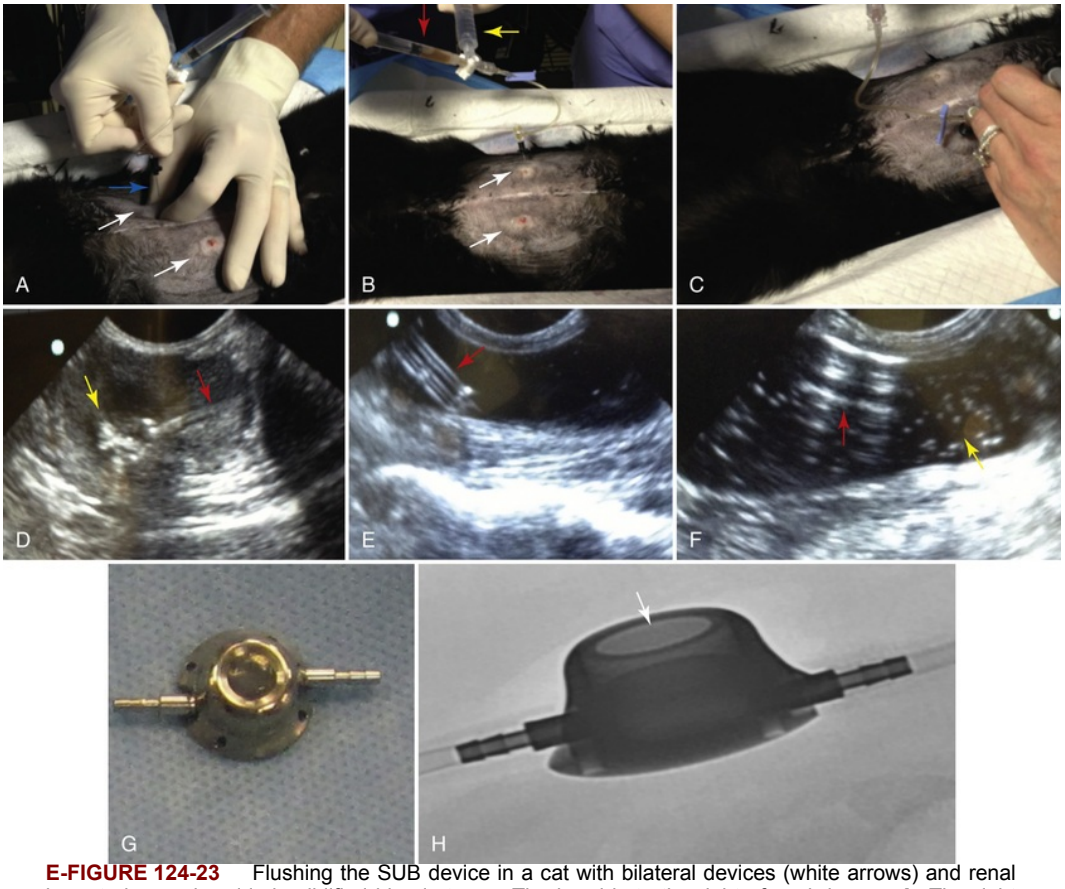
Special Considerations

Proper training on the use of stents and ureteral bypass devices is recommended prior to considering performing these procedures. Good-quality imaging and endoscopic expertise should be available. Endoscopic ureteral stenting in male dogs is possible with flexible cystoscopy, but sometimes percutaneous perineal access for rigid cystoscopy makes this procedure easier.

Follow-up

Patients with ureteral stents or SUB devices need to be monitored very carefully. Feline patients are at high risk of developing post-obstructive diuresis and if careful fluid replacement therapy is not employed, fluid overload can occur (see ch. 129). Care is taken to maintain an appropriate fluid balance using enteral hydration when possible. Treatment with broad spectrum antibiotics (including a fluoroquinolone) for 2 weeks is recommended to help prevent post-operative biofilm development on urinary devices.[62] Routine urinary tract ultrasonography focusing on the renal pelvis diameter, stent location, ureteral diameter, presence of any free fluid, and location of stent/SUB catheters in the urinary bladder, is performed to ensure there is no evidence of stent/SUB device migration, occlusion, or encrustation. The authors recommend performing a urine culture every 3-6 months, and a SUB flush every 3-6 months.

The SUB device should be flushed using either ultrasonographic or fluoroscopic guidance at 1 week, 1 month, and then every 3 months thereafter to ensure both the nephrostomy and cystostomy tubes are patent (E-Figure 124-23).



E-FIGURE 124-23 Flushing the SUB device in a cat with bilateral devices (white arrows) and renal hematuria causing dried solidified blood stones. The head is to the right of each image. **A,** The right access port is being palpated and the Huber needle (blue arrow) is being advanced into the silicone diaphragm of the port in a perpendicular manner. **B,** Once the needle is in place, a urine sample is taken for analysis and culture and to ensure access is appropriate (red arrow). Then, using a 2-way stopcock and T-connector, sterile saline is infused into the port. **C-F,** The infusion is monitored using ultrasound guidance to ensure the renal pelvis does not over-distend and bubbles are seen in the pelvis **(D)** and urinary bladder **(E** and **F)** during infusion. **G and H,** The SUB shunting port **(G)** showing the shape of the flat silicone top **(H)** where the needle should be perpendicularly inserted (white arrow).

Outcome/Complications

The most critical need for success in ureteral interventions is the operator having appropriate training and experience. These are some of the more difficult interventional radiology/interventional endoscopy cases being performed. In addition, the anesthetic procedure should be handled with caution, as these patients have renal disease and, often, concurrent heart disease.

In a recent retrospective study of 128 obstructed cats with 158 obstructed ureters treated interventionally via stenting or SUB device placement, the median survival time was 762-923 days (3 days to >6 years) for all causes of death, and >1442 days for those dying from renal causes.[56] In another retrospective evaluation of 44 dogs (57 ureters) treated with ureteral stents for benign ureteral obstructions, the median survival time was >1158 days and 68% of dogs were still alive at the time of last follow-up.[61] Another study evaluating 13 dogs with pyonephrosis that underwent ureteral stent placement in addition to renal pelvic lavage revealed excellent long-term survival; recurrence of urinary tract infection occurred in ≈50% of dogs, nearly all of which could be cleared without the need for further intervention.[60]

Complications are separated into 4 categories: procedural (during device placement), perioperative (within the first week, typically during hospitalization), short-term (1 week to 1 month) and long-term (>1 month) (see Table 124-3).

Alternatives

A locking-loop nephrostomy tube technique has been reported for successful ureteral decompression in dogs and cats prior to definitive treatment of ureteral obstruction.[63] These tubes work very well, but with the advent of the SUB device, surgical time is similar for a definitive intervention (SUB) as compared to a temporary one (nephrostomy tube), so the locking-loop nephrostomy approach rarely has been necessary, to date, in the authors' practice.

Treatment of Malignant Ureteral Obstructions

Indications

Decompression of a ureteral obstruction secondary to trigonal neoplasia that is resulting in ureterovesicular junction (UVJ) occlusion can be done using an antegrade approach under ultrasonographic and fluoroscopic guidance (see ch. 351).[64]

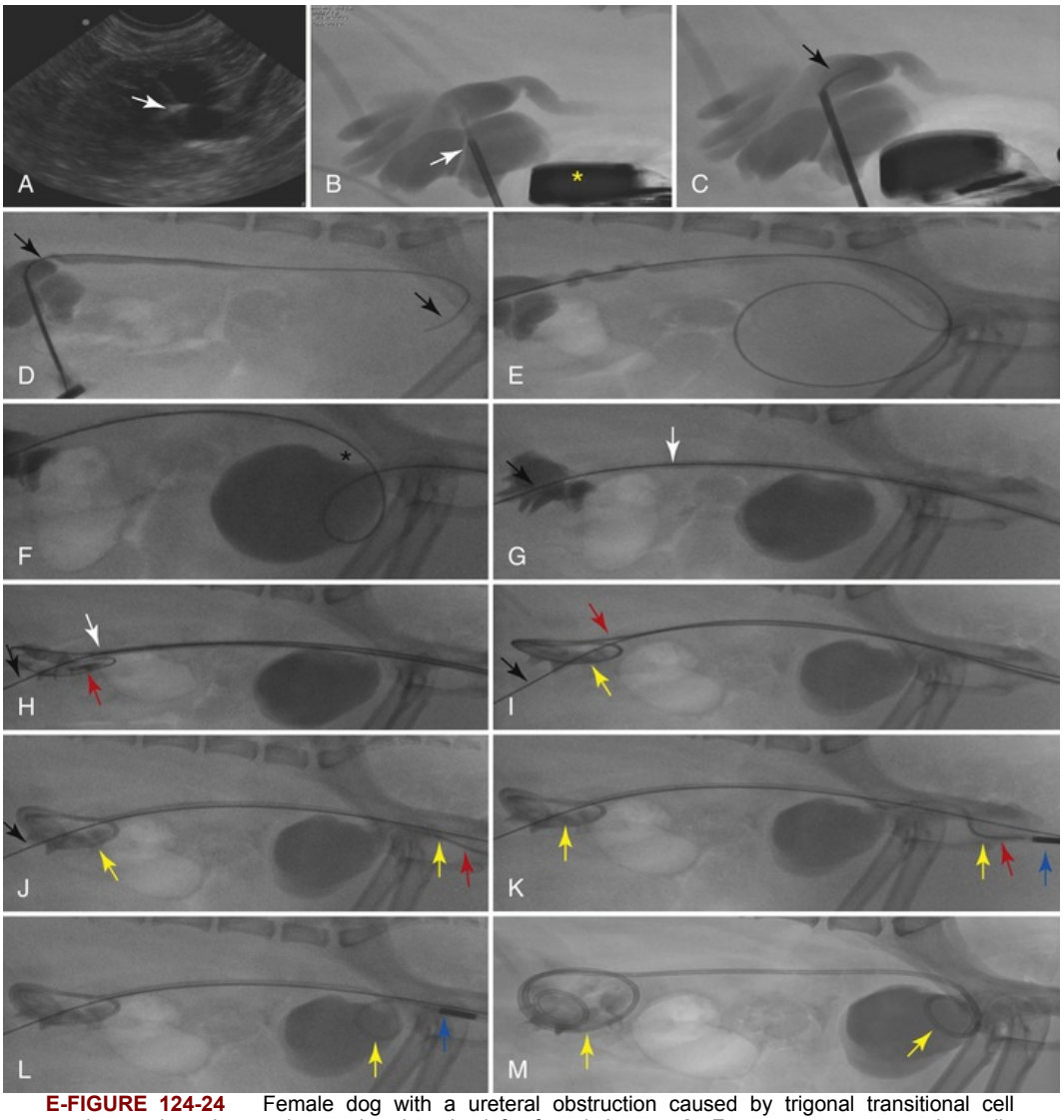
Equipment

Fluoroscopy and ultrasound, in addition to a renal puncture needle, contrast, guidewires, catheters, access sheaths, and ureteral stents, are needed for this procedure.

Procedure

The patient is anesthetized and the area of the kidney and vulva or prepuce is clipped and aseptically prepared. The patient is placed in lateral recumbency, with the obstructed kidney facing up (E-Figure 124-24). A 3 mm skin incision is made where the ultrasound probe shows the best renal access. With ultrasound guidance, an 18 ga renal access trocar needle is used for puncturing the kidney through the greater curvature toward the ureteropelvic junction (UPJ) (see E-Figure 124-24). Once the needle tip is visualized in the renal pelvis, the sharp stylet is removed and an extension set with a 3-way stopcock connected to one empty and one diluted (50%) contrast-filled syringe is connected to the needle. A urine sample is obtained and then contrast is injected to fill the renal pelvis and proximal ureter under ultrasound guidance. Then, a stiff 0.035″ angle-tipped hydrophilic guidewire is used for cannulating the renal pelvis, and is angled down the ureter to the UVJ and into the urinary bladder. This is monitored with fluoroscopic guidance. Once the tumor is crossed, the wire is then advanced down the urethra until through-and-through access is accomplished. Then, a 7 Fr × 45 cm (female) or 55 cm (male) sheath is advanced retrograde, up the urethra, into the ureter through the UVJ, and up to the renal pelvis. Care is taken to ensure the dilator of the sheath does not puncture the renal parenchyma. Once the dilator is removed, a contrast study is performed through the side port of the sheath to obtain a pyelogram for a second guidewire. Then a standard angle-tipped hydrophilic guidewire (0.035″) is advanced up the sheath and coiled within the renal pelvis next to the safety through-and-through wire. The sheath is then withdrawn from the UPJ to the UVJ, leaving both wires in the renal pelvis, while

monitoring under fluoroscopic guidance. This allows measurement of the ureteral length for stent sizing. Finally, the sheath is replaced over the second guidewire, next to the safety wire, is advanced to the renal pelvis as previously described, and the proper-sized stent is placed over this guidewire, through the sheath. Once a coil is seen within the renal pelvis, the sheath is withdrawn, maintaining the stent within the renal pelvis and monitoring the distal end of the stent so that it is appropriately pushed into the urinary bladder under fluoroscopic guidance (see E-Figure 124-24).



E-FIGURE 124-24 Female dog with a ureteral obstruction caused by trigonal transitional cell carcinoma; lateral recumbency, head to the left of each image. **A,** For percutaneous renal needle access (white arrow), ultrasound is used. **B,** Fluoroscopic ureteropyelogram during contrast infusion with ultrasound guidance (yellow asterisk). **C,** The angle-tipped hydrophilic guidewire (black arrow) is advanced down the ureter under fluoroscopic guidance to the level of the UVJ obstruction **(D). E,** The wire is negotiated through the obstruction and into the urinary bladder. It is aimed out the urethra at the trigone. **F,** The wire is passed out the urethra with the assistance of a cystourethrogram. Notice the space-occupying effect of the tumor in the dorsal bladder wall at the UVJ (black asterisk). **G,** A ureteral dilator and sheath (white arrow) are passed retrograde over the guidewire (black arrow) to the renal pelvis. **H,** A second guidewire (red arrow) is advanced through the sheath, retrograde, and coiled up within the renal pelvis. Notice the initial access safety wire (black arrow) is still in place and the sheath (white arrow) remains at the UPJ. **I,** The sheath is removed off both guidewires and the ureteral length is measure by marking the distance from the UPJ to the UVJ. It is then replaced only over the second wire (red arrow); the double pigtail ureteral stent (yellow arrow) is advanced over that guidewire. The safety-wire (black arrow) remains in place. **J,** Once the ureteral stent (yellow arrows) is coiled within the renal pelvis proximally, the guidewire and sheath are pulled back so that the wire is only in the part of the stent within the urethra (red arrow) and the sheath is only within the distal urethra. **K,** The ureteral stent (yellow arrows) is being pushed into the urinary bladder with a pusher catheter (blue arrow). Notice the wire (red arrow) is crossing the junction of the stent and pusher to keep both together. Notice the stent starting to buckle. **L,** The stent is then pushed into the urinary bladder (yellow

arrow) and the pusher catheter (blue arrow) and safety wire are removed **(M).**

Special Considerations

Conversion for surgical placement is rare, but one should be prepared to do this if the interventional procedure is unsuccessful.

Outcome

In a study of 12 dogs (15 ureters) that had ureteral stents placed for ureteral obstructive neoplasia, 1 dog required surgical conversion.[64] All patients survived to discharge and the median survival time from the time of diagnosis was 285 days (range, 10-1571 days) and following stent placement, it was 57 days (range, 7-337 days).

Follow-up

We recommend waiting a minimum of 1 week before starting, or resuming, chemotherapy, due to the risk of post-obstructive diuresis and associated dehydration. Urinary tract ultrasound examinations and urine cultures should be obtained at 2 weeks, 6 weeks, and then every 3 months thereafter. Appropriate complete blood counts and serum biochemistry profiles should also be done. All clients should be encouraged to consult with an oncologist. After stent placement, and if the patient is not azotemic, treatment with chemotherapy and nonsteroidal anti-inflammatory drugs has been shown to prolong survival.

Complications

The biggest risk is ureteral perforation resulting in uroabdomen or a puncture hole in the kidney that remains when access across the tumor is not obtained. If stent placement is unsuccessful, surgical conversion is recommended. If a stent is properly placed, then any puncture should heal within a few days and conversion is not needed. Other potential complications include stent migration, stent irritation, chronic infections, and stent occlusion. All of these are rare.

Alternatives

A SUB system can be used, but it requires surgical placement. For cases where the tumor is localized to the urinary bladder +/− proximal urethra, the entire bladder and proximal urethra have been removed via a radical cystectomy and both renal pelvises have had a SUB catheter placed. Then, both kidney catheters are connected to a 3-way port (Figure 124-25) and a third catheter is placed down the urethra or into the vagina. These dogs have been completely incontinent of urine, but if the procedure is done appropriately, only microscopic disease will remain.

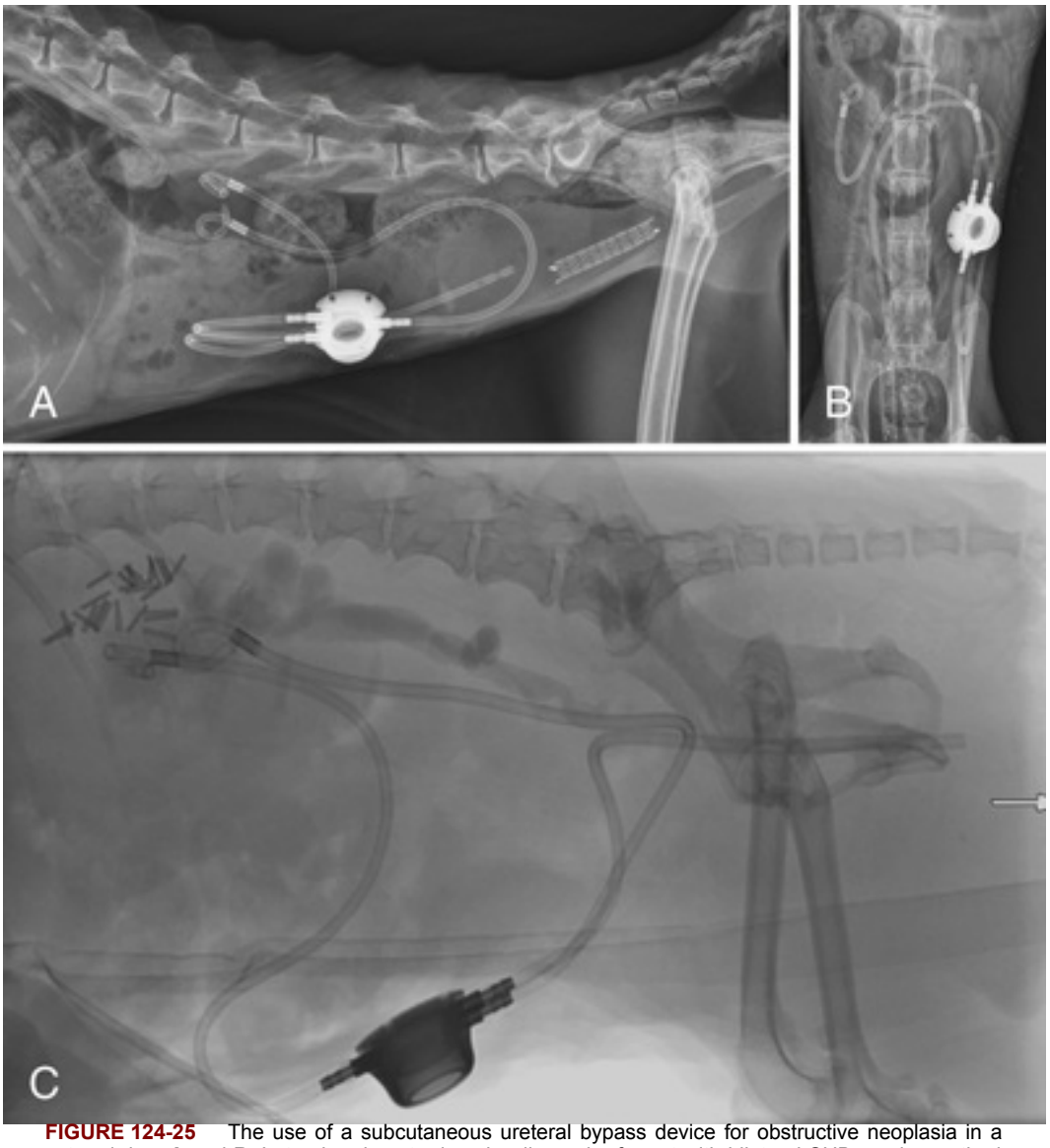


FIGURE 124-25 The use of a subcutaneous ureteral bypass device for obstructive neoplasia in a cat and dog. **A** and **B,** Lateral and ventrodorsal radiograph of a cat with bilateral SUBs and a urethral stent for trigonal obstructive neoplasia. Notice the 3-way shunting port connecting 2 kidney catheters to a bladder catheter. **C,** Fluoroscopic image of a dog after bilateral SUBs and a radical cystectomy. Notice the cystostomy catheter is down the urethra after a radical cystectomy was performed.

Treatment of Idiopathic Renal Hematuria

Indications

Idiopathic renal hematuria is a rare condition that is seen in young, large-breed dogs, and has also been reported in older dogs and cats of various ages. This condition results in persistent port-wine colored urine, and may be progressive, become bilateral, result in ureteral or urethral obstructions due to blood clots, or result in progressive anemia.[65-68] The lesion usually is of benign origin and may be an angioma, hemangioma, or ulcerative lesion of the renal pelvis (pyelitis). If any of these conditions occurs, then treatment for this condition can be considered using a renal-sparing option like sclerotherapy or ureteroscopy with endoscopic electrocautery. Traditionally, ureteronephrectomy has been performed for treatment of this condition, but >30% of affected animals develop bilateral disease over time; however, the lesion is nearly always benign and does not involve the nephrons, making nephrectomy unnecessary.[65-68]

Equipment

A cystoscope (rigid or flexible) is needed to diagnose which renal unit is bleeding. Perineal access should be performed in male dogs once the diagnosis is made based on flexible endoscopy. A UPJ balloon is used for ureteral occlusion sclerotherapy infusions and these come in 5 and 6 Fr sizes; a stiffened 0.035" angle-tipped hydrophilic guidewire is used for placing this catheter. For sclerotherapy, a sterilized liquid 0.5-1% silver nitrate solution, in addition to a 1 : 1 : 3 ratio of 1 part 5% povidone iodine:1 part 76% meglumine diatrizoate (76MD):3 parts sterile 5% dextrose in water (D5W) is used.

Instead of saline irrigation during endoscopy, 5% D5W is used. This helps to prevent red blood cell lysis, improving the visibility during cystoscopy. In addition, D5W prevents silver salt development during sclerotherapy with silver nitrate, and aids conduction during Bugbee electrocautery, if necessary.

For ureteroscopic electrocautery, a 0.035" stiffened angle-tipped hydrophilic guidewire is used with a ureteral access sheath to advance the flexible ureteroscope. Irrigation is done manually through the ureteroscope using D5W. Once a lesion is found in the renal pelvis, a Bugbee cautery electrode (1-2 Fr) is used in either blend or coagulation mode through the working channel of the ureteroscope to ablate the lesion. This small-diameter electrode maintains the flexibility of the ureteroscope within the renal pelvis. If necessary, a ureteral access sheath can be used for maintaining ureteral patency during ureteroscopy. An open-ended ureteral catheter and appropriately sized ureteral stent are needed at the completion of the procedure.

Procedure

Diagnostic cystoscopy is performed to identify which ureter has blood coming from it (Figure 124-26; see ch. 108). Then, using a rigid cystoscope, a guidewire and open-ended ureteral catheter combination are used for cannulating the bleeding ureter/kidney. Once the catheter is midway up the ureter, a retrograde ureteropyelogram using endoscopic and fluoroscopic guidance is performed to assess for any luminal defects.

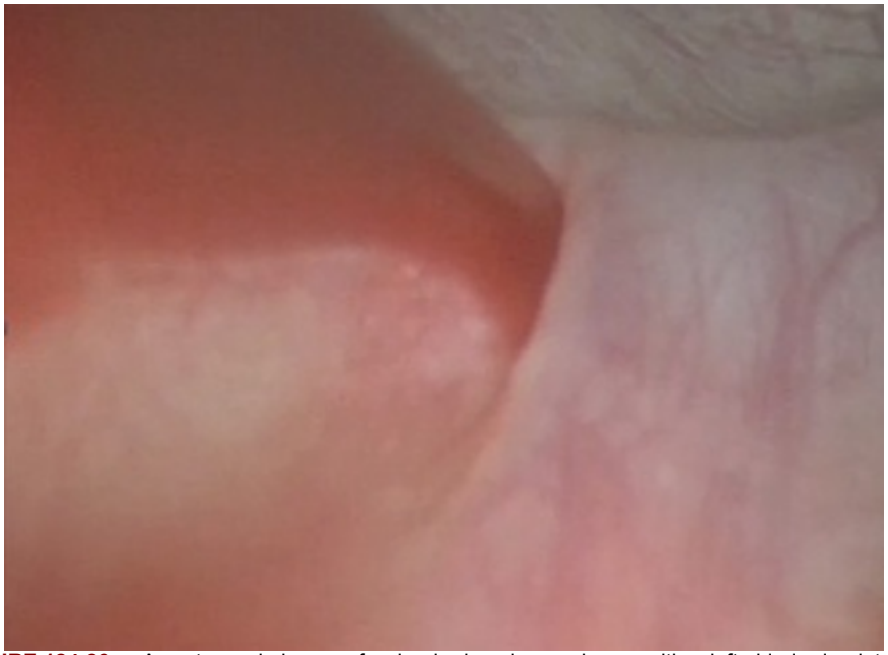


FIGURE 124-26 A cystoscopic image of a dog in dorsal recumbency with a left-sided urine jet with severe upper tract hematuria.

Sclerotherapy

Sclerotherapy typically is performed first (Figure 124-27). The contrast material used is 76% MD, as this is the recommended mixture for povidone iodine to provide cauterization in humans.[69] The guidewire is advanced to the renal pelvis and then a UPJ balloon is advanced over the guidewire. Once the catheter is in the proximal ureter, the balloon is inflated with air (0.4 mL) and the lumen of the ureter is occluded. The patient is tilted into a 20° Trendelenburg position (hindlimbs higher than kidneys) to enhance accumulation of contrast material in the renal pelvis. Next, the contrast is used for measuring the renal pelvis collection;

accurately determining this volume will allow appropriate renal pelvis filling, to avoid overdistension or parenchymal backfilling. Once this volume is determined, then 2 infusions of a povidone iodine solution (1 : 1 : 3; 1× 5% PI: 1× 76% MD: 3× D5W) are performed, with a dwell time of 10-20 minutes each. Once each dwell is passively drained from the catheter, then 2 more infusions of liquid sterile 0.5-1% silver nitrate solution are administered, with a dwell time of 10-20 minutes each. This is not mixed with any contrast nor diluted with any fluid.[70,71] Finally, the solution is drained and a guidewire is re-advanced up the catheter and coiled in the renal pelvis for a ureteral stent to be placed.

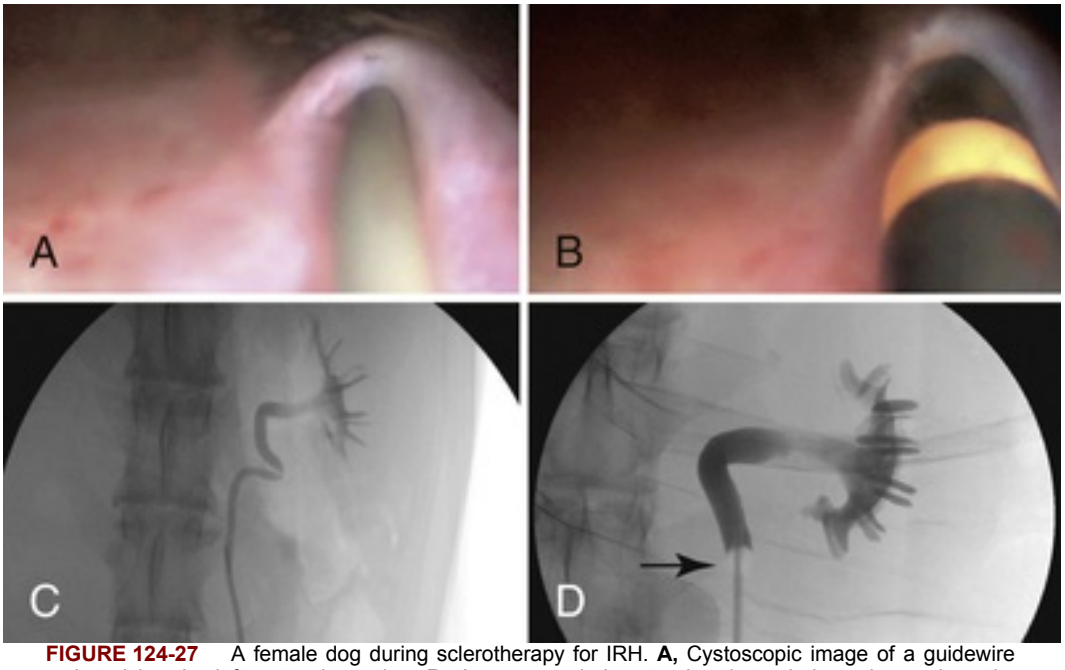


FIGURE 124-27 A female dog during sclerotherapy for IRH. **A,** Cystoscopic image of a guidewire catheterizing the left ureteral opening. **B,** An open-ended ureteral catheter being advanced up the ureter over the guidewire. **C,** A fluoroscopic image during a ureteropyelogram through the ureteral catheter. **D,** A UPJ balloon catheter (black arrow) occluding the ureteral outflow during sclerotherapy infusion.

Ureteroscopy with Electrocautery

Ureteroscopy with electrocautery is reserved for dogs weighing >20 kg, and preferably is performed after a ureteral stent has been in place for at least 1-2 weeks to allow for passive ureteral dilation, which makes navigation in the ureter and renal pelvis easier.[72] A guidewire is passed up to the proximal ureter, avoiding the renal pelvis to prevent iatrogenic trauma. Then, a ureteral access sheath that can accommodate the flexible ureteroscope is advanced over the guidewire under fluoroscopic guidance. Once the sheath is in the ureter, then the ureteroscope is advanced over the guidewire, up the ureter, using D5W for irrigation. Once in the renal pelvis, irrigation is used cautiously to avoid overdistension. Once a bleeding lesion is seen, the Bugbee cautery electrode probe (Figure 124-28) is advanced into the working channel of the ureteroscope and the lesion is cauterized using 12-25 W in contact mode. When complete, then a ureteral stent is delivered over a guidewire and placed as described above.

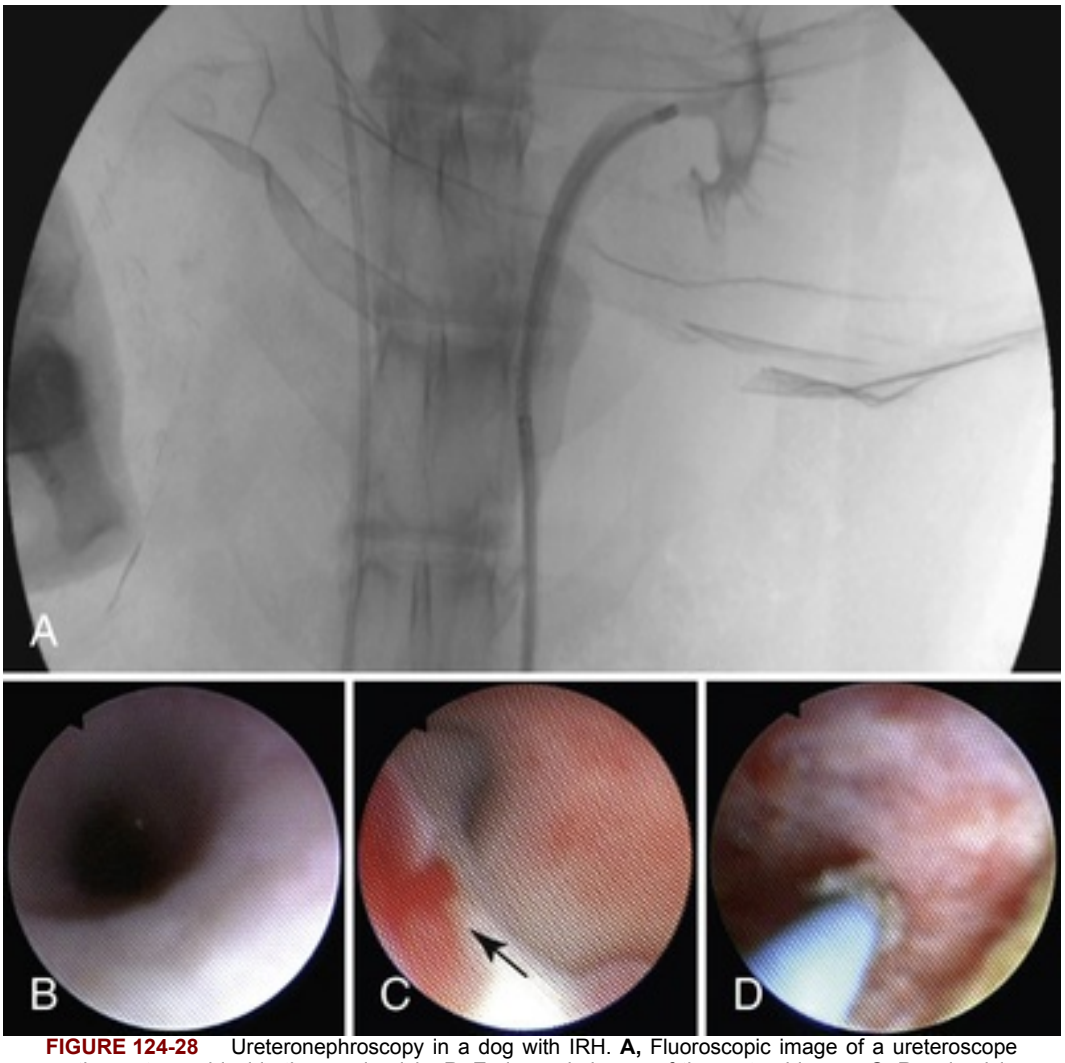


FIGURE 124-28 Ureteronephroscopy in a dog with IRH. **A,** Fluoroscopic image of a ureteroscope up the ureter and inside the renal pelvis. **B,** Endoscopic image of the ureteral lumen. **C,** Renal pelvis bleed visualized (black arrow). **D,** Electrocautery probe within the renal pelvis.

Special Considerations

This procedure should be done by those trained in endourology, ureteral catheterization, and ureteral stenting. It should not be done without fluoroscopic guidance, which is used for measuring the filling volume of the renal pelvis.

Outcome

In a study in which sclerotherapy was used for the treatment of IRH, complete cessation of macroscopic hematuria occurred in 4/6 dogs within a median of 6 hours (range, immediately post-operatively to 7 days).[67] Two additional dogs improved, one moderately and one substantially. None of the dogs required nephrectomy. Ureteroscopy for electrocautery only has been performed in a small number of patients and this is typically reserved for larger patients that have failed sclerotherapy. To date the authors have seen cessation in bleeding in >80% of renal units in which sclerotherapy has been performed.

Follow-up

The bleeding is expected to subside within 24-48 hours after sclerotherapy or electrocautery. Antibiotics are used for 2 weeks after ureteral stenting placement to prevent biofilm formation.[62] After 2-6 weeks, if the bleeding resolves, the stent should be removed. If the bleeding does not stop, then retrograde ureteroscopy

and nephroscopy can be performed, as the stent would have allowed for passive ureteral dilation, making this procedure much easier.

Complications

The most substantial risk is perforating the ureter during cannulation or excessive renal filling/distension resulting in nephritis or pelvic rupture. By using fluoroscopy and endoscopy together, the appropriate filling volume of the renal pelvis during sclerotherapy is ensured. Also, the risk of post-sclerotherapy ureteritis and post-ureteroscopy edema exists, so the operator should be comfortable with retrograde ureteral stent placement.

Alternatives

Selective renal arterial embolization has been considered for this condition, but is not typically needed unless a vascular anomaly is identified on angiography, which has not yet been the case. Ureteronephrectomy should be avoided whenever possible.

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*Cyberwand Dual Ultrasonic Lithotriptor, Olympus, Gyrus/ACMI, Southborough, MA.

†Subcutaneous ureteral bypass (SUB) device, Norfolk Vet Products, Skokie, IL.

CHAPTER 125

Neoplastic Interventional Therapies

Chick Weisse

Interventional radiology (IR) involves the combination of minimally invasive approaches and contemporary imaging modalities to gain access to specific organs in order to deliver a variety of devices or medications for therapeutic purposes (see ch. 120). IR techniques are being increasingly utilized to help manage humans with cancer (interventional oncology, IO) in which traditional therapies have failed or have been demonstrated to provide insufficient benefit. Interventional oncology has been referred to as the "fourth pillar" of oncological care along with medical, surgical, and radiation therapies. Veterinarians have traditionally had little to offer patients with non-resectable or metastatic tumors. Surgery is uncommonly indicated when resections have a high likelihood of substantial morbidity and low likelihood of improved survival times. The relatively limited efficacy of intravenous chemotherapy for macroscopic disease, and the cost, occasional morbidity, and tumor resistance associated with radiation therapy have stimulated the search for additional therapeutic options. Initial results have been promising and regional techniques such as palliative stenting for malignant obstructions, transcatheter chemotherapy, trans-catheter arterial embolization/chemoembolization, and more recently percutaneous tumor ablation, are becoming increasingly investigated.

Palliative Stenting for Malignant Obstructions

Indications and Background

Animals are routinely euthanized for local effects of a tumor rather than the systemic effects associated with a large cancer burden. While these conditions can occur in any lumen such as those of the respiratory (see ch. 121), gastrointestinal (see ch. 123), and cardiovascular (see ch. 122) systems[1-5] (Figure 125-1), one of the more common examples is malignant obstruction of the urinary tract. Life-threatening signs associated with complete urinary tract obstruction or perceived diminished quality of life can lead to owner-elected euthanasia, even when tumor staging confirms localized disease. Minimally invasive endoluminal urethral stenting, and endoscopic or percutaneous ureteral stenting, has been performed in humans to relieve both lower and upper tract obstructions. While endoscopic-guided laser ablation is a common therapy for the typically superficial transitional cell carcinomas (TCCs) experienced in humans, this is not the recommended treatment for the less common and more aggressive, muscle-invasive TCC. Considering the reported TCC laser ablation[6] complications reported in dogs, cost, extended hospitalization times, need for repeat procedures (≈47%), possible limitation to females, and otherwise similar outcomes, stenting appears to compare favorably.

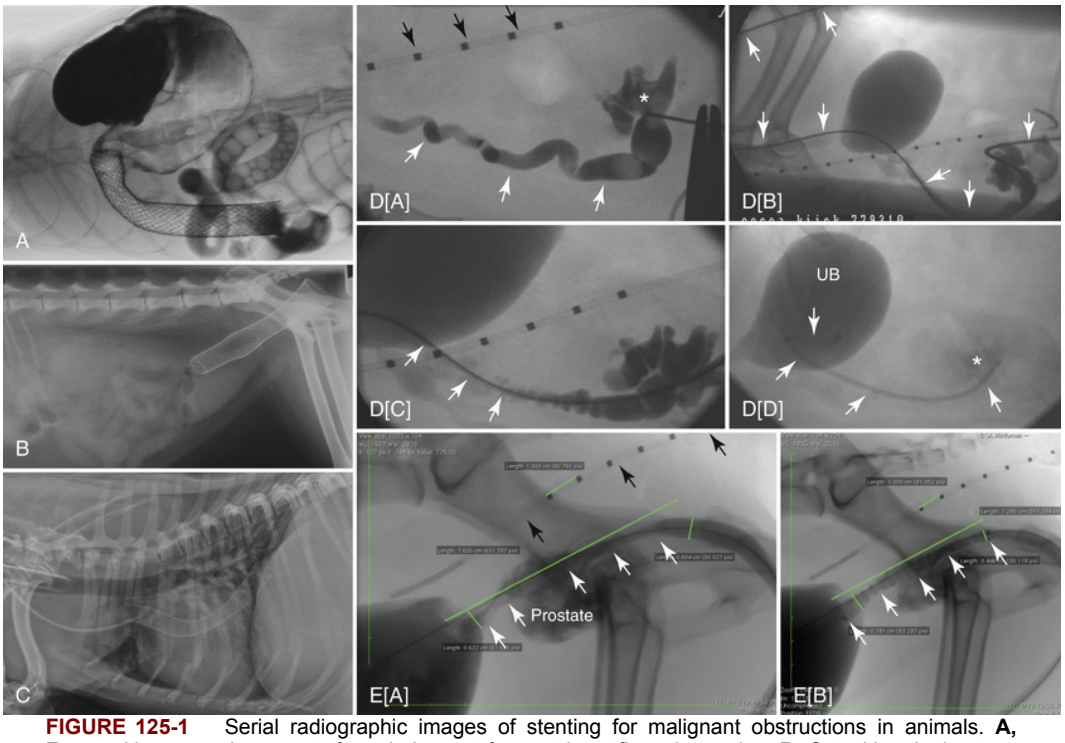


FIGURE 125-1 Serial radiographic images of stenting for malignant obstructions in animals. **A,** Ferret with *per os* placement of a pyloric stent for gastric outflow obstruction. **B,** Cat with colonic stent. **C,** Dog with trans-atrial stent spanning cranial vena cava to caudal vena cava for cardiac mass and venous obstruction. **D,** Dog with percutaneous placement of pigtail stent for urothelial tumor ureteral obstruction (dorsal is to the bottom of the image and cranial is to the right). **D[A],** Needle placement in renal pelvis (asterisk) with contrast ureterogram (white arrows); a measuring catheter (black arrows) shows radiopaque marks that are 1 cm apart from the beginning of one mark to the beginning of the next mark. **D[B],** Guide wire (white arrows) advanced down ureter and out urethra. **D[C** and **D],** Pigtail stent advanced over guide wire spanning obstruction. **E,** Canine prostatic tumor with urethral obstruction (white arrows) before **[A]** and immediately following **[B]** stent placement. Measuring catheter (black arrows, as in **D[A]**) is seen in the descending colon.

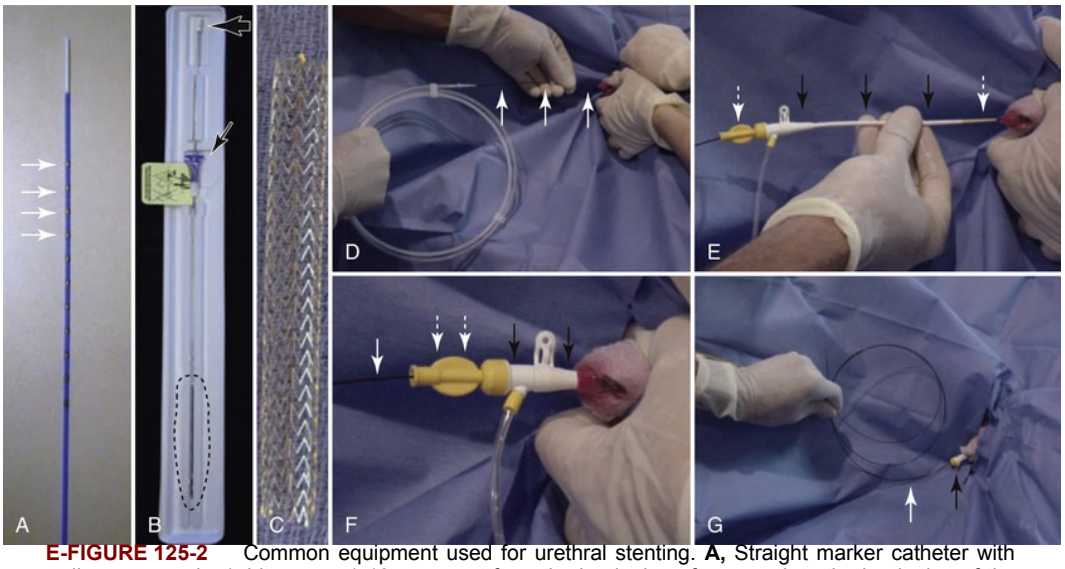
Equipment

Common equipment used for urethral stenting is listed in Box 125-1 and E-Figure 125-2.

Box 125-1

Equipment for Urethral Stenting

- Straight marker catheter[a] with 14 Fr red rubber catheter
- Angiography procedure pack (drapes, bowls, etc.)
- 0.035″ angled, hydrophilic guide wire[b]
- 7 or 8 Fr (or appropriately sized) vascular introducer sheath[c]
- 3-0 Nylon suture material
- 4 Fr hockey stick (“Berenstein”) catheter[d]
- Iohexol contrast agent[e]
- Sterile saline irrigation solution
- Laser-cut, self-expanding metallic stent on delivery system[f]



E-FIGURE 125-2 Common equipment used for urethral stenting. **A,** Straight marker catheter with radiopaque marks (white arrows) 10 mm apart from the beginning of one mark to the beginning of the next mark. This catheter is usually placed within a 14 Fr red rubber catheter that is advanced into the rectum and colon. **B,** Stent delivery system with constrained laser-cut, self-expandable metallic (nitinol) stent (SEMS) (black dotted line) inside the delivery sheath with Y-piece (black arrow) containing diaphragm and side-port. The hub (block arrow) is flushed with saline, as is the side-port (black arrow), prior to use in order to flush out any air. **C,** A deployed urethral SEMS—these should NOT be deployed outside the patient as they are typically NON-RECONSTRAINABLE stents. **D,** 0.035″ angled, hydrophilic guide wire (white arrows) advanced into urethra of a male dog. **E** and **F,** ≈7 Fr introducer sheath (black arrows) and dilator (white dotted arrows) advanced over-the-wire up to the penis and sutured to the prepuce. **G,** The dilator is removed and the penis released. The sheath (black arrow) provides access throughout the procedure. (From Weisse C: Urethral stenting. In Weisse C, Berent A, editors: *Veterinary image-guided interventions,* ed 1, Hoboken, NJ, 2015, Wiley-Blackwell.)

Urethral Stenting Technique (Figure 125-3)

The patient is placed under general anesthesia and positioned in lateral recumbency on a fluoroscopy table. A marker catheter[a] is placed within a 14 Fr red rubber catheter, introduced per rectum, and gently advanced into the descending colon under fluoroscopic guidance. Perioperative antibiotics are routinely used, unless the patient is already receiving systemic antibiotic therapy. A 0.035″ angled, floppy-tip hydrophilic guide wire[b] is inserted into the urethral orifice and advanced into the urinary bladder under fluoroscopic guidance. A 7 or 8 Fr vascular sheath[c] and dilator are placed over the guide wire and advanced into the urethra. In males, a 4 Fr angiographic catheter[d] is advanced over the wire and into the urinary bladder; in females use of the sheath is sufficient. After achieving bladder access with the catheter (male) and/or sheath (female), the urinary bladder is distended with an approximately 50 : 50 mixture of iohexol[e] and sterile saline. It is important to completely fill the urinary bladder so you do not mistake an undistended urinary bladder for the proximal urethra.

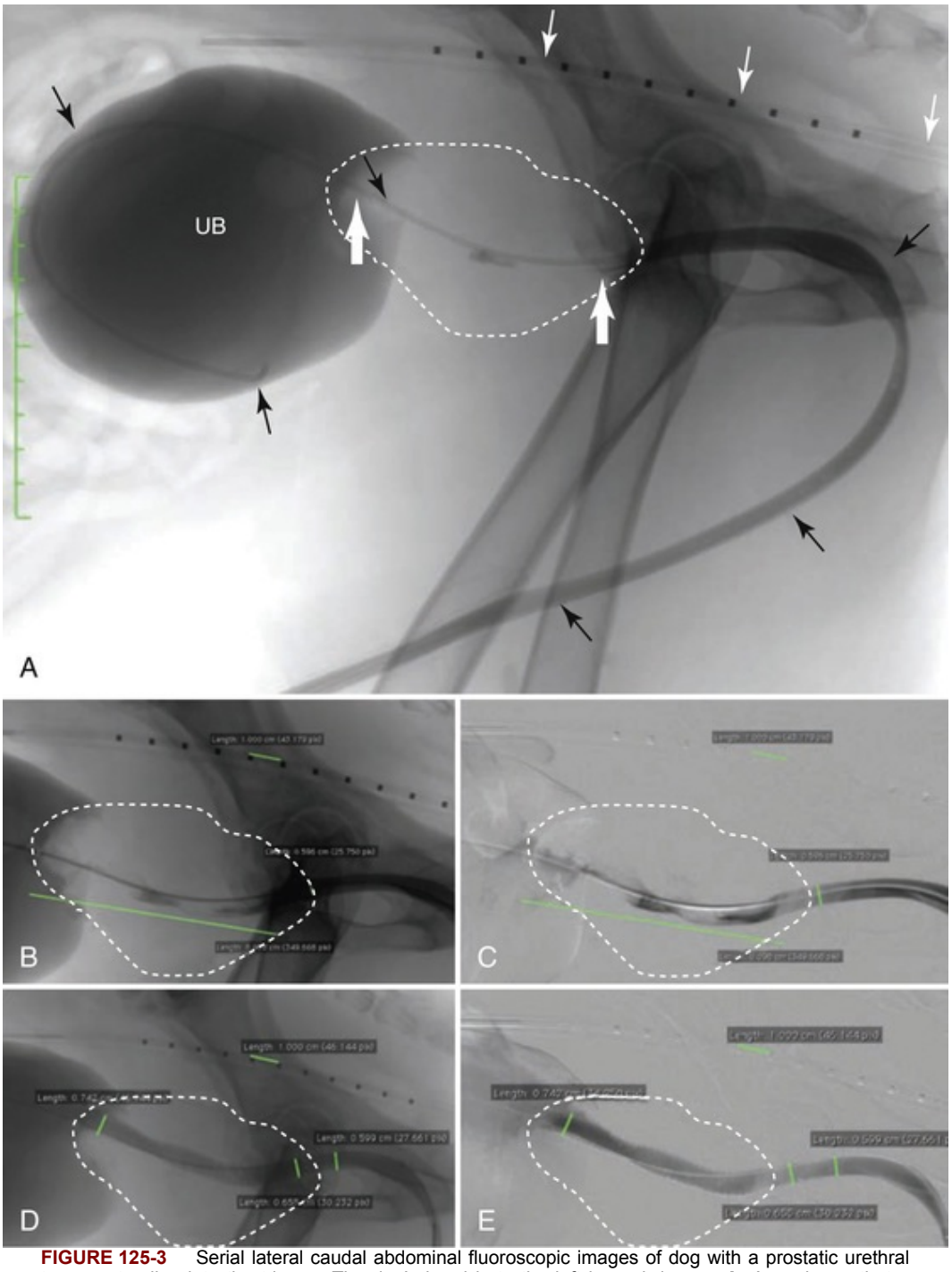


FIGURE 125-3 Serial lateral caudal abdominal fluoroscopic images of dog with a prostatic urethral tumor extending into the trigone. The dog's head is to the left in each image. **A,** A marker catheter (white arrows) has been placed within a 14 Fr red rubber catheter and introduced per rectum in order to calibrate the radiographic images for magnification. A 4 Fr Berenstein catheter (black arrows) has been placed into the bladder over a 0.035″ angled hydrophilic wire that was subsequently removed to fill the bladder with saline and contrast. A urethrogram is performed through the sheath (alternatively the Berenstein catheter can be used) demonstrating a filling defect/obstruction caused by the tumor (white dotted lines) at the level of the trigone and proximal urethra. The urethral narrowing is observed between both white block arrows. Fluoroscopic **(B)** and subtracted **(C)** images with maximal urethral measurements showing both views can be helpful in identifying the extent of the obstruction. Maximal urethral diameter of ≈6 mm and necessary stent length determined to be ≈80 mm. Fluoroscopic **(D)** and subtracted **(E)** contrast urethrocystogram images following 8 × 80 mm laser-cut SEMS placement demonstrating patency of the urethra through the malignant obstruction has been re-established. (From Weisse C: Urethral stenting. In Weisse C, Berent A, editors: *Veterinary image-guided interventions,* ed 1, Hoboken, NJ, 2015, Wiley-Blackwell.)

Following bladder distension, a fluoroscopy run is recorded to determine the stenosis length and normal

urethral diameter. The length of the urethral obstruction and maximal diameter of the adjacent normal urethral lumen are extrapolated using the colonic marker catheter as a reference to account for radiographic magnification. The stent diameter is chosen by matching the normal urethral diameter caudal to the urethral obstruction. The stent length is chosen to span the obstructed portion of the urethra. The author prefers laser-cut self-expanding metal stents (SEMS)[f] due to ease of use, predictable and precise placement, available lengths, flexibility, biocompatibility, self-expanding nature, and documented outcomes. In general, it should be assumed that laser-cut SEMS are not reconstrainable unless otherwise specified on the stent packaging. The stent delivery system is flushed with sterile saline according to manufacturer recommendations. Using fluoroscopic guidance it is advanced over the wire, positioned across the malignant obstruction, and deployed. A repeat positive contrast cystourethrogram is performed to document immediate patency of the previously occluded urethra.

Follow-up

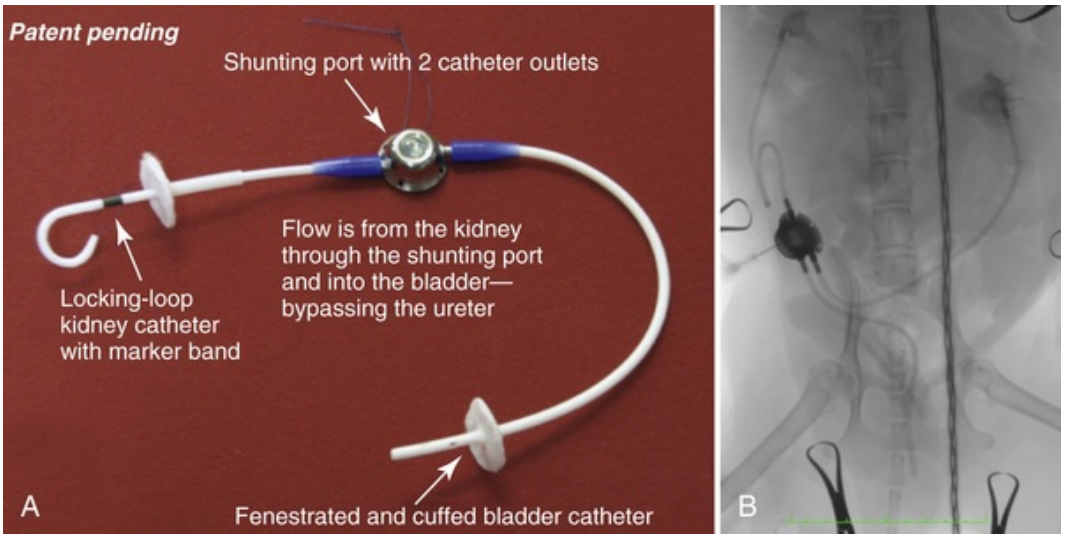
Patients are routinely discharged the same day as the procedure after demonstrating the ability to urinate. Analgesics are uncommonly necessary, antibiotics are prescribed until urine culture results are available, and nonsteroidal anti-inflammatory drugs (NSAIDs) are continued if not contraindicated. Recheck is typically performed through the oncology service for continuation of chemotherapy according to the delivery schedule.

Outcomes and Possible Complications

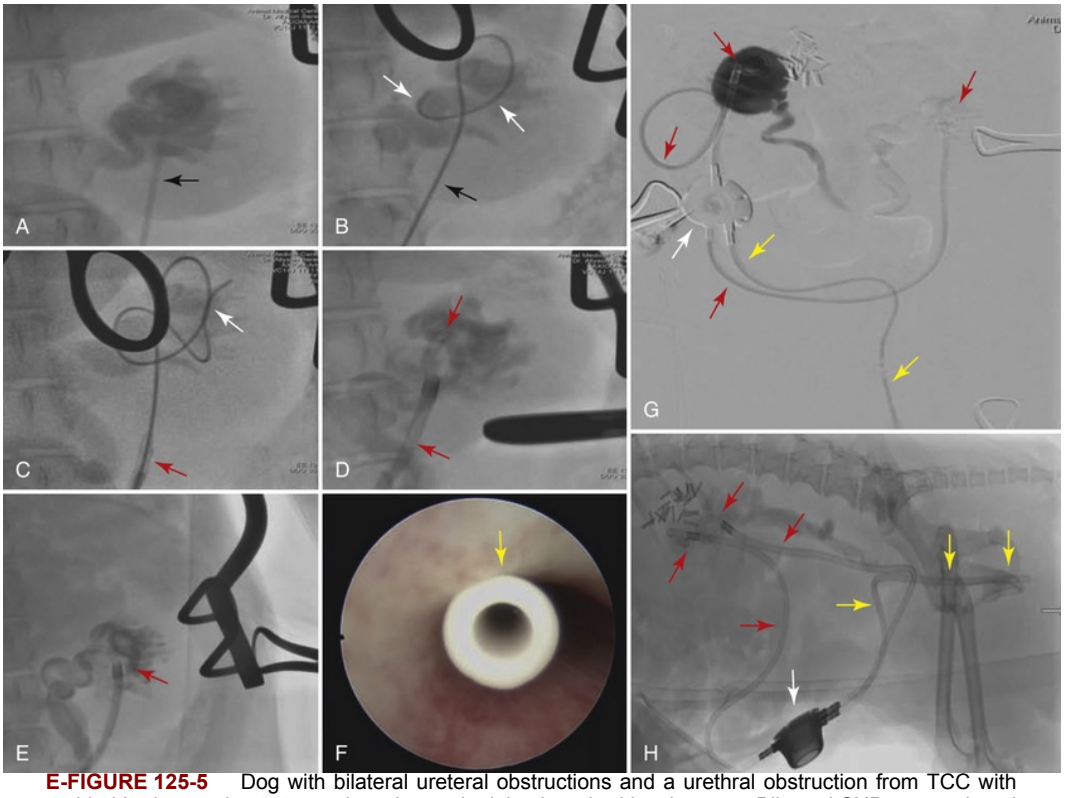
IO techniques involving the urinary tract are generally rapid, safe, minimally invasive, and effective, and reported complications have been minor and uncommon. Stented malignant urethral obstructions are immediately relieved in 97% of patients with mild to absent stranguria in 75% of patients and performed on an outpatient basis.[7-9] Animals receiving chemotherapy and NSAIDs (in addition to stenting) demonstrated prolonged survival times (250 days) in partially to completely obstructed patients with low morbidity (limited to 25% major incontinence rates).[9] Recently, similar positive outcomes, low morbidity, and similar incontinence rates have been reported with urethral stenting in cats with benign or malignant urethral obstructions.[10] A recent series of canine malignant ureteral obstructions treated with percutaneous ureteral stent placement demonstrated that similar techniques can be used in upper tract obstructions. The technique was successful in 11/12 dogs with all azotemic patients demonstrating reduction in blood urea nitrogen (BUN) and creatinine levels, and a reduction in the degree of hydronephrosis in the 10 dogs for which it was evaluated post-operatively.[11] This (typically) outpatient procedure is technically demanding when done percutaneously, but it can be performed via a small open surgical technique for those without prior interventional training.

Special Considerations and Alternatives

Local surgical resection is often incomplete due to the common trigonal location, or non-durable when apical tumors are removed due to skip metastases or *de novo* TCC tumors elsewhere within the lower urinary tract. Recently, a combination interventional/surgical procedure has been described to facilitate en bloc resection of the distal ureters, bladder, and proximal urethra to provide more aggressive oncological resections in hopes of improving tumor-free margins in these often diffuse, complex surgical cases (E-Figures 125-4 and 125-5).[12] Alternatively, regional chemotherapy administration may provide improved biological response rates as described below.



E-FIGURE 125-4 Subcutaneous ureteral bypass (SUB).[9] **A,** The SUB device *ex vivo* demonstrating the components. **B,** SUB device with 3-way shunting port placement following radical excision of distal ureters, urinary bladder and proximal urethra, and placement of bilateral nephrostomies and urethral catheter in a dog with extensive TCC.



E-FIGURE 125-5 Dog with bilateral ureteral obstructions and a urethral obstruction from TCC with no bladder lumen due to tumor invasion and minimal urethral involvement. Bilateral SUBs were placed with a radical cystectomy to remove all gross disease. Fluoroscopic images **A-E** and **G** are in dorsal recumbency during surgery. **A,** Renal access using an 18-ga catheter (black arrow) into the renal pelvis from the caudal pole of the kidney. **B,** Guide wire (white arrows) coiling within the renal pelvis, advanced through the catheter (black arrow). **C,** Nephrostomy catheter (red arrow) being advanced over the guide wire (white arrow). **D,** Locking-loop pigtail nephrostomy tube (red arrows) within the renal pelvis. **E,** Contrast study through the catheter (red arrow) during a pyelogram, showing patency of the catheter and no leakage. **F,** Cystoscopy image of the urethral catheter (yellow arrow) coming down the urethra after radical cystectomy. **G,** Dorsoventral projection during a digital subtraction image while performing a contrast study through the three-way shunting port (white arrow) showing both renal pelvises filling through the two nephrostomy catheters (red arrows) and the urethral catheter (yellow arrows). **H,** Lateral fluoroscopy image showing the entire system with the red arrows outlining the two

nephrostomy catheters and the yellow arrows the urethral catheter after the bladder was removed. The white arrow is the three-way shunting port of the SUB device. (From Berent A: Interventional management of canine malignant ureteral obstructions. In Weisse C, Berent A, editors: *Veterinary image-guided interventions,* ed 1, Hoboken, NJ, 2015, Wiley-Blackwell.)

Intra-Arterial (IA) Chemotherapy Delivery

Indications and Background

Current therapies for bulky tumors not amenable to complete surgical resection include chemotherapy, radiation therapy, and surgical debulking, but none is consistently able to produce durable remissions. Specific tumor cell lines tend to be more sensitive to certain chemotherapeutic agents, and increasing the concentration of these drugs tends to increase both tumor cell death and systemic toxicity. Studies confirm both higher achieved levels of chemotherapy within the targeted tissues as well as improved tumor remissions in laboratory animals when IR techniques are used to deliver drugs superselectively.[13-15]

Equipment

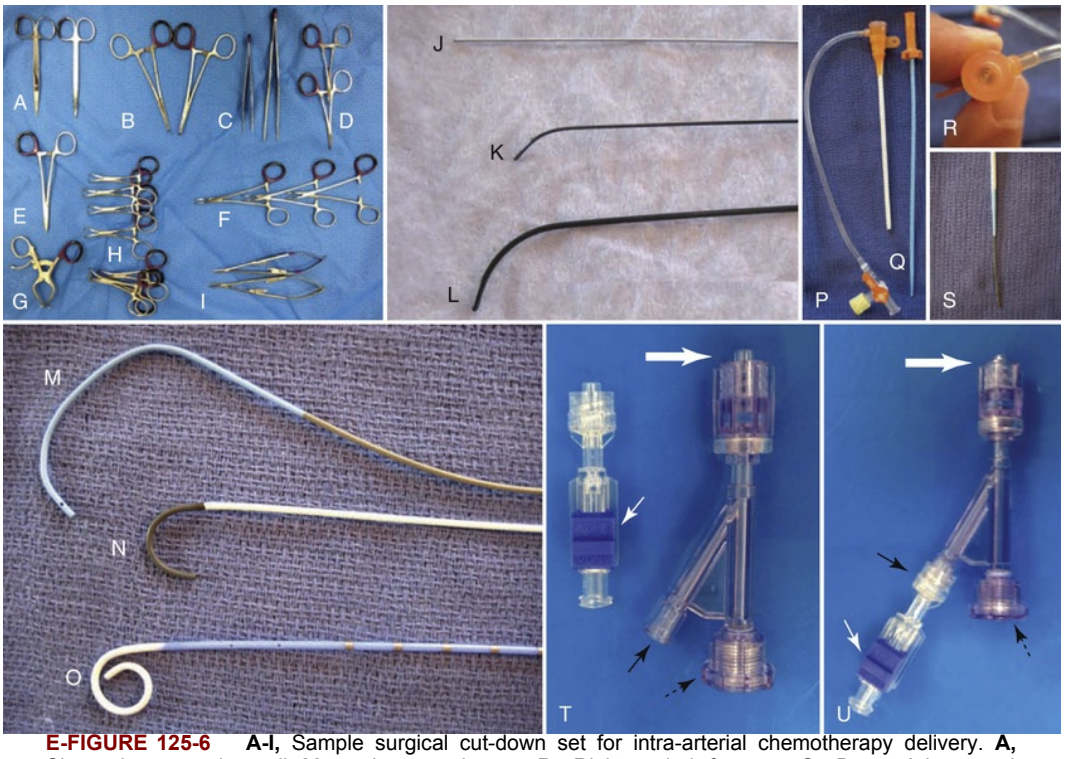
Common equipment used for intra-arterial chemotherapy delivery is listed in Box 125-2 and E-Figure 125-6. IA chemotherapy procedures require a fluoroscopy unit with exceptional imaging detail to identify very small caliber vessels using digital subtraction angiography (DSA) and road mapping, as well as the ability to obtain orthogonal imaging when necessary. Failure to identify collateral vessels could lead to non-target delivery and potentially severe consequences.

Box 125-2

Equipment for Intra-Arterial Infusion

- Surgical cut-down set (see E-Figure 125-6)
- Angiography procedure pack (drapes, bowls, etc.)
- 18 Gauge intravenous catheter
- 0.035″ angled, hydrophilic guide wire[b]
- 4 or 5 Fr (or appropriately sized) vascular introducer sheath[c]
- 3-0 Nylon and 3-0 monofilament absorbable suture material
- 4 Fr hockey stick (“Berenstein”), Cobra and or Rim catheters[d]
- Tuohy-Borst adapter[h] and Flo-Switch[i]
- 1.7 to 3.0 Fr microcatheter[j,k] with compatible 0.014-0.018″ microwire[l,m]
- Iohexol contrast agent[e]
- Sterile saline irrigation solution
- Chemotherapy

[l]0.018 Transend or V-18 microwire, Boston Scientific, Natick, MA.



E-FIGURE 125-6 **A-I,** Sample surgical cut-down set for intra-arterial chemotherapy delivery. **A,** Sharp-sharps and small Metzenbaum scissors. **B,** Right-angled forceps. **C,** Brown-Adson and DeBakey forceps. **D,** Mosquito hemostats. **E,** Needle drivers. **F,** Kelly hemostats. **G,** Small Gelpi retractors. **H,** Small Babcock towel clamps. **I,** Castroviejo needle drivers for vessel repair. **J-L,** Guide wires. **J,** 0.018″ microwire. **K,** 0.018″ angled, hydrophilic guide wire. **L,** 0.035″ angled, hydrophilic guide wire. **M,** 4 Fr Cobra catheter. **N,** 4 Fr reverse curve RIM catheter. **O,** 4 Fr marker pigtail catheter for aortogram and measurements if needed. **P-S,** Vascular introducer sheath. 4 Fr vascular introducer sheath **(P)** made up of shaft (white) with 4 Fr inner diameter, hemostasis valve **(R)** to prevent bleeding, three-way stopcock (yellow cap) to flush and/or aspirate, and 4 Fr dilator (blue, **Q**) to make smooth transition from the sheath down to the 0.035″ guide wire **(S). T-U,** Flo-switch (**T,** small white arrow) and Tuohy-Borst adapter (**T,** black arrows and white block arrow), which connect (**U**, black arrow) to form a hemostasis valve (dotted black arrow) and side-port that can be switched on or off (white arrow) for flushing or aspirating. This device is attached to the hub of the 4 Fr catheter (at white block arrow) and allows coaxial passage of a microcatheter/microwire through the 4 Fr catheter. (From Weisse C: Intra-arterial chemotherapy infusion. In Weisse C, Berent A, editors: *Veterinary image-guided interventions,* ed 1, Hoboken, NJ, 2015, Wiley-Blackwell.)

Technique (see E-Figure 125-6)

The patient is placed under general anesthesia and the groin or neck is clipped and scrubbed for either femoral or carotid arterial access via surgical cut-down. A 4 or 5 Fr introducer sheath[a] is placed and a combination 0.035″ angled, hydrophilic guide wire[b] and 4 or 5 Fr reverse-curve catheter[c] (femoral) or 4 Fr Berenstein catheter[d] (carotid) is advanced under fluoroscopic guidance to the terminal aorta. A DSA delineates the vascular anatomy and a microcatheter/microwire combination is used to gain super-selective access to one of the terminal arteries feeding the tumor (e.g., prostatic artery or vaginal artery in the case of lower urinary tract tumors). Standard therapy involves the total systemic chemotherapy dose mixed with an equal volume of iohexol contrast injected under fluoroscopic guidance to ensure flow down the target artery without reflux into non-target vessels. The catheter and sheath are removed and the femoral or carotid artery ligated. The cut-down site is closed in three layers and the patient recovered.

Follow-up

The patient is typically discharged the same day with the same medications prescribed following intravenous (IV) use of the same chemotherapies. Oral NSAIDs are continued if indicated and typically IA treatments are alternated with IV therapies to address systemic (non-regional) disease. Restaging is often performed according to the oncologist's recommendations.

Outcomes and Possible Complications

These techniques have been described in clinical veterinary cases,[16] and a study performed at the author's institution is supporting the potential of this therapeutic approach. Retrospectively, two statistically similar populations of dogs with urothelial carcinoma received either (1) intravenous carboplatin and oral NSAIDs, or (2) super-selective intra-arterial carboplatin and intra-arterial meloxicam (see E-Figure 125-2). The intra-arterial group demonstrated statistically significantly greater reduction in tumor length, and percent length, width and unidimensional measurements compared with the intravenous group. The intra-arterial group was also statistically more likely to achieve a positive tumor response as characterized by modified RECIST criteria. In addition, the intra-arterial group was statistically significantly less likely to develop certain adverse events, including anorexia and lethargy, following chemotherapy compared to the intravenous group. Complications are uncommon and typically limited to the same adverse events anticipated following intravenous therapy.

Special Considerations and Alternatives

Although reported to be safe, care must be taken during repeated carotid access. The author has seen temporary neurological sequelae (blindness, circling, etc.) following bilateral carotid artery ligation in dogs, even when staged. This is uncommonly necessary, as performing femoral access distally provides ample opportunity to re-use the femoral artery more proximally on multiple occasions. The author has successfully used a unilateral femoral artery up to five times.

Trans-Arterial Embolization (TAE)/Chemoembolization (TACE)

Indications and Background

Embolization refers to the delivery of a device or material to interrupt blood flow. Chemoembolization involves super-selective intra-arterial chemotherapy delivery in conjunction with subsequent particle embolization. Intra-arterial chemotherapy for liver tumors has been shown to result in a 10- to 50-fold increase in intra-tumoral drug concentrations when compared to systemic intravenous chemotherapy administration.[17] Subsequent particle embolization results in tumor cell necrosis through ischemia and paralyzes tumor cell excretion of chemotherapy resulting in increased local concentrations and minimized systemic toxicity. While TAE and TACE have been performed in other areas, the liver is the most commonly treated organ.

Equipment

Common equipment used for TAE/TACE is listed in Box 125-3 and E-Figure 125-7. Embolization procedures require a fluoroscopy unit with exceptional imaging detail to identify very small caliber vessels using DSA and road mapping, as well as the ability to obtain orthogonal imaging when necessary. Failure to identify collateral vessels could lead to non-target delivery and potentially severe consequences.

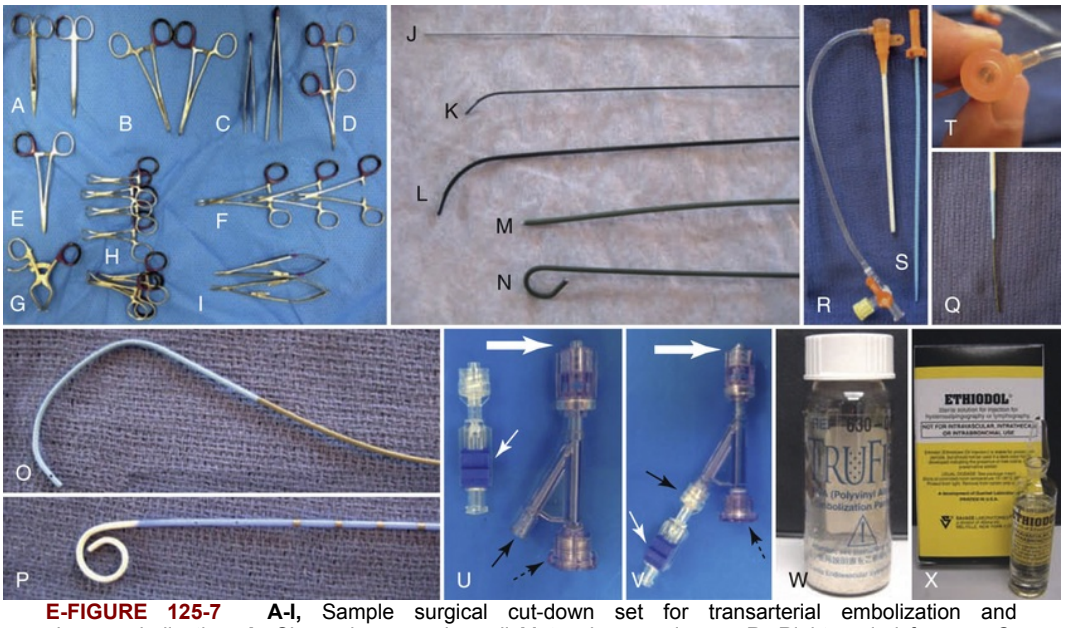
Box 125-3

Equipment for TAE/cTACE/DEB-TACE

- Surgical cut-down set (see E-Figure 125-7)
- Angiography procedure pack (drapes, bowls, etc.)
- 18 Gauge intravenous catheter
- 0.035″ angled, hydrophilic guide wire[b]
- 4 or 5 Fr (or appropriately sized) vascular introducer sheath[c]
- 3-0 Nylon and 3-0 monofilament absorbable suture material
- 4 Fr hockey stick (“Berenstein”), Cobra and or Rim catheters[d]
- Tuohy-Borst adapter[h] and Flo-Switch[i]
- 1.7 to 3.0 Fr microcatheter[j,k] with compatible 0.014-0.018″ microwire[l,m]
- Iohexol contrast agent[e]

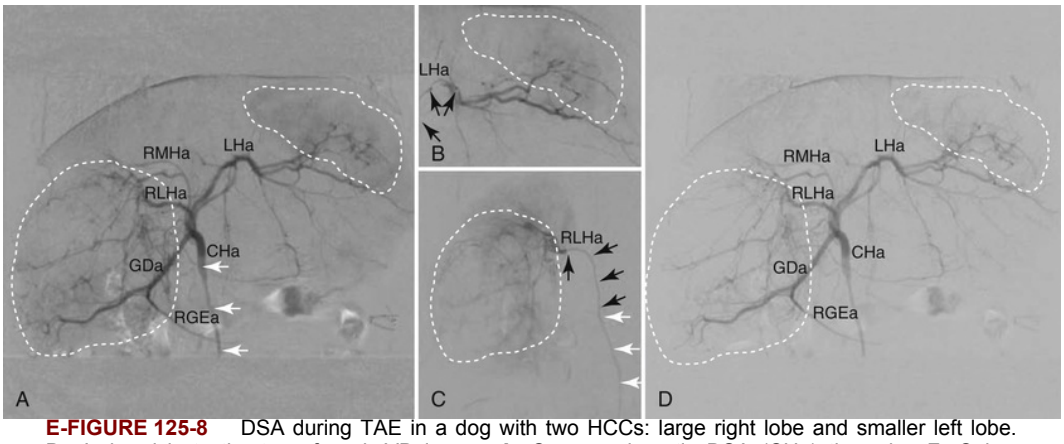
- Sterile saline irrigation solution
- Chemotherapy
- PVA[n], lipiodol[o], and/or drug-eluting beads (DEBs)[p]

[P]LC/DC Bead 100-300 mcm hydrogel microspheres, Biocompatibles UK Limited, Farnham, UK.



E-FIGURE 125-7 **A-I,** Sample surgical cut-down set for transarterial embolization and chemoembolization. **A,** Sharp-sharps and small Metzenbaum scissors. **B,** Right-angled forceps. **C,** Brown-Adson and DeBakey forceps. **D,** Mosquito hemostats. **E,** Needle drivers. **F,** Kelly hemostats. **G,** Small Gelpi retractors. **H,** Small Babcock towel clamps. **I,** Castroviejo needle drivers for vessel repair. **J-N,** Guide wires. **J,** 0.018″ microwire. **K,** 0.018″ angled, hydrophilic guide wire. **L,** 0.035″ angled, hydrophilic guide wire. **M** and **N,** 0.035″ straight PTFE wire **(M)** and 0.035″ Rosen PTFE wire **(N),** both of which are uncommonly used for this procedure. **O,** 4 Fr Cobra catheter. **P,** 4 Fr marker pigtail catheter for aortogram and measurements if needed. **Q-T,** Vascular introducer sheath. 4 Fr vascular introducer sheath made up of shaft (white) with 4 Fr inner diameter, hemostasis valve **(T)** to prevent bleeding, three-way stopcock (**R,** yellow cap) to flush and/or aspirate, and 4 Fr dilator (**S,** blue) to make smooth transition from the sheath down to the 0.035″ guide wire **(Q). U-V,** Flo-switch (**U,** small white arrow) and Tuohy-Borst adapter (**U,** black arrows and block white arrow), which connect **(V)** to form a hemostasis valve (dotted black arrow) and side-port that can be switched on or off (white arrow) for flushing or aspirating. This device is attached to the hub of the 4 Fr catheter (at white block arrow) and allows coaxial passage of a microcatheter/microwire through the 4 Fr catheter. **W,** Polyvinyl alcohol particles. **X,** Iodinated poppyseed oil. (From Weisse C: Liver tumors/metastases (TAE/cTACE/DEB-TACE). In Weisse C, Berent A, editors: *Veterinary image-guided interventions,* ed 1, Hoboken, NJ, 2015, Wiley-Blackwell.)

Technique for Hepatic TAE/TACE (E-Figure 125-8)



E-FIGURE 125-8 DSA during TAE in a dog with two HCCs: large right lobe and smaller left lobe. Dog's head is to the top of each VD image. **A,** Common hepatic DSA (CHa) through 4 Fr Cobra catheter (white arrows) demonstrating left hepatic artery (LHa) feeding left tumor (white dotted line) and right lateral hepatic artery (RLHa) feeding right tumor (white dotted line). Also visible are the right medial hepatic artery (RMHa), gastroduodenal artery (GDa), and right gastroepiploic artery (RGEa). **B,** Superselective microcatheterization (black arrows) of the LHa with DSA showing perfusion of left tumor prior to TAE. **C,** Microcatheterization (black arrows) of the RLHa with DSA showing perfusion of right tumor prior to TAE. **D,** Post-TAE CHa DSA demonstrating similar hepatic perfusion (no non-target embolization) with absent perfusion/embolization of both tumors (white dotted lines). (From Weisse C: Liver tumors/metastases (TAE/cTACE/DEB-TACE). In Weisse C, Berent A, editors: *Veterinary image-guided interventions,* ed 1, Hoboken, NJ, 2015, Wiley-Blackwell.)

Femoral artery sheath access followed by a 4 Fr Cobra catheter and 0.035″ angled hydrophilic guide wire (E-Figure 125-7) are used in combination to select the celiac artery and common hepatic artery. Common hepatic arteriography is performed using a 50 : 50 dilution of iohexol[e] : saline. A 1.7 to 3 Fr microcatheter[j,k]/microwire[l,m] combination is used to super-select the particular vessel supplying the tumor bed, ensuring catheter placement is not occlusive within the often very small caliber vessels. Super-selection is the goal to minimize non-target embolization. The appropriate size of polyvinyl alcohol (PVA) or other embolization particles is chosen on the basis of vascular architecture. Use of undersized particles carries the risk of extreme distal vascular occlusion and increases the risk of necrosis and tissue sloughing. The use of inappropriately large particles carries the risk of proximal vessel thrombosis, which may allow for development of collateral vessels that bypass the proximal occlusion and re-establish perfusion to the tumor. The author has used PVA-200 particles[m] (180-300 micron) or 100-300 micron PVA hydrogel microspheres[n] for liver embolization. The chosen embolic is prepared as a slurry with iodinated contrast material and embolization is performed under fluoroscopic visualization using digital road-mapping software. Care is taken to prevent reflux of particles into non-target vessels. A similar technique is used for oily ("conventional" or cTACE) or drug-eluting bead (DEB)-TACE; however, refer to manufacturer instructions for information regarding handling, drug loading, and administration. The systemic dose of chemotherapeutic agent (typically doxorubicin) is selected and either mixed with iodinated poppyseed oil[o] to form the oily suspension (cTACE) or with the drug-eluting beads (DEB-TACE). A lobar treatment can be performed using the cTACE technique but only superselective access should be used for DEB-TACE. Embolization can continue until near-stasis of blood flow if the treatment is to be repeated; if performed once, complete stasis can be attempted. Selective arteriography is performed to evaluate the success of the procedure after all particles are flushed out. If embolization is successful, no flow is seen in the target artery feeding the tumor. The microcatheter is withdrawn and repeat common hepatic (or other) angiography is performed through the 4 Fr catheter to identify other feeding vessels. If more vessels are found, the procedure can be repeated or performed subsequently in the future.

Following embolization, all catheters and sheaths are removed. Hemostasis is typically achieved with femoral artery ligation. All animals recover from anesthesia in an intensive care unit for monitoring. Peri-operative medical management is standard for these patients.

Follow-up

The procedure is generally repeated at 6-week intervals and tumor response (restaging) evaluated following two treatments.

Outcomes and Possible Complications

These techniques have demonstrated improved tumor responses and prolonged survival times when compared to more traditional therapies in humans with HCC.[18-20] The author has performed TAE, Lipiodol-based TACE, and DEB-TACE in dogs with benign and malignant liver tumors in which surgery was unsuccessful or was declined. In general, stable disease or partial remissions are anticipated following therapy, with better responses in more vascular tumors. These procedures require an intimate knowledge of the local vascular anatomy to prevent non-target embolization but can otherwise be expected to result in fewer than 10-15% major complications when performed by experienced operators. Reported complications[21] in the human literature include hemorrhage at the vascular access site, non-target embolization complications (skin necrosis, damage to normal parenchyma), hepatic infarction/abscessation, acute renal failure (for liver tumors), and post-embolization syndrome, a collection of clinical signs characterized by malaise, fever, and pain. The author's experience over the past 10 years suggests similar risks in veterinary patients as well as reduced systemic exposure to chemotherapy, minimal morbidity, and improved tumor response rates when compared to systemic chemotherapy.[22-24] In a small, prospective series of HCC dogs receiving DEB-TACE, the identical canine patient had serum chemotherapy measurable for only a median 30-180 minutes (versus 720 minutes following intravenous administration) and 1/40th of the total systemic chemotherapy exposure (area under the curve) versus the same dose administered intravenously.[24] Chemoembolization has been performed elsewhere throughout the body and its use will likely expand.

Special Considerations and Alternatives

For smaller tumors, percutaneous ablation techniques can be considered, although these have not been routinely performed in veterinary patients.[25-27] Radiofrequency ablation as well as microwave ablation, laser thermal ablation, cryoablation, and percutaneous ethanol injection tend to be most effective with a few (<3) small (<4 cm diameter) lesions. These circumstances are fairly uncommon in the author's clinical experience; however, with the routine use of more advanced imaging techniques in veterinary medicine, lesions of this size and number may become increasingly apparent during tumor re-staging procedures, making tumor ablation techniques a reasonable option in the future.

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[a]Measuring catheter, Infiniti Medical, Menlo Park, CA.

[b]Weasel wire, Infiniti Medical, Menlo Park, CA.

[c]Vascular introducer sheath, Infiniti Medical, Menlo Park, CA.

[d]Berenstein Catheter, Infiniti Medical, Menlo Park, CA.

[e]Omnipaque (iohexol) injection, Amersham Health Inc., Princeton, NJ.

[f]Vet Stent-Urethra, Infiniti Medical, Menlo Park, CA.

[g]Subcutaneous ureteral bypass device (SUB), Norfolk Vet, Skokie, IL.

[h]Tuohy-Borst adapter, Cook Medical, Bloomington, IN.

[i]Flo-switch, Boston Scientific, Natick, MA.

[j]Renegade or Tracker microcatheter, Boston Scientific, Natick, MA.

[k]Microcatheter, Infiniti Medical, Menlo Park, CA.

[m]0.014 Microwire or 0.018 Weasel wire, Infiniti Medical, Menlo Park, CA.

[n]PVA-200 particles, Cook Medical Inc., Bloomington, IN.

[o]Lipiodol/Ethiodol, Guerbet LLC, Bloomington, IN.

SECTION VII

Critical Care

OUTLINE

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CHAPTER 126

Pain Physiology, Identification, and Management in the Acute Care Setting

Lisa Moses

Contemporary practice of veterinary medicine recognizes pain assessment and management as an integral part of good medicine. Rapidly changing cultural attitudes about the importance of companion animals have focused veterinary attention on pain management as both a welfare issue and a client demand. Accordingly, the practice of pain medicine has shifted and expanded. This chapter will provide an update on the understanding of the basic mechanisms of pain biology besides giving the reader an overview of pain behaviors, clinical pain assessment, and practical approaches to pain management in the acute care setting. Specifics of analgesic therapy are covered in ch. 164 and 166. Chronic pain is covered in ch. 356. Drug dosages, routes, and intervals in this chapter are based on published references and the author's experience, and should be confirmed by the attending clinician and adapted as necessary based on the specifics of each case.

Understanding the basic nature of pain as a biological process removes some of the uncertainty of pain assessment and treatment in patients who cannot self-report. In the most simplistic description, the sensation of pain is the final result of central nervous system processing of sensory stimuli. The stimuli must be sufficiently intense (i.e., noxious) to cause depolarization of high threshold pain receptors, *nociceptors*.[1] The standard, widely used definition of pain from the International Association for the Study of Pain (IASP) is "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[2] Although pain is a conscious perception and this perception is subjective, there are biochemical events caused by pain that accompany this perception and these events can occur even without conscious perception (i.e., during general anesthesia). This definition of pain includes verbal and non-verbal humans and non-human animals. It is generally accepted that animals are likely to experience pain in a way that is similar to humans, since the "machinery" by which pain happens in the body is nearly identical.[3] Despite this commonality, the clearly different behavioral and emotive components of pain complicate our assessment of pain in veterinary species. Because of this, the cornerstone of reasonable pain assessment and management is an anthropomorphic approach of identifying expected pain levels we would feel for any given noxious event.[4]

Current Concepts of Pain Physiology

Pain signaling is the heavily modified sum of complex processes at multiple anatomic levels. The signal consists of peripheral nerve excitation, regional exchanges within the dorsal horn of the spinal cord, and activation of ascending and descending circuits between the spinal cord and supraspinal locations. The entire system has a large capacity for change in response to persistent or intense signals (plasticity) and can be thought of as a pro-nociceptive positive feedback loop.[5]

Nociception is the biological process by which noxious stimuli (i.e., those capable of producing tissue damage) are detected and transmitted by unique sensory receptors called nociceptors. This process might or might not result in the conscious perception of pain.[6] Neural processing of the encoded information can be thought of in several steps, each of which encompasses complex modification of the information. The steps are: *transduction* of the signal into an action potential, *transmission* of the information from the periphery to the spinal cord, *modulation* of the information within the spinal cord, *projection* from the spinal cord to the brain and lastly, *perception* of pain (Figure 126-1). Because of the complexity of signal modification, there rarely is a linear relationship between noxious stimulation and pain perception.[7]

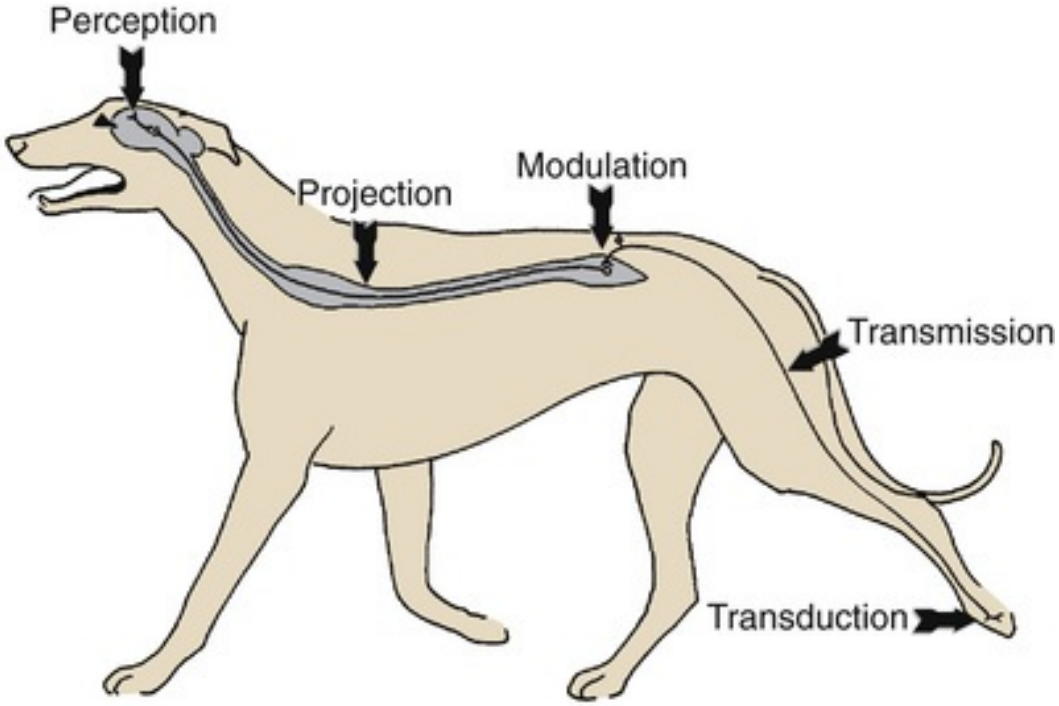

FIGURE 126-1 Schematic pathways in the neuroanatomic description of pain. Noxious stimuli are transduced into electrical stimuli, transmitted to the spinal cord (where peripheral ascending and descending modulation occurs), and finally are relayed to the brainstem and brain for perception. Descending pathways from higher centers also modulate pain signals.

Transduction

Transduction of the initial noxious stimuli occurs via nociceptors. Nociceptors are peripheral, free nerve endings of some C-fiber and A-delta–fiber sensory neurons (and fewer A-beta–fiber neurons).[8] These afferent pseudounipolar neurons have cell bodies in the dorsal root ganglia and the trigeminal ganglia (for cranial nerves) and terminate in the superficial layers of the dorsal horn of the spinal cord[5,9] (Figure 126-2).

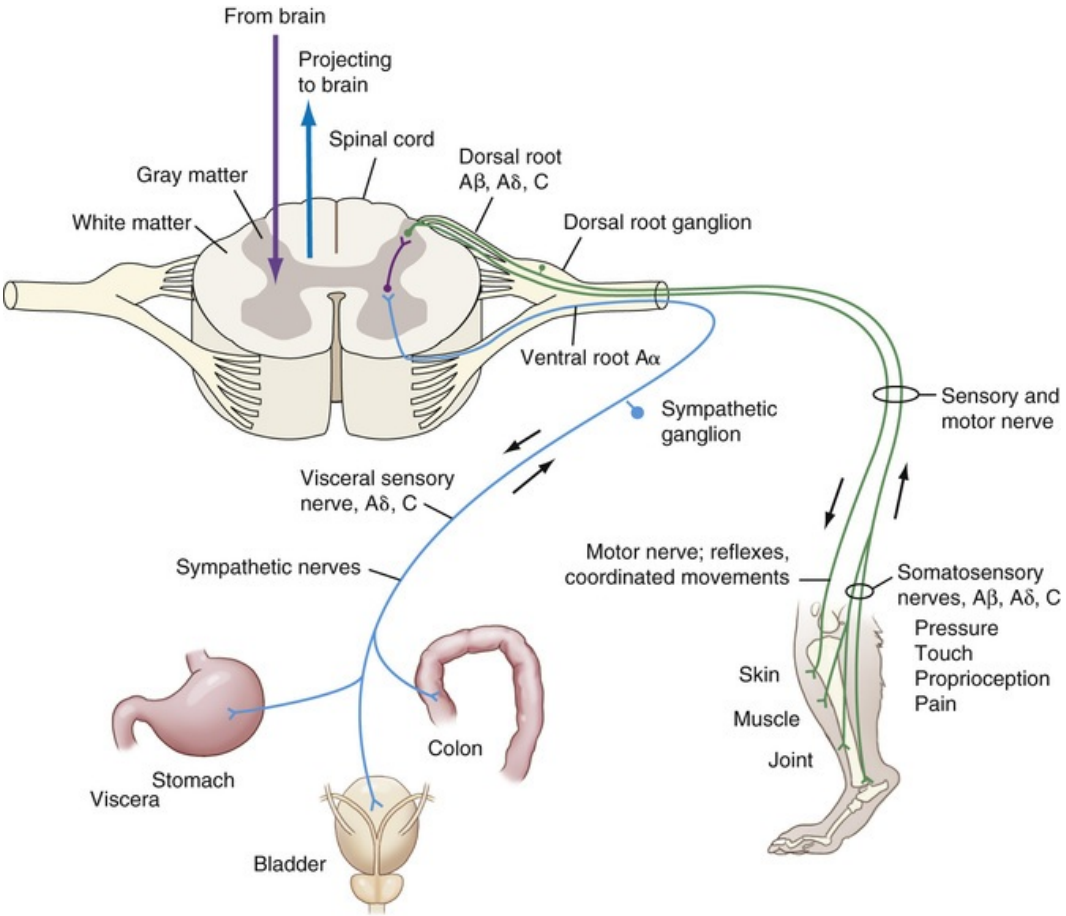

FIGURE 126-2 This illustrates a highly simplified schematic view of transduction and transmission via afferent sensory nerve fibers pathway from the periphery and viscera to the spinal cord. (Adapted from Muir WW: Physiology and pathophysiology of pain. In Gaynor JS, Muir WW, editors: *Handbook of veterinary pain management*, ed 2, St Louis, 2009, Mosby Elsevier, p 33.)

Unmyelinated C-fibers' nociceptors respond to chemical, mechanical, and thermal (termed polymodal) noxious stimulation. Myelinated A-delta–fibers rapidly respond to high intensity mechanical stimulation, with some also responding to thermal stimulation.[5] Transduction of the stimulus occurs by triggering a conformational change in an ion channel leading to the generation of an electrical action potential. Many chemicals released by tissue damage can trigger signal transduction, among them protons, bradykinins, leukotrienes, substance P, histamine, potassium, and prostaglandins.[10] Identification of the specific receptor molecules, ligands, and details of the subsequent signal is an active area of research and a therapeutic target. Acid-sensitive ion channels (ASIC), transient receptor potential vanilloid 1 channels ($TRPV_1$, activated by heat and various ligands including capsaicin), tetrodotoxin (TTX)-sensitive and -resistant sodium channels, purine receptors, and voltage-gated calcium channels all are examples of receptors expressed on nociceptors.[1,5]

Transduction of noxious stimuli is different than in other types of sensory processing. Nociceptors only respond to noxious stimuli and do not adapt to persistent stimulation by firing less. Indeed, rather than causing a decrease in firing of the nociceptor, continuous or rapid stimulation can lead to a decrease in the threshold of response.[4] This is termed sensitization, and it contributes to peripheral sensitization and hyperalgesia (described in more detail below).[6] Thirty to fifty percent of C-fiber and A-delta–fiber nociceptors are classified as silent nociceptors because prior to exposure to inflammatory mediators and neuropeptides, they are either unresponsive or responsive only to very high mechanical stimulation. However, after exposure to these chemical activators, they are recruited and respond to stimuli (i.e., become sensitized), thereby increasing the response to further noxious stimuli.[9]

Transmission and Dorsal Horn Processing

Transmission of the pain signal from the nociceptor delivers it to the superficial layers of the gray matter of

the dorsal horn of the spinal cord. Transmission of the nociceptive signal continues via the axons of second-order neurons that cross the spinal cord and form ascending spinothalamic tracts that extend to the thalamus, where they synapse on third-order neurons that project to the sensory cortex.[5]

Within the dorsal horn are three functional groups of neurons that interact with first order, afferent neurons: interneurons, propriospinal neurons, and projection neurons.[11] The transmitted action potential causes opening of pre-synaptic voltage-gated calcium channels and the release of either excitatory or inhibitory neurotransmitters at synapses on second-order neurons. Substance P and glutamate are important excitatory neurotransmitters. Glutamate can bind to N-methyl-D-aspartate (NMDA), AMPA and mGlu types of excitatory amino acid receptors.[1] Substance P is a ligand for G-protein coupled neurokinin-1 (NK-1) receptors. Gamma-aminobutyric acid (GABA) and endorphins are common inhibitory signalers that interact with GABA receptors and mu and delta opioid receptors, respectively.[1]

The interneurons and projection neurons that encode nociceptive information are either wide dynamic range neurons (WDR or convergent neurons) or nociceptive-specific neurons.[9] Nociceptive-specific neurons only respond to high intensity noxious stimuli, but WDR neurons can be stimulated by low intensity stimulation from A-beta, A-delta, and C fibers. WDR second-order neurons can change their response to match patterns of persistent response in nociceptors experiencing sustained discharge (i.e., after tissue injury).[5] This is one of the many mechanisms of neuroplasticity in pain signaling and it is important in chronic inflammatory and chronic neuropathic pain.[12]

The neurotransmitters produced by cell bodies in the dorsal root ganglia are released at both the central and peripheral ends of the neuron. This dual signal triggers both central pain processing events and peripheral tissue effects like redness, swelling, and tenderness.[5]

Projection of Pain Signals (Ascending Pain Pathways)

Neurons that project to supraspinal locations synapse in the medulla, midbrain, and thalamus, and then project further to cortical centers.[13] The subcortical sites include the reticular formation, the periaqueductal gray matter of the midbrain, and the nucleus raphe magnus of the medulla. The subcortical sites are responsible for the non-conscious reactions to pain like arousal and physiological responses including endocrine responses.[7]

Modulation of Pain Signals

An important concept in pain physiology is *neuroplasticity,* here specifically referring to the ability of neurons to change their excitability, gene expression (i.e., changes in receptors and neurotransmitters), and structure in response to noxious stimuli and tissue injury. Neuroplasticity is how heightened pain sensitivity, or sensitization, can follow noxious stimuli. This sensitization can occur at the level of peripheral signal transduction *(peripheral sensitization)* or in the dorsal horn at the second order neurons *(central sensitization).* Sensitization can occur within minutes or over the course of a long period of time and at many levels.[1] When the noxious stimulus is prolonged or sufficiently intense to cause sensitization, then hyperalgesia and allodynia may occur. *Hyperalgesia* is increased pain from a given noxious stimuli including both a lower threshold to response and a more intense response. This change can occur in the injured tissue (primary hyperalgesia), but can also occur in adjacent, non-injured tissue (secondary hyperalgesia). *Allodynia* means pain from a stimulus that does not normally cause pain. A recognizable example of this is the burning sensation caused by tepid water on sunburned skin. Primary hyperalgesia occurs from peripheral sensitization, while secondary hyperalgesia and allodynia are believed to be a consequence of central sensitization.[14] *Windup* is a phenomenon related to, but different from primary hyperalgesia and central sensitization. Windup is defined as a progressive increase of activity in dorsal horn cells *during* repetitive activation of primary afferent C-fibers. Central sensitization is a phenomenon that occurs *after* noxious stimulation, which can be propagated autonomously or with a low level noxious stimulation and can amplify subsequent responses.[15]

Besides central sensitization, there is substantial communication between signaling pathways and many different pathways that further result in modification and plasticity of the signal and ultimately, pain perception.[1]

Pain signals are subject to both facilitation and inhibition by way of descending pathways from supraspinal regions to the dorsal horn. Important neurotransmitters involved in the process of descending facilitation

include: substance P, glutamate, cholecystokinin, and nerve growth factor. Important neurotransmitters involved in the process of descending inhibition of pain signals include: adenosine, cannabinoids, dopamine, GABA, norepinephrine, and serotonin.[1] An example of the complexity of this system is that there is no anatomical separation between facilitation and inhibitory pathways. This means it is possible for a single supraspinal stimulus and the same neurotransmitter to simultaneously trigger both facilitation and inhibition of pain.[12]

Descending inhibitory pathways, originating from multiple supraspinal locations, constitute an endogenous pain-relieving system thought to be responsible for the huge variation in pain perception noted between individuals, and for the placebo effect.[16] The endogenous pain-inhibiting system is of great interest to clinicians and researchers, since most of the pharmacological and non-pharmacological methods of producing analgesia (e.g., the placebo effect, transcutaneous electrical nerve stimulation, acupuncture) manipulate this endogenous system.[12,13,16] The descending inhibitory circuits are largely opioid-sensitive systems and three groups of endogenous opioids have been well-studied: enkephalins, endorphins, and dynorphins.[10,16] Analgesic drugs, including nonsteroidal anti-inflammatories (NSAIDs), serotonin/norepinephrine reuptake inhibitors, cannabinoids, and exogenous opioids work, at least in part, by mimicking the effect of endogenous opioids.[16] A few of the specific inhibitory mechanisms worth noting are (1) the descending noradrenergic system, in which spinal alpha$_2$ adrenergic receptors are the main players, (2) the stress-induced analgesia system associated with endogenous cannabinoids and beta endorphins, and (3) the diffuse noxious inhibitory control system, which, when lost, plays a major role in chronic pain states.[16]

Perception of Pain Signals

Cortical signals determine the three parts of the experience of pain: sensory-discriminative, motivational-affective, and evaluative-cognitive.[9] The sensory-discriminative component includes the location, intensity, and type of pain perceived. The motivational-affective component includes behaviors that lead to avoidance of pain and to emotional reactions. The evaluative-cognitive component includes past experiences of pain and behaviors learned as a result. This can positively or negatively affect the perception of pain. The above mentioned "stress induced analgesia system" is one mechanism by which the evaluative-cognitive component of pain perception is affected (i.e., the perception of pain is reduced by physiological stress). Perception of pain is controlled by various cortical regions, the most important of which are the primary and secondary somatosensory cortices, the insular cortex, the anterior cingulate cortex, the thalamus, and the amygdala.[9]

Visceral pain perception is quite different from somatic pain perception for a number of structural reasons. Visceral afferent innervation is much less dense than are somatic afferents, it is spread over multiple spinal segments rostral and caudal to the origin, the spinal neurons involved also receive concurrent input from somatic regions, and the viscera have dual extrinsic innervation from either vagal or pelvic and spinal nerves.[9] As a result of this architecture, visceral pain is poorly localized, diffuse and can be *referred pain* (perceived as adjacent to, or even distant from, the site of origin).[10] Clinically, visceral pain can have a poor correlation with the extent of tissue injury and it is often accompanied by obvious autonomic and emotional reactions. Although distention, traction, ischemia, and inflammatory mediators are noxious to visceral organs, some visceral organs do not respond to noxious stimuli unless they are already inflamed or distended.

Clinical Pain Taxonomy and Nomenclature

The IASP publishes a regularly updated list of pain term definitions and clinical pain classifications, which is used as the general reference for this information.[17] Pain can be classified on the basis of location, intensity, character, etiology, pathophysiology, or even response to treatment.[18] Because of the many variables, the IASP uses a five-axis model (region, system, temporal pattern, intensity, and etiology) of pain taxonomy for use in human patients. For veterinary patients, there is no standardized method of classifying clinical pain. Most of the veterinary literature focuses on etiology and temporal pattern, so knowledge of the related terminology is important. It is important to note, however, that many references have slightly different definitions of relevant terms because they use different pain classification schemes.

Nociceptive pain arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors. *Physiological pain* is the transient, protective process that initiates avoidance strategies *prior* to tissue damage. Clinical pain (sometimes called *pathological pain*) results from *actual* tissue damage and it

provokes a longer or more intense avoidance/behavior pattern. *Acute pain* results from surgical or other trauma to tissues, responds to treatment, resolves when the tissue lesion is healed, and is considered a clinical sign.[7] In some classification schemes *inflammatory pain* (pain produced by tissue inflammation) is considered to be another term for acute pain. *Neuropathic pain* is pain associated with damage to, or a lesion of, peripheral or central nervous system tissue. The damage can be caused by deformation, compression of surrounding tissues, or an altered milieu; direct injury is not required to cause neuropathic pain. *Chronic pain* (which is, confusingly, also sometimes called pathological pain) is a maladaptive disease state defined by the IASP as "pain without apparent biological value that persists beyond normal tissue healing time."[2] Further refinement of this definition includes the idea that chronic pain is a disease of the nervous system that can be present without a demonstrable or sufficiently significant structural lesion to explain its persistence. As discussed above, pain-related neuroplasticity can ensure that pain is maintained without external stimulation, or can be due to abnormal processing of pain signals *(functional pain)*.[3] Chronic pain can be a changeable fusion of inflammatory, neuropathic, and functional pain.[1] Woolf elegantly simplifies the classification of pain into three different entities. Two are functional and adaptive: nociceptive pain and inflammatory pain (acute could be used interchangeably here). The third classification is maladaptive, non-protective pathological pain, which is further subdivided into neuropathic and dysfunctional pain. Dysfunctional pain occurs with no damage or inflammation.[19] This system has the advantage of being encompassing and clinically relevant.

Pain Identification in the Acute Care Setting

As pain is a subjective state and our patients cannot speak to us, we are obligated to assess their pain through the lens of our own observations and prejudices. Despite this handicap, it is quite possible to manage acute pain effectively. Box 126-1 details key principles of acute pain identification that form the foundation for effective pain identification. This information is a synopsis of research into species differences in pain response and extensive work validating pain scaling for dogs and cats. Veterinarians often are reluctant to treat pain unless they have abundant evidence that pain is present. Unfortunately, this approach fails to effectively treat animal pain. Unlike other vital signs, there is no objective measure of this fundamentally subjective state.[3] Our patients can mask signs of pain until pain is substantial, and pain is harder to treat when it is more severe. A judicious approach avoids under- and overtreatment of pain and adapts to the patient's needs as they evolve.

Box 126-1

Key Principles for the Identification of Acute Pain

- Signs of pain vary widely between species, age, and between individuals.
- Knowledge of the patient's normal behavior and temperament, particularly prior to the onset of pain, improves pain assessment.
- Frequent re-assessment and identification of trends improves pain assessment accuracy.
- Reassessment at regular intervals after providing analgesic therapy provides a clinically useful guide to adjusting pain management plans.
- Having a single or a few trained observers improves pain assessment accuracy by reducing interobserver variability.
- The most accurate observer is often the person who spends the most time with the patient.
- Acute pain is most accurately assessed when objective measures are combined with behavioral observations and response to interaction.
- There are no universal or pathognomonic pain behaviors or objective measures.
- Likewise, the lack of certain behaviors or objective measures does not negate the possibility of pain in a patient.
- Pain scales are not sensitive enough to justify withholding or reducing analgesic therapy; they are most useful to confirm the suspicion of pain or to suggest continuing analgesic therapy.
- Anxiety, fear, non-pain related discomfort (like nausea or a full bladder), and opioid-caused dysphoria may confuse pain assessment. Since behavioral states of distress can worsen pain perception, addressing these conditions may improve analgesia.

Pain identification in animals requires that we consciously use observational skills developed by our experiences as clinicians. Our prior knowledge of the patient's posture, reactions to examination, vocalizations, and gait are tremendously helpful in assessing pain because we usually recognize deviations from those earlier observations. Pain can be indicated by the expression of abnormal behaviors and/or the change in, or absence of, normal behaviors.[20] We might already subconsciously register these changes without interpreting them as evidence of pain, but they are often key pieces of evidence. For example, noticing that a cat no longer makes a greeting noise when approached could be subtle but also significant. Box 126-2 lists behaviors typical of dogs and cats with acute pain.

Box 126-2

Acute Pain Behaviors in Dogs and Cats

Movement/Activity

- Restlessness or continuous activity
- Circling or thrashing
- Reluctance to move, lie down, or rise
- Excessive sleeping (cats, in particular)
- Escalating aggression when approached or handled
- Hiding (cats, in particular)
- Tail flicking (cats)

Vocalizations

- Spontaneous vocalizations without movement or interaction
- Purring, hissing, spitting, yowling (cats)
- Whimpering/howling/growling (dogs)
- Increased vocalization with movement or on palpation of affected area

Posture

- Sleeping or resting positions that are unusual or different from normal (i.e., lateral recumbency in a hospitalized cat)
- "Prayer" position (see ch. 143)
- Leaning against side of cage or wall, slumping
- Hunched posture when standing
- Weight shifted off affected limbs or difficulty standing still
- Rolling over on back or other submissive posture
- Abnormal tail carriage
- Rigid posture

Gait

- Lameness
- Stiff gait

Changes in Facial Expression

- Squinting of eyes
- Abnormal carriage of ears
- Holding whiskers in abnormal position (cats)
- Avoidance of gaze

Loss of Normal Bodily Functions

- Anorexia
- Reluctance to eliminate

- Poor or excessive grooming

Social Behavior

- New or escalating aggression or fear when approached, handled or when near other animals
- Avoidance of familiar people or avoidance of any interaction
- Seeking of constant reassurance

Physiological Indicators

- Panting or tachypnea, open-mouth breathing (cats)
- Tachycardia
- Hypertension

Note: Many of these indicators may also be generated by anxiety, fear, sedation, or the effects of medications in addition to pain. Patients exhibiting these behaviors should be screened for other potential causes such as dysphoria or discomfort from non-painful sources.

Pain recognition starts with assigning a level of expected pain for the specific patient in its specific situation. Several authors have used this process as a pre-emptive scoring system to guide analgesic therapy.[4,7] Box 126-3 lists expected levels of pain for common surgical or diagnostic procedures, injuries, and illnesses. This information can be used as a starting point when formulating a pain management plan.

Box 126-3

Expected Levels of Pain for Common Surgical or Diagnostic Procedures, Injuries, and Illnesses

Severe to Excruciating Pain

- Acute neuropathic pain such as that experienced with cervical intervertebral disc herniation, nerve injury due to trauma, or widespread neurological tissue inflammation
- Bone tumors
- Pathological fractures
- Extensive necrotizing cutaneous or visceral inflammation as in necrotizing fasciitis or peritonitis
- Severe polytrauma
- Necrotizing pancreatitis or cholecystitis

Moderate to Severe Pain

- Hollow organ distension
- Visceral organ capsule distention
- Mesenteric, gastric, testicular or splenic torsions
- Pleuritis and peritonitis
- Ureteral, urethral or biliary obstructions
- Limb amputation
- Post-operative fracture repair or intra-articular surgery
- Ear canal ablation
- Post-operative thoracotomy
- Thrombosis or ischemia
- Intra-ocular or corneal disease or injury/enucleation
- Onychectomy
- Cancer pain
- Postoperative routine laparotomy
- Soft tissue trauma
- Whelping or queening
- Thoracolumbar intervertebral disc disease

- Polyarthritis
- Juvenile inflammatory musculoskeletal diseases such as panosteitis and hypertrophic osteodystrophy
- Extensive dental extractions and oral mucosal inflammation

Mild to Moderate Pain

- Minimally invasive orthopedic procedures such as removal of an external fixator
- Diagnostic endoscopy
- Dental procedures
- Cutaneous mass removals
- Cystotomy
- Anal sacculectomy
- Castration

Mild or Brief Pain

- Bone marrow aspiration
- Urinary catheterization or cystocentesis
- Phlebotomy
- Placement of nasogastric or nasoesophageal feeding tubes, nasal oxygen cannulas, intravenous and arterial catheters
- Drain and suture removal
- Bandage change

This information is intended to provide a rough estimate of expected pain and will vary depending upon the specific context and individual patient factors.

Adapted from Mathews KA: Pain assessment and general approach to management. *Vet Clin North Am Small Anim Pract* 30:729-752, 2000.

Physiological and Behavioral Indicators of Pain

No measurable physical exam or biochemical parameter is pathognomonic for pain or free of influence from non-pain sources. Blood pressure, heart rate, and respiratory rate are non-specific indicators of pain that are most useful when combined with behavioral indicators.[21] Noting trends in these measures can help confirm that a patient has uncontrolled pain and can also help assess the efficacy of the chosen pain management plan.

Assessment of posture, mobility, interactive behavior, and vocalization generally are more valuable measures of pain in animals (see Box 126-3). As with all pain assessment, changes, and trends in these indicators are probably the most accurate use of this information.

Pain Scales

Many pain scoring tools have been developed for use in veterinary patients and they are the subject of intense research. Despite this, few of them are fully validated using accepted methods of statistical analysis and they are not widely used in clinical practice. Most pain scales for dogs and cats were designed for use in post-operative and trauma patients and may not be applicable to those with spontaneous non-surgical pain, as in acute pancreatitis.[22] This is particularly true in patients who are sedated or too ill to generate typical pain behaviors.

Pain scales are valuable when they serve to trigger regular pain assessment and adjustment of pain management. They are too insensitive and nonspecific to justify withholding of analgesics. A frequent criticism of pain scoring tools is that they cannot distinguish dysphoria, stoicism, or anxiety from pain. Use of good clinical judgment should override a pain score if there is a suspicion that the score is inappropriate. The principles listed in Box 126-1 should be kept in mind regardless of whether a specific scaling tool is used.

Downloadable examples of well-researched acute pain scales (including the CGMPS short form and the CSU tool for dogs and cats) can be found by searching key words "pain scales" on the home page for the International Veterinary Academy of Pain Management (IVAPM; www.IVAPM.org) and on the home page of

the Association of Veterinary Anaesthetists (http://www.ava.eu.com/vets-and-nurses).[22,23]

Pain Management as a Standard of Practice

Reluctance to recognize and treat pain in veterinary patients has changed dramatically in the past decade. The American Animal Hospital Association's mandate that pain be considered a vital sign and assessed in every patient is a strong statement of this change. Nevertheless, repeated surveys of veterinary practitioners across the world have shown large variability in both pain recognition and treatment.[24,25] Particularly insidious are persistent myths about analgesia provisions in animals: namely, that some postoperative pain is beneficial for recovery and that treatment often carries the risk of serious side-effects.[26] Both ideas are contradicted by research and practice guidelines issued by the American College of Veterinary Anesthesia and Analgesia, the World Small Animal Veterinary Association Global Pain Council, and the American Animal Hospital Association.[3,27]

Treatment of acute pain achieves important medical goals, besides fulfilling our professional obligation to prevent and relieve suffering of animals. Pain produces biological stress, or a physiological attempt to preserve biological functioning in the face of threats (i.e., environmental, emotional or physical) to homeostasis. Distress can be defined as a biological state when the physiological cost of stress is high enough to cause negative effects on primary biological functions.[26] Pain has a complex relationship with biological stress and distress, being both a cause and an effect. It is intuitively obvious that pain *causes* distress. Pain also can result *from* distress because anxiety and fear lower the nociceptive threshold and amplify pain perception. An understanding of the implications of the stress response on physiology has led us to realize that untreated or undertreated pain is an important contributor to neurohumoral, immunological, and hematological effects of biological stress. The pathophysiologic consequences of pain can include increased cardiac work and oxygen demand, vagal inhibition, hypoxemia, hypercarbia, atelectasis, ileus, nausea, vomiting, oliguria, thromboembolism, fatigue, sedation, and fear.[26,27,29] Many of these effects are due to pain's ability to stimulate an autonomic response. Additionally, pain causes dysfunction in the immune system due to neuroendocrine-mediated pathways.[9] These effects can demonstrably increase morbidity, mortality, and prolong hospital stays in people and, we infer, veterinary patients.[30]

Strategies for Acute Pain Management

Ch. 138, 164, and 166 provide drug dosing guidelines and clinical essentials. In addition, the World Small Animal Veterinary Association has freely downloadable pain management guidelines for a variety of clinical situations (http://www.wsava.org/educational/global-pain-council).

Having a goal-directed strategy has been shown to improve outcome and reduce adverse events in many disciplines of clinical medicine. Pain management is likely no different, and, at the very least, goals ensure that all facets of pain control are being considered. General goals of acute pain management are: (1) maximize comfort, (2) normalize physiologic homeostasis as much as possible, (3) reduce the risk of future chronic pain and (4) minimize adverse effects of pain management.[31] The clinical recommendations below will reference how they meet these goals.

An important starting place is the understanding that pain is harder to treat when it has been untreated or undertreated and windup or hyperalgesia has already occurred. Since this can happens in minutes after initiation of nociception, treatment plans should be geared towards providing comprehensive pain relief immediately rather than losing an opportunity for pain prevention by gradually ramping up to full treatment.

Other factors should be considered when formulating an acute pain management plan. The patient's age, general health and body condition, temperament, pain history, expected course of treatment, and whether the patient is being treated in a hospital setting or as an outpatient should be weighed when developing a plan. The patient's caretakers must be taken into consideration, since financial constraints, compliance and expectations will have a large impact on the plan. Although the consideration of all these factors transforms the planning process into a skilled art, success depends upon this calculation.

Perhaps the most important factors for ensuring successful acute pain management are individualization of the treatment plan and the use of frequent assessment of response to treatment as a guide for plan adjustments. Becoming comfortable with the usual response to commonly-used therapies provides a solid starting point and some degree of predictability. It can be helpful to design standardized strategies for mild, moderate, and severe pain to provide an initial basis for formulation of an individualized plan.

When analgesic therapy fails to provide pain relief, factors other than inadequate dose should be

considered. Although it seems obvious, we might not realize that some patients will experience much more severe pain than others, and some can have atypical responses to analgesic strategies that are usually effective. Unexpected signs of pain can also be due to non-pain-related distress from various conditions such as nausea, a full bladder, or hypothermia. Compliance by the patient or the person administering drugs should be evaluated as well. Some patients' pain might not be relieved without the use of more complicated multi-modal strategies or the use of non-pharmacological therapies.

Pharmacological methods of analgesia are the cornerstone of therapy, whether given regionally or systemically. The main categories of analgesic drugs are local anesthetics, NSAIDs, opioids, and adjunctive analgesics. Non-pharmacological methods of pain control can greatly improve analgesia in veterinary patients, while lowering the risk of adverse effects of drug therapy.

Preventive Analgesia

As mentioned previously, management of pain ideally begins as *preventive analgesia.* The concept of *pre-emptive analgesia* did not bear up to expected success, but new understanding of surgical nociception has updated this concept.[32] In contrast to other types of pain etiologies, the patient is anesthetized when surgical nociception first occurs (incision), so administering analgesics prior to surgery seems not as important as continuing sufficient analgesia during and after the procedure. During other pain states, the most significant nociception occurs during the injury itself. In patients undergoing diagnostic and surgical procedures, effective analgesia is most successful when the level and duration of analgesia are capable of sufficiently quashing nociception until the nociceptive input has stopped.[31] The patient can benefit from this powerful tool when the clinician includes analgesic agents in anesthesia protocols. Using opioids, alpha$_2$ agonists, and ketamine in premedication and induction protocols will accomplish this and will also augment sedation. Local and regional anesthesia/analgesia provisions should be included in every protocol, since they are capable of blocking nociceptive input completely. NSAIDs are also fundamental to preventive analgesia because of their ability to block and treat inflammation. The beneficial impact of simple approaches like local infiltrative blocks and single doses of NSAIDs should not be underestimated. They are cost-effective, low-risk, and can have significant benefit for current and future/chronic pain control in a given patient.

Multimodal Analgesic Strategies

Of course, preventative analgesia is not possible for patients with trauma and spontaneous illness. *Multimodal analgesia* (sometimes called balanced analgesia) strategies can be the most effective by improving analgesia while reducing risk of adverse effects. Multimodal analgesia can also reduce sensitization and the subsequent development of chronic pain. The rationale for multimodal analgesia is that combining two or more therapies (drugs or non-pharmacological therapy) is more effective because different therapies target a different part of the complex signaling process and work synergistically.[33] This also can allow lower overall dosages of drugs that carry the risk of adverse effects. Reviews of multimodal analgesia in human postoperative patients show that NSAIDs, local anesthetic techniques, parenteral alpha$_2$ adrenergic agonists, and alpha-2-delta–1 subunit calcium channel blockers (e.g., gabapentin, pregabalin) are opioid-sparing and effective.[34] Empirical data to show the effectiveness of multimodal analgesia in veterinary medicine are limited mostly to experimental situations and combinations of opioids and NSAIDs in clinical patients.

Locoregional Analgesia

Local and regional analgesia using agents such as lidocaine (e.g., up to 1-2 mg/kg SC, total cumulative dosage if given in multiple sites), bupivacaine (e.g., 0.5-1 mg/kg SC, total cumulative dosage if given in multiple sites), mepivacaine, or ropivacaine can fulfill many of the goals stated above for analgesia. Other classes of drugs, like opioids and alpha$_2$ agonists, are increasingly being used in combination with local anesthetics to extend the duration and efficacy of local analgesia.[35] Although complete anesthesia can be achieved with many of these techniques, published dosages for local anesthetic infusions more often provide analgesia without complete loss of sensation or motor function.

Most techniques are simple enough to require only minimal training (e.g., local infiltrative blocks, topical anesthesia, incisional line blocks, ring blocks). Some techniques require extra training, but still are easily mastered, safe, and cost-effective (e.g., intra-testicular blocks, oral/dental blocks). Single-dose epidural injections have low complication rates and can provide analgesia for up to 24 hours in patients undergoing

orthopedic surgery, celiotomy or thoracotomy, or those who have sustained major trauma.[36]

Surgical placement of wound diffusion (soaker) catheters for provision of continuous local blockade after limb amputation, thoracotomy, laparotomy, or total ear canal ablation, for example, enables patients to be comfortable and mobile without the need for large doses of systemic analgesics.[37] A related technique, continuous peripheral nerve block, involves percutaneous placement of an indwelling catheter near a peripheral nerve for continuous blockade. This technique still is rarely used in veterinary medicine and does require ultrasound guidance. It allows human patients to have improved analgesia postoperatively, reduced opioid use, and shortened hospital stays.[38]

Other regularly used techniques require more specialized equipment and training. These techniques, including single dose nerve-locator and ultrasound guided regional blockade and epidural catheter placement are capable of substituting for all or part of the commonly used systemic analgesic drugs associated with more side effects.[39]

Step-by-step techniques for provision of locoregional analgesia are widely available in the veterinary literature and in multi-media formats (see above). Additionally, hands-on workshops are part of major veterinary conferences throughout the year.

Systemic, Pharmacologic Analgesia

Pharmacological provision of systemic analgesia given orally or via parenteral routes is the mainstay of acute pain management.

NSAIDs are highly effective against acute pain due to their diverse anti-inflammatory effects. Examples include (as initial dosages for dogs) carprofen 2.2 mg/kg PO q 12 h or meloxicam 0.1 mg/kg PO q 24 h, or for cats, robenacoxib 1 mg/kg PO q 24 h × 3 days. Although chronic use of NSAIDs carries a substantial risk of adverse effects in patients with pre-existing gastrointestinal (GI), renal, or hepatic disease, they have minimal cardiovascular risks in veterinary patients. They also can provide effective analgesia when given short-term, thereby avoiding some of the risks of chronic use. Acetaminophen (paracetamol), usually considered to be an analgesic without anti-inflammatory effects, is being re-evaluated as a possible anti-inflammatory agent and might be useful in the dog (e.g., 10-15 mg/kg PO q 12-24 h), despite being highly toxic to cats.[40,41]

Opioids are considered the prototypical therapy for acute pain management due to their safety and efficacy. Opioids have few or easily-managed cardiovascular effects, are in large part reversible, and are readily titrated to effect. Current understanding of the diversity of opioid receptor types, location, and pharmacogenomics has led to novel delivery methods, new clinical uses, and reduction in unwanted effects.[42] For example, buprenorphine administered via the oral transmucosal route in cats has become routine in veterinary medicine after it was realized that buprenorphine administered by this route is highly bioavailable and produces reliable analgesia in the cat.[43] Another example is the growing interest in peripheral effects of opioids because of the premise that targeting opioid receptors in the periphery would avoid undesirable central nervous system effects.[7]

Opioids are underutilized in clinical veterinary medicine[44] despite their relative safety and efficacy. Commonly cited reasons are fear of adverse effects and controlled substance restrictions. In general, adverse effects are dosage-related and can be minimized when dosing is titrated to effect. Sedation, dysphoria, respiratory depression, and emesis are less when pain is more severe.[45] Respiratory depression rarely is clinically significant in conscious veterinary patients, in contrast to human patients.[46]

For hospitalized patients, injected opioids (e.g., in dogs, methadone 0.1-0.4 mg/kg IV or IM, or hydromorphone 0.025-0.1 mg/kg IV or IM; in cats, buprenorphine 0.02 mg/kg IV or PO transmucosally, or oxymorphone 0.05 mg/kg IV or IM) can be given as needed, as bolus therapy, and/or as continuous rate infusions (CRI). Although CRI use often is relegated to patients with severe pain, it may help avoid adverse effects in patients with less severe pain. Combining opioids of different functional classes often occurs in veterinary patients, but the effects are unpredictable.[47,48] Layering of different pure mu-receptor agonists (i.e., oral or bolus dosing in addition to a CRI) can allow for fine-tuning of pain control and adverse effect management.

Other Analgesics Useful for Acute Pain Management

Alpha$_2$ adrenergic receptor agonists (alpha$_2$ agonists) have profound analgesic effects besides their well-known sedative, anxiolytic, and muscle relaxant properties. Analgesia is increased when alpha$_2$ agonists are used with opioids.[49] The precise mechanism of action for anti-nociception is not fully understood, but it appears to

relate to spinal alpha$_2$ adrenergic receptor stimulation, which is involved in pre- and post-synaptic modulation of pain signals and the descending modulation system.[49] Alpha$_2$ agonists do have profound cardiovascular effects even at very low dosages. They also have effects on most other body systems due to the widespread nature of the adrenergic receptor and some non-adrenergic receptor effects. Many of these effects are dosage-dependent, however, and do not preclude cautious use. Alpha$_2$ agonists (e.g., dexmedetomidine 0.5-1 mcg/kg IV as a bolus and 0.5-1 mcg/kg/h CRI) can be used as part of sedation or anesthesia protocols to provide analgesia, as intermittent injections or CRI in hospitalized patients or as part of epidural and locoregional drug combinations.

Gabapentin and pregabalin, related antiepileptic drugs with anti-hyperalgesic and anxiolytic effects, may have a role in the management of acute pain (e.g., for gabapentin in dogs, for short term acute/perioperative analgesia and possibly anxiolysis, in gabapentin-naïve patients: 10-15 mg/kg PO q 8-12 h; this will be sedating in naïve patients; and for pregabalin: 1-2 mg/kg PO q 12 h for cats and 2-4 mg/kg PO q 12 h in dogs, but probably best used for chronic pain). These medications have long been used for managing neuropathic pain, but more recently have been studied in perioperative pain. Gabapentin premedication reduces pain score, opioid use, the incidence of postoperative nausea and vomiting (PONV), and development of chronic pain in human patients undergoing a variety of orthopedic and soft-tissue surgeries.[50] Pregabalin produced a dose-related decrease in postoperative opioid use and PONV when used in a variety of perioperative situations.[51] There are pharmacokinetic data for gabapentin and pregabalin in dogs and cats but very limited investigation of them as analgesics.[52] Extrapolation from use in people has generated anecdotal reports of use in veterinary acute pain management. It seems likely that some of the sedative and anxiolytic effects can be beneficial in acute pain management in addition to direct anti-nociceptive effects. Of note is that gabapentin and pregabalin are excreted completely via renal mechanisms and that the dosage range is very large.

NMDA receptor inhibitors: Ketamine is a well-researched analgesic agent in veterinary species. Use of sub-anesthetic bolus or CRI doses (e.g., 0.5-1 mg/kg IV in dogs and cats +/− IV CRI at 5-20 mcg/kg/min) reduces anesthesia and opioid requirements, increases opioid efficacy and probably reduces the development of chronic pain. Methadone (e.g., 0.1-0.4 mg/kg IV or IM) also has NMDA inhibitory properties that augment its usefulness as an analgesic.

Serotonin and norepinephrine reuptake inhibitors have a greater role in chronic pain management, but tramadol has been used extensively in veterinary medicine. Most veterinary research has focused on the use of injectable tramadol as a way to decrease anesthetic requirements. There is scant evidence in the veterinary literature that tramadol is an effective analgesic for acute pain; most clinical studies utilizing tramadol for post-operative pain show that it is less efficacious than NSAIDs.[53] Tramadol (e.g., for dogs: 3-5 mg/kg PO q 6-12 h, and for cats: 1-2 mg/kg PO q 12-24 h) has a unique combination of effects: weak mu opioid receptor activity and serotonin/norepinephrine reuptake inhibition. In laboratory dogs, tramadol has limited metabolism to the active opioid form and shows large interindividual variation in bioavailability.[54] Anecdotally, some treated patients appear to have much more pronounced opioid effects than others. Additionally, efficacy appears to be very individually variable. New information about adverse effects in people, including serious hypoglycemia and hyponatremia, could temper the idea that tramadol is a safer alternative to NSAIDs.[53] Tramadol does lower seizure threshold and is now Food and Drug Administration controlled as a schedule IV drug in the United States.

Corticosteroids certainly inhibit inflammatory pain, but their far-reaching effects on non-target tissues limit their use as analgesics. For treatment of inflammatory diseases, e.g., immune-mediated polyarthritis or steroid-responsive meningoencephalitis, corticosteroids fulfill a dual role of treating the underlying disease and providing analgesia. They have a role in local or regional analgesia, as part of protocols for intraarticular, epidural, topical, ocular, otic, or other localized inflammation and acute pain. As long as a patient has no specific contraindication and is not concurrently receiving an NSAID, corticosteroids can be useful as a very short-term and/or localized anti-inflammatory agent.[56]

Anxiolytic drugs have an important role in acute pain management, particularly in the hospitalized patient (e.g., gabapentin [see dosage listed above], dexmedetomidine [see dosage listed above], or acepromazine [not an anxiolytic, but does produce physiologic tranquilization] at a starting dosage of 0.01-0.02 mg/kg IM, IV, or PO transmucosally). Understanding of the physiological connection between anxiety and altered pain signaling has led to the realization that reducing anxiety can directly impact pain perception. In addition, benzodiazepines and other sedatives that provide muscle relaxation can augment analgesia in patients with pain caused by musculoskeletal disease. The potential drawback that must be considered is whether excessive sedation with anxiolytic drugs could mask pain behaviors. See ch. 138 for essential clinical use.

Non-Pharmacological Methods of Analgesia

In the context of acute pain management, non-pharmacological therapies can provide analgesia largely through manipulation of endogenous pain-inhibitory systems. Some interventions like distraction via feeding or going for a walk are similar to effective methods used in babies, like suckling and swaddling.[57] We often mistake the effectiveness of these interventions as proof that our patients are not painful, although distraction and environmental modification are recognized methods of invoking endogenous analgesia.[58] More active analgesic interventions can also be useful in acute pain management. Widely used examples are rehabilitative therapies including massage, aqua- and cryotherapy, orthoses, acupuncture, low level laser therapy and transcutaneous electrical nerve stimulation (see ch. 355). Published studies establishing clinical success of many of these methodologies remain sparse despite the elucidation of mechanism of action in experimental settings, in particular for acupuncture.[59] This likely will continue to be true given the difficulties in designing adequate methods for providing controls with non-pharmacological therapies. Anecdotally, these methods can augment analgesia and reduce the need for pharmacological management.

Management of Distressing, Non-Painful Conditions

Patients can experience unnecessary suffering from non-pain-related sources during the course of medical treatment. Common examples are nausea, sleep deprivation, hunger, delayed eliminations, fear, uncomfortable bandages, and uncomfortable ambient environments. We tend to accept these conditions as part of medical therapy, but most of them can be reduced easily with thoughtful treatment and environmental enrichment. Reduction of non-pain-related suffering can immediately reduce pain perception and analgesic requirements, thereby reducing adverse effects.

Pain Management for Diagnostic Procedures

Diagnostic and minor medical procedures rarely are investigated in terms of pain, and frequently are overlooked as sources of pain in small animal patients.[60,61] For hospitalized patients, minor procedures can substantially increase pain and distress, particularly since the cumulative effects from different types of interventions might not be recognized. In adults and children, procedural pain, as it is termed, is a well-researched subject.[63] Likewise, pain due to husbandry procedures in farm animals and minor experimental procedures in laboratory animals is better researched than in small animal patients.

Examples of pain-inducing procedures often performed with inadequate analgesia include diagnostic imaging, endoscopy, bone marrow aspiration, centesis of visceral cavities or joints, cerebrospinal fluid collection, bandage changes, and central line placement. It is important to consider whether individual patients undergoing minor procedures are at higher risk for pain due to preexisting chronic pain, distress/anxiety, or from exacerbation of pain due to the primary diagnosis. Use of short-term analgesics, particularly local anesthetic techniques, single doses of opioids, NSAIDs, alpha$_2$ agonists, or anxiolytics are very effective for this purpose. Equally important is attention to non-pharmacological methods of comfort such as padded surfaces, care with joint manipulation while under anesthesia, removal of insufflated gas or fluid after endoscopy, management of the ambient environment to minimize noise, temperature extremes, etc., and grouping treatments to give patients adequate undisturbed time to recover and rest.

Adverse Effects of Acute Pain Treatment

Treatment of acute pain rarely is accompanied by serious adverse effects. Most adverse events can be "treated" by passage of time and adjusting future treatments to the individual. Few other aspects of clinical practice need to be individualized as much as drug choice and dosages for pain management, despite the abundance of published doses and protocols. Perhaps the most common adverse event is excessive sedation or excitation/dysphoria that impairs normal functioning in outpatients or delays discharge from the hospital. This can be prevented by adjusting starting dosages of opioids and other medications that have sedative effects, like alpha$_2$ agonists and gabapentin, at the beginning of therapy. Knowledge of the patient's past reactions to analgesics and sedatives and their baseline temperament are very helpful. Sedation might be a welcome effect immediately post-op and usually does not require treatment. If oversedation or dysphoria requires treatment, then opioids can be partially reversed with low dosages of butorphanol (starting at 0.05 mg/kg IV) or titrated mu-receptor antagonists (e.g., naloxone 0.002-0.01 mg/kg IV, titrated to effect and given in a diluted form to help reduce full reversal of analgesia). If oversedation is a common problem, the

clinician should consider starting with lower dosages of opioids and sedatives as a rule. Use of shorter-acting opioids, like fentanyl, can help as well. Some opioids are associated with less sedation or dysphoria; methadone and buprenorphine are examples.

Gastrointestinal effects of acute pain therapy (excluding NSAID induced GI toxicosis) do not necessarily mean that analgesic therapy has to be stopped. Consider whether inadequate treatment of pain, particularly visceral pain, potentially is the cause of the signs rather than analgesics. Visceral pain can be responsible for all of the same signs. Layering of anti-emetics and pro-kinetic treatments commonly is used for people and can be helpful in veterinary patients. Reduced dosing or multimodal therapy that allows lower dosing of individual drugs may be all that is required.

Other opioid adverse effects that can be seen with acute pain management are urine retention and opioid-induced hyperalgesia (OIH). Urine retention is a rare complication that can occur with both systemic and epidural opioid administration. This effect resolves as the drugs are metabolized, but until then can be managed with opioid antagonists, detrusor muscle stimulants, and catheterization.[46] OIH is reported rarely in veterinary medicine, but could be underrecognized. Anecdotally, it is most often seen in veterinary patients given high dosages of mu-receptor agonists for longer than typical periods, i.e., in severe polytrauma patients or hospitalized, terminally-ill cancer patients. OIH may be hard to distinguish from inadequately treated pain because opioid dosages are escalated as pain increases. In experimental animals and human patients, OIH can be prevented or improved by concurrent use of NMDA blockade with ketamine or methadone, dosage reduction, and multimodal analgesia.[62]

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CHAPTER 127

Shock

Teresa M. Rieser

A brief history of the development of understanding of the cardiovascular system and shock demonstrates how far we have progressed in our knowledge of this crucially important topic. Cladius Galen, also known as Galen of Pergamum, began our understanding of circulation by proposing that there were two types of blood: nutritive blood which was enriched within the liver with nutrients and vital blood which was imbued with pneuma, the vital spirit inspired from the air which was crucial to life. Galen did not, however, believe that blood returned to the heart for recirculation.[1,2] Galen's ideas were widely accepted until 1628 when William Harvey who was the court physician of both King Charles I and King James I, published *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*. This work questioned Galen's teachings and proposed that the heart pumped blood through the arteries and into the veins and then back to the heart. Harvey lacked, however, the ability to demonstrate how the arteries and veins communicated; this was done in 1661 by Malpighi when he visualized capillaries microscopically.[2,3] These works set the groundwork for our modern understanding of the circulatory system.

Shock has been appreciated as far back as the early Greeks including both Hippocrates and Galen.[3] In the 1700s, descriptions of shock and death were documented, and many different terms were used to describe shock including "final sinking of vitality."[2,4] The term "shock" did not become popular until Edwin A. Morris used the term in his American Civil War text *A Practical Treatise on Shock after Operations and Injuries*. Now, we appreciate a variety of underlying causes of shock and the profound danger it poses to our patients. In this chapter we discuss what shock is, the different types of shock, the hemodynamic alterations unique to each type of shock and treatment goals.

Shock has been defined as the state in which profound and widespread reduction of effective tissue perfusion leads first to reversible, and then if prolonged, to irreversible cellular injury.[5] To understand that definition and its implications some understanding of basic physiology is essential.

Molecular oxygen is a substrate for a variety of enzymatic cellular reactions needed for biosynthesis, energy production and molecular modification. The majority of the oxygen is used within cells by the mitochondrial electron transport system in order to generate adenosine triphosphate (ATP) via aerobic respiration.[6] The rate of mitochondrial oxygen consumption is primarily determined by the rate of ATP utilization by the cell. When the mitochondrial electron transport system becomes deranged, then the consumption of oxygen continues but the generation of ATP does not.[6] As the mitochondria consume oxygen, the intracellular pO_2 decreases and a gradient is created which favors the movement of oxygen from the interstitial space into the cell. In steady state conditions, the rate of oxygen utilization will match that of oxygen diffusion into the cells.[6] The gradient between the mitochondrial and extracellular pO_2 has been found to be about 2 to 4 mm Hg. In addition, mitochondrial pO_2 will increase or decrease in parallel with the extracellular pO_2.[6] As extracellular pO_2 decreases, the availability of oxygen to the mitochondria decreases as well until it reaches a critically low level. Now electron transport and oxygen consumption within the mitochondria becomes oxygen supply dependent. When the extracellular supply of oxygen decreases even further, aerobic oxidative phosphorylation stops and ATP levels fall. At this point, phosphofructokinase is stimulated and anaerobic glycolysis commences. This switch to anaerobic metabolism results in the rapid depletion of cellular glycogen stores and the accumulation of intracellular lactate and inorganic phosphates.[7] Anaerobic generation of ATP is inefficient but it does allow the cell to survive for a brief period of time. Some cell types such as neurons are unable to generate ATP anaerobically and therefore are especially vulnerable to hypoxic injury. Eventually the depletion of ATP causes failure of the Na^+K^+ pumps in the cell membrane, cell swelling and death.[6,7]

The vascular system's main purpose is to always provide an adequate supply of oxygen to every cell in the

body.[6] Oxygen delivery (DO_2) is the product of cardiac output (CO) and arterial oxygen content (CaO_2). CO is determined by heart rate (HR) and stroke volume (SV). Another way to consider cardiac output is its relationship to systemic vascular resistance and blood pressure using the following equation:

$$CO = (MAP - RAP)/SVR$$

where MAP is mean arterial pressure, RAP is right atrial pressure and SVR is systemic vascular resistance. RAP is much lower than MAP so this can be further simplified to:

$$CO \cong MAP/SVR$$

This is a useful relationship to bear in mind when considering how to address shock clinically.[8]

CO can be measured invasively in veterinary patients using multiple different types of indicator dilution methodologies or non-invasively using a partial carbon dioxide rebreathing method (NICO). Although this is not commonly done,[9] CaO_2 is determined by hemoglobin concentration (Hb), hemoglobin saturation (SaO_2) and the partial pressure of oxygen dissolved in the arterial blood (PaO_2) (see ch. 75 and 128). The hemoglobin concentration must be multiplied by the Huffner factor, which is a species-specific constant that describes the amount of oxygen in milliliters that can be carried per gram of hemoglobin.[10,11] The Huffner factor is 1.39 in the cat and ranges from 1.34 to 1.39 in the dog.[10] The PaO_2 must be multiplied by 0.003, which is the Bunsen solubility coefficient for oxygen in blood. This converts the PaO_2 from mm Hg to milliliters.[11] Putting this all together results in the following equation:

$$DO_2 = [(1.34 \times Hb \times SaO_2) + (0.003 \times PaO_2)] \times (HR \times SV)$$

Because the contribution from the PaO_2 is very small compared to that of saturated hemoglobin this portion of the equation is sometimes omitted for expediency. This equation is useful to keep in mind as it underscores the various therapeutic targets that may be altered during treatment of the shock patient. Oxygen consumption (VO_2) is relatively constant at rest but may be altered by changes in metabolic rate. Examples include exercise or the pathophysiologic stress of sepsis.[10] VO_2 can be expressed with the following equation:

$$VO_2 = CO \times (CaO_2 - CvO_2)$$

where CvO_2 is the oxygen content of venous blood. This equation can be more practically expressed as:

$$VO_2 = CO \times 1.34 \times Hb\ (SaO_2 - SvO_2)$$

where SvO_2 is the venous oxygen saturation. Bringing all of this together is the idea of the oxygen extraction ratio (OER). The OER describes how efficiently the body is extracting oxygen for use at the end tissues.[10]

$$OER = VO_2 / DO_2$$

A normal OER has been estimated to be roughly 0.25. This means that in a normal animal only 25% of the delivered oxygen is extracted for cellular use.[10]

Types of Shock

In older references, shock was usually divided into three broad categories: hypovolemic, cardiogenic and distributive (also called vasodilatory).[12] While these types of shock clearly exist, there are additional clinical groups that must be considered[13-15] (Box 127-1). It is also valuable to remember that clinical patients may have components of different types of shock. An example would be a patient with septic shock; this animal will have evidence of distributive shock but it may also have signs of hypovolemic shock due to third space losses of volume and metabolic shock.

Box 127-1

Functional Classifications of Shock with Examples

Hypovolemia: a decrease in effective circulating volume
- Blood loss
- Trauma
- Profound dehydration

Distributive: inappropriate vasomotor tone
- Sepsis/SIRS
- Anaphylaxis
- Neurogenic

Cardiogenic: decreased forward flow
- Congestive heart failure
- Cardiac arrhythmias
- Drug overdose (anesthetics, calcium channel blockers, beta-blockers)

Obstructive: decreased forward flow or venous return
- Cardiac tamponade
- Massive pulmonary thromboembolism
- Neoplasia
- Tension pneumothorax
- Gastric dilatation-volvulus

Metabolic: abnormal cellular metabolism
- Toxic: bromethalin, cyanide
- Hypoglycemia
- Cytopathic hypoxia in sepsis

Hypoxemic: decreased CaO_2
- Anemia
- Severe pulmonary disease
- Methemoglobinemia
- Carbon monoxide intoxication

Hypovolemic shock occurs when there is a decrease in the effective circulating volume. This may be seen with blood loss but it may also be seen with contraction of the extracellular fluid compartment due to profound dehydration. All animals that have dehydration have some degree of hypovolemia but they do not all exhibit shock. Distributive shock has a decrease in systemic vascular resistance but may also have focal regions of vasoconstriction. The most common example is sepsis or systemic inflammatory response syndrome but this can also be seen with neurogenic shock or anaphylactic shock. In cardiogenic shock, there is failure of the heart to generate adequate forward flow. This may be due to either systolic or diastolic disease. An example would be a patient with severe dilated cardiomyopathy or severe cardiac arrhythmias. In obstructive shock, there is either an impediment to forward flow or an impediment to venous return. Examples include cardiac tamponade and gastric dilatation-volvulus. Metabolic shock occurs when DO_2 is adequate but VO_2 is deranged. Examples include the cytopathic hypoxia that is seen in sepsis[16] or bromethalin intoxication where there is an uncoupling of oxidative phosphorylation.[17] Finally, hypoxic shock can occur when there is a decrease in CaO_2. This could be seen with anemia where the decrease in hemoglobin can have profound effects on DO_2 or with severe pulmonary disease where hemoglobin concentration is adequate but poor gas exchange prevents saturation with oxygen.

Clinical Signs

Shock is a remarkably dynamic process and its clinical signs may vary with not only the underlying cause but also if the shock is compensated or uncompensated. Detection of compensated shock may be challenging as the clinical signs can be quite subtle. One finding that tends to be found across all types of shock is altered mental status. Patients with shock will range from obtunded to comatose with the more severe impairments of mentation found in decompensated shock. Indeed, this physical exam parameter is considered a "window" to the patient's status in human medicine.[13,18] The other clinical signs of shock are similar for most types of shock. This is due to the compensatory mechanisms that shock triggers within the body. As cardiac output and blood pressure decrease, first there is an increase in sympathetic tone. This results in peripheral vasoconstriction and increase in heart rate and an increased respiratory rate. Next there is an upregulation of the renin angiotensin aldosterone system, which promotes the reabsorption of sodium and water to bolster the effective circulating volume.[19] There is also additional direct vasoconstriction and the release of vasopressin, which causes further vasoconstriction and sodium and water reabsorption.[20] These compensatory mechanisms are seen clinically as pale mucous membranes, tachycardia and tachypnea. As shock progresses from a compensated to an early decompensated state, additional signs such as a prolonged capillary refill time and poor pulse quality may be appreciated. In addition, the increased vasoconstriction will result in cold extremities. Measurement of blood pressure will usually reveal hypotension (see ch. 99 and 159). A decrease in urine output may also be seen. Initially this may be in response to a decrease in effective circulating volume and is an appropriate response but as hypotension worsens, renal blood flow and glomerular filtration rate will be negatively impacted, resulting in pathophysiologic oliguria.[21] As shock progresses even further into late decompensated or irreversible shock the animal may now be bradycardic, comatose, have a prolonged capillary refill time, weak to absent pulses and marked hypothermia (see ch. 49).

In addition to the physical examination, a number of diagnostic tests and monitoring parameters may be used to determine the severity of shock and to guide therapy. One of the basic tests that can be used in both diagnosis and monitoring is the blood pressure. Patients in decompensated shock will often have a decreased blood pressure (see ch. 99). Central venous pressure may also be of utility in guiding therapy, especially in judging the response of the patient to intravenous fluids (see ch. 76). Blood lactate measurement is another valuable tool (see ch. 70). Animals with shock will tend to have an increased lactate level. Lactate is also useful in guiding therapy, with the goal of normalizing lactate as promptly as possible. Normal lactate is less than 2.5 mmol/L and an elevation greater than 7.0 mmol/L would be considered severe.[22-24] While some confounding factors such as liver disease and sample collection may affect lactate measurements, it is still an important part of the management and diagnosis of the shock patient.[22,23] Base excess is another value that has been shown to be of value in humans with shock and recently was correlated with transfusion requirements and mortality in veterinary patients with blunt trauma.[25] Mixed venous oxygen saturation (SvO_2) and central venous oxygen saturation ($ScvO_2$) are two additional values that are closely monitored in human shock resuscitation. Because the measurement of SvO_2 requires sampling from the pulmonary artery, $ScvO_2$ which is taken from the cranial vena cava is more readily accessible. A decrease in $ScvO_2$ is indicative of either a decrease in DO_2 or an increase in VO_2 while an increase in $ScvO_2$ may be seen with cytopathic hypoxia. Because the normal OER is about 25%, a goal of an $ScvO_2$ of greater than 70% is recommended.[13,18,26] A study in critically ill veterinary patients showed a failure to normalize $ScvO_2$ despite the normalization of the more traditional parameters that we seek to correct in shock.[26] A final area of interest is the direct visualization of the microcirculation using side-stream darkfield imaging. This methodology allows for the capillary density as well as the proportion of perfused capillaries and increases in heterogeneity of blood flow to be evaluated in readily accessible areas such as the sublingual area in humans. Abnormalities detected with this type of imaging have been associated with negative outcomes in human medicine.[13]

Treatment

The treatment of shock can be distilled down to the idea of improving oxygen delivery as soon as possible; there is a narrow therapeutic window before cellular energetics become deranged and cannot be reversed. In humans, this early goal directed therapy has been shown to be of considerable benefit and in veterinary medicine there is evidence that it is a desirable goal as well.[13,27] With the equations for DO_2 and CO in mind, treatment can be approached logically. Fluid therapy is indicated for most forms of shock with the exception of cardiogenic. Here the goal is to normalize blood pressure, central venous pressure, and the physical

parameters of heart rate, pulse quality, capillary refill time, mentation and urine output (Figure 127-1). In most instances a balanced crystalloid solution is reasonable but synthetic colloids and hypertonic saline can also be used. In the case of the shock patient with head trauma, hypertonic saline is the preferred fluid for resuscitation.[28,29] "Small volume resuscitation," which is also known as limited volume resuscitation, uses resuscitative fluids in small volumes to achieve moderate increases in hemodynamic stability. In this type of resuscitation, synthetic colloids and hypertonic saline take center stage as they allow for expansion of the effective circulating volume in excess of the administered fluid volume. The goal here is to minimize the deleterious effects seen with over-aggressive crystalloid resuscitation.[30] If the animal is not responsive to fluid therapy or the animal is deemed to be volume replete, a catecholamine vasopressor such as dopamine or norepinephrine may be considered. Another option would be the drug vasopressin, which may be efficacious in patients that are refractory to other pressor agents.[20] If the patient has cardiogenic shock, fluids should be avoided and instead drug therapy with an inotrope or antiarrhythmic may be indicated to improve cardiac function. Other treatment goals include the maximization of hemoglobin saturation with oxygen therapy and if the animal is anemic, blood products should be used to increase hemoglobin concentration (see ch. 130). If additional abnormalities are identified such as hypoglycemia or intoxications, these issues must also be addressed promptly. Early recognition of shock and prompt therapy to restore oxygen delivery to the tissues are key in the successful treatment of shock (Figure 127-1).

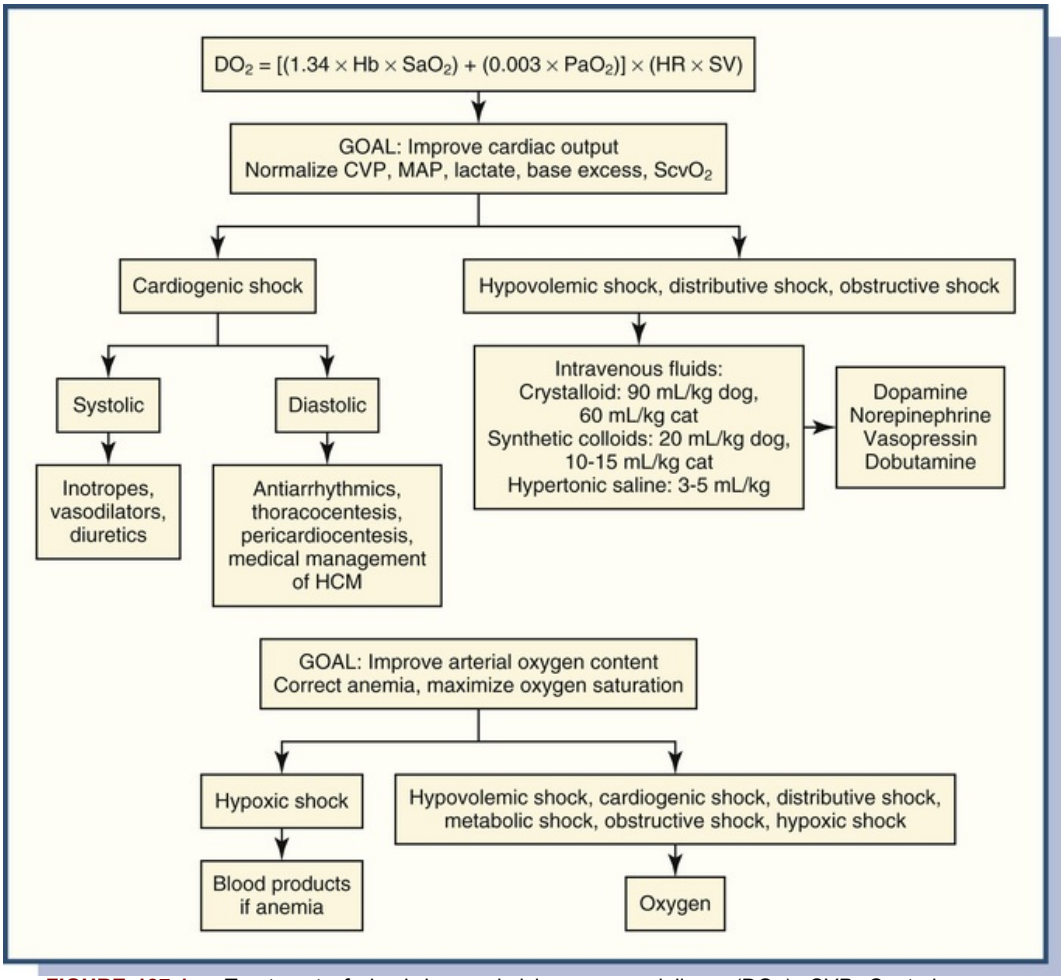

FIGURE 127-1 Treatment of shock by maximizing oxygen delivery (DO_2). *CVP,* Central venous pressure; *HCM,* hypertrophic cardiomyopathy; *MAP,* mean arterial pressure.

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CHAPTER 128

Acid-Base, Oximetry, and Blood Gas Analysis

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Acid-base and oxygenation disorders are common in dogs and cats with respiratory or metabolic abnormalities secondary to trauma, intoxication, or naturally occurring disease. Accurate point-of-care testing devices are widely available and affordable, making blood-gas testing a standard of care for emergency and specialty practices. Correct test interpretation and appropriate therapeutic response rely on maintaining a working knowledge of both acid-base and respiratory physiology and pathophysiology.

Blood gas testing may be performed using either arterial or venous blood. However, only arterial blood can be used to assess oxygenation; acid-base parameters other than partial pressure of oxygen (PO_2) may be evaluated using either arterial or "mixed venous" samples. The term "mixed venous" refers to venous blood collected from the main pulmonary artery, which is obviously not practical in a clinical setting. Jugular or peripheral venous blood is used, since those samples are easier to obtain (see ch. 75 and 76). Samples should be drawn into syringes that are coated with 1 : 1000 heparin to prevent clot formation, or into specialized blood gas syringes (Vital Signs, Englewood, CO) containing pelleted heparin (Figure 128-1, *A* and *B*). The syringe should be made airtight immediately following collection to prevent contamination with room air, which could alter gas measurements. The sample should be analyzed within 15 minutes of collection or placed on ice.

FIGURE 128-1 **A,** Arterial blood gas sampling kits contain a heparinized syringe and devices to render the syringe impervious to air. The advantage of these syringes is that arterial pressure will cause blood to fill the syringe chamber to the level at which the plunger is drawn. **B,** The syringe in the arterial blood gas sampling kit contains pelleted heparin as an anticoagulant in a sufficient amount to anticoagulate the maximum quantity of blood in the syringe.

Basic Acid-Base Physiology

An acid is a hydrogen ion (H^+, i.e., proton) donor, and a base is a proton acceptor. Hydrogen ions are nonvolatile or fixed acids produced by normal metabolism of proteins and phospholipids, and excreted by the kidneys. Acids are represented by the notation HA, which signifies a hydrogen ion and any negatively charged particle. When placed in solution, HA dissociates into H^+ (acid) and A^- (base). A base combines with an acid to lower the amount of acid in solution, or to buffer the solution.

Carbon dioxide (CO_2) is a volatile acid, or fat-soluble gas, that can combine with water in the presence of carbonic anhydrase to form carbonic acid (H_2CO_3). Carbon dioxide is formed during normal carbohydrate and fat metabolism and is excreted via the respiratory system. These two sources of acid (H^+ and CO_2) are interrelated, as is shown in the carbonic acid equation:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$$

This chemical reaction can proceed in either direction, depending on the availability of substrate on either side of the equation. Carbonic anhydrase catalyzes this reaction, and this enzyme is found widely in multiple body tissues and on red blood cells.

By definition, *pH* is the negative log of the hydrogen ion concentration. An acid gain results in a decrease in blood pH (acidemia), whereas an acid loss results in an increased pH (alkalemia). Acid can be gained

systemically from reduced renal elimination of a naturally occurring compound or from ingestion of an exogenous acid source. Changes in CO_2 influence the H^+ concentration, as evidenced by the carbonic acid equation. As CO_2 is eliminated by increasing respiratory rate and alveolar ventilation, carbonic acid dissociates to form more CO_2. In turn, H^+ and bicarbonate (HCO_3^-) combine to form more carbonic acid. Elimination of CO_2 through ventilation effectively lowers the H^+ concentration and increases pH. Conversely, as CO_2 concentration increases from hypoventilation, pH decreases.

Buffers act to bind H^+, preventing large fluctuations in pH. Buffer systems include nonbicarbonate buffers (proteins and phosphates), which are primarily intracellular, and HCO_3^-, which is the primary extracellular buffer. Bicarbonate is an effective buffer because it exists in relatively large concentrations compared with other buffers, is generated by renal tubular cells, and participates in the carbonic acid equation to produce CO_2 that can be eliminated through ventilation. The HCO_3^- buffer system, therefore, is considered an open system that can continue to buffer as long as the respiratory system is functional. In disease states causing HCO_3^- to be lost excessively from the urinary or gastrointestinal (GI) system, CO_2 and H_2O combine to form carbonic acid, which dissociates to increase H^+ and causes acidemia. For more in-depth discussion, readers are referred to references provided.[1-3]

Acid-Base Disorders

According to the Henderson-Hasselbalch equation, which is

$$pH = 6.1 + \log(HCO_3^- / (0.03 \times PCO_2))$$

pH can be characterized by changes in HCO_3^- and partial pressure of carbon dioxide (PCO_2). Because a predictable change in HCO_3^- occurs with gain or loss of H^+ ions, HCO_3^- can be used for correctly identifying acid-base abnormalities arising from metabolic disorders. Acidemia or alkalemia resulting from a primary respiratory disorder will show a corresponding change in PCO_2. Increases in PCO_2 occur with respiratory acidosis, and decreases in PCO_2 occur with respiratory alkalosis. In metabolic acidosis, acid accumulation results in gain of H^+ that is buffered by bicarbonate, resulting in low measured HCO_3^-; and in metabolic alkalosis, an H^+ decrease has the opposite effect. Commonly available commercial blood gas analyzers typically measure pH and PCO_2 and calculate HCO_3^-.

This equation also can be used for predicting the way compensatory mechanisms engage to lessen the degree of change in pH. When metabolic acidosis develops, the respiratory system is stimulated to increase the respiratory rate to eliminate CO_2 from the lungs and create respiratory alkalosis. Likewise, with a primary respiratory disorder, the opposite metabolic disorder is generated. The respiratory system provides rapid compensation, changing with the onset of a metabolic disorder in minutes. Metabolic compensation occurs more slowly, taking days before becoming maximally effective. With either system, compensatory mechanisms should slow as the pH approaches normal, and compensation should never completely normalize the pH.

Base excess, which is expressed in milliequivalents per liter (mEq/L), is the amount of base above or below the normal buffer base, a value calculated by taking into account the expected change in HCO_3^- secondary to acute changes in PCO_2. The general rule of thumb is that the HCO_3^- concentration rises about 1 to 2 mEq/L for each acute 10 mm Hg increase in $PaCO_2$ above 40 mm Hg, to a maximum increase of 4 mEq/L, and that the HCO_3^- concentration falls 1 to 2 mEq for each acute 10 mm Hg decrease in $PaCO_2$ below 40 mm Hg, to a maximum decrease of 6 mEq/L. This negative base excess may be referred to as a *base deficit*.

By convention, a simple acid-base disorder is limited to the primary disorder and the appropriate compensatory response. A mixed disorder is one in which at least two separate abnormalities occur simultaneously. These abnormalities can both result in acidosis (i.e., metabolic acidosis and respiratory acidosis), can both result in alkalosis (i.e., metabolic alkalosis and respiratory alkalosis), or can be a combination of acidosis and alkalosis (e.g., metabolic acidosis and respiratory alkalosis). It takes cautious examination of a patient and blood gas results to avoid attributing the latter scenario to simple compensation.

Normal values at sea level for venous blood gas interpretation are pH, 7.35 to 7.45; PCO_2, 40 to 45 mm Hg; and HCO_3^-, 19 to 24 mEq/L. Base excess normally should be −5 to 5 mEq/L. An algorithm for interpretation of blood gas values is provided in Figure 128-2.

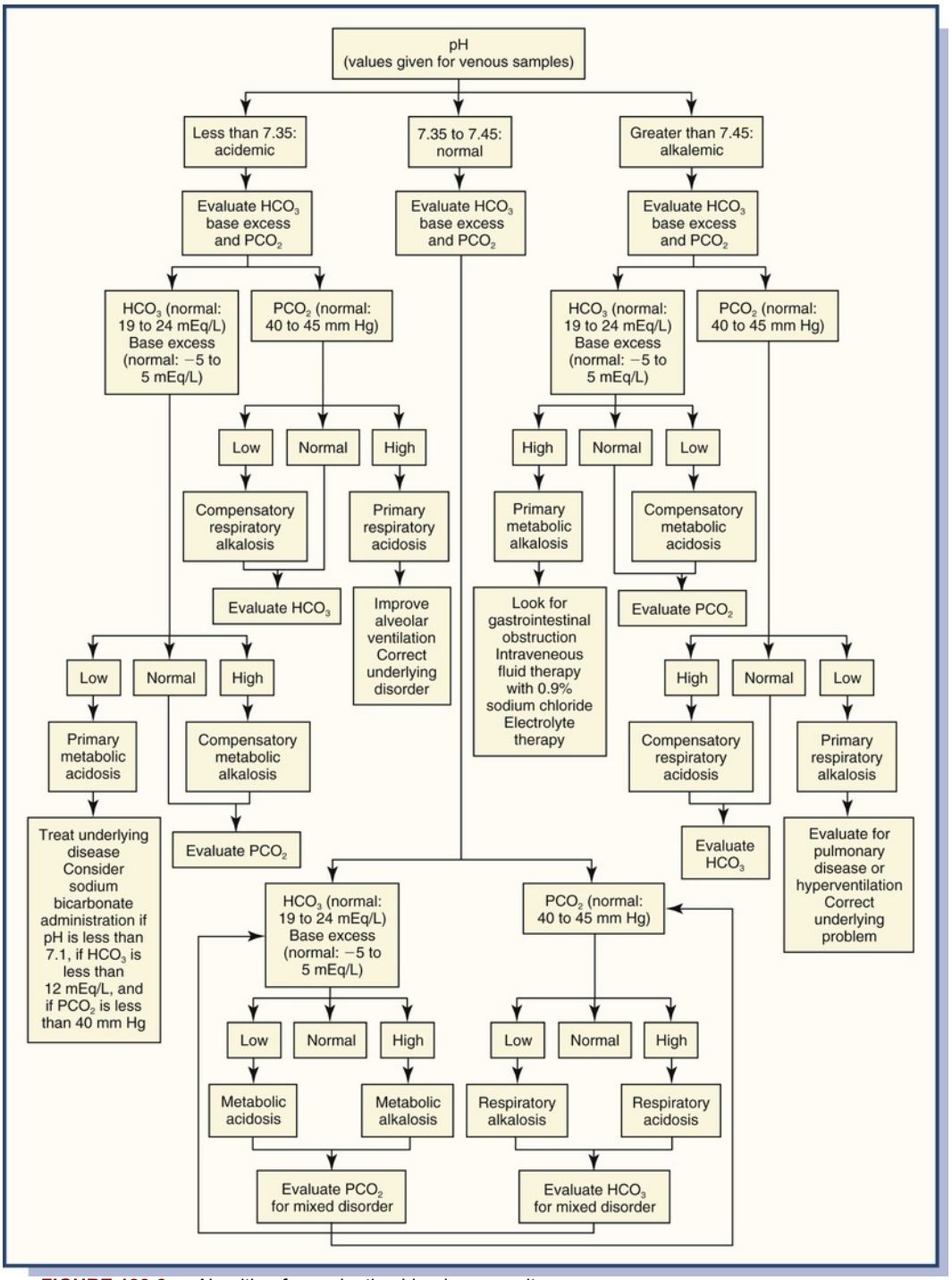

FIGURE 128-2 Algorithm for evaluating blood gas results.

Respiratory Acidosis

Respiratory acidosis results from an increased partial pressure of CO_2 in the blood (hypercapnia). Hypercapnia can be caused by any condition that prevents normal pulmonary gas exchange, including

impaired circulation, reduced respiratory rate or effort, circulation of blood to nonventilated portions of the lung, or impaired gas diffusion. Diffusion impairment is the least likely cause of hypercapnia, because CO_2 is ≈20 times more diffusible than is oxygen. Therefore, profound diffusion impairment is necessary before hypercapnia results. Disorders that can cause respiratory acidosis include circulatory failure from cardiopulmonary arrest, nervous system disease (central, spinal, or neuromuscular junction), respiratory muscle failure (e.g., severe hypokalemia), physical impairment of ventilation (e.g., pleural space disease, pain, thoracic wall disease, external constriction), or primary pulmonary disease (e.g., alveolar flooding, interstitial disease, pulmonary thromboembolism).[4] Iatrogenic respiratory acidosis results from inadequate ventilatory monitoring and assistance under general anesthesia.

Clinical signs of hypercapnia are consistent with the disorder that is causing hypoventilation. While some causes of hypoventilation are easier to detect clinically (e.g., upper airway obstruction), others present a greater diagnostic challenge. Lower motor neuron disease causing decreased chest wall movement can be difficult to identify without a complete neurologic examination (see ch. 259) and careful observation. End-tidal CO_2 can be monitored noninvasively in animals under general anesthesia when they have endotracheal tubes in place and are on closed-circuit breathing loops, or are receiving mechanical ventilation. In animals with regular respirations in which alveolar gas exchange is occurring, end-tidal CO_2 approximates $PaCO_2$.[5]

Treatment for respiratory acidosis involves correcting the underlying disorder by increasing alveolar ventilation. Chronic respiratory acidosis should be corrected slowly. Sodium bicarbonate should not be administered to treat respiratory acidosis because this drug exacerbates hypercapnia by donating substrate for the carbonic acid equation. Increasing the inspired oxygen concentration can be lifesaving; however, with severe hypercapnia, stimulation for respiration becomes driven by hypoxemia. In those situations, oxygen therapy and resolution of hypoxemia can result in decreasing the rate of voluntary respiration, which in turn can promote hypercapnia. The hypoxic drive for respiration remains adequate below a dissolved oxygen content of arterial blood (PaO_2) of 60 mm Hg. It is not necessary to administer supplemental oxygen with the goal of normalization of oxygenation.

Respiratory Alkalosis

Respiratory alkalosis results from an increase in ventilation through which more CO_2 is eliminated than is produced by normal metabolic function. Hypocapnia develops, and alkalemia ensues. Causes of respiratory alkalosis include hypoxemia produced by pulmonary, circulatory, or other abnormalities that result in hyperventilation; primary pulmonary diseases that stimulate ventilation independently of hypercapnia; central nervous system disorders; and iatrogenic tachypnea/hyperpnea in animals receiving assisted ventilation. Chronic respiratory alkalosis is usually well-compensated.

Treatment of animals with respiratory alkalosis primarily is aimed at the underlying cause of tachypnea or hyperpnea (e.g., treatment for bacterial pneumonia, resolution of anxiety-associated tachypnea via administration of a sedative). As with respiratory acidosis, there are few clinical signs suggesting this specific acid-base disorder. Oxygen supplementation (see ch. 131) can be useful in support of these animals while the underlying disease is addressed.

Metabolic Acidosis

Metabolic acidosis often results from a gain of H^+ through ingestion of an acid into the body, increased production of an endogenous acid, or failure to eliminate an acid load by the renal tubular cells. Metabolic acidosis also can be caused by a loss of HCO_3^- buffering ability. Differentiating these two causes of metabolic acidosis is important both for the diagnosis of the underlying disorder and for determining the correct therapeutic intervention.[6]

Dissociation of acid into the H^+ ion and the corresponding anion occurs in the circulation. When acid accumulates, HCO_3^- combines with H^+ to buffer the acid load, while the anion remains in solution. Because electroneutrality must be maintained as anions accumulate following acid dissociation, some other circulating anion must decrease correspondingly. The anion gap (AG), the difference between measured cations and measured anions, is useful in the classification of disorders causing metabolic acidosis. Anion gap, which is calculated from four common cations and anions measured on a serum biochemistry profile, is calculated using the following formula:

$$AG = [Na^+ + K^+] - [Cl^- + HCO_3^-]$$

Although ranges for AG can vary somewhat based on the reference ranges of serum electrolyte concentrations for various laboratories, a reference value of 16 ± 4 mEq/L is typical. When metabolic acidosis exists with an increased AG, there usually has been a gain of organic acid. Causes of anion gap metabolic acidosis include ethylene glycol intoxication, uremia, tissue hypoxia (e.g., lactic acidosis), diabetic ketoacidosis, salicylate intoxication, and other unusual intoxications (e.g., drugs, alcohol). Metabolic acidosis characterized by a normal anion gap is caused by loss of bicarbonate buffers or a failure to excrete H^+ ions, with a corresponding increase in chloride to maintain electroneutrality. This often is referred to as a *hyperchloremic metabolic acidosis*. Hyperchloremic metabolic acidosis occurs less commonly than metabolic acidosis with an increased anion gap, and is caused by renal tubular acidosis (failure of the renal bicarbonate buffer or hydrogen excretory system) or by severe diarrhea and loss of intestinal bicarbonate.[7] Iatrogenic hyperchloremic metabolic acidosis also can occur with administration of an alkali-free chloride-containing crystalloid solution, such as 0.9% sodium chloride (0.9% NaCl) for intravenous volume replacement.

Abnormalities associated with metabolic acidosis include lethargy, decreased cardiac output, systemic hypotension, and decreased hepatic and renal blood flow. These changes can be referable to the acidemia, to the underlying disorder causing the acid-base disorder, or both. Unless the patient has some impairment of normal ventilatory ability, compensatory mechanisms cause an increase in the respiratory rate, which allows the animal to eliminate CO_2 generated by carbonic acid formation, mitigating acidosis.

One study has described the incidence, nature, and etiology of metabolic acidosis in ill and injured dogs and cats. Blood gas values from dogs and cats were reviewed retrospectively when they presented for emergency care at a university teaching hospital over a 13-month period. Metabolic acidosis was defined as a standardized base excess (SBE) in dogs of <−4 mmol/L and in cats <−5 mmol/L. A total of 1,805 dogs and cats were included; of these, 887 (49%) had a metabolic acidosis (753 dogs, 134 cats). Primary metabolic acidosis was the most common disorder in dogs, whereas the mixed acid-base disorder of metabolic acidosis and respiratory acidosis was most common in cats. Hyperchloremic metabolic acidosis was more common than a high AG metabolic acidosis; 25% of dogs and 34% of cats could not be classified as having either a hyperchloremic metabolic acidosis or a high AG metabolic acidosis. Metabolic acidosis was associated with a wide variety of disease processes. Mixed acid-base disorders occurred frequently in this population and routine categorization of metabolic acidosis based on the presence of high AG or hyperchloremia could be misleading in a large proportion of cases.[8]

A second study reviewed blood gas results obtained following cardiopulmonary arrest in dogs and cats at a university teaching hospital. Venous samples were obtained either during cardiopulmonary resuscitation (CPR, 24 samples) or following return of spontaneous circulation (ROSC, 18 samples). Changes indicating metabolic acidosis and hyperlactatemia were present in all samples, and increased PCO_2 was identified in 88% of samples collected during CPR and in 61% of samples obtained following ROSC. Hyperkalemia was seen in 65% of the samples. When compared to samples obtained during CPR, samples obtained within 5 minutes of ROSC had a higher pH and venous PO_2.[9]

Treatment should be aimed at correcting the underlying disorder, which typically involves improving tissue perfusion (e.g., appropriate intravenous fluid therapy), eliminating ingested toxin, and/or correcting metabolic, renal, or GI disease. Intravenous fluid treatment with a balanced electrolyte solution is a reasonable choice to manage most etiologies of small animal metabolic acidosis, since these fluids provide a buffer that is converted to bicarbonate. With severe metabolic acidosis (pH <7.15 and HCO_3^- <12 mEq/L), injectable sodium bicarbonate may be administered judiciously according to the following formula:

$$\text{Bicarbonate dosage (mEq)} = 0.3 \times \text{body weight (kg)} \times \text{base deficit}$$

Half of this dose should be administered slowly intravenously over 6 hours, and the acid-base status should be reevaluated prior to continuation of therapy. Rapid correction of metabolic acidosis can cause a number of undesired side-effects, including hyperosmolarity, hypernatremia, and hypokalemia. Hypocalcemic tetany (see ch. 298) can be caused by shifting of calcium from the ionized to the complexed form after bicarbonate administration. Paradoxical central nervous system acidosis occurs when CO_2 generated following bicarbonate administration crosses the blood-brain barrier and provides substrate for conversion to carbonic acid and hydrogen ions, essentially fueling acid production in the central nervous

system. Iatrogenic metabolic alkalosis also can occur after administration of bicarbonate.

Metabolic Alkalosis

Metabolic alkalosis is generated by loss of chloride in excess of extracellular fluid volume, which often occurs as a result of upper GI fluid loss or sequestration. Administration of a thiazide diuretic also can cause chloride wasting. Rarely, metabolic alkalosis could be caused by overzealous administration of sodium bicarbonate or another organic anion, or by hyperaldosteronism (i.e., Conn's syndrome), which causes sodium retention in excess of chloride. The most common clinical problem associated with metabolic alkalosis in small animal practice is gastric outflow obstruction. During gastric outflow obstruction, appropriate renal compensation prevents an acid-base disorder until hypovolemia induced by vomiting results in aldosterone release. Aldosterone increases renal uptake of sodium. Normally, sodium is reabsorbed with bicarbonate or chloride, or is exchanged for potassium. Because gastric fluid has high chloride and potassium concentrations, animals with gastric outflow obstruction become systemically depleted of these electrolytes so that renal reabsorption of sodium can only occur with concurrent bicarbonate uptake.

As with other acid-base disorders, clinical signs of metabolic alkalosis are dictated by the underlying disorder generating the acid-base abnormality. Muscle twitching and seizures have been reported in animals with metabolic alkalosis. Signs associated with concurrent potassium depletion can include weakness, cardiac arrhythmias, renal dysfunction, and GI motility disturbances (see ch. 68).

Treatment of metabolic alkalosis is directed at resolving the underlying cause. Intravenous 0.9% NaCl is the fluid of choice to replace volume deficits and normalize chloride concentrations since these patients often are chloride-depleted. Fluids should not contain buffer (e.g., not lactated Ringer's solution). Pyloric outflow obstruction often is addressed through surgical modification of the pylorus, or by removal of an obstructing foreign body. In animals with profuse vomiting not associated with obstruction, drug therapy to minimize gastric hydrochloric acid excretion could be warranted (e.g., famotidine, omeprazole). Because animals with metabolic alkalosis often have concurrent hypokalemia, cautious intravenous potassium chloride supplementation often is indicated.

Oxygenation

Hypoxemia can occur as a result of a low concentration of inspired oxygen, hypoventilation, diffusion impairment, ventilation-perfusion mismatch, or pulmonary shunting.[4] Two methods are available to assess oxygenation in an emergency setting: measurement of PaO_2 and measurement of peripheral oxygen saturation (SpO_2) by pulse oximetry. A pulse oximeter is a noninvasive device that calculates hemoglobin oxygen saturation by measuring differences in absorption of two wavelengths of light (red and infrared) by oxygenated and deoxygenated hemoglobin (see ch. 98). The measured light absorption values are applied to a preset nomogram, and a value for SpO_2 is determined. If tissue perfusion is adequate, SpO_2 approximates arterial hemoglobin saturation (SaO_2).[5]

The advantage of oximetry as a monitoring tool is that it provides continuous, noninvasive determination of hemoglobin oxygen saturation. Technical aspects that help ensure accuracy include placing the probe on nonpigmented, moist skin with adequate perfusion (usually the tongue, the buccal, vaginal, or preputial mucosa, or the ear pinna), avoiding probe movement and light pollution, and monitoring the pulse rate to ensure accurate pulse signal transmittance. In poorly perfused tissues, the SpO_2 can be falsely low compared with the SaO_2. If inaccuracy of oximetry is suspected, the arterial blood gas PaO_2 should be obtained to evaluate oxygenation (see ch. 75). In patients with alterations of hemoglobin concentration causing increased carboxyhemoglobin or methemoglobin, oximetry can be normal despite severe patient hypoxemia. Oximetry does not evaluate the PCO_2 and cannot be used for determining ventilation status.

The hemoglobin saturation of oxygen and partial pressure of oxygen (PaO_2) both contribute to arterial oxygen content (CaO_2) according to the following formula:

$$CaO_2\ (O_2\ mL/dL) = \{SaO_2\ (\%) \times \text{hemoglobin}\ (g/dL) \times 1.34\ (O_2\ mL/g)\} + \{PaO_2\ (mm\ Hg) \times 0.003\ (O_2\ mL/dL/mm\ Hg)\}$$

Therefore, SpO_2, which approximates SaO_2, provides an estimation of hemoglobin saturation, whereas PaO_2 estimates dissolved oxygen in blood. According to the formula listed, hemoglobin saturation is the biggest determinant of arterial oxygen content. Increasing the PaO_2 by increasing the inspired oxygen concentration has a minimal effect on blood oxygen content, whereas increasing the SaO_2 has a greater potential effect. In an anemic patient, increasing the arterial oxygen content would best be accomplished by increasing hemoglobin by transfusion of a product containing red blood cells (see ch. 130).

According to the oxyhemoglobin dissociation curve, an SaO_2 of 90% corresponds to a PaO_2 of 60 mm Hg. This value is clinically important in that small decreases beyond this point in either partial pressure of oxygen or oxygen saturation of hemoglobin can have tremendous clinical consequences for oxygenation. The goal of treatment for hypoxemia is to maintain the SpO_2 above 90% and the PaO_2 above 60 mm Hg. Sometimes this can be accomplished through supplemental oxygen therapy. Methods of increasing the inspired oxygen content include use of an oxygen chamber, tent or mask administration, placement of an indwelling nasal oxygen catheter, or mechanical ventilation with an increased fraction of inspired oxygen (see ch. 131). Other methods to correct hypoxemia are related to correcting the underlying cause. For instance, hypoxemia in an animal with severe pneumothorax or pleural effusion would be accomplished through thoracic drainage while hypoxemia related to airway obstruction would be addressed by relief of the obstruction.

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CHAPTER 129

Crystalloid and Colloid Fluid Therapy

Christopher G. Byers

Client Information Sheet: Crystalloid and Colloid Fluid Therapy

Fluid Distribution and Microvascular Barrier

Fluid Compartments

Total body water (TBW) comprises 60% of body weight.[1] The two main fluid compartments in the body are the intracellular fluid (ICF) and extracellular fluid (ECF). The ICF compartment comprises approximately 60% of TBW and the ECF compartment makes up the other 40% (Figure 129-1).[1] Intracellular fluid is found inside the bi-layered cell plasma membrane and is in osmotic equilibrium with the ECF. While ICF and ECF differ markedly in electrolyte composition, their osmolalities are essentially equal due to the high water permeability of most cell membranes.

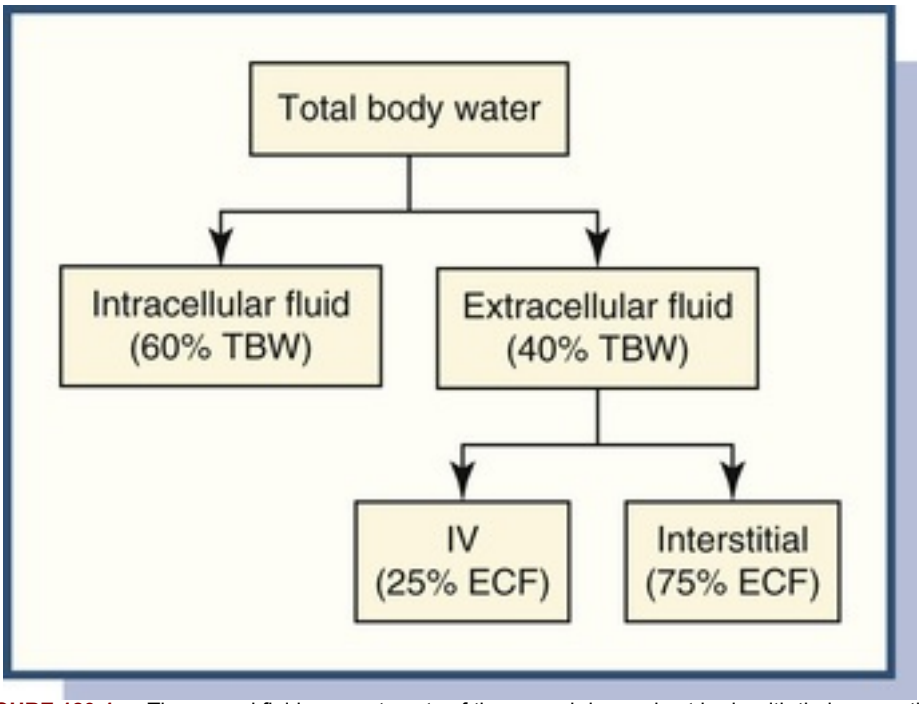

FIGURE 129-1 The normal fluid compartments of the normal dog and cat body with their respective contributions to total body water. *ECF*, Extracellular fluid; *IV*, intravascular; *TBW*, total body water.

The ECF is divided into three chambers: the interstitial compartment, the intravascular compartment, and the third space (see Figure 129-1).[1] The interstitial compartment is the fluid space that surrounds cells and allows movement of ions, proteins, and nutrients across cell membranes. Approximately 75% of ECF is located in the interstitial compartment and is continuously turned over and recollected by the lymphatic vessels. The intravascular compartment comprises approximately 25% of the ECF, and fluids do not normally

collect in the third space.[1] Common examples of the third space, also referred to as transcellular fluid, are the peritoneal fluid, pleural fluid, cerebrospinal fluid, aqueous humor of the eye, fluid within the digestive tract, synovial fluid, and renal tubular fluid.

Traditional Starling's Forces

Movement of fluid across capillary walls is essential for maintaining a continuous exchange of oxygen and carbon dioxide between the body's cells and the blood supply. As mentioned earlier, fluid within the body is contained in distinct compartments; some resides in cells (intracellular compartment), some resides around the cells (interstitial fluid), and some resides within blood vessels (intravascular space).[1] There is a continuous exchange between these compartments that provides nourishment to cells and removes waste products. Two major forces, hydrostatic pressure and oncotic pressure, are involved that work against each other to produce this fluid movement.

Hydrostatic pressure is the pressure exerted by any fluid in a confined space. If fluid is in a container, there will be some pressure applied to the wall of that container. If one pictures a column-shaped container, one can see the pressure pushing against its wall is greater at the bottom than at the top partly due to the force of gravity. Capillaries are the equivalent of a column-shaped container turned on its side. As fluid moves through a capillary, hydrostatic pressure causes fluid to move into the interstitial compartment. This movement also means the hydrostatic pressure decreases as the blood moves from the arteriolar to the venous end of the capillary. The fluid pushed out through the capillary wall by hydrostatic pressure is called filtrate.

Another force that contributes to fluid movement across capillary walls is oncotic pressure. Blood contains plasma proteins that displace some water in blood, and less water in the intravascular compartment creates a concentration gradient between the intravascular and interstitial spaces. Plasma proteins seemingly pull water into the intravascular compartment while the force of osmosis equalizes the amount of water in the intravascular compartments and the interstitial fluid.

The relationship between hydrostatic pressure and oncotic pressure to promote fluid movement across capillary walls can be described by the following equation[2]:

$$J_v = K_f([P_c - P_i] - \sigma[\pi_c - \pi_i])$$

where:

- J_v is the net fluid movement between compartments
- K_f is the filtration coefficient
- P_c is capillary hydrostatic pressure
- P_i is interstitial hydrostatic pressure
- σ is the reflection coefficient
- π_c is capillary oncotic pressure
- π_i is interstitial oncotic pressure

Endothelial Glycocalyx

According to traditional Starling's forces, hydrostatic pressure pushes water out of capillaries and oncotic pressure pulls fluid into the intravascular compartment.[2] The difference between these pressures decides whether water leaves capillaries or is pulled back into them. Since Dr. Starling originally published his hypothesis, further research regarding fluid dynamics has emerged. We now know the luminal surface of endothelial cells is lined with a glycocalyx of membrane-bound macromolecules comprised of sulfated proteoglycans, hyaluronan, glycoproteins, and plasma proteins; simply the key role of the endothelial glycocalyx (EGC) was not appreciated by Dr. Starling, but it is a vital regulator of vascular permeability.[3]

The high resorption of interstitial fluid in the venular segments of the microcirculation postulated by Dr. Starling does not happen. Filtration across the vascular barrier is largely independent of the bulk colloid concentration surrounding the vessel. In regions with high intravascular pressure, the inwardly directed oncotic pressure gradient across the EGC prevents flooding of the interstitial space in conjunction with the

high resistance to flow within the narrow strand gaps of the endothelium.[3] Within low-pressure sections, free and easy access of plasma constituents toward the parenchymal cells allows a highly effective exchange of nutrients and waste products, but the fluid shift is modest if the endothelial surface layer is intact because of the low hydrostatic and oncotic pressure gradients in these segments.[3]

The EGC is present throughout a diverse range of microvascular beds and macrovessels. The principal role of the EGC is to maintain the vascular permeability barrier.[3] Other meaningful roles of the endothelial glycocalyx include shielding vascular walls from direct exposure to blood flow and mediating shear-stress-dependent nitric oxide production by the endothelium.[3] The EGC also promotes retention of vascular protective enzymes (i.e., superoxide dismutase) and helps preserve the intravascular concentration of coagulation inhibition factors (i.e., antithrombin, the protein C system and tissue factor pathway inhibitor) in the endothelium.[3] The EGC also helps modulate the inflammatory response by preventing leukocyte adhesion and binding of chemokines, cytokines and growth factors in the endothelium.[3]

Tissue Safety Factors

Extracellular edema forms as excess fluid accumulates in the interstitial compartment; this accumulation occurs as a result of abnormal leakage from the intravascular compartment to the interstitial compartment and/or a failure of the lymphatics to return fluid from the interstitium to the intravascular compartment. Altered capillary filtration occurs due to an increased capillary filtration coefficient, increased capillary hydrostatic pressure (i.e., excess renal retention of water and sodium; elevated venous pressure and constriction; decreased arteriolar resistance) and/or decreased capillary oncotic pressure (i.e., loss of and/or reduced production of plasma proteins). Inadequate lymphatic return of fluid to the intravascular compartment occurs secondary to neoplasia, various infections, postoperative complications and/or congenital/developmental abnormalities.

Several mechanisms exist in the body to help prevent the formation of extracellular edema.[4] The interstitial compartment does not accommodate a large volume of fluid, and thus the interstitial hydrostatic pressure increases rapidly to prevent further extravasation.[5] Increased movement of fluid from the intravascular compartment to the interstitium reduces the interstitial oncotic pressure; combined with increased lymph flow, albumin is washed out of the interstitium, thus reducing the interstitial oncotic pressure.[6] Lastly, increased interstitial pressure drives augmented lymph flow that helps remove the fluid.[7]

Fluid Types

Crystalloids

Crystalloids contain variable amounts of electrolytes, water and dextrose (Table 129-1); crystalloids may also be characterized by tonicity and their effect on acid-base status. Crystalloids are used either to *replace* sodium loss or *maintain* the status quo. *Replacement* fluids contain sodium at concentrations similar to normal plasma (≈140 mmol/L) while *maintenance* fluids have sodium concentrations similar to normal total body concentration (70 mmol/L). Replacement crystalloids and maintenance crystalloids may also be classified as isotonic and hypotonic, respectively (Table 129-2). Approximately one-third of administered isotonic replacement fluid remains in the intravascular space and two-thirds enter the interstitial space.

TABLE 129-1

Composition of Commonly Available Crystalloids Used in Dogs and Cats

FLUID	pH	Na^+ (mEq/L)	Cl^- (mEq/L)	K^+ (mEq/L)	Mg^{2+} (mEq/L)	Ca^{2+} (mEq/L)	GLUCOSE (g/L)	OSMOLARITY (mOsm/L)	BUFFER (mEq/L)
0.9% NaCl	5.0	154	154	0	0	0	0	308	0
Normosol-R	6.4	140	98	5	0	3	0	296	Acetate 27
Veterinary Plasma-Lyte A	7.4	140	98	5	3	0	0	294	Acetate 27
LRS	6.5	130	109	4	0	3	0	272	Lactate 28

0.45% NaCl	5.0	77	77	0	0	0	0	154	0
D5W	4.0	0	0	0	0	0	50	252	0
Normosol-M in 5% dextrose	5.5	40	40	13	3	0	50	364	Acetate 16
Plasma-Lyte M in 5% dextrose	5.5	40	40	16	3	5	50	376	Acetate 12

D5W, 5% dextrose in water; *LRS*, lactated Ringer's solution.

TABLE 129-2

Common Commercially Available Fluids Used in Dogs and Cats

FLUID TYPE	EXAMPLES
Isotonic crystalloid/replacement	0.9% sodium chloride Normosol-R Plasma-Lyte Lactated Ringer's solution (LRS)
Hypotonic crystalloid/maintenance	0.45% sodium chloride (with or without dextrose) 5% dextrose in water (D5W) 0.45% sodium chloride Normosol-M in 5% dextrose Plasma-Lyte M in 5% dextrose
Hypertonic saline	7% sodium chloride (HTS)
Colloids	Plasma (fresh frozen, frozen) Hydroxyethyl starches (i.e., Hespan, VetStarch) Human serum albumin (HSA) Canine serum albumin (CSA)

Common examples of *replacement* fluids are lactated Ringer's solution (LRS), Plasma-Lyte, Normosol-R and 0.9% sodium chloride. The first three have potassium concentrations similar to plasma and contain a lactate, acetate, or gluconate buffer to maintain a physiological pH. Animals, particularly cats, normally lose potassium through urine, and this loss is augmented during dehydration, aldosterone release and sodium conservation. Accordingly, replacement fluids should be supplemented with potassium when used long-term. Normal saline (0.9% sodium chloride) contains no potassium or buffers, and is the fluid of choice for hypercalcemia and hyperkalemia given it contains no calcium or potassium. Normal saline may exacerbate volume overload, metabolic acidosis, heart disease, and hypertension.

Maintenance fluids are simply designed to replace daily sodium losses and are appropriate for long-term administration. Dextrose is commonly supplemented to approximate plasma tonicity and prevent hemolysis. These lower-sodium fluids do not stay in the intravascular space, do not meaningfully expand blood volume, and thus should never be used for volume resuscitation.

Hypertonic saline may be used for rapid intravascular volume expansion, as it pulls fluid primarily from the interstitial compartment. Volume expansion is short lived, as the sodium redistributes throughout the extracellular compartment quickly. Hypertonic saline is available as both 7-7.5% and 23% solutions, and the latter must be diluted prior to administration. Do not administer hypertonic saline faster than 1 mL/kg/min to avoid vagally mediated bradycardia and potential cardiopulmonary arrest.

Colloids

Colloids are large molecules that remain in the intravascular space due to the Gibbs-Donnan equilibrium. Smaller volumes compared to crystalloids are required to achieve intravascular expansion, and thus when used appropriately are less likely to induce hemodilution, hypoproteinemia, extracellular edema and fluid overload.[8]

Synthetic colloids, most notably dextrans and hydroxyethyl starches (HES), contain high molecular weight particles that allow these fluids to increase colloid osmotic pressure (COP). As albumin is the main

contributor to COP, colloids are advantageous in the treatment of hypoalbuminemia due to their ability to increase COP. The HES most commonly used in veterinary medicine are hetastarch, pentastarch, and tetrastarch. The differences between hetastarch, pentastarch, and tetrastarch are the average molecular weight of the particles and the degree of substitution of glucose units on the starch particle with a hydroxyethyl group. Serum alpha-amylase degrades HES, and elimination occurs through the kidneys. Therefore, measured serum amylase levels will increase in patients receiving artificial colloid solutions.

Several numbers are used to describe unique qualities of HES solutions, including:

1. *Concentration:* Concentration mainly influences the initial volume effect. A common concentration, 6%, is iso-oncotic *in vivo*, and thus 1 L replaces 1 L of blood loss. Concentrations range from 6-10%.
2. *Mean molecular weight (MW):* Hetastarch has an average molecular weight (450 kDa), pentastarch (260 kDa) and tetrastarch (130 kDa). Larger molecules are degraded more slowly, and accordingly, solutions with a higher average molecular weight last longer.
3. *Molar substitution (MS):* Molar substitution refers to the modification of the original substance by the addition of hydroxyethyl groups. The higher the degree of molar substitution, the greater the resistance to degradation; consequently, the fluid remains in the intravascular space longer. A value of 0.7 indicates the HES preparation has an average of seven hydroxyethyl residues per 10 glucose subunits. Starches with this level of substitution are called hetastarches, and similar names are applied to describe other levels of substitution (0.4—tetrastarch; 0.5—pentastarch; 0.6—hexastarch).
4. *C2:C6 ratio:* The C2-C6 ratio refers to the site where substitution occurs on the initial glucose molecule. The higher the C2:C6 ratio, the longer is the T1/2 and subsequently the longer is the persistence in the blood. Synthetic colloids have been associated with side effects, including affecting coagulation and increasing the potential for volume overload due to the efficacy of expanding intravascular volume.

Hemoglobin-based oxygen carriers (HBOC; i.e., Oxyglobin) are ultra-purified, polymerized, stroma-free bovine hemoglobin products that promote oxygen off-loading at the tissue level and are potent colloids. The hemoglobin is suspended in a modified LRS solution, has an osmolality of 300 mOsm/L, and has a 3-year shelf life. Administration of HBOCs does not required blood typing and/or cross matching. The potential beneficial effects of HBOCs stem from their COP and vasoconstrictive properties; they are efficient scavengers of nitric oxide (NO) and thus can help combat severe vasodilation commonly observed in patients with systemic inflammatory response syndrome (SIRS), severe sepsis and septic shock.[9,10] Given these fluids are bovine products, one-time use is recommended because of the potential for antibody formation and subsequent immunologic reactions. HBOCs do cause a patient's mucous membranes, sclera and urine to turn red or yellow, and will affect colorimetric diagnostic blood and urine tests. The availability of HBOCs is currently extremely limited due to decreased commercial production.

Natural colloids are also available for infusion. Fresh frozen plasma (FFP) is collected and spun within 6 hours and frozen ideally at −70°C for up to 1 year. This fluid contains stable clotting factors (II, VII, IX, X), labile clotting factors (V, VIII), von Willebrand factor, fibrinogen and albumin; it does not contain red blood cells and platelets. Indications for FFP administration are replacement of all clotting factors, anticoagulant rodenticide intoxication, von Willebrand disease and hemophilia (A and B). A common dosage for replacement of clotting factors is 10-20 mL/kg. Frozen plasma (FP) is collected similarly to FFP but is stored for longer than 1 year. It contains stable clotting factors, fibrinogen and albumin, but does not contain red blood cells, platelets and labile clotting factors. Fresh plasma may be used for hemophilia B, and is administered at similar doses as for FFP. Use of FFP and FP to treat hypoalbuminemia is not practical or safe except in very small patients (cats, toy breed dogs) due to the potential for hypervolemia.

With progressive hypoalbuminemia, the COP similarly decreases, contributing to a fluid shift from the intravascular space to the interstitial space to potentially cause edema if tissue safety factors are overwhelmed. Serum albumin (SA) has been used in critically ill patients to help support blood pressure and to aid in the treatment of significant hypoalbuminemia. Currently two types of serum albumin are available for administration: human serum albumin (HSA) and canine serum albumin (CSA). Human serum albumin has been used successfully in both dogs and cats, but both acute and delayed immunologic reactions have been documented.[11,12] This product is available as a solution, and may be infused in 4-hour aliquots over 4-72 hours. Canine serum albumin is available as a lyophilized powder for reconstitution with sterile saline. Concentrations currently range from 4-25% and do not contain any preservatives and thus must be administered within 6 hours. Infused albumin remains in the intravascular space for 24 hours, and therefore close monitoring for fluid overload is required. The reported dosages for both HSA and CSA range from 100 mg/kg to 6.3 g/kg.

Fluid Plans

Hypovolemia vs. Dehydration

Hydration status is a measure of interstitial fluid content and is determined by evaluating skin turgor, moisture (or lack thereof) of the mucous membranes and possibly enophthalmos. Volume status is a measure of tissue perfusion and is initially evaluated by checking heart rate, capillary refill time (CRT), mucous membrane color and blood pressure (see ch. 99). Hypovolemic animals commonly have prolonged capillary refill times, tend to have pale mucous membranes and are often (but not always) hypotensive; while dogs may present with tachycardia, most cats either have normal heart rates or bradycardia. If hypovolemia is severe, one may see obtundation, weak peripheral pulses, and lack of venous distension when the veins are occluded. Hypovolemia may, of course, exist concurrently with dehydration but one must replace volume before rehydrating.

One should not treat hypovolemia by determining the patient's hydration status and then calculating (based on % dehydration and body weight) the fluid administration over the next 6-12 hours. Treatment of hypovolemia should be finished within 1-2 hours of presenting to the hospital. This type of resuscitation routinely requires rapid administration of large volumes of fluids intravenously. These are known as "shock boluses" of replacement crystalloids: 40-50 mL/kg for cats, 20-90 mL/kg for dogs (see below). Typically, one should give a portion (1/3 or 1/4 dose) of the total volume and then reassess endpoints of resuscitation to determine if more volume is truly necessary. Indiscriminate use of the terms dehydration and hypovolemia risks confusion and therapeutic errors. The pathophysiology of both dehydration and volume depletion must be understood if these conditions are to be properly recognized and appropriately treated whether they occur separately or together.

Route of Administration

Common routes of fluid administration in dogs and cats include intravenous (peripheral, central or peripherally inserted central [PIC]) catheters (see ch. 75 and 76), subcutaneous, enteral, intraosseous (see ch. 77), and intraperitoneal (see ch. 90 and 109). According to Poiseuille's Law, flow of non-compressible/Newtonian fluids, including blood, is maximal when diameter is widest and length is shortest. Accordingly for patients with hypovolemia, a short length and large bore intravenous catheter is recommended. If venous access is not immediately possible, the intraosseous route may be used until vascular access is achieved. Commonly accessed intraosseous sites in the emergency room are the proximal femur and cranial tibial crest (see ch. 77). The subcutaneous route is not appropriate for hypovolemic patients as peripheral vasoconstriction severely limits absorption. With mild dehydration, the subcutaneous route may suffice. Dextrose should not be delivered subcutaneously, and potassium delivered via this route may induce patient discomfort. Subcutaneous fluids are commonly administered at 10-20 mL/kg per site.

Enteral water supplementation is commonly used in the intensive care unit, but is generally under-utilized in veterinary medicine. Given that a patient's gastrointestinal tract is able to receive and handle fluids, enteral water may be used to help prevent villous atrophy, and may be combined with other forms of enteral nutritional support (see ch. 189).

Volume and Rate of Administration

When determining the most appropriate fluid volume and rate of administration, the astute clinician should ask the following questions (Figure 129-2):

- Is the patient hypovolemic?
- Is the patient dehydrated?
- What are the patient's daily physiologic requirements?
- Are there any ongoing losses? If yes, how much?

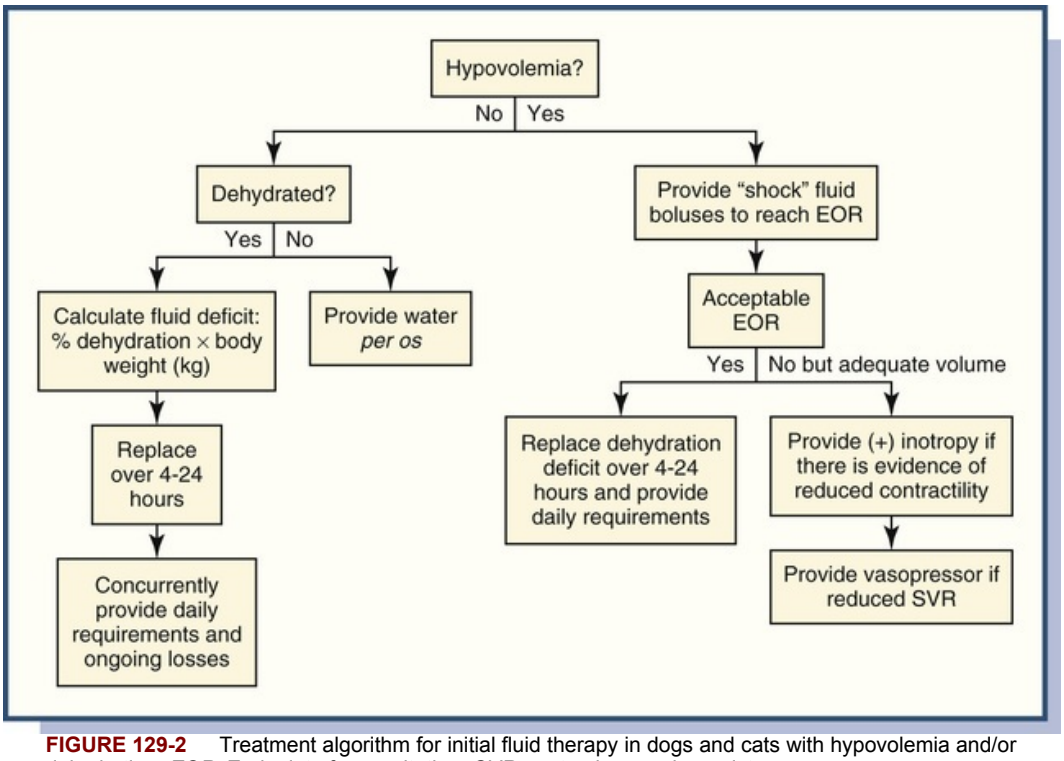

FIGURE 129-2 Treatment algorithm for initial fluid therapy in dogs and cats with hypovolemia and/or dehydration. *EOR*, Endpoint of resuscitation; *SVR*, systemic vascular resistance.

By answering these questions, one is addressing the three major components of fluid administration (Table 129-3):

1. Resuscitation
2. Replacement
3. Maintenance

TABLE 129-3

Components of Fluid Therapy

COMPONENT	QUESTIONS ADDRESSED
Resuscitation	Is the patient hypovolemic?
Replacement	Is the patient dehydrated? Are there any ongoing losses?
Maintenance	What are the patient's daily physiologic requirements?

During fluid resuscitation, intravascular volume is restored with intravenous fluid administration. Hypovolemic patients required fluid resuscitation, and the volume infused depends on the stage of shock (Table 129-4 and ch. 127).

- *Compensatory:* Cardiac output is increased due to catecholamine release; common clinical signs include normal vital signs (or mild tachycardia), injected mucous membranes (see Video 144-1), rapid CRT, normotension and normal blood pressure.
- *Early decompensatory:* Blood is preferentially distributed to the heart and brain, and lactic acidosis with tissue hypoxia occurs; common clinical signs include tachycardia, pale mucous membranes, prolonged CRT, depressed mentation, hypothermia and hypotension.
- *Late decompensatory:* This is a stage of autoregulatory escape, indicating the brain and heart can no longer maintain sympathetic-mediated vasoconstriction so vasodilation occurs in all organs (including heart/brain) to cause circulatory collapse; common clinical signs include bradycardia, severe hypotension, absent CRT, weak or absent peripheral pulses, hypothermia, obtundation, and oliguria.

TABLE 129-4

Stages of Shock and Associated Clinical Signs

CLINICAL STAGE	CHARACTERISTICS	CLINICAL SIGNS
Compensatory	CO increases due to catecholamine release	Normal vitals or slightly increased HR Injected mm (d) Rapid CRT (<1 second) Normal BP Normal mentation
Early decompensatory	Blood preferentially distributed to heart and brain Lactic acidosis and tissue hypoxia occur	Tachycardia (d) Pale mm Prolonged CRT Depressed mentation Hypothermia Hypotension
Late decompensatory	Autoregulatory escape	Bradycardia Severe hypotension Absent CRT Weak or absent pulses Hypothermia Oliguria Obtundation

BP, Blood pressure; *CO*, cardiac output; *CRT*, capillary refill time; *(d)*, dog; *HR*, heart rate; *mm*, mucous membranes.

Stabilizing interventions for patients with shock (see ch. 127) should target endpoints of resuscitation (EOR), particularly:

- Restoration of normal vital signs
- Normalization of abnormal mentation
- Restoration of normal blood pressure (systolic >80-90 mm Hg; see ch. 99 and 159)
- Normal serum lactate (<2.5 mmol/L; see ch. 70)
- Central venous oxygen saturation ($S_{cv}O_2$) >70%
- Packed cell volume (PCV) >25%
- Urine output (UOP) >1 mL/kg/h
- Pulse oximetry (S_pO_2; see ch. 98) >93% at F_iO_2 = 21%
- Central venous pressure (CVP; see ch. 76) = 5-10 cm H_20

An isotonic crystalloid should be administered at "shock" rate (dogs: 20 mL/kg, up to 90 mL/kg; cats: 10 mL/kg, up to 50 mL/kg) over 15 minutes and then one should reassess EOR.[13] With hypoproteinemic hypovolemia, administration of a synthetic colloid (i.e., hydroxyethyl starches) may be appropriate; these fluids should be delivered over 20-30 minutes (dogs: 5 mL/kg, up to 20 mL/kg; cats: 2-5 mL/kg, up to 10 mL/kg) and EOR should be reassessed after each bolus.[13]

After effectively addressing hypovolemia, an appropriate fluid therapy plan must address dehydration, daily physiologic requirements, and ongoing losses. Isotonic crystalloids should be used for fluid replacement (correcting dehydration and replenishing ongoing losses). Clinical signs of dehydration include tacky mucous membranes, decreased skin turgor, enophthalmia, and prolonged capillary refill time. The volume required to correct dehydration is the product of the estimated percentage of dehydration and body weight in kilograms, and should be delivered over approximately 4-24 hours depending on a patient's risk for hypervolemia (Table 129-5). After correcting dehydration, a patient's fluid therapy plan should be reevaluated. Ongoing losses may be estimated by weighing diarrhea and vomitus, and frequent weight monitoring is recommended to help gauge a patient's fluid status.

TABLE 129-5

Estimating Dehydration Based on Clinical Signs

% DEHYDRATION	PHYSICAL EXAMINATION ABNORMALITIES
<5	No specific abnormalities; history of fluid loss (diarrhea, vomiting)
6-8	Enophthalmia, dry mucous membranes, mildly/moderately decreased skin turgor
10-12	Enophthalmia, dry mucous membranes, weak peripheral pulses, depression, markedly decreased skin turgor
12-15	Stupor, coma, death

Daily physiologic requirements, also termed maintenance requirements, may be calculated with one the following formulas:

- (30 × BW in kilograms) + 70 = mL/day
- $80 \times BW^{0.75}$ = mL/day

Both isotonic and hypotonic crystalloids may be appropriate and the ultimate choice of crystalloid type should be determined based on a patient's volume status and serum electrolyte concentrations. Fluids should always be titrated to effect. Fluid therapy is commonly employed during the peri-anesthetic period. Potential benefits of providing fluids to healthy patients during the peri-anesthetic period include cardiovascular support, the ability to counter potential anesthesia-induced adverse reactions (i.e., vasodilation), and the correction of normal ongoing losses.

Hypotensive Resuscitation

Hypotensive resuscitation is a method of fluid resuscitation that has been advocated by some for stabilization for patients with uncontrolled hemorrhage and planned surgery to attain hemorrhage control. Two types of hypotensive resuscitation have been described: limited volume resuscitation (permissive hypotension) and delayed resuscitation. To perform limited volume resuscitation, conservative volumes of intravenous fluids are administered prior to achieving definitive control of hemorrhage. The fluids improve but do not normalize blood pressure and tissue perfusion, but rather target a specific pre-operative blood pressure range (mean arterial pressure 40-60 mm Hg). Patients who receive delayed resuscitation receive no volume resuscitation until definitive control of hemorrhage has been attained. Suitable fluid resuscitation targeting appropriate endpoints of resuscitation is instituted once hemorrhage has been controlled.

The value of hypotensive resuscitation in veterinary patients is relatively controversial.[14-17] The timing of resuscitation and reestablishment of hemostasis is seemingly critical, as most studies documenting successful use of this technique had uniquely short preoperative times. The majority of veterinary trauma patients with intra-abdominal hemorrhage spontaneously achieve hemostasis, do not require surgical intervention, and should not receive hypotensive fluid resuscitation. Patients with non-traumatic hemorrhage commonly have pre-operative wait times longer than those in published studies, and therefore hypotensive resuscitation results in protracted hypotension and contributes to the development of SIRS and multiple organ dysfunction syndrome. While hypotensive resuscitation may be beneficial for some patients, one must carefully weigh the benefits against the potential risks of prolonged hypotension in a patient.

Early Goal-Directed Therapy

The profound inflammation associated with SIRS and sepsis induces vascular leakage secondary to endothelial dysfunction. Subsequently, fluid extravasation results in relative and absolute hypovolemia, hypoperfusion and possibly septic shock. Fluid therapy is the mainstay of resuscitation of patients with SIRS, sepsis, severe sepsis and septic shock. In 2001 Rivers et al introduced the concept of early goal-directed therapy (EGDT), a specific algorithm for managing patients presenting with septic shock.[18] Aggressive fluid resuscitation to achieve specific endpoints was recommended. In-hospital mortality was 30.5% in the EGDT group and 46.5% in standard therapy group, a finding that was statistically significant.[18] Patients in the EGDT group also had significantly higher mean $S_{cv}O_2$, lower lactate, lower base deficit, and higher pH than the patients assigned to standard therapy.[18] Subsequently clinical guidelines, the Surviving Sepsis Campaign Guidelines (SSCG), for the management of human patients with severe sepsis and septic shock were developed and are routinely updated.[19,20]

Aggressive initial fluid resuscitation is considered the cornerstone of initial therapy for human and veterinary patients with severe sepsis and septic shock. The SSCG recommend immediately instituting

volume resuscitation in affected people according to an explicit protocol; specifically crystalloids are the recommended initial fluid of choice and the initial fluid challenge should be at least 30 mL/kg. Within the first 6 hours of therapy, one should target:

- Mean arterial pressure (MAP) ≥65 mm Hg
- Central venous pressure (CVP) 8-12 mm Hg
- Urine output (UOP) ≥0.5 mL/kg/h
- Central venous oxygen saturation ($S_{cv}O_2$) ≥70%

Interestingly, despite the SSCG, there is marked variation in the type of resuscitation fluid used in human patients worldwide. In the United States, crystalloids are the initial recommended resuscitation fluid. More than 50% of fluid resuscitations in Australia are performed with mainly albumin and in European countries almost 50% of resuscitations are done with mainly hydroxyethyl starches. Vasopressors should be used within 6 hours for those patients with hypotension despite aggressive initial fluid resuscitation. Transfusion with packed red blood cells to maintain a packed cell volume (PCV) greater than 30% and vasopressor therapy may also be indicated. Serial monitoring of perfusion parameters, most notably lactate, should be pursued, and one should seek to normalize lactate levels as rapidly as possible.

Despite the SSCG, to date the optimal composition and volume of resuscitation fluid is not known, and remains a highly controversial topic in human emergency and critical care medicine. Furthermore, prospective randomized controlled trials have not been conducted in veterinary medicine; thus, the ideal guidelines for resuscitation of veterinary patients with SIRS, sepsis, severe sepsis and septic shock are similarly unknown at this time.

Since the publication of the sentinel study by Rivers et al, subsequent studies have been conducted to document the potential benefits of early goal-directed therapies. Results have been mixed depending on patient population studied. The ARISE study in 1600 human patients with early septic shock failed to show a reduction of all-cause mortality at 90 days despite utilizing EGDT interventions.[21] Certainly continued investigation, particularly prospective studies in dogs and cats, is sorely needed.

Fluid Additives

Potassium supplementation is commonly required for veterinary patients, particularly those who receive large volumes of replacement fluids. Common causes of hypokalemia include gastrointestinal fluid loss, diuresis and anorexia, and administration of bicarbonate, insulin and/or dextrose can induce a hypokalemic state due to intracellular shifting if concurrent potassium supplementation is not provided (see ch. 68). Common clinical signs of hypokalemia are muscle weakness, abnormal gait/ambulation, ileus, cervical ventroflexion (particularly in cats), and dysrhythmias (atrial and/or ventricular premature contractions). Electrocardiography may also document a prolonged Q-T interval (>0.25 seconds). Potassium deficits may be quite variable, and supplementation is patient-dependent; the rate of supplementation should generally not exceed 0.5 mEq/kg/h without strict attentive patient monitoring.

Supplementation of B vitamins is relatively commonplace in veterinary patients, particularly in a critical care setting. These vitamins will be inactivated with exposure to ultraviolet light, but are relatively stable for approximately 72 hours in environments with fluorescent lights and minimal exposure to natural sunlight. All B vitamins are water-soluble, and thus are only stored in the body for a few days. They are also commonly lost in polyuric diseases, and deficiency can contribute to anorexia. Thiamine deficiency has been associated with neurologic deficits (see ch. 12), and cobalamin deficiency is common in patients with exocrine pancreatic insufficiency and distal small intestinal disease (see ch. 292 and 276). Supplementation with pure thiamine or cobalamin, respectively, is recommended if deficiency in either vitamin is suspected or confirmed, as vitamin B complex solutions do not contain enough of either thiamine or cobalamin.

Magnesium has multiple important functions as a cofactor in enzymatic reactions, contributor to the tertiary structure of proteins, and participant in cell membrane function (see ch. 68). Hypomagnesemia is relatively common in veterinary critical care patients, and deficiency has been associated with prolonged hospitalization.[22] Hypomagnesemia should be suspected in patients with refractory hypokalemia. Mild hypomagnesemia is often corrected by infusing magnesium-containing fluids, and marked deficiency (ionized magnesium <0.35 mmol/L) should be addressed with a constant rate infusion of magnesium sulfate or chloride at an initial dose of 0.75-1 mEq/kg/day for 24 hours followed by a 50% dosage reduction for an additional 3 to 5 days.

Monitoring

With the provision of fluid therapy comes the requirement to monitor a patient's response to that intervention. Multiple parameters may be readily evaluated to assess a patient's response to prescribed fluid therapy. Common physical variables are:

- Body weight: The change in a patient's body weight is a non-invasive method for evaluating fluid gain or loss on a day-to-day basis. As several variables (feces in colon, degree of urinary bladder filling, insensible losses, etc.) predispose this measurement to errors, one is encouraged to measure a patient's body weight at the same time of day using the same scale to minimize variability.
- Mucous membranes: Dehydrated patients frequently have dry mucous membranes. Thus, a change from tacky mucous membranes to moist ones commonly indicates a positive response (i.e., improved hydration) to fluid therapy.
- Capillary refill time: Patients with poor perfusion typically have prolonged capillary refill times (>2 seconds), and poor perfusion frequently arises from hypovolemia. An improving CRT suggests improved perfusion.
- Skin turgor: Evaluation of a patient's skin turgor or degree of "skin tenting" has been historically used to assess various degrees of dehydration. Overhydrated patients are commonly described as having a gelatinous feeling to their skin and may readily develop gravity-dependent edema (see ch. 18). Geriatric patients and underweight patients have reduced turgor normally and overweight/obese patients commonly have increased skin turgor; thus, evaluation of skin turgor in these patients is an unreliable indicator of hydration status and response to prescribed fluid therapy.
- Heart rate: Compensatory and early decompensatory hypovolemic shock in dogs and occasionally cats is associated with a reflex tachycardia. Cats do not consistently develop this compensatory response due to concurrent sympathetic and vagal stimulation. Providing appropriate bolus fluid therapy to hypovolemic dogs and some cats will resolve the compensatory tachycardia, indicating a positive response to prescribed fluid therapy.

In addition to readily measured physical variables, trained medical personnel may easily measure other values with minimal patient discomfort, particularly:

- Blood pressure (BP; see ch. 99): Marked hypovolemia can overwhelm a patient's homeostatic responses to result in hypotension (mean arterial pressure <60 mm Hg). Hypertension is exceedingly rare in patients with fluid overload due to the large capacitance of the venous circulation, and patients may manifest hypotension without hypovolemia due to either reduced cardiac contractility and/or reduced systemic vascular resistance.
- Urine output (UOP): A normal UOP is 1-2 mL/kg/h, and values of 0.5-1 mL/kg/h and less than 0.3 mL/kg/h indicate oliguria and anuria, respectively.
- Central venous pressure (CVP; see ch. 76): Central venous pressure is the pressure within the lumen of the cranial vena cava and is believed to be equivalent to right atrial pressure. A patient's CVP is influenced by cardiac output (CO), venous return and venous tone, and thus this variable estimates the relationship between blood volume and capacity. Excluding myocardial dysfunction and/or increased pulmonary resistance, CVP is a reliable indicator of an effective circulating blood volume. In dogs and cats, a normal CVP range is 0-10 cm H_2O, and measurements should always be compared with previous data; trends in CVP are uniquely more useful than singular measurements for assessing a patient's response to fluid therapy.
- Lactate (see ch. 70): Hypoperfusion secondary to a reduction in effective circulating volume readily results in tissue hypoxia that induces Type A lactic acidosis. Improving tissue perfusion via fluid resuscitation may resolve the Type A hyperlactatemia. However, tissue hypoxia may occur without volume depletion (i.e., reduced cardiac output [CO], decreased SVR, decreased arterial oxygen content [PaO_2]) and Type B lactic acidosis may occur without hypoxia, and thus lactate values must be interpreted carefully.

Measuring the amount of fluid provided to a patient, as well as all of the eliminations of a patient, is essential for providing the best fluid therapy. Serially and accurately monitoring a patient's "ins and outs" is invaluable and potentially challenging, but the astute clinician must be keenly aware of all possible sources of fluid loss from a patient, particularly losses via urine, feces, vomitus, blood, and cavitary effusions. A patient's treatment sheet should accurately document both the volume of fluid administered to and the total amount of eliminations from a patient in a given time period.

Complications/Controversies

Fluid Overload

While healthy animals are generally quite tolerant of excessive fluid administration, debilitated patients are less able to endure excessive volume. Signs of fluid overload and overhydration include weight gain, restlessness, tachypnea, dyspnea, serous nasal discharge, chemosis (cats), adventitious lung sounds (i.e., crackles), tachycardia, gallop rhythm (cat), coughing and jugular venous distension.

Synthetic Colloids

Measurements of urine specific gravity should be made prior to administration of certain hydroxyethyl starches, particularly hetastarch. Hetastarch molecules greater than 50 kD are freely filtered by the glomerulus, and falsely cause high refractometer readings. Total solids (TS) measurements via refractometry are also affected, as hetastarch yields a value of 4.5 g/dL alone and 3.0 g/dL when mixed 1 : 1 with a hypooncotic diluent.[23] Thus, TS measurements in patients receiving hetastarch as a constant rate infusion for more than 24 hours tend to trend toward a range of 3.0-4.5 g/dL. Thus, direct measurement of serum albumin and/or colloid osmotic pressure (COP) in these patients provides a more accurate assessment of a patient's oncotic status.

Hydroxyethyl starches have been recommended for resuscitation in patients with hypoalbuminemia and/or sepsis given their ability to induce a more rapid and lasting circulatory stabilization than crystalloids. The use of HES has been called into question and, indeed, advised against in some human patients given various adverse reactions reported in randomized clinical trials, most notably coagulation alterations, immunologic reactions, increased incidence of acute kidney injury and need for renal replacement therapy (see ch. 110).[24]

To date, no study in dogs or cats has documented acute kidney injury secondary to HES administration, and thus clinicians are cautioned not to extrapolate and apply experience with these fluids in humans to dogs and cats. With that being said, it may be prudent to limit the use of HES in patients with pre-existing renal injury and/or those at risk for renal tubular injury.

Hydroxyethyl starches have been implicated in inducing several coagulation abnormalities in various patient populations, including dogs and cats. Certainly the potential to induce a bleeding disorder must be considered when contemplating the use of HES in septic patients. Both *in vitro* and *in vivo* studies in dogs and cats have documented adverse effects on platelet function and coagulation.[25-27] However, the clinical relevance of these studies is not yet truly known, and clinical prospective investigation is warranted. At this time, use of HES in patients with pre-existing coagulation abnormalities is cautioned.

Although immediate and delayed immunologic reactions to HES have been rarely documented in humans, only anecdotal reports of such reactions exist in veterinary medicine to the author's knowledge.

Albumin

Although human and canine albumins have significant amino acid homology, some important differences exist between the two molecules, thus raising concerns over antigenicity. A recent retrospective study of 64 dogs that received HSA did not identify any significant problems.[28] Nevertheless, the current recommendation is that one should not administer HSA after more than 1 week from the initial dosing due of the increased risk of foreign antigenicity. Both HSA and canine albumin are hyperoncotic solutions, and thus fluid overload and overhydration are possible.

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CHAPTER 130

Blood Transfusions, Component Therapy, and Oxygen-Carrying Solutions

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Client Information Sheet: Blood Transfusions and Blood Component Therapy

Sources of Blood Products

Transfusion refers to infusion with whole blood (WB) or its components, listed with indications in Table 130-1. Components are prepared by WB centrifugation and separation. Component use focuses transfusion on specific patient needs, minimizes wastage, and reduces risk of reactions. WB and components may be purchased from commercial blood banks. Alternatively, WB may be collected in a clinic using human or veterinary blood bank supplies. Donors should be negative for regionally relevant infectious diseases.[1,2] Details of donor selection and blood collection are provided in videos for this chapter (Videos 130-1 to 130-5) and references.[3-16] Blood component preparation is not advocated for most clinics because of the need for specialized equipment and quality assurance programs. If a clinic wishes to produce its own blood products, extensive descriptions are available.[8-11,17-21]

TABLE 130-1

Blood Products and Their Indications

PRODUCT	DESCRIPTION	COMMENT*	SPECIFIC INDICATION
Fresh whole blood (fresh WB)	Stored at RT <24 hours. Refrigerated for 48 hours (hemostatic properties likely maintained for longer times). One dog unit ≈450 mL. One cat unit ≈60 mL.	Minimal red cell storage lesion. Maximum hemostatic properties.	Acute blood loss.
Stored whole blood (stored WB)	Refrigerated >48 hours. One dog unit ≈450 mL. One cat unit ≈60 mL.	Stored in CPDA$_1$ up to 3 weeks. Vitamin-K dependent clotting factors are stable.	Acute blood loss. Suitable to treat vitamin-K antagonist poisoning.
Packed red blood cells (pRBC, referred to as red cells in human medicine)	Prepared by hard centrifugation of fresh WB and removal of plasma. Stored under refrigeration.	Stored in Adsol, Nutricel, Optisol up to 3 weeks.[170-173]	Hemolytic anemia. Chronic non-regenerative anemia. Acute blood loss (+ crystalloid or colloid).
Fresh-frozen plasma (FFP)	Prepared by centrifugation of whole blood for pRBC or PRP and removal of plasma.	Stored for up to 1 year. 8 hour restriction is based on preserving temperature-labile human FVIII; loss is 20-30%. Dog FVIII is more stable and the 8 hour definition is overly restrictive for dogs. Dog vWf	Bleeding or anticipated bleeding due to coagulopathy of any cause or vWD. Was advocated in past for

	Frozen solid at −18° C or colder within 8 hours of collection. Fresh plasma is plasma transfused <8 hours after collection. Treating donor with DDAVP may increase vWf yield.	is stable for ≥24 h, and FFP frozen within this period is acceptable for treating vWD.[174]	the treatment of pancreatitis but there is no supporting evidence. Colloidal plasma volume expansion.
Regular plasma (RP)	FFP >1 year old, or plasma separated from red cells >8 hours, stored at −18° C or colder.	Stored up to 5 years. Lower level of vWf than in FFP; slightly lower FVIII, FV; negligible differences between FFP and regular plasma with respect to albumin, globulins, alpha-macroglobulins, vitamin-K dependent factors and antithrombin. Minimal loss FV and FVIII in fresh RP over 2 weeks.[36,150]	As good as FFP to treat vitamin-K antagonist poisoning. Colloidal plasma volume expansion.
Cryoprecipitate (CRYO)	Prepared by removal of supernatant (cryopoor plasma) of partially thawed FFP. Treating donor with DDAVP may increase vWf yield. 1 unit is CRYO prepared from 1 unit of plasma.[175]	Enriched in FVIII and vWf. Stored at −18° C or colder for up to 1 year.	Bleeding or anticipated bleeding due to hemophilia A or vWD.
Cryosupernatant	See CRYO.	Enriched in albumin and antithrombin.	Nephrotic syndrome.
Albumin solution	Prepared by ethanol extraction of cryopoor plasma.	Human preparations of 5%, 20%, 25%. Lyophilized dog albumin commercially available from ABRI.	Short-term colloidal plasma volume expansion.
Intravenous immunoglobulin (IVIG)	Prepared by ethanol extraction of cryopoor plasma.	Inconsistently available to veterinarians.	Human IVIG has been used intermittently in treatment of canine ITP and other immune disorders. Of no benefit and potentially harmful in canine IMHA.[176]
Platelet-rich plasma (PRP)	Prepared by light centrifugation of fresh WB and removal of platelet-poor plasma. 1 unit is PRP extracted from 1 unit of WB.	Stored at RT under constant agitation for 3-7 days.	Bleeding or anticipated bleeding due to thrombocytopenia.
Platelet concentrate (PC)	Prepared by hard centrifugation of PRP; or by hard centrifugation of fresh WB followed by centrifugation of buffy coat; or by plateletpheresis.	Stored at RT under constant agitation for 3-7 days. Cryopreserved leukoreduced PC by plateletpheresis commercially available from ABRI. AABB standards specify ≥ 5.5×10^{10} platelets in ≥90% of units; CoE standards specify ≥ 6.0×10^{10} in ≥75% of units.	Bleeding or anticipated bleeding due to thrombocytopenia.
Granulocyte concentrate (GC)	Prepared by centrifugation of fresh WB and removal of buffy coat; or by leukapheresis.	Rarely used in clinical veterinary medicine. Stored at RT 24 hours without agitation.	Neonatal sepsis. Sepsis secondary to neutropenia. Dosage: 1×10^9 granulocytes/kg in a

	1 unit GC is extracted from 1 unit of WB. Donor may be treated with granulocyte colony stimulating factors.		volume of 15 mL/kg.
Pooled adult serum	Prepared by centrifugation of clotted blood. Serum from several donors is pooled.	Pups: 20 mL/kg PO or 20-40 mL/kg SC. Kittens: 50 mL/kg IP or SC q 8 h.	Failure of passive transfer. The higher dosage in kittens was more effective and may be considered for pups.

*Storage times are those used at authors' institution.[170]

AABB, American Association of Blood Banks; *ABRI*, Animal Blood Resources International, Stockbridge, MI, USA; *CoE*, Council of Europe; *FVIII*, factor VIII; *IMHA*, immune-mediated hemolytic anemia; *RT*, room temperature; *vWD*, von Willebrand disease; *vWf*, von Willebrand factor; *WB*, whole blood.

Blood banking was developed for logistics. It is acceptable to only have donors in-clinic or on-call, but a blood donation may not be completed in sufficient time to treat an emergent patient. Also, blood may not be delivered in sufficient time from a blood bank. For these reasons, having a unit of WB always on hand is recommended, although there is the economic risk the unit may expire. Although blood banking facilitates logistics and component use, there is evidence of deleterious effects of transfusing older red cells in humans, although these effects are not as well documented in dogs and not in cats.[22-28] Fresh WB also has superior hemostatic properties than many combinations of components.[29-32] These points must be considered when deciding between storing blood in donors or in plastic bags. The change in blood components during banking is referred to as a storage lesion.[33] Leukoreduction, the removal of white cells from blood components, is extensively practiced in some human blood banks, and is emerging in dogs, to reduce storage lesions and certain transfusion reactions.[34-39] There are various techniques, which all increase expense and result in some loss of red cells and platelets. Leukoreduction is most often accomplished by filtration at the time of blood collection.

Indications for Transfusion and "Triggers"

Anemia is the most common reason to give a transfusion (see ch. 198 and 199). A transfusion trigger refers to a specific cell count at which a transfusion will be recommended.[40] Triggers are guidelines only and should not be acted on without supporting clinical signs, other indicators and/or anticipated cell losses.[41-49] For acute bleeding causing hypovolemia, a common trigger for red cell transfusion is a packed cell volume (PCV) of 20-25% for dogs and 15-20% for cats. For immune-mediated hemolytic anemia (IMHA), a common trigger is 15-20% for dogs and 10-15% for cats. These are lower than for blood loss because animals are less hypovolemic and there are concerns with aggravating the primary disease. For chronic non-regenerative anemia, a common trigger is 12-15% in dogs and 8-12% in cats. Dogs adapt to anemia with increased synthesis of 2,3-diphosphoglycerate. Cats with chronic anemia have water retention such that PCV underestimates red cell mass.[50,51] The amount to be transfused is *estimated* with[52-54]:

$$\text{Volume of donor blood to be transfused (mL)} = \text{Recipient weight (kg)} \times \text{90 (dog) or 66 (cat)} \times \frac{\text{Recipient desired PCV} - \text{current PCV}}{\text{PCV of anticoagulated donor blood product}}$$

Alternatives to red cell transfusion include hypertonic saline for hemorrhagic shock, and oxygen-carrying

solutions for anemia of all causes.[55-58] The only commercially available oxygen-carrying solution is Oxyglobin (OPK Biotech), a hemoglobin-based oxygen carrier (HBOC) based on polymerized bovine hemoglobin. It is currently available in the EU and South Africa, and potentially in other countries by special import. The benefits of Oxyglobin are universal compatibility, low infection risk and 3-year shelf-life. Disadvantages are short duration of effect (half-life of 18-43 hours) and development of hemoglobinemia, hemoglobinuria and icterus, which may interfere with patient monitoring. An HBOC increases systemic and pulmonary arterial pressure by causing plasma volume expansion and vasoconstriction. This may be beneficial in hemorrhagic shock, but may cause circulatory overload, especially in cats, with chronic anemia, heart or kidney disease. The product is licensed for dogs at a dosage of 15-30 mL/kg at a maximum rate of 10 mL/kg/h. It may be given in 5 mL/kg increments as a vasoconstrictor. It is not licensed for cats, but recommended dosages include 5-10 mL/kg at a maximum rate of 2 mL/kg/h, and, for hypotension, 0.2-3 mL/kg boluses over 5-10 minutes, to a maximum of 10 mL/kg over 30 minutes.[56,57,59]

The main indication for transfusion of plasma products is coagulopathy with overt or anticipated bleeding.[60-64] Initial dosages are 10-30 mL/kg of fresh-frozen plasma (FFP) or regular plasma, and 1 unit/10 kg of cryoprecipitate (CRYO). FFP is not a specific treatment for disseminated intravascular coagulation (DIC) or pancreatitis and should only be used when there is bleeding.[60,65] Plasma is occasionally used in dogs and cats to transfuse albumin as a colloid to treat hypovolemia, but synthetic colloids are preferred. Plasma is not used in humans as a colloid, but this is because albumin solutions are available for this use. Human and bovine albumin solutions have been used in dogs and cats without side effects, but severe acute and delayed hypersensitivity reactions have also been reported.[55,66-75] Commercial canine albumin is available as an alternative.[76] Plasma and albumin solutions may also be used to improve plasma oncotic pressure and reduce edema. Unfortunately this is inefficient, but will provide short-term benefit. About 22.5 mL/kg is required to raise plasma albumin by 0.5 mg/dL (5 g/L).[53] 40% of total body albumin is normally found in the plasma and 60% in the interstitium, with the ratio shifted towards plasma in hypoproteinemia. Upon albumin transfusion, the ratio shifts back towards the interstitium. Frequent large volume plasma transfusions or albumin transfusions are needed to maintain albumin levels, especially if hypoproteinemia is caused by protein loss.

Platelet transfusion is best with thrombocytopathia or thrombocytopenia due to reduced platelet production, less beneficial with platelet consumption (DIC), and least beneficial in immune-mediated thrombocytopenia (ITP).[17,42,77-80] A dose of 1 unit/10 kg of platelet-rich plasma (PRP) or platelet concentrate (PC) will raise the platelet count in a dog by ≈30 × 10^9/L, and one third of the transfused platelets will be consumed per day. Transfusing when bleeding is noted or prior to invasive procedures will reduce the number of transfusions compared to transfusion to prevent spontaneous bleeding. Red cell transfusion will also reduce bleeding as bleeding time is inversely correlated with PCV, and thus transfusions to correct anemia in ITP will also ameliorate bleeding.[81-83] FFP contains platelet microparticles and will also ameliorate bleeding.

Compatibility Testing

Many components of blood are antigenic; a blood incompatibility exists when a donor antigen will incite an immunologic response in the recipient. Red cell incompatibilities are due to blood groups, which are inherited antigens on red cell surfaces.[84] A simple blood group is where an individual is either positive or negative for the antigen (two alleles). A blood group system is where there are three or more alleles. Knowledge of blood group phenotypes across species has evolved from early experimental transfusions, to serologic studies using polyclonal antisera prepared from sensitized animals or animals with natural antibodies, to the development of monoclonal antibodies (MoAbs) and flow cytometry to recognize antigens, and molecular studies to define antigen structure. Most recently DNA studies have been used to describe genotypes. Breeding studies and pedigree analyses have been used to determine modes of inheritance. Common or high frequency antigens are those expressed in >92% of individuals.

Severity of a hemolytic reaction depends on recipient alloantibody titer (the higher the worse), class (IgM worse than IgG), temperature of activity (warm antibodies worse than cold), binding affinity (the higher the worse), donor red cell antigen expression (the higher the worse) and antigen dose (the more red cells transfused the worse). The severity of reaction varies from peracute shock to delayed hemolysis, where a transfusion does not last as long as expected.

Serologic compatibility tests to prevent hemolysis include crossmatching, antibody screening, and blood-

typing.[85-89] A crossmatch is an *in vitro* simulation of what will happen *in vivo* with transfusion, and is the most comprehensive. It may be performed using slide (E-Box 130-1) and tube methods (Figures 130-1 through 130-3). Detecting agglutination/hemolysis at any step indicates incompatibility, but the quicker/stronger the test reaction, the worse the transfusion reaction. If a laboratory reports incompatibility, the point in the crossmatch at which it was detected and its strength should be clarified. Antibody screening is a modified major crossmatch using red cells of a known blood group thus screening for recipient antibodies against that group. Blood-typing is a modified minor crossmatch, where antiserum specific to the antigen in question is used. For some antigens, MoAbs, plant lectins or other agents have replaced polyclonal antiserum. Agglutination reactions using serologic techniques by experienced personnel remain the reference methods for blood-typing.

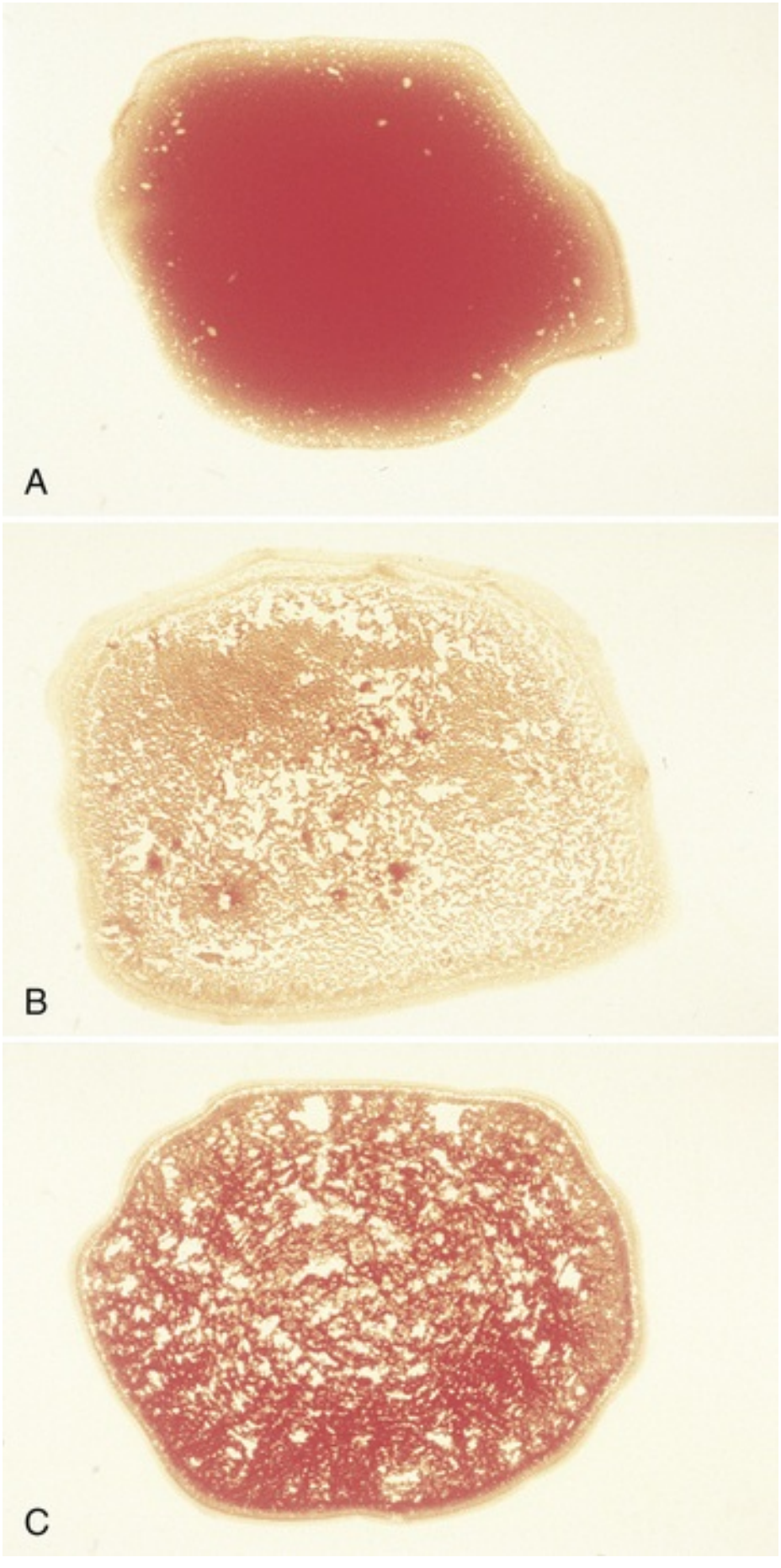
A
B
C

FIGURE 130-1 Macroscopic agglutination and rouleaux in a crossmatch. **A,** Negative result (2 min), type A plasma and type B red cells. **B,** Positive result (2 min), type B plasma and type A red cells. **C,** Strong rouleaux (10 min), type A plasma and type A red cells.

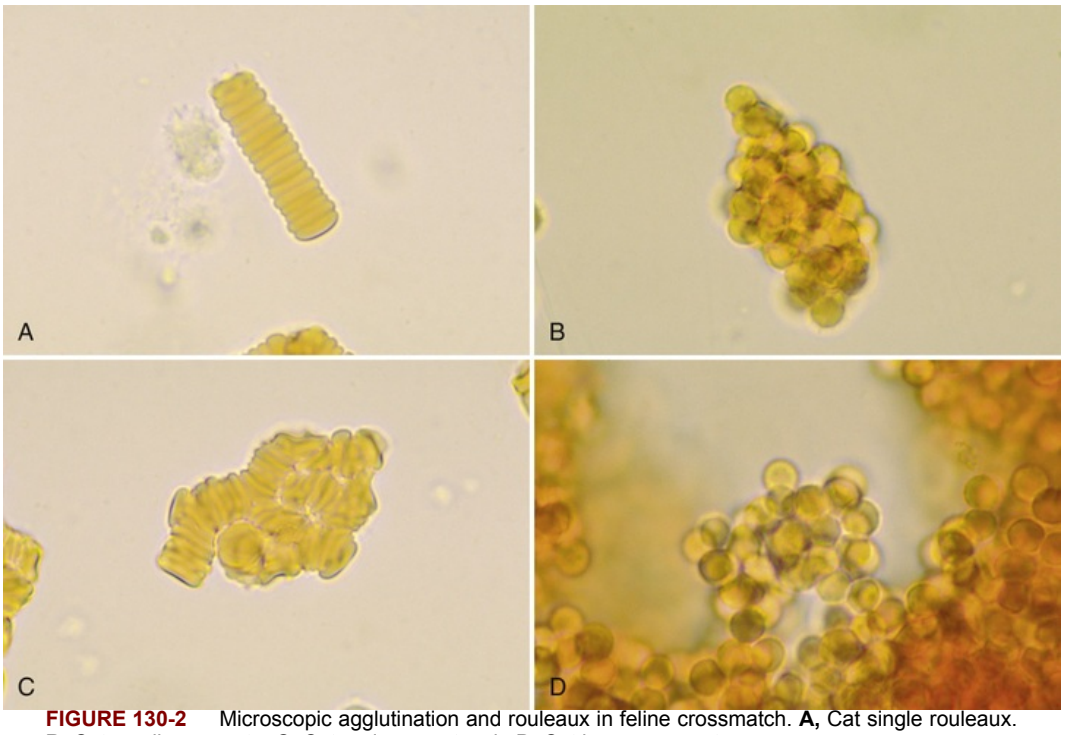

FIGURE 130-2 Microscopic agglutination and rouleaux in feline crossmatch. **A,** Cat single rouleaux. **B,** Cat small aggregate. **C,** Cat rouleaux network. **D,** Cat large aggregate.

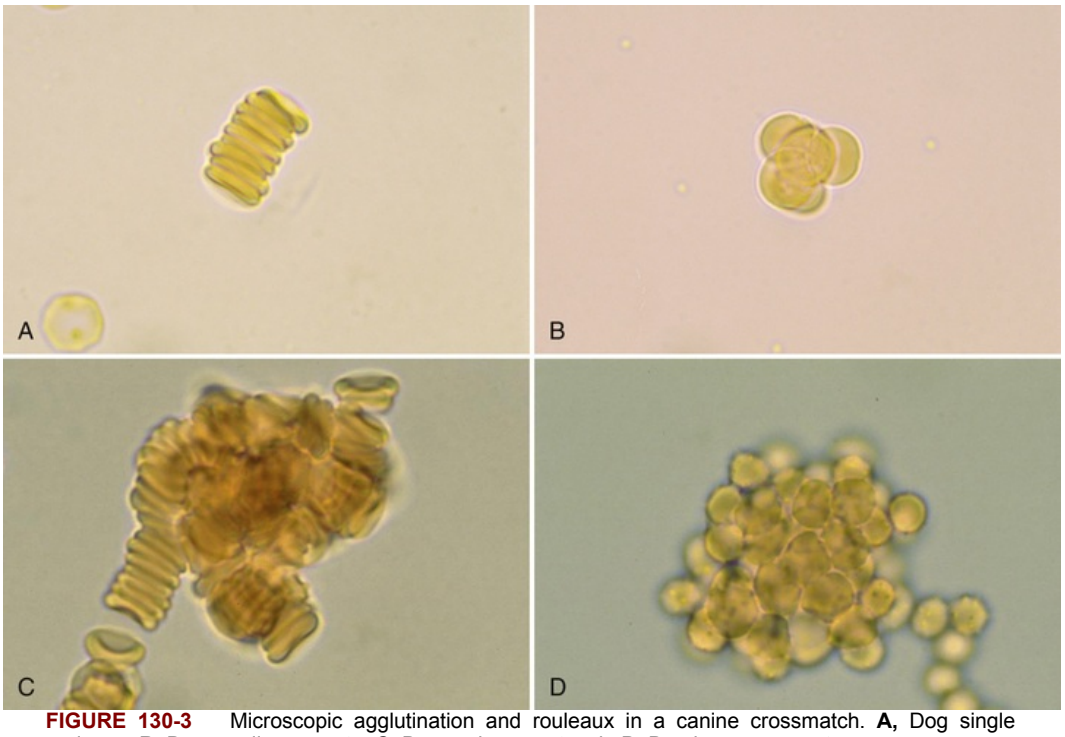

FIGURE 130-3 Microscopic agglutination and rouleaux in a canine crossmatch. **A,** Dog single rouleaux. **B,** Dog small aggregate. **C,** Dog rouleaux network. **D,** Dog large aggregate.

E-Box 130-1

Rapid Slide Crossmatch and Blood-Typing[53,112,168,179]

Either serum or plasma can be used. Serum may reduce rouleaux. Plasma is more convenient and in cats rouleaux formation is nearly as strong in serum as in plasma. Rouleaux is increased with hyperglobulinemia and inflammation. Donor and recipient controls are important to observe for rouleaux and autoagglutination. Separate pipettes or syringes must be used for all solutions and care taken not to touch red cells with an agglutinating solution pipette/syringe or vice versa.

A. Performance of crossmatch

1. Collect 0.5-1 mL blood in an EDTA tube from recipient and donor. A segment of anticoagulated blood from the donor blood bag may be used. Clearly label tubes.
2. Centrifuge tubes at standard speed for the centrifuge in use (usually about 1000 × g for 5-10 minutes) to separate red cells from plasma/serum. If a centrifuge is not available, allow EDTA specimens to sit at room temperature for 1 hour until red cells have settled. Using separate pipettes for each sample, transfer plasma to separate tubes. Clearly label.
3. Optional: Wash red cells. Add 0.5-1 mL of packed red cells to a tube and fill the remainder of the tube with saline/phosphate-buffered saline (PBS). Mix by inverting the tube and centrifuge at 1000 × g. Discard supernatant and repeat twice.
4. Optional: Prepare ≈4% donor and recipient red cell suspensions by mixing 0.2 mL packed red cells and 4.8 mL saline. Use a separate pipette for each mixture and clearly label. Dilution of red cells in saline retards rouleaux formation and facilitates microscopic observation, but results in less dramatic macroscopic agglutination.
5. Label four glass slides as: (a) Donor control, (b) Major X-match, (c) Minor X-match, and (d) Recipient control. Onto each slide place: (a) Two drops (50 mcL) of plasma and one drop (25 mcL) of undiluted red cells; or (b) One drop (25 mcL) of plasma and one drop (25 mcL) of red cell suspension.

a. Donor control: Donor red cells and donor plasma
b. Major X-match: Donor red cells and recipient plasma
c. Minor X-match: Recipient red cells and donor plasma
d. Recipient control: Recipient red cells and recipient plasma

6. Gently rock slides back and forth and observe for *macroscopic agglutination within 1 minute* (see Figure 130-1). The macroscopic agglutination reaction may be graded as:

0 (neg): no agglutination
1+: small aggregates after 30 sec
2+: many small aggregates with 15 sec
3+: large aggregates within 10 sec
4+: large aggregates within 5 sec

This may also be used to grade reactions on agglutination typing cards.

7. Place on a coverslip and observe the wet mounts for *microscopic agglutination within 2 minutes*. Agglutination must be distinguished from rouleaux. This is easy to do with strong agglutination but is difficult with weak agglutination. Rouleaux formation may be very intense, especially when using undiluted red cells, and is macroscopically indistinguishable from agglutination (see Figure 130-1, *A*-*C*). Microscopically, in aggregates of agglutinated red cells, the cells are rafted together, randomly oriented, and superimposed on each other (see Figures 130-2 and 130-3). Rouleaux appear as a "stack of coins" (see Figures 130-2 and 130-3). Small aggregates and single rouleaux can be distinguished, but strong rouleaux will clump together and form a tertiary structure, thus resembling medium-to-large aggregates. Close inspection of the edges of the clumps helps in making the distinction. Note that rouleaux can form concurrently with aggregates, and may stick to them. Under 5 minutes most rouleaux will be single formations. Placing a coverslip on the preparation will disperse some rouleaux. Both rouleaux and aggregates can be observed to be "sticky" as they pull apart.

A slide test using *undiluted* red cells is superior for comparing strong macroscopic agglutination to rouleaux. Strong agglutination is usually evident within 1 minute and reaches a maximum reaction within 3 minutes (see Figure 130-1). After 1 to 2 minutes desiccation of the sample on the slide results in

rouleaux formation beginning at the edges of the sample. However, rouleaux formation of equivalent intensity to strong agglutination requires 5-10 minutes to form. Microscopically large aggregates and rouleaux can be identified, but small aggregates cannot be identified because of the high density of red cells.

A slide test using *diluted* red cells is superior for distinguishing agglutination and rouleaux microscopically and for detecting weak agglutination. Macroscopic rouleaux formation begins within 2 to 3 minutes; as the slides are rocked the red cells swirl and become unevenly distributed, mimicking macroscopic rouleaux.

B. Interpretation of crossmatch

8. Positive *major* crossmatch: Use of this donor will result in a severe transfusion reaction. In cats, macroscopic agglutination denotes type B recipient and type A or AB donor. (Minor crossmatch is negative.) In dogs, macroscopic agglutination denotes probable anti-DEA 1, anti-DEA 4, or anti-*Dal* antibodies.
9. Positive *minor* crossmatch: In cats, macroscopic agglutination denotes type A or type AB recipient and type B donor. (Major crossmatch is negative.) In the likely event that the recipient is type A, use of this donor may cause a mild acute transfusion reaction and/or delayed hemolysis due to anti-A antibodies in donor and anti-B antibodies in recipient. In dogs, minor crossmatch is rarely of significance.

C. Back-typing (cats)

10. Major crossmatch is performed as above using red cells from a known type A or type B donor. A saline control should be performed at the same time.

D. Blood-typing (cats)

11. To detect type A red cells or A antigen on type AB red cells, minor crossmatch is performed as above using plasma from a known type B donor. Plasma is stable at −18° C or colder for at least 1 year.
12. To detect type B red cells or B antigen on type AB cells, *Triticum vulgaris* lectin ("wheat germ agglutinin") is used.
    a. Source of lectin is Sigma-Aldrich, *Triticum vulgaris* lyophilized powder, SKU L9640, available in 10 mg, 25 mg, and 100 mg quantities.
    b. Dissolve the lectin powder in saline/PBS to prepare a stock solution of 1 mg/mL (100 mcg/mL), e.g., mix 10 mg with 10 mL saline/PBS. Freeze in 0.1 mL to 1.0 mL aliquots. The frozen stock solution is documented to be stable for at least 1 month; anecdotally it has been used for at least 2 years.
13. Mix one 0.1 mL aliquot stock solution with 0.16 mL saline/PBS to achieve a ≈64 mcg/mL test solution. Other dilution volumes may be calculated using the formula: (100 mcg/mL) (volume of stock solution) = (64 mcg/mL)(volume test solution), and solving for volume of test solution. The test solution is stable under refrigeration for at least several days.
14. Mix two drops (50 mcL) of test solution and one drop (25 mcL) of undiluted red cells and grade agglutination reaction as per crossmatch.

Cat Red Cell Antigens

The main blood group in cats is the A-B system.[89-94] Simplified, the A antigen is due to *N*-glycolyl neuraminic acid (NeuGc) and the B antigen is due to *N*-acetyl neuraminic acid (NeuAc) (mnemonic: type B has Ac).[95,96] The enzyme CMAH converts NeuAc to NeuGc. The genes encoding CMAH of type A and type B cats have been sequenced and mutations identified in the gene of type B cats that render the enzyme non-functional, leaving type B cats with NeuAc.[97,98] A cat's phenotype may be type A, type B or type AB. Type A and type B are allelic and follow simple Mendelian inheritance with *A* dominant *b*.[99] A type A cat may be *AA* or *Ab;* a type B cat is *bb*. The inheritance of type AB is not fully understood.[100] There is not an *ab* allele at the same locus as *A* and *b,* and type A and type AB CMAH genotypes are the same.[91] Proposed genetics of the A-B system is $A > a^{ab} > b$, where a^{ab} is at a different gene locus.[91] Most domestic shorthair (DSH) cats are type A, with prevalence of type B <10% in eastern North America, northern and southwest continental Europe, northern England and Scotland, and South Africa. Areas with DSH type B prevalence of 10-20% include the west coast of North America, Ireland, regions in southern England, Italy, Greece, Israel, and New Zealand. Areas with >20% type B cats include regions in southern England, Turkey and Australia. For pedigree cats, in

all breeds except the British Shorthair, Rex breeds, Turkish Angora and Turkish Van, type A is most common, while in these four breeds type A and type B are about equally distributed. Abyssinians, Birmans, Himalayans, Somalis, Persians, Scottish Folds and Persians are 10-25% type B. Type AB is rare in all breeds with the notable exception of the Ragdoll cat in Italy with a prevalence of 25%.[101]

The majority of type B cats have natural high-titer anti-A antibodies.[102,103] About one third of type A cats have low-titer anti-B antibodies. Type AB cats do not have either. Natural antibodies are not present at birth, but develop by 2-3 months.[102,104] The average half-life of transfused type-matched red cells is 21-29 days. Transfusing a type A cat with type B (or type AB) blood may cause delayed hemolysis but only a minimal, if any, overt reaction; average transfused red cell half-life is 2 days. The cat may become sensitized and have a more severe reaction upon subsequent transfusions. Transfusing a type B cat with type A (or type AB) blood is likely to cause a severe, often fatal, reaction, which may occur with as little as 0.5 mL; average transfused red cell half-life is 1.3 hours.[105-109] Type AB cats are compatible with type A or type AB blood, and are compatible with type B red cells, but not with type B whole blood because of anti-A antibodies in the latter.

Point-of-care typing is easily accomplished with current commercial kits, including the Rapid Vet-H Feline (DMS) agglutination card, and the immunochromographic (IC) Quick Test A + B (Alvedia) and Rapid Vet-H IC (DMS) tests. Grading the reaction is encouraged (see E-Box 130-1). The A antigen is detected using anti-A MoAb and the B antigen is detected using wheat germ lectin or using anti-B MoAb.[95,110,111] The Rapid Vet-H Feline card has been available for two decades and accurately identifies the type A antigen in type A cats and the type B antigen in type B cats, typically with strong (2-4+) reactions (see E-Box 130-1). However, the A and B antigens are not always identified in type AB cats, and both type A and type B cats have been mistyped as type AB.[112-116] Mistyping a type A cat as type AB is not that serious as it is likely to be transfused with type A blood. Mistyping a type AB cat as type B is more concerning, because of the potentially severe anti-A reaction following transfusion of type B blood, and this is one reason confirmation of type B is recommended. Fortunately type AB is rare. However, for this reason any type AB card result should be confirmed. Confirmation of type B or type AB may include washing red cells and repeating a test, performing back-typing, and submission to a reference or research laboratory. Genotyping may also be performed to distinguish type B from type A/AB cats.[91,98] Confirmation of any result is recommended for any weak reaction (1+), autoagglutination, or result in a FeLV-positive cat. The newer IC tests both use anti-A and anti-B MoAbs. They are not affected by rouleaux and autoagglutination. They have even better performance than the typing card, and will likely replace it.[115,117] However, problems with AB typing still occur and the same caveats apply as with the agglutination cards for confirming certain results.

Many studies have calculated risks for transfusion reactions based on blood type prevalence and alloantibody titers, but acting on these risks is misguided. The risks may be low but the consequences high. A compatibility test is easy to perform and no risk is worth taking. The admonition "B careful" should be remembered whenever performing a transfusion.

In addition to the A-B system, the *Mik* blood group was reported in 2007.[118] *Mik* appears to be a high-frequency antigen, but *Mik*-negative cats may have natural antibodies that can cause an acute hemolytic reaction.[98,118] The only way to detect *Mik* incompatibility is by crossmatch.

Mild crossmatch incompatibilities have been seen in type-matched transfusion-naïve cats, and have also developed in repeatedly transfused cats.[119-121] These incompatibilities suggest that other blood groups exist, but are more likely to be associated with delayed hemolysis rather than acute reactions. In addition, incompatibilities have been associated with chronic kidney disease, neoplasia and other disorders, suggesting that alloantibodies to unidentified blood groups may be acquired.[86,119] Crossmatching in addition to blood-typing is not routine in cats, but is recommended if possible, especially in cats receiving repetitive transfusions. Expertise is required to detect subtle incompatibilities; therefore crossmatching is usually performed at reference laboratories. There is now a gel column crossmatch kit for dogs and cats (RapidVet-H, DMS), and a kit by Alvedia for cats is under development, which should facilitate point-of-care crossmatching. However, the number of donors is often restricted, and there may be no choice but to give a transfusion with A-B matched but mildly crossmatched incompatible blood. The ultimate incompatibility is with dog blood. Transfusion of dog blood to cats is discouraged, but cats do not have natural antibodies against dog red cells (although dogs have NeuGc and NeuAc). Over 60 cats have received xenotransfusions with no acute reactions and this may be considered if a life-saving transfusion is needed.[122] However, delayed hemolysis and sensitization will occur, and repeat transfusion is likely to be fatal.

Dog Red Cell Antigens

Over 12 antigens have been reported in dogs.[87,88,123,124] In the DEA (dog erythrocyte antigen) system, 1.1, 1.2, 3, 4, 5, 6, 7, and 8 were defined by internationally standardized antisera. Antisera for DEA 6 and 8 are no longer available; limited supplies of the others are available, although more may be produced by sensitization. Reactions to DEA 1.1/1.2 have the most significance. Recent studies by flow cytometry indicate that DEA 1.1 and 1.2 are not separate antigens, but represent a continuum of antigen expression.[125,126] The recommendation was made to type dogs as DEA 1 positive or negative. As with other dog antigens, the molecular structure and genotype of DEA 1 is not known,[127] and there may be other factors that accompany the varying expression of DEA 1 rendering some DEA 1 dogs incompatible with each other. That accounts for earlier reports of incompatibilities between DEA 1.1 and DEA 1.2 dogs. Overall world-wide prevalence of DEA 1 is about 45%, with some breed and regional differences.[124,128-132] Boxers, Border Collies, Doberman Pinschers, German Shepherd Dogs, Flat-Coated Retrievers and Greyhounds are more likely to be DEA 1-negative, while Bernese Mountain Dogs, Dalmatians, Golden Retrievers, Great Danes, Rottweilers and Saint Bernards are more likely to be DEA 1-positive. A survey in São Paulo, Brazil, reported a >90% prevalence of DEA 1. Native Turkish breeds had an overall prevalence of DEA 1 of 65%.

In addition to DEAs, some Dalmatians, and then Doberman Pinschers, Shih Tzus and other breeds were reported negative for *Dal* antigen.[133,134] It is a high-frequency antigen in mixed-breed dogs and may be the same antigen as DEA 6.[124,134]

Dogs have either no, or only weak, natural antibodies and there is no evidence that they are sensitized by pregnancy.[123,135,136] An acute alloimmune hemolytic reaction will not occur in a naïve recipient, but dogs lacking a certain DEA will be sensitized upon transfusion of red cells bearing that DEA, and will be at risk for future IgG-mediated hemolytic reactions. By convention, a dog is considered potentially sensitized by 4 days post-transfusion. Acute reactions with hemoglobinemia, hemoglobinuria and icterus have been described for DEA 1, DEA 4, *Dal*, and an undefined common antigen.[133,137-139] Sensitization to other antigens will reduce half-life of transfused red cells, which normally ranges in dogs from 43-104 days. Regardless of prevalence rates, all dogs should be either typed for DEA 1 or transfused with DEA 1-negative blood. Current commercial kits that use anti-DEA 1 MoAb for point-of-care typing are the Rapid Vet-H Canine (DMS) agglutination card, the IC Quick Test DEA 1.1 (Alvedia), and, in the European Union, QuickVet (DMS) that detects agglutination by altered light transmission.[140-144] Grading the reaction is encouraged (see E-Box 130-1) and 1+ results should be taken as inconclusive. The cards reliably detect DEA 1-negative dogs, but some false-positive reactions occur, especially in IMHA.[142,145] Because of the risk for sensitizing a mistyped DEA 1-negative dog, some clinics restrict the cards for selecting DEA 1-negative donors. The IC test has excellent performance and false-positives are rare.[140,142] False-negatives may occur in anemic dogs because the reaction line is hard to see, and for such a result the test should be repeated after concentrating the red cells.[142] The QuickVet test had a similar performance to the agglutination card.[141] Blood-typing and antibody screening for DEA 3, 4, 5, and 7 are only available at ABRI. Ideally all donors should have such typing done, but this is often not practical and incompatibilities to DEA 3, 5 and 7 are likely to be mild.[124] Crossmatching is not standard-of-care for a dog receiving its first transfusion, although mild crossmatch incompatibilities may exist.[87,123,124,135-137] However, *crossmatching is essential for any dog receiving a subsequent transfusion,* and historically was ideally performed in a reference laboratory that could incorporate an indirect Coombs test. In addition to the RapidVet-H gel kit, the LAB TEST XM (Alvedia) is available which incorporates a Coombs reagent. Studies evaluating these kits are in progress. If these are not available, a slide or tube crossmatch will identify risk of severe reaction.

Non-Red Cell Incompatibilities

These are discussed in Transfusion Reactions. The only readily available compatibility test is to give a test dose of the transfusion, where the transfusion is given at an initial rate of 0.25 mL/kg/h for the first 15-30 minutes. A negative test dose does not preclude a later or delayed reaction.

Autotransfusion

Autotransfusion addresses both the need for a donor and compatibility problems. There are three types: preoperative donation, perioperative acute normovolemic hemodilution, and scavenging/salvaging. In

preoperative donation, patient blood is collected and banked using standard techniques 2-3 weeks before a procedure to give time for regeneration while minimizing red cell storage lesions.[146] In perioperative hemodilution, blood is collected from the patient immediately before surgery and replaced with three times the withdrawn volume with crystalloid or equivalent colloid solution to a target hematocrit of 20-28%. In acute blood loss, the main problem is volume depletion and not red cell loss. In salvaging, intrathoracic or intraabdominal blood is collected and reinfused. It has been practiced for >30 years for trauma patients in veterinary emergency clinics and the reader is referred to detailed descriptions.[147-149]

Administering a Transfusion

Hands should be thoroughly washed prior to handling blood products and extreme care taken when connecting transfusion lines to avoid contamination.

Refrigerated WB and pRBC are not routinely warmed as this may decrease red cell viability and promote microbial growth. For rapid administration, where chilled infusions may cause arrhythmias, and for animals at risk for hypothermia, the products may be warmed to room temperature over 30-60 minutes or the IV line passed through an infusion warmer. Warming by immersing the blood bag in warm water or microwave warming is discouraged. Frozen plasma products should be thawed in a 37-38° C water bath or incubator. A canine unit (≈200 mL) takes about 30 minutes to thaw.[150] Agitating the bag will speed up the process. Microwaving is possible.[151]

A transfusion may be given through any vein (or artery). If IV access is not possible, the intraosseous route (see ch. 77) is preferred. Intraperitoneal transfusion is not recommended. The smallest recommended catheter size for red cell transfusion in dogs is 20 ga and in cats 22 ga.

A transfusion should be given via special sets that contain in-line filters and spikes to connect to the blood bags. A set for an adult human contains a 170-260 micron filter and may be used for standard dog units. Cat and toy-breed dog transfusions are better delivered through human pediatric sets (which contain 40-200 micron filters), because less volume remains in the line when the transfusion is complete. A cat, but not dog, transfusion may also be given through an 18 micron neonate filter.[152,153] If a pediatric set is not available, an adult set may be used and crystalloid fluid used to slowly flush in the remaining transfusion, or the transfusion may be placed in a burette and aseptically "piggy-backed" into the regular fluid line. The same IV line should not be used to deliver 5% dextrose (may cause clumping and hemolysis) or lactated Ringer's (calcium may facilitate microcoagulation). Normal saline, PlasmaLyte 148, and PlasmaLyte A may be given concurrently and may also be used to dilute a transfusion. If a transfusion is being given with intent to deliver platelets, the set should be free of latex, which may trap platelets. Ideally an IV line is changed after transfusion to minimize risk of microbial growth in the line. Transfusions may be delivered by gravity, volumetric infusion pumps (verify safety with manufacturer), syringe pumps, or intermittent slow bolus injection.

During the test dose, the patient is continually observed and vital signs recorded every 5 minutes. After the test dose, the standard transfusion rate is 5-10 mL/kg/h and vital signs are recorded every 15-30 minutes. The maximum rate is 22 mL/kg/h, reserved for critical situations. Human standards specify a transfusion should be complete within 4 hours to reduce risks of microbial growth, but this time may be extended if the risk of volume overload is considered greater than the risk of infection. Units may be subdivided into aliquots and one aliquot refrigerated. When dividing a unit, care must be taken to transfer red cells gently to avoid hemolysis and to avoid contamination. A transfusion log should be kept, recording information from the blood bag label, recipient, date, time, and patient parameters.

Adverse Consequences of Transfusions (Transfusion Reactions)

Transfusion reactions are categorized as immunological and non-immunological, and as acute and delayed. Immunological reactions are due to red cell, plasma protein, and white cell and platelet antigens. Acute reactions are those occurring within 2 days (often within 1-2 hours) of starting a transfusion. Delayed reactions are typically clinically less severe and occur 2 days or longer post-transfusion. The signs of an acute immunological reaction include weakness, tremors, agitation, vocalization, fever, tachycardia/arrhythmias, hypotension, polypnea/dyspnea, salivation, vomiting, elimination, seizures, urticaria/angioedema, and cardiopulmonary arrest. Transfusion reactions are probably under-recognized, but are reported to occur in 3.3-28% of dogs and 1.2-8.7% of cats.[18,44-47,61,78,154-157] Transfusion reactions are not linked with increased risk of death in type-matched dogs receiving pRBC transfusions, but complications impact patient clinical

status.[22]

Acute Immunologic Transfusion Reactions

The pathogenesis of hemolytic reactions is discussed in Compatibility Testing. The severe reaction of type B cats to type A red cells resembles anaphylaxis (see ch. 137).[105,107-109] The most common signs are recumbency, stretching of limbs, hypotension, bradycardia and apnea within two minutes of starting the transfusion and lasting up to five minutes. Less severe reactions are associated with milder hypotension, tachycardia and polypnea. Hemoglobinuria and hemoglobinemia may be undetectable. Tachycardia and polypnea occur during recovery, which may take several hours. Hypertension and arrhythmias follow a severe reaction for about 30 minutes. Pulmonary edema may develop.

Acute hemolysis in dogs causes signs of an immunologic reaction plus hemoglobinuria and hemoglobinemia.[133,137-139] Fever is common but angioedema is not. Acute kidney injury and DIC are uncommon sequelae. Severity of the reaction is correlated with the number of red cells destroyed.

Febrile, non-hemolytic reactions, characterized by a temperature increase of >1 °C, are the most common immunologic reactions of type-matched transfusions in cats and dogs.[18,22] Fever may occur during or after transfusion, range from mild to >41.0° C, be accompanied by vomiting and tremors, and resolve in 1-12 hours. It may be caused by white cell antigens, and bioactive substances that accumulate in stored blood. These reactions are not life-threatening, but interfere with patient status and monitoring for sepsis and hemolysis. Pre-treatment with acetaminophen in dogs may help prevent such reactions, but is only recommended if there is a history of previous deleterious febrile reactions. Donor rotation and fresh red cell products may also reduce risk. Leukoreduction reduces risk in humans and may do so in dogs.

Transfusion-related acute lung injury (TRALI) is one of the most common causes of transfusion mortality in humans. It is characterized by non-cardiogenic pulmonary edema. The majority of human cases are due to *donor* antibodies reacting with *recipient* leukocytes, when using blood from previously pregnant donors who have developed antibodies through exposure to fetal blood. TRALI is unlikely to occur in dogs and cats due to the low rate of previously pregnant donors and different placentation. However, TRALI may arise from different mechanisms, and post-transfusion non-cardiogenic pulmonary edema has been seen in dogs.[22,158] Such dogs were critically ill and the role of transfusion and primary disease in causing acute respiratory distress syndrome (ARDS) is not known.

Allergic transfusion reactions range in severity from mild urticaria, angioedema and erythema, to severe anaphylaxis, bronchoconstriction and effusions, and occur within minutes to hours of starting a transfusion, even if there has been no reaction to a test dose.[53] These are believed to be primarily reactions to gamma globulins and are IgE-mediated. Fever is not typical. The risk of allergic reactions increases with transfusion rate, possibly because some reactions are anaphylactoid. Allergic reactions can occur in a naïve recipient and the risk may increase with multiple transfusions. For animals receiving multiple transfusions, donor rotation and pre-treatment with antihistamines may be considered, especially if there is a history of allergic reactions. Pre-treatment with antihistamines should be considered if a rapid transfusion rate is necessary, but does not guarantee that a reaction will not occur. If a recipient requiring a red cell transfusion has a history of severe allergic reactions, then red cells should be washed prior to transfusion.

Delayed and Other Immunologic Transfusion Reactions

Delayed hemolysis is discussed in Compatibility Testing. *Immune-complex disease* is at least one mechanism of delayed reaction to human serum albumin. *Platelet alloimmunization* occurs rapidly with repetitive transfusions in dogs, resulting in platelet transfusions becoming ineffective. The onset of platelet alloimmunization may be delayed or prevented by donor rotation, leukoreduction, blood product irradiation, and cyclosporine.[159-161] *Post-transfusion purpura* may rarely occur within 1 to 2 weeks post-transfusion and last up to 2 months. Antibody response to transfused platelets is generalized to the recipient's platelets. Immunosuppression may hasten recovery.[162] *Transfusion-related immunomodulation* (TRIM) is a broad term encompassing both the pro-inflammatory and immunosuppressive effects of transfusion, and is associated with beneficial and detrimental effects.[48-63] Factors in TRIM include neutrophils, lymphocytes, proteins and cytokines. The main beneficial TRIM effect is reduced rejection of solid organ transplants. Negative effects include hematopoietic stem cell transplant rejection, transfusion-related graft-versus-host disease (immunological attack on recipient bone marrow causing pancytopenia), and increased susceptibility to infection. Both pro-neoplastic and antineoplastic effects have been associated with TRIM. Leukoreduction and

blood product irradiation help reduce neutrophil and lymphocyte contributions to TRIM, respectively.

Acute Non-Immunologic Transfusion Reactions

Pre-transfusion hemolysis may be caused by improper blood banking, bacterial contamination of blood bags, and rough handling of blood during administration. Reactions to hemolyzed blood mimic alloimmune hemolytic reactions.[154] *Bacterial contamination* of blood products is always a risk, especially in leukoreduced products, resulting in signs of acute sepsis that mimic other reactions.[164] Several reactions are related to *large volume transfusions*, especially *massive transfusions* that exceed patient blood volume. Blood products exert a significant colloid effect, and, as with HBOCs, higher and/or rapid volume transfusions may cause *circulatory overload*. Most blood products use citrate as anticoagulant, which is metabolized to bicarbonate after transfusion. Large transfusion volumes can overwhelm this metabolic pathway, leading to hypocalcemia (citrate intoxication). Liver dysfunction, hypothermia, and hypovolemia increase risk. Clinical signs include tremors, seizures, and arrhythmias. Confirmation requires measurement of ionized calcium. Other complications of massive transfusions include dilution thrombocytopenia, dilution coagulopathy, hypomagnesemia, acid-base disturbances, and hypothermia.[165,166] Ammonia accumulates in stored red cells and ideally products <2 weeks old should be used with liver dysfunction.

Diagnosis and Treatment of Transfusion Reactions

A transfusion should be immediately stopped at the first sign of a reaction; treatment is then symptomatic.[53,157,167-169] Because signs of transfusion reactions overlap, the patient must be re-examined and observed for other signs that may indicate which reaction is occurring. With red cell transfusions, a blood sample should be examined for hemoglobinemia; a urine sample should be examined later for hemoglobinuria. Fluid therapy should be continued to ensure renal perfusion and kidney function should be monitored. Hypotension, regardless of cause, should be treated with fluid boluses ± pressor agents. The cornerstone of treating an acute anti-A reaction in a type B cat is treatment of hypotension; antihistamines with corticosteroids are not routinely used. If fever is present, rule-outs include hemolysis, febrile non-hemolytic reactions, and sepsis. If there are signs of an allergic reaction, antihistamines and/or corticosteroids may be given. If a rate-dependent allergic-like reaction has subsided, the transfusion may be resumed at 10-25% of the previous rate.

The blood bag should be re-examined for particulate matter and discoloration. If the transfusion is cancelled, the blood bag and IV line should not be discarded but kept in a refrigerator in the event that culture of the blood bag, microscopic examination, or post-transfusion crossmatching is desired.

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CHAPTER 131

Oxygen Therapy

Kate Hopper

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Oxygen therapy is an essential supportive care measure routinely administered to critically ill pets. Oxygen therapy increases the fraction of inspired oxygen (F_IO_2) in an attempt to increase the oxygen content of the arterial blood (CaO_2). In order to provide appropriate oxygen therapy, it is necessary to choose the most appropriate method of administration, to be able to measure or estimate the F_IO_2 provided, and to monitor the effects of therapy. The F_IO_2 may be recorded as a percentage (21% to 100%) or a decimal (0.21 to 1.0). The concentration of oxygen in room air is always 21%. Supplemental oxygen can provide an F_IO_2 of 30% to 100% depending on the technique and equipment utilized.

Indications and Goals of Oxygen Therapy

Oxygen therapy aims to increase the delivery of oxygen to the tissues (DO_2). The determinants of DO_2 are hemoglobin concentration ([Hgb]), arterial blood oxygenation, and cardiac output (CO) as described by the equation in Box 131-1.[1]

Box 131-1

The Oxygen Delivery (DO_2) Equation

$$DO_2 = CO \times CaO_2$$

$$CaO_2 = ([Hgb] \times 1.34 \times SaO_2) + (0.003 \times PaO_2)$$

CaO_2, Arterial blood oxygen content; *CO,* cardiac output; *Hgb,* concentration of hemoglobin in g/dL; *PaO_2,* partial pressure of oxygen in arterial blood in mm Hg; *SaO_2,* arterial saturation of hemoglobin.

Decreased blood oxygen concentration (hypoxemia) and the associated respiratory distress are the primary indication for oxygen therapy. Hypoxemia can be suspected based on the patient's clinical signs and/or may be documented directly with pulse oximetry or arterial blood gas analysis. Clinical signs suggestive of hypoxemia include respiratory distress (dyspnea), tachypnea, cyanosis, and even apnea. Hypoxemia is confirmed based on a partial pressure of arterial oxygen (PaO_2) <80 mm Hg or an arterial oxygen saturation of hemoglobin (SaO_2) <95%. Severe hypoxemia is present when the PaO_2 is <60 mm Hg or the SaO_2 is <90%.[1] Ideally, oxygen therapy is adjusted as needed for the patient to maintain a PaO_2 of 80 to 120 mm Hg, and an SaO_2 between 95% and 100%. A higher PaO_2 is of little clinical benefit assuming the patient has an adequate hematocrit and stable cardiovascular status, since these animals often will tolerate mild to moderate hypoxemia (PaO_2 of 60 to 80 mm Hg).

Other indications for oxygen therapy include severe anemia (decreased [Hgb]), hemodynamic compromise (decreased CO) and carbon monoxide poisoning. Provision of oxygen therapy can improve DO_2 in situations of low [Hgb] and/or low CO, based on the DO_2 equation. Unfortunately, however, this improvement will be minimal if hemoglobin is already maximally saturated, since oxygen dissolved in the plasma (PaO_2) only accounts for a small percentage of overall DO_2 compared to hemoglobin-bound oxygen. In these cases, definitive therapy should involve blood transfusion to increase [Hgb] and measures to improve CO, respectively. Thus, the goal of oxygen therapy in patients with anemia or hemodynamic compromise is to maximally increase CaO_2 in an attempt to increase DO_2 until more definitive therapy can be instituted. To this aim, the highest possible F_IO_2 should be provided.

An uncommon but important indication for oxygen therapy is carbon monoxide poisoning. In these cases, oxygen therapy will both attenuate tissue hypoxia and accelerate the elimination of carbon monoxide binding to hemoglobin.[2]

Supplemental oxygen is recommended in all unstable emergency patients until they are adequately stabilized and their requirement for ongoing oxygen therapy can be fully assessed.

Techniques

Oxygen therapy requires a source of oxygen, either from an oxygen tank, an in-wall system, or an oxygen concentrator. There are several ways in which this oxygen can be delivered to the patient. The chosen technique is based on availability of equipment, patient demeanor, and severity of disease. Techniques for providing oxygen therapy are listed below in order from least invasive to most invasive. These include an oxygen cage, flow-by, mask, modified Elizabethan collar or oxygen hood, nasal prongs, nasal cannulae, transtracheal, and endotracheal with or without positive pressure ventilation.

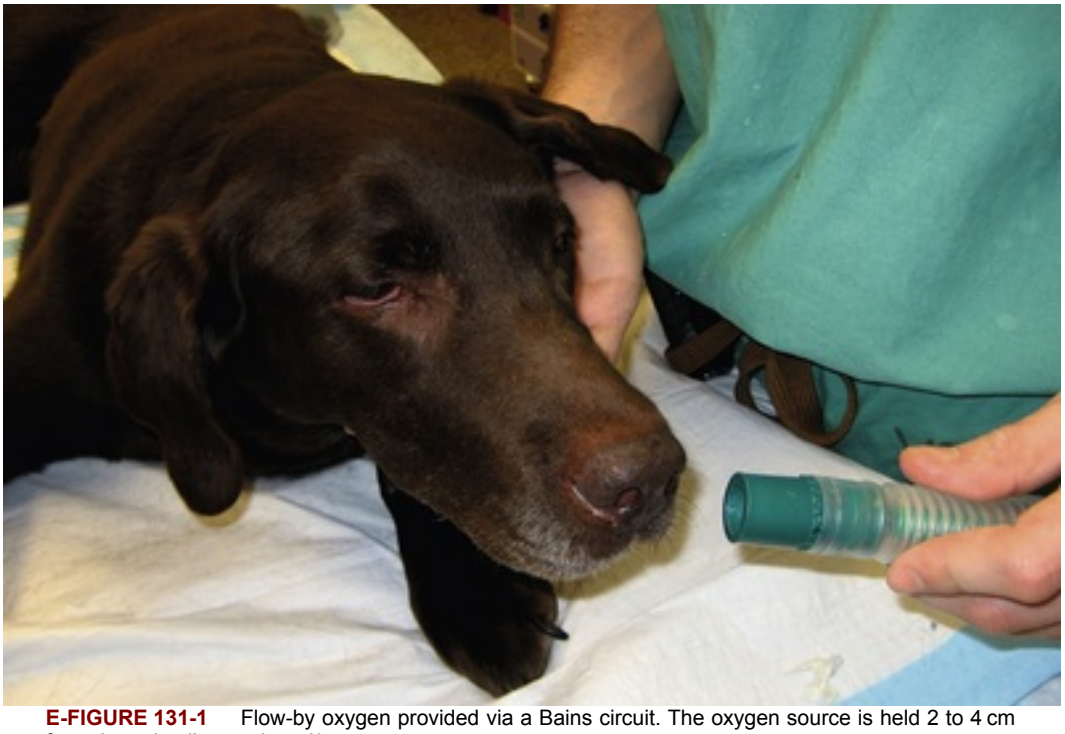
Oxygen Cage

An oxygen cage allows administration of a known F_IO_2 to patients, in a low-stress, noninvasive manner. It is particularly effective for cats in respiratory distress, as they may quickly decompensate when handled. Advantages include patient comfort, the ability to control F_IO_2 accurately, and the ability to provide very high F_IO_2 when required. Additionally, purpose-built, commercially available oxygen cages are able to remove carbon dioxide (CO_2) (soda lime) and tightly control temperature and even humidity. Disadvantages may be that oxygen cages are expensive and can require high oxygen flow rates, so they are a more expensive method of oxygen delivery than most other methods. It has been suggested that monitoring and treatment might necessitate interruption of oxygen delivery when using an oxygen cage. However, this problem is rare if the small patient-handling doors are used and if constant oxygen flow and/or addition of flow-by oxygen is utilized during animal handling. Large dogs can become overheated in oxygen cages, and the temperature should be monitored closely. A temporary oxygen cage can be made by covering a cat carrier with a plastic bag and inserting an oxygen hose. It is important to make several holes in the bag to allow heat and CO_2 to escape. This technique is particularly useful for the cat that looks so distressed that handling the cat might be detrimental, or for transport of a small patient that requires oxygen therapy. If a "homemade" oxygen cage is utilized, there is also a concern that dangerous levels of CO_2 and heat can accumulate.[3] As such, it has been recommended that adequate cage ventilation is essential and CO_2 concentrations should be monitored using a portable CO_2 meter.[3]

Flow-by Oxygen

The simplest way to administer oxygen is by directing oxygen gas flow toward the patient's mouth and nose (E-Figure 131-1). Tubing or a Bains circuit connected directly to a regulator and flow meter on an oxygen source is ideal for this technique. A Bains circuit or circle system (with anesthetic gases flushed out) attached to an anesthetic machine also is effective. An oxygen flow rate of 2 to 3 L/min will provide an F_IO_2 of approximately 25% to 40%.[4] This technique is most suitable for short-term administration of oxygen during initial triage and stabilization of emergency patients. This is an easy mode of administration and generally is well tolerated. The disadvantages are that it is labor intensive, wastes oxygen, and the exact F_IO_2 delivered cannot be determined. Additionally, some pets resent gas flow directed at their face, precluding effective

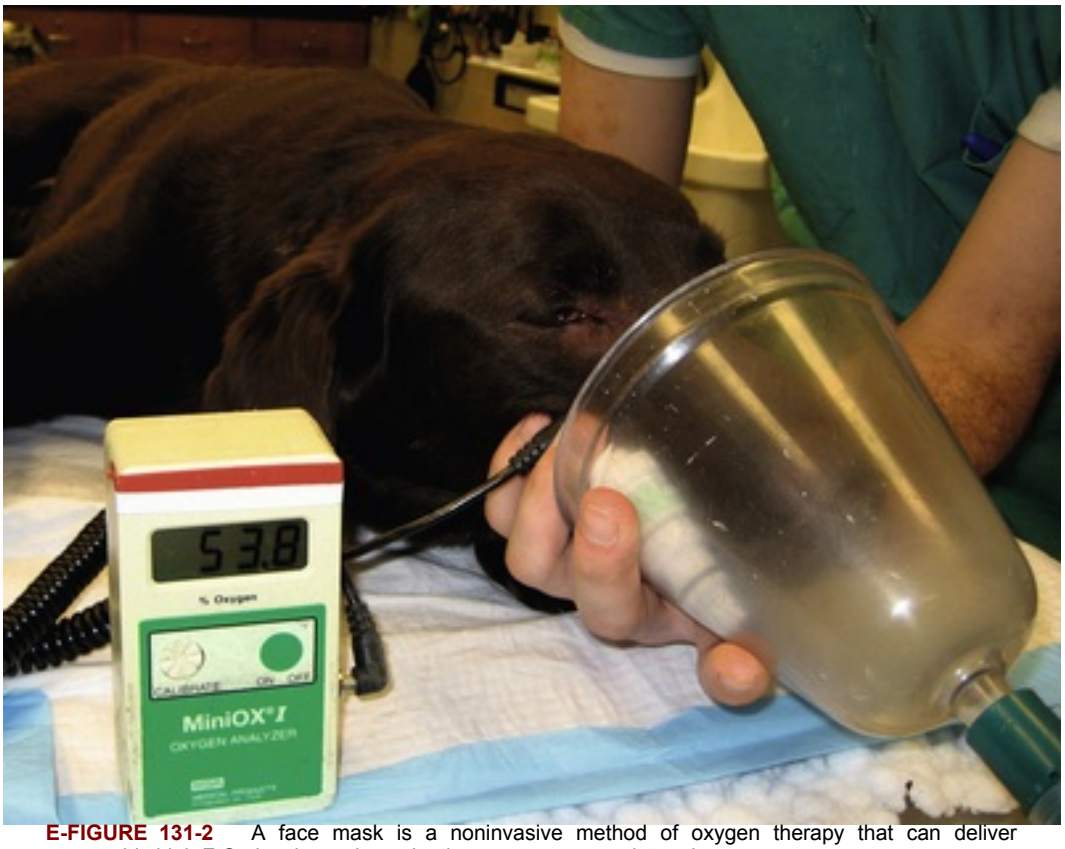
oxygen delivery using this technique.



E-FIGURE 131-1 Flow-by oxygen provided via a Bains circuit. The oxygen source is held 2 to 4 cm from the animal's mouth and/or nose.

Mask Oxygen

A face mask will allow administration of a higher F_IO_2 than can be achieved with flow-by oxygen. It is possible to deliver 60% or higher F_IO_2, and the exact F_IO_2 can be measured by placing an oxygen sensor in the mask alongside the animal's nose (E-Figure 131-2).[4] Disadvantages include the possibility for heat and CO_2 to accumulate in tight-fitting face masks, and animals in respiratory distress often resent the placement of a face mask. Care must be taken when using a face mask to avoid causing corneal trauma with the edge of the mask.



E-FIGURE 131-2 A face mask is a noninvasive method of oxygen therapy that can deliver reasonably high F_IO_2 levels as shown by the oxygen sensor pictured.

Elizabethan Collar

An Elizabethan collar with an oxygen source secured inside and the front covered with clear plastic wrap is a cheap, readily available method by which a reasonable F_IO_2 can be administered (E-Figure 131-3). It is important to make a window in the top of the plastic wrap to prevent accumulation of heat and CO_2. There are also commercially available oxygen hoods that function in a similar manner. Flow rates of 0.5 to 1 L/min can provide an F_IO_2 of 30% to 40%.[5] At higher oxygen flow rates, an F_IO_2 of 60% to 70% can be delivered and oxygen therapy for long periods of time is feasible. It may be difficult to tightly control the F_IO_2 with this approach, and some animals with respiratory distress will not tolerate the placement of the collar.

E-FIGURE 131-3 An Elizabethan collar covered with clear plastic wrap can be used to provide oxygen therapy for long periods of time. As the oxygen sensor pictured shows, this technique can deliver high F_IO_2 levels. It is essential to have a window in the plastic wrap to reduce the accumulation of heat and carbon dioxide.

Nasal Prongs

A simple method of oxygen administration is placement of human nasal prongs (Figure 131-4). These tend to be practical only in medium-sized dogs or larger. The advantages of nasal prongs are their ease of placement and ready availability. The disadvantages include the ease in which they can be dislodged and the fact that the exact F_IO_2 delivered cannot be measured. It can be assumed that the F_IO_2 delivered would be less than that achieved with a nasal oxygen catheter at a similar flow rate (Table 131-1), since the prongs are short and some oxygen is likely lost to the environment.

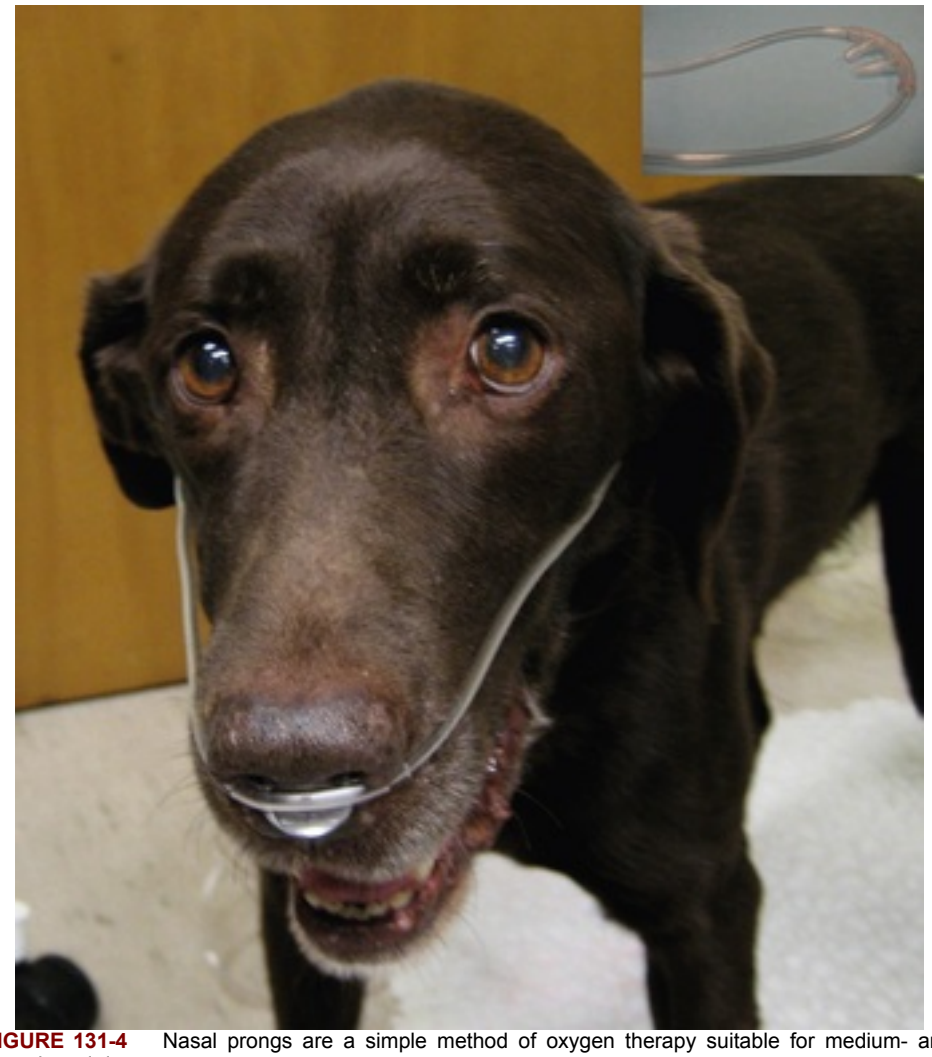


FIGURE 131-4 Nasal prongs are a simple method of oxygen therapy suitable for medium- and large-breed dogs.

TABLE 131-1

F_IO_2 Reported for Unilateral and Bilateral Nasal Oxygen Catheters at Varying Oxygen Flow Rates

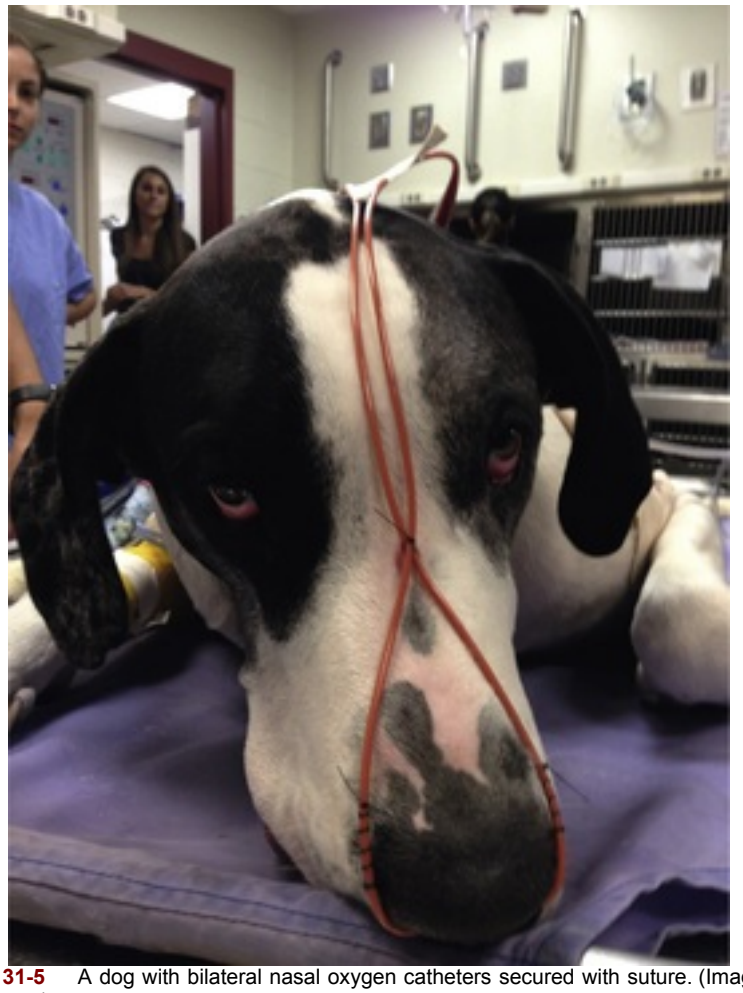
	F_IO_2 (%) MEAN ± SD	
OXYGEN FLOW RATE (mL/kg/min)	UNILATERAL CATHETER	BILATERAL CATHETERS
50	29.8 ± 5.6	36.4 ± 5.9
100	37.3 ± 5.7	56 ± 11.9
200	57.9 ± 12.7	77.3 ± 13.5

From Dunphy ED, Mann FA, Dodam JR, et al: Comparison of unilateral versus bilateral nasal catheters for oxygen administration in dogs. *J Vet Emerg Crit Care* 12:245-251, 2002.

Nasal Oxygen Catheter

A nasal oxygen catheter generally is well accepted by most pets and can supply an F_IO_2 of 37% to 58% with oxygen flow rates of 50 to 200 mL/kg/min. Bilateral nasal oxygen catheters can provide an F_IO_2 of up to 77%

(see Table 131-1) (E-Figure 131-5).[6] Nasal oxygen catheters have the advantage of allowing hands-on patient assessment and management without interruption of oxygen therapy. Unfortunately, many patients with severe respiratory distress will not tolerate the restraint required for placement, and some individual animals are extremely adept at removing the catheters. Other disadvantages include nasal mucosal irritation and difficulty in determining the actual F_IO_2 delivered (although it can be approximated from the information in Table 131-1). In order to reduce nasal irritation, the administered oxygen should first pass through a bubble humidifier and local anesthetic should be administered into the nose as required.



E-FIGURE 131-5 A dog with bilateral nasal oxygen catheters secured with suture. (Image courtesy Dr. Claire Sharp.)

The nasal oxygen catheter should be a soft, smooth-tipped catheter such as an infant feeding tube, red rubber catheter, or commercially available nasal oxygen catheter. Such catheters should be placed in the ventral meatus of the nose after application of local anesthetic (such as proparacaine ophthalmic drops, or 2% lidocaine gel) with the tip advanced to the level of the medial canthus of the eye (Figure 131-6). The catheter should be secured as close to the nares as possible and then across the side or dorsal aspect of the head with sutures, staples, and butterfly tape or cyanoacrylate adhesive (see Figure 131-6).

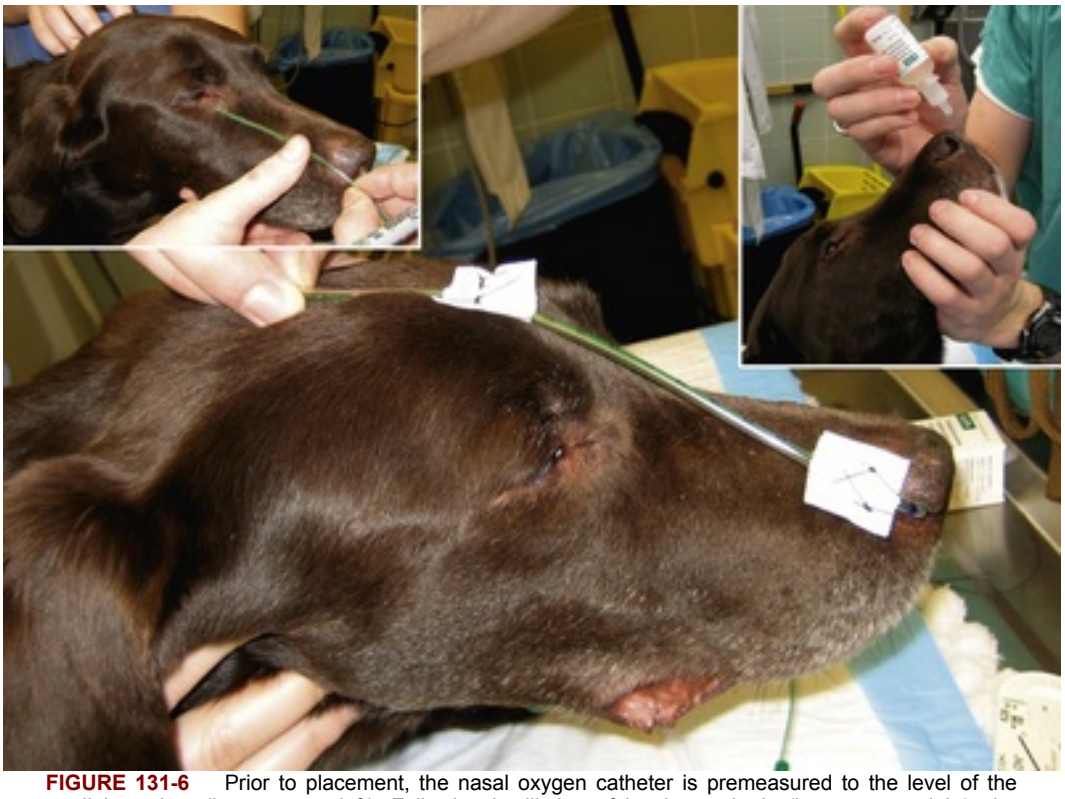


FIGURE 131-6 Prior to placement, the nasal oxygen catheter is premeasured to the level of the medial canthus (inset, upper left). Following instillation of local anesthetic (inset, upper right), the catheter is guided into the ventral meatus to the premeasured length. It is then secured with sutures, staples, and/or suitable adhesive.

Transtracheal Oxygen

Transtracheal oxygen delivery requires the placement of a catheter into the trachea. A humidified oxygen source is then connected directly to the catheter and flow rates of 50 to 200 mL/kg/min used. Transtracheal oxygen therapy will provide a higher F_IO_2 for the same oxygen flow rate compared to nasal oxygen administration. A flow rate of 50 mL/kg/min is reported to provide an F_IO_2 of 40% to 60%.[7] A transtracheal catheter can be placed percutaneously or via a keyhole incision in the trachea. Both techniques require some operator skill, and strict aseptic technique is required. This technique can be useful for the mobile animal and those intolerant of other oxygen administration methods. It also could be indicated when other less invasive methods of oxygen administration have not been successful. The placement of a transtracheal catheter requires animal restraint and/or general anesthesia, which may be contraindicated in an animal with respiratory distress. This technique also can be utilized as a short-term life-saving procedure in pets with a complete upper airway obstruction, and oxygen can be administered through a tracheostomy tube. Aggressive gas flow rates in this setting should be avoided to prevent barotrauma.

Positive Pressure Ventilation

When hypoxemia cannot be corrected with oxygen therapy, or if a patient requires an F_IO_2 >60% for long periods of time (24 to 48 hours), endotracheal intubation and positive pressure ventilation, ideally with a mechanical ventilator, is indicated. Positive pressure ventilation often will allow correction of hypoxemia at a lower F_IO_2.

Humidification

Inspired gases are normally humidified by the upper airways. The delivery of dry gas to the nose, trachea, or lower airways can cause irritation, inflammation, and thickening of airway secretions. For this reason any oxygen administration method that delivers high gas flows intranasally or intratracheally should use

humidified gas.[8] This is especially important if oxygen therapy is provided for more than a few hours. Humidification is most simply achieved by use of a bubble humidifier, filled with sterile water, and attached to the oxygen source (E-Figure 131-7). The entire unit can be sterilized between patients. Intubated patients on mechanical ventilation need humidification by either a passive heat-moisture exchanger or an active heated humidifier.

E-FIGURE 131-7 A bubble humidifier attached to the oxygen regulator. The black hose is the oxygen tubing to the patient. This is a simple and effective method of humidification of oxygen.

High-Flow Oxygen Therapy

High-flow oxygen therapy (HFOT) is a newer approach to nasal oxygen therapy that requires a specialized machine that provides heated humidified gas at high flow rates. This technique increases the patient's F_IO_2 (most machines allow the operator to adjust the amount of oxygen in the delivered gas so F_IO_2 can be manipulated). In addition, the high flow rates will increase the pressure in the upper airways, a form of continuous positive airway pressure (CPAP). The heated, humidified gas increases patient comfort and acceptance of the high flow rates. It is used in human patients as an alternative to noninvasive ventilation, usually with flow rates ranging from 40 to 60 L/min.[9] These high flow rates are needed to increase airway pressure enough to gain benefit from the CPAP effects. A small pilot study of sedated normal dogs reported a significantly higher PaO_2 in the animals receiving HFOT at 20 to 30 L/min compared to traditional nasal oxygen administration.[10] Veterinary patients may be less tolerant of HFOT without sedation and it is unknown if the higher flow rates of 40 to 60 L/min would be feasible in small animal patients. Gastric distension is a potential concern with this technique. One of six dogs in the pilot study developed gastric distension with relatively low flow rates of HFOT.

Monitoring

Patient monitoring is essential to determine when oxygen therapy is indicated, to ensure that sufficient oxygen supplementation is provided, and to avoid excessive oxygen supplementation. The first priority of oxygen administration should be the resolution of life-threatening hypoxemia, improvement of oxygen delivery and the relief of respiratory distress. As effective monitoring often is impossible during acute respiratory compromise, high F_IO_2 levels should initially be used.

Monitoring of pets receiving oxygen therapy includes physical examination, arterial blood gases, and/or pulse oximetry. Respiratory rate and effort, heart rate, and anxiety levels are usually easily evaluated and can be useful in assessing response to oxygen therapy.

Arterial blood gas analysis includes measurement of the PaO_2 and is the gold standard for evaluation of arterial oxygenation. Assessment of arterial blood gases requires an arterial blood sample and a blood gas analyzer. The normal or "expected" PaO_2 is dependent on the F_IO_2 and the barometric pressure. A useful rule of thumb is that the normal PaO_2 in a patient at sea level is approximately 5 times the F_IO_2 measured in percent. For example, for a patient breathing room air (21% oxygen) at sea level, the normal PaO_2 is approximately 100 mm Hg while the normal PaO_2 with an F_IO_2 of 100% at sea level is approximately 500 mm Hg. The expected PaO_2 for a given F_IO_2 when at a high altitude is lower due to the decrease in barometric pressure. As previously mentioned, the goal of oxygen therapy is to maintain a PaO_2 of 80 to 120 mm Hg. If the PaO_2 is <70 to 80 mm Hg, the F_IO_2 should be increased; if the PaO_2 is >120 to 150 mm Hg, the F_IO_2 should be decreased. The exact range of PaO_2 targeted with oxygen therapy will depend on the clinical scenario and the accuracy and frequency of monitoring. Reevaluation of oxygenation status following any change in F_IO_2 is always important.

In the absence of arterial blood gas analysis, pulse oximetry can be utilized. Pulse oximetry evaluates the arterial saturation of hemoglobin with oxygen (SpO_2). Hemoglobin saturation is determined by the PaO_2, and this relationship is defined by the oxygen-hemoglobin dissociation curve. A PaO_2 of 80 mm Hg correlates to an SpO_2 of approximately 95%, while a PaO_2 of 60 mm Hg correlates to an SpO_2 of approximately 90%. Consequently the aim of oxygen therapy is to maintain an SpO_2 >90% and where possible >95%. When the SpO_2 is 99% to 100% consistently, the F_IO_2 should be gradually decreased until the F_IO_2 at which the SpO_2 decreases is identified. The F_IO_2 should then be set at or just above this point in an attempt to avoid the use of unnecessarily high F_IO_2.

Oxygen Toxicosis and Guidelines for Oxygen Administration

Intensive oxygen therapy places patients at risk of oxygen toxicosis. Oxygen toxicosis is associated with pulmonary dysfunction and failure; the associated damage often is severe and irreversible. Oxygen toxicosis is thought to occur as a result of lipid peroxidation, increased endothelial permeability and leukocyte infiltration into the lung. Blindness also has been reported as a consequence of oxygen toxicosis in people, especially neonates.

Oxygen toxicosis is a function of the F_IO_2 administered and the duration of oxygen exposure. The general recommendation for dogs and cats is to avoid the administration of 100% oxygen for longer than 12 to 24 hours and in situations of long-term oxygen therapy the F_IO_2 should be maintained at <60%.[11,12] In addition, there is no way to predict an individual animal's susceptibility to oxygen intoxication. This leads to the recommendation that the F_IO_2 should always be titrated to the lowest level a patient can tolerate.[12]

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CHAPTER 132

Sepsis and the Systemic Inflammatory Response Syndrome

Amy E. DeClue

The systemic inflammatory response syndrome (SIRS) refers to the clinical manifestations of a complex physiologic response to a nonspecific insult of either infectious or noninfectious origin. Heart rate, respiratory rate, body temperature, and white blood cell count are the clinical criteria used for categorizing patients with SIRS in veterinary medicine (Table 132-1), though these criteria have neither ideal sensitivity nor ideal specificity. These criteria have been used for determining the severity of illness and prognosis in critically ill animals. In one study of 500 dogs, mortality was significantly associated with the number SIRS criteria fulfilled.[1] Terminology used for describing the severity of sepsis and SIRS is listed in Box 132-1.[2]

TABLE 132-1

SIRS Criteria in Dogs and Cats

SIRS CRITERIA	DOG	CAT
Body temperature	>102.6° F (39.2° C) or <99° F (37.2° C)	>103.5° F (39.7° C) or <100° F (37.8° C)
Heart rate (beats/min)	>140	>225 or <140
Respiratory rate (breaths/min)	>40	>40
White blood cell count	>19,500/mcL or <5,000/mcL or >5% bands	>19,500/mcL or <5,000/mcL or >5% bands

Box 132-1

Definitions Pertaining to Sepsis and SIRS[2]

Bacteremia—the presence of viable bacteria in the blood stream.

Systemic inflammatory response syndrome (SIRS)—a clinical syndrome caused by systemic inflammation of infectious (i.e., sepsis) or noninfectious origin. In dogs, the diagnosis of SIRS is based on fulfillment of at least 2 of 4 criteria: tachycardia, tachypnea, hypo- or hyperthermia, and either leukocytosis, leukopenia or >5% bands.

Sepsis—1. systemic inflammatory response to infection or 2. life-threatening organ dysfunction caused by a dysregulated host response to infection.

Severe sepsis—this terminology has fallen out of favor and is generally not used.

Septic shock—1. the systemic inflammatory response to infection with hypotension despite adequate fluid resuscitation along with the manifestations of hypoperfusion or 2. subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Generally, this is sepsis with either persisting hypotension requiring vasopressors to maintain a MAP ≥65 mm Hg or a serum lactate >2 mmol/L despite adequate volume resuscitation in people.

Multiple organ dysfunction syndrome (MODS)—altered function of 2 or more organs secondary to SIRS such that homeostasis cannot be maintained without intervention.

Acute respiratory distress syndrome (ARDS)—a pulmonary inflammatory disorder characterized by noncardiogenic pulmonary edema, neutrophilic inflammation and hypoxemia.

Data from Singer M, Deutschman CS, Seymour CW, et al: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 315(8):801-810, 2016.

In dogs and cats, Gram-negative bacterial infections are the most common cause of sepsis, with *E. coli* being the most common isolate.[3-12] However, any organism (e.g., fungus, parasite, virus, protozoan) could result in sepsis. Sepsis most commonly originates from the abdomen, followed by the respiratory tract in dogs,[3,4] and in cats, sepsis commonly is associated with septic peritonitis, pyothorax, and hepatic abscessation (Figure 132-1).[8-13]

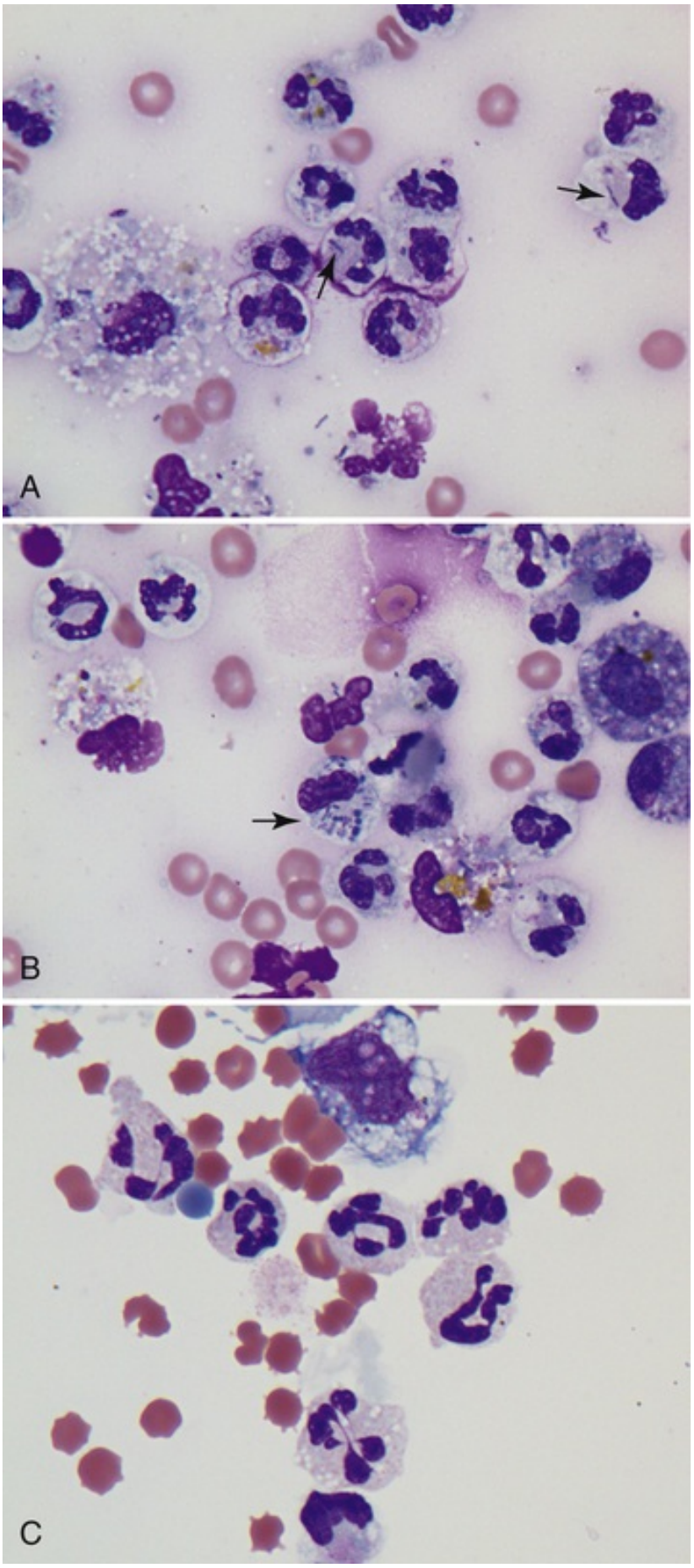
A
B
C

FIGURE 132-1 Photomicrographs of peritoneal fluid from a dog with bacterial peritonitis **(A** and **B)** and with sterile peritonitis **(C).** Suppurative inflammation is noted in all photos. Note the many intracellular bacteria (arrows) in the septic exudate **(A** and **B)** but not in the sterile exudate **(C).** (Photos courtesy Dr. Linda Berent from the University of Missouri.)

Pathogenesis

Sepsis is a complex, variable, and prolonged host response that is triggered by infection. Both pro- and anti-inflammatory responses are involved and, based on the type of response, can result in inflammation and tissue damage, immunosuppression and infection, or recovery. The manifestations of sepsis vary based on both pathogen and host factors. Pathogen factors include the type of pathogen, load, virulence, and site of inoculation, while host factors include genetic factors, anatomic regions of infection, and comorbid diseases. Sepsis is not simply the induction of inflammation, but rather it is induction of an imbalance in the immune system such that physiologic homeostasis can no longer be maintained.

Classically, sepsis has been considered an imbalance between hyper-inflammatory and hypo-inflammatory responses.[14] The hyper-inflammatory response largely has been blamed for the morbidity and mortality associated with sepsis. The hyper-inflammatory response is observed in the beginning of sepsis and is characterized by activation of the innate immune system and production of a cytokine storm. This leads to leukocyte recruitment and the classic manifestations of sepsis. Billions of dollars and many years have been spent trying to identify treatments to dampen the hyper-inflammatory response during sepsis. Little attention was previously given to the hypo-inflammatory response, also known as the compensatory anti-inflammatory response syndrome (CARS). Increasingly, the importance of the anti-inflammatory aspects of the immune response to sepsis-induced morbidity and mortality has been realized.[15]

The innate immune system is predominately responsible for the initial manifestations of sepsis and is primarily activated by danger associated molecular patterns (DAMPs). DAMPs include highly conserved molecules found in or on pathogens. These molecules are referred to as pathogen associated molecular patterns (PAMPs). The innate immune system recognizes PAMPs using pattern-recognition receptors including Toll-like receptors, C-type lectin receptors, retinoic acid inducible gene 1-like receptors, and nucleotide-binding oligomerization domain-like receptors. A second class of DAMPs involved in sepsis come from the host. Tissue damage leads to release of damage-associated molecular patterns or alarmins such as high-mobility group protein B1, S100 proteins, RNA, DNA, and histones.

In the initial phases of an infection, PAMPs (e.g., endotoxin from Gram-negative bacteria; exotoxins, peptidoglycans, and superantigens from Gram-positive bacteria; and fungal cell wall material) induce systemic inflammation initially through activation of local innate immune cells (Figure 132-2). For example, during Gram-negative sepsis, lipopolysaccharide (LPS), the glycolipid component of the cell wall of Gram-negative bacteria, is released. The lipid A portion of LPS binds to LPS binding protein. LPS is recognized via macrophage cell surface receptors like CD14. The main function of CD14 is to transfer LPS to Toll-like receptor (TLR)-4 and MD-2 for subsequent cellular activation. Once LPS binds to these cell surface receptors, the macrophage becomes activated. Activation of inflammatory cells results in the production of multiple inflammatory mediators that have been implicated in the induction and maintenance of sepsis.

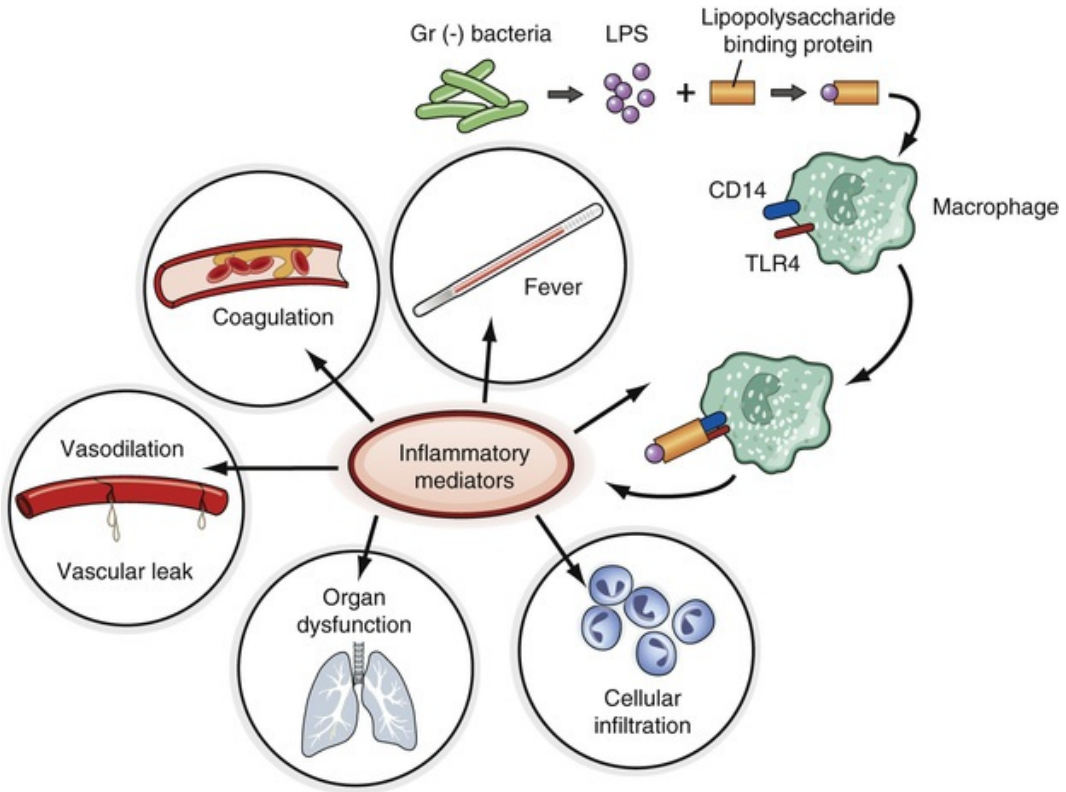

FIGURE 132-2 Pathophysiology of Gram-negative sepsis.

There are many inflammatory mediators involved with sepsis and SIRS. Tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, nitric oxide, and leukotrienes are examples of important mediators contributing to the process of sepsis in dogs and cats.[16-22] Production of these inflammatory mediators results in activation of vascular endothelial cells and upregulation of adhesion molecules. These inflammatory messages enter into the local milieu and then into the systemic circulation. Neutrophils, monocytes, and lymphocytes travel to the site of infection based on these inflammatory mediator signals, secrete a second wave of inflammatory mediators, and provide killing mechanisms for microorganism clearance. Neutrophils also release neutrophil extracellular traps that consist of filamentous DNA containing histones and granular proteins. Neutrophil extracellular traps have beneficial effects such as enhanced bacterial killing but they also interact with the coagulation system and may promote thrombosis. The transition from a localized infection/ inflammatory focus to sepsis is dependent on the systemic circulation of inflammatory messages and activation of immune cells distant to the initial source of infection.

The adaptive immune system is involved in the pathogenesis of sepsis. Antigen presenting cells that have ingested a pathogen activate the adaptive immune response. Subsequently, naïve T cells proliferate and effector cells are generated. Early in the course of sepsis, naïve T cells differentiate into Th1 cells and Th17 cells, which produce additional cytokines such as TNF, IL-2, IL-12, interferon (IFN)-gamma, and leukotrienes or IL-17A, respectively, which typically drives a pro-inflammatory phenotype. Conversely, an anti-inflammatory phenotype is observed when there is a Th2 response, in part due to production of cytokines such as IL-4, IL-5, IL-9, IL-10 and IL-13. The balance between the Th1/Th17 and Th2 response contributes to the clinical manifestations of a pro-inflammatory shift, anti-inflammatory shift, or recovery.

The compensatory anti-inflammatory response syndrome (CARS) is characterized by varying immunoparalysis or relative lack of immune response to infection.[15,23,24] Immunoparalysis is the result of a loss of lymphocytes, dendritic cells, endothelial cells, gastrointestinal (GI) epithelial cells, and thymocytes. The predominant mechanism for this loss is apoptosis.[25] During the hyper-inflammatory response, activation of inflammatory cells leads to nuclear translocation of NF-kappa-B and IL-1beta activation, both of which induce apoptosis of adaptive immune cells. People with sepsis have depletion of CD4+ and CD8+ T cells, B cells, and dendritic cells.[23] The anti-inflammatory cytokine IL-10 is produced in abundance, leading to suppressed CD8+ T cell function and reduced monocytic production of pro-inflammatory cytokines. A reduction in cytokine production by, and expression of, inhibitory receptors on T cells also is observed during

immunoparalysis. There is an increase in T regulatory cells and myeloid-derived suppressor cells, which contributes to immune cell quiescence.[23] The neuro-inflammatory reflex leads to norepinephrine release in the spleen and production of acetylcholine by CD4+ T cells, which in turn targets alpha-7 cholinergic receptors on macrophages, suppressing cytokine production. There is a reduction in HLA-DR expression by myeloid cells, which results in a reduction of antigen presentation. Clinically, immunoparalysis leads to an inability to fight and eliminate infection, and the development of new infections from opportunistic or otherwise normally weakly virulent organisms.[25] Reactivation of latent viruses is another possible sequela.

The classical pathophysiologic model of sepsis is a systematic progression through a hyper-inflammatory phase followed by resolution during the hypo-inflammatory phase.[23] However, this paradigm has changed. It is now recognized that sepsis is a continuum, where the animal may vacillate between hyper- and hypo-inflammatory states and that the hypo-inflammatory state itself plays a role in morbidity and mortality.[23,24] Therefore, animals with sepsis can have a pro-inflammatory shift or an anti-inflammatory shift. Ultimately, the unchecked pro-inflammatory cascade leads to inflammatory cell infiltration, altered thermoregulation, vasodilation, vascular leakage, activation of coagulation, hemodynamic instability, and multiple organ failure. Conversely, animals that have an anti-inflammatory shift develop opportunistic infections that could also result in death.[25]

Clinical Aspects

Clinically, dogs can have either a hyperdynamic or hypodynamic response during sepsis. The hyperdynamic response is characterized by fever, brick red mucous membranes, tachycardia, and bounding pulses. As the disease process progresses, a hypodynamic response characterized by hypotension, pale mucous membranes, and hypothermia can be observed. Often, dogs will have GI or respiratory signs associated with endotoxemia. Hyper- or hypoglycemia, hypoalbuminemia, azotemia, hyperbilirubinemia, and increased alanine aminotransferase and/or alkaline phosphatase concentrations, leukocytosis, neutrophilia with a left shift or leukopenia, anemia, and thrombocytopenia are clinicopathologic abnormalities that have been recognized during sepsis. Evidence of coagulopathy, including decreased protein C and antithrombin concentrations, prolonged prothrombin time and partial thromboplastin time, and increased D-dimer concentrations, has been documented in dogs with naturally acquired sepsis.[3,26] Many dogs with sepsis have myocardial dysfunction and vasodilation, leading to hypotension. Poor perfusion, tissue hypoxia, and cellular metabolic derangements can lead to metabolic acidosis (see ch. 128).

Cats with sepsis can develop clinical signs and clinicopathologic abnormalities that are similar to those of dogs during sepsis with a few exceptions. Bradycardia, hypothermia, and signs of abdominal pain are frequent, unique findings in cats with sepsis.[6,11,13] Cats also appear to develop septic shock more readily than dogs do, and typically the hyperdynamic phase is not recognized during feline sepsis. The mechanisms by which these characteristic manifestations develop are unknown.

Sepsis commonly results in multiple organ dysfunction syndrome (MODS) in humans. Pathogenesis of organ failure (e.g., kidney injury) during MODS is multifactorial but centers around the development of mitochondrial dysfunction. Circulatory collapse, microcirculatory changes, hypoxemia, and inflammation lead to tissue ischemia, reduced mitochondrial function, and thus reduced cellular energy production.[27] The current definition of MODS in dogs is ≥2 forms of organ dysfunction (Table 132-2) in an animal with appropriate risk factors although the criteria to define individual forms of organ dysfunction vary and are at times conflicting.[27,28] The incidence of sepsis-induced MODS is not known in dogs or cats with sepsis although cardiovascular, GI, hepatic, renal, endocrine and respiratory dysfunction/failure have been recognized.[29-34]

TABLE 132-2

Definitions of Organ Dysfunction in Dogs

ORGAN SYSTEM	CRITERIA
Renal	An increase in creatinine concentration ≥0.5 mg/dL from presurgical values without evidence of pre- or postrenal azotemia

Cardiovascular	Hypotension sufficiently severe to require vasopressor therapy
Respiratory	Need for supplemental oxygen administration or mechanical ventilation; determined based on clinical assessment, blood gas analysis (alveolar-arterial gradient >10 mm Hg) and/or results of pulse oximetry (SpO_2 < 95%)
Hepatic	Plasma or serum total bilirubin >0.5 mg/dL
Coagulation	PT or PTT >25% above the upper reference limit and/or platelet count ≤100,000/mcL

Adapted from Kenney EM, Rozanski EA, Rush JE, et al: Association between outcome and organ system dysfunction in dogs with sepsis: 114 cases (2003-2007). *J Am Vet Med Assoc* 236:83-87, 2010.

Diagnosis

A complete patient evaluation including history, physical examination, blood pressure, complete blood count (CBC), serum biochemical profile, urinalysis, blood gas analysis, coagulation profile, and appropriate diagnostic imaging should be performed in any critically ill patient. The diagnosis of sepsis is accomplished by demonstrating evidence of infection and systemic inflammation (i.e., SIRS). Infection can be identified via culture, cytology (see Figure 132-1), histopathology or serology. In patients where bacterial infection is suspected, culture and sensitivity should always be performed so that antibiotic selection can be tailored to the particular organism. Based on clinical findings, specimens should be collected from blood, urine, wound exudate, peritoneal fluid, bronchoalveolar lavage fluid and synovial fluid prior to antibiotic administration. For patients with suspected bacterial peritonitis, a peritoneal fluid glucose concentration that is at least 20 mg/dL lower than a blood glucose concentration measured concurrently is diagnostic for septic peritoneal effusion.[5] In some cases, identification of infection is difficult and/or delayed, and a presumptive diagnosis of infection based on the clinical picture will be necessary. However, care should be taken to consider noninfectious differentials for SIRS when appropriate (e.g., acute pancreatitis, autoimmune disease, and envenomation).

Treatment

The severity of sepsis varies from patient to patient. Some patients will require advanced life support measures to survive while others will require only general supportive care. The key aspects of sepsis treatment include (1) initial hemodynamic stabilization, (2) alleviating the inciting cause and (3) intensive supportive care. The treatment of sepsis can be organized roughly into initial resuscitation (i.e., first 1-6 hours) and long-term management (i.e., >6 hours until discharge from the hospital). Initial resuscitation includes not only restoration of hemodynamic homeostasis, but also alleviating the inciting cause through administration of antimicrobial drugs and/or debridement. Recently, the concept of early goal-directed therapy has become more prevalent in human medicine. Goal-directed therapy is based on the idea of tailoring treatment to specific physiologic parameters thought to be associated with restoration of homeostasis and improved outcome.

Initial Resuscitation: Restoration of Hemodynamic Stability

Initial hemodynamic resuscitation of animals with sepsis is important for restoration of homeostasis. While there are no generally accepted, standardized initial resuscitation protocols for animals, guidelines have been established for people. These guidelines are outlined in the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock.[35] The authors recommended protocolized, quantitative resuscitation (i.e., goal-directed therapy) of patients with sepsis-induced tissue hypoperfusion. The purpose of early goal-directed therapy in people is to achieve each of the following goals during the first 6 hours of intervention: (1) central venous pressure = 8-12 mm Hg, (2) mean arterial pressure ≥65 mm Hg, (3) urine output ≥0.5 mL/kg/h, (4) superior vena cava oxygenation saturation ≥70% or mixed venous oxygen saturation ≥65%, (5) resuscitation that is targeted to normalize lactate in patients with increased blood lactate concentrations.[35] While these goals have not been specifically tested in randomized, multicenter trials in animals, the general concepts behind the goals could have value in veterinary patients if tailored to the unique physiologic parameters of the species.

Achieving hemodynamic support goals can be accomplished using boluses of isotonic crystalloids or colloids (see ch. 129). Then, ongoing fluid therapy should be tailored to the needs of the patient to provide for maintenance requirements, correct interstitial hydration deficits, replace ongoing losses, and continue to

correct any hemodynamic derangements. Animals with sepsis will have a propensity to develop interstitial edema, including subcutaneous and pulmonary edema, because of increased vascular permeability and decreased blood colloid osmotic pressure. Administration of colloid fluids (e.g., hydroxyethyl starch) may help prevent interstitial edema and should be considered for volume resuscitation and during maintenance of sepsis patients, in addition to crystalloid fluid support. In several clinical trials in people with sepsis, hydroxyethyl starch has increased the risk of acute kidney injury and mortality. However, in goats with experimental endotoxemia, hydroxyethyl starch did not alter creatinine clearance or ultrastructural tubular integrity, indicating that there might be species variation in patients' responses to colloids.[37] No prospective evidence supporting or refuting this phenomenon is available in dogs and cats with sepsis at this time. However, in a retrospective study, critically ill dogs receiving hydroyxethyl starch did not have significantly increased blood creatinine or incidence of acute kidney injury compared to dogs receiving crystalloid fluids for up to 90 days post treatment.[53] Additionally, there are readily available, affordable, and safe alternative colloids (e.g., human albumin) that are used in people, but such alternatives (e.g., fresh frozen plasma), when used in appropriate quantities, might not be as effective at rapid volume expansion, can be cost-prohibitive in dogs and cats, and could be associated with additional risks (e.g., transfusion reaction, disorders of coagulation, transmission of infectious disease). Thus, while the judicious use of hydroxyethyl starch should be considered, the possible risk of kidney injury should not impede its use in animals requiring colloid oncotic pressure support. Additionally, the use of 0.9% NaCl has fallen out of favor in people with sepsis because of the amount of chloride in the solution (Table 132-3). Administration of a chloride-rich solution induces shock in animal models, promotes metabolic acidemia, induces a pro-inflammatory shift, reduces renal perfusion, increases the risk of acute kidney injury in people with sepsis, and increases mortality in adult and pediatric human patients with sepsis.[38] In dogs, administration of 0.9% saline reduces renal blood flow and glomerular filtration rate.[39] For these reasons, the use of a balanced electrolyte solution like Plasmalyte is recommended.

TABLE 132-3

Composition of Common Crystalloid Fluids and Plasma

FLUID	Na (mEq/L)	Cl (mEq/L)	pH	BUFFER
0.9% NaCl	154	154	5.6	None
Lactated Ringer's solution	130	109	6.6	Lactate
Normosol R	140	98	6.6	Acetate/gluconate
Normosol M	40	40	5.0	Acetate
Plasmalyte-148	140	98	7.4	Acetate/gluconate
Plasma	140	100	7.4	Bicarbonate

Despite aggressive volume resuscitation, some patients will require additional support to maintain normal blood pressure and perfusion. The most efficacious, safest treatment for septic shock has not been determined in dogs or cats. Prior to administration of any sympathomimetic drug, care should be taken to ensure that the patient is not hypovolemic. Since the goal of treating septic shock is to maintain tissue perfusion, medications that cause vasoconstriction should be used only if necessary. Positive inotropic drugs (e.g., dobutamine) can be a good initial management choice for septic shock since they help combat decreased cardiac output caused by myocardial dysfunction without inducing peripheral vasoconstriction. If volume resuscitation and positive inotropic support have failed to restore blood pressure, a vasopressor agent (e.g., dopamine, norepinephrine, epinephrine, or vasopressin) could be added. Although there are no clinical trials evaluating these drugs for the treatment of naturally-occurring sepsis, epinephrine was found to adversely affect organ function, systemic perfusion, and survival compared to the use of norepinephrine or vasopressin[40] and had detrimental effects on gastric mucosal pH and plasma lactate concentrations compared to dobutamine and norepinephrine[41] in experimental canine sepsis. Relative adrenal insufficiency has been documented in dogs with sepsis and refractory hypotension[32] and should be considered in any dog or cat requiring vasopressor therapy during sepsis (see ch. 133).

Initial Resuscitation: Alleviate the Cause

A key aspect of treating sepsis centers on the identification and eradication of the inciting cause. Shock is a primary contributor to morbidity and mortality during sepsis (see ch. 127). Since the pathogen is the driving force for immunostimulation, physiologic response, and shock, eradication of the pathogen should downregulate these responses.[42] Therefore, clinicians should consider how to improve the rapidity of pathogen clearance. Optimizing pathogen clearance involves early administration of appropriate antimicrobials and source control when indicated (E-Table 132-4).[42]

E-TABLE 132-4

Factors to Consider When Administering Antimicrobials to Optimize Pathogen Clearance during Sepsis

GOALS	CONSIDERATIONS
Early administration	Administration within 30-60 minutes of presentation or of identification of sepsis
Maximizing antimicrobial potency	Maximize bioavailability (IV administration)
	Maximize the speed at which the antimicrobial becomes bioavailable
	Consider loading doses for some antimicrobials
	Use -cidal antimicrobials when possible
	Apply pharmacokinetic principles to maximize potency; time- vs. concentration-dependency
	Consider combining multiple antimicrobials with different mechanisms of action
	Provide broad-spectrum coverage
	Consider antibiotic penetration into the infection microenvironment and anatomic location; community- vs. hospital-acquired infection
Pathogen removal/reduction in pathogen exposure	Source control via surgical debridement

Adapted from Kumar A: An alternate pathophysiologic paradigm of sepsis and septic shock: implications for optimizing antimicrobial therapy. *Virulence* 5:80-97, 2014.

Although stringent efforts should be made to identify the cause of sepsis, early antimicrobial treatment is critical for survival and should not be withheld pending culture results in a patient showing clinical features consistent with sepsis. Broad-spectrum, bactericidal antimicrobial agents (e.g., fluoroquinolone + penicillin) administered IV should be instituted as quickly as possible, ideally within the first 30-60 minutes. Antibiotic therapy should be selected based on the most likely type of organism given the site of infection. Depending on the source of infection, surgical debridement may be necessary for infection control. Once culture-specific antibiotic sensitivity is determined, the antibiotic with the narrowest spectrum of activity should be chosen and administered until there is complete clinical resolution. The remainder of therapy centers on maintenance of tissue perfusion, management of organ failure, and intensive supportive care (Figure 132-3).

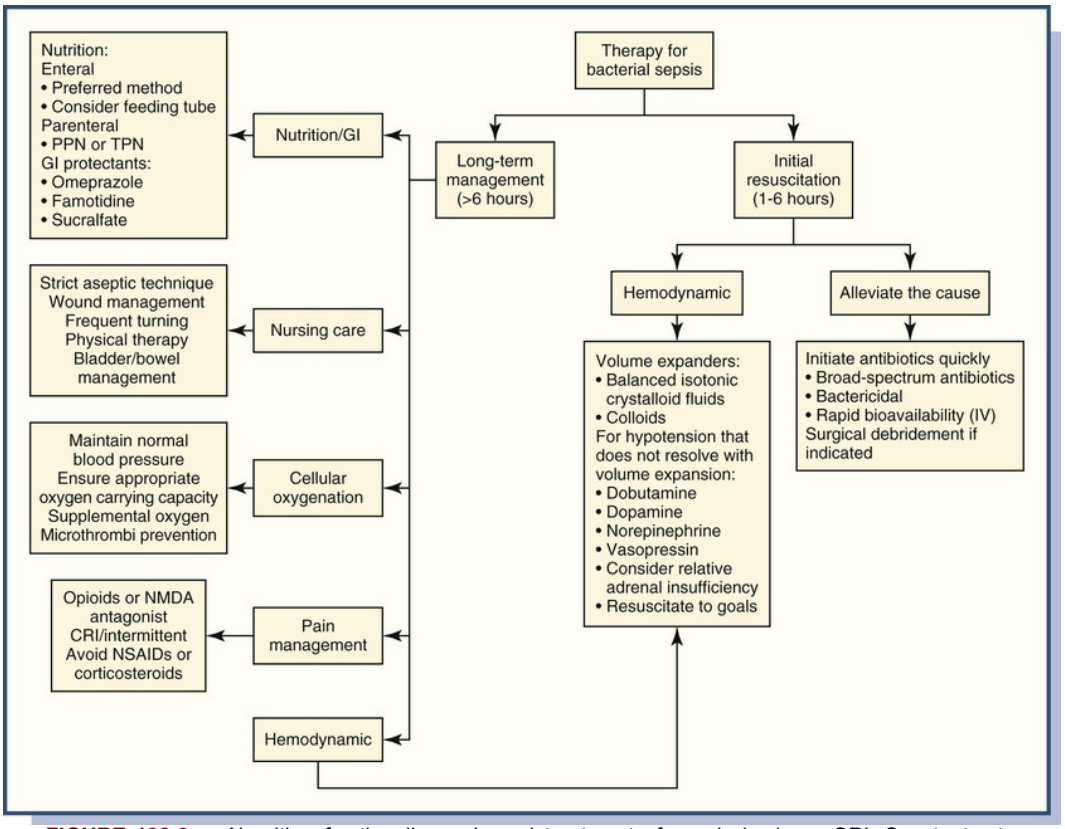

FIGURE 132-3 Algorithm for the diagnosis and treatment of sepsis in dogs. *CRI*, Constant rate infusion; *GI*, gastrointestinal; *NMDA*, N-methyl d-aspartate; *NSAID*, nonsteroidal anti-inflammatory drug; *PPN*, partial parenteral nutrition; *TPN*, total parenteral nutrition.

Long-Term Management: Supportive Care

Bacterial translocation from the GI tract can contribute to systemic inflammation during sepsis. Early placement of a feeding tube (see ch. 82) and initiation of enteral or, in patients with vomiting, parenteral nutrition will help maintain GI barrier function (see ch. 189). Additionally, medication aimed at maintaining normal GI protective mechanisms (e.g., omeprazole, famotidine, sucralfate) could be considered. Hyperglycemia can be a complication of nutritional therapy, especially parenteral nutrition. Hyperglycemia has been associated with increased inflammation and a poorer prognosis in people with sepsis and SIRS. Although the importance of glucose homeostasis in cats with sepsis is unknown, iatrogenic hyperglycemia should be avoided.

Oxygenation, acid-base status, packed-cell volume or hemoglobin concentration, and organ function should be closely monitored. Along with maintaining good tissue perfusion, maximizing cellular oxygenation will help maintain tissue viability and avoid multiple organ dysfunction. This can be accomplished by ensuring good oxygen carrying capacity, providing supplemental oxygen when indicated (see ch. 131), and preventing microthrombi formation (see ch. 197 and 256). For the majority of patients with sepsis, acid-base abnormalities are related to lactic acidosis secondary to poor tissue perfusion (see ch. 128). Typically these abnormalities will resolve with resolution of hypotension and normalization of perfusion (see ch. 129). Therefore, bicarbonate administration rarely is needed and in fact might be contraindicated. When organ dysfunction is recognized, specific therapy aimed at maintaining homeostasis should be considered. In some cases, peritoneal or hemodialysis (see ch. 109 and 110), plasma or blood transfusion (see ch. 130), positive inotropic agents (see ch. 159) and mechanical ventilation (see ch. 139) could be necessary.

Finally, care should be taken to ensure adequate patient comfort including management of pain (see ch. 126), careful catheter maintenance (see ch. 106), bladder/bowel care, and frequent patient turning/movement to prevent decubital ulcers. Almost all patients with sepsis will require analgesic administration for pain management. Although many analgesics like ketamine[43] and buprenorphine[44] can offer specific anti-inflammatory advantages during endotoxemia, some might be detrimental. Morphine, for instance, augments the inflammatory response to endotoxin, has a detrimental effect on mean arterial pressure, and increases

mortality in endotoxemic rats.[44,45] It is not known if morphine is detrimental during canine or feline sepsis.

Sepsis is a systemic inflammatory disease, so it is logical that strategies aimed at immunomodulation or altering the consequences of inflammation have been proposed as novel therapies for sepsis. Many anti-inflammatory therapies have been evaluated in human clinical trials with little success. For example, despite their strong anti-inflammatory properties, the use of corticosteroids for the treatment of sepsis has fallen out of favor due to their lack of efficacy combined with their immunosuppressive, GI ulcerogenic, and prothrombotic effects.[46,47] One exception could be the use of low or physiologic dosages of corticosteroids for management of relative adrenal insufficiency during sepsis (see ch. 133).[48] Although relative adrenal insufficiency is recognized in dogs with sepsis, the administration of corticosteroids in this subset of patients has not been studied.[32]

The only anti-inflammatory therapy with some positive benefit that has been tested in canine clinical trials is polymyxin E. Polymyxin E binds to endotoxin from Gram-negative bacteria, preventing the interaction between endotoxin and the immune system. In a placebo-controlled clinical trial, dogs with parvoviral enteritis that were treated with polymyxin E (12,500 IU/kg, IM q 12 h) had significantly improved hydration, capillary refill time, pulse quality, and lower plasma TNF concentrations than did the control group.[49] Possible adverse events associated with polymyxin E include neurotoxicosis, nephrotoxicosis, respiratory arrest, cardiovascular dysfunction and histamine-mediated hypersensitivity. However, the adverse effects of polymyxin are dosage-dependent; thus, the use of low-dosage (1-2 mg/kg) polymyxin, which maintains considerable anti-endotoxin activity yet avoids adverse effects, has been advocated. Although our experience in dogs is limited, and the adverse effects should be carefully considered, polymyxin E could be a potential treatment for Gram-negative sepsis in dogs, and further study is warranted. Newer immunomodulatory therapies including immunostimulants are being evaluated in experimental models and human clinical trials and could be options for management of sepsis in animals in the future.

Prognosis

Mortality rates for dogs and cats with sepsis range from 48-79% despite comprehensive management.[11,26,32,50-52] In the dog, multiple organ dysfunction and ionized hypocalcemia and, in the cat, persistent ionized hypocalcemia, are associated with a poorer outcome. As our understanding of sepsis grows, new therapies aimed at more effective supportive care and restoring a normal pro- and anti-inflammatory balance could help decrease morbidity and mortality.

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CHAPTER 133

The Endocrine Response to Critical Illness

Johan P. Schoeman

Overview

Investigations into the endocrine alterations that accompany critical illness have led to identification of endocrine biomarkers of severity, predictors of mortality and harbingers of recovery.[1-13] Critical illness, caused by any of a plethora of disparate conditions, can result in activation of adrenal gland glucocorticoid (GC) and catecholamine synthesis, which are fundamental components of the stress response and essential for survival.[14] The magnitude of response is dependent on, *inter alia,* marked individual variation, gender differences, stages of illness, severity, degree of systemic inflammatory response, sepsis or septic shock.[15-19] Further, the conditions accompanying critical illness, i.e., hyper- or hypoglycemia, hypotension and pain, together with any pre-admission treatment or use of endocrine response-modifying medications, also influence endocrine responses at the various stages of critical illness.[20,21] The focus of this chapter is a review of endocrine alterations in response to severe homeostasis disruption. It will cover the hypothalamic-pituitary-adrenal (HPA) axis, the hypothalamic-pituitary-thyroidal (HPT) axis, and, in less depth, the somatotropic, lactotropic and gonadal response to critical illness.

Hypothalamic-Pituitary-Adrenal Axis

The HPA axis is generally upregulated through extensive immune-neuroendocrine interactions in response to critical illness. This process culminates in increased serum total and free cortisol concentrations, commensurate with the degree of illness and positively correlated with mortality.[10,22-35] The increases in circulating cortisol concentrations have been attributed to cytokine-CRH mediated adrenocorticotropic hormone (ACTH) secretion (interleukin [IL]-6, IL-1beta and tumor necrosis factor [TNF]-alpha) as well as non-ACTH factors that directly stimulate the adrenals and decrease the rate of cortisol metabolism. Slowing cortisol metabolism significantly prolongs the half-lives of endogenous and exogenous cortisol.[36-40] Adrenal microenvironment and the integrity of the adrenal endothelial vasculature also have roles in these responses.[41,42]

In contrast to these processes, impaired HPA responses have also been demonstrated and attributed to some of the same cytokines.[43-45] These impaired responses have been given several descriptions: adrenal failure/insufficiency (AI) in critical illness, relative adrenal insufficiency (RAI), and critical illness-related corticosteroid insufficiency (CIRCI).[24,31,46-56] Studies have been carried out to characterize and diagnose this ill-defined adrenal dysfunction in critically ill humans,[57] dogs,[49,58,59] mice,[60] and rabbits.[61] The test used most often to diagnose this condition was the ACTH stimulation test.[62] However, results were not consistent, in part because different ACTH preparations, routes of injection, dosages and testing protocols were employed.[63-68] Further, some studies assessed total cortisol, while others assessed "free," "salivary," or interstitial cortisol concentrations.[69-73] The magnitude of the free cortisol response to ACTH was much higher than the total cortisol response, especially if the patient was hypoalbuminemic due to decreases in corticosteroid binding globulin (CBG).[22,74-76] Further, different studies used different criteria to define AI, including basal total cortisol, ACTH-stimulated cortisol, delta cortisol (the ACTH-stimulated minus the basal cortisol), and the cortisol to ACTH ratio.[19,77-79]

For example, one study noted that the incidence of AI varied from 6.25% to 75% depending on which criterion was employed.[19,51,80] Uncertainty regarding the endocrine response to critical illness is due, in part, to current test protocols failing to identify the patients who are GC-deficient at the cellular level. These are the

individuals who should benefit from supplementation with GCs.[19] In this regard, the measurement of nuclear and cytosolic GC receptors may become important biomarkers for diagnosis and treatment of CIRCI.[81,82]

The quest to better understand adrenal dysfunction in critical illness has also led to changed thinking regarding GC therapy. Several studies in adrenalectomized animals demonstrated that the adrenal response was essential for survival.[83-85] In addition, GCs were shown to have physiologically logical ubiquitous effects that could be beneficial for patients in shock: increases in blood glucose concentrations, stabilization of membranes, sensitization of vascular receptors to the vasoconstrictive effects of catecholamines, reducing the overwhelming inflammatory response and other immune-modulating effects.[86-90] However, several meta-analyses demonstrated that the massive GC doses advocated in the 1960s and 1970s worsen prognosis, explaining why this approach was discontinued.[91-94]

Identifying relative forms of adrenal dysfunction in critical illness, in contrast, led to recommendations of low-dose GC usage, an approach further supported with documentation of rather incredulous positive responses in critically ill people in Scotland with extremely low agonal serum cortisol concentrations.[95,96] Another study then documented survival benefits of supplementing both GC and mineralocorticoids in a large French multicenter study.[97] Low-dose GC supplementation in critical illness then became the standard of care and the practice gained momentum in people. Yet, studies from countries in which the adrenal function–modifying sedative etomidate was not used demonstrated much lower incidences of RAI. Then, the confounding effect of this drug on the above studies became known, prompting re-evaluation of low-dose GC use in critical illness, which found no survival benefits.[20,98-106] On the contrary, higher re-infection rates and more side-effects in the GC-treated group were demonstrated. Yet, more rapid shock reversal in GC-treated patients has been consistently shown in this and other studies.[106-109]

Thus, the current consensus is that a vasopressor-resistant hypotensive condition responsive to GCs exists in critical illness. Since this condition can be independent of adrenal dysfunction, ACTH stimulation testing is no longer recommended.[106,110-113] Recent findings further called into question the AI theory, since cortisol responsiveness to ACTH was shown to be normal despite prolonged illness.[114] Additionally, the diminished ACTH concentrations in more prolonged illness are now explained by negative feedback from the elevated cortisol, rather than by pituitary failure.[40] Despite having demonstrated the existence of a GC responsive condition, the issues of GC dosage and for whom it is indicated are still matters of debate.[115-119] A seminal study demonstrated that a portion of the increased GC concentrations in some critically ill patients was a result of decreased GC metabolism, rather than increased synthesis. The result is prolonged GC half-life.[40] Thus, the current hydrocortisone dosage for humans (200 mg/day; 3 mg/kg/day) may be as much as 3 times more than is needed.[40]

While RAI has been demonstrated in septic dogs and another case report, it is not known whether GC supplementation is indicated for such conditions.[49,58,120] Neither is it known which GCs are most efficacious nor their optimal dosing strategy. Results from studies on dogs and extrapolation from the human experience over the past 40 years suggest that GC therapy be reserved for a cohort of hypotensive, septic dogs that do not respond to adequate fluid therapy and vasopressor support. In this scenario, it is recommended that 0.5 mg/kg/day of hydrocortisone be given.

Hypothalamic-Pituitary-Thyroid Axis

In contrast to the HPA axis, the function of the HPT axis is uniformly downregulated during critical illness.[121-127] Longitudinal studies in critically ill humans have shown marked initial reductions in tri-iodothyronine (T_3) and increases in reverse T_3 (rT_3) concentrations in the circulation, within 2 hours of an acute illness. This pattern is the result of altered peripheral conversion of thyroxine (T_4).[128,129] These changes are often accompanied by transient increases in T_4 and thyroid-stimulating hormone (TSH) concentrations. T_4 and TSH concentrations then return to low normal levels, inappropriate for the degree of T_3 suppression and suggesting an altered feedback set point for the HPT axis.[11,130] Conversely, reduced thyroid-releasing hormone (TRH) expression, indicating a central origin to HPT axis dysfunction, has also been demonstrated.[131-134] As illness progresses, the normal nocturnal surge in TSH is abolished and pulsatile TSH release is markedly reduced.[129,135-137] During more prolonged illness, T_4 and TSH concentrations decline while circulating T_3 concentrations are low to undetectable, indicating that central neuroendocrine dysfunction is potentially superimposed upon peripheral adaptations.[138] Low thyroid hormone

concentrations correlate with degree of illness. Thyroid hormone concentrations have been incorporated in endocrine predictive indexes for critically ill humans that have shown similar associations with mortality in critically ill dogs.[10,139-146] Marked reductions in T_3, T_4 and free T_4 concentrations have been documented in dogs with sepsis and free T_4 is less affected by illness than is total T_4 (see ch. 299).[143,144,147]

Pathophysiological studies have demonstrated the role of three deiodinase enzymes (D1, D2 and D3) in these thyroid hormone reductions. For example, reduced D1 and D2 activity cause decreased peripheral conversion of T_4 to T_3, whereas upregulated D3 activity causes T_4 to be converted to rT_3.[148] Similarly, cytokines such as TNF-alpha, IL-1 and IL-6 have been investigated as putative mediators of the low T_3 syndrome.[131,149-151] GCs and dopamine have been implicated in longer-term central HPT axis suppression.[21,152-157] TSH is the first hormone of the HPT axis to rise as the disease process resolves and, in human critical care, is interpreted as a positive prognostic indicator—a sensitive harbinger of recovery.[11-13]

These changes in the thyroid axis seen during acute illness have been interpreted as an adaptation to reduce energy expenditure, similar to those during starvation, and are seen as beneficial, not requiring intervention.[158,159] Nonetheless, clinicians became interested in whether long-term critically ill patients would derive hemodynamic or survival benefit from thyroid hormone supplementation. In this regard, supplementation with T_3 would be preferable, given the decreased peripheral conversion of T_4 in critical illness. However, due to the putative involvement of hypothalamic and pituitary dysfunction in this condition, the use of TRH therapy would be more sensible.[138] Moreover, treatment with hypothalamic-releasing factors allows the body to make use of its feedback systems to ensure optimal levels of circulating and tissue hormones.[138] As a result, several studies using different thyroid hormone preparations have been performed.[160,161] The combined treatment with TRH and growth hormone–releasing peptide (GHRP) has led to normalization of the thyroid axis with concomitant normalization of insulin-like growth factor 1 (IGF-1) levels and a reduction of catabolism markers.[137,162] Certain patients, especially those that had myocardial infarcts or cardiac surgery, seem to derive hemodynamic benefit from thyroid hormone supplementation.[163-165] In contrast, some studies have shown no benefit of thyroid hormone supplementation and others have demonstrated deleterious effects and an increased risk of mortality.[166-170]

There is no indication that thyroid hormone treatment is either beneficial or harmful in critically ill dogs.[171] Accordingly, extrapolation from human studies suggests to refrain from supplementing critically ill dogs with thyroid hormones. If a patient is on prolonged life support, it is indicated to administer both GHRP and TRH.[124]

Somatotropic, Gonadal and Lactotropic Axes

These axes have not been thoroughly investigated in critically ill dogs. Studies on people during the first few hours to days of an acute illness have demonstrated dramatic changes in the growth hormone (GH) profile and a state of peripheral growth hormone resistance, partly triggered by cytokines.[172] Both the amount of circulating GH and its pulse frequency increase, yet levels of insulin-like growth factor 1 (IGF-1) and several IGF-binding proteins decrease.[172,173] This disparate response of the somatotropin axis is appropriate because the direct lipolytic and insulin-antagonizing effects of GH are enhanced, while the IGF-1–mediated effects are attenuated. Resultantly, circulatory glucose and fatty acid levels increase, whereas costly and less vital anabolism, which is largely IGF-1–mediated, is postponed.[174] The relative hyposomatotropism resulting from a lack of pulsatile growth hormone secretion is believed to contribute to the wasting syndrome that characterizes prolonged human critical illness.[175,176]

Regarding the lactotropic axis, pulsatile release of prolactin, which is initially activated in response to disease, becomes impaired in chronic phases of critical illness.[177,178] Similarly, there is evidence for hypogonadotropism and Leydig cell failure, particularly in men with prolonged critical illness, ostensibly due to a hypothalamic-pituitary-gonadal dysfunction.[179-181] Testosterone concentrations become extremely low in the presence of suppressed mean luteinizing hormone (LH) concentrations and pulsatile LH secretion.[180,181] Currently, no consensus has been reached on the value of supplementation with GH, prolactin or testosterone in critical illness.

In conclusion, critical illness is characterized by uniform dysregulation of the hypothalamic-pituitary-peripheral axes, independent of the underlying condition. A clear biphasic pattern is discernable in most axes.

Low peripheral effector hormone levels of T_3, testosterone and IGF-1, despite an active pituitary, typify the acute phase. Herein, the high cortisol levels, in the presence of low ACTH levels, are notable exceptions. Conversely, low peripheral effector hormone levels, coinciding with uniform suppression of the neuroendocrine axes predominantly of hypothalamic origin, are characteristic of the prolonged phase of critical illness.

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CHAPTER 134

Heatstroke

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Client Information Sheet: Heatstroke/Hyperthermia

Hyperthermia is defined as a severe elevation in body temperature that ranges from 40.5° C (104.9° F) to 43° C (109.4° F) after an animal has been exposed to elevated ambient temperature or has performed strenuous activity.[1,2] Pyrogenic hyperthermia is associated with an increase in the hypothalamic thermoregulatory center set point in response to a variety of endogenous or exogenous pyrogens, and in most cases is a normal physiologic process (see ch. 48).[2,3] Nonpyrogenic hyperthermia, however, is abnormal and results from an inability to dissipate heat.[1] Exertion or exercise by animals in locations with high environmental temperature and elevated ambient humidity can cause hyperthermia in as little as 30 minutes, particularly in animals without access to shade or opportunity to cool down and rest.[2,4,5] This can result in exertional heatstroke or exertional hyperthermia when animals cannot dissipate heat.

Pathophysiology

Body temperature is maintained by the hypothalamic thermoregulatory center. Thermoregulation allows the core body temperature to remain constant despite exposure to a wide range of environmental and physiologic conditions.[3] Heat balance occurs through the actions of heat gain and dissipation mechanisms. Heat gain occurs through oxidative metabolism of foodstuffs, exercise or increased metabolic activity, and elevated environmental temperature.[2,3] Heat-dissipating mechanisms help prevent the excessive gain of heat and include behavioral changes such as seeking a cooler location, circulatory changes such as peripheral vasodilation, evaporative cooling primarily in the form of respiratory heat exchange, radiation, and convection (see ch. 49).[2] When environmental temperature increases and approaches body temperature, evaporative heat loss becomes important to maintain normothermia.[2,3] Animals that lack sweat glands depend primarily on the dissipation of heat from evaporative cooling from the respiratory system by panting.[2,6] When body temperature increases, the thermoregulatory center in the hypothalamus is activated and sends a relay of signals to the panting center. This is a basic reflex mechanism by which an animal responds to heat excess and dissipates heat to prevent hyperthermia. As air comes in contact with the mucous membranes of the upper airways, evaporative cooling occurs (see ch. 238).[6] If high ambient humidity is present, however, evaporative cooling mechanisms are not as effective and body temperature can continue to rise despite the body's efforts to cool itself.[2,7] As core body temperature rises, there is a concomitant increase in metabolic rate, which results in further accumulation of heat. A second method of cooling can occur by convection, in which an overheated animal lies on a cooler surface and the body heat is passively transferred to the cooler surface.

A number of factors can increase the risk of heatstroke, including high ambient humidity, upper airway obstruction, laryngeal paralysis, brachycephalic airway syndrome, collapsing trachea, obesity, and a previous history of hyperthermia or heat-induced illness.[4] In addition, lack of shade and a lack of a cooling down period after exercise can predispose an animal to developing exertional heatstroke or exertional hyperthermia. It is recommended that any animal that works or exercises in a hot, humid climate without acclimation must be allowed time to rest in a cool, shady place with plenty of water every 30 to 60 minutes.

The differential diagnosis of heatstroke or hyperthermia must be considered in any animal with a rectal temperature >40.5° C (>104.9° F) and no signs of infection. Pyrogenic hyperthermia results from a reset and increase in the hypothalamic thermoregulatory center set point in response to any number of endogenous or

exogenous pyrogens. Nonpyrogenic hyperthermia, however, results from the body's inability to adequately dissipate heat. Therefore, antipyretic agents are often ineffective in reducing body temperature in animals with heat-induced illness and are actually contraindicated due to potentially adverse side-effects. Differential diagnoses in patients with rectal temperatures >40.5° C (>104.9° F) include inflammatory diseases of the central nervous system such as meningitis and encephalitis, and hypothalamic mass lesions that affect the thermoregulatory center. Other potential differential diagnoses include malignant hyperthermia in affected animals, particularly Labrador Retrievers, and unwitnessed seizure activity. Toxins such as xylitol, amphetamines, metaldehyde, bromethalin, strychnine, and tremorgenic mycotoxins can also cause seizures and muscle fasciculations to such an extent that core temperature rises.

Early in hyperthermia, an increase in dead space ventilation occurs, with little effect on carbon dioxide elimination.[6] As hyperthermia progresses, however, metabolic acidosis can occur.[3] The effects of prolonged hyperthermia override the body's normal adaptive mechanisms, and cerebrospinal fluid hypocapnia and alkalosis, factors that normally decrease panting, are no longer effective, and panting continues. Additionally, as core body temperature increases, the body compensates by triggering peripheral vasodilation.[3,6] Increased blood flow to the skin and periphery can help to decrease heat by convective mechanisms. To help maintain adequate blood pressure, splanchnic vessels constrict to maintain adequate circulating volume.[6] Further, circulating catecholamines increase heart rate and cardiac output in an attempt to increase peripheral circulation in the face of relative and absolute hypovolemia caused by vasodilation and a decrease in circulating plasma volume.[3] Early in hyperthermia, there is an increase in cardiac output and decrease in peripheral vascular resistance.[6] As hyperthermia progresses, however, blood pressure and cardiac output decrease.[6] As perfusion to vital organs is decreased, widespread organ damage can result.

As body temperature rises, thermal injury occurs to neuronal tissue, cardiac myocytes, hepatocytes, renal parenchymal and tubular cells, and the gastrointestinal (GI) barrier.[3] Additionally, oxidative phosphorylation and enzymatic activities are reduced, causing a decrease in the production of energy. The combined effects of decreased organ perfusion, enzyme dysfunction, and uncoupling of oxidative phosphorylation lead to a decrease in aerobic glycolysis and an increase in tissue oxygen debt, both of which contribute to increased lactate production and lactic acidosis within 3 to 4 hours of initial heat-induced injury (see ch. 70 and 128).[3]

The kidneys are affected by direct thermal injury to the tubular and parenchymal cells. Decreased renal blood flow and hypotension further contribute to hypoxic damage to the tubular epithelium and cell death (see ch. 322). With disease progression, thrombosis of renal vessels can occur with disseminated intravascular coagulation (DIC). Consistent findings in the urinalyses of severely hyperthermic animals with severe renal injury are renal tubular casts and glycosuria. Rhabdomyolysis also can be associated with severe myoglobinuria and pigment-associated damage to the renal tubular epithelium.[3]

The GI tract is a key player in multiorgan failure associated with hyperthermia.[3] Decreased mesenteric perfusion and thermal injury to enterocytes often results in a disruption of the GI mucosal barrier with subsequent bacterial translocation (see ch. 274). Bacteremia and elevation of circulating bacterial endotoxin concentrations can lead to sepsis, systemic inflammatory response (SIRS), and multiorgan failure.[3] In one study that investigated mesenteric blood flow in experimentally-induced prolonged hyperthermia in dogs, circulating plasma endotoxin concentration increased significantly, and was associated with a higher risk of death.[7] Clinically, patients with severe hyperthermia often present with hematemesis and severe hematochezia with sloughing of intestinal mucosa.

Thermal injury to hepatocytes results in decreased hepatic function, with elevations in concentrations of hepatocellular enzyme activities (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), and total bilirubin (see ch. 282 and 283).[1,4] Necropsy findings in one retrospective study of 42 dogs with hyperthermia found centrilobular hepatic necrosis, diffuse tissue congestion, evidence of hemorrhagic diathesis, and pulmonary infarction.[4] Persistent hypoglycemia in affected patients can be associated with hepatocellular dysfunction and depletion of hepatic and muscle glycogen stores. Decreased hepatic macrophage function and portal hypotension can also predispose the patient to bacteremia with associated sepsis and SIRS.

Hyperthermia also induces widespread endothelial damage, one of the key players in the development of DIC (see ch. 197).[8] All elements of Virchow's triad, which consists of vascular endothelial injury, venous stasis, and a hypercoagulable state, occur during hyperthermia. Sluggish blood flow during periods of hypotension and decreased production of clotting factors due to hepatic injury both contribute to DIC. Exposure of subendothelial collagen and tissue factor causes widespread platelet activation, consumption of clotting factors, activation of the fibrinolytic pathway, and subsequent DIC. A study in which hyperthermia

was induced by extracorporeal circulation of heated blood caused thrombocytopenia, elevated fibrin degradation products, prolonged clotting times and spontaneous bleeding.[9] Massive global thrombosis associated with DIC can result in multiorgan failure and death. In a retrospective study of naturally occurring heatstroke in dogs, DIC occurred in more than 52% of cases, and was a risk factor for death.[1]

Finally, hyperthermia can cause direct damage to neurons, neuronal death, and cerebral edema.[10,11] Thrombosis or intracranial hemorrhage can also occur with DIC. Damage to the hypothalamic thermoregulatory center, localized intraparenchymal bleeding, infarction, and cellular necrosis can all lead to seizures. Altered levels of consciousness are among the most common clinical signs of heat-induced illness (see ch. 148). As hyperthermia progresses, severe central nervous system depression, seizures, coma, and death can occur. The potential for reversal of cerebral edema is related to the duration of the neurons' heat exposure. Severe mentation abnormalities are associated with a negative outcome. In one retrospective study of dogs, the only presenting clinical sign that was negatively associated with outcome was the animal being comatose.[4] An unfavorable outcome also was associated with the development of stupor, coma, or seizures within 45 minutes of presentation.[4]

Clinical Signs

Patients with heat-induced illness or hyperthermia often have a history of excessive panting, collapse, vomiting, ataxia, hypersalivation, seizures, or diarrhea. Listlessness, muscle tremors, altered level or loss of consciousness, hematuria, cyanosis, epistaxis, swollen tongue, head tremors, vocalizing, stridor, and mydriasis have been described with less frequency. Changes in mentation, oliguria, vomiting, hematemesis, diarrhea, respiratory distress, icterus, and petechiation can occur almost immediately after heat-induced illness, or could become apparent 3 to 5 days after the inciting event. Therefore, all animals that have sustained heatstroke and hyperthermia should be watched carefully during this period of time.

Laboratory Changes

Animals with hyperthermia should have serial complete blood counts, serum biochemical analyses, coagulation profiles, arterial blood gases (see ch. 75 and 128), venous lactates (see ch. 70), and urinalyses (see ch. 72) performed. In many cases, elevated blood urea nitrogen (BUN) and creatinine concentrations[1,4] exist, reflecting both prerenal (hypovolemia, dehydration) and renal (tubular necrosis) azotemia. Serum creatinine concentration >1.5 mg/dL has been associated with a higher fatality rate.[1] Alterations and elevations in hepatocellular enzyme function secondary to hepatocellular thermal injury or hepatic thrombosis are also demonstrated with elevated ALT, AST, alkaline phosphatase, and total bilirubin concentrations.[1,4] However, hypocholesterolemia, hypoalbuminemia, and hypoproteinemia were associated with a less favorable outcome. Total bilirubin and creatinine were higher in nonsurvivors than survivors. Elevations in creatine kinase (CK) and AST are secondary to rhabdomyolysis. Blood glucose is inconsistently decreased. In patients whose blood glucose concentration remains low despite aggressive supplementation, or is <47 mg/dL, a less favorable outcome is observed.[1,4] Packed cell volume and total solids may be increased secondary to hypovolemia and dehydration with subsequent hemoconcentration.[1] Thrombocytopenia, prolonged prothrombin time and activated partial thromboplastin time and elevated fibrin degradation products can be observed if DIC is present. Destruction or consumption of clotting factors can occur. In some dogs and cats, thrombocytopenia might not become apparent until several days after the initial insult. Thrombocytopenia is one of the most common clinicopathologic abnormalities observed in animals with heat-induced illness.[1] However, there was no significant difference in platelet counts of survivors versus nonsurvivors in one case series.[1] The presence of coagulation abnormalities might or might not be associated with an increased risk of mortality.[1] In one study, a calculated discomfort index, but not environmental temperature, was significantly associated with the development of DIC.[1] Nucleated red blood cells (nRBC) occur in 68% of dogs with heatstroke, with higher relative and absolute nRBC numbers significantly associated with an increased risk of acute kidney injury, DIC, and death.[12,13] Results of arterial blood gas analyses can be variable, as respiratory effort can be increased in heatstroke, producing a respiratory alkalosis. However, metabolic acidosis, with increased circulating lactate, can produce a metabolic acidosis, thus a mixed acid-base disturbance can occur. The need for administration of sodium bicarbonate is a negative prognostic indicator.[3,4]

Treatment

Treatment goals are to manage the hyperthermia, provide cardiovascular support, and treat any complications associated with hyperthermia. Cornerstones of therapy include restoration of circulating blood volume, improving glomerular filtration and renal blood flow, stabilizing electrolyte balance, and providing broad-spectrum antibiotics to minimize complications of bacterial translocation and sepsis.

Early recognition of hyperthermia and instituting early cooling measures are important. First, the clinician should move the animal to a cool area in the shade or indoors, away from direct sunlight. Next, the animal should be sprayed with cool but not cold water. Cool packs can be placed in the axillary and inguinal regions. Air conditioning or cool fans can also help dissipate heat and improve convective cooling mechanisms. It is important to cool the patient to 39.4° C (103° F) within 30 to 60 minutes of initial presentation but to avoid overcooling. As the thermoregulatory center becomes deranged in animals with heat-induced illness, overcooling below 39.4° C will cause a rapid drop in core temperature. Animals brought to a veterinarian within 90 minutes of the inciting event have a more favorable prognosis than animals seen later.[1] Animals cooled prior to presentation by their owners may or may not have a more favorable prognosis and decreased risk of mortality than animals not cooled at the time of initial injury.[1,4] Overcooling can also be injurious, as patients who were hypothermic when presented were more likely to die.[4] If cooling persists when body temperature is <39.4° C (103° F), shivering can occur, which will increase metabolic rate and further increase core body temperature. Immersion in ice baths or cold water is absolutely contraindicated, as cold water immersion causes peripheral vasoconstriction and prevents vasodilation, one of the animal's primary methods of cooling. Vasoconstriction results in further elevation of core body temperature and thus should be avoided at all costs. Massaging the skin can increase peripheral circulation, improve peripheral blood flow, and improve heat loss. Other methods of cooling that have been described but offer no real advantage or improvement of clinical outcome include administration of cool intravenous fluids, gastric lavage, cold-water enemas, and cool peritoneal lavage. Placing alcohol on the footpads has been described, but can further complicate overcooling and thus should not be performed.

Intravenous fluid administration should be tailored to each patient's individual needs, and can be selected and delivered based on central venous pressure (see ch. 76), acid-base and electrolyte status (see ch. 128), blood pressure (see ch. 99), thoracic auscultation, and colloid oncotic pressure. A balanced electrolyte fluid such as Normosol-R, Plasmalyte-M, or lactated Ringer's can be given as determined by calculated dehydration deficits (see ch. 127). If a free water deficit is present, as evidenced by hypernatremia, the clinician should calculate the free water deficit and replace it slowly over a period of 24 hours, to prevent further cerebral edema from occurring. Experimental evidence has also suggested that the use of hydroxyethyl starch may be superior to the use of saline alone to resuscitate animals with hyperthermia.[14]

Oxygen should be administered to animals with signs of upper airway obstruction (see ch. 139). If laryngeal paralysis is present, sedative and anxiolytic agents such as acepromazine should be considered. In cases of severe upper airway obstruction and laryngeal edema, glucocorticoids can also be administered to decrease airway edema. General anesthesia with airway intubation or the placement of a temporary tracheostomy to bypass upper airway obstruction should be considered.

The use of empiric glucocorticoids in patients without signs of airway obstruction is controversial, as they can further impair renal perfusion and predispose to GI ulceration. Their empiric use is not justified and is not advised.

Broad-spectrum antibiotics such as a second-generation cephalosporin (cefoxitin 30 mg/kg IV q 8 h), ampicillin (22 mg/kg IV q 6 h) or ampicillin-sulbactam (20-30 mg/kg IV q 8 h) in combination with enrofloxacin (10 mg/kg IV q 24 h), and sometimes metronidazole (10 mg/kg IV q 8 h) should be administered to decrease bacteremia. Non-nephrotoxic antibiotics should be administered; since compromised renal function is a serious concern in patients with hyperthermia, aminoglycoside antibiotics should be avoided.

Antipyretic agents such as dipyrone, flunixin meglumine, deracoxib, meloxicam, carprofen, and etodolac are contraindicated for a number of reasons. First, these agents act to decrease the set point of the thermoregulatory center in patients with a fever, not hyperthermia, and are therefore ineffective for heatstroke. Antiprostaglandins are only effective on lowering body temperature in dogs with a true fever. Their use may also worsen hypothermia, if present. Second, at high dosages these agents have been shown to decrease renal perfusion and can predispose the patient to GI ulceration.

Urine output should be quantitated and calculated to observe if oliguria or anuria is present (see ch. 105 and 106). After volume resuscitation, urine output should be 1 to 2 mL/kg/h (see ch. 322). If urine output is less, a constant rate infusion of dopamine at 3 to 5 mcg/kg/min can be started to increase renal perfusion and urine output. The presence of persistent oliguria or anuria potentially can be treated with peritoneal or

hemodialysis (see ch. 109 and 110). Ventricular dysrhythmias should be monitored via ECG and treated when necessary (see ch. 248).[5] Seizures should be controlled with diazepam (see ch. 136).

Prognosis

Severe hyperthermia can result in widespread organ failure and must be recognized and treated promptly. In most cases, the prognosis is guarded to grave, depending on the presence of underlying diseases and complications. Mortality rates are directly associated with the duration and intensity of hyperthermia. In one study, the mortality rate was 50%.[1] Obesity, acute kidney injury, and DIC all increase the risk of death associated with hyperthermia.[1] Permanent damage to the kidneys, liver, and brain can occur, including permanent changes in the hypothalamic thermoregulatory center that can predispose the patient to further hyperthermic episodes.[3] In most cases, the clinician must give a guarded prognosis. If death is going to occur, it usually happens within the first 24 hours of the incident.[1,4] If an animal survives past 48 hours of hospitalization, the outcome is generally good.[4] Animals who present with coma or hypothermia after a hyperthermic event generally have a very grave prognosis, even with extremely aggressive therapy (Figure 134-1). A newer approach to severity scoring for heatstroke in dogs has been proposed, and it could help provide a more accurate prognosis for affected dogs.[15]

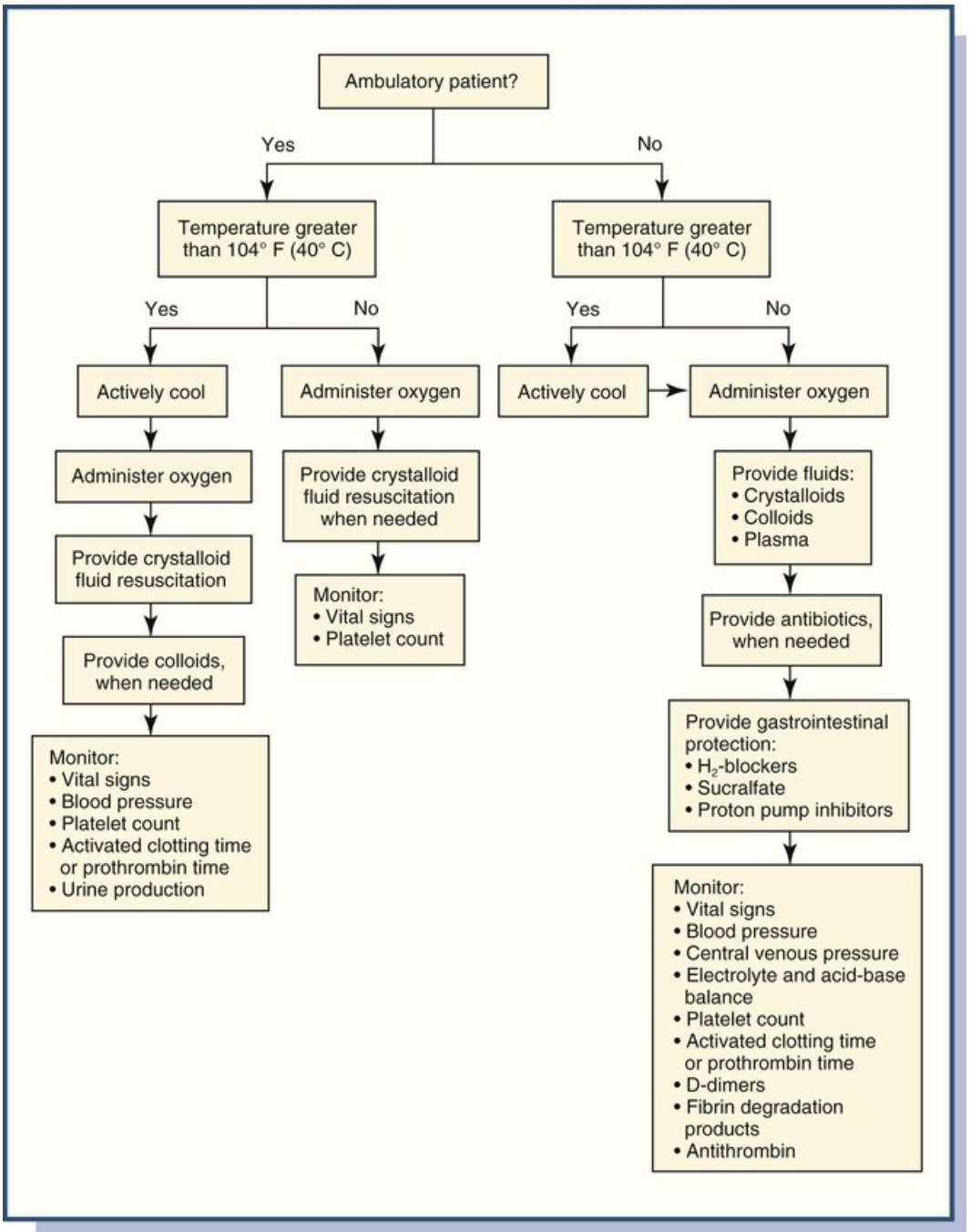

FIGURE 134-1 General algorithm for approach to the patient with heatstroke. The approach can be tailored to the individual patient, with more aggressive monitoring in the most critically ill animals.

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CHAPTER 135

Hemorrhage

Armelle de Laforcade

Client Information Sheet: Hemorrhage

Hemorrhage stems from the ancient Greek word *haimo* (blood) and *rrhagia* (excessive flow) and refers to escape of blood from the circulatory system. While bleeding and hemorrhage are often used interchangeably, the term "hemorrhage" refers to *excessive* bleeding that might be difficult to stop. Clinical manifestations of hemorrhage can vary and cardiovascular compromise from resulting hypovolemia might require emergent therapy. Hemorrhagic shock refers to a state of reduced tissue perfusion and tissue oxygen delivery, where cellular oxygen demand outweighs supply.

Acute hemorrhage in companion animals is a common consequence of blunt or penetrating trauma, but can also occur secondary to coagulopathy, neoplasia, or as a complication following surgery.[1,2] While external bleeding is readily identified, internal hemorrhage can be difficult to recognize, as clinical signs can vary based on organs affected; a higher index of suspicion might be required for rapid diagnosis. The most common sources of blood loss in the traumatized patient include wounds (external bleeding), abdomen (due to hepatic or splenic injury), retroperitoneal space (due to renal or perirenal injury), the pleural space, and at the site of pelvic or long bone fractures. Neoplasia is a leading cause of non-traumatic internal bleeding in both dogs and cats, resulting from tumor rupture or invasion of local vessels by tumor cells. Hemangiosarcoma (both primary tumors and metastases) is the most common tumor associated with hemorrhage in dogs and cats, and it can result in intermittent, slow, or acute hemorrhage in the clinical setting.[3-5] Other reported forms of neoplasia associated with hemorrhage in the dog include malignant mesothelioma, metastatic carcinoma, rib osteosarcoma, pulmonary carcinoma, and lymphoma.[5,6] Nearly half of cats with tumor-associated spontaneous hemorrhage have hepatic involvement.[4,7] Hemostatic alterations can result in clinical signs of blood loss. Bleeding disorder-associated hemorrhage results from toxin ingestion (anticoagulant rodenticide), immune-mediated thrombocytopenia, and severe reductions in hemostatic factors and platelets. Finally, iatrogenic causes of hemorrhage should be considered, following surgery or any invasive procedure (Box 135-1).

Box 135-1

Diseases Associated with Hemorrhage

Anticoagulant rodenticide ingestion
Neoplasia
Hepatic failure
Immune-mediated thrombocytopenia
Thrombocytopathia
Congenital factor deficiency
Disseminated intravascular coagulation
Iatrogenic

An acute drop in circulating blood volume of <20% of total blood volume can often be compensated for in the absence of severe underlying disease through modifications of the cardiovascular system. In the short term, reduced venous return to the heart results in a drop in cardiac preload and end-diastolic left ventricular volume. The resulting drop in cardiac output and systemic arterial blood pressure increases baroreceptor

activity in the walls of the aortic arch and in the carotid sinus, leading to venoconstriction (increasing venous return), increased cardiac contractility and increased heart rate. These changes have the net effect of increasing cardiac output. Increased systemic vascular resistance secondary to arteriolar vasoconstriction contributes to normalization of systemic blood pressure. These are considered non-sustainable, short-term changes to restore perfusion and tissue oxygen delivery. A more sustainable mechanism for restoring circulating volume occurs through renal changes in salt and water retention mediated by the renin angiotensin aldosterone system. Renin release triggered by a drop in systemic arterial blood pressure ultimately causes angiotensin II and aldosterone synthesis/release from the adrenal cortex. Other factors contributing to the release of renin include sympathetic stimulation and reduced glomerular filtration rate (GFR) resulting in reduced flow through the distal renal tubule. Aldosterone increases renal sodium resorption by the late distal tubule and collecting ducts, while angiotensin II acts directly on the proximal tubule to enhance sodium resorption and causes vasoconstriction of the renal efferent arterioles, minimizing the fall in GFR.[8]

Clinical signs associated with hemorrhage vary depending on the nature and severity of bleeding. Acute loss of 15-30% of blood volume classically results in an elevated resting heart rate while cardiovascular collapse becomes apparent with losses exceeding 40% of blood volume (30-35 mL/kg in dogs and 20-25 mL/kg in cats). In the emergent setting, hyperdynamic femoral pulses in the presence of mucous membrane pallor is very useful in establishing an early index of suspicion for blood loss and the resuscitative strategy can be modified accordingly. The physical exam finding of a pendulous abdomen or a severely swollen limb in the case of long bone fractures likewise is useful for raising the index of suspicion for bleeding. Bleeding into the retroperitoneal space is usually painful, and a hunchbacked stance (lordosis) can be helpful to prompt an abdominal ultrasound examination. For both retroperitoneal and pleural space hemorrhage, the use of a bedside ultrasound for AFAST and TFAST exams, respectively, can allow for rapid identification of bleeding (see ch. 143 and 149).[9] In the absence of melena or hematochezia, severe gastrointestinal bleeding resulting from immune-mediated destruction of platelets can be difficult to detect yet it can lead to acute and profound blood loss requiring emergent therapy.

Hemorrhage commonly is manifested by a parallel reduction in packed cell volume (PCV) and total solids (TS) (Table 135-1). Cortisol-induced splenic contraction in the dog, however, often masks the drop in PCV in acute hemorrhage, and reduced TS (often with a normal or even slightly increased PCV) is considered a more sensitive indicator of acute blood loss. A reduction in both PCV and TS more commonly is seen following fluid resuscitation. In instances where sampling of effusion is possible, a fluid PCV close to or even exceeding the peripheral PCV is most common with acute hemorrhage while a PCV < 10% typically is indicative of a non-hemorrhagic effusion.

TABLE 135-1

Changes in Hematocrit and Total Solids in Response to Hemorrhage

	PACKED CELL VOLUME	TOTAL SOLIDS
Acute hemorrhage	Normal	↓
Subacute hemorrhage	↓	↓

As with hypovolemic shock (see ch. 127), emergent therapy for hemorrhage consists of intravascular volume replacement to minimize the detrimental effects of systemic hypoperfusion on oxygen delivery. However, subtle changes in resuscitative strategy with early identification of acute hemorrhage are required. In the setting of acute hemorrhage, large volumes of crystalloids over a short period of time can accelerate blood loss due to the sharp rise in intravascular hydrostatic pressure. Clinically, then, an initial positive response to fluid therapy is followed by accelerated bleeding and worsening signs of hypoperfusion (tachycardia, mucous membrane pallor and poor pulse quality), weakness/collapse, and worsening anemia. Unlike with hypovolemic shock, optimal resuscitation in the setting of hemorrhage consists of conservative administration of isotonic crystalloids, and early administration of blood products (see ch. 129 and 130).[10] The term "hypotensive" or "low volume" resuscitation is used to indicate this type of conservative approach where isotonic crystalloids are administered in 10-20 mL/kg aliquots to achieve a blood pressure considered minimally acceptable for renal perfusion. Generally, a systolic blood pressure of 80-90 mm Hg is considered a reasonable target to ensure a mean arterial pressure of 60 mm Hg.[11,12]

Red blood cell transfusions are generally recommended when the PCV drops to 20-25% or when clinical signs of anemia including resting tachycardia, weakness, and lethargy become apparent (see ch. 130). General guidelines such as these are complicated in the setting of acute and ongoing hemorrhage, where the most striking finding could be a profound reduction in TS in the face of milder drop in PCV. In these cases, it is considered acceptable to initiate blood transfusions earlier, at a PCV of 26-28%. The use of blood products early in resuscitation should be considered in cases of severe hemorrhage. Hemorrhage results in the loss of all blood components (red blood cells, platelets, and plasma) so that fresh whole blood is a logical choice when a transfusion is needed. Since fresh whole blood often is not immediately available, the use of stored blood products is most commonly employed in this situation. Packed red blood cells are administered first, using a starting dosage of 10 mL/kg. With severe ongoing hemorrhage, packed red blood cell transfusions often are repeated, and at some point during or soon after resuscitation, a dilutional coagulopathy should be ruled out through coagulation testing. If available, fresh frozen plasma or frozen plasma should be coadministered, especially in cases where a need for surgical disease is identified.

Administration of blood products equivalent to one complete blood volume (90 mL/kg in a dog, 40-60 mL/kg in cats) in a 24-hour period, or half of a blood volume in a 3-hour period, is referred to as *massive transfusion*. The most predictable complication of massive transfusion is hypocalcemia due to cumulative administration of anticoagulant. Other possible complications include thrombocytopenia, prolonged prothrombin time and activated partial thromboplastin time, transfusion reaction, and hypothermia.[2,13]

Autologous transfusion can be considered in dogs with cavitary hemorrhage where blood can be removed easily. Various methods have been described for autotransfusion using commercially available kits as well as basic supplies. Blood that is autotransfused must always be administered using a filter. Another important consideration is potential dissemination of neoplastic cells or gastrointestinal material in the case of a ruptured viscus.[14,15]

Recent attention has been given to the potential role of fibrinolysis in the bleeding patient. In people, fibrinolysis is considered a contributing factor in the coagulopathy associated with trauma, and anti-fibrinolytic agents have been incorporated into practice. Excessive fibrinolysis has been found to play a role in post-operative bleeding in Greyhounds, and the pre-operative administration use of aminocaproic acid in this breed is now commonly employed (3-4 mg/kg [500 mg per Greyhound] PO q 8 h for 5 days beginning the night of surgery).[16] A recent study has also documented hyperfibrinolysis in a population of dogs with spontaneous hemoperitoneum.[17] Given the limited availability of blood products and their impact on the overall cost of care, the potential role of altered fibrinolysis and anti-fibrinolytic agents is of growing interest in veterinary medicine. Identification of altered fibrinolysis is challenging, and the growing use of viscoelastic testing such as thromboelastography and rotational thromboelastometry in the veterinary setting will likely be useful in identifying disease states where fibrinolysis should be investigated as a potential cause for hemorrhage (see ch. 196).

Other therapies in the patient with hemorrhage should target the underlying disease. Vitamin K therapy is initiated concurrently with coagulation factor replacement when anticoagulant rodenticide intoxication is strongly suspected or confirmed. Animals bleeding as a result of an invasive procedure should be re-evaluated frequently, and a second procedure may be required to correct the defect in vascular integrity if there is ongoing hemorrhage. Studies evaluating blood product use have suggested that gastrointestinal blood loss accounts for a significant portion of total blood products administered.[18]

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CHAPTER 136

Status Epilepticus

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Client Information Sheet: Status Epilepticus

Status epilepticus (SE) is a serious medical emergency with significant morbidity and mortality. It is most often defined as an epileptic seizure lasting longer than 5 minutes or two or more seizures without return of consciousness in between the episodes.[1] This is different than acute repetitive seizures in people, which are usually referred to as cluster seizures (CS) in veterinary patients. Although the definition of cluster seizures is inconsistent in the veterinary literature, clinically it is considered to be two or more seizures within a 24 hour period of time, between which the patient regains consciousness[2,3] (Video 136-1; also see ch. 35, 258, and 260).

The true prevalence of SE and CS is questionable in veterinary medicine, since no large-scale studies have been performed to date. However, according to the information that is available in the literature, the prevalence of SE in dogs varies from 2.5%, to 16%, to 59% in separate studies.[4-7] The prevalence of CS in dogs with idiopathic epilepsy has been reported to be 41%.[5] The true prevalence is most likely lower since most published studies consist of the skewed population of patients that presented to referral centers. No association exists between the occurrences of SE and CS.[5]

In one study, intact male dogs had twice as many episodes and intact female dogs had significantly more frequent CS than neutered male or female dogs.[5] The effect of sex hormones on seizure activity is well known in people.[8] It has been shown that estrogen and progesterone consistently enhance and inhibit neuronal excitability, respectively, while the effect of testosterone on neuronal excitability is less consistent.[8] Therefore, neutering intact female dogs with SE or poorly regulated and frequent seizures appears to be of clinical value in improving the seizure control while the efficacy of neutering intact male dogs with SE or CS to improve their seizure control is questionable. Another study indicated that no reliable conclusions could be made about the effects of sterilization on control of seizures in male or female dogs.[9] Further studies are required to determine the effects of sex hormones in dogs and cats.

Although natural death occurs in a fairly small number of cases with SE (2% to 5%), the overall mortality, mainly from euthanasia, has been reported anywhere from 23% to 38% in dogs.[4,5,7] Euthanasia is directly associated with the frequency of the cluster seizure episodes.[5] This study suggests that the frequency of CS is a more important factor for an owner's decision for euthanasia than is the severity of the seizure episodes.[5]

In dogs with idiopathic epilepsy, the mean lifespan of the SE group was 8.3 years compared to dogs without SE having a median life span of 11.3 years.[4] The only variable that was significantly different between dogs with and without SE was body weight. The dogs with higher body weight were more likely to develop SE.[4] The same study indicated that early and appropriate seizure treatment was not a significant factor in reducing the possibility of SE in dogs with idiopathic epilepsy. Low serum antiepileptic drug (AED) concentrations in epileptic dogs has been associated with SE (5.7% of dogs with SE were due to low drug levels).[6] Similar to people and experimental studies in rodents, presence of high seizure density (CS or SE) and not high seizure frequency increases the risk for being refractory to AEDs.[10] German Shepherds and Boxers were significantly more likely to suffer from CS.[5]

The underlying pathophysiology for SE is complex and multifactorial. Overall, the routine mechanisms that terminate an isolated seizure episode become ineffective. The failure could be due to excessive excitation or inadequate inhibition.[11-13] Alterations in the functional characteristics of gamma-aminobutyric acid receptors, glutamate-mediated excitotoxicity, defects in adenosine receptor agonism, and activation of N-methyl-D-

aspartate receptors are some likely contributing factors.[11-13]

It is a known fact that prolonged seizure activity could cause substantial neuronal injury in the brain. Concurrent hypotension, hyperthermia, and hypoxia are important contributing factors to further brain damage. Inability to meet the significantly increased metabolic demands of the brain during an ongoing seizure is detrimental to the brain. There is a significantly higher potential for permanent brain damage with a seizure lasting 30 minutes or longer. This is the main reason why historically SE was defined as a seizure lasting longer than 30 minutes. One of the major rationales for changing the definition to the recent one (5 minutes) is to start medical intervention prior to the high risk of irreversible neuronal injury.[14,15]

Systemic consequences are often present with prolonged seizure activity. High levels of catecholamines are released, which could result in cardiovascular effects such as systemic hypertension, sinus tachycardia, and other cardiac arrhythmias. Hyperthermia is another consequence of SE resulting from excessive muscle activity and increased sympathetic tone that could result in body temperature elevating to life-threatening levels (see ch. 134). Impaired respiratory function and hypoxemia are some of the other concerns with prolonged seizure activity, which in severe cases could lead to multi-organ failure (see ch. 132).

The underlying causes of SE in dogs were idiopathic in 37.5%, symptomatic in 39.8%, and reactive in 22.7% of cases.[11] In another study the underlying causes of seizures were idiopathic in 26.8%, symptomatic in 35.1%, reactive in 6.7%, due to low serum antiepileptic drug concentrations in 5.7%, and undetermined in 25.8% of cases.[6] Dogs with SE secondary to idiopathic epilepsy or intoxication tend to have a more favorable outcome.[6,11] A negative outcome (death or euthanasia) has been correlated with granulomatous meningoencephalitis, development of partial status epilepticus, and loss of seizure control after 6 hours of hospitalization.[6] In dogs with juvenile epilepsy, SE has been associated with poor outcome.[16] Identification of the underlying cause of seizure is important in treatment of SE and ideally should be treated before resulting in irreversible brain damage. Some of the abnormalities that require immediate assessment and treatment include glucose (see ch. 61), sodium (see ch. 67), and calcium (see ch. 69) dysfunctions.

A complete history and minimum database of hematology, serum biochemical profile, and urinalysis should be performed in every patient presenting with SE. If the patient is receiving maintenance AEDs, blood drug levels should be evaluated. Many of these patients will require advanced imaging such as brain magnetic resonance imaging (MRI) and cerebrospinal fluid analysis once they are more stable to undergo general anesthesia. One should keep in mind that elevated liver values (especially alanine aminotransferase) are commonly observed immediately following seizure activity, predominantly secondary to hypoxemia. Elevated muscle enzyme concentrations could also be present secondary to prolonged seizure activity. Metabolic acidosis is often observed in SE patients and resolves with cessation of seizure activity (see ch. 128). Patients with respiratory acidosis and hypoxemia may require oxygen therapy (see ch. 131). Continuous and repetitive assessment of neurological status (see ch. 259), cardiovascular and respiratory status, urine output, and body temperature is of paramount importance in SE patients. Routine monitoring of blood pressure and heart rate to indirectly evaluate for increase in intracranial pressure (Cushing's reflex) may be warranted. For more information regarding differential diagnoses, diagnostic approach, and treatment for seizures, refer to ch. 35, 260 and 261.

The basic principle and goal of treatment for patients with status epilepticus, like any other acute seizure, is immediate cessation of all of the seizure activity. The current treatment of SE, not only in veterinary patients but also in human patients, is predominantly by use of drugs that were developed decades ago. The treatment recommendations are predominantly based on clinical experience and data from human medical and experimental rodent studies.[14] In veterinary medicine, the response to treatment is usually evaluated by termination of gross seizure activity. Electroencephalographic (EEG) monitoring in dogs and cats with SE has shown that even with cessation of clinical seizures after induction of anesthesia, distinct epileptiform patterns (Figure 136-1) were present in all animals.[17] This finding strongly suggests that EEG monitoring would be useful in SE patients, but continuous EEG monitoring is presently rarely available in veterinary intensive care unit settings. Non-convulsive seizures (Video 136-2) have also been sporadically reported in veterinary patients.[18] Further investigations are necessary to evaluate EEG monitoring in SE patients and define therapeutic endpoints.[17,18]

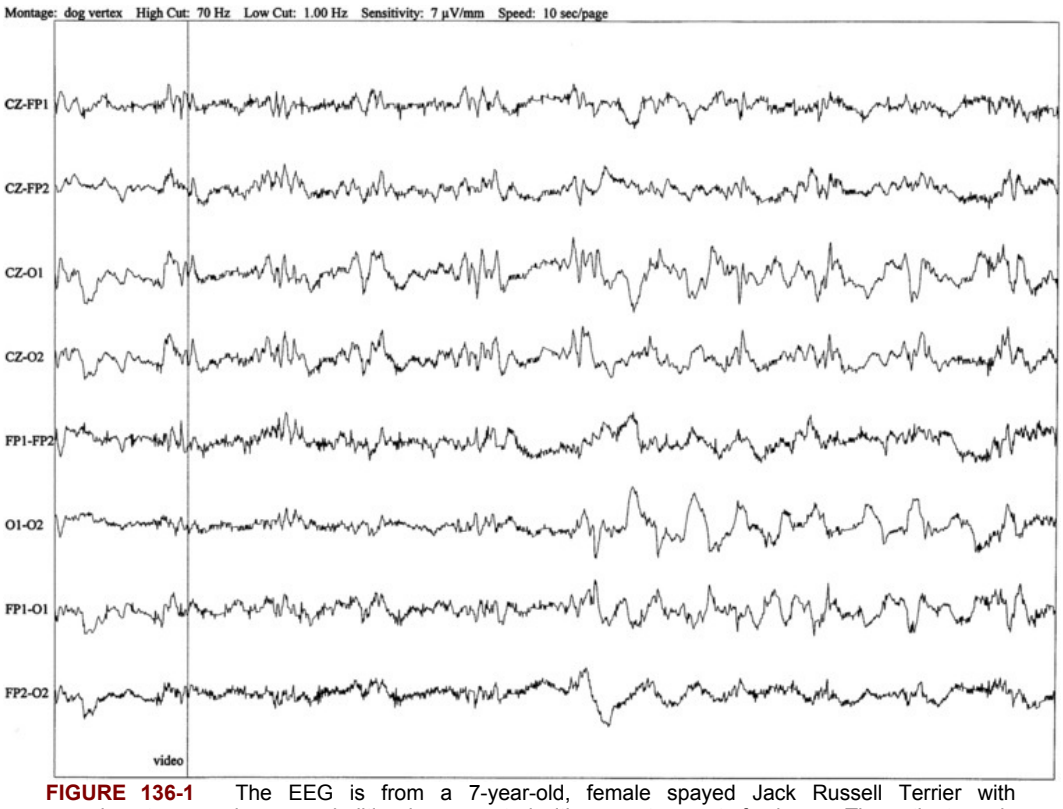

FIGURE 136-1 The EEG is from a 7-year-old, female spayed Jack Russell Terrier with granulomatous meningoencephalitis who presented with an acute onset of seizures. The patient was in non-convulsive SE (only little eye and ear twitches) but unconscious with epileptiform spikes on the EEG (EEG showed continuous seizure activity indicating this was non-convulsive SE). (Courtesy Dr. Dennis O'Brien.)

When treating a patient in SE, an AED should be administered IV immediately. Due to their rapid onsets of action and strong antiepileptic properties, benzodiazepines are the drug of choice for the initial treatment.[19] Diazepam is the drug of choice in small animals.[19] Intravenous administration (0.5-1 mg/kg in dogs and 0.25-0.5 mg/kg in cats) is the preferred method but if this route is not possible, diazepam could also be given rectally (1-2 mg/kg in dogs and 1 mg/kg in cats) or by the intranasal route (0.5 mg/kg in dogs).[19-21] Dogs receiving maintenance phenobarbital require the upper end of the dosages for intravenous or rectal administration of diazepam.[22] In dogs, mean plasma concentration is achieved in about 2, 10-15, and 5 minutes after intravenous, rectal, and intranasal administration of diazepam, respectively.[19-21] Intramuscular administration of diazepam is unreliable and not recommended. Fatal hepatic necrosis has not been reported with intravenous diazepam administration in cats. Lorazepam is the benzodiazepine of choice for treatment of SE in people but does not appear to have any advantage to diazepam in dogs.[23,24] Midazolam (0.2-0.4 mg/kg in dogs and 0.07-0.2 mg/kg in cats) has also been used for treatment of SE.[2,25] Intravenous administration is the route of choice but midazolam could also be administered intramuscularly and achieve reliable peak plasma concentration in 15 minutes.[25,26] Intranasal administration of midazolam (0.2 mg/kg) also appears to be effective in dogs.[27] Rectal administration of midazolam is not recommended as absorption is unreliable which results in erratic systemic availability and plasma concentrations.[24] Midazolam exhibits stronger effects against lidocaine-induced seizures compared to diazepam in dogs but further studies are required in clinical patients.[26]

Immediately after successful use of benzodiazepines, barbiturates should be administered for long-term management of seizures. Phenobarbital is the drug of choice and the most commonly used barbiturate in veterinary patients. Intravenous loading of phenobarbital (16-24 mg/kg IV) will allow the drug to achieve a rapid steady state serum concentration.[2] This could be given in one dose or divided in a few doses (often time to effect) over 12-24 hours. The author prefers administering small boluses in 30-120 minute intervals not to exceed 20 mg/kg over 24 hours. Maintenance phenobarbital therapy should be continued after completing the loading dose. If clinically warranted, a constant rate infusion of benzodiazepines could be used

simultaneously while administering the loading dose of phenobarbital.

Since benzodiazepines and phenobarbital possess cardiopulmonary depression properties, continuous respiratory and cardiovascular monitoring is necessary. This is especially important when using higher dosages or the combination therapy.

If phenobarbital is ineffective or clinically contraindicated, parenteral levetiracetam could be utilized in combination with or as an alternative to phenobarbital. A prospective controlled study in dogs showed that levetiracetam (30-60 mg/kg IV) was safe and appeared to be effective in treatment of SE in dogs.[28] The drug seems to be most effective when administered at 8 hour intervals. The dosage is 20 mg/kg IV q 8 h in cats.[29] The drug causes noticeably less sedation compared to phenobarbital and has a wide safety margin, making it a desirable medication for refractory cases.[28,29] Rectal administration of levetiracetam appears to be effective in dogs.[30] In the author's experience, when AEDs are used appropriately, the majority of patients do respond to the aforementioned treatments. Mannitol or hypertonic saline may be required if evidence of increased intracranial pressure is present. In refractory SE patients, additional treatment (predominantly anesthetic agents) may become necessary. Propofol has been used as intermittent boluses (2-8 mg/kg IV) or as a constant rate infusion (0.1-0.6 mg/kg/min titrated to effect or up to 6 mg/kg/h) to stop the motor activity associated with seizures.[31-33] Anesthetic agents such as ketamine (2-8 mg/kg IV boluses) or isoflurane (1% to 2% minimum alveolar concentration) are additional alternatives for treatment of refractory SE patients.[14,34,35] Some of the other potential therapeutic options include administration of sodium bromide (600 mg/kg IV over 24 hours), pentobarbital (3-15 mg/kg IV to effect or 0.5-4 mg/kg/h), or zonisamide (8-12 mg/kg PO q 12 h).[32,33,36] Anesthetic agents could cause profound sedation and cardiopulmonary depression; therefore, close monitoring and possible respiratory support (endotracheal intubation and/or ventilator support) may be required. Anesthetic agents often stop the motor activity associated with seizures; however, additional investigations are required to determine their effect on seizure activity present on continuous EEG monitoring. Initiation of long-term chronic treatment is of paramount importance after controlling the seizure activity in SE patients.

In summary, SE is a serous medical condition with complex and multifactorial underlying pathophysiologic mechanisms. Benzodiazepines are the first-line treatment options followed by phenobarbital or levetiracetam as second-line therapy options. In refractory cases, anesthetic agents such as propofol are the third-line therapy options. A timely, methodical, and common sense approach is essential for successful treatment of patients with SE.

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CHAPTER 137

Anaphylaxis

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Anaphylaxis is an acute, life-threatening allergic reaction resulting from massive, generalized release of mast cell mediators, including histamine. Anaphylaxis can be triggered by venoms from insects and reptiles (see ch. 156); medications such as hormones, antibiotics, nonsteroidal anti-inflammatory drugs, anesthetics, and sedatives; parasiticides; and other miscellaneous drugs and foods (Box 137-1; see also ch. 191). Immediate recognition and treatment of anaphylaxis in a dog or cat are essential for a successful outcome.

Box 137-1

Causes of Anaphylaxis

Venoms

Insects of the Hymenoptera order—bees, wasps, ants
Spiders—black widow, brown recluse
Lizards—Gila monster, Mexican beaded lizard
Snakes—pit vipers (rattlesnakes, copperheads, water moccasins), coral snakes

Hormones

Insulin
Corticotropin
Vasopressin
Parathyroid hormone
Betamethasone
Triamcinolone
Glucocorticoids

Antibiotics

Penicillins—amoxicillin, ampicillin, procaine penicillin
Chloramphenicol
Lincomycin
Gentamicin
Tetracycline
Sulfonamides
Cephalosporins
Polymyxin B

Nonsteroidal Antiinflammatory Drugs

Aspirin
Ibuprofen

Anesthetics and Sedatives

Acepromazine
Ketamine
Barbiturates
Lidocaine and other local anesthetics
Narcotics

Diazepam

Antiparasitics

Dichlorophen
Levamisole
Piperazine
Dichlorvos
Diethylcarbamazine
Thiacetarsamide

Miscellaneous

Blood products
Aminophylline
Asparaginase
Doxorubicin
Calcium disodium edetate
Iodinated contrast media
Neostigmine
Amphotericin B
Vaccines
Allergen extracts—pollens, molds, foods
Enzymes—chymotrypsin and trypsin
Vitamins—vitamin K, thiamine, and folic acid
Dextrans and gelatins

Foods

Milk
Egg white
Shellfish
Legumes
Fruits—citrus
Chocolate
Grains

Physical Factors

Cold
Heat
Exercise

Pathogenesis

Hypersensitivity reactions are classified as one of four types, depending on immunologic response: type I, immediate (immunoglobulin E [IgE]-dependent); type II, cytotoxic (IgG-, IgM-dependent); type III, immune complex (IgG- or IgM-complex-dependent); and type IV, delayed (T lymphocyte-dependent). Anaphylaxis can be caused by either an anaphylactic or anaphylactoid reaction. Anaphylactoid and anaphylactic reactions have exactly the same clinical appearance and are treated identically. Anaphylaxis is defined as a type I, IgE-mediated hypersensitivity reaction with an interaction of antigen and IgE antibody on the surface of sensitized mast cells. This interaction causes the release of histamine and other inflammatory mediators. Sensitization requires previous exposure to an antigen or hapten, which can range in size from a protein to a small, low–molecular weight drug. Proteins act directly as an antigen, while the smaller drug molecules bind to cells and act as haptens. IgE is produced by and bound on the surface of mast cells and basophils by high-affinity receptors (FcεRI) for the Fc portion of the immunoglobulin. When an antigen causes cross-linkage of two surface IgE molecules, the mast cell is activated and primary and secondary mediators are released (Table 137-1).

TABLE 137-1

Mediators of Inflammation in Anaphylaxis

MEDIATORS	EFFECTS
Primary	
Histamine	Increased vascular permeability, vasodilation, constriction of smooth muscle of bronchi and GI tract, increased mucus production
Proteases	Kinin production, activation of complement, initiation of disseminated intravascular coagulation
Heparin	Anticoagulation, urticaria, immune modulation
ECF-A	Eosinophil chemotaxis
NCF-A	Neutrophil chemotaxis
Secondary	
Prostaglandin E_2	Vasodilation, increased vascular permeability
Prostaglandin D_2	Bronchoconstriction, increased vascular permeability, pulmonary vasoconstriction, peripheral vasodilation
Prostacyclin	Vasodilation, inhibition of platelet aggregation
Leukotrienes	Bronchoconstriction, increased vascular permeability, vasodilation, increased WBC chemotaxis
Thromboxane A_2	Increased platelet aggregation, smooth muscle contraction
Platelet-activating factor	Platelet aggregation, platelet sequestration, increased platelet thromboxane production, increased vascular permeability, vasoconstriction, and bronchoconstriction

ECF-A, Eosinophilic chemotactic factor of anaphylaxis; *GI*, gastrointestinal; *NCF-A*, neutrophil chemotactic factor of anaphylaxis; *WBC*, white blood cell.

The cross-linking of the FcεRI receptors activates tyrosine kinases, which cause activation of phospholipase C, leading to production of diacylglycerol and inositol triphosphate. These mediators increase intracellular calcium concentrations and activate multiple protein kinases. Phosphorylation of myosin, found in intracellular filaments, causes granules to move to the cell surface, fuse, and release the primary mediators of anaphylaxis: histamine, heparin, tryptase, kallikreins, proteases, proteoglycans, eosinophilic chemotactic factor of anaphylaxis (ECF-A), and neutrophil chemotactic factor of anaphylaxis (NCF-A). Cross-linking of the FcεRI receptors also activates phospholipase A_2, which produces arachidonic acid from membrane phospholipids, resulting in release of the secondary mediators: leukotrienes, prostaglandins, thromboxanes, and platelet-activating factor. The protein kinases also alter gene expression, causing synthesis and secretion of other cytokines (interleukin [IL]-4, IL-5, IL-6, IL-13, tumor necrosis factor-alpha, macrophage inflammatory protein-1alpha), responsible for the late-phase inflammatory response. Release of the inflammatory mediators is rapid: granule exocytosis occurs within seconds to minutes, activation of the arachidonic acid cascade in minutes, and cytokine synthesis and secretion within 2-24 hours.

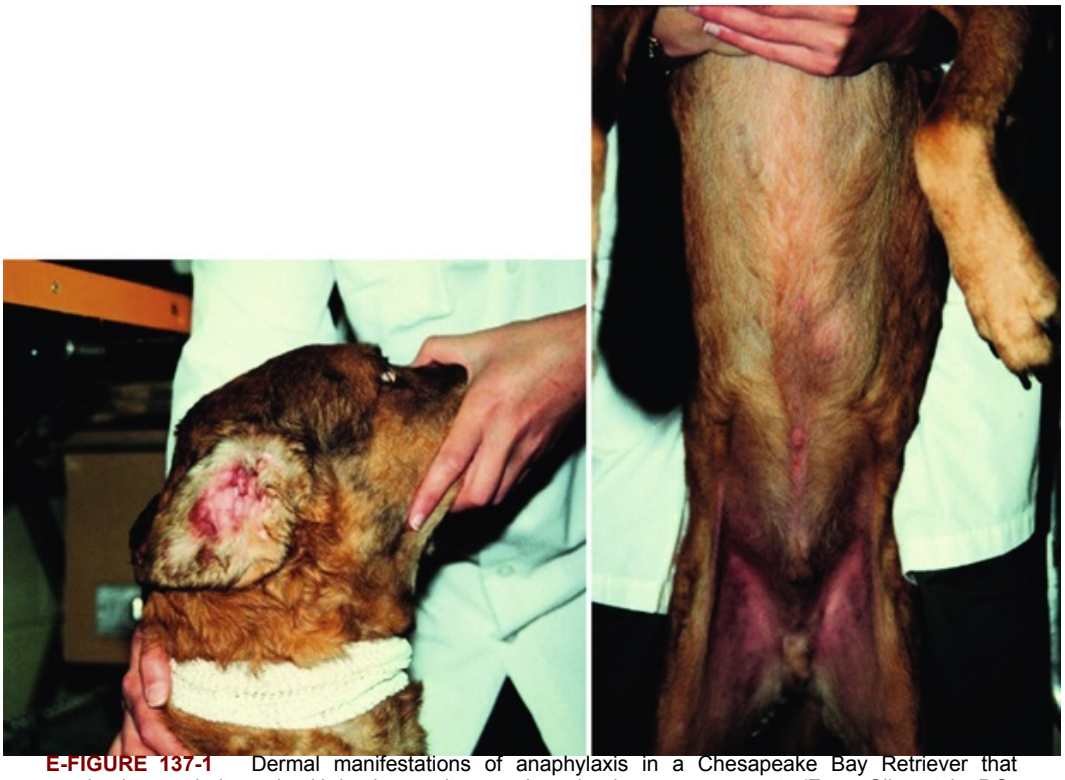
Anaphylactoid reactions cause anaphylaxis without IgE. There are two types; the first results from antigen binding to IgG molecules, which then cross link the IgG (FcyRIII) receptors on macrophages. This results in complement activation, coagulation activation, and release of platelet activating factor but not histamine release. The second occurs when a substance directly triggers degranulation of mast cells and basophils without immunoglobulin. Heat, cold, exercise, some drugs including nonsteroidal drugs and opioids, ethanol, and contrast agents can trigger this type of reaction and do not require previous sensitization. The term anaphylactoid is not typically used anymore as it is clinically indistinguishable from anaphylaxis and the clinical diagnosis and treatment are the same.

Anaphylaxis results in hypovolemia and vasodilation, potentially leading to severe hypovolemic shock (see ch. 127 and 129). Histamine and the leukotrienes are potent vasodilators that also increase vascular permeability, allowing leakage of protein and fluid into the interstitial space. There are three types of histamine receptors that contribute to the signs seen during anaphylaxis. Activation of H_1 receptors results in pruritus and bronchoconstriction and stimulates endothelial cells to produce nitric oxide, a potent vasodilator that significantly contributes to hypotension. H_1 receptors also mediate coronary artery vasoconstriction and cardiac depression. H_2 receptors stimulate gastric acid production, as well as causing coronary artery and systemic vasodilation and increasing heart rate and myocardial contractility. H_3 receptors are located on presynaptic terminals of sympathetic effector nerves that innervate the heart and systemic vasculature and

they inhibit endogenous norepinephrine release from sympathetic nerves.[1] Activation of the H_3 receptors results in worsened signs of anaphylactic shock because it inhibits normal compensatory sympathetic responses.

Clinical Manifestations

Anaphylaxis can result in hypotension, bronchospasm, urticaria, erythema, pruritus, pharyngeal and laryngeal edema, arrhythmias, vomiting, and hyperperistalsis. Clinical signs are dependent on species and method of exposure. In dogs, the liver and gallbladder are considered the shock organs, and clinical signs result from hepatic vein congestion and portal hypertension. Abnormalities on bloodwork typically include increased alanine aminotransferase (ALT) values. Ultrasound examination will show a thickened gallbladder with a distinctive striated pattern.[2] Initial signs can include excitement, vomiting, defecation (often diarrhea), and then can progress to respiratory distress, collapse secondary to hypovolemic shock, and death within 1 hour if not treated. A dog with anaphylaxis can have generalized wheals, angioedema (particularly of the face), pruritus (E-Figure 137-1), pale mucous membranes, poor capillary refill time, tachycardia, poor pulse quality, and appear depressed or even collapsed. Severe cases can result in respiratory distress secondary to upper airway obstruction from laryngeal and pharyngeal edema.



E-FIGURE 137-1 Dermal manifestations of anaphylaxis in a Chesapeake Bay Retriever that received a cephalosporin. Urticaria, pruritus, and angioedema are present. (From Silverstein DC, Hopper K, editors: *Small animal critical care medicine*, St Louis, 2009, Saunders.)

In cats, the lungs are considered the shock organ, and respiratory distress is the first sign in cats with anaphylaxis. Respiratory distress results from airway obstruction secondary to laryngeal edema, bronchoconstriction, and increased mucus production. Other signs in cats include severe pruritus, vomiting, diarrhea, depression, hypotension, and death. On physical examination, cats in anaphylactic shock usually present in severe respiratory distress, with pale mucous membranes, poor capillary refill time, poor pulse quality, and wheezes on auscultation.

The most severe anaphylactic reactions are generally seen if the antigen is given by parenteral injection. Oral ingestion often causes vomiting, diarrhea, urticaria, and angioedema. Inhalation can result in rhinitis and bronchospasm. Topical administrations can cause conjunctivitis and urticaria with or without systemic signs. In general, patients that have the most rapid onset of clinical signs after exposure to an antigen develop the most severe signs of anaphylactic shock.

Diagnosis

Diagnosis of systemic anaphylaxis is based on the history of exposure and peracute onset of clinical signs. Clinical signs often occur within seconds to minutes of exposure. Oral exposure can cause a delay of ≥30 minutes before clinical signs appear.

Treatment

Initial treatment of a dog or cat with anaphylaxis consists of the basics of emergency medicine and the administration of epinephrine (Figure 137-2). A patent airway and effective breathing/ventilating should be confirmed immediately. Respiratory distress can result from upper airway obstruction, necessitating intubation with an endotracheal tube or tracheostomy if intubation is not possible. If respiratory distress without airway obstruction is present, oxygen should be administered by mask or flow-by during initial assessment and stabilization, and then by nasal catheter or oxygen cage (see ch. 131). Cardiovascular dysfunction must be treated with drugs and/or fluids as indicated. Vascular access is essential for treatment. Hypovolemic shock is a significant contributor to morbidity and mortality in anaphylaxis. Hypovolemia occurs secondary to increased vascular permeability and venous pooling. Fluid therapy, often starting with a shock bolus of crystalloids at a dose of 90 mL/kg in dogs and 60 mL/kg in cats, is indicated (see ch. 127 and 129). Ongoing crystalloid therapy usually will be necessary at rates higher than maintenance to keep up with ongoing losses and will need to be tailored to the individual patient. Additional fluid therapy may include artificial or natural colloids. If a coagulopathy is present, blood products, especially fresh frozen plasma, could be necessary (see ch. 130). This should be given at a dose of 10 to 20 mL/kg over several hours (or faster if needed for volume resuscitation). Fluid therapy is guided by clinical parameters including heart rate, pulse quality, mucous membrane color, capillary refill time, respiratory rate and effort, and packed cell volume (PCV) and total solids.

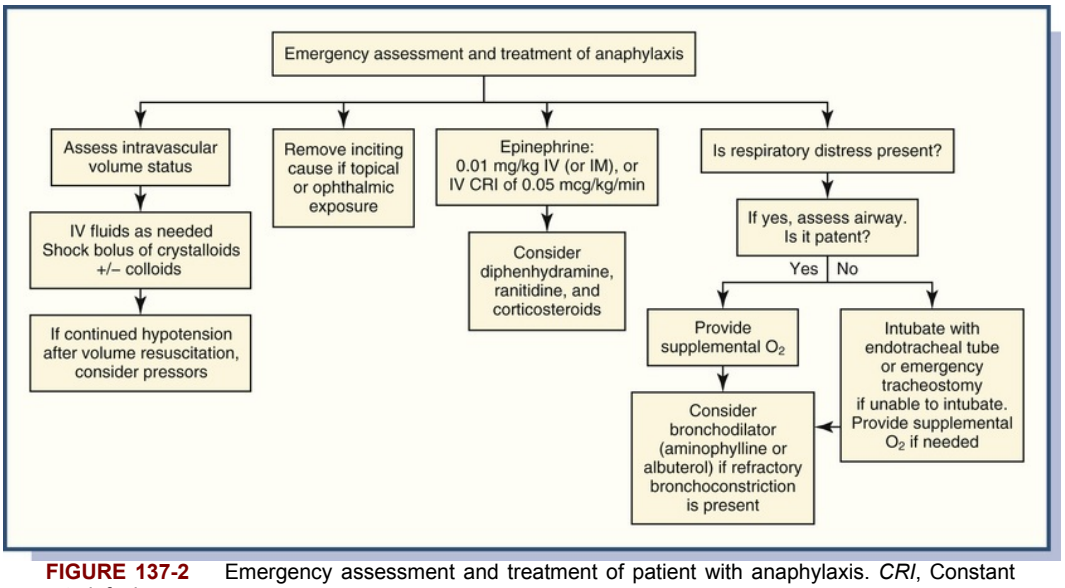


FIGURE 137-2 Emergency assessment and treatment of patient with anaphylaxis. *CRI*, Constant rate infusion.

Epinephrine is the mainstay of therapy for treatment of systemic anaphylaxis. Traditionally, a dosage of 0.01 mg/kg given slowly IV is recommended, although 0.02 mg/kg can be given into the trachea if the patient is intubated and IV access cannot be obtained. A maximum dose of 0.5 mg IV for patients weighing >40 kg is recommended. Epinephrine also can be administered IM at a dosage of 0.01 mg/kg. Doses can be repeated every 5-15 minutes as needed. Epinephrine is useful because of its inotropic and chronotropic effects on the heart as well as vasoconstriction. Epinephrine also causes bronchodilation and increased intracellular concentrations of cyclic adenosine monophosphate, which decreases synthesis and release of inflammatory mediators of anaphylaxis. A single dose of epinephrine given IV, IM, or SC after maximal hypotension had developed did not produce a sustained improvement in hemodynamic parameters in a study on dogs with induced anaphylactic shock; only the IV dose produced a transient improvement (<15 minutes) in mean

arterial pressure, stroke volume, and pulmonary wedge pressure.[3] A later study of anaphylaxis induced in dogs showed that administration of epinephrine by constant rate intravenous infusion (CRI) was the only route that caused sustained improvement in hemodynamic parameters compared to the nontreatment group and the groups that received a bolus given IV, SC, or IM.[4] The dosage used for the IV CRI was 0.05 mcg/kg/min. These studies suggest that epinephrine acts primarily as a vasopressor rather than specifically improving immunologic recovery. Consideration should be given to administering epinephrine as a CRI rather than an IV bolus. Heart rate, rhythm, and blood pressure should be monitored when giving epinephrine, especially when it is given IV, because of its ability to cause cardiac arrhythmias and systemic hypertension. Epinephrine and fluid therapy should begin to improve clinical signs within minutes of being administered. Dogs and cats ideally will be fully stabilized within an hour.

Other medications that can be useful in the treatment of systemic anaphylaxis include vasopressors, glucocorticoids, antihistamines, aminophylline, and atropine. Dopamine at a dosage of 5-10 mcg/kg/min IV CRI or norepinephrine at a dosage of 0.01-1 mcg/kg/min IV CRI can be used if refractory hypotension is present.[5] Vasopressin (0.5-1.25 mU/kg/min IV CRI) can be used if the patient is refractory to fluid and catecholamine therapy.[5] Aminophylline or a selective beta$_2$ agonist such as albuterol may be used if bronchoconstriction is refractory to epinephrine. It will cause bronchodilation, increase respiratory drive, and increase contractility of the muscles of respiration. An aminophylline dosage of 10 mg/kg IV for dogs and 5 mg/kg IV for cats is recommended. Atropine at a dosage of 0.02 to 0.04 mg/kg IV or IM should be used if bradycardia is present despite epinephrine administration. Glucocorticoids are useful in blocking the arachidonic acid cascade and reducing the severity of late-phase anaphylactic reactions. Dosages of 1 to 2 mg/kg IV for dexamethasone have been recommended unless the patient has developed anaphylaxis from administration of one of the glucocorticoids, as cross-reaction may occur. It is essential that glucocorticoids not be used in place of epinephrine in the emergency situation because they have little effect on the immediate stages of anaphylaxis. Antihistamines competitively bind at the histamine receptors and block its effects. Diphenhydramine, an H_1 blocker, should be administered at 1-4 mg/kg IM in dogs and 0.5-2 mg/kg in cats to reduce pruritus and angioedema. If given IV, it should be given slowly, over 5-10 minutes at a lower dosage of 0.5-1 mg/kg, to reduce the risk of cardiac arrhythmias and hypotension. The H_2 blockers such as ranitidine (1 mg/kg IV) or famotidine (0.5 mg/kg IV) can be used for decreasing gastric acid secretion stimulated by histamine. These antihistamines are not very useful in the acute, life-threatening stage of anaphylaxis, but can be helpful after a dog or cat has been stabilized. In one study, pretreatment of dogs with the experimental H_3 blocker thioperamide maleate resulted in increased heart rate and improved left ventricular stroke work, but its clinical usefulness in naturally-occurring anaphylaxis after the onset of signs remains to be determined.[1]

Intense monitoring of a dog or cat for 72 hours after the anaphylactic episode is essential. There are reports of biphasic reactions that can occur up to 3 days later.[5] Monitoring should include respiratory rate and effort, heart rate and rhythm, blood pressure, pulse oximetry and/or arterial blood gases, coagulation parameters, renal and hepatic function, PCV, total solids, and glucose. Additional supportive care, such as ventilatory support, should be provided as needed. Avoidance of the trigger for anaphylaxis is prudent in the future. Careful questioning of the owner about recent exposure to insects, reptiles, foods, topical therapies, and medications and prevention of re-exposure is essential (see Box 137-1). The prognosis for a patient presenting with anaphylaxis is variable, depending on the severity of onset and progression of reaction. The earlier the patient receives appropriate therapy, the better the prognosis. This is especially important since death can ensue in 1 hour or less from time of exposure.

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CHAPTER 138

Sedation and Anesthesia in Critical Care

James S. Gaynor

Who Deserves Sedation and Anesthesia in the Critical Care Unit?

Sedation and anesthesia for critically ill patients in the intensive/critical care unit deserves the same attention to detail as does anesthesia for patients undergoing a surgical procedure. The patients most likely to require sedation or anesthesia likely have some degree of dysfunction related to one or more organ system (renal, hepatic, cardiac, or respiratory). These patients may need to be sedated or anesthetized for a number of reasons, including but not limited to urethral obstruction; ultrasound-guided biopsies of the kidney, liver, or other organ; endoscopy; bronchoscopy; long-term ventilation; long line placement; or just calming based on a patient's underlying demeanor or due to current disease.

Drugs for Sedation and Anesthesia

There are multiple drugs that can be used to sedate or anesthetize critically ill patients. They are covered in much greater detail elsewhere.[1,2] The concepts of drug reversibility and short duration are important to consider for this particular set of patients. It is key to recognize that a drug that has a short duration of action may not have a short metabolic half-life. This can occur due to redistribution of the drug to muscle and fat.

Opioid Agonists and Antagonists (Table 138-1)

The opioids of greatest concern are the mu receptor agonists. The mu receptor agonists provide variable degrees of sedation (drug and dosage dependent) but induce the greatest amount of analgesia. They are completely reversible. Opioids always have the potential to induce dysphoria with or without sedation in dogs and cats. This undesirable effect occurs less often in older, sicker, debilitated dogs. Opioid-induced dysphoria occurs more frequently in cats. All opioids can increase parasympathetic tone with subsequent decrease in heart rate. There is no clear recommendation with regard to co-administration of a low-dose anticholinergic to prevent bradycardia or whether to wait for bradycardia to occur. An advantage of most opioids is that they minimally decrease cardiac contractility, cardiac output and perfusion, making them ideal for sicker patients.

TABLE 138-1

Drugs Used for Sedation and Anesthesia

DRUG	DOG DOSAGE	CAT DOSAGE	COMMENT
Opioid Agonist and Antagonists			
Fentanyl	2-5 mcg/kg IV 2-10 mcg/kg/h IV 5-10 mcg/kg SC, IM	2-5 mcg/kg IV 2-10 mcg/kg/h IV	SC, IM administration likely to induce dysphoria
Hydromorphone	0.05-0.1 mg/kg IV 0.05-0.1 mg/kg/h	0.05-0.1 mg/kg IV 0.05-0.1 mg/kg/h	May induce hyperthermia in cats

	IV 0.1-0.2 mg/kg SC, IM	IV 0.1 mg/kg SC, IM	
Oxymorphone	0.05-0.1 mg/kg IV 0.05-0.1 mg/kg/h IV 0.1 mg/kg SC, IM	0.05-0.1 mg/kg IV 0.05-0.1 mg/kg/h IV 0.05-0.1 mg/kg SC, IM	May induce hyperthermia in cats
Morphine	0.1-0.3 mg/kg IV 0.25-1 mg/kg SC, IM	NA	Cats are unlikely to develop analgesia at conventional dosages due to their low ability to convert morphine to morphine-6-glucuronide
Methadone	0.1-0.3 mg/kg IV 0.25-1 mg/kg SC, IM	0.05-0.1 mg/kg IV 0.05-0.1 mg/kg/h IV 0.1-0.3 mg/kg SC, IM	Feline euphoria likely, rather than dysphoria
Butorphanol	0.1-0.4 mg/kg IV 0.25-0.5 mg/kg SC, IM	0.1-0.25 mg/kg IV 0.2-0.4 mg/kg SC, IM	Mild to moderate pain control only; duration of analgesia ≈45 min in dogs, 4 h in cats
Nalbuphine	0.1-0.5 mg/kg IV 0.1 mg/kg/h IV 0.25-1 mg/kg SC, IM	0.1-0.25 mg/kg IV 0.05-0.1 mg/kg/h IV 0.25-0.5 mg/kg IM	Mild to moderate short-term pain control only; no inherent behavioral effects when used alone
Buprenorphine	0.01-0.03 mg/kg IV, SC, IM	0.24 mg/kg SC	Canine dosage provides mild to moderate pain control of short duration; feline dosing provides maximal analgesia for 24 h
Naloxone	1-2 mcg/kg IV 10 mcg/kg IV, SC, IM	1-2 mcg/kg IV 10 mcg/kg IV, SC, IM	Low-dose for partial reversal and to aid extubation; high dosages to completely reverse opioid
Alpha-2 and Benzodiazepine Antagonists			
Dexmedetomidine	0.5-1 mcg/kg IV 0.5-1 mcg/kg/h IV 3-5 mcg/kg IV, SC, IM	0.5-1 mcg/kg IV 0.5-1 mcg/kg/h IV 3-10 mcg/kg IV, SC, IM	Low dosages to potentiate opioid-induced analgesia sedation in the ICU; higher dosages to induce sedation with or without an opioid
Midazolam	0.1-0.2 mg/kg IV, SC, IM	0.1 mg/kg IV	Doses greater than 5 mg induce little more sedation but likelihood of greater excitement
Diazepam	0.1-0.2 mg/kg IV	0.1 mg/kg IV	Doses greater than 5 mg induce little more sedation but likelihood of greater excitement
Anticholinergics			
Glycopyrrolate	0.005-0.01 mg/kg IV, SC, IM	0.005-0.01 mg/kg IV, SC, IM	Does not cross blood-brain or placental barriers
Atropine	0.01-0.04 mg/kg IV, SC, IM	0.01-0.04 mg/kg IV, SC, IM	Crosses blood-brain and placental barriers and may induce sedation
IV Induction Agents and Sedatives			
Propofol	3-4 mg/kg IV to	3-5 mg/kg IV to	Give slowly to effect to decrease dosage, apnea, and hypotension

	effect 10-20 mg/kg/h IV	effect 10-20 mg/kg/h IV	
Etomidate	1 mg/kg IV 0.5-1 mg/kg/h IV	1 mg/kg IV 0.5-1 mg/kg/h IV	Precede with IV benzodiazepine to prevent myoclonus
Alfaxalone	2-3 mg/kg IV 6-9 mg/kg/h IV	5 mg/kg/h IV 7-11 mg/kg/h IV	Give slowly to effect to decrease dosage, apnea, and hypotension

ICU, Intensive care unit; *NA*, does not apply.

Fentanyl

Fentanyl is a potent opioid with relatively short duration of action in most dogs: approximately 20-30 minutes when administered intravenously.[3] Duration of action extends to 40 minutes when administered by other routes. Intravenous fentanyl with or without another sedative may be ideal for short duration needs.

Hydromorphone

Hydromorphone has a relatively short duration of action when administered intravenously: approximately 40-60 minutes.[4] Duration of action extends to approximately 3 hours when administered subcutaneously or intramuscularly.

Oxymorphone

Oxymorphone is more potent than hydromorphone, indicating that the dosage required to get an equivalent effect is actually lower. Duration of action is similar to hydromorphone.

Morphine

Morphine has the highest likelihood of inducing vomiting with the initial dose. Morphine can also induce histamine release and potentially hypotension in hypovolemic dogs when administered IV.[5] These properties may make morphine less desirable in more critically ill animals. An exception might be in dogs with pulmonary edema. The increased capacitance of large vessels may improve clinical signs associated with pulmonary edema and induce some sedation with low dosages IV in dogs.[6] The ability of morphine to induce analgesia is related to morphine's conversion to morphine-6-glucuronide (M6G) via the first-pass effect. Data suggest that cats produce little to no M6G.[7] As such, morphine should not be administered to cats for analgesia purposes.

Methadone

Methadone induces less sedation than morphine but does not induce vomiting in virtually 100% of patients.[8] Duration of action lasts about 45 minutes when given IV and about 4 hours IM or SC. Methadone tends to induce euphoria rather than dysphoria in cats, a great advantage for this species and the people around them.

Butorphanol

Butorphanol works as a kappa receptor agonist and a mu receptor antagonist. It induces mild sedation and has a ceiling effect for analgesia, providing only mild to moderate pain control. Even at higher dosages, butorphanol induces pain control for only 45 minutes in dogs,[9] with sedation lasting for several hours. Mild to moderate analgesia duration lasts about 4 hours in cats. Butorphanol should be used cautiously, as it precludes the use of other opioids that are better analgesics for a period of time since butorphanol will antagonize these drugs effects at the mu receptor.

Nalbuphine

Nalbuphine has a similar receptor profile as butorphanol but is very unlikely to induce sedation by itself.[10] It can induce a synergistic analgesic and sedative effect when combined with alpha-2 agonists, such as dexmedetomidine. The lack of inherent behavioral affects can be advantageous when it is desirable to antagonize an opioid's sedation but still retain some analgesia.

Buprenorphine

Buprenorphine has been classified as a partial mu agonist and a mu antagonist, indicating that at typical dosages, it can only induce mild to moderate pain control. Newer data indicate that at higher dosages, buprenorphine can induce maximal pain control in cats for a duration of 24 hours.[11,12] This may be desirable in some cats but buprenorphine should be used with caution in the critical care unit as opioid antagonists do not easily reverse it. As a mu receptor antagonist, buprenorphine can reverse the effects of mu receptor agonists, such as hydromorphone. There is little to no benefit to the use of buprenorphine for significantly ill dogs.

Naloxone

Naloxone can be used in a dose-response manner to induce different effects. Low-dose naloxone can partially reverse an opioid and facilitate extubation by increasing laryngeal reflex activity. Some analgesia and sedation will remain. Higher-dose naloxone can completely reverse the sedative and analgesic effect of opioids (except buprenorphine). Depending on time of administration compared to that of the opioid, the patient may become re-narcotized since naloxone has a relatively short half-life.[13] Redosing of naloxone may be necessary.

Dexmedetomidine

Dexmedetomidine is an alpha-2 agonist which can provide moderate to intense sedation, analgesia, and muscle relaxation. Micro-doses can also synergistically increase sedation and analgesia already induced by opioids. These beneficial effects do not come without potential side-effects. Dexmedetomidine increases parasympathetic tone and decreases sympathetic tone, resulting in bradycardia, decreased stroke volume, decreased cardiac contractility, decreased cardiac output, and decreased overall perfusion.[14] Dexmedetomidine also decreases oxygenation. As such, dexmedetomidine should always be used cautiously but even more so in sicker patients. As mentioned above, the low dosage of dexmedetomidine is useful in patients already receiving opioid infusions. Micro-dose dexmedetomidine appears to have minimal cardiac effects.

Midazolam and Diazepam

These benzodiazepines can be very useful in combination with opioids as patients become older and more debilitated. Benzodiazepines have a much higher likelihood of inducing excitement in younger, healthy dogs. As patients get sicker, it is possible to even intubate a patient with just a benzodiazepine. The greatest difference between midazolam and diazepam is that the former is water soluble and the latter is in a propylene glycol base.[15] The aqueous solubility of midazolam makes it more user-friendly, allowing it to be mixed with virtually any drug without the concern of precipitation. Midazolam also has better uptake via non-IV routes. Diazepam should be administered slowly as large doses of propylene glycol can induce bradycardia.

Sevoflurane

Although sevoflurane is thought of as an anesthetic, low dosages can be safely used for sedation. Sevoflurane does not possess a noxious odor compared to isoflurane and therefore is very amenable to be used as an inhaled sedative.[16] Patients can be masked or boxed for moderate to heavy sedation without producing high anxiety and escape behavior. Because the negative effects are dose-dependent and the likelihood for significant decreases in cardiac output is minimized, sevoflurane may be the most desirable approach to sedation for sicker, highly stressed (fractious) cats. The noxious odor associated with isoflurane precludes its humane use for box or mask sedation or induction of anesthesia.

Sevoflurane is also the most desirable gas anesthetic for maintenance of anesthesia. Its low blood gas solubility coefficient allows rapid induction, recovery, and most importantly changes in depth of anesthesia. Practitioners should always strive for maximal control for anesthetized patients. Sevoflurane provides that control better than any other gas anesthetic and is insignificantly more expensive than others.[17]

Atropine and Glycopyrrolate

These anticholinergics can be used to prevent and/or treat bradycardia from increases in parasympathetic tone related to opioid and alpha-2 agonist administration. Their use with alpha-2 agonists is a bit controversial but one can argue the benefit of increasing heart rate to increase cardiac output. Under anesthesia, all patients benefit from a normal sinus rhythm. Awake, non-anesthetized patients tolerate deviations from normal sinus rhythm much better than those who are anesthetized. Anesthetics disturb cardiac function to a significant degree.

The greatest differences between atropine and glycopyrrolate revolve around penetration of the blood-brain barrier and placental barrier, the former being more important in more critical patients. Atropine crosses the blood-brain barrier and can induce sedation.[18] It can also cross the placental barrier and induce sedation in neonates during a cesarean section. Glycopyrrolate does not induce these effects and is preferred.[18]

Propofol

Propofol can be administered at low dosages for sedation or higher dosages for induction of anesthesia and maintenance of anesthesia. Propofol can induce vasodilation, decreased cardiac contractility and respiratory depression in a dose-dependent manner. The slower that propofol is administered IV for induction of anesthesia, the lower the dosage becomes with fewer side-effects. Propofol is appropriate for most sick patients. Other choices should be considered for patients with significant cardiac disease or those with significant hemodynamic dysfunction. Continuous infusion propofol may be desirable to gas anesthesia, relative to some cardiovascular variables.[19] This approach does not allow quite the same control as sevoflurane or as rapid recovery.

Etomidate

Etomidate has been the stand-by drug for higher risk patients for centuries. It induces less overall effect on the cardiovascular system. There are side-effects to consider. In addition to adrenal cortical suppression of debatable clinical importance, etomidate produces myoclonus upon induction.[20] It should be preceded by or followed with an IV benzodiazepine. Prior benzodiazepine administration may be more desirable as it will prevent the myoclonus; however, there is a possibility of transient excitement from it. It is possible that a benzodiazepine following etomidate will not prevent the myoclonus, resulting in undesirable muscle rigidity for the duration of the effects of etomidate.

Alfaxalone

Alfaxalone is a newer drug which can be used in a similar fashion as propofol for sedation, induction, and maintenance of anesthesia. Slower administration permits lower dosage and fewer cardiopulmonary and other adverse effects. Propofol induces a better recovery than alfaxalone when administered for short-term sedation alone or as an infusion.[21] Alfaxalone and propofol provide better hemodynamic stability than gas anesthesia.

Protocols (Figure 138-1)

There is an infinite combination of protocols for sedation and anesthesia. One first needs to determine the goal to be accomplished and then whether sedation or anesthesia is most appropriate. The practitioner then should determine the combination of drugs that can achieve the goal with the fewest undesirable effects. Common sedation protocols may encompass a combination of a benzodiazepine and an opioid or a low-dose alpha-2 agonist and an opioid. A combination of an opioid and propofol or alfaxalone can also be appropriate. In sicker patients, drugs via the IV route facilitate better control. All patients should receive supplemental oxygen regardless of the protocol. Anesthesia is typically accomplished with a sedation protocol followed by induction to anesthesia.

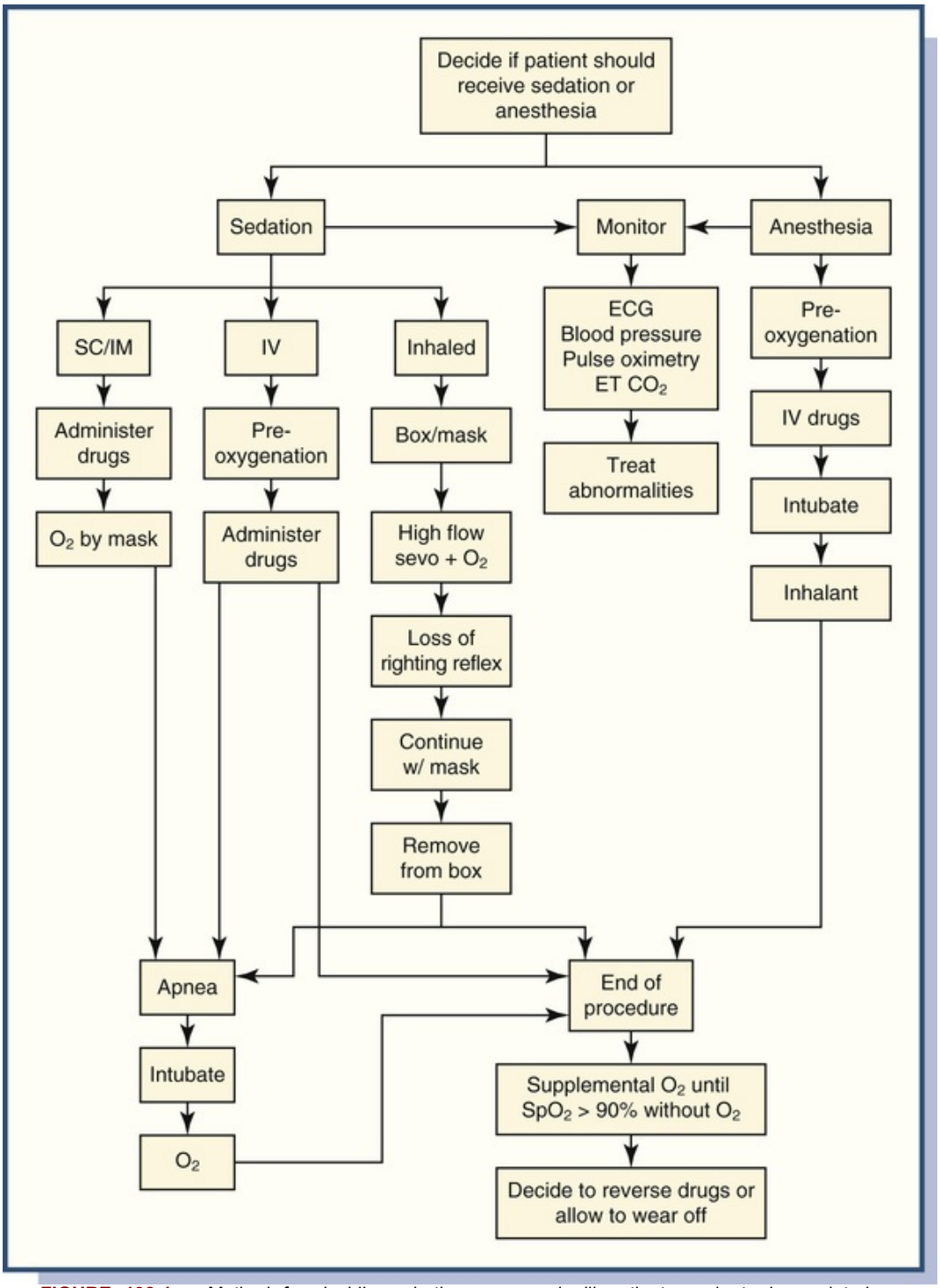

FIGURE 138-1 Method for deciding whether a severely ill patient needs to be sedated or anesthetized. *ECG,* Electrocardiogram; *ET,* end-tidal; *sevo,* sevoflurane; *SpO2,* oxygen saturation (%).

Monitoring and Recovery

Monitoring of vital signs by a dedicated anesthetist is always important when sedating or anesthetizing patients. This concept becomes even more important in more critical patients. Monitoring of sedated patients should include blood pressure and ECG monitoring at a minimum (see ch. 99 and 103). Pulse oximetry (see ch. 98) and capnography should be included if possible. Sedated patients should always receive supplemental oxygen, especially if pulse oximetry is not possible (see ch. 131).

Anesthetized patients should have ECG, blood pressure, and oxygen saturation monitored at the minimum. Capnography should be monitored if available, as a rapid decrease in expired carbon dioxide can represent acute changes in cardiac output.[22]

Recovery from sedation and anesthesia should be closely monitored for adverse events. Patients should have oxygen saturation monitored until it is proven they can maintain adequate oxygenation (>90% saturation) without supplemental oxygen. Patients may need to remain intubated, receive oxygen by mask or nasal cannula or be placed in an oxygen cage for some period of time to allow appropriate oxygenation until sedation or anesthesia have worn off.

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CHAPTER 139

Initial Evaluation of Respiratory Emergencies

Carol R. Reinero

Dogs and cats presenting with the chief complaint of respiratory distress require determination of the general cause in order to streamline the diagnostic and therapeutic approach in a timely fashion. One scheme to classify the causes of respiratory distress involves the following eight categories: (1) upper airway obstruction, (2) lower airway obstruction, (3) flail chest, (4) abdominal enlargement, (5) pulmonary parenchymal disease, (6) pleural cavity disorders, (7) pulmonary thromboembolism (PTE), and (8) "look-alike" syndromes. This classification system is useful because the first four causes usually can be recognized quickly at the time of initial assessment by the physical appearance of the dog or cat, the cycle of respiration predominantly affected, and audible sounds that might be heard resulting from certain disorders. The remaining four causes will require additional diagnostic testing to establish a definitive diagnosis. Also, see ch. 28 for additional information about chief complaints involving abnormal respirations.

Eight Major Categories of Respiratory Distress

Upper airway obstruction is due to mechanical or functional narrowing of the large airways (pharynx, larynx, or trachea cranial to the thoracic inlet) and includes intraluminal or extraluminal masses (neoplasia, granuloma, abscess, blood clots, polyps), foreign bodies, laryngeal paralysis, laryngeal collapse, elongated soft palate, everted laryngeal saccules, tracheal collapse, tracheal stenosis, or tracheal stricture (see ch. 238, 239, and 241). Obstruction of the trachea within the thoracic cavity is included in the category of *lower airway obstruction*. Lower airway obstruction also can be caused by narrowing of the bronchial lumen due to bronchospasm, accumulation of mucus or other exudate, bronchial wall edema, or diffuse bronchomalacia. The classic example of a disease associated with the first three of these changes is feline asthma. Asthma in dogs is an exceedingly rare diagnosis, but lower airway obstruction in dogs can be seen with severe chronic bronchitis due to bronchomalacia, which is associated with passive collapse of the airways on exhalation. *Flail chest* results from trauma to the thoracic cavity, where there is destabilization of a portion of the rib cage (i.e., multiple adjacent ribs are fractured at two different locations, leaving a segment that is detached from the rest of the rib cage). Paradoxical respiration is seen so that, as an animal inhales, the thoracic wall segment is sucked inward, and as the animal exhales, the segment is displaced outward (see ch. 245). *Severe abdominal enlargement* can put pressure on the diaphragm and make it more difficult for the thoracic cavity to expand on inhalation. Examples of conditions associated with abdominal enlargement include ascites, gastric dilation, hepatosplenomegaly, abdominal masses, pregnancy, or pyometra (see ch. 18). *Pulmonary parenchymal diseases* are disorders affecting the terminal and respiratory bronchioles, interstitium, alveoli, or vasculature. They can be associated with infiltration by infectious microorganisms, inflammatory cells, or neoplastic cells; the airspaces can be filled with edema fluid or foreign material; or lung tissue can be replaced with fibrotic tissue. Examples of conditions affecting the pulmonary parenchyma include infectious pneumonia (bacterial, fungal, viral, protozoal, and parasitic), aspiration pneumonia/pneumonitis, interstitial lung diseases, pulmonary edema (cardiogenic or noncardiogenic), hemorrhage, neoplasia, and acute respiratory distress syndrome (ARDS) (see ch. 242). *Pleural cavity disorders* arise when the space between the parietal and visceral pleura, which normally contains just a small amount of fluid for lubrication, fills with fluid (pleural effusion), air (pneumothorax), a mass, or abdominal organs (e.g., diaphragmatic hernia) (see ch. 244). *Pulmonary thromboembolism* refers to obstruction of blood flow in the pulmonary arteries by a thrombus or by an embolus formed in the systemic venous system or right side of the heart. Any condition causing an abnormality in blood flow, endothelial damage, or hypercoagulability can predispose to thromboembolism (see ch. 243). Finally, *look-alike syndromes* are conditions that result in apparent difficulty in breathing due to nonrespiratory causes, such as pain, severe anemia, hyperthermia, acidosis, drugs (e.g., opioids), and hypotension.

Evaluation of the pattern of breathing (Figure 139-1) can be useful to help localize the region of the

respiratory tract that is affected. A "distance" examination in which the animal is observed for auditory and visual clues should be followed by a "hands-on" examination. In an emergency situation, the first four causes of respiratory distress (upper and lower airway obstruction, flail chest, and abdominal enlargement) should be discernible on initial examination of a patient. Dogs and cats with upper respiratory obstruction (Video 139-3) will have a characteristic stridorous or squeaking noise that is readily audible, even without a stethoscope. Additionally, respiratory distress will occur on inhalation. Dogs and cats with a lower airway obstruction should have an audible wheeze (although sometimes a stethoscope is required to hear quieter wheezes). In these cases, respiratory distress will occur predominantly on exhalation, the so-called "expiratory push" (Video 139-2). Visual examination will reveal if flail chest (with paradoxical respiration) or abdominal enlargement (with increased inspiratory effort and no audible noise) is present.

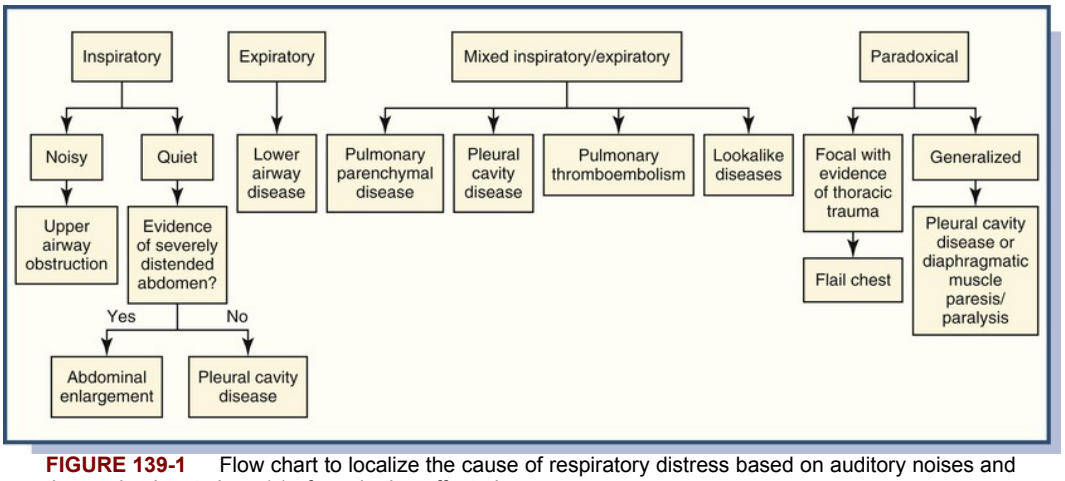


FIGURE 139-1 Flow chart to localize the cause of respiratory distress based on auditory noises and the predominant phase(s) of respiration affected.

For the remaining four causes of respiratory distress, physical examination could provide additional useful clues. Thoracic auscultation might reveal absent or quiet lung sounds, which are compatible with pleural cavity disease; crackles, which support pulmonary parenchymal disease; and murmurs or arrhythmias, which could indicate pulmonary parenchymal disease associated with underlying cardiac disease (cardiogenic pulmonary edema), pleural cavity disease (especially in cats), or PTE. Physical examination can increase the index of suspicion for look-alike diseases if very pale/white mucous membranes are seen (severe anemia), substantially elevated body temperature is measured, or signs of pain are elicited on palpation. Additional diagnostics commonly are required to discriminate these four causes of respiratory distress.

In an emergency situation, if there are decreased pulmonary or cardiac sounds on auscultation or while not absolutely pathognomonic for pleural cavity disease, if there is a paradoxical breathing pattern (Video 139-1), it is prudent to proceed directly to thoracocentesis both as a diagnostic and as a therapeutic measure; focused assessment with ultrasound can quickly identify a pocket of pleural effusion, if one exists, for safest thoracocentesis (see ch. 149). Removal of any air or fluid will help stabilize the patient for further diagnostics (see ch. 102).

Radiography

Radiography likely is the single most important diagnostic tool for patients in respiratory distress. It is important to attempt to localize the cause of respiratory distress as described above, because if disease is localized to the upper airways, cervical and thoracic radiographs should be performed. For suspected dynamic airway collapse, inspiratory and expiratory cervical and thoracic radiographs are required to highlight the obstructed area during the different phases of the respiratory cycle. Even with upper airway obstruction, it is still important to obtain thoracic radiographs to evaluate for noncardiogenic pulmonary edema (which can result from severe upper airway obstruction) and for metastatic disease if the airway obstruction is due to a mass. Significant thoracic radiographic changes can include intrathoracic tracheal narrowing (collapse or obstructive mass), a bronchial pattern with or without hyperinflation (lower airway disease), an interstitial or alveolar pattern (pulmonary parenchymal disease), or evidence of pleural cavity

disease (pleural effusion, pneumothorax, pleural mass, loss of a clear border of the diaphragm, or a blunted tortuous vessel with uneven vascular diameters and distribution of blood flow between lung lobes [PTE]). Other nonspecific thoracic radiographic findings can include cardiomegaly, pulmonary nodules, or atelectasis.

Additional Diagnostics

Additional diagnostic testing beyond the scope of this chapter can be planned based on results of the radiographic examination to more precisely identify the underlying disease process. Other useful diagnostics can include some of the following: complete blood count, serologic titers for infectious diseases, fecal examination (see ch. 81), heartworm testing (see ch. 255), advanced thoracic imaging (ultrasound, fluoroscopy, or computed tomography), abdominal imaging (looking for related disease in the abdominal cavity; see ch. 88), fundic examination (see ch. 11), arterial blood gas analysis (see ch. 75), fine needle aspiration for cytology/culture (see ch. 89 and 93), laryngeal examination, transtracheal or endotracheal wash, bronchoalveolar lavage (see ch. 101), bronchoscopic examination (see ch. 101), bronchial mucosal or mass biopsies, and biopsies obtained by a key-hole procedure, thoracoscopy, or thoracotomy.

Management

It is crucial to keep in mind that many diagnostic tests must await appropriate patient stabilization. Any dog or cat with respiratory distress should benefit, to some degree, from the provision of supplemental oxygen (see ch. 131). In patients with suspected upper airway obstruction, sedation can minimize struggling and markedly improve respiratory comfort (see ch. 28 and 138). Securing an airway by oral intubation or tracheostomy can be required in some cases. In dogs, monitoring body temperature and cooling as needed is an important aspect of medical management, since panting to dissipate heat can be markedly impaired. Finally, an anti-inflammatory dose of corticosteroids can help reduce swelling in the upper airways. For cats with lower airway obstruction, minimal handling, bronchodilators (injectable or inhaled) to relieve bronchoconstriction, and corticosteroids, can provide symptomatic relief (see ch. 97). Bronchodilators likely are of less benefit to dogs with lower airway obstruction, as the most common diseases in this category are intrathoracic tracheal collapse and diffuse bronchomalacia—neither of which is associated with smooth muscle constriction of the bronchi. Sedation and an anti-inflammatory dose of corticosteroids also could be useful in these cases. For animals with flail chest in the emergent situation, placing the patient in lateral recumbency with the affected side down, and pain management, are important. For patients with abdominal distension, addressing the underlying disorder in the abdominal cavity is required. For patients with pulmonary parenchymal disease, initial therapeutics can include: empiric trial with furosemide if there is evidence of heart failure; judicious fluid therapy if there is no evidence of heart failure; airway humidification; nebulization; coupage; antimicrobials; and/or anti-inflammatory drugs (see ch. 97). For animals with pleural cavity disease, thoracocentesis can be helpful therapeutically if there is fluid or air accumulation (see ch. 102). For patients with PTE, oxygen supplementation is usually the main means of stabilization, although the ventilation : perfusion mismatch that is a hallmark of PTE can limit the efficacy of oxygen supplementation; once a diagnosis of the condition is made, anticoagulants and/or thrombolytics can be considered (see ch. 131 and 243). Finally, patients with a look-alike syndrome generally will not be oxygen-responsive since the disease is not primarily of the respiratory system, and a search for nonrespiratory diseases should be made and the underlying disorder addressed appropriately.

Summary

Having a scheme to classify the causes of respiratory distress can help in the approach to patients presenting in an emergency situation. Identification of audible noises (stridor and wheeze) and breathing patterns (inspiratory distress, expiratory distress, paradoxical breathing, and mixed inspiratory and expiratory distress) assists in localizing the site of respiratory disease. After stabilizing the patient, appropriate diagnostics and therapeutics can be targeted to focus on the location and underlying cause of the respiratory signs.

CHAPTER 140

Cardiopulmonary Arrest and CPR

Daniel John Fletcher, Manuel Boller

Cardiopulmonary arrest (CPA) is a complete cessation of blood flow, ventilation, and oxygenation of the blood. Left untreated, CPA results in irreversible ischemic injury and ultimately death. Treatment is referred to as cardiopulmonary resuscitation (CPR). It is initially focused on restoring blood flow and oxygen delivery to tissues using chest compressions and positive pressure ventilation, delaying the onset of ischemic injury to the brain and other vital organs, and restoring blood flow to the heart to achieve return of spontaneous circulation (ROSC). Rapid identification of CPA and immediate institution of high quality CPR are essential if the progression of CPA to death is to be interrupted. In 2012, the Reassessment Campaign on Veterinary Resuscitation (RECOVER) initiative published the first evidence-based veterinary CPR guidelines.[1,2] The results of this extensive evidence review are summarized in the algorithm shown in Figure 140-1.

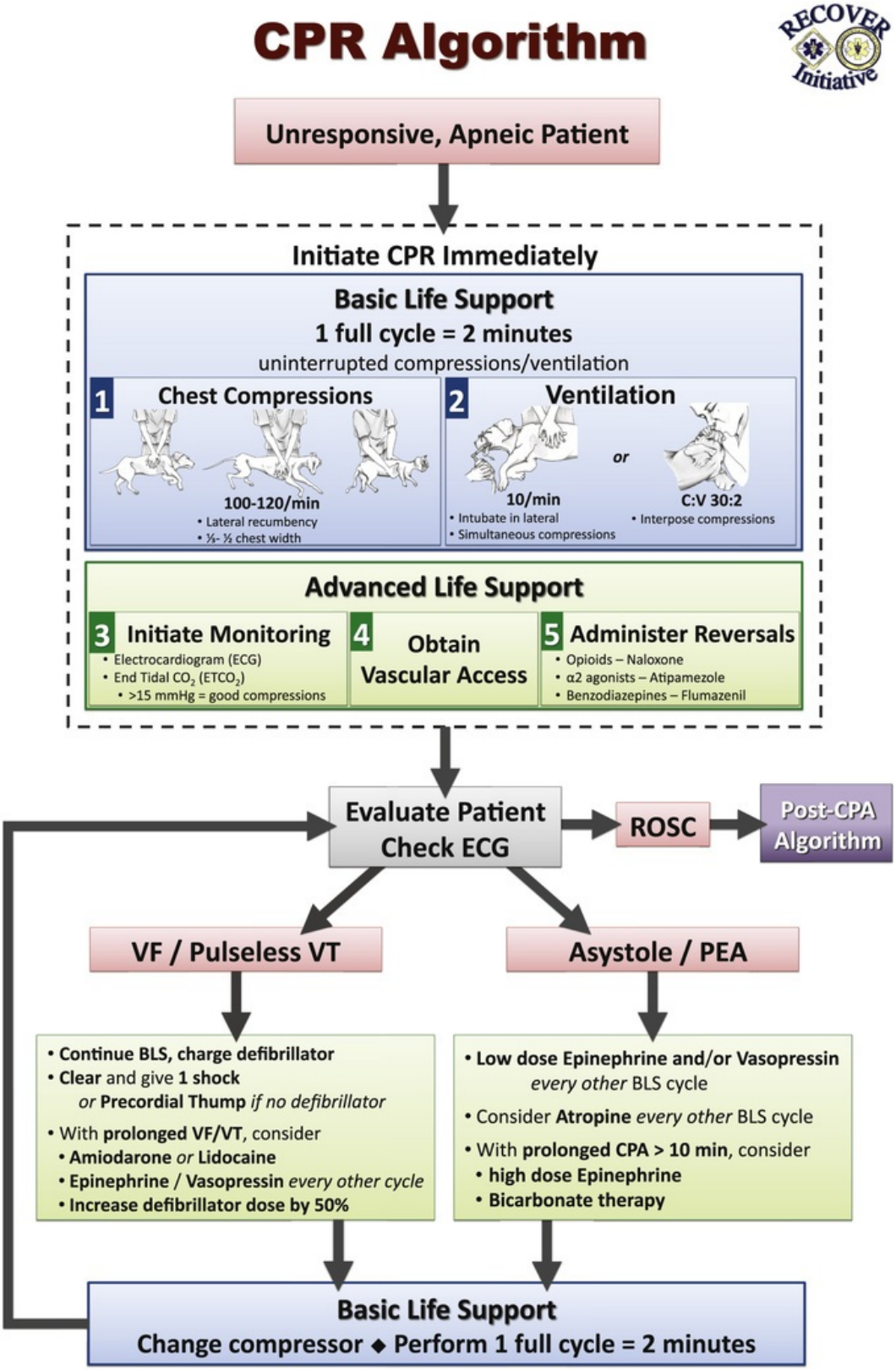


FIGURE 140-1 RECOVER CPR algorithm chart. *BLS,* Basic life support; *CPA,* cardiopulmonary arrest; *CPR,* cardiopulmonary resuscitation; *C:V,* compression to ventilation ratio; *$ETCO_2$,* end tidal CO_2; *PEA,* pulseless electrical activity; *ROSC,* return of spontaneous circulation; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia. (Reproduced with permission from Fletcher DJ, Boller M, Brainard BM, et al: RECOVER evidence and knowledge gap analysis on veterinary CPR. Part 7: Clinical guidelines. *J Vet Emerg Crit Care [San Antonio]* 22[Suppl 1]:S102-131, 2012.)

Diagnosis of CPA

Cardiopulmonary arrest is an important differential diagnosis in any acutely unresponsive patient. It is a clinical diagnosis based on the presence of unconsciousness and apnea. A rapid, standardized airway-breathing (AB) assessment of 5-10 seconds duration and focused on ruling out CPA should be undertaken immediately when a patient is unresponsive.

Visual inspection of the airway should include opening the mouth, pulling out the tongue, and examining the oral cavity to identify any masses, swellings, or foreign objects. Suction or gentle swabbing should be attempted first to clear the airway, and digital palpation reserved for cases in which that approach does not resolve the issue. A laryngoscope should be used if available. In all cases, if the patient responds to manipulation of the airway, the AB exam should be halted as CPA has been ruled out.

The breathing assessment in an unresponsive patient is targeted at the rapid identification of apnea by observing the patient for chest excursions, by feeling for chest movements, by ausculting for lung sounds, or by using a glass slide or cotton in front of the nares to identify airflow. In obviously apneic patients, the airway exam may be done using a laryngoscope during intubation as described in the Basic Life Support (BLS) section below.

Although a full ABC assessment (airway, breathing and circulation) was previously advocated, a circulation assessment when evaluating an unresponsive patient is currently not recommended as it was found unreliable.[1,3-7] Nevertheless, if a circulation assessment is undertaken, it should not prolong the ABC assessment beyond 5-10 seconds. If uncertainty about the diagnosis of CPA persists after these 10 seconds, CPR should be initiated immediately rather than performing any additional diagnostic assessment.[1] Evidence suggests a strong association between delay in initiation of CPR and mortality.[8-10]

Initiation of CPR

The two primary aspects of CPR are basic life support (BLS) and advanced life support (ALS). The dashed box at the top of the CPR algorithm (see Figure 140-1) encloses the essential steps in initiating CPR. The goal is to complete all five of these tasks in the first 2 minutes, but the team should complete them in the order recommended.

Basic Life Support

BLS is focused on restoration of circulation, ventilation, and oxygenation of the blood. In the absence of good quality BLS, ROSC is unlikely. BLS consists of chest compressions and positive pressure ventilation.

Chest Compressions

The goals of chest compressions are to provide (1) pulmonary blood flow for excretion of carbon dioxide (CO_2) and oxygenation of pulmonary capillary blood, and (2) oxygen delivery to tissues to maintain cellular metabolism. If optimal external chest compressions are provided, only approximately 25 to 40% of a normal cardiac output may be generated.[11,12] Therefore, chest compression technique must be meticulous.

After a 5-10 second AB assessment for confirmation of CPA, chest compressions must be initiated immediately. Any delays may worsen outcomes.

In most cases, the patient should be placed in right or left lateral recumbency for chest compressions, and the chest compressed one third to one half its width with each compression. Full elastic recoil of the chest in between compressions is important to maximize blood flow to heart and brain.[13,14] The chest should be compressed at a rate of 100 to 120 per minute in all dogs and cats. Because it can take a full minute of chest compressions to attain a steady state arterial blood pressure, compressions should be delivered in uninterrupted 2-minute cycles whenever possible.[15-17] Rotation to a new compressor after each cycle reduces rescuer fatigue and poor compression quality.[18,19]

The two theories explaining the generation of systemic blood flow using external chest compressions (i.e., cardiac pump and thoracic pump theory) direct the recommended hand position on the chest based on chest conformation.[20,21] In medium- and large-breed dogs with round chest conformations (width and depth of the chest approximately equal, e.g., Labrador Retrievers, Golden Retrievers, Mastiffs), compressions over the highest point on the lateral thoracic wall with the patient in lateral recumbency will maximally compress the chest and increase intrathoracic pressure (E-Figure 140-2, *A*). In contrast, in medium to large breed dogs with a keel-chested conformation (significantly deeper than wide, e.g., sight hounds), compressions should be

focused directly over the heart (E-Figure 140-2, *B*). In markedly flat-chested dogs (chests significantly wider than deep, e.g., English Bulldogs), placing the patient in dorsal recumbency and focusing compressions over the sternum may be the most effective approach (E-Figure 140-2, *C*).

E-FIGURE 140-2 Recommended chest compression techniques according to chest conformation and animal size. **A,** For large, round-chested dogs, chest compressions over the widest portion of the chest are reasonable, with the animal in either left or right lateral recumbency. **B,** In keel-chested (i.e., deep, narrow-chested) dogs, chest compressions directly over the assumed location of the heart are reasonable, with the animal in either left or right lateral recumbency. **C,** In barrel-chested dogs such as English Bulldogs, compressions over the mid-sternum may be considered, with the animal in dorsal recumbency. **D,** In cats and small dogs (<10 kg) with compliant chests, the use of a one-handed technique with the stronger hand wrapped around the sternum directly over the heart and the other hand around the back may be considered.

Compressor posture also affects chest compression quality. Using locked elbows with fingers interlaced and one hand on top of the other while keeping the shoulders directly above the hands allows compressions to be driven by core abdominal muscles rather than the arms (Figure 140-3). This approach reduces fatigue, allowing maximal compression force for a longer period of time. To optimize posture, the rescuer should stand on a stool, kneel on the table behind the patient, or place the patient on the floor and kneel behind, as necessary.

FIGURE 140-3 Correct posture during chest compressions. The open arrows indicate the four critical elements of rescuer posture: (1) the hands are stacked such that one focal compression point results, (2) the shoulders are positioned vertically above the compression site, (3) the arms are straight with locked elbows, and (4) the compression force is generated by the core muscles and not the arms. Note that the resuscitator is positioned towards the dorsal aspect of the animal to minimally compromise access of other team members to the limbs and trunk.

Small dogs and cats have higher thoracic compliance due to their narrow chest conformation and more elastic rib cages. Chest compressions should be focused over the heart in most cases (E-Figure 140-2, *D*). A one-handed technique may be attempted in these patients by wrapping the hand around the chest at the level of the sternum (see E-Figure 140-2, *D*). Compressions are accomplished by pushing the thumb against the fingers on the other side of the chest, aiming to compress from the apex to the base of the heart. Because of the high thoracic compliance in these patients, this one-handed technique may reduce the risk of over-compressing the chest to more than one half its width.

Ventilation

The second priority of BLS is positive-pressure ventilation. The RECOVER guidelines recommend initiating ventilation as soon as possible in dogs and cats with CPA.[1,3] Dogs and cats commonly experience primary respiratory arrests, so ventilation is a critically important component of resuscitation, unlike adult people with out-of-hospital cardiac arrest that predominantly have CPA of primary cardiac etiology.[10,22-26]

The animal should be intubated as soon as possible. Intubation in lateral recumbency in both dogs and cats is easily accomplished, so chest compressions should continue during endotracheal (ET) tube placement. Mouth-to-snout or mask-to-snout ventilation is an acceptable, but inferior alternative if an ET tube is not immediately available. Mouth-to-snout ventilation is accomplished by closing the patient's mouth with one hand, extending the neck to align the nares and the spine, and making a seal over both nares with the mouth. Two quick breaths (i.e., inspiratory time of 1 second) are administered by blowing firmly into the nares to inflate the lungs while watching the chest rise to ensure breath delivery.

Compression of the lungs during chest compressions makes simultaneous chest compression and mouth-to-snout ventilation ineffective. For non-intubated patients, the 30:2 BLS technique is used, in which 30 chest compressions are delivered and compressions are then paused briefly while two breaths are administered as quickly as possible. Alternating compressions and ventilations are done in 2-minute cycles, with compressor rotation every 2 minutes to reduce fatigue. In intubated patients, chest compressions and ventilations can be administered concurrently as long as the ET tube cuff is inflated. This approach minimizes pauses in chest compressions, improving blood flow to the tissues. Patients that are intubated with an inflated ET tube cuff

should receive one breath every 6 seconds with an inspiratory time of 1 second. Excessive ventilation is harmful and should be avoided.[27]

Advanced Life Support

The next priority is implementation of the initial aspects of ALS. ALS includes drug and fluid therapy, as well as defibrillation. The RECOVER CPR algorithm lists in priority order the first three steps of ALS initiation, including attachment of monitoring devices, obtaining vascular access, and administration of reversal agents (see Figure 140-1). The CPR team leader should assign ALS interventions in the order listed on the algorithm.

Initiate Monitoring

Many commonly used monitoring devices, such as pulse oximeters and blood pressure monitors, are of little to no use during CPR because of motion artifact.[28] However, electrocardiogram (ECG; see ch. 103) and end tidal carbon dioxide ($ETCO_2$) monitors are essential, and should be attached as soon as possible after the initiation of BLS.[1]

Drug and defibrillation therapy will largely be guided by the ECG arrest rhythm. Therefore, the highest priority during the initiation of ALS is attaching ECG leads so that at the end of the first 2-minute cycle of chest compressions the ECG can be evaluated during the brief pause during the change in compressor when motion artifact is not present. If the ECG is not attached by the end of the first cycle of BLS, it will be another 2 minutes before an opportunity to diagnose the rhythm emerges, delaying the institution of ALS therapies.

$ETCO_2$ monitors are resistant to motion artifact, and $ETCO_2$ monitoring is strongly recommended during CPR. The $ETCO_2$ reflects the amount of CO_2 present in the alveoli. Because alveolar CO_2 arises from the tissues and is delivered to the lungs by blood flow, it is proportional to pulmonary blood flow and positively correlates with cardiac output.[29-31] If good blood flow is being generated by high quality chest compressions, the $ETCO_2$ will be higher than if blood flow is low. Because minute ventilation also affects $ETCO_2$, consistent ventilation according to the BLS guidelines is essential if $ETCO_2$ is used to evaluate the effect of BLS on blood flow. If the $ETCO_2$ is less than 15 mm Hg, the approach to BLS should be critically evaluated by team members and altered in an attempt to address the issue.[32] Another use of $ETCO_2$ during CPR is early identification of ROSC without stopping compressions.[33-35] Identification of a sudden, rapid rise in $ETCO_2$ is indicative of the increased blood flow of ROSC, and should prompt the rescuers to assess the pulse.

Obtain Vascular Access

If the patient has an intravenous (IV) catheter in place, its patency should be confirmed. In dogs and cats, presence of an IV catheter prior to CPA was associated with ROSC.[10] In patients without pre-existing IV access, a catheter should be placed as soon as possible (see ch. 75 and 76). Repeated or prolonged attempts at percutaneous catheterization are not recommended. Venous cutdown procedures are relatively simple and facilitate more rapid catheter placement.[36] Veins closest to the heart (cephalic or jugular) should be prioritized over those more distant (lateral and medial saphenous).[37] During chest compressions, cephalic cutdowns may be less challenging than jugular cutdowns. The dependent limb is usually easier to access because the vessel runs medially. Intraosseous (IO) catheters in the femur are often easy and quick to place in puppies and kittens (see ch. 77).[36] In adult animals, commercial IO drill devices facilitate very rapid placement, usually along the medial humerus.

Administer Reversals

Naloxone (0.04 mg/kg IV/IO) may be used to reverse opioids, flumazenil (0.01 mg/kg IV/IO) for benzodiazepines, and atipamezole (0.1 mg/kg IV/IO) or yohimbine (0.1 mg/kg IV/IO) for alpha$_2$-agonists. A drug and dosing chart including recommended dosing of reversal agents should be readily available (Figure 140-4).

CPR Emergency Drugs and Doses

		Weight (kg)	2.5	5	10	15	20	25	30	35	40	45	50
		Weight (lb)	5	10	20	30	40	50	60	70	80	90	100
	DRUG	DOSE	ml	ml	ml	ml	ml	ml	ml	ml	ml	ml	ml
Arrest	Epi Low (1:1000; 1mg/ml) every other BLS cycle x3	0.01 mg/kg	0.03	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5
Arrest	Epi High (1:1000; 1 mg/ml) for prolonged CPR	0.1 mg/kg	0.25	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
Arrest	Vasopressin (20 U/ml)	0.8 U/kg	0.1	0.2	0.4	0.6	0.8	1	1.2	1.4	1.6	1.8	2
Arrest	Atropine (0.54 mg/ml)	0.04 mg/kg	0.2	0.4	0.8	1.1	1.5	1.9	2.2	2.6	3	3.3	3.7
Anti-Arrhythmic	Amiodarone (50 mg/ml)	5 mg/kg	0.25	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
Anti-Arrhythmic	Lidocaine (20 mg/ml)	2 mg/kg	0.25	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
Reversal	Naloxone (0.4 mg/ml)	0.04 mg/kg	0.25	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
Reversal	Flumazenil (0.1 mg/ml)	0.01 mg/kg	0.25	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
Reversal	Atipamezole (5 mg/ml)	100 ug/kg	0.06	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
Defib Monophasic	External Defib (J)	4-6 J/kg	10	20	40	60	80	100	120	140	160	180	200
Defib Monophasic	Internal Defib (J)	0.5-1 J/kg	2	3	5	8	10	15	15	20	20	20	25
Defib Biphasic	External Defib (J)	2-4 J/kg	5	10	20	30	40	50	60	70	80	90	100
Defib Biphasic	Internal Defib (J)	0.2-0.4 J/kg	1	2	2	3	4	5	6	7	8	9	10

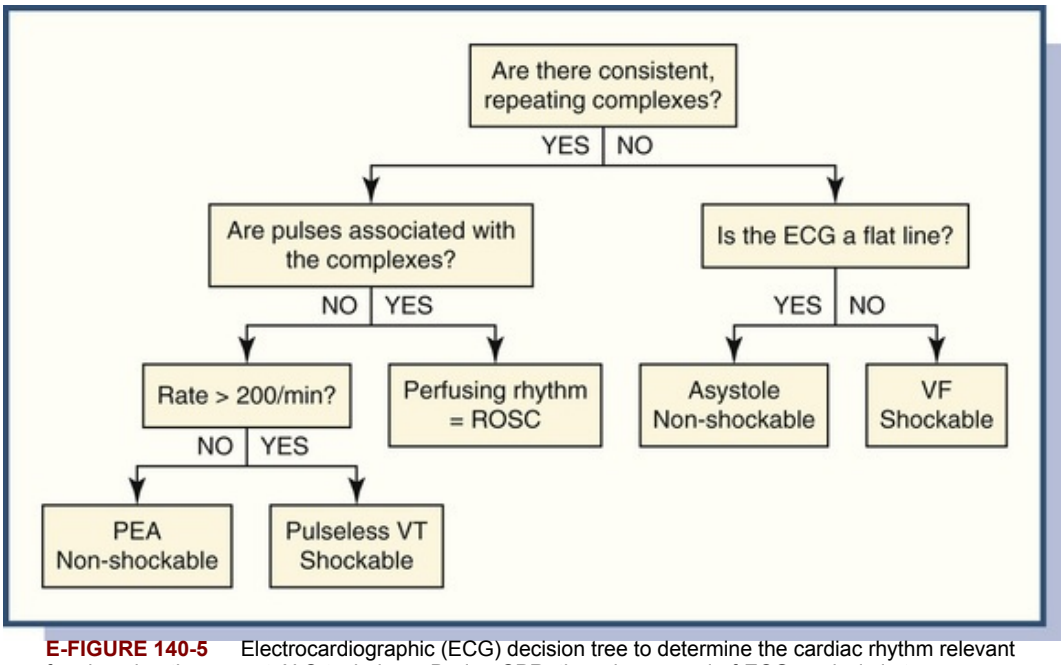
FIGURE 140-4 RECOVER CPR drug dosing chart. Drugs are separated by indication and volumes (mL) are provided by body weight to prevent calculation errors. Defibrillator dosing is for both monophasic and biphasic electrical defibrillators. *CPR*, Cardiopulmonary resuscitation; *Defib*, electrical defibrillation; *Epi*, epinephrine. (Reproduced with permission from Fletcher DJ, Boller M, Brainard BM, et al: RECOVER evidence and knowledge gap analysis on veterinary CPR. Part 7: Clinical guidelines. *J Vet Emerg Crit Care [San Antonio]* 22[Suppl 1]:S102-131, 2012.)

Evaluation of the ECG

The next step in the ECG algorithm (see Figure 140-1) is evaluation of the ECG (also see ch. 248). The correct ALS therapies can only be chosen if the ECG rhythm diagnosis is accurate. All members of the team should look at the ECG monitor during the pause in chest compressions between cycles, and the team leader should call out the rhythm diagnosis. If team members disagree about the rhythm diagnosis, opposing views should be debated after chest compressions have been restarted. The primary goal of CPR ECG analysis is to differentiate: (1) shockable arrest rhythms, (2) non-shockable arrest rhythms, and (3) perfusing rhythms.

ECG Algorithm

A simple algorithm can be used to make a rhythm diagnosis during the inter-cycle pauses in BLS (E-Figure 140-5). The rescuers should take only 3-5 seconds to evaluate the ECG, and if ROSC has not obviously occurred, resume chest compressions. Before pausing chest compressions, one rescuer should prepare to palpate a pulse or apex beat.



E-FIGURE 140-5 Electrocardiographic (ECG) decision tree to determine the cardiac rhythm relevant for choosing the correct ALS technique. During CPR, the primary goal of ECG analysis is to answer a single question: is the rhythm shockable or non-shockable? *ECG*, Electrocardiogram; *PEA*, pulseless electrical activity; *ROSC*, return of spontaneous circulation; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia.

Once chest compressions are paused, determine if there are consistent, repeated complexes present in the ECG. The shape of the complexes is inconsequential. In some cases, there may be more than one type of complex, but the complexes will repeat consistently. If there are repeated complexes and no clear signs of effective circulation (e.g., no apex beats, no pulse, and $ETCO_2 < 30$ mm Hg), the team should quickly estimate the rate. If the rate is less than 200 per minute, this rhythm is most likely pulseless electrical activity (PEA), a non-shockable arrest rhythm. If the rate is greater than 200 per minute, the rhythm is most likely pulseless ventricular tachycardia (pulseless VT), a shockable rhythm.

In the absence of consistent, repeated complexes in the ECG, the next question is whether the ECG is a flat line. If so, this is most likely asystole, a non-shockable arrest rhythm. If there is random, non-flat activity on the ECG, this is most likely ventricular fibrillation (VF), a shockable arrest rhythm. VF can take on different appearances, but the random, chaotic activity is a consistent feature.

Choosing the Correct ALS Therapy

If a shockable arrest rhythm is diagnosed (VF or pulseless VT), defibrillation therapy is the highest priority. If a non-shockable arrest rhythm is diagnosed (asystole or PEA), vasopressor therapy and, potentially, vagolytic therapy are prioritized. If ROSC is diagnosed, post-cardiac arrest (PCA) care is initiated to reduce the risk of recurrence of CPA.[1,38]

Regardless of the arrest rhythm, BLS should be resumed for a full 2 minutes while the correct ALS therapies are administered (blue box at the bottom of the CPR algorithm, Figure 140-1). At the end of each 2-minute cycle of BLS, the arrest rhythm is diagnosed, BLS resumed and the correct ALS interventions are administered. These repetitions of 2-minute cycles are continued until ROSC is achieved or the CPR attempt is aborted.

ALS Therapy

Differentiation of shockable and non-shockable arrest rhythms is imperative because ALS measures for these two types of arrest rhythms are markedly different.

Treatment for Shockable Arrest Rhythms

Electrical defibrillation is the most efficacious therapy for the shockable arrest rhythms.[39] Other therapies

have been investigated, but in the absence of electrical defibrillation, the prognosis is grave.[40,41] However, shockable rhythms were reported to occur in about 1 out of 3 dogs, and 1 out of 5 cats during CPR, suggesting that many patients may be resuscitated successfully even in the absence of an electrical defibrillator.[10]

The goal of defibrillation is to stop the uncoordinated ventricular contractions by simultaneously transitioning as many myocardial cells as possible into a refractory period, allowing synchronized electrical activation of the heart with restoration of coordinated contractions.[42,43] Electrical defibrillators may be either monophasic or biphasic. Biphasic defibrillators are preferred, as lower currents are required for defibrillation and VF is terminated more effectively.[1,39] The dosing chart in Figure 140-4 can be consulted for recommended dosing schemes for both types of defibrillators.

When a shockable rhythm is identified at rhythm check, chest compressions should continue until everything is ready for defibrillation. After defibrillation, chest compressions should immediately resume for 2 minutes until the next rhythm check, as direct conversion to a perfusing rhythm is less likely. In a recent prospective observational study, only 27% of successfully defibrillated animals achieved a perfusing rhythm immediately post-shock.[10] At the end of each 2-minute cycle of BLS, the patient should be defibrillated as long as the rhythm identified is shockable. Subsequent defibrillator doses may be increased by 50% to a maximum dosage of 10 J/kg. All team members should be trained on equipment operations and safety precautions pertinent to defibrillation to prevent injury.

If an electrical defibrillator is not available, a precordial thump (mechanical defibrillation) may be attempted. A precordial thump is a strong blow administered directly over the patient's heart. Although there are a few case reports of successful conversion to a perfusing rhythm using a precordial thump, more recent data show a dismal success rate, and a precordial thump should never be used if an electrical defibrillator is available.[40,41,44]

For patients with prolonged CPA due to a shockable arrest rhythm despite multiple defibrillation attempts, adjunctive antiarrhythmics can be considered. Amiodarone is the most efficacious drug for this purpose, but has only been shown to be useful as an adjunct to electrical defibrillation.[39] Lidocaine may be considered as an alternate but less efficacious therapy. The use of a vasopressor may be considered in patients unresponsive to repeated attempts of defibrillation to redirect blood flow from the periphery to the core organs.

Treatment for Non-Shockable Arrest Rhythms

ALS therapies for the non-shockable arrest rhythms are primarily focused on maximizing perfusion to the heart, lungs and brain, counteracting conditions that may have contributed to CPA, and addressing metabolic derangements secondary to ischemia.

Vasopressors

By increasing peripheral vascular resistance, vasopressors lead to preferential distribution of blood flow toward the core (e.g., heart, lungs, brain), maintaining perfusion to these vital organs.[45] In contrast to defibrillation, which should be done every cycle (i.e., every 2 minutes), vasopressors should be administered every other cycle (i.e., every 4 minutes).

The best studied vasopressor used for CPR is epinephrine, a catecholamine that causes peripheral vasoconstriction by stimulating alpha$_1$ receptors.[46] Using 1 : 1,000 dilution (1 mg/mL) initially, low dosages (0.01 mg/kg IV/IO) are recommended. With prolonged CPR (greater than 10 minutes), a higher dosage (0.1 mg/kg IV/IO) may be considered, but has been associated with lower rates of survival to discharge and should only be used with that understanding. Epinephrine also may be administered via ET tube (0.02 mg/kg low-dose; 0.2 mg/kg high-dose). It should be administered through a long catheter (such as a red rubber feeding tube) fed through the ET tube after diluting the epinephrine 1 : 1 with sterile isotonic saline or sterile water.

Vasopressin is an alternative to epinephrine during CPR; it can be expected to be of similar or higher efficacy.[39,47-52] Its vasoconstrictive effects are achieved via activation of peripheral V1 receptors. Vasopressin may be used instead of or in addition to epinephrine during CPR at a dosage of 0.8 U/kg IV/IO. As with epinephrine, it should be administered every other cycle of BLS (i.e., every 4 minutes). Vasopressin also can be administered via ET tube using the same technique as described for epinephrine.

Anticholinergics

Studies examining the use of atropine, an anticholinergic drug, during CPR provide no evidence of a harmful

effect at the recommended dosage but also show no consistent benefit.[39] Therefore, atropine at a dosage of 0.04 mg/kg IV/IO may be considered for routine use during CPR in dogs and cats with non-shockable arrest rhythms. In addition, in dogs and cats with evidence of increased vagal tone at the time of CPA, it is reasonable to administer atropine as part of ALS. Therefore atropine may be administered every other cycle (i.e., every 4 minutes) during CPR in patients with documented bradycardic arrest or in animals with diseases predisposing to high vagal tone, such as gastrointestinal, respiratory, or ophthalmic diseases. Atropine also may be administered via ET tube (0.08 mg/kg) as outlined previously.

Other ALS Therapies

Intravenous Fluids

In patients with documented or suspected hypovolemia, IV isotonic crystalloid fluid boluses may improve cardiac output during CPR by increasing cardiac preload and should be considered using standard dosing protocols (20-30 mL/kg over 20 minutes in dogs, 10-20 mL/kg over 20 minutes in cats) (also see ch. 129). In euvolemic or hypervolemic patients, IV fluids may increase right atrial pressure with no increase in aortic pressure, decreasing perfusion of the brain and heart.[53] Fluid bolus administration should therefore be avoided in these patients.

Alkalinization Therapy

Sodium bicarbonate (1 mEq/kg IV, once) may be beneficial in patients with pre-existing severe acidemia (e.g., pH < 7.1) or with prolonged CPA, as severe tissue acidosis will lead to peripheral vasodilation and metabolic disturbances (see ch. 128).[39] However, these may be rapidly resolved with ROSC, and bicarbonate should be reserved for patients with prolonged CPA (greater than 10 minutes), ideally only after documenting severe acidemia (pH < 7.0).

Open-Chest CPR

While closed-chest CPR generates approximately 30% of a normal cardiac output, direct cardiac massage during open-chest CPR (OC-CPR) yields markedly better results and improves ROSC rates and survival to discharge.[54-59] Because OC-CPR is more invasive and expensive, and requires intensive aftercare, clients frequently decline this option. However, if a client requests OC-CPR, it should be implemented without delay if CPA occurs. In patients with pleural space disease, pericardial disease, or significant thoracic wall defects, OC-CPR should be strongly recommended. Closed-chest CPR is also unlikely to be effective in giant-breed, round-chested dogs. In patients that develop CPA during abdominal or thoracic surgery, direct cardiac massage is likely the only viable option for CPR.

Prognosis

Unfortunately, little epidemiological CPR data are available in veterinary medicine, limiting our ability to infer prognostic information for dogs and cats with CPA.[10,22,32,60] Reported survival rates are very low, but as in human medicine, it is likely that one of the most important prognostic indicators is the underlying cause. Patients with untreatable or progressive chronic diseases have a poor prognosis if they develop CPA. However, dogs and cats developing CPA in the perianesthetic period have survival-to-discharge rates approaching 50%.[26] Therefore, the circumstances of the arrest are important. Prompt identification of CPA, rapid initiation of high quality CPR, and adherence to these evidence-based guidelines have the potential to improve survival rates.

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CHAPTER 141

Cardiac Emergencies

Manuel Boller

Cardiac emergencies in dogs and cats constitute a group of acutely occurring conditions clinically characterized by respiratory distress, circulatory crisis, or both. Implicated precipitating problems include "backward failure" (e.g., congestive heart failure, CHF), or "forward failure," e.g., cardiogenic shock due to cardiac arrhythmias, obstructive shock due to cardiac tamponade or thromboembolic disease, or a combination thereof. While cardiac emergencies often are life-threatening and require expedient and effective care, therapy is distinctly different from the treatment given for non-cardiac causes of respiratory distress and circulatory shock. Timely identification of a cardiac etiology predominantly is based on the physical examination and cageside tests. A two-phase therapeutic approach is recommended. The initial step consists of early initiation of the appropriate emergency care with the aim of stabilizing the patient. Once this is achieved, further characterization of the cardiac condition and refinement of treatment as appropriate becomes possible. This chapter discusses recognition, acute management, and expected outcome of dogs and cats with cardiac emergencies.

Heart Failure

Cardiac failure, in broad terms, is a condition in which the heart is reduced in its capacity to eject blood into the pulmonary and systemic arterial circulation in a way that achieves sufficient tissue perfusion, or to receive venous blood to allow adequate draining of the microvascular beds. When the heart's inability to eject and receive blood leads to pleural or peritoneal effusion or edema, the resulting syndrome is referred to as CHF (see ch. 246).

Breathing difficulty is the most common presenting complaint for dogs and cats with acute CHF in the emergency setting.[1] It indicates advanced heart failure, most commonly due to chronic valvular heart disease (CVHD) or dilated cardiomyopathy (DCM) in dogs and hypertrophic cardiomyopathy (HCM) in cats.[1,2] The challenge initially exists in differentiating a cardiac cause of respiratory distress from causes other than heart disease. The severity of dyspnea in many dogs or cats with CHF precludes important diagnostics such as thoracic radiography from being performed until stabilization of the patient is achieved. Combined consideration of findings from history, signalment, physical exam, initial cageside diagnostics, and the response to initial therapy is applied in a pattern recognition process to accept or refute the preliminary working diagnosis of CHF. Information on congestive heart failure also is presented in ch. 246 and 247.

Signalment and historical findings can provide important information in support of cardiac causes of respiratory distress. Dogs with CHF due to CVHD are typically of old age and small size (<20 kg), including small mixed-breed dogs.[3] In contrast, CHF with DCM occurs more commonly in middle-aged dogs of large to giant breeds.[2,4] CHF in cats occurs more frequently in young to middle-aged animals but cats of any age can be affected.[1,5-8] Domestic short- and long-haired cats predominate, but inherited HCM has been reported for several breeds (e.g., Maine Coon, Ragdoll, British Shorthair, Persian, Himalayan).[1,8-11] CHF is more common in male dogs and cats.[1,2] Historical findings can include coughing, which is commonly reported in dogs but is not specific for CHF. In cats, coughing is more commonly associated with asthma, not CHF. History-taking should also include inquiries on alternative explanations for respiratory distress, e.g., clinical signs of laryngeal paralysis, the occurrence of vomiting or regurgitation, etc.

A focused initial major body system assessment will allow for rapid gathering of more evidence for or against CHF. Animals with CHF typically have an increase in respiratory rate and effort commensurate with the severity of pulmonary edema or pleural effusion. As characteristic for pulmonary parenchymal disease, but not specific to CHF, an increased inspiratory and expiratory effort is in support of pulmonary parenchymal diseases, including cardiogenic pulmonary edema. An increase in respiratory effort that is

predominantly inspiratory, with stertor or stridor, can be interpreted as evidence against a cardiac etiology, as these signs suggest the upper airway as the source of dyspnea (see ch. 28). In some cases however, the addition of CHF as co-morbidity may lead to exacerbation of a pre-existing, subclinical upper airway obstruction or a latent tracheal collapse. In the absence of an upper airway issue, an asynchronous or paradoxical breathing pattern can suggest the presence of pleural effusion (see ch. 139).[12,13] Dyspnea with markedly prolonged expiratory time provides evidence for obstructive lower airway disease. In cats, this points towards feline asthma, a major differential diagnosis for CHF, especially if it coexists with coughing.[12,14] On pulmonary auscultation, end-inspiratory crackles can indicate pulmonary edema, but are found inconsistently in dogs and infrequently in cats with CHF.[1] Dull ventral lung sounds can indicate pleural effusion. In small-breed dogs, the absence of a heart murmur renders CHF a less likely diagnosis. The likelihood of CHF increases with the intensity of the systolic heart murmur[15,16]: in a retrospective study of 578 dogs (<20 kg) with CVHD, a murmur of soft (grade I-II/VI), moderate (grade III/VI), loud (grade IV/VI) and thrilling (grade V-VI/VI) intensity was associated with a CHF probability of 0%, 8%, 20% and 47%, respectively.[15] In contrast, dogs afflicted by DCM can have a soft systolic murmur, if any, and an auscultable tachyarrhythmia.[4] Approximately 50% of cats with CHF are found to have an auscultable heart murmur, gallop sound, arrhythmia, or some combination thereof at presentation[7]; while heart murmurs also are common in cats without CHF (e.g., 52% of cats with normal hearts),[7] gallop sounds and arrhythmias are markedly more prevalent with cardiomyopathy, particularly when CHF is present.[7] Pale mucous membrane color, prolonged capillary refill time, and poor pulse quality can be signs of cardiogenic shock, but similar signs occur in patients with hypovolemic shock. A large proportion of dogs and cats with respiratory distress due to CHF, however, will present without concurrent cardiogenic shock. Hypothermia is a more common occurrence in cats than in dogs with CHF.[1,8]

Three-lead ECG is a suitable initial diagnostic that can be conducted with minimum animal restraint, and is essential for characterization of common arrhythmias and the basis for specific antiarrhythmic therapy (see ch. 103). Focused cageside ultrasonography of lungs and heart can be executed with the patient in sternal recumbency, and with minimal distress to the animal; it can provide important information concerning the presence or absence of CHF. A focused ultrasound examination of the thorax (TFAST), abdomen (AFAST), or both allows identification of pneumothorax and pleural, pericardial, and abdominal effusions (see ch. 143 and 149).[17] The characteristic sonographic appearance of wet lung as opposed to dry lung supports the presence of a pulmonary parenchymal disease process.[17] Distribution of the lung fields identified as wet (e.g., dorsal versus ventral, and cranial versus caudal) provides initial clues on the etiology of the lung abnormality, and assists in the diagnosis of cardiogenic pulmonary edema.[18] Echocardiographic determination of left atrium (LA) size in proportion to the aortic diameter (Ao) on the level of the aortic valve (LA/Ao ratio) in 2-D parasternal short axis view is of great value.[19] The presence of moderate to marked LA enlargement, especially an LA/Ao ratio >2 : 1, makes CHF the most likely diagnosis in the dyspneic pet (Figure 141-1).[7,20-22] The extent of training required to gain proficiency in focused critical care echocardiography remains open, but it appears feasible for clinicians who are not specialists in cardiology to acquire such skills.[23,24] Thoracic radiography is highly effective in differentiating non-cardiogenic from cardiogenic origin of respiratory distress, but may not be well-tolerated. While thoracic radiographs should never cause stress or worsen dyspnea, a dorsoventral projection, taken with the patient in sternal recumbency, often can be obtained with the least stress to the patient because this posture already is preferred spontaneously by these animals (versus dorsal recumbency). The radiographic diagnosis of CHF is based on the presence of cardiomegaly, venous congestion and distribution of pulmonary interstitial to alveolar opacities, whereby species differences exist between dogs and cats. Determination of the vertebral heart scale (VHS) can be used to objectively describe cardiomegaly, with normal values described as 9.7 ± 0.5 in dogs, and 7.5 ± 0.3 in cats.[25,26] A VHS > 9.0 has been identified as a highly specific marker for CHF in cats with respiratory distress.[27] Radiographs are not a sensitive, but are a specific, tool for identifying left atrial enlargement in cats with CHF.[28,29] The radiographic appearance of the lungs of dogs with CHF is characterized by predominantly perihilar, interstitial to alveolar opacity, with unilateral involvement being common in dogs with CVHD.[30] No particular distribution of pulmonary edema predominates in cats.[1,28,31] Pleural effusion and pulmonary venous enlargement (> than pulmonary artery) have been found in 51% and 49% of cats with CHF, respectively.[28] Compared to cats, dogs with CHF due to either CVHD or DCM more commonly have radiographic evidence of pulmonary venous congestion and less commonly have pleural effusion.[1,4]

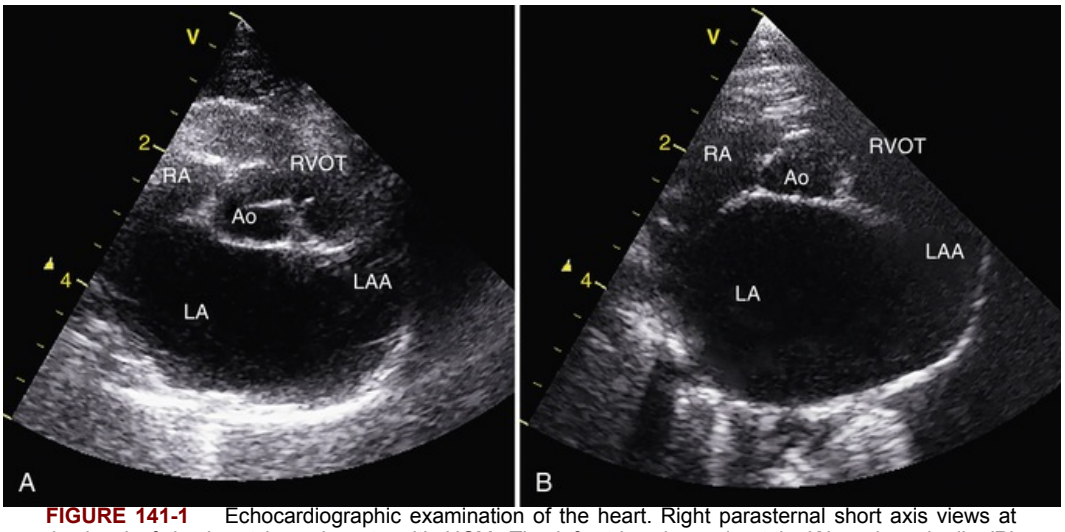

FIGURE 141-1 Echocardiographic examination of the heart. Right parasternal short axis views at the level of the heart base in cats with HCM. The left atrium is moderately **(A)** and markedly **(B)** enlarged when compared to the aortic diameter. *Ao,* Aorta; *LA,* left atrium; *LAA,* left atrial appendage, left auricle; *RA,* right atrium; *RVOT,* right ventricular outflow tract. (Images courtesy Dr. John Rush.)

Clinicopathological changes, foremost electrolyte abnormalities, azotemia, and liver enzyme alterations, are common in dogs and cats presented with CHF and tend to worsen during hospitalization.[1] Recognizing these changes primarily is of importance for therapeutic decision-making, but can also be of prognostic value in some instances (e.g., hyponatremia, azotemia).[2,32,33] Similarly, the assessment of global hemodynamic indices, such as arterial blood pressure (see ch. 99) or lactate values (see ch. 70), can help in determining the extent of circulatory instability of the patient. Hypotension was found in 15% of cats and dogs with CHF at presentation, and twice as often over the course of hospitalization, in one case series.[1]

An increasing body of literature examines the value of circulating cardiac biomarkers to identify heart disease. The neuroendocrine markers amino-terminal pro B-type natriuretic peptide (NTproBNP), c-terminal BNP (cBNP) and the myocardial cell injury marker cardiac troponin-I (cTnI) have received particular attention in veterinary medicine. Canine and feline assays have been validated for all three markers and, at the time of writing, point-of-care tests for cTnI and feline NTproBNP are available. Evidence suggests that these biomarkers can assist in differentiating cardiac from non-cardiac causes of respiratory distress in dogs and cats, albeit with varying accuracy.[34-41] The adjunct diagnostic value of these tests is undisputed, while their limitations as stand-alone tests require consideration.[42-47] They are discussed further in ch. 246 and 247.

The emergency therapeutic approach to dogs and cats with CHF consists of oxygen supplementation, stress minimization, and administration of drugs to resolve pulmonary edema and cardiogenic shock, as applicable, and will temporally overlap with the diagnostic evaluation mentioned above. All animals with respiratory distress should receive supplemental oxygen by the least stressful methodology available (see ch. 131).[48] Placement of a peripheral IV catheter on presentation is recommended whenever possible (see ch. 75). Mild sedation by means of opioid administration can be considered in select patients with CHF and high levels of anxiety, for the purpose of reducing oxygen consumption, sympathoadrenergic tone, and possibly cardiac preload (see ch. 138). Titration of butorphanol in increments of 0.05 mg/kg IV or IM (dog and cat) to a total dosage of 0.2 mg/kg IV or IM constitutes a reasonable approach. For acute management of cardiogenic pulmonary edema, furosemide is of central importance as it reduces *de novo* edema formation through reduction of pulmonary capillary pressure, thereby re-establishing the balance between edema clearance and production.[49] High initial dosing (e.g., 2-6 mg/kg q 2-6 h, dogs and cats) should be given IV whenever possible, using judicious and brief physical restraint to minimize stress; the IM route is an alternative route when IV access cannot be achieved but often is less effective. A good response consists of visibly improved respiratory effort in 20-45 minutes. Generally, a daily maximum cumulative dose should not exceed 12 mg/kg IV and/or IM, and a more judicious approach is required for animals where CHF is complicated by hemodynamic instability, azotemia, or serum electrolyte abnormalities. Accordingly, continuous monitoring of circulatory function and judicious determination of serum electrolyte concentrations and renal values are recommended during the initial intensive diuresis of dogs and cats, with a higher frequency of such assessments in patients who have pre-existing kidney disease or who are inappetent.[49] A furosemide loading dose followed by a constant rate infusion has been proposed as more effective and safer alternative to

intermittent bolus administration, but insufficient evidence currently exists to recommend this approach for routine implementation.[50,51] Once respiratory distress has resolved, the acute IV dosage is reduced to the minimum effective oral dosage for chronic administration, typically in the range of 2-4 mg/kg/day.

Nitroprusside, a potent arterial and venous vasodilator, can be used in normo- or hypertensive dogs and cats with severe acute CHF in which initial administration of diuretics alone failed to achieve rapid resolution of respiratory distress. Its administration as a constant rate infusion requires careful titration under continuous monitoring of arterial blood pressure to prevent harm due to hypotension (see ch. 99). To achieve this, the infusion rate is started at a very low rate (1-2 mcg/kg/min constant rate infusion [CRI] IV in dogs; 0.5 mcg/kg/min CRI IV in cats). The rate is increased in 0.5-1 mcg/kg/min increments (maximal infusion rate 5 mcg/kg/min) every 15 minutes as long as the systolic or mean arterial blood pressure remains above 100 mm Hg or 70 mm Hg, respectively, and until pulmonary congestion (e.g., crackles, respiratory distress) resolves.[52]

Oral vasodilators used for afterload reduction in refractory CHF include amlodipine in dogs (0.05-0.1 mg/kg PO q 8-12 h) and cats (0.625 mg/cat PO q 24 h) and hydralazine in dogs (0.5-2 mg/kg PO q 8-12 h) and they require titration under arterial blood pressure monitoring.[3] The angiotensin converting enzyme inhibitors enalapril (0.5 mg/kg PO q 12-24 h, dog; 0.5 mg/kg PO q 24 h, cat) and benazepril (0.25-0.5 mg/kg PO q 12-24 h, dog; 0.125-0.25 mg/kg PO q 24 h, cat), are best used once a stable diuretic dosage has been established. Dosage reduction is required in animals with azotemia. Dogs presenting with cardiogenic shock due to CVHD or DCM could benefit from an intravenous constant rate infusion of dobutamine (3-10 mcg/kg/min IV), a preferential $beta_1$-adrenoceptor agonist with positive inotropic, lusitropic, chronotropic and dromotropic effects. Additional agonistic effects on $beta_2$-adrenoceptors are associated with vasodilation, so that the net effect on cardiac output may be larger than on arterial blood pressure. The proarrhythmic effect of dobutamine limits its use at higher dosages and in animals with pre-existing ventricular tachycardia. Pimobendan, a drug frequently used in dogs with CHF, is recommended for use in dogs with CVHD and DCM in the acute or chronic stages of CHF (0.25-0.3 mg/kg PO or IV q 12 h).[3,53,54] Pimobendan currently is not licensed for use in the cat with heart failure, but evidence points towards a beneficial effect in patients with CHF in this species as well.[55-58] Thoracocentesis should be conducted in dogs and cats with voluminous pleural effusion because it provides diagnostic information and, depending on its relative contribution to dyspnea, can lead to substantial and immediate relief from respiratory distress. Thoracocentesis, as it is a low risk procedure if executed correctly (see ch. 102), can be conducted on the basis of physical examination only, with no preceding radiographic or sonographic confirmation of pleural effusion required, if a strong suspicion of pleural effusion exists. A transudative effusion is expected with CHF. Finally, dogs and cats in which dyspnea is severe enough to pose an imminent threat to the animal's life may require positive pressure ventilation to allow more time for other treatment to become effective. A recent retrospective study including six cats and 10 dogs with severe CHF reported relatively short ventilation times (30 ± 21.3 hours) and favorable survival to discharge rates (62.5% overall; 77% in cases treated after 2005) compared to other pulmonary parenchymal diseases requiring mechanical ventilation.[59-62]

The majority of dogs and cats with new-onset acute CHF are expected to survive this initial episode and be discharged for chronic care. Reported survival to discharge percentages range from 56% to 80%.[1,2] For animals surviving to hospital discharge, the median duration of hospitalization was 3 days (range, 1-9 days) in one study.[1] However, it is important for the pet owner to understand early that, except for CHF caused by surgically correctable defects (e.g., patent ductus arteriosus, pulmonic stenosis) or reversible diseases (e.g., taurine-deficient DCM in dogs), the underlying heart condition will be irreversible; daily treatment and ongoing monitoring will be required; additional episodes of respiratory distress requiring hospitalization will occur; and a large proportion of animals will have a good quality of life but will survive for 1 year or less. Reported survival times differ based on species, pathophysiology, disease severity and co-morbidities. In animals presenting with CHF severe enough to require hospitalization, reported median survival times are 2.5-5 months (range, 0-14) for dogs with DCM, 9 months (8-15) for dogs with CVHD, 18 months for cats with HCM (0-147), and 3 months (0-27) for cats with any cardiomyopathy.[8,33,63-66]

Arrhythmias

Cardiac arrhythmias are commonly encountered in the canine and feline emergency population either as a consequence of systemic disease or due to a primary cardiac disorder. Arrhythmias consist of a disturbance of rate or site of cardiac electrical impulse formation or its conduction through the heart (see ch. 248). The

primary acute concern is the resulting impediment to effective cardiac blood flow generation, with the consequence of clinically relevant reduction of tissue perfusion (e.g., circulatory shock, syncope) or deterioration into a sustained non-perfusing rhythm (e.g., pulseless ventricular tachycardia, ventricular fibrillation) (see ch. 30 and 140). An ECG examination subsequent to the physical exam finding of an inappropriately high or low heart or pulse rate, or an irregular heart beat or pulse is of central importance to identify and characterize an arrhythmia and to guide therapeutic decisions (see ch. 103).

Severe bradyarrhythmias can cause weakness or syncope. Intoxication with calcium blockers, beta-blockers, digoxin, and other compounds, and the presence of electrolyte abnormalities (e.g., hyperkalemia) should be considered as possible etiologies, as treatment of these reversible disorders is distinctively different from treatment of arrhythmias caused by primary cardiac disorders.[67,68] Sinus node dysfunction (sick sinus syndrome, SSS) and third-degree atrioventricular blocks (AVB) are primary cardiac disorders that are common causes of syncope (Figure 141-2, *A*). While most asymptomatic dogs with SSS or high-degree AVB do not need treatment, those with clinical signs often require pacemaker therapy (Figure 141-2, *B*) to improve quality of life and survival (see ch. 249).[69-72] Temporary cardiac pacing as a short-term bridge to permanent pacemaker implantation or transthoracic pacing should be considered in acute, life-threatening conditions such as patients with SSS or third-degree AVB causing syncope and a heart rate <40 beats/minute (dogs) or <90 beats/minute (cats).[73-78]

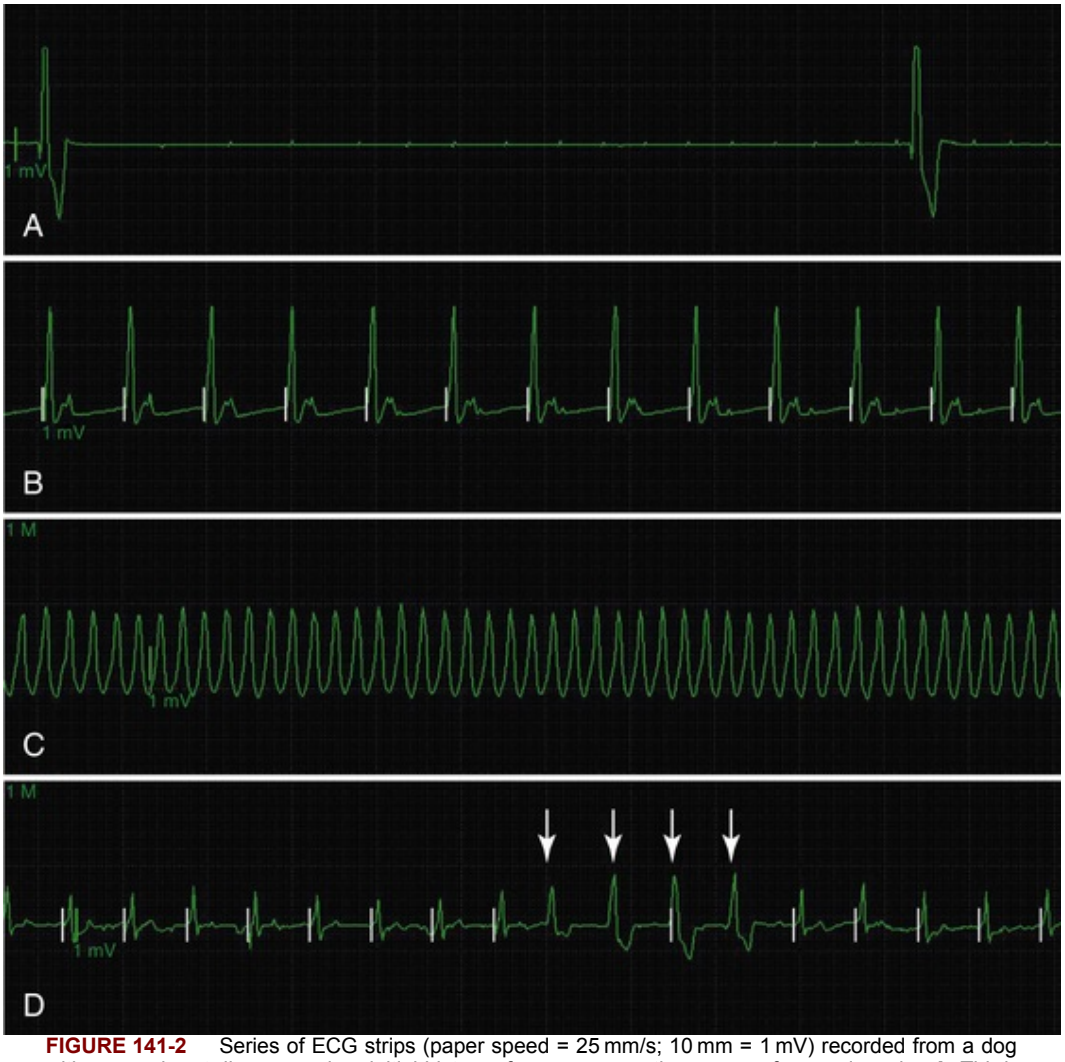

FIGURE 141-2 Series of ECG strips (paper speed = 25 mm/s; 10 mm = 1 mV) recorded from a dog with severe heart disease and an initial history of syncope over the course of several weeks. **A,** Third-degree atrioventricular block with two escape beats occurring with an interval of 10.5 seconds. **B,** Appropriate ventricular capture at a rate of 65 beats per minute after pacemaker implantation, which resolved initial syncope. White vertical bars represent pacing markers. **C,** Ventricular tachycardia (VT) at 230 beats per minute and syncope occurred several weeks after pacemaker implantation. **D,** Normal sinus rhythm with persistence of ventricular premature complexes (white arrows) during antiarrhythmic

treatment. (Images courtesy Dr. John Rush.)

Severe tachyarrhythmias can lead to weakness, syncope, cardiogenic shock, and sudden cardiopulmonary arrest. This can arise as an isolated cardiac rhythm abnormality, as a complicating component of structural heart disease (e.g., DCM), or as an exacerbation of low cardiac output conditions in such systemic diseases as severe sepsis or septic shock.

Differentiation between supraventricular (SVT) and ventricular tachycardia (VT) is important, and is discussed in ch. 248. Atrial fibrillation (AF) is the most common SVT in dogs and is indicative of structural heart disease in non-giant-breed dogs and of severe left atrial enlargement in cats.[79-81] The ECG findings of AF are characterized by a highly irregular rhythm (i.e., variable beat-to-beat R-R interval) with varying conduction dependent rate, by the absence of P waves, and by an undulating baseline (f waves) (Figure 141-3). Other forms of SVT occurring in both dogs and cats do often have P waves, even though these are sometimes buried in the preceding QRS complexes or T waves and often are difficult to identify. These forms of SVT can be sustained or intermittent, typically have constant R-R intervals, and, in their more severe forms, can create significant circulatory compromise with weakness or collapse. Examples include atrial flutter and atrioventricular reciprocating tachycardias, and they occur much less commonly in dogs and cats than in humans. Beyond the immediate decrease in cardiac output that these SVTs can cause when they are very rapid, SVTs that are sustained for several days to weeks can lead to remodeling of the heart with a resulting DCM-like phenotype.[82,83]

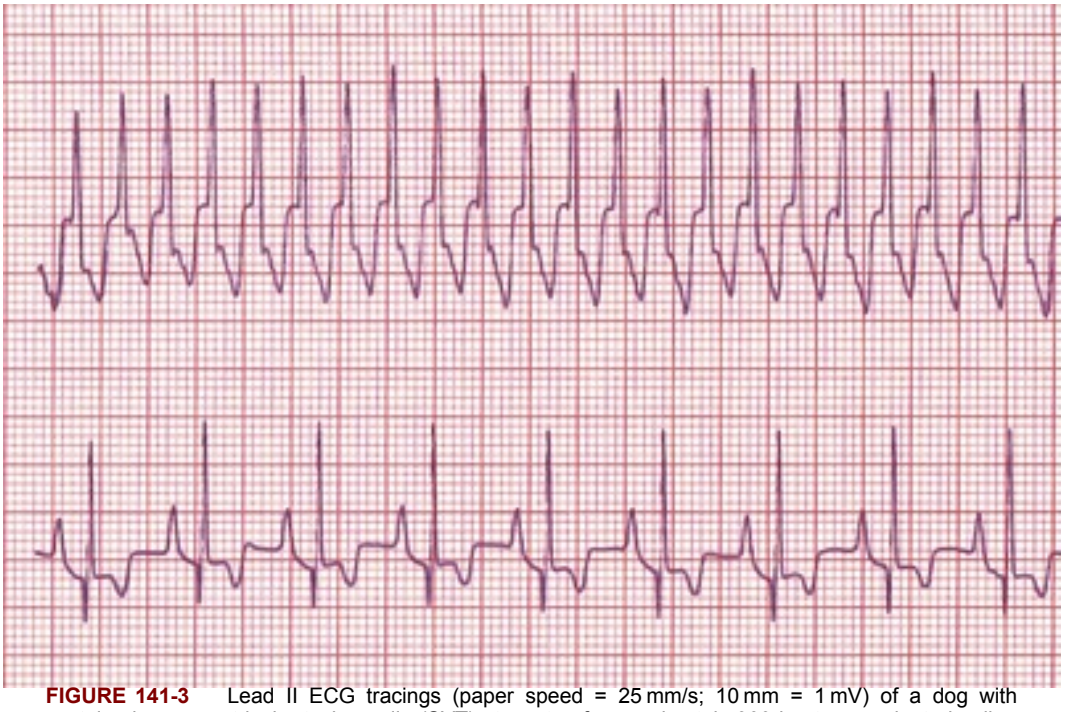

FIGURE 141-3 Lead II ECG tracings (paper speed = 25 mm/s; 10 mm = 1 mV) of a dog with sustained supraventricular tachycardia (SVT) at a rate of approximately 300 beats per minute leading to collapse of the animal (top tracing). Intravenous administration of diltiazem led to conversion to sinus rhythm at a rate of 120 beats per minute (bottom tracing). (Images courtesy Dr. John Rush.)

In addition to the reversal of potential precipitating causes (e.g., electrolyte and acid-base disturbances, anemia), the control of CHF as appropriate, and the application of the inconsistently and only temporarily effective ocular or carotid vagal maneuvers (see ch. 248), administration of antiarrhythmic drugs is recommended. In syncopal patients or those with very rapid SVT (e.g., sustained heart rate >200/min in large dogs, >240/min in small dogs, >260/min in cats), acute therapy can consist of diltiazem (dogs: 0.1-0.2 mg/kg IV over 2-3 minutes; begin low and uptitrate to effect; consider even lower starting dosage if structural heart disease, e.g., DCM; follow by 5-20 mcg/kg/min CRI IV if needed) or esmolol (dogs and cats: 0.1-0.5 mg/kg IV, in 0.1 mg/kg increments; followed by 50-100 mcg/kg/min CRI IV if needed). The negative inotropic effects of esmolol warrant careful use in dogs with severely diminished left ventricular systolic function. In less acute cases, oral diltiazem (0.8-1.5 mg/kg PO q 8 h, dog [plain, non-sustained-release formulation]; 3 mg/kg PO q

12 h, dog [sustained-release formulation]; 7.5 mg/animal PO q 8 h, cat [plain formulation; sustained-release not recommended in cats]), atenolol (0.25-1 mg/kg PO q 12-24 h, dog; 6.25-12.5 mg/cat PO q 12-24 h), or sotalol (1.5-3.5 mg/kg q 12 h PO, dog; 10 mg/animal PO q 12 h, cat) can be used for initiating chronic control of arrhythmias. Consultation with or referral to a cardiologist is recommended. Sotalol is a reasonable choice in animals with coexisting SVT and VT.

The requirement for treatment of VT depends on the heart rate, whether the rhythm is associated with circulatory compromise (e.g., if there is concurrent structural heart disease), and whether there are ECG features that suggest a heightened risk for deterioration into a non-perfusing rhythm, such as pulseless VT or ventricular fibrillation (see ch. 140). In any case, treatment should be accompanied by an investigation into causes of VT, such as electrolyte abnormalities (e.g., hypokalemia, hyperkalemia, hypocalcemia, hypomagnesemia), intoxications (e.g., chocolate, bronchodilators), myocardial hypoxia (e.g., hypoxemia, anemia, myocardial ischemia), trauma (i.e., traumatic myocarditis), inflammation (i.e., myocarditis), conditions associated with systemic inflammatory response syndrome (SIRS), sepsis or ischemia/reperfusion injury (e.g., GDV), splenic disease, cardiac neoplasia, and adult-onset or congenital heart disease in advanced stages. Reversible causes of VT need to be addressed before or in conjunction with pharmaceutical reduction of the arrhythmia load. Ventricular premature contractions occurring at a low rate of 60-120 per minute (i.e., accelerated idioventricular rhythm, or AIVR) commonly occur in critically ill dogs and typically do not warrant pharmaceutical intervention, but instead continuous monitoring and correction of reversible precipitating causes. High-rate VT (e.g., dog >180 bpm, cat >250 bpm) can lead to circulatory compromise and generally needs to be treated with antiarrhythmic drugs (see Figure 141-2, *C* and *D*). In veterinary medicine, the importance of the R on T phenomenon (i.e., ectopic QRS complex superimposed on the preceding T wave) is unclear and the benefit of antiarrhythmic treatment solely based on this abnormality has not yet been established.

Acute treatment of VT is first attempted with lidocaine boluses (2 mg/kg IV, repeat up to a total of 4 doses in no less than 30 minutes, dog; 0.5-1 mg/kg IV once, cat) titrated to terminate the VT, and once achieved, is followed by a continuous rate infusion (30-80 mcg/kg/min CRI IV, dog; 10-40 mcg/kg/min CRI IV, cat). Vomiting and sedation can occur at higher dosages. If not effective, slow boluses of procainamide (2-4 mg/kg IV, q 3-5 min, 16 mg/kg maximum dose, dog; 1-2 mg/kg IV once, cat) can be administered, followed by a CRI (25-50 mcg/kg/min IV, dog; 10-20 mc/kg/min IV, cat). Amiodarone is very effective in terminating VT and its use can be considered in dogs where lidocaine and procainamide failed to control the arrhythmia. A single slowly administered dose (5 mg/kg IV, dog) is followed by an oral regimen (10 mg/kg PO q 1 h for 7 days; 5 mg/kg PO q 12 h thereafter, dog). Intravenous amiodarone administration will predictably lead to an acute hypersensitivity reaction in dogs, including hypotension, collapse, urticarial and facial edema, an effect caused by the solvent in the intravenous formulation.[84] A new aqueous formulation of amiodarone is available and is devoid of this side-effect.[85] Subacute and chronic treatment may succeed with oral administration of antiarrhythmics, including mexiletine, sotalol and amiodarone with efficacy of maintenance treatment being preferentially assessed by Holter monitoring (see ch. 248).

Cardiac Tamponade

An abnormal accumulation of fluid between the visceral and parietal pericardium is referred to as pericardial effusion (PE).[86-95] The clinical syndrome of cardiac tamponade occurs when this fluid accumulation increases to the extent that right ventricular diastolic collapse occurs and hemodynamic compromise ensues, leading to hypoperfusion due to circulatory (obstructive) shock with weakness, collapse and, if left untreated, ultimately death. The volume of PE required to cause cardiac tamponade is influenced by the rate of fluid accumulation and pericardial compliance, such that a relatively small effusion can elicit a profound hemodynamic effect in some cases, but not in others. The details of clinical presentation, diagnostic confirmation, and treatment of cardiac tamponade are discussed in ch. 254, and pericardiocentesis is described in ch. 102.

Feline Aortic Thromboembolism

While aortic thromboembolism is a rare occurrence in dogs, it is a frequently-seen feline cardiac emergency.[8,96-112] Feline aortic thromboembolism (FATE) most commonly occurs in association with severe heart disease. FATE is thought to be initially very painful and can lead to local ischemic tissue loss and severe systemic illness due to reperfusion injury. It is difficult to treat effectively, will often reoccur, and carries an overall guarded short-term and poor long-term prognosis.[98-100] Most commonly, thromboembolic occlusion occurs in the distal aorta as it bifurcates into the iliac arteries; however, occasionally other vessels such as the

brachial, mesenteric, renal, or cerebral artery can be affected in isolation or in combination.[98,99,101] Cats of any age and gender can be affected with the more common signalment being male (especially when HCM is concurrently present), and middle aged to old.[98,99] Please see ch. 256 for a detailed discussion of FATE.

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CHAPTER 142

Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome

Mauria O'Brien

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHS) are two serious and potentially life-threatening complications of diabetes mellitus (DM) whose pathophysiology and treatment are similar. It is reasonable to suggest that the conditions are two points on the spectrum of decompensated diabetes. Both disorders are characterized by hyperglycemia that stems from an absolute or relative insulinopenia combined with an excess of counterregulatory or "stress" hormones. Patients with DKA or HHS are often quite ill, their management challenging, and concurrent conditions that can substantially affect prognosis common. Fluid, electrolyte and acid-base disturbances can be significant (see ch. 128).

The definition for each entity varies slightly depending on the reference consulted. The diagnosis of DKA includes the presence of hyperglycemia, glucosuria, ketonemia or ketonuria with an increased anion gap metabolic acidosis.[1] HHS is now defined as a syndrome of severe hyperglycemia (>600 mg/dL) and, depending on species and veterinary reference, a serum osmolality >320 mOsm/kg.[2-6] The syndrome was previously defined by a lack of ketones but now includes those with and without detectable ketonemia/ketonuria.[7,8] HHS is uncommon, with few original veterinary studies published. Many conclusions have been drawn from human reviews.[7,8]

Pathophysiology

Hyperglycemia develops when insulin is absent or deficient. Insulin is the key which allows cells to utilize glucose. Despite increased serum glucose concentrations, cells become starved for energy without insulin. Most cells then use free fatty acids (FFAs) as an energy source. Lipolysis generates and liberates FFAs into the circulation. Hepatocytes uptake FFAs and convert them primarily into triglycerides and, to a lesser degree, into ketones.[9] Insulin hinders lipolysis through the inhibition of hormone-sensitive lipase, the enzyme responsible for the hydrolysis of triglycerides into FFAs. Brain cells are unique in that they do not require insulin for glucose uptake, but unlike most tissues, the brain cannot use fatty acids for energy but can utilize ketones.[9] Ketone bodies can provide as much as two-thirds of the brain's energy needs during fasting or starvation.[10] Uncomplicated diabetics, in a state of starvation, convert most excess FFAs to triglycerides and ketone production is low enough as to be manageable by the body.[9]

DKA is characterized by an increased glucagon (GC) to insulin ratio, leading to a state of enhanced gluconeogenesis via inhibition or stimulation of certain glycolysis-pathway enzymes.[11-13] A study of diabetic dogs in which GC and insulin concentrations were measured suggested that the ratio is more relevant than the individual hormone values.[12] Another study supports this concept, as a few dogs with DM had normal insulin concentrations but still developed measurable ketones.[14] With a relative or absolute lack of insulin in DKA, cellular demand for glucose stimulates the release of GC, which increases gluconeogenesis and promotes glycogenolysis. In the absence of insulin, GC activates adipose cell lipase thereby increasing the concentration of FFAs and inhibiting hepatic storage of triglycerides. Due to a complex second messenger cascade system, a small amount of GC leads to synthesis of large amounts of glucose. Even with depleted hepatic glycogen stores, GC accelerates gluconeogenesis and increases the extraction rate of amino acids from the circulation to act as available substrates. As a result, serum glucose concentrations increase and, without insulin present, hyperglycemia develops.[9]

GC also promotes ketogenesis by shifting hepatocyte production of triglycerides to the production of FFAs. Normally, insulin inhibits malonyl CoA, which in turn inhibits fatty acid oxidation and production of FFAs.

In the absence of insulin, malonyl CoA activity is low and GC stimulates FFA uptake into the mitochondria by increasing hepatic levels of carnitine. Carnitine is a carrier protein used by the enzyme carnitine palmitoyltransferase I which shuttles FFAs into the mitochondria. From this point the FFAs can either enter the citric acid cycle or be converted into acetoacetate (AcAc) and beta-hydroxybutyrate (BHA). In DKA, the citric acid cycle becomes overwhelmed and ketogenesis prevails. As ketone concentrations increase, they cannot be efficiently metabolized and hyperketonemia results. The normal ratio of serum BHA to AcAc is 3 : 1; in DKA states this ratio can increase as high as 10 : 1 (Figure 142-1).[10]

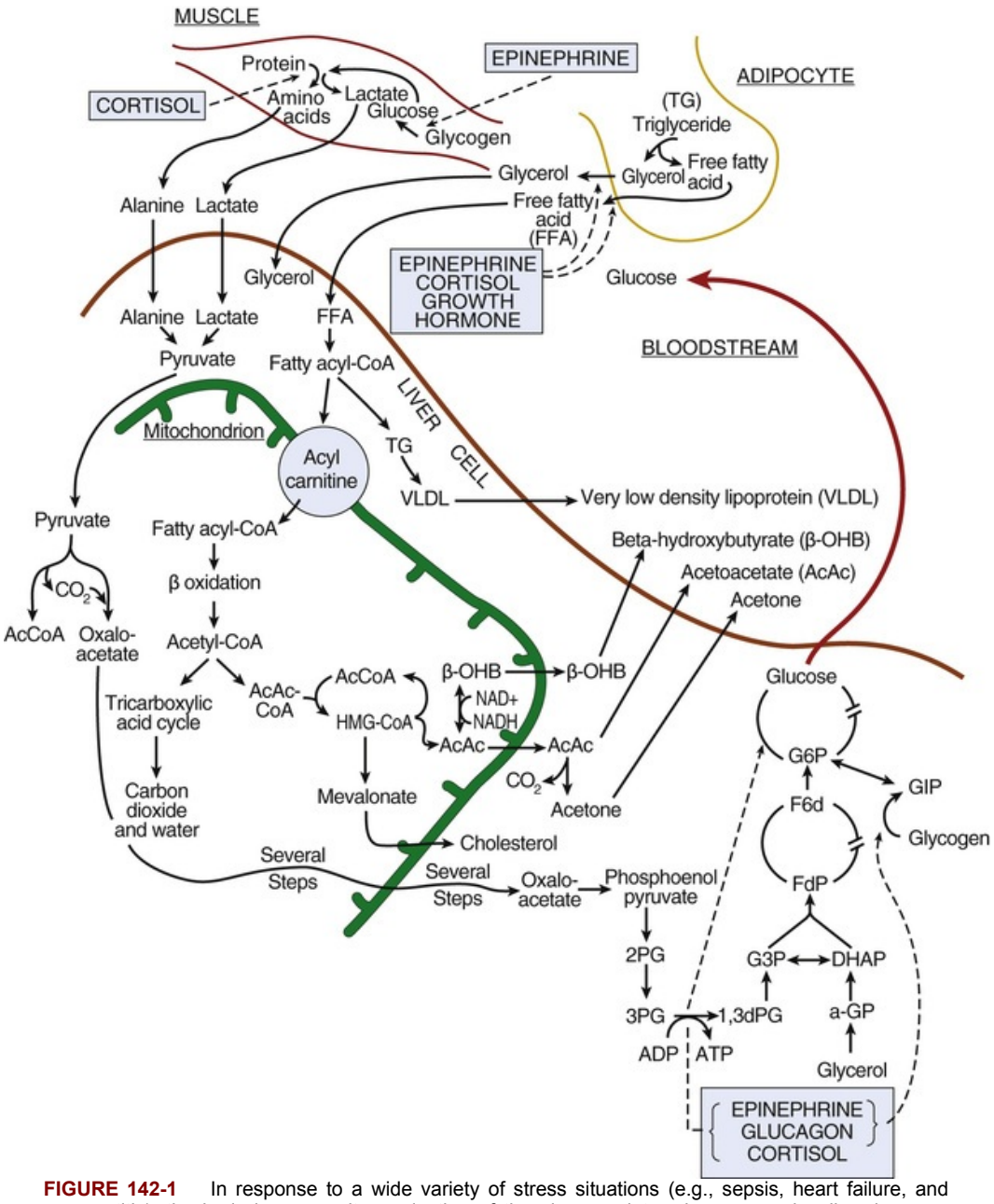

FIGURE 142-1 In response to a wide variety of stress situations (e.g., sepsis, heart failure, and pancreatitis), the body increases its production of the glucoregulatory hormones—insulin, glucagon, epinephrine, cortisol, and growth hormone. In diabetes, the lack of insulin allows the glucogenic effects of the stress hormones to be unopposed in liver, muscle, and adipose tissue. This results in excessive ketone formation, fat and muscle breakdown, and a classic catabolic state. *ADP,* Adenosine diphosphate; *ATP,* adenosine triphosphate; *DHAP,* dihydroxyacetone phosphate; *GIP,* gastric inhibitory polypeptide; *HMG,* hydroxymethylglutaryl; *NAD+,* nicotinamide adenine dinucleotide; *NADH,* nicotinamide adenine dinucleotide (reduced form). (Adapted from Feldman E, Nelson R: *Canine and feline endocrinology and reproduction,* Philadelphia, 1987, Saunders.)

What distinguishes DKA from uncomplicated DM is the absolute or relative lack of insulin *in combination* with an increase in counterregulatory hormones. GC, cortisol, epinephrine (Epi) and growth hormone (GH) comprise these diabetogenic hormones. They contribute to the pathogenesis by promoting lipolysis and stimulating gluconeogenesis and glycogenolysis. Cortisol increases protein catabolism, providing amino acid precursors for gluconeogenesis.[1] Cortisol and Epi, and to a lesser extent GH, stimulate hormone-sensitive lipase, which mediates the breakdown of triglycerides to glycerol and FFAs in adipose tissue.[15] High Epi and low insulin concentrations reduce peripheral tissue glucose uptake and hyperglycemia develops.[16]

Although DKA and HHS are similar in pathogenesis, ketone production is perhaps minimal or absent in HHS because these patients possess enough insulin to limit lipolysis but not enough to counter hyperglycemia.[13] Other explanations for a lack of ketones include lower FFA concentrations and/or increased portal vein insulin concentrations.[17] Patients with HHS tend to be more dehydrated, less acidemic and may have lower counterregulatory hormone concentrations than those with DKA. HHS patients typically develop "hypernatremic dehydration" as free water losses exceed those of sodium.[7] Glucosuria impairs renal concentrating capacity, exacerbating this water loss. As blood volume decreases, renal perfusion decreases, and the kidneys' capacity to excrete glucose is reduced. This cascade of events can lead to marked hyperglycemia.[18]

Secondary or concurrent diseases are precipitating events that contribute to DKA or HHS by stimulating synthesis and secretion of the stress hormones. In people, the two most common precipitating factors are inadequate insulin dosing and infection.[19] In veterinary patients, acute pancreatitis, urinary tract infection, hyperadrenocorticism, neoplasia, pneumonia, pyelonephritis, and chronic kidney disease (CKD) have been associated with DKA or HHS.[5,20-22] Cats with DM and CKD or congestive heart failure are at increased risk of developing HHS. Cats with HHS are less likely to have pancreatic or hepatic disease as the co-morbid process as compared with DKA cats.[5]

Impaired neutrophil function may explain the increased risk of infection in poorly regulated diabetics.[23] Hyperglycemic states are pro-inflammatory, capable of producing reactive oxygen species.[24-26] Increased concentrations of GH, cortisol, and cytokines (markers of cardiovascular risk and oxidative stress) have been demonstrated in patients with DKA. People in a hyperglycemic crisis may have leukocytosis without obvious infection due to increased pro-inflammatory mediators.[24] Insulin therapy is anti-inflammatory since pro-inflammatory biomarkers decrease with its administration.[27,28]

History and Physical Examination

Some dogs and cats with either DKA or HHS may already be receiving insulin; some are newly diagnosed diabetics; some are yet to be diagnosed and have a recent history of polyuria, polydipsia, and weight loss, but in the day or days preceding veterinary care, owners often note seeing lethargy, partial to complete anorexia, vomiting, diarrhea, and/or generalized weakness.[20] Cats may specifically exhibit posterior paresis secondary to diabetic neuropathy (see ch. 305).[22] Severe metabolic acidosis may result in Kussmaul respirations: a slow and deep breathing pattern, sometimes misinterpreted as respiratory distress.[8] In one study, cats with HHS had been diabetic for a longer time than cats with DKA. Neurologic and respiratory signs are seen more frequently in HHS cats.[5] Physical examination should be complete, as these pets often have concurrent illness. Estimating hydration status and assessing mentation and mucous membrane color is valuable.

Diagnostics

Overview

Any dog or cat suspected of having DKA or HHS should undergo a thorough diagnostic evaluation to assess not only the current condition with regard to DM, but to identify any co-morbid conditions. Minimum testing should include urinalysis (to diagnose DM and presence of ketones), complete blood count (CBC), serum chemistry analysis, serum electrolytes, blood gas, urine culture, abdominal ultrasound, and thoracic radiographs.

Urinalysis and CBC

Urinalysis will be positive for glucose and may be positive for ketones. Urinary tract infections are common.

Bacterial culture of urine should be performed regardless of sediment observations. 20% of dogs with DKA were found to have positive growth on aerobic urine culture despite lack of pyuria (see ch. 72).[20] The hematocrit may be increased secondary to dehydration. Anemia is common in both dogs and cats. Cat red blood cells are susceptible to Heinz body formation and oxidative injury.[29] In one study, 50% of dogs with DKA had nonregenerative anemia, left shift neutrophilia, and thrombocytosis.[20] Leukocytosis is more common in cats.[22,30]

Liver Enzyme Activities, Kidney Testing (see ch. 62 and 65)

In cats, increased hepatic enzyme activities may be seen with concurrent hepatic lipidosis, cholangiohepatitis or pancreatitis. Dogs may have increased alkaline phosphatase activities as well as elevated serum triglyceride and cholesterol concentrations in association with DM, hypercortisolism, or pancreatitis. Increases in serum creatinine and blood urea nitrogen (BUN) concentrations can be due to dehydration; however, some pets have CKD with or without acute kidney injury (AKI). Dogs with HHS and ketones tend to have acute pancreatitis, shorter duration of clinical signs, higher body temperature and higher white blood cell (WBC) counts as compared with those that have HHS without ketones. HHS dogs without ketones tend to be more azotemic with higher osmolalities.[6] The hyperosmolality integral to HHS may cause altered mentation.[31]

Sodium (Na) and Potassium (K) (see ch. 67 and 68)

The combined effects of hyperglycemia, ketonemia, acidosis and many co-morbid processes often causes significant electrolyte derangements in both DKA and HHS. Hyperglycemia-induced osmotic diuresis results in severe fluid and electrolyte losses. Ketones contribute to the solute diuresis via excretion of ketoanions, which obligates urinary cation excretion of Na, K and ammonium salts.[13] Decreases in Na can also follow hyperglycemia, estimated as every 100 mg/dL increase in serum glucose being associated with a 1.6 mmol/L decrease in Na.[16,32,33] This formula may underrepresent the effect on Na.[34] Low Na concentrations can also be seen with hypertriglyceridemia, "pseudohyponatremia." Insulin deficiency also contributes to solute loss as insulin stimulates salt and water reabsorption from both proximal and distal tubules and phosphate from proximal tubules.[13]

Significant hypokalemia is common in DKA. Initially, many DKA patients have normal to slightly elevated serum K concentrations but have severe total body depletion.[16] The acidosis of DKA leads to displacement of K from intracellular stores to the extracellular space in exchange for hydrogen ions.[35] Volume depletion, from lack of intake combined with vomiting, diarrhea and osmotic diuresis, may cause secondary hyperaldosteronism, promoting urinary K excretion.[36] Inter-compartmental K shifts can vary depending on the type of acidosis (mineral vs. organic), by tissue type, and by pH of body fluids.[35] Renal dysfunction, by promoting hyperglycemia and reducing urinary K excretion, contributes to the initially normal or increased K concentrations.[37] Insulin deficiency, by promoting intracellular proteolysis, further impairs K entry into cells. Paradoxically, plasma K concentrations increase initially despite whole body depletion.[1] Magnesium, calcium and phosphorus are also depleted in DKA, mostly as renal losses.[16]

Acid-Base, Ketones

DKA is characterized by metabolic acidosis with an increased anion gap. BHA and AcAc overproduction are key contributors to this acidosis. Both dissociate completely at physiologic pH, resulting in the production of hydrogen ions and ketoanions. The rapid accumulation of hydrogen ions overwhelms the bicarbonate buffering system, resulting in metabolic acidosis. The accumulation of ketoanions is reflected by an increased anion gap. Significant fluid losses and hypovolemia can lead to lactic acidosis, contributing to the metabolic acidosis. Concentrations of acetone, a ketone formed after spontaneous decarboxylation of acetoacetate, are increased in patients with DKA but do not contribute to acidosis because acetone does not dissociate; it is slowly excreted by the lungs and generates the distinctive, "sweet"-smelling breath of DKA.[10] This slow excretion of acetone may result in longer time requirements to correct ketonemia than hyperglycemia.[16,38] Severity of acidosis may be masked in dogs and cats due the metabolic alkalosis associated with vomiting or diarrhea.

The presence of ketones is most commonly assessed using commercially available urine reagent strips. The

methodology utilizes the nitroprusside reaction and a color change to indicate the presence of ketones. These strips measure only AcAc and acetone but the majority of ketone bodies are made up of BHA and AcAc, thus leading to the occasional false negative result. Beta-hydroxybutyrate is formed from AcAc in the presence of hydrogen ions; therefore, the more acidotic the animal, the more BHA is formed.[10] Some patients are significantly dehydrated on presentation with an empty bladder and no urine for assessment. Heparinized plasma can be tested using urine ketone reagent strips. Results correlate with serum concentrations in diabetic dogs and cats.[39,40] Plasma may be more accurate than urine in dehydrated animals since excretion of ketones relies on normal renal perfusion and function. Ketones will be evident in plasma before being detectable in urine.[40] Assays and hand held meters to detect BHA in blood have improved and are considered reliable for diagnosis and monitoring response to therapy; hand held meters are an alternative to using urine ketone tests.[41-47]

Most HHS patients are not acidotic. This reduces cationic exchanges and limits urine electrolyte losses. Unbalanced free water loss eventually leads to profound dehydration masked by preservation of intravascular volume secondary to the hyperosmolar state.[7] HHS patients are reported to have more extensive fluid losses than those with DKA. Severe hyperglycemia can only occur with reduced glomerular filtration rate (GFR) because glucose entering the kidney in excess of the renal threshold should be excreted in the urine. The profound hyperglycemia of HHS then exacerbates the osmotic diuresis.[31] Co-existing disease processes may further decrease fluid intake which, together with losses through diarrhea or vomiting, contribute to the dehydration.

Osmolality

The severity of hyperosmolality can be variable in DKA, but patients with HHS are hyperosmolar by definition. Osmolality is measured by an osmometer that uses the freezing point of a solution to estimate the amount of osmotically active particles. Measurement of osmolality is superior to a calculated osmolality because of the ability to measure volatile substances in a solution.[3] Since most veterinarians do not possess an osmometer, equations have been devised to estimate osmolality. The most commonly used equation, referred to as total calculated osmolality (Osm_T) is: Osm_T (mOsm/kg) = 2 ($Na^+ + K^+$) + Glucose/18 + BUN/2.8.[3] The calculated reference interval ranges from 290-310 mOsm/kg.[48,49] The effective osmolality (Osm_E) is based on the simplified equation: Osm_E = 2 (Na^+) + Glucose/18.[50] Hypertonicity in DKA and HHS patients is due to an increase in concentration of solutes that do not cross the cell membrane (Na and glucose). Urea is not considered an "effective osmole" because it is equally distributed across membranes and its accumulation does not induce an osmotic gradient.[8] Absolute serum ketone concentrations are not routinely measured in DKA but are known to contribute to the osmolality. Measurement of the osmole gap (measured Osm_T − calculated Osm_T) in DKA produces a mean osmolar gap of 29 mOsm/kg, which can decrease to insignificant values within 24 hours of initiating therapy.[51-53] Ketoanions presumably fully dissociate at physiologic pH and therefore do not contribute significantly to tonicity but do contribute to osmolality based on the osmolar gap.[53,54] Hyperosmolality is defined as serum osmolality >320 mOsm/kg in people, >330-350 mOsm/kg in cats, and >325-330 mOsm/kg in dogs.[2-7] Cats with HHS had a median Osm_T of 384 mOsm/kg and median Osm_E of 344.1 mOsm/kg.[5]

With an increase in the osmolality or tonicity of the extracellular fluid, cellular dehydration results as water shifts from the intracellular compartment to the extracellular compartment. The nervous system is the principal organ affected by this shift and neurologic dysfunction (disorientation, ataxia, lethargy, seizures and coma) develops with worsening cellular dehydration. In defense against glucose-induced hypertonicity, neural cells produce osmotically acitve molecules called idiogenic osmoles. Formation of such osmoles occurs over 4-6 hours and should be taken into consideration during management.[55] It has been suggested but not well substantiated that the higher the osmolality, the worse the neurologic signs and risk of cerebral edema.[56-59]

Overview of Management Strategies

Successful treatment of DKA or HHS patients is complex, involving correction of many derangements while anticipating or responding to the various interactions among therapies. Goals of treatment include (1) restoring intravascular volume, (2) resolving dehydration, (3) attending to electrolyte disturbances, (4)

correcting acid-base imbalance, (5) decreasing blood glucose concentrations, (6) ridding the body of detectable ketones, (7) identifying and (8) treating any underlying or co-existing disease. Ideally, patients with DKA or HHS should be hospitalized in a facility that can provide 24-hour biochemical testing, electrolyte testing, and care.

Many DKA and HHS patients are severely hypovolemic, requiring initial fluid resuscitation. Perfusion parameters (heart rate, pulse quality, mentation, mucous membrane color, capillary refill time, blood pressure) should dictate the need for fluid boluses, before rehydration rates are instituted. Insulin is not recommended for hypovolemic animals, as this can cause fluid shifting from the extracellular to the intracellular compartment, worsening the already depleted intravascular volume.[7] Most patients should be rehydrated for several hours before initiating insulin therapy. Close monitoring of perfusion, hydration status and serum electrolytes is critical, regardless of the crystalloid fluid chosen. Fluids contribute to initial decreases in glucose, ketones and counterregulatory hormones by increasing GFR and their excretion.[19]

Fluid Therapy

DKA and HHS

Most commercially available crystalloid solutions are adequate for resuscitation and rehydration (see ch. 129). While the initial fluid of choice has been 0.9% sodium chloride (saline) because most patients are initially hyponatremic, it may cause a temporary hyperchloremic metabolic acidosis, resulting from a loss of bicarbonate rather than gain of organic acid.[19,60,61] Buffered crystalloid solutions have adequate Na content and lactate, acetate, or gluconate to aid in resolving the metabolic acidosis.[62] The saline-induced acidosis is considered temporary and may have serious sequelae.[63,64]

Fluid deficits are calculated based on estimations of dehydration (with % dehydration expressed as a decimal, e.g., 10% = 0.1):

$$\%\ \text{dehydration} \times \text{body weight (kg)} \times 1000\ \text{mL/kg} = \text{mL of fluid deficit}$$

These estimates are subjective, requiring frequent reassessment in the early phases of therapy. Rehydration should take place over a relatively short time (6-24 hours), although speed of replacement depends on the patient's hemodynamic, osmotic, cardiovascular, and neurologic status. Most patients have been hyperglycemic and ketonemic for hours to days, contributing to continued osmotic diuresis. Urine output must continually be assessed when adjusting fluid rates. Rehydration of the HHS patient often requires more conservative fluid therapy than it does in those with DKA because of the combination of severe dehydration and hyperosmolality.

Cerebral Edema

Sudden changes in glucose or Na concentration, affecting the Osm_E, should be avoided. Rapid decreases in Osm_E may lead to fluid shifts from the extracellular to intracellular compartments in the central nervous system (CNS). Water moves from least to most concentrated spaces through semi-permeable membranes. CNS cells may contain the previously discussed idiogenic osmoles, balancing their interior osmolality, initially, to that of the dehydrated extracellular space. Administering IV fluids (extracellular) provides free water, lowering osmolality and promoting flow into cells. This influx of water into brain cells is cerebral edema.

Although it occurs rarely, children and infants with DKA are more prone than adults to developing cerebral edema early in therapy. Cerebral edema occurs in roughly 1% of children with DKA and is associated with a mortality rate of 40-90%.[55] Proposed pathophysiologic mechanisms for cerebral edema remain complicated, with ischemia and reperfusion injury, inflammation, increased blood flow, intracellular osmolyte generation, osmotic "imbalance" and cytotoxins being implicated.[26,57] Additional contributing factors include initial blood glucose concentration, excessive IV fluid administration, persistent hyponatremia despite resolution of hyperglycemia, hypocapnia, acidemia, hyperkalemia, increased BUN/creatinine ratio,

and sodium bicarbonate administration.[55,59,65]

Cerebral edema in DKA is usually noted within 12-24 hours of initiating therapy. Some suggest cerebral edema may precede onset of therapy.[66] Previous studies have associated IV fluid-induced rapid changes in Osm_E with cerebral edema.[67] One current concept is the "cytotoxic theory": osmotic gradients are created by overzealous fluid and insulin dosing.[66] Another concept holds that cerebral edema is vasogenic and independent of fluid therapy. In this context, edema follows increased brain water diffusion coefficients in the acute phases of illness.[68,69] Current recommendations are for initial slow rehydration rates and low insulin dosing to gradually decrease the Osm_E, as should be reflected by decreases in serum glucose and concomitant increases in serum Na.[57,70] Recent investigations in children with DKA compared half-strength saline versus saline, but without clear conclusions.[64,71,72] Since most commercially available isotonic IV solutions are Na-based, deficiencies are addressed with standard IV therapy.

Neurologic Signs

Severe neurologic signs related to increased Osm_E were not observed in either a group of cats with DKA nor another group with HHS, nor were any other complications noted with fluid therapy.[4,5] If neurologic signs are present on presentation, treatment should be more conservative: rehydrate over 24-48 hours and use a lower insulin dosage (Box 142-1). Severely affected patients with altered mentation (obtunded, stuporous or comatose), abnormal cranial nerve reflexes, or seizures should be treated with mannitol (0.5-1.5 g/kg IV over 15-20 minutes).

Box 142-1

Recommended Dosages for Various Conditions in DKA and HHS

Stepwise Treatment for Diabetic Ketoacidosis

1. **Fluid Therapy**
   - Rehydrate over 6-8 hours
   - Place central line (see ch. 76) → repeat electrolytes/PCV/TS
   - After 6-8 hours, start insulin in peripheral line, fluids in central line
   - Fluid rate = 1.5-2× maintenance (due to osmotic diuresis) until glucose "normal"
   - Weigh every 6-8 hours

BG (mg/dL)	FLUID TYPE	DILUTED INSULIN SOLUTIONINFUSION RATE	
		Dog:	**Cat:**
>250	Plasmalyte-A or Norm R	10 mL/h	5 mL/h
200-250	P-lyte + 2.5% dextrose	7 mL/h	3 mL/h
150-200	P-lyte + 2.5% dextrose	5 mL/h	2 mL/h
100-150	P-lyte + 2.5% dextrose	5 mL/h	2 mL/h
<100	P-lyte + 5% dextrose	Stop	Stop

2. **Blood Glucose, Dextrose, Insulin**
   - Regular insulin dosage (add to 250 mL fluid bag):

   Dosage: 2.2 U/kg/day (1.1 U/kg/day if HHS)
   Cats run at half the dog rate (see table, right)
   Change out insulin bag (250 mL bag) every 24 hours
   - Run 50 mL of insulin solution through IV tubing before use
   - Recheck BG every 2-3 hours
   - Repeat PCV/TS every 12 hours (prepare for pRBC transfusion in cats)
3. **Electrolytes**

CHEC

	K EVERY	ADDITIVE	CURRENT VALUES	ADDED TO FLUID	RATE (mL/kg/h)	NOTES
Potassium	8-12 hours	*KCl* 2 mEq K^+/mL	3.6-5.0 mEq/L	20 mEq/L	26	*K^+ Maint = 20-24 mEq/L* At high rates/concentrations, account for K^+ mEq provided by KPhos and fluids
			2.6-3.5 mEq/L	40 mEq/L	12	
			2.1-2.5 mEq/L	60 mEq/L	9	
			<2.0 mEq/L	80 mEq/L	7	
Phosphorus	12 hours	*KPhos* 3 mmol P/mL	1-2 mg/dL	0.03 mmol/kg/h		KPhos = 4.4 mEq K+/mL
			<1.0 mg/dL	0.06-0.12 mmol/kg/h		
Magnesium	8-12 hours	*$MgSO_4$* 4 mEq Mg/mL	<1.2 mg/dL	0.75-2 mEq/kg/***day***		*Put into D5W or saline* For refractory hypokalemia Keep at high rate instead of topping out the K^+ supplementation

4. **Maintenance**
   - Continue on insulin CRI until ketones have resolved and eating/drinking
   - Shut off insulin at noon → at 6 pm: give ¼-½ U/kg NPH SC in dogs, 1 U/cat insulin of choice SC q 12-24 h

From Dr. Brittany H. Perry.

Potassium (K)

Virtually all DKA and HHS dogs and cats are initially hypokalemic. Although serum concentrations can be normal or increased initially, whole body K depletion is typical and needs should be addressed immediately and reassessed frequently until patients are eating, drinking, and no longer receiving IV fluid therapy. Hypokalemia can lead to muscle weakness, cervical ventroflexion in cats, cardiac arrhythmias and respiratory failure, if severe (see ch. 68).[73,74] K supplementation should be initiated once urine production is confirmed. Fluid therapy increases GFR, increases renal K excretion, and alleviates metabolic acidosis. All these factors shift K from the circulation to the intracellular space. Life-threatening hypokalemia ensues. KCl can be added to IV fluids, with the dosage based on serum K concentrations (see Box 142-1). While some sources warn against administering more than 0.5 mEq/kg/h, life-threatening hypokalemia (<2.0 mEq/L) should be treated using 0.5-0.9 mEq/kg/h for the first hour followed by reassessment.[75,76] Insulin therapy should be withheld until K concentrations are >3.5 mEq/L to avoid further loss of K to cells.

Insulin

Initial Considerations

After 4-8 hours of fluid therapy, or when the patient appears to be better hydrated, a central venous catheter should be placed to allow frequent blood sampling without repeated venipuncture (see ch. 76). Insulin therapy should be initiated and glucose levels monitored frequently to adjust insulin dosage accordingly (see Box 142-1). Insulin is essential in managing DKA, in part because no other drug directly turns off ketone synthesis. Insulin decreases ketone body concentrations by inhibiting lipolysis and thereby lowering FFA availability for ketogenesis, by interfering with ketone body production within the liver, and by enhancing peripheral ketone utilization.[77] Although not necessarily ketotic, patients with HHS also need insulin to reduce hyperglycemia in a controlled manner.

Insulin Choices

Regular insulin administered in a constant rate infusion (CRI) is recommended for the initial treatment of critically ill DKA or HHS patients, rather than via IM injections.[21] "Low-dose" regular insulin CRI is considered the standard of care for people with DKA or HHS, with lower mortality rates than seen with repeated IM injections.[1,19] IM insulin should be reserved for uncomplicated cases or those with financial restrictions. IM regular insulin, not administered until patients have been adequately rehydrated with a stable cardiovascular system, is given at dosages of 0.2 U/kg initially and then 0.1 U/kg IM hourly until the blood glucose drops below 250 mg/dL, when insulin is given SC every 6 to 8 hours at dosages of 0.5 to 1 U/kg.[78] Dextrose should be supplemented in the patient's fluids as needed based on the patient's blood glucose level (see Box 142-1 and E-Box 142-2).

Insulin Analogs

The introduction of insulin analogs has resulted in potential alternatives to CRIs. In a small cohort of dogs with DKA, lispro insulin was safe and as effective as regular insulin CRI.[79] Studies in people evaluating SC glargine combined with low-dose regular insulin CRI have noted faster resolution of acidosis, shorter hospital stays, and reduction in rebound hyperglycemia when CRI was stopped.[80,81] Similarly, cats with DKA treated with regular insulin CRI were compared to those given regular insulin CRI combined with IM or SC glargine. The combined insulin group had quicker resolution of hyperglycemia, ketonemia and acid-base status, shorter hospitalization stays, but no advantage to survival.[82] A study of cats with DKA cats given IM and SC glargine shows promise as an alternative to insulin CRI (E-Box 142-2).[83]

E-Box 142-2

Use of Glargine Insulin for Managing Cats with DKA

Glargine can also be used for treatment of diabetic ketoacidosis (DKA) in cats. In one study, 15 cats presenting with DKA were treated with intramuscular glargine (1 IU in 14 cats and 2 IU in one cat), combined with subcutaneous glargine (1-3 IU) in 12 cats. Subcutaneous glargine was continued every 12 hours, with cats receiving 1-3 doses of IM glargine (0.5-1 IU) over the first 22 hours. Subsequent doses of IM glargine were not required in 6 cats, while a second (4 cats) or third dose (5 cats) was required, and cats (3) not receiving subcutaneous glargine on admission required 3 IM doses. All 15 cats survived and were discharged within 5 days of admission on twice daily glargine, and 33% of cats achieved remission within 29 days.

From Marshall R, Rand J, Gunew M, et al: Intramuscular glargine with or without concurrent subcutaneous administration for treatment of feline diabetic ketoacidosis: a preliminary study. *J Vet Emerg Crit Care (San Antonio)* 23:286-290, 2013.

IM or SC Insulin

Critically ill dogs and cats with DKA or HHS often have severe fluid deficiencies. Circulatory compromise in dehydrated patients may hinder or alter delivery of any medication given IM. Unpredictable insulin action could increase risk of hypoglycemia or sudden changes in osmolality. Therefore, patients should be rehydrated adequately before giving IM insulin, with a goal of decreasing glucose concentrations by no more than 50 to 75 mg/dL/h.[84] If the glucose level drops below 250-300 mg/dL and ketones are still present, glucose should be added to the IV solution (see Box 142-1). Once the patient is hydrated and eating, longer acting insulin formulations should be employed.

Serum Phosphate (PO_4) and Magnesium (Mg)

As discussed, serum or plasma K and PO_4 concentrations must be closely monitored, especially after insulin administration begins. Insulin is one of several treatments (IV fluids, sodium bicarbonate as well) that drives K and PO_4 into cells, leaving the vascular space depleted. Clinical signs of hypophosphatemia include muscle weakness and hemolytic anemia. PO_4 can be added to IV fluids in the form of potassium phosphate (KPO_4;

0.03 to 0.12 mmol/kg/h).[85] Alternatively, one-third to one-half of K supplemented can be added as KPO_4 mixed with KCl (see Box 142-1).[78] KPO_4 is reportedly incompatible with lactated Ringer's solution and should be added to balanced, calcium-free, crystalloid fluids.[86] Serum PO_4 concentrations should be monitored at least every 4-6 hours after starting insulin therapy. Serum PO_4 concentrations <1.5 mg/dL may be associated with a risk of intravascular hemolysis.[87]

Magnesium (Mg) is a required cofactor for most adenosine triphosphatases and deficiencies can have detrimental effects on cellular function. For example, low Mg may decrease ATPase activity at the sodium-potassium pump.[89] Magnesium depletion has been correlated with insulin resistance.[90] Hypomagnesemia has been noted in critical illness and DKA.[88] Clinical signs are subtle or non-existent, but low Mg concentrations are associated with refractory hypokalemia, promoting urinary losses. In some patients, serum K concentrations normalize only after Mg replacement.[91,92] Cats tend to be more hypomagnesemic than dogs.[93] Magnesium sulfate is added to the IV fluids and given as a CRI at a dosage of 1 to 2 mEq/kg/day.

Anemias

Many complications encountered in treating DKA or HHS can be prevented or mollified by diligent monitoring and appropriate responses to results. Such monitoring may require repeated blood sampling that can lead to anemia and need for blood transfusions. Cats, having eight reactive sulfhydryl groups on each hemoglobin tetramer, are prone to Heinz body anemia in critical illness and there is evidence to suggest that ketosis can enhance the risk.[29] Acute hemolytic anemia can also contribute to transfusion needs if extracellular PO_4 concentrations drop precipitously with insulin therapy.

Acidosis

The metabolic acidosis of DKA typically resolves with fluid therapy and insulin alone. Sodium bicarbonate, used to help correct the acidosis of DKA, is no longer recommended. The American Diabetes Association does list it as a treatment option for patients with a pH < 7.0 1 hour after onset of fluid therapy, without prospective randomized studies to demonstrate efficacy.[19] Bicarbonate drives K into cells, potentially worsening hypokalemia; shifts the oxyhemoglobin curve to the left, decreasing oxygen release at the tissue level; and can contribute to paradoxical CNS acidosis, fluid overload, lactic acidosis, persistent ketosis and cerebral edema.[1,94,95]

Prognosis

Prognosis in DKA and HHS is largely dependent on the concurrent disease process. Previous retrospective veterinary studies have listed mortality rates ranging from 26-30% for DKA[20-22] and 38-65% for HHS.[5,6] Although mortality rates are lower overall, there is a worse prognosis with HHS compared with DKA in human patients (10-50% vs. 2-10%, respectively).[7,13,19] Regardless of species, without resolution of co-morbid processes, the outcome of DKA or HHS worsens. A recent study showed that the two most important factors predicting mortality in human DKA were severe concurrent illness and blood pH <7.0.[96] The complicated pathogenesis of DKA and HHS creates a considerable medical challenge for the veterinary practitioner. Clients and clinicians should be prepared for the financial, emotional and unpredictable outcome of these diabetic complications.

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CHAPTER 143

Acute Abdomen

Søren Boysen

Acute abdomen classically is defined as a sudden onset of severe abdominal pain, evolving in less than a week, and of unclear etiology.[1,2] However, advanced states of shock and/or concurrent decreased mentation (e.g., chemical sedation) can mask an obvious pain response, deferring the diagnosis of acute abdomen until mentation improves, pain worsens, or both. A high index of suspicion in these cases is necessary to identify subtle manifestations of abdominal pain and facilitate early diagnosis and treatment (see ch. 126).

Due to the variety of underlying causes, both medical and surgical, the diagnosis of acute abdomen in small animals is challenging. Clinical signs vary and range from the stable patient with a self-limiting condition to the unstable patient requiring immediate intervention. Additionally, many underlying conditions causing acute abdomen are dynamic and progressive, and can lead to necrosis of abdominal tissues if left untreated.[3] Prompt identification and treatment are essential to decrease the risk of serious complications, including hollow viscus perforation, septic or chemical peritonitis (see ch. 279), and the systemic inflammatory response syndrome (see ch. 132).

The primary objectives in the patient presenting with acute abdomen are to rapidly assess cardiopulmonary status and establish hemodynamic stability, initiate therapy to relieve discomfort (i.e., analgesia), exclude life-threatening surgical conditions, and determine a specific cause.[3] In many cases, emergency surgery is required to further stabilize the patient and correct the underlying cause, making a prompt diagnosis critical.

Pathogenesis

Understanding somatosensory pathways (see ch. 126) helps explain why some patients with acute abdomen caused by disorders such as pancreatitis or peritonitis appear to be in more pain than animals with obstructive gastrointestinal (GI) disorders or organ enlargement.[4] In general, abdominal pain can be classified as visceral or somatic. Most cases of abdominal pain probably are associated with visceral pain receptors.[5] Visceral pain results when nociceptors located in the muscles and mucosa of hollow organs, and in the mesentery and on serosal surfaces of abdominal organs, are stimulated by distension, stretching, vigorous contraction, and ischemia.[5,6] Examples include masses that cause stretching of an organ capsule (e.g., splenic hemangiosarcoma), or thrombosis of the mesenteric artery and subsequent ischemia, inflammation, and cytokine release.[7] Visceral pain tends to be difficult to localize because the afferent nerves of the pathway have fewer nerve endings in the gut, and are primarily mediated by unmyelinated C fibers; these enter the spinal cord bilaterally at several locations, resulting in a dull pain that is more generalized.[8] Inflammation and tissue congestion associated with the inciting disorder can lower the threshold for stimuli, further sensitizing nerve endings, and can secondarily stimulate autonomic nerves, which results in patients also showing signs of nausea and vomiting.[5]

Somatic (parietal) pain receptors tend to be more A-delta fibers and are located principally in the parietal peritoneum, muscle, and skin. These pain receptors typically respond to stretching, tearing, or inflammation, and probably are most active in cases of peritonitis and following surgical procedures. The nerves that convey somatic pain are more numerous, travel within specific spinal nerves that are myelinated, and transmit impulses to specific dorsal root ganglia. Therefore, the pain is more localized, associated with one side or the other, more intense, and more often is described as having a sharp quality.[5] Movement has been shown to aggravate this pain pathway, which often results in the patient remaining still or splinting when walking or during palpation of the abdomen.[5,8]

Localizing abdominal pain can be confounded by referred pain from non-abdominal sites (e.g., intervertebral disc disease, neoplasia). Care must be taken to rule out non-abdominal causes of acute

abdomen. Pain also can be referred from sites outside the abdomen as a result of shared central pathways at the spinal cord level for afferent neurons originating in distant locations.[5,8,9] A common example in people occurs in patients with pneumonia who present with abdominal pain because the distribution of sensory nerves arising from a single spinal nerve ganglion (T9 dermatome) is shared by the lung and the abdomen.[8,9] If an obvious cause of pain cannot be found on workup of the abdomen, thoracic radiographs to rule out referred pain from pleural or lung parenchymal disease have been suggested.[10]

Clinical Signs

The presence of abdominal stretching while in lateral recumbency or the classic "prayer position" should alert the clinician to the possibility of severe acute abdomen (Video 143-1). Subjectively, this often-described abnormality has a low sensitivity and specificity for abdominal pain. Reluctance to move, or a stilted and/or short choppy gait when ambulating, could also reflect abdominal pain.[11,12] Other patients with acute abdominal pain can exhibit excessive salivation due to nausea.[11,12] Although non-specific and variable depending on the underlying cause, signs of vomiting, decreased appetite/anorexia, lethargy, diarrhea, and a distended abdomen often are noted.[11,12]

Differential Diagnosis

Injury to almost any intra-peritoneal organ can cause abdominal pain and an acute abdomen, including hepatic, pancreatic, intestinal, renal, urinary, splenic, and reproductive diseases. In addition, certain disorders of the mesenteric and vascular system also can result in an acute abdomen. Differential diagnoses with key clinical findings and indications for medical or surgical management are included in Box 143-1.

Box 143-1

Differential Diagnoses for the Acute Abdomen

Gastrointestinal System

Foreign body (FB) *(C)*
- Particularly younger animals; linear FBs more frequent in cats. US, radiography often confirmatory. *Surgery required, may be urgent.*

Gastric dilation-volvulus *(C)*
- More common in large-/giant-breed dogs. History of unproductive retching and abdominal distension. Right lateral abdominal radiograph is confirmatory. *Emergency surgery required.*

GI ulceration *(U)*
- History of NSAID ingestion, hematemesis, and/or "coffee grounds" vomitus possible. US and/or endoscopy can be helpful; often diagnosed based on history and response to therapy. *Non-surgical unless refractory to medical management or perforation suspected.*

Gastric or intestinal perforation *(LC)*
- Consider underlying causes (e.g., GI ulcer, foreign body, mass; history of GI surgery if dehiscence). AFAST and abdominocentesis with fluid cytology/ analysis and low effusion glucose level to detect septic effusion. Imaging may identify underlying cause. *Emergency surgery required.*

Gastroenteritis: *Non-surgical*.
- *Bacterial (U)*
  - Consider history of raw food diet, carrion/offal ingestion (see ch. 276).
- *Hemorrhagic gastroenteritis (HGE) (U)*
  - High PCV and normal to low TS in the absence of other diseases are characteristic.
- *Parasitic (U)*
  - More common in younger animals; fecal flotation (see ch. 81).
- *Toxin (C)*
  - Can affect any age patient. History of exposure? (see ch. 13).
- *Viral (C)*
  - Parvoviral enteritis more likely in younger dogs and kittens with suboptimal vaccination history.

Mechanical ileus (obstruction) *(C)*

Consider foreign body; neoplasia in older animals; intussusception in younger animals. Imaging often supportive or conclusive. *Surgery required, may be urgent.*

Functional ileus *(U)*

US often identifies ileus. Fasting/anorexia decreases GI motility. Recent surgery and/or opioids may predispose patients. *Non-surgical.*

Intestinal volvulus *(U)*

More common in large-breed dogs, notably German Shepherds. Severe clinical signs. Abdominal radiography often diagnostic. *Emergency surgery required.*

Intussusception *(LC)*

Younger animals with recent gastroenteritis, abdominal surgery, or opioid Tx overrepresented. US "target lesion" pathognomonic. *Surgery required, may be urgent.*

Ischemia *(U)*

Has been reported following trauma. Angiography, DPL, or surgery often required to confirm the diagnosis. *Surgery required, may be urgent.*

Neoplasia *(U)*

More common in older animals. Imaging to identify masses/lesions. FNA and/or biopsy for diagnosis. *Surgery required, may be urgent.*

Cecal inversion *(U)*

Dogs > cats. History of parasitism or typhlitis possible; US and endoscopy can confirm diagnosis. *Surgery required, may be urgent.*

Obstipation *(U)*

Cats > dogs. History of tenesmus and dry, firm feces on exam. Abdominal palpation and radiography confirmatory. *Non-surgical.*

Colitis, acute *(U)*

Diagnosis based mainly on history, exam, and fecal flotation; US may be helpful. *Non-surgical.*

Hepatobiliary System

Acute hepatitis *(U)*

Toxic, infectious causes (see ch. 282, 283, and 286). Serum liver enzyme levels often very high; US with FNA or Bx generally required for diagnosis. *Non-surgical.*

Hepatic abscess *(U)*

Abdominal radiography/US often identify lesions. FNA for cytology and C&S helpful. Percutaneous drainage with alcoholization has been reported. *Surgery required, may be urgent.*

Hepatic trauma *(U)*

Suspected based on hemoabdomen after trauma, rarely confirmed. *Rarely surgical, may be urgent.*

Hepatic rupture *(U)*

AFAST confirms hemoabdomen but non-localizing. Abdominal US and radiography may identify cause. *May require surgery, may be urgent.*

Hepatobiliary neoplasia *(U)*

Serum liver enzyme levels often high. Masses possible on US; FNA can help identify tumor type: Bx with histopathology confirmatory. *May require surgery, may be urgent.*

Liver lobe torsion *(U)*

More common in large-breed dogs. Serum liver enzyme levels often high. US helpful, particularly with Doppler assessment of hepatic vessels. *Emergency surgery required.*

Biliary obstruction *(U)*

Hyperbilirubinemia. US often diagnostic of obstruction but may not identify underlying cause. *May require surgery, may be urgent.*

Biliary rupture *(U)*

Hyperbilirubinemia. US with FNA of free abdominal fluid (bilirubin concentration: fluid > serum). *Emergency surgery required.*

Cholecystitis *(U)*

High serum liver enzyme concentrations +/− hyperbilirubinemia. Radiography may show gas in biliary tree; US helpful. *May require surgery, particularly if necrotizing (urgent).*

Cholangiohepatitis *(U)*

Cats > dogs. Serum liver enzyme concentrations elevated. US and FNA with cytology/C&S may be helpful. *Non-surgical.*

Cholelithiasis *(U)*

Small-breed dogs overrepresented. High serum liver enzyme concentrations, hyperbilirubinemia. US may detect non-radiopaque choleliths. *May require surgery, may be urgent.*

Gallbladder mucocele *(U)*

Adult/older, smaller breed dogs predisposed, especially Shetland Sheepdogs. High serum liver enzyme concentrations, hyperbilirubinemia. US diagnostic. *May require surgery, may be urgent.*

Pancreatic System

Acute pancreatitis *(C)*

Consider diet-induced, idiopathic, drug-induced, or traumatic. Female Miniature Schnauzers, exposure to garbage, table scraps, or high-fat diet. US, PLI helpful. *Rarely surgical unless abscess, severe necrosis, or neoplasia.*

Pancreatic abscess *(U)*

US and FNA with cytology often helpful. *Surgery required, may be urgent.*

Pancreatic neoplasia *(U)*

US and FNA with cytology helpful; Bx with histopathology may be required. *Surgery required, may be urgent.*

Urinary System

Acute nephritis, pyelonephritis *(U)*

Azotemia with polyuria, oliguria, or anuria typical. US, U/A, and urine C&S most helpful. *Non-surgical.*

Upper urinary tract obstruction (renal, ureteral) *(U)*

Azotemia with polyuria, oliguria/anuria, and hematuria typical. Radiography and US often diagnostic. *May require surgery, may be urgent.*

Lower urinary tract disease (cystic calculi, urethral obstruction) *(C)*

Stranguria, pollakiuria, hematuria common. Urethral obstruction: cats > dogs, males > females; acute azotemia common. Physical exam, history, and response to therapy often diagnostic of urethral obstruction. Radiography and US diagnostic of cystic calculi. *Surgery may be required, may be urgent.*

Trauma-avulsion-rupture *(LC)*

Urinary bladder most commonly ruptured urinary organ, particularly following trauma. Acute azotemia. Uroabdomen often present. US, abdominocentesis with fluid cytology/analysis +/− contrast radiography. *Surgery required, may be urgent.*

Renal artery thrombosis, renal infarct *(U)*

Ultrasonography with Doppler may be helpful. Acute azotemia may be present. *May require surgery, may be urgent.*

Renal neoplasia *(U)*

Acute azotemia common. Lymphoma: bilateral renomegaly +/− CNS metastases typical. *Radiography, US, and Bx may be helpful. May require surgery.*

Reproductive System

Female

Pyometra/uterine rupture *(C)*

Intact female with vulvar discharge and recent heat cycle. Radiography and US strongly supportive. *Emergency surgery required.*

Uterine torsion *(U)*

Intact female. Radiography and US often diagnostic. *Emergency surgery required.*

Uterine neoplasia *(U)*

Intact female. Radiography and US often helpful. *Surgery required.*

Dystocia *(C)*

Pregnancy at term. Physical exam findings often diagnostic. Radiography and US for assessing number and viability of fetuses. *May require surgery, may be urgent.*

Ovarian cyst *(U)*

Intact female. US often identifies lesions. *May require surgery.*

Ovarian neoplasia *(U)*

Uncommon cause of acute abdomen. Intact female. Radiography and ultrasonography often identify masses. *May require surgery.*

Male

Acute prostatitis *(C)*

Common cause of acute abdomen in older, intact male dogs. Rectal, radiography, US often localizing; see ch. 111. *Non-surgical.*

Prostatic abscess *(U)*

Intact older male dogs. Rectal, radiography, US with FNA, cytology, and C&S often diagnostic. *Surgery required, may be urgent.*

Prostatic cysts *(U)*

Intact older male dogs. Rectal, radiography, US with FNA, cytology, and negative C&S often helpful. *Surgery required.*

Prostatic neoplasia *(U)*

Intact older male dogs. Rectal, radiography, US often localizing. Traumatic prostatic wash and/or FNA with cytology and C&S may be required (see ch. 111). *Surgery required.*

Testicular torsion/abscess *(U)*

Intact older male dogs. Physical examination, US may be helpful. *Emergency surgery required.*

Hematopoietic System: Spleen

Splenic neoplasia *(C)*

Typically older dogs. Radiography and US +/− FNA and cytology (depending on vascularity of mass on US). *Surgery required, may be urgent.*

Splenic rupture (mass, trauma) *(C)*

AFAST with fluid FNA and cytology confirms hemoabdomen. Radiography and US +/− FNA and cytology (if minimally vascular splenic mass on US). *Emergency surgery required.*

Splenic torsion *(U)*

Consider in large and deep-chested breeds. US helpful. *Emergency surgery required.*

Splenitis *(U)*

May be diagnosis of exclusion or incidental surgical finding. *May require surgery.*

Splenic abscess *(U)*

US with FNA, cytology, C&S may be helpful. *Surgery required, may be urgent.*

Splenic infarction *(U)*

US with Doppler may be helpful. *Non-surgical.*

Peritoneum and Mesentery

Peritoneum

Septic peritonitis (U)

Consider underlying rupture of hollow viscus or abscess, or intestinal translocation. Shock, sudden collapse common. AFAST and abdominocentesis with fluid cytology: septic effusion, low effusion glucose level. Radiography, US may identify underlying cause. *Emergency surgery required.*

Bile peritonitis (U)

AFAST and abdominocentesis with fluid cytology: bilious effusion. Radiography, US may identify underlying cause. *Emergency surgery required.*

Uroabdomen (LC)

AFAST and abdominocentesis with fluid analysis: free fluid with creatinine > serum creatinine. Contrast radiography, US may identify underlying cause. *May require surgery, may be urgent.*

Viral peritonitis (FIP) (U)

Polysystemic clinical signs, laboratory results (see ch. 224). *Non-surgical.*

Disseminated neoplasia *(U)*

US often identifies lesions. FNA with cytology and/or Bx with histopathology often diagnostic. *May require surgery.*

Pansteatitis *(U)*

Cats > dogs. Fish diets predispose. US may identify diffuse hyperechoic fat. Fat Bx required for diagnosis. *Non-surgical.*

Mesentery

Mesenteric traction: large masses *(U)*

Radiography and US helpful to identify large masses. *Surgery required, may be urgent.*

Mesenteric lymphadenopathy *(U)*

US with FNA and cytology often diagnostic. *May require surgery, may be urgent.*

Mesenteric lymphadenitis *(U)*

US with FNA and cytology often diagnostic. *Non-surgical.*

Adhesions with organ entrapment, internal hernia *(U)*
History of past surgery/surgeries suggestive. US often diagnostic. *Surgery required, may be urgent.*
Retroperitoneal disease *(U)*
Consider abscess, trauma, urine leakage. US often localizing. *May be surgical, may be urgent.*

Vascular

Mesenteric avulsion *(U)*
Doppler US, angiography may be diagnostic. *Emergency surgery required.*
Mesenteric artery thrombosis *(U)*
Doppler US, angiography may be diagnostic. Preoperative diagnosis often difficult. *Emergency surgery required.*
Portal vein thrombosis *(U)*
Ascites, high liver enzyme levels. US with Doppler and angiography often diagnostic. *Often managed medically.*

Abdominal Wall

Trauma: blunt *(C)*
History of trauma and physical exam findings of abdominal wall bruising/injury. *May require surgery.*
Trauma: penetrating *(LC)*
History of trauma and physical exam finding of punctures diagnostic. *Emergency surgery required.*
Abscess *(U)*
Physical exam, US and FNA with cytology and C&S often diagnostic. *Surgery required, may be urgent.*
Strangulated hernia *(U)*
Physical exam, radiography and US often diagnostic. *Emergency surgery required.*
Surgical site dehiscence/infection *(LC)*
History of surgery and physical examination often diagnostic. *Surgery required, may be urgent.*
Neoplasia *(U)*
FNA and cytology and/or histopathology often diagnostic. *May require surgery.*

Referred Pain

IVDD
Back pain, spinal cord signs; imaging to confirm.
Discospondylitis
Back pain, spinal cord signs; lytic vertebral endplate lesions on radiographs.
Spinal neoplasia
Asymmetrical spinal cord signs; imaging to confirm.
Vertebral fracture/luxation
History of trauma; back pain, spinal cord signs; imaging to confirm.
Pelvic trauma
History of trauma; hindlimb lameness/inability to rise; radiographs to confirm.

Note: Common (C), less common (LC), and uncommon (U) refer to whether the disorder is a frequent cause of acute abdomen in small animal practice (not simply the prevalence of the disorder).

AFAST, Abdominal focused assessment with sonography for trauma; *Bx,* biopsy; *C&S,* bacterial culture and sensitivity; *CNS,* central nervous system; *DPL,* diagnostic peritoneal lavage; *FB,* foreign body; *FIP,* feline infectious peritonitis; *FNA,* fine-needle aspirate; *GI,* gastrointestinal; *IVDD,* intervertebral disc disease; *NSAID,* non-steroidal anti-inflammatory drugs; *PCV,* packed cell volume; *PLI,* species-specific pancreatic lipase immunoreactivity test; *TS,* total solids; *Tx,* treatment; *U/A,* urinalysis; *US,* ultrasound.

Modified from the previous edition version created by Jennifer Devey.

Triage

Patients presenting with an acute abdomen generally can be classified into one of four categories: (1) stable patients that do not require surgery and can be managed medically (e.g., stable pancreatitis patient), (2) critically ill patients that do not have a surgical disorder but require rapid stabilization followed by ongoing medical management (e.g., unstable parvovirus patient), (3) urgent patients that require surgery but can be

supported medically to allow further stabilization prior to surgery (e.g., markedly azotemic patient with a ruptured urinary bladder) and (4) critically ill animals that require immediate surgery following rapid stabilization (e.g., gastric dilation and volvulus [GDV] patient).

A rapid triage examination focusing on vital organs (cardiovascular, neurologic, respiratory) is extremely helpful in classifying acute abdomen patients as stable or unstable. The triage exam should be performed at the time of presentation and intensive resuscitative efforts (Airway, Breathing, Circulation) should be initiated in any patient determined to be unstable (see ch. 127 and 140). Once resuscitative efforts have commenced, or if the animal is stable at the time of presentation, a more complete history and examination should be conducted in conjunction with a search for the underlying cause.

History and Signalment

Acute abdominal pain is a cardinal symptom underlying a vast number of possible causes and a detailed history is important to help narrow and prioritize differential diagnoses.[7] However, obtaining a thorough history should be delayed in favor of hemodynamic stabilization if the patient is deemed to be unstable based on the triage examination.

Important information to be gathered includes any possibility of toxin or foreign body exposure. Inadequate vaccination status and exposure to other animals can point toward viral enteritis. The presence of vomiting and diarrhea should be determined, and if present, explored further (see ch. 39 and 40). Projectile vomiting or vomiting soon after eating often is associated with a proximal GI obstruction[10,12] while hematemesis or vomitus with coffee-ground appearance is suggestive of gastric ulceration, neoplasia, or bleeding disorder.[12] Lower intestinal tract obstruction can result in malodorous vomit that smells like feces.[12] Unproductive retching should prompt consideration of GDV. Hematuria, stranguria, dysuria, and pollakiuria indicate a primary or secondary urinary tract problem (see ch. 46 and 47). Altered gait often accompanies abdominal adhesions, prostatic disease, or muscular, skeletal, or spinal cord disease.[10-12] Tenesmus and dry stool suggest obstipation in cats and prostatic disease in dogs (see ch. 42).

Physical and Abdominal Examination

In addition to the general physical examination (see ch. 2), there are important points to consider when evaluating patients with an acute abdomen. The abdomen should be visually inspected for distension, altered contours (e.g., due to hollow organ dilation, abdominal fluid, or organomegaly), obvious masses, bruising/hemorrhage, and lacerations or punctures. It may be necessary to clip the hair to see smaller lesions. The area under the tongue should be assessed for the presence of linear foreign bodies, particularly in vomiting cats. Examination of the vulva can reveal discharge associated with pyometra, while examination of the testes may detect the presence of retained testicles. A rectal examination is recommended to detect the presence of melena, masses, prostatic pain/enlargement, or the presence of uroliths that could be palpable within the pelvic urethra.

Palpation findings that confirm the presence of abdominal pain include the animal crying out or trying to escape or bite, tensing of the abdominal muscles, or shifting from side to side.[10] However, with severe depression or generalized peritonitis, signs of pain might not be evident on the physical examination.[10] Palpation of the abdomen should start with light pressure to evaluate the abdominal wall and superficial structures (e.g., presence of body wall hernia), followed by deeper palpation of the abdominal organs (detections of masses, foreign bodies, organomegaly, etc.). In some patients it might not be possible to perform deep palpation due to associated pain. In this case, analgesics should be given and the patient re-assessed when they have taken effect, although response of the patient can be decreased following analgesics. Pain localization can help narrow the differential diagnosis and help to direct diagnostic testing in some instances; for example, pain on palpation of the retroperitoneal space can suggest upper urinary tract disease, cranial abdominal pain suggests pancreatic, hepatic, gastric and duodenal disorders, and caudal abdominal pain can suggest lower urinary tract or reproductive disorders.[10] The clinical utility of abdominal auscultation and percussion in small animals has not been studied; however, auscultation of abdominal sounds has diagnostic utility in detecting states of ileus (obstructive or paralytic) and the presence of peritonitis in human medicine, despite having poor inter-observer agreement.[13] It is recommended that at least 5 minutes of abdominal auscultation be performed to assess increased or decreased frequency of GI sounds as well as the intensity and pitch of the sounds.[10,13] Absence of gut sounds can reflect ileus, chronic intestinal obstruction, peritonitis, or abdominal effusion while increased gut sounds can reflect acute

obstruction, enteritis, or toxin ingestion.[10,11]

It also should be noted that some animals with spinal or other extra-abdominal injury might show signs of referred pain that must be evaluated carefully to prevent misdiagnosis of an acute abdomen. It is important to check carefully to see if pain is present on palpation of the spine or pelvis in patients with an altered gait, to rule out referred pain.[9,10]

Diagnostic Testing

The clinical signs and examination findings in acute abdomen cases can be non-specific and could overlap with many conditions, which necessitates use of diagnostic laboratory tests and imaging.[8] Concurrent with attempts to stabilize the patient if hemodynamically unstable, cageside emergency diagnostic tests should be started as soon as possible. These tests include the minimum database (packed cell volume [PCV], total solids [TS], glucose, blood urea nitrogen [BUN], lactate [see ch. 70], electrolytes, and an arterial blood gas [ABG; see ch. 75 and 128]), urine specific gravity (see ch. 72), electrocardiogram (ECG; see ch. 103), arterial blood pressure (see ch. 99 and 159), abdominocentesis (see ch. 90), pulse oximetry (see ch. 98), and rapid evaluation of the abdomen with ultrasonography (abdominal focused assessment with sonography for trauma [AFAST; Video 143-2]) and/or diagnostic peritoneal lavage (DPL; see ch. 90). When the patient is stable, and if history, physical examination and emergency cageside tests fail to identify an underlying cause, advanced diagnostic tests including a complete blood count and serum biochemistry profile, abdominal radiography, comprehensive abdominal ultrasonography (see ch. 88), and possibly abdominal computed tomography (CT) or laparoscopy (see ch. 91) should be considered. Blood samples and urine ideally should be collected prior to starting fluid therapy. In some cases, exploratory laparotomy could be required in the absence of a definitive diagnosis, particularly in patients that remain unstable or are rapidly deteriorating once non-surgical disorders have been ruled out.

Minimum Emergency Database

The PCV and TS can alert the clinician to the presence of abdominal hemorrhage, or if both are elevated, suggest dehydration. In acute hemorrhage, it is common to see the TS fall before the PCV falls below the reference interval, and it is recommended to rule out a source of hemorrhage or follow the PCV and TS serially in patients that have a relatively low TS following a traumatic event.[14] A low blood glucose concentration in the patient with an acute abdomen can be reflective of sepsis. A high blood urea nitrogen concentration can be reflective of prerenal, renal or postrenal disease and should be evaluated in conjunction with the physical examination and urine specific gravity. High serum hepatic enzyme concentrations can reflect hepatic or posthepatic causes of acute abdomen. Measurement of blood lactate concentration in conjunction with blood pressure provides an indication of tissue perfusion and can be followed serially to guide resuscitative efforts. The ECG should be followed continuously to evaluate the patient's initial response to resuscitative efforts, to help determine the patient's response to analgesic therapy, and to detect cardiac arrhythmias, which are not uncommon in patients with acute abdominal syndromes secondary to splenic masses, GDV, organ torsions, pancreatitis, pain and trauma (see ch. 141 and 248). Pulse oximetry and ABG analysis, although not specific to cases with acute abdomen, can detect concurrent underlying lung disorders (e.g., aspiration pneumonia secondary to vomiting).

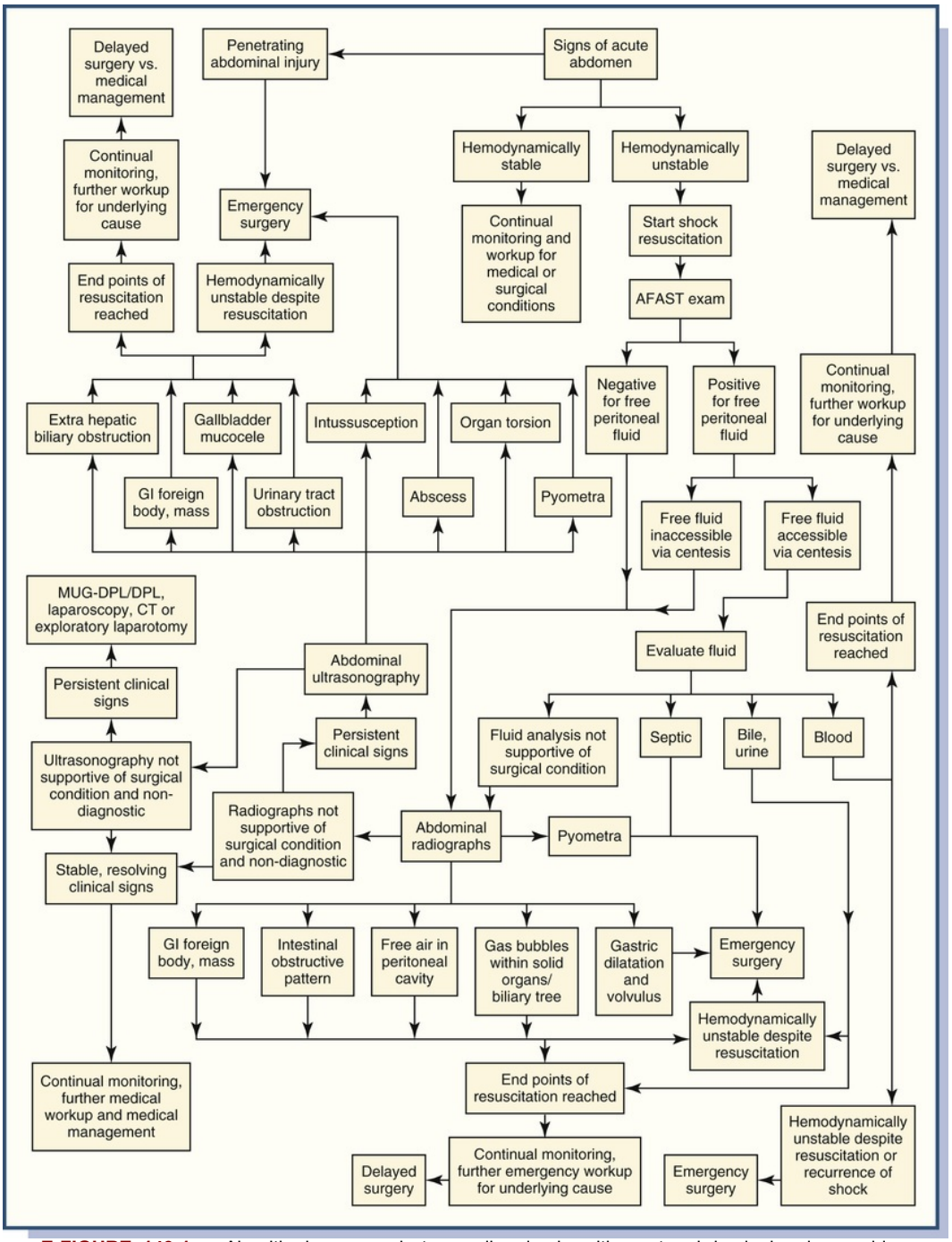
Emergency Ultrasound

Small animal patients presenting with an acute abdomen secondary to trauma should have an AFAST scan performed to detect the presence of free peritoneal fluid, which most often represents hemorrhage, although biliary, intestinal, and urinary tract rupture could also account for posttraumatic free abdominal fluid (see Video 143-2).[14,15] AFAST scans also are indicated in the unstable patient with acute abdomen unrelated to trauma. A study investigating dogs and cats presenting to an emergency service or hospitalized in the intensive care unit found that AFAST exams performed in non-trauma patients identified free peritoneal fluid in 75% of unstable patients compared to only 9% in stable patients.[16] Advantages of AFAST scans to detect the presence of free fluid are that they can be completed in under 5 minutes, require minimal ultrasound training, can be done at the cageside while unstable patients are being resuscitated, and can be repeated as necessary.[14-16] The detection of free peritoneal fluid, concurrent with fluid analysis including cytologic evaluation, can be critical in pursuing prompt surgical intervention. In some cases, free peritoneal fluid will

accumulate in the peritoneum following fluid resuscitation, and serial AFAST exams (repeated in 2-4 hours) can prove valuable in detecting delayed free peritoneal fluid accumulations.[15]

Abdominocentesis and Diagnostic Peritoneal Lavage (see ch. 90)

Abdominocentesis is easy to perform, can be done at the time of initial resuscitation, and is a key diagnostic step in helping determine the need for emergency abdominal surgery (E-Figure 143-1). Abdominocentesis, performed either ultrasound-guided or blind, and combined with fluid analysis and cytologic evaluation, allows for the detection of infection (septic peritonitis), blood (hemoabdomen), urine (uroabdomen), bile (bile peritonitis), or another non-septic effusion (see ch. 74). Abdominocentesis is indicated in acute abdomen patients when there is evidence of abdominal fluid (palpable abdominal fluid wave, loss of detail on radiographs, or detection of fluid with ultrasound), or when an unidentified cause of shock is present and ultrasonography is unavailable.



E-FIGURE 143-1 Algorithmic approach to small animals with acute abdominal pain requiring emergency and delayed surgery. *AFAST,* Abdominal focused assessment with sonography for trauma; *CT,* computed tomography; *DPL,* diagnostic peritoneal lavage; *GI,* gastrointestinal; *MUG-DPL,* modified ultrasound-guided diagnostic peritoneal lavage.

In acute abdomen cases where the underlying cause remains uncertain, and a strong suspicion of septic peritonitis persists, or small quantities of free peritoneal fluid are found that cannot be directly aspirated via centesis, DPL or modified ultrasound-guided DPL (MUG-DPL) should be considered (see ch. 90). Although ultrasonography has replaced DPL in many situations, DPL may still prove valuable in some cases of acute abdomen, including acute mesenteric ischemia.[17] A modification of the DPL technique using ultrasound guidance has been described.[18] Briefly, following ultrasound guidance of a catheter tip within close proximity to free peritoneal fluid, warmed sterile saline in 3-5 mL/kg quantities is allowed to flow through the catheter via gravity until the infused fluid mixes with the existing free peritoneal fluid. A sample can be obtained via the catheter if it becomes continuous with the pre-existing free peritoneal fluid, or alternatively, the catheter

can be removed and ultrasound guided abdominocentesis performed to obtain a sample of the diluted free peritoneal fluid.

Abdominal Radiography and Comprehensive Abdominal Ultrasonography

Survey radiography and ultrasonography are considered the standard imaging modalities for evaluation of the small animal patient with acute abdominal signs.[19] A recent study comparing imaging modalities (radiography, B-mode ultrasonography, contrast-enhanced ultrasonography and contrast-enhanced multi-detector CT) in dogs with acute abdomen found survey radiography and ultrasonography correctly identified cases requiring surgery (intestinal mechanical obstruction, GI perforation, traumatic diaphragmatic hernia, and visceral abscess) 89% of the time.[19] However, given the two imaging modalities have different sensitivities and specificities at detecting different disorders causing an acute abdomen, they should be considered to be complementary. Ultrasonography can be advantageous over radiography in the detection of GI foreign bodies and detection of mechanical ileus.[20,21] Conversely, radiography may be advantageous over ultrasonography in cases with suspected hollow viscus perforation and pneumoperitoneum.[19] Furthermore, the diagnostic imaging test chosen will vary depending on the suspected underlying disease. For example, radiography is preferred to confirm the diagnosis of suspected GDV while ultrasonography is preferred for confirmation of suspected free abdominal fluid as it is more sensitive at detecting small quantities and facilitates ultrasound-guided centesis.[19] Radiographs should be assessed carefully for the presence of free air, fluid, masses, organ position, and focal or diffuse bowel loop distension.[11] See ch. 88 for details on abdominal ultrasonography.

Advanced Imaging

Targeted helical CT is considered the modality of choice for evaluation of acute abdomen in people[22-24] and its use in small animals with acute abdominal signs is likely to increase as it becomes more widely available. Furthermore, awake and minimally sedated contrast-enhanced multi-detector CT protocols using 16-slice technology have been used safely and successfully in the evaluation of canine patients with acute abdominal signs.[25] If radiography and ultrasonography fail to identify a cause and clinical suspicion of an abdominal disorder persists, CT should be considered when available.

Treatment

Once a diagnosis for the cause of acute abdomen is made, therapy should be directed toward that specific cause. However, several therapeutic interventions should be instituted early in the management of an acute abdomen patient, often before a diagnosis can be confirmed. This includes initial stabilization of patients presenting in shock (see ch. 127), analgesia to alleviate abdominal discomfort (see ch. 126), and, when indicated, emergency surgery to prevent deterioration of the patient. Hemodynamic stabilization should be attempted immediately following identification of shock or other forms of hemodynamic instability on triage examination and should be completed prior to anesthesia and surgery to decrease the risk of associated complications (anesthesia-induced vasodilation and hypotension, and further fluid losses and hemorrhage from surgery). There are many analgesics that can be used in patients with acute pain, although opioids often are indicated and should be administered early. While giving opiates to human patients with acute abdominal pain appears to alter the physical examination, the administration of opiates leads to virtually no increase in incorrect management decisions.[26-28] Cardiac arrhythmias should be treated if they result in clinical signs of decreased cardiac output or put the patient at risk of arrest (see ch. 141 and 248). Cases with GI perforation or sepsis should have abdominal fluid or blood samples collected for culture and sensitivity testing prior to antibiotic therapy.[29] Although supportive evidence is lacking in small animals, broad spectrum intravenous antimicrobial coverage should be started within an hour of detecting the presence of sepsis.[29,30] In many cases, the underlying cause of acute abdomen is a life-threatening surgical condition, which requires prompt identification to proceed to surgery.

Deciding if Surgery Is Indicated

A number of underlying conditions causing acute abdomen may require delayed or emergency surgery (see

Box 143-1), and deciding if and when surgery is indicated to prevent patient deterioration is often challenging (see ch. 144). Dealing with such acute emergency patients involves a highly complex decision-making process, which may be simplified with the application of a clinical algorithm (see E-Figure 143-1). In some cases, patients will require emergency surgery based on history and physical examination findings without the benefit of further diagnostic testing, or a confirmed diagnosis. However, attempts should be made to rule out medical causes and to achieve hemodynamic and metabolic stabilization prior to surgery.

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CHAPTER 144

Gastrointestinal Emergencies

Amie Koenig

Animals frequently are presented on emergency for evaluation of gastrointestinal (GI) signs including vomiting, diarrhea, and signs of abdominal pain. Any of these can be signs of primary GI or non-GI illness (E-Box 144-1). One of the most important decisions in such situations is whether the animal with a GI emergency can be managed medically or requires surgical intervention. Sometimes the answer to this question is obvious, while other times the question is only answered after careful assessment of history, physical examination, and diagnostic test results (Figure 144-1; also see ch. 143).

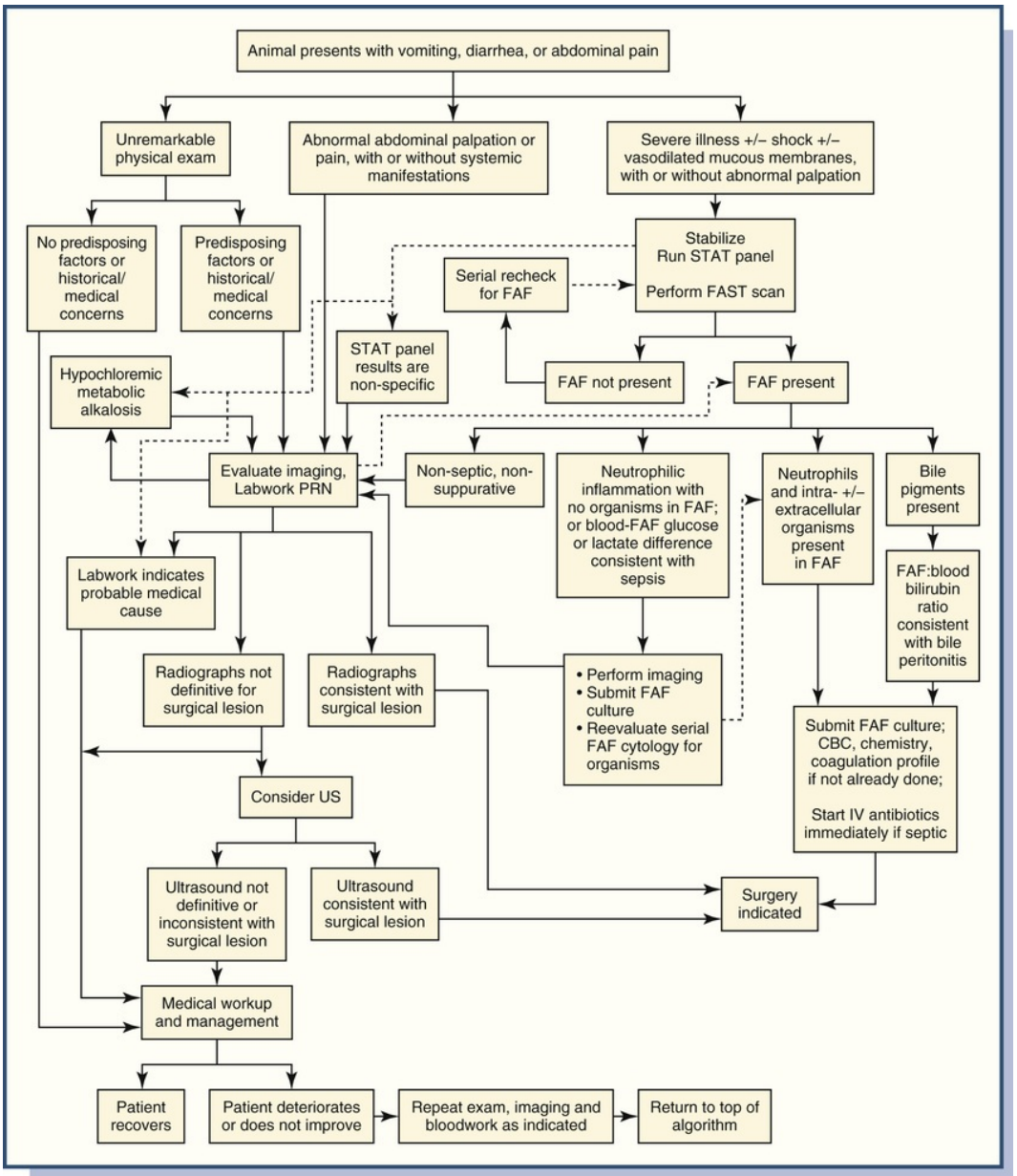

FIGURE 144-1 Algorithm for differentiating a medical from surgical case of gastrointestinal signs. Dotted lines indicate possible courses of action in certain cases. *FAF,* Free abdominal fluid; *FAST,* focused assessment with sonography in trauma, triage, and tracking; *PRN,* as needed; *STAT, statim* (Latin: "immediately"). Dotted lines indicate possible courses of action in certain cases.

E-Box 144-1

Examples of Gastrointestinal and Non-gastrointestinal Causes of Vomiting, Diarrhea, or Abdominal Pain

Gastrointestinal Causes

Infection
- Bacterial (e.g., *Clostridium, Salmonella*)
- Viral (e.g., canine parvovirus, feline panleukopenia virus, canine distemper virus)
- Parasitic (hookworms, roundworms, whipworms)
- Protozoal *(Giardia, Entamoeba, Tritrichomonas)*

Inflammation—inflammatory bowel disease, hemorrhagic gastroenteritis, GI ulceration

Neoplasia—lymphoma, adenocarcinoma, leiomyoma
Obstruction—intussusception, foreign body, GDV, stricture, pyloric hypertrophy
Dietary indiscretion
Functional ileus

Non-gastrointestinal Causes

Cardiovascular/GI hypoxia—Shock of any etiology (especially in the dog), pericardial effusion, GDV, mesenteric torsion, intestinal volvulus, GI thrombosis
Endocrine—hypoadrenocorticism, hyperthyroidism, DKA
Acid-base/electrolyte abnormalities—hypercalcemia
Hepatobiliary—hepatitis, hepatic failure, cholangiohepatitis, cholangitis
Pancreatic—pancreatitis, pancreatic neoplasia
Genitourinary—uremia, pyometra
Nervous system—vestibular disease, increased intracranial pressure or CNS disease affecting CRTZ/emetic center
Toxin/drug reaction—many plants, chemicals, heavy metals, medications, blood products

CNS, Central nervous system; *CRTZ,* chemoreceptor trigger zone; *DKA,* diabetic ketoacidosis; *GDV,* gastric dilation-volvulus; *GI,* gastrointestinal.

Signalment

The first step in evaluating any patient is to review the patient's signalment and a thorough history. Age and breed can help with prioritizing differential diagnoses for GI emergencies. Infectious causes of GI disease are common in younger dogs and cats, as are GI foreign bodies.[1-6] Pancreatitis is more common in toy, terrier, and nonsporting dog breeds while hypoadrenocorticism is seen more commonly in Great Danes, Portuguese Water Dogs, Rottweilers, Standard Poodles, and West Highland White and Wheaten Terriers.[7-10] Certain causes of GI signs or signs of abdominal pain are gender-specific including pyometra, dystocia, uterine torsion, testicular torsion, and prostatitis. Urethral obstruction is more common in males.

History

Information regarding type of GI signs, including vomiting and character of the vomitus, character of any diarrhea, presence of hematemesis, hematochezia or melena, weight loss, and appetite should be gathered. Vomiting should be differentiated from regurgitation, which is more a characteristic of esophageal disorders (see ch. 39). The characteristics of a patient's diarrhea can help identify the segments of the GI tract that could be involved. Urgency, mucus, and frank blood are characteristic of large bowel diarrhea while watery diarrhea, digested blood, and less urgency are more a characteristic of small bowel diarrhea (see ch. 40-42 and 276). Weight loss also is more consistent with small bowel disease. Other signs, such as polyuria and polydipsia, vulvar discharge, or icterus, can point towards non-GI disease.

Onset and duration of illness, progression of clinical signs, and response to any therapy can assist in working through differential diagnoses. Recent antibiotic usage can disrupt GI flora and contribute to development of diarrhea, vomiting, and hyporexia. Duration of clinical signs does not differentiate need for medical versus surgical intervention. As an example, a patient with a foreign body can be presented after months of GI signs and weight loss, or after minimal duration of signs. Waxing and waning GI signs can suggest hypoadrenocorticism.

Vaccination history, diet, and potential exposure to toxins, foreign bodies, or infectious agents also are important. Animals ingesting raw food diets can be at risk for *Salmonella* enteritis or other enteric infections (see ch. 191 and 192).[11-13] Recent dietary indiscretion could lead to gastroenteritis, pancreatitis, or foreign body ingestion and obstruction. Infectious causes can be suggested by recent exposure to other animals such as in dog parks, wilderness, or daycare settings.

Physical Examination

Physical examination of any patient presented on emergency should include both primary and secondary surveys. The primary survey includes evaluation of the cardiovascular, respiratory, and neurologic systems and is aimed at identifying imminently life-threatening abnormalities. The secondary survey, which includes the remainder of a thorough physical examination, follows or accompanies stabilization of abnormalities

identified in the primary survey.

Animals with either surgical or nonsurgical illness can present with similar signs depending on the type, duration, and severity of the underlying disease (see ch. 143). Shock can be hypovolemic, cardiogenic, obstructive, distributive, or metabolic in origin (see ch. 127). Additionally, the GI tract is the shock organ in the dog, and GI signs are a common sequela to shock of any etiology in this species. Hypovolemic shock is common in animals with GI signs due to water losses via vomiting and diarrhea when there is a concurrent inability to either drink or retain water. Signs of compensatory shock include tachycardia, tachypnea, pink mucous membranes with normal or brisk capillary refill time (CRT), normal pulse quality, normal body temperature, normal mentation, and normal blood pressure. Signs of early decompensatory shock include tachycardia (dog or cat) or relative bradycardia (cat), pallor, prolonged CRT, a weak pulse, tachypnea, hypothermia, depressed mentation, and low-normal or low blood pressure. Late decompensatory shock, also called terminal shock, is marked by bradycardia, muddy mucous membranes, markedly prolonged (or absent) CRT, hypothermia, stupor or coma, and extremely low blood pressure, if it can even be measured. Identification of shock should prompt immediate fluid resuscitation with crystalloids +/− colloids, pressors, inotropes, and other treatments as indicated (see ch. 129 and 130). Presence of bright pink to red mucous membranes, especially in the face of shock and hypotension, should prompt careful evaluation for sepsis (Video 144-1). Although there are many other causes of bright red mucous membranes, septic peritonitis should be a top rule-out in an animal with GI signs.

A full physical examination, including careful abdominal palpation, should be performed as part of a secondary survey (see ch. 2). Notable findings can include auscultation of muffled heart sounds in patients with severe hypovolemia but also in patients with pericardial effusion, who often present with concurrent vomiting. Via palpation, it can be possible to localize the source of GI signs to a region of the abdomen or a specific organ based on location of pain or abnormal margination, size, or location of intra-abdominal structures. In cats, diffuse nonspecific abdominal pain has been identified regardless of the site of origin of sepsis.[14] Free abdominal fluid (FAF) can be noted by presence of a fluid wave (see ch. 17).

Specific physical examination findings that suggest a need for surgical intervention include palpation of foreign material within the GI tract, severe small bowel distention, severely distended or tympanic stomach, palpation of a sausage-like intussusception, and identification of a linear foreign body (FB) lodged under the tongue. Only 6% of linear FBs have been reported to be visible under the tongues of dogs.[3] In animals with GI foreign bodies, the object or its subsequent intestinal abnormalities are palpable in 60% and 76% of awake and anesthetized patients, respectively.[1]

Diagnostic Tests

Diagnostic testing might or might not be indicated, and the extent of the workup is based on history and physical examination findings. Bloodwork, survey and advanced imaging, and infectious disease testing are the most commonly performed diagnostic tests for patients presenting with GI emergencies. Abnormalities will depend on the type, duration, and severity of the underlying problem.

Initial Blood Tests

While a routine minimum database (complete blood count, serum biochemistry profile, urinalysis) cannot differentiate a surgical from nonsurgical patient, it can help direct the clinician towards primarily non-GI sources of vomiting and diarrhea, such as liver disease, kidney disease, or hypoadrenocorticism, which are usually treated nonsurgically. Degenerative left shifts, thrombocytopenia, and coagulation abnormalities typically indicate a greater severity of the underlying disease process. Additionally, for those patients ultimately identified as having a surgical lesion, laboratory results can provide prognostic information. For example, preoperative hypoalbuminemia has been associated with an increased risk of mortality or post-operative dehiscence of GI incisions in some, although not all, studies.[15-23] Baseline lactate and delta lactate concentrations (see ch. 70) have been associated with gastric necrosis and mortality in gastric dilation-volvulus (GDV).[24-26]

For unstable, extremely ill, and/or markedly dehydrated patients, cageside diagnostics rapidly deliver information that can impact therapy and outcome. A STAT panel consisting of packed cell volume and total protein, cytology of a stained blood smear, and measurements of blood glucose and venous blood gases with serum electrolyte and lactate concentrations allow assessment of hydration, oxygen carrying capacity, white cell and platelet estimates, glycemic state, electrolyte balance, and oxygen delivery (shock). Metabolic acidosis

can result from shock associated with lactate production or due to ketosis, production of uremic acids or toxins, or hyperchloremia, any of which can be associated with GI signs (see ch. 128). In animals with GI obstruction due to FBs, commonly reported blood gas abnormalities include an elevated bicarbonate (in approximately 75% of patients), hypochloremia (51%), metabolic alkalosis denoted by elevated base excess (≈45%), and hyperlactatemia. Presence of hypochloremic, hypokalemic metabolic alkalosis does not differentiate proximal from distal GI obstruction in dogs.[2]

Analysis of Free Abdominal Fluid

Any FAF should be collected via centesis for evaluation (see ch. 74 and 90). Cytologic indications for immediate surgery include presence of bacteria or bile pigment. Suppurative effusion with no overt bacteria can be seen with early proximal GI (stomach, proximal duodenum) perforation but can also be seen with other causes of peritonitis such as pancreatitis or splenic torsion. Bacterial culture is still considered the gold standard for identification of a septic abdomen; however, culture results are not rapidly available. In the absence of visible organisms on cytologic assessment of fluid, the difference between blood and FAF glucose concentrations on concurrently obtained samples can be suggestive of septic peritonitis. Using measurements obtained on a laboratory biochemical analyzer, a blood glucose concentration >20 mg/dL (>1.1 mmol/L) higher than the FAF glucose concentration was reported to be 100% sensitive and 100% specific for the diagnosis of septic peritoneal effusion in dogs and 86% sensitive and 100% specific in cats.[27] However, measuring a whole blood to FAF difference using a hand-held glucometer results in a large number of false negatives; measuring a plasma-FAF or plasma-FAF supernatant glucose difference on a hand-held glucometer is more sensitive.[28] A lactate concentration that is >2.0 mmol/L higher in FA than in whole blood was reported to be 100% sensitive and specific for a diagnosis of septic peritoneal effusion in dogs.[27]

Fecal Cytology and Infectious Disease Testing

Since intestinal parasitism is such a common cause of GI disease in dogs and cats, a basic fecal flotation is rational for most animals with GI signs. A Romanowsky-stained (e.g., Diff-Quik) cytologic smear of feces and/or of a rectal scraping sometimes can reveal organisms such as *Histoplasma* or *Giardia,* or bacteria consistent with *Clostridium* or *Campylobacter*. A normal, stained smear should show a heterogeneous bacterial population and few red and white blood cells, if any. Potential abnormalities include abundant red cells consistent with hemorrhage, abundant neutrophils consistent with inflammation or infection, macrophages consistent with potential fungal infection, and a bacterial population that lacks diversity, suggesting overgrowth, imbalance, or recent use of antimicrobials. See ch. 81 for more information about fecal examination.

Fecal polymerase chain reaction (PCR) panels for infectious organisms are available from multiple diagnostic laboratories (see ch. 207 and 271). Because some infections tend to occur in certain age groups of animals, different PCR panels may be available for young animals and adults. PCR tests are considered desirable since most are sensitive and specific. However, the tests can also identify nonviable organisms and organisms that are transiting through the GI tract rather than causing disease. As such, in some cases, a positive fecal PCR result will not differentiate true infection from colonization; therefore, PCR testing ideally should be done in animals with compatible clinical signs, rather than as a screening test. For instance, *Salmonella* testing could be indicated in patients with fever, hemorrhagic diarrhea, neutropenia, fecal neutrophils, and possibly an enlarged cecum. A positive fecal *Salmonella* PCR result subsequently should be confirmed with culture and serotyping.

Parvovirus infection should be suspected in very young or unvaccinated dogs and cats with vomiting and watery, hemorrhagic diarrhea with mucosal sloughing. Subclinical disease and peracute disease with sudden death also are possible. Canine parvovirus (CPV) and feline parvovirus (FPV, feline panleukopenia virus) can be identified using cageside antigen test kits.[29] While CPV SNAP test kits are sensitive and specific, a negative test result in a young or unvaccinated animal with compatible clinical signs does not rule out infection. Additional testing with fecal PCR or by repeating cageside ELISA after 24-48 hours should be considered; in cats, FPV antigen might only be detectable in feces for 24-48 hours after infection.[30] Rising convalescent serum titers, viral isolation, and fecal electron microscopy are additional confirmatory methods (see ch. 225).

Imaging

Imaging is a critical component of the diagnostic workup of many patients with GI emergencies. Definitive

imaging modalities must often wait until the patient is stabilized. A FAST scan (focused assessment of sonography in triage, trauma and tracking) can be a valuable point-of-care tool for identifying FAF and other major ultrasonographically visible abnormalities in the critical patient during stabilization (see ch. 143). Ultrasound has been shown to be a more sensitive tool than radiographs for detecting small volumes of FAF.[31] The FAST scan uses four standardized views to attempt to identify FAF in areas where it is most likely to accumulate and easiest to find, namely the diaphragmaticohepatic, splenorenal, cystocolic and hepatorenal views.[32] Serial FAST scans can be used to monitor for FAF that may develop after restoration of vascular volume and improvements in hydration.

Abdominal radiographs are often the first modality utilized for imaging patients with GI disease. There are many radiographic findings that indicate a need for immediate surgery. Dilation and displacement of the stomach ("double bubble") in a right lateral projection is consistent with GDV. Free air in the abdomen in the absence of recent abdominal surgery is most commonly associated with GI tract perforation, although free air can persist in the peritoneal cavity for as long as 2 weeks post-laparotomy. Radiographic signs suggestive of GI obstruction include segmental intestinal dilation and intestinal plication. In the cat, the probability of small intestinal obstruction is >70% if the ratio of the small intestinal diameter (SID) to the dorsoventral height of the cranial endplate of the second lumbar vertebra is >3.0 on a lateral projection. For the dog, a normal ratio of SID to the height of the narrowest point of the L5 vertebral body on a lateral projection is ≤1.6 and there is a >80% probability of obstruction if the ratio is >1.95.[33]

If plain radiography does not identify obstruction or foreign material in an animal with a suspected GI FB, positive or negative contrast can be used. A barium series can be useful in outlining the FB, although it may be vomited prior to reaching the obstruction or retained in the stomach or intestine due to ileus. Gastric foreign material also can be identified using pneumogastrography with either air or a carbonated beverage as the negative contrast medium.[34] Pneumocolonography can be used for distending the colon, to help differentiate it from distended small intestine.

Patients with signs of acute abdomen without significant radiographic abnormalities may need to be evaluated with other modalities such as ultrasound (see ch. 88 and 143). Ultrasound has largely superseded contrast radiography as the preferred method for evaluating patients for potential obstructions or other surgical GI emergencies and has been shown to be better than survey radiography for identifying obstruction when performed by skilled sonographers.[35-37] In one study, obstructed dogs were differentiated from nonobstructed dogs in 70% of cases based on radiographic findings, compared to 97% of cases when based on sonographic findings.[36] In another study of animals with small intestinal obstruction, obstruction was correctly ruled out by ultrasound in 74% of cases and correctly identified in 23% of cases (100% sensitive and 96% specific).[38] Ultrasonographic findings consistent with small intestinal obstruction include intestinal plication, segmental dilation, a jejunal diameter >1.5 cm, and/or identification of the actual obstruction.[36] Ultrasound has a reported sensitivity of as high as 100% for identification of FBs, which are identified by distal acoustic shadowing and surface reflection.[35,37,38]

Ultrasonography also can identify FAF, perforation, free gas, GI wall thickening, loss of GI tract layering, and enlarged lymph nodes that might not be identified with radiography.[35,37] Focal or regional hyperechoic fat, peritoneal effusion or pneumoperitoneum, fluid-filled stomach or intestines, and thickening or loss of GI wall layering are the most common ultrasound findings in dogs and cats with GI tract perforation. Additional reported findings include corrugated or undulating intestine, regional lymphadenopathy, hypomotility, pancreatic changes, presence of a mass or foreign object, gastroduodenal junction "crumpling" and gastric wall mineralization.[39,40]

Additional organ-specific changes consistent with causes of acute abdomen or abdominal pain such as gastroenteritis, pancreatitis, colitis, pyometra, pyelonephritis, splenic or liver lobe torsion, hepatopathy, biliary obstruction, vascular thrombosis, and others also can be identified via ultrasound (see ch. 143).

Management

Identification of a surgical lesion should prompt surgical intervention as soon as possible once the patient is fluid resuscitated and hemodynamically stable. Antibiotic treatment should be initiated immediately upon identification of bacteria within FAF, as early antibiotic therapy has been shown to improve outcome in humans with septic shock.[41] Medical management for vomiting and diarrhea can be as simple as withholding food and water for short periods followed by their slow reinstitution, to in-patient therapy with intensive monitoring. Etiology-specific therapies, such as antiparasitics, antimicrobials, or general supportive care,

including fluid and electrolyte therapy, antiemetics, gastric-acid reducers and nursing care should be included on a case-by-case basis. Good supportive care also should be included as part of the preoperative and postoperative surgical plan.

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CHAPTER 145

Hepatic and Splenic Emergencies

Amanda K. Boag

Overview

Dogs and cats seen as emergencies with an underlying hepatic or splenic condition may have a wide variety of clinical signs. As with all emergency patients, a thorough history and physical examination is required to guide the choice of diagnostics and therapeutics. Pets with splenic or liver conditions that become life-threatening usually have hemodynamic instability (hypovolemic, distributive or cardiogenic shock) or neurological signs (coma or seizures). The latter may be seen with hepatic encephalopathy (HE), hypoglycemia or intracranial hemorrhage. Empirical stabilization should be initiated while the diagnostic evaluation is ongoing.

Diagnostic Approach

The clinical signs and historical information associated with hepatic and splenic emergencies can be vague and non-specific; however, most patients seen as emergencies will have evidence of one or more of the following: shock (collapse/weakness; see ch. 21 and 127), icterus (see ch. 53), or neurological signs (see ch. 33, 34, 35, and 259, and Figure 30-1). Historical questions should help identify pre-existing signs (e.g., polyuria and polydipsia [PU/PD], weight loss), access to toxins, and potential for infectious disease. The cardiovascular system examination may suggest the type of shock and helps to prioritize differential diagnoses. For example, the patient likely has hypovolemic shock if there is hemoperitoneum or distributive shock with hepatic abscess. Icterus, if seen, should prompt discrimination of pre-hepatic, hepatic or post-hepatic conditions (see ch. 53).

An initial diagnostic database should include a packed cell volume and total solids (PCV/TS), electrolytes, venous blood gas (see ch. 128), glucose (see ch. 61), lactate (see ch. 70), and blood smear. Clotting tests (prothrombin time and activated partial thromboplastin time) are indicated in emergencies involving the liver or spleen to help identify DIC (disseminated intravascular coagulation) or presence and severity of coagulopathies. Complete blood count (CBC), biochemistry panel, and serum thyroxine (in cats) should be assessed, with attention to indicators of liver function (albumin, blood urea nitrogen [BUN], cholesterol, bilirubin and glucose) and liver enzyme activities. Further laboratory testing may include ammonia concentrations, infectious disease screening, dynamic bile acid testing, pancreatic lipase immunoreactivity and thromboelastography.

A free fluid (FAST) ultrasound (US) scan is the "kennel-side" imaging test of choice in pets suspected of having hepatic or splenic disease (see ch. 143).[1] If free fluid is identified, abdominocentesis should be performed and the fluid analyzed (see ch. 17 and 74). Fluid may be non-clotting blood, a septic or non-septic exudate, chyle, a modified transudate or a transudate. Knowing the nature of fluid is vital for refining any differential list and in determining if surgical intervention is warranted. Evaluation of the bilirubin gradient (i.e., difference in bilirubin from the abdominal fluid as compared with a concurrent serum sample) can confirm biliary tract rupture. If no free fluid is present, US remains valuable for evaluating organ internal architecture, for identification of a mass, and to evaluate vascular flow. US can be integral for diagnosing splenic torsion or portosystemic shunts. Radiographs, while generally not as definitive as US, may aid in identifying free fluid, microhepatica, organ enlargement, or masses involving either liver or spleen. Timing of computed tomography (CT) scans for evaluation of abdominal emergencies in dogs and cats is being evaluated. Focal or diffuse hepatic or splenic abnormalities can be further defined with histologic evaluation of US-guided fine needle aspirates (FNA) or needle core biopsy (see ch. 89). Tissue may also be obtained via laparoscopy or celiotomy (see ch. 91). The sampling technique chosen is based on judging risk versus benefit in each patient, including consideration of coagulation status.[2-4]

Patient Stabilization

Early stabilization protocols of pets severely ill secondary to hepatic or splenic disease commonly include fluid therapy and, less commonly, antiarrhythmic medications for cardiovascular stabilization and/or medications to improve neurological status (see ch. 127, 129, and 141). Blood glucose should be measured as a priority and supplemented if low (see ch. 61). Fluid therapy should be tailored to individual patient needs, based on severity of signs, knowledge of any concurrent disease, initial test results and likely differential diagnoses. Lactate, an objective indicator of shock severity, can be used to help guide therapy (see ch. 70). However, lactate kinetics are altered in some dogs and cats with severe hepatic failure or distributive shock (sepsis).[5,6] Most commonly, IV isotonic crystalloid fluid boluses are used at dosages of 10-40 mL/kg administered quickly (over 15-60 minutes) to improve cardiac output and tissue perfusion. Colloid fluids, hypertonic saline, HBOCs (hemoglobin-based oxygen carriers) and blood products may also be indicated (see ch. 129 and 130). Administration of packed red blood cells may be vital for ensuring adequate oxygen delivery in patients with significant blood loss. Fresh frozen plasma may be useful for pets with a concurrent coagulopathy associated with either acute hepatic failure or DIC (see ch. 197). Electrolyte and acid-base parameters should be assessed and fluid therapy, supplemented as indicated, used in correcting abnormalities. Clotting tests should identify bleeding tendencies that rarely lead to intra-cranial bleeding and neurological signs. Use of fresh frozen plasma (initial recommended dose 20 mL/kg over 4-6 hours) may be beneficial.

The optimal fluid strategy for resuscitating patients in hemorrhagic shock is not well defined, with few studies critically evaluating timing or volume of fluid therapy for patients who are actively bleeding (see ch. 135).[7] Early aggressive fluid resuscitation using "full" shock doses (up to 60-90 mL/kg of isotonic crystalloid or 20 mL/kg of colloid in the dog) is no longer recommended, as it may lead to dilution of clotting factors, increased bleeding, and deleterious effects on cellular metabolism. Current recommendations are to administer fluids in a controlled manner to meet defined end-points, such as a systolic blood pressure of 80-90 mm Hg (see ch. 99).[8] Meta-analyses of studies on people do not suggest any benefit in using colloid over crystalloid fluids.[9] Caution is recommended regarding use of starches due to their potential relationship to acute kidney injury.[10]

Use of hypertonic saline may have beneficial immunomodulatory effects. Evidence in small animals is limited, but results from one study indicated that resuscitation end-points are reached more rapidly when limited-volume fluid resuscitation is used.[11] A small percentage of patients with splenic disease have severe arrhythmias that may lead to cardiogenic shock, identified by an irregular heart rhythm and pulse deficits on the physical examination (see ch. 2, 140, and 141). Such findings should be confirmed by an ECG and appropriate medication given (see ch. 103 and 248).

Patients with severe liver disease may be suffering from HE, whose management should begin with IV fluid therapy and multiple enemas to clear as much stool (and ammonia) from the colon as possible before using oral or rectal lactulose and antibiotics to further reduce the number of ammonia producing bacteria (see ch. 281 and 284).[12] Both hypokalemia and alkalosis can worsen signs of HE. In patients that are actively seizuring, propofol or levetiracetam is recommended (see ch. 136).[13] Although diazepam would be considered routine for most patients with seizures, its use in patients with HE is controversial.[14]

Specific Conditions

Hemoperitoneum

Hemoperitoneum, not always associated with trauma, is a common hepatic/splenic emergency. Depending on severity, patients who bleed into their abdomen can have mild signs of episodic weakness to severe signs of unconsciousness and shock. Pets seen for collapse without a history of trauma may previously have had one or more episodes of weakness, presumably due to less severe bleeding episodes. Dogs in hypovolemic shock have pallor, tachycardia, and changes in pulse quality. They may or may not have abdominal distention but are expected to have reductions in PCV and TS and a metabolic (lactic) acidosis. Hematology and clotting tests may be consistent with DIC. FAST scans demonstrate free fluid, typically non-clotting blood with a PCV similar to that of peripheral blood. Use of abdominal compression bandages may help with stabilization. Cats with hemoperitoneum may have signs of lethargy, anorexia and vomiting.[15]

If one or more cavitated masses is/are visualized with more detailed abdominal US scanning, the most likely diagnosis is hemangiosarcoma although other malignant and benign masses occur (see ch. 206 and

347).[16-18] Surgery is indicated once the patient is stable in the majority of non-traumatic cases and perioperative survival rates are good. Risk factors for death include need for massive transfusions, non-splenic sources of bleeding and development of respiratory signs.[19] Metastasis may be present and thoracic imaging (radiography or CT) is recommended prior to surgery. Risk factors for malignancy are reported to include lower TS and platelet counts and relatively small masses.[16,20] Echocardiography (see ch. 104) to identify right atrial hemangiosarcoma may be performed, although the relationship between right atrial and abdominal hemangiosarcomas is not clear.[21] Pets with traumatic hemoperitoneum often stabilize following fluid therapy, abdominal compression, and/or transfusion therapy. If they remain unstable, surgery should be considered.[22]

Acute Hepatic Failure

Dogs and cats with acute hepatic failure are often seen for collapse, neurological signs (obtundation or seizures) and/or GI signs (see ch. 280). Alternatively, some have acute progression of clinical signs following chronic liver disease. These latter pets are more likely to have a chronic history of weight loss, inappetence, PU/PD, and they may have ascites (secondary to portal hypertension and/or hypoalbuminemia; see ch. 17). Most of these pets are icteric on physical examination (see ch. 2 and 53). Pets with hereditary porto-systemic shunts are not usually jaundiced, but have signs of hepatic dysfunction (particularly HE; see ch. 284). Causes of acute hepatic failure include viral, bacterial and other infectious agents (see ch. 282 and 283), toxicoses (drugs, anesthetic agents, chemicals or biotoxins; see ch. 286), neoplasia (see ch. 287), and metabolic disease (hepatic lipidosis in cats or copper storage disease in dogs, for example; see ch. 285).[12] Sampling of the hepatic parenchyma may be necessary for a definitive diagnosis but is not without risk due to coagulopathies. Prognosis is variable.

Extrahepatic Biliary Disease

Extrahepatic biliary disease includes biliary obstruction (secondary to pancreatitis or less commonly intraluminal obstruction) and biliary rupture (secondary to trauma, cholecystitis or gallbladder infarction; see ch. 53 and 288). Pets with traumatic biliary rupture usually develop signs progressively over a period of 5-7 days and have signs of peritonitis (see ch. 279). Diagnosis is made following the approach previously discussed, with emphasis on imaging and abdominal fluid analysis. Most of these pets benefit from surgery to identify and repair traumatized tissue. Survival rates are reported to be around 70% when a population of dogs with a variety of causes were included, but only 50% when dogs with bile peritonitis were evaluated. Septic bile peritonitis in dogs and cats carries a particularly poor prognosis.[23-26] Some extrahepatic biliary obstructions, such as with pancreatitis, are not usually treated surgically (see ch. 143).

Splenic and Liver Lobe Torsion

Dogs with splenic torsion have signs of acute progressive abdominal disease (see ch. 143 and 206). They may also have ventricular arrhythmias when first examined or during treatment. Large breed, deep chested dogs appear to be at increased risk. Other risk factors are possible.[27] After torsion, the spleen becomes quite prominent on physical examination and radiographs. Abdominal US findings of a hypoechoic pattern within the splenic parenchyma together with decreased venous blood flow is strong support for splenic torsion. Once the patient is stabilized, surgery is indicated to remove the spleen and to perform a gastropexy, if indicated, to reduce risk of subsequent gastric volvulus. Prognosis is good when appropriate resuscitation and management are combined with prompt diagnosis and surgery.

Liver lobe torsion occurs rarely in dogs and cats.[28] Clinical signs and laboratory data are non-specific. A distended abdomen or a palpable abdominal mass can sometimes be detected on physical examination. The diagnosis is confirmed at exploratory laparotomy. The affected liver lobe is resected either manually or with stapling equipment and submitted for histopathologic evaluation.

Hepatic and Splenic Abscesses

Hepatic and splenic abscesses are uncommon (see ch. 143). Clinical signs are typically non-specific.[29,30] On physical examination, patients are often febrile, and exhibit signs of pain and hepato- or splenomegaly on abdominal palpation. Blood test results often reveal leukocytosis, thrombocytopenia, hypoalbuminemia, and

increased liver enzyme activities. Radiography is often unrewarding. The diagnosis is often suspected on abdominal US and confirmed via fine needle aspiration and cytology of the abnormal area or of any abdominal fluid (see ch. 74, 89, and 93). Aerobic and anaerobic culture and sensitivity testing should be performed. The etiology of hepatic and splenic abscesses is debated and probably multifactorial. Hematogenous bacterial spread is one potential cause and possible reservoirs of bacterial infection such as the respiratory system, urinary tract and heart valves should be investigated; radiographic evidence of alveolar infiltrates consistent with pneumonia were found in nearly half the patients.[29] Treatment involves surgical resection of the abscessed liver lobe(s) or splenectomy, long-term antibiotic administration, and periodic US evaluations. US-assisted drainage and alcohol ablation of hepatic abscesses was employed successfully in five dogs and one cat.[31]

Splenic Infarction

Splenic infarction has been rarely diagnosed in dogs. This condition is often associated with altered blood flow and/or coagulopathies, secondary to other diseases. Identification and treatment of the underlying disease(s) is vital for a successful outcome.[32] Splenectomy may be performed but is reserved for those patients with life-threatening complications such as hemoabdomen or sepsis.

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CHAPTER 146

Reproductive Emergencies

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Reproductive Emergencies in Females

Pyometra

Pathophysiology

Pyometra is a severe uterine infection in female dogs and cats currently or recently under the influence of progesterone, i.e., dogs and cats most commonly develop this condition during diestrus.[1,2] Progesterone places female dogs and cats at risk for excessive intrauterine secretions, bacterial growth, inflammation and overwhelming infection. This process, in turn, causes accumulation of purulent exudate within the uterine lumen. About 80% of dogs and cats with pyometra have *Escherichia coli* isolated from uterine content. Most *E. coli* isolates and sensitivity patterns from uterine content are identical to isolates found in urine or blood.[3] Release of bacterial endotoxins, alone, could explain the severe illness, dehydration, and decompensated septic shock that may precede death in dogs with untreated pyometra[3,4] (see ch. 316 for a full discussion).

Clinical Signs and Diagnosis

The severity of clinical signs is related to bacterial endotoxins, on whether the cervix is "open" sufficiently to allow drainage of the purulent uterine content ("open-cervix pyometra"), and how quickly an owner seeks veterinary care after seeing a vaginal discharge or realizing the pet is ill.[4-7] Pets with closed-cervix pyometra do not have the purulent vaginal discharge to alert owners of a problem. Retention of purulent uterine content (an internal abscess) explains the generally more severe clinical signs in pets with closed-cervix pyometra. They may require rapid intervention to prevent overwhelming septic shock and death (see ch. 132).[3,4]

Clinical signs of pyometra include anorexia, lethargy, obtundation, vomiting, polyuria and polydipsia with or without vaginal discharge. Most pets are seen 4-8 weeks after their most recent estrus. Dogs and cats may be brought to the veterinarian on an emergency basis simply because the owner notices a vaginal discharge. A minority of dogs with open cervix pyometra and most with closed cervix pyometra will be seen on emergency basis due to signs of systemic illness. Diagnosis is based on observation of a purulent vaginal discharge (Figure 146-1), palpation of an enlarged uterus, and/or visualization of an enlarged and fluid-filled uterus with imaging (Figure 146-2) in a female who was recently in estrus.[5,8] It is important to be certain the female is not in early-to-mid pregnancy with concurrent vaginitis. This distinction is best accomplished with abdominal ultrasonography (see ch. 88). Review of the complete blood count (CBC), serum biochemical profile and urinalysis can be extremely important for identification of abnormalities associated with pyometra that need attention: renal parameters, serum electrolyte concentrations, acid-base status, blood glucose, or any other issue that may require attention in a critically ill animal (see ch. 316).

FIGURE 146-1 Purulent vaginal discharge can be seen on the hair below the vulva of a bitch with pyometra.

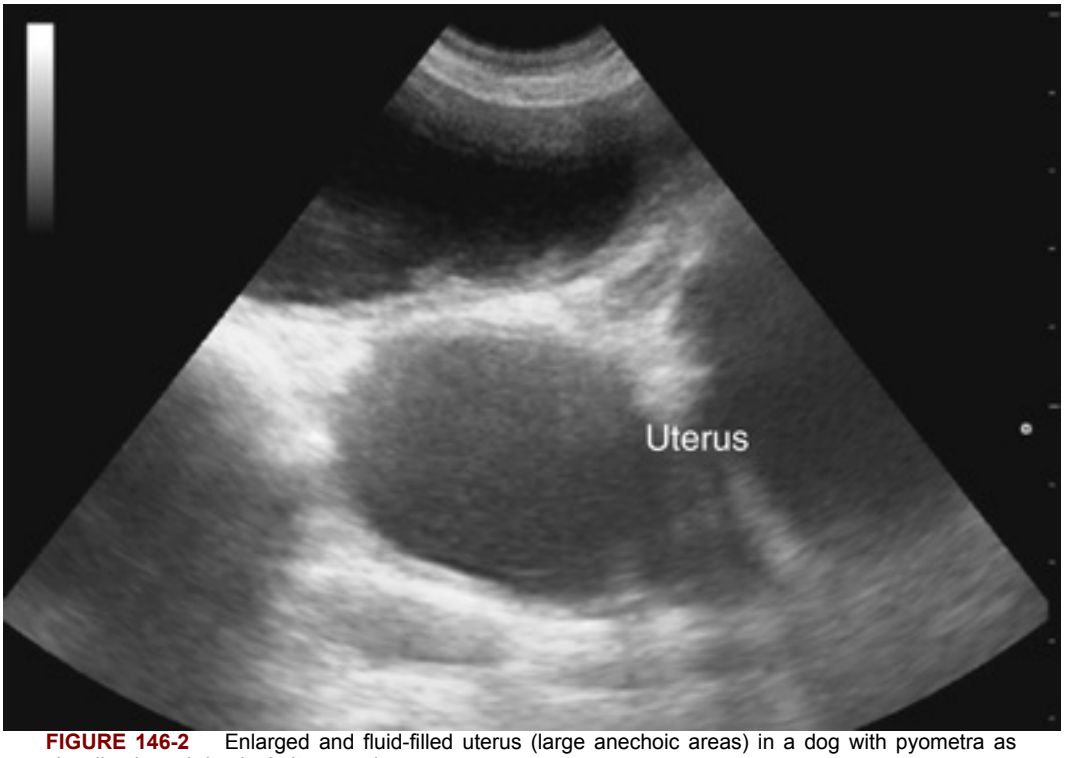

FIGURE 146-2 Enlarged and fluid-filled uterus (large anechoic areas) in a dog with pyometra as visualized on abdominal ultrasound.

Management

Overview

Ovariohysterectomy is considered the only treatment option for seriously ill dogs and cats with pyometra.[4,9] Medical management of pyometra is contraindicated in systemically ill pets[2] (see ch. 316). Surgical removal of the infected uterus results in rapid elimination of bacteria, their endotoxins, and prevents recurrence.[6,10]

Anesthesia and Surgery (Figure 146-3 and Video 146-1)

Anesthesia should be delayed until treatment for hypotension, shock, dehydration, and other serious concerns have been initiated (see ch. 127, 129, 132, and 159). Determining the safest time to begin anesthesia and then surgery may not be obvious. Dire consequences can follow if anesthesia begins before the patient is stable or if one waits too long. Epidural anesthesia is recommended because less general anesthesia will be required for an extremely ill animal. Combining 0.5% ropivacaine with 0.1 mg/kg of morphine is recommended.[11] Ropivacaine is dosed accurately using the formula of 0.1 mL/cm of occipito-coccygeal length (back of the head to the base of the tail).[11,12] Pre-oxygenation is often beneficial. Depending on estimated severity of obtundation, one may consider using fentanyl (3-5 mcg/kg q 20 min) and acepromazine (0.01-0.02 mg/kg) for pre-medication. If the patient is severely depressed, propofol can be used for induction without pre-medication. Anesthesia is typically maintained with isoflurane or sevoflurane, depending on patient stability.[12,13]

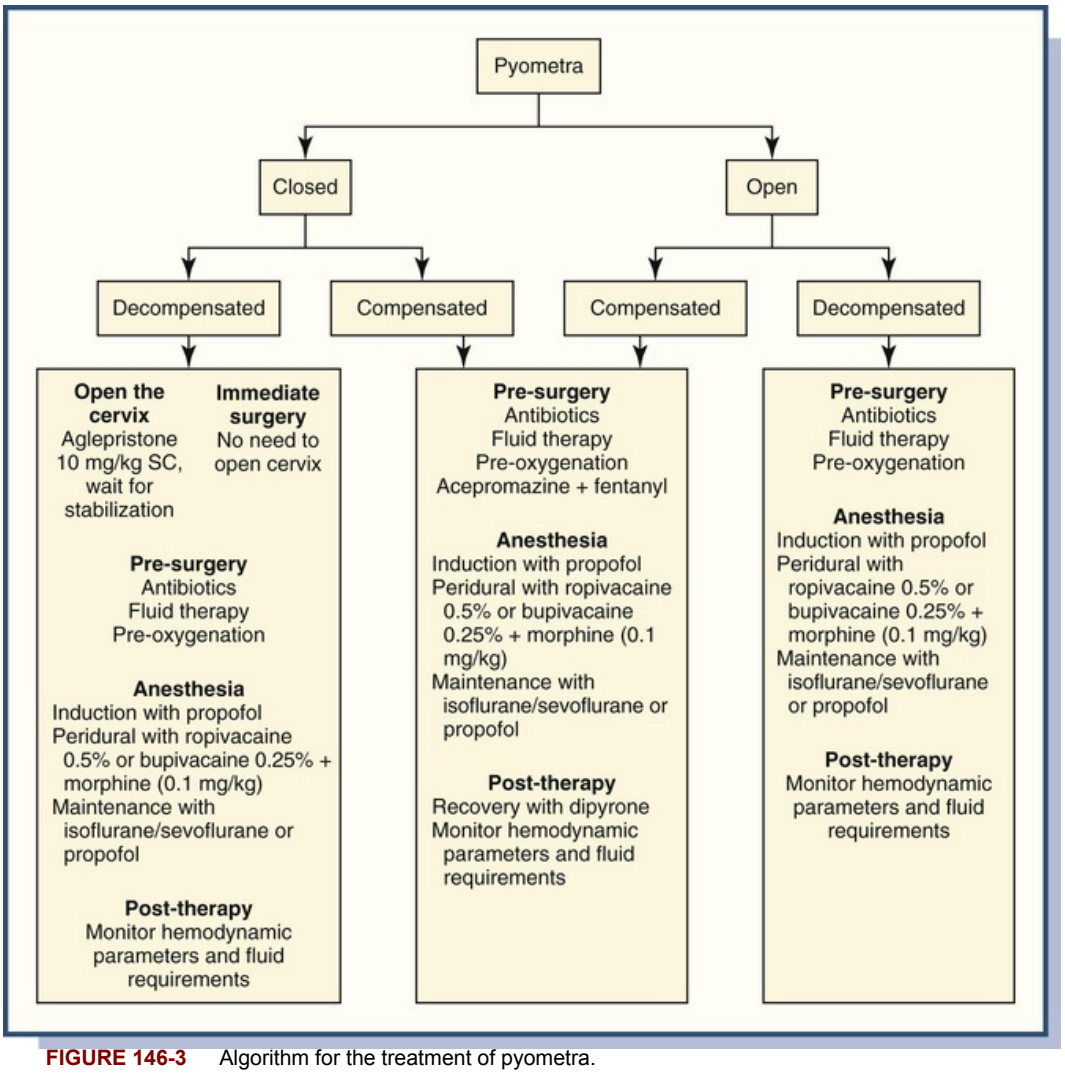

FIGURE 146-3 Algorithm for the treatment of pyometra.

Medical Management

Alterations due to toxemia should be treated as soon as recognized, never forgetting that the infected uterus

must be removed as soon as possible.[5,9,14] White blood cell (WBC) counts can be quite increased in pets with pyometra, but this is an unreliable test that does not necessarily correlate with severity of illness. Normocytic, normochromic, nonregenerative anemia is seen occasionally.[2,5,9] Pets with pyometra may be severely azotemic, uremic, acidotic, and hyper- or hypocalcemic. Serum sodium and potassium concentrations are unpredictable but abnormalities should be addressed. Hypoglycemia, the result of anorexia, vomiting, diarrhea, bacteremia, toxemia, and/or leukocytosis, should be corrected (see ch. 61). However, some pets with pyometra are hyperglycemic. Increases in serum hepatic enzyme activities are common. All these issues underscore the need to identify and treat the many unpredictable problems seen in pets with pyometra.[8] Broad-spectrum antibiotics should be given, IV, prior to surgery. Recommended antibiotics include trimethoprim-sulfonamides, ampicillin, amoxicillin/clavulanic-acid, cephalosporins, enrofloxacin, marbofloxacin and metronidazole.[15,16]

Dystocia

Practical Descriptions

Dystocia is defined as the inability to deliver a fetus through the birth canal[17,18] (Table 146-1).

TABLE 146-1

Causes of Maternal and Fetal Dystocia

MATERNAL ORIGIN	DIAGNOSIS	TREATMENT
Primary uterine inertia	Absent or weak and unproductive contractions	Oxytocin and calcium, usually ineffective. C-section recommended
Narrow birth canal	Radiograph	C-section
Uterine torsion	Ultrasound: not easy to diagnose	C-section
Secondary uterine inertia	Absent or weak and unproductive contractions	Oxytocin and calcium. If after three trials there is no success, C-section recommended
FETAL ORIGIN	**DIAGNOSIS**	**TREATMENT**
Increased fetal size	Radiograph	C-section
Fetal death	Ultrasound	Surgery
Abnormal presentation Abnormal posture	Radiograph	Obstetric manipulation or C-section

C-section, Cesarean section.

The Uterus

Uterine causes of dystocia include uterine weakness or insufficient uterine force to propel the *conceptus* through the birth canal.[19-21] This is the form of dystocia most likely to respond to medical management with oxytocin.

The Pelvis

If the birth canal is too small to allow passage of the *conceptus*, dystocia results. Such a constriction may be a congenitally small pelvic canal size or an acquired defect, such as the sequela to a pelvic fracture. Dystocia may also occur with various breeds that have relatively large heads and shoulders but a small pelvis (Bulldogs, Boston Terriers, etc.). These forms of dystocia require surgical intervention.[21,22]

The Fetus

Occasionally the fetus is too large for the birth canal. The most common explanation for fetal oversize is a single fetus, potentially resulting in a fetus that is too large for the pelvic canal[19,20,23] (see ch. 315). Abnormal

fetal presentation to the pelvic canal causes "relative" oversize. These problems usually require surgical intervention.

Vaginal Vault

A bitch may be examined and found to have a neonate in the vaginal vault. This may be caused by fetal oversize or an undersized pelvis. The vaginal vault itself may be too small, as occurs with a vaginal stricture (see ch. 319). The vaginal band of tissue obstructs fetal passage. This form of dystocia resolves if the stricture can be broken down or incised. Alternatively, cesarean section may be necessary. Vaginal strictures may interfere with natural breeding but may not prevent artificial insemination.

Criteria for Suspecting Dystocia

Diagnosis of dystocia is usually based on owner observation. Those observations also represent the reasons for emergency presentation. Dystocia is considered likely and immediate veterinary consultation or examination is recommended whenever an owner reports one or more of the following in a pregnant dog: (1) 20 to 30 minutes of strong abdominal contractions without successful delivery; (2) after delivering one or more neonates, more than 4 to 6 hours pass without another delivery in a female known or suspected of having additional fetuses; (3) a bitch fails to deliver pups 24 to 36 hours after the rectal temperature was noted to decrease below 99-100° F (≈37° C); (4) a bitch cries and licks or bites at the vulvar area during whelping; (5) a bitch fails to progress to stage II labor after 8 to 12 hours of apparent stage I labor; or (6) a bitch has prolonged gestation, lasting beyond a well-established due date, beyond 70 to 72 days from the first breeding, or beyond 59 days from the first day of diestrus[24] (see ch. 312 and 315).

It is extremely important to remember that "false pregnancy" has been noted to include signs of parturition and a concern of dystocia in a few dogs. It is also possible for an owner to believe that fetuses are present *in utero* when, in reality, an entire litter has been successfully delivered. Thus, one must confirm pregnancy before considering intervention.

History

Ideally, the first step in any emergency is to obtain a thorough history from the care giver (see ch. 1). However, examination of the vaginal area should take precedence to determine whether a fetus is present within the vaginal canal. If no fetus is detected, knowing the patient's age, reproductive history, and previous or current medical conditions may be pivotal. Age, for example, is important because the 2-year-old bitch is less prone to primary uterine inertia than is a 6- or 7-year-old. Heart problems, regardless of age, may worsen during labor. In most cases of suspected dystocia, there is time for obtaining a thorough history, leaving questions regarding this current pregnancy to the end. At that time, one should ascertain if there is an "expected date of whelping" and how this was determined. For example, whelping dates can be rather precisely determined from vaginal cytology, vaginoscopy, or serial serum progesterone concentrations prior to and following breeding (see ch. 312 and 315). Has pregnancy been confirmed? Are the fetuses alive? If yes, when and how was this determined?

Physical Examination

If no fetus is visible or palpated in the vaginal canal, a quick but thorough physical examination should be completed to be certain that contributing problems (e.g., cardiac arrhythmias, dehydration, fever) are not missed (see ch. 2). Sometimes, a concurrent problem is of greater concern. Occasionally, correction of an underlying problem such as hypoglycemia or hypocalcemia simultaneously treats the dystocia. If a bitch is nervous or trembling, the veterinarian must differentiate anxiety, pain, and hypocalcemia (see ch. 298).

The reproductive examination should include careful abdominal palpation, as well as digital examination and assessment of the vaginal vault. If no fetuses are identified *in utero* or in the vaginal vault, the bitch may have completed whelping or she could be in exaggerated clinical pseudopregnancy. The vaginal vault can also be assessed for the presence of strictures, bands, or other defects. One can attempt to determine the presence and strength of uterine contractions by gently stroking the dorsal vaginal wall (Ferguson reflex). Ideally, direct uterine monitoring is used. While less ideal, one can periodically assess the litter via traditional abdominal ultrasonography. One may benefit from knowing the number of fetuses, and their size, position and posture. Pelvic canal anatomy, depth, and width can be estimated with abdominal radiographs. Assessment of fetal viability is critically important and can best be accomplished with a fetal monitor. Fetal heart rates less than 180 bpm, in two measurements less than 10 minutes apart, are evidence of fetal distress potentially due to hypoxia, and this is an indicator for urgent intervention.[20] Fetal heart rate below 130 bpm

are associated with poor survival rate and quick delivery is imperative (Figure 146-4).[17,20]

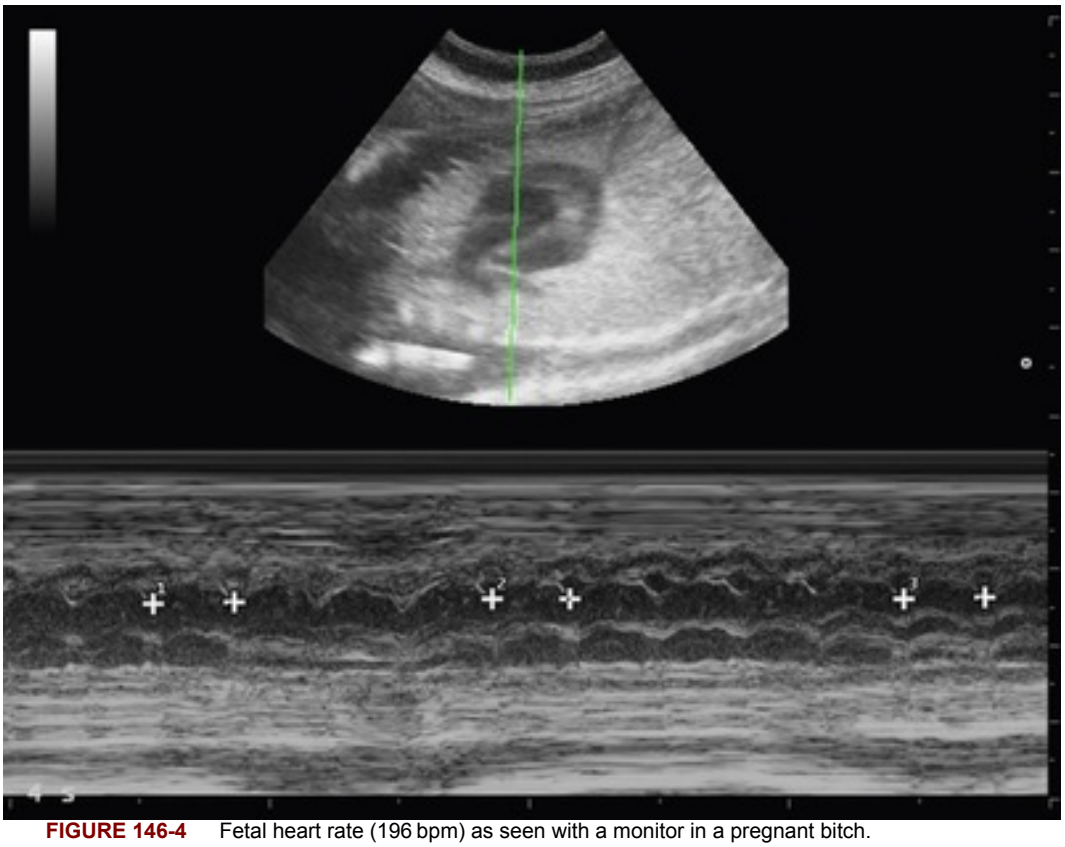

FIGURE 146-4 Fetal heart rate (196 bpm) as seen with a monitor in a pregnant bitch.

The finding of significant amounts of fresh blood in the vaginal vault can be confusing. The presence of blood may be caused by normal events during whelping, but can also be caused by separation of placental sites, a condition that may be best managed with cesarean section. Other causes of hemorrhage (bleeding disorders, trauma to the vaginal lining, etc.) must always be considered.

Fetus Palpated in the Vaginal Vault

If a fetus is palpated in the vaginal vault, its physical position and viability must be assessed. Digital manipulation and delivery should be attempted. First, one may try to deposit lubricant, using a soft urinary catheter, cranial to the fetus. Then, an attempt can be made at delivery via gentle traction using the limbs, head or mandible of the fetus. Traction is in a caudoventral arc while rotating the fetus's shoulders or pelvis through a dorsoventral plane to help passage through the pelvis.

Uterine and Fetal Monitors

The use of uterine and fetal monitors allows veterinarians to detect the onset of labor and to manage labor with greater accuracy. Such systems for monitoring labor and delivery in the bitch are available.[25-27] The uterine monitoring system consists of a tocodynamometer (sensor) that detects changes in intrauterine and intra-amniotic pressures. The sensor is maintained over the caudolateral abdomen with an elasticized strap. Fetal Doppler cardiac monitoring is performed with a hand-held unit on bitches in lateral recumbency. Directing the Doppler perpendicularly over a fetus causes amplification of fetal heart sounds, distinct from maternal arterial or cardiac sounds.

The canine uterus exhibits characteristic patterns of activity during late gestation and labor, varying in strength and frequency. Owners using such systems may note a concern resulting in their bringing the bitch into the hospital. Such systems are valuable in a hospital (see ch. 315). The two drugs most commonly recommended to treat uterine inertia are calcium and oxytocin. Administration of calcium gluconate increases strength of myometrial contractions. Administration of oxytocin increases the frequency, strength and

duration of contractions. Calcium is recommended when ineffective and weak uterine contractions are detected. Oxytocin is recommended when uterine contractions are less frequent or weaker than expected for the stage of labor and when fetal heart rates are normal. Uterine hyperstimulation with elevated baseline levels of contractility compromising placental blood supply or a uterine obstructive pattern negate use of calcium or oxytocin. Fetal distress is reflected by sustained deceleration of heart rates. Transient accelerations are noted with fetal movement. If fetal stress is evident and response to medication is poor, surgical intervention (cesarean section) may be indicated.

Laboratory Assessments

Timing of veterinary intervention in dystocia patients is important. Premature intervention causes stress, may delay onset of normal parturition, and could place both mother and fetuses at risk.[18,21] Whenever there is uncertainty about gestation length or whether parturition has begun, the serum progesterone (P_4) concentration should be determined. A P_4 concentration below 1-2 ng/mL is required for parturition. A result >2 ng/mL indicates that labor (contractions) have not likely begun.[28] To avoid premature uterine stimulation of parturition or cesarean section, the serum progesterone concentration should be <1 ng/mL. All pets with known dystocia should have blood obtained for a CBC and complete serum biochemical profile. Some results may specifically explain uterine inertia, e.g., decreases in serum calcium, potassium or glucose concentration. Hematocrit decreases progressively throughout gestation due to increases in plasma volume. Values as low as 30% are considered "normal" in the bitch and results as low as 20-25% are "normal" in queens. Results that are significantly lower should be investigated.

Imaging

One of the most valuable tests that a veterinarian can perform on a pet with possible dystocia is abdominal imaging (see Table 146-1). Radiographs can identify or refute the presence of pregnancy. Radiographs are also excellent for locating fetuses and for identifying a malpositioned fetus that is unlikely to be delivered vaginally. Ultrasonography is superb for assessing fetal viability (see ch. 88 and 143). The first condition established by the radiographs is the presence or absence of pregnancy. The non-pregnant bitch either has completed whelping or is pseudopregnant. If pregnancy is confirmed, the veterinarian must ask the following: Are the fetuses viable? How many are present? Where are they? Abdominal auscultation may answer the question of fetal viability if heart beats are heard, but not if heart beats cannot be auscultated. Fetal death is likely if the veterinarian finds on radiographs (1) evidence of collapse of the spinal column, (2) intrafetal gas patterns, (3) overlapping or misalignment of the bones that make up the skull, or (4) fetal positioning not compatible with life. Ultrasonography definitively identifies contracting fetal hearts and is therefore a means of assessing viability if specific fetal monitors are not available. If medical management is being considered without a fetal monitor, ultrasonography should be frequently repeated.

Medical Therapy

Medical treatment should be considered only if there is no evidence of an obstruction.[18,21,29] Parenteral oxytocin, with or without calcium, is commonly employed. Recommended dosages of oxytocin include 0.25-2 IU/dog IM or IV.[22,30] Such dosages increase both strength and duration of uterine contractions.[21,30] Higher dosages are not beneficial and can be detrimental by causing uncoordinated uterine contractions. Doses of oxytocin IM or IV may be repeated two or three times at 30-minute intervals or after each successful birth.

Some bitches who do not respond initially to oxytocin may respond if 10% calcium gluconate is given slowly IV (1 mL/min at 20-40 mg/kg) before or concurrent with any subsequent dose of oxytocin, even if serum calcium concentrations are within reference limits. Calcium solutions should be administered either undiluted or diluted with isotonic fluids. Calcium chloride should not be used. Continuous electrocardiographic monitoring is recommended and calcium discontinued if bradycardia or arrhythmias are detected (see ch. 298). If no fetus is delivered after three doses of oxytocin (± calcium and/or glucose), cesarean section is recommended.

If labor begins and a fetus is delivered after oxytocin, one should wait approximately 30-45 minutes to determine if another dose is indicated for a subsequent neonate. Sometimes a single dose of oxytocin may be sufficient to start parturition, which continues without the need for additional doses. Sometimes one fetus is delivered after each dose. Each additional dose of oxytocin may elicit a weaker response. It is imperative to know, prior to beginning oxytocin, whether or not the mother is pregnant and, if so, the number of fetuses yet to be delivered. Supportive treatment with IV isotonic fluids should be given to maintain or restore

hydration. Dextrose can be administered as a 2.5-5% solution if hypoglycemia is confirmed or suspected. If the female is clinically hypoglycemic, a 0.25 g/kg body weight (BW) bolus can be given.[30]

Anesthesia and Cesarean Section (*Figure 146-5*; Video 146-2)

Epidural anesthesia is recommended for C-section, whenever possible. The aim is to avoid using drugs that can cross the placental-blood barrier and depress or otherwise harm the neonates. After pre-oxygenation, the patient is induced with propofol, allowing the peridural technique to be performed.[31] Lidocaine 2% is recommended as it promotes quick recovery of both proprioception and sensation. This protocol does not interfere with the normal maternal instincts of the bitch towards her new puppies. The dosage of lidocaine is 0.1 mL for each centimeter of occipito-coccygeal length.[12] Anesthesia should be maintained with oxygen and propofol. After all neonates have been delivered, anesthesia can be maintained with isoflurane.[32] C-section anesthesia, surgery and neonatal resuscitation are demonstrated in Video 146-2.

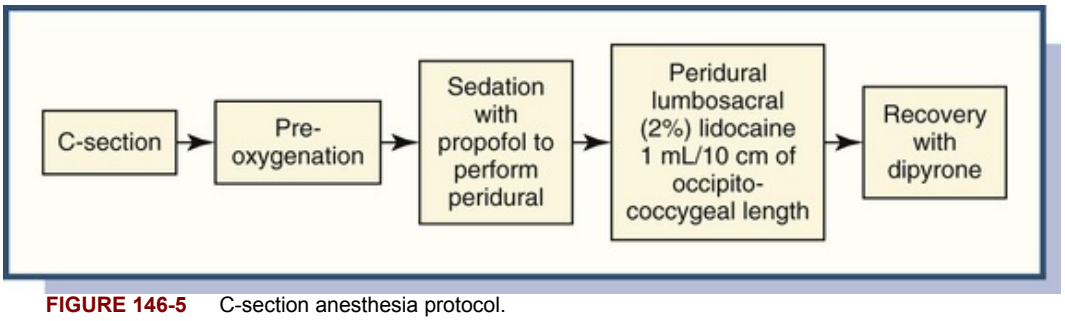

FIGURE 146-5 C-section anesthesia protocol.

Uterine Torsion and Uterine Rupture

Both conditions obstruct the birth canal and are life-threatening conditions. Either can occur late in pregnancy, at the time of parturition, or with pyometra.[23] Some dogs may be suspected of having dystocia. Uterine rupture is a potential side-effect of administering ecbolic drugs such as PGF_2alpha to a patient with closed-cervix pyometra or during labor. Such drugs are dangerous if high doses are used or if the patient is obstructed. In addition to signs typical of dystocia, clinical signs may include abdominal pain, shock, hypothermia, hemorrhagic vaginal discharge, vomiting, and restlessness (see ch. 143). Ultrasonography could show presence of a fluid-filled uterus, fetal stress or death and peritoneal effusion.[20] Exploratory surgery is usually required for definitive diagnosis and treatment.[20] Taking into account the gravity of both situations, quick diagnosis and treatment are essential for survival.[23]

Vaginal Hyperplasia/Vaginal Prolapse

Background and Clinical Features

The vaginal wall of healthy bitches thickens in response to estrogen during proestrus and estrus. An exaggerated response to normal estrogen stimulation may result in a condition frequently called vaginal hyperplasia or vaginal hypertrophy. Such prolapsed vaginal membranes are histologically described as markedly edematous tissue. Protrusion of edematous vaginal tissue through the opening of the vulva will prompt owners to seek veterinary care. Some of these dogs develop urinary obstruction and may be brought to the veterinarian with owner concerns of difficulty or straining to urinate. Vaginal hyperplasia/prolapse is usually seen in younger (<2 to 3 years of age) large-breed bitches in proestrus or estrus. Uncommonly, this condition has been seen in smaller and older dogs. Other owner concerns may include inability or unwillingness to breed or that the male appears unable to penetrate the bitch. Most bitches with vaginal prolapse persistently lick the tissue, but only a small percentage of these have stranguria.

Diagnosis

The diagnosis is straightforward because of the obvious mass protruding from the vulva or a bulging perineum in a young bitch in proestrus or estrus (Figure 146-6). One differential diagnosis for the mass is

clitoral enlargement, usually due to presence of a bone within the clitoris that is a palpably hard, thin, and tubular structure. Benign polyp or a tumor are additional causes for a protruding mass. Polyps are usually small and have a narrow pedicle or base. Tumors are typically irregular in shape, occur in older females, and are not associated with the proestrus or estrus phases of the ovarian cycle. The exception to this rule is transmissible venereal tumor, which most often is identified in bitches that are young and sexually active (see ch. 351).

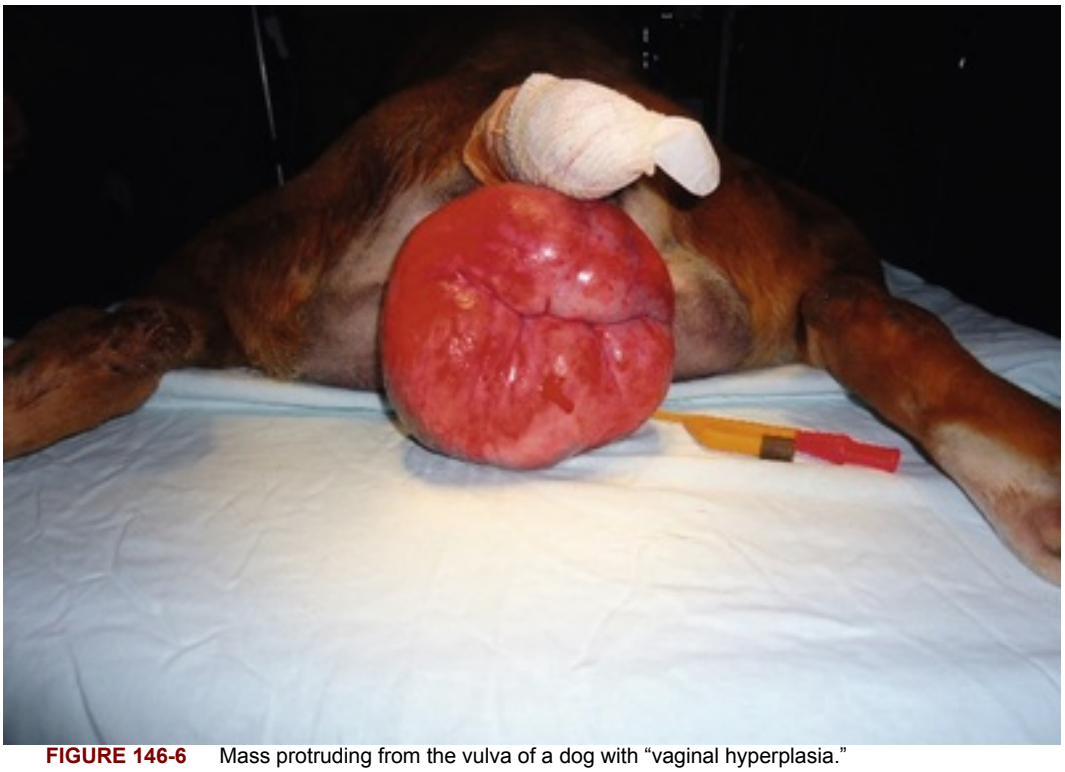

FIGURE 146-6 Mass protruding from the vulva of a dog with "vaginal hyperplasia."

Vaginal prolapsed tissue is usually relatively large and soft, often reducible. The tissue is in the form of a smooth, rounded mass with folds rising in a wide base from the floor of the vaginal vault. The tissue usually arises cranial to the urethral opening. Less commonly, the vaginal prolapse is more severe and may include the entire circumference of the vaginal wall, in which case the tissue takes on the appearance of a large doughnut (Figure 146-6).

Treatment

Management of vaginal hyperplasia can be difficult. If the bitch can urinate despite the presence of the mass and no necrosis is present, hyperplasia is much less of an emergency. If urination is not possible, an indwelling urethral catheter (see ch. 105 and 106) needs to be placed following identification of the urethral papilla (note the foley catheter in the dog with vaginal hyperplasia in Figure 146-6). Virtually all vaginal prolapses shrink and disappear during diestrus, given enough time. Therefore, initial efforts are directed at keeping the tissue (1) clean with saline washes, (2) lubricated with appropriate jellies, and (3) non-traumatized. One can prevent trauma to exposed vaginal tissue by keeping the bitch indoors on smooth and padded surfaces and by placing an Elizabethan collar around the neck of the bitch to prevent her from causing any self-mutilation. Necrotic tissue requires surgical debridement. Some eversions can be surgically reduced. Decisions regarding ovariohysterectomy should not be made on an emergency basis.

Surgical extirpation of the excess vaginal tissue should be considered only if the vaginal prolapse is associated with an inability to urinate, if it is large and likely to become infected, or if it has recurred in more than one cycle. Surgery can be associated with a great deal of blood loss, can be complicated, and is recommended only if the vaginal tissue is extremely necrotic, if the bitch is unable to urinate, or if compromise of the vascular supply to that tissue, the uterus, or the bladder is suspected.

Hypocalcemia (Eclampsia)

Hypocalcemia is an acute, life-threatening condition that occurs most commonly in small to medium-sized bitches nursing large litters during the first 3 weeks of lactation (see ch. 315).[8,33,34] Eclampsia less often affects queens nursing large litters before weaning and, occasionally, bitches during late gestation. Clinical signs of eclampsia include nervousness, acting anxious, rubbing the muzzle with the paws or the floor, biting at their paws, acting aggressive or any obvious change in behavior, crying as if in pain, panting, hypersalivation, tremors and stiffness (see ch. 298, Video 298-1). Signs may progress to severe hyperthermia, generalized tetany, seizures and death.[8,33] Ionized calcium, the free and biologically active form, is usually <0.6 mmol/L in eclampsia cases. Besides the determination of calcium, a glucose measurement is necessary because signs could be quite similar and both problems could happen concurrently.[33,35,36] Treatment is administration of 10% calcium gluconate (2-20 mL) to effect.[8,34,35] Cardiac auscultation or electrocardiography should be used to identify bradycardia or arrhythmias. If either occurs, calcium administration must stop.[8,34,37] Body temperature should be closely monitored because the hyperthermic dog in tetany may develop hypothermia once calcium has been given and tetany has ceased (see ch. 134).[8,37] The litter should be removed from the mother for 24 hours and fed by bottle. Nursing should be discontinued if hypocalcemia recurs.[8] Calcium supplementation during the remaining period of lactation is recommended (calcium carbonate 100 mg/kg/day).[8]

Reproductive Emergencies in Males

Paraphimosis

Overview

Paraphimosis is the inability to retract the penis into the preputial cavity.[38,39] It is considered a reproductive emergency not due to the severe pain caused by inflammation and tissue swelling, but because it can lead to blood stasis, thrombosis of the corpus spongiosum and necrosis.[8,38,40] Untreated dogs often become severely ill.[38,41] Paraphimosis can be congenital or acquired. Among the conditions encountered are narrow preputial opening, short foreskin, persistent frenulum, preputial constriction secondary to hair entanglement, inability of the preputial muscles to retract the penis, and hypospadias.[40,41] This condition is most commonly seen in young intact males. Transient paraphimosis may follow breeding or masturbation. Treatment is straightforward if no serious tissue trauma is present.[42,43] The primary differential diagnoses are hematoma (vascular thrombosis), chronic urethritis, foreign body, paralysis of the retractor muscle of the penis, penile fracture, chronic priapism (Figure 146-7) and abnormal preputial opening.[39,43,44]

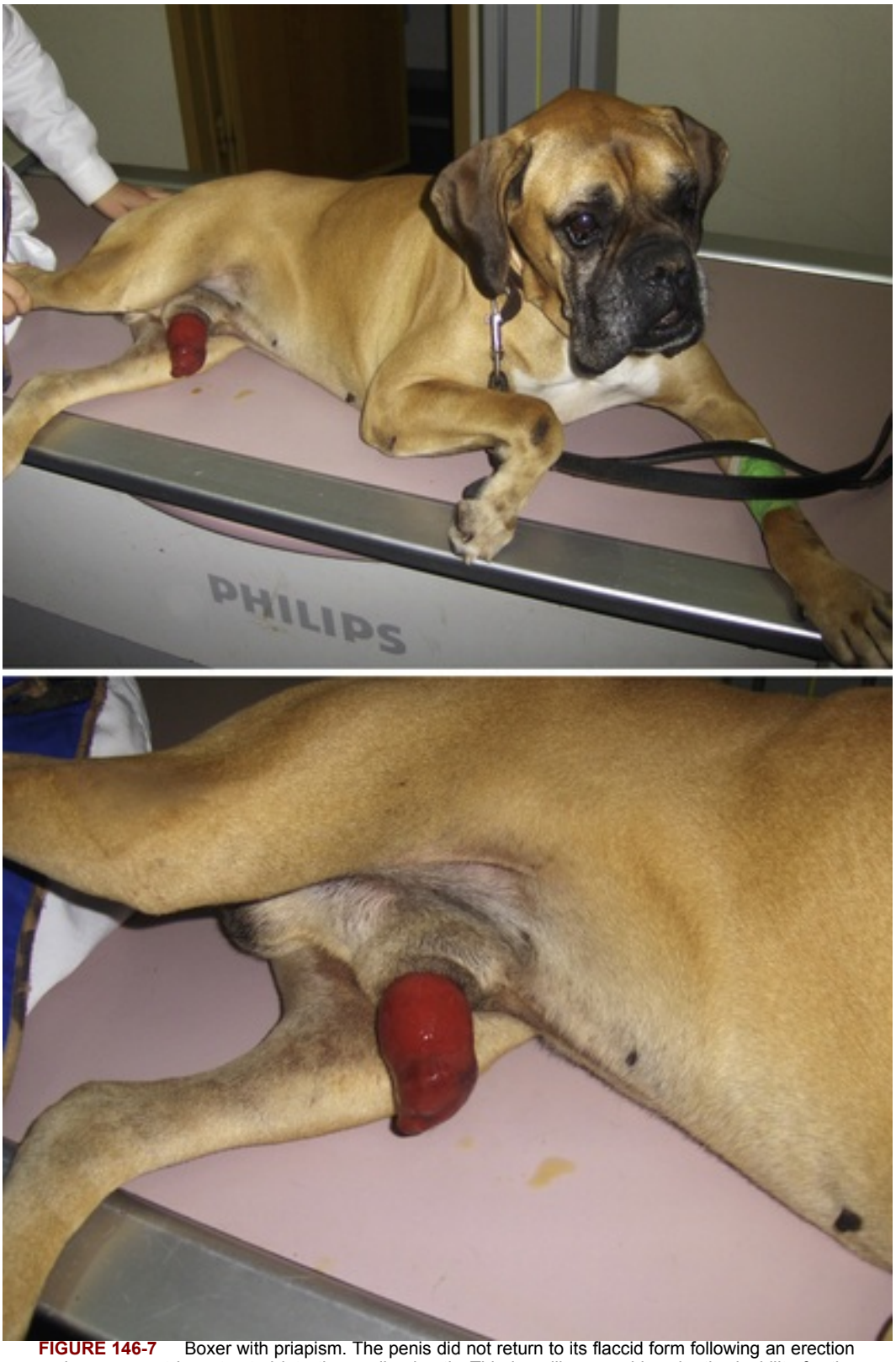

FIGURE 146-7 Boxer with priapism. The penis did not return to its flaccid form following an erection and now cannot be retracted into the penile sheath. This is unlike paraphimosis, the inability for the sheath of the penis to cover the glans penis.

Treatment

The initial approach consists of cleansing the area with a cool saline solution to remove any foreign material.

This can be followed by applying adequate lubricant to all exposed tissue in an effort to ease retraction. One may also use hyperosmotic solutions (50% glucose) or ice packs to reduce inflammation and ease retraction. If the penis is successfully covered by the prepuce, a "purse-string" or "tobacco pouch" suture pattern can be employed, but only for less than a day or two. One may need to catheterize the bladder if stranguria is seen.[40,43,44]

Testicular Torsion

Testicular torsion causes ischemia and necrosis, leading to pain, systemic signs, shock and death.[42,45,46] This condition most commonly involves the retained neoplastic testicle in a cryptorchid male, probably due to the space for torsion to occur within the abdomen.[8] When the testicles are located in the scrotum, the vaginal tunic restricts movement. Therefore, this condition is rare in animals whose testicles are normally positioned.[8,45] Clinical signs are nonspecific and include abdominal pain, "walking on eggshells," abdominal splinting, and lethargy.[42,46]

The diagnosis is based on the physical examination finding of a severely painful abdomen, painful abdominal mass, or simply palpating a mass. These are typically located ventral to the kidney. Abdominal ultrasonography can be quite helpful. However, if hypoechoic and globe-shaped masses are visible within the scrotum, fine needle aspiration and cytology is recommended.[8,42,46] Prognosis depends on the duration of the condition prior to diagnosis. Treatment is removing the abnormal testicle without releasing the torsion.[42,46]

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CHAPTER 147

Global Approach to the Trauma Patient

Kenneth J. Drobatz

Trauma is defined as a "wound or injury" caused by an "accident." Severity of injury secondary to any trauma can range from undetectable to fatal. Trauma may affect only one organ system or multiple organ systems, either directly or indirectly. Therefore, a global and thorough approach is required to improve survival and decrease morbidity in traumatized dogs and cats. The initial approach to a critically ill traumatized pet often makes the difference in the eventual outcome. The veterinary staff should be well versed in the evaluation and therapy of a traumatized dog or cat. Initial trauma assessment includes evaluation of tissue oxygen delivery (respiratory and cardiovascular systems), the central nervous system, and the urinary system. This primary survey should be followed by complete examination of all other systems.

Primary Survey

The first goal with a critically injured trauma patient is to optimize oxygen delivery to the tissues. This has been demonstrated to improve outcome in human patients and has been demonstrated recently in dogs with sepsis secondary to pyometra. All initial assessments and therapeutics are oriented toward this goal. Emphasis on early detection and aggressive reversal of impaired tissue perfusion or oxygen delivery improves survival and minimizes multiorgan dysfunction. Oxygen delivery depends on the blood oxygen content and tissue perfusion (Figure 147-1).

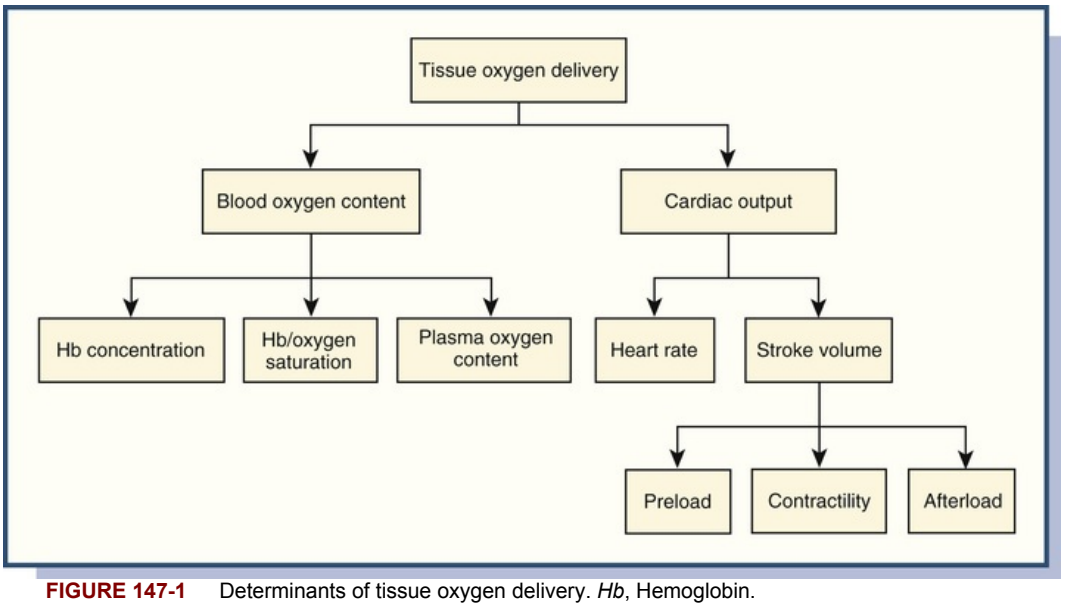

FIGURE 147-1 Determinants of tissue oxygen delivery. *Hb*, Hemoglobin.

Blood Oxygen Content

Maintaining oxygen saturation of hemoglobin through assessment and treatment of respiratory abnormalities is one of the first goals of the critical care team in maintaining oxygen delivery. Pale, cyanotic, or gray mucous membranes; signs of respiratory distress, such as increased respiratory rate and effort, extended head and

neck, open-mouth breathing; loud upper airway sounds and abnormal or diminished breath sounds on auscultation are all potential indicators of inadequate oxygen saturation of hemoglobin. More objective assessments of the oxygenation of blood include pulse oximetry (see ch. 98) and arterial blood gas analysis (see ch. 75 and 128). Thoracic focused assessment with sonography for trauma (TFAST) has been demonstrated to localize or identify pulmonary problems in dogs experiencing trauma (see ch. 149). Supplemental oxygen should be provided to any critically ill traumatized animal until it is proved that oxygen supplementation is not necessary (see ch. 131).

A variety of conditions associated with trauma can result in respiratory distress and decreased oxygenation of hemoglobin (Figure 147-2; also see ch. 28 and 149), but the most common are pneumothorax and pulmonary contusions. In animals suspected of having pleural space disease (decreased lung sounds with signs of respiratory distress), thoracocentesis should be performed even before thoracic radiographs are taken (see ch. 102). If done correctly, benefit far outweighs risk. Tension pneumothorax is rare but represents an acute, life-threatening pleural space abnormality. It is characterized by extreme respiratory distress, poor tissue perfusion and, rarely, a "barrel chest" appearance. Rapid thoracocentesis is immediately indicated. A small incision in the intercostal space may release the air more quickly in animals in which death or collapse is imminent.

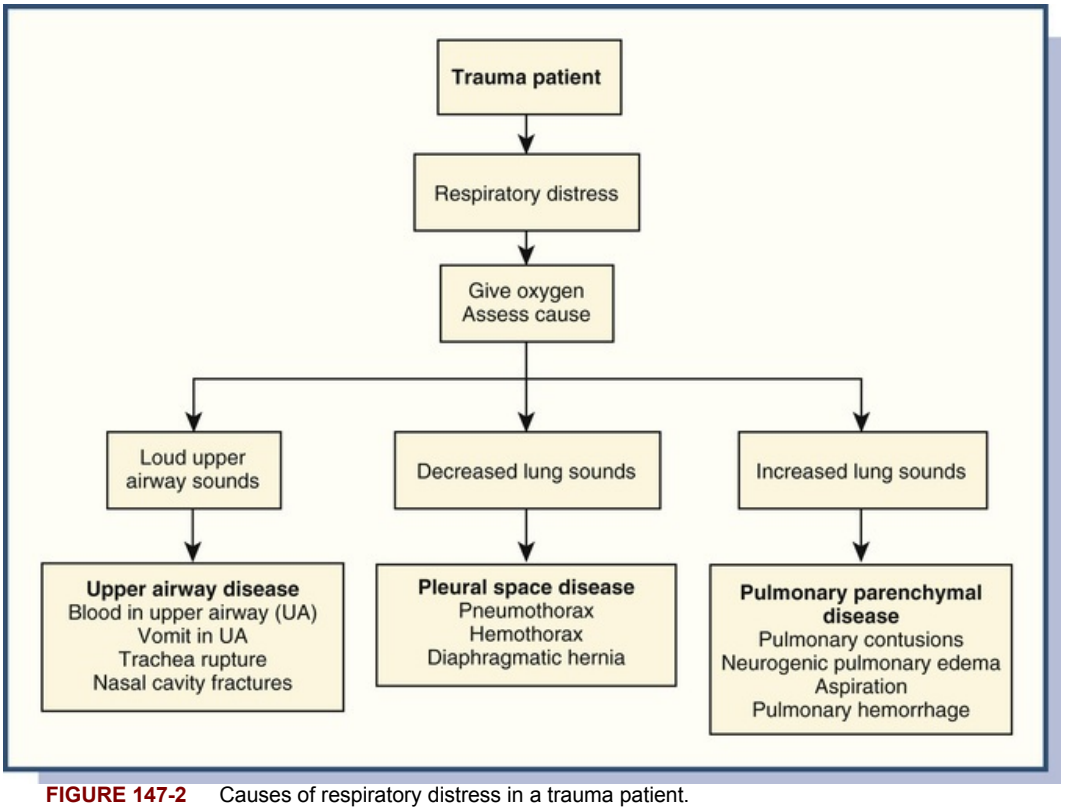

FIGURE 147-2 Causes of respiratory distress in a trauma patient.

Increased bronchovesicular sounds in a traumatized animal are commonly a result of pulmonary contusions (see ch. 242). Pulmonary contusions often worsen before they improve. Intravenous fluid therapy for other conditions should be given with caution in these dogs and cats. There is no specific therapy for pulmonary contusions. Supportive care with oxygen supplementation and pain relief is the mainstay of treatment. Most dogs and cats with pulmonary contusions begin to improve 24 to 36 hours after the initial insult (see ch. 149).

Other respiratory conditions include open chest wounds, flail chest, and rib fractures (see ch. 139). Open chest wounds should be covered and sealed as soon as possible. Once accomplished, the closed pneumothorax should be resolved by thoracocentesis. Treatment of an animal with a flail chest or rib fractures involves oxygen supplementation and pain management. Surgical repair is rarely necessary.

Neurogenic pulmonary edema occurs rarely but is most often associated with severe head trauma (see ch. 148 and 242). This form of pulmonary edema can range from mild to severe enough to require mechanical

ventilation. Most of these pets can be managed successfully with supportive care, such as oxygen supplementation and judicious diuretic therapy. Generally, respiratory problems in animals with neurogenic pulmonary edema caused by head trauma improve substantially within 48 hours, or death ensues due to the severe respiratory compromise.

An adequate amount of hemoglobin in the vascular space is essential to maintenance of tissue oxygen delivery. Decreased hemoglobin content severely limits the oxygen-carrying capacity of the blood and can contribute to decreased tissue oxygen delivery. The packed cell volume (PCV) provides the most rapid estimate of the hemoglobin concentration in a traumatized dog or cat, but it should be interpreted in conjunction with assessment of the vascular volume status (see Tissue Perfusion, below) to get a complete assessment of the total hemoglobin content of the vascular space. Typically, acute blood loss is not reflected by the initial PCV measurement because of splenic contraction in the dog and the length of time it takes for interstitial fluid to shift into the vascular space to dilute the PCV. Initial total solids (TS) and serial measurements of both PCV and TS as intravenous fluids are administered can be more sensitive indicators of acute blood loss (see ch. 135). There is no specific PCV at or below which transfusion is required. Transfusion therapy (see ch. 130) should be based on whether the animal is affected by the decreased hemoglobin content, which is indicated by clinical signs such as pale mucous membranes, tachycardia, tachypnea, bounding or weak pulses, depressed mentation, or cardiac arrhythmias. As with any animal in critical condition, it is best to anticipate and treat problems before they cause physiologic compromise. For example, if the PCV is dropping rapidly, it is best to start a blood transfusion or administer hemoglobin solutions before the hemoglobin content drops to a life-threatening level.

Tissue Perfusion

Physical assessments of tissue perfusion on the first examination include mucous membrane color, capillary refill time, and pulse rate and quality (Figure 147-3; also see ch. 2 and 127).

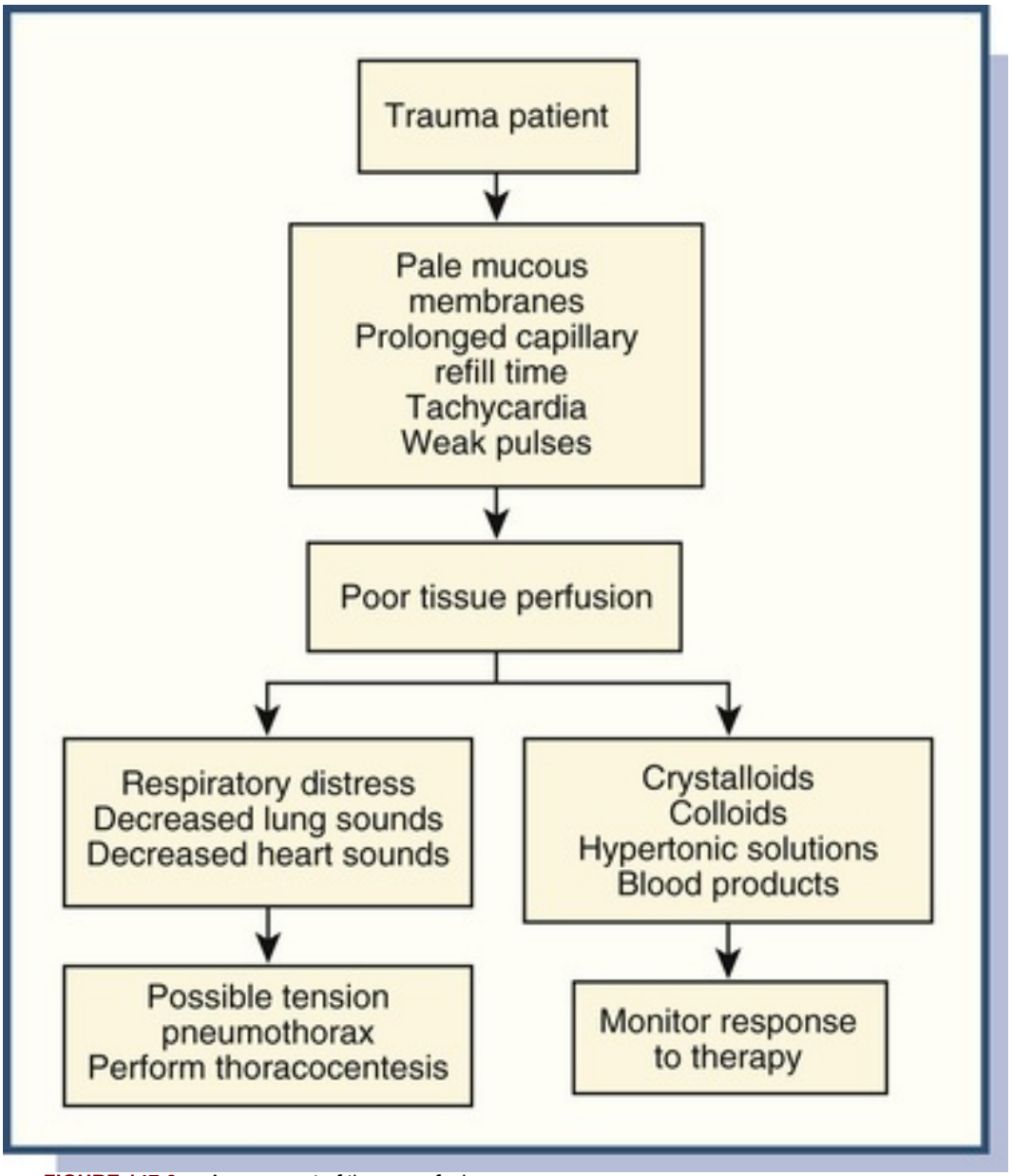

FIGURE 147-3 Assessment of tissue perfusion.

The arterial blood pressure should be measured directly or indirectly by Doppler or oscillometric techniques when possible (see ch. 99). Measurement of blood lactate or central venous oxygen saturation are objective assessments of adequacy of tissue perfusion with the former being more practical (see ch. 70). The most common clinical signs indicative of poor tissue perfusion are pale or gray mucous membranes, a prolonged capillary refill time, a rapid heart rate, and weak pulses. The most common cause of poor tissue perfusion after a traumatic event is hypovolemia secondary to hemorrhage.

Administration of a balanced electrolyte solution at a rate of 90 mL/kg body weight/hr in the dog (40 to 60 mL/kg body weight/hr in the cat) is indicated with physical evidence of poor tissue perfusion (see ch. 129). Two separate, large-bore, intravenous catheters may be required in large dogs (i.e., body weight exceeding 20 to 30 kg). Mucous membrane color, capillary refill time, pulse quality, heart rate, and blood pressure (if available) should be assessed continuously and the intravenous fluid rate adjusted as perfusion parameters improve or worsen. In most uncomplicated situations, improvement in tissue perfusion often is seen by the time one half of a vascular volume of fluid (45 mL/kg in the dog, 20 to 30 mL/kg in the cat) has been administered. As mentioned above, aggressive fluid therapy should be applied cautiously to animals known or suspected of having pulmonary contusions.

If clinical perfusion parameters or the blood pressure has not significantly improved after this volume of

fluid has been administered, an investigation into causes of nonresponsive cardiovascular shock should be pursued. Such causes include ongoing intravascular volume loss (most commonly due to ongoing hemorrhage) or, less commonly, cardiogenic causes, such as arrhythmias, pericardial effusion, myocardial depression or failure, electrolyte abnormalities, decreased venous return (e.g., tension pneumothorax), or ischemic organs. The peritoneal space is the most common location of substantial hemorrhage that can lead to hypovolemia and can be easily detected by abdominal focused assessment with sonography (AFAST, see ch. 143). Less common locations are the pleural space (see ch. 149) and retroperitoneal space (see ch. 88), external hemorrhage, and hemorrhage into the muscles surrounding the femur (see ch. 135).

Abdominal binding may help control ongoing intra-abdominal hemorrhage. However, this is no substitute for adequate intravascular volume supplementation. In human beings, some physicians advocate delayed resuscitation. In animals with severe hemorrhage, the fluid of choice is whole blood, packed red blood cells and plasma, hemoglobin substitutes (e.g., Oxyglobin), and/or colloid supplementation, such as hydroxyethyl starch or dextran 70 (see ch. 129 and 130). Hypertonic solutions can be considered after head trauma if a dog or cat is hypovolemic (see ch. 148) or if an animal appears to be in severe hypovolemic shock and may die before an adequate amount of balanced electrolyte solution can be administered (see ch. 127). Limited volume resuscitation in dogs with spontaneous hemoabdomen has been shown to provide more rapid hemodynamic stabilization compared to conventional crystalloid resuscitation, though further studies are warranted before this therapy can become standard.

Traumatized animals are physiologically dynamic and should be continuously monitored until physiologic parameters are stable. Close monitoring of cardiovascular and respiratory trends allows early detection of problems, before they become life threatening.

Central Nervous System and Urinary Tract

The central nervous system (CNS) (brain and spinal cord) and the renal system are two other organ systems that should be assessed and supported as priorities (see ch. 148 and 150). Compromise of either of these systems can result in irreversible damage. After the initial assessment and treatment of the cardiovascular and respiratory systems, the clinician should complete a thorough neurologic examination, including assessment of mentation and of cranial nerve and spinal cord function (see ch. 259). The results of such an evaluation establish a baseline for further monitoring and therapy. Brain dysfunction may be a result of poor oxygen delivery, direct tissue damage, intracranial hemorrhage, cerebral edema, ischemia, and/or increased intracranial pressure. Therapeutic considerations with head trauma and brain dysfunction include optimization of tissue perfusion, administration of mannitol (0.5 to 1.5 g/kg given intravenously), mild elevation of the head (30 degree from horizontal tilt board with head at the higher end, avoiding flexion of the neck and occlusion of the jugular veins), and maintenance of oxygenation (see ch. 148). Spinal cord assessment should include palpation of the spine and assessment of spinal function, including voluntary motor movement, conscious proprioception, ambulation, spinal reflexes, and pain sensation.

Neurologic function should always be evaluated in light of how well the central nervous system is perfused. In most animals, head trauma is obvious. However, those with severely compromised perfusion may have severely depressed mentation, as well as diminished pain sensation. The mentation and sensation abnormalities may normalize with correction of the poor tissue perfusion.

Manifestations of urinary tract injury or dysfunction may not be immediately evident and may not be detected until several hours of continuous monitoring have passed (see ch. 150). Potential renal/urologic system abnormalities include direct kidney damage (e.g., contusions, hematomas, avulsion), ureteral rupture, bladder rupture, and urethral trauma. Any animal that has been traumatized may have experienced renal/urologic system trauma. Serial assessment of the blood urea nitrogen, creatinine, and serum potassium concentrations, as well as of urine output, should be considered (see ch. 105 and 106). It should be remembered that animals with a ruptured urinary bladder might still urinate. Ureteral rupture may result in urine accumulation in the retroperitoneal space, a situation in which abdominocentesis fails to obtain fluid. Abdominal radiographs, abdominal ultrasound scans, and intravenous contrast studies may be necessary to diagnose ureteral rupture. If free abdominal fluid is present, it should be analyzed for the creatinine and potassium concentrations, which should be compared to the concentrations in peripheral blood. If the abdominal fluid is urine, its creatinine and potassium concentrations are higher than those of blood.

Secondary Survey

After assessment of tissue oxygen delivery, CNS function, and renal function, a full physical examination

should be performed (see ch. 2). Limb function should be evaluated and should include palpation of the entire appendicular and axial skeletal system as well as assessment of the animal's ability to support weight and ambulate. The eyes and oropharyngeal area should be examined for evidence of trauma. The mouth should be manually opened and closed to assess for malocclusion, pain, or crepitus. The roof of the mouth should be checked for split palate, a common finding in cats that have fallen from heights. A rectal examination should be performed, and attention should be paid to palpation of the pelvic canal for fractures or instability and evidence of blood in the rectum. The skin should be thoroughly examined for lacerations, abrasions, and bruising.

Monitoring

After the initial assessment, all the above systems should be monitored for at least 24 to 48 hours, despite how well the animal looks when first examined. In general, if problems are going to occur, they usually occur within this time frame. The intensity and duration of the monitoring should be proportional to the degree of compromise. Owners should also be warned that rarely, complications might arise several days later. For example, clinical signs of a ruptured gallbladder are not often manifested until several days after the traumatic injury. Assessment of tissue oxygen delivery should be performed at presentation and treated appropriately. Assessment should also include the CNS and renal/urologic systems, as well as the musculoskeletal, cutaneous, and peripheral nervous systems. A global approach, with emphasis on the most life-threatening conditions first, optimizes the outcome.

CHAPTER 148

Head Trauma

Eileen Kenney

Traumatic brain injury (TBI) is a significant cause of morbidity and mortality in veterinary patients, with etiologies including motor vehicle accidents, crush injuries, human or animal attacks, falls, and gunshot or other penetrating wounds.[1-3] The severity of brain injury can be quite variable, ranging from minor deficits to life-threatening neurologic impairments. An understanding of the pathophysiology of TBI, along with appropriate and rapid management of the injured patient, is critical to maximize survival and a functional recovery.

Pathophysiology

The pathophysiology of TBI involves both primary and secondary neuronal injury. Primary injury occurs at the moment of the initial trauma from mechanical damage to the brain parenchyma. Primary injury is broadly classified as focal or diffuse, and can be further defined based on the location and type of injury. Types of primary injuries include concussions, contusions, lacerations, diffuse axonal injury, and vascular disruption.

Secondary injury occurs hours to days subsequent to the trauma from a variety of processes that cause continued neuronal damage. Mechanisms of secondary injury include: ischemia, ATP depletion, failure of ionic homeostasis, glutamate excitotoxicity, free radical production, vasogenic and cytotoxic cerebral edema, mitochondrial dysfunction, cerebral lactic acidosis, inflammatory mediator release, activation of the coagulation cascade, and apoptotic and necrotic cell death. Systemic contributions to secondary brain injury include hypotension, hypoxemia, hypoglycemia, hyperglycemia, hypocapnia, hypercapnia, hyperthermia, acid-base disturbances, and electrolyte abnormalities. Intracranial contributions include intracranial hypertension, compromise of the blood brain barrier (BBB), hematoma formation, cerebral edema, infection, vasospasm, and seizures. Prevention and management of secondary injury are the main treatment goals for patients with TBI.

In the healthy brain, cerebral autoregulation maintains a constant cerebral blood flow (CBF) through changes in cerebral vascular resistance (CVR), with the relationship CBF = CPP/CVR. The cerebral perfusion pressure (CPP) is determined by the mean arterial pressure (MAP) minus intracranial pressure (ICP), or CPP = MAP − ICP. Given that normal ICP is generally low (5-14 mm Hg in dogs and cats),[4,5] CPP is mainly dependent upon MAP. Autoregulation can maintain CBF over a MAP range of 50-150 mm Hg, but above and below this limit, CBF becomes pressure-dependent. In TBI, cerebral autoregulation may be compromised regionally or globally, such that even small decreases in CPP (from either a decrease in MAP or increase in ICP) can lead to decreased CBF, causing cerebral ischemia.

ICP is dictated by three components within the skull: the brain parenchyma, arterial and venous blood, and cerebrospinal fluid (CSF). Intracranial compliance normally maintains these components in a balanced dynamic equilibrium by shifting fluids in the brain vasculature and CSF pathways. When TBI occurs, the limits of intracranial compliance can be overwhelmed due to hemorrhage or edema, leading to increased ICP, decreased CPP, and cerebral ischemia. The Cushing reflex, or cerebral ischemic response, is triggered by a severe acute increase in ICP which causes systemic hypertension in order to maintain a normal CPP, along with a vagally induced reflex bradycardia. This response signifies potentially life-threatening intracranial hypertension with imminent brain herniation, and should be treated immediately.

Patient Assessment and Diagnostics

Patients presenting for trauma are often in hypovolemic shock and/or respiratory distress, having sustained multisystemic injuries that impair systemic perfusion, oxygenation, and mentation (see ch. 127). Initial assessment should focus on treating imminently life-threatening abnormalities such as hemoabdomen,

pneumothorax, pulmonary contusions, and upper airway trauma (see ch. 147). Once normovolemia and appropriate oxygenation and ventilation are established, a secondary assessment of additional injuries and neurological evaluation can occur. An abbreviated neurologic examination should be done before analgesic administration to allow accurate assessment, and should focus on level of consciousness, motor ability, and brainstem reflexes (pupil size, pupillary light response, and oculocephalic reflex). Patients should be graded using the Modified Glasgow Coma Scale (MGCS), which provides an estimate of prognosis (Table 148-1; Video 148-1).[2] A more detailed neurologic examination can be performed (see ch. 259) once treatment for neurological stabilization has been initiated.

TABLE 148-1

Modified Glasgow Coma Scale

LEVEL OF CONSCIOUSNESS
6: Occasional periods of alertness and responsive to environment
5: Depression or delirium, capable of responding but response may be inappropriate
4: Semicomatose, responsive to visual stimuli
3: Semicomatose, responsive to auditory stimuli
2: Semicomatose, responsive only to repeated noxious stimuli
1: Comatose, unresponsive to repeated noxious stimuli
MOTOR ACTIVITY
6: Normal gait, normal spinal reflexes
5: Hemiparesis, tetraparesis, or decerebrate rigidity
4: Recumbent, intermittent extensor rigidity
3: Recumbent, constant extensor rigidity
2: Recumbent, constant extensor rigidity with opisthotonus
1: Recumbent, hypotonia of muscles, depressed or absent spinal reflexes
BRAINSTEM REFLEXES
6: Normal pupillary light reflexes and oculocephalic reflexes
5: Slow pupillary light reflexes and normal to reduced oculocephalic reflexes
4: Bilateral unresponsive miosis with normal to reduced oculocephalic reflexes
3: Pinpoint pupils with reduced to absent oculocephalic reflexes
2: Unilateral, unresponsive mydriasis with reduced to absent oculocephalic reflexes
1: Bilateral, unresponsive mydriasis with reduced to absent oculocephalic reflexes

MGCS SCORE	PROGNOSIS
3-8	Grave
9-14	Guarded
15-18	Good

Quick assessment blood work should include a packed cell volume and total solids to assess for hemorrhage, blood glucose to assess the severity of injury, and blood gas and lactate to assess acid-base status, ventilation, and perfusion (see ch. 70, 75, and 128). Electrolyte and renal values should also be obtained before initiating treatment to assess for derangements that could preclude administration of medications. Sampling from the jugular vein should be avoided as temporary occlusion of this vessel could rapidly increase ICP.[6]

Skull radiography can be used to screen for calvarial fractures, but will not otherwise provide clinically useful information about brain injury. Advanced intracranial imaging is indicated if the patient fails to

respond to aggressive medical therapy or neurologically deteriorates. Computed tomography is the modality of choice in the acute setting, due to its rapid scan time and ability to identify intracranial hemorrhage, cerebral edema, cerebral herniation, and fractures.[7,8] Beyond the acute setting, magnetic resonance imaging is indicated in more stable patients that fail to respond to medical therapy due to its higher sensitivity for contusions, diffuse axonal injury, subdural and epidural hematomas,[9-11] and the fact that it can provide prognostic information in dogs.[3]

Treatment

Before initiating therapy directed at lowering ICP, it is essential that hypoxemia, hypovolemia, and blood loss anemia are treated to endpoint resuscitation parameters to minimize secondary brain injury caused by shock (see ch. 127 and 129). The MAP should be maintained ≥80 mm Hg in order to maintain CPP. Oxygen supplementation is recommended during the initial stabilization and should be continued if needed to maintain a SpO_2 > 97% or a PaO_2 > 90 mm Hg (see ch. 131). The patient should tolerate the method of oxygen supplementation, since coughing, sneezing, struggling and anxiety may transiently increase ICP. If the patient is hypoventilating, resulting hypercapnia will cause cerebral vasodilation, which increases CBF and ICP. If $PaCO_2$ cannot be maintained within the normal range (35-45 mm Hg), or if PaO_2 is below 80 mm Hg despite oxygen supplementation, endotracheal intubation with mechanical ventilation is required.

Once the patient's cardiovascular and respiratory systems have been addressed, neurological stabilization can ensue by administering hyperosmolar agents to decrease ICP (Figure 148-1). Mannitol is an osmotic diuretic with an immediate plasma volume expansion effect, which improves CBF while causing a reflex vasoconstriction that decreases ICP. In addition, mannitol may scavenge free radicals and its rheologic effects improve microcirculation.[12,13] Mannitol is administered as a slow bolus over 15-20 minutes at dosages from 0.25 to 1 g/kg. Administration of mannitol is contraindicated in hypovolemic patients due to its diuretic effect causing further volume contraction and thus worsening CPP. An alternative choice is hypertonic saline, especially in hypovolemic patients, since it expands plasma volume while decreasing ICP via osmotic mobilization of water across the BBB. Hypertonic saline also improves microcirculation, decreases excitotoxicity, and modulates the inflammatory response.[14,15] It is administered at a dosage of 3 to 5 mL/kg of 7.5% NaCl in dogs (2 to 3 mL/kg in cats) over 3-5 minutes. Co-administration of hypertonic saline with 2 to 3 mL/kg of an artificial colloid has also been demonstrated to be effective at lowering ICP.[16,17] Elevating the head to a 30° angle reduces ICP by facilitating venous drainage from the brain.[18] Care should be taken to avoid obstructing the jugular veins with constrictive wraps, jugular catheters, or excessively bending the neck. Corticosteroids were historically advocated for treatment of TBI, but have been associated with increased mortality and are now contraindicated.[19] The administration of furosemide has also not been shown to be beneficial and may worsen hypovolemia, so is not recommended.[20] Hyperglycemia is associated with increased mortality rates in humans with TBI,[21] whereas in animals the degree of hyperglycemia is associated with the severity of TBI but not outcome.[1] Glycemic control is an active area of research in humans with TBI, but further studies are needed to advocate its use in veterinary patients.[22,23]

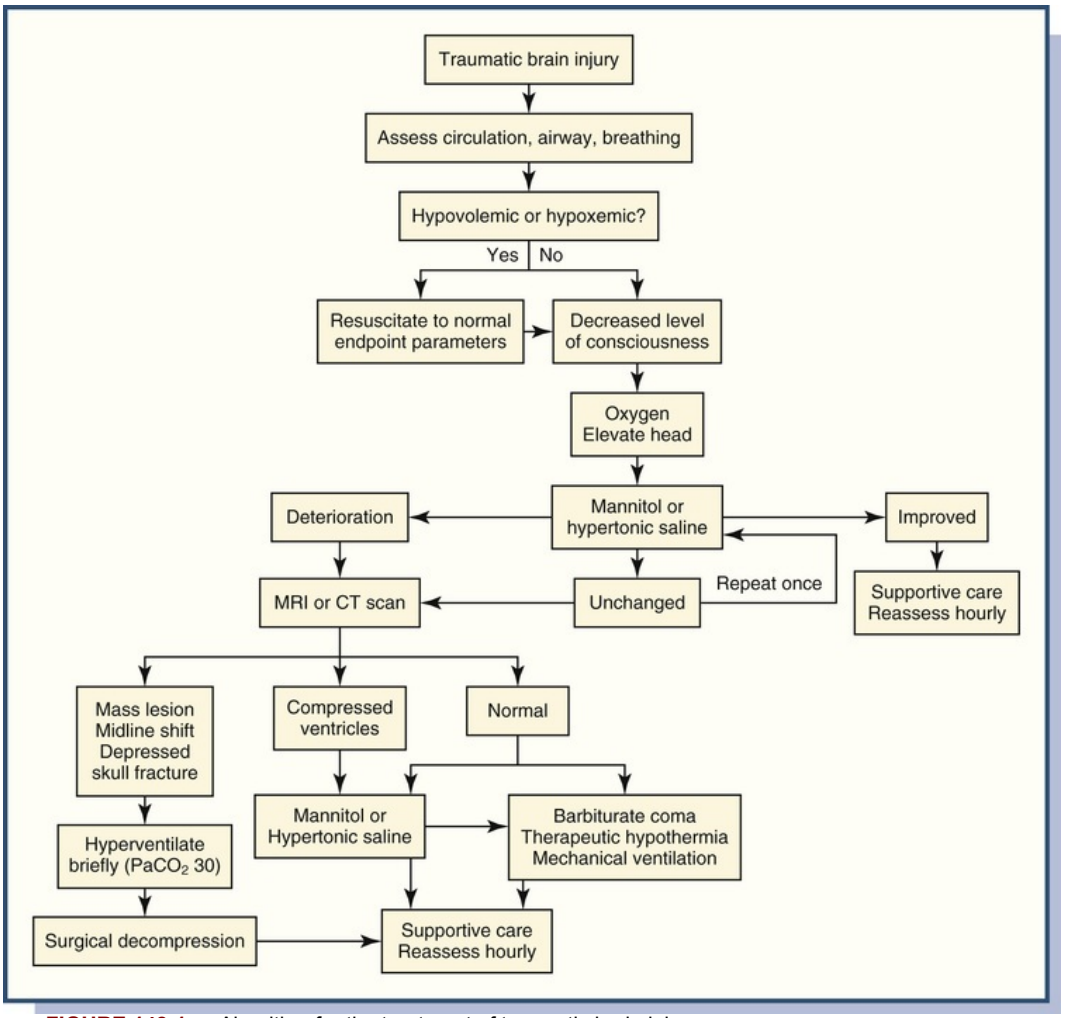

FIGURE 148-1 Algorithm for the treatment of traumatic brain injury.

Other beneficial therapies include therapeutic moderate hypothermia which is utilized in humans and animals to decrease the cerebral metabolic rate, inhibit release of glutamate and inflammatory cytokines, and decrease ICP via reflex vasoconstriction.[24-26] Induction of a barbiturate coma can be used to decrease the cerebral metabolic rate and decrease seizure activity.[26] Use of hyperbaric oxygen therapy in TBI (see ch. 84) has been shown to decrease ICP, secondary brain damage, and improve cerebral oxygenation without an increase in inflammatory markers.[27,28] Decompressive craniectomy with durotomy is effective at decreasing ICP in dogs,[29] and may be indicated with open or depressed skull fractures, ongoing hemorrhage, contaminated foreign body or hematoma removal, and declining neurologic status despite aggressive medical therapy. Patients suffering an acute neurologic deterioration can be hyperventilated to a $PaCO_2$ not less than 30 mm Hg while additional medical or surgical stabilization is initiated. Hyperventilation should be brief, since the resulting cerebral vasoconstriction not only decreases cerebral blood volume and ICP, but globally decreases CBF and perpetuates ischemia.[30]

After initial fluid resuscitation, continued fluid therapy is required to account for maintenance needs, deficits, and ongoing losses. Fluid restriction should be avoided as it places the patient at risk for a negative fluid balance, which is shown to worsen patient outcome.[31] A hypermetabolic and catabolic state occurs after TBI, increasing the demand for energy substrates.[32] Decreased and delayed nutritional support is associated with a worse neurologic outcome and increased mortality, so institution of nutritional support within 48 hours post-injury is recommended.[33,34] Analgesia is often indicated but must be balanced with preservation of blood pressure and ventilation, and should ideally not impede neurologic re-assessment. Opioid agonists administered as a CRI are preferred since they can be titrated to effect and are easily reversible. In-hospital seizures have been reported in 10-28% of dogs after TBI,[3,35,36] so anticonvulsant medication (levetiracetam or phenobarbital) should be administered during the recovery period if seizures are noted (see ch. 35 and 136).

Nursing care should provide clean dry bedding, frequent turning, and physical therapy to prevent urine scalding, pressure sores, and limb contracture.

Patient Monitoring

Cardiovascular, respiratory, and neurologic status should be reassessed hourly to evaluate treatment efficacy and to assess for deterioration. Blood pressure, $PaCO_2$ or $ETCO_2$ (if intubated), and PaO_2 or SpO_2 should be monitored to ensure systemic stability. Serial monitoring of the initial blood work values is essential since dramatic changes can occur due to therapy or changing patient status. Serial MGCS scores should be recorded as an objective assessment of changes in neurologic status. ICP monitoring is frequently employed in human hospitals to guide therapy when ICP exceeds 20 mm Hg, rather than relying on gross neurologic signs. Methods of monitoring ICP have been described in cats and dogs, but are not widely used or available.[4,5]

The animal can be discharged when neurologic signs have improved or plateaued and the patient is able to maintain hydration and nutritional requirements (voluntarily or with a feeding tube). Neurologic recovery may be complete, but owners should be prepared that residual deficits may persist. Dogs and cats have a remarkable ability to compensate for loss of cerebral tissue, so it is important to not reach hasty prognostic conclusions based on initial appearance.[37]

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CHAPTER 149

Thoracic Trauma

Elizabeth Rozanski

Trauma, including thoracic trauma, is a common presenting complaint in small animal emergency medicine. The basic tenets of emergency medicine focus on the primary survey of the patient, including evaluation and stabilization of the major body systems (heart, brain, lungs) and then the secondary survey with complete patient evaluation (Figure 149-1). The focus of this chapter is on thoracic trauma. The interested reader is also directed to the Veterinary Committee on Trauma (VetCOT) at https://sites.google.com/a/umn.edu/vetcot/home. The purpose of this chapter is to provide an overview of the approach to the thoracic trauma patient, with a specific focus on pulmonary injury. However, it is important to evaluate the entire patient, rather than to just focus on the thoracic cavity.

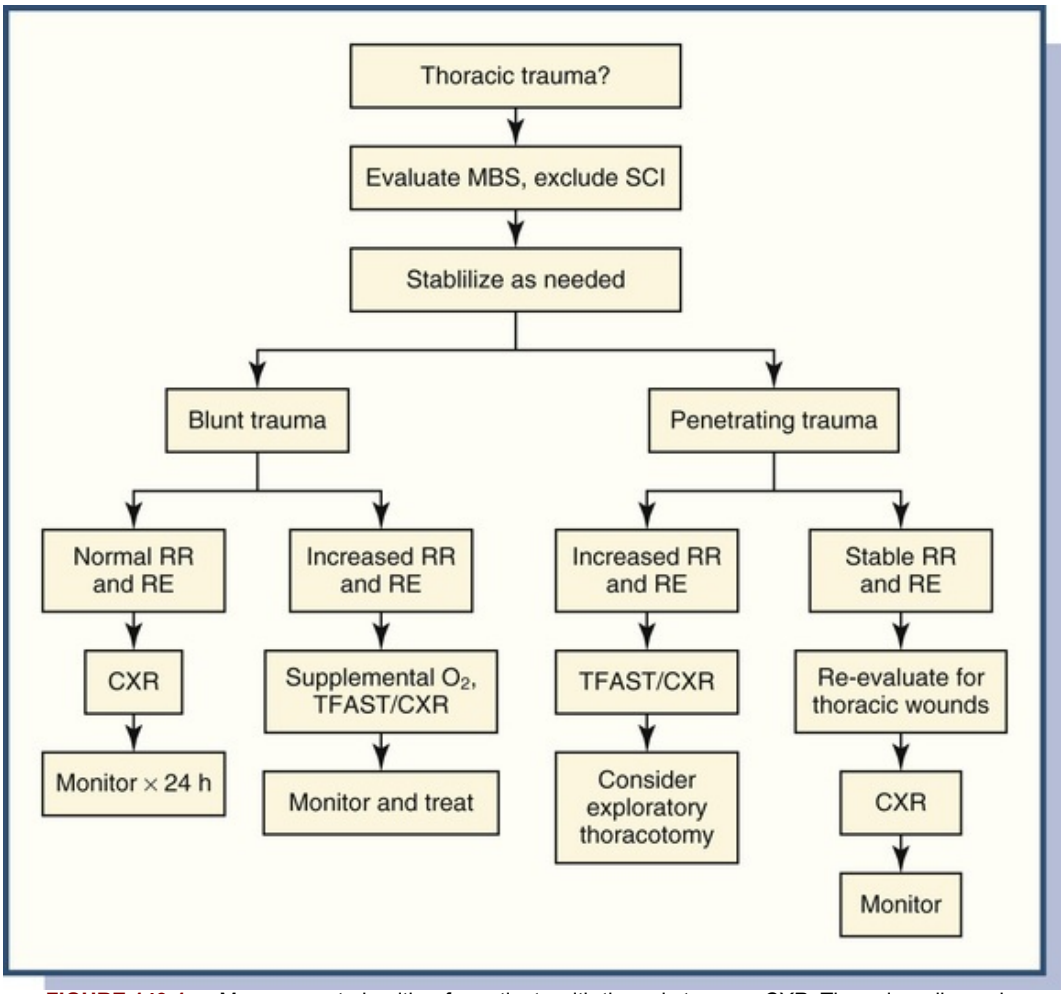


FIGURE 149-1 Management algorithm for patients with thoracic trauma. *CXR,* Thoracic radiograph; *MBS,* major body systems, namely the heart, brain and lungs; *RE,* respiratory effort; *RR,* respiratory rate; *SCI,* spinal cord injury; *TFAST,* focused sonography for trauma—thoracic.

Mechanism of Injury

Trauma can be divided loosely into blunt (e.g., hit by car [HBC]) and penetrating trauma (e.g., bite wound). It is helpful to know the mechanism of injury if possible; however, owners are notorious for misidentification of the circumstances surrounding trauma, such as the speed of the car or the breed of an attacking dog. It is helpful to ask if the patient walked away from the accident using all four limbs, and if the patient lost consciousness at the scene. In rabies-endemic areas, the vaccine status of the victim and the attacker should be established.

Initial Assessment and Stabilization

By nature, trauma cases present on an emergency basis. Each case should be evaluated immediately for life-threatening injuries. With the recent growth of 24-hour veterinary hospitals, each practice should develop policies on which cases should be hospitalized for ongoing care at the primary care veterinary clinic, and which cases should be referred for more specialized care. These policies will reflect geographic constraints and individual practice philosophy. Any pre-existing patient history is helpful, but is unremarkable in most trauma patients, who tend to be younger and healthy. Clinicians are advised to be aware of the possibility of non-accidental injury, consistent with abuse.

Initial assessment focuses on the cardiovascular, neurologic, and respiratory systems. Evidence of cardiovascular compromise includes tachycardia and weak pulses. Hypotension is uncommon but is a crucial finding if detected (see ch. 99 and 159). The shock index (heart rate/blood pressure) has been described as a method of identifying shock in patients with more subtle abnormalities and can be useful if blood pressure is recorded routinely.[1] Treatment of cardiovascular dysfunction revolves around volume resuscitation, most commonly with intravenous crystalloid infusions or blood transfusions (see ch. 129 and 130). Recently, synthetic colloids have been falling in popularity, and the indications for the use of colloids in the resuscitation of traumatized patients are now considered limited.[2] Neurologic dysfunction includes traumatic brain injury, spine cord injury, and peripheral nerve damage, such as brachial plexus avulsion (see ch. 148, 267, and 268). Treatment of neurological dysfunction is dependent on the type of damage; for example, animals with thoracic trauma also can have vertebral fractures or luxations (Video 149-1). Pulmonary dysfunction is recognized by labored ventilation, or by short and shallow respiration, and most commonly is caused by pulmonary contusions or pneumothorax.

Point of Care Blood Tests

Initial testing is useful to evaluate the *presenting* packed cell volume, total solids, and lactate level. Other laboratory testing (complete blood count, serum biochemistry profile, urinalysis) can be indicated on an individual patient basis and is especially important in older patients, those with co-morbidities, or when large surgical procedures are planned (e.g., fracture repair). In general, laboratory testing will document increased liver enzyme concentrations associated with blunt hepatic trauma with little clinical significance. In dogs in particular, marked splenic contraction can result in a normal or near normal hematocrit at presentation, even with severe hemorrhage. However, the total solids (total protein) concentrations will fall, providing a useful clue of blood loss. Total solids concentrations <6 g/dL (<60 g/L) warrant further evaluation, especially if coupled with persistent tachycardia (or bradycardia in cats). Occasionally, pre-existing chronic diseases can be the cause of hypoproteinemia, but the safest approach is to assume hemorrhage when a low total solids concentration is detected at presentation.

Lactate is generated most commonly as a marker of anaerobic metabolism (type A) and can be used to help confirm hypovolemia when elevated (>2.0 mmol/L). Lactate clearance, or the rate of fall of lactate during initial treatment, is also emerging as a useful tool for monitoring response to therapy (see ch. 70).

FAST Scan

Point-of-care thoracic ultrasonography is very useful in trauma. Boysen and colleagues initially introduced the concept of focused assessment with sonography for trauma (FAST) scanning in veterinary medicine, and since that time, multiple studies have documented its utility.[3,4] Following the initial patient survey, and institution of resuscitative measures, a standardized approach with ultrasound will help identify free fluid or air more quickly and easily than with radiographs. FAST involves a limited use of ultrasound to primarily answer the question "Is there fluid or not?" and is not designed to evaluate the entire cavity being scanned.

The clinician should learn specific sites to scan and record these in the medical record. TFAST refers to screening the thorax for free air (traumatic pneumothorax), pleural or pericardial effusion, and pulmonary infiltrates. Pneumothorax is identified by the loss of the glide sign (Video 149-2). Sonographically, it is harder to appreciate pneumothorax than pleural effusion. Ultrasound also is used for identifying "lung rockets" which signify pulmonary infiltrates, consistent with pulmonary contusions.[4] It is essential to recall that in trauma patients, large volumes of pleural effusion are more likely to result in signs of hypovolemia than in respiratory embarrassment because pleural effusion in trauma is typically frank blood, although injury-associated urothorax and bilothorax rarely have been reported.

The focus of this chapter is on thoracic injuries seen in trauma. However, upper airway injuries can occur in conjunction with thoracic trauma and are discussed first.

Upper Airway

The most severe injuries in the upper airway occur in conjunction with bite wounds. Bite wounds to the neck can affect any of the soft tissues in the neck, notably the jugular veins, carotid arteries, esophagus, or trachea. Tracheal damage can result in subcutaneous emphysema or pneumomediastinum.[5] In our practice, we have also identified dogs with damage to the recurrent laryngeal nerves, resulting in laryngeal paralysis. Treatment of tracheal injuries includes primary repair with closure of the defect, or in some cases of a presumed small tear, simple observation (Figure 149-2). Laryngeal paralysis can require surgical palliation with arytenoid lateralization while laryngeal collapse can require a permanent tracheostomy.

FIGURE 149-2 A severe bite wound to the neck in a Corgi. Extensive tracheal damage was present.

Pulmonary Contusions

Pulmonary contusion occurs when blunt thoracic trauma causes alveoli to fill with blood and fluid (inflammation). Although comprehensive data are not available, pulmonary contusion probably occurs in a large percentage of animals with thoracic trauma. Damage to the lung parenchyma develops from capillary injury and subsequent leakage of blood into the interstitium. This hemorrhage triggers an inflammatory response, and results in the influx of inflammatory cells. Pulmonary contusions decrease lung compliance and alter gas exchange, causing hypoxemia and possibly hypercarbia in severe cases. Decreased lung compliance means a higher inspiratory pressure is needed to result in the same tidal volume. Animals typically compensate for reduced compliance with more rapid respiration.

Pulmonary contusions can be suspected clinically by tachypnea and increased respiratory effort. They may be confirmed radiographically as interstitial to alveolar infiltrates. Location is consistent with the site of injury. TFAST may also be used to identify lung rockets, or evidence of lung edema.[4] Computed tomography, while uncommonly performed in veterinary patients with acute trauma, would also confirm pulmonary contusions. Due to influx of inflammatory cells and edema, pulmonary contusions typically will worsen radiographically over the first 12-36 hours. However, radiographs may be taken at any point after the patient is assessed as stable enough for radiographs. Follow-up radiographs are rarely taken if the patient is recovering as predicted, and radiographic clearance is likely to take up to a week.

Therapy for pulmonary contusions is supportive and can include oxygen supplementation (see ch. 131) and fluid therapy as needed to maintain adequate circulating volume (see ch. 127). Large volumes of intravenous crystalloids should be avoided when possible, since they can magnify lung injury by contributing to volume overload and extravasation of lung water. Synthetic colloidal therapy has not been evaluated formally in animals with pulmonary contusions.[2] In people, recommendations are for adequate fluid resuscitation, but with efforts to avoid volume overload. Most dogs with pulmonary contusions show marked improvement in 2-3 days and recover completely in less than one week.

Complicated pulmonary contusions are uncommon, but include the development of pneumonia or acute respiratory distress syndrome (ARDS). Pneumonia is very rare in dogs with pulmonary contusions, despite the perception of blood being a good medium for bacterial growth. Dogs with traumatic pneumocysts can have an increased incidence of subsequent infections.[6,7] Antibiotics should be avoided in isolated pulmonary contusions. Diuretics are not indicated in pulmonary contusions, and there is no role for glucocorticoids. Analgesics may be considered, because pulmonary contusions imply concurrent, substantial chest wall and pleural damage, which are painful. Furthermore, untreated thoracic pain can limit deep breathing, which then promotes atelectasis and worsens lung function.

Pneumothorax

Pneumothorax refers to free air within the pleural space (Figure 149-3). In traumatic pneumothorax, free air reaches the pleural space either from outside the patient due to chest wall damage (typically a bite wound) and/or via air leakage from the pulmonary parenchyma (e.g., lung laceration). A lacerated lung will leak air into the pleural space down the pressure gradient, with some air going into the pleural space during each inspiration. Damaged lung will also bleed. Radiographs, TFAST scanning, thoracocentesis, or possibly auscultation will identify pneumothorax. Auscultation of dogs with pneumothorax can be misleading if respiratory sounds are louder than average due to concurrent pulmonary contusions, or in a thin, smooth-coated dog (e.g., Greyhound) versus an over-conditioned Labrador. In some emergency practices, dogs showing respiratory distress undergo thoracocentesis before radiography, based on the history of trauma and the increased respiratory effort. There is little risk of harm associated with a negative needle thoracocentesis. TFAST, showing the absence of the normal "glide" sign, is diagnostic of pneumothorax. Video 149-2 shows an ultrasound of a normal dog, showing the typical glide sign.

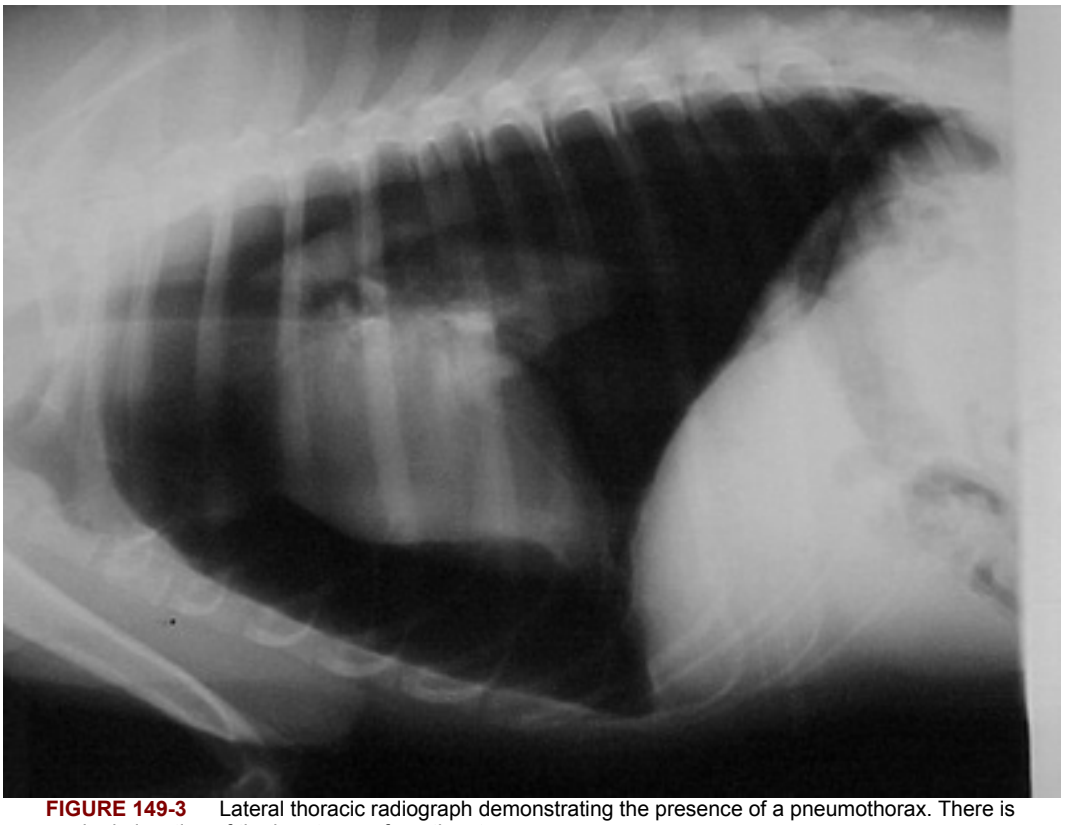


FIGURE 149-3 Lateral thoracic radiograph demonstrating the presence of a pneumothorax. There is marked elevation of the heart away from the sternum.

Approximately 25-30 mL/kg of air generally needs to be removed to provide significant improvement to respiratory status (see ch. 102). Thoracocentesis for pneumothorax is performed as for pleural effusion at the 7-9th intercostal space; some clinicians elect to enter more dorsally to try to remove more air, or the patient can be placed in lateral recumbency (if comfortably tolerated) and the centesis performed at the high point of the thorax, midway between dorsal and ventral midlines. Occasionally, a thoracostomy tube is required to provide either continuous or intermittent chest drainage (see ch. 100). Generally, a dog is considered a candidate for a chest tube if it requires >3 needle thoracocenteses in <12-18 hours, or if no end-point is reached during thoracocentesis. Animals typically will breathe with a restrictive pattern (short shallow breaths) with pneumothorax, but this might not be apparent in all cases (see ch. 139). Surgical therapy for traumatic pneumothorax can be warranted, especially with penetrating wounds (clean and debride damaged tissue, remove or repair ongoing leak). For blunt trauma (HBC), surgical intervention is rarely required, and spontaneous healing usually occurs within a few days. Use of a continuous suction device to keep the lung parenchyma inflated and avoid the cyclic inflation/collapse cycle associated with intermittent suction may facilitate healing (Video 149-3).

Hemothorax

Hemothorax is another possible sequela of thoracic trauma. Pleural effusion can develop from blood loss from damaged pulmonary parenchyma, or damage to the soft tissue structures; small arteries and veins may also bleed. It is unlikely that a patient suffering damage to a large vessel (vena cava or aorta) would survive long enough to reach the hospital unless there was a clot covering most of the damaged vessel and it was subsequently dislodged. The impact of hemothorax is more likely from hypovolemia associated with the blood loss, than from pleural effusion. Hemothorax usually is a presumptive diagnosis after identification of pleural effusion on chest radiographs from a trauma patient. Treatment is supportive, including rest and transfusions. Autotransfusion could be considered in blunt trauma patients, as the blood is unlikely to be contaminated. Typically, thoracocentesis may be avoided unless otherwise indicated by concurrent pneumothorax. Interestingly, in people, evacuation of hemothorax is advised to prevent the development of adhesions; hemothorax in dogs and cats appears to be better tolerated and does not require removal unless there is another indication. Surgical exploration is a last resort and would most likely be associated with

massive hemorrhage. If surgical exploration is entertained, preparations should be made for massive transfusion, and vascular clamps should be available.

Rib Fractures

Rib fractures are common in the patient with thoracic trauma. Rib fractures appear to be painful, particularly on inspiration. Individual fractured ribs do not typically affect lung function, but reflect a severe injury to the chest. Animals with rib fractures almost invariably have associated pulmonary contusions. Radiographic identification of rib fractures can be straightforward, but often requires careful assessment of two or more orthogonal views. Pain can decrease ventilatory efforts and coughing, which, by promoting atelectasis, could be associated with the development of pneumonia. Therapy for rib fractures typically is conservative and includes pain management (typically opioids and local blocks). Nonsteroidal anti-inflammatory agents may be considered if the patient is otherwise eating and drinking, and has normal renal function.

If two or more adjacent ribs are fractured at two or more sites on each rib, an unstable piece or "flail segment" can be formed, termed a flail chest.[8] This flail segment moves paradoxically with respiration, meaning when the patient inspires, the segment moves inward. Flail segments occasionally can be confused with intercostal muscle tears, which are simple muscle lacerations between the ribs that also show paradoxical movement during inspiration; the absence of rib fractures in a patient showing these signs is consistent with intercostal muscle tear. Intercostal muscle tears are particularly common in bite wounds, and can be located some distance from the site of the puncture wound due to the mobility of the skin (Video 149-4). Various methods of stabilization have been described for flail chest; however, the underlying contusions often are the principal detriment to lung function and therefore, supportive care is adequate. If animals undergo exploratory thoracotomy for other reasons, such as bite wounds, torn intercostal muscles should be re-apposed, and fractured ribs may be approximated. Figure 149-4 shows a reconstructed computed tomographic (CT) scan of a dog with multiple rib fractures associated with severe vehicular trauma.

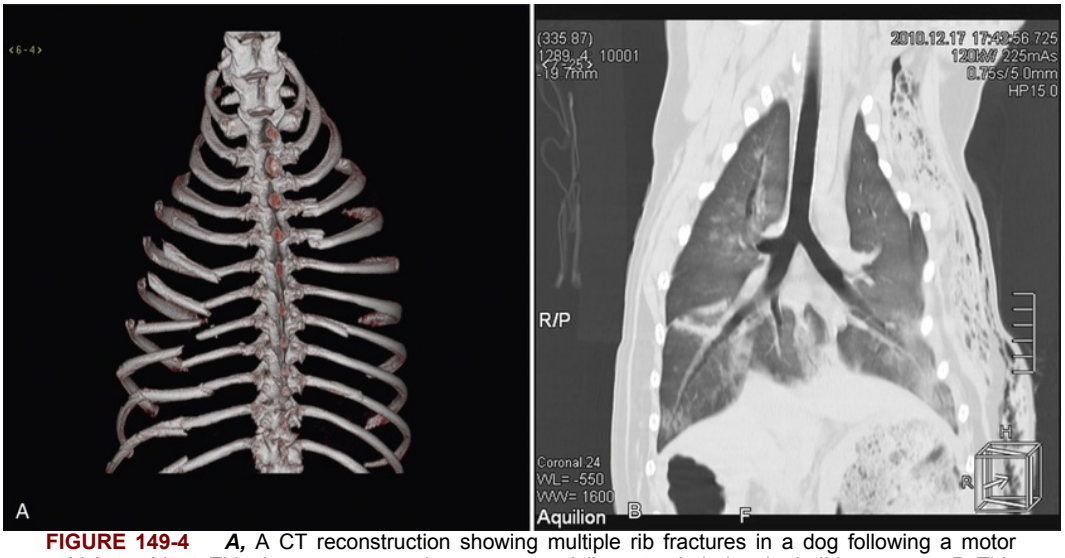
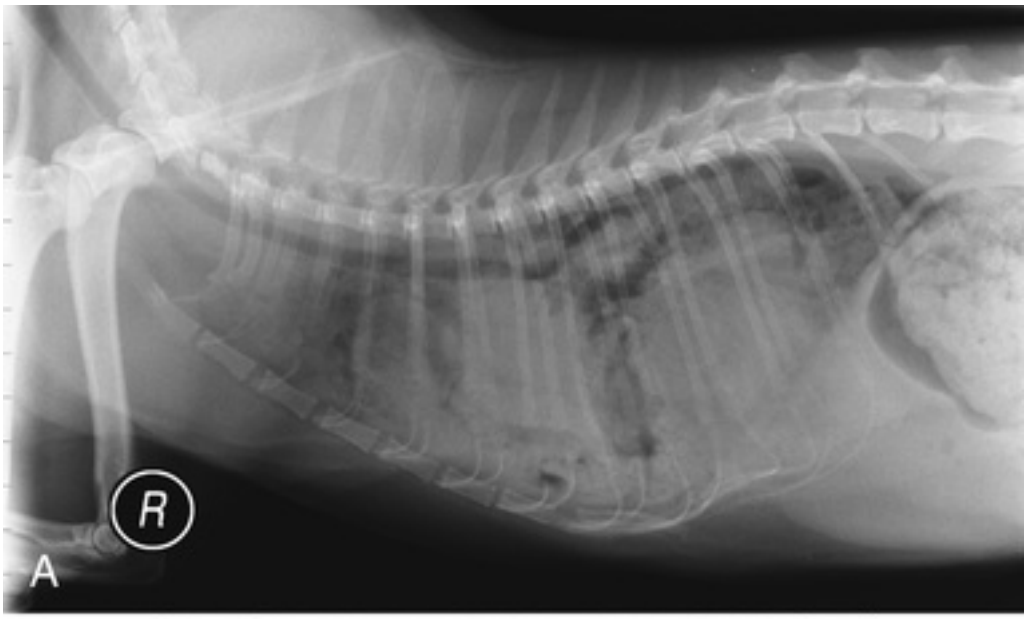


FIGURE 149-4 ***A,*** A CT reconstruction showing multiple rib fractures in a dog following a motor vehicle accident. This dog was run over by an express delivery truck during the holiday season. ***B,*** This image of the same dog shows areas of increased pulmonary opacity consistent with pulmonary contusions.

Diaphragmatic Hernia

Diaphragmatic hernias can also occur in animals with significant thoracic injuries but are less common than sometimes believed. The diagnosis usually is based on thoracic radiographs (Figure 149-5) (see ch. 245). In some cases, it can be hard to visualize on survey radiographs and advanced imaging such as ultrasonography or CT is required (Figure 149-6). The timing of surgery can be important for a successful outcome. Surgery should be undertaken promptly, ideally within 12-24 hours of the injury. In some cases, more urgent surgical repair is required, such as if the stomach is in the thoracic cavity, because the stomach can distend with air

and severely compromise ventilation. If undetected at the time of injury, chronic diaphragmatic hernia can become much harder to repair due to the formation of adhesions within the thoracic cavity.



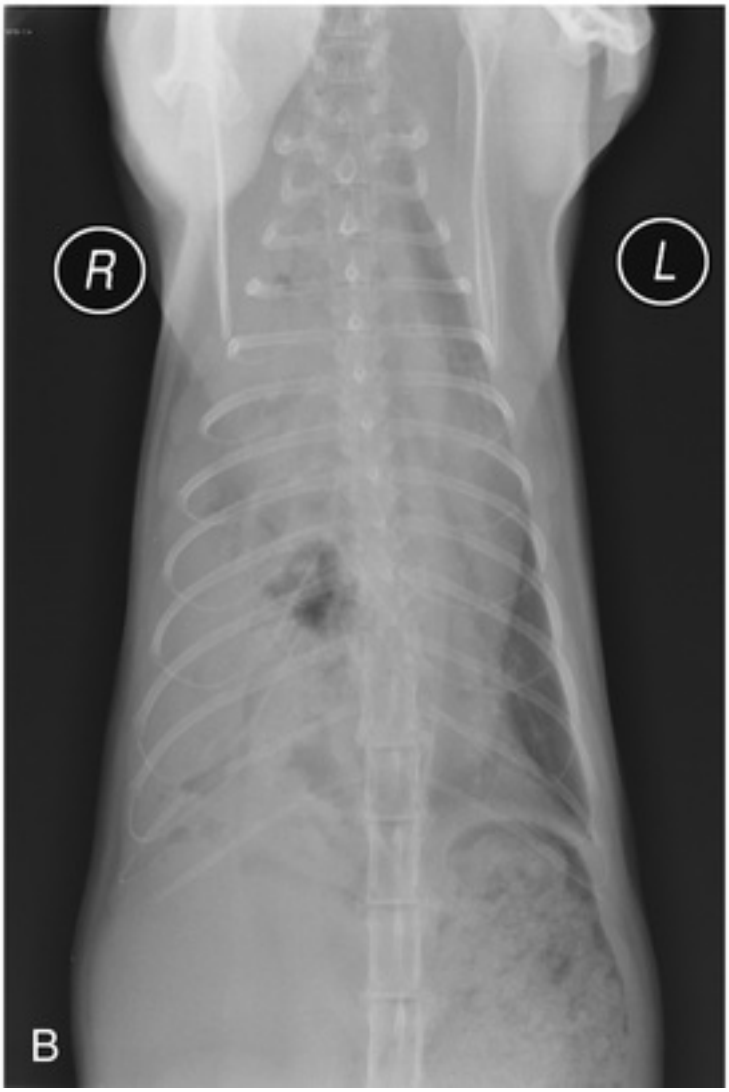


FIGURE 149-5 Lateral **(A)** and ventrodorsal **(B)** radiograph of a cat with a diaphragmatic hernia. Note the presence of bowel loops within the thoracic cavity.

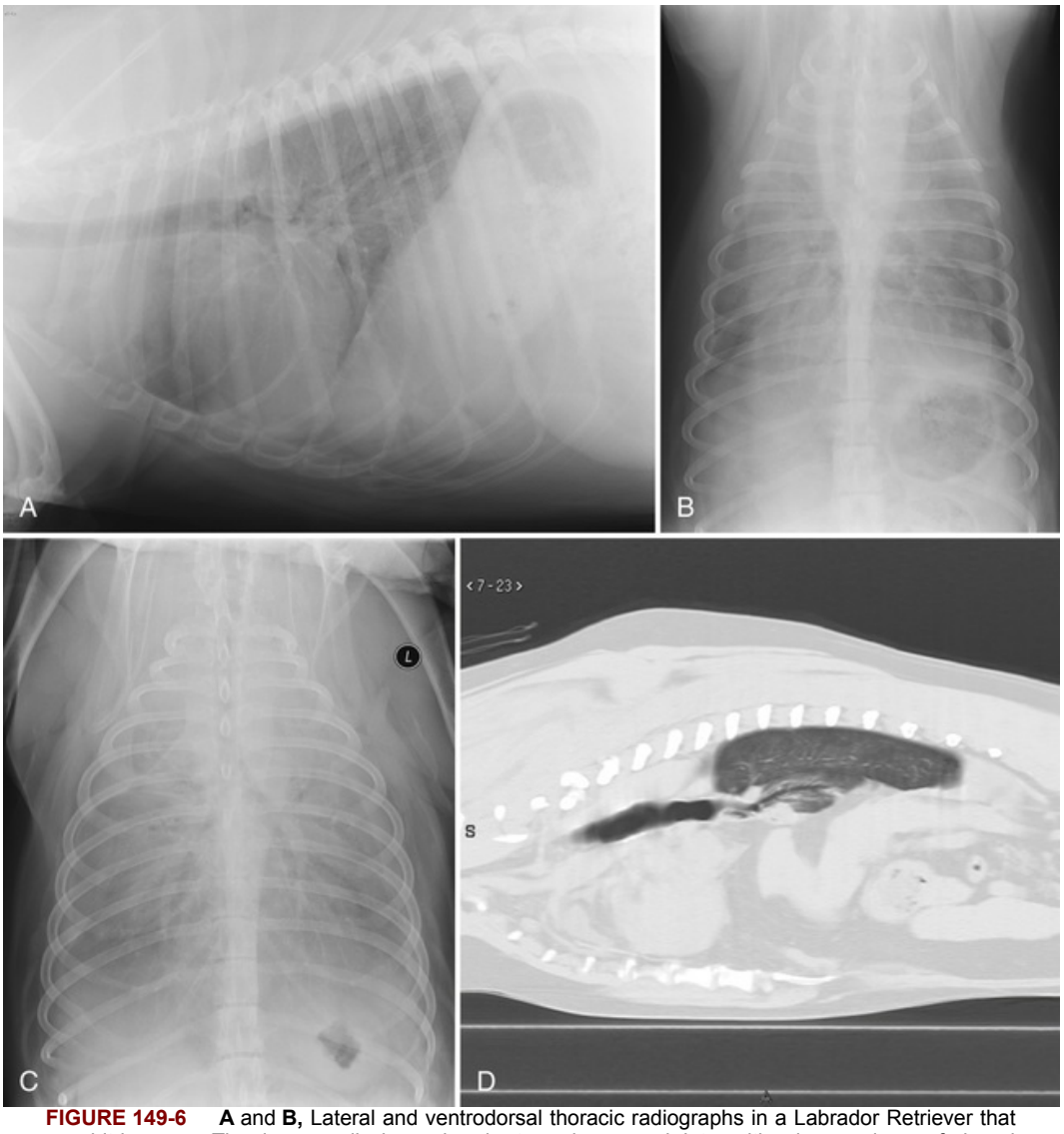


FIGURE 149-6 **A** and **B,** Lateral and ventrodorsal thoracic radiographs in a Labrador Retriever that was hit by a car. The dog was discharged and returned one week later with a large volume of pleural effusion **(C),** and on CT scan, a diaphragmatic hernia was identified **(D).**

In the patient with an acute diaphragmatic hernia, associated injuries can also play a significant role in deciding the time of surgery. Safe anesthetic techniques include rapid intubation and positive pressure ventilation from the time of entry into the abdominal cavity until the integrity of the diaphragm is restored. It can be helpful to tilt the surgery table so the patient's head is raised, to prevent migration of the abdominal contents into the thoracic cavity. As in all trauma patients, all efforts should be made to limit anesthesia and surgery time.

Cardiac Injury

Cardiac arrhythmias are common following trauma in dogs and are generally self-limiting (see ch. 141 and 248). Serum cardiac troponin elevations, consistent with myocardial damage, are common although they are rarely evaluated. Valvular damage or even acquired Gerbode defects have been reported in dogs with blunt trauma.[9,10]

Positive Pressure Ventilation (PPV)

In rare cases, PPV may be used in dogs or cats with pulmonary contusions or flail chest.[11] PPV is useful for eliminating hypoventilation associated with pain or chest wall instability and for improving oxygenation by delivery of positive end-expiratory pressure (PEEP). PEEP will recruit alveolar units, and permit ventilation with lower inspired oxygen concentrations. This can be useful to limit the potential for oxygen toxicosis (see ch. 244). Mechanical ventilation may be considered in patients with evidence of hypoxemia or persistent respiratory distress unresponsive to supplemental oxygen. When mechanically ventilated, dogs with pulmonary contusions, and possibly cats, are prone to the development of ARDS, and consideration should be given for a conservative, low-tidal-volume, low-peak-inspiratory-pressure, moderate-PEEP approach if possible.

Summary

Most dogs and cats with traumatic thoracic injuries recover uneventfully from their injuries with no lasting complications. The standard course is for the patient to look worse for the first 24 hours after presentation and then to make relatively rapid recovery. Successful management includes appropriate identification of injuries and well-timed interventions.

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CHAPTER 150

Urinary Tract Trauma

Amy M. Koenigshof

Urinary tract injury is common following trauma and, in veterinary medicine, frequently is caused by vehicular trauma. However, other types of blunt and penetrating trauma also can lead to injury of the urinary tract.[1] Trauma to the urinary tract can range from contusions and hematuria to full-thickness lacerations or avulsions. Delayed identification of urinary tract trauma can increase morbidity and mortality, so careful evaluation of the urinary system following trauma is essential.[1]

Patient Stabilization

Following trauma, patients often present with injuries to more than one body system. A thorough exam should be performed and the most life-threatening injuries identified and treated first (see ch. 147).

Uroperitoneum

Diagnosing Uroperitoneum

The reported incidence of uroperitoneum following trauma is 0.8-39%.[2-7] In particular, patients with pelvic fracture have a higher incidence of urinary trauma (up to 39%).[2] Uroperitoneum can occur from rupture of the bladder due to increased intravesical pressure, laceration from a fracture, or from a penetrating wound.[1,8] Male dogs are thought to be at an increased risk for rupturing the bladder due to increased intravesical pressure because the longer urethra does not allow for rapid expulsion of urine at the time of trauma.[1,9] Disruption of the proximal urethra or avulsion of the distal ureters also can result in uroperitoneum. Avulsion of the proximal ureters or disruption of the renal pelvis results in uroretroperitoneum if the retroperitoneum is intact; however, if it was disrupted during trauma, these injuries also can cause uroperitoneum.

Uroperitoneum should be suspected in patients presenting with a painful abdomen following trauma. In addition, patients presenting with bradycardia 2-3 days after trauma should be carefully evaluated for hyperkalemia from uroperitoneum. The presence of a palpable bladder or observation of freely voided urine does not rule out uroperitoneum.[1,8,10] If uroperitoneum is suspected, several diagnostic imaging techniques can be considered for initial patient evaluation (Figure 150-1). Abdominal radiographs are useful to evaluate a patient for urinary tract trauma. Loss of detail in the peritoneal cavity or retroperitoneum may be indicative of free fluid in the peritoneal cavity or retroperitoneal space. In addition, avulsion of a kidney can be noted radiographically. Visualization of a urinary bladder on radiographs does not confirm an intact bladder or urinary tract.[1]

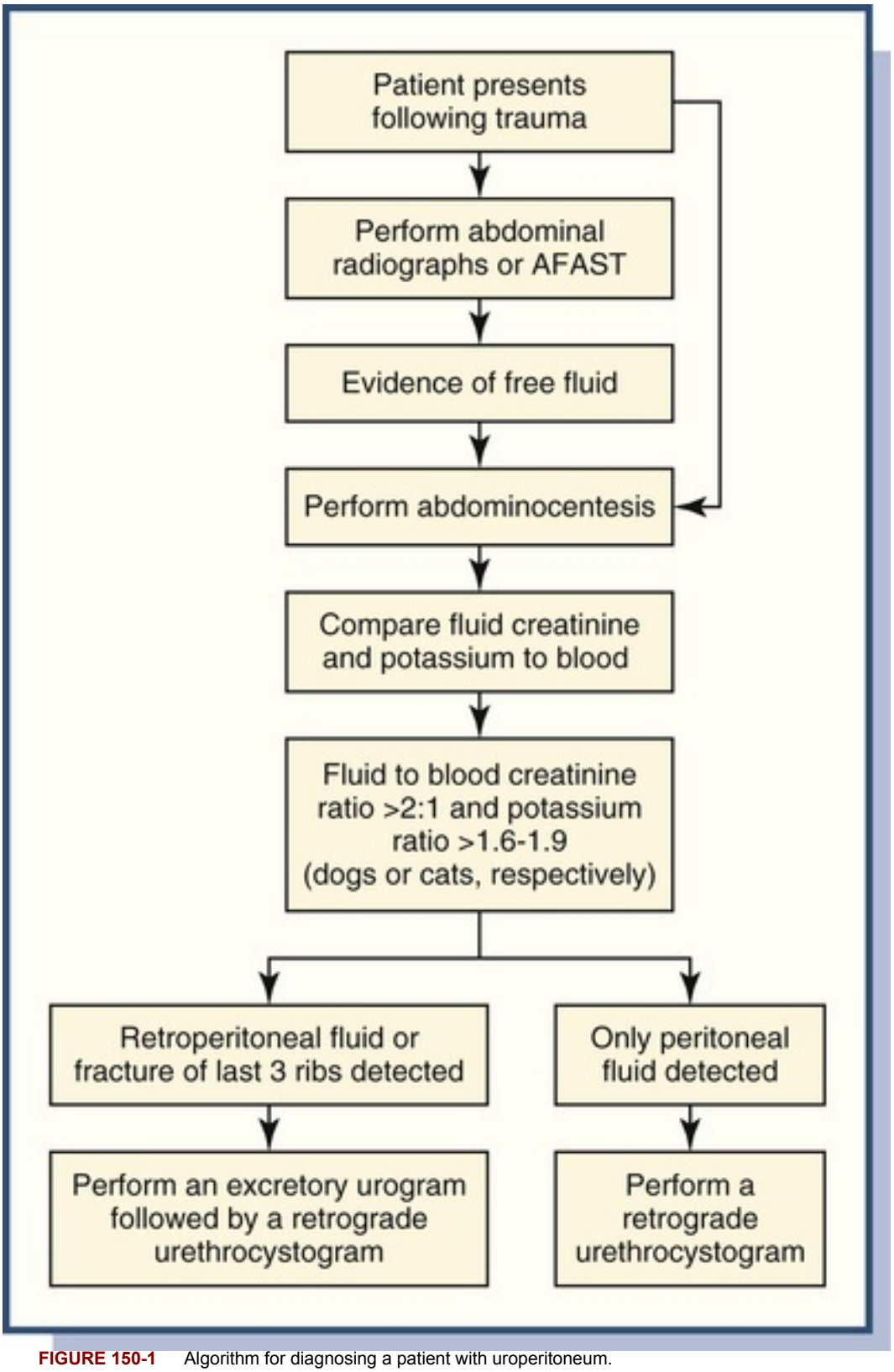

FIGURE 150-1 Algorithm for diagnosing a patient with uroperitoneum.

In addition to radiographs, an abdominal focused assessment with sonography for trauma (AFAST) can be used to identify free fluid in the abdomen or retroperitoneal space (see ch. 143).[5,11] Following the identification of free fluid in the abdomen, ultrasound-guided or blind abdominocentesis can be performed. If ultrasonography is not available, a four quadrant abdominocentesis can be performed to evaluate the patient for free fluid (see ch. 90). Once abdominal effusion has been collected, comparisons between the abdominal

fluid and blood concentrations of creatinine and potassium can be made to help rule in or out uroperitoneum.[8] In cats, abdominal fluid that has at least 1.9 times the concentration of potassium when compared to blood and at least 2 times the concentration of creatinine when compared to blood is consistent with uroperitoneum.[8,12,13] In dogs, abdominal fluid that has at least 1.6 times the concentration of potassium when compared to blood and at least 2 times the concentration of creatinine when compared to blood is consistent with uroperitoneum.[8,12] Urea nitrogen is not as useful for identifying the presence of uroperitoneum because it is a small, non-charged particle that easily moves across membranes.[8]

After confirming the presence of uroperitoneum or uroretroperitoneum, the location of the disruption to the urinary tract should be identified. The most common source of urine leakage is the bladder, followed by the urethra. Ureteral avulsion or rupture of the renal pelvis or parenchyma is uncommon, due to the mobility of the ureters and the protection that the spine, ribs and dorsal body musculature provide to the kidneys.[1] If the patient has uroperitoneum but no evidence of fluid in the retroperitoneal space, a positive contrast retrograde urethrocystogram can be performed to identify the source of the leak. If the patient has either only uroretroperitoneum or fluid in both the peritoneal and retroperitoneal spaces, or if there is fracture of the spine or last 3 ribs, an excretory urogram should be completed first to identify involvement of the kidneys or ureters.[1,8] This should be followed with a positive contrast retrograde urethrocystogram to evaluate for disruption of the urethra or bladder.

Additional Diagnostics for Peritoneal Effusion

Besides measuring creatinine and potassium levels to identify patients with uroperitoneum, additional diagnostics should be considered to further evaluate the fluid.[14] If the fluid is red, a packed cell volume and total protein should be measured to identify concurrent hemorrhage. Cytology should be performed to look for concurrent sepsis, either from a previously existing urinary tract infection or from a concurrent injury (e.g., bowel rupture).[1] Glucose and lactate measurements can also help identify concurrent sepsis. Glucose measurements that are at least 20 mg/dL (1.1 mmol) lower in the abdominal fluid than the blood and lactate measurements that are at least 2 mmol/L higher in the abdominal fluid than in the blood are supportive of, but not diagnostic for, a septic abdomen.[15]

Treatment of Uroperitoneum

Following patient stabilization, the patient's injuries should be prioritized and the most life-threatening injuries should be addressed first. If the patient has significant serum electrolyte derangements from the presence of uroperitoneum, correction of the electrolyte abnormalities should occur prior to anesthesia for any surgical procedures.[16] Life-threatening hyperkalemia leading to bradycardia and electrocardiographic changes such as a prolonged P-R interval, absent P waves, and/or wide bizarre QRS complexes (see ch. 68) should be treated with slow intravenous administration of 10% calcium gluconate (0.5-1.5 mL/kg IV).[1] Administration of crystalloids for volume expansion will help lower potassium concentrations through dilution. Establishing drainage of the urine through temporary placement of a peritoneal drain also can help lower potassium levels (see ch. 90).[8] Peritoneal drainage catheters can be placed using aseptic technique and local anesthesia. Ideally, a dialysis catheter is used for the peritoneal drainage catheter because the presence of multiple fenestrations reduces the chances of obstruction of the catheter. Alternatively, a soft tube drain such as a chest tube (see ch. 100) can be used as a peritoneal drain[17]; additional fenestrations should be created in the tube to reduce the risk of obstruction. A urinary catheter can be placed at the same time to allow drainage of any urine in the bladder (see ch. 105 and 106). If the patient is severely compromised, the peritoneal drainage catheter can be used for peritoneal dialysis until the patient is stable for anesthesia (see ch. 109).[1] Following patient stabilization, treatment is based on the location of urine leakage.

Urinary Bladder Rupture

For patients with urinary bladder rupture, following patient stabilization, an abdominal exploratory laparotomy should be performed and the defect in the bladder identified and corrected.[1,16] Necrotic tissue must be debrided; if a large portion of the bladder needs to be resected, the bladder can be closed over a cystotomy tube.[17]

Urethral Rupture

Many small urethral defects can be managed with placement of a urinary catheter during hospitalization for 7-10 days, while allowing the urethra to heal by second intention.[18,19] A retrograde urethrocystogram should be repeated at this time to ensure the urethra is healed. If a defect is still present, a catheter can be placed again for another 2-3 days followed by repeated imaging. Tears that are close to the bladder or that do not heal by second intention may need to be surgically repaired. Large defects or transection of the urethra requires primary surgical repair.[19]

Ureteral Avulsion or Disruption of the Renal Pelvis

Traumatic ureteral avulsions or disruption of the renal pelvis are uncommon.[10,20] Prompt surgical repair of ureteral avulsions is recommended in human medicine.[1,16] If reimplantation into the bladder or primary repair is not possible (see ch. 124), a ureteronephrectomy could be required.[10]

Subcutaneous Leakage of Urine

Trauma to the distal urethra can result in leakage of urine into the subcutaneous tissue of the hindlimbs and perineal region. This leads to extensive cellulitis and tissue necrosis; fistulas can form if the condition is left untreated.[8] Diagnosis and treatment are the same as described above for urethral trauma leading to uroperitoneum.

Injuries to the Vasculature of the Kidney

Injuries to the vasculature of the kidney can result in life-threatening hemorrhage. Patient stabilization should focus on volume resuscitation and blood transfusions as needed. For patients with ongoing hemorrhage, surgical exploration of the abdomen is warranted and ureteronephrectomy is often performed.[21]

Contusions of the Bladder

The true incidence of bladder contusion is unknown. Hematuria may be the only clinical sign and it may go unnoticed if patients' urinary habits are not closely monitored following trauma.[2] While no treatment is needed specifically for bladder contusions, they should prompt the clinician to look for other more serious concurrent urinary tract injuries.

Herniation of the Bladder

Traumatic body wall defects can lead to herniation of the bladder.[22] These are most commonly caused by bite wounds, and surgical intervention is required.[22] Other rare hernias of the bladder have been described, such as herniation of the bladder through a rectal tear caused by pelvic fractures.[23]

Summary

The prognosis for animals with urinary tract trauma is largely dependent on concurrent injuries.[6] Rapid recognition and treatment of all injuries is key to improving outcome in trauma patients.

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SECTION VIII

Toxicology

OUTLINE

Chapter 151 Toxin Exposure Therapy/Decontamination
Chapter 152 Chemical Toxicoses
Chapter 153 Prescription and Over-the-Counter Drug Toxicoses
Chapter 154 Recreational Drugs Toxicosis
Chapter 155 Plant Intoxications
Chapter 156 Venomous Bites and Stings (Zootoxicoses)

CHAPTER 151

Toxin Exposure Therapy/Decontamination

Camille DeClementi

On presentation, all patients exposed to toxicants should be stabilized prior to attempts at administration of antidotal medications (Table 151-1) or patient decontamination.[1] Stabilization refers to correction of life-threatening disorders that can be hemodynamic (e.g., systemic hypotension [see ch. 127 and 159] or cardiac arrhythmias [see ch. 141 and 248]), respiratory (e.g., respiratory distress [see ch. 28, 131, and 139]), neurologic (e.g., seizures [see ch. 35, 136, and 260]), or immunologic (e.g., anaphylaxis [see ch. 137]). Once the patient is stable, decontamination of the patient should then be considered to prevent systemic absorption of the toxicant. The exposure circumstances, such as species involved, time since exposure, chemical nature of the toxicant, and amount ingested, will determine the appropriate method of patient decontamination. The clinician has multiple options for patient decontamination including dilution, induction of emesis, gastric lavage, and the use of adsorbents and cathartics. In many cases, the best treatment plan will include more than one of these methods.

TABLE 151-1

Antidotal Therapies[10,12]

ANTIDOTAL MEDICATION	TOXICANT INDICATIONS	DOSAGE AND COMMENTS
Acepromazine	Amphetamines	• Dog: 0.02-0.1 mg/kg IV, IM, SC. • Can cause hypotension.
Atipamezole (Antisedan)	Amitraz	• Dog: 50 mcg/kg IM. • Reverses the CNS depression, bradycardia, GI stasis, and hyperglycemia associated with amitraz toxicosis. • In cases of ingestion of an amitraz collar, atipamezole may need to be repeated until the collar is removed from the GI tract.
Atropine	Carbamates, organophosphates (OPs)	• Dog/cat: 0.2 mg/kg, ¼ of the dose given IV and the remainder IM or SC. • Used for countering muscarinic effects (SLUDDE: salivation, lacrimation, urinary incontinence, diarrhea, dyspnea, emesis). • For suspected cases, a test dose of 0.02 mg/kg can be given. If this dose results in mydriasis and tachycardia, the patient has NOT been poisoned by a carbamate or OP.
Cyproheptadine (Periactin)	Selective serotonin reuptake inhibitors (SSRIs) 5-hydroxytryptophan (5-HTP) Baclofen	• Dog: 1.1 mg/kg PO or per rectum up to every 8 hours if effective. • Used for countering serotonin syndrome (hyperthermia, tremors, seizures, ataxia, excitation, depression, hyperesthesia, GI distress).
Digoxin immune fab (Digibind)	Digoxin Cardiac glycoside-containing plants *Bufo* toad	• Dog: 1-2 vials slow IV administration (over 30 minutes). • Patient is expected to improve rapidly within 20-90 minutes. • Monitor for hypokalemia and hypersensitivity.

Ethanol	Ethylene glycol	• Details provided in ch. 152: Box 152-2. • Causes severe respiratory and CNS depression, and metabolic acidosis. • In cats, treatment must be started within 3 hours of exposure or prognosis is grave.
Flumazenil (Romazicon)	Benzodiazepines	• Dog/cat: 0.01-0.02 mg/kg IV. • Has a short half-life so may need to be repeated. • Reserved for cases of severe CNS and respiratory depression.
Fomepizole (4MP, 4-methylpyrrazole)	Ethylene glycol	• Dog: initial dose of 20 mg/kg IV, then subsequent doses at 12 and 24 hours with 15 mg/kg and 36 hours with 5 mg/kg. • Cat: initial dose of 125 mg/kg IV, then subsequent doses at 12, 24 and 36 hours with 31.25 mg/kg. May cause CNS depression. • In cats, treatment must be started within 3 hours of exposure or prognosis is grave.
Intralipid emulsion (ILE)	Bupivacaine Verapamil Propranolol Clomipramine Lidocaine Moxidectin	• Dog/cat: using a 20% solution, initial bolus of 1.5 mL/kg slowly IV, then CRI of 0.25 mL/kg/min IV for 30-60 minutes. • Can be useful in intoxications with other lipid-soluble toxicants including ivermectin, cholecalciferol, amlodipine, baclofen, diltiazem, marijuana, permethrin, bupropion, trazodone, barbiturates, and tricyclic antidepressants.
Methocarbamol (Robaxin)	Permethrin Metaldehyde Strychnine Tremorgenic mycotoxins	• Dog/cat: 55-220 mg/kg slow IV or PO. Total dosage should not exceed 330 mg/kg/day. • Can be useful in other intoxications causing severe tremors.
Naloxone (Narcan)	Opioids	• Dog: 0.04 mg/kg IV, IM, SC. • Cat: 0.02-0.04 mg/kg IV. • Used for reversing respiratory and CNS depression. Does not reverse GI effects.
N-acetylcysteine (NAC)	Acetaminophen	• Dog/cat: use a 5% solution; loading dose of 140 mg/kg PO or IV, then 70 mg/kg PO or IV every 6 hours for 7 treatments. • Can cause oral mucosal ulceration if not diluted to 5% solution.
Pamidronate (Aredia)	Cholecalciferol (vitamin D_3) Vitamin D_3 analogs Calcipotriene (Dovonex)	• Dog: 1.3-2 mg/kg slow IV. • Should not mix with calcium-containing IV fluids. • Most effective if given within 24-36 hours of exposure.
Pralidoxime (2-PAM)	Organophosphates (OPs)	• Dog/cat: 20 mg/kg q 8-12 h. Initial dose IM or slow IV. Subsequent doses given IM or SC. • Used for countering nicotinic effects (tremors, muscle weakness). • Works best when used in combination with atropine.
Vitamin K_1	Anticoagulant rodenticides Warfarin	• Dog/cat: 1.5-2.5 mg/kg PO q 12 h. • Oral route preferred. • Should be given with a fatty meal to enhance absorption.
Yohimbine (Yobine)	Amitraz	• Dog: 0.1 mg/kg IV. • Has a short half-life so may need to be repeated.

CNS, Central nervous system; *CRI*, constant rate infusion; *GI*, gastrointestinal; *IM*, intramuscular; *IV*, intravenous; *PO*, per os.

Dilution using a small amount of water or milk is recommended in cases where the patient has ingested an irritant or corrosive material. A dosage of 2-6 mL/kg is suggested, which for an average-sized cat, would be approximately only 1-2 teaspoons.[1] Giving only a small amount is important, since using excessive amounts could lead to vomiting and re-exposure of the esophagus to the damaging material.[2] Dilution is not appropriate in patients who are at an increased risk for aspiration, including those who are actively seizuring or obtunded.[2] Dilution with dairy products, such as milk, yogurt, and cottage cheese, has been useful in cases of oral irritation following ingestion of plants containing insoluble calcium oxalate crystals (e.g., *Philodendron* species).[3]

Emetics generally empty 40-60% of the stomach contents and are usually most effective if used within 2-3

hours after ingestion of a toxicant.[2,4] If the substance ingested could coalesce to form a bezoar in the stomach, emesis can be effective later than 3 hours after the ingestion. Chocolate and chewable medications are examples of products which may form bezoars.[5] Feeding a small moist meal before inducing vomiting can increase the likelihood of adequate emesis (Video 151-1).

Induction of emesis is *contraindicated* with ingestion of corrosive agents including alkalis and acids, due to the risk of caustic effects on the esophageal and oral mucosa. Emesis is also not recommended after petroleum distillate ingestion due to the risk of aspiration.

The clinician must take into account, when deciding whether to induce emesis, any pre-existing conditions of the patient that can cause vomiting to be hazardous; these include severe cardiac disease (risk of vagally-mediated syncope) or seizure disorder (risk of aspiration). In all instances, the attending veterinarian must carefully weigh the benefits of emesis against the risks. Emesis may not be needed if the animal has already vomited, and it is not appropriate if the animal is already exhibiting clinical signs such as coma, seizures, or recumbency, which make emesis hazardous. Additionally, if the patient has ingested a stimulant and is already agitated, the additional stimulation of vomiting could lead to seizures.[2]

Hydrogen peroxide (3% concentration), apomorphine hydrochloride, and xylazine hydrochloride are commonly used emetics in the veterinary clinical setting. Data from the ASPCA Animal Poison Control Center (APCC) toxicology database indicate that 3% hydrogen peroxide and apomorphine are effective emetics in dogs. Induction of emesis, with either hydrogen peroxide (2.2 mL/kg PO once; can repeat once) or apomorphine (0.03 mg/kg IV; or 0.04 mg/kg IM [least preferred]; or ¼ to ½ tablet crushed and dissolved with a few drops of saline in a syringe [without a needle] and instilled in the conjunctival sac, then rinsed free with saline after vomiting has occurred) was successful in 92% of dogs. Hydrogen peroxide can be repeated if vomiting does not occur within 20 minutes. No significant adverse effects were reported in dogs after such use.[6] Apomorphine is poorly effective as an emetic in cats and using it in cats is controversial. Xylazine (0.44 mg/kg IM [can reverse with yohimbine 0.1 mg/kg slow IV after vomiting is complete]) is an effective emetic in only 42% of cats.[7] Some clinicians are also using dexmedetomidine (40 mcg/kg IM, reversed with 0.4 mg/kg atipamezole IM after vomiting is complete) as an emetic in cats.[7]

Gastric lavage can be considered in cases where emesis is contraindicated, is not possible, or has been unsuccessful (see ch. 112).

Adsorbents may be utilized instead of, or in addition to, emetics and gastric lavage, to prevent systemic absorption of a toxicant. These agents act by adsorbing to a toxicant in the gastrointestinal (GI) tract and facilitating its excretion in the feces.[2] Activated charcoal is the most commonly used adsorbent. In asymptomatic patients, activated charcoal can be given with an oral dosing syringe, or can be offered to the patient in a bowl mixed with a small amount of canned food or chicken broth. In symptomatic patients, activated charcoal is administered via an orogastric tube while the patient is under general anesthesia (see ch. 112).

Repeated doses of activated charcoal should be considered if the ingested toxicant is known to undergo enterohepatic recirculation. In enterohepatic recirculation, the toxicant is carried to the liver by the portal circulation after absorption from the GI tract. Once in the liver, the toxicant enters the bile and is excreted into the GI tract where it is again available for absorption. Examples of toxicants known to undergo this type of recycling include most nonsteroidal anti-inflammatory drugs, marijuana, and digoxin. When repeated doses are indicated, half the original dosage should be given at 4- to 8-hour intervals.[8]

Administration of activated charcoal does carry some risks and it does not bind all compounds equally. Some chemicals that are not bound effectively include alcohols, fertilizers, petroleum distillates, most heavy metals, iodides, nitrates, nitrites, sodium chloride, and chlorate. Activated charcoal should not be given to animals that have ingested caustic materials since it is unlikely to bind these materials, can be additionally irritating to the mucosal surfaces, and can make visualization of oral and esophageal burns difficult.[9]

Activated charcoal administration carries a substantial risk of aspiration. The prognosis is poor for a patient that aspirates activated charcoal; therefore, proper placement of a stomach tube and a protected airway are required in symptomatic patients. Constipation can occur and black bowel movements are expected, making it difficult to determine if melena is present. If the activated charcoal resides within the GI tract for an extended period of time, it can release the toxicant. It is for this reason that activated charcoal is frequently administered with a cathartic. Many commercially-available preparations contain a cathartic like sorbitol.

Hypernatremia is another possible adverse effect of activated charcoal administration. The mechanism for hypernatremia is attributed to a water shift from the intracellular and extracellular spaces into the GI tract as

a result of the osmotic pull of the activated charcoal product.[7] The APCC has received reports of high serum sodium concentrations following activated charcoal administration in dogs. Hypernatremia appears to be reported more often in small dogs receiving multiple doses of activated charcoal, but it has also been reported in large dogs and in cases receiving only a single dose. Furthermore, unlike human case reports, high serum sodium concentrations also have been noted in cases where no cathartic was present in the charcoal.[10] With activated charcoal–associated hypernatremia, the APCC has found that administration of a warm water enema is effective at lowering the serum sodium and controlling the resultant central nervous system (CNS) effects.[10]

Cathartics enhance elimination of substances, including administered activated charcoal, by promoting their movement through the GI tract. Activated charcoal only binds to toxicants by weak chemical forces, so without cathartics, the bound toxicant can eventually be released and reabsorbed.[2] When used with activated charcoal, the cathartic is given immediately following, or mixed with, the charcoal. Cathartics are *contraindicated* if the animal is dehydrated, has diarrhea, if ileus is present, or if intestinal obstruction or perforation is possible.[8]

There are bulk, osmotic, and lubricant cathartics. The most commonly used bulk cathartic is psyllium hydrophilic mucilloid (e.g., Metamucil). Another bulking cathartic that can be used in dogs and cats is unspiced canned pumpkin. Osmotic cathartics have limited absorption from the GI tract so they are able to draw water into the GI lumen, thereby increasing the fluid volume and stimulating motility to hasten expulsion in the feces. Sorbitol is the most commonly used osmotic cathartic; it is the cathartic of choice and frequently is combined with activated charcoal in commercially prepared charcoal products. Of the lubricant cathartics, mineral oil is the most often used. Mineral oil is not recommended following activated charcoal administration as the mineral oil can render the charcoal less effective.[9,11] Since all cathartics alter the water balance in the GI tract, serum electrolyte abnormalities, especially hypernatremia, are a potential risk when using them. Hydration status should be monitored frequently and fluids administered, intravenously or via an enema, as needed.

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CHAPTER 152

Chemical Toxicoses

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According to the ASPCA Animal Poison Control Center (APCC), approximately 150,000 animals are exposed to a variety of toxicants in the United States each year. Approximately 40% of the calls to the ASPCA APCC[a] comprise exposures to human and veterinary medications, with the remaining exposures occurring secondary to a variety of toxic foods, insecticides, rodenticides, plants, household products, herbicides, cleaning products, lawn and garden products, and miscellaneous toxicants. Ch. 13 presents ways of differentiating intoxications from nontoxicologic illness when a history is lacking. In this chapter, a review of some of the most common—or most deadly—chemical toxicants will be discussed.

Rodenticides

One of the top 10 toxicants affecting dogs are rodenticides. Due to U.S. Environmental Protection Agency (EPA) regulations that were mandated in 2011, second-generation anticoagulant rodenticides (ACR) such as brodifacoum and bromadiolone are being removed from the U.S. market. As a result, antidotal therapy (e.g., vitamin K_1) will be less frequently required; instead, the use of non-anticoagulant rodenticides, notably bromethalin and cholecalciferol, have become more prominent as active ingredients.

Bromethalin

Bromethalin, a neurotoxic rodenticide, works by uncoupling oxidative phosphorylation in the brain and liver mitochondria.[1] This results in decreased adenosine triphosphate (ATP) production, which affects cellular sodium and potassium pumps; as a result, lipid peroxidation occurs, resulting in sodium accumulation within the cell.[1] Edema of the central nervous system (CNS) can result.[1] Bromethalin is *not* an anticoagulant rodenticide and should *not* be treated with vitamin K_1 as an antidote. It is sold under several popular brand names: Assault, Tomcat Mole Killer, Talpirid, Real Kill, Clout, Fastrac, Vengeance, etc.

Bromethalin has a narrow margin of safety. In dogs, the LD_{50} of bromethalin is 2.38-3.65 mg/kg, with a minimum lethal dosage being 2.5 mg/kg (corresponding to 120 grams [4 ounces] of typical 0.01% bait consumed by a 5 kg dog).[1] A typical, otherwise healthy 5 kg dog would only need to ingest approximately 12 grams (or 0.4 ounces) to develop clinical signs. Cats are more sensitive to the effects of bromethalin, and the LD_{50} is markedly lower (0.54 mg/kg).[1] Clinical signs are dosage-dependent, and the onset of clinical signs depends on the amount ingested. Typically, with acute ingestion, signs can be seen within 2-24 hours.[1] Clinical signs of CNS stimulation or depression, abnormal behavior, ataxia, hyperesthesia, seizures, and coma can be seen.[1] Other common signs include paresis, hindlimb paralysis, anisocoria, nystagmus, changes in the pupillary light reflex, and tremors.[1] Treatment includes early decontamination of the patient, prevention of cerebral edema, and supportive care. With recent ingestion in an asymptomatic patient, the use of appropriate decontamination (e.g., emesis induction, gastric lavage [Video 152-1], activated charcoal; see ch. 151) is warranted. As bromethalin undergoes enterohepatic recirculation, the use of multiple oral doses of activated charcoal (without a cathartic) is recommended (e.g., q 6 h for 24 h). Patients should be monitored for signs of neurotoxicosis. The use of intravenous (IV) fluid therapy (see ch. 129), oxygen support (see ch. 131), head elevation in recumbent patients, mannitol (to decrease cerebral edema; see ch. 148), anticonvulsant therapy (see ch. 35 and 136), and thermoregulation is warranted, as needed. The use of corticosteroids to decrease intracranial pressure is no longer recommended; rather, mannitol is preferred. With bromethalin toxicosis, the prognosis varies depending on the amount ingested and the severity of clinical signs. In general, the prognosis is fair to excellent with appropriate decontamination of the patient and treatment *prior* to

development of clinical signs. With persistent seizures or paralytic syndrome, the prognosis is poorer.

Phosphides

Phosphide rodenticides result in the production of phosphine gas. When zinc phosphide combines with gastric acid or moisture (or the presence of food), liberated phosphine gas is absorbed rapidly across the gastric mucosa and is distributed systemically, where it exerts its toxic effect. Phosphine gas is considered a corrosive and a direct irritant to the gastrointestinal (GI) tract. While this rodenticide has not grown in popularity compared to others (e.g., ACR, bromethalin, etc.), veterinarians must be aware of this rodenticide as it carries a public health risk to pet owners and veterinary staff.

Phosphide rodenticides have been used since the 1930s and are still available on the market.[3] Aluminum phosphide, a pelleted product, is used as a fumigant in grain storage. Zinc phosphide, which is more readily used, is labeled to kill mice, rats, squirrels, voles, nutria, muskrats, gophers and other vermin.[3] Zinc phosphide is available as a 2-10% concentration, and comes as powder, paste, pellet or tablet formulations.[3] Commercially available zinc phosphide products are sold under popular names such as Sweeney's Poison Peanut Mole, Gopha-Rid, Zinc-Tox, ZP, Arrex, Gopha-Rid, Gopher Bait II, etc.[2] Formulations of phosphides have a malodorous, unique odor similar to rotten garlic, fish or acetylene.[2]

The toxic dosage of zinc phosphide in dogs is approximately 20-40 mg/kg, but up to 300 mg/kg on empty stomachs.[3] In a patient suspected of zinc phosphide toxicosis, the administration of food (e.g., bread, milk, etc.) is contraindicated, as it triggers gastric acid secretion, promoting hydrolysis and further production of phosphine gas.[3] With zinc phosphide toxicosis, clinical signs can be seen within 15 minutes to 4 hours of ingestion; while rare, death has been reported within 3-48 hours.[3] Clinical signs include severe GI (e.g., vomiting, bloat, abdominal pain, hematemesis, melena), CNS (e.g., tremor, seizures, death), and rarely, cardiopulmonary signs (e.g., pulmonary edema, tachypnea, pleural effusion) or other organ dysfunction.[3]

Zinc phosphide carries a public health risk. Emesis—whether intentionally induced or occurring due to clinical signs—can result in secondary exposure of phosphine gas to the pet owner or the veterinary professional. In humans, clinical signs of nausea and difficulty breathing have been reported. To minimize these risks, emesis induction should always be performed in a well-ventilated area (e.g., opening the car window if the patient vomits or inducing emesis outside). Pet owners should be appropriately educated on the risks of toxic gas exposure to themselves. Pet owners should be informed *not* to feed their pet to prevent further production of phosphine gas. In addition, the administration of an antacid (e.g., aluminum hydroxide, milk of magnesia) prior to emesis induction or veterinary attention can help decrease the production of phosphine gas. With recent ingestion in an asymptomatic patient, the use of emesis induction (following antacid administration) and one dose of activated charcoal with a cathartic is warranted to minimize toxic effects of zinc phosphide. Supportive care, including antiemetic therapy, IV fluid therapy, and gastric protectants, is warranted. With treatment, the prognosis is excellent with supportive care.[2]

Cholecalciferol

Cholecalciferol, the chemical name for vitamin D_3, is one of the most deadly rodenticides to pets. Ingestion of toxic levels of cholecalciferol can result in severe hypercalcemia and hyperphosphatemia, with secondary acute kidney injury (AKI) developing from dystrophic mineralization of soft tissue, especially the kidneys (see ch. 322). Other common sources of vitamin D_3 include over-the-counter (OTC) or prescription vitamins (typically found in a calcium/vitamin D_3 combination) and psoriasis creams (in the form of calcipotriene). Cholecalciferol-containing rodenticides have a very narrow margin of safety, and only a minute amount of rodenticide needs to be ingested before clinical toxicosis occurs. In dogs, the LD_{50} is 85 mg/kg (based on the rodenticide concentration of 0.075%)[4]; however, dosages as low as >0.1-0.5 mg/kg can result in clinical signs and hypercalcemia, respectively (i.e., a 30 kg dog would only need to ingest approximately 1 ounce [30 grams] to develop clinical signs of toxicosis).[4]

Typically, clinical signs of toxicosis do not develop for 1-3 days, until the patient has already developed overt manifestations of AKI.[4] Azotemia can develop as early as 12-36 hours following toxic ingestion. Clinical signs and clinicopathologic findings (see ch. 69) include polyuria and polydipsia, weakness, lethargy, anorexia, vomiting, generalized malaise, uremic halitosis, dehydration, hypercalcemia, hyperphosphatemia, azotemia, melena, hemorrhagic diarrhea, weight loss, and death.[4]

With cholecalciferol toxicosis, intensive treatment is imperative due to the narrow margin of safety. Treatment should include thorough decontamination (e.g., emesis induction, gastric lavage, charcoal administration; see ch. 112 and 151). As cholecalciferol undergoes enterohepatic recirculation, the administration of multiple oral doses of activated charcoal (without a cathartic) is warranted (e.g., q 6 h × 24 h). Additional treatment includes the aggressive use of IV 0.9% saline fluid diuresis to promote calciuresis, serum calcium concentration monitoring, GI support (e.g., antiemetics, H2 blockers, sucralfate, phosphate binders, etc.), and the use of medications to increase calciuresis (e.g., prednisone, furosemide) and prevent hypercalcemia (e.g., pamidronate, calcitonin). Treatment often is expensive, and requires hospitalization for an extended period of time (e.g., 2-7 days). In hypercalcemic patients, oral therapy (e.g., furosemide, prednisone) often needs to be continued for several weeks following discharge from the hospital. Frequent monitoring of renal parameters and electrolytes is imperative. Serum calcium, phosphorus, blood urea nitrogen, creatinine, and ionized calcium should be evaluated every 12-24 hours during hospitalization, and then every 2-3 days thereafter for the next 2-4 weeks. This will allow the clinician to titrate drug therapy judiciously, and to ensure that the patient does not continue to develop hypercalcemia or azotemia. Even with intensive decontamination and therapy, chronic kidney disease (CKD) can be a secondary sequela. The prognosis for this rodenticide is poor once clinical signs and azotemia develop due to the risk of CKD.

Anticoagulants

First- and second-generation ACR inhibit vitamin K epoxide reductase, resulting in inactivation of clotting factors II, VII, IX, and X. First-generation rodenticides (e.g., warfarin, pindone)[5] initially were replaced by more potent, longer-lasting second-generation ACR (e.g., brodifacoum, bromadiolone, diphacinone, chlorophacinone, etc.).[5] However, the removal of second-generation ACR from the U.S. market was mandated by the U.S. EPA in 2011. While this will take several years to enact, veterinarians will be seeing fewer ACR cases as a result.

It is important to note that the margin of safety and LD_{50} vary between each ACR; some have very narrow margins of safety (e.g., brodifacoum), while some have very wide margins of safety (e.g., bromadiolone). When in doubt, the toxic dosage should be calculated, or the rodenticide company directly contacted (which offer a free, 24/7 medical support line for assistance) to determine if a toxic dose has been ingested. Likewise, the ASPCA APCC can be consulted for life-saving assistance. Finally, it is worth keeping in mind that species differences exist; cats are much more resistant to the effects of ACR compared to dogs, and rarely develop toxicosis from ACR.

	CANINE[5] LD_{50}	FELINE[5] LD_{50}
Difethialone:	4 mg/kg	>16 mg/kg
Brodifacoum:	0.25-2.5 mg/kg	25 mg/kg
Bromadiolone:	11-20 mg/kg	>25 mg/kg
Diphacinone:	3-7.5 mg/kg	>15 mg/kg

When a toxic ingestion of ACR has occurred, prolongation in coagulation factors (prothrombin [PT] or activated partial thromboplastin time [aPTT]) is not observed or measurable for 36-48 hours, based on the half-life of factor VII. Clinical signs typically do not develop for 3-5 days. Clinical signs are due to clotting factor depletion, resulting in generalized hemorrhage secondary to hypocoaguability. The most common clinical signs include lethargy, exercise intolerance, inappetence, pallor, dyspnea, coughing, and hemoptysis. Hemoabdomen, hemothorax, and pericardial effusion also can occur. Rarer clinical signs include gingival bleeding, epistaxis, ecchymoses, petechiae, hematuria, bleeding into the subcutaneous space or joint space, or melena.[5]

Optimal management depends on clinician preference and on the pet owner's commitment to follow up. Ideally, with recent ingestion, the patient should be decontaminated, if appropriate, and have a baseline PT measured at 36-48 hours post-ingestion. If PT is prolonged at that time, initiation of vitamin K_1 2.5-5 mg/kg PO q 24h for 7 (first generation) to 30 (second generation) days is warranted, with rechecking of PT 2-3 days after discontinuation of vitamin K_1. When client compliance is of concern, routine administration of vitamin K_1 therapy for 30 days is warranted. For patients with clinical bleeding or coagulopathy, treatment should include vitamin K_1 therapy; plasma transfusions; intensive care; oxygen therapy; and monitoring of PT 2-3

days after discontinuation of therapy with vitamin K_1.

Veterinary professionals often make errors when it comes to the medical management of ACR intoxication cases. While it is often appropriate to decontaminate a patient with emesis induction and activated charcoal administration, with non-toxic ingestions (based on the LD_{10}), this is often unnecessary (unless the patient is neonatal, geriatric, has an underlying hepatopathy, or has previously ingested an ACR). Also, the administration of a "one-time," parenteral injection of vitamin K_1 at the time of decontamination is unnecessary and potentially detrimental. As factor VII has the shortest half-life, PT will be the first blood test to be prolonged with ACR ingestion, 36-48 hours post-ingestion. Testing *prior* to this time is typically unnecessary (unless the patient has been chronically ingesting an ACR over several days). By administering a "one-time shot" of vitamin K_1, the clinician can cause the patient's PT to be briefly normal at 36-48 hours, followed by coagulopathy and clinical bleeding days later (3-5 days, instead of 2 days).

Insecticides

Certain insecticides carry a wide margin of safety (e.g., pyrethrins, pyrethroids), while those with a narrower margin of safety (e.g., carbamates, organophosphates) have been predominantly removed from the market due to the severity of clinical signs seen with accidental or intentional poisonings.

Pyrethrins and Pyrethroids

Pyrethrins and their synthetic derivative, pyrethroids, commonly are found in household insect sprays and insecticides (e.g., permethrin, cypermethrin, cyphenothrin, etc.). Due to cats' altered liver glucuronidation metabolism, they are markedly more sensitive to pyrethrins than are dogs. While a precise toxic dosage for cats is not well established, products containing >5-10% concentration of pyrethrins can lead to systemic toxicosis. Products such as household insect sprays, topical flea sprays, and shampoos typically contain <1% of pyrethrins; toxicosis due to exposure to these diluted products is unlikely. However, higher concentration products such as canine spot-on pyrethrin/pyrethroid-based insecticides (which typically contain a 40-60% pyrethrin concentration) are extremely toxic to cats. Clinical signs of pyrethrin toxicosis in cats include GI (e.g., hypersalivation, vomiting, nausea), CNS (e.g., disorientation, weakness, hyperexcitability, tremors, seizures) and respiratory signs (e.g., tachypnea, dyspnea).[6]

Treatment in cats with systemic signs of pyrethrin toxicosis include dermal decontamination with a liquid, degreasing dish soap (e.g., Dawn, Palmolive) once the patient has been stabilized. Tremors should be treated with parenterally administered methocarbamol (e.g., 22-220 mg/kg, IV PRN to effect), a centrally acting muscle relaxant.[6] While oral or rectal methocarbamol administration can be considered, it has a very slow onset of action via these routes. Tremors generally are less responsive to benzodiazepines (e.g., diazepam) compared to methocarbamol. Seizures can be controlled with anticonvulsants or general gas anesthesia (see ch. 136). Supportive care including fluid therapy, thermoregulation, and blood glucose monitoring are imperative. Signs can persist for 1-3 days, depending on the patient.[6] The prognosis is excellent with intensive dermal decontamination and treatment.

In dogs, systemic toxicosis or allergic sensitivity is rare; rather, clinical signs of paresthesia can be seen at the area of application. Paresthesia, which is characterized by a stinging or tingling sensation to the skin, can cause secondary pruritus or trauma to the site. The use of dermal decontamination and topical vitamin E ointment are recommended; antihistamines and corticosteroids generally are not of benefit.

Carbamates and Organophosphates

The use of carbamates and organophosphates (OPs) as insecticides has fallen out of favor, due to the narrow margin of safety and severity of clinical signs with intoxications. The EPA has removed many of the more dangerous insecticides from the market, such that pyrethrins and pyrethroids have grown in popularity concomitantly. However, some older products (particularly rose or plant fertilizer/insecticide combination products) may still contain dangerous carbamates or OPs. Carbamates and OPs competitively inhibit acetylcholinesterase and pseudocholinesterase, resulting in excess acetylcholine accumulation and hence, clinical "SLUDGE" signs (e.g., salivation, lacrimation, urination, defecation, GI upset, emesis).[6]

Different carbamate and OP preparations can have varying levels of toxicity, depending on the active ingredient. Clinical signs include severe GI (e.g., hypersalivation, vomiting, diarrhea), cardiovascular (e.g., tachycardia, bradycardia, pallor, shock), CNS (e.g., agitation, sedation, mydriasis or miosis, tremors, seizures,

coma), and respiratory signs (e.g., tachypnea, dyspnea, cyanosis—secondary to voluminous bronchial secretions or secondary aspiration pneumonia). Intensive decontamination (e.g., gastric lavage with an inflated endotracheal tube in place [see Video 152-1; ch. 112], administration of activated charcoal with a cathartic), IV fluid therapy, antiemetics (e.g., maropitant), muscle relaxants (e.g., methocarbamol), anticonvulsants (e.g., phenobarbital, diazepam, levetiracetam), thermoregulation, electrocardiogram and blood pressure monitoring, and supportive care are indicated. Most importantly, proactive use of the antidotes atropine or 2-PAM (which is rarely available) is warranted (see ch. 151).[6] The anticholinergic effect of atropine counters the direct clinical signs of this toxicosis, and typically high dosages are warranted (e.g., 0.1-0.5 mg/kg, IV, IM PRN).

Household Products

Many household products are ingested accidentally by dogs and less commonly, by cats (Box 152-1). In general, the prognosis for household product toxicosis is good to excellent with appropriate decontamination of the patient and supportive care.

Box 152-1

Common Household Products Affecting Dogs and Cats

Alpha Lipoic Acid (ALA)

Commonly used as a human supplement for diabetes mellitus. Narrow margin of safety in dogs and cats; cats are thought to be more sensitive. Toxic dosage warranting decontamination: >5 mg/kg (cats), >50 mg/kg (dogs). Clinical signs: GI (e.g., hypersalivation, vomiting), CNS (e.g., ataxia, tremors, seizures, etc.), AKI and hepatotoxicosis can be seen. Treatment includes dextrose supplementation, blood glucose monitoring, fluid therapy, antiemetics, anticonvulsants, hepatoprotectants (e.g., SAMe, n-acetylcysteine, etc.).

Silica Gel Packs

Rarely result in toxicosis due to wide margin of safety. Rare risk of constipation or foreign body obstruction with massive ingestions in small-size patients.

Food Oxidizer Packs (Commonly Found in Food Product Bags or Containers)

Rarely result in toxicosis. These packages contain iron, where the powder is often black or brown in color and magnetized. Rare risks of iron toxicosis if ingestion by small-size patients. Treatment for iron toxicosis includes antacid therapy (e.g., milk of magnesia), supportive care, monitoring blood iron levels, and potentially chelation (in severe cases). Activated charcoal is not warranted (does not bind reliably to heavy metals).

Amitraz

A formamidine pesticide found in tick collars. Amitraz is a monoamine oxidase inhibitor and an alpha-adrenergic agonist. Toxicosis occurs when the collar is accidentally ingested, resulting in GI absorption. Lethal dosage is 100 mg/kg (dogs, PO), although toxic doses as low as 10-20 mg/kg have been reported. Clinical signs include CNS (e.g., ataxia, sedation, mydriasis, hypothermia, coma), cardiac (e.g., bradycardia, tachycardia), and GI (e.g., vomiting, diarrhea) signs. Treatment includes appropriate decontamination of the patient, removal of the collar from the GI tract (e.g., via endoscopy), alpha-2-antagonists (e.g., yohimbine or atipamezole), and supportive care.

Insect Bait Stations

Typically contain abamectin, hydramethylnon, or fipronil. Rarely toxic due to low-concentration of active ingredients. Rarely, plastic container can result in foreign body obstruction. Treatment is rarely indicated unless the dog has the ABCB1 gene mutation (MDR-1 polymorphism).

Batteries

Several types of batteries: acid dry cell, alkaline dry cell, disk-shaped, lithium. Corrosive injury or current-induced injury potentially can result in GI perforation. Clinical signs of dysphagia, anorexia, tachypnea, abdominal pain, and fever can be seen. Treatment should be aimed at radiographic

confirmation of ingestion, removal (e.g., endoscopy, surgery), antacids, and supportive care.

Diethylene Glycol (DEG)

Used as an industrial solvent for canned cooking fuels, hydraulic fluid, lubrication, and brake fluid. With DEG toxicosis, calcium oxalate crystalluria is *not* observed; however, DEG can result in severe kidney injury. Clinical signs of CNS (e.g., depression, coma), GI (e.g., vomiting), renal (e.g., azotemia) dysfunction can be seen. Treatment and prognosis are similar to those of ethylene glycol.

Paintballs

Paintballs contain polyethylene glycol, sorbitol, glycerin, gelatin, and other ingredients that can result in free water loss and secondary, severe hypernatremia. GI (e.g., vomiting, diarrhea) and CNS signs can be seen (secondary to hypernatremia), including ataxia, tremors, head pressing, seizures, etc. Treatment is aimed at rapidly reducing blood sodium levels with IV fluids; antiemetics, electrolyte monitoring, anticonvulsants, and supportive care also are indicated. The use of activated charcoal is contraindicated with this toxicant.

Tea Tree *(Melaleuca)* Oil

Toxicosis has been reported in dogs and cats when concentrated (100%) oil is used as a holistic remedy. Clinical signs of CNS depression, weakness, ataxia, hypothermia, and muscle tremors can be seen within 1-2 hours after application. Rarely, coma, increased serum liver enzyme activities, dermal or oral irritation, or cardiorespiratory effects can occur (more often in cats). Treatment is aimed at dermal and oral decontamination (e.g., multiple doses of activated charcoal), fluid support, thermoregulation, clinicopathologic monitoring, and supportive care.

Liquid Potpourri

Contains essential oils. Only noted to result in toxicosis in cats, not dogs. Due to their altered glucuronidation, cats are very sensitive to cationic detergents and essential oils. Can result in severe chemical burns in the mouth, along with dermal and ocular irritation. Rarely, CNS depression, pulmonary edema, seizures, and hepatopathy can be seen in cats. Treatment includes oral and dermal decontamination, analgesics, antacids, fluid therapy, clinicopathologic monitoring, and supportive care.

Metaldehyde

Commonly-used pesticide for controlling snails and slugs; often used in the northwestern United States. Less commonly seen as a toxicant in the past few years due to replacement with the safer ingredient, iron phosphate. Metaldehyde toxicosis can result in GI (e.g., vomiting, diarrhea), CNS (e.g., tremors, seizures, secondary hyperthermia), and miscellaneous signs (e.g., DIC, hepatopathy). Treatment aimed at decontamination (e.g., gastric lavage, activated charcoal administration), antiemetic therapy, muscle relaxants, anticonvulsants, muscle relaxants, thermoregulation and supportive care.

Plant Food and Fertilizers

Wide margin of safety; contain natural elements (e.g., nitrogen, phosphorus, potassium). Clinical signs of GI disturbance with direct ingestions from the bag in moderate to large amounts. Treatment includes antiemetic therapy, fluid therapy, and supportive care.

Organic Meal Fertilizers

By-products from the meatpacking industry used as a soil amendment, typically made of bone, blood, feather, fish, etc. Very palatable to dogs. Clinical manifestations include GI signs (e.g., hypersalivation, abdominal distension, vomiting, bloody diarrhea), metabolic (e.g., pancreatitis), and rare risk of foreign body obstruction. Treatment is aimed at emesis induction, fluid therapy, antiemetics, bland diet, and supportive care.

Compost (e.g., moldy food)

Presence of tremorgenic mycotoxins (e.g., penitrem A and roquefortine), which interfere with the release of neurotransmitter amino acids. Clinical signs can be seen within 2-4 hours of ingestion and include GI (e.g., hypersalivation, vomiting, diarrhea, distended abdomen) and CNS signs (e.g., agitation, hyperesthesia, ataxia, muscle tremors, seizures, and secondary hyperthermia). Treatment should be aimed at decontamination of the patient, muscle relaxants, antiemetics, anticonvulsants, fluid therapy, thermoregulation, and supportive care.

Cocoa Mulch

Rarely seen as a toxicant, but can result in secondary theobromine toxicosis. Clinical signs of methylxanthine toxicosis can be seen (e.g., GI, cardiac, CNS). Treatment is aimed at decontamination (e.g., emesis induction, charcoal administration), fluid therapy, anti-emetics, sedation, anxiolytics, beta-blocker therapy, anticonvulsants, and supportive care.

De-Icing Salts

High concentrations of salt mixtures (e.g., sodium chloride, calcium chloride, potassium chloride, magnesium chloride hexahydrate, etc.), which is mildly toxic to dogs when exposed. Typical toxicosis due to dermal exposure (e.g., licking fur off snow-covered sidewalk). Rarely, more severe clinical signs can be seen if directly ingested from the bag. Clinical signs include GI (e.g., vomiting, diarrhea) signs; rarely, electrolyte abnormalities can be seen (e.g., hypernatremia), typically associated with large ingestions. Treatment includes IV fluid therapy, electrolyte monitoring, antiemetics, and supportive care. The use of charcoal is not recommended with salt toxicosis.

AKI, Acute kidney injury; *CNS,* central nervous system; *DIC,* disseminated intravascular coagulation; *GI,* gastrointestinal.

Household Cleaners

Most household surface cleaners are generally benign, and when ingested directly from the bottle, may result in minor GI signs. However, certain concentrated cleaners can be highly toxic or corrosive. Household bleach, which typically contains 3-6% sodium hypochlorite, is a GI irritant, but "ultra" bleach, which typically contains a 5-10% sodium hypochlorite and 0.2-2% sodium hydroxide, can be corrosive, resulting in severe esophageal or upper GI damage. Concentrated lye products, toilet bowl cleaners, and oven cleaners also are corrosive, and immediate flushing of the mouth with tap water for 10-15 minutes should be performed prior to the veterinary visit to minimize tissue injury. On presentation to a veterinary clinic, additional oral flushing should be continued. The use of antacids, a bland soft diet, and analgesics (e.g., tramadol) may be warranted.

Detergents

Most detergents result in direct irritation to the oropharynx, esophagus and GI tract, particularly in cats. Ingestion of hand soaps, shampoos, cleaners, or laundry products can cause hypersalivation, vomiting, anorexia, and oral ulceration. Treatment is based on supportive care (e.g., flushing mouth out, antacid therapy, nutritional support, etc.).

Xylitol

Xylitol is a natural sweetener found in small quantities in certain fruit. Xylitol has gained popularity because it is sugar-free, and it is often found in diabetic snacks, foods, baked foods, mouthwashes, toothpastes, chewing gum, mints, candies, and chewable multivitamins.[7] Sugarless products, particularly those with xylitol listed within the first 3 to 5 ingredients, can result in severe toxicosis within 15-30 minutes of ingestion. Ingestion of xylitol results in an insulin spike in non-primate species, resulting in severe hypoglycemia. Many pieces of candy and gum (e.g., Orbit, Trident, Ice Breakers) contain xylitol ranging in amounts, on average, from 2 mg to 1 g/piece (with a typical piece containing 120-170 mg). Unfortunately, xylitol content is considered proprietary information by some companies, and sources or amounts are not disclosed for all products. With xylitol toxicosis, it is imperative to calculate whether a toxic dose has been ingested whenever possible. Doses >0.1 g/kg are considered toxic and result in profound, sudden hypoglycemia from stimulation of insulin secretion.[7] Higher dosages (>0.5 g/kg) of xylitol have been associated with acute hepatic necrosis.[7] Clinical signs of xylitol toxicosis include lethargy, weakness, vomiting, collapse, anorexia, generalized malaise, tremors, and seizures (from hypoglycemia).[7] When hepatotoxic doses are ingested, clinical signs and clinicopathologic findings can include icterus, diarrhea, melena, hypoglycemia, increased liver enzymes, hypoalbuminemia, hypocholesterolemia, and decreased blood urea nitrogen.

When a patient is presented after ingesting a toxic amount of xylitol, the clinician should measure a blood glucose concentration immediately upon presentation; if the patient is hypoglycemic, a bolus of 1 mL/kg of 50% dextrose, diluted with 0.9% NaCl (in a 1 : 3 ratio of dextrose : NaCl) should be given IV over 1-2 minutes. Emesis induction should not be performed until the patient is euglycemic. Activated charcoal does *not*

reliably bind well to xylitol, and its administration is not routinely recommended for xylitol toxicosis. Hypoglycemic patients should be hospitalized for IV fluid therapy [supplemented with dextrose (2.5-5%, CRI, IV)] for approximately 12-24 hours, and blood glucose concentrations should be measured every 1-4 hours. For patients ingesting a hepatotoxic amount of xylitol, the use of hepatoprotectants (e.g., SAMe, n-acetylcysteine), antiemetics, and supportive care (including frequent liver enzyme monitoring) are warranted (see ch. 286).

Garage Toxicants

Hydrocarbons

Hydrocarbons consist of chemicals containing a hydrogen and carbon group as their main constituents. Examples include liquid fuels such as kerosene, engine oil, tiki-torch fuels, gasoline, diesel fuels, paint solvents, wood stains, wood strippers, liquid lighter fluids, and asphalt/roofing tar. These often are referred to as "petroleum distillates" based on their viscosity, carbon chain length, and lipid solubility. It is *contraindicated* to induce emesis after hydrocarbon ingestion due to the risks of aspiration pneumonia; due to the low viscosity of hydrocarbons, these compounds are more easily aspirated, resulting in respiratory injury and secondary infection. In general, hydrocarbons are GI tract irritants, but also can be irritants to the respiratory system (if inhaled), eyes, and skin. Clinical signs can include nausea/vomiting, tachypnea, and dermal or ophthalmic irritation. Typically, GI irritation is self-limiting. Patients should be treated with antiemetic therapy (e.g., maropitant), fluid therapy (e.g., SC or IV), fasting (no food per os), and a bland diet. Patients demonstrating any coughing, retching, or tachypnea post-ingestion should have thoracic radiographs performed to rule out aspiration pneumonia, for which treatment is supportive (e.g., oxygen therapy, fluid therapy, appropriate broad-spectrum antibiotic therapy, nebulization and coupage; see ch. 242).

Windshield Wiper Fluid (Methanol)

Most windshield wiper fluids are made up of water and methanol; however, certain types designed for extreme cold weather may contain ethylene glycol (EG), ethylene glycol monobutyl ether (EGME), ethanol, isopropyl alcohol, ammonia, or even hydrocarbons (e.g., liquefied petroleum gas). Methanol (methyl alcohol) can result in toxicosis in dogs, but does not result in the retinal toxicosis and blindness as seen with humans. When methanol is metabolized (via alcohol dehydrogenase), it creates formaldehyde, which is rapidly oxidized by aldehyde dehydrogenase to formic acid.[8,9] This is then metabolized to carbon dioxide and water in non-primate species, whereas in primates, formic acid accumulates because of low tissue levels of folate, leading to acidosis and ocular toxicosis (blindness).

Clinical signs include CNS (e.g., ataxia, lethargy, sedation), GI (e.g., vomiting, hypersalivation), and respiratory signs (e.g., tachypnea). With methanol toxicosis, decontamination typically is not warranted, as alcohols are rapidly absorbed from the GI tract.[8] Likewise, the administration of activated charcoal is contraindicated, as it does not bind to alcohols reliably. Treatment includes IV fluid therapy, antiemetic therapy, and supportive care. Administration of fomepizole (4-methylpyrazole, 4-MP), the antidote for ethylene glycol (EG) intoxication, is *not* necessary with methanol toxicosis.[9]

Ethylene Glycol

Accidental or malicious poisoning with EG can be seen in veterinary medicine, as the public generally is well aware of the narrow margin of safety with antifreeze. The minimum lethal dose in dogs is approximately 6.6 mL/kg, while in cats it is 1.4 mL/kg.[9] Sources of EG include automotive antifreeze (radiator coolant, which typically contains 95% EG), windshield deicing agents, motor oils, hydraulic brake fluid, paints, solvents, etc.[9] As little as one tablespoon (15 mL) can result in severe AKI in a dog, while as little as 1 teaspoon (5 mL) can result in AKI in feline patients. Ethylene glycol is metabolized by the body to highly poisonous metabolites including glycoaldehyde, glycolic acid, and oxalic acid, which lead to severe AKI secondary to development of calcium oxalate crystalluria.[9] There are three clinical stages with EG toxicosis:

- Stage 1: This occurs within 30 minutes to 12 hours, and looks similar to alcohol poisoning. Ataxia, hypersalivating, vomiting, seizuring, and polyuria/polydipsia are seen.
- Stage 2: This occurs within 12-24 hours post-exposure, and clinical signs seem to "resolve" to the pet owner; however, during this time, severe internal injury is still occurring. Ataxia might seem to improve during this stage, but signs of dehydration, tachycardia, and tachypnea can be seen.

- Stage 3: In cats, this stage occurs 12-24 hours after EG exposure. In dogs, this stage occurs 36-72 hours post-ingestion. During this stage, severe AKI occurs secondary to calcium oxalate crystalluria. Severe anorexia, lethargy, hypersalivation, uremic halitosis, coma, depression, vomiting, and seizures can be seen.

Any patient suspected of EG toxicosis should have an EG blood test, venous blood gas, and urinalysis performed. The diagnosis of EG toxicosis should be based on the combination of clinical suspicion, accurate interpretation of diagnostic testing, clinical signs, and patient history, because false positive results are well-recognized (see below). A positive EG test in a patient with known or suspected exposure can be sufficient to warrant initiating treatment immediately; metabolic acidosis, elevated anion gap, and calcium oxalate crystalluria offer further support, but confer a much worse prognosis if they already exist before treatment has been initiated.[9] Importantly, EG testing is only accurate within approximately the first 24 hours after ingestion, as false negatives can be found thereafter due to complete transformation of EG to its more toxic metabolites, which are not routinely detected on EG tests. On veterinary-specific EG tests, false positive results can occur with other compounds such as propylene glycol (found in many compounds, notably oral activated charcoal products and injectable drugs including diazepam), isopropyl alcohol (at the venipuncture site), sorbitol, mannitol, etc. Currently available veterinary brands for EG testing include Kacey[10] and Catachem[11]; the PRN test is no longer available. Due to the occurrence of false positive results with these tests, the author recommends submitting samples to a neighboring human hospital for quantitative EG levels.

Treatment for EG toxicosis includes antidote therapy (e.g., fomepizole, ethanol), intensive IV fluid therapy, monitoring urine output and clinicopathologic parameters, antiemetic therapy, and supportive care. Fomepizole is an expensive but life-saving antidote that is preferred over ethanol for the treatment of EG toxicosis.[9] While it is no longer being produced for dogs and cats,[12] it can be compounded by certain veterinary pharmacies. The clinician must keep in mind that antidotal therapy needs to be administered quickly: in dogs, within 8-12 hours of exposure, and in cats, within 3 hours of exposure.[9] If fomepizole is not available, ethanol can also be used, as it competes with alcohol dehydrogenase, thereby preventing metabolism of EG into its more toxic metabolites. Adverse effects of CNS depression, drunkenness, metabolic acidosis, hypoglycemia, bradycardia, hypoventilation, and hypothermia can be seen with ethanol treatment. Once a patient has already developed azotemia, the prognosis is generally poor to grave without hemodialysis (see ch. 110). Please see Box 152-2 for antidote dosing information.

Box 152-2

Antidotes for Ethylene Glycol[9]

Fomepizole (e.g., 4-MP, 4-Methylpyrazole)

- Dogs: Loading dose 20 mg/kg IV, followed by 15 mg/kg IV at 12 and 24 h. Give additional 5 mg/kg IV at 36 h. Can continue to use 3 mg/kg IV q 12 h until evidence of metabolic acidosis and clinical signs resolve.
- Cats: Extra-label. Loading dose 125 mg/kg IV, followed by 31.3 mg/kg IV at 12, 24, and 36 h after initial loading dose.
- Potential adverse reactions in dogs and cats include: anaphylaxis following second dose, CNS depression, tachypnea, hypersalivation, trembling, osmotic diuresis.

Ethanol

- Choose a clear, non-flavored, high concentration/proof alcohol (e.g., vodka, grain alcohol, etc.).
- Note: With U.S. alcohol, the alcoholic proof is twice the percentage of alcohol (e.g., 100 proof = 50% ethanol = 500 mg/mL OR 190 proof = 95% alcohol = 950 mg/mL).
  - To calculate how to make a certain percentage alcohol solution, use the formula: $C_1 \times V_1 = C_2 \times V_2$
  - To make a 7% ethanol solution with an 80 proof alcohol (40% alcohol), remove 175 mL from a 1 L bag of saline; add in 175 mL of an 80 proof alcohol back into the bag of saline.
    - $C_1 \times V_1 = C_2 \times V_2$
    - (40)(X) = (7)(1000)
    - X = 175 mL
  - To make a 7% ethanol solution with a 190 proof alcohol (95% alcohol), remove 74 mL from a 1 L bag of saline; add in 74 mL of a 190 proof alcohol back into the bag of saline.

- $C_1 \times V_1 = C_2 \times V_2$
- (95)(X) = (7)(1000)
- X = 74 mL

- There are two IV treatment recommendations for administering ethanol that are published.
  - CRI method: Using a 7% ethanol (70 mg/mL), give 8.6 mL/kg (600 mg/kg) IV once slowly; followed immediately by 1.43 mL/kg/h (100 mg/kg/h), IV, CRI for 24-36 h.
  - Alternative method: Using a 20% ethanol solution (200 mg/mL), give 5.5 mL/kg q 4 h × 5 doses; follow with 5.5 mL/kg q 6 h × 4 more doses.
- Potential adverse reactions in dogs and cats include: severe CNS depression, sedation, bradycardia, hypoventilation, metabolic acidosis, hypothermia, hypoglycemia.

CNS, Central nervous system; *CRI,* constant rate infusion.

Propylene Glycol

Propylene glycol (PG), an odorless, tasteless, and colorless dihydroxy alcohol, is a component of many household products due to its hydroscopic, emollient and humectant properties.[9,13] It often is found in pet-friendly antifreeze fluids, moist pet foods, disinfectants, medications (e.g., injectable diazepam, oral activated charcoal preparations), room deodorants, suntan lotions, cosmetic creams, paints and varnishes, food coloring, lubricants, and more.[9,13] When ingested by animals, PG is metabolized to both D- and L-lactic acid, contributing to metabolic acidosis. PG is absorbed rapidly from the GI tract. While the LD_{50} for dogs is reported to be as low as 9 mL/kg,[9,13] the author clinically rarely sees severe clinical signs from PG ingestion. Doses of 5 g/kg daily can result in hemolytic anemia, reticulocytosis, and hyperbilirubinemia in dogs.[13] In cats, 1.6 g/kg and 8 g/kg of oral PG chronically for 2-4 weeks resulted in dose-related increases in Heinz bodies of 28% and 92%, respectively.[13] Clinical signs of PG toxicosis include CNS depression, narcosis, tachypnea (secondary to metabolic acidosis), muscle twitching (cats), hypotension (cats), cardiovascular collapse, polyuria/polydipsia (secondary to an osmotic diuretic effect), and hematological changes (e.g., hemolytic anemia, Heinz body anemia).[9,13] Treatment is supportive, including fluid therapy to help correct metabolic acidosis, red blood cell morphology monitoring, and rarely, red blood cell transfusions if needed. There is no need for antidotal therapy with PG exposure.[9,13]

Herbicides

The majority of herbicides are considered to be *mildly* toxic to dogs and cats. There are several types of herbicides that are commonly used, including glyphosate (e.g., Roundup), pyridine herbicides, imidazolinone compounds, chlorophenoxy compounds (e.g., 2,4-D), and dicamba (a translocation herbicide similar to chlorophenoxy compounds). Typically, when herbicides are ingested, clinical signs are limited to GI abnormalities (e.g., hypersalivation, vomiting, diarrhea) or dermal irritation.

Glyphosate, an aminophosphonate (non-cholinesterase inhibitor), is a nonselective post-emergent herbicide. Glyphosate has a wide margin of safety in mammals and generally is regarded as nontoxic to mammalian, aquatic, and avian species.[14] It works by interfering directly with the synthesis of amino acids within the plant. When it is ingested in large amounts or directly from the container, clinical signs of hypersalivation, vomiting and diarrhea can be seen; this likely is due to the inactive surfactants found in the liquid formulation.[14] **Pyridine** herbicides (which commonly end with "pyr") include active ingredients such as thiazopyr, dithiopyr, fluroxypyr, triclopyr, etc. These typically are used as sprays to control the growth of broad-leafed weeds. This class of herbicides works by mimicking auxin, a natural hormone that inhibits growth in plants. **Imidazolinone** herbicides also are used for controlling the growth of broad-leafed weeds, and they work by inhibiting acetohydroxy acid synthase (and thereby inhibiting amino acid formation in plants).

2,4-D or chlorophenoxy compounds are some of the most commonly used herbicides, and they include the commonly known Vietnam War chemical Agent Orange. While it has a wide margin of safety in animals, this class has been shown to uncouple oxidative phosphorylation and affect ribonuclease synthesis, resulting in potential CNS affects (e.g., demyelination of peripheral nerves). In experimental studies, dogs developed GI signs and myotonia when given doses of 175 or 220 mg/kg.[14] Clinical signs reported after exposure include GI (e.g., vomiting, diarrhea, signs of abdominal pain) and CNS signs (e.g., myotonia, muscle stiffness, extensor

rigidity).[14,15] While clinical signs rarely are seen in small animal exposures to 2,4-D, the author has concerns about chronic or large exposures due to the mechanism of action. Several published studies have postulated an association with lymphoma and phenoxy herbicides.[14-17] Lastly, **dicamba** (which is related to the chlorophenoxy compounds such as 2,4-D) is a commonly used benzoic acid herbicide that has a wide margin of safety. With all herbicide exposures, treatment is directed towards supportive care. If large amounts are ingested, decontamination of the patient typically is sufficient.

Summary

In general, the prognosis for the poisoned patient is fair to excellent with immediate recognition and treatment. However, a few of these chemical toxicants have a very narrow margin of safety (e.g., OPs, carbamates, ethylene glycol), and intensive therapy is warranted. When in doubt, the clinician should consult the ASPCA Animal Poison Control Center in cases of life-threatening emergencies, or when the mechanism of action, clinical signs, and treatment are not known.

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[a]Personal communication, ASPCA Animal Poison Control Center, Urbana, IL.

CHAPTER 153

Prescription and Over-the-Counter Drug Toxicoses

Anna G. Brutlag

Client Information Sheet: Prescription and Over-the-Counter Drug Poisonings in Dogs and Cats

Collectively, exposures to human and veterinary prescription and over-the-counter drugs account for approximately 40% of all cases reported to Pet Poison Helpline, a 24/7 veterinary poison control center based out of Minneapolis, Minnesota, serving all of North America.[1] Such exposures most often involve unintentional overdoses (e.g., dog chewing into a bottle of medication) but intentional administration of medication by the pet owner (e.g., giving an ailing cat a liquid children's NSAID) and iatrogenic intoxications also occur.

Calcium Channel Blockers

Calcium channel blockers (CCBs) or calcium channel antagonists, such as amlodipine, diltiazem, and verapamil, are commonly used in both human and veterinary medicine for the treatment of systemic hypertension, cardiac disease including hypertrophic cardiomyopathy, supraventricular tachycardia arrhythmias, and other cardiac issues. In general, CCBs inhibit the transmembrane influx of extracellular calcium through slow or long-lasting (L-type) ion channels primarily located in myocardial and arterial smooth muscle cells. This mechanism results in decreased myocardial contractility, and arterial dilation, with a subsequent decrease in peripheral resistance, blood pressure, and afterload. Slowing conduction in the SA node and reducing AV nodal conduction result in slowing of the cardiac rate, potentially precipitously.

Overdose or intoxication from CCBs results in an exaggeration of therapeutic effects, predominantly sinus bradycardia, bradyarrhythmias (e.g., all degrees of heart block), and hypotension secondary to vasodilation (see ch. 159 and 248). Sinus tachycardia may occur reflexively due to severe hypotension and will typically self-correct if hypotension is resolved. Non-cardiac signs such as vomiting (especially in cats), hypothermia (see ch. 49), central nervous system (CNS) depression, non-cardiogenic pulmonary edema, hypokalemia, hyperglycemia, metabolic acidosis (secondary to hypoperfusion), and increased lactate production can also occur. Rarely, signs of CNS stimulation such as tremors or seizures occur.[2]

Toxic dosages for CCBs in dogs and cats have not been determined and, due to the narrow margin of safety of these agents, most overdoses are considered potentially toxic. Signs of intoxication have been noted at therapeutic dosages in both dogs and cats with additional reported intoxications occurring at 14.5 mg/kg verapamil in a cat and 95-109 mg/kg sustained-release diltiazem in an adult dog.[2,3]

Treatment of CCB intoxication begins with gastrointestinal decontamination if appropriate (see ch. 112 and 151). In any case of potential CCB overdose, close monitoring of heart rate, rhythm, and blood pressure (see ch. 99) should be continued for 12-24 hours after exposure. Symptomatic animals also require laboratory monitoring of electrolytes, blood glucose, acid/base status and lactate (see ch. 70 and 128). Typical first-line agents of treatment include IV crystalloids for hypotension (colloids may also be necessary—see beta-blocker section of this chapter and see ch. 129), atropine for bradycardia (0.02-0.04 mg/kg IV), and calcium gluconate (10% solution, 0.5 to 1.5 mL/kg IV slowly over 5 minutes while monitoring an electrocardiogram [ECG] or as a constant-rate infusion [CRI]; see ch. 298) or calcium chloride (10% solution, 0.1 to 0.5 mL/kg IV slowly over 5 minutes or as a CRI of 0.01 mL/kg/h) to increase transmembrane calcium flow. If the patient is refractory to this suite of therapies, other agents such as intravenous lipid emulsion (ILE) and high-dose insulin (HDI) therapy may be considered.

While the exact mechanism of intravenous lipid emulsion therapy has not been fully elucidated, its beneficial effects are likely to be multifactorial. Current theories include the "lipid sink" theory which postulates that lipophilic agents (i.e., logP > 1.0) are "pulled" from their receptor sites and sequestered in the

lipid compartment of the blood.[4] Additional direct benefit to the myocardium is thought to result from the utilization of free fatty acids as an energy source, an increase in intracellular calcium, an alpha-adrenergic receptor mediated increased vasopressor effect, and the reduction of nitric oxide- and insulin-induced vasodilatation by ILE.[4] The current recommend dosage of ILE is 1.5 mL/kg IV bolus followed immediately with a CRI of 0.25 mL/kg/min until clinical signs resolve or for 30-60 minutes, whichever is shorter. Significant improvement is expected within minutes of ILE administration. If no significant improvement occurs, additional boluses may be administered. The total amount of ILE that can be safely administered is not known and may vary greatly depending on the individual patient, the toxicant, and the severity of clinical signs. In the current human literature, a maximal daily dosing of 8 mL/kg of 20% ILE is recommended but this dosage has been safely exceeded without adverse events in both humans and animals. Experimentally, ILE has been shown to be beneficial in canine verapamil intoxications and is also often utilized in humans with CCB overdoses.[5-7]

High-dose insulin therapy, also referred to as hyperinsulinemia-euglycemia therapy, has also been shown to be successful in treating CCB intoxication in dogs and is currently a first-line agent of care in human medicine CCB overdosage.[7-10] The proposed therapeutic mechanism of HDI is multifactorial and includes enhanced myocardial uptake of glucose, suppression of phosphodiesterase III (increases cAMP leading to increased intracellular calcium influx), and induction of mild hypokalemia resulting in enhanced cardiac inotropy. Administration of HDI requires a central line and concurrent administration of dextrose to support euglycemia (see ch. 76). Prior to beginning treatment, it is important to monitor the blood glucose (BG) concentration and supplement if the BG is <100 mg/dL in dogs or <200 mg/dL in cats. Dosages in veterinary species have not been well established and are still considered novel but typically start with 1 U/kg of regular insulin given as an IV bolus followed by a CRI at 2 U/kg/h.[11] The dosage may be increased by 2 U/kg/h every 10 minutes to a maximum dosage of 10 U/kg/h depending on the response to therapy. Experimentally, measureable inotropic improvement has been seen within 5 minutes after starting HDI.[7] Blood glucose concentrations should be monitored every 10 minutes while titrating the dosage of insulin. A concentrated solution of dextrose, usually greater than 5%, sometimes upwards of 15-30%, is administered concurrently via the central line. When the insulin dosage is stabilized, BG concentrations should be measured every 30-60 minutes and the dextrose dosages adjusted as needed. Additionally, serum potassium concentrations should be monitored hourly. Based on the human literature, it is advisable to keep potassium concentrations in the low therapeutic range but potassium chloride should be administered if the potassium drops below 3.0 mmol/L.[7] When the signs of CCB intoxication have resolved, the insulin dosage can be decreased by 1-2 U/kg/h while continuing to monitor BG and potassium concentrations hourly. Dextrose administration will typically need to be continued for 24 hours following the discontinuation of insulin.[7,11]

Additional therapies for CCB intoxication traditionally include glucagon (50 ng/kg IV bolus followed by a CRI of 10 to 15 ng/kg/min up to 40 ng/kg/min), vasopressors, and temporary pacemakers, although treatment with HDI or ILE is currently preferred.[12] In one reported case, ILE and HDI were successfully used in tandem in a dog that had ingested 79 mg/kg of diltiazem after the patient failed traditional therapies including glucagon.[13]

Beta-Blockers

Beta-blockers (also called beta-receptor antagonists) are frequently used in human medicine for hypertension and other cardiac diseases. As a result of their abundance, accidental exposures, especially by dogs, are commonly reported to Pet Poison Helpline. Although there are no FDA-approved beta-blockers for veterinary use, these agents are used to treat hypertrophic or hypertrophic-obstructive cardiomyopathy in cats and tachydysrhythmias in dogs.

Beta-blockers work primarily by antagonizing beta-adrenergic receptors ($beta_1$ and $beta_2$) and many display specificity for one receptor over the other. For example, atenolol, esmolol, and metoprolol are primarily $beta_1$-selective, whereas carvedilol, propranolol, and sotalol are non-selective beta-blockers. At supratherapeutic dosages, $beta_1$ selectivity may be lost and $beta_2$-blockade can occur. Some agents, such as carvedilol, may also antagonize $alpha_1$ receptors; others, such as propranolol, inhibit fast sodium channels, which create a membrane stabilizing effect, and prolong PR and QRS intervals. $Beta_1$ receptors are located predominately in the myocardium but are also found in the kidney, adipose tissue, eye, and skeletal muscle. Cardiac effects from $beta_1$ antagonism typically result in negative inotropic and chronotropic effects and reduced cardiac output by reducing sinus heart rate and slowing AV conduction. A reduction in blood

pressure and myocardial oxygen demands can also occur. $Beta_2$ receptors are located in bronchial smooth muscle, skeletal muscle, the gastrointestinal tract, pancreas, liver, and blood vessels. Antagonism of these receptors often results in bronchospasm (more likely in animals with concurrent airway disease) and peripheral vasodilation leading to hypotension.

The clinical signs following overdose of beta-blockers can vary slightly depending on the specific agent but often include bradycardia, heart block (first-, second-, or third-degree), reduced cardiac output, hypotension with possible cardiogenic shock, hypoglycemia, and respiratory compromise/bronchospasm. Seizures have also been reported and may be more likely following overdoses of propranolol due to its lipophilicity. Propranolol overdoses may be more likely to result in prolonged PR, QRS, and QT intervals.

Data regarding the toxic dosages of beta-blockers in companion animals are very limited. In general, doses exceeding 2-3 times the therapeutic dosage are considered potentially problematic. In experimental canine studies of propranolol intoxication, IV dosages of 10 mg/kg consistently resulted in severe clinical effects or death.[14]

Treatment for beta-blocker intoxication is fairly similar to that of CCB intoxication and begins with gastrointestinal decontamination, if appropriate (see ch. 112 and 151). In any case of potential beta-blocker poisoning, close monitoring of heart rate, rhythm, and blood pressure (see ch. 99 and 103) should be continued for 12-24 hours after exposure. Symptomatic animals also require laboratory monitoring of electrolytes, and blood glucose, acid/base status and lactate (see ch. 67-70). Typical first-line agents of treatment, similar to CCBs, include IV crystalloids for hypotension (colloids may also be necessary; see ch. 129 and 130), and atropine for bradycardia (0.02-0.04 mg/kg IV). Volume resuscitation with IV crystalloid fluid administration for hypotension is typically dosed at 20 mL/kg for dogs given over 10-15 minutes and 10-15 mL/kg for cats over 10-15 minutes.[11] Boluses may be repeated as needed for stabilization but care should be taken to avoid fluid overload in patients with cardiogenic shock. Additionally, fluid therapy may be ineffective for patients with severe bradycardia and this issue must be concurrently addressed (i.e., atropine administration). Clinical signs consistent with fluid overload include increased respiratory rate/effort, increased lung sounds, decreased pulse oximetry readings, and concomitant blood gas abnormalities. Continuous ECG monitoring to assess conduction and frequent blood pressure monitoring are also recommended (see ch. 99 and 248). As with CCB intoxication, ILE and HDI can be successful therapies and should be considered in severe cases refractory to IV fluids and atropine (for detailed information on ILE and HDI, see CCB section in this chapter).[7,11,15]

Selective Serotonin Reuptake Inhibitors and Others

Prescription antidepressant drugs routinely rank amongst the most commonly prescribed agents in the United States. Additionally, they are commonly used in veterinary medicine for a variety of behavioral disorders including separation anxiety, storm phobias, inappropriate urine marking, stereotypic behaviors, and psychogenic alopecia. While mild adverse effects may be noted at therapeutic doses, severe toxicosis and death may result following overdose, especially if these drugs are ingested along with other drugs with serotonergic properties (such as monoamine oxidase inhibitors or 5-hydroxytryptophan).

Selective serotonin reuptake inhibitors (SSRIs) block the reuptake of serotonin in the presynaptic membrane, which results in an increased concentration of serotonin in the CNS. Common SSRIs include fluoxetine (Prozac), citalopram (Celexa), escitalopram (Lexapro), paroxetine (Paxil), and sertraline (Zoloft), many of which are highly protein-bound and all of which undergo hepatic metabolism.

The range of toxicity varies depending on the drug and species. Cats, as compared to dogs, are more sensitive to SSRIs, necessitating lower therapeutic dosages and exhibiting lower ranges of toxicity.[16] Animals with seizure disorders, or cardiovascular or hepatic impairment may be at greater risk for toxicosis. Small overdoses of SSRIs typically result in sedation or agitation, hypersalivation, vomiting, mydriasis, and tremors. Larger overdoses may cause tremors, seizures, nystagmus, dysphoria, vocalization, aggressive behavior, ataxia, and bradycardia. As the degree of overdose increases, so does the risk for the development of serotonin toxicity (also called serotonin syndrome), a toxidrome characterized by central nervous, autonomic, and neurobehavioral signs. Signs may include muscle rigidity, increased reflexes, tremors, hyperthermia, hypertension, and transient blindness.

Treatment of SSRI overdoses is largely supportive and symptomatic; no specific antidote is available. Appropriate decontamination is recommended. Cyproheptadine (dogs, 1.1 mg/kg; cats, 2-4 mg total dose q 4-6 h, PO or rectally), a serotonin antagonist, is useful in reducing the severity of signs, especially vocalization and dysphoria. Agitation may be treated with acepromazine (0.05-0.2 mg/kg, IV, IM, or SC PRN) or

chlorpromazine (0.5-1 mg/kg, IV or IM PRN). The author prefers IV administration for the first dose due to the more rapid onset of effect. Due to the risk for extreme sedation and hypotension from phenothiazines, it is important to start at the low end of the dosage range and increase as needed. Some animals may require larger dosages than are listed here. For seizures in the absence of serotonin syndrome, benzodiazepines (e.g., diazepam, 0.25-0.5 mg/kg, IV PRN) are effective. In cases of serotonin syndrome, benzodiazepines *may* exacerbate neurologic signs (although they are routinely used in human medicine for this syndrome), so barbiturates (e.g., phenobarbital 3-5 mg/kg repeated q 20 min for 2-3 doses, IV) can be considered instead. Additional treatments include methocarbamol for tremors (55-220 mg/kg, IV slowly and to effect), IV fluids (crystalloids, 1.5-2.5 times maintenance; see ch. 129) for thermal cooling and to maintain hydration and adequate perfusion, and beta-blockers (e.g., propranolol 0.02-0.06 mg/kg, slowly IV) for tachycardia and hypertension if this is not corrected following appropriate sedation.

Overdoses of other antidepressants such as duloxetine (Cymbalta), a serotonin norepinephrine reuptake inhibitor (SNRI), and venlafaxine (Effexor), a bicyclic antidepressant, are clinically similar to SSRI overdoses; however, due to their mechanism of action, these agents have an added element of increased presynaptic concentration of norepinephrine and dopamine (venlafaxine). This may lead to sympathomimetic signs such as mydriasis, tachycardia, hyperthermia, hypertension, etc. Treatment is similar to SSRI overdoses but more focus on sedation may be needed. Extremely high dosages of chlorpromazine (10-18 mg/kg, IV) or acepromazine may be necessary.[16]

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are structurally similar to phenothiazines and act on numerous receptors by inhibiting the neuronal reuptake of norepinephrine, serotonin, and dopamine in the CNS. They also have an affinity for muscarinic and histamine H_1 receptors and can cause a sodium and potassium channel blockade to varying degrees. The most common TCAs used in veterinary medicine include amitriptyline and clomipramine (Clomicalm).

In general, TCAs have a very narrow margin of safety with mild adverse effects possible at therapeutic dosages and serious effects possible following minor (2-3×) overdoses. Thus, any overdose should be considered potentially serious. As opposed to SSRIs and SNRIs, TCAs may lead to profound cardiac toxicosis in addition to neurologic signs. Following ingestion, clinical signs may develop within the first few hours and may include severe CNS depression and seizures along with anticholinergic signs such as mydriasis, tachycardia, urinary retention and a slowed GI transit time. Due to the inhibition of fast sodium channels in the cardiac ventricles, slowed depolarization may lead to bradycardia, hypotension, and arrhythmias. Cardiovascular collapse is often the cause of death in domestic animals.

Treatment of acute ingestions consists of appropriate decontamination and aggressive supportive care; no specific antidote is available. Laboratory values, especially venous blood gasses, electrolytes, and blood glucose should be monitored closely (see ch. 61, 66-70, and 128). If hypoglycemia occurs, supplementation is indicated with dextrose at 2.5-5% in IV fluids. Continuous ECG monitoring is recommended to note arrhythmias, widening QRS complexes, and prolonged PR intervals. Administration of IV crystalloids at 1.5-2.5 times maintenance is indicated to correct hypotension and maintain perfusion. Cyproheptadine may be helpful (see SSRI section). If seizures occur, ruling out hypoglycemia is important and, if needed, treatment can be given with diazepam (0.25-0.5 mg/kg, IV PRN) or barbiturates (e.g., phenobarbital 3-5 mg/kg, IV PRN). Phenothiazines should not be used as they may exacerbate the clinical signs. The duration of signs is highly variable (hours to days) and animals should be hospitalized until they are asymptomatic.

Sleep Aids: Benzodiazepines and Non-Benzodiazepine Hypnotics

Benzodiazepines (BZDs) are commonly used as antianxiety agents, anticonvulsants, muscle relaxants, and sedatives/hypnotics. Non-benzodiazepine hypnotics (non-BZDs) are typically used as sleep aids. Although the two groups have different pharmacological profiles, both exert their effects through the inhibitory neurotransmitter gamma-amino butyric acid (GABA) and have similar clinical effects and treatment regimens. Common BZDs used off-label in veterinary medicine include alprazolam (Xanax), diazepam (Valium), lorazepam (Ativan), midazolam (Versed), and zolazepam/tiletamine, a dissociative agent (Telazol). Other BZDs frequently used in human medicine include clonazepam (Klonopin), oxazepam (Serax), and temazepam (Restoril). Common non-BZDs include zolpidem (Ambien), eszopiclone (Lunesta), and zaleplon (Sonata).

Both families of drugs have a relatively wide margin of safety and fatality is not common following a one-

time overdose. Chronic oral use of oral BZDs in cats, however, can result in fulminant hepatic failure and is not recommended (see ch. 286).[17,18] Following ingestion, clinical signs of acute intoxication may develop rapidly (30-60 minutes) and commonly include CNS depression, ataxia, confusion, and/or aggression. Rare signs include hypotension, hypothermia, coma, or seizures. Paradoxically, 40-50% of animals ingesting these agents display stimulation and excitement.[19]

Treatment of acute ingestions consists of appropriate decontamination, supportive care and, if necessary, the reversal agent/antidote flumazenil. The need for treatment is based on the degree of overdose and the severity of signs. In symptomatic animals, body temperature and blood pressure monitoring (see ch. 99) and warming measures or IV crystalloids are indicated as needed to maintain perfusion, treat hypotension, and correct dehydration. In cases of paradoxical stimulation, benzodiazepines should not be given as they may exacerbate the clinical signs. Instead, acepromazine (0.05-0.2 mg/kg, IV, IM or SC PRN) or medetomidine (1-10 mcg/kg, IV, IM or SC PRN) are recommended. The reversal agent flumazenil (0.01 mg/kg, IV to effect PRN) is the antidote for benzodiazepine overdoses but is only recommended or necessary in cases of severe CNS or respiratory depression. It reverses the sedative and muscle relaxant effects within about five minutes and, due to the short half-life, should be repeatedly given as needed.

Phenylpropanolamine

Phenylpropanolamine (PPA) is a sympathomimetic amine that is FDA-approved for the treatment of urinary incontinence secondary to urethral sphincter hypotonus in dogs. Historically, it was used as an over-the-counter weight loss supplement and cold medication for people but was banned by FDA in 2003 due to human safety concerns. Although the exact mechanism of action is not known, it is believed to directly stimulate alpha-adrenergic receptors, which results in the therapeutic effect of smooth muscle contraction in the urethra. The drug is also believed to increase norepinephrine release from presynaptic sites, thereby resulting in indirect stimulation of both alpha- and beta-adrenergic receptors. The drug has a half-life of 3-4 hours (canines) and is largely excreted, unchanged, in the urine within 24 hours.[16]

Mild clinical signs can be seen with therapeutic dosing (1 mg/kg PO q 12 h) so the lowest effective dosage should be selected. In general, dogs ingesting more than 2-3 mg/kg are at risk for mild to moderate intoxication and should be decontaminated and monitored for 8 hours (see ch. 151). The onset of clinical signs can occur as early as 30 minutes following ingestion but is more likely to begin 2-4 hours after ingestion. Reported signs of intoxication are consistent with $alpha_1$, $alpha_2$, and $beta_1$ stimulation such as vasoconstriction, increased cardiac output through positive inotropic and chronotropic effects, agitation, mydriasis, and piloerection. Reported neurological signs include behavioral changes (lethargy, hiding, vocalization), ataxia, nystagmus, hypermetria, muscle tremors (rare) and seizures (rare).[20,21] Gastrointestinal signs such as vomiting and hypersalivation have also been reported and may lead to dehydration.[20] Common cardiovascular signs include hypertension, ventricular tachycardia, and bradycardia (secondary to hypertension; see ch. 248). Erythema of the abdomen and pinna may also occur. Hyperthermia is less common but should be monitored for.

Reported serious effects as a result of PPA overdoses include a 4-year-old Labrador Retriever with a dosage of 56-69 mg/kg developing severe and sustained hypertension resulting in hypertensive retinopathy and elevated cardiac troponin I concentrations (11.7 ng/mL; reference range <0.3 ng/mL) suggestive of myocardial necrosis. Full recovery occurred within 30 days.[22] A 5-year-old Labrador Retriever ingesting approximately 48 mg/kg of PPA also developed probable myocardial necrosis evidenced by cardiac troponin I concentration >40 ng/mL (reference range 0.00-0.07 ng/mL), multiform ventricular tachycardia, and left ventricular dilatation with a focal dyskinetic region in the dorsal interventricular septum with full recovery after 6 months.[21] Death has been reported in a dog ingesting 145 mg/kg of PPA although the cause of death was unable to be determined as no necropsy was performed.[20]

Common laboratory abnormalities following PPA overdoses include azotemia, myoglobinuria, mild hypokalemia, elevated creatinine kinase, and mild to moderate elevations of alkaline phosphatase (ALP) and alanine aminotransferase (ALT) (secondary to muscle damage and possible hepatic hypoperfusion injury). In cases of severe intoxication, the following diagnostics should be considered: ECG and blood pressure monitoring (see ch. 99 and 103), chemistry values including renal parameters and electrolytes, complete blood count (CBC), urinalysis to evaluate renal function and monitor for myoglobinuria (see ch. 72), creatinine kinase, coagulation panel if disseminated intravascular coagulation (DIC) is suspected (see ch. 197), and cardiac troponin I and other biomarkers to monitor for myocardial necrosis/myocardial infarction (see ch. 246).

Following appropriate and timely decontamination, treatment is symptomatic and supportive, as no antidote exists. Sedation is often best achieved with acepromazine (which also causes peripheral vasodilation, therefore lowering blood pressure). The author recommends starting with a dosage of 0.05 mg/kg IV and titrating to effect. Large doses may be necessary in cases of severe intoxication. Butorphanol may also be effective for agitation/hyperactivity. If sedation alone is not sufficient to resolve hypertension, treatment with hydralazine or nitroprusside may be used. Refractory tachycardia can be treated with a $beta_1$ antagonist such as esmolol or propranolol; lidocaine can be used to treat ventricular tachycardia. Tremors may be treated with muscle relaxants (i.e., methocarbamol). Seizures can be treated with benzodiazepines but paradoxical worsening of clinical signs may occur. Therefore, these agents should be used with caution initially. Phenobarbital is also effective for seizures, especially for those refractory to benzodiazepines. Intravenous crystalloid fluid therapy may be beneficial to maintain organ perfusion but should be used judiciously in dogs with suspected or confirmed hypertension. Prognosis is excellent with appropriate treatment.[20]

Veterinary Approved Nsaids

Nonsteroidal anti-inflammatory drugs (NSAIDs) are most commonly used for their antipyretic, anti-inflammatory and analgesic properties, especially in patients with osteoarthritis and post-operative pain. Products FDA-approved for small animal use include carprofen, deracoxib, firocoxib, ketoprofen, meloxicam, robenacoxib, and tepoxalin. At the time this chapter was authored in 2016, NSAIDs such as mavacoxib (long-acting) and tolfenamic acid were not approved for veterinary use in the United States but were approved in foreign markets.

Mechanistically, NSAIDs inhibit the activity of cyclooxygenase (COX, mainly COX-1 and -2), an enzyme that converts arachidonic acid to several prostanoids, including the prostaglandins, the prostacyclins, and thromboxane. Although both COX-1 and -2 have constitutive effects, COX-1 appears to have more desirable physiological effects such as prostaglandin regulation resulting in gastric mucosal production and normal platelet activity, and regulation of renal blood flow. Conversely, COX-2 is responsible for production of inflammatory mediators. Some NSAIDs, such as carprofen, deracoxib, firocoxib, meloxicam and robenacoxib, are COX-2 preferential or selective, meaning they exert greater inhibition over this enzyme than COX-1, thereby giving these drugs a comparatively wider margin of safety compared to drugs with less selective COX inhibition. In contrast, ketoprofen is a nonselective inhibitor of COX enzymes and tepoxalin inhibits COX-1 and -2 as well as lipoxygenase (LOX) enzymes. In spite of greater safety associated with COX-2 inhibitors, this selectivity is lost following overdose, resulting in COX-1 inhibition and consequent adverse or toxic effects.

The most common sequelae of NSAID intoxication are GI erosion or ulceration, especially of the gastric and proximal duodenal regions, and acute kidney injury.[23] Clinical signs of intoxication include vomiting (possible hematemesis), abdominal pain, melena or hematochezia, and diarrhea, which can lead to secondary dehydration. Gastrointestinal perforation and septic peritonitis are the most serious GI effects (see ch. 275 and 279). Acute kidney injury (AKI) typically occurs at dosages greater than those needed to cause GI signs but, in rare cases, has developed in patients lacking GI signs (see ch. 322). Signs of AKI as a result of multifocal renal tubular necrosis include polyuria, polydipsia, anorexia, lethargy, and vomiting. Pale mucous membranes and tachycardia may occur secondary to blood loss from the GI tract, hypovolemia, and poor perfusion. Platelet function can also be inhibited as a result of NSAID exposure.[24] In severe toxicosis, CNS signs such as weakness, ataxia, and seizures can develop (see ch. 35). Hepatic damage may also occur following massive overdoses (see ch. 286). The onset of clinical signs may begin within an hour after ingestion, although toxic effects such as acute kidney injury or GI perforation may take 48-72 hours before being clinically evident.

The toxic dosage of each NSAID varies widely amongst the various agents and is influenced by the species, concurrent use of NSAIDs and other medications (e.g., corticosteroids), underlying disease (especially renal, hepatic, or GI), and, to a lesser extent, breed. For example, Labrador Retrievers may develop idiosyncratic hepatic damage from carprofen more often than other breeds. As a general rule, acute overdoses exceeding 4-5 times the therapeutic dosage in dogs can result in signs of intoxication and require treatment. Even smaller overdoses may put cats at risk for intoxication for most NSAIDs, especially if the drug is not approved for cats or not approved for chronic use in cats.

The goal of treatment for NSAID overdose and intoxication is focused on appropriate decontamination, GI protection, fluid therapy, and other supportive measures. Gastric emptying via the induction of emesis or lavage should be performed in cases of recent exposure to oral products (see ch. 112 and 151). Depending on the extent to which enterohepatic recirculation occurs, decontamination with multiple doses of activated

charcoal may be appropriate. GI protectants such as H_2 antagonists and proton pump inhibitors are warranted for 7-10 days following exposure. Agents such as misoprostol and sucralfate may also be necessary. For large overdoses or serious clinical signs, all of these agents are recommended. Antiemetics such as maropitant are often needed, especially in the early stage of intoxication. In severe cases, blood products may be necessary in case of blood loss due to ulceration (see ch. 130).

Animals exposed to nephrotoxic doses of NSAIDs require additional treatment including IV crystalloid therapy at fluid rates sufficient to ensure excellent renal perfusion (typically, 2-3 × maintenance) for 1-3 days (see ch. 129 and 322). Concurrent monitoring of daily renal parameters and urinalysis should continue for at least 3 days or until values have normalized. Due to extensive protein binding, hemodialysis following NSAID overdose is not likely to be helpful. If there is no indication of nephrotoxic damage within 3-5 days of exposure, it is no longer expected. Additionally, monitoring for hepatic damage following large NSAID overdoses is advisable and hepatoprotectants such as SAMe can be beneficial. Additional prescription and nonprescription medications with potentially toxic effects in dogs and cats are listed in Table 153-1.

TABLE 153-1

Additional Prescription and Over-the-Counter Agents of Toxicological Concern in Small Animals

DRUG NAME	CLASS OF DRUG	MOST COMMON SIGNS OR PRESENTATION	BASIC TREATMENT
5-Fluorouracil (5-FU)	Anti-neoplastic agent, often used topically in people for treatment of actinic keratosis and superficial basal cell carcinomas.	Rapid onset vomiting, grand-mal seizures, tremors, dyspnea, cyanosis. Other: Ataxia, depression, hypersalivation, diarrhea. Protracted seizures lead to increased intracranial pressure, non-cardiogenic pulmonary edema with cardiopulmonary arrest. Death often in <24 hours. If survives initial phase, then bone marrow suppression and GI toxicosis.	No antidote. Multi-modal anti-seizure support including levetiracetam (seizures often refractory to diazepam) and/or general anesthesia; see ch. 35 and 136. IV fluids, anti-emetics, oxygen supplementation (see ch. 131). Close monitoring of ECG, O_2 saturation, blood pressure (see ch. 98, 99, and 103). Mechanical ventilation.
Acetaminophen (e.g., Tylenol)	OTC analgesic, COX-3 inhibitor	Cats more sensitive than dogs. Methemoglobinemia, respiratory distress, cyanosis. Hepatotoxicosis with icterus, hepatic encephalopathy, etc. Facial and paw edema (more common in cats). KCS.	Antidote: N-acetylcysteine (PO or IV). Supportive care: IV fluids, SAMe. Increase O_2 carrying capabilities if needed: Transfuse with pRBCs, whole blood, Oxyglobin. Methylene blue for severe MetHb (use cautiously). Plasma transfusions and Vit K if coagulopathic (liver failure).
Albuterol	Beta-adrenergic agonist	Apprehension, agitation, depression/weakness (often due to hypokalemia). Ventricular arrhythmias, AV block. Possible tremors, vomiting, hypertension, mydriasis, hyperthermia, hyperglycemia. Rare urinary retention.	Supplemental potassium, beta-antagonists for tachycardia, lidocaine for PVCs, continuous ECG and blood pressure monitoring. Anti-emetics PRN. Hyperglycemia usually resolves with IV fluids.
Alpha lipoic acid (thioctic acid)	OTC dietary supplement, often used for diabetes mellitus or cognitive dysfunction.	Signs due to hypoglycemia. Hypersalivation, vomiting, and ataxia. Possible tremors and seizures. Increased liver enzyme 24-72 hours after ingestion; acute kidney injury	IV dextrose, glucose monitoring and diuresis. Hepatoprotectants. Thiamine *may* be helpful.

		may also occur.	
Baclofen; cyclobenzaprine (Amrix, Flexeril)	Centrally-acting skeletal muscle relaxants used orally for the treatment of spasticity resulting from multiple sclerosis and spinal cord injuries/diseases in people.	Vocalization, vomiting, ataxia, disorientation, depression. May progress to recumbency, flaccid paralysis, seizures, or respiratory arrest.	No antidote, supportive care only. IV fluids for perfusion/shock, diazepam for seizures, atropine for bradycardia, cyproheptadine for vocalization. ILE can be considered in severe cases.
Caffeine	Methylxanthine compound (stimulant), common in "energy" and weight loss supplements. Also sold as single-agent tablets, inhalers, and drink augmentations.	Restlessness, hyperactivity, PU/PD, vomiting, urinary incontinence. Tachycardia, hypertension, weakness, ataxia, hyperthermia, cardiac arrhythmias, seizures. Potential electrolyte imbalances.	No antidote, supportive care only. Sedation with acepromazine or chlorpromazine (helps with hypertension), IV fluids for perfusion and excretion, methocarbamol for tremors, diazepam for seizures. Injectable beta-blockers for persistent tachycardia or hypertension. Urinary catheter or frequent voiding to prevent caffeine reabsorption across bladder wall.
Dexmethylphenidate (Focalin); dextroamphetamine/amphetamine (Adderall); dextroamphetamine (Dexedrine); lisdexamfetamine (Vyvanse); methylphenidate (e.g., Concerta, Metadate, Ritalin)	Prescription CNS stimulants, often used to treat ADD/ADHD or narcolepsy.	Restlessness, hyperactivity, pacing, mydriasis, tachycardia, tachypnea, hypertension with potential reflex bradycardia. Possible hyperthermia, head-bobbing, tremors, seizures.	No antidote, supportive care only. Sedation with acepromazine or chlorpromazine (helps with hypertension), IV fluids, methocarbamol for tremors, injectable beta-blockers for tachycardia refractory to sedatives. Cyproheptadine for serotonin syndrome. CAUTION: Diazepam may cause paradoxical effects; use other anti-seizure agents instead.
Pseudoephedrine (Sudafed, Claritin-D, etc.)	OTC sympathomimetic agent used as a decongestant.	See prescription CNS stimulants (Video 153-1).	See prescription CNS stimulants.
Vitamin D_2 (ergocalciferol); vitamin D_3 (cholecalciferol); calcipotriene (Dovonex, Calcitrene, Sorilux); calcitriol (Calcijex, Rocaltrol, Vectical)	OTC and prescription vitamin D and analogues. Sold OTC in very large doses, prescription use for treatment of hypocalcemia (oral) and psoriasis (topical) in people.	Hypercalcemia and hyperphosphatemia resulting in metastatic mineralization. Depression, weakness, anorexia. Vomiting, PU/PD, dehydration due to renal damage, calciuria. GI ulceration (severe cases). Less common: dyspnea, bradycardia, ventricular arrhythmias.	Multi-dose activated charcoal. Pamidronate, saline diuresis, furosemide, prednisone for hypercalcemia. Oral phosphate binders. GI protectants. Close monitoring of electrolytes and renal values. Prolonged treatment for 2-4 weeks is often necessary. See ch. 152.

ADD/ADHD, Attention deficit disorder/attention deficit hyperactivity disorder; *AV*, atrioventricular; *CNS*, central nervous system; *COX-3*, cyclooxygenase-3; *ECG*, electrocardiogram; *GI*, gastrointestinal; *ILE*, intravenous lipid emulsion; *KCS*, keratoconjunctivitis sicca; *MetHb*, methemoglobin; *OTC*, over the counter (nonprescription); *pRBCs*, packed red blood cells; *PRN*, as needed; *PU/PD*, polyuria/polydipsia; *PVC*, premature ventricular complex; *Vit K*, vitamin K.

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CHAPTER 154

Recreational Drugs Toxicosis

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Most exposures to recreational or illicit drugs in pets occur in dogs and can be accidental, intentional, or sometimes malicious.[1] Accidental exposures are common in part due to enhanced use of certain prescription drugs (e.g., amphetamines, opiates) in humans, thus increasing the probability of their availability in a pet's environment. Police dogs are at higher risk of exposure because of their ambitious nature and occupation.[2] Recreational drug toxicosis in pets is considered an emergency situation and, because of the illegal nature of most of these substances, owners often provide inaccurate or misleading exposure histories, making the diagnosis difficult. Moreover, to make them more potent, recreational drugs often are adulterated with other pharmacologically active substances, making the diagnosis even more challenging due to multiplicity of clinical signs. Different recreational drugs have different street names that vary from area to area. Therefore, in a suspected case, calling a local police station or animal or human poison control center can help facilitate identification of the illicit substance if the street name of the substance involved is known.

An efficient way to rule in or out a suspected case of recreational drug toxicosis is by using a commonly available human over-the-counter (OTC) drug test kit. These kits are widely available in human pharmacies, inexpensive, and easy to use. They are designed to detect drug metabolites in the urine. These can help identify some of the most commonly available recreational substances such as marijuana (note: delta-9-tetrahydro-cannabinol [THC], not synthetic marijuana; see below), amphetamines, cocaine, opioids, benzodiazepines, barbiturates, and antidepressants. The use of these drug kits has not been validated for dogs or cats, so these kits should be used with caution in veterinary medicine. Irrespective of species of patient, the sensitivities and specificities of these test kits can vary and the results of drug test kits need to be interpreted cautiously. Depending on the timing, and if any concurrent medication has been used in the patient (best results are obtained while no prior medication has been used in the patient before performing the test), these test kits can yield false positive or false negative results. A positive test result therefore should be given credence only when presenting history and clinical signs match the positive test substance. Positive test results may be confirmed by sending appropriate samples to a human or veterinary laboratory. Most human hospitals or emergency clinics and some veterinary diagnostic laboratories offer illicit drug screens and can check for the presence of recreational drugs or their metabolites in different body fluids. The presence of a parent drug or its metabolites in blood or urine can help confirm the exposure in suspect cases. Clinicians should contact these laboratories for appropriate sample collection and shipping instructions and time required for obtaining the results. The longer turnaround time usually limits the use of these central laboratory-based tests to retrospective confirmation (e.g., if toxicosis was uncertain, for preventive reasons involving future re-exposure, and in legal matters).

Prescription Drugs

Amphetamines and Amphetamine-Like Compounds

These drugs are central nervous system (CNS) and cardiovascular system stimulants commonly used in humans for appetite control, narcolepsy, attention deficit disorder, parkinsonism, and some behavioral disorders. Different amphetamine salts are available legally by prescription, either alone or in combination with other amphetamines. Some of the commonly encountered amphetamines or related drugs are benzphetamine, dextroamphetamine, pemoline, methylphenidate, phentermine, diethylpropion, phendimetrazine, methamphetamine, and phenmetrazine. Various street names for illegally sold amphetamines are speed, uppers, dex, bennies, or dexies. Caffeine, ephedrine, and phenylpropanolamine are common adulterants.[1]

Amphetamines are well-absorbed orally, with a peak plasma concentration seen in 1-2 hours. Absorption is

delayed in extended-release formulations, with slower onset of clinical signs but longer duration. Clinical signs can be seen as early as 15 minutes after the exposure or can be delayed for a couple of hours depending on the dose and the formulation.[1]

Amphetamines cause CNS and cardiovascular system excitation due to stimulation and release of norepinephrine, affecting alpha- and beta-adrenergic receptors, as well as catecholamine release centrally in the cerebral cortex, medullary respiratory center, and reticular activating system. The main affected neurotransmitters in the CNS are norepinephrine, dopamine, and serotonin.[1]

Clinical signs of toxicosis are manifestations of sympathomimetic stimulation including hyperactivity, pacing, irritability/hyperesthesia, tremors, head bobbing, and seizures. Other reported signs include hyperthermia, vocalization, tachycardia, cardiac arrhythmias (premature ventricular complexes), systemic hyper- or hypotension, salivation, and mydriasis.[3]

Treatment is aimed at early decontamination of the patient and good supportive care. Induction of emesis at home typically is not recommended because clinical signs are usually apparent by the time toxicosis is suspected; however, emesis induction can be useful in an asymptomatic patient under veterinary supervision (see ch. 151). Gastric lavage followed by activated charcoal with a cathartic could be useful in early cases (see ch. 112).

The preferred way to control CNS excitation is with phenothiazine tranquilizers such as acepromazine (0.05-1 mg/kg IV or IM, administered slow IV when using high dosages; IV route is preferred in patients with severe clinical signs such as circling and head tremor; IM route can be considered for mild cases or when IV catheter cannot be placed; repeat as needed) or chlorpromazine (0.5-1 mg/kg IV or IM; same cautions as with acepromazine above). Alternatively, CNS signs can be controlled with diazepam (0.5-2 mg/kg slow IV [watch for paradoxical hyperexcitation; stop administration if seen and use other alternatives listed here]), barbiturates (e.g., pentobarbital 2-6 mg/kg/hour IV constant rate infusion [CRI] or phenobarbital 5 mg/kg IV q 15-20 min, repeated PRN), or isoflurane inhalant anesthesia with varying success. With repeated use, or when used at high dosages as rapid IV boluses, diazepam in some patients can cause paradoxical hyperresponsiveness (aggravated paddling, vocalization, hyperactivity). For such patients, diazepam should be discontinued and alternative medications should be used for controlling CNS excitation signs. For treating serotonin syndrome signs, cyproheptadine (1.1 mg/kg PO or per rectum) may be tried. Treatment of tachycardia depends on the nature of the tachycardia (sinus versus ventricular; see ch. 141 and 248). In all cases, monitoring of clinical signs, respiratory rate and effort, heart rate and rhythm, body temperature, and serum electrolytes is critical, with treatment provided as needed.[1,4]

Sedative/Hypnotics

Opiates and Opioids

The terms opiates and opioids are used interchangeably in the literature. The term opiate refers to natural alkaloids like codeine or morphine obtained from the poppy plant, whereas opioids are synthetic morphine-like medications. The opioids are used therapeutically for their good analgesic and sedative properties. These drugs also frequently are abused by humans due to opioids' psychoactive properties. The opioids include several legal and illegal synthetic drugs. Morphine and codeine are derived from the poppy plant *(Papaver somniferum).* Oxymorphone and hydromorphone are legal prescription derivatives of morphine; heroin is an illegal derivative. Common synthetic opioids include buprenorphine, butorphanol, fentanyl, hydrocodone, meperidine, methadone, oxycodone, and propoxyphene. Oxycodone, hydrocodone, and fentanyl are perhaps the most commonly abused drugs in this group. When animals are exposed, it is typically through accidental ingestion.

Absorption and onset of clinical signs depend on the specific opioid, formulation, and route of exposure; signs vary depending on species, dosage, and age, as well as the opioid. For example, ingestion of prescribed human fentanyl by dogs is fairly common through the ingestion of either fentanyl lollipops or new or used fentanyl patches. Cats and dogs with the MDR-1 gene mutation can be more sensitive to the effects of opioids. In general, opioids are well-absorbed in the GI tract and are metabolized in the liver. Some undergo extensive first-pass hepatic metabolism and are markedly less potent orally (morphine). Opioids exert their pharmacologic effects by interacting with opiate receptors found in the limbic system, spinal cord, thalamus, hypothalamus, striatum, and midbrain. Each opioid can have agonist, mixed agonist-antagonist, or antagonist interaction(s) at these receptors. Clinical signs in dogs include early mild excitation, ataxia, tachypnea, vomiting, diarrhea, and urination, followed by CNS depression, respiratory depression, hypothermia, hypotension, and death due to respiratory failure. Cats can show excitation, aggressive behavior,

hyperthermia, and mydriasis, but not vomiting.

Treatment includes early decontamination of the patient (see ch. 151), cooling measures for hyperthermia (see ch. 134), and supportive care, and reversal with naloxone (0.02 to 0.04 mg/kg IV, repeated as needed based on monitoring of clinical signs and vital parameters).[5] Diazepam (0.25-1 mg/kg slow IV) for dysphoric-type reactions (vocalization, disorientation, excitation) and cyproheptadine (1.1 mg/kg PO or per rectum) can be used for patients showing signs of the serotonin syndrome. Ingested fentanyl patches (also a foreign body hazard) may require endoscopic removal, surgical removal (very rare), or bulking of the diet to facilitate removal in the stool. Mechanical ventilation could be needed for recumbent patients with severe respiratory depression. Isotonic intravenous fluids for volume expansion (see ch. 129) should be given to patients with severe clinical signs (coma, respiratory depression, hypothermia).

Ketamine

Ketamine, an analog of phencyclidine and a Schedule III controlled substance, is used widely in veterinary medicine and less so in human medicine due to the dysphoric and dissociative effects. Illicit production involves evaporation of ketamine injectable solution to produce powder for sniffing or pills, crystals, and capsules for ingestion. Illegally obtained ketamine is popular on the streets and can be referred to as "special k," "green jet," and "cat valium." Pets are exposed when they drink ketamine-spiked party punch, eat baked goods or marijuana laced with ketamine, or inhale contaminated marijuana smoke. It is also used as an adulterant with some stimulants like ecstasy (methylenedioxymethamphetamine, MDMA).

The onset of action depends on the dosage, species and route of exposure. Oral absorption is limited. At low dosages, it produces mild signs of stimulation and hallucinations lasting for 30-60 minutes. With large dosages, commonly reported clinical signs in dogs and cats include opisthotonos, mydriasis, a blank stare, ataxia, agitation, muscle twitching, and increased muscle tone, all signs that are identical to those noted when the drug is used therapeutically. Severe overdose can cause coma, respiratory depression, hyperthermia, seizures and death.

A presumptive diagnosis of ketamine toxicosis is solely based on evidence or history of exposure and development of characteristic clinical signs. There is no rapid test available to determine the presence or absence of ketamine in the body. The goals of treatment are early decontamination of the patient and supportive care. Mildly affected animals may only require supervision for the development of further clinical signs. Severely affected animals should be kept in a quiet, dark room with little physical restraint. Intravenous fluids and mechanical ventilation support should be provided as needed. Diazepam is effective for control of excitation, hyperactivity, and seizures; phenothiazines are contraindicated.[6]

Street Drugs

Marijuana and Synthetic Marijuana

Marijuana *(Cannabis sativa)*, referred to as "grass," "weed," and "pot," is the most common recreational street drug ingestion in dogs since its legalization in some U.S. states. It remains illegal at the federal level. Several cannabinoids are present in the plant resin but THC is considered the most active and main psychoactive agent. THC is highly lipophilic and distributes to brain and other fatty tissues following absorption. With oral ingestion, there is a substantial first-pass effect. The concentration of THC in a marijuana plant can vary from 1-8%, although some genetically-modified plants can contain higher concentrations. Most ingestions by pets are accidental, due to eating home-grown plants, marijuana cigarettes, or marijuana-containing baked goods. Occasionally, pets are deliberately poisoned by people blowing smoke into their face to see what happens, or who feed marijuana to a pet with therapeutic intent. Fortunately, marijuana has a wide margin of safety and death is rarely reported.

The onset of action depends on the route and dosage: clinical signs can develop within 6-12 minutes after inhaling smoke and 30-60 minutes after ingestion. The main clinical signs in dogs are CNS depression, disorientation, ataxia, glassy eyes, mydriasis, recumbency, hypothermia, bradycardia, and behavioral changes.[7] Urinary dribbling/incontinence frequently is reported in dogs. In cats, a commonly described behavioral change is "fly-biting." Other less frequent signs include vomiting or diarrhea associated with gastrointestinal (GI) irritation; stupor; and seizures.

Synthetic marijuana contains synthetic cannabinoids (SCs). It refers to a wide variety of herbal mixtures that were initially synthesized in the early 1960s to investigate therapeutic properties and to also study cannabinoid receptor physiology. In the 2000s, different SCs were produced commercially and sold over the Internet, on the street, and in head shops under several popular brand names such as "K2," "Spice," "Herbal

incense," "Cloud 9," "Mojo," "fake weed," "Yucatan," "Fire," "Skunk," "Moon Rocks" and many others. The use of SC has become a large public health concern in humans due to its unpredictable toxicity and abuse potential. In addition to their psychoactive properties, SCs have gained popularity because these are considered natural and legal, are cheaper and easier to produce, and are undetectable on routine drug screens. Different products often contain more than 1 structure or form of SCs leading to extensive variation in concentration and toxicosis potential.[8]

Similar to natural cannabinoids (THC) in terms of properties, SCs have psychoactive effects when ingested or smoked. The psychoactive effects of both SCs and THC are achieved through binding to the cannabinoid receptor types 1 and 2. The cannabinoid receptors are found mainly in the CNS but are also found in various peripheral tissues including lungs, liver, and kidneys.[8]

SCs are more potent, unpredictable, and more toxic, and in humans, are associated with higher rates of hospital admissions compared to natural cannabis. This enhanced toxicity is due to SCs being known as full cannabinoid receptor agonists, whereas THC is a partial cannabinoid receptor 1 agonist; therefore, SCs bind to the cannabinoid receptors with a higher affinity than does THC. Significant differences in toxicity within SCs could be due to different chemical structures and variable concentration in different formulations, possibly having additive or synergistic effect with each other. These products can also contain unknown contaminants.[8]

Most intoxications are acute and occur in dogs (and occasionally cats) mainly due to accidental ingestion of SC products available in the pet's environment. Like human cases, toxicosis in dogs and cats is variable and unpredictable, and depends on factors like dosage and concentration of SC in the product. In general, these cases are more serious in terms of severity and duration of clinical signs and can be life-threatening, in contrast to natural marijuana toxicosis cases. Commonly reported clinical signs of synthetic marijuana intoxication are severe coma, recumbency, disorientation, hypothermia, seizures, and death.

The diagnosis of SC toxicosis in veterinary patients mainly is based on history of exposure and presence of characteristic clinical signs. There have been more than 20 SC structures identified and more are being characterized. Due to this variability, and differences between SC and THC structures, SCs are not detected in routine drug screens, i.e., OTC illicit drug test kits. Some human clinical or toxicology laboratories can identify SCs in urine, blood, vomitus, and the source (different brands) at increased cost.[8] However, this option for identifying SC might not be useful for treatment due to long turnaround time (up to several days).

Treatment of both SC and natural marijuana toxicosis is primarily the provision of supportive care. Animals with mild intoxications often require confinement and monitoring for a few hours. SC cases with marked clinical signs may require fluid therapy, monitoring of body temperature, respiratory rate, and heart rate for several days. Diazepam (0.5-1 mg/kg IV; repeat as needed) can help reduce agitation, excitation, and seizures. Mechanical ventilation support could be necessary for comatose patients. Renal parameters should be monitored as acute kidney injury has been reported in humans in association with SC toxicosis. Asymptomatic dogs ingesting large amounts of plants or baked goods can benefit from early induction of emesis (see ch. 151); those with CNS depression should have gastric lavage (see ch. 112) followed by administration of activated charcoal with a cathartic (see ch. 151).

Cocaine

Cocaine, an alkaloid obtained from *Erythroxylon coca*, is the most widely abused human street drug and is second only to marijuana in animal abuse potential. Cocaine hydrochloride, the powdered form, is referred to as "coke," "nose candy," and "blow." Cocaine can further be processed into the free alkaloid referred to as "crack," "crank," "ice," and "crystal." Both forms are highly toxic to animals, whether they inhale smoke, inhale the powder, or ingest a plastic bag of cocaine that then ruptures in the GI tract.

Cocaine is rapidly absorbed across all mucosal surfaces including the nose, mouth, GI tract, and respiratory alveoli. Clinical signs can be seen within minutes but vary depending on route, tolerance, and presence of adulterants. Clinical signs of amphetamine and cocaine toxicosis are similar (CNS excitation) and difficult to differentiate clinically. These signs include excitement, agitation, pacing, hyperesthesia, tremor, and seizures. Non-febrile hyperthermia secondary to cocaine-induced heat production can be life threatening (see ch. 134).[9] Other associated signs can include tachycardia, hypertension, arrhythmias, mydriasis, respiratory arrest, and death.

Induction of emesis is not recommended due to rapid absorption and potential for seizures. Gastric lavage can be effective but caution needs to be taken in police dogs or "pack dogs" (dogs fed sealed bags of cocaine as a method of illicit drug transport) so the bags do not rupture. Body temperature must be monitored

closely, and early and intensive cooling measures undertaken when necessary. Acepromazine or chlorpromazine can be used successfully to control muscle tremors and associated hyperthermia, while diazepam or barbiturates can be used successfully to control seizures/CNS excitation (see routes and dosages, above). Propranolol or other beta-blockers (e.g., esmolol) can be effective in treating persistent and rapid sinus tachycardia (see ch. 141 and 248). Dogs with marked hyperthermia should be watched closely for disseminated intravascular coagulation (see ch. 134). All symptomatic patients should be treated intensively with intravenous fluids. Mechanical ventilation may be necessary in dogs with severe respiratory depression.

Heroin

Diacetyl morphine, or heroin, is a synthetic opioid. Common street names are "brown," "horse," "black," "smack," or "H." It is used mostly by IV injection but sometimes is smoked or snorted. Dogs are most often poisoned when used as "pack dogs" or "drug mules" for the illegal movement of heroin. In this context, heroin-filled sealed plastic bags either are fed to the dogs or are surgically inserted into the peritoneal cavity. Extreme care needs to be taken when these products are removed surgically so they are not ruptured. Treatment is similar to opioids toxicosis (above).

Club Drugs

Club drugs or "designer drugs" are synthetic drugs that have become increasingly popular in the past 10 years. Common club drugs include GHB (gamma hydroxybutanoic acid), flunitrazepam, and designer amphetamines such as MDMA/"ecstasy," 4MA, MDEA, and others. GHB and flunitrazepam are often referred to as the "date rape" drugs. There are few reports of accidental animal ingestion.

GHB is a synthetic derivative of GABA that occurs normally in the body. Street names for GHB include "liquid x," "liquid ecstasy," and "scoop." Effects occur within 15-30 minutes after ingestion and usually last only several hours, although signs have persisted for over 8 hours in some humans.[10] Clinical signs are similar to those of benzodiazepine overdose and include severe CNS depression/lethargy, coma, hypotonia, tremors, loss of consciousness, hypothermia, and respiratory depression. The aim of treatment is early decontamination of asymptomatic patients and provision of good supportive care. Emesis at home is contraindicated due to rapid onset of neurologic signs. The short duration of action can limit further treatment.

Flunitrazepam, a prescription benzodiazepine drug, is available in most countries but not in the United States. The blue-colored tablets are referred to as "roofies," "Rohypnol," "Mexican valium," and "rope." Clinical signs in humans occur 20-30 minutes after ingestion and last up to 12 hours. The most common signs include confusion, sedation, amnesia, muscle relaxation, and hallucinations.[11] Treatment with flumazenil, a specific benzodiazepine antagonist, has been successful in humans. The dosage for flumazenil in dogs and cats is 0.01 mg/kg IV, repeated in 1-3 hours if needed. For dyskinesia and extrapyramidal reactions (paddling, vocalization) diphenhydramine (1-2 mg/kg IM) can be given. Diazepam should not be used for controlling paradoxical hyperactivity reaction; instead, low dosages of acepromazine (0.02 mg/kg IV) can be used.

MDMA, or 3,4-methylenedioxymethamphetamine, or "Ecstasy," is also called "lover's speed," "roll," and "disco biscuits." Structurally similar to amphetamine, it has both hallucinogenic and amphetamine-like properties. In dogs, clinical signs can develop as early as 45 minutes and persist for up to 8 hours.[12] Signs are dose-dependent and include hyperactivity, pacing, head tremor, mydriasis, hyperthermia, seizures, and death. Patients with marked, persistent hyperthermia are at increased risk of developing disseminated intravascular coagulation followed by multiple organ failure (especially affecting the liver and kidneys; see ch. 132 and 197). Treatment is similar to treatment for amphetamine toxicosis (above).

Hallucinogens

Lysergic acid diethylamide (LSD, *Lysergsäure-diethylamid*) is a powerful, synthetic hallucinogen. Street names include "purple acid," "cubes," and "dots." LSD is rapidly absorbed orally with signs occurring within 90 minutes and persisting for up to 12 hours. Clinical signs include abnormal mentation associated with hallucinations and euphoria; disorientation; and ataxia. Cats exposed to LSD have developed bizarre postures, yawning, head twitching, body shaking, compulsive scratching, and abnormal movements.[13] Treatment is aimed at providing good supportive care and includes keeping the animal in a dark, quiet room, minimizing stimulation, and providing adequate sedation. Diazepam and haloperidol have been used successfully in humans and may be helpful in animals.

Phencyclidine, a synthetic drug similar to ketamine, is referred to as "angel dust," "rocket fuel," and "love boat." Strictly speaking, phencyclidine and ketamine are classified as dissociative anesthetics and not as hallucinogens. Clinical signs of toxicosis include coma, seizures, muscle rigidity, and systemic hypo- or hypertension. Treatment mainly involves supportive care.

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CHAPTER 155

Plant Intoxications

David C. Dorman

Client Information Sheet: Plant Poisonings

Overview

Ingestion of plants by small companion animals and children is a very common occurrence. For example, the National Capital Poison Center reported that in 2013, plant and mushroom exposures accounted for approximately 3% of all calls involving children under the age of six.[1] The American Association of Poison Control Centers received more than 46,000 reports of poisoning in 2013 due to plant exposure with approximately 12.8% due to unknown plants.[2] Plant exposures account for approximately 2 to 13% of all companion animal poisonings handled by poison centers.[3-5] Certain classes of plants (e.g., oxalate-containing plants, lilies) often make animal poison control center "top ten" lists of dog and cat poisons.[6-8] Most cases involving companion animals relate to accidental ingestion of ornamental household plants rather than wild plants.[3] Information concerning plant hazards doesn't always reach the consumer; for example, despite nearly two decades of veterinary experience with lily intoxications in cats, only 27% of cat owners surveyed in one study were aware of the hazards these plants pose to cats.[9] Thus, client education is a critical component of case management (Figure 155-1). Exposures can also occur through the ingestion of table scraps and other foods, plant extract-based medications, potpourri and other plant containing products, and plant-derived products (most notably tobacco or nicotine). Garlic is even sometimes intentionally given to dogs as a health supplement. Cats are often at greater risk than dogs, presumably because they more frequently chew on plant leaves. In general, the incidence of plant exposure is highest amongst juvenile animals and likely reflects their inquisitive nature.

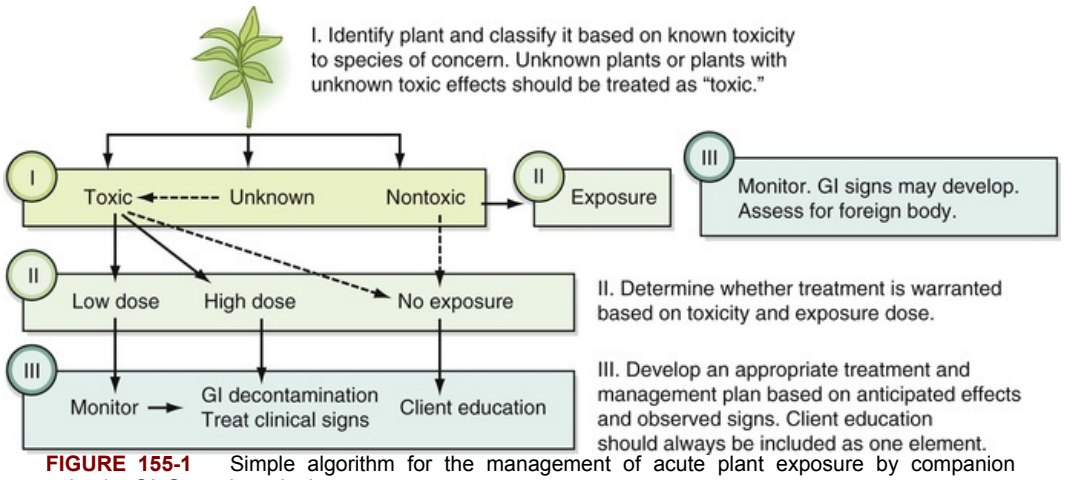

FIGURE 155-1 Simple algorithm for the management of acute plant exposure by companion animals. *GI*, Gastrointestinal.

Veterinary management of plant exposures (see Figure 155-1), including a decision to treat an animal, can be complicated by a number of factors. A significant problem in dealing with plant exposure questions involves the correct identification of the plant. Most plants found in the home or garden have several trivial

or common names and different species may share the same common name (e.g., *Sansevieria* spp. and *Dieffenbachia* spp. are sometimes referred to as "mother-in-laws tongue"). The trivial "lily" or "fern" names are commonly applied to plants from different scientific genera or even families, many of which are not true lilies or ferns. Reliable plant toxicity data for the particular species of interest (e.g., dog, cat, pet bird) are also often lacking (see Table 155-1 for toxicity data for plants discussed in this chapter). Toxicity is also often dependent on the variety, part, growth stage or condition of the plant.[10] In many cases, an owner cannot reliably estimate the exposure dose (e.g., cats frequently tend to nibble whereas dogs often chew and sometimes destroy an entire plant) or deduce when an exposure may have occurred. Species differences in the systemic toxicity of a plant may also occur. For example, the cat appears to display a unique susceptibility to several members of the *Lilium* species of plants while domesticated dogs appear more sensitive to the toxic effects of grapes and raisins. A variety of on-line and iPhone based resources with plant photographs, toxicity, and clinical signs data are readily available to veterinarians and their clients.[11,12]

TABLE 155-1

Toxic Principles and Toxicity Data for Several Common Poisonous Plants of Concern for Small Animal Veterinarians

TOXIC PRINCIPLE	SCIENTIFIC NAMES	COMMON NAMES	VETERINARY SPECIES AFFECTED	ORGAN SYSTEMS AFFECTED	TOXIC DOSAGE
Calcium oxalates (soluble)	*Dieffenbachia* spp. *Zantedeschia aethiopica* *Philodendron* spp. *Schefflera* spp. *Spathiphyllum* spp. *Syngonium podophyllum*	Dieffenbachia, dumbcane Calla lily Philodendron Umbrella plant Peace lily Arrowhead vine	Dog Cat Bird	Gastrointestinal Renal (rare)	Variable
Unknown, aqueous soluble	*Lilium longiflorum* *Lilium tigrinum* or *lancifolium* *Lilium speciosum* *Hemerocallis dumortieri* and *H. fulva*	Easter lily Tiger lily Japanese showy lily "Day" lily	Cat	Gastrointestinal Renal	<1 leaf[24]
Delta-9-tetrahydrocannabinol (THC)	*Cannabis sativa*	Marijuana, kush, hashish	Dog Cat (uncommon) Others	Gastrointestinal Central nervous	Minimal lethal oral dosage in the dog is approximately 3 g/kg.
Azoxyglycosides (e.g., cycasin, neocycasins)	*Cycas revolute* *Zamia* spp.	False sago palm Coontie, Florida arrowroot	Dog Cat (uncommon) Others	Gastrointestinal Liver	1-2 seeds
Andromedotoxin (grayanotoxin)	*Rhododendron* spp.	Rhododendron and azalea	Dog Cat	Gastrointestinal Cardiovascular	2 to 3 leaves
Ricin	*Ricinus communis*	Castor bean	Dog Cat Others	Gastrointestinal	Minimal lethal dose = 1 bean
Abrin	*Abrus precatorius*	Precatory bean	Dog Cat	Gastrointestinal	Minimal lethal dose = 1 bean

			Others		
Various alkaloids including lycorine and narcissine	*Amaryllis* spp. *Narcissus* spp. *Tulip* spp. *Hyacinth orientalis*	Amaryllis Daffodil, jonquil, and narcissus Tulip Hyacinth	Cat Dog Others	Gastrointestinal Central nervous	Oral LD_{50} of isolated lycorine in dogs is approximately 40 mg/kg. The lycorine content in some plant species ranges from 0.097-0.529%.100
Unknown	*Macadamia integrifolia* *Macadamia tetraphylla*	Macadamia nut	Dog	Gastrointestinal Central nervous	Minimum toxic dose 2.2 g/kg69
Methyl and prop(en)-ylcysteine sulfoxides	*Allium cepa* *Allium sativum* *Allium schoenoprasm*	Onion Garlic Chives	Cat Dog	Hemolysis	Variable. Toxicosis was experimentally induced in small dogs at 30 g/kg.78 The toxic dosage has been found to be as low as 5 g/kg in cats and 15 g/kg in dogs.79
Unknown	*Vitis vinifera*	Grapes, raisins, currants	Dog	Renal	0.32 to 0.65 oz/kg. In dogs that develop acute kidney injury, the lowest toxic doses reported are 19.6 g/kg (0.7 oz/kg) of grapes and 2.8 g/kg (0.1 oz/kg) of raisins. The ingested dose does not appear to correlate with the degree of renal damage.
Nicotine	*Nicotiana tabacum* *Nicotiana rustica*	Cultivated tobacco Wild (Indian) tobacco	Dog Cat Others	Nervous Respiratory	Minimal oral lethal dose in dogs and cats is approximately 10 mg/kg.

Diagnosis of plant poisoning generally requires an evaluation of exposure conditions, medical history, and health status. Physical evidence of exposure is also a critical diagnostic indicator (e.g., damaged plant materials, plant remnants in vomitus). On occasion, some analytical chemical methods are available to confirm the presence of plant toxins in gastrointestinal contents, blood, or urine. Animals consuming so-called nontoxic plants may develop vomiting, diarrhea, and other gastrointestinal signs. Irrespective of the plant's innate toxicity, animals ingesting plants are at risk for possible complications associated with a foreign body.[13,14] In some recent (<2 hour) high-dose toxic plant exposures, decontamination of the gastrointestinal tract using species-appropriate emetics and oral activated charcoal (1-2 g/kg) combined with a cathartic is often recommended for asymptomatic animals (see ch. 151). Unless otherwise noted, these decontamination methods are considered applicable to all of the plants discussed in this chapter. Symptomatic and supportive measures are also warranted in affected animals. On occasion, the exposure is significant enough that surgical removal may be required.[13,14] Few plants have effective antidotes. Fortunately, most plant exposures in companion animals result in minimal exposures and often do not constitute a medical emergency. However, a relatively small number of garden and ornamental plants do cause an emergency. This chapter discusses hazards and medical management associated with several garden and ornamental plants that are extremely common or are associated with life-threatening toxic syndromes.

Oxalate-Containing Plants

Plants containing calcium oxalate are one of the most frequent causes of plant poisoning of dogs and cats in the United States.[5] Most oxalate-containing plants of concern to small animal veterinary practitioners (see Table 155-1) contain an insoluble calcium oxalate salt that is arranged in crystallized raphides bundles within

widely-distributed idioblast cells.[15] All parts of the dieffenbachia plant are toxic, with the stem being the most toxic portion of the plant.[16] The raphides are "ejected" from the idioblast upon chewing or contact and may become embedded in exposed tissues. Calcium oxalate and its crystals result in mechanical and inflammatory injury to the skin and mucous membranes.[14,15,17-19] Plant proteolytic enzymes may also contribute to the local inflammation by promoting the release of kinin and histamine from affected cells.[19,20]

The majority of exposures do not result in serious adverse effects. Clinical signs are generally acute (within a few hours) and are often manifested by a local mucosal inflammatory response. Common clinical signs include pain, hypersalivation, variable degrees of oral and peri-oral mucosal edema (tongue, lips, palate, pharyngeal areas), and local pruritus. Animals will often paw at the muzzle or exhibit smacking or swallowing motions. Ingestion is unlikely to result in systemic effects unless very large amounts of plant material have been ingested. Higher-dosage exposures may result in vomiting, dysphagia, dyspnea, abdominal pain on palpation, vocalizing, diarrhea, and hemorrhagic gastritis or enteritis. Most cases resolve with conservative management within 12 to 24 hours, while more significant ingestions may require more aggressive intervention over several days.

Treatments include gastrointestinal decontamination (see ch. 112) and symptomatic and supportive care. Rinsing the oral cavity with water or milk to assist removal of insoluble oxalate crystals is also recommended.[14] Respiratory distress requiring advanced life support, and death due to severe upper airway obstruction, have been reported in humans and animals.[15,18,19,21] Prognosis is generally very good in dogs and cats, and rarely does a life-threatening situation develop.

Liliaceae

Many types of ornamental lilies (see Table 155-1) have been associated with kidney injury in cats.[9,22-24] Poisoning in cats has been associated with the ingestion of flowers, leaves, or plant stems[22-24] and may be associated with an unknown aqueous soluble toxin.[22]

The toxic syndrome is often biphasic. Initially, affected cats frequently (>70% of affected cats) develop increased salivation and moderate to severe vomiting within minutes to hours after ingestion.[25] Vomiting generally subsides after 6 to 12 hours, however, it may recur 24 to 72 hours post-ingestion. The second phase of the clinical syndrome is characterized by oliguric to anuric renal failure, anorexia, central nervous system (CNS) depression, dehydration, and hypothermia. Abdominal (kidney) pain is often present and may be due to swelling and tenderness of the kidneys.[26] Renal damage with polyuria may occur as early as 12 hours after ingestion. Clinical pathology usually reveals moderate to marked increases in serum creatinine, blood urea nitrogen (BUN), phosphorus, and potassium.[27] Serum glucose may reflect a moderate to marked decrease, while liver enzymes may be normal to moderately elevated. Urinalysis generally reveals numerous casts, proteinuria, glucosuria, and isosthenuria (see ch. 72).[22,27] On occasion birefringent crystals, most likely attributable to decreased excretion of oxalates, will also be observed.[27] The most prominent histologic finding is severe necrosis of the proximal convoluted tubules with the basement membranes remaining intact.[22] In addition to the acute gastrointestinal and delayed nephrotoxic effects, approximately 36% of cats exposed to day lilies develop ataxia, depression, tremors, seizures, head pressing, and other neurological signs.[25] Other signs that have been reported include facial and paw edema and dyspnea.

Frequent monitoring of renal function and aggressive clinical intervention have been shown to be effective early in the course of the toxic syndrome.[9] Cats that are decontaminated (oral activated charcoal and cathartic) within hours of clinical onset and undergo aggressive fluid diuresis for a minimum of 24 hours often experience successful recovery (see ch. 112 and 129).[9] Conversely, delays of 18 to 24 hours before intervention are reported to result in renal shutdown and death or euthanasia by 3 to 6 days post-ingestion.

Marijuana *(Cannabis sativa)*

Marijuana (see Table 155-1 and see ch. 154) is a coarse, rough-stemmed annual with opposite or alternate, mostly palmately-compound leaves. This plant was formerly cultivated for fiber production and may be found growing naturally along roadsides, railroads, and pastures. The majority of exposures of concern to veterinarians involve the ingestion of fresh or dried plant material or food products that have been adulterated with marijuana.[28] Companion animal exposure to this plant is considered common.[29] Several states have passed marijuana legalization legislation, which has resulted in increased sales and higher

exposure rates in children and dogs.[30,31] Marijuana contains delta[9]-tetrahydrocannabinol (THC) and other cannabinoids, which interact with brain cannabinoid type 1 (CB1) receptors that form part of the endocannabinoid system. In laboratory animals, agonist interactions with the CB1 receptor result in hypothermia, analgesia, cataplexy, and locomotor suppression—this cluster of signs has been termed the cannabinoid tetrad.[32,33] The amount of THC found in the leaves, stem, flowers and buds vary with plant variety, sex of plant, geographic location, and growing season. Marijuana potency is usually expressed in percent THC by weight—fresh plants can contain up to 1-6% THC while hashish contains as much as 40% THC.[34,35] The most common reported clinical signs of marijuana toxicosis in dogs include ataxia and CNS depression, which is often prolonged for several days.[28,30] Other common clinical signs include mydriasis, increased sensitivity to motion or sound, hyperesthesia, ptyalism, tremors, and urinary incontinence.[10,28,30,36] Less frequent signs can include coma, tremors, tachycardia, or more commonly, bradycardia.

The treatment of marijuana toxicosis relies on gastrointestinal tract decontamination (emetics, activated charcoal and a saline cathartic; see ch. 112) and symptomatic and supportive care.[28] The antiemetic properties of marijuana may limit the effectiveness of certain emetic drugs but these may still be tried before the onset of sedation or ataxia. Because THC is highly lipid-soluble, recent efforts have included the use of intralipid therapy to help reduce the severity and duration of clinical signs (see ch. 153).[28] Dogs with moderate to severe CNS stimulation can be treated with diazepam (0.25-0.5 mg/kg, IV) or chlorpromazine (0.5-1 mg/kg IV).[28] Assisted respiration may be required if significant respiratory depression occurs. Full recovery may require several days to occur in marijuana-poisoned dogs. THC can be detected in plasma or urine in laboratories that are equipped to perform the test.

Cycadales (Cycads)

Several tropical cycads (see Table 155-1) are grown as an ornamental in the subtropical United States. These plants contain azoxyglycosides, which after ingestion are hydrolyzed by intestinal microflora to a hepatotoxic and carcinogenic aglycone (methylazoxymethanol).[37] Cycad amino acids may be involved in the neurologic form of the syndrome.[38,39]

Gastrointestinal and hepatic effects characterize the toxic syndrome seen in dogs.[40] The onset of clinical signs following cycad ingestion can be variable (15 minutes to 3 days) and usually results in vomiting (± hematemesis).[10,40] Less frequent (<50% of cases) signs include CNS depression, diarrhea (± blood), anorexia, and neurological signs including weakness, ataxia, proprioceptive deficits, coma or seizures.[10,40,41] In severe intoxications, persistent vomiting, generalized icterus, generalized subcutaneous ecchymotic hemorrhage, ascites, pulmonary hemorrhage, and congestion may be expected over a 96 hour time period. Serum chemical changes consistent with hepatic injury are frequently seen and include elevated blood levels of alanine aminotransferase, bilirubin, and alkaline phosphatase as well as hypoalbuminemia and prolonged prothrombin (PT) or partial thromboplastin (PTT) times (see ch. 286).[10,40-42] Alterations in white blood cell counts and thrombocytopenia are also frequently (>25%) seen in affected dogs.[10,40] Elevated levels of ammonia and BUN have also been reported.[41] Case fatality rates in excess of 50% have been reported.[40] Acute histopathologic changes can include centrilobular hepatocellular necrosis accompanied by variable amounts of neutrophilic infiltration and hemorrhage.[40,43] One published canine case involving *Zamia floridana* showed microscopic evidence of mild cerebellar nerve fiber degeneration, which may account for some of the observed neurologic effects.[43]

Depending on the amount of plant material ingested, activated charcoal should be re-administered once or twice at 3- to 4-hour intervals.[40] Asymptomatic patients that are successfully decontaminated should be observed for a minimum of 24 hours for evidence of digestive upset, and for the passage of charcoal and or consumed vegetation. Symptomatic animals should be rapidly and carefully assessed and treated for cardiovascular effects (including disseminated intravascular coagulation) as well as respiratory, and neurologic function. Treatment is largely symptomatic and supportive.

Rhododendrons

The Heath, or *Ericaceae*, family includes important ornamentals found throughout the temperate regions of the world. Several members of this plant family are extremely toxic with the ingestion of as little as two or three leaves producing serious intoxication in a dog or cat. One of the more important members of the family

are *Rhododendron* (rhododendron, azalea) species. The stems, leaves, flowers, and nectar contain various derivatives of the toxic parent compound grayanotoxin. Labrador tea includes the dried leaves of *Rhododendron groenlandicum* and represents another possible exposure source.[44] Grayanotoxin intoxication in people is also related to the consumption of honey ("mad honey disease") contaminated with *Rhododendron* nectar.[45,46] Grayanotoxin binds to sodium channels thereby maintaining excitable cell membranes in a state of depolarization.[47] These plants also accumulate high levels of tannins, flavonoids, or phenolic glycosides. These latter compounds are considered most responsible for the significant gastrointestinal effects following ingestion. Grayanotoxin poisoning in veterinary medicine occurs most frequently in livestock and is uncommon in companion animals.[48]

Most of our knowledge regarding grayanotoxin poisoning is derived from the human clinical literature. Clinical signs in animals following *Rhododendron* ingestion generally occur within 2 to 6 hours. Vomiting and diarrhea are acute (can occur within minutes), moderate to severe, and may be protracted and may occasionally be hemorrhagic. Abdominal pain, tenesmus, vocalization, CNS depression, skeletal muscle weakness, dyspnea, tachypnea, hypotension, pulmonary edema, and positive inotropic effects are commonly described.[49] Convulsions, collapse, and cardiopulmonary arrest may also occur. Cardiovascular effects (arrhythmias, hypotension, and shock) may be life-threatening and should be anticipated and monitored very closely.[47] Increased vagal stimulation may contribute to clinical bradycardia; however, tachyarrhythmias may also be noted.[46,47,50] Cardiorespiratory arrest is thought to occur due to sustained grayanotoxin-induced depolarization of the myocardium.

Unless otherwise indicated, vomiting should be induced if it has not occurred spontaneously, followed by gastrointestinal decontamination using oral activated charcoal and a cathartic (see ch. 112). Management depends heavily upon symptomatic care including appropriate use of antiarrhythmic drugs to control cardiovascular effects (see ch. 248). It is noteworthy that several cases of *Rhododendron* ingestion with large numbers of nearly intact leaves required emergency gastrotomy.[51] A rapid liquid chromatography mass spectrometry method has been developed for the quantitative determination of grayanotoxins in gastrointestinal contents and urine.[52]

Castor Bean and Precatory Bean

Castor bean *(Ricinus communi)* and precatory bean *(Abrus precatorius)* are among the most toxic plants. The castor bean is readily recognized by its large lobed leaves and spiny seedpods. Castor bean and precatory bean contain the toxalbumins ricin and abrin, respectively. Castor bean seeds and oil have been used as a laxative and for the treatment of certain other diseases.[53] Castor bean seed hulls are used as mulch and fertilizer while the cake meal residue has been used as a livestock feed supplement.[53] Exposure to these castor bean-based fertilizers and soil conditioners has been implicated in poisonings in domesticated dogs.[54,55]

Ricin consists of a neutral A-chain (32 kDa) bound by a disulfide bond to an acidic B-chain (34 kDa).[56] The B-subunit binds to glycoproteins on the surface of epithelial cells, enabling the A-subunit to enter the cell via receptor-mediated endocytosis.[57] This subunit inactivates ribosomal RNA, thereby inhibiting protein synthesis, which ultimately leads to cell death. All parts of the plants are toxic; indeed, seeds can contain 5% ricin. The seeds of these plants have a tough coat requiring mastication to release the ricin molecule. Toxalbumins are poorly absorbed from the digestive tract[58]; however, even very small absorbed doses can be lethal. Depending upon the exposure dose, the onset and progression of clinical effects can vary between peracute (within 2-4 hours) to delayed (by ≥24 hours). Most commonly, there is a 12- to 24-hour quiescent period followed by the development of severe hemorrhagic gastroenteritis. Systemic delivery of ricin can result in delayed (2 to 5 days) cytotoxic effects on the CNS, kidney, liver, and adrenal glands.[55,59,60] Clinical signs may include hyperthermia, colic, nausea, vomiting, dehydration, leukopenia, hemolysis, hemorrhagic diarrhea, hemoglobinuria, kidney failure, progressing to terminal seizures and death.[54,55,59,60] Lesions can include severe hemorrhagic to necrotizing gastroenteritis, necrosis of lymphoid organs, and multifocal renal tubular degeneration and necrosis.[55,60]

Management of the asymptomatic animal includes induced emesis, followed by gastric lavage and/or activated charcoal plus a small amount (50% of normal dose) of a suitable cathartic (see ch. 112 and 151).[59,61] Shock doses of intravenous fluids and additional digestive system support should be used as indicated by the patient's condition (see ch. 129). Baseline serum chemistries and a complete blood count, with daily reassessment through recovery, are recommended. Confirmation of ricin exposure in veterinary cases has

depended on analytic chemical detection of the biomarker ricinine in gastrointestinal content, liver and kidneys.[55,60] A variety of ELISA-based approaches has also been developed for the detection of ricin in biological samples.[62]

Iris, Amaryllis, and Related Bulbs

The iris (*Iris* sp.) contains irritant resins including irisin, iridin, and irigenin in its bulb. Other toxic ornamental bulbs include amaryllis, daffodil, jonquil, narcissus, tulip, and hyacinth. The toxic constituents in these plants are not well understood although several of these plants contain lycorine, narcissine, and other alkaloids.[63] In general, all parts of these plants are considered toxic.[64] Lycorine is a potent emetic with an incompletely understood pharmacologic mode of action. Lycorine interactions at the neurokinin-1 (NK_1) and to a lesser extent 5-hydroxytryptamine 3 ($5\text{-}HT_3$) receptors are thought to be involved in lycorine-induced emesis in dogs.[65] Lycorine-induced emesis follows the pharmacokinetics of this alkaloid.[66] Lycorine has an elimination half-life in the dog of <1 hour following parenteral administration, which coincides with vomiting.[66] Most poisonings in dogs occur when bulbs are planted, while cats may occasionally ingest leaf and stem materials.[67] Ingestion of the bulb itself may result in severe gastroenteritis, vomiting, tremors, seizures, hypothermia, bradycardia, and hypotension.[64,67] Treatment of intoxications with these plants is strictly symptomatic and supportive, relying primarily on gastrointestinal tract decontamination with emetics (unless vomiting has already occurred) and oral activated charcoal and cathartics (see ch. 112 and 151).

Toxic Foods

Natural plant foods that are toxic to companion animals include macadamia nuts, onion, garlic, chives, grapes, and raisins.[68] Macadamia nut ingestion by dogs is associated with an acute toxic syndrome that generally develops within 1 to 12 hours after ingestion.[68,69] Initial clinical signs often include weakness, CNS depression, vomiting, ataxia, tremors, decreased conscious proprioception, and hyperthermia, while some animals develop hindlimb weakness resulting in recumbency.[68,69] The most noteworthy clinical pathologic change seen is a marked increase in serum lipase that can persist for several days.[69]

Onion, garlic, and chive bulbs, bulblets, flowers, and stems—including dehydrated, powdered, and cooked materials—are toxic and may induce hemolysis in dogs and cats.[68,70,71] These plants contain sulfoxides that can be broken down into N-propyl disulfide. N-propyl disulfide causes oxidative damage to hemoglobin and erythrocyte membranes, resulting in the formation of methemoglobin, Heinz bodies, and eccentrocytes, which then lead to intravascular hemolysis and anemia.[68,72] Cats may be more sensitive to the toxic effects of onions and related plant species because of differences in their hemoglobin that result in an increased sensitivity to oxidative damage.[68] Certain breeds of dogs (such as Japanese Shiba and Japanese Akita) have a low-sodium and high-potassium phenotype due to an active Na-K pump found in the mature red blood cell membrane.[73] These breeds are thought to be more sensitive to oxidant-induced hemolysis and may be at greater risk for *Allium* intoxication.[73,74] In all species studied, hemolysis is associated with Heinz body production.[71,75-77] The initial appearance of Heinz bodies may often be observed within 6 to 24 hours after ingestion. Methemoglobinemia may also be clinically significant in occasional cases, especially where the ingested dose is relatively high.

Clinical signs associated with ingestion of these hemolytic plants include vomiting, diarrhea, and increased salivation.[68,78,79] Clinical signs may not develop for 1 to 5 days and often emerge as hematologic changes begin. Other clinical signs can include pale mucous membranes, weakness, ataxia, anorexia, depression, tachypnea, and tachycardia secondary to anemia. Icterus and hemoglobinuria may be seen secondary to intravascular hemolysis.[68] Hematologic alterations include decreased packed cell volume, hematocrit, and hemoglobin concentration. Increased reticulocyte counts and neutrophilic leukocytosis may be seen in response to the anemia. Clinical chemistry changes include hyperbilirubinemia and increased blood urea nitrogen level caused by transient nephrosis.[68,79]

Ingestion of raw fruit, fruitcakes, mince pies, chocolate bars, malt loaf, scones and snack bars containing grapes, raisins, and related fruits by dogs has been linked with acute kidney injury (see ch. 322). At this time, the toxin and mode of action remain poorly characterized. Clinical signs usually appear within 4 to 6 hours after ingestion. Animals that remain asymptomatic one to two days after exposure are not expected to

develop clinical signs.[68,80] The most common signs seen include vomiting (often present within 2 hours of ingestion), lethargy, anorexia, CNS depression, and diarrhea.[81,82] Severely affected dogs often develop evidence of impaired renal function (azotemia, proteinuria, glucosuria, hematuria, and crystalluria) within 24 to 72 hours of exposure.[80,82] Reduced urine output, ataxia, and weakness are associated with a negative outcome or poor prognosis.[83] Additional clinical chemistry changes including increased serum phosphorus, amylase, glucose, alanine aminotransferase, and alkaline phosphatase concentrations have been reported.[80,82] Blood chemistry values, including renal values, should be periodically monitored for 72 hours following ingestion. Tubular degeneration and necrosis of the kidneys may follow. Acute tubular necrosis of the proximal convoluted tubules with or without mineralization has been reported.[80,84]

Management of an animal with suspected macadamia nut, onion, grape or other toxic food exposure depends on the animal's initial presentation and the agent. Decontamination by emesis, followed by oral administration of activated charcoal with a cathartic, is generally used in all asymptomatic animals with recent toxic food ingestion (see ch. 151). No specific antidotes exist, so most treatment plans depend heavily on symptomatic and supportive care. There are a few additional measures that can be considered for the following agents:

- Onions (and related plants): Ascorbic acid (30 mg/kg PO) has been recommended for the prevention and control of Heinz body anemia and methemoglobinemia.[68,79] Intravenous fluids are recommended to correct dehydration from vomiting and promote diuresis to reduce the potential for hemoglobin nephrosis. The packed cell volume (PCV) should be monitored daily for 5 to 7 days. If anemia becomes severe, transfusions with whole blood or packed red blood cells may be needed (see ch. 130).[68,79] Antioxidants have not been shown to be beneficial.[77]
- Grapes (and related plants): Fluid diuresis for the first 48 hours may help reduce the severity of acute kidney injury.[80] Medications such as furosemide, dopamine, or mannitol can be used in anuric renal failure. Hemodialysis or peritoneal dialysis may be of benefit if available (see ch. 109 and 110).[85]

Tobacco

Sources of tobacco include cigarettes and chewing (smokeless) tobacco. Processed tobacco contains a complex mixture of naturally derived plant products as well as a variety of flavoring and other additives.[86] A description of these components is beyond the scope of the present chapter; instead, the main focus will relate to nicotine toxicity. Plant strain, geographical locale, growing conditions, and other factors contribute to the highly variable nicotine content in tobacco.[87] Individual, commercially-processed United States cigarettes contain approximately 9 to 30 mg nicotine.[10,87] The recent emergence of so-called electronic cigarettes has led to an increase in pediatric human and animal exposures to nicotine.[88,89] These cylindrical devices hold a fluid-filled ("e-liquid" or "e-juice") cartridge containing a liquid solution with up to 80 mg/mL of nicotine.[90] Other constituents found in the liquid include glycerol, propylene glycol, and ethylene glycol.[91] Several over-the-counter nicotine-based 2 or 4 mg polacrilex chewing gums and replacement transdermal patches are available in the United States as nicotine replacement therapy used in smoking cessation. Nicotine polacrilex is a resin complex of nicotine and polacrilin, which is a cation-exchange resin prepared from methacrylic acid and divinylbenzene. The gum may also contain sorbitol as a sweetener and buffering agents to enhance buccal absorption of nicotine. The rate of release of nicotine from the resin complex in chewing gum is variable and depends on the vigor and duration of chewing. Nicotine transdermal patches typically contain 8.3 to 114 mg of the free alkaloid. All patches have significant residues of nicotine (2 to 83 mg) even after 24 hours of application. Some patches consist of a drug reservoir containing nicotine in an ethylene-vinyl acetate copolymer matrix that delivers the drug via a rate-controlling polyethylene membrane. Nicotine can be absorbed from these patches (and other products) following ingestion.[92] Most nicotine gum and transdermal patch formulations are buffered to alkaline pH to facilitate the nicotine absorption through cell membranes.[93] Peak blood nicotine concentrations are often reached within minutes following the ingestion of tobacco or nicotine, making gastrointestinal decontamination more difficult.[89,93]

Nicotine is a cholinergic (nicotinic) receptor agonist that exhibits both stimulant (low-dose) and depressant (high-dose) effects in the peripheral nervous system and CNS.[94] Nicotine's cardiovascular and neurologic effects are usually dose dependent. For example, low dosages of nicotine induce central or peripheral nervous system stimulation with arousal and an increase in heart rate or blood pressure. At high dosages, nicotine

causes ganglionic blockade resulting in bradycardia, hypotension, and depressed mental status.[95] Nicotine is quite toxic (the minimal oral lethal dosage in dogs and cats is approximately 10 mg/kg), and the toxic effects develop rapidly after ingestion.[92,96] Minimal toxic dosages in companion animals are incompletely understood; however, in children, poisoning can occur after ingestion of 1 mg of nicotine per kilogram of body weight.[97] Nicotine-induced clinical effects may include muscle tremors, hypertension, tachycardia, tachypnea, vomiting, hypersalivation, CNS depression or excitation, mydriasis, ataxia, weakness, seizures, and death from respiratory paralysis.[10,89]

Management of nicotine overdose generally involves gastric decontamination followed by symptomatic and supportive therapy (see ch. 151).[89,98] If vomiting has not occurred following an acute ingestion of nicotine, the stomach should be emptied immediately by inducing emesis or by gastric lavage. Activated charcoal and a saline cathartic should be given immediately following gastric emptying. Activated charcoal should be given every 6 to 8 hours following ingestion of transdermal patches because delayed nicotine release may occur. Vigorous intravenous fluid support and additional therapy should be instituted if hypotension or cardiovascular collapse occurs. Seizures should be treated with standard anticonvulsants such as diazepam (see ch. 136). Atropine may be given for bradycardia, excessive bronchoconstriction, or diarrhea. Assisted pulmonary ventilation may be necessary for the management of respiratory paralysis. Nicotine can be detected in gastrointestinal contents, serum, and urine.[99]

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CHAPTER 156

Venomous Bites and Stings (Zootoxicoses)

Michael Peterson

Client Information Sheet: Pit Viper Bite

Snake Bite: Pit Vipers

Pit vipers, the largest group of venomous snakes in the United States, are involved in an estimated 150,000 bites of dogs and cats annually, approximately 99% of all venomous snakebites.[1] In North America, there are three genera of pit vipers: rattlesnakes (*Crotalus* and *Sistrurus* sp.), copperheads, and cottonmouth water moccasins (*Agkistrodon* sp.; E-Figure 156-1). Pit vipers control the amount of venom they inject depending upon the situation. Initial defensive strikes are often nonenvenomating. Offensive bites deliver a controlled amount of venom, and agonal bites deliver the entire venom load. The severity of any pit viper bite is related to the volume of venom injected, its toxicity and location. Location influences rate of venom uptake. Toxicity of rattlesnake venom varies greatly among individuals and species (Table 156-1). Traditionally, pit vipers were believed to have hemotoxic venoms, but many rattlesnake species and several subspecies have venom with potent neurotoxic components. Some may only have neurotoxic venom (E-Box 156-1).[2-4] The primary purpose of the venom is not to kill but rather immobilize the prey and predigest its tissues.

TABLE 156-1

Venom Yields of Selected North American Snakes

SNAKE SPECIES	DRY WEIGHT (MG VENOM)	LD_{50} IV (MICE)
Eastern diamondback *(Crotalus adamanteus)*	200-850	1.68
Western diamondback *(Crotalus atrox)*	175-800	2.18
Mojave rattlesnake *(Crotalus scutulatus)*	75-150	0.23
Eastern coral snake *(Micrurus fulvius)*	2-20	0.28
Cottonmouth *(Agkistrodon piscivorus)*	90-170	4.17
Copperhead *(Agkistrodon contortrix)*	45-75	10.92

E-FIGURE 156-1 Pit viper skull with retractable front fangs. Note secondary and tertiary fangs. (Courtesy Arizona Desert Museum, Tucson, AZ. In Peterson ME: Snake bite: pit vipers. *Clin Tech Small Anim Pract* 21[4]:174-182, 2006.)

E-Box 156-1

Species of Rattlesnakes with Populations Containing Neurotoxins in Venom

Crotalus durissus durissus
Crotalus durissus terrificus var. *cumanensis*
Crotalus horridus atricaudatus
Crotalus Lepidus klauberi
Crotalus mitchellii mitchellii
Crotalus tigris
Crotalus vegrandis
Crotalus viridis abyssus
Crotalus viridis concolor
Crotalus scutulatus scutulatus (venom A)
Crotalus scutulatus salvini
Crotalus catenatus catenatus

Onset of clinical signs after envenomation may be delayed for several hours. In humans, 49% of all severe envenomations are later graded as nonenvenomating or mild. Every pit viper envenomation is different. The victim's body mass, bite location, post-bite excitability, and use of medication affects severity. The snake affects the severity by its species, size, reason for striking, and degree of venom regeneration since last use (Table 156-2). Life-threatening envenomation may occur with no local clinical signs other than the puncture wounds. Severity of local signs may not reflect systemic severity. Local tissue reactions to pit viper envenomation include puncture wounds, which may bleed or swell. Additionally, ecchymoses and petechiae may develop. Fang marks do not indicate that envenomation has occurred, only that a bite has taken place

(Box 156-2). Systemic signs include pain, weakness, dizziness, nausea, muscle fasciculations, regional lymphadenopathy, altered respiratory rate, salivation, cyanosis, proteinuria, bleeding, obtundation and convulsions. Abnormal clotting times, decreased hemoglobin, echinocytosis of red blood cells (RBCs), hypotension, and thrombocytopenia have been seen.

TABLE 156-2

Variables Affecting the Severity of Envenomation

VICTIM	SNAKE
Body mass	Species
Bite location	Size
Time to medical facility	Age of snake
Type of first aid applied	Motivation for bite
Concurrent medications?	Time since last venom use?
	Time of year?

Box 156-2

Common Signs of Envenomation

Pain
Swelling
Ecchymosis
Weakness
Sloughing tissue
Shock
Punctures
Nausea

Severe hypotension follows fluid loss from the vascular space into the subcutis and pooling of blood within "shock organs" (i.e., hepatosplanchnic [dogs] or pulmonary vascular bed [cats]). Clotting abnormalities largely depend upon the species of snake. Bleeding disorders range from direct blockage or inactivation of various factors in the patient's clotting cascade to destruction of megakaryocytes in the circulation and bone marrow. Approximately 60% of patients develop a bleeding disorder, usually consisting of hypofibrinogenemia, prolonged clotting times, and thrombocytopenia (30% of victims). Some venoms lyse mature clots. The "snakebite scoring system" (Box 156-3) has been proven useful for monitoring severity and progression of the clinical syndrome, providing an accurate means of quantifying the patient's condition.[5] Patients should be scored on entry, and 6, 12, and 24 hours after admission.

Box 156-3

Snakebite Severity Score Sheet

Snakebite Severity Score

Pulmonary System

0 Signs within normal limits
1 Minimal—slight dyspnea
2 Moderate—respiratory compromise, tachypnea, use of accessory muscles
3 Severe—cyanosis, air hunger, extreme tachypnea, respiratory insufficiency or respiratory arrest from any cause

Cardiovascular System

0 Signs within normal limits
1 Minimal—tachycardia, general weakness, benign dysrhythmia, hypertension
2 Moderate—tachycardia, hypotension (but tarsal pulse still palpable)
3 Severe—extreme tachycardia, hypotension (non-palpable tarsal pulse or systolic blood pressure < 80 mm Hg), malignant dysrhythmia or cardiac arrest

Local Wound

0 Signs within normal limits
1 Minimal—pain, swelling, ecchymosis, erythema limited to bite site
2 Moderate—pain, swelling, ecchymosis, erythema involves less than half of extremity and may be spreading slowly
3 Severe—pain, swelling, ecchymosis, erythema involves most or all of one extremity and is spreading rapidly
4 Very severe—pain, swelling, ecchymosis, erythema extends beyond affected extremity, or significant tissue slough

Gastrointestinal System

0 Signs within normal limits
1 Minimal—abdominal pain, tenesmus
2 Moderate—vomiting, diarrhea
3 Severe—repetitive vomiting, diarrhea, or hematemesis

Hematological System

0 Signs within normal limits
1 Minimal—coagulation parameters slightly abnormal, PT <20 sec, PTT <50 sec, platelets 100,000-150,000/mm^3
2 Moderate—coagulation parameters abnormal, PT 20-50 sec, PTT 50-75 sec, platelets 50,000-100,000/mm^3
3 Severe—coagulation parameters abnormal, PT 50-100 sec, PTT 75-100 sec, platelets 20,000-50,000/mm^3
4 Very Severe—coagulation parameters markedly abnormal with bleeding present or the threat of spontaneous bleeding, including PT unmeasurable, PTT unmeasurable, platelets <20,000/mm^3

Central Nervous System

0 Signs within normal limits
1 Minimal—apprehension
2 Moderate—chills, weakness, faintness, ataxia
3 Severe—lethargy, seizures, coma

Total Score Possible 0 to 20

PT, Prothrombin time; *PTT,* partial thromboplastin time.

A complete blood count with differential, including platelet count and red cell morphology evaluation, should be obtained. Echinocytosis of RBCs has been reported in 89% of dogs post-envenomation: marked type III echinocytosis (95-100% of mature RBCs affected) in 18/28 dogs (64%) and moderate echinocytosis (15-30% of mature RBCs affected) in 7/28 dogs (25%) in one study.[6] But, pets lacking this abnormality may still have been envenomated. A serum biochemistry panel, serum electrolytes, and coagulation profile should be obtained. This should include activated clotting time, prothrombin time, partial thromboplastin time, fibrinogen, and fibrin degradation products. Urinalysis with macro- and microscopic evaluations including free protein and hemoglobin-myoglobin should be performed. Testing should be repeated as indicated to monitor syndrome progression and effectiveness of therapy. Circumferential measurements of the affected body part at, above, and below the bite site at intervals aid in monitoring progression of swelling secondary to many pit viper bites.

Although many first-aid measures have been advocated for pit viper bite victims, none has been shown to prevent morbidity or mortality.[7] Recommendations are to keep the patient calm and quickly transport the patient to a medical facility to be hospitalized and monitored closely for a minimum of 8 hours. A mainstay of treatment is IV fluids to maintain volume support and combat shock (see ch. 127 and 129). The only proven specific therapy against pit viper envenomation is IV administration of a polyvalent pit viper antivenom effective against North American pit viper venoms (Table 156-3). Coagulation defects, fluid losses, changes in

neurologic status, cardiac conduction abnormalities, and the necrotizing effect of venom can be dramatically reversed when antivenom treatment is initiated appropriately. Coagulopathies have been corrected in both human and veterinary patients if treated within 96 hours of envenomation. Proper reconstitution of lyophilized antivenom is demonstrated in the companion electronic version of this text (Video 156-1). Skin testing prior to administration is unreliable and not advocated.

TABLE 156-3

Antivenoms for Treatment of North American Pit Viper Envenomations

	DONOR SOURCE	BINDING PROTEIN	LYOPHILIZED	IMMUNIZING VENOMS
Boehringer-Ingelheim	Equine	IgG	Yes	Western diamondback rattlesnake Eastern diamondback rattlesnake Fer-de-lance* South American rattlesnake*
BTG Crofab	Ovine	Fab1	Yes	Western diamondback rattlesnake Eastern diamondback rattlesnake Mojave rattlesnake Water moccasin
Venomvet	Equine	Fab2	No	Fer-de-lance* South American rattlesnake* Lance head
Bioclon Antivipmyn	Equine	Fab2	Yes	South American rattlesnake* Fer-de-lance*
Polyvet	Equine	IgG	No	Central American rattlesnake Fer-de-lance*

*May be from different regions of South and Central America.

Antivenom should be diluted in normal saline (100-250 mL) and administered slowly IV for the first few minutes to assess for allergic reactions manifested as facial pruritus, emesis, and hyperemia of ear pinna (see ch. 130 and 137). If no adverse reactions are noted after 5 minutes, the antivenom infusion rate can be increased. If a reaction occurs, stop the infusion, continue IV fluids and treat the patient with diphenhydramine (1 mg/kg IV). Since most reactions are infusion-rate-related, once the patient stabilizes antivenom, administration can be resumed at a slower rate. If the reaction recurs, stop the infusion. Ideally, patients receive their total dose within ½ hour. A single antivenom vial usually suffices; however, some patients will require administration of multiple vials (E-Box 156-4). Patients with severe thrombocytopenia are at risk of recurrence within a week, generally not as severe as the initial condition, and should have daily thrombocyte counts performed. Pain management often is necessary with antivenom administration, and some patients may require further therapy (see ch. 126). Fentanyl is preferred as an IV continuous rate infusion (loading dose 2 mcg/kg, then 2-10 mcg/kg/h). Morphine should be avoided due to its histamine-releasing activity, which may be confused with the onset of anaphylaxis. Corticosteroids and nonsteroidal anti-inflammatory drugs should not be used. Since there has been no definition of a "protective" titer and no canine or feline challenge studies, use of the rattlesnake vaccine is not endorsed.

E-Box 156-4

Indications for Additional Antivenom Administration

Evidence of Progression of Envenomation Syndrome

Quantifiable increase in swelling
Worsening laboratory values
Decreased mental status

Worsening coagulation defects
Severity score increasing

Coral Snakes

Sonoran coral snake envenomation is not clinically relevant, but the Eastern, Texas, and the South Florida coral snakes are dangerous.[8,9] North American coral snakes have a black snout and distinct encircling color bands of black, yellow and red (E-Figure 156-2). They have short fixed fangs and need to hold and chew to deliver venom (E-Figure 156-3).[10] These snakes can be aggressive if disturbed, delivering a pugnacious bite. Venom uptake can be delayed for hours and may take a week or longer to clear the body. The venom is neurotoxic, inducing a non-depolarizing postsynaptic neuromuscular blockade (a curare-like syndrome) with little local tissue reaction. Dogs exhibit acute central nervous system depression, emesis, excessive salivation, quadriplegia with decreased spinal reflexes in all limbs, and respiratory paralysis. Additionally, hemolysis, anemia, hemoglobinuria, and morphologic alterations of red blood cells may become manifest.[11] Cats exhibit acute ascending flaccid quadriplegia, central nervous system depression, reduced nociception, anisocoria, absence of spinal reflexes in all four limbs, hypothermia, and loss of the cutaneous trunci reflex.[12] Hemolysis and hemoglobinuria have not been observed in cats.

E-FIGURE 156-2 Coral snake coloration: black, yellow, red fully encircling bands. (Courtesy Arizona and Poison Drug Information Center, Tucson, AZ.)

E-FIGURE 156-3 Small fixed front fangs. (Courtesy Arizona Poison and Drug Information Center, Tucson, AZ.)

Coral-snake-bitten pets should be transported to a veterinary facility capable of 24-hour critical care and assisted ventilation. An elastic compression bandage, firmly encompassing the bitten limb, will delay venom uptake and should not be removed until antivenom has been administered.[12,13] A bitten pet should be hospitalized for at least 48 hours of continuous monitoring (extreme vigilance) and supportive care that includes managing paralysis and preventing aspiration pneumonia. Any evidence of respiratory distress should be aggressively addressed and endotracheal intubation considered. The only definitive treatment is administration of coral snake antivenom, no longer made in the United States. Studies have shown crossreactivity with either Australian Tiger snake *(Notechis scutatus)* or the Mexican coral snake (Micrurus) antivenoms (may be available at a local zoo).[11,14] Other South and Central American antivenoms do not cross-react with U.S. coral snake venom. Early IV antivenom administration is most effective. Once clinical signs of coral snake envenomation become manifest, they progress with alarming rapidity and are extremely difficult to reverse. The initial recommended antivenom dose is one to two vials, but additional vials maybe required. If antivenom is not available or if administration is delayed, supportive care includes respiratory support. Assisted mechanical ventilation can be used but may have to be employed for up to 48 to 72 hours.

Brown Spider Envenomation

At least 5 species of *Loxosceles* spiders indigenous to the United States (Figure 156-4) have been associated with necrotic arachnidism: *L. reclusa, L. refuscens, L. arizonica, L. unicolor,* and *L. laeta*.[15] These spiders are commonly called "violin spiders," because of the violin-shaped marking on the cephalothorax, with the neck of the violin pointing toward the abdomen (Figure 156-5). Many dermonecrotic lesions are commonly incorrectly diagnosed as brown recluse bites, as up to 60% of the diagnoses are made in geographic regions of the country which do not have indigenous *Loxosceles* spider populations. The long list of differential diagnoses include burns to decubital ulcers. It is important to note that in humans, the primary misdiagnosis is MRSA. A single bite can inflict a lethal envenomation. Male spiders of equivalent size generate half the venom volume of females. Larger mature spiders have more venom. Their venom has eight major and four

minor electrophoretic bands, with sphingomyelinase D recognized as the primary dermonecrotic factor.[16] It binds to cell membranes and chemotactically induces polymorphonecular leukocyte infiltration. The toxin depletes serum hemolytic complement, prolongs activated partial thromboplastin time, and depletes clotting factors VIII, IX, XI, and XII.[17] The venom induces rapid coagulation and occlusion of small capillaries, causing subsequent tissue necrosis. When C-reactive protein and calcium are available, sphingomyelinase D has a direct hemolytic effect. In the presence of amyloid protein, calcium-dependent platelet aggregation can occur, leading to activation of the prostaglandin cascade. The venom releases body lipid fragments into circulation, which subsequently act both as emboli and as inflammatory mediators. The victim's immune response to the venom ultimately determines the severity of the ensuing lesions.[17] Histologically, lesions resemble Arthus and Shwartzman phenomena.

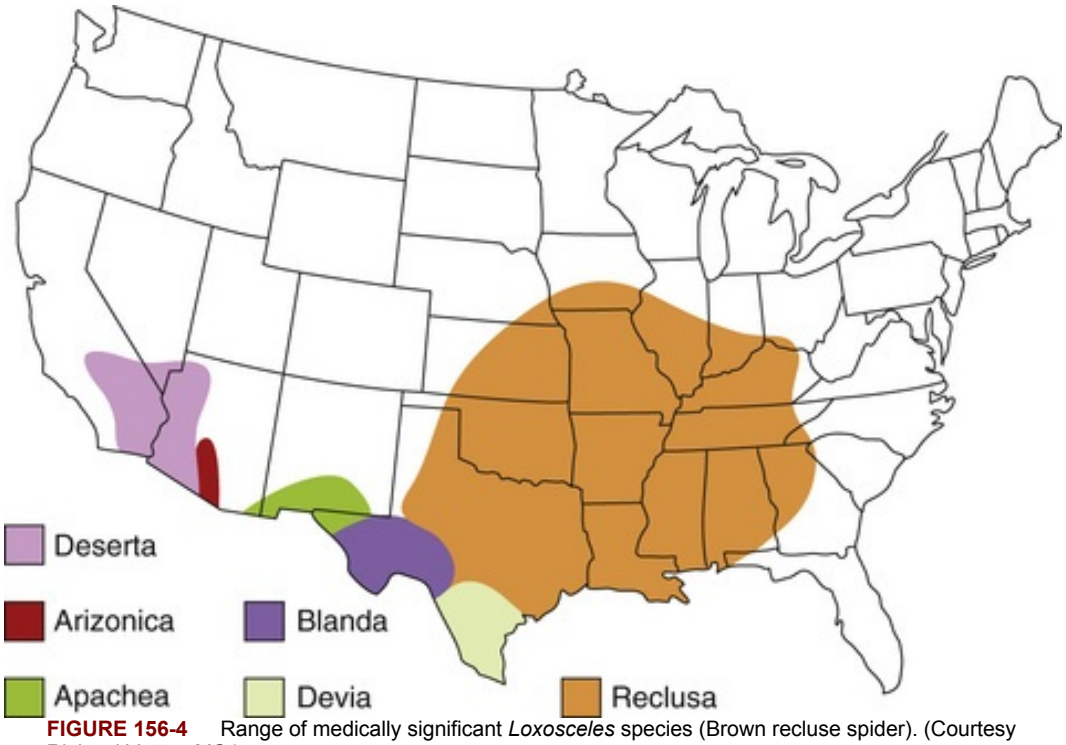

FIGURE 156-4 Range of medically significant *Loxosceles* species (Brown recluse spider). (Courtesy Richard Vetter, MS.)

FIGURE 156-5 Violin marking on cephalothorax of *Loxosceles* spider. (Courtesy Bill Banner, MD, PhD.)

Early clinical diagnosis is difficult since lesions initially appear mild.[4] The ensuing bite severity is determined by the quantity of venom injected, the bite site, and the victim's immune status.[15] Dogs and cats are not often examined before lesions are well-developed with necrosis. Human bite victims describe a mild stinging sensation lasting as long as 8 hours. Subsequent pruritus and soreness develop as vasoconstriction causes local ischemia. Edema follows with development of a classic "bulls-eye lesion" (an erythematous area surrounding a pale ischemic region with a dark necrotic center as the lesion matures). Lesion margins may progress unevenly as gravity pulls venom ventrally, leaving an eccentric lesion with the original center located dorsally. Hemorrhagic bulla may develop within 24-72 hours with a maturing eschar (decubitus ulcer) below. If pets do not disturb the eschar, it usually sloughs within 2 to 5 weeks, leaving an indolent ulcer that does not usually penetrate into the muscle below. Lesions in adipose tissue can be extensive. Healing is slow, and these ulcers may persist for months, leaving a deep scar.

Systemic signs are less common but can be life-threatening. The most common condition is a Coombs' negative hemolytic anemia with significant hemoglobinuria, usually developing within 24 hours of envenomation and persisting for up to one week. Other early-onset clinical signs include fever, arthralgia, vomiting, weakness, and a maculopapular rash. Pets may have a leukocytosis, thrombocytopenia, or disseminated intravascular coagulation (DIC) (see ch. 197). Systemic reaction is not proportionally related to the local reaction or vice versa.[15]

There is no specific antidote. Treatment plans are directed at one or two possible syndromes, local cutaneous lesions, and systemic manifestations of envenomation. The use of the antibiotic and leukocyte inhibitor dapsone (4,4′,-diaminodiphenylsulfone) has been advocated in the past but subsequently has failed to prove clinical efficacy. Surgical excision is not encouraged. Lesions are treated as open wounds with several cleanings daily with Burrow's solution. Some debridement may be necessary. Broad spectrum antibiotics may be indicated. One or two atmospheres of hyperbaric oxygen twice daily for 3 to 4 days may be benefical.[18]

Systemic signs of *Loxosceles* envenomation are potentially fatal and should be treated aggressively. Patients exhibiting signs should be hospitalized for close observation. Anti-inflammatory, antipyretic, and analgesic agents can be useful. Compounds that affect clotting should be avoided. Systemic corticosteroids have a protective effect on red cell membranes, thereby inhibiting hemolysis. Their use should be limited to the first few days of the syndrome and, in the case of prednisolone, should be administered at a rate of 0.5-1 mg/kg/day. Coagulation defects are treated as indicated (see ch. 135). Hospitalization and IV fluid therapy may be indicated to maintain hydration and renal function (see ch. 129).

Black Widow Spider

Female *Latrodectus* spiders are capable of life-threatening envenomation. They are shiny black and globose with an hourglass red/orange marking on the abdomen. Immature females are beige, brown, and reddish which changes to black as they mature, with the hourglass marking becoming more prominent (Figures 156-6 and 156-7). They control the amount of venom injected and a single bite is capable of delivering a lethal dose of venom to pets. Venom promotes calcium-independent release of neurotransmitters (acetylcholine, norepinephrine and others) down concentration gradients and inhibits their subsequent reuptake.[19] Acetylcholine, noradrenaline, dopamine, glutamate, and encephalin systems are all susceptible to the toxin.[19]

FIGURE 156-6 Immature black widow spider; note the paler coloration. (Courtesy Arizona Poison and Drug Information Center, Tucson, AZ.)

FIGURE 156-7 Mature female black widow spider with egg sac. (Courtesy Arizona Poison and Drug Information Center, Tucson, AZ.)

Local signs are generally absent, and systemic manifestations usually occur during the first 8 hours post-envenomation. The condition is extremely painful in moderate to severe envenomations. Progressive muscle pain and generalized muscle cramping is common, especially of the chest, abdomen, and lumbar regions. Abdominal rigidity without tenderness is a hallmark sign. Systemic hypertension and tachycardia are common.[20] Cats are extremely susceptible to the venom. Marked signs of paralysis may occur early. Severe pain is manifested by loud vocalizations. Excessive salivation, restlessness, vomiting, and diarrhea may occur. Muscular tremors, cramping, ataxia, and inability to stand precede complete paralysis.

Bitten pets should be hospitalized for at least 48 hours. Treatment is administration of specific antivenom, usually supplied in a lyophilized state and reconstituted rapidly with 2 mL of supplied diluent.[21] Antivenom should be diluted into less than 20 mL fluids and given by slow IV infusion, as previously described. A single vial is usually sufficient to resolve the clinical syndrome within 30 minutes. Care should be taken with administration of IV fluids since most patients are hypertensive. Complete recovery may take weeks.

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SECTION IX

Blood Pressure

OUTLINE

Chapter 157 Pathophysiology and Clinical Manifestations of Systemic Hypertension
Chapter 158 Treatment of Systemic Hypertension
Chapter 159 Systemic Hypotension

CHAPTER 157

Pathophysiology and Clinical Manifestations of Systemic Hypertension

Serge Chalhoub, Douglas Palma

Pathophysiology of Systemic Hypertension

The product of cardiac output and total peripheral resistance equals systemic blood pressure (BP). Cardiac output is determined by heart rate and stroke volume. Counterregulatory mechanisms normally exist to counteract sustained elevations in BP. Systemic hypertension (SH) is defined as a persistent pathologic elevation in systemic arterial BP, more importantly recognized with sustained elevations in systolic BP. A complex interaction between systems, including the kidneys, nervous system, vasculature, and heart, can lead to altered BP control (Figure 157-1).[1] Guidelines for identification and evaluation of SH have been devised on the basis of probability of target-organ damage (TOD) secondary to SH, and recommended monitoring and therapy guidelines have been established.[2] These guidelines do not take into account interbreed differences, sex, body condition score, age, and other health factors potentially affecting BP.

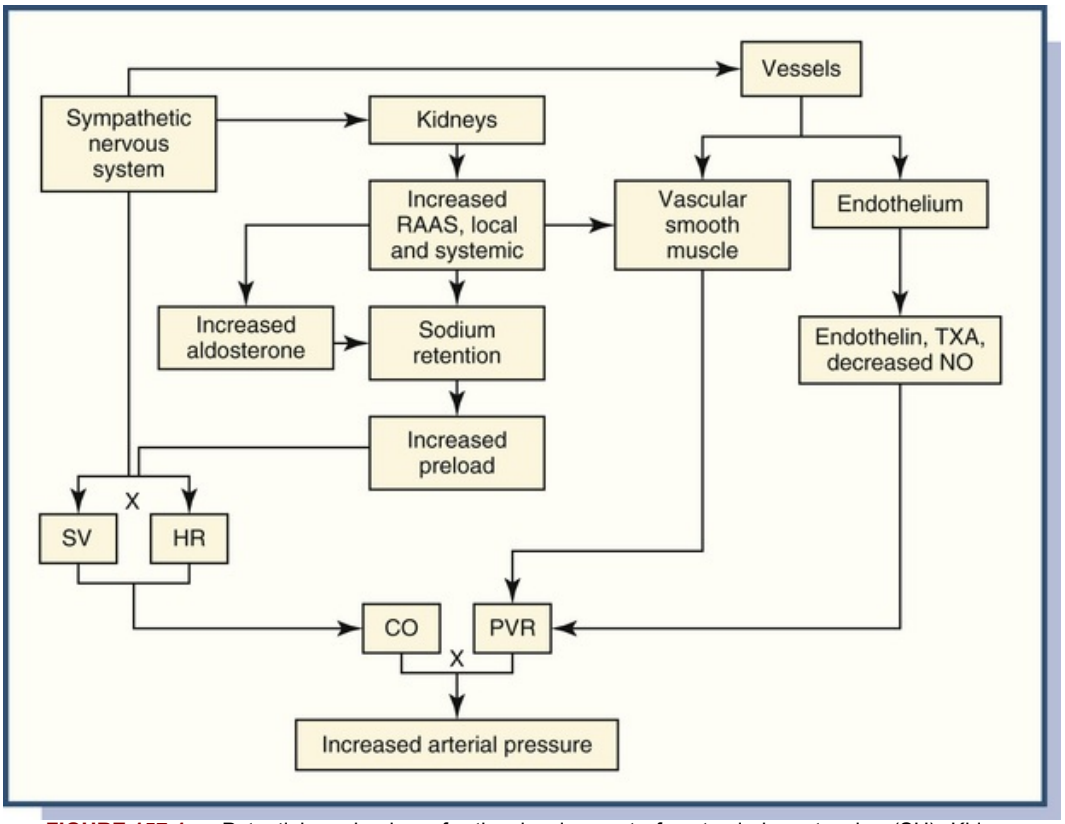

FIGURE 157-1 Potential mechanisms for the development of systemic hypertension (SH). Kidney disease is likely the most common cause of SH in cats and dogs. Increased sympathetic system activation, vascular smooth muscle abnormalities, and endothelial disease are other known mechanisms. *CO,* Cardiac output; *HR,* heart rate; *NO,* nitric oxide; *PVR,* peripheral vascular resistance; *RAAS,* renin angiotensin aldosterone system; *SV,* stroke volume; *TXA,* thromboxane. (Modified from Syme H: Hypertension in small animal kidney disease. *Vet Clin Small*

SH can be divided into two broad categories: secondary hypertension and idiopathic hypertension. Secondary hypertension is induced by clinical disease or medications. Idiopathic hypertension occurs in absence of a readily identifiable cause based on clinical investigations. Secondary hypertension is much more common in cats and dogs, whereas the reverse is true in humans, in whom idiopathic hypertension traditionally is called "essential" hypertension.

Conditions Commonly Associated With Hypertension

Signalment

SH is more common in older male dogs than in females.[3] Recent evidence suggests that both healthy cats and cats with CKD show a significant increase in BP with increasing age, and there also is a correlation with increased heart rate.[4] The cause of SH with increased age is likely multifactorial and unclear at this time.

No relationship exists between breed and BP in cats[5]; however, certain interbreed variations likely exist in dogs. Greyhounds seem to have an average systolic BP that is 10-20 mm Hg higher than in other dogs[2]; however, a recent study of BP in retired racing Greyhounds identified a significant white-coat effect (systolic and mean BP, and heart rate, were significantly lower at home than in-hospital).[6]

Obesity (see ch. 176 and 359)

There appears to be either a small, or no, correlation between obesity and SH in dogs. In obese dogs, SH might be more related to other diseases such as kidney disease, cardiac diseases, and endocrinopathies, but not gonadal status.[5,7,8] In cats, no studies correlate gender, breed, and body weight with increased SH risk.[9] Unlike in dogs and cats, obesity is a major risk factor for the development of SH in humans.[10]

Kidney Disease (see ch. 322-328)

The most common cause of SH in dogs and cats is kidney disease. 65-100% of cats that present with SH and TOD have evidence of reduced kidney function.[9,11,12] The prevalence of SH in cats with CKD varies between 20% and 65%,[9,11-13] and contrary to humans, prevalence does not seem to increase with increased severity of CKD.[13] With CKD, pathophysiology likely is multifactorial and involves systemic renin-angiotensin-aldosterone system (RAAS) activation (Figure 157-2), impaired sodium (Na^+) excretion, increased intravascular volume, sympathetic stimulation, structural arterial changes, endothelial dysfunction, lack of local nitric oxide (NO) to mediate vasodilation, increased production of vascular endothelin, and likely oxidative stress with increased reactive oxygen species production (see Figure 157-1).[9,14,15] Decreased Na^+ excretion in early kidney disease could be the result of defective collecting duct Na^+ handling because decreased Na^+ filtration should lead to compensating decreased tubular Na^+ reabsorption at this stage.[1] No consistent associations among plasma aldosterone or renin concentrations, SH, and feline CKD have been reported.[9,16-18]

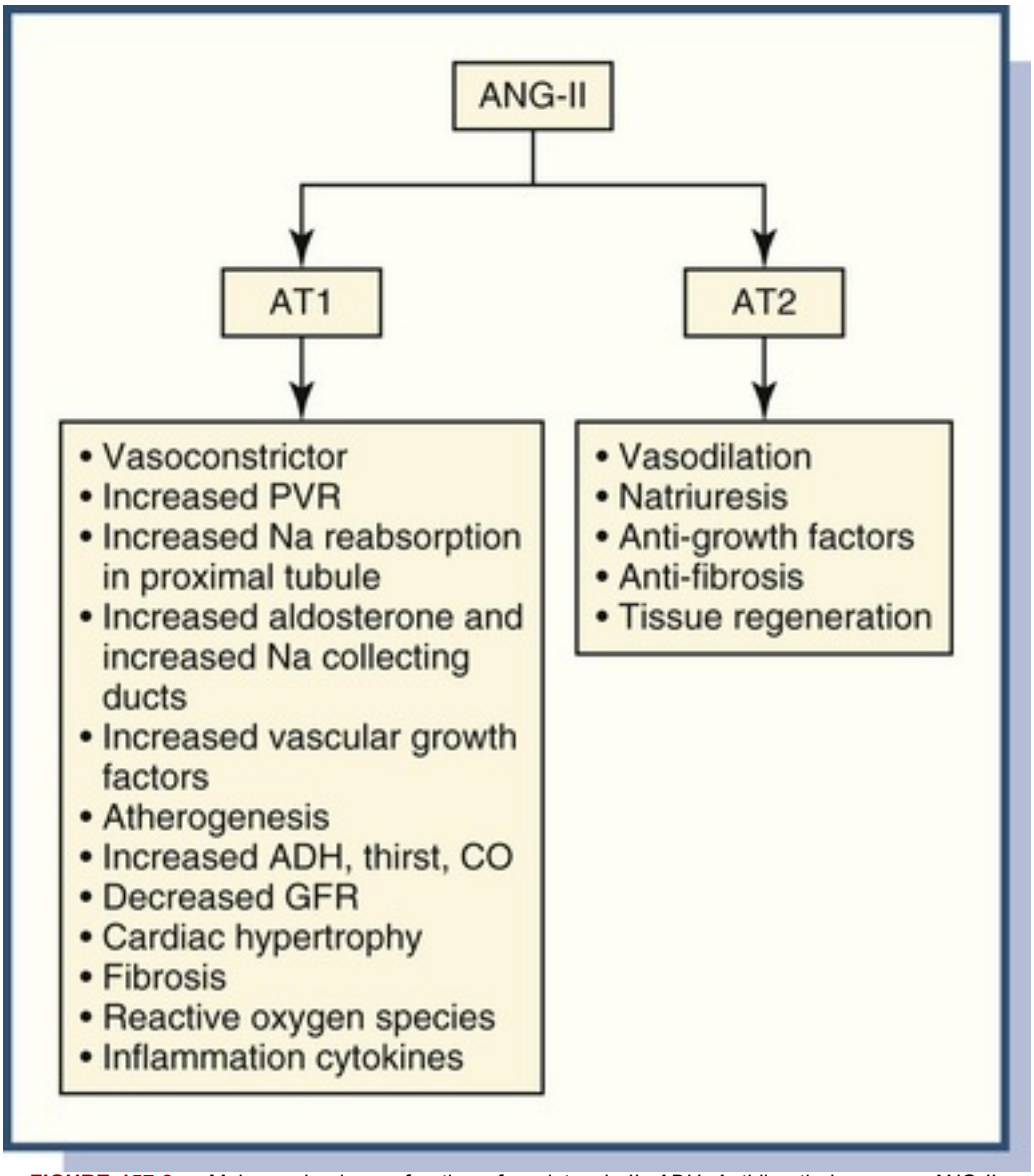

FIGURE 157-2 Main mechanisms of action of angiotensin-II. *ADH,* Antidiuretic hormone; *ANG-II,* angiotensin-II; *AT1,* angiotensin-II receptor, type 1; *AT2,* angiotensin-II receptor, type 2; *CO,* cardiac output; *GFR,* glomerular filtration rate; *PVR,* peripheral vascular resistance.

Angiotensin II also is produced locally, in the renal parenchyma, and intrarenal RAAS likely contributes to and maintains SH in human CKD patients. This promotes glomerular hypertension, worsens proteinuria, leads to oxidative damage, and ends in renal fibrosis.[19-22] Systemic RAAS concentration therefore might not reflect intrarenal RAAS. Systemic aldosterone concentrations are higher in cats with CKD, indicating that elevated aldosterone can contribute to SH and is independent of RAAS. SH in these cats did not respond to treatment with angiotensin converting enzyme (ACE) inhibitors and plasma renin activity was found to be low to normal.[16,17] The pathogenesis of SH in cats could be associated with increased vascular tone, more so than in dogs and humans, and could explain their dramatic response to treatment with calcium channel blockers.[1,23]

Endothelial dysfunction likely is involved in the pathogenesis of SH in human CKD patients. Plasma asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) both affect NO production and action, and circulating concentrations are increased in cats with CKD; levels also correlate with plasma creatinine. However, ADMA concentrations do not seem to be associated with SH, nor is there a correlation between circulating ADMA concentration and cats with TOD. In addition, no difference has been found in plasma ADMA concentrations between normotensive nonazotemic cats and hypertension nonazotemic cats.[1,13]

Proteinuria is an independent variable that is significantly associated with survival in cats with CKD and also in cats with all causes of SH.[23] Protein loss through the glomerulus and tubules likely stimulates the production of inflammatory mediators and cytokines, leading to glomerular hypertension, glomerular sclerosis, and renal fibrosis.[9] With protein-losing nephropathies, SH likely is the result of immune-complex deposition in the glomeruli and subsequent proteinuria and local vascular changes. SH prevalence seems higher in dogs with glomerular disease than in dogs with other forms of CKD.[24,25] SH is prevalent in dogs with leishmaniasis, with 61.5% of dogs with glomerular disease secondary to leishmaniasis developing SH (see ch. 221).[25]

SH occurs with acute kidney injury frequently (see ch. 322), as well as with the use of erythropoiesis-stimulating agents and feline kidney transplants.[26-29] Cats with polycystic kidney disease do not have a high prevalence of SH.[30]

Hyperadrenocorticism (see ch. 306 and 307)

SH is reported in 59-86% of all cases of hyperadrenocorticism in dogs, with those having unilateral adrenal tumors having a higher prevalence of SH.[31,32] In humans with hyperadrenocorticism, SH is suspected to occur secondary to increased intrinsic mineralocorticoid activity, activation of RAAS, and glucocorticoid-induced suppression of vasodilatory mechanisms such as NO production. However, there exists no clear evidence of decreased NO or increased aldosterone concentrations in dogs with hyperadrenocorticism. Many dogs remain hypertensive even after the diagnosis and treatment of hyperadrenocorticism.[31,32]

Adrenal Tumors (see ch. 308 and 311)

SH is common in cats with adrenal tumors, with unilateral cortical tumors such as carcinoma being more prevalent. In these cases, SH has not been found to be associated with survival, and most hypertensive cats return to normal BP after surgical therapy.[33] SH in cats with primary hyperaldosteronism is likely secondary to excess circulating aldosterone and its effects on renal Na^+ reabsorption. Increased Na^+ retention leads to increased intravascular volume and increased potassium secretion.[9] Aldosterone also causes vasoconstriction and increased peripheral vascular resistance, and it increases the effect of the sympathetic nervous system.[9,32] The majority of cats (>90%) with primary hyperaldosteronism have SH as defined by a systolic BP > 180 mm Hg, with SH resolving in all cats in whom BP was measured post-operatively.[9,32,34,35]

Pheochromocytoma is considered uncommon in dogs and rare in cats. Increased catecholamine secretion leads to excessive stimulation of alpha- and beta-adrenergic receptors, causing sustained or paroxysmal SH. At least half of affected dogs have SH at some point, and variable, paroxysmal SH also is possible.[32,36,37]

Hyperthyroidism (see ch. 301 and 302)

Excessive thyroxine in humans will cause a substantial decrease in systemic vascular resistance (SVR), followed by a decrease in diastolic BP. This in turn causes a reflexive increase in cardiac output. In the kidneys, decreased SVR stimulates the activation of RAAS, leading to increased BP. More importantly, thyroid hormones also increase sensitivity to catecholamines, thereby increasing cardiac inotropy and chronotropy.[9,32,38]

The prevalence of SH in cats with hyperthyroidism was once considered to be 5-23% and hyperthyroidism a major risk factor for SH and TOD.[9,32,39-41] However, recent evidence points to a much lower prevalence than previously thought,[42] and studies evaluating cats with TOD such as retinopathy indicate very few cats were hyperthyroid and severe SH seems rare. In dogs, hyperthyroidism is rare but it can occur; SH has been reported secondary to thyroid gland adenocarcinoma, with subsequent return to normal BP after carcinoma therapy.[43]

Diabetes Mellitus (DM) (see ch. 304 and 305)

SH is common in human DM patients, and nephropathy secondary to DM is thought to be the main factor for the development of SH in human type 1 diabetics. In human type 2 DM, a wider range of metabolic syndrome factors (obesity, insulin resistance, hyperlipidemia) could be implicated.[32,44] Loss of insulin can lead to decreased endogenous vasodilatory effects via altered NO generation, increased Na^+ and water retention,

increased intracellular calcium concentrations leading to increased vascular smooth muscle tone, proliferation of vascular smooth muscle, and sympathetic system stimulation.[32,45]

SH occurs in about one third of humans with type 1 DM and in >50% of type 2 DM patients.[46,47] SH is recognized in 35%-46% of acute spontaneous DM in dogs as well as in longitudinal studies.[47,48] However, no associations between hypertension, proteinuria, and retinopathy with time of DM diagnosis or degree of glycemic control have been found, and systolic BP tends to be <160 mm Hg in most diabetic dogs. In diabetic dogs with SH, the elevation in BP usually is mild.[47] Interestingly, recent evidence indicates that BP does not increase significantly over the course of the disease in dogs, suggesting the effect of DM on BP occurs early on.[47] This contrasts with previous evidence that indicated an increase in prevalence with duration of disease.[48] In cats, SH may only occur in a very small percentage of diabetics.[32,49]

Cardiovascular Disease and Diet (see ch. 183)

SH causes cardiovascular changes in cats and dogs, but contrary to the analogous situation in humans, cardiac disease does not seem to produce SH in cats or dogs (see discussion below).[50] There is no known association between high salt diets and the development of SH in cats.[51]

White-Coat Hypertension

White-coat hypertension is defined as a transient increase in systemic BP in the hospital setting compared to the patient's normal setting, and is likely secondary to activation of the sympathetic nervous system by environmental stimuli. White-coat hypertension is recognized in cats and dogs. Evidence is contradictory on whether cats acclimate, and return to normal BP, faster than do dogs.[6,52] In retired racing Greyhounds, adaptation and acclimation might not occur until after many hours or days.[6]

Idiopathic Hypertension

Idiopathic hypertension is quite rare in dogs. In cats, reports indicate 13-20% of hypertensives are idiopathic.[2,9,12,23] However, this could be an overrepresentation, as other diseases such as early CKD may have been overlooked in retrospective studies. When compared to a population of normotensive nonazotemic geriatric cats, cats with SH have had a significantly higher plasma creatinine concentration (but still considered nonazotemic) and lower urine specific gravity.[53] The development of renal biomarkers that are more sensitive might change the prevalence of idiopathic hypertension in cats as earlier stages of kidney disease are recognized in hypertensive cats that previously would have been classified as idiopathic.

Clinical Manifestations of Hypertension

SH can result in both mechanical and functional alterations in vasculature that can lead to the development of TOD.[54,55] Independent risk factors for TOD exist in people and likely do in our patients as well, including neurohormonal alterations, metabolic or inflammatory factors, and patient factors (obesity, diet).[54-57] Changes in the vasculature transmit elevated pressures to tissue, or induce local ischemia. The most common organs affected include the eyes, brain, kidneys, and heart. The magnitude of BP elevation, variability over 24 hours, and speed of development influence TOD in people.[58] Little information exists in animals regarding the development of TOD and magnitude of BP elevation, but it has been suggested that blood pressure be reduced to a systolic BP of 150 mm Hg and a diastolic BP < 95 mm Hg.[2]

Ocular Manifestations

The most common site of TOD is the eye, with the posterior segment most commonly affected (see ch. 11). As BP exceeds retinal autoregulation, a hypertensive choroidopathy/retinopathy leads to the breakdown of the blood-retinal barrier and altered vessel diameter, reducing retinal/choroidal perfusion.[59,60] Hypertensive retinal lesions are common in geriatric feline patients and were reported in 16% of cats >8 years old in one study.[61] Prevalence is unknown in dogs. Common ocular lesions caused by SH include: partial to complete retinal detachment, hemorrhage, multifocal edema, retinal vessel tortuosity, retinal perivascular edema, papilledema, optic nerve atrophy, and vitreal hemorrhage (Figure 157-3, *A* and *B*).[2,12,62,63] Tortuosity of the

retinal vasculature occurs in small animals but might be less distinct than in people.[3,63-65] Changes to the anterior chamber occur less frequently and generally are manifested as hyphema and/or iris hemorrhage.[12,64,66] Extraocular manifestations are rare; retrobulbar bleeding has been reported in a cat.[67] Secondary ocular manifestations include retinal degeneration and glaucoma.[12,68]

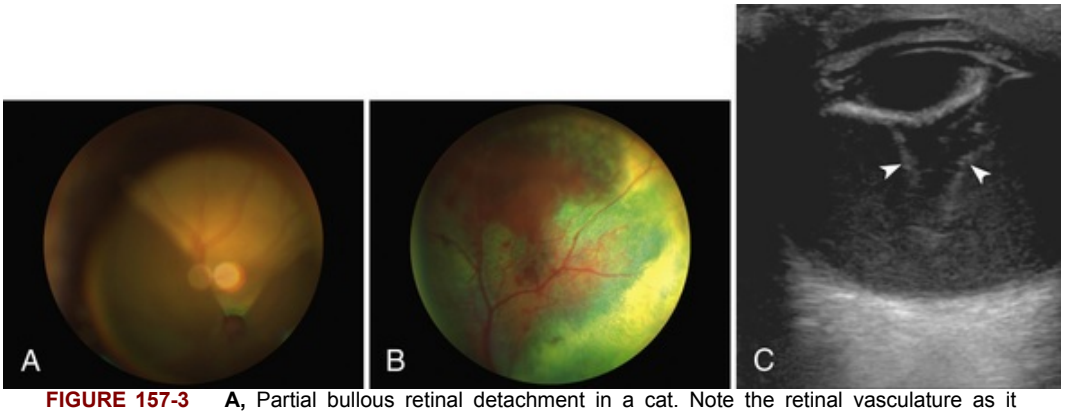

FIGURE 157-3 **A,** Partial bullous retinal detachment in a cat. Note the retinal vasculature as it appears in the non-detached (non-blurry; lower right) region and detached (blurry; center and upper) region. **B,** Hypertensive retinopathy characterized by multifocal retinal hemorrhages on fundic examination. **C,** Ultrasound image of hypertensive retinopathy; retinal detachment with subretinal hemorrhage. Arrowheads indicate detached retina. (**A** and **B,** Courtesy Dr. Alexandra van der Woerdt; **C,** Courtesy The Animal Medical Center.)

Vascular Manifestations

SH can cause a vasculopathy that is characterized by endothelial dysfunction and remodeling of arteries (i.e., arteriosclerosis, arteriosclerotic stenosis) (Figure 157-4).[69] The end result is reduced dilation capability of the resistance vasculature. Vascular changes are less common in dogs and cats relative to people. However, arteriosclerosis has been described in cats.[9,11] Rarely, aortic dissections can occur in dogs and cats (Figure 157-5).[70,71] Vascular remodeling characterized by intimal thickening, fibrosis, and degeneration of the extracellular matrix results in tearing of the tunica intima. Increased intraluminal pressures and pulsatile flow promote formation of a "dissection" between the two layers.[72] Aortic dissections can rupture and/or cause visceral ischemia.

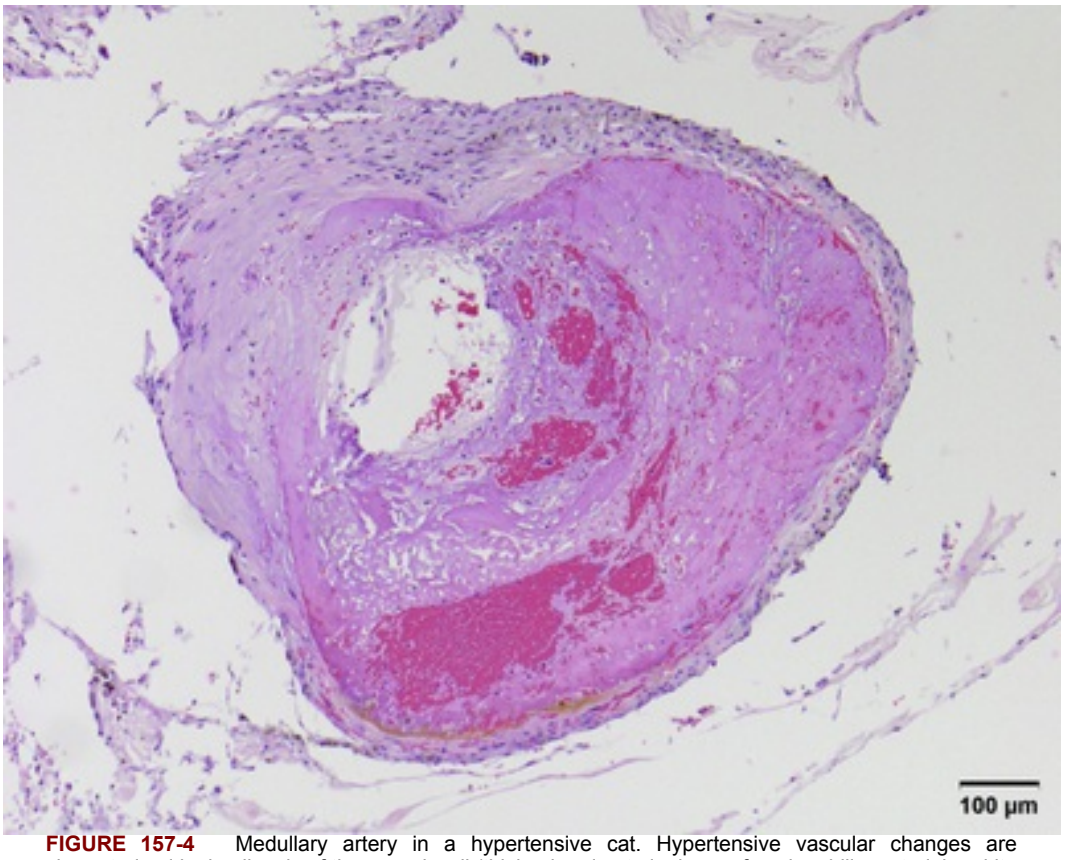

FIGURE 157-4 Medullary artery in a hypertensive cat. Hypertensive vascular changes are characterized by hyalinosis of the vessel wall (thickening due to leakage of eosinophilic material and its deposition in the vessel wall resulting in a hyaline appearance) or as hyperplastic arteriosclerosis (thickening of the vessel wall due to concentric hyperplasia of spindloid cells). Both can be seen in this image. The abnormal vessel is markedly distended by a large thrombus. (Courtesy Taryn Donovan, The Animal Medical Center.)

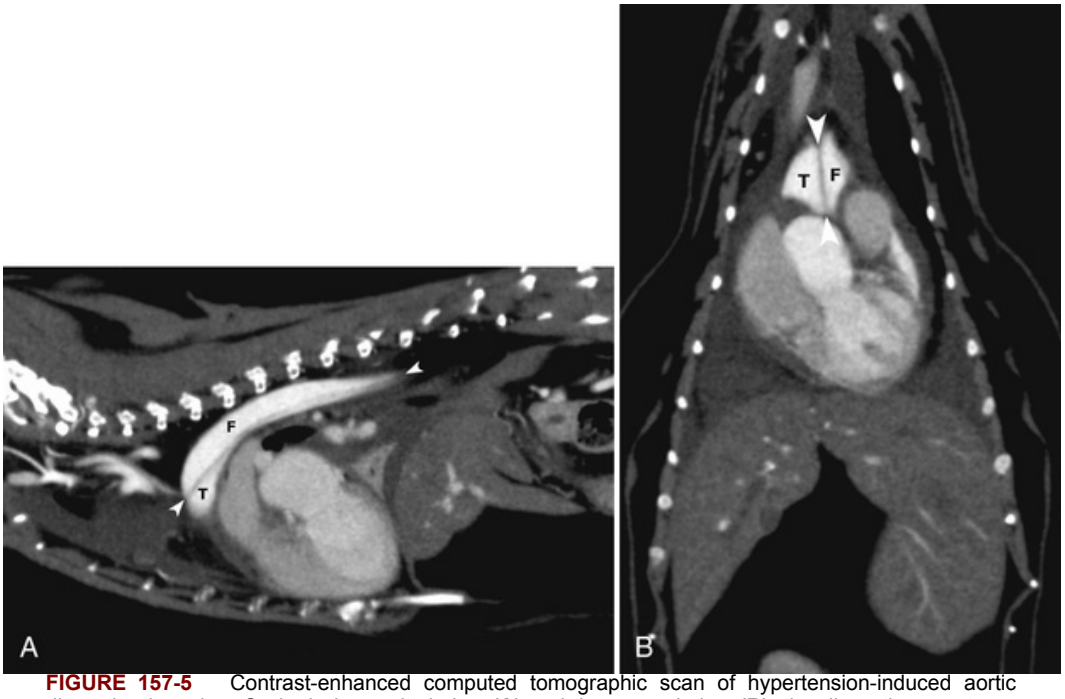

FIGURE 157-5 Contrast-enhanced computed tomographic scan of hypertension-induced aortic dissection in a dog. On both the sagittal view **(A)** and the coronal view **(B),** the dissection creates a false lumen (F) and a true lumen (T), separated by the dissected aortic endothelium (hypointense line;

arrowheads). (Courtesy The Animal Medical Center.)

Cardiac Manifestations

SH can result in both functional and structural cardiac changes.[69] The most common structural change is left ventricular concentric hypertrophy (LVH) in response to increased wall tension (pressure overload). Hypertrophy occurs in an effort to normalize wall stress and preserve left ventricular (LV) chamber function.[73] LVH is non-linearly correlated with SH in cats, with a reported prevalence of 74-85%.[74,75] Left ventricular free wall and interventricular septum thicknesses are significantly different from age-matched controls without SH.[11] Structural alterations occur in experimental models and in 5-91.4% of dogs with spontaneously occurring SH, depending on echocardiographic criteria.[25,76,77] Many patients have limited structural changes and are asymptomatic.[50,78-80] Additional structural alterations can include: aortic root dilation, aortic insufficiency and, potentially, ruptured chordae tendineae.[81]

Remodeling of the coronary vasculature can lead to reduced coronary blood flow reserve. However, direct coronary remodeling is less common in our patients compared to humans. Studies in dogs have documented changes in coronary autoregulation and blood flow distribution independent of vasculopathy.[69] This could predispose to cardiac ischemic injury at lower blood pressures.[82] Reduced coronary reserve has been documented in dogs, increasing their susceptibility to mortality when coronary arterial flow is disrupted.[83,84] Coronary density is further complicated by ventricular hypertrophy. In people, decreased coronary circulation can manifest as angina, a condition not characterized in animals to date.

SH also can induce functional cardiac alterations.[85,86] Hypertensive diastolic dysfunction occurs in people and animals.[79,87] LV relaxation is slowed but overall LV stiffness or rate at which LV stiffness changes with changes in volume is unchanged. Additionally, increases in LV systolic and arterial stiffness exacerbate load-dependent relaxation.[87] Alterations in relaxation frequently precede hypertrophy and fibrosis; however, they also can contribute to these processes.[80,88,89] Echocardiographic features of diastolic dysfunction can include: reversal of the mitral valve E wave (early diastolic filling) to A wave (atrial contraction) ratio, and alterations in tissue Doppler imaging.[80,88,90] Systolic dysfunction, manifested as a reduced velocity of myocardial shortening, stress-corrected mid-wall shortening, and longitudinal LV free wall systolic velocities and gradients, have been observed.[80,88] However, ejection fraction often is normal and other systolic parameters (end-systolic elastance, end-systolic elastance/LV mass, and preload recruitable stroke work) are increased. Additionally, afterload enhancement of systolic performance is maintained. Some of these changes could be contribute to fibrosis, hypertrophy and diastolic dysfunction (Figure 157-6).[87]

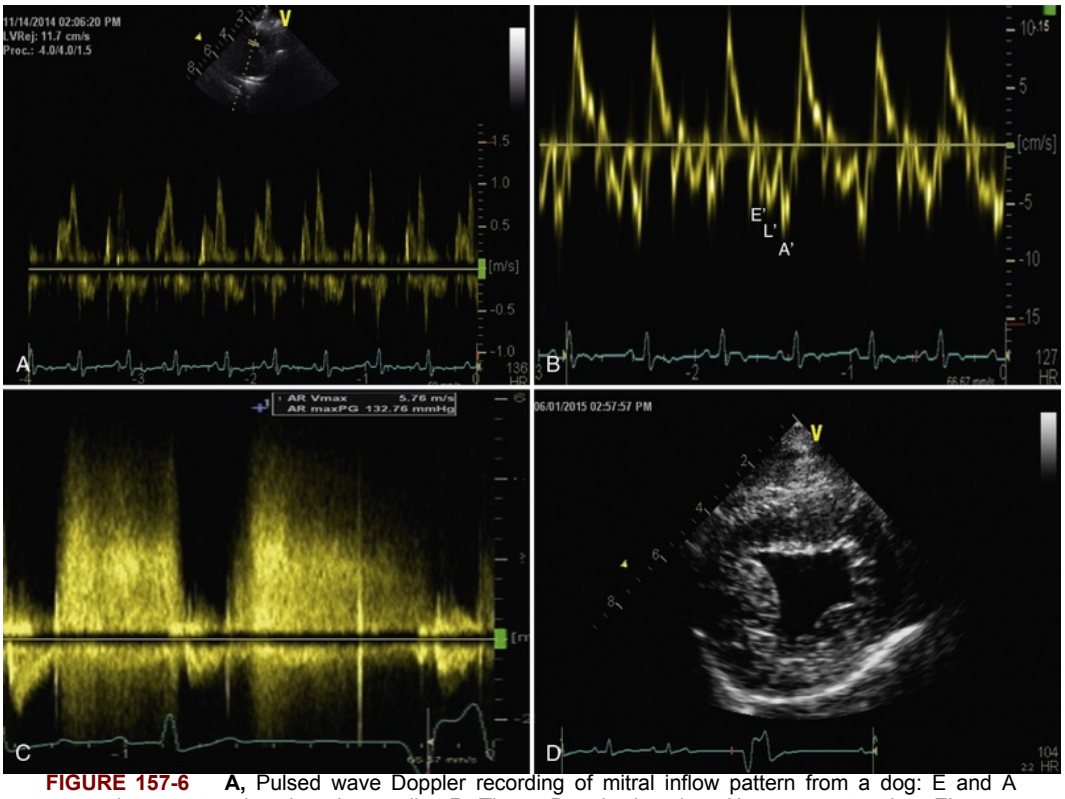

FIGURE 157-6 **A,** Pulsed wave Doppler recording of mitral inflow pattern from a dog: E and A reversal; supports relaxation abnormality. **B,** Tissue Doppler imaging: A' wave greater than E' wave; relaxation abnormality. Mid-diastolic L' wave consistent with diastolic dysfunction. **C,** Continuous wave Doppler; elevated peak aortic regurgitation velocity; consistent with high diastolic BP. **D,** Concentric left ventricular hypertrophy. (Courtesy Dennis Trafney, The Animal Medical Center.)

Both morphologic and functional changes secondary to SH can result in cardiac electrical instability. Ventricular and supraventricular arrhythmias are described in people but are less well characterized in small animals with SH.[91-93] This could be more common in dogs with pheochromocytoma, as catecholamines can contribute independently to arrhythmogenicity: idioventricular rhythms, premature atrial and ventricular contractions, and complete AV block have been documented.[94,95] Hypertension in patients with valvular heart disease can contribute to increased regurgitant volume and decreased stroke volume.

Renal Manifestations

SH can induce a hypertensive nephrosclerosis characterized by glomerulosclerosis, medial thickening of the arteriolar wall, and intimal fibrosis. Due to the common coexistence of hypertension and kidney disease, cause and effect have been questioned, as mentioned before. Additionally, treatment of hypertension could mitigate vascular changes histologically. A reduction in glomerular blood flow from preglomerular arterial narrowing and resultant ischemic injury may contribute. However, glomerular hypertension and hyperfiltration from preglomerular vasodilation also likely occur.[1] Activation of the RAAS could be a key player in the development of hypertensive nephropathy in animals, as has been suggested in people.[73,96,97]

SH also contributes to disease progression in patients with CKD,[97] and hypertension control is directly associated with outcome. SH is linearly associated with death and likelihood of uremic crises in dogs with renal disease.[98] Additionally, SH was correlated directly with histopathological and laboratory evidence of glomerular disease in leishmaniasis in one study, supporting the effect of SH on CKD progression.[99] Experimental canine renal models have shown reduced glomerular injury with ACEI and calcium channel blocker treatment, supporting the association between BP and renal disease progression.[100-102] In cats, glomerulosclerotic changes are slightly more common in hypertensive patients; however, SH has not been correlated directly with increased mortality.[103] The direct association between SH and proteinuria, an independent predictor of renal disease progression, makes correlations between spontaneous (especially proteinuric) kidney disease and SH difficult. Additionally, effective BP control limits the ability to determine

its independent role in disease progression. Blood pressure control in people can delay progression of renal disease/mortality, with some forms benefiting from even aggressive BP targets.[104-108]

Nervous System Manifestations

The nervous system also is affected by SH, with hypertensive encephalopathy being the most common clinical manifestation (Figure 157-7; also see ch. 12). Loss of autoregulation leads to an altered blood-brain barrier and development of vasogenic edema in acute SH. In chronic SH, a rightward shift in the range of blood pressure needed to maintain constant cerebral blood flow occurs. This can lead to changes in the cerebral vasculature, resulting in loss of regulatory tone and changes to vessel walls, potentially leading to hypoperfusion and stroke.[11,98,109,110] Secondary vasoconstriction also can induce ischemia and lead to edema.[11,98,109,110] Hypertensive encephalopathy has a predilection for white matter and predominantly occurs within the cerebrum (parietal and occipital lobes), although it can occur anywhere in the brain. Clinical signs include seizures, altered mentation, blindness, vestibular or cerebellar ataxia and pathologic nystagmus.[111] Cerebellar herniation has been reported in some patients.[110]

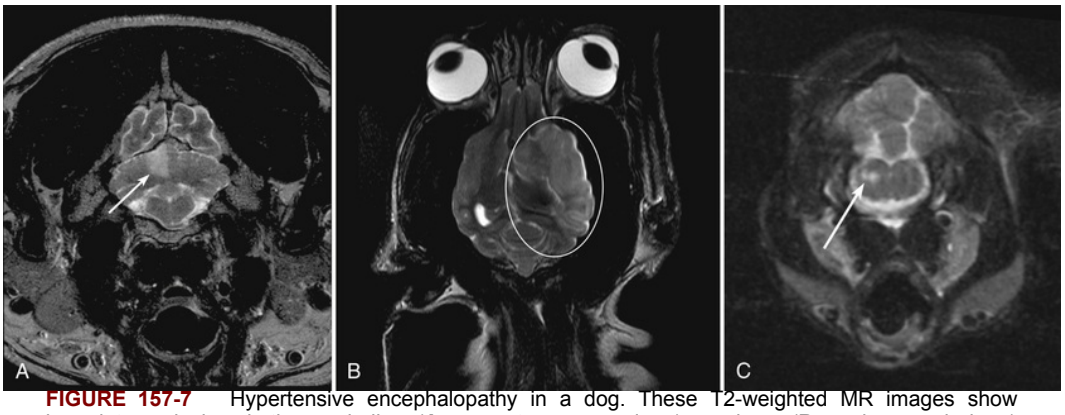

FIGURE 157-7 Hypertensive encephalopathy in a dog. These T2-weighted MR images show hyperintense lesions in the cerebellum (**A,** *arrow;* transverse plane), cerebrum (**B,** *oval;* coronal plane) and medulla (**C,** *arrow;* transverse plane). (Courtesy The Animal Medical Center.)

The spinal cord also is susceptible to SH injury. Ischemic myelopathy secondary to ventral spinal cord white matter ischemia is seen in cats (Figure 157-8). Histopathologic vascular changes (hyalinization, aneurysmal dilation, and/or thrombosis) may be seen.[112] Most cats present acutely, with paresis/plegia and/or cervical ventroflexion. All spinal segments can be affected, but there is a predilection for C1-C5 and most commonly C2 or C3.[113] Intramedullary hyperintense (T2) and isointense > hypointense (T1) lesions are seen on magnetic resonance imaging.[114] Independently, ischemic myelopathy related to perivascular calcification and thrombosis can occur in cats and be associated with myelomalacia.[115,116]

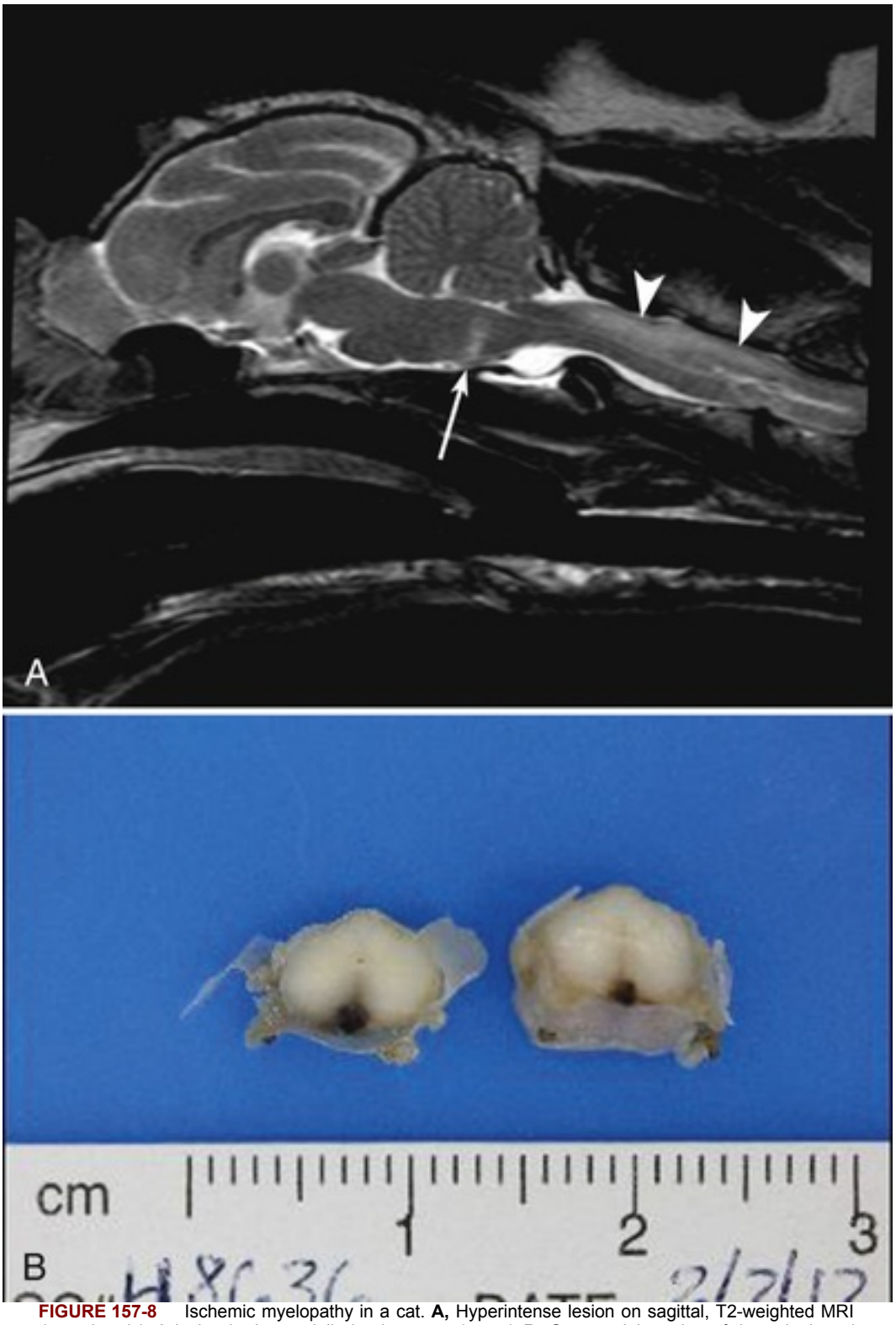

FIGURE 157-8 Ischemic myelopathy in a cat. **A,** Hyperintense lesion on sagittal, T2-weighted MRI *(arrowheads)*. A lesion in the medulla is also seen *(arrow)*. **B,** Gross axial section of the spinal cord demonstrating aneurysmal dilation of vessels. (Courtesy The Animal Medical Center.)

Neurodegenerative conditions in people can be exacerbated by hypertension.[117] Cognitive dysfunction (Figure 157-9), a neurodegenerative condition of small animals, shares pathologic similarities to Alzheimer's disease in humans (see ch. 263).[118] SH is a risk factor for and contributes to progression in Alzheimer's disease, potentially through impaired vascular repair mechanisms.[119]

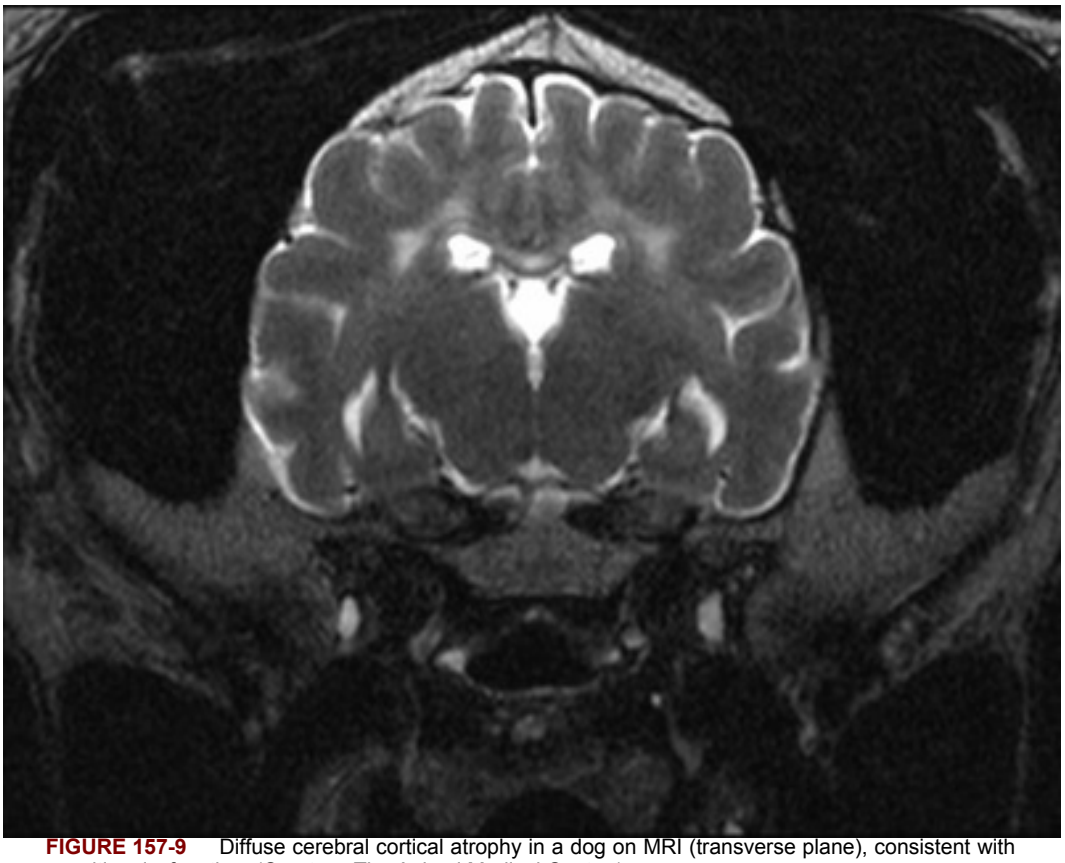

FIGURE 157-9 Diffuse cerebral cortical atrophy in a dog on MRI (transverse plane), consistent with cognitive dysfunction. (Courtesy The Animal Medical Center.)

Cerebral amyloid angiopathy has been reported in geriatric cats and dogs and has been associated with vascular dementia in people.[120-122] Additionally, ischemic infarcts and/or hemorrhages might be more common in patients with cerebral amyloid angiopathy when hypertension is present.[123-129] Antihypertensive therapy can slow the progression of cognitive dysfunction and reduce the incidence of stroke in people.[130,131]

Epistaxis

SH has been suggested to cause epistaxis in small animals. The association in people has been questioned. Additionally, retrospective reviews of epistaxis in dogs and cats have shown, at best, a rare occurrence and questionable association overall.[11,132-134] Concurrent hypertension can complicate management of epistaxis.[135]

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CHAPTER 158

Treatment of Systemic Hypertension

Dan G. Ohad

Client Information Sheet: Treatment of Systemic Hypertension

Systemic hypertension (SHT), even when severe and persistent, may not be associated with clinical signs. Hypertension needs to be controlled once recognized, even if not associated with any apparent clinical signs of secondary "target organ disease" (TOD). To maximize quality and quantity of life, one of the goals of SHT management is amelioration of clinical signs, if present. Overt clinical signs associated with hypertension might include acute blindness (due to retinal or intraocular hemorrhage, retinal detachment or degeneration), neurological signs (such as recumbency, seizure activity, mentation alteration, or vestibular signs), epistaxis, and (rarely) congestive heart failure (where there is severe left-sided heart disease, or circulatory volume overload) following excessive intravenous fluid administration (see ch. 157).[1-3]

Another treatment goal is to slow the progression (if present) or minimize the risk of SHT-related TOD, if not yet present, before it ever develops. This is important as the risk of TOD increases with increasing blood pressure (BP), and vice versa (Table 158-1, Figure 158-1).[4] The prognosis for dogs with chronic kidney disease (CKD) and cats with hyperthyroidism has been shown to be worse with concomitant, uncontrolled SHT.[5,6]

TABLE 158-1

Classification of Hypertension on the Basis of Risk for Target Organ Damage[4]

RISK CATEGORIES	SYSTOLIC BP (mm Hg)	DIASTOLIC BP (mm Hg)	RISK FOR TARGET ORGAN DAMAGE
I	<150	<95	Minimal
II	150-159	95-99	Mild
III	160-179	100-119	Moderate
IV	≥180	≥120	Severe

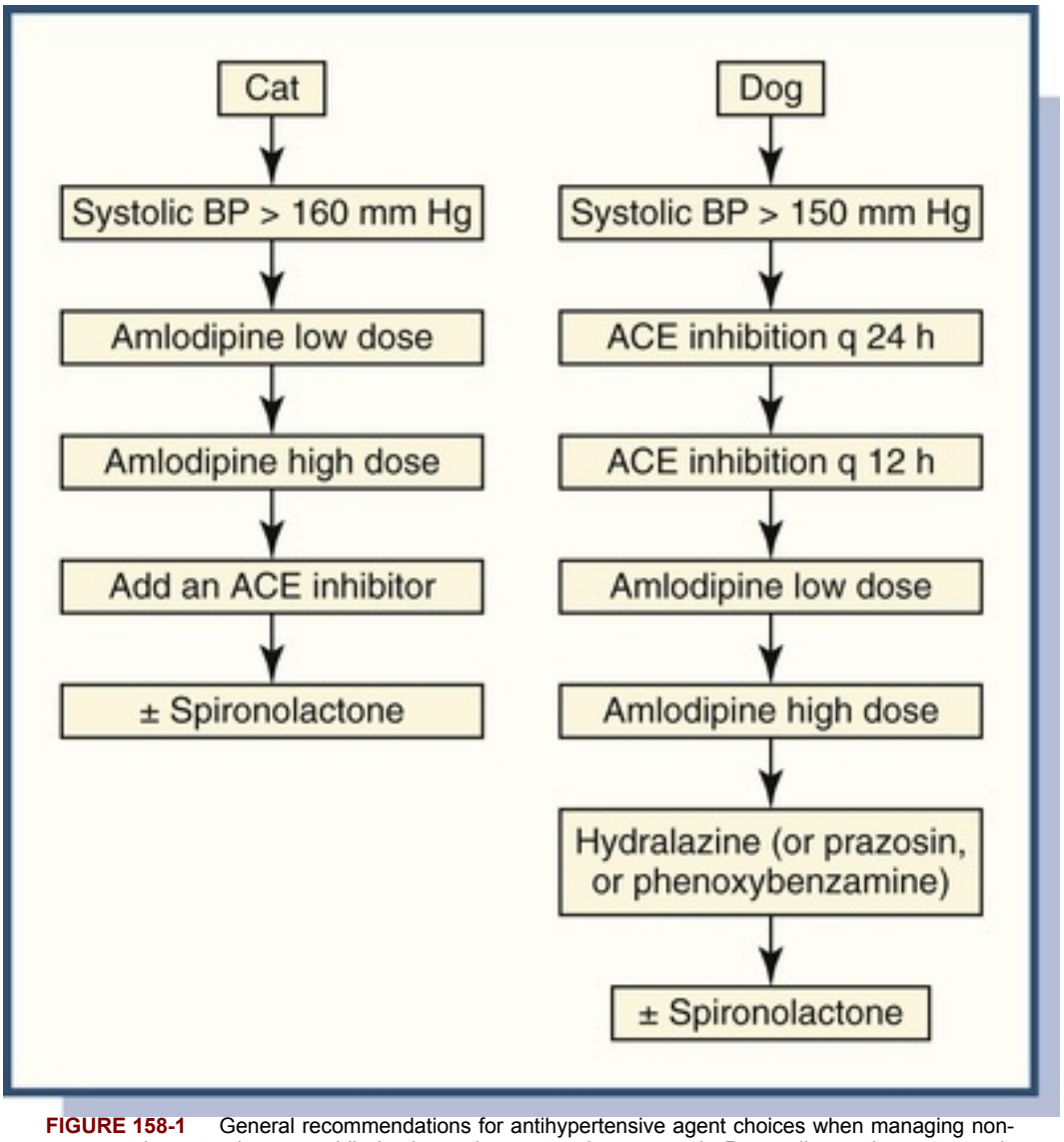

FIGURE 158-1 General recommendations for antihypertensive agent choices when managing non-emergent hypertensive pets while implementing a stepwise approach. Proceeding to the next step is an escalation in treatment, which should be considered when SHT is inadequately controlled. See Table 158-2 and reference #4 for more details.

Systemic hypertension, whether primary (rarely) or secondary (more commonly), is often progressive. In many patients, it remains clinically silent throughout most of the disease course, and yet, often requires lifelong therapy. This may be challenging to justify when communicating the need for chronic therapy to the unsuspecting owner.[4] The fact that control does not mean cure further increases this challenge. The pathogenesis of SHT is multi-factorial and its diagnosis can be elusive. Prior to the onset of lifelong, potentially harmful pharmacotherapy for SHT, its presence, severity, and triggers, if identifiable, should be established. This is attempted based on some or all of the following measures: (1) Multiple BP measurements per examination, repeated on several (at least two) separate occasions, to ascertain SHT persistency (see ch. 99). To minimize over- or underestimation of SHT severity, and to avoid misidentifying trends of change in BP values, every effort should be made to consistently use the exact same measuring instruments, limb-of-choice, and technique, each and every time BP measurements are repeated.[7] This is performed while minimizing auditory and visual stimuli that can trigger a sympathetic-tone mediated, transient, reactive elevation of BP, potentially leading to overestimation of BP values (a "white-coat effect") and to unnecessary side effects or even treatment-related toxicosis. (2) Seeking evidence of ongoing, or of a high risk of, TOD. (3) Ruling out (or controlling, as needed) other conditions that might trigger or contribute to SHT, and that can occasionally be adequately controlled while minimizing the dosage of antihypertensive agents (Table 158-2). While such background conditions are often chronic and incurable, they may account for up to 80% of

hypertensive patients. Control, unfortunately, does not always adequately reduce BP values.[4] These conditions might include any, or even several of the following: renal disease, hyperadrenocorticism, diabetes mellitus, pheochromocytoma, feline hyperthyroidism, primary hyperaldosteronism, obesity, and, rarely, canine hypothyroidism (see ch. 157).[1,4,8,9] (4) Discontinuation or at least a decrease in dosage and/or frequency of drugs that can inadvertently increase systemic BP (e.g., corticosteroids, erythropoietin, or phenylpropanolamine) should be considered.[4]

TABLE 158-2

Dosing Recommendations for Antihypertensive Agents in Alphabetical Order

AGENT	CANINE DOSAGE	REFERENCES	FELINE DOSAGE	REFERENCES
Acepromazine (phenothiazine)	0.05-0.1 mg/kg **SC or IV**	11	0.05-0.1 mg/kg SC or IV	11
	0.5-2 mg/kg PO q 8 h	4	0.5-2 mg/kg PO q 8 h	4
Amlodipine (dihydropyridine calcium channel blocker)	0.0625-0.25 mg/kg PO q 24 h	74	0.125-0.25 mg/kg PO q 24 h	47, 49, 56
	0.05-0.1 mg/kg PO q 24 h	34	0.13-0.3 mg/kg PO q 24 h	11
	0.1-0.25 mg/kg PO q 24 h	4	0.625-1.25 mg/cat PO q 24 h	11, 15, 34
	0.1-0.4 mg/kg PO q 24 h	11, 15	0.1-0.5 mg/kg PO q 24 h	4
Atenolol (cardioselective, beta-1 adrenergic blocker)	0.25-1 mg/kg PO q 24-12 h	11, 15, 74	2 mg/kg PO q 24-12 h	11
	0.25-1 mg/kg PO q 12 h	4	6.25-12.5 mg/cat PO q 24-12 h	11, 15, 34, 74
	1 mg/kg PO q 24-12 h	34	6.25-12.5 mg/cat PO q 12 h	4
Benazepril (ACE inhibitor)	0.25-0.33 mg/kg PO q 24 h	74	0.25 mg/kg PO q 24 h	74
	0.25-0.5 mg/kg PO q 24 h	11	0.25-0.5 mg/kg PO q 24 h	11
	0.25-0.5 mg/kg PO q 24-12 h	15, 34	0.25-0.5 mg/kg PO q 24-12 h	34
	0.5 mg/kg PO q 24-12 h	4	0.5 mg/kg PO q 12 h	4
			0.5-1 mg/kg PO q 24-12 h	15, 47, 56
Enalapril (ACE inhibitor)	0.25-0.5 mg/kg PO q 24-12 h	11	0.25 mg/kg PO q 24 h	74
	0.5 mg/kg PO q 24-12 h	4, 74	0.5 mg/kg PO q 24 h	4
	0.5-1 mg/kg PO q 24-12 h	15, 34	0.25-0.5 mg/kg PO q 24-12 h	11, 15, 34
Hydralazine (direct arteriolar dilator)	0.5-2 mg/kg PO q 12 h	4	1-2.5 mg/cat **SC**	15
	0.5-3 mg/kg PO q 12 h	11	2.5 mg/cat PO q 24-12 h	4
	0.5-3 mg/kg PO q 12-8 h	4, 15, 74	2.5-5 mg/cat PO q 24-12 h	11
	0.2 mg/kg **IV or IM** q 2 h, PRN	4	2.5-5 mg/cat PO q 12 h	74
			0.2 mg/kg **IV or IM** q 2 h, PRN	4
Phenoxybenzamine (alpha-1 adrenergic blocker)	0.25-2.5 mg/kg PO q 12 h	15	Not recommended	11
	0.25 mg/kg PO q 12-8 h or 0.5 mg/kg PO q 24 h	4	Not recommended 2.5 mg/cat PO q 12-8 h or 0.5 mg/cat PO q 24 h	15 4
	0.25-1 mg/kg PO q 12 h	74		
	0.25-1.5 mg/kg PO q 12-8 h	11	2.5-5 mg/cat PO q 24-12 h	74
Prazosin (alpha-1 adrenergic blocker)	0.5-2 mg/dog PO q 12 h	15, 34	Not recommended	11
	0.5-2 mg/dog PO q 12-8 h	11, 74	Not recommended	34
	0.5-2 mg/kg q 12-8 h	4	Not recommended	15
			0.25-0.5 mg/cat PO q 24 h	4
			0.5-1 mg/cat PO q 12-8 h	74

Propranolol (non-cardioselective beta-adrenergic blocker)	2.5-10 mg/dog PO q 12-8 h	34	2.5-5 mg/cat PO q 12-8 h	34, 74
	0.2-1 mg/kg PO q 12-8 h	74	2.5-5 mg/cat PO q 8 h	4
	0.2-1 mg/kg PO q 8 h	4		
Ramipril (ACE inhibitor)	0.125 mg/kg PO q 24 h	15	0.125 mg/kg PO q 24 h	11, 15
	0.125-0.25 mg/kg PO q 24 h	11	0.125-0.25 mg/kg PO q 24 h	47, 56
	0.125 mg/kg PO q 12 h	74	0.5 mg/kg PO q 24 h	74
Sodium nitroprusside (nitrate vasodilator)	1-5 mcg/kg/min IV CRI	53	1-2 mcg/kg/min IV CRI	74
	1-7 mcg/kg/min IV CRI	74	≥0.5 mcg/kg/min IV CRI	53
Spironolactone (aldosterone antagonist diuretic)	1-2 mg/kg PO q 12 h	4, 15, 34	1 mg/kg PO q 12 h	34
	1-4 mg/kg PO q 24-12 h	74	1-2 mg/kg PO q 12 h	4, 15,
			1-4 mg/kg PO q 24-12 h	74

When a dosage range is given, treatment is usually initiated at the low end of the range and titrated upward to effect. Boldface font is precautionary, indicating parenteral routes and dosages for drugs that can be given either orally or parenterally.

ACE, Angiotensin converting enzyme; *CRI*, constant rate infusion; *h*, hour; *IV*, intravenous; *PO*, orally; *PRN*, as needed; *q*, every; *SC*, subcutaneously.

Sustained SHT can involve autoregulatory vasoconstriction in vascular beds that depend on capillary pressure more than they depend on capillary flow, including the myocardium, the brain and retina, and the kidneys.[10] Such vascular beds may consequently develop arteriolar medial hypertrophy, tissue ischemia, microscopic infarcts, and hemorrhage (e.g., in the brain or retina).[11] If SHT is caused by persistent exposure to volume overload, left-sided congestive heart failure can develop in susceptible cardiac patients (see ch. 246). When SHT is caused by an elevated systemic vascular resistance, rather than by fluid volume expansion, the left cardiac ventricle (LV) is forced to contract against a persistently elevated resistance (afterload). This leads not only to a persistently elevated force of LV contraction, but also to compensatory left ventricular concentric hypertrophy, teleologically "aimed at" decreasing oxygen consumption by LV cardiomyocytes.[10] Similarly, if CKD is involved in triggering SHT, the kidneys may also lose their autoregulatory capabilities, normally used to cope with elevated BP and to prevent its transmission into the glomeruli, further exacerbating the already preset renal injury.[12] The choice of a treatment strategy, therefore, should ideally be individually tailored and based on previously gathered knowledge about ongoing comorbidities and the underlying mechanism(s) responsible for the development of SHT in each given patient (see below).

Changes in lifestyle may be considered for companion animals with mild-to-moderate SHT without evidence of TOD, prior or in parallel to the onset of pharmacotherapy. Reducing body weight has been recommended in obese, hypertensive pets,[8] although this recommendation has been recently challenged.[13] As an extrapolation from human medicine, reduction of dietary sodium intake has been advocated in the past,[14] but has not proven beneficial to hypertensive pets.[15] It may, in fact, carry some risks such as volume depletion, leading to reduced renal perfusion with resultant exacerbation of ongoing renal disease, if present. Another possible, and likely more important risk is the activation of the renin-angiotensin-aldosterone system (RAAS) with resultant kaliuresis and hypokalemia, and even exacerbation of SHT.[15-19] If dietary sodium reduction is recommended for other, non-related reasons, it should therefore be achieved gradually and in combination with, rather than as a surrogate for, antihypertensive pharmacotherapy.[20] Avoiding excessive sodium intake, on the other hand, does benefit SHT patients.[4] In renal hypertensive pets, the common practice of avoiding excessive dietary protein intake is considered more important than aggressively limiting dietary sodium intake. Avoiding excessive dietary sodium while arteriolar vasodilators or beta-receptor antagonists are being administered might negate those compensatory hypertensive effects mediated by sodium retention and extracellular fluid volume expansion.[21] Despite such compensatory effects, beta-receptor antagonists also have the potential to reduce BP not only in patients with hyperthyroidism, but also in those with renal hypertension, by decreasing heart rate and stroke volume, as well as by inhibiting the release of renin.[15] Hypertensive pets with pheochromocytoma, too, should receive beta-receptor antagonists, when already receiving phenoxybenzamine (see ch. 311).[22]

Among the diseases associated with secondary SHT, kidney disease is one of the most common underlying etiologies in both dogs and cats (see ch. 157 and 324).[4] When managing a dog or a cat with kidney disease and SHT, gradual and consistent reduction of BP should be the goal, and choices of antihypertensive agents

should be based on the known or suspected underlying mechanism behind SHT. For example, if SHT is thought to involve an elevated serum renin concentration, drugs that interrupt the RAAS such as angiotensin converting enzyme inhibitors (ACEi), or angiotensin receptor blockers (ARBs) should be thought of as a priority. Agents from both groups, however, should not be co-administered if other combination therapies perform better. Nevertheless, ACEi are not highly potent antihypertensive agents and are therefore not expected to control severe SHT when used as a sole therapy. Beta-adrenergic antagonists, renin antagonists, or centrally acting alpha-2-receptor agonists may theoretically be considered in such patients instead of ACEi or ARBs, but are not typically used as first line antihypertensive medications. If, instead of RAAS activation, excessive serum sodium and/or fluid volume-mediated SHT is present, diuretic agents, an alpha-1-receptor antagonist, or a dihydropyridine calcium channel blocker might be more effective and should be prioritized.[15] The latter, in fact, is usually the treatment of choice in severe feline SHT and is often combined with ACEi in hypertensive dogs (see Figure 158-1 and Table 158-2).

Sympathetic nervous system-mediated increases in heart rate and aldosterone-mediated sodium and water retention may moderate the BP-controlling effect of systemic arteriolar vasodilation. Thus, hypertensive patients with kidney disease that are refractory to treatment and therefore need polypharmacy may benefit the most from a combination of antihypertensive mechanisms (which may sometimes also aid in controlling each other's side-effects), e.g., interference with the RAAS while at the same time achieving relaxation of vascular smooth muscle via calcium channel blockade, along with reduction of sodium and fluid volume, rather than from a combination of two different agents belonging to the very same group.

An intricate interplay between multiple organ systems (heart, kidneys, hormonal and autonomic nervous systems) regulates BP, and an imbalance might readily develop between their relative contributions to maintenance of a steady state, in response to silently and subtly progressive disease, or to otherwise changing circumstances. Therefore, even normotensive patients should be regularly reevaluated at 1-3 month intervals, or even more frequently until SHT is controlled. Reevaluation is used to assess BP and renal function, and to make appropriate dose and administration frequency adjustments, so as to achieve and ascertain long-term stability.[1,4] One example of this principle is the gradual loss of muscle mass and lean body weight occurring in some patients with CKD, necessitating decreased dosages of antihypertensive agents unless BP has progressively increased.

In hypertensive cats, physical examination should include evaluation for a thyroid nodule "slip" along with serum biochemistry including thyroxine concentration. Evaluating a bilateral funduscopic examination (see ch. 11), a neurological assessment (see ch. 12 and 259), kidney function evaluation (see ch. 321), careful thoracic auscultation (an intermittent gallop rhythm, an arrhythmia, or a murmur; see ch. 55), and NTproBNP testing (see ch. 246) should all be considered. Relevant findings warrant further evaluation and treatment as addressed in the appropriate chapters in this textbook (see above and ch. 157).[4,23-25]

Treating Canine SHT

Controlling spontaneously-occurring SHT in dogs is reportedly challenging, and may often require multi-drug therapy (see Figure 158-1 and Table 158-2).[1,5] Regardless of the initially documented magnitude of BP, it has been recommended to target a systolic BP of 140-150 mm Hg, when possible, while avoiding systemic hypotension (BP < 110-120/60 mm Hg).[1,4] A target diastolic BP of ≤95-100 mm Hg has also been suggested, if tolerated.[4,11] In stable hypertensive dogs, staged pharmacotherapy has been suggested by some investigators, starting with a once or twice daily administration of ACEi (see Figure 158-1).[20] Many clinicians choose an agent of the ACEi family as the first line of therapy for dogs with CKD-related SHT, not because of its proven efficacy in BP reduction but rather because of its ability to reduce proteinuria (urinary protein-to-creatinine ratio, or UP/C ≥ 0.5 for dogs) in proteinuric kidney disease, as this effect is associated with a lower progression rate in glomerulonephritis, hereditary nephritis, and CKD.[26-28] This also makes intuitive sense as progressive SHT, when transmitted through renal arteries into glomerular afferent arterioles, contributes to proteinuria development and exacerbation, which, in turn, is associated with decreased survival rates.[5,29,30] However, despite evidence of reduced glomerular capillary pressure and reduced histopathological scores of glomerular and tubular injury following ACE inhibition in dogs with experimentally-induced kidney disease, systemic BP values in these dogs were only slightly reduced.[31]

Systolic BP is expected to decrease by up to about 10%, once a new steady state is achieved following the onset of chronic ACE inhibition, which may be all that is needed in dogs with mild SHT.[1] However, if SHT is moderate or severe, or if BP is not sufficiently controlled with ACEi monotherapy, the second generation,

dihydropyridine-type, voltage-dependent calcium channel blocker amlodipine besylate is often co-administered on a once-a-day basis. Due to the long elimination half-life of amlodipine, the once daily administration interval is typically enough to reduce calcium influx into vascular smooth muscle cells and, thereby, to sufficiently relax systemic arteriolar vessels and decrease total peripheral resistance and systemic BP for many hours, in both dogs and cats.[11,32-37] The degree, progression rate, and duration of vasodilation, as well as the timing of its offset following oral amlodipine therapy have all been shown to be dose-dependent, at least in rodents.[38] Binding of amlodipine to vascular smooth muscle L-type calcium channel receptors is slow. Onset of action, therefore, is slow too, which is beneficial in minimizing acute hypotension and resultant reflex tachycardia from activation of vascular baroreceptors. Similarly, the duration of the BP reduction effect is long as well. Hence, the choice of amlodipine besylate is also typically made because amlodipine is associated with less reflex tachycardia than other arteriolar dilators, such as hydralazine.[1] The co-administration of an ACEi and amlodipine might not only provide for (modest) additive BP-reducing effects, but also for treatment safety, as the former helps to blunt the RAAS stimulation (and resultant proteinuria) potentially triggered by the latter.[1,39] Mild and possibly tolerable elevation (0.5 mg/dL, 50 mmol/L, or 10-20%) of serum creatinine is sometimes to be expected following initiation of ACEi therapy,[4,11] but acute azotemia is considered rare in otherwise well-hydrated patients.[40-44] Such elevation, even if mild and seemingly tolerable at first, is considered by some as evidence of acute kidney injury with potential risks, which should, and can be avoided by staged pharmacotherapy as elaborated above.[20] Caution should therefore be exercised, especially in patients with advanced CKD or in those that are prone to dehydration. Glomerular filtration rate may decrease following ACE inhibition, especially in dehydrated or hypovolemic animals. Although single nephron studies have shown that this is not necessarily the case in pets with CKD,[31,41] one has to keep in mind that ACEi, too, can be directly nephrotoxic at very high (70×) dosages, and/or when administered to severely volume-depleted animals, or if co-administered with other nephrotoxic agents such as aminoglycosides or nonsteroidal anti-inflammatory drugs.[11,44]

If combination therapy is still insufficient to control SHT in a dog, the amlodipine dosage is successively increased, based on repeated BP measurements (meticulously repeating the same measurement technique and circumstances whenever possible). In hypertensive pets with no evidence of TOD and when a hypertensive crisis is ruled out (see below), such repeated BP measurements are performed every one to two weeks, until satisfactory BP control is achieved or until reaching the highest recommended amlodipine dosage. Owner understanding of, and compliance with, the dosing schedule should be confirmed prior to increasing amlodipine dosage even further, which allows at least one or two weeks of maximal amlodipine dosage to ascertain that a new steady state has been achieved. Measurement of BP prior to making the decision of increasing the dosage even further, should ideally be made about 12 hours post-amlodipine dose, so as to avoid an underestimation of its performance, based on too early a measurement.[1] Treated patients should be monitored closely for hypotension (e.g., BP values of ≤120/60 mm Hg, accompanied by weakness, syncope or sinus tachycardia) and for azotemia.[4] If even this extreme measure is inadequate for achieving satisfactory BP control, hydralazine, prazosin, or phenoxybenzamine may be considered in addition to amlodipine besylate, although clinical studies in spontaneously hypertensive dogs have yet to support these recommendations. Diuretics should only be used to treat SHT in over-hydrated patients, while exercising extreme caution in animals with CKD that are already prone to dehydration and acute decompensation of the disease. One has to weigh the risks versus the benefits of empirical combination therapy and adopt a conservative approach in terms of dosage and administration frequency, when facing reflex tachycardia and/or hypotension in any patient. If the clinician does not feel experienced enough with using any of the latter agents, using them while the patient is hospitalized for 1-3 days, during which serum biochemistry, hydration status, appetite, BP and heart rate can be monitored, is encouraged.

A cardioselective beta-adrenergic antagonist such as atenolol can be added to control reflex tachycardia resulting from highly potent arteriolar vasodilators, especially if reflex tachycardia is thought to contribute to inadequate BP control. On the other hand, as reflex tachycardia is thought to develop as a compensatory reaction to iatrogenic excessive hypotension, one should exercise extra caution and avoid negating such tachycardia too aggressively. Non-cardioselective beta-receptor antagonists such as propranolol, might, in fact, counteract their own systemic BP-lowering effects by negating arteriolar dilation in vascular beds of skeletal muscle throughout the body. This specific vascular bed comprises a large enough portion of the systemic circulation to compromise the efficacy of antihypertensive therapy, or at least increase total peripheral resistance and systemic afterload.[45] Moreover, beta-receptor antagonists as monotherapy have not been shown to be very effective in the treatment of hypertension in hyperthyroid cats,[46] and might therefore

prove to be a less-than-ideal monotherapy choice in dogs as well.

Treating Feline SHT

A systolic BP of <160, and preferably 140 mm Hg if tolerated, has been recommended as a target value for treated hypertensive cats, while avoiding hypotension.[47] A decrease of as much as 30 to 60 mm Hg in systolic BP can often be achieved upon reaching a steady state based on a once daily dosing regimen of the second-generation calcium channel antagonist amlodipine besylate.[15,35,36,48] In a recent randomized, double-blind, placebo-controlled clinical trial, systolic BP either decreased by at least 15% or to <150 mm Hg in over 60% of 34 hypertensive cats receiving amlodipine at 0.125 to 0.25 mg/kg once daily for up to 28 days, while only 18% of the 27 placebo-treated cats reached these same endpoints.[49] Due to the long (53 hours) elimination half-life of amlodipine in cats,[50] a once-daily administration interval is not only convenient but is also considered safe and effective,[49] other than a rarely documented risk of mild hypokalemia or hypochloremia, both of which should, therefore, be periodically ruled out. Due to the potential of SHT to be silently progressive, BP should ideally be measured about every 6 to 8 weeks, at least until steady BP values are repeatedly documented to be within target range, at which time re-evaluation can be carried out up to every 3 months.[4,51] It has been estimated that amlodipine-treated cats have nearly 8 times greater odds of treatment success than placebo-treated cats.[49] This agent has been shown to be sufficient to prevent the development of hypertensive encephalopathy and ongoing ocular damage, and to stabilize, or even reverse, compensatory concentric cardiac hypertrophy in cats with SHT.[23,52] An initial amlodipine dosage of 0.125 mg/kg once daily has been recommended, following which steady state of plasma concentration is achieved in about 14 days in healthy cats.[50] This initial dosage can therefore be doubled, if needed, within 2 weeks. In cats with CKD associated with SHT, it can even be quadrupled (gradually over 4-8 more weeks) with only minimally negative chronotropic or inotropic effects, should insufficient performance be demonstrated, and prior to being stepped up by a multi-drug administration strategy (see Figure 158-1).[20,47] Feline CKD does not require amlodipine dosage reduction since it undergoes hepatic metabolism and its pharmacokinetic profile, therefore, should not be affected by this condition.[49,53] Calcium channel blockers, however, have not been shown to increase life expectancy in hypertensive cats.[48,54] Nevertheless, they do carry the potential of improving quality of life of such cats, including the maintenance of appetite level and body weight,[35,47,48] which might indirectly increase life expectancy, for example, when decisions around euthanasia are being considered. Dihydropyridine calcium channel antagonists, such as amlodipine besylate, can also act directly to reduce secretion of aldosterone by the adrenal cortex, which may add yet another mechanism by which they contribute to BP reduction in hypertensive cats.[55] This specific effect can theoretically be intensified by the addition of an aldosterone antagonist, such as spironolactone. In contrast, despite some preliminary evidence of normalization of BP values in about 40% of cats treated with ramipril,[56] generally using an ACEi agent as monotherapy has not been shown to be effective enough in controlling severe feline SHT.[1,3,41,48,57-59] As amlodipine besylate preferentially dilates the afferent renal arterioles, it might trigger an elevation of the intra-glomerular pressure in cats with severe, CKD-related SHT, when systemic BP is insufficiently reduced. However, amlodipine usually is able to sufficiently lower systemic BP enough to avoid transmission of SHT into the glomeruli, despite its preferential dilation of the afferent glomerular arterioles.[54] In patients where such transmission cannot be avoided, proteinuria (UP/C ≥ 0.4 for cats) can still be triggered or exacerbated despite adequate control of SHT. Persistent proteinuria, in turn, might promote glomerular and tubular damage, resulting in worsening kidney disease,[60,61] and even decrease survival.[5,54] This is where an addition of ACEi agent administered once daily can theoretically be beneficial, as these agents trigger preferential dilation of the efferent glomerular arterioles, thereby assisting the control of intra-glomerular pressure. Such co-therapy may prove important in proteinuric cats with CKD and renal hypertension, as proteinuria in this population is associated with reduced survival rates.[54] The goal should be reduction of the UP/C to the non-proteinuric range, or at least by 50% of baseline if abolishing proteinuria is impossible. Nevertheless, a small pilot study of hypertensive cats with CKD, comparing benazepril and amlodipine co-therapy to amlodipine monotherapy, did not support this theory.[62] Conversely, when amlodipine administration is successful in substantially reducing BP, it is shown to actually reduce, rather than exacerbate, proteinuria.[15] Until such controversies are resolved by more data, seeking evidence of and reducing proteinuria should probably be considered as highly important goals when managing cats with CKD and renal hypertension.[63]

Due to the potent anti-vasospastic effects of amlodipine, it should not be administered to hypertensive cats

if they also have moderate-to-severe aortic stenosis or left ventricular outflow tract obstructive disease, so as to avoid exacerbation of the trans-obstruction systolic pressure gradient, which may deteriorate their hemodynamic and clinical stability.[64] Similarly, amlodipine therapy is to be avoided when treating pets with myocardial failure, cardiogenic shock, severe bradyarrhythmia, or severe hepatic failure, and caution should be exercised when administered to those concomitantly treated with antifungal azoles, as some of these may trigger negative inotropic effects under certain circumstances, at least in people and dogs.[65-67] In addition, some azoles may also increase the plasma concentration of amlodipine by affecting hepatic/intestinal enzyme CYP3A4 metabolism.[68]

Similar to ACEi monotherapy, the use of beta-adrenergic antagonists or spironolactone as monotherapy for feline SHT has been so far disappointing.[46,57,69] However, cardio-selective beta-adrenergic antagonists can still be useful when attempting to reduce SHT secondary to feline hyperthyroidism, when administered prior to or following the onset of therapy for hyperthyroidism, simultaneously with amlodipine.[1]

Cats with systolic BP > 180 mm Hg prior to the onset of treatment for hyperthyroidism are likely to remain hypertensive after becoming euthyroid. However, even when hyperthyroid cats are normotensive prior to treatment, monitoring of BP values should probably be periodically performed for at least 6 months following reaching euthyroidism.[70] Only then can antihypertensive therapy be gradually weaned off while still consistently monitoring systemic BP values, as SHT can actually be exacerbated or even triggered *de novo* following thyrotoxicosis resolution. This phenomenon is thought to result from an "unmasking" effect of such resolution on an underlying, and previously occult CKD along with renal hypertension. When this is the case, antihypertensive therapy should be adjusted accordingly and maintained long-term, as needed.[6]

Treating a Hypertensive Crisis

Evidence of TOD along with a repeatedly documented systolic BP > 160 mm Hg justifies emergent intervention (Figure 158-2). If TOD is shown and SHT values are >180/120 mm Hg, emergent therapy should be administered based on even a single BP measurement session.[4] The need of continuous aggressive therapy, however, should be re-evaluated once BP values are shown to decrease to target levels and there is evidence of TOD improvement. Conversely, if no evidence of TOD is present and systolic BP is <200 mm Hg, urgent, rather than emergent therapy is indicated.[1] This means that BP reduction should be carried out in a more controlled and gradual manner, so as to avoid reaching mean BP values that are considered physiological in normotensive pets, but might be too low for sustaining adequate cerebral perfusion in those that have been chronically hypertensive up until that point in time.[34,71-73] As with other non-emergent cases, and in light of the above risk associated with too rapid and/or too extreme a decrease in BP values, at least one week should be allowed for a steady state to be achieved, prior to deciding on dosage titration.[1]

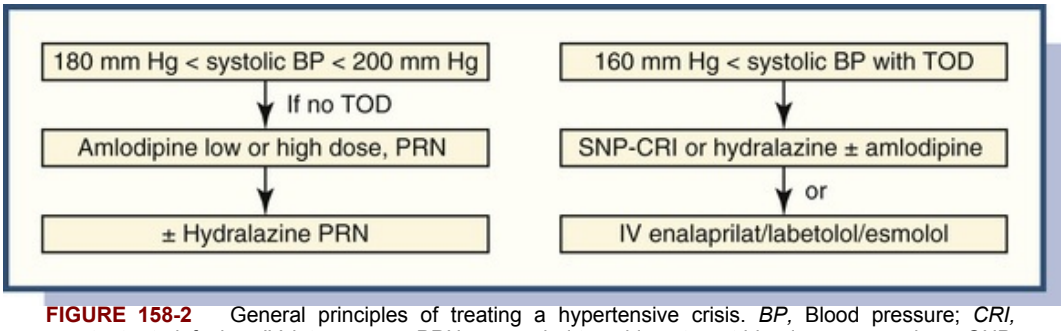

FIGURE 158-2 General principles of treating a hypertensive crisis. *BP*, Blood pressure; *CRI*, constant rate infusion; *IV*, intravenous; *PRN*, as needed to achieve target blood pressure values; *SNP*, sodium nitroprusside; *TOD*, target organ damage.

For emergent patients, constant rate intravenous infusion of sodium nitroprusside (SNP) is a good choice in experienced hands, as it can reach target BP values both rapidly and in a titratable fashion.[1] Moreover, the short plasma elimination half-life of SNP makes its choice a relatively safe one, as long as heart rate and BP can be frequently (i.e., at least hourly), reliably, and consistently documented throughout hospitalization. This is advised to avoid inadvertently reaching excessively low BP values, which might jeopardize pressure-dependent vascular beds such as the renal, cerebral and coronary circulation, an important consideration in

patients with renal disease and in geriatric patients in general. Other adverse effects associated with too rapid, or too extreme a decrease of BP should be looked for. These include reflex tachycardia with weakness, syncope, and even organ failure.[11,34] If SNP is unavailable or deemed too labor-intensive a drug to choose, oral or parenteral[4] hydralazine can serve as a reasonable alternative because of its high potency. However, because it cannot be constantly infused and therefore cannot be abruptly discontinued when needed,[32,53] it is a potentially less safe choice. When combined with amlodipine, oral hydralazine can reduce BP by about 25% over several hours.[1] A high oral dosage of amlodipine can sometimes be a potent enough single-agent alternative to control a hypertensive crisis in cats. Alternative parenterally administered agents, if available, include enalaprilat (0.2 mg/kg IV, repeated q 1-2 h as needed), labetolol (0.25 mg/kg IV over 2 minutes, repeated up to a total dose of 3.75 mg/kg and followed by a constant rate infusion of 25 mg/kg/min), and esmolol (at a 50-75 mg/kg/min constant rate infusion).[4] Note that any parenterally administered antihypertensive agent warrants continuous BP monitoring using a direct, intra-arterial catheter (see ch. 75 and 99). Oral amlodipine besylate can be carefully added once BP values start decreasing, if not yet administered up until this point. High dosages may be employed if necessary, with caution.[4] Once new BP values are stabilized with no intervention-related complications, and oral pharmacotherapy can be maintained with no adverse reactions, discharge from hospitalization can be considered, and a follow-up BP measurement should be scheduled in 1-3 days.[4] In clinically and hemodynamically stabilized patients, BP re-evaluation should be performed 7-10 days later, and then every 1 to 3 or 4 months, depending on the initial extent of SHT during the crisis, on the previously documented rate of TOD progression, and on stability and magnitude of BP values following resolution of the crisis (i.e., the higher they are, the more frequent the re-evaluation).[20]

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CHAPTER 159

Systemic Hypotension

Lori S. Waddell

Arterial blood pressure is measured as systolic, diastolic, and mean. Systolic and diastolic pressures correspond to the phases of the cardiac cycle. Mean arterial pressure (MAP) can be calculated using the equation

$$\text{MAP} = \text{Diastolic} + [(\text{Systolic} - \text{Diastolic})/3]$$

and it is the most important value when considering perfusion of tissues. *Systemic hypotension* is defined as a systolic arterial blood pressure < 80 mm Hg and/or MAP < 60 mm Hg in either dogs or cats.

Causes of systemic hypotension include decreased preload to the heart, decreased vascular tone, and cardiac dysfunction. Untreated hypotension can lead to shock from inadequate tissue perfusion and oxygen delivery to the tissues. Treatment of systemic hypotension should consist of identifying and correcting the underlying problem. Recognition and treatment of systemic hypotension are essential to prevent the development of refractory shock, organ failure, and death (Figure 159-1).

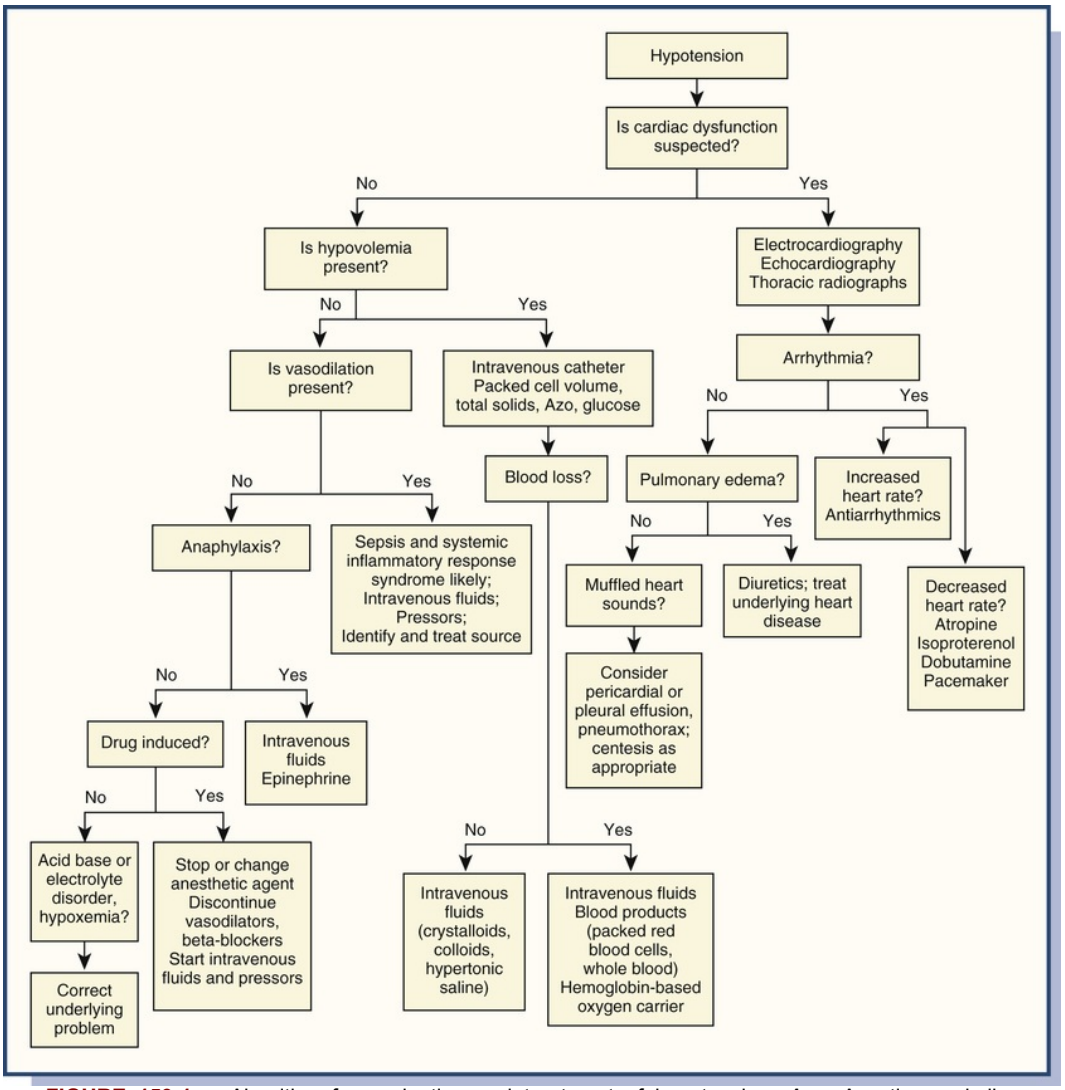

FIGURE 159-1 Algorithm for evaluation and treatment of hypotension. *Azo*, Azostix or similar measurement or blood urea nitrogen.

Blood pressure provides a measurement of tissue perfusion. The two are not equivalent, but blood pressure monitoring is the simplest means of obtaining an objective measurement (see ch. 99). Subjective measures of tissue perfusion are obtained by physical examination; they include pulse quality, mucous membrane color, capillary refill time (CRT), temperature of extremities, and heart rate and rhythm. Combined with blood pressure monitoring, evaluation of these parameters provides the basis for a more accurate assessment of tissue perfusion. A normal blood pressure does not necessarily mean that the tissues are adequately perfused, as blood pressure may be maintained with severe peripheral vasoconstriction with or without increased cardiac output.

Clinical Manifestations

The clinical signs associated with systemic hypotension depend on the severity and cause of the condition. In dogs, hypotension usually is associated with a reflex sinus tachycardia, bounding to weak pulses, pale mucous membranes, slow CRT (>2 seconds), mental dullness, and weakness (Video 159-1). If the underlying cause is sepsis, the mucous membranes can be injected or red with a rapid CRT (<2 seconds; see Video 144-1). Cardiac causes of systemic hypotension can alter the clinical picture, with arrhythmias, weak and irregular pulses, and even severe bradycardia possible. Hypotensive cats also usually have sinus tachycardia, poor pulse quality, pale mucous membranes, slow CRT, mental dullness, and weakness. However, unlike dogs, cats with sepsis or systemic inflammatory response syndrome (SIRS) often have bradycardia rather than tachycardia and rarely have injected mucous membranes. In both species, systemic

hypotension often is associated with decreased urine output, hyperventilation, hypothermia, and cool extremities.

Inability to palpate pulses peripherally can be useful in assessing blood pressure. When the metatarsal pulse is palpable, the systolic blood pressure is >70-80 mm Hg. Although measurement of blood pressure confirms the presence of systemic hypotension, the diagnosis can be made on physical examination findings alone.

Pathogenesis

Systemic arterial blood pressure (ABP) is dependent on cardiac output (CO) and systemic vascular resistance (SVR) (Figure 159-2):

$$ABP = CO \times SVR$$

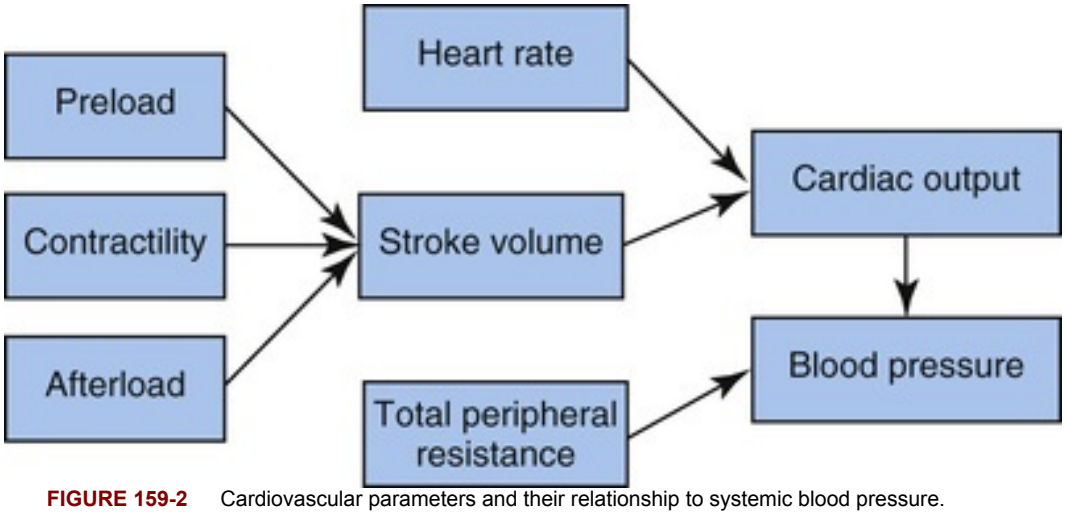

FIGURE 159-2 Cardiovascular parameters and their relationship to systemic blood pressure.

Cardiac output is determined by heart rate, cardiac contractility, preload, and afterload. The three main causes of systemic hypotension are decreased preload, decreased cardiac function, and decreased arterial tone (Box 159-1). These may occur individually or in combination.

Box 159-1

Causes of Systemic Hypotension

Decreased Preload

Hypovolemia

Blood loss
Gastrointestinal losses
Polyuria
Hypoadrenocorticism
Effusions or other third spacing of fluid
Burns
Heatstroke

Decreased Venous Return

Cardiac tamponade
Constrictive pericarditis
Severe pneumothorax
Positive pressure ventilation

Gastric dilation and volvulus
Heartworm disease (caval syndrome)

Decreased Cardiac Function

Cardiomyopathy
Adult-onset valvular disease
Congenital heart disease
Bradyarrhythmias
Tachyarrhythmias
Serum electrolyte abnormalities
Acid-base disturbances
Severe hypoxemia
Sepsis/systemic inflammatory response syndrome (SIRS)

Decreased Vascular Tone

Sepsis/SIRS
Anaphylaxis
Neurogenic
Drug-induced (anesthetic agent, vasodilators [e.g., beta-blockers, calcium channel blockers])
Electrolyte abnormalities
Acid-base disturbances
Severe hypoxemia

Systemic arterial blood pressure is maintained via neural, hormonal, and local mechanisms. Smooth muscle in blood vessel walls is innervated by fibers from the sympathetic nervous system. Activation of this system results in vasoconstriction of vessels in tissue beds with the exception of skeletal muscle, where it causes vasodilation. Sympathetic innervation of cardiac muscle causes increased heart rate and contractility. Sympathetic stimulation occurs when the vasomotor center, located in the medulla oblongata, is activated. Hypovolemia and systemic hypotension can lead to activation of the vasomotor center due to the baroreceptors in the carotid sinuses and aortic body sensing a lack of stretch, and the stretch receptors in the atria and pulmonary artery sensing a lack of distension and atrial filling. The vasomotor center also is activated by local hypoxia or hypercapnia causing stimulation of the chemoreceptors in the carotid sinus and aortic bodies, although this mechanism is less important than the baroreceptor reflex.

Hypotension also causes release of antidiuretic hormone (ADH, vasopressin) and adrenocorticotropic hormone (ACTH) from the pituitary, as well as release of catecholamines (norepinephrine and epinephrine) and cortisol from the adrenal glands. Increased concentrations of these hormones stimulate an increase in heart rate, vasoconstriction, and water retention by the kidneys. Simultaneously, the macula densa in the glomeruli is affected, and the renin-angiotensin-aldosterone system is activated, resulting in sodium retention by the kidneys and further vasoconstriction. These mechanisms serve to increase blood volume by means of sodium and water retention and to preferentially perfuse the brain and heart while decreasing perfusion to the skin, muscles, and abdominal organs, including the kidneys. Recognition and treatment of hypotension are essential to prevent the development of refractory shock and organ failure (see ch. 127). Acute kidney injury and oliguria/anuria are among the most common consequences of systemic hypotension (see ch. 322), but others include decreased coronary artery perfusion due to the increased heart rate, increased risk of bacterial translocation from the gastrointestinal tract (see ch. 274), impaired hepatic function (see ch. 285 and 286), and activation of the coagulation cascade (see ch. 197).

In addition to the mechanisms listed above, there are several other important effectors of blood pressure and vascular tone. Activation of the arachidonic acid cascade leads to production of prostacyclin and thromboxane A_2. Prostacyclin causes vasodilation, but thromboxane A_2 causes vasoconstriction. Nitric oxide (NO), produced by endothelial cells via nitric oxide synthase, is an important regulator of vascular tone, resulting in vasodilation. There are two types of nitric oxide synthase: the constitutive form and the inducible form. In sepsis and SIRS, there is a tremendous increase in NO production from inducible NO synthase, which is activated by a variety of inflammatory mediators including interleukin-1 (IL-1), IL-2, IL-6, and tumor necrosis factor. This overproduction of NO, coupled with depletion of vasopressin, downregulation of catecholamine receptors, and disruption of vascular smooth muscle calcium metabolism, can result in vasoplegia, severe hypotension, and refractory shock.

Hypovolemia results in decreased cardiac output secondary to decreased venous return to the heart. This,

in turn, results in decreased preload. Moderate to severe hypovolemia must be present to affect blood pressure due to the normal compensatory actions that occur, including increased heart rate to maintain cardiac output and increased peripheral vascular resistance secondary to vasoconstriction. The compensatory mechanisms maintain adequate blood pressure until >20-25% of the intravascular volume has been depleted. Hypovolemia can occur with blood loss or increased fluid losses secondary to vomiting, diarrhea, polyuria, or third-spacing of fluid.

Restriction of cardiac filling can also result in decreased stroke volume, decreased cardiac output, and systemic hypotension. Pericardial effusion with tamponade and restrictive pericarditis can result in systemic hypotension by this mechanism. Severe pneumothorax and positive pressure ventilation can also reduce venous return to the heart. Hypertrophic cardiomyopathy in cats reduces left ventricular volume, thereby reducing stroke volume and, therefore, cardiac output.

Bradyarrhythmias can affect blood pressure by reducing cardiac output, especially when the heart rate is extremely slow (see ch. 141). Although pulse quality can be normal or strong in a dog or cat with bradyarrhythmia, cardiac output can be drastically reduced by the infrequency of heartbeats. This low cardiac output can be severe enough to cause syncopal episodes secondary to hypotension and decreased perfusion of the brain (see ch. 30). Tachyarrhythmias can result in systemic hypotension by reducing cardiac preload. At extremely rapid heart rates, filling of the heart chambers is limited by the shortened duration of diastole. This can result in reduced cardiac output despite an increased heart rate because at pathologically high heart rates, the reduction in diastolic filling time is disproportionately more severe than any benefit gained by the higher heart rate. Also, coronary perfusion occurs during diastole, so at rapid rates, cardiac perfusion can be markedly decreased and can worsen the cardiac arrhythmia further (i.e., more rapid and/or refractory to treatment) (see ch. 248).

Decreased cardiac output also can occur due to cardiac disorders characterized by systolic dysfunction and/or valvular regurgitation. Dilated cardiomyopathy is characterized by reduced stroke volume and reduced cardiac output caused by decreased myocardial contractility (see ch. 252). Valvular incompetence, resulting in regurgitant flow, also can lead to decreased stroke volume if compensatory increases in systolic function, and eccentric hypertrophy, have not occurred (see ch. 251). Other causes of decreased cardiac systolic function include myocarditis, myocardial infarction, myocardial depression secondary to sepsis, SIRS, anesthetic drugs, beta-blockers, calcium channel blockers, and acid-base and electrolyte abnormalities.

Decreased systemic vascular resistance can also cause hypotension. Common causes of vasodilation are sepsis/SIRS (see ch. 132); anaphylaxis (see ch. 137); anesthesia; use of vasodilators, including beta-blockers and calcium channel blockers; electrolyte abnormalities; and acid-base disturbances (see ch. 128). Many of these mechanisms also affect myocardial contractility, resulting in systemic hypotension mediated by decreased cardiac output and vasodilation simultaneously.

Measurement of Blood Pressure

Blood pressure monitoring can be divided into two main types: noninvasive and invasive methods (see ch. 99). Noninvasive methods are most commonly used, and in dogs and cats usually consist of either an oscillometric system (Cardell Monitor, Sharn Veterinary, Tampa, FL) or Doppler methods (Parks Electronics, Aloha, OR). Invasive blood pressure monitoring is performed by direct arterial pressure measurement via placement of an arterial catheter and connection to a pressure transducer (see ch. 75); it is considered the gold standard of blood pressure monitoring.

Treatment

It is essential that initial treatment of systemic hypotension always be aimed at correction of the underlying physiologic problem: decreased preload, cardiac dysfunction, or peripheral vasodilation. Differentiation of cardiac and noncardiac causes of systemic hypotension is a critical first step (see Figure 159-1). If the animal is hypovolemic, intravenous fluids and/or blood products should be administered until euvolemia has been attained (see ch. 129 and 130). If hypovolemia is severe enough to cause hypotension, a shock bolus should be given. The standard shock dosages of isotonic crystalloids are 60 to 90 mL/kg for dogs and 45 to 60 mL/kg for cats. If colloids are indicated in place of crystalloids, approximately one fourth of the crystalloid dose should be given. Hypertonic saline (5% to 7.5%) is a rapid intravascular volume expander and can be used when immediate fluid resuscitation is needed. The dosage for hypertonic saline is 5 mL/kg given over 5-10 minutes for dogs and 3 to 4 mL/kg given over the same time period for cats. After administration of hypertonic saline, it is essential to follow with one-third to one-half of a shock bolus of isotonic crystalloids to provide continued

intravascular volume expansion and to replenish the interstitial space. If hypovolemia occurs secondary to blood loss, blood products, such as whole blood or packed red blood cells, or a hemoglobin-based oxygen-carrying solution, might need to be administered to provide adequate oxygen-carrying capacity.

If the volume status is unknown or if there are concerns about overloading the animal with intravenous fluids, a central venous catheter can be placed for central venous pressure (CVP) monitoring (see ch. 76). A low CVP (<0 cm H_2O) indicates hypovolemia due to fluid loss or vasodilation secondary to decreased peripheral resistance. A high CVP (>10 cm H_2O) indicates intravascular volume overload, right-sided heart failure, or increased pulmonary vascular resistance (afterload). If the significance of a low to normal CVP reading is questionable, a small test bolus of fluids can be given. A rapid bolus of 10-15 mL/kg of crystalloid or 3-5 mL/kg of colloid is used. It is important to remember that the vascular bed is a compliant system, able to accommodate changes in volume with minimal changes in pressure. If the animal has a low CVP due to hypovolemia, the CVP will show either no change or a transient rise toward normal followed by a rapid decrease. The MAP also increases transiently. A bolus given to a dog or cat that is euvolemic usually causes a small increase in the CVP of 2 to 4 cm H_2O with a return to baseline within 15 minutes. A large increase (greater than 4 cm H_2O) followed by a slow return to baseline (longer than 30 minutes) is seen with hypervolemia or reduced cardiac compliance.

If the animal remains hypotensive once euvolemia has been achieved, the use of pressors should be considered. Commonly used pressors for treating vasodilation include dopamine (5-15 mcg/kg/min), epinephrine (0.05-1 mcg/kg/min), norepinephrine (0.1-1 mcg/kg/min), or phenylephrine (0.5-5 mcg/kg/min), administered for their alpha-agonist effects, as constant-rate IV infusions. Only phenylephrine is a pure alpha-agonist; the others have varying degrees of beta effects in addition to their alpha effects. Vasopressin (0.5-5 mU/kg/min) also can be used in cases with vasodilatory shock and may be especially useful in cases of sepsis/SIRS as the vessels can become refractory to catecholamines. These drugs need to be titrated to effect, requiring frequent blood pressure monitoring (see ch. 99). They should never be used in place of adequate volume expansion, because most patients with hypovolemic shock already have compensatory vasoconstriction.

Cardiac causes of hypotension must be addressed on a case-by-case basis. With tachyarrhythmias, the cause should be corrected when possible and antiarrhythmic therapy should be administered if necessary (see ch. 248). Bradyarrhythmias may respond to medical therapy or may require placement of a pacemaker (see ch. 249). Obstruction of cardiac filling by pericardial effusion or severe pneumothorax should be addressed by appropriate centesis. Positive inotropes such as dobutamine (5-15 mcg/kg/min), which is predominately a beta-agonist, can be administered as a constant rate infusion when decreased cardiac contractility is suspected.

Diagnostic Plan

Diagnosis of the underlying cause of severe systemic hypotension must often wait until after therapy has been initiated due to the critical nature of such hypotension. History and physical examination abnormalities often can help in the determination of a tentative diagnosis, allowing therapy to be started (see ch. 2). Initial diagnostics in an unstable hypotensive dog or cat should include measurements of packed cell volume, total solids, blood glucose, and an estimate of the blood urea nitrogen level (e.g., Azostix, Bayer Corporation, Elkhart, IN). Serum electrolyte concentrations (see ch. 67-69), acid-base status (see ch. 128), and serum lactate concentration (see ch. 70) also can be helpful. Depending on the clinical signs, an electrocardiogram (see ch. 103), abdominal and thoracic radiographs, abdominal ultrasound exam (see ch. 88 and 143), echocardiogram (see ch. 104), CVP measurement (see ch. 76), and pulse oximetry determinations (see ch. 98), and arterial blood gas analysis (see ch. 75 and 128), can be useful. A complete blood count, serum biochemistry profile, and urinalysis (see ch. 72) also should be performed. If indicated by a suspicion of hypoadrenocorticism, an ACTH stimulation test should be completed (see ch. 309). If sepsis is suspected, blood and urine cultures should be done unless the source of sepsis can be directly cultured, and broad-spectrum antibiotics should be initiated as soon as possible (see ch. 132).

SECTION X

Therapeutic Considerations in Medicine and Disease

OUTLINE

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Chapter 161 Antibacterial Drug Therapy
Chapter 162 Antifungal and Antiviral Therapy
Chapter 163 Antiparasitic Therapy
Chapter 164 Anti-Inflammatory Therapy
Chapter 165 Immunosuppressive Therapy
Chapter 166 Analgesic Therapy
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CHAPTER 160

Principles of Drug Disposition and Pharmacokinetics

Butch KuKanich

Pharmacokinetics describes the absorption, distribution, metabolism and elimination of drugs. For example, morphine is rapidly absorbed into the plasma from the injection site following intramuscular administration in dogs. Morphine distributes throughout the body, including the central nervous system where it elicits its analgesic effects. Morphine is metabolized primarily to the inactive metabolite morphine-3-glucuronide, ending its pharmacologic effect and the inactive metabolite is primarily eliminated in the urine. In contrast to dogs, cats metabolize morphine primarily to morphine-3-sulfate, demonstrating a species-specific difference in morphine metabolism. Although the pharmacokinetics of some drugs is similar between species, similarities should not be assumed.

Absorption

Drug absorption from the site of administration needs to occur for any extravascular dose, assuming systemic effects are desired. Per os (PO)/oral, intramuscular (IM), subcutaneous (SC), transdermal (TD) and transmucosal (TM) drug administration are the most common routes of delivery in dogs and cats. Drug administration by an esophagostomy or jejunostomy tube (see ch. 82) is expected to have very similar absorption to PO administration for most drugs.

Drug absorption can occur by passive diffusion (through lipid membranes or aqueous pores and capillary fenestrations) or through transporters such as anionic, cationic, and amino acid transporters among many others. Diffusion is directly proportional to surface area and drug gradient, and lipid diffusion is directly proportional to the drug's lipophilicity and directly inversely proportional to the thickness of the membrane. Drug absorption by diffusion is not saturable, with higher doses resulting in proportionally greater drug absorption. However, absorption by transporters can be saturated, resulting in decreased rate or extent of absorption with higher doses (less than proportional) as seen with gabapentin in dogs.[1]

Bioavailability is most often referred to as the extent or fraction of drug absorbed after extravascular administration, but also includes the rate of absorption. For the context of this chapter, bioavailability will refer to the extent of drug absorption. Numerous factors can result in incomplete bioavailability. Intramuscular and subcutaneous bioavailability can be decreased by tissue sequestration at the injection site due to tissue binding, granuloma, scarring, etc.; degradation or metabolism at the injection site; incomplete release from pharmaceutic formulation; or inadequate blood flow to site of administration (e.g., shock or inadvertent injection into connective tissue).

Oral drug bioavailability may be decreased due to drug degradation or instability (e.g., acid hydrolysis in the stomach), pre-systemic metabolism, gastrointestinal (GI) motility dysfunction (ileus or hypermotility), binding to ingesta or drugs or the inability to cross the intestinal mucosal cellular membrane due to low lipid solubility, drug ionization or lack of or saturation of appropriate transporters. Oral bioavailability can also be decreased by transporters such as the p-glycoprotein (p-gp) efflux pump effluxing drug that was absorbed back into the intestinal lumen.[2]

Oral drug administration is commonly used in veterinary patients. Tablets, capsules, suspensions, and solutions can all be administered PO. Solid dosage forms must first disintegrate in the gastrointestinal fluid and then dissolve into solution prior to drug absorption. Some drugs are poorly soluble in the GI tract (e.g., itraconazole) and have low bioavailability. Solid dosage forms may be formulated to alter the rate of disintegration or dissolution to decrease rate of absorption (extended release) or target disintegration for a specific part of the GI tract (delayed release). Most of these delayed- or extended-release formulations are designed specifically for people and may not be effective or consistent in dogs and cats due to differences in

GI anatomy and physiology. Delayed or extended release formulas may result in immediate release in dogs and cats or may be passed through the GI tract without release, resulting in little drug absorption. Therefore, unless specific data are available on delayed- or extended-release formulations in dogs and cats, their use is cautioned.

The primary site of drug absorption following PO administration is the small intestine (duodenum and jejunum and to a lesser extent ileum). The large surface area for diffusion and presence of active transporters facilitates absorption of drugs from the intestinal tract. Metabolizing enzymes (both Phase I and Phase II, see metabolism) are also present in the intestine, which can metabolize absorbed drugs before the drugs enter the vasculature, thereby decreasing oral bioavailability.[3] Drugs absorbed from the intestine enter the portal circulation, which carries the drugs directly to the liver. As the drugs pass through the liver they are again exposed to drug metabolizing enzymes (Phase I and Phase II) that can decrease systemic drug exposure. The sum of intestinal and hepatic presystemic metabolism is referred to as first-pass metabolism. It is important to note that the majority of drug absorbed from the rectum and large intestine in dogs and cats also enters the portal circulation; therefore, in contrast to humans, rectal drug administration in dogs and cats does little to decrease first-pass drug metabolism and subsequently results in similar bioavailability, at best, as oral administration.[4,5]

Intramuscular and subcutaneous drug administration deposits drug in the interstitial fluid in the musculature or subcutaneous space, which communicates with the plasma compartment by pores and fenestrations within the capillaries. Therefore, drugs with low lipophilicity like aminoglycosides can still be absorbed without diffusion through cell membranes. First-pass metabolism and its effects on bioavailability are avoided for IM and SC injections. Drugs administered IM or SC as suspensions (solid particles suspended in a liquid) must first dissolve prior to absorption. Some suspension formulations may provide prolonged dosage intervals due to delayed absorption (e.g., procaine penicillin G, methylprednisolone acetate), but not all suspensions provide sustained effects. Drugs administered IM or SC as solutions may result in more rapid absorption compared to suspensions, assuming they are small drug molecules capable of diffusion into the vasculature, but some extended release formulations are solutions (buprenorphine injection, Simbadol). Therefore, the individual formulation pharmacokinetics should be evaluated prior to establishing a patient's dosage.

Pain may occur on injection due to tonicity, inflammation (often delayed by hours), and preservatives such as benzyl alcohol, solvents or due to the active ingredient itself. Acidic or alkaline solutions may result in pain as well, which is the reason adding pH neutralizers to decrease pain is sometimes recommended (e.g., adding sodium bicarbonate to lidocaine or fentanyl extravascular injections). Sterile or aseptic techniques are desired for IM and SC drug administration, as introduction of bacteria or foreign material can result in abscesses, cellulitis and even septicemia in extreme cases. Subcutaneous injections may have decreased and erratic absorption due to dehydration, hypotension, hypothermia and obesity. In patients with dehydration, hypotension, hypothermia and obesity, IM injections are preferred as they are less affected by these conditions.

Transdermal and transmucosal administration avoids first-pass metabolism and may result in greater bioavailability than oral administration. Transdermal drug administration may also result in a depot effect due to sequestration in the stratum corneum. Drugs have to be very lipophilic and un-ionized to undergo TD and TM absorption, which limits the number of drugs available for these routes. It is important to note that very few drugs sold as compounded pluronic lecithin organogel (PLO) formulations actually undergo transdermal absorption and most should be avoided. Compounded drugs are not required to demonstrate safety or efficacy (see Bioequivalence, Generic Drugs and Compounded Drugs). Some transdermal PLO methimazole formulations are effective in some, but not all, cats with hyperthyroidism and some studies suggest phenobarbital and amlodipine have some absorption in cats, but clinical efficacy has not been reported for the latter in PLO formulations (see ch. 168).

Distribution

Drug distribution is dependent on many factors including drug lipophilicity, regional blood flow, anatomic barriers, and plasma protein binding. Drug lipophilicity is a measure of the drug's solubility in lipids. Drugs that are poorly soluble in lipids (low lipophilicity) do not have the ability to reach intracellular targets and tend to have restricted distribution. For example, aminoglycosides are poorly lipophilic and as a result are ineffective for intracellular infections and infections in tissues such as the brain and prostate, due to their inability to diffuse across lipid membranes.

Highly perfused tissues are those that have a high blood-flow-to-tissue-mass ratio (E-Table 160-1). Highly

perfused tissues have faster equilibration between plasma and tissue concentrations and as a result may equilibrate at higher drug concentrations than tissues that are not highly perfused (Figure 160-1). For example, fentanyl brain concentrations equilibrate more rapidly and at higher plasma concentrations after IV injection than less highly perfused tissues such as muscle. As fentanyl continues to distribute into the anatomically large volumes of muscle (in addition to metabolism), the plasma concentrations decrease below the central nervous system (CNS) concentrations. This results in fentanyl diffusing out of the CNS, decreasing CNS fentanyl concentrations and subsequently loss of central opioid effects. Therefore, the loss of central opioid effects of fentanyl is due in part to drug redistribution from the CNS to the plasma.

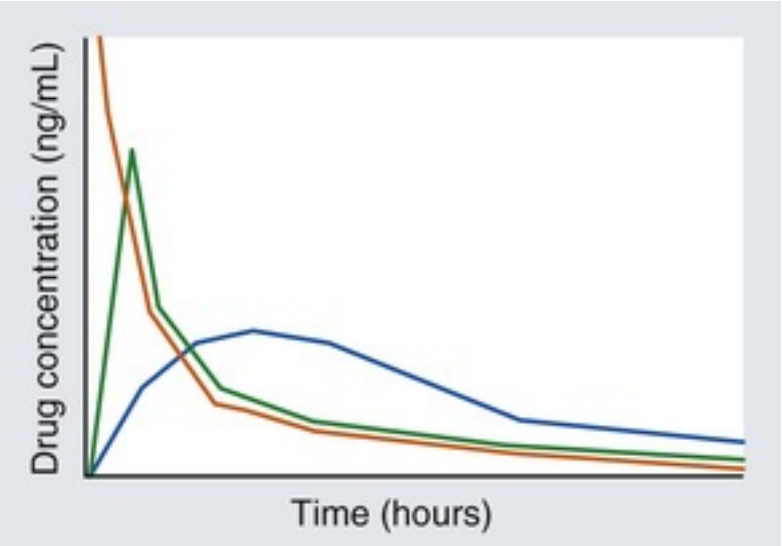

FIGURE 160-1 Theoretical drug concentration versus time profile of IV fentanyl. The red line represents plasma drug concentration, the green line represents CNS fentanyl concentration and the blue line represents muscle drug concentration. Fentanyl is lipophilic and rapidly diffuses into the highly perfused CNS and equilibrates to high plasma concentrations. However, less well perfused tissues such as muscle equilibrate later and at lower drug concentrations. The loss of CNS (analgesic) effects of fentanyl is due in part to fentanyl redistributing from the CNS back into the plasma in addition to metabolism.

E-TABLE 160-1

Examples of Anatomic Locations That Have Different Regional Blood Flows per Gram of Tissue

HIGH PERFUSION	INTERMEDIATE PERFUSION	LOW PERFUSION
Brain	Muscle	Adipose tissue
Kidneys	Skin	Bone
Liver	Gastrointestinal tract	
Heart		
Lungs		
Endocrine glands		

Anatomic barriers can decrease drug distribution into certain tissues for drugs that are not highly lipophilic. The blood-brain barrier consists of a physical barrier including glial cells, which decrease drug penetration into the CNS. Physiologic barriers including efflux proteins such as the p-gp efflux pumps remove drug that penetrates the CNS by pumping the drug back into the vasculature, decreasing CNS drug concentrations. Animals affected by p-gp mutations or receiving p-gp inhibitors can have increased drug concentration in the CNS, resulting in more pronounced central effects of drugs that are p-gp substrates. Examples of drugs that may have increased CNS concentrations with decreased p-gp efflux pump activity

include ivermectin (resulting in ivermectin toxicosis at therapeutic dosages) and loperamide (resulting in pronounced central opioid effects, including sedation) among others. Ivermectin toxicosis in "normal" animals with functional p-gp can occur from drug interactions with a p-gp inhibitor such as spinosad.

The blood-prostate, blood-bronchus and blood-ocular barriers also decrease drug penetration into those tissues. Drugs with high lipophilicity are needed to penetrate these tissues as well. Other anatomic barriers occur in tissues such as the mammary gland, testes, placenta and synovium, but in general are less effective barriers to drug penetration.

Drugs that are highly bound to plasma proteins may have restricted distribution, as the protein-drug complex is too big to diffuse out of the plasma. For example, cefovecin is highly protein-bound, resulting in a low fraction of cefovecin distributing into the tissues at the location of infection.[6] However, it is important to note that plasma protein binding is reversible and there is always some free drug available that can diffuse out of the vasculature. Therefore, some drugs that have high protein binding can still distribute throughout the body. For example, buprenorphine is highly protein-bound in dogs, but it distributes well into the CNS producing central opioid effects.[7] Many references still caution against using multiple highly protein-bound drugs concurrently due to protein binding interactions, but the likelihood of a true interaction is minimal. For a protein-binding interaction to occur, the drugs would have to be administered IV, have a low therapeutic index, and undergo rapid hepatic metabolism.

Metabolism

Drug metabolism results in chemical changes to the drug molecule to enhance renal or biliary elimination. Drug metabolism occurs due to enzymes that catalyze changes in the drug molecule, changing the drug into a molecule (metabolite) that is more readily eliminated by renal or biliary mechanisms. A drug may not undergo metabolism (e.g., gentamicin, which is eliminated as intact drug in the urine or doxycycline, which is eliminated as intact drug in the bile). A drug may undergo a single metabolic process (e.g., morphine, primarily metabolized to morphine-3-glucuronide in dogs, which is eliminated in the urine). A drug may also undergo multiple metabolism processes (diazepam in dogs metabolized to temazepam, followed by temazepam metabolized to oxazepam followed by oxazepam metabolized to oxazepam-glucuronide, which is then eliminated in the urine).

Metabolism does not always inactivate a drug. For example, tramadol is metabolized to the metabolite O-desmethyltramadol in cats, increasing the mu opioid effects by approximately 200 times compared to tramadol. Metabolism may also be different in different species. For example approximately 60% of codeine is metabolized to morphine in humans, but <1% of codeine is metabolized to morphine in dogs and cats with codeine-6-glucuronide being the major metabolite in dogs, but norcodeine the major metabolite in cats.[8]

There are two primary metabolism pathways, Phase I (metabolic) and Phase II (conjugation) reactions. Phase I, metabolic reactions (oxidation, reduction, hydrolysis, and hydration), are catalyzed by different enzymes. Cytochrome P450 (CYP) enzymes are a major group of enzymes commonly involved in Phase I drug metabolism. Cytochrome P450 enzymes are classified into families (>40% amino acid homology) designated with a number, followed by subfamilies (>55% amino acid homology) designated with a letter, and the specific enzyme is finally labeled with a number. For example, dogs have CYP3A12 and CYP3A26 enzymes and humans have CYP3A4 enzymes which have >55% homology, but are different enzymes. Different enzymes may have different specificities for substrates and inhibitors, but some overlap may occur. For example, methadone is metabolized by CYP2B11 in dogs, but diazepam is metabolized by both CYP2B11 and CYP3A12/26 in dogs.

Species similarities and differences occur in CYP substrate and inhibitor specificity. For example, similar metabolism of midazolam occurs by the canine CYP3A12/26 and human CYP3A4 and methadone is metabolized by canine CYP2B11 and human CYP2B6 orthologs. Similarly, ketoconazole inhibits the CYP3A enzyme orthologs in dogs and humans. However, species/ortholog differences also occur. For example, chloramphenicol inhibits CYP2B11 in dogs, but in humans chloramphenicol primarily inhibits CYP2C19, not CYP2B6 (the human CY2B ortholog).

Species similarities and differences in metabolite formation can also occur. For example, methadone is primarily metabolized to EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) in humans by CYP2B6, but EDDP is not a major metabolite in dogs, which metabolize methadone by CYP2B11.[9] Tramadol is primarily metabolized to the inactive metabolite n-desmethyltramadol in dogs, but to the active metabolite O-desmethyltramadol in cats.[10] The difference in primary metabolites formed may be due to the relative amounts of the different CYP isoforms (e.g., cats may have a larger amount of CYP2D than dogs, which form

the active metabolite, but dogs have a relatively larger amount of CYP2B11 and CYP3A isoforms, which form the inactive metabolite). Different affinities of the drugs and enzymes, or lack of certain enzymes can also contribute to species differences in drug metabolism.

Phase I metabolism enzymes can be inhibited or induced, producing clinically relevant drug interactions. Clinically relevant drug interactions due to CYP inhibition are relatively specific and more likely to occur when a drug is a substrate for a specific CYP (not metabolized by multiple CYPs) and has a low therapeutic index. Clinically relevant drug interactions due to CYP induction typically occur due to increase in CYP content (more metabolizing enzymes) resulting in more rapid drug metabolism (E-Table 160-2).

E-TABLE 160-2

Examples of Drug Interactions in Dogs and Cats

SUBSTRATE	Inhibitor/Inducer	CLINICAL EFFECT
Phenobarbital, pentobarbital, propofol, methadone	Chloramphenicol	Phenobarbital toxicosis, prolonged effects of pentobarbital, propofol, and methadone
Theophylline	Enrofloxacin (and other fluoroquinolones)	Theophylline toxicosis
Cyclosporine	Ketoconazole, fluconazole	Increased cyclosporine effects or decreased cyclosporine dosage
Midazolam	Ketoconazole	Prolonged sedative effects of midazolam
Chloramphenicol, diazepam, theophylline, digoxin, levetiracetam, glucocorticoids	Phenobarbital	Decreased substrate efficacy
Phenobarbital	Phenobarbital	Decrease plasma concentrations over time resulting in decreased efficacy if dosage not adjusted
Phenytoin	Phenytoin	Poor efficacy due to rapid elimination

Phase II metabolism pathways are conjugation reactions that add an endogenous substrate to the drug molecule, resulting in a metabolite with larger size and decreased lipophilicity. The Phase II metabolite can then be eliminated by glomerular filtration, renal excretion, or biliary excretion. Glucuronidation, sulfation, acetylation and amino acid conjugation reactions are the most common Phase II metabolism pathways. Specific enzymes are associated with each type of conjugation reaction and there are often subtypes within each reaction. Drug interactions involving induction or inhibition of conjugation enzymes are not well characterized in animals and are thought to be rare.

Species-specific differences in conjugation reactions have been identified. For example, uridine diphosphate glucuronosyltransferase (UGT) is the enzyme family catalyzing glucuronide conjugation, with UGT1A6, 1A7, 1A9, 1A11 and 2B31 present in dogs. Cats are deficient in UGT1A6 and 1A9, which results in decreased or alternate conjugation of some conjugation substrates, including acetaminophen and morphine.[11] The lack of glucuronide conjugation of acetaminophen results in large amounts of acetaminophen undergoing Phase I metabolism, resulting in reactive metabolites and acetaminophen toxicosis in cats even at low (subtherapeutic) acetaminophen dosages. In contrast, the lack of morphine glucuronidation in cats is clinically "irrelevant" as no reactive morphine metabolites are formed and morphine is rapidly eliminated in cats by sulfate conjugation, with a similar elimination half-life in dogs and cats.

Dogs lack N-acetyltransferase enzymes and as such are deficient in forming acetyl conjugates. Clinical effects of the deficiency include lack of N-acetyl procainamide (NAPA) metabolite formation of procainamide, a Class I antiarrhythmic (sodium channel antagonist).[12] The NAPA metabolite is a Class III antiarrhythmic (potassium channel antagonist); therefore, the antiarrhythmic effects of procainamide in dogs are different (Class I effects only) compared to other species (Class I and III antiarrhythmic effects). Sulfonamide metabolism in most species also involves acetylation reactions, but the acetylation deficiency in dogs may contribute to an increased risk of sulfonamide hypersensitivity reactions due to metabolism by other pathways to reactive metabolites.[13]

Drug metabolism (both Phase I and Phase II) may be decreased with hepatic disease, but the extent of decreased drug metabolism may not be proportional to the extent of disease. There are little data evaluating the pharmacokinetics or metabolism of drugs in animals with naturally-occurring liver disease; therefore,

specific recommendations on dosage adjustments are not available. If single parenteral doses or PO doses of drugs with a high oral bioavailability are administered, the maximum drug effect will be similar, but the duration of effect may be markedly longer. However, multiple doses may result in greater than expected drug accumulation due to a prolonged terminal half-life, resulting in dose-dependent adverse effects (see Half-life). Drugs with low oral bioavailability may result in concentration-dependent adverse effects, even with a single dose, due to less first-pass metabolism and a higher PO bioavailability due to the liver disease. The best option for animals with hepatic disease would be choosing a drug with a similar effect, but that undergoes renal elimination (e.g., choosing atenolol instead of propranolol to decrease sinus tachycardia). Another option is to use a drug with therapeutic drug monitoring (TDM) available and adjusting the dose based on plasma concentrations (e.g., theophylline to manage bronchitis), but progression of disease may result in unpredictable changes in plasma concentrations if TDM is not done regularly. Adjusting the dosage based on clinical response is another option, but this option would be limited to drugs with a high therapeutic index and in which responses can be readily monitored (e.g., oral codeine without acetaminophen in a dog with liver impairment and osteoarthritis).

Other metabolism enzymes are present, but contribute less commonly to drug metabolism. Plasma esterases metabolize remifentanil. Xanthine oxidase metabolizes and inactivates 6-mercaptopurine, an azathioprine active metabolite. Ethylene glycol and ethanol are metabolized by alcohol dehydrogenase.

Elimination

Elimination includes the removal of the drug and drug metabolites from the body (E-Table 160-3). Some drugs are not metabolized and as such are primarily eliminated as unchanged drug (e.g., gentamicin undergoing renal elimination by glomerular filtration). Some drugs are eliminated as both intact drug and drug metabolites (e.g., codeine eliminated in the urine as codeine and norcodeine in cats). Other drugs, such as propofol, may be almost completely metabolized prior to elimination and eliminated primarily as metabolites.

E-TABLE 160-3

Factors That Enhance or Decrease Drug Elimination from the Body in Healthy Animals

ENHANCE DRUG ELIMINATION	DECREASE DRUG ELIMINATION
Metabolism, hepatic—Phase I	Renal tubular reabsorption—active transporters
Metabolism, hepatic—Phase II	Renal tubular reabsorption—passive diffusion
Metabolism, hepatic—other	Enterohepatic recycling
Metabolism, extrahepatic	
Biliary excretion	
Glomerular filtration	
Active renal tubular excretion	
Other elimination (e.g., respiratory)	

Renal elimination of drugs and drug metabolites can occur by glomerular filtration and renal tubular secretion. However, renal tubular reabsorption can also occur, decreasing elimination due to drug being reabsorbed from the urine and back into systemic circulation. Approximately 25% of cardiac output goes to the kidneys and as such, renal elimination can be highly efficient. Glomerular filtration is essentially a method of ultrafiltration in which proteins and cells are retained in the vasculature and a portion of the plasma fluid enters the urine through the glomeruli. Protein-bound drugs tend to be retained in the vasculature and as such, highly-protein bound drugs may have slow elimination by glomerular filtration. For example, cefovecin is >95% bound to plasma proteins and persists for weeks after a single administration. Glomerular filtration is not saturable and increases in dosage or drug concentration result in proportional increases in renal elimination by glomerular filtration. Glomerular filtration is dependent on renal blood pressure and plasma oncotic pressure. Therefore, renal hypotension may decrease glomerular filtration and drug elimination or conversely hypoproteinemia may increase renal drug elimination by glomerular filtration.

Drugs may also be actively eliminated in the urine in the renal tubules by transporters. Weak acid (organic

anion transporters; OAT) and weak base transporters (organic cation transporters; OCT) are most associated with renal excretion but other transporters such as the p-glycoprotein efflux pump are also present. Penicillin and other beta-lactams are classic substrates of OAT and cimetidine is the classic substrate of OCT renal excretion. Since these are transporters, they are subject to saturation and competition with the classic example of probenecid (a weak acid) competing with penicillin G (a weak acid) excretion, resulting in decreased elimination of penicillin and prolonged dosing intervals.

Drugs and metabolites can also undergo active renal tubular reabsorption and diffusion from the tubules back into the plasma with a net effect of decreasing drug elimination. Similar to active renal tubular secretion, active tubular reabsorption can be saturated and competition for reabsorption can occur, decreasing reabsorption. Renal tubular reabsorption also occurs by diffusion and undergoes similar principles as any drug movement by diffusion. The rate of diffusion could be decreased (enhancing elimination) by increasing urine flow through fluid diuresis or altering the urine pH. For example, phenobarbital is a weak acid; therefore, alkalinizing the urine results in phenobarbital ionization, which prevents it from diffusing out of the renal tubules back into the vasculature and produces significantly increased phenobarbital elimination in dogs fed a urinary alkalinizing diet compared to dogs fed an acidifying diet (also known as ion trapping).[14] Urinary acidification (for drugs or toxins that are weak bases) and urinary alkalinization (for drugs or toxins that are weak acids) are strategies to help enhance elimination of drugs and toxins that undergo passive renal tubular reabsorption.

Drugs or diseases that result in decreased renal function are expected to result in near-proportional decreases in renal drug elimination. For example, the renal elimination of amikacin will decrease proportionally as glomerular filtration rate decreases and is significantly decreased before changes in urine specific gravity or azotemia are noted. The best strategies for drug choices in an animal with renal dysfunction are to choose a drug eliminated by hepatic metabolism (e.g., marbofloxacin instead of enrofloxacin) or choosing a drug with a higher therapeutic index (e.g., amoxicillin with clavulanate instead of enrofloxacin).

Biliary excretion occurs through active transporters, including OAT and OCT as well as neutral and heavy metal transporters, p-glycoprotein and other active transporters. Drugs and metabolites eliminated by biliary excretion tend to be larger molecules, including some drugs (e.g., doxycycline) and drug metabolites. Once excreted through the bile into the intestine, the drugs and drug metabolites can be eliminated in the feces. However, there are situations in which drug-conjugate (Phase II) metabolites secreted in bile are deconjugated by intestinal flora, resulting in liberation of free drug that has the potential for reabsorption (i.e., enterohepatic recycling). Enterohepatic recycling is the rationale for multiple doses of activated charcoal following some drug or toxin exposures. The activated charcoal can bind the drug conjugates and deconjugated drug preventing, reabsorption and enhancing elimination.

Other mechanisms of drug elimination exist. Respiratory elimination of most inhalant anesthetics occurs by diffusion through the lungs and elimination in exhaled air. Some drug elimination can occur in milk through lactation, but in companion animals is not typically a substantial route of elimination. However, drug elimination in the milk can result in clinically relevant drug exposure to nursing animals. Rifampin can be eliminated in tears, which is a clinically irrelevant elimination route, but can produce red discoloration of tears as an effect that may be alarming to clients.

Pharmacokinetic Parameters

Pharmacokinetic parameters are often determined from studies using a small number of healthy animals, often of the same breed, and typically young adults. For example, the pharmacokinetics of oral gabapentin are described with 6 healthy Greyhound dogs aged 1.5-3 years.[1] The means and ranges are then reported. The pharmacokinetics are typically well described in that specific group of animals, but may not describe the range seen in dogs of all ages, all breeds, and the effects of health, gender, or neutering are not described. Therefore, extrapolation from a small study to a specific patient should be done with the understanding that every dog is not an "average" dog. More recently, population pharmacokinetic studies are being performed in veterinary species in which large numbers of animals are included of various breeds, ages and health statuses to better describe the variability in a population that more accurately represents the target population to be treated. Additionally, as described in the preceding section, numerous factors could alter the pharmacokinetics in a clinical patient, including drug interactions and disease states.

Half-Life

The half-life is a commonly referred-to pharmacokinetic term, most often referring to the terminal half-life which is the half-life of the terminal portion of a plasma-time profile. The terminal half-life describes the amount of time it takes for plasma concentrations to decrease by half (50%). The terminal half-life may be the elimination half-life (the amount of time it takes to eliminate 50% of drug), but may not be, as factors other than elimination can affect the terminal slope.

The terminal half-life is useful for many clinical applications. The obvious utility is to estimate how long drug exposure will persist after administration. The terminal portion of the plasma versus time curve most often decreases in logarithmic decay, in which a fixed portion of drug concentration is decreased per unit time. This is the reason many plasma profiles are presented with a logarithmic drug concentration scale. For example, the plasma concentrations of morphine in dogs and cats decrease by approximately one half every hour. Based on these assumptions, after 3 half-lives (or 3 hours in this case) plasma concentrations will decrease by ≈88%; by 5 half-lives, plasma concentrations will decrease by ≈97%; and by 7 half-lives (or 7 hours in this case), plasma concentrations will decrease by ≈99% (E-Table 160-4).

E-TABLE 160-4

Predicted Percent Changes in Drug Concentrations and Steady State Plasma Concentrations Based on the Number of Half-Lives Elapsed

NUMBER OF HALF-LIVES	% OF ORIGINAL CONCENTRATION	% DECREASE IN ORIGINAL CONCENTRATION	% OF STEADY STATE DRUG CONCENTRATION
0	100	0	0
1	50	50	50
2	25	75	75
3	12.5	87.5	87.5
4	6.25	93.75	93.75
5	3.125	96.875	96.875
6	1.563	98.438	98.438
7	0.781	99.219	99.219
8	0.391	99.609	99.609
9	0.195	99.805	99.805
10	0.098	99.902	99.902

The terminal half-life can be applied to other clinical situations. For example, the duration of a dose of 0.5 mg/kg IM morphine in dogs is about 4 hours. If the dose is doubled to 1 mg/kg IM, then the duration of effect is increased by 1 half-life (1 hour in the case of morphine) since the extra amount will be eliminated in 1 half-life. Doubling the dose does not double the duration of effect, but typically extends it by 1 half-life. However, doubling the dose does double the C_{MAX} (see below) and may markedly increase adverse effects such as morphine-induced sedation. As another example, a dog ingested a bottle of meloxicam in the morning and the owner brings you the dog in the evening. How long will it take for plasma concentrations to decrease in the dog? Meloxicam has a terminal half-life ≈24 hours in dogs; therefore, in 5 days (120 hours) the plasma concentration will decrease by ≈97% from time of presentation and in 7 days, the plasma concentration will decrease by ≈99%. Therefore you may recommend hospitalization and fluid therapy for 5-7 days to minimize renal adverse effects.

The terminal half-life is also an important parameter to predict the amount of time it takes to reach steady state plasma concentrations with multiple doses or drug infusions (see E-Table 160-4). Drugs are often administered for multiple doses. If the second dose is administered prior to complete drug elimination from the first dose, then there will be some additive effects of the first and second dose on the plasma drug concentrations and increases in plasma drug concentrations will continue with subsequent doses until steady state plasma concentrations are reached. Steady state occurs when no further increases in drug concentration occur with continued dosing (i.e., the plasma drug versus concentration curve plateaus) (Figure 160-2). The time to reach steady state can be predicted knowing the terminal half-life, with the amount of time it takes to reach 97% of steady state plasma concentrations being 5 half-lives (see E-Table 160-4). For example,

meloxicam has a terminal half-life of 24 hours; therefore, ≈97% of the steady state plasma concentration will be achieved in 5 half-lives, 120 hours (5 days).

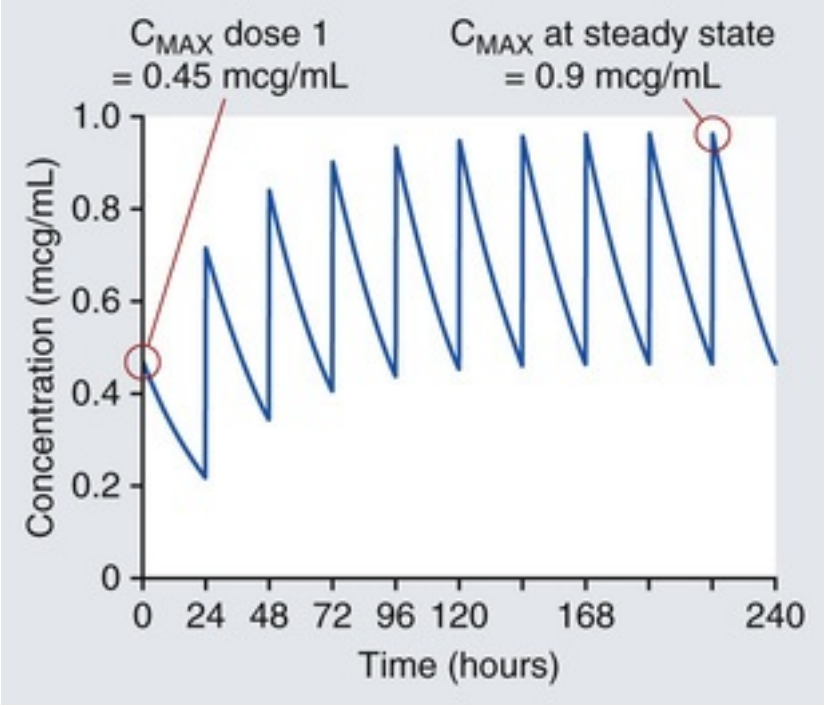

FIGURE 160-2 Steady state plasma concentrations and the extent of drug accumulation can be predicted based on the terminal half-life and dosing interval.

The extent of drug accumulation can also be estimated knowing the terminal half-life and dosing interval (E-Table 160-5; see also Figure 160-2). If the dosing interval is much shorter than the half-life, then extensive accumulation can occur, since the subsequent dose is administered prior to substantial decreases in plasma concentration. If the dosing interval equals the half-life, then a 2-fold increase in plasma concentrations between the first dose and steady state plasma concentrations is predicted. Finally, when the dosing interval is ≥5 times the terminal half-life, then minimal accumulation (<5%) will occur between the first dose and steady state plasma concentrations as the majority of the previous dose will be eliminated prior to the administration of the subsequent dose.

E-TABLE 160-5

Predicted Accumulation and Fluctuation of Peak and Trough Concentrations for Multiple Doses Based on Terminal Half-Life and Dosing Interval

DOSING INTERVAL (HOURS)	HALF-LIFE (HOURS)	HALF-LIFE: DOSING INTERVAL	PREDICTED EXTENT OF ACCUMULATION	FLUCTUATION OF PEAK AND TROUGH PLASMA CONCENTRATIONS
CRI	24	N/A	N/A	N/A
6	24	1 : 4	6.29 ×	1.2 ×
12	24	1 : 2	3.41 ×	1.4 ×
24	24	1 : 1	2.00 ×	2 ×
48	24	2 : 1	1.33 ×	4 ×
72	24	3 : 1	1.14 ×	8 ×
96	24	4 : 1	1.07 ×	16 ×
120	24	5 : 1	1.03 ×	32 ×

For a drug with a half-life of 24 hours administered every 6 hours (a dosing interval to half-life ratio of 1:4), a 6.29-fold accumulation is predicted between the first dose and steady state. Conversely, a drug dosage with a dosing interval:half-life of 5:1 will have minimal drug accumulation between the first dose and steady state plasma concentrations, as most of the drug will be eliminated prior to the next dose being administered. Drugs administered as a constant rate infusion (CRI) will have no fluctuations in plasma drug concentrations, but as the dosing interval increases, the fluctuations in peak and trough concentrations, increase with a 32-fold difference between peak and trough concentrations if the dosing interval:half-life is 5:1.

The fluctuation between peak and trough plasma concentrations can also be predicted by assessing the dosing interval and half-life. A constant rate infusion has essentially no fluctuations in plasma concentrations (at steady state) because the dosing interval is infinitesimally smaller than the half-life for any drug. However, as the dosing interval gets closer to, then exceeds, the terminal half-life, the fluctuations between peak and trough concentration will increase (see E-Table 160-5). Large fluctuations in peak and trough concentrations may be desirable (e.g., gentamicin to reduce risk of renal toxicosis) or minimal fluctuations may be desirable (e.g., morphine infusion to maintain analgesia, but minimize dose-dependent effects such as sedation).

Clearance

The plasma clearance is a measurement of the ability of the animal to remove drug from the plasma through metabolism or elimination. Plasma clearance is the sum of hepatic, renal and other mechanisms of metabolism and elimination. Plasma clearance predicts the steady state plasma concentrations (or average plasma concentrations) for a given dose rate with the following equation:

$$\text{Dose rate} = \text{plasma clearance} \times \text{average plasma concentration}$$

Therefore, if you know the plasma clearance, the dose rate needed to achieve a targeted mean (or steady state) plasma concentration can be calculated. Many pharmacokinetic studies are available for drugs used in veterinary medicine with the clearance reported in most of the studies. For example, the published mean plasma clearance of IV ceftriaxone in dogs is 3.61 mL/min/kg.[15] Therefore, if you wanted to achieve an 8 mcg/mL mean (steady state) plasma concentration, you could calculate the dose rate:

$$\text{Dose rate} = \text{plasma clearance} \times \text{average plasma concentration}$$

$$\text{Dose rate} = 3.61\ \text{mL/min/kg} \times 8\ \text{mcg/mL}$$

$$\text{Dose rate} = 28.88\ \text{mcg/min/kg}$$

$$\text{Dose rate} = 1733\ \text{mcg/h/kg} = 1.73\ \text{mg/h/kg}$$

It is important to remember that the time to reach steady state is still predicted by the terminal half-life, which is 0.9 hours for ceftriaxone. It would take approximately 4.5 hours to reach steady state plasma concentrations for an IV constant rate infusion of ceftriaxone. It is also important to note that the specific animal treated may not have the "average" clearance and as such the dose may need to be adjusted based on other factors such as renal dysfunction or fluid diuresis. If a drug is administered by a route other than IV, then the bioavailability (F) must be included in the equation as follows:

$$\text{Dose rate} = (\text{plasma clearance} \times \text{average plasma concentration}) \,/\, F$$

Volume of Distribution

The volume of distribution is a measure of the dilution of a drug into the body after administration. There are numerous ways to calculate and express volumes of distribution, but they are beyond the scope of this chapter. The primary utility of the volume of distribution is to calculate the loading dose needed to achieve a targeted plasma concentration with the following equation:

$$\text{Dose} = \text{volume of distribution} \times \text{plasma concentration}$$

Loading doses are important for drugs with a long terminal half-life and when you want to immediately achieve an effective plasma drug concentration. For example, you desire to immediately achieve a plasma ceftriaxone concentration of 8 mcg/mL (you do not want to wait 4.5 hours to reach steady state). Ceftriaxone has a mean volume of distribution of 277 mL/kg. A dose can be calculated as an IV bolus to immediately achieve 8 mcg/mL; then the CRI can be started to maintain 8 mcg/mL. The loading dose is calculated by:

$$\text{Dose} = \text{volume of distribution} \times \text{plasma concentration}$$

$$\text{Dose} = 277\ \text{mL/kg} \times 8\ \text{mcg/mL}$$

$$\text{Dose} = 2216\ \text{mcg/kg} = 2.2\ \text{mg/kg}$$

Therefore, an IV bolus of 2.2 mg/kg would immediately achieve a plasma concentration of 8 mcg/mL, combined with an IV infusion of 1.73 mg/h/kg to maintain 8 mcg/mL.

Maximum Plasma Concentration and Time to Maximum Plasma Concentration

The maximum plasma concentration (C_{MAX}) is the highest (peak) plasma concentration achieved after drug administration following extravascular administration (Figure 160-3). The C_{MAX} is often correlated with drug toxicity (e.g., propofol-induced cardiac depression) or efficacy (e.g., aminoglycoside antimicrobial effects). Other drugs may be correlated with maintaining minimum plasma concentrations (e.g., opioids) or achieving a targeted area under the curve. The C_{MAX} for most drugs is directly proportional to the dosage (e.g., doubling the dosage doubles the C_{MAX}, halving the dosage halves the C_{MAX}), but of course there are some exceptions, such as less-than-proportional increases in gabapentin C_{MAX} with increasing dosage due to saturation of active transporter-mediated absorption in the intestine.[1] The time of the C_{MAX} is abbreviated as T_{MAX}. The T_{MAX} is typically unchanged by dosage (e.g., if the dosage is doubled, the T_{MAX} is unchanged), but there are some exceptions.

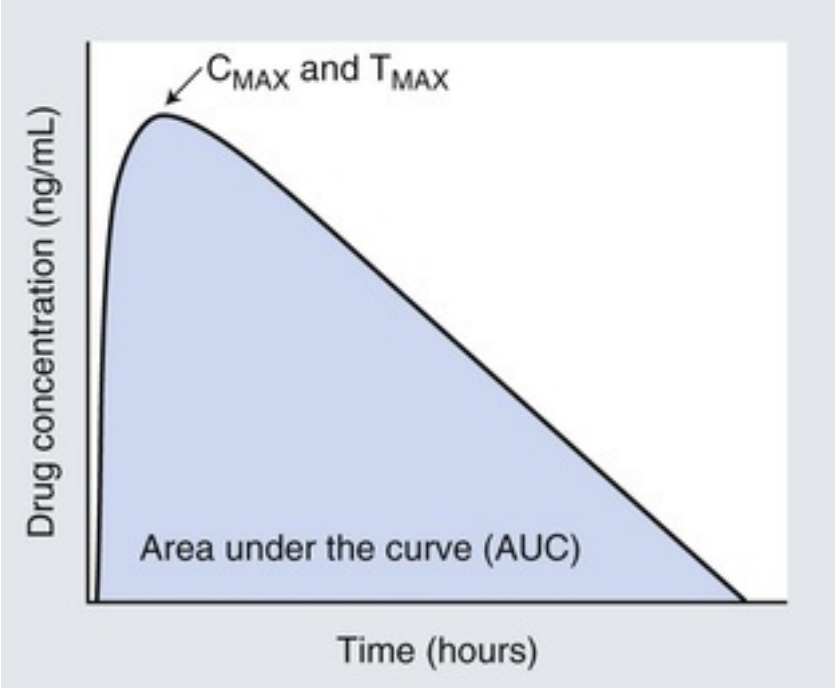

FIGURE 160-3 The maximum plasma concentration (C_{MAX}), time to C_{MAX} (T_{MAX}) and area under the curve (AUC) for a generalized plasma profile.

Area Under the Curve

The area under the curve (AUC) is a measure of total drug exposure and encompasses both the plasma concentrations and the length of time the plasma concentrations persist (see Figure 160-3). The AUC is often correlated with efficacy (e.g., fluoroquinolone clinical cures) or toxicosis (e.g., aminoglycoside-induced kidney injury). The AUC for most drugs is directly proportional to dosage (e.g., doubling the dosage doubles the AUC). Decreased elimination due to disease or drug interactions results in directly proportional effects on AUC (e.g., if the half-life of gentamicin doubles due to renal insufficiency then the AUC doubles). Similarly, increased elimination results in directly proportional decreases in AUC (if the half-life of phenobarbital is halved due to CYP induction, then the AUC is halved).

Bioequivalence, Generic Drugs and Compounded Drugs

Regulatory approval (e.g., Food and Drug Administration [FDA], European Medicines Agency [EMA], et al.) of generic drugs often uses bioequivalence studies and generic drugs may not be required to undergo more extensive safety and efficacy studies that the pioneer products underwent. Generic products must have the same drug and drug content as the pioneer product, be bioequivalent, be manufactured in inspected facilities and demonstrate stability in the dosage form. However, the inactive ingredients can be different.

Bioequivalence studies are pharmacokinetic studies, with the C_{MAX} and AUC being the pivotal parameters assessed. The assumption is that a similar C_{MAX} and AUC will produce a similar drug exposure over time and subsequently similar efficacy and safety. There are specific statistical parameters that must be met for bioequivalence studies. The 90% confidence interval of the mean (CI) for log-transformed data of the generic drug must be 80-125% of the pioneer product for both the C_{MAX} and AUC. The 90% CI is a measure of statistical variability interpreted as having a 90% confidence that the true mean would fall within that range, if the bioequivalence studies were repeated numerous times. For example, a bioequivalent formulation of enrofloxacin is approved by the FDA for dogs. The bioequivalence studies demonstrated a mean AUC of 10963 hr × ng/mL for the generic product compared to 10931 hr × ng/mL for the pioneer product with a 90% CI range of 98.9-103.8% of the pioneer product. The mean C_{MAX} of the generic product was 2811 ng/mL compared to 2785 ng/mL of the pioneer with a 90% CI range of 94.5-107.4% of the pioneer product; therefore, this product was approved as a bioequivalent.

Compounding is the practice of using FDA approved drugs to make a formulation or strength that is not

currently available for a specific patient (see ch. 168). Compounding from bulk ingredients or active pharmaceutical ingredients (API) is not considered by the FDA as legitimate drug compounding, but drug manufacturing and is illegal in the USA. Compounding just to decrease cost is not considered a legitimate reason for choosing a compounded formulation when an approved formulation is available.[16] In contrast to generic drugs, compounded drugs are not required to contain the same drug content, drug form, or have stability and bioequivalence data. In the United States, the state boards of pharmacy have the primary regulatory authority over compounding pharmacies. Since compounded drugs do not undergo bioequivalence assessment, there should be no expectation of similar safety, adverse effects and efficacy as an approved drug. Compounded drugs have been recalled due to poor quality control. For example, routine random testing of compounded drugs (human and veterinary) between 2006 and 2015 by the Missouri State Board of Pharmacy found 13-25% of tested drugs failed to have the correct drug content. The range of content in the failing drugs was as low as 3% to as high 225% of the stated content.[17] Recalls by the FDA for lack of sterility and endotoxin assurance for "sterile" compounded drugs from numerous compounding pharmacies have been conducted.[18,19] Additionally, deaths in animals have occurred due to incorrect compounding practices resulting in incorrect drug content.[20] Therefore, use of compounded drugs in lieu of available FDA-approved drugs increases the risk of adverse effects, including the lack of efficacy, and increases the risk of malpractice and civil lawsuits. Client education, describing the risks and limitations of compounded drugs, is critical when compounded drugs are prescribed. Additional information on veterinary compounding is available in ch. 168, and the American Veterinary Medical Association has a Veterinary Compounding Policy with further details on legitimate compounding practices.[16]

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CHAPTER 161

Antibacterial Drug Therapy

Mark G. Papich

Overview

Antimicrobial therapy is one of the most important therapies performed by small animal veterinarians. Skin/soft tissue infections, urinary tract infections, respiratory infections, blood-borne infections, and post-surgical infections are just some examples that require primary antibiotic therapy. In addition, our small animal patients present with a variety of diseases involving various body systems. Bacterial infections are often secondary to the primary problem and these patients also require antimicrobial therapy. More than ever, veterinarians are under pressure to use antimicrobial agents prudently. Virtually all practicing veterinarians have encountered multi-drug antimicrobial resistance. These strains of bacteria can present significant therapeutic challenges as well as potential public health risks. This chapter will discuss the essential principles of effective and prudent antimicrobial therapy in order to optimize treatment and decrease risks from resistant organisms.

Principles of Therapy

Every veterinarian should ask simple and basic questions before starting antimicrobial therapy (Box 161-1). The factors listed in Box 161-1 emphasize the activity of the drug, achieving adequate concentrations at the site of infection and considerations of drug safety.

Box 161-1

Important Factors to Consider When Starting Antimicrobial Therapy

- Activity of the drug: susceptibility: Will the empirical selection of a drug be active against the pathogen?
- Penetration: Will the drug adequately penetrate the tissue to reach the site of infection?
- Local factors that affect drug activity: Are there any local factors that will affect antimicrobial activity? Such factors can include low pH, anaerobic environment, cellular debris and pus, and compromised blood flow.
- Pharmacokinetic-Pharmacodynamic (PK-PD) factors: Is it possible to deliver a dosage and frequency of administration that are optimal to ensure the proper PK-PD exposure?
- Convenience of dosage regimen: Can the pet owner adequately administer this medication to the pet and achieve the desired compliance?
- Drug safety: Will the drug be safe in this patient? Does the patient have organ disease (liver disease, kidney disease); is the patient young, old, or pregnant?

Selecting a Drug That Is Active Against the Organism

Most of the time, veterinarians will start antimicrobial treatment before a culture and susceptibility test is obtained. In order to begin this treatment, veterinarians should have confidence that their empirical selection will produce the desired results. The first step is to consider the bacteria most likely present at the site of infection. This is accomplished by considering the most common commensal bacteria, opportunistic bacteria, and those most likely to invade the tissue. For example, *Staphylococcus pseudintermedius* is the most common

isolate from the skin of dogs, *Escherichia coli* is the most common urinary tract isolate in dogs and cats, and the respiratory tract can be infected with a mixed population. Clinicians should consider the likelihood of a pathogen infecting a tissue or the aid of other tests. Simple diagnostic tests such as cytologic examination of infected material can be helpful to identify the probable pathogen. If the bacteria are accurately identified, antibiotic selection is simplified because the susceptibility pattern of many organisms is predictable. Initial empirical treatment can begin with—but not be limited to—agents listed in Table 161-1.

TABLE 161-1

Probable Bacterial Susceptibility Based on Wild-Type Strains

ORGANISM	LOCATION	SUSCEPTIBLE TO
Streptococcus species (but not *Enterococcus*)	Respiratory infections, wound infections	Penicillin and penicillin derivatives (amoxicillin, ampicillin)
Pasteurella multocida	Wound infections, bite wounds, post-surgical wounds, respiratory tract, pyothorax	Penicillins, tetracyclines, trimethoprim-sulfonamides, cephalosporins*
Staphylococcus species, particularly *Staph. pseudintermedius*	Skin infections, wound infections, urinary tract infections, bone infections, discospondylitis	Beta-lactamase resistant beta-lactams (e.g., a cephalosporin), or a drug combined with a beta-lactamase inhibitor (e.g., Clavamox). Also generally susceptible to trimethoprim-sulfonamides and clindamycin.*
Anaerobic bacteria: *Clostridium, Peptostreptococcus, Actinomyces, Fusobacterium, or Bacteroides* (including those of the *Bacteroides fragilis* group)	Oral infections, pyothorax, penetrating wound infections. Abdominal infections (peritonitis) usually contain Gram-negative bacilli anaerobes (e.g., *Bacteroides* spp.).	Amoxicillin + beta-lactamase inhibitor (Clavamox), chloramphenicol, metronidazole, clindamycin, or a second-generation cephalosporin: cefoxitin
Enterobacteriaceae: Escherichia coli, Klebsiella pneumoniae, Enterobacter species	Urinary tract infections, pneumonia, sepsis, abdominal infections, and opportunistic pathogens in wound infections	With high drug concentrations in the urine, they may be susceptible to amoxicillin, amoxicillin-clavulanate, and trimethoprim-sulfonamides, and cephalosporins. In non-urinary tract infections, they may be susceptible to cefazolin, cefpodoxime, fluoroquinolones, aminoglycosides, penicillin-beta-lactamase inhibitors (piperacillin-tazobactam), and carbapenems.
Gram-negative non-fermenters: *Pseudomonas aeruginosa*	Chronic wound infections, otitis infections (chronic), urinary tract infections	Fluoroquinolones, ceftazidime, aminoglycosides, carbapenems, penicillin-beta-lactamase inhibitors (piperacillin-tazobactam)
Methicillin-resistant *Staphylococcus* (e.g., methicillin-resistant *Staph. pseudintermedius*)	Skin infections, pyoderma, bone and joint infections, urinary tract infections	These strains are resistant to all beta-lactam antibiotics, and often to fluoroquinolones, clindamycin, and trimethoprim-sulfonamides. Some strains are susceptible to rifampin, chloramphenicol, and tetracyclines (confirm with susceptibility test).
Enterococci *(Enterococcus faecium, Enterococcus faecalis)*	Urinary tract infections, biliary and abdominal infections. Can be identified in some infections, but are not always responsible for disease.	Wild-type strains can be susceptible to penicillins (amoxicillin, ampicillin, amoxicillin-clavulanate). If resistant to penicillins, a susceptibility test should be used to select the appropriate treatment.

*Fluoroquinolones (enrofloxacin, marbofloxacin, pradofloxacin, orbifloxacin) also may be active against these organisms, but are often not used as first-choice empirical treatment.

Treatment for wild-type strains of *Staphylococcus pseudintermedius, Pasteurella* species, and *Streptococcus* species can be accomplished with the administration of drugs that are common in our veterinary practices (see Table 161-1). Treatment for the Gram-negative enteric bacterial infections can be initiated with a fluoroquinolone (enrofloxacin, ciprofloxacin, marbofloxacin, pradofloxacin, or orbifloxacin), an extended-spectrum cephalosporin (ceftazidime, cefotaxime, cefpodoxime proxetil), or an aminoglycoside (gentamicin,

amikacin). However, if initial treatment is not effective, guidance from a susceptibility test is advised. For *Pseudomonas aeruginosa,* methicillin-resistant *Staphylococcus,* or *Enterococcus* spp., a susceptibility test is always advised because these organisms can have unpredictable susceptibility and the drugs to which they may be susceptible may not be familiar to veterinarians.

If anaerobic bacteria are suspected (for example, *Clostridium, Fusobacterium, Prevotella, Actinomyces,* or *Porphyromonas*), predictable results can be attained by administering a penicillin, chloramphenicol, metronidazole, clindamycin, amoxicillin-clavulanic acid, or one of the second-generation cephalosporins (cephamycins). Metronidazole is consistently highly active against anaerobes including *B. fragilis*. The activity of first-generation cephalosporins, trimethoprim-sulfonamides/ormetoprim-sulfonamides, or fluoroquinolones for an anaerobic infection is unpredictable. If the anaerobe is from the *Bacteroides fragilis* group, resistance may be more of a problem because they produce a beta-lactamase that may inactivate first generation cephalosporins and ampicillin/amoxicillin and some *Bacteroides* spp. may also be resistant to clindamycin.

Empirical Selection of Antibacterial Drugs

Empirical treatment of common infections in animals described above can be accomplished by selecting the antimicrobial agent with a high likelihood of success for the suspected clinical infection. Many guidelines have appeared in published proceedings, review papers, consensus documents, and textbooks. But when empirical treatment fails, or when resistance is suspected, a culture and susceptibility test is needed to guide therapy. The empirical choice for initial treatment is based on the assumption that the infection is not complicated and the infection is caused by wild-type bacteria. Wild-type strains of bacteria are those that have an absence of acquired and mutational resistance mechanisms, whereas non-wild-type strains of bacteria are those that have the presence of an acquired or mutational resistance mechanism to the drug in question. Wild-type strains may include bacteria that have inherent resistance to antimicrobials. For example, wild-type anaerobic bacteria are inherently resistant to aminoglycosides by virtue of a lack of an oxygen-dependent drug entry to the bacteria. Gram-negative bacteria of the *Enterobacteriaceae* and *Pseudomonas aeruginosa* are inherently resistant to macrolide antibiotics.

Susceptibility Testing

Culture and antimicrobial susceptibility testing (AST) will provide the best guidance for drug selection when susceptibility is not known, or if the seriousness of the infection warrants an accurate selection. These advantages notwithstanding, it is also understood that even when an agent is selected from the "susceptible" category, treatment may not always be successful. The prediction of whether the bacteria will, or will not, respond to treatment is commonly referred to as the "90/60 rule."[1] The 90/60 rule was derived from the observation that, in general, bacteria treated with antimicrobials to which the strain is sensitive will have a favorable therapeutic response in approximately 90% of the patients. On the other hand, when the bacteria isolate is resistant to the antimicrobial administered, despite the susceptibility result, approximately 60% of patients will respond to therapy. In veterinary medicine, we have no data to confirm or challenge the 90/60 rule.

The most important information for the clinician is simply which drugs have an "S" and which ones have an "R." These are the results that guide their treatment. For the test to be reliable, the laboratory should use the standards for interpretation available from the Clinical and Laboratory Standards Institute—CLSI.[2]

The most common test used by commercial laboratories is to directly measure the minimum inhibitory concentration (MIC) of an organism with an antimicrobial dilution test. Zone inhibition (also known as the Kirby-Bauer test) also is performed but provides only qualitative information. The MIC dilution test is performed by inoculating the wells of a plate with the bacterial culture and dilutions of antibiotics are arranged across the rows. The test is usually performed in modern laboratories using high-throughput plates, but individual tubes or plates can be used for dilution tests also. The MIC is not a measure of efficacy, but instead it is simply an *in vitro* measurement of drug activity and bacterial susceptibility. The lower the MIC value, the more susceptible the isolate is to that drug. The MICs are determined using serial two-fold dilutions of drug to which is added a standardized inoculum that is incubated for a prescribed time. Concentrations are always listed in mcg/mL. For example, if one were to start at a concentration of 256 mcg/mL, the MIC dilution series would be as follows: 128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.12, 0.06 mcg/mL, etc. (Log_2 dilutions). If, for example, bacterial growth occurs at a dilution of 0.12 mcg/mL for a specific drug, but not at 0.25 mcg/mL and above, the MIC is determined to be 0.25 mcg/mL. The MIC dilution test is only

semi-quantitative because there are gaps between each dilution. Realistically, the true MIC lies somewhere between these values, but the MIC is recorded as the highest value. In some laboratories, other methods to measure the MIC are being used such as the Etest (epsilometer test) from bioMérieux, Inc. The Etest is a quantitative technique which measures the MIC by direct measurement of bacterial growth along a concentration gradient of the antibiotic contained in a test strip.

This MIC frequently is expressed as MIC_{50} or MIC_{90}, which is the MIC that inhibits 50% or 90% of the bacteria, respectively. It is sometimes cited in error that the MIC_{50} and MIC_{90} are the average concentrations for 50% and 90% efficacy. These values should not be confused with clinical efficacy (see below).

Interpretation of Susceptibility Tests

Resistance and susceptibility are determined by comparing the organism's MIC to the drug's breakpoint (also known as interpretive category). After a laboratory determines an MIC, it may use the CLSI "SIR" classification for breakpoints (S, susceptible; I, intermediate, or R, resistant). In practice, if the MIC for the bacterial isolate falls in the susceptible category, there is a greater likelihood of successful treatment (cure) than if the isolate were classified as resistant. It does not ensure success; drug failure is still possible owing to other drug or patient factors (for example, immune status, immaturity, or severe illness that compromises the action of antibacterial drugs), and interactions. If the MIC is in the resistant category, clinical failure is more likely because of specific resistance mechanisms or inadequate drug concentrations in the patient. However, a patient with a competent immune system may sometimes eradicate an infection even when the isolate is resistant to the drug in the MIC test.

The intermediate category is intended as a buffer zone between susceptible and resistant strains. This category reflects the possibility of error when an isolate has an MIC that borders between susceptible and resistant. If the MIC value is in the intermediate category, therapy with this drug at the usual standard dosage is discouraged because there is a good likelihood that drug concentrations may be inadequate for a cure. However, successful therapy is possible when drug concentrates at certain sites—in urine, or as the result of topical therapy, for example—or at dosages higher than the minimum effective dosage listed on the label. Prescribing guidelines for some antimicrobials allow for an increase in dosage when susceptibility testing identifies an organism in the intermediate range of susceptibility. For example, fluoroquinolone antimicrobials have been approved with a dosage range that allows increases in dosages when susceptibility testing identifies an organism in the intermediate range ("I") of susceptibility. In these cases, higher drug concentrations make a cure possible if the clinician is able to safely increase the dosage above the minimum labeled dosage. For the example of enrofloxacin in dogs, this would be equivalent to a dosage of 10 to 20 mg/kg/day, rather than the minimum dosage of 5 mg/kg/day.

MIC data should not be used in isolation, but by coupling the MIC from a laboratory report with CLSI breakpoints and other important information such as the virulence of the bacteria and the pharmacology of the antibiotics being considered, the clinician can make a more informed selection of an antibacterial drug.

Tissue Penetration of Antibiotics

The susceptibility interpretation and pharmacokinetic-pharmacodynamic (PK-PD) criteria are based on plasma/serum concentrations. No tissue-specific interpretation can be provided that accounts for differences in drug distribution among tissues. For example, even though it is anticipated that many antibiotics concentrate in the urine, which may be beneficial for treating a urinary tract infection, the susceptibility interpretation is based on achieving adequate concentrations in the blood. There are two exceptions to this because amoxicillin and amoxicillin-clavulanate interpretations allow for high concentrations in urine.

Urinary Tract Infections

For uncomplicated urinary tract infections, high urine antibacterial drug concentrations may be sufficient to achieve a cure.[3] However, this assumption does not hold up when treating a complicated infection, an infection in a patient with dilute urine (e.g., chronic kidney disease) or when other structures are involved such as the layers of the bladder mucosa, kidney, or prostate. In these cases, high urine concentrations alone are not sufficient. In these instances, it is the tissue concentration—which is correlated to the plasma concentration—that will be predictive of a bacteriologic cure.[4]

Drug Penetration to Other Tissues

A frequent mistake in MIC interpretation is to compare the MIC with published tissue concentrations that are derived from whole-tissue homogenized samples. Tissue concentration data are often published by pharmaceutical companies in their product information. These concentrations may be misleading because they may either underestimate or overestimate (depending on the drug's affinity for intracellular sites) the true drug concentration at the site of infection. For most tissues, antibiotic drug concentrations in the serum or plasma approximate the drug concentration in the extracellular space (interstitial fluid). This is because there is no barrier that impedes drug diffusion from the vascular compartment to extracellular tissue fluid.[5] There is really no such thing as "good penetration" and "poor penetration" when referring to most drugs in most tissues. Pores (fenestrations) or micro-channels in the endothelium of capillaries are large enough to allow drug molecules to pass through unless the drug is restricted by protein binding in the blood. Tissues lacking pores or channels may inhibit penetration of some drugs (see below).

If adequate drug concentrations can be achieved in plasma, it is unlikely that a barrier in the tissue will prevent drug diffusion to the site of infection as long as the tissue has an adequate blood supply. Clinicians should be concerned when treating tissues that have poor or impaired blood supply. Drug diffusion into an abscess or granulation tissue is sometimes a problem because in these conditions, drug penetration relies on simple diffusion and the site of infection lacks adequate blood supply. In an abscess, there may not be a physical barrier to diffusion—that is, there is no impenetrable membrane—but low drug concentrations are attained in the abscess, or drug concentrations are slow to accumulate.

Tissue Barriers

In some tissues a lipid membrane (such as tight junctions on capillaries) presents a barrier to drug diffusion. In these instances, a drug must be sufficiently lipid-soluble, or be actively carried across the membrane, in order to reach effective concentrations in tissues. These tissues include: the central nervous system, eye, and prostate. A functional membrane pump (p-glycoprotein) also contributes to the barrier. There also is a barrier between plasma and bronchial epithelium (blood:bronchus barrier). This limits the penetration of some drugs into the bronchial secretions and epithelial lining fluid (ELF) of the airways. However, in the event of treating pneumonia, this barrier is largely broken down and drug concentrations in extracellular fluids can diffuse to pneumonic areas of the lung.[6] If the blood-bronchus barrier is intact, it is difficult to predict the extent of penetration for veterinary antimicrobials. Macrolide antibiotics (e.g., azithromycin) concentrate in these fluids; but their spectrum of activity is limited. The extent of penetration for other classes of antibacterial drugs used in veterinary patients has not been adequately studied. Most of the agents are likely to produce concentrations in these fluids that are lower than the plasma/serum concentration.

Local Factors That Affect Antibiotic Effectiveness

Local tissue factors may decrease antimicrobial effectiveness. For example, pus and necrotic debris may bind and inactivate vancomycin or aminoglycoside antibiotics (gentamicin or amikacin), decreasing their effectiveness. Cellular material also can decrease the activity of topical agents such as polymyxin B. Foreign material in a wound (such as surgical implants or plant material) can protect bacteria from antibiotics and phagocytosis by forming a biofilm (glycocalyx) at the site of infection. Cellular debris and infected tissue can inhibit the action of trimethoprim-sulfonamide combinations through the secretion of thymidine and para-aminobenzoic acid, both known to be inhibitors of the action of these drugs. This may explain why trimethoprim-sulfonamide combinations have not been effective in some infected tissues, particularly anaerobic infections. Cations can adversely affect the activity of antimicrobials at the site of infection. Two important drug groups diminished in activity by cations such as Mg^{2+}, Al^{3+}, Fe^{3+}, and Ca^{2+} are fluoroquinolones and aminoglycosides. (Cations such as magnesium, iron, and aluminum also can inhibit oral absorption of fluoroquinolones.)

An acidic environment of infected tissue may decrease the effectiveness of clindamycin, erythromycin, fluoroquinolones, and aminoglycosides. Penicillins and tetracycline activity are not affected as much by tissue pH, but hemoglobin at the site of infection will decrease the activity of these drugs. An anaerobic environment decreases the effectiveness of aminoglycosides because oxygen is necessary for drug penetration into bacteria.

As mentioned previously, an adequate blood flow is necessary to deliver an antibiotic to the site of infection. Effective antibacterial drug concentrations may not be attained in tissues that are poorly

vascularized (e.g., extremities during shock, sequestered bone fragments, and cardiac valves).

Pharmacokinetic-Pharmacodynamic (PK-PD) Principles (also see ch. 160)

The use of exposure relationships and PK-PD principles for evaluation of antimicrobial compounds has become common in the veterinary literature. Practically all pharmacokinetic papers on antimicrobials published in the last few years in veterinary journals discuss the features of the pharmacokinetics in light of the pharmacodynamics of the drug and how this relates to rational dosage regimens.

PK-PD Terminology

Frequently-used parameters include the time above MIC, peak plasma concentration to MIC ratio, and area-under-the-curve to MIC ratio. There have been important attempts to standardize the terminology for PK-PD indices in antibiotic therapy.[7,8] Shown in Figure 161-1 are some terms used to describe the shape of the plasma concentration versus time profile. The C_{MAX} is simply the maximum plasma concentration (peak) attained during a dosing interval. The C_{MAX} is related to the MIC by the C_{MAX}:MIC ratio. The AUC is the total area-under-the-curve. The AUC for a 24-hour period is related to the MIC value by the AUC: MIC ratio. Also shown in Figure 161-1 is the relationship of time to MIC measured in hours (T > MIC). The value reported is the percent time during a 24-hour interval that the concentration is above the MIC.

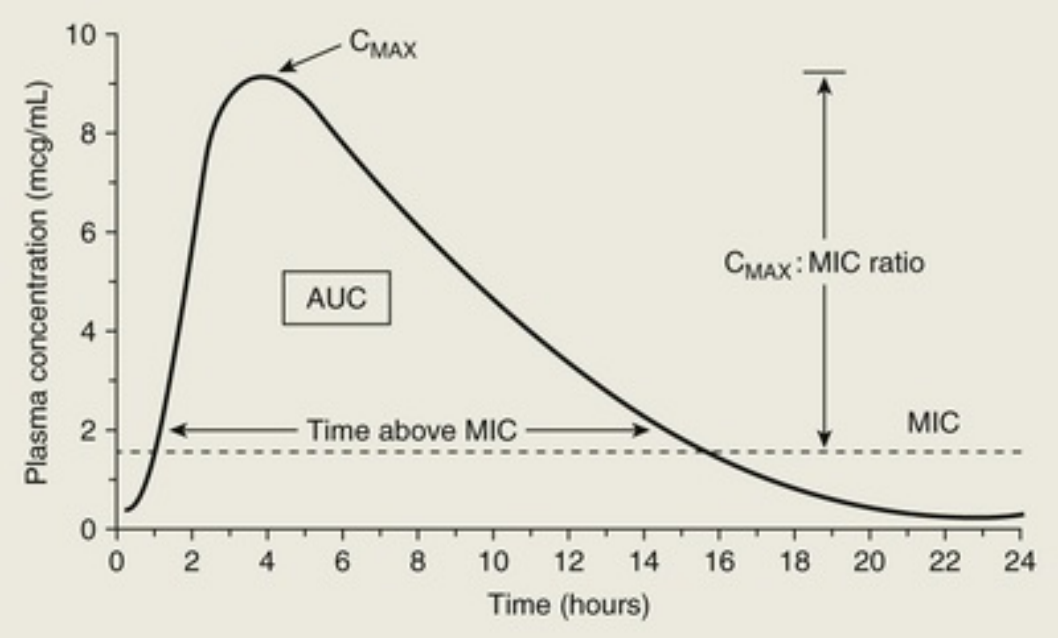

FIGURE 161-1 Plasma concentration vs. time profile illustrating the principal pharmacokinetic-pharmacodynamic relationships for antimicrobial therapy.

As discussed above in the Tissue Penetration section, these parameters refer to the plasma/serum drug concentration. It is preferred to use the protein unbound fraction *(fu)* to differentiate total drug concentrations from the unbound, pharmacologically active concentrations. The unbound drug concentration in plasma theoretically is in equilibrium with the unbound concentration in tissue fluid. Tests performed *in vitro* (susceptibility tests) do not use protein in the media. If the PK-PD indices do not use the unbound fraction, they can overestimate the drug's activity.

Optimizing Dosage Regimens with PK-PD Principles

Pharmacokinetic-pharmacodynamic relationships of antibiotics attempt to explain how these factors can correlate with clinical outcome. Although these concepts were originally derived from laboratory animals, the

principles apply to other species as well and can predict clinical outcomes in veterinary patients.[9]

Aminoglycosides

Aminoglycosides (e.g., gentamicin, or amikacin) are concentration-dependent bactericidal drugs; therefore, the higher the drug concentration, the greater the bactericidal effect. An optimal bactericidal effect occurs if a high enough dosage is administered to produce a peak of 8-10× the MIC. This can be accomplished by administering a single dose once daily. Regimens using this strategy are at least as effective, and perhaps less nephrotoxic, than lower dosages administered more frequently.[10,11] Our current regimens in veterinary medicine employ this strategy.[12] The single daily dose is usually calculated from the drug's volume of distribution (VD). Protein binding here is irrelevant because these drugs are essentially unbound.

Fluoroquinolones

Fluoroquinolones are concentration-dependent antimicrobials. Either the C_{MAX}:MIC ratio or the AUC:MIC has been used to predict antibacterial success, but in recent years the AUC/MIC ratio has become the preferred index. Most experts agree that an AUC:MIC ratio greater than 100-125 has been associated with a cure. There is evidence that for some clinical situations, AUC:MIC ratios as low as 30-55 are adequate for a cure, because studies in which a ratio above 125 was cited involved critically ill human patients or immunocompromised laboratory animals.

To attain the same PK-PD target with fluoroquinolones, treatment of some bacteria may require higher doses. For example, a low dosage is adequate for susceptible organisms with low MIC, such as *E. coli* or *Pasteurella* spp. On the other hand, *Staphylococcus* species typically have a higher MIC and may require slightly higher dosages. To achieve the necessary concentration for bacteria such as *Pseudomonas aeruginosa*, which usually has the highest MIC among susceptible bacteria, the highest dosage in a range is recommended. Bacteria such as enterococci and anaerobes are more resistant. Even at high dosages, a sufficient peak concentration or AUC:MIC ratio will be difficult to achieve for these organisms using currently available veterinary drugs (pradofloxacin is an exception because it has activity against anaerobic bacteria).

Beta-Lactam Antibiotics

Beta-lactam antibiotics such as penicillins, potentiated-aminopenicillins (e.g., amoxicillin plus clavulanate, piperacillin-tazobactam), and cephalosporins are bactericidal but their action may be slower than other bactericidal drugs, and generally a post-antibiotic effect (PAE) is not observed. Therefore, the concentration should be kept above the MIC as long as possible during the dosing interval (T > MIC) for the optimal bactericidal effect.[13] Dosage regimens for the beta-lactam antibiotics should consider these pharmacodynamic relationships. Therefore, for treating a Gram-negative infection, especially a serious one, some regimens for penicillins and cephalosporins require administration 3 to 4 times per day. Some long-acting formulations of penicillin have been developed to prolong plasma concentrations (for example, procaine- and benzathine-penicillin) but these formulations rarely produce plasma concentrations above the MIC for Gram-negative bacilli. Some of the third-generation cephalosporins have long half-lives and less frequent regimens have been used for these drugs (for example, cefpodoxime proxetil, and cefovecin). (The long half-life for ceftriaxone in people does not occur in animals because of differences in drug protein binding.)

Gram-positive organisms are more susceptible to the beta-lactams than are Gram-negative bacteria. Additionally, since the MICs are lower for Gram-positive bacteria, and antibacterial effects occur at concentrations below the MIC (post-antibiotic effect or PAE), longer dose intervals may be possible for infections caused by Gram-positive as compared to Gram-negative bacteria. For example, cephalexin and amoxicillin-clavulanate have been used successfully to treat staphylococcal infections when administered only once daily (although twice-daily administration is recommended to obtain maximum response).

The optimal duration of plasma concentrations above the MIC has varied among studies, but a general assumption is that the drug concentration should be above the MIC for at least 40-50% of the dosing interval.[13] This may vary depending on the immune competence of the animal and specific drug class. The carbapenem class of drugs (for example, imipenem and meropenem) is used with increasing popularity in small animal practice. These drugs are more bactericidal than penicillins and cephalosporins and the T > MIC for successful therapy may be less for these drugs than other beta-lactams (for example, 30% of the dose interval).

Other Time-Dependent Drugs

Many of the other drugs we include in the time-dependent group have post-antibiotic effects and are evaluated using an AUC/MIC ratio, rather than T > MIC. These include the macrolides, tetracycline, clindamycin, and chloramphenicol. These drugs are usually considered bacteriostatic in activity, but the lines between bactericidal and bacteriostatic drugs have become a bit blurred because it can vary with dose and among pathogens. Drugs such as tetracyclines, macrolides (erythromycin and derivatives), sulfonamides, lincosamides (lincomycin and clindamycin), and chloramphenicol derivatives have traditionally been considered bacteriostatic, but under some conditions of dosing can have bactericidal activity.

Most of the drugs grouped under this heading must be administered frequently to achieve this goal, unless they have long half-lives. For some of the drugs in this group, administration two or three times daily may be necessary.

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CHAPTER 162

Antifungal and Antiviral Therapy

Mark G. Papich

Overview

Antifungal and antiviral drugs are used to treat both primary and secondary infections in dogs and cats. Safe and effective antifungal drugs can be vital in treating serious systemic fungal disease as well as skin infections caused by dermatophytes or yeasts. Some dogs and cats have greater risk of developing fungal infection if immunosuppressed, receiving anti-cancer drugs, undergoing radiation therapy, or being given corticosteroids chronically. Since there are few antifungal or antiviral drugs approved for use in dogs and cats, veterinarians have used human-label and experimental drugs to manage such infections, relying on published evidence of efficacy, safety and dosing.

In contrast to antibacterial drugs (see ch. 161), the relationship between plasma drug concentrations and clinical effectiveness has not been established for antifungal and antiviral drugs. Some guidance on the pharmacokinetic-pharmacodynamic (PK-PD) criteria for antifungal drugs is available from treated humans.[1,2] Susceptibility testing is rarely performed on isolated pathogens for antifungal or antiviral agents. Standards, rarely used in veterinary medicine, are available for testing and reporting antifungal and a small number of antiviral drug susceptibilities from the Clinical and Laboratory Standards Institute (CLSI).[3-5]

Antifungal Drugs

Dermatophyte Infections (Box 162-1)

Isolated dermatophyte lesions caused by *Microsporum* spp. or by *Trichophyton* spp. in dogs and cats are usually treated with topical ointments, creams or solutions that can be applied to the skin without concern for systemic effects unless the pet is consuming quantities by licking. Systemic therapies include griseofulvin (Fulvicin), azole antifungal agents, and terbinafine. Included with dermatophyte infections are yeast infections caused by *Malassezia pachydermatis* that most often affect the external ear, but also can occur on the skin. *Malassezia* dermatitis can be treated with topical products, but systemic drugs (e.g., azoles) also have been used.

Box 162-1

Drugs for Treating Dermatophyte Infections in Dogs and Cats

Topical (Creams, Ointments, Solutions)

- Enilconazole (Clinafarm)
- Miconazole (Conofite)
- Clotrimazole (Lotrim)
- Terbinafine (Lamisil)

Systemic Drugs (Oral Products)

- Griseofulvin (Fulvicin)
- Ketoconazole (Nizoral)
- Itraconazole (Sporanox)
- Fluconazole (Diflucan)
- Terbinafine (Lamisil)

Systemic Infections (Table 162-1 and Box 162-1)

The most serious diseases treated with antifungal agents are the systemic mycoses, including the filamentous fungi such as *Aspergillus* spp. (see ch. 234 and 235), *Fusarium* spp., and *Penicillium* spp. and opportunistic fungi such as *Histoplasma capsulatum* (see ch. 233), *Blastomyces dermatitidis* (see ch. 233), *Coccidioides immitis* (see ch. 232), *Cryptococcus neoformans* (see ch. 231), and *Candida* spp. (see ch. 236).

TABLE 162-1

Selected Antifungal Drugs Used in Companion Animals

DRUG	BRAND NAME	FORMULATIONS	DOSING PROTOCOL	COMMENTS
Griseofulvin	Fulvicin	125 and 250 mg capsules, 125, 250, and 500 mg tablets, and oral syrup 125 mg/mL	Dosage has ranged from 22 mg/kg to 110 mg/kg per day. Most common dosage is approximately 50 mg/kg per day.	Administer with food. Do not administer to pregnant cats. Rarely used compared to the azoles and topical products. Consult older references for more information on griseofulvin.
Ketoconazole	Nizoral and generic	200 mg tablets	Dermatophytosis in cats: 10 mg/kg/day. Candidiasis: 10 mg/kg/day for 6 to 8 weeks. Blastomycosis, histoplasmosis, cryptococcosis and coccidioidomycosis: 10 to 20 mg/kg q 12 h. *Malassezia* dermatitis in dogs: dosages of 5-10 mg/kg/day have been recommended. CNS infections (*Cryptococcus* in cats) 10 to 15 mg/kg per day.	Availability has diminished in recent years. Administer with food. Monitor liver enzymes in treated patients. Adverse effects such as suppression of endocrine synthesis, anorexia, vomiting, and hepatic injury are more common than with other systemic azoles. Ketoconazole will inhibit a large range of drug-metabolizing enzymes and p-glycoprotein.
Itraconazole	Sporanox, and generic	100 mg capsules and 10 mg/mL cherry flavored solution	In cats, dosages for dermatophytes have ranged from 10 mg/kg q 24 h to 3 mg/kg q 24 h. For *Cryptococcus* in cats, 8.5 mg/kg per day has been used. Pulse dosing for dermatophytes in cats has used a dosage of 10 mg/kg q 24 h, for 28 days, followed by pulse dosing of one week on, one week off. In dogs, 5 mg/kg per day is usually sufficient. Pulse dosing has been used in which it was administered 5 mg/kg per day for 2 days per week × 3 weeks.	Itraconazole oral capsules should be administered with food; however, itraconazole oral solution can be administered with or without food. Although drug interactions are less likely than with ketoconazole, hepatic enzyme inhibition is possible. Adverse effects are less common than for ketoconazole, but are still possible.
Fluconazole	Diflucan, and generic	50, 100, 150, 200 mg tablets. 10 and 40 mg/mL oral suspension, and injectable solution.	Cryptococcosis in cats: 100 mg/cat/day in one or two divided doses, or 2.5-5 mg/kg once a day. In dogs, the dosage is 10-12 mg/kg/day PO.	Fluconazole is more water-soluble and better absorbed orally than other azole antifungal drugs. The limitation for fluconazole is that it is less active against many fungi compared to other azole antifungal agents.
Voriconazole	Vfend	50 mg or 200 mg tablet, oral suspension	Cats: loading dose of 5 mg/kg PO, followed by 2.5 mg/kg q 48 h. Dogs: 6 mg/kg, per day, PO.	Dosage in cats has not been confirmed through safety or efficacy studies. Administration to cats may cause

		(40 mg/mL) and an intravenous formulation		miosis, neurotoxicosis, and salivation. Safety and efficacy have not been studied in dogs. Hepatic injury is possible and liver enzymes should be monitored during treatment. Like other azoles, it should not be used in pregnancy.
Posaconazole	Noxafil	Oral suspension (40 mg/mL), delayed-release tablet (100 mg), and injectable solution	Cats: 15 mg/kg loading dose, followed by 7.5 mg/kg PO q 24 h. Dogs: 5 mg/kg q 48 h of delayed release tablet, or 10 mg/kg per day of oral suspension.	Dosage in dogs and cats is based on preliminary studies and has not been tested for safety or efficacy.
Terbinafine	Lamisil	1% topical cream (available over the counter) and 125 and 250 mg tablets	Dogs: 30-35 mg/kg PO q 24 h. Cats: 30 mg/kg per day, or ¼ tablet for small cats (62.5 mg), ½ tablet for medium size cats (125 mg) and one tablet for large cats (250 mg), all administered once daily.	Terbinafine has been used in some clinical studies in dogs and cats with mixed results. The dosage is much higher than in people. Some studies have reported efficacy for dermatophyte treatment; other studies have reported limited efficacy.
Amphotericin B	Fungizone	50 mg injectable vial	Pretreatment with 0.9% sodium chloride followed by infusion of 0.5 mg/kg in 5% dextrose over 4-6 hours IV q 48 h; a test dose of 0.25 mg/kg is sometimes recommended	Kidney injury is a serious limitation to therapy. Vomiting, nausea, fever, and phlebitis also can occur with IV infusions.
Liposomal Amphotericin B	Abelcet	Unspecified	2-3 mg/kg IV 3 times per week diluted in 5% dextrose to a concentration of 1 mg/mL for a total of 9-12 treatments (cumulative dosage of 24-27 mg/kg)	The liposomal formulation of Abelcet has been the most frequently used in veterinary medicine. Its use is limited by the high expense.

Amphotericin B

Background

Amphotericin B (Fungizone) is a polyene macrolide antibiotic with antifungal activity effective in treating serious systemic fungal infections. Its use, however, is associated with a high incidence of adverse effects, requiring careful administration and patient monitoring. Amphotericin B is active against *Blastomyces dermatitidis, Histoplasma, Cryptococcus, Coccidioides, Candida, Aspergillus,* as well as *Leishmania* (see ch. 221).

Clinical Use and Administration

Amphotericin B is poorly absorbed from the gastrointestinal (GI) tract; therefore, it is usually administered via IV infusion. Acute kidney injury (AKI; see ch. 322) is the most severe adverse effect and the most common cause for discontinuing therapy before the goal in total dosage has been administered. Early reversible AKI is seen with each daily dose, but permanent damage is related to the total cumulative dosage. Risk of AKI can be reduced by pre-treating each patient with IV saline and administering the drug slowly (over 4-6 hours). Renal function must be closely monitored at least once daily during treatment (SDMA? see ch. 322 and 324), realizing that the amphotericin B may need to be discontinued if persistent azotemia is identified. Other amphotericin B side-effects include vomiting, tremors, pyrexia, and anorexia. These adverse effects may be associated with each daily treatment and can usually be somewhat alleviated with anti-histamines, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or antiemetics.

Liposomal Formulations *(Box 162-2)*

These lipid and cholesteryl formulations of amphotericin B are commonly used in people, but experience is limited in veterinary medicine due to cost. The advantage over traditional formulations is that these forms can be given at higher doses with greater efficacy and less toxicity.[6] Dosages achieved with lipid complex formulations of amphotericin B have been >3 mg/kg body weight (BW) as compared to 0.25 to 0.5 mg/kg of the conventional formulation. Decreased toxicity is attributed to a selective transfer of the lipid complex amphotericin B, releasing the drug directly to the fungal cell membrane, sparing mammalian tissues. Reduced drug concentrations in the kidneys and diminished release of inflammatory cytokines from amphotericin lipid complexes, as compared with conventional formulations, also may help reduce the frequency of adverse reactions.

Box 162-2

Amphotericin B Formulations

- Amphotericin B deoxycholate (conventional formulation)
- Amphotericin B lipid complex (ABLC, Abelcet), a suspension of amphotericin B complexed with two phospholipids. The most extensively evaluated in dogs, shown in one study to be safe and effective in dogs at a cumulative dosage of 8-12 mg/kg.
- Amphotericin B cholesteryl sulfate complex (Amphotec). This is a colloidal dispersion, also called ABCD (amphotericin B colloidal dispersion).
- Liposomal complex of amphotericin B encapsulated in a lipid bilayer (L-AmB, AmBisome)

Azole Antifungal Drugs (see Box 162-1)

Overview

The azole antifungal drugs are the most efficacious oral systemic drugs used in people and animals. Common features shared by the azoles are their high lipophilicity and poor solubility. Their poor solubility limits GI absorption unless the medication is administered with food to stimulate stomach acids to aid in lipid dissolution. Antacids, histamine H-2 blocking drugs (e.g., famotidine), and proton pump inhibitors (e.g., omeprazole) can decrease GI absorption. Azole drugs are not good candidates for compounding because manipulation affects solubility (Figure 162-1).

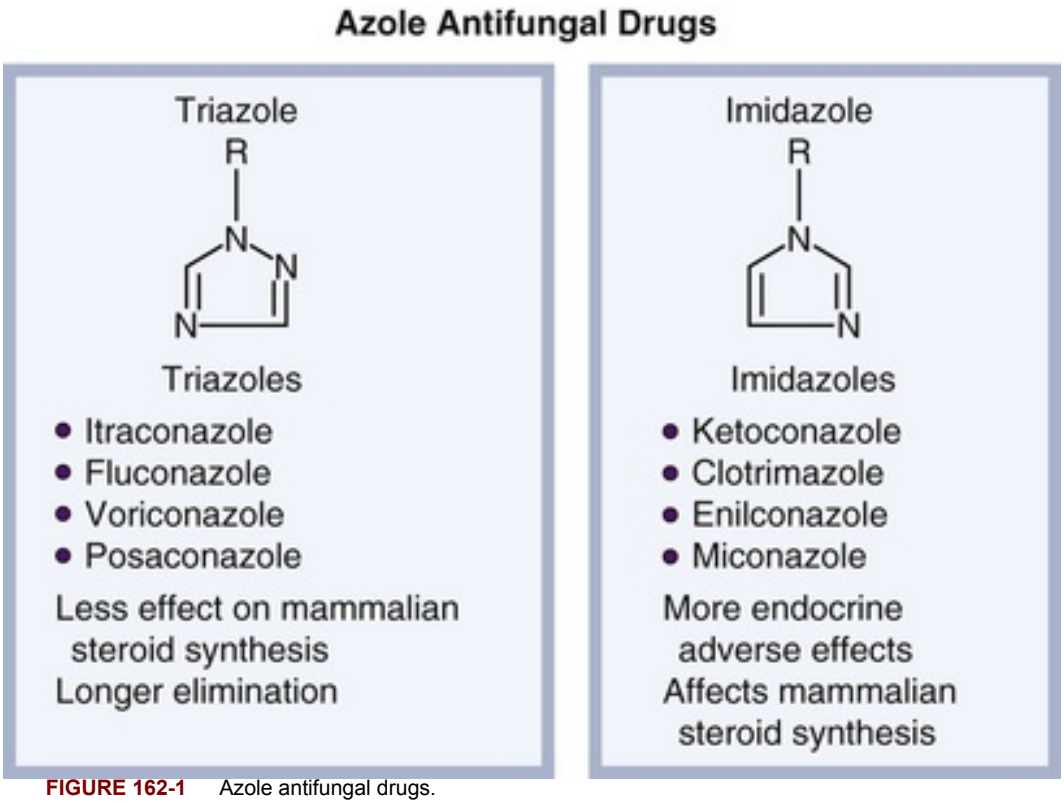

FIGURE 162-1 Azole antifungal drugs.

Ketoconazole

Ketoconazole is one of the first azoles administered systemically for fungal infections in animals. Ketoconazole has a wide spectrum of activity that includes yeast (e.g., *Malassezia pachydermatis*), systemic fungi, and dermatophytes. Although ketoconazole is seldom used in people because of adverse effects and drug interactions, it remains an important and cost-effective antifungal agent for use in animals. Common adverse effects in animals (nausea, anorexia, vomiting) are usually dose-related and may be diminished by decreasing the dosage, dividing the total dose into smaller doses, and/or administering each dose with food. Ketoconazole inhibits synthesis of steroid hormones via inhibition of cytochrome P-450 enzymes, most notably cortisol and testosterone. Although this may be a side-effect of therapy, it has been employed for the temporary management of hyperadrenocorticism in dogs and as an anti-androgen.[7,8] Hepatic enzyme activities may increase with therapy (especially alkaline phosphatase and alanine aminotransferase) and hepatotoxicosis has been reported. The hepatotoxicosis is most likely an idiosyncratic reaction (unpredictable) but it may be more common at higher dosages (see ch. 169). They should not be used in pets with evidence of hepatic disease nor in pregnant animals because fetal death may occur.

Ketoconazole is one of the most potent inhibitors of hepatic and intestinal microsomal enzymes (cytochrome P450 enzymes), potentially altering metabolism and/or elimination of other drugs being given. It also is an inhibitor of the MDR membrane pump, also known as p-glycoprotein (p-gp), involved in drug penetration across intestinal, blood-brain barrier, and other tissues. For example, if ketoconazole is administered with cyclosporine, cyclosporine concentrations are increased 2- to 3-fold in dogs.

Itraconazole *(see Figure 162-1)*

Itraconazole is an azole of the triazole group. Triazoles and imidazoles have antifungal mechanisms of action that are similar. Itraconazole is one of the most widely employed triazoles in animals, used for systemic or cutaneous fungal infections. It is more potent than ketoconazole (5 to 100 times more active), has fewer side effects, and does not cause adverse endocrine effects because triazoles lack affinity for some cytochrome P-450 enzymes in animals. The commercial formulation (Sporanox) is available in capsules and as an oral liquid. The oral solution is better absorbed in cats than the capsule by approximately 3-fold, but, it can be difficult to administer to cats because of its taste. The granules in the capsules or the solution may be added to food for convenience, but granules should not be crushed. Itraconazole is insoluble and is not absorbed well unless

administered as the commercial formulation. Bioequivalence studies in dogs have shown that compounded formulations are not sufficiently absorbed in cats or dogs.[9]

The long half-life of itraconazole in cats (18-24 hours) allows once per day or every-other-day dosing. While some studies report no adverse effects, idiosyncratic liver injury has been reported despite every-other-day administration. In dogs, itraconazole has been used in treating blastomycosis, other systemic fungal infections, dermatophytoses, and *Malassezia pachydermatis* dermatitis. Protocols have been described using pulse or intermittent dosing, involving administration 2 or 3 days per week.

Itraconazole is better tolerated in dogs and cats than is ketoconazole, but it may still produce adverse reactions. Since some reactions (anorexia, vomiting) are dose-related, one is advised to lower the dosage if observed. Hepatopathy is reported in as many as 10% of treated dogs.[10] Liver enzyme activities may increase in 10-15% of treated dogs and hepatic toxicosis in cats may be an idiosyncratic reaction. Itraconazole causes only mild inhibition of cytochrome P-450 enzymes but if given concurrently, concentrations of cyclosporine, digoxin, and/or cisapride increase. Itraconazole also inhibits p-gp, which may cause concentrations of other drugs to increase.

Fluconazole

Because of its availability as an inexpensive generic drug, veterinary use of fluconazole is common. While better tolerated than the other azoles, fluconazole is not as active against dermatophytes, *Blastomyces,* or *Histoplasma*. Fluconazole has good activity against *Coccidioides* spp. and *Cryptococcus neoformans.* Cats with cryptococcosis have been successfully treated with fluconazole. It has been used to treat dermatophytes, yeast infections, as well as some systemic fungal infections in dogs. Fluconazole is more water-soluble than the other azoles, with unique pharmacokinetic characteristics. It is absorbed well regardless of other potential interfering factors.

Voriconazole

Voriconazole (Vfend) is a triazole similar to itraconazole and fluconazole. It has become a valuable drug for humans, especially those with disseminated aspergillosis. Its use in animals has been limited but dosages for mammals and birds are being developed. The advantage of voriconazole is its excellent activity against yeasts, dermatophytes, and some filamentous fungi. Voriconazole is similar in structure to fluconazole, but has much better activity against several species of molds, including *Aspergillus* spp. and *Fusarium* spp (see ch. 234 and 235).

Experimental use of voriconazole in dogs has shown rapid and complete absorption of the drug after oral administration, a short terminal half-life, and induced metabolism (lowering blood concentrations after repeated dosing). These factors may limit its long-term use in dogs. There is concern regarding neurotoxicosis in cats. Since the drug has a long half-life in cats (over 40 hours as compared with about 3 hours in dogs) it may accumulate to toxic concentrations if administered daily. Dosages listed in Table 162-1 are based on preliminary pharmacokinetic studies, while safety and efficacy studies have not yet been reported.

Posaconazole

Posaconazole (Noxafil) is similar to itraconazole, with a slightly different spectrum of activity. It is used in people primarily for *Aspergillus* and *Candida* infections. It is also active against dermatophytes, *Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis,* and *Cryptococcus neoformans*. In contrast to other azoles, posaconazole also has activity against Mucorales (formerly called Zygomycetes: *Mucor* and *Rhizopus*; see ch. 236). Use of posaconazole in animals has been limited to a few case reports in cats and pharmacokinetic studies in dogs and cats. It was well-tolerated in short-term studies in dogs and cats.

Antiviral Drugs (Box 162-3)

Overview

Systemic antiviral drugs have rarely been used in veterinary medicine. Antiviral topical ointments are most commonly used in pets for viral ophthalmic conditions, particularly feline herpes infection. Systemic treatment of viral diseases in dogs and cats has not been thoroughly evaluated, pharmacokinetic information is incomplete, and dosing protocols are mostly anecdotal. Treatment of viral diseases in dogs and cats primarily relies on supportive care together with prevention and treatment of secondary bacterial infections. *Antiviral chemotherapy does not eliminate the virus in infected dogs and cats.*

Box 162-3

Antiviral Drugs

- Zidovudine (AZT): Has produced some benefit in cats with feline immunodeficiency virus infection, but is less effective for cats with feline leukemia virus infection. High dosages have caused adverse effects in cats.
- Stavudine (d4T)
- Didanosine (ddI)
- Zalcitabine (ddC)
- Lamivudine (3TC)
- Suramin
- Foscarnet
- Ribavirin
- Plerixafor
- Famcyclovir: Has produced improvement when administered to cats with feline herpesvirus-1 (FHV-1).

For some diseases, such as feline leukemia virus infections (FeLV), immunomodulators (e.g., acemannan, interferon omega, bacterins) and other products purported to act as "immune stimulants" have little documented evidence of efficacy (see ch. 223). Unfortunately, the terms "immunomodulation" and "immune stimulation" are poorly defined. There is some evidence that interferon-omega may improve survival in cats infected with FeLV, but other evidence is lacking. Use of drugs to stimulate the immune system may seem counterproductive for some diseases (e.g., feline infectious peritonitis [FIP]) because the clinical signs are a result of an immune-mediated process.

For some diseases, the use of antiviral drugs developed for people has resulted in failure or toxicosis. For example, treatment of FIP has been disappointing. Ribavirin should theoretically be effective because of *in vitro* activity, but it failed in clinical trials and resulted in toxicosis. Larger controlled studies using feline interferon have not shown significant benefit. No antiviral or immunomodulatory drug has been shown to substantially affect the outcome of FIP (see ch. 224).

Feline Immunodeficiency Virus and Feline Leukemia Virus

Management of retrovirus-infected cats (feline immunodeficiency virus [FIV] or FeLV) with antiviral drugs has been disappointing (see ch. 222 and 223). No available drug eliminates either virus from infected cats and few controlled studies have been conducted on drug effectiveness. Several drugs have been investigated but few are promising. Among the drugs listed in Box 162-3, some have *in vitro* activity but in each case the agent may not have been investigated sufficiently *in vivo,* or it failed in clinical trials, or the adverse side-effects make use contraindicated.[12]

Zidovudine (AZT) has activity *in vitro* against both FeLV and FIV by inhibiting replication of the virus. This drug is a nucleoside analog that blocks reverse transcriptase of retroviruses. In clinical studies in FIV-infected cats, using dosages of 5-10 mg/kg q 12 h, SC or PO, zidovudine had clinical benefit, improved quality of life, and decreased virus load. But cats with FeLV had no significant improvement after therapy with zidovudine, while high dosages suppressed the bone marrow.

Feline Herpesvirus-1

Systemic treatment with antiviral drugs has been justified in treating feline herpesvirus-1 infections (FHV-1). Agents evaluated for efficacy have been used in people to treat herpes simplex type-1 virus infection. Some drugs have been investigated, such as acyclovir, valaciclovir and ribavirin, but these have either been ineffective, toxic to cats, or both. Penciclovir has been shown to have good *in vitro* activity against FHV-1, but is not well absorbed.[13] However, the pro-drug of penciclovir, famciclovir, is converted to the active compound via de-acetylation in the intestine and liver. Administration of the pro-drug substantially improves bioavailability and, once absorbed, penciclovir is converted in a step-wise process to the triphosphate inhibiting viral DNA polymerase to inhibit viral replication.

Early studies with oral administration of famciclovir at 62.5 mg per cat failed to produce adequate blood

concentrations of penciclovir to be consistently effective.[14] Higher dosages of 125 mg or more, q 8-12 h, are now recommended based on clinical observations.[15] Despite some promising results from the use of famciclovir for skin and ocular lesions, cats with upper respiratory disease caused by FHV-1 or feline calicivirus (FCV) are usually not treated with these agents (see ch. 229). These cats are managed with supportive care and administration of antibiotics for secondary bacterial infections (see ch. 161).

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CHAPTER 163

Antiparasitic Therapy

Byron L. Blagburn, Jane D. Mount

Client Information Sheet: Antiparasitic Therapy

The goals of parasiticide therapy are to reduce or eliminate signs of disease and to remove the causative parasite(s). Antiparasitic agents must be safe, effective, and convenient to use.[1] Additional considerations are spectrum of activity (types of parasites that are eliminated), formulation, sex and age of the target animal, other concurrent health problems, pregnancy and nursing, product approval or off-label use, ease of acquiring the parasiticide, and other current parasite control strategies such as heartworm prevention and flea and tick control. Given the spectrum of parasites in companion animals, and complexity of the parasiticide market, selection of antiparasitic products can be difficult.[2,3]

Accuracy of Diagnosis

Selection of the appropriate parasiticide is dependent on an accurate diagnosis.[4,5] Intestinal parasites and those that are found in the lungs, hepatobiliary system and other organs that open to or communicate with the gastrointestinal tract are usually passage stages that are recovered from feces. These parasites are usually confirmed by properly conducted fecal examination (see ch. 81).[4] Current prevention strategies (heartworms, intestinal parasites) rely less on an initial diagnosis than on the historical risk of parasitic infection. Available products are intended to provide protection against major internal parasites while improving compliance.[1]

Target Animal and Formulation

The spectrum of activity, dosage, and route of administration of antiparasitic drugs are usually developed and approved with specific hosts in mind. To assume that products that are approved for one host species can be used safely and effectively in other hosts is an assumption that could result in either lack of effectiveness or toxicosis. Topical products are often developed and marketed for both dogs and cats, but they are particularly useful in cats because of the difficulty (and safety) of administering oral or injectable products to cats. Also, products are designed to release the active ingredient at a rate that will provide efficacy and safety over the approved period. Using the same product in an alternative species could result in a shorter or longer duration of activity. Formulations of some parasiticides may be the same for more than one host species, but weight ranges in the different animals are often different. For example, some product package sizes may be duplicated for both dogs and cats. It is necessary to remind the client that this is true for only certain product sizes. Even then, the weight ranges covered by the same product package will likely be different for the dog and cat.

Spectrum of Activity

Foremost in our considerations of which parasiticide to select is whether it is label-approved for the target parasite, or if its efficacy is supported by legitimate published research data.[1] Antiparasitic drugs are available as single active ingredients or as combinations of active ingredients. Those with a single ingredient are often effective against several internal parasites. Combining more than one active ingredient in a product usually increases the spectrum of activity against internal parasites and may add external parasites to the label. When common internal parasites (i.e., *Toxocara canis, Ancylostoma* spp., and/or *Trichuris vulpis*) are the targets, several broad spectrum agents that are available as oral, topical and injectable products can be used. Deciding among them is dependent on factors discussed in other sections of this chapter. When heartworm

prevention is needed, the spectrum of available products changes further. Another consideration is whether the goal is to eliminate existing parasites or to prevent additional infections, or both. These are important points because concentrations of the active ingredients(s) often determine the level of efficacy achieved and whether efficacy is against mature or immature stages. Clearly, the landscape of antiparasitic drugs is complex. Consider the following. Examples of single entity broad-spectrum agents are pyrantel pamoate, fenbendazole, milbemycin oxime, moxidectin, praziquantel, epsiprantel, and selamectin. Dual broad-spectrum actives include pyrantel pamoate/praziquantel, ivermectin/pyrantel pamoate, milbemycin oxime/praziquantel, milbemycin oxime/lufenuron, milbemycin oxime/spinosad, and emodepside/praziquantel. A combination of three active ingredients further broadens the spectrum of the formulation. Examples are milbemycin oxime/lufenuron/praziquantel, ivermectin/pyrantel pamoate/praziquantel, and fenbantel/pyrantel pamoate/praziquantel.[1] We must also consider the use of antiparasitic drugs that have not gained regulatory approval, but are often used safely and effectively against problem parasites. Examples are metronidazole, secnidazole, ponazuril and ronidazole, just to mention a few.[1]

Effectiveness

Efficacy of parasiticides is a must when removal of target parasites and elimination of disease are the goals. To reach the market, approved parasiticides must be effective enough to eliminate the majority of the target parasites. Regulatory approval usually requires the removal of 90% of the parasites from treated animals compared to non-treated controls.[6] Heartworm preventives are the only exception. Heartworm preventive products must be 100% effective after either experimental or natural infection (see ch. 255). Interestingly, melarsomine dihydrochloride, the only approved heartworm adulticide, must achieve a high level of efficacy (usually >90%) but is not required to be 100% effective. Many parasiticides that are not approved for specific parasites are used successfully based on either published data or testimony that supports their efficacies. The authors strongly recommend that approved parasiticides are used when possible. Antiparasitic drugs that are not approved should be researched thoroughly and used in a manner consistent with available published data.

Strategic Versus Preventive Parasite Control

The selection and frequency of use of parasiticides will depend on the intended result. Animals that present with acute parasitism caused by parasites confirmed by appropriate and reliable diagnostic tests should be treated with antiparasitic drugs that eliminate the parasites. Additional treatments with other therapeutic agents as well as supportive therapy may also be necessary, depending on the presence of concurrent disease and the condition of the animal. The difference between antiparasitics with therapeutic effects and those with preventive effects is often one of dosage and frequency of administration. Therapeutic products that are administered to eliminate established infections are often administered once or twice at a higher dosage. Preventive products are usually administered at intervals (i.e., monthly or every 6 months). Products used in therapeutic strategies usually are administered at a higher dosage than preventive products. However, this is not always the case. Migrating stages of parasites (i.e., *Toxocara, Ancylostoma*) may require higher dosages of parasiticides and longer treatment regimens. Reasons are not always clear, but are likely due to lower metabolic rates of these stages and the greater difficulty in getting adequate amounts of parasiticide to the parasite's migratory sites. Some parasiticides are both therapeutic and preventive at the same dosage, but this is usually a unique situation involving treatment of one parasite and prevention of another. Examples are the products that eliminate adult intestinal parasites while preventing heartworm infections. In many of these cases, the heartworm preventive dosage is higher than necessary because heartworm is not the dose-limiting parasite. Clearly, understanding both the parasites and the target stages is important in applying preventive or therapeutic strategies successfully.[7]

Environmental Considerations

The environment in which animals are housed as well as their numbers and ages can affect the kinds and intensity of parasitic infections. These variables, alone or in combination, will determine the selection and use of antiparasitic drugs. Treatment and control of parasites in dogs in kennels and cats in catteries presents a different problem than individual pets in households. The same is true of animals in shelters and animal control facilities. Multi-pet households, including homes for fostered pets, may require strategies that are

similar to kennels and catteries. The difficulty in these situations is delivering proper therapies to many individuals in the same environment. Also, the variation in ages and sizes of animals makes population treatments in food or water more difficult. As mentioned above, environmental variables often result in different populations and intensities of parasites in each animal. This requires collection of individual specimens such as feces or urine from each animal. Products approved for application to food or water are lacking. Some parasiticides, such as amprolium for treatment of coccidiosis in dogs, can be added to water, but most cannot. Consequently, animals must be handled individually. Many off-label products are used in these situations. When using products and formulations intended for other host species, it is necessary to understand concentrations of formulations, dosages required for effective use, potential toxicoses, and proper storage.[1]

Compounded Parasiticides

It is common in today's veterinary practice to have some parasiticides reformulated by pharmacists for easier dosage calculations and more convenient product administration. These usually are products that are not approved for routine use, but for which there is a body of evidence that indicates that the active ingredients can be effective if dosages are calculated properly and the entire dose is administered to the target animal. These formulations often have not undergone evaluation for stability over time, or pharmacologic analysis in target animals to ensure that blood levels are achieved that are comparable to approved products or to other formulations for which research has been performed. Veterinarians should always consult with pharmacists about available information on a compounded parasiticide. Actually, the same arguments could be made against using parasiticides from other host species that contain the same or similar active ingredients. Differences in concentration and rates of absorption, distribution and elimination could result in lack of efficacy or unexpected adverse events. In summary, it is best to use formulations that are approved for the target parasite and host species.[8] If alternative products are considered, it is prudent to obtain as much information about them as possible before use.

Reproductive Status of the Host

Many antiparasitic drugs carry a disclaimer for use in pregnant or nursing animals, or more correctly that their safety in pregnant or nursing animals has not been determined. This does not necessarily indicate that they are unsafe. In most cases, it means that sufficient data on reproductive safety are not available to allow a label claim. It is the opinion of the authors that it is best to avoid the use of products in pregnant animals when such products have not been evaluated for reproductive safety. That said, a decision to proceed with therapy using a non-approved product could be justified depending on the severity of parasitism and the prognosis of the animal's recovery without therapeutic intervention.

Repeat Treatments

We are often asked whether additional treatments are necessary following a single therapeutic treatment for parasites. The necessity to retreat is determined by improvement of clinical signs and reduction in stages recovered at post-treatment examinations. A few considerations will help determine if additional treatments are necessary. Animals less than 6 months of age often have migrating stages of parasites that may not be eliminated by the selected antiparasitic agent. Therefore, choosing the correct retreatment interval requires knowledge of the parasite's life cycle. Parasites with longer endogenous cycles (i.e., longer period of migration in the host) would probably require a longer interval between the first and subsequent treatments. Also an initial high number of parasites present before the first treatment may leave a residual burden of parasites that would require additional treatments. It is important to keep in mind that this is also determined by the effectiveness of the parasiticide. A general rule of thumb for most parasites is that if retreatment is necessary, an interval of 1 to 2 weeks should suffice. Treatment efficacy should be the main factor on which decision to retreat is based.

Resistance to Antiparasitic Drugs

Resistance to antiparasitic drugs has been documented for important animal parasites.[9,10] Many view the development of resistance as an indication that subsequent use of these drugs will provide little or no benefit in preventing parasitic disease. Although this may be true for some parasites of livestock and horses, it has

not proven true for companion animal parasites. Resistance has been identified for some field strains of heartworm and rarely for some common intestinal parasites. However, in the majority of cases, antiparasitic drugs remain effective and beneficial to companion animals. There are several things that can be done to deter the development of resistance. First, use approved products at their label doses and according to their approved regimens. Underdosing and use of products at treatment intervals that are too frequent may lead to resistance development. Always monitor the efficacy of antiparasitic drugs by performing post-treatment tests, or at the very least, annual tests. Avoid the use of off-label products unless sufficient research supports that treatments are effective at eliminating the parasite. If a product appears to lose its efficacy, retreat with a product from a different chemical group. The most important aspect of resistance management is to monitor the effectiveness of antiparasitic drugs by regular fecal examination or other appropriate tests.

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CHAPTER 164

Anti-Inflammatory Therapy

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Glucocorticoids and nonsteroidal anti-inflammatory agents (NSAIAs) are commonly used classes of drugs that provide potent anti-inflammatory actions to treat a variety of conditions. The major anti-inflammatory actions of these drug classes include suppression of pro-inflammatory cytokines and other mediators. Glucocorticoids are less specific in their actions compared to NSAIAs, influencing metabolic and immune system functions. Pharmacology, clinical indications, and adverse effects of each drug class are discussed below.

Pharmacology and Clinical Indications for Glucocorticoids

Glucocorticoids enter cells largely through passive diffusion and bind to cytosolic receptors. Receptor number and type vary between tissues. Upon binding, receptors rapidly move into the nucleus where they exert molecular effects. At the level of the nucleus, glucocorticoids influence gene regulation and other transcription factors.[1,2] All types of inflammation, including those arising from infectious, traumatic, hypersensitivity or other immune response, and neoplastic etiologies, can be impacted by glucocorticoids. The inflammatory process is mediated by proinflammatory transcription factors, which in turn produce mediators of inflammation. Glucocorticoids exert anti-inflammatory actions by switching off the genes encoding for cytokines, chemokines, and other mediators of inflammation including adhesion molecules, inflammatory peptides, and mediator receptors. Glucocorticoids decrease movement and activity of white blood cells and fibroblasts, as well as inhibiting expression of cyclooxygenase (COX)-2, cytokines, cellular adhesion factors, complement components, and histamine release (Box 164-1). Many of the anti-inflammatory actions of glucocorticoids also suppress the immune system, especially cell-mediated immunity, and inhibit wound healing. While glucocorticoids can be effective in the treatment of unwanted inflammation, they can suppress the necessary protective responses to infection and healing. Synthetic glucocorticoid drugs are derivatives of endogenously produced cortisol. Modifications of the molecular structure lead to enhanced or diminished glucocorticoid, mineralocorticoid and other properties of synthetic steroid preparations. In addition to potent anti-inflammatory actions, glucocorticoids have widespread actions on metabolic functions (see Box 164-1).

Box 164-1

Selected Actions of Glucocorticoids

Anti-Inflammatory Effects

- Suppression of pro-inflammatory cytokines and chemokines (e.g., interleukin [IL]-1, IL-2, IL-6, IL-8, tumor necrosis factor [TNF]-alpha)
- Decreased expression of endothelial cellular adhesion molecules (e.g., intercellular adhesion molecule [ICAM]-1, E-selectin)
- Diminished inflammatory enzyme activity (e.g., cyclooxygenase [COX]-2, phospholipase [PL] A_2)
- Suppression of T-cell proliferation
- Inhibition of mononuclear phagocytosis and of chemotaxis
- Apoptosis of activated lymphocytes
- Induction of anti-inflammatory cytokines (e.g., IL-10, transforming growth factor [TGF]-beta)
- Stabilization of lysosomal membranes

Hematopoietic Effects

- Increase in circulating neutrophils, monocytes
- Decrease in circulating lymphocytes, eosinophils
- Sequestration of lymphocytes; involution of lymphoid tissue
- Increase in circulating red blood cells, platelets

Metabolic Effects

- Increase in hepatic gluconeogenesis
- Increase in protein catabolism
- Mobilization of free fatty acids
- Antagonism of insulin activity

Endocrine Effects

- Suppression of adrenocorticotropic hormone production
- Decrease in thyroid stimulating hormone and thyroid hormone production

Neurologic and Muscular Effects

- Behavior change
- Muscle weakness and atrophy

Renal Effects

- Increase in glomerular filtration rate
- Inhibition of antidiuretic response in renal tubules
- Proteinuria
- Retention of water, sodium, and chloride
- Excretion of potassium and calcium

Miscellaneous Effects

- Stimulation of appetite
- Increase in bone resorption
- Antioxidant action
- Inhibition of fibroblast proliferation and collagen activity

Synthetic glucocorticoids can be administered systemically (orally or via intramuscular, subcutaneous, or intravenous injection) or locally (e.g., topical skin ointment or aerosol delivery). Synthetic glucocorticoids vary in their glucocorticoid (anti-inflammatory) and mineralocorticoid activity and duration of hypothalamic-pituitary-adrenal axis (HPAA) suppression they exert. Clinicians must be aware of the equivalent dosage range between preparations (Table 164-1). Depot or repositol preparations are not recommended for routine use due to the chronic HPAA suppression, unpredictable blood concentrations, and inability to withdraw therapy associated with such products.

TABLE 164-1

Pharmacologic Properties of Selected Glucocorticoids

	RELATIVE GLUCOCORTICOID (ANTI-INFLAMMATORY ACTION) POTENCY	RELATIVE MINERALOCORTICOID POTENCY	EQUIVALENT DOSAGE (mg)*	DURATION OF ACTION IN HOURS (HUMANS)
Short-Acting				
Cortisol	1	1	20	<12
Hydrocortisone	1	0.8-1	20	<12
Intermediate-Acting				

Prednisone/Prednisolone	3.5-5	0.3-0.8	5-6	12-36
Methylprednisolone	5	0-0.5	4-5	12-36
Triamcinolone	3-5	0	4	24-48
Long-Acting				
Dexamethasone	25-30	0	0.7-0.8	>48
Betamethasone	25-40	0	0.6-0.8	>48

*Typical anti-inflammatory dosage for a 5-10 kg dog (based on glucocorticoid effect).

Effects of glucocorticoids are dosage-dependent, and can vary among species. Dosages should be titrated to maximize therapeutic benefit while minimizing adverse effects. Prednisone, prednisolone, and dexamethasone are commonly used systemic glucocorticoids in dogs. Prednisolone is preferred over prednisone for use in cats, due to its superior pharmacokinetics in this species.[3] Cats might be more resistant to the effects of glucocorticoids and require relatively higher dosages than dogs.[4] However, cats also are more sensitive to serious glucocorticoid adverse effects such as diabetes and congestive heart failure.[5,6] Unfortunately, scientific evidence for glucocorticoid dosing regimens in dogs and cats is lacking. A common initial anti-inflammatory dosage of predniso(lo)ne is 0.5-1 mg/kg/day (dogs) or 1-2 mg/kg/day (cats). In comparison, a physiologic dosage of predniso(lo)ne generally is considered to be 0.1-0.3 mg/kg/day; recommended immunosuppressive dosages range from 2-4 mg/kg/day in dogs and 2-8 mg/kg/day in cats.

Several considerations should be weighed when choosing among the many options for anti-inflammatory glucocorticoid therapy, including desired rapidity of onset, site of activity, and duration of treatment. In cases when rapid onset of activity is needed (e.g., respiratory inflammation leading to airway obstruction), injectable succinate or phosphate salts of glucocorticoids are recommended. More commonly, anti-inflammatory glucocorticoid therapy is needed for days to months. Intermediate-acting products allow for easy dose scheduling. Topical or local application of glucocorticoids can inhibit regional inflammation, while minimizing adverse systemic effects. Common sites of local glucocorticoid therapy include the respiratory and gastrointestinal (GI) tracts, skin, and eyes.

Inhaled glucocorticoids commonly are used for treating inflammatory airway diseases such as chronic bronchitis and allergic airway disease (see ch. 97 and 241). Inhaled fluticasone, budesonide, and beclomethasone are reported to have minimal systemic adverse effects compared to oral glucocorticoids, although HPAA suppression occurs in some veterinary patients.[7-9]

Oral budesonide has a high rate of first-pass hepatic metabolism in humans, enabling its use as a topical treatment for GI disease with fewer adverse effects than systemic glucocorticoids.[10] Similarly, oral budesonide is efficacious in the treatment of inflammatory GI diseases in dogs.[11-13] However, budesonide suppresses the HPAA in dogs and can cause adverse effects at a similar rate as prednisone in dogs with inflammatory bowel disease.[12,13]

Topical glucocorticoids can be used for treatment of atopic dermatitis and other inflammatory skin conditions, adjunct to other efforts aimed at controlling or eliminating the predisposing causes (e.g., ectoparasite control, hyposensitization for allergy-mediated conditions).[14] Long-term use of topical glucocorticoids can lead to significant systemic absorption, especially when dermal barriers are not intact.

Topical ocular glucocorticoids (e.g., 1% prednisolone acetate or 0.1% dexamethasone solutions) achieve good intraocular penetration and provide potent anti-inflammatory action to treat uveitis and other ocular inflammatory conditions, in the absence of corneal ulceration.[15] Frequency of therapy can be titrated to effect (every 1-8 hours).

Adverse Effects and Contraindications for the Use of Glucocorticoids

Adverse effects of glucocorticoid therapy result frequently from prolonged use of high dosages. Exogenous glucocorticoids can suppress the HPAA and cause iatrogenic hyperadrenocorticism. Clinical signs are similar to pituitary and adrenal-dependent hyperadrenocorticism, including polyuria, polydipsia, pendulous abdomen, and dermatologic changes (see ch. 306 and 307).[16,17] Secondary infections, especially urinary tract infections and pyoderma, can result from prolonged glucocorticoid therapy.[16,18] Other adverse effects include muscle wasting, weakness, ligament rupture, obesity, hypercoagulability, insulin resistance and diabetes.[5,19] Glucocorticoid administration can cause a wide range of GI effects, from subclinical gastric mucosal injury to

GI ulceration and perforation at high dosages.[20,21]

Glucocorticoids cause insulin resistance and elevate blood glucose levels; therefore, they should be used sparingly if at all in patients with diabetes mellitus. Due to the immunosuppressive actions of glucocorticoids, their use is relatively contraindicated during infection. However, treatment of some infectious diseases benefits from adjunct glucocorticoid therapy to reduce inflammation or modulate the immune response, when combined with appropriate antimicrobials (e.g., *Malassezia* otitis or *Mycoplasma haemofelis*) (see ch. 360). Glucocorticoids should not be used concurrently with NSAIA therapy due to the increased risk of GI ulceration. Because glucocorticoids may affect cardiac muscle function and cause water retention, cautious use is recommended in patients with heart disease as congestive heart failure is a potential risk, especially in cats.[6] Topical ocular glucocorticoids should not be used in patients with corneal ulceration or infection, as ulcers can worsen and stromal melting can occur.

Nonsteroidal Anti-Inflammatory Analgesics

Nonsteroidal anti-inflammatory analgesics (NSAIAs) are a group of pharmaceutical agents that possess both analgesic and anti-inflammatory properties. The NSAIAs are frequently used in human and veterinary medicine to relieve mild, moderate, or severe pain. The efficacy of many NSAIAs can be superior to that of butorphanol or buprenorphine, and superior or equal to the pure mu agonist opioids (oxymorphone, morphine, hydromorphone, meperidine) in managing soft tissue and orthopedic postoperative pain.[22-36] When used in combination with opioids, NSAIAs appear to confer synergism and can require reduced dosing of the opioid in mild to moderate, but not in severe, pain states. The NSAIAs concentrate in inflamed joints and tissues, likely contributing to duration of effect which varies between 12 and 24 hours.[37] The duration and efficacy of NSAIAs makes them ideal for treating acute[22-36] and chronic pain[38-49] in veterinary patients; however, due to their potential for harmful adverse effects, patient and NSAIA selection must be considered prior to administration (see ch. 126 and 356). Dosage calculations for any NSAIA must be based on the patient's ideal body weight and not on actual weight in overweight/obese patients (Table 164-2). Many veterinary publications review the clinical use of NSAIAs in great depth with extensive citations of original studies,[50-60] including a critical review of published studies.[50]

TABLE 164-2

Indications and Dosing Regimen for NSAIA Administration Based on Ideal Body Weight

DRUG	INDICATION	SPECIES, DOSAGE, ROUTE	FREQUENCY
Ketoprofen	Surgical pain	**Dogs** ≤ 2 mg/kg, IV, SC, IM, PO **Cats** ≤ 2 mg/kg, SC **Dogs and cats** ≤ 1 mg/kg	Once postoperative Once postoperative Repeat q 24 h
	Chronic pain	**Dogs and cats** ≤ 2 mg/kg, PO ≤ 1 mg/kg	Once Repeat q 24 h
Meloxicam	Surgical pain	**Dogs** ≤ 0.2 mg/kg IV, SC ≤ 0.1 mg/kg IV, SC, PO	Once Repeat q 24 h
	Chronic pain	**Dogs** ≤ 0.2 mg/kg PO ≤ 0.1 mg/kg PO	Once Repeat q 24 h
	Surgical pain	**Cats** ≤ 0.2 mg/kg SC, PO ≤ 0.05 mg/kg SC, PO, lean weight	Once Daily × 2-3 days
	Chronic pain	**Cats** ≤ 0.05 mg/kg SC, PO, lean weight. Titrate reduction to comfort ≈0.025 mg/kg ASAP.	Once daily Daily or 3-5 × weekly
Carprofen	Surgical pain	**Dogs** ≤ 4 mg/kg, IV, SC ≤ 2.2 mg/kg PO	Once upon induction Repeat q 12-24 h PRN
		Cats ≤ 2 mg/kg SC, lean weight	Once upon induction
	Chronic pain	**Dogs** ≤ 2.2 mg/kg PO	q 12-24 h
Etodolac	Chronic pain	**Dogs** ≤ 10-15 mg/kg PO	Once daily

Deracoxib	Perioperative pain Chronic pain	**Dogs** 3 mg/kg PO **Dogs** 1-2 mg/kg PO	Once daily × ≤7 days Once daily
Firocoxib	Chronic pain	**Dogs** 5 mg/kg PO	Once daily
Tepoxalin*	Chronic pain	**Dogs** 10 mg/kg PO	Once daily
Tolfenamic acid	Acute and chronic pain	**Cats and dogs** ≤ 4 mg/kg SC, PO	Once daily for 3 days. 4 days off. Repeat the cycle.
Flunixin meglumine	Pyrexia	**Dogs and cats** 0.25 mg/kg SC	Once
	Ophthalmic procedures	**Dogs and cats** 0.25-1 mg/kg SC	q 12-24 h PRN for 1 or 2 treatments
Ketorolac	Surgical pain	**Dogs** 0.3-0.5 mg/kg IV, IM	q 8-12 h for 1-2 treatments
		Cats 0.25 mg/kg IM	Once only
	Panosteitis	**Dogs** 10 mg/**DOG** ≥ 30 kg, PO 5 mg/**DOG** > 20 kg < 30 kg, PO	Once daily for 2-3 days
Piroxicam	Inflammation of the lower urinary tract	**Dogs** 0.3 mg/kg PO	q 24 h for 2 treatments, then q 48 h
Acetaminophen	Acute or chronic pain	**Dogs only** 15 mg/kg PO	q 8 h
Aspirin	Acute or chronic pain	**Dogs** 10 mg/kg PO	q 12 h

*Not available in North America.

ASAP, As soon as possible; *PRN*, as needed.

The indications proposed here assume there are no contraindications to their use. A more in-depth discussion on general considerations, indications, and adverse effects is available in the previous edition of this textbook.[99]

Pharmacology and Clinical Indications for Nsaias

Cyclooxygenase enzymes oxidize arachidonic acid to various eicosanoids and related compounds, or prostanoids[61] (Figure 164-1). Nonsteroidal anti-inflammatory analgesics are, with varying differences, inhibitors of COX-1, COX-2, both, or COX-3, resulting in reduced prostaglandin (PG) synthesis. In addition to the peripheral action, a significant part of the NSAIAs' antinociceptive effect is exerted at the spinal cord and supraspinal levels where both COX-1 and COX-2 isoenzymes are nociceptive transmitters independent of inflammation.[62-68] This action, in addition to pain relief, could account for the observed overall well-being and improved appetite of patients receiving injectable NSAIAs for relief of acute pain (personal observations). COX-1 can be induced in inflammatory states and is increased approximately twofold or threefold in tissue injury, and can also generate PGs at sites of inflammation (e.g., joints). It is present within the central nervous system, and is active in transmission of pain, especially visceral nociception. COX-1 also is a constitutive enzyme (i.e., functions in tissues continuously, noninducible) that ultimately converts arachidonic acid into the prostanoids (thromboxanes, prostacyclin, and prostaglandins [PGE_2, PGF_2, and PGD_2]) involved in many homeostatic functions.[67]

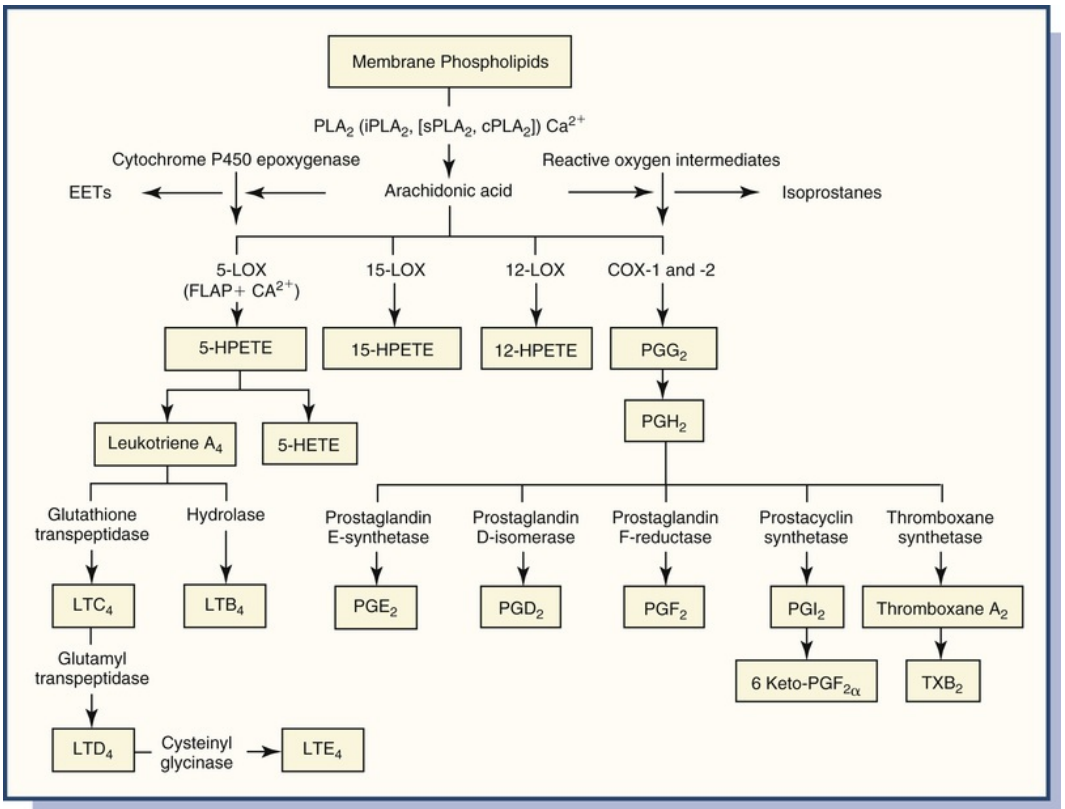

FIGURE 164-1 The arachidonic acid cascade. *COX,* Cyclooxygenase; *EETs,* epoxy-eicosatrienoic acids; *FLAP,* 5-lipoxygenase-activating protein; *HETE,* hydroxyeicosatetraenoic acid; *HPETE,* hydroperoxyeicosatetraenoic acid; *LOX,* lipoxygenase; *LT,* leukotriene; *PG,* prostaglandin; *PLA_2,* phospholipase A_2; *TXB_2,* thromboxane B_2.

Cyclooxygenase-2 also is inducible and synthesized by macrophages and inflammatory cells, potentially increasing by twentyfold over baseline, especially in injured tissue and inflammatory conditions such as osteoarthritis.[63] The increased COX levels increase prostanoid production, where these compounds serve as mediators of inflammation and amplifiers of nociceptive input and transmission in both the peripheral and central nervous systems.[63] By this mechanism, COX-2 is responsible for a substantial amount of pain and hyperalgesia experienced after tissue injury. As COX-2 appears to play an important role in nociceptive transmission, medications that prevent COX-2 activity and spare the constitutive COX-1 functions should be effective, with potentially fewer adverse effects, in the management of pain. Based on these findings, emphasis is placed on COX-1 versus COX-2 activity of NSAIAs, with respect to safety and efficacy; however, it is important to note that COX-2 also has important constitutive functions,[47,48] and the notion of a "good versus bad COX" is misleading. The discovery of COX-3, characterized as being generated from COX-1, is expressed in the brain and brain microvasculature in dogs and has been proposed to be a target of the analgesic/antipyretics acetaminophen and metamizole (Dipyrone).[67,70,71] Currently, the presence of COX-3 appears to be restricted to dogs. Both acetaminophen and metamizole have minimal effect on COX-1 and COX-2[67] and frequently are used for reducing fever in animals with few GI or renal adverse effects. Acetaminophen and metamizole are toxic to cats. The COX-3 isoenzyme is more sensitive to NSAIAs that are analgesic and antipyretic but have low anti-inflammatory activity. As the COX-3 isoenzyme genetic profile is derived from the COX-1 gene, this suggests that the COX-1 gene plays an integral role in pain and/or fever depending on the physiologic context.[65]

Prostaglandins, especially those derived from COX-1, are ubiquitous throughout the body and they regulate many functions such as vascular and bronchial smooth muscle tone and fluid balance, to name a few. Prostaglandins exert a negative feedback effect on cyclic adenosine monophosphate (cAMP) with potential perturbations in many physiologic functions. As an example, renal water reabsorption depends on the action of antidiuretic hormone (ADH), which is mediated by cAMP; inhibition of prostaglandin synthesis could lead to increased levels of cAMP with a potential for enhanced ADH activity. Urine volume can be decreased through this mechanism but without renal injury.[67,72,73] In the inhibition of COX-2 activity when managing

pain, the COX-2 enzyme has some important constitutive functions: there is a protective role for COX-2 in maintenance of GI integrity and ulcer healing.[74] In addition, there is constitutive activity associated with nerve, brain, ovarian, and uterine function and bone metabolism.[72,75] COX-2 has constitutive functions in the kidney, which differ from those of COX-1. COX-2 is important in nephron maturation.[73,76] The canine kidney is not fully mature until 3 weeks after birth, nor is it optimally functional until 6 weeks after birth[76]; continual administration of an NSAIA during this time, or to the bitch prior to birth or during lactation, can cause a permanent nephropathy. Most important is the dual role of the PGs as inflammatory and anti-inflammatory mediators, where COX-2–derived PGs also function in resolution of inflammation.[68,71,77]

On the other hand, COX metabolites have been implicated in functional and structural alterations in glomerular and tubulointerstitial inflammatory disease.[73] Because COX-2 expression also is increased in glomerulonephritides such as lupus nephritis, it is possible that COX-2 inhibitors could alter the natural history of glomerular inflammatory lesions.[73] COX-2–derived metabolite production is regulated and localized to the structures in the kidney that play an essential role in renal blood flow associated with renin activity and fluid-electrolyte homeostasis.[52,73,78] COX-2 is glucocorticoid-sensitive, in that it is reduced following administration of glucocorticoids, which could partially explain the anti-inflammatory and analgesic effects of this class of medications. Of interest, in addition to the COX-2 role in inflammation, aberrantly upregulated COX-2 expression is increasingly implicated in the pathogenesis of Alzheimer's disease and possibly other neurologic conditions and a number of epithelial cell carcinomas, including those affecting the colon, esophagus, breast, and skin.[79,80] The COX-2 inhibitors are being researched as potential anticarcinogenic agents. A good review of the "Coxibs" is available; the background and pharmacology of the Coxibs are reviewed elsewhere.[68,79,81]

Most NSAIAs that inhibit COX have been shown to result in diversion of arachidonate to the 5-lipoxygenase (5-LOX) pathway (see Figure 164-1). This results in an excessive production of leukotrienes (LT), which have been implicated in many pathologic states, including hyperalgesia and the creation of NSAIA-induced ulcers.[67,82,83] Leukotrienes are the products of the 5-LOX cascade, where arachidonic acid is converted by a two-step mechanism into the conjugated triene epoxide leukotriene (LTA_4), the most biologically important intermediate LT.[68,83-85] LTA_4 subsequently is metabolized to LTB_4 and LTC_4. An LTD_4 also is recognized. Cells known to express 5-LOX include circulating neutrophils, monocytes, basophils, eosinophils, tissue macrophages, and mast cells. These cells release LTA_4 and participate in transcellular biosynthesis of either LTC_4 or LTB_4.[86] As with the prostanoids, it is impossible to list all the activities of the LTs as these are also dependent on organ involvement. An in-depth discussion of dual inhibitors is available elsewhere.[60,68,87-89]

Associated with the use of NSAIAs is the risk of perturbation of the constitutive functions of COX-1 and COX-2 potentially resulting in organ dysfunction. Depending on the NSAIA selected, primary plug formation of platelets, modulation of vascular tone of all organs (the kidney and gastric mucosa being of specific importance), cytoprotective functions on the gastric mucosa, healing of intestinal mucosa, smooth muscle contraction, and regulation of body temperature all will be affected.[67,72] However, in this regard not all NSAIAs are created equal, as the COX-1, COX-2, and COX-3 enzymes variably control these functions. Some NSAIAs inhibit both COX-1 and COX-2 (aspirin, phenylbutazone, ketoprofen [Anafen], ketorolac [Toradol], flunixin meglumine [Banamine, Schering-Plough]); while others preferentially can inhibit COX-2 and be weak inhibitors of COX-1 (meloxicam [Metacam], carprofen [Rimadyl], etodolac [Etogesic], vedaprofen [Quadrisol-5], tolfenamic acid [Tolfedine]). Others selectively inhibit COX-2 (deracoxib [Deramaxx], firocoxib [Previcox], robenacoxib [Onsior],[90-92] cimicoxib [Cimalgex]),[93] while still others, such as acetaminophen and metamizole, can weakly inhibit both COX-1 and COX-2 but have greater inhibition of COX-3. Metamizole has been used for postoperative analgesia following ovariohysterectomy in dogs.[94]

Tepoxalin (Zubrin) is a dual COX/lipoxygenase (LOX) inhibitor that is reported to reduce concentrations of COX-1, COX-2, and 5-LOX to some degree in dogs.[95] Licofelone, a new true dual inhibitor being evaluated in people and dogs, could have greater GI safety than other NSAIAs.[96]

Adverse Effects and Contraindications for the Use of Nsaias

As a group, NSAIAs are not reversible; it is, therefore, imperative that the general health of the patient be considered prior to prescribing NSAIAs. Where the large animal formulations of an NSAIA exist, it is not

advised to dilute or estimate a dose for a cat or dog as a very small volume can easily result in serious overdose. Doses should be calculated based on the ideal weight of a patient (see Table 164-2). Anecdotal incidents of single, accidental, large overdoses have been observed with no long-term adverse effects; however, short-term, gastric protection and intravenous (IV) fluids to support renal function are advised with high overdoses. Relative overdose resulting in acute kidney injury also has been observed in obese patients when the dosage was based on true weight rather than ideal weight. Cats and dogs are more susceptible than are people to the adverse effects of NSAIA administration; therefore, the reported safety of any NSAIA approved for the human patient should not be assumed to be so in the veterinary patient and the drug should not be prescribed. Cats are even more of a concern than dogs as the potential for toxicosis with certain NSAIAs is greater than for other species due to their limited ability to glucuronidate NSAIAs, resulting in a prolonged duration of effect.[59] There are many potential interactions between NSAIAs and other medications, many of which are contraindicated during NSAIA use.[97]

Based on the many important physiologic functions the prostanoids perform, one can appreciate the potential perturbation of normal homeostatic functions with administration of NSAIAs. The recommended dosages for the various NSAIAs rarely compromise these functions; however, should a patient be in a prostaglandin-dependent state, administration of NSAIAs frequently results in adverse effects (see ch. 126 and 356). However, even in normal states, the NSAIAs may result in GI, renal, or hepatic abnormalities, or rarely a coagulopathy (predominantly COX-1 NSAIAs) in the genetically predisposed individual. While the incidence of GI signs could be reduced with COX-2–specific targeted NSAIAs, adverse effects can still occur. Cyclooxygenase-2 expression has been identified in the duodenum of dogs, which increased significantly following 3 days of aspirin (10 mg/kg q 12 h) when compared with effects of carprofen and deracoxib at recommended dosages.[98] Upregulation of COX-2 has been identified in the duodenum in response to mucosal erosion/injury, performing an integral role in the daily healing process.[98] Nonsteroidal anti-inflammatory analgesics should not be administered to patients with acute kidney injury or uremia, hepatic insufficiency, dehydration, hypotension, conditions associated with low "effective circulating volume" (e.g., congestive heart failure, ascites), bleeding disorders (e.g., factor deficiencies, thrombocytopenia, von Willebrand disease), concurrent use of any other NSAIAs or glucocorticoids, evidence of gastric erosion (vomiting with or without the presence of "coffee ground" material, melena), spinal injury upon presentation (including herniated intervertebral disc, especially since many of these patients receive glucocorticoids with medical or surgical management). NSAIAs should never be administered to patients in shock, trauma cases upon presentation, or where hemorrhage is evident (e.g., epistaxis, hemangiosarcoma, head trauma). Patients with severe or poorly controlled asthma, or other moderate to severe pulmonary disease, can deteriorate with COX-1–inhibiting NSAIAs, especially aspirin. NSAIAs may have adverse effects on the reproductive tract and fetus, as they can block prostaglandin activity, resulting in cessation of labor, premature closure of the ductus arteriosus in the fetus, and disruption of fetal circulation.[73] As COX-2 induction is necessary for ovulation and subsequent implantation of the embryo,[73] NSAIAs should be avoided in breeding females during this stage of the reproductive cycle. For specific details on reported adverse effects associated with NSAIA administration in dogs and cats, the reader is referred to published reviews on this topic.[29-39] Due diligence on behalf of the veterinarian will reduce the potential for harm.

FDA Newly-Approved Drug

The EP4 receptor, one of the four PGE_2 receptors, has a primary function of mediating the PGE_2-elicited sensitization of sensory neurons and PGE_2-elicited inflammation resulting in inflammatory pain. Piprants are prostaglandin receptor antagonists (PRA), a new class of analgesic agents. The EP4 receptor has been associated with osteoarthritis (OA) in rodents, dogs and cats.[100] Grapiprant (Galliprant, Aratana Therapeutics), an EP4 PGE_2 receptor antagonist, has recently been approved for OA in dogs. In a field study, grapiprant 2 mg/kg q 24 h improved pain scores when compared to placebo (48.1% vs. 31.3%). Based on the specific receptor target, grapiprant was well tolerated with occasional vomiting (17% of dogs) throughout the 28 day study.[101] However, long-term studies are required to further assess safety. In the interim, appropriate patient selection and monitoring, as with other NSAIDs, is advised. Studies in cats are under way.

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CHAPTER 165

Immunosuppressive Therapy

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Immune-mediated diseases are diverse and they range from those that are very organ-specific to those that are systemic. The central therapy for these diseases includes halting ongoing damage by the immune system and can include nonspecific immunosuppression as well as utilization of medications to target specific parts of the immune system; this includes specific phases of the cell cycle and specific enzymes needed for sustained activity of the immune system. In dogs, glucocorticoids commonly are used in addition to another immunosuppressive agent, as dogs are very susceptible to the side-effects of glucocorticoids and can respond favorably to other immunosuppressive medications. In cats, initial immunosuppressive therapy often only includes glucocorticoids, as cats are not as susceptible to their clinically significant side-effects. More options for immunosuppressive medications are now available for small animal patients than ever before. Unfortunately, large controlled prospective clinical studies evaluating these drugs for specific canine and feline immune-mediated diseases are lacking; therefore, making specific recommendations for certain diseases can be challenging. The subject of concurrent infection in patients requiring immunosuppression is discussed in ch. 360.

Glucocorticoids

Glucocorticoids remain as a mainstay of immunosuppression in small animal medicine. Their physiological effects come from interactions with glucocorticoid receptors in the cytosol of the cells of the body. Glucocorticoids enter cells by passive diffusion and interact with these receptors, creating a conformational change and subsequent release of an activated complex that translocates to the nucleus. In the nucleus, this activated complex recognizes and associates with short DNA sequences called glucocorticoid-responsive elements.[1,2] This interaction then modulates gene transcription, with the formation of targeted proteins either being up- or downregulated. Glucocorticoids also can interact with plasma membranes to create cellular responses.

The mechanism of action of glucocorticoids is multifaceted, and includes effects on both the humoral and cell-mediated arms of immunity. Some of these actions include inhibition of production and release of cytokines (interleukin [IL]-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, tumor necrosis factor alpha [TNF-alpha], gamma interferon [IFN-gamma]), chemokines, adhesion molecules, and other mediators of inflammation; impaired macrophage activity through influence on both expression and function of macrophage Fc receptors; decreased macrophage antigen processing and presentation to T helper cells; impaired complement function; decreased antibody binding; inhibition of antibody production; reduction in the numbers of lymphocytes; and decreased migration of inflammatory cells from the bloodstream into tissues.[1,3,4]

Many formulations of glucocorticoids are available. The most commonly used include prednisone and prednisolone. Prednisone is a prodrug that is metabolized to prednisolone. In cats, higher plasma concentrations are achieved with orally administered prednisolone as compared to orally administered prednisone; thus, prednisolone is preferred over prednisone in this species.[5-7] Dexamethasone is an oral and injectable glucocorticoid that is approximately 7 times as potent as prednisolone and prednisone. Additional information on various glucocorticoid types and formulations, and dosage information for specific diseases, can be found in ch. 164 and disease-specific chapters, respectively.

Cyclosporine

Cyclosporine is a potent immunosuppressive agent increasingly being used for the treatment of inflammatory and immune-mediated diseases in dogs and cats. Cyclosporine, a molecule derived from the soil fungus *Tolypocladium inflatum*, was originally developed for renal transplant use in human medicine. It is now a

cornerstone medication in human transplantation medicine. Cyclosporine's primary mechanism of action is the inhibition of calcineurin and the subsequent inhibition of T-lymphocyte function. Once cyclosporine is in the cytosol of cells, it complexes with cyclophilin. This complex has a high affinity for calcineurin, causing an inhibition of calcium-stimulated phosphatase in calcineurin. This inhibited dephosphorylation step does not allow for activation of NFAT (nuclear factor of activated T-cells) which is needed for the nuclear transcription of genes coding for several important cytokines. Ultimately, cytokine production, most notably IL-2, is inhibited. IL-2 plays a key role in the activation and proliferation of T-lymphocytes, and thus its inhibition leads to reduced T-cell function and a blunting of the immune response.[8]

Cyclosporine is a lipophilic molecule that must be solubilized before administration. Two formulations exist for cyclosporine: a vegetable-oil preparation that mainly is of historic interest, and an ultramicronized formulation. The vegetable-oil formulation (Sandimmune) was associated with significant intraindividual and interindividual variations in blood drug concentrations and thus is not recommended for use in clinical veterinary patients.[8] The newer ultramicronized formulation forms a microemulsion upon contact with aqueous fluids, resulting in an increased bioavailability and more predictable absorption. The current United States Food and Drug Administration (FDA)-approved oral veterinary product for dogs and cats is an ultramicronized formulation, Atopica.

Cyclosporine's pharmacokinetic behavior can be complex, and can depend on a number of variables. After oral administration, cyclosporine is absorbed in the small intestine. Food has been shown to decrease the oral absorption of cyclosporine in dogs but not cats; therefore, recommendations exist to administer cyclosporine 2 hours before or after feeding in dogs.[8] Peak cyclosporine concentrations generally occur 2 hours after oral administration, with blood levels then rapidly decreasing over the remainder of the dosing interval. Metabolism mainly occurs in the liver by the cytochrome P450 or CYP enzyme pathway, creating a number of cyclosporine metabolites. A number of medications can influence this metabolism, and thus can increase or decrease cyclosporine blood concentrations. In dogs, the most frequently used medication used concurrently with cyclosporine therapy to purposefully decrease the cyclosporine daily requirements is ketoconazole. Studies of the treatment of perianal fistulas in large breed dogs have shown that significantly decreased daily cyclosporine dosages maintain blood cyclosporine concentrations when ketoconazole is coadministered[9,10]; this strategy for lowering the daily cyclosporine requirements is only beneficial if ketoconazole is appropriately priced. Cyclosporine metabolites mainly are excreted though the biliary system.

To monitor the effectiveness of therapy when using cyclosporine, two options exist: therapeutic drug monitoring and pharmacodynamic evaluation. Evaluation of blood cyclosporine concentrations can be an important tool to help facilitate successful therapeutic management. The intent is to establish and maintain a patient's therapeutic range in order to help avoid toxicosis or therapeutic failure. Whole blood is the preferred sample for measuring cyclosporine blood concentrations, with sampling recommendations including measuring both a peak (2 hours after dosing) and trough (just prior to drug administration) sample.[8] Reference intervals for cyclosporine blood concentrations are specific to each laboratory performing the assay, and decisions on monitoring and on implementing dosage changes should be made in consultation with the laboratory performing the test.

Pharmacodynamic monitoring utilizes assays that measure one or more biomarkers. This approach offers a more individualized approach when cyclosporine blood concentrations do not correlate well with clinical response. In dogs, this has been explored experimentally, with a validated PCR assay emerging.[11] Through this type of testing, individual responses to cytokine suppression were shown to be different in dogs receiving the same dosage of cyclosporine and in dogs having the same cyclosporine blood concentrations.[12] This PCR pharmacodynamic assay, which measures IL-2 and IFN-gamma, is now available to practitioners.

Adverse effects can occur in patients receiving cyclosporine. In dogs and cats, the most common side-effects are gastrointestinal (e.g., vomiting, diarrhea, anorexia).[8] Other side-effects in dogs include lethargy, gingival hyperplasia, hirsutism, coat shedding, cutaneous papillomatosis, and footpad hyperkeratosis.[8] Adverse effects seen in cats can include lethargy, behavioral disorders (hiding, hyperactivity, aggression), hypersalivation, gingival hyperplasia, ocular discharge, and sneezing/rhinitis.[a] In both cats and dogs, long-term administration can result in secondary infections. Hepatotoxicosis and nephrotoxicosis are rare potential complications in dogs and cats; they have not been reported reliably in the veterinary literature.[8,13] Cyclosporine administration has been associated with the emergence of neoplasia, particularly lymphoma in dogs and cats.[8,13] Cyclosporine administration, unlike other immunosuppressive medications, has not been associated with myelosuppression and neutropenia.[8]

Cyclosporine's clinical use has expanded well past transplantation medicine. The veterinary formulation

(Atopica) is approved for the treatment of atopic dermatitis in dogs and allergic dermatitis in cats. With the ultramicronized formulation of cyclosporine as treatment for dogs with non-life-threatening diseases such as skin diseases or mild inflammatory bowel disease, cyclosporine therapy often is started at a lower dosage (e.g., 5 mg/kg PO q 24 h or q 12 h) and the dosage titrated upward as needed, based on clinical efficacy. Cyclosporine blood concentrations often are not measured in these cases because of a lack of correlation of blood concentrations and clinical efficacy. Generally, response to therapy dictates the adequacy of dosage. For the treatment of severe immune-mediated diseases in dogs, the ultramicronized formulation of cyclosporine is administered at a higher dosage. The initial starting dosage often is 5-10 mg/kg PO q 12 h, with therapeutic drug monitoring and/or pharmacodynamic testing strongly recommended to adjust the dosage and ensure adequate immunosuppression with fewest side-effects. To obtain immunosuppression in cats, the ultramicronized formulation of cyclosporine often is initiated at a dosage of 3-5 mg/kg PO q 12 h.[13,14]

Azathioprine

Azathioprine is a purine analogue affecting both the humoral and cell-mediated arms of the immune system, suppressing lymphocyte activation and proliferation as well as macrophage function. The main target is cell-mediated immunity, specifically lymphocytes, because of their lack of a salvage pathway for synthesis of purines.[4,15] Azathioprine's active metabolite, 6-mercaptopurine, resembles adenine and guanine, and is alternately inserted during the S-phase of cell division.[16] This interference with purine synthesis causes ribonucleic acid miscoding, leading to disruption of RNA and DNA synthesis and mitosis.[4] Chromosome breaks can also occur secondary to incorporation into nucleic acids.

The metabolism of azathioprine to 6-mercaptopurine occurs in the liver.[16] Thiopurine methyltransferase (TPMT), xanthine oxidase, and hypoxanthine-guanine phosphoribosyltransferase are the enzymes responsible for the further metabolism of 6-mercaptopurine, resulting in inactive metabolites or active intracellular metabolites (6-thioguanine nucleotides).[4,16,17] Variations in the activity of TPMT in human patients affect clinical outcome: low TPMT activity is associated with a higher incidence of toxic effects, and high TPMT activity is associated with a decrease in effect of azathioprine.[16,17] Breed variations have been documented in dogs, with Giant Schnauzers having lower TPMT activity and Alaskan Malamutes having higher activity compared to other breeds.[17] Caution and a reduced dosage should be considered in canine patients concurrently receiving allopurinol, a xanthine oxidase inhibitor, concurrently with azathioprine, as this could allow increased intracellular concentrations of the active metabolites to occur.[14]

In dogs, azathioprine initially is administered at a dosage of 2 mg/kg PO q 24 h, often in combination with immunosuppressive dosages of glucocorticoids.[2,13,14] This drug is *not* recommended in cats because they are very prone to the myelosuppressive effects of azathioprine due to their low species-specific concentrations of TPMT.[4,15,18] Azathioprine has been used in dogs for treatment of immune-mediated thrombocytopenia (see ch. 201), immune-mediated hemolytic anemia (see ch. 198), autoimmune skin diseases (see ch. 204), chronic hepatitis (see ch. 282), inflammatory bowel disease (see ch. 276), immune-mediated glomerular disease (see ch. 325), systemic lupus erythematosus (see ch. 205), immune-mediated polyarthritis (see ch. 203), perianal fistula (see ch. 278), myasthenia gravis (see ch. 269), meningoencephalomyelitis of undetermined etiology (see ch. 261), as well as part of canine transplantation protocols (see ch. 323).[3,13,15,17,19] Retrospective studies support its use in the treatment of these diseases but prospective controlled studies are lacking.

Adverse effects in dogs associated with the use of azathioprine include gastrointestinal complications (anorexia, vomiting, diarrhea), myelosuppression (leukopenia, anemia, and/or thrombocytopenia), hepatotoxicosis, poor hair growth, secondary infections, and acute pancreatitis.[4,14,15,17,20] Azathioprine-induced myelosuppression and hepatotoxicosis are idiosyncratic, non-dose–dependent drug reactions that typically are reversible once the drug is withdrawn. Regular monitoring of blood counts and serum biochemical profiles should occur during azathioprine therapy to identify such drug reactions early and allow for drug discontinuation should they occur.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is the prodrug of mycophenolic acid (MPA), which is the active immunosuppressive molecule.[21,22] MPA induces its immunosuppressive effects by inhibiting inosine monophosphate dehydrogenase (IMPDH), an enzyme necessary in the *de novo* cellular pathway for purine synthesis. This action inhibits both B- and T-cell proliferation and clonal expansion, suppresses B-cell

antibody formation, and induces apoptosis of activated T-cells, thus affecting both humoral and cell-mediated responses.[21-25] MPA also downregulates expression of adhesion molecules, which decreases the recruitment of lymphocytes and monocytes out of circulation and into sites of chronic inflammation.[22-24] MPA inhibits IMPDH in a selective, reversible, and non-competitive manner. Two isoforms of IMPDH exist, with type 1 existing in most cells and type 2 existing in activated lymphocytes.[25-27] MMF has a 5-fold greater affinity for the type 2 IMPDH isoform.[5,21,23,25-27] MPA specifically inhibits lymphocyte proliferation during the S phase of the cell cycle, due to depletion of guanosine and deoxyguanosine nucleotides.[1] Lymphocytes also are preferentially targeted because they are dependent on the *de novo* pathway for purine synthesis and cannot use the salvage pathway for purine synthesis as other cell lines can.[27]

After oral administration, MMF is rapidly absorbed and completely de-esterfied into MPA.[22,27] The peak MPA blood concentration (Cmax) occurs 1-2 hours after oral administration of MMF.[23] MPA then undergoes hepatic glucuronidation to form mycophenolic acid glucuronide (MPAG), an inactive metabolite.[22] Most of MPA and MPAG circulate systemically, bound to albumin. Part of the MPAG is excreted into the biliary system, with presumed deglucuronidation of MPAG to MPA by the gut flora. Subsequent enterohepatic recirculation and absorption also occurs, explaining the secondary plasma MPA peak seen in dogs 4-12 hours after oral administration of MMF.[22,28] Over 90% of an orally administered dose of MMF is excreted in the urine, mostly as MPAG.[22,23] A small percentage of MPAG is excreted in the feces.[22,29]

Prospective, randomized, double-blinded clinical trials in human transplant recipients treated with a combination of MMF, cyclosporine, and glucocorticoids have demonstrated reductions in rejection episodes and improvement in patient and graft survival.[23] Initially, MMF was used in dogs as part of a protocol to control renal transplant rejection[30]; now, it also is being used for the treatment of various immune-mediated and inflammatory diseases in dogs and cats.[24-27,31-33]

Currently, no MMF products are approved for veterinary use. However, MMF is available as oral and parenteral human products. MMF recently has become much more affordable in the United States. While an early pharmacodynamic study in dogs suggested oral administration every 8 hours, this dosing strategy has not entered common clinical usage.[34] Dosage recommendations for dogs range from 10-40 mg/kg/day PO either given once daily or divided and given twice or three times a day, with many protocols recommending 10 mg/kg PO q 12 h.[3,14,24,31] In cats, dosage recommendations include 10 mg/kg PO q 12 h.[14,25] MMF is thought to have a rapid onset of action, occurring within 2 to 4 hours after dosing.[2,5] In dogs, it often is used as part of a combination protocol, although in one case series of five dogs with immune-mediated thrombocytopenia, MMF monotherapy at a median dosage of 8.5 mg/kg PO q 12 h was associated with complete remission of disease.[31]

Adverse effects of MMF in people include gastrointestinal upset, susceptibility to infection, increased risk of lymphoma, allergic reactions, teratogenic effects, headache, hypertension, peripheral edema, cough, confusion, tremor, and bone marrow suppression (leukopenia, thrombocytopenia, and anemia).[14,23] Based on limited veterinary studies, side-effects in dogs primarily include gastrointestinal complications (inappetence, vomiting, diarrhea, inflammation/ulceration), weight loss, lethargy, papillomatosis, and allergic reactions.[14,32] In a study of 5 dogs with immune-mediated hemolytic anemia receiving MMF 10-15 mg/kg PO q 8 h, the authors concluded that the level of gastrointestinal toxicosis they observed could not justify its use with this dosing regimen, despite achieving remission in four of five dogs.[32] Myelosuppression and hepatotoxicosis have not been documented, although monitoring of complete blood counts should be considered in dogs receiving MMF until more is known about its use in this species. As with any immunosuppressive medication, monitoring for secondary infections should take place.

Leflunomide

In veterinary medicine, leflunomide initially was investigated in canine transplant medicine.[35,36] Gregory and colleagues described its use in a variety of immune-mediated diseases and inflammatory diseases in dogs, with promising initial results.[37] Until recently, it could be cost prohibitive, but now the reasonably priced generic formulation is leading to increasingly frequent use in small animal medicine.

Leflunomide is a prodrug that is metabolized by the intestinal mucosa and liver to its active metabolite, A77 1726 (or teriflunomide).[5,38] Its main mechanism of action is the reversible inhibition of dihydro-orotate dehydrogenase, an enzyme needed for the *de novo* synthesis of pyrimidines.[5,37,39] Lymphocytes are

particularly targeted due to the lack of a salvage pathway for pyrimidines.[5] Effects include inhibition of B- and T-cell proliferation, suppressed production of immunoglobulin, and impaired leukocyte adhesion.[37,39,40] It also causes tyrosine kinase-mediated inhibition of cytokine and growth factors[5,37,41] and has an inhibitory effect on the replication of feline herpesvirus-1 in feline kidney cell cultures.[42]

In humans, leflunomide is used for treating rheumatoid arthritis, Crohn's disease, systemic lupus erythematosus, and is used in the management of transplant recipients.[5] In veterinary medicine, information on leflunomide use in dogs and cats is similar to that seen with MMF, being limited and including single case reports or small retrospective studies. Leflunomide has been investigated in dogs for the treatment of glucocorticoid-resistant immune-mediated hemolytic anemia (see ch. 198), Evans's syndrome (see ch. 198), immune-mediated thrombocytopenia (see ch. 201), immune-mediated polyarthritis (see ch. 203), pemphigus foliaceus (see ch. 204), systemic histiocytosis (see ch. 350), and nonsuppurative encephalitis/meningomyelitis (see ch. 261).[37,39,41] In cats, it has been described in the treatment of feline rheumatoid arthritis.[43]

Reported side-effects in humans include gastrointestinal upset, myelosuppression, secondary infections, headaches, interstitial lung disease, hepatotoxicosis, skin rashes, alopecia, and toxic epidermal necrolysis.[39] Reported side-effects in dogs include vomiting, diarrhea, inappetence, bone marrow suppression, and lethargy.[5]

The current initial dosing range in dogs is 2-6 mg/kg PO q 24 h, with many clinicians beginning at 4 mg/kg PO q 24 h.[13,14,40,44] In cats, the initial starting dosage often is 2 mg/kg PO q 24 h (or often 10 mg total dose PO q 24 h).[13,14,43] The dosage can be adjusted based on the patient's response to therapy as well as through the measurement of blood concentrations. Current recommendations regarding blood concentrations include measuring trough concentrations and targeting 20 mcg/mL to maintain a desired therapeutic effect,[13,40,44] with testing available through the Auburn University Veterinary Clinical Pharmacology Laboratory.

Tetracycline and Niacinamide

This combination of medications is used mainly for treating immune-mediated dermatopathies. It is discussed further in ch. 204.

Alkylating Agents

Alkylating agents mainly are used in antineoplastic chemotherapy protocols in small animal medicine, but they have also been investigated for their use in the treatment of immune-mediated diseases. The drug in this category that has been used most commonly for immunosuppression is chlorambucil. The mechanism of action for alkylating agents is cross-linking DNA, thus interfering with DNA replication and RNA transcription.[1,4,45] These compounds are toxic to both resting and rapidly dividing cells, particularly proliferating lymphocytes, and thus affect both humoral and cell-mediated immunity.

Chlorambucil is a cell-cycle–nonspecific alkylating agent that is cytotoxic.[5] It has a high oral bioavailability and is highly protein-bound. Once in circulation, chlorambucil is metabolized by the liver to its active metabolite, phenylacetic acid.[1,5] Phenylacetic acid then is metabolized further to inactive compounds that are excreted in the feces and urine. Side-effects with its use in dogs and cats mainly can involve gastrointestinal upset (vomiting, diarrhea, anorexia), myelosuppression, and alopecia.[1,5,14] In cats, neurological side-effects have been noted, including facial twitching, myoclonus, and seizures.[1,5,14]

Chlorambucil has been evaluated in dogs and cats for adjunctive therapy of several immune-mediated diseases, including canine and feline pemphigus foliaceus (see ch. 204), feline eosinophilic complex, and feline immune-mediated hemolytic anemia (see ch. 198), immune-mediated thrombocytopenia (see ch. 201), and inflammatory bowel disease (see ch. 276).[1,5,14,15] Different protocols exist for the various diseases, with chlorambucil often either administered q 48-72 h, or given q 24 h for 4 consecutive days, repeated every 3 weeks. Unfortunately, strong evidence for its use through controlled prospective trials is lacking.

Cyclophosphamide is a pro-drug that is metabolized by the liver, mainly to two metabolites, 4-hydroxycyclophosphamide and acrolein.[45] 4-hydroxycyclophosphamide is thought to confer the anti-tumor and immunosuppressive activity of cyclophosphamide while acrolein is thought to induce bladder toxicosis with the resultant possibility of sterile hemorrhagic cystitis.[45] Because it has many clinically significant possible side-effects and there are many other safer and effective therapeutic options in dogs and cats, the author does *not* recommend cyclophosphamide for treatment of immune-mediated diseases in dogs and cats.

It is now mainly saved for specific indications in treating cancer.

Applications and Clinical Decision-Making

For spontaneously occurring immune-mediated diseases, initial therapy often commences with glucocorticoid therapy because of its broad efficacy and low cost. In cats, due to an ability to tolerate glucocorticoid therapy without major side-effects, glucocorticoids often are used as a sole therapy. In dogs with severe, life-threatening diseases, such as immune-mediated hemolytic anemia or immune-mediated thrombocytopenia, the author often begins glucocorticoid therapy with another immunosuppressive medication such as azathioprine, cyclosporine, or mycophenolate mofetil. Which other immunosuppressive medication to consider adding to the therapy is often influenced by cost, potential side-effects, and ability to appropriately dose the medication (see ch. 360 for a review of concurrent immune suppression and infection in the same patient). The reason for beginning a second immunosuppressive medication initially in dogs with life-threatening immune-mediated diseases is twofold: to try to suppress the immune system using 2 drugs with differing mechanisms of action, and to decrease glucocorticoid therapy as soon as possible, because dogs can be very susceptible to the side-effects of high-dosage glucocorticoids. In dogs with milder or non-life-threatening immune-mediated diseases, glucocorticoids as a sole therapy can be considered.

If efficacy has been demonstrated for a specific disease using non-glucocorticoid immunosuppression (such as cyclosporine therapy for canine atopic dermatitis), then a sole non-glucocorticoid therapy should be considered as the initial treatment.

If the treatment is effective and well-tolerated, therapy is tapered slowly (often a 25% dosage reduction in only one medication every 3-4 weeks based on clinical response to therapy) to find the lowest effective dosage of medication(s) needed to maintain disease remission. When more than one immunosuppressive medication is being used, the drug which causes the most side-effects and/or is the most expensive usually is decreased first. In dogs, this often means that the glucocorticoid therapy is tapered first because of overt side-effects seen by the owners. Once glucocorticoids are reduced in dosage enough to minimize or eliminate these side-effects, then the other immunosuppressive medication (if one is being used) can be slowly tapered in a similar fashion. Weaning to the lowest effective dosage to maintain disease remission can take months to occur, and in some patients, eventually it is possible to discontinue all medications. If glucocorticoid therapy is used as a sole therapy and substantial side-effects are encountered or the treatment is not successful, then the addition of another immunosuppressive medication in addition to glucocorticoids (or as a replacement for glucocorticoids altogether) should be considered.

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[a]Product label, Atopica for cats, Novartis Animal Health (2011).

CHAPTER 166

Analgesic Therapy

Kristen Messenger

The International Association for the Study of Pain defines pain as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1] Pain can be challenging to diagnose and treat appropriately in small animal medicine due to deficiencies in pain recognition, limited availability of analgesic options, and side-effects of drugs. However, pain assessment and management of clinically apparent or suspected pain is a vital component of patient care. Ch. 126 and 356 review the pathophysiology of acute and chronic pain and its consequences.

Many companion animal diseases present with a painful component that should be treated with appropriate analgesics. When potentially painful diagnostics, such as tissue biopsies, are performed, pre-emptive analgesia should be administered as a component of the sedative or anesthetic plan for the patient. For patients suffering from either severe acute or chronic pain, such as that associated with pancreatitis, multimodal analgesia improves patient comfort. Multimodal analgesia provides a means to treat different steps in the pain pathway to maximize analgesic effects, while at the same time often minimizing overall doses and side-effects of individual drugs.[2] Importantly, the clinician must remember that individual animals will have differing responses to analgesic therapy and therefore repeated pain assessments on the patient are a critical aspect of treatment.

This chapter summarizes basic clinical pharmacology of commonly utilized analgesic drugs in dogs and cats, with the exception of nonsteroidal anti-inflammatory drugs (NSAIDs). For more detailed information on the drugs discussed here, the reader is referred to several other sources[3,4] and ch. 126, 164, and 356. NSAIDs should be included in pain management protocols unless there are specific contraindications to these drugs.

Opioids

The opioids are considered the drugs of choice for treating moderate to severe pain in dogs and cats.[2] The opioids are either naturally-occurring chemicals derived from the poppy plant, or synthetic compounds. These drugs exert their analgesic effects primarily via the mu opioid receptor, although agonist activity at the kappa receptor also results in mild to moderate analgesia. All of the opioid receptors are G-protein coupled receptors, and are located in many tissues in the body. The analgesic responses are primarily via the receptors located in the central nervous system (CNS; brain and spinal cord), although opioids administered into joints provide local effects as well.[5] Analgesic effects are ultimately due to decreases in postsynaptic neurotransmitter release as well as hyperpolarization on postsynaptic neurons.[6] The pure mu opioid agonists, such as fentanyl, have a linear dose-response curve, such that dosing can be titrated to the optimal analgesic effects while minimizing adverse effects. There are currently 3 FDA-approved opioids available for use in dogs and cats in the United States: buprenorphine (Simbadol), fentanyl (Recuvyra), and butorphanol (Torbugesic). Several other opioid drugs are used in extralabel fashion in dogs and cats in the United States (Table 166-1). Simbadol was recently FDA-approved for once daily use in cats. It is administered subcutaneously as a high-dose single injection (0.24 mg/kg).[7]

TABLE 166-1

Commonly Used Opioid Dosages in Dogs and Cats

DRUG	INDICATION	SPECIES, DOSE, ROUTE, COMMENTS	FREQUENCY
Full Mu Agonists			

Fentanyl and remifentanil	Moderate to severe pain from any etiology	Dogs and cats: 2-5 mcg/kg IV, following by CRI: 2-10 mcg/kg/h, adjusted as needed. Transdermal patches available for off-label use in dogs and cats. Transdermal liquid (Recuvyra): 2.7 mg/kg dosage **in dogs only.** These drugs can result in clinically significant respiratory depression and bradycardia.	CRI recommended due to short duration of action. Recuvyra approved only for a single administration.
Hydromorphone		Dogs and cats: 0.05-0.2 mg/kg IV, IM. Emesis is common, in particular after IM administration.	Every 2-4 hours as needed
Oxymorphone		Dogs and cats: 0.05-0.1 mg/kg IV, IM	Every 4-6 hours as needed
Morphine		Dogs and cats: 0.1-0.5 mg/kg IM. Do not administer rapidly IV due to histamine release. Emesis is common. Epidural and intra-articular dosage is 0.1 mg/kg of the preservative-free solution.	Every 2-4 hours as needed
Methadone	Moderate pain. Particularly useful for patients where vomiting is a major concern, i.e., increased intracranial pressure, laryngeal paralysis, myasthenia gravis, etc.	Dogs and cats: 0.2-0.6 mg/kg IV, IM	Every 4-6 hours as needed
Partial Mu Receptor Agonists			
Buprenorphine	Moderate to severe pain from any etiology	Dogs: 0.01-0.03 mg/kg IV, IM; 0.04 mg/kg OTM small dogs Cats: 0.02-0.04 mg/kg IV, IM, OTM. *SC route not recommended due to erratic and poor absorption.	Every 4-8 hours as needed
Kappa Receptor Agonists			
Butorphanol	Mild to moderate pain. Particularly useful for patients where vomiting is a major concern, i.e., increased intracranial pressure, laryngeal paralysis, myasthenia gravis, etc.	Dogs and cats: 0.2-0.4 mg/kg IV, IM. As a partial reversal for full mu agonists: 0.01-0.1 mg/kg IV, slowly, to effect.	Every 1-2 hours as needed
Nalbuphine	Mild pain	Dogs and cats: 0.1-0.5 mg/kg IV; 0.25-1 mg/kg SC, IM. Not commonly used in veterinary medicine.	Every 1-2 hours as needed
Miscellaneous			
Tramadol	Mild to moderate pain	Cats only: 2-4 mg/kg. Cats may become aversive to bitter taste.	Every 6 hours as needed

CRI, Constant rate infusion; *IM*, intramuscular; *IV*, intravenous; *OTM*, oral-transmucosal; *SC*, subcutaneous.

For dosage ranges listed, it is common to administer the lower end of the dosage range IV, while higher dosages are administered via extravascular routes.

Routes of Administration

Oral administration of opioids is generally discouraged due to very limited data on efficacy and absorption.[8] Overall, these drugs are cleared by first-pass hepatic metabolism, resulting in very low systemic bioavailability.[8,9] Despite discouraging data on oral absorption, there appear to be anecdotal reports of the successful use of orally-administered opioids. This author discourages their use until more controlled trial data are available. Oral-transmucosal (OTM) administration of certain opioids such as buprenorphine is feasible for cats and small dogs. The bioavailability of OTM buprenorphine is highly variable, with an average value of 40% in both dogs and cats, thus requiring a high dosage of 0.02-0.04 mg/kg.[10-12] There are

reports of OTM dosages as high as 0.12 mg/kg in dogs.[9]

Recuvyra (fentanyl) represents a novel route of opioid administration in dogs: the topical liquid has been specifically formulated for rapid transdermal absorption. Recuvyra avoids some of the general concerns of prescribing opioids in veterinary medicine such as drug diversion by owners, although it does not necessarily avoid accidental owner or pet exposure. Currently an online training program provided by the sponsor (Elanco Animal Health) is required before a veterinarian can order Recuvyra.[13] Recuvyra is not approved for use in cats and there are currently no published studies on the use of this formulation in cats. Until information is available, this product should not be used in cats. The transdermal administration of fentanyl via patches (e.g., Duragesic) is commonly used in dogs and cats, and provides effective analgesia although systemic absorption is highly variable due to differences in skin thickness, blood flow, and composition.[14,15] Transdermal buprenorphine in patch form has been investigated in dogs and cats, although the results were not encouraging in the pain models tested.[16,17]

The epidural and intra-articular administration of preservative-free morphine provides potent regional and local analgesic effects, while avoiding side-effects associated with systemic administration.[14,18] The reader is encouraged to review other resources for epidural and intra-articular administration of analgesics, and to utilize these techniques in practice.[19-21]

Adverse and Side Effects of Opioids

General side- and adverse effects of opioids can include vomiting, nausea, ileus and constipation, urinary retention, bradycardia, respiratory depression, sedation and dysphoria.[18,22,23] Many of these side-effects are drug- and dosage-dependent. In cats, opioid administration has been associated with hyperthermia, which resolves with supportive care or partial reversal.[14,24-26] Additionally, opioids may have negative immunomodulatory effects, which would be most concerning in critically ill patients.[6] Some of the side-effects of the opioids, including dysphoria, are believed to occur through effects at the delta receptor. Certain opioids are associated with fewer side-effects as compared to others. For example, buprenorphine, a partial mu-receptor agonist, has fewer and less severe side-effects than the pure mu-receptor agonists such as fentanyl. These features make buprenorphine more attractive for clinical use in at-risk patients, such as those with increased intracranial pressure where respiratory depression would be a major concern.

The opioids and their effects, both analgesic and adverse, are fully reversible with opioid antagonists such as naloxone (0.01-0.04 mg/kg). Butorphanol can be used to partially reverse full mu agonists such as fentanyl, thereby maintaining some level of analgesia for the animal.

Tramadol

There is little to no evidence to support the use of tramadol to treat pain in dogs, although there is seemingly widespread use of this drug in veterinary medicine.[8,27] Recent pharmacokinetic studies reveal that dogs do not produce the opioid metabolite of tramadol (M1) that is responsible for the analgesic effects experienced in humans.[8] Other pharmacologic effects of tramadol include the inhibition of norepinephrine and serotonin reuptake,[28] and some of the observed effects in dogs may be related to these actions.[27] In the United States, tramadol is now a Schedule IV drug. With the exception of serotonin syndrome, there are few major side- or adverse effects of tramadol administration in dogs. Contraindications to tramadol administration include the concurrent administration of serotonin and/or norepinephrine reuptake inhibitor drugs, monoamine oxidase inhibitors, or tricyclic antidepressants.[8]

Tramadol may be more effective as an analgesic in cats, with dosages of 2-4 mg/kg PO q 6-12 h as needed, providing analgesia in a feline thermal threshold model.[8,29] Dysphoria and excessive salivation (due to the bitter taste) may be observed after administration.[8]

Alpha-2 Adrenoreceptor Agonists

Dexmedetomidine is the only alpha-2 agonist approved for use in dogs and cats in the United States. Dexmedetomidine is the active isomer of the racemic formulation, medetomidine, and has a high selectivity for the alpha-2 receptor as compared to the alpha-1 receptor.[30] The potent analgesic properties of this drug are primarily through actions at the alpha-2 receptors in the brain and spinal cord. In cats, dosages ranging from 5-50 mcg/kg have provided analgesia in thermal antinociceptive models,[31,32] although it is important to

note that these doses all resulted in profound sedation.[31] Clinically recommended dosages are in the range of 1-5 mcg/kg IV, or as a constant rate infusion of 1-3 mcg/kg/h (Table 166-2). The use of dexmedetomidine in dogs and cats should be weighed against the potential adverse and side-effects, of which there are many including emesis, diuresis, sedation, and transient hyperglycemia.[33] Most notably, the negative effects on the cardiovascular system need to be considered, including hypertension followed by hypotension, bradycardia, and arrhythmias.[34-36] The effects of dexmedetomidine are fully reversible with atipamezole, at dosages of approximately 0.1-0.3 mg/kg IM, although lower dosages are often effective.[4]

TABLE 166-2

Drug Dosages for Other Commonly Used Analgesics in Veterinary Medicine

DRUG	INDICATION	SPECIES, DOSE, ROUTE, COMMENTS	FREQUENCY
Dexmedetomidine	Moderate to severe pain from any cause in generally healthy dogs and cats	Dogs and cats: 1-5 mcg/kg IV, or CRI 1-3 mcg/kg/h with close monitoring	Every 1-2 hours as needed
Ketamine	Acute and chronic pain, neuropathic pain, somatic pain	Dogs and cats: 0.12-0.6 mg/kg/h, adjusted as needed based on analgesia or development of side-effects	CRI
Amantadine	Osteoarthritis, chronic pain	Dogs: 3-5 mg/kg PO Cats: 5 mg/kg PO	Every 12-24 hours
Gabapentin	Neuropathic pain, possibly acute pain	Dogs and cats: 10-20 mg/kg PO	Every 6-8 hours
Pamidronate (a bisphosphonate)	Bone pain	Dogs: 1-2 mg/kg IV over 2 hours Cats: 1 mg/kg IV (no reports of analgesic use in cats)	
Lidocaine (systemic administration)	Moderate to severe pain from any cause; caution in patients with neurologic, severe cardiac, or hepatic disease	Dogs only: 1-2 mg/kg IV; CRI 1-3 mg/kg/h. Neurologic signs will develop if toxic doses are administered. Cardiac effects may include arrest.	Bolus once, then CRI

CRI, Constant rate infusion; *IV*, intravenous; *PO*, per os.

N-Methyl-D-Aspartate (NMDA) Antagonists

Ketamine

Ketamine is a dissociative anesthetic drug that is used at sub-anesthetic dosages to treat a variety of acute and chronic pain conditions, including severe pain associated with pancreatitis or surgery (see Table 166-2).[28,37,38] This drug successfully prevents pain pathway remodeling in the dorsal horn of the spinal cord, thereby reducing the likelihood of the development of chronic pain resistant to traditional therapies.[28] Ketamine has cardiostimulatory effects through endogenous norepinephrine release, although these effects have been best documented at anesthetic dosages.[39,40] Ketamine may have some additional analgesic benefits through anti-inflammatory effects, which have been documented in both controlled research and clinical trials.[39,41,42] Ketamine should be administered as a constant rate infusion (CRI) to be most effective, thus requiring frequent observation and hospitalization.[28] Although there are very limited veterinary data, the administration of sub-anesthetic doses of ketamine in dogs and cats is associated with few side-effects or contraindications. The drug is metabolized by the liver to norketamine, which possesses some anesthetic activity. In dogs, norketamine undergoes further metabolism, but in cats a large amount of norketamine is excreted unchanged by the kidneys.[43] Ketamine should be used cautiously in cats with severe kidney injury/disease due to the possibility of drug accumulation and enhanced or prolonged effects secondary to the active metabolite norketamine. High dosages of ketamine may result in dysphoria and hallucination, which can be mitigated by discontinuing or reducing the rate of administration as well as by administration of an appropriate sedative.

Methadone and Dextromethorphan

Both of these drugs have weak activity at the NMDA receptor, and studies in humans suggest that both of these agents possess analgesic activity.[28] There are few veterinary studies demonstrating significant analgesic effects in dogs and cats. Methadone is a pure mu-opioid agonist with other pharmacological mechanisms including inhibition of serotonin and norepinephrine reuptake.[44]

Amantadine

Amantadine is an antiviral agent, but has weak activity at the NMDA-receptor as well as good oral absorption in people.[28] Amantadine appears to be well-absorbed following oral administration in dogs and cats[8,45,46] although plasma concentrations corresponding to analgesic effects are not known. There are reports of the successful use of amantadine as an adjunctive analgesic in dogs and cats, with few to no adverse effects.[45,47,48]

Gabapentin

Gabapentin was originally developed and used as an anti-epileptic drug, but was found to have analgesic benefits in people suffering from certain painful conditions, in particular neuropathic pain[28] and more recently acute postoperative pain.[49,50] Gabapentin is a structural analog of GABA; however, it does not interact with GABA receptors or influence endogenous GABA activity. The primary mechanism of action is currently believed to be via inhibition of voltage-gated calcium channels through binding at the alpha-2-beta subunit on these channels,[51,52] although it has been suggested that gabapentin has activity at a variety of other receptors.[28] The use of gabapentin as an analgesic in veterinary medicine has had mixed results. In dogs, gabapentin at a dosage of 10 mg/kg PO per day was not found to improve pain scores following forelimb amputation,[50] but anecdotally gabapentin is believed to be an effective adjunctive analgesic for chronic or neuropathic pain (see Table 166-2).

Pharmacokinetic studies on gabapentin administration in cats have been reported[53] and simulations using data in these studies have recommended dosage regimens of 3-8 mg/kg PO q 8 h to achieve target plasma concentrations that are considered effective in people.[54] Pharmacodynamic data in cats have shown that gabapentin was not effective in a thermal stimulus model of pain, with the drug achieving plasma concentrations between 1-10 ng/mL following oral administration of 5 and 10 mg/kg.[54]

Bisphosphonates

The bisphosphonates include zoledronic acid, tiludronic acid, and pamidronate. These compounds bind to hydroxyapatite in bone and ultimately reduce bone resorption and destruction through the inhibition of osteoclast activity.[55] There is very limited evidence that bisphosphonates may be beneficial in the treatment of pain-associated osteoarthritis and bone cancers in dogs.[55] These compounds are administered as an intravenous infusion (see Table 166-2). In people, there have been reports of bisphosphonate-associated osteonecrosis and renal toxicosis, although adverse effects of these drugs in dogs and cats are largely unknown.[56,57]

Local Anesthetics

A full discussion on the use of regional and local anesthesia is beyond the scope of this chapter; however, these techniques can be of immense benefit in the management of pain in dogs and cats. For example, a sacrococcygeal epidural can be quickly and safely performed in cats suffering from urethral obstruction in order to provide potent analgesia with little to no systemic adverse effects.[58] A description of local anesthetic techniques and indications can be located in several previously listed resources.[20,21] Lidocaine transdermal patches (Lidoderm) have been investigated in dogs and cats, and although there is systemic uptake of lidocaine, the analgesic benefits are likely minimal.[59,60] However, the systemic administration of lidocaine has been advocated for use as both an analgesic and antiinflammatory in dogs (see Table 166-2), but should not be administered to cats due to risk of toxicosis.[36,61] The *systemic* administration of local anesthetics other than lidocaine is contraindicated due to concerns of neuro- and cardiotoxicosis, and risk of death.

Neurokinin-1 Receptor Antagonists

Maropitant is an NK-1 receptor antagonist that is approved in the United States as an antiemetic in dogs and cats. There is very limited evidence that maropitant may provide analgesia for visceral pain in dogs.[22] At this time, further studies are needed before a general recommendation can be made for the use of this drug as an analgesic.

Adjunctive Analgesics for Chronic Pain and Future Directions

Several "nontraditional" analgesic compounds have been utilized as adjunctive treatments for chronic pain. These drugs include antidepressants belonging in the tricyclic antidepressant or selective serotonin (and norepinephrine) reuptake inhibitor classes.[8] The reader is referred to ch. 126 and 356 for information regarding comprehensive management of pain, and to a recent review article.[8] Researchers and pharmaceutical companies are investigating novel therapeutics to treat pain in dogs and cats. Currently these products are still undergoing trials, but promising therapeutics include monoclonal antibody therapies such as anti-nerve growth factor, which is known as tanezumab in human medicine.[62] Toxins targeting specific nerve fibers and ion channels, such as resiniferatoxin, are still undergoing research although there is growing evidence for the clinical use of this compound in veterinary medicine.[63]

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CHAPTER 167

Antioxidants, Nutraceuticals, Probiotics, and Nutritional Supplements

Laura Eirmann

Advances in the understanding of companion animal nutrient requirements and in food science technology allow pet owners to feed complete and balanced diet formulations that meet the animal's nutrient requirements throughout various life stages and often to meet specific needs of an individual. Moving in parallel to these improvements, interest among pet owners regarding the benefits of dietary supplements and nutraceuticals continues to emerge. Although it does not apply to products intended for animals, the Dietary Supplement Health and Education Act (DSHEA) of 1994 defines a dietary supplement as a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, mineral, herb or other botanical, amino acid, dietary substance for use by man to supplement the diet by increasing the total dietary intake or a concentrate, metabolite, constituent, extract, or combination of these ingredients.[1] The National Research Council publication, *Safety of Dietary Supplements for Horses, Dogs, and Cats,* defines an animal dietary supplement as "a substance for oral consumption by horses, dogs, or cats, whether in/on feed or offered separately, intended for specific benefit to the animal by means other than provision of essential nutrients for intended effect on the animal beyond normal nutritional needs, but not including legally defined drugs."[2] There is no legal definition of the term nutraceutical in the United States. It is a portmanteau of "nutrition" and "pharmaceutical" coined by a physician and generally applied to dietary supplements intended for specific therapeutic effects.[3] It is important to recognize that dietary supplements and nutraceuticals are not required to undergo a premarket approval process with the U.S. Food and Drug Administration (FDA) before being sold to the public.

An estimated 10-33% of dogs and cats in the United States are fed a dietary supplement.[2,4,5] However, despite the considerable interest in dietary supplements, knowledge about their efficacy, modes of action, and safety often is lacking. With the myriad products and supplements currently available, veterinarians often are asked by clients to comment on a specific product or to make a recommendation. It is important to obtain an understanding of dietary supplements and to develop a systemic and scientific approach to assess patients and products before making a recommendation. A comprehensive discussion of all dietary supplements is beyond the scope of the chapter. This review, while not exhaustive, will provide a brief overview of the regulatory aspects of dietary supplements marketed for companion animals in the United States and provide guidelines for veterinarians to facilitate accurate assessment and when possible to make sound recommendations supported by studies published in the peer-reviewed scientific literature. A very brief introductory overview of two categories of dietary supplements, antioxidants and probiotics, will be presented.

Regulatory Aspects

Food and drugs for either humans or animals are regulated in the United States under the Federal Food, Drug, and Cosmetic Act (FFDCA) of 1938. Responsibility for enforcing all aspects of the FFDCA that could apply to use in animals rests with the Center for Veterinary Medicine (CVM) of the FDA. The legal distinction between a "food" (an item consumed primarily for taste, aroma, or nutritive value) and "drug" (an item intended to treat or prevent disease or affect structure or function of the body) largely depends on the intended purpose or claims made by the manufacturer or distributor.[3] The DSHEA sets a regulatory framework for dietary supplements marketed for humans that allows a "nutrition support statement" related to "structure-function" claims, but requires a disclaimer that the supplement has not been evaluated by the FDA and that "the product is not intended to diagnose, treat, cure, or prevent any disease."[1] This Act opened

the possibility of certain types of claims (i.e., structure/function claims) to be made without having scientific evidence submitted to the FDA prior to marketing. However, in 1996, the CVM published a notice that the DSHEA does not apply to products intended for use in animals and therefore "dietary supplements for animals are not recognized as a class of products."[6] Under the FFDCA, products marked as dietary supplements for use in animals are classified as either foods or drugs depending on their intended use. For reasons beyond the scope of this chapter, most animal health supplements are considered drugs of low regulatory priority.[7] It behooves the veterinary clinician to understand that some products on the market might not comply with applicable law and could contain unapproved ingredients or make unsubstantiated claims, and that "extralabel" use only applies to approved drugs.[3]

General Guidelines for Dietary Supplement Selection

For legal and ethical reasons, the veterinary clinician must make a critical evaluation before recommending a dietary supplement or nutraceutical. This begins with a complete patient history, including open-ended questioning regarding dietary supplement usage. Up to 70% of human patients do not report supplement use to their physicians.[8,9] Pet owners might not mention these products when asked about medications or could be reluctant to mention alternative therapies not prescribed by the veterinarian. Nevertheless, survey studies report supplement usage ranging from 13-38% for veterinary patients with heart or kidney disease.[10-12] Given the potential for adverse events associated with supplement usage and potential for supplement-drug interactions, this information is critical.

As with any veterinary recommendation, the clinician must first establish an accurate diagnosis. An owner may inquire about a supplement for "joint health" when the patient does not have a condition that warrants this particular supplement. If the veterinarian determines that a particular dietary supplement may be beneficial to the patient, specific product selection is the next step. The acronym PETS has been used for making a product assessment and can be used for assisting discussions with clients about a particular supplement.[13] The key points are summarized as follows:

- Product Quality (P): The manufacturer should be able to provide adequate information about a specific product to assist the veterinarian in assessing product quality. The product must contain an appropriate amount of the substance of interest for both safety and efficacy. Unfortunately, there are examples of products that are mislabeled or do not contain the ingredient listed on the label.[14] The label should be accurate and include information such as a list of ingredients, intended use of the product, adequate directions for use, lot number, expiration date, and manufacturer information. The manufacturer should utilize Good Manufacturing Principles and be willing to provide information regarding quality assurance such as ingredient and final product testing. A specific nutraceutical may require enteric coating, encapsulation, or specific packaging or storage conditions. More detailed questions for manufacturers of nutraceutical products can be found elsewhere.[7] Third party resources may also provide the veterinarian with information regarding a specific product's quality. A non-profit trade organization, the National Animal Supplement Council (www.nasc.cc), offers a voluntary program that provides animal supplement manufacturers with guidelines for product quality assurance, adverse event reporting, and labeling standards. Successful completion of this program allows the member company to display the NASC Quality Seal on their products, website, product literature, and advertisements. Additional third party resources include the U.S. Pharmacopeial Dietary Supplement Verification Program and ConsumerLab.com.
- Efficacy (E): Efficacy, defined as a desired biological response, of any therapy is established by scientific testing. First the compound of interest must be present in a form that is bioavailable to the pet. For example, the oral bioavailability of chondroitin sulfate in dogs increases with decreasing molecular weight.[15] Demonstrating efficacy of a nutraceutical substance requires rigorous and often expensive testing depending on the extent to which claims for a product are being made and the regulatory environment surrounding that substance. Manufacturers should be asked to provide supportive documentation of efficacy. Critical evaluation of studies is required. It is important to ensure the studies were conducted in the target species using the same dosage and form of active ingredient with the same product formulation. The study should be blinded and include an appropriate control group, although it must be recognized that such robust evidence does not always support currently existing recommendations in many aspects of veterinary medicine. Determining if the studies were published in peer-reviewed journals and if the results are applicable to the specific patient being evaluated is also important. Clinicians should be cautious of product support and marketing based solely on testimonials or poorly designed studies.

- Tolerance (T): Tolerance for any nutraceutical or supplement must exist for it to be effective. The treatment plan must be acceptable to the pet owner and patient. For instance, the number of tablets to achieve efficacy and route of administration must be achievable for that client and patient.
- Safety (S): Safety is paramount and must be known before using a dietary supplement. Historical data on usage of certain substances can provide practical information regarding safety. The margin of safety (difference between effective dosage and maximum safe dosage) might or might not be known. Using a particular supplement in the absence of any published safety data in the target species is particularly risky and caution is advised. Safety must be evaluated with regard to the specific patient's medical condition and concurrent treatments. Supplement-drug interactions must be considered. Pet owners are sometimes under the erroneous assumption that "natural" is always "safe." Client education including a discussion of known data, knowledge gaps, and controversies will help enable the owner to make an informed decision.

Select Nutraceuticals of Interest

Antioxidants

Reactive oxygen species (ROS) are ubiquitous and highly reactive in biological systems. They are associated with oxidation-reduction reactions, energy metabolism, biosynthesis, cell signaling, and body defense and detoxification mechanisms. Their reactivity can be beneficial due to oxidative burst reactions and other mechanisms that characterize neutrophil and other inflammatory cell functions. They are produced not only as a result of normal metabolism but also by exposure to environmental stressors including UV radiation, pollutants, and certain chemical agents. When present in excess, oxidative damage and destruction of normal cell membranes and cell function occurs. The ROS are capable of reacting with all biologic molecules including nucleic acids, proteins, carbohydrates, and lipids. Continued oxidative damage is thought to be part of the pathogenesis of many conditions including cancer, degenerative conditions such as arthritis, and the aging process including cognitive decline.

Because of the potential adverse effects of ROS, cell systems utilize numerous antioxidant mechanisms to inhibit oxidative damage and quench the formation of free radicals. These systems include: direct interaction with reducing agents (e.g., vitamin C, glutathione); free radical scavenging (vitamin E, vitamin C, carotenoids, superoxide dismutase); reduction of hydroperoxides (e.g., glutathione peroxidase, catalase); removal of transition metals by protein binding (e.g., ferritin, ceruloplasmin, and other chelators); prevention of reactive oxygen from reaching specific sites; and even repair of oxidative damage.[16]

Because free radicals arising from metabolism or environmental sources interact continuously in biologic systems, the oxidants and antioxidants are in a continual utilization and replenishment cycle that must be balanced to minimize cellular and tissue damage. This makes antioxidant supplementation to augment endogenous antioxidant systems a potential intervention strategy. For instance, decreased hepatic glutathione concentrations have been demonstrated in naturally-occurring liver disease[17] and supplementation with S-adenosylmethionine (SAMe), a glutathione precursor, has been shown to be beneficial to dogs and cats with acetaminophen intoxication.[18,19]

The selection of the correct type, dosage, and/or combination of antioxidants to ameliorate such a complex biological system is challenging. For example, the specific SAMe product utilized in the acetaminophen reports contains 74% of the biologically active SAMe stereoisomer whereas a different SAMe product may contain much less.[20] Certain antioxidants can act as pro-oxidants at certain levels or under certain biological conditions.[21] Some treatment modalities rely on oxidative damage, so supplementation with antioxidants during the specific treatment phase may not be optimal. Therefore, the clinician needs to evaluate the patient, the treatment plan, and the scientific literature regarding safety and efficacy of particular antioxidant or antioxidant combination before making a specific recommendation.

Probiotics

The Food and Agriculture Organization of the United Nations and the World Health Organization define probiotics as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host."[22] They are often lactic acid bacteria and include strains of *Enterococcus, Streptococcus, Bifidobacterium,* and *Lactobacillus* spp. The mechanism of action is complex and likely multifactorial.[23] This is not surprising given that the microbiota composes 90% of the total cells in the mammalian body. Only recently have newer sequencing and bioinformatics technology provided better insight regarding the vast

numbers and diversity of the intestinal microbiota.[24] This research is uncovering a highly complex, diverse intestinal ecosystem that is unique to the individual and differs along the gastrointestinal tract.[25] A better understanding of the intestinal microbiome, its influence on health and disease within and beyond the gastrointestinal tract, and potential for probiotics to modulate the complex interactions between microbiota and host are areas of active research in human and veterinary medicine. Evidence supports the use of specific probiotic organisms in certain human populations for defined disease conditions including necrotizing enterocolitis, antibiotic-associated diarrhea, and pouchitis with expert panels convening to review the research and provide specific recommendations for probiotic use in humans.[26]

Research elucidating the canine and feline microbiota and the potential benefit of probiotics is ongoing and promising. However, the complexity and current limited data make recommendations challenging. It behooves the clinician to use the same general guidelines and "PETS" approach described above when considering a probiotic for a patient. Commercial products have a large variation in quality control.[23] Assessment of product quality includes evaluating the product label. The label should include a guaranteed analysis stating the number of live probiotic bacteria, a list of the specific genus, species, and strain, and an expiration date.[27] Unfortunately, previous studies have shown that many commercially available products contain labeling errors, including failure to list specific microorganisms, misspellings, and failure to list expected bacterial numbers.[14,28] Furthermore, comparison of actual content versus label claims demonstrated some products did not meet viable organism claims, contained organisms without probiotic effect, or contained potentially pathogenic organisms.[14,28] The veterinarian should select a probiotic from a reputable manufacturer and ask questions regarding product quality, including manufacturing practices and stability studies to ensure the probiotic survives production, storage prior to consumption, and passage through the gastrointestinal tract. Safety is of utmost concern. Safety includes testing for virulence and antibiotic-resistance genes as well as patient tolerance. Caution is advised when considering probiotics in patients with marked intestinal mucosa compromise, or those who are immune-compromised or critically ill.[23] Adverse events associated with any dietary supplement should be reported. Current evidence of efficacy is minimal and at times conflicting but there is a growing body of data in the peer-reviewed literature especially regarding gastrointestinal health[29-37] and immune modulatory effects[38-43] of probiotics in dogs and cats. Study design should be critically evaluated and outcome measures should be relevant to the clinical patient. It is realistic to anticipate that with future scientific research using well-designed placebo-controlled blinded studies with proper sample size and study duration, recommendations will become more refined and targeted to specific probiotic strains that impart a desired biological effect to address specific conditions in a defined cat or dog population.

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CHAPTER 168

Compounding Drugs

Ron Johnson, Dinah G. Jordan

One of the greatest challenges to veterinarians can be the availability of appropriate drug dosage forms that enable easier and more accurate dosing of patients and improve owner compliance. Although advances have been made with new drugs and dosage forms approved for veterinary medicine, clearly there remains a need for additional drug formulation options. As such, drugs approved in one animal species are frequently used in another species, including human-approved drugs. Compounded medications have not undergone the rigorous approval process where they are tested for safety, efficacy, and stability. Practitioners must ensure that the administration of compounded drugs to veterinary patients is justifiable, not driven by economics, and is based on meeting an individual patient need that cannot be met by a commercially available, approved product (Box 168-1).

Box 168-1

General Recommendations for the Use of Compounded Medications in Companion Animals

1. The use of compounded veterinary preparations should be based on rational drug therapy determined by a licensed veterinarian within the confines of a valid veterinarian/client/patient relationship.
2. Compounded preparations may be necessary when: (i) a legitimate medical need exists, such as suffering or death resulting from a lack of treating the affected animal, (ii) an appropriate dosage regimen does not exist for the species, size, age, or medical problem of the intended animal or (iii) there is no marketed approved animal or human drug available, whether employed in a labeled or extralabel manner, to treat the condition, or there is reason to believe the approved drugs will not be efficacious or safe in the intended animal.[4]
3. Compounded preparations may be dispensed by a licensed veterinarian for patients within his/her practice. Veterinarians should seek the services of a reputable compounding pharmacy when the complexity of the compounded preparation exceeds the experience, training, equipment and/or facility of the veterinarian.
4. Compounded preparations may be dispensed by a licensed pharmacist for an individual veterinary patient pursuant to valid prescription in accordance with state and federal laws.
5. FDA-approved veterinary and human products should be used for compounding in accordance with AMDUCA whenever commercially available and medically appropriate. In the absence of an appropriate FDA-approved product, APIs should be obtained from a facility registered with the FDA when possible or other reliable source if no FDA-registered site is available. All APIs should be accompanied by a Certificate of Analysis.
6. Compounded drugs dispensed by a veterinarian or pharmacist must be labeled in accordance with the extralabel use provisions of AMDUCA and all applicable state laws and regulations.[3] The required information includes, but is not limited to, patient identification, date dispensed, name of all active ingredients, quantity dispensed, directions for administration, prescriber/pharmacist identification, address of veterinary clinic or pharmacy, auxiliary and caution labels, lot number and beyond-use date. Adequate records of dispensed compounds (including formulas) must be maintained by the dispensing pharmacist or veterinarian.
7. Compounded preparations should be patient-specific and not available for "resale," which implies repackaging and/or relabeling.

8. Veterinarians may legally maintain non-patient-specific "office use" veterinary compounded preparations in some states.
9. The veterinarian should establish objective parameters for monitoring patients, which will indicate whether the compounded medication is clinically effective, subtherapeutic or toxic.[11]
10. The prescribing veterinarian and/or dispensing pharmacist should report any suspected adverse events associated with the use of compounded veterinary preparations.

Veterinary Compounded Drugs: Regulations

Compounding in veterinary medicine remains a topic of regulatory attention and indecision. Compounding is defined by the United States Pharmacopeial Convention as "the preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice."[1] While traditional compounding is regulated primarily at the state level, the United States Congress passed the Compounding Quality Act (Title I, Drug Quality and Security Act of 2013), which addressed many compounding issues in human medicine. This statute, however, pertains only to compounding for human patients and does not address regulations for non-human species.[2]

One of the most glaring and controversial issues regarding veterinary compounding is the ability to compound veterinary medications from bulk substances, also referred to as active pharmaceutical ingredients (APIs). The Animal Medicinal Drug Use Clarification Act (AMDUCA) legalized compounding for veterinary patients from approved veterinary and human products with few restrictions for non-food animals.[3,4] The Act, however, did not include language that specifically included compounding from APIs. The Center for Veterinary Medicine, Food and Drug Administration (FDA) has long held the position that this form of compounding for animals is illegal although necessary in some cases.

Veterinarians and pharmacists acknowledge that there are clearly medications for veterinary patients that must be compounded from bulk substances, including, but not limited to potassium bromide, cisapride, metronidazole benzoate suspension, diethylstilbestrol, transdermal formulations, some poison antidotes and drugs that are currently unavailable due to manufacturer backorders or that are no longer commercially available. The legality of veterinary compounding from APIs has been a longstanding debate among pharmacists, veterinarians, veterinary drug manufacturers, and the Center for Veterinary Medicine and has been the subject of lawsuits filed in the U.S. federal court system.[5,6] It seems absurd that medications for human patients can legally be compounded from APIs, but not for non-human species. On the other hand, it is well known that some compounding pharmacies have generated large amounts of unapproved drugs for veterinary use that are largely copies of FDA-approved drugs, and veterinarians have bought them for their clinic inventory. These practices constitute attempts to bypass the drug approval process and can be construed as illegal manufacturing disguised as compounding.

Another compounding issue that warrants regulatory resolution is the need for veterinarians to buy non-patient-specific compounded medications (stock medications) from compounding pharmacies (anticipatory compounding) not only for administration to patients while they are in the clinic, but also for administration after the patient is discharged to avoid interruption of therapy. These medications may be more complex compounds, such as sterile ophthalmic solutions or ointments. Most veterinarians lack pharmacy experience or training and do not have facilities or equipment for compounding beyond simple reformulations of non-sterile medications; therefore, it is rational for a veterinarian to purchase "office use" preparations from a compounding pharmacy. However, while some states allow "office use" compounds, others do not. The dilemma arises when a veterinarian needs to dispense a medication previously compounded by a pharmacy, which would involve relabeling and perhaps repackaging the medication. This practice is deemed "resale," and is not allowed in most states. Note: California and Virginia are, at the time of publication, the only two U.S. states that allow veterinarians to dispense an emergency 72 hour supply of "office use" compounds.[7,8]

These and other unresolved issues in veterinary compounding resulted in the formation of a Task Force on Veterinary Compounding Legislation by the American Veterinary Medical Association in 2014. The Task Force will examine such issues as "maintaining office stock, compounding from bulk ingredients, adverse event reporting, and quality assurance. They will also consider the role that drug shortages and the preservation of the Food and Drug Administration's approval process play in the access to compounded preparations."[9]

Veterinarians should keep up with current regulatory information regarding veterinary compounding as

the regulatory process evolves. Professional veterinary organizations, along with published literature in reputable journals, represent valuable sources of information on compounding for animals that may assist the veterinarian with the complex and often confusing regulatory environment surrounding veterinary compounding.

Understanding Risks Versus Benefits With Compounded Drugs

Pharmaceutical Issues

Compounding by veterinarians and pharmacists is not equivalent to the formulation of commercially manufactured products by appropriately registered manufacturing pharmaceutical firms. Whether by a pharmacist or a veterinarian, compounding must therefore be done only within the compounder's level of experience, training, equipment and facility. A compounded drug must possess adequate purity, potency and demonstrate stability (shelf-life) to maintain acceptable bioavailability (extent of systemic drug absorption) of the active pharmaceutical ingredient, but not produce toxicosis or an ineffective preparation. Vehicles used in the formulation process can alter drug concentration. For example, vitamin/mineral liquids and some forms of molasses that contain iron, although palatable for many pets, are not good choices for compounding vehicles, as they may chelate the active drug ingredient and render it ineffective. Alterations in pH caused by combinations of active and inactive ingredients, when protective tablet coatings are disrupted or liquids are added, can also result in loss of active drug in a formulation. Evidence of potential loss of active drug and instability of compounded formulations includes color changes that can indicate oxidation, separation of product phases or signs of cloudiness or precipitation in liquid dosage forms, or cracking, swelling or release of odors in solid dosage forms.[10] There may also be no visible evidence of deactivation of the drug. Manipulations of the dosage form can also result in contamination of a sterile product meant for injection or affect drug bioavailability through alterations in drug-release rates. In general, the more extensive the manipulation of a drug preparation from its original formulation the greater the chance that drug efficacy will be compromised.

Because drug pharmacokinetics, safety and efficacy have not been determined for most compounded preparations, and are likely not to be, it is important for the veterinarian to establish objective parameters which will indicate whether the compounded preparation is efficacious, subtherapeutic or toxic.[11] Objective parameters can include hematologic or clinical chemistry changes, serum drug levels when drug monitoring is available, and clinical signs and clinical end-points.

While compounding from the finished formulation of an approved drug is recommended whenever possible, there are circumstances in small animal practice that warrant compounding from an API. Approved drugs may not be available commercially due to backorder or withdrawal from the human market, e.g., cisapride for the treatment of gastrointestinal disorders in cats. In other cases, there has never been an approved drug formulation containing the required ingredient, e.g., potassium bromide for seizure control. Finally, approved drug formulations may be unacceptable for veterinary compounding for various reasons. A pet may have an intolerance for an ingredient in the commercial product, such as the xylitol content in some human-approved products when compounding for dogs. Furthermore, excipients in commercial products are not desirable when compounding transdermal medications. When APIs are needed to compound veterinary preparations, it is critical that the ingredient source be known and that all components of the compounded formulation meet either United States Pharmacopeia (USP), National Formulary (NF), Food Chemicals Codex (FCC) standards or another high-quality source such as analytical reagent or certified American Chemical Society, and be obtained from a facility that is registered and inspected by the FDA whenever possible.[12] If such a facility is not an option, the compounder should use professional judgment in locating a reliable source for the needed chemical based on the company's reputation and its willingness to provide a Certificate of Analysis for its chemicals.[12]

Transdermal Delivery of Drugs

Systemic delivery of drugs using the transdermal route is a convenient method of administering some medications to pets, especially feline patients that have an aversion to orally-administered drugs. While some drugs are suitable for this delivery system, others are not for a variety of reasons. First, a medication must be able to cross the skin and be absorbed into the systemic circulation. Absorption of drug via the transdermal route is primarily passive. As such, ideal drug molecules for this route of delivery are low molecular weight (<400 Daltons), lipophilic in nature, and soluble in both water and oil.[13] Although chemical penetration

enhancers such as pluronic lecithin organogel, Lipoderm, and dimethylsulfoxide may be used in formulations to enhance absorption, there are limitations to what can be accomplished with these agents. Based on studies performed in cats, overall systemic bioavailability for transdermal preparations is low, compared to the oral route; and it takes longer for transdermal medications to reach therapeutic blood levels, if at all.[14]

Second, the dosage of the drug is also a consideration in transdermal therapy. The maximum dosage that can be absorbed on the inside pinna of a cat is approximately 25 milligrams due to limited surface area.[14] Larger dosages are not good candidates for transdermal delivery. Generally, drugs that can be considered for transdermal administration are those that meet the criteria above and have a wide margin of safety and objective monitoring parameters. They are also more often effective in chronic therapy versus acute therapy when it is important to rapidly achieve therapeutic blood levels. Drugs that cannot be recommended for transdermal administration include, but are not limited to, those that are locally irritating to the pinna, toxic to humans or other pets in the household, or have a narrow therapeutic index.

Adverse events can also occur in pets whose owners are undergoing compounded transdermal therapy. Canine alopecia secondary to human topical hormone replacement therapy has been documented in the scientific literature and reported clinically.[15] Compounding antibiotics for transdermal delivery is also not recommended because of the potential for developing resistance due to unreliable blood drug levels. Prodrugs that must be activated by gut enzymes cannot be applied transdermally, since they bypass the gastrointestinal tract. The transdermal route of drug delivery provides for several advantages including owner compliance, patient tolerance, ease of administration and most importantly the ability to bypass first-pass metabolism by the liver.[13,16] However, the skin is also capable of metabolizing drugs.

Compounding by the Veterinarian and Pharmacist: Roles and Responsibilities

It is the responsibility of the veterinarian, as the prescriber, to determine the appropriate drug therapy and dosage. When a compounded medication is needed, the prescribing veterinarian must then decide whether to compound the medication in the clinic or seek the services of a compounding pharmacist. In making this decision, veterinarians should consider whether they have adequate training and experience, appropriate equipment and an adequate facility for compounding, and whether they are covered by their liability insurance carrier should there be a problem with the compound that causes harm to the patient. If the veterinarian decides to prescribe or outsource the medication, he/she should use care in choosing a compounding pharmacy. Veterinarians should ask the following questions:

1. **Is the compounding pharmacy accredited by the Pharmaceutical Compounding Accreditation Board (PCAB)?** Accreditation by this body indicates that the pharmacy has successfully completed an inspection by an independent non-profit organization and meets nationally accepted standards for quality assurance, licensure, and staffing. The accredited pharmacy must demonstrate compliance with USP Standards for Compounding (see section titled "What Is USP?").
   If the pharmacy is not PCAB accredited, additional questions should be asked:
   i. **Does the pharmacy have the appropriate licensure in the state where the medication is to be shipped?** Some states also require that the pharmacy staff include a pharmacist licensed in the state where the medication is to be shipped.
   ii. **Does the pharmacy comply with USP guidelines for assigning beyond-use dates?** (See section titled "What Is USP?")
   iii. **Does the pharmacy provide documentation to support any beyond-use date that exceeds USP guidelines?**
2. **Is there a pharmacist on staff that has specific training in veterinary pharmacy?** This question is very important, since compounds designed for human patients may not be safe for use in pets. Some of the organizations that offer training in veterinary pharmacy and/or veterinary compounding are as follows: Society of Veterinary Hospital Pharmacists, American College of Veterinary Pharmacists, International Academy of Compounding Pharmacists, and Professional Compounding Centers of America.

What Is USP?

Primary areas of concern for veterinarians who prescribe compounded medications are formulation, purity and stability. Veterinarians may hear pharmacists cite USP standards when addressing various recommendations or requirements (both legal and ethical) regarding compounded medications, such as

quality control issues or assigning beyond-use dates. The United States Pharmacopeia (USP) is a compendium legally recognized by the Federal Food, Drug, and Cosmetic Act, that contains standards for drugs, including determination of strength, quality and purity. It is published by the United States Pharmacopeial Convention and revised periodically. The compendium also contains standards for compounding sterile (USP <797>) and non-sterile (USP <795>) medications.[12,17] It contains compounded preparations monographs that include formulas (ingredients and quantities), specific directions to correctly compound the particular preparation, packaging and storage information, labeling information, pH, beyond-use dates based on stability studies, and detailed assays (majority of monographs).

Beyond-use dates are an important consideration when compounded medications are prescribed, especially oral liquids and injections. The USP has published guidelines for both sterile and non-sterile compounded medications (see section on Guidelines for Assigning Beyond-Use Dates for Compounded Preparations). Veterinarians should ask compounding pharmacies for documentation to support beyond-use dates that exceed USP guidelines.

In the U.S., compounding is regulated primarily at the state level through the state boards of pharmacy, and most states now include USP guidelines in their pharmacy practice acts, making the standards legally binding in those states.

Guidelines for Assigning Beyond-Use Dates for Compounded Preparations

The USP has developed guidelines for assigning beyond-use dates to compounded preparations. The term "expiration date" is the date beyond which a commercial product should not be used and is assigned by the manufacturer based on analytical testing and defined storage conditions. On the other hand, a "beyond-use date" is the date after which a compounded preparation should not be used and is determined from the date the preparation is compounded. It should be based either on stability information that is applicable to a specific drug formulation or on USP guidelines in the absence of chemical and physical stability data for a specific formulation. See table below.

COMPOUND CLASS	BEYOND-USE-DATING AND STORAGE
Non-sterile, nonaqueous formulations	180 days, controlled room temperature (20-25° C)
Non-sterile, water-containing oral formulations	14 days, controlled cold temperature (2-8° C)
Non-sterile water-containing topical/dermal, mucosal liquids and semi-solid formulations	30 days, controlled room temperature
Sterile compounds* prepared from sterile ingredients	48 hours controlled room temperature, 14 days controlled cold temperature, 45 days frozen (<–10° C)
Sterile compounds* prepared from non-sterile ingredients	24 hours controlled room temperature, 3 days controlled cold temperature, 45 days frozen

*Sterile compounds include the following: Compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals, including but not limited to the following dosage forms that must be sterile when they are administered to patients: aqueous bronchial and nasal inhalations, baths and soaks for live organs and tissues, injections (e.g., colloidal dispersions, emulsions, solutions, and suspensions), irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants.

United States Pharmacopeia General Chapter <795>: Pharmaceutical Compounding—Non-sterile Preparations, USP37/NF32, 2014; United States Pharmacopeia General Chapter <797>: Pharmaceutical Compounding—Sterile Preparations, USP37/NF32, 2014.[12,17]

The compounding of sterile preparations (including ophthalmic preparations, injections) requires strict adherence to the provisions of *USP <797> Pharmaceutical Compounding—Sterile Preparations*.[17] This form of compounding carries a much higher risk for causing harm to the patient if the preparation is contaminated. For sterile compounds assigned beyond-use dating longer than those indicated by USP <797> standards, the pharmacy must conduct its own sterility testing based on sample size requirements defined in *USP Chapter <71> Sterility Tests* using commercially available media.[18] These sterile compounds are quarantined for 14 days while awaiting test results. If a test result is positive, the sample is sent to the microbiology laboratory for identification and speciation of contaminants.

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CHAPTER 169

Adverse Drug Reactions

Wayne Stanley Schwark

Client Information Sheet: Adverse Drug Reactions

Overview

Drugs manufactured by pharmaceutical companies are submitted to regulatory agencies for human or veterinary use approval. To gain such approval, every drug must satisfy two key criteria: be efficacious and lack toxicity. Initial studies in the approval process are usually based on experimental protocols or clinical trials on relatively limited numbers of individuals. Following approval, when the drug is being used in huge numbers of individuals, unexpected adverse events not detected during the approval process may become apparent. These adverse events are of two major types: (1) the drug may lack effectiveness in a subset of patients or (2) unpredicted and serious toxic events may be observed. While any drug may have undesirable (or desirable) side effects, the "unexpected toxic effects" are worse than those associated with predictable unwanted actions. For the purposes of this chapter, adverse drug reactions (ADRs) and drug toxicity will be considered synonymous.

In the United States, the Center for Veterinary Medicine (CVM), a division of the Food and Drug Administration, has been compiling adverse drug events submitted by veterinarians, drug manufacturers and animal owners since 1987. This process, whereby drugs are monitored in order to detect, assess, understand and hopefully prevent adverse drug effects is called pharmacovigilance.[1,2] The online resource extends beyond those drugs specifically approved for use in dogs and cats and includes drugs manufactured for people that are used in an extra-label manner and drugs made by compounding pharmacies which have not gone through the approval process.

Limitations of the Reporting System

While the data generated by the CVM program are an excellent resource, there are several difficulties in analyzing the information. It must be emphasized that whenever an adverse experience is reported with a drug, there is no absolute proof that the drug was the causative agent. Multiple reports of a similar array of ADRs provide more credible evidence of a cause-effect relationship. Furthermore, there is no indication of the total number of animals treated with any drug listed. Thus, drugs which are more widely employed will generate a greater incidence of adverse effects based simply on their popularity. There is no information on the underlying disease state being treated or the concomitant use of other drugs which may contribute, through drug interaction or some other manner, to the adverse event. For example, if glucocorticoids were used concurrently with non-steroidal anti-inflammatory drugs (NSAIDs), there would be an increased likelihood of gastrointestinal (GI) toxicosis.

Lack of Efficacy as an Adverse Drug Reaction/Event

Ineffectiveness of a drug in producing the clinical benefit for which it was originally approved constitutes an adverse outcome. Ineffectiveness was cited as the most common (11% of dogs; 10% of cats) negative outcome in the CVM reporting system (Figure 169-1).[3] There are numerous reasons for a drug to "lack efficacy," and some of the more common are discussed here. If a condition was misdiagnosed or inappropriately investigated, the drug may have no benefit. Thus, mycoplasma pneumonia would not be affected by beta-lactam antibacterials since mycoplasma lack the cell wall-active site of penicillins and cephalosporins. However, appropriate use may still result in suboptimal clinical outcomes. The condition being treated may

simply have progressed to the extent that no drug will have beneficial effects. Alternatively, adequate drug quantities may not have been administered as, for example in cats, oral drugs are often difficult to administer and inability to administer a drug will preclude beneficial effects. An appropriate chemotherapeutic agent (e.g., antibacterials) may fail to produce the desired effect because of target organism resistance, an increasingly worrisome issue. Some patients develop a tolerance related to receptor down-regulation to some drugs, as with chronic use of beta-adrenergic agonists in feline asthma. If drug dosage remains unchanged, this will lead to diminished drug effect. Pharmacokinetic factors such as impaired absorption (e.g., an orally administered drug undergoing rapid gastrointestinal transit and decreased absorption due to diarrhea), increased elimination rate (e.g., of a hepatically biotransformed drug in an epileptic dog receiving chronic phenobarbital therapy leading to enzyme induction), interactions with concurrently administered drugs (e.g., sucralfate hinders enrofloxacin absorption from the gut) or pathological or physiological barriers for drug access into abscesses, prostate, brain, eye, etc. may result in insufficient concentrations of a drug being delivered to the desired site.

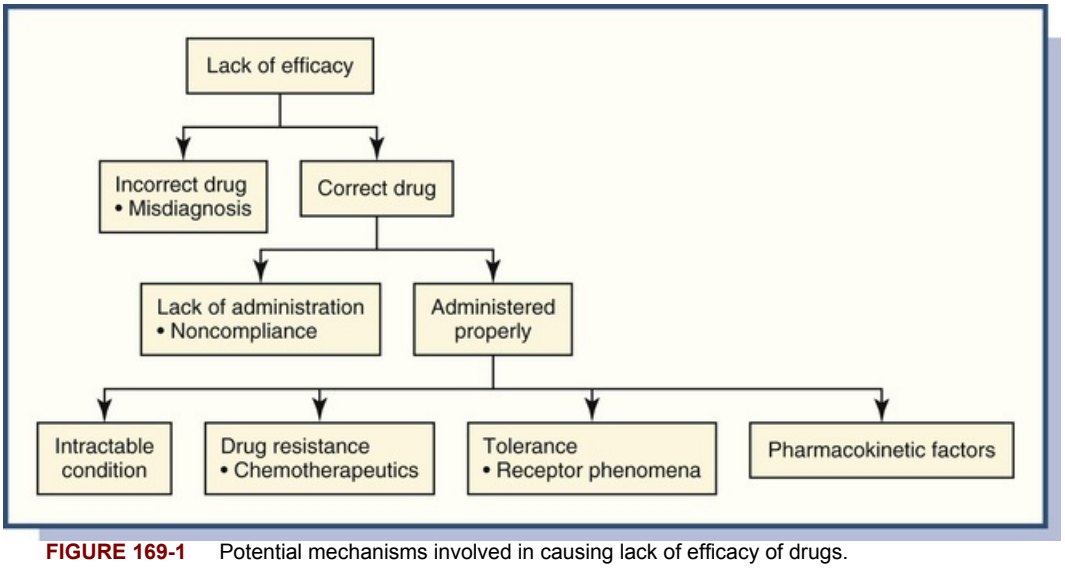

FIGURE 169-1 Potential mechanisms involved in causing lack of efficacy of drugs.

Toxicosis as an Adverse Drug Reaction (ADR)/Event

Overview and Types of ADRs

Toxic ADRs are by far the most common report on the CVM website. The adverse effect may be associated with the drug itself, vehicle-related or due to compounding errors with reformulated drugs (Figure 169-2).[4] Dose-dependent reactions ("Type A") are characterized by an exaggerated expected drug effect and are more likely with low therapeutic index drugs. They may of a physiological (e.g., hypotension with phenothiazine tranquilizers) or a pathological (organ/tissue damage) nature. Drugs with high inherent ADRs (e.g., antineoplastic agents) may not necessarily be reported to regulatory agencies since this is an expected consequence of their mechanism of action. Type B (or bizarre) ADRs, subclassified as being of an idiosyncratic or allergic nature, are unexpected, generally not dose-dependent and initially of unknown mechanism. The cause may become unraveled with further investigation and some are eventually shown to be Type A with a pharmacogenetic origin, e.g., dose-dependent acetaminophen hepatotoxicosis or enrofloxacin-induced blindness in cats.[5,6] Type B ADRs may be catastrophic, causing death, teratogenesis or carcinogenesis.

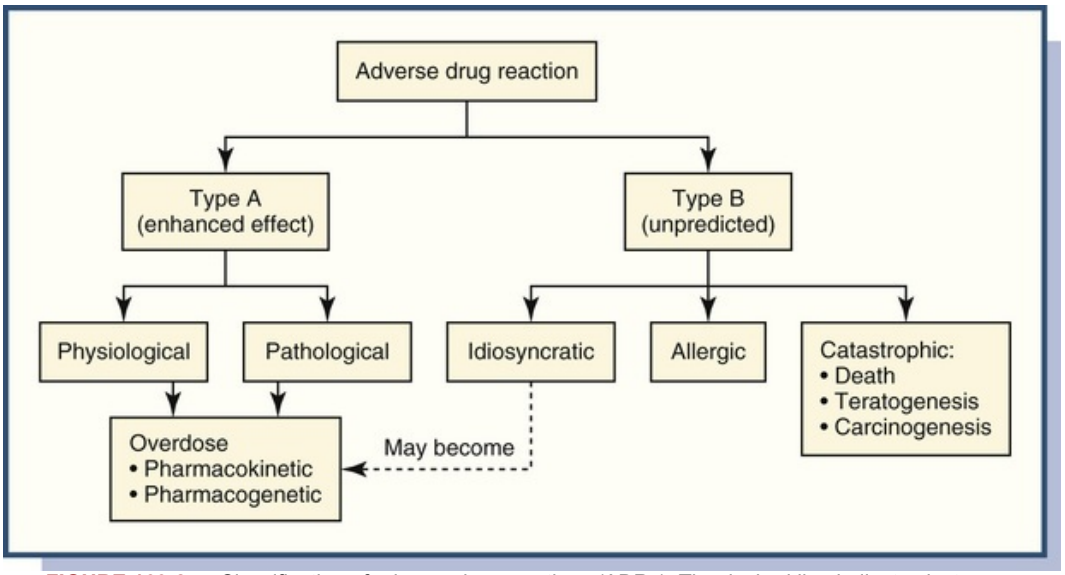

FIGURE 169-2 Classification of adverse drug reactions (ADRs). The dashed line indicates instances where idiosyncratic reactions may eventually be shown to be of a pharmacokinetic/pharmacogenetic nature.

Subclasses of Type A ADRs include those which are delayed in onset (e.g., secondary cancers long after initial chemotherapy for a malignancy) or occur only after withdrawal of a drug following a course of therapy (e.g., iatrogenic hypocortisolism after abrupt cessation of long-term glucocorticoid treatment). Another subclass are toxicoses related to exaggerated drug effects, due to accidental overdose or a reflection of pharmacokinetic anomalies which lead to accumulation of toxic amounts in a tissue. Since liver and kidney are exposed to circulating drugs or their metabolites at greatest levels, these organs are common sites of Type A toxicosis.

Species, Breed, Drug Interaction ADRs

Species or breed differences in drug metabolism can result in enhanced drug effect (e.g., deficient phase 1 metabolism in sight hounds; low glucuronidation capacity in cats). Dysfunction of a key organ involved in drug elimination (liver, kidney) can lead to accumulation of toxic drug levels and warrants dosage adjustment or use of an alternative less reliant on these routes of elimination.[3] Drug interactions, such as one drug inhibiting elimination of a second potentially toxic drug (e.g., enrofloxacin inhibition of theophylline metabolism) is a common cause of toxicosis and becomes more likely as more drugs are given to any patient.[7] Genetic lack of ABCB1 (MDR-1) transporters that prevent exit of drugs from tissue (such as the macrocyclic lactone antiparasitics from the central nervous system) may be a pharmacokinetic/pharmacogenetic anomaly in specific dog breeds (Collie; Table 169-1).[8] Enhanced absorption of phosphate enemas in cats compared to larger species can lead to profound systemic toxicosis, an example of species-specific concerns. Obesity or lean body conformation may affect the volume of distribution or another pharmacokinetic parameter which could lead to over- or underdosing.

TABLE 169-1

Selected Examples of Drugs with Adverse Effects on Different Organ Systems in Dogs and Cats, Particularly Those with Species Predilections

ORGAN SYSTEM/SITUATION	DRUG	TOXIC EFFECTS
Liver	Acetaminophen Phenobarbital (dog) Diazepam (cat)	Hepatocellular necrosis, cirrhosis
Kidney	Aminoglycoside antibiotics	Tubular necrosis
Central nervous system	Avermectin antiparasitics (dog breeds)	CNS depression

	Metronidazole	Seizures, vestibular signs
	Pyrethroid insecticides (cat)	Hyperactivity, seizures
Respiratory	Potassium bromide (cat)	Lower airway disease
	Cisplatin (cat)	Pulmonary edema
Cardiovascular	Anthracycline antineoplastics	Congestive heart failure
Gastrointestinal	NSAIDs	Gastrointestinal ulceration
	Doxycycline (cats, small dogs)	Esophageal strictures
	Anticancer drugs	Gastroenteritis
Skin	Glucocorticoids (dogs)	Bilateral alopecia
Ocular	Sulfonamide antimicrobials (dogs)	Keratoconjunctivitis sicca
Otic	Aminoglycoside antibiotics (dogs)	Deafness; vestibular damage
Hematological	Anticancer drugs Chloramphenicol (cats)	Bone marrow suppression
	Acetaminophen (cats)	Methemoglobinemia
Perinatal	Tetracycline antibiotics	Tooth discoloration/damage
	Fluoroquinolone antimicrobials (dogs)	Arthropathy

Death associated with drug use is the "ultimate toxic consequence." The CVM reporting system indicates a high rate of death associated with oral NSAID use in dogs, possibly a consequence of the GI toxicosis caused by this group of drugs.[2] In cats, the highest death rates were associated with agents used for general anesthesia, attributable to the precarious clinical situations in which these drugs are often employed. Teratogenesis is a rarely reported toxicosis. Suspected or known teratogens are extensively documented in a variety of veterinary resources.[9,10] Griseofulvin, perhaps the most widely recognized teratogen in cats, was not listed as a cause of a single birth defect in the CVM compilation.[2] Mutagenesis and subsequent carcinogenesis following chemotherapy with cytotoxic agents for cancer has been documented in people.[11] There is a paucity of such information in animals, perhaps because of the relatively recent introduction of cancer chemotherapy in dogs and cats. Genotoxicosis has been demonstrated to follow administration of clinically used doses of non-anticancer drugs such as metronidazole. The long-term implications of these concerns are not known.[12]

Organ System ADRs

Extensive compilations of ADRs (many of which were originally classified as idiopathic and with further investigation were shown to be a type A/exaggerated effect) in dogs and cats are available.[9,10,13] Table 169-1 summarizes the widely recognized ADRs in different organ systems with emphasis on those with species predilections. The precise pathogenesis of some ADRs is well-established (e.g., acetaminophen hepatotoxicosis) while others remain obscure (e.g., fluoroquinolone-induced arthropathy in puppies).[14,15] Certain ADRs result in cell damage/death (acetaminophen hepatotoxicosis; aminoglycoside nephrotoxicosis) whereas others cause a readily reversible, quasi-physiological adverse event (ivermectin toxicosis in Collies and other breeds; neurotoxicoses due to metronidazole in dogs and cats or pyrethroid insecticides in cats). Contributory factors may play a role in the development of ADRs. Dehydration and decreased renal blood flow enhance the nephrotoxicosis associated with aminoglycosides and NSAIDs. Increased access to the inner ear of dogs with tympanic membrane rupture increases the likelihood of deafness and vestibular side effects of aminoglycoside-containing otic preparations. The regenerative capacity of the site of a cytotoxic ADR will affect the long-term consequences. Proximal tubular lesions associated with the aminoglycosides or mild hepatocellular insults are usually reversible following withdrawal of the provoking drug. In contrast, retinopathy and blindness associated with fluoroquinolones in cats or tooth damage due to perinatal exposure to tetracycline antibiotics are more likely to be permanent.

Allergic and Hypersensitivity ADRs

Allergic drug reactions are not dosage-related and usually require previous drug exposure. An exception is a

pseudoallergenic/anaphylactoid drug reaction where initial administration may provoke release of mast cell mediators (e.g., histamine) that produce acute anaphylactic-like reactions such as bronchoconstriction and/or hypotension. This is more likely with rapid IV administration of a drug such as morphine. The classical system of Gell and Coombs remains the most widely accepted categorization of drug- (and other allergen) induced hypersensitivity reactions: (1) anaphylaxis; (2) hematological manifestations such as hemolysis or bone marrow damage leading to agranulocytosis and/or thrombocytopenia; (3) antibody mediated; (4) cell-mediated immune damage in tissues such as the skin (skin eruptions, dermatitis, epidermal necrolysis), liver (hepatitis), kidney (glomerulonephritis), vascular sites and articular surfaces. Treatment options for type 1 hypersensitivities (epinephrine, antihistamines, glucocorticoids) are well-established (see ch. 137) whereas those involving types 2, 3, and 4 rely on immune-modulating drugs and supportive measures.

Well-documented examples of drug-induced hypersensitivities in dogs and cats include those involving beta-lactam and sulfonamide antimicrobials, particularly the latter in dogs.[16] The sulfa moiety found in numerous drugs (e.g., antimicrobials, NSAIDs [deracoxib], diuretics [furosemide], drugs for colitis [sulfasalazine], carbonic anhydrase inhibiting antiglaucoma drugs [dichlorphenamide]) preclude their use in pets known to be sensitized to sulfa antimicrobials. There may be cross reactivity between different beta-lactam classes (penicillins, cephalosporins, carbapenems). Documented evidence of hypersensitivity to many others classes of drugs is available for people but not usually for animals. Skin tests or recently developed *in vitro* immunological tests may help to predict the likelihood of allergic ADRs.[16-18]

ADRs in Humans Associated with Veterinary Drugs

The CVM reporting system compiles data on toxic effects associated with use of drugs in veterinary personnel or clients administering drugs to their animals (Table 169-2). Presented data were confined to those drugs where there were at least 100 reports of an adverse effect per drug/route. Exposures were most commonly by the topical (skin) or parenteral (accidental injection) routes. Other reported routes of exposure were orally (accidental/self-medication?—see clomipramine), ophthalmic exposure, or inhalation of volatile drugs. Topical exposure to antiparasitic drugs was by far the most commonly reported route associated with adverse effects. Tilmicosin, a large animal antibiotic with potential for serious toxicosis, including death, in people after accidental self-injection, generated many reports of adverse reactions although none of these was fatal. Preventing exposure of people to any drug administered to animals is critically important and must be explicitly explained, especially when drugs have the potential for profound human toxicosis such as chloramphenicol (rare aplastic anemia in people), misoprostol (abortion in pregnant women) and cytotoxic antineoplastic drugs (mutagenesis/carcinogenesis; teratogenesis).

TABLE 169-2

Veterinary Drugs Commonly Involved in Causing Adverse Effects in Humans Following Inadvertent Exposure (ADRs)

DRUG CLASS	DRUG	ROUTE	MOST COMMON ADVERSE EFFECT (% OF TOTAL ADR)
Antibacterial	Ceftiofur	Parenteral	Injection site pain (35)
	Enrofloxacin	Parenteral	Injection site pain (25)
	Tilmicosin	Oral	Taste abnormality (22)
		Parenteral	Injection site pain (16)
		Topical	Taste abnormality (8)
Antiparasitic	Amitraz	Topical	Rash (25)
	Doramectin	Topical	Nausea (6)
	Imidacloprid/moxidectin	Topical	Nausea (6)
	Ivermectin	Topical	Nausea (8)
	Milbemycin	Oral	Nausea (28)
	Moxidectin	Topical	Nausea (7)

	Selamectin	Topical	Rash (29)
Behavioral	Clomipramine	Oral	Depression/lethargy (33)
Combination	Dexamethasone/neomycin/thiabendazole	Ophthalmic	Eye irritation (59)
Hormone	Altrenogest	Topical	Abnormal menses (20)
	Bovine somatotropin	Parenteral	Injection site pain (26)
NSAID	Carprofen	Ophthalmic	Eye irritation (46)

Based on CVM reports of over 100 ADR per drug/route.

ADR, Adverse drug reaction; *NSAID*, non-steroidal anti-inflammatory drug.

Prevention and Treatment of ADRs

Diligent observation of animals for any ADR once starting a treatment protocol is key to prevention and management. Potential side effects/toxicoses included on package inserts are important information to share with clients if drugs are administered on an outpatient basis. This information may be less readily available with newly released drugs, since novel adverse effects or drug interactions may only become apparent with use. Prophylactic measures (e.g., GI protective drugs in conjunction with NSAID therapy; antinausea medications during cancer chemotherapy; diuresis to allay bladder toxicosis associated with cyclophosphamide) should be considered whenever ADRs are expected. Use of such interventions may not be as readily available or established in dogs and cats as in people (e.g., use of dexrazoxane to prevent doxorubicin cardiotoxicosis).[19]

Investigation of precipitating causes for an ADR may unravel contributing factors, especially with Type A reactions. Special attention to liver and kidney function is warranted, since these organs most dramatically affect pharmacokinetics. Liver or kidney dysfunction could result in drug accumulation to toxic levels. Dose adjustment or elimination of precipitating factors may be sufficient to prevent perpetuation of the toxicosis. If necessary, a drug may be discontinued and substituted with an alternative drug. Particularly in the case of allergic reactions, care must be taken to opt for drugs without the offending chemical moiety.

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SECTION XI

Dietary Considerations of Systemic Problems

OUTLINE

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CHAPTER 170

Nutritional Assessment

Kathryn E. Michel

Client Information Sheets:
Nutritional Assessment of Cats
Nutritional Assessment of Dogs

The purpose of nutritionally assessing a patient is to allow the clinician to answer the question, "Is intervention for this patient necessary?" and to aid the clinician in selecting the most appropriate nutritional intervention for that patient. This simple and rapid process involves evaluating both subjective and objective information regarding the patient, the patient's diet and the patient's feeding management and environment.[1] In addition to aiding in the selection of a suitable diet and feeding management for the patient, nutritional assessment will also help the clinician to anticipate potential problems or complications and to devise strategies to avoid or monitor such developments.

Patient Assessment

In addition to signalment (including life stage and neuter status) and any previous or ongoing medical conditions (including medications), evaluation of body condition is a chief consideration in the assessment of the patient. Although some sophisticated techniques are currently being used in human patients or in a research setting (e.g., multiple-frequency bioelectrical impedance, dual-energy radiographic absorptiometry [DEXA]), they have either not been sufficiently validated in companion animals or do not lend themselves to a clinical setting because of logistic considerations or expense. Body condition scoring (Figures 170-1 and 170-2; Video 170-1) although subjective, is simple to learn, requires no special equipment, and has been shown to be repeatable and consistent among multiple observers.[2] The body condition scoring systems that have been published for companion animals are principally based on characterization of body silhouette and palpation of body fat (see ch. 2). These systems are useful, particularly for identification of patients that have an overweight body condition; however, they may misclassify some malnourished patients. It is important to recognize that catabolism of lean body tissue can occur very rapidly and may account for a disproportionate amount of the body mass lost in sick patients. Although the purpose of adipose tissue is to serve as an energy reserve, no analogous reserve of endogenous protein exists. Because all endogenous protein is serving some function, continuous catabolism will eventually have deleterious consequences for the patient. Therefore, the process of body condition assessment should include not only the standard evaluation of body silhouette and evaluation of adipose tissue as an assessment of energy reserves but also a separate evaluation of muscle mass (i.e., a muscle condition score) as a subjective means of assessing lean tissue status (Video 170-2). This can be accomplished by palpation of skeletal muscle over the axial skeleton and other bony prominences (see also ch. 177).[3]

FIGURE 170-1 Body condition scoring for a dog. (From German A, Holden SL, Morris PJ, et al: Comparison of a bioimpedance monitor with dual-energy x-ray absorptiometry for noninvasive estimation of percentage body fat in dogs. *Am J Vet Res* 71:393-398, 2010; Jeusette I, Greco D, Aquino F, et al: Effect of breed on body composition and comparison between various methods to estimate body composition in dogs. *Res Vet Sci* 88:227-232, 2010; Kealy RD, Lawler DF, Ballam JM, et al: Effects of diet restriction on life span and age-related changes in dogs. *J Am Vet Med Assoc* 220:1315-1320, 2002; Laflamme DP: Development and validation of a body condition score system for dogs. *Canine Pract* 22:10-15, 1997; Global Nutrition Committee Toolkit provided courtesy of the World Small Animal Veterinary Association.)

FIGURE 170-2 Body condition scoring for a cat. (From Bjornvad CR, Nielsen DH, Armstrong PJ, et al: Evaluation of a nine-point body condition scoring system in physically inactive pet cats. *Am J Vet Res* 72:433-437, 2011; Laflamme DP: Development and validation of a body condition score system for cats: a clinical tool. *Feline Pract* 25:13-18, 1997; Global Nutrition Committee Toolkit provided courtesy of the World Small Animal Veterinary Association.)

Other aspects of the physical examination of a patient that should be taken into consideration include haircoat quality and skin condition (see ch. 10), dental abnormalities or disease (see ch. 272), evidence of peripheral edema or ascites (which may indicate hypoproteinemia; see ch. 17 and 18), and clinical signs that may indicate specific micronutrient deficiencies such as neck ventroflexion or tetany (see ch. 21).

Taking a Diet History

The more information that is available about the patient's diet and feeding management, the better the clinician will be able to assess the adequacy of nutrient intake, the suitability of feeding practices, and the urgency for nutritional intervention. At the core of a dietary history is the careful gathering of information that will give an accurate picture of the foods that the patient consumes. Ideally, the person who is most responsible for feeding the patient should be questioned; however, it is important to find out who else resides in the household or has regular contact with the patient, including other pets. The patient's caregiver should be questioned about all foods that the patient receives (Box 170-1) and asked whether the information reflects what is typical for this pet, whether changes have occurred, and if so, when they happened.

Box 170-1

Information to Be Included in a Diet History

- Commercial pet foods (specific type [brand/formulation/flavor] and daily portion; dry foods should be weighed or measured with an 8-oz [250 mL] measuring cup; canned foods should be measured by can size and portion used)
- Commercial treats (brand, size, and frequency of use)
- Table foods or scraps (detailed information about type of food, portion size, and frequency of use)
- Treats for chewing (e.g., rawhide, pig's ears; size and frequency of use)
- Dietary supplements (brand and daily portion)
- Foods used for medication of the patient (type of food, portion size, and frequency of use)
- Pet's access to garbage
- Pet's ability to scavenge or roam
- Timing, location, and method of feeding and storage of food

In addition to particulars about the patient's diet, the history should also include information regarding appetite, feeding management, documented or perceived changes in bodyweight or condition, level of physical activity, and occurrence of any gastrointestinal (GI) signs. Again, the patient's caregiver should be queried as to whether the information reflects what is typical for this pet or whether (and if so when) changes have occurred. Although it is often the case that a pet owner cannot precisely recount an exact weight change, he or she may have an impression of the period of time over which the change occurred. Rapid weight loss and deterioration in body condition, particularly if associated with muscle wasting, suggests a greater degree of metabolic derangement or reduction in food intake (or both) and greater potential for significant malnutrition than a more gradual loss of weight.

Special Considerations Regarding Assisted Feeding

No definitive tests are available for establishing a patient's nutritional status. However, based on the information gathered from the patient's medical and dietary history and physical examination (as described previously), the clinician should be able to classify broadly the patient as being well nourished, mildly malnourished, or severely malnourished. The decision to intervene with some nutritional support has to balance the anticipated benefits with the potential risks and costs of the proposed intervention. Therefore, the intent of nutritional assessment should not simply be to diagnose inadequate food intake or malnutrition, but

rather to identify patients that are at risk of a poor outcome as a result of their compromised nutritional status. Investigations of human patients have found an increased risk of morbidity and mortality associated with various objective markers of nutritional status including hypoalbuminemia, lymphopenia, and attenuated delayed hypersensitivity reactivity. Other investigators have found that clinical assessment of patients based on a carefully performed history and physical examination, as described previously, has a predictive value similar to that of objective markers of nutritional status such as serum albumin concentration.[4] Furthermore, investigations of the effect of nutritional support on improving clinical outcome suggest that the most significantly malnourished patients are the most likely to show benefit from nutritional support.

There has been only limited investigation of the prognostic value of nutritional assessment in veterinary patients. Admission serum albumin concentration has been shown to correlate with risk of poor clinical outcome in critically ill dogs, and elevation of serum creatine kinase activity has been found to be associated with anorexia in feline patients.[5,6] To date, there have not been any investigations of the prognostic value of subjective nutritional assessment or the impact of nutritional support on clinical outcome in companion animals; however, it is not unreasonable to expect results similar to those found in human patients. Therefore, it is recommended that patients assessed to be significantly malnourished on presentation or that are at risk of becoming significantly malnourished in the course of their illness due to decreased food intake, malassimilation of diet, or metabolic derangement, should be considered candidates for assisted feeding.

Monitoring Nutritional Interventions

Once a dietary recommendation has been made, the patient should be reassessed after an appropriate interval of time. The actual timing of reassessment depends on the severity of the patient's illness and the type of nutritional intervention it has received. One should determine whether the prescribed recommendations are being followed, if problems with diet acceptance or tolerance are seen, if the desired outcomes have been achieved, or if any adverse events associated with the diet or feeding management have occurred. A thorough nutritional assessment at the outset will often identify potential problems or complications and thereby determine what parameters should be monitored in the patient. At the least, bodyweight and condition should be reassessed regularly to ascertain that the patient is maintaining, gaining, or losing weight appropriately.

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CHAPTER 171

Neonatal and Pediatric Nutrition

Cecilia Villaverde

Client Information Sheet: Nutrition and Feeding in Growing Animals

Adequate nutrition during the growth period (from birth into adulthood) is very important to ensure an animal achieves the adequate body weight (BW) and size determined by its genetic potential without suffering from nutrient deficiencies or excesses. Puppies and kittens have different nutrient requirements from adults, not only quantitatively but also qualitatively.[1] All essential nutrients are important, but the ones showing more marked differences between growing animals and adults are protein, calcium and phosphorus (required for new tissue formation), and docosahexaenoic acid (DHA). This long chain polyunsaturated omega-3 fatty acid is considered essential for growing animals due to its role in retinal and neural development[2,3] and it has been shown to increase learning performance in puppies.[2,4] Providing DHA directly via marine oils is more efficient than providing its precursor, alpha linolenic acid, due to the limited capacity of dogs and cats to biotransform it.[5]

Nutrient deficiencies and excesses are very rare in puppies and kittens fed commercial diets from reputable manufacturers but can be seen with improperly formulated home-cooked (or raw) diets (see ch. 192); thus, they are not the best choice in growing animals and should be avoided so as to prevent lifelong consequences. Nutrient excesses with implications in skeletal health (calcium, vitamin D, vitamin A) can be seen in growing pets fed a commercial diet plus calcium or other vitamin/mineral supplements. Energy requirements also are higher in growing animals than in adults, especially during the first four months of life,[1] which is why puppy/kitten (or all life-stage) foods usually are more energy dense and digestible than are adult foods. Conversely, pets that are inactive, belong to breeds predisposed to obesity (see ch. 176), or are neutered (see ch. 313) have lower energy requirements than average,[6] which is why the diets have to be carefully evaluated for each patient. Energy requirements expressed as kilocalories of metabolizable energy (ME) per day for puppies can be estimated at 3 times the resting energy requirement (RER; $70 \times BW[kg]^{0.75}$) from weaning to 4 months of age and 2 × RER for the rest of the growth period. For cats, the average daily energy requirement is estimated at 2.5 × RER for the whole period.[7]

Feeding the Newborn

Nursing is the main source of nutrition for newborns. Colostrum (the secretion from the mammary gland during the first few days of lactation) provides nutrients, energy, and passive immunity, and it is very important that newborns receive it within the first 24-72 hours after birth.[8] Adequate nutrition of the mother is very important for sufficient production of quality milk. During lactation, the bitch and queen should eat a nutritionally complete diet formulated and, ideally, one that has undergone feeding trials for reproduction or all life stages. It should have an energy density of at least 4 kilocalories ME per gram of dry matter, which is especially important in large-breed dogs with large litters where the diet can be volume-limiting (i.e., the amount of food the mother would need to consume to have adequate ME is excessive in volume). Large-breed puppy diets usually are not adequate for reproduction due to their reduced energy density. Both food and water have to be available at all times. In newborns, signs like restlessness, continuous vocalization, and failure to grow at an adequate rate signal a maternal health problem, a failure to suckle, or inadequate milk production.[9] BW and body condition score (BCS) should be recorded every 24-48 hours. Puppies should grow 2-4 grams/kg of adult body weight/day and kittens should grow at the very least 10-15 grams per day (average of 100 grams per week).[8-10] If milk production is not adequate, partial or total hand rearing is recommended. Maternal milk is enough as a sole source of nutrients only until weeks 3-4, and solid food

should be introduced at that time (at week 3 for larger breeds and large litters). Despite introducing solids at this time, weaning takes place at weeks 7-9 because early weaning (before week 6) can result in behavioral problems in both species.[11] The bitch's diet, or a growth dry diet, mashed with water (1 part food : 1 part water, by volume) can be used for starting the puppies on solid food at 3-4 weeks of age, although canned puppy/kitten food also is a good choice. For large breeds, using a large-breed puppy diet different from the mother's diet is indicated. Solid food should be introduced slowly and gradually until it is the sole source of nutrition by the time of weaning. Shallow plates can be used so the animals will step on the food and lick their paws, or both the paws and the mouth (never the nose) can be smeared with the gruel. See ch. 315 and 320 for more information on queen and bitch management and newborn care.

Rearing Orphan Puppies and Kittens

Newborns that are orphaned, or whose mother cannot produce enough milk due to disease or to a large litter, have to be completely or partially hand-reared. The mother not only provides nutrition but also warmth, humidity, elimination, sanitation, and security, and all this should be supplied by the care provider as well.[9,10] Regarding nutrition, the best way to rear orphans is to find a foster mother; if this is not possible, milk replacers will be necessary, using either commercial products or home-prepared recipes.[9,12] The latter are not ideal[13] and should be reserved for emergencies, although commercial products are not without problems and a high variability (and deficiencies of nutrients including amino acids, calcium and DHA) has been described among U.S. canine milk replacers.[14] Some of them are very low in energy density (compared to the 1.4 kcal/mL of canine milk). One European study[15] also found issues with nutrient excesses of calcium and vitamin D in canine milk replacers, which could be a risk for fast-growing, large-breed puppies. Thus, it is important to choose a product with at least 1 kcal/mL (reconstituted) and to carefully select the manufacturing company, calling to ask them about their practices and nutritional expertise.[16] Energy requirements of newborn puppies and kittens are estimated at 20-25 kcal/100 g BW.[1] Dividing this by the energy density of the milk replacer will provide the volume per day to provide, divided over several meals per day every 2-4 hours, assuming a stomach capacity of 4 mL/100 g of BW.[8] It is recommended to start slower (50% of energy requirements) the first day to ensure a safer transition. Lower intakes (or formula dilution) also are indicated in cases of diarrhea. Adjustments every 48 hours will be necessary to achieve the desired rate of weight gain. Water requirements are estimated to be 18 mL/100 g body weight/day and additional water should be provided if the milk replacer does not provide it. Strong vital animals can be bottle fed, whereas weak newborns should be tube fed with a 5- to 8-Fr feeding tube,[8,10] placing them horizontally with the head held high to prevent aspiration. Formula should be warmed up to body temperature before use. After feedings, the abdomen should not be overdistended and the perineum has to be massaged with a warm wet cloth or cotton to stimulate elimination. Solid food should be introduced at week 3 as a gruel (puppy/kitten canned or dry food can be mixed with water or with the milk replacer) and slowly increased until weaning. Ch. 320 gives more details about postnatal care.

From Weaning to Adulthood

The puppy/kitten has to be fed a complete and balanced diet formulated for growth (or all life stages). Ideally, the diet is one that has undergone feeding trials, and no nutritional supplements should be part of the regimen. Free-feeding only is indicated for lean puppies and kittens that show an adequate rate of weight gain and a lean BCS (4-5 out of 9). Portion-controlled feeding is recommended for all other animals during growth, particularly for large-breed dogs, obesity-prone breeds, and puppies/kittens that have been neutered. One study[17] found that Labradors kept at a BCS of 4/9 (compared to 6-7/9) from weaning into adulthood and maturity lived longer, with chronic diseases being delayed and appearing at a later age than in their counterparts; thus, keeping puppies lean is extremely important.

Large-breed puppies need special nutritional care[18]: overfeeding can predispose to developmental orthopedic disease and osteoarthritis in adulthood. These dogs should always be fed portion-controlled, aiming for a lean BCS of 4/9, using a specifically formulated, large-breed puppy food. These diets are lower in energy density (to facilitate an adequate energy provision) and also have controlled calcium levels (1-1.5% dry matter), because these puppies have an immature calcium regulation system and are susceptible to excess.[19] Adult foods, a common recommendation for these cases, can result in deficiencies and, depending on the choice, could provide more calcium and energy than desired, and they should not be used in any case.

See ch. 187 for more details on nutrition and orthopedic disease. The puppy/kitten food should be fed until the animal has reached adult body weight and the growth plates have closed (12 months for small- and medium-size dogs and cats; 18-24 months for large- and giant-breed dogs).

Reassessment

A nutritional evaluation (ch. 170) during each visit, and BW and BCS every 2 weeks during the fast growth phase (first six months), are crucial. Evaluation can be done every 3-4 weeks afterwards. BW can be compared to growth curves[20] and BCS should be kept at 4-5/9 (4 for large-breed puppies). The owner has to be taught how to assess BCS[16] and how a healthy lean puppy/kitten should look (see ch. 2 and 170). Adjustments in the calorie allowance can be made by 10% to achieve BW and BCS goals. Switching to a diet that is lower in energy density can help with very hungry puppies or kittens that are not free-fed. Bloodwork is not a very sensitive or specific measure of the nutritional status and both serum biochemistry values (such as calcium, phosphorus, albumin, liver enzymes, lipids) and complete blood cell count can be affected by age in both puppies and kittens,[21,22] and altered values compared to adult reference ranges should not be misconstrued as indicative of malnutrition.

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CHAPTER 172

Nutrition for Healthy Adult Dogs

Martha G. Cline

Client Information Sheet: Nutrition for Healthy Adult Dogs

Data from 2012 indicate a population of almost 70 million dogs in approximately 43 million United States households.[1] Caregivers of these dogs generally strive to provide their pets with quality nutrition. Quality nutrition should begin when dogs are young and healthy, not just considered after an illness is identified. "Young adult healthy dogs" can be defined as a group ranging in age from about 1 to 7 years, depending on breed and size. Nutrition should be at the forefront of discussions on preventative medicine between veterinarians and young healthy adult dog caregivers. Nutrition goals during early adulthood should include optimizing health, providing disease prevention, increasing performance, and enhancing longevity.

Dogs as Omnivores

Dogs are members of the order *Carnivora.* The word carnivore describes both the taxonomic group and its feeding behavior. The diverse order *Carnivora* includes true carnivores such as those in the family *Felidae* and herbivores, such as pandas, in the family *Ailuropodinae.* The dog is in the *Carnivora* family, but its metabolism and nutritional needs approach those of omnivores. Unlike true carnivores, dogs have the capability to synthesize taurine, arachidonic acid, and vitamin A from their metabolic precursors in plants: cysteine, linoleic acid, and beta-carotene, respectively.

Domesticated dogs are also adapted to thrive on a starch-rich diet. Genes that play a role in starch digestion—pancreatic amylase *(AMY2B),* maltase-glucoamulase *(MGAM),* and the sodium/glucose cotransporter *(SGLT1)*—demonstrate changes in expression and activity that favor starch digestion in dogs when compared to wolves.[2] The ability to handle a starch-rich diet may have some breed variability, as demonstrated by a wide variation in *AMY2B* activity amongst dog breeds.[3] Like true carnivores, however, dogs possess metabolic characteristics such as an obligation to conjugate bile acids with taurine and an inability to synthesize vitamin D. Dogs are not simply omnivores, but have developed their own metabolism and nutritional requirements as they evolved.

Meeting Energy Requirements

Energy is supplied by the oxidation of fat, carbohydrate, and protein. The energy needs of adult dogs may be supplied by diets with varying ratios of these three macronutrients. About 80% of food consumed by mature dogs is used to provide their energy needs. The remaining dry matter is used to meet requirements for protein, vitamins, and minerals. Excess energy is disposed of by oxidation to produce adenosine triphosphate or stored in the form of adipose tissue. Mature dogs in energy balance convert all available metabolizable energy (ME) from food into heat. The ME value of a food should be known to calculate the amount of food needed to meet energy requirements (see ch. 170, 173, and 174).

Maintenance and resting energy requirements of adult dogs can be estimated using formulas relating ME requirements to body weight (Box 172-1). Because mature dogs have about fiftyfold range in body weight, and because ME requirements per unit of body weight decrease with body weight, formulas generally include some power function of body weight (e.g., body weight raised to three-fourths power). Resting energy requirement (RER) represents the energy needs of a normally-fed animal at rest in a thermoneutral environment. Various life stage factors can be applied to the RER depending on the activity level and neuter status of an adult dog. Typically, RER × 1.4-1.6 is used to determine adult maintenance energy requirements (MER). Meta-analysis of the MER of adult dogs demonstrated average MERs of 142.8 ± 55.3 kcal/kgBW$^{0.75}$/day

with a suggested allometric equation of 81.5 kcal/kgBW$^{0.93}$/day.[4] The energy requirements of adult dogs in this meta-analysis were impacted by husbandry (highest in racing dogs, then working/hunting dogs, and least in pet and kenneled dogs) and neuter status (decreased in neutered animals versus sexually intact) with no effect of gender. The recommended equation for determining the MER of pet dogs is 62.5 kcal/kgBW$^{0.97}$/day.[4]

Box 172-1

Formulas for Estimating the Energy Requirements (ERs) of Adult Dogs Per Day

Resting ERs (exponential equation): 70 × (BW in kg)$^{0.75}$
Resting ERs (linear equation): 70 × (BW in kg) + 30
This equation is not recommended for use in dogs < 2 kg or > 20 kg as it will overestimate energy requirements.
Maintenance ERs (all dogs): 81.5 × (BW in kg)$^{0.93}$
Applies to racing, working, hunting, kenneled, and pet dogs.
Maintenance ERs (pet dogs only): 62 × (BW in kg)$^{0.97}$
BW, Body weight.

Large variation exists in the prediction interval of MER; therefore, formulas should be used only as starting points when determining MER and dogs should be fed to an ideal body condition.[5] A complete diet history (see ch. 170) together with following the dog's weight and body condition score (BCS) over time will help practitioners accurately determine an individual's MER. These equations can be useful clinically to estimate energy requirements, particularly when a complete diet history is not available to estimate energy intake. This includes recommendations for enteral or parenteral nutrition or making recommendations for either body weight loss or gain.

Macronutrients

Protein and Amino Acids

Protein provides both essential amino acids and nitrogen. Nitrogen is required for synthesis of dispensable amino acids, heme, purines, pyrimidines, etc. Essential and dispensable amino acids are required for protein synthesis and are the precursors for various hormones and neurotransmitters. The crude protein requirement represents the dog's nitrogen requirement. Crude protein is defined as the quantity of nitrogen times 6.25. Protein requirements for healthy dogs have been determined using nitrogen balance and endogenous nitrogen excretion. The National Research Council's (NRC) Nutrient Requirements of Dogs and Cats minimum requirement for crude protein in adult dogs is 2.62 g/kgBW$^{0.75}$ or 20 g per 1000 kcal and recommended allowance is 3.82 g/kgBW$^{0.75}$ or 25 g per 1000 kcal (Table 172-1).[6] Minimum protein recommendations by the Association of American Feed Control Officials (AAFCO; 51.4 g per 1000 kcal) are, in part, based on this information and account for changes in processing that can alter protein digestibility or bioavailability.[7] The NRC and AAFCO also set minimum recommendations for amino acids. After the amino acid requirement is met, additional protein is deaminated by the liver. Ketoacids are used for energy or stored as fat or glycogen. By-products of protein catabolism are excreted by the kidneys. The estimated percentage ME to define low, moderate, and high protein diet when comparing commercial pet foods for a dog is provided in Table 172-1.

TABLE 172-1

Comparison of Protein and Fat Levels in Commercial Dog Foods (% Metabolizable Energy [ME])

	NRC MINIMAL REQUIREMENTS	NRC RECOMMENDED REQUIREMENTS	AAFCO MINIMUM REQUIREMENTS	ULTRA-LOW	LOW	MODERATE	HIGH
Crude Protein	7	9	18		<20	20-30	>30

Total Fat		12	12	<20	20-25	25-35	>35

AAFCO, Association of American Feed Control Officials; *NRC*, National Research Council.

%ME calculated using Modified Atwater Factors (3.5 kcal/g protein, 8.5 kcal/g fat).

Essential Fatty Acids

Polyunsaturated fatty acids (PUFAs), linoleic acid (18:2n-6) and alpha-linolenic acid (18:3n-3), must be incorporated into the diets of dogs because dogs lack enzymes to synthesize these fatty acids *de novo*, making them "essential." Dietary fats are not only an excellent source of energy, but they also provide these essential fatty acids (EFAs), depending on the source. EFAs are required to maintain the structure of cell membranes, to allow intestinal absorption of fat-soluble vitamins (A, D, E and K), and they are precursors of eicosanoids including prostaglandins, leukotrienes, and thromboxanes with both paracrine and endocrine activities. The EFA canine requirement is greatest for linoleic acid, whose deficiency results in hyperkeratosis, water loss through the skin, and testicular degeneration. Linoleic acid is incorporated into sphingolipids in the epidermis of the skin, aiding with barrier function and to help maintain skin and coat quality. Dogs need about 1-2% of total calories as linoleic acid to prevent clinical signs of deficiency, though higher levels of total fat in the diet may result in better coat condition. High concentrations of alpha-linolenic acid can be found in some plant oils such as flaxseed oil. Eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3), found in high concentrations in marine oils, have a nutrient requirement in the dog. However, higher dosages of these fatty acids may have a therapeutic effect due to their anti-inflammatory properties.

Fats provide over twice the calories as protein and carbohydrate; therefore, dog food containing high levels of fat will have increased calorie density. Moderate levels of fat generally range from 25-35% ME, with low being <25%, high >35%, and ultra-low fat diets generally considered to contain less than 20% of ME as fat (see Table 172-1). Low-fat diets are recommended for dogs prone to obesity (see ch. 176).

Fiber

While dogs do not have specific nutritional requirements for carbohydrates or fiber, fiber can be added to dog diets to optimize health through various functions, such as promotion of satiety or maintenance of stool quality. Fiber is a poor source of energy; therefore, its inclusion in pet food will decrease energy density, useful when feeding animals prone to obesity. Fiber is expressed on pet food labels as maximum percentage of crude fiber, which reflects the percentage of cellulose (insoluble fiber) in the diet. Total dietary fiber more accurately reflects the fiber content of a pet food by including both soluble and insoluble fibers, with the exception of certain types of fiber such as oligosaccharides (see ch. 190).

Minerals and Vitamins

Adult dogs require the same minerals and vitamins essential to growing puppies (see ch. 171), although the requirements for adult maintenance are sometimes based on our knowledge of nutrient requirements during growth and are less precise. The function and clinical role of minerals and vitamins have been reviewed.[8,9] Vitamin and mineral requirements are published by the NRC and the bioavailability of minerals must be taken into account when formulating diets. The bioavailability of calcium, phosphorus, and magnesium from plant sources is considerably less than that from mineral salts or bone and should be discounted by 50%. Additionally, the bioavailability of copper and zinc from plant sources is also compromised. In contrast, sodium, potassium, and chloride are readily exchangeable, and no adjustments are necessary concerning their source.

Dogs must consume vitamin D as they cannot synthesize it using ultraviolet light.[6,8] The requirement for vitamin E is a function of total PUFA content in a diet. Canine vitamin K requirements are largely met through intestinal synthesis, making dietary supplementation less critical. Choline, although partially synthesized in the liver, is considered an essential vitamin because it supplies labile methyl groups. Choline is a component of the neurotransmitter acetylcholine, promotes lipid transport in the liver as a component of phosphatidylcholine, and plays a role in platelet activation. Deficiency in methyl groups results in accumulation of fat in the liver. Vitamin C is not essential in dog diets as *de novo* synthesis occurs from glucose via the glucuronic acid pathway. There is insufficient evidence to indicate that healthy dogs benefit from additional dietary vitamin C. L-carnitine (a vitamin-like substance), while non-essential, may benefit certain breeds of dogs with a limited capacity to synthesize this nutrient.

General Feeding Recommendations

A complete nutritional assessment should be completed prior to suggesting dietary recommendations (see ch. 170). Following a nutritional assessment, diet selection, energy requirements, feeding amounts, and feeding methods should be determined. Primary goals for feeding a young adult dog include optimizing health, disease prevention, enhancing performance, and promoting longevity. While we expect young adult dogs to be relatively healthy, obesity and periodontal disease commonly begin during this life stage.[10,11] With advancing age, the development of various disease processes such as chronic kidney disease (CKD), osteoarthritis, cancer, and diabetes mellitus may alter various nutritional goals (see ch. 175). When selecting an appropriate diet for one of these conditions, one should always select a diet that has been evaluated for the intended purpose. Calorie restriction to maintain an ideal body weight throughout life is recommended and has been shown to delay onset of clinical signs associated with chronic disease and increase longevity in Labrador Retrievers by nearly two years.[12] Advising owners to feed measured meals using standard measuring devices (8 oz [250 mL] measuring cup) or by weight (grams) rather than *ad libitum* feeding is recommended to aid in the prevention of obesity (see ch. 176).

Guidelines are available to aid pet owners when selecting commercial pet foods (Box 172-2). Selecting a pet food company with a full-time qualified nutritionist is recommended. Appropriate qualifications include PhD in animal nutrition or board certification with either the American College of Veterinary Nutrition (ACVN) or European College of Veterinary Comparative Nutrition (ECVCN). Additionally, a company should be able to provide a complete nutrient profile (typical analysis) of their diets. Ideally, any AAFCO-required nutrient should be provided on an energy basis (grams per 100 kcal or per 1000 kcal or for macronutrients % ME).

Box 172-2

Guidelines for Selecting Commercial Pet Foods

1. Does the pet food company employ qualified nutritionists full-time? Can the company provide their name and qualifications?
2. Who formulated their foods and what are their credentials?
3. Are the diets tested using AAFCO feeding trials or formulated to meet AAFCO nutrient profiles? If the latter is performed, is the diet formulated to meet the nutrient profile or is an analysis of the finished product performed?
4. Where are the diets produced and manufactured?
5. Which specific quality control measures are used to ensure the consistency, quality, and safety of the diet?
6. Can the company provide a complete nutrient analysis beyond the guaranteed analysis of the finished dog or cat food?
7. Does the company perform product research and if so, is this published in peer-reviewed journals?

AAFCO, Association of American Feed Control Officials.

Adapted from World Small Animal Veterinary Association Global Nutrition Committee: Recommendations on selecting pet foods. Available at: http://www.wsava.org/sites/default/files/Recommendations on Selecting Pet Foods.pdf. Accessed January 15, 2015.

Practitioners should advise clients to choose a commercial diet that has passed an AAFCO feeding trial protocol for adult maintenance or all life stages. Diets designated for all life stages are typically higher in fat and more calorie-dense, as they are also intended for growing and reproducing animals. Therefore, not all adult dogs should be fed this type of diet, especially not if they are overweight or prone to obesity. Diets formulated to meet AAFCO requirements meet specific nutrient requirements based on either a calculated nutrient profile or analysis of the finished product. If a diet formulated to meet AAFCO requirements is chosen by a caregiver, determination of nutrients by analysis of the finished product is recommended. This information is typically only available by contacting the manufacturer. Diets formulated to be complete and balanced and demonstrated to be fully adequate in adult dogs through feeding tests are most ideal when selecting a product.

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CHAPTER 173

Nutritional Management of the Canine Performance Athlete

Joseph J. Wakshlag

Body Condition and Exercise

Sporting activity often dictates the body condition required for various events. Typically, performance dog owners maintain their dogs at a 4-5/9 body condition score (BCS) when utilizing the 9 point system for evaluation (see ch. 2 and 170).[1] Greyhounds, field trial, hunting and sprinting athletes may benefit from being maintained at a body condition score between 3 and 4/9. Dogs in this condition have ribs easily visualized in shorter-haired dogs, prominent spinous processes and wings of the ilia, but with ample paralumbar musculature that extends between the wings of the ilia so that the sacral spinous processes can be identified, yet do not protrude. Being lean is advantageous for sprinting and intermediate activities (10-30 minutes) that are timed events, for ideal performance (Figure 173-1), and restricted meal feeding particularly on event days. In endurance activities where speed is less important, and there is a greater chance for loss of body condition due to extended activity, a body condition score of 4-5/9 may be ideal to prevent severe weight loss in events such as Foxhound trialing or endurance sled dog racing.[2]

FIGURE 173-1 Appropriate body condition for the canine athlete. Notice the rib cage showing just behind the elbow and the prominent musculature of the shoulder and hind limb. This dog would be considered a 4/9 on the BCS chart.

Energy and Activity

The National Research Council estimates that active pet dogs require roughly 130 × (metabolic body weight [BW] in kg)$^{0.75}$ for maintenance energy requirements (MER, kcal/day). The effects of increasing physical activity have been extensively studied in dogs.[3] Caloric expenditure during exercise is directly related to the distance traveled.[4] For example, agility would be expected to require less caloric expenditure as compared to field trials.

Studies in Greyhounds suggest 150-160 kcals/kg$^{0.75}$ energy expenditure on a daily basis, which is only slightly elevated from active dog maintenance values.[5,6] The distance traveled per day in racing Greyhounds is relatively short. This comparatively high MER for the limited activity may be a reflection of the increased muscle mass of Greyhounds.[6] On the opposite end of the spectrum are endurance sled dogs who expend approximately 1,000 kcals/kg$^{0.75}$ BW per day during long-distance pulling activity, suggesting the average 25 kg sled dog expends approximately 10,000 kilocalories per day.[7,8] This shows the variation in energy need for athletic dogs, making it difficult to adjust feed according to daily activity. Thus, many owners and handlers feed according to body weight and body condition, which is evaluated daily.

Fuel: Fat and Carbohydrate

Exactly which substrates are consumed at which point during exercise is debated, but it is generally thought that initial adenosine triphosphate (ATP) production in muscle is synthesized through a creatine phosphate shuttle for immediate ATP synthesis, but is exhausted within seconds. Glycolysis then kicks in to produce ATP from glucose metabolism to pyruvate, with pyruvate feeding into the citric acid cycle for oxidation of carbohydrate. This is the primary energy source for 30-90 minutes of exercise, particularly if dogs are running hard (50% or greater of their maximal oxygen consumption). Within 10 minutes, the rate of beta-oxidation of fat will increase and reach a threshold within 30 minutes that can supply a majority of the energy needed for exercise. However, this cannot sustain very high levels of activity (above 50% of maximal oxygen consumption) because the beta-oxidation of fat is rate-limiting and can only be oxidized at around 30-40% of the mitochondrial maximal capacity for oxidation (Figure 173-2). Amino acid breakdown is also rate-limiting, but will supply the cells with glucose through gluconeogenesis when glycogen stores have been exhausted.[9-13]

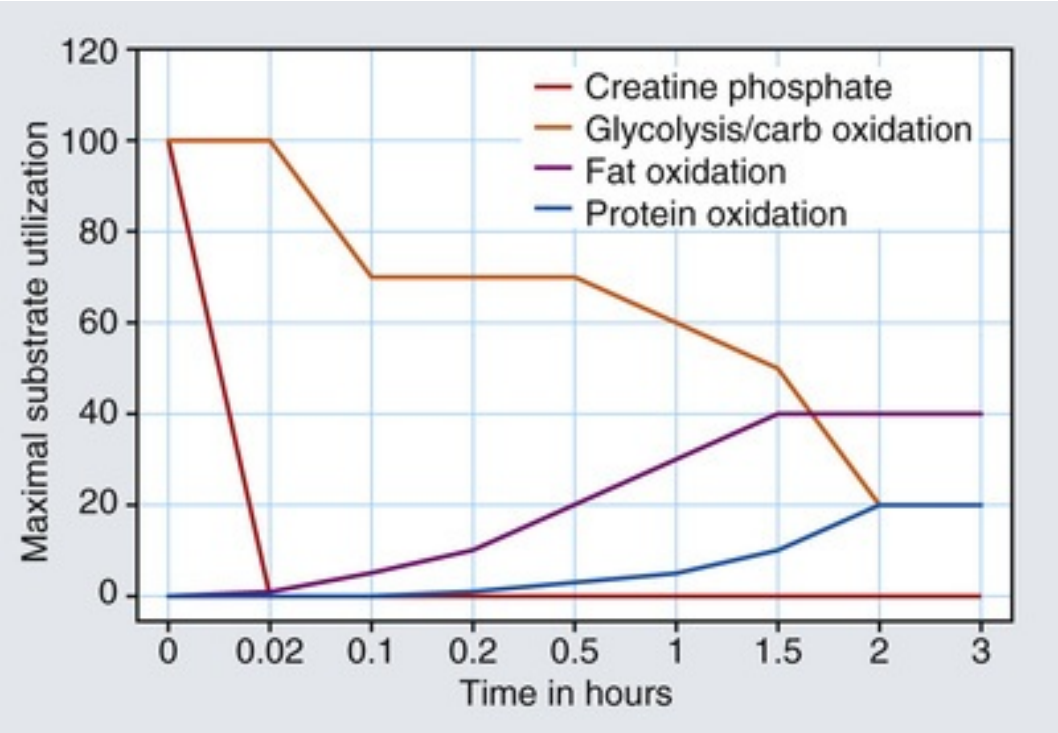

FIGURE 173-2 Substrate utilization and intensity during exercise over an extended period of time.

Carbohydrate oxidation becomes a major source of energy for long-term exercise at greater than 50% of

maximal oxygen consumption (20 minutes to 2 hours) as long as sufficient glycogen is present for glycogenolysis and the rate of conversion of pyruvate to acetyl-CoA is adequate. A recent study in trained endurance dogs suggests that dogs burn glucose at an equal if not greater rate than fat when running at submaximal intensity.[14] Carbohydrate oxidation is the primary fuel for most sprinting and intermediate athletes (less than 20 minutes of exercise) and should not be restricted: up to 50% of the ME as digestible carbohydrate can be utilized successfully in sprinters and 15-30% can be utilized successfully in endurance dogs.[5,6,15]

Fat is a preferred fuel due to the large stores throughout the body; therefore, dietary fat is often seen as a good energy source, with studies suggesting that higher fat and higher protein diets may be advantageous for endurance work.[13,16-20] Diets containing approximately 55 to 70% of ME as fat can provide adequate energy for endurance exercise and this composition is typical of the feed for most endurance athletes.[21,22] Owners and trainers are best advised to introduce fats to the diet slowly, to prevent steatorrhea, which is a common adverse effect from feeding high fat diets too quickly. To get the full benefits of a higher fat ration, it is best to initiate this diet approximately 8-12 weeks before competition to allow for mitochondrial and metabolic adaptation.[23] Excess fat in the diet may require dietary increases in divalent cation nutrients (calcium, iron, zinc, copper and manganese), which may chelate with free fatty acids, thereby reducing their bioavailability.[21]

Fat and Carbohydrates—Special Considerations

Many speculate that fatty acid chain length and saturation affect a variety of issues from inflammation to oxidative stress during exercise, despite very little information regarding optimal dietary fat intakes for canine athletes.[29] Fatty acid composition might also slightly influence detection in scent-trained dogs such as hunting dogs and service dogs. A recent study utilizing corn oil as a source of elevated polyunsaturated fatty acids (linoleic acid) demonstrated slightly improved detection at the lowest scent threshold in scent-trained Labradors.[27] The precise mechanism and magnitude of this effect has not yet been fully elucidated, but elevated polyunsaturated fatty acids may modestly improve performance in dogs that require olfactory acuity as part of their work.

Strategic carbohydrate supplementation can be beneficial for sprinting and intermediate-distance athletes if muscle glycogen is depleted daily, over the course of multiple-day events.[12,30,31] Current recommendations are to provide 1-1.5 grams of maltodextrin supplement for any dog running between five minutes to three hours per day, particularly when expected to perform similarly the following day.

Protein Requirements for the Canine Athlete

There are multiple methods to evaluate dietary protein adequacy, each with its own merits and disadvantages, which are beyond the scope of this chapter. Dietary protein helps maintain muscle integrity and appropriate total protein, albumin and hematocrit. The hematocrit and serum albumin tend to decrease with training and racing, which appears to be a result of an overtraining syndrome[23,24] that may respond in part to increased protein intake. Sled dog studies have postulated that approximately 30% of daily ME (70-80 g protein/Mcal) should come from highly digestible animal-based protein.[22,25] Protein quality and source may also be important, with highly digestible animal based sources being preferable.[26]

Sprinting dogs require less protein for exercise than do endurance athletes, with studies suggesting that 24% of ME may be adequate.[15,25,26] Other working dogs, however, may perform well on lower protein intakes. Scent detection dogs retained normal performance even when fed a high-fat, low-protein diet containing 18% ME.[27] Therefore, the optimal protein requirement for all athletic dogs may be different depending on the intensity of exercise and the specific task. However, there is little detriment associated with a higher protein ration; therefore the recommendation for most athletes is 24% of the ME or above.[21,28]

Electrolytes, Minerals and Vitamins in the Working Canine

As long as a dog is being fed a majority of its calories as a complete and balanced dog food, then electrolyte or mineral deficiencies are unlikely to be a problem. Only in instances where dogs are fed primarily meat and other table foods will there be cause for concern. In fact, one study suggested an increased incidence of gastrointestinal disturbances in dogs when provided a glucose and electrolyte drink.[32] Unlike humans and

horses, dogs cool primarily via panting, which is not associated with the same electrolyte losses as sweating in other species. Therefore, dietary supplements are not necessary, with only extremes such as endurance sled dog racing showing any need for alterations in electrolyte intake, which may be more of a reflection of feeding pattern changes than true need.[33]

Vitamins, if supplied by a complete and balanced pet food, are of little concern since intake is directly correlated to dietary energy needs. Antioxidant vitamins like C and E have received the most attention. Vitamin C is synthesized in dogs through hepatic synthesis from glucose. However, dogs might not synthesize as much as other species.[34] The possibility for limitations in hepatic synthesis combined with observations that serum ascorbic acid concentrations decrease more than 50% after 190 minutes of sled racing have led to suggestions that supplementation may be beneficial.[22] Similarly, vitamin E has been examined in racing sled dogs, with implications of deficiency being associated with performance.[35] Current examination of supplementation of vitamins E and C to racing Greyhounds showed detriment to performance, making any recommendations tenuous at best.[36-39]

Non-Traditional Diets

In the sporting arena more than anywhere else, the feeding of home prepared cooked and raw diets is commonplace. The exact reasons are unclear, but it is often thought that these diets have a higher energy density, since they can often contain more fat, and that digestibility is greater than the average extruded diet.[40,41] Unfortunately, many home prepared rations are not ideally balanced for dogs,[42,43] creating subclinical deficiencies and more importantly, if raw, putting dogs at risk of bacterial or protozoal infection (see ch. 192).[44,45] Though this is not the focus of this chapter, it has already been established by certain governing bodies that certain service dogs cannot be fed raw diets due to the zoonotic risk.[46] For those owners looking for alternatives to traditional kibble and canned diets, a recent study suggests that freeze-dried or pressure-pasteurized foods may be an alternative for those clients, since they rarely test positive for bacterial contaminants.[47]

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CHAPTER 174

Nutrition for Healthy Adult Cats

Jennifer Larsen

Client Information Sheet: Nutrition for Healthy Adult Cats

Overview

Cats have unique metabolic and nutritional needs that reflect their evolution as hunters consuming small mammals, birds, reptiles, and insects. Their dietary requirements set them apart from most other species commonly kept as pets. However, precisely defining the optimal intake of every essential nutrient in order to maintain health throughout life is extremely challenging. There is much controversy regarding the "ideal" cat food. Some argue in favor of feeding prey or meat-and-bone-based raw diets. Others recommend feeding only canned (i.e., high-heat-cooked) or dry kibble diets. Regardless, there is little evidence to support the superiority of any particular feeding style. An increasing focus on disease prevention has led to our better appreciating the importance of body condition with an emphasis on obesity prevention. Also, there has been the adoption of feeding management strategies designed to accommodate the needs of specific households and of individual cats.

the Unique Nutritional Physiology of the Healthy Adult Cat

Protein and Specific Amino Acids

Cats have higher dietary protein requirements as compared with dogs, despite similar amino acid needs. Although cats can adapt protein oxidation to manage excess intake, there is limited ability to conserve nitrogen if protein intake is too low.[1] While the amount required is based on protein serving as a source of nitrogen and essential amino acids, it also provides energy. This reliance on glucogenic amino acids as a source of energy may influence the high protein requirement of carnivorous mammals with relatively large, glucose-consuming, brains.[2] Unlike other species, cats require dietary taurine and arginine due to low enzyme activities in those synthetic pathways.

Vitamins

Essential vitamins in cat diets include vitamin D, vitamin A, and niacin. Unlike other species capable of synthesizing vitamin D when the precursor, 7-dehydrocholesterol in skin, is exposed to UV light, a dietary source of vitamin D is essential for cats whose physiology shunts 7-dehydrocholesterol for metabolism to cholesterol.[3] Similarly, cats have a dietary requirement for niacin despite possessing all its necessary synthetic enzymes. The picolinic carboxylase enzyme activity in cats degrades an intermediate in the pathway which would lead to niacin synthesis. Cats also have low conversion efficiency for beta carotene (the plant-based precursor) to be processed to vitamin A. Therefore, the retinol form of vitamin A is required.[4] A dietary source of arachidonic acid is required for cats to reproduce, due to limited activity of the delta-6 desaturase enzyme. Many of the nutritional peculiarities of cats are likely the result of evolutionary adaptations to a carnivorous diet, which lessened the selection pressure to maintain energetically expensive pathways for nutrient synthesis.[5]

Carbohydrate, Fiber, Starch, Sugar

Due to their natural history as hunters, it has been theorized that cats are metabolically inflexible with regard

to the digestion, absorption, and metabolism of dietary carbohydrate. Indeed, specific saccharides, starches, and fibers are not considered nutritionally essential. However, fiber is a beneficial, but often overlooked, component of feline diets (see ch. 190). The potential role of poorly digestible animal tissue as "animal-sourced fiber" in large cats fed only carcasses has been suggested.[6] Digestible carbohydrates are often included in the diets of both dogs and cats as an energy source that allows a decrease in protein content, which may become increasingly important given emerging issues related to environmental concerns and pet food sustainability.[7] Further, there is lack of evidence that consumption of carbohydrate results in adverse effects when supplied in the moderate concentrations typical of commercial pet foods. It has been well documented that cats are able to digest and absorb sugar and starch despite their carnivorous nature. Cats produce several intestinal disaccharidases (including maltase and sucrose) and pancreatic amylase secretion is stimulated by dietary starch.[8-10] Cats have lower amylase activity than dogs, regardless of diet.[9,11] Even so, cats efficiently digest and absorb ground or cooked starch, even when fed at about 30-35% of total energy intake, similar to concentrations found in commercially available diets.[12,13]

In addition to efficient digestion and absorption, healthy adult cats also capably metabolize dietary carbohydrate despite some important physiologic idiosyncrasies. Once absorbed, glucose must be phosphorylated by gluco- or hexokinase prior to entering one of several metabolic pathways, including glycolysis. Cats only produce hepatic hexokinase rather than glucokinase or fructokinase. Interestingly, cats have higher activities of not just hexokinase but of several other glycolytic as well as gluconeogenic enzymes when compared with dogs.[14,15] Hexokinase is inhibited by its primary product, phosphorylated glucose. The limited hepatic uptake of glucose depends on the conversion rate of "trapped" glucose into energy or other compounds. This limit in hexokinase activity, together with the lack of glucokinase and fructokinase, may contribute to urinary losses of monosaccharides when fed in high concentrations (about 20% of energy supplied as sugar).[16,17] However, lower concentrations of carbohydrate (about 13% of energy supplied as sugar) are well accepted and tolerated.[17] Although higher dietary concentrations of glucose or fructose sometimes result in diarrhea, gluco- or fructosuria, blood glucose concentrations are not impacted. Healthy cats do not have persistent hyperglycemia even with an IV glucose bolus.[17,18] Although academically interesting, gluco- or fructosuria is not a clinical problem in healthy cats consuming commercially available diets since they typically do not contain simple sugars. Regardless, insulin response and adaptive enzymatic activity appear to be adequate compensation for the lack of glucokinase under conditions of both typical and supraphysiologic carbohydrate intakes in cats. Overall, in response to varied macronutrient proportions, the cat has the ability to increase glucose or protein oxidation, increase glycogenesis, and increase lipogenesis, which are remarkable given its evolution as a hunting carnivore.[1,19,20]

Determining the Optimal Feline Diet

Overview

The known nutritional needs of cats are summarized by the National Research Council as "minimal requirements" or "adequate intakes" depending on available data, "recommended allowances," and for some nutrients, "safe upper limits."[21] In addition, minimum and, in some instances, maximum concentrations of nutrients for use in commercial cat foods are suggested by the Association of American Feed Control Officials (AAFCO).[22] These Cat Food Nutrient Profiles, guidance for product labeling, and other aspects of pet food manufacturing and marketing as defined in the AAFCO Model Regulations for Pet Food are adopted by many states into official feed control laws.[23] Despite these well-defined resources regarding nutrient needs and the amounts of certain nutrients required in cat foods, exact quantitative information regarding the optimal intake of both micro- and macronutrients for adult cats remains unknown. Many guidelines are extrapolated from data generated using growing kittens, or represent minimal intakes that prevent defined deficiency syndromes rather than characterizing the ideal diet for longevity or other, more global, health parameters.

The Feral Cat Model

Defining the optimal intake of any nutrient in order to maximize both quality and quantity of life is a challenge. The utility of preference studies is thus far limited due to the lack of relevant measurable outcomes. Analysis of natural diets also has limited data, regardless of the known poor health and short lifespan of free-roaming cats. Although longevity data for small wild feline species are lacking, protracted lifespans for these

as well as feral domestic cats are unlikely to approximate those of pet cats. One study demonstrated a high reproductive rate in managed colonies of feral cats but kitten mortality was high, with only 25% surviving to 6 months.[24] Similarly, another study reported a life expectancy <5 years in feral cats due to infection, trauma, and poisoning.[25] Despite these impacts on longevity, the number of free-roaming cats is sustained due to their young age at sexual maturity and reproductive efficiency.[26] The estimated nutritional profile of free-roaming domestic cats has been reported, but association with health and longevity is lacking.[27,28] Since the life expectancy and general health status of most free-roaming cats differs markedly from that desired by most pet owners, it remains unknown if a "natural" approach to feeding cats would support optimal health and longevity. Regardless, avoidance of feeding practices associated with known problems can help promote health and longevity in the pet cat population.

Feeding Management of Cats

Overview, Avoiding Obesity, Effect of Neutering

The most common nutritionally-related disease in pet cats is obesity (see ch. 176). Avoidance of overfeeding is an important goal in feeding healthy cats. Although dietary carbohydrate and the use of dry cat foods have been blamed for increasing obesity risk in cats, the concept has not been supported by epidemiological data or prospective research.[29-32] Rather, dietary fat has clearly been shown to promote overeating that leads to weight gain, likely due to the increased energy density compared to carbohydrate and protein.[31,32] In addition to diet, epidemiological data have demonstrated that neutering is an important risk factor for obesity in cats, especially in males.[33-36] Overweight cats are more likely to suffer from diabetes mellitus, constipation, orthopedic disease, urinary tract disease, hepatic lipidosis, skin disease, and other issues.[29,37,38] As the majority of pet cats have a known risk factor (neuter status) for a disease that is likely to result in potentially significant morbidity (obesity), feeding management strategies aimed at prevention are indicated.

The relationships among food intake, body weight and condition, and energy expenditure after neutering are complex (see ch. 313). It seems clear that cats fed ad libitum after neutering are most likely to gain weight.[39-42] Food continuously available causes greater body weight and body fat percentage after neutering both male and female cats, as compared with cats that have restricted access to food.[43,44] In addition, greater weight gain and body fat accumulation is seen after neutering when fed energy dense diets.[31,32] As such, unrestricted access to food should be actively discouraged for most cats and energy dense foods should be used with caution.

It has been demonstrated that body weight gain can be avoided after neutering provided that food intake is actively limited, although it seems clear that some cats need fairly severe restriction to maintain pre-neutering body weight.[40,45] This underscores the role of food intake and feeding management in cats after neutering. It also supports an individualized approach to determining the necessary amount of restriction. Some cats need a reduction of 30% or more of their pre-neutering dietary intake.[44] Although using diets high in moisture or fiber may be effective in limiting food intake, more active restrictions on food consumption are probably needed.[46,47] Further, given the marked reduction in voluntary activity in queens after neutering, it is possible that encouraging increased activity may help offset the effect of neutering.[44] Thus, less severe food restrictions are required of active cats. In any case, portion-controlled feeding is recommended and regular monitoring of body weight and body condition may be needed to enable adequate and timely adjustments. Weight loss is difficult to achieve and re-gaining lost weight is always a concern.

Maintenance Requirements

Daily energy maintenance requirements of cats, based on absolute body weight, have been reported to be as low as about 30 to as high as about 100 kcal/kg BW.[21] Many factors likely explain these variations. The National Research Council provides different equations for lean versus overweight adult cats which both use metabolic, rather than absolute body weight[21]:

$$\text{Lean cats: } 100\ \text{kcal} \times \text{kg BW}^{0.67}$$

$$\text{Overweight cats: } 130 \text{ kcal} \times \text{kg BW}^{0.4}$$

Many clinical nutritionists use a simpler equation based on a neuter/activity status factor applied to the resting energy requirement (RER) at the current weight[48]:

$$1.0\text{-}1.4 \times \text{RER}$$

where RER = 70 × (current weight in kg)$^{0.75}$. Regardless, any equation used should be seen as a starting point and recommendations for individuals require reassessment and adjustments as needed to maintain an ideal body condition.

Choosing a Commercial Diet

Most cats are fed commercial food with many options for healthy cats encompassing a wide range of prices, marketing approaches, availability, ingredients, and nutritional profiles. This can be a benefit in that there are products to meet the needs and preferences of most cats as well as most owner financial limitations and any philosophical inclinations. However, the wide range of choices can also be overwhelming, confusing and, at times, misleading. The most important information from the pet food label is the nutritional adequacy statement required on pet food labels in states that adopted AAFCO Model Regulations for Pet Food.[22]

The nutritional adequacy statement on the label should state the intended use of the food (species and life stage) and specify whether it carries a complete and balanced claim versus "for intermittent or supplemental feeding only." The label should also disclose how claims are substantiated (passed feeding trials or formulated to contain nutrient concentrations as specified by AAFCO).[22] Neither method of adequacy substantiation is perfect; however, many nutritionists favor the animal feeding trial method as it at least partially accounts for nutrient digestibility and bioavailability and provides proof of adequacy by direct testing *in vivo*. Ideally, commercial pet foods are formulated to meet the AAFCO nutrient profiles by laboratory analysis (not just by calculation) as well as being subjected to and passing appropriate animal feeding trials.

Owner Education

Underestimation of obesity or a general unawareness of body condition is common among cat owners and can contribute to the development of obesity.[35] One study identified owner underestimation of cat body condition as a main variable influencing feline obesity.[30] Owners should be counseled on appropriate body condition for their pet and encouraged to perform regular home body condition scoring.[49,50] Determination of energy needs should be based on prior intake if known; however, the degree of restriction necessary to avoid weight gain is variable and underscores the importance of monitoring and adjustment.

Free feeding is common for cats and, while convenient for many owners, it may contribute to overeating. Free feeding is practiced by about 80% of cat owners, regardless of their pet's body condition and some studies have found no link between feeding practices and the prevalence of obesity.[30,51-54] It is clear that some cats successfully regulate their food intake to maintain an ideal body weight while others tend to overeat and become overweight or obese. In multi-cat households, individual, portion-controlled meal feeding can be an effective, albeit not as convenient, method for ensuring appropriate food intake and body condition.

Collection of diet history information should be done at every veterinary visit and should include not only the main diet used but also amounts and types of any treats and supplements. Monitoring of the pet's body condition score and body weight (see ch. 2), accompanied by any necessary adjustment in the amount and type of food fed, is a critical component in providing recommendations that meet the needs of individual pets. This process starts with a veterinary assessment and should be maintained by both the owner and the veterinary team.[50]

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CHAPTER 175

Nutrition in Healthy Geriatric Cats and Dogs

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Client Information Sheet: Nutrition and Feeding of Senior Pets

Geriatric dogs and cats are an increasing percentage of the pet population in the U.S.[1,2] Older cats can be classified[3] as "mature" from 7 to 10 years of age, "senior" from 11 to 14, and "geriatric" from 14 onwards. For dogs, size affects life span, with smaller breeds living longer than larger breeds.[4] The American Animal Hospital Association's Senior Care Guidelines Task Force[5] has suggested that pets should be considered geriatric when they are in the last 25% of the predicted life span for their species and breed. Aging is a continuum and individuals vary greatly as to their aging process, so any age classification should only be taken as a guide. Larsen and Farcas[6] proposed that an individualized assessment, where aging "milestones" such as joint disease and muscle atrophy are recorded, would be a better measure of aging rather than a cut-off age. This chapter will focus on the nutritional needs of healthy geriatric patients.

Nutrient-Related Changes Associated Wth Aging Pets

Some of the physiological consequences of aging are related to nutrient and energy utilization,[1] since aging can alter gastrointestinal structure and function, which is well described in humans.[7] Canine studies assessing digestibility of macronutrients (and some minerals) show that geriatric dogs have digestion capacities that are similar to those of young adults,[8,9] despite described anatomical[10] and microbiota[11] changes in the gastrointestinal tracts of geriatric dogs (see ch. 274). On the other hand, macronutrient (protein and fat) digestibility is reduced in geriatric cats.[12,13] As for energy, average canine energy requirements decrease with age.[14] Thus, obesity is a main problem in the senior dog population (see ch. 176). However, older dogs also are more likely than adults to be underweight.[15] As for felines, mature cats (>7 years) have decreased energy requirements compared to adults, but geriatric ones (>12-14 years) tend to have increased energy requirements,[16] which can, in part, be related to the lower digestibility of fat and protein and result in undesired weight loss. Average protein requirements also are changed with aging, with an increase in requirements in both dogs[17] and cats.[18] In cats, again, lower protein digestibility can contribute to this increased requirement. Also, lean body mass tends to decrease in older dogs[19] and cats.[20] As for other essential nutrients, such as vitamins and minerals, there are not enough conclusive data to know if these requirements are affected by old age. For this reason, neither the National Research Council[21] nor the Association of American Feed Control Officials has separate, specific requirements for senior pets in their publications addressing nutrient requirements of dogs and cats. Aging changes that are not related to nutrient utilization but that can respond to nutrient modification include brain aging (see ch. 263), joint degeneration (see ch. 187 and 353), and alterations in the immune system (see ch. 194).[1,2,6]

Aging also can result in a change in feeding patterns, sometimes associated with pain secondary to oral or joint problems or to cognitive disorders. Moreover, it has been described in aged people that their sense of taste and smell is altered,[7] which could also happen in our senior patients.

Nutritional Evaluation of the Senior Pet

The goals of feeding geriatric pets are to slow the changes associated with aging, promote well-being and, if at all possible, promote longevity, while keeping a healthy body weight (BW) and body condition score (BCS). Evaluating each patient is critical because not all animals age in the same way. The World Small Animal

Veterinary Association (WSAVA) nutritional guidelines describe how to perform a nutritional evaluation[22] (see ch. 170). Assessment of the patient, diet, and feeding method can identify risk factors that warrant changes in the diet and feeding method. Particularly, for aged patients,[6] it is important to focus on assessing BCS, energy intake, and feeding behavior, ensuring the diet is complete and balanced, and assessing if there are any age-associated alterations that could be addressed with diet, such as muscle atrophy/sarcopenia (see ch. 177), joint disease, cognitive alterations, and changes in palatability of the diet. This assessment will help decide on the feeding plan: how much to feed, the feeding method, and what to feed (choice of diet). In a patient with no known malnutrition risk factors and that is already healthy and lean, changes to the feeding plan might not be necessary. However, if risk factors are present, changes will need to be made to the feeding strategy accordingly.

How Much to Feed

The amount to feed depends on the energy requirement of the pet (maintenance energy requirements, MER). Ideally, MER can be determined from the current energy intake, if the patient's BW is stable. This is sometimes not possible to achieve, due to several reasons such as *ad libitum* feeding, multiple pets, diet variety, and the use of treats. In these cases, MER can be estimated with formulae[21,23,24] (Table 175-1), but the error associated with them is estimated to be 50%[24]; therefore, monitoring and adjusting the energy allowance is necessary. If there is a history of unintended BW loss or the patient has a low BCS, the current energy intake (or the estimated MER) should be increased by 10-20%. If BW does not improve with an increase in energy intake, or the patient won't eat enough, diagnostic tests will be necessary to identify the cause of the problem. Patients that are overweight and otherwise healthy should be considered for a weight loss plan (see ch. 176). Weight management and keeping lean during the pet's lifetime has been associated (in Labrador dogs) with a longer life span and a delay in the appearance of chronic disease, including osteoarthritis.[25] Therefore, keeping lean during growth and adulthood is the most important management strategy to keep a geriatric dog healthy for a longer period of time.

TABLE 175-1

Formulae to Estimate Daily Energy Requirements Adequate for Senior Pets (Expressed as Kilocalories Per Day)

DOGS		CATS	
Inactive pet dogs21	95 × BW0.75	Lean adult cats21	100 × BW0.67
Older active pet dogs21	105 × BW0.75	Obese adult cats21	130 × BW0.4
Obesity-prone adult dogs24	98 × BW0.75	Obesity-prone adult cat24	70 × BW0.75

BW, Body weight (kg).

Once the energy intake has been determined, the daily ration has to be calculated (Figure 175-1). If treats are to be included in the regime, it is recommended that a maximum of 10% of the daily calories be used for unbalanced items (such as treats, table scraps, supplements). In all cases, frequent reassessment and readjustment are necessary. Senior dogs and cats should be weighed at least once a month, using the same scale, to make adjustments up or down by 10%.

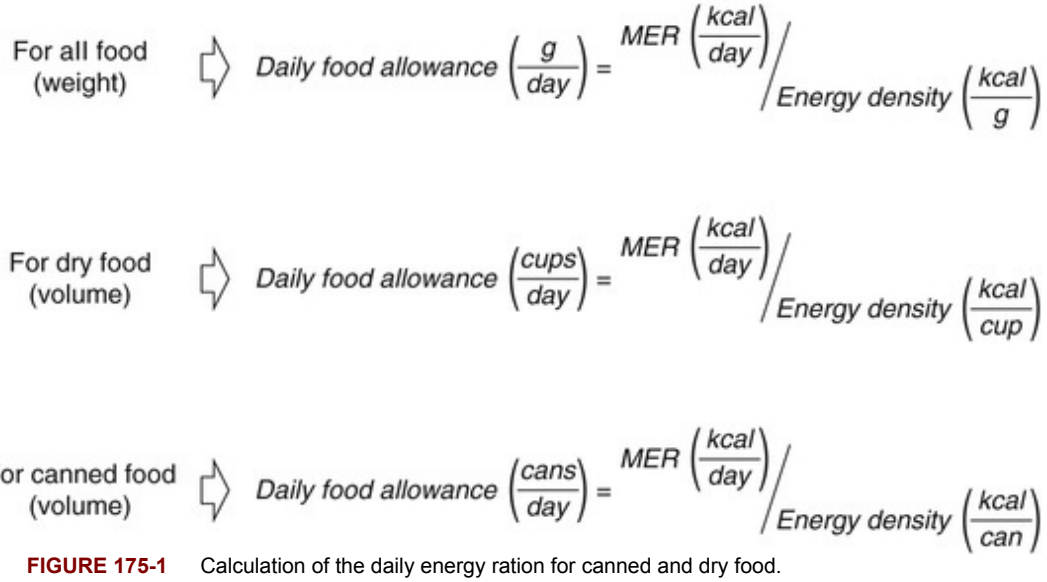

FIGURE 175-1 Calculation of the daily energy ration for canned and dry food.

Feeding Method

Ad libitum feeding, where food is always available, can work well in thin patients and picky eaters. For overweight (or prone to overweight) patients, rationed feeding (where a specific amount of food is fed daily) is the best approach. Diet form also will affect the decision regarding feeding method, since only dry food can be left out all day safely. Rationed feeding can be adequate in most cases, even when weight gain is desired and for picky eaters. This is important in multi-pet households, where different animals have different nutritional needs. Rationed feeding can be done in one or in multiple feedings a day. Multiple feedings have the advantage of both reducing hunger in animals that are energy-restricted and also promoting weight gain in animals that are volume-intolerant or are picky eaters. In thin patients, where the energy allowance should be increased, the options are: feeding *ad libitum*, increasing the volume of each meal, adding one more meal to the schedule, or choosing a more energy-dense diet. The last two are more useful in patients whose intake is volume-limited. Warming the food or using flavor enhancers (such as home-prepared broth) can help bring out the flavor of the food and encourage senior picky eaters to eat (also see ch. 183). In all cases, environmental enrichment, including the feeding method (such as hiding food, using food dispenser toys, etc.), is recommended.[2,6]

Choice of Diet

The diet that is chosen has to be nutritionally complete and be palatable to the specific animal. Senior/mature/geriatric diets are a subset of adult diets because there is no legal definition of what a senior diet is. The nutritional composition of these diets on the market varies widely and reflects the philosophy of each manufacturing company. One study[26] evaluated 37 over-the-counter (OTC) senior canine diets on energy density, protein, fat, fiber, sodium and phosphorus and found huge variations. For this reason, recommending a senior diet for an aging dog or cat is not a useful or precise enough recommendation and the choice of diet has to be tailored to the patient, always considering the current diet. A healthy, lean patient doing well on its current complete adult diet will not necessarily require a diet change. Overweight patients will benefit from therapeutic, nutrient-fortified weight loss diets and a weight loss plan (see ch. 176) while obesity-prone individuals can be either fed less of the current diet or fed an OTC diet higher in fiber and/or lower in fat (thus, lower in energy density). Some senior and light diets will help in the latter case, but the energy density of the particular product of choice has to be compared to the current diet, to ensure the change is made in the correct direction. For thin patients, weight gain can be promoted using diets with higher energy density than the current one (such as kitten/puppy diets, convalescence or performance-type diets, or a variety of OTC adult/senior diets). Regarding nutrient composition, protein is a controversial issue, since there is the mistaken impression that diets higher in protein can cause kidney damage. However, as mentioned above, protein requirements of senior pets are at least as high as those of adults, if not more. Thus,

protein moderation/restriction (less than 20% and 30% protein calories for dogs and cats respectively) provides no benefit and potentially is problematic to senior pets. Appropriate protein content is particularly important in healthy patients showing some degree of muscle mass loss; in such a case, choosing a higher-protein diet than the current one is indicated. If patients have chronic kidney disease and need protein restriction (plus other strategies), they will benefit from therapeutic diets rather than senior OTC diets (see ch. 184). Antioxidants can be useful for the management of age-associated cognitive dysfunction[27,28] and are suggested to improve immune function parameters in dogs[29] and cats[30] (although the clinical significance of the latter is unknown). There are both OTC and therapeutic antioxidant-enriched diets that could potentially help with brain aging (see ch. 263); however, there is a lack of standardized dose-response studies to make a specific (type, combination, and dosage) recommendation at this time. Other nutrients that can help with cognitive dysfunction are long-chain omega-3 polyunsaturated fatty acids (PUFAs) from fish oil and medium chain triglycerides (MCTs). The brain has a high concentration of these omega-3 PUFAs and they are very important for brain development in the young.[31] The data regarding their effects on canine and feline brain aging still are lacking. In one study,[32] middle-aged cats fed a blend of fish oil, B vitamins, antioxidants, and arginine performed better in cognitive tests than control cats did, but it is impossible to separate the effects of the different nutrients. As for MCTs, there are preliminary data in dogs[33] showing that MCTs can help with clinical signs associated with mild cognitive dysfunction and the authors propose that ketone bodies obtained from MCT metabolism provide alternative sources of fuel to the aged brain, which has a reduced glucose oxidation capacity. Some OTC and therapeutic diets contain MCTs (mostly from coconut oil but also from other purified sources). Long-chain omega-3 PUFAs (eicosapentaenoic acid and docosahexaenoic acid) also have been proposed to help reduce clinical signs of joint disease (see ch. 187), although there are no data supporting any nutritional modification to prevent joint disease (as opposed to treating it) except weight management. The use of pre- and probiotics to modify intestinal microbiota (altered during aging[1]) and immune system modification potentially are interesting but data still are lacking. One study[34] in cats showed that long-term feeding of a diet enriched with a blend of chicory root (a prebiotic), antioxidants (vitamin E and carotene) and omega-3 and -6 fatty acids resulted in a longer life and less loss of lean body mass associated with aging compared to the control group, but no difference compared to a group fed the control diet plus only the antioxidants. Even though the results are encouraging, from this study it is impossible to discern each individual nutrient's effects and there are no dose-control studies to give a specific recommendation.

In summary, old age is not a disease, and the feeding plan (diet, amount, method) has to be tailored to the senior patient after a careful nutritional evaluation, since individual variation precludes generic recommendations. Senior pets should be fed a complete and balanced diet for adult dogs or cats (with specific modifications depending on the evaluation), fed in sufficient amounts to maintain an ideal BW and a lean BCS. Adequate weight management from weaning onwards is the best strategy to ensure a healthy geriatric pet. Conditions that cause pain, discomfort, and alterations in cognition should be addressed. The use of antioxidant- and omega-3-PUFA-enriched diets can have positive effects on well-being although no specific recommendations can be made at this time. There are many commercial OTC diets (marketed for both adult and senior pets) that can be used, with different ingredients, processing, and texture to accommodate for palatability preferences. In senior pets with health conditions, specific nutritional management for that specific disease is indicated.

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CHAPTER 176

Obesity

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Client Information Sheets:
Owner-Pet Lifestyle Questionnaire
Pet Obesity: Common Questions

Definition

Obesity is defined as excess body fat, to such an extent that it may compromise health.[1] In general, dogs and cats are considered obese when their excess fat exceeds optimal body weight by 15-20%.[2] It has been estimated that 25-40% of pet cats and 25-44% of pet dogs are obese. Some believe these estimates will become progressively more conservative, in parallel with the human condition.[3-7] Animals who remain moderately overweight for years are estimated to have their life expectancy decrease as much as 2.5 years, while suffering from an obesity-related condition.[8]

The most accurate measure of an animal's obesity is quantitative analysis methodology.[2] Dual-energy X-ray absorptiometry (DXA) and % total body water (TBW) are reliable.[9-13] Bioelectrical impedance analysis (BIA) is commonly used in people, although its validity in dogs and cats has yet to be demonstrated.[2] Veterinary clinicians need a simple, quick, and cost-effective means of estimating obesity, such as body condition scoring (BCS) and morphometric measurements (see ch. 2). BCS is widely accepted for assessing levels of body fat subjectively with a combination of visual assessment and palpation over ribs/spine and presence/thickness of abdominal folds (see ch. 170).[14,15] Each animal is classified on a scale of 1 to 5 or 1 to 9 points.[15-18] The 9-point scale, validated with DXA, establishes ideal weight at 5, with each point above or below representing weight gain or loss of approximately 10-15%.[2,16,17,19] *Morphometric measurements* involve estimating BCS of dogs and cats by measuring various body area circumferences. This method has been validated with DXA and should only be used on obese animals.[2]

Etiology

Obesity has a multifactorial etiology that involves genetic and environmental factors (Table 176-1).[20] Although some diseases (hypothyroidism, hyperadrenocorticism, etc.), drugs (glucocorticoids, anticonvulsants, etc.) and rare genetic disorders (especially in humans) may contribute, obesity is almost always caused by more calories being consumed than used over an extended period of time.[7] The hereditary predisposition to obesity is reported in some purebred dogs and cats (Labrador Retriever, Cavalier King Charles Spaniel, Shetland Sheepdog, Cocker Spaniel, Rottweiler, Yorkshire Terrier, Poodle, domestic short-hair and long-hair cats, mixed-breed cats, Manx cats, etc.).[21-23] Some breeds (Greyhound, et al) are resistant or less prone to obesity.[24] Other predisposing factors in dogs include: age of owner, hours of daily exercise, frequency of treats, amount of food intake, consumption of table scraps, body condition of owner and the pet being a spayed female.[5,21,25] In cats, predisposing factors include frequency of feeding, being middle-aged (over 7 years) and being a neutered male.[4,26,27] Neutering affects both dogs and cats because absence of sex hormones reduces metabolic rates.[22,25,28] In particular, neutering female dogs predisposes them to obesity because estrogen has central effects on food intake and energy expenditure by inhibiting the deposit of adipose tissue and controlling the number of adipocytes.[29]

TABLE 176-1

Risk Factors for Obesity

Related to the Animal	*Age:* middle-aged and older (d and c)
	Breed: Labrador Retriever, Cocker Spaniel, Cavalier King Charles Spaniel (d) and domestic short-hair (c)
	Sex: female (d) and male (c)
	Hormone status: spayed or neutered
	Related disorders: hypothyroidism (d), hyperadrenocorticism
Iatrogenic Effects	*Medication:* anticonvulsants, steroids (d and c), etc.
	Surgeries: thyroid gland removal (d), spay/neuter surgery, etc. (see ch. 313)
Related to the Owner	Older or elderly people, overweight/obese, women, high earners, underestimating the problem, overprotective, etc.
Related to Food and Diet	Non-commercial food, canned food, table scraps (d and c), feeding very often, lots of treats (d), free feeding (c)
Related to Lifestyle and Behavior	Living indoors, humanization (d and c), begging for human food (d), inactivity, substitute for human companionship, anxiety, little time to play (c)

c, Cats; *d*, dogs.

Pathophysiology

Adipose tissue is composed of about 50% adipocytes and 50% other cell types (preadipocytes, stem cells, endothelial cells, pericytes, macrophages, fibroblasts, nerve cells).[20,30-33] It was once thought that fat was a metabolically inert energy storage depot, used during extended fasting. It is now appreciated that fat is a complex and active organ.[20,33,34] An excess accumulation of fat leads to being overweight, an increased burden on both joints and the heart, contributing to their degenerative conditions. In addition to adipose tissue, the gastrointestinal and reproductive systems also have hormonal influences on obesity.

Adipose Tissue as an Endocrine Organ

Introduction to Leptin and Adipokines

Adipose tissue is an endocrine organ, not only producing leptin (the OB protein), but substances called adipokines that have local and systemic effects.[20,35-38] The term adipokine encompasses more than 100 biologically active products, including steroid hormones, cytokines, vasoactive amines, regulators of glucose and lipid metabolism, regulators of cardiovascular function, and other biologically active mediators.[30-32,34,36,37] Adipokines are secreted not only by adipocytes but also by other cells within adipose tissue (e.g., macrophages). Although their physiological mechanisms are not completely known, adipokines are generally divided into those which alter inflammation (pro- or anti-inflammatory) and those that affect energy balance by promoting insulin resistance.[34] Along with leptin, dogs and cats have other adipokines: adiponectin, resistin, components of the renin-angiotensin-aldosterone system (RAAS; e.g., angiotensinogen), certain proinflammatory cytokines (interleukins [IL], tumor necrosis factor alpha [TNF-alpha], etc.) and other inflammatory mediators (C-reactive protein [CRP], etc.).[30-32,36,39,40]

Adipokines have local (apocrine) and systemic (endocrine or inflammatory) effects that may differ depending on the animal species and the physical location of the adipose tissue.[30] If fat deposition in adipocytes is limited or altered by lipodystrophy or age, lipid can be deposited in other organs (liver, pancreas, kidneys and muscle), potentially altering function due to lipotoxicity.[41] In humans, as fat builds up in visceral versus SC deposits, risk of insulin resistance, atherosclerosis and diabetes mellitus increases.[42] Leptin, adiponectin and angiotensinogen have been studied in dogs.[30] Resistin, visfatin and apelin have been studied in people and in laboratory animals.

Leptin

Leptin is an anti-obesity hormone mainly synthesized in adipocytes, although small quantities are produced by gastric mucosa, liver, mammary glands and placenta.[30,43] Obese individuals may be relatively resistant to leptin. Plasma concentrations of leptin increase in dogs and cats that have large amounts of body fat and large number of adipocytes. Conversely, leptin concentrations decrease when animals lose weight.[44-47] The primary action of leptin is binding to brain receptors (called OB-R receptors) that suppress appetite and increase energy expenditure, influencing food-related behavior.[48,49] Leptin also stimulates angiogenesis, suppresses apoptosis, acts as a mitogen (which could explain the higher incidence of cancer in obese people), regulates immune and reproductive functions, modulates insulin sensitivity, exerts proinflammatory (mediated by IL-6 and others) and prothrombotic effects, and inhibits adiponectin.[20,30,50] Although it is considered a long-term regulator of body weight, postprandial concentrations of leptin decrease transiently in lean but not obese people.[51] In dogs, there is a transient increase in circulating leptin concentrations after meals, with a postprandial peak 5-8 hours after eating, concentrations being double or triple those seen when the same dogs are fasted.[52] In cats, increased serum leptin concentrations after meals are mild compared with those of fasted animals.[53,54] Most obese animals have serum leptin levels higher than those of thin animals, perhaps due to leptin resistance.[52,55-57] Resistance to or lower sensitivity to leptin may originate in defective leptin receptors or in reduced target tissue signaling, such as hypothalamic neurons.[48,57] In a study of obese dogs, elevated serum leptin concentrations and deficient leptin transport across the blood–brain barrier were observed.[58]

Adiponectin

Adiponectin is an adipokine thought to be synthesized and secreted by mature adipocytes of dogs and cats. In rodents and humans, it may also be synthesized in cardiac muscle.[59-61] Serum adiponectin concentrations are decreased in obese dogs and cats, perhaps as a result of inhibition caused by secretion of inflammatory cytokines.[45,56,59,62,63] The effects of adiponectin vary by target organ. It contributes to increased insulin sensitivity and lower serum glucose concentrations. Liver and muscle triglyceride concentrations as well as inflammatory responses and atherosclerosis are reduced by adiponectin.[30,37,64,65]

Angiotensinogen and the RAAS

Adipose tissue is an important source of angiotensinogen.[30,66,67] The RAAS has a role in adipocyte differentiation and metabolism, as well as in vascular homeostasis, fluid balance and kidney function.[20,30] In humans, rodents, and dogs, adipose tissue can activate the RAAS via angiotensinogen, renin and angiotensin-converting enzyme, resulting in increased concentrations of angiotensin II, vasoconstriction, and aldosterone synthesis. Aldosterone increases renal retention of Na^+, which contributes to hypertension and kidney impairment.[67,68] Alterations in the RAAS may contribute to local inflammation in adipose tissue, allow insulin resistance to progress, stimulate leptin production and reduce adiponectin production.[67,69-71] Although the role of obesity and the RAAS are not completely understood in cardiovascular or kidney conditions in dogs and cats, studies in people and rodents are suggestive.[20]

Resistin

Resistin, synthesized by adipocytes in mice, may have important physiologic effects in dogs and cats.[72,73] In people, resistin is primarily synthesized by macrophages, but is also expressed in adipocytes.[30,74,75] Plasma resistin concentrations are increased in obese people, but the cell receptor has not been identified.[30,76,77] Its secretion pattern is similar to that of leptin: it increases with food intake and plasma concentrations are proportional to percent body fat.[72] It stimulates proinflammatory cytokine production in macrophages, leading to the elevated resistin concentrations associated with atherosclerosis in people.[30] Serum resistin concentrations increase in acute pancreatitis and diabetic ketoacidosis, but not in pituitary-dependent hyperadrenocorticism.[78-80]

Apelin

Secretion of this adipokine primarily by adipocytes in rodents and humans is directly influenced by insulin. Serum apelin and insulin concentrations increase in obese rodents and people, exerting cardioprotective effects via vasodilation, lowering blood pressure, and reducing vasoconstrictive actions of angiotensin II.[81-85]

Visfatin

Visfatin is produced in adipocytes, lymphocytes, bone marrow, the liver and muscle tissue, and is more prevalent in abdominal fat than in subcutaneous fat. It binds to insulin receptors, thereby stimulating the use of glucose by adipocytes and myocytes, suppressing release of glucose from hepatocytes.[86] It also has proinflammatory and regulatory properties with regard to some immune functions.[87]

the Gastrointestinal System as an Endocrine Organ

Overview

Gastrointestinal hormones affect appetite and satiety (see ch. 310). Disorders in the brain–gut axis can lead to weight gain and obesity. Peptides released from the gastrointestinal tract (primarily ghrelin, cholecystokinin and glucagon-like peptide-1 [GLP-1]) affect the hypothalamic and brainstem regulatory centers that control food intake and eating habits.[88]

Ghrelin

Known as the "hunger hormone," ghrelin is synthesized by oxyntic glands within the stomach fundus and is the only known orexigenic hormone.[89] Its acylated active form, produced after fasting, crosses the blood–brain barrier, binding to receptors that stimulate appetite and synthesis of growth hormone.[90,91] Levels of ghrelin increase during overnight fasting and drop to minimum levels approximately one hour after eating.[92-94] Ghrelin concentrations in humans and dogs are decreased in obese individuals and high in those with anorexia. Secretion is also influenced by calorie intake and diet, decreasing less with high-fat diets than with carbohydrate-rich diets.[47,95-99] Ghrelin concentrations decrease less after meals in obese versus lean people.[100]

Cholecystokinin (CCK)

CCK is an anorexigenic hormone secreted by L-cells of the small intestine in response to food intake.[101] It stimulates digestion by increasing pancreatic and biliary secretions, delays gastric emptying and exerts negative feedback on the appetite at a central level (the dorsomedial hypothalamic nucleus and median eminence).[102-106] In lean people, postprandial CCK concentrations increase more quickly, reaching and maintaining higher concentrations than in obese people.[107] Postprandial levels are also higher after high-fat meals.[108] While CCK is considered important with regard to regulating food intake, there is no clear link with obesity.[33]

Glucagon-Like Peptide-1 (GLP-1)

GLP-1 is produced in intestinal L-cells, and to a lesser extent, in the pancreas and hypothalamus.[88,105] Its secretion is stimulated by the presence of food in the small intestine, by glucose and fatty-acid concentrations or by vagus nerve stimulation.[88] It stimulates beta-cell synthesis of insulin and inhibits glucagon secretion in alpha-cells.[105] GLP-1 suppresses appetite in the central nervous system (CNS) via specific receptors and decreases rates of gastric emptying and food absorption.[109,110] GLP-1 concentrations are higher after eating high-fat meals.[111] Postprandial GLP-1 production is lower in obese versus lean people, probably due to elevated glucose and fatty-acid levels associated with obesity.[112-114] By contrast, in dogs obesity is positively associated with GLP-1 concentrations.[40,44]

Obesity and Reproductive Hormones

Sex hormones, particularly estrogens, affect energy balance in both the central and peripheral nervous

systems.[29] In the CNS, they reduce food intake and increase energy expenditure.[115,116] Estrogens regulate lipid and glucose metabolism, inhibit lipogenesis, and determine the number of adipocytes.[29,117,118] Neutering contributes to the development of obesity via direct action on the satiety and metabolism centers as well as indirectly affecting cell metabolism and interaction with hormones such as leptin.[119] The estrogen/obesity relationship has been extensively studied in people but information is limited in dogs or cats (see ch. 313).[33]

Obesity as Chronic Low-Grade Inflammation

Rapid increases in adipocyte numbers beyond their blood supply reduce available oxygen, stimulating synthesis and secretion of cytokines and angiogenic factors that promote vascularization.[120] Expanding adipose tissue, therefore, may result in increased cytokine and proinflammatory mediator concentrations. Also, production of monocyte chemoattractant protein-1 (MCP-1) is enhanced. Attracted macrophages represent a primary source of inflammatory mediators in adipose tissue. This may explain the increased expression of TNF-alpha and IL-6 in obese animals.[34,121-123] Conversely, decreases in adipose tissue are associated with fewer macrophages and lower inflammatory mediator concentrations.[124,125] In addition to a higher number of macrophages, people have been shown to have "proinflammatory" (M1) and "anti-inflammatory" (M2) macrophage imbalances that increase risk of inflammation and metabolic disorders. Obesity, in this context, may represent a chronic proinflammatory disease.[126-128]

TNF-alpha is a cytokine produced by a large variety of cells, including macrophages, mast cells, neurons, fibroblasts and adipocytes.[2] Serum concentrations of TNF-alpha, which is primarily synthesized by macrophages, are higher in obese versus lean dogs and cats.[123,129-132] In addition to its antitumor activity, TNF-alpha affects energy metabolism by blocking insulin-receptor activation, causing insulin resistance.[37,133-135] TNF-alpha is involved in inflammatory processes, autoimmune disorders, septic shock and fever.[136,137]

Interleukins, which participate in metabolic, regenerative and neurological processes, also have roles in obesity-associated inflammation.[138] For example, in the obese, IL-6 is released into portal circulation by visceral adipose tissue, stimulating hepatic triglyceride secretion, reducing hepatic insulin sensitivity, and actively taking part in the inflammation associated with obesity.[20,139] IL-6 serum concentrations increase in humans with type 2 diabetes and metabolic syndrome, being closely linked to excess body mass.[139]

C-reactive protein (CRP) is generated in the liver in response to the presence of IL-6 and TNF-alpha, with an important role in heightening the inflammatory response.[140-143] It is an excellent marker of obesity-associated inflammation and a good predictor for certain cardiovascular diseases and diabetes.[144]

Consequences of Obesity

General Associations

Disorders associated with being overweight due to excess body fat can be either metabolic, mechanical, or both. Metabolic disorders may follow increased production of metabolites by adipose tissue (inflammatory mediators, hormones, etc.), with local, peripheral and central effects. Mechanical disorders follow increased body mass and weight on bones, joints, the cardiovascular system, etc., and are usually slowly progressive. By the time signs appear, many conditions are already chronic and/or advanced. This is one of the most compelling reasons to persuade owners to use suitable preventive medicine: obesity increases the risk of chronic disease, shortens lifespan and diminishes quality of life.

Osteoarthritis

Osteoarthritis may result from metabolic and mechanical phenomena (see ch. 353, 355, and 356). The inflammatory action of leptin, produced in large amounts by excess adipose tissue, is the triggering factor for certain forms of inflammation (osteoarthritis).[145] Increased leptin concentrations in cartilage (chondrocytes) and synovial fluid in the obese are directly related to body mass index (BMI).[146] Together with increases in other cytokines (IL-1-beta, TNF-alpha), leptin may degrade cartilage in part by increasing expression of specific proteolytic enzymes, including matrix metalloproteinases (MMP-1 and MMP-13) and aggrecanases (ADAMTS-4 and ADAMTS-5).[147] In rodents and people, chondrocytes synthesize not only leptin, but also proteoglycans. This link suggests that leptin may have a role in the anabolic activity seen in

osteoarthritis.[146,148] Chondrocytes, stimulated by leptin, synthesize growth factors (e.g., insulin-like growth factor [IGF]-1 and TGF-beta, with short-term enhancement of cartilage repair but long-term stimulation of osteophyte production and osteoarthritis-related signs).[148-153] Mechanical problems stem from being overweight (even in moderate cases) for extended periods of time. Overweight dogs have a shorter average life expectancy and problems associated with osteoarthritis at younger ages when compared with dogs whose weight is within an ideal range.[8] It has been estimated that one-third of lame cats would improve if they attained an optimal BCS.[27]

Insulin Resistance and Type 2 Diabetes Mellitus

Endocrine Pathways

Insulin resistance associated with obesity is one of many predisposing factors for type 2 diabetes mellitus (DM2; see ch. 305).[154,155] Cats are almost 4 times more likely to develop DM2 if overweight.[155,156] Different endocrine, neurologic and inflammatory pathways are altered in the obese and contribute to insulin resistance.[157] *Fatty acid (FA) concentrations* increase in the obese and, with other factors, activate protein kinases that adversely affect key mediators of insulin receptor function.[158] Hormones produced by adipose tissue (leptin, adiponectin, resistin, etc.) play a fundamental role in insulin resistance. Adiponectin concentrations, synthesized by mature adipocytes, decrease in the obese. In experimental animal models, adiponectin disruption worsens insulin resistance.[159] In the liver, adiponectin increases insulin sensitivity and FA oxidation, reducing hepatic glucose secretion.[160] In muscle, adiponectin stimulates use of glucose and FA oxidation and likely the AMP-activated protein kinase (AMPK).[161] Serum resistin concentrations are elevated in obese animal models, causing insulin resistance because they induce expression of the suppressor of cytokine signaling 3 (SOCS-3), a negative regulator of insulin expression.[162-164] Lack of resistin improves glucose homeostasis in experimental animals.[165]

Inflammatory Pathways

Activation of inflammatory pathways in hepatocytes may cause local and systemic insulin resistance.[166,167] The kinase *Jun N-terminal protein kinase 1* (JNK1) is activated by inflammatory stimuli (e.g., TNF-alpha) and has increased liver, muscle and adipose tissue activity in the obese.[168] Activation of JNK1 leads to phosphorylation of IRS-1, which weakens insulin action and facilitates insulin resistance.[169] Concentrations of *IL-6* are directly proportional to obesity, lowering glucose tolerance, increasing insulin resistance, and having predictive value for development of DM2.[170,171] When administered, JNK1 induces hyperglycemia and hyperlipidemia by reducing insulin receptor substrate (IRS), and increasing SOCS-3.[172,173] *TNF-alpha* concentrations are directly proportional to an individual's adipose tissue and insulin resistance.[123] TNF-alpha activates serum kinases that increase the phosphorylation of IRS-1 and IRS-2, converting them into poor substrates for the kinases that activate insulin receptors and increasing their degradation.[174,175] *Retinol binding protein (RBP4)* is produced in liver and adipose tissue. Serum concentrations of RBP4 increase with obesity, causing insulin resistance in animal models and people by inactivating glucose transporter type 4 (GLUT4) in adipose tissue.[176]

Neurologic Mechanisms

The brain processes the concentrations of substances such as leptin, FAs, and insulin for control of appetite and metabolism in relation to energy storage and expenditure.[157,177-179] Insulin and leptin have critical roles in the central control of peripheral glucose metabolism by acting on the hypothalamus and brainstem to reduce hepatic glucose production and increase peripheral utilization.[180] Central administration of leptin decreases insulin resistance in rodents with lipodystrophy and leptin deficiency.[181,182] Both leptin and insulin induce SOCS-3 expression, which actually reduces sensitivity to both.[183]

Dyslipidemias

Serum concentrations of cholesterol and triglycerides in the obese are often increased and they decrease with weight loss.[97,184] Both cholesterol and triglycerides are transported by blood lipoproteins and classified as

very low (VLDL), low (LDL) and high-density (HDL) (see ch. 182).[185] Abnormalities in lipoprotein profiles from obese dogs with insulin resistance are similar to those in people.[184,186] Obese dogs, cats and humans who have insulin resistance have less lipoprotein lipase (LPL) activity and reduced lipolysis.[186,187] There are also increases in circulating concentrations of non-esterified fatty acids (NEFAs) and VLDL.[188,189] Hypercholesterolemia has been associated with eye damage and hypertriglyceridemia with acute pancreatitis in dogs.[190,191]

Cardiovascular Conditions

A link between obesity, metabolic, and hemodynamic disorders is the associated increase in circulatory volume and vascular resistance, contributing to hypertension.[192-194] Increased circulatory volume increases left ventricular (LV) mass with chamber dilation but without wall thickening (eccentric hypertrophy). Increased vascular resistance causes the LV wall to thicken but the chamber does not dilate (concentric hypertrophy).[195,196] Abdominal obesity, more than general obesity, is associated with heart disease in dogs, by worsening cardiac relaxation (diastolic dysfunction) and reducing LV systolic function.[197-199] This has been associated with portal vein thrombosis and myocardial hypoxia.[200,201] In people, while obesity is clearly a predisposing factor for cardiac disease, the prognosis after a diagnosis of heart failure is better in obese or overweight people than those whose body weight is at or below ideal.[202,203] Several explanations have been suggested for this "obesity paradox": (1) cardioprotective effects of some cytokines and hormones synthesized by adipocytes[203,204]; (2) obese patients may manifest cardiovascular signs at earlier stages of the disease than those who are not overweight[203]; (3) the paradox is more likely related to a lack of weight loss than to actual weight gain, given the adverse effects that wasting syndrome causes in people with heart failure.[205] Dogs with heart failure who gained weight had a significantly longer survival than those whose weight remained stable or decreased.[206] In cats, there may be a link between weight and survival.[207]

Kidney Disease

The link between kidney damage and obesity is a combination of hemodynamic factors (including sympathetic nervous system [SNS] and RAAS activation leading to increasing blood pressure), metabolic factors (diabetes), and still to be defined inflammatory factors.[208] Excess ectopic fat storage in the viscera may cause lipotoxicity and a build-up of renal toxic metabolites derived from lipid metabolism (e.g., diacylglycerols and ceramides).[209]

Obesity increases Na^+ reabsorption, extracellular fluid volume and blood pressure.[210,211] Increased blood pressure (BP) and glomerular filtration rates adjust for excess Na^+ reabsorption initially, but chronic hypertension, renal vasodilation, renal hyperfiltration, SNS and RAAS activation, metabolic issues and inflammatory disorders contribute to progressive renal damage.[208] The obese have mild increases in renal and skeletal muscle SNS activity, the effects of which on BP are mediated within the kidneys.[212,213] Leptin, which activates the SNS to exert its central functions of reducing appetite and increasing energy expenditure, also may be important in raising BP in obese individuals.[211,214]

Cancer

Hormones and growth factors produced by adipose tissue, inflammation, and central mechanisms that regulate energy balance may contribute to obesity-related cancers.[215] This link is evident in endometrial, breast and kidney cancers but is less obvious in colorectal, pancreatic and prostate cancers.[216] Insulin and IGF-1 are potentially critical in cancer development. Calorie restriction, which reduces their concentrations, also inhibits carcinogenesis.[217] Leptin has been extensively described as a mediator of colon and breast cancers, as it increases cellular proliferation and transformation and has anti-apoptotic effects.[218-220] By contrast, adiponectin may have anti-cancer effects by reducing insulin/IGF-1 and the production of nuclear factor kappa-B (NF-kappa-B).[221] Adiponectin levels are inversely related to thyroid and breast cancers.[222-224] The link between adiponectin and endometrial cancer is controversial.[225,226] Inflammatory cytokines (TNF-alpha, IL-6, etc.) increase with activation of NF-kappa-B complexes and steroids are possible cancer-obesity links.[227-229]

Respiratory Diseases

Although respiratory syndromes and airway distress associated with obesity have been widely described in human medicine, only anecdotal reports have linked obesity with greater distress in dogs with tracheal collapse or laryngeal paralysis or cats with asthma.[20] Obesity appears to limit airflow during expiration.[230]

Treatment

Overview

Under physiological conditions, an animal's weight tends to remain relatively constant due to a balance between the calories ingested and those utilized. The energy balance is positive when energy input is greater than utilized and negative if use exceeds intake. Physiologic responses to excess input increase energy expenditure.[231] Treatment of obesity focuses on reducing calorie intake and increasing calorie expenditure. Due to variations in energy utilization (basal metabolic rate [BMR]) and types of physical activity, most pets benefit from an individualized approach.[231,232] An assessment should be made to determine the extent to which a dog or cat is overweight/obese. The easiest method in dogs and cats is to combine body weight (BW) and body condition score (BCS) (see ch. 2).[1]

Essentially, treatment for obesity should be based on four points[233]:

a. Initial assessment (patient, owner, environment, type and amount of food)

b. Reduce calorie intake (change diet amount and/or composition, pharmacological aids)

c. Increase energy expenditure (exercise)

d. Monitoring and maintenance of the objectives attained

Initial Assessment

It is essential to start with a complete history and physical examination. Laboratory tests and diagnostic imaging may help rule out associated conditions. Likewise, BW, BCS and muscle condition scoring (MCS) should guide the clinician in estimating ideal weight (see ch. 177).[233-235] As discussed, one should use the 1-9 point BCS with "5" being ideal and each point above indicating a 10-15% increase in body weight above ideal (see ch. 2).[16,17,19]

Once the pet is examined and confirmed to be overweight, the owner can be asked to fill out a questionnaire, such as that in the provided Client Information Sheet, to establish the conditions that may have led to weight gain and the owner's interest in having his/her pet lose weight. The owner is the key to treatment success. Of pets with a BCS >5, 40-50% of their owners did not consider their pets overweight.[235] Owners must understand their roles modifying feeding habits, feeding times, reducing treats, rationing food into one or two meals (no *ad libitum* feeding), avoiding feeding table food, and increasing both frequency and duration of walks and playtime.[233,236]

Reduction of Calorie Intake

Although each pet must be considered individually, one can begin by reducing the quantity of food offered by 20% for a period of one month.[237] If the amount of food is not known or free feeding is done, daily energy requirement for weight loss is usually about 80% of RER, based on the pet's ideal weight, with re-checks every 2-4 weeks (see ch. 170).[235,238-240] Some studies recommend greater restrictions in RER (60%).[241] Resting energy requirements (RER) can be calculated with the following formula:

$$\text{RER in kcal/day} = 70 \times (\text{ideal weight in kg})^{0.75}$$

Although complete fasting might lead to weight loss, this approach is not recommended.[242,243] The only realistic alternative is use of home-made or commercial diets which contain fewer calories, less fat, more protein, and more micronutrients.[7,231] Changing diet composition can reduce the total number of calories and/or modify the sensation of satiety to improve body composition and metabolic expenditure.[231] Weight loss should progress slowly (0.5-2% per week) in dogs and cats.[232,241,244] For adequate dietary protein, dogs

should be given about 5 g/kg of BW and cats about 2.5 g/kg. Choose and weigh diets according to pet preference, perhaps using a scale for extremely small animals.[238]

Changes in Diet Composition

High-Protein Diets

Because the energy utilization rate for protein (77%) is lower than for fat (94%) and carbohydrate (98%), weight-loss diets should be low in calories and high in protein.[245] Thus, a high protein/calorie ratio should be achieved that increases the percentage of fat loss and minimizes the loss of muscle mass.[246,247] A similar effect is achieved with diets high in protein and low in carbohydrates.[248-250] This metabolic effect is related to postprandial energy expenditure for proteins being greater than that for fats and carbohydrates, improving its effect on satiety.[251-253]

High-Fiber Diets

There is no universal agreement regarding effectiveness of high-fiber diets as part of nutritional treatment for obesity in dogs and cats. Although some studies suggest fiber reduces appetite (satiating effect) and improves weight loss in dogs and cats when combined with high protein diets, others describe no such effect.[254-258] Nevertheless, fiber with its low digestibility provides low caloric density that can replace dietary carbohydrate or fat, useful for reducing the total calories given per meal.[34,256] Fermentable fiber may reduce insulin resistance in obese patients.[259,260]

L-Carnitine Supplements

L-carnitine is an amino acid synthesized in the liver and the kidneys from the amino acids lysine and methionine.[1,7] Its effects include nitrogen retention and FA oxidation, which increases lean tissue mass and reduces the total amount of body fat during weight loss.[261-264] In cats, it reduces hepatic fat accumulation and has a protective effect against fasting ketosis.[265,266] Supplementation is particularly important when the pet is unable to synthesize L-carnitine due to insufficient intake of protein and other nutrients.[261]

Conjugated Linoleic Acid

Conjugated linoleic acid (CLA), from the family of isomers of FA derived from linoleic acid, has anti-adipogenic effects, reducing weight and accumulated fat.[7,267] CLA appears to have a greater effect on preventing weight gain after weight loss than on initial weight loss.[268] Most of its effect on changing body mass comes from the attenuating action of its t10,c12 isomer on adipocyte differentiation, inducing apoptosis in adipose tissue in mice.[269,270] Furthermore, CLA inhibits stearoyl-CoA desaturase activity, which limits monounsaturated FA synthesis due to triglyceride synthesis. In humans, dogs and cats, studies on the effectiveness of CLA for weight loss show mixed results.[271-273]

Diacylglycerols (DAG) and Other Dietary Supplements

Diacylglycerols reduce weight, percentage of fat, and serum concentrations of cholesterol and triglycerides.[274] The isomer 1,3-DAG has been described as having a lipid-lowering effect. Diets with added 1,3-DAG reduce diet-induced insulin resistance through skeletal muscle fat oxidation and suppression of hepatic gluconeogenesis.[274-276] *Saponins chitosan* and *pyruvate* have exhibited some anti-obesity activity.[277-281] Extracts of *Garcinia cambogia, chromium picolinate* and *chia seeds (Salvia hispanica)* have not been consistently helpful.[282-286]

Treats

Many owners give treats to their pet to show affection. It is necessary to limit treats to a <10% of total calories.[240]

Pharmacotherapy

Sometimes increased energy expenditure and a change of the animal's dietary habits can be accomplished with the aid of drugs. Anti-obesity drugs may act by reducing appetite and fat absorption or by increasing energy expenditure and thermogenesis.[287]

Lipase Inhibitors

Tetrahydrolipstatin (THL or Orlistat) is a reversible inhibitor of gastric lipase that does not affect amylase, trypsin or chymotrypsin. It is widely used in people together with fat-containing diets to limit calorie intake by inhibiting triglyceride hydrolysis and reducing absorption of monoglycerides and free fatty acids.[288] THL reduces total cholesterol, low-density lipoprotein cholesterol (LDL-C) and blood pressure, thereby reducing insulin resistance and improving blood glucose concentrations.[289-291] Common side effects include gastrointestinal disorders (diarrhea, flatulence, abdominal pain, dyspepsia and abdominal bloating).[292] Isolated episodes of serious liver damage have been described.[293] Patients must be supplemented with fat-soluble vitamins (A, D, E and K), because treatment with THL interferes with their absorption.

Microsomal Triglyceride Transfer Protein (MTP) Inhibitors

These drugs interfere with intestinal fat absorption. They not only reduce fat absorption, but they release factors that reduce appetite. MTP inhibition involves reduced formation of chylomicrons from FAs and proteins in enterocyte cytoplasm.[294] Its main use in weight loss is to decrease appetite. Intracellular fat accumulation caused by MTP inhibition stimulates the release of peptide YY from enterocytes into the circulation.[294] Peptide YY is a peripheral hormone that helps to regulate food intake by suppressing appetite and producing a satiating effect in the hypothalamus and other centers of the brain.[295] Dirlotapide and mitratapide are MTPs currently approved for use in dogs. They have been effective and safe for as long as a year in achieving slow but constant weight loss.[262,296] Side-effects are generally mild, but can include vomiting, diarrhea and altered liver function tests.[297,298] Dirlotapide is given continuously, with dosage adjustments made as weight changes. Mitratapide is administered in 2-3 week courses separated by 2-3 weeks without treatment. It should be accompanied by diet and behavior-modifying techniques.[262] Owner involvement is essential for establishing correct feeding routines and preventing inappropriate behavior to avoid weight gain when drug therapy is discontinued.

Increase in Energy Expenditure

Weight loss is most likely to be achieved with a combination of calorie restriction and increased exercise (see ch. 359). It increases energy expenditure, preserves muscle mass, and improves the human-animal bond.[299-302] In dogs, the number of walks, duration of walks, and playing periods should be increased. Swimming is a low-impact exercise that may help with weight loss. Hydrotherapy and treadmills may be beneficial if osteoarthritis-related diseases exist (see ch. 355).[7,235] In cats, increasing activity may be achieved with specific toys for cats, feeder balls, "circuits" with tunnels and towers to climb, and placing food in different places to encourage activity.[1,7] When possible, allowing cats to spend time outside the home increases activity, enhances calorie utilization and can lead to weight loss. Some owners can provide restricted space outside that prevents a cat from escaping but allows outdoor activity.

Monitoring and Maintenance of the Objectives Attained

It is easier to maintain a suitable weight if the weight loss is gradual rather than rapid, as this makes a rebound effect less likely.[303] Owners should be instructed to adjust the amount of food to the needs of the pet, changing and adapting according to different situations (e.g., increasing or decreasing the time spent doing physical activity), in addition to weighing pets relatively regularly.[240] It is important to help the owner to understand that maintaining the correct weight for a pet may require life-long strategies and periodic re-evaluations. Owner involvement is critically important.

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CHAPTER 177

Cachexia and Sarcopenia

Lisa M. Freeman

Cachexia and sarcopenia occur in a variety of chronic diseases and aging, respectively. Although cachexia has been recognized in people for over 2000 years, there is burgeoning interest because of the relatively recent finding of its negative effects on morbidity and mortality. This is spurring development of new drugs to combat cachexia and sarcopenia in people. Veterinary patients will benefit from this research, but greater awareness of these syndromes among the veterinary healthcare team and more research in dogs and cats are needed.

Cachexia

Cachexia is a loss of lean body mass (LBM) which occurs commonly in people and companion animals with a variety of chronic diseases, including congestive heart failure (CHF; see ch. 246), cancer, chronic kidney disease (CKD; see ch. 324), and chronic obstructive pulmonary disease (COPD; see ch. 242), as well as acute illness and injury (see ch. 189).[1] Cachexia and sarcopenia change an animal's normal metabolism such that he or she loses primarily muscle, rather than fat. In healthy animals that lose weight, fat is the primary tissue lost and LBM is preserved. The inflammatory mediators elaborated in disease states (e.g., inflammatory cytokines, catecholamines, cortisol, insulin, glucagon) cause an animal to use amino acids as the primary source of energy and to quickly lose muscle and LBM.[1] Therefore, the hallmark of cachexia is a loss of LBM.

The loss of LBM has direct and deleterious effects on strength, immune function, wound healing, and survival.[1] Many of the effects of cachexia, such as weakness, anorexia, weight loss, and perceived poor quality of life, are major contributing factors to an owner's decision of euthanasia.[2] As a result, cachexia may be even more deleterious for dogs and cats because of the option for euthanasia. These important clinical implications underscore the importance of early identification and effective treatment.

Specific Forms of Cachexia

The hallmark of all forms of cachexia is a loss of LBM, which is most readily evident in the epaxial, gluteal, scapular, or temporal muscles. The epaxial muscles over the thoracic and lumbar region are the sites in which muscle loss can be identified in its earliest stages (Figure 177-1 and ch. 170). Temporal muscle wasting is more variably expressed: In some animals, temporal muscle wasting is apparent at an early stage of disease, whereas in others, moderate to severe muscle wasting is present elsewhere before substantial temporal muscle wasting is apparent. There are some unique features to the different forms of cachexia.

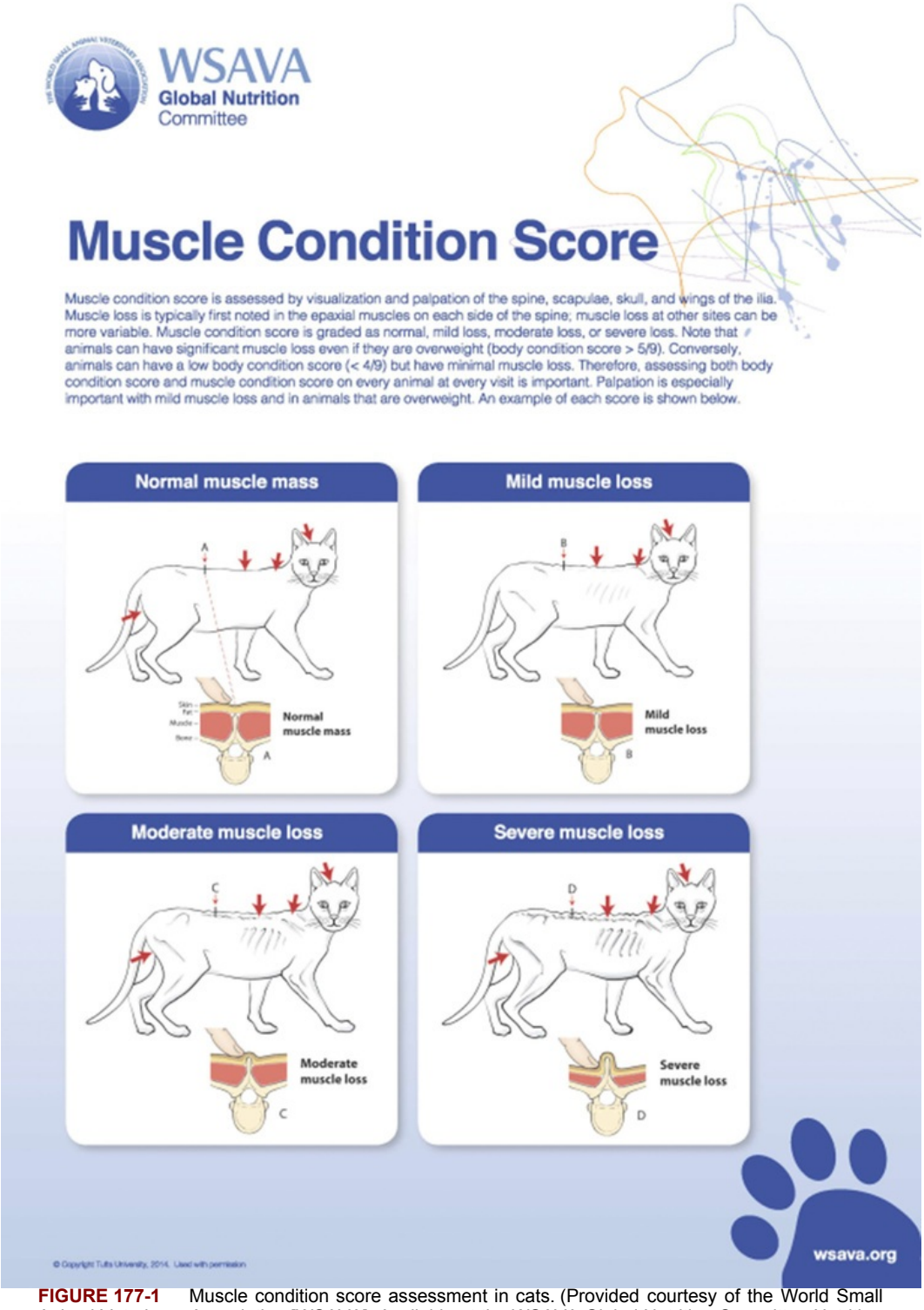

FIGURE 177-1 Muscle condition score assessment in cats. (Provided courtesy of the World Small Animal Veterinary Association [WSAVA]. Available at the WSAVA Global Nutrition Committee Nutrition Toolkit website: http://www.wsava.org/nutrition-toolkit. Accessed June 29, 2016. Copyright Tufts University, 2014.)

Cardiac Cachexia

Depending upon the definition used, cachexia has been identified in up to half of all people with CHF.[3] In 1 study of dogs, over 50% of dogs with dilated cardiomyopathy (DCM) and CHF had some degree of cachexia.[4] In people, cardiac cachexia, even using relatively insensitive measures, is associated with an increased risk for

death.[5] Cardiac cachexia typically is recognized only after CHF has developed. Cachexia is usually recognized more easily in dogs than in cats, but it likely occurs at similar rates in both species. Dogs with right-sided CHF have more advanced muscle loss compared to dogs with left-sided CHF.[4]

Whereas obesity is a risk factor for development of heart disease in people, obesity actually may confer a protective effect once CHF is present—this is known as the obesity paradox, and it occurs in people, dogs, and cats with CHF.[6-9] The benefit of obesity in CHF is likely due to the lack of cachexia, rather than to the obesity *per se*, given the adverse effects of cachexia. This is due to the increased reserve of LBM in obesity, which can provide a greater reserve during the catabolic state of CHF.

Cancer Cachexia

Over 50% of people with cancer lose weight unintentionally, although the prevalence depends on the type of cancer.[10] Low body condition score (BCS) is uncommon in dogs and cats with cancer (4-5%) and obesity is more common,[11,12] but many animals with cancer have experienced weight loss (69% in one study) or muscle loss (35-91%).[11,13] In addition, results of one study showed that cats with low BCS had a significantly shorter survival time compared to those with a BCS ≥5.[13] This underscores the importance of assessing not only BCS which assesses fat stores (see ch. 2 and 170)[14,15] but also muscle condition score (MCS; see Figure 177-1 below) and changes in body weight in order to detect cancer cachexia.

Renal Cachexia

The prevalence of cachexia in dogs and cats with CKD has not specifically been measured, but subjectively is very common. The obesity paradox also exists in CKD. One retrospective study in dogs with CKD showed that underweight dogs had a significantly shorter survival time compared to both moderate and overweight dogs.[16]

Sarcopenia

Sarcopenia, like cachexia, is characterized by a loss of LBM, but unlike cachexia, sarcopenia is a syndrome that occurs during aging in the *absence* of disease. In people, sarcopenia actually begins around 30 years of age and progresses over time. The loss of LBM in sarcopenia often is accompanied by an increase in fat mass so the total weight may not change (or may even increase), thus masking the sarcopenia. Inflammation, reduced physical activity, decreased concentrations of growth hormone and testosterone, changes in type II muscle fibers, insulin resistance, and decreased protein synthesis all contribute to sarcopenia.[17] Like cachexia, sarcopenia is associated with increased morbidity and mortality.[17] Sarcopenia also occurs in dogs and cats during aging.[18] It is important to note that cachexia and sarcopenia can occur concurrently in an animal—i.e., an elderly dog with CKD may have muscle loss due to both sarcopenia (from aging) and cachexia (secondary to CKD).

Diagnosis of Cachexia and Sarcopenia

Cachexia and sarcopenia are processes and not just end-stage syndromes. It is important not to rely on weight loss to diagnose cachexia and sarcopenia since loss of LBM occurs before weight loss. Waiting until weight loss occurs prevents an early diagnosis. In addition, in sarcopenia and certain types of cachexia (e.g., cardiac cachexia with fluid accumulation), weight loss may be masked by accumulation of water or fat. Another important issue is that the muscle in cachexia and sarcopenia is not only lost in quantity but there are qualitative changes in muscle, such as increased collagen content, altered mitochondrial function, and a shift from type I (oxidative) to type IIb (glycolytic) fibers.[17]

To recognize cachexia and sarcopenia in their earliest stages, when intervention is more likely to be successful, BCS and MCS must be consistently assessed at every visit. The goal for BCS in a healthy dog or cat is 4-5 on a 9-point BCS scale. However, in certain diseases (e.g., CHF, CKD), a slightly higher BCS may be desirable (i.e., a BCS of 6-7/9), although further research is required to make specific recommendations. Even in animals with these diseases, obesity (BCS >7/9) should be avoided.

BCS and MCS differ in that the BCS assesses fat stores, while the MCS specifically evaluates muscle mass.[14,15,19] Evaluation of muscle mass includes visual examination and palpation of the head, scapulae, epaxial muscles over the thoracic and lumbar vertebrae, and pelvic bones (see Figure 177-1 and Video 170-2). BCS and MCS are not directly related because an animal can be obese but still have substantial muscle loss (or

conversely, be very thin but have a normal MCS). Palpation is required for accurately assessing BCS and MCS.

Cachexia should be anticipated in animals with chronic diseases such as CHF, CKD, and cancer, as well as in acutely ill or injured animals in which muscle loss can develop quickly. Routinely evaluating body weight, BCS, and MCS will help to identify muscle loss early, rather than waiting until muscle loss is more advanced, when it may be more difficult to successfully manage. Muscle loss also is likely to occur in aging, even in healthy individuals. Therefore, body weight, BCS, and MCS should be assessed at every visit in geriatric cats and dogs.

In addition to body weight, BCS, and MCS, a complete diet history should be obtained at every visit because this can identify factors that may contribute to muscle loss, such as a nutritionally unbalanced diet or insufficient protein or calorie intake (see below).

Mechanisms of Cachexia and Sarcopenia and Potential Interventions

There are 4 major aspects of the pathophysiology of cachexia: increased energy requirements or decreased nutrient absorption (both most common in CHF), decreased energy intake, and alterations in metabolism. However, it is a highly redundant system, which adds to its complexity but also offers multiple opportunities for targeting muscle loss. Currently, few of these interventions have been studied in companion animals, but the enhanced interest in these syndromes in people will likely lead to the development of products that may have benefits in animals or may spur interest within the veterinary pharmaceutical industry.

Decreased Energy Intake

An important problem in most forms of cachexia is a decreased energy (calorie) intake. For example, reduced food intake is present in 34-84% of dogs and cats with heart disease.[2,20,21] Appetite changes may be secondary to medication side-effects or due to the underlying disease. Absolute food intake may decrease in animals with these diseases, but there also may be altered food preferences, cyclical appetite, and other issues that negatively affect overall food intake. Control of food intake is a complex system, which includes numerous anorexigenic or satiety signals (e.g., adiponectin, serotonin, insulin) and orexigenic signals (e.g., ghrelin, neuropeptide Y, agouti-related protein).[22,23] For example, an imbalance between orexigenic and anorexigenic hormones or a resistance to orexigenic signals can negatively affect appetite. Inflammatory mediators play an important role in this dysregulation, which may provide targets for treatment to increase food intake.

In people, food intake is not only affected by the many orexigenic and anorexigenic factors but also by physiological factors, such as social situation, memory, time of day, fatigue, and depression.[22] The role of these factors in dogs and cats is unknown but such factors could be involved because dogs and cats appear to develop aversions to certain foods, particularly when sick, and this can contribute to decreased food intake.

Potential Interventions

A variety of drugs, such as ghrelin agonists and megestrol acetate, have been (and continue to be) studied to improve food intake in people with reduced appetite. It is unclear whether increasing appetite alone will reverse or even minimize the deleterious effects of cachexia if the weight gained is fat and not LBM. However, appetite stimulation may provide benefit for dogs and cats if increased appetite is viewed by the owner as improving the animal's quality of life (and thus, reducing the likelihood of euthanasia).[2]

Altered Metabolism

Although increased energy requirements, alterations in nutrient absorption, and decreased energy intake all play important roles in the pathogenesis of cachexia and sarcopenia by causing a net calorie deficit, metabolic alterations also are primary factors in this syndrome, including increased production of inflammatory cytokines. Tumor necrosis factor-alpha (TNF) was initially thought to be the major cause of cachexia, and cachexia research throughout the 1990s focused on TNF and other inflammatory cytokines. However, it is now apparent that there are multiple metabolic alterations involved in the pathophysiology of cachexia and that it is a redundant system with multiple pathways triggering the muscle loss. At the core of cachexia and sarcopenia is an imbalance between decreased protein synthesis and increased protein catabolism, resulting in a net loss of lean tissue.

Inflammatory Cytokines and Nuclear Factor Kappa-B

The inflammatory cytokines, especially TNF, interleukin-1-beta (IL-1), and interleukin-6 (IL-6), are primary factors in cachexia because they cause anorexia, increase energy metabolism, and accelerate loss of LBM. This loss of LBM results in large part from the activation of the nuclear factor kappa-B (NF-kappa-B) pathway that, in turn, activates the ubiquitin proteosome pathway. TNF and IL-1 also cause cardiac myocyte hypertrophy and fibrosis and have negative inotropic effects that may contribute to progression of the underlying disease.[24] Inflammatory cytokines also are increased in dogs and cats with CHF.[4,25]

Potential Interventions

Anti-TNF agents (e.g., soluble TNF receptors, TNF antibodies) showed promising results in rodent models and in Phase I and II human clinical trials, but were less successful (or even associated with higher mortality rates) in Phase III clinical trials for CHF. TNF antagonists are now a mainstay in rheumatoid arthritis and Crohn's disease in people, and some studies have shown positive effects both on the underlying disease and on muscle mass, but they are avoided in CHF. The effects of blocking TNF or other inflammatory cytokines in dogs and cats are unknown but their use is challenging given the species-specific nature of these antibodies. A variety of other agents with anti-inflammatory effects, such as thalidomide and pentoxifylline, also is being evaluated in cachexia.

Myostatin

Myostatin is a member of the transforming growth factor-beta superfamily that negatively regulates muscle mass. Exercise decreases myostatin concentrations, allowing muscles to increase in size. Several myostatin mutations have been described in various species in which enlarged musculature is present (e.g., double-muscled cattle breeds, "bully" Whippets).[26,27] Myostatin is increased in animal models and people with CHF.[28,29] A variety of factors, such as TNF and angiotensin II, increases myostatin expression, which can then cause muscle loss in CHF.[30]

Potential Interventions

Studies of myostatin antagonists (e.g., activin receptor type IIB antibodies or decoys, myostatin antibodies) have shown benefits in rodent models of cachexia, and studies currently are underway in people with sarcopenia, COPD, cancer cachexia, and critical illness.[31] A small open-label pilot study using a myostatin antagonist showed increases in muscle mass in some dogs with cardiac cachexia.[32] Exercise also decreases myostatin concentrations and may be of benefit in certain chronic diseases.[33]

Neurohormonal Activation

Neurohormonal activation is another mechanism by which cachexia can occur, in addition to the NF-kappa-B pathway. This is especially likely in CHF in which many neurohormonal alterations occur that can affect myocardial and whole body energy metabolism and protein flux (see ch. 246). Catecholamines and neurohormones (e.g., renin-angiotensin-aldosterone system, epinephrine, cortisol, atrial natriuretic peptide, B-type natriuretic peptide) can increase muscle catabolism.[3]

Potential Interventions

Because of its effects on muscle, neurohormonal blockade may provide benefits other than cardiovascular effects. For example, certain beta-blockers have been shown to decrease protein oxidation and muscle atrophy in a rodent model of CHF,[34] and to reduce cardiac cachexia in people.[35,36]

Reduced Anabolic Signals

Although increased protein catabolism is a major contributor to cachexia, decreased protein synthesis also plays a role in the net loss of lean tissue. Inflammatory mediators, such as TNF, contribute to cachexia by reducing growth hormone and insulin-like growth factor-1 (IGF-1), which are both important for maintaining LBM.

Potential Interventions

Although growth hormone treatment has not been overwhelmingly successful for treating cachexia and has important adverse effects, some promising results have been seen with IGF-1 treatment in rodent models of cachexia.[37,38] IGF-1 mediates most of growth hormone's effects so it may offer an effective method for treatment of cachexia and sarcopenia in the future, either by administration of IGF-1 or through nutritional approaches and resistance training.[39]

Another anabolic agent is testosterone, but its adverse effects limit its use in cachexia and sarcopenia. However, non-steroidal selective androgen receptor modulators (SARMs) are being developed which have anabolic activity primarily in muscle and bone, with minimal androgenic effects in other tissues, thus reducing side-effects. SARMs are being studied for use in various forms of cachexia and sarcopenia in people.

Multifactorial Effects

Both cachexia and sarcopenia appear to have highly redundant mechanisms that make it unlikely that there will be a single agent treatment that will result in complete resolution of the syndromes. Finding therapies that target multiple pathways may, therefore, be useful. As an example, ghrelin is an orexigenic hormone. It also stimulates growth hormone secretion (and thus, IGF-1 production), stimulates neuropeptide Y and agouti-related protein, decreases expression of proopiomelanocortin, attenuates cardiac and renal sympathetic tone, stimulates gastric motility, and has anti-cytokine and anti-inflammatory effects.[40,41] Ghrelin is secreted primarily by the stomach in response to fasting and results in increased food intake. People with CHF appear to have ghrelin resistance because ghrelin concentrations are increased but food intake is decreased, although exogenous ghrelin administration may overcome this ghrelin resistance.[41-44] Ghrelin itself has a short half-life, which limits its use, but ghrelin agonists with longer half-lives have been developed and are being tested in people, dogs, and cats. Results from studies being conducted in people with cachexia due to cancer, CHF, COPD, and CKD show promise for this class of agents.[31,44] Ghrelin agonists for dogs and cats also are being tested in clinical trials for anorexia and weight loss.

Practical Implications for the Non-Pharmacologic Interventions

Until effective pharmacologic interventions for treating cachexia and sarcopenia are available for dogs and cats, these important syndromes still can be addressed in a number of ways. These other aspects of therapy also will continue to be important since, to be most effective, a treatment for cachexia should include 3 key components: (1) an anti-catabolic effect to decrease muscle loss, (2) an anabolic effect to enhance protein synthesis, and (3) adequate substrate to support the first 2 actions (i.e., calories, protein, and other nutrients).[45] Treatments with anabolic effects, for example, will not be effective if there is insufficient substrate (i.e., calories and protein) with which to build muscle. Therefore, careful attention to the nutritional aspects of treatment of cachexia and sarcopenia is critical for success.

Nutrition

Optimizing medical treatment for the underlying disease in animals with chronic conditions commonly associated with cachexia (e.g., CKD, cardiac or hepatic failure, cancer, respiratory disease) is of primary importance. Physical factors (e.g., dental disease, back or joint pain) or environmental factors (e.g., multipet households) that can negatively affect food intake must be investigated and addressed. The diet also should be carefully evaluated for information that can provide relatively easy, practical solutions. A brief nutrition screening should be performed in every patient at every visit, including a diet history, body weight, BCS, and MCS.[14,15] For animals that have risk factors identified from the screening (e.g., animals with medical conditions, geriatric animals, and those with altered BCS or MCS), a more thorough nutrition evaluation is required (see ch. 170). The diet history includes not just the pet food, but also treats, table foods, rawhides or other chews, and foods used to administer medications. Clinicians should ensure that the diet being eaten by the animal is nutritionally complete and balanced. If owners are feeding a homemade diet, it is almost always nutritionally unbalanced (sometimes severely so) unless a board-certified veterinary nutritionist formulated the diet and the owner is carefully following the recipe. Even commercial dog and cat foods may be nutritionally unbalanced if they are made by companies with questionnable quality control or the label states "for intermittent or supplemental use." This phrase is acceptable for veterinary diets that are designed to help manage diseases and are used under a veterinarian's supervision, but over-the-counter diets should always be complete and balanced if fed in any substantial amounts to a pet.

The diet history also may reveal that the diet is unbalanced not because the animal is eating an unbalanced diet, but due to intake of a large proportion of calories from treats, rawhides, or table food. In this situation, even if the main diet is well-balanced, the other foods may be fed in a large enough proportion that the overall diet is unbalanced, which can contribute to weight and muscle loss as well as not being optimal for the underlying disease.

It is important to assess not just the brand of food being fed, but also the specific product and flavor because it may reveal factors that can contribute to cachexia or sarcopenia (or that are not optimal for the underlying disease). For example, animals with CHF should not be fed a renal or otherwise reduced-protein diet unless advanced concurrent CKD is present. Providing at least the AAFCO minimum for protein (4.5 g/100 kcal for dogs and 6.5 g/100 kcal for cats)[46] is important, although higher dietary protein levels may be more optimal if muscle loss is present. Dietary protein restriction does not slow progression of disease in animals with CKD (unless proteinuria is present) and can contribute to muscle loss so should be avoided until more advanced CKD is present. Senior diets are highly variable in terms of their protein content[47] so the individual product (and flavor) must be investigated to ensure it is appropriate for an individual patient. Commercial pet foods also vary widely in calorie density—there are dog and cat foods available on the market now that are >600 kcal/cup or <250 kcal/cup. Therefore, it is important to ensure that undesired weight loss is not simply the result of switching to a lower calorie density food.

Dietary supplement use is important to determine. Animals with diseases are more likely to be receiving supplements,[20,21,48] but owners typically do not volunteer this information unless specifically asked. Dietary supplements may contribute to muscle loss by reducing appetite or by interacting with medications used to treat the underlying disease, thus decreasing their efficacy or increasing the adverse effects of the medications.

This emphasizes the importance of obtaining and evaluating a thorough diet history in animals with cachexia or sarcopenia, and will provide important information needed to optimize the nutritional aspects of a patient's care. Board-certified veterinary nutritionists can be helpful in assisting the busy veterinary clinician by consultations in these situations.[49,50]

Addressing Changes in Appetite

Appetite can be a challenging issue in animals with cachexia and sarcopenia. Complete loss of appetite (anorexia) may not be present but owners often note changes in appetite, such as reductions in food intake (hyporexia), or altered food preferences or "cyclical" appetite (dysrexia). Client communication is important to address decreased or altered food intake. Owners who are prepared for changes in appetite appear better able to deal with these changes effectively. Tips for addressing alterations in appetite are included in Box 177-1.

Box 177-1

Tips for Managing Anorexia, Hyporexia, and Dysrexia in Patients with Cachexia or Sarcopenia

- Assess the patient for optimal medical control of any underlying disease(s).
- Assess the patient for side-effects of medications.
- Ask the owner about dietary supplement use, which could be causing side-effects, or having interactions with medications.
- Feed more frequent but smaller meals.
- Provide multiple diet options so owners can rotate foods if hyporexia or dysrexia occurs.
- Warm the food to body temperature (for cats). Try different temperatures of food for dogs—they may prefer it warmed, at room temperature, or even cold.
- Feed the animal from a different type of dish (e.g., a new food dish or a human dinner plate).
- Feed in a different location in the house.
- Add homemade chicken, beef, or fish broth to the food (even low sodium store-bought broths are too high in sodium).
- For animals with heart failure, add a small amount (1-2 teaspoons) of cooked meat (hamburger, chicken, or fish) to the food. Be sure to instruct the owner not to use any prepared foods, such as

rotisserie chicken, lunchmeats, or canned meats or fish due to their high sodium content. Cats typically prefer meat or fish as a palatability enhancer. Meat or fish also may enhance food intake in dogs, but some dogs prefer sweet flavors as a palatability enhancer (e.g., maple syrup, applesauce, fruit-flavored yogurt). These sweet flavorings also can be used for dogs with other medical conditions (except diabetes).

- Supplement fish oil, which is high in n-3 fatty acids, to reduce inflammatory cytokines. This may have modest benefits for appetite.

Appetite stimulants (e.g., mirtazapine) may benefit some animals with decreased or altered appetite, but it is important to carefully monitor body weight, BCS, MCS, and food intake to ensure adequate calorie intake. Owners (and veterinarians) often are comforted by some food intake, even if it is not sufficient to maintain weight or is not comprised of an optimal nutritional profile (e.g., a cat with CKD that will only eat meat or a high-protein, high-phosphorus commercial food). In animals that continue to lose weight and muscle, a feeding tube should be considered (see ch. 82). Early tube placement typically has a better outcome than waiting until the animal is in end-stage disease with severe weight and muscle loss.

Omega-3 Fatty Acids

Increased dietary long-chain polyunsaturated omega-3 fatty acids, either from a highly enriched diet or through supplements, may have a number of benefits in animals with diseases that predispose them to cachexia or in animals with sarcopenia. Omega-3 fatty acids result in less potent inflammatory mediators (eicosanoids) than do omega-6 fatty acids, and omega-3 fatty acids also decrease TNF and IL-1 production. Omega-3 fatty acid supplementation has been shown to decrease the muscle loss in dogs with CHF and, in some animals, to improve appetite.[4]

The optimal dosage of omega-3 fatty acids has not been determined, but the author currently recommends a dosage of fish oil to provide 40 mg/kg eicosapentaenoic acid (EPA) and 25 mg/kg docosahexaenoic acid (DHA) for animals with any degree of cardiac cachexia. Higher dosages may be recommended for other conditions.[51] Unless the diet is one of a few specially designed therapeutic diets, supplementation will be necessary to achieve this omega-3 fatty acid dosage. When recommending a supplement, it is important to know the exact amount of EPA and DHA in the specific fish oil brand because supplements vary widely. Fish oil supplements with good quality control should be used and they should always contain vitamin E as an antioxidant, but other nutrients should be excluded to avoid toxicoses. Cod liver oil should not be used to provide omega-3 fatty acids at this high dose because it contains high concentrations of vitamins A and D that can result in intoxication. Flaxseed oil or other plant-based omega-3 fatty acids also should be avoided because of metabolic differences that make them inefficient (in dogs) or ineffective (in cats) sources of omega-3 fatty acids for these species.

Exercise

Exercise has been an effective method for helping to maintain muscle mass in people with cachexia and sarcopenia. Both aerobic and resistance exercise are beneficial for minimizing cachexia and sarcopenia in people although resistance exercise appears to be most useful. Exercise may be more challenging in some of the diseases associated with cachexia in dogs (e.g., CHF) and particularly in cats, but exercise such as walking may provide an effective treatment for muscle loss in some diseases and in preventing sarcopenia in aging animals (see ch. 355 and 359).

Summary

Veterinarians should be aware of cachexia and sarcopenia and their negative effects, because earlier diagnosis will provide enhanced opportunities for treatment. New drugs, nutritional approaches, and other treatments to specifically target sarcopenia and cachexia are being developed and are likely to benefit dogs and cats, as well as people. In the meantime, careful nutritional assessment and detailed nutritional recommendations can help to optimize the treatment for patients with these common and deleterious syndromes.

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CHAPTER 178

Nutritional Management of Gastrointestinal Disease

Debra L. Zoran

General Guidelines

The gastrointestinal (GI) tract is a complex tubular system primarily responsible for accepting and digesting food, absorbing nutrients and water, and expelling wastes from the body in the form of feces. A proper diet and normally functioning GI tract are integral to the delivery of nutrients, prevention of malnutrition, repair of damaged intestinal epithelium, restoration of normal luminal bacterial populations, promotion of normal GI motility, and maintenance of normal immune function (e.g., both tolerance of and protection from pathogens).[1] Dietary characteristics, such as the amount of food, its form, the frequency of feeding, and the composition of the diet, all have important effects on GI function and can be used for helping to ameliorate signs of disease. Appropriate selection of dietary therapy, tailored to meet the needs of individual, species, and specific to the diagnosis, is an essential component of intestinal recovery and successful management of GI disease.

Traditionally, nutritional management of acute, nonspecific GI disease has included institution of a short-term period of fasting, or alteration of food intake with the general intent to "rest" the gut.[2] Effective treatment of many acute, non–life-threatening GI disturbances includes withholding of food and water for 24 to 36 hours, along with correction of fluid and electrolyte deficits. For example, in acute gastroenteritis due to parvovirus infection where vomiting is a significant problem, a period of nothing *per os* (NPO) for 24-36 hours could be essential for initial therapy to be effective.[3] However, prolonged (i.e., >48 hours) fasting should be avoided, as it can contribute to delayed recovery of intestinal function, development of malnutrition, or lead to problems resulting from a lack of enteral nutrition (e.g., ileus, dysbiosis, bacterial translocation, and reduced digestive function due to villus blunting; see ch. 225).[4] Prolonged fasting also deprives the GI epithelium of its primary metabolic fuel source, glutamine, which is present in chyme and is necessary not only for replacement of the GI mucosal cells lost in normal turnover (every 3 to 5 days) but also for repair of mucosal injury and normal immune function.[5] Thus, a good general rule of thumb for reintroduction of feeding for all dogs and cats with GI disease is to minimize the period of fasting to 12-36 hours, or a maximum of 3 days. Then, a palatable, highly digestible diet is reintroduced gradually—the type of diet can vary for dogs versus cats—depending on the diagnosis, previous diets used, and concurrent diseases. If the dog or cat is unable or unwilling to eat, enteral nutritional support via other means (e.g., nasoesophageal or esophageal feeding tubes; see ch. 82), or other methods of nutritional support (see ch. 189) should be implemented. When indicated, a gradual reintroduction of the original diet, or a more appropriate diet for long-term management, can be given.

Diets Used in GI Disease: Definition and Selection

Selection of a diet for managing dogs or cats with GI disease should be based on several factors: (1) the specific GI disease (if it can be determined), (2) the area of the GI tract affected, (3) any prior diets used in the management of the disease (a dietary history is essential to success in any dietary therapy chosen; see ch. 170), and (4) understanding any other health issues that could influence the diet choice (e.g., pancreatic, endocrine or renal disease). There are several specific characteristics to be considered when selecting a diet for management of GI disease, including the type and amount of protein, carbohydrate (CHO), fat, fiber (type and amount), and digestibility. The foremost consideration in choosing a diet to feed an animal with GI disease is nutrient content and digestibility. If the animal is fed a diet novel in both protein and CHO but the nutrients are not highly digestible or there is too much fat (e.g., especially in cases of protein-losing enteropathy [PLE] in dogs), the malassimilation of those ingredients due to poor digestibility could at the

very least result in no improvement, and at worst, contribute to progression of the clinical signs (e.g., vomiting, diarrhea, flatus, poor appetite, weight loss, or malodorous feces) and, potentially, worsening of the disease itself (e.g., dysbiosis, inflammatory bowel disease [IBD], PLE). Typical commercially available maintenance pet foods have protein and CHO digestibilities ranging from 70% to 85% on a dry matter (DM) basis.[6,7] Less well-known specialty brands or pet foods available from bulk sellers can consist of ingredients with highly variable quality and digestibility. Digestibility information is not required to be available on the pet food label, and typically is only present if the manufacturer wants this information presented. However, it is generally accepted that foods formulated for dietary therapy of GI disease (e.g., highly digestible or enteric diets) ideally should have CHO and protein digestibilities of at least 88% DM.[7,8] Other characteristics of an ideal intestinal diet include: low to moderate levels of fat (15-20% DM in cats or 3-5 g fat/100 kcal consumed, and between 6% and 15% DM in dogs or <3 g fat/100 kcal diet consumed), be lactose- and gluten-free, have no additives, artificial flavoring or coloring, and have reduced amounts of insoluble dietary fiber or other poorly digestible CHO.[9] There are many different, commercially available therapeutic diets, and each formula is unique, and therefore will elicit a different individual response. For example, therapeutic diets are likely to have different protein or CHO sources and varying levels and types of fat (e.g., some formulations contain added omega-3 fatty acids), and some are formulated with ingredients designed to enhance GI health, such as the prebiotic fructo-oligosaccharides (FOS). Although the benefits of feeding any one highly digestible diet could have a variable effect in an individual animal, the benefit of a dietary trial with a highly digestible food (whether it is commercial, homemade or organic or raw) in pets with both acute and chronic GI diseases is widely accepted as important to successful therapy. The hard part is finding which highly digestible diet is the right one for an individual patient based on that animal's individual needs and response to therapy.

Role of Consistency, Frequency, and Meal Size

The amount of food fed should be calculated based on the energy needs of the individual animal and the ability of the GI tract to assimilate different foods. In general, a good rule of thumb for any animal with clinically significant GI disease is “less volume, more frequent, don't try to achieve full-feed.” Although there is ongoing discussion among nutritionists regarding the best method for determining energy requirements of well or sick animals, the goal should be to meet the animal's daily resting energy requirements (RER). One generally accepted equation for determining resting energy requirements (in kcal/day) in neutered or spayed dogs is 70 $(BW_{kg})^{0.75}$ and for castrated or spayed cats 60 $(BW_{kg})^{0.67}$.[6,10] The linear equation $[(BW_{kg}) \times 30] + 70$ is an estimate that is better for animals in the middle of the weight range (20 kg) than it is for those on either end of the scale (<10 kg, >40 kg), but it can be used as a reasonable starting point. Intact animals have a higher RER, but for purposes of feeding sick pets with GI disease, it is best not to overfeed, so use of the RER and not maintenance energy requirements (MER) is suggested.

In most animals with GI disease, small meals (e.g., less than one third of stomach capacity) are recommended several times each day (three to six meals). Feeding small meals reduces gastric acid secretion, reduces gastric distension (which can increase nausea), reduces gastroesophageal reflux, and reduces the risk of vomiting.[2,4] It also increases the mixing and digestion of the food present in the stomach. The feline stomach has a smaller capacity (approximately 60 mL/kg) and is less distensible than the stomach of a dog (capacity is nearly 80 to 90 mL/kg), which has greater capacity due to its distensibility.[4]

In general, liquid diets empty faster from the stomach than do canned foods, and canned foods faster than dry.[6] Therefore, animals with GI disease could benefit from small meals of a canned food, or water added to moisten a dry formula. Commercially available liquid diets primarily have been used in specialized circumstances (e.g., for nasoesophageal or jejunostomy tube feeding) or with certain GI conditions (e.g., esophageal stricture, selected cases of megaesophagus, or gastric outflow disturbances) to reduce the risk of regurgitation or vomiting. However, one disadvantage of liquid diets is that a very large volume of the food is required to meet the caloric needs of a large (>25 kg) dog. Also, if liquid diets are fed too quickly or in large volumes, diarrhea can be induced by too-rapid emptying of the stomach content, which can overwhelm the capacity of the small intestine. A good use of liquid enteral diets is to substitute them for water used for mixing or liquefying a diet for syringe or tube feeding to reduce the caloric dilution.

Diet Composition

A variety of nutritional and non-nutritional diseases affects the GI tract and their treatment can be enhanced by appropriate diet selection, including homemade, organic/holistic, or raw diets. The safe use and

preparation of these alternative diets is discussed in ch. 192. Numerous therapeutic diets are available for treatment of a wide variety of GI diseases in dogs and cats, including highly digestible, novel antigen, hypoallergenic, hydrolyzed protein, or increased fiber content diets. Each of these different dietary options can be used in management of GI disturbances; however, selection of the most appropriate diet requires an understanding of the differences in the nutrient composition of these formulations. Furthermore, specific diets (e.g., homemade or elemental diets) could be required for dietary management of intractable or chronic GI diseases for which commercially available options have not been successful. Examples of these situations can occur in cats with idiopathic chronic diarrhea (requiring a homemade diet with high protein and no carbohydrate to resolve their clinical signs) or dogs with severe PLE due to lymphangiectasia (requiring a homemade diet with extremely low fat content and highly digestible protein to overcome the effects of these patients' inability to digest fat through normal channels). In each of these situations, the clinician may choose to use a non-balanced diet during the 7-10 day trial period, but for therapeutic feeding of the diet for a longer period, a clinical nutritionist or service (e.g., https://secure.balanceit.com) should be consulted to provide a complete and balanced diet.

Protein

Protein in the diet is very important for normal GI tract function.[1,5,11] Dietary protein in the stomach increases lower esophageal sphincter pressure and can be a potent stimulus for secretion of hormones, including gastrin and pancreatic hormones. Protein also decreases (slows) both gastric emptying and intestinal transit.[1,11] However, protein maldigestion due to poor quality protein (low digestibility), lack of digestive enzymes (e.g., exocrine pancreatic insufficiency), or reduced absorptive function (e.g., IBD, dysbiosis, lymphangiectasia/PLE) not only reduces available body protein (for immune function, repair and muscle function), it also has numerous effects on the GI ecosystem. Protein malassimilation can directly impair GI function (including motility and hormone release), normal enterocyte replacement and growth, repair of mucosal injury, and the mucosal immune response.[12,13] In addition, intact protein reaching the distal small intestine and colon increases bacterial ammonia production, alters bacterial numbers, and can alter the bacterial species present (dysbiosis). Change in the bacterial flora can lead to production of abnormal fecal consistency, odor, and flatus initially, and eventually can lead to overt diarrhea due to IBD. More importantly, a change in flora could contribute to development of bacterial enteritis, colitis, or colonic hypersensitivity.[13]

Feeding high-quality protein that is highly digestible is essential in the initial approach to the dietary management of any animal with GI disease. However, in kittens or cats with GI disease, the quantity, quality, and digestibility of protein is one of the most important aspects of nutritional therapy. Due to their shorter GI tract (compared to dogs and other omnivores)[14] and greater need for protein (for maintenance of muscle and amino acid needs),[14,15] cats with GI disease must have high quality, highly digestible protein sources to prevent lean body mass loss, protein malassimilation, and development of dysbiosis. In many situations, this can be achieved by feeding a commercially available, highly digestible, higher protein, lower CHO formula (this includes some of the feline diabetic diets),[16] but in some cats with severe or unresponsive enteropathy, a homemade, lightly cooked, high-protein, no-CHO diet formulated by a nutritionist or nutritional service to be complete and balanced could be required. In the author's experience, this approach has been successful in resolving the clinical signs (vomiting, diarrhea, or weight loss) associated with chronic IBD or dysbiosis in numerous kittens and cats for which antibiotics, immunosuppressive therapy, and a variety of commercially available GI diets had previously failed.

Chronic severe enteropathies of dogs, such as IBD and PLEs, are a group of severe intestinal diseases that can occur as primary enteropathies (e.g., lymphangiectasia) or familial enteropathies (e.g., in Soft-Coated Wheaten Terriers, Basenjis, or Irish Setters). Alternatively, they can occur secondary to infectious, neoplastic, or inflammatory processes that result in inflammation, protein loss (from maldigestion, malabsorption, or leakage across damaged mucosa) and lead to vomiting, diarrhea, appetite changes, and weight loss of varying degrees and severity.[12,13,17] In addition to protein loss, these enteropathies also result in loss of mucosal function, motility disturbances, and loss or disruption of other gut functions.[13,17] Regardless of cause, nutritional therapy is essential in managing chronic enteropathies like IBD and PLE in dogs. In mild forms of either disease, feeding a highly digestible, low-fat diet, in addition to specific therapy for the primary disease, might be sufficient (Table 178-1 illustrates low fat commercial diet options).

TABLE 178-1

Comparison of Dietary Fat Concentrations in Canine Diets

PRESCRIPTION CANINE DIET (dry)	FAT (g/100 kcal)	FAT (% DM)
Hill's i/d	2.5/3.4	7.4/13.9
Hill's z/d	3.4	14.1
Hill's d/d (salmon)	3.6	14.8
Hill's d/d (venison)	4.0	16.3
Hill's w/d	2.8	8.7
Purina EN	3.1	10.5
Purina HA	2.4	8.0
Purina OM	2.8	8.5
Royal Canin Low Fat	1.9	5.0
Royal Canin Hypoallergenic HP	4.7	17.0
Royal Canin Fiber Response	4.8	14.5
Royal Canin Selected Protein PV (pea/venison)	3.2	10.0

DM, Dry matter.

In dogs with severe intestinal disease, such as lymphangiectasia with moderate to marked hypoalbuminemia (serum albumin < 1.5 g/dL), severe inability to digest and absorb fat and protein will occur (see ch. 276). Disease progression can result in subsequent development of GI mucosal edema and further nutrient malassimilation.[17] In these animals, ultra–low-fat diets (fat concentrations <3 g/100 kcal or <10% DM) with a highly digestible protein source to prevent further malassimilation and dysbiosis will be required.[17] In the most severe forms of PLE (albumin < 1.0 g/dL), a combination of parenteral and enteral nutrition could be needed to provide protein for oncotic pressure and help resolve the GI edema until specific immunosuppressive therapy or antibiotic therapy can be put in place to help stabilize the patient.[17,18] Once serum albumin concentrations are >1.5 g/dL, a highly digestible, low-fat commercial diet containing intact protein might be tolerated. However, some dogs with severe chronic enteropathies like PLE could require feeding of ultra–low-fat homemade diets (e.g., non-fat turkey breast, non-fat cottage cheese, egg whites, rice, and cooked potatoes) indefinitely. If a specially formulated diet (either homemade or elemental) is required for management of the disease, a nutritionist should be consulted to ensure the diet recipe is complete and balanced if it will be used for more than 1-2 weeks. There are several elemental diets that may be used as a supplemental diet for dogs with severe GI disease, but the elemental with the lowest fat (≈5%) used most at the author's hospital is Vivonex TEN (Abbott). This is a human product and is not complete and balanced for dogs; however, it can be used as a short-term supplemental diet (see ch. 182). Vivonex (and other human elemental diets) should not be used alone in nutritional support of cats because they do not contain enough protein, essential amino acids (including taurine), or essential fatty acids (e.g., arachidonic acid).

Adverse reactions to food are important causes of signs of GI disease in both dogs and cats (see ch. 191). These clinical disorders generally are classified as immunologic (immune-mediated, e.g., IBD, food allergy/food sensitivity) or non-immunologic (food intolerance or idiosyncratic reactions to food). Diets used for establishing the diagnosis of, or to treat, adverse food reactions should contain: (1) a reduced number of novel protein sources or a protein hydrolysate (no intact proteins, molecular weights <10,000 daltons), (2) highly digestible protein, (3) no food additives; reduced numbers of substances known to cause intolerance (lactose, gluten) or vasoactive substances (e.g., preservatives, antimicrobials, humectants, coloring agents, flavors, flavor enhancers, emulsifying agents, stabilizers, and thickeners), and (4) be nutritionally complete and balanced.[19] The above recommendations can be achieved with a commercial novel protein or hydrolyzed diet or by preparing a homemade elimination diet.

Fats and Fatty Acids

Like protein, dietary fat also has some important direct effects on GI tract physiology and function, including

slowing gastric emptying in dogs and humans but not in cats.[2,4,6] In contrast to the effects of protein, increased levels of dietary fat decrease the tone of the lower esophageal sphincter and could lead to an increased risk of gastroesophageal reflux or vomiting.[6] Therefore, low-fat, highly digestible diets improve gastric emptying in dogs and could reduce vomiting. Undigested fats or fatty acids that reach the distal ileum or colon can increase bacterial fermentation (especially nonbeneficial species), resulting in formation of proinflammatory and prosecretory hydroxy fatty acids, and osmotic diarrhea.[9,17] Furthermore, even though low fat diets are important in the dietary management of many chronic enteropathies of dogs, extremely low levels of dietary fat (or severe disease resulting in poor fat absorption) will lead to a deficiency of essential fatty acids and fat-soluble vitamins, and can have wide ranging impacts on cell function, production of prostaglandins, cholesterol, phospholipids, other cell mediators, and hormones. Dietary fat also is important in pet food as a palatability enhancer—which can create a problem with diet acceptance in some of the low-fat, highly digestible or high-fiber diets.

In general, dietary fat is highly digestible—more so, generally, than CHO or protein—with an average digestibility of fat in commercial foods >85% and as high as 95% in premium diets.[6,7] Therefore, fat malabsorption due to diet source is unusual; however, because digestion and absorption of fat is a complex process requiring multiple steps, malassimilation of fat in dogs with GI disease is common. In commercial, therapeutic, highly digestible diets formulated for dogs with GI disease, a reduced amount of fat, ranging from 4% to 12% DM, or <3-4 g/100 kcal, is present. There is a large variability in fat content in both hypoallergenic and hydrolyzed diets, but higher amounts of fat generally are present because these diets are not formulated for dogs with severe GI diseases (see Table 178-1). The wide variation in dietary fat content can influence response to treatment, especially in dogs with severe enteropathies.

In contrast to dogs, feline diets formulated for GI disease do not have the same reduction in fat content. There are some low-fat diets formulated for cats, but most are weight loss diets or "light" diets formulated to prevent weight gain in adult cats. There is a wide range of fat content in feline intestinal diets, high protein diets, and novel protein diets—but in general, the lowest fat content is about 15-20% (4 g/100 kcal). The reasons for this difference are multiple: (1) There is no current evidence to support a low-fat diet in the therapy of feline intestinal disease (in one recent study the highest fat diet was the most effective),[16] (2) cats have a higher requirement for essential fatty acids, and some fat-soluble vitamins, than dogs do,[14] and (3) most cats will refuse to eat a diet that is too low in fat.

Carbohydrates/Dietary Fiber

There are no requirements for dietary CHO in canine or feline diets; however, dietary CHO is present in pet foods to provide a readily available energy source, to reduce fat or protein content of food, as a source of dietary fiber, and to make the diets more economical to produce. The CHOs present in pet foods primarily are plant starches, such as rice, potato, corn, wheat, and barley, but they also can include a variety of non-grain starches (e.g., legumes and other vegetables).[6] These vary in digestibility, glycemic index (ability to increase blood sugar rapidly), and glycemic load (ability to increase total glucose over time). In diets for dogs with GI disease, the overall quantity of CHO is less important than its digestibility. In cats, an obligate carnivore species, the reduced ability to efficiently digest and metabolize dietary CHO, especially in the presence of GI disease, demands not only the presence of highly digestible CHO but also a greatly reduced quantity.[14] The quantity of CHO also has an impact on other aspects of feline metabolism due to cats' reduced ability to remove glucose from the blood stream following a high glucose meal. This effect does not have an impact on GI disease, but it could have an impact on pancreatic function, so is a relevant concern.[20] Studies in cats with IBD have shown that CHO malabsorption is occurring (detected by the presence of increased breath hydrogen), but is not related to overt changes in clinical signs.[21] Further evidence of CHO intolerance is demonstrated by the resolution of diarrhea in cats and kittens when diets containing high protein/low carbohydrate concentrations are used.

CHO digestibility is determined by its source and by cooking; for example, cooked rice and cracked wheat are highly digestible, whereas uncooked whole corn or potato starch is less digestible.[6] CHO malassimilation can cause osmotic diarrhea, increased intestinal gas (flatus), loss of water and electrolytes, enhanced fermentation of bacteria in both the small intestine and the colon, and overgrowth of pathogenic bacteria. Further, CHO malassimilation contributes to acidification of the colonic luminal environment, which promotes formation of hydroxy fatty acids and other potentially toxic intermediates.[9] White rice is the CHO of choice for most dogs (and is the most commonly used CHO in therapeutic diets), because it is gluten-free,

highly digestible, and nonantigenic.[2,6,7] Other gluten-free CHO sources include potato and tapioca, but they are less digestible than cooked white rice. In short, all commercially available diets formulated for dogs with intestinal disease contain moderately high quantities of highly digestible CHOs.

Another class of CHOs present in some diets are the beta-linked polysaccharides (i.e., those broken down by bacterial enzymes, not mammalian amylases), which include the dietary fibers.[6] Dietary fibers are a large, complex group of CHOs that include starch and non-starch polysaccharides found in plants. They are readily digested by bacterial enzymes but less well digested by mammalian enyzmes.[6] Traditionally, fibers were classified as soluble (highly fermentable) or insoluble (poorly fermented or nonfermentable) based on their digestion by amylase; however, a physiologically relevant classification, based on their activity in the GI tract, currently is recommended (Table 178-2).

TABLE 178-2

Comparison of Fermentable and Nonfermentable Fiber Effects on the Gastrointestinal Tract

EFFECT	SOLUBLE (FERMENTABLE) FIBER (e.g., beet pulp, guar gum, psyllium)	INSOLUBLE (NONFERMENTABLE) FIBER (e.g., cellulose, methylcellulose)
Transit time	No effect on transit in colon, slows transit of ingesta in small intestine	Normalizes transit in the colon by increasing segmentation (mixing) and improving propulsion, appears to increase speed of transit in small bowel
Fecal bulk	Decreased—stool smaller and softer	Increased—stool larger, drier
Bacteria/fermentation	Increases (more fermentation, could support beneficial bacteria such as lactobacilli or bifidobacteria)	Fermentation occurs, but to a very minor extent—minimal change in fecal flora
Water binding	High water binding, forms thick gels, increases fecal water, feces wetter and smaller	Water absorption is efficient—feces can become quite dry if not expelled quickly or if the pet is dehydrated

Fibers are soluble if they form gels in solution (thus attracting water), delay gastric emptying, slow intestinal transit, inhibit absorption of cholesterol and some other nutrients, are poor bulking agents, are highly fermentable in the colon (i.e., increase the numbers of bacteria and increase short chain fatty acids [SCFAs], especially butyrate, an essential colonic fuel source), acidify luminal contents, and stimulate colonic cellular proliferation.[22] Examples of soluble fibers include FOS, pectins, psyllium, oats, barley, guar gum, fruits, and some legumes.[6]

Insoluble fibers do not form gels, have no effect on gastric emptying, increase small intestinal transit and "normalize" colonic (segmentation) transit, have no direct effect on nutrient absorption (except reduced time for digestive action), are good bulking agents (i.e., they dilute colonic contents and thus bind noxious agents in the colon), are fermented less and therefore produce fewer SCFAs, and increase fecal weight.[22] Typical examples of insoluble fibers are cellulose, peanut hulls, wheat and rye fibers (most cereal fibers), and the woody parts of plants (e.g., lignins).[6] Prescription diets containing dietary fiber are used primarily for weight-loss diets, and in treatment of diseases of the colon, with soluble fibers being used for promoting colon health in colitis or other infectious or inflammatory diseases of the colon, and insoluble fibers being used for normalizing motility (e.g., hair or irritant colitis), acting as an adsorptive agent (e.g., colitis due to toxins or bacterial colitis), or in animals prone to constipation that need the propulsive effects of a bulking agent. It should be noted that insoluble fibers acting as bulking agents could worsen constipation or cause recurrence when animals are dehydrated, or when animals have decreased colonic function (obstipation/megacolon).

Nutritional Deficiencies Due to GI Disease

Nutritional deficiencies can occur as a consequence of GI disease (see ch. 192 and 193). Protein and calorie malnutrition is the most common nutritional deficiency in severe or chronic GI disease. A variety of vitamin deficiencies can occur as a result of severe intestinal disease, but deficiencies of B vitamins, especially cobalamin, and of some of the fat-soluble vitamins (E and K), are the most common and clinically important deficiencies recognized in dogs and cats.[13,23] The reader is referred to ch. 276 for more information on

cobalamin and folate therapy in GI disease.

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CHAPTER 179

Nutritional Management of Exocrine Pancreatic Disease

Marjorie Chandler

Client Information Sheet: Nutritional Management of Exocrine Pancreatic Disease

Acute Pancreatitis

Nutritional Risk Factors

Nutritional risk factors for acute pancreatitis (see ch. 289 and 290) in dogs include obesity, ingesting table scraps or food from the trash, a high-fat meal, or a high-fat low-protein diet.[1,2] Middle-aged, neutered dogs are considered to be at increased risk; this age and neutering status also has the highest prevalence of overweight and obese dogs.[3,4] Obesity in humans is a risk factor for a poor outcome in severe acute pancreatitis.[5] Obesity causes a low-grade inflammatory state and adipose tissue secretes numerous cytokines from adipocytes and adipose tissue macrophages.[6] Fat necrosis occurs after release of lipolytic enzymes from the damaged pancreas.[5] Fat necrosis promotes leukocyte infiltration of damaged areas, resulting in increased inflammatory mediators. The unsaturated fatty acids generated from lipolysis also contribute to inflammation and necrosis, processes that are worse in obese humans and mice compared to the non-obese.[7]

The increased risk associated with dogs that have scavenged in trash is the likelihood that they have consumed a large amount of fat present in scraps. Dietary fat has an effect on the Toll-like receptor (TLR)-4 present on macrophages, neutrophils, adipocytes and intestine epithelial cells. Activation of TLR-4 causes release of cyclooxygenase-2 derived cytokines and transcription factor NF-kappa-beta, which synthesizes tumor necrosis factor, further enhancing inflammatory responses. TLR-4 can be stimulated by lipopolysaccharide (LPS) endotoxin. There are similarities in LPS endotoxin and saturated long-chain fatty acids. Saturated long-chain fatty acids can stimulate macrophage receptors, similar in potency to LPS endotoxin. The adipocyte receptor is similarly activated by long chain fatty acids, although with less effect than LPS endotoxin.[8]

In >90% of cats with pancreatitis (see ch. 289 and 291), a cause is not identified and dietary risk factors for this condition are not well described.[9] Hyperlipidemia has been associated with feline pancreatitis.[2] Considering the effects of dietary fatty acids and obesity on inflammation and pancreatitis in other species, it is likely that diet has a role. Pancreatitis occurs in some cats fed high fat diets (Steiner J, personal communication, 2014).

Dietary Therapy for Acute Pancreatitis

Background

In the past, dogs and cats with pancreatitis were given nothing orally to decrease stimulation of pancreatic enzyme secretion and "rest" the inflamed pancreas. It is now appreciated that pancreatic inflammation and necrosis are worsened when exocrine activity is suppressed.[10] The intestine also plays a key role in the pathophysiology of acute pancreatitis. Intestinal ischemia, increased permeability and reperfusion injury may contribute to organ failure during pancreatitis. Withholding food promotes intestinal mucosal atrophy, increases rate of enterocyte apoptosis, decreases glutamine and arginine transport, and increases intestinal permeability.[11] Enteral feeding beneficially increases blood flow to the splanchnic circulation (see ch. 82).[8] In dogs with parvovirus, for example, early enteral nutrition hastened clinical improvement and likely

improved gut barrier function.[12]

People and Dogs

In the past 20 years, several trials involving people with acute pancreatitis have demonstrated the attributes of enteral, rather than parenteral, nutrition, including decreased mortality rates.[13,14] In people with pancreatitis, enteral feeding within 48 hours of hospital admission has been shown to be beneficial.[14] Meta-analysis has also shown that nasogastric feeding was not inferior to feeding into the jejunum.[14] Enteral feeding a low-fat diet via esophagostomy tube in dogs with severe acute pancreatitis, within the first 12-24 hours of admission, was well tolerated and resulted in fewer complications when compared with parenteral nutrition.[15] Dogs with pancreatitis are fed very low fat diets (e.g., less than 25 g fat per 1000 kcal), although no significant difference in the degree of pancreatic physiologic response in healthy dogs fed diets with 16% or 5% crude fat (as fed) was reported.[16,17]

Cats

Dietary management for cats with acute pancreatitis has not been well described. Many clinicians find that cats tolerate a higher fat diet than do dogs with pancreatitis. However, excessively high fat foods should probably be avoided.[18] Early placement of a nasogastric or esophagostomy tube (see ch. 82) is important in anorectic cats due to their risk of hepatic lipidosis. In a study of 55 cats with suspected acute pancreatitis, nasogastric tube feeding was well tolerated. Diarrhea and/or vomiting were not common.[19]

Maintenance Diets

It is recommended that obese or hypertriglyceridemic pancreatitis dogs or cats be fed ultra-low fat diets, with fat percentage on a dry matter basis (DMB) ≤10% for dogs and ≤15% for cats. Non-obese dogs and cats without elevated triglycerides may be fed diets with <15% and <25% fat DMB, respectively.[20] While there are commercial dog foods available which meet these criteria, there are fewer cat foods. Some "low calorie" or "senior" diets, which may not contain sufficient calories for an ill cat, are low in fat. Adverse effects have been reported with tube feeding elemental diets to cats, so a better approach may be to use a liquid diet formulated for use in cats if using a nasogastric tube.[18] If esophageal tube feeding is used or the cat has returned to voluntary eating, a diet with moderate fat content may be used (e.g., most commercial adult maintenance diets). In cats, intrinsic factor, a cobalamin (vitamin B_{12}) binding protein that promotes cobalamin absorption in the ileum, is only produced by the pancreas. In dogs it is synthesized in both stomach and pancreas. Many cats with pancreatitis are cobalamin deficient.[21,22] If a deficiency exists, parenteral supplementation is recommended at 250 mcg weekly for six weeks and then monthly.

Chronic Vomiting and Parenteral Feeding

When vomiting is too intractable to allow enteral feeding, peripheral or central parenteral feeding may be an option (see ch. 189). If possible, a small amount of enteral feeding should still be attempted to maintain gut integrity. In humans, the addition of glutamine has been found to reduce length of hospital stay and decrease overall complications in patients with acute pancreatitis given parenteral nutrition.[23]

Omega-3 Fatty Acids

The provision of omega-3 fatty acids to people with acute pancreatitis decreased complications and length of hospital stay.[23] The omega-3 fatty acid docosahexaenoic acid (DHA) affects the pancreatic acinar cell by inhibiting intracellular signalling, reducing amount of inflammatory cytokines generated, and inducing apoptosis instead of necrosis.[8] While saturated fats stimulate TLR-4, omega-3 fish oils inhibit stimulation of this receptor. No studies have been performed in dogs or cats to prove beneficial effects in the treatment of acute pancreatitis; however, fish oils can be useful in the treatment of hypertriglyceridemia and should be considered in pets with this condition as they are at increased risk of pancreatitis. The fish oils DHA and eicosapentaenoic acid (EPA) are recommended for use in cats and dogs over plant sources of omega-3 fatty acids. A recommended dosage of EPA plus DHA (230 to 370 $mg/kg^{0.75}$) has not been studied in dogs or cats with pancreatitis.[24]

Probiotics

Probiotics have been claimed to benefit people with severe acute pancreatitis by stabilizing intestinal barriers and minimizing bacterial translocation which contributes to infection of necrotic tissue.[25,26] They have also been claimed to stimulate host cell production of antimicrobial peptides and produce antimicrobial factors. However, in the PROPATRIA (probiotic prophylaxis in patients with predicted severe acute pancreatitis) trial, there was a higher mortality rate in people given a multi-strain probiotic compared to those given the control.[27] Because of this study, caution has been advised in the use of probiotics in pancreatitis and certainly the multistrain (Ecologic 641) used in this study should be avoided in pancreatitis.[14] A 2014 meta-analysis of the use of probiotics in the treatment pancreatitis found no evidence for probiotics being either harmful or beneficial in preventing infection, length of hospital stay, or mortality.[25] There are no recommendations for use of probiotics in pets with pancreatitis.

Antioxidants

A commonly accepted pathogenesis of pancreatitis begins with an insult to acinar cells followed by a proinflammatory response, which may then progress to a profibrotic response mediated by stellate cells. The level of oxidative stress in severe acute pancreatitis likely determines the severity of any systemic inflammatory response syndrome (SIRS; see ch. 132), duration of disease, and, potentially, risk of death.[8] The balance of pro-oxidants and antioxidants may be factors in resolving inflammation. In people, antioxidant cocktails (e.g., containing selenium, beta carotene, vitamin C and/or vitamin E) have reduced abdominal pain, disease recurrence, chronicity and length of hospital stay.[28-31] Studies of experimental canine pancreatitis have indicated an increase in free oxygen radical generation.[32-35] However, a study on the effects of superoxide dismutase on experimentally induced pancreatitis showed no improvement in serum laboratory findings or survival rates.[36]

Exocrine Pancreatic Insufficiency (EPI)

Overview

In dogs, progressive, immune-mediated pancreatic acinar and ductal atrophy is a common cause of EPI, although chronic pancreatitis may also be a cause.[37] While EPI is less common in cats, it is being diagnosed more commonly.[38] In cats, chronic pancreatitis is thought to be the most common cause of EPI.[22,34] Regardless, EPI is a condition associated with digestive enzyme deficiencies which may result in malassimilation, voluminous stools, steatorrhea, borborygmus, flatulence, and weight loss. While enzymatic therapy is the cornerstone of treatment (see ch. 292), dietary management is also extremely valuable.

Dietary Fat and Types of Diets

Restriction of dietary fat has previously been recommended for treatment of EPI. The rationale for lowering fat intake is that intestinal bacteria metabolize unabsorbed fat to hydroxylated fatty acids, which stimulate secretion of fluids in the distal small intestine and colon, potentially worsening diarrhea. Steatorrhea may also be a feature of EPI and could be worsened by high dietary fat.[39] Low-fat diets (e.g., 12 to 13% of calories as fat) have been recommended for initial treatment of canine EPI. In the only study to date, there was no control group and the dogs continued to do well when switched to a variety of diets later.[40]

In a canine EPI study, feeding a moderate-fat, low-fiber, highly digestible food decreased flatulence, borborygmi, fecal volume and defecation frequency compared to feeding the original diets. No differences were noted in appetite or fecal consistency.[41] In a later study on fat restriction and diet change in dogs with EPI, feeding a low-fat diet (13% of metabolizable energy [ME] as fat) compared to the original diets (14 to 30% calories ME basis) showed no significant difference in severity of signs.[42] A further study compared three diets in dogs with EPI: a high-fat diet (51% fat ME basis), a high-fiber, low-fat diet (22% fat on ME basis), and a moderate-fat, highly digestible diet (30% fat ME basis).[43] No consistent improvement was associated with any diet, and more importantly the response to the diets varied greatly among the dogs.

A low-fat diet may worsen lipase activity, as high-fat and high-protein diets optimized fat absorption when used with supplemented lipase enzymes in experimentally-induced canine EPI.[44] In three German Shepherd Dogs with EPI, feeding a highly digestible rice and soy protein–based hydrolysate diet with a high fat content

(40.8% fat ME basis) improved diarrhea and dermatological abnormalities.[45] When tolerated, a higher fat diet is likely to promote improvement in body condition, which is often poor in animals with EPI. A low-fat diet may not be necessary unless steatorrhea is uncontrollable. The effect of dietary fat on feline EPI has not been reported. In one retrospective study on EPI in 16 cats, 6 cats had received a "prescription diet."[46] Choice of diet appears to depend on the individual patient, as responses to diets vary. In some cases, a diet change may not be needed. Generally a low fiber, highly digestible diet is appropriate, with fat content adjusted as needed.

Medium Chain Triglycerides (MCTs)

Medium chain triglycerides with fatty acid chain lengths of six to twelve carbons have been suggested as a fat source for pets with EPI; however, results of a study looking at three diets (0%, 16% and 35% of total fat as MCTs) suggested that inclusion of MCTs did not improve clinical signs.[47] Moreover, MCTs are associated with poor palatability in dogs and extremely poor palatability in cats.[48,49]

Vitamins and Minerals

Cobalamin deficiency has been reported in many dogs and most cats with EPI.[38,46,50] Cobalamin should be supplemented parenterally if deficient and may need to be given chronically. Fat-soluble vitamins (A, D, E and K) may be deficient when fat is malabsorbed, but they do not necessarily require supplementation. Vitamin K deficiency has been reported in a cat with EPI.[51] If a coagulopathy is present or suspected, administration of vitamin K at 2.5 mg/kg SC q 24 h for two to three days is indicated. Supplementation of excess vitamins A and D can result in toxicosis, whereas vitamin E supplementation is generally safe.[10] There is no information on macro- and trace mineral absorption in dogs and cats with EPI, although one study found lower serum and tissue concentrations of zinc and copper compared to control dogs.[52,53]

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CHAPTER 180

Nutritional Management of Hepatobiliary Disease

Craig G. Ruaux

Client Information Sheets:
Nutritional Management of Animals with Liver Disease
Nutritional Management of Animals with Hepatic Encephalopathy

Metabolic Energy and Protein Requirements in Chronic Hepatic Disease

Nutritional interventions in pets with hepatic disease must provide sufficient metabolic energy to meet the needs of the patient, while considering the disease state of the animal. Protein requirements to maintain a positive nitrogen balance may be substantially higher in animals with hepatobiliary disease than in normal dogs.[1] Dietary protein restriction in this group of patients may actually slow recovery. If dietary intake is inadequate, a common problem in patients with liver disease,[2] protein-calorie malnutrition can develop, worsening many of the clinical signs accompanying hepatobiliary disease. The first aim of nutritional support for most animals with hepatic disease should therefore be to ensure adequate caloric intake to meet metabolic energy requirements (see ch. 170 and 177).[3] Normal canine maintenance diets utilizing high-quality, readily digestible protein sources are indicated in most dogs with liver disease, unless overt hepatic encephalopathy is present.

While the actual metabolic energy requirements of animals with hepatic disease are not well defined, clinical experience suggests that most of these patients require at least the same dietary metabolic energy input as healthy, active animals. In cats, the provision of adequate protein intake is even more important to maintain lean body mass. Several amino acids (e.g., taurine, arginine, methionine and cysteine) are either essential in cats or become conditionally essential in disease states featuring decreased voluntary intake (see ch. 174).[4] Bile acids in the cat are exclusively conjugated to taurine[5]; as bile acids are deconjugated by intestinal bacterial activity, there is a constant demand for additional taurine, which must be met either from dietary intake or mobilization of muscle protein.[6] Taurine deficiency can thus develop rapidly in cats with hepatic disease.

Representative major nutrient compositions of diets from several manufacturers that are either directly labeled for use in animals with hepatic disease or recommended by the manufacturer for use in liver disease are summarized in Table 180-1.

TABLE 180-1

Major Nutrient Compositions of Representative Veterinary Prescription Diets with a Labeled Indication for Use in Hepatic Disease or Hepatic Encephalopathy

DIET	PROTEIN (% DM)	PROTEIN (g/100 kcal ME)	FAT (% DM)	CARBOHYDRATE (% DM)	MANUFACTURER RECOMMENDED INDICATIONS
Canine					
Hills l/d Dry	17.8	4.1	24.4	48.5	Liver disease, hepatic encephalopathy, copper storage
Hills l/d Canned	17.6	3.9	24.2	49.3	
Purina NF Kidney Function Dry	15.9	3.6	15.7	62.8	Renal failure, hypertension, early CHF, hepatic disease with encephalopathy

Purina NF Kidney Function Canned	16.5	3.6	27.4	50.4	
Purina EN GastroENteric Formula, Dry	27.5	6.6	13.3	47.7	Hepatic disease not associated with encephalopathy, enteritis, pancreatitis, IBD
Purina EN GastroENteric Formula, Canned	33.9	8.0	15.0	43.9	
Royal Canin HEPATIC Dry	14.0	4.0	14.0	49.0	Hepatic insufficiency, hepatic disease, hepatic encephalopathy, portosystemic shunts, disorders of copper metabolism
Royal Canin HEPATIC Canned	15.0	4.1	28.0	57.0	
Feline					
Hills l/d Dry	29.0	7.0	23.1	37.7	Liver disease, hepatic lipidosis, hepatic encephalopathy
Hills l/d Canned	31.6	6.7	23.2	38.0	
Purina NF Kidney Function Dry	28.5	7.2	12.8	50.6	Renal failure, hypertension, early CHF, hepatic disease with encephalopathy
Purina NF Kidney Function Canned	31.1	6.0	29.5	30.6	
Purina EN GastroENteric Formula, Dry	56.2	12.9	18.4	16.7	Enteritis, diarrhea, gastritis, hepatic lipidosis

CHF, Congestive heart failure; *DM*, dry matter; *IBD*, inflammatory bowel disease; *ME*, metabolizable energy.

Values are rounded to one significant figure. Data and indications obtained from respective company websites or printed materials as of March 2015.

The majority of liver diseases encountered in companion animals do not carry a risk of encephalopathy except in end-stage disease (Table 180-2); thus, the use of "liver" diets with markedly reduced protein content is not recommended for all, or even the majority of, animals with liver disease. Diets with mildly reduced protein content, utilizing a high digestibility protein (such as the renal and hypoallergenic diets listed in Table 180-1), are a preferred choice in most companion animals with liver disease.

TABLE 180-2

Common Canine and Feline Liver Diseases

CANINE	FELINE
Vacuolar hepatopathy Glucocorticoid-induced Diabetes mellitus Chronic illnesses (Pancreatitis, IBD)	Vacuolar hepatopathy Glucocorticoid-induced Diabetes mellitus Chronic illnesses (pancreatitis, IBD) Hepatic lipidosis **(very severe cases may have encephalopathy)**
Infiltrative diseases Acute hepatitis Idiopathic chronic hepatitis Lymphoma	Infiltrative diseases Cholangiohepatitis Lymphoma
Biliary tree diseases Major bile duct obstruction Biliary mucocele	Biliary tree diseases Major bile duct obstruction Cholangitis Neoplasia (biliary carcinoma)
Primary or metastatic neoplasia Metastases of hemangiosarcoma Massive hepatocellular carcinoma	Primary or metastatic neoplasia Hepatocellular carcinoma (rare)

Primary portal vein hypoplasia/microvascular dysplasia	
Cirrhosis	**Cirrhosis**
Portosystemic vascular anomalies	**Portosystemic vascular anomalies**
Juvenile fibrotic disorders (rare)	

Conditions associated with risk of hepatic encephalopathy are in **bold** type. Note that the majority of liver diseases diagnosed in companion animals are not associated with hepatic encephalopathy, except in an end-stage state.

Modified from Center SA: Nutritional support for dogs and cats with hepatobiliary disease. *J Nutr* 128(Suppl 12):2733S-2746S, 1998.

Nutraceuticals in Hepatic Disease

A reasonable definition of the term "nutraceutical" would be a food, food-derived compound, or dietary supplement that is given with the intent to modulate disease or provide health benefits. Many nutraceutical compounds have been suggested as supplements in human beings and animals with hepatic disease[7]; however, within the veterinary literature only two compounds/products, S-adenosylmethionine and silymarin, have received meaningful attention.

S-adenosylmethionine (SAMe) is critical for the synthesis and reduction of glutathione (GSH), which is one of the most important early protection mechanisms within the hepatocyte against oxidant stress.[8-10] SAMe has been assessed prospectively in healthy, untreated cats and in healthy dogs receiving chronic prednisolone therapy.[8,11] Increases in hepatic GSH, with an increase in the ratio of reduced GSH to the oxidized glutathione disulfide (GSSG) form, were noted. In the dog study, however, no protective effect was seen against glucocorticoid-induced vacuolar hepatopathy.[11] In one prospective, randomized, non-blinded trial, dogs receiving lomustine (CCNU) chemotherapy and an S-adenosylmethionine/silymarin combination product* showed less pronounced elevations in liver enzyme activities and were less likely to experience treatment delay than the control group receiving CCNU alone.[12]

Cats are particularly susceptible to acetaminophen-induced hepatotoxicosis, and SAMe would appear to be a rational therapeutic for this condition. Unfortunately, controlled studies of the effect of SAMe therapy on a model of acetaminophen hepatotoxicosis in the cat showed little to no effect.[9] There are very few well-controlled clinical studies assessing the efficacy of SAMe as a therapy for spontaneous chronic liver disease in dogs or cats.[13]

Silymarin has been shown to have potent antioxidant efficacy in several models of oxidant-mediated liver disease.[14] There have been very few well-controlled studies of silymarin use in companion animals with spontaneous disease, with the notable exception of the previously cited study using combined SAMe/silymarin in cancer-bearing dogs receiving CCNU.[12] Meta-analysis of clinical trials using silymarin in human beings reveals little evidence for clinical benefit, except in *Amanita phalloides* mushroom poisoning.[20]

Using a strictly evidence-based approach to medical decision-making, there is relatively little evidence of benefit from any current nutraceutical for management of chronic hepatic disease in dogs and cats.[13] While these products are unlikely to cause harm, and in many cases there are compelling physiological arguments for their possible benefit, accurate diagnosis of the primary liver disease and implementation of therapy directed towards this diagnosis are recommended in preference to empirical therapy with nutraceutical compounds at this time.

Copper-Restricted Diets

Copper (Cu) accumulation hepatopathy is well recognized as an autosomal recessive disorder in the Bedlington Terrier (see ch. 282).[15] In several other breeds there is evidence of excessive Cu accumulation in some liver diseases.[16-18] As Cu can accumulate with cholestasis as well as primary hepatocellular disease, the significance of Cu accumulation as a primary pathological event is less clear in many of these dogs. In the Labrador Retriever, studies suggest that chelation therapy and reduced Cu diets are associated with an improvement in chronic inflammatory liver disease and reduction in liver Cu concentrations in subclinical cases.[19,20]

Animals with hepatic Cu accumulation sufficient to cause overt hepatopathy are best treated with specific therapy using chelating drugs such as d-penicillamine, at least until hepatic Cu content is reduced below toxic levels. Dietary Cu restriction can be useful in the maintenance phase of management for dogs with these

diseases. Typical maintenance canine diets will contain a minimum of 7.3 ppm Cu, while Cu-restricted diets may contain as little as 3 ppm Cu on a dry matter basis.

Additional dietary manipulations to decrease hepatic Cu accumulation include supplementation with ascorbic acid and elemental zinc (Zn). Zn supplementation increases the intestinal expression of metallothionein, an avid metal binding protein within the enterocytes. Metallothionein has a higher affinity for Cu than Zn. Administration of Zn between meals leads to increased metallothionein expression in the enterocytes. Cu in the diet is then bound with high affinity within the mature enterocyte and lost in the feces as the enterocyte is shed.[21] Zinc is given at a loading dosage of 100 mg elemental Zn orally twice weekly for three weeks, followed by a maintenance dosage of 50 mg elemental Zn orally twice weekly. Vomiting and nausea may both occur as side-effects of Zn therapy; administration of the Zn with a small amount of food may reduce these side effects.

Vitamin and Mineral Supplementation

Animals with liver disease often have vitamin and/or mineral deficiencies. Several factors, including reduced voluntary intake, fat malabsorption, reduced gastrointestinal mucosal function and loss of reserve stores in hepatic tissue can all contribute to the development of vitamin and mineral deficiencies.

Water-soluble vitamins such as folic acid, thiamine, cobalamin, niacin and riboflavin are often critical cofactors in enzymatic pathways carried out in hepatic cells. In cats with hepatic lipidosis, deficiencies of these vitamins are common.[22] Administration of multivitamin supplements is cost-effective, simple, and should be included in any nutritional support plan for patients with liver disease.

In the cat, cobalamin malabsorption due to small intestinal disease is commonly documented in association with liver disease.[23] It has previously been thought that cobalamin malabsorption due to intestinal disease could not be overcome by increased dietary supplementation, implying that parenteral therapy is necessary.[24] Recent data, however, suggest that a small, but sufficient, amount of orally administered cobalamin is absorbed in both canine[25] and feline (Toresson L, personal communication, 2015) patients with gastrointestinal disease. Further studies of the efficacy of oral cobalamin supplementation in patients with chronic gastrointestinal and hepatic disease are eagerly awaited.

Some patients (particularly fractious cats and dogs) may still be most effectively treated for their cobalamin deficiency via a parenteral route; this route may also be essential during the initial phase of treatment of some patients where oral intake is reduced or absent. The protocol currently recommended for parenteral cobalamin use in cats with cobalamin deficiency due to intestinal disease is 250 mcg/cat injected subcutaneously, once a week for four weeks, one dose one month (4 weeks) later, then a recheck one month later. Further details of the current parenteral cobalamin dosing schedule and recheck recommendations may be found at http://vetmed.tamu.edu/gilab/research/cobalamin-information and in ch. 292. The concentration of cobalamin in standard injectable multivitamin preparations is insufficient to supply this amount of cobalamin in a reasonable injection volume; the use of pure preparations of cobalamin in addition to multivitamin products is recommended in dogs and cats with documented cobalamin deficiency.

Significant elevations in the plasma concentration of proteins induced by vitamin K antagonism (PIVKA) have been documented both in cats with hepatic lipidosis and cats with cholangiohepatitis associated with inflammatory bowel disease.[26] Vitamin E deficiency reduces cellular defenses against oxidant-mediated damage, and potentially plays a role in copper-associated hepatoxicosis.[27,28] Empirically, regular supplementation of vitamin E, A and D at three- to four-month intervals is recommended in companion animals with long-standing liver disease.

Nutritional Intervention in Hepatic Encephalopathy

Hepatic encephalopathy (HE) results from loss of hepatic detoxification function and subsequent accumulation of encephalotoxins within the systemic circulation and central nervous system.[29] These encephalotoxins may be directly toxic to neurons (i.e., ammonia), or may act as "false" neurotransmitters, interfering with central nervous system function.[29] In human patients, HE is graded via a variety of physiological and neurological scoring systems, most of which refer back to the West Haven Criteria.[29] Under this scoring system, HE is scored from 0 (no encephalopathy) to 4 (hepatic coma). Subtle neurological impairments, equivalent to inattention or mild tremor, are difficult to detect in small animals; therefore, most animals with a diagnosis of HE will fall within the West Haven Criteria scores 2-4. According to a consensus statement of the European Society of Parenteral and Enteral Nutrition, protein restriction is not indicated in

human patients with an HE score of 0-2, as negative protein balance and resultant malnutrition are negative prognostic factors.[2] Protein restriction is indicated in human patients with West Haven Criteria scores of 3-4. Such scores are a strong negative prognostic factor, with most dying within one year.[2] A critically important point, however, is that most animals with liver disease *do not* have this degree of HE. In many veterinary patients with hepatobiliary disease, aggressive protein restriction is counterproductive.

Recommendations for dietary protein content in diets fed to animals with severe HE vary. Most dogs can be managed with diets containing 3-4 g of protein per 100 kcal of diet, while cats require at least 6 to 7 g/100 kcal. It is important to note that the recommendation is for protein proportion within the diet, not for protein intake/kg of animal. Several commercially available diets are formulated to meet these recommendations (see Table 180-1).

The amino acid makeup of the diet used in patients with HE is another area of interest and controversy. It has been suggested that aromatic amino acid (AAA)-rich diets are likely to potentiate HE, the AAAs potentially acting as substrates for the production of encephalotoxins.[1] The molar ratio of AAA to branched-chain amino acids (BCAA) in plasma has been shown to be increased in animals with HE.[1] BCAA are important substrates for gluconeogenesis, and thus, the presence of protein/calorie malnutrition will lead to depletion of these amino acids in the plasma. While these changes in the AAA:BCAA are well documented in veterinary and human patients, their significance as a direct cause of HE rather than as an epiphenomenon is unclear. Experimental studies using dogs with surgically-created portosystemic vascular anomalies found more pronounced HE and higher blood ammonia concentrations in the dogs receiving a low AAA:BCAA diet. However, the dogs receiving this diet ate more than those receiving a high AAA:BCAA diet, resulting in greater total protein intake.[30] Based on meta-analyses of studies in human beings with HE, BCAA supplementation is recommended in patients who develop severe HE scores during enteral nutrition.[2] The situation is less clear with lower grade HE human patients, and by extension most veterinary patients. In most cases, BCAA supplementation is unlikely to lead to a net negative benefit, unless voluntary intake is reduced. Most veterinary prescription diets specifically labeled for hepatic disease are formulated to achieve a higher BCAA content and derive a significant proportion of metabolizable energy from fats and carbohydrates.

Feeding of several small meals throughout the day is often of benefit for animals with overt HE, reducing the total ammonia load following each meal. Other strategies used to control HE in small animals include antibacterial therapy with neomycin or metronidazole and the use of enteric lactulose therapy (oral or via enema) to reduce ammonia production and absorption, respectively, from the gastrointestinal tract (see ch. 281 and 284).

Nutritional Management of Hepatic Lipidosis in Cats

Appropriate nutritional management is absolutely central to successful resolution of hepatic lipidosis (HL) in cats (see ch. 285). Most (>95%) cats with HL have an underlying illness that predisposes the cat to enter a catabolic state.[22] Successful management typically requires addressing this underlying disease process, to allow a return to more normal appetite. In the short term, diligent attention to restoration of a positive caloric balance is necessary.

The feline liver has relatively small glycogen stores, making the cat dependent upon systemic lipolysis and hepatic metabolism of triglycerides relatively soon after the onset of anorexia. The underlying biochemical defects leading to hepatic accumulation of these lipids are complex and not fully understood; however, they do appear to be intrinsically linked to the cat's strictly carnivorous diet.[4,31] Arginine, choline and carnitine supplementation are commonly recommended in the nutritional management of cats with hepatic lipidosis. Cats with hepatic lipidosis fed arginine-deficient diets, even if fed in quantities necessary to supply adequate caloric intake, can rapidly develop severe HE as the urea cycle is compromised.[22] Choline and carnitine are both important in mitochondrial fatty acid transport and packaging of fatty acids into very-low-density lipoproteins for export from the hepatocyte. Thus, deficiency of these trace elements may contribute to lipid accumulation. If the diet used for initial feeding is deficient in arginine, as is the case with most human formulations, this amino acid should be supplemented at a dosage of 250 mg/100 kcal of diet delivered. The author empirically supplements HL cats with arginine, carnitine (250-500 mg/day), and taurine (250-500 mg/day) regardless of the enteral nutrition formula used.[22,32]

Most cats with HL are severely anorectic. Assisted feeding should be implemented as soon as feasible in these patients. Oral forced alimentation is not recommended, because many force-fed cats will develop food aversion. Medical agents for appetite stimulation in cats are variably effective, often ineffective in HL cats,

and may require hepatic detoxification.[33] Early placement of a feeding tube, at the minimum an esophagostomy tube, should be considered the standard of care (see ch. 82). Placement of a large-bore esophagostomy tube (10-14 French) can make feeding easier and allow the use of blenderized diets. Percutaneous, endoscopically-placed gastrostomy (PEG) tubes allow greater movement of the head and neck of the cat (as these areas are not bandaged), allowing the cat to self-groom. If a large bore PEG tube can be placed, owners can easily feed the cat at home. Clinicians experienced in this technique can place a tube in a 10-15 minute anesthetic procedure.

With critically ill cats, where even a short anesthetic procedure to place an esophagostomy tube is felt to carry excessively high risk, initial feeding with a nasoesophageal tube (5-8 French) can be attempted (see ch. 82). However, these tubes are more prone to clogging and failure due to vomiting, regurgitation, or removal by the patient.

Many cats show vitamin K deficiency and elevated PIVKA with HL[26]; administration of subcutaneous vitamin K for 1-2 days before feeding tube placement is recommended for cats with documented coagulopathy. Surgical placement of gastrostomy tubes via celiotomy in cats with hepatic lipidosis is associated with high risk of post-operative morbidity and an unacceptable risk of stomach displacement.[22]

During initial reinstitution of feeding, dramatic and potentially life-threatening electrolyte derangements can occur, particularly in serum potassium (K^+) and phosphate (PO_4^{3-}). These electrolyte derangements should be anticipated when beginning assisted feeding in cats with hepatic lipidosis, and may require aggressive management (see ch. 142 and 305).

Many cats with HL have water-soluble vitamin deficiencies. These are commonly supplemented by admixing multivitamin preparations into IV fluids at a dosage of 1-2 mL/1 L bag. IV fluid bags and lines containing supplemental multivitamins should be protected from light.

Thiamine deficiency is particularly insidious in cats with HL. Both thiamine and K^+ deficiencies can result in obtundation, weakness and neck ventroflexion (see ch. 21). These signs may be misinterpreted as HE, and these abnormalities should be screened for and corrected before instituting low-protein diets for presumed encephalopathy. HE is not a feature of most cases of HL, and use of low-protein diets may be associated with an adverse outcome.[34]

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*Denamarin, Nutramax Laboratories.

CHAPTER 181

Nutritional Management of Endocrine and Metabolic Diseases

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Client Information Sheet: Nutritional Management of Diabetes Mellitus in Dogs and Cats

Successful management of many endocrine diseases may be facilitated with appropriate nutritional strategies. Most important is diabetes mellitus (DM; see ch. 304 and 305) and, to a lesser extent, feline hyperthyroidism (see ch. 301). Hypothyroidism (see ch. 299 and 300) and hyperadrenocorticism (see ch. 306 and 307), while treated medically, often require consideration of nutritional management for appetite control, weight loss, and controlling secondary hyperlipidemia (see ch. 182).

Nutritional Management of Diabetes Mellitus

Overview

Nutritional management of DM in both dogs and cats includes choosing a diet, meal schedules, consideration of energy requirements, weight management, and addressing any concurrent disease. Concurrent or historical pancreatitis should be considered, especially in dogs (see ch. 290). In either species, identifying and addressing potential underlying causes of insulin resistance, especially obesity (see ch. 176), is critical. The goal of nutritional therapy for DM is to help improve glycemic control in conjunction with insulin therapy and management of other medical problems or other individual factors.[1] Consideration of the individualized nutritional assessment (body weight, body condition score, appetite, diet history, etc.) as well as feeding management issues that may include owner abilities and limitations is warranted in order to provide a customized and effective nutritional plan (see ch. 170). Further, dietary features such as fat and fiber content, energy density, and palatability can each be key.

Nutritional Background for Dogs with DM

Insulin requirement in DM dogs (see ch. 304) is largely determined by dietary factors such as meal timing, meal size, and the rate of glucose absorption from the intestine. Consistency is an important aspect of the feeding schedule. Ideally, the same amount of the same diet is fed at the same time every day. Two or more smaller meals are preferable to one large daily meal, to minimize wide fluctuations in blood glucose. Most DM dogs are fed two equal-sized meals daily, coordinated with twice-a-day insulin injections. A minority of dogs with DM are finicky eaters and may prefer consuming food in small amounts throughout the day. In these pets, consumption of a significant portion of the daily energy requirement (up to 50%) at the time of insulin administration should be encouraged, to provide adequate concentrations of glucose for the administered insulin. Dogs with DM, whether at the time of diagnosis or after excellent response to therapy, are usually always hungry (polyphagic) and meal feeding is rarely an issue. However, diet palatability remains important to ensure adequate intake of energy and other essential nutrients.

Nutritional Background for Cats with DM

Unlike dogs, cats with DM (see ch. 305) do not appear to require strict control of meals, perhaps due to their longer gastric emptying times and absorption of dietary carbohydrates.[2,3] For example, feeding diets containing various starch sources at concentrations similar to those found in commercially available feline diets (approximately 35% dry matter) had only a minor impact on postprandial glucose and insulin responses

in healthy cats; maximum plasma glucose concentrations were 68 to 93 mg/dL several hours after eating.[4] The largest differences between dogs and cats in response to feeding were noted with diets containing cornstarch (38 and 34% dry matter for dogs and cats respectively). Peak blood glucose concentration for dogs was 92 mg/dL 15 minutes after eating. However, 7.2 hours were needed for cats to reach a similar peak value of 93 mg/dL.[4,5] These findings are consistent with data demonstrating that feline glycemic responses to commercial dry diets are not only prolonged (intestinal absorption occurred over 10-12 hours), but are not associated with dietary carbohydrate concentration or carbohydrate digestibility.[6]

Controlling Postprandial Hyperglycemia in Diabetic Dogs and Cats

Introduction

Diet composition characteristics can reduce the magnitude of postprandial hyperglycemia in dogs and cats with DM. These factors include increased fiber and the use of lower amounts of carbohydrate. Both factors probably contribute to the lower "glycemic index" of some foods, with those higher in fiber and/or lower in starch having lower glycemic indices.[7-9] Overall, the glycemic index concept has not yet been validated in either dogs or cats and is not currently used in assessing carbohydrate sources or pet foods. Other strategies to prolong gastric emptying time, such as increased amounts of fat, might be contraindicated in DM due to obesity or to abnormal lipid metabolism and resultant dietary fat intolerance (e.g., pancreatitis or hyperlipidemia).

Dietary Fiber (see ch. 190)

Fiber comprises a varied group of compounds produced by plants, not digestible by mammalian enzymes. Fiber sources are primarily complex carbohydrates (beta-linked chains of sugar molecules) but also include compounds such as lignin, phytates, and waxes. Fiber is usually categorized by its degree of solubility in water and its degree of fermentation by intestinal bacteria. Fiber is not considered nutritionally essential for dogs or cats, but can be a useful adjunct in managing many conditions. The goals of adding fiber to a diet are typically to achieve satisfactory and consistent stool quality, promote satiety, decrease energy density of food, achieve a prebiotic effect (e.g., fermentation by the intestinal microbiota to produce short-chain fatty acids), or to modulate gastric emptying and nutrient absorption.

Various methodologies are utilized to quantitate different fiber fractions within food. Currently, the quantity of crude fiber (CF) is the standard for reporting fiber content of pet foods. This method quantifies some, but not all insoluble fiber as cellulose, hemicellulose, or lignin. However, soluble fiber content is not assessed. In contrast, total dietary fiber (TDF) is reported for human food. TDF simulates enzymatic digestion within the gastrointestinal tract, captures more insoluble fiber than the CF method, and allows for quantification of soluble plus insoluble fiber. Newer TDF methods also separately quantify low-molecular-weight dietary fibers, such as the indigestible oligosaccharides utilized by intestinal microbes. They are included in the World Health Organization's definition of dietary fiber. These distinctions are important given that CF is a poor measure of true fiber concentration (as determined by TDF) in adult maintenance dog foods, in veterinary therapeutic diets formulated for the management of feline DM or obesity, and in those formulated for canine DM, obesity, or fat-responsive conditions.[10-12] The use of CF in pet foods leads to significant challenges in comparing products based on fiber type and concentration, while also overestimating energy content and carbohydrate concentration. One study found that using CF vs. TDF resulted in carbohydrate overestimates as high as 93% in cat diets formulated for DM.[11] As such, conclusions drawn by previous research utilizing CF to estimate fiber and carbohydrate content of diets may not be accurate.

There are few data describing the impact of dietary fiber on managing feline DM. One randomized crossover study investigating the role of insoluble fiber in the treatment of DM cats demonstrated improved glycemic control in 12/16 consuming a diet high in fiber (61 g TDF/Mcal) and in 4/16 cats who consumed a diet low in fiber (11 g TDF/Mcal) but higher in starch.[13] Another study assessing the efficacy of glipizide included unequal groups of cats on commercial diets varying in fiber content (16 fed a high-fiber diet and 4 a low fiber diet); cats on each diet responded to the treatment but the response rate could not be compared due to the study design.[14] The optimal concentration and type of dietary fiber for nutritional management of cats with DM remains unknown.

Insoluble fiber, in particular, appears to be beneficial in DM dogs, although soluble fiber may have a role as well. One study showed lower mean 24-hour and postprandial blood glucose concentrations when dogs were

fed a high fiber diet (mostly insoluble; 56 g TDF/Mcal) compared to baseline values.[15] There is evidence that diets high in insoluble fiber (73 g TDF/Mcal), when compared to high-soluble-fiber (56 g TDF/Mcal) diets, are beneficial in managing canine DM, including lower mean glucose concentrations, lower maximum blood glucose concentrations and lower areas under the blood glucose curve.[16] However, when fiber types were compared in feeding studies of dogs with experimental DM, diets high in either insoluble (cellulose; 70 g TDF/Mcal) or soluble fiber (pectin; 55 g TDF/Mcal) resulted in lower blood glucose concentrations when compared with a lower fiber diet (24 g TDF/Mcal). There was no difference between groups fed the high fiber diets.[17] With regard to the efficacy of moderate fiber concentrations, no benefit for dogs with DM was noted with diets containing 18-20 g TDF/Mcal when they were compared with modestly-low fiber diets containing 14 g TDF/Mcal (mostly insoluble).[18] In summary, if a higher fiber strategy is desired, it appears that the concentration should exceed 55 g TDF/Mcal from an insoluble or mixed fiber source to provide a beneficial effect.

Feline Diabetes Mellitus

Background

There is no consensus regarding specific dietary strategies for cats with DM and little scientific evidence to support promotion of any particular nutritional approach. Almost all the diets used in studies on cats with DM had carbohydrate and fiber content based on inaccurate calculations using CF. This likely contributed to carbohydrate overestimations in tested diets.[11] Further, clinical trials on the effect of commercially available diets differ in many respects. To date, no studies comparing diets for cats with DM have controlled for ingredients, fiber type, fiber concentration, carbohydrate source, or for other macronutrients (fat and protein). While some clinical product testing is useful with regard to comparing the efficacy of specific diets in treating particular diseases, these studies do not provide definitive information on the effect of any particular nutrient on managing feline DM. It is known that dietary factors other than carbohydrate concentration and source have a role in treating cats with DM. For example, one study demonstrated benefits attributable to higher fiber intake.[13]

Carbohydrates

Recent focus on carbohydrate concentrations may be misguided. Arguably, definitions of what constitutes a "low carbohydrate" diet are subjective, although a range of up to 25% carbohydrate on an energy basis has been suggested.[1,19] Also, in the absence of data from cats with DM fed controlled diets with graded concentrations of carbohydrate, dose-response curves to determine the optimal amounts are also lacking. In addition, the inaccurate calculation of carbohydrate concentrations using CF values may result in needless and incorrect elimination of potentially beneficial dietary options.[11] Feline diets marketed as "low carbohydrate" tend to be high in fat and have high energy density, less than ideal for most overweight cats with DM and especially if the restricted amount is not acceptable to the owner or the cat.[11] This may be somewhat ameliorated by the use of higher moisture (canned) diets.[20] It remains unknown whether the effects of a specific diet are maintained long-term and of sufficient magnitude to sustain weight loss and an ideal body condition.

Diet Comparisons

Limited data examining the effect of diet on control of naturally-occurring DM in cats have been published. Several studies involved feeding only one diet during the test period, important for standardization prior to measurement of dependent variables. However, this approach omits dietary control groups and precludes interpretation of any potential response to nutritional factors.[21-25] To our knowledge, only four studies have compared two or more diets in cats with DM. In each study, improvement or remission of the DM was noted for more than one dietary group.[13,14,26,27] Two of these studies demonstrated that most cats benefited from consuming a higher fiber diet, although statistical analysis of response rates was not possible in one study.[14] A third study found improvement when the cats were fed a lower carbohydrate, lower fiber, higher fat diet.[26] The fourth study found no difference in improvement rates between DM cats fed lower carbohydrate diets and those fed "maintenance" diets; this study also reported a median body weight gain in both diet groups.[27] Overall, it appears that improvement or resolution of the diabetic state may be more likely in cats who were obese and who lost body fat, regardless of diet.[22,26] Further investigation into why some cats achieve

remission while some do not, regardless of diet, is necessary to understand the underlying physiology and identify potential targets for dietary and medical therapy.

An Individualized Approach to Nutritional Management of DM

For both dogs and cats, appropriate dietary management of DM depends, in part, on individual factors: body weight, body condition score, weight trends, diet palatability, food acceptance, exercise, and treats. Energy restriction and maintenance of a lean body condition improves glucose tolerance, and increases quality and quantity of life in healthy dogs (see ch. 2 and 170).[28] It is not known if these apply to dogs with DM, but it has been demonstrated that intake of a very high-fat-diet (80% fat calories) by dogs may lead to obesity, impaired central nervous system insulin transport, insulin resistance and reduced ability to synthesize and secrete insulin.[29,30] Preventing or reversing obesity is important for health, longevity, and improved sensitivity to insulin. Therefore, a lean body condition should be a goal for every patient. Diets that are highly energy dense and high in fat would not be appropriate for achieving a lean condition in an overweight pet. Conversely, a lower-energy-density, high fiber diet would not be ideal for a thin diabetic.

For dogs and cats with evidence of fat intolerance (e.g., pancreatitis or hyperlipidemia), clinical experience suggests that reducing dietary fat by at least 50% on an energy basis (% of calories from fat) is effective. Formulation of an appropriate diet requires not only correct interpretation of a detailed diet history, but determination of the amount of fat routinely consumed before the diagnosis of DM was made. Consideration of relevant patient factors, as well as the willingness and ability of the owner to purchase and feed a specific type of diet, are important aspects of assessment and ongoing management. In the absence of the need to address concurrent issues, diet change may not be necessary if the meal schedule is appropriate and the diet balanced. The optimal approach to feeding dogs and cats with DM is one customized to the individual.

Nutritional Management of Insulinoma

See E-Box 181-1.

E-Box 181-1

Insulinoma

Overview

Insulinoma is a tumor that commonly causes clinical signs attributable to hypoglycemia including seizure, collapse, and weakness among others (see ch. 61 and 303). Although clinical trials assessing the efficacy of dietary modification on signs, prognosis, and other outcomes in dogs with insulinoma have not been reported, nutritional strategies can be successfully employed for varying time periods. Insulinomas tend to be relentless in their progression. The goals of nutritional management of dogs with insulinoma include avoidance of prolonged periods of fasting and minimizing large variations in blood glucose concentrations. Feeding management strategies and specific dietary profiles may help achieve these goals through modifying peripheral, hepatic, and normal pancreatic metabolism of nutrients. Dietary simple sugars may stimulate secretion of profound amounts of tumor-derived insulin and must be avoided.

Feeding Management and Nutritional Profile

Dietary factors such as meal timing, meal size, and meal frequency are important to ensure a steady and low to moderate absorption of glucose from the intestine. Feeding several small meals each day, including a last one at bedtime, is indicated. In addition, controlling the amount of digestible carbohydrate (sugars and starches) will contribute to this effect. Moderate fat and protein intake (20-35% of dietary energy for each macronutrient) will help slow stomach emptying and gastrointestinal transit, but attention to the dietary energy density as well as the total daily amount fed is indicated to prevent unwanted weight gain secondary to the anabolic effect of hyperinsulinemia. Fiber, especially soluble fiber, also slows gastrointestinal transit and promotes a more viscous chyme from which absorption of glucose is slowed or reduced. Veterinary therapeutic diets formulated for canine diabetes mellitus incorporate many of these strategies and remain a good option for dogs with insulinoma.

Nutritional Management of Feline Hyperthyroidism (see ch. 301)

Background

Thyroid hormone is integral for growth, development, and metabolism. Selenium and iodine are among the nutrients required for normal thyroid function, even though the quantities needed may appear small (micrograms). Selenoproteins such as type I iodothyronine 5'-deiodinase, which converts T_4 (thyroxine) to T_3 (triiodothyronine), are impacted by the dietary supply of selenium. As in other mammals, cats fed diets low in selenium have increased circulating T_4 and decreased T_3 concentrations, as well as low serum concentrations of selenium and glutathione peroxidase (another selenoprotein).[31] Despite some degree of variability in selenium concentrations in pet foods, deficiencies in cats consuming commercial food are either rare or not recognized.[32] Likewise, selenium toxicosis is unlikely, not described, and studies have shown that cats appear to increase urinary excretion in order to regulate selenium homeostasis at high intakes.[33,34]

Iodine is necessary for synthesis of thyroid hormones T_3 and T_4. Like selenium, the concentration of iodine in pet foods is highly variable.[35-37] There has been speculation that variability and/or extremes in iodine intake may contribute to the pathogenesis of hyperthyroidism. One report found that serum free T_4 concentrations in 10 cats were not affected by chronic and stable intake of high or low (21 vs. 0.11 mg/kg dry matter) iodine-containing diets over a period of 5 months.[38] However, alternating intake levels every 2 weeks over a 12-week period in 2 groups of 8 cats resulted in a significant inverse relationship between iodine intake and serum free T_4 concentration.[39]

Reduction in iodine intake has been a target for dietary modifications aimed at controlling hyperthyroidism in cats, as dietary deficiency in other species reliably results in hypothyroidism. There are limited data on the effect of iodine deficiency in cats. One study reported thyroid gland hyperplasia but lack of other clinical abnormalities in kittens fed a diet low in iodine for several weeks (0.45 mg/kg dry matter).[40] Another study showed no clinical signs of deficiency nor any impact on thyroid hormone concentrations despite achieving a negative iodine balance in adult cats over a period of 9 months (0.46 mg/kg dry matter).[41] The dietary iodine requirement for hyperthyroid cats is unknown; however, low-iodine diets have been explored as a strategy to reduce the synthesis of thyroid hormone in hyperthyroid cats. There are data supporting successful use of an iodine-restricted diet as a treatment for cats with hyperthyroidism. One uncontrolled prospective study assessed a large number of cats with naturally occurring hyperthyroidism; variable numbers of cats had clinical and bloodwork parameters assessed at baseline and at 4 and 8 weeks after consuming an iodine-restricted diet (0.14 and 0.19 mg/kg dry matter basis for canned and dry formulas, respectively).[42] Total T_4 concentrations normalized in 56/88 cats after 4 weeks of consuming the diet, while clinical parameters such as weight loss and poor coat quality were improved in subsets of cats for which these were assessed.[42] Another smaller, blinded, and randomized study demonstrated that 12 hyperthyroid cats fed a diet low in iodine (0.21 and 0.36 mg/kg dry matter for canned and dry formulas, respectively) for 12 weeks had lower total and free T_4 concentrations when compared to 10 cats fed a control maintenance diet (6.34 and 3.01 mg iodine/kg dry matter for canned and dry formulas respectively). 6/12 hyperthyroid cats on the test diet became euthyroid.[43] Creatinine decreased, while urine specific gravity and body weight did not change.[43] Other data, not yet published, used diets with iodine concentrations at levels that induced and maintained euthyroidism in hyperthyroid cats for as long as 3 years.[44-46]

There is one iodine-restricted (0.2 mg/kg dry matter) veterinary therapeutic diet available for management of hyperthyroid cats. While definitive treatment of hyperthyroidism with radioactive iodine therapy or surgical thyroidectomy is still preferred, dietary therapy is an alternative for cats who are not suitable candidates for those procedures. Dietary therapy is also an alternative when use of anti-thyroid medication is not an option. Due to the need for strict and consistent control of the amount of dietary iodine consumed, issues potentially impacting compliance should be considered. Iodine intake from treats, access to other foods, hunting, and some supplements must be avoided. Therefore, dietary therapy may work best for indoor-only, single cat households or for owners who can control intake of individual cats in multi-cat homes.

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CHAPTER 182

Dietary and Medical Considerations in Hyperlipidemia

Richard C. Hill

Client Information Sheet: Dietary and Medical Considerations in Hyperlipidemia

The metabolism of lipid by dogs and cats has been the subject of several substantial reviews.[1-5] These reports discuss similarities and important differences in how fat is metabolized among mammals, which limits extrapolation of information from people to dogs and cats. Hyperlipidemia is only encountered sporadically in dogs and cats, except in a few breeds. Recommendations are based, therefore, on a few retrospective case-control studies and anecdotes. Careful monitoring of an individual's response to treatment remains essential.

Fat Metabolism

Triglyceride in food is emulsified by bile acids in the intestine and hydrolyzed by pancreatic lipase into fatty acids and monoacylglycerides, absorbed, and then reassembled into triglycerides in the enterocyte. Bile acids are synthesized from cholesterol in the liver and undergo enterohepatic recycling: they are excreted by the liver and are then reabsorbed in the gut. Triglycerides, cholesterol, cholesterol esters and phospholipids are transported in blood packaged as lipoproteins: as chylomicrons from the intestine, very low density lipoproteins (VLDL) from the liver, or as intermediate density lipoproteins (IDL), low density lipoproteins (LDL) and high density lipoproteins (HDL) (Figure 182-1).

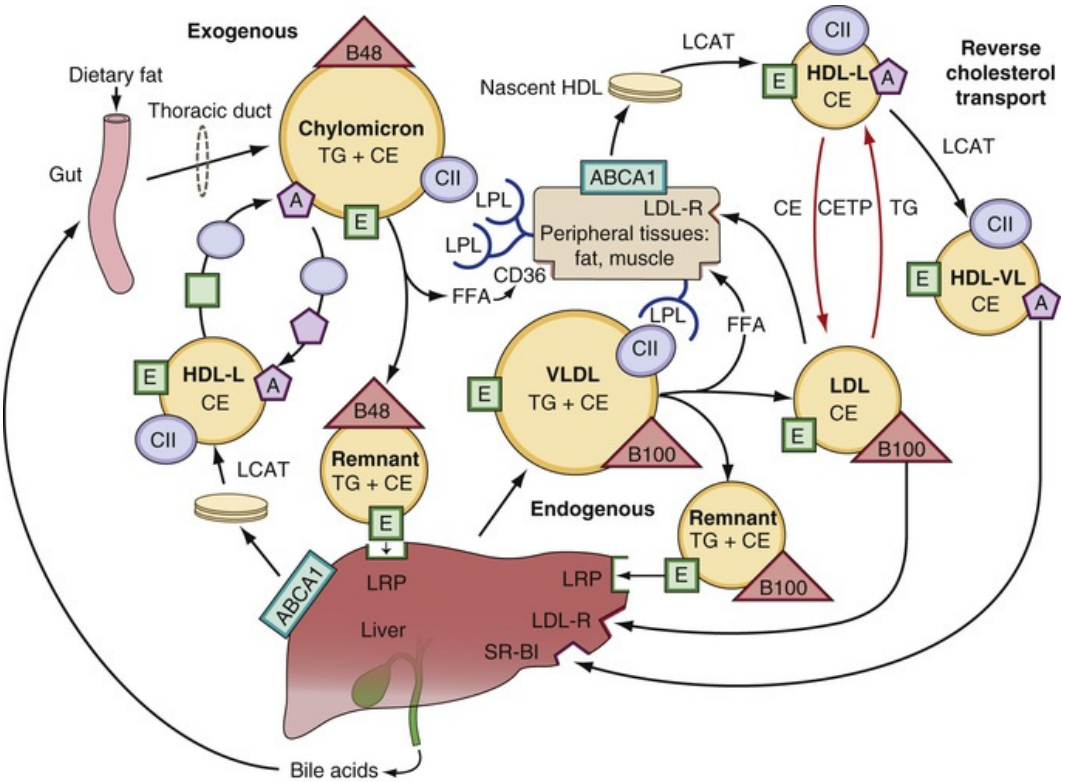

FIGURE 182-1 Exogenous and endogenous lipoprotein metabolism and reverse cholesterol transport involving chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL), large and very large high density lipoproteins (HDL-L and HDL-VL, respectively). Lipoprotein lipase (LPL) hydrolyzes triglycerides (TG) from lipoproteins containing apoprotein CII (blue oval) and the free fatty acids (FFA) generated are taken up by peripheral tissues mediated by the CD36 scavenger receptor. Apoproteins B (pink triangle) and E (green square) are recognized by the LDL receptor (LDL-R) in liver and peripheral tissues and the LDL receptor-related protein (LRP) receptor in the liver. Nascent HDL are secreted by the ATP-binding cassette, sub-family A member 1 (ABCA1) in many tissues and then accumulate cholesterol esters (CE) by the action of lecithin cholesterol acyl transferase (LCAT). HDL also obtain apoprotein A (purple pentagon) in exchange for apoproteins C and E with chylomicrons. HDL transport cholesterol back to the liver and steroidogenic tissues where CE uptake is mediated by the scavenger receptor B, type I (SR-BI). In some animals, but not dogs, there is an additional method of reverse cholesterol transport (red lines) in which CE are exchanged for TG between HDL and other lipoproteins by the action of cholesterol ester transport protein (CETP).

Healthy dogs and cats have adapted to consuming high fat diets. Sled dogs have been fed a diet containing large amounts of fat with impunity.[6,7] Dogs carry more fatty acids on albumin, have mostly aerobic muscle fibers and are able to metabolize fat at twice the rate of less aerobic species.[8,9] Fecal fat is mostly endogenous.[10,11] Dogs appear to lack cholesterol ester transport protein (CETP), which facilitates transfer of cholesterol from HDL to VLDL and chylomicrons. As a consequence, half their high density lipoproteins (HDL) remain large and reverse cholesterol transport is limited. In people, increased CETP activity has been correlated with post-prandial hyperlipidemia and an increased risk of disease.[12] The risk of atherosclerosis increases in people with low HDL and high LDL concentrations but about 66% of fasting lipoproteins are HDL and 33% are LDL in both dogs and cats, whereas in people, 66% are LDL and 33% are HDL, perhaps explaining why atherosclerosis is rare in dogs and cats.[13]

Risk of Disease Relative to Blood Fat Concentrations

Managing hyperlipidemia is difficult. The decision to treat hyperlipidemia should be dependent on the risk of illness it causes (see ch. 63). For example, obese people with a combination of abnormal blood lipids, insulin resistance, and hypertension have the condition "metabolic syndrome" and are at increased risk of type 2 diabetes mellitus (DM), atherosclerosis, coronary heart disease and stroke. Cut-offs for each component of the syndrome are based on threshold values above which disease becomes more likely.[14] Such cut-offs, based on risk of disease, are not possible in dogs and cats because dogs and cats rarely develop atherosclerosis, cardiac thrombosis, or stroke. An attempt to define metabolic syndrome in dogs using reference range cut-offs for

blood lipid and glucose did not account for disease risk and are, therefore, of limited value.[15]

Insulin resistance has been demonstrated in Miniature Schnauzers with hyperlipidemia and obesity (see ch. 176). It has been associated with insulin resistance and hyperlipidemia in dogs and cats.[16-19] Type 2 DM is common in cats but rare in dogs (see ch. 304 and 305).[20] Type 2 DM has been described and an increased prevalence of DM has been noted in obese dogs, but cause and effect were not established.[21-23] Why some obese cats develop DM is not known. Thus, an association between blood lipid concentrations and an increased risk of DM has not been established for dogs or cats. Atherosclerosis in dogs is usually associated with DM and hypothyroidism but has also been described in dogs without endocrinopathy or hypercholesterolemia.[24] Atherosclerosis has been induced in healthy cats and dogs by feeding diets very high in fat (>60 g/Mcal) and cholesterol (>4 g/Mcal), but serum cholesterol concentrations had to be maintained above 750 mg/dL for >6 months in dogs before atherosclerosis developed.[25-27]

Increased prevalence of other conditions and abnormalities has been described in dogs with hyperlipidemia, but causal relationships have not been established. Therefore, it is unclear whether conditions develop as a result of hyperlipidemia or vice versa. For example, hyperlipidemia is about three times more common in dogs with gallbladder mucocele.[28] Miniature Schnauzers with hyperlipidemia are more likely to have increased serum alkaline phosphatase and alanine aminotransferase activities.[29] However, biliary tract obstruction increases serum cholesterol concentrations four-fold and triglyceride concentrations two-fold.[30,31] Thus, serum alterations may be a consequence or a cause of disease. Proteinuria is increased with triglyceride concentrations in Miniature Schnauzers and was most severe with triglyceride concentrations >400 mg/dL.[32] Nephrotic syndrome is associated with hypercholesterolemia. Dogs with chronic kidney disease (CKD) have increased LDL and decreased HDL concentrations (see ch. 324), but triglyceridemia appears to cause the glomerular damage (see ch. 325).[33]

Hyperlipidemia is about 15 times more common in Miniature Schnauzers who have recovered from pancreatitis as compared to Schnauzers without pancreatitis (see ch. 290), suggesting that dogs with lipid abnormalities are more susceptible to pancreatitis.[34] Hyperlipidemia, however, could be secondary to pancreatitis. Hyperlipidemic Miniature Schnauzers had higher pancreatic lipase immunoreactivity (PLI) concentrations than controls and Schnauzers with cholesterol concentrations above 860 mg/dL were 4.5 times more likely to have a PLI concentration consistent with pancreatitis.[35] High PLI concentrations have also been observed in obese dogs with post-prandial triglyceride concentrations >440 mg/dL, but these dogs did not develop overt signs of clinically important pancreatitis for >4 years. It remains to be determined, therefore, whether fat should be restricted in dogs with high pre- or post-prandial PLI concentrations but no overt pancreatitis. It may be prudent, however, to attempt maintaining near normal lipid concentrations while monitoring for signs of clinical disease when normal concentrations are not achieved. Previous recommendations, to maintain pre-prandial triglyceride concentrations <500 mg/dL, may not be sufficient and concentrations may need to be <400 mg/dL to prevent glomerular injury.[4] Serum cholesterol concentrations should be maintained below about 700 mg/dL to prevent atherosclerosis.

Diagnosis and Monitoring of Hyperlipidemia

Background

Hyperlipidemia is often first suspected on physical examination due to abnormal appearance of the eyes or by assessing the appearance of blood (Figures 182-2 and 182-3). Measurement of pre-prandial serum cholesterol and triglyceride concentrations is currently the standard for diagnosing lipid abnormalities and assessing response to treatment. Triglyceride concentrations increase in normal dogs and cats after a small fatty meal, peak after about 2-4 hours, and return to normal after about 8 hours.[36,37] Recent feeding is the most common explanation for increased serum lipid concentrations and usually does not warrant investigation. It may be sufficient to wait 12 hours after a meal to measure fat concentrations in some dogs, but food can take >12 hours to pass through the small intestine.[38] Triglyceride concentrations may increase more and for a longer duration in obese dogs, dogs receiving phenobarbital, and some Burmese cats.[36,37,39] Thus, it may be necessary to wait for longer than 12 hrs after a meal to measure pre-prandial lipid concentrations. It may also be necessary to measure fat concentrations 4-6 hours after a meal because post-prandial hypertriglyceridemia can occur in patients with normal pre-prandial concentrations.[36,39,40] Reevaluation every 6-8 weeks is recommended to assess response to diet change or alternative treatment.[41]

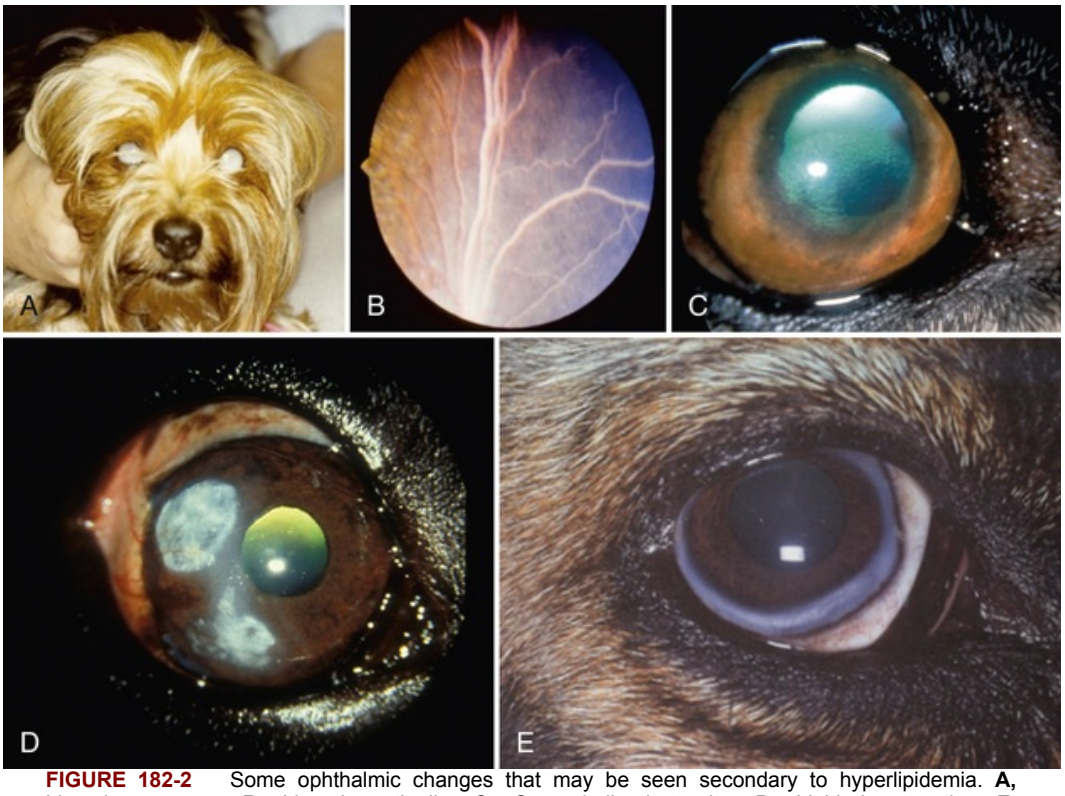

FIGURE 182-2 Some ophthalmic changes that may be seen secondary to hyperlipidemia. **A,** Lipemic aqueous. **B,** Lipemia retinalis. **C,** Corneal lipodystrophy. **D,** Lipid keratopathy. **E,** Arcus. (Photos provided courtesy Drs. DE Brooks, RD Whitley, KE Plummer, all of the University of Florida.)

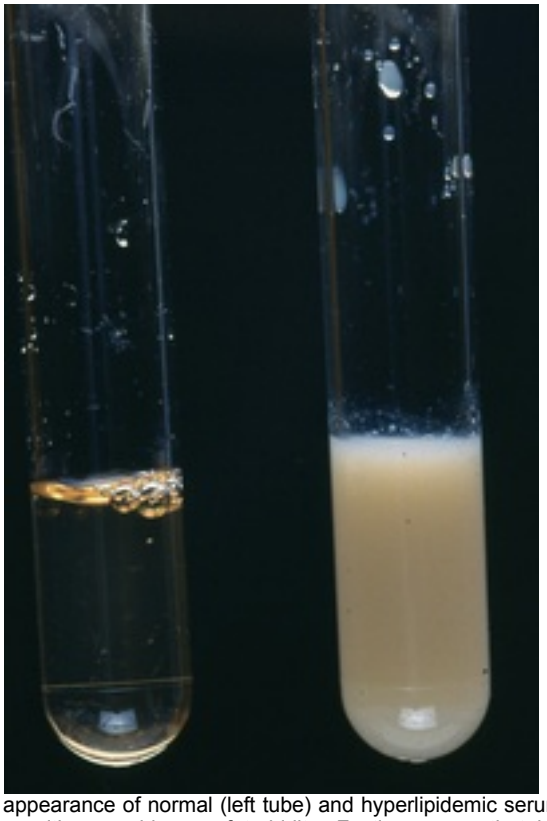

FIGURE 182-3 The appearance of normal (left tube) and hyperlipidemic serum (right tube). Normal serum should be clear, with no evidence of turbidity. Fasting serum that is turbid indicates the

presence of excess lipid in the serum (right tube).

Lipoprotein fractions are measured in people to assess atherosclerosis risk using electrophoresis or ultracentrifugation. If samples from dogs or cats are assessed using a human laboratory, one should be familiar with differences in human and animal lipoproteins (see ch. 63).[1] Lipoproteins responsible for an increase in serum fat concentrations can be better understood by evaluating refrigerated (Figure 182-4) or centrifuged blood (Figure 182-5). Chylomicrons separate as a cream layer, VLDL causes lactescence, and smaller lipoproteins (LDL, HDL) are not visible. Relative increases in triglyceride compared to cholesterol can be informative as chylomicrons and VLDL contain more triglyceride than cholesterol. Distinct lipoprotein fractions can be measured in pets, but their value has not been established.[42]

FIGURE 182-4 Refrigeration test of hyperlipidemic serum. On the left is a fasting hyperlipidemic serum sample from a dog. Following a refrigeration test, a lactescent layer ("cream layer") appears on the top of the serum. This layer is due to increased chylomicron particles present in the serum sample. Note that the serum below the top lactescent layer is also turbid, indicating the presence of other excess lipoproteins.

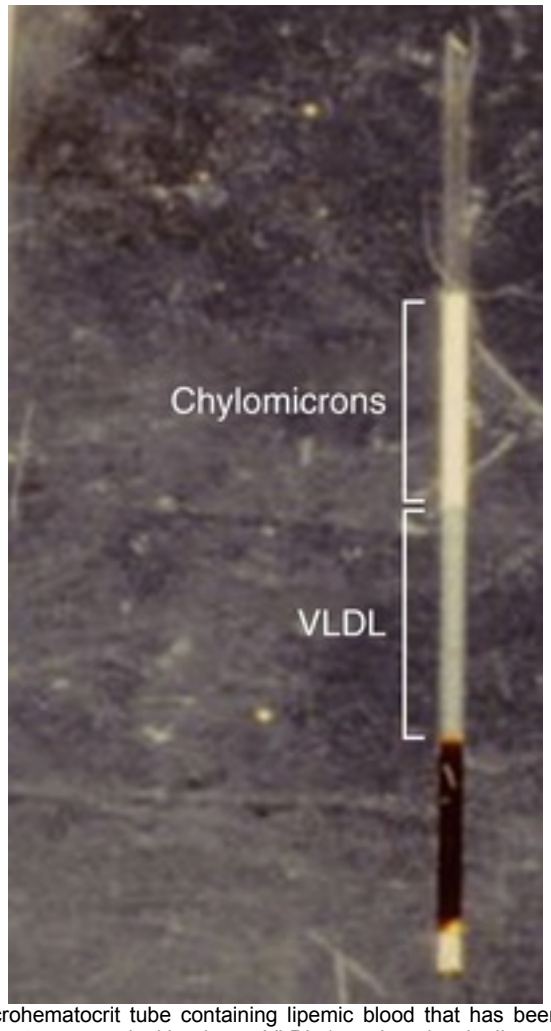

FIGURE 182-5 Microhematocrit tube containing lipemic blood that has been centrifuged. Excess chylomicron causes the top cream-looking layer; VLDL (very low density lipoprotein) causes turbidity (lactescence) below the chylomicron layer.

Secondary Hyperlipidemias

Hyperlipidemia in dogs and cats may occur secondary to feeding a high fat diet (60% ME fat), obesity, certain endocrine diseases (DM, hypothyroidism, hyperadrenocorticism), diestrus, protein loss (nephrotic syndrome), pancreatitis, bile duct obstruction (mucocoele) and certain drugs. Specific treatment of hyperlipidemia in such conditions should not be pursued. Rather, the focus should be on treating the primary condition. Drugs that may be responsible for increased blood lipid concentrations (corticosteroids, phenobarbital, thiazides, beta-blockers with no alpha effect, and estrogens), should be discontinued if possible.[37,43] It has been suggested that dogs and cats with DM be fed low fat diets, but this should not be necessary if abnormalities resolve with treatment and weight loss. Changing the diet of a newly diagnosed diabetic can be detrimental if food aversion develops. Low fat diets may be indicated in obese pets or those with pancreatitis. A new diet should only be introduced once nausea has been medically controlled (see ch. 39). Ovariohysterectomy prevents periodic increased progesterone and lipid concentrations during diestrus.[44] Exercise may decrease triglyceride concentrations.[45] Administration of antioxidants may also benefit obese patients. Green tea extract (0.9 mg/kcal daily) returned plasma triglyceride and VLDL concentrations to normal by stimulating lipoprotein lipase and improving insulin sensitivity by 60% when given to obese dogs fed a high fat diet (47 g fat/Mcal).[46] Each gram of green tea extract contained 36 mg epicatechin, 65 mg epicatechin gallate, 20 mg epigallocatechin and 153 mg epigallocatechin gallate (total: 0.25 mg antioxidant catechins/kcal ME).

Primary Hyperlipidemias

Primary hyperlipidemia has been described in both dogs and cats: hypertriglyceridemia in Miniature Schnauzers and Brittany Spaniels; hypercholesterolemia in Briards, Shelties, Rough Collies, Doberman Pinschers and Rottweillers; increased triglycerides and cholesterol in Beagles. Also, cats with lipoprotein lipase deficiency and, Burmese cats with increased post-prandial but normal fasting triglyceride concentrations may have primary hyperlipidemia. Associated signs can be neurological (seizures and peripheral neuropathy), ophthalmic (lipemia retinalis, lipemic aqueous, corneal dystrophy or keratopathy, and arcus; Figure 182-2), renal (proteinuria), gastrointestinal (vomiting, diarrhea, abdominal pain, pancreatitis), and dermatological (xanthomata).

Dietery Management of Hyperlipidemia

Background

Feeding a low fat diet remains the cornerstone treatment of primary hyperlipidemia. Fat intake is determined by both dietary fat content *and* quantity of food consumed. Thus, it is important to assess fat content relative to the metabolizable energy (ME) of the food as well as the ME required to maintain body condition. Unfortunately, labels are only required to list the guaranteed minimum percent fat as fed. A "low fat" statement on a label is unreliable because the definition of low fat used by the Association of American Feed Control Officials (AAFCO) differs for dry and canned food. An approximate estimate of the fat content relative to ME (g/Mcal) can be obtained by adding 1 to the guaranteed % fat, multiplying that number by 10 and dividing by the kcal ME/g in the diet. It is best, however, to obtain the typical value in g/Mcal ME from the manufacturer. Table 182-1 lists a selection of low and moderate fat diets with published typical fat contents relative to ME.

TABLE 182-1

Fat and Protein Content (g/Mcal ME)[a] of Selected Commercial Foods

MANUFACTURER	BRAND NAME	DRY			CANNED			
		FAT[b]	PROTEIN	EPA+DHA[c]	FAT[b]	PROTEIN	EPA+DHA[c]	
Dog Foods								
Hill's	r/d	27	106		29	85		
	w/d	27	58		26	59		
	light adult	27	74		25	57		
	i/d	33	63		36	70		
	low fat i/d	20	73		23	69		
Iams	weight loss	23	84		38	89		
Nestle-Purina	OM	24	104		34	136		
	ENd	30	63		41e	95		
	HAd	26	62					
	JM	34	81	1.8				
Royal Canin	low fat	19	63	0.4	18	80	0.3	
	calorie control	28	96	0.4	36	121	0.5	
	satiety support	33	103	1				
Cat Foods								
Hill's	r/d	28	111		30	123		
	w/d	27	112		48e	115		
	light adult	26	94			100		

					40[e]			
	i/d	46[e]	93		57[e]	89		
Iams	weight loss/mobility plus	28	110		25	102		
Nestle-Purina	OM	25	166		38	132		
	EN	42[e]	129		61[e]	100		
	HA	27	78					
Royal Canin	calorie control	26	110	0.4	32[c]	140	0.5	(5.8 oz can)
	calorie control				28	123	0.1	(3 oz can)
	satiety support	29	111	0.5				
Mixed Species Foods								
Abbott	CliniCare	51[e]	82	0.9				
Nestle	Vivonex Plus	7	45					
	mixture 1[f]	27	62	0.4				
	mixture 2[f]	20	56	0.3				

[a]Values are typical values reported by the manufacturer in product guides and are dependent on the method by which metabolizable energy (ME) content of the diet was determined. Where manufacturers have used modified Atwater factors to calculate the ME content of digestible but high fiber diets, the fat content relative to ME may be overestimated slightly because using these factors slightly underestimates the ME content of food. Reported values for each diet change over time.

[b]Low fat diets are <25 g fat/Mcal for dogs and <30 g fat/Mcal in cats, but the division between low and moderate is somewhat arbitrary. Restricting energy intake limits fat intake so moderate fat diets containing 25-35 g fat/Mcal ME may provide sufficient fat restriction in animals consuming very few calories such as those undergoing a weight loss program. Higher protein diets (>90 g protein/Mcal) are recommended to maintain lean body mass.

[c]EPA + DHA represents the combined concentration of eicosapentaenoic (EPA) and docosahexaenoic acid (DHA). Diets with more than 1 g EPA and DHA combined/Mcal do not need supplementation with additional fish oil.

[d]Contain medium chain triglycerides.

[e]These higher fat diets are included to show that some diets with a similar name, especially canned diets, are not always similarly low in fat.

[f]Mixture 1 comprises 1 can (250 mL) of CliniCare and 1 sachet of Vivonex Plus diluted to 300 mL. Mixture 2 contains 125 mL of CliniCare with 300 mL of Vivonex.

Commercial foods are reported to contain about 18 to 65 g fat/Mcal ME. Commercial canine therapeutic diets contain the lowest amounts of dietary fat (<25 g fat/Mcal in dog foods and <30 g fat/Mcal in cat foods). There are various inexpensive dry extruded diets and some therapeutic diets designed for weight loss or intestinal disease that contain moderately low amounts of fat (25-35 g fat/Mcal ME). Such diets may lower blood lipid concentrations in obese pets consuming fewer calories to lose weight. Severe fat restriction, however, is often needed. In some instances, it may be of value to formulate a home-cooked diet containing <18 g fat/Mcal. The National Research Council suggested a recommended allowance of 13.8 g fat/Mcal ME based on an adequate intake of 10 g fat/Mcal ME for adult dogs maintaining body condition while consuming about 130 kcal ME/kg body weight $(BW)^{0.75}$ daily.[9] The recommended allowances (g/Mcal ME) for adult dog maintenance are 2.8 for linoleic acid and 0.11 for linolenic acid. The recommended allowance (g/Mcal ME) for adult cats maintaining body condition while consuming 100 kcal ME/kg $BW^{0.67}$ daily was set at 22.5 for fat, 1.4 for linoleic acid and 0.015 for arachidonic acid. A nutritionist should be consulted when formulating home-cooked diets to ensure that enough essential nutrients and fats are included. Minimum fat requirements are not known accurately and may be lower than the recommended allowance in some individuals. How fat requirements change in animals maintaining body condition while consuming fewer than average calories is also not known. Therefore, careful monitoring for signs of fatty acid deficiency (poor hair coat, skin disease, renal compromise, infections, cell fragility, poor wound healing, bruising and reduced neurologic and ophthalmic function) is necessary when feeding very low fat diets.[9]

Low Fat Tube Feeding

In hyperlipidemic patients reluctant to eat, it may be necessary to provide nutritional support with a liquid diet through a nasogastric or jejunal tube or with a blended diet through a wider bore esophageal or gastric tube (see ch. 82). Most liquid diets designed for human beings contain 33 g fat/Mcal and those for dogs and cats contain much more fat. The human liquid amino acid based diet, Vivonex Plus, contains 6 g fat/Mcal and can be mixed with higher fat liquid diets to create an intermediate diet. Vivonex Plus has a pH of about 5 when mixed with water. This is close to the isoelectric point at which casein, found in most liquid diets, precipitates. Thus, it may be necessary to increase the pH of Vivonex Plus solution before it can be mixed with a casein-based diet. This pH correction can be achieved by adding sodium hydroxide (0.5-1 mL of 6N solution) or adding 10-20 mL of 1 mEq/mL (8.4%) sodium bicarbonate to each 300 mL of Vivonex. These liquid mixtures may contain slightly less than the recommended allowance of some essential nutrients, such as calcium, phosphorus, cobalamin, and trace minerals. Nutrient availability is likely to be high, however, so deficiencies are unlikely over the short term.

Low fat commercial diets can be blended with water for administration through a larger bore esophageal or gastric tube. Nevertheless, most commercial low fat foods contain increased amounts of insoluble fiber, which absorbs water. These high fiber foods often have to be diluted with extra water to achieve a suitable consistency for tube feeding, reducing energy density and increasing the volume that must be supplied. A low fat (25 g/Mcal) blended diet of high energy density suitable for administering through a larger bore tube can be obtained by mixing a sachet of Vivonex powder with a 5.5 oz can of kitten food and a small amount of water.

Change the Type of Fat

The type of fat should be changed if a low fat diet fails to adequately resolve hyperlipidemia after 6-8 weeks. Adding fish or krill oil, which naturally contains omega-3 fats, to a diet can lower serum lipid concentrations if given in high dosages.[41] Fish oil and omega-3 fat capsules contain variable amounts and types of omega-3 fats. Dosage recommendations are for eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) combined. Other omega-3 fats, such as alpha-linolenic acid, are not converted well to EPA and DHA by dogs and cats. A standard recommendation for dogs is 0.22 g fish oil containing 66 mg of EPA + DHA/kg BW/day. This is equivalent to about 1 mg of EPA + DHA/kcal ME, assuming a 10 kg dog consumes about 120 kcal/kg$^{0.75}$ daily.[41] Some diets already contain 1 g/Mcal of EPA and DHA (see Table 182-1), in which case additional supplementation may be of no benefit. Dosing relative to ME is preferred to dosing on body weight, which provides a disproportionate amount of EPA and DHA to large breed dogs. Slightly lower dosages may be effective in some pets if their breath has a fish smell.[41]

Studies in other species suggest that replacing dietary fat containing long chain fatty acids with medium chain triglycerides may decrease blood triglyceride concentrations but may also increase cholesterol concentrations.[1] Some commercial diets contain medium chain triglycerides (see Table 182-1). Replacing beef tallow or coconut oil (primarily saturated fat) with cotton-seed or safflower oil (primarily unsaturated fat) prevented the development of atherosclerosis or thrombosis in dogs fed high fat diets.[26,47] The role that cholesterol ingestion plays in the management of hyperlipidemic dogs and cats cannot be assessed because the cholesterol content of pet foods is not reported. Nevertheless, as the fat content of a diet decreases, an increasing proportion of fat must be of plant origin to ensure that adequate essential fats are included. Since plant oils contain no cholesterol, its content must decrease with the amount of fat in the diet.

Other Dietary Changes

Other dietary changes have modified serum lipid concentrations in healthy dogs and may improve concentrations in hyperlipidemic animals. For example, adding beet pulp and fructo-oligosaccharides to diets decreased serum triglyceride and cholesterol concentrations in healthy dogs.[48] Higher blood fat concentrations may be tolerated if antioxidants are provided in sufficient quantity to prevent oxidative damage. Administration of 400 IU vitamin E daily prevented endothelial dysfunction and maintained coronary blood flow in 7 kg dogs fed a high fat–high cholesterol diet that induced atherosclerosis.[49] Vitamin E decreased concentrations of the oxidative marker malondialdehyde and tissue cholesterol without altering serum cholesterol concentrations. This dosage of vitamin E (54 IU/kg, 90 IU/kg$^{0.75}$ daily, or 750 IU/Mcal ME assuming consumption of 120 kcal ME/kg$^{0.75}$ daily) is very high and could inhibit absorption of other fat soluble vitamins. Whether lower dosages provide the same effect is not known. The recommended allowances for adult dogs and cats are 7.5 and 10 IU vitamin E/Mcal, respectively. An intermediate dosage

(100 IU/Mcal) is likely to inhibit oxidation without causing undesirable side-effects.

Medical Management of Hyperlipidemia

Background

Any disease or condition that increases lipid concentrations (e.g., obesity or an endocrinopathy) should be treated in dogs with primary hyperlipidemia. Drug therapy should be considered if dietary management fails to reduce serum lipid concentrations adequately. Fibrates can be considered for animals with hypertriglyceridemia and statins for those with hypercholesterolemia. Niacin has potential benefit in animals with either or both hypertriglyceridemia and hypercholesterolemia.

Fibrates

Fibrates, agonists of peroxisome proliferator-activated receptor-alpha, stimulate lipolysis by lipoprotein lipase. They decrease VLDL and LDL concentrations by increasing hepatic uptake. They are not effective for hypercholesterolemia in dogs, as 25 mg/kg of gemfibrozil daily did not decrease cholesterol concentrations.[50] Reported doses of fibrates for dogs and cats are mostly anecdotal; gemfibrozil (Lopid): 10 mg/kg in cats or dogs or 200 mg (range 150-300 mg) q 12 h in dogs; bezafibrate (Bezalip): 4-10 mg/kg q 24 h in dogs. Fenofibrate at a dosage of 10 mg/kg daily reduced pre- and post-prandial serum lipid concentrations about 30% in obese dogs fed a high fat diet.[51] Large amounts of drug/tablet (600 mg in gemfibrozil and 400 mg for bezafibrate) require compounding for small doses. Fenofibrate comes in a range of tablet sizes. Gemfibrozil was tolerated by dogs at dosages up to 150 mg/kg daily for 12 months but liver abnormalities were noted in some given 300 mg/kg daily for 12 months.[52] Side-effects are also relatively uncommon in dogs, rats and people chronically receiving fenofibrate.[51,53] In people, side-effects have included malaise, muscle pain and arthralgia, skin rash, increased liver enzymes and dose-related chronic liver disease, increased creatinine concentrations, hematuria and acute kidney injury. Kidney stones developed in some dogs chronically given fenofibrate and bezafibrate.[53]

Statins

Statins reduce hypercholesterolemia by inhibiting HMGCoA reductase, the rate-limiting enzyme in cholesterol synthesis. Atorvastatin (Lipitor), 2-5 mg/kg daily, lowered total cholesterol proportional to dosage by 15-30% in normal dogs and was well tolerated during a year-long study at dosages ≤10 mg/kg.[54-57] Rosuvastatin (Crestor), 2 mg/kg daily, and pitavastatin (Livalo), 0.4 mg/kg daily, were well tolerated and reduced total cholesterol by 30% in dogs with experimentally induced heart failure.[58,59] Statins should be administered on an empty stomach 30 minutes before feeding.[60]

Niacin

Niacin at a dosage of 2 g/day (≈1 g/Mcal ME) increases HDL and decreases VLDL and LDL in people. Such a high dosage may be toxic to dogs.[9] A much lower dosage (100 mg) has been reported to reduce fat concentrations in dogs but erythema and pruritus have been reported in dogs receiving only 25 to 100 mg.[61]

Inhibitors of Fat Absorption

Calcium forms soaps in the intestinal tract, which have been shown to decrease fat absorption, especially for long chain and saturated fats.[62] Increasing calcium in diets from 1.1 to 3.6% dry matter, for example, may inhibit fat digestibility by about 5%.[62] The consequences of a high calcium intake should be considered on an individual basis. Microsomal transfer protein inhibitors (Dirlotapide [Slentrol], Mitratapide [Yarvitan]) also inhibit fat absorption. These drugs are licensed for short term administration to aid weight loss by inhibiting appetite (see ch. 176).

Inhibition of Cholesterol Absorption

Healthy dogs given cholesterol absorption inhibitors compensated for the loss of biliary cholesterol by increasing hepatic synthesis. Serum cholesterol concentrations decreased 30 to 60% when the absorption

inhibitor ezetimibe (0.007 mg/kg/d) was co-administered to dogs with an HMGCoA inhibitor (5 mg/kg lovastatin, 5 mg/kg fluvastatin, 2.5 mg/kg pravastatin, 1 mg/kg fluvastatin or 1 mg/kg atorvastatin) for 2 weeks.[56,63] Phytosterols and stanol esters also inhibit intestinal absorption of cholesterol and lower LDL cholesterol concentrations in people but not to the same degree as statins. Cholestyramine, 0.7 mg/kg daily, decreased blood cholesterol by 16% in normal dogs by binding bile acids and increasing their fecal excretion.[64] Dosages up to 4 mg/kg have been administered chronically to normal dogs. Chitin, as chitosan, has been proposed to limit fat absorption, but its efficacy is uncertain.

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CHAPTER 183

Nutritional Management of Heart Disease

Lisa M. Freeman, John E. Rush

Client Information Sheets:
Tips for Addressing Poor Appetite in Pets with Heart Disease
Safe and Effective Tips for Administering Medications to Dogs and Cats with Heart Disease

The goal of nutrition is no longer just to prevent deficiencies. It is now known that modification of diet is an important part of medical therapy for heart disease. In the 1960s, the main nutritional recommendations for dogs with congestive heart failure (CHF) were to feed a low-sodium diet (for all stages of heart disease), to feed a restricted protein diet, and to provide supplemental B vitamins.[1] Few changes to these recommendations were made until the 1970s, when mention of cardiac cachexia appeared in veterinary medicine[2] and when the question of how early to institute sodium restriction was raised in the 1980s.[3] It was also in the late 1980s that the discovery of the relationship between taurine deficiency and feline dilated cardiomyopathy (DCM) was published.[4] Now, research is beginning to show that nutrition may be able to modulate heart disease, either by slowing the progression, minimizing the number of medications required, improving quality of life or, in rare cases, actually curing the disease. Therefore, nutrition is an important adjunct to medical therapy for animals with heart disease.

The main goals of diet therapy for heart disease are to maintain optimal body weight, to avoid nutritional deficiencies and excesses, and to take advantage of the potential benefits of pharmacologic doses of certain nutrients.

Optimal Weight Maintenance

A key goal for the optimal management of heart disease is to maintain optimal body composition, because body weight, muscle mass, and obesity can significantly impact health.

Cachexia

Cardiac cachexia is the muscle loss commonly seen in patients with CHF (see ch. 177). In one study of dogs with DCM and CHF, more than 50% of patients had some degree of cachexia.[5] The weight loss that occurs in animals with CHF is unlike that seen in a healthy dog or cat that loses weight. In a healthy animal receiving insufficient calories to meet requirements, metabolic adaptations allow fat to be used as the primary fuel source, thus preserving lean body mass. Conversely, the primary fuel source in animals with an acute or chronic disease, including heart disease, is amino acids from muscle; therefore, these animals quickly catabolize lean body mass. Thus the distinguishing feature of cachexia is a loss of lean body mass, which has direct and deleterious effects on strength, immune function, and survival.[6] Cachexia is often mistakenly viewed as an end-stage syndrome manifested by an emaciated dog or cat. In fact, cachexia is a progressive process of muscle loss that can be very subtle initially and can even occur in an obese animal. Recognizing the process of cachexia at an early stage provides better opportunities to manage it effectively.

The loss of lean body mass in cardiac cachexia is a multifactorial process caused by decreases/alterations in appetite, increased energy requirements, and metabolic alterations.[6] Animals with CHF can have anorexia (complete loss of appetite), hyporexia (reduced appetite), or dysrexia (changes in appetite and food preferences). Anorexia is present in 34% to 75% of dogs and cats with clinically significant heart disease.[5,7-9] These alterations in appetite may be secondary to fatigue or medication side-effects.[6] However, inflammatory cytokines, such as tumor necrosis factor-alpha (TNF) and interleukin-1-beta (IL-1), are primary mediators of

cachexia.[6] These inflammatory cytokines directly cause reduced appetite, increase energy requirements, and increase catabolism of lean body mass. TNF and IL-1 also cause cardiac myocyte hypertrophy and fibrosis and have negative inotropic effects.

Cardiac cachexia is typically recognized only after CHF has developed. It is more easily recognized in dogs than in cats and is most often seen in DCM or right-sided CHF. Loss of lean body mass is most readily evident in the epaxial, gluteal, scapular, or temporal muscles. Muscle condition score (along with body condition score (BCS), which assesses an animal fat stores—see ch. 2, 170, and 177) should be assessed at every visit for animals with heart disease.[7] The muscle condition score is categorized as normal, mild muscle loss, moderate muscle loss, or severe muscle loss (Figure 183-1).[8] In addition, a complete diet history should be assessed at every visit as this can identify factors that are contributing to muscle loss (e.g., inadequate calorie or protein intake, nutritionally unbalanced diet).[7] Diet history forms are available[8] or one specifically designed for animals with heart disease can be used (Box 183-1). Nutritional considerations for cardiac cachexia should include management of altered appetite, if present. Nutritional modulation of cytokine production also may be helpful. One method of decreasing the production and effects of cytokines is omega-3 (n-3) polyunsaturated fatty acid (PUFA) supplementation (see below). Supplementation of fish oil, which is high in n-3 fatty acids, can decrease cytokine production in dogs with CHF and improve cachexia.[5] In some but not all dogs with CHF-induced anorexia, fish oil supplementation can improve food intake.[5] In addition, n-3 fatty acid intake has been associated with longer survival in dogs with CHF.[9]

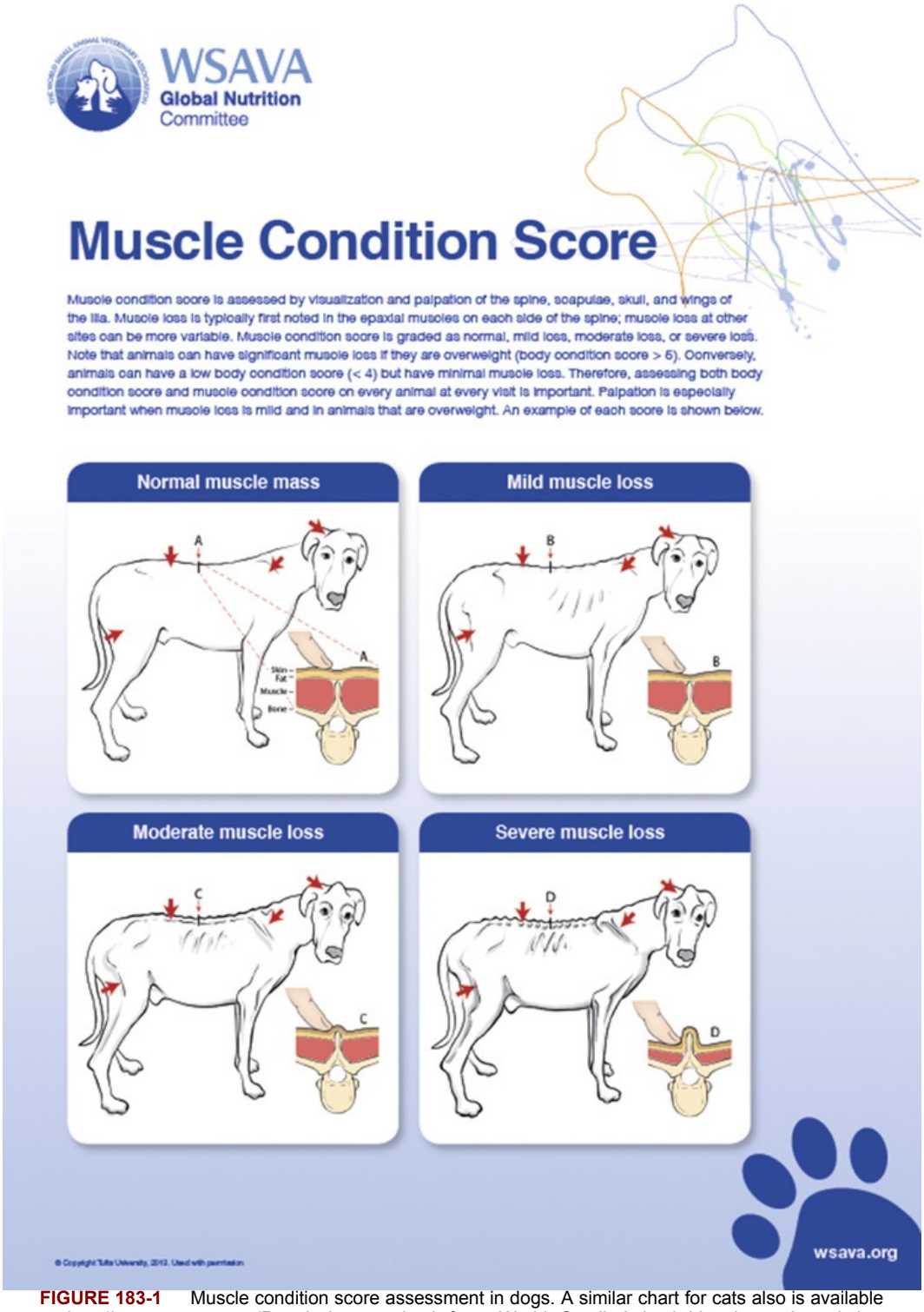

FIGURE 183-1 Muscle condition score assessment in dogs. A similar chart for cats also is available at http://www.wsava.org (Permission received from World Small Animal Veterinary Association (WSAVA). Available at the WSAVA Global Nutrition Committee Nutrition Toolkit website: http://www.wsava.org/nutrition-toolkit. Accessed June 29, 2016. Copyright Tufts University, 2014.)

Box 183-1

Diet History Form for Animals with Heart Disease

Please answer the following questions about your pet

Today's date: _____

Pet's name: _____ Your name: _____

1. How would you assess your pet's appetite? (mark the point on the line that best represents your pet's appetite)
   Poor **Excellent**
   _____

2. Describe your pet's appetite over the last few weeks? (check all that apply)
   ☐Eats about the same amount as usual ☐Eats less than usual ☐Eats more than usual
   ☐Seems to prefer different foods than usual

3. Over the last few weeks, has your pet (check one)
   ☐Lost weight ☐Gained weight ☐Stayed about the same weight ☐Don't know

4. Please list below the brands and product names (if applicable) and the amount of ALL foods, treats, snack, dental chews, rawhides, and any other food item that your pet currently eats.

Food	Form	Amount	How often?	Fed since
Examples:				
Purina Dog Chow	dry	1½ cups	2x/day	Jan, 2011
Science Diet Adult Gourmet Beef Entree	can	½ large can	1x/day	Jan, 2012
90% lean hamburger	microwaved	3 oz	1x/week	Jan, 2011
Milk Bone medium	dry	1	2x/day	Aug, 2010
Rawhide	dry	2x6" strip	3x/week	Dec, 2011

5. Do you give any dietary supplements to your pet (for example: vitamins, glucosamine, fatty acids, or any other supplements)?
   ☐Yes ☐No If yes, please list which ones and give brands and amounts:

			Brand	Tablet/capsule number, size, and frequency
Taurine	☐Yes	☐No		
Carnitine	☐Yes	☐No		
Antioxidants	☐Yes	☐No		
Multivitamin	☐Yes	☐No		
Fish oil or cod liver oil	☐Yes	☐No		
Coenzyme Q10	☐Yes	☐No		
Other (please list)	☐Yes	☐No		

6. How do you administer pills to your pet?
   ☐I do not give any medications
   ☐I give them without any food
   ☐I put them in my pet's dog/cat food
   ☐I put them in a Pill Pocket or similar product
   ☐I put them in foods (list foods):_____

Information below to be completed by the veterinarian:

Current body weight: _____kg

Ideal body weight: _____kg

Current body condition score: _____/9

Muscle Condition Score: ☐normal muscle ☐mild muscle loss ☐moderate muscle loss ☐severe muscle loss

From Smith FWK Jr, Tilley LP, Oyama MA, et al: *Manual of canine and feline cardiology*, ed 5, St Louis, 2016, Elsevier.

Obesity

Overweight (i.e., over ideal body weight) and obesity (i.e., more than 20% over ideal body weight) are common in the pet population, and can have detrimental effects on health (see ch. 176). Therefore, maintaining an optimal body weight and BCS should be a goal for healthy dogs and cats and for those with asymptomatic heart disease. The effects of obesity are less clear in animals with CHF. Obesity is common even in animals with CHF, with 41% of dogs in one study being overweight or obese at the time of diagnosis of heart failure.[9] Although obesity has some physiologic effects which could be detrimental in CHF, numerous studies in people with CHF have shown that obesity actually is associated with a longer survival time; this is called the "obesity paradox."[10,11] Results of one study of dogs with CHF showed that dogs that gained or maintained weight had a longer survival time than those that lost weight.[9] A study in cats also showed that overweight but not obese body condition was associated with longer survival.[12] This supports the concept that weight loss and particularly muscle loss is very detrimental in CHF and careful attention to body weight, muscle loss, and appetite is of critical importance in animals with heart disease. The authors aim

for a BCS of 4-5/9 for healthy animals and those with asymptomatic heart disease and a BCS of 6-7/9 for those with CHF. A BCS > 7/9 may still have detrimental effects so obesity should be avoided, although the authors typically will not try to initiate a weight loss plan in dogs or cats after the onset of CHF (unless obesity is severe and adversely affecting quality of life). It is important to be aware that cachexia (i.e., muscle loss) can occur even in overweight and obese animals, so monitoring of the muscle condition score at every visit is important.[8] Muscle loss in overweight animals is usually most apparent over the epaxial muscles.[8]

Modulation of Specific Nutrients

Nutritional deficiencies once were a common cause of heart disease in people and probably animals. In cats, taurine deficiency was a common cause of heart disease until as recently as the late 1980s. Identifiable nutritional deficiencies are now uncommon in dogs and cats (unless owners are feeding homemade, vegetarian, or otherwise nutritionally unbalanced diets; see ch. 192) but still could play a role in the etiology of some heart diseases. Nutritional deficiencies also may develop secondary to the disease or its treatment. A new area of nutritional research is that of nutritional pharmacology, the concept that supplementation of certain nutrients may provide benefits above and beyond their known nutritional effects. Therefore, providing higher levels of certain nutrients may be recommended for some animals with heart disease.

Protein and Taurine

Protein

Protein restriction should be avoided in dogs and cats with heart disease because these patients are predisposed to loss of lean body mass. Diets that are low in protein, even if they are designed as cardiac diets, diets designed for renal disease, and "senior diets," are not recommended unless severe renal dysfunction is present. Otherwise, a good quality nutritionally balanced food providing at least the canine (4.5 g/100 kcal) and feline (6.5 g/100 kcal) minimum protein levels according to Association of American Feed Control Officials (AAFCO) is recommended.[13]

Taurine

Taurine is an amino acid found in high levels in the myocardium. Despite knowledge of the role of taurine deficiency in feline DCM, a small number of cats still develop DCM (see ch. 253).[4] Most current cases of feline DCM do not involve taurine deficiency but it should be suspected in all cats with this disorder. A dietary history should be elicited from owners to determine whether the cat has been fed a poor-quality, homemade, vegetarian, or otherwise unbalanced diet. Plasma and whole blood taurine should be measured, and treatment with taurine (125 to 250 mg PO q 12 h) should begin concurrently with medical therapy. If the taurine concentration is found to be normal, taurine supplementation can be discontinued, although some benefits may still be derived from taurine's other effects (see below).

Unlike cats, dogs are thought to be able to synthesize adequate amounts of taurine, which is not considered a requirement in canine diets. Most dogs with DCM do not have taurine deficiency, but low taurine concentrations have been found in some dogs with the disorder.[14-20] The most common breeds in which DCM has been reported to be associated with taurine deficiency are the American Cocker Spaniel, Golden Retriever, Labrador Retriever, Portuguese Water Dog, Saint Bernard, English Setter, and Newfoundland (see ch. 252).[14-20]

Diet appears to play some role in the development of taurine deficiency in dogs as very-low-protein, lamb and rice, and some high-fiber diets have been associated with taurine deficiency, as have been diets low in methionine, but the exact role of diet remains unknown.[16-25] Taurine deficiency also may be the result of increased renal or fecal loss of taurine, higher requirements, or other metabolic defects present in certain breeds.[23-25]

While some dogs with DCM have low circulating taurine concentrations, not all of these respond impressively to taurine supplementation. One small prospective study showed that Cocker Spaniels supplemented with taurine and carnitine had clinical and echocardiographic improvements.[26] It is not known whether the response would be similar with either taurine or carnitine alone. A retrospective study of 12 dogs with taurine deficiency and DCM documented improved cardiac contractility after taurine supplementation.[17] In a study of Portuguese Water Dog puppies, plasma taurine was low in all puppies tested, and DCM was diagnosed in eight of nine puppies.[20] Taurine supplementation was instituted in six of

the puppies, which significantly increased circulating taurine concentrations and cardiac function.[20] Finally, in a study of Beagles fed a low-taurine, very-low-protein diet for 48 months, one dog developed DCM but showed significant improvement in cardiac contractility after supplementation of taurine.[21]

Dogs with DCM and taurine deficiency that do respond to taurine supplementation generally do not have as dramatic a response as do taurine-deficient cats with DCM. Nonetheless, measurement of plasma and whole blood taurine concentrations is warranted in the breeds of dogs with DCM listed above, or in breeds that are not typically associated with the development of DCM (e.g., Border Collie, Dachshund). Taurine concentrations also should be measured in dogs with DCM eating lamb meal and rice-based diets, very-low-protein, vegetarian, or high-fiber diets. Taurine analysis is usually not recommended in typical breeds that develop DCM (e.g., Doberman Pinschers, Boxers). Supplementation with taurine (250 to 1000 mg PO q 8-12 h) is recommended in dogs with documented taurine deficiency, although the exact dosage required for repletion is not known. Some of the potential benefits of taurine in dogs with DCM may be due to pharmacologic effects: taurine is a positive inotrope, has antioxidant effects, and plays an important role in myocardial calcium regulation.

Fat

Fat provides calories and increases the palatability of pet foods but it also can significantly affect immunologic, inflammatory, and hemodynamic parameters. The n-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are long chain fatty acids in which the first double bond is at the position of the third carbon from the methyl end (vs. the n-6 PUFAs, namely linoleic, gamma-linolenic, and arachidonic, in which the first double bond is at the sixth carbon).[27] This minor chemical difference conveys different structural and functional characteristics to the fatty acid. Plasma membranes normally contain very low concentrations of n-3 fatty acids, but levels can be increased by a food or supplement enriched in n-3 fatty acids. Dogs with CHF have been shown to have plasma fatty acid abnormalities, including decreased concentrations of EPA and DHA compared to normal dogs.[5] In one study of dogs with DCM and CHF, fish oil supplementation normalized these plasma fatty acid abnormalities.[5]

Another potential benefit of n-3 fatty acid supplementation is that breakdown products of the n-3 fatty acids (3- and 5-series eicosanoids) are, in general, less potent inflammatory mediators than eicosanoids derived from n-6 fatty acids (2- and 4-series eicosanoids). This decreases the production of cytokines and other inflammatory mediators, which may minimize cachexia.[5,27] Finally, n-3 fatty acids have antiarrhythmic effects in a variety of species including Boxers with ventricular arrhythmias (see ch. 252).[28] The authors currently recommend a dosage of 40 mg/kg EPA and 25 mg/kg DHA for dogs and cats with reduced/altered food intake or cachexia. This dose also can be used as an adjunct to medical therapy for arrhythmias. Finally, the authors will discuss the possible benefits of n-3 fatty acid supplementation with all owners of dogs or cats with CHF, advising that there may be some benefit to supplementation in all cases of CHF. With the exception of a few specially-designed veterinary diets, most commercial diets do not achieve this level of n-3 fatty acids, so supplementation is usually necessary. The amount of EPA and DHA in individual fish oil supplements varies widely, so it is important to know the exact amount in the brand of supplement recommended. The most common formulation of fish oil, however, is 1-g capsules that contain approximately 180 mg EPA and 120 mg DHA and can be purchased over the counter at most human pharmacies or health food stores. At this concentration, fish oil can be administered at a dose of one capsule per 10 pounds of body weight to achieve the authors' recommended EPA and DHA dosage. Fish oil supplements should contain vitamin E as an antioxidant, but other nutrients should not be included in order to avoid toxicosis. Cod liver oil and flaxseed oil should not be used as sources of n-3 fatty acids.

Minerals

Sodium

Recommendations regarding the degree of dietary sodium restriction, and when sodium restriction should be initiated, continue to evolve for dogs and cats with heart disease. Studies in the 1960s showed that very–low-sodium diets could help to control fluid accumulation in dogs with CHF.[1] Authors in the 1960s and 1970s recommended changing animals to a severely sodium restricted diet when a heart murmur was first detected, even before clinical signs were present. More recently, questions have been raised about severe sodium restriction in asymptomatic heart disease (and even in CHF) due to activation of the renin-angiotensin-aldosterone system.[29,30] One study of dogs with asymptomatic chronic valvular disease (CVD) showed that a

low-sodium diet resulted in increased aldosterone concentrations and heart rate, with no improvement in cardiac size or function.[30] Because of lack of documented benefits and potential adverse effects of severe sodium restriction in asymptomatic disease, the authors recommend only mild sodium restriction (<100 mg/100 kcal) in asymptomatic heart disease (International Small Animal Cardiac Health Council [ISACHC] Stages 1a and 1b). However, this is an opportune time to begin educating the owner about the animal's overall dietary patterns—the pet food, treats, table food, and how medications are administered—as it is generally much easier to institute dietary modifications at this earlier stage, before the animal develops clinical signs of CHF. Most owners are unaware of the sodium content of pet foods and human foods and need very specific instructions regarding appropriate foods and acceptable low-salt treats.[31]

When CHF first arises, additional sodium restriction is recommended (<80 mg sodium/100 kcal). This can be achieved with a veterinary diet designed for animals with early heart disease or with certain other veterinary diets (which may be designed for other disease) or even some over-the-counter diets. The content of sodium and other nutrients, such as protein, potassium, and magnesium, can be found by consulting manufacturers' product guides, by calling the manufacturers, or from reputable websites.[31] Caution is indicated with "senior diets," which often are reduced in protein (which is not recommended for animals with heart disease). Senior diets also vary tremendously in sodium (and other nutrients). In one study of 37 commercial diets marketed for senior dogs, the sodium content ranged from 33-412 mg/100 kcal.[32] Similarly, diets designed for animals with renal disease are usually not recommended, even though they might be low in sodium content, because of the protein restriction (unless proteinuria or advanced renal dysfunction is present). As CHF becomes more severe, more sodium restriction (i.e., <50 mg/100 kcal) may allow lower dosages of diuretics to be used to control clinical signs.[33] There are no commercial veterinary diets marketed specifically for cats with heart disease, but a number of veterinary and over-the-counter diets are reduced in sodium and may meet an individual cat's nutritional needs.[31]

Potassium

Hypokalemia causes muscle weakness and potentiates arrhythmogenesis. In addition, Class I antiarrhythmic drugs (e.g., mexiletine, lidocaine) are relatively ineffective in the face of hypokalemia. Hypokalemia can be precipitated by the use of loop diuretics (e.g., furosemide), thiazide diuretics (e.g., hydrochlorothiazide), or inadequate dietary intake (often associated with anorexia or hyporexia).

Angiotensin-converting enzyme (ACE) inhibitors cause renal potassium sparing, which can result in increased serum potassium and, therefore, some animals develop hyperkalemia. Spironolactone, now used in some dogs with heart disease, is an aldosterone antagonist and a potassium-sparing diuretic. Whereas animals receiving ACE inhibitors or spironolactone can develop hyperkalemia, hyperkalemia severe enough to affect appetite or clinical status is not a common occurrence, unless they are eating a diet that contains high levels of potassium.

Commercial diets vary widely in potassium concentrations. Commercial reduced-sodium diets range from <150 to >300 mg potassium/100 kcal, with an AAFCO minimum of 170 mg/100 kcal for dogs and 150 mg/100 kcal for cats. If hyperkalemia is present in an animal with heart disease, a diet with a lower potassium content should be selected. Conversely, if an animal is hypokalemic, a diet higher in potassium or oral potassium supplementation is indicated. This information can be obtained by contacting manufacturers.

Magnesium

Magnesium plays an important role in normal cardiac function. Alterations in magnesium homeostasis can occur in people and dogs and can have deleterious effects in a variety of cardiovascular conditions including hypertension, coronary artery disease, CHF, and cardiac arrhythmias. Some cardiac drugs, including loop diuretics, are associated with magnesium depletion. Therefore, animals with CHF receiving these medications have the potential to develop hypomagnesemia. Hypomagnesemia can increase the risk of arrhythmias, decrease cardiac contractility, cause muscle weakness, contribute to renal potassium loss, and can potentiate the adverse effects of certain cardiac medications.

Hypomagnesemia has not been a consistent finding in studies of animals with heart disease, but this may be because serum magnesium concentrations are a poor indicator of total body stores.[34] Therefore, normal serum magnesium does not necessarily mean there are adequate total body stores. However, it still can be useful to routinely measure serum magnesium, especially in animals with arrhythmias or those on large doses of diuretics.

Like potassium, magnesium concentrations vary widely in commercial pet foods. Commercial reduced-

sodium diets for dogs can contain between 10 and 50 mg magnesium/100 kcal (AAFCO minimum of 11 mg/100 kcal for dogs and 10 mg/100 kcal for cats). A diet high in magnesium would be indicated for an animal with a low serum magnesium concentration. In some animals with low serum magnesium concentrations, diet adjustment alone will not correct the problem and oral supplementation will be required.

Vitamins

B Vitamins

Thiamine deficiency is known to be a cause of cardiomyopathy in people, but there has been little investigation into the role of B vitamins as a cause of heart disease in dogs and cats. Anorexia and urinary loss of water-soluble vitamins can contribute to low B vitamin concentrations in patients with CHF. In one study of human CHF patients, for example, 33% were thiamine-deficient.[35] As with other nutrients such as potassium, B vitamin deficiencies may have been much more common when furosemide was the primary means of therapy for patients with CHF. Research suggests that vitamins B_6, B_{12}, and folate may be significantly lower in cats with cardiomyopathy than in healthy controls, an effect that appeared to be unrelated to diet or furosemide use.[36,37] Animals with heart disease (at least those receiving diuretics) may have higher B vitamin requirements. Routine supplementation of B vitamins in animals with heart disease on good quality commercial diet is likely unnecessary; however, empirical supplementation may be tried in animals on high dosages of diuretics, especially those with anorexia or hyporexia, or in animals on an unbalanced diet.

Other Nutrients

Carnitine

L-carnitine is concentrated in skeletal and cardiac muscle and is critical for fatty acid metabolism and energy production. Carnitine deficiency is associated with primary myocardial disease in a number of species, and has been described in a family of Boxer dogs.[38] Anecdotal reports exist regarding the efficacy of L-carnitine in canine DCM, but no blinded prospective monotherapy studies have been done so its role in DCM remains unclear. Even if carnitine deficiency is not the inciting cause of DCM, L-carnitine supplementation could be beneficial by improving myocardial energy production. A study of rapid pacing–induced CHF in dogs showed that myocardial concentrations decreased in normal dogs after the onset of CHF;[39] however, effects of supplementation in dogs that do not have a primary deficiency are unknown. There are few side-effects of L-carnitine supplementation but high cost is a deterrent for some owners. We currently discuss the option of L-carnitine supplementation (50 to 100 mg/kg PO q 8 h) to owners of dogs with DCM.

Antioxidants

Much attention has been given to antioxidants for their potential role in the prevention and treatment of human heart diseases. Reactive oxygen species are a byproduct of oxygen metabolism for which the body normally compensates through the production of endogenous antioxidants. An imbalance between oxidant production and antioxidant protection, however, could increase the risk for heart disease. Antioxidants are produced endogenously but also can be supplied exogenously. The major antioxidants include enzymatic antioxidants (e.g., superoxide dismutase, catalase, glutathione peroxidase) and oxidant quenchers (e.g., vitamin C, vitamin E, glutathione, and beta-carotene). Most of the research in human cardiology has been in coronary artery disease, but in dogs with CHF due to either DCM or CVD there is an imbalance between increased oxidant production and reduced antioxidant protection, particularly as the disease becomes more severe and particularly for the fat-soluble vitamins (e.g., vitamin E).[40,41] Supplemental antioxidants are now included in many commercial veterinary diets, including at least one cardiac diet, and can increase circulating antioxidant concentrations and reduce oxidation.[30] However, potential clinical benefits of antioxidant supplementation require additional study.

Coenzyme Q10

Coenzyme Q10, like carnitine, is a cofactor in a number of energy-producing reactions but is also an antioxidant. Studies in people suggest a beneficial effect of this supplement. Possible reasons for the purported benefits of supplementation include correction of a deficiency, improved myocardial metabolic efficiency, or increased antioxidant protection. Although coenzyme Q10 supplementation has anecdotally

been reported to be beneficial in dogs with DCM, controlled prospective studies are necessary to accurately judge the efficacy of this product. One study of experimentally-induced CHF in dogs showed that serum coenzyme Q10 levels were not reduced and that coenzyme Q10 supplementation increased serum, but not myocardial, concentrations.[42] The current recommended dosage in dogs is 30 mg PO q 12 h, although up to 90 mg PO q 12 h has been recommended for large dogs. Further research is needed in dogs with DCM.

Practical Aspects of Feeding the Patient With Heart Disease

There is not a single "best" diet for managing heart disease. It is important to match the nutritional needs of an individual patient to the diet or diets that best suit those needs. Patients with heart disease vary in terms of their clinical signs, laboratory parameters, and food preferences, and these all affect diet selection. For example, animals with asymptomatic heart disease require less severe sodium restriction than animals with CHF. Dogs with cardiac cachexia require a calorically dense diet while an overweight dog without CHF should be fed a calorically restricted diet. Concurrent diseases also influence diet choice and, in one study, were present in approximately 61% of dogs and 56% of cats with heart disease, respectively.[43,44] For example, a cat with hypertrophic cardiomyopathy and a history of struvite urolithiasis would need a diet that is sodium restricted but also one that has nutritional modification to reduce the risk of struvite urolith formation. Finally, laboratory results, such as the presence of moderate to severe azotemia, or alterations in potassium or magnesium, also can affect selection of optimal diet(s).

Performing a nutritional assessment on every patient at every visit can optimize nutritional and medical management (see ch. 170). The nutritional assessment helps to identify whether the current diet could be contributing to the heart disease (e.g., in a dog with DCM eating a vegetarian diet or a cat with CHF eating a diet very high in sodium), if the current diet is optimized for managing the heart disease, and what the animal's and owner's preferences are. In addition, the nutritional assessment identifies all components of the animal's diet that will need to be addressed in making a nutritional plan. Nutritional screening can be done with only a short diet history form and a physical examination, and includes a diet history, body weight, body condition score, muscle condition score, and the knowledge of other medical conditions that also require nutritional modification (e.g., gastrointestinal disease, feline lower urinary tract disease, chronic kidney disease).[7,8] The diet history includes the main pet food being provided (or the home-prepared diet recipe being used, if any), but also treats, table food, dietary supplements, and foods used for medication administration (Box 183-1).

Based on these and other patient parameters, diets can be matched to the individual patient. There currently are several commercial veterinary diets available that are specifically designed for animals with heart disease. Specific characteristics of these foods vary, but they are moderately to severely sodium-restricted, generally contain increased levels of B vitamins, and vary in their protein content; ensuring adequate protein intake is critical. Some cardiac diets also may include increased levels of taurine, carnitine, antioxidants, or n-3 fatty acids. There also are many veterinary diets designed for other diseases or even over-the-counter diets that may have the desirable nutritional profile.[31] Above all, the diet must be palatable enough that the animal will willingly eat it. The authors typically determine several diets that would be appropriate for an individual animal. These diets are offered as choices for the owner and the pet. Having dietary choices is particularly beneficial for more severely affected patients, in which a cyclical or selective loss of appetite is common. A starting goal for calorie recommendations in animals with CHF is 1.0-1.2× resting energy requirements, but adjustment is necessary to maintain ideal body and muscle condition. All diet recommendations should also include discussion of treats, table food, and foods used for medication administration (Box 183-2).[7,8]

Box 183-2

Methods for Administering Medication to Dogs and Cats

1. Teach the owner to pill the animal without using foods.
2. Use a pill administration treat but be sure to check the individual brand for content of sodium and other nutrients of concern for an individual patient. This becomes particularly important the more of these treats per day are used for medication administration.
3. Use a pet piller or pet pill gun.
4. Use a compounded, flavored liquid medication instead of a pill. Note: Compounding may alter the

pharmacokinetics of a drug and be sure to check the sodium content of a compounded product (see ch. 168).

5. Insert medications into appropriate foods, such as the following:
   - Fruit (e.g., banana, orange, melon, berries [not grapes])
   - Low-sodium cheese
   - Low-sodium canned pet food
   - Peanut butter (labeled as "no salt added")
   - Home-cooked meat (without salt); not lunch meats

As mentioned earlier, appetite changes are a common problem in animals with CHF and can contribute to the syndrome of cachexia. Another important problem with reduced appetite is that it may affect survival by influencing an owner's decision to euthanize the pet. In one study of owners of dogs euthanized for CHF, reduced appetite was one of the most common contributing factors to the euthanasia decision.[45] Anorexia, hyporexia, and dysrexia become more common as the heart disease becomes more advanced. Owners often report a variable or cyclical appetite, where the animal will eat one food well for a few days and then refuses it, but will eat a different food well. This dysrexia is common in animals with advanced CHF. Recommendations for managing reduced appetite are listed in Box 183-3. In animals with an acute episode of CHF, avoid changing the diet until the patient is stabilized. Once the animal is home and stabilized on medications, a gradual change to a new diet can be made. Forced dietary changes when the animal is sick or starting new medications may induce food aversions.

Box 183-3

Keys to Managing Anorexia, Hyporexia, and Dysrexia in Patients with Heart Disease

- Assess the patient for optimal medical control of heart failure.
- Assess the patient for side effects of medications (e.g., dehydration, azotemia, hyperkalemia, drug toxicosis).
- Feed more frequent but smaller meals.
- Provide multiple diet options so owners can rotate foods if hyporexia or dysrexia occurs.
- Warm the food to body temperature (for cats). Try different temperatures of food for dogs—they may prefer it warmed, at room temperature, or even cold.
- Feed the animal from a different type of dish (e.g., a new food dish or a human dinner plate).
- Feed in a different location in the house.
- Add homemade chicken, beef, or fish broth to the food (even low sodium store-bought broths are too high in sodium).
- Add a small amount (1-2 teaspoons) of cooked meat (hamburger, chicken, or fish) to the food. Be sure to instruct the owner not to use any prepared foods, such as rotisserie chicken, lunch meats, or canned meats or fish due to their high sodium content. Cats typically prefer meat or fish as a palatability enhancer. Meat or fish also may enhance food intake in dogs, but some dogs prefer sweet flavors as a palatability enhancer (e.g., maple syrup, applesauce, fruit-flavored yogurt).
- Supplement fish oil, which is high in n-3 fatty acids, to reduce inflammatory cytokines. This may have modest benefits for appetite.

In many cases, the desired nutrient modifications can be achieved through diet alone. However, supplementation of certain nutrients may be desirable if they are either not in a particular diet or not at high enough levels to achieve the desired effect. It is important to be aware that dietary supplements currently do not require proof of safety, efficacy, or quality control to be marketed. Therefore, veterinarians should consider recommending specific brands of dietary supplements that bear the logo of the United States Pharmacopeia Dietary Supplement Verification Program, which tests human dietary supplements for ingredients, concentrations, dissolvability, and contaminants. Another good resource is Consumerlab.com, which performs independent testing of dietary supplements (primarily human supplements but also some pet products).

In addition to finding a diet that has the desired nutritional properties and palatability, it also is important to devise an overall dietary plan that meets the owner's expectations. This includes finding a diet that the owner perceives the pet to enjoy, providing acceptable treats, and devising a satisfactory method for administering medications. In one study, over 90% of dogs with heart disease received treats and these treats are often high in sodium.[43] Fewer cats (33%) receive regular treats but this additional source of nutrients also should be addressed with cat owners.[44] In addition, the majority of people administering medications to their dogs use foods as a way to administer the medication,[43] so appropriate methods of medication administration should be provided to owners (see Box 183-2). Only 34% of cat owners use foods to administer medications,[44] but because of the difficulty of this activity in cats, special care should be taken to ensure that the cat owner can be successful and adherent in medication administration. Including information regarding all sources of food from pet food, treats, table food, and medication administration in the overall diet plan is important to achieve success with nutritional modification.

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CHAPTER 184

Nutritional Management of Renal Conditions

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Client Information Sheet: Nutritional Management of Chronic Kidney Disease

Chronic Kidney Disease (CKD)

Chronic kidney disease is common in dogs and cats (see ch. 324) and is characterized by an irreversible decrease in renal function that may stabilize or plateau for periods, but invariably, the condition progresses. Clinical studies of dogs and cats with CKD have demonstrated that dietary modifications can slow disease progression, prolong survival, and improve quality of life.[1-5] The American College of Veterinary Nutrition recommends an assessment of patient, food, and feeding methods (see ch. 170). Then, plans can be developed that include a diet and feeding strategies. Periodically, these should be re-evaluated using this two-step process.[6] Because CKD is progressive, there is no set period for adjustments; this is dictated by the patient's condition.

Two-Step Process in Developing Feeding Recommendations for Dogs and Cats with CKD

Assessment Phase

The Patient

Some dogs and cats with CKD appear healthy while others have changes consistent with chronic disease: an unkempt appearance, poor hair coat, weight loss, and/or muscle wasting. Signs of chronic disease are negative prognostic indicators (see ch. 177).[7,8] Additional signs of uremia may be present, such as gastrointestinal (GI) ulcers or uremic halitosis. The International Renal Interest Society (http://iris-kidney.com/) developed a system for staging severity of dysfunction in dogs and cats with CKD (see ch. 324) based on degree of azotemia, presence of proteinuria and/or hypertension.[9] Some pets with CKD have anorexia and nausea due to retention of uremia toxins, dehydration, biochemical alterations (azotemia, metabolic acidosis, electrolyte imbalances, mineral imbalances), anemia, renal secondary hyperparathyroidism (R2HP), or uremic gastroenteritis.[10,11] Gastric ulcers occur less commonly in dogs and cats than in people; however, many dogs and cats with CKD have gastric lesions that include vascular changes, edema, and hyperacidity due to hypergastrinemia from decreased renal excretion (see ch. 275).[12,13] Administration of maropitant, mirtazapine, or ondansetron may be beneficial in uremic gastroenteritis.[14-18]

The Diet

Energy

Body weight and body condition vary among dogs and cats with CKD. The obese may be prone to systemic arterial hypertension (see ch. 157 and 176), while those that are underweight or cachectic may be prone to medication intolerance, secondary infections, and/or poor quality of life (see ch. 177).[19] Dogs with CKD and poor body condition have shorter life-spans when compared with CKD dogs that are of optimal condition or overweight.[8] Decreased energy intake due to inappetence or advanced renal failure may lead to poor body condition.

Fatty Acids

The average fat content of adult dog and cat foods is about 12% (dry matter basis), containing predominantly n-6 polyunsaturated fatty acids, unless fish oil is added. Cytokines derived from membrane-bound n-6 fatty acids include prostaglandins, thromboxanes, and leukotrienes of the 2- and 4-series. These cytokines are typically pro-inflammatory and vasoactive. In people with CKD and dogs with induced CKD, intra-renal free radical production and antioxidant depletion occur, which may promote CKD progression.[20-22]

Antioxidants

CKD is a pro-oxidant state, beginning early in the condition and progressing as the disease worsens.[22,23] Modification of oxidative stress may have benefit in managing CKD, including improved neutrophil function and decreased DNA damage.[21,24-28]

Water-Soluble Vitamins

Theoretically, water-soluble vitamins are lost at an increased rate in pets with CKD due to their polyuria. No study has documented vitamin loss. One study did not find differences in plasma concentrations of water-soluble vitamins in dogs with CKD.[29]

Electrolytes

Hypokalemia and whole-body potassium (K) depletion occur in 20-30% of cats with CKD (possibly associated with primary hyperaldosteronism in some; see ch. 308 and 324), but are uncommon in dogs (see ch. 68). Hyperkalemia was reported in 13% of 186 cats with CKD.[30] Consequences of hypokalemia include a polymyopathy and secondary weakness, hyporexia, and progression of CKD.[31] Amlodipine may promote hypokalemia in some cats with CKD[32] while enalapril and benazepril may promote hyperkalemia in dogs and cats with CKD.

Serum sodium (Na) concentrations are typically normal in CKD and the interactions between dietary Na, systemic arterial hypertension, and CKD are not completely understood (see ch. 67). High salt intake has not been associated with systemic arterial hypertension in dogs or cats; however, these studies were in healthy animals, animals with induced disease, or those ill for a short time.[32,33] A 2-year study of non-azotemic, aged cats did not show an effect on glomerular filtration rate, blood pressure, or other routine laboratory variables when cats were fed a 3.1 g/Mcal Na diet versus a 1.0 g/Mcal Na diet. In a 3-month crossover study of cats that were healthy, obese, older, or who had IRIS stage 2 CKD, consumption of a 2.9 g/Mcal "high Na" diet increased water intake and urine output in cats, except for those with CKD, when compared with consumption of a 0.9 g/Mcal "low Na" diet.[34] Consumption of the 2.9 g/Mcal Na diet was not associated with increased blood pressure in any group; however, it paralleled increases in serum concentrations of urea nitrogen, creatinine, and phosphorus in all cats. The greatest increases were noted in those with CKD.[34]

Acid-Base Balance

Metabolic acidosis is common in dogs and cats with CKD due to retention of metabolic acids, lactic acid production, electrolyte imbalances, and/or consumption of dietary acids. As renal function declines, capacity to excrete hydrogen ions and reabsorb bicarbonate ions is reduced. Metabolic acidosis may exacerbate hypokalemia, increase muscle catabolism, cause loss of lean mass, disrupt intracellular metabolism, and promote osteodystrophy. Cats appear to adapt to CKD and metabolic acidosis does not appear to occur until later in the course of their disease.[35] Provision of an alkalinizing agent, such as potassium bicarbonate or potassium citrate, to dogs and cats with azotemic CKD has been beneficial.[36,37]

Moisture

Due to the polyuric nature of CKD, dehydration may occur, especially in cats. Canned formulated diets contain 70-80% moisture and dry formulated diets contain 10-12%; therefore, dehydration is more likely to occur in animals consuming a dry formulated diet.

Protein

Azotemia is, by definition, an increase in nitrogenous compounds in the blood, most of which are derived from dietary protein or catabolism of endogenous protein. Formulating a diet that contains reduced quantity, but highly biologically available protein and adequate non-protein calories is based on the premise that reducing non-essential protein results in decreased production of nitrogenous compounds.[38] This may aid in amelioration of clinical signs associated with renal azotemia. Whether reducing dietary protein alters

progression of CKD is less certain.[39-47] Dietary protein restriction does decrease urinary protein excretion and increase serum albumin concentrations in azotemic and nonazotemic dogs with proteinuria.[48,49]

Minerals

Renal secondary hyperparathyroidism (R2HP) occurs commonly in dogs and cats with CKD.[1,50] Deficiencies of calcitriol (vitamin D_3) have been hypothesized to play a pivotal role in development of R2HP, but phosphorus retention also likely has a role.[51] Phosphorous retention and hyperphosphatemia occur early in CKD and play a primary role in R2HP and progression of renal failure. It suppresses fibroblast growth factor 23, which may be integral in progression of chronic kidney disease.[36,41,42,52-56]

The Feeding Method

The most important aspects of nutritionally managing CKD are whether the pet is eating and whether food intake is adequate. Questioning owners as to the volume of food provided, how frequently it is provided, how much of the meal is consumed, and whether the pet has a preference for a certain form of diet is important.

Initiation and Monitoring Phase

Selection of a Diet

The second phase in nutritional planning for pets with CKD is selecting the most appropriate diet and means of providing nutrition. Once the new diet is started, one must monitor and adjust as needed. Several commercial diets are formulated and marketed for feeding dogs or cats with CKD. While these diets are somewhat similar in their components, different ingredients and other nutritional variations exist. Homemade diets should be formulated by certified veterinary nutritionists (E-Box 184-1). While commercial diets tend to be consistent in composition, several studies have shown variability in nutrient content and some imbalances in homemade diets.[57,58]

E-Box 184-1

Veterinary Nutrition Centers and Online Sites That Can Formulate Complete and Balanced Homemade Diets for Use in Chronic Kidney Disease in Dogs and Cats*

- Angell Animal Medical Center: telephone consults (617) 522-7282
- Balance IT: http://www.balanceit.com/
- Michigan State University: telephone consults (517) 432-7782; diet analysis (517) 353-9312
- Ohio State University: telephone consults (614) 292-1221 or (614) 292-3551
- Red Bank Veterinary Hospital: telephone consults (732) 747-3636
- Tufts University: telephone consults (508) 839-5395 extension 84696; VetFax (800) 829-5690
- University of California, Davis: telephone consults (530) 752-1387 (veterinarians); (530) 752-1393 (clients)
- University of Tennessee: telephone consults (865) 974-8387

*This is a partial listing (see ch. 192, Table 192-1).

Energy

Sufficient energy must be provided to maintain body condition and body weight. Thus, sufficient energy is necessary to minimize protein catabolism that can result in malnutrition and exacerbate azotemia and uremia. Caloric requirements for dogs and cats with CKD are not precise, but are likely similar to those of healthy dogs and cats (see ch. 172 and 174).[59] Remember that daily resting caloric requirements are only estimates and individual variability can be significant. Therefore, body weight, body condition, and appetite should be monitored closely and adjustments made as needed.

Cats and dogs with CKD often have periods of partial or complete anorexia causing weight loss and other issues consistent with chronic illness. Therefore, diets that are more calorically dense than maintenance adult foods promote adequate energy intake without requiring the patient to eat a large volume. This can help reduce gastric distention and nausea. Because dietary fat is more calorically dense than protein or carbohydrate, CKD diets are usually higher in fat as compared with maintenance adult foods. Diets formulated for CKD usually contain 12-30% crude fat (dry matter basis). Nausea and anorexia associated with CKD may be due to hypergastrinemia and gastric hyperacidity.[12] Giving histamine-2-receptor antagonists, other antacids, neurokinin-1 inhibitors, or a medication that works via serotonin pathways may be beneficial in CKD.

Fatty Acids

In people, CKD is associated with increased free radical production and antioxidant depletion that may promote disease progression. Dogs fed diets containing 15% fat with fish oil had more sustained glomerular filtration rate (GFR) when compared with dogs fed beef tallow or safflower oil.[60] This benefit has not yet been demonstrated in cats.

Antioxidants

Cats fed a therapeutic diet formulated for managing CKD that was supplemented with vitamin E (742 mg/kg), vitamin C (84 mg/kg) and beta-carotene (2.1 mg/kg) had a significant reduction in oxidative DNA damage.[28] In an unpublished study of 6- to 8-year-old Beagles using the remnant kidney model, dogs were divided into 4 dietary groups: high n-3 fatty acids, high n-3 fatty acids plus antioxidant supplementation, high n-6 fatty acids, and high n-6 fatty acids plus antioxidant supplementation.[21] Specific antioxidants were vitamin E, carotenoids, and lutein (amounts not specified), and dietary total (n-6 + n-3) polyunsaturated fatty acid content was approximately 2.5% (dry matter basis). Results demonstrated independent and additive protective effects of antioxidant therapy and n-3 fatty acids. The rate of decline of GFR was slowed by n-3 fatty acids and the antioxidants; effects were additive and were associated with reduced magnitude of proteinuria, glomerulosclerosis, and interstitial fibrosis.

Water-Soluble Vitamins

Although B-vitamin deficiency has not been demonstrated, many diets formulated for managing CKD contain higher amounts of B-vitamins when compared with adult maintenance diets. B-vitamin supplementation may also stimulate appetite.

Electrolytes

Diets formulated for CKD are typically higher in potassium (K) than adult maintenance foods; K-citrate is used to supply the K and as an alkalinizing agent with a goal of maintaining serum K concentrations in the middle to upper half of the laboratory reference range. If necessary, K can be supplemented orally as gluconate or citrate salts. K-chloride is not recommended because of poor palatability and acidifying nature. K-gluconate (2 to 6 mEq/cat/day) and K-citrate (40-75 mEq/kg/day) can be given orally. The dosage depends on the size of the pet and severity of hypokalemia. Routine low-dosage K supplementation has been recommended for cats with CKD. However, one study failed to demonstrate that K-gluconate (4 mEq/day) improved muscle K stores when compared with Na gluconate.[61] In this study, median muscle K content did increase in the supplemented group to a level approaching that of normal cat muscle, with no significant adverse effects. Based on current data, no recommendation can be made for or against low-dose K supplementation to cats with CKD.

Whether dietary Na content should be restricted with CKD is controversial. In one study, high dietary Na intake in cats with naturally occurring CKD was associated with worsening azotemia.[34] In a separate study of induced CKD in cats, Na restriction was associated with hypokalemia.[32] Thus, salt supplementation and salt restriction must be done cautiously and patients should be monitored. Increased dietary Na may increase urinary Ca excretion, can contribute to ongoing renal damage, and may contribute to formation of Ca oxalate urolithiasis (see ch. 331 and 332).

Acid-Base Balance

Treatment options for managing the metabolic acidosis associated with CKD include dietary modification and alkalinization therapy. Dietary protein is a major source of organic acids; therefore, reduction of dietary protein decreases metabolic acidosis. Diets formulated for CKD usually have less protein and contain K-

citrate, an alkalinizing compound. Oral Na bicarbonate may be used for additional alkalinization. The effects of gastric acids on oral Na bicarbonate are unpredictable; therefore, doses should be individualized. The starting dosage is 8-12 mg/kg PO q 8-12 h. Since many dogs and cats refuse oral Na bicarbonate, an alternative with the advantage of providing K is K-citrate. Starting dosages are about 40-80 mg/kg, PO, q 12 h-q 8 h.

Moisture

Voluntary water intake may be insufficient to maintain hydration, especially in cats. Feeding a canned formulated diet, which contains 70-80% water, does supplement fluid intake. In pets that cannot maintain hydration via voluntary consumption, additional fluids may be administered SC or by a nasogastric, esophagostomy, or gastrostomy feeding tube (see ch. 82 and 324).

Protein

Minimal dietary protein requirements for dogs and cats with CKD are not precisely known. Diets formulated for managing dogs with CKD typically contain 13-18% protein (dry matter basis) and those for cats typically contain 25-32% protein (dry matter basis). To decrease blood concentrations of nitrogen-containing compounds (blood urea nitrogen and creatinine) one can facilitate nitrogen excretion via the GI tract by providing probiotics or soluble fiber (see ch. 167 and 190). New supplements with fiber-like polysaccharides derived from chitin and bacteria are available as phosphate binders and agents that reduce azotemia. Limited data exist as to efficacy, and maximal effect occurs when combined with nutritional therapy.[62-66]

Minerals

Dietary phosphorus restriction decreases the degree of hyperphosphatemia, hyperparathyroidism, and slows progression of CKD in dogs and cats.[3,41,42,52,67] Dietary phosphorus content for management of CKD should be 0.2-0.5% (dry matter basis) while maintaining a Ca : P ratio of 1.1-1.3 : 1. In stage I and II CKD, feeding a phosphorus restricted diet may normalize parathyroid hormone concentrations (see ch. 324).[53,67]

Clinical Studies

Several studies have demonstrated, in part due to dietary management, longer survival times and better quality of life in dogs and cats that have naturally occurring CKD.[1-4] Most studies showed at least a two-fold increase in survival in dogs and cats fed a "renal failure" diet. Diets were most effective with stage II CKD. Efficacy with stage I CKD has not been demonstrated although dogs with stage I CKD and proteinuria benefit from dietary protein restriction.[48]

Selection of Feeding Method

Most dogs and cats with CKD are fed orally; however, nutritional support can be provided using feedings tubes (see ch. 82 and 324).[68] The formulation of the diet, dry versus canned, may be modified to stimulate adequate nutritional intake as well as moisture intake. Feeding canned diets increases moisture intake and may help prevent dehydration. It may also be necessary to modify feeding frequency if animals are unable or unwilling to consume one or two meals per day. Some dogs and cats respond best to 3 or more small meals each day (see ch. 177).

Monitoring Patient Response

Chronic kidney disease is progressive; therefore, monitoring is important. Monitoring of nutritional management of CKD involves body condition score, body weight, appetite, quality of life, and biochemical parameters. Frequency of monitoring should be individualized to the patient and to the stage of disease. Most animals should be monitored every 4 to 6 months in stage I or II CKD and more frequently in stage III and IV, or if CKD is unstable or progressing rapidly (see ch. 324).

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CHAPTER 185

Nutritional Management of Lower Urinary Tract Disease

Yann Queau, Vincent C. Biourge

Client Information Sheet: Dietary Management of Urinary Stones

Lower urinary tract disease (LUTD) encompasses a variety of disorders characterized by dysuria, stranguria, pollakiuria, hematuria, periuria and sometimes urethral obstruction. Urolithiasis accounts for 18% and 7-22% of LUTD cases in dogs (see ch. 331)[1] and cats (see ch. 332)[2-5] respectively, while idiopathic cystitis (IC) is predominant in cats, representing approximately two-thirds of cases (see ch. 334).[2-5]

It is crucial that the precise etiology (or the lack thereof in the case of IC) of the LUTD signs be sought for nutritional management to be successful. Collecting dietary history and information on the patient's environment, obtaining quantitative stone analysis, and diagnosing any potential metabolic disorder are essential to guide and optimize dietary treatment.

Urolithiasis

Uroliths are polycrystalline structures that form under certain conditions affecting urinary concentrations of crystalloids, inhibitors or promoters of crystallization, and pH. Relative supersaturation (RSS) is a risk index of crystallization in humans[6] and companion animals.[7] To calculate RSS, urine pH and the concentrations of ten solutes from a representative urine sample are entered in a computer algorithm. RSS defines three levels of urine saturation: *undersaturation* (crystal dissolution, RSS <1), *metastable supersaturation* (neither crystal formation nor dissolution) and *labile supersaturation* (spontaneous crystal formation and growth). To date, RSS is not available in the clinical setting. Urine specific gravity (USG), urine pH, and microscopic evaluation can be performed readily as indirect and imperfect ways of assessing risk of crystal formation. Maintaining USG <1.030 in cats and <1.020 in dogs often is recommended in patients at risk.[8]

General Considerations: Stimulating Diuresis

Whatever the nature of the stone, urine dilution is the paramount strategy for the prevention and/or the dissolution of uroliths. Increased diuresis lowers RSS and stimulates more frequent urination, decreasing the time for crystal aggregation. Using wet diets (dietary moisture > 70%; cans, pouches, trays) is an effective way to enhance water intake and diuresis in dogs and cats.[9-11] In order to bring dietary moisture of dry diets to a comparable level, warm water can be poured onto kibble: adding 1.5 cups of water to 1 cup of kibble yields approximately 80% moisture. Acceptance of such a diet might be a challenge in cats.

An alternative to moisture to stimulate diuresis is sodium chloride supplementation. In a large number of studies, cats and dogs had greater water intake and urine volume, and in most cases lower USG, when fed dry commercial diets with sodium contents >2.5 g/1000 kcal.[11-19] The use of high dietary sodium is subject to controversy. Based on human studies, concerns have been raised regarding renal and cardiac functions, and blood pressure. One study in cats found a reversible increase in creatinine in 4 cats with marginally impaired renal function when fed a diet with a sodium concentration of 2.9 g/1000 kcal.[17] On the contrary, five short[20-23] (1-12 weeks) and two long[18,19,24] (6-24 months) term studies found no effect of a higher sodium intake on renal (including glomerular filtration rate) and cardiac functions. Systemic hypertension was not found in any study. Another potential concern is an increased urinary calcium excretion with high sodium diets.[12,14] However, due to concurrent urine dilution, urine calcium concentration is either unchanged[11,12,14] or

decreased.[15] The urine concentrations of solutes such as oxalate can decrease, thus lowering calcium oxalate (CaOx) RSS.[11,12,15]

Specific Considerations According to Stone Type

A majority of stones occur as pure uroliths, and their specific dietary management is described in this section. Between 5 and 15% may occur as compound or mixed uroliths. In that situation, dietary prevention should be targeting the inner part of the calculus (nidus), which formed first and facilitated the precipitation of the second mineral.

Struvite

Struvite crystals are composed of magnesium, ammonium, and phosphate. They can form in sterile urine (most feline cases; see ch. 332), or secondary to a urinary tract infection (UTI) with urease-producing bacteria (majority, if not all, of canine cases; see ch. 331). Therefore, the goals of dietary management for struvite uroliths depend on the patient's species: prevention and dissolution in cats, and dissolution in dogs. The target is a struvite RSS <1 for undersaturation and 1-2.5 for metastable supersaturation.[7,25]

Promoting urine dilution might help but is less important for struvite than for other uroliths. Urinary pH is the most important factor in the prevention and dissolution of struvite. In alkaline urine, phosphate is in its trivalent state (PO_4^{3-}), making it readily available to form struvite crystals ($NH_4MgPO_4 \cdot 6H_2O$). When urine is acidified, protonation of phosphate (HPO_4^{2-}, $H_2PO_4^-$ or H_3PO_4) decreases its availability. The lower the urine pH, the lower the struvite RSS. However, other factors such as urine dilution and amounts of precursors also influence RSS. The acidification potential of a diet depends on its ingredients and the balance between acidifiers (methionine, calcium or sodium sulfate, calcium or ammonium chloride, etc.) or alkalizers (calcium or sodium carbonate, potassium citrate, etc.). Consumption of small meals throughout the day rather than 1 or 2 large meals blunts the postprandial alkaline tide and is associated with more acidic urine production and less struvite crystalluria.[26] The target urine pH to manage struvite urolithiasis is generally 6.0 to 6.3 (at least for dry diets), to help obtain an RSS <2.5. Excessive chronic acidification increases urinary potassium excretion and can lead to body potassium depletion if dietary potassium is too low.[27,28] It could also promote bone demineralization, although this phenomenon is not supported by studies in cats.[29-31] In dogs, UTI with urease-producing bacteria promotes alkaline urine and ammonia release, thus increasing the risk of struvite formation. In the setting of UTI, acidifying diets cannot significantly decrease urinary pH without the help of antibiotic therapy. There is a direct link between the amounts of precursors of struvite (especially magnesium and phosphorus) in the diet and their excretion in the urine.[32,33] In the absence of urinary pH control, high dietary amounts of those minerals could increase the risk of struvite urolithiasis. Both minerals interact for their absorption. Studies have proven the efficacy of dry and canned commercial diets with controlled amounts of struvite precursors, acidifying and/or diuretic properties, for the dissolution of naturally occurring struvite uroliths in cats.[34-37] In cats, average complete dissolution times varied from 13 to 28 days (range 6-141 days). In dogs, dissolution can take up to 3 months, and protocols must be accompanied by appropriate antibiotic therapy.[38-40]

Calcium Oxalate

To date, calcium oxalate (CaOx) uroliths are not amenable to medical dissolution. The goal of dietary management is to reduce the risk of recurrence. A CaOx RSS between 1-12 corresponds to urine in the metastable supersaturation zone.[25] This can be achieved by stimulating diuresis. Increasing water intake through dietary moisture[9,11,41] or dietary sodium[11-16,41,42] has lowered CaOx RSS in healthy and stone-forming animals in the majority of studies.

The role of dietary precursors in the pathophysiology of CaOx is poorly understood. In a retrospective study, higher dietary moisture, protein, sodium, and potassium were associated with a lower risk of CaOx urolithiasis in cats (see ch. 332).[43] In dogs fed dry and canned diets, the risk of CaOx urolithiasis was higher for dogs that ate diets with the lowest levels of protein, sodium, potassium, calcium, phosphorus, and magnesium (see ch. 331).[42,44,45] Based on current knowledge, prevention of CaOx urolithiasis aims at reducing urinary concentrations of calcium and oxalate. High dietary calcium levels increase its absorption and urinary excretion, leading to higher RSS.[46] However, calcium absorption is affected by dietary phosphorus, magnesium, oxalate, and vitamin D. Oxalate absorption is affected by dietary calcium.[47-49]

Ingredients such as beets, beans, potatoes, and leafy vegetables are high in oxalate concentration but the effect of dietary oxalate on its urinary excretion is variable.[46,50,51] In humans, dietary oxalate can be degraded by intestinal microflora. Endogenous oxalate production, via the metabolism of some sugars (glucose, fructose), amino acids (including hydroxyproline, glycine, serine, etc.), vitamin C, and glycolate also will affect oxalate excretion.[50-52] Deficiency in vitamin B_6 (pyridoxine) leads to increased endogenous production and urinary excretion of oxalate.[53] However, deficiency of this vitamin is very unlikely, and large supplementation does not decrease urinary oxalate concentrations.[54]

In humans, high animal protein diets are associated with metabolic acidosis and hypercalciuria.[55] Therefore, they are considered a risk factor for CaOx urolithiasis. Conversely, high dietary protein appears protective against CaOx in dogs and cats,[43-45] and it leads to increased urine volumes,[56] which can lower concentrations of crystalloids. One study found higher CaOx RSS with increasing dietary protein (35-57% DM) in cats.[57] The differences were very small, however, and probably not biologically relevant. In addition, increasing protein content was not associated with a consistent increase in calcium excretion nor a decrease in urinary pH. Magnesium can form complexes with oxalate. Epidemiological studies found that low dietary magnesium increases the risk of CaOx urolithiasis in cats.[43] However, excessive magnesium supplementation could increase the risk of struvite urolithiasis.

There has been some controversy regarding the effect of urine pH on the risk of CaOx urolithiasis. The increasing prevalence of CaOx stones has been hypothesized to be associated with the general acidification of pet foods in the 1980s and 1990s. Retrospective epidemiological studies have found the urine acidifying potential of a diet (pH <6.25) to be associated with an increased risk of CaOx urolithiasis in cats[43] but not in dogs.[44,45] Chronic metabolic acidosis is believed to promote release of calcium and phosphate from bone, and calciuria,[27] and to decrease urinary citrate, an inhibitor of CaOx crystallization. Studies on the effect of urine pH on CaOx RSS have yielded conflicting results, with one showing higher RSS with lower urine pH despite similar ionized calcium and calciuria,[31] and the other showing no difference in RSS.[58] Potassium citrate often is recommended for decreasing the risk of CaOx urolithiasis by alkalinizing urine and increasing urine citraturia. This strategy has not been supported by one study in dogs, however.[59] In conclusion, the importance of urine pH to manage CaOx remains to be further defined.

Calcium Phosphate

When calcium phosphate uroliths occur as a minor component of calcium oxalate or struvite stones, the management should be directed towards the original urolith (nidus). Pure calcium phosphate stones are associated with metabolic disorders leading to hypercalciuria (e.g., hypercalcemia, hyperparathyroidism; see ch. 297) and/or alkaline urine pH (e.g., renal tubular acidosis; see ch. 326).[60] These uroliths are not amenable to medical dissolution. Treating the underlying cause should be the first step to reduce the risk of recurrence. Diet should promote urine dilution, contain a controlled amount of calcium, phosphorus, and vitamin D, and induce a moderately acidic urine pH.

Urate

Dietary management of urate uroliths focuses primarily on preventing recurrent episodes in susceptible dogs (SLC2A9 mutation, portosystemic shunt) and cats. Medical dissolution only has been reported in Dalmatians (see ch. 326).[61] As for other uroliths, urine dilution by promoting water intake should be the first step. In dogs with uncorrected portosystemic shunts and hepatic encephalopathy, a diet designed for liver disease may be advised (see ch. 284).

Urinary urate results from the catabolism of endogenous or dietary purines. Altering the purine content of the diet is effective to decrease urinary purine metabolite excretion.[62] Very low protein diets have been recommended to reduce 24-hour urinary excretion of uric acid.[63,64] However, the purine content of proteins varies (it is high in organ meats and in fish, for example). By using selected protein sources, severe restriction is not mandatory to achieve low urinary urate concentrations.[62,65] No dietary study has been conducted in cats with urate stones. Diets designed for renal or liver disease, which typically are protein-restricted, currently are recommended. Urate crystals are slightly less soluble in acid urine. Therefore, the diet should not promote acid urine. Finally, allopurinol, which inhibits the conversion of hypoxanthine to uric acid, can be administered to dogs in conjunction with purine-restricted diets to decrease urinary excretion of urate.[66,67]

Xanthine

Xanthine uroliths usually occur secondary to allopurinol use in dogs fed diets high in purines, but also can occur spontaneously. No medical dissolution has been reported. Preventing recurrence of xanthine stones relies on adjustment of allopurinol dosage and a similar but strict dietary strategy as for urate uroliths.

Cystine

Cystine stones can be dissolved, and dietary treatment should be aimed at dissolution and prevention of recurrence (see ch. 331). Again, promoting water intake and urine dilution is of paramount importance. Urinary cystine excretion can be modulated by dietary protein intake, and more specifically methionine and cysteine.[68] Therefore, feeding a diet containing amounts of these essential amino acids close to their minimum requirements is recommended. Most plant protein sources have lower amounts of these sulfur amino acids than do animal proteins. The solubility of cystine is highly dependent on pH, with higher solubility for pH >7.2.[69] Medical treatment with 2-mercaptopropionylglycine (2-MPG) has been successfully used in dogs.[70] In cystinuric dogs, carnitinuria and taurine deficiency have been found[71] and taurine and carnitine are advised to prevent dilated cardiomyopathy, especially if the animal is being fed a diet restricted in their precursor, methionine.

Other

Silica uroliths are uncommon in dogs and cats, and medical dissolution has never been reported. For prevention, emphasis should be put on urine dilution. Preventing pica, avoiding diets high in high-silica plant ingredients (e.g., brown rice or soybean hulls), and offering bottled water in areas with soils high in silica, are recommended. Canned diets, aside from promoting diuresis, typically are lower in vegetable ingredients. The effect of urine pH on silica solubility is unknown.

Practical Implementation of the Dietary Prescription

Prior to dietary prescription, inquiring about the diet history of the patient is important to identify potential dietary risk factors associated with the urolith that is suspected or has been retrieved (see ch. 170). Several commercial prescription diets are available for different uroliths. Wet diets may be preferred for their effect on diuresis. Dry diets with increased sodium or added water are effective alternatives when canned diets are refused. Mixed feeding (dry plus canned) could compromise diuresis; it should be discouraged unless validated by the manufacturer. If homemade diets are chosen, they should be formulated by a veterinary nutritionist and be high in moisture. Treats should not exceed 10% of the daily calories, and should not interfere with the dietary strategy. Fruits and vegetables generally are low in purines. Rawhide chew treats can contain high amounts of oxalate precursors.

Feline Idiopathic Cystitis

Feline idiopathic cystitis (FIC) currently is believed to result from abnormal activation of the stress response system (see ch. 334).[72] Most episodes of FIC are self-limiting within 2-7 days. Treatment is aimed at preventing recurrence using a multimodal approach with environmental enrichment, limitation of social stressors, and improved litterbox management.[73] Diet is part of this multimodal approach. Based on limited evidence, wet diets have been recommended for their effect on diuresis, as diluted urine might be less irritating to the mucosa.[74,75] Oral glycosaminoglycans have been tested, with no benefit.[76,77] A commercial prescription diet decreased the incidence rate of some LUTD signs compared to a control diet differing in several nutrients, although there was no difference in the proportion of relapsing cats over a 1-year period.[78] A casein hydrolyzate (alpha-casozepine), shown to decrease anxiety-related behaviors in cats,[79] might be useful, but studies are needed.

Summary

Diet is a fundamental aspect of the medical management of LUTD in dogs and cats. Promoting water intake and urine dilution is a common management feature regardless of etiology. The management of some uroliths (struvite, urate, cystine) relies strongly on a specific dietary profile. Success of dietary management requires proper identification of the urolith, the management of metabolic disturbances, and owner compliance with feeding the recommended diet.

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CHAPTER 186

Nutritional Management of Dermatologic Disease

Manon Paradis

Client Information Sheet: Nutritional Management of Food Allergy

Nutrition has a fundamental role in the prevention and management of several dermatologic disorders.[1-3] This chapter will discuss the following three distinct areas: (1) food hypersensitivity (cutaneous adverse food reaction); (2) nutritional deficiencies; and (3) nutritional supplementation for the management of skin diseases.

Food Hypersensitivity[4-13]

The development of hypersensitivity to one or more food ingredients in the diet can cause skin or gastrointestinal disorders or both.[14,15] Pruritus is the most frequently observed presenting dermatologic sign, which can be accompanied by subsequent self-inflicted lesions (e.g., alopecia, excoriation, erythema). Allergic otitis externa is a common feature of food hypersensitivity in dogs and sometimes is the only clinical manifestation. Food hypersensitivity can mimic other allergic conditions such as atopic dermatitis[16] or flea allergy dermatitis, and the clinical picture can be complicated further by the presence of these disorders concurrently, as well as with secondary pyoderma or *Malassezia* dermatitis. In cats, food hypersensitivity can present as self-inflicted symmetrical alopecia, excoriations (particularly involving the head and neck), miliary dermatitis, and eosinophilic plaques (see ch. 10 and 191).

Diagnosis of Food Hypersensitivity[17-19]

An elimination diet trial, which involves feeding a home-cooked or a commercial "hypoallergenic" diet exclusively, usually for a period of up to 8 to 10 weeks, is the most important and only reliable diagnostic test to diagnose or exclude food hypersensitivity. Other tests such as intradermal skin testing with food antigens, skin patch testing, and measuring food allergen-specific serum IgE concentrations are of no diagnostic value because of their low sensitivity and specificity.[20]

Before considering initiating an elimination diet trial, it is of outmost importance to first exclude ectoparasites (e.g, fleas, lice, *Sarcoptes, Cheyletiella, Otodectes*) and bacterial and yeast infections as potential causes of pruritus. Usually, the food trial is conducted only if residual pruritus persists after parasitic and infectious causes of pruritus have been excluded or controlled.

Feeding the Elimination Diet

The gold standard for diagnosing food hypersensitivity is to feed the patient nothing but a home-cooked elimination diet containing a novel protein and carbohydrate source for up to 8 to 10 weeks. The food ingredients chosen for the elimination diet trial should be based on the known past exposure of the patient to various foods, avoiding dietary protein and carbohydrate sources to which the patient has been exposed. Because ingested animal proteins often are incriminated as the offending allergen and because of possible cross-reactivity among various meat sources, lentils, kidney beans, or other legumes could be a more suitable protein source for home-cooked diet trials in dogs. Conversely, only a novel animal protein source is sometimes used in cats. Usually, it is not recommended to add supplements (e.g., essential fatty acid [EFA], vitamins, minerals) during the elimination trial since they could be potential sources of allergens (e.g., fish oil, gelatin capsule), and because of the fixed duration of the trial. Home-cooked diets, although incomplete and unbalanced, can be used safely for the diagnostic phase in most otherwise healthy adult pets. Commercial "hypoallergenic diets" containing a hydrolyzed or a novel protein source offer convenience and they are

guaranteed to be nutritionally complete and balanced.[21-24] However, they are not as reliable as home-cooked elimination diets: up to 25% failure rates have been reported, due to presence of preservatives, dye, processing agents, only partially hydrolysed proteins, and/or cross-contamination in processing plants with proteins and carbohydrates not even listed on the pet food label.[25] Another frequent reason for failure of dietary trials is lack of client compliance, which can be avoided with adequate client education.

The trial diet should be introduced gradually over a few days. No other food sources should be given (no treats, bones, table scraps, chew toys with flavoring; glucosamine, vitamins, omega-3 EFAs, oral flavored heartworm preventatives,[26] flavored toothpaste, etc.). Improvement of clinical signs usually is observed within 4 weeks but may take up to 12 weeks for complete resolution in some cats (e.g., eosinophilic plaques).

Dietary Provocation Test (Food Challenge)

If resolution or a substantial decrease in pruritus level is observed during the course of the elimination diet trial, the patient must be rechallenged with all the original dietary components at the end of the trial to confirm the diagnosis of food hypersensitivity. This is to ensure that improvement over this length of time was not only coincidental (e.g., change of season, concurrent new treatments). Recurrence of pruritus within 2 weeks (as early as 15 minutes post-ingestion, and usually within one week) should occur in cases of food hypersensitivity. The diagnosis of food hypersensitivity is confirmed only if pruritus relapses upon challenge with the original diet and subsides again on re-introduction of the elimination diet.

Identifying the Offending Dietary Ingredients[27,28]

Normally, this is done once the patient is fed a suitable commercial hypoallergenic diet and the pruritus is in remission. One food ingredient which is most likely to be the cause of food hypersensitivity (e.g., beef, chicken, dairy, wheat, egg, soy, corn) is introduced and given for a period of two weeks or until pruritus is noted. If the patient eats this food item for 2 weeks with no adverse effect, he/she is not allergic to that ingredient and should be able to consume it without a problem. However, if the patient develops clinical signs on a challenge food item, the owner should avoid giving that food item in the future. The patient should then be fed only with the suitable commercial hypoallergenic diet until the signs have resolved before repeating this process with other suspected ingredients.

Long-Term Management of Food Hypersensitivity[17,21,29]

Long-term nutritional management of food hypersensitivity usually relies on feeding the allergic patient with a diet that is palatable, complete and balanced, and that does not contain the offending allergen(s). This is usually accomplished by feeding a commercial "hypoallergenic diet" tolerated by the patient. Occasionally, once the offending food item(s) is/are identified, it is possible to feed a standard commercial diet that the patient tolerates. Home-cooked diets generally are not recommended for long-term maintenance because they are inconvenient for many owners and need to be supplemented to be complete and balanced. If a home-cooked diet is chosen (because of unavailability of a suitable commercial diet or owner's preference) it is essential that the diet be properly balanced (see ch. 192).

Prognosis of Food Hypersensitivity

The prognosis for animals with food hypersensitivity is generally very good if it is possible to achieve strict avoidance of the food item(s) to which the patient has been shown to be allergic. If there is recurrence or recrudescence of pruritus on a maintenance hypoallergenic diet, one must consider lack of long-term compliance, change in the commercial diet formulation, recent sensitization to the novel food item, or a possible recurrence of a bacterial or yeast skin infection or ectoparasite infestation. Conversely, spontaneous resolution of food hypersensitivity is possible, but it is not known how commonly, or when, it might occur.

Nutritional Deficiencies

The skin is a large organ with high nutritional requirements and diet is crucial in providing nutrients to maintain epidermal integrity and optimize skin healing. Many systemic nutrient deficiencies (e.g., protein, EFAs, zinc, vitamin A, vitamin B) can be associated with dermatopathies[30,31]; however, most produce a similar range of dermatologic clinical signs that can become evident only after feeding a deficient diet for several months. Signs usually are nonspecific and include excessive scaling, erythema, alopecia or poor hair

growth, and greasy skin, which can be accompanied by secondary pyoderma and pruritus.

Dermatologic conditions that occur as a result of nutritional deficiencies currently are rare in developed countries because most dogs and cats are fed complete and balanced commercial diets that meet their nutritional needs. Nonetheless, prolonged or inappropriate storage of the diet (e.g., fatty acid [FA] oxidation), and injudicious oversupplementation (e.g., zinc deficiency following excessive calcium supplementation) can be responsible for nutritional deficiencies (see ch. 167). In addition, with the recent trend of feeding unconventional diets (e.g., raw, home-cooked, or vegetarian diets) it is likely that dermatoses associated with incomplete and unbalanced diets will emerge (see ch. 192). When nutritional deficiency is suspected, it is usually recommended to change the diet to one that is well formulated and has been stored properly rather than to attempt to correct a deficiency by adding FAs and vitamins.

Despite the feeding of an adequate diet, nutritional deficiencies occasionally can arise in animals with chronic gastrointestinal disease (e.g., maldigestion and malabsorption), metabolic disease (e.g., superficial necrolytic dermatitis), and genetic factors (e.g., impaired zinc absorption in Siberian Huskies and Alaskan Malamutes).

There are two syndromes of zinc-responsive dermatosis in the dog.[30,32] Syndrome I predominantly is seen in Arctic breeds, and syndrome II is seen in rapidly growing puppies, often fed poor-quality dog food. Both syndromes present with adherent scaling around the mouth, chin, eyes, pinnae, and foot pads. Dogs with syndrome I require oral zinc supplementation (together with dietary correction, where appropriate), while dogs with syndrome II require a better diet.

Superficial necrolytic dermatitis (also called metabolic epidermal necrolysis and hepatocutaneous syndrome) is a rare disease seen in older dogs in which nutritional deficiencies (e.g., hypoaminoacidemia and possibly deficiency in EFA and zinc) are associated with systemic metabolic disturbances often resulting from hepatic disease.[33] Palliative nutritional management (e.g., feeding of egg yolks, zinc, and EFA supplements) or intravenous amino acid infusions can be of some benefit (see ch. 10, 180, and 285).

Nutritional Supplementation for the Management of Skin Diseases

Nutritional supplements given at supraphysiologic levels have been recommended for the management of several skin diseases.[34-37] Much interest has been paid to the therapeutic value of EFA in the management of canine atopic dermatitis.[38-40] High levels of omega-3 (n-3) FA typically are used for controlling inflammation, and omega-6 (n-6) FA to promote a healthy epidermal barrier. Although there is some evidence that supplements containing n-3 FA and diets enriched with n-3 FA do provide some clinical benefits in the management of atopic dermatitis,[34] the magnitude of these benefits still is poorly documented. It is still unknown if alpha-linolenic acid (ALA, from flaxseeds) is as useful as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both found mainly in cold-water fish. Moreover, there is an ongoing debate as to whether the ratio of n-6 to n-3 FA in food, or an absolute dosage of n-3, is more important in modulating inflammation. Typically, supplementation with EPA 40-50 mg/kg PO q 24 h is recommended. It may take 8-12 weeks to observe a reduction in pruritus (varying from 0 to 40%). Omega-3 treatment often is used in an attempt to reduce the maintenance dosage of glucocorticoid or cyclosporine in atopic dogs (see ch. 164 and 165).[41]

Major pet food companies have formulated prescription diets for the management of canine skin diseases, particularly for atopic dermatitis. Various micronutrients or cofactors are added in addition to high levels of n-3 FA to support the epidermal barrier and immune function. However, their benefits largely are anecdotal, and controlled studies are needed to support these claims. Of note, canine diets specifically formulated to improve joint health and mobility often contain more n-3 FA (e.g., Hill's Prescription Diet j/d Canine Mobility) than those designed for skin health.

Supplements containing n-3 and n-6 FAs (or diets enriched with n-3 and n-6 FAs) also could be of some benefit to dogs with symmetric lupoid onychodystrophy (symmetric lupoid onychitis).[35,42]

Supraphysiologic doses of *natural vitamin A* (800-1,000 IU/kg/day), in lieu of the more expensive synthetic retinoids (e.g., isotretinoin, acitretin), are recommended for the treatment of some cornification disorders such as sebaceous adenitis, ichthyosis, and comedones in hairless canine breeds, as well as in actinic dermatitis, infundibular keratinizing acanthomas, epitheliotropic T-cell lymphoma, and squamous cell carcinoma. Supraphysiologic doses of *niacinamide* (vitamin B_3), usually in combination with tetracycline (or doxycycline) or *vitamin E*, are used for their antiinflammatory and immunostimulatory effects in several immune-mediated skin disorders (e.g., discoid lupus erythematosus, lupoid onychodystrophy, dermatomyositis) with variable effects. Supraphysiologic doses of *zinc* are required in Siberian Husky and Alaskan Malamutes suffering from

zinc-responsive dermatosis syndrome I.

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CHAPTER 187

Nutrition-Related Skeletal Disorders

Ronald Jan Corbee

Client Information Sheet: Nutrition-Related Skeletal Disorders

Introduction

Nutrition-related skeletal disorders include conditions related to imbalances of key nutrients (calcium, phosphorus, vitamin A, and vitamin D), as well as imbalances caused by over-nutrition (i.e., obesity aggravates osteoarthritis; see also ch. 176). Nutritional imbalances can affect the skeleton of dogs and cats of any age but are most detrimental in growing animals because of the higher bone turnover rate in young animals. Furthermore, the incidence of developmental orthopedic disease (DOD; including a diverse group of musculoskeletal disorders that occur in growing animals, most commonly fast-growing large- and giant-breed dogs with an adult weight >25 kg) may be enhanced by dietary imbalances. Understanding the role of nutrition in the pathophysiology of these diseases facilitates prevention, diagnosis, and treatment (see ch. 353 for a medical description of skeletal disorders).

Calcium Metabolism

Although more than 99% of total body calcium (Ca) is stored in the skeleton, it is the extracellular fluid (plasma) calcium concentration ($[Ca^{2+}]$) that is critical for a multitude of cellular, contractive, and enzymatic processes (see also ch. 69 and 297). As a result, plasma $[Ca^{2+}]$ is tightly controlled by a complex homeostatic mechanism involving fluxes of calcium between the extracellular fluid and kidney, bone, and gut. Three major hormones—parathyroid hormone (PTH), calcitonin, and 1,25-dihydroxyvitamin D ($1,25[OH]_2D$)—regulate the influx and efflux of calcium.[1] Increased plasma $[Ca^{2+}]$ inhibits PTH secretion and stimulates calcitonin secretion. The primary function of calcitonin is to prevent increased plasma $[Ca^{2+}]$. This will be achieved by the actions of calcitonin: stimulation of Ca transport to cell organelles, storage of Ca in the labile Ca pool of bone, and increased glomerular Ca excretion.[2]

Decreased plasma $[Ca^{2+}]$ stimulates PTH secretion. The primary function of PTH is to increase plasma $[Ca^{2+}]$ to the normal level. This will be achieved by the actions of PTH: increased mobilization of Ca (and P) from bone, increased renal reabsorption of Ca from the glomerular filtrate, increased urinary P excretion, and stimulation of the conversion of 25-hydroxyvitamin D into $1,25[OH]_2D$. The primary function of $1,25[OH]_2D$ is to mineralize newly formed osteoid and cartilage from the growth plate. This will be achieved by the actions of $1,25[OH]_2D$: increased mobilization of Ca (and P) from bone, increased renal reabsorption of Ca (and P) from the glomerular filtrate, increased absorption of Ca (and P) from the gastrointestinal tract, and finally mineralization of newly formed osteoid and cartilage from the growth plate with the released Ca and P. Furthermore, $1,25[OH]_2D$ inhibits PTH secretion, providing the negative feedback mechanism[3,4] (Figure 187-1).

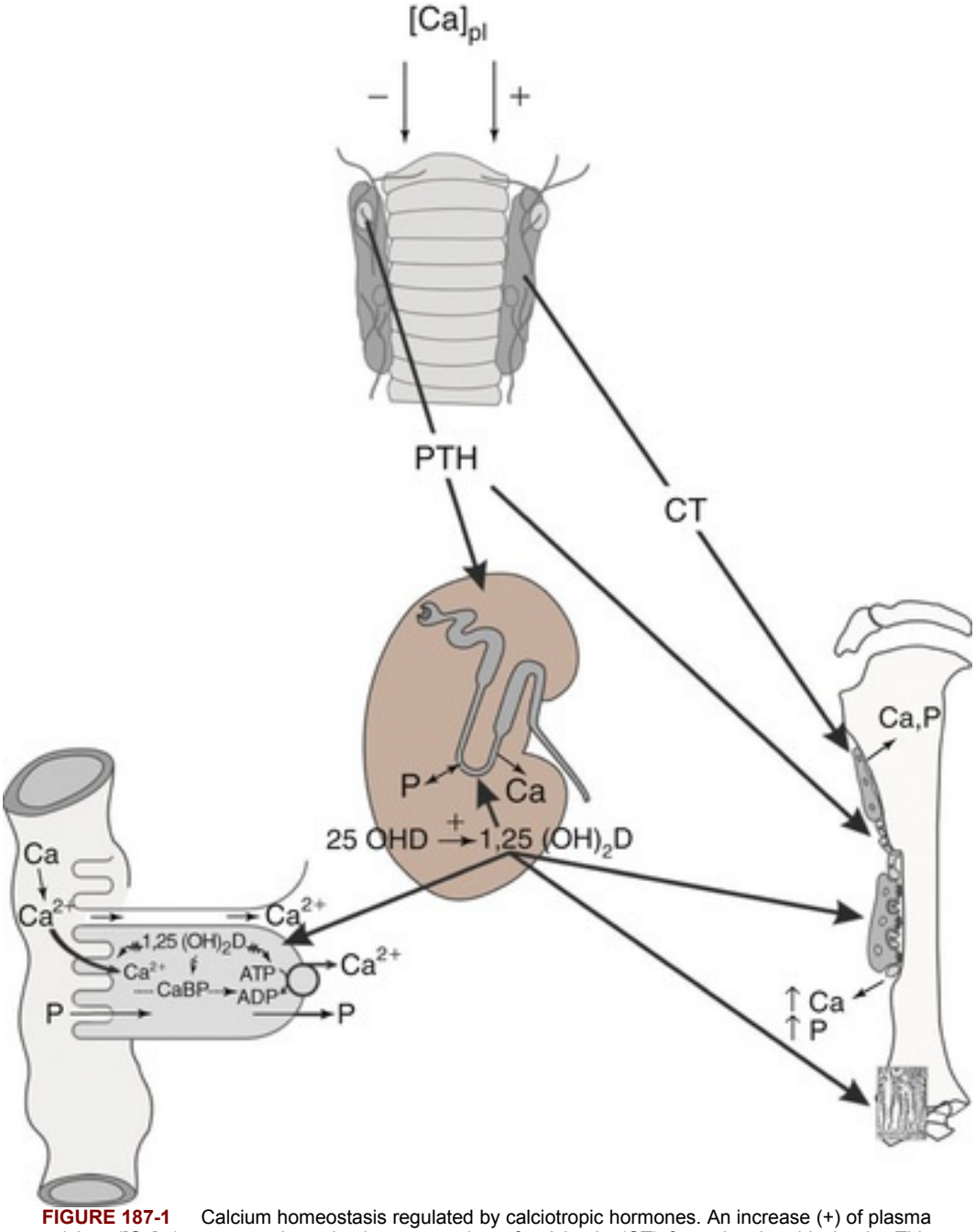


FIGURE 187-1 Calcium homeostasis regulated by calciotropic hormones. An increase (+) of plasma calcium ($[Ca]_{pl}$) concentration stimulates secretion of calcitonin (CT) from the thyroid glands. This enhances renal excretion and inhibits bone resorption of calcium, which in the long term will disturb skeletal remodelling and endochondral ossification. A decrease (−) of $[Ca]_{pl}$ stimulates parathyroid hormone (PTH) secretion from the parathyroid glands, causing (1) shrinkage of osteoblasts, allowing osteoclasts to resorb bone, and (2) increased reabsorption of Ca and excretion of phosphorus (P) and increased formation of $1,25[OH]_2D$ in the kidney. As a result of the latter, active absorption of Ca and P is increased, renal Ca and P reabsorption is increased, and mineralization of newly formed osteoid and cartilage is stimulated.

Nutritional Secondary Hyperparathyroidism

Nutritional secondary hyperparathyroidism occurs when chronic insufficient Ca intake or absorption stimulates continuous PTH secretion.

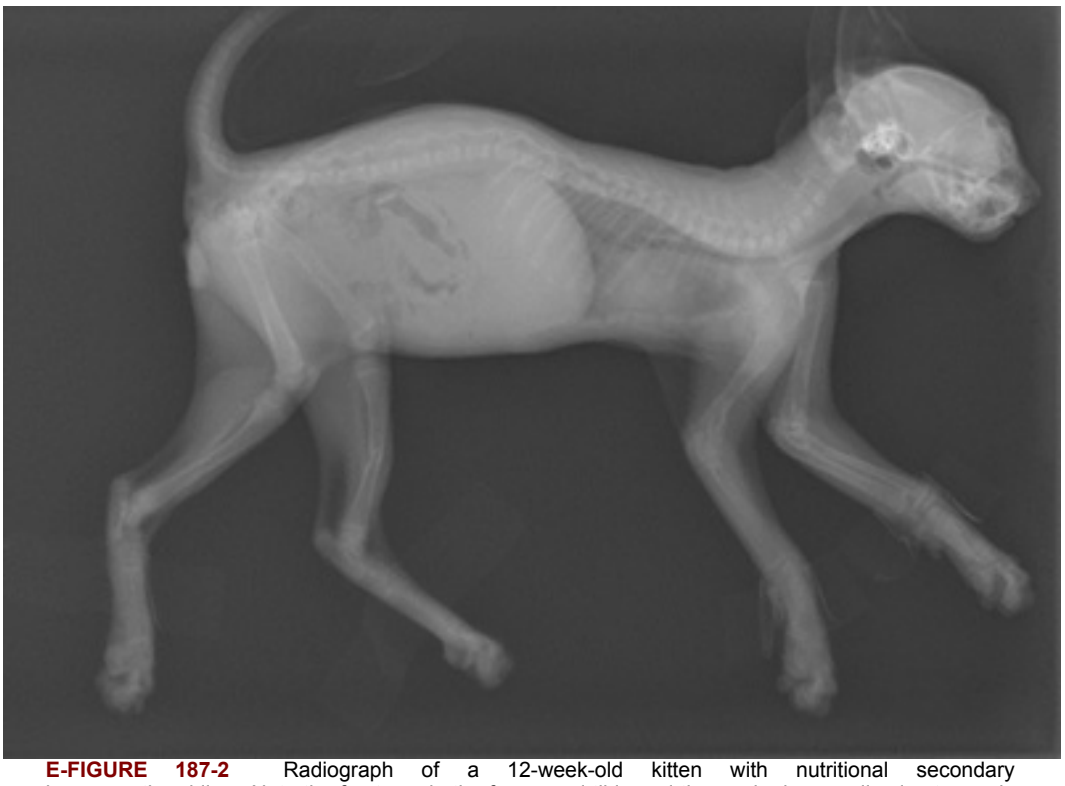
If increased Ca absorption in the intestine is insufficient to meet daily requirements, Ca will be resorbed at the endosteal surface of the diaphyses and in the areas of cancellous bone. In addition to chronic inadequate

Ca intake, excessive phosphorus (P) intake coupled with inadequate calcium intake may result in nutritional secondary hyperparathyroidism. The excess phosphorus reduces the ionized calcium concentration in serum via mass action equilibrium, resulting in hyper-secretion of PTH. Excessive osteoclasia and pathologic fractures of growing bone are the results of long-term hyperparathyroidism. Mineralization of osteoid and cartilage will be undisturbed, resulting in normal-width growth plates.[5,6]

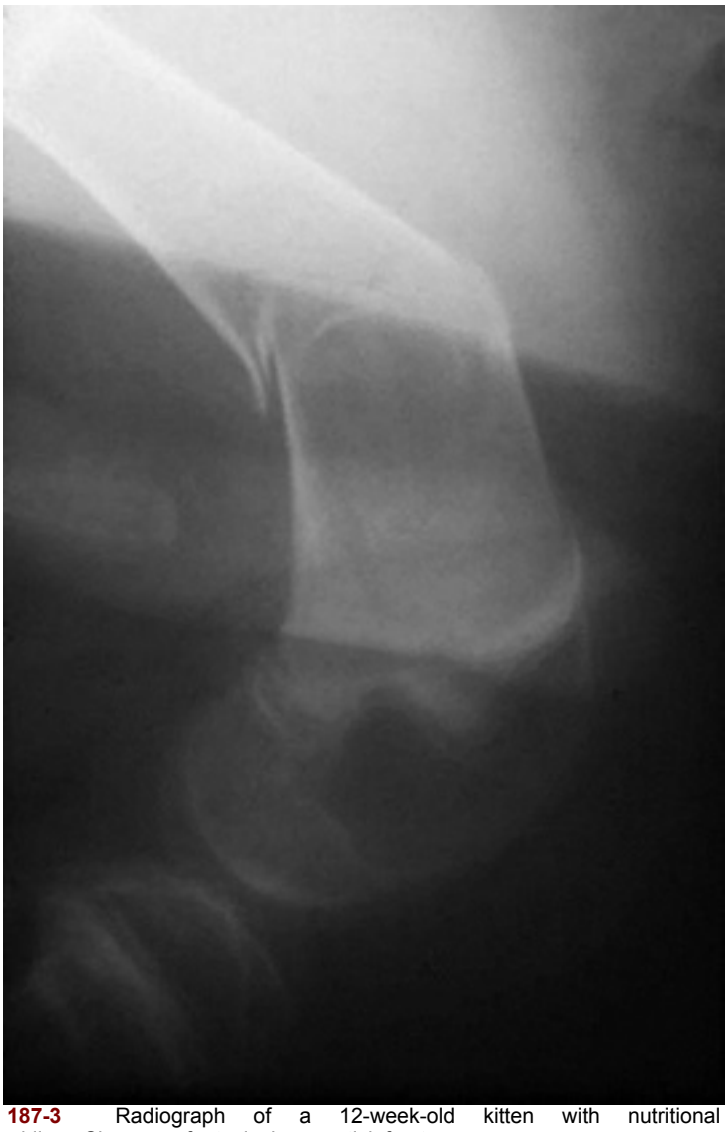
Clinical and Radiographic Examination

Although animals of any age can be affected, most animals with nutritional secondary hyperparathyroidism are young individuals eating foods deficient in Ca.[7] For example, animals fed improperly formulated homemade foods or all-meat diets may receive insufficient calcium and/or excessive phosphorus (see ch. 192). Clinical signs may include reluctance to move and play, lameness, uncoordinated gait, sternal recumbency, loose teeth, and painful mastication.

Blood calcium concentrations are generally within normal limits although such values can, uncommonly, be decreased. Increases in serum PTH and 1,25$[OH]_2$D concentrations can be detected[4,6] (see Figure 187-1). Radiographs may reveal thin cortices, wide medullary cavities, folding (greenstick) fractures, normal width of growth plates with relatively white metaphyseal borders, as well as compression fractures of cancellous bone of epiphyses and vertebrae[5,6] (E-Figures 187-2 and 187-3).



E-FIGURE 187-2 Radiograph of a 12-week-old kitten with nutritional secondary hyperparathyroidism. Note the fractures in the femur and tibia and the marked generalized osteopenia (thin cortices).



E-FIGURE 187-3 Radiograph of a 12-week-old kitten with nutritional secondary hyperparathyroidism. Close-up of a typical greenstick fracture.

Differential Diagnosis

Rule-outs for radiographic abnormalities and pathologic fractures include nutritional secondary hyperparathyroidism and inborn errors of metabolism that include osteogenesis imperfecta, mucopolysaccharidosis, and other rare diseases (Figure 187-4). Hyperparathyroidism may be primary or secondary (i.e., nutritional or renal). Chronic Ca deficiency may be complicated by vitamin D deficiency if all-meat diets are the sole food source.

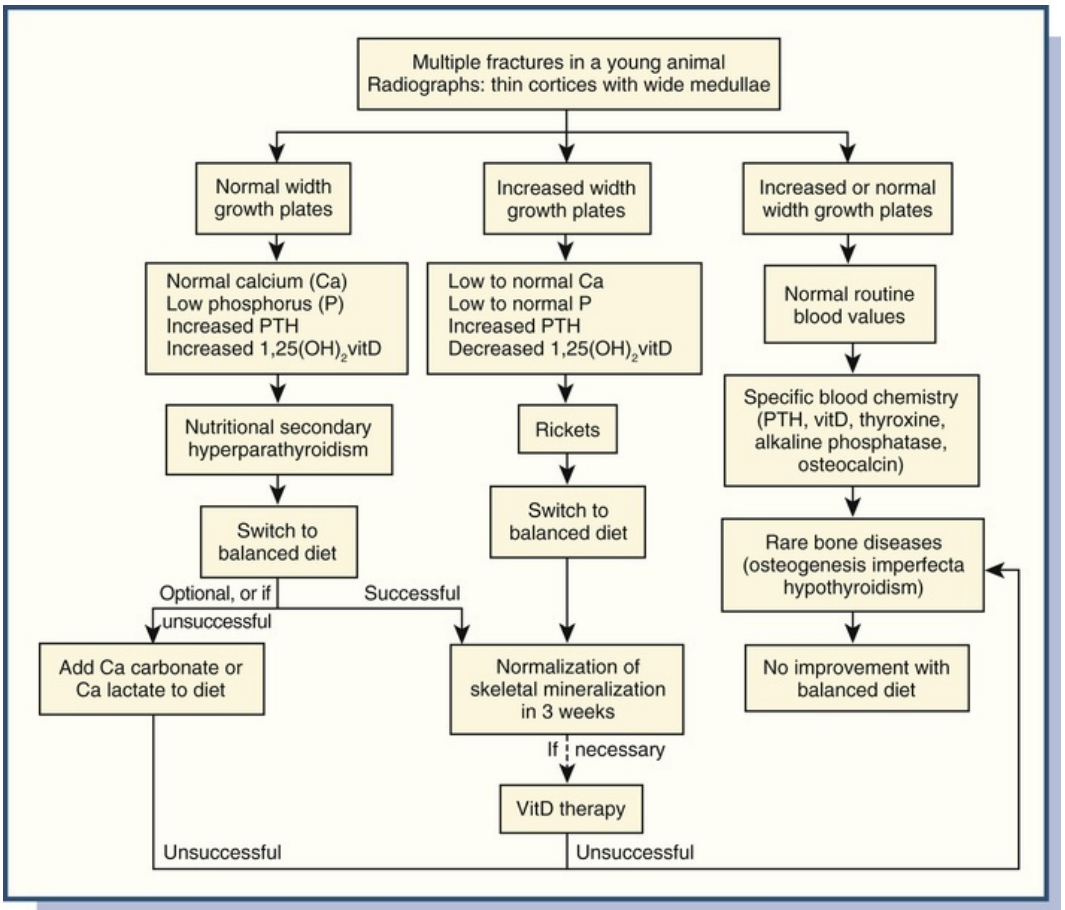


FIGURE 187-4 An algorithm for multiple pathologic fractures in young dogs and cats. *PTH*, Parathyroid hormone; *vitD*, vitamin D.

Therapy

Correction of the diet includes utilizing a commercially available, complete and balanced dog or cat food. The absolute amount of calcium in the food is more important than the calcium-phosphorus ratio in young growing dogs.[8,9] Foods should provide 0.8% to 1.2% dry matter (DM) (or 0.5 to 0.7g/MJ) calcium and the calcium-phosphorus ratio should be kept within physiologic limits (1.1 : 1 to 2 : 1). It is preferred to have the ratio 1.2 : 1.[10] Improved mineralization of the skeleton should be evident in 3 to 4 weeks, because almost 100% of the ingested Ca will be resorbed due to the hyperparathyroid-induced high $1,25[OH]_2D$ levels.[4] During this time it is important to prevent more pathologic fractures, especially of the vertebrae, by reduced handling and cage rest, as the skeleton is too weak for bandages, splints or implants. Non-steroidal anti-inflammatory drugs should be prescribed for proper pain management (see ch. 126, 164, and 356). Supplementing Ca as Ca carbonate or Ca lactate (and not Ca phosphate or bone meal) at 50 mg Ca/kg body weight (BW) may accelerate osteoid mineralization, but correcting the diet is usually sufficient. Corrective osteotomies can be planned, if necessary, after the skeleton is normally mineralized. Even pets with compression fractures of the spinal cord may have a full recovery.

Rickets

Since dogs and cats are not capable of synthesizing vitamin D under the influence of UVB light, they require a source of this essential vitamin (hormone) in their food.[2,5] Vitamin D is absorbed in the small intestine by bile salt–dependent passive diffusion. It is then transported to the liver, where it is hydroxylated into 25-hydroxyvitamin D.[2] A second hydroxylation takes place in the kidney, either to 24,25-dihydroxyvitamin D or to $1,25[OH]_2D$.[2] Both metabolites are necessary for osteoid and cartilage mineralization.[2] Rickets is characterized by defective mineralization of newly formed bone and cartilage as well as metaphyseal

thickening.[5,11] *Rickets* is the term used to describe hypovitaminosis D in young animals; in adults it is referred to as *osteomalacia.* Hypovitaminosis D arises most commonly from inadequate intake of vitamin D, but rickets lesions can also occur secondary to decreased phosphorus intake or by an abnormal calcium-to-phosphorus ratio.[12-14] Additionally, rickets can occur despite normal vitamin D intake if intake of calcium is excessive at an early age (≈3 weeks of life). This causes hypercalcemia, secondary hypoparathyroidism, and tertiary decreased 1,25$[OH]_2$D formation.[6,13]

Clinical and Radiographic Examination

A thorough dietary history is critical. Since commercial pet foods contain 2 to 10 times the Association of American Feed Control Officials (AAFCO) minimum recommended amounts of vitamin D, rickets is generally only seen in animals fed improperly formulated homemade foods such as un-supplemented strict vegetarian foods (see ch. 192). It can also occur in animals with biliary atresia or inborn errors of vitamin D metabolism.[15-19] Radiographs demonstrate thin long-bone cortices and extremely thickened growth plates. Increased growth plate width is not associated with low-calcium/high-phosphorus foods but is a strong indicator of rickets. Despite hyperparathyroidism, plasma $[Ca^{2+}]$ and phosphorus can be normal or low normal. Diagnosis of vitamin D deficiency can be made by measuring the circulating levels of vitamin D metabolites. In rickets, levels of 1,25$[OH]_2$D will be decreased, whereas in nutritional or renal secondary hypoparathyroidism 1,25$[OH]_2$D will be increased.[2,15]

Treatment

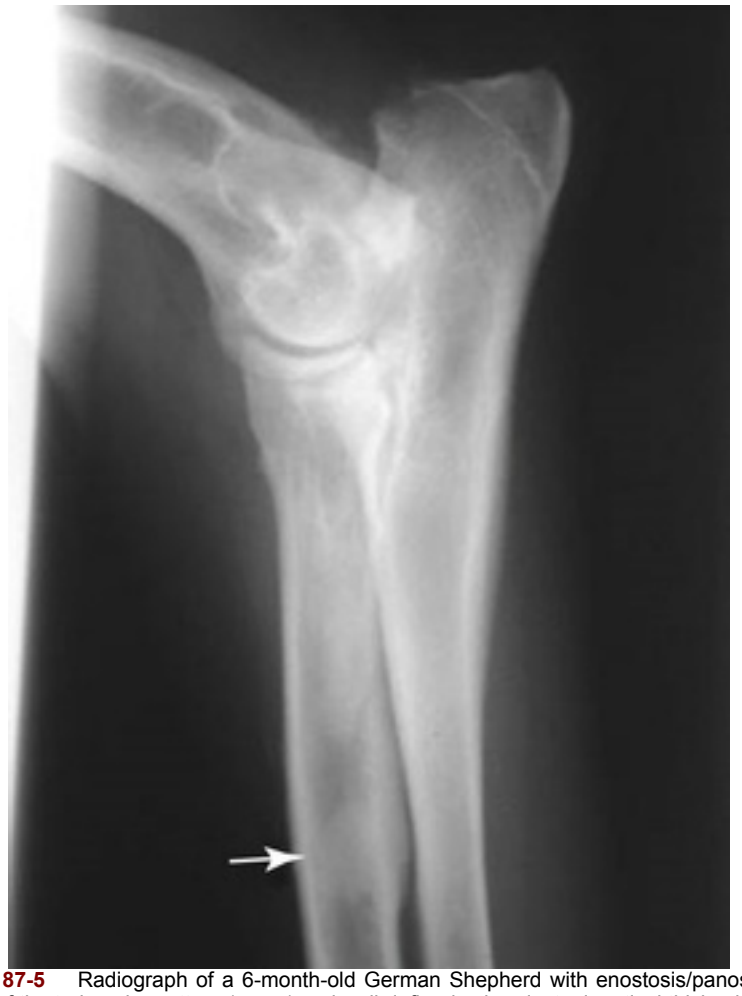
Transition to a nutritionally balanced commercial dog or cat food is generally sufficient to resolve rickets. Mineralization of bone cortices, callus, and growth plates will occur within 3 weeks. If the dog or cat fails to respond to a balanced diet, vitamin D therapy can be recommended.

Panosteitis (Enostosis, Eosinophilic Panosteitis)

High Ca intake in young dogs leads to hyperplasia of calcitonin-producing cells in the thyroid gland. This results in reduced osteoclastic activity, which can last even months after an episode of high Ca intake (see Figure 187-1).[20] In immature dogs, a large blood supply to the metaphyseal area (bordering the growth plates) exists. This network of arteriolae receives blood from branches on the periosteal side and the medullary arteries. The latter enter the bone mainly via the nutrient foramen. The direction of efferent blood flow is through the diaphyseal cortex and runs through rigid bone canals. For the widening of these canals in the growing bone, osteoclastic activity is necessary. Due to hypercalcitoninism, the canals cannot be widened, resulting in edema. This edema may also be present underneath the periosteum and thus makes the periosteum painful in response to pressure or muscle activity. So far, no causes other than high Ca intake have been demonstrated.[21]

Clinical and Radiographic Examination

Panosteitis is mainly seen in medium and large-breed dogs (especially German Shepherd Dogs), starting at 6 months of age, with a sudden onset of shifting lameness showing pain reaction on deep palpation of the long bones. Radiographs demonstrate a blurring of the trabecular pattern and well-defined subperiosteal cortical thickening can be noticed (E-Figure 187-5).



E-FIGURE 187-5 Radiograph of a 6-month-old German Shepherd with enostosis/panosteitis. Note the blurring of the trabecular pattern (arrow) and well-defined subperiosteal cortical thickening.

Therapy

Because the disease is self-limiting and is not diagnosed in dogs over 22 months of age, treatment is limited to administration of non-steroidal anti-inflammatory drugs (see ch. 164), and adaptation of the diet. Dietary treatment consists of a reduced Ca intake by feeding a diet that is close to the minimum Ca requirements, and by feeding an amount of food that is necessary to maintain ideal body condition.

Carpal Laxity Syndrome

Carpal laxity syndrome (CLS) describes hypo-extension, hyperextension, or hyperflexion of the carpal joint. It is mostly diagnosed in male, medium- to giant-breed dogs at the age of 10 weeks (mostly 6-12 weeks).[22] Feeding of a deficient diet and/or excessive food intake are thought to be the cause of CLS, as this results in rapid weight gain before adequate bone development, in combination with weakness of the ligaments due to decreased collagen synthesis. This decreased collagen synthesis can be caused by copper deficiency, as copper is incorporated in lysyl-oxidase, which is needed for collagen synthesis.[23] CLS is treated by adjusting the diet to a complete and balanced puppy food being fed in amounts to prevent rapid weight gain, as well as exercise on traction surfaces (sand, grass or carpeting), and swimming, providing good muscle traction[24] (see ch. 353 and 355). In severe cases, bandage, splints, tenotomy and/or arthrodesis are indicated. Usually, CLS is self-limiting.

Developmental Orthopedic Disease

The pathogenesis of DOD in the dog is multifactorial, involving genetic susceptibility, environmental

influences, and nutrition. DOD is a common cause of secondary osteoarthritis and degenerative joint disease (DJD) in dogs. Osteoarthritis is the most commonly diagnosed non-traumatic orthopedic condition in dogs, with an estimated 20% prevalence in adults.[25,26] Canine hip dysplasia and osteochondrosis make up the majority of DOD with a nutrition-related etiology. Specific risk factors for DOD in young dogs include: (1) large or giant breeds (genetics) (>25 kg adult weight), (2) free-choice feeding (management), particularly of high-energy foods (nutrition), and (3) excessive intake of calcium and vitamin D from food, treats, and supplements (nutrition).[27-35] The key nutritional factors that contribute to DOD are excesses of calcium and energy.[29] Excessive calcium intake (and subsequent hypercalcitoninism) results in disturbed endochondral ossification, retained cartilaginous cores, and delayed skeletal maturation.[5] Insufficient calcium intake results in weakening of bones due to insufficient Ca for mineralization. Weakened bones are more prone to trauma and disturbances of endochondral ossification, resulting in DOD (e.g., radius-curvus syndrome, canine hip dysplasia and osteochondrosis). Excessive energy intake promotes both rapid growth and obesity, and (often) also results in increased Ca intake.

Canine Hip Dysplasia

Canine hip dysplasia (CHD) is a polygenic disease with complex inheritance. As such, environmental factors such as nutrition and lifestyle have a profound influence on both its incidence and its severity.[36] Excessive energy intake appears to be paramount to the phenotypic expression of CHD in growing and adult dogs (more information in ch. 353). One long-term study of dogs genetically predisposed to CHD documented that prevalence and severity of osteoarthritis/DJD (the phenotypic expression of CHD) is greater in dogs with body condition scores (BCSs; see ch. 2 and 170) above normal.[37] Over their lifespan, the median age of dogs with radiographic evidence of CHD/osteoarthritis was significantly lower (6 years) in overweight versus normal weight dogs (12 years).[36] Additionally, the mean age at which 50% of the dogs required long-term treatment for clinical signs attributable to osteoarthritis was significantly earlier (10.3 years, $p < 0.01$) in the overweight dogs as compared to the dogs with normal BCSs (13.3 years) (see ch. 176).[38]

Osteochondrosis

Osteochondrosis (OC) is common in young, rapidly growing, warm-blooded, domesticated species and man. In all species, the etiology is considered multifactorial. In dogs, risk factors for OC include age, gender, breed, rapid growth, and nutrient excesses (primarily calcium and energy).[29,30,32,33] All large- and giant-breed dogs are at increased risk for OC. However, Great Dane, Labrador Retriever, Newfoundland, and Rottweiler breeds are at greatest risk.[32] Osteochondrosis is a disruption in endochondral ossification that results in a focal lesion but is considered a systemic disease.[39,40] Osteochondrosis occurs in the physis and/or epiphysis of growth cartilage, most commonly in the shoulder, stifle, hock and elbow. Acute inflammatory joint disease (or DJD) may ensue when the cartilage surface is disrupted and subchondral bone is exposed to synovial fluid. Inflammatory mediators and cartilage fragments are released into the joint (osteochondritis dissecans), which perpetuates the cycle of DJD (see ch. 353).[41,42]

Developmental Orthopedic Disease Treatment

To help prevent DOD in a large- to giant-breed puppy (>25 kg adult weight), it is best to feed a commercial food specific for its unique nutrient requirements. The recommended intake of most nutrients in fast growing, large- and giant-breed puppies is similar to that of other breeds. However, it is important to note that the recommendations are more stringent for energy density, dietary fat, calcium, and the calcium-phosphorus ratio (energy density = 3.5 to 4.1 kcal/g, fat = 8.5% to 17% DM, calcium = 0.8% to 1.2% DM [or 2.0-3.0g/1000 kcal, or 0.5 to 0.7g/MJ], Ca : P from 1.1 : 1 to 2 : 1 with lower end of range [1.2 : 1] preferred). Several commercial foods specifically formulated for fast-growing, large- and giant-breed puppies are available (see also ch. 171). It is important to select a food that is most similar to the key nutritional factor benchmarks. To prevent imbalances and excesses, the addition of vitamin or mineral supplements to balanced foods is not recommended. This is particularly true for calcium, phosphorus, vitamin D, and vitamin A. If a nutritionally adequate growth food is being fed, supplementation is contraindicated. The large- to giant-breed puppy should be fed to maintain a BCS between 4/9 and 5/9 (see Figures 170-1 and 170-2). Dietary deficiencies are of minimal concern in this age of commercial foods specifically prepared for young, growing dogs; the major potential for harm results from excess consumption of energy and calcium. A balanced food fed at an

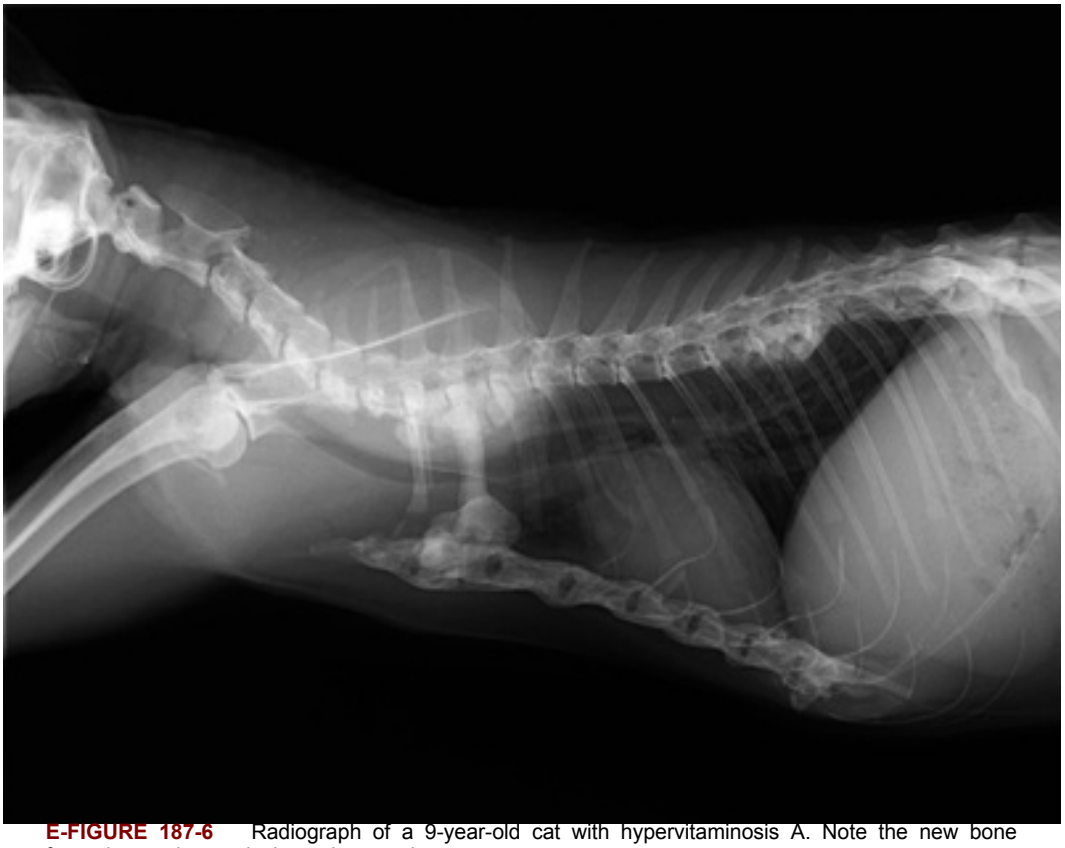
appropriate quantity will help to optimize the conditions of skeletal development and decrease the risk of DOD. When appropriate, surgical correction of underlying conditions should be considered.

Hypervitaminosis A

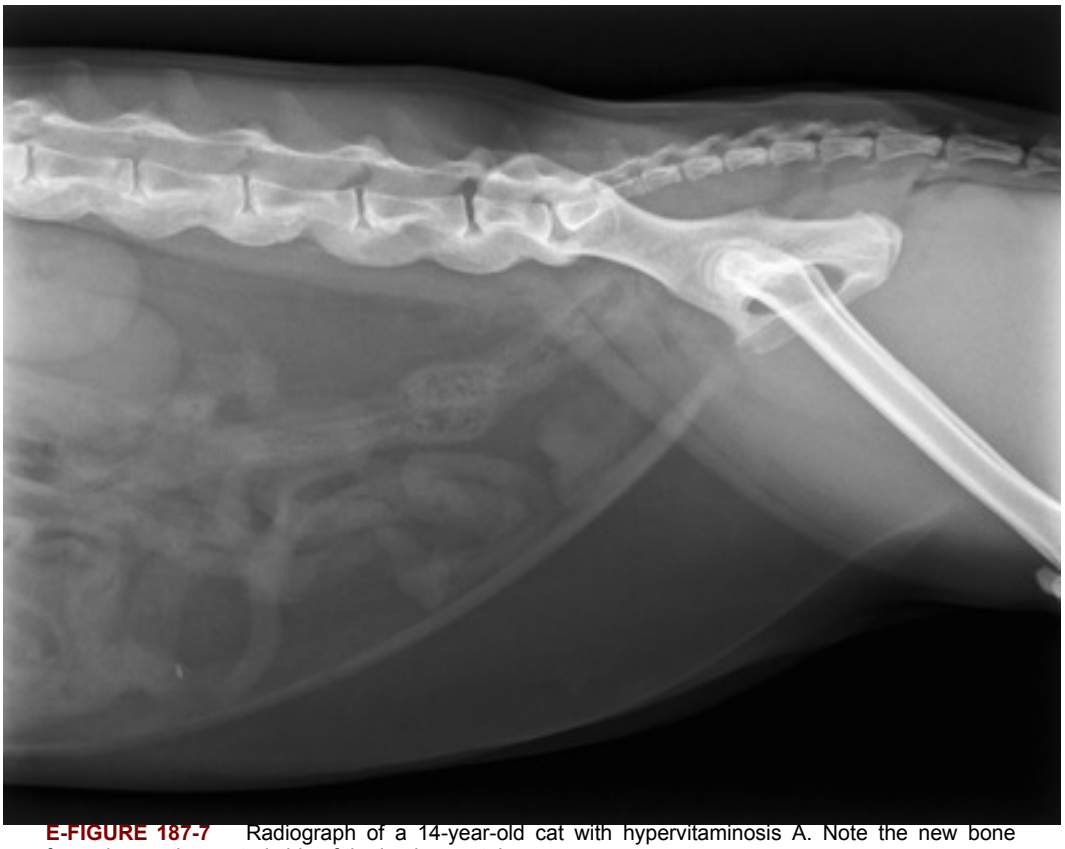
Vitamin A is needed for terminal differentiation and normal function of osteoblasts and osteoclasts. High vitamin A intake in young animals inhibits chondrogenesis in growth plates and inhibits collagen synthesis in osteoblasts in most species causing "hyena disease" due to premature closure of the growth plates. Because cats are unable to excrete large amounts of retinol and retinyl-esters in the urine, cats are more susceptible to hypervitaminosis A. In older cats, hypervitaminosis A is mentioned as a cause of osteoarthritis.[43]

Clinical and Radiographic Examination

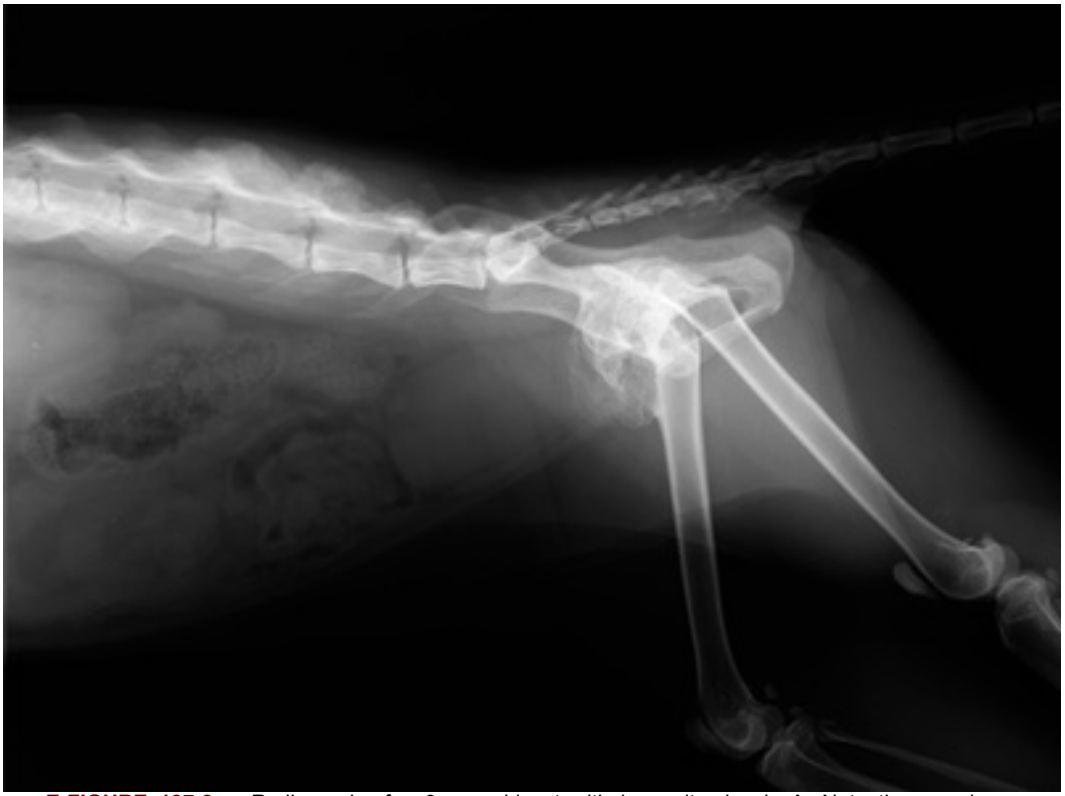
Most cases reporting hypervitaminosis A in cats are due to consumption of large amounts of (pork or beef) liver.[44] In contrast to other species, hypervitaminosis A in cats is characterized by new bone formation without osteolysis, starting at the points of insertion of ligaments, muscles and joint capsules, finally causing ankyloses in vertebrae and large joints which are clearly visible on radiographs (E-Figures 187-6, 187-7, and 187-8). This results in pain, stiffness, and sometimes lameness. Elevated plasma and liver vitamin A concentrations support the diagnosis, as well as characteristic portal-portal bridges, liver fibrosis and swollen hepatic stellate cells seen in liver biopsies.[45]



E-FIGURE 187-6 Radiograph of a 9-year-old cat with hypervitaminosis A. Note the new bone formation on the cervical vertebrae and sternum.



E-FIGURE 187-7 Radiograph of a 14-year-old cat with hypervitaminosis A. Note the new bone formation on the ventral side of the lumbar vertebrae.



E-FIGURE 187-8 Radiograph of a 9-year-old cat with hypervitaminosis A. Note the new bone formation around the hip joint.

Therapy

The ankyloses are irreversible so dietary treatment aims at prevention of further ankyloses by feeding a low vitamin A diet for several weeks followed by a complete and balanced diet for long-term feeding. Supportive treatment consists of administration of nonsteroidal anti-inflammatory drugs (see ch. 164 and 356).

Osteoarthritis Treatment

Once osteoarthritis is diagnosed, the cornerstone of multifaceted therapy is therapeutic nutrition. Nutritional treatment of osteoarthritis should initially focus on weight reduction if the BCS is greater than 5/9 (see ch. 176 and 359). Foods designed for dogs with osteoarthritis should supply age-appropriate nutrition and specific nutrients that may help reduce inflammation and pain, slow the degradation process, complement prescribed medications, and provide tangible improvement in symptoms of osteoarthritis. Clinical studies indicate that nutritional management using a therapeutic food supplemented with n-3 fatty acids helped reduce the clinical signs of osteoarthritis in dogs as noted by pet owners, clinical orthopedic examination, and gait analysis of ground reaction forces.[46-48] Based on these studies, a food designed to aid in the management of osteoarthritis in dogs should provide levels of 0.4% to 1.1% (DM) eicosapentaenoic acid (EPA). Dogs consuming the therapeutic food/supplement should receive an average of 50 to 100 mg EPA/kg body weight (BW) per day. In cats, one study evaluated the effect of a therapeutic diet with EPA, docosahexaenoic acid (DHA), glucosamine, chondroitin sulphate and an extract of green-lipped mussel with naturally occurring osteoarthritis, using clinical signs as well as gait analysis as outcome parameters, demonstrating effectiveness.[49] Another study, performed in client-owned cats with naturally occurring oesteoarthritis, demonstrated effectiveness of an EPA and DHA supplement on clinical signs of osteoarthritis.[50] Based on these studies, a food designed to aid in the management of osteoarthritis in cats should provide levels of 4.5% to 6% (DM) EPA and 1.2% to 3% (DM) DHA. Cats consuming the food/supplement should receive an average of 75 to 100 mg EPA/kg BW per day and 20 to 50 mg DHA/kg BW per day. For other supplements, no clear scientific evidence is currently present. For veterinarians wishing to use glucosamine hydrochloride and chondroitin sulphate, the author suggests a loading dose of 50 mg/kg (body weight) and 40 mg/kg, respectively, followed by a maintenance dosage of 25 mg/kg and 20 mg/kg, respectively. The most recent supplement with promising results in dogs is undenatured type-II collagen from chicken sternum; 10 mg per dog per day demonstrated significant improvement in pain scoring (both observational and by force plate analysis).[51] Apart from dietary treatment, nonsteroidal anti-inflammatory drugs and physical rehabilitation can be prescribed (see ch. 164, 355, and 356). In severe cases, elective surgery may be indicated[52] (Figure 187-9).

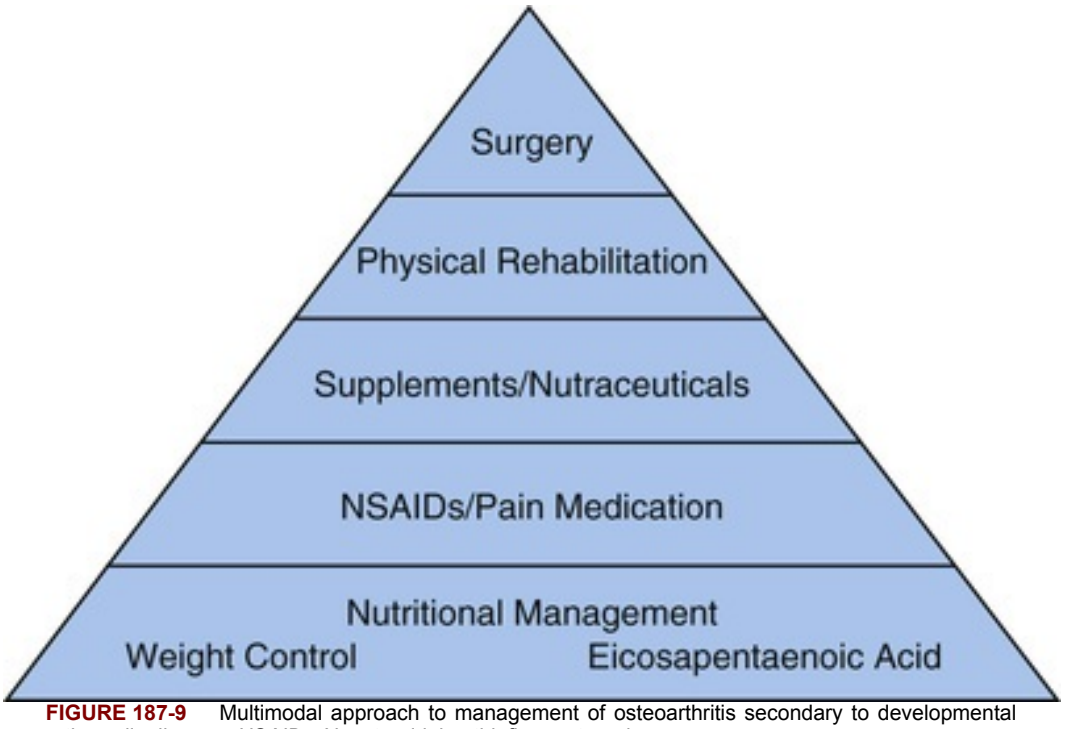


FIGURE 187-9 Multimodal approach to management of osteoarthritis secondary to developmental orthopedic disease. *NSAIDs*, Nonsteroidal anti-inflammatory drugs.

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CHAPTER 188

Nutritional Management of Cancer

Glenna E. Mauldin

Client Information Sheet: Feeding Your Pet That Has Cancer

Cancer-Associated Malnutrition: Cancer Cachexia

"Cancer cachexia" is the complex form of protein-calorie malnutrition classically associated with the tumor-bearing state. It is common in people and also is described in cats and dogs. A recent consensus statement defines cancer cachexia in people as a multifactorial syndrome characterized by loss of >5% of current body weight, or loss of >2% in cases where there is pre-existing depletion. Affected individuals have ongoing loss of skeletal muscle mass, often with concurrent loss of fat stores. Underlying causative metabolic defects have been identified, although decreased food intake as well as functional abnormalities interfering with food digestion or absorption also can play contributory roles. Progressive development of cachexia occurs through stages, from precachexia to cachexia to refractory cachexia, and it is classified based on the degree of depletion of energy stores and lean body mass combined with the severity of ongoing weight loss.[1]

Cancer cachexia is clinically important because it has an independent and negative effect on prognosis. People, cats, and dogs with cancer and concurrent weight loss have increased morbidity and mortality, and poor quality of life. Depletion of lean body mass leads to decreased muscle mass and to weakness. Altered body composition can change drug pharmacokinetics and pharmacodynamics, increasing treatment-related toxicosis and compromising ability to tolerate aggressive therapy. Overall, and regardless of species, individuals with cancer-associated weight loss have shorter survival compared to weight-stable patients with otherwise identical disease.[2-11]

Cancer cachexia is best conceptualized as a paraneoplastic syndrome where energy metabolism is altered by a pronounced systemic inflammatory response: ultimately, consumed calories are used inefficiently and weight loss occurs.[2,12-14] One of the hallmarks of cancer cachexia is that it cannot be reversed simply by increasing food intake.[15] Various cytokines including tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) are implicated in the underlying mechanism, and distinctive biochemical changes such as glucose intolerance, hyperlactatemia, and increased lipolysis are seen in affected individuals.[12-14] Recent work also suggests that chronic inflammation can cause a phenotypic switch from white adipose tissue to brown fat, leading to increased lipid mobilization and energy expenditure.[16,17]

Weight loss appears to be less common in dogs with cancer than it is in people with cancer.[18,19] Although some of the metabolic changes linked with cancer cachexia have been described in dogs with spontaneous tumors,[20-24] a clear association between these changes, weight loss, and outcome is unproven so far; for instance, the most common cause of hyperlactatemia in tumor-bearing dogs is hypoperfusion rather than cancer cachexia.[25,26] Weight loss is relatively more common in cats with cancer, occurring in ≈50% of animals. As would be expected, it has a negative impact on prognosis.[10,11]

Cancer-Associated Malnutrition: Obesity

Despite the traditional correlation between weight loss and cancer, a relationship between obesity and cancer is now widely recognized. Obese people are predisposed to develop cancers including lymphoma and tumors of the esophagus, colon, endometrium, and breast.[27-30] Increased synthesis of factors such as insulin-like growth factor-1, estrogen, and leptin in obesity are believed to promote malignant transformation by stimulating cellular proliferation, as well as through disruption of cellular differentiation and apoptosis. The systemic inflammatory response associated with obesity also might result in an environment that is

permissive for the induction and progression of tumor.[29-33] Only a few studies have examined the relationship between obesity and cancer in cats or dogs,[34] but based on published surveys, 20-30% of dogs with cancer are likely to be overweight or obese.[18,19] While this does not prove a cause-and-effect relationship, links between development of tumor and obesity as well as historical fat intake have been demonstrated among unspayed female dogs with mammary carcinoma.[35-37]

Obesity has a complex impact on cancer prognosis. In many ways, obese individuals with cancer are more difficult to diagnose and treat than their normal-weight counterparts.[30] Diagnoses tend to be made later in the course of disease: physical examinations are difficult to perform, and accuracy of diagnostic tests such as ultrasonography and cross-sectional imaging is compromised. The metabolism of chemotherapeutics can be altered significantly by obesity, and precise dosing is challenging.[38,39] Radiotherapy is more difficult to deliver because of increased mobility of skin and abdominal viscera, and obscured bony landmarks. Finally, obesity increases the likelihood of some types of surgical complications.[40] Some studies show that overweight people with cancer have shorter survival times and higher all-cause, cancer-specific, and cardiovascular death rates.[41,42] However, other studies reveal that moderately increased body mass confers a paradoxical survival advantage, presumably because of greater availability of energy reserves.[4,43,44]

Feeding Cats and Dogs With Cancer: General Considerations

So-called "cancer diets" often are recommended for cats and dogs with neoplastic disease. Most of these diets share two main features: they are high in fat and low in carbohydrate. One justification for this is that animals with cancer generally are assumed to be at risk for weight loss, which could be addressed by feeding a high-fat, energy-dense diet. In addition, neoplastic cells have a preference for carbohydrates and glycolysis, instead of using fat-derived fuels.[45] Theoretically, then, a high-fat cancer diet preferentially supplies usable energy to a patient with increased needs, and limits the energy available to the tumor.

Although high-fat cancer diets may be appropriate in some cases, a diet change is not necessarily indicated when an animal with cancer is eating a good-quality, well-tolerated diet and already is in optimal body condition. Diet changes actually can be contraindicated in animals eating prescription foods for the management of pre-existing conditions such as kidney disease, pancreatitis, or food allergies. Furthermore, high-fat cancer diets likely will be counterproductive in animals that already are obese at the time of their cancer diagnosis.

Careful nutritional assessment is the best way to determine whether or not an individual cat or dog with cancer might benefit from a change in diet (see Figure 188-1 and ch. 170). This process involves the systematic collection of clinical data evaluating individual nutritional status, and consists of three components: food and food related factors such as current diet plus treats, supplements, and medications; animal and animal-related factors, including signalment, medical history, physical examination findings, body weight and condition score, and diagnostic test results; and finally, owner and feeding management factors. The data collected are integrated into routine patient evaluation, and used for making precise nutritional recommendations. A diet change is indicated if nutritional assessment reveals evidence of disease caused by suboptimal nutrition, or disease where nutrition can be used as adjunct therapy.

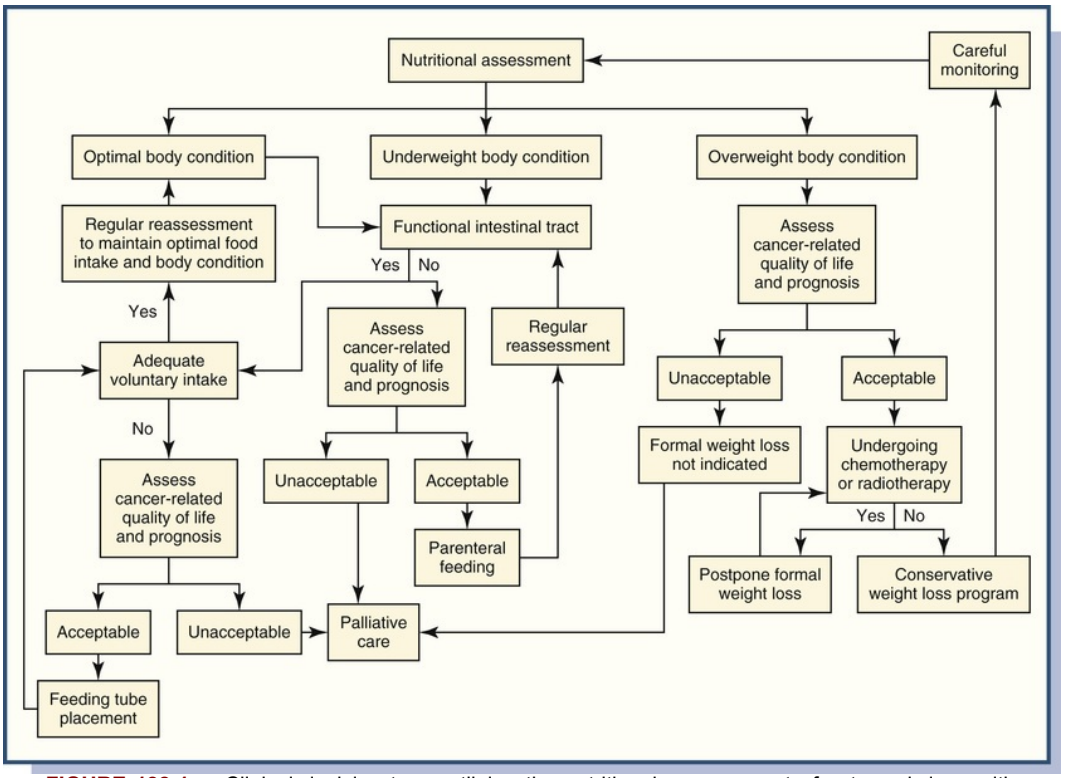

FIGURE 188-1 Clinical decision tree outlining the nutritional management of cats and dogs with cancer. Full nutritional assessments and objective evaluations of the animal's cancer-related quality of life and prognosis must be repeated at regular intervals to ensure that optimal choices are made throughout the course of disease.

If the decision is made to change the diet of a cat or dog with cancer, the first choice always should be a good-quality, commercial ration made by a reputable manufacturer. Over-the-counter products should have clear label claims confirming appropriate testing to prove nutritional adequacy (see ch. 193). Prescription products might not have a label statement of nutritional adequacy, but usually those intended for long-term use have undergone nutritional adequacy testing and this information should be available from the manufacturer. If a home-cooked recipe is followed, it must also be complete and balanced, including added vitamins and minerals.

Once a specific diet has been selected, an appropriate level of intake is calculated. In a self-supportive cat or dog in the home environment, this is based on the estimated maintenance energy requirement (MER). Many different equations can be used for calculating MER; the author uses MER = 110 $(BW_{kg})^{3/4}$ in dogs, and MER = 50 to 80 (BW_{kg}) in cats (varying with activity level). Both of these equations provide an estimate of the number of calories of metabolizable energy needed for daily maintenance. Any new food must be introduced slowly, especially if it is high in fat. Body weight and condition score then are followed through repeated nutritional assessments, moving food intake up or down as indicated to maintain target condition.

Prescription critical care diets often are enriched with nutrients that might be required in greater quantities during illnesses such as cancer, including n-3 (omega-3) fatty acids, branched chain amino acids, arginine, glutamine, and antioxidants; countless other over-the-counter products are promoted for use in cats and dogs with cancer as well. Unfortunately, few studies have evaluated the clinical benefit of such supplements objectively, with the result that indications as well as contraindications must be considered individually on a case-by-case basis. Ideally, before a specific nutritional supplement is recommended or approved for use in a cat or dog with cancer, there should be a clear scientific hypothesis that explains how the product will work; there should be no—or limited—risk of adverse interactions with ongoing cancer therapy; there should be data available from controlled studies investigating the short- and long-term safety of the product when given to cats and dogs; and, there should be some means of ascertaining that the product is of good quality, with consistent concentration, availability of the active ingredient, and lack of contamination.

Feeding Management of Weight-Losing Cats and Dogs With Cancer

Gradual introduction of an energy-dense diet providing 40-60% of calories as fat should be considered for cats and dogs with cancer-associated weight loss, as well as animals at risk for future weight loss. Unless contraindicated by kidney or liver disease, this usually is accompanied by an ample or increased protein intake (from 30 to 50% of calories) to protect existing lean body mass and meet the potentially increased needs of illness.[46] In general, commercial rations fitting the desired profile include performance, puppy and kitten, and prescription critical care diets. A high-fat prescription diet for dogs with cancer also is available (Hill's n/d, Hill's Pet Nutrition, Inc.). MER is calculated as previously described to determine initial food intake, although feeding an increment above MER at the animal's current body weight often will be necessary to prevent or reverse weight loss; once again, a trial and error process with repeated nutritional assessment is used for eventually identifying optimal intake.

Additional strategies beyond a simple diet change can be used for managing weight loss in cats and dogs with cancer. Supplementation with n-3 fatty acids often is recommended, although results in people with cancer are inconsistent: decreased synthesis of pro-inflammatory cytokines and stabilized body condition are reported in some but not all studies.[47-51] Analogous changes in cell membrane fatty acid composition are seen in dogs with increased dietary intake of n-3 fatty acids, which impacts cell membrane eicosanoid production and alters synthesis of cytokines such as IL-1, TNF-alpha, and IL-6.[52] Decreased systemic inflammation in turn could have beneficial effects on cancer cachexia, although this has yet to be proven definitively.[53] Much less information is available regarding the use of n-3 fatty acids in cats compared to dogs[54] but regardless, the appropriate dosage and method of administration for management of cancer-associated weight loss is unknown in either species.

Pharmacologic appetite stimulation is another approach that can be practical and cost-effective in selected cases where voluntary food intake is inadequate. Although progestational agents such as megestrol acetate have a well-established role in treating cancer and cancer-treatment related anorexia in people,[47,55-58] their use is infrequently reported in cats and dogs. Historically, benzodiazepine derivatives and the serotonin antagonist cyproheptadine have been used most often in small animals;[59] more recently, the tetracyclic antidepressant mirtazapine has shown promise, especially in anorectic cats.[59,60] No matter which specific appetite stimulant is chosen, however, careful monitoring of actual food intake is essential. Clinicians must guard against the temptation to postpone more appropriate and efficacious placement of a feeding tube while they await a clinical response to pharmacologic appetite stimulation.

The most aggressive treatment for animals with cancer that are unable to maintain themselves through voluntary food intake is assisted feeding, which usually involves enteral feeding tube placement (see ch. 82). Parenteral feeding may be considered in some cases where intestinal tract dysfunction is very severe (see ch. 189), but increased complications, marginal improvement in nutritional status, and trends toward decreased survival are seen in intravenously fed people with cancer.[61] This is likely to be related at least in part to the compromised gut function and immunity that occurs during parenteral feeding, and a combination of parenteral and enteral feeding should be used whenever possible, rather than parenteral feeding alone, to minimize these potential complications.

Although assisted feeding provides a clear clinical benefit for many cats and dogs with cancer, it also can pose an ethical challenge. When an animal's quality of life is severely compromised and the long-term prognosis is very poor, careful assessment of the expected advantage of assisted feeding is always indicated. Studies in people with terminal cancer show that assisted feeding likely will not improve nutritional or functional status when the expected survival time is very short.[62-65] A frank discussion with the pet owner regarding the realistic value of assisted feeding is an essential part of the decision-making process: it is the veterinarian's responsibility to make certain that assisted feeding is always a humane choice.

Feeding Management of Obese Cats and Dogs With Cancer

The health risks associated with obesity in normal cats and dogs are well-documented.[34] However, the potential benefit of weight loss in an obese animal with cancer must be assessed carefully, especially when the prognosis associated with the underlying neoplastic disease is poor. Weight loss programs can be stressful, labor-intensive and expensive, so the expected cancer-associated survival time must be long enough to justify time and effort needed for weight loss.

The food intake for effective weight loss in otherwise healthy cats and dogs usually is calculated based on the MER at the animal's estimated ideal body weight, and then decreasing that number by 20 to 30% in cats, and 25 to 50% in dogs (see ch. 176). Increments that are more conservative likely are appropriate for many

animals with cancer, and consideration should be given to stopping weight loss at a relatively more overweight body condition than would normally be accepted. Weight loss is contraindicated during critical illness, regardless of the severity of obesity. It is also questionable whether weight loss should be attempted during active anticancer therapy, even when the animal appears clinically stable. Excessive loss of lean body mass during purposeful weight loss could contribute to clinically important complications, including significant loss of muscle and muscle function, reduced performance scores, immunosuppression, and increased risk of cancer treatment-related toxicoses. Ongoing weight loss also can make patient monitoring more difficult, especially in cats: stabilization or reversal of weight loss is a very valuable surrogate marker of remission status in this species.[11]

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CHAPTER 189

Critical Care Nutrition

Daniel L. Chan

Overview

Metabolic responses to illness or injury place critically ill animals at high risk for malnutrition and its deleterious effects. These problems include alterations in energy metabolism, compromised immune function, decreased wound healing, and probably a negative impact on overall survival.[1-4] Whereas healthy animals lose primarily fat when they do not receive adequate calories (simple starvation), sick or traumatized patients catabolize lean body mass when they are not provided with sufficient calories (stressed starvation; see ch. 177). Inadequate calorie intake is a common problem in critically ill animals due to anorexia, an inability to eat or tolerate feedings (e.g., vomiting), or decreased absorptive capabilities.[1,4]

Because malnutrition can occur quickly, it is important to provide nutritional support by either enteral or parenteral means if oral intake is inadequate. The goals of nutritional support are either to prevent development of malnutrition or to treat malnutrition. Although unproven in dogs and cats, it is logical to assume that treatment or prevention of malnutrition decreases morbidity and mortality.[1,2,4,5] Whenever possible, oral nutritional support (enteral) should be used because it is safest, most convenient, most physiologically sound, and least expensive. Although enteral nutrition is preferred in critically ill animals, parenteral nutrition (PN) is an established method of providing nutritional support to patients whose gastrointestinal tracts cannot tolerate enteral feedings.[2,3,5-11]

Although the use of PN support has become more common, there remains a perception that this is technically difficult, associated with complications, and limited to university hospitals and referral centers. In reality, PN support can be adopted in many practice settings. Moreover, complications can be reduced substantially with proper management techniques. The goals of this chapter are to outline the identification process of dogs and cats most likely to benefit from PN; to review the process of formulating, implementing, and monitoring parenteral nutritional support; and to discuss how PN can be incorporated into various practice situations.

Nutritional Assessment

The first step in the consideration of nutritional support is appropriate patient assessment. Assessing nutritional status via objective measurements of body composition (e.g., anthropometry, bioelectrical impedance, dual energy x-ray absorptiometry, or serum indicators of malnutrition) is rarely employed in clinical veterinary medicine. Therefore, subjective clinical assessment (see ch. 170) remains paramount in the identification of malnourished animals that require nutritional support, as well as those imminently at risk for malnutrition. Indicators of malnutrition include weight loss, poor hair coat, muscle wasting, signs of inadequate wound healing, hypoalbuminemia, lymphopenia, and coagulopathies. However, these abnormalities are not specific to malnutrition and do not occur early in the process. In addition, fluid shifts can mask weight loss in critically ill patients. Given these limitations, it is crucial to identify early risk factors that can predispose pets to malnutrition (e.g., anorexia of >3 days' duration), serious underlying disease (e.g., trauma, sepsis, peritonitis, pancreatitis, gastrointestinal surgery), or extensive protein losses (e.g., protracted vomiting, diarrhea, protein-losing nephropathies, draining wounds, or burns).

Nutritional assessment also should identify factors that can affect the nutritional plan, such as specific serum electrolyte abnormalities; hyperglycemia, hypertriglyceridemia, or hyperammonemia; or comorbid illnesses, such as renal or hepatic disease. Such findings require adjustments to be made to the formulation of PN and in some cases prompt changing the nutritional plan. Appropriate laboratory analyses (e.g., serum biochemical profile, urinalysis) should be performed in all dogs and cats to assess these parameters.

Goals of Nutritional Support

The goals of nutritional support are to provide for the animal's ongoing needs, prevent or correct deficiencies or imbalances, minimize metabolic derangements, and prevent further catabolism of lean body tissues. Restoration of optimal body condition should not necessarily be the goal of nutritional support in the acute stages of diseases. In severely malnourished dogs and cats, nutritional support is directed toward preservation of lean body tissue and organ function, rather than complete reversal of malnutrition, which is accomplished when the patient becomes convalescent. The necessity for instituting nutritional support is dictated by individual needs and not necessarily by the specific disease. The ultimate purpose of nutritional support is to provide the necessary nutrients and calories until the dog or cat voluntarily consumes an adequate amount of food in its own environment.

The Nutritional Plan

One key to successful nutritional management of critically ill animals lies in the proper diagnosis and treatment of the underlying disease. While an attempt is made to diagnose and treat that underlying illness, a crucial care factor is selection of an appropriate route for nutritional support (Figure 189-1).

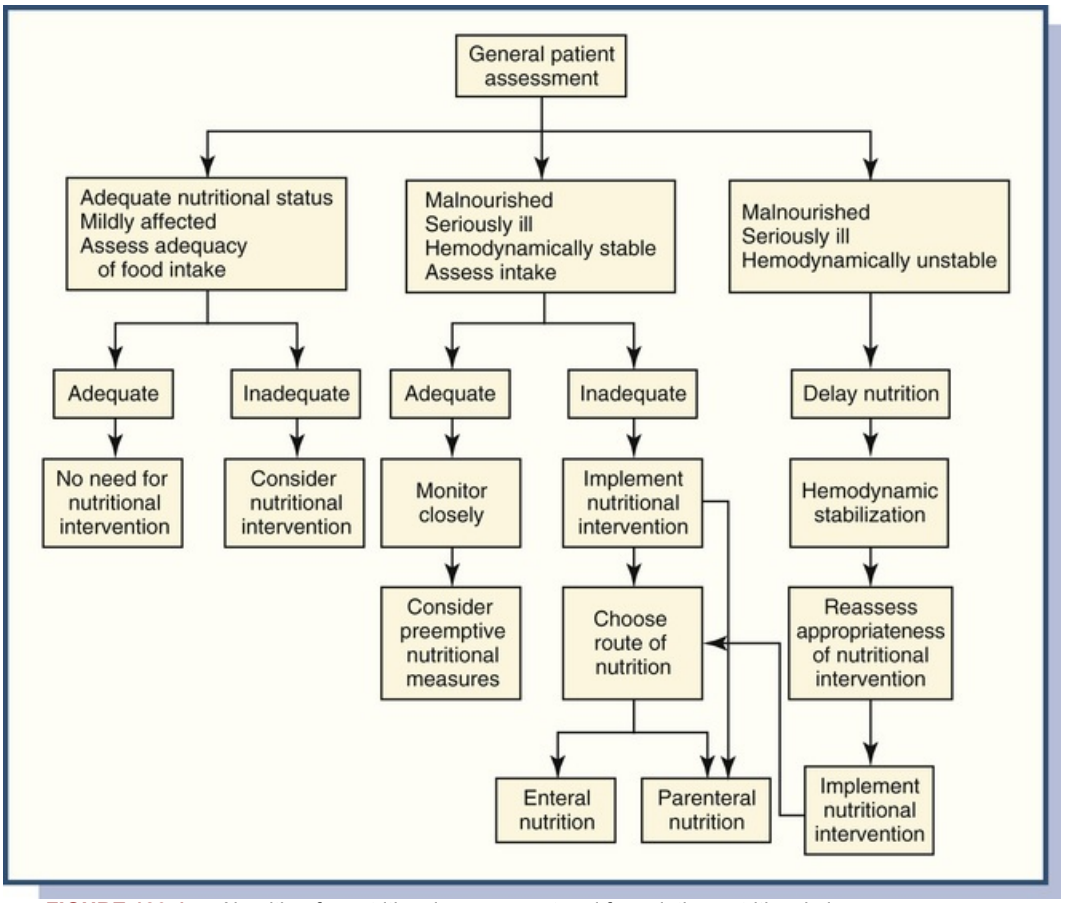

FIGURE 189-1 Algorithm for nutritional assessment and formulating nutritional plan.

Providing nutrition via a functional digestive system is always preferred. Therefore, particular care should be taken to determine whether enteral feedings would be tolerated. Even if only small amounts of enteral nutrition could be tolerated, this route of feeding should be pursued and supplemented with PN only as necessary. The placement of enteral feeding devices is described in ch. 82. Based on the nutritional assessment, anticipated duration of support, and appropriate route of delivery (i.e., enteral or parenteral), a nutritional plan can be formulated.

The first steps of instituting nutritional support include reestablishing proper hydration status, correction of electrolyte or acid-base disturbances, and achieving hemodynamic stability. Commencing nutritional

support before such abnormalities are addressed can increase the risk of complications and, in some cases, further compromise the animal. Implementation of the nutritional plan should be gradual, with an appropriate goal being to reach the target level of nutrient delivery in 48-72 hours.

Calculating Nutritional Requirements

Ideally, nutritional support should provide ample substrates for gluconeogenesis, protein synthesis, and energy necessary to maintain homeostasis. The clinician must ensure that enough calories are being provided to sustain critical physiologic processes (e.g., immune function, wound repair, cell division and cell growth). Therefore, calculating the animal's total energy expenditure is necessary. However, as clinically available direct measurements of energy expenditure in dogs and cats are still in the developmental phase, the use of mathematical formulas is the only practical means of estimating energy requirements. The resting energy requirement (RER) is defined as the number of calories required per day for maintaining homeostasis at rest in a thermoneutral environment while the animal is in a postabsorptive state.[12] While there are several formulas proposed for calculating the RER, a widely used allometric formula that can be applied to both dogs and cats, regardless of body weight, is RER = 70 × (body weight in kg)$^{0.75}$. For animals weighing 2-30 kg, another formula that provides reasonable estimation of the RER is: RER = 30 (body weight in kg) + 70.

Despite the convention of multiplying the RER by an illness factor between 1.0 and 2.0 to account for increases in metabolism associated with different diseases and injuries, less emphasis is being placed now on such subjective and extrapolated factors.[5] The current recommendation is to use more conservative energy estimates (i.e., start with the animal's RER) to avoid overfeeding. Overfeeding can result in metabolic and gastrointestinal complications, hepatic dysfunction, and increased carbon dioxide production.[12] One study demonstrated that use of "illness factors" in calculating energy requirements for cats was strongly associated with the development of hyperglycemia.[13]

As the preservation of lean body mass is a primary goal of nutritional support, close monitoring of body weight, fluid distribution, response or tolerance to feedings, and changes in the underlying condition should dictate whether to increase the number of calories provided in the nutritional plan. Typically, if an animal continues to lose weight on nutritional support, the number of calories provided should be increased by 25% and the plan should be reassessed in a few days. Additional adjustments to the nutritional plan might also include the addition or restriction of electrolytes such as magnesium and potassium, as dictated by serial biochemical profiles.

Nutritional Support

A major advantage of enteral nutrition over PN is superior maintenance of intestinal structure and function. The presence of nutrients within the intestinal lumen elicits trophic effects that mediate mucosal cell proliferation. It has also been proposed that a lack of enteral nutrition contributes to the impairment of mucosal barrier function, which allows for the translocation of intestinal bacteria or endotoxins leading to sepsis and a systemic inflammatory response.

However, in animals unable to tolerate enteral feedings, such as those that are vomiting, regurgitating, or unable to protect their airway, PN should be considered. Inability to tolerate enteral feedings is the only major indication for PN support. Although obtaining enteral access in critically ill animals can be difficult, every effort must be made to ensure that a functional gastrointestinal tract is not bypassed. A more extensive review of enteral nutrition is provided in ch. 82.

Parenteral Nutrition

PN sometimes has been characterized as a technique fraught with complications. In reality, many of the complications attributed to PN in the past might have had more to do with overfeeding or "hyperalimentation," rather than with the route of feeding itself. Although metabolic complications can be associated with PN, these complications generally are mild, have minimal consequences, and rarely require discontinuation of nutritional support. Septic complications associated with PN can be dramatically minimized with careful attention to aseptic technique in the compounding of PN, placement of dedicated PN catheters, and careful monitoring of the catheter site (see ch. 75 and 76).

Types of Parenteral Nutrition

The terminology used for describing the use of PN in veterinary patients has evolved and it is worth reviewing the current nomenclature. Total parenteral nutrition (TPN) previously was defined as the provision of all of the patient's protein, calorie, and micronutrient requirements intravenously, whereas partial parenteral nutrition (PPN) was defined as the provision of only a part of this requirement (typically 40-70% of the energy requirement).[5] More recently, there has been a shift away from describing PN in terms of "meeting energy and nutrient requirements" as they remain largely unknown in animals, and instead, recent recommendations emphasize categorizing PN by the mode of delivery such that PN delivered into a central vein is described as central PN (CPN) and PN delivered into a peripheral vein is described as peripheral PN (PPN).[14]

The lower osmolarity of PPN solutions, as compared to CPN solutions, is achieved by diluting the solution (ideally to less than 800 mOsm/L), which decreases the caloric and protein density but makes it suitable for administration via peripheral veins.

Components of Parenteral Nutrition

PN is formulated as a mixture of a carbohydrate (dextrose), amino acids, and, usually, fat (lipid). Carbohydrate, in the form of dextrose (typically 5% or 50%), can have benefits in addition to acting as a fuel substrate. These potential benefits include stimulation of insulin secretion, reduction of muscle protein catabolism, and inhibition of hepatic glucose output, which can spare muscle protein from being catabolized for gluconeogenesis. However, administration of dextrose or supplementation of maintenance fluids with dextrose as the sole source of calories, in most cases, does not amount to adequate nutritional support and should be discouraged. For example, a 5% dextrose infusion provides only 170 kcal per liter of solution, and would provide less than 25% of the RER for a dog or cat at maintenance fluid rates. Dextrose infusions are more appropriate for the treatment of hypoglycemia rather than for nutritional support.

Crystalline amino acid solutions are an essential component of PN. The importance of supplying amino acids relates to maintenance of positive nitrogen balance and repletion of lean body tissue. This can be vital as critically ill dogs and cats begin to recover from illness. Supplementation of amino acids can support protein synthesis and spare tissue proteins from being catabolized via gluconeogenesis.[8] The most commonly used amino acid solution (Travasol, Clintec Nutrition, Deerfield, IL) contains most of the essential amino acids for dogs and cats. The exception is taurine. However, as PN typically is not used for more than 10 days, the lack of taurine does not become a problem in most circumstances.

Amino acid solutions are available in different concentrations, from 4% to 10%, and the most commonly used is 8.5%. Amino acid solutions also are available with and without electrolytes. Animals with normal serum electrolyte concentrations typically receive amino acid solutions with electrolytes, whereas those with electrolyte disturbances can benefit from amino acid solutions without electrolytes. Special formulations of amino acid solutions containing higher concentrations of the branched chain amino acids are available, although at much greater expense. These solutions originally were thought to be useful in the management of highly catabolic metabolic diseases or when hepatic encephalopathy was present, but studies have not confirmed a clear benefit in overall survival.[15]

Lipid emulsions are the calorically dense component of PN and a source of essential fatty acids. Lipid emulsions are isotonic and are available in 10% to 20% solutions (Intralipid, Clintec Nutrition, Deerfield, IL). These commercially available lipid emulsions are made primarily of soybean and safflower oils. They provide predominantly long-chain polyunsaturated fatty acids that include linoleic, oleic, palmitic, and stearic acids. These solutions are emulsified with egg yolk phospholipids and their tonicity is adjusted with glycerol. The emulsified fat particles are comparable in size to chylomicra and are removed from the circulation via the action of peripheral lipoprotein lipase. A common misconception exists with respect to the use of lipid-containing PN for animals that have pancreatitis. Although hypertriglyceridemia can be a risk factor for pancreatitis, infusions of lipids have not been shown to increase pancreatic secretion nor worsen pancreatitis. Therefore, such therapies are considered safe,[16] except when the serum triglyceride concentration is increased. This would indicate a clear failure of triglyceride clearance. According to the most recent guidelines provided by the American Society of Parenteral and Enteral Nutrition, humans with serum triglyceride concentrations exceeding 400 mg/dL (4.52 mmol/L) should have the lipid proportion in PN markedly reduced or eliminated altogether.[16] Although specific data regarding the maximal, safe level of lipid administration in dogs and cats are not available, it would seem prudent to maintain normal serum triglyceride concentrations.

Another concern regarding use of lipid in PN is its purported immunosuppressive effect. This effect could

develop via impairment of the reticuloendothelial system, particularly when PN solutions containing a high percentage of lipid are used.[9] Despite *in vitro* evidence supporting the notion that lipid infusions also can suppress neutrophil and lymphocyte function, studies have not yet correlated lipid use and increased rates of infectious complications.

Daily vitamin recommendations for dogs and cats receiving PN are extrapolated from established oral nutritional requirements.[5] Multivitamin preparations intended for IV administration provide a convenient and practical means for vitamin supplementation and these can be added to PN solutions. The addition of other parenteral medications to PN admixtures also is possible; however, their compatibility first must be verified. Drugs that are known to be compatible and sometimes are added to PN include heparin, regular insulin, potassium chloride, and metoclopramide. While the addition of insulin to PN often is required in people receiving PN, the hyperglycemia seen in dogs and cats receiving PN does not usually require insulin administration. However, diabetic pets often require adjustments to their insulin regimen when receiving PN. Although a veterinary protocol has been described for the addition of insulin directly to PN, often it is easiest to manage diabetics receiving PN with SC injections of insulin.[2,5]

Parenteral Nutrition Compounding

Based on the nutritional assessment and plan, PN can be formulated according to the worksheets found in Boxes 189-1 and 189-2. For CPN (see Box 189-1), the first step is the calculation of the patient's RER. Protein requirements (grams of protein required per day) then are calculated, taking into consideration factors such as excessive protein loss, severe hepatic disease, or significant kidney disease. Although some recommendations meet all energy requirements with only dextrose and lipids, the protocol listed here also accounts for energy provided by amino acids, and subtracts the calories provided by amino acids from the daily RER to estimate the total nonprotein calories required. Nonprotein calories then are usually provided as a 50 : 50 mixture of lipids and dextrose. This 50 : 50 ratio can be adjusted in cases of persistent hyperglycemia or hypertriglyceridemia (e.g., a higher proportion of calories would be given from lipids in an animal with hyperglycemia). The calories provided from each component (amino acids, lipids, and dextrose) are then divided by their respective caloric densities, and the exact amounts of each component are added to the PN bags in an aseptic fashion. The amount of CPN delivered often will provide less than the daily fluid requirement, and additional fluid can either be added to the PN bag at the time of compounding or be provided as a separate infusion.

Box 189-1

Central Parenteral Nutrition (CPN) Calculations

1. Calculate resting energy requirement (RER)

RER = 70 × (current body weight in kg)0.75	
or for animals weighing between 2 and 30 kg:	
RER = (30 × current body weight in kg) + 70	RER = _____ kcal/day

2. Protein requirements

	CANINE (g/100 kcal)	FELINE (g/100 kcal)
*Standard	4	6
*Reduced (hepatic/renal disease)	2-3	3-4
*Increased (excessive protein losses)	6	7-8

3. Volume of nutrient solutions required
   a. 8.5% amino acid solution = 0.085 g protein/mL

____ g protein required/day ÷ 0.085 g/mL	= ____ mL/day of amino acids

b. Nonprotein calories: The calories supplied by protein (4 kcal/g) are subtracted from the RER to get total nonprotein calories needed.

____ g protein req/day × 4 kcal/g	= ____ kcal provided by protein
RER − kcal provided by protein	= ____ total nonprotein kcal/day required

c. Nonprotein calories are usually provided as a 50 : 50 mixture of lipid and dextrose

*20% lipid solution = 2 kcal/mL	
To supply 50% of nonprotein calories	
____ lipid kcal required ÷ 2 kcal/mL	= ____ mL of lipid
*50% of dextrose solution = 1.7 kcal/mL	
To supply 50% of nonprotein calories	
____ dextrose kcal required ÷ 1.7 kcal/mL	= ____ mL of dextrose

4. Total daily requirements
____ mL of 8.5% amino acid solution
____ mL of 20% lipid
____ mL of 50% dextrose
____ total mL of CPN solution to be administered over 24 h

*Using a common 8.5% amino acid solution containing potassium (i.e., Travasol), CPN made according to this worksheet will provide potassium at higher than maintenance levels. Therefore, it might not be necessary to supplement potassium in any other fluids the patient is receiving. CPN for animals that are hyperkalemic should be formulated using amino acid solutions without electrolytes. Rates of other IV fluids being administered concurrently should be adjusted accordingly.

Box 189-2

Peripheral Parenteral Nutrition (PPN) Calculations

1. Calculate resting energy requirement (RER)

RER = 70 × (current body weight in kg)0.75	
or for animals weighing between 2 and 30 kg:	
RER = (30 × current body weight in kg) + 70	RER = ____ kcal/day

2. Calculate the partial energy requirement (PER)

Plan to supply 70% of the animal's RER with PPN:	PER = RER × 0.7 = ____ kcal/day

3. Proportion of nutrient requirements according to body weight: (Note: For animals ≤3 kg, the formulation will exceed maintenance fluid requirements)
a. Cats and Dogs 3-5 kg:
PER × 0.20 = ____ kcal/day carbohydrate required
PER × 0.20 = ____ kcal/day protein required
PER × 0.60 = ____ kcal/day lipid required
b. Cats and Dogs 6-10 kg:
PER × 0.25 = ____ kcal/day carbohydrate required
PER × 0.25 = ____ kcal/day protein required
PER × 0.50 = ____ kcal/day lipid required
c. Dogs 11-30 kg:
PER × 0.33 = ____ kcal/day carbohydrate required
PER × 0.33 = ____ kcal/day protein required

PER × 0.33 = ____ kcal/day lipids required
d. Dogs >30 kg:
PER × 0.50 = ____ kcal/day carbohydrate required
PER × 0.25 = ____ kcal/day protein required
PER × 0.25 = ____ kcal/day lipid required
4. Volumes of nutrient solutions required:
a. 5% dextrose solution = 0.17 kcal/mL

____ kcal carbohydrate required/day ÷ 0.17 kcal/mL	= ____ mL/day dextrose

b. 8.5% amino acid solution = 0.34 kcal/mL

____ kcal protein required/day ÷ 0.34 kcal/mL	= ____ mL/day amino acids

c. 20% lipid solution = 2 kcal/mL

____ kcal lipid required/day ÷ 2 kcal/mL	= ____ mL/day lipid
	= ____ total mL of PPN to be administered over 24 h

Note: This formulation provides approximately a maintenance fluid rate. Commonly used 8.5% amino acid solutions (i.e., Travasol) with electrolytes contain potassium. For animals ≤35 kg, the PPN solution made according to this worksheet will provide approximately maintenance levels of potassium. For animals >35 kg, the potassium contained in the PPN solution will be lower than maintenance levels. Rates of other IV fluids being concurrently administered should be adjusted accordingly.

For formulation of PPN, Box 189-2 provides a step-by-step protocol in which animals of various sizes can receive 70% of their RER and approximately meet their daily maintenance fluid requirement. In extremely small animals (≤3 kg), the amount of PPN will exceed the maintenance fluid requirement and increase the risk for fluid overload, so volume adjustments are necessary. Also, in animals requiring conservative fluid administration (e.g., congestive heart failure patients), these calculations for PPN might provide excessive fluid volumes. This formulation has been designed so that the proportion of each PN component is dependent on animal weight such that a smaller animal (3-5 kg) will receive proportionally more calories from lipids, compared to a large dog (>30 kg), which would receive more calories in the form of carbohydrates. This allows the resulting formulation to approximate the daily fluid requirement.

Compounding of PN should be done aseptically under a laminar flow hood using a semiautomated, closed-system PN compounder. Regulations implemented by the United States Pharmacopeia in 2004 require strict adherence to sterile compounding of PN solutions.[17] Given these strict conditions, it has become easier to have local human hospitals or human home health care companies (e.g., CORAM–Nourish Nutrition Support Service) compound PN solutions according to protocols outlined in Boxes 189-1 and 189-2 and have the solutions delivered to the practice within hours.

Alternatively, commercial, ready-to-use preparations of glucose or glycerol, amino acids, and lipids are available for IV use (Table 189-1) and clinical experience with such products recently has been published.[18,19] While these ready-to-use preparations are convenient, they provide only 30-50% of caloric requirements when administered at maintenance fluid rates and as a result, they only should be used for interim nutritional support or to supplement low-dosage enteral feedings.[18,19] In practices that do not have access to compounded PN, ready-to-use PN solutions can be a viable option for provision of nutritional support. Some of these products are available in bags with segregated chambers and the solutions are mixed before use by squeezing the bag and breaking the internal seals, yielding an admixture of amino acids, dextrose, and lipids (Video 189-1).

TABLE 189-1

Commercially Available Alternatives to Compounded Parenteral Nutrition

FEATURES	MANUFACTURER

	FEATURES	MANUFACTURER
Clinimix*	2.75% amino acids, 5% dextrose	Clintec Nutrition, Deerfield, IL
Quickmix	2.75% amino acids, 5% dextrose	Clintec Nutrition, Deerfield, IL
ProcalAmine	3% amino acids, 3% glycerol	B. Braun, McGraw Inc., Irvine, CA
Kabiven 5 Peripheral	2.4% amino acids, 6.7% dextrose, 3.5% intralipid	Fresenius Kabi, Bad Homburg, Germany

*Various formulations with different amino acids and dextrose concentrations exist.

Parenteral Nutrition Administration

The administration of any PN requires a dedicated, aseptically placed catheter, used solely for PN administration (see ch. 75, 76, and 77). Most critically ill dogs and cats that receive PN require placement of a new or additional catheter, because PN should not be administered through previously existing catheters placed for reasons other than PN. Long catheters composed of silicone, polyurethane, or tetrafluoroethylene are recommended for use with any type of PN to reduce the risk of thrombophlebitis.[3,5] Multilumen catheters often are recommended for CPN administration. Multilumen catheters can remain in place for long time periods. The non-PN lumens in these catheters can be used for blood sampling, administration of additional fluids, and IV medication administration, and they negate the need for separate catheters placed at other sites.[5,17]

Although placement of multilumen catheters does require more technical skill than conventional jugular catheters, they can be valuable in the treatment of any critically ill animal. The high osmolarity of CPN solutions (often ≈1200 mOsm/L) requires administration through a central venous (jugular) catheter, while PPN solutions can be administered through either a jugular or a peripheral venous catheter. The concern with administering fluids high in osmolarity has been the risk of thrombophlebitis, although this side-effect has not been demonstrated in dogs or cats.

Because of the various metabolic derangements associated with critical illness, PN should be instituted gradually over 48 hours. It is recommended that CPN be started at 50% of the RER on day 1 and then increased to the targeted amount by the second day. In this manner, serum electrolyte, glucose, acid-base status, total fluid requirements, and other parameters can be monitored as CPN is administered. In most cases, PPN can be started without a gradual increase. It is also important to adjust the rates of other fluids being administered concurrently. For both CPN and PPN, the animal's catheter and infusion lines must be handled aseptically at all times to reduce the risk of PN-related infection.

PN should be delivered as a continuous rate infusion over 24 hours via fluid infusion pumps. Inadvertent delivery of massive amounts of PN can result if administration is not properly regulated. Cyclic administration of PN (i.e., alternating PN with other parenteral fluids every 12 hours) also has been described. However, this practice is not recommended, as it circumvents maintenance of a closed system for PN administration and can increase the rate of complications. Once a bag of PN is set up for administration, it should not be disconnected even for walks or diagnostic procedures. The drip regulator can be decreased to an extremely slow rate and can accompany the patient if he or she needs to be moved. Administration of PN through an in-line filter (Air Eliminating Filter, Clintec Nutrition Division, Deerfield, IL) also is recommended; the filter is attached at the time of setup. This setup process is performed daily with each new bag of PN. Each bag should only hold one day's worth of PN, and the accompanying fluid administration sets and in-line filter are changed at the same time using aseptic technique. If using ready-made PN solutions, the recommendation is that the bottle or bag is in use for only 24 hours, and any remaining solution after 24 hours is discarded. However, there are no studies confirming whether this approach is necessary. Discontinuation of PN should be done when the animal resumes consuming an adequate number of calories (i.e., at least 50% of RER). Whereas CPN should be gradually discontinued over a 6- to 12-hour period, PPN can be discontinued abruptly.

Complications

As with any therapy intended for critically ill animals, complications can occur. Complications associated with PN can include mechanical complications of the catheter and lines, thrombophlebitis, metabolic abnormalities, and sepsis. Mechanical complications such as inadvertent catheter removal, catheter occlusion, and line disconnection or breakage probably are not inherently related to PN and likely are no more common

than in any dog or cat with an IV catheter. Metabolic complications are much more likely to be related to PN and include hyperglycemia, hypertriglyceridemia, hyperbilirubinemia, increased alkaline phosphatase activity, azotemia, electrolyte shifts, and hyperammonemia.[2,5,6,10,11,13,14,18,19] The more commonly encountered complications, namely hyperglycemia and hypertriglyceridemia, usually are transient and can be managed effectively without serious consequences. However, one study did demonstrate higher mortality rates in cats receiving PN that developed hyperglycemia within the first 24 hours of PN support.[11] Decreasing the infusion rate for 12-24 hours often is effective, although in some instances reformulation of PN is required. Animals with biochemical changes subsequent to initiation of PN should have more frequent laboratory parameter evaluations.

Septic complications, including catheter-site infection with and without septicemia, have been reported in dogs and cats receiving PN. This complication is uncommon, ranging from 3% to 12% in dogs and cats receiving PN.[2,6,10,11,18] Septic complications can be minimized by strict adherence to established protocols and careful attention to early signs of problems relating to catheter care. Any catheter suspected of causing fever, increase in white blood cell count, or other sign compatible with infection should be removed and cultured.

Monitoring

Given the potential for complications, monitoring of dogs and cats receiving PN is a vital part of nutritional support. This monitoring should be similar to that already in place for any critically ill animal. Careful monitoring of the catheter site is recommended to detect problems early (e.g., signs of inflammation or malposition) and should be done on a daily basis. Catheters should be evaluated for patency, and bandages changed daily. At a minimum, body weight, body temperature, respiratory rate, catheter site, and serum glucose should be evaluated daily. All blood tubes should be inspected for visible lipemia. Monitoring of other parameters (e.g., electrolytes, acid-base status, complete blood count, biochemical profile) also can be indicated. Persistent hyperglycemia, hypertriglyceridemia, or signs of encephalopathy should prompt reevaluation and could necessitate decreasing the rate of infusion or reformulation of PN and serial evaluation of blood work.

Summary

With the growing recognition that nutritional support is an integral part of the therapeutic regimen of many critically ill animals, it is becoming increasingly important for veterinarians to be able to incorporate nutritional support in their practice or to refer these cases to facilities capable of providing such therapy when necessary. Proper identification of dogs and cats most likely to benefit from PN and the ability to formulate, administer, and monitor PN are key factors in ensuring the successful incorporation of parenteral nutritional support in their care.

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CHAPTER 190

Nutritional Uses of Fiber

Amy Farcas

Client Information Sheet: Nutritional Uses of Fiber

Dietary fiber (DF) can be utilized in the management of numerous medical conditions and in maintenance of general health. Several properties/attributes usually associated with DF include its water-solubility (soluble DF [SDF] or insoluble DF [IDF]), capacity to be fermented by intestinal microflora, and its energy contribution to a diet.

Considerations Regarding Therapeutic Use of Dietary Fiber

Dietary fiber has long been known to affect seemingly unrelated physical parameters, such as stool quality, metabolism, and immune status. DF is not a single chemical entity but can be viewed as an "umbrella term" under which many types of fiber can be included. Not all DF is expected to have the same effects and certain pairings of DF are understood to result in opposite clinical responses. To complicate matters, many food and feed sources of DF provide mixtures of several DF compounds and the manner in which DF is supplied (as a whole food/feed item or as a purified compound) also affects its action. Historically, it has not been possible to assay DF accurately. Confidence in dietary fiber intake, in terms of quantity and composition, is needed in order to gain useful information from studies reporting response to DF. However, precise measurements are not always available.

Types of Dietary Fiber

DF may be understood, in part, as a concept as much as it is a specific food component. While this may seem unscientific, it is appropriate since DF represents indigestible plant material. Despite being indigestible by mammalian enzymes, some DF may be fermentable by GI microflora. DF represents a group of compounds distinguished on indigestibility and little else. A selection of DF types and sources common to pet food is included in Table 190-1. Within SDFs, there are categories of high-molecular-weight dietary fibers (HMWSDF) composed of >10 sugar molecules and low-molecular-weight dietary fibers (LMWSDF) composed of <10 sugar molecules.

TABLE 190-1

Classification of Dietary Fibers (DF) and DF Sources Based on Water Solubility

FIBER TYPE	IDF/HMWSDF/LMWSDF
Cellulose	IDF
Lignin	IDF
Hemicellulose	Mixed (IDF/HMWSDF)
Psyllium husk	Mixed (IDF/HMWSDF)
Guar gum	HMWSDF
Carrageenan	HMWSDF
Locust bean meal	HMWSDF

Resistant starch	Mixed (HMWSDF/LMWSDF)
Arabinogalactan	HMWSDF
Beet pulp (source of pectin)	HMWSDF
Pullulan	HMWSDF
Chicory (source of inulin/FOS)	LMWSDF
Yeast cell wall (source of MOS)	LMWSDF
Polydextrose	LMWSDF
Gamma-cyclodextrin	LMWSDF

DF, Dietary fiber; *HMWSDF*, high-molecular-weight dietary fibers; *IDF*, insoluble dietary fiber; *LMWSDF*, low-molecular-weight dietary fibers.

Measurement and Reporting of Dietary Fiber in Pet Food

In theory, DF is easily defined as the indigestible plant portion of a diet. However, there is no assay that accurately discriminates food components based on digestibility. In studies measuring DF, the definition of assayed DF invariably changes from "the indigestible plant portion of the diet" to the result of a test specific to that study. Unfortunately, the currently available test that accurately and completely measures all indigestible plant material present in food is costly and not commonly used. While the definitions and methodologies for assaying DF have improved, none is without issues. There are 3 recognized methods for determining DF quantities in pet food (Figure 190-1). The 200-year-old crude fiber (CF) method continues to be used for detecting variable portions of IDF present in food samples. The CF method is both standard and required for pet food labeling in the United States. Another method, inaccurately termed the total dietary fiber (TDF) method, was developed in the 1970s. This assay measures both IDF and HMWSDF. It is the current standard in human food labeling, but it fails to measure the LMWSDF component that has recently been included in the definition of DF. The method fractionates dietary fiber types somewhat and reports results as total (IDF+HMWSDF), IDF, and SDF (actually HMWSDF). This information should be helpful to clinicians attempting to determine potential clinical effects of a diet or diet change in a particular patient. TDF data have been reported for some therapeutic pet foods, but not widely. Recently, a TDF method that also includes LMWSDF has been developed, but veterinary studies using this new assay have yet to be reported.

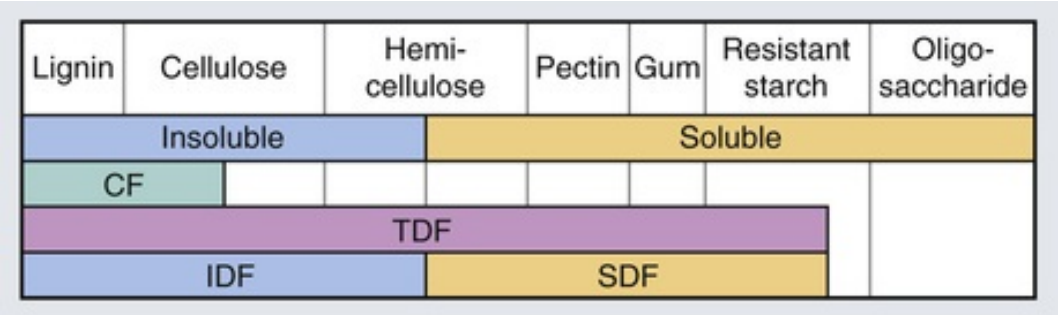

FIGURE 190-1 Simplified comparison of dietary fiber (DF) types to current DF assays. *CF*, Crude fiber; *IDF*, insoluble dietary fiber; *SDF*, soluble dietary fiber; *TDF*, total dietary fiber.

It would be ideal to have the ability to provide DF dosages and to compare responses between studies. However, there have been variables in reporting DF content. Among these variables are whether results were obtained from dry matter (DM) concentrations of experimental diets, whether diets were reported on an as-fed basis or by subject body weight, whether DF was provided as purified substance or whole food item, or whether it was supplemented in addition to a basal diet or incorporated into the basal diet's formulation. Further, there are unavoidable differences in the formulation of basal diets.

Therapeutic Use of Dietary Fiber

Stool Parameters

Perhaps the most widely reported effects of change in DF intake in pets are on stool quantity and quality. This is true for both healthy animals and those with various gastrointestinal conditions. DF affects how ingesta moves through the gastrointestinal (GI) tract, the rate at which nutrients are absorbed, and both structure and water content of feces. IDF tends to create structure for ingesta, but may interfere with nutrient absorption. As the structure adsorbs water, it contributes to larger, "bulkier" stools. This could affect management of anal sac disease, constipation due to functional issues, and soft, non-formed stools. Factors related to stool quality are the primary reason for the addition of an IDF source to most commercial pet food formulations. DF particle size also plays a role.[1,2]

SDF draws water into intestinal content osmotically, creating softer stools with less structure. Such attributes may treat constipation due to nonfunctional causes. Response to the SDF-resistant starch in dog diets varies by breed. Large-breed dogs are more sensitive to development of soft stools with diets that include SDF.[3] Interindividual, as well as interbreed, variability in response to DF supplementation can be expected. Both IDF and SDF increase fecal weight and water content. See Table 190-2 for a summary of DF effects on stools by DF type/source.

TABLE 190-2

Effects of DF on Stool Quality, Fecal Odor Compounds, Fermentation Products, and Microbial Populations

Stool Quality	
Cellulose	Firmer[1,2,24,31,62,63]
Soybean hulls	Firmer[64]
Sugarcane fiber	Firmer[62]
Guar gum	Firmer[37]/no change[65]
Carrageenan	Firmer[37]
Locust bean meal	Firmer[37]
Resistant starch	No change/softer[3]
Beet pulp/pectin	Softer[24,63]
Chicory/inulin/FOS	No change[17,66,67]
Yeast cell wall/MOS	No change[17]
Polydextrose	Softer[68]
Pullulan	Softer[69]
Gamma-cyclodextrin	Firmer[69]
Fecal Odor	
IDF (nonspecific)	Decrease[70]
FOS	Decrease[67]/no change[45]
MOS	Decrease[67]
Fermentation Products	
Cellulose	No change[8,71]
Beet pulp/pectin	Increase total VFA[11,13,63] Increase butyrate[13]
Guar gum	Increase butyrate[72]
Chicory/inulin/FOS	Increase total VFA[73]

	Decrease total VFA[15,74] No change[75] Decrease acetate, propionate[15] Increase butyrate[15] Decrease acetate[15] Decrease acetate, butyrate[74]
Yeast cell wall/MOS	Increase total VFA[73]
Polydextrose	Increase total VFA[68]
Microbial Populations	
Beet pulp/pectin	Increase total bacteria[76] Increase Firmicutes[12,76] Increase Bifidobacter[13,76] Increase Lactobacilli[10,13] Decrease Fusobacteria[12] Increase Proteobacteria[76] Increase *Clostridium perfringens*[10] Increase *E. coli*[10]
Chicory/inulin/FOS	Increase Bifidobacteria[10,13,17,19,74,76,77] Increase Lactobacilli[13,14,19,77] Increase total aerobes[75] Decrease *E. coli*[10,14] Decrease *C. perfringens*[75] No change[15,66,67] No change *Clostridium*[78] No change *E. coli*[78]
Yeast cell wall/MOS	Increase Bifidobacteria[14,17,19] Increase Lactobacilli[16,19] Decrease *E. coli*[17,79] Decrease *C. perfringens*[79] Decrease total aerobes[16,67]
Polydextrose	Decrease *C. perfringens*[68] No change *E. coli*[68] No change Lactobacilli[68] No change Bifidobacteria[68]
Pullulan	Increase Lactobacilli[69]
Gamma-cyclodextrin	Decrease *C. perfringens*[69]
Arabinogalactan	Increase Lactobacilli[58]

DF, Dietary fiber; *FOS*, fructooligosaccharide; *IDF*, insoluble dietary fiber; *MOS*, mannan-oligosaccharide; *VFA*, volatile fatty acids.

Fermentability

Most IDF is not fermentable, in contrast to the typically fermentable SDF (particularly LMWSDF). Psyllium husk is an exception to this generalization because it provides both IDF and non-fermentable SDF.[4] Fermentation of DF by microbes produces the volatile fatty acids (VFA) acetate, propionate and butyrate. Butyrate may be used as an energy source for colonocytes; thus, fermentation of DF increases colonic mass, absorptive capacity, and function.[5] These VFA are also absorbed systemically and can trigger release of

glucagon-like peptide-1 (GLP-1) by intestinal L cells, which contributes to glycemic regulation.[6,7] Blends of fermentable and nonfermentable DF may be used to create specific combinations of improvement in stool quality, in addition to benefits of microbial fermentation.[8] DF is not the only food component with the potential to undergo microbial fermentation. Poorly digestible protein present in digesta also undergoes fermentation by colonic bacteria, contributing to fecal malodor.[9]

Microbiome

The driving force behind DF's effects on fermentation products is its effect on the gut microbiome. Since studies report a high degree of individual variation in this area, variation in response to DF supplementation would also be expected, especially with varied DF dosage.[10-17]

Many studies have evaluated DF's effect on the fecal microbiome (see Table 190-2), but results may not be reflective of changes throughout the GI tract.[18] Few studies have evaluated the effect of DF in more proximal sections of the intestinal tract, but fructooligosaccharide (FOS) and mannan-oligosaccharide (MOS) increase ileal lactobacilli, decrease ileal *Clostridium*, and increase distal colonic total aerobic bacteria.[19,20] Dogs with a clinical diagnosis of small intestinal bacterial overgrowth supplemented with FOS showed fewer aerobic colony-forming units in the duodenum, but no differences in species of small intestinal bacteria.[21]

Mucosa

Given that DF supplementation affects the gastrointestinal microbiome, it is not surprising that changes in mucosal integrity have also been demonstrated. This is particularly true with fermentable DF. Dogs fed fermentable fiber sources such as beet pulp, FOS, or mixtures of these sources had increased small intestinal surface area, intestinal weight, villus height, mucosal mass, and a higher capacity for carrier-mediated glucose uptake as compared with cellulose-supplemented dogs.[22,23] No changes in colon mucosa thickness, crypt area, lamina propria area, goblet cell area, or crypt mean size were demonstrated in cats supplemented with beet pulp, wheat bran, or sugarcane fiber.[24] Inulin supplementation in *Salmonella*-infected puppies decreased the severity of enterocyte sloughing and maintained normal ileal Na^+-dependent glucose transport.[25]

Transit

A delay in intestinal transit may enhance nutrient absorption by increasing contact time between intestinal content, intestinal digestive enzymes, and absorptive surfaces. DF can modulate GI transit time via its physical properties involving water solubility, binding capacity, systemic and local effects on GI motility.[26,27]

In general, SDF increases digesta viscosity, while IDF has minimal effect.[28] Low-viscosity ingesta undergo rapid gastric emptying, whereas higher-viscosity SDF suspensions delay gastric emptying and demonstrate an apparent maximal gastric emptying rate.[29,30] Galactomannan (a LMWSDF) increases frequency and strength of intestinal motility.[29] In cats with chronic constipation, psyllium-enriched diets have improved clinical signs and decreased the need for medical therapy.[30] In dogs, cellulose decreased total intestinal transit time in one study, but both cellulose and corn fiber were reported not to alter transit time in another.[31,32] In cats, a higher-IDF diet did not affect gastric emptying.[33] Oat fiber, tomato pomace, peanut hulls, wheat bran, and guar gum are also reported not to affect GI transit time.[34-36] Studies regarding beet pulp have not provided consistent results.[35,36]

Digestibility

DF is, by definition, indigestible. As such, it may contribute to the formation of viscous ingesta and interact with specific nutrients or dietary components. DF may decrease digestibility by binding or sequestering components from digestive processes. DF may increase digestibility by increasing transit time. Apparent (total tract) digestibility associated with DF may be deceptive, especially with regard to digestibility of protein. The effects of DF, especially fermentable fiber, may also be deceptive when colonic bacterial fermentation processes and products are included in fecal end products evaluated. For these reasons, "apparent digestibility" will be omitted from this discussion. Measuring ileal digestibility largely avoids this issue while providing a clearer assessment of the digestive process alone, without the confounding effects of

colonic fermentation (Table 190-3). DF may affect digestibility of individual diet components, including protein, fat, or minerals, but these generally follow ileal diet digestibility.[15,37] Variability in response is beyond the scope of this chapter.

TABLE 190-3

Effects of DF on Ileal Digestibility of Dietary Dry Matter and/or Organic Matter

Cellulose	Decrease[64] No change[80]
Guar gum	Increase[37]
Locust bean meal	Increase[37]
Carrageenan	Increase[37]
Beet pulp	No change[80]
Chicory/inulin/FOS	Increase[15,75] No change[81]
Yeast cell wall/MOS	Increase[79] Decrease[16]
Pullulan	No change[37]
Gamma-cyclodextrin	No change[37]

DF, Dietary fiber; *FOS*, fructooligosaccharide; *MOS*, mannan-oligosaccharide.

Glucose Metabolism

Some DF have been associated with a "second-meal effect," meaning that DF fed during a first meal will affect the glycemic response to a later glucose meal.[38] Effects of DF on blood glucose, insulin, and GLP-1 concentrations in healthy dogs and cats are summarized in Table 190-4.

TABLE 190-4

Effects of DF Supplementation on Glycemic, Insulinemic, and GLP-1 Response to Meals

Glycemic Response	
Cellulose	No change[23,38,82]
Soybean hulls	No change[38]
IDF (nonspecific)	Decrease[83]
Wheat bran	No change[24]
Soluble corn fiber	Decrease[84-86]
Sugarcane fiber	Decrease[24]
Beet pulp/pectin	Decrease[83,87] No change[23,24,88]
Guar gum	No change[82]
Chicory/inulin/FOS	Decrease[38,87,89] No change[23,88,90]

MOS	Decrease[83]
Pullulan	Decrease[84,85] No change[91]
Insulinemic Response	
Cellulose	No change[82]
Soybean fiber	Decrease[92]
Soluble corn fiber	Decrease[84-86]
Beet pulp/pectin	No change[82,88] Increase[23]
Guar gum	Decrease[88] No change[82]
Chicory/inulin/FOS	No change[88,89] Increase[23]
GLP-1 Response	
Cellulose	No change[23]
Beet pulp/pectin	Increase[23]
Chicory/inulin/FOS	Increase[23]

DF, Dietary fiber; *FOS*, fructooligosaccharide; *GLP-1*, glucagon-like peptide-1; *IDF*, insoluble dietary fiber; *MOS*, mannan-oligosaccharide.

Glycemic and insulinemic responses to DF-containing meals in dogs and cats with diabetes mellitus have been studied. Feeding well-regulated stable diabetic dogs diets classified as high-IDF, high-SDF, or low-DF did not affect insulin dosage. The high-IDF but not the high-SDF or low-DF diet decreased glycemic response to meals and lowered fructosamine concentrations.[39] Of the diets evaluated, however, the high-SDF diet contained less TDF than the high-IDF diet, and the DF in the high-SDF diet was predominantly IDF. Further, neither DF concentration nor composition of the low-DF diet was reported, although the low-DF diet contained both beet pulp and FOS. While the high-IDF diet was associated with improvement in glycemic response as compared with 2 other diets, whether insulin dosage can be attributed strictly to DF type or amount remains unclear. In another study of stable diabetic dogs, guar gum was superior to the control diet alone or to that food with wheat bran added, as assessed by decreased glycemic response to meals.[40] However, the amount and type of DF present in the basal diet were not described. A third study on stable diabetic dogs evaluated 2 diets, one classified as high-IDF and the other low-IDF. Mean fasting and postprandial BG were lower with the high-IDF diet. Most dogs were better regulated with the high-IDF diet, as demonstrated with decreased insulin dosages.[41] In this study, the low-IDF diet contained a moderate amount of DF, which was predominantly IDF. The high-IDF diet had a nearly identical formulation but was supplemented with additional cellulose. The improvement in glycemic control can be interpreted as most dogs responding better clinically to a high, rather than moderate, IDF diet. No interpretation about effects of SDF or a low-DF diet can yet be made. A study of dogs with alloxan-induced diabetes demonstrated that supplementation of cellulose or pectin lowered glycemic response to food.[42] Cats with naturally-acquired diabetes mellitus were fed either high-IDF cellulose-supplemented diets or those described as low-IDF-unsupplemented diets (low in TDF, with TDF composed entirely of IDF). Improved glycemic control was demonstrated in diabetic cats given the high-IDF diet. Most cats were better controlled on the high-IDF diet.[43]

Lipid Metabolism

In addition to potentially affecting digestibility of dietary fat and interfering with enterohepatic recirculation of cholesterol, fermentable DF also may reduce hepatic lipogenesis (Table 190-5; see ch. 182).[44]

TABLE 190-5

Effects of DF Supplementation on Serum Lipid Parameters in Dogs and Cats

Triglycerides	
Flax	No change[93]
Sugarcane fiber	Decrease[24]
Beet pulp/pectin	No change[24] Decrease[87]
Guar gum	Decrease[88]
Chicory/inulin/FOS	No change[88] Decrease[87]
Cholesterol	
Cellulose	Increase[82]
Wheat bran	Increase[24]
Beet pulp/pectin	Decrease[82] No change[24,87]
Guar gum	Decrease[88]
Chicory/inulin/FOS	No change[87]

DF, Dietary fiber; *FOS*, fructooligosaccharide.

Protein/Nitrogen Metabolism

Since feeding fermentable DF promotes colonic bacterial growth involving synthesis of microbial protein from nitrogen, it has been theorized that the feeding of fermentable DF will promote overall loss of nitrogen into stool. FOS, beet pulp, and a blend of SDF fed to dogs increased fecal microbial nitrogen in one study, but no change in fecal nitrogen excretion was seen in cats fed a FOS supplement.[20,45] In these cats, no decrease in serum urea was demonstrated.

Food Intake

Energy derived from absorbed VFA is negligible, yet DF contributes to total volume of food consumed.[46-49] This dilutional effect on energy density, in addition to DF's effects on gastric emptying and on GLP-1, can be beneficial in weight loss programs. In dogs fed IDF-supplemented diets, food intake increased, but calorie intake decreased.[50] Beet pulp and oat fiber increased food and calorie intake in one study of dogs, but peanut hulls, wheat bran, beet pulp or tomato pomace did not affect intake in another.[35,36] Cats supplemented with high concentrations of cellulose decreased their intake with lower levels of supplementation than used in dogs.[51]

Satiety was studied in dogs using an unsupplemented test meal after giving diets supplemented with beet pulp or FOS.[52] Dogs consumed less test meal and less of the supplemented diets. Diets supplemented with IDF, SDF, wheat bran, cellulose, almond shell flour, pea fiber, or lentils and fed to food-restricted dogs in a weight-loss program failed to decrease test meal intake.[53-55] Similar results were obtained with cellulose-fed cats.[51] In dogs, a high-protein, high-TDF diet including cellulose, psyllium husk, beet pulp, and FOS reduced total intake, whereas high-protein or high-TDF diets alone failed to reduce intake.[56]

Beagle puppies fed wheat bran–supplemented diets showed a dose-dependent decline in feed intake, feed and protein efficiency and growth.[57] It should be noted that the concentration of DF at which this effect was seen is quite high and not consistent with commercial pet food. In *Salmonella*-infected puppies, supplementation with inulin or FOS decreased illness-related decline in food intake.[25]

Immune System Effects

Much of the immune system is located in or around the gut. DF also affects parameters related to immune system function.[58] Table 190-6 summarizes effects of DF on white blood cells (WBCs) and immunoglobulins in dogs and cats. Lack of effect on WBC function has also been demonstrated.[59] Supplementation with yeast cell wall in dogs caused decreases in serum concentrations of IgA as well as in saliva and tears.[60] Bitches supplemented with FOS exhibited higher colostrum and milk IgM content without concomitant effect on IgG or IgA. Their puppies showed higher IgM response to *Bordetella* vaccination.[61] A mixture of beet pulp, gum arabic and FOS altered the T-cell composition of gut-associated lymphoid tissue and increased mitogen response in T cells.[59]

TABLE 190-6

Effects of DF on WBC and Immunoglobulin Parameters

WBC Parameters	
Cellulose	No change[13]
Flax	No change[93]
Beet pulp/pectin	No change[13,59]
Chicory/inulin/FOS	No change[13,17,59,67] Decrease lymphocytes[17]
Yeast cell wall/MOS	No change[13,67] Decrease lymphocytes[17] Decrease monocytes[79]
Arabinogalactan (specific forms)	Increase WBC, neutrophils, eosinophils[58]
Immunoglobulins	
Cellulose	No change[13]
Beet pulp/pectin	No change[13]
Chicory/inulin/FOS	No change[13,19,67]
Yeast cell wall/MOS	No change[13,19,67] Increase IgM[60]
Arabinogalactan	No change[58]

DF, Dietary fiber; *FOS*, fructooligosaccharide; *IgM*, immunoglobulin M; *MOS*, mannan-oligosaccharide; *WBC*, white blood cell.

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CHAPTER 191

Adverse Reactions to Foods

Allergies versus Intolerance

Jason W. Gagné

Client Information Sheet: Adverse Reactions to Foods

Adverse food reaction (AFR) is an umbrella term that encompasses both food intolerance and food allergy. Both disorders may lead to an abnormal response clinically manifesting as dermatologic and gastrointestinal (GI) signs. Food intolerance encompasses pharmacologic/metabolic reactions, food poisoning/intoxication, and food idiosyncrasy; it has no immunologic basis. Food allergy (also known as food hypersensitivity) is a term reserved for those with clinical signs due to an immunologic reaction (Figure 191-1).

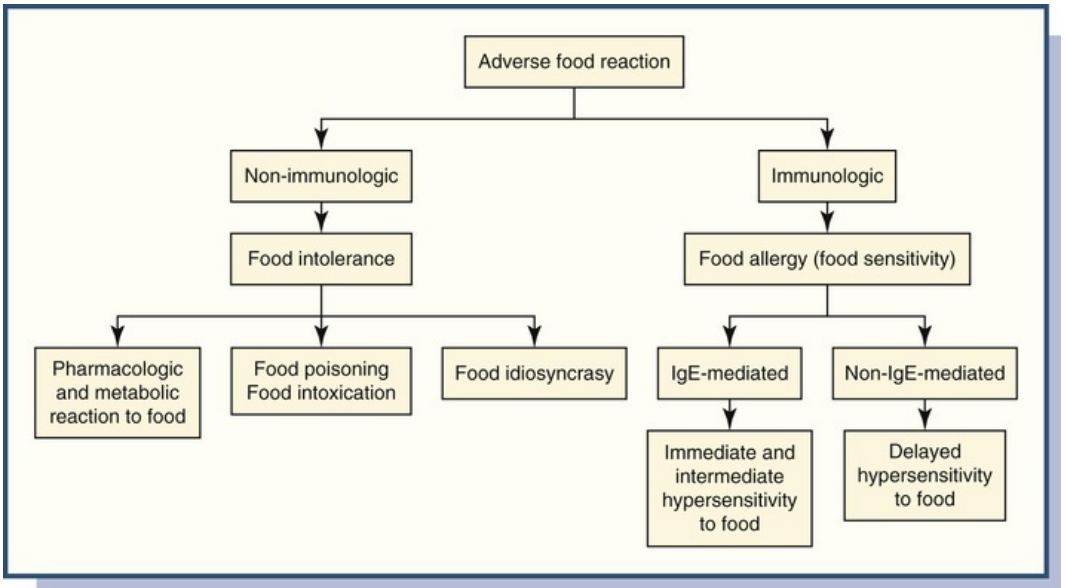

FIGURE 191-1 Classification of adverse reactions to food. *IgE,* Immunoglobulin E. (From Verlinden A, Hesta M, Millet S, et al: Food allergy in dogs and cats: a review. *Crit Rev Food Sci Nutr* 46[3]:259-273, 2006.)

The prevalence of AFR in dogs and cats varies from source to source. Of dogs with nonseasonal pruritic dermatoses, 10-30% are diagnosed as having AFR.[1-6] Of dogs with skin disease, only 1% has been attributed to food allergy.[7,8] Food allergy is the third most common skin allergy behind flea-allergy and atopic dermatitis and accounts for 10-15% of all allergic skin diseases.[9]

The prevalence of AFR in cats is reported to be 1-6% of all feline skin disease and is the third most common hypersensitivity.[10,11] Of dogs and cats diagnosed with food allergy, 15-50% are now recognized to have GI signs.[4,12-14] Additionally, pruritic patients with GI signs are more likely to be diagnosed as food allergic.

Food Intolerance

Since food intolerance has a nonimmunologic etiology, it does not require the stimulation and sensitization of the immune system as documented in food allergy. Therefore, it may occur on a first exposure to a food, "food additive, or substance."

Pharmacologic/metabolic reactions include an array of compounds. This category includes vasoactive and biogenic amines such as histamine found in scombroid fish (mackerel, tuna, skipjack), which may cause adverse reactions within minutes of ingestion. The concentration of histidine available for bacterial conversion to histamine to cause such reactions in unspoiled commercial pet food is low[15,16]; therefore, reactions are more prevalent in raw and spoiled homemade fish diets. The maldigestion with secondary malabsorption that causes an osmotic diarrhea (e.g., lactose intolerance) is an example of a metabolic adverse reaction.[17,18] Undigested lactose is rapidly fermented by small intestinal and colonic bacteria, creating short chain fatty acids, borborygmus, gas, abdominal discomfort, and diarrhea. Lactose activity of puppies drops to 10% at time of weaning compared to at birth.[17] The activity of brush border disaccharidases like lactase may also be decreased by viral infection, fasting, and dietary change.

Food poisoning/intoxication reactions occur in response to ingestion of food containing toxins or microbial contamination. Aflatoxin, a mycotoxin produced by *Aspergillus* spp. commonly found in grains, causes high mortality due to hepatic failure from hepatocellular necrosis (see ch. 286).[19,20] The U.S. Food and Drug Administration has set a maximum level of 20 ppb in human and pet foods,[21] yet dogs and cats are more sensitive to aflatoxin than are other species (rats, sheep, chicken, humans).[22] Therefore, pet food manufacturers set their tolerable levels lower than for human foods and regularly test raw ingredients and finished diets. Strains and toxins of bacteria known to contaminate food and cause acute enteritis in dogs and cats include *Salmonella, Campylobacter,* and *Clostridium* spp. in addition to *Escherichia coli.*

The term food idiosyncrasy is used to describe an abnormal response to food additives and substances such as gelling agents, gums, emulsifiers, preservatives, colors, and humectants. While they have all been implicated as a cause of GI disorders of dogs and cats, minimal evidence exists.[12,23]

Food Allergy

Food allergy is an AFR with an immunologic basis in response to ingestion/absorption of a dietary antigen, usually a dietary protein. The GI tract has a 3-pronged defense to reduce the potential of allergic responses.

The first defense is digestion. Proteins are exposed to various enzymes and compounds, such as pepsin, pH, and pancreatic and intestinal enzymes, which destroy antigenic factors of a protein. A second defense is the inherent functional barrier of the GI tract. One aspect of this is the tight junctions of epithelial cells. Under normal circumstances, only trace amounts (0.002%) of intact proteins will be absorbed, and these small amounts are removed by the reticuloendothelial or Kupffer cells of the liver and mesenteric lymph nodes.[24] In addition, peristalsis, the mucus layer, and secretory IgA found in the lamina propria provide added protection.[25] Lastly, the role of gut-associated lymphoid tissue (GALT) is to distinguish "self" from "nonself," to eliminate those foreign to the body, and to protect components of "self." All dietary antigens are foreign, which speaks to the fascinating ability of the GALT to create an oral tolerance to nutrients while removing pathogens. A compromise in any of these three systems may lead to development of food allergy.

The primary lymphoid tissue where oral tolerance occurs is the microfold (also known as M) cells of the Peyer's patches in the intestinal epithelium. The M cells sample potential antigen and microorganisms from the lumen of the intestine,[26] and oral tolerance occurs with the acceptance of a food antigen through complex interactions of antigen-presenting cells, B cells, dendritic cells, macrophages, and T cells. Alternatively, the process of sensitization and stimulation to a food antigen may occur, resulting in an immunologic response. This response involves antigen-specific lymphocytes and IgE-bearing mast cells leading to inflammation and clinical manifestations of dermatologic and/or GI signs that have been compared to Types I, III, and IV hypersensitivities.[27]

The majority of food allergens that elicit an immune response in humans are water-soluble glycoproteins with molecular weights between 10-70 kDa, which are relatively stable to heat, pH, and digestive enzymes.[28-31] In dogs, all recognized allergic proteins have weighed ≥20 kDa,[32,33] and the most common food allergens are beef, dairy products and wheat. In cats, the most common food allergens are beef, dairy products, and fish.[34] This reflects the most commonly fed ingredients in commercial pet food.

Clinical Features

Dermatologic Responses in Dogs (see also ch. 186)

There are no sex or age predilections for cutaneous disease due to AFR in dogs.[6,8,35,36] The age at which clinical signs have been reported range from 4 months to 14 years,[37] with initial signs reported in those less than 1 year of age in 33-51% of cases. Increased risk has been reported in the following breeds: Boxers, Chinese Shar-Pei, Cocker Spaniels, Collies, Dachshunds, Dalmatians, German Shepherds, Golden Retrievers, Labrador Retrievers, Lhasa Apsos, Miniature Schnauzers, Soft-Coated Wheaten Terriers, Springer Spaniels, and West Highland White Terriers.[6,35,38-40]

Presentation of dogs with AFR occurs on a nonseasonal basis and affected dogs may resemble those presenting with atopic dermatitis. Clinical signs include variable degrees of pruritus that may be generalized or localized to the face, pinnae, and perineal, axillary, inguinal, and paw regions.[6,35,38-40] Secondary bacterial/yeast infections, papules, pustules, epidermal collarettes, and seborrhea may also be observed.[6,8,35,36] Otitis externa has been noted with bacterial and/or *Malassezia* infections. Chronic changes may include hyperpigmentation, lichenification, and alopecia. See Figure 191-2, *A-E* for dermatologic clinical manifestation of canine AFR.

FIGURE 191-2 **A** and **B,** Otitis externa with secondary bacterial and *Malassezia* infection. **C,** Erythematous muzzle. **D,** Erythematous periocular region with scaling of facial region. **E,** Erythematous cervical, axillary, and inguinal regions with secondary bacterial infection. (Images courtesy Dawn Logas, DVM, DACVD, Veterinary Dermatology Center, Maitland, FL.)

Uncommon clinical signs that have been reported include urticaria (hives) characterized by wheals,[41] erythema multiforme,[42] vasculitis,[43] and anaphylaxis (see ch. 137). Angioedema, a localized form, is characterized by edematous swelling of the lips, face, eyelids, ears, conjunctivae, and/or tongue, with or without pruritus. Angioedema may also result from drugs, vaccines, infections, atopic dermatitis, and blood transfusions.

Dermatologic Responses in Cats (see also ch. 186)

There are no sex or age predilections for cutaneous disease due to AFR in cats. The mean age of onset is 4-5 years. The age at which clinical signs have been reported ranges from 6 months to 11 years,[8,44] with 46% of cats experiencing initial signs by the age of 2 in one study.[45] Increased risk has been reported in Siamese, Siamese-cross, and Birman cats.[6]

Clinical signs include nonseasonal, localized or generalized pruritus in 100% of cats with food allergy.[40,45] Pruritus is primarily localized to the head, neck, and ears (which may lead to severe self-trauma) but may spread to the limbs, ventral abdomen, and inguinal region. Alopecia due to "fur-mowing," as well as exfoliative, exudative, and military dermatitis and secondary scaling dermatoses, have been reported. Otitis externa, eosinophilic plaques and ulcers may also develop. Urticaria, angioedema, and conjunctivitis may occur.[44-46]

In cats diagnosed with food allergy, 20-50% have an absolute eosinophilia,[46,47] and 30% have been noted to have a moderate to marked peripheral lymphadenopathy.[37]

Pruritic Threshold

The concept of the pruritic threshold is that each individual dog or cat has a different tolerable level; once it is reached, pruritus develops. The stimuli that cause one to reach or exceed one's threshold include (but are not limited to) ectoparasites, atopic dermatitis, and diet. Regarding ectoparasites and atopic dermatitis, these stimuli may not be present (or may be pharmacologically controlled) at certain times of year and therefore may lower the allergen load to threshold for an individual. This would allow a dog or cat to tolerate a food that he/she could be allergic or intolerant to without experiencing the clinical manifestation of pruritus. This situation would result in food allergy appearing to be seasonal in nature.

It is not uncommon to observe an allergic response that is caused by multiple allergens in the same patient. In dogs, 20-30% of food allergy cases have skin disease including atopic dermatitis and flea allergy.[5,6,38,40] In a study of cats, 35% had concurrent flea allergy.[52] The combination of diseases may hinder diagnosis of food allergy and highlights the importance of diet and dietary history as a means of reducing allergen load to avoid exceeding the pruritic threshold.

Gastrointestinal Responses in Dogs and Cats

There are no sex or age predilections for gastrointestinal disease due to AFR in dogs or cats. Breeds more commonly affected include the Chinese Shar-Pei, German Shepherd, and Irish Setter.[37] Clinical signs may include vomiting, borborygmus, intermittent abdominal pain, and diarrhea (increased frequency, volume, and loosened consistency).[2,5,8,36,44,47]

AFR is included in a vast array of differential diagnoses for GI disease since it can occur in every segment of the GI tract and may present as acute or chronic. Acute onset of AFR is likely food intolerance rather than food allergy.

The well-documented gluten-sensitive enteropathy of Irish Setters appears to be inherited (see ch. 276).[48] Clinical manifestations from gliadin and glutenin (proteins of cereal grains) occur at an early age and are reversible when these dogs are fed a gluten-free diet. This is not the same disease of humans known as celiac disease.[49]

Inflammatory bowel disease (IBD) involves a complex interplay between host genetics, immune status, and microflora. Diet has an effect on quantity and diversity of microflora.[50,51] It is possible that alterations in the

microflora may occur in patients with AFR, which may contribute to development of IBD, but currently the role of AFR is unknown.

Diagnosis

After history (see ch. 1 and 170), physical examination (see ch. 2 and 10), and minimum database (to rule out other causes) have been completed, AFR may be suspected with appropriate clinical signs. A food elimination trial (see ch. 186) is the most important diagnostic tool, although it cannot elucidate the underlying pathogenic mechanism of AFR. A clinical diagnosis is made after resolution of clinical signs on an elimination diet, followed by recrudescence of clinical signs upon reintroduction of the former food after the trial.[27,53] If only GI signs are present, a trial of 2-4 weeks may be sufficient,[23] whereas a trial of 8-12 weeks may be necessary for those with dermatologic signs.[54]

A complete dietary history and owner compliance are of utmost importance. The owner must remove all potential allergens including current diet, flavored medications and toys, treats, food used to administer medications, table scraps and access to other pet food if in a multipet household. Lack of owner compliance has resulted in up to a 33% dropout rate for dogs at referral centers.[2,6,55,56] To increase owner compliance, the elimination diet chosen should be a complete and balanced palatable food for the appropriate life stage, and convenient for the owner to feed. The food chosen should contain a limited number of protein sources that are intact or hydrolyzed, to which the patient has not been exposed previously, and that are highly digestible. For the GI patient, a moderate restriction in fat and a source of fermentable fiber are advised.

Diagnosis by any other means including intradermal skin testing, serology, and gastroscopy should be avoided due to low sensitivity and specificity.[57-62] An outline of how to perform a food elimination-challenge trial may be found in Figure 191-3 and additional infomration is presented in ch. 186.

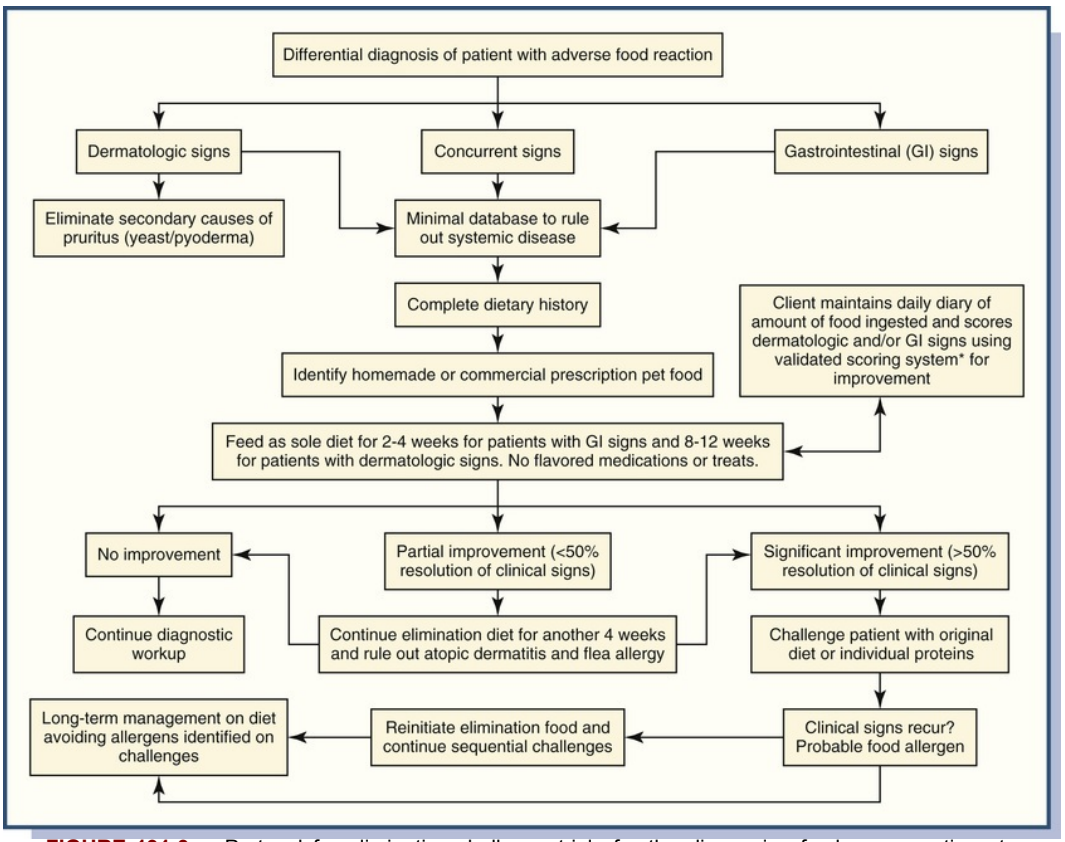

FIGURE 191-3 Protocol for elimination-challenge trials for the diagnosis of adverse reactions to food. (*Pruritus scoring system: From Paterson S: Food hypersensitivity in 20 dogs with skin and gastrointestinal signs. *J Small Anim Pract* 36:529-534, 1995. Fecal scoring system—St. Joseph, MO. Nestlé Purina 2014.)

Homemade Elimination Diets

Homemade diets containing a single protein and carbohydrate source traditionally have been considered the "gold standard" and used as an elimination diet for diagnosis of AFR.[4] This approach is 100% dependent on dietary history, since chosen ingredients are limited to those to which the patient has not been previously exposed. Due to the limited number of ingredients, homemade diets are typically not complete and balanced. They often lack calcium, essential fatty acids, certain vitamins, and other micronutrients, leading to long-term nutritional deficiencies. Previous studies have found that >90% of homemade diet recipes are not complete and balanced according to Association of American Feed Control Officials recommendations.[63,64] If a homemade diet is chosen, the client is encouraged to consult with a board-certified nutritionist (see ch. 192). A list may be found at acvn.org.

Commercial Elimination Diets

This category includes novel protein and hydrolyzed diets. Both options are complete and balanced, convenient for an owner to feed, and do not involve the labor of a homemade diet. If the novel protein diet approach is chosen, dietary history again is critical, and a veterinary prescription diet should be chosen. In a recent study, 75% of over-the-counter (OTC) venison diets were found to contain poultry, soy, and/or beef when analyzed by ELISA.[65] Cross-contamination of common ingredients with those considered novel may occur at various points of manufacturing but is unacceptable. Thus, it is not recommended to use OTC novel protein diets for an elimination diet.

With the expanding variety of "novel proteins" being used OTC, the use of hydrolyzed protein diets has gained popularity. Hydrolysis of a protein results in a reduced molecular weight and altered shape in comparison to the parent protein. The goal is to reduce allergenicity and antigenicity because the hydrolysate is too small to elicit cross-linking of IgE on the mast cell; this therefore prevents degranulation and clinical signs if the AFR is similar to a Type I hypersensitivity. A common misperception is that all hydrolyzed proteins must be less than 10 kDa, when in fact the optimal molecular weight of a protein hydrolysate varies with the type of protein used.[34] In a study of confirmed soy- and corn-allergic dogs, 79% did not experience clinical signs when fed a hydrolyzed soy and cornstarch diet.[66] In a separate study of chicken-allergic dogs, clinical signs improved in 11 of 12 dogs when they were fed a hydrolyzed chicken diet.[67] In a study of canines with naturally occurring chronic small intestinal disease, significantly more dogs were asymptomatic when fed a hydrolyzed diet (as evaluated by the Canine Inflammatory Bowel Disease Activity Index) in comparison to a highly digestible diet.[68]

Treatment

Treatment of AFR entails identifying and avoiding the offending food allergens once identified (see ch. 186). Some dogs and cats may suffer adverse reactions to even trace amounts of an offending food, whereas others may have a higher threshold. Concurrent allergies may influence the threshold level of clinical signs in some animals, in which case pharmacotherapy may be necessary. A complete and balanced diet should be chosen after taking a thorough dietary history. If a homemade diet is chosen, a board-certified nutritionist should be consulted to ensure nutritional adequacy. An attempt should always be made to find an acceptable commercial food that will increase owner compliance. Commercial hydrolyzed diets may be the best practical choice, since relapse is possible if the patient becomes allergic to another protein source, at which point another food trial should be performed.

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CHAPTER 192

Unconventional Diets (Homemade, Vegetarian, and Raw)

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Client Information Sheet: Unconventional Diets (Homemade, Vegetarian, and Raw)

Although most pet owners in the United States feed conventional commercial pet foods, there is a growing interest and market for unconventional diets. Unconventional diets include specialty niches such as vegetarian, natural, organic, and a variety of home-prepared raw and cooked diets. Pet owners' motivation for feeding unconventional diets varies, but much of the changing market has been attributed to the humanization of pets and the importance that food plays in the human-animal bond. Some proponents of home-prepared or raw food diets cite benefits such as control over ingredients, avoidance of artificial preservatives, preservation of natural enzymes, and incorporation of phytonutrients.[1] Other reported motives include a desire to pamper, to provide a more wholesome or nutritious diet, for medical benefits, to improve dental health, or to offer a diet that more closely resembles that of wild canids or felids.[1]

Unconventional Commercial Foods

Among pet owners, there is a growing interest in natural food, organic food, and desire to feed pets according to their own philosophy toward food. In addition, pet owners have a higher concern with pet food safety due to recalls, such as the large-scale recall in 2007 associated with melamine and cyanuric acid. These goals and concerns have resulted in greater interest in unconventional foods that may be perceived to have a higher level of quality and safety.[2]

With this growing interest in unconventional foods, a wide spectrum of products has entered the market with nutritional philosophies that have built upon human trends. Many of these new products have grown what has been called the "natural" pet food segment. As defined by the Association of American Feed Control Officials (AAFCO), the term natural includes "a feed or ingredient derived solely from plant, animal or mined sources, either in its unprocessed state or having been subject to physical processing, heat processing, rendering, purification, extraction, hydrolysis, enzymolysis or fermentation, but not having been produced by or subject to a chemically synthetic process and not containing any additives or processing aids that are chemically synthetic except in amounts as might occur unavoidably in good manufacturing practices."[3] Natural pet food products have expanded this regulatory definition by including ingredients that a pet owner would consider "natural," such as fruits, vegetables, and avoiding ingredients that are not recognizable or familiar.[3] The majority of these diet types are designed within the same nutritional parameters of conventional commercial food but offer choices to pet owners seeking to include or avoid specific ingredients based on real or perceived health needs or benefits. Given the limited amount of data in this area, there is an opportunity for further research to better understand natural pet foods and their effects on growth, performance, nutrient availability, digestibility, and other health parameters.

Although nutritional "adequacy" is not a primary concern with most commercial complete and balanced unconventional pet foods, there are some concerns when feeding a vegetarian or vegan diet, particularly to cats. A segment of pet owners has shown interest in feeding vegetarian- and/or vegan-based diets aligned with their dietary philosophies. Unlike pet owners who seek diets that are more natural for their pet, owners feeding vegetarian or vegan foods may be motivated by ethical reasons.[4] Because cats are obligate carnivores, feeding them vegan or vegetarian foods raises concerns regarding essential nutrients. In addition to their higher protein requirement, cats have a unique need for nutrients such as arachidonic acid, niacin, cobalamin, pyridoxine, vitamin A, vitamin D, and some amino acids such as taurine, arginine, methionine, and lysine.

These nutrients can be limited in vegan and vegetarian diets, making it difficult to meet cats' minimum requirements.[5] One study evaluating two commercially available feline vegan diets by laboratory analysis found multiple nutrient deficiencies, including total protein, methionine, taurine, lysine, arginine, arachidonic acid, calcium, phosphorus, vitamin A, pyridoxine, niacin, and cobalamin.[6] This study reinforced concerns that had been raised about feeding cats vegan or vegetarian foods. Cat owners should be alerted to these risks when electing to feed these food types. Pet owners should be encouraged to feed cats a meat-based diet, but in cases where this is not achieved, monitoring blood and plasma amino acid levels is one assessment that can be offered to help to identify potential deficiencies prior to the development of clinical problems. In addition, more regular veterinary exams (at least every 6 months) are also recommended to help identify potential nutrient deficiencies.

Home-Prepared Diets

Overview

A 2008 survey of pet owners in the United States and Australia showed that noncommercial foods (i.e., table scraps, leftovers, or homemade foods) were fed as part of the main diet in 30.6% of dogs and 13.1% of cats.[1] These noncommercial foods comprised at least one quarter of the diet in about 17% of dogs and 6% of cats. Fewer than 3% of pet owners in this survey reported feeding exclusively home-prepared diets, but approximately 7% of dogs received at least half their diet as home-prepared foods.

A more recent study surveying dog breeders suggests that frequency of feeding home-prepared foods may be on the rise, with about 11% feeding exclusively home-prepared diets for all life stages.[7] Home-prepared diets were fed more frequently by Canadian breeders (35.7%), and fed least frequently by breeders in the southern region of the United States (6.3%). The type of diet fed (home-prepared vs. commercial) was significantly associated with breeder trust for all sources of information on nutrition. Breeders who fed home-prepared diets were about 8 times as likely to rate veterinarians as not very trustworthy or not at all trustworthy as sources of nutrition information, compared with those who fed commercial diets. Additionally, breeders feeding home-prepared diets rated nonveterinarian websites, books, or email groups as very trustworthy or somewhat trustworthy sources of nutritional information. The findings in this study support those from a previous study that pet owners feeding unconventional home-prepared diets are seeking alternatives based on perceptions of quality and safety, as well as a mistrust of pet food manufacturers and veterinarians that recommend conventional diets.[2] This underscores the importance of nutritional education for veterinarians and the ability of veterinarians to provide solid nutritional advice to clients, helping to improve trust and compliance with nutritional recommendations.

Nutritional Adequacy of Home-Prepared Diets

One of the primary concerns with feeding home-prepared foods is appropriate nutritional balance and adequacy. Of 54 pet owners feeding their pet at least half of the diet from homemade foods in the 2008 survey, only 16 used a recipe designed for pets. Of these recipes, 8 were from a veterinarian, 3 were obtained from the Internet, and 5 were from other sources.[1] Although the nutritional adequacy of these diets was not evaluated, it raises concerns regarding potential misinformation available to the public regarding home-prepared diets for dogs and cats. Of more concern is the large portion of owners who fed home-prepared foods not designed for pets.

Nutritional inadequacy and/or improper balance are problems that can affect both home-cooked and raw food diets. One study evaluating the nutritional adequacy of homemade pet diets from six published resources (49 maintenance and 36 growth diets) found that 86% had inadequate levels of various minerals, 62% had inadequate levels of various vitamins, and 55% had inadequate protein or essential amino acids.[8] Another study evaluating the nutritional adequacy of 5 raw diets (2 commercial and 3 home-prepared) found that all had essential nutrients below minimum recommended AAFCO levels.[9] In addition to these deficiencies, all 3 home-prepared raw diets had improperly balanced calcium-to-phosphorus (Ca, P) ratios, two had excessive levels of vitamin D, and one had excessive levels of vitamin E.[9]

One study evaluated 200 recipes from a variety of sources, including veterinary textbooks, pet care books for owners, and on-line websites.[10] This study highlighted the concern that most recipes (92%) contained vague or incomplete instructions concerning ingredients, method of preparation, or supplements. Most (89.5%) recipes did not include feeding instructions. Some had large variations in calorie content for different

recipes recommended for the same-size pet. Vague instructions and lack of feeding guidelines can result in highly variable results depending on pet owner interpretation and may lead to inappropriate feeding practices and increased risk for malnutrition. Overall, most recipes (95%) had at least one essential nutrient at concentrations that did not meet NRC or AAFCO guidelines, and many recipes (83.5%) had multiple deficiencies. The most common nutrient deficiencies were zinc, choline, copper, the combination of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA), Ca, vitamin D, and vitamin E. Nine recipes surpassed the safe upper limit for vitamin D, and 6 surpassed safe upper limits for combining EPA and DHA.

Studies evaluating home-prepared recipes for pets with medical conditions, such as renal disease and cancer, have been published.[11,12] Similar to studies evaluating adult maintenance diets, these studies have shown numerous concerns with nutritional inadequacy and highly variable recipe and preparation instructions. Additionally, some key nutrients for the indicated condition, such as P and omega-3 fatty acids for renal management, were above or below recommended levels and may not have been ideally designed to manage the condition.[11] The key conclusion coming out of these studies is that there is an increasing need for veterinarians to counsel clients on the potential risk of feeding home-prepared diets and to encourage clients to consult with board-certified veterinary nutritionists who have experience in formulating diets to ensure optimal nutrition for both maintenance and disease management.

In addition to deficiencies in nutrient profiles, clinical nutrient deficiencies secondary to unbalanced home-prepared foods have been reported.[13-17] Inadequate Ca and improper Ca-to-P ratios are common problems reported in dogs and cats fed unbalanced home-prepared foods.[13,14,16,17] Calcium deficiency, with or without vitamin D deficiency, may cause nutritional secondary hyperparathyroidism (see ch. 69 and 187). Young, growing animals commonly develop long bone abnormalities, while adult animals have been reported to develop bone resorption of the mandible and maxilla, resulting in a rubber jaw syndrome.[13,14,16] One report of a 6-year-old dog fed an unbalanced home-prepared diet for 18 months to manage lymphocytic-plasmacytic enterocolitis documented nutritional secondary hyperparathyroidism, low serum 25-hydroxycholecalciferol concentration, and clinical and computed tomography findings consistent with rubber jaw syndrome.[14] As with many nutritional deficiencies, underlying Ca deficiency is not commonly recognized until stores are significantly depleted. Thus, pets on unbalanced diets may not display clinical signs of underlying nutritional insufficiency. Similarly, many nutrient deficiencies, such as Ca, are not readily apparent on routine blood work because serum concentrations are tightly regulated despite severe dietary deficiencies.

In growing animals, clinical signs of nutritional deficiency will often be more severe and pronounced. An 8-month-old Shetland Sheepdog fed a commercially available muesli-vegetable powder premix combined with raw ground beef over a 4-month period was reported to be thin and abnormally small in stature, with short thoracic limbs relative to the pelvic limbs. This dog had a sudden onset of neck pain, collapse, and inability to rise.[16] Diffuse osteopenia, polyostotic deformities associated with fracture remodeling, and an apparent floating dental arcade were noted on radiographic evaluation. Hypocalcemia, hypophosphatemia, and low vitamin D values were identified. The severity of clinical signs were similar to those of an 8-month-old Saint Bernard fed an unbalanced home-prepared diet due to chicken intolerance whose hypocalcemia resulted in tetanic seizures. This prompted veterinary evaluation and confirmation of nutritional secondary hyperparathyroidism and taurine deficiency.[17] Although taurine is not an essential nutrient for dogs, taurine deficiency–associated dilated cardiomyopathy has been identified in some breeds, including Saint Bernards.[18] These reports highlight the importance of assessing a complete dietary history at all veterinary examinations, particularly in growing animals in which malnutrition can have more severe consequences (see ch. 170).

Evaluating Nutritional Adequacy of Home-Prepared Foods

Chemical nutrient analysis, usually cost-prohibitive, is the ideal method to assess nutrient composition of a home-prepared food. Most diets are assessed with computer-based analysis. A study that utilized both computer-based and chemical nutrient analysis of 15 home-prepared diets showed that computer-based analysis is highly predictive of deficiencies and excesses.[10] However, the study did show that absolute values of specific nutrient concentrations ranged between 0.21-62.1%. This likely reflects variation in nutrient data on individual ingredients, which can vary seasonally and by geographical location. Nutrient profiles of individual ingredients can be obtained from databases, such as the USDA Nutrient Database (E-Table 192-1). However, they only provide an average and actual ingredients used in home-prepared diets likely vary. For this reason, it is recommended that pets fed home-prepared foods be routinely monitored and that dietary reassessments occur on a regular basis. In addition to seasonal and geographical variations, nutrient content of ingredients can vary by cooking methods, cut of meat, and portion of the plant fed. When collecting a diet

history, it is important to include all foods fed, amounts, and cooking methodologies for any home-prepared ingredients. Once the diet history is complete, the pet's diet can be evaluated with the use of computer-based analysis.

E-TABLE 192-1

Nutrition Resources

Some Institutions with Clinical Nutrition Faculty and Residents Available for Consultation		
Cornell University	http://www.cuvs.org/services-nutrition.php	203-595-2777
Massey University Veterinary Teaching Hospital	http://www.massey.ac.nz/massey/learning/colleges/college-of-sciences/clinics-and-services/veterinary-teaching-hospital/companion-animal-avian-clinic/companion-animal-avian-clinic_home.cfm	+64 06 350 5329
North Carolina State University	http://www.cvm.ncsu.edu/vhc/vhwc/nutrition/index.html	919-513-6999
Royal Veterinary College Queen Mother Hospital for Animals	http://www.rvc.ac.uk/small-animal-referrals/	+44 (0)1707 666366
The Ohio State University	http://vet.osu.edu/nssvet	614-292-3551
Tufts Cummings School of Veterinary Medicine	http://vet.tufts.edu/fhsa/veterinary_specialties/clinical_nutrition.html	508-839-5395 ext. 84696
University of California, Davis	www.vmth.ucdavis.edu/vmth/services/nutrition/nutrition.html	530-752-1387
University of Florida	http://smallanimal.vethospital.ufl.edu/clinical-services/integrative-medicine-services/nutrition/	352-392-2235
University of Georgia	http://vet.uga.edu/vph/people/sanderson	706-542-5870
University of Guelph Ontario Veterinary College	http://www.ovc.uoguelph.ca/hsc/en/aboutovchealthsciences/Nutrition.asp#Link to Clinical Nutrition Information	519-823-8830
University of Pennsylvania	http://www.vet.upenn.edu/veterinary-hospitals/ryan-veterinary-hospital/services/nutrition	215-746-8387
University of Tennessee	http://www.vet.utk.edu/clinical/sacs/nutrition.php	865-974-8387
University of Minnesota	http://www.cvm.umn.edu/vmc/specialties/nutrition/	612-626-8387
University of Missouri	http://www.vmth.missouri.edu/clin_nu.htm	573-882-7821
Universiteit Utrecht	http://www.uu.nl/en/organisation/veterinary-patient-care	+030 253 9411
Virginia-Maryland College of Veterinary Medicine	http://www.vetmed.vt.edu/vth/nutrition/index.asp	540-231-4621
Veterinary Nutrition Consulting Services		
All Creatures Veterinary Nutrition Consulting	http://allcreaturesnutrition.com/	707-429-2433
Davis Veterinary Medical Consulting, Inc.	www.dvmconsulting.com www.balanceit.com	530-756-3862 888-346-

		6362
Gulf Coast Veterinary Specialist, Telemedicine	www.gcvtelemed.com/nutrition.html	713-579-2568
Oradell Animal Hospital	http://oradell.com/services-staff/nutrition-counseling/	201-262-0010
Red Bank Veterinary Hospital	http://www.rbvh.net/medical-services/clinical-nutrition.html	732-747-3636
Vets Now Referrals	http://www.vetsnowreferrals.com/veterinary-referral-glasgow/nutrition-advice-glasgow/	+44 (0)141 332 3212
Veterinary Nutritional Consultations	www.petdiets.com	252-257-1959
Veterinary Nutrition Organizations		
American College of Veterinary Nutrition	www.acvn.org	
American Academy of Veterinary Nutrition	www.aavn.org	
European Society of Veterinary and Comparative Nutrition	http://www.esvcn.eu/society	
European College of Veterinary and Comparative Nutrition	www.esvcn.eu/college	
Human Foods Nutrient Content Information		
USDA Nutrient Database	www.nal.usda.gov/fnic/foodcomp/search/	

While detailed evaluations should carefully assess the nutritional adequacy and balance of a diet, there are ingredients that can be evaluated quickly (Figure 192-1). One should determine the amount of unbalanced food provided daily. Many pet owners feed small amounts of unbalanced foods that still compromise a diet's nutritional adequacy and balance. Unbalanced foods and treats should provide no more than 10% of total daily caloric intake. When unbalanced foods are added to a complete and balanced diet, nutrient dilution occurs and essential nutrients may fall below minimum requirements. For example, meat is high in P and, when added to a complete and balanced diet, may result in unbalanced Ca:P ratios. Treats may cause the total intake of some components to exceed safe upper limits. For example, liver can be high in some vitamins and minerals, such as vitamin A.

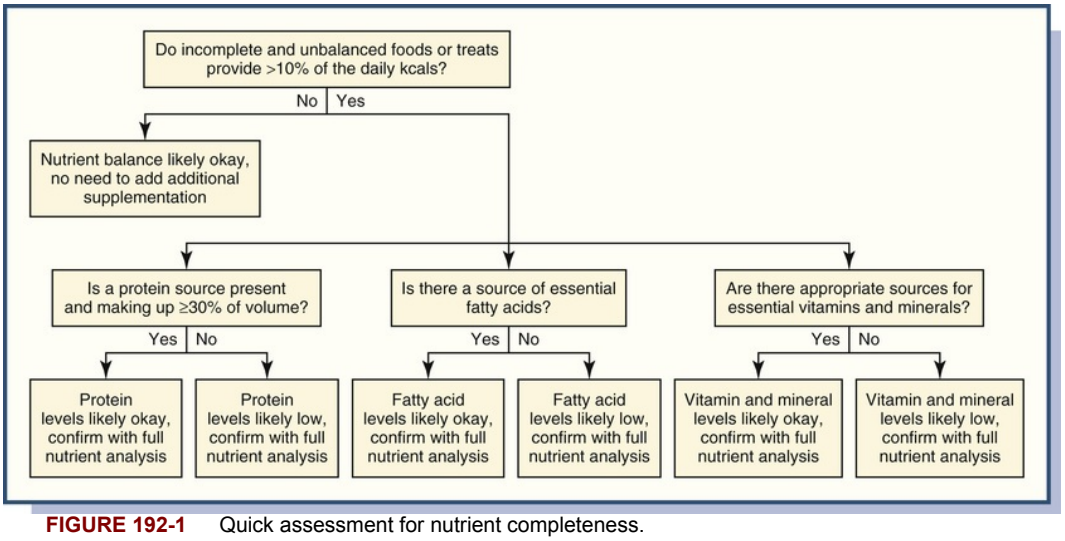

FIGURE 192-1 Quick assessment for nutrient completeness.

If unbalanced foods do provide more than 10% of the total daily caloric intake, they should be assessed for essential nutrients. First, identify the source of protein and essential amino acids, such as meat or a vegetarian (e.g., soy) protein. In general, protein should make up a least one-third of the diet by volume (higher amounts may be required for some vegetarian sources such as legumes). Dogs can generally perform well on vegetarian protein sources, but this is more challenging for cats. Vegetarian protein sources may not have enough sulfur-containing amino acids, such as methionine. Vegetarian protein also lacks arachidonic acid, an essential dietary fatty acid for cats, not dogs. Arachidonic acid, found primarily in animal fat, is difficult to provide in vegetarian diets. However, a recent study in cats demonstrated that feeding high amounts of borage oil, a source of gamma-linolenic acid (GLA), results in arachidonic acid enrichment of red blood cells, suggesting that diets containing high amounts of GLA may be a suitable substitute for preformed arachidonic acid.[19]

In addition to a source of arachidonic acid for cats, both dogs and cats require a source of linoleic acid (18 : 2 n-6). Linoleic acid is important for skin and coat health.[20] Animal fats often provide some linoleic acid, but most diets require additional sources to meet requirements. Vegetable oils (corn oil, walnut oil, canola oil, safflower oil, and soybean oil) can serve as dietary sources of linoleic acid. Of the readily available vegetable oils, corn oil and walnut oil have high concentrations of linoleic acid; therefore, less of these are required to meet minimum requirements and, accordingly, are frequently used by veterinary nutritionists.

Many pet owners like to cook with olive oil and may substitute olive oil for recommended vegetable oils. Olive oil has a high content of monounsaturated fatty acids (MUFAs). Studies in people have shown that MUFAs can help protect against heart disease by controlling low-density lipoprotein (LDL) cholesterol levels ("bad" cholesterol) while raising high-density lipoprotein (HDL) cholesterol levels ("good" cholesterol).[21] Therefore, olive oil is often recommended as part of a healthy diet for humans. However, dogs and cats do not maintain LDLs in circulation, preventing their oxidation and formation of atherosclerotic plaques.[22] Thus, some health benefits promoted for humans do not carry over to dogs and cats. Also, olive oil has low levels of linoleic acid, requiring four to five times the amount of olive oil (compared to corn or walnut oils) to meet requirements, significantly increasing fat content (Table 192-2). Thus, olive oil is avoided or used in combination with other sources of linoleic acid. Coconut oil is suggested and used as a source of medium-chain triglycerides but is a poor source of linoleic acid.

TABLE 192-2

Fatty Acid Contribution of Commonly Supplemented Oil and Fat Sources

				OMEGA-6 FATTY ACIDS		OMEGA-3 FATTY ACIDS		
Ingredient (Quantity) [USDA #]*	Saturated Fat (g)	Total MUFA (g)	Total PUFA (g)	LA	AA	ALA	EPA	DHA
				18 : 2† (g)	20 : 4† (g)	18 : 3† (g)	20 : 05 (g)	22 : 05 (g)
Corn oil (1 tsp–4.5 g) [04518]	0.583	1.241	2.46	2.395	0	0.052	0	0
Canola oil (1 tsp–4.5 g) [04582]	0.331	2.847	1.332	0.855	0	0.411	0	0
Safflower oil (1 tsp–4.5 g) [04511]	0.279	3.359	0.646	0.646	0	0	0	0
Olive oil (1 tsp–4.5 g) [04053]	0.621	3.283	0.474	0.439	0	0.034	0	0
Walnut oil (1 tsp–4.5 g) [04528]	0.410	1.026	2.848	2.38	0	0.468	0	0
Coconut oil (1 tsp–4.5 g) [04047]	3.892	0.261	0.081	0.081	0	0	0	0
Flaxseed oil (1 tsp–4.5 g) [42231]	0.426	0.916	2.992	0.576	0	2.416	0	0
Salmon oil (1 tsp–4.5 g) [04593]	0.894	1.307	1.815	0.069	0.03	0.048	0.586	0.135
Butter, unsalted (1 tsp–4.7 g) [01145]	2.431	0.995	0.144	0.129	0	0.015	0	0
Chicken fat (1 tsp–4.2 g) [04542]	1.27	1.907	0.892	0.832	0.004	0.043	0	0

*Fatty acid compositions acquired from the USDA National Nutrient Database. Nutrient values are expected to have natural variations, and individual sources should be verified.

†Some values approximated from undifferentiated values when n-3 or n-6 differentiation was not reported by the USDA.

AA, Arachidonic acid; *ALA*, alpha-linolenic acid; *DHA*, docosahexaenoic acid; *EPA*, eicosapentaenoic acid; *LA*, linoleic acid; *MUFA*, monounsaturated fatty acids; *PUFA*, polyunsaturated fatty acids; *tsp*, teaspoon; *USDA*, U.S. Department of Agriculture.

Although alpha-linolenic acid (18 : 3 n-3) has not been considered "essential" for dogs and cats, recent studies suggest that providing dietary alpha-linolenic acid provides some benefits for optimal health, especially in growing and reproducing animals.[20] Similarly, DHA is now known to be essential for optimal brain and retinal development in puppies.[23,24] The fatty acid content of commonly supplemented oils and fats are summarized in Table 192-2. Although alpha-linolenic acid can be provided by terrestrial vegetable oil sources (canola or flaxseed oils), algal or fish oil sources must be used to supply dietary long-chain omega-3 fatty acids such as EPA and DHA.

After assessing a home-cooked diet for essential proteins, amino acids, and fatty acids, one should identify the source of essential vitamins and minerals. Many foods contribute to the vitamin and mineral content of a diet, but a supplemental form is generally required to ensure recommended allowances are met. E-Table 192-3 outlines the National Research Council (NRC) recommended allowance of nutrient per 1000-kcal diet for adult dogs, cats, and the nutritional content of an unsupplemented diet consisting of 1/3 roasted chicken breast and 2/3 white long-grain rice. Depending on supplements used, combining multiple supplements may be required to meet all essential needs specific for dogs or cats. Most multivitamin/multimineral supplements designed for people are limited in one or more essential vitamins and trace minerals required to meet canine and feline minimum recommendations. Additional Ca, P, potassium, chloride, iodine, choline, and taurine (for cats) are commonly added to a multivitamin/multimineral supplement. All-in-one veterinary supplements, such as Balance IT (owned in part by author SJD), have been designed to meet nutritional needs of dogs and cats fed home-prepared foods.

E-TABLE 192-3

Comparison of National Research Council (NRC) Nutrient Requirements and Nutrition Composition of an Unbalanced Home-Prepared Chicken & Rice Diet

NUTRIENT	NRC ADULT DOG RECOMMENDED ALLOWANCE PER 1000 kcal	NRC ADULT CAT RECOMMENDED ALLOWANCE PER 1000 kcal	NUTRIENT CONTENT OF 1/3 ROASTED CHICKEN BREAST + 2/3 WHITE RICE*
Crude protein (g)	25	50	81.05
Amino Acids			
Arginine (g)	0.88	1.93	5.19
Histidine (g)	0.48	0.65	2.42
Isoleucine (g)	0.95	1.08	4.15
Methionine (g)	0.83	0.43	2.19
Methionine & cystine (g)	1.63	0.85	3.33
Leucine (g)	1.7	2.55	6.18
Lysine (g)	0.88	0.85	6.23
Phenylalanine (g)	1.13	1.0	3.40
Phenylalanine & tyrosine (g)	1.85	3.83	6.13
Threonine (g)	1.08	1.3	3.34
Tryptophan (g)	0.35	0.33	0.94
Valine (g)	1.23	1.28	4.17
Taurine (g)	NA	0.11	0.015

Total fat (g)	13.8	22.5	9.2†
Fatty Acids			
Linoleic acid (g)	2.8	1.4	1.6†
Alpha-linolenic acid (g)	0.11		0.0†
Arachidonic acid (g)	NA	0.015	0.13
Eicosapentaenoic + docosahexaenoic acid (g)	0.11	0.025	0.066†
Minerals			
Calcium (g)	1	0.72	0.08†
Phosphorus (g)	0.75	0.64	0.71†
Potassium (g)	1	1.3	0.7†
Sodium (g)	0.2	0.17	0.17†
Chloride (g)	0.3	0.24	0.18†
Magnesium (g)	0.15	0.1	0.12†
Iron (mg)	7.5	20	8.2†
Copper (mg)	1.5	1.2	0.5†
Manganese (mg)	1.2	1.2	2.4
Zinc (mg)	15	18.5	2.2†
Iodine (mg)	0.22	0.35	0.04†
Selenium (mg)	0.088	0.075	0.097
Vitamins			
Vitamin A (IU)	1263.3	833.25	43.7†
Vitamin D (IU)	136	70	29.2†
Vitamin E (IU)	17.8	10	0.8†
Thiamine (mg)	0.56	1.4	0.96†
Riboflavin (mg)	1.3	1.0	0.3†
Pantothenic acid (mg)	3.75	1.44	4.0
Niacin (mg)	4.25	10.0	37.2
Pyridoxine (mg)	0.375	0.625	1.77
Folic acid (mcg)	67.5	188	487.2
Vitamin B_{12} (mcg)	9	5.6	0.7†
Choline (mg)	422	637	131†

*Nutrient composition of home-prepared formula is based on computer evaluation using nutrient data acquired from the USDA National Nutrient Database. Nutrient values of finished formulas are expected to have natural variations, and individual formulas should be verified.

†Nutrient level below the NRC Recommended Allowance for Adult Maintenance of Dog and/or Cat.

When using a multivitamin/multimineral supplement designed for people, Ca and P are two key minerals that commonly fall short of necessary levels. Ca can be supplemented as Ca carbonate, Ca citrate, or a Ca and P combination such as dibasic or tribasic CaP or bone meal. Commonly, both a Ca-only and CaP supplements

are required to create an appropriate Ca:P ratio. Bone meal is readily available but has fallen out of favor due to concerns of lead contamination. When using Ca supplements designed for people, care should be taken to account for any added vitamin D. This is especially true when used in combination with other vitamin and mineral supplements that already provide vitamin D.

Salts can be used in home-cooked diets to provide additional Na, chloride, potassium, and iodide, including standard iodized salt, which provides Na, chloride, and iodine. Salt substitutes (potassium chloride mixtures) provide no iodine. Lite salt provides a 50 : 50 mixture of iodized salt and salt substitute. Choline, a component of choline phospholipids and a methyl donor for methylation reactions in the body, may need to be added. Other methyl donors, such as methionine, can serve as dietary choline equivalents. Therefore, dietary methionine levels above those required can serve to meet a portion of the choline requirement. However, because methionine can be a limiting amino acid, especially in reduced-protein diets, additional choline supplementation is generally recommended. Common limiting nutrients such as vitamin B_{12} and zinc may be required. Because simply adding higher quantities of the multivitamin/multimineral supplement can push other nutrients beyond safe limits, separate supplements addressing key limiting nutrients may be necessary.

Raw Food Feeding

In addition to potential nutritional inadequacies, feeding raw food carries risk of pathogenic bacterial infection, environmental contamination, and potential gastrointestinal (GI) obstruction by bones. Contamination with pathogenic bacteria in raw pet foods has been well documented.[25-27] Although the number of pets developing illness when fed raw food is unknown, well-documented cases have been reported, including salmonellosis in two cats from the same household fed a raw beef–based diet.[28] One of the 2 cats died after having clinical signs of weight loss, soft stools, and at least a week of anorexia. Tissue cultures taken from the lung, liver, spleen, and kidney at necropsy were shown to be positive for *Salmonella typhimurium.* Samples from the diet were not cultured. The second cat, examined 9 months later, was obtunded and euthanized at the owner's request. Necropsy revealed suppurative pneumonia and enteritis with villous blunting and erosion. Tissue cultures and subtyping revealed *Bordetella bronchiseptica* in the lung and *Salmonella enterica* serotype Newport in both lung and small intestine samples. Samples of the raw ground beef fed to this kitten were subsequently shown to be positive for *S. enterica* serotype Newport confirming the raw meat as the source of infection.

Many of the studies on raw food feeding practices have been conducted in Greyhound racing and breeding facilities, where feeding raw meat is common. One investigation of an outbreak of diarrheal disease and death of young puppies at a Greyhound breeding facility revealed *Salmonella enterica* infections that were traced back to raw beef fed to the dogs.[29] Necropsies revealed *S. enterica* septicemia, enteritis, and colitis. Multiple samples were collected from the facility, and *S. enterica* was recovered from 88 of 133 samples. 57 of 61 fecal samples (93%) were positive, and 75% of raw meat samples being fed were also positive. Other positive samples were collected from the soil, food bowls, water buckets, the kitchen sink, cleaning tools, floor surfaces, and flies. Serotyping of 88 samples positive for *S. enterica* revealed 94.3% Newport, 3.4% Typhimurium, 1.1% Anatum, and 1.1% Uganda serotypes. The Newport serotype was identified in multiple samples of the raw meat, confirming the raw meat as the primary source of the infection. More recently, commercially available raw foods have attempted to mitigate some of these pathogen risks through the use of high hydrostatic pressure processing (also called high-pressure pasteurization). While this process can reduce the total number of pathogens, it does not eliminate them and there is potential for development of bacterial and viral resistance.[30] There is a need for further research in this area to better define the efficacy of this processing method and the implications in terms of overall animal health and risk of pathogenic infections.

Pets not developing clinical illness when fed contaminated raw meat products still introduce a risk to humans and other pets in the environment through shedding of organisms in the feces.[31,32] Children, seniors, and immunosuppressed or immunocompromised individuals are at the greatest risk through environmental contamination. In response to public health concerns, the FDA prepared a set of guidelines for pet owners on the proper handling of raw pet foods to help minimize risk of pathogen cross-contamination.[33] From this guideline, "The FDA does not advocate a raw meat, poultry or seafood diet for pets, but is stepping up its efforts to minimize the risk such foods pose to animal and human health because we understand that some people prefer to feed these types of diets to their pets." This educational approach is also one that should be implemented by veterinarians when discussing raw pet foods with clients. After discussing risks with owners, alternative feeding options that improve safety can be offered. There are many commercially

available cooked pet foods that provide caloric distributions similar to those of raw foods and incorporate similar feeding philosophies such as avoidance of grains, the use of vegetables, the addition of probiotics, and the use of natural preservatives and ingredients. For pet owners who prefer home-made preparations, a complete and balanced home-cooked diet can be suggested as an alternative.

Indications for Home-Cooked Diets

Because commercial food formulations are consistent, complete, and balanced, they are generally preferred over home-prepared foods that are subject to recipe deviations and inconsistencies. Commercial foods that have undergone Association of American Feed Control Officials (AAFCO) feeding tests also have the advantage of demonstrating food performance within a species and nutrient bioavailability. The major advantages of home-cooked diets are that ingredients and nutrients can be tailored to the pet's needs, important for pets with multiple disease conditions that require nutritional approaches not available in a single commercial food.

When selecting the appropriate nutritional management for any patient, the clinician should ask a series of questions: (1) What is the appropriate caloric distribution of macronutrients in this patient's diet? (2) Are there any micronutrients that should be modified to meet this pet's needs? (3) Are there specific ingredients or dietary antigens that must be avoided? and (4) Are there any commercial foods that meet the needs identified in questions 1 to 3? To address the first question, the clinician should consider if modifications to dietary protein, fat, or carbohydrate levels are indicated. If the clinician concludes that more than one of these macronutrients must be reduced or restricted, the commercial food options may be limited. For example, a patient with a history of renal disease and pancreatitis will require both protein and fat restriction. However, most commercially available foods designed for the management of renal disease are moderate to high in fat. The second and third questions consider which micronutrients in the diet should be modified and if any ingredient must be avoided. Again, if multiple disease conditions are present, the required nutrient modifications may not be available in one diet. For example, a cat with a history of struvite urolithiasis and food allergies may not tolerate the ingredients provided by commercially available foods designed for the management of struvite urolithiasis, but foods designed for the management of food allergies may not provide appropriate levels of P and magnesium to address the struvite urolithiasis.

After determining required nutritional modifications, commercial foods should be explored for potential options. There may be cases where a commercial food addresses all the patient's needs. For the example of concurrent renal disease and pancreatitis, currently available foods designed for the management of renal disease should be evaluated for varying fat levels. The questions should then be asked, “What is this patient's fat tolerance?” and “Are there any commercial foods that can meet these needs?” The level of fat restriction required will vary from patient to patient and is generally related to the level of dietary fat that initially contributed to the pancreatitis episode. If the patient was on a high-fat food when pancreatitis developed, the pet may be able to tolerate a moderate fat level provided by a commercially available food designed for the management of renal disease. However, if the patient is sensitive to fat and cannot tolerate moderate fat levels, most, if not all, commercially available options will be eliminated, and home cooking may be the only viable option to address both conditions.

If the choice is made to treat with a home-cooked diet, the next step is to acquire an appropriate and nutritionally balanced home-cooked diet formulation. Consultation with a board-certified veterinary nutritionist will often provide guidance and individual tailoring of a diet to meet the patient's needs (see E-Table 192-1). Other veterinary software programs and published recipes are options available to veterinarians looking for more standardized dietary formulations or recommendations (see E-Table 192-1). Formal consultations and the use of nutrition software are generally preferred to published recipes, as they provide more up-to-date nutritional strategies and can be formulated for the individual pet. Most important, a diet should be complete and balanced for long-term feeding, and developed by a qualified board-certified veterinary nutritionist. As with all veterinary therapeutic diets, regular rechecks are essential to ensure that the dietary therapy is meeting the patient's needs. Most veterinary nutritionists encourage feedback on how the home-cooked diet formulation is working for the patient and can provide reformulations and adjustments to the diet as needed.

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CHAPTER 193

Pet Food Safety and Regulatory Aspects of Pet Food

David A. Dzanis

Client Information Sheet: How to Report a Pet Food Complaint

Pet foods tend to receive more than their fair share of blame for any observed adverse health effects in dogs and cats. Historically, pet foods have a good safety record in the United States. In fact, despite their high prevalence and frequency of use in pet-owning households, only 1.7% of reports of poisoning in dogs or cats where the cause was confirmed could be attributed to food.[1] In terms of frequency of occurrence, this is far below that for many other sources of toxins often found in the household, such as drugs, insecticides, plants, rodenticides and cleaning products.

In spite of these statistics, adverse signs in pets are very frequently blamed on the animal's food. The massive pet food recall due to contamination with melamine and melamine analogs in 2007, along with the ongoing issues with chicken jerky treats imported from China, has heightened the public's awareness and concern about pet food safety. Notwithstanding efforts of manufacturers to provide safe and wholesome products, incidents of pet food contamination and subsequent adverse effects can and do occur. In the case of a suspected pet food–borne illness, the veterinarian can be instrumental in helping confirm the cause and, if indicated, reporting the findings to appropriate authorities.

Regulation of Pet Foods

In the United States, pet foods are subject to regulation at both the federal and state levels. The Center for Veterinary Medicine within the U.S. Food and Drug Administration (FDA) has authority over all pet feeds (encompassing complete and balanced foods, treats, nutritional supplements, edible chews and ingredients intended to become incorporated into any of these products) in interstate commerce.[2] This also includes pet products containing meat or poultry ingredients. This is different from regulation of foods intended for human consumption, where meat and poultry products are overseen by an agency within the United States Department of Agriculture (USDA). In addition, many states also enforce regulations for pet foods distributed within their respective jurisdictions, often through adoption of, at least in part, the Association of American Feed Control Officials (AAFCO) Model Bill and Model Regulations for Pet Food and Specialty Pet Food.[3]

Under both the Federal Food, Drug, and Cosmetic Act and similarly worded state laws, a pet food that contains a microbiological, chemical or physical contaminant may be subject to enforcement action as an adulterated food.[2] Especially where exposure to the adulterated product may result in health risks to animals or humans, a recall may be the most effective means of containing the risk in a swift manner. Details of how a recall is conducted are provided elsewhere.[4] Until recently, all recalls were voluntary (i.e., the party responsible for the contamination or other cause of health risk had to agree to participate in the process). There is little incentive for a company to refuse a recall request, as the potential repercussions in terms of legal liability and company/brand reputation may be much more costly in the long term than the costs associated with the recall itself. In the rare cases when that occurred, FDA always had other regulatory recourse. Regardless, the Food Safety Modernization Act of 2011 now provides FDA with mandatory recall authority.[5]

The Veterinarian's Role in Pet Food Safety

Veterinary practitioners are on the “front line” and often in the best position to first detect a possible outbreak of pet food–borne illness. As a matter of course, keeping records of dietary histories for all patients may help expose a pattern if multiple animals show similar signs over a short period of time. Such records also could be very helpful if a recall is announced at a later date.

Due diligence must be done to rule out other potential causes of presenting signs, such as drugs, pesticides, household toxins, and other animals. Still, the possibility of illness stemming from food contamination must remain on the differential diagnosis list until ruled out or when the definitive cause is determined. Unfortunately, the signs of food-borne illness are rarely pathognomonic. Contamination of pet foods with *Salmonella* or other pathogenic enteric organisms may cause gastrointestinal signs (e.g., vomiting, diarrhea), lethargy and fever. Most mycotoxins primarily adversely affect the liver. It was found that the combination of melamine and related compounds (fraudulently added as a component of what was represented as "wheat gluten" in pet foods in 2007) results in formation of crystals in the renal tubules, which can lead to acute nephrotoxicosis.[6] A unique finding in many animals reported to have suffered harm from consumption of China-sourced jerky pet treats is the onset of a Fanconi-like syndrome, characterized by renal insufficiency and glucosuria but without concurrent hyperglucosemia (see ch. 326).[7] Despite years of investigation, no cause has been determined.

When a pet food–borne disease is suspected, as much detail as possible about the food should be recorded (Table 193-1). If some of the information isn't immediately available, the owner should be asked to convey those details by phone as soon as possible. It is advisable to check FDA's Center for Veterinary Medicine web site for any existing notice of recall for any suspected food (click "Recalls" tab on www.fda.gov/cvm).

TABLE 193-1

Information Needed or Helpful in Investigation of a Potential Pet Food–Borne Illness

Food	Type of food (e.g., dry, wet, raw frozen) Type of container (e.g., bag, box, pouch, can, plastic sleeve) Where purchased (e.g., store name and street address, web site address) Date of purchase Appearance of food (e.g., mold, off odor, insect infestation, foreign material) Appearance of container (e.g., torn, wet, dented, open or bulging seams, leaking) How stored (e.g., frozen, refrigerated, transferred to another container)? How handled and prepared? Results of diagnostic testing (e.g., microbial, mycotoxin, chemical), if any
Label	Exact brand, product and variety name Intended use (e.g., puppy, kitten, adult) Manufacturer's or distributor's name and address Package size (net weight or volume) UPC (universal product code, i.e., bar code number) Batch identification (e.g., lot code, best by date, any other markings)
Animal	If multipet household, how many animals affected? Signalment and previous health history Onset and progression of signs relative to time of consumption Other foods, treats, supplements, medications? Results of diagnostic testing, if any Tentative or confirmed diagnosis

Beyond physical examination of the animal and laboratory analysis of appropriate biologic specimens, examination of the suspected food is also prudent. Pet food companies report that even slight changes in odor, color or texture unrelated to any safety concern are frequently the cause for alarm by concerned pet owners. Except for overt moldiness, obvious rancidity or visible inclusion of foreign materials, most incidents of pet food contamination are unlikely to be apparent upon gross inspection. Thus, collection of samples for laboratory analysis may be indicated when the food is suspect. Proper handling of the sample as legal evidence may be critical if there is a possibility of a lawsuit at a later date.[1]

Many veterinary diagnostic laboratories (as well as the laboratories at the state feed control officials offices) can perform the necessary analyses on food samples to help in diagnosis of a food-related illness. As much information as possible with respect to clinical signs, clinical pathology findings, and specifics about the timeframe of events (e.g., time between consumption and onset of illness, course of the disease) may be helpful in determining the likely contaminant and types of analyses to perform. A scribbled "check for poison" on a submission sheet is rarely helpful in detecting the presence of a contaminant.

Even when a pet food is already the subject of a recall, timely reporting of a case of pet food–borne illness

may help curtail a larger outbreak. FDA has established a "Safety Reporting Portal" on its web site where pet owners and veterinarians can report a problem (Table 193-2). There are means provided to contact an FDA consumer complaint coordinator by phone as well. Depending on the nature of the complaint, FDA may follow up with the veterinarian and/or client to obtain more information or to arrange to collect samples of the product. Notification of the state feed control official is also prudent, as they can coordinate efforts with FDA to investigate the report and take action against the pet food if needed.

TABLE 193-2

Reporting Suspected or Confirmed Pet Food Contamination

TO WHOM	HOW TO CONTACT	ALTERNATE CONTACT METHOD
Pet food company	Toll-free "800" telephone number on label	Company web site
FDA	To report electronically, go to "How to report a pet food complaint" on main web page for animal and veterinary products (www.fda.gov/cvm) and follow links to the "Safety Reporting Portal"	To report by phone, go to "How to report a pet food complaint" and follow links to find telephone number for consumer complaint coordinator in appropriate FDA district office
State feed control official (agency varies, but most often in state's department of agriculture)	To find contact information for appropriate state office, go to "Consumers" tag on AAFCO web site (www.aafco.org) and follow links	State government web site (most likely under its "commercial feed" program)

AAFCO, Association of American Feed Control Officials; *FDA*, United Stated Food and Drug Administration.

While not required under the regulations, most pet food labels bear toll-free "800" telephone numbers to be used to report complaints. In fact, the pet food company should be contacted promptly any time a food is suspected to be contaminated, as the firm may be in the best position to recognize an emerging pattern if multiple complaints regarding a product are received.

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CHAPTER 194

Immunology and Nutrition

Nick John Cave

Nutrition and Immunity

The interactions between nutrition and immunity are complex and incompletely understood, and there are bidirectional effects between pathogens, immune responses, and nutritional requirements and metabolism (Figure 194-1). Food also contains numerous antigens, which normally stimulate harmless immune responses (oral tolerance) but can elicit harmful hypersensitivities. Nutrition can affect immunity by (1) enhancing or exaggerating, (2) suppressing or limiting, and (3) changing the nature of the response. Any effect can be either good or bad depending upon the specific disease and patient status. Thus, enhancement of an immune response may be desirable for prevention or elimination of infection, or immunity to tumor development, whereas attenuation of an immune response may be beneficial in hypersensitivity diseases, chronic inflammatory disease, or in harmful systemic inflammatory responses. In contrast, immunosuppression during infection can lead to prolonged morbidity or even overwhelming sepsis (see ch. 360). Equally, enhancement of immunity may increase self-damage when there is already excessive or poorly regulated immune activation (e.g., systemic inflammatory response syndrome, hypersensitivity diseases). Clearly then, one diet cannot fit the needs of all. The multiple points where an immune response can be modulated by nutrition are depicted in Figure 194-2.

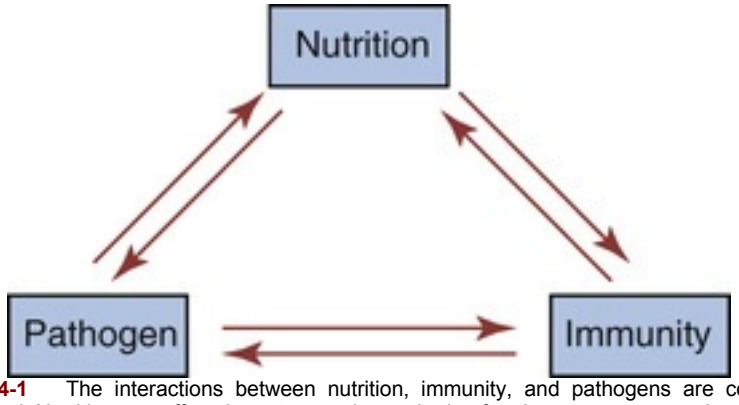

FIGURE 194-1 The interactions between nutrition, immunity, and pathogens are complex and multidirectional. Nutrition can affect the nature and magnitude of an immune response. In turn, immune responses require adequate nutrient supply and alter nutrient delivery to nonimmunological tissues. Diet can also directly modify the microflora and resident opportunistic pathogens, which in turn can influence mucosal pathogens.

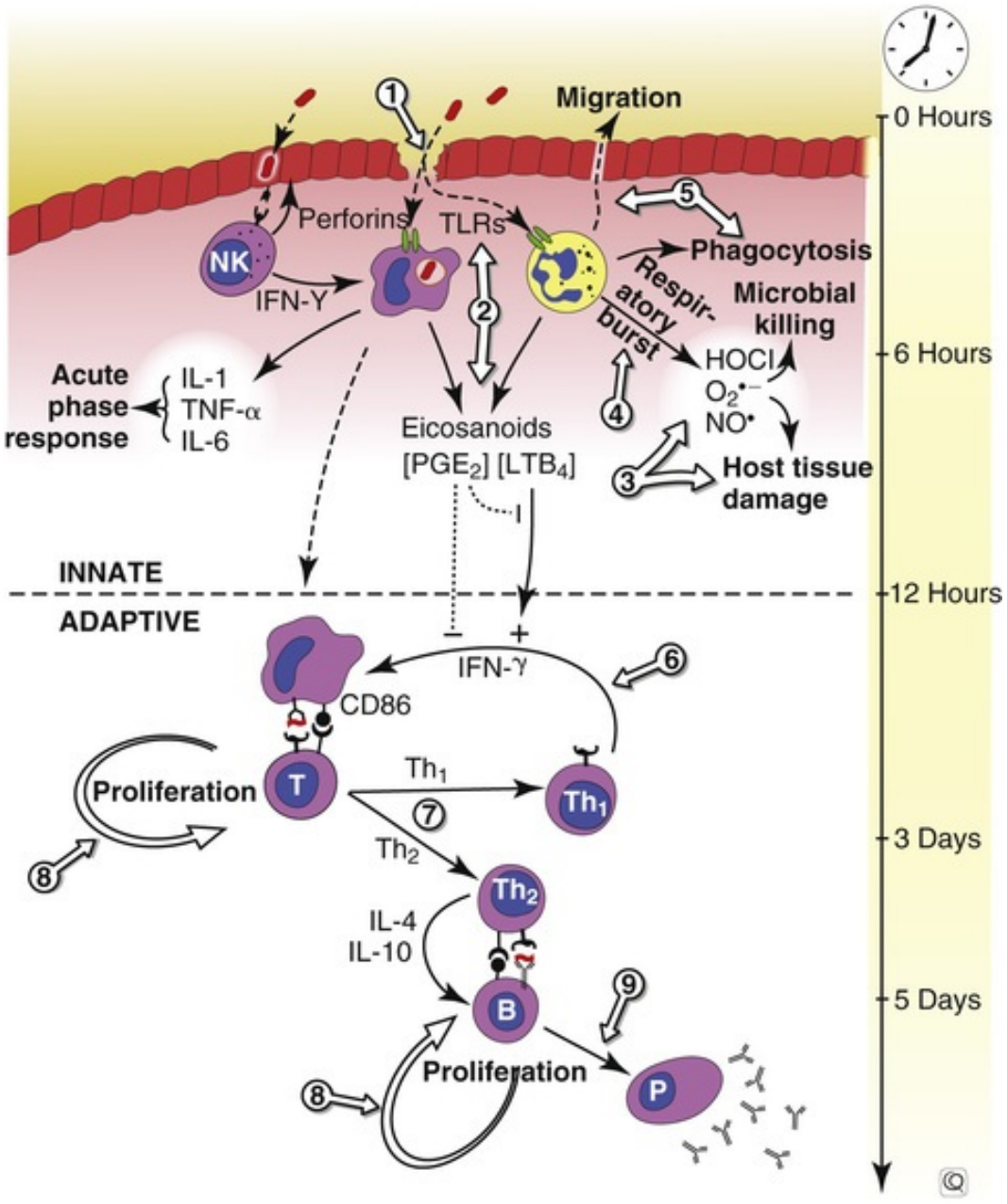

FIGURE 194-2 Schematic to show the multiple points within innate and acquired immune responses that can be modulated by nutrition. (1) Epithelial integrity—vitamin A, protein-energy malnutrition. (2) TLR signaling and eicosanoid production—PUFA. (3) Free radical damage—antioxidants, protein-energy malnutrition. (4) Respiratory burst—antioxidants, arginine, glutamine, genistein, carotenoids, taurine, leptin. (5) Neutrophil migration and phagocytosis—glutamine, genistein, iron, taurine. (6) Th_1 mediated responses—leptin, lutein, genistein. (7) Th_1/Th_2 development—leptin, vitamin E, PUFA. (8) Lymphocyte proliferation—leptin, lutein, genistein, Cu, Zn, B vitamins, glutamine, glucose, antioxidants, PUFA. (9) Immunoglobulin production—lutein, vitamin A, iron, leptin. *B,* B lymphocyte; *IFN,* interferon; *IL,* interleukin; *LT,* leukotriene; *NK,* natural killer; *P,* plasma cell; *PG,* prostaglandin; *PUFA,* polyunsaturated fatty acids; *Th,* T-helper cell; *TLR,* Toll-like receptor; *TNF,* tumor necrosis factor.

Nutritional Requirements for Immunity

Nutritional deficiency can profoundly affect developing leukocytes at any time from *in utero* to throughout life.[1] Table 194-1 lists some of the effects of nutritional deficiencies on immunity. Malnutrition during development can alter the mucosal microbial commensals, impair responses to commensals and pathogens, increase susceptibility to infection, and decrease the ability to clear infecting pathogens. Malnutrition early in

life can produce a lifelong alteration in an animal's immunophenotype.

TABLE 194-1

The Effects of Specific Nutrient Deficiencies on Immunity

NUTRITIONAL DEFICIENCY	IMMUNOLOGICAL DEFECTS	CLINICAL MANIFESTATION
Zinc	Thymic atrophy, lymphopenia, altered T-lymphocyte differentiation, reduced Th1 cytokine production, decreased antibody production	Diarrhea, increased susceptibility to infection from skin commensals
Copper	Lymphopenia, reduced lymphocyte proliferation, increased viral virulence	Neutropenia, anemia
Selenium	Impaired oxidant defense, increased viral virulence	Increased susceptibility to infection, increased organ oxidative damage
Iron	Decreased humoral responses, decreased phagocytosis and respiratory burst, reduced T-lymphocyte proliferation	Anemia, increased susceptibility to infection
Vitamin E	Increased IgE, increased PGE_2 production	Increased atopic disease signs? Increased organ oxidative damage
Vitamin A	Mucosal barrier defects (squamous metaplasia), lymphopenia, depressed antibody production, decreased Th2 responses, depressed neutrophil and macrophage maturation	General increased susceptibility to infection—especially respiratory infections, diarrhea,
Protein	Impaired cell mediated responses, decreased cytokine production,	General increased susceptibility to infection
Protein—energy malnutrition	Thymic atrophy, reduced lymphoid tissue mass (lymph nodes), decreased circulating T-lymphocytes and B-lymphocytes, impaired cell-mediated responses, decreased cytokine production, reduced neutrophil migration	General increased susceptibility to infection from exogenous and endogenous sources, increased morbidity and mortality, diarrhea (villous blunting, chronic enteritis)

IgE, Immunoglobulin E; *PGE2*, prostaglandin E2; *Th1*, T-helper-1 lymphocytes.

At rest, leukocytes utilize both glucose and glutamine for fuel. Following activation of macrophages and neutrophils, or stimulation of lymphocyte proliferation, glucose uptake is dramatically increased and is an essential fuel.[2] Although fatty acids and ketones can be oxidized for ATP production, cellular activation and proliferation of leukocytes do not increase the usage of either.[3,4] Both glutamine and glucose are only partially oxidized, consistent with the need for the cells to survive with low oxygen availability (e.g., in ischemic tissue or unvascularized spaces).[3] In addition to their use as fuel, glucose and glutamine are also used as precursors for nucleotide synthesis by proliferating lymphocytes. Not surprisingly then, low plasma glutamine and glucose concentrations render leukocytes more sensitive to apoptosis and cause immunosuppression.[2,5] The immunosuppressive effect of asparaginase has been shown to be due to its ability to hydrolyze glutamine rather than to the reduction of asparagine.[6] In models of severe sepsis when plasma glutamine is frequently depressed, glutamine supplementation enhances macrophage phagocytosis, helps maintain circulating T lymphocyte numbers, and normalizes lymphocyte function. Predictably, glutamine supplementation of parenteral nutrition solutions has been shown to reduce morbidity in some septic human patients, compared with glutamine-free solutions (see ch. 189).[7]

Several other nutrients affect the nature and magnitude of immune responses. Dietary antioxidants protect leukocytes and host cells against endogenously derived free radical damage and prevent oxidation of lipid within the diet prior to consumption. Intracellular antioxidants in neutrophils and macrophages include taurine, glutathione, ascorbate, and tocopherol. Dietary deficiencies of these can reduce circulating cell numbers and proliferation, whilst dietary enrichment can increase cell activity and antibody production.[8-11] Antioxidants are discussed further in ch. 167.

Normal circulating concentrations of both vitamins A and D are required for optimal leukocyte responses. The vitamin D receptor is expressed in lymphocytes, dendritic cells, and macrophages, and some activated leukocytes produce vitamin D_3. Vitamin D_3 can limit dendritic cell function, alters lymphocyte homing, and

inhibits T cell proliferation, with a bias away from a Th-2 type response.[12] Low vitamin D status is a risk for allergic disease, as well as immune-mediated disease such as multiple sclerosis in humans.[13,14] Vitamin A modulates both innate and acquired immune responses through effects on skin barrier, neutrophils, antibody production, lymphocyte trafficking, T-helper lymphocyte, type 1 or type 2 (Th-1/Th-2) balance, and many regulatory cytokines.[15,16] Canine distemper is rapidly fatal in ferrets fed a vitamin A–deficient diet, but supplementation soon after infection restores protection.[17] Although primary dietary deficiencies of these vitamins are probably rare, chronic intestinal disease in dogs and cats is commonly associated with hypovitaminosis of fat-soluble vitamins and is likely to affect immunity.[18,19]

Effects of Malnutrition on Immunity

Starvation

Malnutrition and simple starvation (see ch. 177) lead to physical and functional defects in the epithelial barriers of the respiratory and intestinal tracts, as well as the dermis. The net result is an increase in susceptibility to infection from both endogenous sources, such as skin and intestinal commensals, and exogenous sources such as hospitals.[8,20]

When mice are fasted for as little as 48 hours, lymphocytes, especially $CD4^+$ T cells, are dramatically reduced in circulation and primary lymphoid tissue.[21] Lymphocytes isolated from fasted mice proliferate less and produce less interleukin (IL)-2 and gamma-IFN. Within 4 days of starvation, otherwise healthy cats have reduced circulating leukocytes, notably $CD4^+$ T cells, which tend to proliferate less.[22] By 7 days of starvation, macrophage phagocytosis is suppressed and antigen presentation impaired.[23] These short-term effects are usually completely reversible upon refeeding.

A principal mediator of the immunosuppressive effects of acute starvation is leptin. The leptin receptor is expressed by neutrophils, macrophages, and lymphocytes, and leptin promotes their development, maturation, activation, and proliferation.[24] As such, leptin is a key regulator of cellular immunity and has a proinflammatory effect on normal and pathological innate and adaptive immune responses. The concentration of leptin drops rapidly during starvation and remains low during prolonged periods of weight loss. Circulating lymphocyte numbers and reduced proliferation responses in fasted rodents correlate with serum leptin concentrations.[25] In an intensive study of the morphometric, inflammatory, metabolic, and endocrine status of hospitalized children with acute severe malnutrition, the marker at the time of admission that best predicted survival was serum leptin.[26] In experimental settings, either leptin administration or recovery of body fat mass restores immune function.[27]

Provision of calories is insufficient to normalize cellular responses, however, and inadequate protein intake severely impairs cell-mediated immunity. Mice fed a protein-deficient diet, which are then infected with influenza, experience higher viral replication, reduced antibody responses, reduced $CD8^+$ T cells, reduced natural killer cell (NK cell) function, and increased mortality, all of which can be abrogated with the introduction of a protein adequate diet.[28,29] The early instigation of nutrition to dogs hospitalized with septic peritonitis shortened hospitalization.[30] Thus, even short-term malnutrition can be detrimental, but restorative feeding can significantly affect outcome in sepsis.

Obesity

In several species including dogs, obesity alters immune responses, which normalize following weight reduction (see ch. 176).[31-33] Reduced NK cell function, altered $CD8^+$:$CD4^+$ lymphocyte ratios, and reduced neutrophil respiratory burst activity have been described.[34] However, obesity is mostly accompanied by an enhanced inflammatory state, characterized by increased circulating inflammatory cytokine concentrations and increased acute phase protein production, which are normalized with weight loss.[35,36] Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), IL-1, and IL-6, and other inflammatory mediators are produced by activated lymphocytes and macrophages that accumulate within the excessive adipose tissue and from the adipocytes themselves.[37,38] The subclinical low-grade inflammation contributes to peripheral insulin resistance in humans and probably does so in obese dogs and cats. Even within a short period of weight gain in dogs, obesity can increase circulating lymphocyte numbers and proliferative responses and increase serum antibody concentrations.[39] Thus, obesity is a state of enhanced immune activation. Leptin is

again central to the immunological state, but in obesity, leptin excess promotes systemic inflammation and, in people, increases the risk of some autoimmune and allergic diseases.[40]

Effects of Immune Responses on Nutrition

Immune responses can affect the nutritional status of patients. An almost universal finding in significant inflammatory disease is a reduction in food intake, which is mediated in part by the action of IL-1, IL-6, and TNF-alpha on central and peripheral nerves.[41] The fact that anorexia of infection is an almost universal effect in mammals and even insects suggests that it might have a benefit. In support of this notion is the observation that force feeding of anorexic septic mice can increase mortality, and in those that survive, the time to survival is increased.[42] In inflammatory diseases, most cells in the body (especially the liver) are relatively resistant to insulin. This resistance reduces peripheral glucose utilization and preserves blood glucose for essential tissues (brain, erythrocytes, leukocytes). A concurrent increase in cortisol induces lipolysis and muscle proteolysis, increasing the delivery of free fatty acids and amino acids to the liver. Hepatic insulin resistance means that feeding does little to prevent hepatic glucose output, and hyperglycemia results.[43] Therefore, systemic immune activation can result in insulin resistance, increased hepatic glucose production, and hyperglycemia (see ch. 304 and 305).[44] It appears that prevention of hyperglycemia in severe inflammatory disease reduces morbidity and mortality.[45] IL-1, IL-6, and TNF-alpha alter insulin signaling intracellularly causing inappropriate signaling in a diseased state. In addition, insulin-independent cells may experience cellular glucose overload, such as neurons, endothelium, alveoli, vascular smooth muscle, and renal tubule cells. The ensuing cellular dysfunction leads to acute kidney injury, anemia, neuropathy, and immunosuppression.

Sepsis is associated with an increase in nitric oxide (•NO) production by activated macrophages and neutrophils. The production of •NO is limited mostly by the availability of free arginine from which it is synthesized, and increasing available arginine increases the •NO produced by any given inflammatory stimulus.[46] In immunity, •NO has many functions, that range from protective to pathogenic.[47-50] Overall it appears that supplemental arginine, either parenterally or orally administered, enhances the depressed immune response of individuals suffering from trauma, surgery, malnutrition, or infection, presumably through its ability to augment the production of •NO.[51] Although beneficial in some patients, it may also contribute to the disease, especially in systemic inflammatory response syndromes.[51,52] Thus, there may be cases where supplementation with arginine, beyond that provided by a conventional protein source, may be beneficial, whilst in other cases it may be detrimental.[51] This may be particularly true of patients with severe sepsis, compared with patients without sepsis.[53,54]

Effect of Route of Nutrition

In addition to the composition and amount of diet fed, the route of feeding (enteral or parenteral) affects innate and adaptive aspects of immunity.[55] A lack of enteral stimulation leads to decreased intestinal and respiratory tract IgA production and established IgA-mediated antiviral and antibacterial immunity.[56] Increased mucosal permeability and bacterial translocation of luminal bacteria to the mesenteric lymph nodes, liver, and spleen are seen with parenteral nutrition (see ch. 189).[57] A lack of luminal nutrients results in intestinal inflammation.[55,58,59] In human trauma patients, enteral feeding decreases the incidence of pneumonia compared with total parenteral nutrition or starvation by increasing sIgA, hastening elimination of virus.[60,61] Patients without preexisting septic shock who received enteral nutrition had fewer episodes of severe sepsis or septic shock, and the length of stay in the intensive care unit was shorter compared with those given parenteral nutrition.[53]

Recommendations for Feeding in Severe Inflammatory Diseases

Clearly, feeding excessive carbohydrate will exacerbate the hyperglycemia and increase morbidity, whilst feeding excessive fat may promote fatty liver development and liver dysfunction. Until more is known about the responses in dogs and cats, the general recommendations are to instigate nutritional support early, preferably enterally. Complete diets are preferable to simple unbalanced solutions such as glucose or electrolytes, but conservative initial rates of approximately 25% of estimated resting energy requirements are recommended, and any increase should be made only if it is tolerated. Conventional diets that are highly digestible, containing more than 1.5× the minimum protein requirements (to allow for hypocaloric feeding),

are probably adequate. Patients should be monitored for hyperglycemia and hypertriglyceridemia, and the rate of feeding or composition of the diet should be adjusted if either develops.

Nutritional Modulation of Immunity

The most common reason for modifying the diet to affect immunity is to reduce immune-mediated disease. Allergic diseases such as atopic dermatitis (see ch. 186), chronic inflammatory diseases such as osteoarthritis (see ch. 187 and 353), autoimmune disease such as pemphigus (see ch. 204), and idiopathic inflammatory diseases such as inflammatory bowel diseases (see ch. 276) are all amenable to dietary modification. Though rarely sufficient as sole therapy, dietary modification can reduce the dosage of immunosuppressive or antiinflammatory drugs required.

Polyunsaturated Fatty Acids

Dietary polyunsaturated fatty acids (PUFA) can modulate immune responses through several mechanisms.[62-68] The proportions of the 20 carbon n-6 and n-3 PUFA within the phospholipid cell membranes of leukocytes and other cell types is determined by the diet. The n-3 PUFA eicosapentaenoic acid (EPA) competes with the n-6 PUFA arachidonic acid (ARA) as a substrate for cyclooxygenase (COX) and lipoxygenase (LOX), and being less efficiently utilized, EPA reduces eicosanoid production. In addition, EPA-derived eicosanoids function differently and range from antagonistic to equipotent to ARA-derived mediators. However, though complex, the net effect is that n-3–derived eicosanoids are less inflammatory than the n-6 PUFA–derived mediators.

PUFA can also directly affect gene transcription by interacting with the peroxisome proliferator-activated receptors (PPARs), which are a family of cytosolic proteins that, once bound to an appropriate ligand, diffuse into the nucleus and either promote or inhibit gene transcription. PPARs are expressed by macrophages, T cells, B cells, dendritic cells, endothelial cells, and other cell types.[69] Long chain n-3 PUFA are ligands for PPAR-gamma leading to reduced TNF-alpha, IL-6 and IL-1 production by macrophages, and IL-2 production by lymphocytes, and induction of regulatory T cells.[69-72]

Incorporation of EPA in place of ARA in phospholipid membranes alters the physical and structural properties of the cell membranes in lymphocytes, affecting the lipid rafts within which most cell surface receptors are localized. This decreases signal transduction through the T-cell receptor and depresses T-cell activation.[68] Lastly, both EPA and docosahexaenoic acid (DHA) antagonize the interaction between Gram-negative lipopolysaccharide (LPS) and Toll-like receptors, reducing the production of COX, TNF-alpha, IL-1, IL-6, and IL-8 and improving morbidity in severe sepsis.[65,73,74]

So dietary enrichment with n-3 PUFA can have immediate effects on immunity (e.g., antagonism of LPS signaling) but will take several weeks before a maximal response is achieved (i.e., saturation of tissue cell membranes). And although the effects and mechanisms of modulation of eicosanoids by dietary lipid are complex, there is value in the generalization that diets enriched in n-3 PUFA reduce inflammation relative to diets enriched in n-6 PUFA. However, the effect a given diet will have is dependent on many dietary and animal factors, and the reduction of the description of the fat content of a diet to a simple ratio of n-6 to n-3 PUFA provides very limited and potentially misleading information.

Supplementation of a diet with a source of n-3 PUFA will have greatly varying effects depending on the nature of the basal diet and patient. Most commercial diets are highly concentrated in n-6 PUFA, and the addition of a small amount of n-3 PUFA (e.g., as marine fish oil), such as is contained in many veterinary fatty acid supplements, achieves little. The best approach is to start by feeding a diet that is already enriched in EPA and not excessive in ARA. Table 194-2 lists some suitable complete diets enriched in n-3 PUFA. None of the listed diets will produce a maximal immunosuppressive effect, and fish oil can be added to the enriched diet. A recommended total fish oil dosage is 0.2% to 2% of diet by weight per day, or a maximum of 0.4 g EPA/100 kcal, including the n-3 content of the diet.[75] Note that the ratio of EPA to DHA in fish oil varies between 1 : 1 and 3.5 : 1.

TABLE 194-2

Polyunsaturated Fatty Acid Content of a Selection of Diets Enriched in Long Chain n-3 Fatty Acids

MANUFACTURER	DIET	N-3	N-6	EPA	EPA + DHA

MANUFACTURER	DIET	N-3	N-6		EPA	EPA + DHA
		g/100 kcal	g/100 kcal		g/100 kcal	g/100 kcal
Nestle-Purina	DRM	0.3	0.3	1.0	—	—
Nestle-Purina	JM	0.3	0.4	1.8	—	—
Royal Canin	Mobility Large Breed	1.2	1.9	1.6	—	0.8
Royal Canin	Mobility	0.9	2.2	2.5	—	0.6
Royal Canin	Skin Support	1.0	3.1	3.1	—	0.6
Royal Canin	Mobility feline	1.2	3.8	3.2	—	0.7
Hill's Pet Nutrition	j/d feline canned	0.3	—	—	—	—
Hill's Pet Nutrition	j/d feline dry	0.4	—	—	—	—
Hill's Pet Nutrition	j/d canine canned	1.0	—	—	0.2	—
Hill's Pet Nutrition	j/d canine dry	1.0	—	—	0.1	—
Eukanuba	Dermatosis FP canine dry	—	—	2.8	—	—
Eukanuba	Dermatosis FP feline canned	—	—	5.0	—	—

Data taken from manufacturers' product information.

Nonnutritive Dietary Compounds

Nonnutritive dietary compounds (see ch. 167) capable of modulating immunity are legion, of which only a few are discussed here. Genistein is an isoflavone compound principally found in plants of the family Leguminosae including soy, clover, and alfalfa.[76] Genistein can interact with estrogen receptors, can inhibit numerous cell cycling cascades by inhibiting tyrosine kinases, and can inhibit cellular proliferation by inhibiting DNA topoisomerase II. This can reduce leukocyte signaling cascades, lymphocyte activation and proliferation, neutrophil activation and superoxide production, bacterial phagocytosis by macrophages, antibody responses, and delayed-type hypersensitivity responses.[77-85] Commercial soy-based diets may contain sufficient genistein to affect mucosal, or even systemic immunity.[86-88] Dietary carotenoids, including beta-carotene and lutein, are incorporated into organelle membranes, especially in the mitochondria or lymphocytes.[89,90] The incorporation of lutein into the diet of cats has been shown to significantly increase cell-mediated and humoral immunity in cats, possibly through localized antioxidant effects.[91]

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SECTION XII

Hematologic and Immunologic Diseases

OUTLINE

Chapter 195 Immunologic and Hematologic Diseases Introduction and Drug Therapy

Chapter 196 Coagulation Testing

Chapter 197 Hyper- and Hypocoagulable States

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CHAPTER 195

Immunologic and Hematologic Diseases

Introduction and Drug Therapy

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The immune system is vital in protecting the body from internal and external insults. Numerous and complex interactions between the cells and mediators of the immune system must be tightly regulated to maintain a healthy homeostasis. Comprehensive understanding of the basic immunologic mechanisms by which the body mounts and regulates an appropriate immune response is essential to effectively manipulate these mechanisms to prevent or treat undesirable immunological reactions.[1-4] In spite of extensive research over the last few decades, dysregulation of the immune system is still poorly understood but is likely multifactorial. Inappropriate presentation of an autoantigen by an antigen-presenting cell coupled with lack of the immunoregulatory effects of T regulatory cells (Tregs) is thought to be the result of an intricate immunological dysregulation in the innate and/or adaptive immune responses.[1-4] Generally, dysregulation of the immune system causes clinical disease by either excessive activation of Th1 cells and cytotoxic destruction of target tissue or Th2 cells and autoantibody-mediated disease.

Autoimmune/Immune-Mediated Diseases and Immunosuppressive Therapy

Susceptibility to autoimmune diseases is dictated by a complex interaction of genetic determinants and environmental triggers. Recent research has shown that genetic background plays a significant part in predisposing dogs to autoimmune diseases.[5-7] The most significant triggering factors are believed to be infectious agents like rickettsial or viral diseases.[8-10] The pathogenesis of most of immune-mediated hematological diseases is Th2-cells-mediated, resulting in the production of autoantibody that recognizes either a self-antigen or a foreign antigen associated with the red blood cells, platelets and/or white blood cells.[11-14] The resulting sensitization and subsequent destruction of these cells occurs via the complement system, cells of the reticuloendothelial system or both.[11-14] In addition to this section, which focuses on immune-mediated anemia (IMHA) (see ch. 198), immune-mediated thrombocytopenia (IMT) (see ch. 201) and immune-mediated neutropenia (see ch. 202), many other chapters in this book provide additional information on immune diseases, including immunology and nutrition (see ch. 194), polyarthritis (see ch. 203), skin disease (see ch. 204), and systemic lupus erythematosus (see ch. 205). Complementary information on immunosuppressive drugs can be found in the following chapters: 165, 261, 266, 268, 269, 276, 281-283, 323, 325, and 354.

Currently available immunosuppressive therapies act by a variety of different mechanisms, but ultimately they suppress antibody production by lymphocytes and/or suppress the clearance of opsonized cells by macrophages or the complement system.[3-6] Importantly, since the antibody class involved in most cases of canine IMHA is IgG and its half-life is approximately 1 week, therapies directed only at suppression of antibody production are unlikely to improve the outcome in the acute phase of the disease.[11,13] Over the past few decades, great advances have been made in the development of several immunosuppressive agents that are more potent, more selective and less toxic when compared to glucocorticoids (GCs).[13-38] The wide array of new drugs offers the opportunity to use multiple drugs that block different pathways of immune activation while at the same time selecting drug combinations with nonoverlapping toxicity profiles.

Mechanism of Action of Common Immunosuppressive Agents and

Procedures

With few exceptions, such as monoclonal antibodies, drugs used to treat immune-mediated diseases have multiple mechanisms beneficial to the patient with immune disease.

GCs are the most widely used agents in veterinary medicine, and they inhibit multiple mechanisms underlying immune-mediated diseases. The following is a general description of the mechanism of action of the immunosuppressive agents and procedures used in dogs and cats. Additional information about the commonly used drugs in dogs and cats is contained in Table 195-1.

- Regulators of gene expression: The classic examples are GCs (see ch. 165, 201, 261, 266, 268, 276, 281-283, 323, 325, 354, 358, and 360). Recent studies have shown that GCs affect inflammation by other (nongenomic) mechanisms.
- Alkylating agents including cyclophosphamide, procarbazine (see ch. 261) and chlorambucil (see ch. 204, 205, 276, and 325) cross-link DNA helices, preventing their separation and thus the formation of a DNA template.[3,45] These agents are toxic to both resting and dividing cells (particularly proliferating lymphocytes).
- Inhibitors of *de novo* purine synthesis: The first-generation inhibitors are 6-mercaptopurine and azathioprine (see ch. 165, 199, 204, 266, 281, 325, and 354). The second-generation inhibitors are mizoribine and mycophenolate mofetil (MMF) (see ch. 165, 203, 205, 323, 325, and 354). The immunosuppressive effect is achieved through suppression of lymphocyte activation and proliferation, resulting in a reduction in antibody production. These agents are less toxic to resting cells, and therefore they have a narrower spectrum of side effects compared to cyclophosphamide.
- Inhibitors of *de novo* pyrimidine synthesis: Similar to the inhibitors of purine syntheses, these agents work through suppression of lymphocyte proliferation. Leflunomide (see ch. 165, 203, 205, 261, and 323) represents this group.
- Kinase and phosphatases inhibitors: These include cyclosporin A (CsA) (see ch. 165, 198, 204, 261, 268, 276, 278, 281, 282, 323, and 354) and tacrolimus (see ch. 204, 278, and 323), which inhibit kinase cascades and ultimately suppress the activation of transcription of many cytokines vital for the proliferation and maturation of T cells.
- Inhibitors of macrophages: liposomal clodronate is the only drug used in veterinary medicine with primary immunosuppressive effects directed against macrophages.
- Procedural immunomodulation: This category includes splenectomy and plasmapheresis.
- Intravenous human immunoglobulin (see ch. 201) has numerous mechanisms of action, including modulation of expression and function of Fc receptors, interference with activation of B and T cells and complement, and a reduction in immunoglobulin production.
- Monoclonal antibodies: Most of these agents are directed against B-cell antigens. Although developed for the treatment of B-cell lymphoma, rituximab is used to treat immune-mediated disease in humans. It is directed against the B-cell antigen CD20. Recently, two caninized monoclonal antibodies have been approved for the treatment of canine lymphoma: one against CD20 and the other directed at CD52 for the treatment of T cell lymphoma. Use of these monoclonal antibodies in canine immune-mediated disease has not been investigated.

TABLE 195-1

Characteristics of Commonly Used Immunosuppressive Agents

AGENT NAME	CYCLOSPORIN A	AZATHIOPRINE	MYCOPHENOLATE	LEFLUNOMIDE
Mechanism of action	Blocks the transcription of cytokine genes in activated T cells (particularly IL-2)	Competitive purine antagonist	Inhibitor of IMPDH, a key enzyme in *de novo* purine biosynthesis	Inhibitor of DHODH, the rate-limiting enzyme in the *de novo* synthesis of pyrimidines
Routes of administration	Intravenous and oral	Oral	Intravenous and oral	Oral
Side effects	Mild to moderate GIT toxicosis and	Myelosuppression, hepatotoxicosis, pancreatitis	Mild to severe GIT toxicosis. In	Mild to moderate GIT toxicosis, rare neutropenia

	hepatotoxicosis, gingival hyperplasia		people; rare neutropenia and anemia	and anemia at high doses
Dosage and indications	5 mg/kg/day PO for IBD, perianal fistula and atopic dermatitis. 4-7 mg/kg PO q 12 h for IMHA, IMT	2 mg/kg/24 h PO for the first week, then 2 mg/kg/48 h for IMHA, IMT. 50 mg/dog/day PO for perianal fistula.	10 mg/kg PO or IV q 12 h for IMT, IMHA and myasthenia gravis	4 mg/kg/day for IMT, IMHA, IMPA when used alone. 1-2 mg/kg PO daily when used with other agents.

DHODH, Dihydroorotate dehydrogenase; *GIT*, gastrointestinal tract; *IBD*, inflammatory bowel disease; *IMHA*, immune-mediated hemolytic anemia; *IMPA*, immune-mediated polyarthropathy; *IMPDH*, inosine monophosphate dehydrogenase *IMT*, immune-mediated thrombocytopenia.

Practice: Selecting the Immunosuppressive Protocol

Throughout this textbook the reader will find GCs are considered first-line therapy for most immune diseases despite a lack of clinical trial–generated evidence to support their use. GCs are widely available and inexpensive. The adverse event profile of GCs is well known and can be reversed when the drug is discontinued. Also obvious throughout this textbook is the frequent use of azathioprine as the second-line therapy. Ideally, the selection of immune suppressive drugs would be made based on controlled randomized clinical trials. In actuality, drugs to treat immune disease are frequently chosen based on cost, adverse event profile, availability, mechanism of action and clinical judgment. The following general recommendations regarding the choice of immunosuppressive agents are based on the authors' interpretation of the available literature.

Prednisolone is commonly used in cats because of prednisone bioavailability concerns.[39] Due to its negligible mineralocorticoids effects, dexamethasone is the preferred GC type in patients in which water retention is detrimental.[40,41] Anecdotally, if resistance to GCs is suspected, switching to an alternative GC may result in remission again (Table 195-2).[40-42] Risks versus benefits for using GCs in cats with advanced concurrent heart disease or diabetes mellitus (see ch. 358) should be carefully analyzed. The delayed onset of action of azathioprine indicates it should not be the first choice in the management of the acute phase of life-threatening diseases like IMHA and IMT.[43-45] Cyclosporine, leflunomide and MMF appear to have a more rapid onset of action and hence are more appropriate for managing the acute phase of diseases.[25-35] It is also advisable to avoid using azathioprine in patients with concurrent liver disease.[46] Azathioprine is a good choice as a steroid-sparing agent for managing the maintenance phase of the immune-mediated disease, especially in large dogs.[47,52] Due to its gastrointestinal side effects, oral MMF should be avoided in patients with preexisting gastrointestinal disease.[28-31] MMF dosages higher than 10 mg/kg PO q 12 h are associated with significant gastrointestinal toxicosis.[30] The following section offers more information on immunosuppressive therapy for IMHA as an example of the thought process behind the management of acute, life-threatening, immune-mediated disease.

TABLE 195-2

Relative Potency, Water Retention and Half-Life of Glucocorticoids

DRUG	ANTI-INFLAMMATORY POTENCY	MINERALOCORTICOIDS AND WATER RETENTION EFFECTS	BIOLOGIC HALF-LIFE
Hydrocortisone	1	1	8-12 h
Prednisone/prednisolone	4	0.4-0.8	12-36 h
Methylprednisone	5	0.4	12-36 h
Dexamethasone	25	0	35-54 h
Betamethasone	25	0	>48 h
Triamcinolone	5	0	24-48 h

Immunosuppressive Therapy for IMHA

GCs (see ch. 165) are the mainstay of immunosuppressive therapy for IMHA (see ch. 198).[48] At this point there is no compelling evidence to support using a second immunosuppressive agent in the acute phase (the first 1-2 weeks).[48] Most clinicians recommend using a second immunosuppressive agent to maintain remission and prevent relapse while the GC dosage is tapered. Cyclophosphamide is no longer recommended for the treatment of IMHA.[17,47-51] One large retrospective study incorporating azathioprine into its management protocol for canine IMHA suggested an improved survival time when compared to historical controls.[52] Due to the lack of evidence to support the superiority of the more expensive alternatives, the study resulted in a noticeable shift in clinical practice. GCs combined with azathioprine became the most common immunosuppressive protocol used for canine IMHA. Several other retrospective studies described the use of azathioprine for this disease, with conflicting results regarding its effects on patient outcome.[17,45] Nevertheless, the severity and the high mortality of IMHA pressure many clinicians to use other immunosuppressive agents in addition to GCs and the low cost and good tolerability of azathioprine make it an attractive choice. The use of CsA for IMHA is also frequently reported. The cost of CsA, the variability of absorption, side-effects, and the lack of evidence to support its superiority compared to other cheaper alternatives limited its use over the last few years.[18,19,53,54] A few retrospective studies and ample anecdotal data reported the use of MMF and leflunomide for IMHA.[30-32] Both of these agents are theoretically more appropriate than azathioprine for the acute phase of IMHA.[27-32] A small report described the use of splenectomy in the initial management of canine IMHA, with positive results; however, the vast majority of clinicians reserve this therapy for refractory and chronic cases.[55,56] Liposomal clodronate and plasmapheresis are other promising options that require further study.[24,38,57]

In patients lacking negative prognostic factors (bilirubin >5 mg/dL, autoagglutination, hypoalbuminemia and intravascular hemolysis), the authors generally use GCs alone.[58] In dogs at risk for severe GC side-effects (large-breed and overweight dogs), azathioprine or leflunomide is added to allow a rapid GC taper. Due to cost and gastrointestinal side effects, the authors rarely use MMF or CsA for patients without negative prognostic indicators. For patients with one or more negative prognostic indicators, the clinician could consider starting GC therapy combined with a steroid-sparing agent. The authors start either MMF at 10 mg/kg PO or IV q 12 h or leflunomide at 2-4 mg/kg PO daily and adjust the dosage based on clinical response and adverse effects.[31,32] The limited literature on feline IMHA supports the use of GCs as the sole immunosuppressive agent in most cats.[59] Adding a second immunosuppressive agent is recommended for cats at higher risk of serious GC side-effects, such as overweight cats or cats with concurrent cardiac disease. MMF can be used at 10 mg/kg PO or IV q 12 h.[60] CsA is an alternative to MMF; however, CsA can cause further insulin resistance in diabetic or overweight cats.[61]

Patient Monitoring

Dogs and cats receiving immunosuppressive therapy require frequent monitoring, not only to assess treatment success or failure but also to monitor for complications and adverse events. The frequency of monitoring is dynamic and varies with the different diseases and medications used. At least weekly rechecks with physical examinations for the first month of immunosuppressive therapy are essential for detecting side effects such as appetite loss, gain or loss of body weight/body condition score, gastrointestinal ulceration, pyoderma, muscular weakness or cruciate ligament rupture.[18,62-72] Physical examination is also critical to detect an adverse effect common to all immunosuppressive drugs, secondary infections.[65-69] For more information regarding concurrent infections and immune suppression, see ch. 360. Many veterinarians include assessment of quality of life in their evaluation of pets treated for chronic diseases and this assessment would be appropriate in pets with immune-mediated disease. In order to establish appropriate monitoring protocols, clinicians should be familiar with each drug's adverse effects profile (see ch. 165 and 343). Hematologic toxicosis is most commonly seen with cytotoxic agents and nucleotide/nucleoside analogues, necessitating monitoring of a complete blood count at intervals appropriate for the particular drug. In general, cytotoxic agents induce neutropenia and thrombocytopenia between 7 and 21 days following administration. If immunosuppressive drugs (like chlorambucil or azathioprine, for example) are administered continuously, hematologic toxicosis can appear months after initiation of therapy.[63,65] Regular monitoring of a biochemical profile assists in the identification of adverse events such as pancreatitis and hepatopathy from azathioprine, GC-induced diabetes mellitus and cyclosporine-induced renal and hepatic

toxicoses.[18,46,63,64] Urinary tract infection occurs in approximately 30% of dogs treated with CsA and GCs.[66,70] This finding suggests routine urinalysis, culture and sensitivity in dogs treated with CsA and GCs are warranted. Similar data are not available for other immunosuppressive agents, but good clinical judgment suggests monitoring for urinary tract infections would be prudent. In an effort to optimize drug therapy, blood levels of some immunosuppressive agents such as CsA can be monitored and adjusted to achieve adequate immunosuppression without excessive toxicosis (see ch. 165).

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CHAPTER 196

Coagulation Testing

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Laboratory hemostasis testing generally is divided into preanalytical, analytical (the test), and postanalytical (interpretation) phases. The preanalytical phase covers all aspects of preparation of the patient, collection of the sample, processing and storage, labelling, and submission. Hemostasis testing requires stringent attention to detail, particularly during the preanalytical phase, due to variation in interpretation associated with hematocrit, hemolysis, choice of anticoagulant, and fill volume (anticoagulant to whole-blood ratios). Discussions are ongoing in human medicine about the preanalytical phase (i.e., which test do I order for these clinical signs?), and interpretative hemostasis services can assist with all phases[1] (Table 196-1 and Figure 196-1). Common preanalytical mistakes include inappropriate choice of anticoagulant (e.g., underfilling the citrate [powder-blue-top] tube, or using EDTA [lavender-top tube] instead of citrate), incorrect ratio of anticoagulant to blood, cooling or heating of samples, delayed laboratory transport and inappropriate centrifugation speeds. All of these factors can impact interpretation significantly and could lead to inappropriate therapeutic decisions. Strict adherence to sample collection and handling guidelines is essential for proper interpretation of the results.

TABLE 196-1

Tests for Prothrombotic States and Fibrinolysis

Strengths and weaknesses (pros and cons) of the five tests that can be used for assessment of a prothrombotic state.

TEST	SAMPLE SPECIFICS	WHAT IS TESTED	PROS AND CONS
Thromboelastometry, thromboelastography	Citrated whole blood; max holding = 30 minutes; strong activator	Global hemostasis from initial enzyme generation to fibrinolysis	Pro: includes cells in evaluation of clotting Cons: poor reproducibility without a strong tissue factor or contact activator, interpretation difficult in animals with altered Hct, platelets
Thrombin-antithrombin complexes	Citrated plasma	A marker of *in vivo* thrombin activity	Pro: use of plasma eliminates Hct and platelet effects Cons: expensive, must be batched
Calibrated automated thrombography	Citrated plasma PPP or PRP	Assesses thrombin generation *in vitro*	Pros: sensitive indicator of enzyme generation and activity, can assess platelet contribution with PRP Con: not widely available
D-dimers	Citrated plasma	Degradation of insoluble cross-linked fibrin	Pro: Specific for breakdown of cross-linked fibrin (clot breakdown) Con: Not available in all labs
Fibrin[ogen] degradation products	Citrated plasma	Degradation of insoluble cross-linked fibrin, soluble fibrin monomer, fibrinogen	Pros: inexpensive, simple to run Con: Not specific: can indicate lysis of fibrinogen, fibrin, or cross-linked fibrin

Hct, Hematocrit; *PPP*, platelet-poor plasma; *PRP*, platelet-rich plasma.

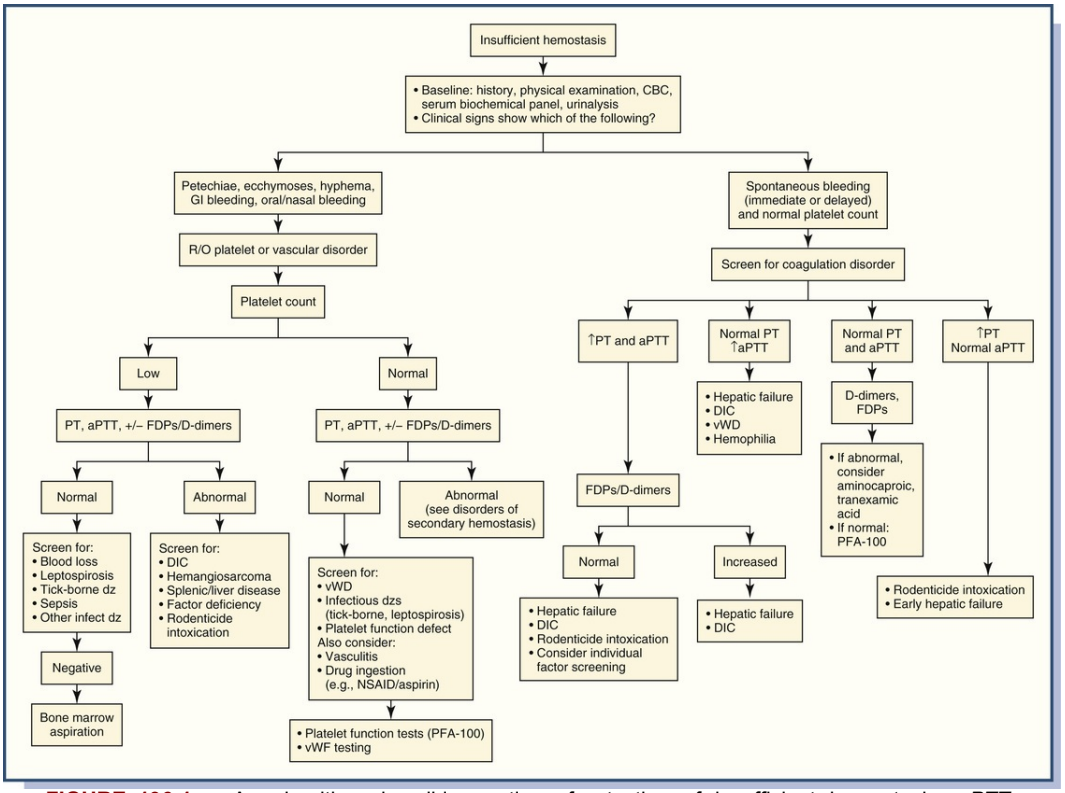

FIGURE 196-1 An algorithm describing options for testing of insufficient hemostasis. *aPTT*, Activated partial thromboplastin time; *CBC*, complete blood count; *DIC*, disseminated intravascular coagulation; *FDP*, fibrin(ogen) degradation products; *infect dz*, infectious diseases; *NSAID*, nonsteroidal anti-inflammatory drug; *PFA*, platelet function analyzer; *PT*, prothrombin time; *R/O*, rule out; *vWD*, von Willebrand disease; *vWF*, von Willebrand factor.

History and Physical Exam

A comprehensive history of a patient with a suspected disorder of hemostasis must include previous bleeding episodes (e.g., associated with ear or tail docking, spay or castration, declawing, loss of deciduous teeth, estrus), the anatomical distribution of bleeding, whether the bleeding was spontaneous or secondary to injury, and whether the bleeding was immediate or delayed. Signalment, breed, age at first episode, travel history, and current medication or toxin exposure should be recorded. Although both congenital and acquired bleeding disorders can cause bleeding anywhere, specific patterns can help to distinguish one bleeding disorder from the other. In general, acquired disorders typically first appear later in life. These patients often have no history of bleeding during previous surgeries (e.g., spay, castration) and could have comorbid conditions. Congenital bleeding disorders often manifest as bleeding episodes associated with challenge to the hemostatic system during youth (e.g., spay, declawing).[2] In patients at risk for thrombosis, essential aspects of the history include predisposing diseases (e.g., hyperadrenocorticism, protein-losing nephropathy, immune-mediated hemolytic anemia [IMHA]), current medications or toxin exposure, and recent interventional procedures (e.g., intravenous catheter placement).[3]

A thorough physical examination is essential, with careful evaluation of the skin, eyes, joints, mucous membranes, urine, and feces for evidence of bleeding (see ch. 135). Disorders affecting the platelet and the vascular wall can include thrombocytopenia, thrombocytopathia, abnormalities of von Willebrand factor (vWF), and vasculitis (see ch. 201). Thrombocytopenia can lead to petechiation if the platelet count is <20,000/mcL, while thrombocytopathia, von Willebrand disease (vWD), and vasculitis more often cause mucosal surface bleeding and bruising.[4,5] Coagulation factor deficiencies or disorders result in ecchymoses, hematomas, and/or muscle, joint, or body cavity bleeding (see ch. 197).[2] In animals at risk for thrombosis, a thorough evaluation of perfusion (e.g., careful palpation of pulses, extremity temperature, mentation, urine output) and the respiratory system are essential. Secondary evaluation of perfusion, to include ultrasound of suspected areas (e.g., distal aorta, femoral vessels, etc.), can be helpful in diagnosing peripheral thromboembolism (see ch. 256). Evaluation of the respiratory system for pulmonary thromboembolism can

reveal an oxygen deficit (tachypnea, pulse oximetry and PaO_2 below accepted range, increased alveolar-arterial gradient; see ch. 128 and 132) with normal thoracic radiographs or mild radiographic changes incongruous with the severity of the clinical signs (e.g., minimal pleural effusion, loss of definition of the pulmonary artery, hyperlucent lung regions; see ch. 243).

Sample Collection and Storage Methods

Ideally, all specimens should be collected prior to therapeutic interventions. Elimination or minimization of preanalytical errors in collection and storage will optimize interpretability of results. Communicating with the laboratory regarding aspects that may affect the test (e.g., hemolysis, icterus, ingestion of a fatty meal) is important. The preanalytical phase recently has been reviewed for veterinary medicine.[6,7] Venipuncture, tube/additive selection, and storage are particularly important. Direct venipuncture into a Vacutainer is the preferred method of collection, as this approach results in less hemolysis than needle and syringe collection.[8,9] Results for prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen for dogs have been demonstrated to agree clinically between the two collection methods.[10] If using a central line for collection, flushing with heparinized saline followed by removal of at least 3 mL of blood from the catheter before specimen collection will minimize contamination with heparin, saline, or other fluids.[10] The clearance blood may be returned to the patient but will have undergone some degree of contact activation. Immediately following filling, tubes should be inverted 4-6 times.[11] The preferred anticoagulant for complete blood count (CBC) and platelet count is K^+EDTA, a chelating agent that binds calcium.[12] Sodium citrate (3.2%, 1 : 9 ratio citrate to blood) is the anticoagulant of choice for most coagulation assays.[13]

Tests of Platelets and the Vascular Wall

Platelet Count

Thrombocytopenia may be due to decreased platelet production, destruction, loss, or sequestration. Sources of error in automated counts include cells (i.e., microspherocytes, cell fragments) of similar size being counted as platelets, giant platelets being counted as other cells, and agglutination.[14] Manual platelet estimates can be performed by evaluation of a peripheral blood smear using EDTA-anticoagulated blood or fresh samples. An estimate of the count is obtained by multiplying 15×10^3/mcL by the average number of platelets counted from at least 5 oil-immersion fields.

Buccal Mucosal Bleeding Time (BMBT)

The BMBT should only be performed on a patient with a normal platelet count and coagulation panel (see ch. 80).

Cuticle Bleeding Time (CBT)

The CBT test is unpredictable and unreliable, in addition to causing pain. Interpretation is affected by paw movement, which can disturb the forming hemostatic plug. Sedation or anesthesia is often needed, especially if multiple nail cuts are required. The CBT test is not recommended in veterinary patients.

Platelet Function Testing

Options for detection of thrombocytopathia include impedance whole blood platelet aggregometry (WBA), plasma-based light transmission aggregometry, and a commercially available platelet function analyzer (PFA-100). There are also adaptations to thromboelastography/ometry (TE) for testing of thrombocytopathia. Aggregometry techniques, due to cost and requirements for trained personnel, have classically been used for research, but a rapid, automated multiple electrode aggregometry technique (Multiplate) has been developed for WBA with potential for clinical use.[15] The PFA-100 measures time to cessation of whole blood flow (closing time) through a central aperture under high shear conditions. The membrane is coated with collagen and either epinephrine or adenosine-5′-diphosphate (ADP). The collagen/ADP cartridge has a higher sensitivity for canine platelets.[16] Whole blood is collected in sodium citrate and held at room temperature prior to processing.[17] The PFA-100 is easy to use and gives accurate and rapid results that are reproducible.

Platelet aggregation is dependent on platelet number and function, as well as functional vWF.[14] Results can be affected by holding time, anticoagulants, hematocrit and medications.[14,17] The PFA-100 is used as a screening test to detect abnormalities of platelet function but is not specific for any particular disease. A normal PFA-100 closing time result generally rules out a severe platelet function defect or severe vWD, but milder forms of these diseases may still be present. The test had a 95.7% sensitivity and 100% specificity in dogs using the collagen/ADP cartridge in one report.[18]

von Willebrand Factor/von Willebrand Disease

vWD is covered in ch. 201.

Tests of Coagulation

Prothrombin Time (PT)

The PT evaluates the tissue factor pathway (extrinsic; FVII) and the common pathway (FX, FV, prothrombin, fibrinogen; see ch. 197).[19] Citrated plasma is added to $CaCl_2$ and tissue factor in a lipid membrane (thromboplastin); the PT is the time until formation of the first fibrin strands. A prolonged PT (with a normal aPTT) indicates FVII deficiency. Heparin does not generally prolong the PT due to the inclusion of heparin antagonists in commercial PT reagents. Due to the short half-life of FVII, PT prolongation in vitamin K deficiency initially is due to FVII deficiency (not associated with bleeding), but the clinical bleeding occurs with development of prothrombin deficiency.[20]

Activated Partial Thromboplastin Time (aPTT)

The aPTT evaluates the contact pathway (prekallikrein, FXII, FXI); the intrinsic pathway (VIII, IX); and the common pathway (FX, FV, prothrombin, fibrinogen). Note that the only coagulation factors that do not impact the aPTT are FVII and FXIII.[14] Citrated plasma is incubated with a contact activator (e.g., celite, kaolin) and lipids to allow for the generation of FXIIa and FXIa, then recalcified to allow for downstream coagulation steps. The aPTT is the time from recalcification until formation of the first fibrin strands. A prolongation of the aPTT (with a normal PT) is consistent with deficiency of FXII, FXI (hemophilia C), FVIII (hemophilia A), FIX (hemophilia B), or with heparin therapy. Note that FXII deficiency (commonly seen in cats) is a clinically irrelevant incidental finding as it is not associated with clinical bleeding.[21,22]

Conditions associated with prolongation of both the PT and aPTT include anticoagulant rodenticide exposure (vitamin K deficiency), liver disease, disseminated intravascular coagulation (DIC), and hypo- or dysfibrinogenemia.[21]

Activated Clotting Time (ACT)

The ACT is a simple, rapid, inexpensive test that is similar to the aPTT (evaluating all factors except FVII and FXIII) except that it uses whole blood. The tube contains a contact activator, and the platelets in the blood sample provide the lipid surface; note that the ACT therefore can be prolonged with severe thrombocytopenia even when the coagulation cascade is intact.[23] The ACT can screen for rodenticide intoxication, hemophilia, hepatopathy-associated coagulopathies, and DIC.[23] The original ACT tubes (Becton Dickinson) are no longer available. The newer MAX-ACT tube (Helena Laboratories, Beaumont, TX) was designed for use in an automated system. It contains 3 FXII activators (celine, kaolin, glass beads) and a magnet. A manual version of the test (using the tubes alone) has been validated using blood from healthy dogs and cats. The MAX-ACT tube needs to be filled immediately after direct venipuncture (needle and syringe) with 0.5 mL of whole blood, gently tapped to mix the sample without inversion, and placed in a 37° C bath for 30 seconds, then rotated every 5-10 seconds. Visible clot formation is the endpoint. The sensitivity and specificity and validation of its use in animals with clinical bleeding have not been reported. Reported normal values are 66 (range: 55-85) seconds for cats and 71 (range: 55-80) seconds for dogs.[23]

Factor Levels

Concentrations of individual coagulation factors can be measured using specialized modifications of the PT

or aPTT. These tests usually only are available in specialized veterinary laboratories. Factor testing is required to confirm a suspicion of FXII deficiency, or hemophilia A, B, or C, in a patient with a normal PT but prolonged aPTT.[24] The laboratory should be contacted prior to phlebotomy to discuss appropriate sample preparation and testing.

Tests of Fibrinogen and Fibrinolysis

Fibrinogen

Fibrinogen defects can be qualitative (dysfibrinogenemia) or quantitative (hypo- or afibrinogenemia) and either acquired (consumption, decreased hepatic synthesis, or inhibitory antibodies) or congenital. In addition to its role in coagulation, fibrinogen is a strong acute phase reactant in dogs, with increases (hyperfibrinogenemia) occurring during inflammation and infection.[25] The most common assay for detection of fibrinogen activity is the Clauss method, which is coagulation assay based. Low fibrinogen concentrations measured by this method can indicate either hypofibrinogenemia or dysfibrinogenemia.[26] With this method, false decreases can occur due to the presence of anticoagulants, elevations in FDP (fibrin[ogen] degradation product) concentrations, hypoalbuminemia, factor XIII deficiency, or amyloidosis.[27]

Thrombin Time (TT)

In the TT, citrated plasma is made to clot through the addition of thrombin. The TT is the time from recalcification until formation of the first fibrin strands. The TT is an indicator of fibrinogen concentration and/or function. As with the Clauss method, TT results can be increased due to the presence of anticoagulants, elevations in FDPs, hypoalbuminemia, factor XIII deficiency and amyloidosis.[27] Similar to the Clauss method, other factors may falsely prolong the TT.

Fibrin[ogen] Degradation Products (FDPs)

FDPs are created when plasmin lyses fibrinogen, soluble fibrin monomers, insoluble fibrin, and/or cross-linked fibrin. The presence of excess FDPs merely indicates plasmin activity; FDPs are not specific for cross-linked fibrin degradation. FDP concentrations can be increased in a variety of disorders, such as DIC, anticoagulant rodenticide intoxication, hepatic disease, thrombosis, IMHA, neoplasia, pancreatitis, gastric dilation-volvulus, heatstroke, and others.[28,29]

D-dimer

D-dimers are a form of FDP that can only be generated from cross-linked fibrin. Most available assays are immunologic, with no cross-reactivity with fibrinogen or fibrin monomer fragments.[30] Increased D-dimer concentrations indicate thrombin generation, fibrin formation, cross-linking by FXIIIa, and plasmin activity. Because D-dimers have a short half-life, their presence indicates recent (≈5 hours) fibrinolysis.[30] Increased D-dimer concentrations have been reported in dogs with IMHA, liver and renal disease, heart failure, neoplasia, internal hemorrhage, and after surgery.[31] D-dimer assays are commercially available and require a single citrate sample,[30] but not all assays designed for human samples cross-react with animal D-dimers.

Antithrombin (AT) Assay

AT is a member of the serine protease inhibitor (serpin) family. It is an important inhibitor of multiple coagulation enzymes, the most clinically relevant of which are thrombin and FXa. The inhibitory action of AT requires the binding of sulfated proteoglycans (either endothelial cell surface–associated heparans or pharmacologically delivered heparins).[32] Plasma levels of AT can be evaluated via a chromogenic functional assay that measures the *in vitro* ability of AT (provided by the patient sample) to inhibit bovine FXa in the presence of added heparin (both provided by the assay kit). Because many animal AT molecules inhibit bovine FXa with different potency than does human FXa, the degree of inhibition is tested against a standard of pooled normal plasma from the species being tested. The results are then reported as a percentage of normal.[33] AT deficiency is a known risk factor for development of thrombosis. Deficiency can occur due to decreased hepatic production, consumption associated with coagulation activation, or renal or enteric loss.[34-

Indicators of Global Hemostatic Potential and *in Vivo* Hemostasis

New research on the contribution of cells (e.g., platelets, red blood cells) to *in vivo* coagulation highlights the deficiencies of standard coagulation tests, which are performed on platelet-poor plasma (PPP) and are contrived in nature. The following is a general overview of assays that have shown promise in the evaluation of global hemostatic potential and prothrombotic states.

Thromboelastography[ometry] (TE)

Viscoelastic coagulation analyzers, using whole blood, can provide an assessment of global coagulation, from the beginning of clot formation through fibrinolysis. In veterinary medicine, clinical use of viscoelastic technology has been reported in dogs, cats, foals, and adult horses.[37-45] There are, however, substantial limitations to their use, including artifactual data in animals with altered red cell mass.[46,47]

Current point-of-care viscoelastic tests, including the Sonoclot, TEG and ROTEM devices, have been reviewed.[48] The use of the Sonoclot has been reported mostly for equine blood. TEG and ROTEM have been reported in both research and clinical settings with blood from small animals. TE results are not dependent solely on generation of coagulation enzymes but also are impacted by the platelets, red cell mass, and fibrinogen. Abnormalities in these parameters can lead to misinterpretation of TE results.[46,47] Specifically, samples with a higher hematocrit (erythrocytosis) display relatively hypocoagulable tracings while samples with lower hematocrit (anemia) display hypercoagulable tracings, likely due to an artifact of the technology.[45-48] Interpretation of TE, especially in anemic states (e.g., IMHA, hemoabdomen, DIC), may not be possible. Note also that, as with the PT and aPTT, results obtained with TE depend on the activators added to the whole blood sample. The handling conditions applied to the sample can also impact the results obtained; for example, in dogs, longer holding times lead to activation of the contact pathway, and this, or addition of incorrect amounts of tissue factor, or lack of use of a contact activator, can produce results that are erroneous or irrelevant to a patient *in vivo.* Attempts have been made to improve standardization.[49]

Calibrated Automated Thrombogram (CAT)

Thrombin is the central enzyme in hemostasis and thrombosis, but the majority of thrombin is produced after formation of the fibrin clot.[50] The CAT assay evaluates the ability to generate thrombin in real time *in vitro* in response to specific stimuli. It can be used with platelet-poor plasma (PPP) or platelet-rich plasma (PRP) but not whole blood (so the artifact associated with red cell mass that occurs with TE is not a concern). The methodology has been reviewed in detail.[51] CAT sensitively evaluates the contributions of all clotting factors except fibrinogen and FXIII and is sensitive to anticoagulant drugs and direct thrombin inhibitors.[51] Contributions of vWF, hypofibrinogenemia, thrombocytopenia, and antiplatelet drugs can be evaluated using PRP.[52] CAT results have been reported in hypercoagulable states in animals; this is mainly for research, but CAT has potential clinical applications (e.g., drug monitoring).[53,54]

Thrombin-Antithrombin (TAT) ELISA

The half-life of thrombin is extremely short *in vivo,* as it is rapidly inhibited by antithrombin (AT). Consequently, it is not possible to measure the concentration of thrombin directly in plasma. Rather, the concentration of the stable TAT complex is an indirect indicator of thrombin generation *in vivo.* TAT was found to be 97% sensitive for DIC in humans.[55] The commercially available ELISA does cross-react with canine, feline, and equine TAT. An increase in TAT complexes has been reported in Cushing's syndrome, malignant neoplasms, and blastomycosis.[43,56,57] The multi–well plate design and cost generally necessitate batch processing of samples, making this assay impractical for routine clinical use.

Summary

Laboratory evaluation of hemostasis should follow a systematic approach starting with a thorough history and physical exam. General screening tests (platelets, PT, aPTT) should be performed with more specific tests to follow. The location (petechiae, mucosal, venipuncture sites) and timing (intermediate vs. delayed) should

guide the differential diagnoses and consequent testing. Petechiae indicate platelet or vascular disorders (platelet count). Delays in bleeding (e.g., 8-12 hours after surgery) suggest fibrinolytic disorders (TE, FDPs, D-dimers). When a prothrombotic state is suspected, global hemostasis tests (TE value limited with anemia), FDPs, or D-dimers may be indicated. All laboratory tests are dependent on preanalytical variables and need to be interpreted in light of clinical presentation and the results of other diagnostic tests.

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CHAPTER 197

Hyper- and Hypocoagulable States

Shauna Blois

Client Information Sheet: Hyper- and Hypocoagulable States

Introduction

The hemostatic system is responsible for controlling hemorrhage while maintaining adequate blood flow. Platelets and plasma coagulation proteins work simultaneously in response to vascular injury and trauma, ultimately generating a thrombin-based blood clot (Figure 197-1). Anticoagulant proteins keep this system in balance by preventing spontaneous generation of clots and eventually lysing formed clots at vascular injury sites.[1] Quantitative and qualitative abnormalities in coagulation process can lead to alterations in normal hemostasis (Box 197-1).

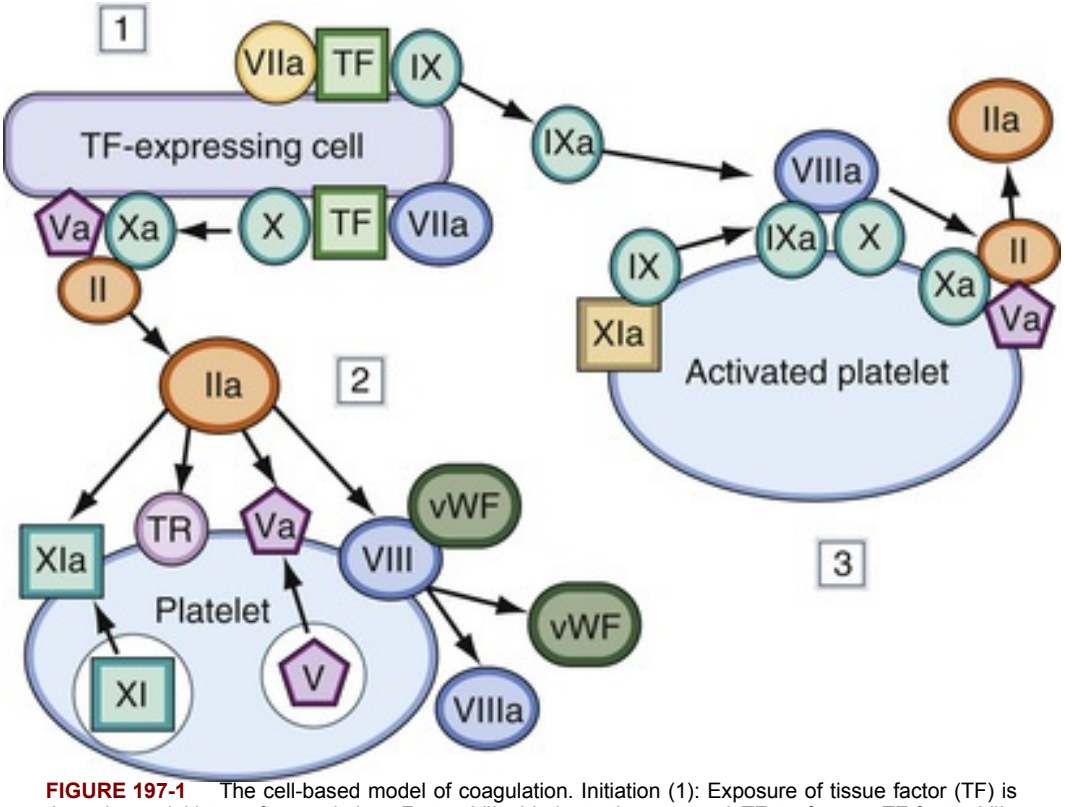

FIGURE 197-1 The cell-based model of coagulation. Initiation (1): Exposure of tissue factor (TF) is the primary initiator of coagulation. Factor VIIa binds to the exposed TF to form a TF-factor VIIa complex. Reactions on the cell surface lead to small amounts of thrombin (factor II) generation. Small amounts of factor IXa diffuse away from the cell surface to activate more platelets or other cells. Amplification (2): The small amount of thrombin generated on the TF-bearing cell surface binds to thrombin receptors (TR) on the surface of platelets. Platelet activation is also facilitated by other stimuli, including von Willebrand factor (vWF) and exposure of collagen in the subendothelial matrix. Upon thrombin binding, platelets undergo morphologic change and release granule contents to further amplify coagulation. Thrombin from the initiation stage activates factor XI and factor V on the platelet surface and liberates vWF from factor VIII to further stimulate platelet activation and aggregation.

Propagation (3): Activated platelets expose ligands to facilitate platelet-platelet interactions and aggregation. Phosphatidylserine is expressed on the surfaces of activated platelets, providing a surface to support the assembly of coagulation factors from the initiation and amplification phases. Factor XIa activates factor IX; factor IXa binds to factor VIIIa to form the tenase complex, leading to activation of factor X. Upon the platelet surface, factor Xa complexes with factor Va, generating a burst of thrombin and converting fibrinogen to fibrin. Fibrin polymerization then forms an insoluble fibrin clot. Roman numerals refer to coagulation factors, "a" denotes activated factor.

Box 197-1

Common Acquired Hemostatic Disturbances in Dogs and Cats

Hypercoagulability

- Immune-mediated hemolytic anemia
- Systemic inflammation
  - Acute pancreatitis
  - Trauma
  - Immune-mediated disease
- Sepsis
- Cardiomyopathy (hypertrophic, restrictive/unclassified, dilated)
- Infective endocarditis
- Heartworm disease
- Protein-losing nephropathy
- Protein-losing enteropathy
- Neoplasia
- Hypothyroidism
- Hyperadrenocorticism
- Corticosteroid therapy
- Diabetes mellitus
- Disseminated intravascular coagulation (initial phase)

Hypocoagulability

- Vitamin K_1 antagonist ingestion (anticoagulant rodenticide)
- Vitamin K_1 deficiency
  - Marked hepatic disease
  - Decreased synthesis by intestinal microflora
  - Severe fat malabsorption (secondary to extrahepatic biliary obstruction, exocrine pancreatic insufficiency, lymphangiectasia)
- Hepatic dysfunction
  - Acute hepatotoxicosis (e.g., *Amanita* ingestion)
  - Cirrhosis
  - Hepatic lipidosis
- Disseminated intravascular coagulation (late phase)
- Acquired anticoagulants (e.g., antiphospholipid antibodies, acquired factor VIII inhibition)
- Neoplasia

Hypercoagulability often is attributed to one or more abnormalities in Virchow's triad: increased coagulability (increased activity of platelets or procoagulant factors, deficiencies of anticoagulant factors, or inhibited fibrinolysis); vascular stasis; and disruption or activation of the vascular endothelium. Thrombosis refers to a blood clot (or thrombus) in a blood vessel occluding blood flow; when a blood clot is dislodged from its origin and travels to a distant site in the circulation, this is referred to as thromboembolism (see ch. 243 and 256). Hypocoagulability can be secondary to decreased platelet or procoagulant activity or excessive fibrinolysis. Such conditions can lead to clinical signs of hemorrhage (see ch. 135).

Hemostatic Testing

Common hemostatic tests include measurement of platelet count, mucosal bleeding times, and coagulation times (e.g., prothrombin time, PT; partial thromboplastin time, PTT; activated clotting time, ACT) (see ch. 196). Activated partial thromboplastin time (aPTT) specifies that the test is potentiated, which was an innovation in test methodology decades ago; today, the test protocol always includes activation, so PTT and aPTT are used interchangeably. Decreased platelet activity can be identified through buccal mucosal bleeding time (see ch. 80), as well as specific platelet function testing (e.g., platelet function analyzer). Prolongation of the PT indicates decreased *in vitro* activity of the extrinsic (factor VII) and common (factors I, II, V, and X) pathways; prolongation of the PTT, the ACT, or both indicates decreased activity of the intrinsic (VIII, IX, XI, XII) and common pathways. Thrombin clot time (TCT) is a direct measure of fibrinogen function (Figure 197-2). In general, PT and/or PTT become(s) prolonged when activity of one or more coagulation factor is/are reduced to <30-50% of normal activity, but this varies depending on the reagents used.[2,3] However, these conventional coagulation tests are insensitive for detection of hypercoagulability.

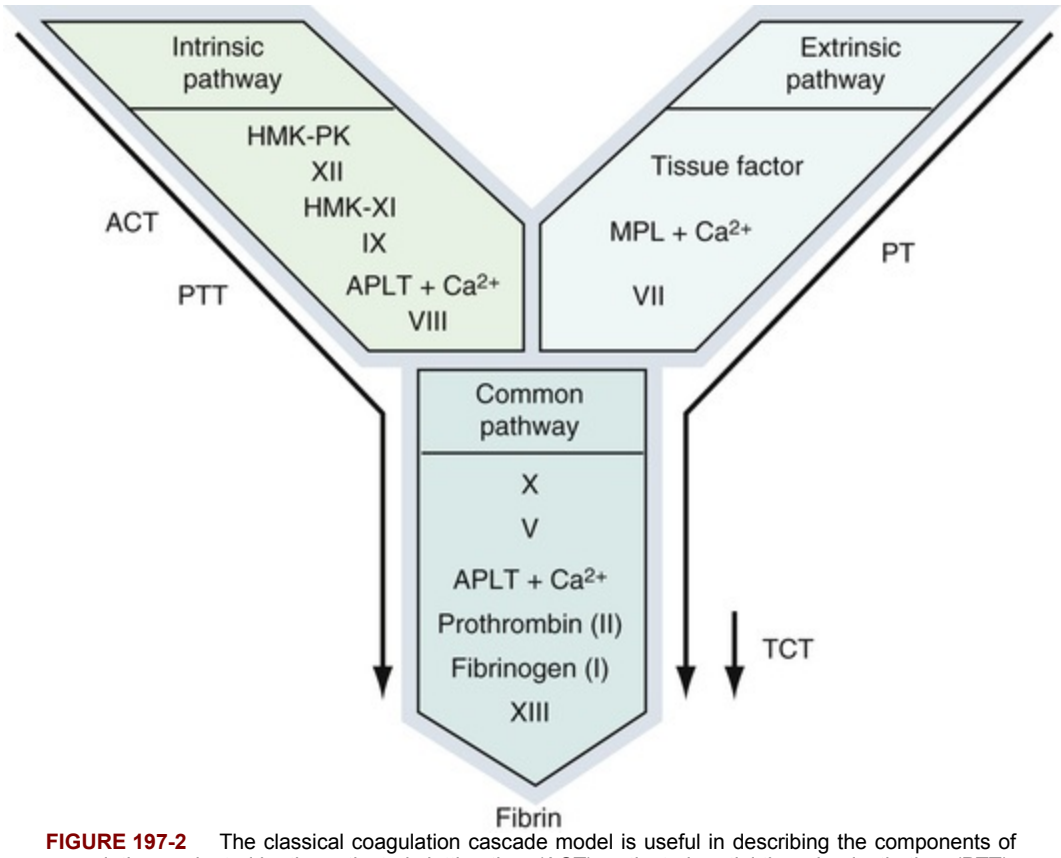

FIGURE 197-2 The classical coagulation cascade model is useful in describing the components of coagulation evaluated by the activated clotting time (ACT), activated partial thromboplastin time (PTT), prothrombin time (PT), and thrombin clotting time (TCT) tests. Roman numerals refer to coagulation factors. *APLT*, Activated platelets; *Ca^{2+}*, calcium ions; *HMK*, high-molecular-weight kininogen; *MPL*, membrane phospholipids; *PK*, prekallikrein.

Viscoelastic testing of hemostasis (thromboelastography, TEG; rotational thromboelastometry, ROTEM) has grown in popularity in veterinary medicine. These whole-blood assays depict clot formation from onset, throughout the process to fibrinolysis. Viscoelastic testing is more likely to correlate with clinical phenotype than is conventional coagulation testing. In one study of dogs, TEG was more sensitive than PT and PTT in detecting hypocoagulability.[4] Viscoelastic testing also is useful in identifying hypercoagulability. However, results of viscoelastic testing can be confounded by several factors. Low hematocrit and hyperfibrinogenemia can produce results consistent with hypercoagulability, while thrombocytopenia can cause results that suggest hypocoagulability.[5,6] Elevated D-dimer concentrations result from lysis of cross-linked fibrin and suggest excessive thrombus formation, but this test has low specificity for thromboembolic disease.[7,8] Thrombin generation assays have been useful in identifying hypocoagulability and could help identify

hypercoagulability.[9,10]

Acquired Hypercoagulable States

Immune-Mediated Hemolytic Anemia

Dogs with immune-mediated hemolytic anemia (IMHA) are prone to thromboembolic disease. Both venous and arterial thromboemboli have been reported in dogs with IMHA, although pulmonary thromboembolism appears to be most common (see ch. 243).

The mortality rate of dogs with IMHA can be up to 80%, with the majority of deaths occurring shortly after diagnosis.[11] Up to half of the deaths are attributed to thromboembolism of major organs, even when preventative anticoagulant therapy is administered.[12,13] Dogs with IMHA usually are hypercoagulable when assessed with viscoelastic testing, although anemia can confound results of these testing methods.[5,14-16] Possible mechanisms of hypercoagulability in IMHA patients include increased platelet reactivity, increased tissue factor expression on monocytes and endothelial cells, exposure of red blood cell membrane phosphatidylserine, circulating procoagulant microparticles, and diminished endogenous anticoagulant activity.[17-20] IMHA creates a systemic inflammatory state in patients, providing further procoagulant stimuli.

Various antiplatelet and anticoagulant treatment strategies are employed to prevent thromboembolic disease in IMHA patients. However, it has been difficult to determine efficacy of these therapies due to lack of controlled studies and difficulty identifying occurrence of thromboembolism in these patients.[20-23]

Cardiac Disease

Hypertrophic cardiomyopathy (HCM) is the most common cause of aortic thromboembolism (ATE) in cats (see ch. 256). The incidence of ATE in HCM cats was reported to be 33% in one study, and reported survival rate of affected cats is approximately 35%.[24,25]

Approximately half of cats with HCM are hypercoagulable.[26] Multiple factors likely contribute to development of hypercoagulability and ATE in cats with HCM. Left atrial enlargement leads to blood stasis and turbulent blood flow. Platelet hyperactivity and endocardial injury also are associated with HCM and could contribute to ATE.[26,27] This complication likely arises after a fragment of thrombus breaks off from the left atrial region and lodges distally, most commonly in the aortic bifurcation.

Prophylactic therapy with anticoagulants or platelet inhibitors is recommended for cats with HCM when high risk of thromboembolism is felt to exist (e.g., a cat with left atrial enlargement that has a history of thromboembolism). Clopidogrel therapy was associated with longer survival times than aspirin in one study of cats with HCM (see ch. 256).[28]

Infective endocarditis and heartworm infection have been associated with thromboembolic disease in dogs.[29] These conditions disrupt normal endothelial integrity and blood flow, promoting development of thromboemboli. Dogs with heartworm disease also have increased platelet reactivity.[30]

Protein-Losing Disorders

Protein-losing nephropathy occurs secondary to glomerular disease (see ch. 325), and it is a common condition in dogs with chronic kidney diseases (see ch. 324). Glomerular damage leads to a protein-losing nephropathy (PLN), whereby low-molecular-weight proteins (albumin, antithrombin) are lost into the urine. Loss of antithrombin appears to be a primary mechanism of thrombosis in PLN patients. Other mechanisms for hypercoagulability in these patients include increased platelet reactivity, hyperfibrinogenemia, and decrease in fibrinolysis.[31,32] The degree of hypercoagulability is not strongly correlated with serum albumin level or antithrombin activity in dogs with PLN.[33]

Dogs with PLN have TEG findings consistent with hypercoagulability.[31,33] PLN is a reported cause of venous and arterial thromboembolic complications in retrospective studies of dogs, and thrombosis has been reported in 14-27% of dogs with PLN.[31,34-36] Hypoalbuminemia might be a marker of thromboembolic risk in patients with PLN, although dogs with normal albumin levels also appear hypercoagulable.[32,33,37]

The prevalence of hypercoagulability also appears high in dogs with protein-losing enteropathy (PLE) based on TEG results, although the reported rate of clinically significant thromboembolic disease is relatively low. Dogs with PLE had marginally low antithrombin levels in one study, a possible mechanism of their

hypercoagulability. However, inflammation itself induces hypercoagulability and therefore the inflammatory condition of these dogs could predispose them to hypercoagulability.[38]

Neoplasia

Coagulation abnormalities frequently are identified in patients with neoplasia, with the majority of these abnormalities being hypercoagulable.[39] Hypercoagulability in patients with neoplasia is hypothesized to be secondary to multiple factors, such as increased soluble or cellular expression of tissue factor, platelet hyperactivity, inflammation, and tumor disruption of vascular endothelium.[40-42] Other risk factors for hemostatic abnormalities in cancer patients are cytotoxic drug therapy and development of disseminated intravascular coagulation (DIC).[35]

Dogs with carcinoma have been shown to be hypercoagulable based on TEG results and have an elevated platelet count and fibrinogen concentration compared to healthy dogs.[43] In a retrospective study, neoplasia was the most common underlying cause identified in dogs with pulmonary thromboembolism (PTE).[35]

Viscoelastic evidence of hypocoagulability was documented in 17% of dogs with neoplasia in one study. Interestingly, all hypocoagulable dogs had metastatic disease.[39] Similarly, prolongation of coagulation times was a common finding in dogs with mammary carcinoma, and it worsened with increasing stage of disease.[44] Cancer patients with hypocoagulability commonly demonstrate thrombocytopenia and prolonged coagulation times. DIC is common in cancer patients, a possible explanation for hypocoagulable tendencies in this population.[45,46] In a large canine study, 20 of 208 dogs (9.6%) presenting with neoplasia were found to have DIC, especially those dogs with hemangiosarcoma, mammary carcinoma, and lung adenocarcinoma.[45]

Therapy of hemostatic abnormalities in cancer patients should target the underlying neoplasm while providing hemostatic support for the patient as needed.

Endocrinopathies

Endocrine diseases appear to increase the risk of thrombosis. Hyperadrenocorticism, hypothyroidism, and diabetes mellitus have been reported as underlying conditions in dogs that develop thrombosis.[35,36,47-49] Furthermore, dogs with hyperadrenocorticism show hypercoagulable tendencies using TEG and other parameters.[50-52] The mechanism of hypercoagulability in dogs with endocrine diseases is unknown. Atherosclerosis has been reported in dogs with hypothyroidism and diabetes mellitus and could be a contributing factor to the hypercoagulable state.[36,53] Therapy for the endocrine disorder is recommended, but hypercoagulability might not resolve with successful therapy.[50] Similar to what is observed with spontaneous hyperadrenocorticism, oral prednisone therapy causes hypercoagulable TEG findings in dogs.[10]

Inflammation and Sepsis

Any disease inducing widespread inflammation, such as acute pancreatitis, sepsis, trauma, and immune-mediated disease, can increase the risk of thrombosis (see ch. 132).[54-57] Inflammation and hemostasis are closely linked processes in the body, and inflammation can induce coagulation via several mechanisms. Systemic bacterial disease was an underlying cause of pulmonary thromboembolism in 20% of dogs in one study.[35]

Proinflammatory cytokines stimulate the production of platelets, and platelet reactivity is enhanced in inflammatory states.[58] Infectious and inflammatory mediators such as endotoxin serve as platelet activators, further increasing platelet activity. Inflammatory cytokines and other mediators increase tissue factor expression on endothelial cells and monocytes, initiating the coagulation via the tissue factor pathway. Anticoagulant activity is diminished in inflammatory states, as is fibrinolysis.[57,59,60] Hypercoagulability associated with systemic inflammatory disorders can progress to DIC. Additionally, hypercoagulability with development of microvascular thrombi is a factor that could contribute to multiple organ dysfunction during sepsis.

Antiplatelet, Anticoagulant, and Thrombolytic Therapy

The most effective methods to treat patients at risk of thromboembolic disease are not well-defined and likely vary depending on the underlying mechanisms. Antiplatelet agents (clopidogrel, low-dose aspirin) and

anticoagulants (warfarin, heparin) are used anecdotally in states of hypercoagulability, but large, prospective, randomized studies investigating efficacy are lacking in many areas. Antiplatelet and anticoagulant therapies do not dissolve existing thrombi but are used for decreasing thrombogenesis and preventing further thrombosis. Reports of systemic and local therapy with tissue plasminogen activator, streptokinase, and urokinase to dissolve existing thrombi are available in the veterinary literature.[61-64] Hemorrhage, reperfusion injury, and embolism are potential adverse effects of thrombolytic therapies. Endovascular stents could be used for treating vascular occlusion (see ch. 122).[62] Multimodal therapy likely is needed to successfully treat patients with severe vascular occlusion secondary to thromboembolic disease.

Acquired Hypocoagulable States

Vitamin K Deficiency

Vitamin K deficiency is one of the most commonly acquired coagulopathies in small animals and it usually is caused by ingestion of vitamin K antagonist rodenticides. Less common causes include decreased vitamin K synthesis from the intestinal microflora and decreased vitamin K absorption.

Vitamin K is an important cofactor in production and activation of the vitamin K–dependent coagulation factors II, VII, IX, and X, and the endogenous anticoagulant proteins C and S. Vitamin K in the reduced form is essential for carboxylation of the glutamic acid residues of these coagulation factors.[65] Anticoagulant rodenticides antagonize vitamin K epoxide reductase, causing rapid depletion of the vitamin K–dependent coagulation factors (Figure 197-3).[66] Factors II, VII, IX, and XI have relatively short half-lives (42, 6.2, 13.9, and 16.5 hours, respectively), and decreased factor levels can be detected shortly after anticoagulant rodenticide ingestion. Dogs and cats consuming rodents intoxicated with anticoagulant rodenticides are unlikely to have coagulopathies result, as the amount of rodenticide within the rodent is small.

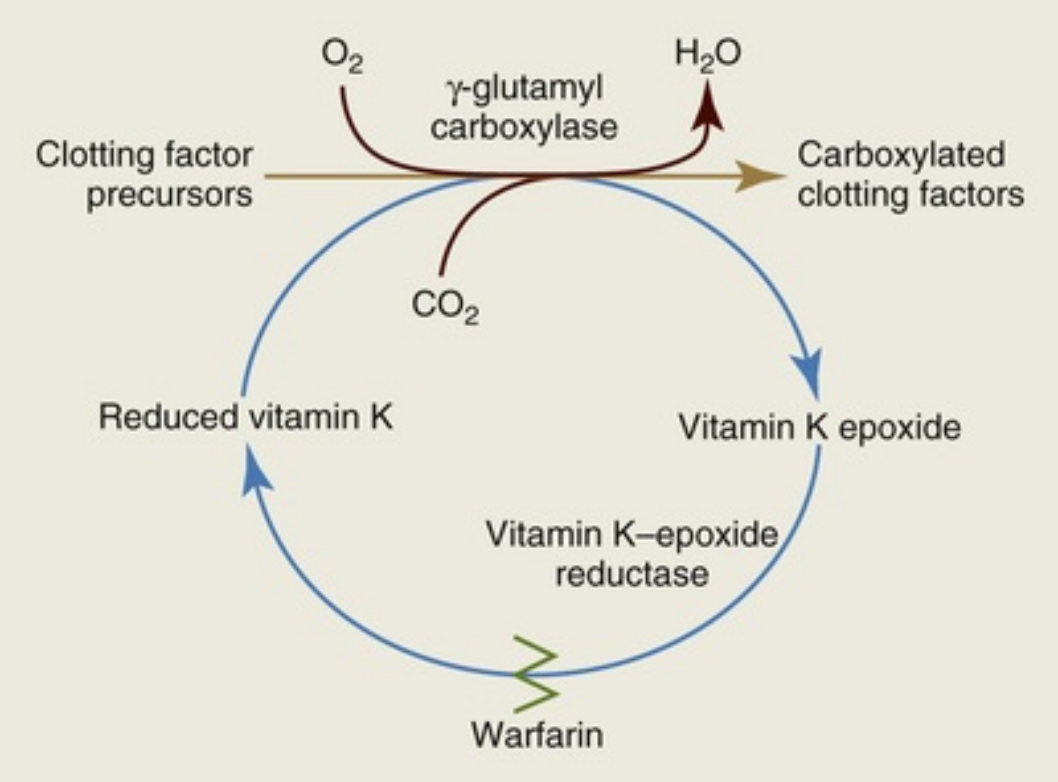

FIGURE 197-3 Vitamin K epoxidase cycle illustrating the carboxylation of clotting factors and the site of warfarin inhibition. (Courtesy Dr. Christian Bédard.)

Clinical signs of bleeding typically are observed 2-5 days after ingestion of anticoagulant rodenticide, and they include epistaxis, melena, hemoptysis, hematochezia, hematoma, ecchymoses, hematuria, and gingival bleeding (see ch. 152). Other clinical signs include dyspnea, coughing, lethargy, collapse, and pallor.[67]

Proteins induced by vitamin K absence/antagonism (PIVKA) levels start to increase within 12 hours of ingestion. PT will be prolonged within 36 to 72 hours, followed by prolongation of PTT and ACT.[67] Blood and serum rodenticide concentrations peak within a few hours of ingestion; liver tissue at necropsy can be used for measuring rodenticide concentration. A point-of-care test is available to detect anticoagulant rodenticide in blood, but it was only useful in detecting warfarin and not second-generation anticoagulant rodenticides in one dog study.[68] A diagnosis of anticoagulant rodenticide intoxication usually is based on consistent history, clinical signs, and coagulation test results.

Following acute ingestion, emetics, adsorbents and cathartics should be given to minimize absorption. Vitamin K_1 (phytonadione) supplementation is recommended. Most commercial anticoagulant rodenticides are second generation (bromadiolone, brodifacoum, and diphacinone) and have a half-life of 5-6 days; therefore, oral vitamin K_1 treatment is recommended for 2-4 weeks (see ch. 152). Prothrombin time typically normalizes 14-36 hours after starting vitamin K_1 therapy.[67] Plasma transfusion quickly will replenish coagulation factors while awaiting the onset of effect of vitamin K_1 therapy, if clinical hemorrhage is significant. Red blood cell transfusion can be necessary in severe hemorrhage cases (see ch. 130). Prothrombin time should be rechecked 36-48 hours after discontinuing vitamin K_1 therapy to ensure normal coagulation status and sufficient treatment duration.

Hepatic Failure

The liver is responsible for synthesizing most pro- and anticoagulant factors, and it plays a central role in hemostasis. Most patients with liver disease have a parallel decline in pro- and anticoagulant proteins, resulting in a relatively balanced hemostatic system *in vivo* in initial disease stages. *In vitro* hemostatic defects (prolonged PT/PTT) commonly are detected in patients with liver disease, but clinical bleeding is uncommon and usually is associated with fulminant or end-stage liver failure.[69-73] Vitamin K deficiency can result from liver disease and it can exacerbate coagulation factor deficiency.

Given the complex and multiple effects that liver disease has on hemostasis, bleeding and/or thrombosis can be consequences. In people with liver failure, the following abnormalities favoring bleeding have been reported: thrombocytopenia, thrombocytopathia, and vessel wall interaction, decreased levels of coagulation factors II, V, VII, IX, X, XI, dysfibrinogenemia, and decreased alpha$_2$-antiplasmin. The following abnormalities favoring thrombosis have been reported: elevated levels of factor VIII and von Willebrand factor and decreased levels of proteins C and S, antithrombin, and plasminogen.[69]

Aside from primary therapy for liver disease (see ch. 281), supportive care in cases of hemorrhage secondary to liver failure can include vitamin K_1 therapy and plasma transfusions.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a systemic activation of coagulation, leading to intravascular fibrin deposition, thrombosis, and organ dysfunction. DIC is a consumptive coagulopathy that can result from many systemic diseases including widespread inflammation, sepsis, and neoplasia.

Tissue factor is a primary mediator of DIC. Normally, tissue factor is not exposed to the circulating blood. However, in states of inflammation and other diseases, proinflammatory cytokines and endotoxins induce tissue factor expression and release. High concentrations of tissue factor can be found on circulating monocytes, endothelial cells, neoplastic cells, microparticles, and other sources. Once in circulation, tissue factor forms a complex with activated factor VII, a potent stimulus for thrombin formation. Excess circulating thrombin cleaves fibrinogen, leaving behind multiple fibrin clots that can lead to microvascular and macrovascular thrombosis. Coagulation inhibitors are consumed in the process, further promoting coagulation. As clots form, platelets become entrapped and thrombocytopenia is identified. Simultaneously, excess circulating thrombin results in the conversion of plasminogen to plasmin, leading to fibrinolysis. Fibrinolysis results in excess amounts of fibrinogen degradation products (FDPs), which have anticoagulant properties, possibly contributing to hemorrhage. Excess plasmin also activates the complement and kinin systems, leading to clinical signs such as shock, hypotension, and increased vascular permeability.[74,75]

During the initial (nonovert, or compensated) stages of DIC, patients are in a hypercoagulable phase. However, procoagulant factors progressively become consumed, leading to a hypocoagulable (overt, or uncompensated) phase. Prolonged coagulation times accompanied by clinical signs of bleeding may be apparent in the hypocoagulable phase. Patients in acute, fulminant DIC present with bleeding; however, in

more chronic forms, patients might show signs only related to the underlying disorder.[74,75]

The diagnosis of DIC can be challenging due to the condition's dynamic nature and considerable variation in coagulation profiles of affected patients. Any animal having experienced prolonged hypotension (see ch. 159), systemic inflammatory response syndrome (see ch. 132), disturbed blood flow to a major organ, or major tissue trauma (see ch. 143 and 147) is at high risk of developing DIC. A combination of clinical and laboratory findings is used for identifying DIC. Typical laboratory findings include prolongation of coagulation times, thrombocytopenia, elevation of fibrinolysis markers (D-dimers and FDPs), hypofibrinogenemia, decreased antithrombin, and signs of red blood cell fragmentation on the blood smear.[74,76] Viscoelastic testing can be used for distinguishing between the various stages of DIC in dogs.[77,78] In one study, the majority of patients suspected to be in DIC were found to have hypercoagulable tracings. In this study, mortality was associated with high D-dimer concentrations, low antithrombin concentrations, and hypocoagulable TEG tracings compared to survivors.[77] Earlier diagnosis of DIC could lead to more prompt intervention, potentially improving survival times. However, viscoelastic test results can be confounded by anemia, thrombocytopenia, and hyperfibrinogenemia, potentially complicating efforts to understand the *in vivo* coagulation status of a patient with DIC.[79]

Treatment of DIC should start by first treating the underlying condition (e.g., antimicrobials for septic patients). Intravenous fluids (see ch. 129) and oxygen therapy (see ch. 131) will promote perfusion and tissue oxygenation. Therapeutic recommendations to address consequences of DIC are controversial. Heparin therapy commonly is used in the hypercoagulable phase of DIC, despite few reports documenting its true benefit.[80] Heparin is an indirect anticoagulant, exerting most of its effect through potentiation of antithrombin activity, which can be diminished in states of DIC. Heparin does not eliminate existing thrombi but could prevent the formation of new thrombi. Use of heparin in veterinary DIC patients has been reported, but optimal dosing regimens are not known.[74,81] Increased morbidity has been reported in people with DIC who receive heparin while actively bleeding; heparin therapy should be avoided in veterinary patients with DIC and evidence of bleeding. Prophylactic plasma transfusion does not show a consistent benefit in humans with DIC, and plasma transfusions usually are recommended only in patients with clinical signs of bleeding.[80] Similarly, fresh frozen plasma or cryoprecipitate therapy (see ch. 130) is recommended in veterinary patients with DIC and signs of bleeding secondary to factor deficiency. Platelet transfusion rarely is indicated in veterinary patients with DIC.[74]

The overall prognosis for DIC is poor and it varies depending on the underlying disorder. Early diagnosis and intervention could lead to improved prognosis.[77]

Acquired Anticoagulants

Spontaneous development of coagulation inhibitors rarely is reported in veterinary patients. Coagulation inhibitors are antibodies (usually IgG) that bind to and inhibit activity of coagulation factor, or cause increased coagulation factor clearance. Acquired anticoagulants can develop secondary to immune-mediated disease, drug reaction, lymphoproliferative disease and other neoplasia, DIC, and following multiple blood transfusions.[82-86] Antiphospholipid protein antibody (i.e., lupus anticoagulant) inhibits interaction between coagulation proteins and cell membranes, causing prolongation of coagulation times such as PTT.[87] Paradoxically, presence of antiphospholipid protein antibodies is associated clinically with thrombosis. Antiphospholipid protein antibodies are reported rarely in veterinary medicine.[88] Development of factor VIII or IX inhibitory antibodies is a reported consequence of multiple transfusions of humans and dogs with hemophilia.[86,89-91]

Clinical signs related to acquired anticoagulants can be absent or can include signs of hemorrhage. Because other aspects of hemostasis might be disrupted, hypercoagulability and thrombosis can be observed concurrently. Coagulation times (PT, PTT) are abnormal depending on which factor(s) is/are affected. A plasma mixing test can be used for supporting a diagnosis of acquired anticoagulant. In this test, various dilutions of patient and control plasma are incubated. If an inhibitor is present, coagulation factor activity in the control plasma will be inhibited and the coagulation test remains abnormal. Confirmatory testing with specific assays can be performed (e.g., Bethesda assay for quantification of factor VIII inhibitor).

General Treatment of Acquired Hypocoagulability

Therapy to address the underlying disorder for hypocoagulability is recommended when possible. Vitamin

K_1 therapy is recommended in anticoagulant rodenticide intoxication cases (see ch. 152) and in liver dysfunction causing coagulopathy (see ch. 281). An initial dose of 2.5-5 mg/kg SC or PO, followed 6-12 hours later with maintenance therapy (0.8-1.7 mg/kg PO q 8 h) can be given. Vitamin K_1 should never be given intravenously as it has been associated with anaphylaxis. Vitamin K_3 therapy is not recommended due to slower onset of action and possible Heinz body formation.

Plasma transfusions can temporarily replenish coagulation factors. Plasma usually is administered at an initial dosage of 10-20 mL/kg (see ch. 130). Fresh frozen plasma contains all coagulation factors and plasma proteins, including the labile coagulation factors (V and VIII). Cryoprecipitate primarily contains factors VIII and XIII, von Willebrand factor, fibrinogen, and fibronectin, at approximately 50-80% of the levels as fresh frozen plasma but in a smaller volume. Cryosupernatant, or cryo-poor plasma, has sufficient quantities of most coagulation factors except for those contained in cryoprecipitate.[92] In comparison, stored plasma contains significantly lower concentrations of factors V and VIII but contains adequate levels of vitamin K-dependent factors and other plasma proteins.[92,93] Either fresh frozen or stored plasma is suitable for replacement of vitamin K-dependent factors, as well as for treatment of other factor deficiencies. Fresh frozen plasma is recommended in patients showing signs of hemorrhage secondary to liver disease or DIC.[94,95]

Hereditary Hypocoagulable States

Scott Syndrome

While Scott syndrome is a defect of procoagulant activity on the platelet surface, it manifests as a coagulopathy because the platelet surface cannot support plasma coagulation protein activity.[96,97] Canine Scott syndrome appears to be an autosomal recessive trait primarily affecting German Shepherd Dogs.[96,98,99] Affected dogs show signs of epistaxis, soft tissue hemorrhage, and surgical hemorrhage; clinical signs can vary in severity.

Scott syndrome is diagnosed by prothrombin consumption assay, or by detecting lack of phosphatidylserine externalized on platelets via flow cytometry. Hemorrhage episodes can be treated with transfusion of platelet products (e.g., cryopreserved platelet-rich plasma), but improvement is only transient.[99]

Hereditary Factor Deficiencies

Single or combined factor deficiencies produce variable clinical signs ranging from asymptomatic states to severe bleeding tendencies. Depending on the deficient factor(s), prolongation of PT and/or PTT is observed (Table 197-1). Measurement of individual coagulation factor activity is required for definitive diagnosis. Genetic testing also is available for some inherited coagulation disorders.

TABLE 197-1

Inherited Coagulation Factor Deficiencies Reported in Dogs and Cats

FACTOR	DEFICIENCY	RESULTS OF ROUTINE SCREENING TESTS
I	Afibrinogenemia; hypofibrinogenemia; dysfibrinogenemia	↑ PT, PTT, ACT ↓ to normal fibrinogen
II	Hypoprothrombinemia	↑ PT, PTT, ACT Normal fibrinogen
VII	Hypoproconvertinemia	↑ PT Normal PTT, ACT, fibrinogen
VIII	Hemophilia A	↑ PTT, ACT Normal PT, fibrinogen
IX	Hemophilia B (Christmas disease)	↑ PTT, ACT Normal PT, fibrinogen
X	Stuart-Prower deficiency	↑ PT, PTT, ACT Normal fibrinogen

XI	Hemophilia C	↑ PTT, ACT Normal PT, fibrinogen
XII	Hageman trait	↑ PTT, ACT Normal PT, fibrinogen
XIII	Factor XIII deficiency	Normal PT, PTT, ACT, fibrinogen
II, VII, IX, and X	Combined vitamin K-dependent factor deficiency	↑ PT, PTT, ACT Normal fibrinogen

ACT, Activated clotting time; *PT*, prothrombin time; *PTT*, partial thromboplastin time.

Hemophilia A and B

Hemophilia A is a deficiency of factor VIII, and hemophilia B is a deficiency of factor IX. Hemophilia A is more common than hemophilia B, and both forms have been documented in dogs and cats.[100-107] Hemophilia A and B are autosomal, X-linked, recessive traits, primarily affecting males while females are carriers.[100] Various genetic mutations are responsible for hemophilia A or B. In some cases, hemophilia within a pedigree can be traced to the original index animal, whereas other cases are suspected to arise from *de novo* mutations.[100,102,108]

Lack of factor VIII or IX inhibits formation of the tenase complex, hindering downstream thrombin generation and blood clot formation. Accordingly, hemorrhage is the principal clinical sign associated with hemophilia A or B, and this hemorrhage typically can manifest as prolonged bleeding after trauma or surgery, subcutaneous or intramuscular hematomas, mucosal bleeding, or lameness due to hemarthrosis.[94,104,106,109]

Hemophilia A or B is suspected in patients with a bleeding diathesis and prolonged PTT or ACT, with a concurrently normal PT. Measurement of coagulation factor activity (FVIII:C or FIX:C) is required for a definitive diagnosis. Normal factor activity levels are 50-150%. Hemophilia is considered mild when the corresponding factor level is ≈6-20%; moderate and marked hemophilia can be defined when factor levels are ≈2-5% and <2%, respectively.[106,110] Severity of factor deficiency correlates with clinical signs in affected people, although additional variables such as function of other hemostatic proteins, the patient's physical condition, and concurrent illness play a role.[111,112] Occurrence of spontaneous bleeding episodes was not significantly different between dogs with mild, moderate, and severe hemophilia A in one study.[106]

Depending on the severity of hemorrhage episodes, transfusion can be used for replacing deficient factors and alleviating short-term bleeding (see ch. 130). While injection of desmopressin temporarily increases circulating factor VIII concentrations in people, the same does not appear to be true in dogs.[113] Prophylactic transfusion might be warranted in patients with hemophilia prior to performing invasive procedures.

The prognosis for dogs and cats with hemophilia appears variable. Severely affected animals likely die at birth. Prognosis did not correlate with degree of factor deficiency in dogs with hemophilia A in one study.[106] Following transfusion, the patient can develop inhibitors to the deficient factor (i.e., factor VIII or IX inhibitors), leading to higher transfusion requirements on subsequent transfusions.[86,90,91] Post-transfusion purpura was reported in a dog with hemophilia A and was successfully treated with corticosteroids.[114] Pedigree analysis and factor activity levels should be analyzed in breeding groups that have given rise to individuals affected by hemophilia. Factor levels often are low-normal in carrier females and can overlap with those of unaffected females, making it difficult to determine carrier status based on factor analysis alone. Lack of clinical signs in carrier or mildly affected animals can lead to propagation of the condition through a pedigree.

Other Inherited Coagulation Factor Deficiencies

Hereditary fibrinogen (factor I) disorders include complete or partial lack of fibrinogen (afibrinogenemia and hypofibrinogenemia, respectively) and qualitative defects in fibrinogen (dysfibrinogenemia).[100,115] Disorders of fibrinogen appear to be uncommon in dogs but have been reported.[100,116-118] Depending on the severity of the disorder, hemorrhage might occur spontaneously or after trauma or surgery. Paradoxically, affected patients also can have thrombosis.[100,115-117] Fibrinogen defects can be suspected when PT, PTT, ACT, and TCT are prolonged; quantitative fibrinogen disorders will have a concurrently decreased fibrinogen concentration. Patients with dysfibrinogenemia typically have normal to low fibrinogen concentrations and

low functional fibrinogen activity (e.g., Clauss test).[117] Due to the uncommon nature of hereditary fibrinogen disorders, more common causes of low fibrinogen concentrations such as DIC or liver disease should be ruled out first.

Other inherited factor deficiencies resulting in hemorrhage have been described, including factor II deficiency in dogs[118]; factor VII deficiency in dogs[107,118-123]; factor X deficiency in dogs[118,124] and cats[125]; factor XI deficiency in dogs[126] and cats[127]; and factor XIII deficiency in a dog.[128]

Feline factor XII deficiency (Hageman trait) is the most common defect of the intrinsic (contact) pathway factors. Cats with factor XII deficiency demonstrate prolonged PTT, but hemorrhage or other clinical signs do not result from this deficiency as *in vivo* clot formation is primarily dependent on factor VII and tissue factor activation.[46,129,130] Concurrent hemophilia A or B has been reported in cats with factor XII deficiency, and it can give rise to clinical signs of hemorrhage.[131,132]

Congenital deficiency of the vitamin K–dependent coagulation factors results from defective gamma-glutamyl carboxylase or vitamin K 2,3-epoxide reductase (VKOR) complex in people. This disorder causes combined factor deficiencies (factors II, VII, IX, and X; anticoagulant proteins C, S, and Z) and results in variable bleeding, as well as skeletal and other developmental disorders in people.[133] A defect in vitamin K gamma-glutamyl carboxylase has been reported in Devon Rex cats, leading to deficiency of vitamin K-dependent coagulation factors and spontaneous bleeding in some affected cats.[134,135] Affected cats have prolonged PT, PTT and ACT, as well as increased PIVKA; factors II, VII, IX, and X activities are diminished. Ingestion of anticoagulant rodenticide should be ruled out prior to pursuing a diagnosis of congenital deficiency of vitamin K–dependent factors. Definitive diagnosis requires hepatic biopsy to identify enzymatic defects.[135] Vitamin K_1 therapy normalizes coagulation factor levels and clinical signs of hemorrhage.[134] Vitamin K–dependent factor deficiency has also been reported in a young Labrador Retriever, although the exact mechanism of deficiency in this case was unknown.[136]

Treatment of Inherited Coagulopathies

Single or combined factor deficiencies can be treated using a plasma product transfusion to temporarily replenish the deficient factor(s) during episodes of hemorrhage (see ch. 130). Plasma dosages are similar to those outlined above for acquired coagulopathies. Fresh frozen plasma can be used for most factor deficiencies, including hemophilia A. Stored plasma lacks factors V and VIII but can be used to treat other factor deficiencies. Cryoprecipitate is suitable for transfusing smaller plasma volumes rich in factors I, VIII, and XIII; cryosupernatant is lacking in those factors but can be used for treating other deficiencies. Factor XII deficiency does not require treatment as it does not result in clinical signs.

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CHAPTER 198

Immune-Mediated Hemolytic Anemias and Other Regenerative Anemias

Christine Piek

Client Information Sheet: Immune-Mediated Hemolytic Anemia (IMHA) in Dogs

Definitions and Overview

Anemia is defined as a reduction in circulating red blood cell (RBC) numbers, hematocrit (Ht) and hemoglobin, causing decreased oxygen carrying capacity of the blood (also see ch. 57). Anemia results from diseases causing decreased RBC production, loss of RBCs, destruction of RBCs or some combination thereof. Documentation of adequate erythropoiesis in response to an anemia is instrumental in differentiating those causal categories. Erythropoiesis is part of hematopoiesis and starts with the production of stem cells in the bone marrow (BM) that subsequently differentiate into RBCs, granulocytes, monocytes, platelets and other cells of the immune system. The organ producing RBCs is called the erythron. In the fetus, erythropoiesis is found in the BM and liver.[1,2] After birth, erythropoiesis takes place in the BM and, in anemia, extramedullary erythropoiesis may take place in the liver and spleen. Circulating RBC mass reflects the balance between production and destruction or loss. The hormone erythropoietin is the physiological regulator of RBC production.[2] Increased erythropoietin concentrations induced by renal cortical hypoxia increases proliferation and differentiation of erythroid precursors in a healthy erythron.[2,3]

In the BM, RBC precursors may be identified in so-called erythroblastic islands. Here, erythroblasts at different stages of development closely surround macrophages that provide the necessary iron for hemoglobin production.[3] These erythroid precursors proliferate and differentiate from proerythroblasts into basophilic erythroblasts, polychromatic erythroblasts, orthochromatic erythroblasts, reticulocytes, and finally, into mature RBCs.[3] This process takes about 5-7 days.[4-7] In health, reticulocytes remain in the BM for 2-3 days before being expelled into the bloodstream. Their residual RNA, which distinguishes them from mature RBCs, is gradually lost during the first 24 to 48 hours in the circulation.[6,7] RBCs that retain small clumps of RNA, visible with new methylene blue or brilliant cresyl blue staining, are called aggregate reticulocytes.[5] After an episode of hemolysis or blood loss, aggregate reticulocytes start to appear within 48 hours. In cats, aggregate reticulocytes develop into punctate reticulocytes in which only one to three small RNA clumps are visible before maturing into RBCs. These punctate reticulocytes may remain in circulation for 2-3 weeks.[5]

Recognizing Regenerative Anemia

The number of aggregate reticulocytes may be counted microscopically or with a hematology analyzer per number of circulating RBCs.[5] They may be reported as a percentage or converted to the reticulocyte number per volume of blood.[5] Because reticulocytes are measured as a percentage of circulating RBCs, they may increase in the early response to anemia after blood loss or hemolysis without an increase in actual RBC production. The reticulocyte percentage must be evaluated in association with the corresponding decrease in Ht. This may be done by assessing the corrected reticulocyte percentage, which can be calculated by multiplying the observed reticulocyte count by the patient's Ht, divided by the Ht in health. The latter may be estimated from Ht reference values. Adequate RBC regeneration is present when the corrected reticulocyte percentage is above the reticulocyte reference range.[5] In health, reticulocyte numbers are low, around 1% of circulating RBCs. Therefore, the coefficients of variation for both manual (8-23%) and automated counts (5-8%) are relatively high.[8] This variation should be taken into account when the adequacy of reticulocytosis is

assessed.

It usually takes 2-5 days for reticulocytosis to develop after a hemorrhagic or hemolytic event.[5] Under the influence of erythropoietin, reticulocytes can be prematurely released from the BM, together with late polychromatophilic erythroblasts or so-called normoblasts.[4,5] Immature reticulocytes may be recognized in a blood smear by their relatively large size and polychromatic cytoplasm. Reticulocytosis in these cases merely reflects early BM release, not increased production. This may present a "flattering image" of RBC production but is not a reliable estimate.[5] It has been suggested that these immature reticulocytes require 2 to 3 times longer before becoming mature RBCs.[5]

Determining whether RBC production is appropriate in anemia, likely after blood loss or hemolysis, rests upon the clinician. One must allow sufficient time for the BM to show a regenerative response following acute hemolysis or blood loss and 4-5 days is usually needed for release of new reticulocytes. Cytological and/or histological examination of a BM biopsy may allow assessment of the RBC response earlier (see ch. 92). It is rarely necessary to perform a BM biopsy for the sole purpose of documenting an adequate regenerative response. In many cases a reevaluation of the Ht and reticulocytes after 1-3 days suffices to document the presence of adequate RBC regeneration.

Diagnostic Approach to Regenerative Anemias

Differential Diagnosis

Regenerative anemia is caused by RBC loss, destruction, or both. The differential diagnosis for erythrocyte destruction can be categorized as acquired non-immune hemolytic anemias, hemophagocytic disorders, and the immune-mediated hemolytic anemias (Box 198-1). Acquired non-immune hemolytic anemias include diseases that destroy RBCs due to direct membrane damage, oxidative damage, infections, erythrocyte fragmentation, and conditions that interfere with RBC energy metabolism. Even a detailed differential diagnosis may not be complete. Diseases in which RBC lifespan is shortened but without anemia and some extremely rare diseases have been omitted from this chapter. Successful diagnosis depends on understanding the characteristics and prevalence of the individual conditions in the differential diagnosis as well as having an appreciation for the diagnostic tests that discriminate them. The diagnostic approach (Figure 198-1) utilizes a rational approach in dogs with regenerative anemia that first aims to make optimal use of information available in the history and physical examination. Additional tests further discriminate between the differential diagnoses.

Box 198-1

Differential Diagnosis of Disorders Causing Hemolytic Regenerative Anemia

Acquired Non-Immune Hemolytic Anemias

- Intoxications
  - Venoms such as snake bites,[36-39] bee stings[40,41]
  - Oxidative substances causing Heinz body anemia[43]: zinc,[45-51] acetaminophen (cats),[53,54] methylene blue (cats),[55] onions (dogs)[44,225-227]
- Infections
  - Canine babesiosis[64,66]
  - *Mycoplasma haemofelis*[88,228]
- Red cell fragmentation syndromes[95]
  - Neoplasia (hemangiosarcoma)[95,97]
  - Hemolytic uremic syndrome[99,229,230]
- Hereditary hemolytic anemias
  - Erythrocyte enzyme deficiencies[101,186]
    - Pyruvate kinase deficiency in cats*[231,232] and dogs†[95,233-236]
    - Phosphofructokinase deficiency in dogs‡[26,32,237]
  - Erythrocyte membrane disorders

Stomatocytosis[§25,31,111-113]

Feline hypophosphatemia

In diabetes mellitus, hepatic lipidosis, and enteral alimentation[57-59]

Hemophagocytic Anemias

Hemophagocytic histiosarcoma[¶116,123]

Immune-Mediated Hemolytic Anemias

Idiopathic immune-mediated hemolytic anemia

Secondary immune-mediated hemolytic anemia

Infectious diseases (viral, protozoal, bacterial)

Neoplasia

Medications[187-189]

Penicillins, cephalosporins,[191] sulfonamides,[192,193] methimazole[194,195]

Autoimmune disorders

Idiopathic immune-mediated thrombocytopenia[131,168]

Alloimmune hemolytic anemia

Feline neonatal isoerythrolysis[218]

Incompatible blood transfusions[238,239]

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[*] Abyssinian, Somali, Domestic Shorthair; PK deficiency-associated single nuclear polymorphisms occur in 12 breeds [231].

[†] Reported breed predisposition: Basenji, Beagle, Cairn Terrier, Chihuahua, Dachshund, Pug, Labrador Retriever, Toy American Eskimo Dog, West Highland White Terrier.

[‡] Reported breed predisposition: English Springer Spaniel, American Cocker Spaniel, Whippet, Wachtelhund.

[§] Reported breed predisposition: Alaskan Malamute, Drentse Patrijshond, Miniature Schnauzer, Standard Schnauzer.

[¶] Reported breed predisposition: Bernese Mountain Dog, Rottweiler, Golden Retriever, Flat-coated Retriever.

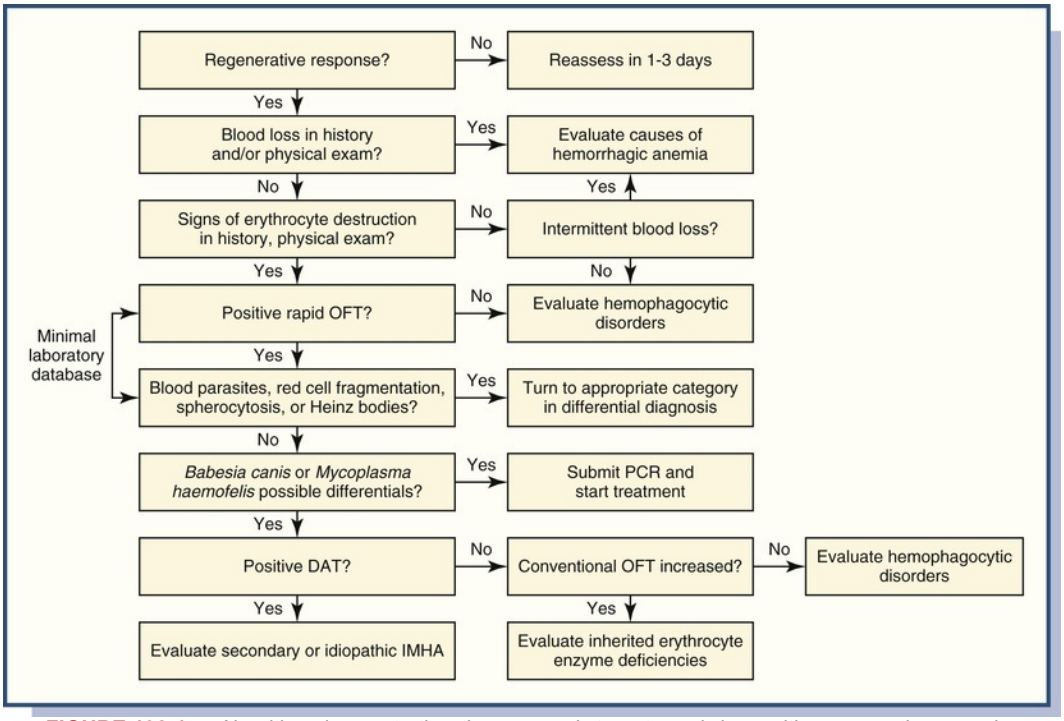

FIGURE 198-1 Algorithm demonstrating the approach to cats and dogs with regenerative anemia. *DAT*, Direct agglutination test; *IMHA*, immune-mediated hemolytic anemia; *OFT*, osmotic fragility test; *PCR*, polymerase chain reaction.

Hemorrhage vs. Hemolysis

The diagnostic pathway starts with differentiating hemorrhagic from hemolytic regenerative anemias. History and physical exam almost always identify external blood loss (see ch. 135). Disorders of abdominal organs, such as neoplasia or amyloidosis, may cause intermittent bleeding that is more difficult to recognize.[9-11] Occult blood loss in the gastrointestinal tract usually begins as a regenerative anemia but ultimately the anemia becomes non-regenerative due to iron deficiency.[12,13] If there is no evidence of blood loss, hemolysis is the next likely explanation for regenerative anemias. Senescent RBCs in health undergo macrophage erythrophagocytosis in the BM, spleen, and liver. In hemolytic diseases, hemolysis may also occur in the intravascular space, causing hemoglobinemia and hemoglobinuria. Clinical signs from hemolysis are usually those of anemia. In severe, acute hemolysis, hypoxemia may cause tissue necrosis and a decrease in hepatic capacity for handling RBCs. In this scenario, icterus may develop. Massive hemoglobin breakdown may result in orange-yellow color of the feces since hemoglobin breakdown products are ultimately excreted via the bile in the duodenum. Hemolysis may be confirmed by the presence of signs such as red urine, yellow feces, and icterus in the history or on the physical exam.

Available Tests

Blood Smears and Rapid Osmotic Fragility Testing

After obtaining a history and physical examination, one should evaluate a blood smear microscopically. In regenerative anemias, macrocytes with polychromasia reflect the degree of reticulocytosis while RBC precursors (e.g., normoblasts) may be seen. Parasites, such as *Babesia* or *Mycoplasma haemofelis,* may be readily identified. In acute anemias, such infections should be excluded by molecular diagnostic testing. One should note presence and numbers of spherocytes. Red cell fragmentation disorders may be detected microscopically, as may Heinz body anemias. Alternatively, the findings on the smear may be indicative of the pathophysiologic route to anemia, such as the finding of microcytes and hypochromasia in iron deficiency anemia.[12,13] The osmotic fragility test (OFT) is of use in discriminating hemolytic from non-hemolytic conditions.[14] Hemolysis can be observed after centrifuging (5 minutes, 2431 × g) RBCs that have first been separated into 2 tubes, one incubated for 5 minutes in 0.9%, the other in 0.55% saline.[14,15] The test is negative if no color difference is observed between the supernatant in the two tubes and positive if the supernatant in the tube with 0.55% saline is obviously more red. A modification includes a negative RBC control (Figure 198-2).

RAPID OSMOTIC FRAGILITY TEST OF ERYTHROCYTES

LABORATORY PROTOCOL

MATERIALS

- 4 clean numbered empty reaction tubes
- 5 mL syringe
- Pasteur's pipette
- Fresh blood sample (EDTA or heparin) of healthy dog or cat as a negative control
- Fresh blood sample (EDTA or heparin) of patient

METHOD

1.
In DOGS: add 0.9% NaCl, (tap) water and (heparin or EDTA) blood in 4 numbered reaction tubes

Tube nr	0.9% NaCl	H_2O	BLOOD NORMAL DOG	BLOOD PATIENT
1	5 mL	--	5 drops	--
2	5 mL	--	--	5 drops
3	3 mL	2 mL	5 drops	--
4	3 mL	2 mL	--	5 drops

In CATS: add 0.9% NaCl, (tap) water and (heparin or EDTA) blood in 4 numbered reaction tubes

Tube nr	0.9% NaCl	H_2O	BLOOD NORMAL CAT	BLOOD PATIENT
1	5.5 mL	--	5 drops	--
2	5.5 mL	--	--	5 drops
3	4 mL	1.5 mL	5 drops	--
4	4 mL	1.5 mL	--	5 drops

2. Mix tubes using vortex
3. Incubate for **5 minutes at room temperature**
4. Centrifuge for 5 minutes at 2431 × g
5. Results:
   Tube 1 and 3 should be clear. Erythrocytes should be intact on bottoms of tubes.
   Tube 2 can be slightly hemolyzed if plasma of patient was already hemolytic.
   Tube 4 will show more hemolysis than tube 2 if osmotic fragility is increased.

FIGURE 198-2 Material needed and protocol to follow for performing a rapid osmotic fragility test of erythrocytes.

Spherocytes and Osmotic Fragility Testing

Immune-mediated hemolytic anemias (IMHAs) are common and often first suspected after noting extensive spherocytosis in blood smears. The identification of spherocytes is subjective, requiring expertise and experience.[15,21] The rapid OFT provides an objective alternative to searching for spherocytes and may be performed as an in-house test, making the results directly available.[14,15] The OFT detects erythrocyte membrane defects and is positive in 85%-100% of dogs with IMHA.[14,15,21] Both the rapid and the conventional OFT may be positive in diseases other than IMHA, however. These include hereditary erythrocyte membrane defects and other diseases affecting erythrocyte membrane stability.[14,22-35]

Direct Agglutination Test (DAT)

Diagnosis of IMHA can be further supported with a positive DAT (Coombs' test) result.[16-20] Starting treatment early in the course of the disease is important, and is one of the determining factors in outcome. Thus, results of diagnostic tests should be available quickly. The conventional DAT offered by most laboratories specializing in veterinary hematology may delay definitive diagnosis of IMHA. Various

alternative DAT techniques have been described that may soon be available for in-house testing.[21] Importantly, DAT results are not influenced by storing samples for a few days, immunosuppression, or transfusions.[21] If the DAT is negative, a diagnosis of alternative conditions should be pursued. A definitive diagnosis of IMHA is based on a positive DAT or spherocytosis. Erythrocyte integrity is not compromised in hemophagocytic disorders and both the OFT and DAT are negative in these conditions. A breed predisposition or the presence of cranial abdominal organomegaly may suggest the presence of a hemophagocytic disorder earlier in the diagnostic pathway.

Differential Diagnosis for Hemolysis

Overview

The differential diagnoses are grouped as acquired non-immune hemolytic, immune-mediated hemolytic, and the hereditary hemolytic disorders (see Box 198-1). Acquired hemolysis may result from direct RBC exposure to chemicals, physical stresses, infection, or may be mediated by antibodies. In hereditary diseases, RBCs may be more susceptible to hemolysis.

Acquired Non-Immune Hemolytic Anemias

Red Cell Toxins

Acquired non-immune hemolytic disorders may result from direct toxicity, such as with snake or bee sting venoms. This may be obvious from the history and physical exam.[36-41] Chemical substances may have an oxidative effect that damages erythrocyte membranes via reactive oxygen species, which denature hemoglobin and result in methemoglobinemia and Heinz body formation. Small numbers of Heinz bodies probably have little consequence, but excessive Heinz body formation increases RBC rigidity, making them susceptible to hemolysis.[42] Heinz bodies stain the same color as RBCs and appear as single masses extending from the more central areas and forming blunt projections from cell membranes.[43] Up to 80% of RBCs from dogs fed onions contained Heinz bodies and up to 6% had eccentrocytes 1-3 days after ingestion.[44] Ingested metal pieces containing zinc may cause Heinz body anemia.[45-51] All 19 dogs in a retrospective case series of dogs with zinc intoxication were anemic and about half had Heinz bodies at presentation.[47] Diagnosis is made by determination of zinc concentrations. Increased numbers of Heinz bodies have been seen in cats with diabetes mellitus, hyperthyroidism, and lymphoma. Hematocrits in these cats were only moderately decreased.[52] Heinz body formation, usually with severe hemolysis, has been reported in acetaminophen and methylene blue toxicosis.[53-55]

Hypophosphatemia

Hypophosphatemia decreases red cell adenosine triphosphate stores, making them susceptible to hemolysis.[56] Severe hypophosphatemia causing hemolytic anemia has been reported almost exclusively in cats with diabetes mellitus, in hepatic lipidosis, and following enteral alimentation.[57-59] It may be diagnosed based on history and plasma inorganic phosphate concentrations.

Red Cell Infections

Background

Infection-associated hemolysis may be due to direct exposure or to products of viral, bacterial or parasitic agents. Babesiosis and feline hemoplasmosis are the two most common infectious diseases that cause hemolysis and regenerative anemias. Feline cytauxzoonosis, most commonly but not exclusively from the Midwestern United States, may cause hemolytic but non-regenerative anemias.[60-63]

Babesiosis

Canine babesiosis is a protozoal tick-borne disease with a worldwide distribution (see ch. 221). The disease may be caused by different *Babesia* species, depending on location.[64-66] *B. gibsoni* infection can follow direct dog-to-dog transmission.[67,68] Feline babesiosis is less common and has mostly been reported from South Africa.[69-71] Regenerative anemia results from acute hemolysis. Intravascular hemolysis is due to direct RBC

damage by intracellular parasitic replication. Depending on the *Babesia* species, hemolysis can be caused by serum hemolytic substances, oxidative damage, or antibody binding to RBCs. Antibody binding stimulates complement activation, spherocyte formation, and increased RBC osmotic fragility.[64,72-76] Extravascular hemolysis may result from increased erythrophagocytosis.[64] Splenic erythrocyte sequestration may contribute to development of anemia.[77,78]

Clinical signs differ between the different *Babesia* species. Nonspecific signs (fever, inappetence, lethargy) may be accompanied by signs of anemia, splenomegaly, icterus, and red urine.[64,79] In most cases, the hemolytic regenerative anemia occurs concurrent with thrombocytopenia.[64,79-81] The DAT may be positive. Antibodies against RBCs have been documented in dogs infected with *B. gibsoni* and *B. vogeli* but not in *B. canis* infections.[64,82-84] The OFT may be increased.[76] Diagnosis, in most acutely ill dogs, is readily confirmed by microscopic examination of a fresh stained blood smear. Capillary blood from the ear tip or toe nail that is concentrated, and stained buffy coat preparations, may have higher levels of parasitemia.[85,86] *Babesia* species appear in the erythrocytes as single or paired, pear shaped, oval, or round parasites measuring around 2-5 microns in diameter. Molecular diagnostic tests have the advantage of higher sensitivity and offer the possibility to differentiate among the different *Babesia* species, even smaller species difficult to identify microscopically.[64] Differentiation of *Babesia* species is relevant since treatment and prognosis may differ. The combination of acute and convalescent antibody titers may also be used to document *Babesia* infection.[64]

Hemotropic *Mycoplasma* Infections

Feline hemotropic *Mycoplasma* infections are erythrocytic bacterial infections that occur worldwide (see ch. 219).[87,88] Among the feline *Mycoplasma* species, *Mycoplasma haemofelis* may cause acute, severe anemia, especially in young cats.[87,88] Prevalence varies widely and may range from 3% to as high as 50%, depending on geographical area and presence of clinical disease or anemia in the population studied.[87,88]

Other feline hemotropic mycoplasmas, *Candidatus Mycoplasma haemominutum* and *Candidatus Mycoplasma turicensis* seldom cause clinical signs.[87,88] Prevalence studies mostly identify chronically infected cats. The absence of a consistent association with anemia in these studies may be due to cats not consistently clearing their infection and becoming long-term carriers, regardless of treatment. Concurrent retroviral infection is a risk factor for hemoplasma infection, which may be due either to immunosuppression or that both infections share similar routes of transmission.[88]

Clinical signs of acute infection include nonspecific signs (lethargy, inappetence, fever) in combination with signs due to anemia. In a minority, icterus may be seen. Chronic infections with *Mycoplasma haemofelis* usually do not cause anemia. Of interest, no significant difference was found in hemoplasma prevalence comparing anemic with non-anemic cats.[89-91] Cats with acute *Mycoplasma haemofelis* infection may have a positive DAT and persistent autoagglutination.[92] Antibodies appear after the onset of anemia.[92] The treatment of choice is doxycycline.[87]

Canine Hemoplasmosis

Canine hemoplasmosis is an extremely uncommon cause of hemolytic anemias and a rare cause of immune-mediated hemolytic anemia in the dog.[93,94]

Red Cell Fragmentation Syndromes

RBC fragmentation syndromes are the consequence of physical trauma to the cells, leading to intravascular hemolysis. Blood smears usually have significant numbers of unusual, triangular, sharply edged, pointy, RBC fragments of variable size and numbers.[95] The cause of the anemia is not always obvious and mechanisms other than hemolysis may contribute.

In microangiopathic hemolytic anemias, RBC fragmentation results from interaction with abnormal vascular endothelium, as in hemangiosarcoma (see ch. 347).[96,97] It may also occur with other cancers, heart failure, glomerulonephritis, and myelofibrosis.[95] Thrombotic microangiopathies begin as microvascular thromboses and cause thrombocytopenia and hemolysis due to RBC fragmentation.[98] In dogs, a hemolytic uremic syndrome has been reported in which renal arterial and arteriolar endothelial lesions induce local thrombi and acute kidney injury.[99] Erythrocyte fragmentation is also seen in disseminated intravascular coagulation when RBCs are damaged due to the multiple venous microthrombi (see ch. 197).[95]

Hereditary Hemolytic Anemias

The hereditary hemolytic anemias are a heterogeneous group of rare diseases (see Box 198-1). Genetic erythrocyte enzyme deficiencies that cause impaired erythrocyte energy metabolism, such as pyruvate kinase deficiency and phosphofructokinase deficiency in dogs, or genetic membrane disorders such as stomatocytosis, are relevant as differential diagnoses in regenerative hemolytic anemias. They should be considered if the OFT is increased and the DAT is negative. As genetic testing becomes more widely available for different, breed-specific mutations, the prevalence of these diseases is expected to decline. Alternatively, enzyme activity may be assessed, but testing is only available in a few research laboratories.[100-102]

Pyruvate kinase deficiencies are autosomal recessive inherited traits that have been reported in several breeds.[100,101] Affected dogs have variable degrees of regenerative anemia.[100,101] Progressive iron overload due to continuous hemolysis may lead to hemosiderosis and liver fibrosis.[103-105] Some dogs, not cats, develop progressive myelofibrosis and sclerosis.[105] In contrast to dogs who are diagnosed young, cats may be older when first diagnosed.[100,101,106] Phosphofructokinase deficiency in dogs is inherited as an autosomal recessive trait.[100,101,107-109] Some dogs have no clinical signs but most have persistent hemolytic anemia exacerbated by sporadic hemolytic crises secondary to exercise-induced hyperventilation alkalemia.[108,110] The rarely seen stomatocytosis is a hereditary disorder of RBCs in which hemolytic anemia is one of the presenting signs.[25,31,111-113] Dogs with hereditary spectrin deficiency have increased osmotic fragility but are not usually anemic.[114]

Feline Hypophosphatemia

Hypophosphatemia inhibits RBC adenosine triphosphate production by interfering with RBC energy metabolism, which results in decreased erythrocyte membrane stability, increased osmotic fragility, susceptibility to oxidative stress, and hemolysis. Hypophosphatemia and hemolysis have been reported in cats with diabetes mellitus, with hepatic lipidosis, and after enteral feeding.[56-58] Hypophosphatemia can follow inadequate intake, shifts from plasma to the intracellular space, gastrointestinal (GI) or renal loss, and has been reported in cats with pancreatitis and GI diseases.[115] Diagnosis is made by measuring plasma phosphate concentrations and treatment involves oral or parenteral replacement.

Hemophagocytic Anemias

Several histiocytic proliferative disorders, or histiocytic sarcomas, have been identified in dogs, but are rare in cats (see ch. 350).[116-122] Predisposed dog breeds are the Bernese Mountain Dog, Rottweiler, Golden Retriever, and Flat-coated Retriever, but the condition has been diagnosed in other breeds.[116,123] Histiocytic sarcomas (HS) are most commonly derived from interstitial dendritic cells and a subgroup of hemophagocytic HS is derived from macrophage cells. The cause of regenerative anemia is erythrophagocytosis, a common concern in hemophagocytic HS. Certain characteristics set hemophagocytic HS apart from other conditions of the HS complex. Pets with hemophagocytic HS do not have mass lesions but erythrophagocytic histiocytes demonstrate infiltrative growth patterns in the spleen, liver, lung, and bone marrow.[116,123] Lymph nodes are less frequently infiltrated.[116,123]

Clinical signs of hemophagocytic HS include vague signs of anorexia, weight loss and lethargy. Many have splenomegaly and hepatomegaly. Laboratory abnormalities include a moderate to severe anemia with abundant reticulocytosis. About half have platelet counts <100,000/microL.[123] The DAT is usually negative. Despite abundant infiltration of organs, the histiocytes usually appear well-differentiated. In general, those within the spleen show more atypia, such as atypical mononuclear and multinuclear giant cells.[116,123] Histiocytes may exhibit phagocytosed RBCs or hemosiderin deposits as evidence of previous erythrophagocytosis.[123] Hemophagocytic HS may be differentiated from other histiocytic proliferative disorders by immunophenotyping for the B-2 integrins CD11/CD18.[123] Rarely, dogs may have hemophagocytic HS from dendritic cell origins.[116,123] Canine hemophagocytic HS has a grave prognosis, with a median survival of only 4 weeks.[123] The anemia caused by hemophagocytic HS may be differentiated from other hemophagocytic syndromes of the BM that typically have non-regenerative anemias and other cytopenias.[124-127]

Immune-Mediated Hemolytic Anemias

IMHAs are due to antibody-mediated RBC destruction and can occur after previous sensitization as in neonatal isoerythrolysis and incompatible blood transfusions. IMHA is most common, however, as an idiopathic autoimmune disease. Autoimmunity may develop in genetically susceptible individuals in whom self-tolerance failure leads to production of functional self-reactive lymphocytes. The onset of the autoimmune disease is thought to follow a random environmental trigger, such as an infection or injury.[128] Integral to the response to one of these triggers is an altered response to self-antigens among the innate and adaptive immune systems.[128]

Idiopathic IMHA is one of the most common immune-mediated diseases of dogs.[102,129-132] In a general veterinary university hospital, the incidence of IMHA diagnoses was estimated as 0.2%.[133] In dogs, familial associations and identification of specific breeds and dog leukocyte antigen (DLA)-haplotypes as risk factors for IMHA suggest a genetic susceptibility.[16,19,134-143] Autoreactive T-cells have been identified in dogs with IMHA as well as in siblings, supporting the hypothesis that DLA-haplotype is indeed a susceptibility locus for IMHA.[144] The risk estimates conferred by breed are, in general, higher than those conferred by DLA-haplotype alone, suggesting that DLA-haplotype is not the sole explanation for the risk on IMHA.[134] The central event in developing IMHA is the loss of self-tolerance towards RBC antigens. As a consequence, antibodies develop to RBCs and cause hemolysis by antibody-mediated erythrophagocytosis, complement-mediated erythrolysis, or both. In dogs with IMHA, the anion-exchange molecule (band 3 protein) and different erythrocyte membrane glycophorins are major target antigens.[145]

Canine Immune-Mediated Hemolytic Anemia

Pathophysiology

Mortality rates in canine idiopathic IMHA have been reported between 21 and 83%, with most fatalities occurring in the first two weeks after diagnosis.[16-20,135,140,146-149] A literature review of studies on canine IMHA suggests that as many as half of the deaths are related to thromboembolism.[19,134,139,150-153] As many as 50% of dogs with idiopathic IMHA have abnormalities in their coagulation parameters consistent with disseminated intravascular coagulation (DIC; see ch. 197).[134] Assessment of platelet activation status and thromboelastography testing indicates that most dogs with IMHA are in a hypercoagulable state at the time of diagnosis.[148,150,154-157]

Several studies using multivariate analyses suggest that icterus, petechiae, increased blood urea nitrogen concentration, prolonged activated partial thromboplastin time (APTT), thrombocytopenia, an inflammatory white cell left shift with monocytosis, and increased concentrations of cytokines involved in macrophage activation are the major determinants imposing an increased death risk.[20,134,138,140,158-162] It has been hypothesized that the hypoxia induced by severe acute anemia causes an inflammatory response, subsequent activation of coagulation, and then liver necrosis and renal failure.[20,134,158,159] Oxygen delivery was impaired in canine isovolemic anemia models at hematocrits <10%, but hypoxia was an identified risk factor in only a few studies on IMHA.[17,138,163,164] This may be explained by the heterogeneity of IMHA patients and because timely blood transfusions modify duration and pathological effects of anemia.[134,158] A pathology study in dogs with IMHA supports the hypothesis that anemia is central to the high mortality risk.[139] Presence of hypoxic necrosis around hepatic central veins was associated with increased white cell counts.[139] Prolonged exposure to increased plasma lactate concentrations caused by anemia increased mortality.[165] In addition, icterus and failing liver function contributing to mortality risk is in agreement with hypoxia as a risk factor.

Clinical Presentation

Signalment

The mean age of dogs with IMHA is 6 years. It is uncommon in dogs under the age of 1 (4% of 222 in one study), but can otherwise occur at any age.[17,18,129,134,135,140,146,160,166] Increased incidences of IMHA have been reported in females, especially when in estrus or during whelping, and in neutered dogs.[16,19,134-137,167]

Signs

Most dogs have non-specific signs: lethargy and loss of appetite. Vomiting and diarrhea has been reported in 15-30% of dogs.[20,134,137,160] The anemia in IMHA usually develops rapidly, as quickly as 3 days, and dogs

may be brought for veterinary care before their BM can mount a response.[134] The physical examination may reveal signs consistent with anemia: tachycardia, tachypnea, rapid heart rate, pale mucous membranes, and a systolic murmur.[18,140] Yellow to orange discoloration of the feces and red urine are consistent with hemolysis.[18,20,134,137,140,160] Red urine is seen in 24-44% of dogs and fever in 46%.[17,18,20,140,149,160] Concurrent thrombocytopenia causing petechiae has been reported in only 2-5% of IMHA cases and may be due to immune-mediated platelet destruction which may be referred to as Evans' syndrome.[18,20,168] Splenomegaly and hepatomegaly is found in up to 40% of cases.[17,18,20,140]

Laboratory Testing

Complete Blood Count

At the time of presentation, most dogs with IMHA have a severe anemia (Ht <12-14%).[17-20,135,137,140,160,166] These results, however, are likely biased toward severely ill dogs, since most IMHA studies are from tertiary referral hospitals. A few dogs have a more chronic form of disease and a higher Ht when first seen.[169] In many dogs, the anemia is not clearly regenerative at the time of diagnosis, with the median corrected reticulocyte counts ranging from 0.9-2.7% in 5 different studies.[17-20,160] Usually, the reticulocyte numbers increase during the first days of hospitalization because adequate time has elapsed for a BM response to begin. An inflammatory leukogram is present in almost all dogs at the time of diagnosis or during the first days of hospitalization.[134,170] Pronounced leukocytosis with a left shift is common and monocytosis is noted in about 50% of IMHA dogs.[17-20,135,137,140,150,160,166,171] Decreased platelet counts are common, with as many as 70% of dogs with IMHA having counts <200,000/mcL. About 40% had platelets counts <100,000/mcL and about 25% have severe thrombocytopenia (<50,000).[17-20,134,137,150]

Coagulation Testing

The prothrombin time (PT) is increased in as many as 50% and the APTT is increased in about 50-60% of dogs with IMHA.[18-20,134,150] This combination, together with thrombocytopenia, is suggestive of DIC (see ch. 197). This conclusion is further supported by the finding of low fibrinogen concentrations in about 20% of dogs, while in many dogs decreased antithrombin (AT), decreased coagulation factor activities, and increased D-dimers and fibrin degradation products are found.[20,150,159] However, one study found fibrinogen concentrations to be increased in 30-90% of dogs, which might be because fibrinogen is secreted during the acute-phase response.[172] Thromboelastography (TEG) tracings in dogs with IMHA are suggestive of hypercoagulability that increases during hospitalization.[157,173,174] Although important, TEG tracings in dogs with severe anemia and hemolysis may not always be reliable.[175-178]

Specific Diagnostic Testing

The diagnosis of IMHA in a dog with hemolytic anemia is made by confirming its immune-mediated pathogenesis. The direct agglutination test (DAT), introduced by the veterinarian Dr. Coombs in 1945, detects erythrocyte-bound immunoglobulins and complement, is species-specific, and is widely available.[179] Several elements of the DAT are essential for reliable results.[21,132,180,181] Erythrocytes are washed several times before performing the test to remove nonspecifically-bound immunoglobulins and plasma proteins that may interfere with the binding of the DAT reagents. The washed erythrocytes are then incubated with the DAT reagent. Agglutination is a positive result. Increasing dilutions of the DAT reagents are added to the erythrocytes to prevent inhibition of agglutination by excess of reagent antibody that may otherwise lead to false negatives. Laboratories traditionally used tubes in performing the DAT but microtiter plates are now commonly employed. Avidity of anti-erythrocyte antibodies may differ at different temperatures and therefore the test may be performed at different temperatures. It has been reported that performing the DAT at 4°C and 37°C as opposed to 22°C improves the quality of the observed agglutination and makes the test easier to read.[15,21,132,182,183] The use of a monovalent DAT in which individual reagents contain anti-IgM, anti-IgG, and anti-complement antibodies reportedly increases sensitivity as compared with using a polyvalent reagent that contains IgG and complement.[184] Positivity for IgM antibodies has been associated with underlying disorders triggering IMHA.[132,184,185]

The sensitivity of the DAT (50-89%) is difficult to assess because no “gold standard” test exists for comparison. It is likely that optimization and standardization of the DAT protocols in laboratories

incorporating the steps discussed above will improve the performance of the DAT.[21] Easily used in-clinic DAT test results correlate well with conventional tube or microtiter assay results.[21,185] DAT's imperfect sensitivity as a diagnostic aid for IMHA may be managed with alternative testing. Spherocytes, from the partial phagocytosis of antibody-coated RBC membranes, are characteristic of IMHA. Spherocytes are not 100% specific, appear as hyperchromatic microcytes in a blood smear, and are seen in 67-94% of dogs diagnosed as having IMHA.[15,17-19,21,132,180,183] Spherocytes may be seen in other hemolytic conditions and in hereditary RBC diseases.[114,186] The presence of spherocytes should be quantified in a standardized manner to avoid false interpretations.

Macroscopic or microscopic agglutinating RBCs are often seen in dogs with IMHA and are suggestive of IMHA (Video 198-1).[16,18,19] Autoagglutination may be caused by proteins other than anti-RBC pathogenic antibodies implicated in IMHA.[21] The degree of autoagglutination and persistence after the first DAT washing step varies. The washing usually causes the agglutinated RBCs to break up.[21] Described protocols that aim to differentiate "true autoagglutination" in IMHA from non-specific agglutination are not validated, not standardized and should not be used (see ch. 130).[21,134]

The OFT can confirm presence of hemolysis but not whether it is immune-mediated. Since the prevalence of hereditary RBC membrane diseases is low and other differentials may be ruled out by history, physical examination, and, if indicated, additional testing, it is fair to use this test to identify IMHA. In the OFT, RBCs are incubated in different saline concentrations (0.10-0.85%), then centrifuged and observed for hemolysis. This protocol has been modified and used for fast in-house OFT using only two saline concentrations (Figure 198-2). Results have been comparable to conventional OFTs in 89-100% of cases.[14,15,21] The increase in osmotic fragility in IMHA may be due to the presence of spherocytes or complement-mediated membrane damage.[14,15] In the Netherlands and Belgium, the rapid OFT is routinely used in the work-up of an IMHA patient.[14,15,20]

Differential Diagnosis

Secondary IMHA develops if antibodies on RBC surfaces occur during or after an infection, neoplasia, administration of some medications or, possibly, vaccination. Secondary IMHA, then, is part of a systemic immune-mediated response.[19,131,146,168,187-195] In 70-80% of dogs diagnosed as having IMHA, no evidence for an underlying trigger is found. These dogs are assigned the diagnosis of idiopathic IMHA.[20,160]

Treatment

Overview

Immunomodulation is the mainstay of treating idiopathic IMHA, to decrease erythrophagocytosis and suppress immunoglobulin production. If the anemia is severe and compromising tissue oxygenation, blood transfusions may be necessary (see ch. 130).[196] Several retrospective studies have found transfusions to be safe.[16,18,19,135] Many treatment protocols using glucocorticoids in combination with other therapies, including immune-suppressive agents, have been described.[16,17,137,140,160,197-204] Treatment of secondary IMHA should be directed at the underlying disorder.

Prednisolone

Conclusions after recent systematic reviews were that no evidence for efficacy of any combined protocol was better than using glucocorticoids alone for idiopathic IMHA.[205] Dosage regimens and related information regarding use of glucocorticoids differ between studies. One retrospective cohort study demonstrated that prednisolone, tapered over about 2 months, controlled IMHA in a large majority of afflicted dogs.[20,160] Their recommended initial oral dosage of prednisolone is 2 mg/kg/day. Dexamethasone (0.2-0.3 mg/kg/day) IV or SC is used when oral medication is not appropriate. Initially, the Ht should be assessed daily and, when it stabilizes, prednisolone is continued at the initial dosage for an additional 3 days, then 1.5 mg/kg/day for 7 days, 1 mg/kg/day for 10 days, and 0.5 mg/kg/day for 14 days. If the dog is continuing to improve, the same dosage is given, but on alternate days for 14 days (7 treatments), and subsequently tapered to 0.25 mg/kg q 48 h for 21 days. Therapy effectiveness should be assessed at visits scheduled 4 and 10 weeks after beginning therapy. If the dog completely recovers, defined as a Ht >36%, the prednisolone protocol should be completed. If relapse is diagnosed, the prednisolone dosage should revert to 2 mg/kg/day. A relapse is

defined as a decrease in Ht after an initial improvement or even complete recovery with Ht >36%. If a dog has improved but the Ht has remained <36%, the duration of each stage of the tapering process should be doubled.

Thromboprophylaxis

Most dogs with IMHA are in a hypercoagulable state and at risk for thromboembolic events. This is the rationale for thromboprophylaxis.[16,149,171,206] A recent review concluded that current evidence is insufficient to provide therapy guidelines regarding thromboprophylaxis in canine idiopathic IMHA.[207]

Prognosis

It is estimated that 65-75% of dogs with IMHA survive the first year.[20,159,160] Most deaths occur in the first 2 weeks after diagnosis (Figure 198-3). Deaths have been attributed to thromboembolism, renal failure, or liver failure.[20,134,158,159] Hemolysis may be difficult to control in some dogs, resulting in need for blood transfusion(s). If intensive in-hospital treatment is successful, the Ht rises into or close to the reference range within 2-3 weeks. These dogs have a high probability of long-term survival. Most dogs will have negative DAT and OFT results by that time.[20,160] Little is known about the incidence of recurrence, but one retrospective case cohort study noted relapses in at least 12% of dogs as many as 5 years after first diagnosis.[208]

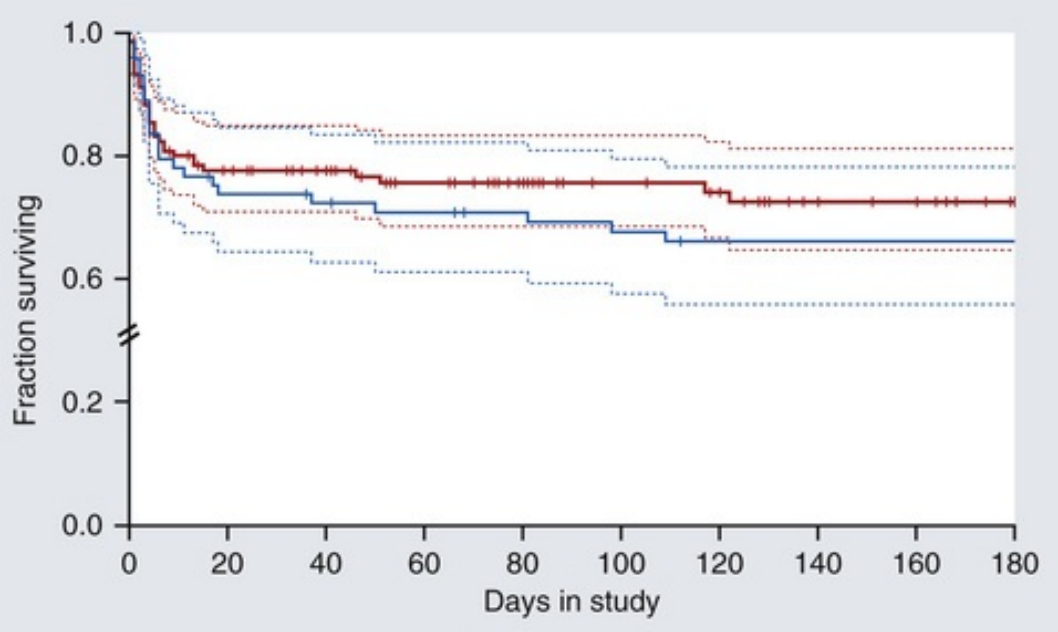

FIGURE 198-3 Estimated Kaplan-Meier survival in dogs with idiopathic IMHA treated with prednisolone alone, or in combination with azathioprine, including 95% confidence intervals (dashed lines). The endpoint was death due to IMHA; other outcomes were censored. All dogs in this study were treated with the same prednisolone protocol as described in detail in the paragraph on canine idiopathic IMHA of this chapter. No statistically significant difference was found for estimated Kaplan-Meier survival times comparing the cohort that received prednisolone only (n = 73, blue) with the cohort that received prednisolone and azathioprine (n = 149, red) acting as a historical control. Side-effects due to azathioprine were noted in 8.1% of dogs.[20,160]

IMHA may be accompanied by severe thrombocytopenia and its impact, when present, is debated.[148,209] Due to lack of access to routine diagnostics for definitive diagnosis of immune-mediated thrombocytopenia, the latter diagnosis often cannot be confirmed. In addition, thrombocytopenia in idiopathic IMHA may be due to DIC, thromboembolism, or their combination. In some dogs with IMHA, their BM is either slow or fails to regenerate RBCs. This may be a so-called non-regenerative IMHA, explained by BM damaged by hypoxia during the initial hemolytic crisis and/or thromboembolism within the BM.[210] Nonregenerative IMHA should be differentiated from pure red cell aplasia (PRCA), since the conditions and responses to

treatment differ (see ch. 199).[211]

Feline IMHA

The paucity of literature on feline IMHA suggests low disease prevalence in cats, but this concept may change. In one study, hemolysis was the cause of anemia in about 10% of 180 anemic cats, many of whom were suspected to have immune-mediated hemolysis.[212] In another study, 20% of 78 cats with anemia had been diagnosed with idiopathic IMHA.[213] Although many features of canine IMHA hold true in cats, there are some differences. The median Ht in cats with IMHA is about 12%.[213] Despite this level of severity, organ failure due to hypoxia or a systemic inflammatory response and hypercoagulability are quite uncommon. In one series, 13 of 19 cats had hyperbilirubinemia, but only 2 had clinical icterus. A slight prerenal azotemia was identified in 6. Only 2 cats had a leukocytosis. At the time of presentation, about half the cats had a regenerative anemia.[213] Severe anemia has been shown to result in volume overload and increased left heart dimensions.[214]

Laboratory diagnosis of feline IMHA can be confirmed with a positive DAT, as in dogs. Increased OFT results may also suggest IMHA.[213] As in dogs, it should be realized that other diseases may increase OFTs.[215] Autoagglutination is present in many cats but not after RBC washings as is required when performing the DAT, and thus does not interfere with results.[215] Spherocytosis in cats is difficult or impossible to assess since their normal RBCs lack the central pallor present in healthy dog RBCs.[102]

Secondary IMHA must be differentiated from idiopathic IMHA. In one study, 36 of 102 DAT-positive cats had idiopathic IMHA.[216] The most common causes of secondary IMHA were infectious diseases: *Mycoplasma haemofelis*, coronavirus, and retroviral infections. Fewer cats had hematopoietic neoplasia and a few had systemic immune-mediated disorders.[216] Since the inclusion criterion was a positive DAT result only, it is possible that mechanisms other than hemolysis contributed to the development of anemia. Persistent absence of a regenerative RBC response may be explained by PRCA.[210,217]

Cats with idiopathic IMHA may be treated with blood transfusions as indicated and glucocorticoids. The same 2-month prednisolone protocol as described for dogs was used in a cohort of cats and resulted in estimated survival times of 75% (Figure 198-4).[216] Also, the mortality rate (about 24%) reported in cats with idiopathic IMHA is similar to that of dogs.[213] It was suggested that about 30% of cats may experience relapse after initial improvement.[213]

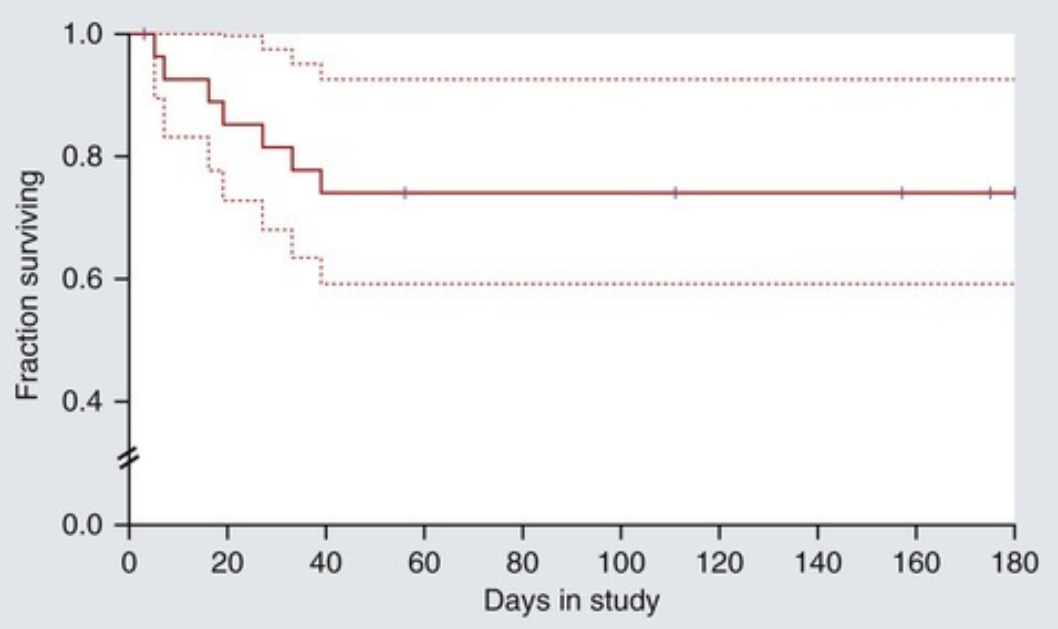

FIGURE 198-4 Estimated Kaplan-Meier survival (solid line) in cats with idiopathic IMHA treated with prednisolone, including 95% confidence intervals (dashed lines). Estimated from the data of a cohort of 30 cats diagnosed with idiopathic IMHA.[216] The endpoint was death due to IMHA; other outcomes were censored. All cats in this study were treated with the prednisolone protocol described in detail in

the paragraph on canine idiopathic IMHA of this chapter.

Feline Alloimmune Hemolysis

Feline alloimmune hemolysis is due to AB blood group incompatibility. Type B cats develop high-titer anti-A antibodies during the first three months of life with hemolyzing and hemagglutinating activity (see ch. 130). These antibodies are the culprit of severe RBC agglutination and destruction in mismatched transfusions and in feline neonatal isoerythrolysis (FNI). FNI occurs when a type A or AB kitten consumes colostrum from a type B cat.[218-221] Signs of hemolytic anemia appear within hours to days and severity is likely determined by the amount of colostrum consumed.[222] The best way to prevent FNI is to avoid incompatible mating. In other cases, kittens should be prevented from suckling incompatible colostrum. In order to prevent transfusion-related hemolysis, cats should always be blood-typed prior to blood transfusion and only AB-matched blood should be given.[221,223,224]

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CHAPTER 199

Nonregenerative Anemia

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Client Information Sheet: Nonregenerative Anemia

Introduction

Anemia is defined as hematocrit (Hct), hemoglobin concentration ([Hb]) or red blood cell count (RBC) below the laboratory's reference range. In veterinary medicine, Hct is most frequently used to make a diagnosis of anemia. Multiple factors influence the frequency of diagnosis of anemia, including defining anemia as one, two or all three of these parameters outside the reference range as well as the demographics of the patient populations studied and if primary care or referral center populations are evaluated. Despite these distinctions, anemia remains a common clinical problem in veterinary medicine, occurring in approximately 4% of all felines and in as many as 31% of canine patients over the age of eight years.[1,2]

Nonregenerative anemia is the most common form of anemia seen in the cat and dog.[1,3-6] Caution should be used when making a diagnosis of anemia in a cat since Hct, [Hb] and RBC count decrease approximately 25% in cats during general anesthesia.[7] In dogs, the [Hb], Hct, and RBC count results depend on the blood vessel sampled. Arterial blood samples give lower values than venous samples and a spurious diagnosis of nonregenerative anemia could be made if arterial samples are compared to venous sample reference intervals.[8]

Nonregenerative anemia can also be described as anemia with reticulocytopenia because the hallmark of nonregenerative anemia is a reticulocyte count less than 60,000/mcL in dogs and less than 50,000/mcL in cats, although these values vary based on method of reticulocyte enumeration.[9] Automated reticulocyte counts have a smaller coefficient of variation and are more reproducible than manual ones.[10,11] Once hypoxemia occurs, 3-7 days are required for production of reticulocytes; thus, blood loss anemia and hemolytic anemia may initially appear nonregenerative. Consequently, anemia in some patients may not be immediately classifiable as regenerative or nonregenerative. Surrogate measures of regeneration including mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red blood cell distribution width are not reliable indicators of regeneration in either dogs or cats.[1,11,12] Observation of polychromasia provides a better estimation of regeneration than do red blood cell indices in dogs.[11,13] Feline reticulocytes occur in at least two forms: punctate and aggregate (see ch. 198). Aggregate reticulocytes are believed to be most important for assessing response to anemia and represent those counted using automated hematology analyzers.

Some automated hematology analyzers have the capacity to measure reticulocyte indices, including those similar to MCV and MCH reported for mature red blood cells. Low reticulocyte hemoglobin content (CHr or CHretic) and reticulocyte mean corpuscular volume (rMCV or MCVretic) have been associated with hematologic and biochemical makers of iron deficiency.[14] Reticulocyte indices may prove useful in the diagnosis of iron deficiency prior to the development of microcytosis and hypochromia.[15] However, changes in reticulocyte indices are not specific for iron deficiency and can also be found in other causes of microcytosis such as portosystemic shunts and breed-associated microcytosis.[16]

A complete understanding of the pathophysiology of nonregenerative anemia, an extensive list of differential diagnoses and a comprehensive diagnostic plan are required to identify the cause and successfully manage patients with nonregenerative anemia (Table 199-1). Determining the cause of nonregenerative anemia is critical to optimal patient management and outcome, as anemia is an important prognostic variable. In dogs with the nonregenerative variant of immune-mediated hemolytic anemia

(IMHA), those infected with *Leishmania infantum,* or diagnosed with lymphoma, anemia predicts outcome.[17-19] Severely anemic cats are less likely to be discharged from the hospital and if anemia is due to chronic kidney disease, cats with anemia have a shorter survival than those without.[3,20]

TABLE 199-1

Differential Diagnoses of Nonregenerative Anemia

MEDULLARY CAUSES	EXTRAMEDULLARY CAUSES

Primary medullary
• Aplastic anemia
• Myelodysplastic syndromes
• Myeloproliferative syndromes
• Dysmyelopoiesis
• Myelophthisis
  • Acute and chronic leukemia
  • Multiple myeloma
• Bone marrow necrosis
Secondary medullary
Infectious:
• Feline leukemia virus (C)
• Feline immunodeficiency virus (C)
• Parvovirus
• Ehrlichiosis
• Sepsis
Drug reactions:
• Antimicrobial agents
• Chemotherapeutic drugs
• Estrogens (D)
• Phenobarbital (D)
• Recombinant human erythropoietin
• Copper deficiency secondary to chelation therapy
Toxins:
• Aflatoxin
Neoplasia:
• Sertoli cell tumor (D)
• Lymphoma
• Histiocytic disease
Congenital:
• Osteosclerosis from pyruvate kinase deficiency (D)
• Cobalamin malabsorption (D)
• Copper deficiency[28] (D)
Immune:
• Nonregenerative variant of IMHA
• Pure red cell aplasia
	Renal
	• Acute kidney injury
	• Chronic kidney disease
	Endocrine
	• Hypoadrenocorticism
	• Hypothyroidism
	Gastrointestinal/Malabsorptive
	• Serum cobalamin deficiency
	Hepatic disease
	Pancreatitis
	Neoplasia
	Iron deficiency
	• Chronic gastrointestinal bleeding (gastrointestinal mass, significant inflammatory bowel disease,[29] vascular ectasia, gastrointestinal parasites)
	• Chronic hematuria (renal hematuria, urogenital mass)
	• Other chronic external losses: dermal mass, high/chronic ectoparasite burden, oropharyngeal bleeding, epistaxis

C, Occurs in cats; *D*, occurs in dogs; *IMHA*, immune-mediated hemolytic anemia.

Clinical Signs and Physical Exam Findings

Clinical signs of anemia are vague in both dogs and cats and are attributable to decreased oxygen delivery to

tissues (Table 199-2). Physical examination reveals findings consistent with a low RBC, [Hb] and Hct: pallor, weakness, and depression. Physical examination will also identify physiologic mechanisms compensating for decreased oxygen delivery such as tachycardia and tachypnea. Thorough physical examination can frequently identify clinical signs of the underlying disease process responsible for anemia.

TABLE 199-2

History and Physical Examination Findings in Dogs and Cats with Anemia[3,21-26]

HISTORY	PHYSICAL EXAMINATION
Lethargy	Pallor
Anorexia	Weakness
Pica (more common in cats)	Depression
Decreased activity	Jaundice
Weight loss	Pyrexia or hypothermia
Drug administration Phenobarbital Estrogen Chloramphenicol	Lymphadenopathy Splenomegaly Hepatomegaly
	Cardiovascular Tachycardia Syncope Heart murmur Gallop
	Respiratory Tachypnea Thromboembolism
	Clinical signs of underlying disease Uremia Coagulopathy Hemoptysis, hematemesis, melena, purpura Endocrinopathy Malabsorption Neoplasia Infection/Sepsis

Characterization of Anemia

To precisely characterize anemia, multiple descriptors of cell size, hemoglobin content and regeneration are required. This characterization of anemia does not provide any indication as to the underlying pathophysiology. Consequently, this chapter categorizes nonregenerative anemia into those caused by bone marrow failure or medullary causes, and secondary or extra-medullary causes. Most cases of blood loss and hemolysis causing anemia (see ch. 198) will become regenerative after a window of time where the bone marrow increases reticulocyte production in response to the anemia (typically 3-7 days). However, certain factors may limit the body's natural response mechanism to produce increased numbers of red blood cells, resulting in nonregenerative hemolytic or blood loss anemia. Causes of these types of nonregenerative anemia include: absolute iron deficiency (as in the case of low-grade chronic bleeding or other blood loss), iron sequestration from chronic inflammation, and decreased erythrocyte half-life or other comorbid conditions that impair the marrow response to a hypoxic trigger. Up to one third of dogs and over 50% of cats with immune-mediated hemolytic anemia may be nonregenerative at the time of diagnosis.[24,27] Additionally, anemia secondary to immune targeting of red blood cell precursors may remain nonregenerative until the patient is adequately immunosuppressed.

Pathogenesis

Many systemic illnesses result in nonregenerative anemia (see Table 199-1) and its pathogenesis is complex and multifactorial (Figure 199-1). Pathologic mechanisms can be typically separated into two main categories: decreased erythrocyte lifespan and decreased or ineffective erythropoiesis.

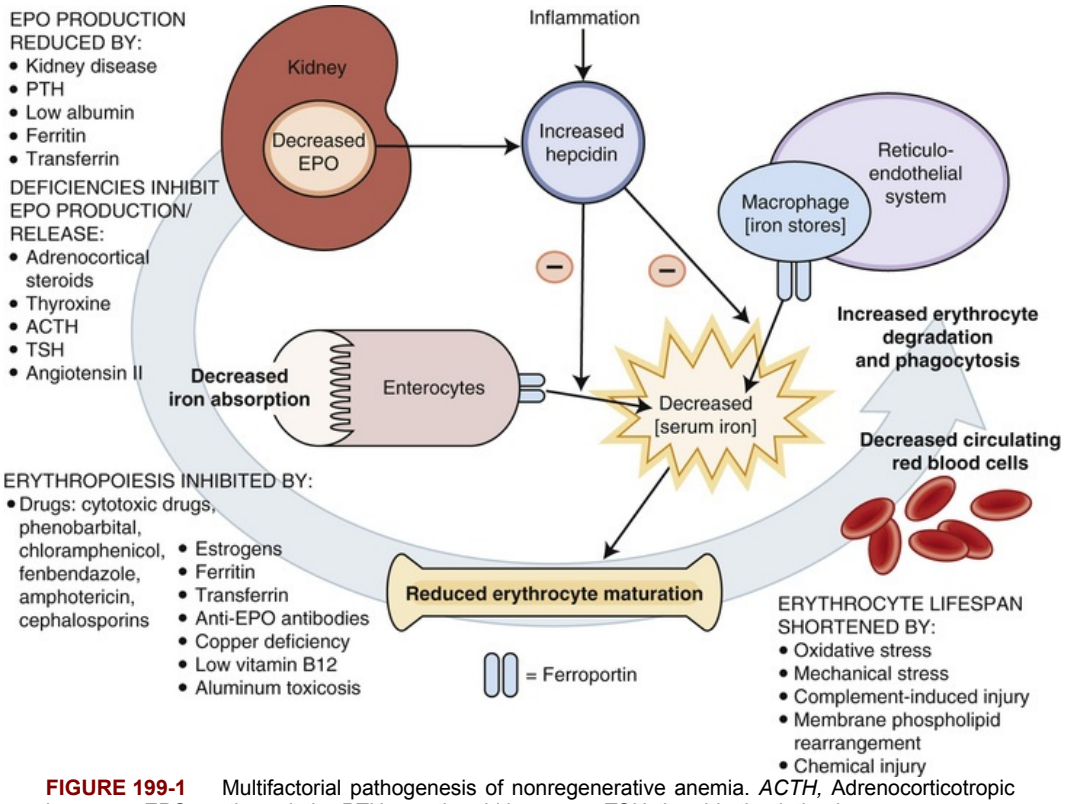

FIGURE 199-1 Multifactorial pathogenesis of nonregenerative anemia. *ACTH*, Adrenocorticotropic hormone; *EPO*, erythropoietin; *PTH*, parathyroid hormone; *TSH*, thyroid-stimulating hormone.

Decreased Erythrocyte Lifespan

The lifespan of a normal red blood cell is 100 days in a healthy dog and 72 days in a healthy cat.[30] During this time, the red blood cell is responsible for oxygen delivery to tissues, and requires maintenance of cellular features of deformability in order to optimize its performance. As the red blood cell ages, numerous biochemical, immunologic and mechanical changes impair its ability to recover from various insults. The accumulation of such injuries triggers the removal of a senescent red blood cell from circulation by the reticuloendothelial system (RES), primarily by mononuclear phagocytic cells within the spleen, liver and lymph nodes. Red blood cell oxidative stress is caused by both endogenous hemoglobin autoxidation and exogenous oxidants that can result in cellular aging and functional impairment, shortening erythrocyte lifespan by triggering removal by the RES.[31] Oxidative stress, mechanical stress, complement-induced injury, rearrangement of membrane phospholipids, contact with cationic proteins released from activated neutrophils, Heinz body formation and hemotropic parasites all alter cytoplasmic viscosity, resulting in impaired deformability and targeting of the red blood cells for early removal from circulation.[32] Similarly, hereditary erythrocyte defects such as membrane protein abnormalities, erythrocyte enzyme deficiencies, hemoglobinopathies and increased osmotic fragility lead to shortened erythrocyte lifespan. Excessive activation of the RES, as seen with certain immune-mediated, infectious, inflammatory and paraneoplastic conditions can also stimulate early removal of red blood cells from circulation. In general, disorders resulting in decreased RBC lifespan cause regenerative anemia in dogs and cats; however, they can also be contributing factors in cases of nonregenerative anemia.

Decreased and Ineffective Erythropoiesis

Erythropoiesis can be decreased due to an absolute or a relative lack of erythropoietin or can be ineffective

secondary to decreased marrow response to erythropoietin. Erythropoietin is produced primarily by the kidney in the peritubular interstitial cells of the inner renal cortex and outer medulla. Renal hypoxia is the main driving factor stimulating erythropoietin synthesis. Renal hypoxia leads to an inhibition of hypoxia-inducible factor 1 (HIF-1) degradation, allowing HIF-1 to bind to hypoxia-response elements of oxygen-regulated genes, leading to an increased production of erythropoietin.[33,34] Erythropoietin production is decreased in both acute and chronic causes of kidney disease, and chronic kidney disease is known to be a common cause of nonregenerative anemia (see ch. 324).[33] The most important extra-renal production site of erythropoietin is the liver, with additional limited production in sites including the brain, vascular endothelial cells, lung, uterus, testis and various solid tumors.[33,35,36] Erythropoietin synthesis from extra-renal tissues cannot be adequately induced to compensate when there is decreased renal production.[35] Hypoxemia does not increase hepatic production of erythropoietin; however, other causes of liver injury can lead to increased erythropoietin production from the liver.[33]

Ineffective erythropoiesis can be secondary to absolute deficiencies in nutrients crucial to hemoglobin biosynthesis and red blood cell maturation or due to a number of different cytokine abnormalities seen in various states of inflammation, commonly designated anemia of chronic disease. In humans, systemic inflammatory states are induced by a number of diseases including infections, autoimmune conditions, malignancies, kidney disease, pancreatitis, diabetes mellitus, cardiac disease, trauma, critical illness, post-surgery, and aging.[37-40] Inflammatory cytokines, such as IL-1, IL-6, TNF-alpha, and interferon-gamma reduce the production of endogenous erythropoietin in the face of hypoxemia, and suppress the erythroid progenitor response to erythropoietin.[38,41] IL-6, in particular, increases the production of hepcidin, an acute phase protein produced by the liver that is responsible for iron homeostasis, resulting in a systemic state of relative iron deficiency. Increased hepcidin levels can also occur secondary to decreased renal clearance and mutations in hepcidin suppressors.[42] Elevated hepcidin levels result in increased cellular internalization and degradation of ferroportin, an integral enterocyte membrane protein responsible for the movement of iron out of the enterocyte and into circulation. The net effect of hepcidin elevation on ferroportin is iron-trapping within the enterocytes, sequestering iron from systemic utilization. Additionally, hepcidin prevents the release of iron stores from macrophages and hepatocytes and blocks luminal intestinal iron absorption. This leads to low blood iron levels and relative systemic iron deficiency.[43] Iron deficiency, whether absolute or secondary to elevations in hepcidin, impairs hemoglobin biosynthesis and causes a blunted erythropoietin response due to reduced erythropoietin sensitivity of progenitor cells in the bone marrow.[43] Copper deficiency is associated with a functional iron deficiency due to decreased hemoglobin synthesis and literature supports that iatrogenic, congenital and nutritional copper deficiencies are an uncommon cause of ineffective erythropoiesis and nonregenerative anemia in the dog.[28,44-46] Deficiencies of vitamin B12 inhibit purine and thymidylate syntheses, impairing DNA synthesis within erythroblasts and causing erythroblast apoptosis.[47] Hypocobalaminemia secondary to hereditary selective cobalamin malabsorption is a cause of nonregenerative, often erythroblastic anemia in the dog.[48-51] While folate deficiency is similarly associated with ineffective erythropoiesis in humans, no documentation of anemia is noted in the veterinary body of literature regarding folate deficiency and anemia. Hypoalbuminemia and elevations in parathyroid hormone, ferritin and transferrin saturation significantly impair the erythropoietic response and can result in ineffective erythropoiesis.[52] Aluminum toxicosis, secondary to chronic high dosages of aluminum hydroxide or other toxic exposure, can result in ineffective erythropoiesis due to interference with erythroid precursor iron utilization and shortened erythrocyte lifespan resulting from morphologic changes to red blood cells.[53] Reports of anemia secondary to aluminum accumulation are limited in veterinary medicine, but are well-documented in human and rodent populations.[53-56] The use of angiotensin-converting enzyme inhibitors can lead to anemia. Although the mechanisms by which this anemia is mediated are not fully elucidated, reduced erythropoietin release as well as ineffective erythropoiesis due to direct drug effects on erythrocyte precursors are suspected.[57,58]

Differentiating iron-deficiency anemia from anemia of inflammation can be difficult and in some cases, both conditions may be driving factors; however, differentiation is essential to selecting the appropriate treatment. Evaluating a variety of iron indices can help distinguish if a component of iron restriction is contributing to the anemia, which helps to guide therapeutic recommendations. Serum iron levels are low in both conditions, and can also be low in dogs with portosystemic shunts.[59] Ferritin, the soluble storage form of iron in tissues, is a positive acute phase protein and in health is a representative measure of total body iron stores. Ferritin levels are classically decreased in iron-deficiency anemia and increased in anemia of

inflammation. However, ferritin can also be increased in acute hepatopathies or hepatic necrosis due to its upregulated production as an acute phase protein or increased release from damaged hepatocytes.[16,44] Transferrin is the main protein in blood that binds and transports iron. In veterinary medicine, transferrin is measured indirectly and reported as total iron binding capacity (TIBC). Transferrin is a negative acute phase protein. Although TIBC levels are typically normal to increased in cases of iron deficiency, concurrent inflammation can hinder interpretation. Elevations in transferrin can also be seen with chronic liver disease or an iron overload state.[60] Iron saturation percentages (serum iron/TIBC) less than 20% can be suggestive of iron deficiency.[60] Because conventional evaluations of MCV and MCHC for microcytosis and hypochromasia are insensitive markers of iron deficiency; reticulocyte indices are better indicators of iron status.[15] Reticulocyte indices have been evaluated in different causes of anemia. While changes in these indices are not specific to dogs with iron deficiency, dogs with decreased reticulocyte hemoglobin concentration (≤26 g/dL) and CHretic (≤20.1 pg), and increased percentage of reticulocytes with low reticulocyte hemoglobin concentration (74%) and low CHretic (>50%) should make the clinician suspicious of a diagnosis of iron-deficient anemia.[16]

Identifying the Underlying Cause of Nonregenerative Anemias

The differential diagnosis list (see Table 199-1 and Box 199-1) for causes of nonregenerative anemia is extensive. Differential diagnoses should be prioritized based on patient signalment, history and presentation. Uncommon causes of nonregenerative anemia should be considered in certain cases. Using an algorithm to guide diagnostic recommendations will help to minimize unnecessary testing while simultaneously maximizing the chances of obtaining a diagnosis (Figure 199-2).

Box 199-1

Uncommon Causes of Nonregenerative Anemia

Medullary Causes

- Primary myelodysplastic syndromes
- Primary myeloproliferative syndromes
  - Chronic granulocytic leukemia
  - Primary myelofibrosis[77]
- Primary dysmyelopoiesis
  - Congenital dyserythropoiesis
    - Springer Spaniel[61]
  - Inherited selective intestinal cobalamin malabsorption (Imerslund-Grasbeck syndrome)[51]
    - Giant Schnauzer
    - Border Collie
    - Beagle
    - Australian Shepherd
- Primary bone marrow necrosis[62]

Extramedullary Causes

- Secondary dysmyelopoiesis
  - Immune hematologic disorders
  - Estrogen-induced aplastic anemia/pancytopenia
    - Exogenous
    - Endogenous Sertoli cell tumor
  - Anticonvulsants
  - Feline retroviral infection[88]
  - Copper deficiency[28,45]
- Secondary myelofibrosis
  - Pyruvate kinase deficiency[63]
  - Feline leukemia virus infection
  - Recombinant human erythropoietin administration

Secondary bone marrow necrosis[62]
  Sepsis
  Neoplasia
  Infection
  Drugs
Myelophthisis

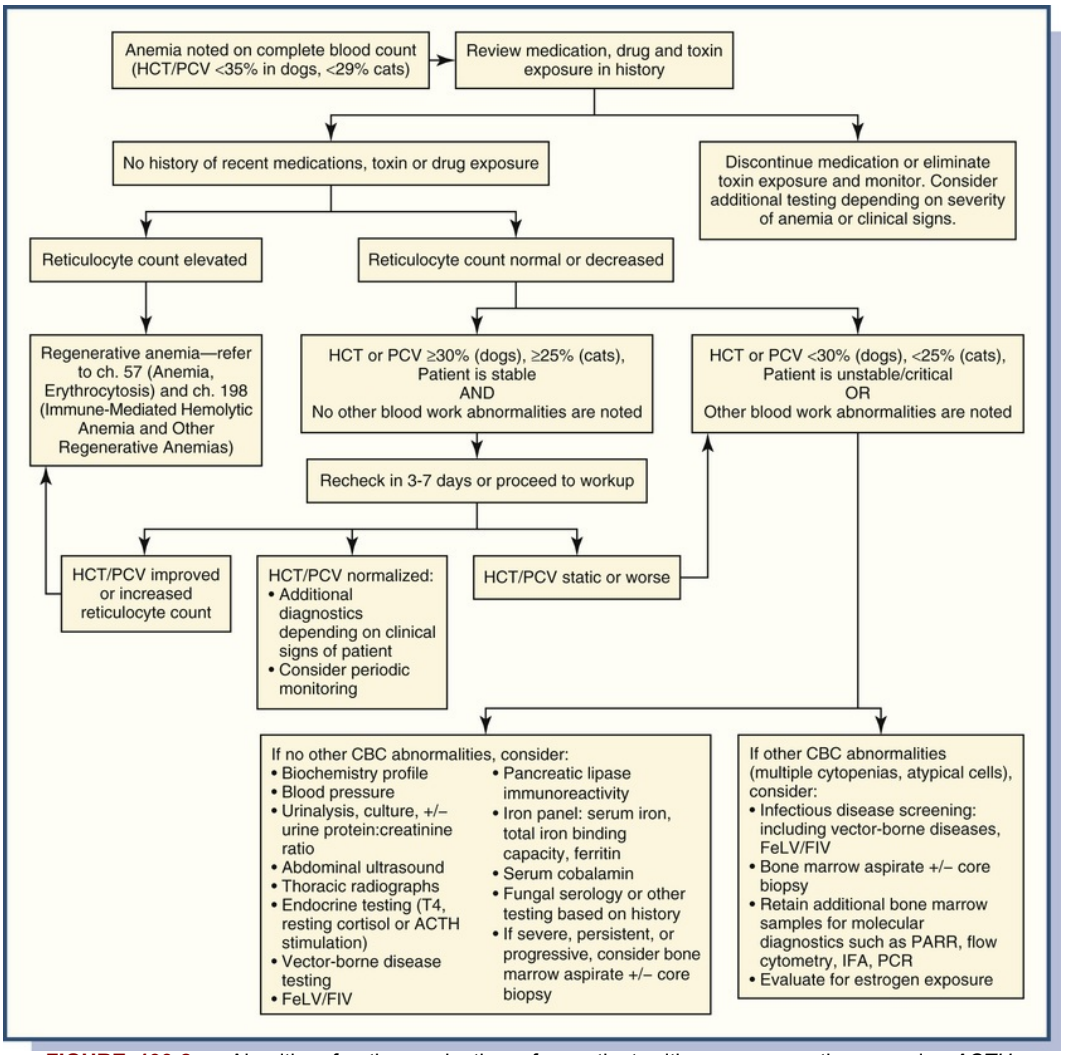

FIGURE 199-2 Algorithm for the evaluation of a patient with nonregenerative anemia. *ACTH,* Adrenocorticotropic hormone; *CBC,* complete blood count; *FeLV,* feline leukemia virus infection; *FIV,* feline immunodeficiency virus infection; *IFA,* indirect fluorescent antibody; *PARR,* PCR for antigen receptor rearrangements; *PCR,* polymerase chain reaction; *T4,* thyroxine.

Bone Marrow Failure as a Cause of Nonregenerative Anemia

Multiple bone marrow disorders produce a nonregenerative anemia (see Table 199-1 and Box 199-1). These include primary medullary disorders: pure red cell aplasia, which may be a more severe form of nonregenerative IMHA, aplastic anemia/pancytopenia, primary myelodysplastic syndromes, primary myeloproliferative disorders, primary dysmyelopoiesis and primary myelofibrosis. Secondary or extramedullary causes of bone marrow failure induce nonregenerative anemia as well, but because these disorders have an extramedullary etiology, treatment targets the primary disorder. Myelophthisis, both primary and secondary, may result in nonregenerative anemia. For more information on tumors causing myelophthisis, see ch. 344, 349, and 350. Pyruvate kinase deficiency and estrogen toxicosis lead to secondary

myelofibrosis and phenobarbital administration causes secondary dysmyelopoiesis. Secondary myelodysplastic syndromes occur in humans as a result of cytotoxic drug therapy or radiation exposure. Their occurrence has not been documented in veterinary patients. For further classification of primary and secondary medullary disorders, see ch. 202.

Diagnosis

The diagnosis of bone marrow failure requires bone marrow aspiration to assess cell morphology and a bone marrow core biopsy to assess cellularity (see ch. 92). When no other cause of a nonregenerative anemia can be identified, bone marrow testing is often the final diagnostic step (see Figure 199-2). Most primary medullary disorders carry a poor prognosis, in part because identification of the underlying molecular defect is lacking in veterinary patients and because, as the least common cause of nonregenerative anemia, their rarity hampers identification of optimal treatment.

Therapeutic Options

Treatments for nonregenerative anemia include symptomatic therapy when needed and identification and treatment of the underlying cause. If patients have clinical signs of anemia, symptomatic therapy by transfusion with packed red blood cells or whole blood may be indicated (see ch. 130). When the anemia is severe, therapeutic options may include supplementation of red blood cell building blocks such as iron and cobalamin as well as targeted use of erythropoiesis-stimulating agents until the bone marrow recovers. For specific treatments of extra-medullary causes of nonregenerative anemia, please review ch. 222 and 223. For regenerative anemia, the reader is referred to ch. 198. For further information on immunosuppressive medications, the reader is referred to ch. 195, 165, and 360.

Symptomatic Therapy

- Transfusion: Although nonregenerative anemia is more common than regenerative anemia, review of the indications for red blood cell transfusion in the dog show transfusion for bone marrow failure is much less common than for blood loss or hemolytic anemia.[64,65] Because of the high frequency of chronic kidney disease in cats, transfusion for nonregenerative anemia is more common than in the dog.[66-68] The low rate of red blood cell transfusion for nonregenerative anemia reflects the moderate degree of anemia present in this condition, its slow onset, adequate compensatory mechanisms and poor prognosis. Certain patients with nonregenerative anemia may receive multiple red blood cell transfusions, increasing the importance of blood typing (see ch. 130) and crossmatching prior to transfusion.[69]

Specific Therapies

- Iron supplementation: Iron supplementation can be administered parenterally or enterally, with parenteral administration being preferable given more reliable absorption, especially if the deficiency is secondary to malabsorption. In dogs receiving iron supplementation, CHretic and MCVretic may be more sensitive to identifying a response in iron body stores.[15] In cases of iron deficiency, parenteral supplementation results in a faster resolution as compared to enteral supplementation when reticulocyte indices are evaluated.[15] Oral supplementation, however, is the least expensive form of supplementation and is also considered the safest. Ferrous sulfate is the most common of the oral supplements, with varied dosing reported in the veterinary literature. The recommended dosage is 100-300 mg/dog per day administered orally (20-60 mg of elemental iron) or 50-100 mg/cat per day administered orally (10-20 mg of elemental iron).[34,70] Side effects with the recommended dosages include gastrointestinal upset, typically mild in nature. Concurrent administration with food may reduce absorption, as does administration with medications that increase gastric pH.[70] Administration of iron may reduce absorption of antibiotics such as fluoroquinolones and tetracyclines and dose spacing should be exercised.[70] Other oral supplements such as ferrous gluconate and ferrous fumarate are available and used for human supplementation. There is less information published regarding dosing of these in veterinary medicine; however, anecdotal information targets the same amount of elemental iron as that with ferrous sulfate administration. A suggested dosage for ferrous gluconate is 16.25 mg/kg/day in cats.[71] Parenteral supplementation includes iron dextran, iron gluconate and iron sucrose. Iron dextran is the most common parenteral supplementation in veterinary medicine. The recommended dosage is 10 mg/kg in

dogs and cats.[70,71] In cats, administration every 3-4 weeks is recommended.[70,71] Administration is recommended to be given intramuscularly, with an increased risk of anaphylactic reaction when given intravenously. It is absorbed slowly via the lymphatic system after injection, with approximately 60% of the drug absorbed within 3 days and up to 90% absorbed after 1-3 weeks.[70] Newer agents without the dextran moiety, such as iron gluconate and iron sucrose, are associated with a lower rate of anaphylactic reactions in humans and can be administered intravenously as well as intramuscularly. One of the newest of the iron-carbohydrate compounds is ferric carboxymaltose, designed to mimic physiologic ferritin.[72] However, data on the use of these newer parenteral iron supplements and intravenous administration are lacking in veterinary populations.[73]

- Erythropoiesis-stimulating agents (ESAs): The use of recombinant human ESAs may be considered in the treatment of nonregenerative anemia. Dogs with a nonregenerative anemia lacking features of primary myelodysplasia respond to the use of ESAs and tend to have a prolonged survival in comparison to dogs with primary myelodysplasia, who typically do not respond to standard therapies.[74] However, ESAs have also been used with positive response in a case of myelodysplastic syndrome with erythroid predominance in a dog.[75] In humans, ESAs are in wide clinical use and are the most commonly used therapy for anemias secondary to myelodysplastic syndromes, despite not being approved by the Food and Drug Administration for this specific use.[76] In dogs with secondary myelofibrosis, the use of ESAs in conjunction with other therapies is associated with a prolonged survival.[77] In humans, these agents are also used to address relative erythropoietin deficiency, as is seen with multiple myeloma and non-Hodgkin's lymphoma.[78]

Several recombinant human erythropoietin products are available on the market including epoetin alfa, epoetin beta and darbepoetin alfa. Significant homology (>80%) between human erythropoietin and canine and feline erythropoietin allows recombinant human products to bind to and interact with erythropoietin receptors in dogs and cats.[79,80] Darbepoetin is hyperglycosylated compared to epoetin, resulting in a circulating half-life that is three times longer than that of epoetin and a reduction in mean clearance time by over 70% (mL/kg × h).[81] The choice of which agent to use should be based on numerous factors. Darbepoetin is only administered once weekly and anecdotally is associated with a reduced risk of pure red cell aplasia secondary to the formation of anti-erythropoietin antibodies as compared to epoetin.[34] In cats, the recommended dosage is 1 mcg/kg SC once weekly initially.[34,82] Once the target PCV is attained, frequency of administration is decreased to every 2-3 weeks with the dosage further adjusted to maintain the PCV within the target range (25-35%).[34] For dogs, the recommended initial dosage in the literature is 0.45 mcg/kg SC once weekly with adjustments accordingly to maintain PCV in target range (37-45%).[70] Epoetin requires administration three times a week, but it may be marginally less expensive than darbepoetin in comparison.[34] The recommended starting dosage in dogs and cats is 100 units/kg subcutaneously three times weekly.[70] Once target PCV is attained, dosing frequency can be reduced to twice weekly as maintenance therapy.[70] Aside from pure red cell aplasia, other side-effects of these agents include hypertension, seizures and iron deficiency.[70] Concurrent monthly parenteral iron supplementation is recommended when ESAs are administered. For epoetin specifically, additional adverse events of local reactions at injection sites (which may be predictive of antibody formation), fever, arthralgia, and mucocutaneous ulcers are also possible.[70]

Treatment of Medullary Causes of Nonregenerative Anemia

Evidence-based treatments for nonregenerative anemia stemming from primary medullary disease are lacking in veterinary medicine. Single case reports and case series predominate in the literature and because multiple classification schemes exist for bone marrow diseases, comparison of treatment outcomes is difficult.

- Glucocorticoids: If, despite the poor prognosis for recovery in pets with bone marrow failure, treatment is pursued, nearly all patients receive initial treatment with immunosuppressive doses of glucocorticoids (see ch. 165). Many dogs with pure red cell aplasia or the nonregenerative variant of immune mediated hemolytic anemia, respond to glucocorticoids with resolution of anemia.[23,83] In other bone marrow disorders, response is more variable.
- Cyclophosphamide: Although most dogs with pure red cell aplasia and the nonregenerative variant of immune mediated hemolytic anemia respond to glucocorticoid immunosuppression, some dogs appear to require additional immunosuppression with cyclophosphamide 50 mg/m^2 PO q 24 h × 4 days, repeated weekly.[23,83] Cyclophosphamide is not currently recommended for the treatment of regenerative immune

mediated hemolytic anemia (see ch. 198).

- Azathioprine: As an alternative to cyclophosphamide, azathioprine (2 mg/kg PO q 24 h × 5 days and then q 48 h) has been recommended for the treatment of pure red cell aplasia and the nonregenerative variant of immune mediated hemolytic anemia.[23]
- Hydroxyurea: Chronic granulocytic leukemia represents an extremely rare primary myeloproliferative disorder in the dog. If treatment is indicated, hydroxyurea 50 mg/kg PO once daily can induce remission.[84,85] If remission is achieved, dosing frequency can be decreased to every 48 to 72 hours. In humans, a chromosomal translocation drives increased production of granulocytes in chronic granulocytic leukemia which can be inhibited by treatment with tyrosine kinase inhibitors. The presence of a similar mutation in dogs with chronic granulocytic leukemia has not been documented.
- Other cytotoxic or immunosuppressive agents: Cytarabine, cyclosporine and combination chemotherapy have been used with variable success to treat myelodysplastic syndromes in feline leukemia virus-positive cats.[89] In humans, cyclosporine coupled with other immunosuppressive agents can induce remission in patients with pure red cell aplasia and certain myelodysplastic syndromes. Evidence for the use of cyclosporine in veterinary patients with pure red cell aplasia and myelodysplastic syndromes is lacking.[86,87]
- Vitamin K2: A preliminary report indicated a vitamin K2 analog (menatetrenone) was beneficial in feline myelodysplastic syndromes when given at a dosage of 2 mg/kg.[89] Menatetrenone promotes cellular differentiation *in vitro*.

New Directions in Therapy

Management of nonregenerative anemia of inflammation using iron and ESAs is ineffective for some patients and there are risks, driving the search for novel therapies targeting the hepcidin-ferroportin axis, including inhibiting hepcidin function with direct hepcidin antagonists, preventing hepcidin transcription with hepcidin production inhibitors (including IL-6 pathway inhibitors and vitamin D), and promoting ferroportin resistance to hepcidin action with ferroportin agonists/stabilizers.[90] As the use of these agents is further explored for humans and their efficacy and safety profiles are established, these novel agents will be considered in veterinary patients to expand our armament of options for long-term management of these challenging cases.

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CHAPTER 200

Primary Polycythemia and Erythrocytosis

Ann E. Hohenhaus

Client Information Sheet: Excessive Numbers of Red Blood Cells

Definitions

The term erythrocytosis indicates an increase in red blood cell count, hemoglobin concentration and hematocrit compared to the reference range and is due to either increased red blood cell mass or decreased plasma volume. Increasing reports of breed-specific reference ranges with red blood cell count, hemoglobin concentration and hematocrit greater than the traditional laboratory reference ranges, suggest a diagnosis of erythrocytosis should not be made in a purebred dog until the breed-specific reference range has been reviewed.[1-3] Polycythemia is often considered synonymous with erythrocytosis, but in this chapter, polycythemia will be used with relative, primary, or secondary to indicate the mechanism for the erythrocytosis (Figure 200-1). Relative polycythemia occurs when plasma water is lost without concurrent loss of red blood cells. Primary polycythemia, or in the lexicon of human medicine, polycythemia vera, is a myeloproliferative disorder where production of red blood cells is constitutive and independent of the production of erythropoietin. In primary polycythemia, the negative feedback loop remains intact and the increased number of red blood cells delivers adequate oxygen to the kidney, inhibiting renal erythropoietin production. In humans with primary polycythemia, white blood cell and platelet counts are commonly elevated and 90% of patients have a mutation in the JAK2 gene. The presence of this mutation has become an important diagnostic criterion for polycythemia vera.[4] A JAK2 mutation has been sequenced in a dog with primary polycythemia.[5] Occasionally, cats with primary polycythemia also have thrombocytosis.[6] Secondary polycythemia is either physiologically appropriate, resulting from an increase in erythropoietin production in response to hypoxemia, or physiologically inappropriate, resulting from an increase in erythropoietin production in the absence of hypoxemia. Physiologically inappropriate secondary polycythemia is most commonly due to paraneoplastic production of erythropoietin. Both erythropoietin mRNA and its protein product have been identified in tumors associated with polycythemia.[7,8] A specific subset of physiologically inappropriate secondary polycythemia is hormone-mediated via thyroxine, growth hormone and cortisol, because of the stimulatory effects these hormones have on the production of red blood cells.[9,10]

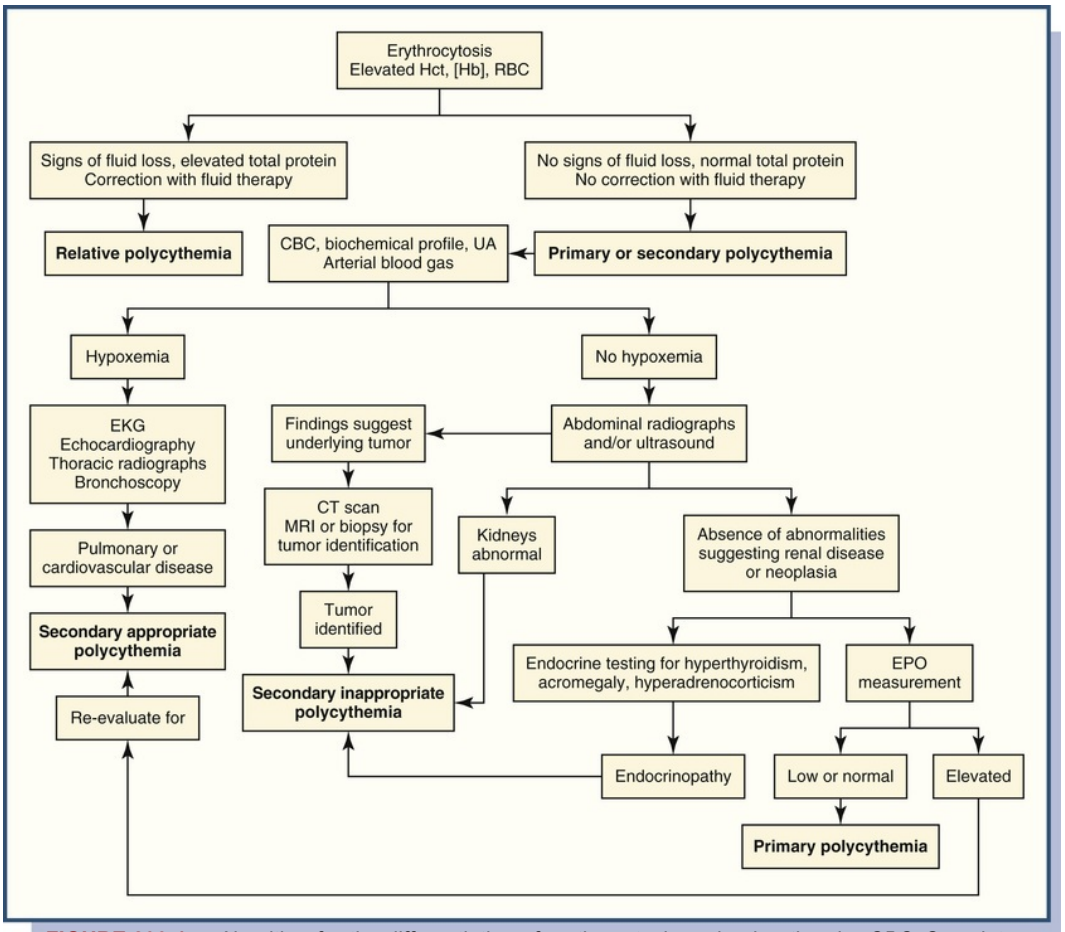

FIGURE 200-1 Algorithm for the differentiation of erythrocytosis and polycythemia. *CBC,* Complete blood count; *CT,* computed tomography; *EKG,* electrocardiogram; *EPO,* erythropoietin; *Hb,* hemoglobin; *Hct,* hematocrit; *RBC,* red blood cell count; *UA,* urinalysis.

Normal Erythropoiesis

Red blood cells, specifically hemoglobin, transport oxygen to tissues. The kidneys serve as the sensor organ for hypoxemia. Renal hypoxia stimulates production of hypoxia inducible factor which in turn stimulates the cortical interstitial fibroblasts to produce erythropoietin.[11] Thyroid hormone directly increases proliferation of erythroid progenitor cells and also enhances hypoxia inducible erythropoietin production.[12] Glucocorticoids synergize with hypoxia inducing factor to stimulate burst forming units—erythroid, cells capable of self renewal.[13] These mechanisms may account for the erythrocytosis seen in patients with hyperthyroidism and hyperadrenocorticism. Growth hormone directly stimulates hematopoiesis or binds to receptors such as those for insulin-like growth factor and prolactin stimulating red blood cell production.[14]

Erythropoiesis in Polycythemia

Control of red blood cell production in polycythemia depends on the type of polycythemia. In relative polycythemia, red blood cell production is not altered. The apparent increase in red blood cells stems from intravascular fluid loss. In secondary polycythemia, the increased red blood cell count results from an increase in erythropoietin in response to hypoxemia in physiologically appropriate polycythemia or an increase in erythropoietin, independent of hypoxemia, often a paraneoplastic process, in physiologically inappropriate polycythemia. Two mechanisms for increased erythropoietin production and subsequent polycythemia secondary to renal disease have been proposed: renal hypoxia as a consequence of the primary disease process and increased or aberrant erythropoietin production by neoplastic cells. The origin of excessive red blood cell production in primary polycythemia is unknown, but a genetic mutation underlies the disease in humans and recent investigations suggest a similar mechanism in dogs.[4,5]

Clinical Signs and Physical Examination Findings in Polycythemia

The clinical signs associated with polycythemia vary, depending on the underlying cause. Hallmarks of relative polycythemia include dehydration and clinical evidence of fluid loss, most commonly from vomiting and/or diarrhea. Excitement, exercise or stress can also result in relative polycythemia. Hyperviscosity and hypervolemia cause clinical signs in both primary and secondary polycythemia, but do not occur in relative polycythemia (Box 200-1). Additionally, dogs and cats with secondary polycythemia may show signs referable to the underlying cardiovascular, renal, respiratory or neoplastic disease (Box 200-2).

Box 200-1

Causes of Clinical Signs and Physical Examination Findings in Primary and Secondary Polycythemia

Hypervolemia

- Ocular manifestations
  - Engorged, tortuous retinal vessels
  - Uveitis[33]
  - Retinal detachment/hemorrhage
  - Glaucoma
- Engorged mucous membranes

Hyperviscosity

Central Nervous System Signs

- Fainting
- Weakness/posterior paresis/ataxia
- Seizures
- Lethargy/depression
- Other central nervous system signs

Unclassified or Multiple Mechanisms

- Hemorrhage
  - Epistaxis
  - Hematochezia
  - Hemorrhagic diarrhea
  - Hematemesis
- Polyuria/polydipsia[34]
- Vomiting
- Diarrhea

Box 200-2

Causes of Secondary Polycythemia

Physiologically Appropriate (Hypoxemia Present)

- Cardiac
  - Right-to-left shunting
    - Patent ductus arteriosus[27,29]
    - Tetralogy of Fallot[35]
    - Persistent truncus arteriosus[36]
- Hematologic
  - Hemoglobinopathy (not reported in animals)
- Respiratory
  - Pulmonary parenchymal disease
  - Pulmonary vascular amyloidosis[37]

High altitude
Obesity
Renal
Lymphoma[38]

Physiologically Inappropriate (Hypoxemia Absent)

Renal
Pyelonephritis[24,39]
Local renal hypoxia
Neoplasia
Nasal fibrosarcoma[40]
Schwannoma[8]
Cecal leiomyosarcoma[7]
Renal cell carcinoma[21,23,26,39,41]
Renal fibrosarcoma[42]
Renal lymphoma[43]

Diagnostic Testing

In dogs and cats identified with erythrocytosis based on results of a complete blood count or a packed cell volume, a point of care hemoglobinometer can be used to accurately confirm elevated hemoglobin.[15] In patients suspected to have relative polycythemia because of obvious fluid loss and elevation of serum total protein concentration, treatment with intravenous fluids and resolution of erythrocytosis confirms the diagnosis.

When erythrocytosis does not resolve with fluid therapy, history, physical examination and diagnostic testing should focus on distinguishing primary from secondary polycythemia. Pet owners should be queried regarding residency in or prolonged travel to a low-oxygen environment as a cause of secondary appropriate polycythemia. Physical examination may reveal organ system abnormalities such as a heart murmur, increased respiratory rate, a tumor or signs consistent with an endocrinopathy. In these patients, diagnostic testing should further evaluate those abnormalities.

Erythrocytosis in the presence of normal arterial oxygen saturation (see ch. 75 and 128) and in the absence of conditions known to be associated with secondary polycythemia is the current diagnostic standard for primary polycythemia in dogs and cats. Since the diagnosis of primary polycythemia is one of exclusion, testing should follow an organized scheme focusing on the respiratory, cardiovascular and renal systems as well as searching for neoplastic causes of polycythemia (see Figure 200-1). Arterial blood gas sampling with arterial oxygen saturation below 92% indicates hypoxemia is present and suggests a secondary physiologically appropriate polycythemia. If metabolic acidosis without hypoxemia is present, the acidosis is most likely the result of increased blood viscosity and sluggish blood flow and could be due to either primary or secondary inappropriate polycythemia.[16] An increase in red blood cell mass can be confirmed using ^{51}Cr labeled autologous erythrocytes, but this is impractical in routine clinical medicine. Thrombocytosis has been reported in association with primary polycythemia in a cat.[6] Primary polycythemia has also been associated with cardiac hypertrophy and a transient glomerulopathy.[17,18]

Erythropoietin Measurement

Measurement of erythropoietin levels cannot substitute for a thorough diagnostic evaluation; however, it will be most helpful in confirming a diagnosis of secondary polycythemia. Arterial oxygen saturation below 92% stimulates the production of erythropoietin in secondary physiologically appropriate polycythemia and paraneoplastic elevation of erythropoietin can be detected in secondary physiologically inappropriate polycythemia. The use of an erythropoietin assay validated for the species being tested is imperative, and the lack of a readily available one limits the clinical utility of erythropoietin measurement. Overlap between the erythropoietin reference range in clinically normal dogs and cats with that found in cases of primary polycythemia means erythropoietin values must be cautiously interpreted.[19,20] Elevated levels of erythropoietin suggest a diagnosis of secondary polycythemia should be strongly considered.

Treatment

The initial goal of treating primary and secondary polycythemia is control of clinical signs through reduction of the hematocrit with phlebotomy. In cases of secondary polycythemia, successful treatment of the underlying cause can resolve the polycythemia without additional therapy.[7,8,21-24] When the primary disease process cannot be corrected, such as in congenital cardiac disease with right to left shunting, management of secondary polycythemia is similar to that of the primary form. Some authors suggest a goal of decreasing the hematocrit to the upper end of the reference range except in patients with cyanotic heart disease, making the target PCV 58-65% (see ch. 250).[25]

Phlebotomy

Rapid reduction of the hematocrit by phlebotomy (15-20 mL/kg) and volume replacement using crystalloids or colloids should be the first line of therapy, although not all patients seem to require fluid replacement.[26-28] Pet and pet owner tolerance of chronic phlebotomy will determine if this treatment can be used as a method of long-term treatment for polycythemia.[28,29] Leeching, a natural form of phlebotomy, has been successfully used to treat primary polycythemia in a cat.[30]

Myelosuppressive Therapy

If phlebotomy is required more than once every four weeks or is difficult due to hyperviscosity, myelosuppressive therapy is indicated. Hydroxyurea is most commonly prescribed. Dosing strategies are empiric: 50 mg/kg q 48 h; 30 mg/kg daily for 7 days followed by a maintenance dosage of 15 mg/kg q 24 h or 12.5 mg/kg q 24 h.[26,27,31] Exact dosage and frequency should be titrated for each individual patient. Chlorambucil has been used in humans with polycythemia vera, but was associated with increased risk of leukemia transformation, limiting its utility. No information regarding its use for primary polycythemia in dogs and cats is available. Radiophosphorus treatment using ^{32}P has proven successful for the treatment of canine polycythemia, but radiological safety issues have made its use uncommon.[32]

Complications of Treatment

Overzealous/chronic phlebotomy can result in iron deficiency, hypoproteinemia, and peripheral edema.[7] Care must be taken when using phlebotomy to control physiologically appropriate secondary polycythemia that balance is maintained between the need to control the clinical signs due to hyperviscosity while still maintaining an adequate number of red blood cells to provide adequate tissue oxygenation. Myelosuppressive therapy may result in leukopenia and thrombocytopenia but these abnormalities are often clinically silent. In humans, thrombosis is the main cause of morbidity and mortality in patients with polycythemia vera. Thrombosis has not been reported as a complication of primary polycythemia in veterinary patients.

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CHAPTER 201

Immune-Mediated Thrombocytopenia, von Willebrand Disease, and Other Platelet Disorders

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Client Information Sheets:
Immune-Mediated Thrombocytopenia
Platelet Function Disorders
Von Willebrand Disease

Primary Hemostasis

Overview

Platelets play a critical role in the initiation, regulation, and localization of hemostasis. The term primary hemostasis refers to the interactions among platelets, von Willebrand factor (VWF), and the vessel wall that culminate in the formation of a platelet plug. These reactions begin with platelets contacting a damaged vessel wall, VWF-mediated adhesion and proceeding through platelet activation, degranulation, aggregation and concluding with development of platelet-dependent procoagulant activity and clot retraction.

Platelet Physiology

Megakaryocytic precursor cells in the bone marrow are programmed, through the action of transcription factors and thrombopoietin, to form platelet-specific organelles and to express platelet cell surface proteins. In the final stages of megakaryocyte maturation, large pseudopodia develop and stretch to form thin proplatelet processes. The processes elongate as platelet organelles move individually over microtubules to the end of the proplatelet, where nascent platelets accumulate. The growing proplatelets branch and form constrictions along their length, giving them a beaded appearance. The entire megakaryocyte is converted into a mass of proplatelets that break away from the megakaryocyte body and fragment into individual platelets. The platelets are released from the marrow and circulate in the vascular compartment as quiescent, nonadhesive, smooth disks. There they act as sentinel cells scanning for sites of vessel damage. Approximately 100 billion platelets are released each day to maintain a peripheral platelet count of 200 million to 500 million cells per milliliter of blood. Platelets have a lifespan of 6 to 10 days in circulation.

Injury to a vessel wall triggers platelet activation within nanoseconds. In the initial step of activation, platelets rapidly transform into adhesive, spiny spheres capable of recognizing and binding to exposed subendothelial matrix components. Surface binding initiates cell-signaling pathways, which then mediate granule secretion. Granule contents include adenine nucleotides, calcium, serotonin, and adhesive proteins such as fibrinogen, VWF, fibronectin, and P-selectin. Secreted compounds accumulate locally, interact with their respective surface receptors, and recruit additional platelets to the site of injury. Large-order platelet aggregates then accumulate and bridge the zone of vascular damage to form a hemostatic plug. Thrombin cleavage of fibrinogen strengthens the platelet plug as a fibrin-platelet meshwork develops.

A subset of collagen and thrombin-activated platelets, termed coated-platelets,[1] scramble phosphatidylserine (PS) from the inner plasma membrane leaflet to the outer platelet membrane surface and release PS-rich microparticles, which act as scaffolding for assembly of highly active tenase and prothrombinase coagulation factor complexes. Expression of platelet procoagulant activity (PCA) greatly amplifies local thrombin and fibrin generation. Contraction of platelet cytoskeletal proteins linked to platelet integrin receptors for fibrin and fibrinogen results in consolidation and subsequent retraction of the growing clot.

Platelet activation requires simultaneous engagement of the platelet membrane surface receptors (Figure 201-1). Species differences in response to platelet stimuli may reflect differences in receptor density and/or subclasses for specific ligands. The endoperoxides prostacyclin (prostaglandin I_2 [PGI_2]), prostaglandin E_2 (PGE_2), and prostaglandin D_2 (PGD_2), which are synthesized by endothelial cells and released into the vascular space, serve as antagonist ligands that react with their respective platelet receptors to dampen platelet reactivity.[2]

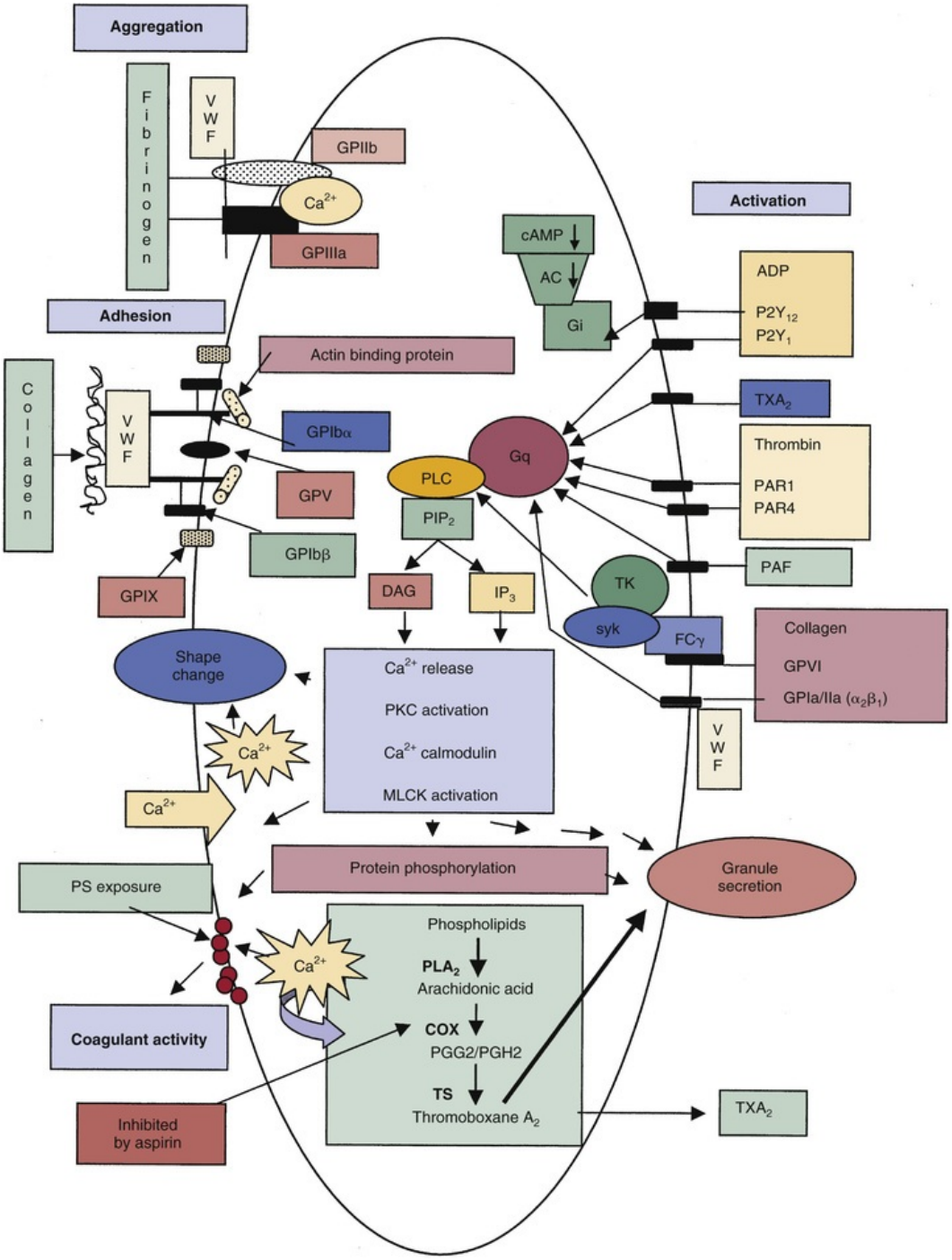

FIGURE 201-1 Major signaling mechanisms involved in platelet activation. *AC,* Adenylate cyclase; *cAMP,* cyclic adenosine monophosphate; *COX,* cyclooxygenase; *DAG,* diacylglycerol; *FCγ,* immunoglobulin-like receptor; *GP,* glycoprotein; *Gq* and *Gi,* GTP-binding proteins; *IP_3,* inositol triphosphate; *MLCK,* myosin light chain kinase; *$P2Y_1$* or *$P2Y_{12}$,* purinergic nucleotide receptors; *PAF,* platelet activating factor; *PAR 1* or *PAR 4,* protein-activated thrombin receptor 1 or 4; *PG,* prostaglandin; *PIP_2,* phosphatidylinositol bisphosphate; *PKC,* protein kinase C; *PLA_2,* phospholipase

A_2; *PLC*, phospholipase C; *PS*, phosphatidylserine; *syk*, syk kinase; *TK*, tyrosine kinase; *TS*, thromboxane synthase; *TXA_2*, thromboxane A_2; *VWF*, von Willebrand factor.

Platelet integrins and nonintegrin glycoprotein receptors play a critical role in adhesion (platelet–subendothelial matrix interactions) and aggregation (platelet-platelet association). The alpha-IIb-beta-3 complex ($GPII_b/III_a$) is the most abundant platelet integrin and functions as the activation-dependent receptor for fibrinogen, fibronectin, and VWF. Binding of fibrinogen to this receptor is essential for aggregation and clot retraction.[3] Platelet adhesion to collagen and collagen-induced signaling are supported by collagen's interaction with the integrin receptor alpha-2-beta-1 (GPI_aII_a) and interaction of collagen with platelet GPVI.

Surface receptors, coupled to G proteins, span platelet membranes and transmit signals induced by agonist binding. In platelets, Gq serves as the link for most agonists and is coupled to phospholipase C, which in turn generates diacylglycerol (DAG) and inositol triphosphate, leading to calcium release from the endoplasmic reticulum, protein kinase C and myosin light chain kinase activation, and phosphorylation of platelet-signaling proteins. During activation, phospholipase A_2 releases arachidonic acid from membrane phospholipids. Cyclooxygenase and thromboxane synthetase convert arachidonic acid to the potent agonist thromboxane A_2 (see Figure 201-1).

Platelet–von Willebrand Factor Interaction

Subendothelial collagen fibrils and bound VWF are exposed after vascular endothelial injury. The affinity and strength of the VWF-collagen bond is proportional to VWF multimer size. Collagen-bound VWF displays a conformational change that allows it to interact with the platelet GPIb/V/IX complex. As platelet GPIb contacts and engages with VWF, platelets slowly roll and become activated by interaction with collagen fibrils. VWF then binds to $GPII_b/III_a$ receptors exposed on the surface of activated platelets. Adhesion and aggregation at high shear rates depend on this VWF binding to activate platelet $GPII_b/III_a$.

Clinical Presentation of Primary Hemostatic Disorders

Surface bleeding is a hallmark feature of primary hemostatic disorders. Petechiae, ecchymoses and epistaxis (see ch. 54) are most commonly observed with severe thrombocytopenia (platelet count <30,000/mcL) but may also be noted with a thrombopathia or vasculopathy (see ch. 59 and 135). Von Willebrand disease (VWD) rarely causes petechiae, although ecchymoses may be observed in some dogs with VWD following trauma and surgical procedures. Mucosal surface bleeding (e.g., epistaxis, melena, hematuria) may be severe and lead to blood loss anemia requiring transfusion therapy (see ch. 130). Life-threatening bleeding into the central nervous system or lungs may occur.[4-6] Although cavity bleeding is more commonly associated with disorders of secondary hemostasis (i.e., coagulopathy), hematomas, hemothorax, hemoperitoneum, and hemarthrosis have been reported in dogs with primary hemostatic disorders.[5,7-9] Excessive bleeding following surgery or trauma might be the first indication of a hereditary bleeding disorder, including primary hemostatic defects, coagulopathy (e.g., hemophilia), or excessive fibrinolysis. Repeated episodes of surface bleeding or similar bleeding in related individuals should prompt evaluation for a hereditary primary hemostatic disorder.

Immune-Mediated Thrombocytopenia

Definitions/Pathophysiology

Primary Immune-Mediated Thrombocytopenia (IMT)

IMT is a disorder in which antibodies bind to platelet surfaces resulting in their destruction, leading to severe thrombocytopenia. Primary IMT, also referred to as idiopathic thrombocytopenic purpura (ITP), is an autoimmune disorder in which antibody is directed against platelet surface antigens. Antibodies directed against epitopes on the platelet GPIIb/IIIa, the fibrinogen receptor, have been identified in dogs with primary IMT.[10] In addition, a novel canine model of primary IMT has been developed using a murine monoclonal antibody, 2F9, against canine GPIIb that causes profound, dose-dependent, thrombocytopenia.[11] A detailed review of the immunopathogenesis of primary IMT is beyond the scope of this chapter, but a recent pilot study documented a reduction in regulatory T (Treg) cells, which play an important role in self-tolerance and regulation of immune responses, in the peripheral blood of dogs with primary IMT, suggesting that loss of Tregs might be causally associated with the onset of primary IMT in dogs.[12]

Secondary Immune-Mediated Thrombocytopenia (IMT)

Secondary IMT develops as a result of an antigenic stimulus, typically from a drug, infectious disease, or neoplasia, leading to antibody production. A retrospective, case-control study of 48 dogs with presumptive primary IMT failed to find an association between recent vaccination (within 42 days) and onset of IMT.[13] Any drug has the potential to cause secondary IMT, but antibiotics, including sulfonamides and cephalosporins, are most common.[14-16] There is a single case report of IMT, in combination with immune-mediated hemolytic anemia (IMHA) and neutrophilic dermatitis, in a young dog that was suspected to be an adverse reaction to carprofen.[17] When a medication is administered for the first time, approximately 5 to 7 days of exposure is typically required to produce sensitization and onset of thrombocytopenia, though subsequent re-exposure to the same drug could result in a rapid thrombocytopenia relapse due to the indefinite persistence of antibodies.[18] Infectious agents that have been associated with development of platelet-bound antibody in dogs include: *Anaplasma phagocytophilum*,[7,19] *Babesia* sp.,[5,7,20] *Ehrlichia canis*,[5,7] *Leptospira* sp.,[5,7] and *Leishmania infantum*.[7,21] This suggests that the thrombocytopenia noted with these conditions might be due in part to secondary IMT. Neoplasia can be associated with thrombocytopenia through several mechanisms (e.g., increased platelet consumption secondary to a bleeding tumor or disseminated intravascular coagulation, splenic sequestration, decreased platelet production due to myelophthisis), in addition to secondary IMT. Neoplastic disorders in which platelet-bound antibodies have been documented include lymphoma,[5,7] hemangiosarcoma,[5] and histiocytic sarcoma.[7] Inflammatory diseases, including chronic hepatitis, pancreatitis, and systemic inflammatory response syndrome (SIRS), have also been associated with platelet-bound antibodies in thrombocytopenic dogs.[7] A single dog was reported to have presumptive secondary IMT following massive Africanized bee envenomation.[22]

Diagnostic Evaluation

Thrombocytopenia is a common laboratory abnormality noted in dogs and cats and may be spurious due to traumatic venipuncture and clumping of platelets. If there is no evidence of bleeding, one should repeat a platelet count on a fresh blood sample and evaluate the blood smear for evidence of platelet clumps (see ch. 59). In a retrospective study of 871 dogs with thrombocytopenia (defined as platelet count <150,000/mcL), primary IMT accounted for only 5.6% of the cases, while thrombocytopenia was attributed to neoplasia and infectious/inflammatory disease in 28 and 35% of the dogs, respectively.[8] However, IMT is considered the most common cause of *severe* thrombocytopenia in dogs.

The diagnosis of primary IMT is always presumptive and based on exclusion of known causes of thrombocytopenia and underlying diseases. This necessitates a complete medical history, physical examination, and diagnostic evaluation that may include imaging and infectious disease screening (see ch. 59). The physical examination of dogs with primary IMT frequently reveals evidence of surface bleeding (petechiae, ecchymoses, epistaxis) and, potentially, pallor, splenomegaly, and fever.[5] Severe thrombocytopenia (≤30,000/mcL) is typical[5,7,8,13,23] and might be the only laboratory abnormality noted. In a retrospective study of 48 dogs with presumptive primary IMT, the median platelet count was 1,000/mcL (range 0-39,500/mcL).[13] A platelet count ≤30,000/mcL has been positively correlated with the occurrence of spontaneous bleeding in dogs with IMT.[5] In clinical practice, the diagnosis of primary IMT is typically based on the finding of severe thrombocytopenia, exclusion of underlying disease, and a response to immunosuppressive therapy (see below).

Documentation of platelet-bound antibody further supports a diagnosis of IMT. A flow cytometric assay to detect platelet-bound antibody (also referred to as platelet surface-associated IgG [PSAIgG]) is considered a sensitive but not specific tool for the diagnosis of primary IMT, as the assay does not differentiate platelet autoantibodies from antibodies induced by underlying infection, neoplasia, or drugs.[5,7,8,20] Increased PSAIgG values were detected in 10 of 13 dogs (77%) with primary IMT and all 4 dogs (100%) with secondary IMT due to *Babesia gibsoni* infection.[20] However, a negative platelet-bound antibody test makes a diagnosis of IMT, either primary or secondary, unlikely.[24] EDTA-anticoagulated blood samples are recommended for evaluation of PSAIgG, and the age of the sample is critical, as PSAIgG values have been documented to increase 3- to 7-fold in normal dog blood samples stored for 24-72 hours.[20] Testing for PSAIgG is available through the Clinical Immunology/Flow Cytometry Laboratory at Kansas State University College of Veterinary Medicine. Other platelet parameters, including mean platelet volume (MPV), mean platelet component (MPC), and plateletcrit, have been evaluated in dogs with primary IMT but are unlikely to aid in

making a diagnosis.[7,23,25,26]

Treatment and Outcome

Immunosuppression

Removal of the offending drug or treatment of the underlying disease is essential for resolution of thrombocytopenia in dogs with secondary IMT. Concurrent immunosuppressive therapy may be necessary in some dogs, though it is generally recommended to treat any underlying infectious disease first and reserve immunosuppression for those dogs not responding to antimicrobial therapy. Glucocorticoids are the mainstay of treatment for primary IMT (see ch. 165 and 195). Vincristine and human intravenous immunoglobulin (hIVIG) have been documented to shorten duration of severe thrombocytopenia in dogs with primary IMT compared to prednisone alone.[27-29] In a prospective study of 24 dogs, 12 treated with prednisone alone and 12 treated with prednisone and vincristine (0.02 mg/kg IV once at the time of initial diagnosis of IMT), dogs that received vincristine had a significantly faster increase in platelet count to >40,000/mcL, with a mean response time of 4.9 days compared to 6.8 days for dogs treated with prednisone alone.[27] A subsequent clinical trial comparing prednisone alone (n = 9 dogs) to prednisone plus a single dose of hIVIG (0.5 g/kg) (n = 9 dogs) documented that adjunctive therapy with hIVIG resulted in a shorter time for platelet recovery (median, 3.5 days vs. 7.5 days).[28] Given the expense associated with hIVIG, another group compared the effect of single dose hIVIG (0.5 g/kg) with vincristine (0.02 mg/kg) on platelet recovery time in dogs with primary IMT receiving concurrent corticosteroid therapy; there was no difference between the treatment groups (10 dogs in each group), both having a median platelet recovery time of 2.5 days.[29] It was concluded that vincristine should be the first-line adjunctive treatment for the acute management of canine primary IMT because of its lower cost and ease of administration as compared with hIVIG.[29] Although vincristine, at a single dose of 0.02 mg/kg IV, is generally well tolerated by dogs with primary IMT (no adverse reactions noted in the 22 dogs receiving vincristine in the above studies), there are potential complications, including perivascular sloughing with extravasation. Since the majority of dogs with primary IMT respond to glucocorticoids alone with 7 days,[27,28] adjunctive treatment may not always be necessary. The duration of treatment for dogs with primary IMT varies, but many dogs are managed with tapering dosages of immunosuppressive drugs over 4 to 6 months while monitoring for relapse.[6]

Immunomodulation

Beyond administration of vincristine and hIVIG for management of acute and severe thrombocytopenia, there are no prospective, controlled studies documenting efficacy of adjunctive immunomodulatory agents in treatment of dogs with primary IMT. However, retrospective studies and case series of canine primary IMT report on use of azathioprine,[5,6,13] cyclosporine,[5,6] and mycophenolate mofetil[6] in combination with corticosteroids (with or without vincristine). It is not possible to make conclusions regarding their efficacy, however. There is a case report describing treatment with mycophenolate mofetil (median dosage 8.5 mg/kg PO q 12 h) as a single agent in 5 dogs with presumptive primary IMT in which corticosteroids were considered contraindicated due to chronic nonsteroidal anti-inflammatory drug administration.[30] All 5 dogs achieved a complete remission, with the time for platelet recovery (platelet count >50,000/mcL) ranging from 2 to 6 days and no evidence of relapse during a median follow-up time of 16 months (range 5 to 32 months).[30]

Transfusion Therapy

In addition to immunosuppressive therapy, blood transfusions (see ch. 130) might be required in dogs with IMT and severe mucosal surface bleeding, most commonly into the gastrointestinal (GI) tract. In such cases, packed red blood cell (PRBC) transfusions are indicated to provide additional oxygen-carrying support. Platelet transfusions are uncommonly administered to dogs with IMT due to the belief that transfused platelets are rapidly destroyed following administration. However, in dogs with IMT experiencing uncontrolled or life-threatening bleeding (e.g., suspected bleeding into the brain or lungs), platelet transfusions may provide short-term hemostasis despite a negligible increase in platelet count post-transfusion. In clinical practice, fresh whole blood is the most readily available platelet source, but other options include fresh platelet-rich plasma (PRP) or platelet concentrate (PC) and cryopreserved platelets.

Although not yet commercially available, lyophilized canine platelets may be an option in the future. The safety and feasibility of administering lyophilized canine platelets to dogs with naturally-occurring thrombocytopenia were evaluated in a multicenter, prospective randomized clinical trial in which 37 dogs

(including 27 dogs diagnosed with primary IMT) were enrolled: 22 dogs in the lyophilized platelet group and 15 in the fresh PC group.[31] The mean pre-transfusion platelet counts were ≈17,000/mcL, and the most common clinical signs of bleeding included petechiae, ecchymoses, and GI hemorrhage. The bleeding severity in each group was described as mild to severe. Fresh PC and lyophilized platelets were dosed at approximately 6.6×10^9 and 3.3×10^9 platelets/kg BW, respectively. Evidence of active bleeding was unchanged immediately post-transfusion in 18 of 22 dogs receiving lyophilized platelets and in all dogs receiving fresh PC. Potential adverse reactions to platelet transfusions were noted in 3 dogs in the lyophilized platelet group (one each: fever, sinus tachycardia, and emesis) and 2 dogs in the fresh PC group (1 each: urticaria and emesis). There was no difference between treatment groups in the need for additional PRBC or platelet transfusions, length of hospitalization, hospital discharge rate, or 28-day survival. While the efficacy of lyophilized platelets could not be evaluated, their administration was easy and associated with a low adverse reaction rate.[31]

Prognosis

Dogs with primary IMT have a good prognosis with appropriate treatment and supportive care, including blood transfusions when blood loss anemia is severe. In one retrospective study of 30 dogs, 29 dogs (97%) survived to 14 days after initial presentation, and 27 (93%) dogs survived at least the following 15 to 1684 days (median 220 days); of 19 dogs observed over an extended period (112 to 1684 days; median 340 days), 5 dogs (26%) relapsed with thrombocytopenia between days 19 to 286 (median 66 days).[5] In another retrospective study of 73 dogs with IMT (25% of which tested positive for vector-borne diseases, and, therefore, may have had secondary IMT), 61 dogs (84%) survived to hospital discharge; of 54 dogs that were followed long-term, 5 dogs (9%) had recurrence of their thrombocytopenia, with a median interval to relapse of 1,743 days (range, 735 to 2,555 days).[6] Similarly, in a third study, the in-hospital mortality rate among 48 dogs with primary IMT was 19%, with 77% of dogs (36 of 47) surviving to at least 1 month after discharge and 43% surviving beyond 1 year of discharge.[13]

Concurrent IMT and IMHA in Dogs

Dogs with IMT infrequently have sequential or concurrent IMHA, a condition referred to as Evans' syndrome in humans (see ch. 198). Two retrospective studies have reported on the outcome of dogs with concurrent IMHA and severe thrombocytopenia, with differing conclusions. 21 dogs with concurrent IMHA and severe thrombocytopenia (defined as <50,000/mcL) were identified and 16 (76%) died or were euthanized within 30 days of hospital admission, leading to a conclusion that concurrent IMHA and severe thrombocytopenia is associated with a poor outcome.[32] In contrast, 12 dogs with concurrent IMHA and severe thrombocytopenia (defined as platelet count ≤15,000/mcL) had a mortality rate of 25%, similar to that reported for dogs with IMT or IMHA alone, suggesting that dogs with concurrent IMHA and IMT do not have a worse prognosis.[33] A potential explanation for differences in these 2 studies is the greater likelihood of excluding dogs with disseminated intravascular coagulation (DIC), known to have a poor prognosis, with the more stringent definition of severe thrombocytopenia in the latter study.[33]

Feline IMT

Primary IMT is diagnosed rarely in cats. Two independent case series described primary IMT in 5 and 4 cats during 8- and 5-year periods, respectively.[34,35] Bleeding in cats with primary IMT is similar to that in dogs, with surface bleeding including petechiae (particularly on the pinnae), ecchymoses, epistaxis, gingival bleeding, hematuria, and hemoptysis.[34,35] Platelet-bound antibodies have been documented by a flow cytometric assay in thrombocytopenic cats.[36] Underlying diseases associated with development of platelet-bound antibodies in cats include viral infections (feline leukemia virus, feline immunodeficiency virus, and feline infectious peritonitis), inflammatory disease (fat necrosis), and neoplasia (lymphoma).[36]

Based on the reported 13 cats with primary IMT, the mortality rate was 15% and 11 survived to hospital discharge.[34] While glucocorticoids are the mainstay of treatment of primary IMT in dogs, oral prednisolone was deemed to be effective in only 5 of 9 cats in the two case series.[34,35] Other immunosuppressive agents administered to these cats included dexamethasone, cyclosporine, and chlorambucil, though there are insufficient cases to comment on efficacy.[34,35] In the series with 4 cats, each had a chronic course with frequent relapses noted and long-term immunosuppressive therapy was required for 3 cats that survived to

hospital discharge.[35]

Hereditary Von Willebrand Disease

Definition and Classification

VWD, the most common hereditary bleeding disorder in dogs, is a platelet adhesion disorder resulting from quantitative (types 1 and 3 VWD) or qualitative (type 2 VWD) deficiencies of plasma VWF. Canine VWD is classified according to the concentration and multimeric structure of plasma VWF, as well as clinical severity. Type 1 VWD is characterized by a low plasma VWF concentration, a full array of VWF multimers, and mild to moderate bleeding tendencies. In type 2 VWD, there is a variable reduction in plasma VWF concentration but an absence of the high molecular weight VWF multimers, causing moderate to severe bleeding tendencies. Type 3 VWD is characterized by a complete absence of plasma VWF, resulting in a severe bleeding tendency.

Diagnostic Evaluation

Screening Tests

Mucosal surface bleeding or excessive bleeding following surgery or trauma in a dog with a normal platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT) should prompt evaluation for VWD. A screening test that can be performed in clinical practice is a buccal mucosal bleeding time (BMBT) test (see ch. 80), with an abnormal result being specific for primary hemostatic disorders.[37] A prolonged BMBT (>4 minutes) in a dog with a platelet count >100,000/mcL and packed cell volume (PCV) >30% is suggestive of VWD, thrombopathia, or, rarely, a vasculopathy. Because VWD is much more common in the dog than are intrinsic platelet function defects, measurement of plasma VWF antigen (VWF : Ag) concentration is recommended before platelet function testing. The Platelet Function Analyzer (PFA-100, Siemens), a point-of-care instrument that assesses platelet adhesion and aggregation under conditions of high shear forces, is sensitive in identifying dogs with type 1 VWD having plasma VWF : Ag concentrations <35%.[38,39] The PFA-100 measures closure time, that required for full occlusion of a 150-micron aperture in a collagen membrane. If the platelet count is >100,000/mcL and PCV >30%, a prolonged closure time is suggestive of VWD or a thrombopathia.

Quantitative VWF Assay

The laboratory diagnosis of VWD is most often based on measurement of plasma VWF : Ag concentration by an ELISA. The Comparative Coagulation Section of the Animal Health Diagnostic Center at Cornell University is the most widely used laboratory in the United States for VWD testing. Results are reported as % VWF : Ag compared to a pooled canine plasma standard of 100%: normal range = 70-180%, borderline (indeterminate) range = 50-69%, and abnormal range = 0-49%. Blood can be collected into evacuated tubes containing EDTA or sodium citrate (3.2 or 3.8%), with the plasma removed following centrifugation and frozen (≤−20°C) until shipped. Sample hemolysis can cause a spurious decrease in plasma VWF : Ag.[40] In addition, temporal variation in VWF : Ag concentration has been documented within individual healthy dogs, though values typically remain in the same range (i.e., normal, borderline, or abnormal).[40] Ill dogs, particularly those with severe inflammatory disease, such as sepsis, could have an increase in plasma VWF : Ag concentration due to endothelial injury and activation.[41] Plasma VWF : Ag concentration also increases during pregnancy and peaks at parturition in both normal dogs and dogs with type 1 VWD.[42] Therefore, screening for VWD (via measurement of plasma VWF : Ag concentration) should not be performed during illness or pregnancy. Testing of puppies from an age of 3 to 180 days indicated that plasma VWF : Ag concentration remains stable during this period of growth.[40]

DNA Testing

DNA tests are commercially available for canine breeds for which the causative mutations (or what is believed to be the causative mutation) for VWD have been identified (Table 201-1).[43-47] The mode of inheritance for type 2 and type 3 VWD is autosomal recessive. In humans, type 1 VWD inheritance has been controversial. It is transmitted either as an autosomal dominant trait[48] or as a complex multifactorial disorder with interrelated genetic and environmental components.[49] In canine type 1 VWD, evidence for autosomal

dominant[50] or recessive[51] modes of inheritance have been reported. The splice site mutation used to diagnose type 1 VWD segregates as autosomal recessive.[43] Although the literature contains reports of type 2 VWD occurring only in the German Shorthaired Pointer and German Wirehaired Pointer, the same mutation (N883S) has been identified in a Collie and a few Chinese Crested dogs, but no clinical data are available for these other breeds (Loechel R from VetGen, personal communication, March 9, 2015). Since the plasma VWF : Ag concentration of heterozygous carriers for type 2 and type 3 VWD can overlap with the low end of the reference range, DNA testing will more reliably detect carriers and, therefore, be of use to breeders trying to eliminate VWD from their lines.[44,46] Use of a DNA test for type 3 VWD in Dutch Kooiker dogs by their breeding club allowed them to eliminate the splice site mutation at the boundary of exon 16 from all breeding stock within a few years. This required no apparent increased inbreeding or preferential sire usage.[47]

TABLE 201-1

Breeds for Which DNA Testing for VWD Is Available

	Breeds	Mutation
Type 1 VWD	Bernese Mountain Dog, Corgi (Cardigan and Pembroke Welsh), Coton de Tulear, Doberman Pinscher, Dutch Partridge dog, German Pinscher, Goldendoodle, Irish Setter, Kerry Blue Terrier, Manchester Terrier, Papillon, Poodle, Stabyhoun, West Highland Terrier	Ancestral splice site mutation in exon 43 (nucleotide 7437 G→A) [Note: All breeds listed have the same mutation]
Type 2 VWD	German Shorthaired Pointer, German Wirehaired Pointer [Collie, Chinese Crested]	SNP A→G in exon 28 (N883S)
Type 3 VWD	Dutch Kooiker,* Scottish Terrier,** Shetland Sheepdog***	*Splice site mutation at boundary of exon 16 **Base deletion in exon 4 ***Deletion of nucleotide T735

Note: With regard to DNA testing, "affected" refers to dogs that are homozygous for the VWD mutation, and "carrier" refers to dogs that are heterozygous for the VWD mutation. Some breeds designated "affected" (ancestral splice mutation, type 1 VWD) may not exhibit a bleeding tendency. Treatment and breeding decisions should be made after veterinary consultation.

DNA testing for VWD is available through VetGen, Animal Genetics, VetNostic Laboratories, and Paw Print Genetics.

N, Asparagine; *S*, serine; *SNP*, single nucleotide polymorphism.

Qualitative VWF Assays

While measurement of plasma VWF : Ag concentration can be used to detect type 1 or type 3 VWD, the diagnosis of type 2 VWD requires documenting an absence of the high molecular weight multimers of VWF through a functional VWF assay or analysis of the size distribution of multimers using SDS-agarose gel electrophoresis. Since the latter is complex, an ELISA measuring plasma VWF : collagen-binding activity (CBA) is often used to diagnose type 2 VWD.[52] The binding of canine VWF to bovine collagen types I and III used in the ELISA is dependent on the presence of high molecular weight multimers. Therefore, dogs with type 2 VWD have decreased VWF : CBA relative to VWF : Ag. Whereas the ratio of VWF : Ag to VWF : CBA is approximately 1 in normal dogs and dogs with type 1 VWD, the ratio is >2.0 in dogs with type 2 VWD.[52]

Treatment

Background

Medical management of VWD is aimed towards controlling spontaneous (e.g., epistaxis, hematuria) or trauma/surgery-induced bleeding. While dogs with type 2 and type 3 VWD inevitably have a severe bleeding tendency, the phenotype among dogs with type 1 VWD is variable, with some dogs having marked

reductions in plasma VWF : Ag concentration but no apparent bleeding tendency.[53] Therefore, the need for prophylactic treatment, particularly with blood component therapy, should be assessed on a case by case basis.

Desmopressin

Desmopressin acetate (1-deamino-8-D-arginine vasopressin [DDAVP]), a synthetic analogue of the neurohypophyseal hormone vasopressin, has been used to control bleeding in a variety of hemostatic disorders, but most commonly VWD in dogs. While administration of DDAVP to humans with type 1 VWD and clinically normal individuals typically results in a 2- to 5-fold increase in plasma VWF : Ag concentration, the effect of DDAVP is less dramatic in dogs. One hour following administration of DDAVP (1 mcg/kg SC) to 16 Doberman Pinschers with type 1 VWD, mean plasma VWF concentration increased from a baseline of 10% to 17%.[54] Despite the modest increase in plasma VWF : Ag concentration, DDAVP resulted in improved hemostatic function as assessed by the PFA-100 and shortening of the BMBT.[39] It has been proposed that the favorable hemostatic effects of DDAVP may be mediated in part by the appearance of new high molecular weight VWF multimers in the plasma.[55] However, plasma VWF : CBA increased concordantly with plasma VWF : Ag, and plasma VWF multimer analysis revealed proportional increases in band intensity for all multimer sizes 1 hour following administration of DDAVP to Doberman Pinschers with type 1 VWD, suggesting that there is a mechanism other than a preferential increase in high molecular weight VWF multimers resulting in improved primary hemostasis.[54]

DDAVP is available as a sterile solution (4 mcg/mL) for IV administration and a nasal spray (100 mcg/mL) that can be administered SC to dogs. The nasal spray preparation is used more frequently in dogs with VWD due to its lower cost, and a recommended dosage is 1 mcg/kg SC administered not more than once daily due to the risk of water retention and hyponatremia associated with its antidiuretic hormone effects, as well as tachyphylaxis, or a failure to elicit VWF release from the Weibel-Palade bodies in endothelial cells with repeated administration. DDAVP should be administered 30 minutes prior to surgery when used prophylactically to prevent excessive bleeding in dogs with VWD.

Blood Component Therapy

Blood products containing VWF include fresh whole blood, fresh frozen plasma (FFP), and cryoprecipitate (CRYO), the latter representing the blood component of choice to treat bleeding in dogs with VWD. Cryoprecipitate is prepared from FFP and contains a concentrated amount of VWF, FVIII, fibrinogen, fibronectin, and FXIII (see ch. 130). Comparison of administration of FFP (1 unit/15 kg BW, with 1 unit containing 250-300 mL) and CRYO (1 unit/15 kg BW, with 1 unit of CRYO [mean volume of 37 mL/unit] prepared from a 250-300 mL unit of FFP) to Doberman Pinschers with type 1 VWD documented that greater increases in plasma VWF : Ag concentration were achieved with transfusion of CRYO.[56] Based on the pharmacokinetics of VWF assessed in dogs with type 1 VWD after administration of FFP and CRYO, the estimated volume required to reach a target VWF : Ag concentration of 35 U/dL was 49 mL/kg for FFP and 4 mL/kg for CRYO, indicating that CRYO is a more efficient means of managing hemorrhage in dogs with VWD and avoids volume overload.[57]

Guidelines for blood component therapy in the management of bleeding in dogs with VWD include administration of CRYO at a dosage of 1 unit/10 kg (1 unit defined as CRYO prepared from 200-250 mL FFP) or FFP at a dosage of 10-15 mL/kg.[58] Although it is expensive to administer 3 to 4 units of CRYO to a Doberman Pinscher or other large-breed dog in a single transfusion event, this high-dose approach will rapidly increase plasma VWF levels to support platelet adhesion, allowing more rapid control of bleeding. Due to the short half-life of plasma VWF (≈12 hours), CRYO or FFP transfusions may need to be administered every 8-12 hours to control severe bleeding. Blood type- and crossmatch-compatible packed red blood cells should be available when dogs with VWD are undergoing surgery, even when DDAVP and CRYO are administered prophylactically, in the event of excessive blood loss.

Acquired Von Willebrand Syndrome

In people, acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder characterized by structural or functional alterations in VWF caused by lymphoproliferative, myeloproliferative, cardiovascular, autoimmune, or other disorders.[59] Potential mechanisms responsible for the VWF abnormalities depend on the underlying disorder but include clearance due to binding of paraproteins, inhibition of VWF, adsorption

to the surface of platelets, and increased fluid shear stress resulting in increased proteolysis of VWF by ADAMTS13 and depletion of high molecular weight VWF multimers.[59] The latter mechanism is responsible for AVWS noted in humans with mitral regurgitation, ventricular septal defects, and aortic stenosis, with improvement in the AVWS and associated bleeding tendency documented after correcting the cardiac defect.[59,60]

Although not reported to cause bleeding in Cavalier King Charles Spaniels or other dogs, AVWS secondary to myxomatous mitral valve disease and subaortic stenosis has been documented, with a decrease in plasma VWF : Ag concentration and a loss of the high molecular weight VWF multimers.[61,62] Transient AVWS was reported in research dogs given a tetrastarch bolus (40 mL/kg IV over 30 minutes), with a significant decrease in plasma VFW : Ag and VWF : CBA (no change in Ag : CBA ratio) noted up to 2 hours post-infusion but resolved by 4 hours. The clinical significance of this finding is not clear.[63] There is a report of possible AVWS secondary to angiostrongylosis in a young Golden Retriever with cerebral and conjunctival hemorrhage.[64] Although likely uncommon in dogs, AVWS should be considered in cases with new-onset bleeding whenever laboratory findings suggest VWD, particularly in the presence of conditions similar to those reported in humans with AVWS.

Feline Von Willebrand Disease

There are only two reported cases of VWD in cats, both diagnosed with type 3 VWD. A 9-year-old neutered male Himalayan experienced persistent oral hemorrhage following tooth extraction with subsequent spontaneous gingival bleeding.[65] A 1-year-old female domestic longhaired cat developed spontaneous epistaxis, which resolved with FFP transfusion but not DDAVP administration.[66] Although VWD appears to be an uncommon disorder in cats, it should be considered as a differential diagnosis in cats with a bleeding tendency, in the absence of severe thrombocytopenia or coagulopathy (i.e., prolonged prothrombin or activated partial thromboplastin times). As with dogs, a diagnosis of VWD in cats can be confirmed by measurement of plasma VWF : Ag concentration.

Platelet Function Disorders

Hereditary Platelet Dysfunction

Background

Hereditary thrombopathia, or intrinsic platelet dysfunction, is an important and potentially under-recognized cause of spontaneous and post-surgical/trauma bleeding. Several inherited platelet function defects have been identified in dogs and cats (Table 201-2).[67-85] The best characterized disorders are Glanzmann thrombasthenia and calcium-diacylglycerol guanine nucleotide exchange factor I (CalDAG-GEFI) thrombopathia, the latter formerly known as Basset thrombopathia.[67-72] Excellent reviews of the clinical features and molecular characterization of these inherited platelet disorders are available.[73,74]

TABLE 201-2

Hereditary Thrombopathias in Dogs and Cats

Platelet Disorder	Specific Defect	Breeds Affected	Diagnosis
Glanzmann thrombasthenia	Absence or deficiency of the fibrinogen receptor, GPIIb-IIIa	Otterhounds Great Pyrenees	DNA testing*,†,68,69
P2Y12 receptor disorder	Impaired binding of ADP to its platelet receptor	Greater Swiss Mountain Dog	DNA testing*,†,80
CalDAG-GEFI thrombopathia	Signal-transduction disorder preventing change in conformation of GPIIb-IIIa necessary for fibrinogen binding	Basset Hound Spitz	DNA testing*,†,72

		Landseer	
LAD-I variant or LAD-III	Signal transduction disorder due to dysfunctional or missing Kindlin-3, impairing integrin activation	German Shepherd	DNA testing*,†,81
Platelet procoagulant deficiency (Scott syndrome)	Impaired platelet membrane phosphatidylserine (PS) externalization and decreased prothrombinase activity, leading to decreased generation of thrombin	German Shepherd	DNA testing‡
Cyclic hematopoiesis	Associated with cyclic neutropenia and stem cell defect Platelet storage pool disorder (serotonin, ATP, and ADP deficiency); impaired phosphorylation of an intraplatelet protein, preventing platelet activation by collagen, PAF, and thrombin	Gray Collie	DNA testing†,§,82
Chediak-Higashi syndrome	Associated with leukocyte and melanocyte abnormalities Platelet storage pool disorder associated with lack of discernable dense granules and deficiency of ATP, ADP, serotonin, Ca^{2+} and Mg^{2+}	Persian cats	Presence of characteristic granules in leukocytes (blood smear) and melanocytes (skin biopsy)85
Platelet delta-storage pool disease	Platelet dense granule deficiency of ADP	American Cocker Spaniel	Increased platelet ATP : ADP ratio83

*DNA testing available through Auburn University.

†Paw Print Genetics.

‡Cornell University.

§VetGen, Animal Genetics, and HealthGene.

CalDAG-GEFI, Calcium diacylglycerol guanine nucleotide exchange factor I; *LAD*, leukocyte adhesion deficiency.

Platelet Procoagulant Deficiency (Scott Syndrome)

Research during the past decade has greatly improved our understanding of canine platelet procoagulant deficiency, also known as Scott syndrome, an autosomal recessive disorder identified thus far only in German Shepherds.[75] Characteristics of Scott syndrome platelets include failure to externalize PS, impaired microparticle release and coated-platelet formation, and decreased prothrombinase activity.[76-78] In the absence of PCA, there is insufficient thrombin generation to support fibrin clot maturation and stabilization, resulting in a bleeding tendency. Hemorrhagic events reported for dogs with Scott syndrome include post-surgical, epistaxis, and soft tissue hemorrhage.[79] Interestingly, affected dogs do not develop spontaneous petechiae and ecchymoses that are characteristic of platelet disorders, suggesting that PCA is not required to maintain general capillary integrity but is needed for maintenance of the nasal cavity arterial microvasculature, as evidenced by the profound epistaxis requiring local embolization in some dogs.[79] Recognition of Scott syndrome can be challenging in clinical practice given that results of hemostatic screening tests (e.g., BMBT, PFA-100, thromboelastography, platelet aggregometry) are normal. A simple flow cytometric assay, based on the inability of canine Scott syndrome platelets to externalize PS when stimulated, and DNA testing for the recently identified mutation causing Scott syndrome in German Shepherds, are available at Cornell University.[79a]

P2Y12 Receptor Disorder

A novel P2Y12 receptor gene mutation, a 3 base-pair (CTC) deletion predicted to eliminate serine 173 (173Sdel) from the second loop of the extracellular domain of this ADP receptor, has been identified across 5 generations in a family of Greater Swiss Mountain dogs and associated with postoperative hemorrhage.[80] Spontaneous bleeding is absent to mild in affected dogs; however, severe and life-threatening bleeding requiring platelet transfusions has been observed following ovariohysterectomy. The prevalence of the P2Y12 mutation in the Greater Swiss Mountain dog breed is reported to be about 60%, including heterozygous and homozygous affected dogs (Boudreaux M, personal communication, March 18, 2015).

Acquired Platelet Dysfunction

In vitro platelet function defects have been documented in association with various systemic disorders, including uremia,[86] hepatobiliary disease,[87,88] and paraproteinemia.[89,90] The mechanisms underlying acquired thrombopathias are not well defined and are likely multifactorial. Anemia can be a contributing factor to a bleeding tendency, potentially due to altered rheological properties of the blood limiting contact of platelets with the vessel wall, as well as a decreased source of ADP (from fewer RBCs) to activate platelets.[91] Many drugs (e.g., hydroxyethyl starch,[92-95] nonsteroidal anti-inflammatory drugs,[96,97] cephalosporins[98,99]) have been documented to have an adverse effect on platelet function *in vitro*, though the clinical significance is unclear. However, use of such medications in a patient with a known bleeding tendency should be done with caution. Two drugs that are frequently administered for their anti-platelet activity to patients predisposed to thromboembolic complications include aspirin, an irreversible inhibitor of cyclooxygenase, and clopidogrel, a platelet P2Y12 ADP receptor antagonist (see ch. 198 and 256).

Diagnostic Evaluation

The classic clinical presentation for many hereditary thrombopathias includes spontaneous bleeding in the form of petechiae, ecchymoses, and mucosal surface bleeding, and excessive bleeding following trauma or surgery. This bleeding history, in conjunction with a normal platelet count, PT, aPTT, and plasma VWF : Ag concentration, should prompt diagnostic evaluation for a thrombopathia (Figure 201-2). As for VWD, a BMBT test and PFA-100 can be performed as screening tests for a thrombopathia. For dogs of a breed with a known mutation for a thrombopathia, the diagnosis can be confirmed by DNA testing (see Table 201-2). Special platelet function testing for dogs and cats suspected to have a hereditary thrombopathia includes platelet aggregation studies (optical or impedance), measurement of ATP release, flow cytometry to evaluate the presence of platelet membrane glycoproteins and activation-specific changes (e.g., CAP-1 monoclonal antibody binding to fibrinogen bound to the GPIIb-IIIa complex), and electron microscopy. Platelet function tests require meticulously collected (to prevent platelet activation) and fresh (less than a few hours) blood samples. This makes remote platelet function testing difficult.

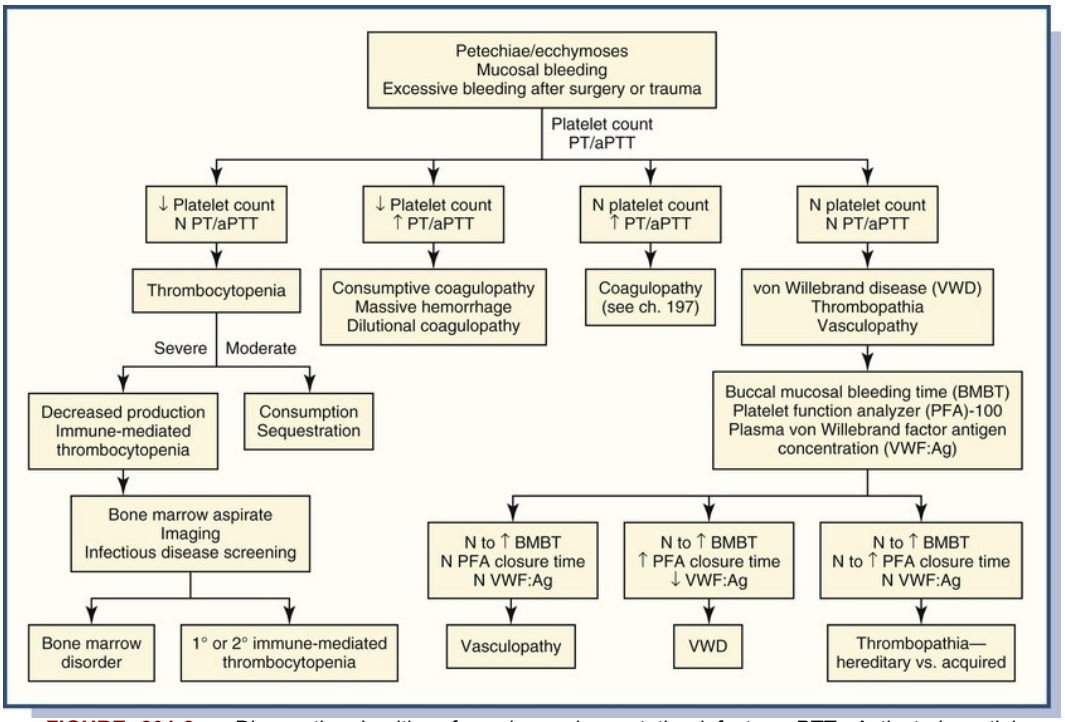

FIGURE 201-2 Diagnostic algorithm for primary hemostatic defects. *aPTT*, Activated partial thromboplastin time; *BMBT*, buccal mucosal bleeding time; *N*, normal; *PFA-100*, platelet function analyzer-100; *PT*, prothrombin time; *VWD*, von Willebrand disease; *vWF : Ag*, von Willebrand factor antigen concentration.

Treatment

Dogs and cats with hereditary thrombopathias experiencing severe (e.g., hemoabdomen resulting in anemia following an ovariohysterectomy) or life-threatening bleeding (e.g., pulmonary or central nervous system hemorrhage) require platelet transfusions to control bleeding. In addition, prophylactic platelet transfusions should be considered in patients with a known bleeding tendency and documented thrombopathia undergoing surgery. As discussed, options for platelet transfusions include fresh whole blood, fresh PRP, fresh PC, and cryopreserved PRP/PC (see ch. 130). Canine cryopreserved platelets have been administered to dogs with Scott syndrome prophylactically prior to elective neutering at a median dosage of 5.7×10^9 platelets/kg body weight, as well as in the management of nonsurgical hemorrhage, mainly epistaxis, with apparent efficacy.[79] Since thawed canine cryopreserved platelets have been documented to externalize PS, it has been hypothesized that cryopreserved platelets may provide an advantage to fresh platelets in promoting thrombin generation in dogs with Scott syndrome.[79]

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CHAPTER 202

Immune-Mediated and Other Nonneoplastic White Blood Cell Disorders

Jennifer L. Johns

Primary/Congenital White Blood Cell Disorders

Chédiak-Higashi Syndrome

Chédiak-Higashi syndrome is reported in humans and various animal species including Persian cats as a primary immunodeficiency with recurrent neutropenia and neutrophil function defects, along with platelet function defects.[1] In humans, the specific mutation(s) in the CHS1 gene is/are documented; one manifestation of the disorder is partial oculocutaneous albinism that manifests in Persian cats as a blue smoke coat color. Neutrophils, eosinophils, and other cells contain abnormally fused granules. Granulocyte colony-stimulating factor (G-CSF) therapy in cats can partially correct neutrophil function defects, though cats appear less prone to infection than are other species with Chédiak-Higashi syndrome.[2] Birman cat granulation anomaly also causes abnormal neutrophil cytoplasmic granulation that can mimic Chédiak-Higashi syndrome, toxic neutrophil granulation, and mucopolysaccharidosis.[3]

Pelger-Huët Anomaly

Pelger-Huët anomaly is an autosomal dominant disorder causing defective terminal granulocyte maturation (a "laminopathy") and it is described in humans and mammals including dogs[4] and cats.[5] Australian Shepherds are overrepresented, with a 9.8% prevalence in one study, with likely incomplete penetrance of the dominant trait.[6] Granulocytes have hyposegmented nuclei with mature chromatin (Figure 202-1, *A* and *B*). No functional defects have been found in studies of neutrophils from dogs with Pelger-Huët anomaly and it is accepted that immunodeficiency does not occur in this condition.[7] The homozygous state can be embryonic lethal, as reported in a cat and theorized in dogs.[6,8] Pseudo–Pelger-Huët anomaly in cats and dogs can be caused by infections, severe inflammation, myeloid neoplasia (e.g., myelodysplastic syndrome), and drug toxicosis.[8]

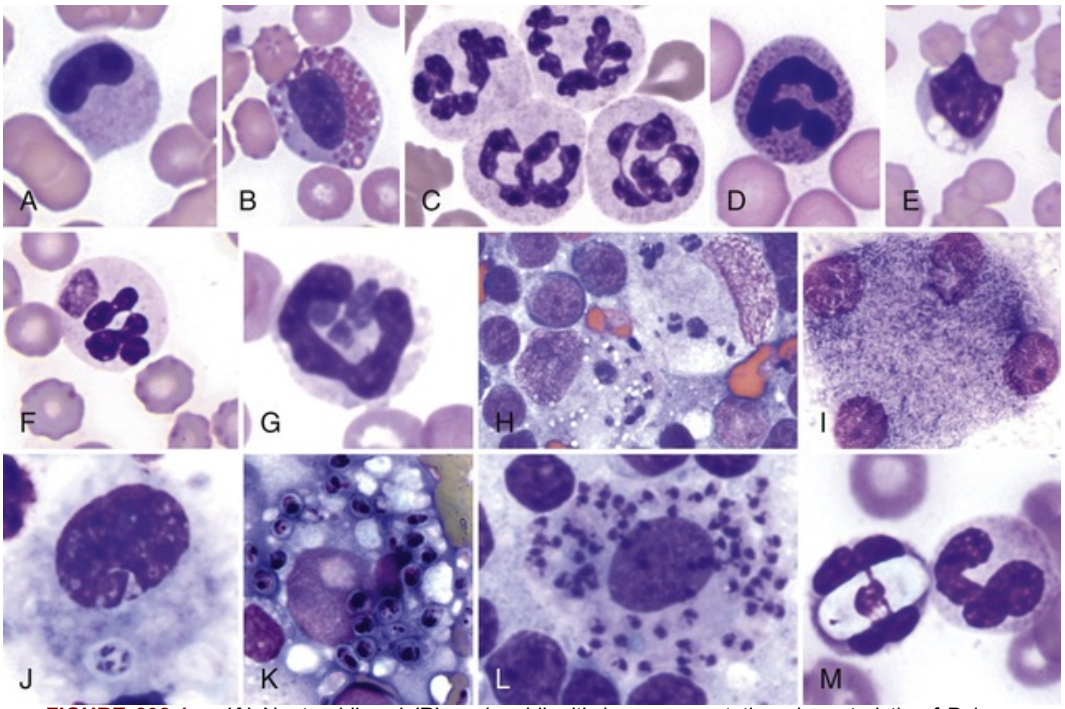

FIGURE 202-1 **(A)** Neutrophil and **(B)** eosinophil with hyposegmentation characteristic of Pelger-Huët anomaly; **(C)** hypersegmented neutrophils in canine leukocyte adhesion deficiency (image courtesy Dr. William Vernau); **(D)** abnormal neutrophil granulation in mucopolysaccharidosis VI; **(E)** abnormal lymphocyte vacuolation in GM2 gangliosidosis; **(F)** neutrophil containing canine distemper virus inclusion; **(G)** neutrophil containing *A. phagocytophilum* morulae; **(H-L)** macrophages containing **(H)** *N. helminthoeca* morulae; **(I)** *Mycobacteria;* **(J)** *P. carinii;* **(K)** *Sporothrix schenkii;* **(L)** *Leishmania;* **(M)** neutrophil containing *Hepatozoon* gamont.

Leukocyte Adhesion Deficiency (LAD)

LADs are due to mutation(s) in leukocyte adhesion proteins and they prevent the normal adherence and migration of white blood cells through luminal endothelium. Type I LAD results from a defect in the beta-2 subunit (also known as CD18) of the heterodimeric integrins and it is described in Irish Setters. The specific mutation was characterized in European Irish Setters[9] and has since been identified in setters in the United States and Australia.[10,11] A clinically similar disease was described in mixed-breed dogs but the mutation described in Irish Setters was not present; CD18 transcription was reduced and additional neutrophil function deficits were described.[12] Marked peripheral neutrophilia with nuclear hypersegmentation (Figure 202-1, *C*) is a typical diagnostic finding in canine LAD, along with absence of neutrophils in tissues. Affected pups initially can present with omphalitis followed by lymphadenopathy, low body weight, and febrile infections.[13] Antibiotic therapy is generally ineffective at prolonging life and most pups succumb or are euthanized by 2-3 months of age.

Trapped Neutrophil Syndrome

Trapped neutrophil syndrome is an autosomal recessive neutropenia in Border Collies, originally described in dogs from Australia and New Zealand. The disorder is characterized by peripheral neutropenia with a degenerative left shift and marked monocytosis, and myeloid hyperplasia in the bone marrow with increased mature neutrophils.[14] Craniofacial development can be abnormal in severely affected animals. Pups with the disorder initially present because of recurrent bacterial or other infections, adverse reaction to vaccination, or because of small size.[15,16] The causative mutation is analogous to that causing Cohen syndrome in human patients, and dogs are one natural model of the human disease.[17]

Pyruvate Kinase Deficiency

Dogs with a congenital pyruvate kinase deficiency (see ch. 198) will develop progressive myelofibrosis and

osteosclerosis of the bone marrow, along with changes in the liver (reviewed in Harvey 2006[18]). These changes are unique to dogs, as cats and humans with pyruvate kinase deficiency do not develop similar bone marrow abnormalities. Progressive myelophthisis leads to bone marrow failure and decreased marrow production of all blood cells. Mechanisms of marrow fibrosis in affected dogs can include iron overload due to hemolytic anemia and excessive intestinal iron absorption, and the effects of prolonged increased erythropoiesis.[19,20]

X-Linked Severe Combined Immunodeficiency (X-SCID)

X-SCID is caused by mutations in the gene encoding the common interleukin-2 receptor (IL-2-R) gamma chain, and is reported in Cardigan Welsh Corgis and Basset Hounds as well as in humans.[21-23] In dogs, the deficiency of the IL-2-R gamma chain primarily affects developing CD4- CD8-thymocytes.[24] Affected pups display stunted growth, develop recurrent and/or chronic infections as maternal antibody protection declines, and rarely survive past four months of age.[25] X-SCID dogs have hypoplastic and dysplastic thymuses, and other lymphoid tissues are hypoplastic or absent. Pups with X-SCID initially have rare peripheral T lymphocytes and increased numbers of B lymphocytes; over time, low numbers of nonfunctional T lymphocytes can appear in circulation.

Autosomal Recessive Severe Combined Immunodeficiency

This severe combined immunodeficiency is characterized by defective recombination events during T- and B-lymphocyte maturation. It is reported in Jack Russell Terriers along with Arabian horses and humans. In dogs, it is caused by a point mutation in the gene encoding the catalytic subunit of DNA-dependent protein kinase.[26,27] Affected pups have severe lymphopenia, decreased serum globulin concentrations due to agammaglobulinemia, and marked lymphoid hypoplasia in the spleen, thymus and other lymphoid tissues.[28] Opportunistic infections and vaccination with modified live virus are frequent causes of death in dogs with this form of SCID.

Cyclic Hematopoiesis in Gray Collies

Also called cyclic neutropenia, this disorder is due to a defect in trafficking of lysosomal membrane proteins and it is reported in gray collie dogs; the gray coat color results from the defect in melanocytes.[29] An insertional mutation in the AP3B1 gene is documented in affected dogs, and it results in cycling of neutrophil and other blood cell counts with an approximately 2-week periodicity.[30,31] The causal mutation, periodicity of cell cycling, presence of hypopigmentation and inheritance (autosomal recessive in dogs) differ from those in the human disorder.[32] Neutrophils in affected dogs are deficient in neutrophil elastase and myeloperoxidase.[33,34] Frequent infections occur in affected dogs and most succumb prior to six months of age. Treatment with recombinant G-CSF eliminated neutropenic episodes but did not correct functional defects in one report.[33]

Common Variable Immunodeficiency

Miniature Dachshunds with *Pneumocystis carinii* pneumonia were found to have lymphocyte function deficits, including hypogammaglobulinemia and absence of B cells in lymph nodes, that resembled those seen in common variable immunodeficiency of humans. Similar immunoglobulin deficiencies were found in Cavalier King Charles Spaniels with *P. carinii* pneumonia.[35,36]

Lysosomal Storage Disorders

Various lysosomal storage disorders are reported in small animals; the most common clinical manifestations are neurologic, but hematologic changes can be seen in some. In dogs and cats, mucopolysaccharidosis type VI (arylsulfatase B deficiency) and type VII (beta-glucuronidase deficiency) can result in abnormal granules in the cytoplasm of neutrophils, monocytes and lymphocytes (Figure 202-1, *D*).[37,38] GM2 gangliosidosis can result in abnormal vacuolation in the cytoplasm of peripheral leukocytes (Figure 202-1, *E*).[39,40]

Secondary/Acquired White Blood Cell Disorders

Immune-Mediated Neutropenia

As with other immune-mediated hematologic diseases, immune-mediated neutropenia (IMN) can be secondary to causes such as tick-borne disease or drug administration, or it can be idiopathic. IMN in small animals can occur in tandem with other immune-mediated disorders, including immune-mediated hemolytic anemia (IMHA; see ch. 198), thrombocytopenia (IMT; see ch. 201) and polyarthritis (see ch. 203).[41,42] A diagnosis of IMN should exclude other causes including acute or overwhelming peripheral demand; decreased production due to hemic neoplasia or other forms of myelophthisis or drug-induced marrow injury; and sequestration due to splenomegaly.[43] Infections, neoplastic diseases, concurrent autoimmune disorders, and drugs are associated with IMN in humans.[44] Anticonvulsants including phenobarbital can induce neutropenia and thrombocytopenia in dogs, as can cephalosporins, and a possible association with ivermectin administration was seen in one case of canine IMN.[43,45,46] Idiopathic IMN was the least common cause of neutropenia in one study (see also ch. 58).[47] Younger age is a risk factor for dogs to develop IMN, and neutrophil counts are significantly lower than in other neutropenic disorders.[48] In a report of pure white cell aplasia in a dog, the patient had absolute granulocytopenia in peripheral blood and absent granulocytic precursors in the bone marrow.[49] Methods to diagnose IMN often require species- and antigen-specific antibodies and are therefore of limited availability in animals. Granulocyte agglutination and immunofluorescence were not considered sensitive for IMN in a study of neutropenic cats.[50] Flow cytometric methods can be used for direct and indirect detection of anti-neutrophil antibodies, and were considered sensitive and specific for the diagnosis of IMN in neutropenic dogs.[51,52] Rapid response to immunosuppressive therapy (e.g., prednisone) is documented in dogs and is considered necessary to confirm the diagnosis of IMN.[41]

Primary Myelodysplastic Syndrome (MDS)

Primary MDSs are clonal disorders arising from mutations within hematopoietic stem and progenitor cells. As clonal (neoplastic) disorders, primary MDSs fall outside of the scope of this chapter but the differentiation between primary MDS and secondary dysmyelopoiesis can be extremely difficult[53]; a brief synopsis is therefore presented here. Nonregenerative anemia is a consistent feature in primary MDS in both dogs and cats (see ch. 199). Feline retroviral infections can cause MDS and dysmyelopoiesis (see ch. 222 and 223).

Evidence of clonality in primary MDS is difficult to obtain in animals and a combination of history, clinical signs, and accurate categorization of hematopathologic abnormalities is needed for diagnosis.[54] Many cases of feline MDS are attributable to feline leukemia virus (FeLV) infection; a clonal origin to FeLV-associated myelodysplasia and acute myeloid leukemia is proven.[55] Primary MDS is rare in dogs, and a clonal origin has not been proven in canine MDS.[56] Microscopic morphologic changes that suggest primary MDS instead of secondary dysmyelopoiesis include increased immature precursors, higher percentages of dysplastic cells, and megaloblastic erythroid precursors.[54,57] Additionally, a history of drug/toxin exposure or concurrent disease can support secondary dysmyelopoiesis instead of primary MDS. Primary MDS is similar to chronic myeloid leukemia; both feature anemia or multiple cytopenias and normal/hypercellular bone marrow with blast cells comprising <30% of all nucleated cells; a key difference is the lack of increased myeloid cells (predominantly mature) in circulation with MDS.[58]

Several classification schemes for MDS in dogs and cats have been proposed. In human medicine, the French-American-British (FAB) working group scheme frequently is used.[59,60] An alternate scheme proposed by the World Health Organization includes molecular genetics.[61] In small animals, the FAB scheme has been modified and applied to consistent disorders.[54] The following is one modified-FAB scheme for classification of primary MDS in small animals.[62]

MDS–Excess Blasts (MDS-EB)

MDS-EB is likely the most common MDS in dogs and it is associated with more severe clinical signs and a poor prognosis on presentation.[63] Neutropenia occurs in this form of primary MDS along with thrombocytopenia and nonregenerative anemia. Increased myeloblasts (up to 20%) and dysplasia of all three cell lines are found in bone marrow.[63,64] Dysplastic changes include asynchronous maturation in all cell lines,

hypersegmented granulocytes, dispersed megakaryocyte nuclei, and erythroid dysplasia as described below for MDS-refractory cytopenia.[53,65] The prognosis for dogs with MDS-EB is poorer than that for other forms of MDS.[57]

MDS-EB affects cats ranging from one year old to advanced age.[66] Studies show that cats with MDS-EB comprise 31%-65% of all cats with primary MDS; cats with secondary dysmyelopoiesis were excluded from these groups.[66-69] In one study, 6 of 13 cats with MDS-EB tested positive for FeLV infection. Other studies found higher percentages of FeLV-positivity; discrepant results could be due to decreasing FeLV prevalence and/or differing prevalence between geographic regions.[66,68,69] Like in dogs, the prognosis for cats with MDS-EB tends to be worse than that for other forms of feline MDS.[66,68]

MDS–Refractory Cytopenia (MDS-RC)

MDS-RC tends to occur in older dogs and has an insidious onset of clinical signs due to progressively worsening nonregenerative anemia. Other cytopenias including neutropenia can occur but are uncommon. Bone marrow can be hypercellular due to erythroid hyperplasia, or normocellular. Erythroid dysplasia including nuclear:cytoplasmic asynchrony, binucleation, and nuclear fragmentation, is a characteristic finding.[63] Rubriblasts can be increased (up to 30% of all nucleated bone marrow cells).[57,58] Descriptions of MDS-RC in cats often include cytopenias and dysplastic changes in multiple blood cell lineages rather than erythroid cells only; it is proposed that such cases represent MDS-RCMD (see below) rather than MDS-RC in this classification scheme.[62,66,68,69]

MDS–Refractory Cytopenia with Multilineage Dysplasia (MDS-RCMD)

MDS-RCMD is defined by dysplasia in at least 2 cell lineages in bone marrow, similar to MDS-EB but without a substantial increase in myeloblasts (<5% myeloblasts for MDS-RCMD). MDS characterized by refractory anemia with sideroblastic differentiation can be included in this category as MDS-RCMD in dogs, as dysplasia occurs in multiple lineages.[62] In cats, experimental infection with FeLV produced hematologic disease resembling MDS-RCMD with cytopenias and dysplasia in multiple cell lines.[70] Several cats with sideroblastic forms of MDS-RCMD are reported.[66,69]

Treatment of Primary MDS

Treatment can be complicated by the difficulty of differentiating primary MDS from secondary dysmyelopoiesis; see Table 202-1 for list of agents used therapeutically.[71-73]

TABLE 202-1

Summary of Treatment Options for Patients with Leukocyte Disorders

DISEASE CATEGORY	NOTES AND RELEVANT CHAPTER REFERENCES
Primary immunodeficiencies	Treatment is unnecessary for asymptomatic Pelger-Huët anomaly. Supportive care for other conditions includes antibiotic therapy as indicted; G-CSF therapy can be useful in neutropenic conditions.33 Curative experimental treatments include gene therapy and bone marrow transplantation.139-141 Also see ch. 360.
Immune-mediated neutropenia	Immunosuppression is indicated but more common causes of neutropenia, particularly infectious disease, should be excluded before starting immunosuppressive therapy. See ch. 165, 195, 198, and 201.
Primary myelodysplastic syndromes	Differentiate from secondary dysmyelopoiesis. Cytotoxic treatment agents for dogs and cats with MDS have included cyclophosphamide, prednisone, cyclosporine, daunorubicin, vincristine, hydroxycarbamide and cytarabine.71-73 Additional therapeutic options include transfusion if indicated (see ch. 130) and erythropoietic agents to support red blood cell production. See ch. 165, 199, 339, 343, and 344.
Secondary dysmyelopoiesis	Eliminate underlying cause if possible. Supportive care can include transfusion, erythropoietin, G-CSF, antibiotics, and/or immunosuppressive therapy.76,142 See ch. 130, 165, and 199.
Myeloproliferative disorders	Treatment is indicated when clinical signs and/or significant cytopenia develops; hydroxyurea is commonly used along with supportive care. See ch. 200 and 344.

Viral infections	Antiviral therapy and/or supportive care varies with specific infection. See ch. 162 and 222-225.
Bacterial, fungal and protozoal infections	Antimicrobial treatment is specific to the infectious agent and/or site(s) of infection. Bacterial infections: See ch. 132, 161, 212, 213, and 218. Fungal infections: See ch. 162 and 231-236. Protozoal infections: See ch. 163 and 221.

G-CSF, Granulocyte colony stimulating factor; *MDS*, myelodysplastic syndrome.

Secondary Myelodysplastic Syndromes

Secondary myelodysplastic syndromes in humans are clonal disorders; mutations are induced by chemotherapeutic agents, toxin exposure, and/or radiation therapy. Dysmegakaryopoiesis and myeloproliferative disorders occur following radiation therapy in dogs, suggesting these syndromes potentially occur in small animals.[68,74,75]

Secondary Dysmyelopoiesis

The most common diseases associated with secondary dysmyelopoiesis (a non-neoplastic disorder) in dogs are IMT and IMHA, myelofibrosis, pure red cell aplasia, and lymphoma; drugs, including chemotherapeutic agents, chloramphenicol, estrogens and phenobarbital; endogenous overproduction of estrogens; heavy metal toxicoses; iron deficiency; adenocarcinoma; and leishmaniasis.[53,56,76,77] Dysplasia can affect one or multiple blood cell lineages, often depending on the underlying etiology. For example, sideroblastic forms of disease are associated with inflammatory disorders and myelofibrosis.[56] Bone marrow cytology alone can be insufficient to distinguish primary MDS from secondary dysmyelopoiesis. Lower percentages of dysplastic cells and non-increased percentages of blast cells are thought to suggest secondary dysmyelopoiesis, although exceptions can include recovery from sepsis or toxic bone marrow injury.[53,54,58,67] Diseases associated with secondary dysmyelopoiesis in cats include immune-mediated hemolytic anemia and thrombocytopenia, pure red cell aplasia, lymphoma, glomerulonephritis, feline infectious peritonitis, and feline immunodeficiency virus (FIV) infection.[66,67,78]

Myeloproliferative Disease (Myeloproliferative Neoplasia)

This category can be difficult to define, as acute leukemias and myelodysplastic syndromes may be included (see ch. 344).[79] The four disease processes listed below are analogous human categories of myeloproliferative neoplasms[80]; evidence of specific genetic mutations in animals is largely lacking.

Polycythemia (Rubra) Vera

Polycythemia vera is a clonal expansion of hematopoietic progenitors (see ch. 200). Leukocytosis and thrombocytosis often occur in addition to erythrocytosis in affected humans, but these abnormalities are rare in animals.

Chronic Granulocytic Leukemia

In humans, chronic granulocytic leukemia is defined by the Philadelphia chromosome translocation. An analogous genetic abnormality is rarely found in small animals, and differentiating chronic granulocytic leukemia from other causes of severe neutrophilic leukocytosis, e.g., paraneoplastic neutrophilia, generally relies on clinical signs, history of concurrent diseases, etc. (see ch. 58 and 352).

Essential Thrombocythemia

Essential thrombocythemia is a clonal disorder primarily affecting megakaryocytes and resulting in platelet overproduction; differentiation from non-neoplastic disorders requires demonstration of the causal genetic mutation and/or use of exclusionary diagnostic schemes.[81] Marked thrombocytosis in dogs and cats usually is due to reactive thrombocytosis (see ch. 59). A few reports appear to describe true essential thrombocythemia based on exclusion of other diagnoses.[82-84]

Primary Myelofibrosis

Primary myelofibrosis in humans is a rare clonal myeloproliferative disease resulting in progressive ablation of marrow space due to fibrosis; extramedullary hematopoiesis can be marked.[85] Confirmation of primary myelofibrosis in humans relies on molecular genetic testing. The occurrence of suspected primary myelofibrosis in all domestic animals is extremely rare,[86] and most cases of myelofibrosis are likely secondary (see below). Several cases of presumptive primary myelofibrosis have been reported in dogs,[87-89] and myelofibrosis without evidence of an underlying disorder has been reported in cats.[67]

Myelophthisis

Myelophthisis, defined as replacement of hematopoietic tissue in bone marrow by abnormal cells or tissue, often is caused by hemic neoplasia. Secondary myelofibrosis is a relatively common, non-neoplastic cause of myelophthisis. In dogs, pyruvate kinase deficiency (see above, see ch. 198) is the most frequently reported cause of secondary myelofibrosis. Other causes in small animals are high-dosage recombinant human erythropoietin, FeLV infection, bone marrow necrosis, infections, and drugs/toxicoses.[90-93] Myelonecrosis is associated with myelofibrosis and marrow ischemia; causes include IMHA, sepsis, hemic neoplasia in bone marrow, and drugs. The specific mechanism linking myelonecrosis and myelofibrosis is unclear.

Myelotoxicosis and Myelosuppression

Due to their high proliferative rate, bone marrow hematopoietic cells are susceptible to injury by numerous drugs, and chemotherapeutic agents are among the most common causes of myelotoxicosis (see ch. 343). Acute myelosuppression also can occur following half-body radiation for canine lymphoma but can be minimized through optimization[94,95]; see "Secondary Dysmyelopoiesis," above, for other drugs and agents of myelotoxicosis.

Viral Infections of Dogs and Cats

Parvovirus Infection

Canine and feline parvoviral infections (see ch. 225) cause bone marrow injury and leukopenia. Neutropenia often is seen in severe canine parvovirus infection but not in all cases; leukopenia was reported in fewer than half of infected dogs on presentation in one case series.[96] 92% of clinically ill dogs and 84% of cats with parvoviral infection had acellular ("complete depopulation of") bone marrow on histologic evaluation in one retrospective study.[97] Treatment with recombinant canine (not human) G-CSF improved total white blood cell counts and neutrophil counts and reduced the duration of hospitalization, but survival times were decreased suggesting potential adverse effects.[98-100]

Distemper and Paramyxovirus Infection

Canine distemper virus (see ch. 228) infects numerous tissues and cells, including lymphoid and other hematopoietic cells. Immunosuppression occurs early in infection and is due to virally mediated lysis of lymphocytes; grossly enlarged lymph nodes and thymic atrophy develop.[101] Secondary lymph node follicles are absent microscopically. Lymphopenia can occur; cytoplasmic (rarely nuclear) viral inclusions can be seen in white blood cells in peripheral blood smears (Figure 202-1, *F*) in early infection.[102] Immunosuppression can be prolonged in some dogs and can exacerbate viral replication and spreading.

Feline Leukemia Virus Infection

In cats, bone marrow suppression frequently is associated with FeLV infection (see ch. 223). Erythroid precursors most commonly are affected but suppression of hematopoiesis can occur in all cell lineages via both direct and indirect/immune-mediated effects. Neutropenia is seen in approximately 50% of cats presenting with FeLV-related illness.[103] Cyclic hematopoiesis has been seen in infected cats.[104] Cats with myelodysplasia and myelofibrosis frequently are FeLV-positive. Myelophthisis due to myelofibrosis and/or other causes, particularly hemic neoplasia, can contribute to decreased leukocyte production.

Feline Immunodeficiency Virus Infection

Acute FIV infection (see ch. 222) can trigger mild leukocyte abnormalities, but substantial changes are variable in any stage of infection. No differences were found between FIV-infected and non-infected cats in

the occurrence of peripheral leukocyte abnormalities in one study[105]; in another, FIV infection increased the odds ratio of neutropenia.[106] Panlymphopenia can occur in acute infection.[107] Viral strain is an important factor: severe neutropenia with lymphocytosis of granular lymphocytes was seen during acute experimental infection with FIV-C-PG.[108] Chronic infection is associated with decreased CD4+:CD8+ T-cell ratios[107] and development of secondary neoplastic and inflammatory disorders.

Feline Infectious Peritonitis

Peripheral blood leukocyte abnormalities, particularly neutrophilia and lymphopenia, are common in feline infectious peritonitis (see ch. 224) but are non-specific. Body cavity effusions usually are modified transudates or exudates with high protein concentrations relative to nucleated cell counts, and mixed inflammatory cell populations of neutrophils, macrophages, and lymphocytes.

Bacterial, Fungal and Protozoal Infections of Dogs and Cats

Rickettsial Infections

In dogs, the rickettsiae that are most often associated with leukocyte abnormalities are *Ehrlichia canis, Ehrlichia chaffeensis, Ehrlichia ewingii, Anaplasma phagocytophilum, Neorickettsia helminthoeca, Neorickettsia risticii* and *Rickettsia rickettsii* (see ch. 218). Natural and/or experimental infections with *E. canis, A. phagocytophilum* and *N. risticii* are reported in cats.[109-112] Acutely, *E. canis* infection can cause neutropenia and/or total leukopenia[113]; bacterial morulae can be found in lymphocytes, monocytes, and macrophages in smears of peripheral blood/buffy coat, bone marrow and lymph node specimens.[114] Severe chronic infection causes pancytopenia and marked panhypocellularity of bone marrow.[115] *E. chaffeensis* is another agent of canine monocytic ehrlichiosis in North America, but hematologic abnormalities are milder and chronic pancytopenia is absent.[116,117] *E. ewingii* and *A. phagocytophilum* cause granulocytic ehrlichiosis and granulocytic anaplasmosis.[118,119] Lymphopenia, neutropenia, eosinopenia, monocytosis and/or total leukopenia are noted in *A. phagocytophilum* infection.[120,121] Morulae of either bacterium can be seen in peripheral blood neutrophils (Figure 202-1, *G*). Neutrophilic polyarthritis can develop in both infections; morulae also can be found in synovial fluid neutrophils.[122] Acute infection with *N. helminthoeca,* the causative agent of salmon poisoning disease in dogs, causes lymphopenia; peripheral and internal lymph nodes are enlarged due to lymphoid reactivity and histiocytic inflammation.[123] Organisms can be found in lymph node cytologic smears stained with Giemsa stain, and vary from irregular inclusions to morulae within macrophages (Figure 202-1, *H*).[124] *Rickettsia rickettsii* natural infection of dogs has been characterized by leukocytosis accompanied by toxic granulation of neutrophils.[125] Experimental infection has produced initial leukopenia progressing to leukocytosis.[126]

Bartonella Infections of Dogs and Cats

Bartonella infections in dogs (see ch. 215) can induce granulomatous inflammation of lymph nodes, heart, liver, and/or other localized sites or systemic inflammation.[127-129] Neutrophilic leukocytosis, monocytosis and eosinophilia occur in *Bartonella vinsonii*-infected dogs.[130] Persistent eosinophilia is seen in some *Bartonella*-infected cats (see ch. 216); neutrophilia can occur with inflammation.[131,132] Lymphoid hyperplasia in lymph nodes and spleen are noted in infected cats, along with pyogranulomatous inflammation in organs.

Mycobacterial Infections

Mycobacterial infections in dogs and cats (see ch. 212) can induce focal or multifocal pyogranulomas or can become disseminated. Cytologic and histopathologic evaluation of lesions often is helpful in diagnosis. Acid-fast stains are required to identify mycobacteria because routine stains "negatively stain" organisms within macrophages (Figure 202-1, *I*).

Fungal Infections

Fungal infections of dogs and cats can cause neutrophilia and monocytosis (see ch. 231-236) as well as pyogranulomatous inflammation in tissues. Some fungal infections, e.g., *Pneumocystis carinii* (Figure 202-1, *J*), are associated with immunodeficiency.[36,133,134] Other fungal pathogens commonly found in macrophages in tissue specimens include *Sporothrix schenckii* (Figure 202-1, *K*), *Histoplasma capsulatum, Blastomyces dermatitidis,*

and *Cryptococcus* spp.

Protozoal Infections

Protozoal infections (see ch. 221) can elicit systemic leukocyte abnormalities, e.g., neutrophilia and eosinophilia. Many protozoa infect leukocytes and can be found on cytologic evaluation of peripheral blood smears and/or tissue aspirates. Intracellular tachyzoites of *Neospora caninum* or *Toxoplasma gondii* can be seen in monocytes or macrophages in samples including airway lavage fluid. *Cytauxzoon felis* schizonts may be found in macrophages in tissue aspirate specimens from infected cats; pancytopenia can occur.[135] *Leishmania* amastigotes are found in macrophages in lymph node and bone marrow aspirates and draining wound impression smears (Figure 202-1, *L*).[136] Marked neutrophilia and monoclonal gammopathy are reported in dogs.[137] Cytologic assessment can be insensitive for detection of *Leishmania* organisms in infected cats.[138] *Hepatozoon* spp. organisms can be seen in blood and tissue leukocytes in infected dogs (Figure 202-1, *M*).

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CHAPTER 203

Immune-Mediated Polyarthritis and Other Polyarthritides

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Polyarthropathies are characterized by neutrophilic inflammation of multiple joints. Clinical signs are lameness, stiffness, and/or reluctance to walk, and some patients show signs of systemic illness. The diagnostic evaluation can identify an etiologic agent or other inciting cause, which then warrants specific treatment. A diagnosis of idiopathic, immune-mediated polyarthropathy (IMPA) is made by excluding the presence of known causes of joint inflammation, and a good response occurs with immunosuppressive treatment of IMPA.

Polyarthritis is defined as neutrophilic inflammation of 2 or more joints. Polyarthritis may be divided into infectious, reactive, and primary (idiopathic immune-mediated) etiologies. Primary IMPA is subdivided further into erosive and non-erosive forms (Box 203-1).

Box 203-1

Classification of Polyarthritis

Infectious (rickettsia, bacteria, *Mycoplasma,* L-form bacteria, fungi, viruses [cats])
Secondary to distant immunogenic stimulus ("reactive")
  Non-joint, infectious focus (bacterial, fungal, protozoal, other)
  Non-joint, inflammatory focus (immune-mediated dermatopathy, enteropathy, hepatopathy)
  Drugs (trimethoprim-sulfa, human albumin, other antibiotics)
  Non-joint neoplasia
  Post-vaccinal
Primary immune-mediated polyarthropathy
  Non-erosive
    Systemic lupus erythematosus
    Breed-associated (Shar-Pei, Akita)
    Idiopathic immune-mediated polyarthropathy
  Erosive
    Breed-associated: Greyhound
    Idiopathic
      Rheumatoid arthritis (primarily subchondral bone lysis)
      Periosteal proliferative polyarthritis (cats; prominent periosteal bone proliferation)

General Diagnostic Overview

Typical Features of Idiopathic, Immune-Mediated Polyarthritis

- Involvement of multiple joints, especially if there has been no response to anti-rickettsial treatment. Degenerative arthropathies are differentiated by mononuclear inflammation of synovial fluid (see ch. 353).
- Fever of unknown origin.
- Neutrophilic inflammation in synovial fluid, if only one joint was evaluated (see ch. 74). Differentiation of mono- from polyarthropathies is sometimes difficult by physical examination alone. Unless a monoarthropathy is obviously present (i.e., previous joint surgery or penetrating injury), analysis of synovial fluid from multiple joints is recommended (see ch. 94).

Typical Features of Septic (Bacterial) Arthritis

- Swelling and pain in a joint that has undergone surgery.
- Swelling and pain in a single, large joint (elbow, shoulder, stifle, or hip). Degenerative joint disease predisposes joints to bacterial arthritis from hematogenous spread. Fever, marked pain, and systemic illness suggest infection rather than exacerbation of degenerative joint disease. In contrast, immune-mediated polyarthropathies affect multiple, smaller, and distal joints.
- Lameness in a patient with a history of immunosuppressive therapy, such as with corticosteroids or cyclosporine.
- Lameness in a patient with history of chronic bacterial infection, most frequently of urinary tract or skin origin.

Exclusion of Infectious Agents from the List of Probable Etiologies

- Tick-borne agents (such as *Borrelia burgdorferi, Anaplasma phagocytophilum, Rickettsia ricketsii* and *Ehrlichia canis*) are most easily excluded with a trial of doxycycline or minocycline. Response to anti-rickettsial treatment occurs within 72 hours. Measurement of serologic titers could be helpful, but clinical signs of disease can occur before the development of serum antibodies and therefore, test results can be negative in acutely infected dogs. *A. phagocytophilum, R. rickettsia,* or *E. canis* infection cannot be excluded by a single negative serologic result.
- Dogs with a single swollen and painful joint should be most carefully evaluated for an infectious etiology. Prior surgery greatly increases the likelihood of a bacterial etiology. The sensitivity of bacterial culture of synovial fluid is low; synovial fluid is best subcultured in blood culture medium prior to laboratory submission.[1] Concurrent cultures of blood and urine should be obtained in cases of suspected hematogenous origin.
- Dogs with systemic infections (such as bacterial endocarditis, deep pyoderma, fungal disease, or leishmaniasis) can develop a secondary immune-mediated polyarthropathy. In these cases, synovial fluid culture often is negative, despite an infectious etiology. Evaluation of patients with polyarthropathy can include serologic testing, thoracic radiographs, echocardiography, abdominal ultrasonography, and/or skeletal radiographs.
- Unusual organisms occasionally are identified as the cause of arthritis. Culture of joint fluid might include evaluation for aerobic, anaerobic, mycoplasmal, fungal and L-form agents.
- Bacterial culture of synovial fluid rarely is positive when multiple joints are involved. However, in some patients, one joint is obviously swollen and involvement of other joints is uncertain. In these cases, centesis of multiple joints is warranted (see ch. 94) and fluid from the most obviously affected joint is submitted for culture.
- Locally endemic diseases are considered when making a differential diagnosis list. Systemic fungal diseases are considered in, or after travel to, endemic areas, for example. Serologic titers, microbial cultures in a specialized laboratory, and/or molecular assays could be useful.

Infectious Polyarthropathies

Tick-Borne/Rickettsial

In endemic areas, vector-borne infectious disease is a common cause of inflammatory polyarthritis. *Borrelia burgdorferi* (see ch. 211), *Anaplasma phagocytophilum, Rickettsia rickettsii, Ehrlichia canis, E. ewingii,* and *E. chaffeensis* (see ch. 218) all have been implicated. In areas where tick-borne diseases are endemic, arthrocentesis rarely is indicated in a dog or cat with multiple swollen joints until there has been failure to respond to a 3-5 day course of doxycycline or minocycline.

Leishmaniasis

Leishmaniasis is a chronic systemic disease caused by a protozoal parasite found mainly in South America, Africa, India, and the Mediterranean (see ch. 221).[2] In the United States, visceral disease has been reported in American Foxhounds. Clinical abnormalities develop 3 months to 7 years after infection and typically consist of inappetence, weight loss, muscle atrophy, and cutaneous lesions. Polyarthritis causing lameness and

exercise intolerance is common and joint radiographs can reveal erosive changes. The diagnosis is made when the organisms are identified cytologically, or by serologic or molecular diagnostic testing.

Bacterial

Large joints such as the stifle, hip, shoulder, or elbow are affected most frequently, but any joint can be involved (see ch. 353).[3] Most non-surgical joint infections develop from hematogenous spread but only rarely does bacterial disease simultaneously involve multiple joints. The most common agents are Gram-positive aerobes. When non-surgical bacterial arthritis is suspected, blood and urine should be collected for culture and if positive, additional imaging (echocardiography [see ch. 104], abdominal ultrasonography [see ch. 88]) performed. See "Reactive Arthritis," below.

Mycoplasmal

There are isolated veterinary reports of polyarthritis associated with *Mycoplasma* species: *M. gatae* and *M. felis* have been isolated from cats and *M. spumans* from dogs. Synovial fluid analysis reveals non-degenerate neutrophils. Routine aerobic and anaerobic cultures of joint fluid are negative, and the diagnosis requires isolation in special mycoplasma medium. PCR assays can be more sensitive than culture for detection of *Mycoplasma* species. Doxycycline and fluoroquinolones are active against most *Mycoplasma* isolates.[4]

Bacterial L-Form–Associated Arthritis

A rare syndrome of subcutaneous abscesses with associated polyarthritis has been described in dogs and cats with L-forms of bacteria suspected as the cause. An L-form is a mutant bacterium that has lost its cell wall. Affected cats have swollen, painful joints, and fever. Fistulating subcutaneous wounds can develop over the affected joints. Cultures for aerobic, anaerobic, mycoplasmal, and fungal organisms are negative, and specific L-form media must be used for growing the organism. L-form bacteria are difficult to recognize with a light microscope, but can be identified on electron microscopy. Treatment with doxycycline or a fluoroquinolone should be effective.[5]

Fungal

Systemic fungal diseases (blastomycosis [see ch. 233], histoplasmosis [see ch. 233], coccidioidomycosis [see ch. 232]) can be associated with direct joint involvement. Reactive, immunologically mediated, culture-negative polyarthritis also can occur, and probably is more common than direct involvement of the joint.

Viral

Both calicivirus infections (see ch. 229) and attenuated liver calicivirus vaccines (see ch. 208) have been associated with transient polyarthritis in 6- to 12-week-old kittens. Clinical signs include lameness, stiffness, and fever, with spontaneous improvement in 2-4 days. Synovial fluid analysis reveals a mononuclear pleocytosis.[6]

Polyarthropathies Occurring Secondary to Distant Immunogenic Stimulus ("Reactive")

Animals with reactive polyarthritis can have vague or few clinical signs referable to their underlying disease and be presented only when joint inflammation makes them reluctant to walk.[7] It is important to perform a thorough physical examination of animals with polyarthritis (Video 203-1), to obtain a complete drug history, and to evaluate for evidence of systemic illness. Screening tests (complete blood count [CBC] with manual differential count, serum biochemical profile, serologic testing for endemic infectious diseases, urinalysis, thoracic radiographs, and abdominal ultrasound) often are performed to screen for an underlying cause of polyarthritis.

Non-Joint Infectious Focus (Bacterial, Fungal, Protozoal, Other)

Patients with infection in sites distant from the joints can develop a secondary immune-mediated

polyarthropathy. Endocarditis, discospondylitis, pyometra, bacterial pyoderma/cellulitis, foreign body abscesses, pancreatitis, prostatitis, pyelonephritis, pneumonia, or actinomycosis can represent a source of chronic inflammation, leading to circulation of immune complexes and systemic inflammatory disease. Even though the underlying inflammatory disease is infectious, polyarthritis in these patients is caused by synovial deposition of immune complexes and synovial fluid cultures will be negative. In some cases, such as those with a positive urine culture, it can be difficult to determine whether the infection represents the origin of hematogenous bacterial spread, the inciting source of inflammation, or incidental disease. The low sensitivity of synovial fluid cultures for the detection of infection contributes to this confusion. Heartworm disease, chronic otitis, and severe gingivostomatitis represent common conundra.

Nonjoint, Inflammatory, Noninfectious Focus (Immune-Mediated Skin Disease, Inflammatory Bowel Disease, and Chronic Hepatitis)

This form of reactive arthritis originates with non-infectious antigenic stimuli distant to the joints. In some cases, these diseases may qualify the patient's disease to be categorized as systemic lupus erythematosus (see ch. 205). It can be difficult to establish whether an inflammatory focus is the primary problem and causing a secondary reactive arthropathy, or if both represent manifestations of a single disease process (i.e., systemic lupus erythematosus).

Drugs and Vaccination

Polyarthritis can develop after the administration of any medication, but is most commonly reported with antibiotics (see ch. 169). Polyarthropathy has been described after administration of sulfonamides, vaccines, human albumin, penicillin, cephalexin, lincomycin, erythromycin, phenobarbital, and erythropoietin, although not all are well-described. With sulfonamides, signs of polyarthritis develop 5-20 days after drug exposure and can be associated with fever, thrombocytopenia, hepatopathy, and skin or oral lesions. Doberman Pinschers appear to be predisposed. Improvement occurs within 7 days of drug cessation.[8]

Vaccination represents a potential cause of polyarthritis (see ch. 208); onset within 30 days of vaccine administration is suspicious. Whether vaccination itself represents a risk, or whether immune stimulation triggers the disorder in a patient with a genetic predisposition, remains difficult to determine. Vaccine-triggered, immune-mediated disease can be self-limiting and could respond more favorably than spontaneously arising disease. Dogs with vaccine-induced polyarthropathy have been reported to recover in 1-2 days without immunosuppressive drug therapy.[9]

In 7 healthy dogs given human albumin, 6 developed signs consistent with immune-complex disease (5 of 7 developed lameness).[10] Signs developed 5 to 13 days after administration of human albumin, and in surviving dogs, resolved after 2 to 37 days.

Distant Neoplasia

Polyarthropathy has been associated with carcinomas of tonsillar, mammary, and renal origin; seminoma; Sertoli cell tumor; and leiomyoma. It can be unclear if the cancer is causing polyarthropathy or if it represents a coexisting condition. In cases where neoplasia is the inciting cause, resolution of the neoplastic condition (for example, by surgical removal) would be expected to eliminate polyarthropathy and associated lameness. In many cases, joint pain is responsive to immunosuppressive therapy, even if the primary neoplasm remains untreated.

Primary Immune-Mediated Polyarthropathies

Nonerosive Primary Immune-Mediated Polyarthropathy (IMPA)

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is defined as an immune-mediated polysystemic disorder, often associated with a positive antinuclear antibody titer (see ch. 205). The most common manifestation of SLE is polyarthropathy. Diagnostic testing reveals additional, immune-mediated manifestations such as proteinuria, hemolytic anemia, thrombocytopenia, immune-mediated skin disease, and/or mucocutaneous oral ulcerations (see ch. 204). Treatment of polyarthropathy associated with SLE is the same as for idiopathic IMPA; however, additional attention is given to monitoring for development and/or progression of systemic disease

manifestations.

Breed-Associated

Shar-Pei

Shar-Pei dogs can experience short (12- to 48-hour) recurrent bouts of fever, accompanied by inflammation of joints (especially the hocks, i.e., swollen hock syndrome). This disorder also is known as familial Shar-Pei fever (FSF). Episodes typically are more frequent during the first years of life and become less frequent with age. Nonsteroidal anti-inflammatory drug (NSAID) administration seems helpful during episodes. The major constituent of the thickened skin of Shar-Peis is hyaluronic acid (HA), and HA is overexpressed in Shar-Peis compared with other canine breeds. The extent of hyaluronanosis varies among individual Shar-Peis, although almost all are affected. The administration of corticosteroids decreases cutaneous mucinosis in Shar-Peis, perhaps by decreasing expression of hyaluronan synthase.[11] The role that excessive HA in Shar-Peis plays in FSF needs to be investigated further. Shar-Pei dogs affected with FSF are at risk of developing reactive systemic AA amyloidosis and subsequent kidney or liver failure. Treatment of FSF-affected Shar-Peis with colchicine (0.025-0.03 mg/kg [maximum per dose: 0.6 mg] PO q 12 h) has been recommended. The benefit of long-term colchicine, corticosteroid, or other immunosuppressant administration, however, remains to be published.

Akita

One report has described 8 Akita puppies (<8 months old) with severe polyarthropathy.[12] Only 2 of 8 were responsive to antimicrobial and immunosuppressive therapy. Affected patients were traced back to a common ancestor and this syndrome does not appear to be widespread.

Idiopathic Immune-Mediated Polyarthritis (IMPA)

Once infectious agents and degenerative disease have been excluded, an idiopathic, immune-mediated etiology is presumed.[7,13-16] The cause is felt to be an immune-system dyscrasia, either targeting the joint directly or involving circulating immune complex (Arthus type III) disease. Immunosuppression is associated with rapid clinical response and avoidance of medication-related side-effects is paramount.

Signalment

Idiopathic immune-mediated polyarthritis is most commonly diagnosed in 3- to 7-year-old dogs, although patients have been diagnosed from 6 months to 12 years of age. There is no sex predilection and all breeds can be affected. IMPA is rare in cats; reported cases are young to middle-aged.

Signs

Most cases present with a stiff gait and reluctance to stand and/or walk. Anorexia, weight loss, and peripheral lymphadenopathy can be present. Fever is reported in one half of affected patients. Joint swelling and pain often are detected, but in some cases, these abnormalities are subtle. The carpal and tarsal joints are preferentially affected. Polyarthritis can occur concurrently with meningitis, polymyopathy, dermatopathy, hepatopathy, gastroenteropathy, or as a paraneoplastic syndrome, and physical findings can reflect concurrent disease. IMPA is a common cause of fever of unknown origin (see ch. 48) and the diagnosis cannot be excluded by physical examination findings alone.[17]

Differential diagnoses include tick-borne/rickettsial disease, hematogenous infectious processes (bacterial, fungal, protozoal), meningitis, polymyositis, panosteitis, hypertrophic osteodystrophy, degenerative joint disease, congenital lesions (i.e., elbow dysplasia, osteochondritis dissecans lesions), and trauma.

Diagnostic Testing

In juvenile dogs, it is important to palpate the diaphysis and metaphysis of long bones to differentiate polyarthritis (no signs of pain expected from deep palpation at these locations) from panosteitis or hypertrophic osteodystrophy (see ch. 187 and 353). The oral mucosa should be evaluated for ulceration (suggesting immune-mediated disease, particularly SLE) and the neck palpated and manipulated for signs of resistance or pain consistent with meningitis. Auscultation can reveal a cardiac murmur suggestive of bacterial endocarditis. All joints are evaluated for swelling, pain, range of motion and instability. The carpi and tarsi are preferentially affected and should receive special attention: palpation for evidence of joint effusion, and gentle but firm hyperflexion for signs of pain are indicated (see Video 203-1). Stifle lameness

commonly is associated with cruciate ligament tear, rather than polyarthritis, and careful evaluation must be performed.

Laboratory testing includes a CBC with manual differential, platelet count, serum biochemical profile, and urinalysis. Mild nonregenerative anemia and mild leukocytosis are common. The presence of thrombocytopenia suggests tick-borne or concurrent immune-mediated thrombocytopenia rather than idiopathic disease. Marked elevations of liver enzymes can prompt additional evaluation (bile acids, ultrasonography, and possibly histopathologic examination of a liver biopsy specimen) to assess for hepatopathy as a distant immunogenic stimulus. Proteinuria should prompt evaluation of urinary protein/creatinine ratio and systemic blood pressure (see ch. 99).

The need for imaging is evaluated on an individual basis. Thoracic radiographs, joint radiographs, and abdominal ultrasonography are most useful for patients with advanced age, joint instability, and/or abnormalities on CBC, serum biochemistry profile, or urinalysis. Joint radiographs are clearly indicated in non-responsive cases or in those with joint instability; however, in most cases, at least at the time of initial diagnosis, results are usually uninformative.[18] Erosive arthropathy might not be radiographically visible at the time of initial evaluation and only be detected with repeated assessment (Figure 203-1).

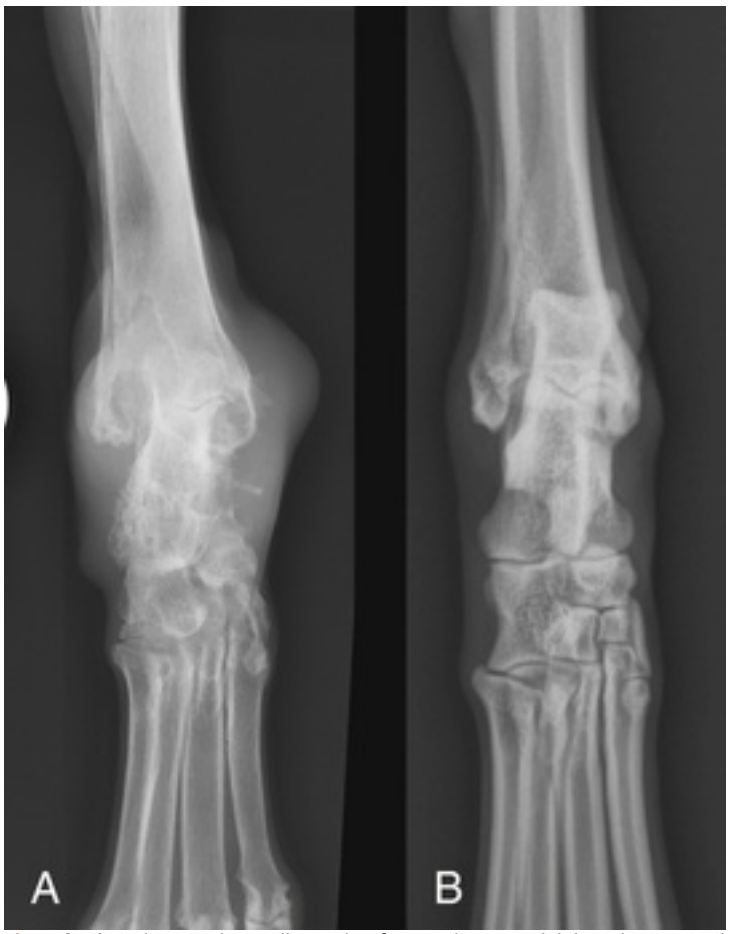

FIGURE 203-1 **A,** Anterioposterior radiograph of a canine tarsal joint, demonstrating extensive subchondral bone destruction, and moderate periarticular soft tissue swelling. These findings are consistent with the diagnosis of erosive arthritis. **B,** Normal canine tarsal joint for comparison.

Antinuclear antibody and rheumatoid factor serologic titers may be evaluated (see ch. 205, and "Erosive Arthropathy," below). The lupus erythematosus prep has low sensitivity. Titers for tick-borne diseases may be performed to help distinguish the cause of polyarthritis; however, in areas where these diseases are endemic, a course of anti-rickettsial antibiotics (doxycycline, minocycline) is always recommended. Because signs of illness can precede development of serum antibodies, acute rickettsial disease cannot be excluded by negative serum titers. Conversely, in endemic areas asymptomatic seroconversion to tick-borne agents is common. Most practically, failure to respond to a 3-5 day course of appropriate antibiotic therapy excludes

the diagnosis of rickettsial disease.

Arthrocentesis is fundamental to the diagnosis of inflammatory joint disorders (see ch. 94). At least four joints (for example, both carpi and both tarsi) are routinely sampled, regardless of physical examination findings. Abnormal synovial fluid can be detected in the absence of either pain or joint swelling. It is common to obtain <0.2 mL of synovial fluid and in many cases only slides for cytologic evaluation can be prepared. Larger volumes allow culture and/or nucleated cell counts; however, slide preparation is sufficient for diagnostic purposes in most cases. The viscosity of synovial fluid is evaluated after its expulsion from the needle. Normal synovial fluid produces a 1-2 cm strand between the needle and slide; abnormal joint fluid loses viscosity and strand formation decreases. Red cell contamination of joint fluid confounds interpretation. Care must be used to avoid surface blood vessels, use gentle technique, and release negative pressure from the syringe prior to removing the needle from within the joint space.

Interpretation of Synovial Fluid Cytology

Degenerative joint disease, trauma, and previous ligament injury are associated with mononuclear inflammation (<10% neutrophils in synovial fluid) whereas immune-mediated and infectious diseases are associated with >10% neutrophils (see ch. 74). Blood contamination alters the differential cell count and makes the interpretation of inflammation less certain. In the presence of marked blood contamination, cytologic results from additional joints, along with comparison to peripheral blood counts, must be utilized.

Treatment (Dogs)

Corticosteroids (prednisone, prednisolone) are highly effective. Prednisone 1-2 mg/kg PO q 24 h is started initially; lower dosages can be effective in less severe cases. High dosages are administered until the disease is in complete remission, defined as resolution of clinical signs as well as laboratory changes that were present initially. After remission is attained, the dosage is tapered, generally by half, for approximately 4 weeks. Reevaluation is performed and if signs of disease are absent (on physical and laboratory evaluation), the dosage is halved again. Tapering is repeated monthly until the animal either relapses or stops medication. The recommended minimum duration of therapy is 4 months. Vaccine- or drug-related cases might not require as long a duration of therapy. If relapse occurs during the taper, the dosage should be increased to the most recently effective dosage.

Combination immunosuppressive therapy with the addition of mycophenolate mofetil often is more effective, and produces fewer adverse effects, than corticosteroid therapy alone (see ch. 165). Prednisone (1 mg/kg PO q 12-24 h) and mycophenolate (10 mg/kg PO q 12 h) are administered in combination. The dosage of prednisone is tapered every 2 weeks while mycophenolate is continued at the same dosage. The goal is to discontinue corticosteroids completely and maintain remission with mycophenolate alone. If, after 2 months, remission is maintained on mycophenolate alone, the dosage is halved for 2 months, and then discontinued. Animals that relapse after discontinuation of mycophenolate are reinduced with a short course of prednisone; mycophenolate (10 mg/kg PO q 12-24 h) is then continued for life. Side-effects of mycophenolate are generally mild (diarrhea) and hematologic side-effects are uncommon.

Inability to control the signs of IMPA using mycophenolate alone may prompt a change of therapy. Mycophenolate is discontinued and leflunomide (2-4 mg/kg PO q 24 h) is administered together with corticosteroids. Corticosteroids are again tapered, with the goal of complete discontinuation. If good control is maintained for several months on leflunomide alone, the dosage may be gradually tapered (2-4 mg/kg PO q 48 h × 3 months, then q 72 h × 3 months, and then discontinued). Relapses are treated with a short course of corticosteroids and the dosage of leflunomide that previously maintained remission. Side-effects of leflunomide generally are mild (anorexia, lethargy, vomiting); however, CBCs and serum levels of liver enzymes should be monitored.

Patients receiving NSAIDs (carprofen, meloxicam, deracoxib, etc.) require special attention. When combined with NSAIDs, corticosteroids are associated with high risk of gastrointestinal ulceration. Therefore, for any transition from NSAIDs to corticosteroids, NSAIDs should be discontinued with a 7-day "washout" period prior to corticosteroid administration. Administration of mycophenolate or leflunomide may begin during this washout period and alternative pain medications (tramadol and/or acetaminophen in the dog) started. After 7 days, corticosteroids may be added if there is a lack of response to initial therapy.

Lack of response or inability to taper corticosteroids may prompt consultation with an internal medicine specialist. Alternative immunosuppressants may include azathioprine, cyclosporine, chlorambucil, or cyclophosphamide.

Treatment (Cats)

Some cats do not respond to prednisone and an alternate corticosteroid (prednisolone, methylprednisolone, triamcinolone, or dexamethasone) needs to be substituted. Chlorambucil may be administered along with corticosteroids for cats that require additional immunosuppression. Chlorambucil is dosed at 15 mg/m^2 PO q 24 h (often 4 mg/cat/day) for 4 days, and the 4-day treatment is repeated every 3 weeks. Alternatively, 2 mg chlorambucil (total dose) may be administered every 2 to 3 days. Potential side-effects can include anorexia and bone marrow suppression. In cats, the dosage of chlorambucil should be tapered before the prednisone is tapered. Treatment with methotrexate and leflunomide also have been described (see "Rheumatoid Arthritis," below).

Follow-Up

The need for and timing of reevaluation are dependent on the clinical response of the patient, requirement for monitoring of concurrent disease, laboratory abnormalities, and avoidance of drug-related side-effects. Since the expected response of idiopathic IMPA cases is good with corticosteroid administration, a lack of response to corticosteroids within 7 days should prompt reevaluation. This should include reconsideration of the diagnosis, assessment of the dosage and proper administration of drugs, and consideration of possible drug-related side-effects.

Previous laboratory abnormalities (anemia, thrombocytopenia, or proteinuria) should be monitored. Rapid resolution of thrombocytopenia, gradual resolution of anemia (most commonly due to anemia of chronic disease with resolution over several weeks) and either slow resolution (months) or stability of proteinuria are expected. Administration of corticosteroids is associated with proteinuria and its effect must be considered. Progressive proteinuria can suggest glomerular injury, and standard treatment for glomerular disease can be warranted in such cases. The skin and urinary tract should be monitored for infection.

Repeated/serial arthrocentesis is not routinely recommended; instead, patients are monitored by clinical evaluation. In selected cases with joint instability or concurrent degenerative change, repeated synovial fluid analysis could be needed to determine if lameness is due to inadequate control of immune-mediated disease. C-reactive protein might represent a serologic marker of clinical response.[19]

Prognosis

A rapid response to immunosuppressant therapy is expected in most (90%) cases. Some patients respond promptly and can be tapered off medication completely. Many others will respond but require some dosage of immunosuppressant to avoid relapse. Some (10%) fail to respond and suffer continued lameness along with progressive joint damage. Many patients suffer side-effects related to corticosteroid therapy effects, especially when long-term administration is needed. Many dogs are euthanized due to these effects and an important goal is avoidance of medication-related harm. Weight gain is a serious problem; many owners are unaware of it and body condition should be carefully monitored (see ch. 2). One successful strategy to decrease glucocorticoid-induced adverse effects is the use of an additional immunosuppressive agent, as described above. Administration of mycophenolate, cyclosporine, or leflunomide is—for most patients—safer than long-term corticosteroid use.

Erosive Immune-Mediated Polyarthropathies

Erosive arthritis is distinguished by the presence of radiographically visible subchondral bone lysis (see Figure 203-1). Destruction of supportive joint ligaments leads to joint instability and luxation.

Breed Associated

A severely erosive polyarthritis has been described in young Greyhounds.[20] A single case suggested *Mycoplasma spumans* as the causative agent; however, *Mycoplasma* was not isolated from two additional Greyhounds. The true cause is unknown and the prognosis is guarded to poor.

Feline Periosteal Proliferative Arthritis

Erosive joint disease in cats includes two syndromes: one showing marked periosteal new bone formation (periosteal proliferative form), and another showing minimal periosteal new bone formation (rheumatoid arthritis).[21] Treatment is as for rheumatoid arthritis (see below).

Rheumatoid Arthritis

In dogs and cats, rheumatoid arthritis (RA) is a rare disorder characterized by inflammation, articular

cartilage loss, erosion of periarticular bone, and joint deformation. Many patients have a positive rheumatoid factor (RF) serologic test result. The cause of RA is unknown and the prognosis guarded. Many patients become severely disabled despite treatment.

Rheumatoid arthritis is suspected by the presence of radiographically visible erosive lesions and/or joint instability. The age at diagnosis in dogs averages 5 years. Approximately 1/3 of cases exhibit fever, lethargy and/or inappetence in addition to lameness.[22] Most dogs demonstrate joint pain, decreased range of motion, and palpable evidence of joint effusion. Joint deformation differentiates these cases from non-erosive polyarthritis. Although by definition RA is a disease that involves the joints, other body systems also can be affected.

Feline RA is very rare. Gradual onset of stiffness with swollen and painful joints is typical. Radiographically, erosive polyarthritis in the cat has been separated into one group with primarily bone lysis (RA) and another with marked periosteal proliferation adjacent to joints (periosteal proliferative polyarthritis). It is unclear if these diseases are separate entities or if they represent different manifestations of the same disease process.

Rheumatoid factor is a collective term for autoantibodies against IgG. These antibodies are thought to play a role in opsonization and elimination of immune complexes. Serum RF levels can be elevated in any inflammatory disease, and the utility of the test is limited by lack of specificity for RA. Approximately 70% of dogs with clinically diagnosed RA are positive for RF; therefore, its absence does not exclude the diagnosis. The concentration of RF, if present, can be useful to follow the course of disease: a decrease in RF concentrations can be associated with effective therapy and an increase with relapse of disease.

Diagnostic testing includes a CBC with manual differential, platelet count, biochemical profile, urinalysis, radiographs of the affected joints and thorax, and synovial fluid analysis. Cats may be tested for feline leukemia virus and feline immunodeficiency virus. Radiographic findings include loss of bone at the epiphyses, narrowing of joint spaces, and irregular joint margins. Erosive mono- or oligoarthropathies prompt synovial fluid culture for bacteria, *Mycoplasma* spp., and if possible, L-form bacteria. Most cases initially are treated with antibiotics pending results of culture. Doxycycline, minocycline, or a fluoroquinolone is the drug of choice.

Immunosuppression is the mainstay of therapy for immune-mediated erosive arthritis. Prednisone and mycophenolate, as described above for treatment of IMPA, are recommended for dogs. Treatment of cats with methotrexate 7.5 mg PO once a week (q 7 days) and leflunomide 10 mg PO q 24 h has been described with marked improvement in 7 of 12 treated cats.[23] When marked clinical improvement occurred, the dosage was decreased to 2.5 mg methotrexate once a week and 10 mg leflunomide every 3-4 days (twice a week). Serious signs of toxicosis were not noted.

Drugs used in humans with RA include the IL-1 antagonist anakinra and the TNF-alpha inhibitors infliximab, adalimumab, certolizumab pegol, golimurnab, and etanercept. There are no published reports of their use in dogs with RA. Adalimumab was used in two dogs with dermatopathy.[24]

Prognosis

RA is a relentlessly progressive disorder and most patients experience joint deterioration over time. Small dogs can fare reasonably well despite obvious joint deformation; larger dogs less well. Pain medications (tramadol, acetaminophen [dogs only], gabapentin, amantadine) often are needed (see ch. 164 and 356). Surgical procedures occasionally can be used for improving joint stability and pain; synovectomy, arthroplasty, joint replacement, and/or arthrodesis can be beneficial in selected patients.[25] Monitoring for side-effects of immunosuppressive medications as well as systemic manifestations of immune-mediated disease is suggested.

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CHAPTER 204

Immune-Mediated Dermatologic Disorders

Petra Bizikova

Client Information Sheet: Canine Pemphigus Foliaceus

Immune-mediated dermatoses encompass a broad spectrum of diseases that result from aberrant immune responses damaging skin and/or skin adnexae. Such immune responses can be directed against self-antigens primarily (autoimmune skin diseases; e.g., pemphigus, epidermolysis bullosa acquisita, cutaneous lupus), or against foreign antigens (drugs, viruses, or bacteria), which leads to an immunological reaction that damages the host tissue (secondary immune-mediated diseases; e.g., erythema multiforme, vaccine-induced vasculitis). Based on reported data, primary immune-mediated skin diseases (excluding hypersensitivity) account for <5% of all canine and feline dermatoses.[1-3] Because of their rarity, they often present a diagnostic challenge for clinicians. This chapter provides an overview of the more common autoimmune dermatoses to assist clinicians in a diagnostic process, while the accompanying table includes a more extensive list of diseases (Table 204-1).

TABLE 204-1

Overview of Selected Autoimmune Skin Diseases of Dogs and Cats*

PATHOGENESIS	DISEASE (SPECIES, BREED PREDISPOSITIONS)†	CHARACTERISTIC SKIN LESIONS	CHARACTERISTIC LESION DISTRIBUTION	MAJOR AUTOANTIGEN‡	DIAGNO
Diseases of the epidermis *Disorders of epidermal cohesion Superficial*	**Pemphigus foliaceus** (dog [Chow-Chow, Akita], cat)	Pustules, shallow erosions and crusts	Nasal planum, dorsal nose, eyelids, concave pinnae, footpads, (+ nail beds and nipples in cats); no mucosal involvement	Desmocollin-1	1. Cli rap ero pre fac 2. His epi pus neu clu ker 3. R/C neu dis tox sta pyc der 4. IF: bou (di circ ant 5. Au det

					circ targ (if a
Deep	**Pemphigus vulgaris** (dog, cat)	Flaccid vesicles, deep erosions	Mucosae and mucocutaneous junctions, concave pinnae	Desmoglein-3	1. Clin mu pre ves ulc 2. His aca 3. IF: bou (din circ ant 4. Au det circ targ
Deep	**Paraneoplastic pemphigus** (dog, cat)	Flaccid vesicle, deep erosions	Mucosae and mucocutaneous junctions, haired skin	Desmoglein-3 + plakins (dog)	1. Clin mu pre ves ulc nec 2. His aca and at r epi 3. IF: bou (din circ ant 4. Au det circ targ and
Disorders of dermo-epidermal cohesion	**Mucous membrane pemphigoid** (dog [GShep], cat)	Tense vesicle, deep erosions, ulcers, scarring, depigmentation	Mucocutaneous junctions, mucosae	Collagen XVII	1. Clin mu pre ves ulc wit 2. His ves var infl 3. IF: to p IF) ant pre epi salt (inc spl 4. Au

					det circ tar or l
	Epidermolysis bullosa acquisita (dog (GD])	Tense vesicle, deep erosions, ulcers	Haired skin predominant (footpads, friction areas) as well as mucosae and mucocutaneous junctions	Collagen VII	1. Cli mu ves dis 2. His sub ves var mo infl 3. IF: to p IF) ant ma sid sub 4. Au det circ tar
	Bullous pemphigoid (dog, cat)	Tense vesicle, deep erosions, ulcers	Haired skin predominant (concave pinnae, friction areas)	Collagen XVII	1. Cli pre and 2. His sub ves var infl 3. IF: to p IF) ant pre epi spl (inc 4. Au det circ tar
Disorders of keratinocyte cell death *Cutaneous lupus erythematosus*	**Discoid lupus erythematosus, classic form** (dog, cat)	Depigmentation, skin atrophy (loss of nasal planum architecture), erosions, scaling, crusting	Nasal planum	n.d.	1. Cli dep atr nas per 2. His int bas thi 3. IF: the epi
	Discoid lupus erythematosus,	Hyperpigmented annular or polycyclic plaques with	Generalized	n.d.	1. Cli pre

	generalized form (dog)	scaling and erosions, scarring			hyp pla and 2. His inte bas thi 3. IF: the epi
	Mucocutaneous lupus erythematosus (dog [GShep])	Erosions,ulcers, reticulated hyperpigmentation	Mucocutaneous junctions (genital/perigenital, anus/perianal, perioral, periocular) and surrounding haired skin	n.d.	1. Cli ulc mu jun 2. His inte bas 3. IF: the epi
	Vesicular cutaneous lupus erythematosus (dog [Col, Shetl])	Papules, flaccid vesicles, polycyclic erosions and ulcers	Groin, axillae, ± mucocutaneous junction	Soluble nuclear antigens	1. Cli pre and 2. His inte pro dea ves 3. IF: the epi
	Exfoliative cutaneous lupus erythematosus (dog [GSP])	Scaling, alopecia, erosions	Head, face, ears, dorsum	n.d.	1. Cli alo on lam her abr 2. His inte occ ade seb 3. IF: the epi
Disorders of melanocytes	**Uveodermatologic syndrome, VKH** (Akita, NB)	Leukoderma/leukotrichia, erythema, erosions, crusts	Face (periocular, nasal planum and muzzle) predominantly; uveitis	n.d.	1. Cli pre leu leu 2. His inte occ ade seb
	Vitiligo (dog [Doberman?], cat [Siamese?])	Macular leukoderma, leukotrichia	Face (nose, lips, eyelids) predominantly	n.d.	1. Cli pre leu leu 2. His

					me me ker lym me
Diseases of skin adnexae *Disorders of hair follicles*	**Alopecia areata** (dog [Dachshund?])	Alopecia, leukotrichia (newly regrown hair)	Face predominantly ("alopecic goggles")	Trichohyaline, hair follicle keratins	1. Cli nor spc wh reg 2. His me ker
Disorders of the sebaceous glands	**Sebaceous adenitis** (dog [Akita, Samoyed, Havanese], cat)	Scaling, follicular casts, poor hair coat quality, alopecia	Generalized (often starting on the head)	n.d.	1. Cli cas silv 2. R/C foll cas der der bac 3. His pyc seb of s
Disorders of the claws	**Symmetric lupoid onychodystrophy** (dog [GShep, GSett])	Paronychia, onychalgia, onychoschizia, onychomadesis, onychodystrophy	Claws and claw beds exclusively	n.d.	1. Cli at t mu fou mis 2. His inte the
Others	**Polychondritis** (cat)	Bilateral pinnae swelling, erythema and deformation	Pinnae (other cartilages can be involved)	n.d.	1. Cli swe def pin 2. His deg and stai the

*Table references for this chapter are found on the companion website at ExpertConsult.com.

†Species in which the disease has been recognized.

‡Major antigen is defined as an antigen recognized by circulating (serum) autoantibodies in more than 50% of affected dogs.

§Test is optional (can further support diagnosis, but test availability varies).

Abs, Antibodies; *BMZ*, basement membrane zone; *Col*, Collie; *GD*, Great Dane; *GShep*, German Shepherd; *GSett*, Gordon Setter; *GSP*, German Shorthaired Pointer; *histo*, histopathological assessment of skin biopsy specimen; *IF*, immunofluorescence; *NB*, nordic dog breeds; *n.d.*, not determined; *R/O*, rule out; *Shetl*, Shetland Sheepdog; *VKH*, Vogt-Koyanagi-Harada syndrome.

Pemphigus Foliaceus (PF)

Pemphigus foliaceus (PF) is the most common autoimmune skin disease of dogs and cats.[4] It is caused by autoantibodies that disrupt desmosomal adhesion between keratinocytes, and induce subcorneal pustules.[5] Desmocollin-1 is a major target autoantigen in canine PF; in cats, target autoantigens remain unknown.[6]

Signalment

Akitas and Chow Chows are predisposed to PF, though PF has been reported in other breeds, such as the English Bulldog, Doberman, Collie, and Australian Sheepdog.[7-10] The mean age of onset is ≈6 years (range: <1-16 years) and there is an equal risk for males and females.[7,8,10,11] In cats, no breed or sex predisposition has been recognized,[8,12] and the median age of onset is ≈5.5 years (range: <1-17 years).[8,12,13]

Clinical Signs

The primary, and diagnostically most valuable, skin lesion characteristic of canine and feline PF is the subcorneal pustule. However, pustules progress rapidly into secondary erosions and crusts, which may represent the only clinical findings during the physical examination. The majority of dogs and cats exhibit initial lesions on the face, particularly on the nasal planum, dorsal aspect of the nose, periocular areas, and the concave pinnae (Figures 204-1 and 204-2).[7,8,12] More than half of patients will progress towards the generalized phenotype involving additional body regions such as the trunk and/or paw pads.[9,10,12] Paw pad lesions are characterized by prominent hyperkeratosis, crusting and fissuring (see Figure 204-1). Pustules occasionally can be found at the margins of the paw pads. In pesticide-triggered PF, a clinical entity described recently in association with flea preventatives such as ProMeris Duo, Certifect, and Vectra 3D, the initial lesion always is present between the dorsal margins of the scapulae, which corresponds to the product application site. In 2/3 of these dogs, lesions can become generalized, and mimic naturally occurring PF both clinically and histologically.[14-16] In cats, ungual folds often are affected, and nipples can be involved (see Figure 204-2).[12] In contrast to other pustular dermatoses such as bacterial pyoderma or pustular dermatophytosis, skin lesions in PF are bilaterally symmetrical.

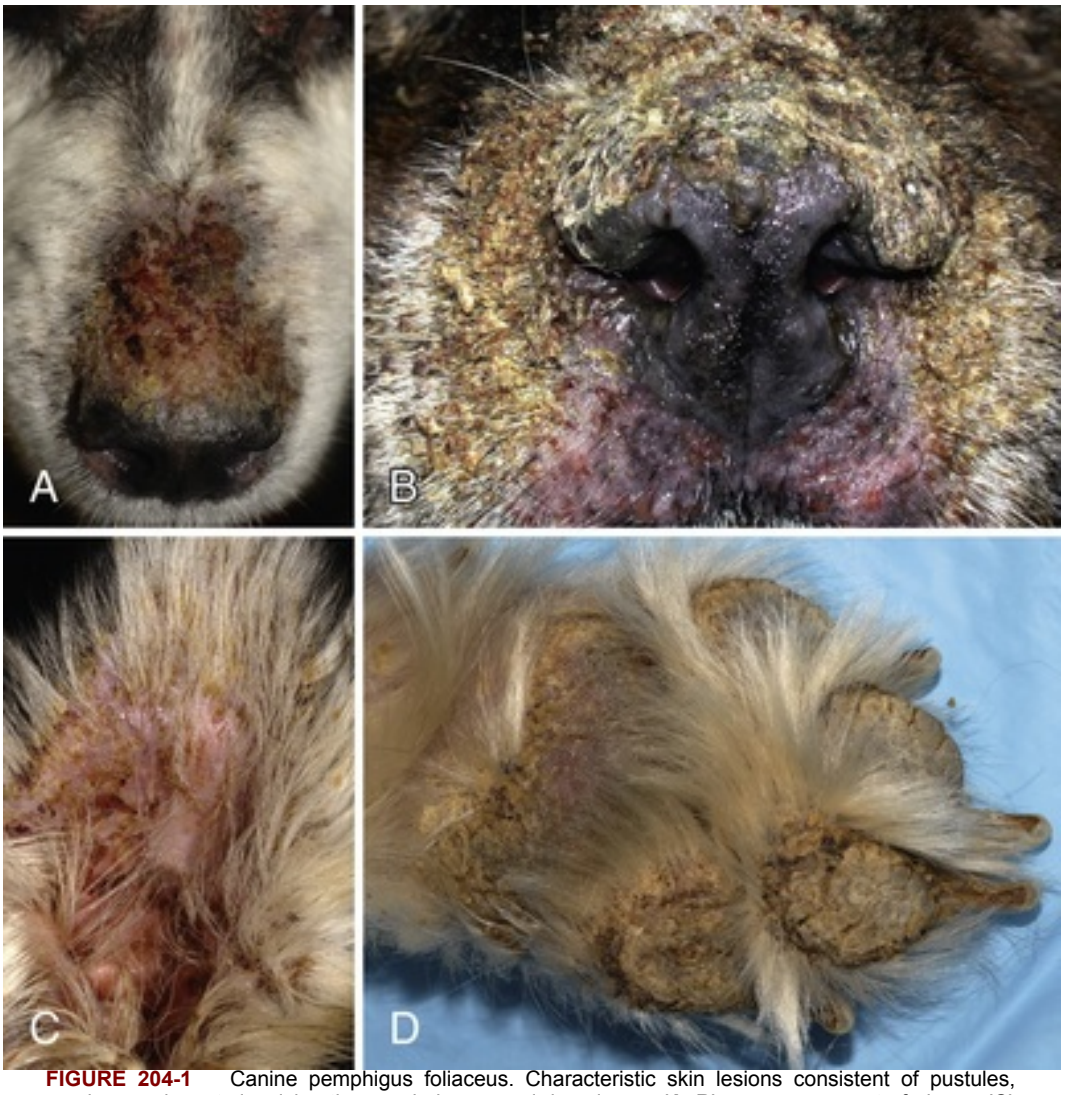

FIGURE 204-1 Canine pemphigus foliaceus. Characteristic skin lesions consistent of pustules, erosions and crusts involving the nasal planum and dorsal nose **(A, B),** concave aspect of pinnae **(C)** and paw pads **(D).**

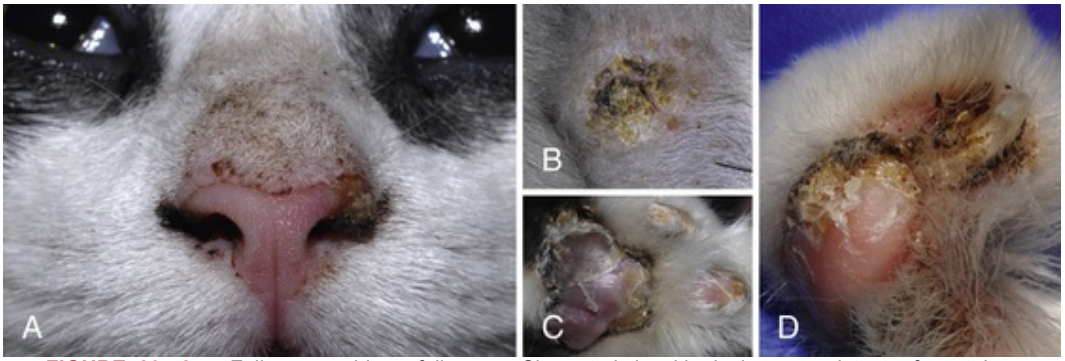

FIGURE 204-2 Feline pemphigus foliaceus. Characteristic skin lesions consistent of pustules, erosions and crusts involving the nasal planum and dorsal nose **(A),** area of a nipple **(B),** paw pads **(C)** and claw folds **(D).**

Diagnostic Approach

Relevant differential diagnoses include other primary pustular dermatoses such as bacterial pyoderma and pustular dermatophytosis. Acantholytic keratinocytes mixed with non-degenerated neutrophils and/or eosinophils on cytologic or histopathologic assessment of specimens raises suspicion of PF; however, acantholysis is not specific for PF and it can be detected with pyoderma or pustular dermatophytosis.[17,18] Therefore, the diagnosis of PF is based on the combination of: (i) skin lesion type and distribution, (ii) exclusion of an infection, and (iii) supportive histopathologic findings.[4] Direct immunofluorescence (IF) or immunohistochemistry (IHC) can be used for demonstrating antikeratinocyte antibodies in skin biopsies of dogs with PF, but results must be interpreted with caution because such antibodies have been detected in skin samples from other dermatoses.[7,8,19-21] Indirect IF demonstrates circulating (serum) antikeratinocyte autoantibodies in up to 84% of tested PF sera depending on the type of substrate utilized.[5,22] Unfortunately, 80% of sera from healthy dogs contain low titers of antikeratinocyte IgGs as well, decreasing the specificity of this test.[5] Finally, anti-desmocollin-1 serologic testing appears to be more specific for PF; however, this test currently is not offered commercially.[6]

Treatment

Historically, the standard of care for treatment of canine and feline PF relied on an immunosuppressive dosage of glucocorticoids (dogs: prednisone or prednisolone 2-6.6 mg/kg PO q 24 h; cats: prednisolone 2-5 mg/kg PO q 24 h or triamcinolone 0.6-2 mg/kg PO q 24 h).[7,8,10,12,23,24] If glucocorticoids alone were unable to provide sufficient resolution of clinical signs and/or if they caused too many side-effects, an additional immunosuppressive drug(s) such as azathioprine (dogs only: 2-2.5 mg/kg PO q 24 h), chlorambucil (0.2 mg/kg PO q 24-48 h) or cyclophosphamide (25 mg/m^2 PO q 24 h) was added.[7,8,10,12,23,25] Recently, cyclosporine at variable dosages (5-18 mg/kg PO q 24 h, with or without ketoconazole co-treatment) has been reported to be of some benefit in management of canine and feline PF.[13,26,27] In addition, treatment with topical glucocorticoids or tacrolimus should be considered in cases with localized skin lesions.

Mucous Membrane Pemphigoid (MMP)

Mucous membrane pemphigoid (MMP) is a subepidermal blistering skin disease recognized in humans, dogs and cats in which autoantibodies target collagen XVII or laminin-332 (laminin 5) of the basement membrane. Although rare, MMP is the most common autoimmune subepidermal blistering dermatosis (AISBD) recognized in veterinary medicine.[28] Because information about feline MMP is limited,[29] the following information pertains to the canine disease.

Signalment

MMP usually is diagnosed in adult dogs (median age 5 years), and males are affected 33% more often than females.[30] It affects a variety of breeds, but German Shepherd dogs are the most common (29%).[30]

Clinical Signs

MMP is a chronic mucosal and mucocutaneous blistering disease with a tendency to form scars (Figure 204-3). Deep erosions and ulcers are the most common lesions, while intact vesicles are seen only rarely. Scarring often is observed in chronic cases. A characteristic of this disease is the remarkable predilection of lesions for the oral cavity, other mucosae (eyes, genitalia, anus), perimucosal areas (mucocutaneous junctions) as well as the nose and concave pinnae. Truly cutaneous, not perimucosal, skin lesions are rare.[30,31]

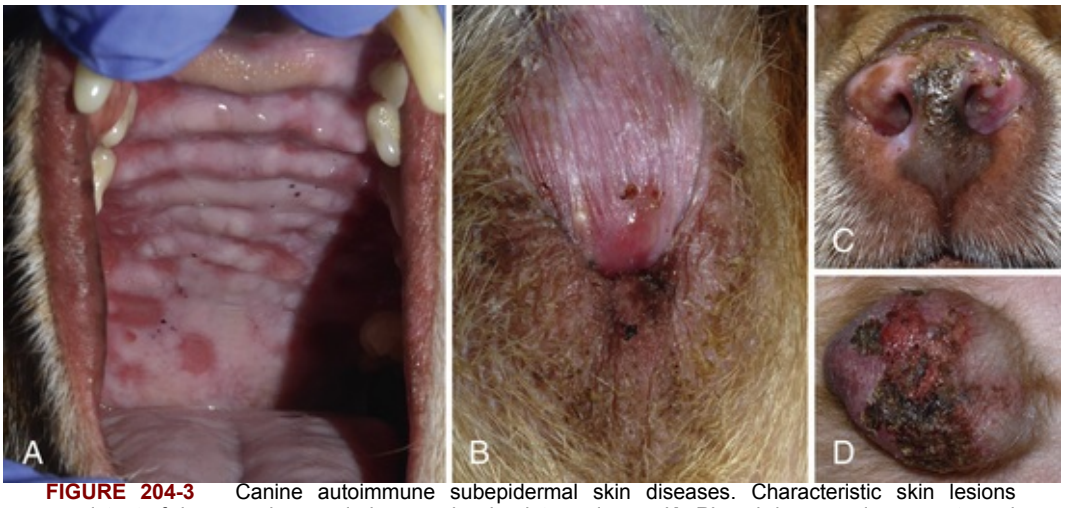

FIGURE 204-3 Canine autoimmune subepidermal skin diseases. Characteristic skin lesions consistent of deep erosions and ulcers on hard palate and anus **(A, B)** and deep erosions, crusts and scarring on the nasal planum and scrotum **(C, D).** (Photos courtesy Dr. H.L. Tham, case material NCSU.)

Diagnostic Approach

Relevant differential diagnoses include other subepidermal blistering diseases, pemphigus vulgaris and paraneoplastic pemphigus, mucocutaneous lupus erythematosus, and erythema multiforme major (see Table 204-1). Biopsies are required to confirm subepidermal vesiculation with or without inflammation and to rule out differentials. If an intact vesicle cannot be sampled, the edge of a fresh erosion may be the best choice to reveal microscopic blistering. Staining with periodic acid-Schiff (PAS) or for collagen IV can be used for demonstrating that the clefting arises above the lamina densa of the basement membrane zone (BMZ).[31,32] In addition, demonstration of tissue-bound and/or circulating anti-BMZ antibodies, and/or, if available, anti-collagen XII or laminin-332 antibodies, can further assist in the diagnostic process.[31]

Treatment

There is limited information about the treatment and outcome of canine MMP. Tetracycline and niacinamide (250-500 mg of each PO q 8 h) have been shown to be effective, especially in mild cases. If quality of life is impaired, treatment with oral glucocorticoids (e.g., prednisone/prednisolone 1-4 mg/kg PO q 24 h), with or without azathioprine, should be considered. Addition of topical glucocorticoids or tacrolimus is beneficial.[30]

Epidermolysis Bullosa Acquisita (EBA)

The diagnosis of EBA is given to approximately 25% of dogs with AISBD, making it the second most common AISBD in this species.[28] Autoantibodies targeting collagen VII, another BMZ protein, have been uncovered in most affected dogs.[33,34] This disease can occur in the context of classical systemic lupus erythematosus (SLE; see ch. 205), at which point it is recognized as a type-I bullous SLE.[35]

Signalment

EBA affects dogs of various breeds and ages, but more than half of them are young Great Danes. Males are twice as often affected as are females.

Clinical Signs

In contrast to MMP, EBA is a haired-skin–predominant disease with concurrent mucosal lesions. Early lesions present as erythematous and urticarial patches, usually on the face, axillae, abdomen, and inguinal region. They progress rapidly into tense vesicles, which rupture and evolve into widespread, often confluent, sharp-edged ulcerations. Oral epithelial sloughing is a common feature. Skin ulceration is most prominent in areas of friction such as axillae, inguinal region, and paw pads. Lethargy, fever, and anorexia are reported in the

majority of dogs with EBA.[36]

Diagnostic Approach

Relevant differential diagnoses include other AISBD with a skin-predominant phenotype (e.g., bullous pemphigoid), as well as other blistering diseases such as pemphigus vulgaris and paraneoplastic pemphigus, vesicular cutaneous lupus erythematosus, and erythema multiforme major/Stevens-Johnson syndrome (see Table 204-1). Biopsies are required to confirm subepidermal vesiculation containing neutrophils and some eosinophils. Staining with PAS or for collagen IV can be used for demonstrating that, in most cases, the blister arises below the lamina densa of the BMZ.[32] Demonstration of tissue-bound and/or circulating anti-BMZ antibodies, and/or anti-collagen VII antibodies, can further assist in the diagnostic process.

Treatment

The treatment outcome is variable. Approximately 30% of cases are euthanized due to lack of response to treatment. In the rest of the patients, the disease appears to be responsive to standard immunosuppressive treatment with glucocorticoids (e.g., prednisone/prednisolone 2-4 mg/kg PO q 24 h) and/or other immunosuppressive drugs.[36]

Cutaneous Lupus Erythematosus (CLE)

Cutaneous lupus erythematosus (CLE) is subdivided into four disease entities in veterinary medicine (see Table 204-1): vesicular cutaneous lupus (VCLE),[37,38] discoid lupus (DLE), which can be either classic facial or generalized,[1,39,40] exfoliative cutaneous lupus (ECLE),[41] and a newly described mucocutaneous lupus (MCLE).[42] The only form of CLE described in cats is the classic form of DLE.

Discoid lupus erythematosus ("classic" nasal variant) affects dogs and cats.[43,44] In both species, the lesions consist of erythema, depigmentation, and atrophy, often accompanied by erosions and ulcers (Figure 204-4, *A*). Lesions usually are present on the nasal planum and surrounding skin. A favorable response to a wide variety of treatments including tetracyclines and niacinamide has been reported.[45,46] Topical treatment with glucocorticoids or tacrolimus might be of benefit as well.[47]

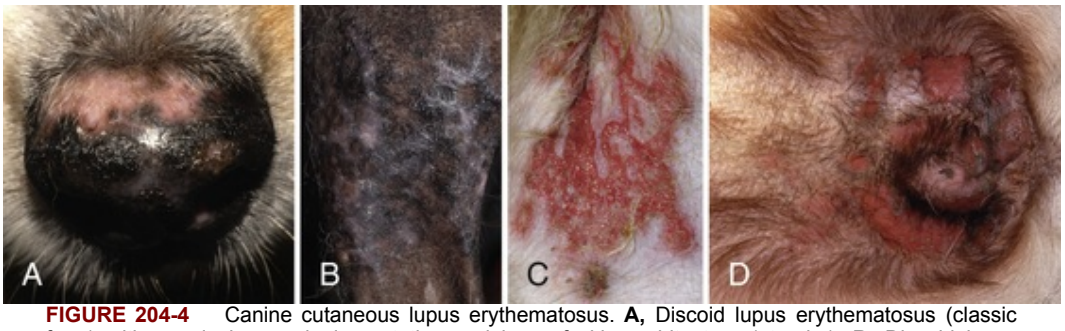

FIGURE 204-4 Canine cutaneous lupus erythematosus. **A,** Discoid lupus erythematosus (classic form) with nasal planum depigmentation and loss of skin architecture (atrophy). **B,** Discoid lupus erythematosus (generalized form) with polycyclic plaques with reticulated hyperpigmentation and central scarring. **C,** Vesicular cutaneous lupus erythematosus with polycyclic erosions and ulceration in the inguinal area. **D,** Mucocutaneous lupus erythematosus with erosions and ulcers affecting the mucocutaneous junction of the vulva and the adjacent haired skin. (**B,** Photo courtesy Dr. U. Oberkirchner, case material NCSU; **D,** Photo courtesy Dr. T. Olivry, case material NCSU.)

Discoid lupus erythematosus (generalized form) has been described in two dogs.[39,40] The main skin lesions consist of hyperpigmented annular plaques with fine scaling, central erosions, and scarring (Figure 204-4, *B*). No progression to systemic lupus erythematosus has been observed in these cases. One of the cases had a favorable response to hydroxychloroquine, while the other was treated successfully with cyclosporine.[39,40]

Vesicular cutaneous lupus erythematosus predominantly affects adult Collies, Shetland Sheepdogs, and their crossbreds. Females outnumber males. Dogs with VCLE present with erythema, flaccid vesicles and ulcers on glabrous skin of the abdomen, axillae, groin and medial thighs. Lesions are sharp-edged annular, polycyclic, or serpiginous (Figure 204-4, *C*). Some patients exhibit ulceration of mucocutaneous junctions, concave

pinnae, and the oral cavity. Skin lesions appear to respond to immunosuppression with orally administered glucocorticoids with or without azathioprine. Oral cyclosporine and topical tacrolimus are effective in some patients.[38,48,49]

Exfoliative cutaneous lupus erythematosus is a hereditary condition of German Shorthaired Pointers.[50] Females outnumber males. The main skin lesions of canine ECLE consist of spontaneous alopecia and scaling, later progressing to erosions. Lesions typically affect the muzzle, pinnae, and trunk. Glomerulonephritis, hematological abnormalities, and systemic signs such as lameness can occur with time, but a positive antinuclear antibody titer has not been reported consistently.[51] Response to therapy is poor. A favorable response might be obtained with high dosages of oral glucocorticoids with azathioprine and/or hydroxychloroquine, though most dogs end up being euthanized.[51]

Mucocutaneous lupus erythematosus predominantly affects German Shepherds, but other breeds can be affected. Females outnumber males. The main skin lesions consist of erosions and ulcers predominantly involving the genital and anal mucocutaneous regions, and spreading to adjacent skin (Figure 204-4, *D*). A favorable response to a wide variety of treatments has been reported, and oral glucocorticoids appear to provide the fastest resolution.[46,52]

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CHAPTER 205

Systemic Lupus Erythematosus

Michael Stone

Client Information Sheet: Systemic Lupus Erythematosus

Veterinary patients with systemic lupus erythematosus (SLE) classically demonstrate at least two separate manifestations of autoimmunity in addition to the presence of antinuclear antibody (ANA). However, some patients demonstrate clinical features of multisystemic autoimmunity yet lack serum ANA.

Pathogenesis

Autoimmune disease may be defined as a clinical syndrome caused by activation of the immune system in the absence of an infection or other discernible cause. With SLE, immune system dysregulation leading to immune complex formation is postulated to induce tissue damage (type III hypersensitivity); however, direct antibody-mediated cytotoxicity (type II hypersensitivity) and cell-mediated autoimmunity (type IV hypersensitivity) also occur.

Effectors of SLE

Pathogenic Antibodies

SLE patients produce antibodies directed against a broad range of nuclear, cytoplasmic, and cell membrane molecules. Autoantibodies can cause damage through the formation of immune complexes, opsonization of target cells, and interference with cellular physiology.[1]

Pathogenic Immune Complexes

Immune complexes, formed when antibody meets antigen, are normally removed by the mononuclear phagocyte system. Elevated levels of circulating immune complexes can occur with persistent autoantibody production and/or defective clearance mechanisms. Immune complexes deposit near blood vessels where there is physiologic outflow of fluid, such as glomeruli, synovia, and choroid plexi. Trapped immune complexes activate complement, attract inflammatory cells, and cause tissue damage.[2]

Autoreactive T Cells

T cells can cause direct tissue damage in SLE. Dermatologic and renal lesions have been associated with cytotoxic T cell–mediated damage.[3]

Genetics of SLE

Many genes have been associated with the development of SLE in humans, most encoding proteins involved with immune system function[1]: the major histocompatibility complex, cytokines, antigen receptors, members of cytokine- or antigen-signaling cascades, and others. Protective genes exist that prevent the development of SLE. In dogs, SLE clearly is inherited and experimental colonies of dogs with SLE have been established.[4-6] SLE in dogs has been associated with the allele DLA A7,[7] the DRB1 locus in Nova Scotia Duck Tolling Retrievers,[8] a specific allotype of the fourth component of complement,[9] and decreased serum IgA.[10] A negative (or "protective") association exists with DLA A1 and B5.[7] SLE might occur more frequently in purebred cats, also suggesting genetic influence.[11]

Environmental Factors and SLE

The lower-than-expected rate of SLE concordance among human identical twins demonstrates the importance of environmental triggers.[12] Exposure to UV light causes disease flares in humans with SLE and has been reported in both dogs[5,13] and cats.[14] 90% of SLE cases occur in women, suggesting influence by estrogen and prolactin, or the protective effects of testosterone; gender predilection has not been identified in the dog or cat. Exposure to infectious agents in early life might suppress the development of allergic and autoimmune disorders.[15] It has been suggested that allergy and autoimmune disease are related to decreased exposure to infectious agents during early development, causing inadequate stimulation.[16]

Drugs and SLE

Certain drugs can induce SLE-like disease in humans[17] (Box 205-1), likely different from true SLE. Clinical manifestations of drug-induced lupus in humans include arthritis, serositis, fatigue, malaise, and low-grade fever; nephritis and neurologic disease are rare. The manifestations disappear in most patients within a few weeks of discontinuation of the offending drug, never to reappear unless reexposure occurs.[18] In cats, ANA has occurred with hemolytic anemia and thrombocytopenia (propylthiouracil)[19] or without clinical signs of SLE (methimazole).[20] Hydralazine has been associated with development of ANA in the dog.[21]

Box 205-1

Causes of Drug-Induced SLE in Humans

Allopurinol	Leuprolide acetate	Prazosin
Aminoglutethimide	Lithium	Primidone
Aspirin	Lovastatin	Procainamide
Atenolol	Mephenytoin	Promethazine
Captopril	Methimazole	Propranolol
Carbamazepine	Metoprolol	Propylthiouracil
Chlorpromazine	Mesalazine	Quinidine
Cimetidine	Minocycline	Spironolactone
Clonidine	Minoxidil	Statins (atorvastatin, lovastatin, etc.)
Danazol	Nalidixic acid	Streptomycin
Diphenylhydantoin	Nitrofurantoin	Sulfasalazine
Disopyramide	Penicillamine	Sulfonamides
Enalapril	Penicillin	Tetracycline
Griseofulvin	Phenothiazines	Timolol eye drops
Hydralazine	Phenylbutazone	Valproate
Isoniazid	Phenytoin	
Labetalol	Piroxicam	

Adapted from Chang C, Gershwin M: Drug-induced lupus erythematosus. *Drug Safety* 34:357-374, 2011.

Infectious Agents and SLE

No infectious agents have been identified that cause SLE. However, it is likely that infections can precipitate the development of clinical signs in patients with the appropriate predisposing genes for SLE. Microbial antigens can initiate autoreactivity through molecular mimicry, polyclonal activation, or the release of previously sequestered antigens.[22] The immunogenicity of autoantigens might be increased by inflammation, explaining why flares of immune-mediated disease can be induced by vaccination or infection. Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) can induce SLE-like disease in cats, and serum ANA can occur early in FeLV infection.[23] Whether FeLV- or FIV-induced disease is truly similar to SLE is debated.[24] Feline ehrlichial disease has been associated with positive ANA.[2,25]

In summary, the development of clinical signs depends on inheriting an appropriate number of

susceptibility genes to SLE, a lack of protective genes, and an environmental stimulus that sets the whole process into action.

Clinical Findings

The typical age at diagnosis in dogs is 3-7 years, although patients from 6 months to 13 years of age have been reported. Cats have been diagnosed at 1 to 11 years of age.

The clinical signs reported in dogs and cats with SLE are summarized in Table 205-1.

TABLE 205-1

Clinical Signs in Dogs and Cats with Suspected SLE

CLINICAL SIGN	PREVALENCE IN DOGS*	PREVALENCE IN CATS*
Nonerosive polyarthritis	236/302 (78%)	9/25 (36%)
Fever	186/275 (68%)	11/21 (52%)
Renal disorders	167/302 (55%)	10/25 (40%)
Dermatologic lesions	138/302 (46%)	15/25 (60%)
Lymphadenopathy/Splenomegaly	66/175 (38%)	
Leukopenia	54/302 (18%)	
Hemolytic anemia	45/302 (15%)	6/25 (24%)
Thrombocytopenia	40/302 (13%)	2/25 (8%)
Myositis	16/275 (6%)	
CNS disorders	16/302 (5%)	6/25 (24%)
Neuropathy	7/302 (2%)	

*Number of patients affected/number of patients described.

Summarized from references 11, 13, 14, 24, and 26-33.

CNS, Central nervous system.

Lameness due to nonerosive polyarthropathy is the most frequent primary complaint in dogs (see ch. 203). Smaller joints (carpi, tarsi, elbows, stifles) are involved most frequently. Synovial fluid analysis reveals neutrophilic inflammation (>10% neutrophils). In cats, articular signs also are common. Some cats can demonstrate joint swelling and abnormal synovial fluid yet lack signs of lameness.

Fever is reported frequently in both dogs and cats, and it can be either persistent or intermittent (see ch. 48).

In humans, the kidney commonly is involved, with biopsies demonstrating involvement in almost all SLE patients.[34] Renal involvement can be benign and subclinical or progressive and fatal. The earliest manifestation is proteinuria. In dogs with SLE, proteinuria (see ch. 72) and glomerular lesions (see ch. 325) also are frequent. Biopsy can reveal mesangial and/or endothelial hypertrophy, proliferative and/or membranous glomerulonephritis, and sclerotic changes. Proteinuria and/or glomerulonephritis is/are also reported commonly in the cat.

Cutaneous manifestations in dogs can include erythema, scaling, crusting, depigmentation, and alopecia. Lesions can develop in the skin, mucocutaneous junctions, and oral cavity. Preferential localization of lesions can occur in areas poorly protected by the hair coat and be exacerbated by exposure to sunlight. The cutaneous lesions in 25 reported cases in cats have included erythema, ulceration, crusts, and depigmentation of the face, ears, and paws in 7, biopsies consistent with pemphigus foliaceus or plasmacytic pododermatitis in 4, ulcerative stomatitis in 3, and a cornification disorder (seborrheic dermatitis) in one case.

Only rarely is anemia, leukopenia, or thrombocytopenia the presenting feature of human SLE without concomitant problems of the skin, joints, central nervous system (CNS), or cardiopulmonary system. In dogs, although the presence of anemia of chronic inflammation is common, hemolytic anemia is uncommon. Mild thrombocytopenia is noted in some patients, although severe thrombocytopenia can also occur. Leukopenia has been reported. Complement concentrations were decreased in three of eight dogs with suspected SLE in one study.[9] As in dogs, hemolytic anemia is uncommon in cats with SLE and severe thrombocytopenia rare.

Complement levels were decreased in one cat.[11]

Presence of the "lupus anticoagulant" has been reported in dogs and cats.[29,35,36] It is an antibody directed against membrane phospholipids. It causes *in vitro* prolongation of the activated partial thromboplastin time, which explains the name "anticoagulant." Paradoxically, the antibody's effect *in vivo* is to cause platelet activation, hypercoagulability, and thrombosis.

Memory impairment, headache, epilepsy, and personality changes can accompany SLE in humans. CNS involvement without other clinical or laboratory features of SLE is unusual. In cats, reported CNS manifestations have included hyperactivity; twitching of the ears, tail, and hindlimbs; hyperesthesia; vocalization; repetitive licking; neck ventroflexion; and seizures.[10] Polymyositis has been suspected in several dogs and cats, and polyneuritis, characterized by hyperesthesia, has been reported in a dog.[13]

In humans, pulmonary fibrosis, pulmonary embolism, pleural effusion, pericardial effusion, cardiac arrhythmias, and/or myocarditis can occur with SLE. Neutrophilic myocarditis was demonstrated in four dogs with SLE.[28] Subclinical lung changes were noted on thoracic radiographs of one cat,[11] but neither pleuritis nor pericarditis has been observed in cats with SLE.

Diagnosis

Criteria have been developed for the diagnosis of SLE in humans (E-Table 205-2), and these criteria can be modified to apply to veterinary patients (Table 205-3). Veterinary patients with SLE classically demonstrate at least two separate manifestations of autoimmunity along with a positive ANA titer. Patients with three or more separate manifestations of autoimmunity may also be considered to have SLE despite the absence of detectable ANA. The most common syndrome recognized in the dog is immune-mediated polyarthritis, in combination with immune-mediated skin disease, glomerulonephritis, hemolytic anemia and/or thrombocytopenia. Similar signs occur in the cat; however, CNS signs might be more common.

TABLE 205-3

Proposed Criteria for the Diagnosis of SLE

1. ANA	Abnormal ANA titer in the absence of drugs, infectious diseases, or neoplasia known to be associated with its development
2. Cutaneous lesions	Depigmentation, erythema, erosions, ulcerations, crusts, and/or scaling, with biopsy findings consistent with SLE
3. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless
4. Arthritis	Nonerosive, nonseptic arthritis involving two or more peripheral joints
5. Renal disorders	Glomerulonephritis or persistent proteinuria in the absence of urinary tract infection
6. Anemia and/or thrombocytopenia	Hemolytic anemia and/or thrombocytopenia in the absence of offending drugs
7. Leukopenia	Low total white blood cell count
8. Polymyositis or myocarditis	Inflammatory disease of the skeletal or cardiac muscle
9. Serositis	Presence of a nonseptic inflammatory cavity effusion (abdominal, pleural, or pericardial)
10. Neurologic disorders	Seizures, peripheral neuropathy, myopathy, or cranial nerve deficits in the absence of known disorders
11. Antiphospholipid antibodies	Prolongation of activated partial thromboplastin time that fails to correct with a 1 : 1 mixture of patient and normal plasma, in the absence of heparin or fibrin degradation products

ANA, Antinuclear antibody; *SLE*, systemic lupus erythematosus.

*A diagnosis of SLE is established if a patient manifests 3 or more criteria simultaneously or over any period of time.

Adapted from references 28 and 39-42.

E-TABLE 205-2

The American College of Rheumatology Revised Criteria for the Classification of SLE*

CRITERIA	DEFINITION
1. Malar rash	Fixed erythema, flat or raised over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless
5. Arthritis	Nonerosive arthritis involving 2 or more peripheral joints
6. Serositis	a. Pleuritis—pleuritic pain or rub or evidence of pleural effusion OR b. Pericarditis—pericardial effusion
7. Renal disorder	a. Persistent proteinuria OR b. Cellular casts—may be red cell, hemoglobin, granular, tubular or mixed
8. Neurologic disorder	a. Seizures—in the absence of offending drugs or known metabolic derangements or electrolyte imbalance OR b. Psychosis—in the absence of offending drugs or known metabolic derangements or electrolyte imbalance
9. Hematologic disorder	a. Hemolytic anemia—with reticulocytosis OR b. Leukopenia—<4,000/mm^3 on 2 or more occasions OR c. Lymphopenia—<1,500/mm^3 on 2 or more occasions OR d. Thrombocytopenia—<100,000/mm^3 in the absence of offending drugs
10. Immunologic disorder	a. Anti-DNA: antibody to native DNA in abnormal titer OR b. Anti-Sm: presence of antibody to Sm nuclear antigen OR c. Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) a positive test result for lupus anticoagulant, or (3) a false-positive serologic test for syphilis
11. Antinuclear antibody (ANA)	An abnormal titer of ANA at any point in time and in the absence of drugs known to be associated with "drug-induced lupus."

*For the purposes of identifying patients in clinical studies, a person shall be said to have SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

From Tan, 1982.[38]

Diagnostic testing of suspected SLE patients should include a complete blood count, serum biochemistry profile, urinalysis, imaging, synovial fluid cytology (see ch. 74 and 94), histopathologic examination of the skin (see ch. 86) and/or kidney (see ch. 89), and serum ANA titer. Cats should be tested for feline leukemia virus and feline immunodeficiency virus. Infectious and neoplastic disease must be excluded through imaging, culture of urine, blood and/or synovial fluid, serologic titers for tick-borne and fungal diseases, and therapeutic antibiotic trials. In tick-infested areas, a 3- to 7-day course of doxycycline should be considered prior to concluding the presence of immune-mediated disease.

Immunodiagnostic investigations may include Coombs' testing; screening for platelet autoantibodies and rheumatoid factor; coagulation testing for antiphospholipid antibodies; and testing for serum immunoglobulin, complement, circulating immune complex concentrations and endocrine autoantibodies (i.e., antithyroglobulin). Immunohistologic investigation may include immunohistochemical and immunofluorescence staining.[43]

Biopsies can be supportive but rarely are diagnostic of SLE by themselves. When the skin is biopsied, care should be taken to avoid ulcers or erosions, since an intact epidermis is necessary to substantiate the diagnosis (see ch. 86). Oral biopsy specimens rarely are beneficial, since ulcers, which are inherently not diagnostic, are common in this location. Erythematous areas adjacent to ulcers yield the most useful diagnostic results.[44] Histopathologic findings can reveal an interface dermatitis consisting of a mononuclear cell infiltrate at the epidermal-dermal junction, apoptosis and vacuolar change of the basal keratinocytes, and epidermal-dermal separation.

The diagnosis of SLE in cats is less well defined. In some studies, all cats with positive ANA test results were diagnosed with SLE but whether or not these patients truly had SLE is debatable. Another unanswered question is how to categorize FeLV- or FIV-positive patients: some reports include FeLV-positive cats while others exclude them.[11,24,29-31,45] Because of the possibility of ehrlichial disease, it has been recommended that all cats receive a course of doxycycline before the diagnosis of immune-mediated disease is made.[46]

Specific Testing

Lupus Erythematosus (LE) Cell Test

An LE cell is recognized as a neutrophil that contains phagocytized nuclear material. Because of technical and sensitivity problems, especially regarding subjectivity of interpretation of results (false-negative results are common), the LE cell test has been largely replaced by the more sensitive ANA test.[26,27,47] LE cells rarely can be seen on smears of pericardial, pleural, peritoneal, joint, cerebrospinal and blister fluid and, when present, are highly suggestive of SLE.

Antinuclear Antibodies

Antinuclear antibodies (ANAs) are a heterogeneous population of antibodies directed against various nuclear antigens. Although ANA testing is a cornerstone of the diagnosis of SLE, it has substantial limitations in veterinary medicine. There is no universally accepted protocol for ANA testing used by veterinary laboratories. The result of an ANA test is commonly reported as a serum titer and, sometimes, pattern of nuclear staining. The most commonly observed patterns are speckled or homogenous staining, but there is no clear association between patterns and the nature of clinical disease. A clinically significant titer must be distinguished from low ANA titers that may be present in up to 10% of normal animals and animals with any chronic inflammatory, infectious or neoplastic disease.[48,49]

In humans, substrates tend to remain comparable in their ability to detect common ANA but differ in the antibody titer.[50] In dogs, it has been suggested that multiple substrates be used in order to increase the sensitivity of the test.[51] Two canine studies found markedly different ANA results when rat liver and HEp2 cell substrate were compared[51,52]; however, results were well correlated in a third report.[53] Feline ANA test results have been found to have a low coefficient of correlation when identical sera are sent to different laboratories.[54]

In conclusion, the most appropriate substrate, conjugate, and methodology for ANA testing remain undefined and each laboratory's value should be interpreted individually. ANA-negative SLE cases have been described in veterinary patients,[5,26-28] and a positive ANA should be neither required nor sufficient in itself to make a diagnosis of SLE.

Autoantibodies

Suspicion of human SLE leads to testing for specific antibodies that provide diagnostic and prognostic information (E-Table 205-4). Similarly, certain autoantibody studies have been performed in veterinary patients (E-Table 205-5).

E-TABLE 205-4

Autoantibody Associations in Human SLE

EPITOPE	COMMENTS
ds-DNA	Highly specific for the diagnosis of SLE
Sm	Highly specific for the diagnosis of SLE. Associated with membranous nephropathy
RNP	Associated with Raynaud's phenomenon, pulmonary and muscle involvement
SS-A/Ro	Associated with cutaneous manifestations, sicca complex, neonatal lupus
SS-B/La	Associated with neonatal lupus
Phospholipid	Associated with thrombocytopenia, thrombosis, infertility

ds-DNA, Double-stranded DNA; *RNP*, ribonucleoprotein; *Sm*, *Ro*, *La*, extractable nuclear antigens named for the first two letters of the

patient from which the antigen was first described (Sm = Smith, etc.); *SS-A,* Sjogren's syndrome A antigen (or its equivalent, Ro); *SS-B,* Sjogren's syndrome B antigen (or its equivalent, La).

Data from Dall'Era, 2013.[34]

E-TABLE 205-5

Positive Autoantibody Results in Suspected Canine SLE Patients

EPITOPE	INCIDENCE*	INCIDENCE (PERCENT)	REFERENCE
ds-DNA	6/38	16	Costa 198455
	1/3		Bennett 198747
	1/47	2	Brinet 198856
	2/100	2	Monier 199257
	0/43		Monestier 199558
Sm	9/34	24	Costa 198455
	2/30	7	Hubert 19885
	12/75	16	Fournel 199213
	0/20		White 199359
	1/64	2	Henriksson 199860
RNP	4/38	10	Costa 198455
	0/12		Monier 19886
	0/30		Hubert 19885
	6/75	8	Fournel 199213
	0/20		White 199359
	5/64	8	Henriksson 199860
SS-A/Ro	1/12		Monier 19886
	0/30		Hubert 19885
	3/75	4	Fournel 199213
	0/20		White 199359
SS-B/La	0/30		Hubert 19885
	0/12		Monier 19886
	1/75	1	Monier 199257
	0/20		White 199359
"Type 1" (antibody to a 43-kd nuclear antigen, also known as hnRNP G)	10/38	38	Costa 198455
	15/75	20	Fournel 199213
"Type 2"	5/38	13	Costa 198455
	7/75	9	Fournel 199213
Phospholipid	1/1		

			Stone 199035
	2/20	10	Scott-Moncrieff 200136
	1/1 (feline)		Lusson 199937

*Number of positive patients/number of tested patients.

ds-DNA, Double-stranded DNA; *RNP*, ribonucleoprotein; *Sm, Ro, La*, extractable nuclear antigens named for the first two letters of the patient from which the antigen was first described (Sm = Smith, etc.); *SS-A*, Sjogren's syndrome A antigen (or its equivalent, Ro); *SS-B*, Sjogren's syndrome B antigen (or its equivalent, La).

Antibodies to DNA

Anti–double-stranded (native) DNA is highly specific for the diagnosis of human lupus, even though only 60-83% of patients are positive. Anti–double-stranded DNA has been found infrequently in dogs with SLE.

Extractable Nuclear Antigens

Extractable nuclear antigens (ENA) are molecules extracted from the soluble fraction of cell nuclei (DNA and histone proteins are insoluble and therefore excluded). The binding of serum antibodies to commercially available tissue extracts is the basis for serologic testing, and important ENA include Sm, Ro, La and ribonucleoprotein. In veterinary medicine, antibodies against ENA have not yet been shown to offer diagnostic or prognostic significance.

Antihistone Antibodies

Histones are a group of proteins that bind the DNA helical structure into supercoil formation. Histone antibodies are characteristic of drug-induced SLE in humans. Investigators at one university[13,56,57] detected antihistone antibodies in 61-72% of dogs with SLE. Antihistone antibodies have been detected in canine sera by other investigators; however, there was no significant difference in concentration between ANA positive and negative sera[52] and antihistone antibodies were detected in conditions other than canine SLE.[55] The use of antihistone antibodies as an indicator of drug-induced SLE in veterinary patients has not been reported.

Antiphospholipid Antibodies

Antiphospholipid antibodies bind to cell-associated phospholipids, such as the cell membrane. The antibody interferes with the function of procoagulant phospholipids in clotting tests *in vitro.* Patients with the lupus anticoagulant have prolonged activated partial thromboplastin time that fails to correct with a 1 : 1 mixture of the patient's plasma and normal plasma. In humans, their presence is associated with thrombocytopenia, thrombosis, and fetal loss. Antiphospholipid antibodies have been described in one dog with SLE,[35] 2 dogs with hemolytic anemia,[36] and one cat with SLE.[29]

Management

Sunlight should be avoided if photosensitization occurs. Most patients also require immunosuppression (see ch. 165 and 360). Prednisone 1-2 mg/kg PO q 24 h is started initially; lower dosages could be effective in cases that are less severe. These high dosages are administered until the disease is in complete remission, defined as resolution of clinical signs and laboratory changes that were present initially. After remission is attained, the dosage is tapered, generally in half, for ≈4 weeks. Reevaluation is performed, and if signs of disease remain absent on both physical and laboratory evaluations, the dosage is halved again. Rechecking and tapering are repeated monthly until the animal either relapses or stops medication. The recommended minimum duration of therapy is 4 months. If relapse occurs during taper, the dosage should be increased to the most recently effective dosage and held there for a few months. If the maintenance requirement is unacceptable because of corticosteroid-associated side-effects, an additional immunosuppressive agent is added.

Some cats do not respond to prednisone,[37] and an alternate corticosteroid (prednisolone, methylprednisolone, triamcinolone, or dexamethasone) should be substituted instead of, or prior to, adding additional immunosuppressant therapies.

For dogs, combination immunosuppressive therapy with mycophenolate mofetil often is more effective and has fewer adverse effects than corticosteroid therapy alone (see ch. 165). Prednisone (1 mg/kg PO q 12-24 h) and mycophenolate (10 mg/kg PO q 12 h) are administered in combination. The dosage of prednisone is

tapered every 2 weeks while mycophenolate is continued at the same dosage. The goal is to discontinue corticosteroids completely and maintain remission with mycophenolate alone. If remission is maintained on mycophenolate alone for 2 months, the dosage is halved for an additional 2 months, and, barring recurrence, then is discontinued. Animals that relapse after discontinuation of mycophenolate are reinduced with a short course of prednisone; mycophenolate (10 mg/kg PO q 12-24 h) then is continued for life. Side-effects of mycophenolate are generally mild (diarrhea) and dosage related; hematologic side-effects are uncommon.

For cats that require additional immunosuppression, chlorambucil may be administered along with corticosteroids. Chlorambucil is given to cats at 15 mg/m^2 (4 mg dose for most cats) PO q 24 h for 4 days and repeated every 3 weeks. Alternatively, 2 mg chlorambucil (total dose) may be administered every 2-3 days. Potential side effects include anorexia and bone marrow suppression; blood counts should be monitored periodically. In cats, the dosage of chlorambucil should be tapered before the prednisone is tapered.

Lack of response or inability to taper corticosteroids while maintaining remission should prompt consultation with an internal medicine specialist. Alternative immunosuppressants may include azathioprine, cyclosporine, chlorambucil, cyclophosphamide, or leflunomide.

One therapeutic approach in dogs included prednisone (1-2 mg/kg PO q 24 h) combined with levamisole (2-5 mg/kg, max 150 mg PO q 48 h).[13] The prednisone was tapered and discontinued after 2 months, while levamisole was given continuously for 4 months and then stopped. If there was relapse of disease, levamisole was readministered for a further 4-month period. Approximately 75% of dogs treated with such therapy were reported to attain remission. Side-effects included agranulocytosis, excited behavior, and aggression.[42]

In humans, an antimalarial drug such as hydroxychloroquine can provide additional relief. Antimalarial agents have multiple sun-blocking, antiinflammatory, and immunosuppressive effects, although their mechanism of action is not understood completely.[61] Their use has not been reported in dogs or cats with SLE.

Marked proteinuria (urine protein/creatinine ratio >2 with normal serum creatinine, or >0.5 if serum creatinine is elevated) should be treated with a protein-restricted diet supplemented with omega 3 fatty acids, enalapril (0.5 mg/kg PO q 12-24 h), and aspirin (1 mg/kg PO q 24 h; caution if corticosteroids are concurrently administered).[62] Blood pressure should be monitored in proteinuric patients, who can be prone to systemic hypertension (see ch. 99). Corticosteroids promote a transient or persistent increase in proteinuria, and their effect should be considered when monitoring. Localized skin lesions can respond to topical corticosteroids or tacrolimus.

Prognosis

The natural course of SLE in veterinary patients is difficult to predict and is variable. Patients can remain well controlled and medications tapered; however, relapses should be anticipated. Routine evaluation should include complete blood count (CBC), serum biochemistry profile, urinalysis, and possibly a serum ANA titer every 1-3 months. The titer of ANA could correlate with clinical severity and fall with clinical improvement, but the antibody might persist at low titer during clinical remission. It has been suggested that therapy should be more aggressive when the clinical presentation includes renal disease.[42] The outcome for lupus nephritis is highly variable, ranging from asymptomatic proteinuria to rapidly progressive glomerulonephritis. Monitoring for change of renal function is important for SLE patients.

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CHAPTER 206

Nonneoplastic Diseases of the Spleen

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"Spleen is like the tongue of an ox [or] the sole of the foot; slightly bowed out on the left side, a little concave on the inner side, toward the stomach. It has an uneven surface and is a little rough with some tubercles…."

William Harvey, Lectures on the Whole of Anatomy (1653)

For many years, the ability to laugh was for long considered a sign that the spleen was working well. Regarded as the repository of the most noxious substance of the body—black bile (in Greek: *melanos kholis*), the spleen prevented the onset of melancholia by containing the bodily fluid that produced this mental state. Understanding of the spleen has greatly improved over the last several centuries. However, clinical evaluation of this organ remains mostly morphologic, based on palpation, diagnostic imaging, and especially ultrasound examination, followed by cytology or histopathology. No biochemical tests have been designed to assess splenic function. Consequently, although splenomegaly is common in clinical practice, identifying the cause can often be a clinical challenge.

Prevalence

The prevalence of splenic disorders cannot be easily estimated in dogs and cats. Splenomegaly can be asymptomatic, and in the absence of splenomegaly, it is difficult to determine, on the basis of clinical signs, that the spleen is responsible for the animal's condition. Most prevalence studies in dogs and cats are based on either necropsy or biopsies. Necropsy-based studies overestimate diseases with a poor prognosis or with no clinical relevance. Diseases that are treated by surgery are overestimated in prevalence studies based on biopsies but are underestimated in prevalence studies based on necropsy data. This might explain the absence of hemangiosarcoma and the low hemangiosarcoma/hematoma ratio found in necropsy studies in dogs. Based on biopsies submitted to a regional diagnostic laboratory from 1372 dogs[1] and 455 cats,[2] spleen samples from dogs represented 1.3% of all submissions to the laboratory, whereas spleen samples from cats represented 0.3%. However, these percentages do not represent true prevalence because biopsies from all species were included in the total submission number.[1]

In two necropsy surveys, nonneoplastic diseases represented approximately 50% of feline splenic disorders.[2,3] Congestion, lymphoid hyperplasia, capsulitis, extramedullary hematopoiesis, and hyperplastic nodules accounted for more than 50% of the cats with nonneoplastic splenic disease. Unfortunately, those were pathologic descriptions, with the underlying disease not apparent in many cases. In two retrospective studies that looked at prevalence of arrhythmias in dogs with splenic masses,[4,5] hematomas were found in 17%[5] to 44%[4] of the cases. In a prospective study that looked at prevalence of arrhythmias in dogs undergoing splenectomy, 38% of the dogs had neoplasia and 32% had hematomas.[6] Nodular hyperplasia, immune-mediated disease unresponsive to medical therapy, and splenic torsion each accounted for 10% of the cases. Nodular hyperplasia, hematoma, extramedullary hematopoiesis, congestion, and lymphoid hyperplasia were the most common nonneoplastic lesions found in the spleens of dogs at necropsy or on biopsies.[1,7-9] In a lifetime study of Beagles chronically exposed to radioactive radium and strontium, splenic abnormalities were present in 105 of the 865 dogs. Hyperplastic nodules with or without hematoma and diffuse lymphoreticular hyperplasia accounted for 66% of the splenomegalies found in these dogs.

Thus, the ratio of nonneoplastic to neoplastic splenic disease in dogs varies among studies. Populations that included all cases of splenomegaly or masses[1,8] show a higher than 50% prevalence of nonneoplastic diseases. A higher prevalence of tumors is found in populations subjected to splenectomy[6,9] and in dogs with splenic masses and arrhythmias.[4,5] Nonneoplastic masses, therefore, are as common as neoplastic masses in the spleen of dogs.

Clinical Manifestations

Owner complaints for dogs and cats with splenic disorders are usually vague, and these signs may arise from the underlying disease. Common complaints include vomiting, anorexia, weakness, collapse, abdominal enlargement, and weight loss (Box 206-1). Polyuria and polydipsia may occur; the mechanism is unclear, but it resolves after splenectomy. Clinical signs are usually related to abdominal distention from a mass, uniform splenomegaly or intraabdominal bleeding. Lethargy and collapse may occur due to hypovolemia, arrhythmias, or anemia.

Box 206-1

Clinical Signs of Splenic Disease in Dogs and Cats

Abdominal distension
Palpation indicating:
- Splenomegaly
- Splenic mass*

Intraabdominal bleeding*
Arrhythmias
Nonspecific signs and signs of the underlying disorder
- Lethargy
- Weakness
- Collapse
- Anorexia
- PU-PD
- Diarrhea
- Pale mucous membranes
- Jaundice

PD, Polydipsia; *PU,* polyuria.

*Signs suggestive of a splenic tumor.

Signs related to the underlying disorder may also be present (Box 206-1). Ventricular tachyarrhythmias appear to be highly prevalent in dogs with splenic masses (hematoma, hemangiosarcoma or leiomyosarcoma),[4-6] particularly if the mass has ruptured.[6] Dogs subjected to splenectomy, regardless of the reason, are also prone to arrhythmias during and after surgery (see ch. 248).[6]

The most reliable clinical sign of splenic disease is palpable splenomegaly. However, not all splenomegalies are abnormal. Breed variations in spleen size exist, particularly in dogs. German Shepherds have large spleens and some other breeds (e.g., Miniature Schnauzer, Cocker Spaniel, Greyhounds) may have their spleens located more caudally in the abdomen artificially making them feel enlarged.[10] It is important to remember that not all enlarged spleens are palpable.

The major laboratory abnormalities accompanying splenic disease are related to the underlying systemic illness. Changes in blood cell counts may be due to the primary disease or caused by the abnormal spleen. Erythrocyte counts are usually normal or decreased, but can be increased in patients with splenomegaly associated with polycythemia vera.[11] Schistocytosis, which is highly indicative of a neoplastic splenic disorder, was observed in 23% of patients with splenic tumors but only in 3% of dogs with nonneoplastic disease.[9] Granulocyte and platelet counts also can be decreased, normal, or increased (see ch. 58 and 59).

Extramedullary hematopoiesis can occur in the spleen. Because the spleen maintains the ability for hematopoiesis but does not retain the normal inhibitory mechanisms present in the bone marrow, it releases young blood cells into the circulation.[12] Increases in nucleated red blood cells and immature white blood cells (leukoerythroblastic effect) may appear in the peripheral blood in patients with splenic disorders.

Diagnostic Approach

Splenomegaly can be detected by physical examination, abdominal radiographs, ultrasound or by advanced

imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI). Although splenomegaly can be identified during palpation, the severity of the enlargement cannot be reliably assessed in dogs with this technique alone. Differentiating between a splenic mass (localized splenomegaly with at least one large mass) and diffuse splenomegaly (uniform enlargement of the spleen) helps to narrow the number of potential diagnoses (Box 206-2). Fine-needle aspiration of the spleen may provide the final diagnosis or characterize the type of inflammation present. However, this should never be performed without appropriate imaging to ensure there is little or no risk of major bleeding from a blood-filled tumor. A sequential approach to diagnose the origin of splenomegaly is shown in Figure 206-1.

Box 206-2

Causes of Splenomegaly in Dogs and Cats

Splenic mass (asymmetric or nonuniform splenomegaly)
- Nodular hyperplasia
  - Lymphoid*
  - Fibrohistiocytic (D)
- Hematoma*
- Malignant tumors*
  - Hemangiosarcoma*
  - Fibrosarcoma
  - Leiomyosarcoma
  - Histiocytic sarcoma
  - Metastatic disease
- Benign tumors
  - Hemangioma
  - Myelolipoma
- Abscess
- Extramedullary hematopoiesis (C)
- Granuloma

Uniform (symmetric)
- Breed variation (D)
- Congestion
  - Drugs*
  - Portal hypertension*
  - Splenic torsion
- Hyperplasia†
  - Chronic infection*
  - Inflammatory bowel disease
  - Systemic lupus erythematosus
  - Polycythemia vera
- Extramedullary hematopoiesis†
  - Chronic anemia*
  - Immune-mediated hemolytic anemia*
  - Immune-mediated thrombocytopenia*
- Neoplasia
  - Neoplastic infiltrative diseases
    - Lymphoma*
    - Leukemias*
    - Multiple myeloma
    - Primary erythrocytosis (polycythemia vera)
    - Primary mast cell tumor (C)
    - Metastatic mast cell tumor
    - Disseminated malignant histiocytosis
  - Nonneoplastic infiltrative diseases
    - Hypereosinophilic syndrome (C)
    - Amyloidosis

Inflammatory‡
- Suppurative
  - Sepsis*
  - Bacterial endocarditis*
  - Infectious canine hepatitis
  - Toxoplasmosis
  - Foreign body
  - Penetrating wounds
  - Tumors
- Granulomatous
  - Cryptococcosis
  - Histoplasmosis (C)
  - Mycobacteriosis
  - Leishmaniasis
- Pyogranulomatous
  - Feline infectious peritonitis* (C)
  - Blastomycosis
  - Sporotrichosis
- Eosinophilic
  - Eosinophilic gastroenteritis
  - Hypereosinophilic syndrome (C)
  - Tumors
- Lymphoplasmacytic
  - Ehrlichiosis*
  - Anaplasmosis*
  - Hemotropic mycoplasmosis* (C)
  - Lymphoplasmacytic enteritis*
  - Pyometra
  - Brucellosis
- Necrotic tissue
  - Torsion
  - Necrotic center of neoplasms
  - Infectious canine hepatitis (D)
  - Anaerobic infection
  - Tularemia
  - Systemic calicivirosis (C)
  - Salmonellosis

C, Cats; *D,* dogs.

*More common diseases.
†The causes of extramedullary hematopoiesis and hyperplasia can overlap.
‡The typical inflammatory response for each organism; some degree of overlap exists.

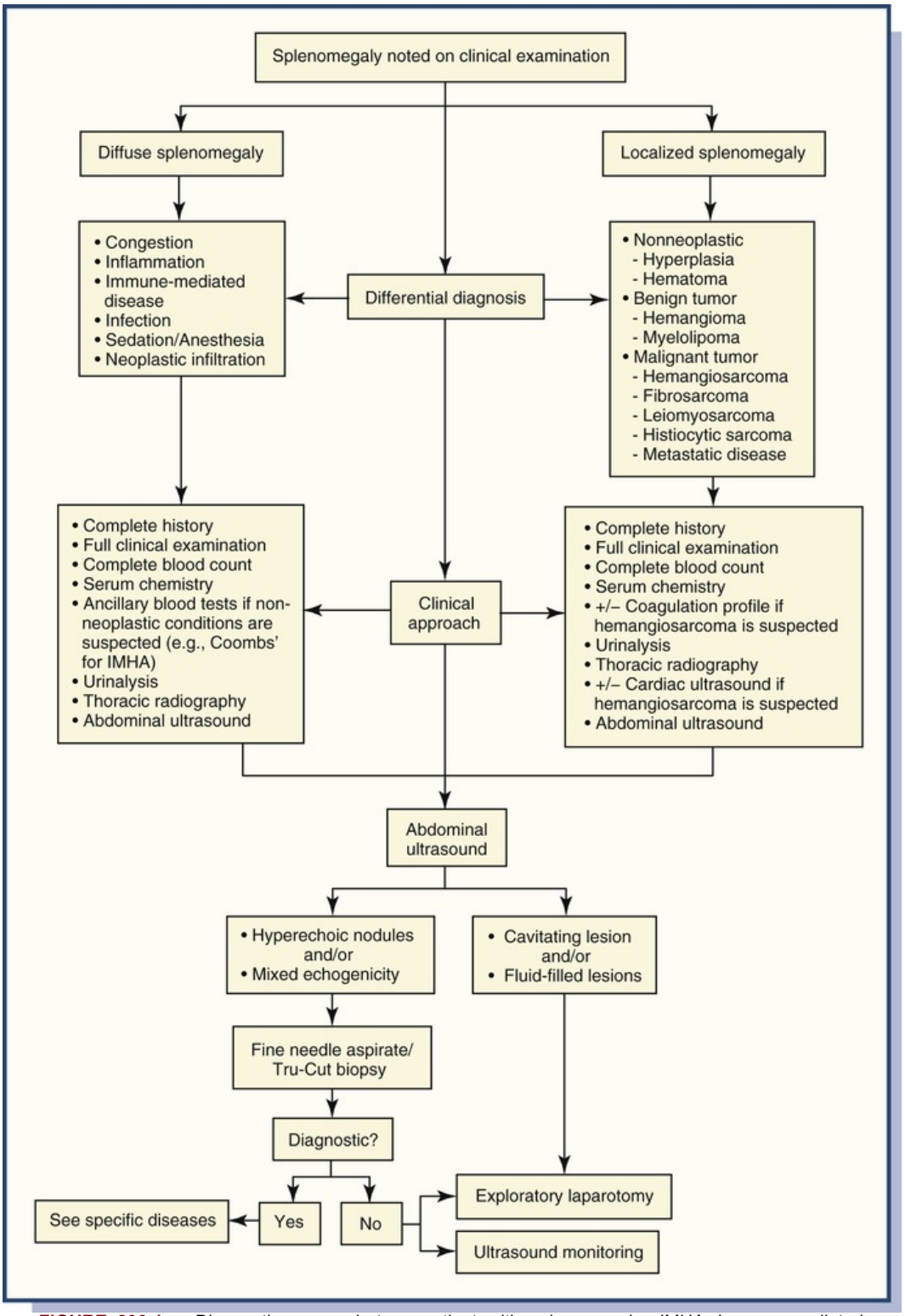

FIGURE 206-1 Diagnostic approach to a patient with splenomegaly. *IMHA,* Immune-mediated hemolytic anemia.

Abdominal Radiography

Radiographically, the spleen is apparent in both the dog and cat. The dorsal extremity (head) is commonly seen on ventrodorsal projections in the cranial left abdomen caudal to the gastric fundus and cranial to the left kidney, along the left body wall. On this projection, the splenic head is triangularly shaped. The body of the

spleen may be directed transversely across the abdomen immediately caudal to the stomach, along the left body wall, or anywhere in between. In dogs, the ventral aspect (tail) is often seen along the ventral body wall immediately caudal to the liver in the lateral projection. Distension of the stomach may caudally displace the tail. The tail of the spleen is uncommonly seen in cats.

Generalized splenomegaly may increase splenic length. The spleen may also fold up from the ventral wall, extending to varying lengths up the right body wall or expand more caudally towards the urinary bladder. In the cat, visualization of the splenic tail along the ventral body wall supports a diagnosis of splenomegaly. Alternatively, with generalized enlargement or focal masses, the spleen produces a mass effect, displacing the intestines caudally. The spleen is a very common origin for masses in the midcranial and left cranial abdomen. Atypical splenic location, with changes in shape, may occur in dogs with splenic torsion. Concurrent peritoneal effusion is common. Lesions rarely cause changes in splenic radiopacity.

Abdominal Ultrasonography

Ultrasonography is a very effective tool for evaluation of the size, shape, and vascular supply of the spleen (see ch. 88). There are no objective criteria for normal splenic size. As a rule, cats have much smaller spleens than do dogs of similar size. Normal variations in dogs include capsular invagination (hyperechoic foci adjacent to splenic veins), a bent spleen, or a portion folded back upon itself. Generalized isoechoic enlargement may be a normal variation in German Shepherds and other dog breeds and in some cats. Overall spleen length and evidence of intestinal displacement are the criteria used to assess for splenomegaly. A true decrease in splenic size (microsplenia) may occur with acute anemia due to contraction of the spleen. Ultrasonography is more sensitive than radiography for detecting alterations in the shape and outer margination of the spleen. Irregularities in shape and focal changes in echogenicity are the major criteria for characterization of splenic disease in dogs and cats.

Nodular disease is easily detected in the middle and tail regions of the spleen. Often the head of the spleen is within the rib cage, and masses in the dorsal extremity may require a rigorous examination with an intercostal approach. Benign masses may be hypoechoic, hyperechoic, or of mixed echogenicity. Benign masses cannot be differentiated from malignant masses solely based on gray-scale ultrasonography. Extramedullary hematopoiesis and nodular hyperplasia (Figure 206-2), which are common regenerative lesions, are usually hypoechoic and are seen in the spleen of older dogs. These lesions are much less common in cats.

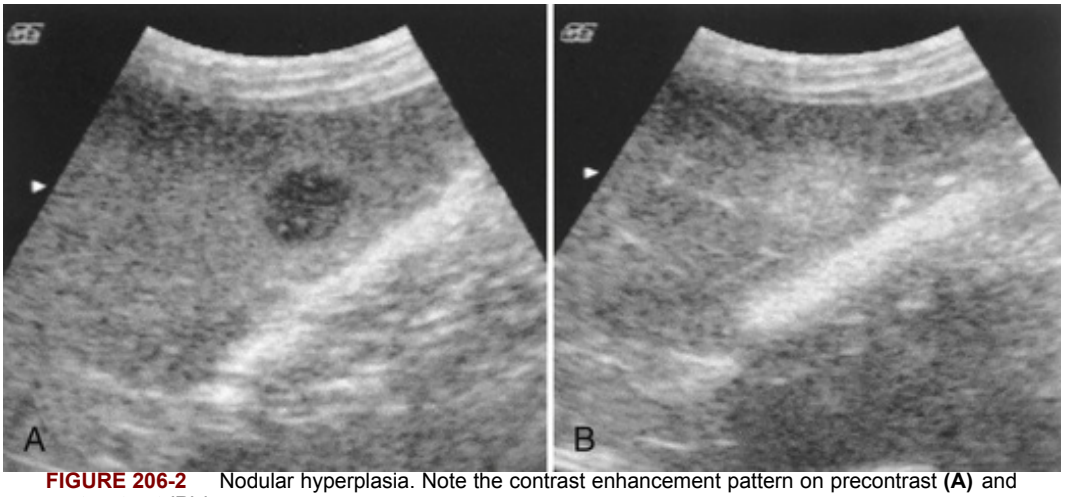

FIGURE 206-2 Nodular hyperplasia. Note the contrast enhancement pattern on precontrast **(A)** and postcontrast **(B)** images.

Certain lesions have a more characteristic sonographic appearance. Myelolipoma, a benign tumor seen in older dogs, is both very echogenic and attenuating. The result is a classic hyperechoic and indistinctly shadowing lesion (Figure 206-3). Unlike with mineralization, the attenuation is not complete, and the internal architecture of the lesion can be seen to varying depths.

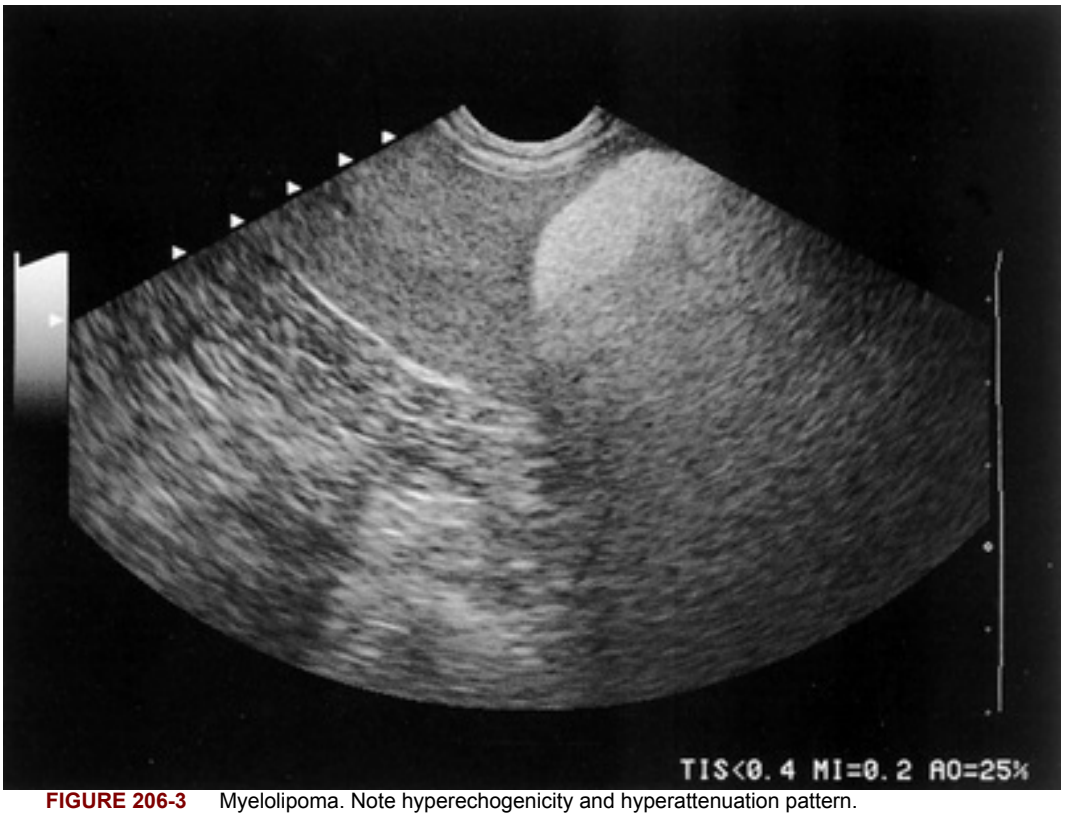

FIGURE 206-3 Myelolipoma. Note hyperechogenicity and hyperattenuation pattern.

The spleen has a predisposition for vascular disease because it is attached at only one pole and is prone to harbor diffuse neoplasia. Splenic torsion and diffuse tumor invasion may result in uniform diffuse hypoechogenicity or a more mixed "Swiss cheese" appearance (Figure 206-4). Doppler examination of the splenic veins is an important step to identify lack of venous return. As with portal vein flow, splenic venous flow is low-velocity and essentially nonpulsatile. Power Doppler is especially valuable, as this modality is more sensitive to very low-velocity flow. Thrombosis may occur after mechanical torsion, tumor vascular invasion, or thromboembolic diseases. Regional infarcts are commonly seen in dogs with disseminated intravascular coagulation (DIC; see ch. 197) and autoimmune conditions, such as immune-mediated hemolytic anemia (see ch. 198) and immune-mediated thrombocytopenia (see ch. 201). Infarcted regions are usually peripheral, hypoechoic, and swollen (Figure 206-5). Necrosis may be seen with chronic severe vascular disease and result in formation of free gas in the spleen and free fluid in the peritoneum.

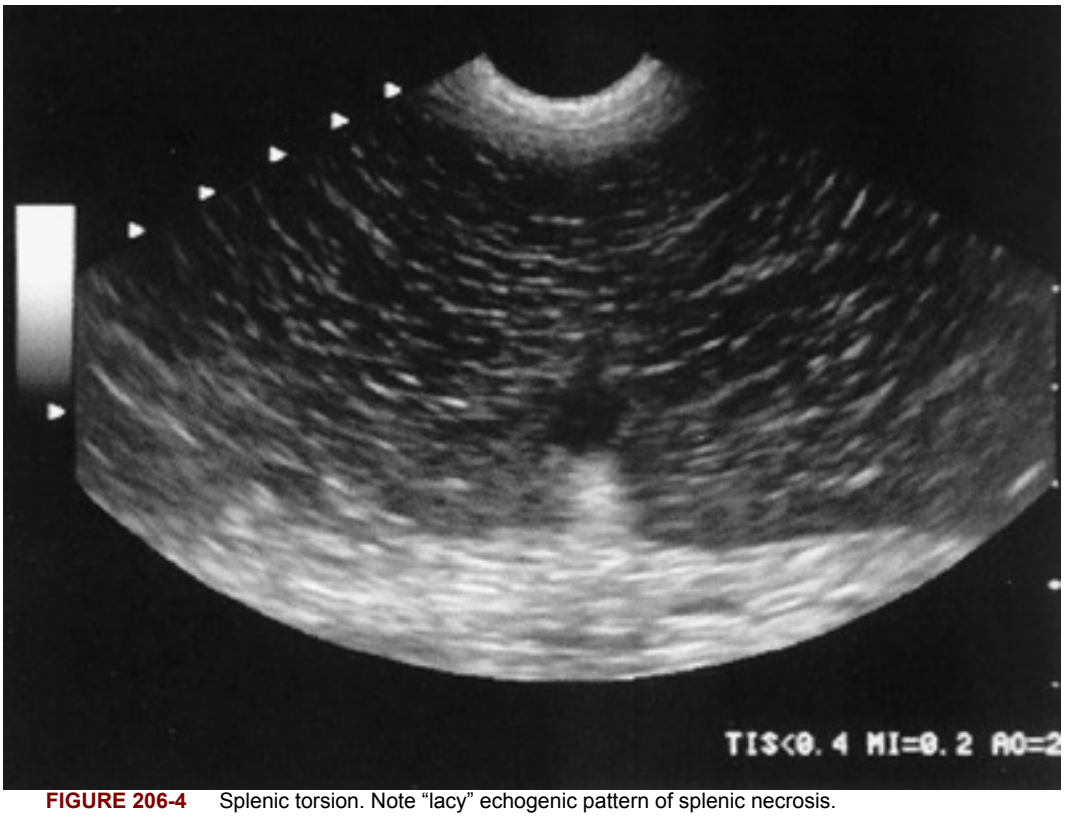

FIGURE 206-4 Splenic torsion. Note "lacy" echogenic pattern of splenic necrosis.

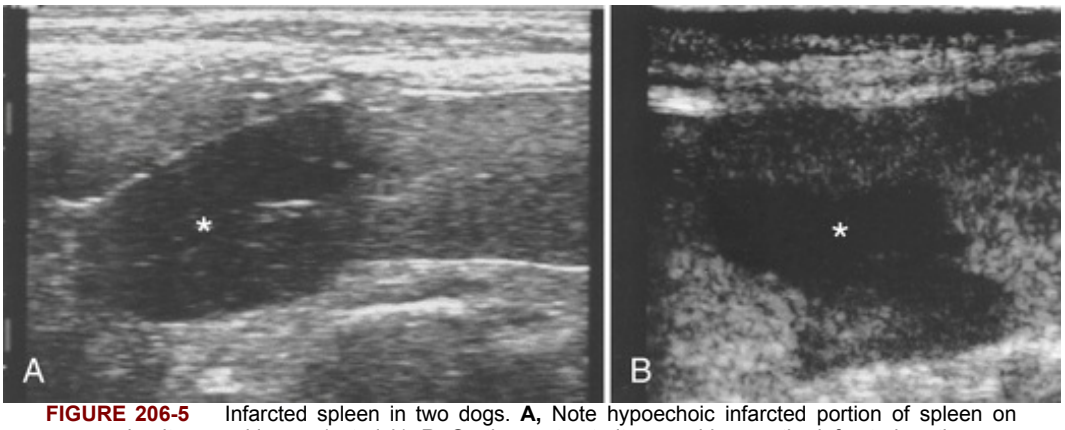

FIGURE 206-5 Infarcted spleen in two dogs. **A,** Note hypoechoic infarcted portion of spleen on gray-scale ultrasound image (asterisk). **B,** On the contrast ultrasound image, the infarcted portion was not seen on gray-scale ultrasound but was hypoechoic compared to surrounding well-perfused, contrast-enhanced spleen (asterisk).

An additional ultrasound modality for evaluation of focal nodular and vascular diseases of the spleen is contrast harmonic ultrasound. Second-generation ultrasound contrast agents are liposome-encapsulated inert gas spheres that are injected intravenously and small enough (3 to 5 microns) to pass through the pulmonary circulation without embolization. Harmonic ultrasound software technology allows detection of sound waves that are multiples of the transmitted frequency. Ultrasound contrast bubbles are very powerful generators of harmonic frequencies, and, combined with tissue signal suppression, they create a novel method to image perfusion of organs. These contrast media, which can be used as blood pool agents, will cause infarcted regions to appear hypoechoic compared to the surrounding normally perfused spleen. Preliminary studies indicate that ultrasound contrast agents may help discriminate between malignant and benign masses by exploiting differences in blood supply. Hemangiosarcomas and hematomas have a very poor overall perfusion pattern, but hemangiosarcomas have distinct tortuous feeder vessels.[13] This perfusion pattern has

been noted in hemangiosarcoma masses in the liver, lung, peritoneum, and the spleen. In the liver, metastatic nodules have a more rapid wash-in and wash-out compared to normal liver or benign liver nodules. Benign hyperplastic nodules in the spleen have good overall perfusion.

Abdominal Computed Tomography

Computed tomography can add greatly to the overall assessment of splenic disease. With the exception of contrast ultrasound, which is not widely available in the United States, contrast CT is the only modality capable of detecting perfusion deficits.[14] In addition, CT provides a more global assessment of the abdomen and can be performed on critical patients without general anesthesia in an emergency situation.[15]

The normal splenic vascular supply is through the splenic arteries, which, very soon after entering the spleen, uniquely lose any distinct vascular identity and enter the red pulp. The perfusion of the spleen is often bimodal, with the presumed red pulp enhancing regionally before the white pulp.[16,17] Timing for CT studies needs to account for this bimodal pattern, and clinicians should plan to use a protocol that will not lead to false lesions due to perfusion deficits.

Reports of the CT findings of nonneoplastic splenic lesions are sparse in the veterinary literature. Splenic infarcts are seen with any preexisting disease that causes hypercoagulability, including autoimmune disease. Infarction results in a persistent regional perfusion deficit in the splenic parenchyma (Figure 206-6). As previously noted, this needs to be verified by use of a protocol that includes a late-venous phase. Splenic torsion, based on a single case report, has a more complex combination of imaging features, including pan-splenic perfusion deficit and poor splenic arterial enhancement. Presumably, CT angiography would add significantly to the overall CT features of this disease. Abscesses of the spleen are very uncommon but can result in regional perfusion deficits and parenchymal gas. Depending on the severity and chronicity of the abscess, concurrent fat stranding, peritoneal free fluid, regional lymphadenopathy and free peritoneal gas can be seen[14] (Figure 206-7). Fat stranding is a nonspecific CT finding of a streaky appearance of the peritoneal fat that has increased water content as a result of cellular infiltration (e.g., white blood cells) or edema of the peritoneal fat. Fat stranding on CT images corresponds to regions of hyperechoic peritoneal fat on ultrasound images (Figure 206-8). The CT appearance of benign and malignant nodules has not been studied.

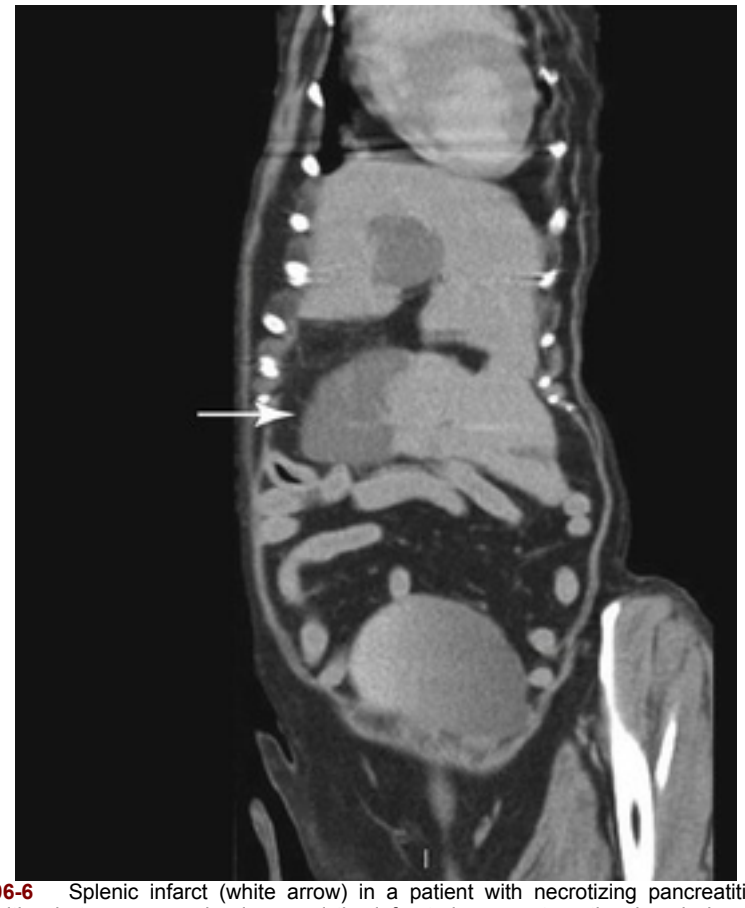

FIGURE 206-6 Splenic infarct (white arrow) in a patient with necrotizing pancreatitis. Note the abrupt transition between normal spleen and the infarcted segment on the dorsal plane multiplanar reconstruction (MPR) postcontrast CT image.

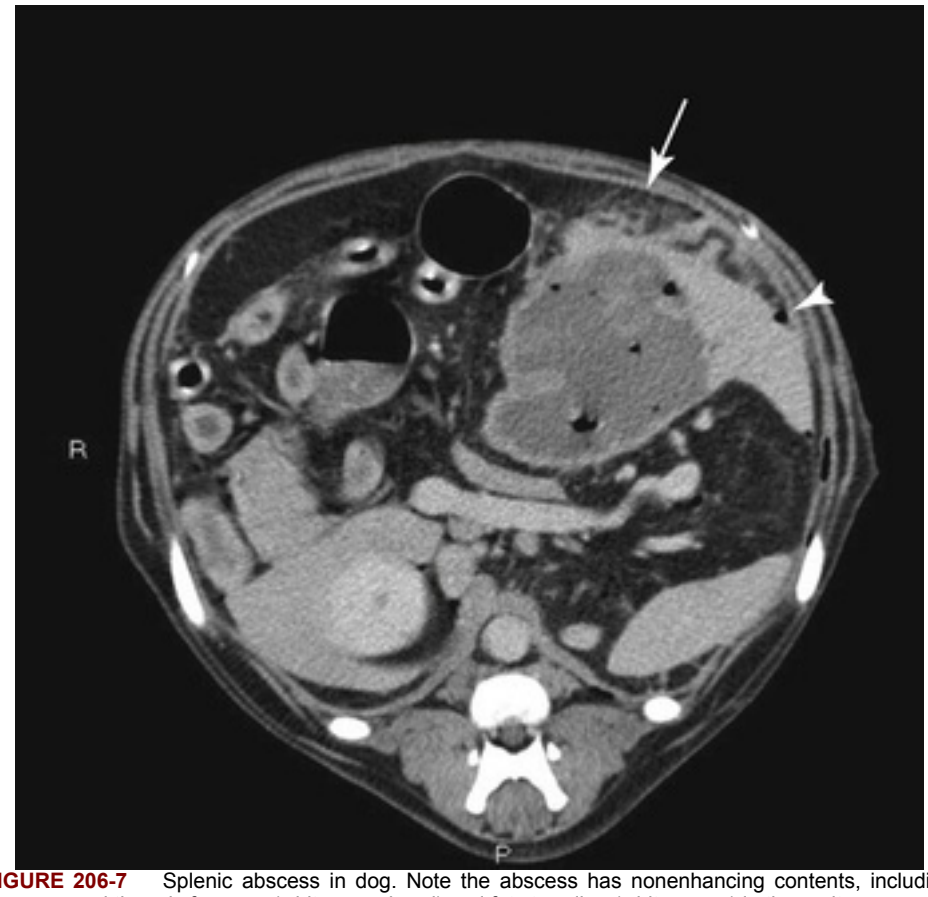

FIGURE 206-7 Splenic abscess in dog. Note the abscess has nonenhancing contents, including free gas, and there is free gas (white arrowhead) and fat stranding (white arrow) in the peritoneum.

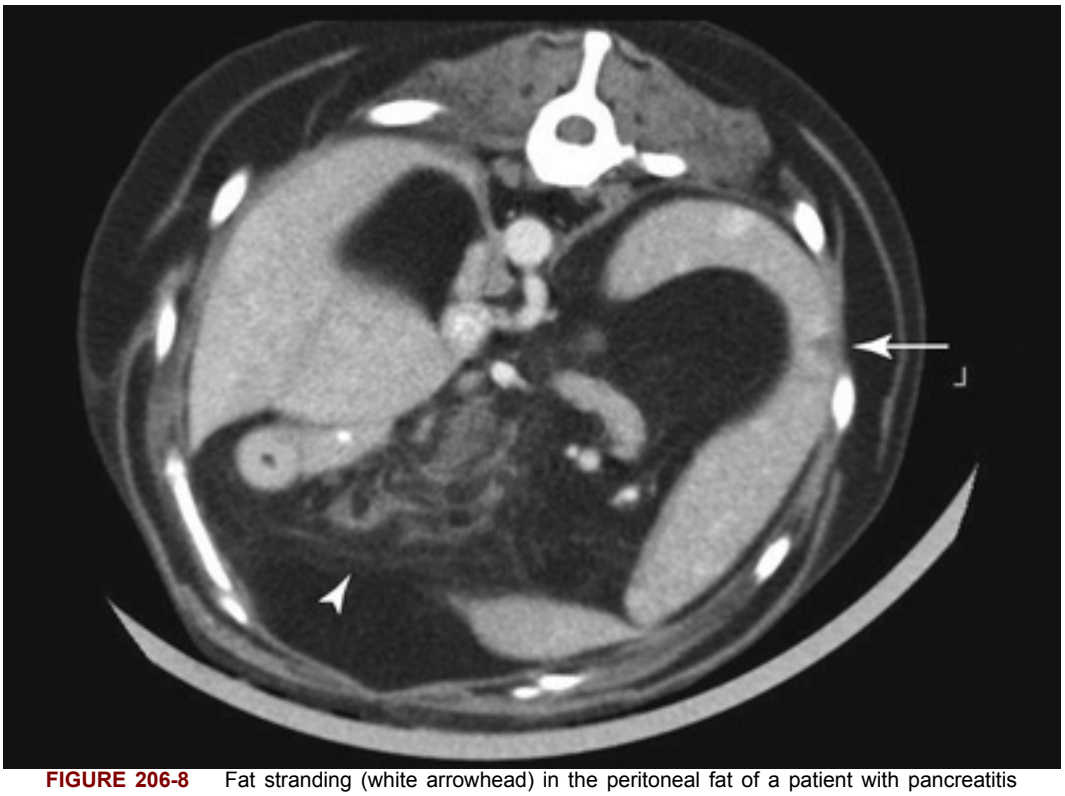

FIGURE 206-8 Fat stranding (white arrowhead) in the peritoneal fat of a patient with pancreatitis

and a small splenic infarct (white arrow).

The comparison of hemangiosarcoma and hematoma based on CT findings has been reported.[18] The most important imaging distinction across all imaging modalities, including contrast-enhanced ultrasound and contrast CT, is aberrant tortuous feeder vessels (Figure 206-9). Additionally, there was a significantly lower attenuation (Hounsfield units, HU) on both pre- and postcontrast images within the mass and greater prevalence of concurrent free peritoneal fluid in patients with malignant masses. The largest masses, relative to the overall size of the remaining normal spleen, were hematomas.

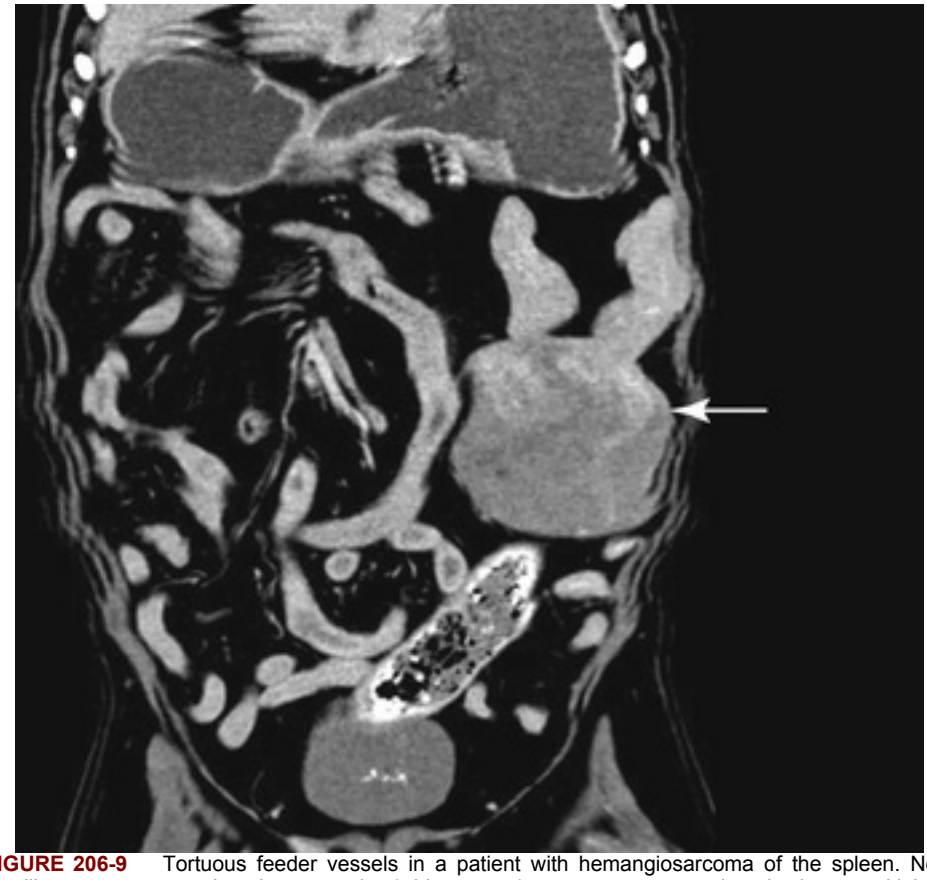

FIGURE 206-9 Tortuous feeder vessels in a patient with hemangiosarcoma of the spleen. Note curvilinear contrast enhancing vessels (white arrow) on postcontrast dorsal plane multiplane reconstruction (MPR) CT image.

Fine-Needle Aspiration

Although imaging of the spleen only rarely results in a diagnosis, an aspirate may provide a cytologic sample and the possibility of a diagnosis (see ch. 89). Core biopsy is possible but is not usually necessary. Most diseases of the spleen exfoliate well and are suitably sampled with fine-needle techniques. Splenic aspirates correctly identified the underlying problem in over 60% of cases in one study. Incorrect diagnosis occurred in 15% of the cases, and histopathology was required to distinguish between neoplastic and reactive conditions in 22% of the cases.[19] Of the fine-needle techniques, the variation that seems to provide the most cells without undue hemodilution involves no negative pressure with the attached syringe and multiple thrusting motions with the needle. With the plunger already pulled back in the barrel of the syringe prior to insertion of the needle, it thereafter is easy to expel the content of the needle by depressing the plunger. This technique works well for nodular hyperplasia and extramedullary hematopoiesis–benign nodules, metastatic carcinomas, and hematopoietic tumors. Solid sarcomas may not exfoliate well with aspiration techniques, and a core sample may provide a better result. Cavitated lesions are rarely sampled, based on the risk to the patient.

Fine-needle aspiration appears to be safe even in presence of coagulopathies or thrombocytopenia.[20] As a

general rule, all abnormal spleens that do not have cavitated lesions should be aspirated. Aspiration is not necessary in patients with splenic torsion whenever lack of adequate blood flow can be determined by Doppler ultrasonography, nor in patients with myelolipoma if only lesions with the classic acoustic properties are present. Aspiration also may not be required for patients with diffuse homogeneous splenomegaly and no clinical signs attributable to splenic disorders and in patients with a known cause of congestion (e.g., tranquilizers, portal hypertension, right-sided heart failure) or for "classic" infarct lesions in asymptomatic patients.

Fine-needle aspiration can provide the final diagnosis in neoplastic disorders or, when the organism can be identified, in infectious disease. Aspirates of normal spleen reveal small lymphocytes with occasional medium and large lymphocytes and rare neutrophils (see ch. 93). A few macrophages and plasma cells may be present.[21] Precursors of all three cell lines may be seen in patients with extramedullary hematopoiesis, but erythroid cells are more common. In hyperplasia resulting from antigenic reaction, there is an increase in medium and large lymphocytes and in macrophages and plasma cells.[21] Patients with splenitis have an increase in inflammatory cells. Identification of the predominant cell type narrows the number of potential diagnoses. Inflammation can be further characterized based on the predominant cell type as suppurative, granulomatous, pyogranulomatous, eosinophilic, or lymphoplasmacytic. The most common causes for each type of inflammation are shown in Box 206-2.

Splenic Biopsies/Splenectomy

Spleen biopsies can be obtained in patients where the primary diagnosis of a mass is not obtained by fine-needle aspiration. Care should be taken with impression smears made from spleen biopsies. Inadvertently making impressions of the capsular surface instead of parenchyma will reveal uniform sheets of loosely attached mesothelium that will be nondiagnostic.[15] Splenectomy should be considered in animals with cavitated masses without metastasis or necrosis.

Other Diagnostic Tests

In addition to imaging techniques and fine-needle aspiration, urinalysis, complete blood count, and biochemical profile are necessary in all patients with splenomegaly. Cats should be tested for infection with feline leukemia virus (FeLV; see ch. 223) and feline immunodeficiency virus (FIV; see ch. 222). Thoracic radiographs should be obtained in patients with splenic masses to rule out metastasis, and bone marrow examination may be indicated in patients with unexplained cytopathies (see ch. 92).

Common Causes of Splenomegaly in Dogs and Cats: Neoplastic Diseases

In both the dog and the cat, the spleen can be the site for both malignant and benign tumors as well as nonneoplastic disease. In dogs, around two thirds of splenic masses are diagnosed pathologically as neoplastic. Of these lesions, around one half to two thirds are diagnosed as hemangiosarcoma. In cats, around one half of splenic lesions submitted for pathologic examination are diagnosed as neoplastic. Tumors of the spleen usually present either as localized or diffuse splenomegaly and can be confused with nonneoplastic conditions. The actual clinical features of primary splenic tumors can be very vague, except in cases of splenic rupture and bleeding.

Malignant Tumors of the Canine Spleen

Hemangiosarcoma

Hemangiosarcoma (see ch. 347) is a highly malignant tumor arising from the vascular endothelium. It is most common in the larger breeds of dog (especially German Shepherd), with the median age of affected dogs being 10 years. The most common primary site of hemangiosarcoma in the dog is the spleen, but it can also affect cutaneous sites. Around 25% of dogs with splenic hemangiosarcoma also have concurrent hemangiosarcoma affecting the right atrium.[22,23]

The classical presentation of hemangiosarcoma in dogs is that of a solitary cavitated lesion that bleeds, causing hemoperitoneum and sudden-onset hypovolemic collapse (see ch. 143). Dogs often present with sudden-onset collapse, pallor, tachycardia and tachypnea, and distended abdomen. Abdominocentesis (see ch. 90) reveals frank hemorrhage. If possible, a platelet count and clotting profile should be performed.

Approximately 50% of dogs that present with abdominal bleeding are in DIC (see ch. 197). Anemia and thrombocytopenia are common. Reticulocytosis and polychromasia may occur depending on when the bleed took place. A peripheral blood smear may reveal schistocytosis as red cells shear as they course through the tortuous lesion in the spleen (microangiopathic hemolytic anemia).[24-27]

Diagnosis and Clinical Staging

Dogs with hemoperitoneum and concurrent hematologic changes such as schistocytosis and thrombocytopenia with concurrent anemia should carry a high suspicion for hemangiosarcoma. Clinical staging to determine the nature and extent of disease should include three-view thoracic radiography (right and left lateral views and dorsoventral), complete blood count and serum chemistry, coagulation profile, cardiac and abdominal ultrasound, and potentially exploratory laparotomy (see ch. 347). The World Health Organization staging system for canine hemangiosarcoma is given in Box 206-3.[28] The only way to definitively diagnose hemangiosarcoma is by histopathology following splenectomy. Even at surgery, distinguishing between hemangiosarcoma or hemangioma is impossible morphologically. Cytology is often unrewarding, and the gross appearance of the spleen is often a poor indicator of the underlying disease. Large hematomas or benign hemangiomas can have an identical "appearance" to hemangiosarcoma at surgery, and no decision should be taken on euthanasia during surgery unless there is evidence of gross metastatic disease. To achieve a good pathologic diagnosis, it is also important to submit the most appropriate samples to the pathologists. If the pathologist is not on site, then it will be difficult to submit a spleen in its entirety, as it will not properly fix in formalin. In addition, multiple sites need to be sampled and fixed because the spleen will also contain multiple areas of hemorrhage and fibrosis that grossly may look like tumor. Large samples can be sliced like a loaf of bread to ensure even penetration of formalin.

Box 206-3

The World Health Organization Staging System for Canine Hemangiosarcoma

Primary Tumor (T)

T0	No evidence of tumor
T1	Tumor confined to spleen
T2	Tumor confined to spleen but ruptured
T3	Tumor that is invading adjacent structures

Regional Lymph Node (N)

N0	No regional lymph node involvement
N1	Regional lymph node involvement
N2	Distant lymph node involvement

Distant Metastasis (M)

M0	No evidence of distant metastasis
M1	Distant metastasis

Stages

I	T0 or T1, N0, M0
II	T1 or T2, N0 or N1, M0
III	T2 or T3, N0, N1 or N2, M1

From Wood CA, Moore AS, Gliatto JM, et al.[28]

Treatment

The treatment of choice for primary splenic hemangiosarcoma is splenectomy (see ch. 347). Dogs that present in acute hypovolemic shock are not surgical candidates and should be stabilized before surgery is contemplated (see ch. 127). Often dogs present following one major bleed, but if bleeding does not continue, these patients will auto-transfuse and become better surgical candidates over the subsequent 24-hour period. It is noteworthy that around 20% of dogs can develop ventricular arrhythmias associated with splenic tumors. Dogs should be monitored electrocardiographically before and during surgery and in the immediate postoperative period (see ch. 103). In some of these dogs, arrhythmias can be difficult to control until the spleen has been surgically removed.[29,30]

Splenectomy will relieve abdominal distension caused by the tumor and prevent any further bleeding. However, the role of surgery alone in improving survival is difficult to determine because of the rapid onset of metastasis. The most common cause of death in dogs is metastasis, and many chemotherapy protocols have been described as adjunctive therapies to improve survival. Survival time following surgery with or without chemotherapy is shown in Table 206-1.[31-41] Overall, the prognosis should be considered poor even with adjunctive chemotherapy. Although stage is considered a negative prognostic factor for survival, a recent study exploring the use of VAC protocol for stage III hemangiosarcoma demonstrated no significant differences between dogs with stage I/II and III disease.

TABLE 206-1

Survival Times for Dogs Treated for Splenic Hemangiosarcoma

TREATMENT	MEDIAN SURVIVAL TIMES
Splenectomy alone (stage 1 or 2)	86 days
Splenectomy plus VAC*	164 days
Splenectomy plus AC*	179 days
Splenectomy plus doxorubicin	60 days if evidence of gross disease after splenectomy
	172 days if no evidence of further disease

*Stage unknown.

AC, Doxorubicin, cyclophosphamide; *VAC*, vincristine, doxorubicin, cyclophosphamide (plus chlorambucil and methotrexate).

Adapted from Murphy and Brearley.[42]

The most promising improvements in survival came from a study that combined both chemotherapy (doxorubicin and cyclophosphamide) and liposome-encapsulated muramyl tripeptides (LMTP) as an immunotherapy. LMTP is a nonspecific biologic that enhances macrophage activation. In this study, the median survival time improved from 179 days (chemotherapy alone) to 273 days.[43] At the time of writing, LMTP is no longer available for veterinary use. However, recently a European license was granted for Mifamurtide (Mepact), an LMTP developed for use in children and adolescents with osteosarcoma. The use in veterinary patients with this product is limited by cost and availability at the current time.

Nonangiomatous, Nonlymphoid Sarcomas of the Spleen

Fibrosarcoma, leiomyosarcoma, myxosarcoma, osteosarcoma, liposarcoma, and undifferentiated sarcoma have all been described as primary splenic malignant tumors (see ch. 346). Unlike hemangiosarcoma, the clinical signs associated with these tumors are usually vague and typically involve progressive anorexia and lethargy. In rare cases where the tumor has become large, it may result in splenic torsion.

The treatment of choice is surgery, with no large-scale clinical trials describing the benefits of adjunctive chemotherapy. As a group, a median survival time following splenectomy is reported to be around 4 months, but there is a large variation depending on tumor type. The mitotic index at histopathologic examination has prognostic implications. Tumors with a mitotic index less than 9 have a better prognosis that those with an

index greater than 9.

Histiocytic Sarcoma

Canine histiocytic disorders represent a range of diseases that are a diagnostic and therapeutic challenge (see ch. 350). This disease is most common in the Bernese Mountain Dog and Retriever breeds but has been reported in a number of other breeds. The spleen can be a site for primary histiocytic sarcoma or a site of dissemination from malignant histiocytosis. Primary splenic histiocytic sarcoma has been associated with a hemophagocytic syndrome characterized by a Coombs'-negative anemia due to erythrophagia by malignant histiocytes. Whether primary or part of a secondary disease complex, histiocytic disease associated with the spleen carries a poor prognosis. Dogs will often die from disseminated disease even after splenectomy. Lomustine (CCNU) or liposome-encapsulated doxorubicin have been suggested as adjunctive therapies, but large-scale clinical studies are still lacking.[44-47]

Benign Tumors of the Canine Spleen

A number of benign tumors have been reported in the canine spleen. In general, these carry a good prognosis with long survival times following splenectomy. Myelolipomas are tumors containing a mixture of adipose tissue and hematopoietic tissue (see Figure 206-3). Lipomas are benign fat tumors that may affect the spleen. Hemangiomas are benign tumors arising from the vasculature. They can be distinguished from hemangiosarcoma only on histopathology. Splenectomy is considered curative.[48,49]

Metastatic Tumors of the Canine Spleen

As well as being a site for primary neoplasia, the spleen is also a site for secondary tumor deposits or infiltrates. Notable among these are lymphoma, leukemias, multiple myeloma, primary erythrocytosis (polycythemia vera), high-grade metastatic mast cell tumors, and carcinomas. The management of secondary splenic tumors revolves around management of the underlying primary malignancy and usually involves systemic chemotherapy.

Malignant Tumors of the Feline Spleen

Mast Cell Tumor (See Ch. 349)

In cats, the spleen is a common site for primary mast cell tumor and mast cell tumor represents the most common differential for splenic disease in the cat. There is no sex predilection, but it tends to occur in cats in the older age range (>10 years). Although the spleen appears to be the primary site of the tumor, other organ systems are often affected, including liver, lungs, bone marrow, lymph nodes and intestine. Some cats will have pleural or peritoneal effusions that are rich in mast cells. Mastocytosis is common. Typically, these patients present with a history of dullness and lethargy, progressive anorexia, occasional vomiting (histamine release), and diffuse splenomegaly on clinical examination.[50,51]

Diagnosis is usually made by ultrasound-directed fine-needle aspirate of the spleen. The treatment of choice is splenectomy, with a mean survival time of around 12 to 18 months following surgery. However, this is a high-risk surgery because excessive handling of the spleen could lead to massive histamine and heparin release leading to shock and ultimately death. Presurgical therapy with antihistamines, careful surgical technique, and proper anesthetic monitoring are essential for success. Following surgery, the mastocytosis usually clears without any chemical therapy. Adjunctive use of chemotherapy is controversial, with no large-scale clinical studies proving their benefit.[50]

Feline Splenic Hemangiosarcoma

Compared to the canine disease, feline splenic hemangiosarcoma is rare (see ch. 347). Cats with this condition will normally present with nonspecific clinical signs such as anorexia, weight loss, and vomiting. Very rarely will cats have hypovolemic shock and collapse. There is a paucity of feline cases reported in the literature, although those that have been described have been associated with metastatic disease. A median survival of 20 weeks following surgery has been reported. There are no large-scale clinical studies showing the benefit of chemotherapy following surgery.[52]

Other Malignant Tumors

As with dogs, other primary sarcomas (e.g., fibrosarcoma) have been reported but are very rare. Treatment of choice is surgery, and there is no information on the use of adjuvant therapies. Histiocytic sarcoma of macrophage origin has been reported in the cat but is very rare and, like the dog, carries a poor prognosis.[53]

Benign Tumors of the Feline Spleen

A number of benign tumors have been reported in the feline spleen. In general these carry a good prognosis with long survival times following splenectomy. These include hemangiomas, which are benign tumors arising from the vasculature. Splenectomy is considered curative.

Metastatic Tumors of the Feline Spleen

The feline spleen can be a site for both primary neoplasia and for secondary tumor deposits or infiltrates. Notable amongst these are lymphoma, leukemias, multiple myeloma (rare in cats), and carcinomatosis. The management of secondary splenic tumors revolves around management of the underlying primary malignancy and usually involves systemic chemotherapy.

Common Causes of Splenomegaly in Dogs and Cats: Nonneoplastic Diseases

Generalized splenomegaly occurs not only with tumor infiltration but also may be caused by congestion, splenic hyperplasia/extramedullary hematopoiesis, inflammation, or cellular infiltration. Splenic masses are usually due to neoplasia, hematoma, abscess, or nodular hyperplasia.

Congestion

Congestion is commonly seen as a consequence of sedation or anesthesia, portal hypertension, or splenic vein thrombosis. Administration of phenothiazine sedatives (e.g., acepromazine) or ultrashort-acting barbiturates (e.g., thiopental) produces substantial splenomegaly. Splenomegaly can be severe because up to 30% of the blood volume can be pooled in the spleen. Administration of propofol to dogs, however, did not produce statistically significant splenomegaly.[54]

Congestion can also be secondary to portal hypertension with hepatic disease and systemic venous hypertension in right-sided heart failure or intrathoracic caudal vena cava compression. Chronic congestion of the spleen may lead to splenic hyperplasia. No changes in echogenicity were subjectively noted in congested spleens, although significant increased attenuation and a trend towards increased backscatter (echogenicity) were noted.[54] Diffuse changes in splenic echogenicity in patients with a known cause of congestion, therefore, are likely due to another underlying condition.

Splenic pedicle torsion is a special cause of congestion in dogs. It usually develops in large, deep-chested dogs, especially the German Shepherd and Great Dane.[55] Males represented 79% of the cases in one study.[55] Acute torsion causes profound systemic signs with shock and abdominal discomfort, whereas chronic torsion is associated with vague signs including vomiting, anorexia, lethargy, and icterus. Radiographically, a decrease in abdominal detail, displacement of other abdominal organs, and loss of visualization of the body of the spleen in the left cranial quadrant of the abdomen are seen in the ventrodorsal view. In the lateral view, the spleen is enlarged, is abnormally positioned or shaped, and may have intrasplenic gas.[56] Ultrasonographically, the spleen is diffusely enlarged and abnormally located. It is usually hypoechoic, with decreased flow through splenic veins. In one study, intravascular thrombi could be identified in 50% of the cases (see Figure 206-4).[55] CT imaging of the spleen during torsion is described above.[57] Supportive therapy should be instituted immediately in these patients and the spleen removed surgically. If appropriately treated, splenic torsion carries a favorable prognosis.[55]

Splenic Infarction

Infarcts can be observed in patients in hypercoagulable states associated with liver disease, renal disease, or hyperadrenocorticism.[58] The most common cause is immune-mediated disease such as autoimmune hemolytic anemia and thrombocytopenia. It also can occur with preexisting uniform splenomegaly[20] or splenic torsion.[56] Splenic infarction is a sign of abnormal coagulation or blood flow, and the clinical signs are

related to the underlying cause. Ultrasonographically, infarct regions are usually peripheral and are visible as hypoechoic, swollen areas (see Figure 206-5). After contrast injection, they appear hypoechoic when compared to the surrounding, normally-perfused spleen. Infarcted regions may resolve with appropriate therapy of the underlying disease.

Splenic Hyperplasia/Extramedullary Hematopoiesis

The splenomegaly seen with splenic hyperplasia and extramedullary hematopoiesis reflects "work hypertrophy" resulting from removal of abnormal blood cells from circulation, increased activity of mononuclear phagocytic and lymphoid cells, and increased blood cell production. In immune-mediated hemolytic anemia and thrombocytopenia, the spleen serves as a site of antibody production and also as an important site of removal of antibody-sensitized cells. Chronic increased destruction of red blood cells in some non–immune-mediated hemolytic diseases also appears to cause hyperplastic splenomegaly in dogs and cats.[59] Chronic antigen stimulation by infectious agents (e.g., bacterial endocarditis), blood parasites, or immune-mediated disease can stimulate hyperplasia of mononuclear phagocytic and lymphoid cells.

In work hypertrophy, the spleen is uniformly enlarged and may be hypoechoic on ultrasonographic examination. Cytologically, small lymphocytes still predominate, but there is an increase in medium- and large-sized lymphocytes, and plasma cells are commonly observed.[59]

Extramedullary hematopoiesis (EMH) may accompany splenic hyperplasia in patients with concomitant anemia, thrombocytopenia, or leukopenia. It is a very common cytologic diagnosis in dogs with uniform splenomegaly[14] and may also occur with a variety of splenic neoplasms. EMH is also common in cats; it was diagnosed in 21% of cats in one study.[60] A nodular pattern is more common in cats with EMH. The presence of nucleated red blood cells in peripheral blood suggests EMH. Cytologically, precursors of all three cell lines may be observed in this condition.[59] A finding of hematopoietic precursors with large numbers of vacuoles in the background suggests the presence of a myelolipoma rather than EMH.[59]

Nodular Hyperplasia/Hematoma

Nodular hyperplasia is a nonneoplastic regional proliferation of component cells normally found in the parenchyma of the canine spleen.[61] Nodular hyperplastic lymphoid proliferation is the most common form in dogs, but it is not common in cats.[1,2] A high percentage of splenic lesions in dogs have features of hematomas and nodular hyperplasia, which suggests that these disorders may be different stages of the same process. Lymphoid elements are usually observed with superimposed hematomas.[1] It has been suggested that marginal zoning distortion caused by nodular hyperplasia disrupts regional splenic blood flow in and around the hyperplastic nodule, eventually leading to hematoma formation.[1] Cats have a "nonsinusal" type of spleen and a different architecture and blood flow pattern of the intermediate circulation bordering the white pulp.[2] Those differences could render the feline spleen less vulnerable to disrupted blood flow and hematoma formation.

Nodular hyperplastic lesions are usually hypoechoic on ultrasonographic examination (see Figure 206-2). Splenic hematomas in dogs are associated with large splenic masses. A history of trauma is rare.[62] Most dogs with splenic hematoma are relatively healthy and do not have acute splenic rupture,[59] although they may develop hemoabdomen.[63] Large hyperplastic nodules and splenic hematoma cannot be differentiated from hemangiosarcoma grossly. Splenectomy is the treatment of choice for hematomas and hyperplastic nodules large enough to cause splenomegaly.[62]

A particular variation of hyperplastic nodule in dogs is the fibrohistiocytic nodule.[61] Nodular fibrohistiocytic proliferation is characterized by a mixed population of histiocytoid or spindle cells intertwined with hematopoietic elements, plasma cells, and lymphocytes. These nodules appear to form a continuum between lymphoid nodular hyperplasia and malignant splenic fibrous histiocytoma.[61] Histologically, the lymphoid: fibrohistiocytic ratio is the most important predictor of survival in these dogs. A higher proportion of lymphoid to fibrohistiocytic-type cells was associated with increased long-term survival.[61]

Inflammatory Splenomegaly

Inflammatory splenomegaly (splenitis) is a uniform splenomegaly usually secondary to infection. In addition

to the inflammatory response associated with hyperplasia, patients with splenitis also have increases in other inflammatory cells. It is important to classify the splenitis according to the predominant cell type because different etiologic agents are associated with different types of inflammation. Some overlap exists, and the same organism can cause a different inflammatory response in a different patient. For example, lymphoplasmacytic splenitis has been observed in patients with feline infectious peritonitis, histoplasmosis, and blastomycosis. Care must be taken in diagnosing suppurative splenitis in patients with peripheral neutrophilia or eosinophilic splenitis in patients with peripheral eosinophilia. The most common causes of splenitis according to the predominant inflammatory response are listed in Box 206-2. Infectious agents that can cause splenitis or lead to splenomegaly by chronic antigen stimulation, disturbances of blood flow, or by causing chronic anemia are listed in Box 206-4.

Box 206-4

Infectious Causes of Splenomegaly/Splenitis*

Viral

Feline immunodeficiency virus (C)
Feline infectious peritonitis (C)
Feline leukemia virus (C)
Infectious canine hepatitis (D)
Systemic calicivirosis (C)

Rickettsial and Mycoplasmal

Ehrlichiosis and anaplasmosis (C, D)
Hemotropic mycoplasmosis
Q fever *(Coxiella burnetii)*
Rocky Mountain spotted fever *(Rickettsia rickettsii)*

Bacterial

Bacteremia
Bartonellosis
Brucellosis (D)
Endotoxemia
Florida borreliosis
Lyme borreliosis
Melioidosis
Salmonellosis
Tularemia

Mycobacterial

Nocardiosis
Plague

Fungal

Blastomycosis
Cryptococcosis
Histoplasmosis
Sporotrichosis
Opportunistic infections
  Paecilomycosis
  Monocillium indicum (D)
  Systemic candidiasis

Protozoal

Babesiosis
Cytauxzoonosis (C)
Hepatozoonosis (*Hepatozoon canis*, D)

Leishmaniasis
Toxoplasmosis
Trypanosomiasis
C, Cats; *D*, dogs.

*Infectious disease may affect the spleen directly or cause splenomegaly by causing chronic anemia, chronic antigen stimulation or disturbances in blood flow (e.g., endotoxemia).

The Patient With A Splenic Nodule

Splenic nodules without associated splenomegaly are a relatively common finding in older dogs undergoing abdominal ultrasound for unrelated reasons. Most splenic nodules in this age group are benign and might require no further action. Myelolipomas can be easily identified, whereas lymphoid hyperplasia, EMH, and splenic infarcts may be more difficult to differentiate from an early neoplastic lesion. Further diagnostics should be attempted in breeds with high risk for hemangiosarcoma, patients with systemic tumors likely to involve the spleen (e.g., lymphoma, hemangiosarcoma), hematologic abnormalities, fever, or other signs of systemic infectious disease.[63] Fine-needle aspiration should be attempted in all splenic nodules (see ch. 89). The main risk associated with the procedure is contamination of abdominal cavity with tumor cells in case of hemangiosarcoma. Hemangiosarcoma is not likely to manifest itself as one or a few small nodules, but it may be a risk in predisposed breeds. A more conservative approach involving repeating the ultrasonographic examination in 4 weeks has been suggested.[27] Any increase in size in the nodule over this period should then be pursued aggressively. It should be remembered that a change in diameter from 1.0 to 1.2 cm is associated with a doubling in volume for a spherical mass.[63]

General Management of A Patient With Splenic Disease

Diffuse splenomegaly is usually managed medically. Most diseases that cause diffuse splenomegaly are systemic, and treatment should be directed at the underlying cause. Splenic torsion in dogs is the exception to the rule. A few tumors and myeloproliferative disease can also benefit from removal of the spleen. Splenectomy can also be considered in patients with immune-mediated anemia or thrombocytopenia refractory to therapy. It is important to demonstrate bone marrow hyperplasia in the cell line with decreased peripheral numbers before splenectomy is performed. Spleen removal is the treatment of choice for patients with splenic masses.

Removal of the spleen may predispose the patient to infections. Splenectomized humans are more likely to die of sepsis, but this predisposition has not yet been confirmed in dogs and cats. A few organisms that infect blood cells (e.g., babesiosis, hemotropic mycoplasmosis, and ehrlichiosis) are known to occur more in splenectomized patients. Ideally, dogs and cats should be tested before splenectomy and treated accordingly if infected.

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SECTION XIII

Infectious Diseases

OUTLINE

General
Bacterial Diseases
Protozoal Diseases
Viral Diseases
Fungal Diseases

General

OUTLINE

Chapter 207 Laboratory Diagnosis of Infectious Disease
Chapter 208 Companion Animal Vaccinations
Chapter 209 Antimicrobial Resistance, Surveillance and Nosocomial Infections
Chapter 210 Zoonoses

CHAPTER 207

Laboratory Diagnosis of Infectious Disease

Michael R. Lappin

There are two primary methods for diagnosing infectious diseases: detection of the organism or detection of antibodies against the organism. Infectious agents are detected in biological specimens most frequently by culture, cytology, fecal examination, histopathology, immunologic techniques, and nucleic acid amplification techniques. Polymerase chain reaction (PCR) assay and reverse transcriptase PCR (RT-PCR) assay are the most commonly used nucleic acid amplification techniques. Detection of the organism gives the most information supporting a clinical diagnosis of an infectious disease, but these assays are neither available nor optimal for all agents. Thus, antibody detection is still commonly used to aid in the diagnosis of some infectious diseases. In some clinical situations, the combination of organism detection and antibody detection assays is indicated.

When evaluating the results of infectious disease diagnostic tests, the *analytical sensitivity* defines the minimum detectable amount of the substance in question that can accurately be measured; the *analytical specificity* defines whether the substance detected cross-reacts with other substances. The *diagnostic sensitivity* is the proportion of positive test results from known infected animals; the *diagnostic specificity* is the proportion of negative test results from known uninfected animals. The *predictive value of a positive test* (PPV) is the probability that a test-positive animal is diseased; the *predictive value of a negative test* (NPV) is the probability that a test-negative animal is normal. The lower the prevalence of disease, the lower the PPV. Disease prevalence has little effect on negative predictive values.

Sensitivity, specificity, PPV, and NPV vary with each assay. Many of the infectious disease agents encountered in small animal practice colonize normal animals, as well as induce disease in some individuals. For example, the DNA of "*Candidatus* M. haemominutum" can be amplified from the blood of approximately 20% of healthy cats and rarely is associated with illness.[1] Thus, when DNA of "*Candidatus* M. haemominutum" is amplified from the blood of a cat with anemia of fever, the test result alone does not prove the agent is the cause of the clinical signs (PPV <100%). Thus, veterinarians generally need to use a combination of findings to aid in the clinical diagnosis of an infectious disease:

- Appropriate signalment and history for the infectious agent suspected
- Clinical signs referable to the agent
- Detection of the agent (cytology, culture, antigen assay, PCR assay) or antibodies against the agent
- Exclusion of other causes of the clinical syndrome
- Response to an appropriate treatment[2]

When these criteria are met, the suspected infectious agent might have been the cause of the clinical disease. However, it is always possible that the disease process resolved in spite of the therapy prescribed.

The following is a discussion of some of the most common infectious disease organism detection and antibody detection techniques used in small animal practice. Also see the individual chapters of the textbook for each infectious agent for more detailed information.

Organism Detection

Culture

Culture can be used to document the presence of some bacteria, rickettsia, fungi, viruses, and protozoans in biologic specimens. However, some bacteria (e.g., hemoplasmas) have never been cultured, and many rickettsia, viruses, and protozoans are difficult to culture. Thus, PCR assays are now being used frequently to document these infections (see Nucleic Acid Amplification section). However, for many bacteria and fungi, culture is still the optimal way to document infection. For example, for most aerobic bacterial diseases, culture

is superior to PCR assay because antimicrobial susceptibility testing can be used to determine optimal drug therapy.

In small animal practice, aerobic bacterial culture is used most frequently. To minimize organism death or overgrowth of normal flora, the material to be cultured should be collected without contamination, the material should be transported to the laboratory as quickly as possible in the most appropriate medium, and the most appropriate culture materials should be used. For routine aerobic bacterial culture, swabs containing transport medium should be used if a delay of greater than 3 hours is expected. If cultures are not to be started within 4 hours, the swabs should be refrigerated (or transported with cold packs) to inhibit bacterial growth; some bacteria will grow more rapidly than others, potentially masking fastidious organisms. Most aerobes will survive at 4° C (routine refrigeration temperature) in tissue or on media-containing swabs for 48 hours. Routine aerobic culture is generally successful on fluid samples (e.g., urine, airway washings) stored at 20° C for 1 to 2 hours, 4° C for 24 hours, or 4° C for 72 hours if placed in transport medium. See the bacterial endocarditis (ch. 251) and *Bartonella* spp. (ch. 215 and 216) chapters of the textbook for a discussion of optimal blood culture techniques.

If feces are to be cultured for *Salmonella* spp. or *Campylobacter* spp., the laboratory should be provided approximately 2 to 3 g of fresh feces for optimal results. A transport medium should be used if a delay is expected. The laboratory should be notified of the suspected pathogen so that appropriate culture media can be used. *Tritrichomonas foetus* and *Giardia* spp. can also be cultured from feces but these techniques are rarely performed because antigen assays (*Giardia* spp.) or PCR assays (both organisms) are now widely available (see ch. 276).[3-5] In addition, it has now been shown that culture is not specific for *T. foetus* and that PCR should be considered to speciate prior to treatment.[3]

In certain situations, anaerobic, *Mycoplasma* spp., *Mycobacterium* spp., or fungal culture may also be indicated. Solid-phase transport media that will support the growth of most aerobes, anaerobes, *Mycoplasma* spp., *Mycobacterium* spp, and fungi for several days if refrigerated are available. Amies medium or modified Stuart bacterial transport medium are also often used to transport materials for *Mycoplasma* spp. culture. *Mycoplasma* and *Ureaplasma* cultures are most commonly performed on airway washings, synovial fluid, and exudates from chronic draining tracts in cats, urine from animals with chronic urinary tract disease, and the vagina of animals with genital tract disease. *Mycobacterium* spp., *Mycoplasma* spp., *Bartonella* spp., and fungal culture may be indicated if pyogranulomatous inflammation is present. Most commercial laboratories do not provide *Mycoplasma* spp., *Mycobacterium* spp., anaerobic bacterial, or fungal antimicrobial susceptibility testing, so positive samples should be saved for transport to specialized laboratories as indicated.

In-house culture systems are available for cutaneous fungal agents. Materials from dogs or cats with suspected systemic fungal infection can be transported to the laboratory as described for bacteria, and the laboratory can be told specifically that fungal culture is needed. The mycelial phase of some systemic fungi like *Blastomyces dermatitidis* and *Histoplasma capsulatum* occurs in culture and can infect humans, so in-house culture for these agents is not recommended.

Viral agents can be isolated from tissues or secretions at some laboratories. However, for most routine viral infections of dogs and cats, PCR or RT-PCR assays to amplify RNA viruses are now available (see Nucleic Acid Amplification section).

Cytology and Histopathology

Cytologic evaluation of exudates (see ch. 74), bone marrow aspirates (see ch. 92), blood smears, synovial fluid (see ch. 74 and 94), gastric brushings (see ch. 113 and 275), duodenal secretions (see ch. 113 and 275), urine (see ch. 72), prostatic washings (see ch. 111), airway washings (see ch. 101), fecal smears (see ch. 81), tissue imprints (see ch. 93), and aspiration biopsies (see ch. 89) is an inexpensive and extremely valuable tool for the documentation of current infections. For demonstration of most blood-borne infectious agents, thin smears are preferred. Cells in airway washings, prostatic washings, urine, aqueous humor, and cerebrospinal fluid (CSF) should be pelleted by centrifugation at 2000 × g for 5 minutes before staining. Multiple slides should always be made. After being placed on the microscope slide, the material is air-dried at room temperature, fixed if indicated by the procedure used, and stained. Slides that are not stained immediately should be fixed by dipping in 100% methanol and air-dried. Cytologic specimens can be stained with routine stains; immunocytochemical techniques for certain pathogens are available (see Immunologic Techniques). Stains routinely used for the diagnosis of infectious diseases in small animal practice include Wright-Giemsa stain, Diff-Quik, Gram stain, and acid-fast stain.

One slide for cytologic evaluation is generally stained initially with Wright-Giemsa or Diff-Quik stains. If bacteria are seen (Table 207-1), Gram stain is applied to another slide to differentiate Gram-positive and

Gram-negative agents that can be used to aid in the empiric selection of antibiotics.

TABLE 207-1

Characteristic Cytologic Morphology of Common Small Animal Bacteria

AGENT	MORPHOLOGIC CHARACTERISTICS
Actinomyces spp.	Gram-positive, acid-fast–negative filamentous rod within sulfur granules
Anaerobes	Usually occur in mixed morphologic groups
Bacteroides fragilis	Thin, filamentous, Gram-negative rods
Campylobacter spp.	Seagull-shaped spirochete in feces
Chlamydia felis	Large, cytoplasmic inclusions in conjunctival cells or neutrophils
Clostridium spp.	Large, Gram-positive rods
Clostridium perfringens	Large, spore-forming rods in feces
Hemoplasmas*	Rod- or ring-shaped on the surface of red blood cells
Helicobacter spp.	Tightly coiled spirochetes in gastric or duodenal brushings
Mycobacterium spp.	Intracytoplasmic acid-fast rods in macrophages or neutrophils
Nocardia spp.	Gram-positive, acid-fast–positive filamentous rod within sulfur granules
Leptospira spp.	Spirochetes in urine; dark-field microscopy required (see ch. 217)
Yersinia pestis	Bipolar rods in cervical lymph nodes or airway fluids

*_Mycoplasma haemofelis_, "_Candidatus_ M. haemominutum," and "_Candidatus_ M. turicensis" infect cats, and _M. haemocanis_ and "_Candidatus_ M. haematoparvum" infect dogs.

Actinomyces (nonacid-fast) and *Nocardia* (generally acid-fast) can be differentiated by acid-fast staining characteristics. If pyogranulomatous inflammation is present, acid-fast staining is indicated to assess for *Mycobacterium* spp. within the cytoplasm of macrophages.

The hemoplasmas (see Table 207-1 and ch. 219), some rickettsial agents (Table 207-2; *Anaplasma* spp., *Ehrlichia* spp.), and some protozoans (*Babesia* spp., *Cytauxzoon felis*) can be noted on cytologic examination of thin blood smears. However, organism numbers can fluctuate and so cytology can be falsely negative. Wright-Giemsa stain is the best stain to use in practice for these organisms. Hemoplasmas can leave the surface of the red blood cell when the blood is placed into EDTA. Thus, making thin blood smears immediately with blood that has not been placed into anticoagulant may give optimal results (Figure 207-1). Collection of blood from an ear margin vessel for blood smear cytology may improve the likelihood of detecting *Ehrlichia* spp. (Figure 207-2) or *Anaplasma* spp. morulae (Figure 207-3) within white blood cells.

TABLE 207-2

Characteristic Cytologic Morphology of Common Small Animal Rickettsial Agents

AGENT	MORPHOLOGIC CHARACTERISTICS
Anaplasma phagocytophilum	Clusters of Gram-negative bacteria (morulae) in neutrophils and eosinophils
Anaplasma platys	Clusters of Gram-negative bacteria (morulae) in platelets
Ehrlichia canis	Clusters of Gram-negative bacteria (morulae) in mononuclear cells
Ehrlichia chaffeensis	Clusters of Gram-negative bacteria (morulae) in mononuclear cells
Ehrlichia ewingii	Clusters of Gram-negative bacteria (morulae) in neutrophils
Neorickettsia risticii	Clusters of Gram-negative bacteria (morulae) in mononuclear cells

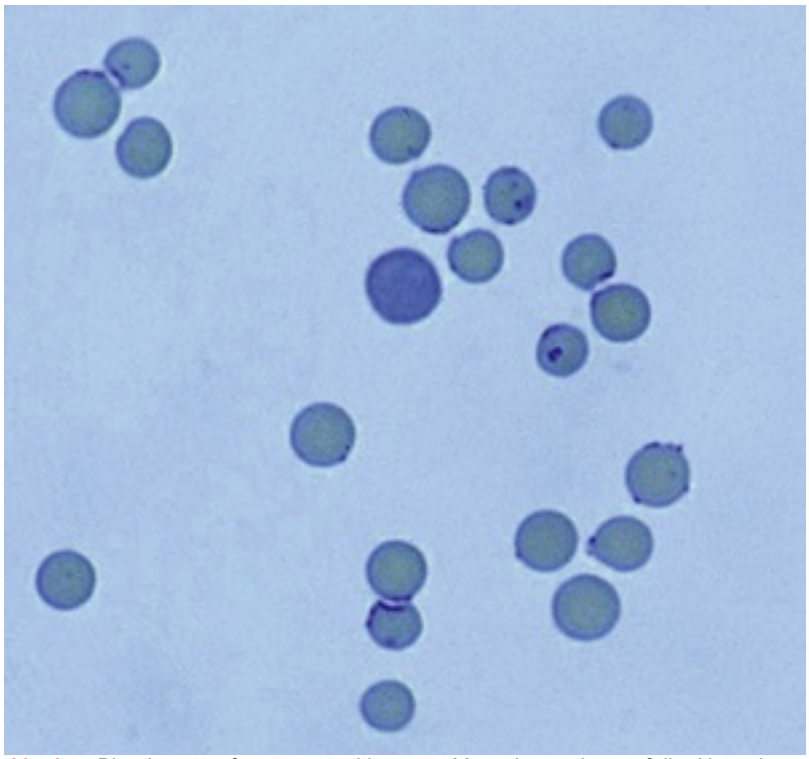

FIGURE 207-1 Blood smear from a cat with acute *Mycoplasma haemofelis.* Note the epicellular location of the organisms (1000×).

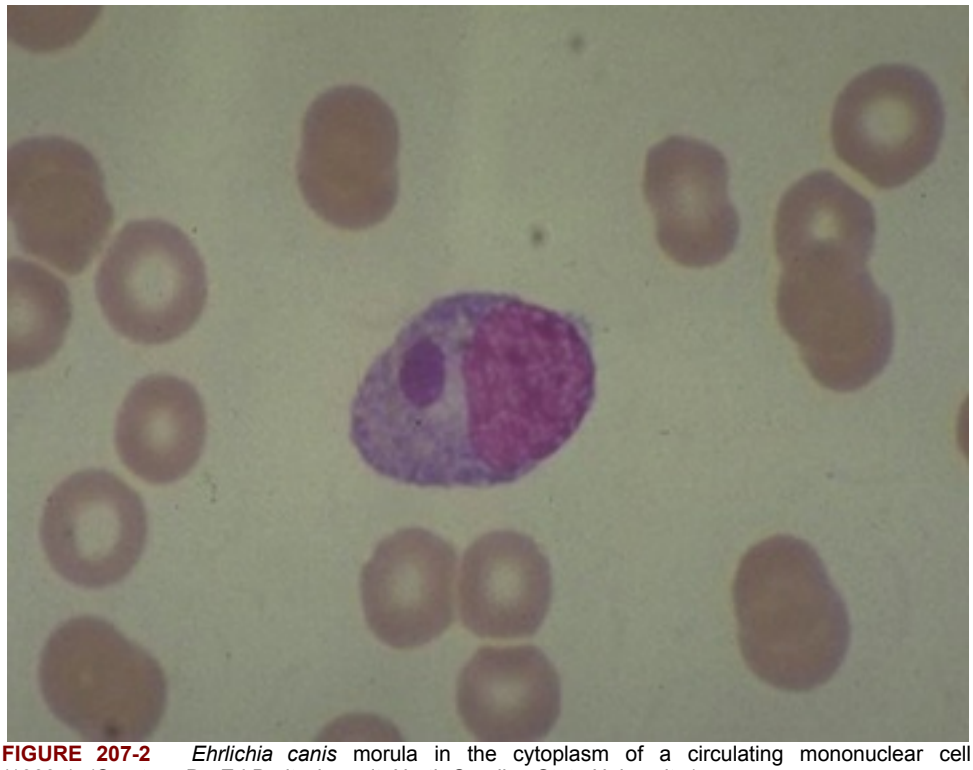

FIGURE 207-2 *Ehrlichia canis* morula in the cytoplasm of a circulating mononuclear cell (1000×). (Courtesy Dr. Ed Breitschwerdt, North Carolina State University.)

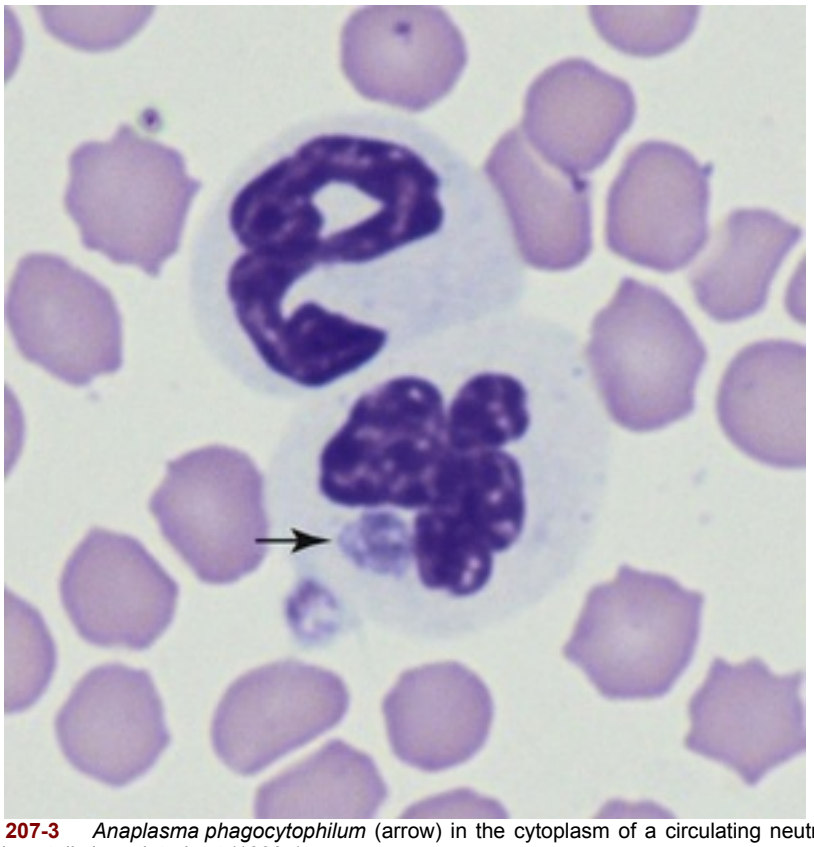

FIGURE 207-3 *Anaplasma phagocytophilum* (arrow) in the cytoplasm of a circulating neutrophil of an experimentally inoculated cat (1000×).

While a definitive diagnosis may not be made with the following techniques, fecal or rectal cytology can be considered for all dogs and cats with diarrhea to help guide the diagnostic or therapeutic plan. A small amount of fecal material should be collected from the surface of the feces or the wall of the rectum by cotton swab, which is rolled on a microscope slide multiple times to give areas with varying smear thickness. After air-drying, the slide is generally stained with Diff-Quik stain and examined for white blood cells and bacteria morphologically consistent with *Campylobacter* spp. (spirochetes; Figure 207-4) or *Clostridium perfringens* (spore-forming rods; Figure 207-5). It is also possible that *H. capsulatum* or *Prototheca* may be observed in the cytoplasm of mononuclear cells. Other stains can be applied to aid in identification of the enteric protozoans (see ch. 221).

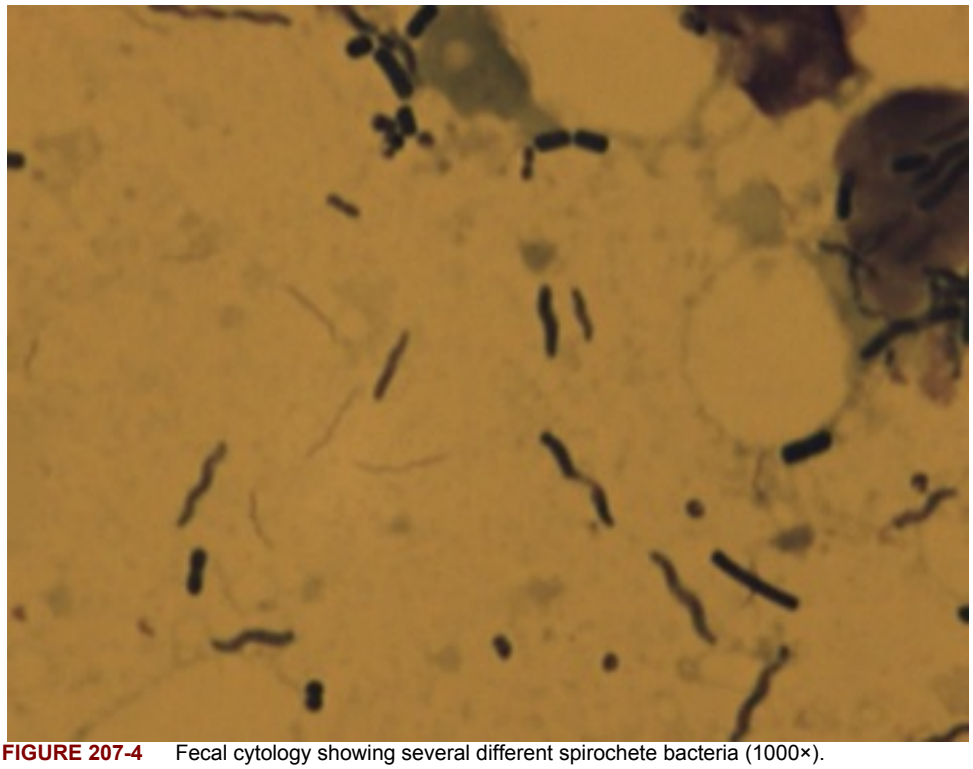

FIGURE 207-4 Fecal cytology showing several different spirochete bacteria (1000×).

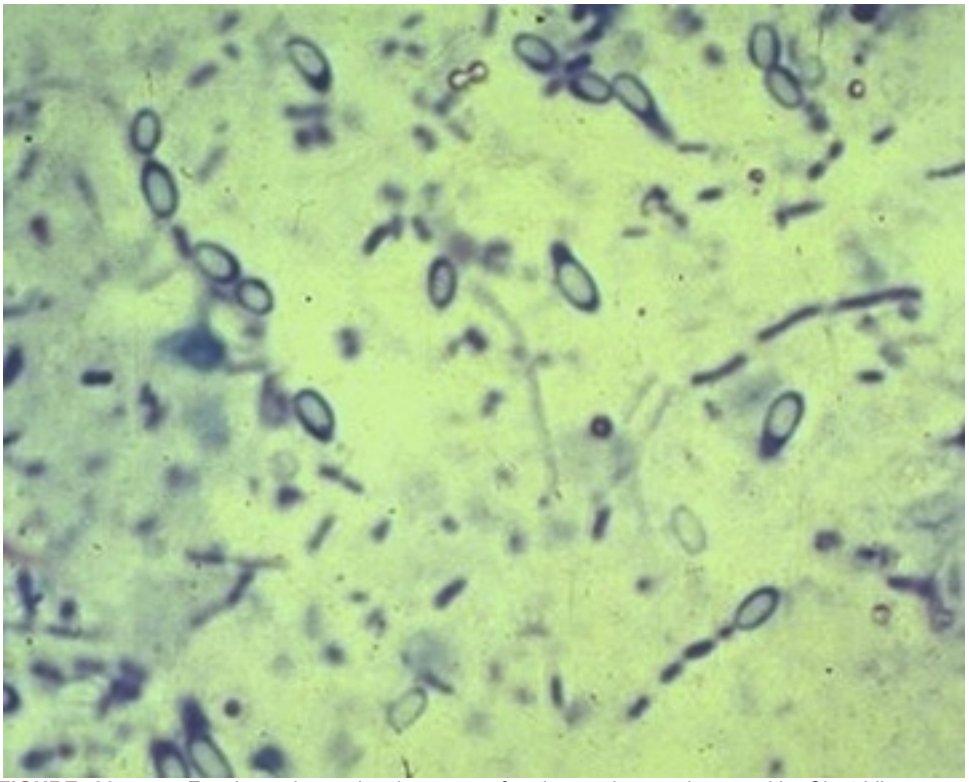

FIGURE 207-5 Fecal cytology showing spore-forming rods consistent with *Clostridium* spp. (1000×).

Arthrospores and conidia of dermatophytes can be identified cytologically. Hairs plucked from the periphery of a lesion are covered with 10% to 20% potassium hydroxide on a microscope slide to clear debris.

The slide is then heated but not boiled, and it is examined for dermatophytes. All dogs or cats with chronic, draining skin lesions should have imprints of the lesions made and evaluated cytologically for the presence of fungal organisms (Table 207-3). This is very important if *Sporothrix schenckii* is on the differential list, as this organism is capable of zoonotic transmission to people (Figure 207-6 and ch. 236).[6]

TABLE 207-3

Characteristic Cytologic Morphology of Small Animal Systemic Fungal Agents

AGENT	MORPHOLOGIC CHARACTERISTICS
Blastomyces dermatitidis	Extracellular yeast, 5 to 20 microns in diameter, thick, refractile double-contoured wall, broad-based bud; routine stains are adequate
Cryptococcus neoformans	Extracellular yeast, 3.5 to 7 microns in diameter, thick unstained capsule, thin-based bud, violet color with light red capsule with Gram stain, unstained capsule with India ink
Coccidioides immitis	Extracellular spherules (20 to 200 microns in diameter) containing endospores, deep red to purple double outer wall with bright red endospores with periodic acid–Schiff stain
Histoplasma capsulatum	Intracellular yeast in mononuclear phagocytes, 2 to 4 microns in diameter, basophilic center with lighter body with Wright's stain
Sporothrix schenckii	Intracellular yeast in mononuclear phagocytes, 2 to 3 microns × 3 to 6 microns in diameter; round, oval, or cigar-shaped

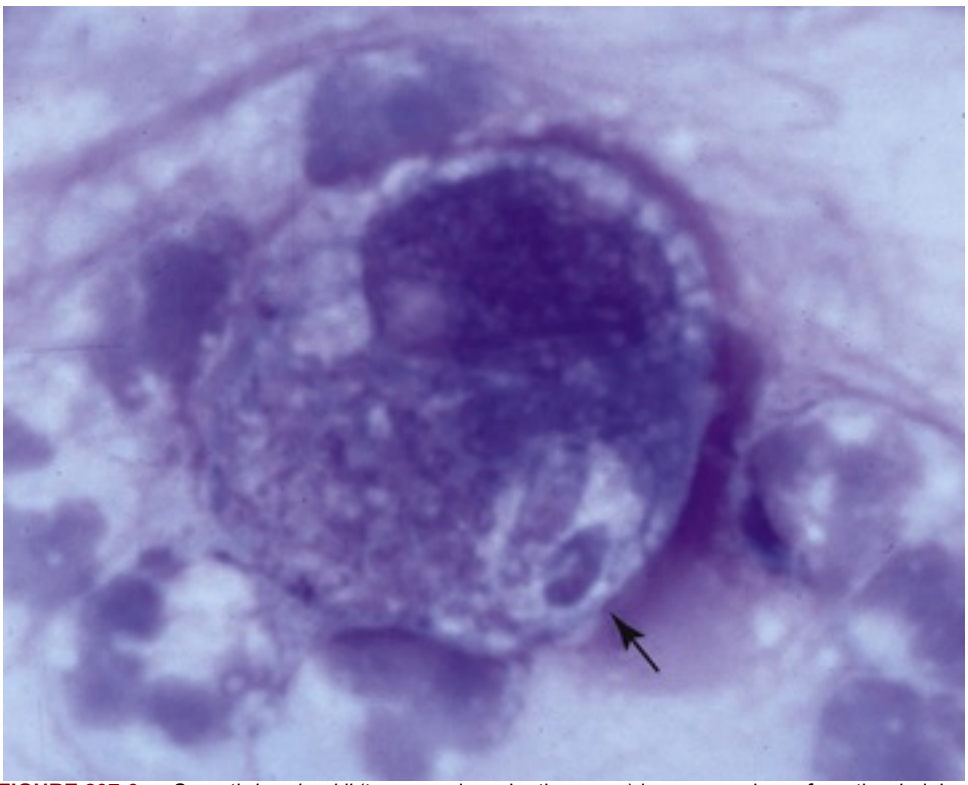

FIGURE 207-6 *Sporothrix schenkii* (two organisms by the arrow) in a macrophage from the draining tract of a cat (1000×).

Canine distemper virus infection causes inclusions in circulating lymphocytes, neutrophils, and erythrocytes of some dogs (see ch. 228). Rarely, feline infectious peritonitis-associated coronavirus results in intracytoplasmic inclusions in circulating neutrophils (see ch. 224). Feline herpesvirus 1 (FHV-1) transiently results in intranuclear inclusion bodies in epithelial cells (see ch. 229). However, cytology is commonly falsely negative for canine and feline viral diseases. Immunocytochemical or nucleic acid amplification techniques

are generally more sensitive and specific than cytology for these agents.

Tissues collected from animals with suspected infectious diseases can be evaluated by several different techniques. Specimens for culture should be collected from the fresh samples and then tissues can be frozen, placed into 10% buffered formalin solution, or placed into glutaraldehyde-containing solutions. Routine histopathologic evaluation is performed on formalin-fixed tissues. Special stains can be used to maximize the identification of some infectious agents, and the clinician should alert the histopathology laboratory to the infectious agents suspected. Frozen specimens can be superior to formalin-fixed tissues for immunohistochemical staining and nucleic acid amplification techniques. Glutaraldehyde-containing fixatives are superior to other fixatives for electron microscopic examination of tissues.

Fecal Examination

Infectious agents are commonly associated with gastrointestinal disease. A number of fecal examination techniques, including direct saline smear, fecal or rectal cytology, fecal flotation, Baermann funnel technique, immunologic techniques, and nucleic acid amplification techniques, are used to evaluate dogs and cats with vomiting or diarrhea (see ch. 276-278). In addition, some fecal examination techniques can aid in the diagnosis of respiratory parasites as these agents are often swallowed and passed in feces (see ch. 81).

Fecal flotation is indicated in dogs or cats with gastrointestinal signs of disease. Cysts, oocysts, and eggs in feces can be concentrated to increase the sensitivity of detection. Most eggs, oocysts, and cysts are easily identified after centrifugation in zinc sulfate solution or Sheather's sugar solution.[7,8] These procedures are superior to passive flotation techniques for identification of most parasites, in particular *Giardia* spp. If diarrhea is present, the fecal flotation is often combined with microscopic examination of fresh, liquid feces or a wet-mount examination for the presence of protozoal trophozoites (*Giardia* spp. [small bowel diarrhea], *T. foetus* [large bowel diarrhea], and *Pentatrichomonas hominis* [large bowel diarrhea]). A 2 mm × 2 mm × 2 mm quantity of fresh feces or mucus is mixed thoroughly with one drop of 0.9% NaCl or water, a coverslip is applied, and the slide is evaluated immediately for motile organisms by examining it under 100× magnification (Video 207-1).

Immunologic Techniques

Several immunologic techniques are used to identify infectious agents or their antigens in body fluids, feces, cells, or tissues. In general, polyclonal or monoclonal antibodies against the agent in question are used in a variety of different test methodologies, including direct fluorescent antibody assay with cells, tissue, or feces, immunohistochemistry with tissues, and agglutination assays and enzyme-linked immunosorbent assays (ELISAs) for antigen detection in serum, plasma, blood, or feces. Sensitivity, specificity, NPV, and PPV vary among assays but are generally high for most assays. Some assays require specialized equipment like fluorescent microscopes and so are only available at diagnostic laboratories. Other assays are available as point-of-care tests.

Currently available antigen assays for use with serum or plasma from dogs or cats include *Dirofilaria immitis, Cryptococcus neoformans, B. dermatitidis, H. capsulatum,* and feline leukemia virus. Parvovirus, *Cryptosporidium parvum,* and *Giardia* spp. antigen detection procedures are available for use with feces. The *Blastomyces* antigen assay has also been shown to have clinical utility using urine.[9]

Immunocytochemistry and immunohistochemistry techniques are available for the documentation of a variety of infectious diseases. These procedures are particularly valuable for the detection of viral diseases, detection of agents present in small numbers, and for differentiating among agents with similar morphologic features. In general, these techniques are more sensitive and specific than histopathologic techniques and are comparable to culture. See individual chapters for further discussion of these assays.

Nucleic Acid Amplification Techniques

The PCR reaction amplifies DNA.[10] Very low DNA copy numbers can be amplified to detectable levels with this technique (Figure 207-7). By use of a reverse transcriptase step, RNA is converted to DNA; therefore, the technique can also be used to detect RNA (RT-PCR). Depending on the infectious agent in question, the techniques can be more sensitive than other available assays. In addition, PCR assay results can often be returned within 24 hours of sample submission, which is generally quicker than culture. However, the assays must always be shipped to a diagnostic laboratory as special equipment is required. If the organism in question is difficult to culture (e.g., *Ehrlichia* spp.) or cannot be cultured (e.g., hemoplasmas), PCR assays are

of particular benefit for documenting infection.

FIGURE 207-7 Conventional polymerase chain reaction assay example. *S,* Standards; *1,* positive amplicon; *2,* positive amplicon; *3,* negative sample.

Specificity of PCR assays can be very high, depending on the primers used in the reaction. For example, primers can be designed to detect one bacterial genus but not others. Primers can also be designed to identify only one species. For example, a PCR assay can be developed to detect all *Anaplasma* spp. or just one species such as *A. phagocytophilum.*

PCR assays are prone to false-positive results if sample contamination occurs during collection or at the laboratory performing the procedure. False-negative results can occur if the sample is handled inappropriately while being collected or transported. Some PCR assay results may also be affected by administration of antimicrobial drugs prior to sample collection. For example, hemoplasma or *Bartonella* spp. PCR results can be transiently negative during antibiotic treatment even though infection persists. Acute infections generally have higher DNA (or RNA) copies in samples than do chronic infections because in chronic infections, the immune response has attenuated the organism. Thus, the optimal sample for assessment by PCR assay is usually one collected during the acute phase of illness prior to antimicrobial treatment.

While many commercial laboratories are offering nucleic acid amplification assays, there is minimal to no standardization of assays. In addition, there may be little external quality control at some laboratories. For example, samples from cats with and without feline immunodeficiency virus (FIV) infection were sent to four different laboratories offering FIV PCR assay.[11] The laboratory with the best performance obtained the correct result on 90% of the samples; two of the laboratories obtained the correct result on <60% of the samples.

While PCR assays are very sensitive, the PPV of many assays can be very low. For example, because the technique detects DNA or RNA of both live and dead organisms, positive test results may be achieved even if the infection has been controlled. When the organism being tested for commonly infects the background population of healthy pets, interpretation of results for a single animal can be difficult. For example, feline calicivirus (FCV) is an important pathogen of cats. However, the organism is also commonly carried by healthy cats and modified live vaccine strains colonize cats.[12] Thus, although FCV RT-PCR is a sensitive way to document infection by FCV, the PPV of a FCV RT-PCR result is actually very low. In one study of cats with and without stomatitis, the PPV of FCV RT-PCR assays results from oral swabs was 0%.[13] Similar problems exist for FHV-1 PCR assay results.[14,15] In one study of cats with and without conjunctivitis, more FHV-1

positive tests were detected in the healthy control group than the group with conjunctivitis.[14]

Real-time PCR or fluorogenic PCR is a type of PCR assay that can be used to determine the amount of microbial DNA in a sample (Figure 207-8).[12-15] This technique can be used to monitor response to drug treatment.[16-19] It is possible that the DNA or RNA load in a sample will correlate to the presence of disease for some agents. However, that does not appear to be true for chronic FHV-1 conjunctivitis, *Mycoplasma haemofelis*, or "*Candidatus* M. haemominutum" infections.[16-18]

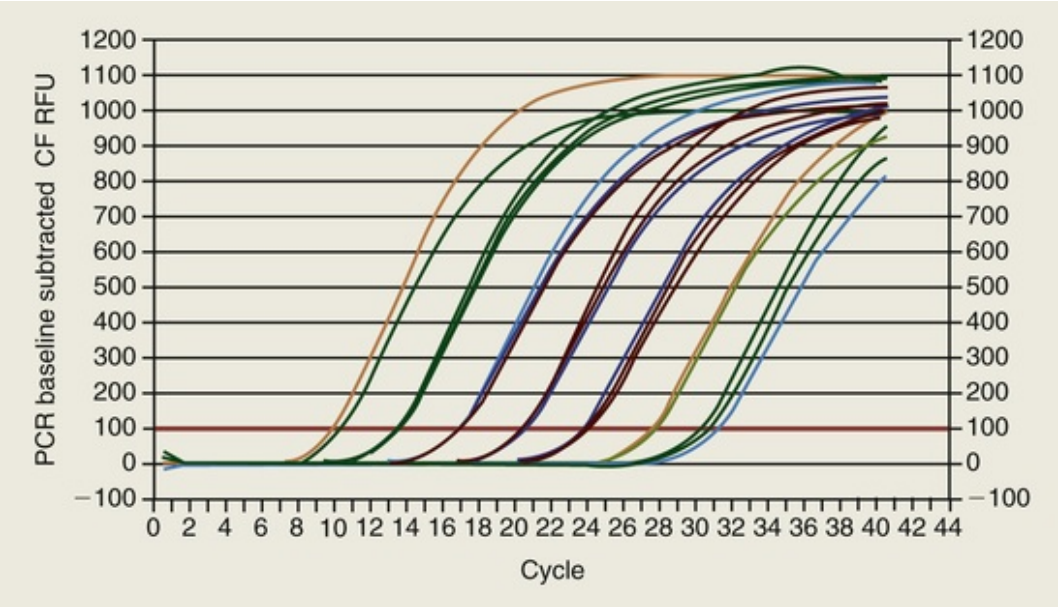

FIGURE 207-8 Example tracing from a fluorogenic real-time polymerase chain reaction *(PCR)* assay. *CF RFU*, Curve-fit relative fluorescence units.

Based on these observations, it is very important that small animal practitioners carefully assess the predictive values of currently available PCR and the expertise and reliability of the laboratory that will be performing the assays. New PCR assays are being developed almost daily. See specific chapters for a discussion of the use of PCR for the detection of individual agents.

Antibody Detection

Serum Antibodies

Once exposed to foreign antigens, the immune system generates serum antibodies (humoral immune response). Complement fixation, hemagglutination inhibition, serum neutralization, agglutination assays, agar gel immunodiffusion, indirect fluorescent antibody assay (IFA), ELISA, and Western blot immunoassay are commonly used to detect serum antibodies against infectious agents. Complement fixation, hemagglutination inhibition, serum neutralization, and agglutination assays generally detect all antibody classes in a serum sample. Specific antibodies most commonly assayed for include immunoglobulin M (IgM), immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin E (IgE). ELISA, Western blot immunoassay, and IFA are the assay types that are usually adapted to detect specific IgM, IgG, or IgA responses. Western blot immunoassays have the potential advantage of allowing the determination of the different antigens recognized by the humoral immune responses (Figure 207-9).

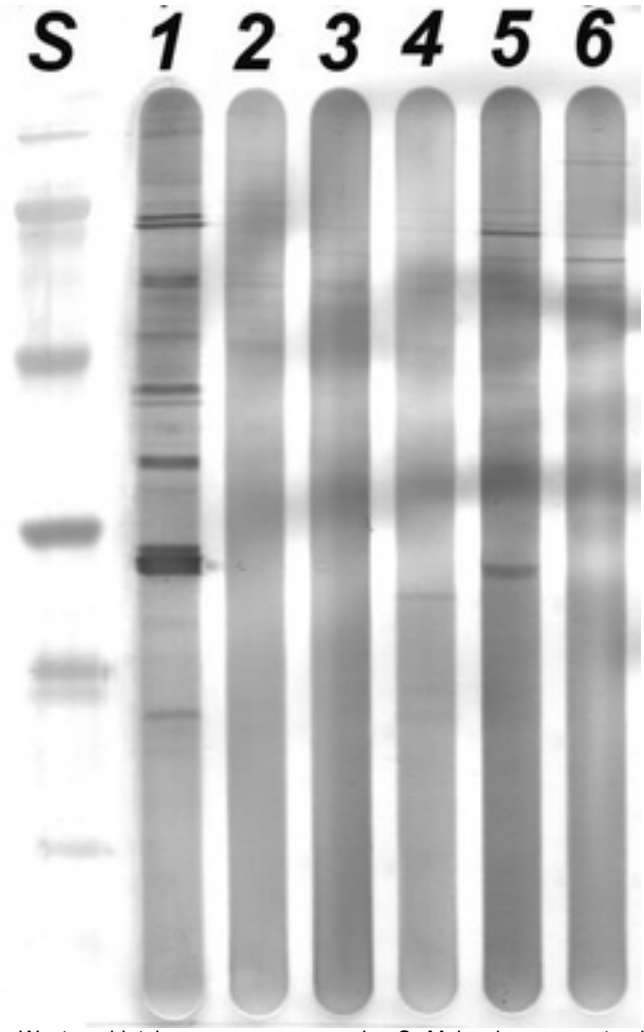

FIGURE 207-9 Western blot immunoassay example. *S,* Molecular mass standards; *1,* positive control; *2,* negative control; *3,* negative sample; *4,* positive sample; *5,* positive sample; *6,* negative sample.

Comparison of IgM, IgA, and IgG antibody responses against an infectious agent can be used to attempt to prove recent or active infection. In general, IgM is the first antibody produced after antigenic exposure.[20] Antibody class shift to IgG occurs in days to weeks. Serum IgA responses often mirror those of IgG (Figure 207-10).

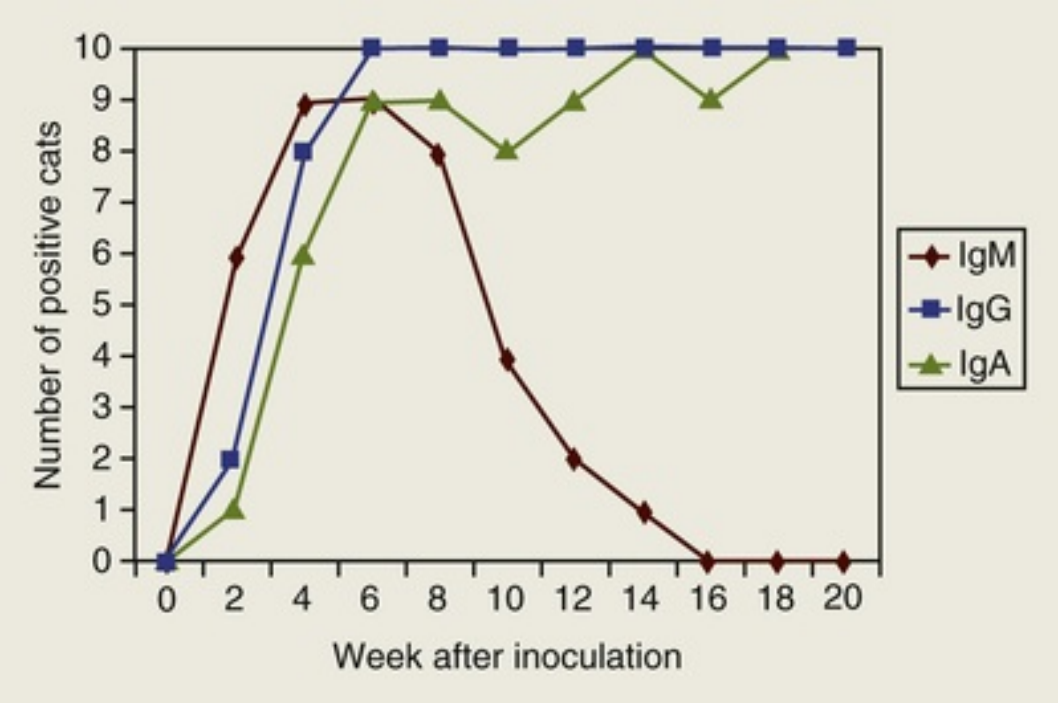

FIGURE 207-10 Hypothetical example of the serum IgM, IgG, IgA responses to an antigen over time.

Timing of antibody testing is important. In general, serum antibody tests in puppies and kittens cannot be interpreted as specific responses until at least 8 to 12 weeks of age due to presence of antibodies from the dam passed to the puppy or kitten in colostrum (see ch. 208). Most infectious agents can induce disease within 3 to 10 days after initial exposure; using many assays, serum IgG antibodies are usually not detected until at least 2 to 3 weeks after initial exposure. Based on these facts, false-negative serum antibody tests during acute disease are probably common in small animal practice. If specific serum antibody testing is negative initially in an animal with acute disease, repeat antibody testing should be performed in 2 to 3 weeks to assess for seroconversion. Documentation of increasing antibody titers is consistent with recent or active infection. Because of a slight potential for interassay variation, it is preferable to assess both the acute and convalescent sera using the same assay on the same day.

Many of the infectious agents encountered in small animal practice infect a large percentage of the population, resulting in serum antibody production, but only induce disease in a small number of animals in the infected group. Notable examples include coronaviruses, *Bartonella henselae, Toxoplasma gondii,* and *Borrelia burgdorferi.*[20-22] For these examples, even though assays with good sensitivity and specificity for the detection of serum antibodies are available, the PPV for presence of disease is extremely low, since antibodies are commonly detected in nondiseased animals. Diagnostic utility of some serologic tests is also limited due to the presence of antibodies induced by vaccination. Examples include feline coronaviruses, some *Borrelia burgdorferi* assays, FHV-1, FIV, parvoviruses, calicivirus, and canine distemper virus (see ch. 208).

Positive results in serum antibody tests should always be interpreted only as evidence of present or prior infection by the agent in question. Recent or active infection is suggested by the presence of IgM, an increasing antibody titer over 2 to 3 weeks, or seroconversion (negative antibody result on the first test, positive antibody result on convalescent testing). If detected, documentation of increasing antibody titers can suggest recent exposure to an antigen. However, the time period from the first positive result and maximal antibody titers can be very short. For example, some cats experimentally inoculated with *T. gondii* will go from the first detectable titer to the maximal titer within 1 to 2 weeks.[20]

Detection of recent infection based on antibody testing does not always prove disease due to the agent in question, especially if most infected animals are subclinical. *Borrelia burgdorferi, T. gondii,* and *B. henselae* are common examples. Conversely, failure to document recent or active infection based on serologic testing does not exclude a diagnosis of clinical disease. For example, many dogs with ehrlichiosis and dogs or cats with systemic fungal infections develop clinical signs of disease after serum antibody titers have reached their plateau.

Individual animals vary in their humoral responses against specific antigens. Some animals are high

responders and produce large concentrations of specific antibody, whereas others do not. Thus, the magnitude of an antibody titer does not definitely document that an antigenic exposure was recent, active, or associated with clinical disease. This is particularly true for the IgG class of antibody and for agents resulting in persistent infections. For example, many healthy cats experimentally inoculated with *T. gondii* have IgG antibody titers >10,000 6 years after the last inoculation.[20] Since there are no antibody test results that alone prove the presence of disease, they must be combined with other clinical parameters.

Antibodies in Body Fluids

Some infectious agents induce disease of the eyes and central nervous system (CNS). Documentation of agent-specific antibodies in aqueous humor, vitreous humor, or CSF can be used to document the involvement of these tissues. Quantification of ocular and CSF antibodies is difficult to interpret if serum antibodies and inflammatory disease are present because serum antibodies leak into ocular fluids and CSF in the face of inflammation. Detection of local production of antibodies within the eye or CNS has been used to aid in the diagnosis of canine distemper virus infection (see ch. 228), FHV-1 (see ch. 229), feline bartonellosis (see ch. 216) and feline toxoplasmosis (see ch. 221). The following is a method to prove local antibody production by the eye or CNS.

$$\frac{\text{Aqueous humor or CSF specific antibody}}{\text{Serum specific antibody}} \times \frac{\text{Serum total antibody}}{\text{Aqueous humor or CSF total antibody}}$$

If this ratio is greater than 1, it suggests that the antibody in the aqueous humor or CSF was produced locally. This formula has been used extensively in the evaluation of cats with uveitis. Approximately 60% of cats with uveitis in the United States have *T. gondii*–specific IgM, IgA, or IgG C values >1.[23] The technique was also used to help prove that FHV-1[24] and *B. henselae*[23] are causes of uveitis in cats.

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CHAPTER 208

Companion Animal Vaccinations

Michael J. Day

Client Information Sheets:
Vaccination of Your Dog
Vaccination of Your Cat

History of Vaccines and Vaccination

Edward Jenner's demonstration of the cross-protection between cowpox (vaccinia) virus and human smallpox in 1796 paved the way for more than two centuries of research and development in human and veterinary vaccinology. The power of vaccination in the control of infectious disease is readily demonstrated by the eradication of human smallpox in 1979 and the subsequent eradication of rinderpest in ruminants in 2011. With the exception of the work of Louis Pasteur on rabies vaccines, small companion animal vaccination has a shorter history, with the introduction of feline parvovirus vaccines as early as the 1940s and canine distemper vaccines in the following decade. Companion animal vaccines are now a major global industry with remarkable advances in technology paralleling, or in the case of cancer vaccines, preceding, the introduction of equivalent new products into human medicine.

The Immunology of Vaccination

Active immunization (as opposed to the delivery of preformed antibodies in passive immunization) involves the administration of an antigen by a means that generates an active immune response and persistent immunological memory in the host. The majority of current vaccines are designed to induce protective effector immune responses to infectious agents, but some vaccines trigger immune responses to cancer antigens (e.g., the canine melanoma vaccine) or induce suppressive immune responses to allergens (e.g., allergen-specific immunotherapy). The focus of this chapter will be on the former class of vaccine.

Delivery of a vaccine aims to replicate the natural protective host immune response to the specific pathogen, and it is now clear that the nature of protective immunity differs for different organisms. Knowing the optimal type of immune response to the target organism enables the development of efficacious vaccines, but being able to detect and measure the immune response after vaccination also provides a "correlate of protection" that indicates that the vaccinated animal now has immunity. For companion animal vaccines, the correlates of protection depend on the organism, its route of entry into the body, the pathogenesis of the disease caused by the infection, and the optimum host immune response. For some vaccines there is a very strong correlation between the induction of circulating organism-specific antibody and protective immunity. For example, in the case of canine distemper virus (CDV), canine adenovirus-2 (CAV2), canine parvovirus-2 (CPV2) and feline parvovirus (FPV), there is a strong association between protection and the presence of serum virus-neutralizing or hemagglutination-inhibiting antibody. In the case of feline herpesvirus-1 (FHV1) the stronger correlate of protection is the presence of a cell-mediated immune response, and in the case of pathogens infecting the upper respiratory tract (e.g., *Bordetella bronchiseptica*) the best correlate of protection is the presence of a local, mucosal immune response. The detection of cell-mediated or mucosal immune responses is technically challenging, but it is now straightforward to measure serum antibody responses in vaccinated animals to indicate that they have been protected by particular vaccines (see below).

The science of immunology has made rapid advances in the past decades, and this new knowledge informs our understanding of how vaccines work and how we might design more effective vaccines. Vaccinal immune responses follow the pattern for induction of active immunity to any foreign antigen.[1] Vaccine antigens must first be detected by antigen-presenting cells (APCs) such as dendritic cells or macrophages, at

the site of vaccine administration or at distant sites reached by vaccine infectious agent. The interaction between vaccine antigen and APC likely involves the detection of "microbe-associated molecular patterns" on or within the vaccine organism with "pattern recognition receptors" on or within the APC. The APC has a series of key roles in the induction of activity immunity: (1) internally processing and presenting small peptide fragments from vaccine antigens associated with class I or class II molecules of the major histocompatibility complex (MHC) on the surface of the cell, (2) carrying the vaccine antigen from the site of delivery to the closest organized lymphoid tissue, (3) engaging with antigen-specific T lymphocytes that carry a T-cell receptor that can recognize the peptide-MHC combination on the APC surface, and (4) activating that T cell by delivery of costimulatory signals including specific soluble messenger proteins (cytokines) that act on cytokine receptors on the target T cell.

The nature of the antigen, the context of its entry into the body, and the signals received from the APC, in turn, instruct the further development of the naïve antigen-specific $CD4^+$ T cell. The naïve T cell starts to divide (clonal proliferation) but also takes on a specific functional phenotype as either a $CD4^+$ T helper (Th) 1, Th2, Th17 or T regulatory (Treg) cell. Th1 cells are characterized by the production of the cytokine interferon (IFN)-gamma and stimulation of cell-mediated immunity involving the activation of $CD8^+$ cytotoxic T cells (Tc) and natural killer (NK) cells. Th17 cells produce cytokines including interleukin (IL)-17 and are important in, amongst others, the immune response to fungal infections mediated by granulocytes and macrophages. Th2 cells produce cytokines including IL-4, IL-5, IL-9 and IL-13 and are key to the generation of humoral immunity via coactivation and clonal proliferation of antigen-specific B lymphocytes, their transformation into plasma cells and secretion of antigen-specific antibody (in the context of vaccines, generally of the immunoglobulin [Ig] G or IgA class). With each of these activation events, long-lived memory T and B lymphocytes will be produced and it is these that mediate the sometimes lifelong vaccinal protective immune response. Treg cells are the population that suppress active immune responses, and it is likely that the delivery of allergen-specific immunotherapy works at least in part by stimulating this population.

Whilst it is likely that many vaccines containing infectious agents stimulate elements of both cellular (Th1) and humoral (Th2) immunity, vaccinal immune responses with strong circulating or mucosal antibody as a correlate of protection might be expected to be dominated by Th2-driven immunity, while those requiring a cellular response might involve Th1-dominated immune responses.

The Epidemiology of Vaccination

In small companion animal practice vaccination is now part of "individualized medicine," and vaccination requirements should be tailored for the needs of the individual pet (see below). However, vaccination is not solely about protecting the individual; it should also be about protecting the population through conferring "herd immunity." The concept of herd immunity simply suggests that the more vaccinated individuals there are in a community, the more difficult it is for many infections to spread through that community when the infections are introduced.

Herd immunity is best demonstrated with the case of canine rabies virus infection, where, because of the relatively low R_0 value, vaccination coverage of 70% of the population will achieve protection of the human and animal population against the disease. R_0 is defined as the number of secondary cases caused by an infected individual in an entirely susceptible population, and for rabies this is around 1.2 (meaning that each rabid dog infects on average 1.2 others). Our aim should always be to maximize the number of vaccinated animals in our herd, but we are far from achieving even 50% vaccine coverage for companion animals in most areas (even in the developed world). A reduction in existing herd immunity can also lead to the recurrence of infectious disease. An excellent example of this was the outbreak of CDV infection in Finland in the mid-1990s. Over 5,000 dogs died during this outbreak, which reflected a reduction in vaccination uptake in the canine herd.[2]

Types of Vaccine

The range of companion animal vaccines has expanded considerably in recent years. It is helpful to consider vaccines as either "infectious" or "noninfectious" in nature. An infectious vaccine contains a live, but attenuated, whole organism that is capable of circulating in the body, infecting cells and replicating within them, establishing a low-level and transient infection that engenders a strong immune response without the need for additional nonspecific immune stimulation (i.e., via incorporation of an adjuvant). For example, an infectious CPV vaccine leads to transient viremia and fecal shedding of vaccine virus post-vaccination.[3]

Infectious vaccines are also known as "live," "live attenuated" or "modified live" vaccines.

A noninfectious vaccine contains a whole organism that is killed and inert, usually after treatment with one of a range of chemical agents. Other types of noninfectious vaccine include selected immunodominant antigens extracted from the organism or produced using molecular biological techniques as recombinant antigens. These are referred to as "subunit vaccines." Noninfectious vaccines cannot therefore produce active infection and often require incorporation of adjuvant. Noninfectious vaccines generally require multiple doses to generate immunity and more frequent readministration (i.e., boosting) to maintain immunological protection and memory. For these reasons, with some exceptions (see below), an infectious version of a vaccine will generally be preferred when there is a choice between an infectious or noninfectious product.

The newest forms of noninfectious vaccine are produced using molecular techniques. "Recombinant vectored" vaccines involve inserting genetic material encoding an immunodominant protein from the target organism (e.g., feline leukemia virus [FeLV], CDV or canine rabies virus) into the genetic material of a benign "carrier" virus that is incapable of causing disease in the target species (e.g., the use of canary pox virus in the dog or cat). "Naked DNA" vaccines remove the need for a carrier organism entirely and rely on administration of a bacterial plasmid containing the gene of interest. These plasmids are taken up by host cells (including APCs) by the process of "transfection," resulting in expression of the immunodominant antigen from the target organism by host cells. The canine melanoma vaccine utilizes this technology.[4]

The means of delivery of vaccines to companion animals is also expanding in range. Most traditional vaccines are given by subcutaneous needle injection, but increasingly certain vaccine organisms are delivered by the intranasal route and one product is now given orally. Administration of vaccine direct to the anatomical site of natural infection will confer the most relevant and potent protective immune response. Recombinant vectored or naked DNA vaccines have also been delivered via a "needle-free" percutaneous route involving use of a high-pressure transdermal system. This route of delivery has the advantage of using a lower amount of vaccine whilst more specifically targeting the key APC populations within the epidermis and dermis of the skin.

Vaccine Licensing

As with any pharmaceutical product, veterinary vaccines must go through a rigorous regulatory procedure before they come to market. Essentially, vaccines must be shown to be safe for use in the target species, must be produced to high-quality standards, and must have demonstrated efficacy in being able to protect from infectious disease. Efficacy testing generally involves experimental challenge studies, in which vaccinated and unvaccinated animals are challenged with virulent infectious agent at a defined time point after vaccination. The vaccine must be able to provide acceptable protection against infection or clinical disease.

These regulatory studies form the basis for the "claim" for the vaccine, which will be detailed (together with other information) on the vaccine datasheet or "summary of product characteristics." Practitioners should be aware that the claim for vaccines may differ and that no vaccine, human or animal, can be guaranteed to provide 100% protection. Some vaccines will claim to prevent infection with the organism, but others will claim only to ameliorate the severity of clinical signs after infection and not to prevent infection or even shedding of the infectious agent.

Adverse Events Following Vaccination

The 60-year history of companion animal vaccination has had profound effects on the health and well-being of the pet population with many infectious diseases no longer as prevalent as they once were in numerous geographical areas. Additionally, in the case of canine rabies vaccination, and more recently canine *Leishmania* vaccination, vaccination of dogs has had a major impact on human health. There is no question that vaccination is a key element of preventive health care for companion animals and must be promoted by the veterinary profession.

With many millions of animals vaccinated throughout the world each year, it is inevitable that on rare occasions some animals may show adverse events post-vaccination. There is a wide spectrum of such vaccine-associated adverse events recognized in companion animals and for most of them the precise pathogenesis (i.e., how a vaccine might mechanistically lead to the reaction) is unknown.[5] At one end of the spectrum is the frequent occurrence of mild and transient pyrexia, lethargy and anorexia for 2-3 days post-vaccination, particularly in young animals. This "adverse event" simply indicates that the vaccine is stimulating immunity with release of proinflammatory cytokines as part of that response. At the other end of the spectrum are lethal reactions such as acute anaphylaxis (see ch. 137), induction of life-threatening autoimmune disease (see ch.

10), or induction of the feline injection-site sarcoma (FISS; see ch. 346). Some studies have attempted to quantify the frequency of such reactions, and the largest epidemiological investigations suggest that these might arise in something like 30 to 50 animals for every 10,000 animals that are vaccinated.[6,7] Veterinarians should be encouraged to report all postvaccinal adverse events to the manufacturer, or in countries where there is such a scheme, to national reporting databases.

There is much Internet discussion about the safety of veterinary vaccines from well-meaning pressure groups, and this continues to cause concern amongst pet owners. It is beholden on the veterinary profession to advise that the very slight risk of adverse event following vaccination is far outweighed by the benefits to the animal of protection against life-threatening infectious disease.

Changes in Vaccination Practice

Driven by professional and public concerns over companion animal vaccine safety, the veterinary profession has established a number of scientific expert panels to consider vaccination and how it might best be delivered in the context of modern veterinary practice. To that end, a number of panels have produced guidelines for the vaccination of dogs and cats. The first of these groups was the American Academy of Feline Practitioners, which produced guidelines as early as 1998 with the most recent iteration published in 2013.[8] The American Animal Hospital Association has produced guidelines for canine vaccination, last updated in 2011,[9] and the Advisory Board on Cat Diseases also published guidelines for feline vaccination most recently in 2013.[10] The most overarching guidelines come from the World Small Animal Veterinary Association (WSAVA) Vaccination Guidelines Group (VGG), which has produced advice for the vaccination of both dogs and cats for practitioners in the 80 WSAVA member countries[11] and, more recently, specifically for practitioners on the Asian continent.[12] The VGG is currently working on a 2015 revision of the world guidelines. In reality, there is now great consistency in the recommendations given in these various guidelines documents and over time, the recommendations given in vaccine datasheets is also moving towards those given in guidelines.

Practitioners should be aware that guidelines are a distillation of the latest scientific thinking on vaccines and vaccine delivery and are designed to provide information to veterinarians such that they may formulate their own practice policies on vaccination. Guidelines recommendations may well differ from those given on vaccine datasheets as guidelines groups consider recent published and unpublished scientific studies that may postdate the production of a datasheet. Vaccine datasheets (or SPCs) are the legal document describing how vaccines should be used, but any veterinarian can use a vaccine "off label" in accordance with guidelines recommendations and with informed client consent. No veterinarian has ever been prosecuted for failing to adhere to manufacturer's recommendations for vaccine delivery.

Core Versus Noncore Vaccines

The vaccination guidelines groups have adopted the concept of classifying vaccines into one of three categories. A "core" vaccine is one which every dog or cat, no matter where or how it lives, should receive because it protects that animal against infectious disease which may be lethal or cause high morbidity. The concept of core vaccination also incorporates rabies vaccination, which should be given to all dogs and cats in any country in which the disease is endemic, even if legislation does not mandate this. In contrast, a "noncore" vaccine is one which every dog or cat does not need to receive. The choice of giving a noncore vaccine should be based on consideration of the geographical prevalence of infection, the lifestyle of the individual pet and the risk for that animal coming in contact with the infection. A third category of "not recommended" is used for vaccines that do not have sufficient scientific evidence base to justify their use in the field.

Core Vaccination for Dogs

The core vaccines for dogs are those that protect against CDV (see ch. 228), CAV (see ch. 228) and CPV (see ch. 225), and for any dog in a rabies-endemic country, rabies vaccine (Table 208-1; see ch. 226). The choice of core vaccines for the dog is therefore simple and uncontroversial. The most efficacious and convenient formulation of the canine core vaccines is a trivalent infectious (modified live virus) product, which should be selected above similar noninfectious products if they are available. In some countries, a recombinant virus-vectored CDV vaccine is available. Although use of core vaccines therefore sounds simple, the complication arises in many countries that the three core antigens are often formulated with additional noncore

components in anything up to an "eight-in-one" combination. This makes it very difficult for practitioners in those countries to vaccinate in accordance with current guidelines, and it is hoped that, in time, industry will provide to these countries the same vaccine range that is available elsewhere.

TABLE 208-1

Recommended Canine Core Vaccination

VACCINE	POSSIBLE PUPPY PROTOCOL	POSSIBLE ADULT DOG PROTOCOL
CDV, CAV and CPV (infectious MLV vaccine; CDV viral vectored recombinant; injectable)	8, 12 and 16 weeks or older with a 12-month booster	Revaccination no more frequently than every 3 years; serology may be used to determine protection
Rabies (noninfectious killed adjuvanted vaccine; injectable)	12 weeks and a 12-month booster	Revaccination every 3 years depending on local law and licensed DOI of products

For full details refer to WSAVA[11] or AAHA[9] Vaccination Guidelines.

CAV, Canine adenovirus; *CDV*, canine distemper virus; *CPV*, canine parvovirus; *DOI*, duration of immunity; *MLV*, modified live virus.

Core vaccination must be started in puppy- or kittenhood. It is well known by practitioners that puppies and kittens acquire passive maternal immunity in the form of antibody by taking in colostrum during approximately the first 24 hours of life. This maternally derived antibody (MDA) circulates in the neonate and provides passive protection from infection over the first weeks of life. Canine MDA has a half-life of around 11 days, meaning that every 11 days there is one half of the amount of circulating MDA remaining than was present 11 days previously. The presence of MDA interferes with the ability of the neonate to mount its own protective immune response to the majority of currently available core vaccines. At some point after birth, the amount of remaining MDA is insufficient to provide complete immunological protection, but still enough to block the endogenous immune response. This short period of time is referred to as the "window of susceptibility." It is not possible to predict accurately when this "window" occurs for any one neonate as the amount of MDA transferred will vary between litters and within litters for individuals. Until recently, it was believed that in the majority of pups the "window" lay between 8-10 weeks of age, and so a core vaccination schedule of 8 and 12 weeks would induce a primary immune response either at 8 or at 12 weeks in all puppies. We now know that this is not the case, and so blocking levels of MDA are likely to persist in 10% of pups at 12 weeks of age (RD Schultz, unpublished study). For that reason, all canine vaccination guidelines now recommend a series of three primary vaccines in the pup: starting at 8-9 weeks of age, with a second vaccine 3-4 weeks later and a third vaccine given between 14-16 weeks (and preferably at the 16-week-or-older end of that spectrum). Crucially, a "boosting" vaccine must be given to pups within the first year of life, and this is often delivered at 12 months of age or 12 months after the final primary vaccine. Where MDA is suspected to be low, in many countries there are products containing CDV and CPV antigens that may be given from 6 weeks of age, but infectious vaccines should not be given to puppies at younger age (particularly before 4 weeks of age).

In endemic areas, pups must also be vaccinated against canine rabies. All canine rabies vaccines are killed and adjuvanted products. The global recommendation is for one of these vaccines to be delivered at 12 weeks of age with a second vaccine given within the first year of life. The WSAVA guidelines also suggest that in highly endemic areas (e.g., in Africa or Asia) a second rabies vaccine may be delivered at 16 weeks of age.

For adult dogs, the delivery of core vaccination is now also relatively straightforward. The core canine vaccines (i.e., CDV, CAV2 and CPV2) are highly efficacious, and there is an extremely strong correlation between the presence of serum antibody against the antigen and protection from disease. One of the biggest global changes in canine vaccination practice has been with respect to the frequency of core revaccination of adult dogs. Core trivalent infectious vaccines were originally licensed with a 1-year "duration of immunity" (DOI), meaning simply that an experimental challenge study had determined that vaccinated dogs were protected 1 year after vaccination from infectious challenge. However, this was always a minimum DOI and it was well recognized that dogs appropriately vaccinated as puppies (and never again) usually had lifelong protective serum antibody concentrations. There are now data that show that the minimum DOI for canine core infectious vaccines is actually 9 years (by experimental challenge)[13] and that protective antibody titers can persist for at least 15 years after puppyhood vaccination. In response to vaccination guidelines, vaccine manufacturers performed new challenge studies that provided evidence for a minimum DOI of either 3 or 4

years. Consequently, over the past decade, most vaccine datasheets have now been changed to reflect this fact and advise revaccination of adult dogs with core infectious vaccines only every 3 or 4 years.

Knowing that triennial revaccination still reflects only the minimum DOI, and that there is an exceptionally strong correlation between protection and serum antibody to CDV, CAV and CPV, many practitioners now elect to perform serological testing every 3 years rather than automatically revaccinate an adult dog. Serological testing has now become more accessible with the availability of in-clinic test kits that can rapidly determine whether a dog has serum antibody to these three viral antigens.[14,15] Serology rather than revaccination is currently a more expensive option but reduces the risk of adverse events post vaccination and has proven very popular with clients in many countries.

Vaccination of adult dogs against rabies may now also be performed triennially as in many countries the internationally produced noninfectious adjuvanted rabies vaccines carry a 3-year licensed DOI. This can become problematic in countries in which there is still a legal requirement to deliver annual revaccination, even where a 3-year product is available. In that situation, the veterinary profession should lead in lobbying to allow the law to keep pace with the science. It is also worth noting that in some countries there are nationally produced vaccines with a 1-year DOI and that there is no evidence that these products can protect for longer periods. Finally, rabies vaccination for individual, owned pet dogs visiting the veterinarian is distinct from mass vaccination campaigns in endemic countries. In the latter context, it is important to maintain annual revaccination, simply because of the high population turnover in communities of "free-roaming" dogs.

Noncore Vaccination for Dogs

The most widely used noncore vaccines for dogs are those that confer protection against pathogens within the group responsible for the canine infectious respiratory disease (CIRD) complex ("kennel cough"; i.e., *Bordetella bronchiseptica,* CAV2 and canine parainfluenza virus [CPiV]; see ch. 227) and against leptospirosis (Table 208-2; see ch. 217). Other noncore vaccines with more restricted geographical availability include those against *Borrelia* (see ch. 211), canine influenza virus (CIV; see ch. 227), canine herpesvirus (see ch. 228), *Leishmania* (see ch. 221) and *Babesia* (see ch. 221).

TABLE 208-2

Recommended Canine Noncore Vaccination

VACCINE	POSSIBLE PUPPY PROTOCOL	POSSIBLE ADULT DOG PROTOCOL
Bordetella bronchiseptica alone or with CPiV and/or CAV2 (infectious intranasal or oral vaccine)	1 dose from 3-4 weeks of age	Annual booster
Leptospira (noninfectious multivalent vaccine most relevant to location; injectable)	2 doses 3-4 weeks apart starting after core viral components, 12-month booster	Annual booster
Borrelia (noninfectious whole organism or subunit injectable vaccine)	2 doses 3-4 weeks apart starting after core viral components, 12-month booster	Annual booster

For full details refer to WSAVA[11] or AAHA[9] Vaccination Guidelines; use of noncore vaccines is selected based on risk assessment.
CAV2, Canine adenovirus type 2; *CPiV*, canine parainfluenza virus.

Where the lifestyle of an individual dog justifies use of a CIRD vaccine, it must be remembered that there are numerous pathogens in this complex that are not represented in current vaccines and that this disease has other (e.g., environmental) aspects. A CIRD vaccine will not prevent clinical disease but may ameliorate its severity. These vaccines are available in different combinations of the three antigens listed above and either as injectable (noninfectious killed *Bordetella bronchiseptica*), intranasal (infectious attenuated *Bordetella bronchiseptica* with or without CPiV and CAV2) and now, oral (infectious attenuated *Bordetella bronchiseptica*) formulations. Intranasal and oral vaccines may be given as a single dose to puppies (intranasal vaccines can be used as early as 3-4 weeks of age and the oral vaccine from 8 weeks of age), whereas injectable vaccines are given by two injections 2-4 weeks apart. All of these vaccines must be given annually to adult dogs to maintain protective immunity.

Canine leptospirosis is currently a disease receiving much research interest (see ch. 217). Numerous studies

are now starting to measure the geographical prevalence of this infection and the serogroups of the bacterium involved in field cases. This new knowledge has led to the introduction of new multivalent noninfectious (killed) canine leptospirosis vaccines.[16] The traditional canine *Leptospira* vaccine contained the serogroups *L. canicola* and *L. icterohaemorrhagiae,* but now trivalent or quadrivalent vaccines (e.g., in the United States *L. canicola, L. icterohaemorrhagiae, L. grippotyphosa* and *L. pomona*) carry a wider range of serogroups. A dog vaccinated against leptospirosis might still be susceptible to disease as there are numerous serogroups (not included in vaccines) that can cause this infection. In many parts of the world, canine *Leptospira* vaccine is regarded as "core" rather than "noncore" because of the belief that this is a highly prevalent and severe disease that also has potential zoonotic implications. However, in other areas the disease is not recognized, and so global guidelines reflect this by classifying the vaccine as noncore.

Advice on vaccinating puppies against leptospirosis differs between vaccine datasheets and guidelines recommendations, although in all cases it is recognized that two doses of vaccine, 2-4 weeks apart, are required. Experimental studies performed by manufacturers have proven that the vaccine can induce immunity when integrated with the timing of the canine core vaccines given to puppies; however, guidelines suggest delaying administration of the vaccine until after completion of the core viral series (i.e., at 16 weeks or older). This recommendation is largely based on traditional concerns that adjuvanted bacterins may be more likely to trigger allergic reactions in young dogs. Whichever *Leptospira* vaccine is used, adult dogs must be revaccinated annually to maintain protective immunity and the WSAVA guidelines also suggest that for dogs at high risk of exposure, 6-monthly revaccination might be considered.

Noninfectious CIV (killed virus) or *Borrelia* (killed bacterium or recombinant subunit vaccines) is given to puppies by injection (twice, 2-4 weeks apart) and then by annual booster to adult dogs.

Not Recommended Vaccines for Dogs

Vaccination guidelines groups do not generally recommend the use of vaccines against canine enteric coronavirus (CCoV) or *Giardia.* CCoV induces only mild gastrointestinal disease in dogs, unless there is concurrent CPV infection, and it has not been possible to induce experimental CCoV disease in dogs over 6 weeks of age, making it impossible to assess the efficacy of any vaccine. Field studies have not shown clear evidence that CCoV is a primary gastrointestinal pathogen in this species. Canine *Giardia* vaccines have now been removed from most global markets but persist in some countries. Canine *Giardia* infection is of low prevalence, is non–life threatening, responds to therapy and is rarely zoonotic. There is no evidence that the strain of *Giardia* included in the vaccine confers cross-protection against the multiple strains that might infect dogs.

Core Vaccination for Cats

The core vaccines for cats are universally considered to be those that protect against FPV (see ch. 225), FHV1 (see ch. 229) and feline calicivirus (FCV; see ch. 229), and in any country where rabies is an endemic disease (see ch. 226), cats should also receive rabies vaccination even if not mandated by law (Table 208-3). Core vaccines for cats are often available as a trivalent combination of infectious (modified live viral) antigens or noninfectious (killed adjuvanted or nonadjuvanted) antigens, and in some countries an intranasal infectious (modified live viral) combination is available. The two respiratory tract components (FHV1 and FCV) are also sometimes formulated as a bivalent vaccine to be used in conjunction with monovalent FPV vaccine. One noninfectious (killed and nonadjuvanted) FCV product contains two strains of the virus. In general, the preference should be for infectious injectable vaccine as inducing the most efficacious protective response to all three components; however, noninfectious vaccines should be selected for use in retrovirus-infected cats or for the rare occasion on which cats might be vaccinated during pregnancy or for use in multicat households where there is no preexisting upper respiratory tract disease. The same noninfectious (killed and adjuvanted) rabies vaccines are used in cats as in dogs, but for the cat there is additionally a noninfectious viral-vectored recombinant vaccine against rabies.

TABLE 208-3

Recommended Feline Core Vaccination

VACCINE	POSSIBLE KITTEN PROTOCOL	POSSIBLE ADULT CAT PROTOCOL

FPV, FHV1, FCV (infectious MLV vaccine; injectable)	8, 12 and 16 weeks or older with a 12-month booster	For FPV, revaccination no more frequently than every 3 years; for FHV1 and FCV revaccination every 3 years for low-risk cat and annually for high-risk cat
Rabies (noninfectious killed adjuvanted or viral-vectored recombinant vaccine; injectable)	12 weeks and a 12-month booster	Revaccination every 3 years depending on local law and licensed DOI of products

For full details refer to WSAVA,[11] AAFP[8] or ABCD[10] Vaccination Guidelines.

DOI, Duration of immunity; *FCV*, feline calicivirus; *FHV1*, feline herpesvirus-1; *FPV*, feline panleukopenia virus.

The same considerations related to MDA apply to kittens as to puppies; however, recent studies suggest that persistence of MDA in kittens may be for even longer than in pups, with some kittens having blocking levels of MDA up to 20 weeks of age.[17,18] Advice for core vaccination of kittens is similar to that for puppies. Vaccination should start at 8-9 weeks of age, with a second dose given 3-4 weeks later and third dose given at 16 weeks or older (moving from some current recommendations for 14-16 weeks). Again, revaccination within the first year of life, often at 12 months of age or 12 months after the final primary vaccination, is crucial. Rabies vaccination of kittens is by a single injection at 12 weeks of age with a second injection at 12 months.

Core vaccination of adult cats is subject to greater debate than that for the dog. A number of FPV vaccines (either monovalent products or where FPV is incorporated into a trivalent vaccine) now have a licensed minimum DOI of 3 years. FPV vaccines, like the core canine vaccines, show strong correlation between the presence of serum antibody and protection, but this is not the case for the FHV1 and FCV components. FPV vaccines also lead to long-lived protection with a demonstrated minimum DOI of 7.5 years for noninfectious vaccine in one study.[19] Therefore, when available product range allows, current recommendations are for triennial revaccination of adult cats against FPV. Given the strong correlation between seropositivity and protection for FPV, some practices now choose to use the in-clinic rapid serological test kit to determine protection and decide on revaccination frequency.[20,21] Note that such serological testing should not form the basis of decision-making for the upper respiratory tract core components.

In contrast, all current feline FHV1 and FCV vaccines carry a licensed minimum DOI of 1 year, although in the same study cited above, a noninfectious trivalent vaccine provided equally good protection against infectious challenge in cats last vaccinated 7.5 years previously compared with cats receiving regular adult core booster vaccines. The recommendations for revaccination of adult cats against FHV1 and FCV are therefore more variable and determined by the risk of exposure of the individual cat. A low-risk cat (i.e., a solitary indoor animal that does not visit catteries) might safely be vaccinated triennially (as for FPV), but a high-risk cat (i.e., an indoor-outdoor cat or a cat within a multicat household or regularly visiting catteries) may better receive an annual or biennial vaccine against the upper respiratory virus components.

Adult cats may be revaccinated against rabies triennially (depending on legal requirements) when using either noninfectious (killed adjuvanted) vaccine or the recombinant virus-vectored vaccine that carries a 3-year licensed DOI.

Noncore Vaccination for Cats

Noncore vaccines for cats include those that protect against FeLV (see ch. 223), *Chlamydia felis* (formerly *Chlamydophila felis*; see ch. 229) and *Bordetella bronchiseptica* (see ch. 227 and 229). The vaccine against feline immunodeficiency virus (FIV; see ch. 222) is variably classified as noncore or not recommended (Table 208-4).

TABLE 208-4

Recommended Feline Noncore Vaccination

VACCINE	POSSIBLE KITTEN PROTOCOL	POSSIBLE ADULT CAT PROTOCOL
Bordetella bronchiseptica (infectious intranasal vaccine)	1 dose from 8 weeks of age	Annual booster if sustained risk of infection
FeLV (noninfectious adjuvanted whole virus or subunit; recombinant viral vectored; injectable)	2 doses 3-4 weeks apart starting at 8 weeks; booster at 12 months	Not more often than every 3 years if sustained risk of infection

Chlamydia felis (noninfectious adjuvanted or infectious; injectable)	2 doses 3-4 weeks apart starting at 9 weeks; booster at 12 months	Annual booster if sustained risk of infection
FIV (noninfectious adjuvanted; injectable)	3 doses 2-3 weeks apart starting at 8 weeks; booster at 12 months	Annual booster if sustained risk of infection

For full details refer to WSAVA,[11] AAFP[8] or ABCD[10] Vaccination Guidelines; use of noncore vaccines is selected based on risk assessment.

FeLV, Feline leukemia virus; *FIV,* feline immunodeficiency virus.

The prevalence of FeLV infection varies geographically and has reduced over recent years, but in many countries it is regarded as important to provide protection for kittens against this virus, and in some countries the vaccine is considered more core than noncore. A range of FeLV vaccines is available, including noninfectious (killed whole virus) and subunit vaccines, both of which are adjuvanted, and a recombinant virus-vectored and nonadjuvanted product. In general, these vaccines may be administered to kittens from 8 weeks of age with a second vaccine given 3-4 weeks later. WSAVA guidelines then recommend a 12-month booster vaccine and subsequent revaccination of adult cats only every 3 years thereafter, which is longer than the 1-year licensed DOI carried by these products.

Chlamydia felis vaccines may be used in multicat groups in which there is a background of infections associated with clinical disease. There are infectious (attenuated live) and noninfectious (killed adjuvanted) injectable vaccines available. These may be used in kittens from 9 weeks of age with a second vaccine 3-4 weeks later and with an annual booster for adult cats at sustained risk of exposure.

The *Bordetella bronchiseptica* vaccine might be considered for cats in similar high-risk situations. The vaccine is an infectious (attenuated) intranasal product that may be used as a single dose in kittens over 8 weeks of age, with an annual booster for adult animals at sustained risk of exposure.

The FIV vaccine has been contentious for a number of reasons: (1) there has been debate as to whether the two clades of virus contained within the vaccine (A and D) effectively cross-protect against other clades dominating in different geographical areas, (2) the vaccine leads to seropositivity that will interfere with diagnosis using serological (but not molecular) methods, (3) the vaccine is adjuvanted and must be given repeatedly (see below). The vaccine is a noninfectious (killed and adjuvanted) product that may be given to kittens from 8 weeks of age with two further injections each 2-3 weeks apart, a 12-month injection and then an annual booster for adult cats deemed at being of sustained risk.

As discussed above, one of the risk factors for FISS (see ch. 346) is regarded as being administration of adjuvanted vaccines. There is varying guidelines advice on how to best minimize the risk of FISS. Clearly, choosing nonadjuvanted over adjuvanted feline vaccines is one possibility and minimizing use of noncore vaccines is another. The site of administration of vaccines, particularly adjuvanted products, should be considered carefully in the cat. Recommendations range from the skin of the lateral abdomen,[11] to the distal hindlimbs,[8] to a new study considering vaccination into the tail.[22] Whichever protocol is adopted, it would be sensible to rotate the sites of injection (of vaccines or any other product) in the skin of a cat and not to inject repeatedly into the scruff of the neck.

Delivery of Vaccination

Vaccination guidelines provide current best-practice scientific advice for canine and feline vaccination; however, they also emphasize that we should change the way in which vaccination is "sold" to clients. The concept of the annual veterinary visit being for a "vaccine booster" should be replaced with the new concept of the "annual health check," which considers the overall health and well-being of the animal, with discussion of which vaccine might be given in any one year being just one part of that discussion. In this way, emphasis should be placed on the professional consultation and expertise, rather than the contents of the needle and syringe.

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CHAPTER 209

Antimicrobial Resistance, Surveillance and Nosocomial Infections

J. Scott Weese

Introduction

Antimicrobial resistance (AMR) has been a clinical concern since shortly after the introduction of antimicrobials, and it now represents a significant problem in both veterinary and human medicine. While the main concerns about AMR have been accentuated in the past 50 years, AMR is not a new phenomenon. Bacteria have developed means of resisting the effects of antimicrobial substances for millennia as a way to counteract the ongoing biological warfare between microbes in the environment. Humans have harnessed this ability for tremendous gain, through development of therapeutic antimicrobials from these naturally occurring substances. However, we also have suffered profound consequences of the ability of bacteria to evade antimicrobials. As antimicrobials become more important for maintaining the health of patients, the implications of AMR become greater. Further, as the ability of bacteria to develop new resistance methods outpaces the ability (or rather, the efforts) to develop new antimicrobials, AMR will undoubtedly continue to have a major impact on companion animal medicine.

Antimicrobial Resistance in Small Animals

Pathogens of Concern

Antimicrobial resistance can be a concern with virtually any pathogen, but issues are greater among certain bacteria because of their tendency to acquire resistance and their role in disease. A list of concerning multidrug resistant (MDR) bacteria might vary between regions, between clinics in the same region, or even between clinical services (e.g., dermatology versus critical care) in the same facility. The list is also continually evolving, as issues of concern now could have been of limited concern, or even unknown, only a few years ago.

Methicillin-resistant (MR) staphylococci are among the most important opportunistic pathogens in animals (and humans). This includes methicillin-resistant *S. pseudintermedius* (MRSP), an increasingly common cause of skin and soft tissue infections in dogs (and, to a lesser degree, cats); methicillin-resistant *S. aureus* (MRSA), a predominantly human-associated cause of opportunistic infections in dogs and cats; and a variety of other methicillin-resistant staphylococcal species of varying pathogenic potential. Beyond their inherent resistance to virtually all beta-lactam antimicrobials, MR-staphylococci, particularly MRSP, often are resistant to a wide range of other antimicrobials, severely limiting treatment options. Zoonotic concerns also exist, particularly for MRSA.

Extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae are Gram-negative bacteria possessing genes that render them resistant to extended-spectrum (third generation) cephalosporins and monobactams. They are increasingly prevalent in veterinary patients and are a cause for concern because of their inherent resistance, the potential for establishment of long-term reservoirs in the gut microbiota, and the potential for zoonotic transmission.[1-3]

Carbapenemase-producing Enterobacteriaceae (CPE) are Gram-negative bacteria that are resistant to carbapenems (e.g., meropenem).[4-6] While carbapenems are used uncommonly in veterinary medicine, CPE typically also are resistant to many other antimicrobials, and the loss of efficacy of last-line drugs such as meropenem is of tremendous concern. Currently, CPE appear to be rare in animals but if (or as) the prevalence of these organisms increases in people in the community, transmission to animals is probably inevitable. Of even greater concern is the emergence of New Delhi metalloproteinase 1 (NDM-1)-producing Enterobacteriaceae, with some isolates approaching pan-resistance.[7] While currently this appears to pose

limited risk to veterinary patients because of its rarity, it could be an emerging issue and, curiously, it appears that one of the first identified NDM-1-containing isolates in North America was from a cat with a urinary tract infection.[8] This highlights a realistic potential for an "untreatable infection," one caused by a bacterium that is resistant to all available options.

Enterococci tend to be of limited virulence compared to other opportunists, but resistance is not uncommon and some infections can be difficult to treat. Because of their inherent resistance to many antimicrobials, acquired resistance to more antimicrobials can hamper treatment through reduction of the already limited number of viable antimicrobial options. Vancomycin-resistant enterococci (VRE) are the subjects of the most attention in humans.[9] While VRE are rare in dogs and cats,[10,11] enterococci that are susceptible to vancomycin but resistant to most other options are relatively common and can be a challenge to treat.

This is far from an exhaustive list and pathogens resistant to only one antimicrobial can be of significant clinical relevance if that antimicrobial is chosen empirically to treat a patient.

Prevalence and Incidence

Most resistant pathogens are opportunists that can be found in healthy individuals.[12-15] Carriage rates vary greatly between different bacteria, different species and different regions, but it is reasonable to assume that a small but appreciable percentage of clinically normal animals is shedding one or more resistant pathogens at any time. These carriers can be sources of infection for themselves, other animals, or people, and shedding of MDR pathogens by healthy animals poses one of the greatest challenges for MDR infection control.

The incidence of infections caused by resistant pathogens is poorly understood. While carriage rates have been well defined for some pathogens such as MRSP, disease incidence data are less well described. In particular, the incidence of disease in primary care (non-referral) facilities is unclear and likely variable between regions. Understanding local and facility-specific infection rates is important for identification of problems, determination of optimal diagnosis and treatment approaches, for implementation of relevant infection control measures and for proper client counseling.

Impact of Antimicrobial Resistance

In humans, infections caused by various resistant pathogens have been shown to be associated with significantly higher morbidity, mortality, and treatment costs.[16-18] Equivalent data largely are lacking in veterinary medicine, mainly because of limited evaluation or study limitations. For example, no difference in mortality was reported for MRSP versus methicillin-susceptible *S. pseudintermedius* in one study[19]; however, most cases involved skin infections, which would not be expected to be associated with mortality, even if ineffectively treated. It is reasonable to assume that infections caused by MDR pathogens are of greater impact to the patient than those caused by susceptible pathogens, but this is the result of failure of empirical antimicrobial therapy. Resistant pathogens are not inherently more virulent than susceptible pathogens because resistance genes just confer antimicrobial resistance. This highlights the need for prompt diagnostic testing to identify resistance, because the outcome of infections caused by resistant versus susceptible infection should be identical if appropriate treatment is started, something that is dependent on diagnostic testing.

Risk Factors

Various risk factors have been identified for shedding different MDR pathogens. These relate largely to antimicrobial and veterinary hospital exposure, but also include factors such as source (e.g., shelter versus household) and contact with human healthcare facilities.[1,20-22] Despite these studies, broad understanding of the epidemiology of MDR pathogens, particularly in the general population, is poorly understood.

Zoonotic Risks

Many AMR pathogens that affect animals can also infect people. Indistinguishable strains of MRSA, MDR enterococci, and ESBL-producing bacteria can be found in humans and animals, supporting concerns that infected or colonized animals could be a source of infection of human contacts. Yet the actual role of animals in human infection and the incidence of zoonotic infection are largely unknown. Reducing the incidence of these infections in animals and use of basic infection control practices to reduce animal-animal, animal-human and human-animal transmission probably are the most important measures to reduce zoonotic

disease risks.

Controlling Antimicrobial Resistance

Antimicrobial resistance cannot be eliminated. Even complete withdrawal of antimicrobials would not result in reversion of all bacteria to a pan-susceptible state. The goals of antimicrobial stewardship are to reduce the incidence of AMR and reduce the clinical impact of AMR (in both animals and humans). While straightforward in concept, this can be difficult in application because of limitations in knowledge about the impact of antimicrobial use and antimicrobial restriction on AMR.

Diagnostic Testing

When pathogen and resistance trends are predictable, diagnostic testing is less important. However, with the widespread emergence of AMR in both veterinary hospitals and the community, it is more difficult to predict pathogen and susceptibility results accurately, complicating empirical antimicrobial choices and increasing the likelihood of empirical treatment failure. This highlights the importance of diagnostic testing. While MDR pathogens are not inherently more virulent than their susceptible counterparts, successful treatment is dependent on prompt and effective diagnostic information so that proper treatment can be started. Additionally, the proliferation of AMR in the commensal microbiota, including in bacteria that can be isolated commonly from clinical specimens as contaminants, indicates the need for proper sample collection and consideration of the clinical relevance of culture results to prevent unnecessary treatment of MDR but clinically irrelevant bacteria. Unnecessary treatment can be reduced by avoiding contamination during sample collection, ensuring that laboratories follow standard testing and reporting practices, and considering the clinical relevance of results (not blindly treating every bacterium that is reported on a culture result).

Treatment Guidelines

In human medicine, extensive efforts have been put towards development of clinical guidelines to optimize diagnosis and management of a wide range of diseases.[23-25] These guidelines are based on thorough review of scientific evidence, which typically includes numerous large and well-designed clinical trials. Clinical guideline development is a relatively recent occurrence in veterinary medicine, but a few clinical guidelines have been released in recent years (Table 209-1), including guidelines directed specifically at antimicrobial therapy as well as broader, disease-based consensus statements that include treatment recommendations. A weakness of most (if not all) veterinary guidelines is the lack of high quality supporting data. In contrast to the numerous large well-designed studies that are often available in humans, veterinary guidelines typically are based on a combination of human data, small veterinary studies, basic information about the disease, principles of antimicrobial therapy, pharmacokinetic studies, and expert opinion. These can still be very useful documents; however, the lack of evidence highlights an important weakness in veterinary infectious disease research that probably hampers optimal diagnosis and treatment.

TABLE 209-1

Examples of Clinical Guidelines

GUIDELINE	REFERENCE
Antimicrobial use guidelines for treatment of urinary tract disease in dogs and cats: antimicrobial guidelines working group of the International Society for Companion Animal Infectious Diseases	29
ACVIM small animal consensus statement on Lyme disease in dogs: diagnosis, treatment, and prevention	30
2010 ACVIM small animal consensus statement on leptospirosis: diagnosis, epidemiology, treatment, and prevention	31
Suggested guidelines for using systemic antimicrobials in bacterial skin infections: part 2—antimicrobial choice, treatment regimens and compliance	32
Bordetella bronchiseptica infection in cats: ABCD guidelines on prevention and management	33
Mycobacterioses in cats: ABCD guidelines on prevention and management	34
Chlamydophila felis infection: ABCD guidelines on prevention and management	35

Antimicrobial Stewardship Programs

Concerns about AMR have resulted in development of comprehensive programs to improve antimicrobial use in human medicine. While mainly focused on hospitals, efforts to improve community-level (e.g., general physician) antimicrobial prescription have also been implemented.[26-28] The overall goals are to limit inappropriate and excessive antimicrobial use, while optimizing patient outcomes. These programs can take many forms, but core elements are outlined in Table 209-2.

TABLE 209-2

Core Elements of Antimicrobial Stewardship Programs[36]

ELEMENT	EXAMPLES
Leadership commitment	Providing necessary personnel, financial and information technology resources Supporting activities
Accountability	Designating a leader, preferably a clinician
Antimicrobial expertise	Appointing a pharmacist leader to help work to improve prescribing
Action	Implementing an action in response to other program experiences or facility-specific observations (e.g., automatic stop orders if prolonged antimicrobial use in hospital is linked to failure of anyone to bother to say to stop, restriction certain drugs, changes in susceptibility reporting)
Tracking	Monitoring prescription and AMR patterns
Reporting	Providing feedback about antimicrobial use and AMR to caregivers and other relevant personnel
Education	Educating prescribers about resistance and optimal prescribing practices

AMR, Antimicrobial resistance.

Antimicrobial Restriction

Restricting access to antimicrobials is a controversial area but one that veterinary medicine needs to address. Some countries (e.g., the Netherlands) have banned the use of certain antimicrobial classes (e.g., carbapenems) while others have restricted when and how drugs such as fluoroquinolones and later (3rd or 4th) generation cephalosporins can be used in animals. It has been recommended that veterinary medicine consider voluntary restriction practices to both optimize use of important antimicrobial classes and to demonstrate a proactive approach (and therefore perhaps reduce the pressure for broad regulatory restrictions). An example of this would be vancomycin restriction guidelines that are used for some facilities, which allow the drug to be used but only in specifically designated situations where there is a clear need. All veterinary facilities would benefit from consideration of their antimicrobial use practices and whether (or which) restriction practices could be implemented to both optimize patient care and limit use of "last resort" drugs.

Prevention of Disease

Perhaps the greatest potential positive impact on antimicrobial use and AMR is reducing infections. If infections are prevented, the need for antimicrobials and the corresponding pressure for AMR are eliminated. While complete elimination of infections is impossible, better use of preventive medicine programs (e.g., vaccination), managing comorbidities that might predispose to infection (e.g., atopic dermatitis, hyperadrenocorticism; see ch. 360) and reducing transmission of pathogens in veterinary hospitals and community sites (e.g., kennels, puppy classes) could have a profound impact.

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CHAPTER 210

Zoonoses

Michael R. Lappin

Introduction

There are many infectious agents that are "common to, shared by, or naturally transmitted between humans and other vertebrates," which is one of the classic definitions for a zoonotic disease. While the majority of concern with zoonoses is directed towards humans acquiring infections from pets or other animals, the predominant pathway of infection from animals to humans or from humans to other animals (anthroponosis) varies by agent. For practicing small animal veterinarians, the major issues concerning zoonotic disease relate to protecting staff and owners and providing accurate information to owners to aid in their decisions about pet ownership as it relates to zoonotic disease risks.

Most of the infectious agents discussed in this chapter can infect and cause disease in immunocompetent people, but disease is generally more prevalent or more severe in people that are immune-suppressed. There are many forms of immunosuppression in people that may influence pet ownership decisions; people with acquired immunodeficiency syndrome (AIDS) are discussed frequently. However, there are many other individuals that could be at greater risk for developing clinical illness if exposed to a zoonotic agent, including the very old, the very young, and those receiving chemotherapy for immune-mediated diseases, organ transplantation, or neoplasia. Immunosuppressed people are sometimes advised to give up their pets. However, if the pet is healthy and appropriate precautions are taken, the health benefits associated with pet ownership may outweigh the potential risk of pet ownership. Work continues around the world to attempt to determine the true risks and benefits associated with pet ownership.[1,2] All human and other animal health care providers should provide accurate information to pet owners concerning the risks and benefits of pet ownership so that an informed decision about acquiring and keeping pets can be made. There are now many online resources that can help owners, veterinarians, and physicians work together to make logical family decisions concerning pet ownership. The Center for Disease Control and Prevention (CDC) website "Healthy Pets Healthy People" is an excellent resource (http://www.cdc.gov/healthypets/index.html). For individuals with conditions associated with immune suppression, the CDC "Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents" is also an excellent resource (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr58e324a1.htm).[3]

Many infectious agents can infect humans by direct contact with pets, their exudates, or their excrement. These agents are the most important to veterinary health care providers and to dog and cat owners and are discussed in this chapter by likely route of exposure. Some agents are "shared vector zoonoses," which includes *Anaplasma* spp., *Bartonella* spp., *Borrelia burgdorferi, Ehrlichia* spp., *Rickettsia* spp., and others. For a number of these agents, the pet brings the vector into the home environment, potentially resulting in exposure of the person. With other zoonotic agents, including *Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis,* and *Cryptococcus neoformans,* the owner and pet are infected by shared environmental exposure to the agent.

The purpose of this chapter is to provide an overview of common canine and feline zoonoses encountered in small animal practice. General guidelines for the avoidance of zoonotic transfer of disease for veterinarians and pet owners are listed in Boxes 210-1 and 210-2. For some of these agents, the reader is directed to other sections of this textbook for further information concerning diagnosis and treatment.

Box 210-1

General Guidelines for Veterinary Staff Members to Lessen Risk of Zoonotic Transfer of Disease

- Veterinary staff members should familiarize themselves with zoonotic issues and take an active role in discussing the health risks and benefits of pet ownership with clients so that logical decisions concerning ownership and management of individual animals can be made.
- Veterinary staff members should teach all owners techniques to avoid being bitten or scratched.
- Veterinary staff members should make it clear to owners that they understand conditions associated with immune deficiency, are discreet, and are willing to help; signs or posters can be effective for this purpose.
- Veterinary staff members should provide pet owners information concerning veterinary or public health aspects of zoonoses, but should not diagnose diseases in humans or discuss specific treatments.
- Veterinary staff members should always refer clinically ill pet owners to a physician for additional information and treatment.
- Veterinarians should volunteer to speak to the pet owner's physician to clarify zoonotic issues when indicated.
- When veterinary staff members offer public health–related advice, it should be documented in the medical record.
- When reportable zoonotic diseases are diagnosed, appropriate public health officials should be contacted.
- Diagnostic plans to assess for presence of organisms with zoonotic potential should be offered, particularly to owners with clinically ill pets.
- Rabies vaccination should be recommended for all dogs and cats.
- Drugs that control hookworms and roundworms should be recommended for all dogs and cats.
- Flea and tick control products should be recommended for all dogs and cats.
- Veterinary clinic staff members should avoid needle sticks contaminated with blood or effusions.

Box 210-2

General Guidelines for Pet Owners to Lessen Risk for Zoonotic Transfer of Disease

- Veterinary care should be sought for all clinically ill pets.
- Physical examination and fecal examination should be performed at least once or twice yearly.
- Fecal material produced in the home environment should be removed daily, preferably by someone other than an immunocompromised individual.
- Use litterbox liners and periodically clean the litterbox with scalding water and detergent.
- Do not allow dogs or cats to drink from the toilet.
- Wear gloves when gardening and wash hands thoroughly when finished.
- Filter or boil water from sources in the environment.
- Wash your hands after handling animals.
- Do not handle animals that you are unfamiliar with.
- Immunocompromised people should not handle clinically ill animals, if possible.
- Pets should be maintained within the home environment to lessen exposure to other animals that may carry zoonotic agents, exposure to excrement of other animals, and exposure to fleas and ticks.
- Pets should only be fed commercially processed food.
- Do not share food utensils with pets.
- Avoid being licked by animals.
- Claws of cats should be clipped frequently to lessen the risk of skin penetration.
- To lessen the risk of bites and scratches, do not tease or physically restrain dogs and cats.
- If bitten or scratched by a dog or cat, seek medical attention.
- Control potential transport hosts, such as flies and cockroaches that can bring zoonotic agents into the home.
- Cook meat for human consumption to 80°C for 15 minutes minimum (medium to well-done).

- Wear gloves when handling meat and wash hands thoroughly with soap and water when finished.
- If a new pet is to be adopted into a household with an immunocompromized family member, the dog or cat least likely to be a zoonotic risk is a clinically normal, arthropod-free, adult animal from a private family.
- Once the animal to be adopted is identified, it should be quarantined from any immunocompromised person until a thorough physical examination and zoonoses risk assessment is performed by a veterinarian.

Enteric Zoonoses

Multiple infectious agents of the gastrointestinal tract can be shared between animals and humans (Table 210-1). Some enteric agents are infectious immediately when passed in feces (e.g., *Campylobacter* spp., *Cryptosporidium* spp., *Giardia*) while others require time out of the body to become infectious (e.g., *Ancylostoma* spp., *Toxocara* spp., *Toxoplasma gondii*). Since there are many enteric zoonotic agents that can be associated with diarrhea, diagnostic workups for enteric infections in dogs or cats with gastrointestinal signs of disease are indicated not just to aid the animal but also because of potential human health risks. Resolving the diarrhea is paramount to lessening zoonotic risk because formed feces is easier to control in the environment and while it can be difficult to eliminate the carrier phase of some agents (e.g., *Giardia*), it is generally believed that dogs or cats with normal stools are passing lower organism numbers than pets with diarrhea. The reader is directed to other individual chapters for more detail concerning diagnostic procedures and treatment for dogs or cats with vomiting or diarrhea.

TABLE 210-1

Common Enteric Zoonotic Infections of Dogs and Cats

AGENT	PRINCIPAL CLINICAL SYNDROMES
Ancylostoma caninum (D) and *A. tubaeforme* (C)* (hookworms)	Dogs and cats: Blood loss anemia, diarrhea, unthrifty Humans: Cutaneous larva migrans; eosinophilic pain
Baylisascaris procyonis (roundworm)	Dogs: Failure to thrive Humans: Visceral larva migrans; CNS disease
Campylobacter jejuni and *C. coli* (bacteria)	Dogs and cats: Diarrhea and vomiting Humans: Diarrhea and vomiting
Cryptosporidium spp.† (coccidia)	Dogs and cats: Diarrhea and vomiting Humans: Diarrhea and vomiting
Escherichia coli (bacterium)	Dogs and cats: Diarrhea and vomiting Humans: Diarrhea and vomiting
Echinococcus multilocularis (cestode)	Dogs and cats: Subclinical infection Humans: Polysystemic disease
Echinococcus granulosus (cestode)	Dogs: Subclinical infection Humans: Diarrhea and vomiting
Entamoeba histolytica‡ (amoeba)	Dogs: Diarrhea and vomiting Humans: Diarrhea and vomiting
Giardia spp.§ (flagellate)	Dogs and cats: Diarrhea and vomiting Humans: Diarrhea and vomiting
Helicobacter spp.‖ (bacteria)	Dogs and cats: Vomiting Humans: Reflux disease and vomiting
Salmonella spp. (bacteria)	Dogs and cats: Diarrhea and vomiting Humans: Diarrhea and vomiting
Strongyloides stercoralis (hookworm)	Dogs and cats: Blood loss anemia, failure to thrive Humans: Cutaneous larva migrans
Toxocara canis and *T. cati** (roundworms)	Dogs and cats: Vomiting, failure to thrive

	Humans: Ocular and visceral larva migrans
Toxoplasma gondii¶ (coccidian)	Cats: Rarely diarrhea, polysystemic disease Humans: Ocular, CNS, polysystemic disease
*Uncinaria stenocephala** (hookworm)	Dogs and cats: Blood loss anemia, diarrhea, unthrifty Humans: Cutaneous larva migrans
Yersinia enterocolitica (bacterium)	Dogs and cats: Subclinical infection Humans: Diarrhea and vomiting

*Larvation of eggs occurs after passage into the environment, so direct transmission is less likely than exposure through environmental contamination.

†Most dogs and cats are infected by *C. canis* or *C. felis*, respectively, and these host-adapted species are rarely found in humans.

‡Infection of dogs in the United States is thought to be rare.

§Host-adapted and zoonotic assemblages exist. Dogs and cats can harbor zoonotic assemblages but whether levels of infection result in re-infection of humans is not established.

||Most *Helicobacter* spp. found in dogs and cats are host-adapted species. When *H. pylori* is detected in a dog or cat, it is likely from reverse zoonotic transmission.

¶Sporulation of oocysts occurs after passage into the environment, so direct transmission is less likely than exposure through environmental contamination.

CNS, Central nervous system.

Visceral larva migrans can be induced by infection of humans with *Toxocara cati*, *Toxocara canis*, or *Baylisascaris procyonis*.[4-6] Antibodies against *Toxocara* spp. are common in humans and a recent review concluded the burden of disease is significant.[5,6] These roundworms are passed as eggs in feces which larvate and become infectious after 1 to 3 weeks. The infectious eggs can survive in the environment for months and are the primary source of human infection. Roundworms are commonly passed by young and adult dogs and cats.[7-9] Embryonated *Toxocara* spp. eggs have been transmitted by earthworms, filth flies and cockroaches, and have been found on the fur of pets.[10,11] Illness in dogs and cats is mild. In humans, larvae are released from larvated eggs, are ingested, penetrate the intestinal wall and migrate through the tissues. Eosinophilic granulomatous reactions involving the skin, lungs, central nervous system (CNS), or eyes then occur, potentially leading to clinical signs of disease.

Ancylostoma caninum, *Ancylostoma braziliense*, *Ancylostoma tubaeformis*, *Uncinaria stenocephala*, and *Strongyloides stercoralis* have been associated with cutaneous larva migrans.[12,13] In one large study of over one million dogs examined at 547 private veterinary hospitals in 44 states of the United States, 4.5% of samples contained eggs of *Ancyclostoma* spp.[8] *Ancylostoma tubaeforme* and *A. braziliense* were found in feces of 75% and 33%, respectively, of cats tested in one study in Florida.[7] After the passage of hookworm eggs into the environment in feces, infectious larvae are released after incubating for 1 to 3 days; humans are infected by skin penetration. In addition, eosinophilic enteritis in humans can occur after ingestion of larvated *A. caninum* eggs.[12] *Trichuris vulpis*, the dog whipworm, has been detected in feces in some people and has rarely been associated with gastrointestinal signs of disease in humans.[14]

Due to the risk of human infection associated with these dog and cat nematodes, it is recommended that animal excrement be controlled in human environments. All puppies and kittens should be routinely treated with an anthelmintic that has efficacy against nematodes. The Companion Animal Parasite Council (http://www.capcvet.org) and the European Council (http://www.esccap.org/) are excellent resources for current information concerning strategic deworming of pets.

Dipylidium caninum, *Echinococcus granulosus*, and *Echinococcus multilocularis* are cestodes of dogs and cats that can infect humans.[15-17] Wild carnivores are more common definitive hosts of *Echinococcus* spp. and shed infective eggs into the environment. *Echinococcus granulosus* eggs can be transmitted in feces of dogs after ingestion of infected sheep or rabbit tissues; *E. multilocularis* can be transmitted in feces of dogs or cats after ingestion of an infected rodent. Transmission to humans occurs after ingestion of the intermediate host (flea, *Dipylidium*) or eggs (*Echinococcus* spp.). Infection of dogs and cats with cestodes is generally subclinical; infection of humans with either *Echinococcus* spp. can result in significant illness.[16] Prevention or control of cestodes is based on sanitation procedures and use of taeniacides. Restricting hunting behavior of dogs and cats and feeding only processed or cooked foods should lessen potential exposure to *Echinococcus* spp. Monthly administration of drugs with activity against cestodes should be considered in dogs and cats allowed to hunt in endemic areas. Flea control should be maintained to lessen risk of *D. caninum* infection.

Cryptosporidium spp. and *Toxoplasma gondii* are the enteric coccidians that people are most likely to come in contact with via fecal contamination (see ch. 221).[18,19] *Cryptosporidium canis* is most common in dogs and *C. felis* is most common in cats; these agents are not considered to be significant zoonotic agents in humans.[18,20,21] Humans are more likely to develop infection with *C. parvum* or *C. hominis,* which are generally associated with ingestion of oocysts in large animal feces or human feces, respectively.[22,23] *Cryptosporidium* spp. have an enteric life cycle that culminates in the production of thin-walled, autoinfective oocysts and thick-walled, environmentally resistant oocysts that are passed in feces already sporulated and so, infectious. The oocysts (approximately 5 microns in diameter) are small, which makes them hard to diagnose but easy to acquire in water or food contaminated with feces. The strains that infect both pets and people cannot be differentiated by light microscopy from those that infect only pets, so all *Cryptosporidium* spp. should be considered potentially zoonotic. Polymerase chain reaction can be used to genotype *Cryptosporidium* spp. in dog or cat feces if owners are concerned about carriage of zoonotic species (www.dlab.colostate.edu). However, dogs or cats are almost never positive for *C. parvum* or *C. hominis.* Routine use of PCR assays as a screening diagnostic tool can have the unintended consequence of detecting the carrier stage of *Cryptosporidium* spp.[24] No treatment is known to eliminate the *Cryptosporidium* spp. carrier state (see ch. 221), but if feces of dogs and cats are normal, the risk of infection of a human should be minimal. Avoiding exposure is the most effective way to prevent acquiring a *Cryptosporidium* spp. infection. Routine disinfectants require extremely long contact with the organism to be effective. Drying, freeze-thawing, and steam cleaning can inactivate the organism. Surface water collected in the field for drinking should be boiled or filtered.

Cats are the only known definitive host of *Toxoplasma gondii* and the risks to humans, cats, and dogs have been recognized for years (see ch. 221).[19] After being passed by a cat, *T. gondii* oocysts sporulate in 1 to 5 days, are then infectious to most warm-blooded vertebrates, and survive in the environment for months. After *T. gondii* infection of cats or intermediate hosts including dogs and humans, an extraintestinal phase with formation of tissue cysts containing the organism develops. Infection of tissue cysts in undercooked meat is a major route of infection of humans.[25] The organism is also transmitted transplacentally in dogs, cats, and humans if the dam is infected for the first time during gestation. Recent evidence based on detection of anti-sporozoite antibodies in serum of humans suggests that ingestion of sporulated oocysts in the environment is a common way for humans to become infected.[26] Infected immunocompetent humans are generally asymptomatic; self-limiting fever, lymphadenopathy, and malaise occur occasionally. Transplacental infection of humans results in clinical manifestations, including stillbirth, hydrocephalus, hepatosplenomegaly, and retinochoroiditis. In addition to all the previous clinical findings associated with *T. gondii* infection, there is a weak to moderate association with *T. gondii* and several behavioral abnormalities in humans.[27,28] Thus, it is clear that avoiding *T. gondii* infection is a good strategy for people. In short, prevention is accomplished by avoiding the ingestion of feline feces that have been passed for >24 hours and avoid ingestion of undercooked meat. However, as discussed in ch. 221, acquiring *T. gondii* infection from an individual cat is unlikely because the oocyst shedding period is so short, oocysts are passed unsporulated, most cats do not leave feces on their body for extended periods of time, and repeat oocyst shedding, even in the face of cyclosporine administration, is unlikely (see Table 210-1).[19,29]

Giardia spp. (flagellate), *Entamoeba histolytica* (amoeba), and *Balantidium coli* (ciliate) are enteric protozoans of dogs and cats that can be transmitted to humans by contact with feces; the cysts of these agents do not require an incubation period to become infectious (see ch. 221). It is unknown how often humans are exposed to *E. histolytica* or *Balantidium coli.* However, *Entamoeba* spp. cysts were identified in 94 of 600 dog fecal samples in Pakistan[30] and *E. histolytica* cysts are found in public parks in Spain.[31] While zoonotic assemblages of *Giardia* (A and B) are occasionally amplified from dog or cat feces, most are positive for the dog or cat adapted assemblages C, D, or F.[32-36] However, determining zoonotic strains of *Giardia* spp. by microscopic examination or antigen testing is not possible, so feces from all dogs and cats infected with *Giardia* spp. are considered a potential human health risk. If infection cannot be eliminated, genotyping is available to prove whether a dog or cat is carrying a zoonotic genotype (www.dlab.colostate.edu). Prevention of zoonotic giardiasis includes boiling or filtering surface water for drinking and washing hands that have handled materials that could be contaminated with feces, even if gloves were worn. In dogs and cats treated for giardiasis, infection can be documented again several weeks later in approximately 75% of animals. Whether these cases are a treatment failure or a reinfection is unknown. Thus, the primary goal for the treatment of giardiasis is elimination of diarrhea. Whether to treat healthy dogs or cats carrying *Giardia* is still controversial (www.capcvet.org).[37]

Salmonella spp., *Campylobacter* spp., *Escherichia coli, Yersinia enterocolitica,* and *Helicobacter* spp. each infect

dogs and cats, are directly infectious, and can cause disease in humans.[38-42] Transmission between animals and humans is by fecal-oral contact. Gastroenteritis can occur in dogs or cats after infection by *Salmonella* spp., *Campylobacter* spp., or *E. coli. Helicobacter* infections cause gastritis, which is commonly manifested as vomiting, belching, and pica. Although *Helicobacter pylori* was isolated from a colony of cats, most dogs and cats are infected with non-zoonotic *Helicobacter* spp. *Yersinia enterocolitica* is probably a commensal agent in most dogs and cats but causes fever, abdominal pain, polyarthritis, and bacteremia in humans and was associated with diarrhea in one puppy.[42]

Diagnosis of *Salmonella* spp., *Campylobacter jejuni, E. coli,* and *Y. enterocolitica* in clinically affected animals is based on culture of feces or PCR (see ch. 220). Culture is preferred so that antimicrobial susceptibility can be provided to use in developing a treatment plan. In general, treatment of bacterial enteric agents is only used to manage clinical illness when indicated. Treatment of subclinical carriers likely just leads to drug resistant strains. Prevention of enteric bacterial zoonoses is based on sanitation and control of exposure to feces. Veterinary clinicians should strive to resolve diarrhea in affected dogs and cats, as normal animals are less likely to be shedding large numbers of enteric pathogens. Immunodeficient people should avoid young animals and animals from crowded or unsanitary housing, particularly if clinical signs of gastrointestinal tract disease are occurring. Feeding raw foods is a risk factor for dogs or cats with bacterial enteric zoonoses and should be avoided (https://www.avma.org/KB/Policies/Pages/Raw-or-Undercooked-Animal-Source-Protein-in-Cat-and-Dog-Diets.aspx), particularly if there is an immune-suppressed family member (see ch. 192).[39-41]

Exudate Exposure Zoonoses

There are several bacterial and fungal agents associated with draining tracts or other skin diseases in dogs or cats that could be directly infectious to the owner or veterinary staff members (Table 210-2). Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus pseudintermedius* (MRSP) are associated with skin infections, wound infections, and can be carried by normal dogs and cats.[43-49] These agents can be spread amongst veterinary or human patients and doctors and are a significant problem in hospitals.[43,49] A recent study of nasal and perianal samples completed in an open-admission shelter showed MRSA in 0.5% of cat samples, MRSA in 0.5% of dog samples, and MRSP in 3% of dog samples.[50] These prevalence rates are generally lower than those from dogs or cats from veterinary hospitals. Healthy dogs or cats carrying MRSA or MRSP are generally not a risk for immunocompetent and otherwise healthy people but care should be taken to avoid contamination of open wounds if an infected animal is being cared for.

TABLE 210-2

Common Scratch-, Bite-, or Exudate-Associated Zoonotic Infections of Dogs and Cats

AGENT	PRINCIPAL CLINICAL SIGNS
Bartonella spp.* (bacterium)	Cats and dogs: Subclinical, fever, hyperglobulinemia, uveitis, lymphadenopathy, others Humans: Fever, malaise, lymphadenopathy, bacillary angiomatosis, bacillary peliosis, others
Capnocytophaga canimorsus (bacterium)	Dogs and cats: Subclinical oral carriage Humans: Bacteremia
Dermatophytes (fungi)	Cats and dogs: Superficial dermatologic disease Humans: Superficial dermatologic disease
Francisella tularensis† (bacterium)	Dogs and cats: Fever, lymphadenopathy, septicemia, pneumonia Humans: Ulceroglandular, oculoglandular, glandular, pneumonic, or typhoidal (depending on route of inoculation)
Rabies (virus)	Cats and dogs: Progressive central nervous system disease Humans: Progressive central nervous system disease
Sporothrix schenkii† (fungus)	Cats: Draining cutaneous tracts Humans: Draining cutaneous tracts
Yersinia pestis† (bacterium)	Cats: Bubonic, bacteremic, or pneumonic (depending on route of inoculation) Humans: Bubonic, bacteremic, or pneumonic (depending on route of inoculation)

Bartonella henselae, B. koehlerae, and *B. clarridgeiae* are transmitted amongst cats and dogs by *C. felis* and so are also listed under flea-borne disease. There are other *Bartonella* spp. with zoonotic implications. Cats generally develop a higher level of bacteremia than do dogs, and so are epidemiologically linked more frequently to human disease. The vectors are unknown for some *Bartonella* spp.

†Dogs rarely shed enough organism to be a public health risk.

Sporothrix schenckii (see ch. 236) and the dermatophytes are the fungi that are most likely to infect owners or veterinary staff members by direct contact.[51-55] *Histoplasma* (see ch. 233), *Blastomyces* (see ch. 233), *Coccidioides* (see ch. 232), *Aspergillus* (see ch. 234 and 235), and *Cryptococcus* (see ch. 231) infections of humans and animals can occur in the same household but generally result from a common environmental exposure (see a following section). Management of zoonotic dermatophytes has been reviewed.[51,52] *Sporothrix schenckii* is a species complex containing *S. schenckii sensu stricto, S. brasiliensis, S. globosa, S. mexicana,* and *S. luriei.* Brazil is one of the most common countries with endemic infections and most are *S. brasiliensis*.[54,55] The organisms are found in the soil around the world. Most cases of zoonotic transfer have been from cats that seem to have higher concentrations of the organism in exudates when compared to dogs. Cats are believed to be infected by scratches from contaminated claws of other cats and sporotrichosis is most common in outdoor males. Cats can develop cutaneolymphatic, cutaneous, or disseminated sporotrichosis and chronic draining cutaneous tracts are common. Humans can be infected by contamination of cutaneous wounds with exudates from infected cats; thus veterinary care personnel are at high risk when treating infected cats. The organism can be demonstrated by cytologic examination of exudates or culture. See ch. 236 for a discussion of the treatment of this syndrome. Gloves should be worn when attending to dogs or cats with infected wounds or draining tracts, and hands should be cleansed thoroughly afterwards.

Bite or Scratch Zoonoses

The number of animal bite injuries has been estimated to be 300,000 to 4.7 million per year in the United States.[56,57] In one study, 70% of bites were from dogs and 13% were from cats.[56] Dogs and cats are subclinical carriers of multiple bacteria in the oral cavity. Most of the aerobic and anaerobic bacteria associated with bite or scratch wounds cause only local infection in immunocompetent individuals. However, cat bites were six times more likely than dog bites to become infected in a recent study.[58] After a person is bitten or scratched, local cellulitis is noted initially, potentially followed by evidence of deeper tissue infection. Severe sequelae, including meningitis, endocarditis, septic arthritis, osteoarthritis, and septic shock, can occur. Immunodeficient humans or those exposed to *Pasteurella* spp., *Capnocytophaga canimorsus* (DF-2), or *Capnocytophaga cynodegmi* more consistently develop systemic clinical illness (see Table 210-2).[59-61] Splenectomized humans are at increased risk for developing bacteremia. Other less common animal bite bacterial infections include *Mycoplasma* spp., L-form bacteria, *Francisella tularensis,* and *Yersinia pestis.*[62] Tularemia and plague are also vector-borne diseases and also can be acquired by inhalation. See those sections of this chapter for further discussion of these two syndromes. Diagnosis of bacterial infections is confirmed by culture. Treatment of clinically affected humans includes local wound management and parenteral antibiotic therapy. Penicillin derivatives are highly effective against most *Pasteurella* infections; penicillins and cephalosporins are effective against *Capnocytophaga* spp. *in vitro*. Treatment of dogs and cats that carry *Capnocytophaga* spp. is not needed.

The most recognized scratch- or bite-associated zoonosis is cat scratch disease (fever) associated with *Bartonella henselae.*[63,64] Dogs, cats and humans can be infected with multiple other *Bartonella* spp., including *B. clarridgeiae, B. koehlerae, B. vinsonii* subspecies *berkhoffi* (dogs and humans), and *B. quintana;* see ch. 215 and 216 for a discussion of the clinical syndromes in small animals. Shortly after the *Bartonella* genus was discovered, *B. henselae* was associated with bacillary angiomatosis and bacillary peliosis, common disorders in humans with AIDS. In the last several years, *Bartonella* spp. have been associated with endocarditis and a multitude of chronic inflammatory diseases in people.[63-67] Neurobartonellosis appears to be a common manifestation and veterinary health care providers are at increased risk.[65,67]

Contact with cats or dogs is a known risk factor for development of bartonellosis. These infectious agents are amongst the most common in the world. *Bartonella henselae, B. clarridgeiae,* and *B. koehlerae* are common in cats and their fleas.[68] *Bartonella vinsonii* subspecies *berkhoffi* DNA has been amplified from fleas and a number of *Bartonella* spp. has been detected in ticks.[69] Thus, *Bartonella* spp. infections should also be considered a shared vector zoonosis. Cats with *B. henselae* infection housed together with naïve cats without *Ctenocephalides felis* do not share the infection.[70,71] However, transmission occurs quickly when fleas are added. *Bartonella henselae* survives in flea frass for days and it appears likely that cat's claws and teeth are contaminated with *B.*

henselae during grooming and then inoculated into humans during bites or scratches. It is also possible that *Bartonella* spp. infections occur after flea frass contaminates broken dermal barriers like hangnails. These findings emphasize the maintenance of flea control on dogs and cats, year round. Use of imidacloprid-containing products has blocked transmission of *B. henselae* amongst research cats.[71,72] *Bartonella* spp. infection has also been associated with needle sticks, so blood from dogs or cats should be handled carefully.

Blood culture, blood PCR, and serologic testing can be used to determine the *Bartonella* spp. infection status of individual cats, dogs, or people. The use of BAPGM culture media with PCR assay has been shown to be one of the most sensitive ways to prove *Bartonella* spp. bacteremia in dogs and people; these assays are available at one commercial laboratory (www.galaxydx.com). In dogs and cats, although serologic testing can be used to determine whether an individual has been exposed, both seropositive and seronegative cats and dogs can be bacteremic, limiting the diagnostic utility of serologic testing. Thus, testing healthy cats or dogs for *Bartonella* spp. infection is not currently recommended by the Centers for Disease Control and Prevention or the American Association of Feline Practitioners.[3,64]

In experimental studies, administration of doxycycline, tetracycline, erythromycin, amoxicillin-clavulanate, or enrofloxacin can limit bacteremia but does not cure infection in all cats and antibiotic treatment of healthy cats has not been shown to lessen the risk of cat scratch disease. Azithromycin was commonly administered to cats with suspected clinical bartonellosis, but is now considered contraindicated for feline bartonellosis due to rapid induction of antimicrobial resistance.[73] Thus, antibiotic treatment of healthy bacteremic cats is controversial and not currently recommended by the Centers for Disease Control and Prevention or the American Association of Feline Practitioners.[3,64] Flea and tick control should be maintained on all dogs and cats. Immunodeficient people should avoid kittens with fleas. Cat claws should be kept clipped or claw covers used and cats should never be teased. Cat-induced wounds should immediately be cleansed, and medical advice sought.

Rabies is still the only relevant direct small animal viral zoonosis in the United States. See ch. 226 for a discussion of this agent as well as the Compendium on Rabies Control 2016.[74] Pseudorabies is a herpesvirus that infects pigs; dogs and humans can develop clinical illness after exposure.[75] To date, there is no evidence that retroviruses of cats infect people.[76] However, because both feline leukemia virus and feline immunodeficiency virus can induce immune deficiency, infected cats should be considered more likely than retrovirus-naïve cats to be carrying other potential zoonotic agents, particularly if clinical signs of disease are present.

A major goal in the prevention of zoonosis is for veterinarians to train pet owners and new veterinary staff members how to avoid bites or scratches.[77,78]

Respiratory Tract and Ocular Zoonoses

There are only a few respiratory pathogens of dogs or cats that are associated with clinical disease in people (Table 210-3). *Bordetella bronchiseptica* is the most common primary bacterial pathogen associated with the canine infectious respiratory disease complex in dogs (see ch. 227) and can be a pathogen in some cats (see ch. 212, 229, and 241). Humans rarely develop clinical disease caused by *B. bronchiseptica* unless they are immunologically compromised.[79-81] Fewer than 100 cases of *B. bronchiseptica* infection in humans have been reported; most of the patients were immune-suppressed. *Bordetella bronchiseptica* infection in humans has been associated with cats as well as dogs. Diagnosis is best confirmed by culture so that antimicrobial susceptibility testing can be performed. Dogs or cats with clinical signs generally respond to the administration of amoxicillin-clavulanate or doxycycline. Immune-suppressed people should avoid handling cats or dogs with suspected infectious upper or lower respiratory tract inflammatory disease until the animals are clinically normal. However, treated animals can still shed *Bordetella bronchiseptica* in low numbers.

TABLE 210-3

Common Ocular or Respiratory Zoonotic Infections of Dogs and Cats

AGENT	PRINCIPAL CLINICAL SYNDROMES
Bordetella bronchiseptica (bacterium)	Dogs and cats: Sneeze and cough Humans: Pneumonia in immunosuppressed
Chlamydia felis (bacterium)	Cats: Conjunctivitis, sneezing

	Humans: Conjunctivitis
*Francisella tularensis** (bacterium)	Cats: Fever, lymphadenopathy, septicemia, pneumonia Humans: Ulceroglandular, oculoglandular, glandular, pneumonic, or typhoidal (depending on route of infection)
Streptococcus group A (bacterium)	Dogs and cats: Subclinical, transient carrier Humans: "Strep throat," septicemia
*Yersinia pestis** (bacterium)	Cats: Bubonic, bacteremic, or pneumonic Humans: Bubonic, bacteremic, or pneumonic

*Also can be vector-borne.

Chlamydia felis (formerly *Chlamydia psittaci*) causes conjunctivitis and mild rhinitis in cats.[82] In Japan, the prevalence rates of antibodies against an isolate of *C. felis* were 51% in stray cats, 15% in pet cats, 3% in the general human population, and 5% in small animal clinic veterinarians, suggesting that transfer between cats and humans may occur.[83] Conjunctivitis in humans after direct contact with ocular discharges from cats has been described.[84] A human isolate of *Chlamydia* spp. was inoculated into cats, resulting in conjunctivitis and persistent infection, suggesting that the isolate was a feline strain. Occasionally the organism is associated with systemic disease including atypical pneumonia, endocarditis and glomerulonephritis. However, DNA of *C. felis* has also been amplified from healthy people.[85] Diagnosis is based on organism demonstration by culture, cytologic documentation of characteristic inclusion bodies, fluorescent antibody staining of conjunctival scrapings, or amplification of specific DNA by polymerase chain reaction. Tetracycline or chloramphenicol-containing eye ointments generally are effective in the treatment of infection. Oral administration of doxycycline is still considered the optimal way to clear the carrier state in catteries. Care should be taken to avoid direct conjunctival contact with discharges from the respiratory or ocular secretions of cats, especially by immunosuppressed persons. Employees should be directed to wear gloves or wash hands carefully when attending to cats with conjunctivitis.

Humans are the principal natural hosts for *Streptococcus* group A bacteria, *Streptococcus pyogenes,* and *Streptococcus pneumoniae,* which cause "strep throat" in humans. Dogs and cats in close contact with infected humans can develop transient, subclinical colonization of pharyngeal tissues and can transmit the infection to other humans. However, this is poorly documented and believed to be unusual. The organism can be cultured from the tonsillar crypts. Culture-positive animals should be treated with penicillin derivatives. If animals are to be treated in a household with chronic, recurrent "strep throat" in children, all humans should also be treated because they also could be chronic subclinical carriers.

Francisella tularensis is the Gram-negative bacillus found throughout the continental United States that causes tularemia. Of the 4 subspecies, *F. tularensis* subsp *tularensis* (type A) and *F. tularensis* subsp *holarctica* (type B) occur commonly in the Northern Hemisphere including all of the United States (except Hawaii), and are most commonly associated with illness in humans and other animals.[86-89] Humans are exposed to the organism most commonly by direct animal contact (primarily rabbits or cats), ingestion, inhalation from aerosolization, or by tick or deer fly bites. Infection of people after inhaling the organism after mowing over infected rabbits or rodents may be common. Cats and dogs are most likely infected by tick bites or ingestion of infected rabbits or rodents. Dogs may be less likely to become ill than cats and are not usually considered a source of infection, but may facilitate human exposure by bringing infected ticks into the environment. Whether clinical signs develop is dependent on the inoculation dose, the strain of *F. tularensis,* and the immune status of the exposed individual. Clinically affected cats or dogs usually develop fever or lymphadenopathy. Ulceroglandular, oculoglandular, glandular, oropharyngeal, pneumonic, and typhoidal forms have been described in humans and develop depending on the route of exposure. Human cases were greatly increased in Colorado, Nebraska, South Dakota, and Wyoming in 2015 (n = 100) compared to 2004-2014.[86] In this report, the pneumonic form of disease (n = 26), ulceroglandular form of disease (n = 26), or fever (n = 25) were the most common presenting complaints. The organism may not be visible cytologically, so infection is confirmed by culture, fluorescent antibody stain, PCR assay, or demonstration of a rising serological titer. Infected humans usually respond to antimicrobial therapy; one death was reported in the 2015 western United States outbreak.[86] Optimal treatment for infected cats and dogs is unknown. Aminoglycosides, doxycycline, chloramphenicol, or quinolones are used in people.[90] The disease is prevented by avoiding exposure to lagomorphs, ticks, and clinically ill infected cats. All cats with fever or lymphadenopathy or with clinical evidence of bacteremia should be handled carefully and a workup performed for tularemia and plague if in endemic areas and/or with appropriate exposure history. Local

authorities should be alerted when a diagnosis of tularemia is made. Animals that are hospitalized should be housed in isolation, handled by as few individuals as possible, and those handling the animals should wear a gown, gloves, eye shield, and respirator if available.

Feline plague is caused by *Yersinia pestis*, a Gram-negative coccobacillus found most commonly in Midwestern and far Western states, particularly Arizona, New Mexico, and Colorado.[91,92] Rodents are the natural hosts for this bacterium; cats are thought to be most commonly infected by ingestion of bacteremic rodents or lagomorphs or by being bitten by *Yersinia*-infected rodent fleas.[91-95] Non-domestic cats in endemic areas are also exposed.[93] Humans are most commonly infected by rodent flea bites, but many cases of transmission by exposure to wild animals and infected domestic cats have been documented. One infected dog was thought to be associated with pneumonic plague in people and a human to human case was also suspected.[94] Animal contact can be associated with *Y. pestis* infection of humans by inhalation of respiratory secretions, through bite wounds, or by contamination of mucous membranes or abraded skin with secretions or exudates.

Bubonic, septicemic, and pneumonic plague can develop in cats and humans; each form has accompanying fever, headache, weakness, and malaise. Untreated pneumonic plague is commonly fatal.[95] Because cats are most commonly infected by ingestion of bacteremic rodents, suppurative lymphadenitis (buboes) of the cervical and submandibular lymph nodes is the most common clinical manifestation. Exudates from cats with lymphadenopathy should be examined cytologically for the presence of large numbers of the characteristic bipolar rods. Fluorescent antibody staining, culture or PCR of exudates, the tonsillar area, or saliva or documentation of increasing antibody titers confirms the diagnosis. People who are exposed to infected cats should be urgently referred to physicians for antimicrobial therapy, and public health officials should be alerted. Doxycycline, fluoroquinolones, chloramphenicol, or aminoglycosides can be used successfully for the treatment of plague.[96] Parenteral antibiotics should be used during the bacteremic phase. Cats with suppurative lymphadenitis should be considered plague suspects, and extreme caution should be exercised when handling exudates or treating draining wounds. Suspect animals should be treated for fleas, housed in isolation, handled by as few individuals as possible, and those handling the animals should wear a gown, gloves, eye shield, and respirator if available. Cats are generally not considered infectious to humans after 4 days of antibiotic treatment but veterinarians should consult with local public health officials for guidance.

Currently, there are no respiratory viruses of dogs or cats in the United States that have been associated with human infection. However, multiple occurrences of inter-species transmission of influenza A viruses have occurred and potential for increased zoonotic risk with these, and other viruses, may occur over time.[97-99]

Genital and Urinary Tract Zoonoses

The most common infectious agents associated with zoonotic transmission via exposure to urine or genital tract materials are *Brucella canis*, *Coxiella burnetii*, and *Leptospira* spp. (Table 210-4).

TABLE 210-4

Common Urogenital Zoonotic Infections of Dogs and Cats

AGENT	PRINCIPAL CLINICAL SYNDROMES
Brucella canis (bacterium)	Dogs: Orchitis, epididymitis, abortion, stillbirth, vaginal discharge, uveitis, fever Humans: Fever, malaise
Coxiella burnetiii (rickettsia)	Cats: Subclinical, abortion, or stillbirth Humans: Fever, pneumonitis, lymphadenopathy, myalgia, arthritis
Leptospira spp. (spirochetes)	Dogs: Fever, malaise, inflammatory urinary tract or hepatic disease, uveitis, central nervous system disease Humans: Fever, malaise

Brucella canis is a bacterium that preferentially infects the testicles, prostate, uterus, and vagina of dogs (see ch. 213). The infection is maintained in dogs primarily by venereal transmission but direct transmission from oral or nasal exposure can occur in puppies. Humans can be infected by direct contact with vaginal and preputial discharges from dogs. Clinical syndromes in dogs are diverse but commonly include abortion,

stillbirth, failure to conceive, orchitis, epididymitis, vaginal discharge, uveitis, discospondylitis, and bacteremia. Intermittent fever, depression, and malaise are common in infected people.[100,101] Diagnosis is based on serologic testing or demonstration of the organism by culture or PCR assay. Seronegative dogs are unlikely to harbor *B. canis* unless the exposure was peracute. Seropositive dogs should have results confirmed by tube agglutination or agar gel immunodiffusion and should be cultured or assessed by PCR assay. Long-term antibiotic treatment (tetracyclines, aminoglycosides, quinolones) does not always clear the infection, so some recommend euthanasia of infected dogs. Ovariohysterectomy or castration will lessen contamination of the environment. Veterinary staff members should avoid direct contact with genital tract secretions while managing cases with suspected brucellosis. Owners should seek advice from their physician concerning ownership of a proven *B. canis*-positive dog.

Coxiella burnetii is a rickettsial agent found throughout the world, including North America. Many ticks, including *Rhipicephalus sanguineus,* are naturally infected with *C. burnetii* but the importance of ticks in the transmission of this agent has been recently questioned.[102] Most humans are infected by inhalation of the organism and so pneumonia is common. Other clinical findings of Q fever include fever, malaise, headache, pneumonitis, myalgia, and arthralgia.[103] Cattle, sheep, and goats are commonly subclinically infected and they pass the organism into the environment in urine, feces, milk, and parturient discharges. Some cats and dogs are also seropositive or PCR-positive for *C. burnetii* and cats have been implicated in human cases of Q fever a number of times.[104-106] Fever, anorexia, and lethargy developed in some experimentally infected cats and abortion has been documented in cats. Tetracyclines, chloramphenicol, and quinolones are usually effective therapeutic agents in humans. Gloves and masks should be worn when attending to parturient or aborting cats or dogs. People who develop fever or respiratory tract disease after exposure to parturient or aborting cats or dogs should seek medical attention and inform the attending physician about the potential for zoonotic Q fever.

Leptospira spp. can be transmitted in urine from infected dogs and cats to humans, resulting in clinical disease.[107-109] Host-adapted species cause subclinical infection; infection by non–host-adapted species commonly results in clinical illness. See ch. 217 for a detailed discussion of the clinical manifestations of this disease and its treatment in dogs and cats. Human clinical syndromes vary with the serovar but are similar to those that occur in the dog. Control of *Leptospira* spp. in hospitalized animals is detailed in the ACVIM Consensus Statement.[109] *Leptospira* spp. vaccine side-effects are minimal and so vaccines containing 4 leptospire serovars should be considered in at-risk dogs[109,110] (https://www.aaha.org/public_documents/professional/guidelines/caninevaccineguidelines.pdf); see ch. 208.

Shared Vector Zoonoses

Some zoonotic agents are transmitted between animals and humans by shared vectors such as fleas, ticks, mosquitoes, sand flies, or kissing bugs (Table 210-5).[111] *Rickettsia rickettsii* (ticks), *R. felis* (fleas), *Ehrlichia* spp. (ticks), *Anaplasma phagocytophilum* (ticks), *Borrelia burgdorferi* (ticks), *Bartonella* spp. (fleas and ticks), *Dipylidium caninum* (fleas), *Dirofilaria immitis* (mosquitoes), West Nile virus (mosquitoes), *Trypanosoma cruzi* (triatomines—kissing bugs) are examples of vector-borne zoonoses common in the United States. In other countries, sandfly-borne *Leishmania* spp. infection is also important. For the flea- and tick-borne zoonoses, the pet brings the vector of the organism into the environment, resulting in exposure of the human being. Veterinary health care providers could have a slightly increased risk of exposure because they handle many animals infested with fleas and ticks. However, the vector, not direct contact with the infested animal, generally results in infection of the person. Flea and tick control should always be maintained in animals (www.capcvet.org), and infested animals that are seen in the clinic should be treated immediately. See other sections of this text for detailed discussions of these agents.

TABLE 210-5

Common Vector-Borne Zoonotic Infections of Dogs and Cats

AGENT	PRINCIPAL CLINICAL SYNDROMES
Fleas	
Bartonella spp.* (bacteria)	Cats and dogs: Subclinical, fever, hyperglobulinemia, uveitis, lymphadenopathy, others Humans: Fever, malaise, lymphadenopathy, bacillary angiomatosis, bacillary peliosis, CNS,

	polyarthritis, endocarditis, others
Rickettsia felis (rickettsia)	Dogs: Subclinical Humans: Fever, CNS
Yersinia pestis (bacterium)	Cats: Bubonic, bacteremic, or pneumonic (depending on the route of inoculation) Humans: Bubonic, bacteremic, or pneumonic (depending on the route of inoculation)
Ticks*	
Anaplasma phagocytophilum (rickettsia)	Dogs and cats: Fever, polyarthritis Humans: Fever, polysystemic
Borrelia burgdorferi (spirochete)	Dogs: Subclinical infection, fever, polyarthritis, nephropathy Humans: Polyarthropathy, cardiac and CNS disease
Ehrlichia spp. (rickettsia)	Dogs: Subclinical infection, fever, polysystemic Humans: Fever, polysystemic
Francisella tularensis (bacterium)	Cats: Fever, lymphadenopathy, septicemia, pneumonia Humans: Ulceroglandular, oculoglandular, glandular, pneumonic, or typhoidal (depending on route of infection)
Rickettsia rickettsia (rickettsia)	Dogs: Subclinical infection, fever, polysystemic Humans: Fever, polysystemic

*_Bartonella_ spp. DNA has been amplified from some ticks but the extent of the role ticks play in the transmission of these agents has not been fully ascertained.

CNS, Central nervous system.

Shared Environment Zoonoses

Some agents that infect both animals and man are not commonly transmitted between the pet and the owner by direct contact but are acquired from the same environmental source. Notable examples include *Histoplasma capsulatum* (see ch. 233), *Coccidioides immitis* (see ch. 232), *Blastomyces dermatitidis* (see ch. 233), *Cryptococcus neoformans* (see ch. 231), and *Aspergillus* spp. (see ch. 234 and 235). See the relevant chapters of this text for detailed discussions of these agents.

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Bacterial Diseases

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CHAPTER 211

Lyme Disease

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Client Information Sheet: Lyme Disease

Introduction

Lyme disease (borreliosis) is the most common tick-borne disease in people in North America. Many dogs and cats are exposed, become chronic carriers, and have persistently high antibody titers, yet only a small fraction becomes ill. Comprehensive reviews[1-7] and opinion papers[8-10] show that controversy still exists regarding diagnosis, treatment, and prevention of canine Lyme disease.

The Agent, the Tick, and the Birds, Mice, and Deer

There are at least 36 *Borrelia* spp. (16 pathogenic) including at least 20 species of *Borrelia burgdorferi* sensu lato, the agent of Lyme borreliosis. The main causes of Lyme disease are *B. burgdorferi* sensu stricto *(Bb)* in North America and *Bb*, *B. afzelii* and *B. garinii* in Eurasia. *Borrelia* spp. DNA was found in ticks embedded in 20 million year-old amber[11] and DNA of *Bb* was found in the 5000-year-old alpine "Tyrolean Iceman" mummy,[12] so the disease is not new, but it was named after a large cluster of children in Lyme, CT (U.S.) that were misdiagnosed with juvenile rheumatoid arthritis in 1976.[13] Maternal activism led to investigations by the Centers for Disease Control and Prevention and Dr. Allen Steere. The organism is named after Willy Burgdorfer, who studied ticks from Shelter Island, NY, for *Rickettsia rickettsii,* and found many *Ixodes scapularis* ticks carried spirochetes.[14] Serologic testing became available, proving exposure to these spirochetes in affected people, and the association was made that the illness was caused by them. Experimental models in laboratory animals and dogs confirmed this association, and the organisms and the disease have been studied extensively, including genomic sequencing. At least 30 strains of *Bb* exist, based on OspC antigen genotypes, and different strains predominate in sick people versus dogs.[15-17]

There is transstadial, but not transovarial, transmission of *Bb* in ticks. In the typical 2-year life cycle of *Ixodes,* eggs hatch outdoors, with larvae being active in the summer, attaching to and feeding on birds, mice, and small mammals that recently acquired *Bb* from infected nymphs which fed on them recently that previous spring. Transmission of *Bb* occurs in the mouse at 53 hours[18] (or less[19]) after tick attachment, which is the time it takes for OspA (the outer surface protein A that acts as a hook onto the tick's midgut) to be downregulated enough to allow the agent to come away and enter the host. By this time, OspC and many other antigens are expressed more than are OspA and antigens expressed by *Bb* within the tick or when cultivated *in vitro*. Tick larvae pick up *Bb* in summer from their first host, overwinter, and emerge as nymphs, with *Bb* intact (transstadial transmission), infecting the next generation of birds, mice, small mammals, as well as dogs, deer, people, and other animal species the next spring. The nymphs feed, moult, and emerge the following autumn, transmitting *Bb* to their third hosts, often large mammals, as adult ticks quest on higher brush.

The geographical range of ticks infected with *Bb* will expand as ticks hitch a ride on migratory birds. As of 2013, 95% of Lyme disease in people occurs in just 14 New England, mid-Atlantic, and Upper Midwestern states: PA, MA, NY, NJ, CT, WI, MN, NH, ME, VA, MD, VT, RI, DE.[20] Results for Lyme-seropositive dogs are similar.[21] In some areas, 70-90% of healthy dogs are Lyme-seropositive.[22-24]

Besides *Bb, Ixodes* ticks can transmit other spirochetes (*B. mayonii,* which is another cause of Lyme disease, tick-borne relapsing fever [TBRF] group agents *B. miyamotoi [Bm]* and *B. davisii*),[25] rickettsia *(Anaplasma phagocytophilum* and *Ehrlichia muris),* a protozoan *(Babesia microti),* a bacterium (*Bartonella* spp.), a virus

(Powassan or tick-borne encephalitis virus), and possibly more agents. Coinfections can occur but could be missed, e.g., with *Bm*, only recently identified. In CT, 35% of *Ixodes* ticks were positive for *Bb* and 6% for *Bm* in one study.[25] In people, *Bm* can cause neurologic and flu-like signs.[26,27] In New England, *Bm*-seropositivity was found in 1% of healthy people, 3.2% of people diagnosed with Lyme disease, and 21% of patients with a flu-like illness in late spring/summer in southern NY State.[27]

Lyme *Borrelia* spp. are spiral-shaped, motile, Gram-negative spirochetes, transmitted by *Ixodes* ticks which infect host mammals and birds, and migrate from the tick bite site interstitially, hiding out extracellularly with collagen and fibroblasts. There may be an L-form, spheroplast, or cystic dormant form of *Bb* in a hostile environment.[28-37] Evasion of the host's immune system also occurs by recombination of DNA cassettes, producing antigenic variation and possibly recurrent signs.[2] In contrast to TBRF *Borrelia* spp., such as *Bm* from *Ixodes* ticks and *B. hermsii (Bh)* and *B. turicatae (Bt)* (from *Ornithodorus* soft argasid ticks that only feed for 15-90 minutes), *Bb* does not generally circulate in blood or body fluids. The TBRF organisms can be seen in peripheral blood smears with dark-field microscopy, or Wright-Giemsa, acridine orange, or silver stains. Blood for TBRF culture (Barbour Stoenner Kelly medium) or PCR analysis (sequencing the 16S rRNA gene, flaB or intergenic spacer domains to identify the specific agent) is best taken before initiating antibiotics. Cross-reactive TBRF antibodies can be seen on the old whole cell IFA or ELISA testing for *Bb* antibodies. *Bh* has been found in a sick dog in Washington state and *Bt* in sick dogs in Texas and Florida.[38,39]

Comparing Human and Canine Lyme Disease: the Canine Experimental Model

In Europe, for many years, it was known that a post-tick bite illness in people (rash and neurologic signs) responded to penicillin. In the US, the expanding rash at the site of the tick bite is more often accompanied by flu-like signs (headache, fever, myalgia/arthralgia) and, later, swollen painful oligoarthritis in a joint near the tick bite site, but subsequent neuroborreliosis, cardiac, and chronic skin manifestations also can be seen.[40,41] An experimental canine model of Lyme disease via tick bite has been studied extensively.[42-56] When infected ticks from New England were placed on 6- to 12-week-old puppies, they showed no acute illness but after 2-5 months showed a self-limiting illness (i.e., 4 days of fever, decreased appetite, and lameness with a hot/swollen joint in the leg closest to where the ticks attached), possibly with a few recurrent episodes in the same or different limb every 2 weeks.[42,45-51] Affected joints showed nonseptic neutrophilic inflammatory changes. When infected ticks were placed on 13- to 26-week-old puppies, only 2 days of this self-limiting illness occurred, with fewer recurrences.[52,53] When ticks were placed on older puppies and adult dogs, no signs of illness occurred even when the dogs were followed for more than a year, yet all the experimental dogs showed carrier status and persistently high antibody titers.[42-44] Subclinical mild synovial histological changes were seen,[42,54] although sometimes such changes also are seen in seronegative and vaccinated dogs.[55,56] Other histologic changes included suppurative and nonsuppurative dermatitis, and lymphoplasmacytic periarteritis and perineuritis.[55]

Interestingly, many experimental dogs have had coinfections from the tick exposure, mostly (35-45%) with *Anaplasma phagocytophilum*[46,53] or sometimes *Babesia microti*[42]; these dogs have not been tested for *Bartonella*, however. Carrier status for *Bb* for more than a year after tick exposure was documented by positive cultures or polymerase chain reaction (PCR) test results on skin biopsies of the tick bite sites. Antibiotics usually have cleared the carrier status; however, 10-15% of dogs have remained carriers despite treatment with 1 month of high-dosage doxycycline (10 mg/kg PO q 12 h), amoxicillin (20 mg/kg PO q 8 h), azithromycin (25 mg/kg PO q 24 h), or ceftriaxone (25 mg/kg IV q 24 h).[45,47-49] Carriers in the experimental model remained nonclinical, persistently seropositive (the magnitude of titers was not correlated with illness), and none developed Lyme nephritis. Some dogs showed lameness after abrupt withdrawal from steroids, but coinfections or trauma could have played a role.[48]

Cats appear more resistant to illness from spirochetal infections; seropositive cats are not more likely to show illness.[57] Screening for coinfections (bartonellosis, anaplasmosis, feline leukemia virus, feline immunodeficiency virus) is recommended. Experimentally, cats exposed to organisms from ticks have shown multiple-limb lameness and joint, pulmonary, lymphoid and CNS inflammation at necropsy.[6]

Signs of Canine Lyme Disease in the Field

Lyme Arthritis

As in the experimental model, a Lyme-positive status in the field, no matter how high the titer, does not predict illness in dogs.[58] Cutaneous rash,[55] neurologic,[59] and cardiac[60] signs of Lyme disease rarely or never occur. Original reports from New England showed that <5% of seropositive dogs had a history of lameness, even when followed for 20 months, and the same percentage of seronegative dogs had similar signs.[61] Even fewer seropositive cats show signs. One study showed that Lyme arthritis is overdiagnosed 40% of the time.[62] Thus perhaps <3% of seropositive dogs have signs due to Lyme arthritis. Clinical signs attributed to Lyme disease include oligo- or polyarthritis with painful, hot, swollen joint(s), joint effusion, local lymphadenopathy, fever, and hyporexia. Differential diagnoses include tick-borne arthritis, immune-mediated polyarthritis, systemic lupus erythematosus, rheumatoid arthritis, bacterial endocarditis, septic arthritis, degenerative joint disease, cranial cruciate ligament rupture, intervertebral disc disease, trauma, panosteitis, osteomyelitis, polymyositis, neoplasia, or immobility due to cardiopulmonary, metabolic, or neurologic disease.[1] Many dogs in Lyme-endemic areas have coinfections with *Anaplasma,* and coinfected dogs could be more likely to show clinical signs.[63] Cytopenia suggests coinfection. Synovial fluid cytology from arthrocentesis shows neutrophilic inflammation, and sometimes *A. phagocytophilum* morulae (see ch. 74 and 94). Radiographs show only soft tissue swelling (a nonerosive arthritis; see ch. 203). Signs typically are self-limiting or respond quickly to antimicrobial treatment (1-2 days); treatment for 1 month is recommended.[1] Doxycycline or minocycline usually is chosen because of possible sensitive coinfection (*Anaplasma, Ehrlichia, Rickettsia, Bartonella, Mycoplasma* spp.) and for anti-inflammatory and anti-arthritic properties (see Treatment, below). *Bb* also is sensitive to amoxicillin, erythromycin, azithromycin, cefovecin, and ceftriaxone.[64,65]

Lyme Nephritis

A smaller percentage (<2%) of seropositive dogs can develop Lyme nephritis, a protein-losing nephropathy (PLN) associated with immune-mediated glomerulonephritis and Lyme-specific antigen-antibody complex deposition in renal glomeruli.[7] Labradors and Golden Retrievers appear at higher risk, although proteinuria was not found to be associated with Lyme-seropositive status in retrievers in one study.[66] It is unknown why so many dogs with high titers and presumably high concentrations of circulating immune complexes do not develop Lyme nephritis. There could be host genetic or immune factors, or infective strain differences. In people, certain genetic haplotypes are predisposed to developing immune-mediated disease triggered by Lyme antigens (HLA-DR4).[1,67] Without an experimental model of Lyme nephritis in dogs, it is difficult to study this aspect of the disease. Perhaps some retrievers are genetically predisposed to having glomerulopathy (e.g., Bernese Mountain Dogs with coincidental seropositivity),[7] possibly due to a podocytopathy or immunodysregulation. It is unknown if Lyme-specific immune complexes are primary (causative of illness) or if they are passively caught in already-abnormal glomeruli. Elution studies on kidneys taken after death showed a variety of Lyme antigen-antibody complexes, but such studies are not available for clinical cases. There are no validated stains to use on renal biopsies for immunohistochemical documentation that immune complexes found in glomeruli are Lyme-specific, so Lyme nephritis is diagnosed presumptively in seropositive dogs with PLN. Clinical signs can be occult (proteinuria), or dramatic, e.g., thromboembolic events causing neurologic deficits, hind limb paresis/paralysis, or respiratory distress (see ch. 243 and 256); hypertensive damage causing blindness or cerebrovascular accidents (see ch. 11 and 157); or the nephrotic syndrome, with edema or effusions, even before signs of uremia (anorexia, vomiting) are seen (see ch. 325). Polyuria/polydipsia is a late sign, signaling secondary tubular damage. Dogs with primary glomerular disease can present with azotemia without isosthenuria, e.g., with urine specific gravity of 1.020-1.030. The differential diagnosis includes leptospirosis and causes of PLN (infectious, immune-mediated, genetic, toxic, vascular, neoplastic, and amyloidosis).[1,7,68-71]

In the original description of Lyme nephritis, only 30% of affected dogs had a history of lameness.[72] Clinical manifestations of PLN can include systemic hypertension, thromboembolic events, edema, effusions, and eventually signs of uremia such as anorexia, weight loss, vomiting, and/or polyuria/polydipsia. Laboratory changes are those seen with PLN, such as proteinuria, cylindriuria, hypoalbuminemia, hypercholesterolemia, possibly anemia, and thrombocytopenia (consumptive or due to coinfection). Some dogs have an active urinary sediment, glucosuria, and isosthenuria due to tubular changes secondary to severe glomerular disease. Tubular changes, hypoalbuminemia, and/or azotemia can be seen due to

leptospirosis and Lyme seropositivity may be coincidental.[71]

Original reports of histopathologic changes in severely affected dogs showed a triad of immune-mediated glomerulonephritis (IMGN), tubular necrosis/regeneration, and interstitial nephritis,[72] but perhaps early or milder forms exist without tubular changes. Original reports included 30% of dogs with prior Lyme vaccine history, but it is unknown if vaccine was given after exposure or was non-protective, or whether Lyme vaccine antigens could cause sensitization or aggravation of immune-complex deposition. Only 30% had a history of lameness.

Diagnostic Tests for Lyme Exposure

The site of the tick bite rarely is known, and *Bb* migrates interstitially, does not circulate in blood, and is rarely found in joint tap or bodily fluids. Therefore, diagnostic tests to document exposure do not rely on cultures or PCR testing but rather on serologic testing for antibodies directed against *Bb* antigens. Older tests, such as whole-cell IFA or ELISA, showed cross-reactions with other spirochetes as well as vaccinal antigens. Western immunoblotting helps to show banding patterns that change over time due to antigenic variation shown by *Bb* in the host during the carrier state. Again, there may be cross-reactions. IgM and IgG titers are not helpful in dogs because of the long incubation time before illness (2-5 months), so that dogs are unlikely to present ill during IgM+/IgG− status. Antigenic variation can induce new IgM peaks during the carrier phase, so IgM+/IgG+ status does not necessarily prove recent exposure.

The SNAP-4DxPlus (IDEXX) cage-side test gives a qualitative result for heartworm antigen, and antibodies against *Ehrlichia canis, E. chaffeensis, E. ewingii, Anaplasma phagocytophilum, A. platys,* and against the Lyme C6 peptide antigen. This antigen is a recombinant replica of the constant region of an antigen (VlsE) that is only expressed by *Bb* when it is in the host, and is not found in the tick, in *Bb* cultivation *in vitro,* nor in any Lyme vaccines. Thus, C6 peptide antibodies are specific for natural exposure. Since the SNAP-4DxPlus test uses no species-specific reagents, the test can be used off-label on cats for identification of exposure antibodies to *Bb* as well as *Anaplasma* spp.

The Lyme C6Quant test (IDEXX) gives a quantitative result. The magnitude of any Lyme titer does not predict illness and is not cause for initiation of treatment in nonclinical, nonproteinuric dogs. In treated dogs, the qualitative SNAP-4DxPlus test is very sensitive and is likely to remain positive for years, even with a low C6Quant level. The C6Quant level has been shown to wane after treatment[73] so that a post-treatment baseline test (3-6 months after treatment) can be useful for future comparisons. If signs of illness suggest Lyme disease recurrence or reinfection, but the C6Quant level is not much higher than the post-treatment baseline, the signs are probably not attributable to Lyme disease and retreatment is not indicated.

The AccuPlex4 (Antech) test gives a qualitative result for heartworm antigen, antibodies to *Ehrlichia canis, Anaplasma phagocytophilum* and 5 Lyme antigens. An algorithm is used for interpreting the magnitude and relationship of antibodies to (1) OspA (p31, the antigen found in all Lyme vaccines but sometimes also expressed in the host and found in non-vaccinated people with chronic non-antibiotic-responsive Lyme disease which could be an immune-mediated disease[74-76]); (2) OspC (which rise 2-3 weeks after natural exposure and decline 3-5 months later if the dog is not reexposed; new bacterin vaccines might induce OspC antibodies); (3) OspF (which rise 6-8 weeks after exposure and persist long-term, possibly despite treatment); (4) p39 (antibodies seen in 88% of naturally exposed animals vs. 47% of vaccinates[77]); and (5) SLP (proprietary). According to Antech Laboratories and studies done at Colorado State University, the AccuPlex4 test may detect antibodies 1 week earlier for Lyme and *Anaplasma* when compared to the SNAP-4Dx test.[78] However, a recent study comparing the tests found the AccuPlex4 was not as repeatable and was less specific and less sensitive than the SNAP-4DxPlus test for Lyme and *Anaplasma* antibody testing.[79] Other tests include the Multiplex (Cornell University Animal Health Diagnostic Center) test, which gives quantitative results for titers against OspA, OspC, and OspF; and the VetScan Canine Lyme Rapid qualitative bedside test (Abaxis) which tests for antibodies against VlsE, OspC, and flagellin (which might cross-react with other bacterial flagellins).

Differentiation of vaccinal from natural-exposure antibodies and early from late infection might not be as straightforward as previously thought. OspA antibodies (seen mostly in vaccinates, protective titer unknown) and OspC antibodies (seen mostly in non-vaccinates) can appear in either vaccinates or non-vaccinates. OspC and OspF antibodies might give a clue regarding when a dog was *last* exposed to these Lyme antigens, but not when it was *first* exposed. Whether an infection (exposure) is early or late might not be clinically useful information in the dog.

Whenever a dog shows evidence of natural exposure, whether it is healthy or sick, at least three important

repercussions are apparent: (1) the dog should be screened for renal proteinuria, so that early intervention for possible early Lyme nephritis can be initiated if indicated; (2) the dog has been exposed to ticks and wildlife, so further testing for exposure or signs of coinfections (anaplasmosis, babesiosis, bartonellosis, ehrlichiosis, Rocky Mountain spotted fever, leptospirosis, other *Borrelia* spp., etc.) might be indicated; and (3) the dog needs better tick control. Seropositive dogs are sentinels, indicating that the owners live in an area where ticks are carrying Lyme disease. Owners are grateful when their veterinarians educate them about tick-borne diseases, tick control, landscaping, and public health issues. For instance, veterinarians can warn people not to wait for the rash or illness before calling their physician when they find an engorged tick on themselves, because for people living in a Lyme endemic area, taking 1 day's dose of doxycycline within 72 hours of removal of an engorged *Ixodes* tick has been helpful in preventing Lyme disease.[80]

Treatment of Lyme Arthritis and Lyme Nephritis (Table 211-1)

Treatment of Nonclinical, Nonproteinuric Dogs

There is debate about whether to treat nonclinical nonproteinuric dogs that have positive Lyme titers.[8,9] The magnitude of Lyme titers is neither predictive of, nor even associated with, illness, and this author does not advocate treatment for all of these dogs. All seropositive dogs should be screened and monitored several times a year for proteinuria (the necessary frequency and duration are unknown). Treatment has not been shown to prevent future illness.

TABLE 211-1

Recommendations for Dogs with Natural-Exposure Lyme Antibodies

	NONCLINICAL	PROTEINURIC	OLIGO- OR POLYARTHRITIS, FEVER
Diagnostic Testing	Screen for proteinuria*	Localize proteinuria (renal?); IRIS staging Rule out other causes of PLN (CBC; serum biochemistry profile; BPM; urinalysis; urine culture; UPC; C6Q; chest radiographs; abdominal ultrasound; possible renal biopsy) (see text)	Screen for proteinuria* Joint tap for cytology and cultures CBC, serum biochemistry profile, radiographs C6Q Consider other causes of lameness/fever (see text)
Consider Coinfections: Lyme+ status may be coincidental and just a marker for tick and wildlife exposure	Consider screening for stealth pathogens: • Anaplasmosis/ehrlichiosis • Babesiosis • Bartonellosis • Heartworm	Screening for infectious diseases: • Anaplasmosis/ehrlichiosis† • Babesiosis • Bartonellosis • Heartworm • RMSF† • Leptospirosis† • Consider possible fungal diseases, brucellosis, hepatozoonosis, leishmaniasis, other infections	Consider screening for infectious diseases: • Anaplasmosis/ehrlichiosis† • Babesiosis • Bartonellosis • Heartworm • RMSF† • Leptospirosis (myositis)† • Brucellosis, fungal, other infections
Treatment and Monitoring	Tick control (see text) Antimicrobial treatment has not been shown to prevent future illness and is controversial. Lyme titer magnitude has not been associated with future illness. If antimicrobials are used, do C6Q at 0 and 3-6 months later for a new baseline for	Tick control (see text). Treat with antibiotics (unknown protocol, possibly 3-6 months) and standard PLN treatments: renal diet, ACEi/RAASi, omega 3-fatty acids, antithrombotics, antihypertensives, phosphate binders, antiemetics/protectants, consider using immunosuppressives, colloids, etc. Check C6Q at 0 and 3-6 months later for a new baseline for future comparisons.	Tick control (see text). Treat with antibiotics (1 month). If non-responsive after 1-2 days, consider another cause for the clinical signs. Avoid NSAIDs in case steroids are needed to be added for suspected IMPA. Check C6Q at 0 and 3-6 months later for a new

	future comparisons.		baseline for future comparisons.

*Check for proteinuria 3-4 times the first year and twice yearly thereafter.

†May need acute and convalescent testing.

ACEi, Angiotensin converting enzyme inhibitor; *BPM*, blood pressure measurement; *CBC*, complete blood count; *C6Q*, Lyme C6Quant test (IDEXX); *FA*, fatty acids; *ICGN*, immune-complex glomerulonephritis; *IMPA*, immune-mediated polyarthropathy; *IRIS*, International Renal Interest Society (www.iris-kidney.com); *NSAIDS*, nonsteroidal anti-inflammatory drugs; *PLN*, protein-losing nephropathy; *RAASi*, renin-angiotensin-aldosterone system inhibitors; *RMSF*, Rocky Mountain spotted fever; *UPC*, urine protein/creatinine ratio.

Treatment of Canine Lyme Arthritis

The experimental model showed Lyme arthritis to be self-limiting; therefore, the necessity for treatment is questionable. In the field, however, dogs with suspected Lyme arthritis usually are treated with doxycycline or minocycline because of common coinfections (e.g., anaplasmosis), typically for 4 weeks at 5-10 mg/kg PO q 12 h, although the best protocol is unknown. Clinical signs generally improve dramatically within 1-2 days of starting therapy, and if not, other diagnoses should be entertained, such as immune-mediated polyarthropathy, which responds to corticosteroids. Most Lyme disease cases will be cleared of the carrier state with 1 month of antibiotics. Lyme C6 Quant (IDEXX) levels are helpful for comparisons (0 and 3 to 6-month post-treatment) since a ≥50% decline commonly is seen if the level was >100 originally and if proper tick control is used for preventing reexposure. The 6-month post-treatment level may then be used as a new baseline, and it is helpful for comparisons should the dog show new signs of possible Lyme disease in the future, to indicate whether reinfection/relapse warrants retreatment or not. Qualitative Lyme tests are likely to remain positive for years, even after treatment, and therefore, they are not an indication of carrier status or need for retreatment. It is unknown whether OspF antibodies wane after treatment, but whole cell IFA or ELISA antibodies do not wane as markedly as C6 peptide antibodies do after treatment.[48,73] The antibodies could be due to immune memory and not necessarily due to ongoing carrier status.

Treatment of Canine Lyme Nephritis

Without an experimental model for Lyme nephritis, the best protocol for treatment is speculative. The duration of antimicrobial treatment usually is prolonged (for 3-6 months or until the Lyme C6Quant [IDEXX] level has waned) because in 10-15% of dogs, the organism might not be cleared with only 1 month's treatment. Standard treatment for PLN[81] (see ch. 325) is indicated, e.g., angiotensin-converting enzyme inhibitors, other inhibitors of the renin-angiotensin-aldosterone system (RAAS) if necessary, modified low protein diet, omega-3 fatty acid supplementation, antithrombotics, antihypertensives, and treatment for chronic kidney disease as needed (see ch. 324) (e.g., phosphate binders, antiemetics, gastric protectants, appetite stimulants, crystalloids/colloids, etc.). Monitoring of proteinuria is recommended every 1-2 weeks when dogs are showing moderate clinical signs, or less frequently in stable patients. Monitoring is based on averaged urine protein/creatinine ratio (UPC) results on a mixture of equal aliquots of 3 daily samples; hematocrit; serum albumin, globulin, creatinine, BUN, phosphorus, calcium, Na, and K; and blood pressure measurement. These results are used for adapting the management protocol as needed. The prognosis is guarded for dogs that are already azotemic, vomiting, and anorexic. Dogs identified earlier, before they present with signs of uremia, can respond to standard treatments for PLN.

Since Lyme nephritis is associated with immune-mediated glomerulonephritis (IMGN), immunosuppressive therapy could be warranted.[70,82,83] Ruling out differential diagnoses and documentation of IMGN by renal biopsy are recommended before immunosuppressive treatment is initiated, if possible.[69] Renal biopsies should be sent to the International Veterinary Renal Pathology Service for examination by thin section light microscopy, special stains, immunofluorescence, and transmission electron microscopy; however, there are no validated stains to prove if any immune complexes are Lyme-specific. If clinical signs of disease are rapidly progressive, immunosuppressive therapy could be warranted even without biopsy confirmation of IMGN.[70] The best protocol is unknown. Mycophenolate is chosen often, but it can cause gastrointestinal side-effects. Other protocols include pulse corticosteroids (2 days), cyclophosphamide every 2 weeks, chlorambucil, azathioprine, or cyclosporine (see ch. 165).

Prevention of Lyme Disease in Dogs

Tick Control

Since there are many tick-borne diseases besides Lyme disease in Lyme-endemic areas, tick control is warranted whether or not Lyme vaccines are used. Tick control/prevention entails landscaping, avoiding tick habitats, tick removal (Video 211-1) and the use of tick control products. Although Lyme transmission does not generally occur until 2-4 days of tick attachment, products which only kill ticks after 24 hours of attachment (e.g., fipronil) are not preferred because other tick-borne agents can be transmitted faster. Therefore, products that prevent tick attachment or that kill ticks soon after attachment are advocated. Examples are topical products that contain permethrin (e.g., K9 Advantix II [Bayer], monthly), pyrethroid collars (e.g., Seresto [Bayer], works for 8 months), amitraz collars (e.g., Preventic [Virbac], works for 3 months), or the new oral (chewable) isoxazoline compounds that inhibit the arthropod-specific GABA-gated chloride channels and kill ticks early after feeding is started, e.g., NexGard (Merial, monthly), Bravecto (Merck, works for 3 months against *Ixodes, Rhipicephalus* and *Dermacentor* ticks and 2 months against *Amblyomma* ticks), or Simparica (sarolaner, Zoetis).

Lyme Vaccines

Several bacterins, a recombinant non-adjuvanted OspA subunit vaccine, and a new chimeric recombinant vaccine (crLyme, Zoetis, which includes OspC material from 7 strains of *Bb*) are available.[10] All of these vaccines induce production of OspA antibodies, to reduce the number of live *Bb* within the tick as it feeds. Currently, all available bacterins also claim induction of OspC antibodies as well as other antibodies that can kill any *Bb* organisms that are transmitted to the host. Lyme vaccines are still controversial because (1) excellent tick control products are available and are needed anyway to prevent other tick-borne diseases in Lyme-endemic areas; (2) Lyme arthritis only occurs in <5% of dogs exposed to *Bb;* (3) Lyme arthritis is self-limiting or easily treatable with antibiotics; (4) Lyme vaccines are less effective, with shorter duration of immunity and more post-vaccinal events, than vaccines for other diseases[1,56,84-88a]; (5) vaccination can give a false sense of security; (6) Lyme vaccines have not been shown to prevent Lyme nephritis; (7) Lyme vaccines can interfere with the interpretation of some diagnostic test results; and (8) the most serious forms of Lyme disease are rare but probably immune-mediated, and it is unknown if Lyme vaccinal antigens could sensitize or aggravate illness in genetically predisposed individuals.[10] In animal models and genetically predisposed people, OspA is inflammatory, sensitizing, and induces a marked T_H1 response; high anti-OspA antibody levels are associated with chronic non-responsive post-Lyme immune-mediated disease; and Lyme antigens including OspA were found in immune-complex deposits in dogs with suspected Lyme nephritis.[7,22,67,89-96]

Future vaccination development could take advantage of other paradigms, e.g., the tick salivary protein, Salp-15, which binds to *Bb* and facilitates early infection in the host.[97-99]

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CHAPTER 212

Mycobacterial Infections, Actinomycosis and Nocardiosis

Joanna Whitney, Carolyn R. O'Brien

Client Information Sheet: Mycobacterial Infections in Dogs and Cats

Mycobacterial Infections

The genus *Mycobacterium* is a member of the order Actinomycetales. Mycobacteria are mostly intracellular, aerobic, acid-fast, non-spore-forming, environmentally resistant bacilli. They are usually saprophytic and non-pathogenic; however, several species are considered primary or opportunistic pathogens. Mycobacterial infections are being more commonly diagnosed in companion animals due to improved diagnostic techniques, use of immunosuppressive medications, and their zoonotic potential. It is likely that the prevalence of mycobacteriosis in dogs and cats is underestimated since there is a low index of suspicion, it causes non-specific signs, and it can be difficult to confirm an antemortem diagnosis.[1]

Mycobacteria are classified on their clinical presentation in human patients (tuberculoid, non-tuberculoid, leproid) or their physical and biochemical properties. In companion animals, mycobacteriosis is generally divided into tuberculous, saprophytic (rapid- and slow-growing) and lepromatous disease. However, there is much overlap within small animal patients. Many different organisms produce similar clinical signs and categorization of such organisms is not consistent.

Tuberculous Mycobacteriosis

Overview

Tuberculosis is an infection caused by members of the *Mycobacterium tuberculosis* (MTB) complex, which are obligate pathogens. Feline tuberculosis has been reported to be caused by infection with *M. bovis, M. microti* and rarely *M. tuberculosis.*[1-12] Canine tuberculosis is less common and associated with *M. tuberculosis* or *M. bovis.*[2,13-29] A dog with *M. microti* tuberculosis has been reported.[12]

Epidemiology and Pathogenesis

Reservoirs

The primary reservoir of *M. bovis* is domestic cattle; however, rats, feral pigs, wild deer, badgers and brush-tailed possums are proposed vectors of infection.[3,30,31] Both cats and dogs are considered to be "spill-over" hosts in the epidemiology of *M. bovis.* Cats appear more susceptible than dogs to infection.[2,32] Humans are the reservoir host of *M. tuberculosis* and infection of cats and dogs is considered a result of close contact with affected humans.[19,29,33-35] High levels of transmission to dogs living in high-risk environments have been demonstrated, although the incidence was low.[25] High levels of subclinical infection have been demonstrated in dogs experimentally infected with *M tuberculosis.*[36] The field vole has been identified as the maintenance host of *M. microti* in Great Britain. Infection with this organism has been reported in people, alpacas, llamas, badgers, pigs, cattle, horses, ferrets and, most commonly, cats.[10,37,38]

Cats and Dogs

Feline tuberculosis, in mutually exclusive clusters based on mycobacterial species, is usually identified in

endemic areas.[2,3,5] Canine tuberculosis is considered rare, particularly in areas in which rates of human and cattle infection are low.[15] Adult non-pedigree cats with outdoor access are most commonly infected with members of the *Mycobacterium tuberculosis* complex, although Siamese cats may be overrepresented in *M. microti* infections. Cats with *M. microti* infection are commonly older males, in contrast to those from which *M. bovis* is isolated.[5] Hunting and catching rodents has been shown to be a risk factor for *M. microti* infection in cats, and immunosuppression may result in reactivation of latent infections.[5,9,29,39] Feline immunodeficiency virus (FIV) infection was proposed as a cause of rapid disease progression (see ch. 222). However, only 2/339 cats with mycobacteriosis were FIV-positive.[5,6] The host immune response and duration of infection are believed responsible for lesion morphology, rather than the specific agent.[40] Tuberculoid lesions develop due to the aggregation of macrophages at sites of infection. This response may determine whether the infection becomes dormant or remains active. Pro-inflammatory mediators released by the macrophages may result in systemic signs of infection.[41]

Route of Infection

Route of infection appears responsible for the initial manifestations of disease and for location of the primary lesion(s). Thus, the disease tends to begin in the skin, gastrointestinal (GI) or respiratory tracts. However, due to the chronicity of infection and the potential for hematogenous dissemination, the primary site may not be identifiable at time of diagnosis. The presence of peripheral lesions and a history of bites from wildlife in cats (and on occasion, dogs) suggest that most infections develop following inoculation of organisms via bite wounds.[7,20,42] A recent case series has highlighted the risk of nosocomial spread of *M. bovis* in cats.[43]

History and Clinical Signs

The most common manifestation of tuberculosis in cats is development of subcutaneous (SC) masses, often with draining tracts and regional lymphadenopathy.[5-7,9,13,42] Cats may have non-specific systemic signs of lethargy, anorexia, weight loss or respiratory distress, in addition to cutaneous lesions.[5-7] The clinical signs of tuberculosis in dogs are nonspecific or reflect the site of infection. Common historical findings include lethargy, anorexia, weight loss, coughing, dyspnea, vomiting and diarrhea.[12,14,15,20,22,28,29,44-46] Less common signs include neurological dysfunction, cutaneous lesions, epistaxis and lameness.[12,14,20,28,29,47] Dogs are frequently pyrexic and in poor body condition at the time of presentation.[12,15,22,28,44]

Diagnosis

Clinical pathology and diagnostic imaging findings are generally non-specific in cases of tuberculosis, although they may reflect the location of infection or severity of disease.[48] Differentiation between individual agents of tuberculosis or differentiating between tuberculous and other mycobacterial infections cannot be based on clinical findings alone.[5] Initial diagnosis of tuberculosis is based on clinical suspicion, geographical location and identification of acid-fast bacilli (AFB) within tissue samples evaluated histologically. Traditionally, confirmation required culture of the organism. Culture may take 4-6 weeks and requires specialized media.[49] A subset of cats has been identified that are negative for AFB on initial laboratory evaluation but from which mycobacteria, particularly *M. bovis* and *M. microti,* can be cultured.[5,50]

Intradermal (ID) tuberculin and *M. bovis* antibody testing in cats and ID testing in dogs are not helpful.[51] Several immunodiagnostic assays for the antemortem diagnosis of *M. bovis* have been evaluated and shown excellent potential.[49,52-54] DNA amplification has been demonstrated to be a rapid and accurate means of identifying members of the *M. tuberculosis* complex.[11,36] Molecular methods are being reported to help identify causative agents in tuberculosis, particularly in dogs.[9,12,15,22,28,47,55]

Treatment and Prognosis

The zoonotic potential of tuberculosis must be explained to owners before treatment begins. Not only are there zoonotic risks, but cats with tuberculosis have a guarded prognosis. Although many respond well to a variety of antimicrobials, inappropriate drug selection and duration of treatment often results in disease recurrence and systemic spread.[50] Successful treatment involves surgical excision or debridement of cutaneous lesions and long-term antimicrobial therapy. Cats should initially be treated for two months with a

combination of rifampicin, a fluoroquinolone (preferably pradofloxacin or moxifloxacin) and clarithromycin or azithromycin, followed by an additional 4-6 months of rifampicin and either the fluoroquinolone or macrolide (E-Table 212-1).[56] Dogs with systemic disease have a grave prognosis. Most have been euthanized due to progression of infection and/or adverse effects of therapy.[12,15,44,45,55] Successful treatment using triple antibiotic therapy has been reported in a dog with acute peritonitis.[22]

E-TABLE 212-1

Antimicrobial Therapy in Dogs and Cats

		CANINE	FELINE	POTENTIAL SIDE EFFECTS
Tuberculous *Mycobacteria*		**Rifampicin** (10-15 mg/kg, max 600 mg/day, PO q 24 h)	**Rifampicin** (10-15 mg/kg PO q 24 h)	**Hepatotoxicosis,** GIT upset, pruritus (cats)
		Enrofloxacin (5 mg/kg IV/IM/SC/PO q 24 h)	**Fluroquinolone** • Marbofloxacin (2.75-5.5 mg/kg PO q 24 h) • Moxifloxacin (10 mg/kg PO q 24 h) • Pradofloxacin (3 mg/kg PO q 24 h)	GIT upset, cartilage abnormalities (young animals)
		Macrolide • Clarithromycin (5-15 mg/kg PO q 12 h) • Azithromycin (5-15 mg/kg PO q 24 h)	**Macrolide/Lincosamide** • Clindamycin (125 mg/cat PO q 12 h) • Azithromycin (5-15 mg/kg PO q 24 h)	GIT upset, esophagitis (cats) GIT upset
		Pyrazinamide (15-40 mg/kg PO q 24 h)	*Pyrazinamide (15-40 mg/kg PO q 24 h)* *Isoniazid (10-20 mg/kg PO q 24 h)*	**Hepatotoxicosis,** GIT upset **Hepatotoxicosis, neurotoxicosis,** thrombocytopenia
Saprophytic *Mycobacteria*	**Rapid growing***	**Enrofloxacin** (5 mg/kg IV/IM/SC/PO q 24 h)	**Fluroquinolone** • Pradofloxacin (3 mg/kg PO q 24 h) • Moxifloxacin (10 mg/kg PO q 24 h) • Marbofloxacin (2.75-5.5 mg/kg PO q 24 h)	GIT upset, cartilage abnormalities (young animals)
		Rifampicin (10-15 mg/kg, max 600 mg/day, PO q 24 h)		**Hepatotoxicosis,** GIT upset GIT upset, erythema (cats) GIT upset, hepatopathy (dogs), esophagitis (cats) Nephrotoxicosis, ototoxicosis, neuromuscular blockade Nephrotoxicosis, ototoxicosis, neuromuscular blockade
		Clarithromycin (5-15 mg/kg PO q 12 h)	**Clarithromycin** (62.5 mg/cat PO q 12 h)†	
		Doxycycline (5-10 mg/kg PO q 12-24 h)	Doxycycline (5-10 mg/kg PO q 12-24 h)	
		Amikacin (10-15 mg/kg IV/IM/SC q 24 h)	Amikacin (peri-op) (10-15 mg/kg IV/IM/SC q 24 h)	
			Gentamicin (peri-op) (5-8 mg/kg IV/IM/SC q 24 h)	
		Cefotaxime (25-50 mg/kg IV/IM/SC q 6 h)	Cefotaxime (22 mg/kg IV/IM/SC q 6-8 h)	
	Slow growing	**Clarithromycin** (5-15 mg/kg PO q 12 h)	**Clarithromycin** (62.5 mg/cat PO q 12 h)	GIT upset, erythema (cats) Skin/eye discoloration, photosensatization (cats)
		Clofazamine (4-12 mg/kg PO	Clofazamine (4-8 mg/kg,	

	q 24 h)	max 25 mg/day PO q 24 h)	**Hepatotoxicosis,** GIT upset GIT upset, hepatopathy (dogs), esophagitis (cats) GIT upset, cartilage abnormalities (young animals)
	Rifampicin (10-15 mg/kg, max 600 mg/day, PO q 24 h)	Rifampicin (10-15 mg/kg PO q 24 h)	
	Doxycycline (5-10 mg/kg PO q 12-24 h)	Doxycycline (5-10 mg/kg PO q 12-24 h)	
		Moxifloxacin (10 mg/kg PO q 24 h)	
Leproid *Mycobacteria*	**Rifampicin** (10-15 mg/kg, max 600 mg/day, PO q 24 h)	**Rifampicin** (10-15 mg/kg PO q 24 h)	**Hepatotoxicosis,** GIT upset GIT upset, erythema (cats) Skin/eye discoloration, photosensitization (cats) GIT upset, hepatopathy (dogs), esophagitis (cats)
	Clarithromycin (5-15 mg/kg PO q 12 h)	**Clarithromycin** (62.5 mg/cat PO q 12 h)	
	Clofazamine (4-12 mg/kg PO q 24 h)	Clofazamine (4-8 mg/kg, max 25 mg/day PO q 24 h)	
	Doxycycline (5-10 mg/kg PO q 12-24 h)	Doxycycline (5-10 mg/kg PO q 12-24 h)	
		Fluroquinolone	GIT upset, cartilage abnormalities (young animals)
		• Marbofloxacin (2.75-5.5 mg/kg PO q 24 h) • Moxifloxacin (10 mg/kg PO q 24 h)	
		Amikacin (10-15 mg/kg IV/IM/SC q 24 h)	Nephrotoxicosis, ototoxicosis, neuromuscular blockade
Actinomyces **spp.**	**Penicillins** • Ampicillin (10-20 mg/kg IV/IM/SC q 6-8 h) • Amoxicillin (10-30 mg/kg IM/SC/PO q 12 h)	**Penicillins** • Ampicillin (10-20 mg/kg IV/IM/SC q 6-8 h) • Amoxicillin (10-30 mg/kg IM/SC/PO q 12 h)	Gatrointestinal upset
	Macrolides/Lincosamides	Macrolides/Lincosamides	
	• Clindamycin (5 mg/kg IV/IM/SC/PO q 12 h) • Erythromycin (10 mg/kg PO q 8 h) Chloramphenicol (50 mg/kg IV/IM/SC/PO q 8 h)	• Clindamycin (5 mg/kg IV/IM/SC/PO q 12 h) • Erythromycin (10 mg/kg PO q 8 h) Chloramphenicol (50 mg/cat IV/IM/SC/PO q 12 h)	GIT upset, esophagitis (cats) GIT upset **Bone marrow suppression,** GIT upset
Nocardia **spp.**	**Sulphonamides** • Trimethoprim-sulphonamide (30 mg/kg PO q 12 h)	**Sulphonamides** • Trimethoprim-sulphonamide (30 mg/kg PO q 12 h)	**Bone marrow suppression, acute hepatitis** (dogs), KCS (dogs), GIT upset Nephrotoxicosis, ototoxicosis, neuromuscular blockade GIT upset, neurotoxicosis, infusion reactions
	Amikacin (10-15 mg/kg IV/IM/SC q 24 h)	Amikacin (10-15 mg/kg IV/IM/SC q 24 h)	
	Imipenem-cilastatin (2-5 mg/kg slow IV q 8 h)	Imipenem-cilastatin (2-5 mg/kg slow IV q 8 h)	
	Cefotaxime (25-50 mg/kg IV/IM/SC q 6 h)	Cefotaxime (22 mg/kg IV/IM/SC q 6 h)	

*Treatment should be based on susceptibility testing.

†Not effective against *M. smegmatis.*

Medications in **bold** are recommended as first-line therapy.
Side effects in **bold** are major or severe.
Medications in *italics* should only be used as a last resort.
GIT, Gastrointestinal tract.

Public Health Considerations

There are, uncommonly, reports of tuberculosis transmission from pets to owners. The zoonotic potential of infected animals is of increasing concern, particularly for immunocompromised owners.[57] Tuberculosis is a notifiable disease in many countries. Public health authorities should be informed of any positive diagnosis in dogs or cats where required. Care should be taken in patient and specimen handling in veterinary hospitals when tuberculosis is a differential diagnosis. Infection of veterinary personnel with *M. tuberculosis* was reported following aerosolization of the organism during necropsy of an infected dog.[29]

Saprophytic Mycobacteriosis

Etiology

Saprophytic mycobacterioses are bacteria found in terrestrial and aquatic environments. Infections caused by these *Mycobacteria* spp. are divided conceptually into rapid-growing mycobacteria (RGM) and slow-growing mycobacteria (SGM; Table 212-2). The *Mycobacterium avium* complex (MAC) are SGM comprised of *M. avium* and *M. intracellulare*. *M. avium* is divided into 4 subspecies. *M. avium* subsp. *paratuberculosis* is the only known obligate pathogen in this group of organisms. Saprophytic mycobacteria are reported as agents of disease more commonly in cats than in dogs.[58-132]

TABLE 212-2

Mycobacterial spp. in Dogs and Cats

		CANINE	FELINE
Tuberculous		***M. bovis***DCP ***M. tuberculosis***DCP *M. microti*D	***M. bovis***CD ***M. microti***CDL *M. tuberculosis*CD
Saprophytic	**Rapid growing**	*M. fortuitum*LC *M. goodii*CP *M. smegmatis*CP *M. chelonae–abscessus*L	***M. fortuitum***PCL ***M. smegmatis***PD *M. chelonae–abscessus*PC *M. alvei*P *M. goodii*D *M. thermoresistibile*PL *M. phlei*P *M. massiliense*C *M. mucogenicum*C
	Slow growing	***M. avium* complex**D *M. ulcerans*C *M. kansasii*DL	***M. avium* complex**CDL *M. ulcerans*C *M. terrae*C *M. xenopi*PD *M. simiae*D *M. celatum*D *M. malomense*C *M. heckeshornense*D *M. genavense*D

Leproid		**Unclassified species**[C]	***M. lepraemurium***[C] *M. visibile*[PCD] Unclassified species[C]

C, Cutaneous lesions; *D*, disseminated disease; *L*, pulmonary disease; *P*, panniculitis.
Common agents in bold.

Epidemiology and Pathogenesis

Slow Growing

The slow growing saprophytic mycobacteria, particularly *M. avium*, cause local and systemic granulomatous disease resulting in syndromes indistinguishable from tuberculosis.[60-62,64,66,68-70,73,74,76,78,80,83,85,86,94-96,98,104,105,107-109,112-114,117,120,123,125-129,132] Unlike other SGM, *M. ulcerans* produces mycolactone, a macrolide toxin believed to be the cause of the distinct lesions associated with infection with this species.[133] *M. avium* is the most common SGM implicated in dog and cat systemic infections (see Table 212-2) although the pathogenicity of the individual subspecies is yet to be fully elucidated. *M. avium* subsp. *paratuberculosis* has been identified in humans with Crohn's disease and from the GI tract of dogs with chronic enteropathies, but its significance is unclear.[134,135] The SGM cause opportunistic infections usually in young and immunosuppressed animals.[61,66,67,71,72,74,75,78,83,85,87,91,94,96,105,107,109,114,118,124,127,129] Breed predispositions have been reported in cats and dogs, suggesting hereditary immune dysfunction in some. Siamese, Somali and Abyssinian cats, Miniature Schnauzers and Basset Hounds are overrepresented in reports of MAC infections.[61,80,98,104,105,107,109,112,123,129,130]

Rapid Growing

The rapidly growing mycobacteria (RGM), in cats, cause diffuse, rather than nodular, SC, or cutaneous infections. Infection is less common in dogs, presumably following inoculation during fighting or trauma.[60,63,77,79,89,90,97,106,122,136] Affected animals are often obese and apparently immunocompetent.[77,89] Female cats are over-represented.[77,89] Sporadic cases of pulmonary and systemic infections with *M. fortuitum*, *M. thermoresistibile* and *M. smegmatis* have been reported.[65,72,115,119,131]

History and Clinical Signs

Pulmonary, GI or disseminated disease associated with SGM infection is indistinguishable from tuberculosis. Typical presenting signs include chronic weight loss, inappetence, vomiting, diarrhea and/or dyspnea.[61,66,83,91,94,96,105,109,114,117] Physical examination often reveals peripheral lymphadenopathy and pyrexia.[61,86,94,105,107,114,117,118,129] The RGM have a predilection for adipose tissue and most commonly cause panniculitis of the ventral abdomen and inguinal areas of cats. The tissue is often firm due to thickening and ulceration of the overlying skin. One or more draining tracts may be seen. Although respiratory infection and systemic spread are rare, infected cats may be pyrexic, inappetent and lethargic.

Diagnosis

Diagnosis of saprophytic mycobacteriosis is usually based on clinical presentation, cytological or histopathological findings and mycobacterial culture or molecular testing. As with tuberculous infections, systemic SGM infections produce non-specific results on routine hematology, serum biochemistry and diagnostic imaging, consistent with disseminated infiltrative disease of the organs affected. Acid-fast staining of tissue obtained from animals infected with *M. avium* and other SGM often reveal greater numbers of organisms than tuberculous infections. However, these are quite slow-growing in culture and molecular methods are often recommended for further characterization. Cytological examination of lesions from RGM infections often reveals granulomatous inflammation in which organisms may not be visible. RGM can often be grown readily on routine culture medium, although different species have specific culture requirements and molecular diagnostics may be required for definitive diagnosis.

Treatment and Prognosis

The SGM, particularly *M. avium,* have greater innate resistance and variable antimicrobial susceptibilities. Sensitivity testing should be performed where possible. Long-term combination therapy has been recommended but appears to be more successful in cats than dogs.[60,61] The prognosis of disseminated MAC in cats is guarded because even some cats who respond to initial therapy have recurrences. Dogs with systemic disease have a grave prognosis with many euthanized soon after diagnosis.

Treatment of granulomatous panniculitis is most successful with preoperative and perioperative antimicrobials (gentamicin), radical surgical debulking and long-term, single or combination, postoperative antimicrobial therapy based on susceptibility testing (see E-Table 212-1).[88,122] Prognosis is geographically variable with some organisms having high reported rates of disease recurrence.[77]

Public Health Considerations

As saprophytic organisms, these mycobacteria may infect immunocompromised humans in the same environmental manner as animal infections. Saprophytic mycobacteriosis has been rarely reported in humans associated with dog bites or cat-scratch wounds.[137-140]

Leproid Syndromes

Background

Leproid syndromes have been described in both cats and dogs.[141-172] These are characterized by discrete cutaneous lesions. Their causative agents cannot be cultured readily on standard mycobacterial media. Molecular diagnostic techniques have allowed further elucidation of the identity of these organisms.

Etiology

Cats

Feline leprosy results from one of a number of mycobacterial species considered saprophytic organisms that cause opportunistic infections. Gene sequencing of tissue samples has implicated *M. lepraemurium* in about half of cases.[142,148,151] *M. intracellulare, M. mucogenicum* and unclassified mycobacterial species have also been isolated from similar lesions.[144,148,173]

Dogs

It has not been determined whether "canine leproid granuloma syndrome" results from infection with a single or multiple agents. To date, genetically identical organisms have been isolated from canine leproid granulomas. However, the species remains mostly uncharacterized due to laboratory culture failures.[161,164,165] This novel species is possibly an opportunist saprophyte that naturally exists in environment.[166]

Epidemiology and Pathogenesis

Cats

Cases of feline leprosy have been reported in Australia, the Pacific coast of Canada, the United Kingdom, the Netherlands, France, Italy, USA, Japan, Greece and New Zealand.[8,141,142,144-152,154-156,158,174] *M. lepraemurium* infection is believed to be transmitted by contact with or bites from rodents. This is supported by evidence of at least some affected animals hunting and eating rats.[145,150] While insect vector transmission has been suggested, there is limited evidence. A higher incidence of feline leprosy has been reported during the colder months in some countries. While this may indicate preference by at least one of the causative organisms for cooler temperatures, other factors (animals spending more time inside allowing for closer observation) cannot be excluded.[152,158] A biphasic age distribution has been described in cats with feline leprosy. The first group comprises young, apparently immune-competent male cats infected with *M. lepraemurium.* The second group comprises older cats with the lepromatous form of disease. It has been suggested that cats in this second group have impaired immune function secondary to chronic FIV infection or concurrent disease.[151] Immunity to *M. lepraemurium* following recovery from infection has been demonstrated experimentally in cats.[157]

Dogs

Canine leproid granuloma was originally reported in dogs from Zimbabwe.[169,170] It is now considered to be a relatively common mycobacterial dermatopathy in Australia and Brazil.[161,163,165-168,171,175] The condition is far less frequent in the United States and New Zealand, and a single case has been reported in Italy.[162,164,171,172] Similarities in the climates of Brazil, Australia and the west coast of the United States support the hypothesis that climate may play an epidemiological role. Canine leproid granulomas are most commonly diagnosed during warmer months in Brazil.[161,164]

Transmission by insect vectors has been implied by the anatomical location of lesions, the conformation of commonly affected breeds, and their common living environments.[166] Although flies and mosquitoes have been reported to be present in the environment of most affected dogs, some contradictory evidence also exists.[161,169,171] Canine leproid granuloma syndrome has been repeatedly shown to have a predilection for large-breed short-haired dogs, with Boxer dogs, in particular, being overrepresented.[161,164,166,167,169-171]

In one case series, affected dogs ranged from 1-11 years of age, with a median of 7 years.[161] It has been suggested that commonly affected types of dogs may have a genetic predisposition and similar coat characteristics or outdoor housing that facilitates insect bites. Case clusters of disease have been identified in related Foxhounds housed together in New Zealand. It has been proposed that this phenomenon may be due to environmental factors associated with hunting, a genetic predisposition, or an immune deficiency in Foxhounds. An insect vector was considered less likely. Similar clusters have been less well described in Australia and the United States.[171]

History and Clinical Signs

Cats

Leproid granulomas in cats may be single or multiple cutaneous or SC nodules with or without ulceration, anywhere on the body, but are most common on the head and limbs.[142,145,151,152,173] Two forms of the disease have been described in conjunction with the biphasic age distribution. Younger cats often develop rapidly progressive and ulcerated lesions on the limbs whereas older cats are more commonly affected by diffuse, non-ulcerated slowly progressive lesions.[151] Ocular lesions have occasionally been reported.[145,149]

Dogs

Canine leproid granulomas most commonly appear as firm, nonpainful well-circumscribed dermal-to-SC nodules on haired skin. The head and dorsolateral pinnae are most commonly affected.[161,164,166,167,171] However, papules, plaques and masses have also been described with lesions on the face and limbs.[161] Multiple lesions usually occur and may range in size from a few millimeters to several centimeters. Nodules are occasionally ulcerated with exudation usually more extensive over larger or protuberant lesions.[160]

Diagnosis

Suspicion of leproid infection may be based on physical and clinical findings. Impression smears of ulcerated lesions stained using a Kinyuon-modified Ziehl-Neelson method often reveal numerous acid-fast bacilli.[142,160] Confirmation usually requires PCR, as the organisms are fastidious and rarely able to be cultured. 16S rRNA gene,16-23S rRNA gene internal transcribed spacer region (ITS) and *hsp*65 gene sequencing have been demonstrated to facilitate rapid and accurate diagnosis of the pathogen without the need for culture.[145,147-149,151,161,162,164,165,171,172,176-178]

Treatment and Prognosis

Treatment of the leproid syndromes may not always be required, as spontaneous remission has been reported in both cats and, more commonly, dogs.[157,164,166,167] Refractory lesions should be treated with surgical resection and prolonged, dual, antimicrobial therapy.[142,151,167] Dogs usually have an excellent prognosis, although persistent lesions may become disfiguring.[171] Cats should be treated with antimicrobial therapy immediately after diagnosis, as feline leproid disease is generally progressive and may recur after surgical excision if appropriate medical therapy is not administered.[179]

Public Health Considerations

There are no reports of or suspected zoonotic potential associated with the organisms implicated in canine and feline leproid infections.

Actinomycosis

Etiology

Actinomyces spp. are facultatively anaerobic or microaerophilic, Gram-positive, irregularly staining, branching filamentous bacteria that are non-acid-fast, non-sporing and non-motile. These opportunistic pathogens are mucous membrane commensals, particularly in the oral cavity, although they may also inhabit the GI and genitourinary tracts.[180-184] *A. weissii* and *A. canis* have been implicated in canine periodontal disease, while *A. viscosus, A. hordeovulneris, A. bowdenii, A. canis, A. catuli, A. turicensis* have been isolated from lesions at other sites in dogs.[182,185-192] *A viscosus, A. meyeri* and *A. bowdenii* have been isolated from infections in cats.[191,193,194] A number of cases attributed to infection with *A. pyogenes* have been reported; however, this and a number of other *Actinomyces* spp. have been reclassified based on 16S rRNA gene sequencing and are now included in the genus *Arcanobacterium.*[195] These opportunistic pathogens produce disease following inoculation and result in actinomycosis-like manifestations.[196]

Epidemiology and Pathogenesis

The characteristic pyogranulomatous lesions of actinomycosis comprise microcolonies of bacteria and host cells surrounded by macrophages, neutrophils and plasma cells. Subacute and chronic infections result in the formation of granulation tissue, extensive fibrosis and draining tracts.[181] Exudates and effusions are often malodorous and may contain "sulfur granules," macroscopic clumps of bacteria and hyaline.[197,198] Pathogenicity of *Actinomyces* spp. is believed to be enhanced in polymicrobial infections. Synergistic infections have been recognized with facultative and anaerobic bacteria, particularly in association with dental disease. This phenomenon is likely involved in colonization at other sites.[199,200] No specific bacterial toxins that contribute to pathogenesis have been identified in *Actinomyces* spp.; however, adhesions may facilitate oral colonization.[181,201]

Actinomycosis results from introduction of the organism into body tissues. The portals of entry in dogs and cats include loss of the GI mucosal barrier integrity due to chronic gingivitis and periodontal disease, foreign body migration, inoculation via bite wounds or plant material, and aspiration of oropharyngeal material.[194,202-208] Infection typically develops in immune-competent dogs and cats, although it has been reported with concomitant immunosuppressive disease and neoplasia.[209-211]

Young male large-breed dogs kept outside are over-represented in reports of actinomycosis. Hunting and working animals are often affected, particularly with soft tissue abscesses or pyothorax.[205,212,213] There is variability in the signalment of infected cats. Young males are more likely to be infected as a result of aggressive interactions and bite wounds.[214]

History and Clinical Signs

In dogs, *Actinomyces* infections are most commonly seen as periodontal disease, and less commonly as SC or soft tissue abscesses, or pleuritis/pneumonia secondary to penetration or inhalation of contaminated plant material.[205,209,212,215-222] Central nervous system, ocular, peritoneal, cardiac and orthopedic implant infections have been reported.[190,204,216,223-228] Immune-mediated polyarthropathy has been reported in a dog secondary to actinomycosis.[190] Most infected cats develop pyothorax, probably after aspirating oral flora.[202] Other signs include nasal and facial infections, abdominal granulomas, intracranial/spinal empyema and cholecystitis.[203,207,208,210,229-233]

Diagnosis

A provisional diagnosis of actinomycosis may be based on identification of non-acid-fast filamentous organisms on cytological examination of fluid or tissue samples stained using a modified Ziehl-Neelsen (Kinyoun) method. Definitive diagnosis and differentiation from nocardiosis require isolation and

identification of the causative agent. While culture has traditionally been used, it may be time-consuming and phenotypic identification inaccurate due to the large number of novel species. Bacterial genome identification, particularly of the 16S rRNA gene, from clinical specimens is preferred.

Treatment and Prognosis

The combination of surgery and antimicrobial treatment appears to be superior to antimicrobial treatment alone in resolving most actinomycotic infections in dogs and cats.[213] However, while thoracotomy and debridement is recommended in dogs, cats are believed to require only thoracic drainage and medical therapy.[202,212] *Actinomyces* spp. are typically responsive to long-term therapy with high dosages of penicillins as well as a range of other antimicrobials (see E-Table 212-1). The prognosis for pets with SC or soft-tissue infections, and for cats with pyothorax, is good.[202,205] However, survival in dogs with thoracic disease is variable and all reported cases of CNS actinomycosis have been fatal.[203,204,232]

Public Health Considerations

Actinomyces spp. infections may develop in humans following dog and cat bites, but disease transmission from clinically infected animals to humans has not been reported.

Nocardiosis

Etiology

The genus *Nocardia* consists of Gram-positive, variably acid-fast, catalase-positive, non-motile aerobic bacteria that form filaments which may break into bacillus and coccal forms. They are saprophytic soil organisms, ubiquitous in the environment and are involved in the decomposition of plant material. Pathogenic species have been isolated from house dust, garden soil, beach sand, swimming pools and tap water in different regions.[234]

Many reports of nocardiosis in cats and dogs do not include complete or valid identification of the etiological agents and many were reported before reclassification of the actinomycetes.[235] *Nocardia* species reported to be pathogenic in dogs include *N. asteroides, N. abscessus, N. otitidiscaviarum, N. nova* and *N. brasiliensis.*[236-240] Nocardiosis has been reported in cats resulting from infection with *N. tenerifensis, N. africana, N. nova, N. cyriacigeorgica, N. farcinica, N. otitidiscaviarum* and *N. elegans.*[239,241-247]

Epidemiology and Pathogenesis

Infection in dogs and cats is believed to occur following inhalation of aerosolized organisms or inoculation via puncture wounds. The T-cell response is essential in limiting dissemination of nocardial infection following inoculation; however, this is also responsible for the development of the characteristic granulomatous-to-suppurative lesions recognized in nocardiosis.[248] In cats and dogs, nocardiosis commonly causes cutaneous lesions in immunocompetent animals, particularly cats.[213,239,241,247,249,250] Disseminated disease, often involving the central nervous system and thorax, has been reported more commonly in young and immunosuppressed dogs.[237-240,251-254] *Nocardia* spp. have also been isolated from cases of osteomyelitis, cystitis and hepatitis.[236,242,244,255-257]

History and Clinical Signs

Cutaneous and SC lesions may develop as superficial abscesses or more indurated masses (mycetomas) with or without local spread and lymph node involvement.[213,239-243,250] Skin and superficial lesions are often associated with the development of draining tracts and sinuses.[213,214,242,247] Thoracic disease may present as pneumonia or pyothorax resulting in signs of dyspnea, tachypnea, lethargy, weight loss and fever.[212,254,258-260] These signs are non-specific, with similar signs in peritoneal and disseminated disease.[237,240,245,261]

Diagnosis

A presumptive diagnosis of nocardiosis may be made based upon macroscopic and microscopic examination

of clinical specimens. Organisms on Gram-stained slides will appear as Gram-positive, thin, and filamentous within a background of lymphocytes and macrophages. Acid-fast stain may be used to demonstrate "acid fastness" after filamentous organisms are noted with Gram-staining. However, this reaction is unreliable in direct clinical samples and may be dependent on the growth media used and age in culture samples.[262] *Nocardia* spp. can be grown on most culture media over 2-14 days, with marked variation in the appearance of different species. Species identification has traditionally been performed based on biochemical methods, chemotaxonomy and serology. Molecular methods, most commonly 16S rRNA gene sequencing, have become the method of choice in bacterial identification as these provide an accurate and rapid result.[263,264]

Treatment and Prognosis

Like actinomycosis, treatment of nocardiosis relies upon debridement and drainage of the lesion in addition to appropriate antimicrobial therapy. Most *Nocardia* spp. are susceptible to sulphonamide antibiotics and these have historically formed the basis of medical therapy. However, sulfonamides may be poorly tolerated and some species of *Nocardia* are resistant to these drugs.[265,266] A range of other drugs has also been shown to be efficacious with multi-agent protocols advocated for treatment of persistent or disseminated infections (see E-Table 212-1).[238,239] Prolonged therapy of 6-12 months is required in most pets to gain optimal results.[238,247]

Patients with disseminated disease, particularly with CNS involvement, generally carry a grave prognosis, with the majority euthanized or succumbing to their disease.[237,239,253] While cases of superficial disease may initially respond to treatment, many are euthanized due to deterioration despite treatment or recurrence of disease.[239,242,244]

Public Health Considerations

Nocardia spp. infections have been reported in humans associated with cat scratches but disease transmission from infected animals to humans has not been reported.[267-269]

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CHAPTER 213

Brucellosis

David P. Beehan

Client Information Sheet: Brucellosis

Etiology

Canine brucellosis is most commonly caused by the Gram-negative coccobacillus bacterium *Brucella canis*, and less commonly by *Brucella melitensis*, *Brucella suis* or *Brucella abortus*. It is predominantly a venereal and orally transmitted bacterium associated with abortion and infertility in dogs. Canine brucellosis can be a reportable disease in certain states or countries, requiring that appropriate local authorities be informed of a positive diagnosis.

Pathogenesis

Brucellosis is most commonly shed in urine, vaginal discharges, aborted tissues, semen and, to a lesser extent, in milk, saliva and nasal secretions.[1] The *Brucella* organism attaches to and crosses mucous membranes (genital, oronasal and conjunctival) and is then phagocytized by macrophages and moved to lymph nodes. Bacteremia begins about 7-30 days after infection and may persist as long as 6 months. Intermittent recurrences can then take place for 66 months or longer.[2] These bacteria have a preference for steroid-dependent reproductive organs (i.e., prostate, epididymides, testes, vagina, uterus and placenta) (Figure 213-1).

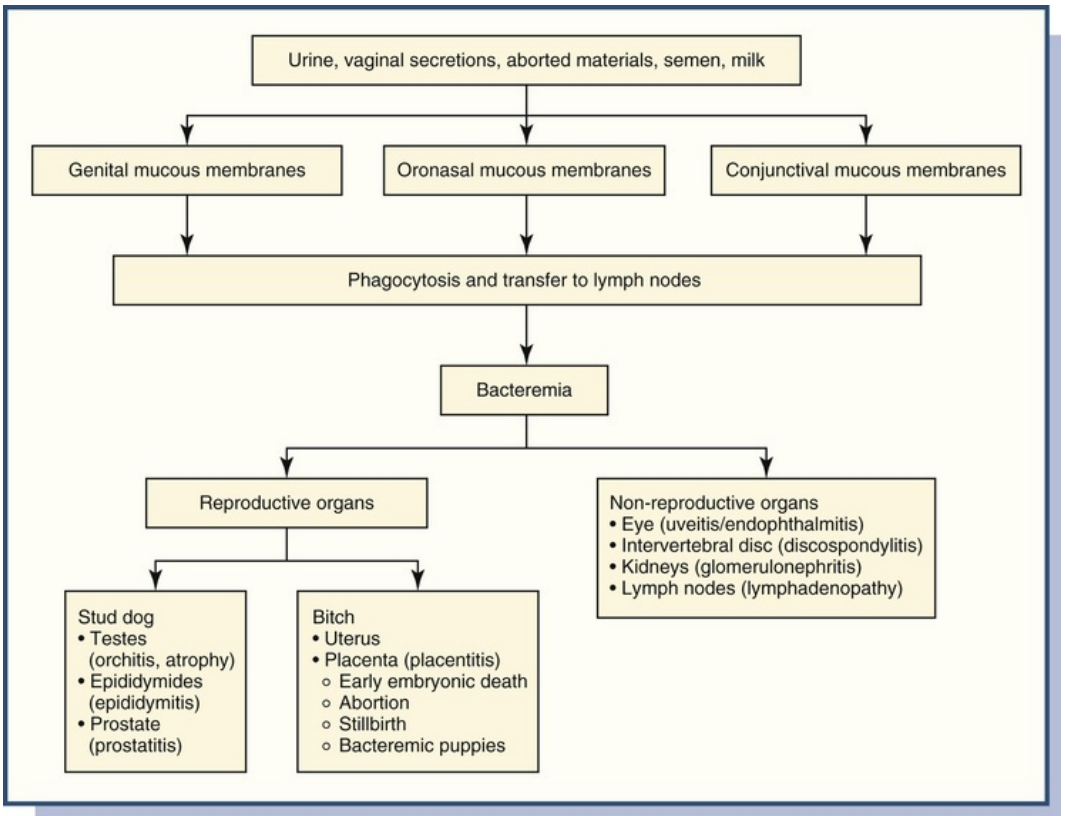

FIGURE 213-1 Pathogenesis of canine brucellosis.

Clinical Signs

Overview

Signs vary by organ and system affected. The most common clinical signs are abortion and infertility. However, other reported clinical signs include poor hair coat, listlessness, fatigue, lethargy, exercise intolerance, weight loss, lameness, back pain, lymphadenopathy, poor vision and behavioral changes.

The Male

Clinical findings in the male may begin as acute epididymitis and orchitis that causes scrotal pain, swelling, and dermatitis. Inflammation and irritation can cause persistent scrotal licking and secondary scrotal dermatitis. Pain on palpation of the testes at semen collection might be noted (see ch. 111). Semen evaluation may reveal asthenospermia, teratospermia, sperm head to head agglutination and white blood cells.[3,4] Finally, testicular atrophy results in the loss of functional seminiferous tubules and azoospermia. Enlarged or firm epididymides and unilateral or bilateral testicular atrophy may be noted. In neutered males, *Brucella* organisms can persist in the prostate and can be shed in the urine.

The Female

In the pregnant bitch, *Brucella* replication occurs inside placental tissues, resulting in abortion usually after 45-59 days of gestation.[3,5] A viscous, serosanguineous vulvar discharge may be observed for a number of weeks post-abortion, containing up to 10^{10} bacteria/mL.[6,7] Infection in females may also result in early embryonic death, stillborn fetuses, or repeated abortions. Some infected bitches have what appears to be a normal litter. However, puppies will begin to die within days or remain bacteremic. Other non-reproductive diseases secondary to *Brucella* infection include endophthalmitis, discospondylitis, lymphadenopathy, and granulomatous responses in skin, testes and organs (see Figure 213-1).[3,8-12]

Diagnosis

Overview

There is no commonly available test that reliably confirms a diagnosis of brucellosis. Reliance on any single test is not recommended. Diagnosis based solely on history or clinical signs is unwise, since canine infertility and abortion have many differential diagnoses (see ch. 315). In addition, many household pets are now adopted from shelters, already neutered. However, they can be infected and asymptomatic. A complete blood count, biochemistry profile and urinalysis can be performed to help rule out other potential differential diagnoses. Results in dogs with brucellosis are usually unremarkable.

Diagnostic Tests

Choices

Serological testing can begin 4 weeks after infection. Available choices include the rapid slide-agglutination (RSAT and ME-RSAT), tube-agglutination (TAT), indirect fluorescent antibody (IFA) and agar gel immunodiffusion (AGID-cell wall antigen or AGID-cytoplasmic protein antigen) tests. The smooth-walled *B. suis* and *B. abortus,* which may also infect dogs, do not cross-react with the serologic tests used to diagnose *B. canis*.

RSAT, AGID, TAT

The RSAT is a highly sensitive, commercially available, relatively inexpensive card test that can rapidly screen dogs for brucellosis. Results, precipitation of antibody-antigen complexes, are available within two minutes, with a low incidence of false negatives. Test sensitivity is >95%.[13,14] False positives, up to 40-60%, occur because antibodies in the assay cross-react with other Gram-negative bacteria.[4] When a positive result occurs, the test should be repeated with the addition of 2-mercaptoethanol (2ME), which inhibits IgM cross-reaction, increasing test specificity.[14] If the RSAT is negative, the dog can be considered *Brucella*-free unless infection occurred in the previous 4-12 weeks. Seroconversion occurs as early as 4 weeks after infection and is delayed in some animals for as long as 12 weeks. Repeating any RSAT is recommended. If positive after the addition of 2ME, it is recommended that AGID or TAT be performed to confirm the diagnosis. These tests can be performed 12 weeks after infection and have a higher sensitivity and specificity than RSAT, but false positives are still possible.

Blood Culture or Polymerase Chain Reaction (PCR)

Blood culture or PCR of *Brucella* organisms provides a definitive diagnosis. However, a negative result still cannot be presumed to indicate a true negative. PCR screening for canine brucellosis is now available and *Brucella*-positive dogs have been identified from serum, blood, lymph nodes, semen, vaginal swabs, urine and uterine tissue.[15-19] PCR is considered more sensitive than blood culture and allows earlier diagnosis than serologic testing.[19,20] Using PCR, vaginal swabs showed good sensitivity. PCR is a useful screening test for dogs being added to a kennel.[18,19] Bitches presenting for abortion should have vaginal discharges, placentas and aborted fetuses submitted for culture or PCR.

Treatment

Brucellosis is an intracellular bacterium, making it difficult to eradicate. No antibiotic, either alone or in combination, has been shown to be 100% effective. Enrofloxacin has shown some promise, potentially preserving fertility in a kennel outbreak situation with no adverse effects on pregnancies.[21] If born infected, puppies facilitate persistence of the infection in any exposed dogs. Antibiotics will decrease circulating bacteria numbers, which can alter serological test results and their interpretation if dogs are treated for as long as 4-6 weeks or treated multiple times. Bacterial re-emergence may happen during periods of animal stress and periods of increased reproductive hormone concentrations, as in estrus. *Brucella* organisms persist in lymph nodes, spleen, uterus and prostate.[21,22] The major disadvantages of antibiotic treatment include cost, drug availability, drug administration routes, periods of treatment, owner compliance, and need for retesting 6-12 months later. There is always the potential for future infection of other dogs and humans. Euthanasia is the treatment of choice for many owners, breeders and veterinarians.

Prevention

There is no commercially available canine *Brucella* vaccine to prevent infection of healthy animals. New animals should be kept isolated and screened, e.g., RSAT monthly, until 2 negative tests results are returned.[3] Similarly, any animals showing clinical signs should be immediately isolated and kept isolated until similar results are available.

Kennels should be designed to be easily cleaned, with run-off into drains and not adjacent kennels. Good kenneling must prevent animal-to-animal contact. There should be no shared equipment between dogs, e.g., bowls and bedding. Preferably, gloves should be worn by workers when handling animals. *Brucella* organisms will not survive free in the environment for very long. Presence of organic material, e.g., wood, paper, feces, or moist warm conditions will prolong its survival. *Brucella* sensitive disinfectants include quaternary ammonium, 1% sodium hypochlorite (bleach), iodophor solutions, 70% ethanol, and formaldehyde. For breeders, artificial insemination (AI) is strongly recommended to help reduce exposure to brucellosis. Canine AI will only prevent infection of males by female dogs and not vice versa. Female dogs can become infected through insemination. No commercially available semen extender effectively inhibits the transmission of *B. canis*.[4]

Zoonosis

Despite having strong host preferences, *B. canis* can cause disease in humans. Infection is most commonly reported in people occupationally exposed to intact breeding animals, i.e., blood, semen and placentas. The prevalence in these workers is higher than expected. All persons in contact with dogs are susceptible.[23] Incubation in humans can be between 5 days and 5 months before the onset of any clinical signs.[24] Acute signs of infection are similar to those of influenza, i.e., fever, sweats, headaches, back pain, malaise and weakness. Chronic infection may recur years later, with symptoms including recurrent fever, joint pain and fatigue. Human brucellosis is a federally reportable disease in the U.S.

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CHAPTER 214

Tetanus and Botulism

Simon R. Platt

Clostridial organisms are Gram-positive, anaerobic, spore-forming bacteria found ubiquitously in the environment. Neurotoxins produced by the bacteria are responsible for both tetanus (manifested as spastic paralysis) and botulism (manifested as flaccid paralysis) in humans and domestic animals. The basic underlying mechanism of action of these zinc metalloprotease toxins is inhibition of neurotransmitter release in both diseases, despite the dramatically different clinical signs observed.[1]

Tetanus

The prevalence of tetanus in cats and dogs is relatively low because they are considered to be reasonably resistant to the infection, especially when compared with horses and humans. Cats are approximately 10 times more resistant to infection than are dogs and dogs are 600 times more resistant to tetanus than are horses.[2] The resistance in these species is due in part to the inability of the toxin to penetrate and bind to nervous tissue.

Etiology

Tetanus is caused by the actions of neurotoxins formed in the body by *Clostridium tetani*, a motile, Gram-positive, non-encapsulated, anaerobic, spore-forming, rod-shaped bacterium. The toxin is produced during vegetative growth of the organism in a suitable environment.[3,4] The DNA for this toxin is contained in a plasmid and is antigenically homogenous. The organism's resistant spores are ubiquitous, with a natural habitat in moist, fertile soil; however, they can survive indefinitely in dusty indoor environments. The spores are resistant to boiling water and an autoclave temperature of 120° C for up to 20 minutes.[2] However, the vegetative phase of this bacterium is susceptible to chemical and physical inactivation. Organisms can be isolated from the feces of dogs, cats, and humans, but presence of the organism does not indicate infection because not all strains possess the plasmid.[3]

Pathogenesis

Tetanus develops when spores are introduced into wounds or via penetrating injuries. Most cases develop after skin wounds, but infection can follow teething, dental fractures, nailbed infections, parturition, or surgeries such as ovariohysterectomy.[5-7] Occasionally, no obvious wound can be found.[8] Under anaerobic conditions found in necrotic or infected tissue, the tetanus bacillus secretes two exotoxins: tetanospasmin and tetanolysin. Tetanolysin is capable of locally damaging otherwise viable tissue surrounding the infected area and optimizing the conditions for bacterial multiplication.[3]

Tetanospasmin leads to the clinical syndrome of tetanus. This toxin can constitute >5% of the weight of the organism.[3] It is a two-chain, 150,000 dalton polypeptide that initially is inactive, and is made up of a light and a heavy chain. The heavy chain has a high affinity for ganglioside surface receptors on neuromuscular endplates and is responsible for internalization, cytosolic translocation, and fast retrograde axonal transport of the light chain.[9,10] The light chain is the actual neurotoxin and it acts pre-synaptically to prevent neurotransmitter release from affected neurons. Tetanospasmin binds to the membranes of the local motor nerve terminals. If toxin load is high, some can enter the bloodstream, from where it diffuses to bind to nerve terminals throughout the body and even can enter the central nervous system (CNS) through an intact blood-brain barrier. The toxin then is internalized and transported intraaxonally and in a retrograde fashion to the cell body at a speed of 75 to 250 mm per day.[2,3] Transport occurs first in motor and later in sensory and

autonomic nerves. Further retrograde intraneural transport occurs with toxin spreading to the brainstem in a bilateral fashion, up the spinal cord. This passage includes retrograde transfer across synaptic clefts by a mechanism that is unclear.

The tetanospasmin light chain becomes activated after internalization into inhibitory neurons; at this stage, the toxin is no longer accessible for neutralization by antitoxin.[10] It prevents neurotransmitter release by cleaving and inactivating synaptobrevin, a membrane or "docking" protein necessary for the export of intracellular vesicles containing the neurotransmitter.[11] Synaptobrevin is a member of the SNARE (soluble N-ethylmaleimide-sensitive-factor attachment receptor) protein family, a highly conserved group of proteins essential for docking and fusion of neurotransmitter vesicles with the presynaptic membrane (Figure 214-1).[1,9-12] In addition to disrupting docking proteins, the toxin can lead to cross-linking of synaptic vesicles to the cytoskeleton, further preventing neurotransmitter release.[13]

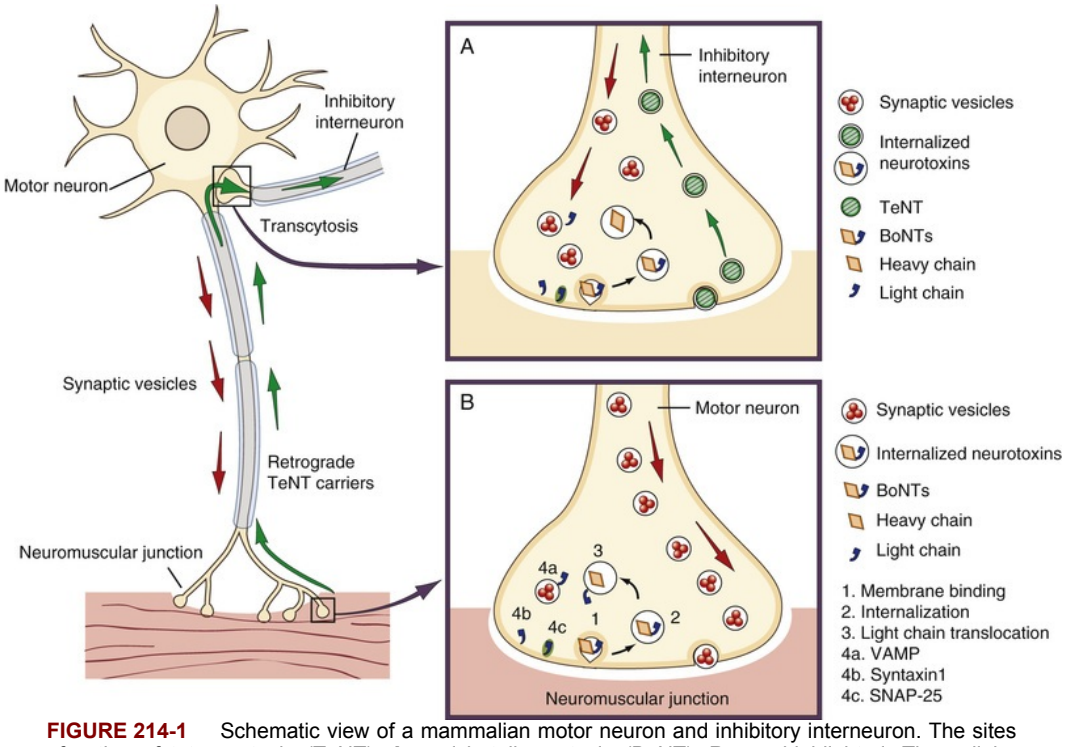


FIGURE 214-1 Schematic view of a mammalian motor neuron and inhibitory interneuron. The sites of action of tetanus toxin (TeNT), **A,** and botulinum toxin (BoNT), **B,** are highlighted. The cellular mechanisms of the clostridial neurotoxins are illustrated; both TeNT and BoNT follow a four-step mechanism to enter and inhibit neurons: membrane binding (1), internalization (2), translocation (3) and intracellular action (4). *SNAP-25*, Soluble NSF attachment protein-25; *VAMP*, vesicle-associated membrane protein.

The toxin predominantly affects inhibitory interneurons, inhibiting release of glycine and gamma-aminobutyric acid (GABA).[3] Interneurons inhibiting alpha-motor neurons are affected first, and the motor neurons lose inhibitory control. The disinhibitory effect on the motor neuron can cause diminution of function at the neuromuscular junction; therefore, the clinical effect is dissimilar to that of the related botulinum toxin. Medullary and hypothalamic centers also can be affected. Disinhibited autonomic discharge leads to disturbances in autonomic control, with sympathetic over-activity and excessive plasma catecholamine levels.

Neuronal binding of toxin is thought to be irreversible. Recovery requires the growth of new nerve terminals, which explains the long duration of clinical tetanus.[14]

Clinical Presentation

Tetanus most commonly affects young, large-breed dogs and is rare in cats.[7] Clinical signs can take up to 3 weeks to become apparent from the onset of infection, although most cases exhibit signs within 5 to 12 days.[5,7,8] The clinical signs initially can be localized or generalized, with the former more common in cats. Only a few cats with tetanus have been documented in the literature; most had predominantly localized

clinical signs.[15-19] A study of 38 dogs with tetanus revealed that ocular and facial changes were the most common initial signs.[5] Localized signs begin proximal to the site of introduction of the infection and can include single muscle rigidity, entire limb rigidity, and facial muscle spasms; cats might be more likely to experience carpal flexion, whereas dogs exhibit extension.[15,16] Clinical signs can progress with more extensive muscle involvement.[20] Generalized signs include a stiff gait affecting all limbs, increased muscle tone, dyspnea, an elevated tail and a "sawhorse stance," although the animal can become uncomfortable standing with such excessive muscle activity. At least 50% of dogs progress within a median of 4 days (range 0 to 14 days) to recumbency with severe muscle spasms.[5,7,8]

Involvement of the head can lead to spasm of the masticatory and pharyngeal muscles, causing trismus (lockjaw) and dysphagia. Trismus is not pathognomic for tetanus on its own and must be differentiated from other causes, which include temporomandibular joint disease or subluxation, masticatory myositis, and retrobulbar abscess.[21] Trismus can be exacerbated functionally by increased salivation, increased bronchial secretions, and increased respiratory rate resulting from involvement of the parasympathetic and somatic cranial nerve nuclei. Regurgitation and gastroesophageal reflux can result rarely from esophageal hiatal hernia and megaesophagus, which could lead to aspiration pneumonia when combined with the problems described earlier.[22] Excessive contraction of the facial muscles causes erect ears and a wrinkled forehead (E-Figure 214-2) and gives the animal a characteristic sneering of the lips known as *risus sardonicus* (sardonic grin) (Figure 214-3 and Video 214-1). In addition, the patient can exhibit protrusion of the third eyelid and enophthalmos resulting from retraction of the globe due to hypertonus of the extraocular muscles.[2] Severe progression of signs can cause recumbency, opisthotonus, seizure-like activity, respiratory paralysis, and central respiratory arrest, potentially causing death if not rapidly recognized and managed. The mortality rate ranged between 8% and 50% of dogs in three recent retrospective studies, and many of the dogs that died demonstrated concurrent autonomic signs.[5,7,8]

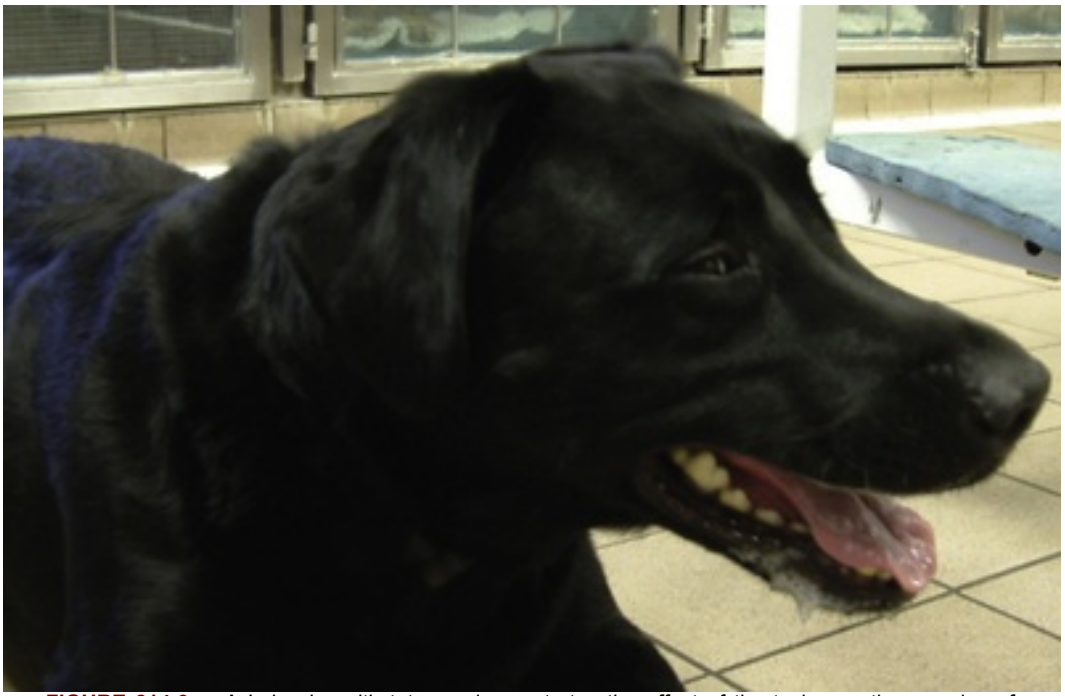
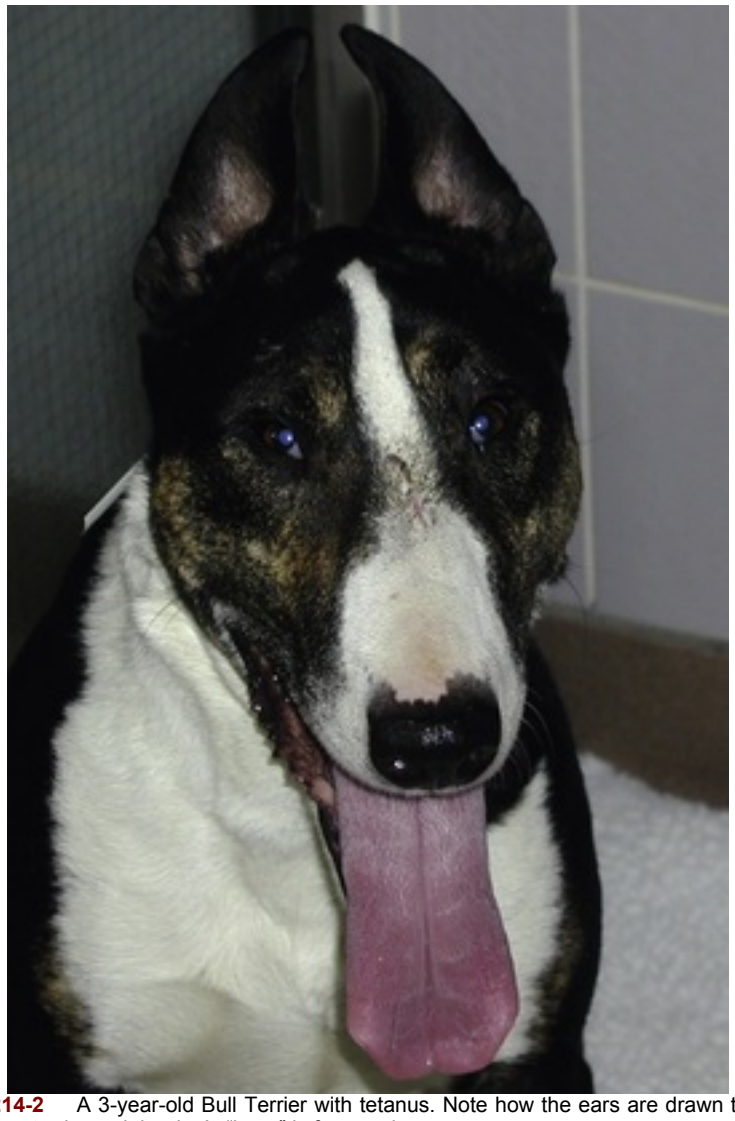


FIGURE 214-3 A Labrador with tetanus demonstrates the effect of the toxins on the muscles of facial expression creating the classical *risus sardonicus* appearance.



E-FIGURE 214-2 A 3-year-old Bull Terrier with tetanus. Note how the ears are drawn together, the third eyelids protrude, and the dog's "brow" is furrowed.

It is possible to see an effect on the autonomic system, evidenced by episodes of bradycardia and tachycardia, systemic hypertension, marked vasoconstriction, and hyperthermia.[7] A study of 38 dogs with tetanus revealed that 37% demonstrated abnormalities of blood pressure or rectal temperature, or both, consistent with autonomic disturbance.[5] In mild generalized cases, autonomic involvement can be manifested by dysuria and urinary retention, constipation, and gaseous distention of the gastrointestinal (GI) tract. In affected humans, "autonomic storms" occur, causing marked cardiovascular instability, severe hypertension alternating with profound hypotension, and even recurrent cardiac arrest.[3] During these "storms," plasma catecholamine levels are increased tenfold, similar to levels seen in animals with pheochromocytoma.[3]

A tetanus severity classification system has been proposed in dogs[5]: class I dogs have only facial signs of tetanus; class II dogs have generalized rigidity or dysphagia, with or without class I signs; class III dogs have class I or II signs and are recumbent or have seizures; and class IV dogs have class I, II, or III signs as well as abnormal heart rate, respiratory rate, or blood pressure measurements.[5] Survival rate decreases with increasing severity class.

Diagnosis

The patient's history and clinical signs usually are sufficient to make a presumptive diagnosis of tetanus. Differential diagnoses considered in patients with tetanus should include immune-mediated polymyositis, strychnine intoxication, spinal trauma, hypocalcemia, or meningoencephalitis.

If general anesthesia is used for diagnostic tests such as cerebrospinal fluid acquisition, the muscle spasms can be reduced but rarely are abolished. Intubation can be difficult in patients with trismus, and a stylet-assisted intubation should be anticipated in severely affected animals.

A complete blood count (CBC) can suggest an infectious process from a wound, whereas serum biochemistry profile (with the exception of muscle enzymes) and cerebrospinal fluid analysis findings are normal.[2] Because of the persistent muscle spasticity, high activities of creatine kinase (1599-18405 U/L [reference range 61 to 394 U/L]) have been documented in >50% of affected dogs.[8] Radiographs can be helpful to identify involvement of the esophagus, diaphragm, and secondary changes in the lungs resulting from aspiration pneumonia.

Electrodiagnostic abnormalities in patients with tetanus are nonspecific and consist of prolonged electric discharges after needle insertion on electromyography (see ch. 117).[19] There is a subsequent persistence of motor unit discharges occurring as "doublets," which are double discharges of the same motor unit at short intervals and often simultaneous activity of agonist and antagonist muscles.[19] Nerve conduction velocities are normal.[23] F waves have been reported to be abnormal in cats with localized tetanus.[19]

Measurement of serum antibodies to tetanospasmin can be performed by some laboratories and used for a definitive diagnosis. Values have to be compared with those of control animals. Polymerase chain reaction (PCR) testing has been used for detecting the tetanus toxin gene in wounds but it is not commercially available at this time in veterinary medicine.[24]

Attempts to isolate *C. tetani* from wounds often fail because of the low concentration of organisms and the requirement for strict anaerobic culture conditions at 37° C for at least 2 weeks.[2] A Gram stain of a smear from an open wound can identify Gram-positive rods and dark-staining spheric endospores, but the morphology of the bacterium is nonspecific and similar to that of many other bacteria.[2]

Treatment

There are three treatment strategies for dogs and cats with tetanus: (1) toxins present in the body outside the CNS should be neutralized; (2) organisms present in the body should be destroyed to prevent further toxin release; and (3) the effects of the toxin already in the CNS should be minimized. Intensive care management of affected animals is essential.

Neutralization of Unbound Toxin

Antitoxin neutralizes any toxin that is unbound to the CNS. Therefore, the timing of administration in relation to the onset of the disease is essential to its effectiveness. The antitoxin can be either anti-tetanus equine serum or human tetanus immune globulin. The latter could be more likely to produce reactions if given intravenously.[25] Early intervention has been recommended as a matter of routine, but there are no prospective studies objectively evaluating antitoxin use in dogs or cats, and its efficacy in cases with no evidence of a recent wound is unknown. There has been no significant benefit in survival, severity of clinical signs, or duration of clinical signs shown for dogs treated with antitoxin.[7] Additionally, a benefit of earlier administration of antitoxin on progression of clinical signs (i.e., worsening tetanus severity classification) or mortality rate has not been demonstrated.[5]

The recommended dosage of equine antitoxin for dogs and cats is 100 to 1000 U/kg (maximum 20,000 U/kg) IV, SC, or IM.[2] Intravenous administration is preferred to IM or SC administration. However, IV use of antitoxin is associated with a high incidence of anaphylaxis (see ch. 137).[2] To reduce this risk, a test dose (0.1 to 0.2 mL of 1 : 10,000 solution) should be administered intradermally 15 to 30 minutes before the intravenous dose.[2] A wheal at the site of injection can indicate that an anaphylactic reaction will develop. Epinephrine (0.1 mL/kg IV of the 0.1 mg/mL dilution), glucocorticoids, and an antihistamine (e.g., diphenhydramine) should be readily available in case of an adverse reaction, or the latter two even are sometimes given on a prophylactic basis. Repeated doses of antitoxin are more likely to cause adverse reactions and are not recommended or necessary because therapeutic levels persist for approximately 14 days.

Intramuscular injection at and proximal to the wound site (1000 U) could be helpful in localized forms of tetanus.[2] Although intrathecal administration of antitoxin has not been proven effective, experimental studies have suggested that it may be of use in dogs, reducing the morbidity and mortality in affected patients.[2]

Removal of Source of Infection

Any obvious wounds should be radically debrided after the administration of antitoxin. Flushing the wound with 3% hydrogen peroxide increases oxygen tension, which inhibits anaerobic organisms, although wound healing also could be impaired.[2]

Antimicrobials are essential to kill vegetative *C. tetani* organisms and thereby reduce the amount of circulating toxin. Although local administration of antimicrobials at the wound site has been advised, parenteral administration is recommended more routinely.[2] Classically, penicillin G has been the drug of choice, either IV as an aqueous potassium or sodium salt or IM as the procaine salt (20,000 to 100,000 U/kg q 6-12 h for 10 days in cats and dogs). However, metronidazole (7 to 10 mg/kg PO or IV q 8-12 h for 10 days) has been shown superior to penicillin G in clinical tetanus because it achieves bactericidal therapeutic concentrations in anaerobic tissues.[2] Other options include clindamycin (10 mg/kg PO, IV, or IM q 8-12 h) and tetracycline (22 mg/kg PO or IV q 8 h) or doxycycline (5 to 10 mg/kg PO or IV q 12 h).[2]

Control of Rigidity and Spasms

Prevention of unnecessary sensory stimulation is mandatory, but the mainstay of treatment is sedation with a benzodiazepine. Benzodiazepines augment GABA agonism at the $GABA_A$ receptor. Diazepam (0.5 to 1 mg/kg PO q 8 h in dogs [maximum 10 mg], 0.25 to 0.5 mg/kg in cats [maximum 5 mg, caution with oral diazepam in cats because of hepatotoxicosis], or a continuous IV infusion of 0.1 to 1 mg/kg/h in dogs and cats) or clorazepate (0.5 to 1 mg/kg PO q 8 h in dogs; 0.2 to 0.5 mg/kg PO q 12-24 h in cats) can be used in this regard, although both may cause over-sedation in some patients. As an alternative, midazolam can be used as a continuous IV infusion (0.2-0.5 mg/kg/h).

Additional sedation can be provided with anticonvulsant therapy, particularly phenobarbital (1 to 4 mg/kg PO or IV q 12 h or IM q 6 h), which further enhances GABAergic activity. Phenothiazines can be highly effective in controlling the hyperexcitable state; chlorpromazine (0.1 to 0.5 mg/kg IM, IV, or PO q 6-12 h) is the drug of choice, although acepromazine (0.005 to 0.05 mg/kg IV q 2 h as needed [maximum 3 mg in any dog]) is a useful substitute.

With severe signs such as generalized tonic-clonic seizure activity, generalized body stiffness, and opisthotonus, a propofol IV infusion may be necessary, but cardiorespiratory parameters should be monitored closely and careful consideration should be given to whether the patient should be intubated and placed on positive-pressure ventilation. Sedation with propofol has been shown to assist with muscle spasm and rigidity control in humans, without the use of neuromuscular-blocking drugs.[26] Neuromuscular blocking agents can be an option for the most severely affected veterinary patients, but assisted ventilation is imperative. Recently, the use of magnesium sulfate ($MgSO_4$) infusions or supraphysiologic magnesium therapy has been documented as a potential adjunct therapy in the management of spastic paralysis in dogs with tetanus.[27] However, a recent human meta-analysis of tetanus patients treated with magnesium could not detect a difference in mortality.[28] A dose of 70 mg/kg over 30 minutes followed by an initial IV CRI of 100 mg/kg/day has been recommended for dogs, based on human literature. The goal of this treatment is to increase total serum magnesium to 2 to 4 mmol/L (4.86 to 9.73 mg/dL) based on a target therapeutic range derived from the human literature.[27]

The use of botulinum toxin for tetanus-induced rigidity in humans recently has been suggested.[29] The effects of botulinum toxins remain fairly confined to the nerve terminals of lower motor neurons, inhibiting release of acetylcholine and activation of voluntary muscles. For this reason they could have a role in reducing the muscular hyperactivity in tetanus patients.

Supportive Intensive Care

Intensive nursing care is essential for successful treatment of patients with tetanus. The dog or cat should be isolated in a dark and quiet environment, with cotton wool balls placed in the external ear canals to reduce the effect of even mild auditory stimuli (Figure 214-4). Minimal handling is optimal, and all treatments therefore should be coordinated to occur together at set times through the day. A study of 13 dogs with tetanus documented the complications that occurred in these dogs during treatment; these included aspiration pneumonia, upper respiratory tract obstruction requiring tracheostomy, hiatal hernia, hyperthermia, and coxofemoral luxation.[8]

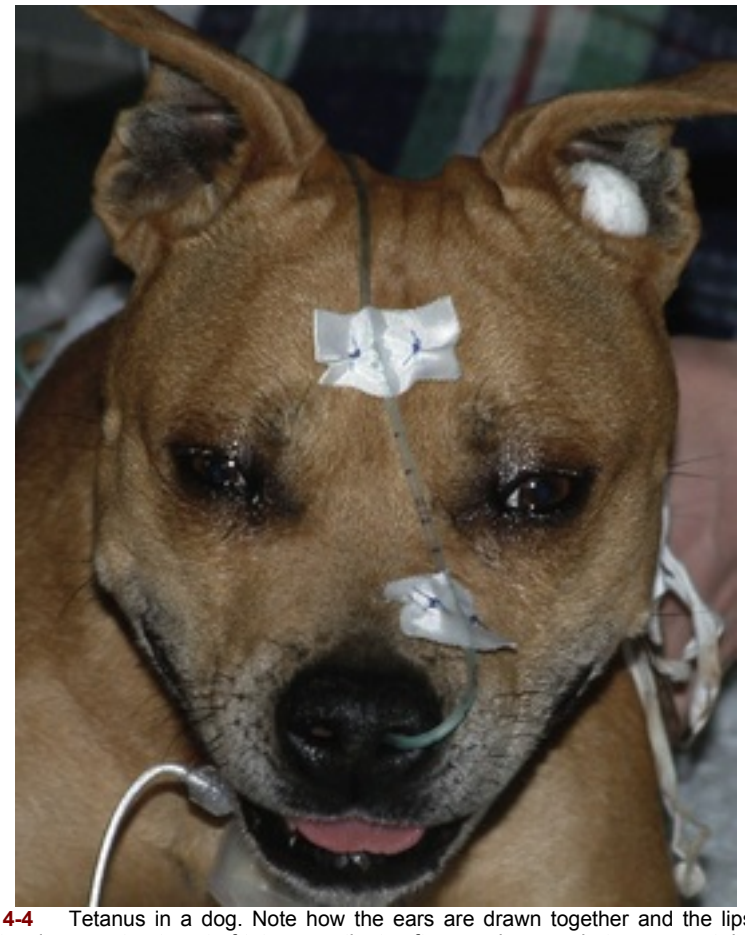


FIGURE 214-4 Tetanus in a dog. Note how the ears are drawn together and the lips are drawn caudally. Intensive care treatment of tetanus patients often requires respiratory support; in this patient intranasal oxygen and a tracheostomy were necessary. Supportive therapy includes reducing the environmental stimulation which can be accomplished by placing cotton wool balls in the external ear canals as can be seen in this dog, and even using sleep masks.

Percutaneous gastrostomy tube placement (see ch. 82) can prevent the complications associated with nasogastric tube feeding, particularly the stress that could be associated with an indwelling intranasal tube. Gastrostomy- or gastrojejunostomy-assisted tube feeding also can reduce the risk of aspiration pneumonia, a potential complication in dogs with severe forms of tetanus and those that are recumbent for a prolonged period. If airway obstruction develops because of laryngeal spasm or an accumulation of saliva or tracheal secretions, intubation and mechanical ventilation could be necessary. A tracheostomy often is performed in these patients to decrease the need for continuous anesthesia. Urinary and fecal retention occur in some patients with hypertonic anal and urinary sphincters. An indwelling urinary catheter (see ch. 106) might be beneficial in these patients, although the urine should be analyzed regularly for evidence of nosocomial infection. Pressure sores or decubital ulcers should be prevented with appropriate soft or padded bedding and frequent turning.

Prognosis

Recovery in dogs with tetanus depends on successful support of the animal while new axonal terminals form. Most dogs that recover (58% to 77%) show some improvement within 5 to 12 days, although the presence of autonomic abnormalities is a poor prognostic indicator.[5,7] Median length of hospitalization for dogs has been reported to be 13 days (range: 6 to 42 days). One study estimated the mortality rate to be ≈18% in affected dogs, but it also has been reported to be as high as 50%.[27] Mortality likely is related to the severity of clinical signs; one study revealed that all dogs with class I or II clinical signs survived and only 58% of dogs with class III or IV signs survived.[5] However, actual mortality might be difficult to estimate given the financial burden of long-term intensive care on a patient's owners; therefore, many animals are euthanized humanely instead of treated long-term. A full recovery might not be possible in at least 15% of dogs that survive, but

continued improvement can be seen for 3 to 5 months.[5,7,8] Cats are reported to recover well from localized tetanus, with some residual deficits remaining several months later[15-18]; there are no large studies assessing the prognosis in cats with generalized tetanus.

Botulism

Botulism is relatively uncommon in veterinary patients and the majority of cases can be linked to eating food that has spoiled, or carrion, allowing the growth of botulinum-toxin–producing bacteria.

Etiology

Botulinum toxin usually is produced by *C. botulinum,* which are a heterogeneous group of Gram-positive, anaerobic, spore-forming, rod bacteria distributed in the soil worldwide. Seven antigenically distinct types of toxin are described (A, B, C1, D, E, F and G).[30] All reported canine and feline cases to date have been caused by type C toxin, with the exception of two dogs reported from Senegal (type D toxin) and one dog in France (type B toxin).[30,31] This could be at least in part because *C. botulinum* type C appears to be an obligate parasite of animals and birds and can be found in carrion.[32] The spores formed by these bacteria, which are highly resistant to severe environmental conditions, will germinate in anaerobic conditions such as those provided by rotten carcasses of dead animals. Lysis of the spore is necessary for the release of the inactive, progenitor toxin complex, which becomes active following consumption, within the alkaline environment of the intestinal tract.[33] The activated toxin consists of a heavy and light chain.

Pathogenesis

Botulism occurs following ingestion of preformed toxin in rancid food or carrion, particularly dead birds, but in occasional cases, botulism can occur following colonization of anaerobic tissues by *C. botulinum,* with local toxin production.[30,31,34-36] There also is some anecdotal evidence of ingestion of botulism toxin through coprophagia in kenneled dogs. The only known natural outbreak of botulism in cats was associated with ingestion of a pelican carcass.[37] The toxico-infectious form of botulism described in humans, in which the toxin is produced by the bacteria multiplying within a wound or the GI tract has not been described in dogs or cats.[30]

Following cell or spore lysis, the toxin is released and it binds with other protein complexes to form progenitor toxins. These progenitor toxins are extremely stable, particularly at low pH, and they pass through the stomach into the small intestine where the toxin is released and absorbed. The toxin is absorbed from the small intestine by endocytosis; it enters the lymphatic system and from there, the bloodstream. The botulism toxin heavy chain then binds rapidly and with extremely high affinity to presynaptic peripheral nerve terminals, affecting the limb, trunk and head muscles. The process of neuronal binding comprises: (1) binding with neuronal cell surface receptors, (2) endosomal internalization of the toxin, (3) membrane translocation, and finally (4) modification of target SNARE proteins required for exocytosis of acetylcholine at the neuromuscular junction (see Figure 214-1).[9,10,30] Targeting of the SNARE proteins by the botulism toxin light chain prevents presynaptic release of acetylcholine at the neuromuscular junction, resulting in flaccid (lower motor neuron) paralysis and evidence of autonomic nervous system dysfunction.[10,38,39] Action of the toxin is prolonged, and functional recovery depends on sprouting of new axon terminals and reformation of the functional neuromuscular endplates.[40]

Clinical Presentation

Botulism is characterized by an afebrile, acute-onset, progressive, flaccid paresis, with additional involvement of the autonomic nervous system[30,34,35] (Videos 214-2, 214-3, 214-4, 214-5, and 214-6). Clinical signs typically develop rapidly within 12 hours (but the latent period can be up to six days) following ingestion of the toxin.[30,41] The onset and severity of clinical signs are dependent on the total dose of toxin ingested and the individual susceptibility of the animal. Some animals can quickly progress to tetraplegia while others will only show a mild ascending weakness predominantly affecting the pelvic limbs. Consistent with a lower motor neuron lesion, reflexes and muscle tone are decreased to absent. Cranial nerve deficits (e.g., facial nerve paralysis, depressed gag reflex, decreased jaw tone, reduced vocalization, and megaesophagus) are common

in severely affected animals, but sensory function, including pain perception and level of consciousness, are unaffected. Cholinergic signs can be seen, including alterations of heart rate (increased or decreased), pupil changes (mydriasis with depressed pupillary light reflexes), keratoconjunctivitis sicca, urinary retention, and constipation.[30,42]

In severe cases, the respiratory musculature can be affected, with decreased abdominal tone and primary diaphragmatic respiration. The diaphragm is more resistant to botulism toxin and only is affected in very severe cases.[30] Death can result from paralysis of the respiratory muscles or secondary to aspiration pneumonia and complications resulting from prolonged recumbency.

Diagnosis

The diagnosis of botulism is primarily based on the history and suggestive clinical presentation. Due to the dietary origin of the toxin, multiple cases can occur within the same group of animals and there may be a history of exposure to carrion.[30,34,36] Differential diagnoses for the clinical presentation include acute polyradiculoneuritis, tick paralysis, fulminant myasthenia gravis, acute polymyositis, coral snake envenomation, lasalocid poisoning and rabies poliomyelitis. In many cases of botulism in domestic animals and human patients, the underlying organism is not identified.

The results of routine investigation (including CBC, serum biochemistry profile, urine and cerebrospinal fluid analyses) are usually normal or reflect secondary complications of recumbency and paralysis. Conscious thoracic radiographs should be performed to assess for evidence of megaesophagus and secondary aspiration pneumonia.

Definitive diagnosis is based on the demonstration of botulinum toxin early in the course of the disease, either in blood (10 mL of serum should be collected) or intestinal contents (50 g of feces, vomitus, or food sample should be collected) using a mouse protection assay.[43] Alternatives to the mouse biological assay include enzyme-linked immunosorbent assays and PCR to detect botulism toxin in food, but many of these tests currently are still being validated.[41] The more rapidly the sample is collected after the onset of signs, the higher the likelihood of confirming the diagnosis. The samples should be refrigerated, but not frozen (freezing affects the vegetative form of *C. botulinum,* but does not affect the toxin). The sample should be labeled as a biological hazard, particularly as people are considerably more susceptible to botulism toxin than are dogs or cats. Culture of the organism from food or the environment is not helpful, but culture of the organism from a patient's feces or gastric contents could be very helpful in supporting the diagnosis. *C. botulinum* can be successfully cultured from the feces or gastric contents of ≈60% of human patients, but this requires strict anaerobic handling.

Electrodiagnostic evaluation of muscle and nerve function can assist in the diagnosis, but is not definitive (see ch. 117).[35,42,44-47] The typical electrodiagnostic feature of botulism is a marked reduction in compound motor action potential amplitude during motor nerve conduction, in the presence of normal nerve conduction velocity and no evidence of temporal dispersion of the compound motor action potential.[34,35,42,44,46,47] The reduction in amplitude reflects the decrease in transmission at the neuromuscular junction. In addition to the reduction in amplitude, there are some reports of identification of mild fibrillation potentials and increased insertional activity on electromyography after prolonged periods of paralysis (around 2 weeks), followed by positive sharp waves on recovery, and subtly decreased motor nerve conduction velocities in some canine patients.[35,42] Repetitive nerve stimulation at low frequency rates (3 Hz) can produce a small decrement in compound motor action potentials; rapid stimulation rates (50 Hz) are likely to produce an increment in successive compound motor action potentials and this increment is highly supportive of botulism, although it has not been reported in dogs.[35,42]

Treatment

Supportive care represents the mainstay of treatment in botulism, in particular the avoidance of problems associated with prolonged recumbency, namely bladder management (including prevention of retention cystitis; see ch. 106), avoiding the development of pressure sores, access to food and water, cleanliness, support while patients return to normal exercise, and physical therapy (see ch. 355 and 356). In more severe cases, respiratory support might also be required. In cases that have recently presented and where toxin could still be present within the GI tract, an attempt should be made to remove the material, taking care to avoid aspiration pneumonia. This may include using gastric lavage (see ch. 112), enemas (see ch. 114), and cathartics.

Bladder management is important, as recumbent animals will tend to retain urine and can develop retention cystitis. The bladder should be kept as empty as possible to minimize residual urine volume, either through support for urination, manual expression, intermittent catheterization, or indwelling closed collection systems. Intermittent catheterization is associated with the lowest incidence of urinary tract infections, followed by manual expression and finally indwelling closed urinary collection systems.

All recumbent patients should be maintained on soft bedding in order to avoid the development of pressure sores, and they should be turned frequently. Physical therapy (massage and passive range of joint movement) will also help to maintain joint movement (see ch. 355). The animals should also be kept clean in order to avoid urine and fecal scald and contamination of any pressure sores with fecal material.

Antitoxin Administration

Antitoxin administration currently is the only specific therapy for botulism. Antitoxin only is effective in limiting the severity of the clinical signs if administered early in the disease course. Antitoxin administration will not reverse established weakness or paralysis. Most canine cases are due to type C botulism and the human trivalent antitoxin acts against types A, B and E; therefore the available antitoxin is not effective. If type C antitoxin is available, then anaphylaxis and other hypersensitivity reactions are possible; a small subcutaneous or intradermal test dose should therefore first be administered.

Prognosis

Animals with botulism have the potential for complete recovery with no long-term deficits if they can be supported through the period of flaccid paralysis, and secondary complications can be avoided. Most dogs will recover within 2 to 3 weeks. Despite an apparently full recovery, muscle weakness still can be present for up to a year after recovery. The overall mortality in human patients with botulism is around 7 to 10%, but this is doubled in patients over 60 years of age. No such data are available in veterinary medicine. There are substantial costs associated with the duration of nursing required, and the owner should be made aware of these at the outset.

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CHAPTER 215

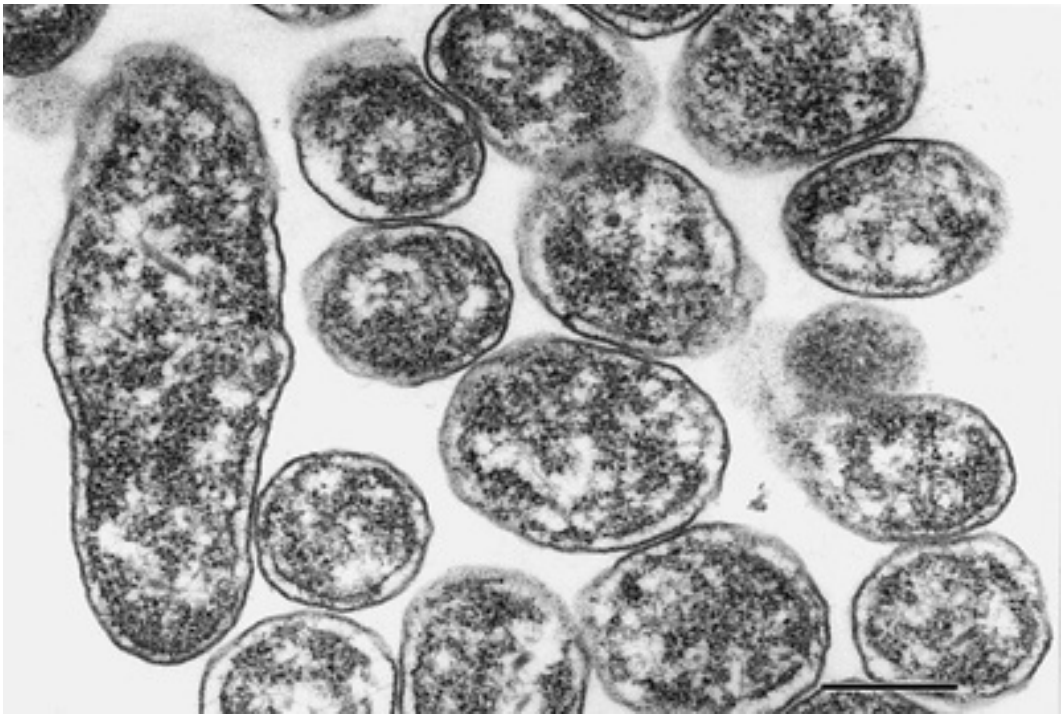
Bartonella—Canine

Pedro Paulo V.P. Diniz

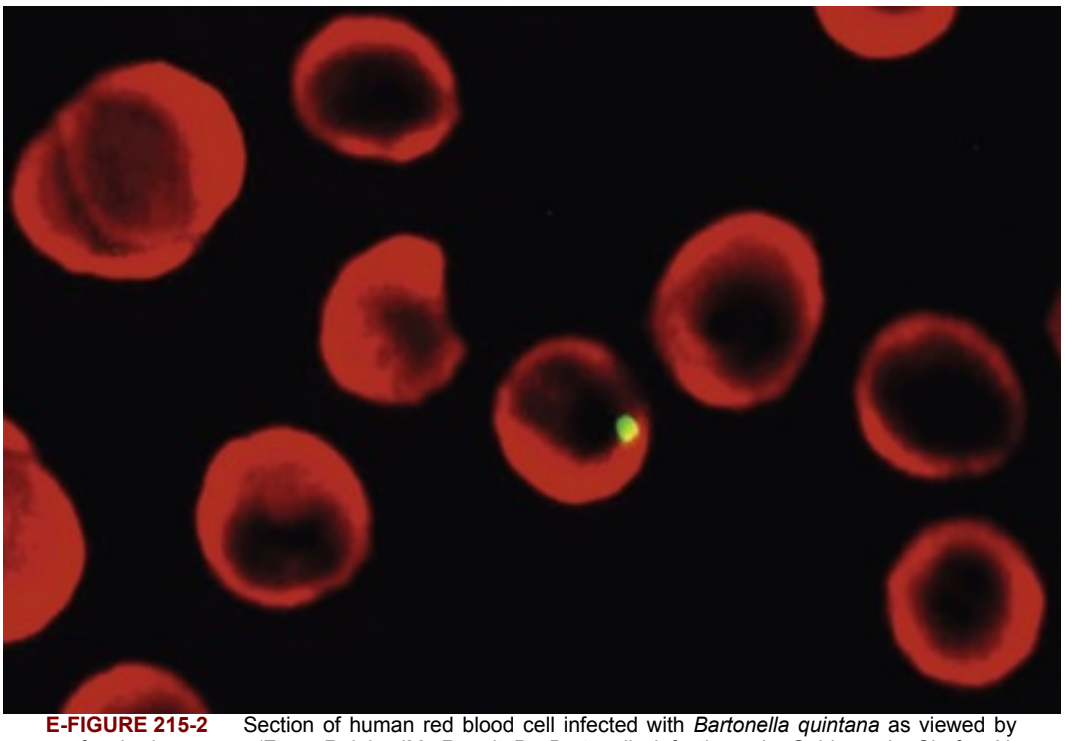
Client Information Sheet: *Bartonella*—Canine

Introduction

Bartonella species are fastidious Gram-negative bacteria transmitted by blood-sucking arthropods and capable of infecting many domestic and wild animal host species (E-Figure 215-1). Genetically, members of the genus *Bartonella* are closely related to the genus *Brucella* and plant pathogens from the genus *Agrobacterium.*[1] *Bartonella* species can cause a long-lasting infection by targeting primarily erythrocytes (E-Figure 215-2), endothelial cells and bone marrow progenitor cells.[2] *Bartonella* species have coevolved and adapted to a primary mammalian host, where persistent bacteremia may occur without clinical signs. Some examples include *B. henselae* and *B. clarridgeiae* in cats; *B. vinsonii* subsp. *berkhoffii* and *B. rochalimae* in domestic dogs and wild canids; *B. bovis* in cattle; *B. washoensis* in ground squirrels; and *B. quintana* and *B. bacilliformis* in humans. However, when *Bartonella* infect a non-adapted incidental host, clinical manifestations are more commonly seen, especially in immunocompromised hosts. To date, over 14 species, subspecies or species candidatus of *Bartonella* have been described in dogs. Of note, most of the species detected in dogs can also infect humans. In people, *Bartonella* species are an important cause of fever of unknown origin, endocarditis, arthritis, lymphadenitis, and encephalitis, among several other medical conditions. Professionals with frequent exposure to animals and blood-sucking arthropods, such as veterinarians, are at high risk of infection with *Bartonella* species.[3,4]



E-FIGURE 215-1 Electron photomicrograph of *Bartonella henselae.* Gram-negative cell wall structures including outer membrane, peptidoglycan layer and the inner cell wall are visible. Magnification ×66,000. Bar = 0.25 micron. (From Guptill L, Wub C-C, Glickman L, et al: Extracellular *Bartonella henselae* and artifactual intraerythrocytic pseudoinclusions in experimentally infected cats. *Vet Microb* 76(3):283-290, 2000. Reprinted with permission.)



E-FIGURE 215-2 Section of human red blood cell infected with *Bartonella quintana* as viewed by confocal microscopy. (From Rolain JM, Raoult D: *Bartonella* infections. In Goldman L, Shafer AI, editors: *Goldman's Cecil medicine,* ed 25, Philadelphia, 2016, Elsevier. Reprinted with permission.)

Transmission and Risk Factors

Cat fleas *(Ctenocephalides felis)* are considered one of the main vectors of *Bartonella* in companion animals and humans. It has been shown that *B. henselae* can multiply in the digestive system of the cat flea and survive several days in flea feces.[5] In shelters, fleas from cats are frequently infected with *Bartonella* species (generally above 40% of fleas), whereas *C. felis* from dogs have a lower frequency of infection (2.8% to 11.3% of fleas).[6,7] This difference is associated with the lower level of persistent bacteremia in dogs when compared to cats, which are the natural reservoirs for several *Bartonella* species (see ch. 216). *Bartonella* DNA was also detected in other canine blood-sucking arthropods, such as *Pulex* flea species, *Ixodes* spp. and *Rhipicephalus sanguineus* ticks.[7,8] Epidemiological evidence indicates that dogs infested with ticks have higher chances of being seropositive for *Bartonella* species.[9] However, experimental studies have not yet confirmed the capacity of ticks to transmit *Bartonella* to dogs. Lice and biting flies are also suspected vectors for transmission to dogs. Other risk factors for canine exposure to *Bartonella* species include living in rural environments or multi-dog households, having outdoor access, and being a herding breed.[9,10] Wildlife reservoirs may play a significant role in the ecology of *Bartonella* species. Coyotes, foxes, raccoons and other mammals can be infected with the same species of *Bartonella* detected in dogs and humans.[11-13] In California, coyotes are a major reservoir for *Bartonella* species, and are often asymptomatic despite 21% to 28% of them being bacteremic.[11,13] Cats and rodents may also serve as reservoirs for *Bartonella* transmission to dogs by sharing infected fleas. Circumstantial case-based evidence also suggests that cats may transmit *Bartonella* species to dogs by way of a scratch or bite, as they do to humans.

Epidemiology

Bartonella species have been described in all continents except Antarctica. Subtropical regions tend to have lower prevalence than tropical areas, but the frequency of seroreactive or infected dogs varies widely among countries. The two most frequent *Bartonella* species in dogs are *B. henselae* and *B. vinsonii* subsp. *berkhoffii* (E-Table 215-1). *B. vinsonii* subsp. *berkhoffii* and *B. rochalimae* can establish prolonged bacteremia in dogs, which may serve as natural reservoir hosts. Based on serologic testing of 14,430 dogs suspected of having vector-borne diseases in the United States, the overall seroreactivity to *Bartonella henselae* and *B. vinsonii* subsp. *berkhoffii* was 3.8% and 1.5%, respectively, but varied among regions from 1.7% to 4.2% of dogs that were seroreactive to *B. henselae* and from 1% to 1.6% for *B. vinsonii* subsp. *berkhoffii.* The highest percentage of seroreactive samples was observed from Northeast, mid-Atlantic and Southern regions of the United States.[14] However, serologic tests may underestimate the real prevalence of *Bartonella* species in the canine population because over half of the infected dogs do not mount a detectable antibody response.[2] Based upon enrichment culture coupled with polymerase chain reaction (PCR), the presence of *Bartonella* species in blood samples of sick dogs suspected of vector-borne diseases in the United States was 9.2% of 663 dogs.[15] Asymptomatic dogs may also be infected with *Bartonella* species, with two studies in the United States reporting 18% to 20% of clinically healthy dogs as being infected with *B. henselae* or *B. vinsonii* subsp. *berkhoffii.*[16,17] In other countries, the frequency of dogs that are bacteremic with *Bartonella* species varies widely, from 16.7% of 54 healthy dogs in Korea, 11.6% of 60 healthy dogs in southern Italy, and 6.3% of 80 dogs in Algeria, to 1.4% of 73 dogs in Grenada, and 1% of 198 sick dogs in Brazil.[2] Although seemingly less frequently, dogs can be infected with other *Bartonella* species for which the cat, the rat, and squirrels serve as reservoir hosts.

E-TABLE 215-1

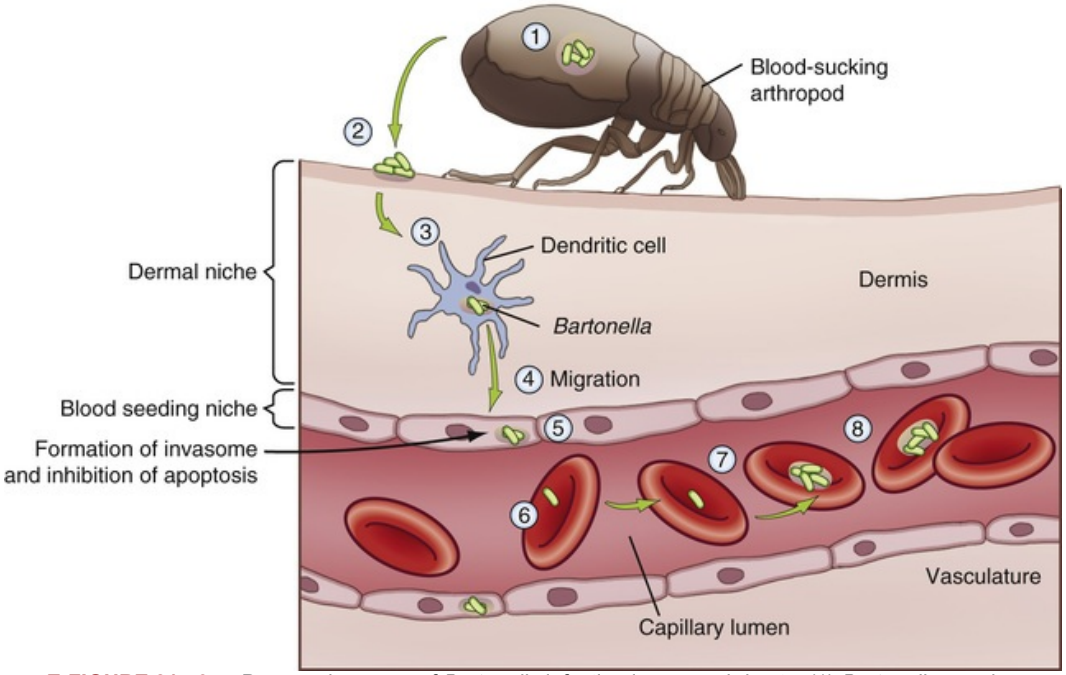
***Bartonella* Species Detected in Dogs and Reported Hosts**

MOST COMMON SPECIES	PRIMARY HOST	OTHER HOSTS
B. henselae	Cat	Human, dog, horse, rat, sea turtle, porpoise, beluga, wild felids, mockingbird, blackbird, woodpecker
B. vinsonii berkhoffii	Dog, coyote	Human, cat, fox, sea turtle
UNCOMMON SPECIES	**PRIMARY HOST**	**OTHER HOSTS**
B. bovis	Cattle	Dog, cat, deer, elk
B. clarridgeiae	Cat	Human, dog
B. elizabethae	Rat	Human, dog
B. grahamii-like	Rat	Dog, human
B. koehlerae	Cat	Human, dog
B. quintana	Human	Human, dog, cat, monkey
B. rochalimae	Dog, gray fox, red fox	Human, coyote, raccoon
B. taylorii	Wild mouse	Dog
B. vinsonii subsp. *arupensis*	Wild mouse, vole	Dog, human
Candidatus B. merieuxii	Dog	Not reported
Candidatus B. volans	Squirrel	Dog, human, sea otter
Candidatus B. washoensis	Squirrel	Human, dog, chipmunk

Pathogenesis

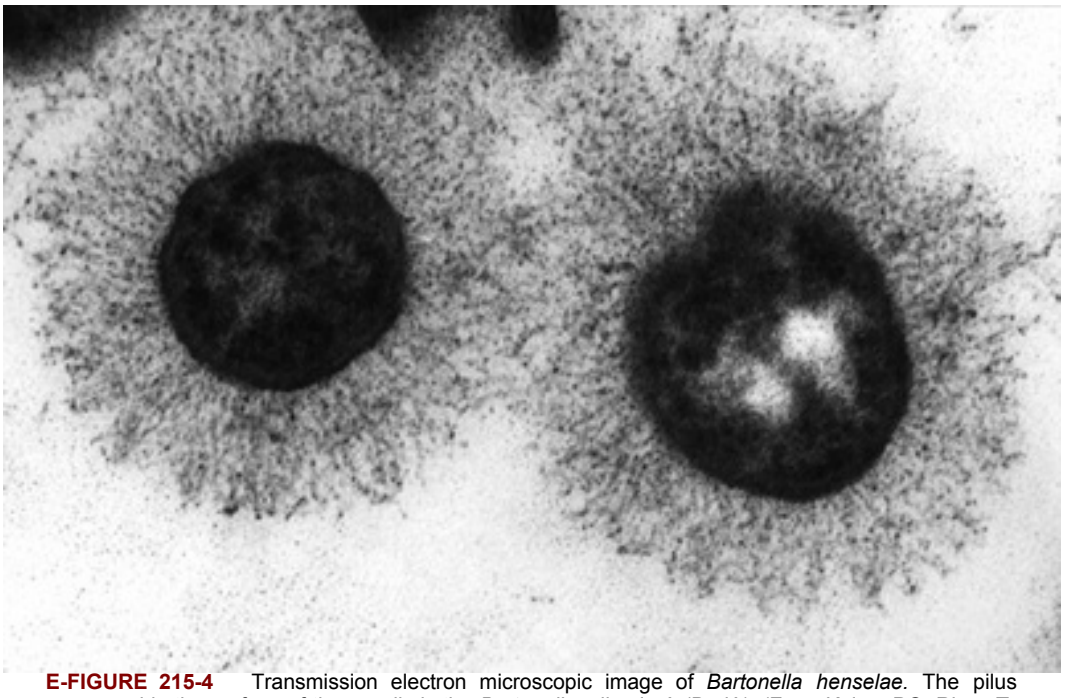
The pathophysiologic mechanisms of *Bartonella* infection have been investigated in detail based on

experimental rodent models or cell cultures, but information derived from experimental infection in dogs is still limited. Recent reviews have detailed the molecular and cellular mechanisms of *Bartonella* pathogenesis[18-21] that go beyond the scope of this chapter, but the main steps and factors are summarized as follows (E-Figure 215-3). While in the vector, *Bartonella* species replicate in the midgut of the arthropod and are excreted in the feces. *Bartonella* species are then inoculated through the bite or scratching associated with the arthropod bite. Once in the dermis, *Bartonella* species will start invading targeted cells, most likely dendritic and endothelial cells, which are called "dermal and blood seeding niches," respectively.[21] *Bartonella* species can also infect microglial cells, macrophages and CD34+ progenitor cells in the bone marrow.[22] This invasion is mediated by two groups of virulence factors: adhesins and type IV secretion systems (T4SS). Adhesins, such as *Bartonella* adhesin A (E-Figure 215-4), mediate bacterial adherence to endothelial cells and extracellular matrix proteins,[18] whereas T4SS are capable of transporting DNA and effector proteins to the targeted host cell. Two T4SS are present in *B. henselae* and *B. vinsonii* subsp. *berkhoffii:* the Trw and VirB/D4 systems, while *B. rochalimae* only has VirB/D4 T4SS.[19] Using these T4SS, these pathogens translocate *Bartonella*-effector proteins (Beps) into the targeted cells. At least seven Beps associated with inhibition of host cell apoptosis, cell invasion, bacterial persistence in erythrocytes and endothelial cells, and endothelial sprouting have been described to date.[18,21] The invasion of endothelial cells by *Bartonella* species is characterized by the formation of the *invasome,* a large well-organized bacterial aggregate that is engulfed and internalized by the targeted cell mediated by Beps and other pathogenicity factors.[18,23] Once *Bartonella* species establish persistent infection of the blood seeding niche by inhibiting cell apoptosis, they are periodically seeded into the bloodstream. Bacteria are released from the blood seeding niche, where they bind to and invade mature erythrocytes, and they replicate until they reach a critical number without causing hemolysis. Continuous replication of the pathogen in the blood seeding niche causes release into circulation at approximately five-day intervals, causing persistent bacteremia to facilitate the acquisition of the organism by the vector.[21] Experimental infection of dogs with *B. vinsonii* subsp. *berkhoffii* induced immunosuppression characterized by sustained suppression of peripheral blood CD8+ lymphocytes.[24] Immunosuppression caused by *Bartonella* infection may predispose the host to opportunistic infections, including infection by other pathogens transmitted by the same vector.



E-FIGURE 215-3 Proposed process of *Bartonella* infection in reservoir hosts. (1) *Bartonella* species replicate first in the midgut of the arthropod vector and are excreted in its feces. (2) *Bartonella* species are inoculated by scratching infected insect feces into the dermis. (3) *Bartonella* species colonize the "dermal niche." (4) Bacteria colonize endothelial cells mediated by *Bartonella*-effector proteins. (5) From this "blood seeding niche," the bacteria are periodically seeded into the bloodstream where they invade erythrocytes and spread the infection (6). After limited replication (7), they persist for the remaining lifespan of the red blood cell (8) and are thus competent for transmission by a bloodsucking

arthropod. (From Siamer S, Dehio C: New insights into the role of *Bartonella* effector proteins in pathogenesis. *Curr Opin Microbiol* 23:80-85, 2015. Reprinted with permission.)



E-FIGURE 215-4 Transmission electron microscopic image of *Bartonella henselae.* The pilus expressed in the surface of these cells is the *Bartonella* adhesin A (BadA). (From Kaiser PO, Riess T, O'Rourke F, et al: *Bartonella* spp.: Throwing light on uncommon human infections. *Int J Med Microbiol* 301(1):7-15, 2011. Reprinted with permission.)

Clinical Manifestations and Physical Examination Findings

From a clinical perspective, *Bartonella* species can be disseminated throughout all of the tissues in the body, which can result in disease in a single organ or multiple organs. Lesions have been described in the heart, liver, lymph nodes, joints, eye, nasal cavity, central nervous system (CNS), skin, and subcutaneous tissue. While a wide array of clinical signs is seen in dogs naturally infected with or exposed to *Bartonella* species experimental infection of dogs with *B. henselae, B. vinsonii* subsp. *berkhoffii* or *B. rochalimae* generally does not cause clinical signs or hematological abnormalities.[25-27] One study reported severe necrotic lesions at the site of inoculation associated with high inoculum doses while another study reported transient pyrexia.[24,28] Despite the lack of experimental models, clinical and epidemiological evidence supports the association between *Bartonella* infection and clinical manifestation in dogs. The described signs and lesions may be potentially associated with five intrinsically related mechanisms: intravascular infection, host immune-mediated response, lymphatic infection, pyogranulomatous lesions and abnormal vascular proliferation. (E-Box 215-1).

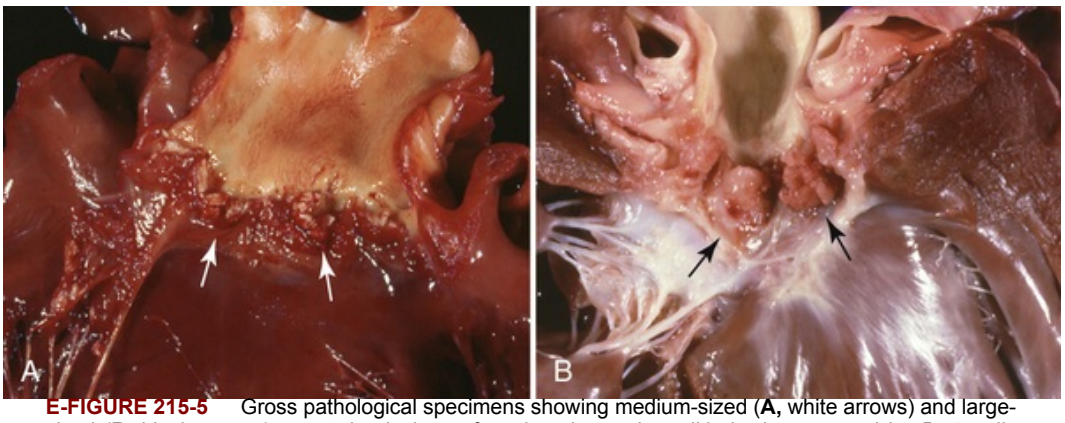
E-Box 215-1

Potential Mechanisms Associated with Disease Manifestations in Dogs Infected with *Bartonella* Species

POTENTIAL MECHANISM	CLINICAL MANIFESTATION OR DISEASE PROCESS
Intravascular infection	Endocarditis, fever of unknown origin, thromboembolic disease, polyarthritis

Host immune-mediated response	Polyarthritis, immune-mediated thrombocytopenia, immune-mediated hemolytic anemia, uveitis, vasculitis, meningoencephalitis, hyperviscosity syndrome
Lymphatic infection	Pleural effusion, pericardial effusion, abdominal effusion, seroma
Pyogranulomatous lesions	Dermatitis, panniculitis, lymphadenitis, chronic lymphocytic hepatitis, granulomatous hepatitis, meningoencephalomyelitis, systemic pyogranulomatous disease
Abnormal vascular proliferation	Peliosis hepatis, hemangiopericytoma, bacillary angiomatosis

Endocarditis is the most recognized consequence of *Bartonella* infection in dogs, with *B. vinsonii* subsp. *berkhoffii* being the most commonly identified species by molecular methods.[29-31] Approximately 19% to 28% of canine cases of infective endocarditis are caused by *Bartonella* infection,[32,33] with five of 11 dogs (45%) with culture-negative blood culture being seroreactive for *Bartonella* species in one study.[33] *Bartonella* endocarditis differs from endocarditis caused by other bacteria by affecting the aortic valve more frequently (E-Figure 215-5), and commonly being paired with concomitant congestive heart failure (see also ch. 251).[32] Frequent findings include murmur (89%), lameness (43%), respiratory abnormalities (28%), and weakness and collapse (17%).[33] Fever is a commonly reported finding, but it was less frequent in endocarditis caused by *Bartonella* species than by other bacteria in one study.[32] Endocarditis predisposes to septic thromboembolic disease, which can be associated with lameness, recumbency, anisocoria, and obtundation, among other neurologic signs.[29,34] Cardiac arrhythmias, secondary to myocarditis, can be detected in dogs lacking echocardiographic evidence of endocarditis. Dogs with *Bartonella* endocarditis have 2.7 times higher the risk of death than dogs with endocarditis caused by other bacteria.[32] Therefore, clinicians should always consider *Bartonella* infection in the differential diagnosis of infective endocarditis, as early introduction of specific therapy may increase survival.



E-FIGURE 215-5 Gross pathological specimens showing medium-sized (**A,** white arrows) and large-sized (**B,** black arrows) vegetative lesions of aortic valve endocarditis in dogs caused by *Bartonella clarridgeiae*. (Photo courtesy Bruno Chomel, DrSc, DVM, MS, PhD, Department of Population Health and Reproduction, University of California, Davis School of Veterinary Medicine, Davis, USA.)

The association of *Bartonella* infection and arthritis has been described in dogs and humans.[10,35] Dogs seroreactive to *Bartonella* species have three times the chance for presenting arthritis-related lameness compared to seronegative dogs.[10] In addition, *Bartonella* species have been implicated in dogs with granulomatous inflammation involving the skin, lymph nodes, liver, spleen or in association with disseminated granulomatous lesions.[36-39] Signs vary with the tissues and organs affected. Diverse neurologic signs have also been reported in dogs infected with *Bartonella* species. We also detected infection in dogs that were diagnosed with pleural, pericardial (restrictive pericarditis), and abdominal effusions and subcutaneous seroma,[40,41] suggesting that *Bartonella* species can cause lymphatic infection and potentially lead to obstruction of lymph flow. Despite the fact that no direct cause-and-effect association can be implicated in these cases, the detection of these pathogens in effusions considered "aseptic" based upon conventional

culture approaches may prove to be clinically relevant when facing a suspected case of idiopathic effusion.

Based on review of medical records of 47 dogs tested at North Carolina State University and confirmed to be infected with *Bartonella* species by enrichment blood culture, PCR and DNA sequencing, the most frequent signs were: fever (40% of dogs), lethargy (40%), weight loss (34%), anorexia (32%), lymphadenopathy (30%), diarrhea (23%), neurological signs (21%), heart murmurs (21%), respiratory signs (21%), polyuria/polydipsia (21%), lameness (19%), vomiting (15%), and splenomegaly (13%).[42] Weight loss occurred more frequently in sick dogs infected with *Bartonella* species than in dogs suspected of other vector-borne diseases.[43] However, such signs are of limited help in distinguishing *Bartonella* infection from other causes of special vector-borne diseases in dogs; therefore, other vector-borne pathogens should always be ruled out in any cases suspected of *Bartonella* infection.

Diagnosis

Because *Bartonella* species can be detected or isolated from clinical specimens of asymptomatic dogs, positive culture or PCR results do not necessarily indicate disease causation. Consequently, the diagnosis of canine bartonellosis relies on the presence of clinical abnormalities (see E-Box 215-1), histopathologic findings, and positive culture or PCR results on blood and affected tissues. For life-threatening illnesses such as endocarditis, myocarditis and neurologic disease, the presence of *Bartonella* species should be promptly investigated and patients should be presumptively treated with specific antibiotic therapy (see therapy section below). In all cases of suspected canine bartonellosis, other possible causes of disease must be investigated. For dogs presented with other local abnormalities (such as organomegaly, lymphadenopathy, panniculitis, etc.) or systemic disease (vasculitis, immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, systemic lupus erythematosus, polyarthritis, etc.), an extensive work-up should be performed to rule out other causes such as fungal, bacterial (including mycobacterial) infections, parasites, neoplastic, genetic, degenerative or immune-mediated disorders. Of note, if immunosuppressive therapy is necessary to address immune-mediated causes, concomitant *Bartonella* infection should be ruled out by serology, enrichment culture and PCR prior to therapy, as immunosuppression may predispose to *Bartonella* endocarditis and poor outcome.[44] An algorithm of the diagnostic approach is provided in Figure 215-6.

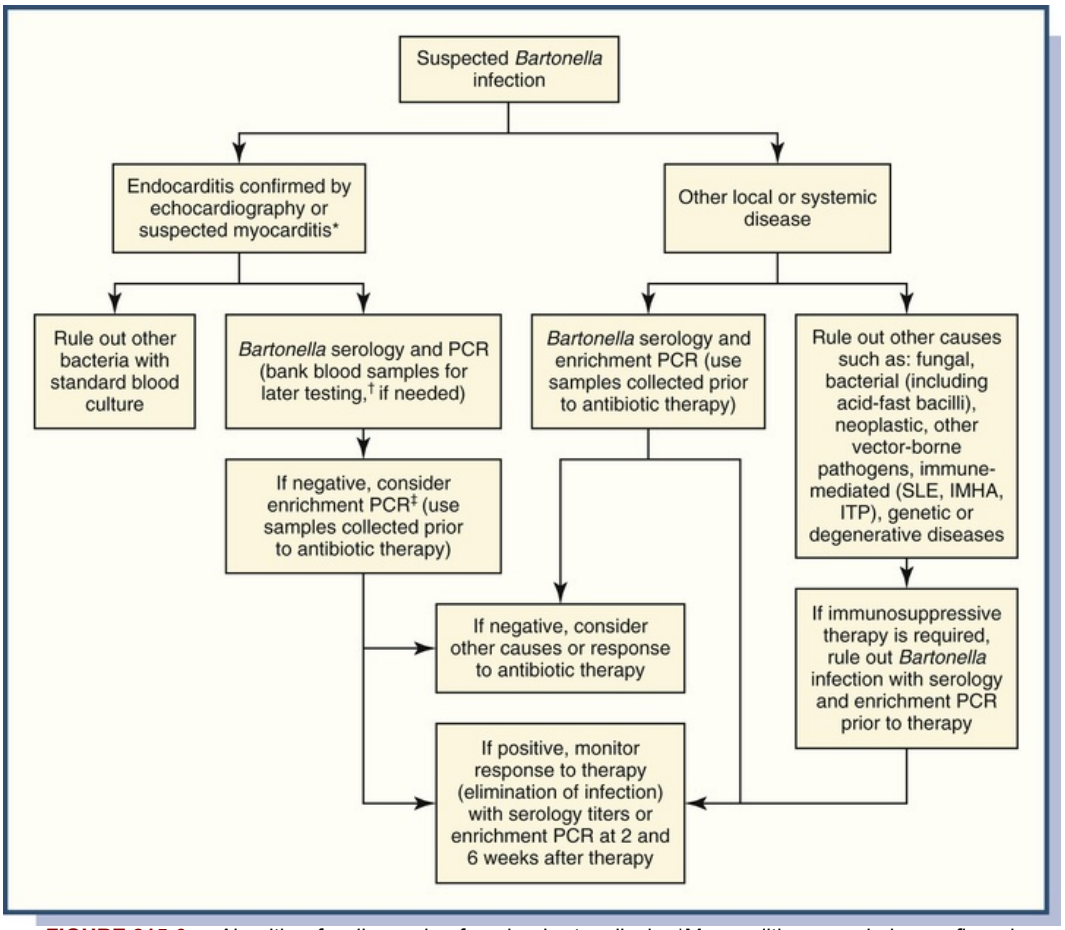


FIGURE 215-6 Algorithm for diagnosis of canine bartonellosis. *Myocarditis can only be confirmed by histopathology, but it may be suspected by elevated cardiac troponin I levels, abnormal echocardiographic findings and the presence of cardiac arrhythmias. †Samples can be refrigerated at 2–8°C for up to a week or frozen at −20°C for longer periods of time. ‡Diagnostic platform comprised of BAPGM enrichment culture coupled with PCR. See text for details. *BAPGM*, *Bartonella* alpha-Proteobacteria growth medium; *IMHA*, immune-mediated hemolytic anemia; *ITP*, immune-mediated thrombocytopenia; *PCR*, polymerase chain reaction; *SLE*, systemic lupus erythematosus.

Laboratory Abnormalities

Frequently, infected dogs have no hematologic abnormalities, and when present, they are nonspecific and often mild. In a recent study, the most common laboratory findings among 47 dogs confirmed to be infected with *Bartonella* species were: proteinuria (40%), anemia (38%), leukocytosis (36%), thrombocytopenia (34%), elevated liver enzymes (32%), hyperbilirubinemia (30%), hyperglobulinemia (26%), hypoglobulinemia (23%), azotemia (21%), monocytosis (17%), abnormal coagulation panel (PT/PTT) (13%), leukopenia (11%), and lymphocytosis (11%).[42,43] Cylindruria, bilirubinuria, and isosthenuria may be present in some dogs. When the frequency of laboratory findings was compared to dogs suspected of other vector-borne diseases, dogs presented with hypoglobulinemia (not associated with protein-losing nephropathy or enteropathy) had four times higher risk of being infected with *Bartonella* species than those who did not present with it.[43] These findings may be associated with potential immune suppression, since experimental infection with *B. vinsonii* subsp. *berkhoffii* in dogs was associated with defects in monocytic phagocytosis, cyclic CD8+ T lymphopenia, and impaired antigen presentation within lymph nodes.[24,27] Dogs infected with *Bartonella* species may have a positive Coombs' test associated with immune-mediated hemolytic anemia (see ch. 198). Antinuclear antibodies also may be present, which can result in a misdiagnosis of systemic lupus erythematosus (SLE; see ch. 205). In dogs with *Bartonella* endocarditis, myocarditis or cardiac arrhythmias, other common hematologic and biochemistry abnormalities include eosinophilia and neutrophilia (rarely accompanied by left shift).[45]

Electrocardiography

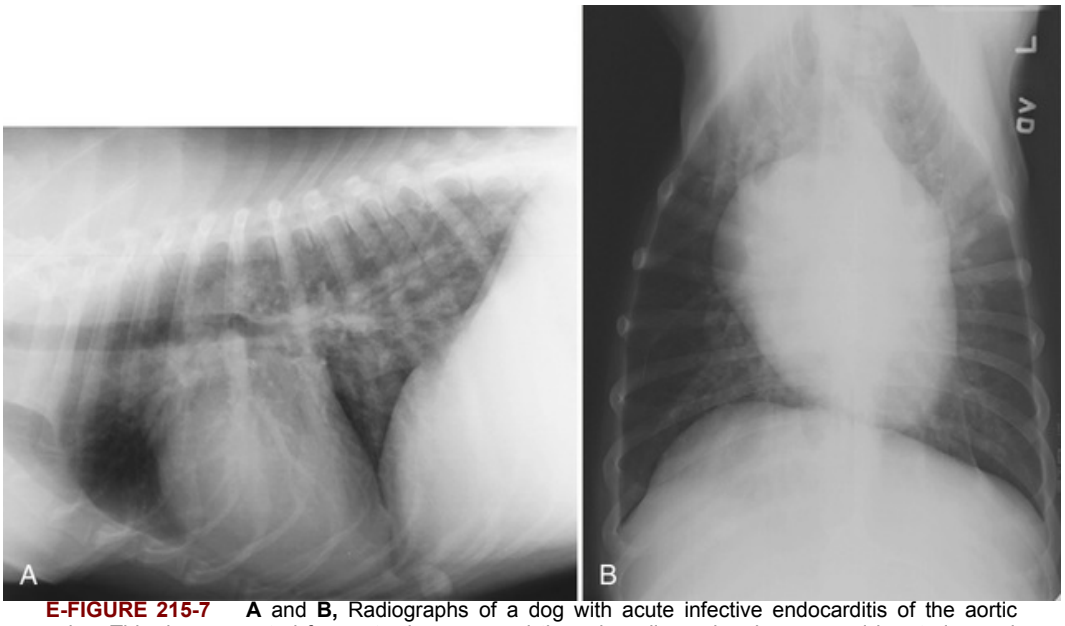
Cardiac arrhythmias can be detected in 9% to 60% of dogs infected with *Bartonella* species (see ch. 103).[15,42,45] Higher frequency of arrhythmias was seen in cases with endocarditis or myocarditis, characterized by sinus tachycardia, atrial fibrillation, intermittent ventricular premature complexes, ventricular tachycardia or third-degree atrioventricular block (see ch. 248).[45]

Cardiac Biomarkers

Cardiac troponin I (cTnI) was elevated (0.28 to 3.05 ng/mL, normal ≤0.11 ng/mL) in three out of eight dogs infected or exposed to *B. henselae* or *B. vinsonii* subsp. *berkhoffii* in Brazil; these dogs also presented other cardiovascular abnormalities such as hypotension and myocardial dysfunction.[46] Since other vector-borne diseases such as ehrlichiosis and babesiosis can also cause increases in cTnI levels,[47] it is important to rule out other infectious and non-infectious causes of myocardial injury (see ch. 246).[48]

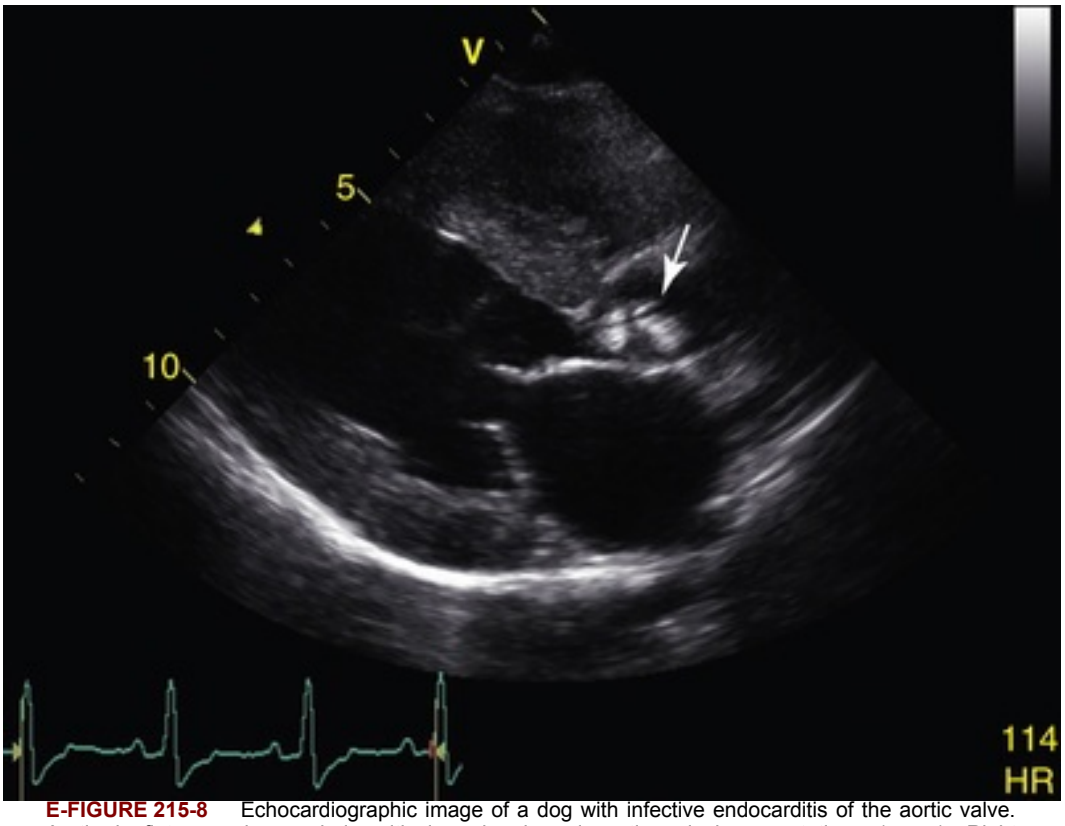
Diagnostic Imaging

Dogs with *Bartonella* endocarditis often present with cardiogenic pulmonary edema, identified on thoracic radiographs by perihilar to caudodorsal interstitial to alveolar pulmonary infiltrates with absence of left atrial enlargement or global cardiomegaly (E-Figure 215-7).[34] Echocardiography is very sensitive for detecting abnormalities suggestive of endocarditis, such as hyperechoic, oscillating, and irregular-shaped valvular vegetations or thickened and hyperechoic valve leaflets (E-Figure 215-8 and Video 215-1; see ch. 251). Insufficiency of the affected valve is always present, and most often is moderate to severe.[34] In dogs with *Bartonella*, decreased systolic function (characterized by decrease in fractional shortening) and left ventricular enlargement or eccentric hypertrophy have been reported.[46] Ultrasonography should be used to evaluate the presence of lymphadenopathy, organomegaly, peritoneal fluid or suspected pyogranulomatous disease (see ch. 88). The ultrasound findings reported in a dog infected with *B. henselae* and presenting with peliosis hepatis included hepatomegaly with multiple, small, nodular masses and fluid-filled cyst-like structures.[49] Granulomatous disease can be identified on ultrasound by the presence of enlarged lymph nodes, but must be confirmed by histopathology.[39]



E-FIGURE 215-7 **A** and **B,** Radiographs of a dog with acute infective endocarditis of the aortic valve. This dog presented for acute dyspnea, and thoracic radiographs show normal heart size and diffuse interstitial pulmonary infiltrates of the caudal lung lobes. The pulmonary veins are mildly distended. Because of the lack of cardiomegaly, there was debate about whether the infiltrates were cardiogenic, and measurement of markedly elevated pulmonary capillary wedge pressure confirmed left heart failure as the cause of the infiltrates. This dog had acute aortic insufficiency from *Bartonella* endocarditis of the aortic valve, causing acute cardiogenic pulmonary edema without overt

cardiomegaly. (From MacDonald K: Infective endocarditis in dogs: diagnosis and therapy. *Vet Clin North Am Small Anim Pract* 40(4):665-684, 2010. Reprinted with permission.)



E-FIGURE 215-8 Echocardiographic image of a dog with infective endocarditis of the aortic valve. Aortic leaflets are hyperechoic with irregular-shaped aortic valvular vegetations (arrow). Right parasternal long axis left ventricular outflow tract view. (Photo courtesy Kursten Roderick, DVM, Cummings School of Veterinary Medicine, Tufts University, North Grafton, MA, USA.)

Specific Techniques

Molecular Diagnostic Methods

In all cases of suspected bartonellosis, clinical samples (EDTA-blood, serum, plasma, tissues, etc.) should always be collected prior to antibiotic therapy and stored in −20°C, as antimicrobials rapidly decrease the chances of detection of *Bartonella* species by culture or PCR assays. Samples from tissue and non-blood fluids (effusion, synovial fluid, etc.) from affected organs should be preferentially tested by culture and PCR, as they may provide better clinical sensitivity than blood samples. Molecular diagnostic tests such as PCR assays are highly sensitive and specific for the targeted pathogens and have faster turnaround time (1 to 3 days) than culture. PCR assays for the genus *Bartonella* or selected species are available at private veterinary reference laboratories and at selected university laboratories in the United States as part of vector-borne PCR panels; however, analytical sensitivity and specificity among laboratories may vary. The diagnostic value of PCR assays depends upon the type of sample tested. Dogs generally maintain very low bacteremic levels of *Bartonella* species (<1 to 10 organisms/mcL),[2] that can be below the limit of detection of the PCR assay. Therefore, in cases other than endocarditis, blood samples may not be the optimal diagnostic clinical specimen. In addition, negative PCR or culture results do not rule out *Bartonella* infection in dogs. Formalin-fixed paraffin-embedded tissues can be used for the detection of *Bartonella* species; however, stringent procedures must be established to avoid cross-contamination of *Bartonella* DNA in the necropsy room and during the processing of tissue samples.[50]

Serologic Methods

The detection of antibodies to *Bartonella* species can be performed by immunofluorescent antibody (IFA), enzyme-linked immunosorbent assay (ELISA) or Western immunoblot assays.

High *Bartonella* serologic titers (>1 : 512) are useful to diagnose aortic valve endocarditis due to *Bartonella* species.[33] However, in dogs with other local or systemic disease, serology results alone may be of limited diagnostic value as bacteremia may occur in the absence of detectable antibodies in over half of the dogs.[43] Species-specific assays for *B. henselae, B. vinsonii* subsp. *berkhoffii* and *B. rochalimae* and *B. clarridgeiae* are available. However, some degree of cross-reactivity was initially suggested based on the frequent number of naturally exposed dogs seroreactive to more than one antigen.[10] Conversely, a recent experimental study in dogs demonstrated that canine antibody response was not only species specific for *B. henselae* or *B. vinsonii* subsp. *berkhoffii* but also genotype or serotype specific within each species.[51] Therefore, a dog infected with a specific *Bartonella* type may not mount a detectable antibody response to other bacterial types under the same species, which may explain the discrepancy between serology and culture/PCR results. With four distinct genotypes of *B. vinsonii* subsp. *berkhoffii* reported in dogs (I-IV), as well as two serotypes of *B. henselae* (I and II), these new findings may indicate that the use of serologic methods may be problematic unless extensive serology panels are made available for several *Bartonella* species, genotypes and serotypes.[51] At the time of writing, no commercially available *Bartonella* serology panel provides differentiation among genotypes and serotypes of *Bartonella* species.

Culture Methods

The gold standard for microbiologic detection of *Bartonella* species is achieved by obtaining isolates in solid culture media, which may take 4 to 8 weeks. However, some wild types of *Bartonella* do not easily adapt to laboratory conditions. Often, PCR-positive samples fail to yield isolates and can only be characterized based on DNA amplification and sequencing. In addition, the low level and cyclic bacteremia in dogs and the slow growth of *Bartonella* species limit the diagnostic value of culture methods.

A combined approach using enrichment culture coupled with DNA amplification and sequencing (so-called "enrichment PCR") is available in the United States.* This combined approach uses a chemically modified insect-based cell liquid media (*Bartonella* alpha-Proteobacteria Growth Medium [BAPGM])[52] to increase the number and variety of organisms for PCR detection and solid media isolation. This approach provides results in 3 weeks, with a broader spectrum of *Bartonella* species detected.[2] However, similar to serology and PCR assays, negative results do not rule out infection. Currently, this is one of the most successful diagnostic techniques available, detecting 55% more dogs infected with *Bartonella* species than a single PCR assay from blood or tissue.[43] In humans, higher clinical sensitivity was reported when blood samples were drawn on three separate days over the course of a week (so-called "triple draw") because of relapsing bacteremia.[53] A similar approach may be considered in dogs suspected of bartonellosis that are chronically and systemically ill when serology and single enrichment PCR tests fail to identify exposure to or infection with *Bartonella* species.

Microscopy

Blood smear examination for detection of intraerythrocytic *Bartonella* species has very limited diagnostic value due to the size of the bacterium and intermittent bacteremia. *Bartonella* species can only be visualized on tissue samples stained with modified silver stains (e.g., Warthin-Starry stain or Dieterle's stain) but other pathogens can also be stained. At research laboratories, immunohistochemistry and fluorescent *in situ* hybridization has been used for specific identification of *Bartonella* species in tissue samples.

Treatment

To date, an optimal protocol has not been established for the treatment of *Bartonella* infections in cats, dogs, or people.[2,54] Randomized controlled trials using sensitive diagnostic tools and evaluating several outcomes of interest (persistent bacteremia, clinical cure, adverse effects, development of endocarditis, relapse rate, and mortality) are needed to support antimicrobial protocols.[54] Current recommendations are based upon limited case series, experimental studies, clinical experience and data extrapolated from the human literature. Single-agent therapy with doxycycline or azithromycin is no longer recommended because of treatment failure and the risk of rapid development of antimicrobial resistance.[40,41,55] Currently, long-term therapy with a combination of two antibiotics with different modes of action, one achieving high plasma concentrations and the other achieving high intracellular concentrations (E-Table 215-2), is the best available recommendation

until other antibiotics or antibiotic combinations are proven to be effective. A third-generation fluoroquinolone (pradofloxacin) has demonstrated better antimicrobial activity against human and feline *Bartonella* isolates than enrofloxacin,[55] but to date this drug has only been approved for use in cats in the United States. Minocycline could be considered in case of doxycycline shortage, since it has demonstrated good *in vitro* antimicrobial activity against *B. henselae* isolates from cats and humans in one study,[56] but its activity against *Bartonella* isolates from dogs is unknown. For seroreactive dogs, response to therapy can be monitored based upon decrease in antibody titers after weeks to several months with effective antimicrobial therapy. Monitoring bacteremia by enrichment PCR at two and six weeks after completion of antibiotic therapy may also be used to infer about therapeutic cure. However, it is unclear if true elimination of the pathogen can be achieved with any antibiotic regimen. If the patient is reasonably stable, the second antibiotic should be started five to seven days after the first antibiotic, in order to decrease the risk of Jarisch-Herxheimer reaction.[57] The reaction, characterized by lethargy, fever, and vomiting (signs similar to bacterial sepsis), tend to occur within the first week after starting antibiotics. It is caused by rapid death of bacteria caused by the adequate intracellular and intravascular drug concentrations, with consequent release of endotoxins triggering the systemic inflammatory response syndrome (SIRS; see ch. 132). Clinicians should avoid interrupting antimicrobial therapy or switch antibiotics based on a suspected adverse drug reaction in such cases. A short-term course of corticosteroids at anti-inflammatory dosages can be used for alleviating these signs.

E-TABLE 215-2

Current Recommended Antibiotic Dosages for Canine Bartonellosis

ANTIBIOTIC COMBINATION	DOSE	INTERVAL (HOURS)	ROUTE	MINIMUM DURATION (WEEKS)	RECOMMENDED SCENARIO
Doxycycline with enrofloxacin*	5–10 mg/kg 5 mg/kg	12 12	PO PO	6 6	Long-term home therapy
Doxycycline with rifampin	5–10 mg/kg 5 mg/kg	12 24	PO PO	6 4–6	CNS infections
Azithromycin with rifampin	5–10 mg/kg 5 mg/kg	24 24	PO PO	6† 6	CNS infections
Doxycycline with amikacin	5–10 mg/kg 15–20 mg/kg	12 24	PO IV/IM/SC	6 See notes‡	Endocarditis or during hospitalization

*Other fluoroquinolones might be considered, but experimental or clinical data are not available. See text for details.

†Initially given every 24 hours for 7 days, followed by every other day for an additional 5 weeks.

‡It should be used only during inpatient treatment, because it requires parenteral administration and renal function monitoring.

CNS, Central nervous system.

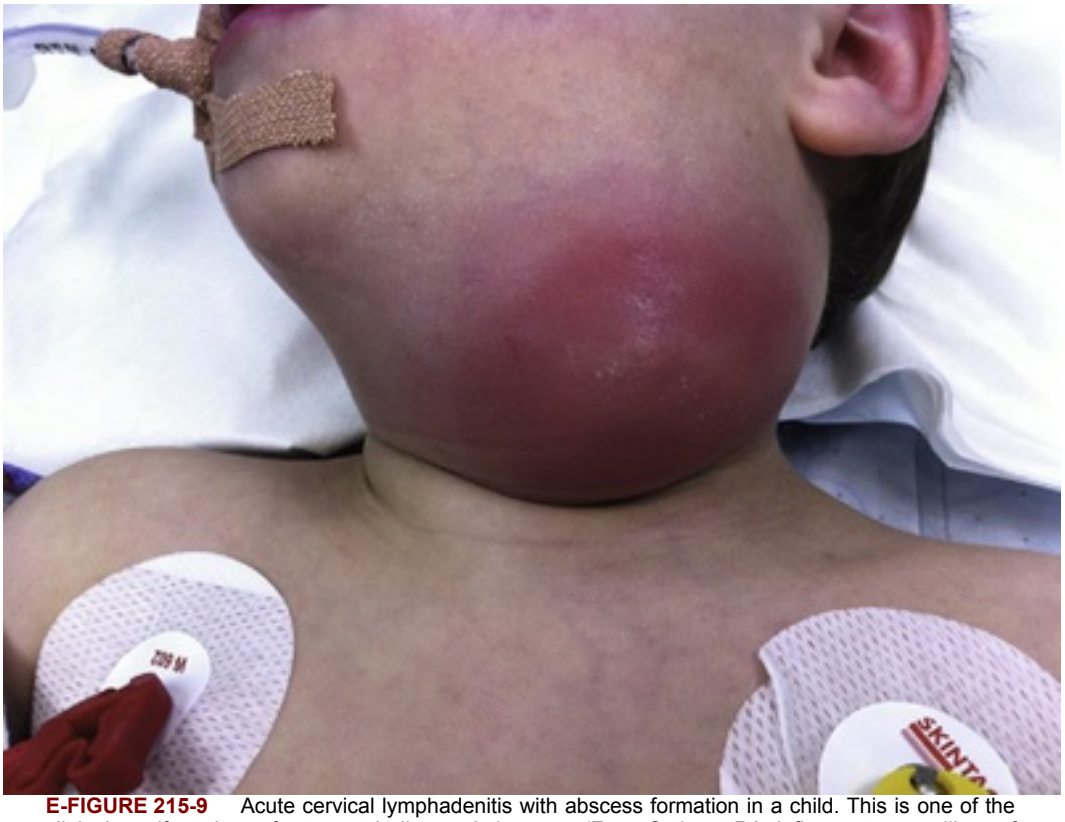
Prevention

Currently, there are no available vaccines against *Bartonella* species for dogs, cats or humans; therefore, the prevention of infection is based on vector control. Veterinarians should educate clients about the importance of year-around ectoparasite control for dogs and cats to prevent the transmission of *Bartonella* species, as well as other vector-borne pathogens.

Public Health Considerations

The most commonly recognized manifestation of *Bartonella* infection in humans is cat scratch disease, a syndrome characterized by a cutaneous papule or pustule associated with regional lymphadenopathy ipsilateral to the inoculation site (E-Figure 215-9), and fever caused by *B. henselae* and potentially *B. clarridgeiae.* However, similar to dogs, *Bartonella* infection in humans can cause an array of clinical manifestations. An increasing number of publications has suggested *Bartonella* as a newly recognized occupational hazard for veterinarians and veterinary technicians, among other professions with frequent

contact with animals and exposure to blood-sucking arthropods.[4,58] In a recent report on 114 veterinary subjects, over one in four of those was infected with *Bartonella* species, with headaches and irritability being more frequently reported among infected subjects than uninfected veterinarians.[4] Other reports describe infected veterinarians experiencing chronic fatigue, frequent headaches, chronic undulant fever, persistent back pain, and lymphadenopathy.[59,60] Consequently, veterinarians not only must be aware of their risk of infection with *Bartonella* species, but also must play an important role in public health by advising clients about the disease and the steps towards minimizing or eliminating exposure.[61] Precautions should be taken to avoid exposure to fleas and other potential vectors, contact with arthropod feces, bites and scratches from animals, and direct contact with bodily fluids from sick animals.[2] Direct transmission of *Bartonella* species from dogs to humans through bites or scratches has not yet been clearly established, but dogs should not be allowed to lick open human wounds, as *Bartonella* DNA was detected in dog saliva.[62]



E-FIGURE 215-9 Acute cervical lymphadenitis with abscess formation in a child. This is one of the clinical manifestations of cat scratch disease in humans. (From Cathcart RA: Inflammatory swellings of the head and neck. *Surgery* 30(11):597-603, 2012. Reprinted with permission.)

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CHAPTER 216

Bartonella—Feline

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Client Information Sheet: *Bartonella* Infection in Cats

Background

Bartonella spp. are small, vector-transmitted, facultatively intracellular, Gram-negative bacteria. Most *Bartonella* species appear to be highly adapted to mammalian reservoir hosts. Bartonellae often cause a long-term, intermittent bacteremia in clinically normal animals.[1,2] The mechanisms that facilitate persistent *Bartonella* bacteremia in mammals are not yet completely understood. Intracellular localization, frequent genetic rearrangements, and alteration of outer membrane proteins are strategies for immune system evasion and bacterial persistence.[1-5] Location in erythrocytes (RBCs) may facilitate efficient vector transmission and potentially contribute to decreased antimicrobial efficacy.[6] *Bartonella* species are also reported to colonize vascular endothelial cells, and, based on work done in a rodent model, may be periodically released from these cells into the circulation, where they may be found extracellularly and within RBCs.[3,7] This discussion will focus on *B. henselae,* the *Bartonella* species most commonly isolated from domestic cats. Other species that may naturally infect cats, *Bartonella clarridgeiae, B. koehlerae, B. bovis,* and *B. quintana,* are also discussed.

Epidemiology

Since the first recognition of feline *B. henselae* infection in 1992, results of serologic, blood culture, and polymerase chain reaction (PCR) tests indicate that exposure to *Bartonella* spp., most frequently *B. henselae,* is prevalent among cats in the United States and throughout most temperate regions of the world.[8] Prevalence is higher in areas with warmer temperatures and higher humidity, in feral cats, and in cats infested with fleas. Older cats appear more likely to be seropositive and younger cats to be bacteremic.[9-14] *B. henselae* bacteremia affects about 5% to 40% of domestic cats in the United States depending on geographic location.[10,12,15-17] A prevalence of over 90% was reported in one cat colony.[18] *B. clarridgeiae* infections accounted for about 10% of cats with *Bartonella* bacteremia evaluated in the United States, and 16% to 31% of cats with *Bartonella* bacteremia in France and the Philippines.[19,20] *Bartonella koehlerae* was recently detected in approximately 4% of cats tested in Israel. *Bartonella bovis* and *B. quintana* have been isolated or detected by PCR in a few healthy domestic cats.[21-23]

Domestic cats are considered the primary reservoir and vector for human infection with *B. henselae.* Cats are also likely reservoirs for *B. clarridgeiae* and *B. koehlerae.* Cattle appear to be the reservoir for *B. bovis.* Molecular methods have detected *B. quintana, B. koehlerae, B. henselae, B. clarridgeiae,* and a range of other *Bartonella* species in cat fleas, along with rickettsial pathogens.[24,25] While this may suggest flea involvement in transmission of all of these *Bartonella* species, the fleas may have just fed on an infected host. Flea competence for transmitting some *Bartonella* species has not yet been verified. Wild felids, including panthers, bobcats, mountain lions, pumas, African lions, and cheetahs, are also exposed to *Bartonella* species.[23]

There are multiple genetically diverse strains of *B. henselae.* Two recognized 16S rRNA types of *B. henselae* exist, with at least two subgroups within each type.[26,27] Other methods of classifying *B. henselae* include multilocus sequence typing and amplified fragment length polymorphism. Each method has identified multiple genetic types of *B. henselae.*[28] Cats can be co-infected with multiple genetic types of *B. henselae* and multiple *Bartonellas,* with regional differences.[15,19,28-31] All molecular methods also show remarkable genetic

diversity among *Bartonella* isolates and evidence of genomic variations during the course of infection.[5,32-40] Such variation may enhance the ability of *B. henselae* to persist in infected cats for prolonged periods. Genetic variation makes vaccine development difficult, but is useful in epidemiologic studies, and in further understanding the pathogenicity of various *Bartonella* isolates.

Pathogenesis

Bartonella henselae is naturally transmitted among cats by cat fleas. *Bartonella henselae* was transmitted among cats by transferring fleas fed on naturally infected cats to specific pathogen–free (SPF) cats and by intradermal (ID) inoculation of excrement collected from fleas fed on *B. henselae*–infected cats.[41-43] Transmission via flea saliva has not been documented.[41] However, a recent study suggests that *B. henselae* may be transmitted via flea regurgitation during feeding, similar to what is described for *Yersinia pestis* transmission.[44] Ticks may also have a role in transmission; *B. henselae* and other *Bartonella* spp. were detected by PCR in questing ticks.[45-47] Transstadial transmission of *B. henselae* has been demonstrated in *Ixodes ricinus* ticks, likely competent vectors for *B. henselae.* Blood-feeding arthropods have been proposed as vectors for transmission of *Bartonella* infections in cats, human beings, dogs, and other mammals.[48-52]

Cats may become infected through IV or IM inoculation with infected cat blood or by IV, SC, ID, or oral routes of inoculation with plate-grown bacteria. Infection did not occur when cats were injected with urine of bacteremic cats.[53-59] *Bartonella henselae* transmission fails when infected cats cohabit with uninfected cats in a flea-free environment. Thus, transmission among cats does not normally occur through cat bites, scratches, grooming, or sharing of food dishes and litterboxes. Transmission does not occur between bacteremic females and males during mating, or to kittens of infected females during gestation or in the neonatal period in flea-free environments.[53,57,60] Chronic, relapsing bacteremia is believed to facilitate transmission of *Bartonella* by blood-feeding arthropods. Experimentally infected cats maintained relapsing *B. henselae* or *B. clarridgeiae* bacteremia for as long as 454 days.[54] Naturally infected cats maintained recurrent bacteremia for up to 3 years; however, reinfection of these cats via fleas likely occurred.[61,62]

While cats mount a strong immune response to *Bartonella* infection, a lack of heterologous protection against reinfection was demonstrated in previously infected cats. Cats previously infected with *B. henselae* 16S rRNA type II were susceptible to infection with *B. henselae* 16S rRNA type I.[63] Cats infected with *B. henselae* type I or II were susceptible to challenge infection with *B. clarridgeiae,* and cats infected with *B. koehlerae* or *B. clarridgeiae* were susceptible to challenge infection with *B. henselae* type I or type II. However, cats infected with *B. henselae* type I were partially or completely protected against challenge infection with *B. henselae* type II.[64] Cats can become immune to challenge with homologous strains of the organism. The level of bacteremia and degree of susceptibility to reinfection following challenge inoculation is likely to vary with *Bartonella* species and strain.[62] Chronic location of *Bartonella* in cats has not been completely determined. Bartonellae have been detected within RBCs of naturally infected cats.[65] *Bartonella* may localize within vascular endothelial cells, as has been suggested for rodents, and may also infect dendritic cells or other cells in SC tissue after ID inoculation.[66,67]

Clinical Findings

Existing data indicate that few cats naturally infected with *Bartonella* have clinical signs. Uveitis may be a manifestation of natural *Bartonella* infection.[68] Natural *Bartonella henselae* type I infection was associated with fatal blood-culture–negative vegetative aortic valve endocarditis in one cat and an experimentally infected cat developed fatal myocarditis.[69,70] Whether *Bartonella* spp. contribute to argyrophilic bacteria in lymph nodes of young cats with persistent lymphadenomegaly is unknown.[71] Naturally infected cats usually have subclinical signs. Clinical signs in cats experimentally infected with *B. henselae* are usually mild. Cats with experimental intradermal inoculation developed areas of induration or abscess at inoculation sites 2 days to 4 weeks later. Pure *B. henselae* cultures were obtained from those sites (Figure 216-1).[54,56,58,59,72]

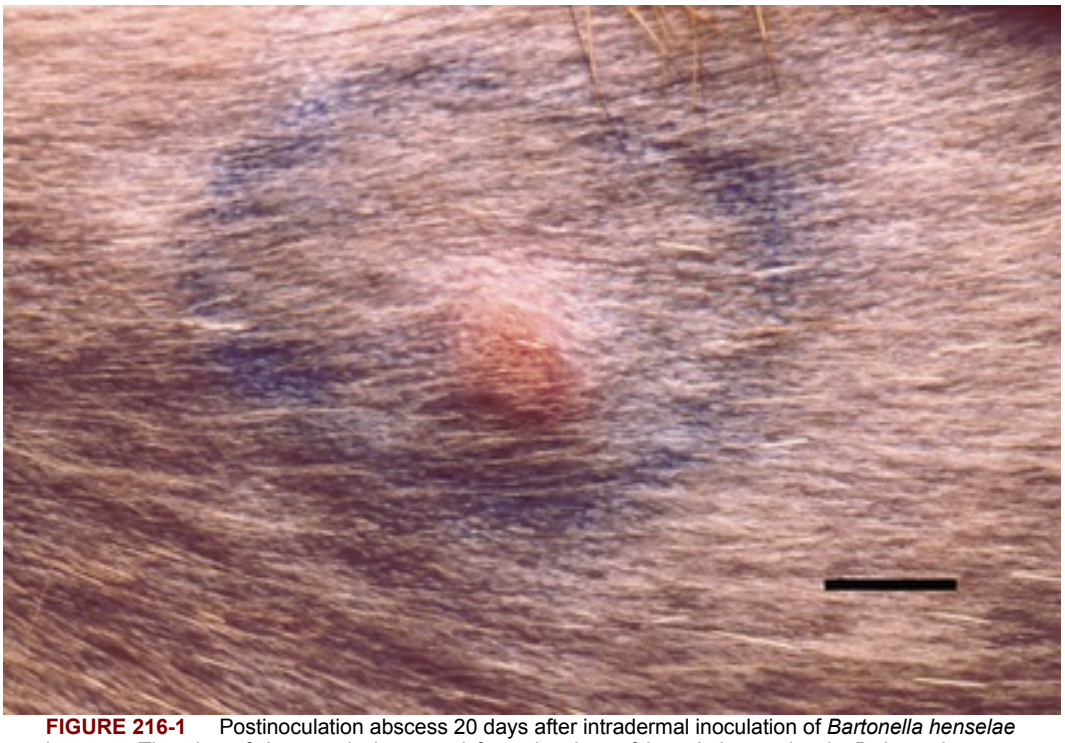

FIGURE 216-1 Postinoculation abscess 20 days after intradermal inoculation of *Bartonella henselae* in a cat. The size of the papule increased from the time of inoculation and only *B. henselae* was isolated from bacterial culture of an aspirate. Bar = 1 cm. (Courtesy Lynn Guptill-Yoran, Purdue University, West Lafayette. In Greene CE: *Infectious diseases of the dog and cat*, ed 4, St Louis, 2012, Saunders.)

Other transient clinical findings in many experimentally infected cats included generalized or localized peripheral lymphadenomegaly (lasting for about 6 weeks following inoculation), and brief periods of fever (>39.4° C [103° F]) in the first 48 to 96 hours and again about 2 weeks later. Mild neurologic signs (nystagmus, whole body tremors, focal motor seizures, decreased or exaggerated responses to external stimuli, behavior changes) and epaxial muscle pain were seen in a few experimentally inoculated cats. Some cats were lethargic and anorexic during febrile periods.[54,56,58,59] Reproductive failure occurred in some cats experimentally infected with *B. henselae*.[60] Cats experimentally infected with *B. koehlerae* exhibited no clinical signs.[73] A potential causative role of *Bartonella* spp. in chronic diseases of cats seems likely. One study suggested that co-infection of cats with *B. henselae* and feline immunodeficiency virus (see ch. 222) was more likely to be associated with gingivitis or lymphadenomegaly than either infection alone.[74] One study suggested possible associations between *B. henselae* seroreactivity and stomatitis or unspecified urinary tract disorders.[75]

Because of the high *Bartonella* prevalence in cats, extensive, controlled, epidemiologic studies are needed to determine whether particular clinical conditions are associated with infection. Some studies have investigated potential associations between *Bartonella* infection or exposure and clinical conditions such as neurologic disease, stomatitis, uveitis, plasmacytic pododermatitis, anemia, hyperglobulinemia, high serum pancreatic lipase immunoreactivity, inflammatory polyps, chronic rhinosinusitis, peliosis hepatis and fever. There was no statistically significant association of *Bartonella* with most of the aforementioned conditions in cats, though power may not have been sufficient to detect some associations.[74-86] *Bartonella* infection may be associated with hyperglobulinemia.[80] Association between oral disease in cats and *Bartonella* exposure has varied among studies; an association between seroreactivity and stomatitis was suggested in one study, no association was reported in another, and then an association was reported between *Bartonella* bacteremia and oral disease, but not between *Bartonella* seroreactivity and oral disease.[74,87,88] There was an inverse relationship between *Bartonella* seroreactivity and pain associated with degenerative joint disease in a group of cats.[89] Studies that rely solely on *Bartonella* seroreactivity to evaluate disease associations should be interpreted with caution. The high prevalence of *Bartonella* exposure among cats makes it difficult to determine which clinical conditions may be truly associated with infection, particularly in cats exposed to arthropod vectors.

Diagnosis

Overview

Most clinical signs or clinical pathological abnormalities attributed to feline *Bartonella* are nonspecific. Determining which cats are likely infected with *Bartonella* and whether that infection is responsible for clinical signs, is difficult. In addition to testing for *Bartonella* infection in sick cats, veterinarians may be asked to test healthy pet cats belonging to clients with *Bartonella*-related illnesses. One may screen healthy cats being considered as blood donors or as pets for people considered most susceptible to *Bartonella* infections (see Public Health). It is important to approach the diagnosis of feline bartonellosis in a careful, systematic manner.

Routine Laboratory and Pathologic Findings

Most experimentally infected cats have no abnormalities on complete blood count (CBC), serum biochemistries, or urinalysis. Some cats had early transient anemia and some had persistent eosinophilia.[54] Mature neutrophilia occurred in some cats during periods of skin inflammation.[56] Hyperglobulinemia has not been reported in experimental *Bartonella* infections of cats, but results of a study on samples collected from a commercial veterinary laboratory reported a potential association between hyperglobulinemia and *B. henselae* seroreactivity.[80] However, no clinical or historical data were available and *B. henselae* DNA was not detected. If cats have unexplained hyperglobulinemia, it may be useful to evaluate for *Bartonella* using culture and PCR.

Visualizing *B. henselae* in RBCs of infected cats has not been effective using conventional staining methods and microscopy. Confocal microscopy and special staining has been effective, and intra-RBC locations of *B. henselae, B. clarridgeiae,* and *B. koehlerae* have been documented in cats using fluorescence methods.[90,91] Acute and chronically infected cats had hyperplasia of lymphoid organs and small foci of lymphocytic, pyogranulomatous, or neutrophilic inflammation in lung, liver, spleen, kidney, or heart (Figures 216-2 and 216-3).[54,56]

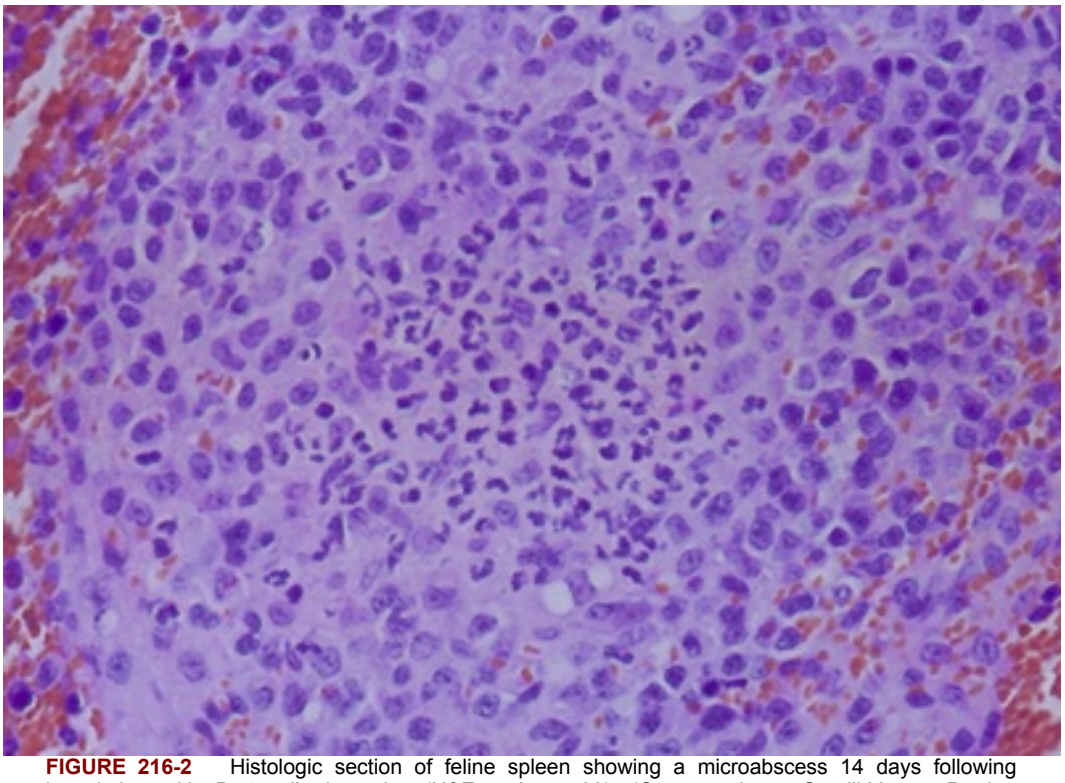

FIGURE 216-2 Histologic section of feline spleen showing a microabscess 14 days following inoculation with *Bartonella henselae* (H&E stain, ×400). (Courtesy Lynn Guptill-Yoran, Purdue University, West Lafayette. In Greene CE: *Infectious diseases of the dog and cat,* ed 4, St Louis, 2012, Saunders.)

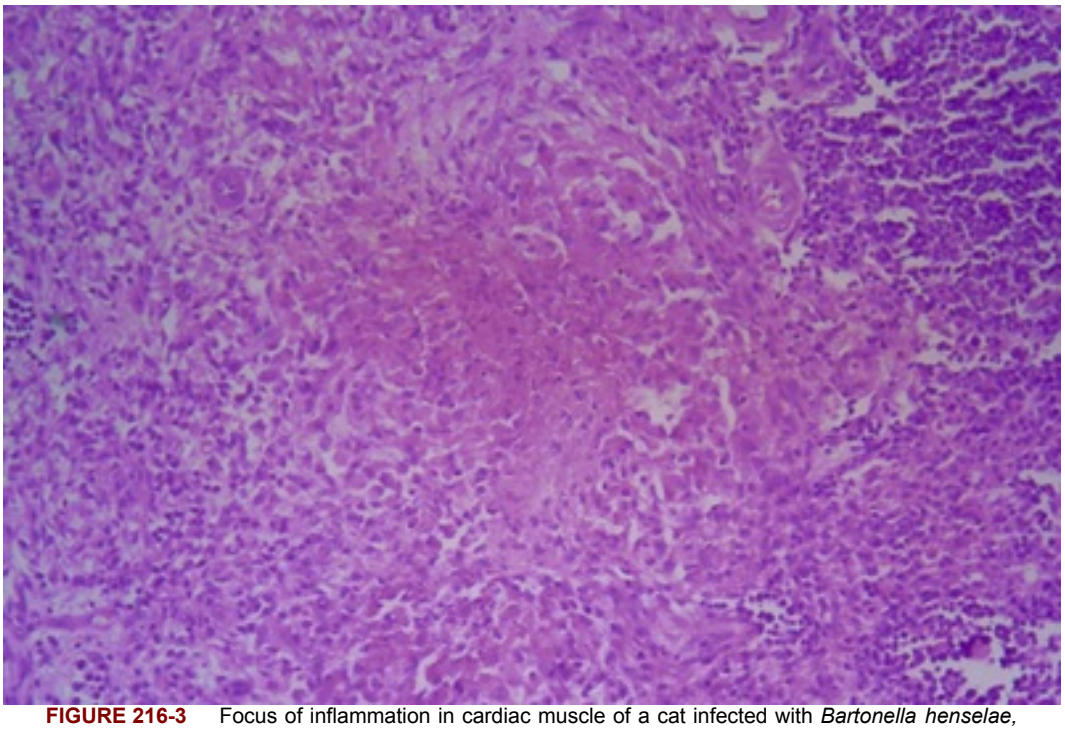

FIGURE 216-3 Focus of inflammation in cardiac muscle of a cat infected with *Bartonella henselae*, days following inoculation (H&E stain, ×400). (From Guptill L, Slater L, Wu CC, et al: Experimental infection of young specific pathogen-free cats with *Bartonella henselae*. *J Infect Dis* 176:206-216, 1997.)

Bacterial Isolation

A positive blood or other tissue culture is definitive for active *Bartonella* infection. However, because of the relapsing nature of detectable *Bartonella* bacteremia in cats, culture is not always sensitive. Use of enrichment media improves culture sensitivity, as does testing more than one sample.[92,93] Blood culture is indicated for ill cats whose history and clinical presentation suggest *Bartonella* infection or when a client's physician requests testing. Blood for culture should be obtained using sterile technique and the blood placed in EDTA-containing or lysis centrifugation blood culture tubes (Isolator tubes, Wampole, Cranbury, NJ). If collected into EDTA tubes, blood should be chilled or frozen for shipment.[94,95] Blood should be sent to laboratories familiar with culture of these fastidious organisms. The laboratory should be contacted for specific instructions regarding sample collection and submission. *Bartonella* growth from blood or other tissue samples is often slow and may be several weeks.

Serologic Testing

Serum antibodies have limited value for diagnosing active *Bartonella* infection since serologic tests overestimate infection. Serology is useful for epidemiologic surveys. Serum IgG antibodies persist in experimentally infected cats for prolonged periods; how long antibodies persist after clearing infection is not known. Indirect fluorescent antibody (FA), enzyme immunoassay (EIA), and Western blot tests are available. Because of the genetic diversity of *Bartonella* organisms, infections with some strains or species of *Bartonella* may be missed regardless of the method used.[96,97] The positive predictive value of FA or EIA (IgG) serologic tests for bacteremia was only 39%-46%; however, methods used to establish bacteremia were not ideal.[23,28] The utility of a negative serologic result may be greater, as the negative predictive value for these tests is 87%-97%.[10,15,30,31] However, some seronegative bacteremic cats exist. No cutoff values for serologic results have been established as confirmatory of current *Bartonella* infection.[64] In people, variability in Western blot testing results has been problematic.[97,98] No difference in Western blot patterns was noted from infected cats evaluated over the course of infection.[54] Results of one study[99] agree with our findings: antibodies in sera of infected cats react with an increasing number of bands of polyacrylamide gel-separated proteins over the course of infection.

Nucleic Acid Detection

Standard PCR testing for DNA may be no more sensitive than blood culture in detecting active *Bartonella* infection. Detection of DNA does not always equate to presence of living organisms. Use of high resolution melt PCR improves sensitivity for detecting *Bartonella* infections in cats. With either culture or PCR, some infections are missed. Combining these two methods is better than either alone.[23,28] PCR has the added benefit of identifying the species and/or strain of *Bartonella* by sequencing the reaction product. Results of PCR testing are available more quickly than results of blood culture. Blood samples for PCR should be obtained using sterile technique. Care must be taken in sample collection and processing to avoid sample contamination and DNA degradation. Laboratories experienced in molecular diagnostics should be used and should be contacted for submission guidelines and test validation data.

Summary

When testing ill cats for *Bartonella* infection, the combination of bacterial culture and PCR appears to be the most sensitive diagnostic approach. Serology can be sensitive for evaluating exposure to *Bartonella* species, but positive serologic results may not indicate active infection.

Therapy

Antibiotic Review

Documenting clearance of *Bartonella* infections through antibiotic treatment is difficult due to the prolonged and relapsing nature of bacteremia. No antibiotic regimen has proven effective in controlled studies with long-term follow-up.[72,100-102] Enrofloxacin (5.4 to 7.6 mg/kg PO q 12 h) for 14 or 28 days appeared to clear *B. henselae* or *B. clarridgeiae* infection in 4 of 6 or 5 of 7 treated cats, respectively, followed for 12 weeks after treatment.[101] However, enrofloxacin causes retinal degeneration in cats and use of dosages of greater than 5 mg/kg/day is contraindicated.[103] Pradofloxacin was effective *in vitro;* however, resistance to pradofloxacin developed in *B. henselae* after 5 *in vitro* passages.[104,105] This potential for acquired resistance should be taken into consideration when planning treatment. Fluoroquinolones are not recommended for single agent treatment of humans with bartonellosis.[106,107] Doxycycline (4 to 12 mg/kg PO q 12 h) cleared bacteremia in 1 of 6 cats treated for 14 days and 1 of 2 cats treated for 28 days.[101] In some experimental infections, an effective doxycycline dosage in cats was 10 mg/kg q 12 h (Greene CE, personal communication). Antibiotics tested in other studies, including erythromycin, amoxicillin, amoxicillin-clavulanate, and tetracycline, rapidly decreased the level of bacteremia in infected cats. However, in one study, treated and untreated cats became blood-culture negative after the same period of time, making proof of antibiotic efficacy challenging. In some studies, cats were not followed for more than 8 weeks, making it difficult to assess drug efficacy due to the possibility of chronic relapsing bacteremia.[72,102] Azithromycin was previously recommended for treatment of infected cats, but data from controlled efficacy studies with long-term follow-up are lacking. One study indicated *in vitro* resistance to azithromycin develops quickly.[108]

Treatment Recommendations

Treatment of people with *Bartonella* infections varies depending on the clinical manifestation and the patient's immunocompetence.[107] There are not enough data regarding different clinical forms of feline bartonellosis to allow development of guidelines specific to particular clinical conditions. Currently, doxycycline and pradofloxacin may be preferred initial antibiotics to consider for cats thought to have *Bartonella* infection. Successful treatment of endocarditis was reported in one cat with a treatment regimen including marbofloxacin and azithromycin.[109]

Because treatment with antibiotics may induce resistant strains, treatment should be reserved for use only in *Bartonella*-positive cats showing clinical signs. Although treatment reportedly decreases the level of bacteremia, there is little evidence that treatment will decrease probability of *Bartonella* transmission to fleas, other cats, or humans. Client education regarding the uncertainty of treatment efficacy, the need for prolonged follow-up, and the possibility of reinfection following treatment is essential. The importance of flea control and other means of preventing transmission (see Prevention) should be strongly emphasized.

Prevention

Prevention of *Bartonella* infections in cats is best accomplished by avoiding exposure to infected animals and fleas. Since *Bartonella* can be transmitted through inoculation of infected cat blood, cats should not receive blood transfusions from untested cats or cats known to be PCR-, culture-, or serologically positive for *Bartonella*.[55,110] No vaccine to prevent *Bartonella* infection in cats is available. Flea and tick control programs are of utmost importance in preventing infection. Flea control products have shown excellent efficacy in preventing transmission of *Bartonella henselae* via fleas.[70,111,112]

Public Health

Cat owners should be informed of the current understanding regarding how cats acquire *Bartonella* infections, how infection may be transmitted to people, the possibility of transmission by ticks, and the association of flea infestation with transmission. Multiple *Bartonella* species or subspecies are considered zoonotic or likely zoonotic.[113] Cats are the reservoir for several zoonotic *Bartonella* species, and may serve as a vector for transmission of *Bartonella* species to people. Transmission of *B. henselae* from cats to people is believed to occur most commonly through contamination of cat scratches or other wounds with flea excrement. Further study will determine whether flea bites may also be a source of zoonotic *Bartonella* transmission.[44] Transmission may also occur through cat bites, particularly if cat blood or flea excrement contaminate the bite site.[48,49]

Bartonella spp. cause a wide variety of clinical syndromes in people, including cat scratch disease (typical and atypical forms, including encephalopathies); bacillary angiomatosis and peliosis; parenchymal bacillary peliosis; relapsing fever with bacteremia; endocarditis; retinitis; pulmonary, hepatic, and splenic granulomas; osteomyelitis; and others.[107] Immunocompetent individuals usually have more localized infection, whereas infections in immunocompromised individuals may more often be systemic and can be fatal. *Bartonella* exposure is much greater in individuals that have exposure to animals than among individuals in the general population. Exposure to fleas and flea excrement should be considered a risk for transmission of *Bartonella*. Two reports suggest that needle-stick injuries, in addition to exposure to fleas, flea excrement, cat scratches, and cat bites may also represent risks for *Bartonella* transmission.[114,115]

Individuals working in the veterinary medical professions should consider bartonellosis an occupational hazard and take appropriate precautions (e.g., wearing gloves when handling animals infested with fleas and samples collected from these animals, avoiding needle-stick injuries, avoiding animal bites and scratches, washing hands after all animal encounters).[116,117] Common sense precautions to share with pet owners regarding avoiding transmission of *Bartonella* spp. from pets to people include: ongoing flea and tick control, avoiding interactions that result in scratches or bites, thoroughly washing bite or scratch wounds, washing hands after handling pets (particularly when pets are infested with fleas), seeking medical attention when necessary, and acquiring new pets of known good health status that are and have been ectoparasite-free.

Stray or shelter cats less than 1 year old are more likely to be *Bartonella* bacteremic. There is no evidence that declawing cats decreases the probability of transmission of *B. henselae* between cats and human beings. Guidelines from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America recommend the following when acquiring a new cat: adopt a cat older than 1 year of age that is in good health, avoid rough play with cats, maintain flea control, wash any cat-associated wounds promptly, and do not allow a cat to lick wounds or cuts.[106] The Guidelines note that there is no evidence to indicate any benefit to cats or their owners from routine culture or serologic testing of cats for *Bartonella* infections.[106]

Summary

Bartonella infections are zoonotic and have the potential to cause serious illness in people. Veterinarians must make it a priority to educate staff, volunteers, and clients regarding the risks for transmission of *Bartonella.* A large proportion of domestic cats harbor persistent *Bartonella* spp. infections. Ongoing and future studies will help to ascertain possible ramifications of chronic *Bartonella* bacteremia for feline health. Veterinarians should be aware of the high prevalence of feline *Bartonella* bacteremia and carefully consider their approach to evaluating cats for possible *Bartonella*-related clinical conditions. Based on current knowledge, healthy cats should not be routinely tested for *Bartonella,* and antibiotic treatment should not be recommended for healthy cats. When ill cats are treated, treatment should always be accompanied by comprehensive vector control

measures and client education. Client education should emphasize the role of fleas in *Bartonella* transmission and the importance of vector control programs in preventing transmission. Education should also emphasize other potential avenues for transmission and address the potential risks associated with antibiotic treatment, the likelihood of reinfection of a cat following antibiotic treatment, and the zoonotic potential of *Bartonella.*

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CHAPTER 217

Leptospirosis

Simone Schuller

Client Information Sheet: Leptospirosis

Etiology

Leptospirosis is a zoonotic disease of worldwide distribution that affects most mammalian species.[1] It is caused by spirochetes of the genus *Leptospira.* Leptospires are thin, elongated, highly motile, helically coiled organisms that can be differentiated from other spirochetes by their distinct hooked ends[2] (Video 217-1). Leptospires have Gram-negative staining properties but have phenotypic features of both Gram-negative and Gram-positive bacteria.[3] The taxonomy of the genus *Leptospira* is fairly complex and a source of confusion, as serological and genotypic typing are used in parallel. Serological classification is based on differences in the carbohydrate component of leptospiral lipopolysaccharide.[2] Antigenically related serovars are grouped into serogroups. Currently, over 250 known pathogenic serovars have been identified, belonging to 24 serogroups.[4] Genotypic classification based on DNA hybridization has defined 20 species of *Leptospira* including 9 pathogenic, 6 saprophytic, and 5 intermediate species, and new species are being added as they are discovered. Serologic and genotypic classifications do not always concur, in that serovars of the same serogroup can belong to different genomic species. The accepted nomenclature is the name of the genus, followed by species name, followed by serovar, followed by strain (if appropriate). Genus and species are italicized, with the serovar name not italicized and with an upper-case first letter (e.g., *Leptospira interrogans* serovar Australis).

Epidemiology

Leptospires are maintained in the environment by chronically infected reservoir hosts, which harbor leptospires in their renal tubules and shed the organisms via urine. Small rodents are considered the most important reservoir hosts, but it is likely that a large spectrum of animals, including dogs[5] and cats[6] and also humans,[7] can act as reservoir hosts for pathogenic *Leptospira.* Hosts become infected either by direct contact of mucous membranes or broken skin with urine from infected animals, or indirectly, via contact with contaminated soil or surface water (Figure 217-1). In contrast to reservoir hosts, which typically show no clinical signs of illness, incidental hosts can develop acute, severe, and potentially lethal disease.

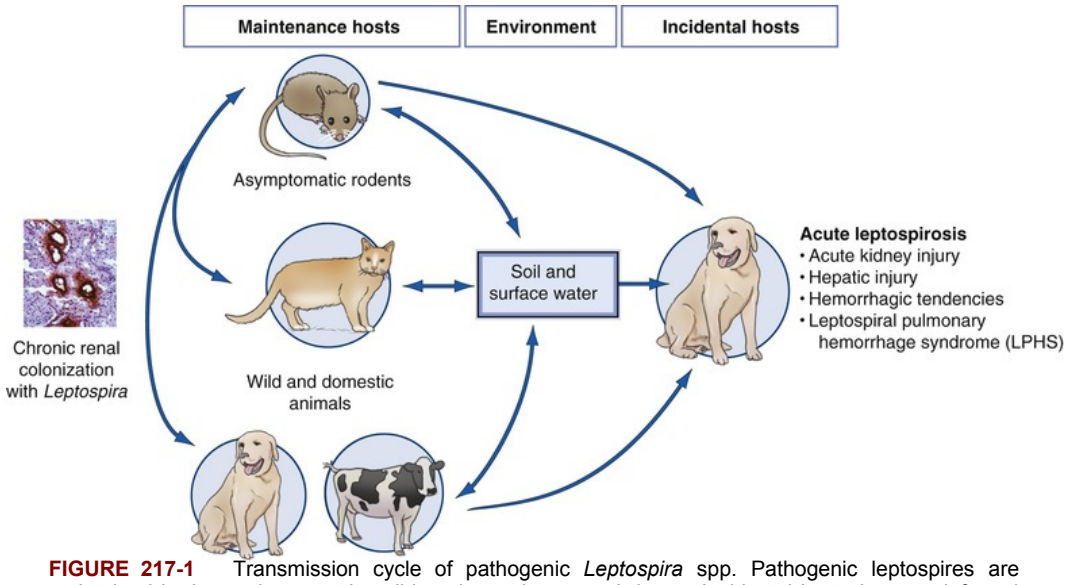

FIGURE 217-1 Transmission cycle of pathogenic *Leptospira* spp. Pathogenic leptospires are maintained in the environment by wild or domestic reservoir hosts. Incidental hosts become infected either via direct contact with reservoir hosts or contaminated soil and surface water. Cats probably are more likely to become infected via contact with prey due to their natural aversion to water. The role of dogs and cats as reservoir hosts requires further study.

In the past, acute infection in dogs most commonly was associated with the presence of antibodies to the serogroups Canicola and Icterohaemorrhagiae, but it is now clear that dogs are susceptible to infection with serovars belonging to a wide range of serogroups, including, but not restricted to, Australis, Grippotyphosa, Pomona, Autumnalis, and Sejroe.[9-11] Leptospirosis is a seasonal disease, with peak incidence during the warmer parts of the year and a link to rainfall or flooding.[12] As a consequence, seasonal patterns of leptospirosis are dependent on regional climate.[13] Dogs living in proximity to outdoor water, who swim or drink from outdoor water sources, and who are exposed to wildlife, have a higher risk of infection.[14] Males, herding dogs, hounds, working dogs, and mixed breeds have been reported to be at increased risk in the USA.[15] In a cohort of dogs from Switzerland, puppies (<1 year) and male dogs were significantly overrepresented compared to the general dog population.[16] However, other studies have not confirmed any sex, age, or breed predispositions.[17,18] Veterinarians therefore should suspect leptospirosis in any dog with suggestive clinical signs regardless of signalment and lifestyle.

Pathogenic Mechanisms of Leptospirosis

After entering the host, pathogenic leptospires quickly establish a systemic infection via hematogenous spread. Unlike bloodstream infections with other Gram-negative bacteria, leptospires do not cause fulminant septic disease shortly after the onset of infection. This has been attributed to the low endotoxic potential of leptospiral lipopolysaccharide.[19] During this initial phase, leptospires evade the host immune response by binding inhibitors of complement activation on their surface.[20,21] Leptospiremia continues until the host mounts an effective acquired immune response, which clears the organism from the bloodstream and most tissues. Thereafter, leptospires can persist in immune-privileged sites, such as the eye and the renal tubules.[8] Leptospirosis is a multisystemic disease, particularly affecting the kidneys and liver, but also many other organs, such as the lungs, spleen, endothelial cells, uvea/retina, skeletal and heart muscle, meninges, pancreas, and the genital tract. The exact mechanisms through which pathogenic leptospires cause organ dysfunction and tissue damage are not known and can vary among different organ systems. While vasculitis can be a feature in some cases of leptospirosis, most studies in humans and experimental animals do not support vasculitis as a consistent primary event responsible for tissue damage.[22]

During the acute phase, the predominant renal lesions are those of an acute interstitial nephritis, with tubular cell necrosis, apoptosis, and regeneration.[23,24] Tubular lesions are assumed to be due to direct effects of the organisms because they are generally associated with the presence of *Leptospira.* Leptospiral outer membrane components also have been shown to induce cell damage and inflammation in tubular epithelial

cells *in vitro*.[25] Glomerular abnormalities have been described in both dogs and experimental animals with leptospirosis and indicate structural and functional glomerular involvement.[26,27] Leptospires can cause a specific hypokalemic, nonoliguric form of acute kidney injury due to inhibition of the tubular Na^+-K^+ ATPase (see ch. 322).[28] Hyposthenuria can occur due to an acquired vasopressin resistance of the inner medullary collection ducts.[29]

Hepatic lesions described in humans and animals with leptospirosis include a cholestatic hepatitis with complete or partial liver-plate disruption, hepatocellular necrosis, binucleation of hepatocytes, periportal edema with inflammatory cell infiltration, and proliferation of Kupffer cells along the sinusoidal lining (see ch. 282).[23,24] Hyperbilirubinemia does not appear to be correlated with hepatocellular necrosis in humans.[30] In experimentally infected hamsters, hyperbilirubinemia coincided with the invasion of hepatic intercellular junctions by migrating leptospires and subsequent disruption of bile canaliculi.[31] In human patients, both icteric and nonicteric forms of leptospirosis have been described, the icteric form being considered more severe and rapidly progressive.[32] Similarly, a serum bilirubin of ≥0.6 mg/dL (≥10 micromole/L; reference range 0.03-0.2 mg/dL [0.5-4.0 micromole/L]) was strongly associated with death or euthanasia in a cohort of 254 dogs with acute leptospirosis.[16]

Leptospiral pulmonary hemorrhage syndrome (LPHS) increasingly has been recognized in humans, dogs, and many other species in recent years and has become a major cause of mortality.[16,33] LPHS lung tissue shows various degrees of intra-alveolar hemorrhage in the absence of a marked inflammatory cell infiltrate or vasculitis (Figure 217-2).[34] Intra-alveolar edema, fibrin, and hyaline membranes, which are characteristic of disorders with diffuse alveolar damage, such as acute respiratory distress syndrome (ARDS), also can be present but are not a predominant feature.[34,35] In contrast to what is seen in liver and kidney, few leptospires are observed in affected lung tissue in immunocompetent hosts and they do not colocalize with the pulmonary lesions.[24] Several hypotheses, including systemic inflammatory, immune-mediated, and direct leptospiral effects, currently are under investigation. It is likely that the pathogenic mechanisms of LPHS are multifactorial, with both host- and pathogen-related factors playing a role.[22] It has been suggested that introduction of clones with enhanced virulence might be a contributing factor to the recent emergence of LPHS.[4] However, at present, available evidence to link specific leptospiral serovars with particular clinical manifestations in both humans and animals is weak.[36-38] This might be partially due to the limitations of current serological tests to correctly identify the infecting serogroup or serovar in acutely infected patients.[39,40]

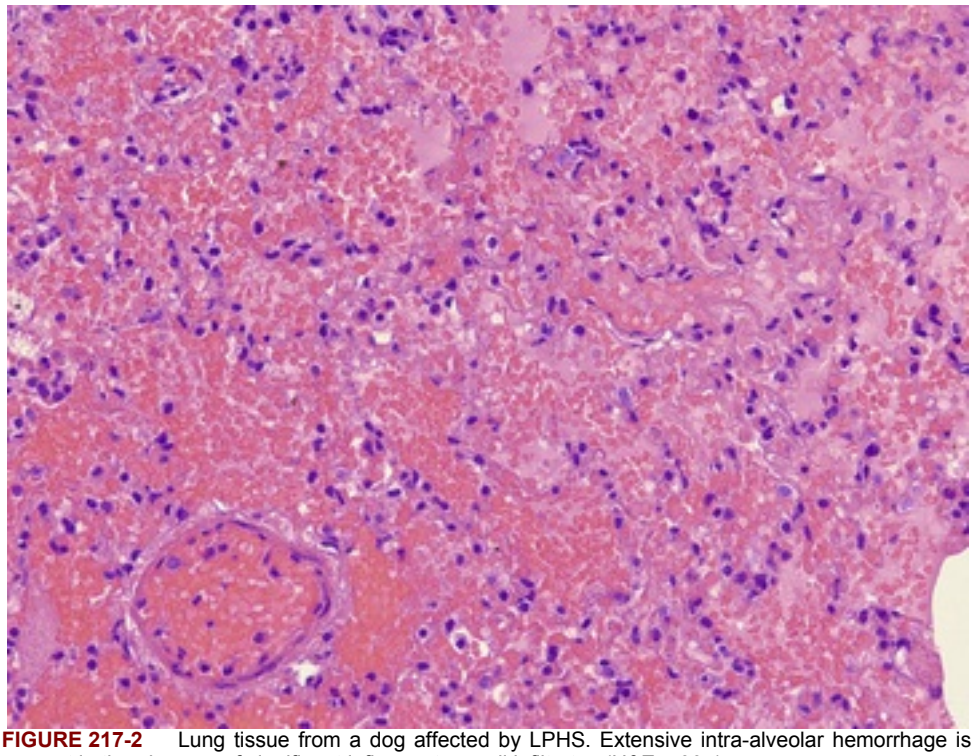

FIGURE 217-2 Lung tissue from a dog affected by LPHS. Extensive intra-alveolar hemorrhage is present in the absence of significant inflammatory cell infiltrates (H&E, 400×).

Diagnosis

Clinical Findings

The clinical signs of leptospirosis are nonspecific and most commonly relate to acute renal and hepatic injury. The most common clinical signs reported in dogs are anorexia, vomiting, lethargy, abdominal pain, diarrhea, jaundice, dehydration, stiffness and musculoskeletal pain, fever or hypothermia, dyspnea and tachypnea, weakness, and weight loss.[16,26,33,36,41-48] Polyuria and polydipsia are common, while oliguria or anuria were present in approximately 30% of dogs with acute leptospirosis in a referral population.[16] In a recent study of a large cohort of dogs with acute leptospirosis, the predominant clinical syndromes were renal (99.6%), hepatic (26%), and pulmonary (76.7%). Signs consistent with disseminated intravascular coagulation (DIC) were present in 18.2% of dogs. This study reflects the recent emergence of LPHS as a common complication in acute canine leptospirosis. Isolated hepatic involvement was very uncommon in this cohort but has been described in 14% of dogs diagnosed with acute leptospirosis by others.[48]

Other clinical abnormalities can include ventricular tachyarrhythmias, abdominal pain due to intussusception,[49-51] ocular signs,[52-54] and skin calcifications.[55,56] In contrast to large animal species, dogs rarely appear to develop reproductive disorders associated with leptospiral infection.[57,58]

The role of chronic leptospiral infection as a cause of chronic kidney disease in both cats and dogs requires further studies. Progression of tubulointerstitial nephritis to tubular atrophy and renal fibrosis has been described in dogs infected with serovar Canicola and rats infected with serovar Icterohaemorrhagiae.[59,60] In a recent study, cats with kidney disease (acute and chronic) were more likely to have antibodies against *Leptospira* spp. and to shed pathogenic leptospires in their urine than were cats without kidney disease.[6]

Chronic hepatitis has been described in case reports in association with infection by serovar Grippotyphosa and serovar Australis.[61,62] Amplification of leptospiral DNA from liver biopsies of dogs with chronic hepatitis was, however, unrewarding.[63] Therefore, at present, it is not clear whether *Leptospira* spp. can be the causative agent of chronic hepatitis in dogs.

Hematology, Clinical Biochemistry, Urinalysis

Mild to moderate anemia is present in approximately half of dogs with leptospirosis. Causes of anemia can be

blood loss via the respiratory or gastrointestinal (GI) tract and anemia of inflammatory disease. Hemolysis due to the effect of leptospiral toxins on erythrocytic membranes appears to be less common in dogs compared to cattle.[64] Neutrophilic leukocytosis, with neutrophilia, left shift, lymphopenia, and monocytosis are often present. Mild to severe thrombocytopenia is common in dogs with leptospirosis and can be caused by platelet or endothelial activation, immune-mediated destruction, or splenic sequestration.[65,66]

Blood urea nitrogen and creatinine concentrations are increased in the majority of dogs at presentation or during the course of disease. Hepatic injury as evidenced by increases in the activity of serum alanine aminotransferase (ALT), aspartate aminotransferase, alkaline phosphatase (ALP), and hyperbilirubinemia occurs almost exclusively in conjunction with azotemia.[16] Increases in serum activity of ALP and total bilirubin are more frequent than are increases in serum ALT activity.

Electrolyte abnormalities, such as hypo- and hyperkalemia, hyper- and hypophosphatemia, hyponatremia, and hypochloremia, are common in canine leptospirosis and usually parallel the degree of renal and GI dysfunction. Hypokalemia can occur due to renal and/or GI losses, as well as potassium wasting due to the leptospiral-induced inhibition of Na^+-K^+-ATPase.[28] Hemostatic disorders in dogs with leptospirosis vary widely in severity and are multifactorial. Hypocoagulable conditions from DIC, failure of coagulation factor synthesis, thrombocytopenia, and thrombocytopathy compete with prothrombotic conditions associated with inflammation and renal disease (see ch. 197).[67] Urinalysis reveals isosthenuria in the majority of dogs with leptospirosis, but hyposthenuria also has been described.[26,37,41,44] Glucosuria, hematuria, pyuria, and granular casts can be present. Proteinuria is present in many affected dogs and can be due to glomerular and/or tubular dysfunction.[26,68] The width of leptospires is below the resolution of light microscopy and therefore, the organisms are not typically visible by routine urinary sediment examination.

Diagnostic Imaging

Radiographic and computed tomographic changes in dogs with LPHS have been described. Initially, pulmonary changes appear in the caudodorsal parts of the lung fields and range from a mild interstitial to severe reticulonodular pattern with focal alveolar infiltrates.[69] Mild mediastinal and/or pleural effusion can be present.[70]

The most common abdominal sonographic findings relate to the kidneys and include cortical hyperechogenicity, renomegaly, mild pyelectasia, a medullary band of hyperechogenicity, and mild perirenal fluid accumulation.[71] Other findings can include hepatomegaly, splenomegaly, ascites, enlargement and hypoechogenicity of the pancreas, thickening of the gastric and (rarely) intestinal walls, and mild lymphadenomegaly.[26,33,41,43,44]

Confirmatory Testing

Leptospirosis is a zoonotic disease. Therefore, confirmation of a clinical suspicion of leptospirosis in veterinary patients is important from a public health perspective. A positive culture of biological samples (blood, urine, tissue) is the definitive proof of infection, but culturing leptospires is difficult, requiring up to six months, and is not routinely performed by diagnostic laboratories. Darkfield microscopy to identify intact leptospires in urine (see Video 217-1) has poor sensitivity and specificity and needs to be performed on fresh urine. Testing for antileptospiral antibodies via the microscopic agglutination test (MAT) or ELISA and polymerase chain reaction (PCR) to detect leptospiral DNA currently are the most useful diagnostic tools available for practitioners.

Serologic Tests

Microscopic Agglutination Test (MAT)

Despite marked limitations, the MAT still is considered the gold standard test for confirmation of acute leptospirosis. The MAT is based on determining the ability of serial dilutions of patient serum to agglutinate live leptospiral serovars *in vitro.* MAT reactivity to a serovar suggests exposure to a serovar within the broader serogroup, but not necessarily to the serovar tested. The panel of serovars ideally should be based on antibody prevalence data in the relevant geographic location, as failure to include the infecting serogroup can lead to false-negative results. MAT results are strongly dependent on quality control in the laboratory, with considerable interlaboratory variability.[40] Therefore, practitioners are encouraged to submit diagnostic

samples to laboratories that adhere to a proficiency scheme.[72] The MAT has marked limitations with regards to sensitivity, specificity, and repeatability, especially if single titers are interpreted.[40,73] Infected dogs can be antibody negative in the acute phase of the disease, due to the normal delay in appearance of serum antibodies. On the other hand, noninfected dogs vaccinated with bi- or quadrivalent whole-cell antileptospiral vaccines can have postvaccinal titers of 1:6400 or higher to both vaccinal and nonvaccinal serovars.[74-76] While the majority of vaccinated dogs has been shown to become antibody-negative by week 15 postvaccination, vaccinal titers can persist for 12 months in a small percentage of dogs.[75] Reactivity of antileptospiral antibodies with multiple serogroups often prevents the determination of the infecting serogroup. Moreover, the serogroup with the highest MAT titer can vary over time, indicating that the MAT does not reliably predict the infecting serogroup in acutely infected animals.[40]

For a dog with consistent clinical signs vaccinated with a bivalent vaccine against Canicola and Icterohemorrhagiae, a single titer ≥ 1:800 for one or more serogroup(s) has in the past generally been considered suggestive of leptospirosis. However, the best way to confirm a recent infection using MAT is to test paired samples, collected one or two weeks apart, which greatly increases the sensitivity of the MAT.[40,48,73] Obtaining a sample for a follow-up titer at the time of discharge from the hospital can be a practical approach. A fourfold or greater rise in MAT is highly suggestive of leptospirosis (for example, a titer of 200 rises to 800, corresponding to the fact that the serum is positive for two more consecutive dilutions) or when an initially antibody-negative dog exhibits a convalescent titer ≥ 800 to one or multiple serovars. An algorithm summarizing the confirmatory diagnostics in dogs suspected to have leptospirosis is presented in Figure 217-3.

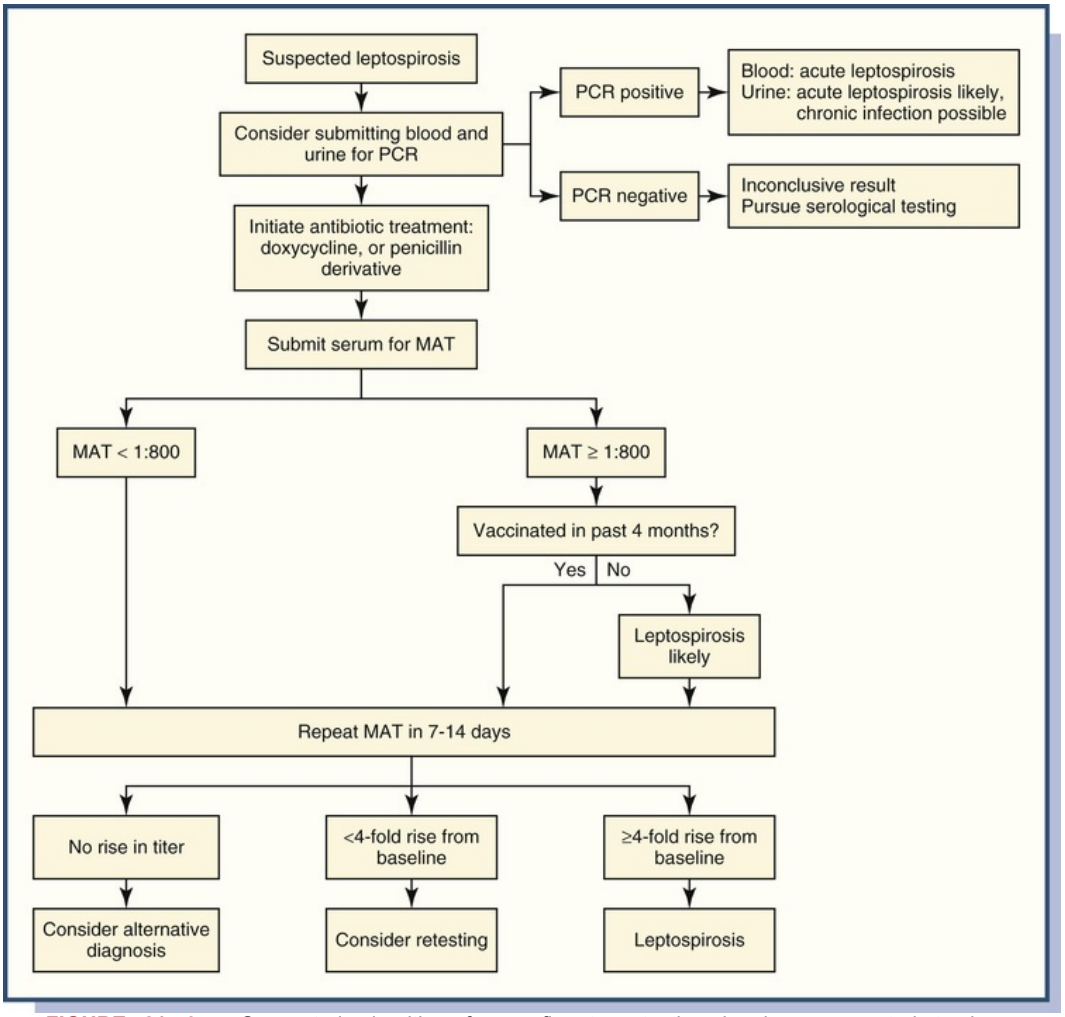

FIGURE 217-3 Suggested algorithm for confirmatory testing in dogs suspected to have leptospirosis. The interpretation of MAT titers can be particularly difficult in recently vaccinated dogs because in these dogs, vaccinal titers cannot be reliably distinguished from acute infection. In dogs

that have received early antibiotic treatment, a rise in titer can be blunted due to early eradication of the pathogen. *MAT*, Microscopic agglutination test; *PCR*, polymerase chain reaction.

Enzyme Linked Immunosorbent (ELISA) and Immunofluorescence Assays (IFA)

Detection of antileptospiral IgM and/or IgG via ELISA is gaining popularity, as more patient-side assays are becoming commercially available. These assays provide results within minutes but suffer from the same limitations as the MAT with regard to the possible absence of antibodies in early infection or their presence due to recent vaccination. Measurement of antileptospiral IgG and IgM via IFA can be helpful in differentiating vaccination from recent infection, but correct interpretation of these tests can be challenging. Retesting of initially antibody-negative animals within a few days is advised. Further studies assessing the diagnostic performance of these tests in well-characterized patient populations are needed. In the meantime, it is advised to use these tests in conjunction with paired MAT titers.

Polymerase Chain Reaction (PCR) Tests

PCR assays for detection of leptospiral DNA can be performed on blood, urine, or tissue specimens. In experimentally infected dogs, leptospiral DNA can be found in blood during the first week of infection and thereafter in urine.[77] Because the exact time of infection typically is unknown in naturally infected dogs, PCR testing of both blood and urine should be performed, ideally before antibiotic administration. The stability of leptospiral DNA in canine blood and urine has not been examined systematically. In the absence of well-established general recommendations, clinicians are encouraged to follow the guidelines of their specific laboratories with regards to sample collection, storage, and shipment conditions. Several PCR assays for diagnosis of canine leptospirosis have been described, targeting the *lipL32/hap1* gene, which is specific for pathogenic *Leptospira* spp.[5,77,78] or 23S rDNA.[79] These PCRs provide no information on the infecting serovar. Diagnostic performances of all PCR assays are not equivalent, and PCR assays validated for use in human clinical specimens, probably used by some veterinary diagnostic laboratories, might not perform similarly when applied to specimens from dogs.[80,81]

As long as there is a lack of data on sensitivity, specificity, and positive and negative predictive value of different PCR assays in dogs, MAT remains the preferred confirmatory test for leptospirosis. PCR can be used in conjunction with MAT in patients with high vaccinal titers because previous vaccination does not lead to positive results by PCR.[76]

Treatment

Effective treatment of canine leptospirosis consists of appropriate antimicrobial therapy and supportive care for the different organ systems involved. Leptospires are susceptible to a wide range of antibiotics *in vitro*, but the capacity of antibiotics to completely eradicate infection *in vivo*, in particular renal carriage, varies.[82] Penicillin and its derivatives have been shown to reduce leptospiremia but fail to reliably clear the organisms from the kidney.[8,83,84] Doxycycline has been shown to clear leptospires from blood and organs including kidneys in rodent models.[83] Therefore, currently it is recommended to treat dogs with leptospirosis with oral doxycycline (5 mg/kg PO q 12 h or 10 mg/kg PO q 24 h) for 14 days. Unfortunately, doxycycline often is not well tolerated in the early phase of treatment because GI signs are common in acute leptospirosis. In these cases, initial therapy with an intravenous penicillin derivative (e.g., penicillin G, ampicillin, amoxicillin) often is recommended until doxycycline can be used. Macrolide antibiotics such as azithromycin and third-generation cephalosporins have been assessed in animal models and have been proposed as alternative treatment in humans who cannot tolerate doxycycline treatment.[84-86]

Treatment of LPHS largely is supportive. Radiographic screening is recommended even in the absence of respiratory signs, in order to detect early lesions and implement precautionary measures (see ch. 242). These include avoidance of stress and overhydration/hypervolemia (see ch. 129) and control of systemic hypertension (see ch. 99 and 158). Depending on the severity of pulmonary hemorrhage, oxygen therapy and in severe cases, mechanical ventilation may be required (see ch. 131 and 139). Based on the hypothesis of an immune-mediated mechanism of LPHS, the efficacy of immunomodulatory treatments has been assessed. Results of small and often not well-controlled clinical trials in humans suggest that immunosuppressive treatment with methylprednisolone,[87] dexamethasone alone or in combination with desmopressin,[88] or plasmapheresis,[89] can improve survival in patients with LPHS. Further studies have to be performed in order to determine whether immunosuppression is an effective treatment for LPHS in dogs.

After initial stabilization (see ch. 322 and 110), renal recovery can continue for several months. A follow-up study of dogs with leptospirosis indicated that ≈50% of dogs surviving the acute phase of the disease displayed impairment of renal function more than one year after hospital discharge.[90] Long-term monitoring of renal function therefore is strongly recommended in these dogs.

Concurrent infection of other dogs that reside in the same household can occur, probably following infection from the same environmental source. Treatment of dogs living with dogs diagnosed with leptospirosis with doxycycline for 2 weeks therefore is currently recommended.

Leptospirosis in Cats

Cats can become infected with leptospires and can shed leptospires in their urine, but clinical signs of acute disease are rarely described.[6,91-97] In experimentally and naturally infected cats, interstitial nephritis is the most consistent histopathologic finding,[92,95,98,99] and in one study, cats with kidney disease (acute and chronic) were more likely to have serum antibodies against *Leptospira* spp. and to shed pathogenic leptospires in their urine.[6] Therefore, the role of healthy cats as reservoir hosts, as well as the role of leptospirosis as a clinical disease in cats, deserves further study and might have been underestimated in the past.

Prevention of Leptospirosis

Vaccination

Prior to 1960, serovars Icterohaemorrhagiae and Canicola were thought to be responsible for most cases of canine leptospirosis. Since the introduction of a bivalent vaccine against serogroups Icterohaemorrhagiae and Canicola, infection with serovars that belong to these serogroups likely have become rare based on MAT antibody testing, and acute infections in dogs vaccinated with bivalent vaccines now are commonly caused by other serogroups, such as Grippotyphosa and Australis.[9,100] Quadrivalent vaccines that contain serogroups Canicola, Icterohaemorrhagiae, Grippotyphosa, and Pomona have been available in the USA since 2001. Recently, new vaccines containing serovars belonging to three (Icterohemorrhagiae, Canicola, and Grippotyphosa) or four (Icterohemorrhagiae, Canicola, Grippotyphosa, and Bratislava) serogroups have been developed in Europe in an effort to increase the spectrum of protection.[101] However, more data are required to determine whether addition of these serovars will protect more dogs from leptospirosis than the available bivalent vaccines, as limited data suggest in the USA.[100]

Public Health Considerations

Leptospirosis is a zoonotic disease, and humans are at increased risk of infection if they perform activities that involve animal contact, such as hunting, abattoir work, dairy farming, and veterinary practice.[32] Recreational activities, such as swimming, canoeing, fishing, potholing, and caving, also are associated with a significant risk of exposure due to intense contact with water or soil.[102,103] Dog-to-human transmission of leptospirosis has been suggested by several authors.[104-106] However, seropositivity to *Leptospira* spp. was uncommon in pet owners exposed to dogs with confirmed acute leptospirosis and staff in a veterinary referral hospital with a very high leptospirosis caseload.[107] Appropriate precautions should be taken when handling dogs suspected to have leptospirosis. Owners should be informed that their dog likely contracted leptospirosis through direct or indirect contact with wild or farm animals, which could represent an ongoing risk for humans and animals. Owners should be instructed to wash hands after handling their pet and to wear gloves when cleaning up urine spills until the course of antimicrobial drug therapy is completed. Routine household disinfectants should be used for cleaning urine spills, and dogs should be taken outside to urinate in places that are not intensely frequented by humans and other animals.

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CHAPTER 218

Ehrlichiosis, Anaplasmosis, Rocky Mountain Spotted Fever, and Neorickettsiosis

Jane E. Sykes

Client Information Sheet: Ehrlichiosis, Anaplasmosis, Rocky Mountain Spotted Fever, and Salmon Poisoning Disease

General Considerations

The primary causes of canine ehrlichiosis are the intracellular Gram-negative bacteria *Ehrlichia canis, Ehrlichia ewingii,* and *Ehrlichia chaffeensis,* belonging to the family Anaplasmataceae. Other bacteria within this family are *Anaplasma platys* and *Anaplasma phagocytophilum,* which cause canine thrombocytic and granulocytic anaplasmosis, respectively, and *Neorickettsia helminthoeca,* the agent of salmon poisoning disease (SPD). *Rickettsia rickettsii,* the cause of Rocky Mountain spotted fever (RMSF), and other spotted fever group (SFG) rickettsiae belong to the family Rickettsiaceae. The families Rickettsiaceae and Anaplasmataceae are related through the order Rickettsiales (Table 218-1).

TABLE 218-1

Members of the Order Rickettsiales That Are Established Pathogens in Dogs and Cats

FAMILY	GENUS	SPECIES
Anaplasmataceae	*Ehrlichia*	*E. canis* *E. chaffeensis* *E. ewingii*
	Anaplasma	*A. phagocytophilum* *A. platys*
	Neorickettsia	*N. helminthoeca*
Rickettsiaceae	*Rickettsia*	*R. rickettsii*

These organisms are transmitted to dogs and cats by arthropod or trematode vectors (Table 218-2). They are maintained in nature through infection of wild animal reservoir hosts and can also be transmitted by blood transfusion. Their geographic distribution is restricted to that of their vectors and intermediate hosts. Several of these pathogens cause human disease. Dogs, therefore, serve as potential sentinels for human infection and precautions should be taken to prevent transmission while handling engorged ticks, blood, and tissue from dogs with suspected infections. Because of shared arthropod vectors and/or concurrent exposure to multiple vector ticks, coinfections with more than one of these pathogens (as well as other vector-borne pathogens) can occur and may complicate the clinical picture. Severity of clinical signs depends on the size of the inoculum, host immunity, and pathogen strain virulence.

TABLE 218-2

Important Ticks Involved in Transmission of Members of the Order Rickettsiales

TICK SPECIES	COMMON NAME	VECTORED AGENTS	GEOGRAPHIC DISTRIBUTION
Rhipicephalus sanguineus	Brown dog tick	*Ehrlichia canis* *Anaplasma platys?* *Rickettsia rickettsii*	Worldwide, primarily between latitudes 35 degrees south and 50 degrees north
Amblyomma americanum	Lone star tick	*Ehrlichia chaffeensis* *Ehrlichia ewingii*	West-central Texas, north to Iowa, and eastward in a broad belt spanning the southeastern United States; Atlantic coast up to Maine
Ixodes scapularis	Black-legged tick, deer tick	*Anaplasma phagocytophilum*	Northeastern, north central, and southeastern United States
Ixodes pacificus	Western black-legged tick	*Anaplasma phagocytophilum*	West coast of the United States
Ixodes persulcatus	Taiga tick	*Anaplasma phagocytophilum*	Eastern Europe and Asia
Ixodes ricinus	Castor bean tick	*Anaplasma phagocytophilum*	Europe, including the United Kingdom
Dermacentor variabilis	American dog tick	*Rickettsia rickettsii*	East of the Rocky Mountain states as far north as Massachusetts and Nova Scotia, west coast of the United States to southwestern Oregon
Dermacentor andersoni	Rocky Mountain wood tick	*Rickettsia rickettsii*	Rocky Mountain states of the United States, primarily Montana, Idaho, and Oregon

The Ehrlichioses

Ehrlichia canis

Etiology and Epidemiology

Ehrlichia canis causes canine monocytic ehrlichiosis (CME), an important disease of dogs exposed to ticks worldwide. The organism infects circulating monocytes and forms morulae (Latin for "mulberry"), a cluster of bacteria, within the monocyte cytoplasm. *E. canis* is transmitted by *Rhipicephalus sanguineus* ticks. Infection has been reported in dogs from Asia, Africa, Europe, and the Americas. In the United States, disease is diagnosed most frequently in dogs living in the southeastern and southwestern states, but because of chronic, subclinical infection, dogs can be incidentally transported to nonendemic regions before developing the condition. Ticks acquire infection by feeding as larvae or nymphs on infected dogs. Jackals, foxes, and possibly coyotes may also act as reservoir hosts. The organism is transmitted transstadially but not transovarially within the tick.[1] No age, breed, or sex predilection for CME has been clearly documented. Cross-bred dogs may be less likely to develop disease.[2]

Pathogenesis and Clinical Signs

The course of CME has been divided into acute and chronic phases, although these phases are not always clinically distinguishable. Transmission can occur within hours of tick attachment and acute signs of disease occur 8 to 20 days after infection.[3] Common vague signs include lethargy, inappetence, fever, and weight loss. Replication of the organism in reticuloendothelial tissues is associated with generalized lymphadenopathy and splenomegaly. Ocular and nasal discharge, peripheral edema, and less commonly, petechial and ecchymotic hemorrhages may occur. Neurologic signs include twitching, ataxia, seizures, vestibular signs, hyperesthesia, and cranial nerve deficits. These signs are likely caused by meningeal inflammation or hemorrhage. Thrombocytopenia and sometimes mild leukopenia and anemia occur 1 to 4 weeks after infection. Transient proteinuria has also been reported, which resolves within 6 weeks of infection.[4,5] Dogs may recover from the acute phase after 2 to 4 weeks without treatment.

After the acute phase, some dogs remain subclinically infected for months to years. They may have mild persistent thrombocytopenia. Organisms may sequester within the spleen and evade host immune systems through antigenic variation.[6] This phase may persist for months to years.

Chronic ehrlichiosis ranges in severity from mild to life-threatening, with signs that include lethargy,

inappetence, bleeding tendencies, pallor, fever, weight loss, lymphadenopathy, splenomegaly, anterior uveitis, retinal hemorrhage, retinal detachment, polyuria/polydipsia, and edema[7-10] (Figure 218-1). Bleeding tendencies result from thrombocytopenia and platelet dysfunction.[11] Cutaneous and mucosal petechial or ecchymotic hemorrhages, epistaxis, melena, hematochezia, hematuria, and prolonged bleeding from venipuncture sites have been reported (see ch. 197).[9] Polymyositis may develop, with muscle atrophy and tetraparesis (see ch. 354).[12] Secondary opportunistic infections such as viral papillomatosis, protozoal infections, and bacteriuria have also been described, although the precise underlying mechanism of immune suppression and how it relates to persistence of *E. canis*, has not yet been elucidated (Figure 218-2).[13,14]

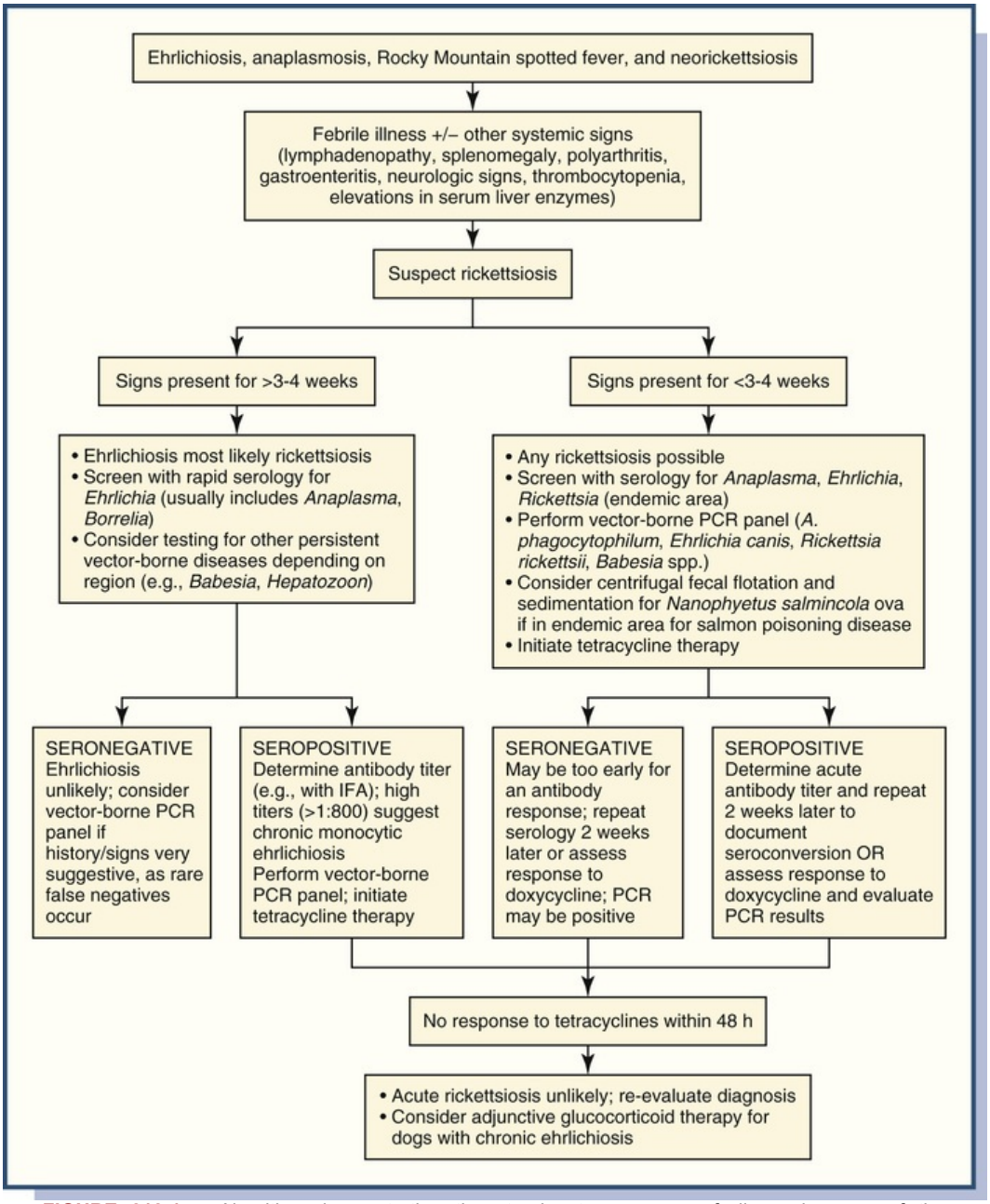

FIGURE 218-1 Algorithm demonstrating the step-by-step process of diagnosing one of the rickettsial diseases in dogs. *IFA*, Indirect fluorescent antibody test; *PCR*, polymerase chain reaction test.

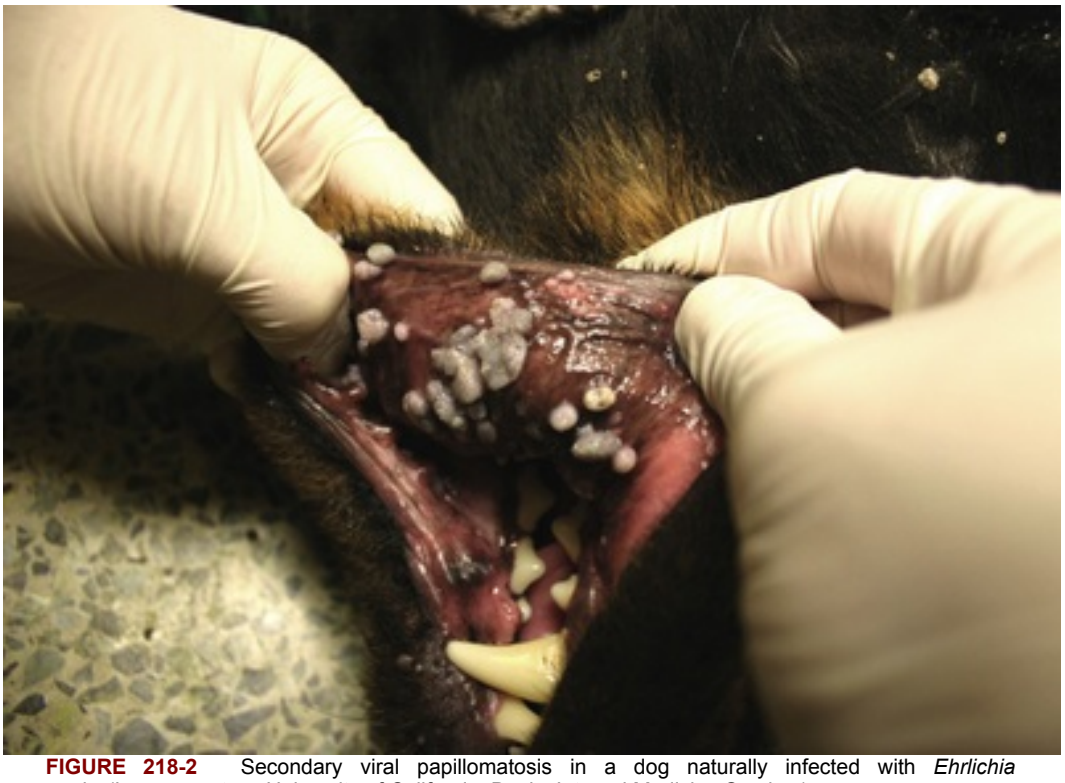

FIGURE 218-2 Secondary viral papillomatosis in a dog naturally infected with *Ehrlichia canis*. (Image courtesy University of California, Davis, Internal Medicine Service.)

Pancytopenia on results of a complete blood count (CBC) typifies the severe chronic form of ehrlichiosis (see ch. 58 and 202). It is caused by hypoplasia of all bone marrow cells.[9] Thrombocytopenia and nonregenerative anemia are common. Moderate to marked granular lymphocytosis (up to 17,000/mcL) and bone marrow plasmacytosis may occur. Some dogs have a monoclonal gammopathy, similar to that seen with some lymphocytic leukemias or multiple myelomas (see ch. 60). Dogs with well-differentiated lymphocytosis or an otherwise unexplained monoclonal gammopathy should be tested for *E. canis* infection.[15] Serum chemistry abnormalities in chronic ehrlichiosis include hypoalbuminemia, hyperglobulinemia, and elevated alanine aminotransferase (ALT) and alkaline phosphatase (ALP) activities. The hyperglobulinemia is usually due to a polyclonal gammopathy.[7] A protein-losing nephropathy may develop as a result of an immune-complex glomerulonephritis, which can be associated with azotemia (see ch. 325). Dogs with central nervous system (CNS) involvement may have increased cerebrospinal fluid (CSF) protein concentrations and cell counts.[16]

Diagnosis

Detection of morulae within monocytes using cytologic evaluation is diagnostic for monocytic ehrlichiosis but is insensitive. It is important to note that the morulae of *E. canis* and *E. chaffeensis* cannot be discriminated. In one study, morulae were found in 2 of 19 dogs with chronic monocytic ehrlichiosis.[9] Diagnosis of ehrlichiosis is usually confirmed with serology, using indirect fluorescent antibody (IFA) or enzyme-linked immunosorbent assay (ELISA). Antibodies can be detected between 7 and 28 days after initial infection. Therefore, dogs with acute ehrlichiosis may have negative test results if antibody production has not yet occurred. Retesting should be performed after 2 to 3 weeks to demonstrate seroconversion. A positive serum antibody titer for *E. canis* may occur with previous exposure and does not equate with diagnosis. Serology results must be interpreted in the context of the clinical signs and results of testing for other conditions. Dogs with chronic *E. canis* infection typically have extremely high IFA titers, sometimes >1 : 600,000. Antibodies may persist despite treatment, suggesting persistence of the organism.[9] These test results do not correlate with severity of hyperglobulinemia or disease. Serologic cross-reactivity to other *Ehrlichia* species occurs, including *E. ewingii* and particularly *E. chaffeensis*. Cross-reactivity to *Anaplasma phagocytophilum* antigens can occur but is minor.[15]

A variety of ELISA assays detect antibodies to *E. canis*.[17-19] A point-of-care lateral flow ELISA device

detects canine heartworm antigen, antibodies to *E. canis* or *E. ewingii,* antibodies to *Borrelia burgdorferi,* and antibodies to *A. phagocytophilum* in canine serum, plasma, or whole blood (SNAP 4Dx Plus, IDEXX Laboratories, Westbrook, ME.). This test includes recombinant surface proteins of *E. canis* and *E. ewingii.* The antigens of *E. canis* and *E. ewingii* are combined together in a single spot, so a positive result reflects either seroreactivity to *E. canis, E. ewingii,* or both pathogens. The sensitivity of this assay for detection of antibodies to *E. canis* when compared with IFA was 131/134 (97.8%) and specificity was 217/235 (92.3%).[20] Other point-of-care ELISA assays detect *E. canis* antibodies. In addition, a diagnostic laboratory-based ELISA assay detects antibodies to *E. canis, B. burgdorferi, A. phagocytophilum* and *D. immitis* (Accuplex 4, Antech Laboratories). It is recommended that dogs incidentally identified to have *E. canis* seroreactivity when screened using ELISA assays that simultaneously detect heartworm antigen should undergo a thorough physical examination and have a complete blood count, chemistry panel, and urinalysis to evaluate for thrombocytopenia, hyperglobulinemia, and proteinuria. Treatment of seroreactive clinically healthy dogs is controversial, since it does not change their outcome and has the potential to lead to antimicrobial resistance or adverse effects of drug therapy (see ch. 169).

PCR is widely available for routine diagnosis of *E. canis* infection as part of "vector-borne pathogen" panels offered by veterinary diagnostic laboratories. Assay results must be interpreted in the context of the history, clinical signs, and serologic assay results. *E. canis* DNA can be detected using PCR on blood, lymph node aspirates, splenic aspirates, or bone marrow. However, sensitivity of PCR from bone marrow for diagnosis of chronic ehrlichiosis can be as low as 25%.[9] Thus, PCR alone is not suitable for screening potential blood donors for infection but may be useful for confirming infection in the first week of illness, when serologic assays are often negative.

Treatment

The recommended treatment for CME is doxycycline (10 mg/kg PO q 24 h) for 28 days.[15] Shorter periods of treatment (e.g., 16 days) may be effective for dogs with acute CME.[21] Most dogs show clinical improvement within 24 to 48 hours, but those with severe chronic disease may not respond to therapy or their "cytopenias" may gradually resolve over several months. Platelet counts generally improve and normalize within 2 weeks of initiating therapy. Following therapy, titers may decline and become negative over 6 to 9 months, while some retain high titers for years. Treatment for such dogs should be based on resolution of platelet counts and decreases in hyperglobulinemia. Hyperglobulinemia may take months to resolve after treatment is discontinued. Platelet counts should be reassessed 1 and 3 months after discontinuation of therapy because of the potential for relapse or reinfection. Other causes of illness should be considered in dogs that fail to respond to treatment.

Alternative drugs, used with variable success, include chloramphenicol, imidocarb dipropionate, and enrofloxacin.[15,22-25] Members of the *E. canis* genogroup appear to have intrinsic gyrase-mediated resistance to fluoroquinolones.[26] While enrofloxacin therapy may lead to clinical improvement, its use is not recommended. The efficacy of imidocarb diproprionate has been controversial.[22-24]

For dogs that are dehydrated or anemic, intravenous fluids (see ch. 129) or blood products (see ch. 130) may also be required. Use of darbepoetin or granulocyte colony-stimulating factor could be considered for dogs with severe chronic ehrlichiosis.[27] If thrombocytopenia fails to respond to doxycycline administration, adding a short course (up to a week) of immunosuppressive doses of glucocorticoids may be beneficial.

Prevention and Public Health Significance

Prevention of canine monocytic ehrlichiosis relies on tick control combined with careful searching for and prompt removal of attached ticks (see ch. 211). DNA of an *E. canis*-like organism has been detected in people with clinical signs of monocytic ehrlichiosis.[28] Appropriate precautions are indicated when handling engorged ticks, blood, or tissue specimens from infected dogs.

Ehrlichia ewingii

Ehrlichia ewingii has caused granulocytic ehrlichiosis in people and dogs in North America and, possibly, dogs from Brazil and Cameroon.[29-31] Infection has been primarily identified in south-central and southeastern areas of the United States, where exposure is widespread and *E. ewingii* is the predominant cause of canine ehrlichiosis.[32] Like *E. chaffeensis, E. ewingii* is transmitted primarily by *Amblyomma americanum* ticks from the reservoir white-tailed deer, whose expanding population has likely contributed to the emergence of these

pathogens.[33] Like *Anaplasma phagocytophilum, E. ewingii* infects and forms morulae within granulocytes. Infection causes fever, headache, and cytopenias in people and dogs may be subclinically affected or may exhibit lethargy, anorexia, vomiting, diarrhea or neurologic signs.[34] Dogs may have fever and a neutrophilic polyarthritis (see ch. 203). Persistent *E. ewingii* infection lasting more than a year has been reported in laboratory-infected dogs without clinical signs of illness. This may support dogs acting as a reservoir.[35-37] Laboratory testing may reveal anemia, mild leukopenia or leukocytosis, thrombocytopenia, hyperglobulinemia and elevated activities of serum ALP.[34,35,37-39]

E. ewingii has yet to be cultivated. Antibodies to *E. ewingii* can be detected using a point-of-care lateral flow ELISA device (SNAP 4Dx Plus, IDEXX Laboratories, Westbrook, ME.). This assay's sensitivity for detection of *E. ewingii* antibodies, as compared with a plate ELISA, was 109/113 (96.5%) and its specificity was 154/164 (93.9%).[20] Granulocytic morulae are commonly detected in blood smears and synovial fluid from affected dogs. *E. ewingii*–specific PCR assays have been developed, providing the only method for confirming infection. Treatment with doxycycline for 2 to 4 weeks results in rapid clinical improvement and may be sufficient to eliminate infection.

Other *Ehrlichia* Species

Ehrlichia chaffeensis causes human monocytic ehrlichiosis in North America, a disease that is characterized by fever, headache, myalgia, thrombocytopenia, leukopenia, and increases in liver enzyme activities[40] (see Figure 218-1). In the United States, human monocytic ehrlichiosis occurs primarily in the south-central, southeastern and mid-Atlantic states, coinciding with the distribution of *Amblyomma americanum* and the reservoir, white-tailed deer. Experimental infection of dogs with *E. chaffeensis* results in prolonged fever, mild anemia, leukopenia, and thrombocytopenia, or the infection is subclinical.[41,42] Naturally infected dogs have developed lymphadenopathy and epistaxis.[43] Dogs maintain high antibody titers and are PCR-positive for months after infection, supporting their role as a reservoir.[42] As for *E. canis* infection, diagnosis of *E. chaffeensis* infection may be made using acute and convalescent serology or PCR. Serologic cross-reactivity has the potential to occur with other *Ehrlichia* species. Although clinical improvement occurs following doxycycline therapy, doxycycline may not completely eliminate infection.[43] Treatment for a minimum of 28 days is suggested.

Other *Ehrlichia* species detected include an *Ehrlichia muris*–like organism in dogs from the upper Midwest[44] and an *Ehrlichia ruminantium*–like organism in dogs from South Africa.[45] The significance of these infections is unknown.

Anaplasmosis

Anaplasma phagocytophilum

Etiology and Epidemiology

Anaplasma phagocytophilum causes canine granulocytic ehrlichiosis. The organism infects a variety of domestic and wildlife host species and is an important emerging pathogen in people worldwide. Clinical infections have been documented in dogs, horses, cats, and people. In Europe, infections have also been documented in domestic ruminant species (sheep, cattle, goat). Different strains of *A. phagocytophilum* exist worldwide and differ in their host tropism and virulence.[46] *A. phagocytophilum* forms morulae in neutrophils more frequently than in eosinophils (Figure 218-3). *A. phagocytophilum* is spread by several Ixodid tick species, is transmitted only transstadially within ticks (see Table 218-2), and ticks must be attached for 24 to 48 hours for transmission to occur. *Ixodes scapularis* is the vector in the upper midwestern and northeastern United States and southeastern Canada. *Ixodes pacificus* is a vector on the west coast of North America, from California to British Columbia. In Europe, including the United Kingdom, the vector is *I. ricinus.* Ticks (commonly *I. persulcatus*) with *A. phagocytophilum* have been detected in Asia and Russia.[47] Ticks with molecular evidence of *A. phagocytophilum* have been noted in the Middle East, South Africa, and South America.[48-50] Small mammals, including mice, woodrats, chipmunks, voles, shrew, and deer, serve as reservoir hosts for *A. phagocytophilum.* Because *Borrelia burgdorferi* is transmitted by the same Ixodid ticks, coinfections with *B. burgdorferi* and *A. phagocytophilum* are frequently detected and, together, pathogenicity is enhanced (see ch. 211).[51] In the upper midwest and northeastern United States, infection is most common from spring to early summer and in the fall. Labrador and Golden Retrievers account for half of reported cases, possibly reflecting

their popularity for outdoor activities.[52] The median age of infected dogs was 8 years, although dogs of any age are at risk.[52,53]

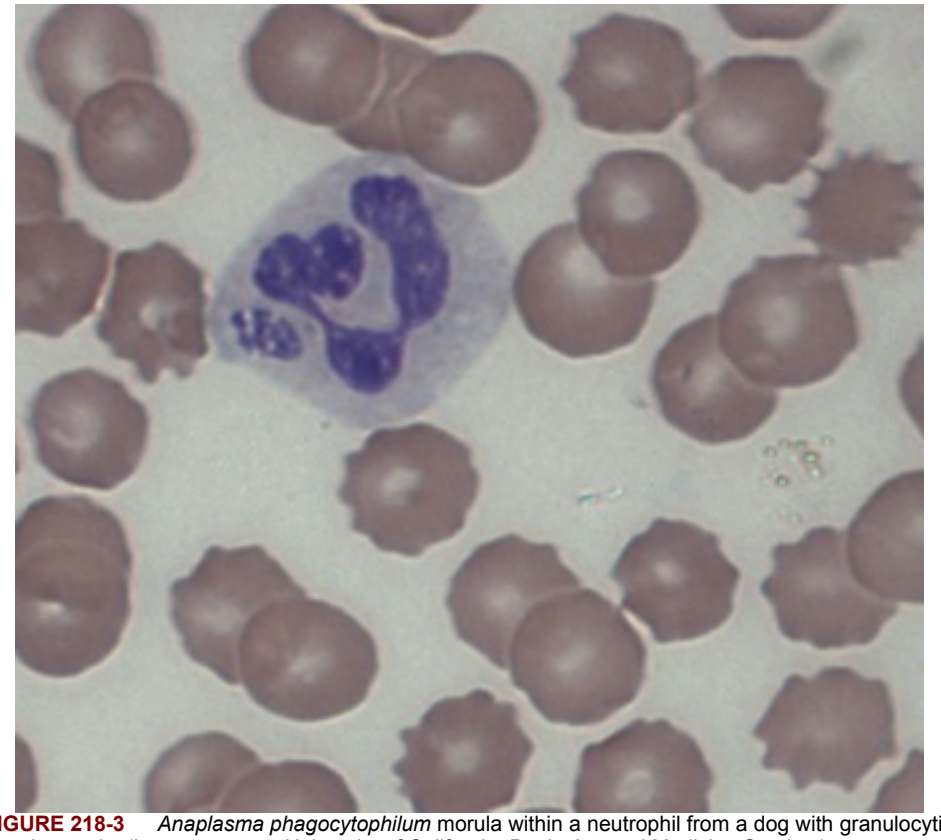

FIGURE 218-3 *Anaplasma phagocytophilum* morula within a neutrophil from a dog with granulocytic anaplasmosis. (Image courtesy University of California, Davis, Internal Medicine Service.)

Clinical Signs

In many dogs, infection is subclinical. Common signs, when seen, occur after an incubation period of 1 to 2 weeks and are nonspecific: fever, lethargy, inappetence, scleral injection, lameness, stiffness and reluctance to move. Infrequent soft and nonproductive coughing may be noted.[54,55] Mild lymphadenomegaly, splenomegaly (see ch. 206), and neutrophilic polyarthritis (see ch. 203) may occur.[53,55] Less common signs include polydipsia, vomiting, diarrhea, CNS signs (abnormal placing reactions), and cervical pain.[52-55] Infection appears to be self-limiting in dogs, since chronic disease (>30 days) has not been described. Thrombocytopenia is documented in >80% of infected dogs. Less common abnormalities include lymphopenia, eosinopenia, or mild nonregenerative anemia.[52,54,55] Serum chemistries may reveal hypoalbuminemia and mild to moderately increased activities of serum ALT and ALP.

Diagnosis and Treatment

The finding of morulae within neutrophils in an endemic area is highly suggestive of infection with *A. phagocytophilum,* although the morulae cannot be distinguished from those of *E. ewingii* (see Figure 218-1). Morulae, when present, are found in 7% to 37% of circulating neutrophils.[52,53] Diagnosis can also be accomplished using acute and convalescent phase serology using IFA or ELISA assays. A point-of-care lateral flow ELISA device (SNAP 4Dx Plus, IDEXX Laboratories, Westbrook, ME.) can also be used to detect antibodies to *A. phagocytophilum,* with a reported sensitivity of 93% and specificity of 99% when compared with IFA.[39] However, many acutely ill dogs with granulocytic anaplasmosis have negative serologic test results because they have not had sufficient time for an antibody response when first brought to a veterinarian. Further, positive titers may reflect previous subclinical exposure (within 8 to 10 months) so demonstration of a fourfold rise in titer is required.[56] With all current serologic assays, serologic cross-

reactivity with other *Anaplasma* species, especially *A. platys* and possibly other *Ehrlichia* species, can occur.[15,43] PCR on whole blood (usually as part of a panel designed to simultaneously test for multiple vector-borne pathogens) can be used to identify infection in acutely ill dogs and allows *A. phagocytophilum* to be distinguished from *E. ewingii* when morulae are seen in granulocytes. Treatment of choice for granulocytic anaplasmosis is a 2-week course of doxycycline (5 mg/kg PO q 12 h). Most dogs show rapid improvement, with signs abating within 12 to 48 hours. Prevention relies on tick control.

Public Health Significance

Anaplasma phagocytophilum causes human granulocytic anaplasmosis, a febrile disease that resembles the disease in dogs. Death is rare but has occurred as a result of complications due to secondary infections. Dogs are an important sentinel for human infection. Dogs may be a source of infection by bringing infected ticks into contact with humans. Precautions should be taken when handling blood or tissue from infected dogs, or during tick removal.

Anaplasma platys

A. platys, the cause of canine thrombocytic anaplasmosis, is yet to be cultured. *Rhipicephalus sanguineus* is the likely vector, although attempts to transmit infection using this tick were unsuccessful.[57] The organism has been reported in South America, Australia, Asia, Africa, Europe, and North America.[58-63] After an incubation period of 1 to 2 weeks, thrombocytopenia occurs and then normalizes within days. Morulae within platelets may be seen in blood smears shortly after infection and in megakaryocytes within bone marrow specimens.[64] The majority of infections reported in the United States have been mild or subclinical. Cases reported from Europe and South America have had more severe clinical manifestations, including fever, splenomegaly, and hemorrhage. However, coinfection with other tick-borne pathogens may have contributed to clinical signs. Diagnosis is based on visualization of morulae within platelets together with acute and convalescent phase serology. Because of cross-reactions with *A. phagocytophilum,* serology is not specific for *A. platys. A. platys*–specific PCR assays have been developed.[65] Treatment of canine thrombocytic anaplasmosis is as for granulocytic anaplasmosis. Recently, persistent human infection with *A. platys* has been documented.[66,67] The extent to which *A. platys* can cause disease in humans is unknown.

Neorickettsioses

Neorickettsia helminthoeca

Etiology and Epidemiology

Neorickettsia helminthoeca causes salmon poisoning disease (SPD), a condition diagnosed from the western slopes of the Cascade Mountains of northern California to southern Vancouver Island, Canada.[68] Disease may occur elsewhere following transportation of infected fish for feeding or in dogs that travel to and from a nonendemic area to a site containing infected fish. Recently, a similar disease was described in Brazilian dogs.[69]

The vector of SPD is *Nanophyetus salmincola,* a fluke that harbors the organism throughout its life cycle. Fluke eggs transform into miracidia, which infect small snails, *Oxytrema silicula,* that live in both fresh and brackish stream water. Cercariae leave the snail and penetrate a fish, most commonly a salmonid fish, although certain nonsalmonid fish have also been reported to be infected.[70,71] Hatchery-reared fish may also be infected. The cercariae transform into metacercariae, usually within the kidneys but also in the muscle and other tissues. Fish may retain the infection for several years.[71,72] Dogs become infected with the rickettsia after ingesting parasitized fish. Following ingestion, the metacercariae transform into adult flukes. Labrador Retrievers and intact male dogs are overrepresented, but dogs of either gender and of any age or breed may be affected.[73] Foxes and coyotes may also become infected, and SPD has also been reported in captive bears.[74] Domestic cats are not susceptible to SPD, but the flukes mature to adults within feline intestinal tracts. SPD may also be acquired after ingesting adult flukes (which could potentially occur following coprophagy), infected snails, and fluke eggs.[75]

Clinical Signs

After the fluke matures and attaches to the intestinal tract, *N. helminthoeca* infects and replicates within cells of

the mononuclear-phagocyte system. Rapid dissemination of the organism to the lymph nodes, spleen, liver, lungs, and brain occurs. After an incubation period ranging from 5 to 33 days, the earliest clinical observations include anorexia and fever as high as 42° C (107.6° F). Later signs include lethargy, weight loss, mild to severe lymphadenomegaly, vomiting, and diarrhea, sometimes containing blood.[71,73,76] Rarely, a history of vomiting or diarrhea is absent. The presence of adult flukes may contribute to the gastrointestinal signs. Dogs lacking peripheral lymphadenomegaly have abdominal lymphadenomegaly on ultrasound examination. Associated laboratory abnormalities include neutrophilia, sometimes a mild to moderate left shift, lymphopenia, and monocytosis. Thrombocytopenia occurs in approximately 90% of affected dogs and may be as low as 16,000/mcL. Serum chemistry abnormalities include hyponatremia, hypokalemia, increased liver enzyme activities, and hypoalbuminemia, which can be profound and sometimes accompanied by hypocholesterolemia and hypoglobulinemia.[71,73,76]

Diagnosis

Diagnosis of SPD may be inferred by finding characteristic trematode eggs in the feces using fecal sedimentation or sugar flotation (see Figure 218-1). Eggs appear 5 to 8 days after infected fish ingestion. A combination of fecal sedimentation and centrifugal flotation increases the sensitivity for detection of fluke ova. In one study, 93% of dogs with SPD tested positive for *N. salmincola* ova using a combination of fecal flotation and fecal sedimentation.[73] The finding of fluke ova on fecal examination may not be diagnostic of SPD, as dogs may be infected with trematodes that do not harbor the rickettsia, and ova may be shed for months after recovery. Nevertheless, *N. salmincola* ova were detected in only 0.2% of over 1800 fecal flotations in dogs seen at a teaching hospital in an endemic area, and all positive test results were in dogs suspected to have SPD. Thus, specificity of fecal flotation is high.[73] Neorickettsiae may also be visible using cytologic examination of lymph node aspirates (Figure 218-4), together with moderate to marked histiocytic inflammation and lymphocytic-plasmacytic reactivity.[77] Organisms may appear as granular to amorphous material filling infected cells, best visualized using Giemsa stain.[77] The use of PCR-based assays on lymphoid tissue to identify infection has been reported.[73]

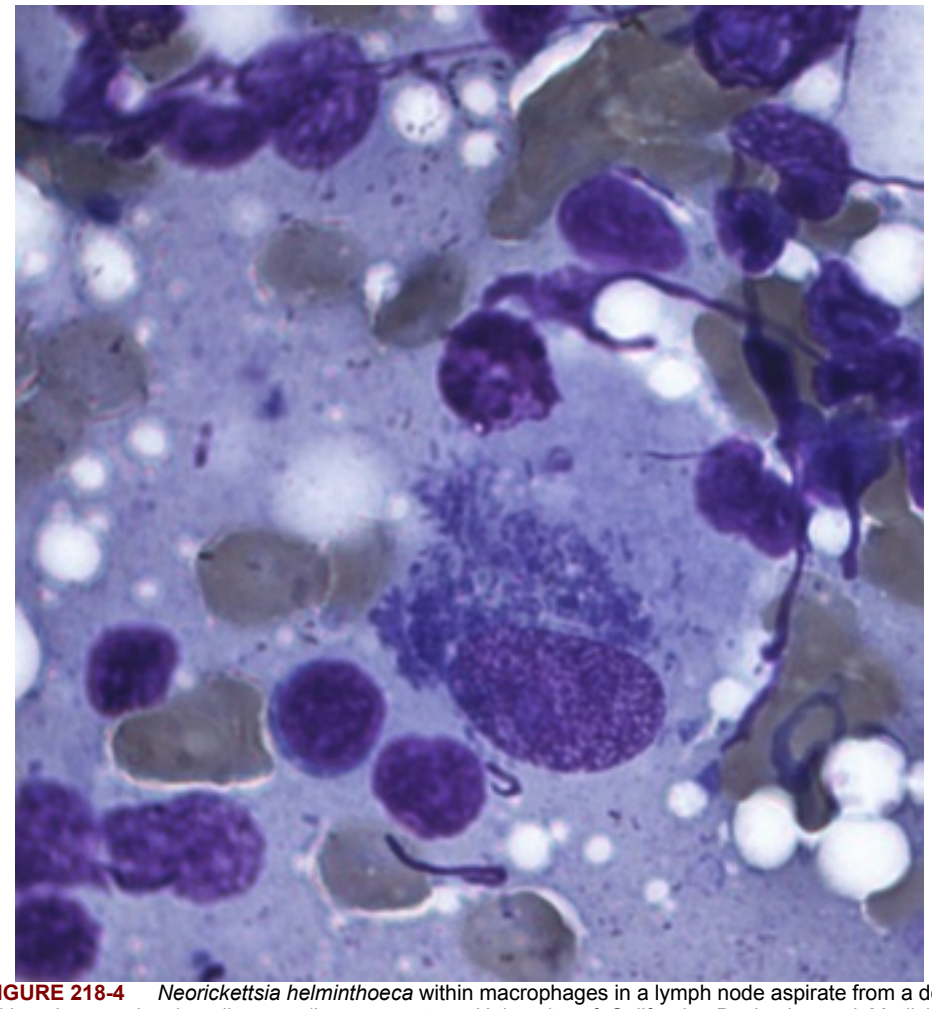

FIGURE 218-4 *Neorickettsia helminthoeca* within macrophages in a lymph node aspirate from a dog with salmon poisoning disease. (Image courtesy University of California, Davis, Internal Medicine Service.)

Treatment and Prevention

The treatment of choice is doxycycline. Parenteral administration may be necessary in vomiting dogs. In addition, supportive therapy using fluids, blood products, and antiemetics may be necessary. Praziquantel should also be administered to treat the helminth infection (see ch. 163). Prevention involves avoiding access to fish and feeding only thoroughly cooked fish. Freezing fish for 24 hours also effectively destroys the metacercariae and rickettsiae.

Neorickettsia risticii

Neorickettsia risticii is the cause of Potomac horse fever. The life cycle of this organism likely involves the trematode vector, *Acanthatrium oregonense.*[78] The fluke miracidia infect aquatic snails (*Juga* spp.) and parasitize caddisflies. Horses may become infected following accidental ingestion of infected caddisflies containing metacercariae. *N. risticii* has been identified using culture and PCR in dogs from the western and southwestern United States with signs mimicking ehrlichiosis.[79] The dogs were seroreactive to *N. risticii* antigens using IFA. Further studies are required to determine the significance of this organism in dogs and cats.

Tick-Borne Rickettsioses

General Considerations

Rickettsia rickettsii, the cause of Rocky Mountain spotted fever (RMSF), belongs to the Rickettsiaceae, a family

that contains a number of pathogenic and nonpathogenic *Rickettsia* species. Many novel species of rickettsiae have been recently characterized using molecular methods.[80] Clinical signs in humans caused by these organisms include fever, lymphadenopathy, headache, eschar formation (tissue slough), and rash. Formation of an eschar at the inoculation site does not usually occur in RMSF.[80] The ability of novel *Rickettsia* species to cause disease in dogs and cats, and the role of dogs and cats as reservoirs, requires further study. Tick-borne SFG rickettsiae cause disease after infecting vascular endothelial cells and increasing microvascular permeability.[81] Organisms inhibit apoptosis, favoring rickettsial growth. Widespread endothelial injury is associated with production of proinflammatory cytokines and activation of the coagulation cascade without disseminated intravascular coagulation.[81]

Rocky Mountain Spotted Fever (RMSF)

Etiology and Epidemiology

RMSF is a severe, life-threatening illness of humans and dogs caused by *Rickettsia rickettsii,* most commonly diagnosed in the south-central, southeastern, and south Atlantic United States. It also occurs in Central America and parts of South America (Brazilian spotted fever).[80] Approximately 2000 cases of RMSF are reported annually in people in the United States.[82]

Rickettsia rickettsii is transmitted primarily by *Dermacentor* ticks in North America, although transmission by *R. sanguineus* occurs in Arizona.[83,84] The American dog tick *(Dermacentor variabilis)* is the primary vector in the southeastern states, and the Rocky Mountain wood tick *(Dermacentor andersoni)* transmits the rickettsia in the Rocky Mountain region and Canada (see Table 218-2). *R. sanguineus* and *Amblyomma* spp. ticks have been implicated as vectors in Central and South America, respectively.[85,86] The organism is transmitted transstadially and transovarially within ticks. Uninfected larvae and nymphs also become infected when they feed on small wild mammals, such as ground squirrels. In the United States, most cases occur between March and October. In humans, the highest incidence has been reported in Caucasian males <10 years and 40-64 years of age.[85] Most cases originate from rural or wooded areas. Exposure to dogs is a risk factor.[87,88] The disease occurs sporadically, but may cluster in small geographic regions. Rarely, familial clusters occur, sometimes including the family dog.[89,90] A history of a tick bite is present in <70% of infected people and is even less common in dogs.[91,92]

Pathogenesis and Clinical Signs

Following tick attachment, a reactivation period lasting 4 to 24 hours is necessary. Disease in humans and dogs is similar with incubation periods of 2 to 14 days (mean: 7). Common nonspecific observations include fever, lethargy, anorexia, and lymphadenopathy. Extreme headaches may occur early in the course of human illness and be accompanied by myalgia, vomiting, anorexia, and abdominal pain.[85] Early RMSF is often misdiagnosed as a viral illness in humans.[85] About 60% to 70% of infected people, within 2 weeks of the tick bite, have the characteristic triad of rash, fever, and headache. The rash initially appears as small macules on the wrists and ankles and spreads to involve the arms, legs, and trunk, eventually becoming maculopapular with central petechiae.[85] Dogs may develop edema and erythema of extremities, including the lips, muzzle, scrotum, penile sheath, pinnae and, rarely, the ventral abdomen.[92-94] Continued tissue damage in these regions may lead to necrosis and gangrene, requiring amputation in some cases.[89,93] Stiffness and reluctance to walk may be apparent.[91] Ocular manifestations are common, including conjunctivitis, mucopurulent ocular discharge, scleral injection, uveitis, hyphema, iridal and retinal hemorrhage, and retinal edema (see ch. 11).[95] Petechial and ecchymotic hemorrhages have been noted.[91,96] Epistaxis, melena, and hematuria may occur in severely affected dogs. Neurologic signs (ataxia, tremors, vestibular signs, hyperesthesia, opisthotonus, seizures) have been reported in up to 80% of dogs with RMSF.[89,91,92,96,97] Other signs include respiratory distress and cough due to pulmonary edema, cardiac arrhythmias due to myocarditis, hepatomegaly, icterus, and development of acute kidney injury (see ch. 322). Death can result from progressive neurologic signs, acute oliguric renal failure, or cardiovascular collapse and shock.[85,91] Death is reported in 2-10% of humans, although a study from Mexico reported a mortality rate of 22% in children.[88] The median time from onset of illness to death is only 8 days, making early recognition and treatment crucial.

Laboratory abnormalities include leukocytosis, sometimes with a left shift, anemia, and thrombocytopenia.[91,92,94,96] Serum chemistry abnormalities may include increased liver enzyme activities and

creatine kinase concentrations, hypoalbuminemia, and electrolyte disturbances. In severe cases, azotemia and hyperbilirubinemia are noted. Cerebrospinal fluid analysis may reveal increases in protein concentration (usually <100 mg/mcL) and in neutrophil and mononuclear cell counts (see ch. 115).[89] Neutrophilic polyarthritis has been documented using synovial fluid analysis (see ch. 94 and 203). Thoracic radiography may reveal an interstitial pattern.

Diagnosis

Antibody detection using microimmunofluorescence is the serologic reference method, but ELISA assays are also used.[98] Wide antigenic cross-reactions exist among pathogenic and nonpathogenic SFG rickettsiae. Thus, positive titers are not specific for *R. rickettsii.* Because antibodies are generally not detectable until 7 to 10 days after disease onset, a fourfold rise in IgG titer using acute and convalescent phase sera is necessary to confirm recent infection. A single titer exceeding 1 : 1024 is also considered diagnostic of recent infection, if associated with clinical signs.[91] Given the acute nature of RMSF, serology is of limited usefulness for early diagnosis.

Direct immunofluorescence or immunoperoxidase staining of infected tissues, including biopsies of affected skin, can be used to detect *R. rickettsii* antigen in tissue early in the course of disease or at necropsy, with high specificity and a sensitivity of about 75%.[97,99-101] PCR assays for *R. rickettsii* can be used on blood or tissue. The number of rickettsiae circulating in blood is generally low with poor PCR sensitivity.[102,103] Use of PCR together with immunohistochemistry on skin biopsy specimens in acute disease improves laboratory confirmation of RMSF (see ch. 86 for skin biopsy procedure). Real-time PCR assays that differentiate between SFG rickettsiae–infecting dogs are available.[104] *R. rickettsii* has been classified as a biosafety level-3 agent, and cultivation requires special facilities and is not routine. Laboratory-acquired infections have been reported.[105]

Treatment

Doxycycline is recommended for RMSF and it results in rapid (12-24 h) clinical response. Other tetracyclines, chloramphenicol, and fluoroquinolones are effective.[106,107] Treatment should be continued for at least 7 days. Parenteral antimicrobial drug therapy may be needed if vomiting or neurologic signs are present. Treatment delays have been correlated with more severe disease and increased mortality in humans. Treatment should not be delayed while awaiting results of diagnostic testing. Other supportive therapy may be required for dogs in shock, including IV fluids (see ch. 129) and blood products (see ch. 130). Care may be required to avoid pulmonary or cerebral edema after IV crystalloids.[91] Residual neurologic signs, renal insufficiency or cutaneous scarring may persist despite treatment, especially if treatment is delayed.

Prevention

Natural infection is followed by development of solid immunity, and reinfection has not been documented in naturally infected dogs. Prevention relies on tick control (see above). Prophylactic antibiotic administration is not indicated to prevent RMSF after a tick bite, as this only appears to delay onset of illness.[85]

Public Health Aspects

Dogs are important sentinels for human infection with *R. rickettsii.* Recognition of the disease in dogs has contributed to prompt diagnosis and treatment of RMSF in humans interacting with those dogs.[89] Veterinarians that manage dogs with RMSF should educate their clients about the disease and their potential for infection and should contact human health care providers should humans become ill in association with canine disease. Dogs may carry unattached infected ticks, which may subsequently attach to people. People may become infected through improper removal of attached ticks from their dogs. Guidelines for safe removal of ticks have been published (also see video, ch. 211).[85] Ticks should be lifted from the skin using fine forceps. Gloves should be worn. Hands should be washed with soap and water after removal. The skin should be thoroughly examined for attached ticks after these activities.

Feline Rickettsial Disease

Cats are rarely infected with rickettsial agents.[108-130] The DNA of *E. canis*–like organisms has been detected in cats from North America, Europe and South America.[108-111] One of the three North American cats showed signs of polyarthritis and the other two had cytopenias. None of these three cats was seroreactive in an IFA assay using *E. canis* antigens. *Ehrlichia*-like morulae have been identified in mononuclear cells in cats from the

United States, Kenya, France, Brazil and Thailand.[112-116] Clinical signs including fever, lethargy, anorexia, pallor, and splenomegaly were reported in these cats, although some had coinfections with hemoplasmas or retroviruses. The most consistent laboratory abnormalities in infected cats have been nonregenerative anemia and hyperglobulinemia. Many infected cats respond rapidly to treatment with doxycycline. Cats infected with monocytic ehrlichiae should be treated with doxycycline at 10 mg/kg PO q 24 h for a minimum of 28 days.[15]

Several case series of cats with suspected or proven *A. phagocytophilum* infection have been described from Europe and the United States. The diagnosis was based on cytologic evaluation of morulae within circulating granulocytes with or without PCR confirmation of infection.[117,118,126-130] Clinical abnormalities in these cats included lethargy, anorexia, fever, pallor, epistaxis, hyperesthesia, lameness, lymphadenopathy, hepatomegaly, ataxia, vomiting, and thrombocytopenia. Experimental infection of cats with *A. phagocytophilum* has resulted in development of morulae within granulocytes and clinical illness.[131] These cats showed signs of fever, anorexia, and lethargy, and some had thrombocytopenia. Signs in cats infected with *A. phagocytophilum* resolve following treatment with doxycycline.[126,128]

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CHAPTER 219

Hemotropic Mycoplasmas

Séverine Tasker

Client Information Sheet: Hemotropic Mycoplasma *(Haemoplasma)* Infections

The hemotropic mycoplasmas (hemoplasmas) are small (0.3-1 micron) wall-less bacteria that parasitize erythrocytes, living on the surface of the erythrocyte membrane (Figure 219-1). They infect a variety of hosts including cats, dogs, rodents, pigs, cattle, deer, horses and beetles. Infections also have been described in humans with novel hemoplasma species,[1,2] as well as species that possibly have originated in animals such as the cat,[3] pigs,[4-6] sheep,[1,7] or dogs,[8] raising the possibility of zoonotic infections. Hemoplasma infections have been reported throughout the world. Please note that *Babesia* infections are described in ch. 221 and *Bartonella* infections are described in ch. 215 and 216.

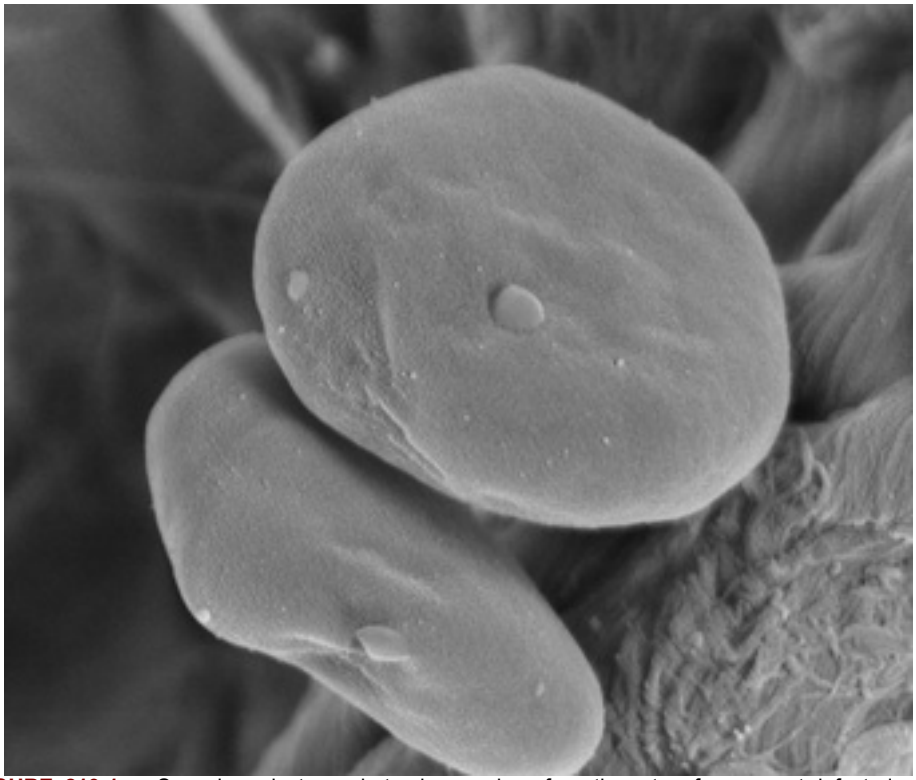

FIGURE 219-1 Scanning electron photomicrography of erythrocytes from a cat infected with *Mycoplasma haemofelis*, showing a rounded organism within an indentation on the erythrocyte surface (×1000).

Initially, the hemoplasmas, as members of the genus *Haemobartonella,* were classified as rickettsial organisms, but gene (mainly 16S rRNA-based) sequencing analysis and phylogenetic studies resulted in their reclassification within the genus *Mycoplasma.*[9-11] Though similarities between the hemoplasmas and mycoplasmas are recognized, such as the absence of a cell wall, their small (including genome) sizes, and their fastidious growth requirements, the hemoplasmas' niche environment of the blood is not one that is

commonly recognized for *Mycoplasma* species, which are most commonly found on the mucosal surfaces of the respiratory and urogenital tracts.[12] Indeed, recent work using non-16S rRNA gene-based phylogeny suggests that, although the hemoplasmas probably rightly belong to the family *Mycoplasmatales*, they should reside in a genus separate to that of the *Mycoplasma* species.[13,14]

Gene sequencing analysis also has revealed the existence of different species of hemoplasmas, and five major hemoplasma species are now known to infect cats and dogs (Table 219-1). Renaming of the hemoplasmas accompanied their reclassification as mycoplasmal organisms. In renaming, some of the species were assigned the status *Candidatus;* this status is used in bacterial nomenclature for newly described organisms for which sequence data are available, but which cannot be phenotypically characterized to meet the needs of the International Code of Nomenclature of Bacteria[15] due to the inability to grow them *in vitro.* Although none of the hemoplasmas can be grown *in vitro,* only newly described hemoplasma species were given the *Candidatus* status as those species previously defined and named (in the genus *Haemobartonella*) could not be assigned the *Candidatus* status as a rule in bacterial nomenclature exists that forbids the demotion of any bacterial species.

TABLE 219-1

Feline and Canine Hemoplasma Species, Their Prevalence (Using PCR as Method of Detection), and a Summary of Each Species' Pathogenicity

SPECIES NAME	HOST	REPORTED PREVALENCE	PATHOGENICITY
Mycoplasma haemofelis	Cat	Up to 46.6%	Acute infection often results in hemolytic anemia
'*Candidatus* Mycoplasma haemominutum'	Cat	Up to 46.7%	Acute infection can induce a drop in erythrocyte parameters but not usually severe enough to cause anemia unless cat has concurrent disease or is immunocompromised (e.g., retrovirus infection)
'*Candidatus* Mycoplasma turicensis'	Cat	Up to 26%	
Mycoplasma haemocanis	Dog	Up to 52.4%	Infection can result in hemolytic anemia, primarily in splenectomized dogs
'*Candidatus* Mycoplasma haematoparvum'	Dog	Up to 33.3%	Anemia not usually reported unless the dog has concurrent disease or is immunocompromised (e.g., chemotherapy)

In addition to the five main feline and canine hemoplasmas described in Table 219-1, the feline hemoplasma species' '*Candidatus* M. haemominutum' also has been detected occasionally in dogs,[16,17] as has the ovine hemoplasma *Mycoplasma ovis*[18] and the bovine hemoplasma '*Candidatus* M. haemobos.'[19,20] A '*Candidatus* M. haematoparvum'-like organism also been reported in a small number of cats in two studies.[21,22] The clinical importance of these additional hemoplasma species in dogs and cats remains unclear.

Prevalence and Risk Factors for Infection

Prevalence studies for feline hemoplasma species have been performed worldwide, with very varied results (see Table 219-1). '*Candidatus* M. haemominutum' is usually the most common species found in prevalence studies, with prevalences ranging from 0 to 46.7% (median 14.4%) of cats being infected.[21-51] *M. haemofelis* and '*Candidatus* M. turicensis' infections generally are less common, although occasionally, high prevalences are reported. Reported prevalence for *M. haemofelis* have ranged from 0 to 46.6% (median 4.8%)[21-43,45-51] and for '*Candidatus* M. turicensis' have ranged from 0 to 26% (median 2.0%).[21,22,28,31,32,38,39,43,45,48-52] Variable numbers of cats infected with more than one hemoplasma species are also reported in different studies, and one recent study of Brazilian cats reported that over 80% of hemoplasma-infected cats harbored more than one hemoplasma species.[45] '*Candidatus* M. turicensis'–infected cats often are coinfected with another hemoplasma species, particularly '*Candidatus* M. haemominutum,' and indeed, in some studies, no cats were

found to be infected with '*Candidatus* M. turicensis' alone.[31,45,51]

The characteristics of the cats sampled for these different prevalence studies have varied enormously, from healthy cats to anemic cats suspected of having hemoplasmosis or retrovirus-infected cats, and from client-owned indoor cats to outdoor feral cats, which likely explains the wide differences in prevalences reported. Additionally, geographic variation in prevalence appears to exist, with cats in warmer countries having a higher prevalence of infection. Different polymerase chain reaction (PCR) methods, likely with differing sensitivities and specificities, were also used, likely contributing to the variation, too.

In most studies, feline hemoplasma infections are found more commonly in male, nonpedigree cats with access to the outdoors.[21,24-26,28,32,34,39,41,43,45,48,50-53] Infection with '*Candidatus* M. haemominutum' usually is more prevalent in older cats, presumably because the chance of acquiring chronic subclinical infection increases with time. Some studies have shown an association between hemoplasma infection with any species and feline immunodeficiency virus (FIV),[33,38] whereas others have not,[28] but these same studies failed to show an association between hemoplasma infection with any species and feline leukemia virus (FeLV) infection.[28,33,38] (Table 219-2). However, studies looking at individual hemoplasma species infections and retroviral status have shown variable results (see Table 219-2).

TABLE 219-2

Overview of Retrovirus Infection as Risk Factors for Hemoplasma Infections in a Selection of Published Studies

STUDY NAME (NUMBER AND TYPE OF CATS)	HEMOPLASMA SPECIES (SPECIES DETECTED BY PCR METHODS USED ARE LISTED IN BRACKETS)	FeLV INFECTION	FIV INFECTION
Luria et al. 200426 ($_n$ = 484, feral cats, northern Florida)	• '*Candidatus* M. haemominutum'	✓	✓
	• *M. haemofelis*	✗	✓
Willi et al. 200628 ($_n$ = 996 healthy or sick cats, Switzerland)	• Any hemoplasma species ('*Candidatus* M. haemominutum,' *M. haemofelis* and/or '*Candidatus* M. turicensis')	✗	✗
Bauer et al. 200834 ($_n$ = 262 cats presented to a university clinic or diagnostic laboratory, Germany)	• '*Candidatus* M. haemominutum'	✓	✓
	• *M. haemofelis*	✗	✗
Sykes et al. 200832 ($_n$ = 310 cats either suspected of having hemoplasmosis and/or with a regenerative hemolytic anemia, USA)	• '*Candidatus* M. haemominutum'	✗	✗
	• *M. haemofelis*	✓	✓
	• '*Candidatus* M. turicensis'	✗	✗
Macieira et al. 200833 ($_n$ = 149 cats admitted to a clinic and tested for retroviruses, Brazil)	• Any hemoplasma species ('*Candidatus* M. haemominutum' and/or *M. haemofelis*)	✗	✓
	• '*Candidatus* M. haemominutum'	✗	✓
	• *M. haemofelis*	✗	✗
Gentilini et al. 200938 ($_n$ = 91 cats admitted to a clinic and tested for retroviruses, Brazil)	• Any hemoplasma species ('*Candidatus* M. haemominutum' and/or *M. haemofelis*)	✗	✓
Roura et al. 201039 ($_n$ = 191 healthy or sick cats presented to a university clinic, Spain)	• Any hemoplasma species ('*Candidatus* M. haemominutum' and/or *M. haemofelis* and/or '*Candidatus* M. turicensis')	✗	✓
Tanahara et al. 201050 ($_n$ = 1770 cats with outdoor access in Japan)	• Any hemoplasma species ('*Candidatus* M. haemominutum' and/or *M. haemofelis* and/or '*Candidatus* M. turicensis')	✗	✓
Georges et al. 201251 ($_n$ = 152 rescue cats presenting	• Any hemoplasma species ('*Candidatus*	✓	✓

for euthanasia or neutering, or samples submitted to a diagnostic laboratory, Trinidad and Tobago)	M. haemominutum' and/or *M. haemofelis* and/or '*Candidatus* M. turicensis')		
	• '*Candidatus* M. haemominutum'	✓	✓
	• *M. haemofelis*	✗	✗

✓, Identified as risk factor; ✗, not identified as risk factor.

Reported prevalences for canine hemoplasma infection also vary widely in different studies (see Table 219-1); generally *M. haemocanis* is more prevalent (0 to 54.4% of dogs infected, median 5.9%),[18-20,35,39,46,54-61] but occasionally '*Candidatus* M. haematoparvum' (0 to 33.3% of dogs infected, median 1.5%)[18-20,35,39,46,55-57,59-61] is found in higher numbers. Geographic variation is marked, possibly due to the presence of the proposed canine hemoplasma tick vector *Rhipicephalus sanguineus*,[56,60] and kenneled dogs, young dogs, crossbreeds, and dogs with mange were more likely to be infected in one study,[60] whereas other studies found no association with age.[39,56,59]

Pathogenesis

Mycoplasma haemofelis is the most pathogenic of the feline hemoplasma species. Cats do not need to be immunocompromised or splenectomized to succumb to clinical disease with *M. haemofelis*, and splenectomized cats infected with '*Candidatus* M. haemominutum' do not seem to show increased pathogenicity with this organism.[62]

Acute infection often results in severe hemolytic anemia (primarily extravascular, but occasionally intravascular hemolysis is reported), although in some cases, only mild anemia results. In experimental studies, clinical signs typically occur around 2 to 34 days after infection, with anemia lasting from around 18 to 30 days. The onset of anemia usually is followed by a significant regenerative response with reticulocytosis. Chronic infection usually is not associated with significant anemia.[28] Experimental infections have shown that *M. haemofelis* blood organism numbers can fluctuate greatly over short periods of time, especially in the first few weeks of infection (Figure 219-2). Antigenic variation to evade the host immune system could mediate these *M. haemofelis* organism number fluctuations,[63] as a very large portion (62%) of the *M. haemofelis* genome encodes a set of uncharacterized hypothetical proteins arranged in series of paralogous repeats that could mediate differing expression of hemoplasma surface proteins over time. Young cats could be more likely to develop severe clinical disease due to *M. haemofelis* compared to older cats.[32,64] Epidemiological studies have, however, only variably demonstrated associations between anemia and *M. haemofelis* infection.[23,34] This might be because these studies usually include asymptomatic, chronically *M. haemofelis*–infected cats.

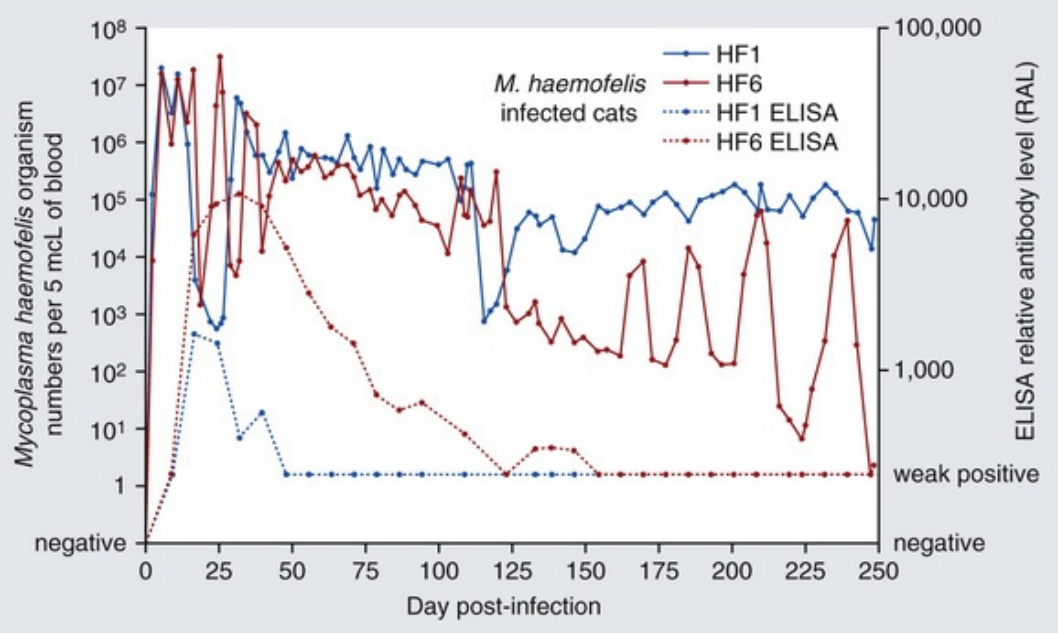

FIGURE 219-2 Graph made from data collected from two cats in the study by Barker et al. in 2010.[97] The solid lines indicate *M. haemofelis* organism numbers in the blood (detected by quantitative PCR) whilst the hashed lines indicate the relative levels of antibodies against a recombinant dnaK *M. haemofelis* protein present in the blood (detected by an enzyme linked immunosorbent assay). The marked fluctuations in *M. haemofelis* organism numbers in the blood over time is evident in both cats, but especially Cat HF6. Antibody levels peak, and are quantifiable, during acute infection only, after which they are detectable but nonquantifiable; antibody assays may be useful in the future to differentiate acute and chronic hemoplasma infection but are currently only available as a research tool.

Persistent autoagglutination or positive Coombs' testing, indicating the presence of erythrocyte-bound antibodies, has been demonstrated in anemic cats with acute *M. haemofelis* infection.[64-66] One detailed study[64] showed that erythrocyte-bound antibodies reactive at 4° C (cold reactive antibodies; both IgM and IgG) appeared a few days earlier than those reactive at 37° C (warm reactive antibodies, primarily IgG). However, in most cats, these antibodies appeared only *after* the development of anemia had started. The absence of erythrocyte-bound antibodies at the onset of development of anemia could reflect a problem with the sensitivity of their detection or that erythrocyte-bound antibodies appear as a result of hemoplasma-induced hemolysis rather than initiating it. In line with the latter, it has been found that these antibodies disappear with antibiotic and supportive treatment alone, without the need for specific glucocorticoid treatment.[64] Osmotic fragility[66,67] and reduced erythrocyte lifespan[68] also have been reported with *M. haemofelis* infection.

Although acute '*Candidatus* M. haemominutum' infection is associated with a fall in red blood cell parameters,[64] anemia usually is not induced except in cats with concurrent diseases or infections (e.g., lymphoma or FeLV infection).[69,70] '*Candidatus* M. haemominutum' also has been associated with the development of myeloproliferative disease in cats with FeLV infection in one experimental study.[70] Although concurrent problems usually are present in '*Candidatus* M. haemominutum'–infected cats that develop anemia, cases of so-called primary '*Candidatus* M. haemominutum' anemia (i.e., without any apparent concurrent disease or infection present) also have been reported,[71] so infection with this species cannot be ruled out as a cause of anemia in an individual case. However, conflicting data exist, as one US study actually documented that '*Candidatus* M. haemominutum'–infected cats were less likely to be anemic than non–'*Candidatus* M. haemominutum'–infected cats.[21]

'*Candidatus* M. turicensis' infection has resulted in anemia[67] or a small fall in red blood cell parameters in some experimental studies,[64] but generally anemia is uncommon following infection. Both concurrent disease and immunosuppression are thought to be involved in the pathogenesis of '*Candidatus* M. turicensis' disease,[52] in a similar way to the pathogenesis described for '*Candidatus* M. haemominutum.' Determining the pathogenicity of '*Candidatus* M. turicensis' in naturally infected cats has been difficult in epidemiological studies because cats often are coinfected with other hemoplasma species, which confounds disease associations.

It is possible that different strains of each of the feline hemoplasma species reported exist, and that these also vary in pathogenicity. This might explain some of the conflicting data reported in different studies. However, other factors, such as the underlying health status of the cat, and possibly even the transmission route of infection, might play a role in the outcome of hemoplasma infection.

Studies regarding the pathogenicity of canine hemoplasmas are sparse. Hemoplasma infection in dogs usually results in hemolytic anemia only in splenectomized or immunocompromised dogs,[72-75] and asymptomatic latent *M. haemocanis* infections can be reactivated following splenectomy. However, recognition of the possibility of hemoplasma infection is important to differentiate such cases from cases of primary immune-mediated hemolytic anemia, as some cases show evidence of erythrocyte-bound antibodies in positive Coombs' tests.[76,77]

Carrier Status

Long-term carrier status can occur with feline hemoplasma infection, with infected cats often being asymptomatic.[24,78] The author's experience is that this is particularly common with '*Candidatus* M. haemominutum' infection, although suspected clearance of infection has been reported by others with and without antibiotic treatment.[28] We have observed that a large proportion of *M. haemofelis*–infected cats spontaneously clear infection from peripheral blood a few months following acute infection; this also has been reported with '*Candidatus* M. turicensis' infection. However, generalized statements regarding long-term carrier status cannot be made since great variation exists, likely because of differences in the host-organism interaction and hemoplasma isolates. Often, carrier cats have subclinical infections, but reactivation of infection can occur and could result in clinical disease[79,80]; this is uncommon in our experience.

Little work has been done regarding the time course of carrier status with canine hemoplasmas, but asymptomatic carrier dogs infected with '*Candidatus* M. haematoparvum' and *M. haemocanis* are thought to exist.[56]

Transmission

The natural route of transmission of hemoplasma infection between cats and dogs in the field has not yet been determined, and it could be that different routes predominate for the different hemoplasma species that exist.

Canine and feline hemoplasma DNA has been found in fleas and ticks,[42,49,53,81-85] although this does not equate with vectors mediating transmission, as it could reflect their hematophagous activity on infected hosts. The clustered geographical distribution of infection in some studies supports the role of an arthropod vector in hemoplasma transmission.[21] The cat flea, *Ctenocephalides felis,* has been implicated in feline hemoplasma transmission, but only very transient *M. haemofelis* infection has been reported in cats infected experimentally via the hematophagous activity of fleas, and clinical and hematological signs of *M. haemofelis* infection were not induced in the recipient cat.[86] Additionally, a recent study found no evidence of hemoplasma transmission by fleas in an experiment involving the introduction of fleas into groups of cats housed together.[87] Transmission of *M. haemocanis* by the brown dog tick, *Rhipicephalus sanguineus,* has been demonstrated experimentally, although this was before PCR was available to confirm diagnosis of infection.[82]

The association between hemoplasma infection and male gender and/or retrovirus status (particularly FIV) seen in some studies could suggest that cat fights are involved in transmission of infection. Studies in Switzerland have found that subcutaneous inoculation of '*Candidatus* M. turicensis'–containing blood resulted in infection transmission, whereas the same inoculation method using '*Candidatus* M. turicensis'–containing saliva did not. This suggests that hemoplasma transmission by social contact (e.g., saliva via mutual grooming) is less likely than transmission by aggressive interaction (e.g., blood transmission during a cat bite incident).[88] However, a recent study[87] on '*Candidatus* M. haemominutum' and *M. haemofelis* transmission found evidence of horizontal transmission of '*Candidatus* M. haemominutum,' but not *M. haemofelis,* by direct contact between cats in the absence of aggressive interaction and vectors. Vertical transmission has not been definitively shown using molecular methods with canine or feline hemoplasma infections but has been suggested for other hemoplasma species.[89] Blood transfusion is another potential route of transmission, and blood donors should be screened for hemoplasma infection.[90]

Clinical Presentation and Laboratory Abnormalities

The clinical disease that follows hemoplasma infection is influenced by the stage of infection, the host response to the organism, the health status of the host, and which species of hemoplasma is involved. *M. haemofelis* and *M. haemocanis* in splenectomized dogs are most likely to be associated with clinical signs during acute infection. On the other hand, '*Candidatus* M. haemominutum,' '*Candidatus.* M. turicensis' and '*Candidatus* M. haematoparvum' generally are not associated with clinical signs unless concurrent disease or immunosuppression is present.

Common clinical signs associated with hemoplasmosis are lethargy, pallor, and weakness. Inappetence, dehydration, weight loss and intermittent fever also are reported. Splenomegaly also can be evident in cats with feline hemoplasmosis; in contrast, this is not commonly seen in dogs with clinical hemoplasmosis because such dogs usually no longer have a spleen due to a previous history of splenectomy, the latter increasing their susceptibility to clinical hemoplasmosis.

Affected animals with severe anemia can have tachycardia, tachypnea, and weak or bounding femoral pulses with hemic cardiac murmurs. Icterus is very rare, despite the severe nature of the anemia involved. Moribund cats can be hypothermic.

Pathogenic hemoplasma infections typically cause a regenerative anemia that is macrocytic and hypochromic, although pronounced reticulocytosis is not always evident.[91] Normoblasts can be present. Positive Coombs' test results, particularly with cold agglutinins, and persistent autoagglutination, have been reported in acute hemoplasmosis, indicating the presence of erythrocyte-bound antibodies. Hyperbilirubinemia is seen occasionally, due to hemolysis, and hypoxic liver injury can result in increased activities of alanine aminotransferase (ALT). Hyperproteinemia is sometimes seen in affected cats. Retrovirus testing can be positive in cats.

Differential Diagnoses

Hemoplasmosis should be considered as a differential diagnosis in cats or dogs presenting with regenerative (although occasionally nonregenerative) anemia and possibly associated fever. Other diagnoses to consider are primary immune-mediated hemolytic anemia (see ch. 198), secondary immune-mediated hemolytic anemia (e.g., secondary to drugs, neoplasia, infections; see ch. 198), cytauxzoonosis (cats; see ch. 221), retroviral infection (cats; see ch. 222 and 223), babesiosis (see ch. 221), Heinz-body–associated hemolysis (cats; see ch. 152 and 198), hypophosphatemia (see ch. 69), and inherited red blood cell disorders such as pyruvate kinase deficiency (see ch. 198).

Diagnosis

Cytology

Cytologic examination of blood smears can show hemoplasmas on the surface of erythrocytes (Figure 219-3) (occasionally in chains, especially with *M. haemocanis* [Figure 219-4]), but this is known to be very insensitive for diagnosis (0 to 37.5%),[23,24,48,92] with huge numbers of organisms needed in the blood before they can be visualized cytologically. Additionally, cytologic evaluation cannot differentiate easily between hemoplasma species,[93] despite reports in cats suggesting that '*Candidatus* M. haemominutum' organisms are smaller than *M. haemofelis.*[94] '*Candidatus* M. turicensis' has never been visualized cytologically,[95] probably due to the low numbers of organisms seen in blood during infection with this species.[64] As well as having poor sensitivity, specificity can be an issue for cytological diagnosis of hemoplasma infection, as the untrained eye can fail to distinguish stain precipitate from true hemoplasma organisms, and careful staining with a properly prepared, filtered Romanowsky-type stain solution (e.g., Wright Giemsa or Diff-Quik) is essential. Organisms also need to be differentiated from Howell-Jolly bodies and basophilic stippling. In experienced hands (e.g., board-certified clinical pathologists, with whom specificity is reported as 84 to 98%),[23,24,48,92] the finding of epicellular organisms on the surface of erythrocytes in association with clinical signs of hemoplasmosis can be supportive of the diagnosis, but PCR testing should be performed for confirmation.

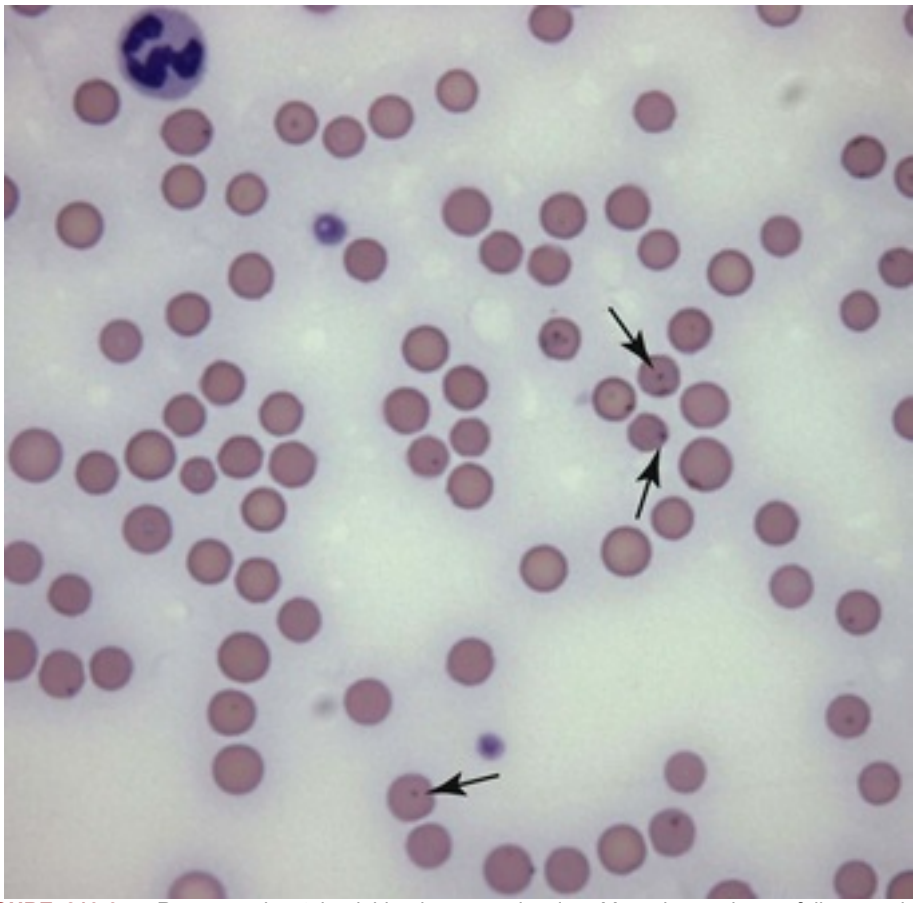

FIGURE 219-3 Romanowsky-stained blood smear showing *Mycoplasma haemofelis* organisms (arrows) on the surface of erythrocytes. Cytology is, however, an insensitive method for diagnosing hemoplasma infections. (Image courtesy Dr. Jane Sykes.)

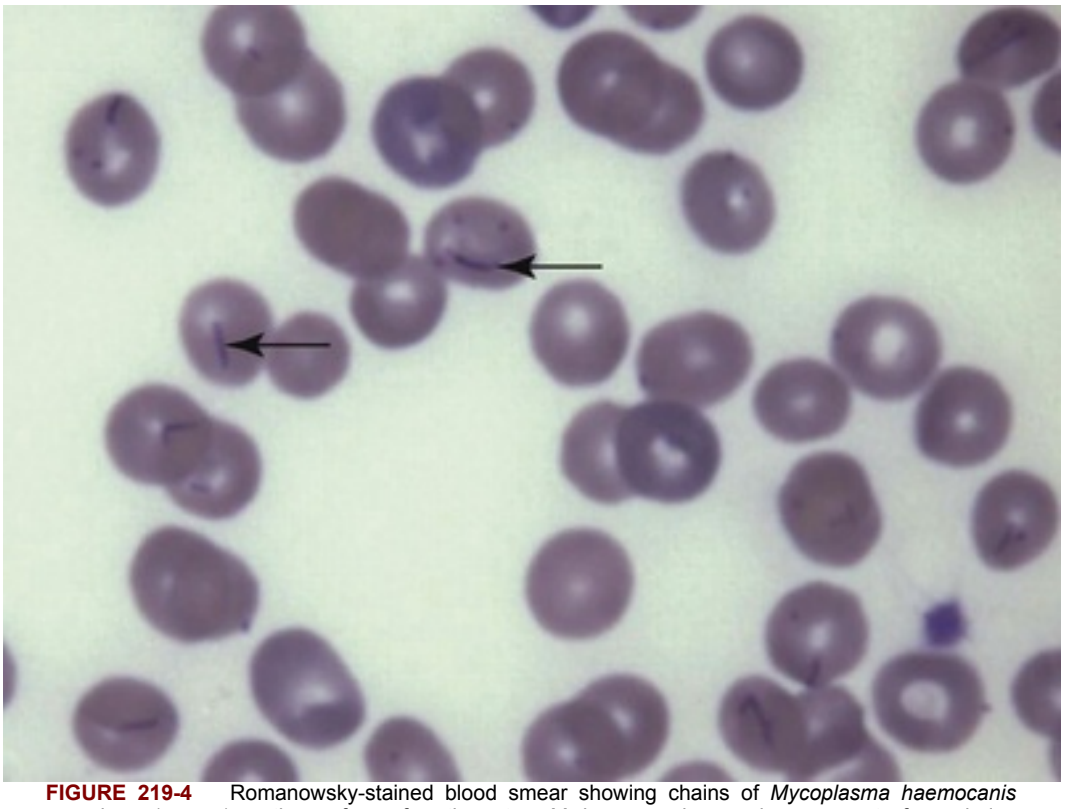

FIGURE 219-4 Romanowsky-stained blood smear showing chains of *Mycoplasma haemocanis* organisms (arrows) on the surface of erythrocytes; *M. haemocanis* organisms seem to form chains more commonly than other species but cytology is still insensitive for diagnosis. (Image courtesy Dr. Jane Sykes.)

Polymerase Chain Reaction Assays

PCR is now the diagnostic method of choice for hemoplasma infection. When properly designed and executed, PCR is far more sensitive than cytologic examination of blood smears, although PCR might not detect organisms in some asymptomatic carrier cats that have very low numbers of organisms in the blood, below the detection limit of the PCR assay. Some hemoplasma PCRs have been duplexed with a host housekeeping gene (such as the 28S rRNA gene) PCR[96]; the inclusion of such an internal control is important in order to prevent false-negative results for hemoplasma infection due to the failure of DNA extraction, presence of PCR inhibitors, or qPCR setup errors. Specificity also is a valuable feature, with diagnostic PCRs being available for each of the feline and canine hemoplasma species. Real-time quantitative PCR (qPCR) assays also exist that allow quantification of hemoplasma DNA in the patient's blood; this can allow one to monitor the course of hemoplasma infection and evaluate any response to treatment, such as a decrease in the level of hemoplasma DNA in the blood following institution of effective antibiotic treatment. The fluctuations in blood organism numbers that can occur during *M. haemofelis* infection (see Figure 219-2) should be considered when interpreting qPCR results, as decreases in organism number cannot always be deemed a consequence of effective antibiotic treatment or host immune response. When a positive PCR result is obtained for hemoplasma infection, the result must always be interpreted with the clinical signs, clinicopathological results, and any concurrent disease or immunosuppression present because asymptomatic carrier cats exist. The pathogenicity of the agent detected also should be considered when deciding whether the positive result represents the cause of the animal's signs.

Serology

Serologic assays to detect antibodies to feline hemoplasma proteins currently are only available for research (see Figure 219-2). One study, using an ELISA based on recombinant *M. haemofelis* DnaK, suggested that serologic assays could differentiate acute from chronic *M. haemofelis* infection,[97] and another study found that a similar serologic assay was more sensitive than PCR in detecting exposure to '*Candidatus* M. turicensis.'[98]

Further work is required to determine the specificity of these assays before they can be used commercially in naturally infected cats.

Treatment

Antibiotic treatment is indicated for cats and dogs with clinical signs and clinicopathological abnormalities consistent with hemoplasmosis. Treatment also should be considered for cats that test positive for *M. haemofelis* in view of the potential for recrudescence of disease with this hemoplasma species. However, no antibiotic treatment regime exists that is known to predictably eliminate hemoplasma infection with any species of these organisms. Antibiotics typically are given for 4 weeks.

Several antibiotics, notably tetracyclines[75,99] and fluoroquinolones,[99-103] have been shown to be effective in reducing hemoplasma organism numbers in reports in cats and dogs, although the vast majority of studies are with *M. haemofelis* only. Doxycycline (10 mg/kg PO q 24 h for 4 weeks) often is used as a first-line agent for treating hemoplasmosis; longer treatment courses (e.g., 6-8 weeks) are recommended by some clinicians to increase the likelihood of elimination of infection, although longer treatment courses do not guarantee elimination. Because of the possibility of esophagitis in cats, administration of the hyclate preparation of doxycycline always should be followed by food or water. Marbofloxacin (2 to 5.5 mg/kg PO q 24 h [please note different licensed dosages exist in different countries]) or pradofloxacin (3 to 5 mg/kg PO q 24 h [depending on drug formulation]), both fluoroquinolones, can be used as second-line agents. Pradofloxacin could be more effective at clearing *M. haemofelis* infection than doxycycline.[103] Enrofloxacin also is usually effective, but permanent retinotoxicosis has been reported in cats, and so, although this adverse effect is rare, great caution must be exercised with the use of enrofloxacin in cats. Azithromycin was not effective in one study of cats infected with *M. haemofelis* and/or '*Candidatus* M. haemominutum.'[92]

Different hemoplasma species respond to antibiotic treatments differently. Although marbofloxacin resulted in a marked and sustained lowering of blood *M. haemofelis* organisms in cats in one study,[102] a similarly designed study showed only a temporary lowering of numbers of '*Candidatus* M. haemominutum' organisms in blood.[101] Another study suggested that '*Candidatus* M. haemominutum' infection was not treated as effectively with doxycycline as was *M. haemofelis*,[62] and PCR-positive results for '*Candidatus* M. haemominutum' infection were reported in five cats following either enrofloxacin or doxycycline treatment.[22] Little work has been done on the response of '*Candidatus* M. turicensis' infection to antibiotics, but one report described a successful response to doxycycline in a case.[28] Some cases appear to be refractory to antibiotic treatments, and in one *M. haemocanis* case report, oxytetracycline, and then enrofloxacin, treatment, did not markedly reduce organism numbers, although clinical signs did improve.[74] One isolate of the porcine hemoplasma *M. suis* was able to penetrate porcine erythrocytes and its subsequent intracellular location was associated with marked resistance to antibiotic therapy[104]; it is possible that this could occur with hemoplasmas in other species. Occasionally, dual antibiotic therapy (typically doxycycline and marbofloxacin) has been tried, with variable success; it may be worth considering introduction of an additional agent if monotherapy with doxycycline or a fluoroquinolone is inadequate.

Ideally, response to antibiotics should be monitored by qPCR to ensure organism numbers are decreasing with therapy because response to treatment is not predictable. However, repeat qPCR might not be necessary if the patient shows a rapid and favorable clinical response to treatment. Repeated complete blood counts also should be performed. Affected dogs and cats also could require supportive treatment with crystalloids or blood products (blood transfusion or treatment with an oxygen-carrying hemoglobin compound, if available; see ch. 130). Clinical improvement usually occurs within 2 to 3 days of effective treatment.

The use of immunosuppressive dosages of glucocorticoids to suppress the associated immune-mediated hemolytic process is controversial, because treatment with antibiotics and supportive care alone usually is adequate, even in animals with erythrocyte-bound antibodies.[64] Glucocorticoids have the potential to cause reactivation of hemoplasma infection, and in one case, negative PCR results for *M. haemocanis* were only obtained once prednisolone therapy for presumed immune-mediated hemolytic anemia had stopped.[75] However, in cases with a lack of response to antibiotics and persistent erythrocyte-bound antibodies, cautious use of glucocorticoids (e.g., prednisolone 1-2 mg/kg PO q 24 h) can be considered.

Prevention

Blood donors should be screened via PCR for hemoplasma infection to help prevent inadvertent transmission

from asymptomatic carrier cats or dogs. Keeping cats indoors also is likely to prevent infection, as outdoor status has been identified as a risk factor and, in view of the potential for vector transmission, preventive flea and tick treatment is recommended.

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CHAPTER 220

Enteric Bacterial Diseases

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Overview

The Quandary in Confirming a Diagnosis of Enteric Bacterial Diseases

Veterinarians face a quandary when attempting diagnosis of dogs and cats with enteric bacterial disease because isolation rates for putative bacterial enteropathogens are similar in diarrheic and nondiarrheic animals and the incidence of bacterial-associated diarrhea is extremely variable.[1-3] Indications for performing a "fecal enteric panel" in a dog or cat are poorly defined, causing indiscriminate testing and misinterpretation of results. Specific practice guidelines have been published for diagnosis and management of infectious diarrhea in people to improve the cost effectiveness of diagnostic testing and to maximize the diagnostic yield for detection of bacterial enteropathogens.[4]

Although fecal cultures are commonly submitted in people with diarrhea, their usefulness has been questioned because, in part, their diagnostic yield is low.[5,6] 28/260 dogs with diarrhea (10.8%) had positive fecal bacteriologic panels ($650/positive test result).[2] The 28 positive results may have included false-positives, as causality was not established. These tests are relatively insensitive for the most likely pathogens, and results were likely affected by the poor selection of specimens for culture. The advent of real-time polymerase chain reaction (PCR) panels for dogs and cats with diarrhea has provided a new paradigm for rapid and sensitive detection of toxin genes or organisms associated with disease. However, interpretation of these panels can also be problematic because virtually all of these bacterial organisms have been frequently isolated from the feces of clinically healthy dogs and cats. *Bona fide* bacterial enteropathogens of dogs and cats include *Clostridium difficile, Clostridium perfringens, Salmonella, Campylobacter jejuni,* and *Escherichia coli* associated with granulomatous colitis (GC). Available methodologies to detect these enteropathogens lack sensitivity and, in some cases, specificity. Determining etiology in cases of bacterial-associated gastroenteritis is a problem magnified by the challenges of defining what exactly constitutes a pathogen. Many strains of non-*jejuni Campylobacter* spp., *C. difficile, C. perfringens,* and *E. coli* can be detected in the absence of diarrhea.[2,5,6]

Recommendations Regarding Fecal Enteric Panels

The specific indications for performing fecal enteric panels consisting of fecal cultures, toxin analysis, and genotyping are poorly defined. Most veterinary microbiologists recommend enteric panels for dogs and cats developing diarrhea after kenneling or show attendance, in animals with an acute onset of bloody diarrhea in association with evidence of sepsis, and in diarrhea outbreaks occurring in more than one household pet. Since *C. difficile, Campylobacter jejuni,* and *Salmonella* spp. are zoonotic, judicious screening for these organisms is warranted when an immunocompromised person is in close contact with a potentially infected animal or the animal is in contact with children.

Clostridium perfringens

Description

Clostridium perfringens is an anaerobic, spore-forming, Gram-positive bacillus associated with outbreaks of acute, often severe diarrhea in humans, horses, dogs, and cats. The elaboration of four major toxins (alpha, beta, epsilon, and iota) is the basis for typing the organism. There are 5 toxigenic phenotypes, A-E. Each

biotype may also express a subset of at least 10 other established toxins, including *C. perfringens* enterotoxin (CPE), a well-characterized virulence factor whose production is coregulated with sporulation.[7] In recent years, it was shown that a novel toxin, NetB, was produced by most type A isolates from chickens with necrotic enteritis (NE) and to play an important role in the pathogenesis of NE.[8] There is increasing evidence that related necrotizing genes such as *netF* are associated with canine acute hemorrhagic diarrhea syndrome (AHDS).[8a] CPE was detected in the feces of 8/12 dogs that had clinical signs consistent with AHDS. Each of 4 dogs with peracute clinical signs died, and each had fecal specimens positive for CPE. Although several studies have shown an association between immunodetection of CPE in fecal specimens and canine diarrhea, the pathogenesis of *C. perfringens*–associated diarrhea in the dog and cat is not fully understood, as CPE is also detected in up to 14% of nondiarrheic dogs.[1,9] In our experience, no CPE was detected in fecal specimens collected from 51 healthy nondiarrheic cats but was positive in 9/62 (14%) specimens from diarrheic cats. It is important to use caution when interpreting results of fecal enzyme-linked immunosorbent assays (ELISAs) for CPE and *C. difficile* toxin A and B in neonatal kittens, due to the high incidence of positive ELISAs (up to 50%) documented by the author in apparently healthy kittens.

Pathogenesis

CPE is a 35-kDa protein encoded by the *cpe* gene, whose expression is coregulated with sporulation of the organism.[7,9] *Clostridium perfringens* strains that carry a chromosomal *cpe* have primarily been associated with human foodborne disease, whereas strains with a plasmid *cpe* gene have been associated with human nonfoodborne diseases and animal diseases, including canine diarrhea. Nonfoodborne diseases associated with CPE are thought to involve commensal enterotoxigenic strains that are triggered to undergo massive sporulation. The trigger may be one of several factors, including sudden change in diet, antibiotic administration, or coinfection with another intestinal pathogen. Once released into the intestinal lumen, CPE interacts with specific epithelial tight junction proteins, forming a small protein complex of ≈90 kDa, where it then becomes trapped on membrane surfaces.[10] Small CPE complexes then interact with additional host proteins, forming larger complexes. Studies have suggested a ≈155 kDa complex is responsible for the cytotoxic and histopathological damage, which provides CPE access to occludin, causing alterations in tight junction structure and function, leading to paracellular permeability changes that contribute to diarrhea.[10]

Diagnosis

Signs

No gold standard exists for confirming a diagnosis of canine or feline *C. perfringens*–associated diarrhea. Diagnosis in dogs and cats is optimally based on detection of CPE in fecal specimens in conjunction with PCR detection of the enterotoxin gene *(cpe)*.[1] There are no pathognomonic clinical signs for *C. perfringens*–associated diarrhea in dogs. Infection can cause small intestinal, large intestinal, or diffuse clinical signs (see ch. 40).[2] Dogs with *C. perfringens*–associated diarrhea typically have large-bowel diarrhea characterized by increased frequency, tenesmus, fecal mucus, and hematochezia. However, clinical signs of enteritis or enterocolitis are also commonly seen.[2]

CPE, Hematocrit

There appears to be a strong association between ELISA-detected CPE and AHDS.[2] *C. perfringens* warrants consideration in a dog with acute hemorrhagic diarrhea, as a causative or associative enteropathogen. Many dogs with acute hemorrhagic diarrhea associated with CPE have increased hematocrits and low-normal total protein concentrations.

Fecal Culture

Quantitative fecal culture and fecal spore counts are of little diagnostic value, as the organism is isolated from more than 80% of healthy dogs. There is no correlation between spore counts and detection of CPE, or between fecal consistency and detection of CPE.[1,11] A commercially available ELISA kit (Techlab Inc., Blacksburg, VA) for detecting CPE in fecal specimens has not yet been validated in the dog or cat. Further, as many as 14% of healthy dogs have detectable concentrations of CPE, based on this ELISA's results.[1]

Polymerase Chain Reaction (PCR)

PCR detection of enterotoxigenic *C. perfringens (cpe)* was shown to be a valuable diagnostic test when combined with immunodetection of CPE. In that study, fecal specimens from nondiarrheic dogs were far less likely to be positive for both CPE and *cpe* (4%) compared to diarrheic dogs (28%).[1] Quantitation of the alpha toxin gene of *C. perfringens* via RT-PCR is performed to help diagnose *C. perfringens*–associated diarrhea in dogs and cats; however, the alpha toxin gene is often detected and increased in healthy nondiarrheic animals, decreasing the diagnostic utility of this particular test.

Treatment

Animals that are systemically ill (e.g., fever, hemorrhagic gastroenteritis, inflammatory or toxic leukogram) merit appropriate antimicrobial therapy. There is no evidence supporting use of antimicrobial therapy in dogs with uncomplicated diarrhea associated with *C. perfringens.* Antibiotics that have been recommended for the treatment of canine *C. perfringens*–associated diarrhea include ampicillin (22 mg/kg q 8 h for 5 days), metronidazole (10 mg/kg q 12 h for 5 days), and tylosin (5-10 mg/kg q 24 h for 5 days). Tetracycline use should be avoided due to a high incidence (21%) of *in vitro* resistance.[12] Reports touting the benefits of increasing dietary fiber or administering probiotics to infected animals to alter the commensal microflora have not been validated.

Clostridium difficile

Description

Clostridium difficile is a fastidious Gram-positive, anaerobic spore-forming bacillus. It is the most common cause of antibiotic-associated pseudomembranous colitis in people. *Clostridium difficile* has also been associated with diarrhea and enterocolitis in foals, adult horses, and dogs. An outbreak of *C. difficile* infection (CDI) was reported in dogs at a veterinary teaching hospital with an incidence of 19 cases per 1000 admissions.[13] There is far less information about CDI in cats, although it less prevalent than in dogs. ELISA testing for *C. difficile* toxin A was negative in all of 219 diarrheic cats.[14] Two toxins, toxin A (TcdA, an enterotoxin) and toxin B (TcdB, a cytotoxin), are thought to be primarily responsible for the disease, although other toxins may also play a role. In addition, a small percentage of healthy individuals can carry *C. difficile* in their intestinal tracts without any signs of disease.

Pathogenesis

Clinical disease begins with intestinal growth of toxin-producing strains of *C. difficile* followed by release of toxins and subsequent development of disease. In people, antimicrobials may disrupt normal commensal microflora with subsequent overgrowth of toxigenic strains of *C. difficile.* There is no convincing evidence of a similar pathogenesis in dogs or cats. The primary virulence factors involved in the pathogenesis of CDI are TcdA and TcdB.[15] Some *C. difficile* strains can produce a binary toxin (CDT), although its role is unclear.

Diagnosis

Fecal Culture

There are no pathognomonic clinical signs in dogs and cats, although a strong association was found between the detection of *C. difficile* TcdA and the presence of AHDS in dogs, similar to that described for *C. perfringens*.[2] Selective culture media, such as cycloserine cefoxitin fructose agar or *C. difficile* moxalactam norfloxacin agar, should be used, with fecal-direct inoculation or after-broth enrichment. Isolation of the organism alone is not sufficient for diagnosis due to the presence of nontoxigenic strains; however, appropriately processed and cultured specimens that are culture-negative have good negative predictive value. Detection of common antigen (glutamate dehydrogenase), an enzyme produced constitutively by toxigenic and nontoxigenic strains, is a sensitive but nonspecific test commonly performed in human and veterinary laboratories. A recent study evaluating the performance characteristics of the common antigen test in dogs showed a sensitivity of 100% but low specificity. The value of this test is to screen dogs suspected of having CDI.[16]

ELISA and Cell Culture Cytotoxicity Assay (CTA)

Traditionally, diagnosis of CDI is based on detection of TcdA and/or TcdB in fecal specimens via ELISA. Commercially available ELISAs are commonly used in veterinary reference laboratories; however, the performance characteristics of these human-based assays are inconsistent and poor in dogs, with sensitivities ranging from 7-60%.[16] The current gold standard test for CDI is the CTA, which detects TcdB activity.[17] Due to expense and time, it is not routinely used.

Recommended Approach

Diagnosis of CDI in dogs and cats should be based on combination testing, including a positive fecal culture and/or common antigen test, followed by ELISA for detection of TcdA and TcdB. Antigen- or culture-positive but toxin-negative results are difficult to interpret because of the marginal sensitivity of available tests. Positive results indicate a *possible* diagnosis of CDI in an animal with diarrhea and no other identifiable cause, but such testing cannot be considered definitive. There are currently no validated PCR tests for *C. difficile* in dogs and cats. Performing direct PCR from stool can be associated with false-negative results due to PCR inhibitors. Direct PCR for diagnosis of CDI in dogs and cats is not recommended.

Treatment

In general, CDI is treated like any other diarrheal disease. Supportive therapy should be administered based on clinical signs. If CDI is suspected to be antimicrobial-associated, antimicrobial therapy should be stopped if possible. Parenteral antimicrobial therapy rarely is indicated for CDI unless the animal is systemically ill. Metronidazole (10 mg/kg q 12 h for approximately 5 days) is the therapy of choice for dogs and cats with suspected CDI. Although metronidazole-resistant *C. difficile* isolates obtained from foals and adult horses have been reported, a study evaluating the susceptibilities of 70 canine *C. difficile* isolates showed all were susceptible to ≤1 mcg/mL.[12] The second drug of choice in humans and occasionally in horses is vancomycin; however, it is used only in cases of nonresponsive CDI or when metronidazole-resistant strains have been demonstrated.

Campylobacter spp.

Description

Campylobacter spp. are small (0.2 to 0.5 micron × 0.5 to 5 micron), microaerophilic, Gram-negative, curved, slender, rod-shaped bacteria with more than 37 species and subspecies in the genus. Most are thought to be nonpathogenic. *Campylobacter* species implicated in canine enteric disease include *C. jejuni, C. coli, C. helveticus,* and *C. upsaliensis. Campylobacter helveticus* and *C. upsaliensis* are the most common isolates identified in cats. Some selective media have an inhibitory effect on a number of *Campylobacter* spp. This increases the possibility of more sensitive species (*C. upsaliensis* or other catalase-negative or weakly-positive species) being missed.[18] Fecal shedding of *C. jejuni* is significantly greater in puppies <6 months old and during the summer and autumn.[19] The higher prevalence of infection in pups versus adult dogs may reflect their confinement and increased exposure to excrement. In addition, naïve puppy immune systems may increase susceptibility to intestinal colonization by *C. jejuni.* Other enteric pathogens, such as parvovirus, *Giardia,* or *Salmonella* may have synergistic roles. Isolation of *Campylobacter* spp. from a diarrheic animal does not necessarily implicate *Campylobacter* as a cause of the diarrhea. *Campylobacter* spp. was isolated from 21 of 219 (9.6%) diarrheic cats versus 15/54 (27.8%) of nondiarrheic cats, similar to other studies.[14,20,21]

Pathogenesis

Campylobacter spp. have a fecal-to-oral route of transmission either through direct contact or via objects contaminated with feces. Various virulence factors are associated with colonization, adhesion, invasion, persistence within the host, and host cell damage. The cause of diarrhea due to *Campylobacter* infection is poorly understood, and the only exotoxin characterized in *Campylobacter* is cytolethal distending toxin, or CDT.[22] This toxin has 3 proteins, CdtA, CdtB, and CdtC, all of which are required for cellular damage. A bowel neutrophilic inflammatory response has been described in association with *Campylobacter* infection, and active intestinal fluid secretion may be due to *Campylobacter* products that increase cAMP, prostaglandin E_2, and leukotriene B_4.

Diagnosis

Fecal Examination

Dogs and cats are often healthy carriers of *Campylobacter* species. If ill, clinical signs include anorexia, occasional vomiting, and watery to bloody diarrhea with mucus. The animal can be febrile, and severely affected animals can be lethargic and dehydrated. Diagnosis is confirmed via several different methodologies, beginning with examination of a direct-stained fecal smear (Gram stain or Romanowsky-type stain) for the organism's characteristic appearance (slender, curved rods with an "S" shape or seagull–shaped appearance). The major limitation of direct examinations is that the procedure fails to differentiate among *Campylobacter* spp. or between it and related organisms including *Helicobacter* spp., and *Anaerobiospirillum* spp. In addition, identification of *Campylobacter*-like organisms (CLOs) alone on a stained fecal smear is not sufficient to warrant a diagnosis of *Campylobacter*-associated diarrhea, as many healthy dogs and cats can harbor CLOs in their intestinal tract.[2]

Fecal Culture

For optimal recovery of *Campylobacter* spp., feces or fecal swabs should be fresh or placed immediately into anaerobic transport medium before refrigeration at 4° C. For isolation, use of a formulated selective medium containing antimicrobial agents (e.g., Campy-CVA containing cefoperazone, vancomycin, and amphotericin B) is recommended over other direct-plating selective media. Microaerophilic incubation conditions should be maintained, and the plates incubated at 37° C, or at 42° C, when isolation of *C. jejuni* and *C. coli* from feces is attempted. Suspect colonies should be Gram-stained and subcultured to 5% SBA. Biochemical tests can then be performed to speciate all *Campylobacter*-like organisms isolated. The selective medium containing cefoperazone should be used when attempting to isolate *C. upsaliensis*, as the organism is more resistant to cefoperazone than to cephalothin.[23]

Molecular Techniques

Several molecular techniques have been used to identify and differentiate *Campylobacter* spp. These assays include direct sequencing of the 16S rDNA and comparison with databases such as GenBank, DNA hybridization with probes specific for different species, PCR amplification of specific regions of 16S rDNA or the *lpx*A gene, and amplified fragment length polymorphism. These tests may aid in differentiating a variety of *Campylobacter* species, such as *C. coli, C. jejuni, C. lari,* and *C. upsaliensis*.[21]

Treatment

The majority of cases are uncomplicated, self-limiting and resolve with supportive therapy. Because isolation of *Campylobacter* does not confirm causation, treatment may not be warranted. Antibiotics may further disrupt intestinal microflora. However, in animals that are immunocompromised, febrile, or with evidence of hemorrhagic diarrhea, antimicrobial treatment may be indicated. It is now recognized that *Campylobacter* are a leading cause of enteric disease in people and that diarrheic and nondiarrheic dogs can serve as sources of infection for humans.[24] The drugs of choice are the macrolides (erythromycin at 10 to 15 mg/kg q 8 h) or fluoroquinolones (enrofloxacin at 10 mg/kg q 24 h). Fluoroquinolones are not used initially due to their high rate of mutational resistance. The macrolides such as erythromycin (10-20 mg/kg q 8 h for 7 days, despite possible gastrointestinal side-effects) or azithromycin (5-10 mg/kg q 24 h for 7 days) are the drugs of choice.[25] Bacterial shedding can last as long as 4 months. Infected animals should be quarantined away from children for this period.

Salmonella spp.

Description

The salmonellae are Gram-negative, motile, non–spore-forming facultative anaerobic bacilli belonging to the family *Enterobacteriaceae.* The genus *Salmonella* consists of only 2 species, *Salmonella enterica* and *Salmonella bongori. S. enterica* is divided into 6 subspecies: *S. enterica* subsp. *enterica, S. enterica* subsp. *salamae, S. enterica* subsp. *arizonae, S. enterica* subsp. *diarizonae, S. enterica* subsp. *houtenae* and *S. enterica* subsp. *indica.*[26] *Salmonella* spp. are among the most common causes of human foodborne disease: an estimated 1.4 million cases occur annually in the United States.[27] Clinical salmonellosis in dogs and cats is rare, although the prevalence is

higher in puppies and kennel populations. Isolation of *Salmonella* spp. from adult dogs range from 0 to 2% in nondiarrheic and 0 to 1% in diarrheic dogs.[2] Isolation rates are similar in nondiarrheic and diarrheic cats. *Salmonella* was isolated from 80% of raw chicken diet samples and from 30% of the stool samples from dogs fed these diets.[28]

Pathogenesis

Salmonella infections begin with ingestion of organisms in contaminated food or water, followed by invasion of M-cells in the Peyer's patches. *Salmonella* express several fimbriae that contribute to their ability to adhere to intestinal epithelial cells.[29] *Salmonella* pathogenicity islands (SPI-1 and SPI-2) encode the genes necessary for the invasion of intestinal epithelial cells, induction of intestinal secretory and inflammatory responses, intracellular replication, and establishment of systemic infection.[30] *Salmonella* spp. inject an array of bacterial effector molecules into host cytoplasms, triggering reorganization of actin cytoskeletons and resultant membrane ruffling. Cell internalization of *Salmonella* occurs within minutes of bacterial contact. Invasion is followed by inflammation, influx of neutrophils and macrophages, and consequent secretory diarrhea. This is likely mediated by activation of inositol-signaling pathways within affected host cells. The presence or absence of additional virulence factors plays an important role in determining whether septicemia occurs.

Clinical Signs

Signs of clinical salmonellosis in dogs and cats are typically acute and characterized by fever, malaise, anorexia, diarrhea, and vomiting. The diarrhea is frequently watery or mucoid and can be bloody. Most *Salmonella*-infected dogs and cats are asymptomatic, although some animals may manifest clinical signs of sepsis (see ch. 132).

Diagnosis

The traditional diagnosis of salmonellosis is made based on isolation of the organism in conjunction with clinical signs and assessment of potential risk factors such as hospitalization, age, environmental exposure, and antibiotic administration. However, isolation of *Salmonella* is not necessarily indicative of its involvement, as similar isolation rates can be detected in healthy nondiarrheic animals.[2] Hematological abnormalities are variable and include a nonregenerative anemia, lymphopenia, thrombocytopenia, and neutropenia with a left shift. Toxic neutrophils may be seen in animals with systemic disease and endotoxemia, findings similar to those documented with canine parvovirus (see ch. 225). Fresh fecal specimens should be placed onto one or more selective media, including MacConkey agar, XLD agar, and brilliant green agar. For enrichment, selenite F broth, tetrathionate broth, or Gram-negative (GN) broth is recommended. Biochemical testing can be used to identify presumptive *Salmonella* colonies, followed by serological testing of isolates for further discrimination. Conventional and real-time PCR are promising diagnostic tools that are increasingly used by reference laboratories.

Treatment

It is widely accepted (although supportive scientific evidence is lacking) that the administration of antimicrobials is not warranted for uncomplicated episodes of *Salmonella* infection. Only supportive therapy is recommended. Intravenous fluid therapy may be required depending on the severity of the diarrhea. Antibiotics reported to be effective against *Salmonella* include fluoroquinolones, chloramphenicol, trimethoprim-sulfonamide, and amoxicillin.[31] Salmonellosis is a disease of major zoonotic importance, and all *Salmonella* organisms with the exception of those causing human typhoid fever infect humans and animals.

Enteric *Escherichia coli (E. coli)* Infections

Description

E. coli is a pleomorphic, Gram-negative, non–spore-forming bacillus. It is a member of the family *Enterobacteriaceae*. *E. coli* is among normal intestinal microflora but can be associated with gastroenteritis in the presence of bacterial virulence factors and impaired local or systemic immunity. Seven distinct pathogenic categories (pathovars) of diarrheagenic *E. coli* are recognized, each defined by a characteristic set of virulence

factors acquired by horizontal gene transfer that act in concert to determine the clinical, pathologic, and epidemiologic features of the diseases they cause. The 7 pathovars include enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), enterohemorrhagic *E. coli* (EHEC), necrotoxigenic *E. coli* (NTEC), enteroinvasive *E. coli* (EIEC), enteroaggregative *E. coli* (EAEC), and adherent-invasive *E. coli* (AIEC) strains.[32-34] Many strains have been isolated from dogs with and without diarrhea, and the role of many of these strains in ill dogs and cats is poorly defined. In contrast, there is evidence for the role of AIEC strains in susceptible dog breeds such as the Boxer, French Bulldog, and the Border Collie. Little is known about pathogenic *E. coli* in cats, although EPEC was isolated from approximately 5% of samples from cats with diarrhea, enteritis or septicemia.

Escherichia coli Associated With Granulomatous Colitis

Overview

Granulomatous colitis (histiocytic ulcerative colitis; GC) of Boxer dogs was first described by Van Kruiningen in 1965.[35] The colonic lesion also has been described infrequently in the French Bulldog and the Border Collie. Historically, GC of Boxer dogs was considered an idiopathic immune-mediated disease with a poor prognosis. Poor response to immunosuppression, however, led to reassessment of antibiotic therapy, and there is now convincing evidence documenting dramatic improvement in clinical signs and histological lesions of Boxer dogs treated with enrofloxacin.[36,37] Documentation of periodic acid–Schiff (PAS)-staining positive macrophages in people with Whipple's disease together with the dramatic response to antibiotics in Boxer dogs with a similar enteropathy precipitated the search for an infectious agent.

Diagnosis

Affected Boxer dogs typically have a history of severe large bowel diarrhea often accompanied by marked weight loss, inappetence, and loss of body condition. Hematological changes often are mild and nonspecific, but dogs with severe GC can develop microcytic anemia caused by chronic blood loss. Boxer dogs with GC commonly are hypoalbuminemic. Histopathologic lesions in Boxers with GC are pathognomonic and include mucosal infiltration with large numbers of PAS-positive macrophages, evidence of mucosal ulceration and loss of goblet cells.[35] Colonic biopsies are warranted in Boxer dogs with signs of colitis to eliminate other causes of colitis and to optimize therapy when culture and sensitivity testing of mucosal biopsies is feasible. The identification of Gram-negative coccobacilli within macrophages can be confirmed using fluorescent in situ hybridization (FISH) probes.[35] Colonic tissue culture can be used to isolate *E. coli* and optimize antibiotic selection given the increasing incidence of antibiotic resistance in Boxers.[36]

Treatment

Dogs with GC can show dramatic responses to treatment with enrofloxacin (10 mg/kg q 24 h for 8 weeks). Administration of fluoroquinolones is usually associated with rapid resolution of both clinical signs and the cellular infiltrative nature of this disorder. Antimicrobials that penetrate intracellularly, such as chloramphenicol and trimethoprim-sulfonamides, are potentially viable alternatives for management of dogs with GC, particularly in resistant cases. Drugs should be selected based on results of susceptibility testing.

Zoonotic Implications of Enteric Bacteria

Clostridium Perfringens

There have been no documented cases of zoonotic transmission from dogs or cats. Contaminated food products can lead to enterotoxemia, underscoring the importance of adequate hygiene.

Clostridium Difficile

The risk of zoonotic transmission is currently unclear, and transmission of *C. difficile* from animals to humans has not been documented. Nevertheless, it is recommended to assume that *C. difficile* is potentially zoonotic because the strains of *C. difficile* that infect dogs are often indistinguishable from those found in people with CDI.

Campylobacter spp.

Campylobacter spp. are potentially zoonotic from dogs to humans with subsequent development of diarrhea.[38] An estimated 6.3% of 218 human cases of *C. jejuni* or *C. coli* enteritis was attributed to exposure to diarrheic animals. Other sources of infection in people include consumption of contaminated food and food products, water and raw milk. Pasteurization of milk and thorough cooking of meats and poultry carcasses destroys *C. jejuni.*

Salmonella spp.

Most human *Salmonella* infections are acquired by handling or consuming contaminated food products, particularly foods of animal origin. Infections also are acquired by direct and indirect contact with farm animals, reptiles, chicks, and occasionally, pets. Infected animals usually shed *Salmonella* organisms in their feces.

Escherichia Coli

The potential for zoonotic transmission is unclear; however, some of the strains of pathogenic *E. coli* found in dogs and cats are indistinguishable from those found in people. While this does not confirm a zoonotic risk, it is prudent to treat cases of *E. coli* diarrhea as potentially zoonotic. This is particularly true for *E. coli* O157 because of the potential for severe disease in humans and the very low infective dose. Careful attention to hand hygiene, the use of contact precautions and proper cleaning and disinfection is important.

Hospital Infection Control (see ch. 209)

Dogs and cats diagnosed with *C. perfringens, C. difficile, Campylobacter jejuni, Salmonella* spp., or *E. coli*–associated diarrhea should be housed under contact precautions in an isolation area. Direct and indirect contact should be prevented between infected animals and all other animals. Barrier precautions, consisting of a gown and gloves, should be used when handling infected animals. Hands should be washed thoroughly with bactericidal soap and water after any contact with the animal or the isolation environment, even when gloves have been worn. Hand washing is recommended over alcohol-based hand sanitizers, especially when working with *C. difficile*–infected animals, because the spores are alcohol-resistant. Spores can survive up to 70 days in the environment and can be transported on the hands of staff members who have direct contact with other patients.

Strict adherence to hand washing techniques and the proper handling of contaminated wastes are effective in preventing the spread of the disease. Infected animals should be walked in an area separate from other patients, and feces should be promptly removed. *Clostridium difficile* spores are highly resistant to most disinfectants. Bleach (1 : 10 to 1 : 64 dilution of regular household bleach) has good sporicidal activity, as long as there is minimal organic debris and there has been adequate contact time. Bleach is an effective disinfectant for *Salmonella* and *Campylobacter,* and one can make a solution of household bleach and water by adding ¼ cup bleach to 1 gallon of water, or to make a smaller amount in a spray bottle, add 1 tablespoon bleach to 1 quart of water. Saturate area with solution. DO NOT rinse. Air dry.

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Protozoal Diseases

OUTLINE

Chapter 221 Protozoal Infections

CHAPTER 221

Protozoal Infections

Michael R. Lappin

Multiple pathogenic protozoans infect dogs and cats. The group can be divided into amoeba, ciliates, coccidians, flagellates, Microspora, and Piroplasmida. Protozoans generally cause either gastrointestinal (GI) tract disease (enteric protozoans)[1,2] or polysystemic disease.[3]

Enteric Protozoal Diseases

The most common protozoal agents infecting the GI tract of dogs and cats are:

- The flagellates, *Giardia* spp. *Tritrichomonas foetus (blagburni),* and *Pentatrichomonas hominis;*
- The coccidians, *Besnoitia* spp., *Cryptosporidium* spp., *Cyclospora cayetanensis, Cystoisospora* spp., *Hammondia* spp., *Neospora caninum, Sarcocystis* spp., and *Toxoplasma gondii;*
- The ciliate, *Balantidium coli;* and
- The amoeba, *Entamoeba histolytica*.

Cystoisospora spp., *Sarcocystis* spp., *Besnoitia* spp., *Hammondia* spp., *N. caninum,* and *T. gondii* complete the intestinal cycle in only one species. Some isolates of *Cryptosporidium* spp., *C. cayetanensis, Giardia* spp., *E. histolytica,* and *B. coli* will replicate in multiple warm-blooded vertebrates and therefore can potentially be zoonotic. In addition, *N. caninum* antibodies have been detected in some people[4,5] and DNA of *T. foetus* was amplified from the feces of a person,[6] findings that also suggest zoonotic transmission.

With the exception of *C. cayetanensis,* for which the route of transmission is unknown, fecal-oral transmission occurs with the enteric protozoans. The coccidians produce oocysts. *Cryptosporidium* spp. oocysts are immediately infectious when passed by the host; *T. gondii, N. caninum,* and *Cystoisospora* spp. must sporulate outside the host to be infectious (Figure 221-1).

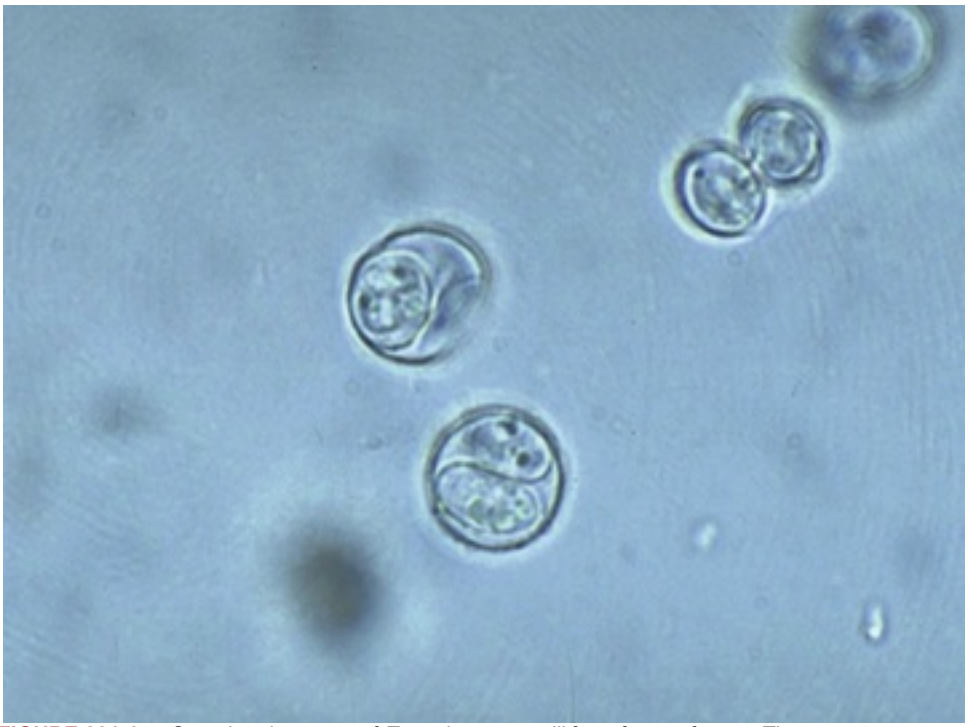

FIGURE 221-1 Sporulated oocysts of *Toxoplasma gondii* from feces of a cat. The oocysts measure approximately 8 microns × 10 microns.

In the flagellate group, both trophozoites and cysts of *Giardia* spp. are potentially infectious; however, transmission occurs most frequently after ingestion of cysts because gastric secretions generally kill trophozoites. Only trophozoites are detected in cats or dogs with *T. foetus* or *P. hominis* infections. Ingestion of the organism in the tissues of transport hosts can also result in infection by *Cystoisospora* spp., *Besnoitia* spp., *Hammondia* spp., *N. caninum,* and *T. gondii* (Figure 221-2).

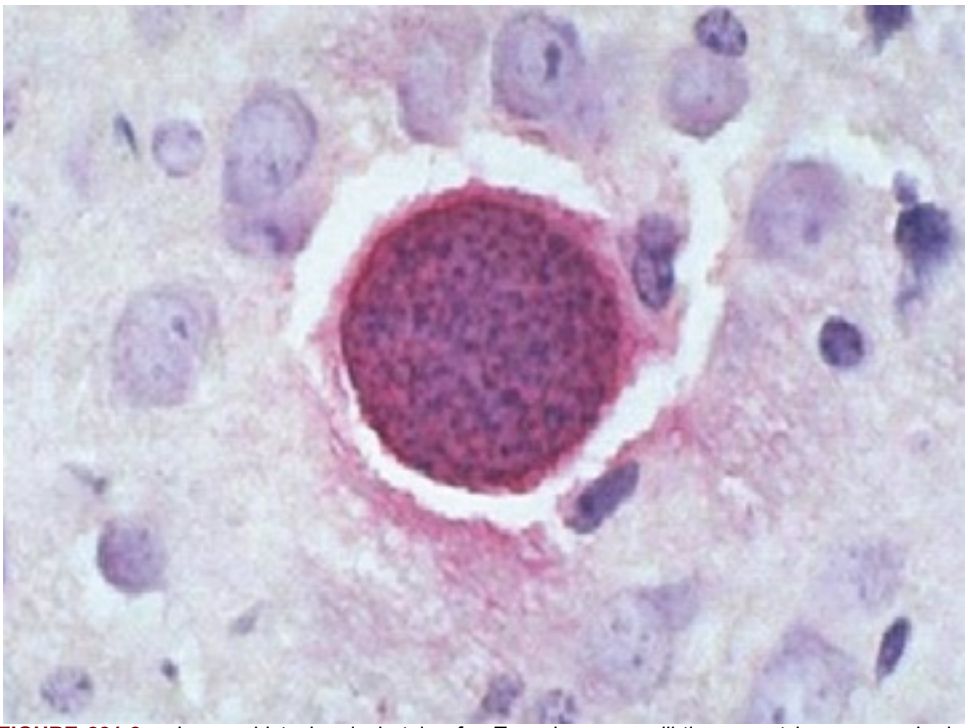

FIGURE 221-2 Immunohistochemical stain of a *Toxoplasma gondii* tissue cyst in a mouse brain. The cyst is approximately 100 microns in diameter and contains approximately 500 organisms.

Carnivorism can result in infection by other enteric protozoans like *Cryptosporidium* spp., *Giardia* spp., *E. histolytica,* and *B. coli* if the organisms are present in the intestines of the prey species. The gastrointestinal phase of infection can be self-limiting for each of the agents; however, fecal shedding periods are variable. After tissue cyst ingestion, infected cats rarely shed oocysts of *T. gondii* for more than 2 weeks.[7] For the other enteric protozoans, fecal shedding can be of longer duration. For example, cats infected with *T. foetus* or *Cryptosporidium* spp. can shed the organisms continuously or intermittently for months.

The enteric protozoans have worldwide distribution. Because they are maintained in nature primarily by fecal-oral transmission, more cases are associated with crowded and unsanitary environments. In general, *Giardia* spp., *T. gondii, N. caninum, Cystoisospora* spp., *Cryptosporidium* spp., and *T. foetus* (cats) infections are common[8-18] and *E. histolytica, B. coli,* and *C. cayetanensis* infections are thought to be rare.[19-22] However, in a 2015 study in Pakistan, *Entamoeba* spp. cysts were identified in 94 of 600 dog fecal samples[23] and *E. histolytica* cysts are found in public parks in Spain.[24] Currently it is unknown how many dogs and cats harbor *P. hominis.*[25,26] Antibodies against *T. gondii* (30%) and *Cryptosporidium* spp. (8.3%) are commonly detected in serum from client-owned cats, suggesting that exposure is common (Figure 221-3).[27,28] Prevalence of the agents varies by region in coprologic studies.

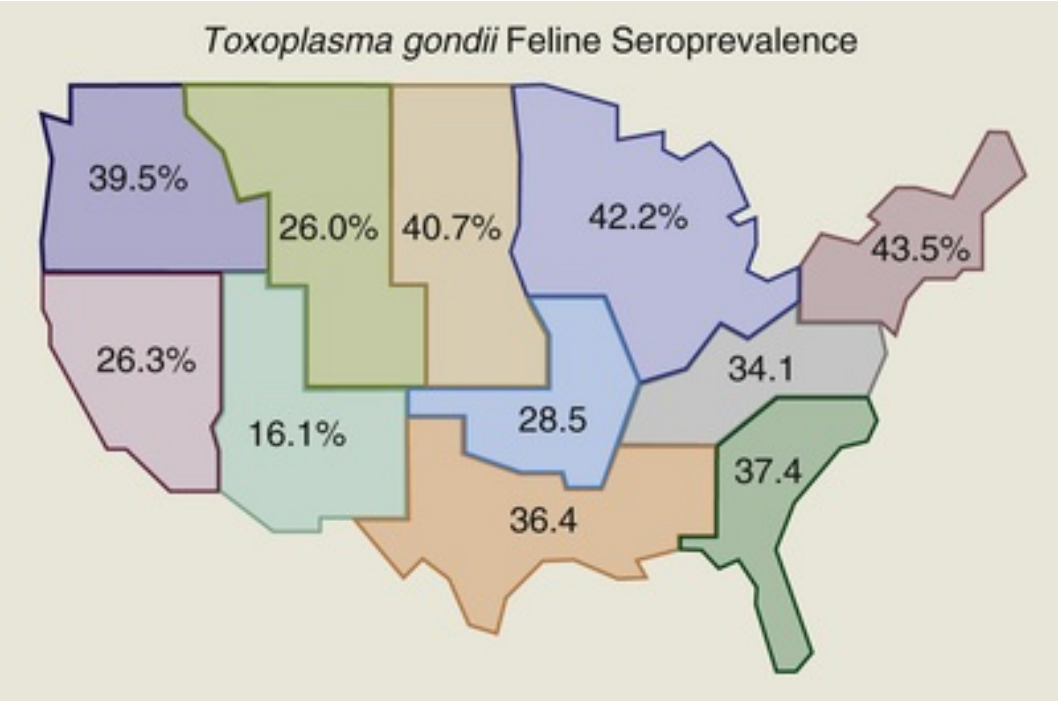

FIGURE 221-3 Map of the United States showing the distribution of *Toxoplasma gondii* antibody test results in cats. (From Vollaire MR, Radecki SV, Lappin MR: Seroprevalence of *Toxoplasma gondii* antibodies in clinically ill cats in the United States. *Am J Vet Res* 66:874-877, 2005.)

Pathogenic mechanisms have not been ascertained for each of the enteric protozoans. *Cystoisospora* spp. and *T. gondii* replicate in intestinal cells and may result in clinical illness from cell destruction. Tissue invasion also can occur with *E. histolytica.*[21,22] *Giardia* spp. and *Cryptosporidium* spp. are found on the surface of enterocytes, so pathogenesis is unlikely secondary to direct cell damage. Some of the pathogenic mechanisms proposed for these enteric agents include production of toxins, disruption of normal flora, induction of inflammatory bowel disease (IBD), inhibition of normal enterocyte enzymatic function, blunting of microvilli, and induction of motility disorders. *Cystoisospora* spp. and *T. foetus* infections are more commonly associated with clinical GI disease in puppies or kittens. *Sarcocystis* spp., *Besnoitia* spp., *Hammondia* spp., *T. gondii,* and *N. caninum* are almost never associated with GI disease. Clinical illness associated with *T. gondii, N. caninum,* and *Sarcocystis* spp. generally results from the tissue phase of the infections.[7,29-32] *Giardia* spp. and *Cryptosporidium* spp. infections are common in young animals, but GI signs can occur in animals of any age. Clinical disease is more common, and duration of organism shedding into the environment may be prolonged in dogs and cats with immunodeficiency-inducing concurrent diseases.

Owner concerns in dogs or cats with enteric protozoal infections generally are vomiting, inappetence, or diarrhea; fever is uncommon. *Giardia* spp., *Cryptosporidium* spp., and *T. gondii* infections are most commonly associated with small-bowel diarrhea; *E. histolytica, B. coli,* and *T. foetus* infections are most commonly associated with large-bowel diarrhea. *Cystoisospora* spp. infections can cause clinical signs of large- or small-bowel diarrhea. Physical examination findings in dogs or cats with enteric protozoal infections are nonspecific but can include abdominal discomfort, increased gas or fluid in the intestinal tract, or thickened intestinal loops.

All dogs and cats with large-, small-, or mixed-bowel diarrhea should be assessed for enteric protozoal infections. Diagnosis of GI protozoal infection is based primarily on documentation of oocysts, trophozoites, or cysts on direct fecal examination or fecal flotation (see ch. 81).

A direct smear of diarrheic stool can be used to examine for trophozoites of *E. histolytica, B. coli, Giardia* spp., *P. hominis,* or *T. foetus*. More frequently, a small quantity of fresh feces or mucus is mixed with a drop of 0.9% NaCl on a clean microscope slide and examined at 100× after placing a coverslip. When a motile organism is noted, examining at 400× assesses structural features. Application of a stain such as Lugol's solution, methylene blue, or acid methyl green to the wet mount at the edge of the coverslip will aid in visualizing internal structures of protozoa. Trophozoites are rarely found in formed stools. Duodenal aspiration for cytologic examination for *Giardia* trophozoites is effective for the diagnosis of giardiasis in the dog. However, this technique is not effective in the cat because the organism lives in the distal small intestine.

Protozoal cysts or oocysts are best demonstrated after fecal concentration; Sheather's sugar centrifugation and zinc sulfate centrifugation are inexpensive techniques commonly used in clinical practice (see ch. 81).[33] These solutions are inexpensive and generally effective. Sugar solution is hypertonic and will distort *Giardia* spp. cysts; the cytoplasm is pulled to one side and appears as a half- or quarter-moon.

Due to small size and limited number in feces of infected dogs and cats, *Cryptosporidium* spp. oocysts are almost never seen when concentrated feces are examined at 100×. Acid-fast staining or fluorescein-labeled monoclonal antibody staining of a fecal smear and fecal polymerase chain reaction (PCR) assay can aid in the diagnosis of cryptosporidiosis in dogs and cats.[34,35] Oocysts stain pink with acid-fast stain (Figure 221-4).

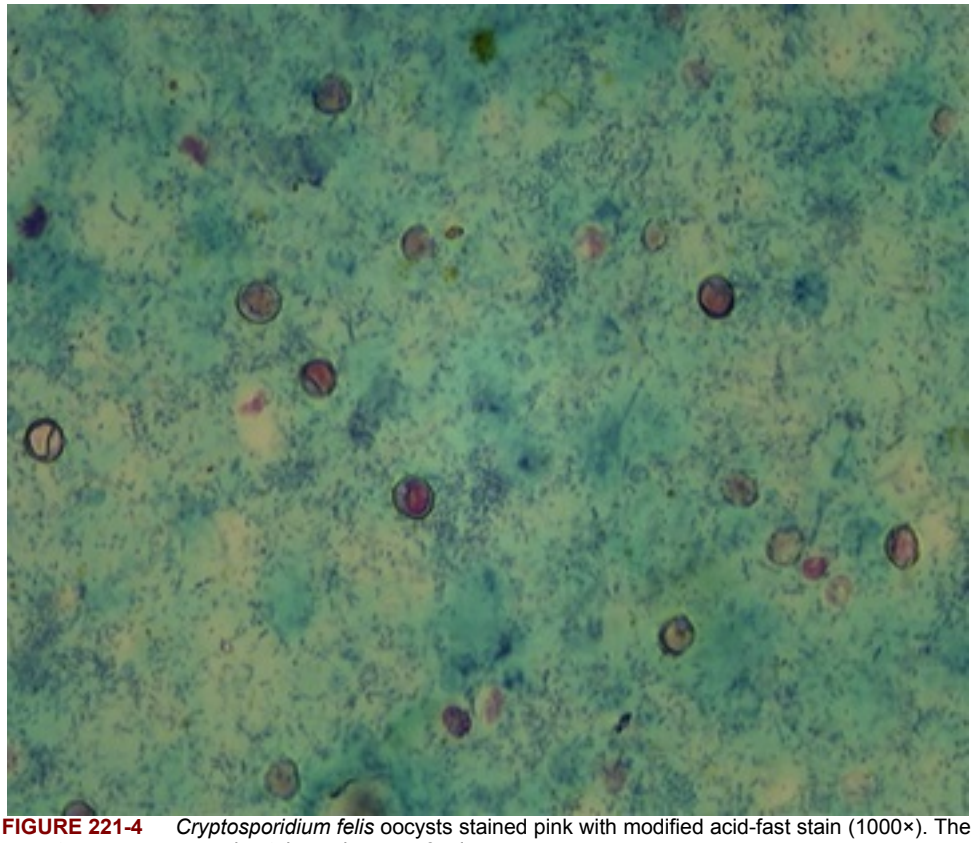

FIGURE 221-4 *Cryptosporidium felis* oocysts stained pink with modified acid-fast stain (1000×). The oocysts measure approximately 4 microns × 6 microns.

The fluorescein-labeled monoclonal antibody system also detects *Giardia* spp. cysts of dogs and cats, and so this test is an excellent screening procedure for dogs or cats with small-bowel diarrhea. Enzyme-linked immunosorbent assay (ELISA) for detection of *Cryptosporidium* spp. antigens in feces is generally inaccurate as it is based on antibodies against *C. parvum;* it is now known most dogs are infected with *C. canis* and most cats are infected with *C. felis*.[36,37] In addition, while zoonotic assemblages of *Giardia* are occasionally amplified from dog or cat feces, most small animals carry dog or cat assemblages.[36-38] Antigens of *Giardia* spp. can be detected in feces by ELISA, and these assays appear to be accurate for use with dog and cat feces.[39,40] However, *Giardia* antigen assays are best used in combination with fecal flotation, which detects more parasites overall.[40] PCR assays for the amplification of *Giardia* spp. and *Cryptosporidium* spp. DNA from feces are offered by multiple diagnostic laboratories in the United States. However, the sensitivity, specificity, and predictive values of these assays are generally unknown and there is no standardization between laboratories at this time. In general, these assays are not indicated unless the animal is known to be positive and the clinician or owner wishes to determine the genotype of the organism. PCR assays are also available for *T. foetus* and *P. hominis*. While fecal culture can also be used to identify *T. foetus (blagburni),* PCR assay results are returned more quickly.

The presence of enteric protozoans in diarrheic stool does not prove that disease was due to the organism. Some enteric protozoans, especially *Giardia* spp., *Cryptosporidium* spp., *T. foetus,* and *Cystoisospora* spp., live chronically in the intestinal tract of normal animals; other conditions causing GI tract disease can induce repeat shedding. Thus, animals with enteric protozoal infections that do not respond to therapy should be evaluated for underlying causes of disease. *Giardia* spp., *Cryptosporidium* spp., *Cystoisospora* spp., and *Sarcocystis* spp. are commonly found in animals with normal stools.

Withholding food for 24 hours is indicated for animals with acute vomiting but feeding is initiated as soon as possible (see ch. 39). Highly digestible, bland diets are used most frequently if vomiting and small-bowel diarrheas are the primary manifestations of disease (see ch. 276). High-fiber diets are generally indicated if large-bowel diarrhea is occurring (see ch. 277). However, feeding a high-fiber diet may also aid in the treatment of giardiasis due to inhibition of trophozoite attachment to duodenal epithelial cells. Use of probiotics may also have clinical benefit in some cases (see ch. 167).[41-44]

Optimal treatments for *E. histolytica* and *B. coli* infections in dogs or cats are unknown. *Giardia* spp. infections of dogs and cats generally respond clinically to the administration of metronidazole, fenbendazole, or febantel-pyrantel-praziquantel, but infection is usually not eliminated.[45-53] Metronidazole also helps correct the anaerobic bacterial overgrowth or *Clostridium perfringens* overgrowth that commonly accompanies giardiasis. In addition, metronidazole may also be beneficial due to inhibition of lymphocyte function. In a recent study of cats, administration of liquefied metronidazole benzoate at 25 mg/kg PO q 12 h for 7 days was 100% effective during the time period studied.[48] Central nervous system (CNS) toxicosis occasionally occurs with this drug; it is unlikely if no more than 50 mg/kg is given orally per day.[54,55] Secnidazole was used at 30 mg/kg PO once for the treatment of *Giardia* in 17 cats; increased liver enzyme activities were reported for 1 cat.[56] This drug could be an option for difficult-to-treat cats but more controlled studies should be performed to evaluate safety. Fenbendazole (50 mg/kg PO q 24 h for 3 to 5 days) and albendazole are commonly prescribed alternate anti-*Giardia* spp. drugs; albendazole is associated with neutropenia in dogs and cats and so should not be used.[57,58] Furazolidone (cats), paromomycin (dogs or cats), and nitazoxanide (dogs or cats) are other drugs with anti-*Giardia* effects. Lastly, use of the commercially available *Giardia* spp. vaccines as immunotherapy has given variable treatment responses; this vaccine is still available in some countries but not the United States (see ch. 208).[59,60]

The majority of drugs prescribed to cats with diarrhea due to *T. foetus (blagburni)* has failed. Recently, ronidazole and tinidazole have been evaluated, with ronidazole administered at 25 mg/kg PO q 24 h for 14 days appearing to be the most likely to eliminate infection.[61-65] However, ronidazole can be neurotoxic.[66] In addition, some *T. foetus (blagburni)* are resistant to tinidazole and ronidazole is not always effective.[63,65] In one case series of 104 cats, only 64% were graded as good responses to ronidazole.[65]

Paromomycin, tylosin (10 to 15 mg/kg PO q 12 h), azithromycin (10 mg/kg PO q 24 h), and nitazoxanide (25 mg/kg PO q 12 h) have all been used to lessen diarrhea in dogs, cats, calves or people with cryptosporidiosis, but no treatment has consistently stopped *Cryptosporidium* spp. oocyst shedding.[67-72] The drugs are generally prescribed initially for 7 to 10 days. However, it sometimes takes as long as 4 to 6 weeks to achieve total resolution of diarrhea. The most commonly prescribed drugs to treat *Cystoisospora* spp. infections of dogs and cats are trimethoprim-sulfonamide, sulfadimethoxine, furazolidone, amprolium, or amprolium-sulfadimethoxine. Quinacrine, spiramycin, toltrazuril, roxithromycin, and ponazuril have been

used on a limited basis. Ponazuril appears to be safe in most puppies and kittens and can eliminate infection after one dose (50 mg/kg PO). However, administration of ponazuril daily for 3 days at 50 mg/kg was the most effective protocol in one study.[73]

Cryptosporidium spp., *T. gondii, Giardia, E. histolytica,* and *B. coli* are potentially zoonotic (see ch. 210). *Entamoeba histolytica* and *B. coli* infections are extremely uncommon, and pets are unlikely sources of human infections.[74-80] Most people are infected with *Cryptosporidium* spp. or *Giardia* spp. from contaminated food or water, not contact with pets.[74] It is now known that *Cryptosporidium* spp. and *Giardia* spp. exist that are specific to people or pets. However, most people, cats, and dogs are infected with host-specific genotypes, so zoonotic transmission appears to be unlikely. However, some dogs and cats are infected with human genotypes, suggesting shared infection can occur.[77,78] Therefore, infected animals, particularly those with diarrhea, should be managed as a potential zoonotic risk. Genotyping for both *Cryptosporidium* spp. and *Giardia* spp. is commercially available (Veterinary Diagnostic Laboratory, Colorado State University, Fort Collins, CO). As no drugs eliminate *Cryptosporidium* spp., treatment of subclinical carriers is likely of no benefit. Whether to treat normal dogs or cats with *Giardia* infection continues to be controversial.[80]

Polysystemic Protozoal Diseases

The most common protozoal agents inducing disease in dogs or cats are the coccidians *Hepatozoon americanum, Neospora caninum,* and *Toxoplasma gondii,* the flagellates *Leishmania* spp. and *Trypanosoma cruzi,* and the piroplasms *Cytauxzoon felis* and *Babesia* spp. *Acanthamoeba castellanii* and *A. culbertsoni* are free-living amoebae rarely associated with disease in dogs.[81-85] *Encephalitozoon cuniculi* is a microspora that may be common based on seroprevalence.[86] The organism has been detected in some clinically ill dogs and cats, but infection appears to be uncommon.[87-90] Uveitis potentially associated with *E. cuniculi* has been detected in dogs and cats and further study in this area is indicated.[88a,88b,89] *Encephalitozoon cuniculi* was not associated with feline chronic kidney disease in one study.[90] *Pneumocystis carinii* (see ch. 202 and 242) is a saprophytic organism with worldwide distribution that has characteristics of protozoans, yeast, and fungi that has been detected in diseased dogs that generally have some form of immune function deficit.[91-96]

Coccidians

Hepatozoonosis

Hepatozoon canis and *H. americanum* both infect dogs.[97-102] In North America, *H. americanum* predominates, but *H. canis* and mixed infections have been detected.[102] *Hepatozoon americanum* is transmitted by *Amblyomma maculatum* and is most common in the Texas Gulf Coast, Mississippi, Alabama, Georgia, Florida, Louisiana, and Oklahoma.[98,101-103] In Africa, southern Europe, and Asia, *H. canis* predominates and is transmitted by *Rhipicephalus sanguineus*. A *Hepatozoon* species is occasionally found in the blood of cats in Europe.[104-106] The tick ingests the organism from infected dogs during a blood meal and oocysts develop. After a dog ingests an infected tick, sporozoites are released and infect mononuclear phagocytes and endothelial cells of the spleen, liver, muscle, lungs, and bone marrow, and they ultimately form cysts containing macromeronts and micromeronts. *Hepatozoon americanum* can also be transmitted to dogs by predation.[107,108] Clinical disease results from pyogranulomatous inflammation; glomerulonephritis or amyloidosis may occur secondary to chronic inflammation and immune-complex disease.

H. americanum has resulted in illness in all age groups, but disease is most commonly recognized in puppies.[109-113] Fever, weight loss, and severe hyperesthesia over the paraspinal regions are common findings. Anorexia, pale mucous membranes from anemia, depression, oculonasal discharge, and bloody diarrhea occur in some dogs. Clinical signs can be intermittent and recurrent.

Neutrophilic leukocytosis (20,000 to 200,000 cells/mcL) with a left shift and normocytic, normochromic nonregenerative anemia are the most common hematologic findings. Thrombocytopenia is unusual unless coinfection with *Ehrlichia canis* or *Anaplasma* spp. occurs. Increased activity of alkaline phosphatase, hypoalbuminemia, hypoglycemia, and, rarely, polyclonal gammopathy occur in some dogs. Inflammatory reactions directed at tissue phases in muscle result in periosteal reactions that can occur in any bone except the skull. These reactions do not occur in every case and are most common in young dogs. Presence of serum antibodies against *H. americanum* were compared with tissue biopsy; the sensitivity and specificity were 93% and 96%, respectively.[114] Definitive diagnosis is based on identification of gamonts in neutrophils or

monocytes in Giemsa- or Leishman-stained blood smears or by demonstration of the organism in muscle biopsy sections (Table 221-1). In one study, DNA of *H. americanum* (27.2%), *H. canis* (2.3%), or DNA of both organisms (2.3%) were amplified by PCR assay from blood of 614 dogs suspected hepatozoonosis.[115]

TABLE 221-1

Characteristic Cytologic Morphology of Small Animal Systemic Protozoal Agents

AGENT	MORPHOLOGIC CHARACTERISTICS
Babesia canis	Paired piroplasms (2.4 × 5 micron) in circulating red blood cells
Babesia gibsoni	Single piroplasms (1 × 3.2 micron) in circulating red blood cells
Cytauxzoon felis	Piroplasms (1 × 1.5 micron "signet ring" form; 1 × 2 micron oval form; 1 micron round form) in circulating red blood cells; macrophages or monocytes of lymph node aspirates, splenic aspirates, or bone marrow
Hepatozoon canis and *H. americanum*	Gamonts in circulating neutrophils and monocytes
Leishmania spp.	Ovoid to round amastigotes (2.5-5 × 1.5-2 micron) in macrophages found on imprints of exudative skin lesions, lymph node aspirates, or bone marrow aspirates
Neospora caninum	Free or intracellular (macrophages or monocytes) tachyzoites (5-7 × 1-5 micron) in cerebrospinal fluid, airway washings, or imprints of cutaneous lesions
Toxoplasma gondii	Free or intracellular (macrophages or monocytes) tachyzoites (6 × 2 micron) in pleural effusions, peritoneal effusions, or airway washings
Trypanosoma cruzi	Flagellated trypomastigotes (1 flagellum; 15-20 microns long) free in whole blood, lymph node aspirates, and peritoneal fluid

While clinical signs of hepatozoonosis rapidly resolve with drug therapy, no therapeutic regimen has been shown to eliminate *H. canis* or *H. americanum* infection from tissues. For treatment of *H. americanum,* the combination of trimethoprim-sulfadiazine (15 mg/kg PO q 12 h), pyrimethamine (0.25 mg/kg PO q 24 h), and clindamycin (10 mg/kg PO q 8 h) for 14 days is very successful in the acute stage.[112] Use of decoquinate (10 to 20 mg/kg q 12 h) with food lessens the likelihood of recurrence of clinical disease and prolongs survival time. Imidocarb dipropionate (5 to 6 mg/kg IM or SC once or twice, 14 days apart) is the drug of choice for treatment of *H. canis* and may also be effective for *H. americanum.* Administration of nonsteroidal antiinflammatory agents may lessen discomfort for some dogs (see ch. 164).

Tick control is the best form of prevention. Glucocorticoid administration should be avoided because it may exacerbate clinical disease. No evidence exists for zoonotic transfer of *H. americanum* or *H. canis* from infected dogs to people.

Neosporosis

Neospora caninum is a coccidian previously confused with *T. gondii* due to similar morphology.[116-119] The sexual cycle is completed in the GI tract of dogs and results in the passage of oocysts in feces.[120-129] Sporozoites develop in oocysts within 24 hours of passage. Tachyzoites (rapidly dividing stage) and tissue cysts containing hundreds of bradyzoites (slowly dividing stage) are the other two life stages. Infection has been documented after ingestion of infected bovine placental tissue and tissue from naturally infected deer.[130] In one study, *N. caninum* antibodies were most common in dogs living on dairies.[131] Transplacental infection has been well documented; dams that give birth to infected offspring can repeat transplacental infection during subsequent pregnancies.[132] Although organism replication occurs in many tissues, clinical illness primarily reflects neuromuscular infection in dogs. Although encephalomyelitis and myositis develop in experimentally infected kittens and some naturally exposed cats are seropositive for *N. caninum* antibodies, clinical disease in naturally infected cats has not been reported.[133-135] Canine neosporosis has been reported in many countries around the world.

Several clinical syndromes associated with neosporosis have been reported in dogs.[134-150] Congenitally infected puppies develop ascending paralysis with hyperextension of the hindlimbs; muscle atrophy occurs

in many cases (Figure 221-5). Polymyositis and multifocal CNS disease can occur alone or in combination. Clinical signs can be evident soon after birth or may be delayed for several weeks. Neonatal death is common. Although disease tends to be most severe in congenitally infected puppies, dogs as old as 15 years have been clinically affected. In some dogs, myocarditis, dysphagia, ulcerative dermatitis, pneumonia, central nervous system disease, and hepatitis occur. Dogs on immunosuppressive therapy for other conditions can have activated subclinical infections or severe clinical illness if exposed to *N. caninum* for the first time while immune suppressed (see ch. 165).[143-146] Dogs with central nervous system neosporosis generally have multifocal disease, which can affect the cerebellum, cerebral cortex, and brainstem (see ch. 261). If not treated, most affected dogs die.[146,149,150]

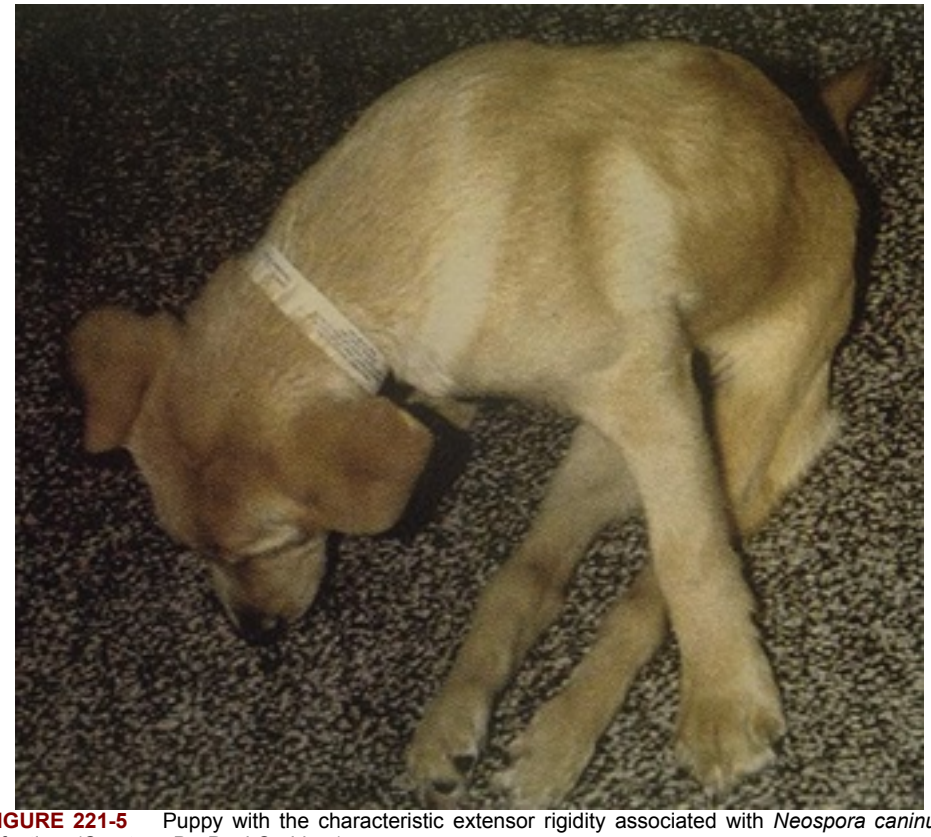

FIGURE 221-5 Puppy with the characteristic extensor rigidity associated with *Neospora caninum* infection. (Courtesy Dr. Paul Cuddon.)

No specific hematologic or biochemical findings exist, but increased creatine kinase and aspartate transaminase activities are common in dogs with myositis. Cerebrospinal fluid (CSF) abnormalities (see ch. 115) include increased protein concentration (20 to 50 mg/dL) and a mild, mixed inflammatory cell pleocytosis (10 to 50 cells/dL) consisting of monocytes, lymphocytes, neutrophils, and, rarely, eosinophils. Interstitial and alveolar patterns can be noted on thoracic radiographs. Demonstration of the organism in CSF or tissues gives a definitive diagnosis. Tachyzoites are rarely identified on cytologic examination of CSF, imprints of dermatologic lesions, and bronchoalveolar lavage (see Table 221-1).[146] Dogs with central nervous system neosporosis usually have multifocal disease on magnetic resonance imaging.[149,150] *Neospora caninum* tissue cysts have a wall thickness greater than 1 micron; *T. gondii* tissue cysts have a wall thickness less than 1 micron. The organism can be differentiated from *T. gondii* by electron microscopy, immunohistochemistry, and PCR.[139,151-154] Molecular techniques have also been used to show that varying strains of *N. caninum* exist and could be one explanation for variability of clinical signs of disease.[154]

A presumptive diagnosis of neosporosis is made by combining appropriate clinical signs of disease and positive serology with the exclusion of other causes inducing similar clinical syndromes, in particular *T. gondii.*[155] Immunoglobulin G antibody titers greater than or equal to 1 : 200 have been detected in most dogs with clinical neosporosis; minimal serologic cross-reactivity with *T. gondii* occurs at titers greater than or equal to 1 : 50 when measured by indirect fluorescent antibody (IFA) testing. Antibodies of *N. caninum* DNA

can also be detected in CSF of some affected dogs.[152]

The prognosis for dogs with severe neurologic involvement is grave. Some have survived after treatment with trimethoprim-sulfadiazine combined with pyrimethamine, sequential treatment with clindamycin hydrochloride, trimethoprim-sulfadiazine, and pyrimethamine, or clindamycin alone.[136-139,141] Newer drugs have been studied *in vitro* and should be evaluated *in vivo* in an attempt to improve clinical outcomes.[156] Glucocorticoids or other immune-suppressive drugs may exacerbate clinical disease.

Neospora caninum antibodies have been detected in people, including those with acquired immunodeficiency syndrome (AIDS) and neurologic disease.[157-160] However, in one study there was no link to repeated abortion in women.[159] Overall, the zoonotic link is unclear, but it seems prudent to avoid ingesting canine feces or undercooked meat. There has been an epidemiologic link between dogs and cattle; therefore, efforts should be made to lessen dog fecal contamination of livestock feed, and dogs should not be allowed to ingest bovine placentas or venison.[131,161-163] Bitches that whelp clinically affected puppies should not be bred.

Toxoplasmosis

Toxoplasma gondii is one of the most prevalent parasites infecting warm-blooded vertebrates.[164-166] Only cats complete the coccidian life cycle and pass environmentally resistant oocysts in feces. Dogs can mechanically pass oocysts after the ingestion of feline feces but new oocysts are not produced by dogs.[167] Sporozoites develop in oocysts after 1 to 5 days of exposure to oxygen and appropriate environmental temperature and humidity (see Figure 221-1). Tachyzoites disseminate in blood or lymph during active infection and replicate intracellularly rapidly until the cell is destroyed (Figure 221-6).

FIGURE 221-6 *Toxoplasma gondii* tachyzoites.

Bradyzoites are the slowly dividing, persistent, tissue stage that form in the extraintestinal tissues of infected hosts as immune responses attenuate tachyzoite replication. Tissue cysts form readily in the CNS, muscles, and visceral organs. Infection of warm-blooded vertebrates occurs after ingestion of any of the three life stages of the organism or transplacentally.[168] Most cats are not coprophagic and are usually infected by ingesting *T. gondii* bradyzoites during carnivorous feeding; oocysts are shed in feces from 3 to 21 days. Sporulated oocysts can survive in the environment for months to years and are resistant to most disinfectants. Bradyzoites may persist in tissues for the life of the host. *Toxoplasma gondii* has also been shown to be transmitted in semen of dogs.[169] Approximately 30% to 40% of cats and 20% of the dogs in the United States

are seropositive and therefore presumed to be infected (see Figure 221-3).[164-166,170]

Clinical disease associated with the GI phase of infection is rare, and detection of *T. gondii* oocysts in feces is rarely reported in studies of naturally exposed cats with diarrhea.[171-173] Most clinical signs are systemic and can include death in dogs and cats that develop overwhelming intracellular replication of tachyzoites after primary infection; hepatic (see ch. 283), pulmonary (see ch. 242), CNS (see ch. 261), and pancreatic tissues are commonly involved (Figure 221-7).[174-178]

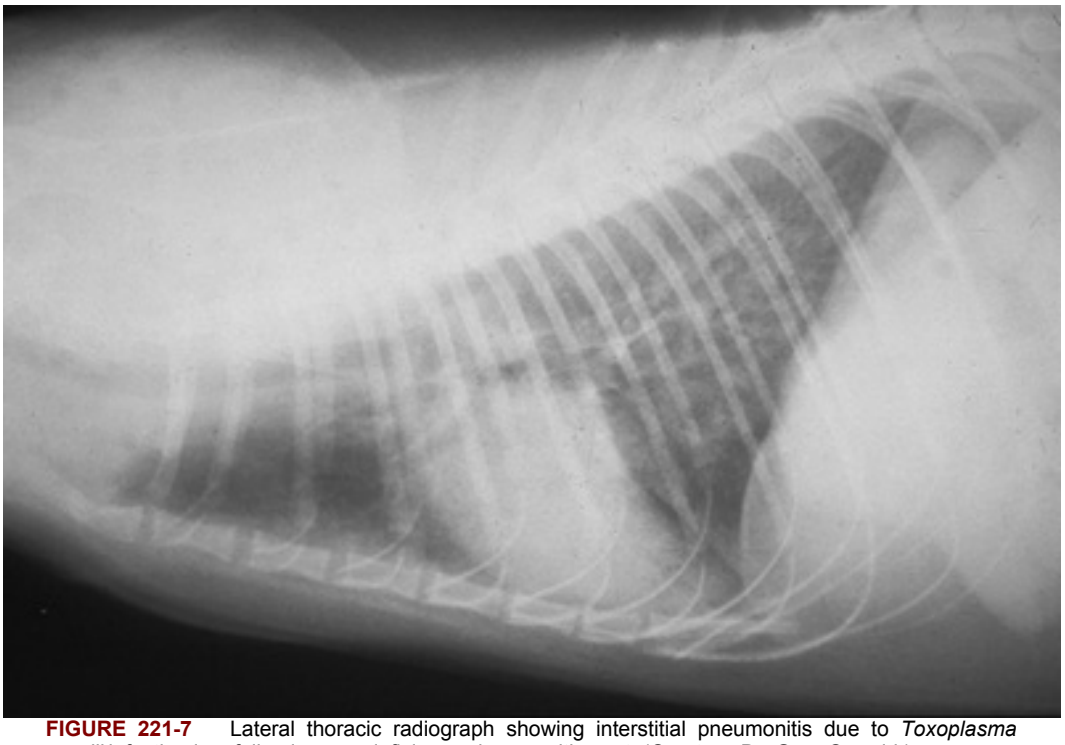

FIGURE 221-7 Lateral thoracic radiograph showing interstitial pneumonitis due to *Toxoplasma gondii* infection in a feline immunodeficiency virus–positive cat. (Courtesy Dr. Gary Oswald.)

Immune deficiency secondary to viral infection or immune-suppressive therapy can also induce fatal toxoplasmosis.[179-183] Common clinical findings in cats with disseminated toxoplasmosis include depression, anorexia, and fever followed by hypothermia, peritoneal effusion, icterus, and dyspnea.

Chronic toxoplasmosis occurs in some dogs and cats. *Toxoplasma gondii* infection should be on the differential diagnoses list for cats with anterior or posterior uveitis, fever, muscle hyperesthesia, weight loss, anorexia, seizures, ataxia, icterus, diarrhea, cutaneous disease, and pancreatitis.[184-189] However, in one study there was no association between *T. gondii* antibodies and chronic kidney disease in cats.[90]

In dogs, respiratory, GI, or neuromuscular infection resulting in fever, vomiting, diarrhea, dyspnea, cutaneous disease, and icterus are most common and occur most frequently in immune-suppressed dogs, such as those with canine distemper virus (CDV) infection (see ch. 228) or those receiving cyclosporine to prevent rejection of a transplanted kidney (see ch. 323).[180,190-195] Neurologic signs are dependent on the location of the primary lesions and include ataxia, seizures, tremors, cranial nerve deficits, paresis, and paralysis. Dogs with myositis have weakness, stiff gait, or muscle wasting. Rapid progression to tetraparesis and paralysis with lower motor neuron dysfunction can occur. Some dogs with suspected neuromuscular toxoplasmosis probably had neosporosis.[116] Myocardial infection resulting in ventricular arrhythmias occurs in some infected dogs. Dyspnea, vomiting, or diarrhea can occur in dogs with polysystemic disease. Retinitis, anterior uveitis, iridocyclitis, and optic neuritis occur in some dogs with toxoplasmosis but are less common than in the cat (see ch. 11). Keratitis due to *T. gondii* infection has also been reported.[194]

Dogs or cats with clinical toxoplasmosis can have a variety of clinicopathologic and radiographic abnormalities but none documents the disease.[170,196] Nonregenerative anemia, neutrophilic leukocytosis, lymphocytosis, monocytosis, neutropenia, eosinophilia, proteinuria, bilirubinuria, increases in serum proteins and bilirubin concentration, as well as creatinine kinase, alanine aminotransferase, alkaline phosphatase, and

lipase activities occur in some animals. Pulmonary toxoplasmosis most commonly causes diffuse interstitial to alveolar patterns or pleural effusion (see ch. 242).[197] CSF protein concentrations and cell counts are often higher than normal (see ch. 115 and 261). The predominant white blood cells (WBCs) in CSF are small mononuclear cells, but neutrophils also are commonly found.

The antemortem definitive diagnosis of toxoplasmosis can be made if the organism is demonstrated; however, this is uncommon. Bradyzoites or tachyzoites are rarely detected in tissues, effusions, bronchoalveolar lavage fluids, aqueous humor, or CSF (see Table 221-1). Detection of 10 × 12 micron oocysts in feces in cats with diarrhea suggests toxoplasmosis but is not definitive, because *Besnoitia* and *Hammondia* infections of cats produce morphologically similar oocysts.

Toxoplasma gondii–specific antibodies (dogs or cats), antigens (cats), immune complexes (cats), and DNA (dogs or cats) can be detected in the blood of normal animals, as well as in those with clinical signs of disease; therefore, it is impossible to make an antemortem diagnosis of clinical toxoplasmosis based on these tests alone.[198-204] Of the serum tests, IgM correlates the best with clinical toxoplasmosis because this antibody class is rarely detected in serum of healthy animals. Because the organism cannot be cleared from the body, most animals will be antibody-positive for life; therefore, repeating serum antibody titers after clinical disease has resolved is of little use. The combination of aqueous humor or CSF *T. gondii*–specific antibody detection and organism DNA detection by PCR is the most accurate way to diagnose ocular or CNS toxoplasmosis in cats (Diagnostic Laboratory, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO).

Clindamycin hydrochloride, trimethoprim-sulfonamide combination, and azithromycin have been used successfully for the treatment of clinical toxoplasmosis.[170,184,205] Pyrimethamine combined with sulfa drugs is effective for the treatment of human toxoplasmosis but commonly results in toxicosis in cats. Ponazuril was used successfully for the treatment of *T. gondii* keratitis in one dog.[194] Cats or dogs with uveitis should be treated with topical, oral, or parenteral glucocorticoids to avoid secondary glaucoma and lens luxations.[170,206] Optimal treatment duration for clinical toxoplasmosis in dogs or cats is unknown but generally is recommended for at least 4 weeks.

Toxoplasmosis is associated with a large number of clinical abnormalities in people that are most severe in the fetus and immune-suppressed individuals (see ch. 210). Recently, several studies have identified associations between *T. gondii,* cats, and behavioral abnormalities in people and these associations are being studied further.[207-209] However, it is clear that avoiding *T. gondii* would be prudent for all people. Risk factors associated with *T. gondii* infection in humans in the United States have been studied.[210] Avoiding tissue cysts in undercooked meat, including chicken, can lessen the risk of acquiring toxoplasmosis.[211] Based on detection of antibodies against *T. gondii* sporozoites in human sera, it is now known that a high percentage of *T. gondii* infections occur in humans from ingestion of sporulated oocysts.[212] Thus, at-risk people should also avoid old feline feces by cleaning the litterbox daily, washing hands or wearing gloves while gardening or otherwise coming in contact with soil, and washing (or cooking) produce well before it is eaten.

Although owning a pet cat is occasionally epidemiologically associated with acquiring toxoplasmosis,[213] touching individual cats is probably not a common way to acquire toxoplasmosis for the following reasons:

- Cats generally shed oocysts only for days to several weeks after primary inoculation.
- Repeat oocyst shedding is rare, even in cats receiving glucocorticoids or cyclosporine, and in those infected with feline immunodeficiency virus (FIV) or feline leukemia virus (FeLV).[214-216]
- Cats with toxoplasmosis inoculated with tissue cysts 16 months after primary inoculation did not shed oocysts.[217]
- Cats are fastidious and usually do not allow feces to remain on their skin for time periods long enough to lead to oocyst sporulation; the organism was not isolated from the fur of cats shedding millions of oocysts 7 days previously.[217]
- Increased risk of acquired toxoplasmosis was not associated with cat ownership in human immunodeficiency virus (HIV)–infected people or in veterinary health care providers.[218]

Because humans are not commonly infected with *T. gondii* from contact with individual cats, testing healthy cats for toxoplasmosis is not recommended. No serologic assay accurately predicts when a cat shed *T. gondii* oocysts in the past, and most cats that are shedding oocysts are seronegative. Most seropositive cats have completed the oocyst shedding period and are unlikely to repeat shedding. Most seronegative cats would shed the organism if infected. If owners are concerned that they may have toxoplasmosis, they should see their doctor for testing.

Flagellates

Leishmaniasis

Leishmania spp. are flagellates that cause cutaneous, mucocutaneous, and visceral diseases in dogs, humans, and other mammals. Rodents and dogs are primary reservoirs of *Leishmania* spp.; people are incidental hosts. Leishmaniasis was considered unimportant in the United States until recently, with cases reported only occasionally.[219-226] In 2000, *Leishmania donovani* infection was confirmed in multiple dogs in a Foxhound kennel in New York State.[221] Further investigation documented *L. donovani* or *Leishmania* spp. infection in 30 other Foxhound kennels in 20 states and Ontario, Canada. Infection of dogs other than Foxhounds in the United States appears to be uncommon.[223] Transmission appears to be primarily from dog to dog in Foxhounds in the United States, but transmission by shared needles, blood transfusions, breeding, and congenital transmission can occur.[221,225-230] In other countries, the sandfly is the primary vector. Flagellated promastigotes develop in the sandfly and are injected into the vertebrate host when the sandfly feeds. Promastigotes are engulfed by macrophages and disseminate through the body. After an incubation period of 1 month to 7 years, amastigotes (nonflagellate) form and cutaneous lesions develop; sandflies are infected during feeding. The intracellular organism induces extreme immune responses; polyclonal (and occasionally monoclonal) gammopathies, proliferation of macrophages, histiocytes, and lymphocytes in lymphoreticular organs and immune complex formation resulting in glomerulonephritis and polyarthritis are common in dogs. In endemic areas, *Leishmania infantum* DNA has been amplified and the organism grown from *Rhipicephalus sanguineus* suggested a potential role of this tick as a vector.[231,232]

Cats have been infected experimentally with some *Leishmania* spp.[233] Cats in endemic areas are commonly seropositive or PCR-positive.[234-240] A cat with naturally occurring *Leishmania infantum* infection was capable of infecting sandflies.[241] Most clinically affected cats in Europe or the United States *(Leishmania mexicana)* have dermatological abnormalities, many consisting of nodular, ulcerative lesions on the ear pinna or muzzle.[239,240] The primary histopathological abnormalities are diffuse granulomatous inflammation with macrophages containing numerous amastigotes.

Visceral leishmaniasis is most common in dogs. Subclinical infection may persist for months or years. When clinical signs occur, weight loss, normal to increased appetite, polyuria, polydipsia, muscle wasting, depression, vomiting, diarrhea, cough, epistaxis, sneezing, and melena are common presenting complaints. Splenomegaly, lymphadenopathy, facial alopecia, fever, rhinitis, dermatitis, increased lung sounds, icterus, swollen painful joints, uveitis, and conjunctivitis are commonly identified on physical examination.[242] Cutaneous lesions are characterized by hyperkeratosis, scaling, thickening, mucocutaneous ulcers, and intradermal nodules on the muzzle, pinnae, ears, and footpads (Figure 221-8 and ch. 10). Subclinical *Leishmania* infection was associated with infertility and chronic prostatitis in a dog.[243]

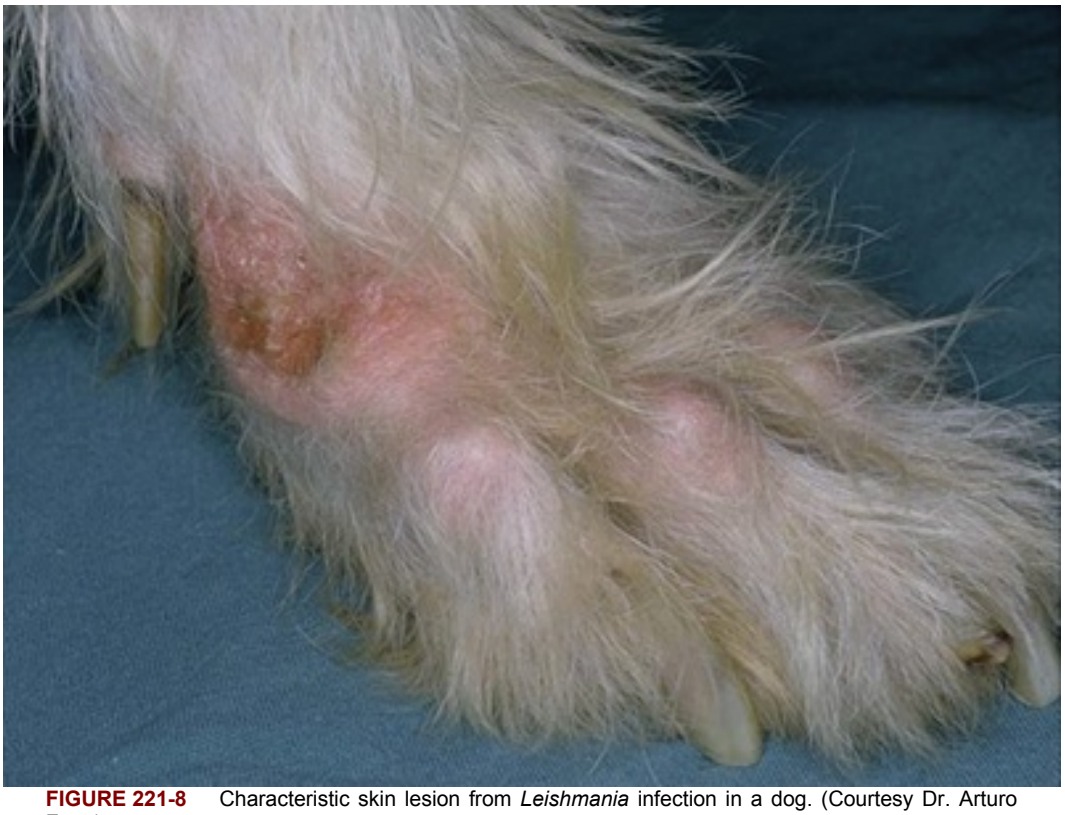

FIGURE 221-8 Characteristic skin lesion from *Leishmania* infection in a dog. (Courtesy Dr. Arturo Font.)

Hyperglobulinemia, hypoalbuminemia, proteinuria, increased liver enzyme activities, thrombocytopenia, azotemia, lymphopenia, and leukocytosis with left shift are common in dogs. Hyperglobulinemia is usually polyclonal, but an IgG monoclonal gammopathy was reported in a dog.[244] *Leishmania*-infected dogs can be positive for antinuclear antibodies in serum, which may lead to the erroneous diagnosis of primary immune-mediated disease.[245]

Leishmaniasis can be confirmed by detecting the organisms by cytology, histopathology, PCR assay, or laboratory animal inoculation, or by detecting antibodies against *Leishmania* in serum.[246-256] Demonstration of amastigotes (2.5 to 5 microns × 1.5 to 2 microns in lymph node aspirates, bone marrow aspirates, or skin imprints stained with Wright's or Giemsa stain gives a definitive diagnosis (Figure 221-9). PCR assays can be performed on EDTA-anticoagulated blood, bone marrow aspirates (see ch. 92), lymph node aspirates (see ch. 95), splenic aspirates (see ch. 89), cells collected on conjunctival swabs, or tissue samples. Dogs are unlikely to eliminate *Leishmania* infection spontaneously, and so a true positive antibody test indicates infection. However, serological cross reaction amongst antibodies against *Leishmania* and antibodies against other common vector-borne diseases like *Trypanosoma cruzi, Ehrlichia canis, Toxoplasma gondii, Neospora caninum* and *Babesia canis* occurs in some assays.[248]

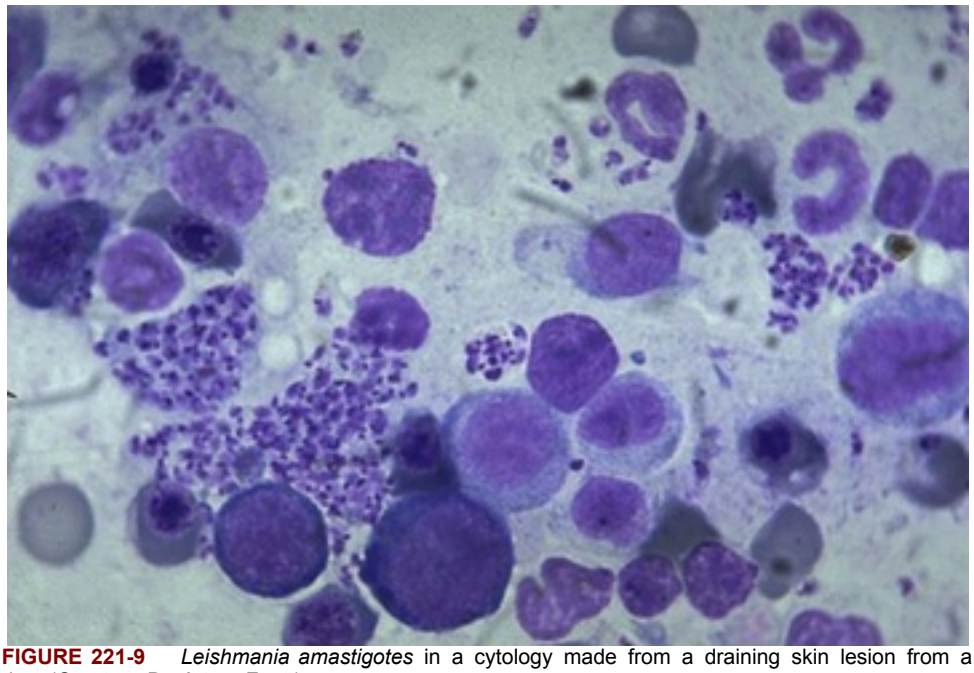

FIGURE 221-9 *Leishmania amastigotes* in a cytology made from a draining skin lesion from a dog. (Courtesy Dr. Arturo Font.)

Many treated dogs respond clinically, but *Leishmania* cannot be eliminated from the body with drugs.[246,251,256-263] The combination of antimony and allopurinol was superior to treatment with either drug alone.[257,264] As antimonial drugs are not routinely available in the United States, affected dogs could be treated with allopurinol, marbofloxacin, or liposomal amphotericin B initially.[247,260,262] The prognosis is variable; many cases given monotherapy are recurrent.

Avoidance of infected sandflies is the only means of prevention.[265-267] If in endemic areas, pet owners should house animals during nighttime hours, control breeding places of sandflies, and consider use of an insect repellent.[266,267] A vaccine is available for use in some countries.[268,269] Foxhounds and other dogs from endemic areas to be used as potential blood donors should be screened serologically or by PCR assay on blood.[227,270] The primary zoonotic risk for canine leishmaniasis is from dogs acting as a reservoir host for the organism. Direct contact with amastigotes in draining lesions is unlikely to result in human infection. In one study in the United States, none of the 185 persons with potential exposure to infected Foxhounds had evidence of infection.[221]

Trypanosomiasis

Trypanosoma cruzi infection of mammals is diagnosed primarily in North and South America, including the Caribbean Islands.[271-281] Infected reservoir mammals (dogs, cats, raccoons, opossums, armadillos) and vectors (reduviid bugs, kissing bugs) are found in the United States, but clinical infections in dogs or people are not commonly reported; this may relate to differences in vector behavior and sanitation standards in the United States. A number of studies have evaluated risk factors for acquiring trypanosomiasis.[277-281] As dogs and cats can be reservoirs, housing them separate from human sleeping quarters and reducing their exposure to triatomine bugs were predicted to strongly reduce transmission risks.[279] It appears that connatal transmission can occur in dogs as it does in humans.[282]

The organism should be on the differential list for dogs in endemic areas with cardiomyopathy, conduction disturbances, ventricular arrhythmias, and supraventricular arrhythmias (see ch. 252).[271,283-291] Laryngeal paralysis and neurologic disease may occur occasionally. Laboratory abnormalities include lymphocytosis and increased activities of liver enzymes and creatine kinase. Thoracic radiographic, abdominal radiographic, and echocardiographic findings are consistent with cardiac disease and failure, but they are not specific for trypanosomiasis. The primary electrocardiogram (ECG) findings are ventricular premature contractions, heart block, and T-wave inversion (see ch. 248).

Definitive diagnosis is based on organism demonstration. Trypomastigotes (1 flagellum, 15- to 20-microns long) can be identified during acute disease on thick blood film or buffy coat smears stained with Giemsa or

Wright's stain (see Table 221-1). The organism is sometimes detected in lymph node aspirates or in abdominal effusions. Histopathologic evaluation of cardiac tissue may reveal amastigotes (1.5 to 4 microns). Trypomastigotes can also be cultured from blood or grown by bioassay in mice. In North American cases, positive serologic test results correlate with infection.[292-294] However, there can be serological cross-reaction amongst antibodies against some vector disease agents in some assays.[248] PCR assay can also be used to amplify *T. cruzi* DNA from fluids or tissues.[278,291] *Trypanosoma caninum* is a related but nonpathogenic organism that can be cultured or amplified by PCR from the skin of dogs in some regions of Brazil.[295]

There are no approved drugs available for *T. cruzi* infection in the United States, but in a recent study of allopurinol in an experimentally infected mouse model, a positive response was noted.[296] Ravuconazole was safe in one experimental dog model and suppressed *T. cruzi* infection, lessening cardiac inflammation.[297] Administration of benznidazole temporarily suppressed *T. cruzi* infection in dogs but did not prevent the development of cardiomyopathy.[298] Simvastatin administered at 20 mg/dog lessened heart expression and serum levels of interferon-gamma (IFN-gamma) and tumor necrosis factor-alpha (TNF-alpha) improving cardiac parameters in a dog *T. cruzi* model.[299] Glucocorticoid therapy may improve survival of infected dogs. Therapy for arrhythmias (see ch. 248) or heart failure (see ch. 247) should be instituted as needed.

Dogs in endemic areas should be kept from other reservoir hosts such as opossums and should not be fed raw meat. Vector control is the primary means of prevention.[300-302] Potential blood donors from endemic areas should be serologically screened. Infected dogs can serve as a reservoir of *T. cruzi* for vectors, and blood from infected dogs can be infectious to humans. Research on a vaccine against *T. cruzi* infection is promising.[303-305]

Piroplasmida

Babesiosis

Multiple *Babesia* spp. infect dogs throughout the world.[306-323] *Babesia canis* can be subgenotyped by PCR and the various genotypes differ in geographical distribution and disease inducing potential.[307-310] *Babesia canis* subgenotypes have worldwide distribution including Africa, Asia, Australia, Europe, Central America, South America, Japan, and the United States. *Babesia rossi* is transmitted by *Haemaphysalis leachi* and is the most pathogenic. *Babesia canis* is transmitted by *Dermacentor reticulatus* and is moderately pathogenic. *Babesia vogeli* occurs in the United States, is the least pathogenic, and is transmitted by *Rhipicephalus sanguineus*. A separate large *Babesia* spp. and *B. conradae* also infect dogs in the United States.[312-314]

Babesia gibsoni infects dogs in most countries of the world and the organisms differ between regions.[315-325] In the United States, the vector for *B. gibsoni* is unknown but the organism is known to be transmitted by biting and is common in American Pit Bull Terriers.[319,320,324] *Babesia* spp. can also be transmitted by blood transfusion.[325]

None of the *Babesia* spp. that infect cats—*B. cati* (India), *B. felis* (South Africa and Sudan), *B. herpailuri* (South America and Africa), or *B. pantherae* (Kenya)—is found in the United States. However, *B. vogeli* DNA has been amplified from the blood of cats in Brazil, a country with high prevalence rates for *R. sanguineus*.[311]

While *Babesia* spp. can be associated with many clinical signs of disease and laboratory abnormalities in dogs, in the United States,[306,316,321,323,326-331] subclinical *Babesia* spp. infections are most common.[322,332] Following infection with pathogenic strains of *B. canis, B. conradae,* or *B. gibsoni,* the incubation period varies from several days to several weeks. The degree of parasitemia varies by the organism studied, but parasitemia can be detected transiently in some dogs as soon as day 1.[306,326] In some infected dogs, the intracellular replication in red blood cells (RBCs) results intravascular hemolytic anemia (see ch. 198). Immune-mediated reactions against the parasite or altered self-antigens worsen the hemolytic anemia and commonly result in a positive Coombs' test. Severity of disease depends on the species and strain of *Babesia* and the host immune status; chronic, subclinical infection can occur. Presence of coinfections, such as *Bartonella* spp., may increase the pathogenic potential.[328,331] Clinical manifestations are those of acute anemia and include fever, pale mucous membranes, tachycardia, tachypnea, depression, anorexia, and weakness. Icterus, petechiation, azotemia, and hepatosplenomegaly are present in some dogs depending on the stage of infection and the presence of disseminated intravascular coagulation (DIC). Administration of glucocorticoids or splenectomy may activate chronic disease. Common laboratory abnormalities include regenerative anemia, hyperbilirubinemia, bilirubinuria, hemoglobinuria, thrombocytopenia, metabolic acidosis, azotemia,

polyclonal gammopathy, and renal casts.[306,321,326]

A presumptive diagnosis of clinical babesiosis can be based on historical findings, physical examination findings, test results, and positive serology. Many dogs are seropositive but clinically normal; therefore, serology alone cannot be used to make a definitive diagnosis.[306,326,327] Demonstration of increasing antibody titers over 2 to 3 weeks are consistent with recent or active babesiosis. Definitive diagnosis is based on organism demonstration in RBCs using Wright's or Giemsa stains on thin blood smears. *Babesia vogeli* and *B. canis* are typically found as paired, piriform bodies measuring 2.4 × 5 microns. *Babesia gibsoni* is typically found as single, annular bodies measuring 1.0 × 3.2 microns (see Table 221-1). PCR assays for *Babesia* spp. are now available commercially and can be used to document organism presence, but positive results do not always correlate to clinical illness.[333-335]

Supportive care, including blood transfusions (see ch. 130), should be administered as indicated. Several drugs including diminazene aceturate, phenamidine, pentamidine isethionate, parvaquone, atovaquone, and niridazole have also been used in an attempt to treat different *Babesia* spp. infections.[314,336-343] In the United States, dogs with suspected *B. canis* associated clinical illness often respond to imidocarb dipropionate administered at 5 to 6.6 mg/kg SC or IM twice, 14 days apart or 7.5 mg/kg SC or IM once.[326,336] Adverse effects include transient salivation, diarrhea, dyspnea, lacrimation, and depression. Imidocarb is not as effective for the treatment of *B. gibsoni* infection. In the United States, dogs with suspected *B. gibsoni* or *B. conradae* associated clinical illness often respond to azithromycin (10 mg/kg PO q 24 h for a minimum of 10 days) combined with atovaquone (13.3 mg/kg PO q 8 h for at least 10 days). If these drugs are not available, the combination of doxycycline (7-10 mg/kg q 12 h), enrofloxacin (2-2.5 mg/kg q 12 h), and metronidazole (5-15 mg/kg q 12 h) for 6 weeks had 85.7% efficacy in one study in Taiwan.[343] The addition of diminazene did not improve response rates in this study.[343] Clindamycin administered at 12.5 mg/kg PO q 12 h for at least 10 days may control clinical signs.[339] However, treatment of *Babesia* spp. infections is unlikely to eliminate the carrier state.[338] As there are no drugs available that are known to consistently eliminate infection, treatment of healthy, seropositive dogs is unlikely to be of benefit and prevention is of utmost importance. In addition, since infection may not be cleared, following antibody titers or PCR may be of minimal benefit.[344] Following the clinical and laboratory abnormalities is probably of great importance. For example, the proteinuria associated with babesiosis can lessen following treatment.[330]

Ticks should be controlled if possible (see ch. 163).[345-348] If it is difficult to control ticks in a *B. canis* or *B. vogeli*–infected kennel, one dose of imidocarb at 7.5 mg/kg IM may eliminate the carrier state. Dog fights should be avoided. Administration of immunosuppressive drugs and splenectomy should be avoided in previously infected dogs. Dogs in high-risk breeds (Greyhound, American Pit Bull Terrier) and dogs from endemic areas to be used as blood donors should be assessed for infection by PCR assay or serologic screening and positive dogs eliminated from the program.[270] Vaccines for *B. canis* have been studied in some countries.[349] Currently no evidence exists to suggest that *Babesia* spp. infecting dogs and cats can cause human disease.

Cytauxzoonosis

Cytauxzoon felis infects cats, pumas, and bobcats in many regions of the United States and is occasionally identified in cats in Europe.[350-368] In one study of 961 cats in Florida, North Carolina, and Tennessee, the prevalence rate was 0.3%.[355] When first discovered, *C. felis* infection was thought to be uniformly fatal. It is now apparent that less virulent strains exist and many cats will survive and be subclinical carriers.[355-358,361,366] Bobcats and pumas are usually subclinically affected and approximately 50% of the strains evaluated were identical to domestic cats and the others were unique.[367] The organism can be passed experimentally from infected bobcats to domestic cats by *Dermacentor variabilis;* clinical illness occurs after an incubation period of 5 to 20 days.[368] However, *Amblyomma americanum* is also a competent vector, and based on the distribution of cases in the United States, is the most likely vector to cats.[350,353] Perinatal infection of kittens appears to be unlikely.[354]

Cytauxzoon felis–infected macrophages line the lumen of veins throughout the body, and merozoites released from the infected macrophages infect erythrocytes. Clinical disease results from obstruction of blood flow through tissues by mononuclear infiltrates and from hemolytic anemia. Some infected cats develop coagulation abnormalities, and cats that died in one study had greater concentrations of tumor necrosis factor-alpha and interleukin-1 beta, suggesting an immune-pathogenic component to disease.[369,370]

Most cases of cytauxzoonosis are in cats allowed to go outdoors that live by wooded areas that support the presence of ticks.[350,352] Fever, anorexia, dyspnea, depression, icterus, pale mucous membranes, and death are the most common clinical findings.[350,351,371] A primary differential diagnosis is hemoplasmosis (see ch. 219). Ticks are generally not identified on affected cats. Cytauxzoonosis is suspected in cats with regenerative anemia and neutrophilic leukocytosis; thrombocytopenia occurs in some cats. Hemoglobinemia, hemoglobinuria, bilirubinemia, and bilirubinuria are uncommon. Antemortem diagnosis is based on demonstration of the erythrocytic phase on thin blood smears stained with Wright's or Giemsa stains. Infected macrophages can be detected cytologically in bone marrow, spleen, liver, or lymph node aspirates.

The organism is easily identified on histologic evaluation of most organs. Serologic testing is not commercially available but PCR assay can be used to amplify organismal DNA from blood, aspirates, or tissue samples.[350,372]

Supportive care should be administered as indicated. However, stress can exacerbate death in clinically ill cats and so minimal manipulations should be used. Administration of atovaquone (15 mg/kg PO q 8 h) and azithromycin (10 mg/kg PO q 24 h) is currently the treatment protocol of choice; in one study, 14 of 22 cats survived.[373,374] Treatment with diminazene or imidocarb is inferior to this protocol.[375,376] Ticks should be controlled, and cats in endemic areas should be housed during periods of peak tick activity. The use of an imidacloprid 10%/flumethrin 4.5% collar (Seresto, Bayer) that repels ticks was effective in one study.[377] This collar was accepted without significant side-effects by approximately 95% of cats owned by veterinary students or employees of a teaching hospital.[378] Vaccine research is currently ongoing. *Cytauxzoon felis* is not known to be zoonotic.[379]

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Viral Diseases

OUTLINE

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CHAPTER 222

Feline Immunodeficiency Virus Infection

Julia A. Beatty

Client Information Sheet: Feline Immunodeficiency Virus Infection

Feline immunodeficiency virus (FIV) is a common infection of domestic cats worldwide. Transmission occurs primarily during aggressive territorial encounters and results in lifelong infection. Although the immunological consequences of FIV infection in cats mirror many of those seen in human immunodeficiency virus (HIV)–infected humans, the clinical manifestation of most FIV infections is mild or absent. In those cats that do succumb to FIV-associated diseases, there are no pathognomonic signs, so assigning clinical relevance to FIV infection in an individual cat is challenging. Diagnostic investigation of sick, FIV-infected patients frequently reveals specific, treatable problems. Screening diagnostic tests detect circulating antibodies to the virus. Depending on the circumstances, additional serology or molecular testing can assist in determining a cat's true infection status. Confinement of uninfected cats is the most effective way to prevent transmission. FIV presents no known zoonotic risk.

Etiology and Epidemiology

FIV, family *Retroviridae*, subfamily *Orthoretrovirinae*, genus *Lentivirus*, describes a large group of closely related viruses that are endemic in domestic cats and other carnivores including lions, leopards and spotted hyenas.[1,2] Antibodies to FIV are found in domestic cat populations across the globe. Seroprevalence varies from <5% to >30% depending on the region and the population tested.[3] Risk factors for FIV infection include age, sex, environment, breed and health status; adult, male, free-roaming, crossbred cats and sick cats at high risk (Table 222-1).[4-6] The average age of FIV-infected cats in epidemiological studies is 5 to 6 years.[7]

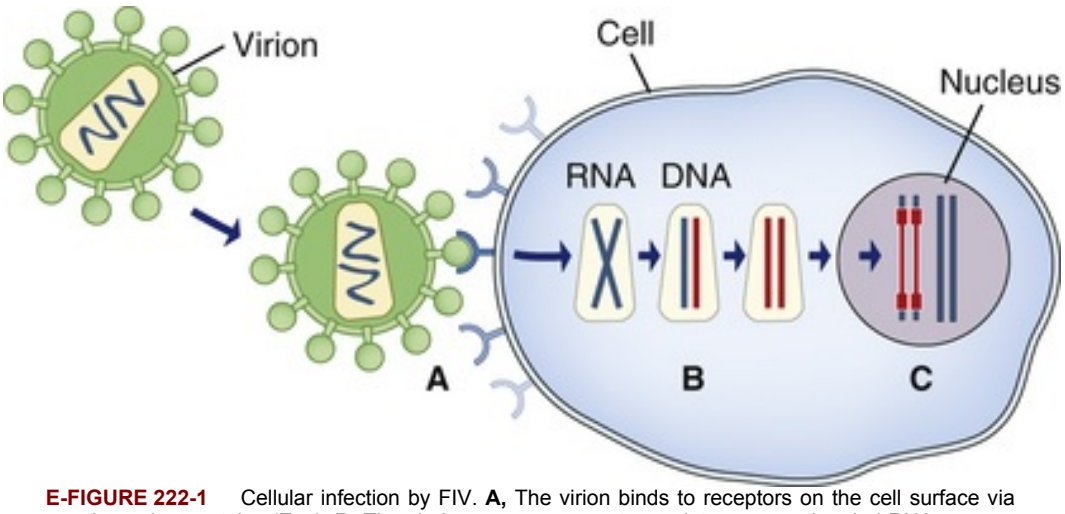
TABLE 222-1

Risk Factors for FIV Infection

VARIABLE	HIGH RISK	LOW RISK
Sex	Male	Female
Neuter status	Unneutered	Neutered
Breed	Mixed breed	Pure breed
Environment	Free roaming	Confined
Health status	Sick	Healthy
Age	Adult	Juvenile

An understanding of virus structure and replication cycle informs the basis for diagnostic testing methodologies as well as persistent infection as an invariable outcome. Each FIV virion contains a duplicate, single-stranded RNA genome (E-Figure 222-1). Three major genes *gag*, *pol* and *env* encode viral core proteins (matrix [p15], capsid [p24] and nucleocapsid [p10]), enzymes (reverse transcriptase, protease, integrase) and envelope glycoproteins (transmembrane [gp41], surface [gp120]), respectively.[8] Env binds the primary receptor for FIV, CD134, to initiate infection. A conformational change in Env exposes the binding site for the co-receptor CXCR4, triggering cell entry.[9] The viral genome is released and copied into DNA by the viral

RNA-dependent DNA polymerase, reverse transcriptase. This DNA copy, once integrated into the host chromosomal DNA and flanked by long terminal repeats which control its transcription, is known as provirus (see E-Figure 222-1). Provirus can either remain latent or form the template for the production of new virions.



E-FIGURE 222-1 Cellular infection by FIV. **A,** The virion binds to receptors on the cell surface via envelope glycoproteins (Env). **B,** The viral enzyme, reverse transcriptase, uses the viral RNA genome as a template to make a DNA copy. **C,** The DNA copy becomes integrated into the infected host cell DNA as provirus. (Reproduced with permission, Wiley. Hosie MJ, Beatty JA: Vaccine protection against feline immunodeficiency virus: setting the challenge. *Aust Vet J* 85:5-12, 2007.)

Within an infected cat, FIV mutates frequently, creating a pool of variant viruses. The principal underlying mechanisms are point-mutations introduced during reverse transcription and recombination between viruses co-infecting a single cell. Variable regions in *env* form the basis for the phylogenetic classification of FIV into major subtypes or clades, A to E. Regional variation in the prevalence of subtypes exists with subtypes A, B and C being most common.[10,11] Classification of FIV subtypes has become complex. Sequences used for subtyping do not detect all recombinations within *env* and variants with *gag, pol* and *env* sequences that are not consistent with a single subtype occur.[12,13] The clinical relevance of subtype classification is uncertain, as subtype does not consistently predict biological properties, such as virulence, or vaccine protection.

FIV is transmitted by direct inoculation of saliva or blood during fighting.[4,14] Other routes of transmission are of minor epidemiological significance. Horizontal transmission of FIV between cats in stable households is rare, in sharp contrast to the major feline retroviral pathogen, feline leukemia virus (FeLV; see ch. 223), which spreads rapidly between housemates.[7,15,16] Vertical or perinatal transmission of FIV in the field is documented infrequently, although primary infection of the queen during pregnancy may increase the risk of transmission.[16-19] Natural sexual transmission of FIV is not documented.

In veterinary hospitals, no special precautions over and above those for any feline patient are necessary for dealing with FIV-infected cats. Virus shed in secretions is rapidly inactivated in dry conditions and routine cleaning and disinfection procedures to prevent the spread of feline herpesvirus-1 (FHV-1), feline calicivirus (FCV), and feline panleukopenia virus (FPV) (see ch. 225 and 229) effectively eliminate any residual risk of environmental contamination. Nosocomial FIV infection is virtually impossible unless there is parenteral inoculation of contaminated blood or saliva from an FIV-infected cat. Cats used as blood donors should be demonstrated to be free from FIV infection since iatrogenic transmission by this route is inevitable.[20] Cats should not be housed in isolation facilities solely on the basis of their FIV status since this places potentially immunosuppressed cats at risk.

FIV strains are highly host-specific. Cross-species transmission, even between carnivore hosts, is rare.[21] One group has been able to demonstrate productive infection of human cells *in vitro* and experimental infection of non-human primates with FIV.[22,23] Owners can be counseled that any zoonotic risk posed by FIV is minimal; a serosurvey of veterinary workers with occupational exposure found no evidence of FIV infection and human CD134 does not support cellular entry by the virus.[24,25] However, immunosuppressed human patients, such as transplant recipients, should avoid FIV-infected cats or observe meticulous hygiene

precautions to avoid the possibility of exposure to shared opportunistic pathogens.

Pathogenesis

FIV infection can be broadly considered to progress in three stages: a transient "primary stage," a chronic "asymptomatic stage" and a terminal "second stage" (Figure 222-2). In contrast to HIV where, without antiretroviral treatment, patients progress through predictable, well-characterized clinical stages to the terminal acquired immunodeficiency syndrome (AIDS) stage, the consequences of FIV infection are not predictable.[5,26,27] It is expected that a large proportion of FIV-infected cats will remain free from significant disease and have a normal life expectancy.[15,27-29]

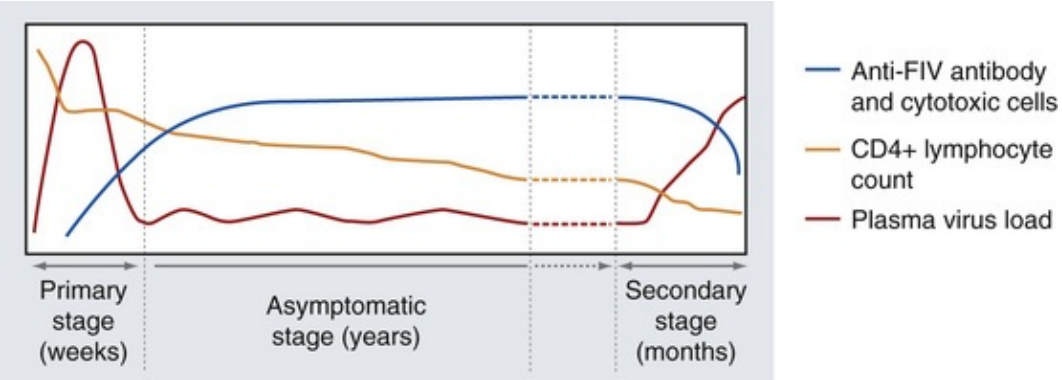


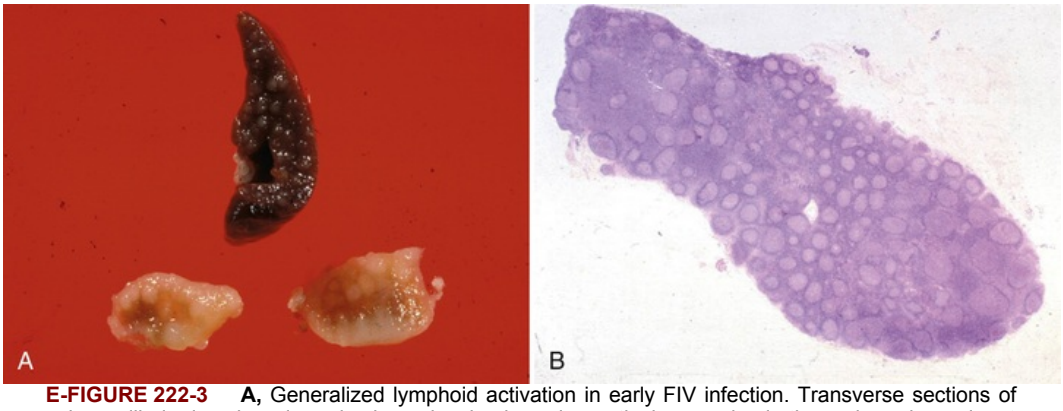
FIGURE 222-2 Course of FIV infection. Following infection, there is an initial burst of virus replication. This may be accompanied by a transient, non-specific "primary stage" illness. Strong cellular and humoral immune responses dramatically reduce plasma virus load but fail to clear infection and the "asymptomatic stage" begins. A fall in CD4+ lymphocyte numbers, the primary target of early FIV infection, begins early and progresses throughout infection. After several years, in a minority of cats, lymphoid tissues become depleted, antiviral immunity wanes and plasma virus levels rise again. "Second-stage" disease is characterized by clinical signs of immune dysfunction, lymphoma, unexplained wasting or neurological signs.

During the primary stage, which lasts for 6 to 8 weeks, virus replicates rapidly and viremia is detectable by virus isolation and polymerase chain reaction (PCR).[30] Dissemination to lymphoid tissues follows and virus can be detected in saliva within 3 weeks of experimental infection.[31,32] A robust immune response comprising CD8+, cytotoxic T-lymphocytes and antibodies to viral proteins can be detected from 2 to 6 weeks after experimental infection.[33,34] Virus replication is contained but, crucially, not cleared by host immunity. Clinical signs accompanying the primary stage, such as transient fever, neutropenia and lymphadenopathy, are sometimes seen after experimental infection of young cats, but are rare following natural exposure.[31,35]

The asymptomatic stage—which lasts for years and, often, for the cat's lifetime—is characterized by a low level or absent viremia. Hence, antigen testing is not used for FIV diagnosis (see Diagnosis). Importantly, immune dysfunction begins early after FIV infection and progresses during the asymptomatic stage. Mild or intermittent clinical signs can be seen during the asymptomatic stage. The main targets of early FIV infection, lymphocytes (T-helper cells), which promote cell-mediated and humoral immunity, decline progressively in number.[36,37] Deficits in lymphocyte function begin early and progress.[38-40] T-cell priming to novel antigens is disrupted within 5 weeks following experimental infection.[38] In clinically normal FIV-infected cats, impaired immunity to opportunistic pathogens has been demonstrated. Primary challenge with *Toxoplasma gondii* resulted in severe, systemic toxoplasmosis in FIV-infected cats compared with only mild, transient signs in FIV-uninfected cats.[41] Innate as well as adaptive immunity is affected; delayed clearance of *Listeria monocytogenes* in experimental FIV infection was attributed to defective natural killer (NK)-cell function.[42]

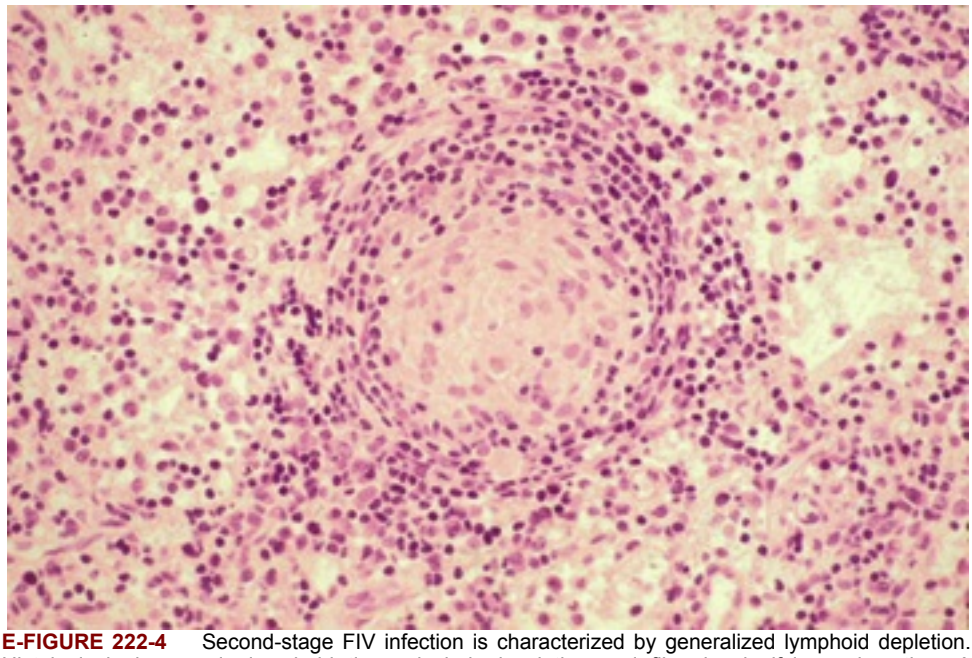
Immune hyperactivation, as well as suppression, contributes to overall immune dysfunction in FIV infection. An early rise in an activated subpopulation of lymphocytes expressing low levels of CD8, CD8(low), exacerbates a reduced CD4:CD8 ratio.[43] Lymphoid hyperplasia, follicular dysplasia and expansion of B- and T-cell areas develop in lymph nodes and other organs including spleen, tonsils and mucosa-associated lymphoid tissue (E-Figure 222-3).[33,35,44] Polyclonal B-lymphocyte stimulation results in hypergammaglobulinemia.[45] Chronic antigenemia activates T-cell subpopulations which function as immune

suppressors. These include CD4+ and CD8+ lymphocytes expressing B7 and CTLA4, which contribute to immune anergy and apoptosis in lymph nodes, as well as CD4+CD25+ T-regulatory cells, which function as non-specific suppressors, thereby impacting immunity to FIV and to opportunistic pathogens.[46,47]



E-FIGURE 222-3 **A,** Generalized lymphoid activation in early FIV infection. Transverse sections of submandibular lymph node and spleen showing irregular cortical expansion in the node and prominent white pulp in the spleen 2 months after experimental infection. **B,** Prominent and irregular follicular expansion in the submandibular lymph node from the same cat (H&E). (Courtesy Professor John (Sean) J. Callanan.)

Eventually, in some cats, second-stage infection ensues. Second-stage FIV is characterized by profound lymphoid depletion (E-Figure 222-4), escape of virus from immunological control and terminal disease.[44,48,49] The term "second-stage" FIV infection is preferred to "feline-AIDS," as criteria to define AIDS in cats are not determined. Further, "feline AIDS" carries negative connotations for some owners and the term is frequently misused to apply to any FIV-infected cat.



E-FIGURE 222-4 Second-stage FIV infection is characterized by generalized lymphoid depletion. Histological changes in lymphoid tissue include involution and fibrosis signifying exhaustion. A depleted secondary follicle and an overall decrease in cell density are shown (H&E). (Courtesy Professor John (Sean) J. Callanan.)

Clinical Signs

All FIV-infected cats should be considered to be at risk from immune dysfunction which can manifest as

immune deficiency or immune-mediated disease. Healthy FIV-infected cats should be carefully examined and even apparently minor problems fully investigated. Immune dysfunction can manifest clinically as atypical and refractory bacterial, viral or protozoal infections and parasitoses (Figures 222-5 through 222-9). Respiratory infections, bacterial pyoderma, generalized demodicosis, mycobacterial infection, disseminated cowpox, pulmonary cryptococcosis and lungworm infections are reported.[4,50-52] Persistent cytopenias, particularly neutropenia or lymphopenia are described in advanced FIV infection.[27,53-55] FIV infection has been linked to feline chronic gingivostomatitis (FCGS), a painful and debilitating condition that can greatly impact quality of life (Figure 222-10).[56]

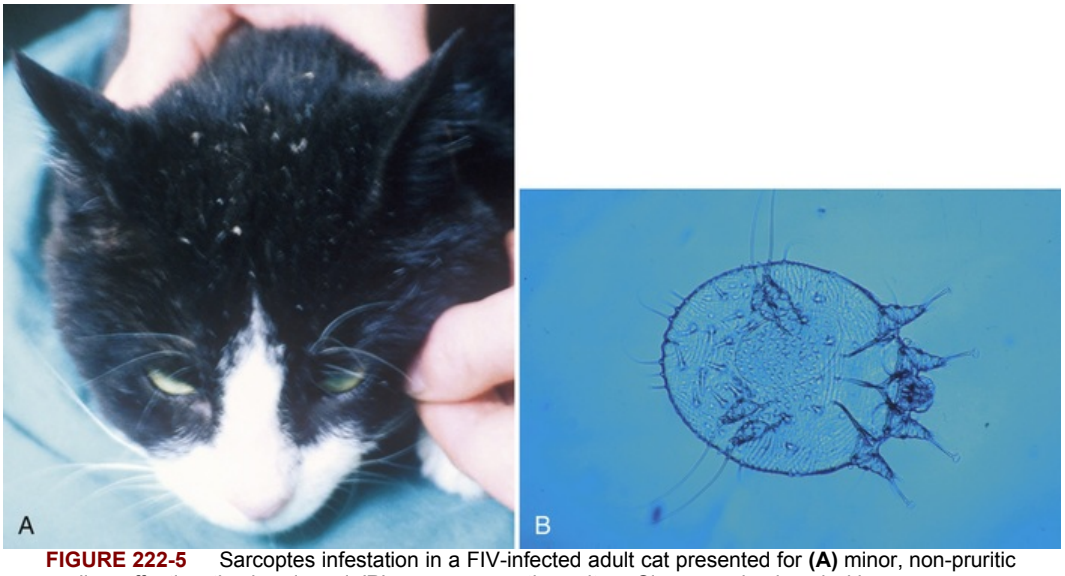


FIGURE 222-5 Sarcoptes infestation in a FIV-infected adult cat presented for **(A)** minor, non-pruritic scaling affecting the head, and **(B)** numerous active mites. Signs resolved and skin scrapes were negative within 1 week of ivermectin treatment.

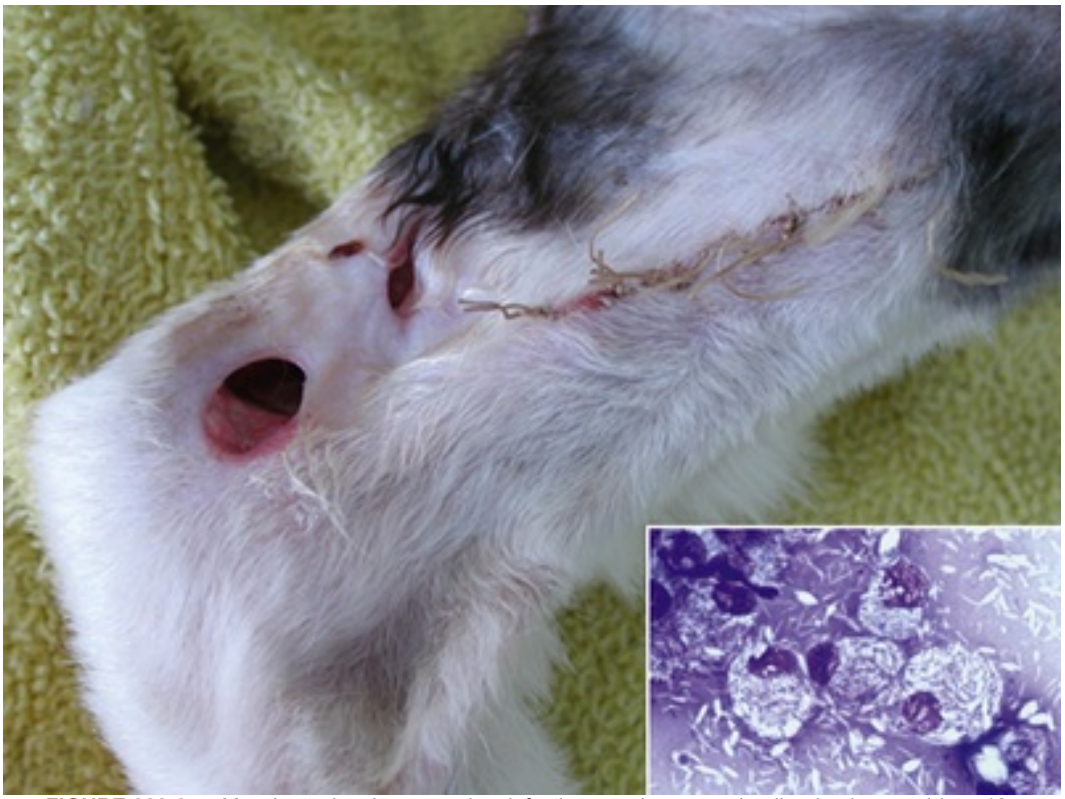


FIGURE 222-6 *Mycobacterium lepraemurium* infection causing a non-healing hock wound in a 12-year-old cat with second-stage FIV infection. Inset: Fine-needle aspiration and cytology shows numerous negatively staining intracellular bacilli. Modified Wright-Giemsa. (Courtesy Professor Vanessa Barrs.)

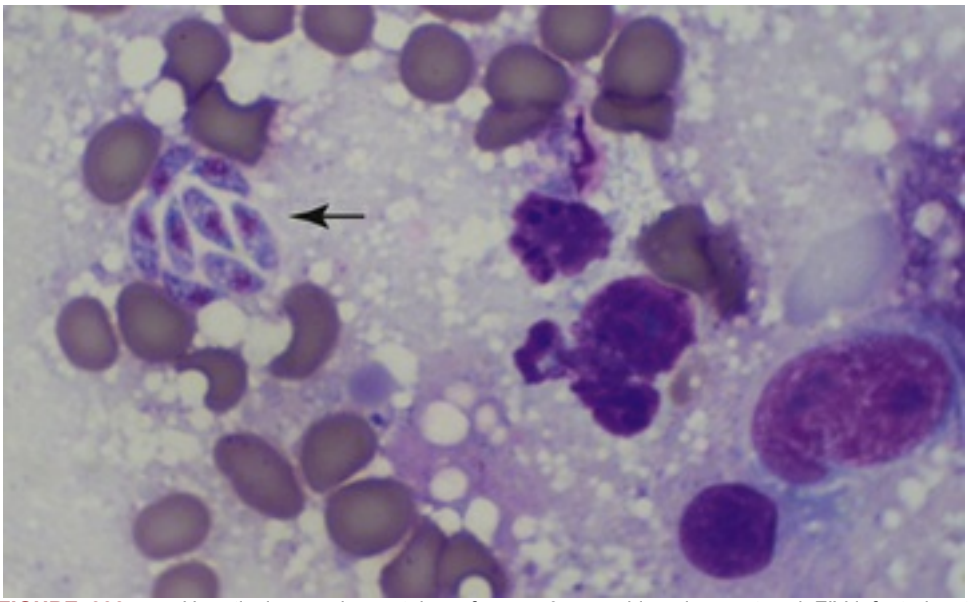


FIGURE 222-7 Hepatic impression cytology from a 9-year-old male, neutered FIV-infected cat investigated for a hepatopathy. *T. gondii* tachyzoites (arrow) are surrounded by red blood cells. Modified Wright-Giemsa.

FIGURE 222-8 A heavy *Eucoleus (Capillaria) aerophilus* burden identified in bronchoalveolar lavage fluid from an adult cat with second-stage FIV infection. Inset shows characteristic ova. (Courtesy Professor Vanessa Barrs.)

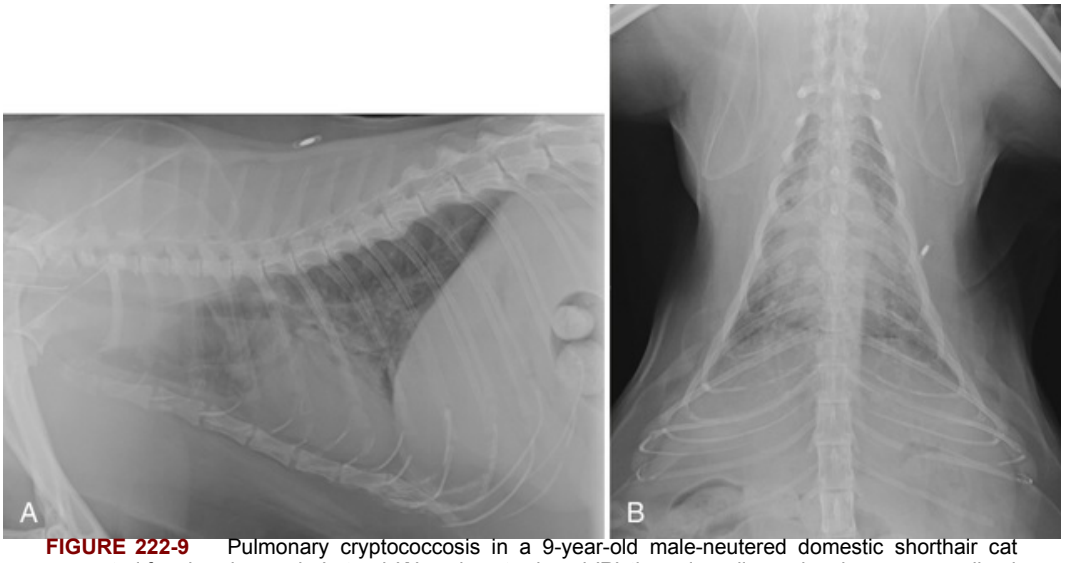


FIGURE 222-9 Pulmonary cryptococcosis in a 9-year-old male-neutered domestic shorthair cat presented for chronic cough. Lateral **(A)** and ventrodorsal **(B)** thoracic radiographs show a generalized mixed, predominantly bronchointerstitial, pulmonary pattern. *Cryptococcus neoformans* was cultured from bronchoalveolar lavage fluid (BAL). No yeasts had been identified on cytology of the BAL.

FIGURE 222-10 Gingivostomatitis with marked caudal oral cavity involvement.

The risk of lymphoma is increased in FIV infection by 5 to 6-fold.[59] This risk is small in comparison to the 60-fold increased risk of lymphoma in FeLV infection. FIV-associated lymphomas are typically high-grade, extranodal, B-cell tumors, similar to HIV-associated diffuse large B-cell lymphoma (Figure 222-11).

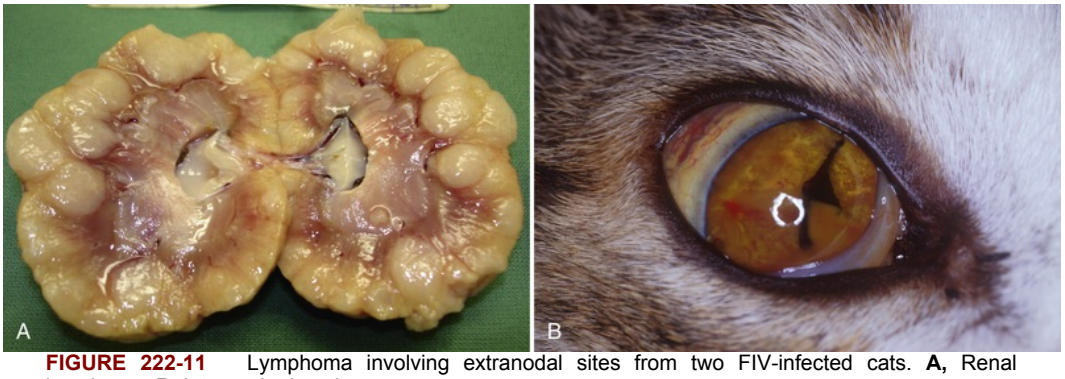


FIGURE 222-11 Lymphoma involving extranodal sites from two FIV-infected cats. **A,** Renal lymphoma. **B,** Intraocular lymphoma.

The etiology of FCGS is ill-defined and it is likely to be multifactorial. Epidemiological evidence identifies FIV as a risk factor in some studies and, while FIV is clearly not causal, a role for the virus in disease manifestation and severity in infected cats seems likely.[57,58] Immune stimulation triggered by FIV may contribute to chronic oral inflammation while immune suppression may delay clearance of other pathogens, such as feline calicivirus or secondary bacterial infections.

Direct oncogenesis by FIV is rare: integration site mapping in a single case demonstrated truncation of a gene on chromosome B3 and down-regulation of the unaffected allele consistent with a loss of function mutation.[60] FIV-induced immune dysfunction may play a role in lymphomagenesis. Reduced CD4+ lymphocyte counts, a known risk factor for HIV-associated lymphoma, have been demonstrated in cats developing FIV-associated lymphoma.[61] Interestingly, in HIV-associated lymphomas, co-infecting gammaherpesviruses are causal in over 80% of cases. The oncogenic potential of the recently identified widely endemic, gammaherpesvirus of domestic cats, *Felis catus* gammaherpesvirus 1, is under

investigation.[62,63] Hyperstimulation of the B-cell compartment in FIV infection might also contribute to oncogenesis, with amplification of normal somatic mutations predisposing to B-cell tumors. Increased numbers of circulating B-cells, plasma immunoglobulin and interleukins 1 and 6 (IL-1 and IL-6), which stimulate B-cell proliferation and differentiation, have been documented in FIV-infected cats that develop lymphoma.[61] Many other neoplasms are described in FIV-infected cats but the role of FIV, if any, in these cancers is unknown.

Wasting syndrome is multifactorial with changes in protein and lipid metabolism, altered energy requirements, anorexia, cytokine derangements, malabsorption, endocrinopathies and myopathies all contributing.[64] An increased risk for renal diseases in FIV infection is suspected but a causal association has been difficult to prove. Renal proteinuria but not renal azotemia has been associated with natural FIV infection.[65]

Following experimental infection, FIV provirus can be detected in the central nervous system from 2-4 weeks. The virus targets non-neuronal cells, primarily macrophages and microglia, resulting in a progressive encephalitis.[69] Histopathological lesions are generally less severe in FIV than in HIV infection. This might be partly due to FIV being less macrophage-tropic than HIV, since macrophages carry virus across the blood-brain and blood–cerebrospinal fluid barriers. However, some FIV isolates induce severe neuropathology.[70] These lesions may be clinically silent or induce progressive neurological deficits including behavioral changes, stereotypic motor behaviors, increased aggression and delayed righting and pupillary light reflexes.[68] In natural FIV infection, compulsive roaming, changes in sleeping patterns, aggression, seizures, ataxia, tremors, movement disorders and paraparesis have been reported but the extent to which other etiologies were excluded is unclear.[4,71,72] Some deficits accompanying HIV-associated neurodegeneration, such as cognitive impairment (reduced concentration, memory, learning) and psychological problems, cannot be routinely diagnosed in cats.[67]

Severe unexplained weight loss can occur in second-stage disease (Figure 222-12). This presentation resembles "wasting syndrome," an AIDS-defining condition in HIV infection, indicating weight loss of 10% or more over 30 days with no identifiable cause other than HIV infection.

FIGURE 222-12 Severe, unexplained wasting in second-stage FIV infection.

FIV-associated neuropathology has been studied extensively as an experimental model for neurodegenerative diseases in HIV infection.[66-68] The incidence of neurological signs accompanying natural FIV infection is unknown.

Diagnosis

FIV-infected cats should be identified to optimize individual health care and to prevent new infections. Ideally, the current retrovirus status of all cats should be known. Priorities for FIV-testing include free-roaming cats, sick cats, cats presenting with fight-wounds, blood donors, adult cats being rehomed, kittens born to FIV-infected queens and any cat prior to FIV vaccination (Figure 222-13).[73,74]

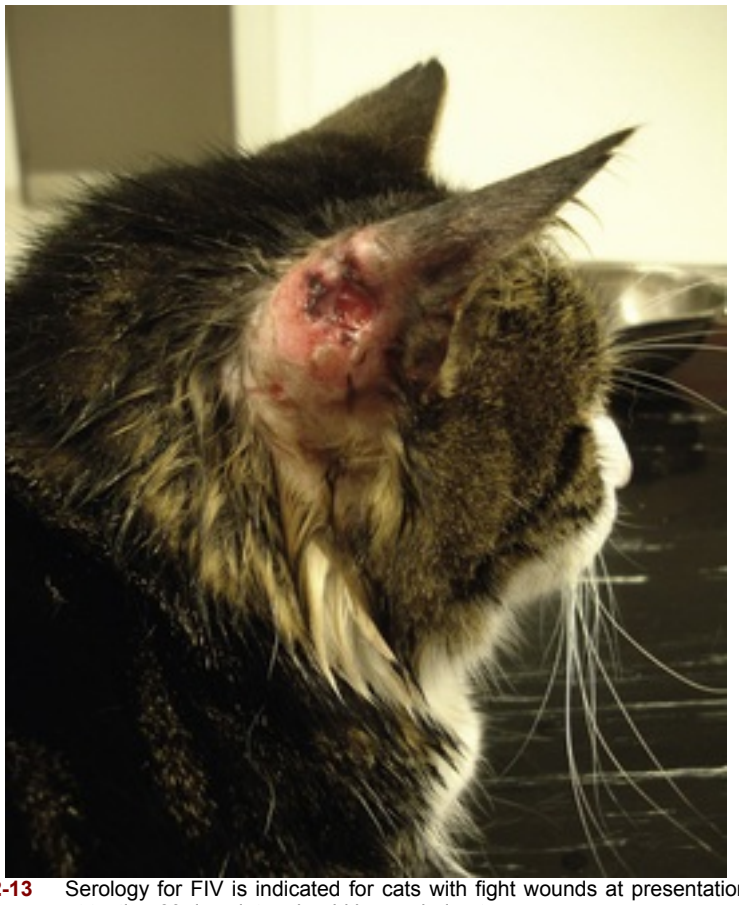


FIGURE 222-13 Serology for FIV is indicated for cats with fight wounds at presentation. If the cat tests negative, repeat testing 60 days later should be carried out.

Commercial FIV tests detect either anti-FIV antibodies by serology or viral nucleic acid by PCR. Virus isolation from peripheral blood mononuclear cells is not commercially available. Serology is the first line for testing. FIV causes a persistent infection so antibody is a marker of infection. Kits designed for in-clinic use capture antibodies from plasma, serum or whole blood using enzyme-linked immunosorbent assay or rapid immunomigration technologies. The antigens used vary between manufacturers and include p15, p24 and gp41. The diagnostic sensitivity and specificity of in-clinic kits was compared using 536 randomly selected serum samples.[75] Confirmatory testing using Western blot was performed on positive samples and a random selection of negative samples. Six of 7 FIV test kits had diagnostic sensitivities >92% and specificities >99%. The interpretation of results from serological screening tests requires the integration of clinical findings from the individual cat to guide whether repeat serology or a PCR test is indicated and what the timing of any repeat testing should be (Figure 222-14).

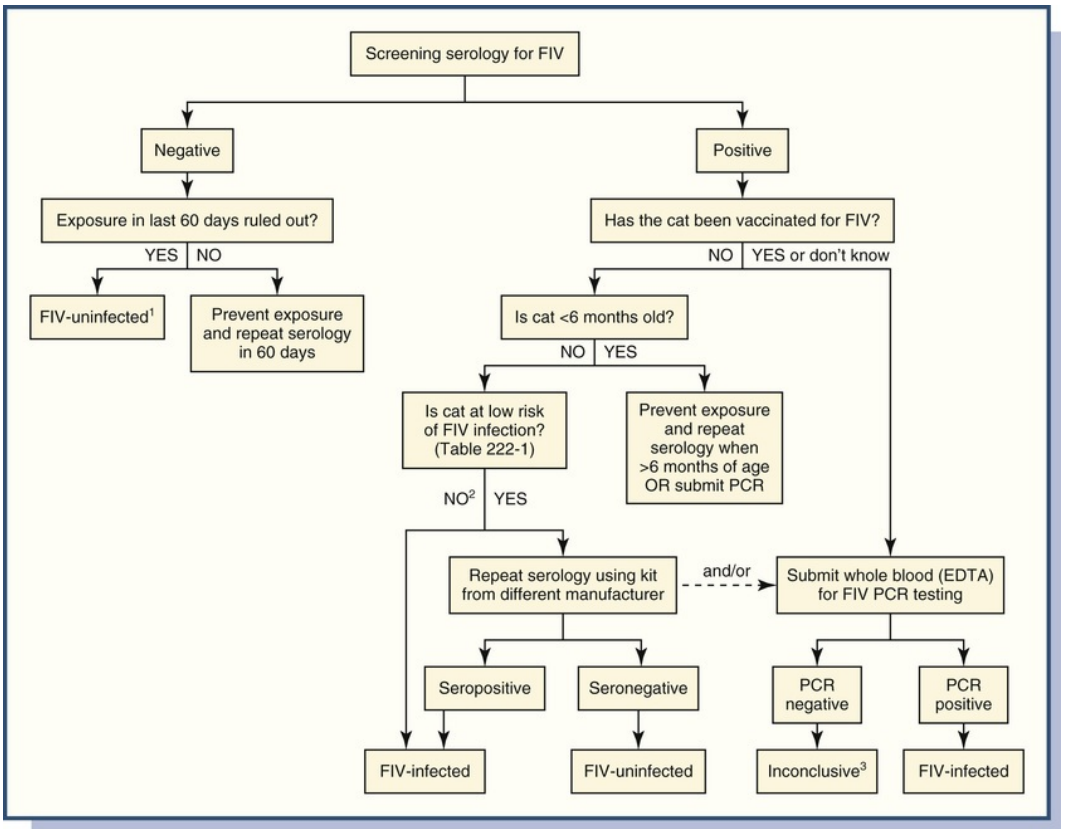


FIGURE 222-14 Determining FIV status using serology and PCR. No single test is 100% accurate. The infection status derived from this algorithm gives a working diagnosis. [1]False negative serology results are rare. Confirmation by repeating serology, preferably using a kit from a different manufacturer, could be considered for high-risk cats. No delay is necessary before repeating serology. Rarely, cats with advanced FIV infection can be seronegative, so consideration should be given to the clinical findings. [2]Repeat serology (no delay necessary) can be considered for high risk cats but positive serology in a high risk cat is highly likely to indicate infection. [3]In this scenario, the cat may be uninfected, or infected with an FIV variant not recognized by the PCR assay or the FIV load may be below limit of detection of the assay. NOTE: At the time of writing, new data on point-of-care serology tests became available. The reader is referred to the section on diagnosis.

Molecular tests target DNA provirus and some also detect viral RNA in plasma. Data to assess the performance of FIV PCR tests are limited and variability in performance between laboratories has been demonstrated.[76] Diagnostic sensitivity that is 5-15% lower than serology and specificity comparable with serology have been reported for commercial PCR tests.[77-79] Sequence variability between isolates likely contributes to the lower sensitivity of PCR because primers may not detect all field isolates. Low provirus or virus load, poor sample quality and technical issues may also contribute. FIV PCR is recommended as an adjunct to serology to determine the true FIV status of cats in certain circumstances. PCR is not indicated as a screening test for FIV.

Interpretation of FIV Serology

Negative serology results are generally reliable because the sensitivity of serological tests is high (Table 222-2). Even in cats at high risk of FIV infection, the risk of a false negative result is low. The time to seroconversion following natural infection is variable and can be prolonged. A seronegative cat that may have been recently exposed should be isolated from FIV-infected cats or cats of unknown FIV status and retested after 60 days.

TABLE 222-2

Interpretation of a Negative FIV Serology Result

INTERPRETATION OF NEGATIVE SEROLOGY RESULT	COMMENTS
The cat is NOT infected with FIV.	This is the most likely explanation.
The cat is FIV-infected, but has not yet seroconverted.	If recent exposure has not been ruled out, repeat serology in 60 days.
False negative	This is unlikely because the diagnostic sensitivity is high BUT the higher the risk of FIV infection in the cat being tested, the higher the risk of a false negative result. If the cat is from a high risk group, repeat serology is optional.
Terminal FIV-related disease	Rarely, cats with terminal disease can be seronegative because FIV-antibody production falls or antibody is complexed. Infection may be detected with PCR.

The following considerations apply when interpreting positive serology results for an individual cat (Table 222-3).

TABLE 222-3

Interpretation of a Positive FIV Serology Result

INTERPRETATION OF POSITIVE SEROLOGY RESULT	COMMENTS
The cat is infected with FIV.	Infection-induced antibody is a marker of FIV infection (not recovery from infection).
False positive	The positive predictive value of serology is reduced in cats at low risk from FIV infection. If the cat is from a low-risk group, repeat the serology using an alternative kit or submit PCR.
The cat is NOT infected, but maternal anti-FIV antibodies are being detected on serology.	Maternal antibodies can persist for months. Repeat serology when the cat is over 6 months of age. If this is not practical, submit PCR.
The cat has been vaccinated for FIV.	Cats vaccinated with Fel-O-Vax FIV test positive on some serological tests.[82,83]

Cats at Low Risk of Infection

The possibility that a positive result is a false positive is increased in cats at low risk of infection because the positive predictive value of the test is reduced. The reason for this is that, in a cat from a low risk group, the prevalence of FIV in that (low risk) population approaches the expected frequency of false positives. So for each positive test result obtained in cats at low risk, there is a higher chance that the result is a false positive.

Maternal FIV Antibodies

Absorbed from colostrum of vaccinated and infected queens, may result in false positive results in kittens. Maternally derived anti-FIV antibodies can persist for months. Young cats returning positive results on serology should be retested after 6 months.

Prior Vaccination with Fel-O-Vax FIV (Boehringer Ingelheim, Germany)

A commercial FIV vaccine is available in regions including the United States, Canada, Australia, New Zealand and Japan. Vaccinated cats seroconvert, requiring that anti-FIV antibodies associated with vaccination be differentiated from the serological response to natural infection. On Western blot testing, vaccine-induced antibodies to all major virus proteins have been detected.[80] Vaccine-induced antibodies are also detected using point-of-care serology tests and, for many years, this has created difficulties in determining whether seropositive cats are vaccinated, infected or both.[81] However, in a recent study of vaccinated (n = 119) and unvaccinated (n = 239) cats, two point-of-care kits, Witness FeLV/FIV (Zoetis Animal

Health, France) and Anigen Rapid FIV/FeLV (BioNote, Korea), accurately detected infection regardless of vaccination status.[82] However, subsequently, in a prospective study of 19 kittens using one of these tests (Witness FeLV/FIV), transient vaccine-induced antibodies were detected in almost half of vaccinates.[83] Further clarification of the utility of point-of-care kits from different manufacturers in detecting true infection status is expected. The reliability of a negative serology result is unchanged by the introduction of FIV vaccination.

PCR can be used with serology to assist in determining the true infection status of seropositive cats that may be vaccinated against FIV, seropositive cats less than 6 months of age and seronegative cats that have been recently exposed to FIV. After experimental exposure, PCR can detect viral RNA within 1 to 2 weeks and DNA within 3 weeks but differences in virus strain, dosage and assay sensitivities mean that it is hard to predict how long after natural exposure PCR can be used to detect FIV infection. Positive PCR test results indicate that the cat is almost certainly infected, whereas negative PCR results are inconclusive.

Prognosis

Controlled studies demonstrate comparable survival time between FIV-infected and uninfected cats.[5,27-29,84] In a study of almost 10,000 retrovirus-tested pet cats, including 1100 seropositive for FIV, the survival rate at 6 years was 65% compared to 90% for uninfected cats.[28] In the same study, if deaths during the first 100 days were excluded, survival of FIV-infected cats was 94% and 80% at 3 and 6 years, respectively, compared with controls. There is no justification for the euthanasia of healthy cats on the basis of FIV status. Regrettably, this practice does occur.[29,85,86]

Even though a negative effect of FIV infection on survival is minor or non-existent when groups of cats are studied, the effect of FIV on morbidity is potentially underestimated. The progressive immune dysfunction that accompanies FIV infection means that the clinician should "expected the unexpected" in FIV-infected cats, even when they are reported to be healthy.

Management

Comprehensive international guidelines for the management of FIV-infected cats from the American Association of Feline Practitioners and the European Advisory Board on Cat Diseases are available to download.[87,88]

Healthy FIV-Infected Cats

FIV-infected cats are the source of new infections and they should be prevented from contacting uninfected cats. This means confining FIV-infected cats indoors or in an enclosure, singly or with other FIV-infected cats. Where a cat in a multicat household is identified as FIV-infected, all cats in the household should be tested. If the household is stable and closed, the benefits of belated segregation may be small as the virus is unlikely to spread, although owners should be made aware of this possibility.

Veterinary check-ups of FIV-infected cats every 6 months will facilitate early detection of any emerging health problems. Evidence on which to base recommendations for vaccination of FIV-infected cats against FHV-1, FCV and FPV is limited.[89,90] Killed products should be selected over modified-live vaccines for FIV-infected cats because of the potential for reversion to virulence with the latter in cats at risk from immunosuppression (see ch. 208).[91,92] Individual risk assessment will guide the frequency of vaccination and the choice of immunogens.[92,93] Control of ectoparasites, endoparasites and the importance of dental prophylaxis and a balanced diet should be stressed to owners.

Sick FIV-Infected Cats

In the absence of surrogate markers that reliably predict disease progression, the prognosis for an individual FIV-infected cat should be determined without regard to its FIV status. Many sick FIV-infected have treatable diseases. Knowing that a cat is FIV-infected is not a reason to curtail the investigation but, rather, will inform the list of differentials and help to guide the diagnostic investigation and treatment selection.

Where antibiotics are indicated, selection should be based on the results of sensitivity testing, and bactericidal agents and dosing protocols used. Clinicians should be vigilant for drug reactions (see ch. 169). Severe drug-induced neutropenia following griseofulvin administration has been reported in FIV-infected

cats.[94] Glucocorticoids may be indicated to treat intercurrent inflammatory or immune-mediated problems arising in FIV-infected cats. Glucocorticoids should be used judiciously, only where specifically indicated, and patients should be monitored closely.

Investigation of chronic gingivostomatitis includes consideration of a range of contributing etiologies, including feline calicivirus-associated disease, inflammation associated with dental disease, immune-mediated and neoplastic causes, and eosinophilic granuloma complex (see ch. 36 and 272).[56] The degree and duration of response to symptomatic and supportive treatments such as teeth cleaning, antibiotics such as amoxicillin clavulanate, interferons and anti-inflammatory doses of glucocorticoids are variable.[95] Extraction of premolars and molars is reported to improve signs in 60-80% of affected cats.[96,97]

In cats presenting with intermediate or high-grade lymphoma, there is no evidence that FIV infection *per se* is a negative prognostic indicator for response to multiagent chemotherapy, although data are limited.[98] Close monitoring of the neutrophil count during therapy is warranted. Where neurological impairment is identified and localized in FIV-infected cats, investigation for potentially treatable causes is indicated (see ch. 261).

Management of FIV-associated wasting (see ch. 177) involves investigation for treatable diseases including enteropathies (see ch. 276) and exocrine pancreatic insufficiency (see ch. 292), supportive care, nutritional support and appetite stimulation.

Severe or persistent cytopenias in FIV-infected cats should be investigated for treatable causes, since cytopenias are common in sick cats regardless of their FIV status.[27,54] There is currently no suitable supportive treatment for FIV-associated neutropenia. Recombinant human granulocyte colony-stimulating factor (rHuG-CSF) increased neutrophil counts in the short term in young cats experimentally infected with FIV, but this effect ceased with the development of antibodies to rHuG-CSF.[99] Further, cross-neutralization with feline (Fe)G-CSF risks refractory agranulocytosis. Pegylated FeG-CSF showed promising results with less frequent dosing, but this compound is not commercially available.[100] Anemia is associated with FIV infection, although less commonly than neutropenia, and supportive care may be indicated. Recombinant human erythropoietin (rhEPO) was effective at increasing PCV in FIV-infected cats without inducing anti-rhEPO antibodies in one small study.[101] Darbepoetin, which is longer-acting and less antigenic than rhEPO, is effective in cats, although studies in FIV-infected cats specifically are not reported.[102]

Immune Modulation and Antiviral Therapies

Before embarking on any treatment trial using immunomodulators or antiviral drugs, the owners' expectations should be carefully managed. FIV infection cannot be cured. The small chance of improving clinical signs should be balanced against the potential risks and costs, including monitoring costs, involved.

Data to support the use of immunomodulators in FIV infection are very limited.[103,104] Non-specific immune stimulation risks unintended outcomes including increased virus replication and the activation of immune suppressor cells. In a placebo-controlled study using human recombinant interferon-alpha (rHuIFN-alpha) (oral transmucosal, 50 IU/cat q 24 h, 7 days on, 7 days off for 6 months) in natural FIV infection, no effect on plasma virus or provirus load was detected although improved clinical signs were reported.[105] Improvements in clinical parameters were also reported using recombinant feline interferon-omega (rFeIFN-omega,Virbagen Omega, Virbac) at 1 MU/kg SC q 24 h for 5 days, repeated on days 14 and 60 or a lower-dosage oral protocol (0.1 MU/cat rFeIFN-omega PO q 24 h for 90 days).[106,107]

Antiretroviral therapies have dramatically improved the prognosis for HIV-infected humans. Combinations of drugs that inhibit HIV reverse transcriptase, protease or integrase avoid the rapid emergence of drug-resistant mutants. Virus load and CD4 count are used to guide the timing of initiation of treatment and to assess response in asymptomatic HIV-infected patients. In contrast, there are limited data to evaluate antiretrovirals in FIV infection and there are no licensed products.[108] Combination therapy for FIV to avoid the emergence of resistant mutants is hampered by the limited choice of drugs; most inhibitors of HIV protease are ineffective against FIV and data on potential inhibitors of FIV integrase are limited to *in vitro* activity.[109,110] Several nucleoside analogues can inhibit FIV reverse transcriptase, including zidovudine (AZT, 3'-azido-3'-deoxythymidine), lamivudine (3TC, 2',3'-dideoxy-3'-thiacytidine) and adefovir (PMEA, 9-[2-phosphonomethoxyethyl]adenine). Improvements in clinical scores, virus load and CD4 counts are reported in some studies but adverse effects, including anemia, neutropenia and gastrointestinal signs are common and can be severe. The pharmacokinetics of AZT have been studied in cats and this drug was associated with improvement in stomatitis in a blinded, placebo-controlled study.[111,112] Precautions for AZT use are shown in

E-Box 222-1.

E-Box 222-1

Precautions for AZT (Reverse Transcriptase Inhibitor) Use in FIV-Infected Cats

- Cats with bone marrow suppression should not be treated.
- Dosage: 5-10 mg/kg q 12 h PO or SC.
- Side-effects are more common at the higher dosage.
- For SC injection, reconstitute with 0.9% NaCl.
- Monitor for anemia; complete blood count weekly × 4, then monthly if stable.
- Mild, transient anemia in the first 3 weeks usually resolves even if treatment is continued.
- Discontinue treatment if hematocrit falls below 20%. Resolution of anemia after withdrawal is expected.
- Long-term use for months or years is reported.

Data from European Advisory Board on Cat Diseases. Hosie MJ, Addie D, Belák S, et al: Feline immunodeficiency. ABCD guidelines on prevention and management. *J Feline Med Surg* 11:575-584, 2009.

In an alternate approach, CXCR4 antagonist AMD3100 (1,1'-bis-1,4,8,11-tetraazacyclotetradekan), which blocks the co-receptor for FIV entry, has been evaluated in client-owned, FIV-infected cats. A prospective, placebo-controlled, double-blind trial showed a mild reduction in proviral load, minimal side-effects and no emergence of resistance over a 6-week period.[113]

Prevention

The most effective way to prevent FIV infection is to confine uninfected cats. Free-roaming cats are at high risk from FIV infection and they represent an important source of new infections. Confining owned FIV-infected cats is also advised to prevent new infections. Providing an enriched environment that prevents roaming is effective, not just in reducing infectious disease risk, but also in preventing trauma, straying and hunting.

A commercial, inactivated, infected-cell vaccine, Fel-O-Vax FIV, has been available in some regions for over a decade. This vaccine is currently categorized, according to international feline vaccination guidelines, as "non-core."[92,93] There are two principal reasons why the use of the FIV vaccine has been controversial. The first concerns its efficacy. The vaccine contains subtypes A and D and, in most published studies, it performs well. Sterilizing immunity against homologous and heterologous FIV strains including subtype B viruses has been demonstrated.[114,115] In studies performed by the vaccine developers, preventable fractions between 80-100% are demonstrated as well as protection from contact challenge and duration of immunity of 12 months or more.[116,117] In a single independent study, the vaccine provided no protection against challenge with a subtype A isolate.[118] Additional independent data on the efficacy of the vaccine in the field in different regions are awaited.

A second area of concern has been that uninfected cats that are vaccinated will test positive on serological tests for FIV.[81] This situation was partly addressed by the introduction of commercial PCR testing for FIV. However, recent data support that point-of-care FIV serology tests from some manufacturers are able to reliably predict FIV infection regardless of vaccination history (see Diagnosis).[82] The availability of tests or testing combinations for FIV infection that are unaffected by the serological response to vaccination is likely to reduce opposition to FIV vaccination.[82,119,120]

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CHAPTER 223

Feline Leukemia Virus Infection

Katrin Hartmann, Julie K. Levy

Client Information Sheet: Feline Leukemia Virus Infection

Background

Feline leukemia virus (FeLV) is a retrovirus present throughout the world's domestic cat population. Infection is associated with a variety of illnesses, including neoplasia, bone marrow suppression, and immunodeficiency. The RNA of FeLV is reverse-transcribed into DNA in infected cells and the DNA copies (provirus) are inserted randomly into the host genome. Cell divisions then result in daughter cells containing this provirus. The viral genome encodes for the major proteins *gag* (group-specific antigens), *pol* (reverse transcriptase), and *env* (envelope). One of the *gag* proteins, p27, is abundant in the plasma of infected cats and is the basis for most currently used diagnostic tests. The envelope protein gp70 defines the virus subgroup and is important for inducing immunity.

The prevalence of progressive FeLV infection is similar world-wide: about 1% of healthy cats and up to 15% of high-risk and sick cats are infected.[1,2] Risk factors for infection include illness, male gender, adulthood, outdoor access, and large-scale cat hoarding. Indoor lifestyle and neutering are associated with low infection rates.[1,3-5] Certain diseases are associated with a high prevalence of progressive FeLV infection, such as lymphoma (12.7%),[43] cutaneous abscesses and bite wounds (8.8%), and oral inflammation (7.3%).[6,7] The prevalence has been decreasing these last decades due to common use of FeLV vaccines and widespread test and removal/separation programs.[1,3,8-11]

Pathogenesis

Outcomes of Infection

When FeLV was first discovered, it was believed that most cats cleared the virus after a period of transient viremia, but polymerase chain reaction (PCR) has revealed that most (or even all) cats remain infected for life.[12] There are 3 major outcomes of FeLV infection: progressive infection (antigen-positive, provirus-positive cats), regressive infection (antigen-negative, provirus-positive cats), and abortive infection (antigen-negative, provirus-negative, but antibody-positive cats).[7,13,14] These 3 outcomes can be distinguished through testing for antigen, proviral DNA, and antibodies (Table 223-1). Infection outcome depends on the cat's immune function and the amount of infective virus to which the cat was exposed. In addition to these 3 outcomes, focal infections have been described as rare events in which FeLV infection is restricted to certain tissues, i.e., spleen, lymph nodes, small intestine, or mammary glands. These focal infections are unlikely to play an important role in naturally infected cats.[15,16]

TABLE 223-1

Feline Leukemia Virus Infections Status Possibilities

	SOLUBLE FeLV P27 ANTIGEN IN BLOOD	PROVIRAL DNA IN BLOOD	ANTIBODIES IN BLOOD	REPLICATING VIRUS IN BLOOD	VIRAL RNA IN BLOOD	VIRAL SHEDDING	FeLV-ASSOC DISEA
	ELISA or other						

Test	immunochromatography test	PCR	available	Viral culture	RT-PCR		
Progressive infection	Positive	Positive	Low or negative	Positive	Positive	Yes	Commor
Regressive infection	Negative	Positive	High	Negative	Negative	No	Uncomm reacti possi
Abortive infection	Negative	Negative	High	Negative	Negative	No	None
Not FeLV-infected	Negative	Negative	Negative	Negative	Negative	No	None

After mucosal or cutaneous inoculation of FeLV, the virus replicates in local lymphoid tissues before infected cells carry the virus to target tissues, such as thymus, spleen, and lymph nodes. The virus then populates salivary glands and mucosal glandular epithelium, the sites that eventually secrete most FeLV responsible for horizontal transmission. At the same time (about 3 weeks after infection), bone marrow cells also become involved, producing infected neutrophils and platelets that circulate in the blood.

FeLV genetic material is usually detectable by PCR within 1 week of infection. In most cats, antigenemia (presence of viral proteins in the blood) correlates with viremia (presence of infectious virus that can be cultured from the blood), although some cats have discordant findings.[17] Infected cats can either remain viremic and antigenemic (progressive infection) or revert to an aviremic state (regressive infection) in which neither antigen nor culturable virus is detected but in which FeLV proviral DNA can still be identified.[13,18] Some cats become negative in antigen and proviral DNA but remain antibody-positive (abortive infection). In the course of infection, regressive and progressive infections can be distinguished by repeated testing for FeLV antigen in peripheral blood. Progressive cats remain antigen-positive, while regressive cats revert to an antigen-negative status.[18] They also can be distinguished by their provirus load.[12] During early infection, all cats have similar proviral loads. After a few weeks, provirus load drops in regressively infected cats while it stays high in progressively infected cats.[13,19]

Progressive Infection

In progressive infection, insufficient FeLV-specific immunity results in extensive virus replication that occurs first in the lymphoid tissues and then in the bone marrow. Spread to mucosal and glandular tissues and excretion of infectious virus occur simultaneously with bone marrow infection. The number of cats developing progressive FeLV infection varies by "infection pressure," which ranges from about 3% (after single contact with a FeLV-shedding cat) to about 30% (when living together for several weeks with a shedding cat).[4] Progressively infected cats have a decreased life expectancy. In a long-term follow-up study on experimentally FeLV-infected cats, progressively infected cats lived an average of 3.1 years (range from 0.6 to 6.5 years).[12] Progressively infected cats are persistently antigenemic, continuously shed the virus, and frequently succumb to FeLV-associated diseases within a few years.

Regressive Infection

In regressive infection, an effective immune response limits virus replication prior to or at the time of bone marrow infection. In recent studies, 2% to 10% of FeLV-antigen-negative cats were positive for FeLV provirus by PCR, and thus, regressively infected.[13,20,21] In these cats, FeLV antigen is sometimes detectable in peripheral blood 2 to 3 weeks after virus exposure but then disappears 2 to 8 weeks later or, in rare cases, after several months. Some regressively infected cats fail to ever develop detectable antigenemia. Cats with regressive infection have persistent integration of FeLV DNA in their genome.[22] Complete clearance of FeLV viral RNA or provirus was never detected in cats with regressive infection, even up to 12 years after exposure.[12] However, regressively infected cats only rarely develop FeLV-associated disease, such as lymphoma or bone marrow disorders.[20,23-27] Even though viral shedding does not occur, it is possible for cats with regressive infection to transmit FeLV via blood and tissue donation since the proviral DNA can be infectious.[28,29] It is also possible that the regressive state can convert to a progressive state (reactivation). In a long-term follow-up study on experimentally infected cats, 5/10 regressively infected cats had infection

long-term follow-up study on experimentally infected cats, 5/10 regressively infected cats had infection reactivated and became antigen-positive at different time points over a period of up to 8.5 years.[12] This is more likely to occur soon after exposure to FeLV, but has been described in cats that were antigen-negative for many years.[30]

Abortive Infection

In abortive infection, cats are negative for culturable virus, antigen, viral RNA, and proviral DNA, but remain antibody-positive.[18,31] The incidence of abortive infection is unclear under natural circumstances, but it is more common than once estimated.[21] These cats are assumed to have lifelong protection against new infection and probably do not need vaccination.

Transmission

Under normal circumstances, only progressively FeLV-infected cats transmit the virus to others. Infectious virus is found in highest concentrations in saliva, but also in milk, nasal secretions, feces, and urine.[16,32] FeLV is mostly transmitted horizontally via the oronasal route and bite wounds. Intimate contact between cats is optimal for transmission, such as mutual grooming, and sharing of dishes and litterpans. Transmission can occur during mating, during intrauterine fetal development, or via milk from infected queens to kittens. A recent study found that indirect transmission through FeLV-containing feces is also possible, but those infected cats only develop abortive infection.[33,34] Blood transfusions are also a mode of transmission from both progressively and regressively infected cats.[29]

Susceptibility to FeLV is much higher for kittens than for adult cats. All newborn kittens and most cats up to 2 months of age experimentally infected with FeLV developed progressive FeLV infection, whereas only 15% of cats inoculated when they were 4 months or older became progressively infected.[35] Some studies, however, have demonstrated efficient natural and experimental infection of adult cats as well.[36] Thus, although the risk is lower than in kittens, adult cats can sometimes become progressively infected.

Clinical Signs

Clinical Signs Described in the Field

Although progressively FeLV-infected cats can remain clinically healthy for years, several disease conditions are associated with FeLV infection, including bone marrow disorders (mainly anemia), neoplasia (mainly lymphoma), and immunosuppression leading to susceptibility to secondary infections.[4,8,37,38] FeLV-infected cats have a reduced life expectancy.[11] A comparison between 823 progressively FeLV-infected cats and 7476 age- and sex-matched controls revealed that the median survival of FeLV-infected cats was 2.4 years from the time of diagnosis compared to 6.3 years for controls.[39] Progressive FeLV infection increases the risk for a wide variety of conditions, but it is not always possible to determine whether concurrent diseases are a consequence of FeLV infection or are independent. In 3712 FeLV-infected cats seen for veterinary care, 29% were free of clinical signs.[3] Weight loss was most common in symptomatic cats (63%), followed by fever (42%), dehydration (35%), rhinitis (18%), diarrhea (17%), conjunctivitis (17%), oral inflammation (15%), lymphadenopathy (13%), and abscesses (12%).[3] In another study of 8756 FeLV-infected cats seen at veterinary medical teaching hospitals, anemia (18%) was the most common concern, followed by upper respiratory infection (11%), lymphoma (10%), myeloproliferative diseases (6%), stomatitis (5%), leukopenia (3%), hemoplasmosis (3%), lymphadenopathy (3%), and uveitis (2%).[8]

Bone Marrow Disorders

Bone marrow suppression, especially anemia, is the most common clinical syndrome associated with FeLV infection, resulting from infection of both hematopoietic stem cells and bone marrow stromal cells.[40] Progressive infection with active viral replication is usually required for bone marrow suppression. Regressive infection is only rarely associated with myelosuppression.[27,41] Thus, in a FeLV antigen-negative cat with bone marrow suppression, testing bone marrow for FeLV by PCR is only sometimes helpful.[27] The most common form of FeLV-induced anemia is pure red cell aplasia, a severe nonregenerative anemia with

finding of a lack of reticulocytes but a high mean corpuscular volume [MCV]). Regenerative anemia in FeLV-infected cats, indicated by increased reticulocytes and, in some cases, nucleated red blood cells (RBCs), is less common than nonregenerative anemia and is often associated with coinfection with *Mycoplasma haemofelis* or other hemotropic *Mycoplasma* spp. (see ch. 199 and 219). Some cats with immune-mediated hemolytic anemia are progressively FeLV-infected, and in some, hemolysis precedes the emergence of myeloproliferative disease or lymphoma.

FeLV is also an important cause of thrombocytopenia and granulocytopenia in cats (see ch. 201 and 202). FeLV and myeloproliferative diseases accounted for 44% of cats with thrombocytopenia in one report.[42] Cyclic and persistent neutropenia can occur due to a secondary immune-mediated condition, since some cats respond to immunosuppressive prednisone therapy. Cytopenias can wax and wane in FeLV-infected cats and some are associated with myelodysplasia that eventually evolve into a terminal myelodysplastic syndrome (see ch. 202) or leukemia (see ch. 344). In addition to FeLV's direct bone marrow suppression, nonregenerative anemia, neutropenia, and thrombocytopenia can be a consequence of effects secondary to FeLV, including bone marrow infiltration with neoplastic cells (e.g., lymphoma), infectious agents, myelofibrosis, and osteosclerosis.

Neoplasia

The most common tumors associated with FeLV infection are those of the lymphoid and hematopoietic systems (see ch. 344). Progressive FeLV infection results in a 60-fold increased risk of lymphoma compared with non-infected cats. About 25% of cats with progressive FeLV infection develop lymphoma within 2 years of diagnosis. Multicentric and mediastinal lymphoma are most common, although spinal, renal, ocular and other forms of lymphoma have been diagnosed in FeLV-infected cats.

As the prevalence of FeLV has decreased since its discovery, so has the incidence of FeLV-associated lymphoma.[10,43] The most important mechanism by which FeLV causes malignancy is by inserting the FeLV genome into the cellular genome near a cellular oncogene (most commonly *myc*), activating and overexpressing that gene and causing uncontrolled proliferation of these cells (clone). FeLV can also incorporate the oncogene to form a recombinant virus (e.g., FeLV-B, FeSV) containing cellular oncogene sequences that are rearranged and activated. Upon entering a new cell, the recombinant viruses are oncogenic. In a study of 119 cats with lymphomas, transduction or insertion of the *myc* locus had occurred in 38 cats (32%).[44] Thus FeLV-induced neoplasms are caused, at least in part, by somatically acquired insertional mutagenesis in which the integrated provirus activates a proto-oncogene or disrupts a tumor suppressor gene. Twelve common integration sites for FeLV associated with lymphoma development have been identified in six loci: c-myc, flvi-1, flvi-2 (contains bmi-1), fit-1, pim-1, and flit-1.[45] Some studies also show that variations in the FeLV surface glycoprotein can determine the development of tumors.[46]

If FeLV is the cause of lymphoma, it is usually through progressive infection, but regressive FeLV infection can also be involved. Cats from FeLV cluster households have a 40-fold higher rate of development of FeLV-negative lymphoma than cats from the general population. FeLV proviral DNA was detected in lymphomas of FeLV antigen-negative cats, and lymphomas have also occurred in FeLV antigen-negative laboratory cats known to have been infected previously with FeLV.[47,48] Results of studies on the incidence of regressive FeLV infection in cats with lymphoma vary significantly. Recent studies found evidence of provirus in only 1/10[41] and in 0/50 FeLV antigen-negative lymphomas[26] suggesting that regressive infection is only rarely involved in tumor development.

Immunosuppression

Diseases associated with immunosuppression account for much of the morbidity and mortality in cats with progressive FeLV infection. Thymic atrophy and depletion of lymph node paracortical zones are common, particularly in cats infected as kittens. Neutropenia and lymphopenia can further exacerbate immunosuppression. Poor response to T cell mitogens, prolonged allograft rejection, reduced immunoglobulin production, depressed neutrophil function, complement depletion, cytokine dysregulation, and poor responses to vaccination are common in FeLV-infected cats.[38] Many FeLV-infected cats have concurrent bacterial, viral, protozoal, or fungal infections. Few studies prove these cats have higher rates of infection than non-infected cats or that they have a less favorable response to therapy. Thus, although FeLV is well known to suppress immune function, it should not be assumed that all concurrent infections are a result of FeLV infection.

of FeLV infection.

Miscellaneous Disorders

Transient generalized lymphadenopathy has been observed in young, progressively infected cats. Abortion due to endometritis or transplacental infection of fetuses has been observed. An FeLV "panleukopenia-like syndrome" mimics feline parvovirus infection with low white cell counts, crypt necrosis, and high mortality. Some cats were identified to be coinfected with parvovirus. Lymphocytic-plasmacytic stomatitis, although more common in cats infected with feline immunodeficiency virus (FIV; see ch. 222), is also common in FeLV-infected cats. Neurologic infection can cause neurologic disorders, such as urinary incontinence and pupillary spasm leading to D-shaped pupils and anisocoria. FeLV-associated myelopathy results in vocalization, hyperesthesia, and paresis progressing to paralysis. It has been suggested that FeLV is disrupting intracellular thiamine uptake by blocking a putative thiamine receptor (THTR1), complicating these conditions further.[49]

Diagnosis

Timepoints of Testing for FeLV

Diagnosis of FeLV infections is important in all cats as identification and segregation of infected cats is considered to be the most effective method for preventing transmission. The American Association of Feline Practitioners recommends testing for retrovirus infection when cats are newly acquired, sick, about to be vaccinated against FeLV, or believed to have been exposed to a potentially infected cat.[7] Diagnosis of progressive and regressive infection requires testing for both FeLV antigen and FeLV provirus (Figure 223-1). Detection of the circulating soluble FeLV p27 antigen is commonly done through in-clinic test kits that use serum, plasma, or whole blood. Some results are positive on whole blood but negative on serum or plasma. Thus, one should repeat testing on serum when positive results are seen on whole blood. Tests usually become positive within 30 days of exposure but might take far longer.[17] If results of soluble FeLV antigen testing are negative but recent exposure cannot be ruled out, testing should be repeated a minimum of 30 days after the last potential exposure. Kittens can be tested at any time because passively acquired maternal antibodies do not interfere with testing for viral antigen. Vaccination against FeLV does not interfere with testing.

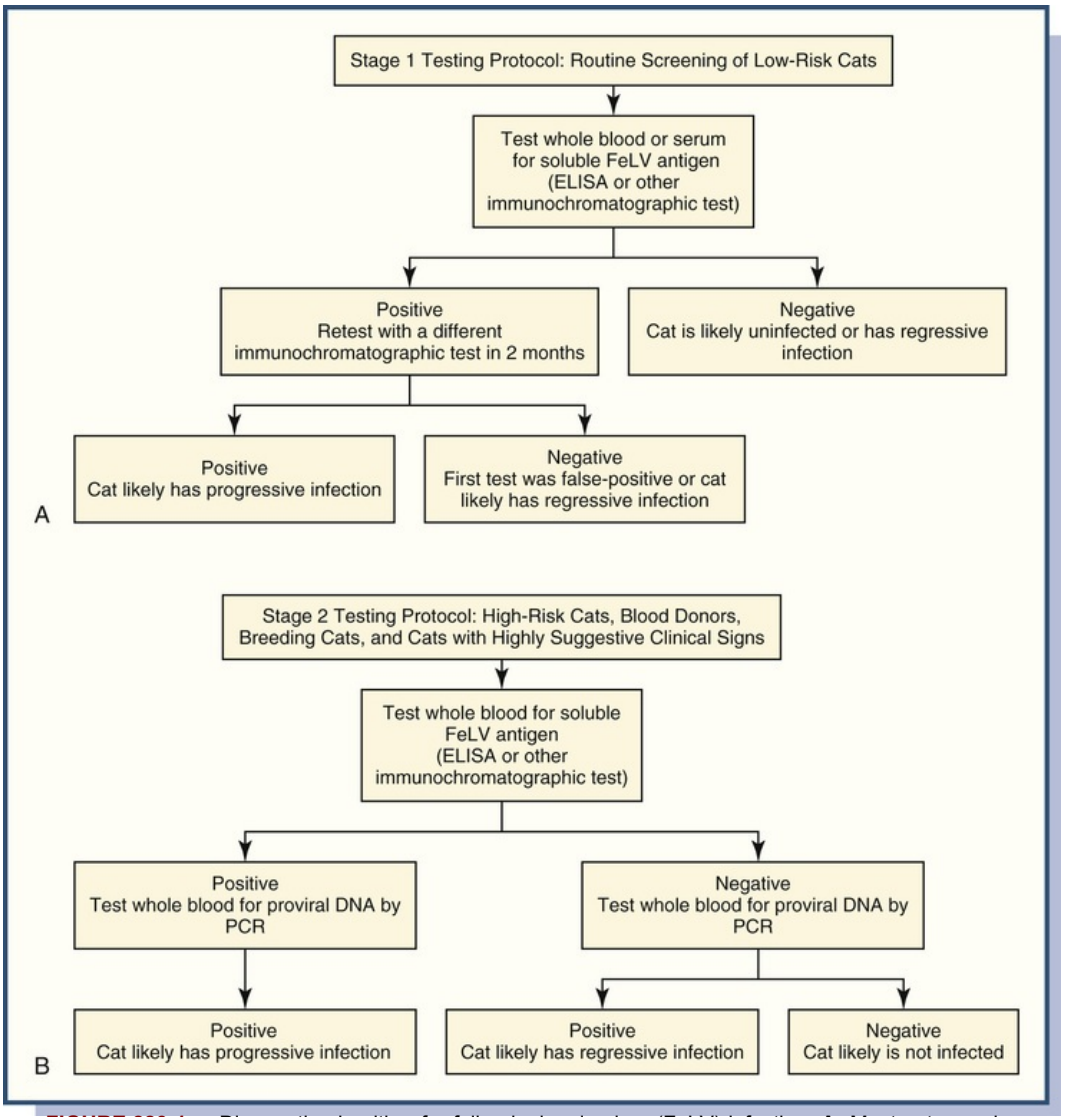

FIGURE 223-1 Diagnostic algorithm for feline leukemia virus (FeLV) infection. **A,** Most cats can be accurately diagnosed with the Stage 1 screening protocol. **B,** The Stage 2 protocol is indicated if Stage 1 test results are unexpected or if there is a need for additional certainty regarding FeLV infection status, such as for blood donors and breeding cats.

In-House Testing for FeLV Antigen

In-house tests for soluble FeLV antigen (such as enzyme-linked immunosorbent assay [ELISA] or similar immunochromatographic tests) are generally highly reliable for detecting progressive FeLV infection. Industrial tests detecting soluble antigen are not superior.[50-52] However, positive results should be confirmed, especially in low-risk and asymptomatic cats in which the predictive value of a positive test is low.[7,53] Due to high test sensitivity and low prevalence of infection (high negative predictive value), a negative test result is highly reliable (see Figure 223-1). Multiple options exist for confirmation of a positive in-house test result, such as IFA or PCR. Ideally, testing for soluble antigen should first be repeated using a test from a different manufacturer.[50,54]

Immunofluorescence Assays (IFA) for FeLV Antigen

IFA detects intracellular FeLV p27 antigen within infected blood cells following bone marrow infection. In blood smears, neutrophils and platelets are most likely to be infected. Thus, this test usually becomes positive several weeks after tests that detect soluble antigen (such as ELISA). False negatives can occur in cats with neutropenia, thrombocytopenia, or lack of bone marrow infection. The IFA is also negative in cats with

regressive infection. Discordant test results in soluble antigen in-house tests and IFA can make determination of the true FeLV status difficult. The most common scenario occurs when the soluble antigen test is positive and the IFA test is negative. This can be due to an early stage of infection (<3 weeks), the variability of host responses, technical problems with testing, or the lower sensitivity of the IFA. Cats with discordant test results should be considered potential sources of infection. Their status should be clarified through repeated testing.

Polymerase Chain Reaction (PCR) for FeLV Provirus

PCR is used to detect FeLV provirus (the viral DNA integrated into the cats' genome), while RT-PCR (in which a reverse transcription step is required first) detects RNA and thus, replicating virus. RT-PCR to detect RNA is not used for routine diagnostics and does not provide any further information as it is always positive when soluble FeLV antigen tests are positive. Provirus PCR is highly sensitive and necessary to detect regressive FeLV infection.

Tests for FeLV Antibodies

FeLV antibody tests, such as antibodies against FeLV transmembrane protein p15E, would be necessary to confirm abortive infection but are not yet widely available.[55]

Prevention

Control of FeLV is facilitated by its short survival (only minutes) outside the host. Transmission among cats usually requires direct contact and can be prevented at home, in veterinary clinics, and in animal shelters by simple segregation and effective disinfection. A nonadjuvanted recombinant FeLV vaccine and several injectable inactivated adjuvanted vaccines are commercially available. Studies of vaccine efficacy vary in methodology, making comparisons difficult.[56,57] Nonadjuvanted vaccines might be less likely to cause feline injection-site sarcoma formation.[58] FeLV vaccine-induced immunity has been shown to persist for at least 1 to 3 years.[59-61] Protection is not absolute and vaccination cannot be used as a substitute for testing to identify and isolate infected cats. While FeLV vaccination significantly reduces risk of progressive infection, it does not induce sterilizing immunity and does not prevent development of regressive infection. Cats can become positive for circulating proviral DNA subsequent to FeLV exposure.[13,18,62,63] Nonetheless, efficacious FeLV vaccines are valuable. Protection against progressive infection can prevent FeLV-associated diseases.[62,64] FeLV vaccines are considered noncore and are only recommended for cats at risk of exposure (e.g., cats permitted outdoors, cats residing with FeLV-infected cats, or cats living in multiple-cat environments) in countries where FeLV remains common.[65] Cats should be tested for infection before initial FeLV vaccination. Administration of FeLV vaccines to infected cats has no value and FeLV vaccines are not without risk (such as development of injection-site sarcoma).[7]

Management and Treatment

The FeLV status of all cats should be known. FeLV-infected cats should be confined indoors to contain the spread of the viruses and to protect affected cats from other infectious agents carried by other animals.[7] Specific management measures for multi-cat households with FeLV infection and for individual FeLV-infected cats should be considered (Box 223-1).[7,66,67] Vaccination programs to prevent common infectious diseases should be maintained. Cats infected with FeLV might not adequately respond to vaccination. It is important to protect those cats from exposure to sick cats or contaminated environments.[68] Although it is recommended that FeLV-infected cats be given inactivated and not modified-live virus (MLV) vaccines (when available), little evidence supports increased risk of adverse effects through MLV vaccines.[7]

Box 223-1

Management of Multi-Cat Households with FeLV-Infected Cats and of Individual Cats with Progressive FeLV Infection[7,64]

Management of Multi-Cat Households with FeLV-Infected Cats

- FeLV is mainly transmitted through social contact, but also through biting and fighting.
- If a progressively FeLV-infected cat lives in a household with otherwise FeLV antigen-negative cats, many of the other cats might already have been exposed and developed abortive, regressive, or progressive infections. Cats with regressive and abortive infections are likely immune to new infection.
- The risk of new infections arising in cats with pre-existing long-term exposure to FeLV-infected cats is low. If they eventually become antigen-positive, this is more likely caused by reactivation of a regressive FeLV infection than by transmission from the other cats in the household. However, transmission cannot be totally excluded, and thus the only 100% safe prevention is to separate infected and uninfected cats.
- If owners refuse to separate housemates, the uninfected cats should receive FeLV vaccination to enhance their natural level of immunity. However, owners should be informed that vaccination does not provide complete protection in these high exposure environments.

Management of Individual FeLV-Infected Cats

- Progressively FeLV-infected cats should be kept indoors to avoid spread to other cats and exposure of the cat to other infectious agents carried by other animals.
- "Routine vaccination programs" should be maintained in cats with progressive FeLV infection (see ch. 208). They might not be able to mount an adequate immune response to vaccines and protection might not be comparable to that in a healthy cat. Therefore, testing for the immune response (e.g., antibody measurement after feline panleukopenia virus vaccine) and protecting against exposure should be considered.
- Progressively FeLV-infected cats should have health care visits at the veterinarian at least semi-annually in order to promptly detect changes in the health status. A complete blood count should be performed every 6 months, and a biochemistry profile and urinalysis once a year.
- Intact male and female cats should be neutered to reduce stress associated with estrus and mating behavior and the desire to roam outside the house and interact aggressively.
- Surgery is generally well tolerated, but perioperative antibiotic administration should be used.
- Cats with progressive FeLV infection can be housed in the same ward as other hospitalized patients, but in individual cages. They should not be placed in a "contagious ward" with cats suffering from other infections.
- If progressively FeLV-infected cats are sick, prompt identification of the secondary illness is essential to allow early therapeutic intervention.
- Most cats with progressive FeLV infection respond as well as uninfected cats do to appropriate medications, although a longer and more aggressive course of therapy (e.g., antibiotics) might be necessary.
- Corticosteroids and other immune-suppressive as well as bone marrow-suppressive drugs should be avoided in progressively and regressively infected cats, if possible.

Prompt and accurate identification of FeLV-associated as well as secondary diseases is important, to allow early therapeutic intervention and a more successful outcome (Box 223-2). Many cats infected with retroviruses respond as well as their uninfected counterparts to appropriate symptomatic treatment and therapy of secondary infection. Antiviral drugs and drugs aimed at modulating the immune system are commonly used in FeLV-infected cats (E-Table 223-2). Unfortunately, few large controlled studies have been conducted in naturally infected cats and most of them have shown no effect of the used antiviral drugs or immunomodulators.[69-73]

Box 223-2

Suggested Treatment Recommendations for Cats with Progressive FeLV Infection[14,74]

If No Clinical Signs Are Present

- No treatment is indicated
- Cats should be kept strictly indoors

If Clinical Signs Are Present

- Always look for underlying diseases first (FeLV itself might not be responsible for the clinical signs, e.g., secondary infections could be present)
- Treat underlying diseases

Treatment of FeLV-Infected Cats with Lymphoma

- Use chemotherapeutic drug protocols (e.g., protocol that includes cyclophosphamide, vincristine, and prednisone; see ch. 344)
- Inform owners about the more guarded prognosis

Treatment of FeLV-Infected Cats with Anemia

- Give blood transfusions if anemia is severe (see ch. 130)
- Look for underlying diseases causing the anemia
- Treat underlying diseases
- If hemolytic anemia is present, treat for occult hemotropic *Mycoplasma* spp. infection with doxycycline (see ch. 219)
- If underlying diseases have been ruled out, consider glucocorticoids (because anemia in FeLV-infected cats can have an immune-mediated origin; see ch. 198)

Treatment of FeLV-Infected Cats with Neurologic Signs

- Look for underlying diseases causing the neurologic signs (e.g., lymphoma)
- Treat underlying diseases
- If no underlying disease is present (and the neurologic signs are assumed to be indeed caused by FeLV), treat with zidovudine (5 mg/kg PO q 12 h)

Treatment of FeLV-Infected Cat with Recurring Infections

- Treat recurring infections aggressively (e.g., long-term antibiotics)
- Consider treatment with feline interferon-omega (10^6 IU/kg SC q 24 h for 5 consecutive days)

E-TABLE 223-2

Antiviral Drugs and Immunomodulators for Progressively Feline Leukemia Virus-Infected Cats (Including Evidence-Based [EBM] Grades for Judgment of the Available Efficacy Data and Personal Opinion of the Authors)[64,66,74]

DRUG	EFFICACY *IN VITRO*	CONTROLLED STUDY *IN VIVO*	EFFICACY *IN VIVO*	PERSONAL OPINION	EBM LEVEL (1-4)
Nucleoside Analogue Reverse Transcriptase Inhibitors					
Zidovudine (AZT)	Yes[75]	Yes	No[72,76]	Not very effective	1
Stavudine (d4T)	n.d.	No	n.d.	Possibly effective, but no data in cats available	4
Didanosine (ddI)	Yes[75]	No	n.d.	Possibly effective, but no data in cats available	4
Zalcitabine (ddC)	Yes[75,77,78]	Yes	No[77,78]	Not very effective, but toxic	2
Lamivudine (3TC)	No	No	n.d.	Possibly effective, but also toxic	4
Nucleotide Analogue Reverse Transcriptase Inhibitors					
Adefovir (PMEA)	Yes[79]	Yes	No[70]	Poorly effective, but relatively toxic	2

Tenofovir (PMPA)	Yes[80]	No	n.d.	Possibly effective, but likely also relatively toxic	2
Non-Nucleoside Reverse Transcriptase Inhibitors					
Suramin	No	No	n.d.	Possibly effective, but too toxic	2
Nucleotide Synthesis Inhibitors					
Foscarnet (PFA)	Yes[81]	No	n.d.	Effective *in vitro*, but too toxic	4
Ribavirin	Yes[82]	No	n.d.	Possibly effective, but too toxic in cats	4
Receptor Homologues/Antagonists					
Plerixafor	n.d.	No	n.d.	Very likely ineffective	4
Integrase Inhibitors					
Raltegravir	Yes[83]	No	n.d.	Possibly effective	4
Interferons					
Human interferon-alpha (IFN-alpha)					
SC high-dose	Yes[84]	Yes	No[76]	Ineffective	1
PO low dose	Yes[84]	Yes	No[71]	Ineffective	1
Feline interferon-omega					
(IFN-omega)	Yes[85]	Yes	Yes[86]	Some effect (most likely more on secondary infections)	1
PO low dose	Yes[85]	No	n.d.	Potentially some effect (most likely more on secondary infections)	1
Other Cytokine Inducers					
Staphylococcus protein A (SPA)	n.d.	Yes	Yes[71]	Weakly effective	1
Propionibacterium acnes	n.d.	No	n.d.	Likely ineffective	3
Bacille Calmette-Guérin (BCG)	n.d.	Yes	No[87]	Ineffective	2
Serratia marcescens (S. marcescens)	n.d.	Yes	No[88]	Ineffective	2
PIND-AVI/PIND-ORF	n.d.	Yes	No[69,73]	Ineffective	1
Acemannan	n.d.	No	n.d.	Possibly weakly effective	3
Other Drugs with Immunomodulatory Activity					
Levamisole	n.d.	No	n.d.	Likely ineffective	3
Diethylcarbamazine citrate (DEC)	n.d.	Yes	No[89]	Ineffective	2
Lactoferrin	n.d.	No	n.d.	Possibly effective in cat with stomatitis	4

n.d., Not determined; *PIND-AVI*, Parapoxvirus avis; *PIND-ORF*, Parapoxvirus ovis.

EBM, Evidence-based medicine: EBM level 1 = confirmed by at least one placebo-controlled double-blind field study; EBM level 2 = shown in a controlled experimental study; EBM level 3 = supported by case series; EBM level 4 = only based on expert opinion.

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CHAPTER 224

Coronavirus Infections (Canine and Feline), Including Feline Infectious Peritonitis

Katrin Hartmann

Client Information Sheet: Feline Coronavirus Infections

Coronaviruses (family Coronaviridae, order Nidovirales) are large, single-stranded RNA viruses that are responsible for enteric and/or respiratory diseases in mammals—including humans—and birds.[1,2] Coronaviruses are classified into 3 different antigenic groups. Group 1 contains, among others, the canine enteric coronavirus (CECoV) and the feline coronavirus (FCoV), while the canine respiratory coronavirus (CRCoV) belongs to group 2.[1,3] Coronaviruses mutate easily, and mutation can result in more virulent strains; this has been shown for CECoV and FCoV, resulting in fatal pantropic canine coronavirus (pantropic CCoV) infection or feline infectious peritonitis (FIP), respectively.

Canine Coronavirus Infection

In dogs, 2 different coronaviruses, CECoV and CRCoV, have been recognized.[4] In addition, a highly virulent CECoV strain (pantropic CCoV) was responsible for an outbreak of fatal systemic disease in puppies.[5]

Canine Enteric Coronavirus, Including Pantropic Coronavirus

CECoV first was isolated in 1971 in dogs with acute enteritis in a canine military unit in Germany,[6] and experimental administration of the isolated strain to young dogs reproduced the gastrointestinal (GI) signs.[7]

Epidemiology

Since then, several CECoV outbreaks have been reported worldwide, showing that CECoV can be an enteropathogen in dogs. However, the true importance of CECoV as a pathogen is unknown, since many clinically healthy dogs shed CECoV. Most likely, changes in virulence and tissue tropisms leading to disease outbreaks occur through genetic variations in structural and/or non-structural proteins.[8-14] Antibody and RNA prevalence studies have shown that CECoV is widespread in the dog population, primarily in kennels and shelters.[15-21]

Clinical Signs

It is unclear how often and why clinical signs appear, and differentiation of CECoV from other infectious causes of enteritis is difficult, since many healthy dogs shed CECoV. Therefore, concurrent presence of CECoV infection and diarrhea is not proof of causation.[22] Infection usually is restricted to the alimentary tract, with sudden onset of signs typical of GI involvement, including loss of appetite, vomiting, diarrhea, dehydration, and rarely death. Fatal disease can occur as a consequence of mixed infections, e.g., with canine parvovirus[23] or canine distemper virus.[24] CECoV can mutate to more virulent strains; severe outbreaks have been reported in the USA,[25] England,[26] Sweden,[27] and Australia.[28]

Although CECoV usually is restricted to the enteric system, mutations can result in systemic spread, leading to high mortality in puppies.[5,29] In 2005, a highly virulent variant (CB/05) was detected in Italy[5]; it evolved through genetic mutation (truncated form of the ORF3b product and point mutations in the spike protein) of CECoV, and was classified as "pantropic CCoV" because it had acquired the ability to spread to

other tissues.[13] In addition to GI signs, pantropic CCoV infection caused severe leukopenia, neurologic signs (ataxia, seizures), and death within 2 days. Experimental infection with strain CB/05 reproduced the severe disease.[30] At necropsy, lesions in lung, liver, and renal tissues also were found in affected dogs.[29]

Treatment and Prevention

Treatment is supportive and needs to resolve dehydration (see ch. 129), acidosis (see ch. 128), and hypovolemic shock (see ch. 127 and 159). Inactivated and modified live virus (MLV) vaccines available in the USA are considered safe, but they provide incomplete protection[26,31,32] and probably no protection against pantropic CCoV (see ch. 208).[1] Necessity of vaccination has been questioned because CECoV usually causes no or only mild clinical signs.

Canine Respiratory Coronavirus

In 2003, a canine respiratory coronavirus (CRCoV) was first identified in the respiratory tract of dogs housed in a rehoming kennel in England with a history of endemic respiratory disease.[3] CRCoV is very closely related to the bovine coronavirus (BCoV) (sequence homology 97.3%),[3] and it has been suggested that originally, transmission of the virus occurred from cattle to dogs.[33]

Epidemiology

Since its first description, CRCoV has been detected in many countries. Antibodies against CRCoV were found in the USA, Canada, England, Ireland, Italy Greece, New Zealand, Japan, and Korea in 12-59% of investigated dogs.[34-41] CRCoV RNA was detected in the lower respiratory tract of 1-27% dogs with respiratory disease in Canada, England, Italy, Germany, Japan, and Korea.[3,37,38,42-45]

Clinical Signs

CRCoV can be responsible for mild respiratory signs and it is one of the etiological agents of canine infectious respiratory disease (CIRD), together with *Bordetella bronchiseptica,* canine adenoviruses type 1 and type 2, canine parainfluenzavirus, canine herpesvirus, reoviruses, canine pneumovirus, and influenza viruses (see ch. 227).[4,44,46] However, the true role of CRCoV as primary single pathogen is not completely clear. In one study, CRCoV RNA was detected only in the respiratory tract of dogs with respiratory signs, but not in healthy dogs,[44] confirming its pathogenicity. In addition, replication in the respiratory epithelium can damage the mucociliary system,[4] and this can lead to a more severe clinical course of infections caused by other respiratory pathogens.

Treatment and Prevention

Symptomatic treatment usually leads to complete cure (see ch. 276). Antiviral treatment is not recommended.[47] A vaccine is not available.

Feline Coronavirus Infection and Feline Infectious Peritonitis

Feline coronavirus (FCoV) is extremely common in the cat population worldwide, especially in multi-cat environments. Presence of FCoV-specific antibodies in up to 90% of cattery cats and in up to 50% of those in single-cat households demonstrates the high frequency of exposure. FCoV is transmitted by the fecal-oral route between felids, but is not infectious for other species (including humans). FCoV usually does not cause clinical signs, and only rarely is considered to be responsible for transient and mild diarrhea with or without vomiting,[48] due to replication of FCoV in enterocytes.[49] Kittens infected with FCoV develop diarrhea more commonly than do adults, and the diarrhea rarely is accompanied by stunted growth. Occasionally, the virus can be responsible for severe, acute or chronic vomiting and/or diarrhea with weight loss, which can be unresponsive to treatment and continue for months.[50]

Sporadically, these harmless viruses can be the cause of FIP in individual cats. It has been estimated that about 5% of FCoV-infected cats develop FIP in a multi-cat environment.[51,52] FIP is a fatal, immune-mediated disease and it is the most common infectious cause of death of cats.[53-56] It also is a frequent reason for referral, with approximately 1 of every 200 new feline cases presented to U.S. veterinary teaching hospitals having

FIP.[56] There is increasing evidence that FIP develops after spontaneous mutations of the genome of nonpathogenic FCoV within infected cats.[11,57] These mutations allow for successful virus replication in macrophages,[58] which is regarded as a key event in the pathogenesis of FIP.[9,59] Many different genes, including the S, 7a, 7b, and 3c genes, have been discussed as sites for the mutations that are crucial for the pathotypic switch and changes in tissue tropism.[9,11,60-70] In contrast to previous studies, in which none of the sequence changes appeared to be associated consistently with the virulent FIP-causing variant, a recent study found nucleotide differences in two regions in close proximity in the S (spike) gene (nucleotide 23531 and nucleotide 23537) that resulted in amino acid variations in the putative fusion peptide. These two mutations were correlated with the FIP phenotype in >95% of cases.[71] Considering the importance of the coronavirus S protein fusion peptide in cell entry,[72] these findings could explain the alteration in viral tropism. It also was shown that substitutions in a furin cleavage site within the S protein of FCoV can be detected in cats with FIP, which likely are leading to a modulation of proteolytic cleavage, thereby enhancing virus uptake in macrophages.[73] It even has been suggested that not only a single mutation in one gene but a combination of mutations (such as one mutation in the spike gene and one mutation in the 3c gene) might be necessary for the change in virulence.[60]

If a cat fails to eliminate the cells infected with the mutated virus, the presence of the virus within macrophages initiates the ultimately fatal immune-mediated reaction that defines FIP. In this aberrant modulation of the immune system, overproduction of proinflammatory cytokines plays an important role, such as through activation of the p38 MAPK pathway that regulates production of tumor necrosis factor-alpha (TNF-alpha) and interleukin-1-beta.[74] Granulomatous lesions in the target organs also are caused by overproduction of cytokines by infected macrophages, including neutrophil survival factors (TNF-alpha, GM-CSF, G-CSF),[75] that lead to systemic activation of neutrophils (such as increased expression if the alpha-chain of macrophage-1 antigen [Mac-1]) causing them to extravasate and form granulomas.[76] In addition, cats with FIP have a severe suppression of natural killer cells and regulatory T cells, leading to a decreased capacity of the immune system to battle the virus and suppress immunopathologic functions.[77]

Granulomatous lesions can occur in the central nervous system, eyes, and parenchymatous organs (including the intestine, commonly at the ileocecal junction, appearing as masses in the abdominal cavity).[78,79] Vasculitis leads to fluid accumulation in body cavities, including the pleural and peritoneal spaces and even the pericardium.[80] In addition, some unusual manifestations have been described, such as a mediastinal cyst-like mass in the thorax,[81] skin fragility syndrome,[82] and other skin lesions (e.g., skin papules and nodules, pododermatitis),[83,84] orchitis[85] or priapism (with FCoV antigen immunohistochemically being detected in penile tissue).[86]

Diagnosis

Once the clinical disease FIP develops, it almost always leads to death within a few days or weeks, and currently there is no treatment with proven efficacy.[87,88] Thus, a definitive diagnosis is essential but often challenging. A weighted score system for the diagnosis of FIP, taking several parameters into account, including background of the cat, history, presence of clinical signs, laboratory changes, and level of antibody titers, has been suggested.[89,90] Although useful to prioritize differential diagnoses and helpful to select further tests, the score only assesses the likelihood of FIP and thus does not help to definitively confirm the diagnosis. At present, necropsy or immunostaining of FCoV antigen (immunohistochemistry) in tissue samples obtained by laparotomy are considered the gold standard for the diagnosis of FIP.[91-94] Thus, the definitive diagnosis can only be achieved with invasive laparotomy and biopsies of multiple organs, or might not be possible at all. A suggested diagnostic algorithm for FIP is provided in Figure 224-1.

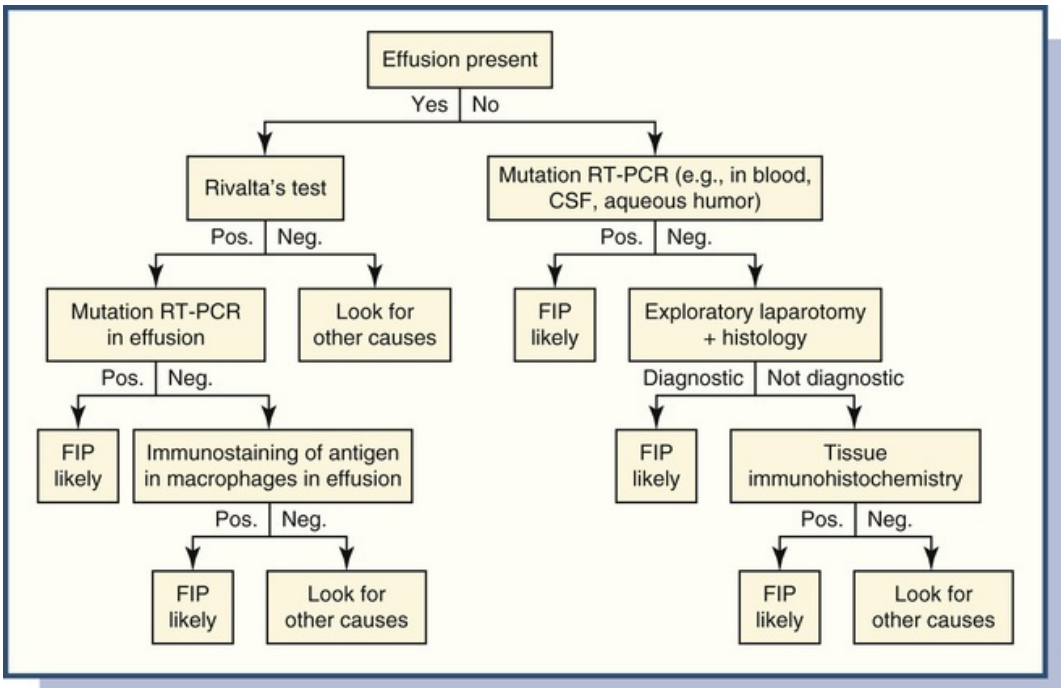

FIGURE 224-1 Algorithm for the diagnosis of feline infectious peritonitis (FIP) in a cat in which FIP is suspected. *PCR*, Polymerase chain reaction. *FIP*, Feline infectious peritonitis; *Neg.*, negative; *Pos.*, positive; *RT-PCR*, reverse transcriptase polymerase chain reaction.

Laboratory Values

Laboratory values often are altered in cats with FIP, but the changes are not pathognomonic. Lymphopenia often is present, but in combination with neutrophilia in sick cats, it commonly is part of a typical stress leukogram. A common finding in cats with FIP is an increase in total serum protein concentration caused by a rise in globulins, mainly gamma-globulins.[93,95-98] One mechanism leading to this massive antibody production is an overproduction of B cell differentiation/survival factors by virus-infected macrophages that promote B cell differentiation into plasma cells.[99] The hyperglobulinemia, together with the commonly-observed hypoalbuminemia, leads to a low albumin-to-globulin ratio. A low albumin-to-globulin ratio should raise the suspicion of FIP, but is never diagnostic by itself. Serum protein electrophoresis is not very helpful, because both polyclonal and monoclonal hypergammaglobulinemia can occur in cats with FIP, as they do in some tumors, such as multiple myeloma, and with other inflammatory conditions. Other laboratory parameters (liver enzymes, bilirubin, blood urea nitrogen, creatinine) can be elevated variably, depending on the degree and localization of organ damage. Acute phase proteins commonly are elevated, but this finding is not specific either.[100] Hyperbilirubinemia often is observed[93,101] and it can be caused by hepatic granulomatous inflammation. In addition, an increase in serum bilirubin concentration without evidence of hemolysis, primary liver disease, or extrahepatic cholestasis (hematocrit and alkaline phosphatase [ALP] and alanine aminotransferase [ALT] activities within the reference range and no sonographic bile duct changes) sometimes is present in cats with FIP and likely is caused by compromised bilirubin metabolism and excretion into the biliary system due to high levels of TNF-alpha that inhibit transmembrane transport (otherwise observed only in septic animals).[93,102]

Analysis of Effusion Fluid

Whenever effusion can be detected somewhere, the next diagnostic step always is to sample and analyze the fluid (see ch. 74 and 90), because tests on effusion have a much higher diagnostic value than tests performed on blood. In general, half of cats with body cavity effusion suffer from FIP.[103] Although effusions of clear yellow color and sticky consistency (Figure 224-2) often are considered "typical," the presence of this type of fluid alone is not diagnostic. Sometimes the fluid has a totally different appearance and, for example, cases of FIP with pure chylous effusion have been reported.[104] The effusion's protein content usually is high (>3.5 g/dL [>35 g/L]) and consistent with an exudate, whereas the cellular content is rather low (<5000 nucleated

cells/mcL) and resembles that of a modified transudate. Other diseases causing similar effusions include lymphoma, heart failure, cholangiohepatitis, and bacterial peritonitis or pleuritis. Cytologic evaluation of the effusion in cats with FIP usually shows a pyogranulomatous inflammation with a predominance of macrophages and neutrophils (Figure 224-3). Cytologic findings can appear similar in cats with bacterial serositis (although in these cases, cell counts usually are higher) or with lymphoma (although in these cases, malignant cells usually are present). A simple, inexpensive, and very robust method (fluid can be stored in the refrigerator for at least 3 weeks before performing the test) for evaluating the effusion,[105] the "Rivalta's test," can help to differentiate FIP from effusions of other origins (Box 224-1; Video 224-1).[93] Positivity (Figure 224-4) is caused by not only the high protein content, but also other components, such as high concentrations of fibrin and inflammatory mediators. The Rivalta's test had a sensitivity of 91.3% and a specificity of 65.5% in a recent study of 851 cats, with a high positive predictive value of almost 90% in cats <2 years old (due to the high prevalence of FIP in young cats).[106] Thus, a negative Rivalta's test makes FIP very unlikely; a positive Rivalta's test at least increases the likelihood of FIP, especially in a young cat. False-positive Rivalta's test results can occur in cats with bacterial serositis or lymphoma; those effusions, however, can usually be differentiated through cytologic evaluation and/or bacterial culture.

FIGURE 224-2 Yellow, clear, sticky effusion that is considered "typical" in a cat with feline infectious peritonitis obtained through ultrasound-guided abdominocentesis. (From Hartmann K: Feline infectious peritonitis. *Vet Clin North Am Small Anim Pract* 35:39-79, vi, 2005.)

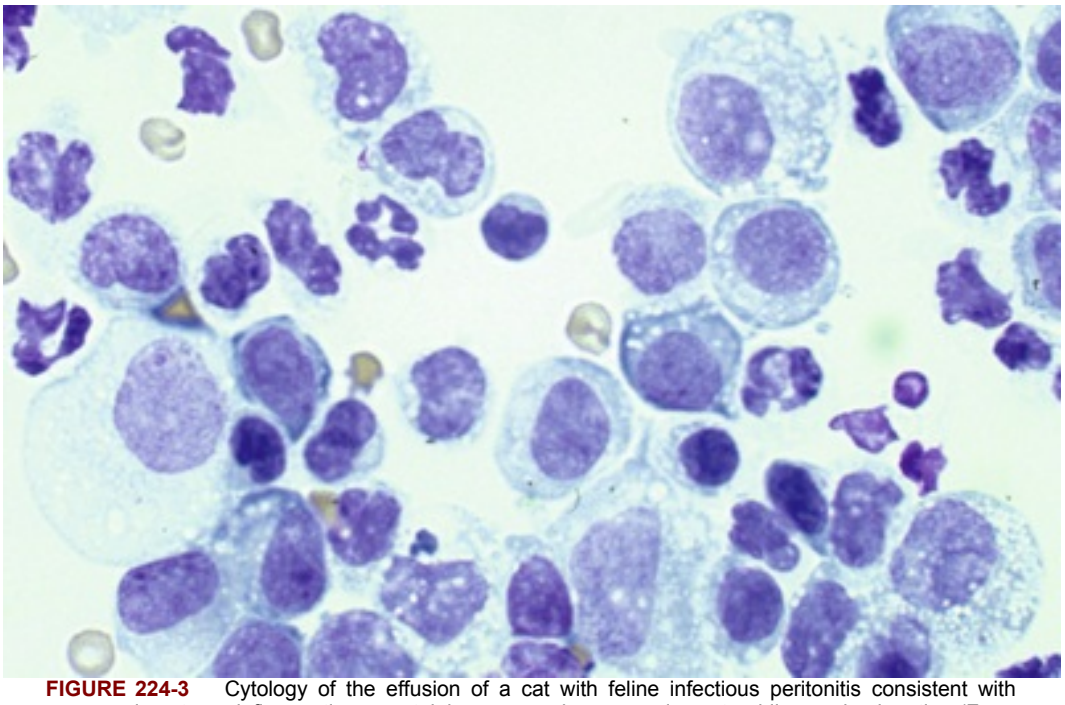

FIGURE 224-3 Cytology of the effusion of a cat with feline infectious peritonitis consistent with pyogranulomatous inflammation, containing macrophages and neutrophils predominantly. (From Hartmann K: Feline infectious peritonitis. *Vet Clin North Am Small Anim Pract* 35:39-79, vi, 2005.)

Box 224-1

Procedure and Interpretation of the Rivalta's Test

Rivalta's Test Standard Procedure

- A plastic test tube (volume 10 mL) is filled with 7 mL of distilled water
- 20 mcL (1 drop) of acetic acid (100%) is added
- The solution is thoroughly mixed
- 20 mcL (1 drop) of the effusion is layered on the surface of this solution
- The outcome of the drop is observed

Rivalta's Test Interpretation

- The Rivalta's test is defined as **positive**
  - If the drop stays attached to the surface
  - If the drop retains its shape and keeps a connection to the surface
  - If the drop slowly floats down to the bottom
  - If the drop does not stay in shape, but changes to an "upside-down jelly fish"
  - If the drop disperses in little cloudy pieces that can be observed falling down to the bottom of the tube
- The Rivalta's test is defined as **negative**
  - If the drop disappears and the solution remains clear
  - If clear or cloudy cords seen are falling down, which dissolve before reaching the bottom of the tube, but no drop or "upside-down jelly fish" is visible

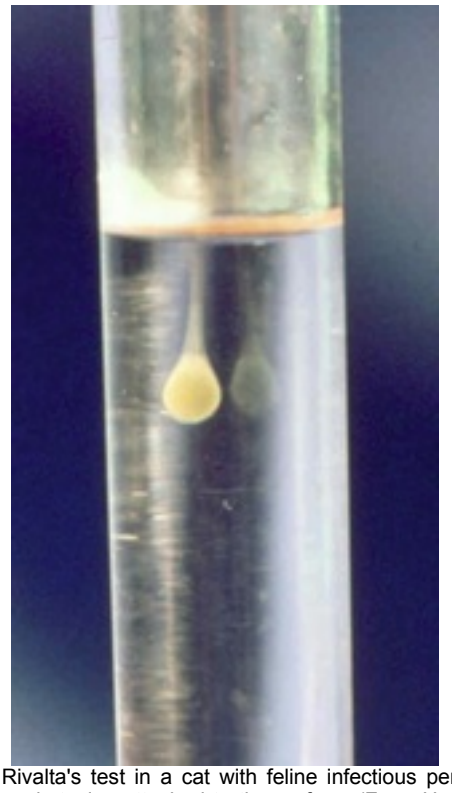

FIGURE 224-4 Positive Rivalta's test in a cat with feline infectious peritonitis, with a drop of the effusion retaining its shape and staying attached to the surface. (From Hartmann K: Feline infectious peritonitis. *Vet Clin North Am Small Anim Pract* 35:39-79, vi, 2005.)

Analysis of Cerebrospinal Fluid (CSF)

Analysis of cerebrospinal fluid (CSF) from cats with neurologic signs due to FIP can show elevated protein concentrations (50-350 mg/dL [500-3500 g/L] compared to a normal value of <25 mg/dL [<250 g/L]) and pleocytosis (100 to 10,000 nucleated cells/mcL) containing mainly neutrophils, lymphocytes, and macrophages (see ch. 115).[107,108] These are, however, relatively nonspecific findings. Some cats with neurologic signs caused by FIP have normal CSF results, and even if CSF changes indicate inflammation, they are not useful in differentiating FIP from other causes of inflammatory central nervous system disease.[108]

Antibody Titers

Antibody titers can be measured in blood, effusion, and CSF, but detection of antibodies in any of these fluids is not helpful in the diagnosis of FIP. Most cats with current or previous contact to FCoV, as well as vaccinated cats, have antibodies. Presence of antibodies in blood does not predict FIP and their absence does not exclude FIP, since in terminal FIP, titers often decrease,[109] and approximately 10% of cats with FIP have no antibodies because large amounts of virus in the cat's body bind to antibodies and render them undetectable, or antibodies are lost into the effusion when protein is extravasated due to vasculitis. The presence of antibodies in effusion is correlated with the presence of antibodies in blood,[110] and thus, antibody measurement in effusion also is not helpful.[111] Cats with neurologic signs due to FIP have had CSF antibody concentrations that were no different from those in cats with other neurologic diseases, indicating that measurement of antibodies in CSF also is not useful.[112] However, blood antibody testing still has a certain role in the management of FCoV in multi-cat households or catteries; for example, if all cats are known to be antibody-negative, then a FCoV-free colony can be maintained by admitting only new cats that are negative on antibody testing.[113]

Coronavirus-Specific Antibody-Antigen Complex Detection

Coronavirus-specific antibody-antigen complex detection can be performed in blood with a competitive ELISA. The rationale is that a diagnostic clue could be obtained if one looked for circulating complexes in

blood and effusions, but the usefulness of this test was shown to be limited.[93]

FCoV Antigen in Macrophages

FCoV antigen in macrophages can be detected using immunofluorescence staining or immunocytochemistry (in effusion macrophages) or immunohistochemistry (in tissue macrophages). Immunostaining cannot differentiate between the "harmless" FCoV and the mutated FIP-causing FCoV. However, only FIP-causing virus is considered able to replicate in the sufficiently large numbers in macrophages required to obtain positive staining (Figure 224-5), and replicating virus is associated with macrophages by immunohistochemistry.[119] In one study in which a large number of cats with confirmed FIP and controls with other (confirmed) diseases were investigated (n = 171), immunofluorescence staining of intracellular FCoV antigen in macrophages of the effusion had a positive predictive value of 100%, thus confirming the diagnosis of FIP. Unfortunately, the negative predictive value was not very high (57%), which mainly can be explained by low numbers of macrophages on effusion smears (even though cats have FIP), resulting in negative staining.[93] In another study, however, 2 cats with false-positive immunofluorescence staining were reported,[120] calling into question the credibility of the method as a confirmatory test. This was additionally shown in another study that used immunochemistry instead of immunofluorescence staining, with few false-positive control cats.[121] Recent studies have focused on the diagnostic utility of immunostaining of material other than effusion[121a] or aqueous humor,[121b] yielding similar results, such as false-positive results in cats with definitive other diseases. Immunohistochemistry is considered the gold standard in the diagnosis of FIP and has been proven to be 100% predictive if positive.[94,122] However, invasive methods (e.g., laparotomy or laparoscopy; see ch. 91) usually are necessary to obtain appropriate tissue samples. The diagnostic sensitivity between core biopsy (see ch. 89) and fine needle aspiration (FNA; see ch. 89 and 93) of liver and kidney tissue was compared in one study and the sensitivity of FNA was similar to that of core biopsy, with a higher sensitivity in the liver versus the kidney,[123] but the value of ultrasound-guided FNA to diagnose FIP as a routine method is limited.

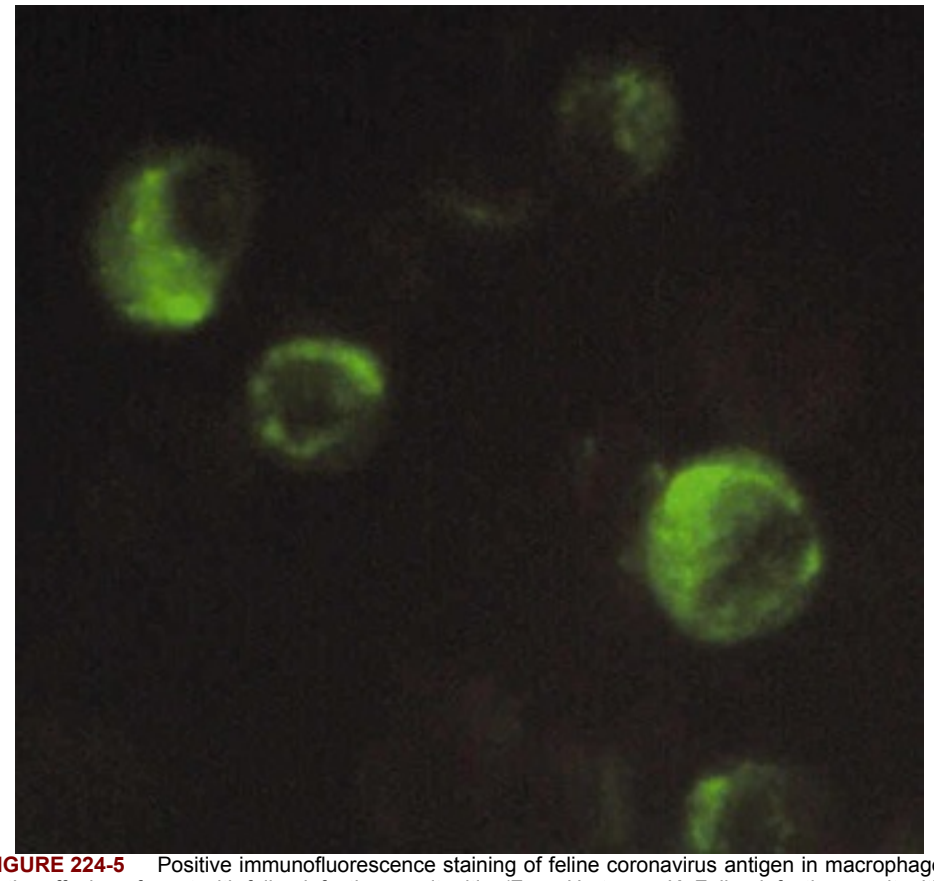

FIGURE 224-5 Positive immunofluorescence staining of feline coronavirus antigen in macrophages in the effusion of a cat with feline infectious peritonitis. (From Hartmann K: Feline infectious peritonitis.

Vet Clin North Am Small Anim Pract 35:39-79, vi, 2005.)

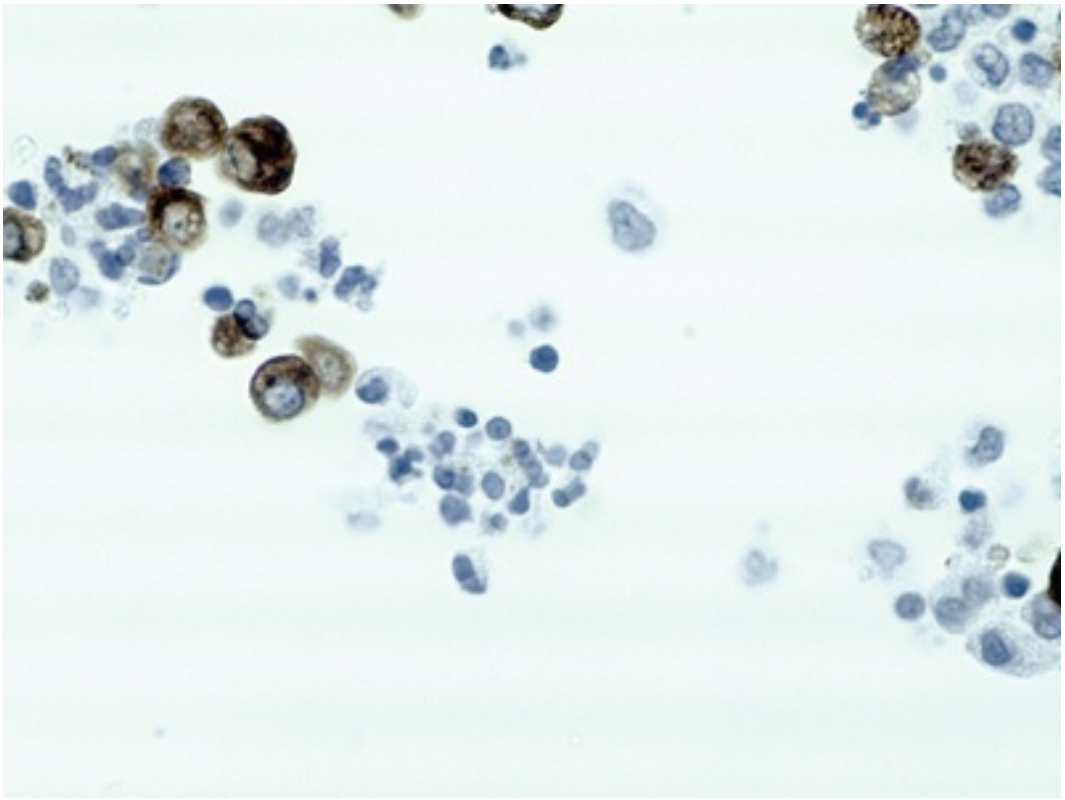

FIGURE 224-6 Positive immunocytochemical staining of feline coronavirus antigen in macrophages in the cerebrospinal fluid of a cat with feline infectious peritonitis. (From Hartmann K: Feline infectious peritonitis. *Vet Clin North Am Small Anim Pract* 35:39-79, vi, 2005.)

Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) Detecting FCoV or Detecting the Mutated Virus

Most RT-PCR (a reverse transcription of viral RNA to DNA has to be performed prior to amplification of DNA in order to detect RNA viruses) that are routinely used detect all FCoV because PCR primers do not discriminate between FIP-causing viruses and harmless enteric FCoV.[114] Several studies support the hypothesis that FCoV viremia occurs not only in cats with FIP but also in healthy carriers.[115,116] Thus, presence of FCoV viremia does not predict, nor does it predispose cats to, the development of FIP.[117] Therefore, the results of routine RT-PCR are not diagnostic for FIP. In addition, blood RT-PCR commonly is negative in cats with FIP due to the low viral load. However, while not useful in the diagnosis of FIP, RT-PCR used for detecting FCoV in fecal samples is sensitive and useful for documenting that a cat is shedding FCoV.[91] Identification of fecal shedding is an important step in management of cat populations when prevention of FCoV introduction or elimination of endemic infection is desired.

A RT-PCR that specifically detects nucleotide changes at positions 23531 and 23537 of the S gene,[71] and thus detects a virus with a crucial mutation in the spike gene that is considered the pathogenic pathotype,[72] is now commercially available. In one study, detection of one of the two mutations was 100% specific for FIP.[118] However, in a very recent study specificity was only 96.0% using this pathotype-specific PCR.[118a] In this study, a positive RT-PCR detecting one of the mutations also occurred in control cats with confirmed other diseases. It is unclear whether these were true false positives or whether early-stage FIP was detected in cats with separate diseases. Sensitivity of this test is high in effusion, but very low in blood, which is a problem because diagnosis of FIP in cats without effusion remains a challenge.[118a]

Treatment and Management

Virtually every cat with confirmed FIP dies from the disease. However, some cats can survive for several months and enjoy some quality of life with symptomatic treatment.

Prognosis

The prognosis for a cat with FIP is extremely poor. In a prospective study including 43 cats with FIP, the median survival time after definitive diagnosis was 8 days.[88] Some cats, however, live for several months; one cat has been documented that lived 200 days after a definitive diagnosis.[88] Some parameters can predict survival time: poor general condition, low platelet count, low lymphocyte count, high serum bilirubin concentration, and a large amount of effusion indicate a poor prognosis.[88] Seizures also have to be considered an unfavorable prognostic sign, since they occur significantly more frequently in animals with marked extension of the inflammatory lesions to the forebrain.[124]

Environmental Considerations

Often, the question arises as to whether it is dangerous to bring a cat (with confirmed FIP) back into a household with other cats. When a cat in a household develops FIP, other cats that have been in contact with the cat already have been exposed to FCoV, but the key question remains whether the mutated virus is transmitted from cat to cat. In general, this does not seem to be the case. Most studies have failed to detect mutated virus in secretions or excretions from cats with FIP.[125] A recent study showed that cats with FIP actually stopped shedding FCoV. Analysis of 27 cats with FCoV infection and 28 cats with FIP from the same households revealed that most cats that had developed FIP had no detectable intestinal FCoV and seemingly cleared the primary FCoV infection. In those with detectable intestinal FCoV, sequence analysis revealed that the virus was different and seemed to have been acquired by FCoV superinfection.[60] Therefore, if a cat with FIP starts to shed virus again, this is due to a new superinfection from other cats in the household and not the original virus of the cat. Mutated FCoV that was found in FIP-associated organ lesions was not found in the feces, except in 1 cat. In this cat, a single-residue deletion in the 3c protein was found in ascitic and intestinal virus. Likely, the presence of the virus in feces resulted from leakage of systemic virus into the intestine, e.g., in case of intestinal granuloma.[60] In one study, the genomic RNA sequence of a field FCoV strain isolated postmortem from the jejunum and the liver of a cat with FIP revealed 100% nucleotide identity between the enteric- (jejunum) and nonenteric- (liver) derived viral RNA sequences, a finding that demonstrates that FIP-causing virus could be shed under some circumstances.[126] However, even if the mutated virus is shed on very rare occasions, it still would not cause FIP in another cat because this virus would not be able to replicate in the intestine of another cat after transmission. Studies have demonstrated that feces of cats with FIP will not cause FIP in another cat.[63] On the basis of current knowledge, the appropriate advice seems to be that it is relatively safe to bring the cat with FIP back into the household to the cats that have already been in contact, as these cats will have a certain immunity to the FCoV strain endemic in the household. It is, however, not recommended to allow contact of the cat with FIP to any new, "naïve" cat.

Supportive Treatment

As FIP is an immune-mediated disease, supportive treatment is aimed at controlling the immune response to FCoV, and the most successful approach consists of high dosages of immune-suppressive and antiinflammatory drugs that slow down disease progression, such as prednisolone (2-4 mg/kg PO q 24 h). Although glucocorticoids have been used in nearly every published case, their effect never has been substantiated in controlled studies. If effusion is present, some cats benefit from daily centesis for removal of the fluid (see ch. 90 and 102), and injection of dexamethasone into the abdominal or thoracic cavity (1 mg/kg q 24 h until effusion is no longer produced). Cyclophosphamide (2-4 mg/kg PO 4 times/week), alone or in combination with glucocorticoid, sometimes is used but there are no data available on its efficacy. Cats should also be treated with broad-spectrum antibiotics and supportive therapy (e.g., fluids; see ch. 129) in addition to the immunosuppressive treatment. A thromboxane synthetase inhibitor (ozagrel hydrochloride) that inhibits platelet aggregation and cytokine release has been used in 2 cats with some improvement of clinical signs.[127] Propentofylline has been used because it appears to down-regulate proinflammatory cytokines, which in turn can reduce vasculitis. However, in a placebo-controlled, double-blind study in cats with confirmed FIP, there was no significant difference in survival time, quality of life, or any clinical or laboratory parameter in cats treated with this drug versus cats receiving placebo.[87]

Antiviral Chemotherapy and Immunomodulators

The search for an effective antiviral compound has not been very successful in the past (Table 224-1). There are some promising experimental approaches, including protease inhibitors,[127a] inhibition of the FCoV spike protein that binds to receptors on the host cell membrane and mediates fusion of the viral envelope with host cell membranes,[128,129] circular triple helix-forming oligonucleotide RNA targeting viral RNA,[130] or small interfering RNAs (siRNA) leading to RNA interference and thus inhibition of virus replication,[131] but these compounds are still in an investigational stage. Some drugs are effective *in vitro,* but too toxic for cats, such as ribavirin[132-134] or chloroquine.[135] Others only have been investigated *in vitro,* but *in vivo* efficacy is unknown, such as vidarabine,[136] which inhibits polymerases; nelfinavir, a protease inhibitor of human immunodeficiency virus; *Galanthus nivalis* agglutinin (GNA), a carbohydrate-binding agent that binds to FCoV-glycosylated envelope glycoproteins, thereby inhibiting viral attachment to the host cell[137]; or cyclosporine A, which binds to cellular cyclophilins, thereby inhibiting calcineurin, which is required by many viruses for replication.[138,139] For many of these drugs, evaluation of data is hampered by the lack of well-controlled clinical trials in which new treatments are compared against standard care or placebo, and the fact that the presence of FIP was not even confirmed before treatment was initiated, making an assessment of the outcome impossible.[140]

TABLE 224-1

Treatment Options (Including Antiviral Drugs and Immunomodulators) for Cats with Feline Infectious Peritonitis (Including Evidence-Based [EBM] Grades for Judgment of the Available Efficacy Data and Personal Opinion of the Author)[91,169,170]

DRUG	EFFICACY *IN VITRO*	CONTROLLED STUDY *IN VIVO*	EFFICACY *IN VIVO*	PERSONAL OPINION	EBM LEVEL (1-4)
Nucleoside Analogue RNA Synthesis Inhibitors					
Vidarabine (Ara-A)	Yes136	No	n.d.	Likely ineffective	4
Nucleotide Synthesis Inhibitors					
Ribavirin	Yes136	Yes	No133,134	Not effective and toxic132 if given systemically	2
Alkylating Agents Interfering with RNA					
Melphalan	n.d.	No	n.d.140,171	Likely ineffective	4
Protease Inhibitors					
Nelfinavir	Yes137	No	n.d.	Potentially effective	4
GC376140a	Yes	Yes	Yes	Effective in experimentally infected cats	2
Viral Attachment Inhibitors					
Galanthus nivalis agglutinin (GNA)	Yes137	No	n.d.	Potentially effective	4
Interferons					
Human interferon-alpha (IFN-alpha)					
SC high dosage	Yes134	Yes	No141	Some effect in prolonging survival	4
PO low dosage	Yes134	No	n.d.	Contraindicated because of immuno-stimulatory effect	1
Feline interferon-omega (IFN-omega)	Yes142	Yes	No88	Ineffective	1

Interferon and Other Cytokine Inducers					
Staphylococcus protein A (SPA)	n.d.	No	n.d.	Contraindicated	4
Propionibacterium acnes	n.d.	Yes	Yes[141]	Weakly effective	2
Bacille Calmette-Guérin	n.d.	No	n.d.	Contraindicated	4
PIND-AVI/PIND-ORF	n.d.	No	n.d.[144,145]	Contraindicated	4
Polyriboinosinic-polyribocytidylic acid (poly-IC)	n.d.	No	n.d.	Contraindicated	4
Acemannan	n.d.	No	n.d.	Contraindicated	4
Other Drugs with Immunomodulatory Activity					
Tylosin	n.d.	No	n.d.[146,147]	Contraindicated	4
Promodulin	n.d.	No	n.d.[140,148]	Contraindicated	4
Levamisole	n.d.	No	n.d.	Contraindicated	4
Diethylcarbamazine (DEC)	n.d.	No	n.d.	Contraindicated	4
Polyprenyl immunostimulant (PI)	n.d.	No	n.d.[149]	Effective in 3 cats without effusion	3

n.d., Not determined; *PIND-AVI*, Parapoxvirus avis; *PIND-ORF*, Parapoxvirus ovis.

EBM, Evidence-based medicine: EBM level 1 = confirmed by at least one placebo-controlled double-blind field study. EBM level 2 = shown in a controlled experimental study. EBM level 3 = supported by case series. EBM level 4 = only based on expert opinion.

Interferons are used frequently in cats with FIP. Human interferon-alpha was effective against an FIP-causing FCoV strain *in vitro*, but in a placebo-controlled treatment study including 74 specific pathogen-free cats in which FIP was induced experimentally, neither the prophylactic nor the therapeutic administration of high dosages (10^4 or 10^6 IU/kg) of interferon-alpha, of feline interferon-beta (10^3 IU/kg), of the immunomodulator *Propionibacterium acnes* (0.4 mg/cat or 4 mg/cat), or of a combination of these agents significantly reduced mortality in treated versus untreated cats. However, in cats treated with 10^6 IU/kg interferon-alpha in combination with *Propionibacterium acnes*, the mean survival time was prolonged, but only by 3 weeks.[141] As an explanation of the limited efficacy of interferon-alpha, it has been suggested that ORF-7-encoded accessory protein 7a of FIP-causing strains can act as type-I interferon antagonists and counteract the interferon-alpha–induced antiviral response.[68] FCoV replication also is inhibited by feline interferon-omega *in vitro*,[142] which is licensed in some European countries and Japan. Promising results were obtained in one uncontrolled trial, but in the cats that were studied, FIP was not confirmed.[143] In a randomized, placebo-controlled, double-blind treatment trial in 37 cats with confirmed FIP, feline interferon-omega was not more effective than glucocorticoids alone.[88] Some older case reports suggest some effect through immunomodulator treatment, such as tylosin, promodulin, acemannan, or "paraimmunity inducers," but again FIP was not confirmed in these studies.[140,144-148]

A drug that has shown promise for immunomodulation is polyprenyl immunostimulant.[149] In a case series of three cats, polyprenyl immunostimulant was associated with prolonged survival in cats with FIP without effusion.[149] No placebo group was included for comparison; thus, definitive conclusions about the effectiveness of this drug cannot be drawn so far. The idea behind immunomodulator treatment is that these products might stimulate the immune response toward a cell-mediated response or to reduce an overactive Th2 response. An imbalance in T cell versus B cell response has been suggested to contribute to the development of FIP, although this hypothesis has been questioned recently.[119] A nonspecific stimulation of the immune system might in fact even be contraindicated, since the clinical signs develop and progress as a result of an immune-mediated response. Therefore, treatment with these drugs is not recommended as long as there is a lack of documented efficacy in well controlled studies.[140]

Prevention

Preventing FIP is extremely difficult. The only way to truly prevent the development of FIP is to prevent

infection with FCoV.

Management to Control FCoV in Infected Cats

Under natural circumstances, cats go outside to defecate and bury their feces, in which case FCoV usually remains infectious only for hours (or up to days in freezing conditions). However, domesticated cats have been introduced to littertrays in which FCoV can survive for several days and possibly up to 7 weeks in dried-up feces. Elimination of FCoV in multi-cat households is extremely difficult. Management recommendations for private households, breeding catteries, and shelters are summarized in Box 224-2.

Box 224-2

Management of Multi-Cat Households with FCoV-Infected Cats[102]

Management of Cats in Private Households with FCoV-Infected Cats

- In most households with >5 cats, FCoV is endemic. If FCoV is detected in a household, usually all cats are infected and many are shedding FCoV. Usually, most cats will have antibodies, as 95-100% of cats exposed to FCoV become infected and develop antibodies 2-3 weeks after exposure).
- A few cats might be "resistant" to FCoV infection. Some cats in FCoV-endemic multiple-cat households remain antibody-negative[91] (mechanism unknown). These cats should be used for breeding.
- Owners should be reassured that presence of antibodies is not necessarily associated with a poor prognosis. Most cats infected with FCoV will not develop FIP, and many cats in single-, 2-, or 3-cat households eventually clear the infection, and become antibody-negative months to years later.
- Owners should be advised that cats infected with FCoV have a better chance of eliminating FCoV if allowed to go outside, reducing reinfection with virus in their own feces.[50]

Management of Shelters with FCoV-Infected Cats

- "Normal" isolation procedures are ineffective for preventing transmission of FCoV because of the ease with which FCoV is transported on clothes, shoes, dust, and cats.
- Keeping previously uninfected cats together in a shelter leads to exponential increase of infection rates. In a study in which stray cats were tested at the time they were brought into local shelters (in which multiple cats were kept in one room) and at 1- to 2-week intervals thereafter, only a low number of cats had antibodies at the time of entering, but the percentage increased rapidly until virtually all cats in the shelters were infected with FCoV.[178]
- Prevention of occasional cases of FIP is extremely difficult in a shelter setting where FCoV prevalence is high and compounded by stress and co-infections. Cases usually are sporadic and unpredictable, and tend to cluster in litters of predisposed kittens.
- Comparison of shelters with different types of handling revealed a significant correlation between increases in number of handling events outside the cages and increases in the percentage of FCoV antibody-positive cats.
- Shelters should minimize crowding and length of stay, design facilities for easy sanitation, and optimize husbandry to minimize virus spread and stress levels.[91]
- The Advisory Board of Cat Diseases (ABCD) provides specific shelter guidelines that can help in the management of FCoV infection.[179]

Management of Breeding Catteries with FCoV-Infected Cats

- Ideally, breeding catteries should be free of FCoV. This, however, rarely is the reality.
- Catteries with <5 cats can spontaneously and naturally become FCoV-free, but in catteries with >10 cats, this is almost impossible as the virus will pass from one cat to another, maintaining the infection.[91]
- The most important tactic to eliminate FCoV from a cattery is to reduce the number of cats (especially kittens <12 months old).
- It is also important to keep potentially FCoV-contaminated surfaces clean, to minimize the environmental load of FCoV.
- Antibody testing and segregating cats are methods aimed at stopping exposure.[50,172] FCoV is excreted

by ≈1/3 of antibody-positive cats,[173] and every antibody-positive cat should be considered infectious. After 3-6 months, antibody titers can be retested to determine whether cats become negative.

- Alternatively, RT-PCR testing of fecal samples (4 samples, each 1 week apart) can be performed to detect chronic FCoV carriers shedding high virus loads.[174] In large, multi-cat environments, 40-60% of cats shed virus in feces at any given time.
- If a cat is persistently fecal RT-PCR-positive for >6 weeks, it should be eliminated from the cattery and placed in a single-cat environment.[91,175,176]
- An early weaning protocol for preventing FCoV infection in kittens from infected queens has been proposed. The queen is isolated for 2-3 weeks prior to parturition, the queen and kittens are strictly quarantined, and kittens are weaned early (4-6 weeks old). Rationale: it has been proposed that young kittens have mucosal immunity to the virus, and kittens of FCoV-shedding queens have been considered protected from infection by local maternal antibodies until they are 5-6 weeks old.[51] However, early weaning failed and viral infection of 2-week-old kittens was demonstrated in a study in Switzerland. In addition, early weaning might exact a social price on the kittens. Thus, this procedure should only be undertaken with careful consideration and consultation with the breeder.[91]
- If possible, maximizing heritable resistance to FIP is recommended. Genetic predisposition plays a role (not completely understood).[177] Full-sibling littermates of kittens with FIP have a higher likelihood of developing FIP. If a cat has ≥2 litters in which kittens develop FIP, that cat should not be bred again. Particular attention should be paid to pedigrees of tomcats where FIP is overrepresented.[91]

Vaccination

There have been many attempts to develop effective vaccines, but most have failed, mainly because of the so-called antibody-dependent enhancement (ADE). ADE is caused by enhancement of the infection of macrophages[150] and it describes a phenomenon whereby cats that develop antibodies after vaccination and are subsequently infected with FCoV will develop FIP faster and will die earlier than cats that are not vaccinated.[151-156] A vaccine available in the USA and several European countries contains a temperature-sensitive mutant of an FCoV strain that can replicate in the cool lining of the upper respiratory tract but not at higher internal body temperature.[157-160] This vaccine, administered intranasally, produces local immunity (IgA antibodies) at the site where FCoV enters the body (the oropharynx) and also induces cell-mediated immunity. Safety concerns always raised are whether the vaccine could cause FIP or produce ADE. Although some experimental trials using this vaccine have recorded ADE on challenge, field studies have demonstrated that this vaccine is safe. In neither of 2 extensive placebo-controlled double-blind field trials did cats develop FIP or ADE after vaccination.[161-163] There were a few immediate side-effects after vaccine application, such as sneezing, vomiting, or diarrhea, the incidences of which were not significantly different in the vaccinated group compared to the placebo group.[162] However, efficacy of this vaccine is questioned constantly. Experimental studies have published data on preventable fractions between 0%[164,165] and 50% to 75%[160,166] depending on the investigator. In a survey of 138 cats belonging to 15 cat breeders, in which virtually all of the cats had antibodies prior to vaccination, no difference was found in the development of FIP between the vaccinated group and the placebo group.[162] Thus, vaccination in FCoV-endemic environments or in households with known cases of FIP is not effective. In a placebo-controlled double-blind trial FCoV-naive cats before vaccination, a small but statistically significant reduction in the proportion of cats that developed FIP was noted.[167] As the vaccine is ineffective when cats have already had an encounter with FCoV, antibody testing might be beneficial before vaccination. One disadvantage is that cats develop antibodies after vaccination, making establishment and control of an FCoV-free household difficult. In conclusion, study results do not clearly identify whether vaccination has no effect versus a small effect in reducing the probability of FIP.[168] Although only marginally, if at all efficacious, the vaccine is at least safe.

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CHAPTER 225

Canine and Feline Parvovirus Infection

Andrew Lambert Leisewitz

Client Information Sheet: Canine and Feline Parvovirus Infection

Etiology and Epidemiology

Members of the Parvovirus genus infect a wide range of mammalian hosts but do show host specificity. Canine parvovirus (CPV) and feline panleukopenia virus (FPV) are the two important parvoviruses of dogs and cats, respectively, and are classified according to the hosts from which they have been isolated. Both CPV and FPV are considered to be host range variants among the feline parvoviruses.[1] The genetic sequences of CPV and FPV differ by only around 2% and antigenically they are very similar.[2] The virion is a simple, small, non-enveloped, single-stranded DNA virus with a genome size of around 5000 base pairs. The capsid proteins are the key structures determining host specificity and antigenicity. The host range of these two viruses differs and is determined by fewer than 10 amino acid differences in the capsid.[3] The virus makes use of the transferrin receptor to gain entry to cells and polymorphisms in this receptor are responsible for host specificity.[4] FPV replicates in feline cells *in vitro* and *in vivo* but not in canine cell cultures. CPV replicates in feline and canine cells in culture and in dogs *in vivo.* FPV is able to replicate to a limited extent in dogs but without causing illness. It infects the dog thymus and bone marrow and hence is also unable to spread among dogs.[1] The first CPV discovered in 1967 was called the minute virus of canines (later called CPV-1).[5] It is clinically insignificant today.[6] CPV-2 was discovered in dogs in 1978 in the United States and it was responsible for a devastating global pandemic within months.[7] It is now well established worldwide and is probably the single most common infectious disease of dogs with a high morbidity and mortality. This virus has subsequently mutated into CPV-2a, CPV-2b and lately to CPV-2c, which was first identified in Italy in 2000[8,9] but is now reported worldwide. CPV-2a and CPV-2b are capable of infecting cats and causing a clinical illness indistinguishable from panleukopenia, although this is rare.[10,11]

The fecal-oral route is the traditionally understood means of transmission, but fomite transmission also is very efficient. Diseased dogs can shed the virus at very high titers (up to 10^9 tissue culture infective dose-50 [$TCID_{50}$] per gram of feces) in their stool.[12] In the author's hospital, the caseload is directly correlated with wind speeds and inversely with humidity.[13] There is also evidence for seasonality in CPV in Canada[14] and in FPV across North America that corresponds to a peak in the susceptible kitten population.[15] There is evidence that certain breeds are more susceptible to infection, with Rottweilers, American Pit Bull Terriers, Doberman Pinschers, English Springer Spaniels, and German Shepherds being at increased risk. The odds to develop CPV enteritis were higher in purebreds compared to mixed-breed puppies in one study.[16] There is no published evidence of breed susceptibility among cats. Because immunity is conferred by antibody, maternally derived titers mean that neonates are almost never affected. Approximately 90% of maternally derived antibody is from colostrum and it has a half-life of around 10 days.[17] Susceptibility increases as maternal immunity wanes at around 12-14 weeks of age. Vaccination is highly effective at protecting from infection. The age at which puppies and kittens are affected also means that periods during which there is an abundant supply of susceptible animals will increase disease incidence. Introduction of infected animals into shelter environments also can result in explosive outbreaks. Other factors that contribute to infection include intestinal parasites, overcrowding, and unsanitary and stressful environmental conditions. Both CPV and FPV are extremely stable in the environment, which makes indirect transmission important and environmental decontamination difficult. Care should be taken in veterinary clinics where unvaccinated or inadequately vaccinated puppies are likely to come into contact with contaminated surfaces. Dogs admitted

to hospital for treatment should be kept isolated from the rest of the hospital population. Recently, it been shown that flies also play an important role in the spread of the infection among dogs.[18]

Pathogenesis and Clinical Signs

CPV and FPV share a very similar pathogenesis and clinical presentation. The virus is unable to induce mitosis in the cells it infects and hence it relies on the rapidly multiplying cells of the body for its success. The virus thus shows a tropism for cells of the thymus, bone marrow, spleen, and crypt cells of the gut epithelium. Stress factors, in particular parasitic and other nonspecific factors such as weaning, can predispose dogs to infection by increasing mucosal cell activity.[19] FPV disease has been documented to be enhanced by feline leukemia virus (FeLV),[20] *Clostridium piliforme*,[21] and feline coronavirus.[22] Because a robust antibody response is very protective, parvoviral infections are almost exclusively a disease of animals under a year of age that are past the age at which maternally derived antibodies provide protection, or are unvaccinated or inadequately vaccinated. For both CPV and FPV, vaccination status plays a very important role in susceptibility.

Following oral infection, the virus disseminates to the regional lymph nodes of the pharynx and the tonsils. In an experimental study in dogs, fecal shedding was present from day 3 following oral infection, peaked on days 3 and 4, and was greatly reduced by day 7.[23] Shedding could well occur for a day or 2 before clinical signs are apparent. The incubation period of this disease varies from around 4 days (under experimental conditions) to the more typical 1 to 2 weeks usually seen under natural conditions. Following infection of lymphoid tissues of the upper gastrointestinal (GI) tract, including the tongue, a cell-free viremia ensues. Under experimental conditions, this lasts from day 1 to day 5 post-infection, with the first signs of serum antibodies developing on day 5 and peaking from day 7 onwards.[23] Thymic and lymphoid tissue infection leads to thymic atrophy, lymphoid depletion, lymphopenia, and immunosuppression. Viral antigen is detectable in the proliferative zone of the crypt epithelium of the intestinal tract from day 4. Very little antigen remains in either the lymphoid tissues or gut epithelium from day 7 onward. Subclinical infection probably is common, especially in older, immune-competent animals.

The earliest clinical signs include fever, depression, and a loss of appetite. This is followed by diarrhea and vomiting. This is true of CPV and most cases of FPV. The diarrhea initially is clinically characteristic of small bowel disease (see ch. 40). It may quickly become melenic and then frankly hemorrhagic, and take on the character of a mixed small and large bowel type diarrhea (Figure 225-1, *B*). These puppies carry a very characteristic fetid odor. The vomiting usually increases in frequency and can become very severe and frequent with little more than foam produced. Hematochezia can be present and ascarids also can be observed in the vomitus. In peracute FPV, young cats can die within 12 hours of showing depression, due to profound septic shock, dehydration, and hypothermia, and vomiting and diarrhea may be minimal or absent.

FIGURE 225-1 The typical clinical presentation of advanced parvovirus infection in a young German Shepherd Dog puppy. The dog is moribund **(A)** and in hypovolemic shock, with hemorrhagic diarrhea **(B)** and pale, dry mucous membranes **(C).**

Bone marrow infection can lead to bone marrow necrosis in both dogs and cats.[3] This leads to leukopenia and also can contribute to the anemia seen in some cases. In most cases of CPV and FPV, leukopenia is present by the time hemorrhagic diarrhea and vomiting are present. Thrombocytopenia, however, is not a feature of the disease.[24] An increased concentration of granulocyte-colony stimulating factor (G-CSF) has been documented in dogs with CPV and this is likely to be a response to the neutropenia.[25] The neutropenia also is partially due to an overwhelming demand in the gut. The immunosuppression associated with CPV does mean these dogs are very susceptible to acute secondary infections. The most common of these are bacterial bloodstream infections, which manifest clinically as endotoxic shock (see ch. 127 and 132); on recovery some puppies develop skin necrosis (Figure 225-2), bacterial polyarthritis, and discospondylitis (Figure 225-3) (R. Kirberger, personal communication). The immune-suppressed condition also means that barrier nursing practices should be strictly enforced (Figure 225-4). Puppies with other infectious diseases should not be kept within the same facility. The most important differential diagnosis for systemic CPV-like signs is canine distemper virus infection. Every effort must be made to exclude this highly contagious disease from being cared for in a facility that admits CPV-infected puppies or by the same caregivers.

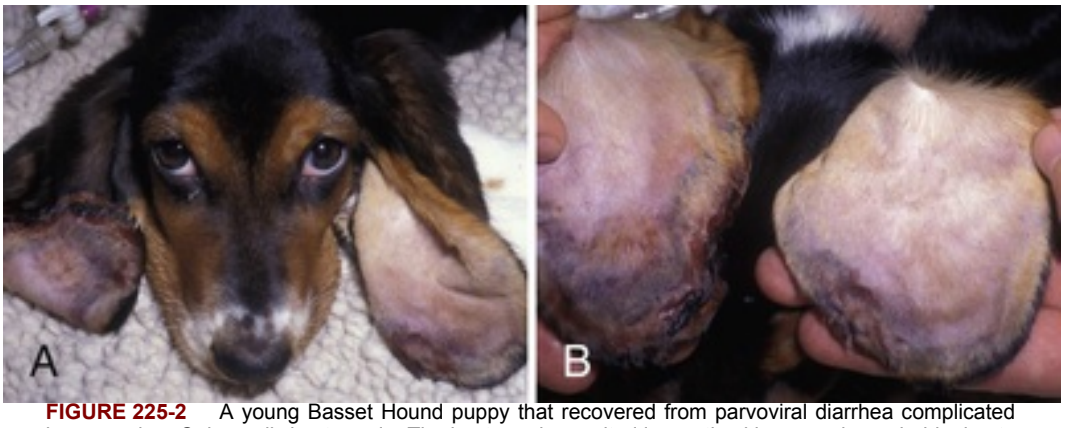

FIGURE 225-2 A young Basset Hound puppy that recovered from parvoviral diarrhea complicated by secondary *Salmonella* bacteremia. The bacteremia resulted in ear-tip skin necrosis, probably due to micro-embolization of the peripheral vasculature.

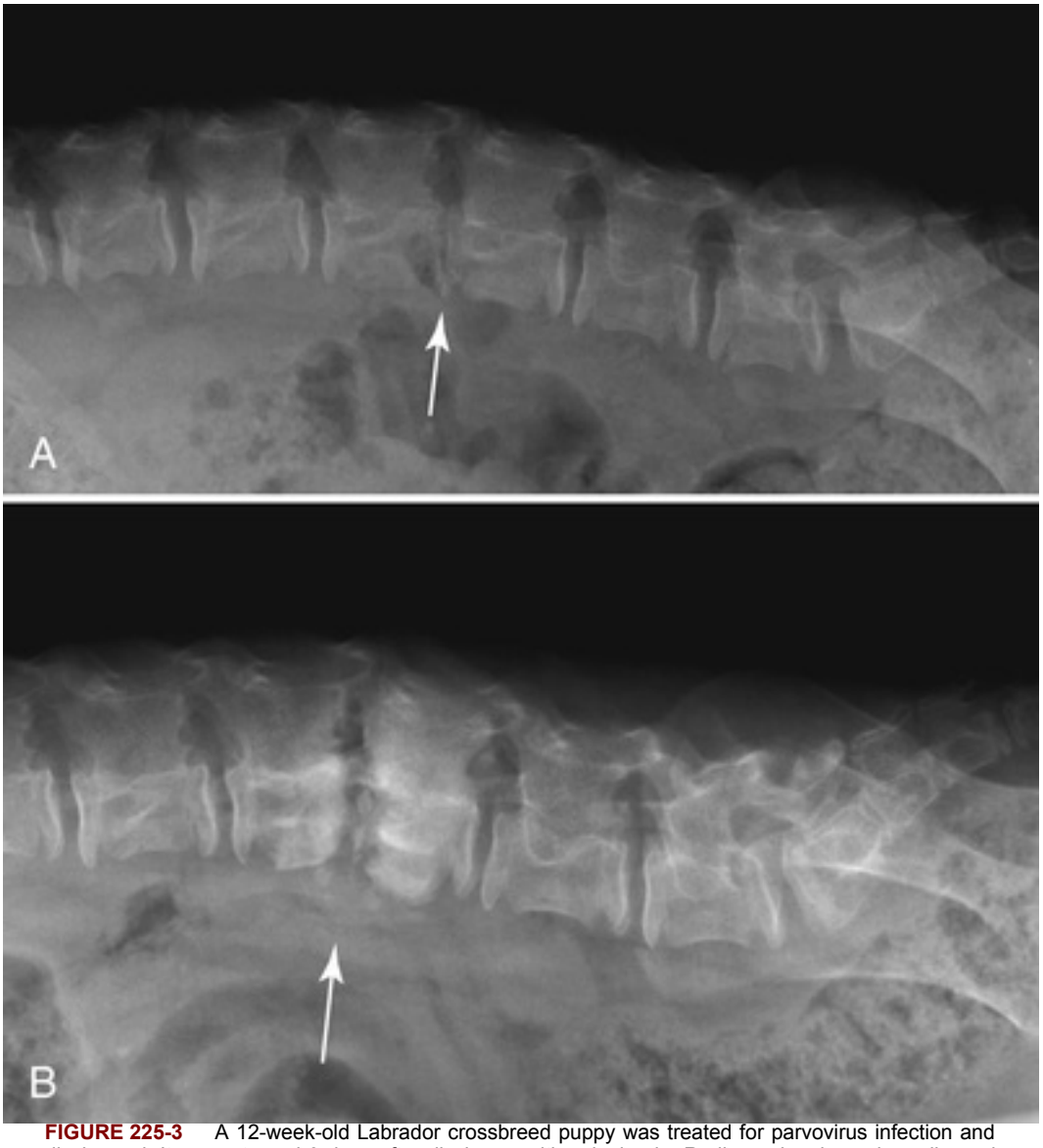

FIGURE 225-3 A 12-week-old Labrador crossbreed puppy was treated for parvovirus infection and discharged. It was returned 3 days after discharge with spinal pain. Radiographs showed a collapsed lumbar 4-5 disc space with mild subluxation **(A).** Follow-up radiographs up taken 2 weeks later showed findings typical of discospondylitis with subluxation (**B,** arrow) with a new lesion in a cervical space (not

shown). (Images courtesy R. Kirberger.)

FIGURE 225-4 The isolation ward of the Onderstepoort Veterinary Academic Hospital where dogs with parvovirus are treated. The highly contagious nature of the disease necessitates barrier nursing, as shown. The resistant nature of the virus requires that the facility be easily disinfected.

Viral infection of the gut leads to crypt necrosis and villous collapse; loss of the normal gut barrier function has serious consequences, as elements of the gut content can no longer be kept out of the bloodstream.[26,27] *Escherichia coli* was recovered from the lungs and liver of 90% of 98 CPV-infected puppies in one study.[28] Blood loss into the gut may be significant, resulting in melena, hematochezia, and anemia (which can be masked in dehydrated animals). Ascarid infestations can result in additional blood loss and are known to aggravate the disease. This comorbidity is common. Less common are concurrent giardiasis and coccidiosis.

Devastating fluid and electrolyte losses can be caused by vomiting and diarrhea. This leads to dehydration and electrolyte deficiencies, the most notable of which is hypokalemia. The dehydration would be classified as isotonic or hypotonic (due to hypertonic fluid loss) and it results in dry mucous membranes, increased skin turgor, increased capillary refill time, tachycardia, hypotension, collapse, and reduced urine production. The acid-base disturbances have been shown to be complex and heavily influenced by chloride, free water, and albumin. Severely affected animals tend to demonstrate hypochloremic alkalosis, whereas mildly affected puppies typically have a hyperchloremic acidosis. The strong ion model proposed by Stewart provides better insights into pathological mechanisms than does the traditional Henderson-Hasselbalch model.[29] Coagulation abnormalities also have been documented in a small study of 9 dogs with parvoviral infection. The study showed a high prevalence of clinical thrombosis or phlebitis and laboratory evidence of decreased antithrombin activity, prolonged activated partial thromboplastin time, increased maximum amplitude in the thromboelastogram, and increased fibrinogen concentrations. This cohort thus demonstrated hypercoagulability without disseminated intravascular coagulopathy.[24] Although this was a very small study, the older work that seemed to suggest the presence of disseminated intravascular coagulopathy should be questioned. Clinically obvious petechiation and hemorrhage from sites other than the gut are not a feature of CPV infections.

FPV is a well-known cause of cerebellar hypoplasia in kittens exposed to the virus either *in utero* or in the early neonatal period. The virus destroys Purkinje cells and granule precursor cells in the developing

cerebellum.[30] Affected kittens can show a wide range of disease, from very severe hydranencephaly, hydrocephalus, and porencephaly to milder cerebellar disease. Less seriously affected animals can make acceptable pets, as the disease is non-progressive. Clinical signs vary widely and can be multifocal depending on the areas of the brain affected and the degree to which they are affected. Seizure activity is possible with cerebral involvement.

Early in the CPV-2 disease pandemic, when dogs were not vaccinated and dams transferred no maternal antibodies to their pups, very young (<8 weeks of age) pups or pups *in utero* became infected and the clinical presentation was somewhat different to what it is today. Myocardial disease due to CPV now is very rare[31] although it does still occur in isolated unvaccinated populations.[32] Enteric signs were not always present with cardiac signs. A wide range of cardiac signs has been described, from peracute congestive failure to more chronic failure becoming evident only months after infection. It would appear, however, that CPV is not a common trigger for myocardial disease in dogs anymore.[33] Using molecular methods, FPV was identified by polymerase chain reaction (PCR) in 10 of 31 cats with cardiomyopathy but in none of the 17 controls in one study, suggesting a possible role of viral infection in the pathogenesis of feline cardiomyopathy.[34]

The ultimate cause of death in acute CPV and FPV infection is septicemia, endotoxemia, and shock (see Figure 225-1). It has been shown that endotoxin and the subsequent inflammatory cascade initiated by endotoxin are related to disease severity and outcome.[35,36] One study showed that 22% of the IV catheter tips used for fluid infusion were infected. Most of the organisms involved were Gram-negative, gut-associated bacteria.[37] Hypoglycemia is a common finding and this is likely due to the young age of most affected dogs, and the concomitant anorexia and the hypermetabolic state associated with endotoxic shock. The most likely cause of seizures in puppies with CPV infection is hypoglycemia (neuroglycopenia).

Diagnosis

The diagnosis of parvoviral disease is not problematic and is usually based on combining a cluster of findings that include the presentation of the typical signalment (young and un- or inadequately vaccinated), classic chief complaints of depression, anorexia, vomiting and diarrhea (which can be hemorrhagic) and the typical clinical findings of fever, dehydration, fluid-filled and gassy intestine on abdominal palpation, and leukopenia on peripheral blood smear. In many cases, no further diagnostic tests are performed and a legitimate presumptive diagnosis is made. The next step in diagnosis typically would involve the use of a fecal parvovirus antigen enzyme-linked immunosorbent assay (ELISA) test to confirm the clinical suspicion. These tests are used widely and will detect CPV 2a, b and c, but do have some problems with sensitivity.[38] It must be remembered that fecal viral shedding is transient and fecal antibodies can bind the virus, making it unavailable in the assay. Specificity, however, is not a problem with these tests. False positives can occur following vaccination due to the shedding of the vaccine virus for 4 to 8 days following vaccination with modified live CPV vaccines. A similar problem has been reported following FPV vaccines.[39] Serology seldom is used. ELISA assays that are semi-quantitative for anti–CPV-2 antibodies are more typically used for determining the need for vaccination rather than diagnosis. Fecal electron microscopy, although useful, also is seldom used as its availability is limited. Polymerase chain reaction also is well described but seldom used clinically. The diagnosis of FPV is based on finding the typical clinical evidence as seen in dogs, and the use of the same point-of-care fecal ELISA tests used for detecting CPV.[40,41] These tests suffer from the same problems in the detection of FPV as they do with CPV. A fecal flotation and wet-prep examination should be routine in all cases of suspected CPV or FPV to rule out concomitant parasitoses (see ch. 81).

Clinical Management

The level of care strongly affects outcome. There is no specific antiviral treatment available and hence supportive care is the mainstay of therapy. Outpatient-based treatment is not recommended as the standard of care, because in most cases owners are unable to maintain hydration orally. It might be necessary to provide subcutaneous or intraperitoneal fluids and oral antibiotics in some cases because of the financial constraints of some owners. Preliminary results of an outpatient-type protocol, consisting of intravenous fluid resuscitation followed by cefovecin (8 mg/kg SC once), maropitant (1 mg/kg SC q 24 h × 5 days) and SC fluids PRN, showed a survival rate rivaling that of inpatient treatment.[42] However, the prognosis could worsen when treatment relies on client involvement (compliance, home monitoring and treatment) if such involvement continues to be insufficient, as indicated by a history of inadequate basic preventive care like vaccination. Affected dogs and cats should be admitted to a facility that can provide isolation and barrier

nursing. The often small size of the patients and the intensive nature of the treatment and monitoring required necessitate a high level of care.

Intensive treatment with crystalloid fluids, synthetic and natural colloids, correction of hypoglycemia and any electrolyte disturbances, and a combination of antimicrobials, antiemetics, analgesics, enteral nutritional support, and anthelmintics, usually form the basis of the treatment plan. Fluid therapy to treat dehydration, re-establish effective circulating blood volume, and correct electrolyte and acid-base disturbances is the mainstay of managing more severely affected puppies (see ch. 129).[43] Fluid therapy in these patients can be complex, and careful attention should be paid to physical examination in addition to electrolyte and acid-base status.[44] The preferred route of administration is intravenous, but intraosseous administration, although rarely used, can be useful in patients that need rapid fluid administration when intravenous access is impossible (see ch. 77). All intravenous catheters should be replaced every 72 hours. The initial fluid of choice is a balanced electrolyte solution that is isotonic to blood (e.g., lactated Ringer's solution). The initial rate of fluid administration will depend on the condition of the patient. IV fluid boluses can be necessary in patients with hypovolemic shock (see ch. 127). Fluid deficits should be replaced as soon as possible (within 1 to 6 hours of presentation).[43] Once perfusion is restored, the intravenous fluid rate is reduced to a maintenance rate plus estimated ongoing losses. Hypokalemia is common and potassium chloride (KCl) should be added to the IV fluids until serum potassium concentrations have normalized (see ch. 68). Hypoglycemia also is common, and in severe cases, 25% dextrose should be given as a bolus to correct this (see ch. 61 and 303). Following this, the IV fluid infusion can be supplemented with 2.5-5% dextrose to maintain normoglycemia.

Hypoalbuminemia is common as a result of protein-losing enteropathy (see ch. 60 and 276). Colloid oncotic pressure could require support with a synthetic colloid such as hydroxyethyl starch if the serum albumin concentration should drop below 2 mg/dL (20 g/L) or if there is an obvious third space fluid loss. The role of blood products in the treatment of CPV is controversial. Patients suffering from anemia secondary to hemorrhagic diarrhea or concurrent endoparasitism should be transfused with packed red blood cells or whole blood (see ch. 130). Fresh frozen plasma (FFP) transfusion has been recommended in the treatment of CPV enteritis for its ability to provide oncotic components (albumin), immunoglobulin, and serum protease inhibitors, which can help to neutralize circulating virus and control the systemic inflammatory response associated with this disease.[45] However, FFP infusion has been shown to be a poor means of supporting colloid oncotic pressure, as very large volumes need to be infused to improve this measure significantly.[46]

Evidence supports the use of early enteral nutrition. In a randomized controlled trial, puppies receiving early enteral nutrition via a nasoesophageal tube (see Video 225-1 for placement technique; see also ch. 82), when compared with puppies that received nothing per os until vomiting ceased, showed earlier clinical improvement, significant weight gain, and improved gut barrier function, which could limit bacterial or endotoxin translocation.[26] Once vomiting has ceased, an oral deworming program should be initiated (see ch. 163).

The most commonly used antiemetic drugs for CPV enteritis are metoclopramide (0.2-0.4 mg/kg SC q 8 h or 1 mg/kg/day IV constant rate infusion [CRI]), prochlorperazine (0.1 mg/kg IV q 8-12 h), ondansetron (0.1-0.5 mg/kg IV q 12 h), or maropitant (1 mg/kg SC q 24 h × 5 days maximum). In cases of intractable vomiting, and when intestinal obstruction has been ruled out, combination therapy and continuous intravenous infusions of these drugs could be more effective than monotherapies or boluses. A retrospective study showed that in a high number of cases, antiemetics did not completely control vomiting, and puppies that received antiemetics generally required longer hospitalization. Although this study demonstrated an association between antiemetic use and prolonged hospitalization,[47] a cause-and-effect conclusion cannot be drawn, and antiemetics are definitely indicated in the management of this disease.

Treatment with intravenous, broad-spectrum, bactericidal antibiotics is warranted in puppies suffering from CPV enteritis, due both to the disruption of the intestinal barrier and to severe leukopenia. A combination of a beta-lactam antibiotic (e.g., ampicillin, 20 mg/kg IV q 8 h) or a beta-lactamase-resistant penicillin (e.g., amoxicillin/clavulanate, 20 mg/kg IV q 8 h) with an aminoglycoside (e.g., amikacin, 20 mg/kg IV, IM, or SC q 24 h once the dog has been rehydrated; used for a maximum of 5 days) will provide broad coverage. Metronidazole (15-20 mg/kg PO q 12 h for up to 10 days) is indicated in cases where motile protozoa are found on fecal wet preparation.

Despite the lack of canine-specific interferon products, several studies have shown recombinant interferons (IFNs) to significantly ameliorate severe enteritis caused by CPV and to reduce mortality.[48-50] In one multicenter, double-blind, placebo-controlled field trial that compared 43 IFN-omega treated dogs (2.5 million units/kg IV q 24 h × 3 consecutive days) with 49 placebo-treated dogs, there was a >4-fold reduction in

mortality in the treated group.[50] Another study using a recombinant feline IFN-omega preparation (1-5 million units IV q 24 h for the first 3 consecutive days) also showed a significant treatment benefit when compared to the placebo-treated group in both experimental and field trial conditions.[48]

Analgesia is an important component of case management in almost all cases, as the enteric pain can be severe; even in very depressed dogs, abdominal palpation can elicit immediate abdominal splinting due to pain. The most commonly used drugs include buprenorphine (e.g., 0.005-0.02 mg/kg IV q 8-12 h) and fentanyl (e.g., 2-5 mcg/kg/h IV CRI).

Several other adjunctive agents have been investigated, including recombinant human G-CSF (rhG-CSF) and recombinant bactericidal/permeability-increasing protein (rBPI21) but neither of these has demonstrated any benefit.[51,52] Oseltamivir, an antiviral drug that inhibits neuraminidase (NA), was recently investigated and also found to be of minimal benefit.[53]

Daily monitoring to allow treatment adjustments and assessment of progression is crucial. Clinical data (including a full physical examination) to specifically assess hydration, frequency of vomiting and defecation, abdominal palpation (to specifically palpate for intussusception), and levels of pain are standard care. Under normal circumstances, the following laboratory data should be monitored at least daily, and in some cases more frequently: hematocrit, total serum solids (or total serum protein and albumin), serum electrolytes (Na, K, Cl), and blood glucose.

Prognosis

Outcome varies greatly, with a survival rate of around 10% in untreated puppies to in excess of 90% with intensive treatment, and this is very much a function of what owners can afford.[54,55] The earlier in the disease course the animal presents for care and the sooner intensive treatment is initiated, the better the outcome. Various hematological variables have been negatively associated with prognosis, including leukopenia, lymphopenia, monocytopenia, and neutropenia.[16,56] The presence of a systemic inflammatory response syndrome at the time of admission also is a negative indicator.[16] Other factors that have been correlated with outcome include season of presentation,[55] pure breed,[14,54,57] body weight,[58] vomiting, hypercoagulability,[24] hypercortisolemia,[59] hypothyroxinemia,[60] hypoalbuminemia, elevated C-reactive protein,[61] increased tumor necrosis factor, hypocholesterolemia,[62] and hypocitrullinemia.[58]

Prevention

The cornerstone of protection is vaccination. Live attenuated and inactivated vaccines are widely available and are part of the core vaccination program for both dogs and cats (see ch. 208). Immunity is antibody-dependent and sterile. Immunity following the clinical disease is probably lifelong. It is unsafe to vaccinate pregnant animals with the live vaccine, as the fetuses could be affected negatively. Inactivated vaccines are not as quick at providing protection, which translates to a much longer period of susceptibility early in life. By far the most common cause for vaccine failure remains vaccine neutralization by maternally derived antibodies. Traditional vaccination programs start at 4 to 6 weeks, are boosted a month later and again a month after this (with the last and most effective vaccine occurring at 14 to 16 weeks of age). Where problems exist in breeding establishments, very early vaccination programs can be used in an attempt to reduce the window of vulnerability. It has been shown that a high-titer modified live virus vaccine can provide protection for pups vaccinated as early as 4 weeks old.[63] The frequency of boosting through life is contentious but it is generally accepted that a booster should be given at a year of age and then every 3 years thereafter.[64] The need for repeated vaccination through a dog's life has come under scrutiny and there is a growing tendency to assess the antibody titer against a viral pathogen before booster vaccinations are administered. One study has suggested that a CPV titer of ≥1:80 (measured by an on-site ELISA) was a practical way of separating protected from unprotected dogs admitted to a shelter.[65]

Some concern has been raised about the ability of available CPV-2 strain vaccines to protect against CPV-2c.[66] However, challenge studies using dogs vaccinated with CPV-2 have demonstrated good protection against CPV-2c.[67,68]

The highly contagious and very resistant nature of the virus make barrier nursing of infected animals and very stringent disinfection protocols (such as with 1:30 dilutions of hypochlorite bleach in tap water) crucial to preventing contagion. Because natural environments cannot be disinfected, only vaccinated animals should be allowed onto potentially contaminated surfaces.

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CHAPTER 226

Rabies

Cathleen A. Hanlon

Client Information Sheet: Rabies

Overview

The word *rabies* may invoke keen attention, concern, or fear among veterinarians, pet owners, caregivers of domestic and wild animals, and the public. Rabies continues to have the highest mortality rate of any known infectious agent. In contrast to Ebola and Lassa fever, which have mortality rates as high as 50-90%, rabies is still virtually 100% fatal, despite reports of a recent human survivor and continuing attempts to treat infected individuals. The global burden of rabies continues to be associated with transmission among domestic dogs, mainly in Asia and Africa (Figure 226-1). The threat of exposure to humans and domestic animals in Europe and North America was significantly reduced several decades ago by eliminating dog-to-dog perpetuation of canine rabies virus variants. This was achieved through coordinated, methodical, population-based vaccination of dogs against rabies, as well as control of stray dog populations. In practicality, these techniques could be applied globally.

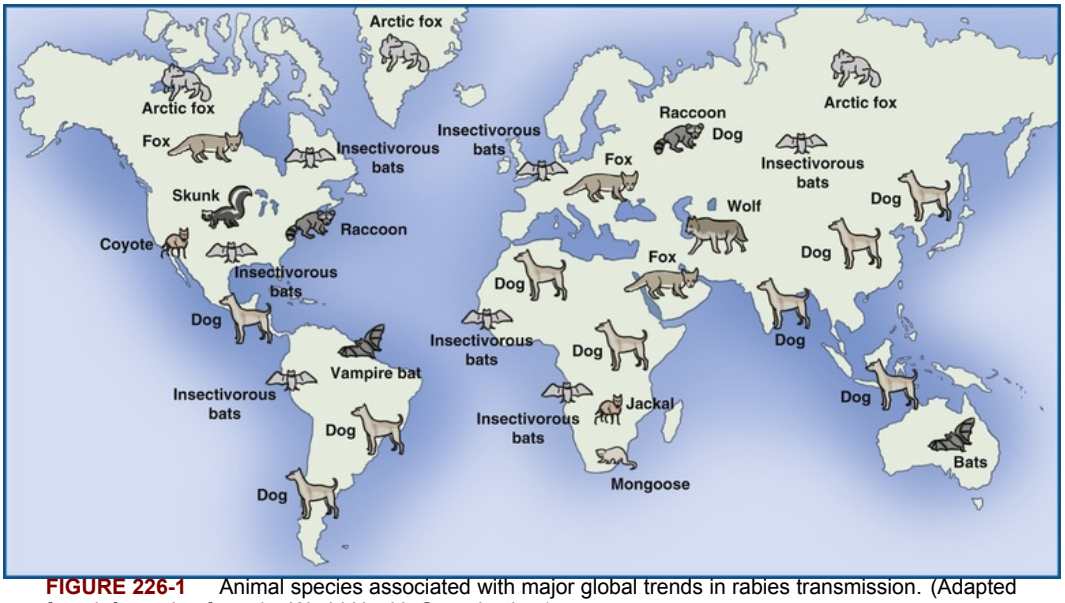

FIGURE 226-1 Animal species associated with major global trends in rabies transmission. (Adapted from information from the World Health Organization.)

Due to elimination of dog-to-dog transmission, the trend in animal and human rabies in North America has changed substantially in the last 50 years. The number of people infected with rabies decreased due to fewer exposures and better prophylactic biologics. At the same time, increase in rabies transmission among wildlife was detected. This increase was due, in part, to enhanced surveillance among other wildlife reservoir species, including skunks in the 1970s and 1980s, then bats, and also geographic expansion of the raccoon rabies virus variant. Substantial improvement in canine rabies control over the past two decades has occurred in Latin America. Overall, reports of animal rabies trends in North America have decreased from over 20,000 cases per

year a decade ago to the current level of approximately 10,000 per year. About 85% of those cases occur in the United States (Figure 226-2). These trends reflect the recent success in canine rabies control in Mexico and a decline in cases in Canada due to oral rabies vaccination of red foxes. By contrast, rabies represents a continuing enzootic disease in the United States and Canada caused by the geographic spread of raccoon rabies. Despite the historic extinction of canine rabies virus variants in most of North America, numerous rabies virus variants are found in various wildlife species and they constitute an ever-present risk of exposure (Figure 226-3). Those reported are a subset of all naturally occurring cases (Figure 226-4). Human and animal travel and contact with bats maintain the global risk of rabies.

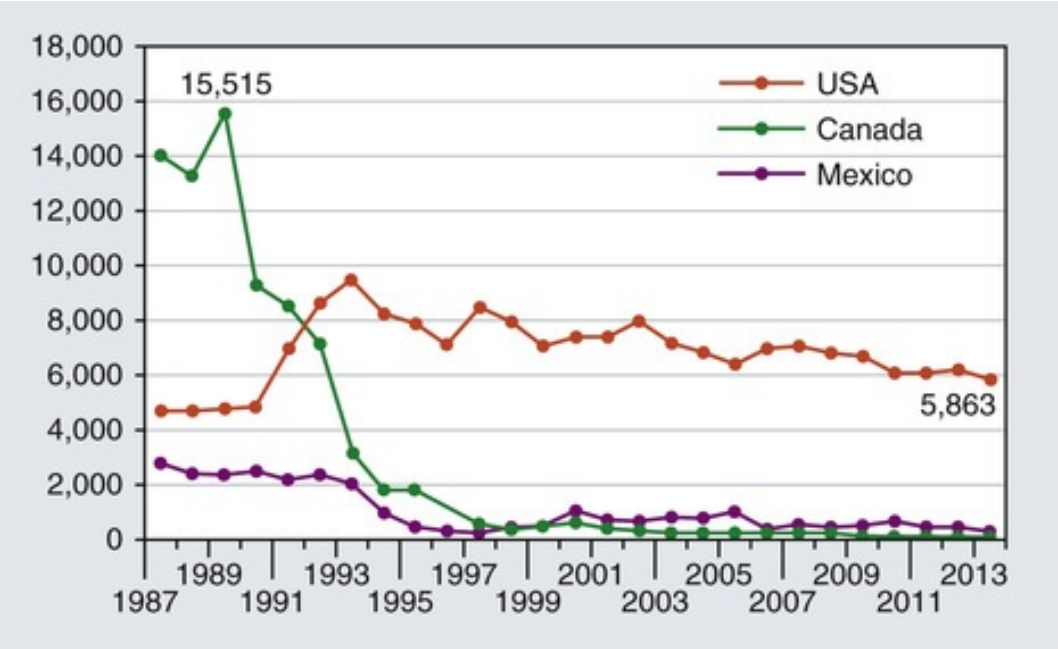

FIGURE 226-2 Animal rabies cases in North America by country, 1987-2013.

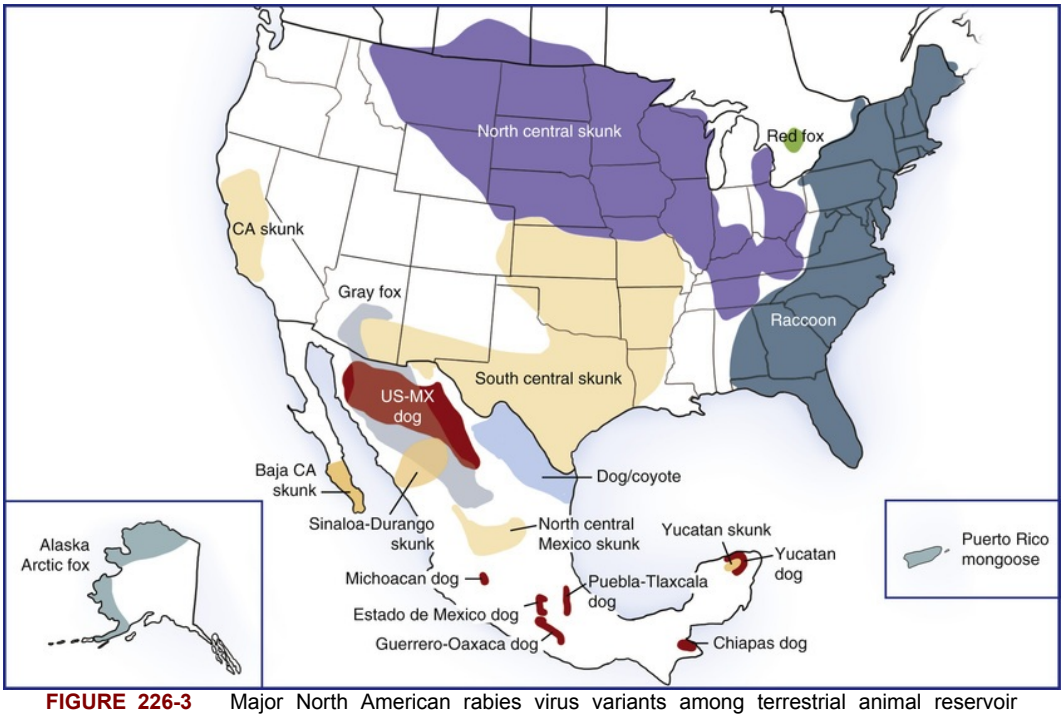

FIGURE 226-3 Major North American rabies virus variants among terrestrial animal reservoir

species. *CA,* California; *MX,* Mexico; *US,* United States.

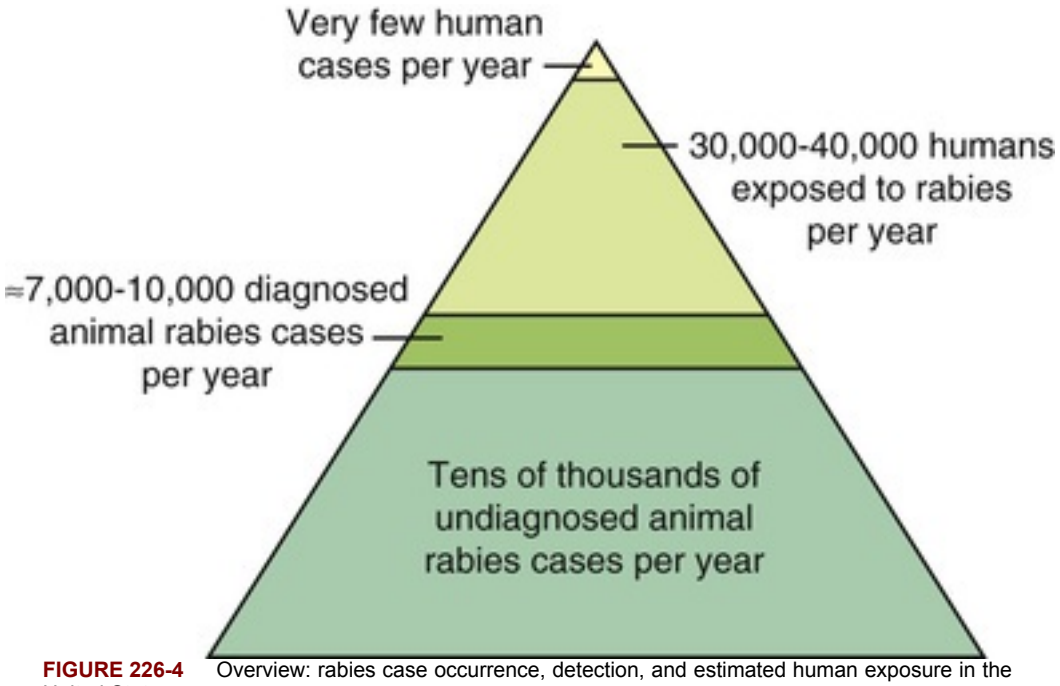

FIGURE 226-4 Overview: rabies case occurrence, detection, and estimated human exposure in the United States.

Cause and Epidemiology

The term *rabies* describes an acute fatal disease of the nervous system caused by viruses in the genus *Lyssavirus,* family Rhabdoviridae. The viruses are bullet-shaped and enveloped with a negative-sense, single-stranded genome. In addition to these rabies viruses, the *Lyssavirus* genus has six additional recognized members and four newly described members. The rabies-related Lyssaviruses are Lagos bat, Mokola, Duvenhage, European bat Lyssaviruses 1 and 2, Australian bat Lyssavirus and the Eurasia bat viruses: West Caucasian, Irkut, Aravan, and Khujand Lyssaviruses. The viruses are perpetuated in Chiroptera (bats) and Carnivora. Mammals are susceptible to rabies in varying degrees; the disease does not occur in amphibians, reptiles, birds, or invertebrates.

During 2013, 49 states and 4 other jurisdictions reported 5,865 cases of rabies in animals and 3 cases in humans to the Centers for Disease Control and Prevention (CDC). This was a 4.8% decrease from the 6,162 rabid animals and 1 human case reported in 2012. About 92% of the cases were in wildlife and 8% were in domestic animals. Relative contributions by the major animal groups were as follows: 1,898 raccoons (32.4%), 1,598 bats (27.2%), 1,447 skunks (24.7%), 344 foxes (5.9%), 247 cats (4.2%), 86 cattle (1.5%), and 89 dogs (1.5%). One human, from Maryland, was determined to have been infected via organ transplantation. Infection in the organ donor, a North Carolina resident, was retrospectively diagnosed. Both the donor and the recipient were infected with the raccoon rabies virus variant. A third human report, from Texas, involved a Guatemalan resident who was detained while crossing the US border. The infection was determined to be caused by a canine rabies virus variant that circulates in Central America. On a national level, the number of cases reported in 2013 had decreased from 2012 among cats, cattle, raccoons, bats, and skunks. The number increased for dogs and foxes. The United States remains free of dog-to-dog transmission of canine rabies virus variants. The 5% increase in the number of rabid dogs was likely due to infections from local wildlife sources.

The rabies viruses in North America are associated with wildlife and are perpetuated mainly through animal-to-animal transmission within a single reservoir species. The epizootiologic patterns of "spillover" to other species are strongly influenced by the ecology of the reservoir species and the co-occurrence of susceptible wild or domestic mammalian hosts. There are four major geographic areas within North America where rabies is transmitted primarily among skunks or raccoons. The raccoon rabies virus variant is found from Florida to Maine and into Ontario and New Brunswick, Canada, with extension westward to the

Appalachians and Ohio. Throughout the mid-western United States, there are two distinct skunk-associated viruses termed *North-Central* and *South-Central skunk rabies* virus variants. Another skunk rabies virus variant is found in southern California. The emergence and establishment of a rabies virus variant previously associated with Big Brown bats *(Eptesicus fuscus)* is transmitted among skunks in the Flagstaff area of Arizona. Rabies virus variants have been identified in Texas and southern Arizona gray foxes and a coyote/dog rabies virus variant from Mexico has been identified in Texas. A variant of rabies virus is found in Alaskan and Canadian arctic foxes and another variant identified in Puerto Rico mongooses (see Figure 226-3). Superimposed and extending beyond these geographically distinct sources are the numerous rabies virus variants found in various species of insectivorous bats.

In the United States, cats with rabies are seen 3 times more commonly than dogs (Figure 226-5).[1] Cats are less likely than dogs to be vaccinated against rabies, they are more likely to roam outdoors, and they are more likely to be outdoors at night. These factors contribute to increased likelihood of encounters with reservoir species—for example, with skunks, raccoons, or bats. Livestock occasionally develop rabies, which has potential public health impact if the animal was in contact with the public on farms, petting zoos, competitions, or through the sale of raw products. Exotic or native wildlife are at risk for exposure unless conscientiously avoided while considering extra-label use of animal rabies vaccines.

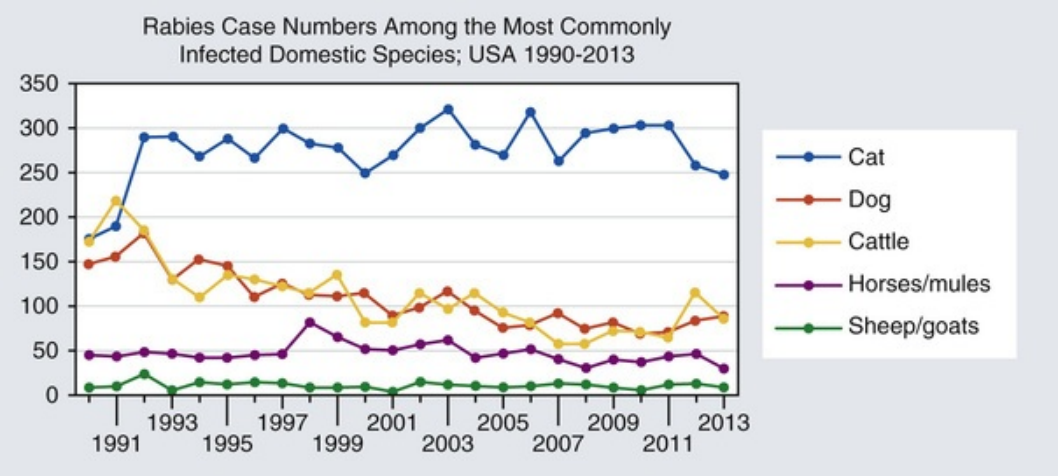

FIGURE 226-5 Rabies case numbers among the most commonly infected domestic species, United States, 1990-2013.

Exposure and Related Considerations

Natural Transmission and Vaccination Status

The predominant and natural route for rabies virus transmission is via bite wounds.[2] Rabies virus infection, in a reservoir host, causes unique behavioral changes that may favor transmission. For example, infection may cause an adult animal to sound like a juvenile, attracting other animals. In particular, those of the same species may be more likely to investigate the vocalization source, enhancing chance for bites and transmission. In one study, 13 of 264 rabid dogs (4.9%) and 22 of 840 rabid cats (2.6%) had histories of having received rabies vaccination. Of these, 2 dogs and 3 cats were classified as "currently vaccinated"; 1 dog and 5 cats had received 2 rabies vaccines in their lifetime. These results suggest that rabies is uncommon in vaccinated dogs and cats but can occur. Veterinarians should include rabies in the differential diagnosis for any dog or cat with clinical signs, regardless of vaccination history. Continued surveillance is imperative to document vaccination failure and to identify trends in vaccination failure.

Contact Transfer

Contact transfer of rabies via animate or inanimate objects has not been found to cause infection. Transmission of rabies was demonstrated experimentally when freshly collected saliva from an infected dog was "painted" on a wound of another dog that had been inflicted by investigators, more than 100 years ago.

Thus, contamination of an open wound with infectious saliva or tissue from a rabid animal is clearly an exposure to rabies. Inadvertent nosocomial transmission of rabies has occurred via corneal, organ, or vascular transplantation from people infected and dying with rabies without the condition being recognized until the recipients became ill and died. Infection via oral exposure or ingestion is not common. However, such a mode of transfer could occur if a predator with an oral wound (a site of viral entry) consumes any portion of a rabid animal. Virus is inactivated by stomach acidity.

Aerosolization

The natural history of rabies virus transmission does not rely upon aerosolization, although artificially created aerosols cause serious risk of infection. For example, two laboratory workers were infected after manipulating rabies virus–laden material and inadvertently forming an infectious aerosol. Conditions that allow aerosolization of rabies viruses are stringent and would be rare in nature. The greatest potential for this to take place is in humid, cool, small caves occupied by high densities of a natural reservoir species—for example, the Mexican free-tailed bat *(Tadarida brasiliensis).* These bats live in dense colonies. If active rabies infects even a small percentage of the several million bats in a colony, tremendous quantities of virus-laden droplet secretions descend from bats roosting on cave ceilings and walls. People entering such caves are exposed to rabies virus through bites, inhalation, contamination of mucous membranes, or open wounds. Therefore, appropriate precautions (immunization, clothing, respiratory, etc.) are vital.

Other Exposure-Related Considerations

For people, contact with infectious material on intact skin is not considered "an exposure to rabies." Thus, petting a rabid animal does not constitute an exposure to rabies.[2] The assessment of exposure risk from a contact encounter of a pet with a wild animal or other suspect- or proven-rabid animal may be difficult. Close contact of a pet or other animal with a suspect- or proven-rabid animal is, in most cases, considered a "potential exposure" by local or state public health professionals. The authority for determination of whether a domestic animal experienced a potential exposure to rabies varies by jurisdiction. Generally, a known bite from or direct contact with a potential or proven-rabid animal is considered an exposure to rabies. Other, less clear but still risky, scenarios include: (1) an animal returns from unsupervised activity with a wound compatible with a bite; (2) an animal returns from unsupervised activity smelling of skunk (especially in a skunk or raccoon rabies enzootic area); (3) sounds of animals fighting are overheard by people who suspect their pet was involved; and (4) a dead animal (especially a high-risk species such as a raccoon, skunk, or bat) is found in the vicinity of the pet. Even cats maintained indoors are at risk for exposure if a bat or other wild animal enters the home. Some "indoor" cats do roam outdoors on occasion. Pet owners should be encouraged to routinely examine their animal companions for wounds, especially following any unsupervised activity outdoors. Any wound should be assessed and treated by a veterinarian.

Rabies viruses are relatively fragile. Once saliva or contaminated tissue has dried, the material is no longer infectious. The envelope bilayer of virions is readily disrupted by commonly used disinfectants. If a currently vaccinated animal is potentially exposed to rabies, the Compendium of Animal Rabies Control indicates that a booster rabies vaccination should be administered as soon as possible and then the animal should be observed for 45 days (see Figure 226-7).[3] Observation periods may vary by locality and observation is imposed as a precaution. If a rabies exposure to a currently vaccinated animal is recognized in a timely manner and treated with local wound cleansing and a vaccine booster, the chance of vaccine failure is minimized. If a failure were to occur, clinical signs of rabies would have the highest likelihood of occurring within the 45-day observation period.

If an unvaccinated animal or one whose vaccination status is outdated is potentially exposed to rabies, euthanasia is recommended to prevent rabies. If an owner refuses, a quarantine of 6 months is imposed. It is extremely unlikely for rabies to manifest after this length of time. Quarantine conditions are determined by local or state authorities. An updated Compendium of Animal Rabies Control will likely include another option for managing dogs and cats outdated on rabies vaccination status: immediate wound cleansing, obtaining a blood sample, rabies booster administration, and collection of a second blood sample 5-7 days later (see Figure 226-7). The blood samples should be evaluated for neutralizing rabies antibodies. In a pilot study, a robust anamnestic response was observed in all animals, regardless of the time from previous vaccination.[4] Results to date are supportive. This option will help avert the unneeded euthanasia of many dogs and cats potentially exposed to rabies, while also protecting the public.

Clinical Signs

The initial clinical signs of rabies are often nonspecific and may include general lethargy, inappetence, diarrhea and/or vomiting. The clinical course is persistent and progressive, with daily, if not hourly, irreversible deterioration. Changes in behavior may be among the first clinical signs, consisting of episodic mild-to-dramatic changes. An animal may become more reclusive or attention-seeking. It may unpredictably and intermittently attack animate (humans or other animals), inanimate, or unseen objects (e.g., humans report hallucinatory episodes; animals may appear to be "snapping at flies"; see ch. 9). Rabies is neurotropic and may result in irritation or paresthesias at the site of initial infection, even if the wound has healed. A combination of increased volume of saliva and a decreased ability to swallow may cause profound contamination of the mouth, chin, and forelegs with potentially infectious saliva. Cranial nerve involvement may be focal and unilateral, such as anisocoria, facial paralysis, tongue paresis, or altered phonation. As the condition progresses, unpredictable episodes of biting may be invoked by auditory, visual, or tactile stimuli. Aggression may escalate to self-mutilation. In the final stages, most animals become profoundly moribund.

Pathogenesis

Once an animal potentially has been exposed to rabies, the probability of the animal becoming infected depends upon the individual host, host species, rabies virus variant, amount of virus, severity and route of exposure. Multiple deep bites to the head and face from a proven-rabid animal would be more likely to cause infection than a superficial wound in a distal extremity. Regardless, any potentially exposed rabies-naïve animal is at risk for developing the condition any time within a 6-month period following exposure. Virus is introduced into tissue via bites from the infected host (Figure 226-6). Only limited amounts of viral replication take place locally, however.

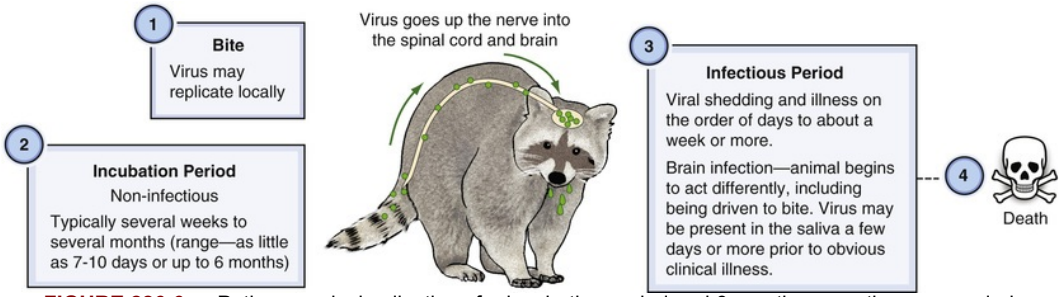

FIGURE 226-6 Pathogenesis: implications for incubation period and 6-month quarantine versus viral shedding and 10-day observation period.

At present, there is no reliable method to determine exposure or probability of infection. The virus is highly neurotropic; there is no period of viremia or of shedding via the urogenital or gastrointestinal tracts. Timing from infection of local neurons at the bite location to the time virus reaches the central nervous system (CNS) is not predictable. The incubation period is variable and is generally inversely related to virus dose and severity of exposure. Most infected animals become clinically "rabid" within weeks to a few months of exposure. Based on experimental and field data, a 6-month quarantine (or euthanasia to prevent the development of rabies) is imposed on exposed, unvaccinated (or outdated) domestic animals. This is the likely maximum incubation period. Once virus reaches the CNS, infection usually spreads quickly along multiple neuronal tracts to all major organ systems. Large numbers of virus are produced in the salivary glands, leading to virus in the saliva. The clinical period is on the order of days rather than weeks. Profound neuronal dysfunction occurs and, even with assisted preservation of an airway and ventilation, may manifest as autonomic instability and death.

Traditional pathogenesis studies have been conducted in dogs, cats, and ferrets. These studies provide the basis for a 10-day observation period (Figure 226-7). If a healthy dog, cat, or ferret bites or otherwise potentially exposes a person or animal to rabies, that animal, regardless of vaccination status, should simply be observed for 10 days. If the animal remains alive and well throughout the 10 days, there is little risk of rabies having been transmitted. If viral shedding and transmission had occurred during the bite, the biting animal would have signs of clinical rabies (sometimes including acute death) within the 10 days. If an animal develops clinical illness compatible with rabies (or dies or is euthanized) during the 10-day period, the body should be tested for rabies. This determines need for post-exposure prophylaxis for exposed people and

animals. If a bite takes place or if a person is exposed in another manner, risk of transmission is assessed on local transmission patterns, severity, and other related factors. Local and state public health authorities may allow extrapolation of data on which the 10-day observation is based, to domestic livestock and exotic hooved stock and impose a prolonged observation period of up to 30 days. If these animals remain well, the potentially exposed person does not need to undergo post-exposure prophylaxis. The animal may still develop clinical rabies in the future, but was not infectious at the time of biting or other exposure to the person.

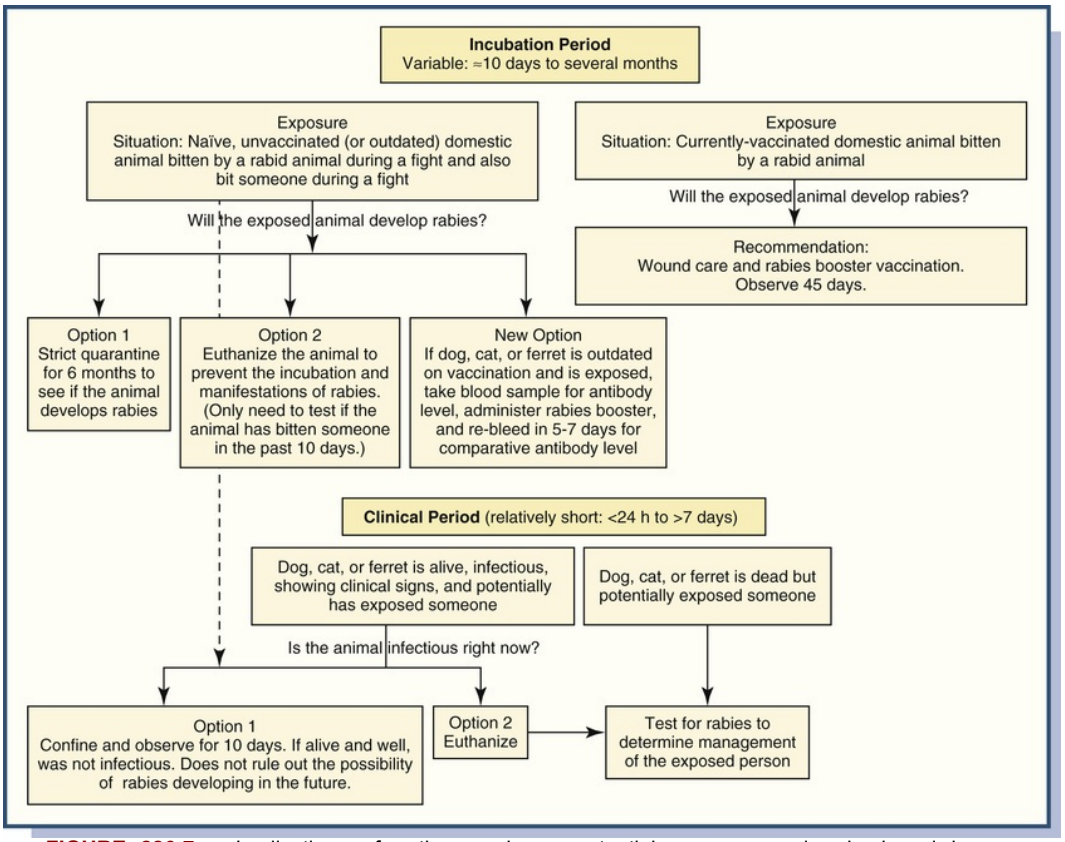

FIGURE 226-7 Implications of pathogenesis on potential exposure and animal and human management.

Diagnosis

The direct fluorescent antibody (dFA) test is the gold standard for rabies diagnosis. A definitive result is obtained through postmortem testing since a full cross-section of fresh brainstem and cerebellum is required by the National Standard Protocol for diagnosis of rabies.[2] Historically, rabies diagnosis was based on special silver-based staining (Seller's stain) to detect Negri bodies when applied to formalin-fixed brain tissue. Although specialized immunohistochemical tests for rabies may be performed at reference laboratories, the more sensitive gold standard dFA test requires fresh brain tissue. When laboratory testing for rabies is necessary, brain material fixed with formalin should be avoided as it delays definitive diagnosis. Delayed diagnosis is highly undesirable. It may lead to starting rabies post-exposure prophylaxis in a person with its expense and risk of adverse events, while waiting for a definitive answer.

Treatment

There is no medically recognized treatment for rabies. Once clinical signs are present, the disease is fatal. There are extremely rare exceptions.

Prevention

Pre-Exposure Vaccination and Exposure Management

The Compendium of Animal Rabies Control is updated and published annually.[3] It is the guiding document on animal rabies control in the United States. Pre-exposure vaccination of domestic animals, with booster vaccination if exposed, is an effective method of disease prevention. Although no vaccine is 100% effective, rabies vaccines are licensed only when a majority of vaccinated test group animals survived a lethal rabies virus challenge that killed the majority of the control (unvaccinated) group. The greatest risks for rabies in a vaccinated animal occurs: (1) when the vaccine coverage period has expired; (2) when the animal is young and has received only a single vaccination; (3) when a severe exposure has occurred; and (4) when the potential exposure is not recognized, no primary wound care is given, and no post-exposure booster vaccination is administered. Rabies is prevented in most exposed animals if currently vaccinated, if wound care consists of copious flushing to reduce probability of productive infection, and if a booster rabies vaccination is administered. As a precaution, the animal should also be confined and observed for as long as 45 days.

Prevention of rabies in wildlife is conceptually achievable through oral vaccination.[5] The greatest successes have been achieved in rabies control of red foxes in Europe and Canada. The practicality of oral vaccination depends upon: (1) the ease of orally vaccinating a particular species; (2) population densities; (3) ecologic characteristics (e.g., family groups with dominant animals interfere with vaccinating all equally); and (4) accessibility of the target population to efficient bait distribution methods and constraints near human population densities. Novel biologics are often required. Veterinarians may be consulted when domestic animals contact or consume baits distributed free-choice for oral wildlife vaccination. It is ideal for veterinarians to be familiar with wildlife vaccination projects and the associated biologics as they may pose a risk for infection and adverse events in uniquely susceptible humans and domestic animals.[6,7]

According to the Advisory Committee on Immunization Practices, pre-exposure rabies vaccination should be offered to persons at frequent or high-risk for potential rabies exposure, such as veterinarians and their staff, animal handlers, and some laboratory workers.[2] Pre-exposure vaccination also should be considered for persons whose activities bring them into frequent contact with rabies virus or potentially rabid bats, raccoons, skunks, cats, dogs, or other species at risk for having rabies. Persons in the frequent-risk group should have a serum sample tested for rabies virus neutralizing antibody every 2 years. If the titer is less than complete neutralization at a 1 : 5 serum dilution by the rapid fluorescent focus inhibition test, the person should receive a single booster dose of vaccine. If vaccinated persons are exposed to rabies, they are considered immunologically primed against rabies and simply require post-exposure prophylaxis (i.e., vaccination boosters on days 0 and 3).

Post-Exposure Management

Post-exposure rabies prophylaxis of rabies-naïve humans is practiced with essentially 100% success when administered promptly and appropriately. The practice consists of prompt wound cleansing, infiltration of rabies immune globulin of human (or equine) origin, and 5 IM doses of vaccine administered on days 0, 3, 7, 14, and 28. In theory, this approach could be applied to naïve, exposed animals and has been experimentally successful in dogs.[8] However, the global supply of human rabies biologics is limited. Insufficient vaccine supplies and their cost limits deployment of the ideal treatment approach. About 55,000 people are estimated to die each year from rabies, mainly in Asia and Africa. While these strategies could be used to prevent rabies in exposed domestic animals in the United States when owners may have neglected to have them vaccinated, it is far safer and less expensive to educate the public regarding the importance of pre-exposure vaccination of animals. This allows biologics to be available for human rabies prevention, especially in regions of the world with continuing human mortality.

Vaccination Requirements in Travel

Humans and animals may travel extensively, increasing risk of disease introduction. Despite extinction of dog-to-dog types of rabies viruses through enforcement of stray dog control measures and mandatory vaccination, risk of reintroducing related variants remains a real and compelling reason for continuing to require vaccination of domestic animals, especially dogs. Even though vaccination of an individual animal simplifies exposure management of endogenous wildlife rabies virus variants, required vaccination of the population provides a measure of biosecurity against potential introduction of exogenous canine rabies virus variants.

Recently, young dogs from Puerto Rico, Thailand, India, and Iraq have been moved to Massachusetts, California, Washington, Alaska, and New Jersey. These dogs, exposed to rabies prior to traveling, demonstrate the risk of moving an infectious disease from place to place.[9] Risk of disease translocation can be mitigated through carefully crafted requirements for animal identification, vaccination, serologic monitoring, and advanced planning for a risk-reducing waiting or quarantine period. The most critical component of risk mitigation is education of animal owners and other members of the public as to the importance of these requirements for the prevention of rabies in domestic animals and the prevention of human exposure to rabies from domestic pets and livestock.

Like many zoonoses and other emerging infections, rabies control and prevention requires the cooperation of animal control personnel, law enforcement, environmental conservation or natural resource agency personnel, veterinarians, diagnosticians, public health professionals, physicians, and others. Responsibilities start locally and on the state level. Rules and regulations pertinent to rabies control may exist under the purview of public health, agriculture, or, less commonly, wildlife agencies. With the majority of rabies cases now in a variety of wildlife species, animal control officers in some localities have been trained and authorized to manage a variety of domestic and wildlife species, not just dogs and cats. At present, a majority of the diagnostic, educational, epidemiologic, and rabies control and prevention responsibility is borne by public health agencies. Close coordination between multiple local, state, and federal entities is necessary for updating current regulations and being prepared for disease emergence or reintroduction, be it unintentional or intentional. This is done through the improvement and practice of comprehensive prevention and preparedness strategies. The need for an accessible, interactive, real-time, geographic information systems–based tool is critical for timely display of disease occurrence, planning of interactions, and assessment of disease prevention strategies. It will also be a powerful tool for spatiotemporal analysis of land-use features and their interaction with intensity and occurrence of rabies and other diseases and environmental conditions, as well. Diligent attention and dedicated effort will be required to maintain and indeed, even advance, emerging and zoonotic disease control, with rabies as a tangible "best-practices" template, beyond the major advances made in the last 50 years.

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CHAPTER 227

Canine Infectious Respiratory Disease

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Client Information Sheet: Kennel Cough

Background

Canine infectious respiratory disease (CIRD), also known as "kennel cough" or infectious tracheobronchitis, is a clinical syndrome of multifactorial etiology (see ch. 240-242). Several pathogens have been associated with the disease complex, with canine parainfluenza virus (CPIV), canine adenovirus type 2 (CAV-2) and canine herpesvirus 1 (CHV-1) traditionally considered the main viral causes, often in conjunction with or preceding *Bordetella bronchiseptica* infection.[1-3] Clinical signs such as coughing, nasal discharge and dyspnea are rarely associated with a single pathogen and more often attributed to multiple agents which act sequentially or synergistically to cause disease.

There are several multivalent vaccines which offer protection against these known pathogens (see ch. 208); however, outbreaks of respiratory disease occur in dogs despite routine vaccination, suggesting a role for other pathogens in CIRD.[4] Research into the causes of CIRD has revealed a number of additional pathogens, but it should be remembered that they are only part of a multifactorial process that also includes host factors (stress, immune status, previous exposure) and environmental conditions (overcrowding, poor ventilation) which all contribute to the clinical expression of CIRD.

Etiology and Epidemiology

Viruses

Canine Parainfluenza Virus (CPIV)

CPIV is an enveloped, single-stranded RNA virus in the *Paramyxoviridae* family. CPIV is the most commonly recognized viral pathogen associated with clinical CIRD. A recent study identified positive CPIV tests in almost 38% of dogs with acute respiratory signs. There has been almost no substantive published research on CPIV in the last few decades, despite its worldwide prevalence as a viral component of CIRD. This is particularly interesting as vaccination, both as part of a core vaccine and a specific "kennel cough" vaccine, is routinely performed, suggesting the virus is highly variable and/or current vaccines are not particularly effective.

Canine Adenovirus 2 (CAV-2)

CAV-2 is a non-enveloped double-stranded DNA virus in the *Adenoviridae* family that is genetically and antigenically related to CAV-1. Although there are some geographic variations in prevalence, CAV-2 is seldom isolated from dogs with CIRD in Europe, perhaps due to effective vaccination strategies. Only one CAV-2 PCR-positive dog was identified among 90 healthy controls.[5] This mirrors a previous longitudinal study within a rehoming kennel which failed to identify a single positive case of CAV-2 in any dog with CIRD.[6]

Canine Herpesvirus 1 (CHV-1)

CHV-1 is an enveloped, double-stranded DNA virus in the *Herpesviridae* family. Serology surveys have demonstrated higher viral prevalence in kenneled dogs than household dogs in Europe, but few studies have documented the prevalence in dogs in the United States. Although controversial and not clearly defined,

CHV may have a secondary role in CIRD, with activation of viral replication induced by more virulent respiratory pathogens. In one study, almost 13% of dogs with CIRD were positive by PCR for CHV; however, more recently the incidence of CHV as a respiratory pathogen seems to be greatly reduced, with no cases reported in some studies.[5,6]

Canine Distemper Virus (CDV)

CDV was once considered a component of the CIRD complex, but this multi-systemic morbillivirus is capable of causing fatal disease in its own right and is not grouped with the other viral causes of CIRD. Vaccination is widely practiced in much of the Western world (see ch. 208) and the incidence of the disease in dogs is reduced (see ch. 228).

Canine Respiratory Coronavirus (CRCoV)

CRCoV is a large, enveloped, single-stranded RNA virus in the *Betacoronavirus* genus of the *Coronaviridae* family. It is most closely related to bovine coronavirus (BCoV) and human coronavirus OC43.[7] CRCoV is serologically and genetically distinct from canine coronavirus (CCoV), an etiological agent of enteric disease, although pan-tropic CCoV strains have been identified.[8] The discovery of CRCoV in 2003 was prompted by the apparent lack of protection provided by commercially available vaccines to kenneled dogs who developed CIRD despite a rigorous vaccination regime.[9] A strong association was shown between exposure to CRCoV and the development of CIRD in dogs entering a kennel. Since the initial report, serological or PCR-based surveys have revealed CRCoV is the second most prevalent virus in CIRD, after CPIV. About 50-60% of dogs in North America and 20-40% of dogs in Europe have antibodies to CRCoV.[10,11] In one study, CRCoV was detected in almost 10% of dogs with acute CIRD.[5]

Canine Influenza Virus (CIV)

CIV was first detected in racing Greyhounds in Florida in 2004.[12] Genetically, this single-stranded RNA virus, part of the *Orthomyxoviridae* family, is most closely related to equine influenza virus H3N8, suggesting direct transmission from horses to dogs.[12-14] CIV is transmitted directly from dog to dog and antibodies are detected widely in dogs across the United States.[13,15] Seropositivity to CIV is as high as 50% in at-risk dog groups, those in multi-dog households or rehoming kennels, and can spread rapidly among immunologically naive animals regardless of age.[16] Evidence of infections and even antibodies to CIV are distinctly lacking outside North America.

Strictly speaking, CIV refers to infection with H3N8, but other influenza subtypes have been detected in dogs. In 2007, in South Korea, a number of outbreaks of respiratory disease in kenneled dogs was attributed to avian H3N2 influenza. Subsequently, a novel rearrangement between pandemic H1N1 and canine H3N2 in Korean dogs resulted in the novel and potentially more pathogenic H3N1 CIV.[17,18] Perhaps most worrisome is the recent demonstration that the low pathogenic avian influenza virus, H5N2, is capable of dog-to-dog transmission, causing mild clinical signs of respiratory disease and demonstrating that dogs can play a role in transmission and spread of influenza viruses.[19]

Canine Pneumovirus (CnPnV)

CnPnV is a single-stranded RNA virus in the *Paramyxoviridae* family, isolated from kenneled dogs in the northeastern United States with acute respiratory disease in 2010.[20,21] CnPnV is related to human and bovine respiratory syncytial virus, but shares closest homology with murine pneumovirus. Since its discovery, CnPnV has been detected in kenneled dogs in 8 US states and, recently, was identified as a cause of CIRD in the United Kingdom and Italy.[21-23] Extensive serological testing, surveillance surveys, and pathogenesis studies are needed to determine the prevalence of CnPnV globally, and to fully establish an association with clinical disease.

Bacteria

Bordetella Bronchiseptica

B. bronchiseptica, a Gram-negative, aerobic coccobacillus, is a known contributor to CIRD, but also is considered a normal inhabitant of canine upper respiratory tracts. Although capable of acting as a primary pathogen, the bacterium more commonly is recognized as a secondary pathogen, complicating otherwise

mild and often self-limiting viral infections. In one study, *B. bronchiseptica* was isolated from about 80% of dogs with acute respiratory disease, but also from about 45% of healthy dogs.[5] Most dogs with CIRD are co-infected with the bacterium and CPIV. Despite years of specific and widespread vaccination, co-infection with these two pathogens remains the principal cause of CIRD worldwide.

Mycoplasma Cynos

Mycoplasmas are members of the class Mollicutes, unique bacteria because they lack a cell wall and they are the smallest living organism capable of independent existence. *Mycoplasma cynos* was first isolated from the lungs of a dog with pneumonia in 1972.[24] Since then, limited data are available regarding prevalence, pathogenesis and nature of the immune response after *M. cynos* infection. Mycoplasmas are regularly isolated from both diseased and healthy dogs; however, *M. cynos* is the only mycoplasma significantly associated with respiratory disease.[25] *M. cynos* has been isolated from several dogs with CIRD, but its role in CIRD is not well understood.[26-29]

Streptococcus equi subsp. *Zooepidemicus*

S. zooepidemicus is a Gram-positive coccus and is a recognized cause of sporadic disease in dogs. *S. zooepidemicus* is a beta-hemolytic, Lancefield group C bacterium. It is distinct from group G bacteria such as *Streptococcus canis,* commonly isolated as commensal organisms from dogs. While there are occasional reports of the bacterium causing chronic nasal discharge and rhinitis, it is more frequently associated with acute hemorrhagic, fibrinosuppurative, sometimes fatal, bronchopneumonia in kenneled and racing dogs from a number of countries.[30-35] The prevalence of the bacterium in the canine respiratory tract and whether it is a true cause of CIRD, and/or a primary pathogen in its own right, remains to be determined.[36]

Pathogenesis

All the described respiratory viruses are transmitted by oronasal exposure through direct contact with virus-contaminated respiratory secretions and environmental fomites. Transmission can follow inhalation of aerosolized respiratory droplets generated by sneezing or coughing. CHV-1 is also transmitted in genital secretions and transplacentally. The incubation period ranges from 3 to 10 days, and virus shedding in respiratory secretions generally ceases within 10 days of primary infections, or in the case of CHV-1, reactivation of latent infection.[37,38] Transmission of the bacteria is less well characterized and while *Bordetella* and various mycoplasmas can be carried within the upper respiratory tract of healthy dogs, the role of carriers in *S. zooepidemicus* infections is far from clear.

In most dogs with CIRD, initial infection takes place in the ciliated epithelial cells (and sometimes goblet cells) of the upper respiratory tract and, for most uncomplicated viral infections, seldom spreads further than the nasal cavity, sinuses, trachea and perhaps bronchi. Detailed histopathological and functional studies of the effects of CIRD viruses on the canine respiratory tract have only been performed for CRCoV; however, it is expected that the other viruses result in similar changes. Viral replication causes loss of coordinated beating of cilia, followed by ciliostasis, and later loss of cilia.[39] In primary viral infections, dogs can be asymptomatic or have mild clinical disease consisting of rhinitis, sinusitis, tracheitis, and bronchitis, or a combination of these. CIV is an exception in that it also seems to result in a greater incidence of lower respiratory tract involvement and infected dogs develop necrotizing tracheitis, bronchitis and in some cases also bronchiolitis and pneumonia.[40]

In uncomplicated viral infections, ciliated cells are replaced from a reserve stem cell population. This process takes time and often the ciliated cells are replaced initially by goblet cells (hyperplasia) before the differentiation pathway allows production of ciliated epithelium. It is during this early phase of the viral infection that the main defense of the upper respiratory tract, the "mucociliary escalator," is rendered ineffective. This can allow secondary pathogens, principally bacteria, to invade and establish infection.

B. bronchiseptica produces a range of toxins to aid colonization and infection, such as tracheal cytotoxin that induces ciliostasis, and adenylate cyclase that inhibits neutrophil phagocytosis. Infection with CPIV or CRCoV creates an environment in which *Bordetella,* which may be carried harmlessly in the upper tract, colonizes and invades. In essence, it is a pathogenic synergy that has evolved unparalleled in veterinary medicine. *S. zooepidemicus* appears to act somewhat differently and, similar to CIV, is able to cause much more severe, acute or even peracute and rapidly progressive respiratory disease. It is likely that as yet unidentified exotoxins produced by the bacteria and the host's overly exuberant immune response to these toxins lead to

the often fatal disease which characterizes outbreaks involving this bacterium.

Clinical Presentation

The principal reason for veterinary consultation, and the dominant physical exam finding, typically is a cough that can be very loud, persistent, and usually has been noted for a few days (see ch. 26). The medical history classically includes a new exposure to other dogs, such as in a boarding kennel or dog park. Medications, whether by prescription or over-the-counter, usually have not produced any benefit. Appetite can be decreased slightly but anorexia of 24 hours' duration or longer is very uncommon except in patients showing other, more serious abnormalities to suggest systemic inflammation and/or complications such as pneumonia.

On presentation, affected dogs usually are bright, alert, and afebrile. Exceptions can include the more serious, systemic clinical syndromes described above for certain etiologies. Typically, the patient's respiratory effort and respiratory rate are normal. Pulmonary auscultation can reveal increased bronchovesicular sounds but wheezes and crackles are very uncommon. Tracheal sensitivity is a frequent finding, and a cough often can be elicited with mild tracheal palpation (Video 227-1) if it does not occur spontaneously during the exam. The intensity and sound of the cough often are much more severe (and of greater concern to the owner) than any other respiratory, or any systemic, effects of the disease. Likewise, ocular discharge is usually limited to a mild serous discharge if there is one at all. Mucopurulent discharges warrant further evaluation. Mucopurulent nasal discharge is not expected in uncomplicated cases; its presence suggests canine distemper infection (see ch. 228), secondary bacterial pneumonia (see ch. 242), or virulent disease with or without immunosuppression.

Coughing is usually not associated with significant phlegm or material produced at the end of tussive gagging. Occasionally, a small amount of white phlegm is produced. Increased expectoration suggests a deeper or more serious problem that could warrant further evaluation.

Diagnosis

The diagnostic evaluation of a dog suspected of having CIRD is adapted to the clinical severity of disease (Figure 227-1). In an otherwise healthy dog with a recent history of exposure to new dogs, and who manifests a cough and no other physical abnormalities, diagnostic tests beyond the physical exam can be deferred or excluded. Conversely, a febrile, inappetent, or lethargic patient, or a patient with concurrent illness that could predispose to immunoincompetence, or a patient with a cough of more than 1 week's duration, or a patient whose owner expresses concern beyond that which can be alleviated by the veterinarian's opinion, could benefit from orthogonal-view thoracic radiographs to rule out pneumonia, radiopaque foreign body, or other abnormalities. A complete blood count can be evaluated for a left shift and/or toxic changes to neutrophils, which would suggest systemic inflammation. A Baermann fecal examination (see ch. 81) is appropriate in geographic regions where lungworms are endemic. Advanced diagnostic testing to isolate the causative pathogen rarely is undertaken in mild cases without systemic signs. In patients with radiographic evidence of pneumonia, sampling for bacterial culture and sensitivity is warranted (see ch. 101, 240, and 242), ideally before the start of antibacterial therapy. Culture and sensitivity of nasal swab samples generally is unrewarding, due to contamination by nasal flora. Often, patients showing no other abnormalities beyond a cough are treated empirically without diagnostic testing, and the owner is instructed to return if the cough does not resolve after 7 days or at any time if additional clinical signs emerge.

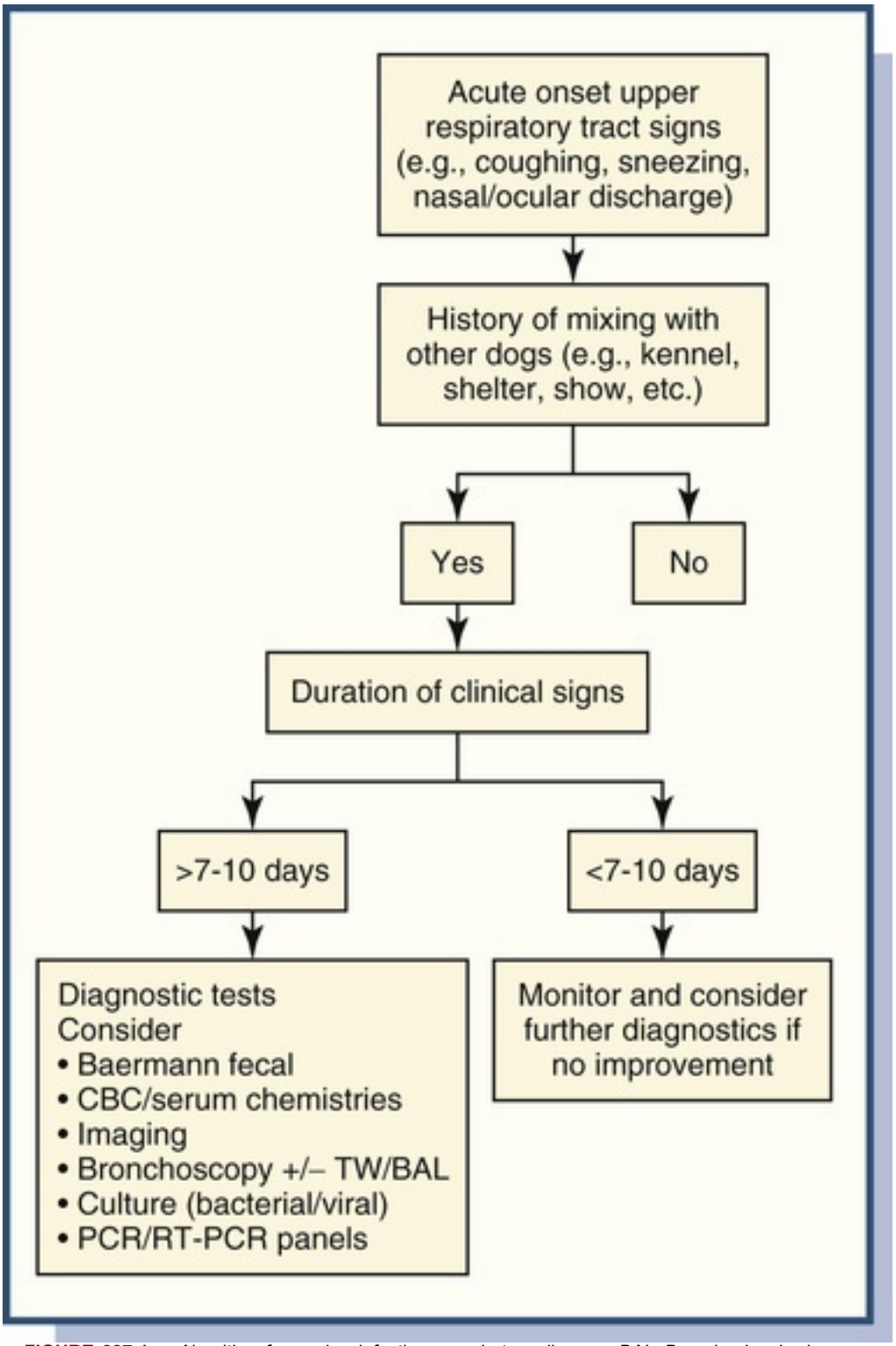

FIGURE 227-1 Algorithm for canine infectious respiratory disease. *BAL,* Bronchoalveolar lavage; *PCR,* polymerase chain reaction; *RT,* real time; *TW,* tracheal wash.

Treatment

Therapeutic options likewise are selected based on the severity of the patient's signs. Cough that is distressing to the owner and/or the patient can be treated with antitussives (e.g., hydrocodone 0.25 mg/kg PO q 6-8 h PRN) if no other clinical signs are present. Over-the-counter antitussive agents or antihistamines can be

helpful in making the owner cognizant of the problem and occasionally alleviate some of the more racking efforts at coughing, perhaps via sedation. Antibacterial therapy is controversial because *Bordetella* and *Mycoplasma* often are present in healthy dogs; their roles as pathogens in a specific case, the need for their eradication, and their susceptibility profiles, often are unproven. Doxycycline (10 mg/kg PO q 12 h × 14-21 days in adults, 7-9 days in puppies to reduce risk of dental discoloration) has efficacy against both *Bordetella* and *Mycoplasma;* minocycline, amoxicillin-clavulanate, or trimethoprim-sulfa also have been used for *Bordetella,* whereas fluoroquinolones have been used for *Mycoplasma.* The usual precautions regarding antibiotics should be recognized and fluoroquinolone use in growing puppies is contraindicated (see ch. 169). Supportive care and monitoring are implemented if needed for dogs with pneumonia (see ch. 242) or other complications.

Prognosis and Transmission Control

The prognosis for most cases of CIRD is good: the cough typically resolves within 10 days and few or no permanent changes occur. Patients with systemic signs have a more guarded prognosis due to pathogens that are more virulent, immunoincompetence, and/or the effects of progressive systemic complications.

Contagion is a very substantial concern with CIRD, as organisms can be transmissible between dogs via aerosol or fomites. *Bordetella* shedding persists for up to 3 weeks after the resolution of cough, which justifies sequestration of affected dogs for this period after illness. Except in cases of canine distemper, permanent sequelae are uncommon, but as described above, immunity against future reinfection is limited because organisms can mutate rapidly. Vaccination prior to the occurrence of clinical signs is a cornerstone of prevention of transmission (see ch. 208).

It is strongly recommended that dogs with suspected infectious respiratory disease not be kenneled or taken to dog parks where other animals' health may be compromised. Likewise, if a dog is to be exposed to such facilities, twice yearly vaccinations are recommended. Vaccination for CIRD, where available, should be administered at least 7 days before the dog is taken to a boarding kennel for the dog to be properly immunized. It is important to recognize that these vaccines are not 100% effective in preventing CIRD but they may modify or lessen the severity of the disease should it develop.

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CHAPTER 228

Canine Distemper and Other Canine Viral Infections

Thomas Wilhelm Vahlenkamp

Canine Distemper

Etiology and Epidemiology

Canine distemper is an acute to subacute systemic disease with high mortality rate in dogs and other carnivores worldwide. Affected dogs frequently develop neurologic manifestations. The causative agent, canine distemper virus (CDV), is an enveloped, single-stranded RNA virus belonging to the family Paramyxoviridae. CDV is capable of infecting a large variety of species including canids, mustelids (e.g., ferret, marten, mink, otter), and procyonids (e.g., raccoon) and large felids (e.g., lion, cheetah). Host range is defined by the viral surface hemagglutinin protein. There are six major lineages based on hemagglutinin genetic variability.[1] Each lineage contains biotypes or strains that differ in pathogenicity patterns affecting the type and/or extent of clinical signs. However, despite genetic variation, CDV isolates are serologically homogeneous. Due to the large reservoir in dogs and non-dog hosts allowing continuous exposure, especially for free-roaming dogs, CDV still is prevalent in many countries despite vaccination of dogs for more than 50 years. Although nowadays distemper is seen less commonly in veterinary practices, outbreaks occur frequently in shelter facilities. Several regional canine distemper epidemics have been documented in the past. Some of these were characterized by an unusually high morbidity and mortality, rapid spread over the country, and infections of several wild carnivore species. Molecular changes in the hemagglutinin gene are likely to be responsible for these biological features.[2]

Transmission

All ages and breeds are susceptible to CDV infection. CDV is transmitted by oronasal exposure to virus-contaminated respiratory secretions, vomitus, feces, urine, and environmental fomites. CDV also is spread efficiently by aerosols generated by coughing and sneezing, as well as aerosols of other excretions. The incubation period typically ranges from 1 to 3 weeks. Virus shedding starts within 7 to 10 days of exposure, coinciding with the hematogenous spread of the virus to epithelial and central nervous system (CNS) tissues irrespective of the severity of clinical signs. Virus is shed in all body excretions during the acute systemic disease. Dogs with subclinical infections also shed virus. Infected dogs can be contagious for up to 3 months, although shorter periods of shedding are more typical. To prevent viral transmission within a facility, infected dogs should be housed in isolation and cared for by staff adhering to strict biosecurity measures.

Pathogenesis

CDV causes systemic infection of epithelial tissues in many organ systems. Initially, the virus replicates locally in macrophages and monocytes in the tonsils, upper respiratory tract epithelium, and regional lymph nodes, reaching peak virion production by 2 to 4 days after inoculation.[3,4] The signaling lymphocyte activation molecule (SLAM, CD150) is the cellular receptor that is expressed on the surface of the cells of the immune system. Viremia occurs 4 to 6 days later, with systemic spread of virus to the stomach, small intestine, spleen and hepatic macrophages, bone marrow, and other lymphoid tissues. The widespread increase in virus production is associated with fever, lymphopenia caused by lymphocytic apoptosis, and immunosuppression. Further hematogenous spread of the virus is responsible for infection of epithelial cells in multiple organs, including the eyes, skin, and CNS. Virus shedding from the respiratory, gastrointestinal, and urogenital tracts coincides with epithelial infection. Virus persists for long periods of time in the uvea, uroepithelium, epidermis, and CNS.[1]

After 9 to 14 days, the clinical outcome of infection depends on the host's immune response. Viral infection in bone marrow and other lymphoid tissues can result in profound and protracted immunosuppression due to T-cell depletion and other undefined mechanisms.[1] In convalescing puppies, cell-mediated immunosuppression can persist after CDV infection for more than 10 weeks. Dogs with poor immune responses develop viral infection of several additional tissues, including skin and other glandular and epithelial organs. These animals generally exhibit severe clinical signs and are likely to die. Animals that do recover from the initial clinical signs maintain virus in tissues and are likely to develop clinical signs of CNS disease subsequently. In animals that mount an intermediate level of immune response, mild or clinically silent infection may develop, with virus persisting in the lungs, skin, or CNS (Figure 228-1). These animals can develop signs of CNS disease or can undergo complete recovery. Animals that mount strong immune responses are unlikely to develop signs of systemic infection but still can develop signs of CNS disease.

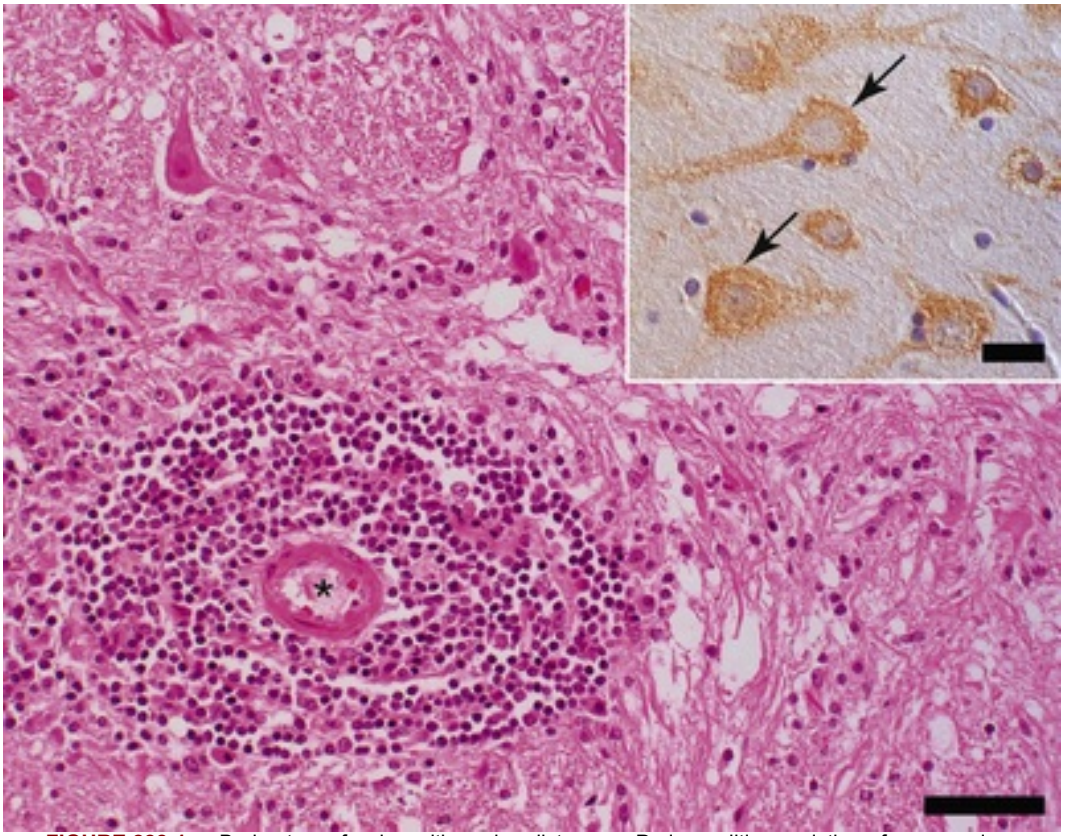

FIGURE 228-1 Brain stem of a dog with canine distemper. Perivasculitis consisting of mononuclear cells surrounding an arteriole (asterisk). Bar = 50 microns. Inset: Immunohistochemical demonstration of canine distemper virus antigen located in the cytoplasm of neurons (arrows). Bar = 20 microns. (Courtesy Dr. Denny Böttcher, Institute of Veterinary Pathology, University of Leipzig, Germany.)

Hematogenous spread of CDV into the CNS results in infection of choroid plexus epithelial cells, astrocytes, and neurons, which in general coincides with MHCII and proinflammatory cytokine upregulation. Dogs, especially the young or immune-suppressed, can develop acute demyelination attributed to direct viral injury in the absence of inflammatory reactions. Subacute to chronic CDV encephalitis appears to be a consequence of inflammatory responses to viral antigens in the CNS, with macrophage activation and release of cytotoxic mediators playing a role in destruction and demyelination of CNS cells.

Clinical Signs

The severity of the clinical course is a function of the animal's age, pathogenicity patterns for different viral strains, and immune responses.[1,3,4] Many dogs, particularly those that are older or have partial immunity, have asymptomatic infection or mild disease. Puppies are more likely to suffer from severe and protracted illness and have the highest mortality rate.

Within the first week of infection, systemic virus spread in lymphoid organs corresponds to a rise in body temperature and lymphopenia affecting both B- and T-cells. Affected dogs can be lethargic, anorexic, and dehydrated, and frequently develop conjunctivitis and respiratory signs. These include serous or mucopurulent oculonasal discharge and cough that progressively worsens if no adequate immune response develops. Viral infection of the lower respiratory tract results in pneumonia that might or might not be evident clinically but can be documented via radiographs. Viral pneumonia complicated by secondary bacterial infections can be life-threatening (see ch. 242). Infected dogs with mild clinical signs can be indistinguishable from those with other causes of kennel cough (see ch. 227). Depending on viral strain, affected dogs also can have vomiting and mucoid or hemorrhagic diarrhea from viral replication in epithelial cells of the gastrointestinal tract.

Viral infection of ocular tract epithelium can cause photophobia, anterior uveitis, and chorioretinitis. Recovered animals can have hyperreflective retinal lesions that develop from retinal atrophy and scarring, as well as keratoconjunctivitis sicca from scarring of the lacrimal glands. Optic neuritis can cause blindness or mydriasis; blindness also can result from serous retinal detachments. Production of large amounts of virus occurs in uroepithelium, including the kidneys and lower urinary tract, which can cause clinical signs associated with kidney and bladder dysfunction. Viral infection of the epidermis can result in a pustular rash and hyperkeratosis or "hardening" of the nasal planum and footpads. Infection of developing enamel buds in young puppies prior to eruption of the permanent dentition results in dental enamel hypoplasia. Some dogs, especially young large-breed dogs, are susceptible to metaphyseal osteosclerosis of long bones, which typically is not associated with lameness.

Neurologic signs can develop starting 1 to 3 weeks after recovery from systemic signs or can develop months later. Neurologic signs can develop in dogs that had no noticed evidence of systemic disease. Neurologic signs, whether acute or chronic, typically are progressive, and are the most significant factors affecting prognosis and recovery from infection. Curiously, certain features of clinical disease tend to correlate with the likelihood of developing neurologic disease. Dogs that develop pustular skin lesions are less likely to develop CNS disease, but hyperkeratosis of the nasal planum and digital footpads frequently is associated with the development of neurologic signs. Neurologic abnormalities can reflect lesions in any CNS site and include seizures, ataxia, hypermetria, paraparesis or tetraparesis, and severe cervical pain (see ch. 261 and 266). Myoclonus, either generalized or focal, is a common clinical sign and is strongly suggestive of CDV infection (see ch. 31). Hippocampal alterations can progress to the point of causing status epilepticus (see ch. 136). Puppies infected *in utero* or as neonates can develop CNS signs during the first 4 to 6 weeks of life. Abortion and neonatal death have been observed (see ch. 146 and 315).

Diagnosis

Due to the systemic infection and the variety of respiratory, gastrointestinal, and/or neurological signs, a firm diagnosis of CDV based solely on clinical signs can be difficult to achieve. Poor vaccination history might support a suspicion, but CDV also has been described in vaccinated dogs.[5,6] Intranuclear and intracytoplasmic viral inclusions can be seen in monocytes, lymphocytes, neutrophils, or erythrocytes during examination of a stained blood smear, but inclusions often disappear within 1 to 2 weeks after the onset of clinical signs. There are no pathognomonic laboratory abnormalities. Lymphopenia is the most consistent abnormality on the complete blood count. Biochemical profile abnormalities can include hypoalbuminemia and hypoglobulinemia. The cerebrospinal fluid (CSF) can have increased numbers of lymphocytes and monocytes and varying protein concentrations.[5] Dogs with respiratory disease can have interstitial or alveolar patterns on thoracic radiographs. Radiographs of long bones in lame animals can show metaphyseal lesions consistent with hypertrophic osteodystrophy. Animals with CDV-associated neurologic disease can be diagnostic challenges if there is no history or evidence of systemic signs. Abnormalities on magnetic resonance imaging (MRI) of the brains of dogs with acute CDV have been described and, though not specific, potentially could help support a diagnosis in dogs with few or no systemic signs.[7]

A definitive diagnosis of CDV hinges on the detection of viral antigen or nucleic acid in antemortem or postmortem samples, virus isolation, and serologic titers. Demonstration of viral antigen in cells on blood smears, smears from nasal, conjunctival, or pharyngeal swabs, or postmortem tissues by immunological methods such as fluorescent antibody or immunohistochemical testing confirms the diagnosis. CDV titers might not be sufficiently sensitive because they decrease beyond 3 weeks of infection.[3] Reverse-transcription–polymerase chain reaction (RT-PCR) assays are highly sensitive and specific for detection of CDV in clinical cases and can be performed on virtually any sample type, including conjunctival, nasal, and pharyngeal

swabs; whole blood; feces; urine; CSF; and postmortem tissues, particularly the urinary bladder.[8-10] However, CDV PCR assays offered by commercial laboratories do not discriminate between vaccine and field CDV strains in samples collected from dogs recently vaccinated with modified-live CDV. Duration of post-vaccine interference is variable but could be as long as 3 weeks.[10] An exception to vaccine interference with PCR testing is a recombinant canarypox-vectored CDV vaccine. Sequence analysis can discriminate between vaccine and CDV field strains.[11-13]

Serologic tests are widely available for documentation of CDV specific antibodies. However, due to profound immunosuppressive effects during acute CDV infections, the amount of antibody can be low or even remain below the detection limit for serological tests.[14] Immunofluorescent assays (IFA) are used for measuring immunoglobulin M (IgM) and IgG antibodies to CDV; detection of IgM antibodies, which can persist for 3 months, is supportive of CDV infection. The serum neutralization assay is considered the "gold standard" for quantifying total CDV antibodies. Diagnosis of recent active infection by this assay requires collection of paired acute and convalescent sera to determine seroconversion, defined as at least a fourfold increase in the antibody titer from the acute to the convalescent sample. Infection also is supported by demonstration of higher concentrations of CDV antibody in the CNS (see ch. 115) as compared with the serum, although not all animals will have CSF antibodies.[5]

Treatment

Treatment of dogs with CDV is largely supportive. Parenteral administration of fluids can be necessary in dogs with vomiting or severe diarrhea. Animals with secondary bacterial bronchopneumonia or other bacterial infections are candidates for antibiotics. In puppies, resolution of bronchopneumonia could require combinations of broad-spectrum bactericidal antibiotics administered for several weeks (see ch. 161). Seizure control with anticonvulsant drugs can be necessary (see ch. 35 and 260). Ribavirin inhibits CDV replication *in vitro,*[15] but its use has not been described in dogs. The prognosis for dogs with neurologic disease is considered guarded to poor.

Prevention

The key to CDV prevention is vaccination. CDV vaccines are considered a "core" vaccine that should be administered to all dogs (see ch. 208).[16] Maternal antibodies interfere with immunization and determine the proper time of vaccination of puppies. Transplacental uptake of maternal antibodies can range from 3-20% of the bitch's serum level. The predominant portion (approximately 80%) is absorbed in the pup's intestine from colostral antibodies mainly during the first day of life. Recommended vaccines contain high-titer, low-passage, modified-live CDV or a canarypox vector that contains CDV hemagglutinin and fusion genes. These vaccines are better able to effectively immunize dogs during the period of maternal antibody interference.[17] The canarypox-vectored CDV vaccine also is more likely to boost antibody titers in seropositive dogs compared to modified-live vaccines.[18] The duration of immunity following immunization with modified-live and recombinant vaccines is at least 3 years.[19-23] Current American Animal Hospital Association (AAHA) guidelines[16] recommend vaccinating dogs at 6 to 8 weeks of age, with repeat vaccinations performed every 3 to 4 weeks until 16 weeks of age. All dogs should receive a booster vaccine 1 year after completion of the initial series, followed by booster revaccination every 3 years. Immunization of dogs with modified-live CDV vaccine has been associated with post-vaccination complications, the most common of which is encephalitis, which can produce clinical signs of neurologic disease and variable neurological abnormalities 7 to 14 days after vaccination. However, onset of distemper-like disease shortly after vaccination is most likely due to infection with field strains of CDV prior to or at the time of vaccination, rather than disease due to reversion of modified-live vaccine strains to virulence.[1] CDV infection in previously-vaccinated dogs usually is associated with failure to induce immunity from improper vaccination schedules or improper storage of the vaccine.

In-clinic enzyme-linked immunosorbent assay (ELISA) kits can be used for measuring CDV antibodies.[24] Dogs that have recovered from CDV infection are considered immune to reinfection for long periods, most likely lifelong. Establishment of protective immunity can be determined by testing post-vaccination serum for protective neutralizing antibody titers, as serum titers correlate well with level of protection. A titer of ≥32 has been considered protective, which can vary between individual dogs and laboratory methods applied.

Besides immunization, isolation of CDV-diseased dogs appears to be the most important measure in

controlling disease spread. As an enveloped virus, CDV does not survive for long periods in the environment outside the host. The virus is susceptible to ultraviolet light, heat, and drying. Survival times are longer at colder temperatures. At near-freezing temperatures (0° C to 4° C), CDV can survive in the environment for weeks. The virus is susceptible to inactivation with a number of disinfectants such as phenolic (0.75%) or quaternary ammonium (0.3%) compounds. Routine disinfection procedures are usually effective in destroying CDV in a kennel or hospital.

Canine Herpesvirus

Etiology and Epidemiology

Canine herpesvirus (CHV) is an enveloped, double-stranded DNA virus belonging to the family Herpesviridae. The host range is restricted to domestic and wild canids. Herpesviruses have very large genomes encoding many structural and non-structural proteins involved in viral replication and modulation of the host's immune response. CHV is genetically related to other herpesviruses known in cats and horses.[25,26] CHV has a worldwide distribution. Serologic surveys in Europe have demonstrated a higher viral prevalence in kenneled dogs than in household dogs, but few studies have documented the prevalence in dogs in the United States. Although controversial and not clearly defined, CHV is considered part of a complex of pathogens causing the canine infectious respiratory disease complex (CIRD) or "kennel cough" (see ch. 227). The virus has been isolated repeatedly from dogs with respiratory disease and was found to replicate in the respiratory tract of dogs. However, clinical signs were not seen after experimental exposure. CHV might have a secondary role, with activation of viral replication induced by infection with more virulent respiratory pathogens.

Transmission

The virus is transmitted by oronasal contact with infectious respiratory or genital secretions and transplacental transmission also can occur. The source of infected material can be body excretions from young puppies, respiratory secretions from infected older dogs, or vaginal secretions from infected bitches. The incubation period for primary infection is 6 to 10 days. Virus shedding occurs for 7 to 10 days after primary infection or reactivation of latent infection.[25,26] In newborn pups, infection spreads rapidly and all puppies in an infected litter usually die. Spread of infection among older dogs appears to be slower and, even in close contact, not all dogs become infected. Fetuses can be infected *in utero* during primary infection of the pregnant bitch.

Pathogenesis

Transplacental infection during primary infection of dogs results in fetal resorption, abortion, stillbirths, or birth of weak puppies that die within days. Immunity following primary infection protects future litters. Infection of naïve puppies younger than 2 weeks old causes fatal generalized necrotizing and hemorrhagic disease. Neonatal puppies are infected by oronasal contact with the dam's infectious birth canal secretions with actively replicating virus, or via grooming by the dam. CHV first replicates in the epithelial cells of the oropharynx and tonsils. Virus subsequently enters macrophages, which allows spread to other tissues hematogenously, including the lymph nodes, spleen, adrenal glands, kidneys, lungs, liver, and CNS. The lower body temperature of neonates, in conjunction with a limited capacity to mount a febrile response, facilitates systemic spread of the virus.

Infection of older pups and adults is confined to the respiratory, ocular, or genital tract without systemic spread. Most infections are subclinical or can present as mild and self-limiting respiratory, ocular, or genital disease. Following a short replication period, CHV establishes latent infection in neurons of the trigeminal and lumbosacral ganglia, lymphocytes in the retropharyngeal lymph nodes and tonsils, and epithelial cells in the parotid salivary gland.[25,26] Reactivation of viral replication can be provoked by stress or immunosuppressive disease/therapy.

Clinical Signs

The incubation period appears to be 4 to 6 days. Bitches remain overtly healthy and milk production continues unchanged. The disease course in puppies is rapid. Infected neonatal puppies exhibit persistent crying, anorexia, signs of abdominal pain, dyspnea, and petechial hemorrhages. Most puppies in affected

litters die between 1 and 4 weeks postpartum, 24 to 48 hours after onset of clinical signs. Petechial hemorrhages in the liver, kidneys, and lungs are typical lesions observed on necropsy. Older puppies develop mild signs of respiratory disease (rhinitis, pharyngitis) with spontaneous recovery, but latent infections can emerge later as a cause of neurologic disease, with signs of ataxia, blindness, or central vestibular disease being most common. Puppies with maternal antibodies are readily infected by CHV. The infection, however, remains localized and there is no systemic clinical disease. Infection in adult dogs usually remains subclinical, but some dogs have rhinitis, pharyngitis, vaginal or preputial hyperemia, hyperplasia of vaginal mucosal lymphoid follicles, and sometimes submucosal hemorrhages. Corneal ulceration has been reported in adult dogs during natural infection with CHV,[27] while conjunctivitis occurred in experimentally infected dogs.[28] The clinical significance of CHV infections in ocular diseases is not defined, but CHV should be considered a potential cause of conjunctivitis or corneal disease after more common causes have been excluded.

Diagnosis

The diagnosis is made by observation of clinical signs in puppies of susceptible age in conjunction with necropsy lesions. Viral inclusion bodies can be observed in cells surrounding areas of necrosis and hemorrhage. A definitive diagnosis of CHV infection centers on demonstration of virus, viral antigen, or nucleic acids by PCR, electron microscopy, or immunohistochemical techniques. PCR assays also can be performed on ocular, nasal, pharyngeal, vaginal, or preputial swabs collected from older puppies and adults. Serologic testing for neutralizing antibodies confirms exposure but not necessarily active infection.

Treatment

Treatment is supportive but often ineffective at preventing neonatal losses. Injection of immune sera pooled from bitches that have had recent losses of litters might help reduce mortality during outbreaks. Keeping puppies warm and hydrated can lessen mortality in affected litters, primarily by limiting the spread of infection among uninvolved puppies.

Prevention

CHV is poorly immunogenic. Maternal antibody levels usually are low, but they suffice to protect puppies from disease (but not always from infection) for the first 2 weeks of life. Infection of older puppies usually remains subclinical. In individual kennels, CHV often is self-limiting. Dams that have lost litters to CHV infection subsequently have healthy litters; therefore, artificial insemination or caesarean sections are not considered useful approaches to limit the spread of infection. Disease outbreaks with CHV can be restricted by reducing contact with infected dogs. Currently, no vaccine is available in the United States. In Europe, a subunit vaccine licensed for pregnant dogs provides protective immunity to newborn puppies.

CHV is not stable in the environment and is inactivated by most common disinfectants such as quaternary ammonium products.

Canine Adenovirus Type 1

Etiology and Epidemiology

Canine adenovirus type 1 (CAV-1), a non-enveloped double-stranded DNA virus belonging to the family Adenoviridae, is the cause of infectious canine hepatitis (ICH). CAV-1 is closely related genetically and antigenically to CAV-2. In addition to the domestic dog, red foxes, wolves, and coyotes seem to be most sensitive. In foxes, the disease is manifested primarily as encephalitis and it does not spread as readily among wild foxes as among dogs, probably because of differences in social behavior. Gray foxes and raccoons are less susceptible and probably—like many of other members of the Canidae family—become infected but do not develop clinical signs of disease. The incidence of ICH in dogs in the United States and Europe has decreased with vaccination, although sporadic cases are identified, particularly in unvaccinated or improperly vaccinated puppies imported from countries where the disease is more prevalent.

Transmission

Infection occurs after oronasal exposure to virus-contaminated body secretions and excretions and environmental fomites. Unlike canine distemper virus, CAV-1 is not airborne. The incubation period is 4 to 9

days.[25] Virus shedding occurs during acute infection in all body secretions (saliva, respiratory) and excretions (feces, urine) and is shed in the urine of dogs that have recovered from clinical disease for up to 6 to 9 months.[25] Infected urine therefore seems to be the most important source of virus transmission.

Pathogenesis

CAV-1 causes systemic infection, with a tropism for endothelial cells, epithelial cells, and hepatocytes.[25] After exposure, CAV-1 replicates in lymphoid tissue of the tonsils and regional lymph nodes. Viremia follows 3 to 4 days post-infection, leading to infection of other tissues. Direct cytopathic effects of the virus in the liver, eyes, and kidney contribute to early clinical signs, which can become apparent in naïve dogs 4 to 9 days after exposure. Hemorrhages, which can be seen in many tissues, are the result of vascular damage after viral replication in endothelial cells. The extent of hepatic necrosis (Figure 228-2) is a function of the level of antiviral antibody present at the time of infection: animals with minimal antibody exhibit extensive necrosis that often is fatal; those with high levels of antibody exhibit minimal clinical signs; and those with intermediate antibody levels are susceptible to persistent hepatic inflammation.[25] Clinical signs of corneal edema and anterior uveitis ("blue eye") initially develop as a consequence of the inflammation following infection of corneal endothelial cells and the deposition of immune complexes (hypersensitivity reaction type III) as the antibody response to the virus increases.

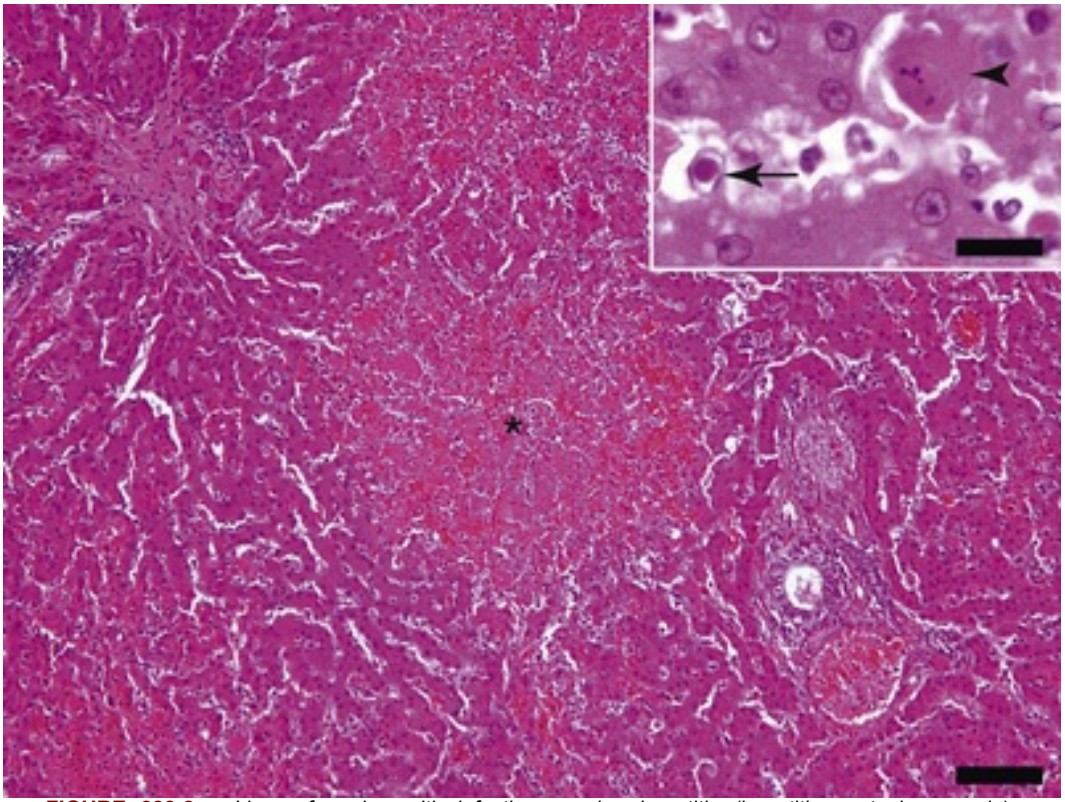

FIGURE 228-2 Liver of a dog with infectious canine hepatitis (hepatitis contagiosa canis). Centrilobular acute hepatic necrosis and hemorrhages (asterisk). Bar = 100 microns. Inset: Intranuclear viral inclusion (arrow) within a hepatocyte. A necrotic hepatocyte is indicated by the arrowhead. Bar = 20 microns. (Courtesy Dr. S. Schöniger, Institute of Veterinary Pathology, University of Leipzig, Germany.)

Clinical Signs

Dogs of all ages are susceptible to CAV-1 infection and disease; however, most dogs are infected early in life. Initial clinical signs include fever, depression, and lethargy. Later, development of signs of abdominal discomfort, mucous membrane pallor, and inflammation of the tonsils and pharynx with tonsillar and cervical lymph node enlargement occur. Leukopenia develops and persists until the febrile period is over.

Abdominal fluid and hepatomegaly can be detected in some dogs. Laryngitis, tracheitis, pneumonia, coughing, vomiting, and diarrhea occur in some. In severe cases, petechial and ecchymotic hemorrhages and epistaxis can develop from coagulation abnormalities secondary to hepatic dysfunction and disseminated intravascular coagulation (DIC; see ch. 197). Icterus is uncommon despite the presence of hepatic necrosis. Neurologic signs can be seen as a consequence of hepatic encephalopathy or CNS infection; serum bile acid or plasma ammonia concentrations, if elevated, would support hepatic encephalopathy as a cause of neurologic signs (see ch. 283). Dogs with severe disease can die within hours of showing clinical signs, whereas dogs with less severe disease can exhibit clinical improvement 5 to 7 days after onset of clinical signs. Anterior uveitis and glomerulonephritis from deposition of immune complexes can occur within a month of recovery.

Diagnosis

The diagnosis of ICH usually is based on finding evidence of acute hepatic disease in a dog with a poor vaccination history. No specific laboratory abnormalities are pathognomonic for CAV-1 infection.[25] There can be leukopenia or leukocytosis depending on whether the patient is seen early or later in the course of disease, respectively. Thrombocytopenia is possible and could contribute to bleeding disorders in the setting of DIC or abnormal platelet function. Increases in serum alanine aminotransferase (ALT) and alkaline phosphate (ALP) activities are expected, but the magnitude of activity will depend on the extent of hepatic necrosis and the timing of sample collection. Prolongations of activated partial thromboplastin time (aPTT) and prothrombin time (PT) are common as a result of decreased hepatic synthesis of coagulation factors, DIC, or both. Proteinuria also is expected as a sequel to renal injury during viremia or immune complex injury later in the course of disease.

Definitive diagnosis of CAV-1 infection can be established by PCR performed on secretions or excretions; ocular, nasal, and pharyngeal swabs; and tissues.[25] PCR assays are sensitive and can differentiate CAV-1 from CAV-2. Serologic titers and tissue staining by immunofluorescent antibody and immunohistochemistry cannot distinguish between CAV-1 and CAV-2.[25] Intranuclear inclusion bodies observed during cytologic or histologic examination of tissue, particularly the liver, can be strongly supportive of the diagnosis.[25]

Treatment

Therapy is directed at provision of supportive care and management of clinical signs and complications. Intravenous fluid therapy to replace losses from vomiting or diarrhea is important (see ch. 129), as is administration of blood products to manage the complications of hemorrhage and DIC (see ch. 130 and 197). In patients with neurologic signs from hepatic encephalopathy, administration of lactulose via enema (or orally if the patient is not vomiting) can help reduce circulating concentrations of encephalotoxins (see ch. 281 and 284).

Prevention

Vaccination is the foundation of prevention of CAV-1 infection. Vaccines for CAV-1 are considered a "core" vaccine that should be administered to all dogs (see ch. 208).[16] Vaccination of dogs and induction of active immunity has controlled CAV-1 in the canine population very effectively. Therefore, the disease rarely is seen today. Most commonly used vaccines for CAV-1 use modified-live CAV-2 isolates that, through the production of cross-reactive antibodies, will elicit a protective immune response without the complications, such as corneal edema, associated with vaccines using CAV-1 isolates. The duration of immunity following immunization with modified-live and recombinant vaccines is at least 3 years.[19-23] Current AAHA guidelines[16] recommend vaccinating dogs at 6 to 8 weeks of age, with repeat vaccinations performed every 3 to 4 weeks until 16 weeks old. All dogs should receive a booster vaccine 1 year after completion of the initial series, followed by booster revaccination every 3 years.

The virus is relatively hardy, surviving in the environment for days to months. The virus is resistant to most disinfectants except some quaternary ammonium compounds, bleach (1 : 32 dilution in tap water), potassium peroxymonosulfate, and hydrogen peroxide products.

Canine Adenovirus Type 2

Etiology and Epidemiology

Canine adenovirus type 2 (CAV-2) is a non-enveloped double-stranded DNA virus belonging to the family Adenoviridae. CAV-2 is genetically and antigenically related to CAV-1. CAV-1 and CAV-2 share the same host range. CAV-2 together with canine parainfluenza virus (CPiV), an enveloped single-stranded RNA virus belonging to the family Paramyxoviridae, are part of a complex of pathogens causing CIRD or "kennel cough" (see ch. 227). High-density, high-turnover populations in kennels, pet stores, or shelters are at risk for infection.

Despite the same host range and serologic cross-reactivity between CAV-1 and CAV-2, the tissue tropism of the two viruses is entirely different. Vascular endothelial cells as well as hepatic and renal parenchymal cells are the main targets of CAV-1, whereas the respiratory tract epithelial cells and, to a limited degree, intestinal epithelial cells, are targets of CAV-2.

Vaccines for CAV-2 are recommended for dogs at risk for exposure in shelters, boarding/training kennels, pet stores, and breeding kennels.[16] However, CAV-2 is included in parenteral "core" vaccines containing CDV and canine parvovirus, with CAV-2 providing cross-protective immunity to CAV-1 (see ch. 208). Therefore, when using these combination or multivalent vaccines, the frequency of vaccination against CAV-2 follows the schedule recommended for the "core" components, including booster vaccination every 3 years following the initial immunization series.[16] For dogs at risk for exposure, intranasal vaccines containing modified-live CAV-2 can be given as early as 3 weeks of age, with repeat administration 2 to 4 weeks later, and every 6 to 12 months thereafter.[16] Additional information regarding CAV-2 is presented in ch. 227.

Canine Papillomavirus

Etiology and Epidemiology

Papillomaviruses are non-enveloped double-stranded DNA viruses belonging to the family Papillomaviridae. Different papillomaviruses have been described in dogs. Canine oral papillomavirus (COPV-1) is the most familiar. Oral papillomas typically occur in dogs younger than 2 years of age. Although benign and usually self-limiting, oral papillomas can cause serious inconvenience by interfering with mastication. Other incompletely classified papillomaviruses in dogs cause ocular and cutaneous papillomas. Ocular papillomas occur in dogs 6 months to 4 years of age, and cutaneous papillomas, including those causing lesions on footpads and interdigital spaces of the feet of adult and immunosuppressed dogs, occur in older dogs.[29,30]

Transmission

Papillomaviruses are highly species- and tissue-specific, contagious, and transmitted by direct or indirect contact. Through small wounds in the skin or mucosal surfaces, papillomaviruses get access to the basal cell layer where infection and virus replication occurs. Papillomas typically develop 1 to 2 months after infection.

Pathogenesis

Papillomaviruses cause benign mucocutaneous proliferations (warts) of epithelial origin. The viruses primarily infect cells in the basal layer of the epithelium of the oral cavity, penis, vulva, conjunctiva, and skin, and it is likely that different papillomaviruses account for differences in lesion distribution.[31] Once infected, basal cells increase mitotic activity to produce the characteristic warts (Figure 228-3). Infectious virus particles are synthesized finally in the differentiated cells of the cornified layers of the skin or mucosal surfaces. Lesions usually regress spontaneously, but regression can vary from weeks to years.

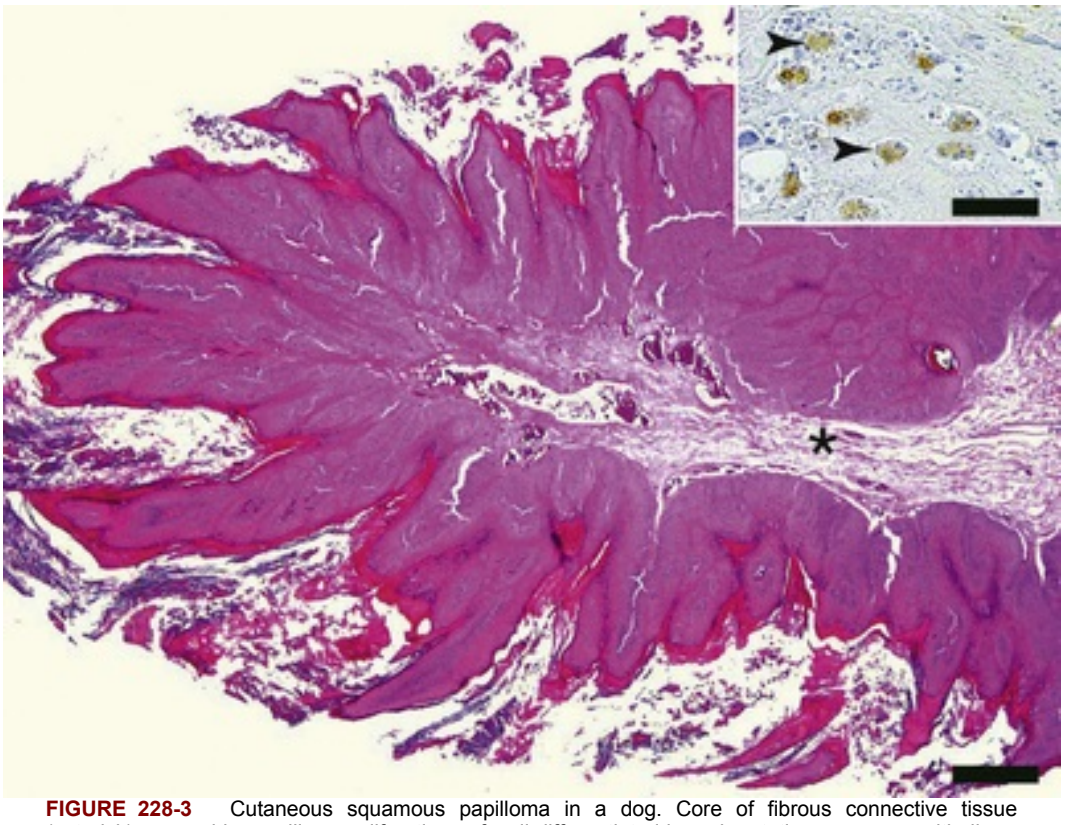

FIGURE 228-3 Cutaneous squamous papilloma in a dog. Core of fibrous connective tissue (asterisk) covered by papillary proliferations of well differentiated hyperkeratotic squamous epithelium. Bar = 200 microns. Inset: Immunohistochemical demonstration of intranuclear papillomavirus antigen (arrowheads). Bar = 20 microns. (Courtesy Dr. S. Schöniger, Institute of Veterinary Pathology, University of Leipzig, Germany.)

Clinical Signs

The primary clinical sign of COPV infection is the appearance of one, a few, or even dozens of smooth, fingerlike raised lesions measuring a few mm height and diameter (papillomas) in the oral cavity or on other epithelial sites (see ch. 218). Papillomas typically regress within 4 to 8 weeks (and occasionally longer) when cell-mediated immune responses cause T-cell infiltration into the warts.[32] Humoral immune responses, although capable of preventing infection, do not seem to play a role in regression of lesions. Although lesions can become quite extensive, especially in the oral cavity, the functional impact of papillomas to the affected animal is usually minimal unless warts develop in locations that lead to dysphagia or respiratory obstruction.

In contrast to COPV, additional incompletely classified papillomaviruses cause ocular and cutaneous papillomas. A papillomavirus designated as *Canis familiaris* papillomavirus type 2 (CfPV-2) has been described more frequently on the footpads or in the interdigital spaces of the paws and has not been incriminated as a cause of oral warts.[29,33,34] The lesions associated with this virus have been more endophytic (inward growing) than exophytic (outward growing) and have persisted for much longer periods of time. In addition, CfPV-2 has been associated with the development of squamous cell carcinomas (SCC) in immunosuppressed dogs. It is quite likely that early initial reports of SCC in mucosal and cutaneous sites associated with a novel papillomavirus reflect associations with CfPV-2.[35,36] This virus might also play a role in the development of pigmented cutaneous papillomatosis.[37]

Diagnosis

Diagnosis of COPV usually is based on the observation of characteristic lesions and is supported by histopathologic evaluation of biopsied lesions. Immunohistochemistry, electron microscopy, and PCR can be used for virus detection.

Treatment

Because COPV-related disease usually regresses spontaneously in the majority of dogs, treatment is not necessary unless warts compromise eating or respiration. In such cases, warts can be removed by surgical excision, cryosurgery, or electrosurgery. Refractory cases could benefit from autogenous vaccination, in which the superficial parts of warts containing complete virus particles are removed for making a crude vaccine that is then injected into the same dog.[32] Etretinate, a retinoid, has been used to treat viral-associated pigmented plaques.[30] The optimal treatment for lesions of the digit pads and other sites associated with CfPV-2 has not been established, but surgical resection and histopathologic examination are reasonable considerations, particularly to evaluate for the presence of malignant changes.

Prevention

No preventive vaccine is available for dogs. Dogs that have recovered from COPV generally are immune to reinfection. Some dogs, presumably those that are older or immunosuppressed, can be susceptible to repeated bouts of clinical disease. These viruses are relatively stable in the environment.

Canine Rotavirus

Etiology and Epidemiology

Canine rotavirus enteritis most often is caused by group A rotaviruses belonging to the family Reoviridae, which are non-enveloped, double-stranded RNA viruses. Group C rotaviruses, which are found more commonly in pigs and other species, also have been documented in diarrheic dogs.[38,39] Compared with other enteric viruses, clinical disease caused by canine rotavirus appears to be less common.[40-42] Nevertheless, rotavirus antigens were detectable in fecal samples in about 7% of young dogs with diarrhea in one study.[43] Canine rotavirus infections cause subclinical or mild gastroenteritis in puppies younger than 3 months old. Severe fatal enteritis has been reported in puppies younger than 2 weeks old. Investigations showed a high seroprevalence (60-80%) to group A rotavirus in adult dogs. Rotaviruses are generally considered species-specific, but genetic sequence analyses suggest interspecies transmission events between animals including dogs and humans.[43-45] A canine-like rotavirus isolate was associated with enteritis in a child.[44]

Transmission

Infection usually occurs via oronasal exposure to virus-contaminated feces or fomites. Virus shedding can start within 2 days of infection and continue for 7 to 10 days. However, animals that have recovered from diarrhea occasionally can shed virus for prolonged periods of time.

Pathogenesis

After exposure, rotavirus infects epithelial cells of the villus tip of the jejunum and ileum from the luminal side of the gastrointestinal tract. Loss of villous epithelial cells ensues, with development of villous atrophy. Virus is shed early as infected, necrotic epithelial cells are sloughed from the villus.

Clinical Signs

Anorexia, vomiting, and mild diarrhea, which occasionally can be bloody, are the typical clinical signs of rotaviral gastroenteritis. Without secondary infections, recovery is expected in most animals within 5 to 7 days of onset of clinical signs.

Diagnosis

Commercially-available tests are available to detect group A rotaviral antigens but are not employed commonly in small animal practice. Other methods to obtain a definitive diagnosis include demonstration of virus in feces by electron microscopy or RT-PCR. Sequence analysis can resolve the genotype (G- and P-) of the rotavirus involved.

Treatment

Therapy of rotaviral gastroenteritis is supportive care, with attention to maintenance of hydration status in puppies with anorexia and vomiting (see ch. 39, 40, 129, and 276).

Prevention

There is no vaccine currently available for prevention of rotaviral infection in dogs. Rotaviruses are durable in the environment and require disinfectants such as bleach, potassium peroxymonosulfate, or accelerated hydrogen peroxide products for complete inactivation.

Pseudorabies Virus

Etiology and Epidemiology

Pseudorabies is an uncommon but fatal disease of dogs caused by an enveloped, double-stranded DNA virus in the alpha-herpesvirus family. Affected dogs usually have a history of having been in contact with pigs, the primary virus reservoir that causes this disease colloquially referred to as "mad itch."

Transmission

Most cases in dogs are believed to result from ingestion of infected raw pork. The incubation period is 3 to 6 days. Despite the presence of an envelope, pseudorabies virus is relatively stable in the environment.

Pathogenesis

After ingestion, the virus enters nerve endings in the mucosa and spreads to the brain along nerve axons. Inflammation and functional abnormalities in brain cells result in clinical signs.

Clinical Signs

Signs of neurologic dysfunction are common features of the disease.[46] Neurologic abnormalities can be variable and have included ataxia, abnormal pupillary light responses, restlessness, trismus, and cervical rigidity. Ptyalism, tachypnea, and hyperpnea are common. Intense pruritus of the head and neck area can lead to self-induced excoriation. In some dogs, vomiting and diarrhea predominate. The clinical course of pseudorabies infection in dogs is usually swift, with most dogs dying within 48 hours after onset of neurologic signs.

Diagnosis

The diagnosis is suspected based on history of exposure to pigs or pork products, and clinical signs. A definitive diagnosis can be established by virus detection based on immunofluorescent antibody or PCR testing of brain and tonsillar tissue.

Treatment

Treatment is supportive, but most affected dogs succumb to the disease irrespective of treatment.

Prevention

There is no approved pseudorabies vaccine for dogs, so prevention relies on limiting exposure of dogs to pigs and preventing ingestion of raw pork products.

West Nile Virus

West Nile virus (WNV) is an enveloped, single-stranded RNA virus belonging to the family Flaviviridae. WNV is found worldwide and is maintained in natural settings via transmission from infected to naïve birds via mosquitoes.[47] Mosquitoes are able to transmit the virus to dogs.[48-50] Epidemiologic studies have demonstrated that, in endemic areas, higher seropositive rates can be found in dogs than in people, suggesting the potential for the dog as a sentinel species.[51]

Experimental infection has shown that dogs are able to develop viremia, which generally is of low

magnitude and of short duration.[48-50] Despite dogs' being able to support viremia, clinical disease in naturally-exposed or experimentally infected dogs is uncommon, even when dogs are pretreated with high dosages of glucocorticoids.[48-50] Signs of CNS disease, reflecting meningoencephalitis, and fever have been observed most consistently in naturally infected dogs; multisystemic disease also has been reported.[52-55] Reports in dogs suggest that the organs most likely to have virus are the brain, kidney, and heart.[52-55] The factors that determine the outcome of infection, and the pathogenic events underlying clinical signs in affected dogs, are unknown. Definitive diagnosis requires demonstration of viral antigen or nucleic acid in infected tissues; one report[52] of viral antigen present in renal cellular casts and other renal tubular debris raises the possibility that urine-based tests could be diagnostically useful. There are no specific treatments beyond supportive therapy. Experimental vaccination of dogs has prevented viremia after challenge,[49] but there is no approved vaccine to prevent infection in dogs and the value of vaccinating species in which disease manifestations are uncommon is uncertain.

Bornavirus

Bornavirus (BV) is an enveloped, single-stranded RNA virus belonging to the family Bornaviridae. BV causes a fatal disease of the CNS in horses and other animals. Clinical disease in dogs appears to be relatively uncommon, and seropositivity in the absence of clinical signs appears possible.[56] The pathogenesis of the disease in dogs is unknown, but clinical signs in dogs have included tremors, salivation, mydriasis, and circling.[57,58] The infection is suspected based on the histopathologic observation of non-suppurative encephalomyelitis predominantly in the gray matter of the brain. Demonstration of viral RNA by *in situ* hybridization or PCR-based assays has provided a definitive diagnosis.

Circovirus

Circoviruses are non-enveloped, single-stranded DNA viruses with a circular genome. They belong to the family Circoviridae. Recently a canine circovirus (DogCV) was described in dogs with vasculitis, granulomatous lymphadenitis and/or hemorrhagic diarrhea in the United States and Europe.[59-61] DogCV has been detected in animals with different clinical signs. The virus was detected by PCR in fecal samples from 19/168 dogs (11.3%) with diarrhea and 14/204 healthy dogs (6.9%), and in the blood of 19/409 dogs (3.3%) with thrombocytopenia and neutropenia, fever of unknown origin, or past tick bite. Co-infections with other canine pathogens were detected in 13/19 DogCV-positive dogs with diarrhea (68%).[60] DogCV also was detected in an outbreak of acute gastroenteritis in a litter of Dachshunds. The animals were 5 to 6 months of age and had completed the first year vaccination protocol against CPV, CDV, CAdVs and *Leptospira* spp.[61] Clinical signs in the dogs were severe, with hemorrhagic diarrhea, vomiting, and death of 2 animals after one week of illness. The other dogs recovered completely within 12 to 15 days after the onset of clinical signs.[61] There are no specific treatments beyond supportive therapy. Despite these reports, currently it is unknown whether DogCV really contributes to clinical disease, as experimental infections to reproduce the observed clinical signs have not yet been performed in dogs. The detection of DogCV in tissues or excretions of infected dogs can be done using published PCR protocols.

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CHAPTER 229

Feline Upper Respiratory Infections

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Client Information Sheet: Feline Upper Respiratory Infections

Overview

Feline viral respiratory disease is most commonly seen where cats are grouped together, such as in breeding and boarding catteries, and in rescue shelters. The two main causes of viral respiratory disease in cats are feline herpesvirus (FeHV-1) (feline rhinotracheitis virus) and feline calicivirus (FCV). FeHV-1 generally induces a more severe disease than FCV, but FCV appears to be more common. Bacterial pathogens such as *Bordetella bronchiseptica, Chlamydia felis,* and possibly *Mycoplasma felis,* are also involved in infectious respiratory and ocular disease in cats. Other viruses implicated albeit rarely in the syndrome include feline reovirus and cowpox virus (see ch. 230).

Recently, there has been a resurgence in interest in influenza biology in cats, largely driven by the demonstration that cats are susceptible to highly pathogenic and zoonotic avian influenza H5N1; although likely to be very rare in most settings, this is a rapidly changing area and so an update is included at the end of this chapter.[1]

Causative Agents

FeHV-1 is an alpha herpesvirus affecting both domestic cats and other members of the *Felidae.* Only one serotype of the virus exists, and genetically, all isolates are similar. The virus contains double-stranded DNA and is enveloped, making it relatively labile.

FCV is a small non-enveloped RNA virus. Although FCV is quite variable, it is generally considered that there is only one genotype and one serotype of the virus.[2-4] There is some evidence of two genetic clusters/genotypes in Japan, although the international significance of this remains uncertain.[5,6] Most strains of FCV are closely related enough antigenically to induce some degree of cross-protection and this has been utilized in developing vaccines. FCV affects both domestic cats, and some nondomestic *Felidae.* Interestingly, FCV-like viruses have also been isolated from dogs; however, their clinical significance in both dogs and cats is uncertain.[7,8] In addition, epidemiologic evidence of a possible association between dogs and FCV infection in cats is conflicting.[9,10]

B. bronchiseptica is a Gram-negative coccobacillus, and is considered to be a primary as well as a secondary pathogen of domestic cats. It is also a significant if seemingly infrequent zoonosis of immunocompromised people,[11] and can be transmitted between animal species.[12,13]

C. felis is an obligate intracellular Gram-negative rod-shaped coccoid bacterium.[14] A possible association between rare cases of conjunctivitis in humans and *C. felis* has been reported, though such cases are difficult to substantiate without genetic typing.[15]

M. felis is a small prokaryote lacking a cell wall. It belongs to the class Mollicutes. Several studies suggest that mycoplasmas are more common in cats with respiratory and/or ocular disease (conjunctivitis) than those without. Although their role as a primary pathogen in upper respiratory and conjunctival infection is still unclear, there is some evidence that they may be a primary pathogen in some cases of lower respiratory tract disease in cats.[16]

Clinical Signs

FeHV-1 causes upper respiratory tract (URT) disease (Figure 229-1), with oculonasal discharges, conjunctivitis, sneezing, and sometimes hypersalivation and coughing (Video 229-1).[17] Occasionally, more severe signs including pneumonia and generalized disease may be seen, particularly in young or debilitated animals. Viral replication can also lead to osteolytic changes in the turbinate bones that are believed to predispose some cats to develop more chronic rhinitis. Abortion occurs rarely, and is probably due to severe systemic disease and not to the virus itself. The role of FeHV-1 in conjunctivitis and, in some cases, ulcerative keratitis, has long been known. However, improved viral detection using polymerase chain reaction (PCR) has led to increasing recognition of this role in the acute disease as well as in more chronic ocular lesions such as stromal keratitis.[17-19] The role of FeHV-1 in other ocular conditions such as eosinophilic keratitis, corneal sequestration, and uveitis is less clear.[17,18,20] Skin ulcers and an ulcerative facial and nasal dermatitis characterized by eosinophilic infiltration have also been described.[17,21,22]

FIGURE 229-1 Cat with severe nasal, ocular and oral discharge caused by feline upper respiratory viral infection. (Courtesy Bryan Langlois, DVM.)

In FCV infection, considerable strain diversity may lead to some variation in clinical signs. The most characteristic sign is oral ulceration, typically on the tongue, but lesions may also occur elsewhere in the mouth or on the skin. Classic URT disease signs, such as sneezing, ocular and nasal discharges and conjunctivitis, also commonly occur, but these are generally milder than those seen with FeHV-1. With some strains of FCV, lameness and pyrexia may be a feature, with or without respiratory/oral disease; other strains may induce an interstitial pneumonia with infection of alveolar macrophages,[23] and some appear apathogenic.[24] In addition, FCV infection is associated with chronic stomatitis, although its precise role in the condition is not clear and other factors are likely to be involved.[4,25]

More recently, hypervirulent strains (virulent systemic FCV; VS-FCV) have emerged across North America and in several European countries. In addition to URT disease, affected cats show to varying degrees pyrexia,

cutaneous edema, ulcerative dermatitis, anorexia, and jaundice, with a high mortality rate.[26-31] Adult cats are frequently affected more severely than kittens, and in the field, disease is seen in both vaccinated and unvaccinated individuals. Each outbreak appears to be caused by a distinct strain; so far none of these VS-FCVs appears to have become widely established in the population.[32]

Experimental studies confirm that *B. bronchiseptica* can be a primary pathogen of cats, inducing mild clinical signs consisting of fever, coughing, sneezing, oculonasal discharge and submandibular lymphadenopathy.[33,34] In addition to the above, field infection may also lead to more severe disease, usually in younger kittens, including pneumonia with dyspnea, cyanosis and death.[35,36] It is likely that factors such as overcrowding and poor hygiene may lead to higher challenge doses and more severe disease.

Infection with *C. felis* is generally associated with both acute and chronic conjunctivitis, though upper and lower respiratory signs may sometimes also be seen.[15] Cases that start in one eye can rapidly progress to become bilateral.[14] Affected eyes can be markedly painful with profound conjunctival hyperemia, chemosis, blepharospasm, and watery followed by mucoid or mucopurulent ocular discharges. In some cases adhesions of the conjunctiva may develop although keratitis and corneal ulcers, and other systemic illness, are not common and this can help differentiate *C. felis* from FeHV-1. Whilst it is best considered an ocular pathogen and not a respiratory pathogen, it is mentioned here as part of the differential for FCV and FeHV-1, both of which can cause ocular as well as respiratory disease.

Diagnosis

Diagnosis of FeHV-1 and FCV infection has classically been confirmed by virus isolation in cell culture from oropharyngeal or conjunctival swabs, although immunofluorescence has also been used, particularly for FeHV-1. In many laboratories, PCR is used for diagnosis of FeHV-1, because it is significantly more sensitive than traditional methods, especially in the chronic stages of the disease.[17,37] Such PCRs also allow an estimate of viral quantity, thereby allowing some laboratories to stage disease and predict whether FeHV-1 is likely to be the cause of any acute signs, or a more chronic infection. A comparison of PCR tests available does show considerable differences in sensitivity between the published assays.[38]

For FCV, reverse-transcriptase PCR (RT-PCR) is also used, but in some cases may be less sensitive than isolation largely because of the variability between strains and the difficulty of finding suitably cross-reactive primers. Veterinarians relying on RT-PCR tests should discuss this with their laboratory. In addition to diagnosis, RT-PCR followed by sequencing is useful for differentiating between FCV strains in investigating the epidemiology of infection and disease, and in particular, can help pinpoint where an individual cat became infected from.[39-41] Unfortunately, despite some effort, there are no reliable molecular markers to predict from a given strain's sequence the type of clinical signs it may produce.[4,30,32] Such a test would be particularly valuable to confirm if an FCV isolate obtained from a cat with signs of VS-FCV was truly the cause of the signs, or just a coincidental infection with a more typical FCV strain. In order to identify cases of VS-FCV it is advisable to both demonstrate FCV infection, and to confirm antigen in what are otherwise considered unusual sites such as the liver.[26] Interpretation of test results for either FeHV-1 or FCV can be problematic. A positive result can support a clinical diagnosis but may also indicate a shedding carrier. In countries where intranasal vaccines are available, a positive result may also indicate recent vaccination.

Diagnosis of *B. bronchiseptica* can be by isolation or PCR.[35] As with FCV and FeHV-1, recovered cats can continue to shed the organism, so care must be taken when interpreting a positive result. The demonstration of *B. bronchiseptica* in samples obtained by bronchoalveolar lavage from cats with lower respiratory signs is considered to be diagnostic.

A PCR is the preferred method of diagnosing acute *C. felis* infection.[42]

Because of the high prevalence of FCV, FeHV-1, *B. bronchiseptica* and *C. felis*, serology is generally not useful for diagnosing clinical infection. It can help determine how widespread previous infection is in a group of cats, and may help shelters manage housing cats in the face of an outbreak by rapidly identifying those most at risk because of immune naivety. Although serologic tests are gaining some traction in dogs as a pre-vaccination check to help identify those that most need vaccination, their use in cats is generally not recommended.[43,44] High *C. felis* antibody titers may also be used to imply a role for *C. felis* in rarer cases of chronic ocular disease.[14]

Treatment

Primary treatment involves supportive therapy. Care should always be taken when using antimicrobials in order to minimize the risk of resistance—the use of antimicrobials should therefore be reserved for the more severe cases where bacterial infection is clearly evident, and best follows local or national guidelines (see ch. 161). For general treatment of severe cases a broad spectrum antimicrobial may be indicated (e.g., potentiated amoxicillin)[45]; other drugs should be restricted to those cases where resistance testing indicates their use. Tetracyclines are generally indicated if *B. bronchiseptica*[46] or *C. felis*[42] is involved; in the youngest kittens, potentiated amoxicillin may be preferred to avoid potential side-effects.[15] For *C. felis*, treatment should be continued for two weeks after resolution of clinical signs to reduce the likelihood of recrudescence.

Although several topical and systemic antivirals and other putative treatments have been investigated for use against FeHV-1, none of these is widely used except in cases of ocular disease.[37] Some anti-herpes viral drugs used in human medicine, such as acyclovir, are not sufficiently active against FeHV-1 or are too toxic for systemic use in cats,[17,47] although famciclovir may show some efficacy (see ch. 162).[48,49] Others such as trifluridine have been used topically with some success in cats with ocular herpesvirus lesions, and even acyclovir may have some effect when applied frequently.[17,50,51]

The value of recombinant interferon in cats with viral respiratory or ocular disease is uncertain, although its use may reduce FCV shedding (see also ch. 224).[25,51-54] Similarly, robust evidence that orally administered L-lysine ameliorates the signs of FeHV-1 infection is lacking, and any effect may require lysine supplementation before infection, or be limited to reducing shedding.[37,55,56] In some countries, passively acquired antibodies are available, and may shorten the duration of clinical signs.[57]

Epidemiology

Both FCV and FeHV-1 are primarily transmitted by direct contact between cats, although indirect transmission may also occur in the short term through contact with infectious discharges. Feline calicivirus may also be shed in urine[58] and feces of cats[59] and fleas,[60] although these routes are not thought to be of major significance. Aerosols are also not a major route of transmission because tidal volumes are believed to be too low, although sneezed macrodroplets may transmit infection over a distance of 1 to 2 meters (see Video 229-1).

Acutely infected cats are clearly an important source of virus, but infection also commonly occurs from clinically recovered carrier cats. For FeHV-1, it is generally believed that all cats recovering from acute infection develop a lifelong latent infection. In such cats, the virus persists in a latent or quiescent form largely in trigeminal ganglia, though other tissues may also be involved.[17,61] During this latent phase, infectious virus is generally not detectable from oronasal secretions. Periodically, particularly after a stressful event, virus reactivates in such carriers and they can then infect other animals. Stresses that may induce virus shedding include a change of housing (including going into a cattery), kittening and lactation, and corticosteroid treatment. Some cats may show clinical signs during a reactivation episode, which can be a useful indicator that they are likely to be infectious.

The FCV carrier state is defined as a cat shedding virus for more than 30 days after infection. In a minority of cats, the FCV carrier state appears to be lifelong.[4] However, most carriers appear to eliminate virus at some point, but remain susceptible to reinfection. During the carrier phase, FCV carriers shed virus more or less continuously and are therefore always infectious to other cats. The virus persists in the tonsils and other oropharyngeal tissues. FCV carriers appear to be common, with approximately 10% of cats in the general population shedding FCV, rising to almost 100% in some more densely populated environments such as rescue shelters and larger colonies.[10,41,62-66] From studies of endemically infected colonies, it appears that only a minority of carrier cats are true persistent shedders; the majority are undergoing cycles of reinfection from other cats in the environment.[41]

Prevention and Control

Prevention and control may be achieved through a combination of vaccination and management. Both modified live virus (MLV) vaccines and inactivated adjuvanted vaccines are marketed for parenteral injection against FeHV-1 and FCV (see ch. 208). More recently, a non-adjuvanted inactivated FCV and modified live FeHV-1 vaccine has become available in some countries. Modified live intranasal vaccines are also available in some countries but are not widely used. Several recombinant vaccines have also been created, including FeHV-1 deletion mutants, baculovirus constructs, a myxoma FCV recombinant, and an FCV DNA vaccine,

but none is licensed.

Both MLV and inactivated FeHV-1 and FCV vaccines are reasonably effective at protecting against disease, but none protects against infection or the development of the carrier state.[4,17,67] For FCV, various strains are used in commercial vaccines, such as FCV-F9 or FCV-255 in isolation, or two strains such as FCV-431 and FCV-G1.[68] Most seem to be reasonably cross-reactive against the majority of recent FCV isolates when assessed *in vitro,*[66,69] and there are some publications that point to their continued ability to induce heterologous cross-protection following challenge.[30,70] Partial efficacy has also been reported with some vaccines against some VS-FCV strains.[24,27,30] In the United States, one vaccine is available that has incorporated a single strain of VS-FCV. However, since each outbreak is caused by a different strain, the broad applicability of this approach remains to be proven in the field.

Parenteral MLV vaccines are generally safe, but disease may occasionally occur following their use. This may be due to inadvertent oronasal exposure to the vaccine that may occur if the vaccine virus has leaked onto the skin surface and the cat, or an in-contact cat, licks the injection site.[39,62,67,71] Inactivated vaccines may therefore be safer in disease-free colonies. However, most inactivated vaccines are adjuvanted, and this can sometimes cause local or systemic reactions. Very rarely, sarcomas may develop at the site of injection of both vaccines and non-vaccines (feline injection site sarcomas [FISS; see ch. 346]). To date there is little evidence to suggest one type of vaccine is safer than another.[44]

Intranasal MLV vaccines induce better protection but often at the expense of slight side-effects, such as transient sneezing and occasionally other signs.[72] They are, however, useful for rapid onset of protection.

Historically, vaccination schedules were entirely the remit of vaccine companies, with frequency of vaccination largely driven by duration of immunity studies needed for licensing. Now there is a growing number of guidelines to inform clinicians, namely the American Association of Feline Practitioners (AAFP) Feline Vaccine Advisory Panel Report,[44] the World Small Animal Veterinary Association (WSAVA) Vaccination guidelines[43] and the European Advisory Board on Cat Diseases guidelines.[25,37] These are in general recommending less frequent vaccination driven by a growing understanding of the duration of immunity of feline vaccines, and also by a better understanding of the potential side-effects of vaccination.

Primary vaccination in young kittens is generally at 8 to 9 weeks of age with a second dose at 12 weeks. Some guideline groups recommend repeated vaccinations every 3 to 4 weeks, from as early as six weeks, until 16 weeks of age[43,44]; others recommend this only where the kittens concerned are believed to be at a heightened risk due to vaccine interference by high levels of maternally derived antibodies (MDA).[25,37]

All cats should receive a booster within one year of this primary course. Thereafter, annual revaccination has traditionally taken place. However, there is now a growing consensus towards revaccination every 3 years, apart from cats living in or going into high-risk situations where more frequent vaccination may still be considered.

Live attenuated *B. bronchiseptica* intranasal vaccines are available for cats.[73] For *C. felis,* both inactivated and MLV vaccines are available as part of multivalent preparations. Guideline groups recommend these as non-core, to be used in situations where the pathogen is known or strongly suspected.[14,35,43,44]

Management measures are aimed at preventing spread of viruses within a cattery, through both direct and indirect contact between cats. Upper respiratory infections can be particularly problematic in rescue shelters where many animals of uncertain history are brought together.[41,74,75] Many cats can be shedding pathogens when they arrive, and there is often a significant increase in the proportion shedding in the days following admittance.[76,77] In boarding catteries and rescue shelters, cats should be individually housed with solid partitions between pens and good hygiene and disinfection procedures employed. FCV can persist in the environment for up to several weeks, compared to a day or so for FeHV-1, and is less susceptible to some disinfectants.[4,17] However, a diluted hypochlorite/detergent mixture should be effective for both viruses. In breeding colonies, young kittens are most at risk as they lose their MDA. Overcrowding should be avoided and cats kept as stress-free as possible. Ideally, queens should kitten in isolation and/or early weaning of kittens or earlier vaccination schedules implemented if required. Such measures have been described in detail elsewhere.[78]

Influenza in Cats

In areas in Asia where H5N1 infection is endemic in poultry, localized outbreaks of H5N1 with high mortality have been described in various felids including domestic cats, tigers and leopards.[79-82] Infection was

considered to be by ingestion of contaminated poultry meat, but horizontal transmission may also have occurred. Occasional asymptomatic infections have also been seen in domestic cats in Europe, where there was close contact with infected aquatic birds.[83]

Experimental studies have shown that cats can become infected both through contact with infected cats and by consuming infected poultry.[80,84] Infected cats developed a severe respiratory disease with a high mortality. Virus has been detected in feces and in oropharyngeal swabs from infected animals.[84,85] Influenza H5N1 should be considered in cats in contact with birds where highly pathogenic H5N1 is currently circulating.

More recently, population and experimental studies have shown that cats are susceptible to a wide range of influenza viruses including H1N1, H3N2, H3N8, H5N2 and H9N2 and in some cases developing clinical signs.[86-91] It seems likely that as further studies are undertaken, the range of influenza viruses cats are shown to be susceptible to will only grow.

It is now increasingly clear that cats can be infected with zoonotic influenza viruses, but there is no clear evidence of cats infecting humans: the vast majority of human risk is either from infected humans or direct from avian species. Heterologous vaccination of cats has been shown to protect against lethal infection of cats with H5N1, and reduce shedding, leading some to suggest vaccines may have a role in reducing risk of onward transmission from cats.[82]

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CHAPTER 230

Other Feline Viral Infections

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There are several viruses that infect cats. Some of these, such as panleukopenia (parvo) virus (see ch. 225), the respiratory viruses (see ch. 229), and the retroviruses (see ch. 222 and 223, and see Table 230-1) are significant pathogens of cats and both the viruses and the diseases they cause have been well characterized. Others such as cowpox virus and Hantavirus are essentially pathogens of other animal species and only occasionally infect cats. Although possible new feline viruses continue to emerge (e.g., kobuvirus infection), in comparison with humans and some other species the list of known cat viruses is not very long. This almost certainly reflects the relatively limited amount of investment there has been in feline virology, but it may also be a reflection of the fact that cats evolved to live mainly singly, and not in groups, which can restrict virus transmission. Thus, in order for viral pathogens to survive in the cat population, they may have had to develop techniques such as long-term persistence within the host (e.g., feline respiratory viruses: feline herpesvirus and feline calicivirus) or outside the host (e.g., feline panleukopenia virus). However, many cats are now kept in large groups in catteries and shelters, and this increased population density may encourage rapid transmission and evolution of viruses leading to potentially more virulent or emerging diseases.[1,2]

TABLE 230-1

Recognized Virus Infections of Cats

VIRUSES	DISEASES
Upper Respiratory Tract (URT) Viruses (see ch. 229)	
Feline herpesvirus type 1 (FeHV-1)	URT disease; sometimes ocular and skin lesions
Feline calicivirus (FCV)	URT and oral disease; sometimes lameness
Feline reovirus	Conjunctivitis/respiratory lesions/diarrhea, experimentally; no evidence important in the field
Enteric Viruses	
Feline parvovirus (FPV; see ch. 225)	Enteritis and panleukopenia; cerebellar hypoplasia; fetal death
Feline coronavirus (see ch. 224)	Mild enteritis (FECoV); feline infectious peritonitis (FIP)
Feline rotavirus	Mild diarrhea; disease uncommon
Feline astrovirus	Persistent watery diarrhea; disease uncommon
Feline torovirus	Putative torovirus detected in cats; possible association with protruding nictitating membrane and diarrhea syndrome in cats
Kobuvirus	Recently identified in cats and possible association with diarrhea
Retroviruses	
Feline leukemia virus (FeLV)	See ch. 223
Feline immunodeficiency	See ch. 222

virus (FIV)	
Feline foamy virus (FFV)	Previously feline syncytium-forming virus; no definite disease association
Miscellaneous Virus Infections of Cats	
Cowpox virus	Sporadic disease in cats; mainly skin lesions; cowpox virus endemic in small wild rodents
Hantavirus	Endemic disease in rodents; serologic evidence of infection in cats; zoonotic (but cats are unlikely source)
Rabies virus	See ch. 226
Aujeszky's disease virus/pseudorabies virus (see also ch. 228)	Herpesvirus infection in pigs/swine; cats occasional host; disease signs are severe behavioral changes, pruritus, paralysis, coma, and death
Canine distemper virus (CDV; see ch. 228)	Evidence from field serology and experimental studies indicate that cats can be infected subclinically; however, severe disease with neurologic signs seen in large felids.
Feline morbillivirus	Recently identified in urine and blood of cats. Some, yet to be proven, association with renal disease.
Paramyxoviruses: Hendra and Nipah viruses	Fatal zoonotic respiratory disease of horses in Australia (Hendra virus) and pigs in Malaysia (Nipah virus); endemic in certain species of fruit bats; cats can be infected experimentally with both viruses
Paramyxovirus: unclassified	Report of demyelinating lesions in central nervous system of cats
Avian influenza virus	Cats are susceptible to a range of influenza viruses, most notably H5N1. This virus can replicate in cats after experimental inoculation leading to severe respiratory disease, and some evidence of cat-cat transmission; feline infection may occur occasionally in the field during avian influenza outbreaks.
Borna disease virus (BDV; see also ch. 228)	Rare but fatal neurologic disease that occasionally occurs in cats
Arthropod-borne viral infections	Cats in some parts of the world may become infected with several arthropod-borne diseases; usually asymptomatic, occasionally cause encephalitis

In addition, newer technological approaches such as metagenomics[3] are identifying an increasing number of viruses in the cat population which may revolutionize our understanding of cat viral diseases.[4,5]

Borna Disease Virus (Feline Staggering Disease)

Borna disease (BD) is a rare but fatal neurologic disease caused by a negative-stranded RNA virus, Borna disease virus (BDV; see also ch. 228). The disease occurs predominantly in horses and sheep. A number of other species may also be affected, and increasing evidence indicates that cats are also susceptible (see ch. 270).[6,7] The disease in cats has been reported mainly in Europe but also occurs in other parts of the world, including Japan.[8] The true global distribution remains somewhat uncertain as some early reports remain controversial.[9] Affected cats show motor dysfunction and behavioral changes including an unsteady "staggering" gait and a progressive hindlimb stiff ataxia. Other signs may include fever, depression, anorexia, constipation, with absent or decreased postural reactions and menace responses on examination.[10]

Diagnosis is challenging. Whilst the clinical signs are not pathognomonic, other neurological signs such as generalized seizures, compulsive walking, facial paralysis or vestibular signs are generally not a feature of BDV infection, and if present, can help rule out BDV as a likely cause. In addition, BDV specific antibodies and/or BDV-RNA can be detected in the serum of a high proportion (≈89%) of patients, much higher than in unaffected cats (≈16%), and may therefore aid in the clinical diagnosis of affected cats.[11] The disease is generally progressive, and despite supportive treatment, affected cats die or are euthanized. The virus persists in the central nervous system of both experimentally and naturally infected cats.[10]

At necropsy, there is a characteristic nonsuppurative meningoencephalomyelitis, mainly in the gray matter of the cortex, brainstem, and spinal cord. In some cases, infection is present in cats with no neurologic disease. It has been suggested that BDV or a related virus may be involved in psychiatric disorders in humans.[10]

Poxvirus Infection

Cats are susceptible to cowpox virus, a member of the Orthopoxvirus family.[12-14] Occasional cases of parapoxvirus infection in cats have also been reported.[15] Cowpox virus is found only in Eurasia, and the reservoir hosts are small wild mammals such as voles and wood mice. In North America, orthopoxvirus infections affecting the skin of cats are extremely rare, but a case of raccoonpox has been reported in a Canadian cat.[16]

Cowpox is mostly seen in rural cats that hunt rodents, and most cases are seen in summer and autumn, when opportunities for contact with the reservoir hosts are highest. Cat-to-cat transmission only rarely occurs and generally causes only subclinical infection.

The disease typically starts with a single primary lesion, generally on the head, neck, or forelimb, which may be ulcerated or crusting and can become secondarily infected. Although some cats may only have a primary lesion, in many cases widespread secondary skin lesions also develop after 1 to 3 weeks. These appear as randomly distributed, small epidermal nodules that increase in size over a few days to well-circumscribed ulcers about 1 cm in diameter. These gradually become scabbed and heal over a period of 4 to 5 weeks and most animals recover uneventfully. Occasionally, especially in immunosuppressed cats, systemic illness including pneumonia may develop.[17] Exotic felids (e.g., cheetahs) are particularly susceptible, and a rapidly fatal pneumonia often develops.

Diagnosis is most likely to be by polymerase chain reaction (PCR) of skin crusts material, although virus culture, electron microscopy (EM) and serology may also still be used.[13,18] Characteristic histopathologic lesions include the presence of intracytoplasmic, eosinophilic inclusion bodies, and if necessary, viral antigen can be confirmed by immunostaining.

Treatment includes broad-spectrum antibiotics to control secondary bacterial infection and general supportive therapy with fluids where necessary (see ch. 129). Glucocorticoids are contraindicated as they can predispose to the development of secondary lesions, more severe disease, or both.

Cowpox is zoonotic and cases of suspected cat-human transmission may occasionally occur, resulting in localized lesions and sometimes, severe systemic illness in infected people, particularly those who are immunosuppressed.[13,19,20] There is some suggestion that discontinuation of human smallpox vaccination is leading to an increase in the susceptibility of the human population.[21] However, the risk of cat-human transmission remains small if basic hygiene precautions are taken, with the majority of human infections likely to come from indirect or direct contact with infected rodents.[22-24]

Feline Foamy Virus (Feline Syncytium-Forming Virus) Infection

Feline foamy virus (FFV) is a member of the foamy virus group (spumaviruses) in the retrovirus family. Spumaviruses have been isolated from many species, but they generally do not appear to be pathogenic. Their main importance lies not in clinical medicine but as potential contaminants in research and vaccine production, and more recently, as possible viral vectors in recombinant vaccine technology.

FFV infection is very common in cats, with seroprevalences of up to 90%, depending on the population tested.[25,26] Infected cats harbor virus indefinitely; therefore, being seropositive equates with infection. As well as horizontal transmission, FFV can in some cases be transmitted vertically from infected queens to kittens.

The virus has been isolated from both clinically healthy cats and cats with a variety of diseases, although no clinical signs have been seen experimentally, at least for the 6 months post-infection that were studied.[27] However, in the same study, a mild glomerulonephritis and moderate interstitial pneumonia were observed in infected cats, although there were no contemporaneous controls available for comparison. As such, FFV remains an enigma, a virus in search of a disease. It remains possible that FFV may predispose to disease in conjunction with other agents, or particular major histocompatibility types, such has been suggested for FFV in feline progressive polyarthritis syndrome.[28] However, it is also entirely possible that infection is asymptomatic.

Astrovirus Infection

Astroviruses have been detected in a number of species including cats, and in humans are a common cause of gastroenteritis. These viruses have been detected in the feces of both kittens and cats with and without diarrhea.[4,5,29]

Diarrhea associated with astrovirus infection has been described as persistent (4 to 14 days) and watery and

may be accompanied by vomiting, pyrexia, and depression. Mild diarrhea was reproduced experimentally.[30] How commonly such disease occurs in the field is not clear. A recent study in Korean hospitalized cats found that 19% and 15% of diarrheic and normal feces, respectively, were positive for astroviruses, but the difference was not statistically significant.[31] A limited serologic study has reported that fewer than 10% of cats in the United Kingdom have antibodies, although this may be an underestimate as only one serotype was examined.[29]

Serologic cross-reactivity has been reported between feline astrovirus and human sera, although whether this represents zoonotic transmission or more likely antigenic cross-reactivity between distinct viruses is not known. Astroviruses show genetic diversity and a propensity for recombination, and sequence data suggest an evolutionary link between pig, human, and feline astroviruses.[32,33] However, these are thought to be historical associations[5] and there is no evidence of ongoing human-animal transmission.

Feline Reovirus Infection

Reoviruses have been isolated from both healthy and diseased cats with a variety of signs. Serologic surveys suggest infection is widespread, although the clinical importance of reovirus infection in cats is unknown.[34] Three serotypes of the virus exist. Experimental inoculation of kittens with serotype 3 induced predominantly conjunctivitis, photophobia, and serous ocular discharges; type 2 induced mild diarrhea, and newborn kittens inoculated with type 1 nursed poorly and died 2 days later with respiratory lesions identified at necropsy.[34-36] Little evidence suggests that these conditions occur in the field.

Rotavirus Infection

Rotaviruses are a major cause of enteritis in humans and in many animal species such as cattle and pigs. Typically, rotavirus infections occur in neonatal animals, although older animals may also be affected.

In cats, rotavirus infection is widespread, with up to 100% of cats seropositive depending on the population sampled.[29,37] Molecular studies have found prevalence of 3-13% in fecal samples from various populations, with a higher prevalence of infection in summer.[38] Recently, highly divergent strains of rotavirus have also been found in cats.[5] Clinical disease appears to be uncommon and diarrhea, when it occurs, tends to be mild and of only short duration.[29,39,40] Diagnosis of rotavirus infection may be carried out from fecal samples by EM, polyacrylamide gel electrophoresis of viral RNA, or by PCR.[29] Because of serologic differences between strains, enzyme-linked immunosorbent assays (ELISAs) developed for diagnosis of human rotavirus infections may not necessarily detect all feline rotaviruses.[29]

Cross-species transmission is known to occur with rotaviruses experimentally, though to what extent this happens under natural conditions is not known. Several recent reports have shown close phylogenetic relationships between some feline and some human rotavirus strains,[29,38,41] with additional evidence for recombination,[42] leading to the suggestion that cross-infection between cats and humans may sometimes occur.

Hantavirus Infection

Hantaviruses are enzootic worldwide in wild and laboratory rodents and are zoonotic.[43,44] Strains vary in their pathogenicity to humans. Disease syndromes seen in man include hemorrhagic fever with renal syndrome in Asia and Hantavirus pulmonary syndrome in North America. Only mild or subclinical disease is seen with most European strains.[45]

Hantavirus antibody has been detected in up to 16.9% of cats from a variety of backgrounds including pet cats in the United Kingdom, mainland Europe and North America.[46-48] In addition, virus has been isolated from a cat in China. Seroprevalence is higher in cats that roam, or are allowed outdoors, and a recent study has shown a significantly higher prevalence in cats from more densely forested areas in Belgium, consistent with the ecological variations of Hantavirus risks in humans.[49] However, the clinical significance of Hantavirus infection in cats is not known. Hantaviruses are an important zoonosis. Most humans are believed to be infected by inhaling dust after disturbing infected rodent habitats. There is little evidence to suggest that cats are a likely source of human infection, although an increased risk of human infection associated with cat ownership has been reported in China.[50,51]

Torovirus Infection

Toroviruses are a group of viruses similar to coronaviruses, but with a characteristic rod or doughnut-shaped core. They have been detected in a number of species, including cattle (Breda virus), horses (Berne virus), and humans, and tend to be associated with enteritis. There is some evidence for a torovirus of cats, which may be associated with protruding nictitating membrane and diarrhea syndrome.[36] Others have been unable to substantiate this.[52]

Kobuvirus Infection

The Kobuvirus genus represents an emerging potential pathogen of the Picornaviridae. Human aichivirus was the first described member and was found in humans with oyster-associated gastroenteritis. Other members of the kobuvirus genus have been associated with enteric infections in pigs, cattle, sheep, wild boars, bats, rodents and dogs. A recent serosurvey indicated that cats might be susceptible to kobuvirus infection.[53] Subsequently molecular studies have identified kobuviruses by reverse transcription PCR (RT-PCR) in 13-14% of fecal samples of cats with diarrhea in South Korea[54] and Italy, but not in normal feces.[55] Genetic analysis of a feline kobuvirus has shown it belongs to a group of aichiviruses which include mouse and canine kobuvirus.[54,56]

Morbillivirus Infection

Feline morbillivirus belongs to the Paramyxoviridae family and was first identified in Asia.[57-59] The virus may be associated with tubulointerstitial nephritis, although concrete evidence is still lacking.

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Fungal Diseases

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CHAPTER 231

Cryptococcosis

Joseph Taboada

Client Information Sheet: Cryptococcosis

Cryptococcosis is an opportunistic systemic fungal infection of worldwide significance that usually initially infects the nasal cavity, paranasal tissues, or lungs. It can then disseminate, most commonly to the skin, eyes, or central nervous system (CNS). Disease occurs in a wide variety of mammalian species. Among domestic animals, it occurs most commonly in the cat, in which it is the most common of the systemic mycoses.[1] Unlike the other systemic mycoses, cryptococcosis does not follow strict geographic boundaries but is most common in the southeastern and southwestern United States, southern California, the western part of British Columbia, and the east coast of Australia.

Cryptococcosis is caused primarily by *Cryptococcus neoformans* and *Cryptococcus gattii,* saprophytic, round, basidiomycetous yeasts separated on the basis of numerous differences such as geographical distribution, ecological niches, epidemiology, pathobiology, clinical presentation, and molecular characters.[2] The genus *Cryptococcus* includes over 37 species, of which only a few have been implicated in causing clinical disease. *C. neoformans* (serotypes A, D, and AD) most commonly causes disease and is environmentally associated with pigeon droppings or other avian habitats. In people, infection with *C. neoformans* is most often associated with immunosuppression but the organism appears to be a primary pathogen of immunocompetent cats and dogs.[3] *C. gattii* (serotypes B and C) is a second species capable of causing disease that is generally seen to be restricted to the tropics and subtropics and is associated with bark and leaf litter of certain eucalyptus trees. Recently molecular typing techniques have been used to identify genotypes of cryptococcal organisms that cause disease. Eight major molecular types have been identified based on polymerase chain reaction (PCR) fingerprinting and other molecular techniques. *Cryptococcus neoformans* is now classified as VNI and VNII (which belong to serotype A), VNIII (serotype AD), and VNIV (serotype D), while *C. gattii* is classified as VGI and VGII (which belong to serotype B), VGIII, and VGIV (serotypes B or C).[2] Different molecular types have been correlated with geographic regions as well as with differences in *in vitro* drug susceptibility.[4]

Outbreaks of *C. gattii* have been noted in cats and dogs as well as humans residing in or traveling to the coastal Douglas fir biogeoclimatic zone of Vancouver Island in British Columbia, with recent spread of the species along the northwestern coast of the United States.[5-9] Molecular typing has been used to determine that the *C. gattii* species responsible for the outbreak in the Pacific Northwest was most likely of Australian or South American origin.

Cryptococcus is considered infectious as a desiccated yeast cell or basidiospore in the environment that enters the body primarily through the respiratory tract, where it infects nasal, paranasal, or lung tissue before disseminating more widely with a predilection for the CNS. In infected tissue, and often when cultured, the organism is a variable-sized yeast (3.5 to 7 microns) with a large heteropolysaccharide capsule (1 to 30 microns). Both species have been shown to cause disease in cats, dogs, and humans. *C. neoformans* is a more important cause of disease in situations of immunocompromise, while *C. gattii* often causes disease in patients with normal immune function.

The pigeon and other avian species are thought to be the most important vectors of *C. neoformans.* The *Cryptococcus* organism can be found in high numbers in pigeon roosts, barn lofts, haymows, and along cupolas and cornices where pigeons often sit. In the desiccated state, the *Cryptococcus* organism may be no larger than 1 micron and may survive up to 2 years.

Pathophysiology

Cryptococcosis is not a contagious disease. Infection occurs most commonly via inhalation of yeast from the environment. Debris and droppings in and around avian habitats, especially pigeon habitats, contain the largest numbers of *Cryptococcus* organisms. Most yeasts are probably too large to be inhaled into the lungs and settle out in the nasal cavity or nasopharynx, where they can produce disease or result in animals becoming asymptomatic carriers of the organism.[5,6,9] In one study, cryptococcal organisms could be cultured from nasal washings in 14% of asymptomatic dogs and 7% of asymptomatic cats.[7] The small, desiccated forms of the yeast are also infective and can be inhaled into the small airways and alveoli, leading to pulmonary disease but pulmonary disease is seen in less than 10% of dogs and cats. After inhalation into the nasal cavity, paranasal sinuses, or lungs, a cell-mediated immune response results in granuloma formation. Dissemination can occur by either direct extension or hematogenous spread. Direct extension from the nasal cavity through the cribriform plate to the CNS or to the paranasal soft tissues and skin is common. Although dissemination can be to any organ system, the skin, eyes, and CNS are most often affected.

Lesions consist of either granulomatous inflammation with few organisms or gelatinous masses of organisms with little inflammation. The large capsule surrounding the cryptococcal organism contributes to pathogenicity by inhibiting phagocytosis, plasma cell function, and leukocyte migration. As with the other systemic mycoses, the immune response determines the severity of clinical disease. Antibodies are readily produced by the humoral immune system but are not considered protective. Recovery, therefore, is dependent on cell-mediated immunity. Most human cases of cryptococcosis are associated with immune suppression, especially lymphoreticular neoplasia and HIV/AIDS. While immune suppression may play an important role in some veterinary species, especially with *C. neoformans* infection, *Cryptococcus* spp. are often a primary pathogen of immunocompetent cats and dogs. An association with feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) infections in cats has been reported, and chronic glucocorticoid use has been implicated as a predisposing factor in both cats and dogs.[10-13] The picture is complicated by the fact that infectious diseases such as cryptococcosis may cause changes in the immune system, making it difficult to determine if the immune system compromise is a cause or an effect of the disease process.[14]

Clinical Signs

Cats are more commonly affected by cryptococcosis than are dogs.[9,15] No apparent sex or age predilection exists in cats, but one large case series from southeastern Australia identified Siamese, Birman, and Ragdoll cats as being significantly overrepresented.[16] Clinical findings are usually related to upper respiratory, nasopharyngeal, cutaneous, ocular, or CNS involvement.[17] Unlike in other systemic mycoses, the lungs are not commonly clinically affected. Nonspecific signs such as depression and anorexia are common in chronic cases, but fever is uncommon. Upper respiratory signs associated with nasal cavity involvement are the most common clinical signs in cats, seen in 50% to 80% of affected cats. In these cats, sneezing and snuffling are common, and unilateral or bilateral mucopurulent nasal discharge with or without blood is typically seen. Proliferative soft tissue masses or ulcerative lesions within the nasal cavity, on the nasal planum, or over the bridge of the nose are seen in approximately 70% of cases with upper respiratory involvement (Figure 231-1).

FIGURE 231-1 Nasal cryptococcosis in a cat. (Courtesy Dr. Carol Foil.)

Oral ulcerations are occasionally noted but are not common. Nasopharyngeal mass lesions causing snoring, stertor, and inspiratory dyspnea are occasionally noted.[13] The skin or subcutaneous tissues are affected in approximately 40% to 50% of infected cats. Primary lesions include papules or nodules that may ulcerate and drain. Multiple lesions are typical, and regional lymphadenopathy is common. Hematogenous spread from the respiratory system may result in lameness secondary to osteomyelitis, renal failure secondary to renal disease, and generalized lymphadenopathy.

The eyes are affected in 20% to 25% of infected cats, especially those with CNS involvement (see ch. 11). Granulomatous chorioretinitis with or without exudative retinal detachment is the most common ocular manifestation and can lead to panophthalmitis. Less often, optic neuritis can be seen, resulting in blindness. Anterior uveitis is not as common as posterior segment disease.

CNS involvement is reported in approximately 20% of affected cats. This may be an underrepresentation of the actual number of cases with nervous system involvement.[13] The forebrain is most commonly affected, because invasion through the cribriform plate is thought to be common. Signs may include depression, behavior changes, seizures, circling, ataxia, blindness, head pressing, cranial nerve deficits, and paresis. Nasopharyngeal granulomas may occlude the auditory tube resulting in otitis media/interna and resultant peripheral vestibular signs.[18] Cats with concurrent FeLV or FIV infection tend to be more severely affected and may be more likely to develop neurologic or ophthalmic signs.

Canine cryptococcosis is typically seen in dogs younger than 4 years of age. No apparent sex predilection exists, and American Cocker Spaniels, Labrador Retrievers, Great Danes, and Doberman Pinschers appear to be overrepresented. In dogs, clinical findings associated with CNS involvement are most common, with other clinical findings most often related to upper respiratory, ocular, or cutaneous involvement.[17,19,20] As in cats, depression and anorexia are common but fever is not. CNS involvement is reported in approximately 50% to 80% of affected dogs. The brain is affected in most of these dogs.[20,21] The spinal cord may be affected along with the brain, and rarely the spinal cord alone is affected, causing signs consistent with either meningitis or an extradural compressive lesion.[22-24] Signs of nervous system involvement may include mental depression, vestibular syndrome, ataxia, cranial nerve deficits (especially cranial nerves V, VII, and VIII), seizures, paresis, blindness, hypermetria, and cervical pain. In dogs with CNS signs, other systems are usually affected as well, reflecting multisystemic dissemination.

The upper respiratory system or paranasal tissues are affected in approximately 50% of dogs with cryptococcosis (Figure 231-2).[19] The caudal nasal cavity and frontal sinuses are affected more often than is the rostral nasal cavity. Signs may include upper airway stridor, nasal discharge and sneezing, epistaxis, or firm swellings over the bridge of the nose.

FIGURE 231-2 Periocular swelling in a female Siberian Husky, caused by cryptococcal infection.

The eyes or periorbital tissues are affected in approximately 20% to 40% of affected dogs. Granulomatous chorioretinitis with or without exudative retinal detachment is the most common ocular manifestation and can lead to panophthalmitis. In addition to chorioretinitis, fundic examination may reveal retinal hemorrhage or retinal scarring (see ch. 11). Optic neuritis may be noted as a cause of blindness. As with the other systemic mycoses, anterior uveitis is less common than posterior segment disease.

The skin is affected in approximately 10% to 20% of dogs with cryptococcosis. Subcutaneous nodules with ulcerative draining lesions, often on the head, feet, nail beds, and mucous membranes of the mouth, occur most commonly. Proliferative lesions in the ear canals may result from cryptococcal otitis externa. Direct extension from the ears to the CNS may occur.

Abdominal or gastrointestinal involvement, either alone or with multisystemic involvement is occasionally reported.[25-27] Multiorgan dissemination is more common in dogs than in cats. Disease may be subclinical or may result in clinical signs referable to the organ systems affected. In one study, *C. neoformans* was the most likely isolated species in dogs, while *C. gattii* was the most often isolated species in cats.[9]

Diagnosis

Hematology and clinical chemistries are often normal in animals with cryptococcosis. Mild nonregenerative anemia and mature neutrophilia or neutrophilia with a mild left shift may be seen. Because the nervous system is so commonly affected, cerebrospinal fluid (CSF) tap for culture, cytology, and antigen determination should be considered (see ch. 115). CSF commonly yields increased opening pressure, increased protein, and mixed mononuclear and neutrophilic pleocytosis. Organisms are visualized in the CSF in approximately 90% of dogs with CNS cryptococcosis.[15,22] Because opening pressures are often high and may result in shifting of CNS tissue during CSF collection, CSF tap is only recommended if diagnosis cannot be made by less invasive means. Organisms can be visualized on cytology of other affected tissues between 50% and 70% of the time. Organisms are found on cytology more often from cats than from dogs.[9]

Nodular infiltrates, an interstitial pattern, pleural effusion, and tracheobronchial lymphadenopathy are occasionally seen on thoracic radiographs. Nasal radiographs and computed tomography may demonstrate increased soft tissue opacity and soft tissue and fluid opacification of the nasal cavity or frontal sinus, contrast-enhancing mass lesions of the nasal planum, and lysis of the nasal bones or cribriform plate. Brain

magnetic resonance imaging (MRI) findings in cats with CNS involvement include single or multifocal contrast-enhancing mass lesions (cryptococcomas) that tend to be hyperintense on T2-weighted (T2W) images and hypointense on T1W images. In some cats, lesions appear fluid-filled on T2W images but with more T1W intensity than expected for acellular fluid. The lesions may have surrounding T2 hyperintensity, consistent with edema.[15,28]

Organism identification allows for definitive diagnosis and can usually be made cytologically or histologically. Cytology from affected tissue is the quickest and easiest means of identifying cryptococcal organisms. Nasal swabs, exudate from cutaneous lesions, aspirates of masses, subretinal or vitreal aspirates, and CSF often reveal organisms. Organisms are apparent in approximately 50% to 75% of cases. The large capsule makes identification easy (Figure 231-3). Gram's stain is useful in looking for cryptococcal organisms, because the cells retain the crystal violet and the capsule stains lightly red with the safranin. If India ink is used, the organism and capsule appear unstained and silhouetted against the black background (Figure 231-4). Care must be taken in interpreting India ink preparations, as lymphocytes, fat droplets, and aggregated ink particles may be confused with the organism. Budding is occasionally noted. The thin wall and the large capsule differentiate *Cryptococcus* from *Blastomyces*.

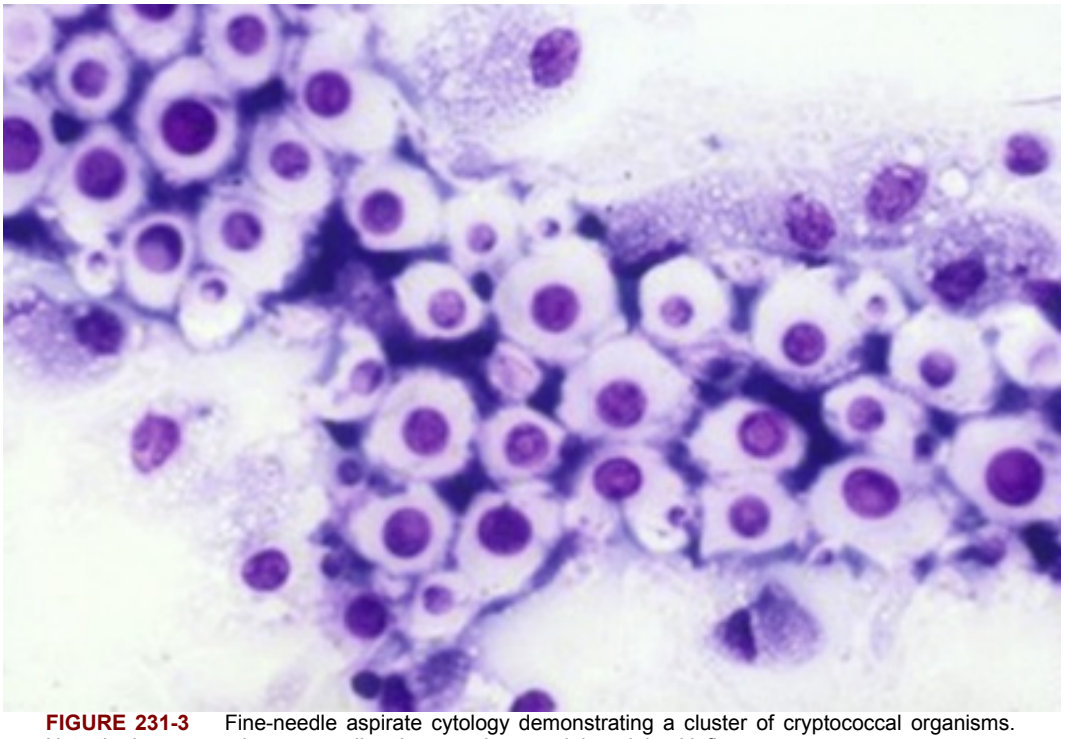

FIGURE 231-3 Fine-needle aspirate cytology demonstrating a cluster of cryptococcal organisms. Note the large capsules surrounding the organisms and the minimal inflammatory response.

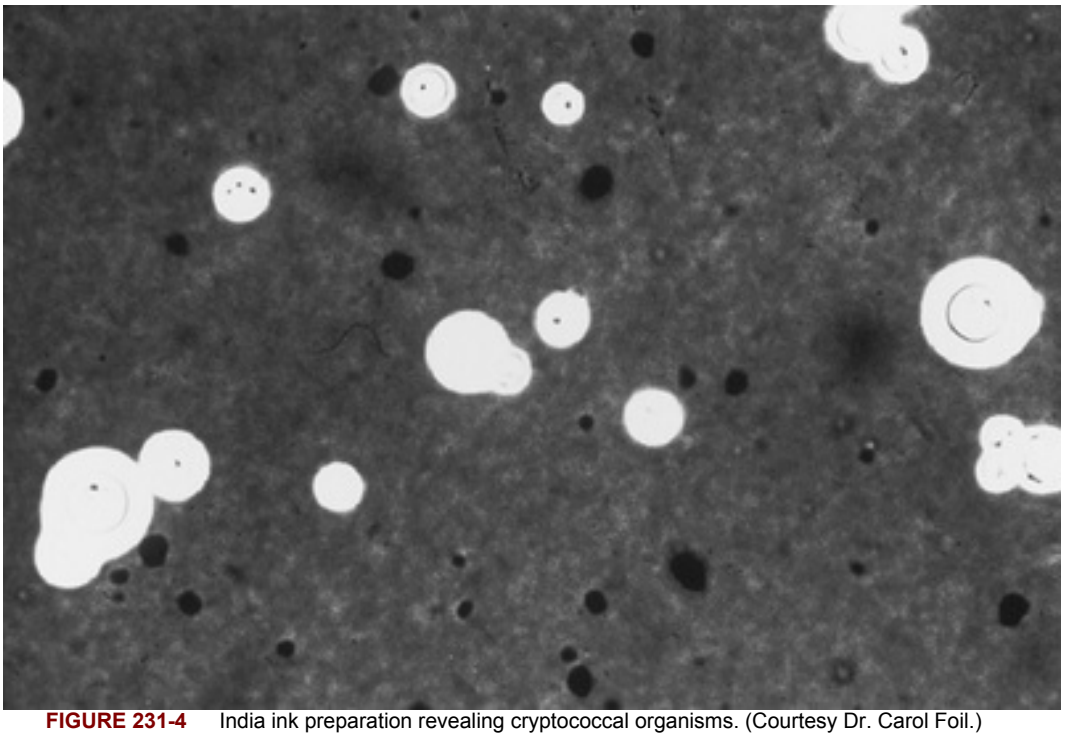

FIGURE 231-4 India ink preparation revealing cryptococcal organisms. (Courtesy Dr. Carol Foil.)

Histopathology should be used if cytology fails to identify organisms. Nodular to diffuse granulomatous lesions or areas of degeneration with little inflammation are seen in infected tissue. Yeastlike organisms are usually numerous. Special stains such as periodic acid–Schiff (PAS), Gridley's fungal, and Grocott's Methenamine Silver or Gomori methenamine silver (GMS) stain are best at demonstrating organisms. Mucicarmine stains best demonstrate the capsule.

Cryptococcal organisms grow readily when cultured. The organism can be cultured from infected tissue, exudate, CSF, urine, joint fluid, and blood if large enough samples are submitted. Yeastlike growth occurs in 2 days to 6 weeks on Sabouraud's dextrose agar. Hyphae rarely grow, even at 37° C. Care must be taken in interpreting positive cultures from the nasal cavity, because 14% of asymptomatic random-source dogs and 7% of asymptomatic random-source cats were culture-positive in one study.[5,6,10] Animals in the previously mentioned study were all negative on serum latex agglutination tests and did not have macroscopic or microscopic findings supportive of cryptococcal infection.

Serology is useful as an inexpensive and noninvasive diagnostic test and should be performed early in the diagnostic evaluation when cryptococcosis is suspected. Antibody titers are not useful diagnostically, because most infected animals do not mount a humoral immune response.[22] Commercially available latex agglutination assays for cryptococcal capsular antigen are both sensitive and specific tests that can be used on serum, urine, or CSF. CSF is the best sample to use in animals with neurologic signs, and serum is the best sample to use in animals with upper respiratory, cutaneous, or systemic signs but without neurologic signs. Most cases are positive with titers between 1 : 10 and 1 : 100,000. The median titer in infected cats in one study was 1 : 1000.[22] False-negative antigen titers are rare but may occasionally be seen in localized disease or if the organism fails to produce a capsule. False-positive antigen titers are uncommon and are usually related to technique or interfering substances such as rheumatoid factor (RF). Pretreatment of serum samples with pronase, a proteolytic enzyme, reduces the number of false-positive test results by eliminating nonspecific interference with macroglobulins, such as rheumatoid factors, as well as other unknown factors.[29] The latex agglutination antigen titer tends to correlate well with the extent of disease but does not correlate well with prognosis.[30] It may be used to evaluate the treatment progress and in determining how long to maintain an animal on antifungals.

Treatment

Cryptococcosis is a challenging disease to treat in cats and dogs and it typically requires protracted therapy and long-term follow-up. Few case-control or cohort studies with extensive treatment information are

available, but treatment evidence has recently been reviewed by the European Advisory Board on Cat Diseases.[31] While amphotericin B is the most effective treatment, azole monotherapy with either fluconazole or itraconazole is effective in many cases with and without CNS involvement.

Amphotericin B is the most effective drug *in vitro* against cryptococcal isolates and is generally recommended in infected people. Both itraconazole and fluconazole have proven to be equally efficacious to amphotericin B in treating CNS cryptococcosis in people, but the length of treatment can be quite long and the azole antifungals are generally recommended for consolidation therapy and for maintenance therapy after a course of amphotericin B has been given. Amphotericin B appears to be very effective in treating cryptococcosis in dogs and cats, but less information is available comparing it to using azole antifungals. Amphotericin B may be the treatment of choice in severely affected animals with CNS or systemic involvement but single agent azole antifungal therapy has been successful. Amphotericin B is synergistic with flucytosine. Flucytosine can be used at a dosage of 11.4 to 22.7 mg/lb (25 to 50 mg/kg) orally four times a day and has been used in dogs and cats. The combination of amphotericin B and flucytosine may be especially useful for treating CNS infections in cats. Cryptococcal organisms may rapidly develop resistance to flucytosine, so it has limited efficacy as a sole treatment agent. The dosage of flucytosine should be adjusted downward in animals with concurrent renal failure. Toxicosis from flucytosine includes ulcerative drug eruptions on the skin (especially on the face) and mucocutaneous junctions, enterocolitis, leukopenia, and thrombocytopenia that are especially prominent in dogs. Amphotericin B has also been effective when combined with azole antifungal agents.

Subcutaneously administered amphotericin B alone or in combination with azole antifungals or flucytosine has been used to successfully treat both feline and canine cryptococcosis.[3,32] Amphotericin B (0.22 to 0.36 mg/lb; 0.5 to 0.8 mg/kg) is diluted in 0.45% saline containing 2.5% dextrose (400 mL for cats, 500 mL for dogs <20 kg, 1000 mL for dogs >20 kg) and administered subcutaneously two to three times per week. This protocol may allow larger cumulative doses of amphotericin B to be given with reduced toxicosis. Concentrations greater than 20 mg/L of amphotericin B resulted in local irritation and sterile abscess formation; therefore, more concentrated formulations of amphotericin B should not be used subcutaneously.

The azole antifungals have expanded the treatment options available and are central to successful treatment either as sole agents or in consolidation therapy following amphotericin B–containing protocols. There was no significant difference in outcome between cats treated with amphotericin B–containing protocols and those treated with fluconazole or itraconazole.[3] Fluconazole (50 mg/cat PO q 12 h; 2.2 mg/lb [5 mg/kg] PO q 12 to 24 h for dogs) is very effective and is the treatment of choice for cryptococcosis in cats and probably dogs with mild to moderately severe disease. Fluconazole is considered the maintenance treatment of choice for human patients with or without HIV/AIDS diagnosed with cryptococcal meningoencephalitis.[33] However, recent work in murine models and in people with treatment failures has suggested that fluconazole monotherapy may not be an appropriate treatment, at least for meningoencephalitis.[4] Itraconazole (4.5 mg/lb [10 mg/kg] PO daily) is effective in cats and dogs but appears to require longer treatment times than fluconazole does. In one uncontrolled study evaluating long-term follow-up in cats and dogs with cryptococcosis, cats that were cured required median treatment times of 4 months for fluconazole and 9 months for itraconazole.[3] Controlled trials in people have revealed the two drugs to be equally efficacious but itraconazole monotherapy is considered more appropriate than fluconazole monotherapy for meningoencephalitis caused by azole-resistant molecular genotypes. Ketoconazole (4.5 to 13.6 mg/lb [10 to 30 mg/kg] PO q 12 h) is variably effective as a sole treatment agent but is ineffective in cases with CNS involvement. Terbinafine (4.5 mg/lb [10 mg/kg] PO q 24 h) can be used in combination with azole antifungals or in cases where azole antifungal resistance is suspected.

Resolution of clinical signs is the best means of patient monitoring, but the resolution of clinical signs is insufficient evidence that the infection has been eradicated, as improvement occurs well before all viable fungus has been cleared from host tissues. Serially monitoring latex agglutination antigen titers can significantly augment the clinician's clinical observations, but recurrence can occur despite a marked reduction in the serum antigen titer and even after the sterilization of the CSF in CNS infections.[12,30]

Rechecks should be performed at least monthly while dogs or cats are being treated with azole antifungals and should include a chemistry panel to evaluate liver enzymes and a latex agglutination antigen titer. Sequential titers should differ by two or more dilutions before they are considered significantly different. A decline of twofold to fourfold per month during the initial few months of antifungal therapy generally corresponds to an adequate clinical response. Ideally, treatment should be continued until the titer is negative or for at least 2 months beyond resolution of clinical signs. In some animals, detectable cryptococcal polysaccharide antigen persists in the circulation long after the infection has been successfully treated. This is

thought to be caused by continued elimination of unviable organisms and capsular material from infected tissues and macrophages. Most of these animals have low titers. High residual titers may indicate insufficient therapy and thus persistence of viable organisms.[12] One recommendation is to continue antifungal drug treatment to a titer of less than 1.[30] In cases in which there has been a 32-fold decrease and resolution of clinical signs, treatment may be discontinued; however, titers should be reevaluated periodically to ensure that they continue to decline or at least remain stable. Animals should be reevaluated at least 3 and 6 months after discontinuing treatment to assess for relapse. Negative antigen titers are occasionally seen in animals with localized disease, so they do not always indicate clinical cure.

Dogs or cats with cutaneous or subcutaneous granulomas may require surgical excision of the granulomas to effectively clear the organisms. Latex agglutination titers may not decrease until granulomas have been surgically excised and organisms within the granulomas may serve as a nidus for relapse. Because resolution may occur without surgery in some cases, it is recommended to first treat medically and to monitor the size of granulomas before deciding on a surgical option.

The prognosis is good for cats with extraneural disease, and it is guarded for dogs with any form of the disease and for cats with CNS involvement. About 75% of cats and 50% of dogs have been noted to respond successfully to treatment. Cats responding completely to treatment appear to have about a 15% to 20% relapse rate.[3] Cats with FIV do not appear to be less likely to respond nor does the species of *Cryptococcus* appear to significantly influence prognosis.[28]

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CHAPTER 232

Coccidioidomycosis

Jane E. Sykes

Client Information Sheet: Coccidioidomycosis (Valley Fever)

Etiology and Epidemiology

Coccidioidomycosis is a disease caused by soil-borne fungi belonging to the genus *Coccidioides.* In the environment, *Coccidioides* exist as a mycelium and in tissues as *spherules.* A mycelium is a chain of barrel-shaped arthroconidia (or arthrospores). The arthroconidia remain in the soil for long periods, ultimately fragment apart, are subsequently aerosolized and are inhaled by animal hosts. This in turn can lead to a localized pulmonary disease *(pulmonary coccidioidomycosis)* or a serious multisystemic disease *(disseminated coccidioidomycosis)* if there is an inadequate immune response.

In the soil, *Coccidioides* spp. are distributed in regions characterized by semi-arid to arid soils, low elevations above sea level and hot summers. *Coccidioides* spp. are found in the southwestern and western USA, eastern Washington state, Mexico, and parts of Central and South America. In the USA, highly endemic regions include the south-central valley of California ("valley fever") and Arizona, especially the greater Tucson and Phoenix areas.[1] Infections have also been reported in non-endemic areas in dogs and humans that have a history of travel to endemic regions. Two species of *Coccidioides* have been identified, *C. posadasii* and *C. immitis,* that appear to cause similar clinical manifestations with similar antifungal drug susceptibilities.[2] The geographic range of *C. immitis* is limited to the central valley of California, whereas *C. posadasii* is found elsewhere.[3]

Infection of animals and humans often follows a cycle of moist conditions, a dry period, then soil disruption, such as may occur with heavy rainfall, earthquakes, dust storms, prolonged droughts, or construction.[4-6] Dogs of any breed, age, or sex may be affected, although young adult dogs are at greatest risk.[7-9] Weimaraners, Dalmatians, Hungarian Vizslas, Norfolk Terriers, and Greyhounds appear to be predisposed.[9] Risk factors for infection in dogs from Arizona included being housed outdoors during the day, roaming an area > 1 acre, and walking in the desert.[10] Among dogs seen at the University of California, risk factors were digging behavior (which increased risk 6.7-fold) and a history of travel to or residence in the central valley of California or Arizona (which increased risk 4.4-fold).[9] Latent infections can occur in dogs and reactivate following treatment of other conditions with glucocorticoids or chemotherapeutic agents. Relapse can also occur with immunosuppressive drug treatment in dogs that have previously recovered from coccidioidomycosis. Coccidioidomycosis occurs in cats, but is rare.[11]

Pathogenesis and Clinical Features

Following inhalation, arthroconidia are phagocytosed by alveolar macrophages and then enlarge into a spherule (8 to 100 microns in diameter; Figure 232-1). Hundreds of endospores (3 to 5 microns in diameter) develop within each spherule and are released when the mature spherule ruptures. This is associated with a pyogranulomatous to granulomatous inflammatory response. Surviving endospores then enlarge into new spherules. In hosts unable to mount an effective immune response, endospores disseminate to lymph nodes in the respiratory tract and elsewhere. Inoculation coccidioidomycosis with a focal cutaneous lesion has been described rarely.[12] Most infections in endemic areas are subclinical.[13] Development of clinical signs often follows a subacute to chronic course, with mild systemic signs such as intermittent fever (range, 103 to 106° F [39.4-41.1° C], but typically low-grade), lethargy, inappetence, and weight loss.[7,14] Many dogs otherwise

appear healthy with only brief periods of inappetence.[7] Signs may be present for months to years before dogs are brought to a veterinarian.[8] Signs of respiratory tract involvement include a harsh cough, increased respiratory effort, tachypnea and/or exercise intolerance.[8,14] Rarely, diffuse fungal pneumonia follows a fulminant course.

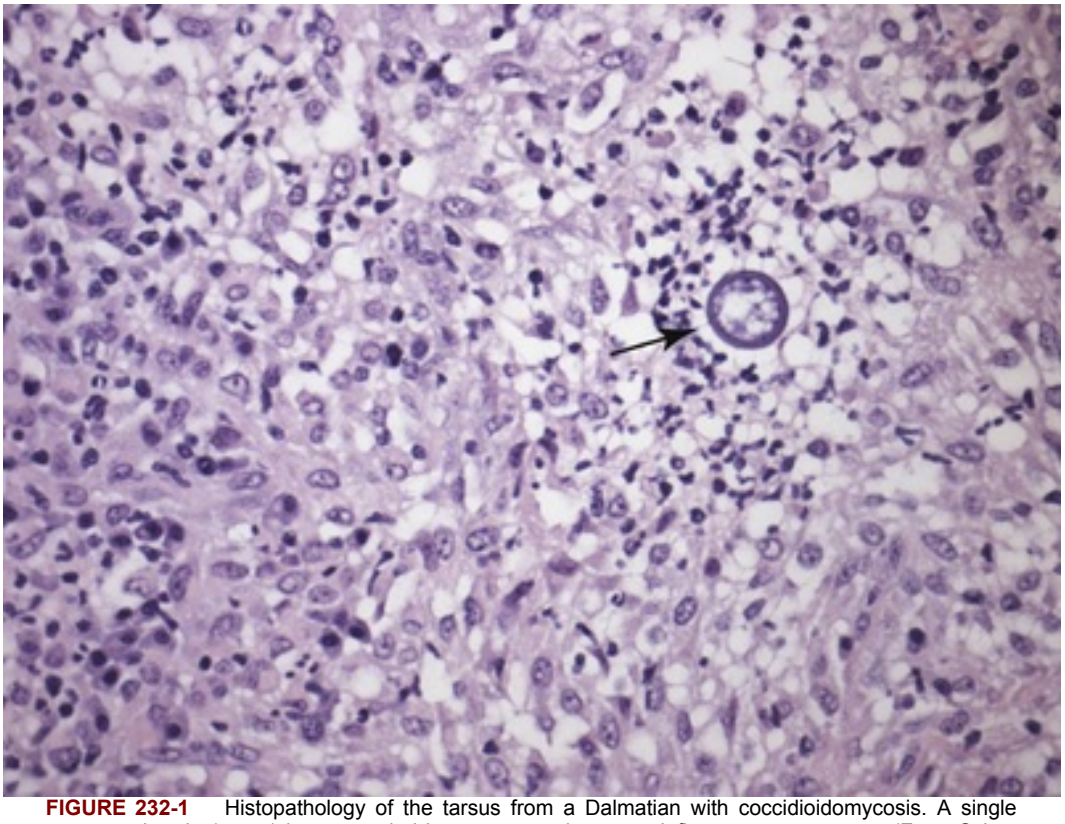

FIGURE 232-1 Histopathology of the tarsus from a Dalmatian with coccidioidomycosis. A single mature spherule (arrow) is surrounded by a pyogranulomatous inflammatory response. (From Sykes JE: *Canine and feline infectious diseases*, St Louis, 2014, Saunders.)

Sites of dissemination include bone, the central nervous system (CNS), skin, peripheral lymph nodes, and the pericardium.[8,15] Less commonly, joints, eyes, testes, gastrointestinal tract, prostate, liver, spleen, and urinary systems are affected.[7] Sometimes dissemination to only one site is detected. Evidence of past or current pulmonary involvement may be absent.[7] Bone involvement may be manifest as nonspecific pain, lameness, and/or one or more firm swellings associated with the appendicular or axial skeleton. Dogs with skin involvement may have ulcerated skin lesions that drain serosanguineous fluid, or subcutaneous mass lesions.[7] Neurologic signs resulting from fungal meningoencephalitis include obtundation, blindness, nystagmus, absent menace reflex, ataxia, postural reaction deficits, pacing, circling, cervical pain, tetraparesis, and seizures (see ch. 261).[8,16,17] Ocular manifestations include chorioretinitis, uveitis, and endophthalmitis (see ch. 11).[8,18,19] Liver or gastrointestinal tract infection can lead to gastrointestinal signs.[7] Pericarditis may lead to signs of right-sided heart failure, with development of ascites and pleural effusion (see ch. 254).[7] More than 50% of 48 cats with coccidioidomycosis had skin lesions.[11] Respiratory signs were present in 25% of affected cats, and lameness, ocular abnormalities, and neurologic signs in less than 20% of cats.

Diagnosis (Figure 232-2)

History, Physical Examination, Laboratory Results

Early diagnosis of coccidioidomycosis requires a high index of suspicion based on consistent clinical findings and a history of travel to or residence in an endemic region. Digging behavior or exposure to soil disturbance should increase suspicion. The diagnosis is usually confirmed with cytologic examination of aspirates or body

fluids, serologic tests that detect antibodies to *Coccidioides* spp., histology of biopsy specimens, or fungal culture.

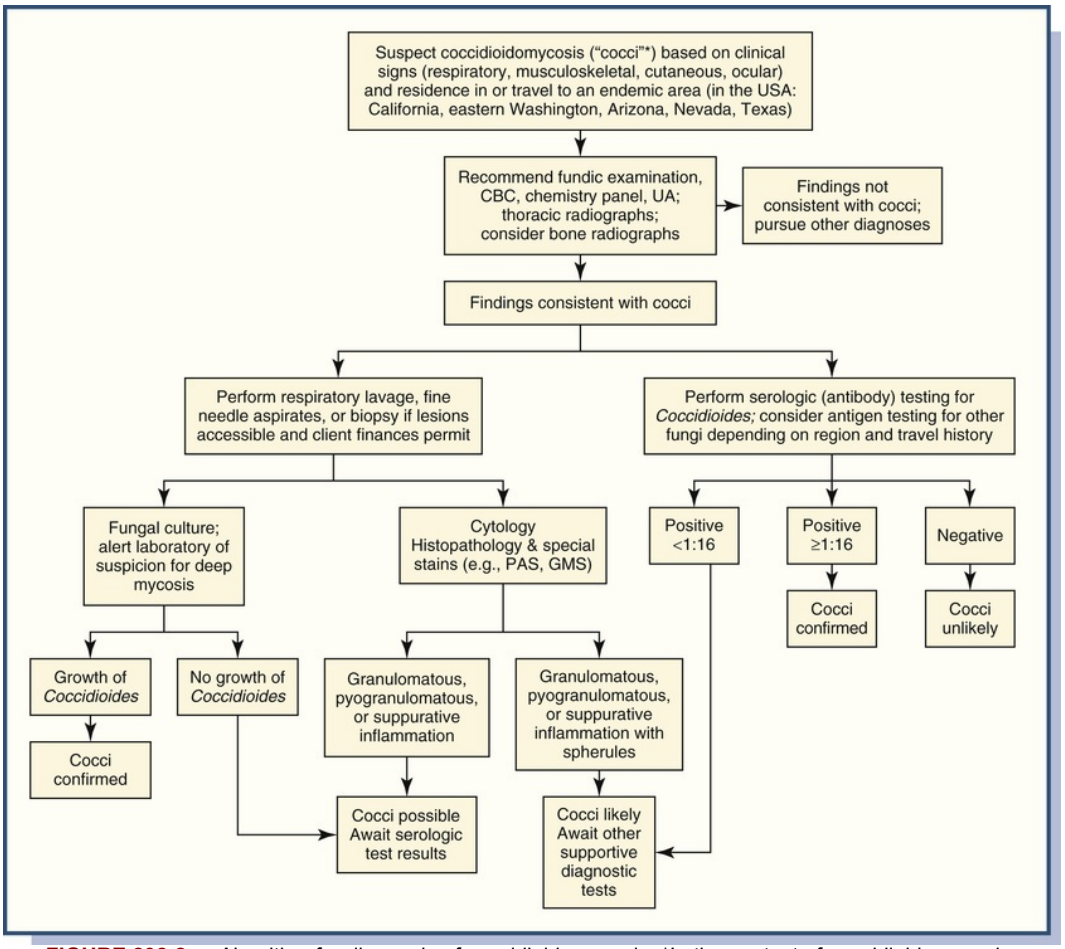

FIGURE 232-2 Algorithm for diagnosis of coccidioidomycosis. *In the context of coccidioidomycosis, "cocci" is pronounced "coxy." *GMS,* Gomori's methenamine silver; *PAS,* periodic acid-Schiff.

Laboratory testing of most affected dogs reveals mild non-regenerative anemia, mild neutrophilia, and hypoalbuminemia.[8,20] About half of affected dogs and cats are hyperglobulinemic.[8,11] Proteinuria has been detected in 60% of dogs, and can be severe (urine protein to creatinine ratios as high as 9.5, reference range < 0.5).[21] Some dogs have renal pathology consistent with immune-complex glomerulonephritis at necropsy and fewer had pyogranulomatous nephritis with intralesional spherules.[21] Cerebrospinal fluid (CSF) analysis (see ch. 115) in dogs with CNS involvement can reveal an increase in protein concentration (generally < 300 mg/dL; reference range < 25 mg/dL), and increases in nucleated cell counts (usually < 50 cells/mcL; reference range < 2 cells/mcL).[8] The differential cell count may show mixed or neutrophilic pleocytosis.

The most common radiographic finding in dogs with pulmonary coccidioidomycosis is hilar lymphadenomegaly (Figure 232-3).[8] Most dogs with hilar lymphadenopathy have mild to moderate pulmonary interstitial infiltrates. Nodular interstitial, interstitial-alveolar, bronchointerstitial infiltrates, and/or sternal lymphadenomegaly may also be present.[8,14] Dogs with pericarditis may have cardiomegaly and pleural effusion, with hepatomegaly and decreased abdominal detail.[20] Thoracic computed tomography (CT) findings include contrast-enhancing miliary nodular pulmonary lesions; single or multifocal masses; tracheobronchial, sternal, or mediastinal lymphadenopathy; focal regions of alveolar or peribronchial infiltrates; lobar consolidation; pleural or mediastinal thickening and rarely pleural effusion. Radiographs of affected bones reveal local periosteal proliferation as well as osteolysis and soft-tissue swelling (Figure 232-4).[7,11] Echocardiography in dogs with pericarditis may reveal thickening and mass lesions of the pericardium, pericardial and pleural effusion, and evidence of cardiac tamponade (see ch. 104 and 254).[20] Magnetic

resonance imaging (MRI) of the brain in dogs with CNS coccidioidomycosis may show focal hyperintense lesions within the brain on T2-weighted images. These are typically isointense on T1-weighted images and they enhance with contrast. Other findings include ventricular dilation and/or evidence of meningeal enhancement.

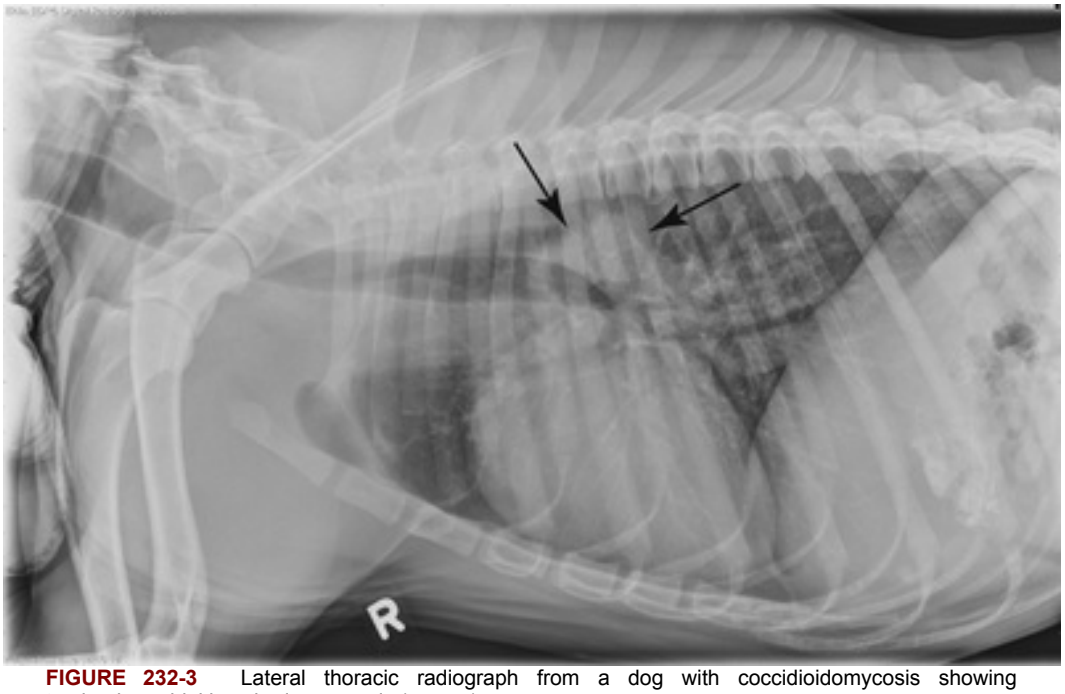

FIGURE 232-3 Lateral thoracic radiograph from a dog with coccidioidomycosis showing tracheobronchial lymphadenomegaly (arrows).

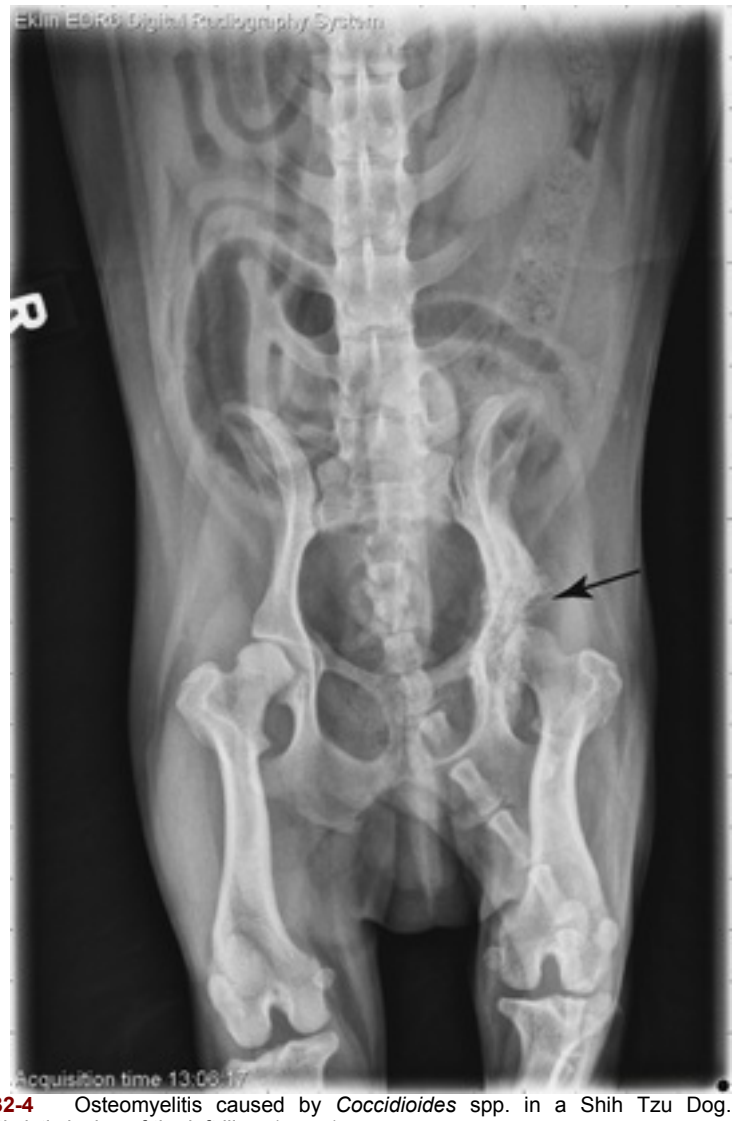

FIGURE 232-4 Osteomyelitis caused by *Coccidioides* spp. in a Shih Tzu Dog. There is a predominantly lytic lesion of the left ilium (arrow).

Cytologic examination of tissue aspirates (see ch. 86, 87, 89, and 93) or respiratory lavage specimens (see ch. 101) usually reveals granulomatous or pyogranulomatous inflammation. Uncommonly, spherules are visualized as deeply basophilic structures 8 to 70 microns in diameter (Figure 232-5).

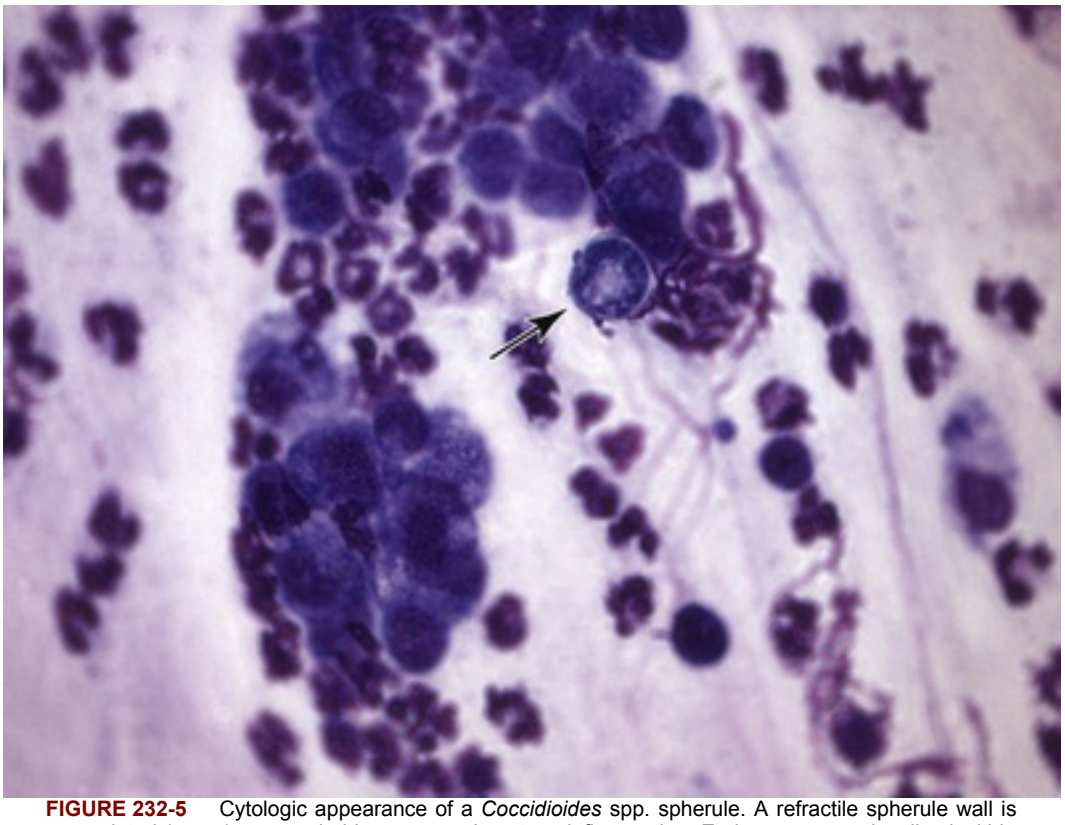

FIGURE 232-5 Cytologic appearance of a *Coccidioides* spp. spherule. A refractile spherule wall is appreciated (arrow) surrounded by pyogranulomatous inflammation. Endospores are visualized within the spherule as granular material.

Microbiological Tests

Serologic assays that detect antibodies to *Coccidioides* spp. are important diagnostic aides because cytology and histology are not sensitive for detection of this condition. Most laboratories screen specimens with qualitative gel immunodiffusion assays for IgG or IgM antibodies. Detection of IgM (tube precipitin) or IgG (complement fixating) antibodies is reported, depending on the antigen preparation used. In dogs, IgM is detectable within 2 to 5 weeks of infection, and IgG appears after 8 to 12 weeks.[15] Quantification of an IgG antibody response can then be performed with quantitative immunodiffusion.[13] False negative results are quite rare in dogs with coccidioidomycosis from California but have been described in dogs from Arizona.[8,20,22,23] Antibody titers typically range from 1 : 2 to 1 : 256; with a median of 1 : 32 in one study.[8] Dogs with active infection may have titers as low as 1 : 2, and healthy dogs in hyperendemic areas in Arizona have had titers as high as 1 : 16.[13] Positive titers of 1 : 16 or lower should always be interpreted in the context of clinicopathologic abnormalities. In hyperendemic areas, additional tests should be employed for diagnosis confirmation. A serologic assay that detects *Coccidioides* antigen in urine has unacceptably low sensitivity (≤20%) and is not recommended.[24] *Coccidioides* spp. can be isolated from clinical specimens on routine fungal media. Culture of *Coccidioides* spp. is a laboratory health hazard and should only be performed in suitably equipped locations. The laboratory should be warned of the suspicion for a dimorphic fungal infection.

Treatment and Prognosis

Treatment generally consists of a combination of prolonged antifungal drug therapy, supportive care, and in some cases, surgery. Animals with pulmonary coccidioidomycosis may respond well to monotherapy with fluconazole (5-10 mg/kg PO q 12 h) or itraconazole (5 mg/kg PO q 24 h). Itraconazole is preferred for animals with bone involvement and may be effective in dogs that fail to respond to treatment with fluconazole. Treatment with deoxycholate amphotericin B or lipid-complexed amphotericin B is recommended either alone or in combination with an azole antifungal for dogs with refractory or disseminated disease. The reader is referred to ch. 162 and 233 for dosing protocols for amphotericin B. Voriconazole and posaconazole have

been used to treat refractory coccidioidomycosis in people.[1] Voriconazole could be considered for treatment of refractory meningoencephalitis in dogs due to its excellent CNS penetration, if client finances permit its use.

Dogs with persistent osteomyelitis may require amputation for infection control. Enucleation may be required in dogs with endophthalmitis. *Coccidioides* pericarditis has been successfully managed after subtotal pericardiectomy, epicardial excision, and antifungal drug therapy. Perioperative mortality rate was reported as 24%.[20] Other treatments that may be required for dogs with severe pulmonary coccidioidomycosis include oxygen supplementation (see ch. 131), drainage of thoracic effusions (see ch. 100 and 102), nutritional support (see ch. 82 and 189), anti-inflammatory drugs (see ch. 164) and IV fluid therapy (see ch. 129). Concurrent treatment with glucocorticoids and anti-seizure medications may be necessary in dogs with CNS coccidioidomycosis (see ch. 35 and 261). Topical prednisolone acetate solution and anti-glaucoma agents may be required for dogs with ocular lesions.

Treatment duration ranges from 6 months to many years. In some dogs, life-long treatment is needed. IgG titers decrease with successful treatment, which should be continued until lesions resolve and the titer is 1 : 2 or lower. Dogs with localized pulmonary infection have the best prognosis.

Public Health Aspects

Coccidioidomycosis is a serious infection in people. Individuals involved in construction, agriculture, and excavation are at high risk in endemic areas.[1] African American and Filipino patients, as well as patients with acquired immunodeficiency syndrome (AIDS) and women in the third trimester of pregnancy, are at risk for disseminated disease, which occurs in approximately 0.5% of infected humans.

Dogs have been used as a sentinel for human exposure to environmental sources of *Coccidioides* spp.[25] Direct transmission as a result of contact between infected pets and humans has not been reported. However, inoculation coccidioidomycosis may follow bites from animals with disseminated infections or after injury with a contaminated instrument. If accidental inoculation occurs, people should seek immediate medical attention. Prolonged fluconazole prophylaxis is generally recommended with monitoring of *Coccidioides* serology and liver function tests. Necropsies should be performed without delay with suitable protective clothing, and the carcasses of animals that die from coccidioidomycosis should immediately be incinerated, because conversion of the organism to a mycelial form can occur after death. For the same reason, burial is not recommended because of the potential for contamination of the environment. Prophylaxis is also indicated after accidental laboratory exposure.[26]

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CHAPTER 233

Blastomycosis and Histoplasmosis

Andrea Dedeaux, Joseph Taboada

Client Information Sheets:
Blastomycosis
Histoplasmosis

Blastomycosis

Blastomycosis is a systemic fungal infection that usually originates in the lungs and then disseminates. In endemic areas, blastomycosis usually occurs as a sporadic event, but outbreaks are occasionally observed in both dogs and people.[1-4] Epidemiologically, outbreaks can often be traced back to a common point source in the environment from which infective spores had been aerosolized for a limited period of time.

The dimorphic fungus *Blastomyces dermatitidis* is the causative agent of blastomycosis. In infected tissue or when cultured at 37° C, the organism is a thick-walled yeast that reproduces by budding. Most often, organisms in tissue have a single bud, attached to the mother cell by a broad base. When cultured at 25° C, mold colonies grow slowly and contain branching, septate 1- to 2-micron mycelia.

Disease occurrence is reported primarily in a geographically restricted distribution that follows the Mississippi, Ohio, Missouri, Tennessee, and St. Lawrence Rivers, the southern Great Lakes, the southern Mid-Atlantic states, northern California, Pacific Northwest, and the Canadian provinces of Alberta, Manitoba, Ontario, Quebec, and southern Saskatchewan (Figure 233-1).[4,5] Within these geographic regions, infections are generally limited to smaller geographic pockets, with most affected animals living within a quarter of a mile of water.[2,6,7]

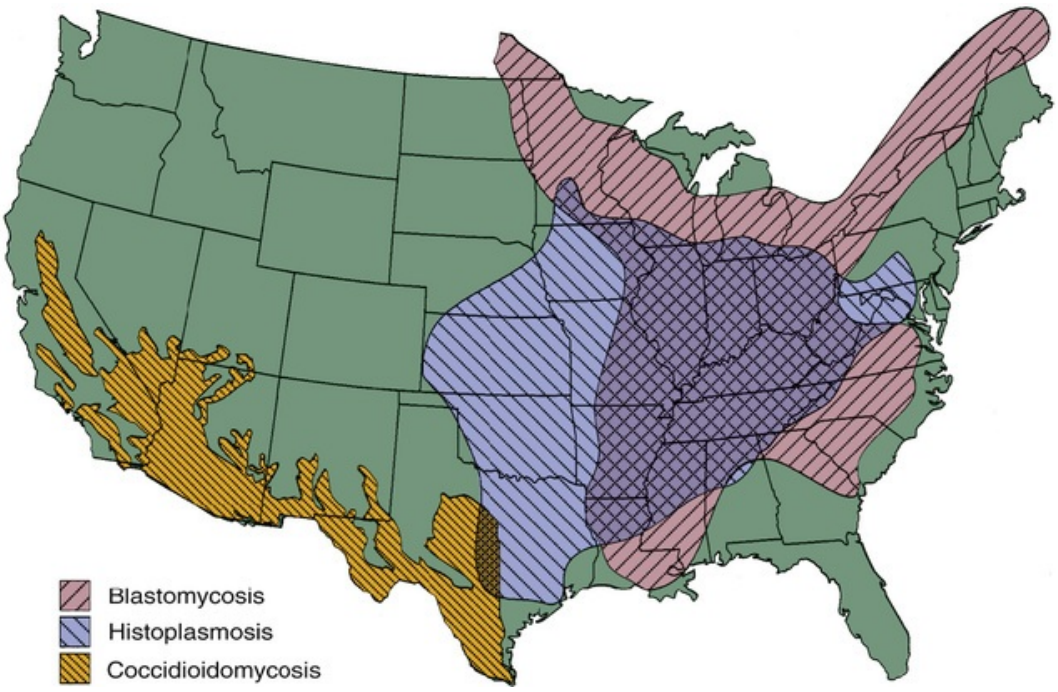

FIGURE 233-1 Areas in North America where blastomycosis, histoplasmosis, and coccidioidomycosis are endemic.

Pathophysiology

Blastomycosis is not a contagious disease. It follows contact with the organism in the environment. Infection usually occurs via the respiratory route after the host inhales infective conidiophores. Rarely, subcutaneous disease may be seen after direct inoculation.[8] The incubation period varies from 5 to 12 weeks. Rain, dew, fog, or mist may play a critical role in liberating conidiophores. In addition, activities that disrupt the soil such as digging or construction may play a role in spore aerosolization. After inhalation, conidia are phagocytized by alveolar macrophages and transform from the mycelial phase to the yeast phase. The yeast stimulates local cell-mediated immunity, which results in a marked suppurative to pyogranulomatous inflammatory response. In some cases, the cell-mediated immune response controls infection locally; in others, phagocytized yeasts are transported into the pulmonary interstitium, where they gain access to both lymphatic and vascular systems. Hematogenous and lymphatic dissemination then results in multisystemic pyogranulomatous disease. Although dissemination can be to any organ system, the lymph nodes, eyes, skin, bones, subcutaneous tissues, and prostate are organs commonly affected in dogs[6,9,10]; skin, subcutaneous tissues, eyes, central nervous system (CNS), and lymph nodes are most commonly affected in cats.[11,12]

The immune response determines the severity of clinical disease. Recovery from infection is dependent on cell-mediated immunity. An adequate immune response may result in mild respiratory disease that resolves spontaneously. If dissemination has occurred, disease may be obvious in other organ systems, even without apparent pulmonary involvement.

Clinical Signs

Bluetick Coonhounds, Treeing Walker Coonhounds, Pointers, Weimaraners and retrievers have the highest risk of infection.[4,5,13] Males are affected more commonly, and although any age dog can be affected, those in the 2- to 4-year age group have the highest incidence of disease. Exposure to possible environmental sources of infection, close proximity to water, and the likelihood of being housed in outdoor kennels probably explain the breed association.

Nonspecific signs such as anorexia, depression, weight loss, cachexia, and fever are common. Approximately 40% of dogs are febrile. Pulmonary signs are seen in 65% to 85% of affected dogs, ranging from mild respiratory distress when exercised to severe dyspnea at rest. Hypoxemia resulting in cyanosis has a negative prognostic significance.[10] A dry, hacking cough is common. Enlarged perihilar lymph nodes compressing primary bronchi, as well as infiltrative bronchointerstitial and alveolar disease, contribute to the cough. Pleural effusion, pleuritic pain, chylothorax, solid granulomatous masses, and pulmonary thromboembolism are uncommonly reported complications of blastomycosis.

Diffuse lymphadenopathy is seen in about 40% to 60% of dogs with blastomycosis. Cutaneous signs are reported in about 30% to 50% of affected dogs and are also commonly noted in affected cats. The reported prevalence of skin disease is likely underestimated as lesions are small and easily can be overlooked. Single or multiple papules, nodules, or plaques that can ulcerate and drain a serosanguineous to purulent exudate characterize typical skin lesions. The nodular lesions are often quite small in dogs, but large abscesses occasionally occur, especially in cats. Paronychia is common in dogs, so the feet and nail beds should be closely examined.

Ocular involvement is noted in 20% to 50% of cases, with approximately 50% of affected dogs having bilateral involvement. Posterior segment disease usually occurs initially. Optic neuritis may signify more diffuse CNS involvement and a poorer prognosis. Anterior segment disease is usually secondary to the posterior segment involvement. It may be characterized by conjunctivitis, keratitis, iridocyclitis, and eventually anterior uveitis and endophthalmitis. Secondary glaucoma is common. Dogs that are blind at the time of initial diagnosis rarely regain vision.

Lameness caused by fungal osteomyelitis or painful paronychia is noted in about 25% of dogs with blastomycosis, and fungal osteomyelitis is noted in about 10% to 15% of dogs with blastomycosis. The pain and swelling are usually noted over epiphyseal regions below the elbow or stifle. Single lesions are more common than multiple.[14]

Mycotic mastitis or fungal prostatitis or orchitis is seen in approximately 5% to 10% of affected dogs.[15]

Testicular infection with blastomycosis without evidence of disseminated disease has been reported.[16]

Neurologic signs, often associated with diffuse or multifocal disease, are seen in less than 5% of dogs but are more common in cats (Figure 233-2); however, brain involvement may be present without neurologic signs, making the prevalence of CNS infection greater than expected.[17] Computed tomography (CT) or magnetic resonance imaging (MRI) should be considered in any dogs and particularly cats diagnosed with blastomycosis, even if obvious neurologic signs are not apparent. Other potential sites of infection include heart, pericardium, cranial mediastinum, liver, spleen, kidney, and nasal cavity.[18-20]

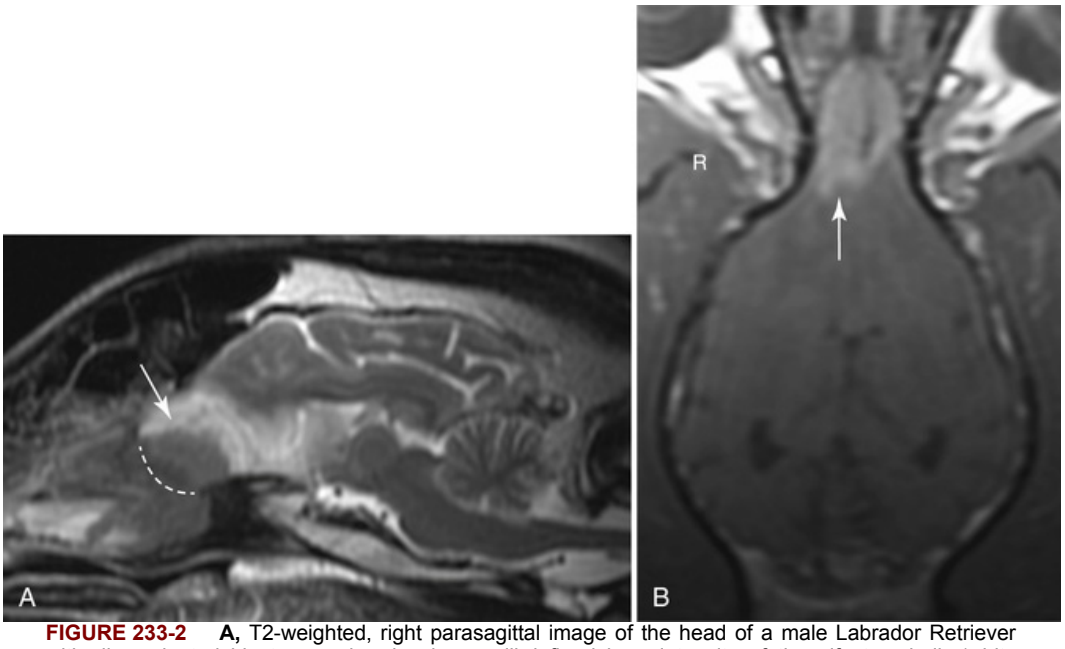

FIGURE 233-2 **A,** T2-weighted, right parasagittal image of the head of a male Labrador Retriever with disseminated blastomycosis, showing an ill-defined hyperintensity of the olfactory bulb (white arrow) extending from the cribriform plate (dotted line) to the level of the sella turcica and involving the right frontal lobe. **B,** T1-weighted, post-contrast enhanced coronal image of the head showing enhancement of the right olfactory bulb (arrow), cribriform plate, ethmoid turbinate with extension to the left olfactory bulb. (Courtesy Dr. Lorrie Gaschen.)

Feline blastomycosis is less common than canine blastomycosis.[5,11,12,21-23] Most of the clinical signs observed in dogs are also noted in cats. The main differences are that large abscesses are more common in cats than in dogs, and neurologic involvement is often noted.

Diagnosis

Blastomycosis is usually fairly easy to diagnose because of the large numbers of characteristic yeasts found within lesions, especially within infected skin, eyes, and lymph nodes.[6,22,24,25] Complete blood count (CBC) results are often normal. A mild nonregenerative anemia and mature neutrophilia or neutrophilia with mild left shift may be seen.[26] Chemistry results are often unremarkable, although hypoalbuminemia is the most consistent abnormality. Mild hypercalcemia is noted in up to 10% of cases.[27] Severe hypercalcemia requiring treatment is occasionally seen. Excessive production of 1,25-dihydroxy-vitamin-D has been reported in a cat. Ionized hypercalcemia resolved with antifungal treatment.[23] Hypercoagulability is also a sequela of *B. dermatitidis* infection.[26]

Thoracic radiographs reveal an interstitial pattern in about 70% of canine cases. Although a nodular interstitial pattern is classically observed (41% of cases), diffuse interstitial (24%) and bronchointerstitial (5%) patterns may also be prominent findings (Figures 233-3 to 233-5). An alveolar or mixed interstitial-alveolar pattern is observed in about 20% of dogs, and tracheobronchial lymphadenopathy is noted in about 30%. Radiographic patterns mimicking other diseases are not as common. Pleural effusion and pneumothorax are rarely observed.[28] Osteolytic bone lesions may be noted on the ends of long bones of distal limbs (Figure 233-6). The forelimbs are affected more commonly than the rear limbs, with most limb lesions being distal to the

elbow or the stifle. Periosteal proliferation and soft-tissue swelling are noted in about 50% of lesions.

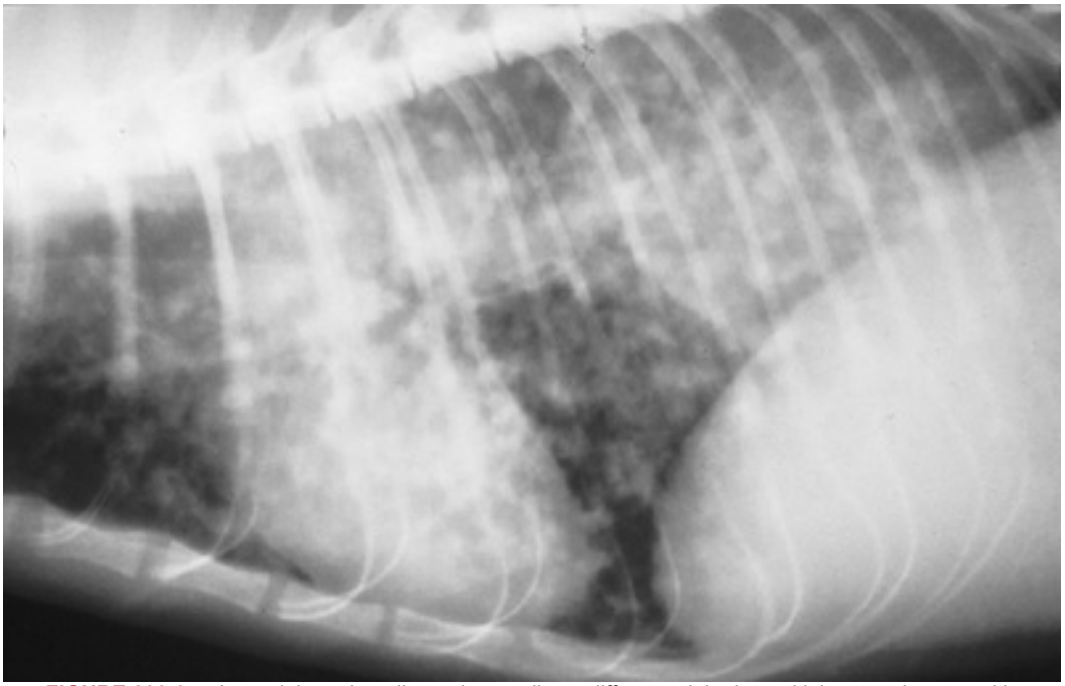

FIGURE 233-3 Lateral thoracic radiograph revealing a diffuse nodular interstitial pattern in a cat with blastomycosis.

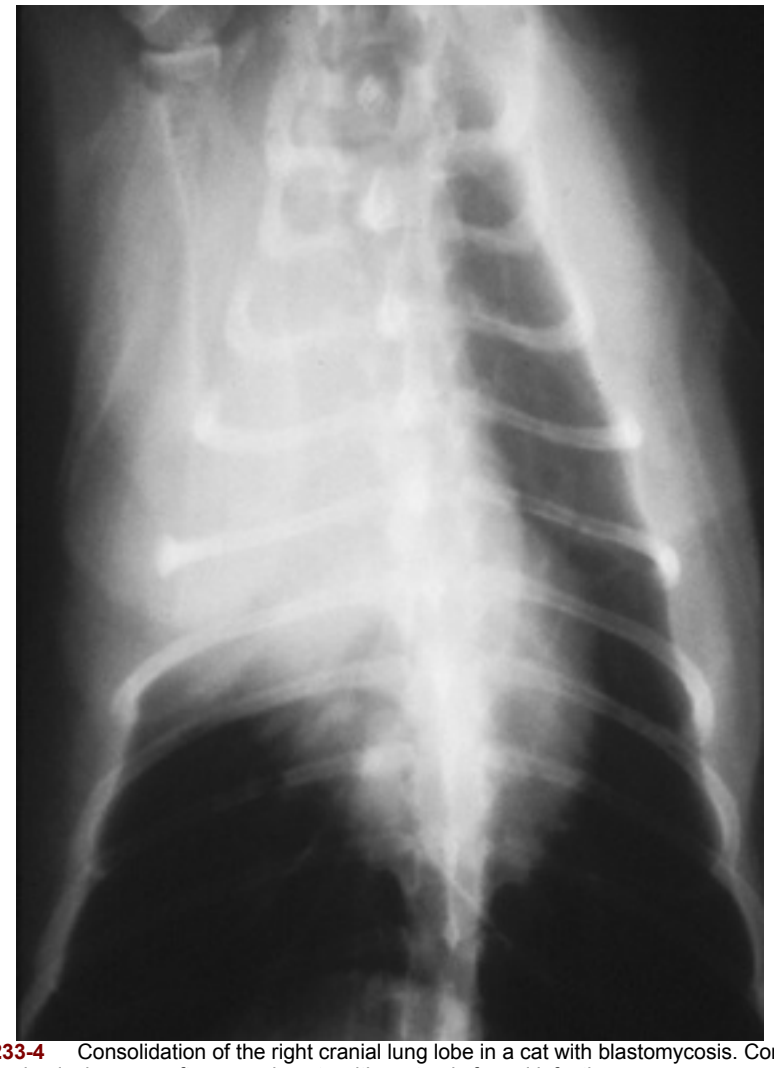

FIGURE 233-4 Consolidation of the right cranial lung lobe in a cat with blastomycosis. Consolidating and abscessing lesions are often seen in cats with systemic fungal infections.

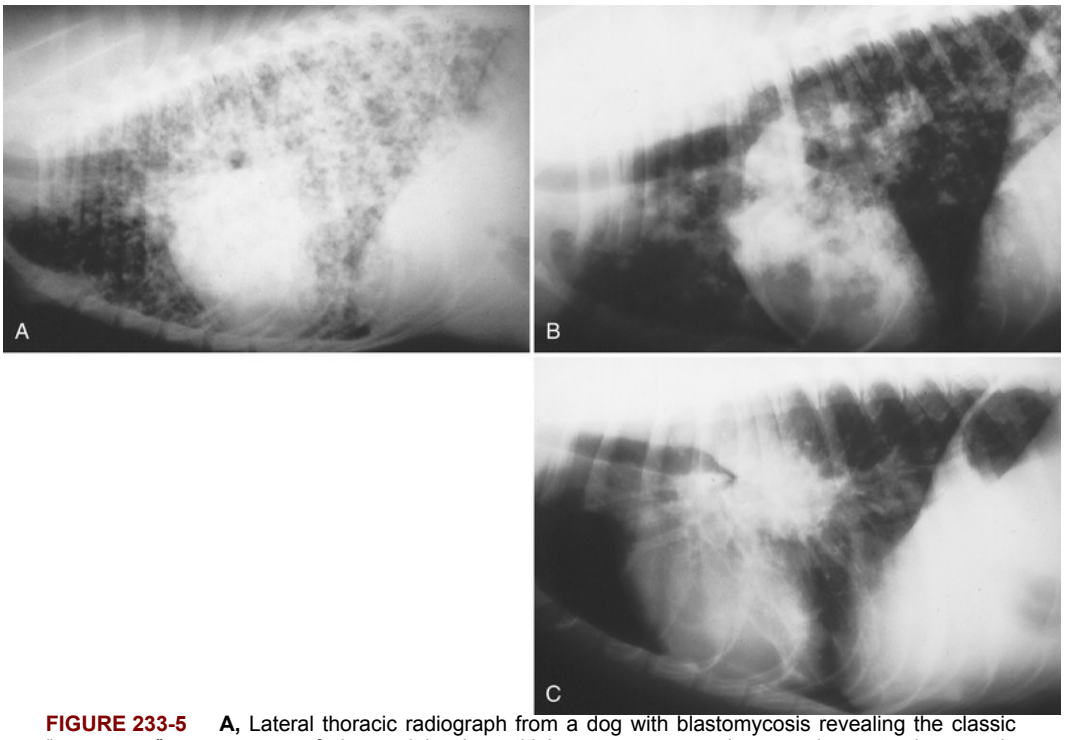

FIGURE 233-5 **A,** Lateral thoracic radiograph from a dog with blastomycosis revealing the classic "snowstorm" appearance of the nodular interstitial pattern commonly seen in systemic mycotic infections. **B,** Lateral thoracic radiograph from a dog with blastomycosis showing multiple large, ill-defined nodules and a bronchointerstitial pattern. **C,** Lateral thoracic radiograph from a dog with blastomycosis showing perihilar lymphadenopathy and a patchy interstitial pattern. Perihilar lymphadenopathy is common in systemic fungal infections, especially histoplasmosis and coccidioidomycosis.

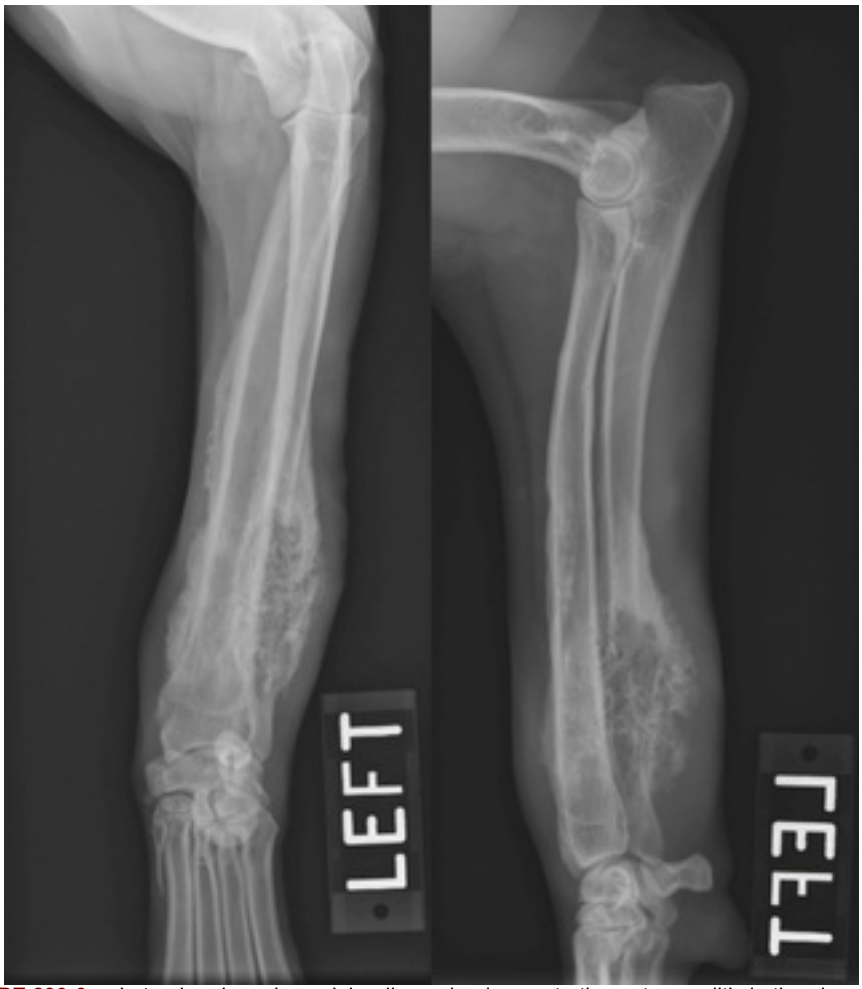

FIGURE 233-6 Lateral and craniocaudal radiographs demonstrating osteomyelitis in the ulna of a 5-year-old female spayed Doberman that presented for lameness and suspected osteosarcoma. Cytologic evaluation revealed *Blastomyces dermatitidis*. (Courtesy Dr. Kyle Vititoe, University of Illinois.)

Cross-sectional imaging has become an important tool in evaluating patients for potential CNS involvement. On magnetic resonance imaging (MRI), CNS lesions are often characterized as broad-based, extra-axial intracranial lesions that commonly occur in the frontal lobe with meningeal enhancement and perilesional edema present. These lesions appear hypo- to isointense on T1, hyperintense on T2, and enhance after contrast administration. Most dogs with evidence of CNS infection also have disseminated disease, although primary CNS blastomycosis has been reported.[29] Lesions may occur secondary to hematogenous spread or as a result of extension of disease from the nasal cavity, sinuses, and orbit and into the calvarium.[17,29,30] Instead of a mass-like lesion, some affected animals only demonstrate evidence of inflammation and ventriculomegaly on MRI and CT.[31,32] Cerebrospinal fluid (CSF) analysis (see ch. 115) often reveals neutrophilic pleocytosis and increased protein concentration. Organisms may not be identified on cytological examination of CSF.[29]

Definitive diagnosis is made by organism identification. This can be done by cytology or histology. Cytology from affected tissue typically reveals pyogranulomatous or suppurative inflammation, often with thick-walled yeasts (8 to 12 microns in diameter, with 0.5- to 0.75-micron-thick walls) that bud to form daughter cells from a broad base (Figure 233-7).[24,33] Skin lesions yield organisms about 80% of the time and are the easiest and most useful site for cytologic diagnosis (see ch. 86). Vitreal aspirates yield organisms from almost all affected eyes, and lymph node aspirates yield organisms approximately 60% of the time (see ch. 95). Bone and lung aspirates, transtracheal wash cytology, and bronchoalveolar lavage each yield organisms less often (see ch. 101).[6,34] Urinalysis or prostatic wash cytology rarely reveals organisms (see ch. 111).[33] Rarely, organisms may appear on fecal examination (see ch. 81).[35] Care must be taken when handling samples that may contain yeast cells. Direct inoculation of organisms from needle-stick injury may result in

localized cutaneous disease.[8]

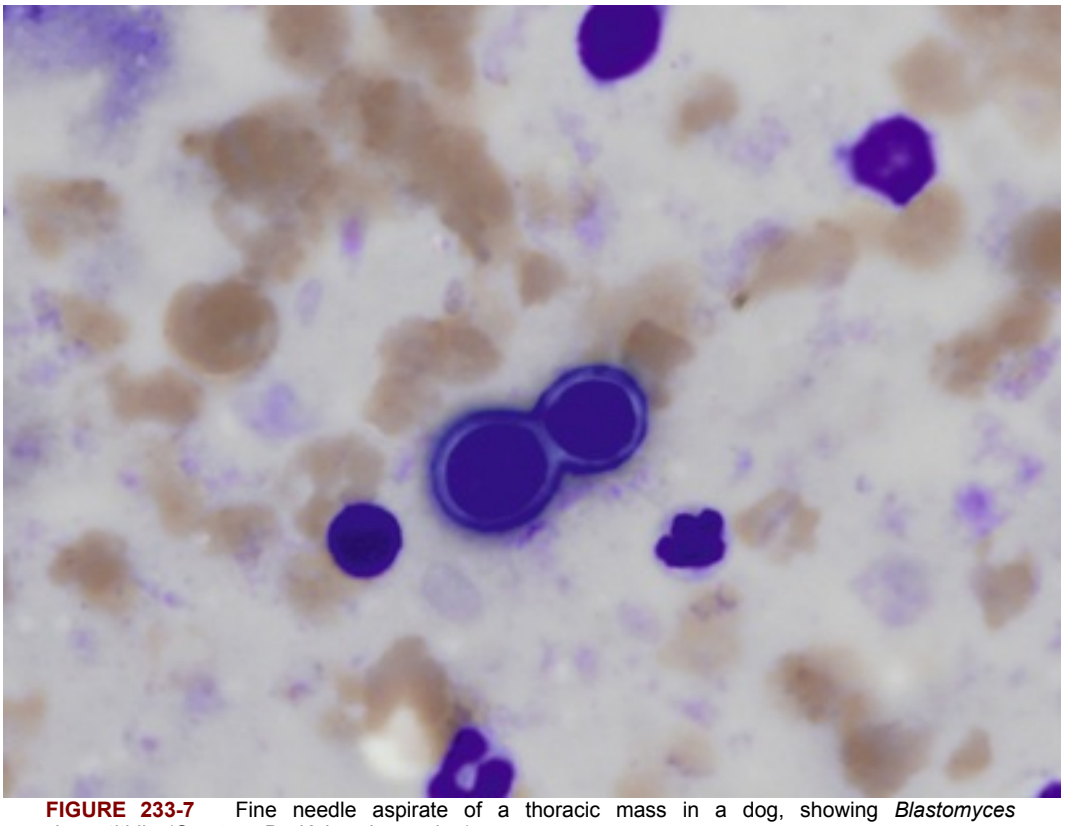

FIGURE 233-7 Fine needle aspirate of a thoracic mass in a dog, showing *Blastomyces dermatitidis*. (Courtesy Dr. Kelsey Legendre.)

Histopathology is generally characterized by purulent to pyogranulomatous inflammation, with broad-based organisms usually being apparent. Special stains such as periodic acid–Schiff (PAS), Gridley's fungal, and Gomori's methenamine silver (GMS) stain are best for demonstrating organisms. Polymerase chain reaction (PCR) has recently been used to identify organisms in tissue.[36]

Culture is not needed for definitive identification in clinical cases. Culturing the organism from the environment is rarely achieved. Culture of blastomycosis presents a significant health risk to diagnostic laboratory personnel if specimens are not handled properly.[37]

A *Blastomyces* antigen enzyme immunoassay (EIA) has been used in both serum and urine to detect cell wall galactomannan that is immunologically indistinguishable in histoplasmosis and blastomycosis.[38] Antigen testing was sensitive in a group of dogs with blastomycosis. Testing urine yielded a higher sensitivity when compared to testing serum. The antigen test shows cross-reactivity with histoplasmosis, and other fungal diseases. Therefore, the test is useful in supporting a diagnosis of fungal disease but is not effective in making a definitive diagnosis of a specific fungal infection. Antigen concentrations correlate with severity of disease and will decrease with successful treatment, making the test useful in following response to therapy and as a predictor of relapse.

Serology assessing for the presence of antibodies against *Blastomyces* is generally considered to have low sensitivity and specificity. In one recent study, serology was positive in only 50% of dogs with confirmed blastomycosis.[33] Antibody titers, most commonly measured via agar gel immunodiffusion (AGID), have not proven useful in following response to therapy and are not more sensitive than antigen testing.

Treatment

All dogs and cats with blastomycosis should be treated. Itraconazole is presently considered the treatment of choice, except in cases of moderate to severe hypoxemia or CNS infection, when amphotericin B should still be considered the drug of first choice (see ch. 162).[10] Clinical cures can be expected in 70% to 75% of treated

cases. Treatment failure is most likely in dogs that are hypoxemic or have three or more organ systems affected. In cats, treatment failure has been associated with latent CNS involvement. The dosage of itraconazole that has proven effective is 5 mg/kg orally once a day or divided twice a day. The drug should be continued for 2 to 3 months or until active disease is not apparent. Response to itraconazole treatment is minimal during the initial 1 to 2 weeks. A loading dose of 10 mg/kg daily for the first 3 days of treatment may minimize this lag time. Recurrence occurs in approximately 20% of treated dogs from months to years after treatment has been discontinued.[6,10] Cats require a higher dosage of itraconazole: 10 mg/kg once a day or divided twice a day, and longer courses of treatment as compared to dogs.

Fluconazole is generally considered to be less effective in treating blastomycosis compared to itraconazole. Relapse rates may be higher.[39] However, fluconazole treatment may be more cost-effective than itraconazole or newer azole antifungal drugs. Longer duration therapy using fluconazole has proven effective in treating blastomycosis, making it often the first choice drug. Because fluconazole is excreted in the urine and crosses the blood-brain, blood-ocular, and blood-prostatic barriers well, it may be a more appropriate treatment choice for urinary tract, prostatic, and CNS infections.[39]

Adverse effects of the azole antifungal agents are similar across the class. Ketoconazole is the least tolerated, and fluconazole appears to be the best. Dosage-related gastrointestinal (GI) side-effects (anorexia and vomiting) are most common, especially in cats. When these occur, dividing the dose into two treatments or reducing the dosage may be of benefit. Liver enzymes should be monitored in animals being treated with azole antifungals. Asymptomatic increases in transaminase concentrations are seen in about half of animals treated with itraconazole and about 20% of dogs treated with fluconazole but do not warrant a change in therapy unless the patient is experiencing concurrent anorexia, vomiting, depression, or abdominal pain.[39] Enzyme concentrations often return to normal over time without intervention. Symptomatic hepatotoxicosis is occasionally seen with itraconazole use, but is unusual after fluconazole administration. Cutaneous reactions secondary to vasculitis (Figure 233-8) are seen in approximately 7% of dogs receiving itraconazole at a dosage of 10 mg/kg and usually resolve after drug discontinuation.[10]

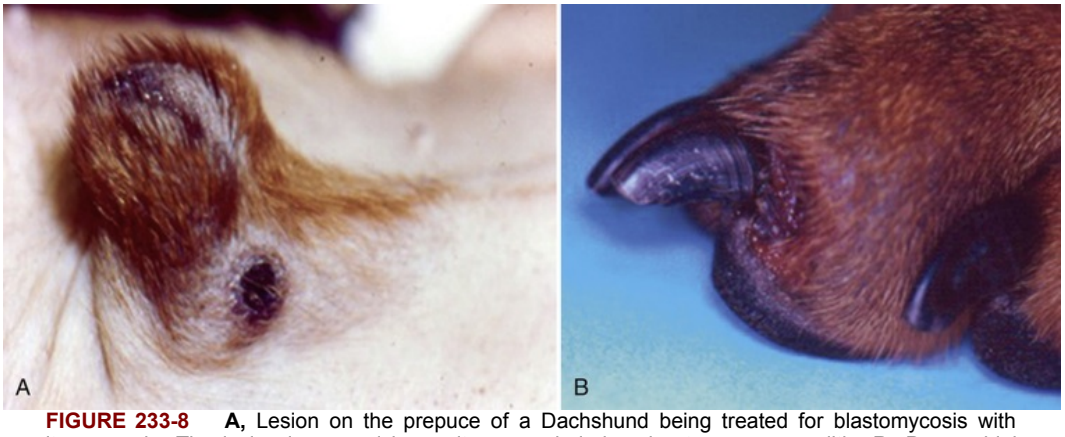

FIGURE 233-8 **A,** Lesion on the prepuce of a Dachshund being treated for blastomycosis with itraconazole. The lesion is caused by an itraconazole-induced cutaneous vasculitis. **B,** Paronychial lesion caused by an itraconazole-induced cutaneous vasculitis in a Doberman Pinscher.

Amphotericin B is often used in combination with itraconazole or fluconazole for severely affected, hypoxemic animals or animals with CNS involvement. ABLC (Abelcet), a lipid-complexed formulation of amphotericin B is recommended due to reduced toxicity.[40] A dose of 2 to 3 mg/kg IV every other day to a total dose of 24 to 27 mg/kg has been recommended for dogs with blastomycosis.

The deoxycholate formulation, although much less expensive, carries a higher risk of toxicosis. The dosage is 0.5 mg/kg for dogs, 0.25 mg/kg for cats, intravenously every other day to a total dose of 4 mg/kg when used in combination with azole antifungal drugs. A higher dosage of 0.5 to 1 mg/kg to a total dose of 8 mg/kg is recommended in dogs if amphotericin B is the sole treatment agent. Amphotericin B should be discontinued if the dog or cat becomes azotemic (blood urea nitrogen [BUN] ≥50 mg/dL, creatinine ≥3 mg/dL). The efficacy of amphotericin B when combined with fluconazole or itraconazole is equal to that seen with itraconazole alone, but side-effects are much more likely.

Ancillary therapy in hypoxemic animals should include oxygen (see ch. 131), bronchodilators, and possibly antibiotics. Anterior uveitis and secondary glaucoma should be treated appropriately (see ch. 11). Oral

glucocorticoids may result in an increased probability of retaining vision in dogs with ocular involvement without significantly reducing prognosis for systemic involvement.[41] They also may improve survival in dogs with dyspnea resulting from airway edema and severe inflammation following initiation of treatment.

Resolution of clinical signs is the best means of patient monitoring. Monthly rechecks, consisting of physical and fundic examinations, as well as thoracic radiographs and chemistry panels, should be performed as long as the patient is receiving antifungal therapy. Treatment should be continued for 1 month beyond resolution of clinical signs, and animals should be re-evaluated 3 and 6 months after discontinuing therapy to assess for relapse. Antigenuria should become negative or decrease below 1 ng/mL with successful therapy. Increasing urine antigen concentration may suggest relapse.[38,42] Serology is not useful in monitoring response to therapy or evaluating for relapse.

Dogs that die are usually those with severe respiratory disease and hypoxemia. Dogs that live through the first 10 days of therapy generally do well. Hypoxemia and the involvement of three or more body systems are poor prognostic factors.[10] Relapse occurs in 15% to 20% of treated dogs. It usually occurs in the first 6 months after treatment but can occur after a year or more. Relapses should be treated as new infections and are no less likely to respond.

Public Health Significance

Blastomycosis is not likely to be transmitted from animal to animal or from animal to person. Localized *Blastomyces* infections have occurred after needle-stick injuries when obtaining fine needle aspirates from infected lesions, and laboratory workers can potentially be infected from fungal cultures. Outbreaks in which both people and dogs are affected are due to exposure to a common environmental source rather than to zoonosis.

Histoplasmosis

Histoplasmosis is a systemic fungal infection that usually originates in the lungs and potentially the GI tract, then disseminates to the lymphatics, liver, spleen, bone marrow, eyes, and other organs. A wide variety of mammalian species can be affected, and cats may be more susceptible to infection than dogs. As with most systemic fungal diseases, animals younger than 4 years old are at an increased risk, but any age can be affected.

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*. In infected tissue, the organism is a yeast. In the environment, *H. capsulatum* is a soil saprophyte endemic throughout most of the temperate and subtropical regions of the world. Most cases of histoplasmosis in North America occur in the upper midwestern area of the United States and south central Canada, with the geographic distribution following the Mississippi, Ohio, and Missouri Rivers (see Figure 233-1).

Pathophysiology

Histoplasmosis is not a contagious disease. Infection is via inhalation or ingestion of infective conidia from the environment. The respiratory system is likely the primary route of infection in cats, humans, and dogs, but the GI system may also be an important route in the dog.

After inhalation or ingestion, conidia transform from the mycelial phase to the yeast phase and are phagocytized by cells of the macrophage monocyte system, where they grow as facultative intracellular organisms. Hematogenous and lymphatic dissemination results in multisystemic disease. Dissemination can be to any organ system, resulting in a granulomatous inflammatory response. The lungs, GI system, lymph nodes, liver, spleen, bone marrow, eyes, and adrenal glands are common organs affected in dogs; lungs, liver, lymph nodes, eyes, and bone marrow are most commonly affected in cats. The incubation period is 12 to 16 days in dogs and humans.

The cell-mediated immune response determines the severity of clinical disease, with subclinical infection probably being common. Most cases of infection are sporadic events, but point-source outbreaks of disease are occasionally reported in both dogs and humans. Epidemiologically, these outbreaks are usually associated with exposure to areas heavily contaminated with *Histoplasma* organisms such as chicken coops, bat habitats, or starling roosts. While histoplasmosis has been reported in strictly indoor-only cats, the source of exposure may have been houseplants or unfinished basements.[43]

Clinical Signs

Feline histoplasmosis occurs most commonly in cats younger than 4 years of age. No breed or sex predilection exists. Disease in cats is usually insidious in onset and nonspecific. Depression, anorexia, fever, pale mucous membranes, and weight loss are common. Pulmonary involvement, as evidenced by dyspnea, tachypnea, or abnormal lung sounds, is seen in less than 50% of affected cats. Cough is uncommon. Hepatomegaly, splenomegaly, or lymphadenopathy is noted in about a third of affected cats. Ocular involvement may result in abnormal retinal pigment proliferation, retinal edema, granulomatous chorioretinitis, anterior uveitis, panophthalmitis, or optic neuritis (see ch. 11). Retinal detachment and secondary glaucoma are less common than in animals affected with blastomycosis. Fungal osteomyelitis may cause lameness in one or more limbs. Cutaneous lesions consisting of multiple small nodules that may ulcerate and drain or crust over are noted less commonly than in animals affected with blastomycosis. GI signs other than anorexia are uncommon in cats with histoplasmosis when compared to dogs. Oral and lingual ulceration has been reported as an unusual manifestation. Icterus is occasionally seen in cats with hepatic involvement. Primary cutaneous infection as well as skin fragility secondary to histoplasmosis infection of the skin have been reported in cats.[44,45] In a retrospective study of 22 cats with histoplasmosis, disseminated disease was found in the majority of cases (15/22) with primary GI disease and primary pulmonary disease occurring in 3/22 and 4/22 cases respectively.[46]

Canine histoplasmosis is most commonly seen in dogs younger than 4 years of age. Male dogs are affected 1.2 times as frequently as female dogs, and Pointers, Weimaraners, and Brittany Spaniels may be overrepresented. The clinical findings are related to the route of infection and the extent of systemic dissemination. Clinically inapparent infection is probably common after inhalation of organisms. In those dogs showing clinical signs, findings vary greatly, but GI signs are most common. Both small and large bowel diarrhea may be seen, as well as protein-losing enteropathy, depending on the portion of the GI tract affected.

Nonspecific clinical signs such as fever, anorexia, depression, and severe weight loss are common and may be caused by elaboration of inflammatory mediators such as tumor necrosis factor (TNF) and interleukin-1 (IL-1). Abnormal lung sounds with or without coughing, tachypnea, or dyspnea are seen in less than 50% of affected dogs. Pleural effusion is seen in rare cases and may contribute to respiratory signs.[47] Splenomegaly, hepatomegaly, and lymphadenopathy are occasionally seen.

Diagnosis

Normocytic-normochromic nonregenerative anemia, the most common CBC abnormality, likely has a multifactorial cause in these patients, with chronic inflammation, GI blood loss, and bone marrow infection playing a role in severity.[43,46] Neutrophilia and monocytosis are often seen, but leukocyte counts are variable. Neutropenia or pancytopenia is noted in a minority of affected animals, especially in cats. Fungemia is rare in dogs and cats. *Histoplasma* organisms are only occasionally seen in monocytes or neutrophils and rarely in eosinophils. Thrombocytopenia due to increased use or platelet destruction is seen in as many as one half of affected dogs and one third of affected cats. Hypoalbuminemia is the most consistent chemistry abnormality.[43,46] Increases in serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin may indicate hepatic involvement. Hypercalcemia is more common in cats than in dogs.[48] It should be noted that hypoalbuminemia may mask subtle hypercalcemia. In a retrospective review of 22 cats with histoplasmosis, 42% had hypocalcemia on serum chemistry panel; all hypocalcemic cats were also hypoalbuminemic.[46] Cats are usually retrovirus-negative. Urinalysis is unremarkable in most cases.[46] *Histoplasma capsulatum* can lead to vasculitis and disseminated intravascular coagulopathy.[49]

Thoracic radiographs often reveal a diffuse interstitial or linear interstitial pattern that tends to coalesce to a nodular interstitial pattern (Figure 233-9).[43] Alveolar infiltrates are rarely reported. Hilar lymphadenopathy is common in dogs but unusual in cats. Calcified pulmonary infiltrates or hilar lymph nodes may indicate inactive disease in dogs. Lytic bone lesions, periosteal new bone formation, and subperiosteal bone proliferation are rarely noted. Bones of the distal appendicular skeleton, especially carpal and tarsal bones, are affected most commonly. Cats are more commonly affected with osseous lesions than are dogs.

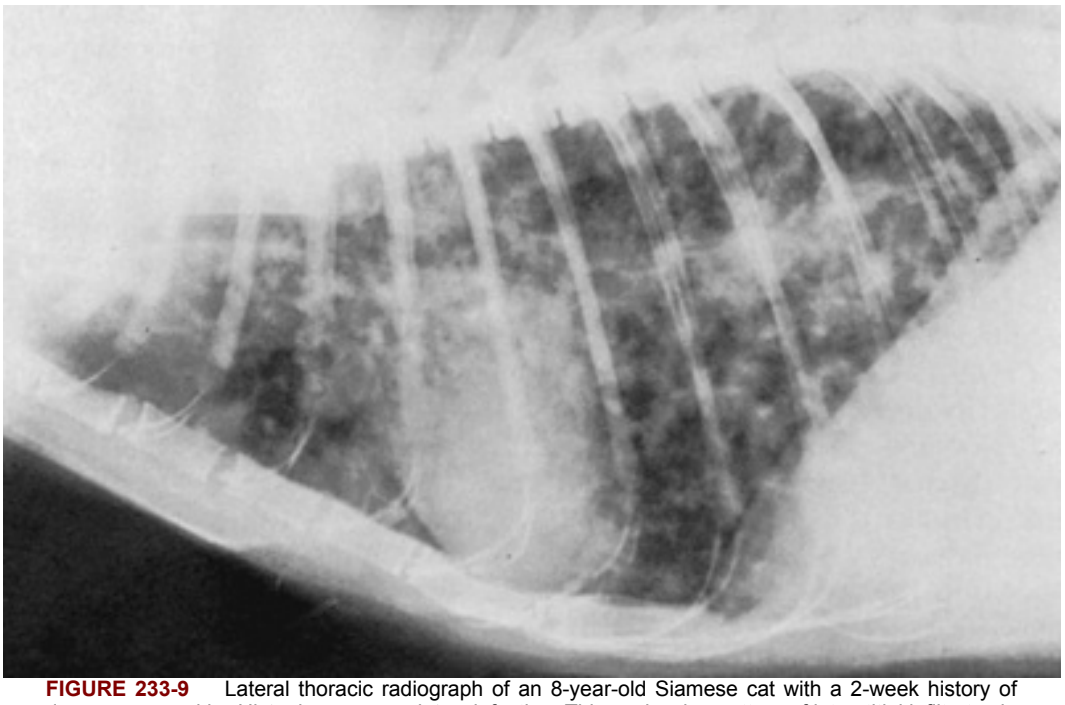

FIGURE 233-9 Lateral thoracic radiograph of an 8-year-old Siamese cat with a 2-week history of dyspnea caused by *Histoplasma capsulatum* infection. This coalescing pattern of interstitial infiltrates is commonly seen in cats with pulmonary histoplasmosis.

Abdominal ultrasonographic examination (see ch. 88) may reveal hepatomegaly, changes in hepatic or splenic echo texture, abdominal lymphadenomegaly, peritoneal effusion, renomegaly, and adrenomegaly.[43,46] The discovery of an enlarged and hypoechoic spleen on ultrasound should increase suspicion for splenic involvement.[50]

Organism identification is required for definitive diagnosis. The most common means of organism identification is cytology. Cytology from affected tissue reveals pyogranulomatous inflammation, often with numerous small, round to oval intracellular yeast cells (2 to 4 micron in diameter) characterized by a basophilic center and a light halo caused by shrinkage of the cell away from the cell wall during fixation (Figure 233-10).

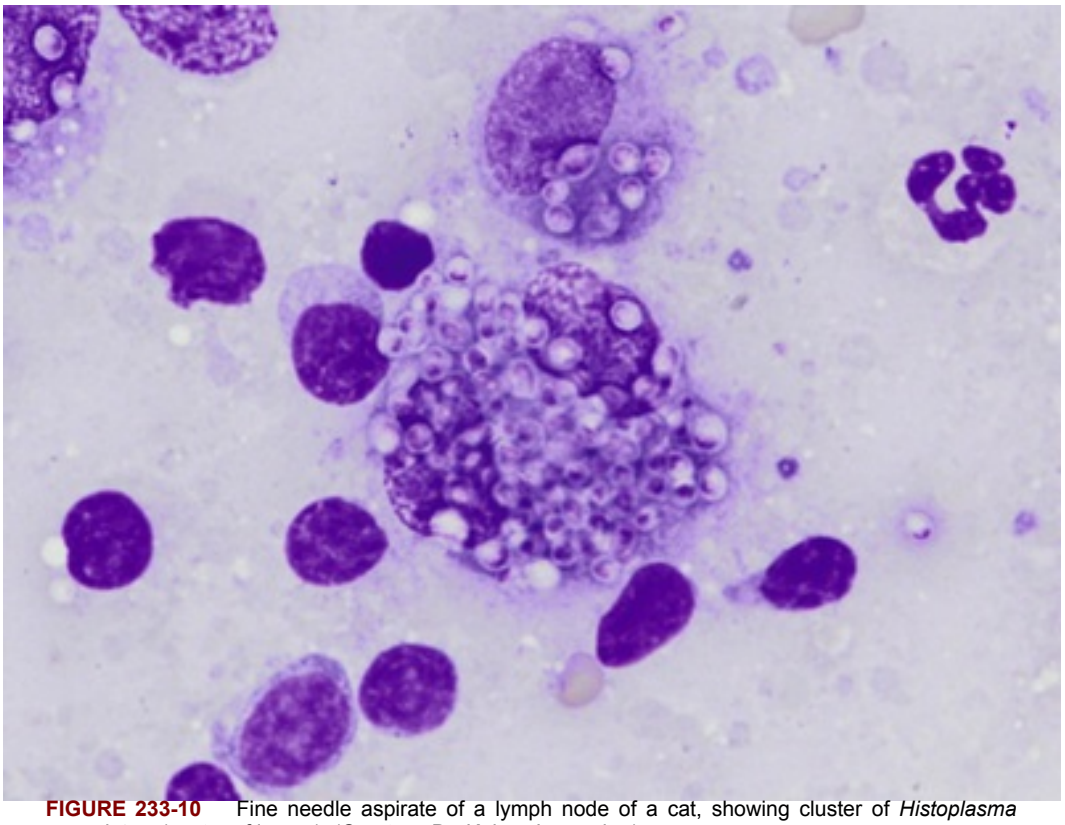

FIGURE 233-10 Fine needle aspirate of a lymph node of a cat, showing cluster of *Histoplasma capsulatum* (center of image). (Courtesy Dr. Kelsey Legendre.)

Although multiple *Histoplasma* organisms are usually found within phagocytic cells of the mononuclear phagocyte system, a small number of the organisms can be released from cells during slide preparation and may be seen free on the slides stained with a Wright-Giemsa-type stain. Samples for cytology should be collected from tissue with apparent abnormalities. In the cat, aspiration cytology from bone marrow, spleen, or lymph nodes or cytology from tracheal wash or bronchoalveolar lavage is most likely to yield organisms. In the dog, cytology from rectal scrapings or biopsies and aspiration cytology from bone marrow (see ch. 92), liver (see ch. 89), lymph nodes (see ch. 95), spleen, or tracheal wash or bronchoalveolar lavage (see ch. 101) are most likely to yield organisms. Buffy coat smears, cytology of pleural or peritoneal effusions, aspirates of lytic bone lesions, and aspirates or impression smears of nodular skin lesions (see ch. 86 and 87) may also yield organisms (see ch. 74).

Pyogranulomatous lesions with multiple intracellular organisms within macrophages are usually apparent. Histoplasmosis should be considered when granulomatous hepatitis or other granulomatous or pyogranulomatous disease is seen on biopsy.[51] The yeast does not stain well with routine hematoxylin-eosin (H&E) stains, so special stains such as PAS, Gridley's fungal, and GMS stain are often used to demonstrate organisms. In rare cases, hyphae may be seen admixed with yeast forms in histopathology samples.[52]

Fungal culture from affected tissue can be used for diagnosis but is rarely needed in clinical cases. The cultured organism has pathogenic potential, which precludes culture attempts in a practice setting.

Antibody detection is presently an ineffective method of diagnosis, as both false-positive and false-negative results are common. A galactomannan antigen is released from the cell wall during active infection and can be detected in the urine or serum. Antigenemia and antigenuria may be demonstrated using a *Blastomyces* antigen EIA for cell-wall galactomannan. A positive test is not specific for histoplasmosis but is indicative of systemic mycoses and may allow for an early diagnosis and treatment.[37] Antigen concentrations decline during treatment and increase with relapse. In the author's experience, use of EIA in urine may have a limited sensitivity in cases of localized infection, such as pulmonary histoplasmosis, as is the case in humans.[53] Hence, a negative titer should be followed by additional diagnostics, such as airway sampling, if disease is thought to be confined to the respiratory system (see ch. 101). PCR has been used to identify *Histoplasma capsulatum* from feline tissues in several case reports.[45,54]

Treatment

Pulmonary histoplasmosis may have a self-limiting clinical course, but antifungal treatment is still recommended because there is significant potential for chronic dissemination. Dogs or cats with disseminated histoplasmosis usually die without treatment. Treatment protocols are similar to those described for blastomycosis, although they have not been as well studied. Longer treatment times are probably needed in most cases, but this is highly variable.

Itraconazole 10 mg/kg PO once a day or divided twice a day is considered the treatment of choice for feline histoplasmosis. At least 2 to 4 months of therapy is required. Few studies have evaluated the efficacy of itraconazole treatment, but in one study all eight of eight treated cats were cured, while in another study only half of cats were ever discharged from the hospital.[46,48] The addition of amphotericin B to ketoconazole treatment regimens may improve efficacy, especially in severely affected cats. Fluconazole, posaconazole, voriconazole, and isavuconazole, new generation azoles, are likely effective but have not been well studied (see ch. 162).[55] Fluconazole therapy appears to have similar relapse and mortality rates compared to treatment with itraconazole in cats with histoplasmosis.[43] Fluconazole is less effective than itraconazole in treating people with histoplasmosis and posaconazole is often used in patients who cannot tolerate itraconazole and fail fluconazole treatment. Voriconazole is used in patients with CNS disease but CNS involvement is not as common as it is in blastomycosis. Similar observations have not been made in dogs and cats.

In dogs with histoplasmosis, ketoconazole has been described as the treatment of choice with amphotericin B being added to the protocol in fulminant cases; however, few studies have evaluated treatments for histoplasmosis in dogs, and ketoconazole studies were performed before newer azole antifungals were readily available. Itraconazole is the treatment of choice for histoplasmosis in people. Itraconazole and fluconazole are safer and may result in better efficacy than ketoconazole in dogs as well. Ancillary respiratory therapy may include oxygen (see ch. 131) and bronchodilators in hypoxemic animals and antibiotics in dogs with secondary bacterial pneumonia, although this is uncommon in dogs with systemic mycoses.[28] Corticosteroids have been recommended for treating dogs with airway obstruction secondary to hilar lymphadenopathy caused by histoplasmosis.[56]

Resolution of clinical signs is the best means of patient monitoring. Rechecks should be performed monthly during treatment and should include physical and ocular examinations, thoracic radiographs, and a chemistry panel in animals receiving azole antifungals. Urine antigen concentrations should be monitored every 3 months. Treatment should be continued for 1 month beyond resolution of clinical signs, and animals should be re-evaluated 3 and 6 months after discontinuing therapy to assess for relapse. Urine antigen tests will decline with successful treatment and increase with relapse, making repeated assessment of urine antigen concentration an appropriate method of following therapy. Serology is not useful in monitoring response to therapy or evaluating for relapse.

The prognosis is good for dogs with only pulmonary signs, but dogs with GI disease or severe dissemination have a guarded prognosis. The prognosis is fair to good for cats treated with itraconazole, although long-term therapy may be required. Severely debilitated cats have a guarded prognosis. Survival of cats with histoplasmosis varies from 55-66% with median survival times between 19-28.9 months.[43,46]

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CHAPTER 234

Aspergillosis—Canine

Frédéric Billen, Dominique Peeters

Client Information Sheet: Canine Aspergillosis

Background

Aspergillus species are saprophytic and ubiquitous filamentous fungi involved in environmental recycling that may also act as opportunistic pathogens. Their small size (2-3 microns) enables them to remain airborne and penetrate the respiratory tract.[1] Most humans inhale several hundred conidia daily.[2] The respiratory defense system (mucociliary escalator, cell-mediated immunity and soluble mediators) eliminates these pathogens, preventing colonization within the respiratory system. However, change in any component of the defense system may lead to development of infection.[3] In dogs, two forms of *Aspergillus* infection are reported: *sinonasal aspergillosis* (SNA), in which the infection is restricted to the nasal cavities and the frontal sinuses, and *systemic aspergillosis*, in which the infection spreads deeper in the body.[4]

Sinonasal Aspergillosis (SNA)

Etiology

Fungal rhinosinusitis is one of the most common causes of chronic nasal discharge in dogs (see ch. 27).[5-7] The disease is most often caused by *A. fumigatus*, while *A. niger, A. nidulans, A. flavus, A. tubingensis* and *A. uvarum* or *Penicillium* spp. have occasionally been reported.[4,8] On rare occasions, other mycotic agents such as *Cryptococcus neoformans* or *Scedosporium apiospermum* may affect the nasal cavities of dogs (see ch. 231).[9,10]

Pathogenesis

The reason for *A. fumigatus* causing disease in only a small proportion of exposed dogs remains unclear. In rare cases only, a predisposing factor such as nasal foreign body, facial trauma, nasal tumor, or an impacted tooth is present.[11,12] Typically, affected dogs are not systemically immunocompromised, fungal infections are restricted to the nose and/or frontal sinuses, and there is no fungal invasion of respiratory mucosa.[13] Therefore, local nasal mucosal immune dysfunction is suspected to be involved in the pathogenesis of the disease. In affected dogs, there seems to be disequilibrium in the balance between pro-inflammatory (Th1 immunity) and anti-inflammatory (Th17 immunity and possibly T regulatory cells) signals that could perpetuate infection and its associated inflammatory response.[14] A defect in Toll-like receptor (TLR) expression or function might constitute the primary dysfunction leading to *Aspergillus* infection in these dogs.[15,16] SNA is characterized by severe nasal turbinate destruction, likely due to the inflammatory response and dermonecrolytic fungal toxins.[13] Severely affected dogs have bony destruction that may allow inflammation to extend into perisinusal and periorbital soft tissues and/or into the brain.[17]

Signalment and Clinical Findings

SNA affects primarily young to middle-aged dogs from large mesaticephalic and dolichocephalic breeds.[18] Sneezing, reverse sneezing, unilateral (bilateral later in the course of the disease) epistaxis, and muco- or sanguinopurulent nasal discharge may be present weeks to months prior to examination. Nasal planum depigmentation and ulceration (Figure 234-1), normal or even increased ipsilateral nasal airflow, facial

discomfort, lethargy and decreased appetite are common clinical findings that will usually not be present with other causes of nasal discharge in dogs. Rarely, inflammation extension into the forebrain due to cribriform plate destruction may result in dullness or even seizures.[12]

FIGURE 234-1 Depigmentation and ulceration of the nasal planum of a dog with bilateral (L > R) sinonasal aspergillosis.

Diagnosis

Overview

Even when SNA is highly suspected based on signalment and a typical clinical presentation, fungal infection must be confirmed prior to therapy. No test is 100% accurate and a combination of diagnostic procedures is required.[12] These include observation of destructive, "cavitating" changes of the nasal cavity by diagnostic imaging or rhinoscopy, and the demonstration of a fungal etiology with endoscopic visualization of fungal plaques, cytology, histology, fungal culture and/or serology.

Imaging

Diagnostic imaging studies should be performed prior to rhinoscopy because resultant hemorrhage may obscure subtle lesions and induce imaging abnormalities.[19] Several studies have demonstrated the higher sensitivity of computed tomography (CT) and magnetic resonance imaging (MRI), as compared to radiography, for the diagnosis of sinonasal diseases in dogs.[20-22] CT is particularly superior to radiography for defining the extent of the sinonasal lesions, detecting cortical bone lesions and in assessing integrity of the cribriform plate (see ch. 238).[19,23] The latter may be essential when choosing a therapeutic plan.[24] The most common CT findings in SNA are (1) moderate to severe cavitary destruction of the turbinates with presence of variable amount of abnormal soft tissue (secretions and/or fungus) in the sinus and/or nasal cavities (Figure 234-2), (2) non-specific thickening of the mucosa adjacent to the inner surface of bones of the frontal sinus, maxillary recess and nasal cavity, and (3) thickened reactive bone.[17] There is no clear advantage of using MRI versus CT in the diagnosis of canine SNA.[19]

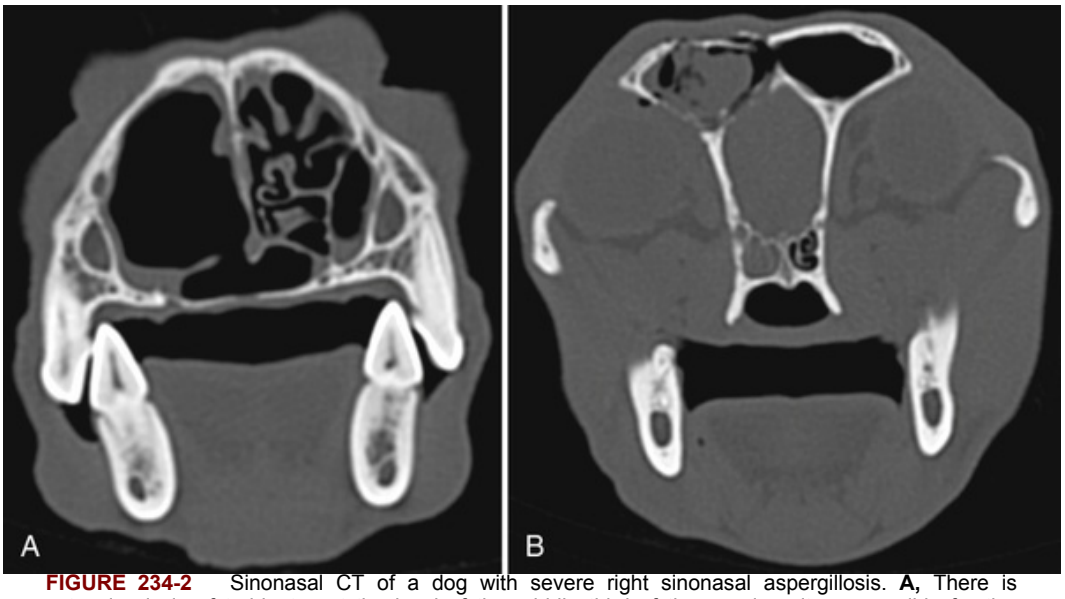

FIGURE 234-2 Sinonasal CT of a dog with severe right sinonasal aspergillosis. **A,** There is extensive lysis of turbinates at the level of the middle third of the nasal cavity responsible for the "cavitary-like" appearance. **B,** There is soft tissue attenuating material with a fragmented gas pattern present into the right frontal sinus. There is severe destruction of right frontal bone that involves the wall between the frontal sinus and cranial cavity, between the frontal sinus and orbit, and dorsally leaving a communication with the subcutaneous tissues.

Endoscopy

Endoscopic examination of the sinonasal cavities is the only procedure that may allow diagnosis (fungal plaques visualization and/or target sampling) and treatment (debridement ± foreign body retrieval, and infusion catheters placement) of the infection during one general anesthetic (see ch. 96).[11,12,25-27] Typical rhinoscopic findings include moderate to severe destruction of the turbinates, resulting in a typical cavity-like appearance, roughening of the mucosa, presence of intranasal (sanguino-) mucopurulent secretions and fungal colonies (Video 234-1). In some cases, nasal septum destruction and bilateral disease may be observed.[19,28] Fungal colonies typically appear as white or greenish fuzzy plaques adherent to the nasal or sinusal mucosa.[29] In some cases, fungal colonies may not be present in the nasal cavities, and frontal sinus access is required for the diagnosis of SNA (Figure 234-3). In one study, sinus trephination with sinuscopy was necessary to confirm the diagnosis of SNA in 17% of dogs with CT lesions suggestive of the disease.[11]

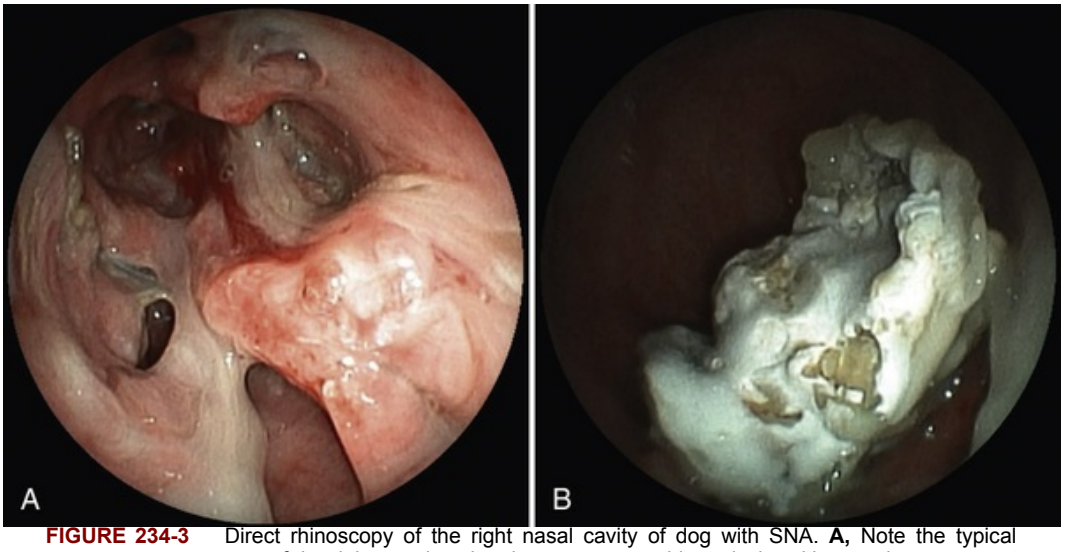

FIGURE 234-3 Direct rhinoscopy of the right nasal cavity of dog with SNA. **A,** Note the typical cavernous appearance of the right nasal cavity, due to severe turbinate lysis, with a moderate amount

of sanguino-mucopurulent secretions. **B,** Fungal granuloma was present only in the right frontal sinus.

Rhinoscopy is usually performed with a 0° or 30° viewing angle rigid endoscope, but a flexible small endoscope should be used whenever possible to facilitate entry into the frontal sinus in some dogs (see ch. 238).[19] This is generally feasible in medium- to large-breed dogs with moderate to severe turbinate destruction. The major limitations of endoscopy are its inability to evaluate bony structures and, especially, the integrity of the cribriform plate. For this reason, endoscopy and CT are considered complementary diagnostic procedures.[19,29]

Cytology

Cytology may be used to confirm the diagnosis of SNA (see ch. 93). The sensitivity of this technique depends on the sampling method. Direct smears from nasal exudate and blind endonasal swabs detected fungal hyphae in only 13% and 20% of the cases, respectively, while brushing of suspected lesions under endoscopic guidance and squash preparation of biopsies of suspected lesions detected fungal hyphae in 93% and 100% of cases, respectively.[25] As with cytology, sensitivity of histology for detection of fungal hyphae is highly dependent on the biopsy specimen. It usually requires sampling fungal plaques rather than adjacent mucosa or erroneously identified plaque-like exudate or necrotic debris.[13,30,31]

Culture

Recent data demonstrated fungal cultures to be 100% specific for diagnosis of SNA in dogs with nasal discharge.[26,32] Suboptimal laboratory methodology and inability to obtain appropriate nasal specimens most likely contributed to earlier low sensitivities. A recent study has shown that increasing the incubation temperature from room temperature to 37° C not only enhanced the sensitivity of fungal culture but also shortened time until fungal growth. The type of nasal sample obtained is of major importance. Sensitivity is the highest when fungal plaques are sampled (88%) followed by mucosal biopsies (75%). Blind endonasal swab samples are completely unreliable (19%) for diagnosing SNA.[26]

Serology

Tests detecting serum *Aspergillus*-specific antibodies use commercially available, standardized, highly purified *Aspergillus* antigen solutions. However, only a few studies have evaluated the diagnostic value of these standardized solutions in canine SNA. The agar-gel double immunodiffusion is a highly specific (98 to 100%) but poorly sensitive (57 to 76.5%) diagnostic method, while enzyme-linked immunosorbent assay (ELISA) yields a higher sensitivity (88.2%) with equal specificity (96.8%).[30,32,33] Because of its overall moderate sensitivity, serology is not considered a good screening test for SNA in dogs suffering from chronic nasal discharge. Serum galactomannan antigen (a cell wall component released during fungal growth) and quantitative whole blood or nasal tissue fungal DNA detection are not reliable for diagnosis of canine SNA.[33,34]

Treatment

Overview

Effective treatment of SNA remains challenging despite various available therapeutic options, including orally administered systemic therapy, topical application of antifungal solutions and more invasive surgical procedures (Table 234-1).

TABLE 234-1

Summary of First and Overall Treatment Success Rates of Studies Reporting the Use of Moderate/Non-Invasive Topical Treatment Techniques in Dogs with Sinonasal Aspergillosis

TREATMENT PROCEDURE	NUMBER OF DOGS	FIRST TREATMENT SUCCESS: RANGE (MEAN)	OVERALL TREATMENT SUCCESS: RANGE (MEAN)
(A) Infusion—1% clotrimazole—sinus catheters—temporary	84	54.1-76.9%	83.7-86.9%

trephination18,43,51		(63.8%)	(84.9%)
(B) Infusion—1% clotrimazole or enilconazole—nasal catheters—blindly placed18,23,28,30,43,48,50	208	40-76% (56.1%)	89.5-98% (94.3%)
(C) Infusion—2% enilconazole—nasal & sinus catheters—endoscopically placed28,48	19	58.3-85.7% (68.4%)	83.3-100% (89.5%)
(D) Infusion—2% enilconazole + 1% bifonazole cream depot—nasal & sinus catheters—endoscopically placed26,*	25	60%	96%
(E) Flush & cream depot—1% clotrimazole—temporary trephination18,45,53	48	58-86% (68.7%)	86-100% (94.8 %)
Total dogs from all studies listed above	384	40-86% (60.2%)	83.3-100% (91.9%)

*Billen et al, unpublished data.

Adapted from Sharman MJ, Mansfield CS: Sinonasal aspergillosis in dogs: a review. *J Small Anim Pract* 53:434-444, 2012.

Antifungal Drugs

Antifungal drugs that are used for treating SNA belong to the azole group: the second-generation imidazoles (ketoconazole, clotrimazole, enilconazole) and the more potent third-generation triazoles (itraconazole, fluconazole).[35] Through interaction with the fungal cytochrome P450 system, their primary mechanism of action is blocking synthesis of ergosterol, a key component of fungal cytoplasmic membranes. Many azoles also interact with mammalian P450 isoenzymes responsible for side-effects (hepatotoxicosis, anorexia, vomiting) and some drug interactions.[36] Triazole drugs are more specific in targeting fungal cytochrome P450 with fewer side-effects.[37] Because of poor to moderate efficacy, need for long-term administration (2-3 months), side-effects and cost, oral systemic therapy is not recommended as single therapy for SNA.[12,18] The use of topical antifungal administration is the most widely used method of therapy.[18] However, systemic therapy may still be indicated as part of the treatment regimen in cases of extra-nasal extension of the disease.[38]

Topical Drug Choices

Topical therapy mainly includes use of enilconazole and clotrimazole because of their poor solubility (see Table 234-1). To avoid severe local side-effects, only polyethylene glycol-based clotrimazole solutions should be used for intranasal infusion.[39,40] Enilconazole has the advantage of being less toxic, less irritating, and is active in the vapor phase over a distance of up to 1 cm.[24,41]

Debridement and Infusion Therapy

Various procedures have been developed to administer antifungal agents topically. The recommended mode of administration uses meticulous debridement of sinonasal cavities (see Video 234-1) followed by 1-hour infusion of 1% clotrimazole or 1-2% enilconazole through blindly placed catheters into each nasal cavity or through an endoscopically placed catheter into the nasal cavity and affected sinus.[28,42,43] This procedure has the advantage of being noninvasive and has now replaced the older technique necessitating implantation of the infusion catheters into the sinus and nasal cavities via temporary sinus trephination (see Table 234-1).[43,44]

Temporary Trephination and Infusion (+Debridement)

As topical infusion techniques require long-lasting anesthesia (mean: 2 h), a shorter but more invasive technique requiring temporary trephination of the frontal sinuses has been developed. This method consists of a 5 minute 1% clotrimazole flush followed by a depot of 1% clotrimazole cream (10-20 g) in the frontal sinuses (see Table 234-1).[45] Viscosity of the cream provides greater retention time in the frontal sinus than the solutions used during infusion procedures, thereby increasing drug contact time with fungal elements despite a shorter anesthesic. The average duration of anesthesia is reported to be reduced to 30 minutes. Another method combines endoscopic debridement, 1-hour 2% enilconazole infusion and the depot of 1% bifonazole cream in the affected frontal sinus through an endoscopically placed catheter (see Table 234-1).[27]

Infusion Complications

Leakage of antifungal drugs at the level of the trephination holes or around the infusion catheters is common and usually without adverse effect.[28,38] Perforation of the cribriform plate, in contrast, could allow leakage of antifungal solutions into the cerebral cavity, inducing meningoencephalitis and cortical signs that can include seizures, altered mental status, or even death. Infusions have been administered to a few dogs with a damaged cribriform plate without complication.[28,30,31,38,43] Development of mucosal blebs and/or scar tissue formation after enilconazole infusion has been reported but does not appear to have clinical relevance apart from occasional obstruction of the nasal-frontal opening.[12,28] Rarely, a nasal tumor has developed after intranasal enilconazole or clotrimazole infusion/depot.[12,46,47]

Treatment Response

Assessing response to treatment remains difficult because if clinical signs disappear 1-2 weeks after therapy, this is not predictive of long-term cure.[30,43,48] Serial serum *Aspergillus*-specific antibody titers cannot be used to assess response to treatment because they tend to decline quite slowly. Positive results may persist for several years in dogs that remain free of disease.[49] Assessment of the response to therapy with CT has not been evaluated, but the "cavernous" nasal cavity and hyperostosis of surrounding bone will persist. Thus, it seems unlikely that repeating CT after treatment will be able to differentiate cure from persistent disease. The only way to correctly assess therapeutic efficacy is endoscopic reexamination of the sinonasal cavities within 1 month after treatment. The sinuses must be reexamined either by nasal passage of a flexible endoscope via the nasal-frontal opening or observation through the previously placed trephine hole.[28,30,50] Absence of any fungal colony within the sinonasal cavities is in favor of cure (Video 234-2).

Treatment success rates of most studies reporting topical therapy are summarized in Table 234-1.[18,27,28,30,43,45,48,50-53] Despite methods for determining "cure" not being standardized, interpretations can be made from such studies with large numbers of dogs. The mean overall first treatment success rate is 60% (40 to 86%). Multiple treatments are usually required (most often 2) to definitively resolve the infection. The mean global treatment efficacy is 92% (83 to 100%). Treatment success seems to be associated with a younger age.[18] Chronicity of clinical signs, bilateral disease and adjunctive oral systemic antifungal therapy are reported to be associated with first treatment failure, but worse disease at time of diagnosis might account for this observation.[18] In some cases with only focal disease and very mild turbinate destruction, access to the infected part of the sinonasal cavity may be difficult, resulting in insufficient debridement and poor outcome.[31]

Reasons for treatment failure are likely to be multifactorial. The ability to effectively debride fungal plaques is probably a major factor contributing to treatment efficacy.[18,31] As high concentrations of antifungal agents are achieved locally with topical treatments, antifungal resistance is unlikely to be clinically significant for canine SNA.[31]

Surgical Treatment

Several surgical techniques have been described. They consist of rhinotomy, extensive debridement, and then topical application of povidone-iodine 10% "paint," povidone-iodine impregnated dressings, or enilconazole 2% soak. All procedures result in favorable outcomes.[54,55] Surgery can be quite destructive and should be used only in dogs with fungal lesions that cannot be otherwise debrided, in patients with cribriform plate damage, or refractory cases. Care must be taken to cause as little damage as possible to nasal mucosa and turbinectomy should be avoided.[38] Finally, bone flap replacement after rhinotomy is not recommended.[55]

Long-Term Outcome

Long-term outcomes after "successful" topical therapy have been investigated in few studies. One study reported follow-up periods of 5 to 64 months in which episodic or permanent mild to moderate nasal discharge and/or sneezing was seen in 52% of dogs.[48] In another study, follow-up ranged from 1.5 to 108 months with only 11% of dogs remaining completely free of clinical signs, while the others showed occasional sneezing and/or nasal discharge. Extensive and irreversible turbinate destruction probably predisposes to chronic lymphoplasmacytic rhinosinusitis and/or secondary bacterial infections. Some dogs were indeed successfully treated with local glucocorticoids or antimicrobials, respectively.[18,48,50] Recurrence of SNA has

been noted 2 months to 4 years after successful treatment.[30,43,48,50,56] Because of the very short time between cure and diagnosis of the new infection in some cases, persistent fungal infection could have been missed during follow-up reexamination and reinfection cannot definitively be excluded.

Systemic Aspergillosis

Systemic or disseminated aspergillosis usually involves multiple organs (such as intervertebral discs, bones, lungs, kidneys, eyes, lymph nodes, brain, gastrointestinal tract) without history of nasal infection. *Aspergillus* spp. are thought to gain entry via the respiratory tract with subsequent hematogenous spread.[57,58] The disease is most often caused by *A. terreus* or *A. deflectus*, but other *Aspergillus* species have also been reported.[57,59-61] Systemic aspergillosis has been mostly reported in young to middle age German Shepherd Dogs in which dysfunction in the mucosal innate immunity is suspected. Immunosuppressive drugs or disease are usually not identified in affected dogs.[57]

The clinical signs associated with systemic aspergillosis are chronic, non-specific and related to organ involvement. Spinal pain ± paraparesis, bone pain, anorexia, weight loss, lethargy, muscle wasting, and fever are the most common signs. Lung and ocular involvement are also frequently reported.[57,58] Pulmonary cavitary lesions, without evidence of further dissemination, have been reported in German Shepherd Dogs with chronic cough and hemoptysis.[62,63]

Diagnostic imaging findings are nonspecific and vary greatly with organ involvement.[57,63] Culture of *Aspergillus* spp. from a suspected lesion (lymph node, lung, intervertebral disc) or fluid (urine, bronchoalveolar lavage) together with visualization of hyphae on cytological or histological examination are considered the gold standards for diagnosis of canine systemic aspergillosis.[57,64] Detection of galactomannan antigens is a promising diagnostic tool with sensitivity and specificity higher than 85% in serum or urine.[64]

The prognosis for recovery is poor despite aggressive antifungal therapy and supportive care. In a series of 30 cases, 17 dogs were euthanized within 1 week and 3 were discharged without treatment.[57] Amphotericin B, ketoconazole, itraconazole, fluconazole, or voriconazole have all been reported but comparisons of their efficacy have not been reported. In some dogs, lifelong azole therapy is required.[58] Surgical excision of fungal granulomas may be helpful, if feasible.[63]

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CHAPTER 235

Aspergillosis—Feline

Vanessa R. Barrs

Client Information Sheet: Aspergillosis—Feline

Upper Respiratory Tract Aspergillosis (URTA)

Aspergillosis can be divided into invasive and non-invasive syndromes based on histopathological evidence of tissue penetration and invasion by fungal hyphae.[1] In cats there are two forms of URTA: sino-nasal aspergillosis (SNA) and sino-orbital aspergillosis (SOA). SNA is typically non-invasive and characterized by superficial mucosal fungal plaques[2-4] whereas SOA, which comprises two-thirds of all reported cases of URTA, is invasive.[5] Feline URTA occurs worldwide, with cases reported in Australia,[5-11] the United States,[2-4,12-17] the United Kingdom,[9,18] mainland Europe[4,11,19-21] and Japan.[22,23]

Etiology

Aspergillus species found in soil cause feline URTA (Table 235-1).[5,9-11,22-24] The majority are from two species complexes in section *Fumigati:* the *A. fumigatus* complex and the *A. viridinutans* complex (Figure 235-1). Cryptic species within these complexes, so-called because they are indistinguishable from each other and from *A. fumigatus* sensu stricto using standard morphological features, are associated with invasive disease and have high levels of innate antifungal resistance compared to *A. fumigatus.* Molecular techniques are required for their definitive identification. Two cryptic species in the *Aspergillus viridinutans* complex, *A. felis* and *A. udagawae,* are the most frequent isolates in SOA. The two most common causes of SNA, *A. fumigatus* and *A. niger,* have not been associated with SOA, at least not where definitive molecular identification of the pathogen has been performed (see Table 235-1).[5,9,14,16,20,21]

TABLE 235-1

Etiological Agents of Feline Sino-Nasal Aspergillosis and Sino-Orbital Aspergillosis in Genus *Aspergillus*, Based on Molecular Identification

Sino-Nasal Aspergillosis			
SUBGENUS	**SECTION**	**SPECIES COMPLEX**	**SPECIES**
Fumigati	*Fumigati*	*A. fumigatus*	*A. fumigatus*[5,9-11]
Fumigati	*Fumigati*	*A. fumigatus*	*A. lentulus*[9]
Fumigati	*Fumigati*	*A. fumigatus*	*Neosartorya pseudofischeri* (*A. thermomutatus*)[9]
Fumigati	*Fumigati*	*A. viridinutans*	*A. felis*[9]
Circumdati	*Nigri*	*A. niger*	*A. niger*[24]
Circumdati	*Flavi*	*A. flavus*	*A. flavus*[11]
Sino-Orbital Aspergillosis			
SUBGENUS	**SECTION**	**SPECIES COMPLEX**	**SPECIES**

Fumigati	*Fumigati*	*A. viridinutans*	*A. felis*[9]
Fumigati	*Fumigati*	*A. viridinutans*	*A. udagawae*[9,10,22,23]
Fumigati	*Fumigati*	*A. viridinutans*	*A. wyomingensis*[10]
Fumigati	*Fumigati*	*A. viridinutans*	*A. viridinutans*[23]
Fumigati	*Fumigati*	*A. fumigatus*	*Neosartorya pseudofischeri (A. thermomutatus)*[9]

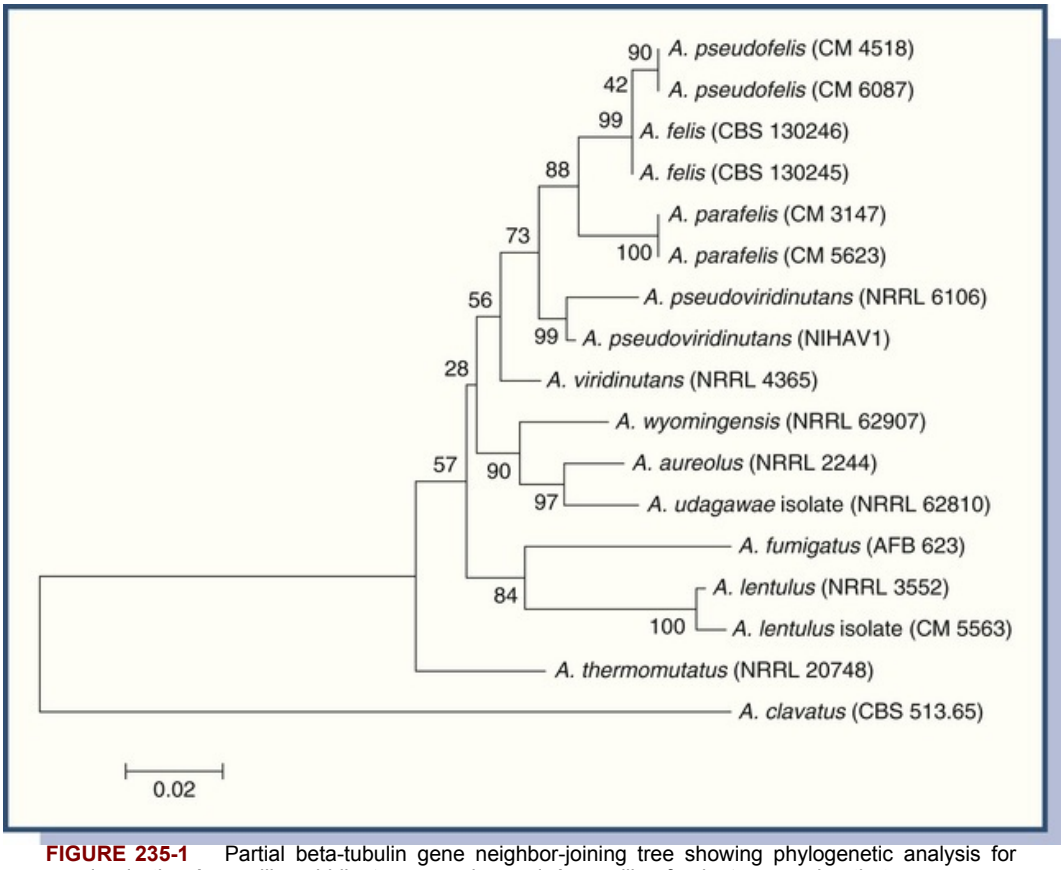

FIGURE 235-1 Partial beta-tubulin gene neighbor-joining tree showing phylogenetic analysis for species in the *Aspergillus viridinutans* complex and *Aspergillus fumigatus* complex that cause upper respiratory tract aspergillosis in cats. Drawn to scale with branch lengths expressed in units of the number of changes over the whole nucleotide sequence. (From Barrs VR, Beatty JA: Upper respiratory tract aspergillosis. In August JR, editor: *Consultations in feline internal medicine,* vol 6, St Louis, 2010, Saunders, pp 36-52.)

Pathogenesis

The nasal cavity is the portal of entry for *Aspergillus* conidia in both forms of URTA. Colonization of sinonasal mucosa occurs when immune defenses are inadequate. The route of extension to involve the orbit in SOA is via direct naso-orbital communication following bone lysis.[5,10,20,21] The propensity for cryptic species to cause invasive disease may be due, in part, to fungal virulence factors. *A. felis* is more virulent than *A. fumigatus* in bioassays using mice or *Galleria mellonella* larvae.[25] Most cats with URTA do not have identifiable systemic immunodeficiency and test negative for feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV), although diabetes mellitus, a risk factor for aspergillosis in humans, has been reported in several affected cats.[2,7,26] Brachycephalic pure-breed cats of Persian lineage including Persians, Himalayans, Exotic Shorthair, British Shorthair, Scottish Shorthair and Ragdolls are overrepresented and account for over a third of all cases.[11] The basis for this predisposition for URTA is unknown. An immunogenetic disorder is possible, but has not been investigated. Brachycephalic skull conformation may also be a risk factor for fungal

colonization from impaired mucociliary clearance and mucosal edema with turbulent air-flow.[4] A role has also been proposed for viral upper respiratory infection and recurrent antibiotic therapy.[4,5,18] Feline URTA occurs occasionally in association with local damage to the sino-nasal mucosal barrier from facial trauma, nasal neoplasia and nasal foreign bodies.[24]

Clinical Signs

Infection can occur at any age (reported range 1 to 15 years, median 6.5 years) and there is no sex predisposition. Clinical signs in SNA include sneezing, serous to mucopurulent nasal discharge (unilateral or bilateral), stertor and mandibular lymphadenopathy. Less common signs are epistaxis, fever and a discharging sinus or mass involving the nasal or frontal bones. Cats with SOA are usually presented for signs associated with an invasive unilateral orbital granuloma (Box 235-1, Figures 235-2 and 235-3). In severe, chronic infections, bilateral orbital involvement can occur.[5,6,20] Nasal signs are absent in 40% of SOA cases at presentation, although the medical history usually reveals signs in the preceding 6 months.[5] Orbital granulomas can invade paranasal soft tissues, extending ventrally into the oral cavity and into the brain (Figures 235-2 and 235-4). In advanced disease, blindness due to optic nerve or optic chiasm involvement[5,20] and neurological signs including seizures, head tilt, circling, ataxia, facial muscle fasciculation and hyperesthesia have been reported (see ch. 259).[5,14,21]

Box 235-1

Common Clinical Signs at Presentation in Sino-Orbital Aspergillosis

- Exophthalmos with dorsolateral deviation of the globe
- Conjunctival hyperemia
- Third eyelid prolapse
- Exposure keratitis
- Oral mass or ulcer in the pterygopalatine fossa
- Paranasal soft tissue swelling
- Mandibular lymphadenopathy

FIGURE 235-2 Unilateral exophthalmos with prolapse of the third eyelid (OD) in two cats with sino-orbital aspergillosis with **(A)** dorsolateral deviation of the globe; **(B)** conjunctival hyperemia and edema and severe corneal ulceration. (From Barrs VR, Beatty JA: Upper respiratory tract aspergillosis. In August JR, editor: *Consultations in feline internal medicine,* vol 6, St Louis, 2010, Saunders, pp 36-52.)

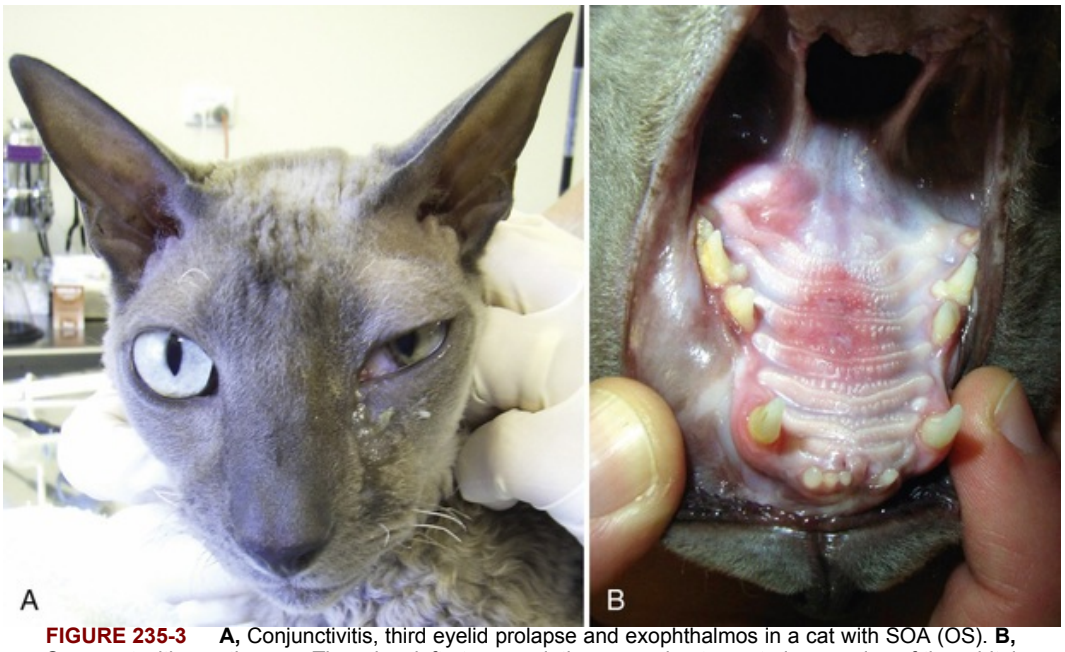

FIGURE 235-3 **A,** Conjunctivitis, third eyelid prolapse and exophthalmos in a cat with SOA (OS). **B,** Same cat with mouth open. There is a left pterygopalatine mass due to ventral expansion of the orbital mass, and ulceration of the hard palate. (From Barrs VR, Beatty JA: Upper respiratory tract aspergillosis. In August JR, editor: *Consultations in feline internal medicine,* vol 6, St Louis, 2010, Saunders, pp 36-52.)

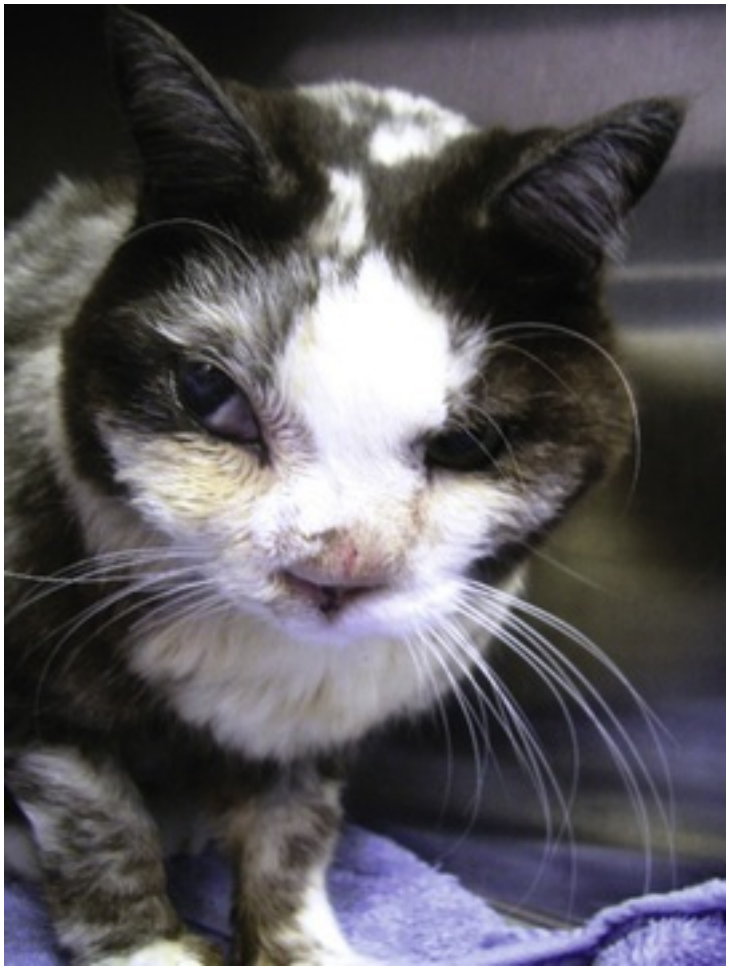

FIGURE 235-4 Exophthalmos and third-eyelid prolapse (OD) and paranasal soft tissue swelling of the nasal bridge and maxillary soft tissues in a cat with sino-orbital aspergillosis. (From Barrs VR, Beatty JA: Upper respiratory tract aspergillosis. In August JR, editor: *Consultations in feline internal medicine,* vol 6, St Louis, 2010, Saunders, pp 36-52.)

Diagnosis

Differential diagnoses for SNA and SOA are listed in Box 235-2. Definitive diagnosis is based on detection of fungal hyphae on cytological or histological examination of tissue biopsies or sino-nasal fungal plaques. Fungal species identification should always be attempted.

Box 235-2

Differential Diagnoses of Nasal Signs in Cats with SNA or SOA and of Orbital Mass Lesions in Cats with SOA

Differential Diagnoses of Nasal Signs

Neoplasia (lymphoma, carcinomas, other)
Inflammatory (CRS, nasal polyps, NP polyp or stenosis)
Infectious
  Viral (FHV-1, FCV)
  Mycotic rhinitis (cryptococcosis, aspergillosis, sporotrichosis, phaeohyphomycoses, zygomycosis, other)
  Bacterial (*Bordetella, Mycoplasma, Chlamydia felis,* Actinomycetes)
Foreign body
Congenital (choanal atresia, palatine defects)
Dental disease (tooth root abscess, oronasal fistula)

Differential Diagnoses of Orbital Mass Lesions

Neoplasia (lymphoma, carcinomas, sarcomas, other)
Infectious
  Bacterial abscess/granuloma (odontogenic, penetrating bite wound, hematogenous)
  Mycotic granuloma (as for nasal signs)
  Pythiosis
Inflammatory
  Orbital myofasciitis
  Orbital pseudotumor (idiopathic sclerosing inflammation)
  Zygomatic or lacrimal adenitis
Foreign body (e.g., grass awn)
Orbital fat prolapse

CRS, Chronic rhinosinusitis; *FCV,* feline calicivirus; *FHV-1,* feline herpesvirus type 1; *NP,* nasopharyngeal.

Hematological and serum biochemical changes are non-specific. Peripheral eosinophilia is uncommon. Mild to severe hyperglobulinemia was present in over half of cases of SOA in one study.[5] Detection of serum galactomannan, a fungal cell wall antigen, has low sensitivity and specificity for diagnosis, and is not recommended for routine testing.[27] Serological detection of anti-*Aspergillus* immunoglobulin G (IgG) by a customized enzyme-linked immunosorbent assay (ELISA) and a commercial agar gel double immunodiffusion assay (AGID) were evaluated in cats with URTA.[11] Diagnostically useful cross-reactivity of anti-*Aspergillus* IgG from cats with infections caused by *A. fumigatus* and cryptic species (including *A. felis* and *A. udagawae*), with a commercial antigen derived from fungal elements of *A. fumigatus, A. flavus* and *A. niger* was demonstrated using both assays. The sensitivity of the AGID was 43% and specificity was 100%. In contrast, the IgG ELISA had high sensitivity (95%) and specificity (92%) demonstrating that IgG detection by ELISA is a useful screening test for URTA in cats with clinical signs. Positive results should be corroborated with other diagnostic tests such as computed tomography/magnetic resonance imaging (CT/MRI) findings, rhinosinuscopy, cytology, histology and fungal culture.

CT findings in feline SNA are more variable than in canine SNA and mimic those of nasal neoplasia and chronic rhinosinusitis.[10,13] CT findings in SOA must be differentiated from invasive nasal neoplasia, and include nasal cavity involvement and an expansile ventromedial orbital mass with heterogeneous contrast enhancement (Figure 235-5). MRI is recommended for cats with concurrent central nervous system (CNS) signs. Orbital masses on MRI are T1- and T2-hyperintense and show heterogeneous contrast enhancement.[14,21,26] Rhinoliths or sinoliths are occasionally detected in SNA or SOA.[4,10]

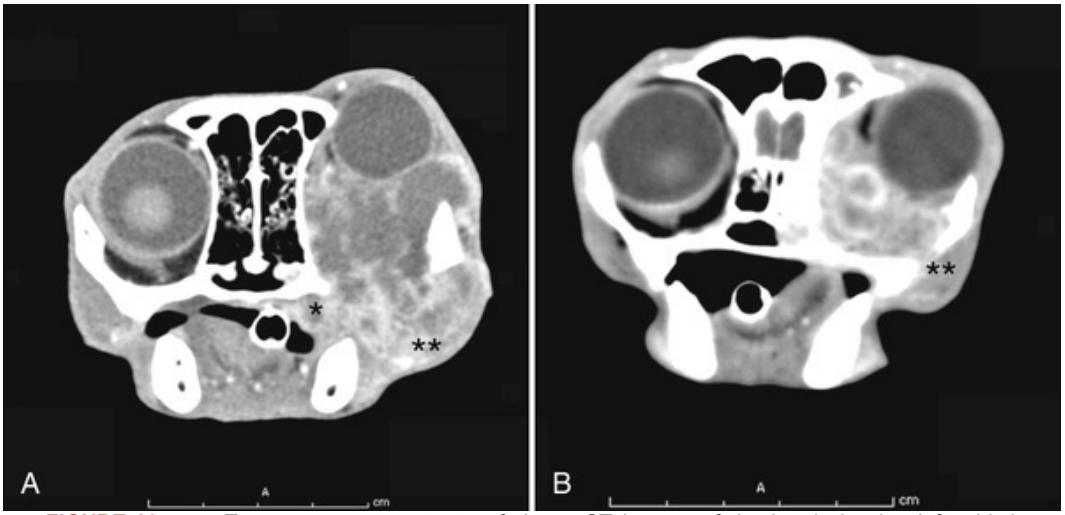

FIGURE 235-5 Transverse post-contrast soft-tissue CT images of the head showing left orbital masses in two cats with SOA and *A. felis* infection. There is heterogeneous contrast enhancement, with central coalescing hypoattenuating foci and peripheral rim enhancement. There is compression and dorsal displacement of the globe **(A** and **B),** and extension into the oral cavity **(A)** (asterisk), nasopharynx **(B),** and adjacent paranasal maxillary soft tissues (**A** and **B**) (double asterisks). (From Barrs VR, Beatty JA, Dhand NK, et al: Computed tomographic features of feline sino-nasal and sino-orbital aspergillosis. *Vet J* 201:215-222, 2014.)

Fungal plaques adherent to the nasal mucosa may be visualized on endoscopic examination in SNA[2] (Figure 235-6, *A*). In cats with invasive infections, mass lesions of variable appearance may be present within the nasal cavity, choanae or nasopharynx (Figure 235-6, *B*). Biopsies of orbital masses can be obtained with CT guidance or via the oral cavity where there is pterygopalatine invasion. Fungal pathogens can be readily cultured from tissue biopsies or fungal plaques using commercial culture media at 37° C.[5] Demonstration of growth at 50° C of a suspected *A. fumigatus* isolate with consistent morphology is adequate for identification since cryptic species are unable to grow at this temperature.[25,28] Antifungal susceptibility testing of isolates other than *A. fumigatus* is recommended.

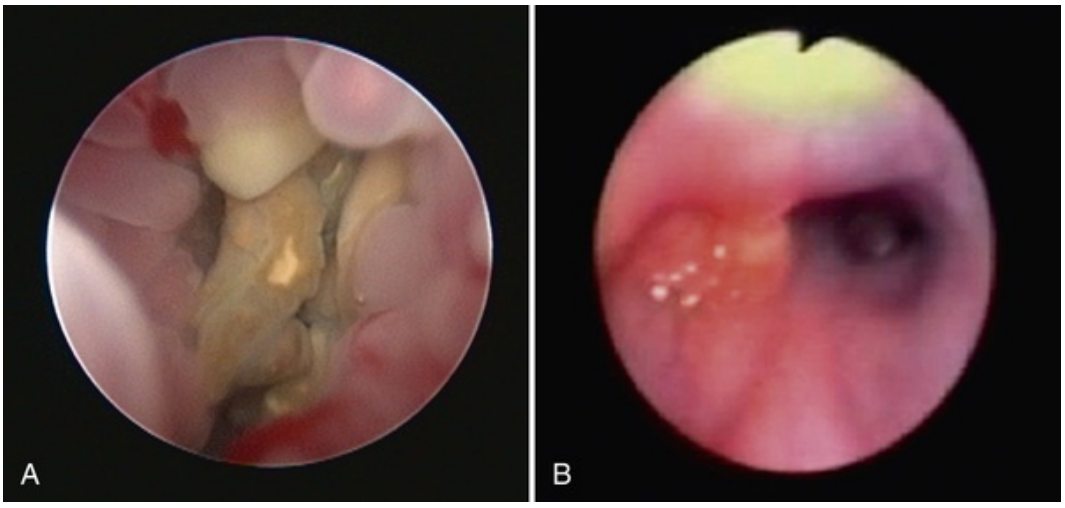

FIGURE 235-6 **A,** Rhinoscopic visualization of fungal plaques adherent to the nasal mucosa in a cat with sino-nasal aspergillosis caused by *A. fumigatus.* **B,** Choanal mass in a cat with SOA caused by *A. felis.* (**A,** Courtesy Dr. Elise Robertson, Feline VetReferrals, Brighton, UK.)

For molecular identification of cryptic species, fungal DNA is extracted from fungal culture material or, in culture negative cases, from frozen biopsies.[9,22] Comparative sequence analysis of the internal transcribed spacer (ITS) region of the ribosomal DNA gene complex (a multicopy gene common to all fungi), coupled with at least one additional gene region enables accurate identification to subgenus and species level, respectively.[25,29,30] Formalin-fixed paraffin-embedded tissues are less useful for polymerase chain reaction (PCR) due to low sensitivity of fungal DNA extraction.[31]

Histological changes in SNA include severe inflammatory rhinitis with lymphoplasmacytic or mixed-cell inflammatory infiltrates, necrosis, and mats of fungal hyphae on mucosal surfaces or in luminal exudates.[2-5] Cats with SOA have invasive granulomatous mycotic rhinitis[5,9] and orbital granulomas comprised of multifocal areas of coagulative necrosis with centralized fungal hyphae and peripheral zones of inflammatory cells.

Treatment

Non-invasive SNA due to *A. fumigatus* and *A. niger* is treated similarly to SNA in dogs (see ch. 234), although some cases have resolved with systemic triazole therapy alone.[3-5] Meticulous sino-nasal fungal plaque debridement and lavage is an important aspect of therapy and may require sinus trephination.[2-5] Intranasal 1% clotrimazole or 1-2% enilconazole solutions in polyethylene glycol were tolerated in cats where cribriform plate integrity was demonstrated.[2,5] Intranasal antifungal azole cream preparations used for treating canine SNA are not recommended in cats, because of the greater potential for airway obstruction from reluctance to mouth-breathe or brachycephalic conformation. Repeat debridement of fungal plaques and multiple intranasal azole infusions may be required to resolve infection. For cryptic species infections, or where *Aspergillus* species identity has not been confirmed, or where there is histological evidence of hyphal invasion of the sinus or nasal epithelium, additional treatment with oral itraconazole or posaconazole is recommended. Treatment should be continued until there is resolution of clinical, CT and endoscopic signs of active disease. The prognosis for feline SNA is favorable, although months of treatment may be required and only small numbers of treatment outcomes have been reported. Signs resolved in 11 of 14 cases where follow-up was available.[2-5,18]

Optimal treatment protocols for SOA have not been identified. *In vitro* resistance to azoles including itraconazole, posaconazole and voriconazole has been reported among some cryptic species isolates.[9,25,32] For susceptible isolates, based on treatment responses in individual cases, oral posaconazole or itraconazole given as monotherapy or combined with amphotericin-B or terbinafine is recommended.[5,14,16,23] Caspofungin was efficacious in one cat with SOA that failed treatment with amphotericin-B and posaconazole.[5] Anorexia and severe adverse neurological effects (hind limb paraplegia and blindness) can occur with oral voriconazole administration in cats[5,14,15] and further pharmacological studies are needed before its use can be recommended. Administration of systemic antifungals for 6 months or longer may be necessary and re-infection or relapse can occur. Surgical debridement of large granulomas by orbital exenteration has not been demonstrated to confer a treatment advantage over medical therapy alone. SOA carries a poor prognosis overall.

Disseminated Invasive Aspergillosis

Disseminated invasive aspergillosis (IA) is uncommon in cats.[33-37] Focal forms of IA affecting lung, gastrointestinal tract or urinary bladder have been described.[34,38-43] Molecular confirmation of *Aspergillus* species identified in disseminated IA has not been reported. There is no sex or breed predisposition. Disease has been most commonly reported in cats less than 2 years of age with systemic immunodeficiency from feline panleukopenia virus infection. Other cases have had concurrent FeLV infection or feline infectious peritonitis.

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CHAPTER 236

Miscellaneous Fungal Infections

Amy M. Grooters

Infections caused by miscellaneous fungal organisms include sporotrichosis; candidiasis; pythiosis, lagenidiosis, and paralagenidiosis (caused by pseudofungal pathogens in the class Oomycetes); zygomycosis; and a myriad of opportunistic fungi that uncommonly cause disease in dogs and cats, more often affecting those being treated with immunosuppressant medications.

Sporotrichosis

Sporotrichosis is a chronic granulomatous disease of worldwide significance caused by dimorphic saprophytic fungi in the *Sporothrix schenckii* species complex. The organism lives as a mycelium in the soil or when cultured at room temperature, and as a yeast in tissues at body temperature. The mycelia are thin, finely branched, and septate. They produce clusters of conidia, which are the infective stage. The yeast form exists in infected tissue and is characterized as pleomorphic round, oval, or cigar-shaped cells that measure 2 by 3 microns to 3 by 10 microns (Figure 236-1).

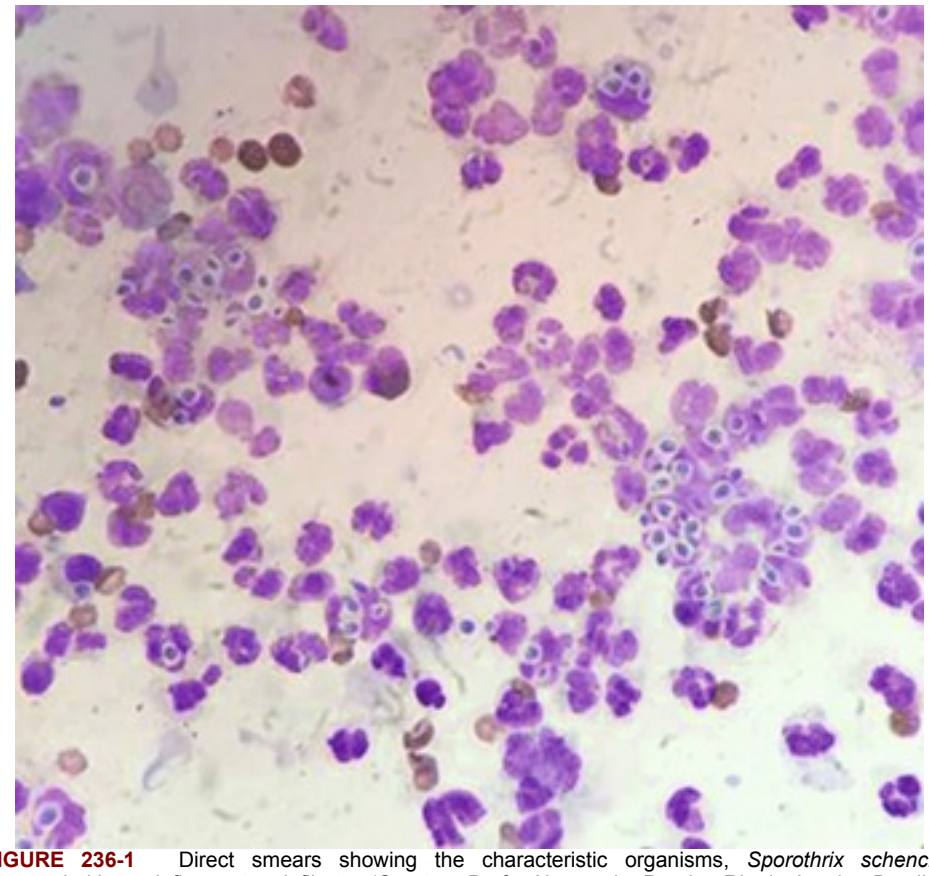

FIGURE 236-1 Direct smears showing the characteristic organisms, *Sporothrix schenckii,* surrounded by an inflammatory infiltrate. (Courtesy Profa. Alessandra Pereira, Rio de Janeiro, Brasil.)

The yeast morphology is fairly characteristic, and a diagnosis can usually be made from a cytologic

preparation. Both dogs and cats can be infected, but dogs are only rarely infected and typically have only cutaneous or subcutaneous disease. Cats are infected much more frequently and often have systemic dissemination.

Pathophysiology

Infection with *S. schenckii* in dogs and cats usually occurs after trauma that results in inoculation of infective conidia. Yeast from cutaneous lesions can be infective and are a potential source of zoonotic infection via contamination of wounds or via scratches or bites. The skin is the primary organ system affected. Traditionally it has been accepted that dissemination is via lymphatics from cutaneous sites and that this is common in cats and less common in dogs. However, an epidemic of *Sporothrix* infections in Rio de Janeiro, Brazil, studied between 1998 and 2012 allowed large numbers of cases to be evaluated and brought into question this traditionally accepted theory relative to infection and dissemination.[1-8] In a study that included 759 humans, 64 dogs, and 1503 cats with sporotrichosis, approximately 85% of dogs and humans were reported to have had contact with cats with sporotrichosis, with over half reporting cat bites or scratches.[1,3] People who were the care givers of infected cats were 4 times more likely to become infected than others in the same household. These observations support the importance of zoonotic transmission, especially in urban environments in which numbers of susceptible cats are high. In a separate study, 34% of 49 cats with sporotrichosis were fungemic, an observation that would appear to support a hematogenous role in dissemination.[4] Immune suppression has been reported to predispose to infection and increase the likelihood of dissemination. However, cats with feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) infection did not appear to be more likely to have disseminated disease in cases from Rio de Janeiro.

Sporotrichosis occurs in three primary forms: (1) cutaneous, (2) cutaneolymphatic, and (3) disseminated disease. In the dog, the infection is usually cutaneous or cutaneolymphatic. Disseminated disease is rare and usually follows immunosuppression with corticosteroids. All three forms appear to be common in the cat, with dissemination seen in more than 50% of feline cases. The nasal cavity and lungs are commonly affected, raising speculation that the respiratory tract may be an important site of entry, similar to other systemic mycoses. Cutaneous lesions in cats are characterized by large numbers of yeasts, making zoonotic transmission more likely from cats than from dogs.

Clinical Signs

Most affected cats are younger than 4 years of age, and males are affected approximately twice as often as females. Young hunting dogs may be predisposed. Multiple subcutaneous or dermal nodular lesions that occur most commonly on the head, neck, trunk, and distal limbs characterize the cutaneous form of the disease. The tail base may also be involved in cats. The nodules typically ulcerate, drain a purulent exudate, and crust over (Figure 236-2). They are often mistaken for bacterial bite wound abscesses or cellulitis. Lesions on the distal limbs commonly result in regional lymphadenitis, which is manifested as linear ulcerating lesions and regional lymphadenopathy. Lesions in cats may be associated with extensive areas of necrosis. Otitis externa has been reported.

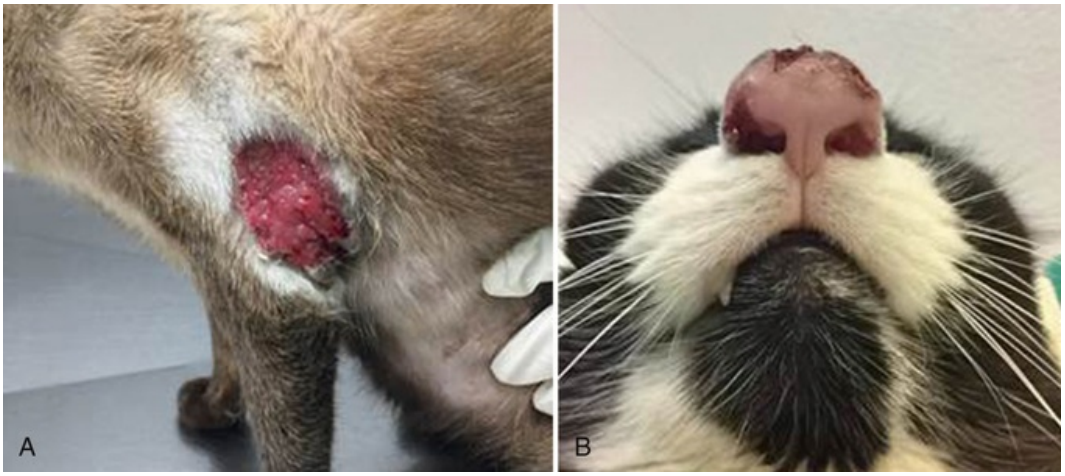

FIGURE 236-2 **A,** Skin lesion of sporotrichosis, showing an alopecic, erythematous, moist, proliferative area of skin over this cat's elbow and triceps region. **B,** Nasal lesion of sporotrichosis, showing swelling and ulceration of the rostral aspect of the nose in a cat. (Courtesy Profa. Alessandra Pereira, Rio de Janeiro, Brasil.)

Dissemination may occur and be subclinical or may result in overt systemic disease. Cats with multiple lesions and those with evidence of systemic illness such as respiratory signs or weight loss are more likely to have dissemination. Nasal and oral cavities, lung, liver, lymph nodes, spleen, eyes, bones, muscles, and central nervous system (CNS) may all be affected.[1,6,7]

Diagnosis

Cytology from skin lesions is the most common means of diagnosis. Lesions from cats typically contain large numbers of organisms, making cytology and histopathology sensitive tools for diagnosis,[9] although there are exceptions.[10] In contrast, lesions from dogs usually contain very few organisms. The organisms may be seen intracellularly within macrophages or neutrophils or may be present extracellularly. Culture and molecular techniques can be used to make a definitive diagnosis.

Material for culture should include exudate from deep within a draining tract and tissue samples from biopsy specimens. Nasal and oral swabs may result in positive cultures in cats with systemic infection, especially if nasal signs are prominent. Blood cultures are also commonly positive in cats with disseminated disease. Cultured organisms pose a serious threat to persons working in the laboratory, so the laboratory should be notified whenever a sample is submitted from a dog or cat with suspected sporotrichosis. Histopathology reveals pyogranulomatous inflammation. Numerous organisms are commonly seen in lesions from cats, even when stained with hematoxylin and eosin (H&E). Fungal stains may aid in identifying the organisms.

Therapy

Historically, sporotrichosis was most often treated with potassium iodide, ketoconazole, or combinations of the two. Approximately 55% of treated cats in the literature responded to one or both of these drugs. Fluconazole may also be effective. Currently, however, itraconazole (10 mg/kg PO q 24 h) is the treatment of choice, and is especially valuable in cats because of the species' tendency to develop adverse effects when treated with potassium iodide or ketoconazole.[6,11] Therapy should be administered for at least 30 days beyond resolution of clinical signs, with a minimum of 4-6 months. Response to itraconazole in cutaneous and cutaneolymphatic cases is generally good. Based on observations from the epidemic in Rio de Janeiro, systemically affected animals may also respond well. Recurrence after discontinuation of treatment is not uncommon. Cryosurgery has been used successfully as adjunctive therapy in a small number of cats.[12]

Public Health Significance

Canine sporotrichosis appears to be of minimal zoonotic potential, but feline sporotrichosis is a significant zoonotic disease. Veterinarians and veterinary assistants are at the highest risk of infection, but owners who care for infected cats are likely at increased risk as well. Care should be taken to limit contact with exudate and lesions from infected cats. Gloves should always be worn when handling cats suspected of having sporotrichosis, and owners should be advised of the possibility of infection and the need for strict hygiene. After any contact, gloves should be removed carefully and disposed of, and hands, wrists, and arms should be washed thoroughly with either chlorhexidine or povidone-iodine scrub.

Candidiasis

Candida spp. are normal inhabitants of the GI, genitourinary, and upper respiratory systems. Overgrowth of these organisms may result from prolonged broad-spectrum antibiotic use, structural changes in local tissues (such as urethrostomy or urogenital neoplasia), or immunosuppression associated with corticosteroid therapy or systemic disorders such as diabetes mellitus or hyperadrenocorticism.[13,14] Animals with prolonged neutropenia are especially predisposed to infection. Common sites for *Candida* overgrowth include wounds, the oropharynx, the urinary tract, and the gastrointestinal (GI) tract. Infections may be localized, or dissemination may occur hematogenously, resulting in microabscesses at multiple sites.

Localized candidiasis is usually characterized as a non-healing ulcer covered by a whitish-gray plaque in

the oral cavity, ears, GI tract, or on the genitourinary mucosa. Chronic moist, exudative lesions may occur on the skin or at the nail beds. *Candida* urinary tract infections are most often diagnosed incidentally during the evaluation of patients with concurrent urinary or systemic disease (such as diabetes mellitus), and typically do not cause lower urinary tract signs unless accompanied by concurrent lower urinary tract disease.[14]

Treatment of localized candidiasis should include identification and correction of any identifiable predisposing factors, if possible, and this alone may allow spontaneous resolution of *Candida* infections in some cases.[14] Primary therapies for skin lesions include topical azoles and pH-modifying agents, combined with systemic itraconazole or fluconazole if lesions are severe (see ch. 162). For urinary tract infections, systemic fluconazole is likely the treatment of choice because it is mainly eliminated unchanged in the urine. In addition, intravesicular clotrimazole has been used successfully in a dog and a cat with urinary candidiasis, both of which were diabetic.[15,16] It should be noted that when underlying predisposing factors cannot be corrected, prolonged azole therapy may not clear *Candida* infections, and may result in azole resistance.[14] It should also be noted that some *Candida* species (such as *C. krusei* and *C. glabrata*) are likely to be inherently azole-resistant, so identification of organisms to species level and susceptibility testing may be important to guide therapy.

Disseminated candidiasis is typified by fever and the acute appearance of multiple raised erythematous skin lesions in dogs. Pain is often caused by myositis and osteomyelitis, and other signs are referable to the systems affected. Cats are less likely to have multiple skin lesions. The complete blood count (CBC) in systemically affected animals is often characterized by leukopenia and thrombocytopenia. Renal involvement is common, and yeast may be found in the urine, especially in cats. Itraconazole and amphotericin B lipid complex are considered the treatments of choice, but few reports of successful treatment are available.

Pythiosis

Pythiosis is a devastating and often fatal cause of chronic GI or cutaneous disease in dogs and cats. It is caused by *Pythium insidiosum,* an aquatic pathogen in the class Oomycetes in the Kingdom Stramenopila (Chromista). Oomycetes differ from true fungi in that ergosterol is not a principal sterol in the oomycete cell membrane. In the United States, pythiosis is encountered most often in the Gulf Coast states, but has been recognized in animals living as far north as New Jersey, Virginia, Kentucky, Wisconsin, and southern Illinois/Indiana, and as far west as Arizona, California, Oklahoma, and Kansas. Globally, pythiosis is most often encountered in Southeast Asia, eastern coastal Australia, and South America. Pythiosis, lagenidiosis, paralagenidiosis, and zygomycosis often are difficult to distinguish from one another because they share similar clinical and histologic features, including pyogranulomatous and eosinophilic inflammation associated with broad, poorly septate hyphae. However, differentiating among them is clinically important because prognosis and response to therapy differ.

Pathophysiology

The infective form of *P. insidiosum* is thought to be the motile biflagellate zoospore, which is released into aquatic environments and likely causes infection by encysting in damaged skin or GI mucosa. Many dogs with pythiosis have a history of recurrent exposure to warm freshwater habitats. However, some cases are observed in suburban housedogs with no history of access to lakes or ponds. Affected animals are typically immunocompetent and otherwise healthy.

Clinical Findings

In dogs, pythiosis most often affects young, large-breed dogs and is especially common in outdoor working breeds such as Labrador Retrievers. Infected dogs are presented to the veterinarian more often in the fall, winter, and early spring than in the summer months. Pythiosis is uncommon in cats; when it does occur, animals less than a year of age are often affected.

Cutaneous pythiosis in dogs typically causes non-healing wounds and invasive masses that contain ulcerated nodules and draining tracts, most often involving the extremities, tail head, ventral neck, or perineum.[17,18] Cats with pythiosis may have nasopharyngeal lesions, invasive subcutaneous masses in the inguinal, tail head, or periorbital regions, or they may have draining nodular lesions or ulcerated plaque-like lesions on the extremities, sometimes centered on the digits or footpad.[18,19]

GI pythiosis in dogs is characterized by severe segmental transmural thickening of the stomach, small

intestine, colon, rectum, or (rarely) the esophagus or pharyngeal region (Figure 236-3).[17,20] Mesenteric lymphadenopathy is common and is occasionally observed without accompanying GI tract lesions. The gastric outflow area, duodenum, and ileocolic junction are the most frequently affected portions of the GI tract. Involvement of the mesenteric root may cause severe enlargement of mesenteric lymph nodes, which are often embedded in a single, large, firm granulomatous mass in the mid-abdomen. Extension of disease into mesenteric vessels may result in bowel ischemia, infarction, perforation, or acute hemoabdomen. Focal intestinal lesions caused by pythiosis were described in two cats that were both treated successfully with surgical resection.[21]

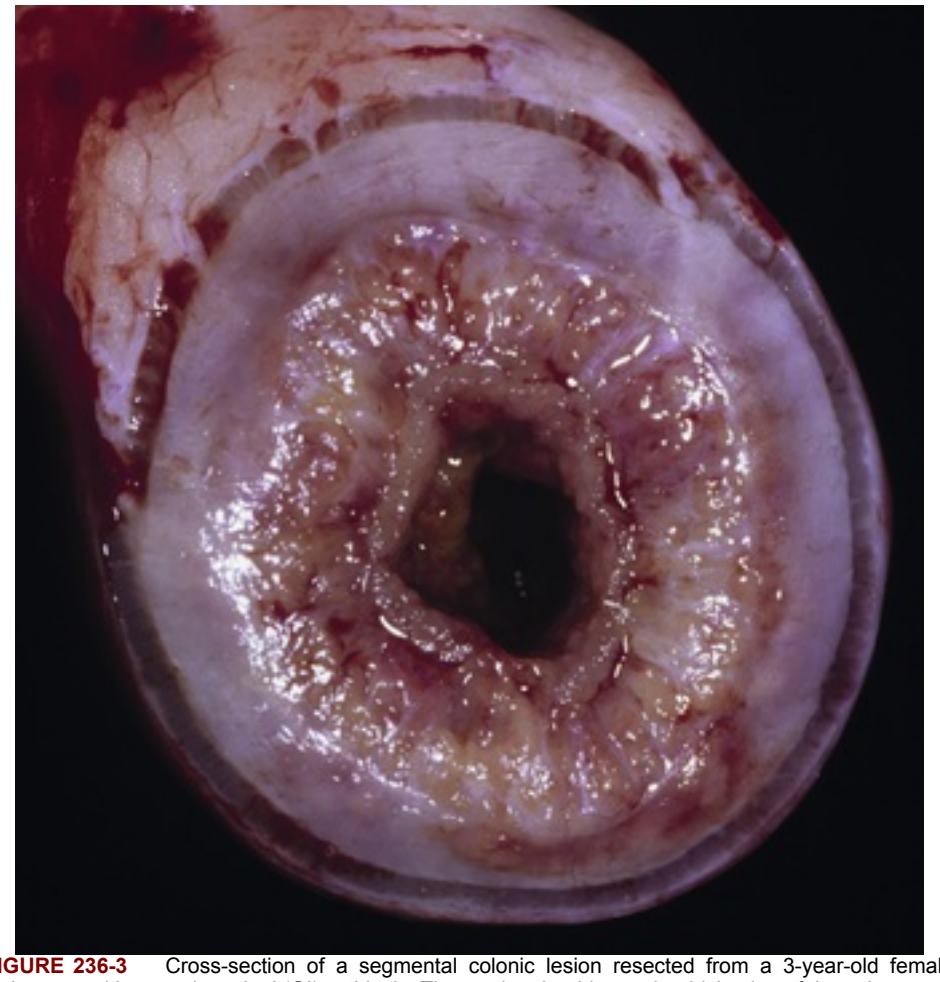

FIGURE 236-3 Cross-section of a segmental colonic lesion resected from a 3-year-old female Doberman with gastrointestinal (GI) pythiosis. The reader should note the thickening of the submucosa and narrowing of the colonic lumen.

Clinical signs associated with GI pythiosis include weight loss, vomiting, diarrhea, and hematochezia. Physical examination often reveals a thin body condition and palpable abdominal mass. Signs of systemic illness are not typically present unless intestinal obstruction, infarction, or perforation occurs. Laboratory abnormalities that may be associated with pythiosis include eosinophilia, anemia, and hyperglobulinemia. In dogs with GI pythiosis, abdominal radiographs usually reveal an abdominal mass, thickened segment of the GI tract, or partial bowel obstruction. Ultrasonography typically demonstrates severe segmental thickening of the GI tract and mesenteric lymphadenopathy.

Diagnosis

Histologically, pythiosis is characterized by eosinophilic pyogranulomatous inflammation. Although *P. insidiosum* hyphae are difficult to visualize on H&E-stained sections, they are easily identified in sections stained with Gomori methenamine silver (GMS) as broad (mean, 4 microns; range, 2 to 7 microns), rarely

septate, occasionally branching structures. Because inflammation in GI pythiosis centers on the submucosal and muscular layers rather than mucosa and lamina propria, the diagnosis may be missed on endoscopic biopsies that fail to reach deeper tissues. Therefore, pythiosis should be considered when endoscopic biopsies reveal eosinophilic or pyogranulomatous inflammation without identification of a causative agent.

Isolation of *P. insidiosum* from infected tissues is not difficult when appropriate sample handling and culture techniques are used. For best results, unrefrigerated tissue samples should be wrapped in a saline-moistened gauze sponge and shipped at ambient temperature to arrive within 24 hours at a laboratory with experience culturing oomycetes. Identification of *P. insidiosum* should be based on morphologic features; growth at 37° C; production of motile, reniform, biflagellate zoospores; and specific polymerase chain reaction (PCR) amplification or ribosomal RNA gene sequencing. Although the production of zoospores is an important supporting feature for the identification of pathogenic oomycetes, it is not specific for *P. insidiosum.*

An enzyme-linked immunosorbent assay (ELISA) for the detection of anti–*P. insidiosum* antibodies in dogs and cats has been found to be highly sensitive and specific for the diagnosis of pythiosis.[22] In addition to providing a means for early, noninvasive diagnosis, this assay also appears to be useful for monitoring response to therapy. Immunohistochemical techniques have previously been used to confirm the diagnosis of pythiosis. However, the specificity of these antibodies has not always been well established.

Therapy

Aggressive surgical resection is the treatment of choice for pythiosis. When cutaneous lesions are limited to a single distal extremity and there is no regional lymphadenopathy, amputation is recommended. In animals with GI pythiosis, segmental lesions should be resected with 5-cm margins if possible. Because enlarged mesenteric lymph nodes are usually reactive rather than infected, they should be biopsied but do not need to be resected. Unfortunately, many dogs with GI pythiosis are not presented until late in the course of disease, when complete excision is not possible. Local postoperative recurrence of pythiosis is common, especially when wide surgical margins could not be obtained, and can occur either at the site of resection or in regional lymph nodes. For this reason, medical therapy with a combination of itraconazole (10 mg/kg PO q 24 h) and terbinafine (5 to 10 mg/kg PO q 24 h) is recommended when the surgeon is not confident that a minimum 5-cm margin was achieved. To monitor for recurrence, ELISA serology should be performed prior to and 2 to 3 months after surgery. In animals that have had a complete surgical resection and go on to have no recurrence of disease, serum antibody levels usually drop 50% or more within 3 months of surgery,[22] allowing medical therapy to be discontinued.

In general, pythiosis does not respond well to medical therapy, likely because ergosterol (the target for most currently available antifungal drugs) is generally lacking in the oomycete cell membrane. Despite this fact, clinical and serologic cures occur in some patients treated with a combination of itraconazole (10 mg/kg PO q 24 h) and terbinafine (10 mg/kg PO q 24 h). Dogs with non-resectable GI pythiosis are often treated with anti-inflammatory dosages of corticosteroids in an effort to palliate clinical signs and to decrease vomiting so that oral antifungal medication can be administered. Prednisone (1 mg/kg PO q 24 h) routinely causes improvement in clinical signs in the short term. Surprisingly, the author has observed complete and long-term resolution of GI lesions in a small number of dogs treated with prednisone alone. Although this is certainly not recommended as a primary treatment for animals with resectable lesions, it is a reasonable option in animals with non-resectable GI lesions, especially when financial concerns preclude the use of antifungal medication.

Lagenidiosis and Paralagenidiosis

Like *Pythium insidiosum,* species in the genera *Lagenidium* and *Paralagenidium* are members of the class Oomycetes, with most described as parasites of algae, fungi, nematodes, crustaceans, and insect larvae. The best-studied species, *Lagenidium giganteum,* is a mosquito larval pathogen previously approved for use as a biocontrol agent for mosquito populations. In the late 1990s, two novel oomycete pathogens that appeared to be members of the genus *Lagenidium* were recognized in dogs as causes of cutaneous lesions that resemble those associated with pythiosis. More recently, multigene phylogenetic analyses have allowed formal names to be published for these pathogens.[23] The first pathogen, which causes severe and often fatal progressive cutaneous disease, lymphadenopathy, pulmonary nodules, and great vessel invasion,[24] has been formally described as *Lagenidium giganteum* forma *caninum* because of its close phylogenetic relationship with *Lagenidium giganteum.* The second pathogen causes more slowly progressive disease that is limited to skin and subcutaneous tissues. Although it shares many antigenic and morphologic similarities with *L. giganteum* f.

caninum and other *Lagenidium* species, recent phylogenetic analyses support placement of the second novel pathogen in the new genus *Paralagenidium,* with the species name *Paralagenidium karlingii.*[23]

Clinical Findings

The epidemiologic and clinicopathologic features of lagenidiosis and paralagenidiosis are similar in many respects to those previously associated with cutaneous pythiosis. Infected animals are typically young to middle-aged dogs living in the southeastern United States. Although most have been from Florida or Louisiana, cases have been identified as far west as Texas and as far north as Maryland and southern Indiana. Many infected dogs have had frequent exposure to lakes or ponds.

Dogs with lagenidiosis are typically presented for progressive solitary or multifocal cutaneous or subcutaneous lesions involving the extremities, mammary region, perineum, or trunk.[24] Grossly, these lesions appear as firm dermal or subcutaneous nodules or as ulcerated, thickened areas with areas of necrosis and numerous draining tracts (Figure 236-4). Similar to the clinical course associated with cutaneous pythiosis, skin lesions in dogs with lagenidiosis tend to be progressive, locally invasive, and poorly responsive to medical therapy. Regional lymphadenopathy is often present and may occur in the absence of obvious cutaneous lesions. Unlike dogs with cutaneous pythiosis, these dogs typically have occult lesions in the thorax or abdomen, including involvement of the great vessels, sublumbar and/or inguinal lymph nodes, lung, pulmonary hilus, and cranial mediastinum. Animals with great vessel or sublumbar lymph node involvement typically have cutaneous or subcutaneous lesions on the hind limbs and often develop hind limb edema (see ch. 18). Sudden death caused by great vessel rupture and associated hemoabdomen may occur in these patients.

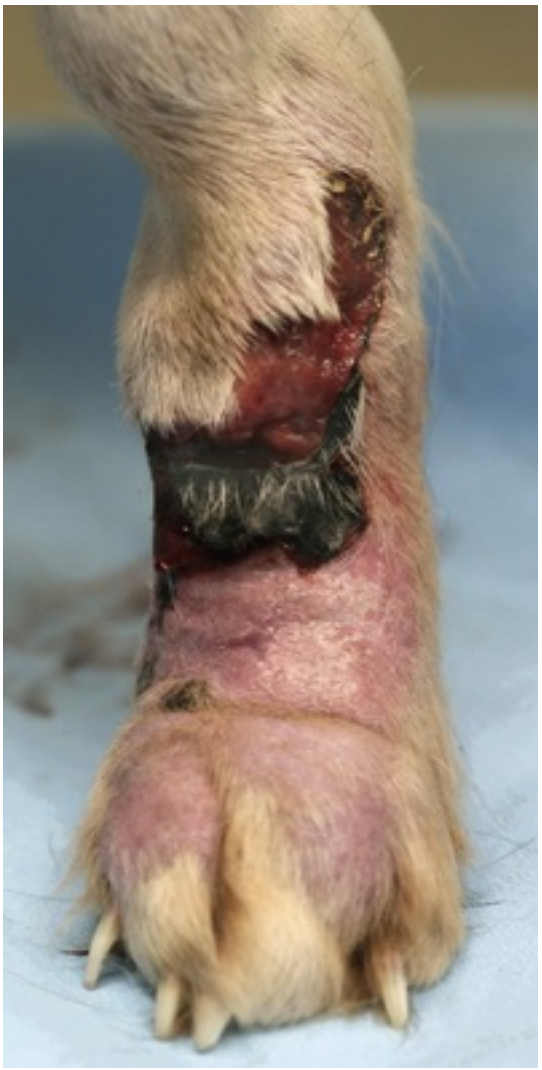

FIGURE 236-4 Ulcerative dermatitis caused by *Lagenidium giganteum* forma *caninum* infection in a 2-year-old female Border Collie presented for progressive skin lesions and generalized lymphadenopathy. This dog had similar lesions on all four limbs. Note the large eschar distal to the ulcerative lesion.

In dogs with paralagenidiosis, skin lesions are characterized by solitary or multifocal dermal nodules or thickening (sometimes without alopecia) or an ulcerative dermatopathy that may become extensive but rarely invades beyond cutaneous and subcutaneous tissues. Lesions in the chest, abdomen, and regional lymph nodes have not been identified, and the clinical course appears to be chronic and slowly progressive, with some patients having lesions that expand slowly or are somewhat stable for years.

Diagnosis

The histologic features of lagenidiosis and paralagenidiosis are similar to those associated with pythiosis and zygomycosis and are characterized by pyogranulomatous and eosinophilic inflammation associated with broad, irregularly branching, sparsely septate hyphae. In contrast to *P. insidiosum, Lagenidium giganteum* f. *caninum* and *Paralagenidium karlingii* hyphae are often visible on H&E-stained sections, and may be surrounded by a thin eosinophilic sleeve. On GMS-stained sections, numerous broad, thick-walled, irregularly septate hyphae are easily recognized. *Lagenidium giganteum* f. *caninum* hyphae typically demonstrate a great deal of variability in size but in general are much larger than *P. insidiosum,* ranging from 7 to 25 microns in diameter, with an average of 12 microns. *Paralagenidium karlingii* hyphae are closer in size to *P. insidiosum,* with a mean diameter of 7.5 microns.

An ELISA for quantitation of anti–*L. giganteum* f. *caninum* antibodies has recently been described as a sensitive but non-specific serologic test for the identification of *L. giganteum* f. *caninum*–infected, and to a

lesser degree, *Paralagenidium karlingii*–infected dogs.[25] Because of extensive cross-reactivity with anti–*P. insidiosum* and anti–*Paralagenidium karlingii* antibodies, positive ELISA results are often observed in dogs with pythiosis or paralagenidiosis in addition to those with lagenidiosis. In addition, some dogs with non-fungal dermatopathies have also had false positive results. Because of these limitations, definitive diagnosis of *Lagenidium giganteum* f. *caninum* and *Paralagenidium karlingii* infections should be based on culture followed by ribosomal RNA gene sequencing.

Treatment

Aggressive surgical resection of infected tissues is the treatment of choice for both lagenidiosis and paralagenidiosis. In animals with lesions limited to a single distal extremity, amputation is recommended. Because dogs with lagenidiosis often have occult systemic lesions, radiographic imaging of the chest and abdomen and sonographic imaging of the abdomen is recommended to determine the extent of disease prior to attempting surgical resection of cutaneous lesions. Unfortunately, many of these patients have non-resectable disease in regional lymph nodes or distant sites by the time the initial diagnosis is made. Because response to medical therapy is poor, dogs with lagenidiosis typically have a grave prognosis.

In contrast, for dogs with paralagenidiosis, surgery that achieves 3- to 5-cm margins is often curative. Although medical therapy for paralagenidiosis is usually ineffective, a combination of itraconazole (10 mg/kg PO q 24 h) and terbinafine (10 mg/kg PO q 24 h) along with repeated aggressive surgical resection was effective in resolving *Paralagenidium karlingii* infection in one dog with recurrent multifocal cutaneous lesions.

Zygomycosis

The term *zygomycosis* refers to infections caused by fungi in the class Zygomycetes, including the genera *Basidiobolus* and *Conidiobolus* in the order Entomophthorales, and the genera *Rhizopus, Absidia, Mucor, Saksenaea,* and others in the order Mucorales. Although infections caused by the Mucorales have not been well documented in small animals, the Entomophthorales typically cause chronic localized infections characterized by pyogranulomatous and eosinophilic inflammation in subcutaneous tissue, upper respiratory tract, or retrobulbar space. As *Basidiobolus* and *Conidiobolus* species are saprophytes found in soil and decaying organic matter, cutaneous infection likely occurs by direct implantation of spores via minor trauma or insect bites. Infection may also result from inhalation or ingestion of spores. Affected animals are typically immunocompetent, but pneumonia caused by *Conidiobolus* spp. has been reported in a single canine patient receiving immunosuppressive therapy.[26]

Clinical Findings

In mammals, conidiobolomycosis occurs most often as a nasopharyngeal infection with or without local dissemination into tissues of the face, retropharyngeal region, or retrobulbar region. Clinical manifestations may include nasal or facial swelling or deformity, nasal discharge, ulceration of the nasal planum or hard palate, exophthalmos, chemosis, ocular discharge, and sometimes skin lesions.[27] *Conidiobolus* infection has also been described in a single dog as a cause of multifocal nodular draining subcutaneous lesions and regional lymphadenopathy[28] and as a cause of pneumonia in a dog that was receiving chemotherapy.[26]

Basidiobolomycosis is a rare cause of ulcerative draining skin lesions in dogs and has also been reported in a single case as a cause of respiratory disease.[29] Disseminated *Basidiobolus* spp. infection involving the GI tract and other abdominal organs has also been described.[30]

In cats, confirmed cases of zygomycosis are rare, limited to single reports of cats infected with fungi in the order *Mucorales. Rhizomucor* was associated with duodenal perforation in a 7-month-old cat,[31] and *Cokeromyces recurvatus* was isolated from peritoneal fluid in a 16-year-old cat following jejunal perforation caused by lymphoma.[32] In addition, a subcutaneous mass caused by *Mucor* infection on the dorsum of the nose of a 14-year-old cat was treated successfully with posaconazole.[33]

Diagnosis

The histologic features of zygomycosis are similar to those associated with pythiosis, lagenidiosis, and paralagenidiosis. On GMS-stained sections, hyphae appear broad, thin-walled, and occasionally septate. The histologic hallmark of entomophthoromycosis is the presence of a wide eosinophilic sleeve surrounding the

hyphae. In general, hyphal diameter tends to be significantly larger for *Basidiobolus* spp. (mean, 9 microns; range, 5 to 20 microns) and *Conidiobolus* spp. (mean, 8 microns; range, 5 to 13 microns) than for *P. insidiosum* (mean, 4 microns; range, 2 to 7 microns).

The diagnosis of zygomycosis is based on isolation of the pathogen from infected tissues. Identification of zygomycetes in the laboratory is based on morphologic characteristics of asexual reproductive structures (conidia) and sexual reproductive structures (zygospores).

Treatment

Attempted therapy has only been described in a few patients with confirmed zygomycosis. Although anecdotal information and a small number of cases in the literature suggest that cutaneous entomophthoromycosis may be less aggressive than pythiosis or lagenidiosis, progression of cutaneous lesions and sometimes even dissemination despite treatment have also been described. Perhaps the most appropriate current recommendation for the treatment of entomophthoromycosis is aggressive surgical resection of infected tissues whenever possible, followed by itraconazole therapy for a minimum of 3 months. If resection is not possible, therapy with itraconazole, posaconazole, or amphotericin B lipid complex should be recommended. For nasopharyngeal conidiobolomycosis, the author's current recommendation is to treat with itraconazole (10 mg/kg PO q 24 h) for at least 6-12 months (see ch. 162). Because recurrence is common after discontinuation of medical therapy, a prolonged course of antifungal medication is essential.

Opportunistic Fungal Infections

Opportunistic fungi are those with low inherent virulence that most often cause infection only when normal host barriers or resistance mechanisms are compromised. They comprise a large number of genera and species with names that are often unfamiliar to veterinary clinicians, and traditionally have caused disease only sporadically. Over the past 10 years, the frequency with which opportunistic fungal infections are encountered in small animal patients has increased substantially with the use of multi-agent immunosuppressive therapy (especially with cyclosporine) to treat immune-mediated disease in dogs (see ch. 165).

Unlike the more easily recognized endemic fungal pathogens (for which a diagnosis can usually be made by visualizing unique morphologic features in cytologic or histologic samples), opportunistic fungi can only be identified to genus and species level by culture or molecular methods. However, they can be assigned to categories based on their morphologic features in tissue, such as pigmentation, hyphal diameter, organism distribution, and frequency of septation. These categories include **phaeohyphomycosis** (pigmented hyphal or yeast forms), **hyalohyphomycosis** (non-pigmented hyphal forms), and **eumycotic mycetoma** (fibrosing granuloma with black or white tissue grains comprised of aggregates of pigmented or non-pigmented fungi, respectively).

Although definitive identification of a pathogen based on culture is ideal, categorization of opportunistic mycoses is often adequate for choosing initial therapies and predicting clinical course and prognosis. It should be noted that many opportunistic fungi are common contaminants found on skin, nasal mucosa, and other non-sterile sites. Therefore, culture or PCR-based identification of a potential opportunistic fungus from a skin sample, nasal swab, or exudate should not be considered evidence of fungal infection unless there is supportive histologic or cytologic evidence of tissue invasion by a morphologically compatible organism.

Phaeohyphomycosis

The term *phaeohyphomycosis* refers to cutaneous, subcutaneous, cerebral, or disseminated infections caused by pigmented (dematiaceous) fungi that contain melanin in their cell walls. Infection usually results from traumatic implantation. Fungal genera that have been identified as agents of phaeohyphomycosis in veterinary patients include *Alternaria, Bipolaris, Cladophialophora, Curvularia, Exophiala, Fonsecaea, Moniliella,* and *Phialophora,* among others. The most common clinical presentations in immunocompetent small animals are cutaneous distal extremity, nasal, and pinnal lesions in cats.[34-40] The most common presentation in immunocompromised small animals is multifocal cutaneous lesions in dogs being treated with multi-agent immunosuppressive therapy.[41-43] In general, patients are presented with cutaneous nodules or a visible nasal mass. Infected tissues may appear grossly pigmented. Histologically, fungi that cause phaeohyphomycosis appear as dark-walled, irregularly septate hyphae or as yeast-like cells. The presence of melanin in the walls of lightly pigmented hyphae can be confirmed by the examination of unstained sections, by lowering the

microscope condenser during examination, or by utilization of a Fontana-Masson stain for melanin.

Lesions associated with phaeohyphomycosis tend to be locally invasive. Dissemination is not common in immunocompetent patients, but does occur in patients receiving immunosuppressive therapy. Because pigmented fungi are often poorly responsive to medical therapy, aggressive surgical resection is the treatment of choice for phaeohyphomycosis when lesions are solitary. It is important to obtain wide margins at the time of the initial surgery because post-operative recurrence is common. Digit amputation is usually indicated for lesions involving the distal phalanx. Although phaeohyphomycosis has traditionally been difficult to treat medically (in part because melanin is a virulence factor), in this author's experience, cutaneous phaeohyphomycosis that occurs in dogs receiving immunosuppressive therapy can be resolved in many cases with itraconazole (10 mg/kg PO q 24 h; see ch. 162) administered for at least 6 months if the immunosuppressive therapy can be tapered quickly (see ch. 165). Discontinuation of cyclosporine in these patients appears to be essential for achieving a good outcome. In cats with non-resectable phaeohyphomycosis, long-term therapy is essential. Recurrence of lesions after discontinuing medical therapy is very common. This author most often treats these patients with itraconazole or posaconazole administered for 12 months or longer.

Hyalohyphomycosis

The term *hyalohyphomycosis* refers to infections caused by fungi that are non-pigmented (hyaline) in tissue. Genera that have been described as agents of hyalohyphomycosis in veterinary patients include *Fusarium, Acremonium, Paecilomyces, Pseudallescheria, Sagenomella, Phialosimplex,* and *Scedosporium,* among others. By convention, infections caused by *Aspergillus* and *Penicillium* species are not included in the term *hyalohyphomycosis* because aspergillosis and penicilliosis can usually be identified as such based on their clinicopathologic features.

In general, hyalohyphomycosis is less frequently encountered in small animal patients than is phaeohyphomycosis. Dogs are much more often infected than cats, with affected animals presented with lesions ranging from local disease confined to the skin, nasal mucosa, or cornea, to disseminated disease.[44-50] Traditionally, the disseminated form has been most common. Therefore, animals that present with cutaneous lesions and no overt signs of systemic disease should still be evaluated for occult lesions in the chest and abdomen. However, in this author's experience, immunosuppressed patients that develop cutaneous hyalohyphomycosis may not have lesions at other sites, whereas immunocompetent patients that develop hyalohyphomycosis most often do have disseminated disease, or at least disease that is not confined to the skin.

Treatment of hyalohyphomycosis has traditionally been unrewarding because most patients have had disseminated disease. However, hyalohyphomycosis that develops while an animal is receiving immunosuppressive therapy seems to respond better to medical therapy (assuming that immunosuppressive therapy can be quickly tapered) than would have been expected based on previous experience with hyalohyphomycosis in immunocompetent patients, especially if the detectable lesions are confined to the skin. The prognosis should still be considered guarded, and aggressive antifungal therapy should be pursued. For treatment of hyalohyphomycosis, this author most often uses itraconazole (10 mg/kg PO q 24 h) administered for at least 6-12 months. Other options include amphotericin B lipid complex, voriconazole, or posaconazole (see ch. 162). Unfortunately, recurrence of clinical signs often occurs during the course of initial treatment.

Mycetoma

The term *mycetoma* refers to localized mycotic or actinomycotic infections characterized by the presence of colonies or aggregates of organisms that form "grains" in tissue. Eumycotic mycetomas are caused by soil fungi, with lesions developing from traumatic implantation of organisms into tissue. Tissue grains associated with eumycotic mycetomas are characteristically pigmented (black grain mycetoma) or hyaline (white grain mycetoma), depending on the type of fungal organism involved.

Black grain mycetomas are often caused by *Curvularia* species, and are typically manifested as chronic non-healing wounds or cutaneous nodules that develop on the extremities weeks to months after a traumatic incident. Draining tracts are common, and black grains may be present in the exudate. White grain mycetomas, usually caused by *Pseudallescheria boydii* or *Acremonium* species, typically occur as body wall and/or intra-abdominal granulomas that develop subsequent to contamination following surgical wound contamination or dehiscence. Lesions may not be evident until months or even a year or more after the

surgical event. Affected animals may be presented with a draining mass on the body wall, or may develop clinical signs of peritonitis. The treatment of choice for eumycotic mycetoma is aggressive surgical excision of infected tissues, including amputation if clinically indicated. Response to medical therapy is routinely poor. Dissemination of eumycotic mycetoma beyond local tissues is rare, but local extension of disease within the abdomen may be extensive.

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SECTION XIV

Diseases of the Ears, Nose, and Throat

OUTLINE

Chapter 237 Diseases of the Ear
Chapter 238 Diseases of the Nose, Sinuses, and Nasopharynx
Chapter 239 Diseases of the Larynx

CHAPTER 237

Diseases of the Ear

Emmanuel Bensignor, Olivier Gauthier, Didier-Noël Carlotti †

Client Information Sheet: Otitis Externa: Treating Ear Infections

Otitis Externa

Introduction

Otitis is considered to be one of the most frequent causes of consultations in small animal practice. Although often considered part of dermatology, it should instead be emphasized that otitis is often a consequence of an underlying disease, and the investigation and management of ear disease should therefore be viewed by the veterinarian as needing a full diagnostic approach.[1]

Definitions

Otitis is "any inflammation of the ear canal," whatever the cause or clinical presentation. Depending on the history and clinical signs observed, it is useful to differentiate some entities depending on the time of onset of clinical signs, the rate of relapse, and/or the clinical presentation, because the clinical approach and therapy will vary.[1] Specifically, *erythematous otitis* is characterized by inflammation of the ear canal without secretion (Figure 237-1): *erythemato-ceruminous otitis* involves inflammation of the ear canal and presence of an abundant ceruminous exudate (Figure 237-2); *suppurative otitis* is marked by erosions in the ear canal and presence of pus (Figure 237-3); and *stenotic otitis* is characterized by hyperplastic changes of the ear canal (Figure 237-4 and Box 237-1). It is also useful to differentiate, depending on the depth of the inflammatory phenomenon, between otitis externa (OE), otitis media (OM) and otitis interna (OI). OE is an inflammatory condition affecting the external auditory canal, from the pinna up to the tympanic membrane. OE is very common in dogs and cats, with a reported incidence of 5-12% of consultations in dogs and up to 2% of cats referred to a dermatologist.[2,3] OM is present as soon there is inflammation within the middle ear. Both canine and feline OM often are secondary to an accompanying OE. In dogs, cases of primary OM are very rare (e.g., "glue ear syndrome" of Cavalier King Charles Spaniels) but in the cat, primary OM is recognized regularly. The reported prevalence of OM varies from low to high; the latter may be especially true in cases of chronic or recurrent OE.[4] OI is defined as an inflammation within the inner ear. OI generally results from an extension of OM. Clinical signs are principally neurologic, identical to those of peripheral vestibular disease (see ch. 265).[5]

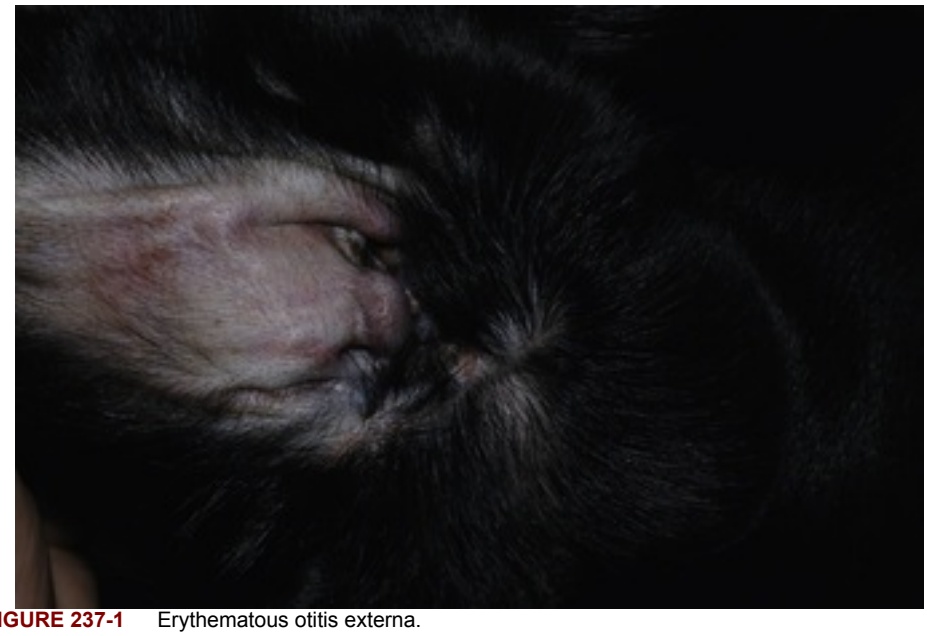


FIGURE 237-1 Erythematous otitis externa.

FIGURE 237-2 Erythemato-ceruminous otitis externa.

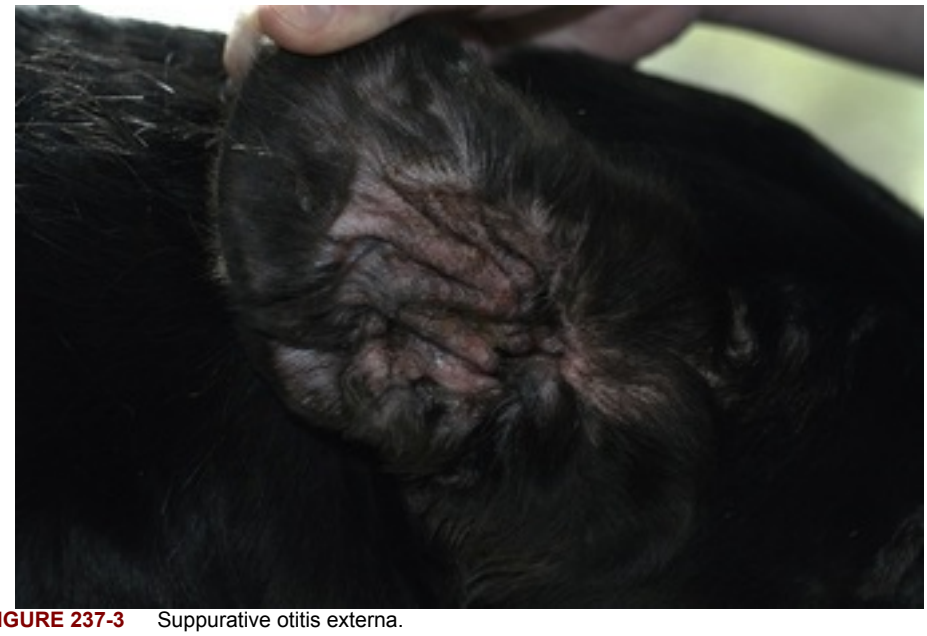


FIGURE 237-3 Suppurative otitis externa.

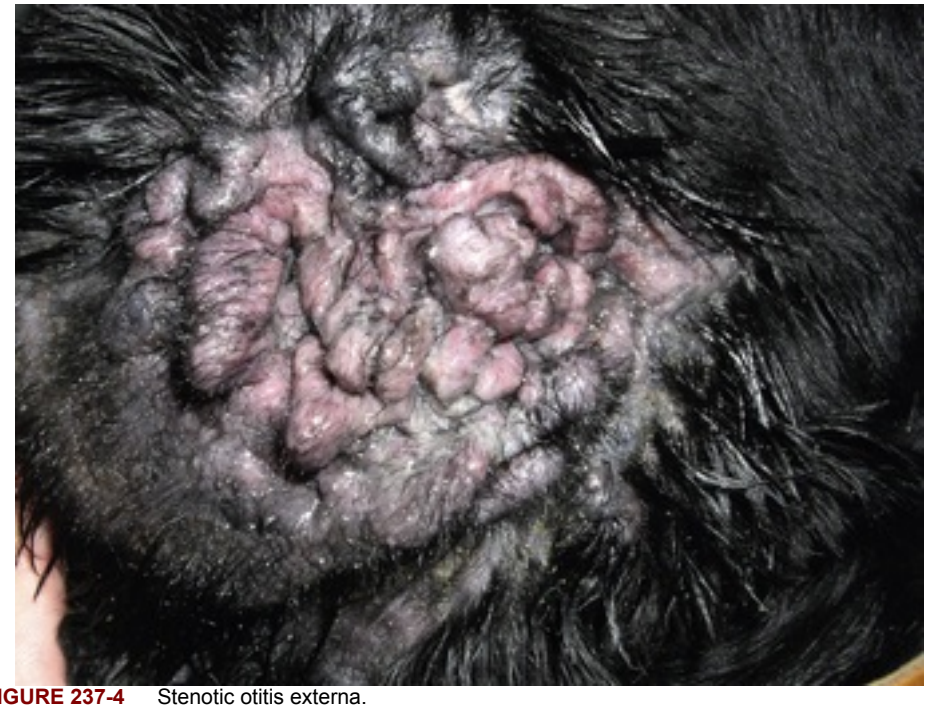


FIGURE 237-4 Stenotic otitis externa.

Box 237-1

Various Clinical Presentations of OE in Dogs and Cats

- Acute—clinical signs present for <7 days
- Subacute—clinical signs present for >7 but <30 days
- Chronic—clinical signs present for >30 days
- Recurrent or relapsing—episodes cured after proper treatment but reappearing on a regular basis
- Erythematous—the only clinical sign noted is inflammation of the auditory canal (this is mainly seen in

acute cases); typically associated with pruritus and/or head shaking

- Erythemato-ceruminous—the inflammation is associated with the presence of excessive cerumen, which may occlude the ear canal; pruritus is variable but usually present
- Suppurative—the secretions are variable, but usually the discharge is liquid and malodorous; pruritus may be seen but these cases tend to be more painful than pruritic; head shaking is frequent
- Stenotic—with these cases, the hyperplastic changes of the ear canal eventually lead to occlusion of the external parts of the auditory tube; this is often present in chronic disease

Pathogenesis

Otitis should usually not be considered as just a local phenomenon but rather as one manifestation of an underlying disease[6,7] because it nearly always has a multifactorial etiology. *Predisposing factors* are responsible for an alteration of the microclimate of the ear canal, increasing the likelihood of otitis (Box 237-2). *Primary factors* are responsible for the inflammation, and therefore are able to directly cause otitis. *Perpetuating factors* are responsible for chronicity. All these factors need to be properly identified and corrected in order to successfully manage patients with recurrent otitis. Typically, the pathogenesis involves inflammation of the auditory canal (erythematous phase) initially; this phenomenon is usually very acute and in most cases is not noticed by the owner except if pain and/or pruritus is/are severe (e.g., foreign body in the ear). This first phase is followed by hyperplasia of the epithelium and the ceruminous glands, resulting in excess cerumen production (ceruminous phase). OE also can impair the housekeeping mechanism that results in a movement of cerumen up and out of the ear canal, further contributing to the accumulation of discharge within the auditory canal.[8] These anatomic and inflammatory modifications allow the change in the environment that is favorable to the growth of, and infection with, commensal microorganisms such as *Malassezia* spp. and *Staphylococcus* spp. These microbial components contribute to further inflammation and perpetuate the vicious circle. For more chronic cases, extensive epidermal hyperplasia develops and can reduce the diameter of the ear canal, as apocrine glands become hyperplastic and dilated.[8] Sometimes, ulceration of the epithelium occurs, especially in cases of secondary bacterial infection with Gram-negative bacteria. A dense dermal inflammatory infiltrate occurs, followed by fibroplasia that further exacerbates canal obstruction.[9] Ossification of the cartilages and skin may occur in longstanding cases. When the tympanum is ruptured, the microbial infection can involve the tympanic bulla and OM develops. This further contributes to clinical signs and is a factor in recurrence of disease following apparently successful therapy.

Box 237-2

Predisposing, Primary and Perpetuating Factors of OE in Dogs and Cats

Predisposing Factors

- Conformation of the ear
- Humidity
- Inappropriate cleaning
- Irritant treatments
- Excessive hair growth in auditory canals

Primary Factors

- Ectoparasites
- Allergic dermatitis
- Keratinization disorders
- Pyoderma
- Autoimmune dermatosis
- Foreign bodies
- Tumors

Secondary and Perpetuating Factors

- Yeasts
- Bacteria
- Epidermal and sebaceous hyperplasia
- Ulcerations
- Otitis media

From Griffin CE: Otitis externa and otitis media. In Griffin CE, et al, editors: *Current veterinary dermatology: the science and art of therapy*, St Louis, 1993, Mosby, pp 245-264.

Clinical Scoring of Otitis in Dogs

A recent study described a clinical score (Otitis Index Score [OTIS]) that was demonstrated to be clinically relevant, with good inter- and intraobserver reliability, sensitivity to change, and ability to distinguish affected ears from healthy ears or ears in remission.[10] This score evaluates four different clinical parameters (erythema, edema/swelling, erosion/ulceration and exudate) both in the horizontal and the vertical canal on a scale of 0 to 3. We recommend its use on a regular basis to better evaluate ear disease and the objective improvement obtained after therapy. The evaluation of pain is not yet codified in otitis and further studies are needed.

Diagnosis and Treatment of Acute Otitis Externa[11]

Clinical presentation includes a fairly rapid onset of head shaking and ear scratching, sometimes accompanied by malodor and erythema of the ear canal. These findings should prompt the clinician to undertake a rigorous diagnostic plan instead of just prescribing a topical medication.

History and Examination

A brief history should be taken to help establish possible contributory factors to the episode; early identification of predisposing and primary factors can help to prevent chronicity (Boxes 237-2 and 237-3). A general physical and dermatologic examination should be performed, which should include examination of the ventral and skin fold areas including the feet and the anal area for signs of erythema that would orient the clinician towards a diagnosis of atopic dermatitis. This is followed by an examination of the pinnae and external ear canals.

Box 237-3

History Taking in Chronic Otitis Externa

- Age of onset
  - Young animals are predisposed to ectoparasites, notably *Otodectes cynotis*
  - Adult animals are prone to allergic otitis externa
  - Old animals are predisposed to tumors or autoimmune dermatoses
- Development of signs and seasonality
  - An acute episode of unilateral otitis should prompt a search for a foreign body
  - Recurrent, bilateral OE occurring every spring should suggest allergic otitis
  - A gradually-developing unilateral OE is more suggestive of a neoplastic process
- Evidence of contagion is often (but not always) noted in case of ear mite infestation
- The environment should be studied to evaluate for the presence of foreign bodies, excessive humidity (swimming dogs), and aeroallergens. Free-roaming animals are prone to otoacariasis.
- Feline retroviral status should be assessed, as chronic OE is often linked to FeLV/FIV infection in cats; in this species, one should also remember that herpesvirus infection may trigger facial dermatitis with OE, or a generalized erythema multiforme with frequent ear involvement.
- Prior therapies should also be noted. OE is sometimes linked to trauma induced by poor cleaning technique by the owner (use of cotton buds) or by the use of inappropriate treatment (e.g., alcohol, ether). Allergic reactions to neomycin or glucocorticoids may also occur.

Cerumen Examination

Direct examination of the cerumen should be planned each time a parasitic cause is suspected, because otoacariasis (ear mite infestation) is still a frequent presentation, especially in young dogs.[2] Mites usually are easily demonstrated using the low-magnification objective (×4) of the microscope. The use of a curette instead of a cotton swab is better suited for this examination.

Cytologic Examination

Cytologic examination should be performed in all cases of OE. This allows the clinician to record which microorganisms, if any, are present and will help the clinician decide which therapy is more appropriate and best targeted. Cytologic evaluation also is helpful on follow-up consultation for assessment of the efficacy of treatment and progression of the disease over time. A cytologic evaluation is easy to perform: a cotton swab is inserted into the vertical ear canal to collect material, and usually the best place to sample is at the junction of the vertical and horizontal canals. The swab is then rolled onto a glass slide, which is air-dried and stained with a modified Romanowsky-type stain such as Diff-Quik, Rapi-Diff or RAL (see ch. 87). There are many cytologic presentations in acute OE. Typically, in acute OE associated with underlying atopic dermatitis, there can be increased numbers of squamous epithelial cells but no evidence of microbial infection. In acute OE associated with infection, there may be *Malassezia* yeast overgrowth (Figure 237-5) or numerous cocci (usually *Staphylococcus pseudintermedius*). Cocci appear as round, often grouped, bacteria, whereas rods are elongated. It is unusual to see rod infections in acute OE.

FIGURE 237-5 *Malassezia* yeasts on cytological examination (×1000).

Otoscopic Examination

An otoscopic examination is indicated in every case of otitis (see ch. 85). Both ears, even with unilateral complaints, need to be examined. The unaffected ear is examined first if the problem appears to be unilateral. This is aimed at avoiding the transfer of infection from one ear to the other. Every effort not to cause the animal further discomfort must be made and therefore the practice of inserting a cold, hard otoscope cone into a painful inflamed ear is to be discouraged. Sedation and analgesia should be used anytime the procedure is likely to result in any significant discomfort (see ch. 138).

Otoscopic examination should assess the presence of foreign bodies, the presence of *Otodectes cynotis* (

Video 237-1), the presence and nature of any discharge, the patency of the ear canal and the degree of stenosis, the appearance of the ear canal lining and the presence of ulceration, the appearance of the tympanic membrane, and the presence of neoplasms or polyps (Figure 237-6).

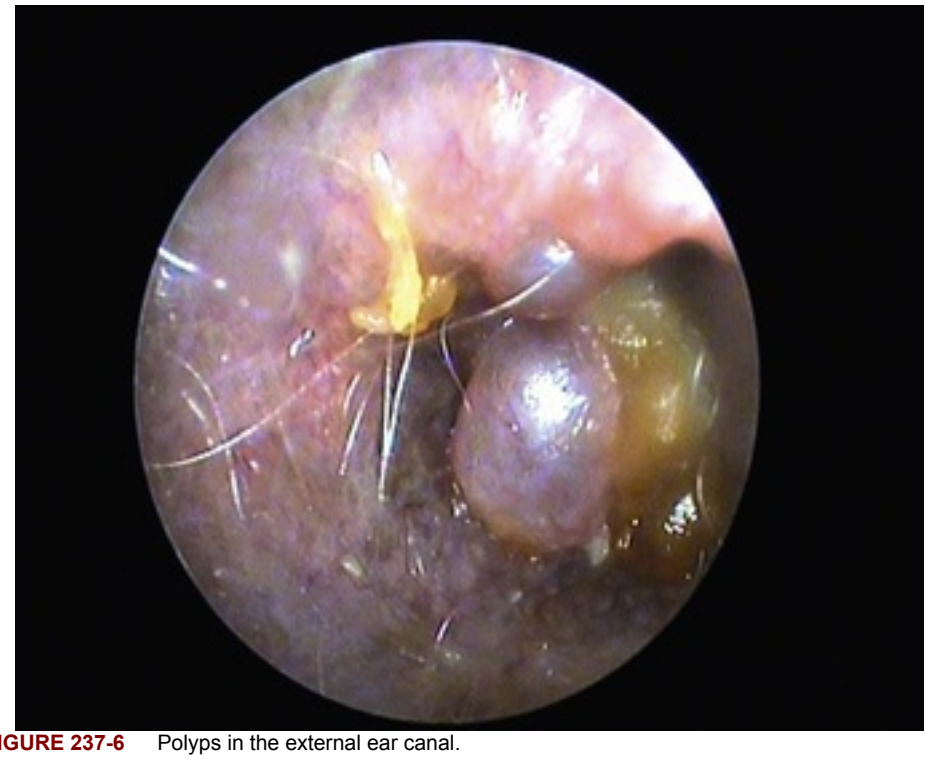


FIGURE 237-6 Polyps in the external ear canal.

Treatment

Treatment for acute OE is aimed at cleaning, resolution of specific primary causes, relief of inflammation, and elimination of any microbial infection.

Cleaning

Ear cleaning is important because it facilitates examination of the ear canal, removes material that can harbor microorganisms and inactivate topical medications (in particular the biofilm), and removes small foreign bodies, toxins, and damaged/degenerated cells.[5,12] Manual cleaning is appropriate in most cases of acute OE, provided this does not result in pain. Owners need to be carefully instructed on the use of topical therapy with a practical demonstration (see Client Information Sheet at ExpertConsult.com). Following application of the ear cleaner, the ear canals should be massaged for 30-60 seconds. Any discharge should be wiped away from the external ear canal using a gauze swab or cotton wool but the practice of inserting cotton buds into the vertical canal should be discouraged as this merely results in impaction of material within the canals. Manual ear cleaning will not remove tightly adherent or material deep within the ear canal and consideration should be given to ear flushing under general anesthesia if there is a significant accumulation of discharge (see below, and see ch. 85). There is a wide variety of topical ear cleaners available with varying actions including ceruminolytics and surfactants that dissolve and soften cerumen, astringents that have a drying effect within the ear canal, and antimicrobial agents. Some ingredients are contraindicated in the presence of a ruptured tympanic membrane.

Topical Antimicrobial and Anti-Inflammatory Therapy

Reflecting the complex etiology of OE, proprietary topical therapies typically contain a combination of an antifungal, antibacterial, and glucocorticoid, and some also have an antiparasitic effect. The clinician should be familiar with the various active ingredients. The selection of a topical antimicrobial should be based on the results of cytological examination. The animal should be reexamined at least weekly and treatment continued until there is both clinical and cytologic resolution of disease (typically longer than generally stipulated on the

label of most ear products).

Systemic Therapy

Systemic therapy is not usually needed in acute cases of OE except for those rare cases where pain prevents the application of topical therapies. For these rare cases, the judicious use of systemic glucocorticoid therapy for 2 to 3 days to resolve inflammation and pruritus prior to the application of topical therapy can greatly facilitate ease of application for the owner.

Diagnosis and Treatment of Chronic Otitis Externa[11]

Uncontrolled, chronic OE is responsible for the development of irreversible lesions (OM, microbial resistance, ear canal stenosis and calcification). As a consequence, these cases require an in-depth investigation and consideration should be given to referral to a veterinary dermatologist.

Chronic Erythemato-Ceruminous Otitis Externa (CECOE)

Clinical presentation includes erythema, ceruminous discharge, pruritus, malodor, and variable degrees of stenosis of the external ear canal. Discharge in these cases is generally creamy yellow to dark brown and is visibly ceruminous rather than purulent. The most common primary cause of CECOE is underlying atopic dermatitis, but other primary diseases include adverse food reactions, otodectic and demodectic otitis, primary keratinization defects, endocrinopathies, and neoplasia.[7]

History

A thorough history can give vital clues regarding the underlying etiology. For example, a first presentation of gradual-onset, unilateral OE in an older animal should greatly raise the index of suspicion for neoplasia, whereas atopic dermatitis would be suspected in a young dog with recurrent OE along with facial and pedal pruritus.

Examination

Before inspecting the ears, a full physical and dermatologic examination should be performed. The clinician should check for evidence of pain on opening the mouth, referable to the ear canals. The pinnae and external ear canals are then examined closely and the ear canals should be palpated for evidence of calcification. Otoscopic examination follows (see ch. 85). Swabs are then taken from both ears for cytologic examination (see ch. 87).

Bacterial Culture and Sensitivity Testing

Samples for bacterial culture and sensitivity testing usually are not needed in cases of CECOE because discrepancies exist between *in vivo* and *in vitro* data, and because the high drug concentrations achieved with topical therapy normally can overcome apparent *in vitro* resistance.

Imaging

Imaging is useful for those chronic cases where severe ear canal stenosis is present, because evidence of marked calcification and/or OM would be expected to respond poorly to medical management and be an indication for surgical intervention.[5,12] Radiography, positive contrast ear canalography, computed tomography (CT) and/or magnetic resonance imaging (MRI) generally are indicated, the latter two techniques being more sensitive for the detection of fluid within the tympanic bulla.[13,14] Impedance audiometry and brainstem auditory evoked response (BAER) may also be useful techniques in the future.

Treatment of Chronic Otitis Externa

Every effort should be made to return the environment within the ear canal to normality. Cleaning the ears to remove discharge, debris, and microorganisms is therefore as much mandatory as the use of topical and/or systemic antimicrobials to treat infection. The use of topical and/or systemic glucocorticoid therapy to relieve inflammation, swelling, stenosis and reduce glandular secretions and hyperplasia also is mandatory.

Cleaning

Manual ear cleaning (see acute OE) rarely is helpful in chronic cases and, therefore, retrograde ear flushing under general anesthesia is indicated whenever there is discharge present in the horizontal and proximal

vertical canals. If stenosis of the external ear canal precludes thorough cleaning and examination, prednisolone 0.5-2 mg/kg PO q 24 h or methylprednisolone 0.4-1.6 mg/kg PO q 24 h for a period of 1-3 weeks should be considered before cleaning. Failure of the ear canals to dilate with glucocorticoid therapy would indicate a guarded prognosis for medical management.

The use of a video-otoscope greatly facilitates retrograde ear cleaning (see ch. 85). Animals undergoing treatment for CECOE should be reexamined on a weekly basis, and if further accumulation of cerumen within the ear canal is observed, flushing procedures need to be repeated until it is clear than manual ear cleaning alone is effective in keeping the ear canals clean.

Antimicrobial Therapy

Antibacterial therapy should be selected on the basis of cytologic evaluation and culture if available.[5] The use of fluoroquinolones to treat Gram-positive infections should be discouraged. Nystatin, miconazole, clotrimazole and the azoles are effective against *Malassezia* spp. Systemic antibiotic therapy should be considered only if there are secondary changes present within the ear canal such as swelling, stenosis or ulceration or in cases involving OM (see suppurative OE, below).

Glucocorticoid Therapy

Glucocorticoids are extremely useful in the treatment of CECOE because they reduce swelling, inflammation and glandular secretion, resolve ear canal stenosis prior to ear flushing, counteract the pro-inflammatory effects of deep ear cleaning, and relieve pruritus.

Further Investigation

As already discussed, CECOE usually is a manifestation of a generalized dermatosis and the diagnosis and treatment of the associated skin disease is the key to prevention of further episodes of otitis. This may include a diet trial to rule out adverse food reactions and intradermal or immunoglobulin E (IgE) serologic testing to identify causative allergens (see ch. 186), histopathologic examination, complete blood count, serum biochemistry profile, urinalysis, and endocrine work-up.

Long-Term Management of CECOE

Antimicrobial therapy should be continued until cytologic resolution of infection. However, it is worth appreciating that the ear canals can take many months to return to complete normality.[12] The topical administration of glucocorticoids on a "pulse" regimen (e.g., twice a week) is very useful to achieve this goal.

Suppurative Otitis Externa (SOE)[11]

Clinical presentation includes the presence of a malodorous, often liquid, discharge, the color of which varies depending on the type of bacteria involved (from dark grey to greenish yellow, the latter often being seen with *Pseudomonas aeruginosa*). Purulent otitis frequently is accompanied by ear canal erosions or ulcerations (Figure 237-7). Pain often is acute, and pruritus minimal, which may help to differentiate this condition from CECOE.

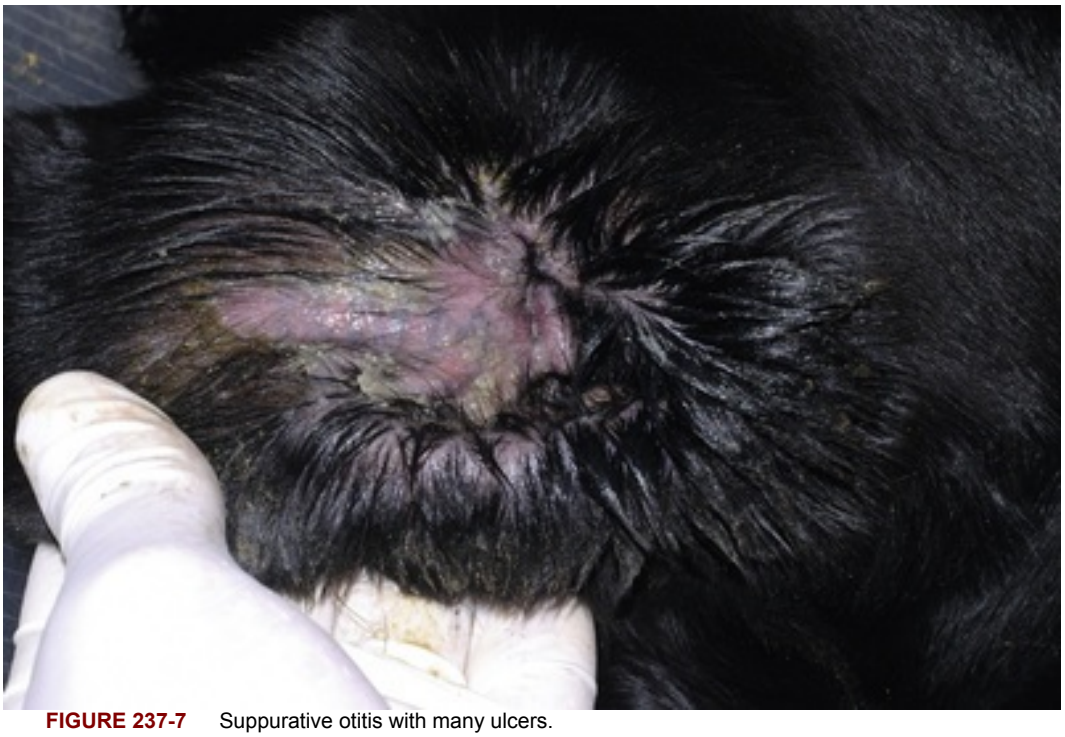
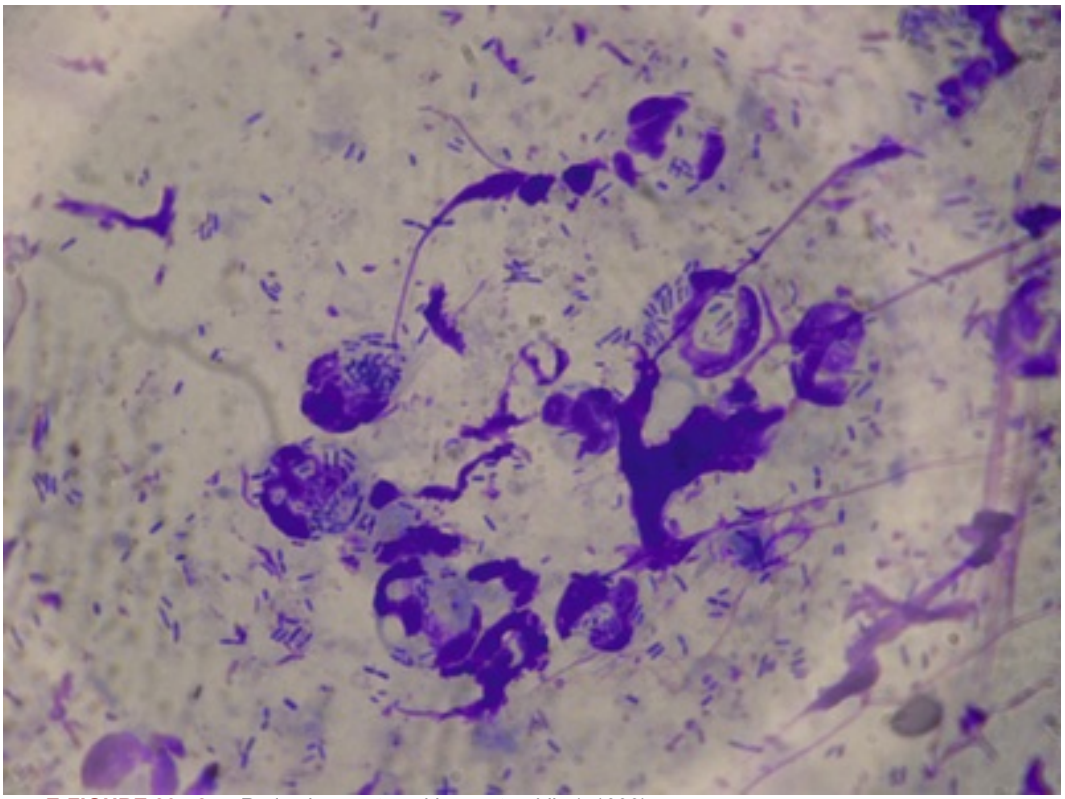


FIGURE 237-7 Suppurative otitis with many ulcers.

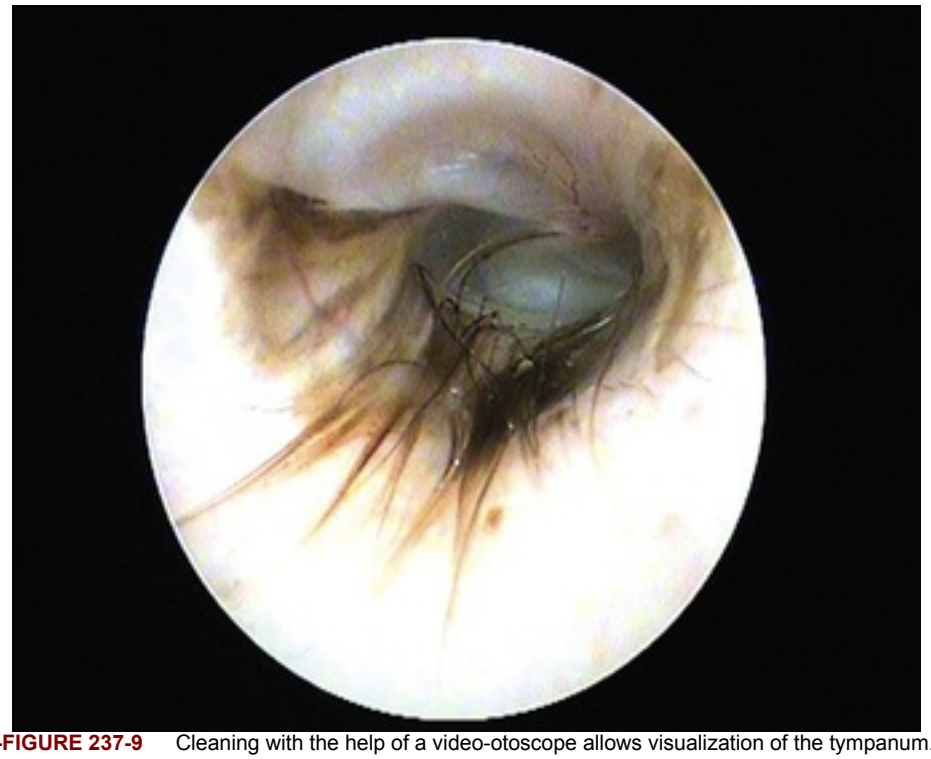
Diagnosis

Definitive diagnosis requires microscopic examination of the exudate, with the presence of large numbers of neutrophils and sometimes macrophages confirming the suppurative nature of the otitis. Most commonly, cocci or rods are seen, but in rare cases of SOE, yeasts (e.g., *Malassezia* sp.) may be seen. The clinician should search for phagocytosis of bacteria specifically, which is diagnostic for active infection.

The work-up of SOE is similar to CECOE (see above). In cases of SOE involving rods (E-Figure 237-8), if OM is suspected, a bacterial culture is indicated to rapidly identify the presence of *Pseudomonas aeruginosa,* which has an unpredictable pattern of antibacterial sensitivity and can present a real therapeutic challenge.[4] Referral should be discussed at the outset with the owner, as diagnosis of OM is not straightforward. Recognition of OM is important because pus in the tympanic bulla can be the source of chronic and/or relapsing OE. Pro-inflammatory toxins and debris may constantly be released from this area.[5] Additionally, treatment will vary depending on whether or not there is infection in the middle ear, as topical antibiotics do not penetrate well into the tympanic bullae. In cases of suspected OM, samples should be obtained from the tympanic bulla(e) for cytologic evaluation and bacterial culture and sensitivity testing. It is necessary to perform myringotomy in order to aspirate material from the tympanic bulla (see ch. 85). Various complementary aids are available to diagnose OM: classic otoscopy may be helpful if the tympanic membrane is visualized and ruptured, but video-otoscopy is much more sensitive (E-Figure 237-9) (see ch. 85). In OM, the tympanic membrane appears either ruptured (small tear or total destruction) or abnormal (inflamed, bulging, grey, not translucent). Radiography and other imaging techniques can be useful for the diagnosis of OM (see CECOE, above).



E-FIGURE 237-8 Rods phagocytosed by neutrophils (×1000).



E-FIGURE 237-9 Cleaning with the help of a video-otoscope allows visualization of the tympanum.

Treatment

Treatment of SOE should focus on killing the bacteria (usually needing antimicrobial therapy), elimination of

the inflammatory process (usually needing glucocorticoid therapy) and proper cleaning of the ear to eliminate the biofilm (usually needing repeated and thorough ear flushing). It is also mandatory to diagnose and control any underlying disease process to minimize the risk of recurrence.

For those cases without involvement of the tympanic bullae, topical treatments are effective, and for these cases the use of systemic agents is debatable as the condition is mainly localized to the ear canal. Systemic therapy is indicated only for treatment of OM, for reasons already discussed.

Antibacterial agents are indicated in the overwhelming majority of cases of suppurative OE/OM. Selection depends on the type of bacteria demonstrated cytologically. *Pseudomonas aeruginosa* is a special case because it is inherently resistant to many antibacterials. Various molecules are available but fluoroquinolones are usually the first choice treatment for *Pseudomonas* otitis. These are concentration-dependent antibiotics; therefore, it is best to use high dosages, such as 10-20 mg/kg PO q 24 h for enrofloxacin and 4-8 mg/kg PO q 24 h for marbofloxacin. Unfortunately, a recent meta-analysis of treatments available for *Pseudomonas* otitis concluded that currently, there is insufficient evidence for or against recommending the use of any treatment for *Pseudomonas* otitis in dogs, due to the paucity of trials, which moreover lack randomization.[15]

Glucocorticoid therapy may be required to control the inflammatory component of OE/OM. Glucocorticoids are a component of the majority of commercial topical preparations and may also be administered systemically. The use of orally administered glucocorticoids can be highly beneficial where there is severe inflammation and exudation, as these medications help restore a normal ear epithelium, decrease the pain, the pruritus and the ear canal hyperplasia. However, they may be detrimental if inflammation is not an important part of the clinical signs and/or if ulcers are present.

Ear cleaning is another essential step for the adequate treatment of SOE, as pus and inflammatory debris inhibit penetration of topical therapies and can inactivate some medications. The initial flushing should be done under general anesthesia (see CECOE, above, and ch. 85). Cleaning agents selected should be non-irritant, especially in case of ulceration, and non-ototoxic, especially in case of a ruptured tympanum. An aqueous solution is best suitable for SOE. Manual ear cleaning should be continued by the owner at home; otherwise, secretions will rapidly reaccumulate.

Follow-Up

The first recheck visit should take place after a few days to ensure good compliance. A decision should be made on whether to continue or withdraw systemic glucocorticoids. Usually, follow-up visits then are done every 2 to 3 weeks (but may be considered weekly in severe cases) to monitor clinical improvement and to perform a complete examination of the ear canal including the tympanic membrane. Cytologic examination of smears should be repeated at each visit and antimicrobial therapy should continue until clinical and cytologic resolution. It may be necessary to reassess therapy if response is unsatisfactory.

Surgery

Surgery is not the treatment for chronic OE/OM by itself. Clinical outcome may first depend on the efficacy of nonsurgical treatment to eliminate the underlying cause of the otitis that must be clearly identified and appropriately treated medically. Two main procedures are usually indicated as part of the treatment for chronic otitis: lateral wall resection of the vertical ear canal, and the total ear canal ablation associated with a lateral bulla osteotomy (TECALBO).

Lateral Wall Resection of the Vertical Ear Canal

Lateral wall resection of the vertical ear canal is indicated when tissue changes related to OE are limited to the vertical ear canal. The skin that covers the lateral part of the external ear canal is resected and symmetrical incisions are made in the auricular cartilage down to the junction with the annular cartilage of the horizontal ear canal to create a lateral cartilage flap, the distal part of which is removed. The proximal part of the cartilage flap is usually reflected ventrally that creates a draining surface still covered by the aural epithelium, and gives access to the entrance of the horizontal canal (Figure 237-10). Lateral wall resection can improve ear canal drainage, increase airflow within the remaining vertical canal and provide better access for potential topical local treatments both on the horizontal canal and the remaining medial part of vertical one. The prognosis for lateral wall resection largely depends on whether the disease was only located to the vertical canal, with the horizontal one being unaffected and the dermatologic problems of the pinna under control. Thus, indications for lateral wall resection of the vertical ear canal remain limited. Even though the surgical procedure is not very demanding technically, despite a few critical surgical points, the rate of failure for lateral wall resection is 40-55%, mainly because it does not respond properly to the indications; in most of the

cases, such a limited surgical procedure is not aggressive enough to eliminate chronic deep infection. In breeds with ear canal abnormalities such as stenosis, excessive hair growth, or extensive thickening of the ear canal epithelium, lateral wall resection usually is unsuccessful. For example, in Cocker Spaniels that usually do not obtain resolution of OE by medical treatment, lateral wall resection has been reported to fail in almost 90% of dogs with OE/OM.[16] A recommendation for TECALBO may be considered earlier in the course of the disease to avoid further progression and complications.

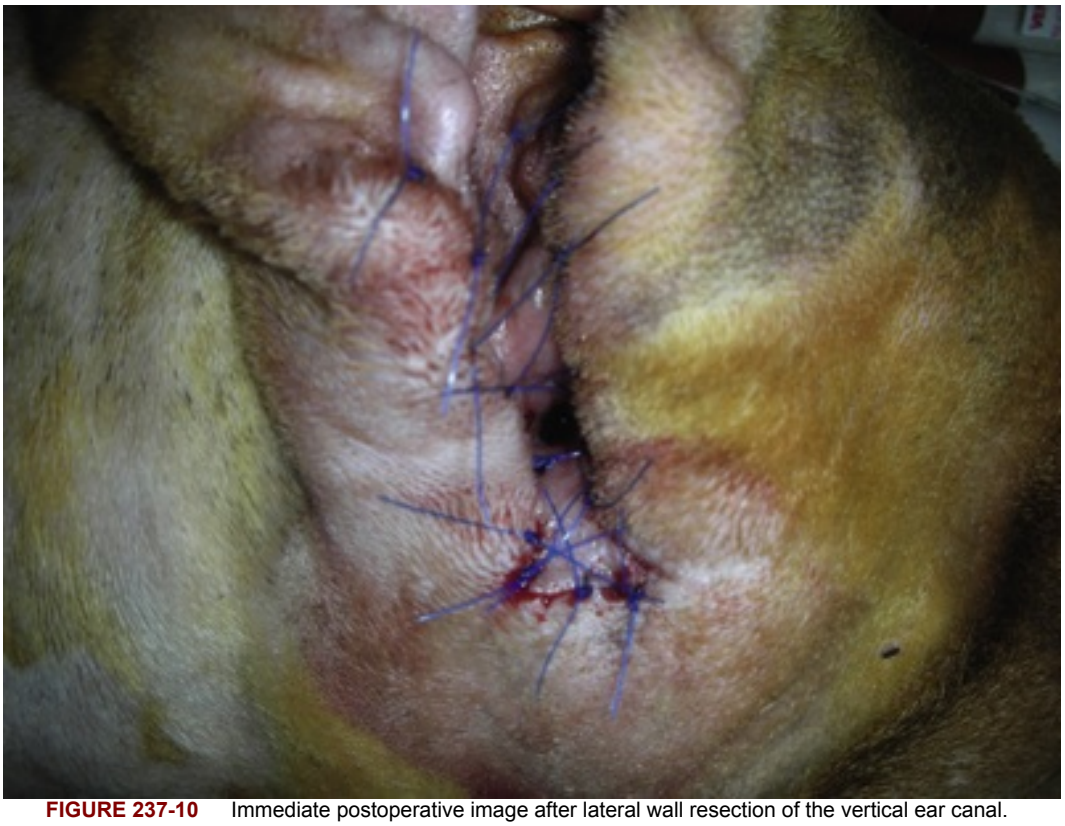


FIGURE 237-10 Immediate postoperative image after lateral wall resection of the vertical ear canal.

Complications of lateral wall resection are mainly local, with prolonged postoperative pain and wound dehiscence or drainage. Wound dehiscence may heal by second intention with appropriate wound care.

If the procedure improves exposure of the ear canal and visualization of masses, the remaining vertical and horizontal parts of the canal can be responsible for persistent chronic infections, and most of the time, lateral wall resection fails to treat chronic end-stage OE/OM.

Total Ear Canal Ablation and Lateral Bulla Osteotomy

TECALBO usually is the treatment of choice for chronic end-stage inflammatory non-neoplastic ear disease such as chronic OE/OM.[17] The long-term success rate for the treatment of chronic otitis is now established around 90%.[18] Although TECALBO is performed by many surgeons and is quite a straightforward procedure, it is not an easy surgery, given the risk for iatrogenic damage of nearby structures and the limited surgical exposure. The surgery by itself has to be sufficiently thorough to ensure the complete elimination of all infected tissues, while sparing important neurovascular structures.

A comprehensive description of the surgical anatomy of the ear canal and bulla has been published.[19] In most cases of end-stage chronic otitis, the thickened but brittle lining epithelium from the ear canal usually is in continuity with the epithelium from the bulla as the tympanic membrane has usually been destroyed by the infectious process (Figure 237-11; Video 237-2). Video-otoscopy with a dedicated endoscope (usually a 30° arthroscope) can be used perioperatively to check the complete elimination of the epithelium from the tympanic cavity (see Videos 237-2 and 237-3). In cases of bilateral disease, it is usually recommended that surgical treatment be staggered, but bilateral single-stage TECALBO can be performed without any additional risk for complications. TECALBO also is indicated in cats, but the incidence of neurologic

complications (facial nerve deficit, Horner's syndrome) is much higher compared to dogs. A ventral approach, while commonly used in cats to treat middle ear inflammatory polyps, is not adequate for the surgical approach to otitis as it does not allow complete removal of the infected tissues from the ear canal.

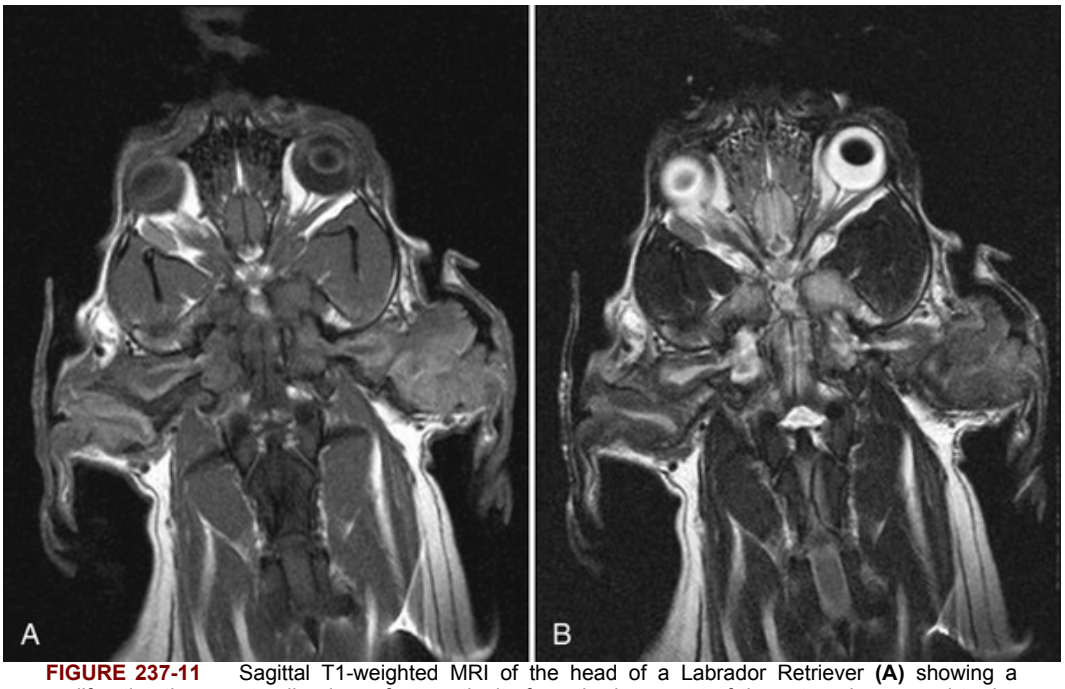


FIGURE 237-11 Sagittal T1-weighted MRI of the head of a Labrador Retriever **(A)** showing a proliferative tissue extending in perfect continuity from the inner part of the external ear canal to the tympanic cavity. The sagittal T2-weighted image **(B)** shows the presence of liquid inside the right tympanic cavity. This dog presented severe chronic bilateral otitis externa and media.

The overall complication rate has been reported to range from 30% to 80%. Common short-term complications include facial nerve neuropraxia (up to 50% of animals; median duration of 2 weeks in dogs and 4 weeks in cats), peripheral vestibular syndrome (can resolve gradually, and either partially or completely), hemorrhage, persistent pain, and wound dehiscence (Figure 237-12).[18] TECALBO usually results in substantial postoperative pain, and local anesthetic infusion has been investigated for postoperative analgesia. However, local infusion of bupivacaine has not significantly improved postoperative analgesia compared to systemic morphine injections.[20] Preexistent preoperative neurologic signs usually do not resolve after surgery. Residual facial nerve deficits after 1 year have reported to be 8% in dogs and 33% in cats. Permanent Horner's syndrome is rare in dogs but is reported in up to 25% of cats. The duration of preoperative clinical signs of ear disease does not appear associated with postoperative facial nerve deficits.[21] Dermatitis of the pinna (up to 20% of cases) and abscessation with para-aural fistulous tracts and pain on opening the mouth (5-10% of cases, occurring 1 month to 2 years postoperatively) are recognized. The risk of such complications can be lowered with thorough surgical removal of cartilage, epithelium, and debris initially, and with the use of antimicrobials that are based on bacterial culture and sensitivity testing obtained from the bulla, because bacteria isolated from the ear canal differ significantly from those isolated from the tympanic cavity.[22] A secondary surgical excision can then be performed with a higher risk of recurrence.[23] Cholesterol granuloma is a long-term complication of TECALBO that can necessitate a second surgical treatment as long as 3 years postoperatively.[24] Although reported by some owners, hearing loss usually is not related to the surgical procedure but is mostly a preexistent consequence of end-stage chronic OE/OM; TECALBO usually does not lead to complete hearing loss, as bone-conducted brainstem auditory evoked potentials may prevent dogs from complete deafness.[25] TECALBO remains a salvage procedure, and although owners' satisfaction after TECALBO usually is about 90%, veterinarians and owners must be aware that serious complications remain possible, particularly long-term infectious ones. As surgical anatomy and techniques have now been precisely described, postoperative outcome may be mostly related to the severity of the ear disease, and TECALBO should probably be proposed earlier in the course of the disease, once appropriate medical treatments are no longer effective to treat or control chronic otitis.

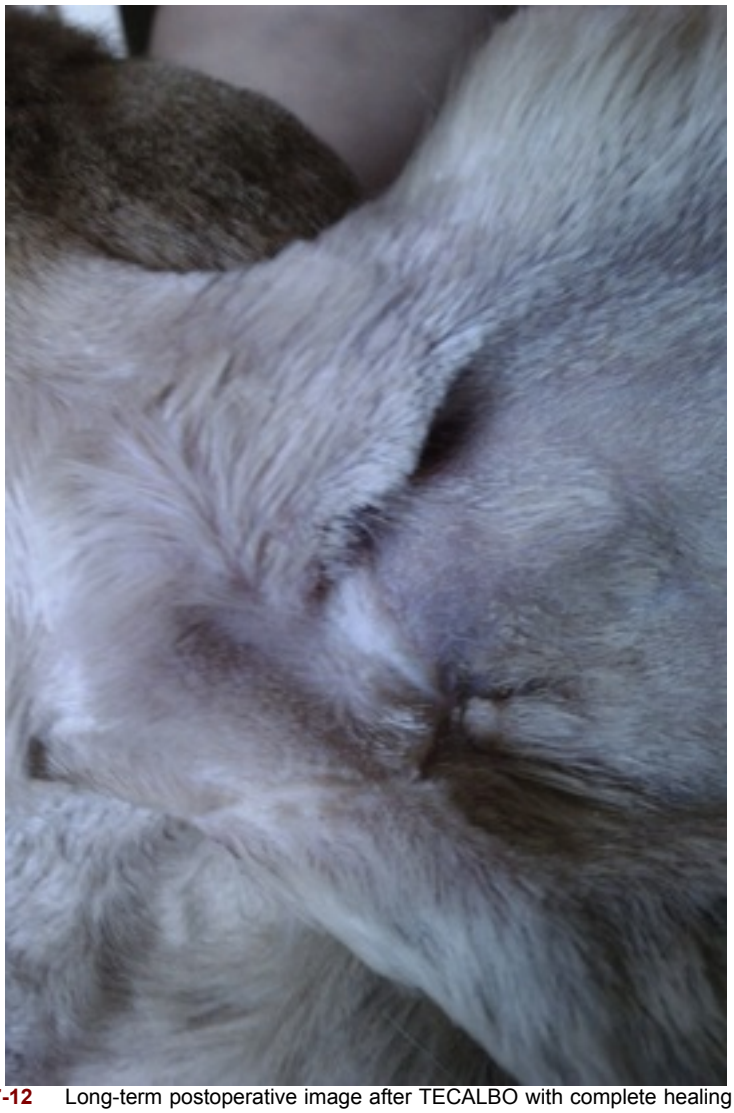


FIGURE 237-12 Long-term postoperative image after TECALBO with complete healing in a Cocker Spaniel.

Otoacariasis

Parasites should always be considered in cases of OE. *Otodectes cynotis,* recovered from the auditory canal of domestic animals (dog, cat, ferret), is a psoroptid mite characterized by long legs with unjointed stalks with stickers (see Video 237-1). These mites live on the surface of the skin, particularly in the auditory canal, and feed on epidermal debris and tissue fluids, irritating the ear epithelium and generating an allergic reaction from susceptible hosts. *O. cynotis* infestation could represent 7-10% of cases of OE in dogs and up to 50% in cats.[26] It is very contagious. Other parasites may rarely be responsible for OE in dogs and cats (e.g., *Demodex* spp., *Otobius megnini*). Otoacariasis often is associated with pruritus, pinnal erythema, and excessive cerumen in the ear canal (usually but not necessarily dark brown). Direct microscopic examination of the cerumen is easy to perform. The use of a curette or a swab allows the sampling of cerumen, which is then diluted into chloral lactophenol or liquid paraffin. Observation at a magnification of ×40 is usually adequate to detect parasites. This procedure must be completed even if there is little cerumen present, particularly in cats.[26] Therapy involves the topical and/or systemic use of acaricidal molecules. Various treatments have demonstrated to be effective for this condition.

Foreign Bodies

Foreign bodies must always be considered in case of acute unilateral otitis, particularly in dogs with

pendulous and hypertrichotic ears and/or if the disease is acute. Young hunting dogs are at increased risk. Generally, grass awns or grass seeds are involved. Some cases of chronic bilateral ear disease may also be due to grass awn. The most frequent clinical presentation is an acute episode of head shaking and/or pain. There is a risk for penetration of the tympanic membrane and OM if the foreign body is not identified and removed. Therapy involves the mechanical extraction of the foreign body and for inflammatory cases the topical application of a steroid-containing ear drop preparation.

Aural Hematoma

Aural hematoma usually is secondary to severe pruritus of the head and/or ear. However, some cases can occur without associated pruritus and a few authors have proposed that initial vascular damage secondary to vasculitis might be responsible for this condition.[27] Blood accumulates within the fractured cartilage of the pinna. Clinical lesions are mainly characterized by swelling and deformation of the involved pinna. Treatment must always be considered, even for small hematomas, because of the risk for a permanent deformation of the ear.[26] Symptomatic therapy includes puncture and bandaging, *in situ* injection of corticosteroids, Penrose drain placement, or surgical incision followed by curettage and closure with mattress sutures. The latter usually is preferred because it leads to better cosmetic results. It is mandatory to look for an underlying cause, which includes a thorough inspection of the ear canal (see ch. 85), to prevent recurrence.

Deafness

Auditory function is a complex process involving all structures of the ear: collection of sound by the pinna and ear canal, vibration of sound waves on the tympanic membrane, transmission of the vibrations through the ossicles, to the oval window of the cochlea and further to the scala tympani and scala vestibuli, with depolarization and synaptic connections occurring between hair cells and spiral ganglion neurons resulting in transmission of information through the vestibulocochlear nerve.[28] Hearing can be evaluated clinically (behavioral response to various noises) but, as vibrations through air can also be felt via extracochlear mechanoreceptors, is best recognized by functional testing, notably BAER testing. Deafness is classified as follows, depending on various factors: inherited/acquired, congenital/late onset, and sensorineural/conductive.

Hearing Testing Principles

Currently, there is no validated, easy-to-use scoring system for hearing evaluation in dogs and cats. Different scales have been proposed both for pet owners and veterinarians, but these scales do not seem to be sensitive or specific.[29] The only noninvasive technique allowing a sensitive objective measurement of hearing is BAER testing. It helps to evaluate the functionality of the various components of the auditory system. Electrical activity arising from the cochlear and auditory pathways is measured in response to stimulation using unilateral click stimuli. BAER recordings include five different waves: peak I (cochlear nerve) and peaks II to V (brain).[30]

Congenital Sensorineural Deafness

Congenital deafness is due to a genetically inherited degeneration of the stria vascularis associated with Reissner's membrane and cochlear alterations usually (albeit not always) associated with pigmentation genes. The loss of hearing usually occurs after 3 to 4 weeks of age. There are strong breed predispositions, notably in white-coated animals. In cats, this condition has been demonstrated to be autosomal dominant with incomplete penetrance (gene W)[31] and is most often associated to other melanocyte problems, such as blue irides. In dogs, the trait is associated with the dominant merle gene (M) in Collies, Australian and Shetland Sheepdogs, Great Danes, and with the autosomal recessive piebald (SP) or extreme piebald (SW) gene in Bull Terriers, Bulldogs, Great Pyrenees and Dalmatians. It seems that the risk is higher in dogs with blue irides, if one of the parents is deaf, and if the coat is white. In other breeds, such as Doberman Pinschers, deafness is due to a direct loss of cochlear cells without primary involvement of stria vascularis.[32] Diagnosis usually is possible after 1 month of age. Clinical diagnosis is not straightforward, as in young puppies the behavior is not easy to detect, especially in case of unilateral deafness. Therefore, BAER testing usually is needed as an objective measure of hearing. Complete lack of waveforms is expected for these cases.

Acquired Sensorineural Deafness

Also named presbycusis, this syndrome is associated with a loss of hearing with age due to various causes (degeneration of the organ of Corti, cochlear nerve, stria vascularis, or basilar membrane). In one study, animals >12 years of age presented modified BAER waves with a higher threshold than younger animals, notably in high frequencies. Histopathologic examination showed a loss of cochlear cells and a neuronal degeneration as observed in humans. Older dogs presented with hearing loss should always be evaluated for any other cause of conductive deafness such as OE or OM before the diagnosis of presbycusis is made. It should also be remembered that various diseases may be responsible for hearing loss in adult animals (e.g., ototoxic substances, trauma, hypothyroidism). Diagnosis is best made by BAER, which demonstrates normal waveforms in response to high-intensity sound.

Post-Inflammatory Deafness

Conductive deafness is associated with any condition that blocks sound transmission through the ear canal to the ossicles and inner ear. This can be seen in any case of inflammation of the ear structures (OE, OM and/or OI). In one study evaluating chronic cases of OE without concomitant OM, defects of hearing were demonstrated, with a complete loss of hearing and BAER showing decreased wave amplitude and increased wave latency in the most severe cases. These defects disappeared after repetitive flushing of the ear canal, which demonstrates the impact of secretions accumulating in the ear canal on the transmission of sound. Owners may state that the dog has a hearing problem, but the diagnosis is best made by BAER with increase in hearing threshold, a loss of air conductive hearing, and the presence of normal bone-conducted hearing.

Aural Neoplasia

Various cutaneous neoplasms can affect the ear, notably squamous cell carcinoma and ceruminous gland tumors. These neoplasms are discussed in ch. 345.

Ototoxicosis[5]

Ototoxicosis is defined as damage to the cochlear and/or vestibular system caused by a medication as a direct effect following topical application, through local inflammation of the tympanic bulla, or by systemic absorption.

Ototoxicosis is potentially of concern with application of any topical treatment in the ear canal. In cases with tympanic membrane rupture, it is theoretically possible that no medication at all should be instilled into the ear, as most products carry some degree of risk. In human medicine, aminoglycosides, cisplatin, and carboplatin, among others, have been demonstrated to be responsible for permanent hearing loss. In veterinary medicine, substances incriminated most frequently are aminoglycosides, polypeptides, chlorhexidine, and iodine products. However, some recent *in vivo* studies have demonstrated in the dog that the topical application of chlorhexidine, gentamicin, Tris-EDTA, and ofloxacin did not modify the BAER responses and therefore, the risk is probably less than previously suspected. The drug concentration, the chemical composition, the vehicle of the preparation, and the duration of administration probably are also important factors leading to ototoxicosis. Therefore, it is mandatory to evaluate the integrity of the tympanic membrane before applying any potentially ototoxic drug.

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[†]Deceased.

CHAPTER 238

Diseases of the Nose, Sinuses, and Nasopharynx

Gerhard Ulrich Oechtering

Client Information Sheet: Brachycephalic Syndrome

Nose

The nasal airways of the dog and cat are both anatomically and physiologically an impressively complex structure. On the one hand, they provide a portal through which air can stream to three different locations, each serving a distinct, vital function: (1) the concha nasalis ventralis for thermoregulation and conditioning of air, caudodorsally the (2) conchae ethmoidales for olfaction and via the caudal passageways the (3) pulmonary alveoli for gas exchange. They are not only simple passageways but complicated branches of the nasal conchae providing two huge, functionally different surface areas, serving as active organs of thermal homeostasis and olfaction.

The two nasal cavities are separated by the nasal septum; each cavity is composed of four main functional segments (Figure 238-1). The nasal airway communicates with the paranasal sinuses and connects caudally to the nasopharyngeal airway. Although the nasal part of the upper airway has a parallel oral passageway, dogs breathe predominantly through the nose, except for when they are exercising or panting. The importance of nasal breathing for dogs and cats is often severely underestimated: Human noses fulfill two crucial tasks—respiration and olfaction. Dogs' and cats' noses fulfill a third, vital function—that of thermoregulation.

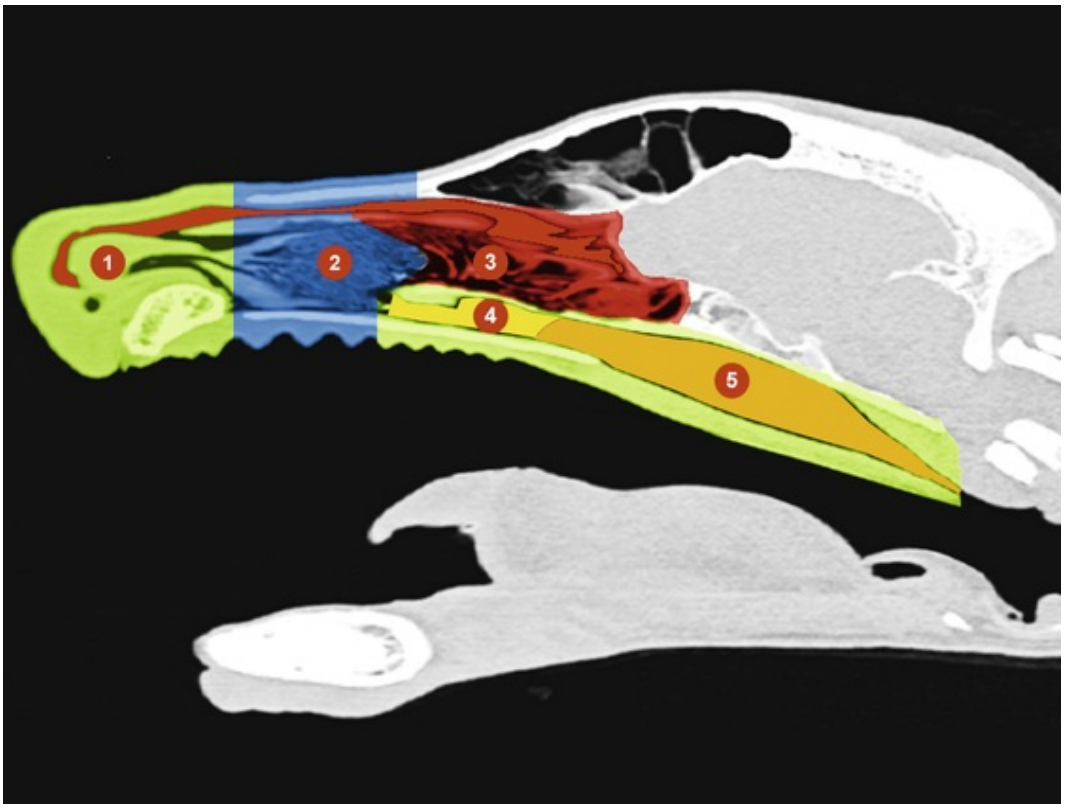

FIGURE 238-1 **Functional segments** of the nasal-pharyngeal airway. **1, Nasal entrance:** distribution and regulation of in- and exhaled air. **2, Respiratory chamber:** thermoregulation and conditioning of inhaled air. **3, Olfactory chamber** (with dorsal meatus): olfaction, the dorsal nasal meatus serves as bypass during sniffing. **Nasal exit** (4 & 5). **4, Meatus nasopharyngeus:** connection to nasopharyngeal airway. **5, Nasopharynx:** functional occlusion during swallowing. Dorsal partition of Waldeyer's tonsillar ring and connection to middle ear.

Anatomy and Functional Considerations of the Nasal-Pharyngeal Airway

The nasal-pharyngeal airway can be partitioned into **four functional segments** between the nares and the ostium intrapharyngeum. This can be useful both for understanding flow-relevant pathologies as well as for a systematic endoscopic examination or systematic interpretation of cross-sectional images. Functional segments of the nose are (1) the **nasal entrance,** (2) the **respiratory chamber,** (3) the **olfactory chamber,** and (4) the **nasal exit** (see Figure 238-1). A rostral to caudal overview of the nasal-pharyngeal passageways gives Video 238-1 as a computed tomographic (CT) study and Video 238-2 as anterior rhinoscopy.

The nasal airway begins with the **naris,** the visible rostral opening plane of a short passageway through the vestibulum nasi. It is formed like a comma with a vertical broad head and a smaller curved tail that rotates horizontally and laterally (Figure 238-2). The **nasal vestibule** is primarily responsible for distributing the in- and expired air and has the highest airway resistance of the upper airways. Unlike in humans, the canine and feline nasal vestibule is not empty. It is filled nearly entirely by a voluminous bulb, evolved from the fusion of the cranial termination of the plica alaris (alar fold) with the internal part of the ala nasi (nasal wing). It is the most mobile portion of the nasal entrance, because it receives the terminal fibers of the levator labii maxillaris and levator nasolabialis muscles. These muscles abduct the bulb laterally, thereby increasing the perpendicular opening within the vestibule (Video 238-3). The configuration of this bulb modifies the nasal entrance into a complex three-dimensional opening. It circles about 300° from ventrolateral around the bulb dorsolateral into a lateral recess, the rostral continuation of the atrium of the medial nasal meatus (see Figure 238-2). The **nasolacrimal duct** that conducts lacrimal secretions from the eye opens into the vestibule by an orifice located rostro-medially to the vestibular bulb (Video 238-4).

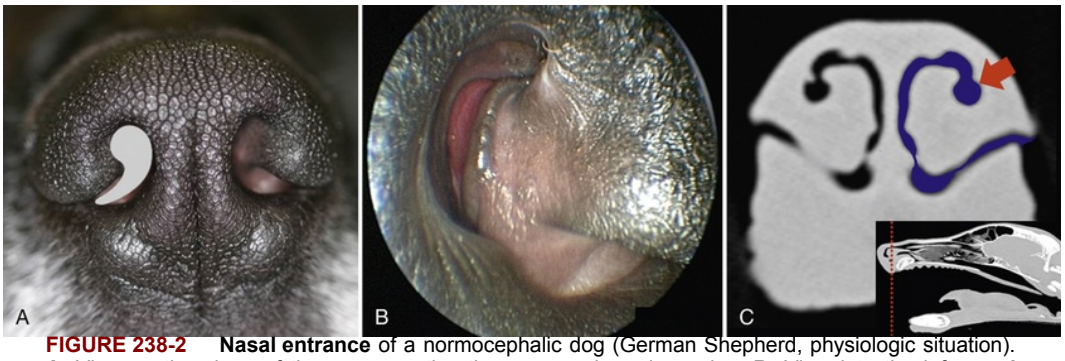

FIGURE 238-2 **Nasal entrance** of a normocephalic dog (German Shepherd, physiologic situation). **A,** View on the plane of the **nares;** notice the comma-shaped opening. **B,** View into the left **nasal vestibule;** notice the voluminous **bulb** that modifies the nasal entrance into a complex three-dimensional opening. **C,** CT image: This opening circles about 300° from ventro-lateral around the bulb into a dorsolateral vestibular recess (arrow). This region serves the tasks of airflow regulation and distribution. See also Video 238-2.

The **nasal cavities** are separated by the **nasal septum.** A medial septal wall, a lateral wall, a roof, and a floor define each nasal passage of the main nasal chamber. Attached to the septum are two vertical protuberances, dorsal and ventral septum swell bodies. The inferior one passes caudally into the wing of the vomer. Each nasal cavity is divided into four air passages: the dorsal, middle, ventral, and common **nasal meatuses** (Figure 238-3). Understanding and differentiating the nasal meatuses as air passages becomes most obvious in the region caudal to the vestibule and cranial to the branching of the ventral concha. Here, the so-called 5-folds-view[1] explains exactly the relation of the nasal folds with the nasal meatuses. Moving further caudally, the alar fold branches intensely into the ventral conchae, nearly filling the entire cross-sectional area of the nasal cavity, and disintegrating the contour of all meatuses except for the dorsal meatus (Figure 238-4). Functionally, the dorsal meatus, located above the straight fold, turns out to be a bypass for odorant-bearing

inspired air around the complicated structure of the ventral concha during sniffing for olfaction (see Figure 238-1).[2,3]

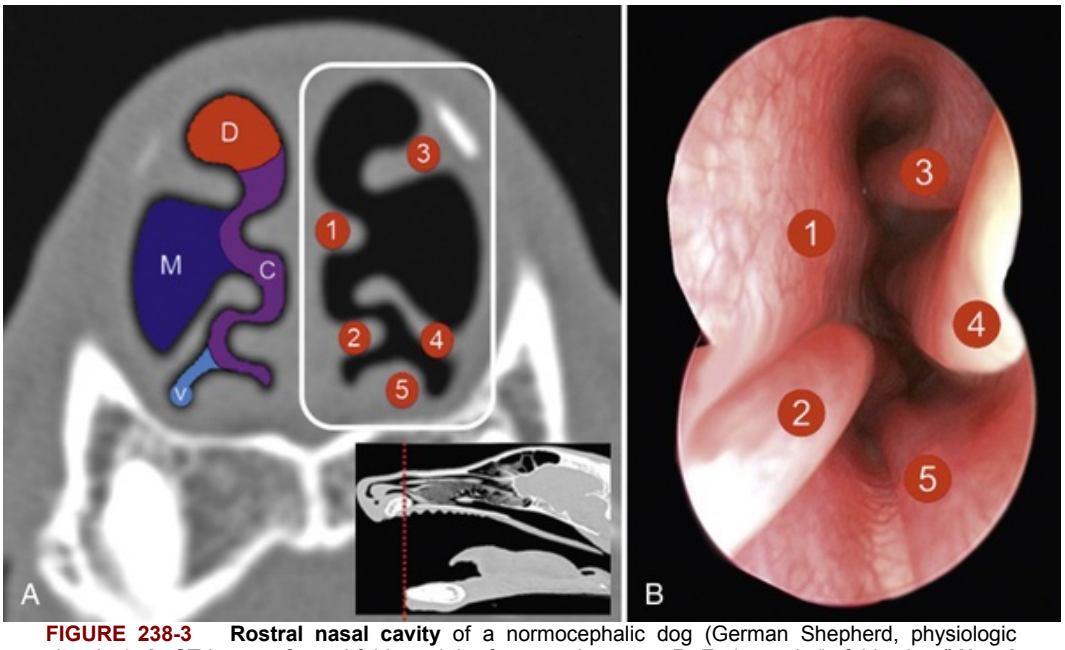

FIGURE 238-3 **Rostral nasal cavity** of a normocephalic dog (German Shepherd, physiologic situation). **A,** CT image of nasal folds and the four nasal meatus. **B,** Endoscopic "5-folds-view." **Nasal meatuses:** C, common; D, dorsal; M, medial; V, ventral. **Five-folds view of nasal folds:** 1, dorsal septal swell body; 2, ventral septal swell body; 3, plica recta; 4, plica alaris; 5, plica basalis.

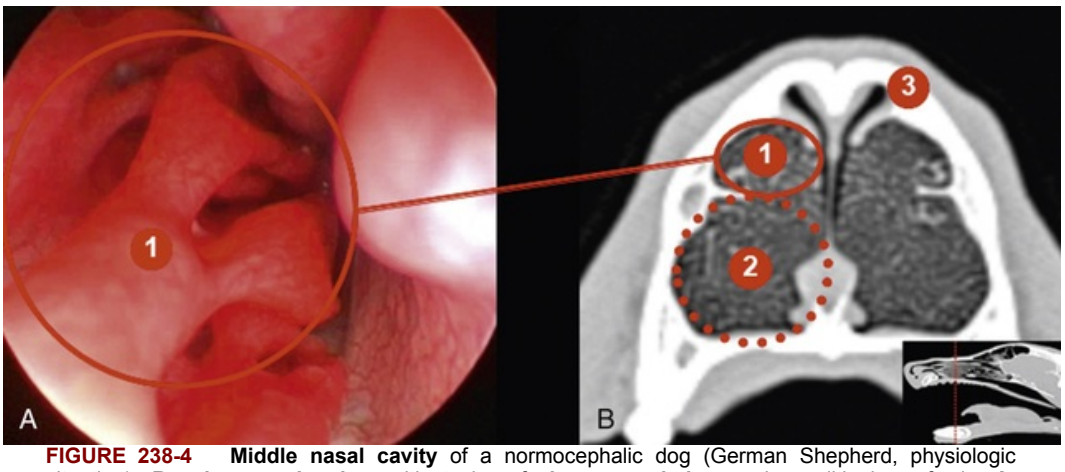

FIGURE 238-4 **Middle nasal cavity** of a normocephalic dog (German Shepherd, physiologic situation). **Respiratory chamber** with tasks of **thermoregulation** and conditioning of air. **A,** Endoscopic view of the (1) dorsal spiral lamella of the left ventral nasal concha. **B,** CT image of the ventral nasal concha with (1) dorsal and (2) ventral spiral lamellae. There are no more meatuses except the (3) dorsal meatus as bypass for sniffing.

Two types of conchae dominate in the nasal cavity; in the middle part is the huge **ventral concha,** formerly called the maxillo-turbinate because of its attachment to the maxilla. The caudal-dorsal part of the nasal cavity is filled with turbinates that are attached to the cribriform plate of the ethmoid and therefore called **ethmoidal conchae.** Both conchae differ not only in function, but also in the anatomical structure of the scrolls and in their relative surface areas. The ventral concha, with the respiratory functions of thermoregulation and air conditioning, shows a branching that is quantitatively more contorted, revealing a very complex airway network. The ethmoidal conchae, with their olfactory function, show a less complicated structure of the turbinates. The total surface area contained within the ethmoidal region is, however, nearly twice the size of

the ventral concha.[2,4]

The **nasal exit** is formed by the **nasopharyngeal meatus,** beginning with a wing of the vomer that crosses dorsally from medial to lateral and ending caudally with the **choanae** (Figure 238-5). This meatus is very delicately constructed: Behind the large diameter of the nasal cavity, the "outlet" is located as a comparatively tiny tube at the bottom. In small dogs, this is only 1 to 3 mm high (see Figure 238-9). This hole can very easily be obstructed. Dogs can usually compensate for the functional loss of one opening as, for example, when a tumor is expanding into the nasopharyngeal meatus. However, as soon as the contralateral meatus shows the first signs of obstruction as well, nasal respiration is impaired severely and clinical signs start becoming obvious. Morphologically and functionally distinct epithelia line the nasal passages—olfactory, respiratory, squamous and transitional.

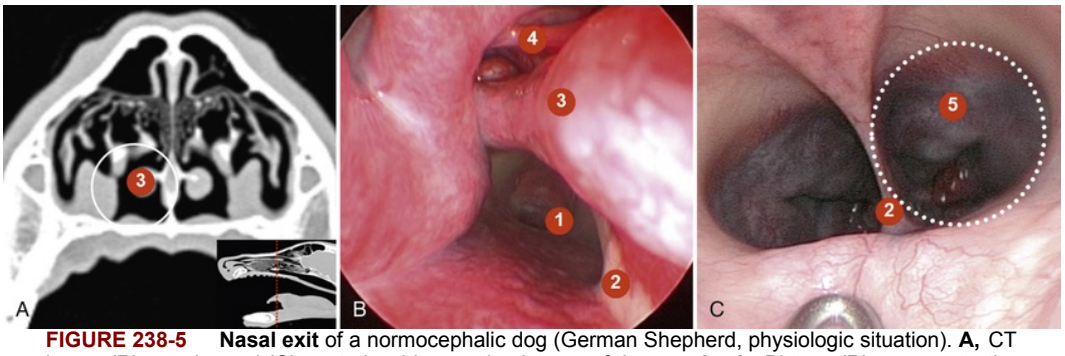

FIGURE 238-5 **Nasal exit** of a normocephalic dog (German Shepherd, physiologic situation). **A,** CT image **(B)** anterior and **(C)** posterior rhinoscopic pictures of the **nasal exit.** Picture **(B)** represents the white closed circle in picture **(A).** 1, View into nasopharynx; 2, nasal septum; 3, right wing of the vomer; 4, entrance into the right sphenoid sinus; 5, view into the right meatus nasopharyngeus with the choanae (white dotted circle), the internal nares as counterpart of the external nares.

Caudal to the vestibulum, most of the luminal surfaces of the nasal mucosa are covered by a watery, sticky material called mucus. Its physical and chemical properties are well suited for its role as an upper airway defense mechanism, filtering the inhaled air by trapping inhaled particles and certain gases or vapors. Goblet cells and subepithelial glands produce mucus. The **mucociliary apparatus** with its synchronized beating of surface cilia propels the mucus at different speeds and in different directions depending on the intranasal location. Mucus covering the olfactory mucosa moves very slowly, with a turnover time of probably several days. By contrast, the mucus covering the transitional and respiratory epithelium is driven along rapidly (1 to 30 mm/min) to the oropharynx where it is swallowed into the esophagus.[5]

The luminal surface of the vestibulum is lined by a **squamous epithelium** similar to that of external skin. A narrow zone of nasal **transitional epithelium** covers the transition into the main nasal chamber. The majority of the non-olfactory nasal epithelium is **ciliated respiratory epithelium.** The ethmoidal conchae and the caudal surface of the septum are covered with **olfactory epithelium.** This olfactory surface is about twice as large as the area covered with respiratory mucosa. Olfactory mucosa is covered with non-motile sensory cilia, enabling the dog to detect odorant concentration levels of roughly 10,000 to 100,000 times that of the human.[2,4,6-8] Of note is the fact that organized nasal-associated lymphoid tissue (NALT) was not identified in normal puppies or adult dogs, although the nasopharyngeal tonsil in this species is well developed.[9,10] The frontal sinuses are covered with respiratory epithelium except where ethmoturbinates extend into these cavities; here olfactory epithelium is found.[11,12]

The normal canine respiratory tract is endowed with a range of different **immune cell populations** and they have the greatest concentration in the mucosa of the nose.[9] The lamina propria of the mucosa of the respiratory part also contains **serous, mucous, and mixed tubuloalveolar glands.** These glands are also present in the mucosa of the nasal vestibule. **Goblet cells** are present throughout the respiratory region, and **olfactory glands** that contain yellow pigment granules (!) are located in the olfactory epithelium, giving this surface a very typical color.[13]

Airway mucus plays a vital role in maintaining respiratory homeostasis. It provides the first line of defense against airborne irritants in the nasal cavity, and is essential in the mucociliary process, ensuring that no foreign particles reach the lungs. Not only does its thick consistency trap foreign particles, but its protein constitution additionally contains bactericidal enzymes, thereby reducing the risk of infection.[14]

Thermoregulation in the Dog

The **lateral nasal gland,** more commonly called Steno's Gland,[15] is the largest of the nasal glands. The gland is located beneath the wall of the maxillary sinus and it releases its product into an extremely long excretory duct, which opens latero-medially at the transition from the nasal vestibule into the antrum of the medial meatus. The functional significance of the lateral nasal gland is that it is part of the **thermoregulatory system** in the dog.[16,17] Whilst humans sweat to evacuate heat from the body, dogs cannot sweat; they pant. But contrary to common beliefs, **dogs do not cool primarily using the surface of the tongue.** Studies have shown that panting dogs inspire through the nose and expire through the mouth, and this begs quite a different understanding of why dogs pant.[16] The ventral nasal concha has an extremely large, richly vascularized surface of mucous membrane rolled into very fine, space-saving, spiral lamellae. The inspired air flows through these. In order for cooling by evaporation to occur, water is required. For this purpose, the dog has a special gland, absent in humans: the lateral nasal gland (glandula nasalis lateralis or Steno's gland), located in the maxillary recess. An excretory duct extends rostrally and opens laterally into the nasal vestibule (Video 238-5). Here, the secretion drips into the gutter-like channel of the antrum of the middle nasal meatus and runs caudally, driven by the inspired air. Where the plica alaris branches into the concha nasalis ventralis, the liquid drips onto the broad ventral concha and is distributed across the whole surface of this concha by the inspired air. The liquid can then evaporate rapidly in the strong airflow, producing cooling by evaporation (Video 238-6). Reduction of nasal airflow or thermoregulatory active surface of the ventral concha or both can lead to serious heat susceptibility, as, for example, in brachycephalic animals (see Figure 238-20).

A rise of air temperature from 25 to 42° C caused a threefold increase in the mucous secretion rate.[18] The excellent vascularization of the nasal mucous membranes enables heat to be exchanged rapidly and effectively. Nasal and lingual blood flow increase during panting.[19] Studies from Baker and Chapman[20] showed that in exercising and panting dogs, brain temperature is lower than the temperature in the carotid artery. They describe a vascular rete that is cooling arterial blood of the carotid artery with cold blood draining from the nose. In another study they had shown that brain temperature rises during physical exercise and panting if dogs are not able to use intact upper respiratory passages but were forced to breathe directly through an experimental tracheostomy.[21] This might be another argument to **consider the decision for a permanent tracheostomy very carefully.**

Clinical Manifestations of Nasal Disease

Clinical signs of nasal disease (E-Box 238-1) can vary; they are, however, rarely specific for the particular underlying cause. Even systemic diseases like coagulopathies can cause nasal clinical signs (see ch. 29 and 197). A thorough medical history can best be obtained by structured questions to the owner (E-Box 238-2).

E-Box 238-1

Clinical Signs of Nasal Disease

- Sneezing
- Reverse sneezing
- Nasal discharge
  - Serous
  - Mucoid
  - Mucopurulent
  - Purulent
  - Sanguineous
  - Mixed
- Stridor (nasalis and/or pharyngealis)
- Open-mouth breathing and/or expiratory cheek puff
- Dyspnea
- Exercise intolerance
- Heat intolerance
- Sleeping problems
- Respiratory problems during feeding

Halitosis (see also ch. 36)
Facial deformity or ulcerations of the nasal dorsum

E-Box 238-2

Key Questions for Obtaining a History in Nasal Disease

- Duration of nasal disease, acute or progressive onset, first signs, progress since then, previous therapies and results?
- Occurrence of sneezing/reverse sneezing, nasal discharge (quality, frequency, uni-/bilateral, changes over time)?
- Problems with breathing (respiratory noise during inspiration or expiration, distinguishing between stridor nasalis and pharyngealis)
- Difficulties with breathing during sleep, specific noise during sleep, expiratory cheek puff, open-mouth breathing at rest?
- Influence of exercise and ambient temperature on breathing?

Sneezing and Reverse Sneezing (also see ch. 27)

Sneezing is a protective reflex. It manifests as an explosive expiratory airflow that is able to dislodge and expel foreign particles from the nasal cavities. Any cause of nasal mucosal irritation or nasal discharge is a differential diagnosis for sneezing. **Reverse sneezing** is defined as a **mechanosensitive aspiration reflex.** It is a labored, short and often stertorous inspiratory effort. Sometimes dogs get into a position with head and neck extension and elbow abduction. Other times, reverse sneezing occurs paroxysmally in certain conditions (i.e., after drinking), though often without recognizable trigger or cause (Video 238-7; also see Video 27-1). Powerful contraction of inspiratory muscles and adduction of laryngeal cartilages generate negative pleural and tracheal pressure. The strong tracheal occlusion pressure with a sudden opening of the glottis while the mouth is closed produces a rapid inspiratory airflow through nose and nasopharynx. This rapid inhalation tends to tear off irritant particles and accumulated mucus, resulting in aspiration from the nasopharynx to the oropharynx, effectively supporting mucociliary clearance and allowing subsequent elimination by swallowing or coughing.[22,23]

While most owners are used to seeing their dog sneeze, they sometimes panic when witnessing their dog with a reverse sneezing attack for the first time (see Videos 238-7 and 27-1). In spite of the fact that reverse sneezing is not associated with obstructive dyspnea, dogs may appear as if they are having extreme air hunger and being close to asphyxia. In general, dogs behave normally again right after the reverse sneezing episode. Even regular episodes of reverse sneezing can be seen in individual dogs without any detectable nasal or nasopharyngeal pathology and it has to be regarded as a physiological cleaning procedure of the nasal-pharyngeal airway. However, as it is the case with sneezing, a sudden onset and continuation of pronounced reverse sneezing attacks can be the first clinical sign of a nasopharyngeal problem (for example, a foreign body). If frequency, duration and intensity of reverse sneezing seem unusual, posterior rhinoscopy should be recommended (see ch. 27).

Nasal Discharge (also see ch. 27)

In contrast to humans, mucopurulent nasal discharge in dogs is generally not a symptom of a transient and self-terminating rhinosinusitis! Often, owners of affected dogs assume that their pet had a head cold and tolerate mucopurulent or purulent nasal discharge for a while. However, usually **mucopurulent nasal discharge in dogs has a serious underlying cause,** requiring intensive diagnostics. Nasal discharge can be produced within the nasal cavity as a reaction to mucosal inflammation and/or infection. Discharge can also drain from the paranasal sinuses, predominantly the frontal sinus. This can be due to blockage of the natural caudal drainage way through the nasopharyngeal duct and the nasopharynx as, for example, with nasopharyngeal stenosis or a completely obstructing nasopharyngeal polyp. Pure mucous congestion can turn purulent after secondary bacterial infection.

Neither quality, nor laterality, nor duration of nasal discharge confirms a diagnosis of nasal disease and none of this information can replace subsequent advanced diagnostics.[24]

Airflow Obstruction

Knowing the unique importance of nasal breathing for dogs and cats, one can conceive of the consequences of nasal airway obstruction. Obviously, the nose is provided with such a reserve capacity that a 50% loss of function, meaning the obstruction of one of the two nasal cavities, may be tolerated at rest.[22,25] During resting respiration, the nasal cavity accounts for about 79% of inspiratory resistance and about 74% of expiratory resistance.[26] Dogs attempt to complete inspiration through the nose, even against a high anatomic nasal resistance. Dogs with partial bilateral nasal obstruction showed other systemic effects, such as a considerable loss of body weight.[25] Taking this into account and considering the meaning of nasal thermoregulation, the dog should be considered an obligatory nose breather.

Obstruction of the nasal-pharyngeal airway, either as a consequence of a permanent stenosing process or due to intermittent collapse of the nasopharyngeal airway, can lead to severe sleeping problems and subsequent day sleepiness (see Video 238-29). Owners of affected animals often report on attempts to sleep in a sitting position and on sleeping pauses of variable length, regularly interrupted by waking up and gasping for breath.[27] This corresponds quite well to the problem of obstructive sleep apnea (OSA) in humans[28] (see also Brachycephalic Syndrome, below).

Examination of the Nose

The diagnostic approach to nasal disease can be challenging. Medical history and physical examination of the awake patient alone rarely provide a definitive diagnosis.[29] Further means of diagnosis require general anesthesia of the patient. However, a well-planned combination of clinical examination, diagnostic imaging and endoscopy with tissue biopsies is a promising approach, establishing a diagnosis in over 90% of dogs[30] and cats.[31]

Physical Examination

A thorough medical history (see E-Box 238-2) is followed by an examination of the external nose. The symmetry or deformity of the face and the external nose, the size of the nares, possibly the mobility of the alae nasi (see Video 238-3), the pigmentation of the planum nasale and the character of unilateral or bilateral nasal discharge can be visible. Expiratory puffing of the cheeks might also be visible, indicating a complete obstruction of the nasal airway (Video 238-8). Stridor or stertor indicate stenotic airway segments within the nose or the nasopharynx, respectively. The rostral movable portion of the external nose is palpable (E-Box 238-3).

E-Box 238-3

Specific Physical Examination of the Nose

- Breathing sounds (stridor)
- Symmetry of the face and muzzle
- Character of nasal discharge, laterality
- Facial deformity or ulceration
- Patency of airflow through each nostril
- Condition of the teeth and gums
- Examination of the roof of the mouth to the pharynx (to degree possible)
- Ability to retropulse the eyes
- Pain on opening the mouth or manipulating the muzzle
- Epiphora
- Pigmentation/Depigmentation of the nasal planum
- Size and texture of submandibular lymph nodes

Special Diagnostic Procedures

However detailed the obtained medical history is and however thorough the clinical examination of the

patient was, in the vast majority of cases with suspected nasal or nasopharyngeal disease, this will neither provide a reliable diagnosis nor allow specific treatment in the awake patient.[30,32] It is advisable to communicate this to the owner early on. Even in the anesthetized patient, many important structures are more or less hidden behind bony walls inside the skull, being neither visible nor palpable. Advanced diagnostic tools like endoscopy and/or cross-sectional imaging in combination with histologic examination are often indispensable to establish a definitive diagnosis.[30,33,34] Once the decision for anesthesia is made, careful planning is required: which special diagnostic procedures should be used within the timeframe of anesthesia and in which order. The owner should be advised that in some cases, combining different special examinations might be a better option to the conventional—and usually preferred—stepwise diagnostic evaluation. The likelihood of establishing a diagnosis of a specific nasal disease relies on a combination of techniques, including radiologic examination (cross-sectional preferred), rhinoscopy (rigid preferred), cytology/histopathology of biopsy samples and culture.[31,32] The final choice of diagnostic modalities depends on both the availability of technical equipment and the owner's preferences and means.

Radiography

For many decades, plain film nasal radiographs have been a key diagnostic feature in nasal disease. Today, computed tomography (CT) or magnetic resonance imaging (MRI) provides significant, additional information and increases diagnostic sensitivity. However, questions of availability and cost may still be a limitation.

CT and MRI

Both CT and MRI allow excellent evaluation of the structures within the lumen and the tissues adjacent to the nasal cavities, the nasopharynx and the paranasal sinuses. Depending on their physical working principle, the depiction of bone, air and soft tissue is different. Nasal CT is a powerful tool and it greatly enhances the ability to establish an accurate, definitive diagnosis of nasal disease in dogs (see Video 238-1). It provides an accurate assessment of the extent of nasal disease and readily identifies areas of the nose to examine via rhinoscopy, as well as suspicious regions to target for biopsy.[33] When there is suspicion of a neoplastic process, MRI is considered the superior technique.[35] For a comparison of imaging techniques for dogs with nasal disease, see E-Table 238-1 and Figure 238-6.

E-TABLE 238-1

Comparison of Imaging Techniques for Dogs with Nasal and Paranasal Disease

	PLAIN RADIOGRAPHY	CT	MRI	RHINOSCOPY
Sensitivity to detect bony changes (lysis or proliferation)	Moderate	Excellent	Good	Poor
Show cribriform plate integrity	Impossible	Excellent	Good to excellent	Poor
Sensitivity to detect soft-tissue changes	Poor to moderate	Good	Excellent	Excellent for intraluminal structures
Ability to discriminate between tissue and mucus	Impossible	Moderate to good (with contrast)	Excellent	Excellent
Ability to take controlled biopsies	Impossible	Moderate	Poor	Excellent
Detection of foreign bodies	Poor	Good to excellent	Good to excellent	Excellent
Guided extraction of foreign bodies	Impossible	Moderate	Poor	Excellent
Visualize mucosal surfaces/fungus plaques	Impossible	Poor	Poor	Excellent
Visualize conchal structure	Poor	Good to excellent	Good	Good to excellent
Mucosal contact points	Impossible	Moderate	Poor	Excellent

Visualize nasolacrimal duct	Moderate	Good	Excellent with contrast	Excellent for the opening
Visualize duct of lateral nasal gland	Moderate	Excellent with contrast	Excellent with contrast	Excellent for the opening
Ability to evaluate the lumen of the paranasal sinuses	Moderate	Excellent	Good to excellent	Moderate to good for maxillary recess and sphenoid sinus Excellent for frontal sinus in advanced sinonasal aspergillosis Poor for intact frontal sinus

Modified from Cohn LA: Canine nasal disease. *Vet Clin North Am Small Anim Pract* 44:75-89, 2014.

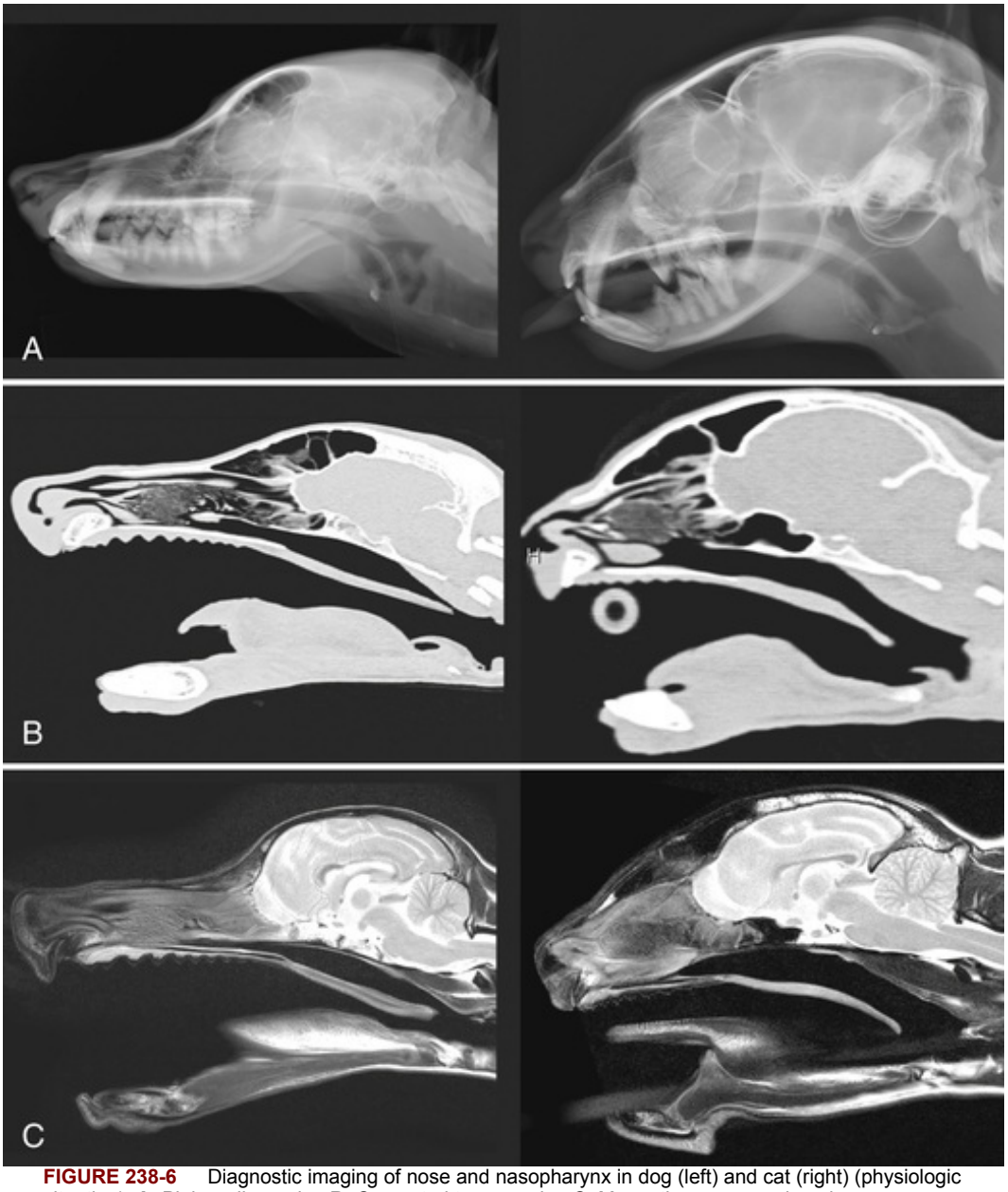

FIGURE 238-6 Diagnostic imaging of nose and nasopharynx in dog (left) and cat (right) (physiologic situation). **A,** Plain radiography. **B,** Computed tomography. **C,** Magnetic resonance imaging.

Rhinoscopy

See ch. 96 (E-Box 238-4 and Video 238-9).

E-Box 238-4

Endoscopic Landmarks for Anterior Rhinoscopy

Nares and Nasal Vestibulum

Nares and alar wing
Vestibular bulb
Plicae parallelae
Plica alaris
Opening of nasolacrimal duct
Opening of the duct of the lateral nasal gland (advanced experience level)

Nasal Cavity (5-Folds-View Dog, 4-Folds-View Cat)

Nasal septum with dorsal and ventral swell body
Plica recta
Plica alaris
Plica basalis
Nasal meatus (dorsal, medial, ventral, common)
Concha nasalis ventralis

Nasal Exit (After Decongestant, Advanced Level)

Ethmoid turbinates and olfactory mucosa
Ala vomeris
Meatus nasopharyngeus
Choanae
View into nasopharynx

Rhinotomy

In the past, without today's possibilities of modern endoscopic equipment (especially rigid rhinoscopy) and knowledge of intranasal explorative rhinoscopy, rhinotomy was a helpful diagnostic tool in certain cases of nasal disease. There is, however, no longer a real indication for explorative rhinotomy. Together with modern cross-sectional imaging techniques, anterior and posterior rhinoscopy provides a sufficient diagnostic spectrum. In most dogs, an experienced endoscopist can visualize nearly all compartments of the nose and the **standard landmarks** (see E-Box 238-4) should be recognizable even for the less-experienced endoscopist.

Diseases of the Nose

Stenoses and Obstructions of Nasal Passageways

Hereditary malformations due to excessive breeding selection for morphological extremes (miniaturization, exaggerated brachycephaly) can cause obstructions on all three segmental levels—the nasal entrance, the nasal cavity itself and the nasal exit (see Diseases of the Nasopharynx below and Figure 238-9).

Stenoses of the Nasal Entrance

Injuries of the nasal entrance due to trauma (bite wounds, car accidents, gunshot injury), chronic ulcerative inflammation (e.g., long-lasting sinonasal aspergillosis) or surgery at the nasal entrance using excessive thermal energy (HF-surgery, electrocautery, surgical lasers) can lead to constrictive and stenosing wound healing (Figure 238-7). Surgical therapy can be challenging due to a high tendency for re-stenosing and temporal stenting; a flap technique may be used to prevent this.

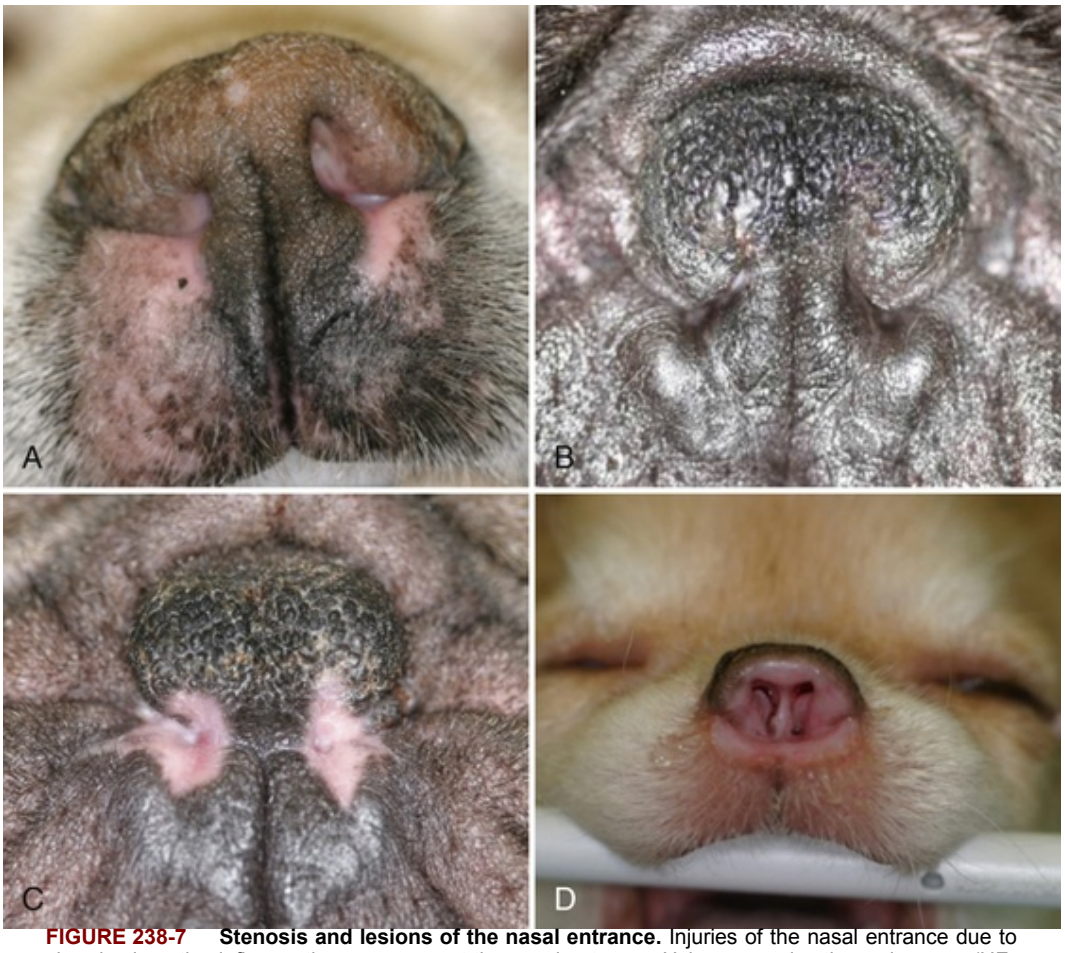

FIGURE 238-7 Stenosis and lesions of the nasal entrance. Injuries of the nasal entrance due to chronic ulcerative inflammation or surgery at the nasal entrance. Using excessive thermal energy (HF-surgery or surgical lasers) can lead to severe lesions and constrictive and stenosing wound healing. **A,** Nares stenosis after long-lasting sinonasal aspergillosis (Golden Retriever). **B,** Stenosis after failed nares surgery with CO_2-laser (French Bulldog). **C,** Stenosis after failed nares surgery with HF-technique (French Bulldog). **D,** Severe lesion of the nares after failed surgery with diode-laser (Chihuahua).

Stenoses of the Nasal Cavity

Causes of intranasal obstruction can be any kind of benign or malignant mass: tumors, expanding granulation tissue induced by chronic inflammation and intranasal cysts of varying origin. Foreign bodies frequently lodge in the nasal cavity. However, they rarely obstruct the intranasal airway due to their size but induce inflammation and purulent discharge. The inspissated discharge can cause complete obstruction of the affected nasal cavity, especially in smaller dogs and in cats. Oronasal defects and other diseases causing purulent rhinitis can lead to intranasal obstruction via the same pathomechanism (Video 238-10). Deviations of the **nasal septum** have probably been more often recognized now that computed tomography (CT) and magnetic resonance imaging (MRI) examinations are widely available. The incidence seems to be higher in small dog breeds and particularly in brachycephalic dogs.[1,36,37] Septal deviations are also described in cats.[38] With that, the question about the clinical relevance of marked deviations arises. In principle, there should be no rise in intranasal airway resistance as long as the smallest intranasal cross-sectional area is larger than the cross-sectional area of the nasal entrance (within the vestibulum) and exit (nasopharyngeal duct). Usually the size of the ventral nasal concha coapts both in the smaller and in the larger nasal cavity, filling the entire lumen.

Stenoses of the Nasal Exit

Because of functional considerations, the stenoses of both the meatus nasopharyngeus and the nasopharynx are described together (see Diseases of the Nasopharynx below; also see ch. 121).

Nasal Foreign Bodies

Various materials have been found lodged in the nasal cavity, mostly parts of plants or foreign material. They can enter the nose either from anterior inhaled via the nares or from posterior during swallowing or regurgitation into the nasopharynx or nasal cavity, respectively. If not immediately expelled by sneezing or removed by a reverse sneezing maneuver, they cause direct trauma and irritation of the nasal mucosa. Depending on the time a foreign body is lodged, its size and location, chronic irritation, inflammation and local tissue destruction may occur. Nasal foreign bodies often result in an acute onset of sneezing and facial pawing, but they can remain in place for a long period, resulting in chronic nasal discharge. **Removal techniques** for nasal foreign bodies vary. In simple cases, the foreign body is endoscopically detected "at first sight" and can be **grabbed with a small forceps** that is introduced alongside a rigid endoscope (Video 238-11). In any case, a thorough systematic endoscopic exploration of the nasal cavity is indicated (see also ch. 96). There is no guarantee that there is not more than one part of the foreign body. Larger pieces in the posterior part of the nasal cavity can possibly be pushed through the nasopharyngeal meatus into the nasopharynx.

Oronasal and Oronasopharyngeal Communications (also see ch. 272)

Congenital or acquired communications between the oral cavity and the nose, respectively the oropharynx and the nasopharynx, allow food and fluids to enter the nasal-pharyngeal passageways. Solid particles, if not expelled by the sneezing reflex or removed with the reverse sneezing maneuver, can cause pronounced inflammatory reactions of the nasal-pharyngeal mucosa. Secondary bacterial infection is common and sometimes even fungal growth can be observed. After severe mucosal damage stenosing wound healing is not uncommon. **Congenital deformities** are **clefts of the lip and palate.** Palatal defects usually affect the midline; however, lateral clefts can be seen in the soft palate as well (Video 238-12). Although the exact cause of clefting is unknown, it is commonly agreed to be multifactorial with a hereditary component. There are a variety of problems associated with facial clefting. Nursing is the major problem of neonates. Due to the close embryologic, anatomic and physiologic connection of the nasopharynx and the middle ear, soft palate clefts, especially the lateral ones, are likely to affect the auditory tube and the middle ear.[39-41] **Acquired oronasal communications** result from trauma of car accidents or due to high-rise trauma (cats). Acquired oronasopharyngeal defects can be the result of oral stick lacerations or complications after palatal surgery. Dental problems, malocclusion and deformity of the normal nasal architecture and lips occur in more rostral defects. In longer-lasting processes, expanding granulation tissue due to chronic secondary bacterial inflammation and/or inspissated discharge can obstruct nasal passageways (Video 238-13).

Rhinitis

Bacterial Rhinitis

Primary **bacterial rhinitis** is uncommon in both dogs and cats. In dogs, bacterial rhinitis occurs most commonly as a sequela to the presence of a foreign body or as a consequence of gross anatomic changes (primarily loss of turbinates) resulting from prior mycotic disease, trauma, or irradiation.[42] Antibiotics can improve clinical signs temporarily. However, when administered in patients with sinonasal aspergillosis, after initial improvement antibiotics can cause a dreadful worsening of the aspergillosis infection.

Lymphoplasmacytic Rhinitis

Idiopathic **lymphoplasmacytic rhinitis** (LPR) is an important cause of chronic nasal disease in dogs with clinical signs similar to those of other chronic nasal disorders and may be more common than previously believed. In a recent study, idiopathic LPR was diagnosed in 30% of the total population that was evaluated.[43] It is one of the most common forms of chronic, non-infectious rhinitis in dogs and cats[30] and it possibly has to be considered a key contributor to chronic nasal disease in dogs. The diagnosis is made by the histopathological identification of a lymphoplasmacytic infiltrate within the nasal mucosa and exclusion of other specific causes of chronic nasal disease. Although the etiology of idiopathic LPR has not been determined, infectious, allergic and immune-mediated mechanisms have been suggested.[34,44-46] Windsor et al[44] reported LPR in dogs of various ages and predominance in large dogs. Nasal discharge was both unilateral and bilateral, and the mean duration of signs was several months. In a recent study, the best response to therapy was seen in dogs that underwent desensitization therapy, followed by those that were treated with both corticosteroids and cyclosporine.[43]

Allergic Rhinitis

Allergic rhinitis is either an unusual or an underdiagnosed condition in small animals. There are sporadic reports of rhinitis of presumptive allergic basis in the dog and cat. Such animals present with oculonasal discharge, sneezing, nose rubbing or head shaking and significant numbers of eosinophils can be demonstrated in nasal exudate or nasal lavage fluid, and infiltrating the nasal mucosa on tissue biopsy.[9,46]

Viral Rhinitis

Despite the widespread use of vaccines (see ch. 208), respiratory disease caused by feline herpesvirus-1 (FHV-1) and feline calicivirus (FCV) remains a significant clinical problem (see ch. 229). In general, the disease is most commonly seen where cats are grouped together, particularly in young kittens as they lose their maternally derived antibody. The initial clinical signs are paroxysmal sneezing, conjunctivitis, and serous ocular and nasal discharge. About 5 days after the onset of sneezing, the nasal discharge becomes mucopurulent and there may be ocular complications. The condition usually persists for 2 to 3 weeks.[47] Viral rhinitis is a prominent clinical sign of **canine distemper** (see ch. 228). Vaccination has reduced the occurrence of the disease to sporadic cases in countries where stray dogs are rare and veterinary care is adequate (see ch. 208). Herpesvirus infection in newborn puppies is characterized by profuse mucopurulent nasal discharge. The diagnosis is usually made at autopsy[47] (see ch. 228).

Nasal, Sinonasal and Nasopharyngeal Tumors

Sinonasal tumors are rare in dogs and occur mostly in middle-aged and old dogs. Approximately one-third of all dogs with chronic nasal disease have nasal neoplasia. 80% to 90% of the nasal masses are **malignant.** They are primarily locally invasive; metastasis is, however, uncommon, or occurs late in the cause of the disease. 60% to 75% of malignancies are epithelial in origin. The three most common ones are adenocarcinoma, lymphoma, and undifferentiated carcinoma. Mesenchymal tumors include fibrosarcoma, chondrosarcoma, osteosarcoma, hemangiosarcoma, and undifferentiated sarcomas. Clinical signs in dogs and cats with nasal tumors include respiratory, ocular, and nervous system–related signs. The most common clinical signs are attributed to upper airway obstruction with decreased airflow through the affected nasal passage, epistaxis, and sneezing. In unilateral nasal obstruction, clinical signs may become obvious to the owner only after the mass has grown through one meatus nasopharyngeus, expanding caudally to the septum and obstructing the contralateral meatus. Other reported signs include reverse sneezing, stertorous breathing, serous, mucoid or mucopurulent nasal discharge, dyspnea, lethargy, weight loss, facial deformity or swelling, and pain. Central nervous system signs include seizures and behavior changes. Sinonasal tumors in dogs can rarely be cured without treatment and euthanasia is generally elected within a few months due to the progression of local disease. Radiation therapy, with or without aggressive cytoreduction, can significantly improve the expected median survival time, and constitutes the treatment of choice.[24,30,31,34,48-51]

Non-Malignant Nasal Masses

Non-malignant nasal masses are rare and infrequently described. Benign tumors, intranasal cysts, inflammatory granulation tissue and other miscellaneous tissues (e.g., hamartoma) have the potential to expand intranasally. They can obstruct the nasal passageways completely. Angioleiomyomas are benign tumors that originate from the smooth muscle of vessels.[52] In dogs, there are few descriptions of nasal or nasopharyngeal angioleiomyoma resulting in clinical signs of sneezing and bilateral nasal discharge[53,54] (Video 238-14) (see ch. 344, 346, and 348).

Nasopharynx

Anatomy and Functional Considerations

The nasal portion of the pharynx extends from the choanae to the intrapharyngeal ostium (see Figure 238-1). While the lumen of the **rostral part** is completely bound and protected against compression or collapse by bony structures (hard palate, vomer and palatine bones), the **middle part** is only dorsally (skull base) and laterally (hamuli of the pterygoid) protected by a bony boundary, and the lumen of the **caudal part** only dorsally (skull base). The non-bony walls are formed by palatopharyngeal muscles, and therefore susceptible to compression from outside or collapse due to negative intraluminal pressure. Nearly all muscles of the pharynx and the soft palate serve as constrictors, protecting the nasal airways during swallowing from aspiration of food or fluids. Only a few (stylopharyngeus and tensor veli palatini muscles) keep the lumen of

the soft part of the nasopharynx open.[13,55] **Collapsibility** of the nasopharynx is a major problem in brachycephalic animals and will be discussed below.

Functionally, the nasopharynx is important for **breathing and swallowing.** During swallowing, the pharynx closes completely, whereas it must be open when nasal breathing. Because of these antagonistic tasks, collapsibility of the pharyngeal wall is precisely regulated by complicated neuromuscular mechanisms.[56] However, in dogs, the functional separation of respiratory and feeding activities might be lost. There is evidence that dogs cannot breathe during lapping or mastication, and it is suggested that this might be due to specializations of the soft palate and epiglottis in order to enable **thermal panting.**[57]

Connection Between the Nasopharynx and the Middle Ear

There is an important and **complex connection between the nasopharynx and the middle ear.** Embryologically, the lumen of the middle ear is an extension of the pharynx. The auditory tube (Eustachian tube) connects the middle ear cavity with the nasopharynx. Opening and closing functions of the Eustachian tube are both physiologically and pathologically important. Normal opening of the Eustachian tube equalizes atmospheric pressure in the middle ear; closing of the Eustachian tube protects the middle ear from nasopharyngeal secretions. Mucociliary clearance drains mucus away from the middle ear into the nasopharynx, thus preventing infection from ascending to the middle ear. Usually, the Eustachian tube is closed; it opens during actions such as swallowing, yawning, or sneezing, and thereby permits equalization of middle ear and atmospheric pressures. Solely the tensor veli palatini muscle induces active dilation/opening during each act of swallowing.[58,59]

Clinical Manifestations of Nasopharyngeal Disease

Clinical signs of nasopharyngeal disorders can vary considerably because the nasopharynx is directly connected to three different systems: Rostrally to the respiratory system of the nose; caudally to the oropharynx and thereby to the crossing of the respiratory pathway with the digestive system; and dorsolaterally via the Eustachian tube to the middle ear. Accordingly, clinical signs can be of **respiratory, digestive** as well as **otological** or **neurological** nature, or a mixture thereof. Typical signs are difficult, noisy and in particular stertorous breathing; reverse sneezing; nasal discharge; expiratory cheek puff (indicates complete obstruction of the nasal-pharyngeal airway); retching (indicating velopharyngeal incompetence); and vestibular signs (when together with Eustachian tube dysfunction).

The lumen of the nasopharynx can either be too small (up to totally obstructed), or "too open" because the closing mechanisms fail during feeding and drinking. Breathing problems predominate if the nasopharyngeal lumen is obstructed (polyp, tumor, stenosis, dynamic collapse). If nasopharyngeal closure is incomplete due to congenital or acquired palatal defects (cleft palate, palatal fistulas after "stick-wounds" or complication after palatal surgery), nasal discharge, digestive and/or middle ear problems dominate the clinical picture. Similar to oronasal communications, food and fluids are pressed into the lumen of the nasopharynx during swallowing and, from there, into the nasal cavities, causing local foreign body reactions and nasal discharge (see below).

Examination of the Nasopharynx

In the conscious dog, a physical examination of the nasopharynx is more or less impossible. Decisive diagnostic procedures for this area require general anesthesia. This should be thoroughly discussed with the owner. Some potentially treatable diseases may otherwise be missed or necessary treatment not instituted. Initially, the soft palate is inspected orally. Digital palpation starts rostrally between the pterygoid boundaries and advances caudally. Advanced diagnostic tools like endoscopy and/or cross-sectional imaging in combination with histologic examination are often indispensable to establish a definitive diagnosis.

Endoscopy

Endoscopic examination is the key diagnostic tool for the nasopharynx (see ch. 96). It can be performed with both rigid and flexible endoscopes, depending on the examiner's preference. Endoscopic access is possible from both directions; in dogs and cats, usually from posterior through the oral cavity (rigid, 120°, 4 mm or flexible) (Video 238-15) and in most dogs also from anterior through one of the nasal cavities (rigid, 0° or 30°, 2.7 or 1.9 mm) (see Video 238-2). The **anatomic landmarks** that should be recognized are listed in E-Box 238-5. Even minor manipulations within the nasopharynx are very irritating and can provoke strong

reactions, particularly in cats. A potent analgesic component should be part of the anesthetic regime; the instillation of a local anesthetic is usually helpful.

E-Box 238-5

Endoscopic Landmarks for Posterior Rhinoscopy

Nasopharynx

Hamuli of the pterygoid (bilateral)
Opening of the auditory tube (bilateral, located directly caudal to the pterygoid bone)
Pharyngeal tonsil

Nasal Exit

Choanae (bilateral)
Nasopharyngeal meatus (bilateral)
Vomerine ala (bilateral)
(see Video 238-15)

Computed Tomography

If a nasopharyngeal mass is palpable or endoscopically visible, or an association to a lesion of the middle ear is suspected, a CT examination is highly recommended. CT gives information on the extension of a mass and on possible relations to the tympanic bulla. Wrong positioning during CT examination can obscure certain pathologies. Recommendations on how to position patients with suspected nasal-pharyngeal disease for CT examination are listed in E-Box 238-6.

E-Box 238-6

Recommendations to Position Patients with Suspected Nasal-Pharyngeal Disease for CT Examination

Prone position
Upper jaw in fixed maxillary suspension
Hard palate parallel to scanning table
Mouth open
Mandible freely moving/hanging
Soft palate freely moving, not dislocated dorsally by endotracheal tube or tongue base
If excessive intraluminal fluids present, careful removal with soft suction-tube prior to scan

Diseases of the Nasopharynx

Because of functional considerations the stenoses of both the meatus nasopharyngeus (as part of the nose) and the nasopharynx are described together. Obstruction can occur as a congenital anomaly or secondary to a foreign body, obstructive wound healing after a local inflammation with mucosal ulceration or expanding tissue of a mass.

Stenosis and Obstruction of the Nasopharyngeal Meatus

The nasopharyngeal duct can be obstructed on three levels: (1) the most rostral point is underneath the wing of the vomer, (2) the tubular canal itself and (3) the bilateral caudal openings of the meatus, the choanae (Figure 238-8).

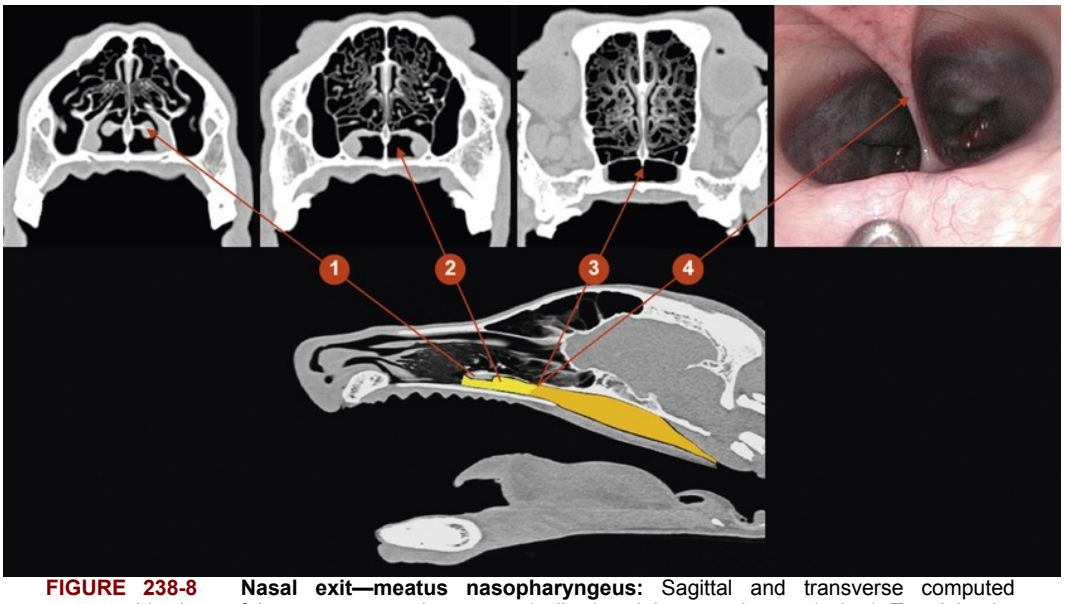

FIGURE 238-8 **Nasal exit—meatus nasopharyngeus:** Sagittal and transverse computed tomographic views of the meatus nasopharyngeus (yellow) and the nasopharynx (ochre). Top right, the postrhinoscopic view into the meatus nasopharyngeus (German Shepherd, physiologic situation). 1, Wing of the vomer; 2, lumen of the meatus nasopharyngeus; 3, caudal border of the septum; 4, caudal border of the septum, postrhinoscopic view.

Hereditary Malformations

Ongoing breeding for exaggerated miniaturization seems to disrupt the anatomical balance between bony boundary and the size of the soft tissues. In toy breeds like Chihuahua, Pomeranian and Shi Tzu the vomerine alae can be too large in relation to the lumen, leaving a passageway of only 1 mm or less (Figure 238-9).

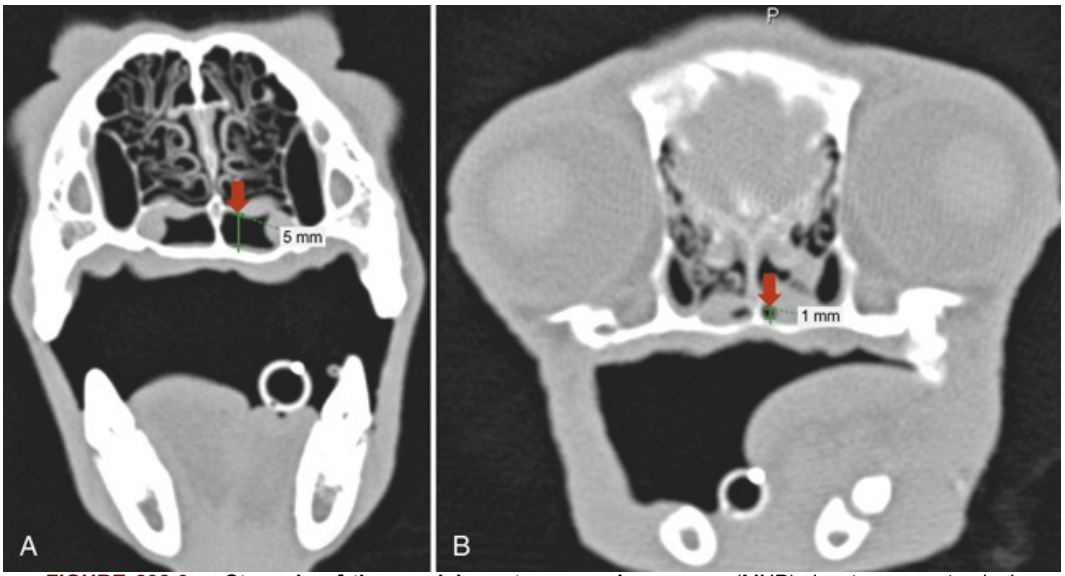

FIGURE 238-9 **Stenosis of the cranial meatus nasopharyngeus** (MNP) due to an anatomical imbalance between the meatus-lumen and the size of the vomerine ala as a consequence of exaggerated miniaturization in certain toy breeds. **A,** Physiologic size of the MNP (5 mm) in an adult Yorkshire Terrier (3 kg BW). **B,** Extreme narrowing of the MNP (1 mm) in an adult Chihuahua (1.1 kg) with clinical signs of upper airway obstruction (stertor, mouth-breathing, respiratory distress during sleeping and feeding).

Obturation of the Lumen

Various reasons can lead to an isolated obstruction within one or both lumina of the nasopharyngeal meatus.

Examples of non-malignant conditions are trauma to the skull base, rhinoliths[60] and hamartoma (Figure 238-10). **Choanal atresia** is rarely reported in dogs and cats.[61,62] It results from an embryological resorption failure of the oronasal membrane that occludes the nasopharyngeal meatuses. The malformation leads to either unilateral or bilateral partial or complete choanal occlusion. The defect can be bony, membranous or a mixture of both.[63] It is probably very difficult to differentiate between a true choanal atresia and obstructing scar tissue resulting from ulceration of mucosal tissue at this location (foreign body, regurgitation into the nasopharynx, infection).

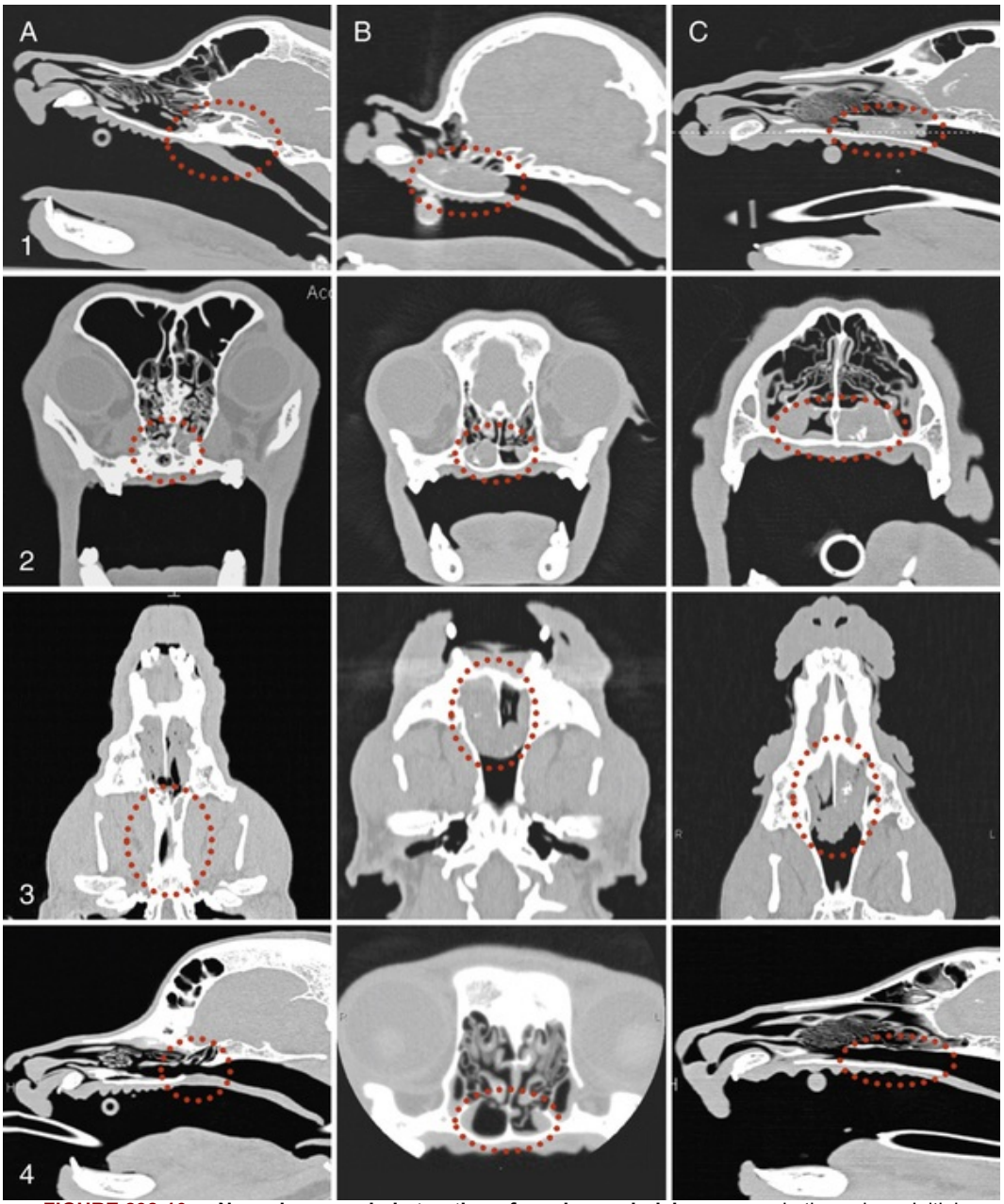

FIGURE 238-10 **Nasopharyngeal obstruction of varying underlying causes** in three dogs. Initial CT images (1) sagittal, (2) transverse and (3) dorsal planes. (4) CT examination after successful transnasal endoscopic intervention. **A,** Trauma—skull base fracture (crossbreed). **B,** Rhinolith with central plant remnant (Chihuahua).[60] **C,** Hamartoma (Weimaraner).

Stenosis and Obstruction of the Nasopharynx

Nasopharyngeal stenosis can occur as a congenital anomaly comparable to choanal atresia or as a

consequence of constrictive wound healing resulting from an inflammatory condition, surgery or trauma. In addition, the lumen can be obstructed by intra- or extraluminal expanding lesions. Intraluminal reasons can be inflammatory polyps (see below) or foreign bodies. Extraluminal reasons are, e.g., expanding lesions from the middle ear like extravasating infections causing inflammation and swelling of the peribullar tissue or other space-occupying lesions like cholesteatoma,[64] intrapalatal masses or subepithelial cysts[65-67] (Figure 238-11).

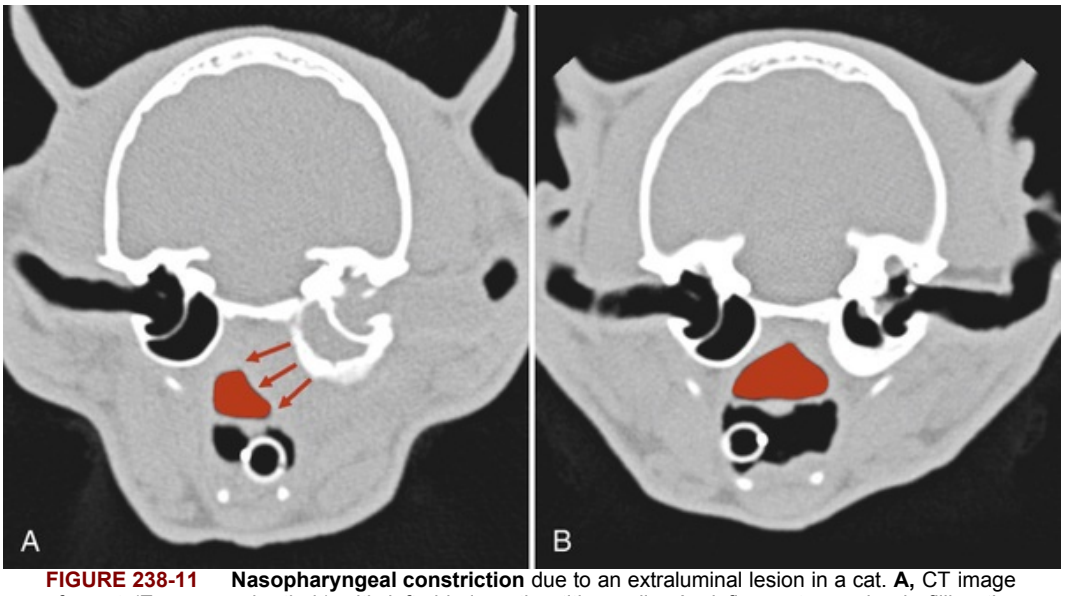

FIGURE 238-11 **Nasopharyngeal constriction** due to an extraluminal lesion in a cat. **A,** CT image of a cat (European shorthair) with left-sided septic otitis media. An inflammatory polyp is filling the external ear canal and both compartments of the bulla tympanica. The extravading infection causes peribullar swelling and narrowing of the lumen of the nasopharynx (arrows). The first clinical sign was stertorous breathing. **B,** Situation 2 months after successful treatment by interventional otoendoscopy.

Treatment of Nasopharyngeal Stenosis

Various methods of treatment have been reported, including surgical mucosal advancement[68] and balloon dilatation (see ch. 121).[65,69] The need for repeated interventions and the occurrence of complications have been reported for all of these techniques—the greatest problem being the recurrence of the stenosis. Promising for treatment in cats and dogs with soft tissue stenoses seems to be the use of a removable silicone stent.[70] For cats, the investigators described a very simple technique for opening the stenosis and preventing re-stenosis with an equally simple technique leaving no foreign material inside the patient. Possibly severe complications like palatal erosion and oronasal fistulation secondary to remaining stent material can thus be avoided.[71] However, even with temporary stenting the function of the auditory tube should be kept in mind. Any occlusion of the nasopharyngeal openings of the Eustachian tube leads immediately to a secondary secretory otitis media (Figure 238-12).

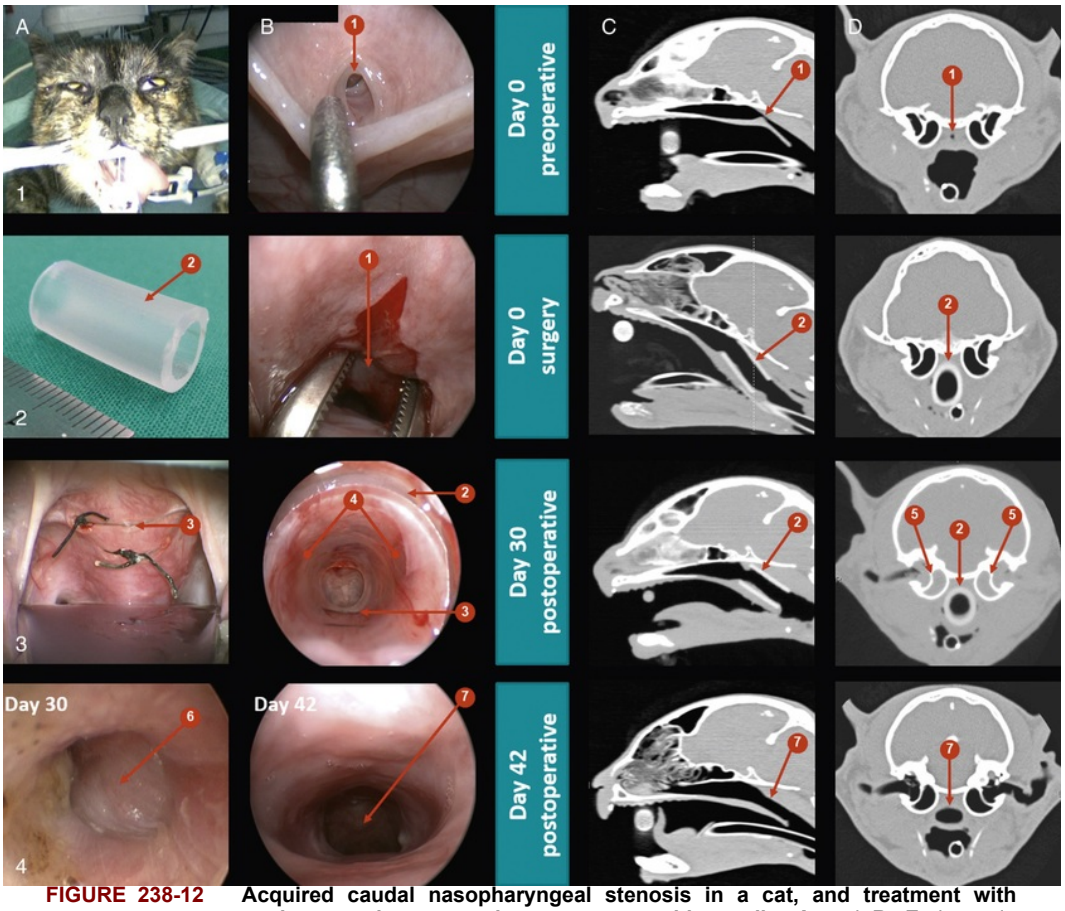

FIGURE 238-12 **Acquired caudal nasopharyngeal stenosis in a cat, and treatment with temporary stent, causing transient secondary secretory otitis media. A** and **B,** Endoscopic images: **(B1)** postrhinoscopic view on stenosis; **(B2)** opening of the stenosis with a curved forceps under postrhinoscopic control; **(A3)** view on the soft palate with transpalatal sutures to prevent stent migration; **(B3)** postrhinoscopic view into lumen of the stent—marks to indicate location of the openings of the auditory tube—the stent obstructs both; **(A4)** day 30, because of the blocked drainage of mucus from the middle ear the congestion bulges the eardrum into the external ear canal—via tympanocentesis the mucus within middle ear was flushed into the nasopharynx; **(B4)** day 42, the lumen of the widened nasopharynx is completely epithelialized and bland. **C** and **D,** Sagittal and transverse CT images: **(C1, D1)** nasopharyngeal stenosis; **(C2, D2)** silicone stent *in situ*; **(C3, D3)** silicone stent *in situ* 30 days later; **(D3)** note the bilateral mucotympanum due to retained mucus; **(C4, D4)** day 42, the physiologic lumen of the nasopharynx is restored; **(D4)** both tympanic bullae are in a physiologic condition again. 1, Caudal nasopharyngeal stenosis; 2, silicone stent; 3, transpalatal sutures; 4, marks to indicate the level of the nasopharyngeal openings of the Eustachian tube; 5, bulla tympanica (dorsolateral and ventromedial compartments filled with mucus); 6, eardrum, bulging into the external ear canal, thickened and non-transparent; 7, restored nasopharyngeal lumen.

Nasopharyngeal Tumors and Non-Malignant Nasopharyngeal Masses

Lymphoma is the most common nasal tumor in cats. 10% were found to be isolated tumors of the nasopharynx; a further 8% involved both nasopharyngeal and nasal tissue.[67,72]

Nasopharyngeal inflammatory polyps are non-neoplastic masses, developing either from inflamed mucosa of the middle ear or the auditory tube. The cause of inflammatory polyps is unknown, and chronic inflammation, ascending pharyngeal infection, congenital origin, and association with feline calicivirus have all been implicated.[73] They usually occur in younger cats. Polyps either extend through the auditory tube into the nasopharynx (nasopharyngeal polyp) or from the bulla tympanica through the eardrum into the external ear canal (aural polyp). When polyps grow within the lumen of the nasopharynx, respiratory signs increase gradually, starting with occasional stertor and possibly leading to a complete obstruction of the nasopharyngeal airway. At this stage, expiratory cheek puff or open-mouth breathing and nasal discharge (even mucopurulent when secondary bacterial infection) can be seen. Owners report increasing breathing problems and restlessness, especially during sleep or attempt to fall asleep. When the polyp grows in size within the tympanic bulla, Horner syndrome and vestibular signs can be seen. When expanding from the

bulla tympanica through the eardrum into the external ear canal, they cause signs of otitis externa with otorrhea and head shaking (see ch. 237). Large polyps can be visible as a mass in the external ear canal. CT is an excellent imaging tool for the supportive diagnosis of nasopharyngeal polyps in cats. Nasopharyngeal polyps are treated by slow traction avulsion. After that, mucus or pus inside the Eustachian tube should be removed with a curved suction pipe attached under videoscopic control to the usually dilated opening of the auditory tube (Video 238-16). The bulla tympanica should be examined, ideally with CT or endoscopically. All remnants of polyp tissue within the tympanic bulla should be carefully removed by endoscopic intervention. The recurrence rate of inflammatory polyps seems to be lower when the patient is treated with corticosteroids.[74]

Nasopharyngeal cysts of varying origin and location can obstruct the cranial nasopharynx and even totally obliterate the lumen. The causes of cyst formation are not fully understood; possible congenital reasons are (1) a pharyngeal bursa of Luschka,[75] (2) a Thornwaldt's cyst[75-77] or (3) a cyst of the Rathke's pouch.[75,78] Acquired conditions can be retentional cysts of the seromucinous glands.[75]

Foreign bodies usually enter the nasopharynx posteriorly and lodge in the middle or rostral segment. Predominant clinical signs are reverse sneezing, and seldom nasal discharge. In cats, often a blade of grass is hooked with its rough surface to the mucosa. Posterior rhinoscopy allows a fast and reliable diagnosis. Extraction of foreign bodies from the rostral nasopharynx can be challenging. A curved forceps is used under endoscopic control (Video 238-17). Foreign bodies remaining undiscovered for a longer time may cause inflammation and serious tissue damage with subsequent nasopharyngeal stenosis.

Nasopharyngeal Closing Failure

Congenital palatal defects result when the two palatine shelves fail to fuse during fetal development.[79] **Acquired defects** of the soft palate can result after stick-wounds or palatal surgery (see ch. 272).

Paranasal Sinuses

Anatomy and Functional Considerations

The reason for the presence of the paranasal sinuses has been a controversial subject for 1,800 years, since the time of Galen, 130-201 A.D.[80] Among many other theories, the following have been discussed for both humans and animals: absorb shock applied to the head for protection of sensory organs, thermally insulate the nervous centers, and lighten the bones of the skull for maintenance of proper balance of the head.[81] In human medicine, the discovery of paranasal sinuses producing nitric oxide (NO) has altered the traditional explanations of sinus physiology.[82] Endogenous NO is continually synthesized in the respiratory epithelium and plays a key role in the physiological regulation of airway functions. NO is upregulated and has diverse roles as a modulator of ciliary function, neurotransmission, bronchodilation, vasodilatation, platelet aggregation and immune function.[83,84]

The frontal sinus, the sphenoid sinus and the maxillary recess are all lined with mucosa and are connected to the middle nasal meatus. In dogs the **frontal sinus** is divided into three different parts *(lateral, medial* and *rostral)* and connects through a nasofrontal opening into the nasal cavity. Ectoturbinates, covered with olfactory mucosa, can extend into the frontal sinus. In brachycephalic animals, the frontal sinus can either be much reduced in size or even absent altogether. A small **sphenoid sinus** is largely occupied by endoturbinate IV. The lumen of the **maxillary recess** is usually empty. The lateral nasal gland (see thermoregulation, above) lies submucosally against the medial wall of the maxilla within the maxillary recess. In the cat there is only one frontal sinus on each side, the maxillary recess is small, and there is a large sphenoid sinus that extends caudally from the nasal cavity into the sphenoid bone, ventrally to the brain.[13,85]

Clinical Manifestations of Paranasal Sinusoidal Disease

Pathologies of the paranasal sinuses are usually associated with diseases of the nasal cavities. Common clinical signs are nasal discharge of varying character and consistency. Smaller amounts of discharge may remain undiscovered as they can be swallowed. The paranasal sinuses are not accessible for clinical examination in the awake patient, except for visible loss of symmetry or deformity of the face. Diagnosis requires general anesthesia, a clinical examination, diagnostic imaging and endoscopy with tissue biopsies (see ch. 96).

Examination of the Paranasal Sinuses

Due to their posterior location and subtle presenting signs, isolated sinusoidal lesions, in the past, have often been missed and were reported as rare occurrences. However, with the availability of endoscopy, CT and MRI, diseases of the paranasal sinuses are now more frequently diagnosed.[86] Studies determining the value of rhinoscopy, radiography, and CT of the head for canine nasal and paranasal disease diagnosis showed that rhinoscopy and rhinoscopy combined with CT contributed significantly to disease diagnosis.[32]

Endoscopy

The endoscopic approach to all three paranasal sinuses is possible, but with a varying degree of tissue perforation. Rigid endoscopes have distinct advantages. They are usually smaller in diameter and provide a larger and clearer view. Various instruments (suction pipe, forceps) can be introduced alongside the endoscope. This allows bimanual manipulation of tissues and foreign material. Flexible tubes and catheters can be guided into certain directions and locations. Flexible scopes allow maneuvering within complex areas like the caudal and lateral compartments of the frontal sinus.

The **sphenoid sinus** is easy to access with anterior rigid rhinoscopy. The endoscope is slowly advanced medially alongside the nasal septum, and navigated at the level of the lower septum swell body through the branches of the ventral concha in the direction of the vomerine ala. The sinus can be entered directly above and caudally to the vomerine ala (Video 238-18).

The **frontal sinus** can be accessed only after perforation of the dorsal concha. In dogs suffering from sinonasal aspergillosis, this passageway is usually already open due to turbinate lysis and destruction. A rigid endoscope (2.7 mm, 30° or 45° in medium- or large-sized dogs, 1.9 mm in smaller dogs and cats) can be used to perforate the thin laminae of the dorsal concha at the caudodorsal border of the ventral concha and is further advanced caudodorsally. This allows the tip of the endoscope at the rostro-ventral part and the view into the rostral part of the sinus is possible in most dogs. If the rigid endoscope is then replaced with a small flexible one, even further exploration of the frontal sinus is possible (Video 238-19).

The **maxillary recess** can be accessed after advancing the endoscope laterally through the middle nasal meatus between the dorsal lamellae of the ventral concha and the dorsal concha. A certain amount of compression upon the ventral concha is necessary to lower the tip of the endoscope behind the ventral concha in order to achieve an angle to look downward into the maxillary recess. Once the pathway through the medial meatus has been widened, the endoscope can be replaced with a small flexible one in order to explore the recess further (Video 238-20).

Diseases of the Paranasal Sinuses

Sinonasal Aspergillosis

The best known sinonasal disease is probably the infection of nasal and sinusoidal cavities with *Aspergillus* spp. Usually, the frontal sinus is affected but large fungal masses can fill the maxillary recess as well (Video 238-21) (see ch. 235 and 236).

Cysts of the Paranasal Sinuses

Cysts of the paranasal sinuses are usually mucous retention cysts. They can be appreciated on routine cross-sectional examinations and are often asymptomatic. The major concern lies in differentiating them from malignant diseases. The mucous retention cyst is found infrequently in brachycephalic and miniature breeds within the sphenoid sinus and seems to be comparable to similar cysts in man[87] (Video 238-22) (see below and ch. 149).

Brachycephalic Syndrome

Brachycephaly is a discrete mutation that has been selected for in many popular dog breeds, e.g., Bulldog breeds, Pug, and Boston Terrier.[88] It is an early-onset, lifelong, ultimately deteriorating and debilitating syndrome with predominantly respiratory restrictions. Brachycephaly predisposes animals to experience severe and unpleasant breathlessness with a strong negative impact on the animal's welfare.[27,89,90] Especially in smaller breeds, adult animals show typical characteristics of young animals addressing the **baby scheme** in many owners.[91] Larger brachycephalic breeds were used in medieval times, until only 200 years ago, in a

blood sport called **bull baiting.** This demanded a maximum of **exercise tolerance** from the dogs and a short head conformation was regarded as advantageous for biting. Today, most brachycephalic dog breeds are described first and foremost as suffering from pronounced **exercise intolerance** due to insufficient breathing. The reason for this dramatic development is an **exaggerated breeding** for a snub-nosed appearance. The shift from functional to aesthetic selection pressure, according to written **breeding standards** of various kennel clubs, malformed the entire upper respiratory tract in these breeds, leading to a series of consecutive airway stenoses. A head conformation that is demanded to be "round" (breeding standard Pug) or "square" (breeding standard Bulldog breeds) is *per se* incompatible with healthy, functional upper airways. However, a pervading acceptance of airway disorders as *"normal for the breed"* may constrain reforms intended to improve the welfare of affected breeds by "blinding" veterinarians, owners and breeders to the welfare impacts of these disorders.[27,92-94] The fact that brachycephaly is a purely man-made disorder with massive consequences on quality of life must raise the question of whether these animals should be bred any longer.[27,89,90,93] Popular **brachycephalic cat breeds** are Persian, exotic shorthair, and Himalayan. In Scottish Folds, the airway malformation is possibly restricted to the nasal entrance.

Pathoanatomy and Functional Consequences of a Multilevel Obstruction

Selective breeding for a short head results in impaired craniofacial development and an obvious discrepancy between the viscerocranium and the neurocranium (Figure 238-13).[95,96] Specific structural deformities lead to the anatomical obstruction of the upper airways. Recent studies have shown that brachycephalic breathing problems are caused by far more numerous obstructing malformations than was previously thought.[1,97-99] Originally, the typical cause of respiratory distress was seen as being threefold: stenotic nares, an elongated soft palate and in some dogs everted laryngeal ventricles (laryngoceles). However, ongoing excessive selection for brachycephaly obviously has changed and deformed the entire upper respiratory tract. E-Box 238-7 lists both well-known and previously less well-recognized anatomical constrictions in the upper airways.

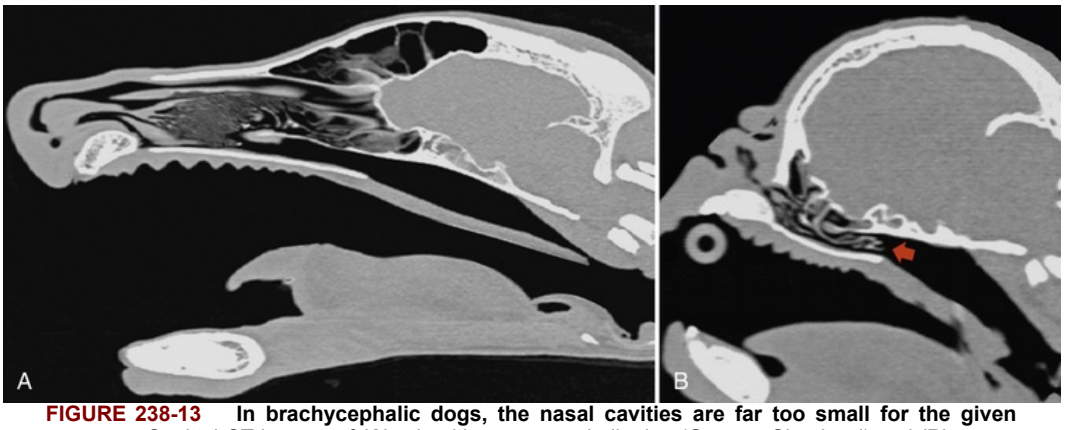

FIGURE 238-13 In brachycephalic dogs, the nasal cavities are far too small for the given contents. Sagittal CT images of **(A)** a healthy normocephalic dog (German Shepherd) and **(B)** a pug. Note the undersized nasal cavity, the missing frontal sinus and the obstruction of the meatus nasopharyngeus in the pug by caudally-growing aberrant turbinates (CATs, arrow).

E-Box 238-7

Overview of Obstructing Malformations in the Upper Airways as a Consequence of Selective Breeding for Brachycephaly

Nasal Entrance

Stenosis of the nares
Stenosis of the vestibulum

Nasal Cavity

Obstruction of intranasal airways due to malformed and aberrantly growing turbinates (rostral aberrant turbinates: RAT) *together with*
Intranasal mucosal contact points

Nasal Exit—Nasopharyngeal Meatus and Choanae

Obstruction due to malformed conchae growing caudally (caudal aberrant turbinates: CAT)

Nasopharynx

Reduced lumen and increased collapsibility of the nasopharynx (see "meat-in-the-box model") due to

- Increased length of the soft palate
- Increased thickness of the soft palate
- Narrowing of the hamuli pterygoidei
- Space-occupying structures in the oropharynx
  - Enlarged palatine tonsils
  - Macroglossia (predominantly Bulldog breeds and Boxer)

Larynx

Collapse due to laryngomalacia with impairment of arytenoid abduction (predominantly Pug)
Obstruction of rima glottidis due to protruding tissue of lateral ventricle (laryngocele) (Pug and Bulldog breeds)
Obstruction of rima glottidis due to malformed over-thick vocal folds
Impairment of opening function (predominantly Pug)

Trachea

Hypotrachea (predominantly Bulldog breeds)
Tracheobronchomalacia (predominantly Pug)

Stenosis at the Nasal Entrance

The stenosis of the canine nasal entrance seems to be influenced by three different factors: a *first and well-described stenosis* is clearly visible to the naked eye. The naris, the visible opening plane into the nasal vestibule, is compressed to a small slit. This slit compromises a vertical and a horizontal part, the latter widening slightly ventrally. In relation to the nose, the exterior part of the nasal wing is far too large and presses against the philtrum/septum from the lateral aspect (Figure 238-14; Video 238-23). A *second stenosis*, less known but even more important and much more difficult to treat, is hidden behind the first stenosis and usually invisible from the outside. It is the obstruction inside the nasal vestibulum due to a large vestibular bulb that is oversized for the given lumen inside the vestibulum (see Figure 238-14; Video 238-24). Finally, as *third stenotic factor*, there is the immobility of the bulb. In brachycephalic animals, its size appears to greatly restrict mobility, thereby impeding abduction. This functional restriction further reinforces the anatomical stenosis.

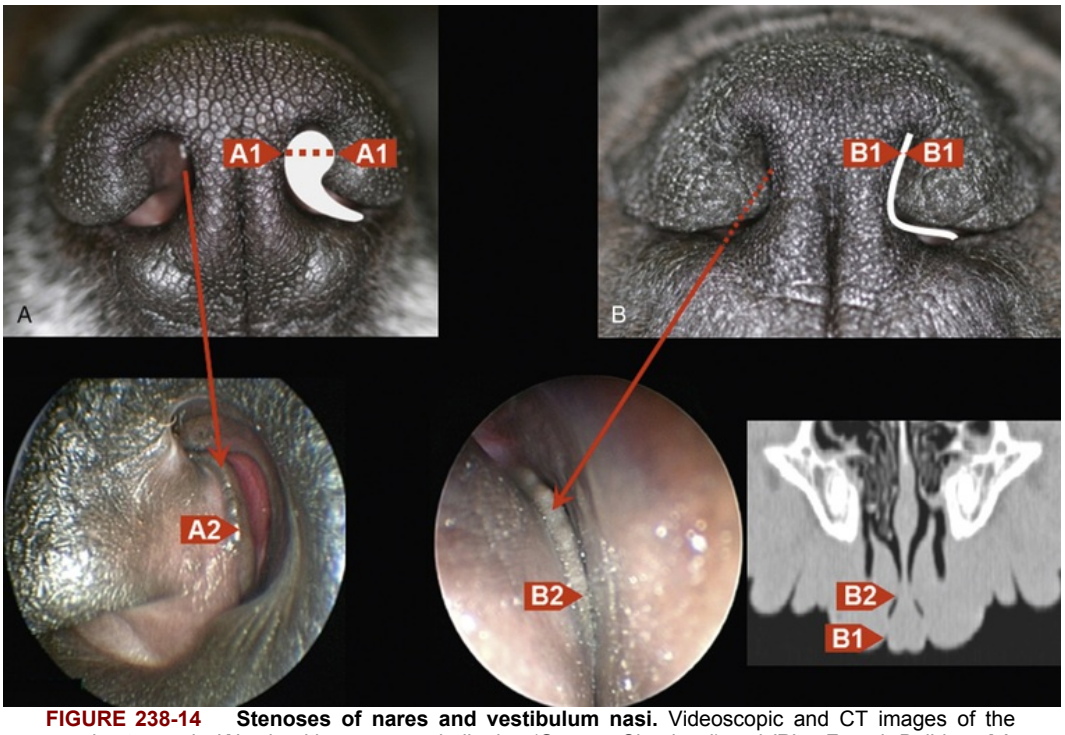

FIGURE 238-14 **Stenoses of nares and vestibulum nasi.** Videoscopic and CT images of the nasal entrance in **(A)** a healthy normocephalic dog (German Shepherd) and **(B)** a French Bulldog. **A1,** Physiologic width of the vertical part of the left naris. The naris is comma-shaped with a wide head of the comma (dotted red line). **B1,** Pathologic narrowing of the vertical part of the left naris—first (visible) stenosis. The naris is slit-shaped, indicating the malformation of the alar wing. **A2,** Voluminous physiologic vestibular bulb. **B2,** Pathologic narrowing within the vestibulum—second stenosis. An immobile vestibular bulb is pressed against the septum. (See Videos 238-23 and 238-24.)

Stenosis Inside the Nasal Cavity and the Nasal Outlet

It is remarkable that the nasal cavity itself has seldom been considered as a contributing factor to airway obstruction despite the fact that the fundamental difference between brachy- and normocephalic dogs is the extremely shortened nose. Various mechanisms contribute to **brachycephalic intranasal airway obstruction:**

The **nasal cavity** itself is far too small for the given contents (see Figure 238-13).[13,37]

The conchae of brachycephalic dogs are **macroscopically**[1,37,100] and **microscopically**[101] **malformed** and **grow aberrantly** into air-conducting spaces, obstructing their lumen and causing a rise in intranasal airway resistance.[102,103] **Conchal configuration** can be assessed as aberrant if turbinates branch into the nasal meatuses, obstructing their lumen. Conchal lamellae spreading rostrally to the point of first branching of the plica alaris into the concha nasalis ventralis (CNV) are classified as *rostral aberrant turbinates* (RAT) (Figure 238-15). Conchal lamellae spreading caudally into the meatus nasopharyngeus (MNP), passing ventrally to the wing of the vomer, are classified as *caudal aberrant turbinates* (CAT) (Figure 238-16).[1]

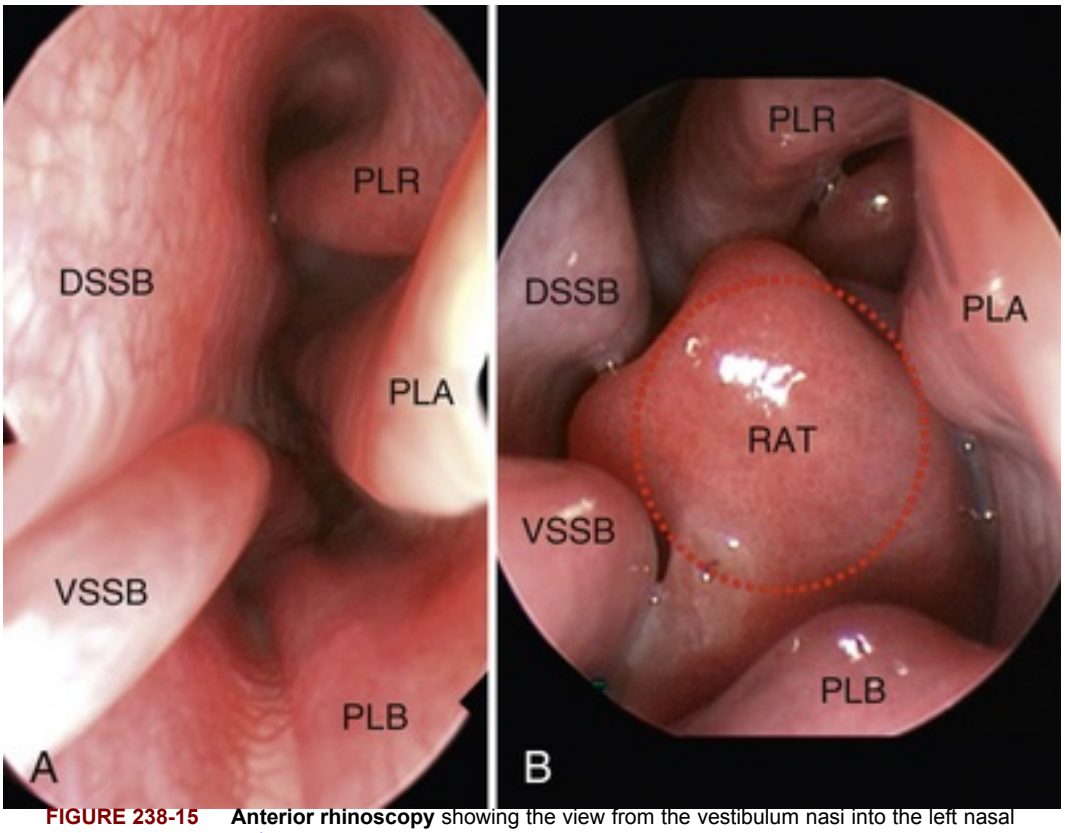

FIGURE 238-15 **Anterior rhinoscopy** showing the view from the vestibulum nasi into the left nasal cavity ("5-folds-view").[1] **A,** In the normocephalic dog (German Shepherd) there is a free view into the nasal meatus and on the five intranasal folds, the ventral septal swell body (VSSB), dorsal septal swell body (DSSB), plica recta (PLR; straight fold), plica alaris (PLA; alar fold), plica basalis (PLB; basal fold). **B,** In the French Bulldog, a huge rostrally growing rostral aberrant turbinate (RAT) arising from the concha nasalis media is obstructing several nasal meatus. Note the multiple points of mucosal contact. (See Video 238-24.)

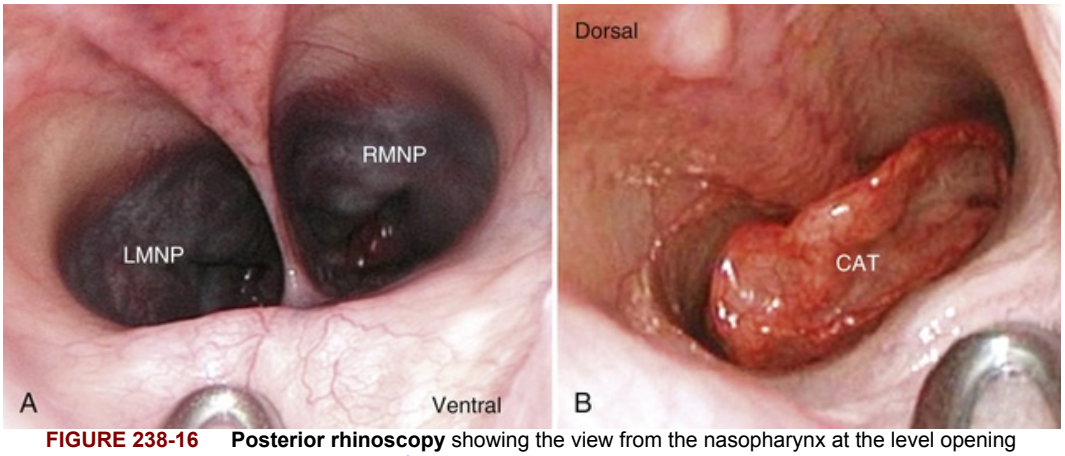

FIGURE 238-16 **Posterior rhinoscopy** showing the view from the nasopharynx at the level opening of the auditory tube (120° rigid optic).[1] **A,** In the normocephalic dog (German Shepherd), both meatus nasopharyngei (left and right MNP) separated by the caudal nasal septum are visible. **B,** In the brachycephalic dog (Pug) the view into both MNPs is blocked by a large caudally growing aberrant turbinate (CAT). (See Video 238-15.)

Intranasal mucosal contact-points contribute to the elevation of intranasal airway resistance. They can be found both between lamellae of the same concha (intraconchal) and between lamellae of different conchae (interconchal), as well as to adjacent mucosal surfaces of the surrounding nasal cavity (see Figure 238-15).[100]

Nasal conchae grow predominantly after birth. Despite the extraordinarily complex structure of the adult

canine conchae, this growth obviously stops before the mucosa of adjacent turbinate lamellae contact each other. The small air gaps surrounding each lamella provide for effective ventilation of the entire turbinate. In healthy non-brachycephalic dogs, even minor direct contact of adjacent intranasal mucosa is extremely rare. Possible intranasal obstruction results from a failure of growth termination, leading to pronounced intranasal mucosal contact. Decreased mucosal shear-stress due to reduced airflow as a consequence of stenotic nares might be involved in this failure of growth termination.

Failure to address intranasal obstruction might be an explanation for the lack of therapeutic success after conventional surgery for the brachycephalic syndrome.

Pharyngeal Obstruction—the "Meat-in-the-Box-Model"

Several factors contribute to the obstruction of the nasopharynx in a very complex mechanism. In general, this can be described as an **anatomical imbalance of the upper airway** with too much soft tissue for a given maxillomandibular enclosure size. A mechanical model can aid a better understanding of its functional importance.[56,104] The **"Meat-in-the-Box-Model"** describes a soft, collapsible tube that runs through a box with rigid outer walls (Figure 238-18). The box is filled with soft material (meat) that surrounds the tube. The tube corresponds to the nasopharynx; the framing outer box is the base of the skull and the lower jaw and cannot expand. Within the box and around the tube is soft tissue in varying quantities and of varying consistency (muscle, fat, connective tissue, tonsils). Since the tube has no rigid wall of its own, like the trachea does, for example, it is collapsible. E-Table 238-2 compares the **factors influencing the width of the nasopharynx** according to this model. The craniofacial malformation in brachycephalic dogs gives rise to a series of factors that either constrict the lumen of the nasopharynx or cause it to collapse:

E-TABLE 238-2

Factors and Measures Affecting the Width and Collapsibility of the Nasopharynx in Brachycephalic Animals

NARROWING/COLLAPSING OF THE NASOPHARYNX	OPENING OF THE NASOPHARYNX
Anatomical	
Increase in tissue mass within the box	Surgical reduction of tissue mass in the box
1. Hypertrophic soft palate 2. Hypertrophic tonsils 3. Relative macroglossia 4. Obesity	1. Reduction of soft palate volume 2. Tonsillectomy/tonsillotomy 3. Ø 4. Weight loss
Increase of stenoses-induced negative pressure during inspiration	Stenoses-reducing surgical intervention
1. Stenotic nares 2. Stenotic nasal vestibule 3. Intranasal obstruction by relative conchal hypertrophy and aberrant conchae	1. Widening of the nares 2. Vestibuloplasty 3. Laser-assisted turbinectomy (LATE)
Functional	
1. Closed mouth 2. Pressure against underside of head/neck (e.g., prone position) 3. Feeding	1. Open mouth

Shortening of the skull, especially of the upper and lower jaw, makes the overall box smaller. As the tissue inside the box is not reduced by the same proportion, narrowing occurs and less space is available for the tube inside the box.

Over-long soft palate: The additional length of the velum *per se* does not reduce the lumen of the nasopharynx anatomically. However, the airtight attachment to the epiglottic surface separates the oropharyngeal from the nasopharyngeal airway. This enhances the negative pressure in the nasopharynx during inspiration, thus increasing its collapsibility (Video 238-25).

Over-thick soft palate: The thickness of the soft palate in brachycephalic dogs can be many times over that of normocephalic breeds of the same or of larger size (Figure 238-17). Amazingly, the increased thickness of the soft palate seems not to be muscle hypertrophy, but due to increased stroma and increased proportions of salivary tissue while muscle mass was reduced. These findings can be interpreted as a consequence of both

acute and chronic muscle degeneration and necrosis due to constant tissue trauma.[105,106]

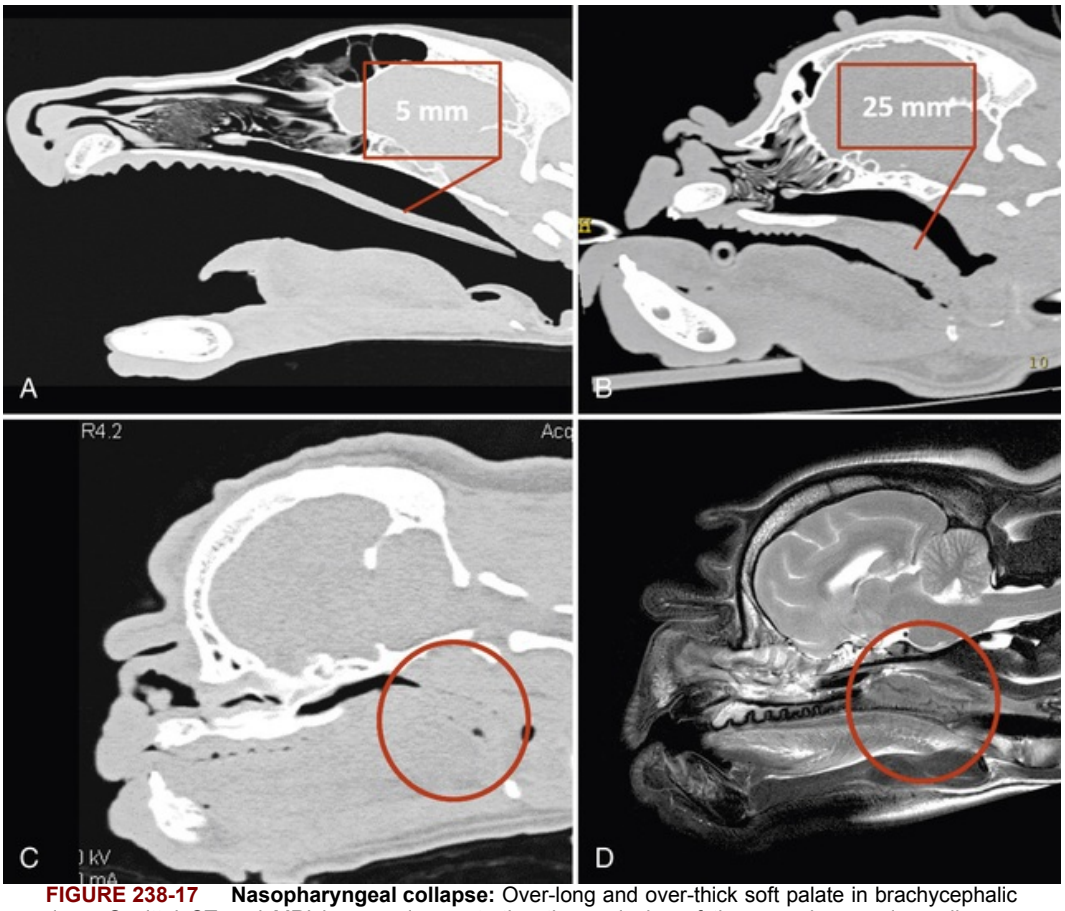

FIGURE 238-17 **Nasopharyngeal collapse:** Over-long and over-thick soft palate in brachycephalic dogs. Sagittal CT and MRI images demonstrating the occlusion of the nasopharynx depending on thickness of the soft palate and position of the lower jaw. **A,** Healthy normocephalic dog (German Shepherd). **B,** English Bulldog. The mouth gap is open and the nasopharyngeal airway open. **C,** Pug, sagittal CT. The mouth is closed and the nasopharyngeal airway occluded. **D,** Pug, same situation as **C** shown in an MRI image.

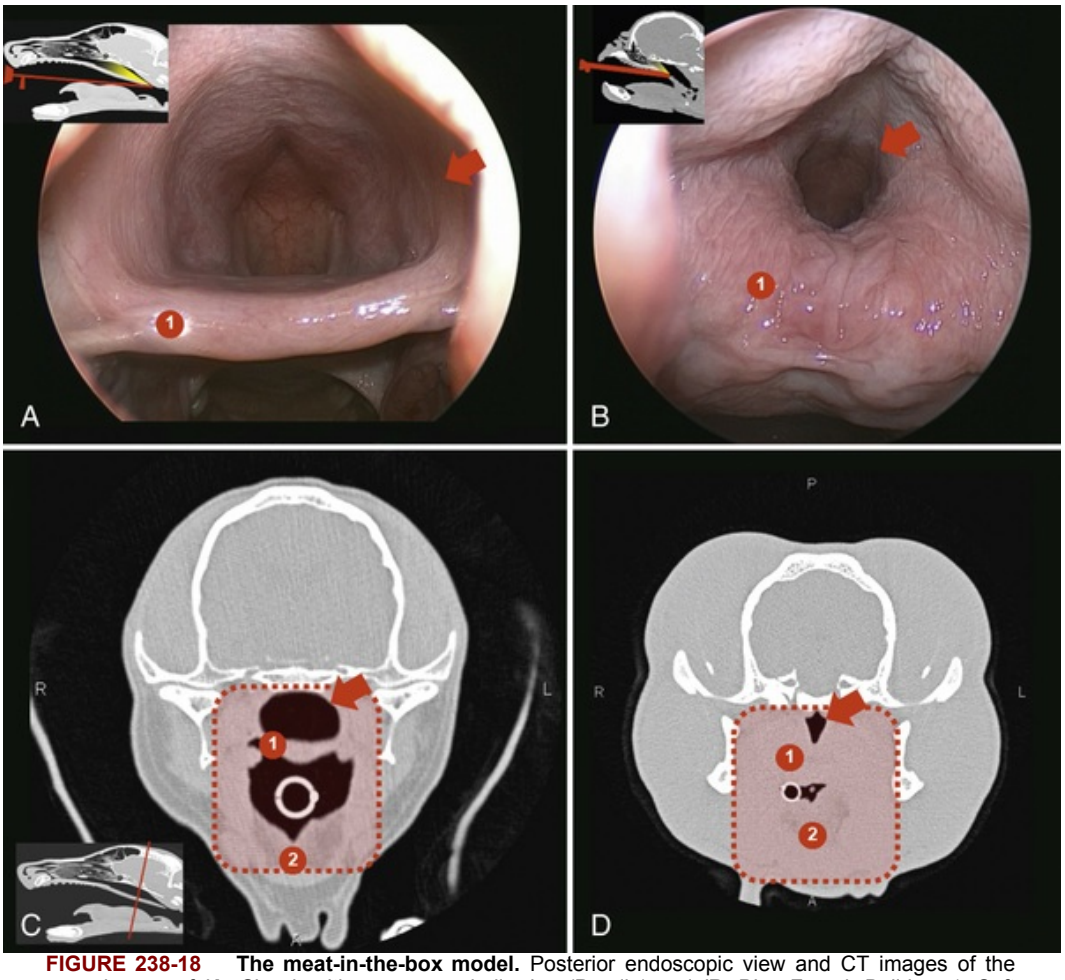

FIGURE 238-18 The meat-in-the-box model. Posterior endoscopic view and CT images of the nasopharynx of **(A, C)** a healthy, normocephalic dog (Poodle) and **(B, D)** a French Bulldog. 1, Soft palate; 2, tongue. The red dotted line indicates the "box" surrounding the "meat." The more "meat" is in the box, the smaller is the lumen of the nasopharynx (arrow).

Obesity probably plays an important role here. Additional fatty tissue stored in the box further narrows the tube.

Hypertrophic palatal tonsils and macroglossia can also be regarded as additional tissue mass. Both are pressed out of the oropharynx against the soft palate, forcing it dorsally into the nasopharynx. This causes compression, and possibly even complete obstruction, of the tube especially when the jaw is closed.

Closing the jaw or any ventral pressure in the head and neck region can hinder respiration in brachycephalic animals considerably (see Figure 238-17). This is why conscious animals very often dislike lying prone with their head stretched forward on the floor. With anesthetized brachycephalic animals, this position, for example, after extubation, can cause asphyxia. Feeding may have a comparable effect.

All the above factors cause constriction of the nasopharynx due to compression from the outside. However, there are also **factors that cause functional collapse** of the tube due to negative pressure in the airways during inspiration. If collapse occurs rhythmically, the tube walls clap together, producing a typical noise: **snoring.** If there is an elevated, pathological negative pressure in the pharynx, the causative stenosis must be located rostrally, in the nose. This is where the typical stenoses in brachycephalic dogs occur: (a) stenosis of the outer nares, (b) stenosis of the nasal vestibule and (c) stenosis of the intranasal airways due to hypertrophic and dysplastic conchae. Mathematically, halving the radius of the airways raises resistance 16-fold. In brachycephalic animals, particularly strong negative pressure has to be generated in the thorax to overcome the resistance produced by the complex nasal stenoses. Typical for this situation is the visible labored breathing. This strong negative pressure causes the tube of soft tissue that forms the nasopharynx to collapse. However, increased upper airway collapsibility enhances this vicious circle even further.

E-Table 238-2 lists the **therapeutic measures that can decrease nasopharyngeal collapsibility.** Again, the "meat-in-the-box" model helps illustrate what effects these measures can have. Too much tissue in the rigid box results in compression of the lumen of the tube. If the tissue is partly fat, it is necessary to reduce that fat

by prescribing weight-loss measures. Even in severe cases, this can be very beneficial, but the clinician is reminded that, as a rule, weight loss has only a supporting, hardly ever a curative, effect. The typical, often impressive enlargement of the soft palate seen in brachycephaly has to be reduced as well, either simply by shortening it or, in severe cases, also by thinning it. If large tonsils are protruding from the tonsillar crypt, they should be surgically removed, or at least reduced in their volume in order to create more space for the nasopharynx.

Larynx (see ch. 239)

Malformations of the brachycephalic larynx can be very pronounced and cause serious clinical consequences. Both the laryngeal skeleton and intralaryngeal structures seem to be affected. They all result in a clinically relevant reduction of the rima glottidis, thus increasing resistance to air flow through the larynx[107] (see E-Box 238-7). In spite of the fact that the brachycephalic pathoanatomy has been known for a long time and is relatively well described, the ongoing debate on etiopathology, especially on the question of primary and secondary abnormalities, is probably of a more anecdotal character. The **eversion of the lateral ventricles** was initially regarded as a single entity[108]; later on, the same author speculated that it could be the first stage in the pathogenesis of laryngeal collapse; additionally the author described a stage II with loss of rigidity and medial displacement of the cuneiform processes of the arytenoid cartilage, and a stage III with collapse of the corniculate processes of the arytenoid cartilages with loss of the dorsal arch of the rima glottidis. He presumed that this eversion and the other stages of the laryngeal collapse could be a consequence of persistent dyspnea causing negative inspiratory airway pressure and subsequent laryngeal overstress.[109] This assumption has been retained by the majority of the veterinary literature since then; it was, however, never proven. There are several indications to question the early interpretations and we probably have to distinguish between two different entities: malformation of **internal laryngeal structures** (everted lateral ventricles and the vocal folds) (Video 238-27) and, malformation of the **laryngeal skeleton** (Video 238-28). **Everted ventricles** rather seem to be a herniation of tissue alongside the caudal border of the ventricularis muscle and can therefore be regarded as a **"laryngocele"** (Video 238-26). The **vocal folds** of brachycephalic animals are often overly thick and have lost their typical slim structure. This also contributes considerably to the narrowing of the rima glottidis. An additional problem within the brachycephalic larynx can be the formation of vocal fold contact granulomas (Figure 238-19). Laryngeal overstress causes continuous microtrauma and direct damage to the tissue covering the vocal process of the arytenoid, leading to the formation of vocal fold contact granulomas. The mechanical trauma can be aggravated by regular contact of the glottis with gastric acids due to regurgitation and laryngopharyngeal reflux.[110] Malformation of internal laryngeal structures seems to occur independently from the stability of the laryngeal skeleton. There are indications that the "collapse" of the skeleton might have different causes: Pugs obviously suffer from a substantial loss of cartilage rigidity—both in larynx and trachea—while in Bulldog breeds the cartilages of larynx and trachea have a firm consistency[111] (see ch. 240).

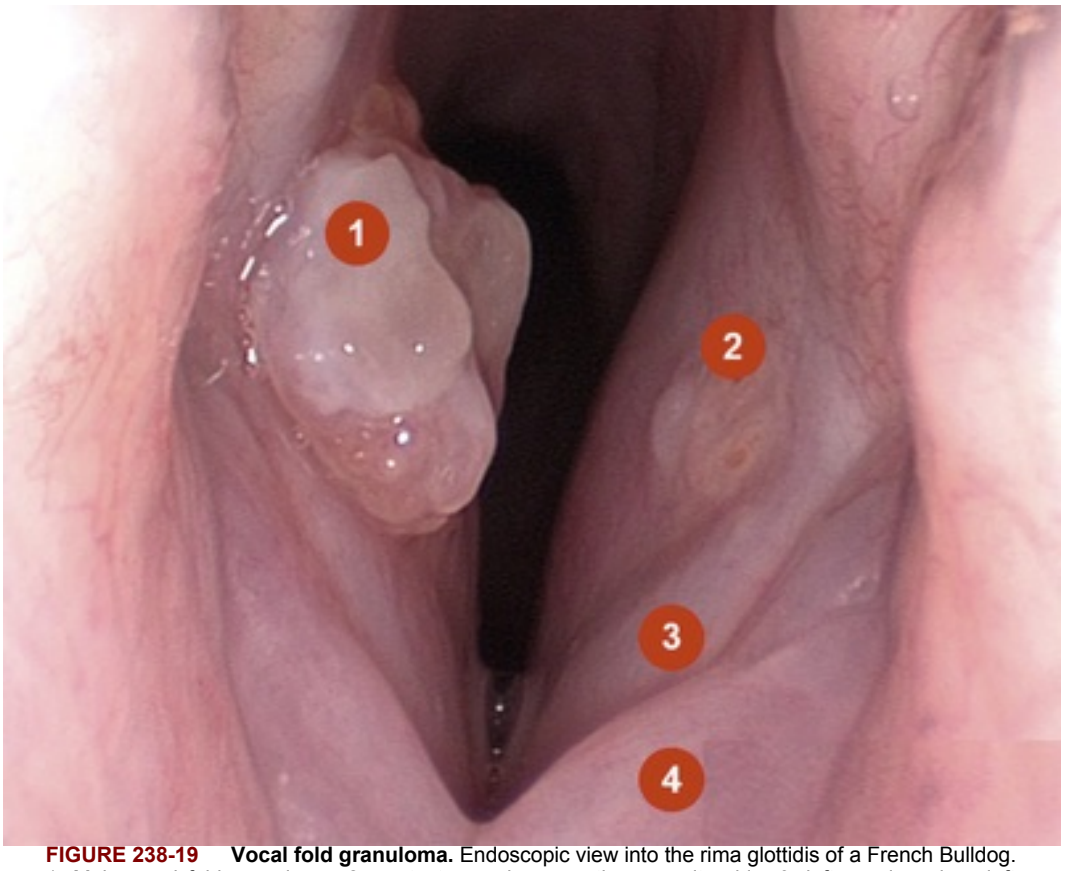

FIGURE 238-19 Vocal fold granuloma. Endoscopic view into the rima glottidis of a French Bulldog. 1, Main vocal fold granuloma; 2, contact granuloma on the opposite side; 3, left vocal cord; 4, left everted lateral ventricle (laryngocele).

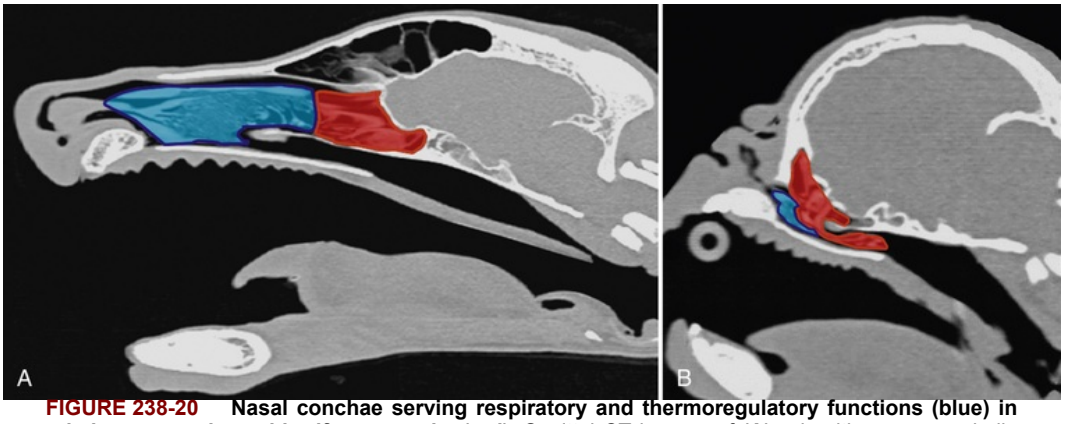

FIGURE 238-20 Nasal conchae serving respiratory and thermoregulatory functions (blue) in relation to conchae with olfactory tasks (red). Sagittal CT images of **(A)** a healthy normocephalic dog (German Shepherd) and **(B)** a Pug. The extreme reduction of thermoregulatory active conchal surface in brachycephalic animals in combination with an impaired nasal airflow possibly contributes to exercise/heat intolerance and collapse far more than impaired pulmonary ventilation.

Trachea (see ch. 241)

Tracheal hypoplasia is a congenital abnormality commonly seen in Bulldog breeds in which the ends of the tracheal rings are apposed or overlap, resulting in a narrow but rigid and mostly round tracheal lumen. Kaye et al[112] describe short dorsal tracheal membranes and tracheoscopic hypoplasia in 100% of the examined bulldogs with no or mild clinical symptoms. In Pugs, the tracheal lumen can also be narrow but contrary to Bulldogs, and comparable to the laryngeal problem, this is a result of a weak cartilage skeleton with flattened

tracheal rings and a widened dorsal membrane that may bulge into the tracheal lumen.

Clinical Manifestations of Brachycephalic Malformations

Brachycephalic dogs show signs of nasal, pharyngeal and laryngeal stridor, expressed as inspiratory dyspnea, loud snoring accompanied by gagging and possibly coughing. Episodes of severe dyspnea can occur with cyanosis, syncope and collapse and even death. Gastrointestinal signs are dysphagia, regurgitation and vomiting. Acute signs of respiratory distress may be seen more frequently if the patient is obese or in stressful situations like high ambient temperatures, excitement or exercise. Brachycephaly may have a severe impact upon the welfare of dogs, compromising their ability to exercise, play, eat, and sleep.[27]

In a recent study, owners of dogs (Pugs and French Bulldogs) that needed surgical therapy described in a structured questionnaire how they perceived frequency and severity of their dogs' impairments. In addition to the well-known clinical signs, they reported exercise intolerance (95%); 75% could go for a walk for at most 10-30 minutes in summer and only 30% of those dogs had recovered afterwards within 15 minutes. Restrictions became obvious above 19° C ambient temperature. 68% of the dogs had sleeping problems; nearly 30% showed signs of sleep apnea or tried to sleep in a sitting position (Video 238-29). 77% of the French Bulldogs had experienced problems with feeding.[27]

Examination of Brachycephalic Animals

Anamnesis and Physical Examination

Initial evaluation involves taking a history of clinical signs, along with an assessment of the degree of respiratory compromise. Depending on the stress level of the dog and ambient temperature, clinical signs may or may not be clearly visible during examination. A structured questionnaire is recommended to obtain comprehensive and comparable information, and to reveal the true extent of compromise. However, it is also known that owners of brachycephalic dogs assess respiratory signs as "normal for the breed."[113] A recently published study showed a disparity in recognition and perception of clinical signs associated with brachycephaly. Dog owners reported a high frequency and severity of respiratory signs but did not perceive them as problems.[93] Therefore, the structure of a questionnaire should address this problem by asking questions that use objective criteria, such as time needed for recovery and questions about activities that could easily be observed by a dog owner.[27] **Physical examination** includes the assessment of the size of the nares with particular attention paid to the width of the vertical slit (see Figure 238-14). Laryngeal, tracheal, and thoracic auscultation helps to determine the location and assess the quality of respiratory noise. In addition, respiratory rate, mucous membrane color, and characteristics of respiratory noise can help to determine the severity.

Surgical Management

The first concerns about respiratory problems in these breeds were raised within the veterinary profession in the 1930s, approximately 60 years after organized breeding in kennel clubs began. This urged veterinarians to criticize these breeding practices and to develop new surgical techniques to correct the problems.[108,114,115] Surgical techniques have remained amazingly unchanged since then, with the exception of relatively minor modifications. Various techniques have been recommended to **enlarge the stenotic nares,** to **shorten the elongated soft palate** and to **resect everted laryngeal ventricles.**

The latest changes in the surgical approach describe a new technique for palatal surgery.[116] In the past, surgery has focused primarily on the shortening of an overlong soft palate. Today, considering the complex relations between the collapsibility of the nasopharynx and the thickness of the soft palate, there are also recommendations to make the over-thick soft palate thinner. However, from human medicine we know the important role of palatal muscles (m. tensor veli palatini) for the physiological function of the auditory tube.[59,117,118] So it is not yet clear how much muscle tissue can be removed without negative consequences for the ventilation of the middle ear.

A more complex and comprehensive approach simultaneously addresses the well-known and the more recently described obstructions by a **multi-level surgery.** The principle of this approach is the aim to treat all serial, multiple airway stenoses at the same time. Novel aspects are (a) the more radical opening of the nasal entrance than is possible with the common "wedge technique" by performing an ala-vestibuloplasty, and (b) the interventional endoscopic resection of malformed obstructing turbinates using diode laser light (laser-

assisted turbinectomy, LATE) to establish intranasal airway patency. These procedures are combined with (c) a bilateral tonsillotomy, (d) a staphylectomy in combination with palatal volume reduction, and (e) a microlaryngoscopic laser ablation of everted laryngeal ventricles.[100,119]

In a recent study examining the results of this multi-level approach using a pre- and postoperative structured owner questionnaire, surgery managed to reduce the clinical signs associated with brachycephaly in all dogs. There was a reduction in life-threatening events by 90% (choking fits decreased from 60% to 5% and collapse from 27% to 3%). The incidence of sleeping problems decreased from 55% to 3%, and the occurrence of breathing sounds declined by 50%. There was a marked improvement in exercise tolerance but only a modest improvement in heat tolerance. However, despite the remarkable improvement perceived by the owners, these dogs remained clinically affected and continued to show welfare-relevant impairments.

Non-Surgical Management

Non-surgical management might have several tasks and covers medical management, emergency treatment of acute respiratory distress and client education. Non-surgical management cannot replace surgical treatment.

Medical Management

The vast majority of brachycephalic dogs with some degree of respiratory distress have been treated, at some time or other, with corticosteroids, often in combination with an antibiotic. However, there seems to be no evidence for the use of these medications.[113]

Emergency Treatment

The first therapeutic goal in acute respiratory distress is sedation and the prevention of hyperthermia (see ch. 139). This is achieved by pharmacological means (see ch. 138) in combination with non-pharmacological measures to prevent overexcitement. Advantages of acepromazine are, besides the desired tranquilizing effects, the usually unwanted effects of central and peripheral mediated hypothermia.[120] Non-pharmacological means, especially for hospitalized animals, are to take them out from a box or kennel into a cool and quiet environment. An easy and fast technique to treat or prevent hyperthermia (see ch. 134) is to moisten the dog's hair coat, if necessary not only with wet compresses but by pouring water over the animal, making the hair coat wet. Mainly Bulldogs seem to suffer from some kind of claustrophobia; a narrow oxygen cage can cause a life-threatening situation for such animals, and there is a considerable number of patients in this stressful situation that simply do not want to be left alone and need human company.

Client education may begin prior to the decision of buying a new dog. Clients should be carefully informed that brachycephalic dogs might suffer lifelong from respiratory and non-respiratory (Figure 238-21) disorders; that puppies usually breathe normally and clinical signs mostly develop not earlier than 6 months; and that the assurance the parents were “free-breathing” should be regarded with caution because it has been shown that many owners of brachycephalic animals do not perceive their animals' respiratory distress as dyspnea but as “normal for the breed.”

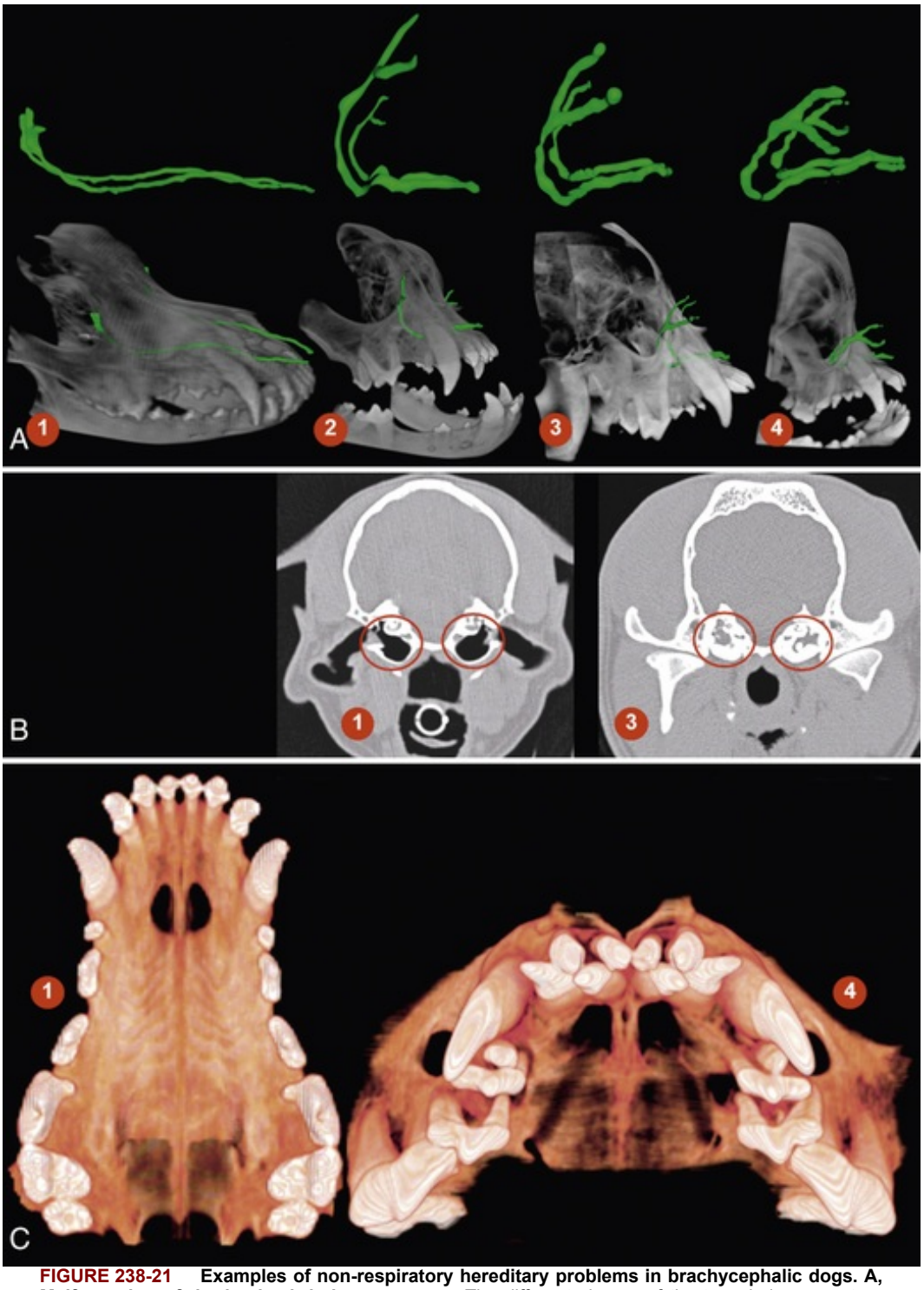

FIGURE 238-21 **Examples of non-respiratory hereditary problems in brachycephalic dogs. A, Malformation of the lacrimal drainage system:** The different shapes of the tear drainage system (green) in a (1) normocephalic dog (Rhodesian Ridgeback) and three brachycephalic dog breeds; (2) English Bulldog; (3) French Bulldog; (4) Pug.[121] **B, Malformation of the middle ear:** CT images showing the air-filled physiologic bulla tympanica with a thin ventral bony boundary in a (1) normocephalic dog (Poodle) and the fluid-filled bulla with a malformed bony structure in a (3) French Bulldog. **C, Malformation of the upper jaw:** three-dimensional CT images showing the physiologic superior dental arch of a (1) normocephalic dog (Beagle) and the impact of an undersized upper jaw on the dental arch and tooth position in a (4) Pug.

Owners of brachycephalic breeds should be educated in the specific features of thermoregulation in dogs and its impairment in brachycephalic animals in particular. Using the "meat-in-the-box-model," it can be explained why obesity worsens upper airway obstruction and why keeping the dog lean often helps to reduce

breathing problems. Dogs with pronounced problems in a warm environment can be put in a tub with water prior to a walk in order to wet their haircoat.

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CHAPTER 239

Diseases of the Larynx

Catriona M. MacPhail

Client Information Sheet: Laryngeal Paralysis and Laryngeal Collapse

Overview

Cartilage Anatomy

The cartilages surrounding the rima glottidis are called the larynx and include the paired arytenoids and the unpaired epiglottis, cricoid, and thyroid. Each arytenoid cartilage has a cuneiform process rostrally, a corniculate process dorsally, a muscular process dorsolaterally, and a vocal process where the vocal folds attach ventrally. The glottis consists of the vocal folds, the vocal process of the arytenoid cartilages, and the rima glottides. The laryngeal saccules are mucosal diverticula rostral and lateral to the vocal folds. Unlike dogs, feline arytenoid cartilages lack cuneiform and corniculate processes and true aryepiglottic folds. The sides of the epiglottis are connected directly to the cricoid lamina by laryngeal mucosa.

Muscles and Their Action

The intrinsic muscles of the larynx (cricoarytenoideus dorsalis, cricoarytenoideus lateralis, thyroarytenoideus, vocalis, ventricularis, arytenoideus transversus, hyoepiglotticus, and cricothyroideus) are responsible for laryngeal function. The cricoarytenoideus dorsalis muscle, solely responsible for opening the glottis, originates on the dorsolateral surface of the cricoid and inserts on the muscular process of the arytenoid cartilages. Contraction of this muscle results in external rotation and abduction of the arytenoid cartilages that pulls the vocal processes laterally. The caudal laryngeal nerve is the terminal segment of the recurrent laryngeal nerve, which innervates all but one of the intrinsic laryngeal muscles. The cricothyroid muscle is innervated by the cranial laryngeal nerve.

Laryngeal Function

The larynx regulates airflow, protects the lower airway from aspiration during swallowing, and controls phonation. Diseases most commonly affecting the larynx include paralysis, collapse, stenosis, and masses. Each of these conditions results in some degree of upper airway obstruction. Dogs and cats with any of these conditions are typically brought to their veterinarian due to respiratory stridor, voice change, coughing, or gagging. Progression of clinical signs is highly variable.

Canine Laryngeal Paralysis

Signalment and Etiologies

Acquired Disease

Laryngeal paralysis is a common unilateral or bilateral respiratory disorder that primarily affects older (>9 years) large and giant breed dogs. The Labrador Retriever is the most common breed reported to acquire this condition, but Golden Retrievers, St. Bernards, Newfoundlands, Irish Setters, and Brittany Spaniels are also overrepresented.[1] Acquired laryngeal paralysis, caused by damage to the recurrent laryngeal nerve or intrinsic laryngeal muscles, is most often attributed to a polyneuropathy, polymyopathy, accidental or iatrogenic trauma, or intra- or extrathoracic masses. Many other causes have been proposed (Box 239-1). In most dogs, cause is undetermined and classified as “idiopathic.” However, many dogs thought to have

idiopathic acquired laryngeal paralysis develop systemic neurologic signs within a year, consistent with a progressive generalized neuropathy.[2] Abnormalities in electrodiagnostic tests (see ch. 117) and histopathologic analysis of nerve and muscle biopsy specimens (see ch. 116) were consistent with a generalized polyneuropathy in a small number of dogs with acquired laryngeal paralysis.[3] Thus, it has been proposed that some dogs with idiopathic laryngeal paralysis have a progressive generalized polyneuropathy.[4,5] The abbreviation GOLPP (geriatric-onset laryngeal paralysis polyneuropathy) has been proposed as a more accurate term for dogs with acquired laryngeal paralysis, where other causes have been ruled out.[3,6]

Box 239-1

Proposed Etiologies of Laryngeal Paralysis

- Congenital
  - Genetic trait
  - Laryngeal paralysis—polyneuropathy complex
- Accidental trauma
  - Cervical penetrating wounds
  - Strangulating trauma
- Iatrogenic surgical trauma
  - Cranial thoracic surgery
  - Thyroidectomy/parathyroidectomy
  - Tracheal surgery
  - Ventral slot
- Cervical/intrathoracic neoplasia
  - Lymphoma
  - Thymoma
  - Thyroid carcinoma/ectopic thyroid carcinoma
- Neuromuscular disease
  - Geriatric-onset laryngeal paralysis polyneuropathy syndrome (GOLPP)
  - Endocrinopathy (hypothyroidism, hypoadrenocorticism)
  - Immune-mediated
  - Infectious
  - Myasthenia gravis
  - Polymyopathy
  - Systemic lupus erythematosus
  - Toxins (lead; organophosphates)

Congenital Disease

A congenital form of laryngeal paralysis has been reported in Bouviers des Flandres, Siberian Huskies, Bull Terriers, and white-coated German Shepherd Dogs.[7,8] An autosomal dominant trait in Bouviers des Flandres causes recurrent laryngeal nerve Wallerian degeneration and nucleus ambiguus abnormalities.[9] Although precise modes of inheritance are not established, hereditary predispositions have been identified in Siberian Husky dogs, Alaskan Malamutes, and crosses of those two breeds.[10,11] Laryngeal paralysis-polyneuropathy complexes have been described in Dalmatians, Rottweilers, Leonberger dogs, and Pyrenean Mountain Dogs.[12-15]

Clinical Signs

If the arytenoid cartilages and, consequently, the vocal folds remain in a paramedian position during inspiration, an upper airway obstruction is created called *laryngeal paralysis.* Dogs typically have noisy inspiratory respiration and exercise intolerance. Early clinical signs include voice change, mild coughing, and gagging. Severe airway obstruction results in respiratory distress, cyanosis, and collapse. Some have signs of dysphagia. Progression of clinical signs is highly variable, and dogs may have clinical signs for several months to years before worrisome respiratory distress ensues. Clinical signs are usually worsened by

exercise, high environmental temperature, and/or humidity. These factors can contribute to an acute exacerbation of a chronic condition. As respiratory rate increases, the mucosa covering the arytenoids obstructing airflow may become inflamed and edematous, causing further airway obstruction (see ch. 238). A vicious circle ensues that, if untreated, may become life-threatening.

Diagnostic Testing

Routine Testing

Diagnostic evaluation of dogs thought to have laryngeal paralysis includes physical examination, orthopedic (see ch. 353) and neurologic (see ch. 259) examinations, complete blood count (CBC), biochemical profile, urinalysis (UA), thyroid function screening (see ch. 299), thoracic radiographs, and laryngeal examination. Dogs with bilateral laryngeal paralysis are at risk of aspiration pneumonia both before and after surgery; therefore, thoracic radiographs are necessary in evaluating dogs suspected to have laryngeal dysfunction (see ch. 242). Radiographs are used to rule out aspiration pneumonia and to identify, if present, megaesophagus, pulmonary edema, cardiac, or lower airway abnormalities (Figure 239-1). Dogs with dysphagia or vomiting may be assessed with a positive contrast esophageal study to rule out dysfunction or megaesophagus, sometimes not apparent on survey thoracic radiographs (see ch. 273). Severe progressive esophageal dysfunction has been reported in a series of dogs with idiopathic laryngeal paralysis, consistent with the proposed generalized progressive polyneuropathy syndrome.[3] Acquiring information from esophagography should be weighed against potential risk of aspiration.[16] Hypothyroidism occurs concurrently in up to 30% of dogs with acquired laryngeal paralysis, although a direct causal link has not been established.[1,17] Thyroid function screening is considered important when evaluating a dog for laryngeal paralysis and supplementation begun if indicated, although this does not seem to improve the clinical signs associated with laryngeal paralysis (see ch. 299).

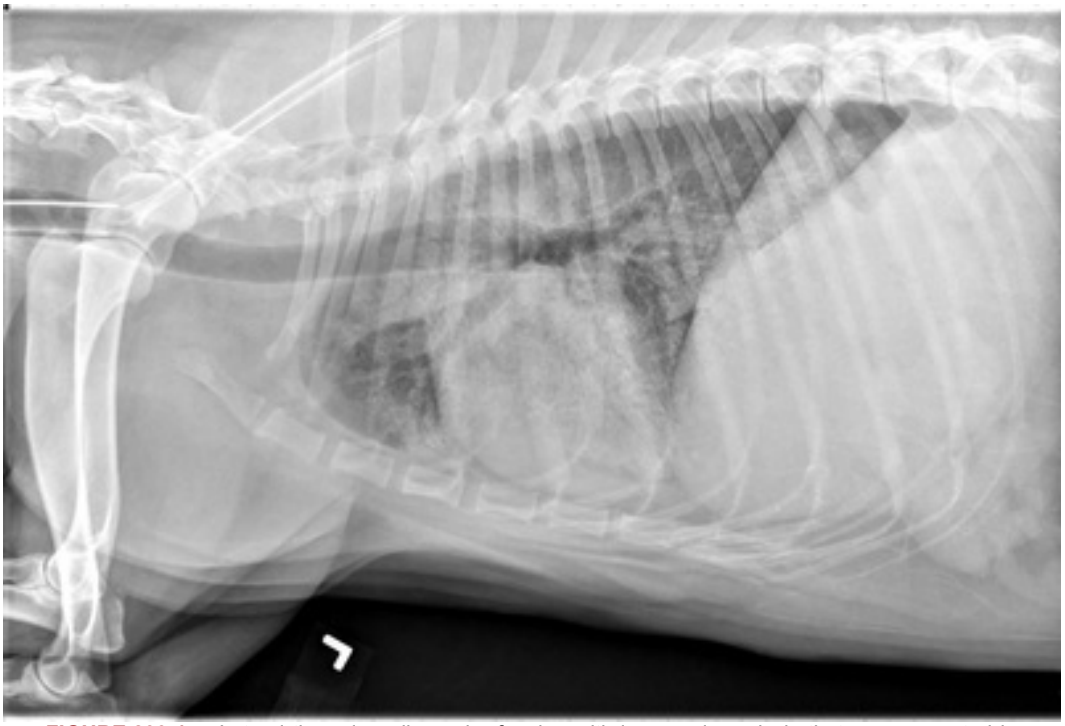

FIGURE 239-1 Lateral thoracic radiograph of a dog with laryngeal paralysis that was presented in acute crisis with noncardiogenic pulmonary edema.

Definitive Diagnosis

Definitive diagnosis of laryngeal paralysis requires examination of the larynx to document lack of arytenoid abduction during inspiration (Video 239-1) . This can be accomplished by direct visualization of the larynx

with a simple laryngoscope, oral video-endoscopic laryngoscopy, transnasal laryngoscopy (TNL), ultrasound (US; echolaryngography), or computed tomography (CT). Findings indicative of laryngeal paralysis on US include asymmetry or absence of motion of the cuneiform processes, abnormal arytenoid movement, paradoxical movement, caudal displacement of the larynx, and laryngeal collapse.[18] CT findings in dogs with laryngeal paralysis included failure to abduct the arytenoid cartilages and collapse into the rima glottis on inspiration, stenosis of the laryngeal inlet, and air-filled lateral ventricles.[19] Laryngoscopy, regardless of method, can be confounding as false-positive results are common due to the influence of anesthetic agents and sedatives (see Video 239-1). Echolaryngography, TNL, and CT avoid need for heavy sedation or general anesthesia. However, none of these tools has been shown to be superior to traditional oral laryngeal examination for definitive diagnosis.[20]

Traditional Oral Laryngeal Examination

Laryngeal paralysis should not be diagnosed based solely on the lack of arytenoid movement; inflammation and swelling of the laryngeal cartilages may also be apparent. Diagnosis may be challenging when there is paradoxical arytenoid movement, resulting in a false-negative result because the arytenoid cartilages move inward during inspiration due to negative intraglottic pressure created by breathing against the glottic obstruction. The cartilages then passively return to their original position during the expiratory phase, creating the impression of abduction. An assistant should state the phase of ventilation during laryngoscopy to help distinguish normal from abnormal motion.

Anesthetic Agents *(Box 239-2)*

Intravenous thiopental administered to effect was believed to be the best choice to allow assessment of laryngeal function; however, thiopental is not currently manufactured. Propofol is the most often used induction agent for laryngeal examination in dogs, even though significant respiratory depression often occurs with this drug, with apnea related to dosage, speed of injection, and use of concurrent premedications. While ketamine has been shown to better preserve laryngeal function in people over thiopental, a recent study found no benefit for laryngeal examination when combining propofol and ketamine; no dosage reduction in propofol was achieved and respiratory depression was more marked.[21] Alfaxalone (2-4 mg/kg IV), a safe and effective anesthetic induction agent in dog, can be used as an alternative to propofol.[22] While alfaxalone still causes respiratory depression, apnea is less likely.[23] However, no study has evaluated the effect of alfaxalone on laryngeal function. Doxapram HCl (1 mg/kg IV) has been advocated for routine use during laryngoscopy to increase respiratory rate and effort and improve intrinsic laryngeal motion. Doxapram significantly improves the ability to discriminate normal from abnormal function.[24,25]

Box 239-2

Drugs Used During Functional Laryngeal Examination

Premedications:
- Glycopyrrolate: 0.005-0.01 mg/kg IV, IM, SC ***and***
- Butorphanol: 0.2-0.4 mg/kg IV, IM, SC ***or***
- Buprenorphine: 0.005-0.02 mg/kg IV, IM, SC ***or***
- Hydromorphone: 0.1-0.2 mg/kg IV, IM, SC

Induction:
- Propofol: 4-8 mg/kg IV, administered slowly
- Alfaxalone: 2-4 mg/kg IV, administered slowly

To stimulate respiration:
- Doxapram HCl: 1-2 mg/kg IV

To decrease laryngeal swelling:
- Dexamethasone: 0.1-1 mg/kg IV

Treatment

Acute Respiratory Distress

Initial treatment for acute respiratory distress is directed at improving ventilation, reducing laryngeal edema,

and minimizing stress (see ch. 139). Typical treatment regimens involve oxygen supplementation (see ch. 131) and use short-acting steroids (e.g., dexamethasone) and/or sedatives (e.g., acepromazine) (see ch. 138). Administration of buprenorphine or butorphanol may be considered (Box 239-3). These dogs are often hyperthermic, and appropriate cooling procedures should be instituted (see ch. 134). If respiratory distress cannot be abated, intubation or a temporary tracheostomy should be considered. However, use of a temporary tracheostomy tube in dogs with laryngeal paralysis has been shown to be a negative prognostic indicator following surgery, as dogs that received a temporary tracheostomy preoperatively were more likely to experience major complications.[1] The presence of a tube within the tracheal lumen causes epithelial erosion, submucosal inflammation, and inhibition of the mucociliary apparatus from the level of the tracheostomy to the bifurcation. Mucus production dramatically increases, and the tube must be suctioned and cleaned frequently to prevent clogging. Intensive monitoring is required of any patient with a temporary tracheostomy tube, to avoid life-threatening complications. Complications (clinical and incidental) have been documented in 86% of dogs with a temporary tracheostomy.[26] 16 different complications were noted, but the most significant and frequent (≈25%) were airway obstruction, tube dislodgement, aspiration pneumonia, and stoma swelling.

Box 239-3

Drugs Used for Acute Respiratory Distress

To decrease laryngeal swelling:
- Dexamethasone 0.1-1 mg/kg IV

To abate anxiety:
- Acepromazine 0.01-0.02 mg/kg IV
- Buprenorphine 0.005-0.01 mg/kg IV
- Butorphanol 0.1-0.25 mg/kg IV

Conservative Long-Term Treatment

Often, dogs are not severely affected clinically until they have bilateral laryngeal paresis or paralysis. Therefore, dogs with unilateral laryngeal dysfunction are not surgical candidates. The goal of conservative management of dogs with laryngeal paralysis is to improve the quality of life through environmental changes, reduction of daily exercise, owner education, weight loss (see ch. 176 and 359), and consideration of antiinflammatory drugs to minimize laryngeal swelling. Unfortunately, this medical treatment path has proven inadequate for long-term management. Dogs diagnosed with concurrent hypothyroidism should be supplemented, but this rarely improves the clinical signs of laryngeal paralysis.

Surgery

Overview

For dogs with bilateral laryngeal paralysis, the decision to recommend surgery is based on the dog's quality of life, severity of clinical signs, and time of year. Surgical intervention is indicated in dogs severely affected by laryngeal paralysis. Numerous techniques have been described. Unilateral arytenoid lateralization is the technique employed by most surgeons, but various types of partial laryngectomy (bilateral vocal fold resection, partial arytenoidectomy) are also performed. Bilateral arytenoid lateralization is not recommended due to unacceptable morbidity.[1] Other techniques include castellated laryngofissure, reinnervation of the laryngeal musculature, and permanent tracheostomy. Castellated laryngofissure is performed rarely because it is technically difficult and outcomes have been inconsistent. Reinnervation does not provide immediate clinical relief and is not practical. Permanent tracheostomy is considered a salvage procedure for dogs most at risk of aspiration pneumonia but is associated with a high rate of major and minor complications and requires diligent postoperative and long-term care. In a series of 21 dogs with permanent tracheostomies, 50% had major complications, 20% required revision surgery, and 26% acutely died, most likely from airway obstruction.[27]

Unilateral Arytenoid Lateralization

Several variations of unilateral arytenoid lateralization have been described. The most common technique

involves suturing the cricoid cartilage to the muscular process of the arytenoid cartilage, mimicking the directional pull of the cricoarytenoid dorsalis muscle and rotating the arytenoid cartilage laterally (Figure 239-2). An alternative technique involves suture placement from the muscular process of the arytenoid cartilage to the caudodorsal aspect of the thyroid cartilage. This pulls the arytenoid cartilage laterally rather than rotating it and increases the area of the rima glottidis to a lesser degree than the cricoarytenoid suture.[28]

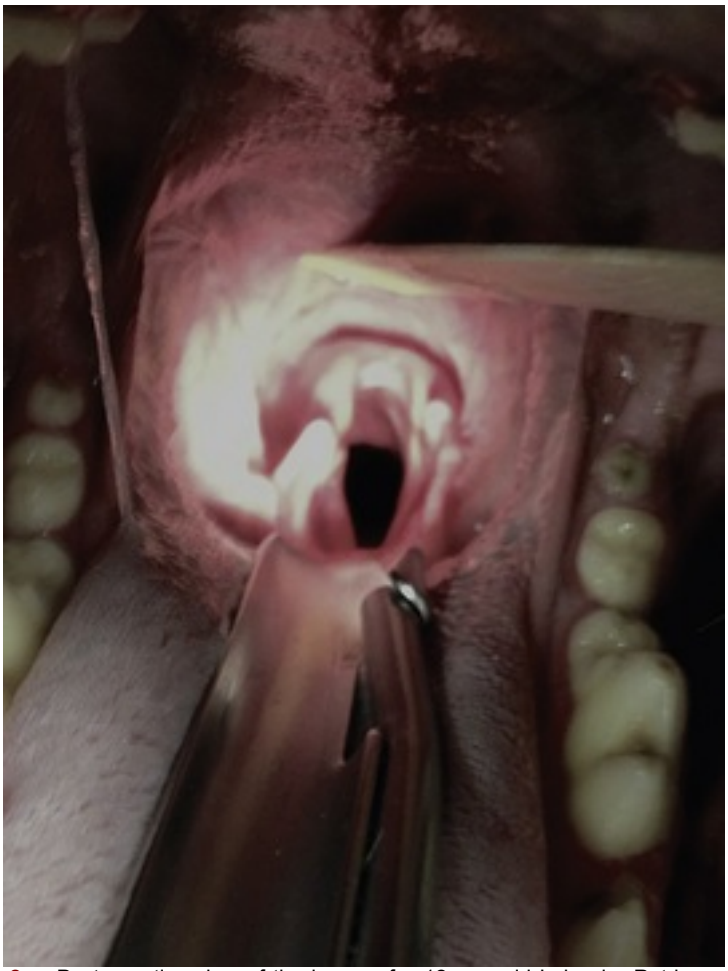

FIGURE 239-2 Postoperative view of the larynx of a 12-year-old Labrador Retriever following left unilateral arytenoid lateralization.

Differences in surgical technique and the degree of increase in surface area of the rima glottidis do not appear to affect postoperative clinical signs and outcome. Increasing the surface area of the rima glottidis beyond the edges of the epiglottis may put dogs at higher risk of aspiration. Limited lateral displacement of the arytenoid cartilage significantly reduces airway resistance within the larynx and may decrease risk of postoperative aspiration pneumonia.[29] This is accomplished by minimizing dissection: separation of the cricothyroid articulation, transection of the sesamoid band connecting the paired arytenoid, and complete disarticulation of the cricoarytenoid joint are not necessary. A partial opening of the cricoarytenoid articulation allows accurate visualization of needle placement through the muscular process of the arytenoid but limits the degree of cartilage abduction. Outcomes are similar to other reports.[30]

Partial Laryngectomy and Bilateral Ventriculocordectomy

Partial laryngectomy encompasses various techniques for vocal cord excision and partial arytenoidectomy aimed at increasing glottis diameter. This procedure has been associated with complications: laryngeal webbing, laryngeal scarring, and aspiration pneumonia. High complication rates have been reported by some; however, bilateral vocal fold resection alone resulted in fewer complications and better postoperative outcome than other partial laryngectomy techniques because it allows better laryngeal protection during

swallowing and decreased laryngeal irritation because the corniculate processes of the arytenoid cartilages are left intact.[1,31-33] Bilateral vocal fold excision and thyroarytenoid lateralization performed through a ventral laryngotomy improved clinical signs and were associated with a low rate of aspiration pneumonia; however, recurrence of clinical signs is common, likely because of narrowing of the rima glottidis.[34] Successful partial arytenoidectomy by photoablation of the left arytenoid cartilage tissue using a diode laser has been reported.[35] Bilateral ventriculocordectomy via ventral laryngotomy has a reasonable long-term outcome (>6 months) with a low incidence of major complications (7%).[33] A direct comparison of outcome between dogs treated with either unilateral arytenoid lateralization or bilateral ventriculocordectomy found dogs that had bilateral ventriculocordectomy were more likely to have chronic lifelong respiratory complications.[36]

Aspiration Pneumonia and Other Complications

Aspiration pneumonia (see ch. 242) is the most common complication in dogs surgically treated for laryngeal paralysis: 10 to 21% of dogs undergoing unilateral arytenoid lateralization.[1,37,38] Although aspiration pneumonia is most likely in the first few weeks after surgery, it has been recognized that these dogs are at risk for the rest of their lives. Factors that have been found to be significantly associated with a higher risk of developing complications and a negative effect on long-term outcome include preoperative aspiration pneumonia, development of esophageal dysfunction, progressing generalized neurologic signs, temporary tracheostomy placement, and concurrent neoplasia. In one study, 10 of 32 dogs had neurologic signs at the time of enrollment into the study, but all dogs had neurologic signs by one year.[2] In the absence of surgical complications, unilateral arytenoid lateralization results in less respiratory distress, less stridor, and improved exercise tolerance. Owner satisfaction with this procedure has been excellent, with the majority believing that the quality of their dog's life was improved dramatically.[1,37]

Feline Laryngeal Paralysis

Laryngeal disease is uncommon in cats, but laryngeal paralysis constituted 40% of cases.[39] Clinical presentation is similar to that of dogs: It occurs most often in middle-aged to older cats (mean 9 to 14 years), and both unilateral and bilateral conditions have been documented. Significant unilateral dysfunction has been reported in 10 to 57% of affected cats. A prevalence of left-sided unilateral laryngeal paralysis is similar to that reported in humans and horses.[39-41]

The specific cause of laryngeal paralysis in cats often is not known. Several cases have been associated with trauma, neoplastic invasion, or iatrogenic damage (post-thyroidectomy). Neoplastic infiltration can lead to fixed laryngeal obstruction with both inspiratory and expiratory dyspnea and noise. Neoplasia should always be considered in the differential diagnosis of laryngeal paralysis in the cat. In addition to traditional laryngoscopy (direct or endoscopically), the use of echolaryngography has been described for diagnosis of laryngeal paralysis in cats.[39,42]

Cats with unilateral laryngeal paralysis can have severe respiratory distress, often requiring surgery. Conservative management of cats with laryngeal paralysis consists of weight loss (see ch. 176) and minimizing excitement/exercise (see ch. 359). Reported survival in 7 cats treated conservatively for laryngeal paralysis ranged from 120 to 2520 days with a median survival of 811 days.[39] Successful surgical treatment, primarily using unilateral arytenoid lateralization, has been described. The reported median survival time was approximately 150 days.[39-41]

Laryngeal Collapse

Definition and Signalment

Laryngeal collapse is a consequence of chronic upper airway obstruction, most often associated with "brachycephalic airway syndrome," in reference to the condition of obstructive airway distress attributable to anatomic abnormalities of breeds such as English Bulldogs, Pugs, Boston Terriers, and Cavalier King Charles Spaniels (see ch. 238). Laryngeal collapse can occur alone or in association with laryngeal paralysis, nasal and nasopharyngeal obstruction, or trauma in both brachycephalic and mesaticephalic breeds. Concurrent laryngeal paralysis and laryngeal collapse have been reported in a small set of nonbrachycephalic small-breed dogs.[43] Norwich Terriers, specifically, have laryngeal abnormalities: redundant supra-arytenoid folds,

laryngeal collapse, everted laryngeal saccules, and narrowed laryngeal openings.[44] Rhinomanometry has been used to demonstrate that Norwich Terriers have skull dimensions consistent with both brachycephaly and mesaticephaly.[45] Chronic upper airway obstruction increases airway resistance and negative intraglottic luminal pressure. Over time, this results in laryngeal collapse due to cartilage fatigue and degeneration. However, early-onset laryngeal collapse is seen in brachycephalic dogs as young as 4.5 to 6 months of age.[46]

Clinical Stages of Severity

There are three stages of severity for laryngeal collapse. Stage 1 is the eversion of the laryngeal saccules into the glottis, increasing inspiratory effort, creating a vacuum, and causing the mucosa of the laryngeal saccules to prolapse. Once the saccules are everted, the tissue is exposed to highly turbulent airflow, resulting in edema and inflammation, which further obstructs the airway. In most studies regarding brachycephalic airway syndrome, everted laryngeal saccules are present in 50-60% of affected dogs.[47-49] In stage 2, the cuneiform processes of the arytenoid cartilages lose rigidity and collapse into the laryngeal lumen. In addition, the aryepiglottic folds also collapse ventromedially (Figure 239-3). The most advanced phase of laryngeal collapse is stage 3, in which the corniculate process of each arytenoid cartilage fatigues and collapses toward midline, causing complete laryngeal collapse.

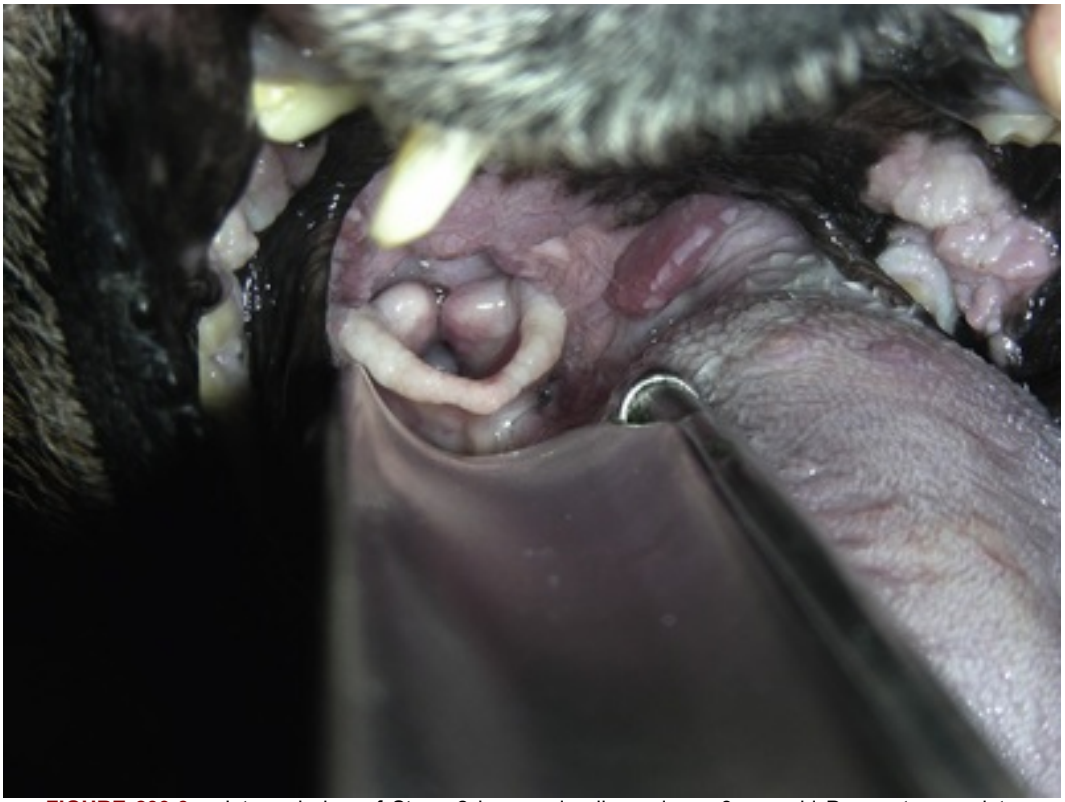

FIGURE 239-3 Intraoral view of Stage 2 laryngeal collapse in an 8-year-old Pug; note complete collapse of cuneiform processes into laryngeal lumen.

Diagnosis

Diagnosis of laryngeal collapse requires oral laryngeal examination under heavy sedation or a light plane of general anesthesia without intubation. Functional and structural examination of the larynx should be performed. CT imaging and three-dimensional internal rendering was used to document laryngeal collapse in 9 dogs with no sedation or general anesthesia required.[50]

Treatment

The early stage of laryngeal collapse is amenable to surgical treatment. Resection of the everted laryngeal saccules is relatively simple as each saccule is grasped with Allis tissue forceps and then transected with Metzenbaum scissors. Options for treating advanced stages of laryngeal collapse are limited. Underlying components of brachycephalic airway syndrome should be addressed and degree of improvement assessed. Dogs with stage 2 and 3 laryngeal collapse have been shown to markedly benefit from surgical removal of everted laryngeal saccules, reduction of elongated soft palates, and correction of stenotic nares (see ch. 238).[49] Unilateral arytenoid laryngoplasty (cricoarytenoid lateralization combined with thyroarytenoid caudolateralization) has been reported to have reasonable long-term outcomes in a small number of brachycephalic dogs with laryngeal collapse, but this technique should be used with caution as the opposite cartilage may continue to collapse medially.[51] Permanent tracheostomy is recommended when dogs do not respond to other medical or surgical treatment, although many owners consider this an unacceptable option due to the high risk of complications and degree of maintenance required.

Laryngeal Stenosis

Acquired laryngeal stenosis most commonly occurs as a complication following bilateral ventriculocordectomy. Other causes include traumatic tracheal intubation, foreign body, or caustic trauma. The most common clinical sign associated with laryngeal stenosis is exercise intolerance, but inspiratory stridor and respiratory distress occur. Ventriculocordectomy performed through an oral approach can lead to laryngeal webbing from scar tissue formation (cicatrix) as the mucosal defects are left to heal by second intention. This procedure is most commonly performed for devocalization (debarking). The American Veterinary Medical Association opposes devocalization except as a final alternative to euthanasia after behavioral modification to correct excessive vocalization has failed and after discussion of potential complications from the procedure with the owner.[52]

Ventriculocordectomy as a treatment for laryngeal paralysis is best performed through a ventral laryngotomy incision so that the mucosa on each side can be closed primarily, decreasing the risk for scar formation. A similar procedure is performed to treat laryngeal stenosis.[53] A ventral midline approach is made through the thyroid cartilage to gain access to the glottis. The scar tissue is sharply excised back to healthy mucosa rostral and caudal to the web. This mucosa is sutured using a 3-0 to 5-0 rapidly absorbable suture (e.g., poliglecaprone 25, glycomer 631, polyglactin 910) in a simple continuous or simple interrupted pattern. A temporary soft silicone intraluminal stent (keel stent) can be inserted through the thyroid cartilage to separate the healing mucosal surfaces but is often not necessary except in small dogs.[54] Regardless, laryngeal web resection with mucosal apposition has been reported to have a good to excellent outcome.[53]

Laryngeal Masses

Tumors

Description

Tumors of the larynx are uncommon in dogs and cats. Numerous tumor types have been reported in dogs: rhabdomyosarcoma (oncocytoma), squamous cell carcinoma (Figure 239-4), adenocarcinoma, osteosarcoma, chondrosarcoma, chondroma, myxochondroma, lipoma, fibrosarcoma, undifferentiated carcinoma, extramedullary plasmacytoma, and mast cell tumor (see ch. 345, 346, 348, and 349). Squamous cell carcinoma and lymphoma are the most common laryngeal tumors in cats, but adenocarcinoma and other poorly differentiated round cell tumors have been reported.[55]

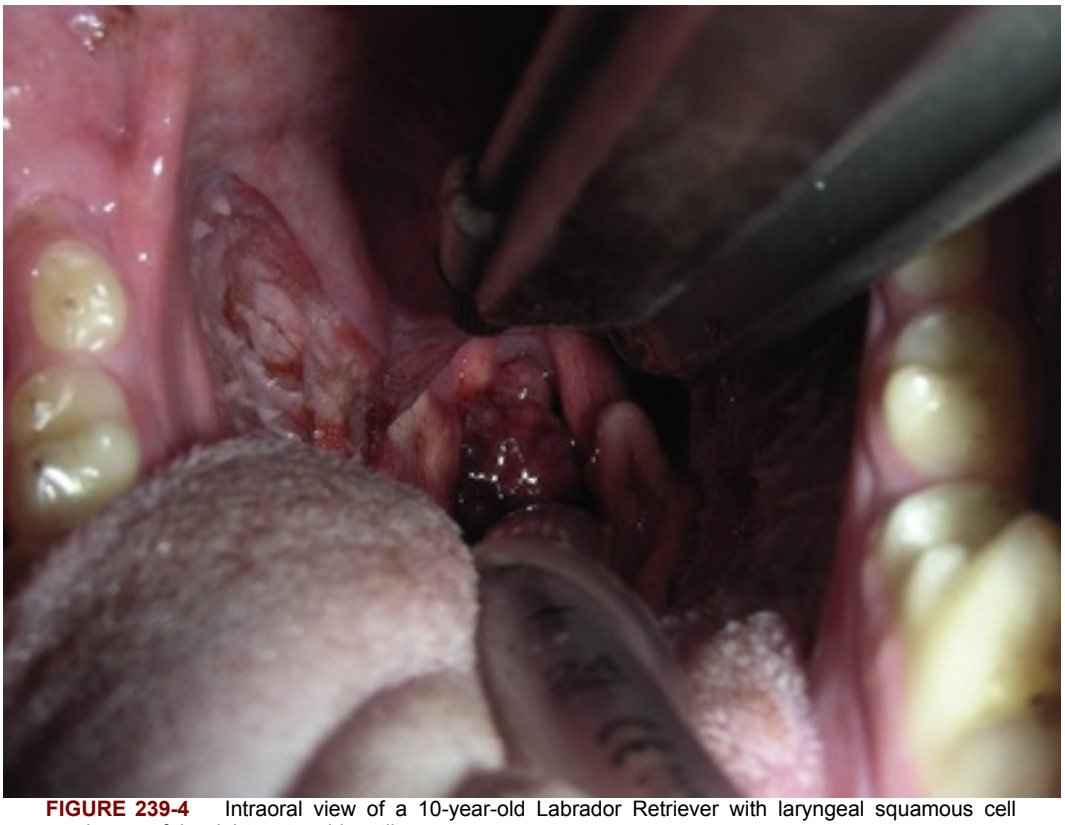

FIGURE 239-4 Intraoral view of a 10-year-old Labrador Retriever with laryngeal squamous cell carcinoma of the right arytenoid cartilage.

Treatment

Small masses may be removed by mucosal resection, partial laryngectomy through an oral approach, or ventral laryngotomy. Cartilaginous tumors (chondroma or chondrosarcoma) can be excised with reasonable success.[56,57] Aggressive intervention involves complete laryngectomy with permanent tracheostomy but has been reported rarely. Radioresponsive tumors may be treated with radiation therapy (see ch. 340). Otherwise, most treatment is palliative, consisting of airflow bypass of the laryngeal area through a permanent tracheostomy.

Prognosis

Prognosis for laryngeal tumors is guarded as most cases are quite advanced at the time of diagnosis. There are only isolated reports of management of canine and feline laryngeal tumors. Treatment of 4 cats with laryngeal squamous cell carcinoma with tube tracheostomy alone resulted in a median survival of only 3 days; chemotherapeutic treatment of 5 cats with laryngeal masses resulted in a median survival of 141 days.[58] Two cats with laryngeal lymphoma treated with chemotherapy survived 60 and 1440 days.[55] In this same study, 1 cat with laryngeal squamous cell carcinoma was treated with prednisolone and had a survival time of 180 days. One study reported on the placement of permanent tracheostomies in 5 cats with laryngeal carcinoma.[59] Survival ranged from 2 to 281 days. Two cats died from tracheostomy site occlusion, and 3 were euthanized because of disease progression.

Inflammatory Laryngeal Disease

Inflammatory laryngeal disease is an uncommon nonneoplastic condition of the arytenoid cartilages in both dogs and cats. It can be granulomatous, lymphocytic-plasmacytic, or eosinophilic. Multiple factors likely contribute to disease development. Severe cases can have laryngeal stenosis and significant upper airway obstruction. Biopsy of the mass is crucial to differentiate this disease from neoplasia, although it is still possible that inflammatory changes may represent a secondary response to underlying neoplasia. Treatment of inflammatory laryngeal disease is palliative: debulking the mass, steroid therapy, or permanent

tracheostomy. Permanent tracheostomy has been associated with a higher mortality in cats with inflammatory laryngeal disease than in cats undergoing permanent tracheostomy for any other reason.[60]

Benign Laryngeal Cysts

Benign laryngeal cysts have been described in a few dogs and cats.[61,62] Cysts are typically epithelial in origin and stem from the ventral aspect of the larynx. Surgical removal is usually curative. Some cysts are very large and can significantly obstruct airflow.

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Respiratory Disease

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CHAPTER 240

Clinical Evaluation of the Respiratory Tract

Stephan Anthony Carey

Introduction

The goal of evaluating a dog or cat with respiratory signs is to obtain a specific diagnosis by the least invasive means. First, one should *verify* that the historical and current clinical signs are consistent with respiratory disease or dysfunction. Then, *localizing* the dysfunction to a specific region or regions within the respiratory system is important. Once respiratory disease has been verified and localized, the tools used to *specify* the exact nature of respiratory disease often become more invasive (e.g., diagnostic respiratory sampling) and expensive (e.g., advanced imaging, endoscopy).

History and Signalment

Overview

The diagnostic approach to a dog or cat with respiratory signs begins in the exam room. Knowledge of breed- and age-specific conditions often helps streamline the localization process. Signalment alone may allow prioritization of a differential list. Juvenile, immunocompromised, or unvaccinated pets are more likely to have an infectious disease. Disorders known or suspected to have a heritable or genetic etiology will often be breed specific (e.g., chronic pulmonary fibrosis in the West Highland White Terrier, congenital laryngeal malformation of Norwich Terriers, asthma in Siamese and Havana Brown cats).[1-3] Conformation may also lend clues. For example, brachycephalic dogs often have thickened and elongated soft palates, stenotic nares, tracheal hypoplasia, or other issues that contribute to airway obstruction.[4,5] Dolichocephalic dogs are overrepresented in categories such as nasal tumors and aspergillosis.[6,7]

Clinicians should strive to obtain a complete and detailed history, including some concept of when the patient was last normal. Understanding any progression, rate of change, or patterns of when or where clinical signs are noted can help. Willingness to demonstrate a clinical sign to an owner (e.g., reverse sneezing) may also help identify the cause of signs. Owners should be encouraged to video their pet when normal and when demonstrating signs. Questions should be crafted to not only localize respiratory dysfunction but also to verify that the respiratory system is the source of the dysfunction (e.g., coughing vs. retching in cats). One may need to confirm that clinical signs previously attributed to other organ systems are actually respiratory (e.g., vomiting vs. post-tussive retching in dogs).

Historical Findings Suggestive of Respiratory Disease

Sneezing

Sneeze (see ch. 27) is defined as an involuntary protective expiratory reflex following irritation of the nasal mucosa that can be difficult to stifle. During a sneeze, the head usually moves sharply downward. This can help clients differentiate between sneezing and reverse sneezing (below). Sneezing is usually an acute response to irritation and often decreases or stops completely in chronic or progressive nasal cavity disease, obstruction, or irritation.

Reverse Sneezing

The reverse sneeze is a voluntary or involuntary process, involving paroxysms or series of strong, abrupt inspiratory efforts (snorts). Reverse sneezing is a response to obstruction or irritation of the nasopharynx. When reverse sneezing, pets are often walking or standing, neck extended, head tilted backward, lips pulled backward, and nostrils flared (see ch. 238). These postural efforts elongate the nasopharynx and can widen

the nasopharyngeal meatus maximally. Paroxysms may last for seconds to a few minutes and they may occur at night or while the pet is at rest, when the nasopharynx narrows. Although not typically associated with respiratory distress, episodes can be quite alarming.

Nasal Discharge

Nasal discharge (see ch. 27) usually follows an increase in nasal cavity fluid secretions, a change in quality or viscoelastic properties of nasal secretions, impaired nasal mucociliary clearance, or any combination of these conditions. When seen, nasal discharge should be characterized by its appearance and consistency (mucoid, serous, hemorrhagic, etc.). This information may help localize the source of, or reason for, the discharge. Importantly, nasal discharge may not always be obvious. Cats and some dogs can be fastidious groomers, removing discharge before owners see it. In these cases, the nasal planum may become ulcerated or hyperkeratotic, and the hair surrounding the nasal planum may be lost due to licking or pawing at the nose. Also, normal nasal airway mucociliary clearance moves secretions from the nasal cavity back toward the nasopharyngeal meatus and the larynx, resulting in an upper airway cough. Overt nasal discharge from the nostrils will not become apparent until the amount or character of the secretions exceeds the mucociliary clearance capacity or until the mucociliary clearance apparatus has been sufficiently damaged or impaired (e.g., *Bordetella* [see ch. 227 and 229], *Mycoplasma* or parainfluenza virus [see ch. 228] infections, squamous metaplasia [see ch. 238]).[8,9] Nasal discharge may also be a manifestation of nonrespiratory disease (e.g., esophagopharyngeal reflux).[10]

Open-Mouth/Postural Breathing

Postural changes reflect attempts to decrease airway resistance by increasing airway cross-sectional area.[11] In dogs, open-mouthed breathing is a common response to upper airway obstruction. In cats, open-mouthed breathing is rare, indicating that the respiratory system's ventilatory reserve capacity is approaching exhaustion. Extending the head and neck minimizes bending in the trachea and pharynx. Flaring the nostrils and opening the mouth minimize inspiratory resistance at the inlet. Animals may also minimize extraneous (nonrespiratory) activity and eliminate actions that exacerbate airway narrowing (swallowing, vocalizing) (see ch. 28).

Audible Respiratory Sounds

Respiratory noises that are audible to clients without the aid of a stethoscope are almost always due to airway obstruction and are usually upper airway in origin (nasal cavity, nasopharynx, oral cavity, larynx, extrathoracic trachea). Since stress and sympathetic tone associated with a hospital visit may facilitate airway opening, it is common for respiratory noises present at home to be absent in the exam room. Owners should be asked to describe whether noises are continuous (stridor) or discontinuous (stertor), constant (fixed obstructions) or intermittent (dynamic or episodic obstructions), and if intermittent, what events precipitate the noise (exercise, sleep, etc.). Having owners provide videos when respiratory noises are produced can be helpful both in characterizing the sound and evaluating the patient's posture during the event. While the determination of the phase of respiration during which the noise occurs is extremely valuable information, it can be difficult for clients to reliably make this type of assessment.

Cough

Cough (see ch. 26) is a defense mechanism that protects lower airways, usually triggered by inhalation of noxious substances or irritants, or by accumulation of substances in any portion of the larynx or tracheobronchial tree. The sound of a cough originates from the larynx as a result of the acute expulsion of intrapulmonary air through a closed glottis. Dogs and cats with irritation or stimulation originating from different regions of the tracheobronchial tree may exhibit subtle differences in the quality of their coughing.

Differences in coughing sounds may be helpful in localizing site and nature of the stimulus. For example, cough originating in alveoli or small airways (bronchopneumonia, chronic bronchitis) is usually preceded by a deep inspiration. Paroxysms may start quietly and grow louder as tracheobronchial secretions are moved up to the central airways (crescendo). These coughs may be productive or nonproductive and are frequently followed by a post-tussive retch, or swallowing of raised secretions. Cough originating in the central airways (trachea, mainstem bronchi) is often associated with a "goose honk" sound, as air is forcefully expelled through segments of narrowed or collapsed airways. Paroxysms of tracheal coughing are often "nonprogressive:" In tracheal coughing, each one sounds like the preceding one, triggers the subsequent one, and the episodes may be quite prolonged (see ch. 241). Cough may also be elicited with stimulation of the

larynx, trachea, and bronchi by postnasal drainage of nasal secretions or oral cavity contents. With laryngeal coughing, the stimulus is often abrupt and unanticipated, causing reflex laryngospasm. This prevents deep inspiration prior to starting the cough and typically results in a rapid-fire cough that may be weak or ineffective due to the small volume of air expelled. These coughs may also be followed by voluntary efforts to clear the upper airways (gagging). Technically, this mechanism is referred to as an *expiratory reflex* rather than a cough reflex, but it is often included in descriptions with other forms of cough.[12]

Coughing can be induced by airway narrowing during expiration, as a result of pleural space disease (primarily dogs; see ch. 245), cardiomegaly (dogs; see ch. 251), or intrinsic airway narrowing secondary to dynamic small airway disease (chronic bronchitis [dogs and cats], asthma [cats]; see ch. 241), tracheal collapse (primarily dogs), or restrictive lung diseases (see ch. 242). These coughs are typically triggered at higher tidal flows and may only be noticed during exercise in early stages of disease but may become more noticeable as cardiopulmonary reserves diminish. Cough "afferents" may originate outside the lower airways. These would include the nose, nasopharynx, paranasal sinuses, ear canals, diaphragm, and pericardium.[13] The exact role of afferents in these locations is not entirely known; however, their presence suggests that extrapulmonary sites may also be important sources of cough.

Physical Examination of the Respiratory Patient

General Observations

Respiratory signs may be due entirely or in part to intrinsic respiratory disease. However, such signs may represent respiratory manifestations of dysfunction in other organ systems (e.g., gastrointestinal, central nervous system (CNS), cardiovascular, hematologic, adrenal, thyroidal). In addition, the stress associated with a nonrespiratory illness may unmask occult respiratory disease, particularly in cats. Therefore, it is always important to perform a complete physical exam whenever patient stability allows. Examination should begin with close observation of the dog or cat at rest, if possible. With stable patients, this should occur while obtaining the history. Patients can be removed from their carriers or unsecured from leashes in an enclosed exam room, allowing them to wander. Respiratory rate, effort, noises, patterns and posture are assessed. If the pet is in respiratory distress (see ch. 28 and 139), it is still prudent to obtain at least a cursory assessment of respiratory pattern and posture prior to handling the patient.

Breathing Patterns

Normal

During normal respiration, the chest wall and abdominal wall move out together during inspiration and in together during expiration. This coordinated movement allows maximal lung expansion with minimal effort during inspiration. Diaphragmatic contraction, passive muscle relaxation, and elastic lung recoil provide expiration.[14] Normal ratios of inspiratory time: expiratory time during tidal breathing are from ≈1 : 1 to 1 : 2. Some animals at rest may exhibit a pronounced pause at the end of expiration, during which no chest or abdominal wall movements are detectable. Increased respiratory workload may result in altered breathing patterns. These alterations are subconscious responses to minimize work of breathing. They vary as a result of the nature of the increased respiratory burden (Figure 240-1).

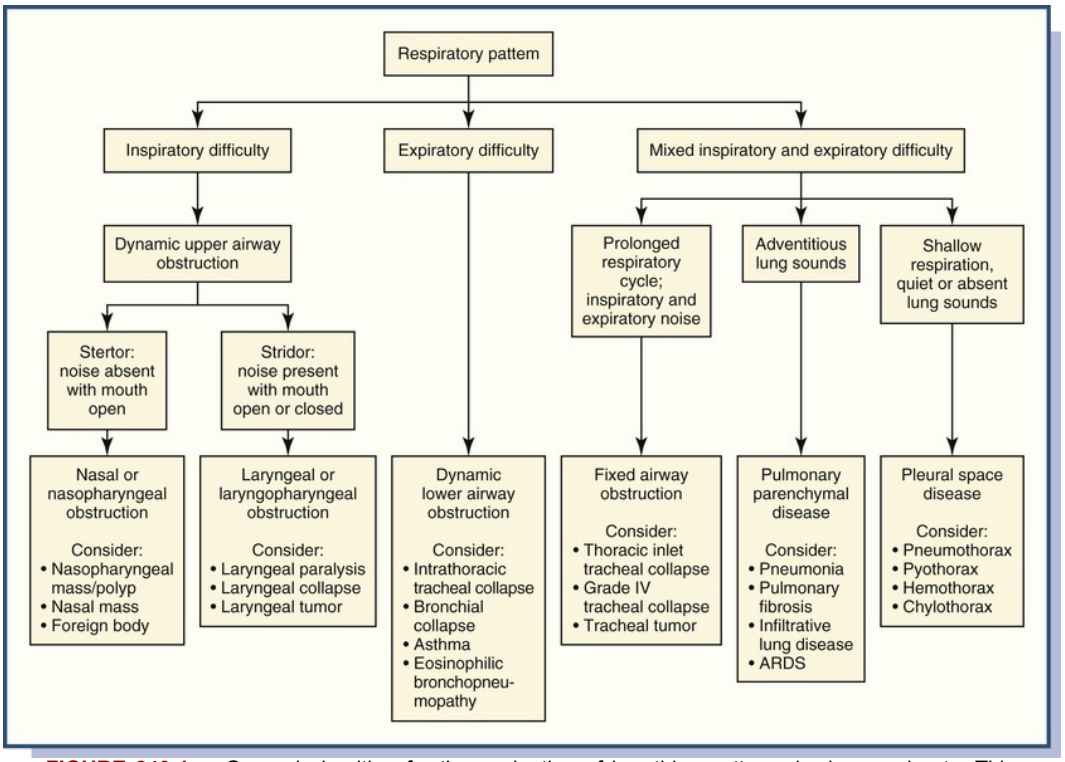


FIGURE 240-1 General algorithm for the evaluation of breathing patterns in dogs and cats. This algorithm is intended to provide general guidelines toward the assessment of respiratory patterns. Exceptions to this algorithmic approach exist. *ARDS*, Acute respiratory distress syndrome.

Obstructive and Restrictive Lung Diseases

Airway *obstruction* causes increased airway resistance or an increase in the pressure necessary to generate airflow. The increase in respiratory effort can exacerbate airway collapse and worsen airflow obstruction. Extrathoracic obstructions (e.g., laryngeal tumors, laryngeal paralysis, nasal or nasopharyngeal obstruction [see ch. 238]) are typically associated with an increase in inspiratory effort and inspiratory noise, while intrathoracic obstructions (small airway disease, mucous plugging, intrathoracic tracheal collapse) are associated with an increase in expiratory effort and expiratory noise. A common compensatory strategy for pets with airway obstruction is to decrease the velocity of airflow to minimize any propensity for airway collapse. The result is slow, deep respirations, often with prolongation of the inspiratory phase with extrathoracic (upper airway) obstructions and expiratory phase prolongation with intrathoracic obstructions.

Restrictive lung disease results in decreased lung compliance or a change in lung volume associated with a measured increase in airway pressure. Pets with conditions causing restrictive breathing patterns (bronchopneumonia, pulmonary fibrosis, pleural space disease) require higher airway pressures to fully expand their lungs. Because the increased workload is associated with lung expansion, restrictive lung or pleural space diseases may be compensated by decreasing tidal volumes and increasing respiratory rates. The result is rapid, shallow breathing.

Obstructive and restrictive conditions each increase the work of breathing. With time, this increased effort can result in respiratory muscle fatigue and a *paradoxical* breathing pattern. As respiratory muscles fail, the negative intrathoracic pressure generated during inspiration will tend to suck the chest wall in. Diaphragmatic fatigue or paralysis can lead to abdominal muscle recruitment, causing outward movement of the abdominal wall during expiration. These chest and abdominal wall movements are the opposite of those seen normally and can be indicative of severe or longstanding respiratory dysfunction. In dyspneic dogs and cats, paradoxical breathing has been strongly correlated with the presence of pleural space diseases (see ch. 244).[15] The presence of this clinical sign can help to prompt implementation of appropriate emergency diagnostic and therapeutic procedures (see ch. 139).

Posture

Pets experiencing significant respiratory compromise may adopt a posture that helps maximize the efficiency

of breathing or decrease airway resistance by increasing airway cross-sectional area and facilitating chest wall expansion. Extending the head and neck reduces redundancy and obstruction in the pharynx. Flaring the nostrils opens the nasal valve (ostium internum). Breathing through an open mouth bypasses nasal and nasopharyngeal resistance altogether and often represents significant loss of cardiopulmonary reserve in cats. Some may sit or prefer to remain sternal with their elbows abducted. Pets may also minimize extraneous activity and eliminate actions that exacerbate airway narrowing (swallowing, vocalizing).

Respiratory System Examination

General

Physical examination of the respiratory system often confirms the historical and observed concerns, but in some cases the history may be vague and overt respiratory signs subtle or absent. Thorough respiratory system examination includes the nasal area (muzzle, head, eyes, dental arcade, hard palate, nasal airflow), oral cavity, palpation of the larynx and trachea, thoracic compression, and auscultation of the thorax and thoracic inlet. Examination of the nasal cavity usually entails visual inspection and palpation of the muzzle, head, eyes, and hard palate for conformation, symmetry, and defects. The external nares and rostral aspect of the nasal passages can be visually inspected for mucous membrane color and for presence and character of any nasal discharge. Each nasal cavity should be evaluated for patency and airflow by holding cotton or gauze in front of each nostril to detect air movement or by placing a refrigerated glass slide in front of the nose during nasal breathing, watching for condensation from each nostril. The hard palate and upper dental arcade should be inspected and palpated, as invasive nasal disease may extend into the oral cavity, and dental disease (e.g., tooth root abscesses) may have nasal manifestations. Eye palpation and retropulsion should be performed to assess symmetry. Invasive nasal tumors or destructive mycotic rhinitis may extend into the orbit. The oral cavity should be inspected for mucous membrane color, capillary refill time, and hydration. The tonsils, tongue, sublingual area, and hard palate should be examined for defects or lesions that may cause airway obstruction and pharyngeal function assessed by checking for a gag reflex. Palpation of the submandibilar and medial retropharyngeal lymph nodes, an otoscopic examination (see ch. 85), and an ophthalmic examination (see ch. 11) are indicated. Signs of systemic or infectious diseases may be first noted on nasal or ophthalmic examination (fungal disease, hypertension).

Sounds

Evidence of upper airway conditions include stertor, stridor, and decreased or absent nasal airflow. Stertor, a discontinuous, low-pitched fluttering sound that usually originates from the nasopharyngeal meatus, is typically associated with inspiratory dysfunction but may be present during both phases of respiration. Because the nasopharyngeal meatus tends to narrow during rest, stertor may be more pronounced at night. Stridor is a continuous, high-pitched inspiratory sound, usually produced as a result of narrowing of the larynx or extrathoracic trachea. In contrast to stertor, stridorous respiratory noise may be absent at rest but exacerbated with large volume airway flows (exercise, panting, etc.). Lower airway conditions may cause adventitious sounds (wheezes, crackles), as well as changes in the character of normal bronchovesicular sounds. Normal inspiratory flow reaches peak velocity near the end of inspiration and normal expiratory flow reaches peak velocity near the beginning of the expiratory phase. Thus, thoracic auscultation of normal airflow is typically loudest at end inspiration and early expiration. Normal bronchovesicular sounds detected via auscultation are primarily generated by laminar flow through larger central airways and are filtered by the alveoli, pleural space, and chest wall. Changes in the volume (increased or decreased) or pattern of bronchovesicular sounds can be early indicators of respiratory disease, even in the absence of adventitious lung sounds. Increased detection of bronchovesicular sounds can occur as a result of increased respiratory effort, while decreases in bronchovesicular sounds can be the result of structural alterations in the pulmonary interstitium, alveoli, or pleural space.

Adventitious respiratory sounds indicate an abnormality. Wheezes (continuous, musical sounds associated with intrathoracic airway narrowing) are usually associated with expiratory dysfunction. High-pitched wheezes can be detected with narrowing of the lower airways or small airways, while low-pitched wheezes may indicate larger airway narrowing. Crackles ("rales;" discontinuous, "popping" sounds most audible during inspiration) represent an equilibration of pressures between two regions of an obstructed airway. Fine crackles, typically alveolar or bronchiolar in origin, are usually loudest near the end of inspiration. Loud, moist crackles often are the result of airflow through airway secretions in central airways, detected throughout inspiration or just during expiration.

A decrease or absence of respiratory sounds can occur as a result of the accumulation of air, fluid, or viscera

within the pleural space (see ch. 28 and 244). Pets with pleural space disorders may exhibit a shallow, rapid (restrictive) breathing pattern. The location of the loss of breath sounds should provide clues as to the nature of the pleural space disorder. Loss of respiratory sounds ventrally is consistent with a fluid accumulation (e.g., blood, pus, transudate, chylous effusion). Loss of breath sounds dorsally is most consistent with pneumothorax. Most pleural space disorders in dogs and cats are bilateral due to their incomplete mediastinums. However, tissue accumulations (e.g., mesothelioma) or visceral herniations may result in asymmetrical auscultation findings.

In many cases, respiratory noises or clinical signs that are present at home may not be present in the exam room. The tremendous reserve capacity of the cardiopulmonary system may necessitate the use of provocative testing during a physical exam. Detection of cardiopulmonary abnormalities may be enhanced by inducing a "sigh" during auscultation (close the mouth and partially obstruct the nostrils for 4-5 breaths), by triggering a cough with gentle tracheal palpation, or with light or moderate exercise. Having owners video- and audio-record abnormalities at home can also help clinicians to accurately verify and localize respiratory disease prior to the implementation of more invasive and expensive diagnostic testing.

Laboratory Diagnostic Techniques

Initial Data Base: Complete Blood Count (CBC), Serum Biochemistries, Urinalysis

Selecting appropriate tests to better understand and manage a pet with respiratory disease depends on the history, signalment, physical examination results, differential diagnoses, and owner choices or limitations. Results of the initial database can help narrow or prioritize likely causes for the signs. Results may also facilitate selection of more advanced diagnostics. On a CBC, polycythemia can result from chronic hypoxemia and tissue hypoxia. Neutrophilic leukocytosis is common in pets with airway infection (canine infectious respiratory disease, feline upper respiratory disease), and those with bronchopneumonia may have either leukocytosis or, in the acute stages, leukopenia. Peripheral eosinophilia is common in dogs with eosinophilic bronchopneumopathy and is occasionally observed in pets with parasitic lung disease, fungal diseases, and in cats with asthma (see ch. 241). Lymphocytosis in a young pet with respiratory disease and fever is consistent with a viral condition. Hypercalcemia in a patient with respiratory signs may be suggestive of a neoplastic or fungal etiology.

The initial database also allows assessment for nonrespiratory diseases that can impact the respiratory system (e.g., hyperadrenocorticism, pancreatitis, severe metabolic acidosis) or may unmask respiratory disease. A systemically ill pet with respiratory distress, an inflammatory leukogram, and hypoalbuminemia may suggest the acute respiratory distress syndrome (ARDS). Severe hypoalbuminemia can lead to pleural effusion and/or ascites with accumulation of a transudate in those cavities. This can cause an increase in respiratory effort. Thrombocytopenia, thrombocytopathia, coagulopathy, and systemic hypertension can all result in pulmonary hemorrhage, hemorrhagic effusions, or epistaxis.

Serologic and Other Advanced Testing

Serologic, urine antigen, fecal, and polymerase chain reaction (PCR) tests can be employed in pets suspected of having infectious or parasitic causes of their respiratory signs. Infectious etiologies (see ch. 227-230) may be influenced by age, geographical location, travel history, lifestyle (e.g., outdoor vs. indoor cats), presence of comorbid nonrespiratory symptoms, or a "herd" health scenario (e.g., multiple affected puppies within a litter, multiple patients from the same boarding facility or shelter, a cat affected after introduction of a new kitten in a household). Recurrent airway or respiratory infections due to opportunistic pathogens are consistent with immunodeficiency. For example, diagnosis of refractory or recurrent nasal cryptococcosis in a cat may warrant testing for feline leukemia virus and feline immunodeficiency virus, while recurrent rhinitis, tracheobronchitis, and pneumonia in a young dog may prompt an investigation for primary ciliary dyskinesia or heritable immunoglobulin deficiencies.[16-18]

The method and timing of sample collection are important factors to consider when screening for infectious or parasitic causes of respiratory disease with laboratory testing, particularly for PCR testing (see ch. 227, 229, and 234). Samples collected for PCR should be obtained using polyester-tipped swabs, as residues found in cotton-tipped or calcium alginate swabs may inhibit PCR assays for the pathogen or pathogen genome. Collection of superficial mucosal samples may yield false-negative results with viral (e.g., canine respiratory coronavirus) or facultative intracellular bacterial (e.g., *Mycoplasma cynos*) pathogens. Pathogen shedding may

cease prior to resolution of clinical signs (e.g., canine influenza virus). PCR testing after the organism has been cleared may yield a false-negative result. In all cases, steps should be taken to ensure that the timing and method of sample collection is appropriate for the differentials being considered (Box 240-1).

Box 240-1

Common Fungal, Viral, Bacterial, and Protozoal Causes of Infectious Respiratory Disease in Dogs and Cats Detectable by Polymerase Chain Reaction Assay

Fungal

Blastomyces
Coccidioides
Cryptococcus
Histoplasma
Aspergillus
Pneumocystis

Viral

Canine distemper virus
Canine adenovirus-2
Canine herpesvirus
Canine parainfluenza virus-2
Canine respiratory coronavirus
Canine influenza virus (H3N2 and H3N8)
Pandemic influenza virus (H1N1)
Canine pneumovirus
Feline herpesvirus-1
Feline calicivirus

Bacterial

Bordetella bronchiseptica
Chlamydia felis
Mycoplasma cynos
Mycoplasma felis
Streptococcus equi subsp. Zooepidemicus

Protozoal

Toxoplasma
Neospora
Acanthamoeba

Diagnostic Imaging of the Respiratory System

Overview

Investigation of suspected respiratory disease relies extensively on diagnostic imaging of the upper airways (nasal cavity, pharynx, larynx, trachea), lower airways (bronchi, bronchioles), pulmonary parenchyma (vasculature, interstitium, alveoli), and nonrespiratory structures (heart, spine, ribs, sternum, abdomen, etc.). Thoracic radiography is the common first assessment. Alternative imaging modalities can provide additional levels of detail and dimension (computed tomography [CT] or magnetic resonance imaging [MRI] scans); an assessment of dynamic airway function in real-time (fluoroscopy, ultrasonography); or be indicative of regional lung function (nuclear imaging). Diagnostic imaging studies should be completed before more invasive procedures (rhinoscopy [see ch. 96 and 238], nasal biopsies [see ch. 96 and 238], bronchoalveolar lavage [see ch. 101]) to avoid iatrogenic hemorrhage and disruption of anatomic structures affecting imaging results.

Radiography of the Upper Respiratory Tract

Introduction

Anatomically, the upper airway extends from the tip of the nose to the thoracic inlet. In animals, investigation of clinical signs and respiratory noises suspected to be localized in the upper airways relies heavily on imaging the upper airway (nasal cavity, pharynx, and larynx; see ch. 238 and 239) and nonrespiratory structures (skull, dental arcade, bony orbits, lymph nodes, salivary glands). Because much of this region lies within the confines of the skull (nasal cavity, nasopharynx) or is surrounded by overlapping soft-tissue structures (larynx, cervical trachea), advanced imaging may be required to confirm abnormalities. Positioning is critical, and motion artifacts must be avoided. Thus, upper airway imaging studies are best performed under heavy sedation or general anesthesia.

Nasal, Facial

Nasal radiographs can be helpful in localization and characterization of intranasal disease (see ch. 238). Nasal and sinus radiographs, however, rarely identify a specific cause for disease (an exception would be a radiopaque foreign body). Benefits of nasal radiographs include the ability to detect asymmetry, bony destruction, and soft tissue opacity in the nasal cavity and surrounding structures. High-quality nasal radiographs can be obtained with minimal cost and no specialized equipment. Nasal radiographs should include a minimum of two orthogonal views. Standard views include dorsoventral, open-mouth ventrodorsal (occlusal), and lateral. Specialized views (oblique lateral view, "skyline" view) can be extremely valuable in detecting frontal sinus and auditory bulla involvement. Dental radiographs can provide detailed information about the involvement of the maxillary dental arcade and tooth roots in the pathogenesis of nasal disease. Nasal radiographs, however, lack the sensitivity and level of detail obtained with CT or MRI scans. The complexity of the canine and feline skull can make detection of early or subtle nasal lesions difficult. While not technically challenging, patient positioning is extremely important because poor positioning provides images of little value or could lead to misdiagnosis.

Pharynx, Larynx, and Cervical Trachea *(see ch. 238, 239, and 241)*

Radiography of the lateral skull or neck is usually adequate when respiratory signs are localized to these areas (e.g., stridor, gagging, ineffective coughing, change or loss of voice). The specific area of interest should be centered in the image to minimize the degree of parallax when viewing symmetrical paired structures (e.g., auditory bulla, arytenoid cartilages). Positioning is critical in evaluating such radiographs, as even the slightest obliquity can make interpretation difficult. Images centered over the larynx are most useful in the assessment of laryngeal stridor, while images centered over the midcervical region are preferred in the assessment of suspected cervical tracheal collapse. Investigation of suspected cervical or thoracic inlet tracheal collapse should also include both inspiratory and expiratory lateral views to document dynamic collapse (when fluoroscopic or tracheoscopic evaluation is not available).

Thoracic Radiography

Technique and Positioning

Survey thoracic radiographs with at least two orthogonal views (a lateral and a ventrodorsal or dorsoventral) may aid in localizing lower airway, parenchymal, and pleural space conditions. Studies including both lateral views and an orthogonal view are ideal. Dependent lung lobes on lateral views tend to collapse due to heart and diaphragm compression and decreased thoracic wall movement during the respiratory cycle.[19] There are occasional cases in which both ventrodorsal (e.g., accessory lobe disease) and dorsoventral (e.g., caudal lobar pulmonary vascular enlargement) projections may be indicated. Positioning and technique are particularly important for evaluation and interpretation of intrathoracic (lungs, heart, mediastinal content) and extrathoracic structures (ribs, spine, sternebrae). Any of these areas may contribute to signs of a respiratory condition. Care should be taken to ensure that the cranial limbs are pulled forward to avoid superimposition over the cranial thorax on lateral projections. Views should be collimated to include the entire pulmonary fields, the cranial abdomen, and the thoracic inlet. Thoracic structures have inherent movement due to respiratory motion and the cardiac cycle, so the length of exposure for thoracic imaging should be kept as brief as possible while still providing adequate contrast.

Classification of Pulmonary Radiographic Abnormalities

Pulmonary radiographic abnormal patterns are interstitial, bronchial, and/or alveolar (see ch. 242). Interstitial pulmonary patterns are further characterized as unstructured or structured (nodular). Unstructured interstitial patterns have a generalized increase in pulmonary parenchymal background opacity and a decreased distinction of the pulmonary vasculature. Common causes of a diffuse interstitial pattern include viral or hematogenous pneumonias, pulmonary edema (cardiogenic and noncardiogenic), neoplastic infiltration (e.g., pulmonary lymphoma), and pneumonitis secondary to systemic diseases (e.g., uremic pneumonitis). Unstructured interstitial patterns may be artefactual due to poor radiographic technique, hypoventilation, or as a variant of normal in an obese patient.[20] Structured or nodular interstitial patterns appear as discrete or coalescing soft tissue nodules within the pulmonary fields. Nodular lesions >2 cm within the pulmonary parenchyma are usually called "pulmonary masses." Nodular lesions may be solitary or multiple and may appear as solid or cavitary. The size, appearance, and number of nodular interstitial lesions may help to narrow the differential list (Table 240-1).

TABLE 240-1

Causes of Interstitial Pulmonary Nodules and Masses

FINDING	CAUSE	PREVALENCE
Multiple solid nodules	Metastasis	Common
	Mycosis	Uncommon
	Septic emboli	Rare
Solitary solid mass	Primary tumor	Common
	Abscess	Rare
Multiple cavitary nodules	Metastasis	Rare
	Parasitic	Rare
	Bullae	Uncommon
Solitary cavitary mass	Primary tumor	Common
	Abscess	Rare
	Bulla	Uncommon

From Thrall DE: The canine and feline lung. In Thrall DE, editor: *Textbook of veterinary diagnostic radiology*, ed 6, St Louis, 2013, Elsevier, pp 608-631.

Alveolar Pulmonary Patterns

An alveolar pulmonary pattern occurs when the air within the alveoli is replaced with soft tissue or fluid, resulting in an overall increase in lung opacity. Pulmonary edema, hemorrhage, and inflammatory or neoplastic exudates are fluids that can replace alveolar air resulting in an alveolar pattern. Atelectasis, or the loss of alveolar air with resulting alveolar collapse, can also cause an alveolar pattern, which usually also results in a mediastinal shift toward the side of the atelectasis. Rarely, solid tumors can result in an alveolar pattern, either by replacing alveolar air or causing bronchial obstruction resulting in atelectasis. The radiographic hallmarks of an alveolar pattern include the presence of air bronchograms, a lobar sign, and soft tissue silhouetting (or border effacement) between the affected lung and the diaphragm, heart, or vasculature. Common causes of an alveolar pattern include bronchopneumonia, pulmonary edema (cardiogenic or noncardiogenic), hemorrhage, and atelectasis. Less common but important differentials for an alveolar pattern include severe inflammatory airway disease (e.g., eosinophilic bronchopneumopathy), pulmonary thromboembolism, and neoplasia (see ch. 242).

Bronchial Pulmonary Patterns

Bronchial pulmonary patterns occur when the bronchial walls become thickened or when the immediate peribronchial space becomes infiltrated with cells or fluid. Radiographically, thickened bronchi appear as rings of soft tissue density with air opacity in the center ("donuts"), or parallel radiopaque lines ("tram lines"). In addition to bronchial wall thickening, other consequences of bronchial disease may alter thoracic radiograph results. These include bronchiectasis, cranial or middle lung lobe atelectasis, and hyperlucent lung

fields due to air trapping and hyperinflation. Common causes for a bronchial radiographic pattern in dogs and cats include allergic airway disease (feline asthma, canine eosinophilic bronchopneumopathy), parasitic bronchitis/pneumonitis, and chronic bronchitis (see ch. 241). The radiographic appearance or distribution of similar conditions may differ between species, e.g., the classic radiographic appearance of left-sided congestive heart failure in dogs is a perihilar interstitial or alveolar pattern while the same condition in cats may be more of a patchy pulmonary distribution; dogs with bronchopneumonia often have a cranioventral alveolar pattern while cats usually have multifocal or patchy, asymmetrical, alveolar patterns (see ch. 242).

Pleural Effusion

The accumulation of fluid (blood, chyle, inflammatory or neoplastic exudates, transudates, modified transudates) within the pleural space can inhibit lung expansion leading to respiratory difficulty, hypoxemia due to hypoventilation, and respiratory distress. Signs can be severe if the fluid volume is large or if it develops rapidly. Presence of clinically significant pleural fluid can be detected with routine thoracic radiographs, understanding that about 100 mL of liquid must be present within the pleural space of a medium-sized dog before it becomes radiographically apparent.[21] Smaller volumes or localized accumulations may require additional imaging modalities (CT, ultrasound) to facilitate detection. Radiographic signs indicative of free pleural liquid include the appearance of pleural fissure lines between lung lobes, retraction of lung lobes away from the chest wall, rounding of the edges of dependent lung lobes, and obfuscation of the diaphragmatic and cardiac silhouettes (see ch. 244).

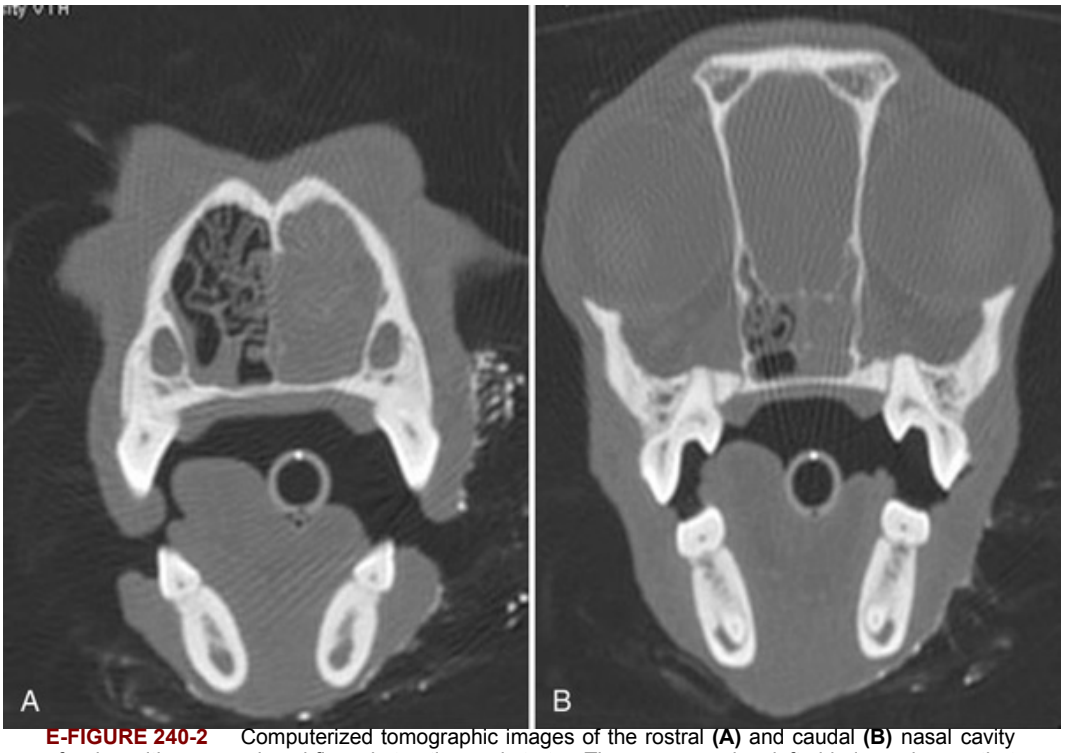
Pneumothorax

Air or other gases within the pleural space (pneumothorax) can cause severe respiratory distress and dysfunction. Air can accumulate within the pleural space from lung rupture, from a mediastinal condition, or from the outside through the chest wall. The most common radiographic appearance of pneumothorax is the retraction of lung lobes away from the thoracic wall on the lateral views.[22] Pneumothorax also causes secondary lung collapse or atelectasis, resulting in an apparent increase in lung opacity. Collapse of the dependent lung lobes on lateral views allows the heart to descend into the dependent hemithorax, resulting in a separation of the heart and the sternum ("floating heart"). Removal of pleural fluid or air via thoracocentesis prior to diagnostic imaging may be required for patient stabilization (see ch. 102) and can also improve the radiographic assessment of the lungs, heart, diaphragm, and mediastinum (see ch. 244 and 245).

Computed Tomography (CT)

Availability and Use in Nasal Conditions

Historically, CT scanning in pets required general anesthesia, but newer scanners with 32- or 64-row detectors can acquire a complete series of images within a few seconds. CT scanning can now be performed in critically ill or unstable pets without anesthesia.[23,24] Avoiding anesthesia allows evaluation of the anatomic position of upper airway structures without the interference of an endotracheal tube.[25] CT provides a detailed, three-dimensional (3-D) view of the nasal cavity, nasopharynx, and sinuses (E-Figure 240-2). Because of its higher sensitivity and resolution, CT is considered the test of choice for evaluating nasal disease (see ch. 238). CT images are excellent for detecting early nasal lesions and for determining the extent of an invasive process (e.g., extension into cribriform plate, orbital involvement). While rhinoscopy and nasal radiography are insensitive in distinguishing noninfectious rhinitis from neoplasia and/or mycotic rhinitis, CT provides valuable detail that may suggest one condition over another. CT is particularly sensitive in detecting changes in bony and cartilaginous structures associated with the nasal cavity. CT alone provides no better distinction of soft tissue structures versus fluid than nasal radiographs. Use of IV contrast enhancement of vascular structures and perfused tissues with CT, however, can aid in delineating the margins of invasive nasal tumors and can be used to distinguish between fluid or mucus accumulation versus soft-tissue structures. Measurements and 3-D reconstructions of CT images can be used to guide subsequent nasal biopsies and are used in planning of surgical approaches and radiation therapy protocols.



E-FIGURE 240-2 Computerized tomographic images of the rostral **(A)** and caudal **(B)** nasal cavity of a dog with progressive airflow obstruction and stertor. The scan reveals a left-sided nasal mass that extends caudally into the nasopharyngeal meatus. The patient was diagnosed with a nasal adenocarcinoma. (Images courtesy Michigan State University Veterinary Medical Center, East Lansing, MI.)

Thoracic CT

One of the major advantages of thoracic CT is the enhanced ability to detect and localize subtle pulmonary, mediastinal, and thoracic wall lesions that may contribute to respiratory signs. The same five radiographic opacities (gas, fat, soft tissue, mineral, and metal) detected on radiography are used in CT interpretations. CT, however, provides better contrast between adjacent opacities (e.g., between air-filled lungs and airway or chest wall) and has higher sensitivity to changes in density within a given opacity. CT (as small as 1 mm) is more sensitive than radiography (7-9 mm) for detecting pulmonary nodules.[26,27] These factors make thoracic CT a preferred method for lung evaluation when staging results may alter treatment recommendations. While CT findings cannot confirm a diagnosis, specific CT findings can strongly correlate with certain diagnoses. In people, a set of CT criteria has been established for a "reasonably accurate" diagnosis of idiopathic pulmonary fibrosis (IPF) with a reduced need for lung biopsy.[28] Similarly, the findings of ground-glass opacities, parenchymal bands, honeycombing, peribronchovascular interstitial thickening, and traction bronchiectasis, with a predominantly subpleural distribution of these lesions, are consistent with canine idiopathic pulmonary fibrosis (see ch. 242). The severity of these findings on CT may closely correlate with pulmonary functional abnormalities and disease severity.[29,30]

The 3-D nature of CT and the ability to obtain thin slices through respiratory structures also contributes to enhanced localization and resolution in the lower airways and alveoli. This level of detail makes CT useful not only in the detection of respiratory abnormalities, but provides methodology for the quantification of morphologic pulmonary lesions. Measurements of airway caliber and bronchial wall thickness relative to adjacent pulmonary arteries can be used to quantify bronchial wall alterations in chronic bronchitis and bronchiectasis.[31,32] Thin-slice CT images through the pulmonary airways can be reformatted into virtual bronchoscopic images used to guide bronchoscopic or surgical intervention.[33] The 3-D localization of pulmonary lesions also facilitates the collection of CT-guided, percutaneous fine-needle aspirates and needle biopsies of chest wall, pleural, and pulmonary lesions in dogs and cats (see ch. 93, 96, and 101).[34]

Magnetic Resonance Imaging (MRI)

MRI provides better resolution of soft-tissue structures than does radiography or CT. It is superior to radiography in the detection of subtle soft-tissue lesions, including early neoplasms and fungal granulomas, and can be used to readily distinguish between soft-tissue structures and accumulated fluid or mucus.[35,36] MRI performs similar to CT in assessment of chronic nasal disease and nasal neoplasia[37] and may be useful in differentiating among different types of nasal tumors.[35] A limitation of MRI is that, compared to CT, it is relatively insensitive in detecting bony or cartilaginous changes in the skull surrounding the nasal cavity. Due to technical and practical limitations, MRI is not well suited for pulmonary imaging. Most MRI sequences are affected by patient motion, so regions with inherent motion, i.e., the lower respiratory system, are not suited to standard MRI. Gas has very little signal on MRI, so gas-filled regions like the lungs tend to image poorly as compared with CT.[19] Other limitations, including cost and the need for specialized facilities, are similar to those of CT.

Fluoroscopy

Fluoroscopy allows real-time visualization of dynamic structures in the upper and lower respiratory tract at rest, when exhibiting a clinical sign (e.g., coughing), or during or immediately after possible triggering events (e.g., swallowing, running). Fluoroscopic studies of the upper airways can be performed during eating and drinking of food or liquid mixed with contrast material (swallowing studies) in cases where the transfer of ingesta across the pharynx may lead to respiratory symptoms. Examples include nasopharyngeal reflux in pets with postprandial sneezing or esophagopharyngeal reflux and aspiration as cause of recurrent bronchopneumonia (see ch. 238). Fluoroscopy is most useful in detecting dynamic tracheal and bronchial disease and is more sensitive than inspiratory and expiratory radiography in detecting dynamic collapse of the trachea, carina, and lobar bronchi. Fluoroscopy is more accurate in estimating magnitude and location of airway collapse.[38] Tracheal and/or bronchial collapse secondary to tracheobronchomalacia can be evaluated with fluoroscopy during tidal breathing, as well as during an elicited cough (Video 240-1). Coughing paroxysms can be elicited with gentle palpation of the cervical trachea. If cough cannot be easily elicited, then intrathoracic pressure can transiently be increased by briefly covering the mouth and nose during expiration. Fluoroscopy also allows assessment of cardiomegaly or cardiac movement as a cause of intrathoracic airway collapse.[39] Tracheal stents can be placed under fluoroscopic guidance, and fluoroscopy can be used as a follow-up procedure to monitor stent function (see ch. 121).

Ultrasonography (US)

Because almost all generated sound waves are reflected at soft tissue/air and bone/air interfaces, US is of limited utility in the evaluation of mural or intraluminal masses in the upper airways. US of the upper respiratory tract can aid in identifying extraluminal masses surrounding or impinging on the airway. US can be useful in determining both the origin (e.g., thyroid, laryngeal, lymph node) and the nature (e.g., fluid-filled, solid) of mass lesions around the upper airway. US has also been evaluated as a diagnostic tool for laryngeal paralysis and tracheal collapse.[40,41] US is sensitive in documenting morphologic abnormalities consistent with tracheal collapse and laryngeal paralysis but insensitive in documenting presence of comorbidities (e.g., laryngeal collapse, bronchial collapse) that must be considered prior to therapeutic interventions. Thus, US is one of several tools that can be used to collate information in determining cause of a respiratory condition. It can be used to identify and characterize chest wall and pleural abnormalities that may impact respiratory function, including pleural fluid or masses in the chest wall or pleural space (see ch. 244). US can be helpful in identifying and characterizing peripheral lung lesions, including pulmonary masses, lung consolidation, atelectasis, and abscesses. US guidance can facilitate collection of fine-needle aspirates of fluid or solid mass lesions and guide percutaneous biopsies from peripheral lung, pleural, or chest wall lesions (see ch. 238 and 239).[42]

Nuclear Imaging

Nuclear scintigraphy is performed by administering a radionuclide (usually technetium 99m [^{99m}Tc]) tagged to a pharmaceutical agent and detecting the radioactive decay. Radionuclide and its pharmaceutical agent are selected to ensure delivery to the region of interest. The primary advantage of nuclear imaging is the ability to provide regional assessments of lung function that are not available by more conventional imaging modalities. Radionuclides can be delivered IV to provide an assessment of regional pulmonary perfusion or

they can be delivered via nebulization to assess regional lung ventilation. Perfusion scans can be used in pets suspected of having pulmonary thromboembolic disease (PTE; see ch. 243). Pulmonary vascular scintigraphy is more sensitive and specific in detecting and localizing PTE than is angiography.[43] However, the cumbersome nature of scintigraphy and the requirement for isolation of potentially critically ill patients makes selective pulmonary angiography more commonly used for diagnosis of PTE. Combination of simultaneous ventilation and perfusion scans (V/Q scan) enables the calculation of regional ventilation-to-perfusion ratios, which can be used to localize areas of low V/Q within diffuse lung disease. V/Q scans can provide important information regarding regional lung function prior to interventional procedures such as lung biopsy or surgical lung lobectomy, as well as an assessment of the response to therapy. Intratracheal or intranasal deposition of ^{99m}Tc has also been used in the assessment of mucociliary transport in dogs and cats.[44-46] The primary limitation of nuclear imaging is poor spatial resolution, so the functional aspects of nuclear imaging are usually combined with other imaging modalities (e.g., CT) when planning intervention or monitoring responses to respiratory therapy.

Endoscopic Examination of the Respiratory Tract

See E-Box 240-2 and ch. 83, 96, 101, and 238.

E-Box 240-2

Endoscopic Examination of the Respiratory Tract

Rhinoscopy (also see ch. 96)

Rhinoscopy provides direct visualization of the lumen of the nasal cavity and nasopharynx. This type of examination is indicated as part of the diagnostic evaluation of any patient presenting with signs referable to the nasal airways (see discussion in main part of chapter). Rhinoscopy can provide information about the location, nature, and extent of nasal disease or airflow obstruction. Rhinoscopy, when combined with nasal cavity imaging (CT) and oral cavity examination, provides a complete evaluation of the nasal cavity. Rhinoscopy is typically performed after advanced imaging of the nasal airways, as the results of nasal CT can be used to guide the rhinoscopic examination, and because the presence of the endoscope can induce bleeding or mild mucosal alterations that may confound interpretation of CT images. Due to extremely sensitive nasal airway reflexes, rhinoscopy must be performed under deep anesthesia. The nasopharynx and caudal nasal cavity can be readily evaluated via retrograde rhinoscopy by maneuvering a flexible endoscope through the oral cavity and over the soft palate, or by visualizing the caudal nasopharynx via the oral cavity using a rigid endoscope with a 120-degree offset. The left and right nasal passages can then be examined via anterograde rhinoscopy by directing a rigid or flexible endoscope through the nares (see ch. 238). Mucosal abnormalities, space-occupying lesions, and excessive airway secretions can be visualized in the nasopharynx or nasal passages via rhinoscopy. Rhinoscopy can also be used to guide nasal biopsies.

In the normal nose, the frontal sinuses cannot be reached via routine rhinoscopy because the ostium entering the frontal sinus lies dorsal and caudal to the nasal cavity and is typically obstructed by normal endoturbinates. In disease processes associated with marked turbinate destruction (e.g., nasal aspergillosis; see ch. 234), the frontal sinuses can be evaluated endoscopically by directing a flexible endoscope through the nasal cavity and into the ostium of the frontal sinus. In cases where imaging studies indicate the presence of frontal sinus disease, but anterograde endoscopy of the sinuses is not possible, trephination of the frontal sinus can be used to gain endoscopic access to the sinuses, as well as to obtain biopsies and administer topical therapy.

Laryngoscopy/Pharyngoscopy (see also ch. 239)

Laryngoscopy and pharyngoscopy is indicated in patients presenting with upper-airway localizing signs, including voice change, stridor, stertor, inspiratory difficulty, or exercise intolerance. Laryngoscopy is useful in the diagnosis of the primary and secondary components of the brachycephalic obstructive airway syndrome (elongated soft palate, laryngeal collapse) and in the evaluation of laryngeal or pharyngeal abnormalities identified on radiographic or fluoroscopic examinations. Laryngoscopy is the test of choice for the diagnosis of laryngeal paralysis and congenital laryngeal malformation (e.g., Norwich Terriers) and is useful in documenting other structural and functional abnormalities of the

laryngeal cartilages and laryngeal mucosa in dogs and cats.[2,46]

Laryngoscopy and pharyngoscopy are most commonly performed via an oral approach under light, general anesthesia, although a transnasal endoscopic approach performed under sedation is also described.[47] Laryngoscopy is performed under light anesthesia, ideally prior to other respiratory diagnostics requiring a deeper plane of general anesthesia (e.g., tracheobronchoscopy, rhinoscopy, CT). Laryngoscopy should be performed with a depth of anesthesia adequate to allow relaxation of the mandible and inhibition of the gag reflex, but shallow enough to permit spontaneous respiration and maintain laryngeal tone and movement.

Direct visual inspection of the oral cavity, laryngopharynx, and larynx can be performed using a laryngoscope and light source. The use of a flexible or rigid endoscope allows closer inspection of the caudal oral cavity and larynx and facilitates recording of still images or video loops to document abnormalities. The oropharynx, laryngopharynx, tongue, tonsils, epiglottis, soft palate, and larynx should be visualized for shape, mucosal appearance, and motility. The epiglottic vallecula should be viewed to look for the abnormal accumulation of secretions or ingesta. The nasopharynx can often be examined by gently retracting the soft palate rostrally with a spay hook and visualizing the nasopharyngeal lumen with a dental mirror. The diagnosis of laryngeal paralysis relies on the documentation of impaired laryngeal abduction during the inspiratory phase of the respiratory cycle. The administration of doxapram (2.2 mg/kg, intravenously) during laryngeal examination has been shown to increase respiratory drive and intrinsic laryngeal motion in dogs and aids in the evaluation of laryngeal function,[48] but may also be associated with transient worsening of upper airway narrowing in dogs with laryngeal paralysis.[49]

Tracheobronchoscopy (see also ch. 101)

Direct visualization of the lower airways can be accomplished via tracheoscopy and bronchoscopy. In small animal patients, tracheobronchoscopy allows evaluation of the lumen and airway walls of the trachea, carina, principal bronchi, lobar bronchi, the segmental bronchi, and, depending on the size of the patient and the length of the bronchoscope, the first few generations of subsegmental bronchi. Most patients with clinical signs referable to the lower respiratory tract would benefit from bronchoscopy and/or ancillary procedures accompanying bronchoscopy (e.g., endobronchial biopsy, bronchoalveolar lavage). Bronchoscopy is the test of choice to determine the cause of unexplained cough, wheeze, and hemoptysis, to investigate radiographic pulmonary abnormalities (infiltrates, atelectasis, hyperlucency), and to assess airway integrity (tracheal/bronchial tears and rupture, bronchoesophageal fistula, tracheal/bronchial collapse, lung lobe torsion). Tracheobronchoscopy is the most reliable method for documenting the presence and grade of tracheal collapse (Video 240-2) and is also the only technique available to document collapse of the principal, lobar, and segmental bronchi.[50] Occasionally, bronchoscopy is also indicated for therapeutic intervention, including removal of foreign bodies, therapeutic lavage, and removal of excessive airway secretions.

Because of the sensitivity of the larynx and lower airways, tracheobronchoscopy must be performed under general anesthesia. In larger patients, the bronchoscope can be introduced through an endotracheal tube fitted with a T- or Y-shaped adapter that also allows concurrent delivery of oxygen and anesthetic gases. In smaller dogs and cats, bronchoscopy can be performed without endotracheal intubation. General anesthesia can be maintained with injectable anesthetic agents, and oxygen can be delivered to the patient through the working channel of the bronchoscope or through a tracheal catheter inserted adjacent to the bronchoscope.[51]

Diagnostic Sampling of the Respiratory Tract

Introduction

In dogs and cats with respiratory disease, results of the physical examination, history, laboratory testing, and radiographic imaging are often nonspecific. Further, it is difficult to perform pulmonary function testing in dogs and cats. Thus, collecting fluid or tissue samples directly from the respiratory tract for culture, cytology and/or histological evaluation can be quite valuable (see ch. 93). Specimens can be obtained from the nasal airways by swabbing, brushing, flushing, and closed biopsy. Bronchoalveolar lavage, endotracheal wash, and transtracheal wash are techniques used to collect fluid samples from the lower airways, while a variety of endoscopic, surgical, and thoracoscopic techniques are available for collection of tissue samples from the

lower respiratory tract (see ch. 96, 101, 102, 244, and 245).

Sampling of the Nasal Airways (see ch. 238)

Nasal Swabbing and Nasal Brushing

Nasal swabbing is a minimally invasive technique which often fails to yield accurate or specific diagnoses.[52] In many instances, collected cells are representative of superficial secondary inflammation and microorganisms representative of colonization rather than true infection.[53,54] For these reasons, culture of nasal swabs is rarely indicated and the utility of nasal swabs is limited to cytological diagnosis of certain specific conditions (e.g., nasal cryptococcosis in cats)[52,55] or for samples to be submitted for PCR testing for respiratory pathogens. Nasal swabbing is most used when a specific diagnosis is suspected. Brush techniques may yield cells that lie deeper within the nasal mucosa than those collected by nasal swabbing and may be more useful for separating inflammatory from neoplastic conditions.[56] However, both false-negative and false-positive results remain possible in identifying neoplastic nasal conditions with nasal brushing. Indications for nasal brushing are similar to those for nasal swabbing (see ch. 96).

Saline Hydropulsion

Saline hydropulsion utilizes a high-pressure saline flush to dislodge fragmented tissue samples from masses or lesions within the nasal airways and may also provide therapeutic benefit to some pets by mobilizing accumulated nasal secretions or debulking space-occupying lesions (see ch. 96).[57] When successful, saline hydropulsion can yield tissue samples suitable for histology, which increases the likelihood of reaching an accurate diagnosis. Because of the sensitivity of the nasal airways and sinuses plus the risk of aspiration, nasal flushing procedures should always be performed in anesthetized patients with a cuffed endotracheal tube in place.

Nasal Biopsy

Nasal biopsy samples can be procured by techniques that are less invasive than via surgery (see ch. 96). Specifically, pinch nasal biopsy using endoscopic forceps is relatively easy. Nasal biopsies can be collected via rhinoscopic guidance, CT guidance, or blindly. The high diagnostic yield of this method comes at the expense of the invasiveness of the procedure. Specific precautions must be taken to decrease likelihood of complications. Nasal biopsy is performed under general anesthesia to allow for repeated sampling and to ensure patient comfort. Samples collected via nasal biopsy can be ideal for both light microscopic evaluation and microbiological cultures. Nasal biopsies can also be a source of motile cilia for the diagnosis of ciliary dyskinesia via transmission electron microscopy. Coagulation status should be evaluated in all pets prior to nasal biopsy as bleeding is expected and can be serious (see ch. 80, 99, and 196).

Diagnostic Sampling of the Lower Airways

Bronchoalveolar Lavage (BAL)

BAL, performed under general anesthesia with or without bronchoscopic guidance, allows one to obtain samples from the alveoli, small distal airways, and the interstitium for cytology and/or culture (see ch. 93 and 101).[52,58,59] BAL is performed by wedging the tip of a bronchoscope into a small distal airway, instilling lavage fluid and then withdrawing as much fluid as possible. For nonbronchoscopic BAL, the pet is intubated with a sterilized endotracheal tube, avoiding oropharyngeal contamination as much as possible.[60] For cats and small dogs, a sterile 7- to 10-French polypropylene or red rubber catheter is used (Figure 240-3). The catheter should be at least as long as the distance from the tip of the nose to the last rib and, while maintaining sterile technique, advanced into the lumen of the endotracheal tube until resistance is encountered after it becomes wedged in a small airway. A sterile adapter may be necessary to tightly connect the catheter to a syringe.

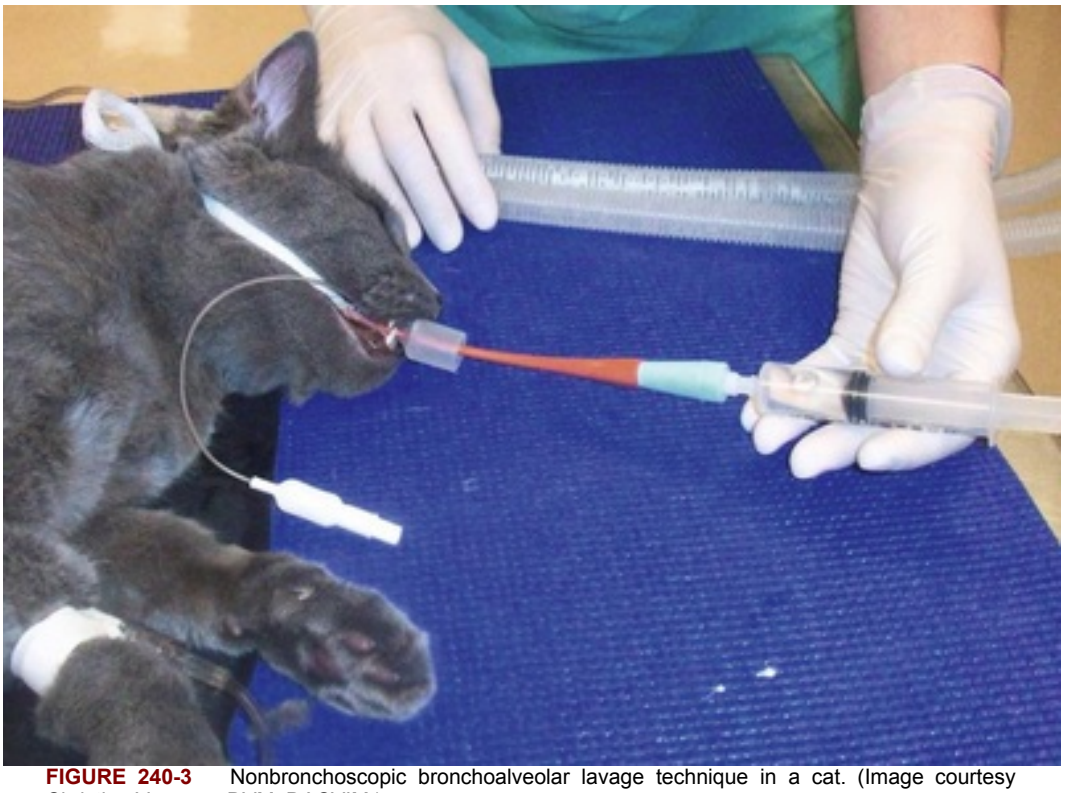


FIGURE 240-3 Nonbronchoscopic bronchoalveolar lavage technique in a cat. (Image courtesy Christine Venema, DVM, DACVIM.)

1 to 2 mL/kg per aliquot of warmed lavage solution (nonbacteriostatic 0.9% saline)[58] can be instilled in large dogs and 2-4 mL/kg in smaller dogs and cats. Fixed volumes of 10-25 mL can be used. Each bolus of fluid should be followed by 5 mL of air to be assured that all instilled fluid has passed through the length of the catheter. The bolus of lavage solution and air is infused into the bronchoscope or catheter via an attached syringe, then immediately aspirated through the catheter using the same syringe. Alternatively, mechanical suction can be used to aspirate a fluid sample into a sterile specimen trap.[59] Recovery of about 40-60% of the instilled volume is expected from dogs and cats,[61] but as much as 80% has been recovered from cats.[62] Sampling of at least two sites is recommended, even in patients with diffuse disease, as BAL cytology can vary in different areas of lung.[63] Collected fluid samples may be submitted for cytological analysis, general aerobic, anaerobic, *Mycoplasma*, and fungal cultures.[52,64,65] BAL samples can also be submitted for PCR analysis for respiratory pathogens. Hypoxemia due to ventilation-perfusion mismatch is the most common complication of BAL and can be severe.[66,67] Administration of supplemental oxygen following BAL is usually sufficient to resolve hypoxemia induced by the procedure, even in severely ill pets (see ch. 131).

Tracheal Wash *(see ch. 101)*

Indications

Tracheal wash is usually used to collect fluid samples from large proximal airways[52,68] in pets with a productive cough, since such samples can yield evidence of lower airway pathology. Since the majority of the instilled fluid does not reach the gas exchange interface, severe hypoxemia is unlikely to occur during or after this procedure. Either endotracheal wash (ETW) or transtracheal wash (TTW) is used. ETW requires intubation and general anesthesia, and as a result, may be a more appropriate option for pets that will not tolerate the restraint required for TTW.

Endotracheal Wash (ETW)

Technique and guidelines for processing retrieved samples are similar to those for BAL. Pets are anesthetized and intubated with a sterile endotracheal tube. A red rubber feeding tube or polypropylene catheter is advanced to the 4th intercostal space, which approximates the location of the intrathoracic tracheal bifurcation (carina). Volumes of 0.5-5 mL/kg of nonbacteriostatic 0.9% saline per aliquot have been

recommended. Up to three aliquots can be instilled and aspirated until an adequate sample is retrieved. Samples can be submitted for cytology, culture, immunologic, and PCR analyses. Complications associated with ETW are rare. Transient deterioration in respiratory status, exacerbation of cough, and bronchospasm may be noted during and following the procedure, which are typically mild and readily reversible.[68]

Transtracheal Wash (TTW)

ETW and TTW samples are similar, but TTW is performed in an awake or lightly sedated patient.[52,59,68,69] TTW avoids concern of oropharyngeal contamination, which can occur with ETW.[70] TTW is limited to dogs >15 kg that are amenable to restraint and is contraindicated in patients with hemostatic abnormalities or ventral cervical pyoderma.[69] TTW has limited utility in evaluating pets with interstitial or alveolar disease because little fluid reaches the distal lung. The pet is usually restrained in sternal recumbency or sitting upright with the nose tipped dorsally. An area of skin around the larynx and proximal trachea is clipped and aseptically prepared.

In medium-sized dogs, a catheter can be inserted through the cricothyroid ligament. In large dogs, the needle can be inserted on the ventral midline of the cervical trachea between two tracheal rings.[68,70] Inserting the needle through the cricothyroid ligament avoids risk of penetrating both tracheal walls in medium-sized dogs. Local anesthesia (2 to 5 mg/kg, 2% lidocaine) is instilled intradermally and SC at the intended needle insertion site and then a stab incision is made through the skin using a #11 blade at that site to facilitate passage of a sterile 14-gauge needle through the cricothyroid ligament. Some clinicians specifically displace the skin upward/cranially before entering the skin and trachea with the needle, so that an open tract is not left by the needle after withdrawal. Prior to inserting a sterile 3.5-French red rubber or polypropylene catheter through the needle (Figure 240-4), the distance from the intended insertion site to the fourth rib should have been marked on the catheter to estimate the distance to the carina. Once the needle is seated, the catheter is inserted through the needle and advanced into the lumen of the trachea to the premeasured distance. Recommendations for lavage volumes vary from 0.5 to 5 mL/kg per aliquot, as for ETW. The sample yield for tracheal washes is often less than that obtained with BAL but can be sufficient for cytology, culture, and/or PCR. After removal of the catheter and needle from the trachea, the area is covered with a sterile, nonadherent gauze sponge and lightly bandaged to avoid leakage of air from the needle insertion site. Samples obtained by TTW should be handled, prepared, and analyzed as recommended for samples retrieved by ETW or BAL.

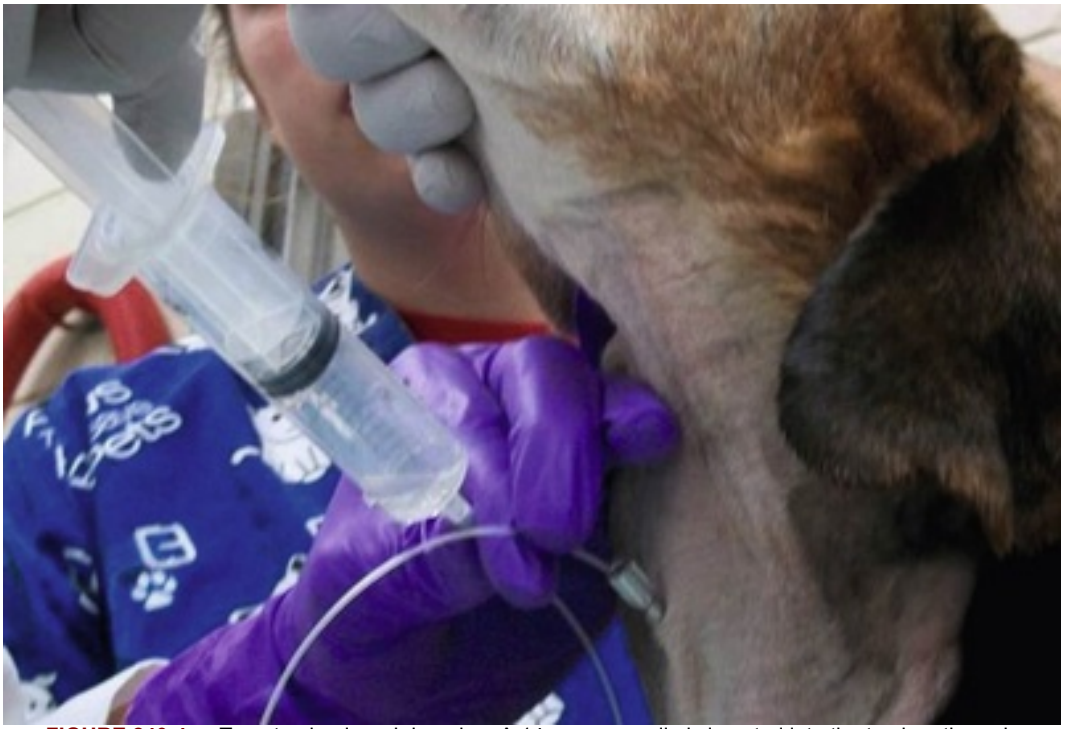


FIGURE 240-4 Transtracheal wash in a dog. A 14-gauge needle is inserted into the trachea through the cricothyroid ligament, and a 3.5-Fr polypropylene catheter is inserted through the needle into the

trachea for instillation and retrieval of lavage fluid. (Image courtesy Christine Venema, DVM, DACVIM.)

Complications associated with TTW are mild, self-limiting, and uncommon. They include SC emphysema due to air leakage from the needle insertion site, hemorrhage, cardiac arrhythmias, hemoptysis, and tracheal laceration leading to pneumomediastinum, and rarely, pneumothorax. Respiratory status may deteriorate during or following the procedure as a result of airway obstruction from hemorrhage or hematoma, but this is uncommon. Exacerbation of cough may also be noted following the procedure. Infection of the needle tract may develop if a significant break in sterile technique occurs.

Endobronchial Brush and Needle Cytology

Endobronchial samples of the tracheal and bronchial airways can be collected under bronchoscopic guidance using cytology brushes and transbronchial aspiration needles. Endobronchial needles and cytology brushes allow for the targeted sampling of focal airway lesions. Endobronchial sampling of focal mucosal lesions is more sensitive in detecting airway inflammation than bronchoalveolar lavage, but comparable to BAL in detecting epithelial alterations.[61] Endobronchial brushing is safe and well-tolerated in dogs but does increase anesthetic time and cost. Complications of endobronchial needle aspirations have not been widely reported from dogs or cats. Complications described in people include pneumothorax, airway hemorrhage, and pneumomediastinum.[71]

Transthoracic Needle Aspirate and Biopsy

Fine-needle aspirates and needle biopsy samples of lung can be obtained percutaneously from pets with diffuse interstitial disease or in those with peripheral pulmonary mass lesions (Figure 240-5). Fluoroscopic, ultrasonographic, and CT guidance are helpful in maximizing diagnostic yield and accuracy of sampling and also can help to minimize complications.[72,73] Contraindications to transthoracic sampling include bleeding tendency, cystic or bullous lesions, pneumothorax, pulmonary hypertension, and respiratory distress or instability. Potential complications of transthoracic sampling include bleeding, pneumothorax, seeding of the needle tract with neoplastic cells, and death.[74]

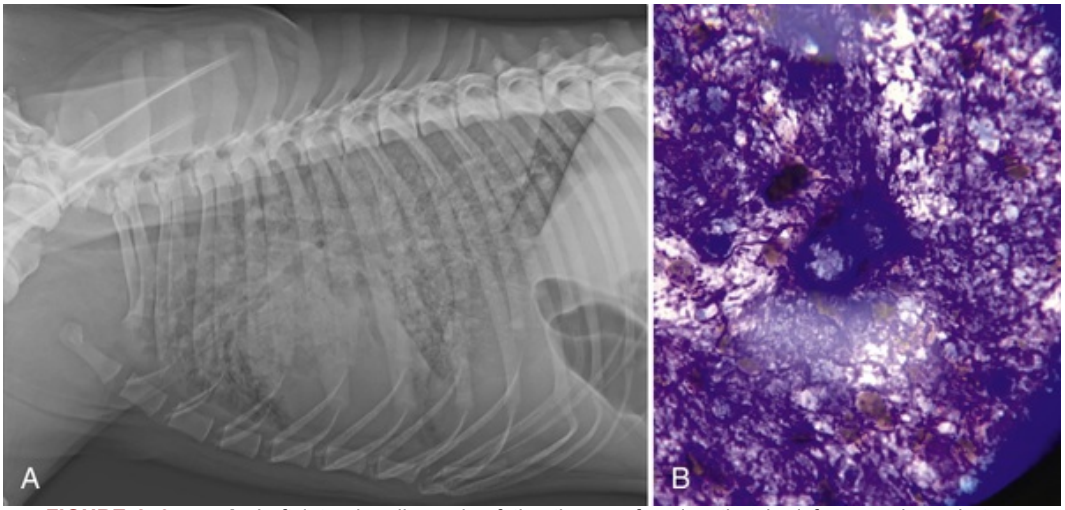


FIGURE 240-5 **A,** Left lateral radiograph of the thorax of a dog that had fever and respiratory distress. **B,** Cytology of a transthoracic fine-needle aspirate of the lung in **(A),** including a thick-walled, broad-based, budding yeast consistent with *Blastomyces*. (Images courtesy Valerie Chadwick, DVM.)

Surgical and Thoracoscopic Lung Biopsy

In cases where needle biopsies or endobronchial biopsies may not be adequate to confirm a diagnosis, larger biopsy samples can be obtained using surgical or thoracoscopic approaches. Standard intercostal or median sternotomy surgical approaches provide good visualization of the lung and access to large biopsy samples. In cases with peripheral or diffuse lung disease, a keyhole or minithoracotomy approach has been effective in providing a diagnosis of canine and feline interstitial lung diseases while also minimizing surgical time and

tissue trauma.[75]

Thoracoscopy is a minimally invasive technique that allows diagnostic evaluation of the lungs and pleural space through a series of 5- to 10-mm diameter portals rather than a large, single incision, minimizing tissue trauma and recovery time.[76] Video-assisted thoracoscopic surgery (VATS) provides better visualization of the pleural surfaces, lungs, mediastinal structures, and chest wall than open thoracotomy. VATS is indicated for the biopsy or removal of pulmonary or mediastinal masses, pleural masses, sampling of pleural and pericardial fluid, biopsy or removal of tracheobronchial lymph nodes, and in the investigation of spontaneous pneumothorax.[76] In one study, VATS was found to be comparable to open thoracotomy in surgical and diagnostic outcome for dogs undergoing lung lobectomy.[77]

Pulse Oximetry and Arterial Blood Gas Analysis

See E-Box 240-3 and ch. 75, 98, and 128.

E-Box 240-3

Pulse Oximetry and Arterial Blood Gas Analysis

Pulse Oximetry (see ch. 98)

Pulse oximetry is a widely available, noninvasive method for estimating the oxygen saturation of hemoglobin in peripheral blood. Standard pulse oximetry is a bedside test that is rapid, inexpensive, and easy to use and interpret. Pulse oximetry has a wide range of clinical utility, including determining the need for oxygen supplementation, monitoring the biochemical response to supplemental oxygen, and monitoring patients undergoing invasive respiratory diagnostic procedures (e.g., bronchoalveolar lavage). A hemoglobin saturation of 95% to 100% is considered normal in most dogs and cats. Saturations between 94% and 91% are consistent with mild to moderate hypoxemia, while values below 90% are consistent with severe hypoxemia. Despite its ease of use and wide range of clinical utility, there are several limitations to the use of pulse oximetry. Severe anemia, hypothermia, hypoperfusion, and hypovolemic shock can cause erroneous values that limit the utility of pulse oximetry in critically ill patients.[78] Excessive ambient light, skin pigmentation, and excessive patient movement may also cause erroneous results.

Arterial Blood Gas Analysis

Arterial blood gas analysis is considered the gold standard for evaluating the gas exchange function of the lung. Oxygenation and ventilation can both be assessed with arterial blood gas analysis. These functions are briefly reviewed here and are covered more extensively (along with acid-base balance) elsewhere in the text (see ch. 128). Arterial blood samples can be collected from the dorsal pedal (metatarsal), femoral, coccygeal, sublingual, and aural arteries in dogs, although the dorsal pedal and femoral are most commonly used in dogs (see ch. 75). The femoral artery is typically used for arterial blood sampling in cats. Arterial blood samples should be collected in heparinized syringes and should be capped immediately after collection to prevent gases dissolved in the plasma from equilibrating with ambient air.

Arterial blood gas sampling provides accurate measurements of the partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) in arterial blood. Pulmonary oxygenation is assessed by evaluating the PaO_2. Hypoxemia is defined as a PaO_2 less than 80 mm Hg. Differentials for hypoxemia include a low partial pressure of inspired oxygen (low PiO_2), alveolar hypoventilation, ventilation-perfusion inequality (due to pulmonary disease), right-to-left shunt, and diffusion impairment (interstitial disease, emphysema). Arterial blood gas analysis also provides a method for estimating of the alveolar partial pressure of oxygen (PAO_2) by using the alveolar gas equation:

$$PAO_2 = [FiO_2 \times (PB - PH_2O)] - (PaCO_2/RQ)$$

where PB = barometric pressure in mm Hg, PH_2O = water vapor pressure (at body temperature) in

mm Hg, FiO_2 = the fraction of inspired oxygen, *RQ* = respiratory quotient (ratio of oxygen consumed and carbon dioxide produced during metabolism of mixed metabolic fuels (normally 0.8), and $PaCO_2$ = partial pressure of carbon dioxide in arterial blood.

The difference between the estimated alveolar partial pressure of oxygen and the measured arterial partial pressure of oxygen ($PAO_2 - PaO_2$), also referred to as the *A-a gradient,* is normally < 15 mm Hg in patients breathing room air (see ch. 128). Calculation of the A-a gradient provides a method for quantifying gas exchange dysfunction and also provides a means of differentiating among the causes of hypoxemia. Hypoxemia associated with an elevated A-a gradient is due to ventilation-perfusion inequality, diffusion barrier, or right-to-left shunt. Hypoxemia with a normal A-a gradient is either due to a low PiO_2 (e.g., breathing at altitude) or alveolar hypoventilation and suggests that the gas exchange function of the lung is normal.

Alveolar ventilation refers to the delivery of CO_2 out of the alveolus. Alveolar ventilation is assessed on an arterial blood gas by the partial pressure of carbon dioxide in arterial blood, $PaCO_2$. As alveolar ventilation is impaired, alveolar (and arterial) CO_2 is retained and $PaCO_2$ rises above normal (hypoventilation). Common causes of hypoventilation include central nervous system depression, airway obstruction, pleural space disease, thoracic wall abnormalities, and anesthesia. Hypoventilation also occurs as a compensatory response to a metabolic alkalosis (see ch. 128). As alveolar ventilation increases, CO_2 excretion via the lungs increases and $PaCO_2$ decreases (hyperventilation). Common causes of hyperventilation include hypoxemia, central nervous system stimulation, pain, and excitement. Alveolar hyperventilation can also occur as a compensatory response to a primary metabolic acidosis (see ch. 128).

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CHAPTER 241

Diseases of the Trachea and Small Airways

Cecile Clercx

Tracheal Diseases

Most tracheal disorders can involve both the intra- and extrathoracic tracheal segments. Tracheitis refers to an inflammation of the epithelial lining of the trachea. This inflammatory response can be infectious or noninfectious.

Noninfectious tracheal diseases (leading to tracheal mucosal inflammation) are common, and they include tracheal dorsal membrane flaccidity, tracheal collapse, tracheal injury/laceration, posttraumatic stenosis, foreign body, intratracheal tumor, smoke inhalation, prolonged barking (dogs), and tracheal avulsion (cats).

Tracheal disorders also can result from extratracheal diseases, such as extreme cardiac enlargement, mediastinal enlargement (lymph node tumor or thymoma, or megaesophagus [Figure 241-1]), or even parenchymal masses, which can cause deviation of the trachea, with possible effects on tracheal shape or lumen size (Figure 241-2), and subsequent obstruction and/or inflammation. Allergic lower airway disease also can lead to secondary tracheitis.

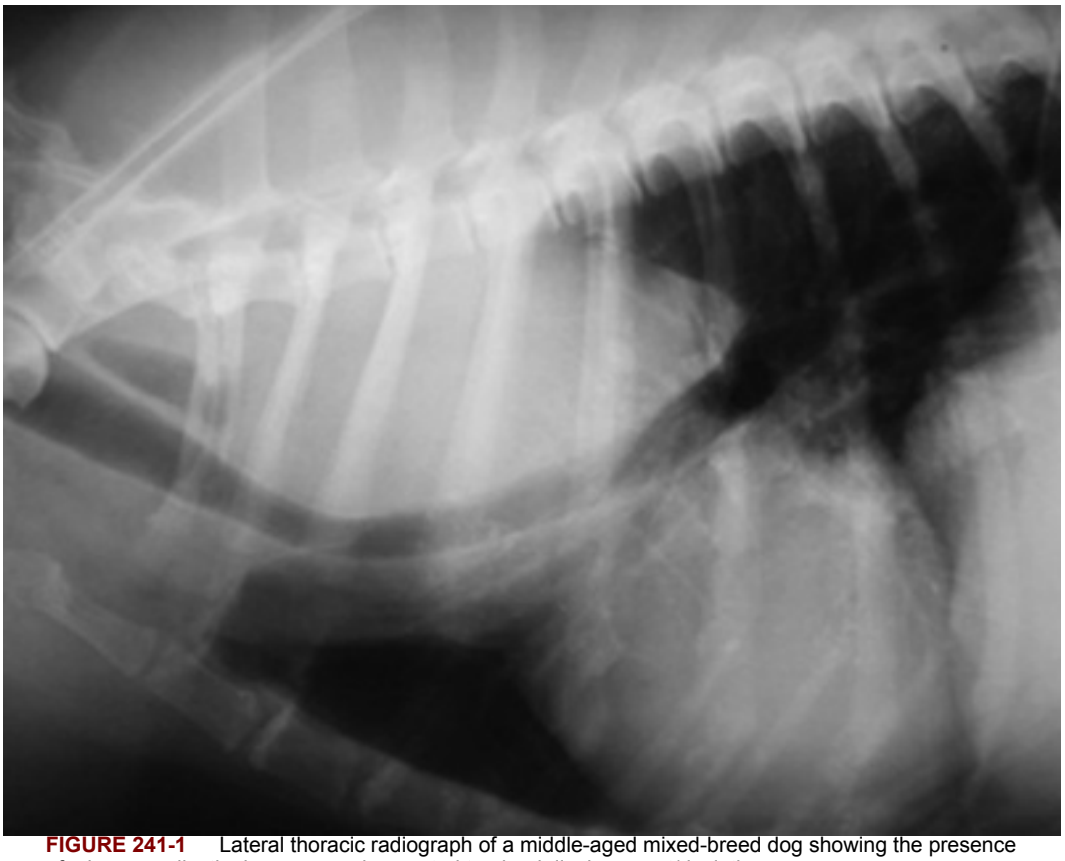


FIGURE 241-1 Lateral thoracic radiograph of a middle-aged mixed-breed dog showing the presence of a large mediastinal mass, causing ventral tracheal displacement/deviation.

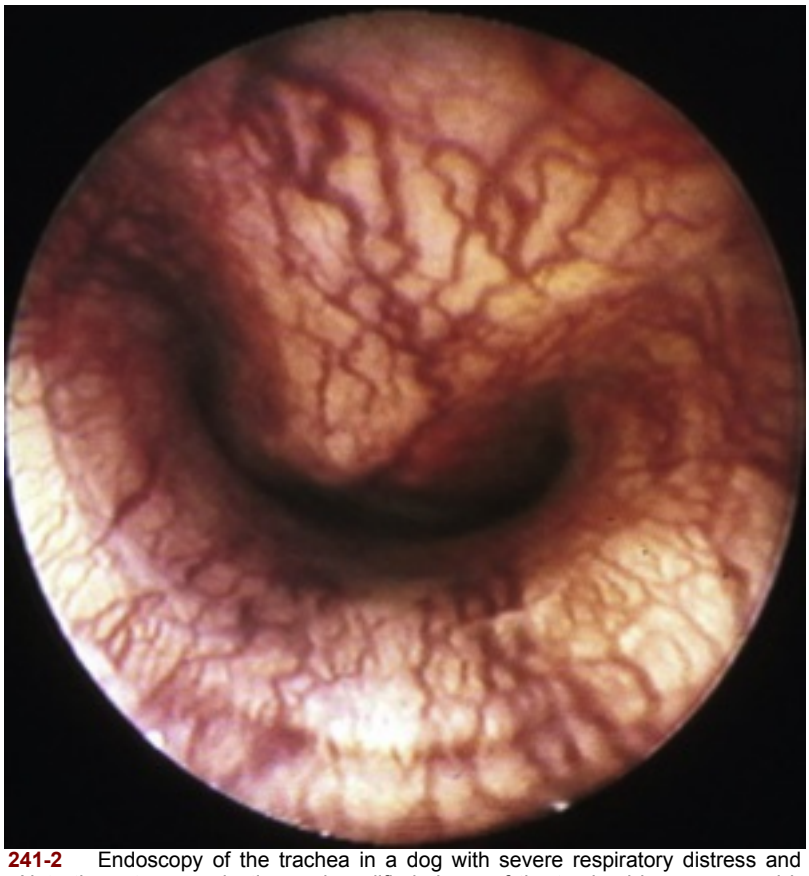


FIGURE 241-2 Endoscopy of the trachea in a dog with severe respiratory distress and cyanotic mucosae. Note the extreme reduction and modified shape of the tracheal lumen, caused by a huge mediastinal mass.

In cats, tracheitis is most likely to be associated with infectious feline respiratory disease (see ch. 229). Tracheitis in cats does not always induce significant cough, as it does in dogs.

Tracheal Collapse (Dogs)

Introduction

Tracheal collapse (collapsing trachea) is a very common disorder, characterized by dorsoventral flattening of the tracheal rings with laxity of the dorsal tracheal membrane. Malacic airways (or bronchial collapse) often can be associated with tracheal collapse, and this would negatively impact therapy and prognosis. The "goose-honk" sound of the cough is characteristic (Video 241-1).

Etiology and Pathophysiology

The cause of primary tracheal collapse is complex and best regarded as multifactorial. The development of the clinical condition requires both a primary cartilage abnormality, resulting in intrinsic weakness of the tracheal rings, and secondary factors capable of initiating progression to the symptomatic stage. Softening of cartilage rings seems to be due to a reduction of glycosaminoglycan and chondroitin sulfate content, which leads to a decreased ability to maintain functional rigidity, i.e., a weakness and flattening of the tracheal rings.[1,2] Potential triggering factors include obesity, cardiomegaly, inhalation of irritants and allergens, periodontal disease, respiratory infections, and recent endotracheal intubation.[3] The dynamic changes of tracheal collapse can be confined to either the cervical or the thoracic regions of the trachea, or both, and frequently are more pronounced at the cervicothoracic junction. The cervical trachea will collapse during inspiration, and the thoracic trachea will collapse during expiration due to the pressures developed during the respiratory cycle (Figure 241-3). Dorsoventral flattening of the tracheal cartilaginous rings causes a stretch of the dorsal tracheal membrane, which becomes inflamed and pendulous, and can prolapse into the tracheal lumen, further reducing tracheal luminal diameter, as soon as extraluminal pressure exceeds intraluminal pressure.[4] Inside the thorax, during inspiration, the redundant dorsal membrane is aspirated by/subjected to

negative intrathoracic pressure during inspiration and it can enlarge the tracheal lumen excessively, as seen on lateral radiographs (see Figure 241-3). In dogs with tracheal collapse, bronchomalacia often is encountered concurrently and does not appear to be related to airway inflammation.[5] On the other hand, bronchomalacia also can occur independently of tracheal collapse.

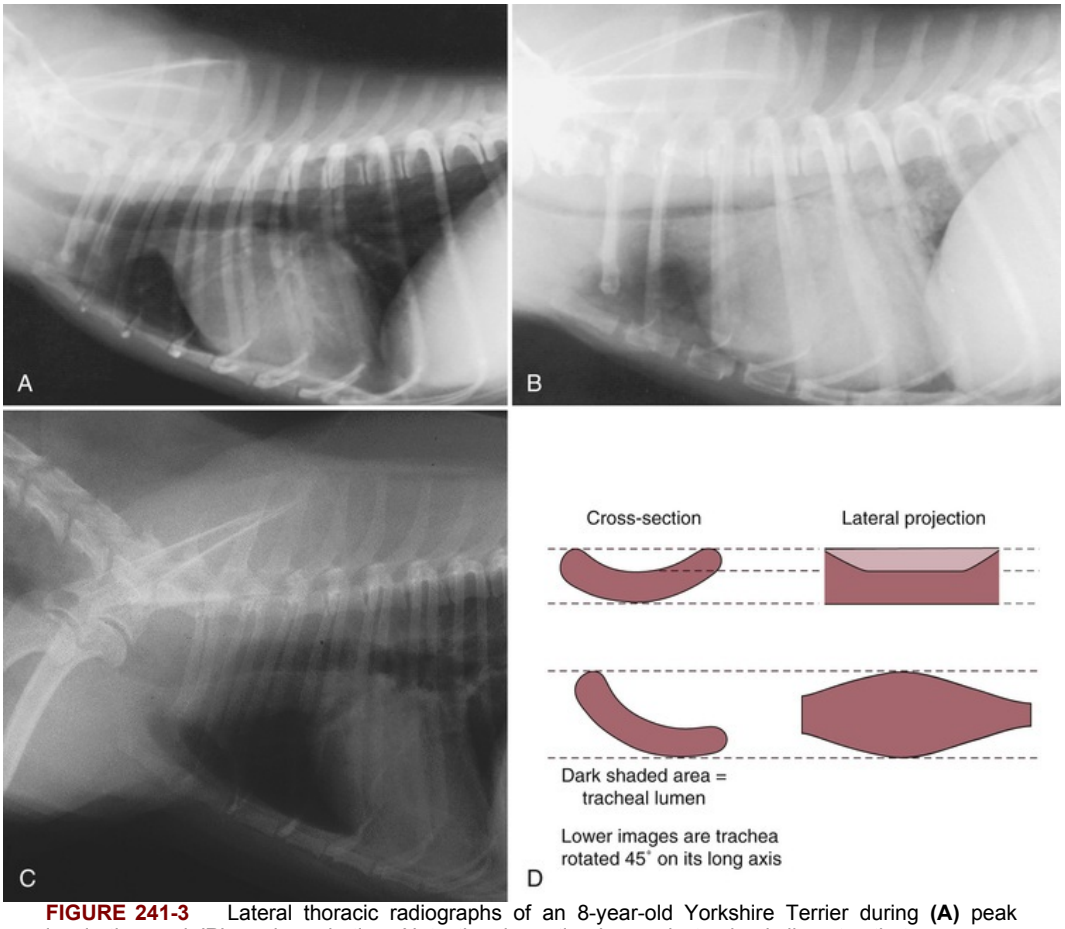


FIGURE 241-3 Lateral thoracic radiographs of an 8-year-old Yorkshire Terrier during **(A)** peak inspiration and **(B)** peak expiration. Note the dramatic change in tracheal diameter that can occur during the respiratory cycle in animals with collapsing trachea and how important it is to obtain inspiratory and expiratory views. In severe cases such as this, the expiratory collapse is not limited to the thoracic segment of the trachea but extends into the cervical region as well. **C,** Collapsing trachea observed at the thoracic inlet in a dog with moderate rotation of the trachea. As a result of the rotation, the trachea appears wide rather than collapsed in the lateral view. **D,** Diagram of the effect of obliquity on radiographs of cervical tracheal collapse. A narrowed tracheal lumen is visible on an inspiratory lateral radiograph (upper right). In the same patient, tracheal collapse is masked when the same view is obtained with the trachea rotated on its longitudinal axis (lower right).

It also appears that tracheal collapse could be induced secondarily by other disorders. In the West Highland White Terrier (WHWT) with idiopathic pulmonary fibrosis (IPF), tracheal collapse is encountered frequently, at least in advanced cases.[6] Since tracheal collapse is not described in WHWT exempt of IPF, it can be suggested that tracheal collapse might be secondarily induced due to increased pressures exerted because of the lack of elasticity/compliance of the fibrotic lung (see ch. 242 for further discussion of IPF).

In either classical or possibly secondary tracheal collapse, when clinical signs are apparent, the syndrome is perpetuated by the cycle of chronic inflammation of the tracheal mucosa, which exacerbates and, in turn, is exacerbated by the cough.

Clinical Presentation

Primary tracheal collapse commonly is seen in middle-aged to older miniature, toy, and small breed dogs. Overrepresented breeds include the Yorkshire Terrier, Pomeranian, Pug, Poodle, Maltese, and Chihuahua.[3,5,7]

Clinical signs include chronic cough in all cases, mild to severe panting, exercise intolerance, and varying

degree of inspiratory and expiratory dyspnea (respiratory distress), as well as a varying degree of cyanosis in advanced cases. A prolonged clinical history is common.

The cough is harsh, is generally described as "honking"/"goose honk," and is precipitated by activity, excitement, tracheal pressure (such as that caused by pulling on a leash), or drinking. This characteristic cough can be easily elicited by palpation of the trachea. A paroxysm of cough often ends with a terminal retch. Collapse of the cervical trachea sometimes can be appreciated as a flattening of the tracheal rings on cervical palpation. In some cases, cough is not audible as such and owners only report a "goose-honk" or "pig-grunt"/"growl-like" sound (Video 241-2). In severe cases, coughing almost never subsides, leading to muscular fatigue and exhaustion of the animal. In rare cases, excitement can lead to cyanosis and syncope (see ch. 30) because of partial or complete airway obstruction, vagally mediated bradycardia, or pulmonary hypertension,[4] especially when concomitant bronchomalacia is present.

Auscultation over the trachea can reveal stridorous sounds on both inspiration and expiration, and this must be differentiated from laryngeal paralysis, which has been reported in dogs with tracheal collapse.[4] During thoracic auscultation, crackles on both inspiration and expiration can be appreciated in dogs with small airway collapse and/or concurrent bronchitis.

Thorough cardiac auscultation is recommended, since a heart murmur associated with mitral regurgitation can be heard; indeed, concurrent myxomatous/degenerative mitral valve disease is a common finding in the same population affected by tracheal collapse, i.e., older, small-breed dogs. However, the role of cardiomegaly and specifically left atrial enlargement causing airway compression and collapse remains unclear. A recent study reported airway inflammation as the likely cause of cough in dogs that had both left atrial enlargement and airway collapse.[8] Hepatomegaly is common in dogs with tracheal collapse and could be a reflection of obesity, although hepatic dysfunction has been reported in dogs with tracheal collapse.[9]

Differential Diagnosis

Differential diagnoses include chronic mitral valvular heart disease, which can be a concurrent disease; chronic bronchitis and/or tracheitis, both possibly induced secondarily by tracheal collapse; and chronic pulmonary parenchymal disorders (e.g., IPF).

Diagnosis

The diagnosis of tracheal collapse is strongly suspected based on signalment, history of cough, and physical examination findings.

Additional diagnostic evaluation (radiography, fluoroscopy, echocardiography,[10] bronchoscopy, and pulmonary function testing)[11] can be used for confirming the extent and severity of the tracheal collapse, for identifying concomitant diseases (e.g., bronchomalacia, cardiomegaly, lower airway diseases), and is needed to obtain adequate measurements to assess the dimensions of a stent, in case stenting is considered as a therapeutic approach (see ch. 121).

Radiographic examination of animals with collapsed trachea can use both still and motion studies. The most useful radiographic examinations include lateral projections of the thoracic inlet, a tangential (rostrocaudal) projection of the thoracic inlet (in this skyline projection, the collapsed trachea is seen as an oval, "C" or crescent shape), and fluoroscopic investigation to demonstrate movements of the dorsal tracheal membrane during the respiratory cycle.

On lateral radiographs, a redundant dorsal tracheal membrane that invaginates into the tracheal lumen can be seen as a soft tissue opacity along the dorsal aspect of the caudal cervical tracheal lumen, while during inspiration, it will cause an increased tracheal diameter. This condition can be seen in both small- and large-breed dogs as a consequence of coughing and must be differentiated from a superimposed esophagus. Therefore, lateral radiographs made during both the maximal inspiratory and expiratory phases of the respiratory cycle are needed to demonstrate a dynamic collapse. Indeed, collapse of the cervical tracheal segment occurs in inspiration because of the decreased pressure within the trachea, whereas the thoracic portion tends to collapse during the expiration phase as a consequence of increased intratracheal pressure. These dynamic changes are best viewed in real time using image-intensified fluoroscopy.[7] When radiography is compared with fluoroscopy, assuming fluoroscopy is correct, radiographic evidence of collapse is noted at the incorrect location in 44% of dogs and is not detected in 8% of dogs with radiographs alone.[7] Moreover, radiographic measurements of the canine trachea consistently underestimate tracheal size, and computed tomography (CT) measurements are preferable for selecting tracheal stent size.[12]

Cervical lung lobe herniation (CLLH), or protrusion of lung parenchyma beyond the musculoskeletal

entrance of the thorax, recently has been identified fluoroscopically as a frequent finding in dogs.[13] Collapse of the intrathoracic trachea and of major bronchi (assessed fluoroscopically) were strongly associated with CLLH in one study; although a redundant dorsal tracheal membrane on radiographs was associated with CLLH, extrathoracic tracheal collapse was not.[13]

Tracheoscopy, although rarely needed to confirm the diagnosis, reveals a decreased dorsoventral diameter due to flattening of the cartilaginous rings with a pendulous dorsal membrane, up to a severe collapse leading to complete obstruction of the tracheal lumen (Figure 241-4). Therefore, tracheobronchoscopy can be helpful in determining the degree of severity of the tracheal and especially bronchial collapse, and for assessing concomitant airway disease (see ch. 101). Indeed, radiographs greatly underestimate the incidence of bronchomalacia.[7] Therefore, bronchoscopy should be proposed in all cases of suspected tracheal collapse, before stent placement can be considered, since the presence of severe bronchomalacia and/or lower airway disease greatly impacts the prognosis after stent placement (Videos 241-3 and 241-4).

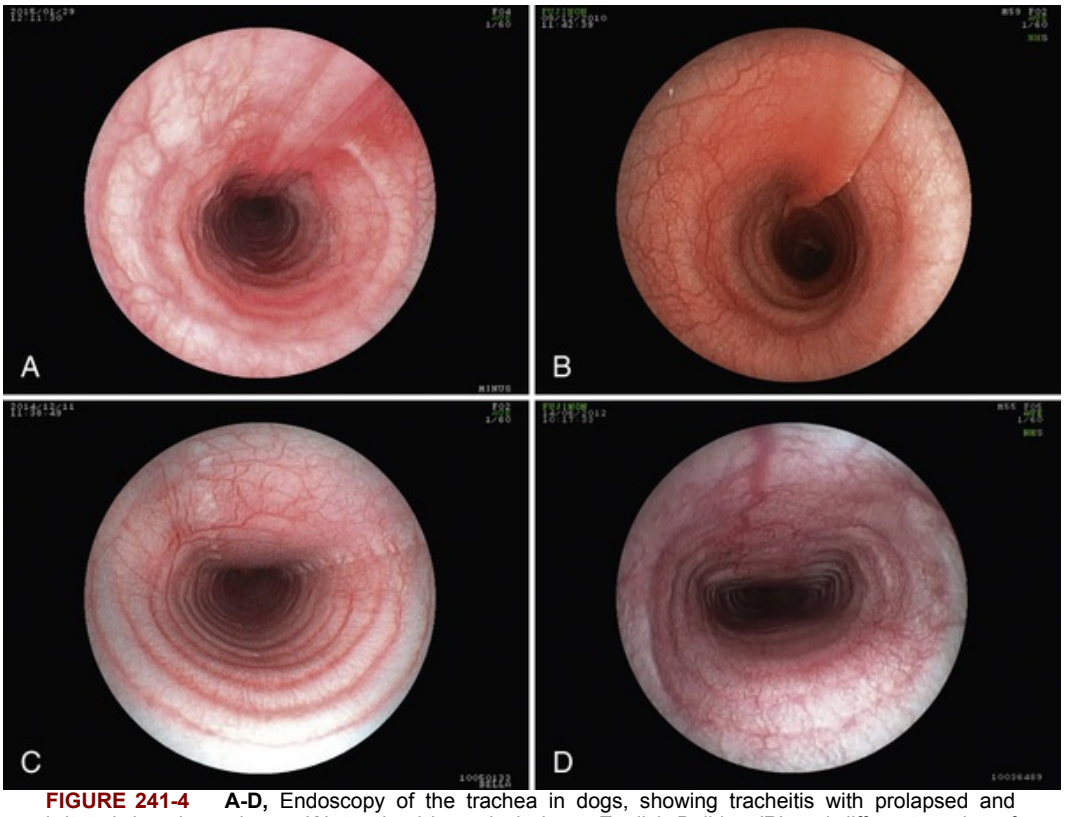


FIGURE 241-4 **A-D,** Endoscopy of the trachea in dogs, showing tracheitis with prolapsed and irritated dorsal membrane **(A),** tracheal hypoplasia in an English Bulldog **(B)** and different grades of severity of tracheal collapse, including grade 1 **(C)** and grade 3 **(D).**

Management

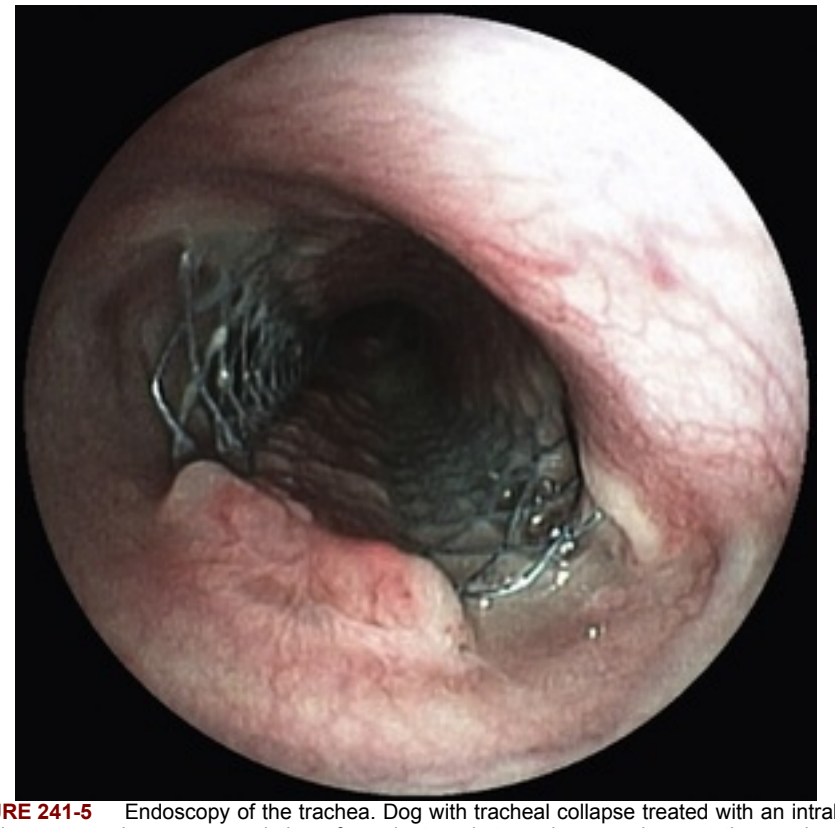
In animals with marked respiratory difficulty, oxygen supplementation can be delivered (see ch. 131), and sedation and antitussive agents are needed (see ch. 138). Butorphanol (0.05-0.2 mg/kg q 4-6 h) or acepromazine (0.01-0.1 mg/kg) can be injected SC, and prednisolone sodium succinate (15-30 mg/kg IV) can be administered to decrease acute inflammation.

Long-term treatment mainly aims to decrease all potential promoting factors and the level of inflammation of the tracheal mucosa.[3,4] Weight reduction in the obese animal is essential (see ch. 176 and 359). Weight loss alone can be curative of clinical signs. Likewise, replacement of neck collars with harnesses can be effective. Removing the dog from respiratory irritants such as noxious gases, smoke, and dust is common sense and should be explained clearly to the owner. It is also important to detect and treat other diseases, including chronic airway disease, cardiac disease, and hyperadrenocorticism.

Long-term therapy consists of very low-dosage corticosteroids (prednisone 0.2 mg/kg PO q 24 h × 1-2 weeks, at 3-month intervals, for instance), or by inhalation (fluticasone, one 120 mcg puff q 12 h using a face

mask and spacer; see ch. 97), often in combination with a sedative-antihistamine. Oversedation must be avoided, since the animal must keep moving to avoid gaining weight and to promote clearance of tracheal secretions. Oral antitussive agents that are effective in controlling cough include hydrocodone (0.22 mg/kg PO q 12 h) and butorphanol (0.55 mg/kg PO q 12 h). Bronchodilators (methylxanthines or beta agonists) also can be used; their possible benefits are attributable to reduction in smaller-airway spasm, which lowers intrathoracic pressures and thus reduces the tendency of the larger airways to collapse; improvement in mucociliary clearance; and reduction of diaphragmatic fatigue.

In dogs that fail medical management, extraluminal tracheal rings are indicated for cervical tracheal collapse and excellent outcomes have been reported in dogs managed by skilled surgeons.[14] If intrathoracic tracheal collapse is diagnosed and cannot be managed medically, treatment may involve the placement of intraluminal self-expanding stenting devices[15,16] (see ch. 121 and E-Figure 241-5).



E-FIGURE 241-5 Endoscopy of the trachea. Dog with tracheal collapse treated with an intraluminal tracheal stent, causing accumumulation of purulent pockets and a granuloma at the proximal edge (note the broad-based, raised lesion at the bottom left of the image).

Prognosis

Most animals can improve with an individualized treatment plan, but the condition generally is progressive, and the long-term prognosis poor, especially when irreversible airway collapse is present.

Tracheoesophageal or Bronchoesophageal Fistula

Tracheoesophageal or bronchoesophageal fistula is a rare disease in dogs. Clinical signs include chronic cough, recurrent lower respiratory tract infections, and gas accumulation in the gastrointestinal (GI) tract due to the passage of air from the trachea into the GI tract. The connection between the trachea and esophagus can be evaluated by bronchoscopy, contrast radiography, fluoroscopy, or CT.[17,18] This disorder is discussed in greater detail under Bronchial Diseases—Primary, below, and in ch. 273.

Obstructive and/or Traumatic Tracheal Diseases

Etiology

Tracheal subobstruction may be caused by collapsed tracheal rings, stenosis subsequent to injuries, foreign bodies, neoplasia, granulomas, external compression, or a complication of tracheostomy.[19,20]

Tracheal Injuries

Tracheal injuries range from small lacerations to tracheal avulsions and can be caused by intraluminal or external trauma. Intraluminal trauma mostly is associated with endotracheal intubation, while external trauma most commonly is seen secondary to a dog fight or automobile accident. In cats, a well-reported problem of intraluminal trauma concerns stenosis after necrosis/rupture following overinflation of an endotracheal tube cuff.[21] Stenosis after intrathoracic tracheal (or bronchial) rupture after blunt trauma to the neck or thorax is a reported cause of external trauma[22,23] (Video 241-5). These problems rarely have been reported in dogs.

Tracheal Foreign Bodies

Generally, when foreign bodies do enter the trachea, they are small enough to pass into a bronchus. Once lodged in a bronchus, a typical foreign body is a cause for bacterial bronchopneumonia, which is responsive to antibiotics but recurrent. When the foreign bodies are too large, they usually lodge at the carina and cause airway obstruction that can be life-threatening (Figure 241-6). Reported cases of tracheal foreign bodies in dogs and cats are rare but have involved mineral oil, hair, bullets, bones, plant material, and toys.[19]

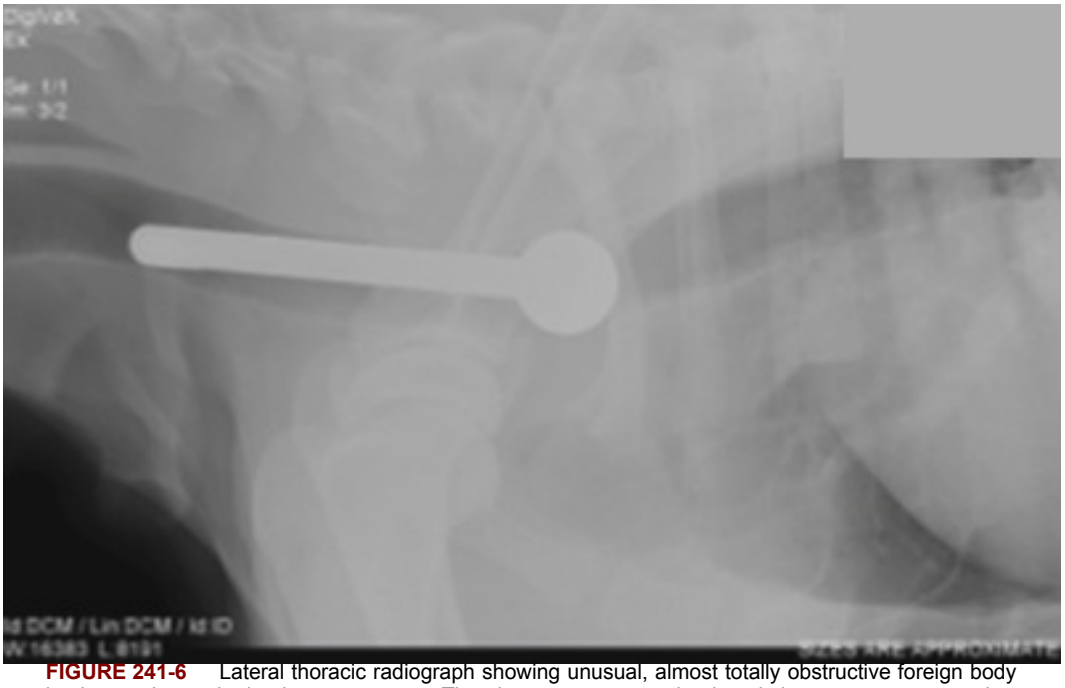


FIGURE 241-6 Lateral thoracic radiograph showing unusual, almost totally obstructive foreign body in the trachea, obtained post mortem. The dog was sent to the hospital as an emergency but unfortunately died just before arrival. (Courtesy G. Bolen.)

Intratracheal Tumors

Intratracheal tumors are uncommon in dogs and cats. In young dogs, osteochondroma can be found while in older dogs or in cats, many other tumor types can be found (e.g., mast cell tumor, squamous cell carcinoma, adenocarcinoma, osteosarcoma, extramedullary plasmacytoma, leiomyoma, or fibrosarcoma).[19,24-26]

Tracheal Granulomas

Tracheal granulomas can be a complication after intraluminal stent placement in dogs with tracheal collapse and can result in a severe reduction of the tracheal lumen. Treatment with corticosteroids, either orally or by nebulization, leads to a decrease in the size of the granuloma in most cases (see ch. 121).[15,27,28]

Parasitic Granulomas

Parasitic granulomas have also been described. Lungworms *(Oslerus osleri; Filaroides osleri)* have been described in dogs, and tracheal cuterebrosis has been described in cats (see differential diagnosis for eosinophilic bronchopneumopathy, below). With tracheoscopy, *Cuterebra* larvae have been described in the trachea, at or just cranial to its bifurcation. Successful treatment consists of removal of the larva during tracheoscopy or via thoracotomy.[29]

Clinical Presentation

Tracheal injuries characteristically result in subcutaneous emphysema over the cervical and thoracic areas due to air escaping from the trachea into the subcutaneous tissue. This is typically associated with inspiratory stridor with a prolonged inspiratory phase followed by a variable expiratory phase. Other clinical signs include coughing, exercise intolerance, gagging, exertional distress, fever, change in bark, intermittant cyanosis or collapse, and open-mouth breathing in cats.[19,20] Furthermore, pneumomediastinum, although rare, can occur. In a recent study, endotracheal intubation and positive pressure ventilation were the most common causes of pneumomediastinum, followed by trauma and tracheal foreign bodies.[30]

After tracheal avulsion injury, the airway lumen is thought to be maintained by either intact tracheal adventitia or by thickening of mediastinal tissue leading to the development of a pseudoairway. Stenosis of the lumen then occurs at both ends of the injury. Therefore, clinical signs are delayed and are due to tracheal obstruction, such as inspiratory distress and tracheal stridor.[22] In tracheal foreign bodies, clinical signs are of acute onset.

Diagnostic Tests

Diagnosis is confirmed by thoracic radiography (see Figure 241-6) and tracheoscopy (Video 241-6, *A* and *B*).

Management

Surgical management of tracheal lesions consists of resection of the stenosed ends of the injured trachea, or portion of trachea involved by a tumor and subsequent repair by anastomosis, and the prognosis is good.[22]

Infectious Tracheitis/Tracheobronchitis

Canine infectious respiratory disease (CIRD) complex is also known as "kennel cough."[4,29,31-39] The disease is commonly seen in young dogs, especially in boarding kennels. This contagious disease is often self-limiting in dogs, but a wide range of respiratory signs can be found. Etiology and pathophysiology are discussed in detail in ch. 227.

Signalment

Young dogs are more susceptible, especially those housed in high-density environment, since the viruses and *Bordetella* are highly contagious. Despite the widespread availability of *Bordetella* vaccines, the disease is still common.

Clinical Presentation

This contagious disease often is self-limiting in dogs. In the classic infection, a mild dry cough is the only clinical sign. Nasal discharge can be present. However, infection with *Bordetella* can provoke chronic cough, which is more challenging to cure. Also, a wide range of respiratory signs can be found, from mild illness to severe pneumonia leading to death, depending on severity of infection and presence of other viral or bacterial pathogens, as well as immune and vaccination status.[29,37]

Diagnostic Tests

The diagnosis of bordetellosis relies on positive bacterial culture or, more recently, on positive polymerase chain reaction (PCR), from bronchoalveolar lavage fluid (BALF; see ch. 101 and 240). More laboratories offer PCR assessment of samples, but studies investigating the reliability of this method are lacking. As *B. bronchiseptica (Bb)* has been isolated regularly in clinically healthy dogs by culture from the upper respiratory tracts and lungs[38] and, more recently, by qualitative PCR from BALF,[36] and since infection and aerosol

shedding can persist for weeks, it is still unclear how a positive PCR result must be interpreted as diagnostic of the disease, or whether it could be considered as an incidental finding, or indicative that the dog is a carrier. The finding of pleomorphic cocci or coccobacilli adhering to the cilia of the epithelial cells is reported as a characteristic cytologic feature (Figure 241-7). The diagnostic accuracy of demonstrating *Bb* in cytological preparations, such as cytocentrifuged smears of BALF or bronchial brush fluid, has been evaluated,[34] together with the respective diagnostic value of qPCR analysis and bacterial culture of BALF, for the diagnosis of canine *Bb* infection. In 24 young dogs with kennel cough, BALF culture and qPCR detected *Bb* in more than half and 100% of dogs (at high CT levels), respectively.[34] Coccobacilli were found adhering to ciliated epithelial cells in most BALF preparations.[34]

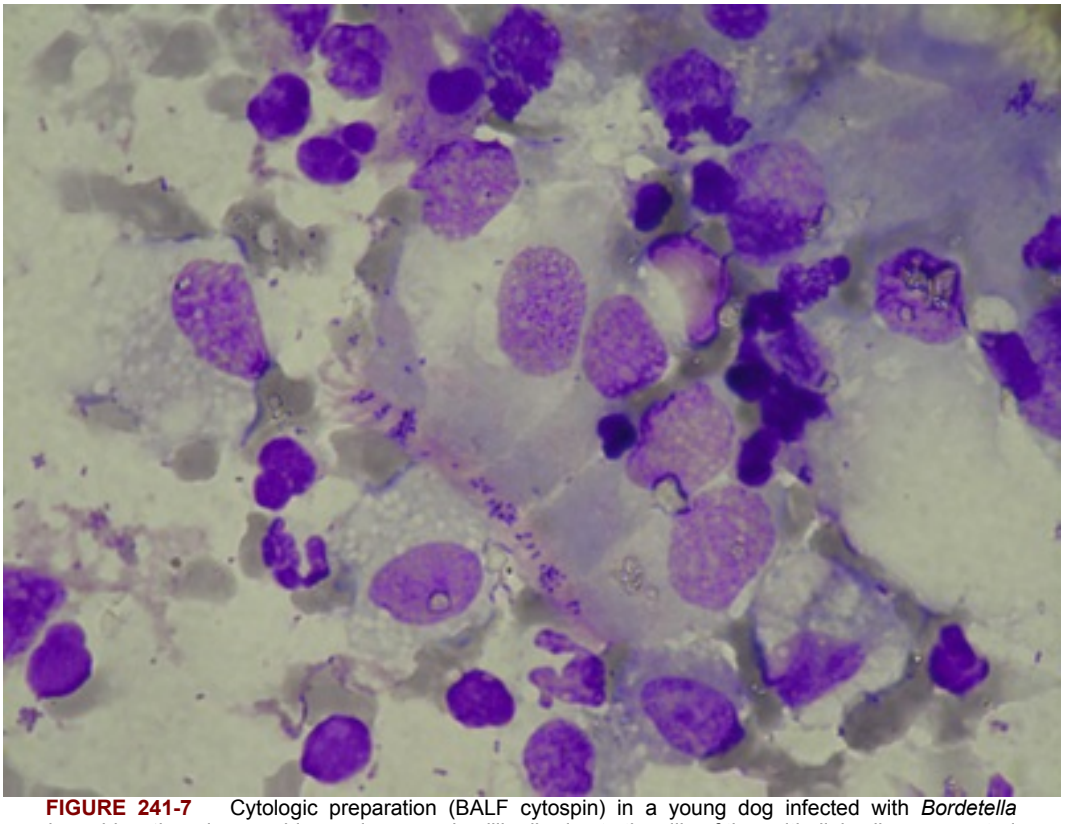


FIGURE 241-7 Cytologic preparation (BALF cytospin) in a young dog infected with *Bordetella bronchiseptica:* pleomorphic cocci or coccobacilli adhering to the cilia of the epithelial cells are reported characteristic cytological features.

Management

Uncomplicated cases of tracheobronchitis probably do not require antimicrobials (see ch. 227). Vaccination has not been proven to have any positive effect in dogs with active infection.[38] Treatment generally consists of empirical antimicrobial therapy; doxycycline (5 mg/kg PO q 12 h) is the antimicrobial of choice due to its efficacy against *Bb*, its low cost, and its ease of use. Dogs that are unresponsive to oral or parenteral administration of antibacterials could respond to nebulized antibacterials. Aerosolized, topically nonabsorbable antibacterials such as gentamicin have been shown to be effective in reducing the population of *Bb* in the trachea and bronchi of infected dogs (see ch. 97).[4,39]

In a recent study of dogs with kennel cough where *Bb* was confirmed, most dogs had been treated unsuccessfully with various oral antibiotics including amoxicillin or amoxicillin/clavulanic acid, doxycycline, marbofloxacin, or enrofloxacin, whereas treatment with nebulized gentamicin for 3 weeks or longer was associated with significant clinical improvement.[34]

Bronchial Diseases—Primary

Chronic Bronchitis in Dogs

Definition and Overview

Chronic bronchitis (CB) is an incurable disease of insidious onset, characterized by chronic and persistent cough, related to chronic inflammation of the airways, and not related to any identifiable, persistent, specific primary cause. It is a syndrome more than a final diagnosis.[40] Therefore, in dogs, it is also called nonspecific/aspecific chronic bronchitis.

Chronic bronchitis in dogs is defined when 3 diagnostic criteria are met: (1) chronic cough (for at least 2 months); (2) evidence of excessive mucus or of mucous hypersecretion; and (3) exclusion of other chronic cardiopulmonary diseases (e.g., congestive heart failure, chronic infectious bronchopneumonia, pulmonary neoplasia, or eosinophilic bronchopneumopathy). However, two separate diseases can coexist (e.g., congestive heart failure and airway collapse), which can complicate diagnosis and treatment. In humans, the most functional sequela of chronic bronchitis is chronic airway obstruction, referred to as chronic obstructive pulmonary disease (COPD), and subsequent emphysema. This mechanism appears to be less frequently observed in dogs, although the diagnosis of COPD relies on documentation of airflow obstruction by pulmonary function tests, which are not widely available in veterinary medicine. Dogs with severe and longstanding chronic bronchitis can exhibit either bronchiectasis (dilation and destruction of the walls of the bronchi) or bronchomalacia (airway collapse during expiration and cough).

Etiology, Epidemiology, and Risk Factors

Primary causes of chronic bronchitis are poorly understood, which is the reason it also is called nonspecific chronic bronchitis. The major difficulty is that the disease is detectable only in its advanced stages, since it has an insidious onset and lengthy pathogenesis. Therefore, the diagnostic evaluation is based on exclusion of all potential specific primary or secondary causes, which can be frustrating for both the clinician and the owner. Indeed, typical clinicopathological findings are variable and inconclusive. Nonspecific chronic bronchitis is diagnosed mostly in middle-aged to older, smaller-breed dogs, but it can also occur in larger breeds. Many dogs with chronic bronchitis are overweight and have periodontal disease, both of which appear to be risk factors.

In humans, the most important etiologic factors include smoking or passive smoking, atmospheric pollution, and infection. The same factors probably account for the development of chronic bronchitis in dogs. Moreover, in dogs, chronic/previous infection with *Bordetella bronchiseptica* or canine distemper virus, or with parasites leading to eosinophilic chronic bronchitis, or the presence of other diseases like tracheal collapse, or chronic cardiac disease, are all potential causes leading to development of chronic bronchitis. A recent study investigating potential demographic and historical factors associated with chronic cough did not identify exposure to environmental tobacco smoke as a risk factor.[41]

In people, gastroesophageal reflux disease (GERD) generally is considered among the most common etiologies of chronic cough. Indeed, cough management guidelines published by numerous respiratory societies worldwide recommend evaluation and treatment of GERD as an integral component of the diagnostic/therapeutic algorithm for the management of chronic cough. However, consensus is lacking in terms of whether this relationship between reflux and cough proves a causal link.[42] Although currently suggested in canine medicine, such a link has not been widely appreciated in dogs.

Pathophysiology

Chronic bronchitis results in inflammatory changes within the bronchial mucosa, including increased mucus production. Bronchial wall thickening and possibly progressive bronchomalacia contribute to airflow obstruction and further worsen inflammation, which induces cough, which, in turn, sustains inflammation.

Clinical Presentation

A persistent, sonorous cough, with paroxysms of coughing often followed by a terminal retch, and without any identified cause, is generally the only major complaint.

Diagnosis

Chronic cough related to specific causes should be ruled out, mainly tracheal collapse, lung fibrosis, eosinophilic bronchopneumopathy, parasitic lung diseases, bronchial or lung primary or secondary tumors, and mitral valve disease (see ch. 26, 240, and 251).

Diagnostic tests are performed to rule out other causes of chronic cough. Results of a complete blood count

usually are normal. Peripheral eosinophilia is of particular interest in baseline laboratory results because circulating eosinophilia can be associated with pulmonary eosinophilia or parasite infection. Other laboratory testing that should be considered includes heartworm antigen testing (see ch. 255), fecal analysis for both eggs and lungworm larva (see ch. 81), and evaluation of circulating concentrations of N-terminal prohormone (NT) of pro–brain natriuretic peptide (BNP), which are elevated in the presence of left atrial enlargement/congestive heart failure, as well as in pulmonary hypertension (see ch. 246). Elevated NT pro-BNP levels should prompt further evaluation with echocardiography.[43]

Thoracic radiographs show bronchial wall thickening or a generalized increase in airway-oriented interstitial opacity, or both. Thoracic radiographs also are useful to exclude other conditions that cause cough, such as congestive heart failure, lung masses, pleural effusion, and interstitial lung disease. Fluoroscopy is useful for evaluating the tracheal and larger airway for collapse. Ultrasound is useful if an isolated peripheral lesion is found on radiographs or in the presence of pleural effusion but is not useful in bronchitis.

CT, which is used widely in people with airway diseases, is growing in popularity for identification of canine bronchial disease as well. CT scanning usually requires brief general anesthesia, so it is commonly combined with evaluation of laryngeal function, bronchoscopy, and collection of cytologic airway samples in dogs suspected of having chronic bronchitis.

Bronchoscopic findings are variable. They can include irregular mucosal surfaces with a loss of the normal glistening appearance, a granular and roughened aspect, and sometimes signs of partial bronchial collapse. However, similar findings have been reported in aging healthy dogs, together with some degree of bronchiectasis,[44] and therefore, such findings must be interpretated with caution. The presence of excessive, thickened, sticky mucus in the airways also is consistent with chronic bronchitis.

Cytologic evaluation of BALF typically reveals excess mucus, possibly with hyperplasia of epithelial cells, and increased numbers of neutrophils, goblet cells, and macrophages.[45] Analysis of bronchial brushings might be a more sensitive indicator of airway inflammation than cytologic examination of BAL, by showing greater percentages of leukocytes and neutrophils.[46] If a sample shows marked eosinophilia, eosinophilic bronchopneumopathy or parasitic infection (heartworm/angiostrongylosis/*Crenosoma* infection) should be considered since these infections are markedly emergent in certain geographic regions, especially in Europe.[47-50]

Echocardiography (see ch. 104) helps to diagnose mitral valve disease, which can occur concomitantly in these older patients and deserves specific treatment, as well as to detect right heart enlargement and pulmonary arterial hypertension, which can occur secondary to chronic tracheobronchial disease.

Management and Monitoring

The bronchial alterations are not readily reversible, if at all. Therefore, treatment does not cure the disease but ideally will prevent or slow disease progression and improve clinical signs. Therapy is based on an assessment of the nature and severity of the individual animal's problems and relies on client education.

Treatment goals for dogs with chronic bronchitis include avoiding exacerbating factors, reducing inflammation, limiting cough, and improving exercise capacity.

Any environmental pollutants should be eliminated. Owners should be advised not to smoke indoors and to limit exposure of dogs to any airborne irritants, including perfumes.

Control of body weight is very important (see ch. 176 and 359). Obesity should be treated intensively because it markedly worsens cough and limits activity. Furthermore, obesity impairs lung function and increases airway hyperresponsiveness as measured by barometric whole body plethysmography (BWBP) and six-minute walk test (6MWT).[51,52] Weight loss induces a significant improvement of cardiopulmonary function assessed by the 6MWT associated with heart rate and blood oxygen saturation monitoring.[52] In obese dogs with chronic bronchitis, marked improvement in clinical signs is often seen with weight loss alone, without addition of any drug.

A harness should be used in place of a collar, and episodes of excessive barking should be curtailed with appropriate behavior modification.

Control of oral/periodontal infection and dental hygiene are advocated since bacteria from dental plaque could be inhaled and reach and deposit in the lower airways, especially during panting.

Glucocorticoids are the mainstay of treatment of chronic bronchitis because they are supposed to reduce mucous hypersecretion and bronchial mucosal thickening, which reduces cough. Glucocorticoids can be administered orally or via inhalation. Prednisone is the most commonly used glucocorticoid and is dosed at 1-2 mg/kg PO q 24 h initially and then tapered to the lowest effective dosage that controls clinical signs. Alternate-day therapy is preferred to allow normalization of the hypothalamic-pituitary axis and to limit

clinical signs associated with the use of exogenous glucocorticoids.

Inhaled glucocorticoids have been used widely in people and are used with growing frequency in dogs with chronic bronchitis. One study has demonstrated benefits of therapy with fluticasone, delivered via a spacer chamber and face mask designed especially for dogs (e.g., AeroDawg).[53] Of clinical relevance, inhaled glucocorticoids currently are more expensive than oral glucocorticoids, although the systemic steroid-sparing effect can be worthwhile in improving quality of life. Bronchodilators (beta-2 agonists, theophylline) are used frequently, although their effectiveness in the treatment of chronic bronchitis has not been widely addressed.

Antibiotics are warranted in dogs with an acute exacerbation of chronic bronchitis and a reasonable suspicion of infection. Doxycycline and macrolides (azithromycin) are good choices for dogs with chronic bronchitis because these drugs have antiinflammatory properties as well as antimicrobial effects.[40] Fluoroquinolones also have good tissue penetration; however, concurrent administration of fluoroquinolones with theophylline can result in theophylline toxicosis (see ch. 169).[54]

Cough suppressants are helpful for the comfort and relief of both dogs and owners, when cough is exhausting and refractory to antiinflammatory therapy. Over-the-counter cough suppressants rarely are effective in dogs, and narcotic cough suppressants are most effective. In some countries, oral preparations containing opioids have become less widely available. In countries where no oral preparation of butorphanol can be prescribed, a couple of drops of injectable solution deposited on the tongue can be effective, but neither the dosage needed nor the dose-effect relationship has been studied (Table 241-1). A study in human medicine has reported on the efficacy of gabapentin for control of cough related to hyperactive cough reflex sensitivity in people.[55]

TABLE 241-1

Cough Suppressants Used in Canine Chronic Bronchitis

DRUG	DOSAGE	COMMENT
Opioids		
Butorphanol	0.25-1.1 mg/kg PO q 8-12 h	Most effective. Potential side-effects include excessive sedation. Tolerance can occur over time.
Hydrocodone	0.2-0.3 mg/kg PO q 6-12 h	
Tramadol	2-5 mg/kg PO q 8-12 h	
Nonopioids		
Gabapentin	2-5 mg/kg PO q 8 h	Unestablished efficacy
Methocarbamol	15-30 mg/kg PO q 12 h	

Modified from Rozanski E: Canine chronic bronchitis. *Vet Clin North Am Small Anim Pract* 44:114, 2014.

Eosinophilic Bronchopneumopathy in Dogs

Etiology and Pathophysiology

Canine eosinophilic bronchopneumopathy (EBP) is a disease characterized by eosinophilic infiltration of lung and bronchial mucosa, considered to be manifestations of immunological hypersensitivity. Although the etiology of EBP still is unknown, the association of eosinophilic infiltration and predominance of CD4+ T cells favors a dominant Th2 immune response in the lower airways.[56] Suspected and known causes of pulmonary hypersensitivities in humans and animals include fungi, molds, drugs, bacteria, and parasites. However, in many cases, no underlying cause is found. The role of inhaled allergens in EBP still is unclear. Eosinophilic bronchopneumopathy mostly is diagnosed in young dogs. Siberian Huskies and Malamutes are affected predominantly, but many other breeds can be affected.

Clinical Presentation

Usually, the patient's general condition on presentation is good, unless the disease is associated with concomitant bacterial bronchopneumonia. Clinical signs mainly include cough, gagging and retching, which

are present in 100% of cases. In acute cases, gagging and retching are sometimes the main complaint, extending the differential diagnosis to dyspeptic problems. Dyspnea is a very frequent sign. A less commonly encountered sign is nasal discharge (≈50% of affected dogs).

Diagnostic Tests

Diagnostic elements for the diagnosis of EBP include signalment-associated and historical factors (breed, young age, previous response to corticosteroids), clinical signs, radiographic and bronchoscopic findings, blood eosinophilia, tissue eosinophilic infiltration as demonstrated by cytological and histopathological examinations, response to adequate treatment, and exclusion of other disorders. The most common radiographic finding is a mixed, moderate to severe, bronchointerstitial pattern (Figure 241-8). Computed tomographic findings associated with EBP are variable and heterogeneous and include marked to moderate bronchial wall thickening, plugging of the bronchial lumen by mucus/debris, bronchiectasis, pulmonary nodules, and lymphadenopathy.[57] Bronchoscopy (see ch. 101) can reveal typical macroscopic features, which include the presence of abundant yellow-green mucus or mucopurulent material, severe thickening of the mucosa with an irregular or polypoid surface and, in some cases, partial airway closure during expiration. Peripheral blood eosinophilia is frequent (≈60% of cases). BALF or brush cytologic examination demonstrates a marked eosinophilic component (E-Figure 241-9); frequently, >50% of inflammatory cells are eosinophils. In most cases, eosinophilic infiltration of the bronchial mucosa also can be observed in biopsies. Elevated BALF levels of procollagen type III amino terminal propeptide (PIIINP), a protein used as a marker of collagen type III synthesis, have been found in dogs with EBP, possibly due to secondary fibrotic changes.[58]

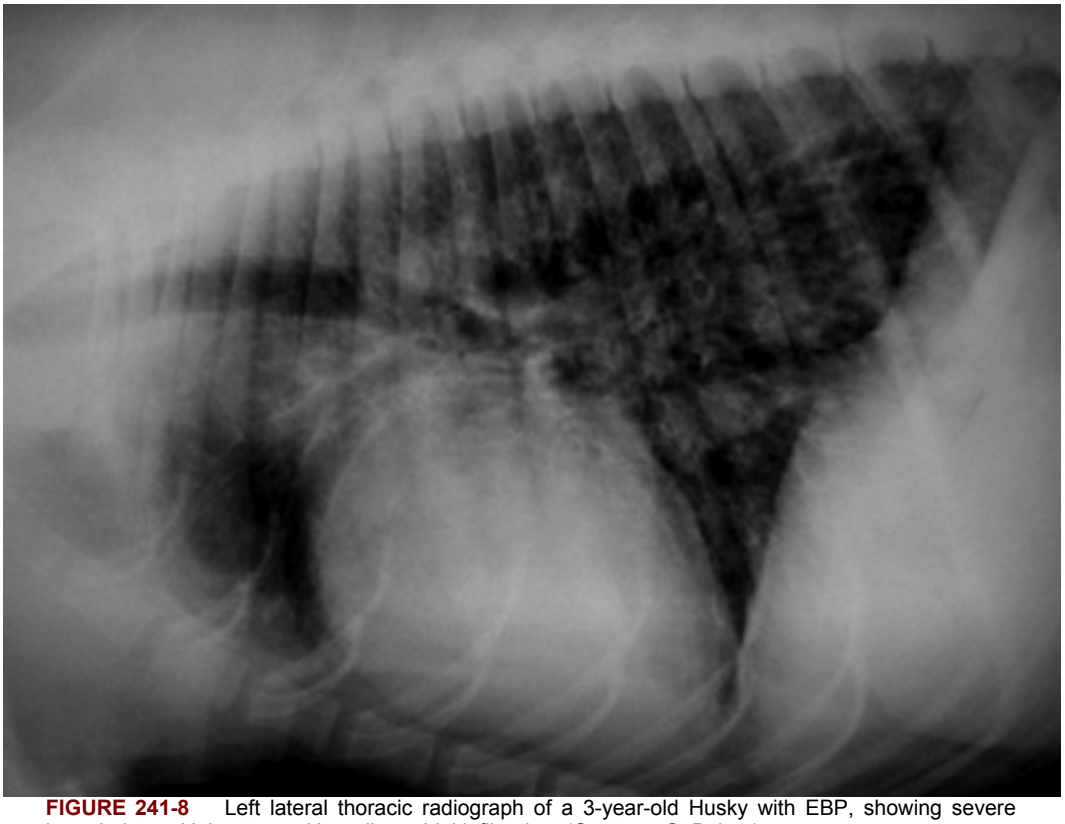
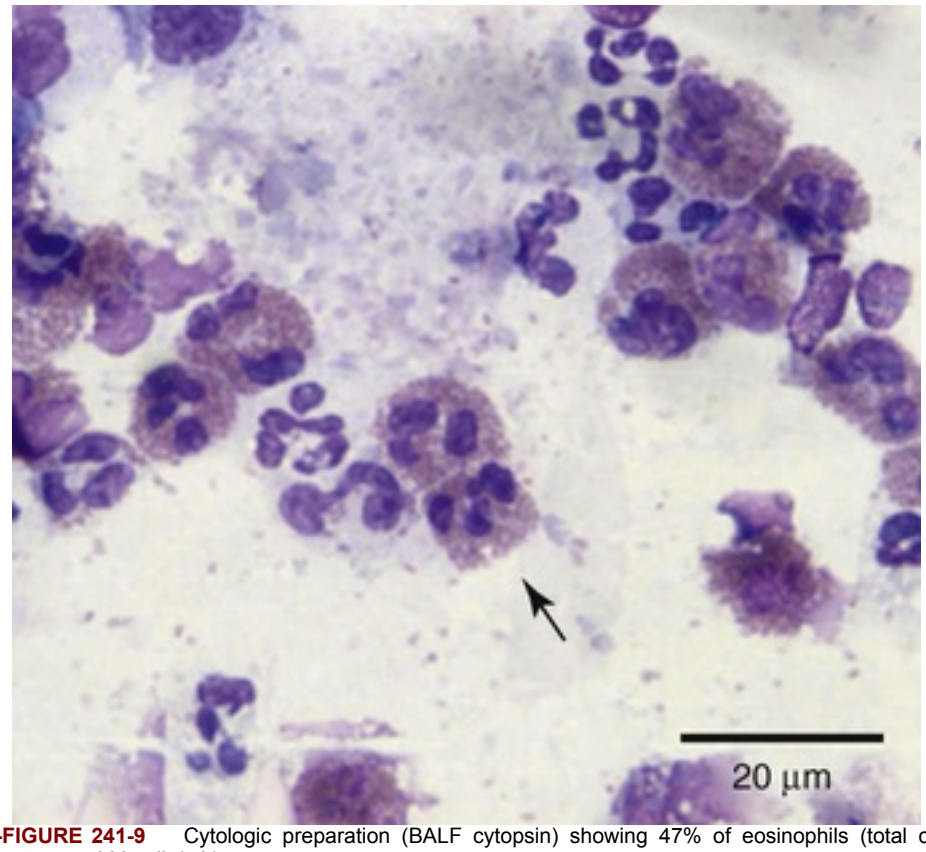


FIGURE 241-8 Left lateral thoracic radiograph of a 3-year-old Husky with EBP, showing severe bronchointerstitial pattern with peribronchial infiltration. (Courtesy G. Bolen.)



E-FIGURE 241-9 Cytologic preparation (BALF cytopsin) showing 47% of eosinophils (total cell count was 7000 cells/mL).

Differential Diagnosis

Several parasites, like *Strongyloides* spp., *Ascaris* spp., *Toxocara canis*, and *Ancylostoma* spp. can lead to eosinophilic pneumonia in humans, and probably in dogs as well; respiratory signs are only mild and GI signs usually predominate.

In the dog, occult heartworm disease caused by *Dirofilaria immitis* can cause eosinophilic pneumonitis. Migration of larvae of *Angiostrongylus vasorum* through pulmonary parenchyma also can result in eosinophilic pneumonia in dogs (Video 241-7). Infection by this nematode worm (also called the French heartworm disease) is an emerging disease, with reported increases in both distribution and incidence in the United Kingdom, Europe, South Africa, and Newfoundland (Canada). The expanding geographic range might be related to the influence of climate on parasite distribution. The worm infects dogs and foxes and is spread through ingestion of intermediate hosts, including slugs and snails. The main clinical signs include respiratory signs, bleeding disorders, and neurologic signs[59] and are very variable in severity, with a course of disease that often is chronic and subtle. However, early and correct diagnosis is required, since angiostrongylosis can be fatal if left untreated. In cases with respiratory clinical signs and in endemic regions, radiographic pulmonary changes alone can be suggestive of the diagnosis, and they include moderate to severe bronchointerstitial or alveolointerstitial changes, often more severe in peripheral and/or caudodorsal areas (Figure 241-10). Other bronchopulmonary parasites, like *Capillaria aerophila, Oslerus osleri, Filaroides hirthi, Crenosoma vulpis* (Video 241-8), or *Paragonimus kellicotti,* also are implicated in the influx of eosinophils into the airways *(O. osleri)* or lungs (other parasites) in dogs and can mimic EBP. A higher frequency of bronchial disease caused by infection with *Crenosoma vulpis* also is becoming apparent in continental Europe.[60]

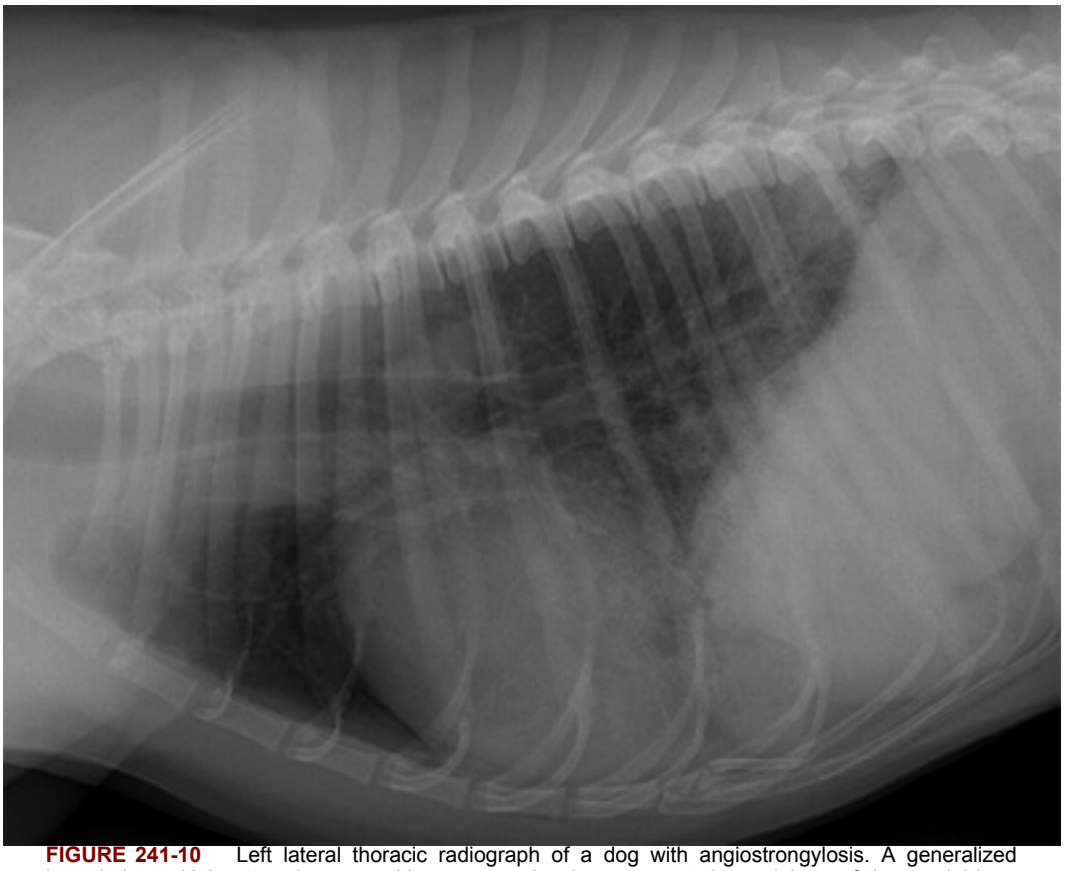


FIGURE 241-10 Left lateral thoracic radiograph of a dog with angiostrongylosis. A generalized bronchointerstitial pattern is seen, with a severe alveolar pattern at the periphery of the caudal lung lobes (note air bronchograms). A pleural fissure line between the left cranial and the caudal lobes and mild lung lobe retraction from the thoracic wall are consistent with mild pleural effusion. The pulmonary arteries and veins are enlarged.

For these reasons, screening for parasites is warranted, using BALF analysis or serial fecal examinations (Figure 241-11, ch. 81). In-clinic detection of an antigen released by *A. vasorum* adults in a plasma or serum sample is possible (Angio Detect, IDEXX Laboratories),[61] or *A. vasorum* PCR detection in BALF can be undertaken.[50] In endemic areas, it is strongly advised to perform a heartworm antigen test to rule out occult heartworm disease. Alternatively, in the meantime, appropriate antihelminthic drugs can be used in order to treat the animal against potential parasites.[47]

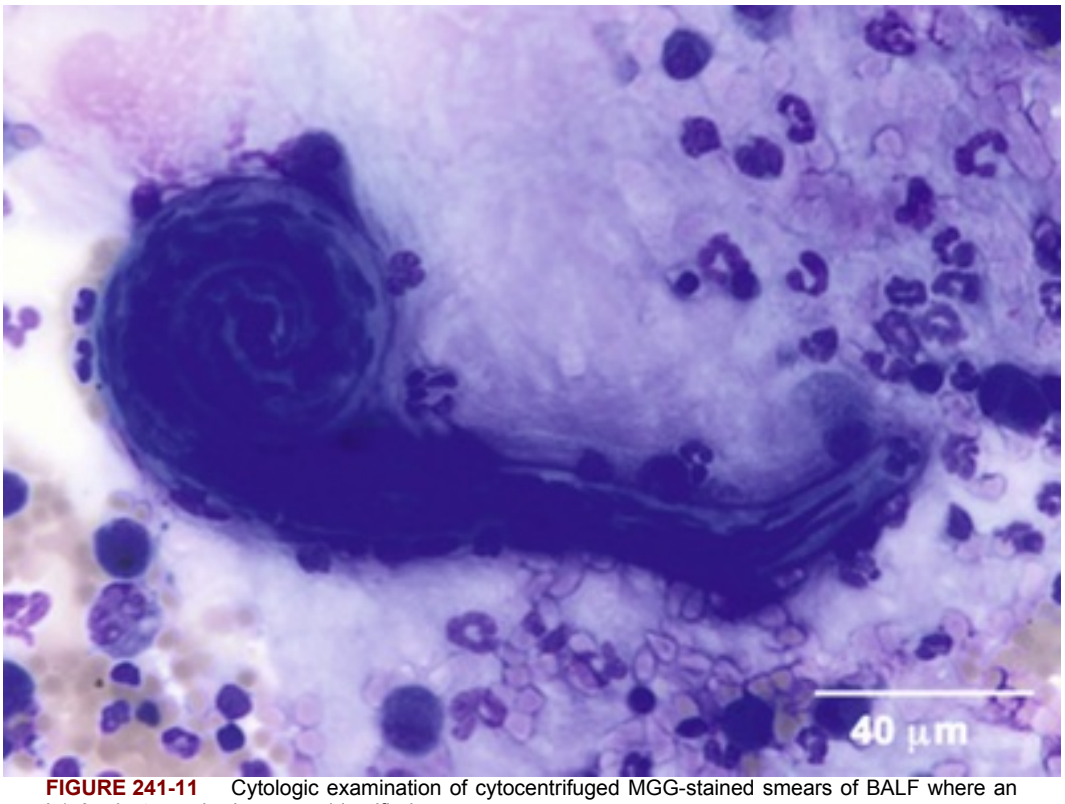


FIGURE 241-11 Cytologic examination of cytocentrifuged MGG-stained smears of BALF where an L1 *Angiostrongylus* larva was identified.

Management

The response to corticosteroid therapy generally is very good, but complete abolition of clinical signs is not always obtained. Prednisolone is initiated at a dosage of 1 mg/kg PO q 12 h × 1 week, then 1 mg/kg PO q 12 h but on alternate days × 1 week, then 1 mg/kg PO q 24 h on alternate days × 1 week, followed by a gradual decrease until maintenance dosage. Since chronic oral corticosteroid therapy unfortunately can lead to well-recognized systemic side-effects (i.e., iatrogenic hyperadrenocorticism), and since its use also can be contraindicated in dogs with other concomitant health problems such as diabetes mellitus, obesity or cardiac diseases (see ch. 358), alternative treatment with inhaled steroid therapy (IST) has been used increasingly in past years in both human and veterinary medicine, with the suggested advantages of providing both high drug concentrations within the airways and a reduced systemic absorption and potentially deleterious secondary effects. Inhaled corticosteroid therapy is well-tolerated, results in improvement in clinical signs and reduction in side-effects, and allows a reduction of oral steroid dosage in steroid-dependent animals.[53,62] However, it seems that treatment of EBP with long-term IST alone does not allow complete management in all affected dogs and that sustained, long-term IST can induce inhibition of pituitary–adrenal axis (PAA).[62] Other drugs with immunomodulatory effect have been proposed, but no trial results are available to date.

Prognosis

Relapse frequently occurs within weeks to months after drug discontinuation, although some dogs can remain free of clinical signs after discontinuation.

Primary Ciliary Dyskinesia (PCD)

Presentation

PCD, previously referred to as immotile cilia syndrome, results from a heterogeneous group of inherited diseases that cause defective ciliary motility. These changes mostly are associated with ultrastructural abnormalities and cause recurrent bacterial infection of the upper and lower airways. In affected dogs, as in affected humans, the ineffectiveness and incoordination of ciliary function result in ineffective clearance of mucus from the airways, which in turn leads to chronic mucus plugging and inflammation of nasal cavities

and airways. The dysfunction of the monocilia of the embryonic node also can lead to the randomization of left-right body asymmetry and transposition of the thoracic and/or the abdominal organs in 50% of the cases called the Kartagener's syndrome.[63] Kartagener's syndrome represents a triad of signs that includes bronchiectasis, complete left-right transposition of viscera (situs inversus) and chronic rhinosinusitis. This syndrome has been reported in humans and in dogs with PCD. In dogs, PCD is a rare disease that has nevertheless been reported in more than 19 breeds.[64-68]

Etiology

Currently, PCD-causing mutations have been identified in more than twenty human genes.[68] Each causative gene can be associated with particular ultrastructural ciliary defects, and these 20 genes explain only 50% of human PCD cases. Dog cases often focus on one individual from a specific breed, but sometimes littermates are affected or different cases can segregate within the same breed.[65,66,68] This genetic disease usually is inherited in an autosomal recessive mode. In dogs, a recent mutation in a new causative gene *(CCDC39)* has been identified in the Old English Sheepdog.[67] This new mutation is dispersed worldwide and is responsible for PCD in this breed. A new genetic test has been developed and is currently available for prebreeding evaluation in this breed, but not yet in other dog breeds.

Clinical Presentation

As a consequence of impaired mucociliary clearance, clinical signs include chronic respiratory abnormalities caused by rhinosinusitis, bronchitis, bronchopneumonia and bronchiectasis. Although the respiratory system signs usually are the presenting complaint, other signs related to dysfunction in other tissues with ciliated epithelia or microtubules can occur, such as otitis media, infertility in females, asthenoteratospermia in males, hydrocephalus, and renal fibrosis or dilation of renal tubules. The signs typically begin at an early age in a purebred, vaccinated dog; however, some dogs have remained asymptomatic until several months to several years of age. Hallmark clinical features, i.e., recurrent bilateral nasal discharge and repeated episodes of bronchitis or bronchopneumonia since birth, should alert the clinician to include PCD in the differential diagnosis.

Diagnosis

Finding the hallmark clinical features in combination with situs inversus is even more suggestive. Most other potential possible causes should be excluded by a complete physical examination, as well as currently available complementary tests. Confirmation of PCD requires both *in vivo* and *in vitro* functional and ultrastructural analysis of cilia. *In vitro* functional analysis of cilia in dogs suspected of having PCD uses scintigraphy as the diagnostic tool to evaluate mucociliary clearance. *In vivo* functional analysis in PCD patients consistently demonstrates an uncoordinated or a dyskinetic ciliary beat.

Motile cilia are composed of a microtubule backbone, the axonema, consisting of nine microtubule doublets surrounding a central pair. Inner and outer dynein arms extend from each outer microtubule doublet and generate the force needed for motility in an ATP-dependent process. Ciliary dysmotility or immotility often is associated with ultrastructural defects of the cilia such as total or partial absence of the outer dynein arms (ODAs) and/or inner dynein arms (IDAs), defects of radial spokes or nexin links and general axonemal disorganization with microtubular transposition.[69] Transmission electron microscopy can reveal specific ultrastructural abnormalities (Figure 241-12), although making the distinction between PCD and secondary ciliary defects caused by another primary disease, based on ultrastructural findings alone, often is difficult. Therefore, the use of a ciliary culture technique, ciliogenesis, has been shown to definitively distinguish primary from secondary eitologies.[64] In the Old English Sheepdog, a Taqman assay with excellent sensitivity and specificity was developed and has led to evaluation of the mutation's prevalence in the breed. The mutated allele has been found both in European and in American Old English Sheepdogs, suggesting a worldwide distribution.[68] This genetic test also allowed the initiation of a breeding program detecting silent carriers and preventing the birth of affected individuals.

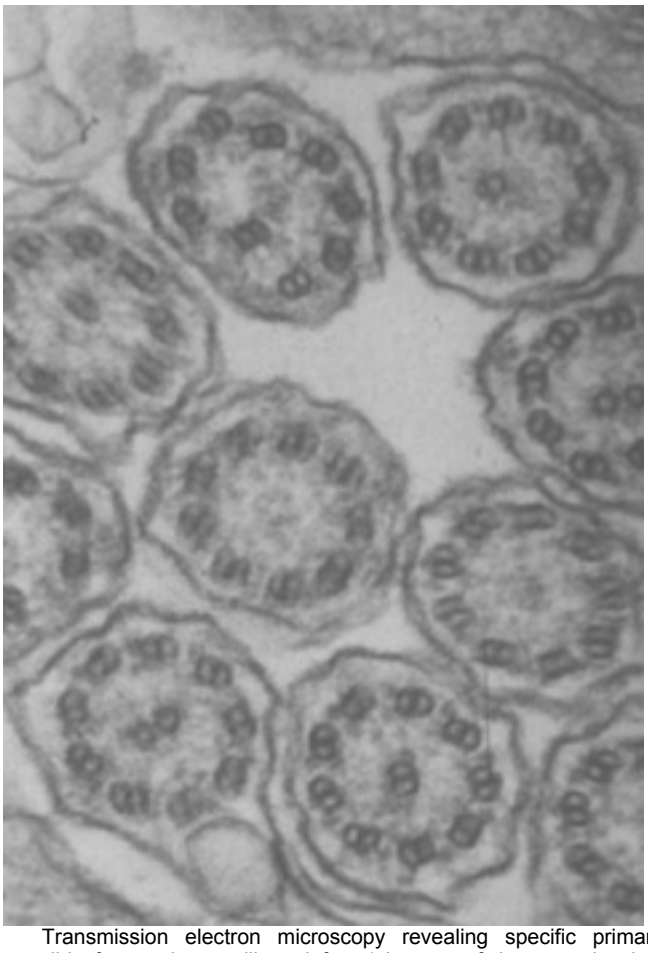


FIGURE 241-12 Transmission electron microscopy revealing specific primary ultrastructural abnormalities responsible for a primary ciliary defect (absence of the central pair, with occasional transposition of a peripheral doublet).

Differential Diagnosis

Other causes of recurrent bacterial infection of the upper (in early cases) and lower airways should be investigated, such as the presence of an immune deficiency, resistant bacteria, or a bronchial foreign body. In Irish Wolfhounds, a rhinitis/bronchopneumonia syndrome, characterized by transient to persistent mucoid or mucopurulent rhinorrhea, cough, and dyspnea since an early age has been described; so far, PCD has not yet been formally identified as the cause of the disease.[70]

Management

Even though PCD is not a curable disorder, frequently it can be managed for some years (see ch. 97 and 242). A key element in this successful management is the adequate monitoring of infecting microorganisms and judicious use of antibiotics over time. Moreover, adequate systemic and local hydration together with daily coupage and vigorous exercise will help to clear mucus from the airways.

Prognosis

Once the diagnosis is established, medium- to long-term prognosis is poor, because despite adequate management, the disease generally progresses over time and the response to treatment becomes poorer.

Bronchoesophageal Fistula[17,29]

A bronchoesophageal fistula is defined as a communication between the esophagus and one or more bronchi. Most cases are seen secondary to foreign body ingestion and penetration in young to middle-aged dogs (very unusually in cats). Clinical signs involve both the respiratory and GI tracts, with noisy rales, depression, fever, and a loss of appetite. Pleural effusion also can occur, in addition to a localized pneumonia.

The diagnosis usually is made on plain radiographs, with evidence of pneumonia, an esophageal foreign body, gas distention of the esophagus, and possible pleural effusion being present. On a complete blood count, an increased white blood cell count with a left shift is expected. Confirmation is best obtained with thoracic radiographs taken following oral administration of a small amount of a barium suspension. Endoscopic examination can provide a direct view, but radiography is considered more likely to be diagnostic. Successful correction of the fistula is best accomplished with thoracic surgery to reduce the defect, lavage the affected area, and very likely perform a lobectomy to remove the infected tissues. If the disorder is identified early and treated properly, the prognosis for recovery can be good. Complications arising from esophageal stricture can be a problem, particularly if identification and treatment are delayed.

Bronchial Mineralization, Broncholithiasis[29]

Bronchial mineralization is rarely encountered. It can occur secondary to any chronic inflammatory or infectious condition. Bronchial mineralization may in fact be totally unassociated with clinical evidence of dysfunction. Peribronchial mucous glands can mineralize in normal cats, appearing as multifocal mineralized opacities.[71]

Bronchial Diseases—Secondary

Bronchiectasis

Introduction

Bronchiectasis is defined as an abnormal and permanent dilation and distortion of subsegmental airways, which results from chronic airway inflammation that damages elastic components of the bronchi and which leads to bronchial wall destruction and impaired clearance of respiratory secretions.[72] It is considered a unique disease entity, although several congenital or acquired conditions that lead to a cycle of chronic airway infection and inflammation can result in bronchiectatic changes.

Etiology and Pathophysiology

In humans, bronchiectasis can be categorized into cystic fibrosis (CF)-related bronchiectasis and non-CF bronchiectasis. CF is an inherited disease caused by a mutation in the gene for the protein cystic fibrosis transmembrane conductance regulator (CFTR). Viscous mucus plugging results in infection and inflammation, leading to airway wall destruction and bronchiectasis. Individuals with CF can be diagnosed before birth by genetic testing or by a sweat test in early childhood. So far, naturally occurring cystic fibrosis (CF)-causing mutations in the CFTR gene have not been identified in any nonhuman animal species. A study conducted in dogs revealed that naturally occurring CFTR mutations are relatively common in domestic dogs but failed to identify a higher expression rate of CFTR mutations in dogs with bronchiectasis.[73] Therefore, bronchiectasis in dogs and cats probably is mainly due to non-CF bronchiectasis. In both humans and dogs, non-CF etiologies of bronchiectasis include congenital or inherited diseases. In dogs, congenital disorders predisposing to bronchiectasis include PCD, with or without Kartagener's syndrome. Whether PCD and Kartagener's syndrome really occurs in cats is an open question; if it exists, it is extremely rare. In dogs and cats, focal bronchiectasis most often results from foreign body aspiration and/or bronchial obstruction.[4,74]

Diffuse bronchiectasis often occurs subsequent to acquired diseases,[4,41,76] including aspiration or inhalation injury, chronic infectious bronchopneumonia (including parasitic origin), chronic infection with *B. bronchiseptica* or *Pneumocystis carinii* in dogs with immune deficiency, eosinophilic bronchopneumopathy, chronic bronchitis and potentially, allergic bronchopulmonary aspergillosis (a rare cause of localized cavitary bronchiectasis).[76] In cats, chronic bronchial inflammation has been suggested as the most common etiology associated with bronchiectasis, especially chronic bronchitis, neoplasia, and bronchopneumonia,[77] and has been described in a case of diffuse fibrotic lung disease.[78] The affected airways are usually partially obstructed by purulent or viscid exudates, since the dilation greatly interferes with normal airway clearance.

Dysfunction of mucociliary clearance, in turn, allows pooling of mucus, exudate, and microbes, and secondary infection stimulates a host inflammatory response, creating a vicious circle of further damage to the airway wall and predisposition to recurrent bronchopulmonary infections (Figure 241-13).

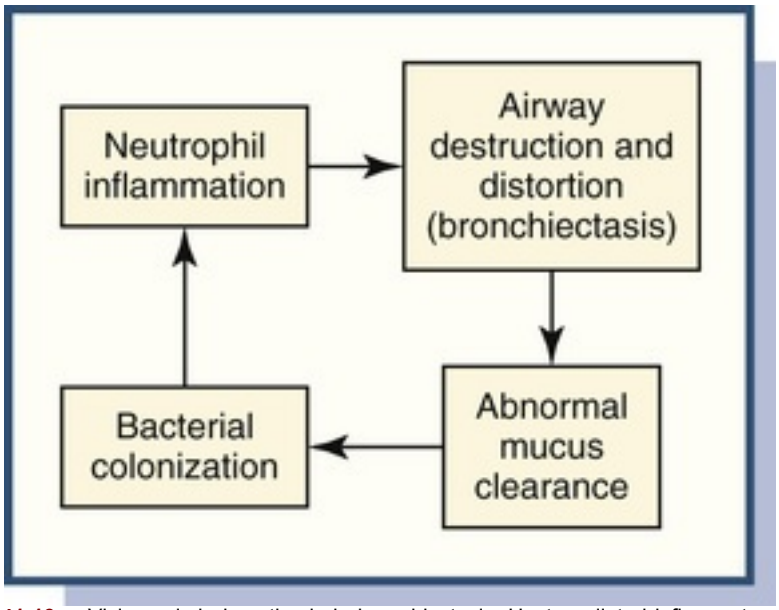


FIGURE 241-13 Vicious circle hypothesis in bronchiectasis. Host-mediated inflammatory response to foreign material and bacteria in the airway causes tissue damage, resulting in bronchiectasis, which contributes to abnormal mucus clearance and further bacterial colonization.

Signalment, Clinical History, and Presentation

In dogs, there appears to be a breed predilection because bronchiectasis is more prevalent in certain breeds such as the American Cocker Spaniel, Miniature Poodle, Siberian Husky, and English Springer Spaniel.[74] Moreover, most dogs with bronchiectasis are ≥7 years old.[74] Clinical signs likely reflect the underlying disease process and generally include cough (most common), gag, tachypnea, dyspnea, and occasionally fever.[74] Bronchiectasis can be detected by thoracic radiography, high-resolution computed tomography (HRCT) or bronchoscopy (Videos 241-9 and 241-10). Radiographic and bronchoscopic characteristics of bronchiectasis in dogs have been described.[74,75] Bronchoscopy is not considered the gold standard, but it is highly helpful to recognize/visualize bronchiectatic lesions and, more importantly, to enable collection of samples for identification and potential treatment of possible underlying diseases (see ch. 101). Bronchoscopic evaluation identifies mucopurulent plugs in the dilated airways and hyperemic, roughened bronchial wall linings.

In people, survey thoracic radiography is not considered a very sensitive technique for evaluation of bronchiectatic changes, nor is bronchography used for this purpose any longer. HRCT has been described as the noninvasive gold standard for diagnosing bronchiectasis. Primary CT features of bronchiectasis in people include abnormal bronchial dilation, lack of peripheral bronchial tapering, and identification of distinct airways within 1 cm of the pleural surface. Secondary features include bronchial wall thickening, mucus plugging within the bronchial lumen, and peripheral air trapping as reflected by measurable reduced pulmonary density in affected regions.[79] The most widely used CT criterion for quantifying abnormal bronchial dilation is the bronchoarterial (BA) ratio (the ratio of the cross-sectional bronchial luminal diameter to accompanying pulmonary artery diameter) >1.[79] In dogs, a recent study revealed that healthy dogs can have a BA ratio of up to 2.0.[80] In a retrospective study of dogs with bronchiectasis diagnosed via bronchoscopy and/or histopathology, the most common CT characteristics of bronchiectasis were dilation, lack of peripheral airway tapering, and lobar consolidation.[80]

In a large series of dogs with EBP, CT revealed bronchiectasis in 60% of the dogs.[57]

Since there is a lack of studies correlating CT with bronchoscopic features of bronchiectasis in dogs, the sensitivity of bronchoscopic diagnosis of bronchiectasis is questionable. Age has been shown to influence bronchoscopic findings in healthy Beagle dogs: bronchiectasis has been described as a normal endoscopic finding in older Beagles, and this finding does not seem to be associated with an increased neutrophilic content of the BALF.[44] Such age-related differences should be considered when interpreting bronchiectasis in old dogs with respiratory disease.

Culture and sensitivity of BALF for both aerobic and anaerobic bacteria are suggested because this is likely

to be helpful in treating the patient. Bacteria frequently isolated from people with bronchiectasis include *Pseudomonas aeruginosa, Haemophius influenzae, Staphylococcus aureus,* and some others.[81] In dogs, no conclusion regarding the frequency of distribution of bacteria in patients with bronchiectasis can be drawn.[74]

Cytologic evaluation of such fluid typically identifies neutrophilia, eosinophilia if allergic in nature or in the presence of parasitic infection, and squamous metaplasia of the epithelial cells. PCR performed on BALF can be useful to identify *Bordetella* spp., *Mycoplasma* spp. or *Aspergillus* spp., since allergic bronchopulmonary aspergillosis might be a cause of localized cavitary bronchiectasis,[76] as described in people.

Management

The goal of therapy for bronchiectasis is to control clinical signs and treat or even prevent bacterial infections. In human medicine, the therapeutic approach includes airway clearance, reducing chronic infection and inflammation, and treatment of exacerbations. Inhaled therapies form the backbone of treatment (see ch. 97). In combination with antibiotics delivered directly into the airway, mucoactive drugs, including mucolytics and hyperosmolar agents, are utilized to improve mucociliary clearance and to reduce infection and inflammation. Antibiotics, especially in the inhalational form, reduce exacerbations and inflammation by decreasing bacterial density. Macrolides reduce exacerbation frequency and are a mainstay of antiinflammatory therapy in bronchiectasis.[82] Macrolide antibiotics have antiinflammatory and immunomodulatory properties (without suppression of the immune system) in addition to antibacterial activity. They are used widely in the treatment of bronchiectasis in humans.[82,83] The advantage of using macrolides instead of glucocorticoids to manage inflammation is immunomodulation without immunosuppression. Studies investigating the risks and benefits of long-term use of macrolides in dogs or cats with bronchiectasis are lacking. At present, there are no definitive data to support the routine use of glucocorticoids, even via inhalation, unless the patient suffers from coexisting asthma or EBP.

Prognosis

Addressing the underlying pathological process is vital to attempt to slow the progression of destruction of bronchial walls. Despite substantial clinical abnormalities, dogs with bronchiectasis can survive for years.[74] Patients with focal bronchiectasis are exceptions because surgical resection of the affected lung lobe can be curative.

Bronchomalacia

Overview and Etiology

Bronchomalacia (BM) is characterized by weakness of the walls of principal or smaller bronchi, leading to collapse of the bronchial wall. In veterinary medicine, bronchomalacia recently has been increasingly recognized.[5,84-86] The etiology is unclear. Based on endoscopy, BM can be classified as static, dynamic, or both.[86] While static BM is common in brachycephalic dogs,[85] dynamic BM (Video 241-11) most frequently occurs in association with tracheal collapse and is called tracheobronchomalacia. Indeed, in a population of 115 dogs admitted for evaluation for respiratory disease and examined by bronchoscopy, tracheobronchomalacia was documented in 50% of dogs examined, with tracheal collapse in 21% and bronchomalacia in 47%.[5] This shows that dynamic BM also can occur as an isolated clinical entity, associated with bronchial infection and/or inflammation[84] or not. Indeed, the role for airway inflammation in BM cannot be confimed in many cases.[5,87] Furthermore, the role of cardiomegaly in the disorder recently has been investigated, but no association between left atrial enlargement and airway collapse could be identified.[9]

Clinical Presentation

Since BM frequently is associated with tracheal collapse, Poodles and Yorkshire Terriers, especially when overweight or obese, are affected most commonly.[5,84] Many brachycephalic dogs show static BM.[85] However, other breeds can be affected, especially older individuals.

Clinical signs include chronic cough, wheezing, intermittent or continuous dyspnea, difficulty in clearing secretions, and possibly signs of recurrent bronchitis and pneumonia. Pulmonary crackles can be heard on lung auscultation.[84] Since radiographs seem to be poorly sensitive for the detection of airway collapse, documentation of BM requires bronchoscopy (see ch. 101).[5] Static and dynamic types of BM can exist concurrently, particularly in larger dogs, those with pulmonary hypertension, a bronchial radiographic

pattern, and nodularity on endoscopic examination.[86]

Diagnosis

Bronchosopy can reveal that both lungs are affected; in about half of cases, the disease appears to affect the left lung predominantly.[84] Analysis of BALF and biopsies of the bronchial mucosa are warranted and can reveal evidence of infectious bronchitis in about half of affected dogs.

Treatment and Prognosis

Treatment is supportive and nonspecific; it should be based on clinical findings in each case. So far, there is a lack of studies investigating how dogs with BM respond to treatment, and detailed information about the prognosis is unavailable.

Feline Lower Airway Disease

In cats, cough is an infrequent clinical sign, unlike in the dog. Furthermore, in cats, cough is fairly specific for tracheobronchial disease since cough of cardiac origin is rare. Feline lower airway disease (FLAD) is a term that encompasses all bronchial diseases, including inflammatory and noninflammatory bronchial diseases. Inflammatory bronchial diseases are by far much more common.

Feline inflammatory bronchial disease (feline asthma or bronchitis) is characterized by inflammation of the lower airways without an obvious identifiable cause. It is recognized clinically by various combinations of cough, wheeze, exercise intolerance, and respiratory distress, attributable to airway obstruction caused by bronchial inflammation.

Many confusing terms are found in the literature, such as chronic bronchitis, allergic bronchitis, eosinophilic bronchitis, and bronchial asthma. Discriminating asthmatic bronchitis from nonasthmatic bronchitis is still challenging. Whether feline asthma and chronic bronchitis are truly separate entities or two facets of the same disease remains uncertain.[88] According to some authors, feline asthma and chronic bronchitis should now been considered as two distinct diseases.[89] Differences in etiology, thoracic radiographic features, bronchoalveolar eosinophil/neutrophil percentages, and response to airway responsiveness testing (ART) have been described, but no clear-cut discriminatory test exists.[106,118,145] Categorization is based on eosinophil and neutrophil percentages in BALF. Several studies have reported values for cell types in feline BALF,[94] but specific reference ranges have not been established. Consequently, both eosinophil and neutrophil thresholds for defining asthma and chronic bronchitis are assigned arbitrarily.[105,106]

Due to this lack of consensus regarding the exact definition of feline asthma, most published studies fail to discriminate spontaneous feline asthma from feline chronic bronchitis. Despite the excellent reviews that have been published recently,[96] it is difficult to present information for both diseases separately. Therefore, information will be presented here under the broader heading of feline inflammatory bronchial disease.

A large volume of interesting information has been gathered by studying feline asthma models. These represent a pivotal advance in the study of this condition, allowing both pharmacological and immunological investigations. However, although interesting and promising experimental results have been obtained (for details, see Reinero's excellent review[90]), great caution must be exercised before results from research can be transposed to practice. Clinical studies are needed to further explore the potential value of the proposed inhaled medications, immunotherapy, or other treatments in feline patients with inflammatory bronchial disease. Additionally, discriminating feline inflammatory bronchial disease from noninflammatory chronic lower airway diseases (e.g., infectious or chronic bronchitis due to a variety of parasitic infections) is necessary because of differences in pathogenesis, treatment, and prognosis.[96]

Feline Inflammatory Bronchial Disease

Pathogenesis and Pathophysiology

According to Reinero,[90] asthma and chronic bronchitis in cats should be considered as two distinct syndromes. Chronic bronchitis is thought to arise secondarily to a previous insult that has damaged the airway permanently, leading to many clinicopathological features that are similar to those of asthma. Feline asthma is thought to be allergic, although presently, it is not yet clear whether an allergic form can be differentiated from a chronic disease of other origin. In humans, asthma is mediated by an allergic response

after exposure to inhaled allergens. This induces stimulation of a T helper 2 response, leading to the secretion of an array of cytokines that drive the immune response responsible for the pathologic changes in the airways. Details of the immunopathogenesis of allergic asthma and evidence to support that allergic asthma exists in cats have been reviewed.[90] In human asthma, clinical signs are related to 3 hallmark features: (1) reversible airway inflammation and (2) consequent obstruction/airflow limitation, linked to (3) airway hyperresponsiveness but also to smooth muscle hypertrophy, excessive mucus production (mucous gland hypertrophy) and accumulation, and bronchial wall edema.[91] Those changes are sometimes reversible. However, chronic inflammation can lead to severe lower airway obstruction, which causes lung hyperinflation, because cats are unable to exhale completely past the narrowed airways, resulting in air trapping. Lung hyperinflation can lead to permanent change, evidenced by progressive airway remodeling, including bronchiectasis, fibrosis, and/or emphysema.

Signalment and Clincal Signs

Young to middle-aged cats are most commonly affected. No clear gender or sex predisposition has been reported,[88,92-95] although middle-aged females (2-8 years)[4] and possibly Siamese cats[92,95] seem to be represented more frequently. Clinical signs consist of cough and increased breathing effort, which vary in severity.[90,96] Clinical signs often are chronic or slowly progressive. In some cats, signs go unnoticed by the owner for long periods of time. In others, complaints include vomiting or attempts at hacking up hairballs, which can mistakenly deviate the clinical management plan toward GI work-up and/or treatment. Mildly affected patients can have only occasional and brief episodes of cough separated by long periods without clinical signs, while in moderately or severely affected cases, cough occurs daily and cats can have a decreased quality of life with breathing discomfort. Cats with severe exacerbations ("asthmatic crisis" or "status asthmaticus") can present acutely with open mouth breathing, dyspnea, and cyanosis. Exacerbation can occur in association with exposure to potential allergens or irritants, such as aerosol sprays, cigarette smoke, or environmental dust, or after stress or exercise, such as the stress associated with a visit to the veterinarian.

Diagnosis

In cats experiencing an asthmatic crisis, excessive handling of the patient is contraindicated. Auscultation, when possible, can reveal decreased heart sounds, due to extreme lung hyperinflation. Cats should first be stabilized as soon as possible (see ch. 131 and 139). In cases that are less severe, physical examination findings are variable; physical examination can be normal at rest or it can include a positive tracheal reflex and/or the presence of tachypnea or obstructive expiratory dyspnea. Auscultation can be unremarkable or it can reveal wheezes during the expiratory phase or, more rarely, crackles. Cardiac function is not impaired, unless the cat suffers from concomitant heart disease. At this stage, additional testing is required because diseases that can mimic clinicopathologic features of asthma need to be ruled out.

Imaging

The classic thoracic radiographic pattern in cats with inflammatory bronchial disease includes evidence of bronchial wall thickening (doughnuts or railroad tracks) or a bronchointerstitial pattern; air trapping also can be evident (increased lucency and flattening of the diaphragm), and some cats show evidence of right middle lung lobe atelectasis.[95,97] In many cases, radiographic findings are not specific enough to confirm the diagnosis, and in some cats, radiographic findings are within normal limits. Thoracic CT can identify abnormalities such as bronchial wall thickening, patchy alveolar patterns, and bronchiectasis[98] and identify lesions that are not appreciated on plain radiographs. In cats, CT can be performed using a plexiglass chamber (the VetMousetrap) allowing acquisition of images without chemical restraint,[99] which is of great benefit in cats that are unable to tolerate stress. Current studies are ongoing to determine the impact of this promising and elegant approach in feline bronchitis.[100]

Bloodwork

Approximately 20% (17-46%, depending on the study) of affected cats have a peripheral eosinophilia,[92,93,95,101] which is not correlated with the degree of airway eosinophilia. A stress leukogram can be observed, and nonspecific hyperglobulinemia is noted in 14-50% of cases.[102] A heartworm antibody/antigen test can be used if clinical features are consistent with heartworm-associated respiratory disease (see ch. 255).

Fecal Analyses

Fecal examination (see ch. 81) is recommended as part of the diagnostic work-up, in an attempt to rule out/detect a parasitic origin for the eosinophilic infiltration such as *Aelurostrongylus abstrusus* (using the Baermann test) or *Toxocara cati* (by fecal flotation).

Bronchoscopy and BALF Analysis

In cats, bronchoscopy is considered less safe than in dogs, mainly due to the small size of the airways and the relatively higher airway responsiveness of the cat.[103] Moreover, as soon as the cat is dyspneic, the procedure is more hazardous since the risks of anesthesia increase, and complications during the procedure or during recovery could be serious and life-threatening. Bronchoscopic findings are not highly specific and can include moderate to large amounts of mucoid or viscous material, with or without airway mucosal hyperemia (see Video 241-11).

Cytologic examination of airway samples, obtained by BAL or endotracheal wash (ETW) (see ch. 101) generally provides evidence of airway inflammation, with increased numbers of eosinophils and/or neutrophils. Although a predominance of eosinophils can be found in fluids from healthy cats, the numbers of eosinophils and neutrophils in BAL fluid have been shown to correlate with disease severity, in cats with either spontaneous disease[94] or experimentally induced bronchial disease.[104] Feline asthmatic disease certainly is primarily characterized by a predominance of eosinophils in BALF; however, so far there is no clear cut-off for distinguishing normal from abnormal based on BALF cellular percentages. According to some authors, in inflammatory conditions, the infiltration can be qualified as being predominantly eosinophilic when the following criteria are met: >20% eosinophils and neutrophil percentage within reference limits, or >50% eosinophils; the infiltration can be qualified as being predominantly neutrophilic when BALF contains >7% neutrophils with eosinophil percentage within reference limits, or >50% neutrophils; finally, inflammation is considered to be mixed when concurrent increases in both eosinophil and neutrophil percentages or absolute numbers are found.[105] On the other hand, many studies mention that eosinophilic infiltration relates to the presence of >17% eosinophils while chronic bronchitis relates to the presence of >7% neutrophils in the BALF, with cats with >17% eosinophils and >7% neutrophils being grouped with asthmatic cats.[106] Such definitions are even less useful when a cat was treated previously with glucocorticoids, which decrease the eosinophil count. A recent study has confirmed that in healthy feline airways a BALF eosinophil percentage of <5% can be expected, and that there is good correlation between the findings (in particular the relative concentration in eosinophils) in BALF and in tissue in feline asthma.[107]

Samples of BAL and ETW fluid may be submitted for culture or PCR testing for bacterial, mycoplasmal and parasitic organisms. *Mycoplasma* infection can cause lower respiratory tract infection in cats[88,108,109] and might be associated with feline bronchial disease,[88,109] and infection with *Aerulostrongylus abstrusus* and *Troglostrongylus* spp. can cause a similar clinical picture.[110] *Mycoplasma* species also can be detected in the BALF of sick cats without respiratory signs and might represent commensal organisms of the lower respiratory tract of cats.[109]

Several inflammatory biomarkers (such as cytokines involved in the allergic reponse, e.g., interleukin-4, interferon-gamma and tumor necrosis factor alpha) have been measured in BALF from cats with feline bronchial disease, in an attempt to distinguish between asthma and chronic bronchitis, but the study failed to detect any difference, even compared with control cats.[106] Concentration of endothelin-1 (ET-1) in BALF has been shown to differentiate normal cats from those with experimentally-induced asthma; therefore, BALF-ET1 might be a potential diagnostic biomarker for asthma.[111] Potential biomarkers might also be assessed by a noninvasive method of exhaled breath condensate collection,[112] and hydrogen peroxide has been suggested as a possible noninvasive biomarker for monitoring lower airway inflammation in allergen-challenged *Ascaris suum* (AS)-sensitized cats.[113]

Pulmonary Function Tests

An important clinical feature of asthma is airflow limitation that is at least partially reversible with bronchodilators. In human medicine, pulmonary function testing is commonly used in the diagnosis and monitoring of therapeutic response in patients with asthma or chronic bronchitis. In cats, spirometry is inadequate since it requires patient compliance to exhale forcefully through a mouthpiece. However, some noninvasive tests have been developed, such as tidal breathing flow volume loops (TBFVL) using a tightly fitting face mask,[94,101] BWBP,[104,114] or a combination of TBFVL and BWBP[115] and forced expiratory flow-

volume curves using a thoracic compression technique[116,117] in healthy cats and/or cats with experimentally-induced asthma. BWBP can be used for estimating basal functional parameters, as well as airway hyperresponsiveness, usually quantified by calculating the concentration of bronchoconstrictor agent that induces a 300% increase in basal enhanced pause (Penh).

TBFVL and BWBP have been used in clinical case series,[101,107,115,118,119] associated with airway responsiveness testing using either carbachol,[118,119] 5amp,[120] or methacholine[121] as bronchoprovocative challenge.

During TBFVL, the presence of airflow limitation is affected by the overall extent of granulocyte infiltration, while most BWBP studies provide supportive evidence of a correlation between airway eosinophilic inflammation and plethysmographic measures of bronchoconstriction and airway responsiveness. The latter suggests that BWBP associated with airway responsiveness testing could offer a new method for the identification of cats with inflammatory lower airway disease, and possibly for monitoring disease progression or response to therapy.

In anesthetized cats, ventilator-acquired lung mechanics recently have been proven to be useful.[121]

Differential Diagnosis

The differential diagnosis for feline inflammatory bronchial disease includes mainly feline bronchial disease of noninflammatory origin (see below) and pulmonary parenchymal diseases (see ch. 242), including infectious pneumonia/bronchopneumonia (e.g., bacterial, viral, parasitic, protozoal)[5,105,122] that are rare but probably are underdiagnosed; airway foreign bodies; neoplasia; pleural effusion of various etiologies (see ch. 244); and rarer diseases such as feline pulmonary fibrosis[123,124] and endogeneous lipid pneumonia.[125]

Feline bronchial diseases of noninflammatory origin include the following:

- Pulmonary parasitic diseases, including infection with *Aerulostrongylus abstrusus, Troglostrongylus brevior,*[126] *Eucoleus aerophilus* (formerly *Capillaria aerophila*),[127] *Dirofilaria immitis,* and *Wolbachia*[128] (in endemic regions), which can result in similar clinical findings including eosinophilic airway inflammation. It is not easy to confidently rule out these diseases because of imperfect test sensitivity; therefore, empiric curative or preventive treatment with relevant drugs (in endemic regions) is recommended.[128a]
- Infection with *Toxocara cati* (see ch. 81 and 276).
- Bacterial/*Mycoplasma* infection[109,129,130] (see ch. 227 and 242).
- Neoplastic origin (see ch. 244, 344, and 346).

Management/Treatment and Monitoring

Acute Respiratory Distress

In cats with severe acute respiratory distress, stress should be minimized and an oxygen-enriched environment should be provided (see ch. 131 and 139). Parenteral therapy with a bronchodilator (e.g., the beta-2 agonist terbutaline 0.01 mg/kg IV, IM or SC) or a rapidly acting corticosteroid (e.g., dexamethasone 0.25-0.5 mg/kg IV or IM) should be administered promptly.[4] Inhaled treatment with a bronchodilator can be used as well, provided that a minimal amount of drug can reach the bronchi (which is uncertain in an animal with severe respiratory embarrassment). These treatments aim to quickly relieve, at least partly, bronchoconstriction. When the cat fails to respond, the presence of spontaneous pnemothorax needs to be considered and emergency thoracocentesis must be considered as a possible life-saving procedure (see ch. 102, 149, and 244). Indeed, asthma has been shown to be the most common cause of spontaneous pneumothorax in cats (4/16 cases, 25%).[131] In this study, all 4 cats with asthma-associated secondary spontaneous pneumothorax survived the initial episode of spontaneous pneumothorax to discharge with medical management.

Chronic Management

Most retrospective studies in cats with lower airway diseases have documented beneficial response to oral or parenteral glucocorticoids and/or bronchodilators.[92-94] Classic therapy for chronic forms of bronchial disease includes the use of long-term, oral corticosteroid (e.g., prednisolone 1-2 mg/kg PO q 12 h for 1-2 weeks, followed by gradual taper), which remains a consistent, reliable, and effective treatment to date.[132] It has been suggested that oral administration of propentofylline, a methylxanthine derivative with bronchodilating actions, to cats with bronchial disease, in addition to a low dosage of prednisolone, might be superior over

monotherapy with prednisolone.[133]

Currently, there are few easily measured parameters to closely assess/monitor response to therapy. Therefore, in practice, treatment monitoring generally relies mainly on improvement of clinical signs. Both airway eosinophilia and airway hyperresponsiveness are considered hallmarks of the disease and would be interesting parameters to monitor during treatment.

A recent study evaluated the correlation between the resolution of clinical signs in cats with lower airway disease receiving oral glucocorticoids and the resolution of inflammation based on BALF cytologic findings.[134] Ten cats with inflammatory bronchial disease received oral glucocorticoids (average prednisolone dosage: 1.8 ± 0.2 mg/kg/day) for at least 3 weeks. All had resolution of clinical signs but 7/10 cats had persistent inflammatory BALF cytologic findings despite resolution of clinical signs. Such a study clearly shows that current recommendations to taper therapy based on resolution of clinical signs are inadequate, and that proper adaptation of oral therapy should rather rely on BALF cytologic evaluation.

BWBP and pseudo-tidal breathing flow-volume loop are noninvasive means of evaluating lung function in conscious, spontaneously breathing cats; both also have been proven to be useful in monitoring response to treatment in both experimental models and spontaneous cases.[118-120,135]

The use of inhaled medications using a face mask and spacing chamber, first described by Padrid,[136] is becoming commonplace (see ch. 97).[137] Medications given via inhalation offer the advantage of high drug concentrations within the the airways while attenuating systemic side effects. Inhaled corticosteroids (e.g., fluticasone propionate), utilized essentially as chronic therapy, and bronchodilators (e.g., albuterol), used for palliating an acute exacerbation of signs, are the most commonly used and were first used in experimental models.[138-140] Several studies have evaluated the response to nebulized therapy in feline patients. One of them showed that inhaled budesonide 400 mcg q 12 h could be withdrawn in 20 cats while in the cats still receiving inhaled budesonide, clinical improvement was noted, as well as improvement of the airway reactivity indices measured by BWBP.[119] The same study showed that although corticosteroid-induced side-effects were not observed, hypothalamic-pituitary-adrenal axis suppression was detected in 3 of 15 cases. In another study, cats were treated with inhaled fluticasone propionate (Flixotide, GlaxoSmithKline, 2 puffs, 250 mcg/puff, q 12 h).[118] Despite a significant improvement in clinical scores—and in some cats, apparent resolution of clinical signs—BWBP values did not change significantly by first recheck, providing further evidence that overt clinical resolution can precede recovery of normal airway function. This does not appear to be due to insufficient dosage of nebulized fluticasone. Indeed, in a study of a feline asthma model, a twice-daily dosage of 44 mcg had an effect that was identical to a twice daily dosage of 220 mcg of inhaled fluticasone[141]; these findings suggested that this low dosage should be evaluated for the management of cats with naturally occurring inflammatory bronchial disease. As only oral prednisolone is capable of eliminating the late-phase asthmatic reaction,[139] a combination of both oral and inhaled glucocorticosteroid medications can be started, followed by a single inhaled therapy in the follow-up period.

Bronchodilators, such as inhaled albuterol (also called salbutamol), are very useful to alleviate clinical signs quickly, but as they fail to control airway inflammation, they should not be used alone (for monotherapy). They should be used with caution, due to possible adverse effects, including tachycardia, central nervous system stimulation, tremors, and hypokalemia. Besides, chronic daily racemic albuterol administration has been associated with increased severity of airway inflammation in experiental models of feline asthma.[142]

Other Therapies

Weight loss should be encouraged in obese cats (see ch. 176). A recent study compared pulmonary function variables between obese and nonobese cats using BWBP.[143] Although obesity was not associated with a significant increase in bronchoconstriction index variable, as previously reported in humans and dogs, a significant impairment in pulmonary function was confirmed, suggesting that weight loss should be encouraged in obese cats with FLAD.

Saline nebulization and use of mucolytics or phytotherapeutic agents (either oral or by nebulization) have not been proven to be beneficial and should be administered with great caution. In cats, all nebulized substances potentially can trigger a bronchospastic reaction and/or occasion extra stress, all having a negative impact on a cat with FLAD. In cats with experimentally induced asthma, endotracheal nebulization of N-acetylcysteine, a drug with mucolytic and antioxidant properties, has caused increased airway resistance and other adverse reactions[144] and therefore is not recommanded.

Prognosis

Feline bronchial disease is associated with substantial morbidty and even mortality in cats. Although most cats are well controlled with oral or nebulized therapy, or both, they generally require lifelong treatment. Importantly, unchecked airway inflammation can lead to irreversible remodeling, resulting in a decline in lung function.

In chronic cases, when remodeling has taken place, alleviation of clinical signs can become challenging and can lead to euthanasia.

Contribution of Experimental Feline Asthma Models in Developing Possible Future Therapies

Development and implementation of feline asthma models have greatly contributed to understanding pathophysiologic mechanisms and diagnosis and facilitated the search for novel therapies. Indeed, by combining structural/morphological imaging (thoracic CT) and functional analyses, models offer the unique possibility for repeated and standardized follow-up of clinical features, lung function, and airway inflammation and immunology.

Two different feline asthma models have been described, based on artificial sensitization to either *Ascaris suum*[104,145] or Bermuda grass allergen/house dust mite allergen.[146] A huge number of novel therapies that might be effective or might help to reverse the immune events in asthma have been or are presently being investigated in experimental asthma models. Indeed, the amount of data generated by one team using the feline asthma model is fabulous and provides interesting and sometimes very promising experimental results (for details, see reviews by Reinero[89] and Trzil[96]). Novel therapeutic approaches evaluated in feline models include nutraceuticals (omega-3 polyunsaturated fatty acids plus luteolin),[147] different bronchodilators,[139,148] the salivary immunomodulatory peptide feG-COOH,[149] leukotriene antagonists,[150] antiserotoninergic drugs,[151] doxycycline,[139] rush immunotherapy,[152-154] inhaled lidocaine,[155] the tyrosine kinase inhibitor masitinib,[121] and long-term evaluation of mesenchymal stem cell therapy.[100]

However, although these investigations in models are very useful, they do not necessarily reflect the situation in feline patients with spontaneous disease.Therefore, these new therapeutic strategies, tested in experimental settings, cannot yet be recommended for clinical practice.

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CHAPTER 242

Diseases of the Pulmonary Parenchyma

Leah A. Cohn

The structure of the pulmonary parenchyma permits the primary function of the lung-gas exchange. The lung consists of millions of alveolar airspaces each bathed by a dense network of capillaries. Fine, lacey, supporting interstitial tissues are interposed between the epithelial lining of the alveoli and the surrounding vascular endothelium of the capillary network; these interstitial tissues contain the slightly larger pulmonary arterioles and veins. Parenchymal disease includes disease focused on the alveoli, pulmonary microvasculature, or the interstitial tissues while excluding disease of the larger airways (see ch. 241), pulmonary vessels (see ch. 243), and pleural space (see ch. 244).

Manifestations of Pulmonary Parenchymal Disease

Dogs and cats with pulmonary parenchymal disorders have a variety of clinical signs related either to respiratory dysfunction or to systemic disease. Often, clinical signs and physical examination abnormalities in animals with pulmonary disease are similar to those found in animals with airway, mediastinal, or pleural space disease. Additionally, nonrespiratory diseases (e.g., neuromuscular disease, anemia, acidosis) can cause signs that mimic respiratory disease. Common respiratory manifestations of pulmonary parenchymal disease include cough, exercise intolerance, tachypnea, excessive panting, and increased respiratory effort or respiratory distress. Most often, respiratory distress caused by pulmonary parenchymal disease results in mixed inspiratory and expiratory effort. This contrasts with the predominantly inspiratory effort observed in animals with upper airway obstruction (see ch. 28) or pleural space disease (see ch. 244) or the expiratory effort observed in animals with lower airway/bronchial disorders (see ch. 241). Certain interstitial lung diseases that limit pulmonary compliance offer exceptions to this general rule, in that they are associated with a predominantly inspiratory effort. Less common manifestations of pulmonary parenchymal disease include hemoptysis, collapse or syncope, and cyanosis. It is also possible for animals with marked respiratory compromise to demonstrate minimal clinical evidence of respiratory disease. This is especially true in cats; in this species the first sign of marked pulmonary parenchymal disease can be sudden death.[1-5]

Physical examination of animals with pulmonary disease can be unremarkable or can identify marked systemic or thoracic disease. Weight loss, fever, lymphadenomegaly, and distal limb swelling from hypertrophic osteopathy (E-Figure 242-1) are a few of the many potential systemic manifestations of pulmonary diseases. Abnormalities in respiratory rate or effort, cyanosis, increased or decreased bronchovesicular lung sounds, and/or adventitial sounds (i.e., crackles and wheezes) on auscultation are suggestive of airway, thoracic space, or pulmonary disease (Figure 242-2). Examination of the patient with respiratory disease is described in detail in ch. 2, 28, and 240. Any animal presenting with marked respiratory distress should receive supplemental oxygen during evaluation (see ch. 131 and 139).

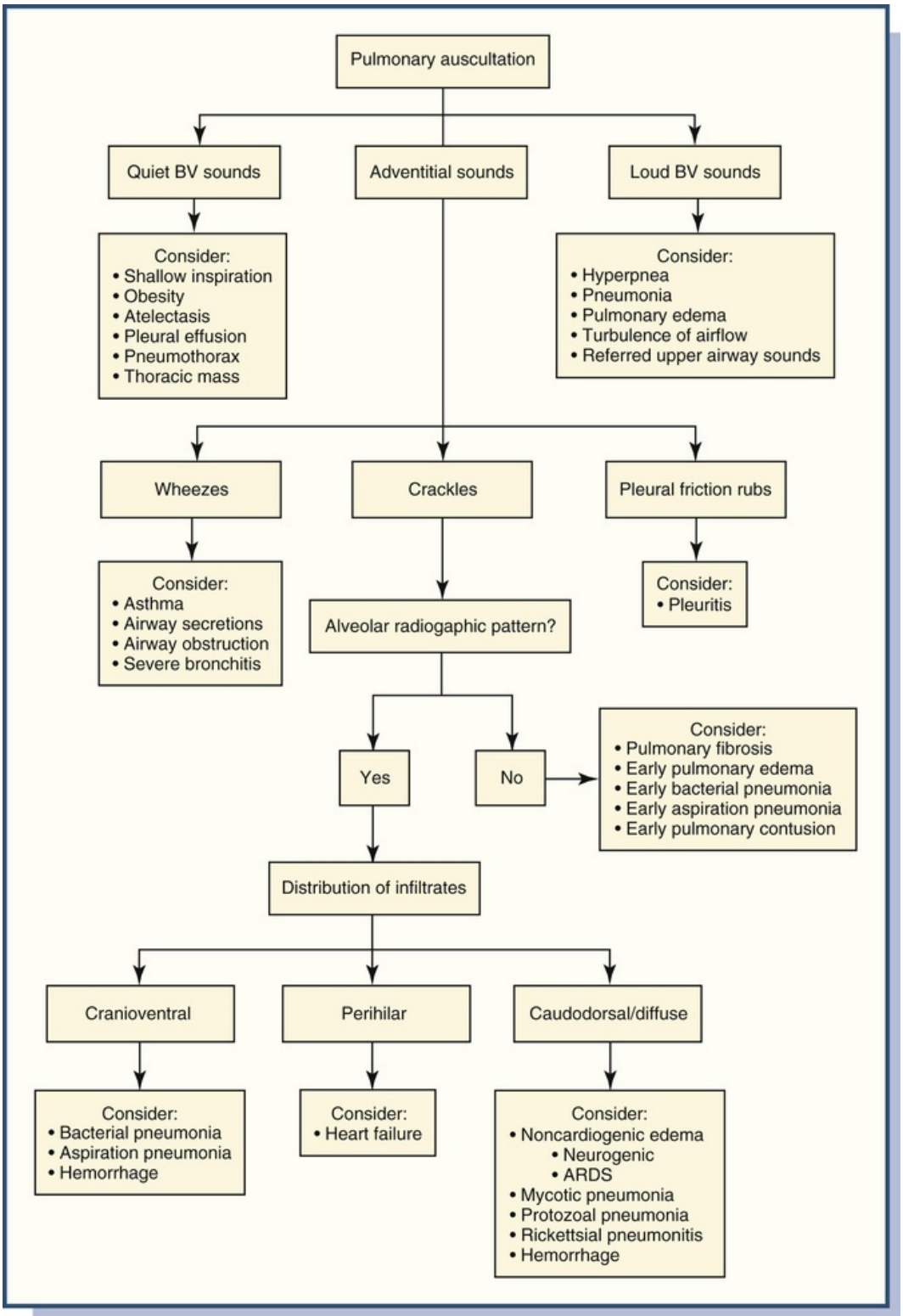
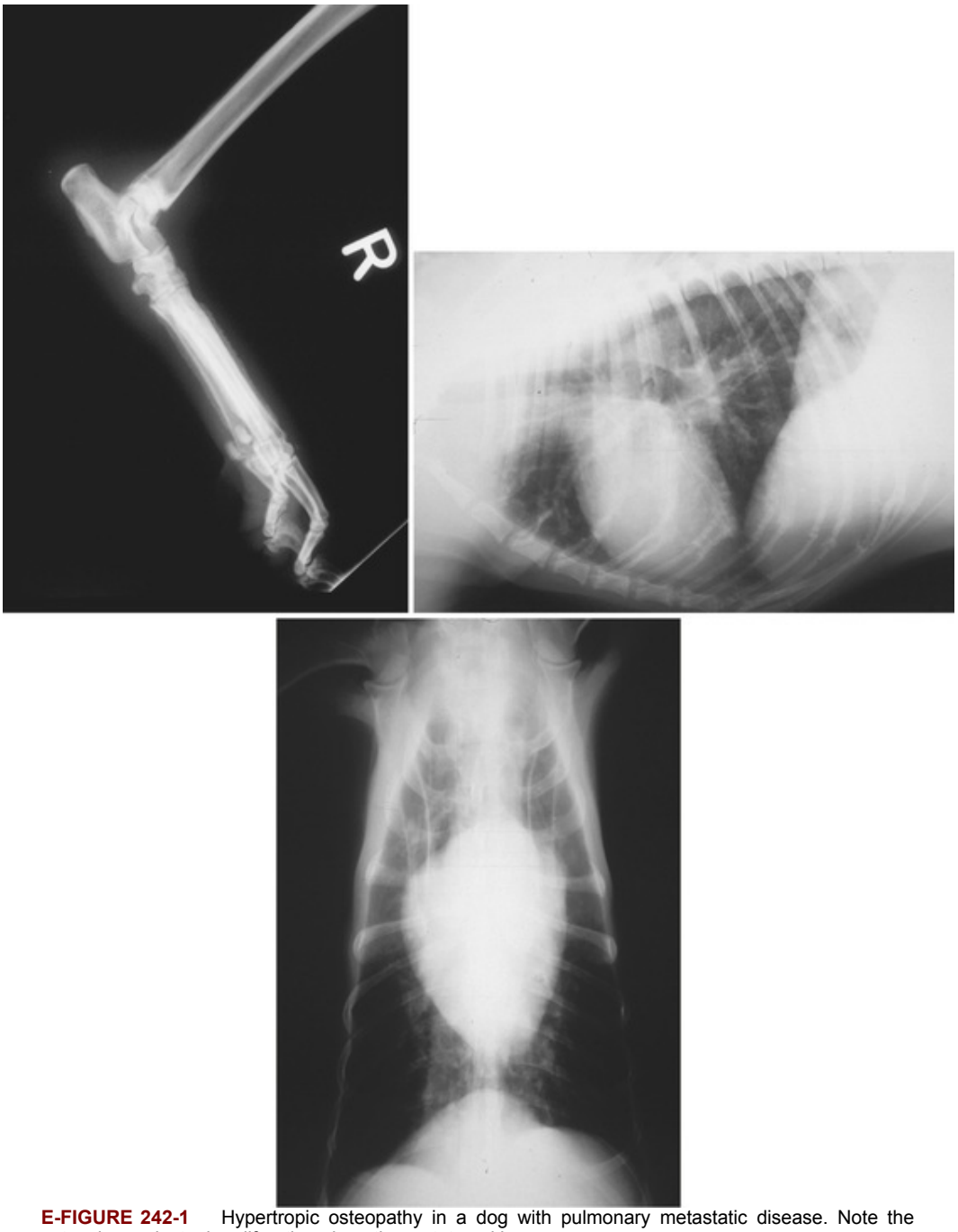


FIGURE 242-2 Thoracic auscultation. *ARDS,* Acute respiratory distress syndrome; *BV,* bronchovesicular.



E-FIGURE 242-1 Hypertropic osteopathy in a dog with pulmonary metastatic disease. Note the extensive periosteal proliferation along the metatarsal bones.

Diagnostic Evaluation of Pulmonary Parenchymal Disease

Oxygenation

Evaluation of oxygenation often is useful for animals with suspected pulmonary parenchymal disease, although nonparenchymal diseases also can cause hypoxemia. Visual recognition of cyanosis confirms the presence of hypoxemia but is insensitive, subjective, and not useful in anemic animals. Better tests of oxygenation include pulse oximetry (see ch. 98) and arterial blood gas analysis (see ch. 128). Blood gas analysis can be used for making decisions regarding the need for supplemental oxygen or mechanical ventilation and to monitor response to therapy. Additionally, $PaCO_2$ and simple calculations of alveolar-arterial gradients (E-Box 242-1) can be used to help determine the most likely mechanism for hypoxemia (E-Table 242-1).

E-Box 242-1

Calculation of Alveolar-Arterial (A-a) Gradient

Impaired oxygen diffusion or, more commonly, ventilation-perfusion (V/Q) inequality results in increased A-a gradient (A-a gradient = $PAO_2 - PaO_2$) where PaO_2 is the partial pressure of O_2 in the artery and PAO_2 is the partial pressure of O_2 in the alveoli. Normal A-a gradient is <10 torr, whereas a gradient >20 torr suggests V/Q inequality. There are several methods by which to calculate actual or approximated A-a gradient.

1. Complete calculation:

$$= ((FiO_2 \times (P_{atm} - P_{H_2O})) - (PaCO_2/R)) - PaO_2$$

where FiO_2 is the fraction of inspired oxygen, P_{atm} is the atmospheric pressure, P_{H_2O} is the water vapor pressure, $PaCO_2$ is the measured arterial carbon dioxide tension, and R is the respiratory quotient (ratio of carbon dioxide produced to oxygen consumed).

2. Assuming common values at sea level on room air:

$$= ((0.21 \times (760 - 47)) - (PaCO_2 / 0.8)) - PaO_2$$

3. Extreme simplification, making similar assumptions as earlier:

$$= 150 - (PaO_2 + PaCO_2)$$

E-TABLE 242-1

Mechanisms of Hypoxemia

MECHANISM OF HYPOXEMIA	SELECTED EXAMPLES	CLUES TO RECOGNITION
Hypoventilation	• Drug-induced respiratory depression • Central nervous system or peripheral nerve disorders • Upper-airway obstruction	• Increased $PaCO_2$ • Normal (A-a) gradient • Absent radiographic pulmonary infiltrates
Ventilation : perfusion (V : Q) mismatch	• Bacterial pneumonia • Pulmonary edema • Pulmonary thromboembolism	• Increased A-a gradient • Mildly increased $PaCO_2$ • Improves with O_2 supplementation (except thromboembolism) • Pulmonary radiographic changes variable but common
Right-to-left shunting (intrapulmonary or cardiac)	• Right-to-left patent ductus arteriosus (cardiac) • Pulmonary arteriovenous fistulae with marked pulmonary hypertension (pulmonary vascular) • Atelectatic lung (pulmonary) • Pulmonary thromboembolism	• Increased (A-a) gradient • Fails to improve with O_2 supplementation • Cardiac or pulmonary radiographic changes common
Diffusion impairment	• Asbestosis • Idiopathic pulmonary fibrosis	• Marked interstitial radiographic infiltrates common

		• Improves with O_2 supplementation
Reduced inspired oxygen partial pressure	• High altitude • Anesthetic accident • Suffocation	• Resolves with O_2 supplementation

Screening Tests

Diagnostic modalities used in dogs and cats with pulmonary disease range from the simple to the complex, from noninvasive to invasive, and from the inexpensive to the costly. Screening health examinations such as a complete blood count (CBC), serum biochemical profile, and urinalysis rarely provide a specific explanation for pulmonary signs but sometimes provide clues to an underlying disease process (E-Box 242-2). Results of these tests also are relevant to planning for anesthesia required for many of the more specific respiratory diagnostic techniques. Tests such as fecal flotation, fecal Baermann sedimentation (E-Box 242-3 and E-Figure 242-3), or heartworm antigen tests occasionally provide a definitive diagnosis for pulmonary disease. For some infectious diseases with pulmonary manifestations, specific serologic or polymerase chain reaction (PCR) tests support a suspected diagnosis. Simple blood tests also are available to help distinguish animals with respiratory signs due to heart failure from those with primary respiratory disease.

E-Box 242-2

Implications of Routine Screening Examination in Dogs or Cats with Pulmonary Disease

Complete Blood Count

Neutrophilia: consider infectious pneumonia and inflammatory lung disease, including acute respiratory distress syndrome (ARDS)
Neutropenia: consider sepsis, ARDS
Eosinophilia: consider hypersensitivity disorders, eosinophilic pneumonia, or parasitic disease
Monocytosis: consider mycotic lung disease, histiocytic disease
Thrombocytopenia: consider sepsis, pulmonary thromboembolism, vasculitis, pulmonary hemorrhage
Erythrocytosis ("polycythemia"): supports chronic hypoxemia

Serum Chemistry Profile

Hypoalbuminemia: consider pulmonary thromboembolism resulting from protein-losing nephropathy or enteropathy, systemic inflammatory and infectious disease with pulmonary manifestation
Hypercholesterolemia: consider pulmonary thromboembolism resulting from protein-losing nephropathy
Hyperglobulinemia: consider infectious and inflammatory disease
Hypercalcemia: consider neoplasia and granulomatous fungal disease
Increased alanine aminotransferase: supports hypoxemia

Urinalysis

Proteinuria: consider pulmonary thromboembolism resulting from protein-losing nephropathy, systemic inflammatory disease
Bacteruria: consider sepsis

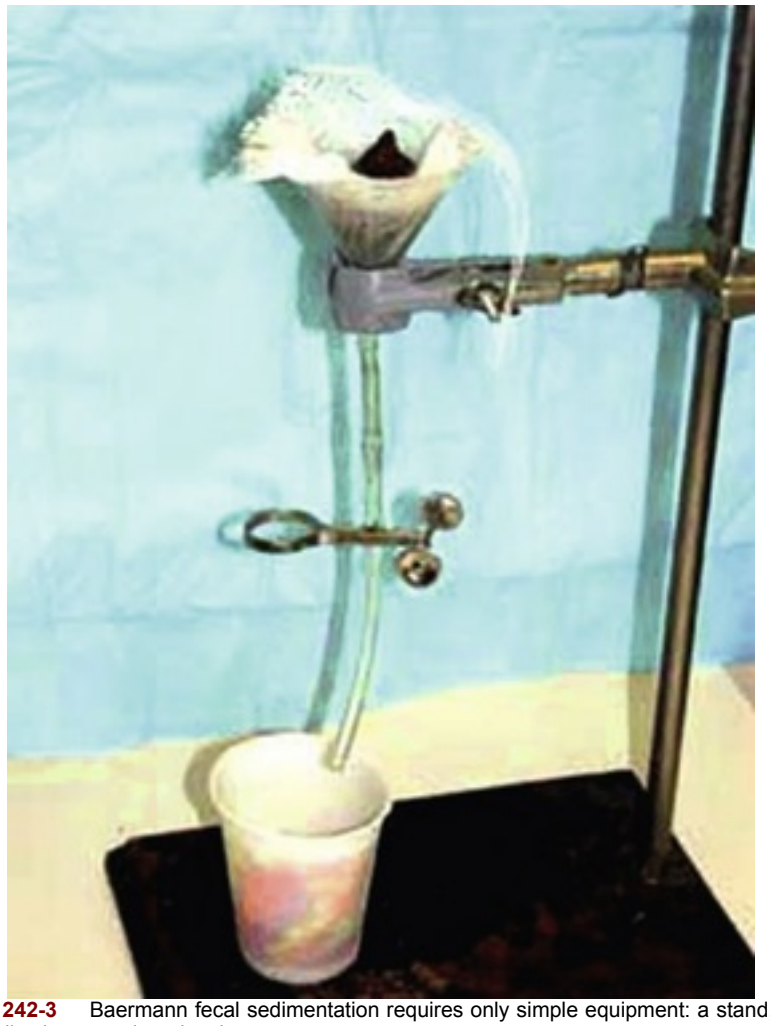
E-Box 242-3

Baermann Fecal Sedimentation Technique (see E-Figure 242-3)

Several types of pulmonary parasites are more likely to be identified via Baermann fecal sedimentation than by routine fecal flotation. However, intermittent fecal shedding associated with all pulmonary parasites makes any fecal technique relatively insensitive. Ideally, at least three negative examinations from different stool samples would be required to effectively rule out pulmonary parasites. Fresh feces should be used because larvated parasite ova from older specimens can confuse results, as can free-living soil nematodes from samples allowed to sit outdoors for more than 20 minutes after defecation. If testing

must be delayed by several hours, stool should be refrigerated. Baermann sedimentation is simple to perform and requires no specialized tools. A step-by-step technique is as follows:

1. Attach a piece of rubber tubing to the bottom of a medium-sized glass funnel.
2. Suspend the funnel and tubing from a stand to keep it upright.
3. Attach a clamp across the tubing and close clamp.
4. Collect ≈10 grams of fresh feces.
5. Place feces in double-layered cheesecloth.
6. Place feces-containing cheesecloth inside the funnel.
7. Fill the funnel with warm water.
8. Allow the feces to stand in the water undisturbed 4 to 5 hours or overnight.
9. Carefully release the clamp and collect the first 10 mL of fluid from the tubing.
10. Centrifuge the collected fluid at 500 to 650 G (similar to the speed used for serum separation) for ≈5 minutes.
11. Place a cover slip on the sample and examine the sediment under a light microscope.
12. If larval movement is detected, a drop of dilute iodine is placed at the edge of the cover slip and allowed to wick through. The iodine kills the parasites and facilitates a more complete morphologic examination.



E-FIGURE 242-3 Baermann fecal sedimentation requires only simple equipment: a stand, a funnel, tubing, a collection vessel, and a clamp.

Natriuretic Peptides

Natriuretic peptides are a group of related hormones that affect circulatory homeostasis.[6] Many have been used as biomarkers of cardiovascular disease. Chief among these is B-type natriuretic peptide (BNP; i.e., brain natriuretic peptide), which promotes natriuresis, increases glomerular filtration rate, causes vasodilation, and antagonizes the renin-angiotensin-aldosterone system in animals with increased extracellular fluid volume.[6] The circulating concentration of BNP increases in animals with volume overload, pulmonary hypertension, and especially with cardiac dysfunction and heart failure (see ch. 246). The peptide is synthesized as a preprohormone and rapidly processed to a prohormone, which is then cleaved into the active BNP and the inactive NT-proBNP fragment. The inactive fragment has a longer half-life than the active hormone, making it convenient for diagnostic measurement. Because it is often difficult to quickly establish if respiratory distress is due to primary respiratory or primary cardiac disease, and because these conditions are treated quite differently, it can be useful to have a simple, safe, rapid test to distinguish the two. Dogs with congestive heart failure have been found to have higher median circulating BNP concentrations than either normal dogs or dogs with respiratory causes of cough or distress.[7,8] However, BNP was also elevated in dogs with noncardiac causes of cough and concurrent heart disease.[7] Similarly, ELISA tests of NT-proBNP have been evaluated in dogs and cats with cardiac and noncardiac causes of cough or respiratory distress. Higher concentrations of NT-proBNP were found in pets with cardiac than respiratory disease.[9-13] In cats, measurement of NT-proBNP in pleural fluid can be used for distinguishing between cardiac and noncardiac origin effusions.[14] Unlike in humans, age and gender do not appear to affect natriuretic peptide concentrations[7,12]; however, NT-proBNP concentrations do increase in association with increases in creatinine. This could be problematic when using the test in animals with azotemia.[12] Although these tests might well have a role in evaluation of pets with acute dyspnea, for now they should be viewed as ancillary tests that do not replace more standard evaluations such as imaging studies.[9,10,13,15]

Diagnostic Imaging Studies

Imaging studies help to rule out airway, mediastinal, or pleural space disease as a cause of respiratory signs and provide substantial information regarding disease of the pulmonary parenchyma. Thoracic radiographs are perhaps the single most important diagnostic test (after history and physical examination) for the pet with lung disease. The presence, location, and intensity of abnormal radiographic patterns provide a wealth of information to guide differential diagnosis and diagnostic plans (Box 242-4). Lung disease sufficient to cause respiratory signs occasionally occurs in the absence of radiographic change in the pulmonary parenchyma. For example, radiographic changes can lag behind acute development of respiratory signs in animals with aspiration pneumonia, acute respiratory distress syndrome (ARDS), or pulmonary thromboembolism. However, when thoracic imaging studies fail to demonstrate abnormalities in animals with lower respiratory signs, additional consideration should be given to conditions that can mimic respiratory disease, such as anemia, pain, acidosis, or nervous system disorders.

Box 242-4

Differential Diagnosis Associated with Common Radiographic Patterns

Alveolar Infiltrate

Pneumonia (bacterial, parasitic, protozoal, viral, aspiration, interstitial)
Edema (cardiogenic or noncardiogenic)
Hemorrhage/contusion
Primary lung neoplasia
Metastatic neoplasia
Atelectasis
Pulmonary thromboembolism
Drowning
Smoke inhalation

Bronchiolar Infiltrate

Feline asthma

Chronic bronchitis
Eosinophilic bronchitis
Peribronchiolar cuffing (e.g., edema, inflammation)
Bronchial calcification

Interstitial Patterns

Aging change (i.e., "old dog lung") (U)
Pulmonary fibrosis (U)
Lymphoma (U)
Primary lung neoplasia (S > U)
Pulmonary metastasis (S > U)
Fungal pneumonia/granuloma (S > U)
Eosinophilic pneumonia (S > U)
Foreign body reaction (S > U)
Hematoma (E)
Abscess (S)
Cyst (S)

Vascular Pattern

Heartworm disease
Thromboembolic disease
Pulmonary hypertension
Congestive heart failure

E, Either structured or unstructured pattern; *S*, structured interstitial lung pattern; *U*, unstructured interstitial lung pattern. Any disease that causes an alveolar pattern can begin with an unstructured interstitial pattern that progressively becomes more severe.

Computed tomography (CT) and ultrasound are used less frequently than plain thoracic radiographs to image the lungs of pet animals. CT offers advantages over standard thoracic radiography including increased sensitivity for the detection of small lesions such as metastasis, a truer three-dimensional image of the thoracic cavity and its contents, minimization of summation artifact, and the ability to view images in axial, coronal, or sagittal planes.[16,17] Until recently, CT scan has required anesthesia or heavy sedation, thus limiting its utility as a screening test. The combination of newer machines with faster image acquisition and the availability of restraint devices (e.g., VetMousetrap, Urbana-Champaign, IL) easily used for cats or small dogs with dyspnea have overcome some of these limitations (Video 242-1).[18] Nonetheless, the best thoracic images still require anesthesia and, ideally, controlled ventilation.[19] Because sound waves do not produce good images when they traverse airspaces, ultrasound is not a particularly useful modality for evaluation of pulmonary parenchyma. Ultrasound sometimes is helpful for evaluation of consolidated lung tissue or to evaluate vascular patency, and it can be used for guiding needle aspirates from thoracic masses.[20,21]

Invasive Tests

Often, invasive tests are required for the diagnosis of pulmonary parenchymal disease. The most commonly employed tests include transtracheal or endotracheal lavage, bronchoalveolar lavage (BAL, with or without bronchoscopic guidance; see ch. 101), fine-needle aspiration (FNA) of lung lesions, and lung biopsy (see ch. 240). Unfortunately, it seems that culture of simple deep oral/pharyngeal swabs is not an acceptable substitute for tracheal or alveolar lavage in dogs with bacterial pneumonia.[22] Tracheal lavage offers a minimally invasive and relatively safe means of collecting airway fluid samples for microbiologic culture and cytologic examination. Because samples are collected from the large airways rather than the parenchyma, tracheal lavage is particularly useful for pulmonary disease accompanied by a productive cough (e.g., bacterial pneumonia). BAL produces diagnostic samples from deeper within the lung and is therefore useful in animals lacking a productive cough. Bronchoscopy can guide BAL collection such that specimens are obtained from a specific site in the lungs.[23] When diffuse disease is present, BAL can be collected in a "blind" fashion without regard to collection site in the lungs.[24] Although FNA of the pulmonary parenchyma is invasive, it is inexpensive and relatively safe. When a focal mass or consolidated lesion is present, the diagnostic yield of FNA is high. However, sensitivity diminishes when lung disease is diffuse.[20,25,26] Lung

biopsy is more invasive than airway lavage or lung aspirates but also provides more information. Biopsy is indicated for the evaluation of animals with continued or worsening lung disease when less invasive techniques fail to yield a diagnosis. Biopsy is required to definitively demonstrate the presence of many interstitial lung diseases. For instance, pulmonary fibrosis cannot be definitively identified in any way other than histologic examination of lung tissues.[1] Lung biopsy can be acquired via thoracoscopy, a key-hole approach, or thoracotomy.[27]

Specific Pulmonary Disorders

Pulmonary Parasites

Parasitic pulmonary disease is caused by both lungworms and non-lungworms. Some intestinal worms, especially *Toxocara* (roundworms) but also *Ancylostoma* (hookworms), undergo pulmonary migration before the adult worm reaches its final destination in the intestine. Usually, pulmonary migration causes little disease and few (if any) respiratory signs. However, massive larval migration can result in both direct and indirect inflammatory damage to the lung, causing verminous pneumonia. Such profound infections typically occur in puppies who may present with cough and tachypnea. A CBC often is not performed in young puppies with cough, but eosinophilia would be expected. Fecal flotation can be negative because larval migration occurs before the mature worms have reached the intestine. Empiric treatment is reasonable if pulmonary migration is suspected as a cause of cough. An anthelmintic (e.g., pyrantel pamoate 5 mg/kg PO) should be administered at least twice, 2 weeks apart. Fortunately, most animals require no further treatment. A short course of an antiinflammatory dosage of glucocorticoid can ameliorate severe cough but should not be used before ruling out other causes of infectious pneumonia.

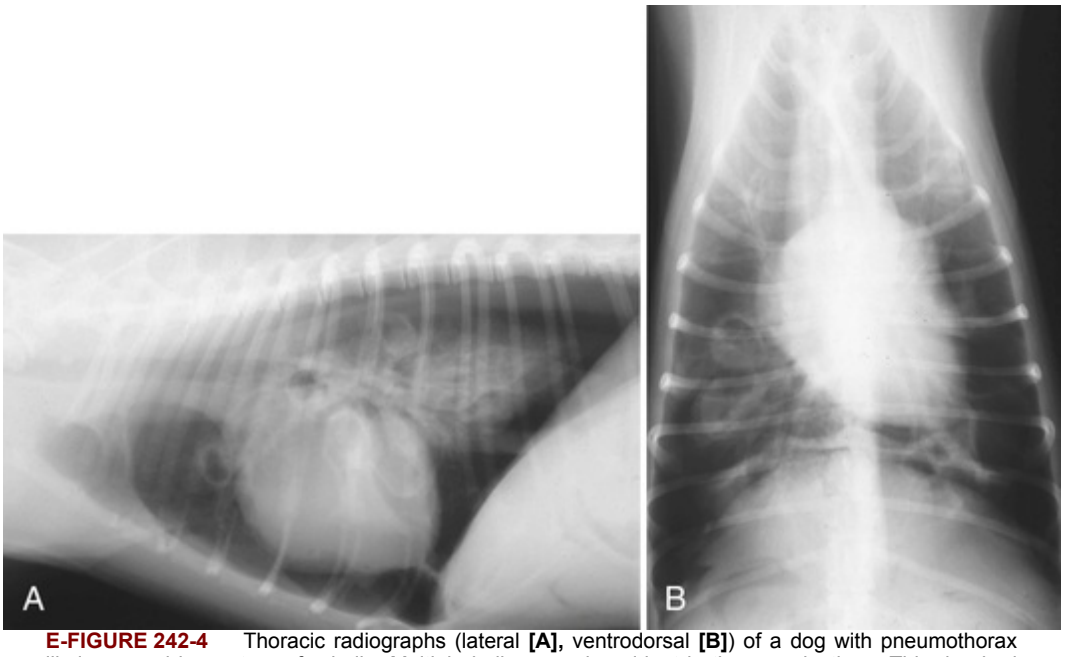
In contrast to intestinal worms that migrate through the lungs on their way to a final destination, for lungworms the final destination is the respiratory tract.[28,29] Several types of lungworms are of relevance to dogs and cats. These parasites can reside primarily in the pulmonary parenchyma, in the airways, or both. Parasitic lung disease easily can be confused with other conditions such as bronchopneumonia, eosinophilic pneumonia, asthma, pulmonary granulomatosis, or even pulmonary neoplasia. Unfortunately, intermittent fecal shedding of parasite ova or larvae after expectoration means that fecal examination is an insensitive diagnostic method. For this reason, therapeutic trials often are employed when lungworms are suspected. High-dosage fenbendazole (50 mg/kg PO q 24 h for 10-14 days) or ivermectin usually are used.[28] Ivermectin must be used with caution in Collies and other breeds with a high prevalence of the MDR-1 (ABCB1) mutation.[30] Although albendazole is an effective therapy for lungworms, it has a greater potential for bone marrow toxicosis than does fenbendazole.[31-33]

Pulmonary Parenchymal Parasites

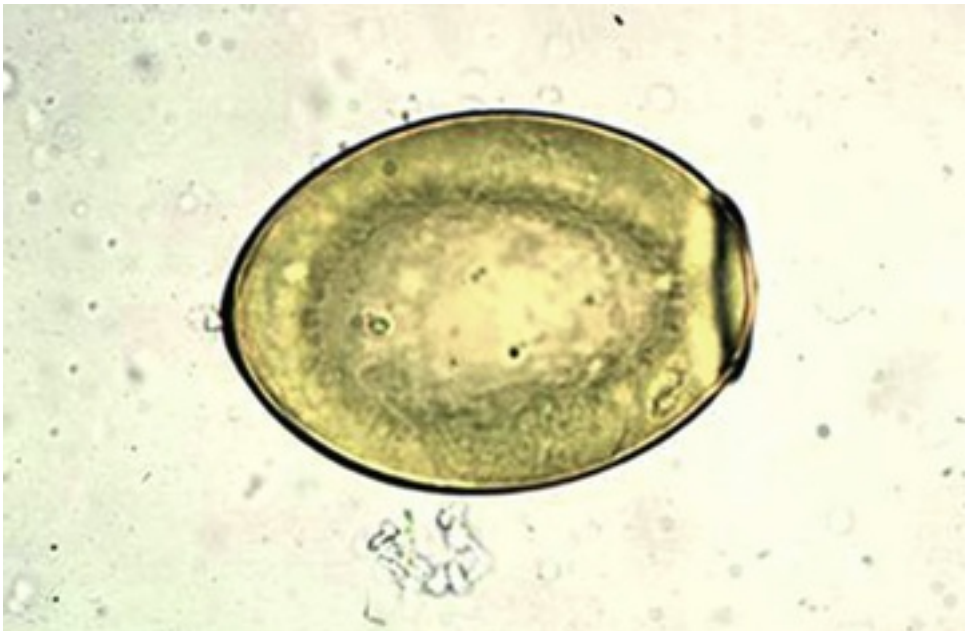
Paragonimus kellicotti

This trematode lung fluke can infect dogs and cats. Found worldwide, in the United States lung flukes are particularly endemic in the Great Lakes region, the Midwest, and the South. As with most pulmonary parasites, an intermediate host is involved in transmission. Pets are infected after eating crayfish. The parasite migrates from the intestine into the peritoneum, across the diaphragm, and into the pleural space. Soon thereafter, immature flukes invade the subpleural tissues, where they cause eosinophilic and neutrophilic inflammation.[34,35] Often, the parasites form bullae and cysts within the pulmonary parenchyma. The mature flukes have access through a series of communicating "tunnels" to the bronchioles, allowing ova eventually to be coughed up and swallowed before fecal shedding.

Animals infected with *P. kellicotti* are usually well but can present with cough or even respiratory distress.[36,37] Rupture of cavitary pulmonary lesions can lead to hemoptysis or pneumothorax (E-Figure 242-4).[36] Often, the diagnosis is suspected when animals with respiratory signs have concurrent eosinophilia or based on radiographic findings.[38] Although radiographic lesions are not identified uniformly, they can include nodular or cystic lesions or bullae, especially involving the right caudal lung lobes.[34,38-40] Serial CT scans from experimentally infected dogs initially identified pleural effusion and a subpleural ground-glass appearance along with linear opacities. After 1 month, persistent peribronchial nodules, bronchial dilation, and cavitary changes were observed.[41] Ova can be demonstrated either from airway lavage fluid or in feces.[34] Fecal sedimentation techniques are preferred over other methods of fecal analysis for demonstration of parasite ova (E-Figure 242-5).



E-FIGURE 242-4 Thoracic radiographs (lateral **[A],** ventrodorsal **[B]**) of a dog with pneumothorax likely caused by rupture of a bulla. Multiple bullae remain evident in these projections. This dog had *Paragonimus kellicotti* infection.



E-FIGURE 242-5 Ovum of *Paragonimus kellicotti.* (Courtesy Dr. Richard Meadows, University of Missouri.)

In addition to fenbendazole, praziquantel (25 mg/kg PO q 8 h for 3 days) has been used successfully for treatment of *P. kellicotti*[38,39,42] Efficacy of treatment should be assessed with repeated fecal examination for ova.[39] Pneumothorax that results in respiratory embarrassment requires specific therapy (i.e., thoracocentesis; see ch. 100, 102, and 139).

Filaroides

Filaroides spp. are relatively uncommon pulmonary parasites of dogs. Adult nematodes of both *Filaroides hirthi* and *Filaroides milksi* (also known as *Andersonstrongylus milksi*) species reside in the alveolar spaces and

terminal bronchioles; differentiation of these very similar parasites is not necessary.[43,44] *Filaroides* spp. frequently have been recognized as endemic in research dog colonies.[45-51] The ovoviviparous parasite is transmitted directly via the fecal-oral route, allowing transmission between an infected dam and her pups or between infected and uninfected pups. Repeat infection (autoinfection) of the host with larvae before they even leave the host also is possible and increases the potential for "superinfections."[52-57] Dogs can remain healthy while parasitized or can develop severe or even fatal disease. Severe disease is especially likely in young, small-breed dogs, immunosuppressed dogs, or dogs with superinfections.[43,44,56,58,59]

Clinical signs, when they occur, can include cough and respiratory distress. Diffuse bronchointerstitial and alveolar infiltrates result from granulomatous inflammation in reaction to the dead or dying worms.[43,55,56,60] Zinc sulfate centrifugation fecal flotation is used for identifying larvae but lacks sensitivity due to intermittent shedding (a common feature of most lungworm infections). Recognition of ova and/or larvae via airway lavage is an alternative method of diagnosis. A variety of anthelmintic treatments has been employed, but fenbendazole (25-50 mg/kg PO q 24 h for 10-14 days) or ivermectin (0.4-1 mg/kg IV or SC for dogs lacking MDR-1 mutation) is used most often.[28,44,51] An inflammatory reaction to dying worms can worsen disease severity shortly after treatment, a complication that can be ameliorated by a short course of corticosteroids at antiinflammatory dosages (e.g., predniso[lo]ne 0.5-1 mg/kg PO q 24 h for 3-7 days).[44,61]

Airway Parasites

Aelurostrongylus abstrusus

A. abstrusus is a common feline lungworm found throughout the world; in the United States, it is most common in the southern states.[62,63] Although most infected cats remain well, infection can produce clinical signs that mimic feline bronchopulmonary disease. Mature worms reside in the bronchioles; inflammation of these small airways can result in cough, wheezing, and/or respiratory distress. Thoracic radiographs of parasitized cats can appear unremarkable or can demonstrate a diffuse interstitial nodular and/or peribronchiolar pattern, or sometimes an alveolar pattern.[64] In endemic regions, *A. abstrusus* should be considered an important differential diagnosis for feline "asthma," especially in cats with outdoor exposure, which are more likely to ingest the mollusk intermediate host of the parasite. Diagnosis is based on detection of larvae in either airway lavage samples or the feces via Baermann sedimentation (E-Figure 242-6).[28,63,65] A very sensitive and specific diagnostic PCR using either feces or pharyngeal swab material has been developed but is not currently commercially available.[66] Fenbendazole (25-50 mg/kg PO q 24 h for 10-14 days), ivermectin (300-400 mcg/kg SC), or selamectin (6 mg/kg applied topically) can be used for treatment.[29,63] Oral or inhaled antiinflammatory dosages of glucocorticoids can be useful during therapy, as can bronchodilators for cats with increased respiratory effort.

E-FIGURE 242-6 Larva of *Aelurostrongylus abstrusus* recovered from feces via Baermann sedimentation. (Courtesy Dr. Richard Meadows, University of Missouri College of Veterinary Medicine.)

Crenosoma vulpis

Dogs but not cats can be infected with *C. vulpis,* an airway nematode.[28,67] Indirect infections follow ingestion of mollusk intermediate hosts. The infection is reported most often in the northeastern United States and Atlantic Canada but also occurs in Europe. The parasite matures in the airways, where it produces larvated eggs that can be coughed out of the respiratory tract and swallowed. The majority of dogs infected with *C. vulpis* remain healthy, but lower respiratory signs (e.g., cough) and sometimes upper respiratory signs (e.g., nasal discharge) can occur. Diagnosis is accomplished by recognition of the immature parasites either on airway lavage or through fecal Baermann sedimentation or zinc sulfate centrifugal flotation techniques (E-Figure 242-7). Treatment with fenbendazole (50 mg/kg PO q 24 h for 3 days), ivermectin, or milbemycin oxime (0.5 mg/kg PO, once) can be effective.[68-70]

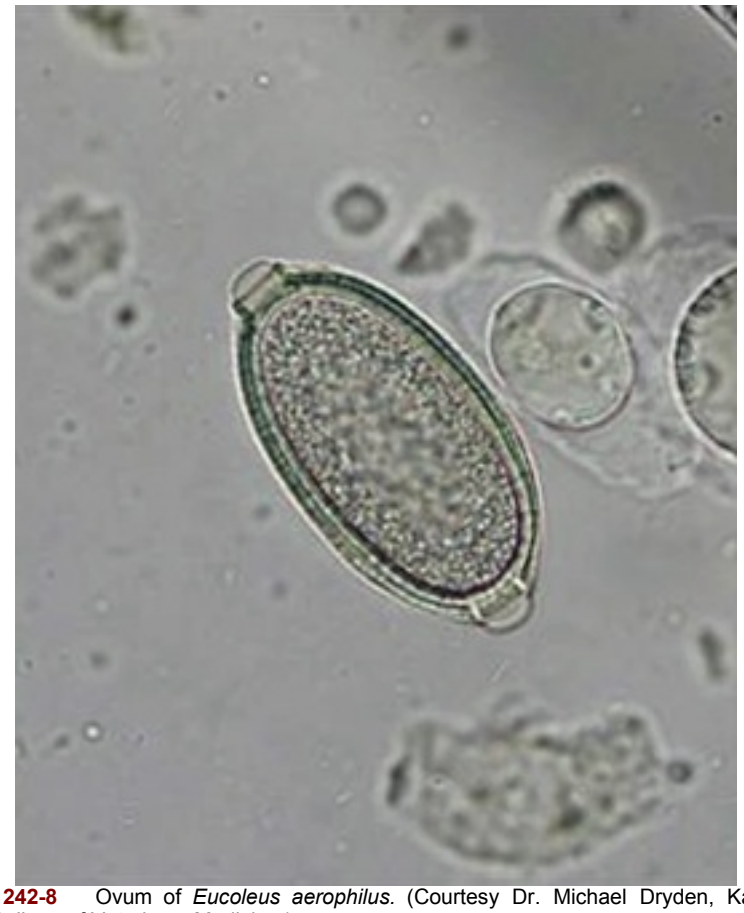
E-FIGURE 242-7 Iodine stained and killed *Crenosoma vulpis* first-stage larva recovered from feces via Baermann sedimentation. After parasite movement is detected on initial examination of the cover-slipped sample, a drop of iodine is allowed to wick through the sample, killing the parasite and facilitating a more complete morphologic examination. (Courtesy Dr. Gary Conboy, University of Prince Edward Island, Atlantic Veterinary College.)

Oslerus osleri

Also known as *Filaroides osleri,* this parasite is morphologically similar to *F. hirthi* and *F. milksi* and, like those pathogens, is transmitted directly without an intermediate host. The primary site of mature residence for *O. osleri* is the distal trachea and the most proximal bronchi, where granulomatous mucosal nodules form.[28,71] Usually subclinical, infection can result in cough or even less commonly exercise intolerance or respiratory distress due to airway obstruction or pneumothorax. Because the parasite-containing nodule can interfere with physical respiratory defenses (e.g., the mucociliary escalator), secondary bacterial infection can occur. Zinc sulfate centrifugal fecal flotation or bronchoscopic identification of the worm nodules can confirm infection.

Eucoleus aerophilus

This nematode respiratory parasite, also known as *Capillaria aerophila,* has a worldwide distribution. The parasite infects the airway mucosa of both dogs and cats. *E. aerophilus* becomes embedded in the tracheal and bronchial mucosa, sometime resulting in eosinophilic bronchitis.[28,72] Although most infections remain subclinical, chronic cough or even occasional respiratory distress can occur. As opposed to most lungworm infections, fecal diagnosis is better accomplished by routine flotation rather than Baermann technique. Airway lavage cytology also can aid identification of the characteristic double-operculated eggs that are similar to, but smaller than, those of the intestinal whipworm *Trichuris vulpis* (E-Figure 242-8).



E-FIGURE 242-8 Ovum of *Eucoleus aerophilus*. (Courtesy Dr. Michael Dryden, Kansas State University College of Veterinary Medicine.)

Troglostrongylus spp.

These metastrongyloid nematodes recently have been recognized to infect domestic as well as wild cats.[29,73] While some species infect the sinuses or trachea, others (especially *T. brevior*) inhabit the bronchi and bronchioles of the definitive host. Reported mostly in cats from Europe and Africa, these parasites are larger than *A. abstrusus* and have the potential for increased pathogenicity, including fatal infection.[73,74] While larvae can be identified in fresh feces, they are difficult to distinguish from other metastrongyloids.[73] A duplex-PCR has been developed that can detect and distinguish between *T. brevior* and *A. abstrusus,* but it is not commercially available.[75]

Other Parasites of Relevance to the Lung

Dirofilaria immitis

D. immitis is responsible for heartworm disease, an important cause of pulmonary and cardiac disease in temperate climates throughout the world. Although heartworm infection of dogs has been well described for many decades, only recently have we begun to understand heartworm infection in cats.[76-80] The host-parasite interaction, clinical consequences, diagnosis, and treatment of *D. immitis* differ greatly between dogs and cats (E-Table 242-2), but efficacious prophylactic mediations are readily available for use in both species. More detail on heartworm infection can be found in ch. 255.

E-TABLE 242-2

Comparison of *Dirofilaria immitis* Infection in Dogs vs. Cats[78-80,468-474]

DOGS	CATS

Host-parasite interaction	• Natural host. • Parasite burden variable but often many mature worms present. • Mature worms persist 5-7 years. • Mature infection often accompanied by microfilaremia. • Prevalence varies with geographic region.	• Atypical host. • Parasite burden typically 1-3 worms. • Mature worms persist 2-3 years. • Mature infection very rarely accompanied by microfilaremia. • Larval forms often eliminated by immune response. • Prevalence of mature infection ≈10% of that in dogs in a given geographic region.

Diagnosis	• Diagnosis of mature infection straightforward.
	  • Recognition of microfilaria on blood smear or via concentration technique (e.g., Knott's test, filtration test) often allows diagnosis. Microfilaria are absent early in infection, with low worm burdens, or in dogs receiving heartworm prophylaxis.
	  • Antigen recognition via ELISA offers excellent sensitivity and specificity for infection in dogs. Antigen becomes detectable ≈5 months after infection.
	• Heat-treatment of sample could increase sensitivity of antigen testing.
	• Thoracic radiographs can be suggestive but not diagnostic of heartworm infection. Radiographs often demonstrate prominent pulmonary artery segments, arterial tortuosity and pruning, and sometimes right ventricular enlargement. A variety of pulmonary parenchymal abnormalities also is possible.
	• Echocardiography can demonstrate right-sided cardiomegaly, worms within the pulmonary artery or right heart.
		• Diagnosis of infection difficult. Often a combination of tests is required to confirm infection in cats with low worm burdens.
		  • Microfilaria seldom present.
		  • Sensitivity of ELISA antigen tests is low due to low worm burden, absence of antigenically detectable female worms, or immature worms. However, antigen test specificity is high.
		• Heat-treatment of sample will increase sensitivity of antigen testing.
		• Feline-specific heartworm antibody tests are moderately sensitive; can miss 15% or more of infections.
		• Feline-specific heartworm antibody tests are moderately specific and confirm only exposure to parasite. They cannot confirm that an infection is mature or active.
		• Radiographic changes inconsistent, although caudal lobar arterial enlargement and parenchymal changes are sometimes identified.
		• Echocardiography may detect mature infection but sensitivity and specificity are operator-dependent (30%-100%). Useful when infection is suspected despite negative ELISA antigen test.

Clinical signs	• Dogs remain well for prolonged periods during infection. • When clinical signs do develop, the most common are exercise intolerance and cough. • Right-sided congestive heart failure occurs eventually in some untreated dogs. • Heartworm caval syndrome is an uncommon emergent complication of infection that occurs when the adult worms occupy the right side of the heart. Caval syndrome includes a tricuspid regurgitant murmur, intravascular fragmentation hemolysis with hemoglobinuria, right-sided congestive heart failure, and disseminated intravascular coagulation. • Antigen-antibody complex deposition can cause glomerulonephritis. • Rarely, aberrant migration leads to disease of other organ systems (e.g., eyes, brain, spinal cord, skin, liver).	• Cats frequently remain well during infection. • Cats can develop a syndrome resembling feline asthma as a result of larval infection without adult worm burden (i.e., HARD). • Cats with mature worm burdens can present with GI signs including hypersalivation and vomiting or respiratory signs including cough or tachypnea. • Cats with mature worms can die suddenly without prior clinical illness or can present with acute onset dyspnea and/or CNS signs.

		• Unlike dogs, right-sided congestive heart failure is rare in cats. • Rarely, aberrant migration leads to disease of other organ systems (e.g., eyes, brain, spinal cord, skin, liver).
Prophylaxis	• Chemoprophylaxis is extremely effective. Options include ivermectin, milbemycin oxime, moxidectin, and selamectin.	• As for dogs, chemoprophylaxis with the same compounds is extremely effective.
Treatment	• Adulticide treatment should be preceded by staging to identify comorbid conditions and severity of disease, and usually by doxycycline treatment for eradication of *Wolbachia.* • Melarsomine is the only approved heartworm adulticide. • If not used beforehand, chemoprophylaxis should be begun when adult infection is identified. If microfilaria are present, the dog should be observed for anaphylaxis after the first dose is administered. • Caval syndrome is treated via physical (surgical) removal of worms. • Complications of infection may require specific therapy (e.g., treatment of congestive heart failure, treatment of glomerulonephritis).	• Adulticide treatment in cats is not recommended due to toxicity, lack of efficacy, and fatalities associated with thromboembolism. • If not used beforehand, chemoprophylaxis should be begun when adult infection is identified. • Cats with bronchopulmonary disease could benefit from corticosteroid therapy. • Bronchodilator therapy and oxygen may be useful in cats with respiratory distress. • Surgical removal of mature worms has been described but entails risk.

CNS, Central nervous system; *ELISA*, enzyme-linked immunosorbent assay; *GI*, gastrointestinal; *HARD*, heartworm-associated respiratory disease.

Angiostrongylus vasorum

Infection with this metastrongylid parasite of canids occurs in Europe, Asia, and Africa, as well as in an endemic focus in Newfoundland, Canada.[70,81-83] It has been dubbed "French heartworm" because, like *D. immitis,* the mature parasites reside in the pulmonary artery, right heart, and pulmonary arterioles. Dogs are infected after consuming infected intermediate (i.e., mollusk) or paratenic (i.e., frog) hosts; L3 larvae are liberated into the dog's intestine before eventually making their way to the pulmonary vasculature. Ova from the mature worms are carried to the pulmonary capillaries, where they hatch. The L1 larvae then migrate into the alveoli. After gaining entrance to the airways, the larvae can be coughed up and swallowed.

Infected dogs can appear healthy or have a range of clinical signs. The predominant syndromes associated with infection are respiratory disease related to an inflammatory response to the parasite and a syndrome of bleeding diathesis.[83] The cause of bleeding is poorly understood but could be related to a consumptive coagulopathy initiated by the parasite, and bleeding can occur without respiratory signs.[84,85] Neurologic signs have been reported in infected dogs as a consequence of central nervous system hemorrhage.[86,87] Severe pulmonary hypertension with resultant cor pulmonale and syncope are reported occasionally, as is spontaneous pneumothorax.[88-91] Although cardiopulmonary disease related to thrombosing pulmonary arteritis can be severe, the most common findings are chronic cough and general unthriftiness. Unlike with heartworm disease caused by *D. immitis,* vascular changes are not appreciated on thoracic imaging. Instead, some combination of bronchial, interstitial, and/or peripheral alveolar lung patterns is described and is seen best on thoracic CT (Figure 242-9).[92,93] Laboratory findings associated with infection can include anemia, eosinophilia, thrombocytopenia, abnormalities of coagulation time, and often, hypercalcemia.[84,94-97]

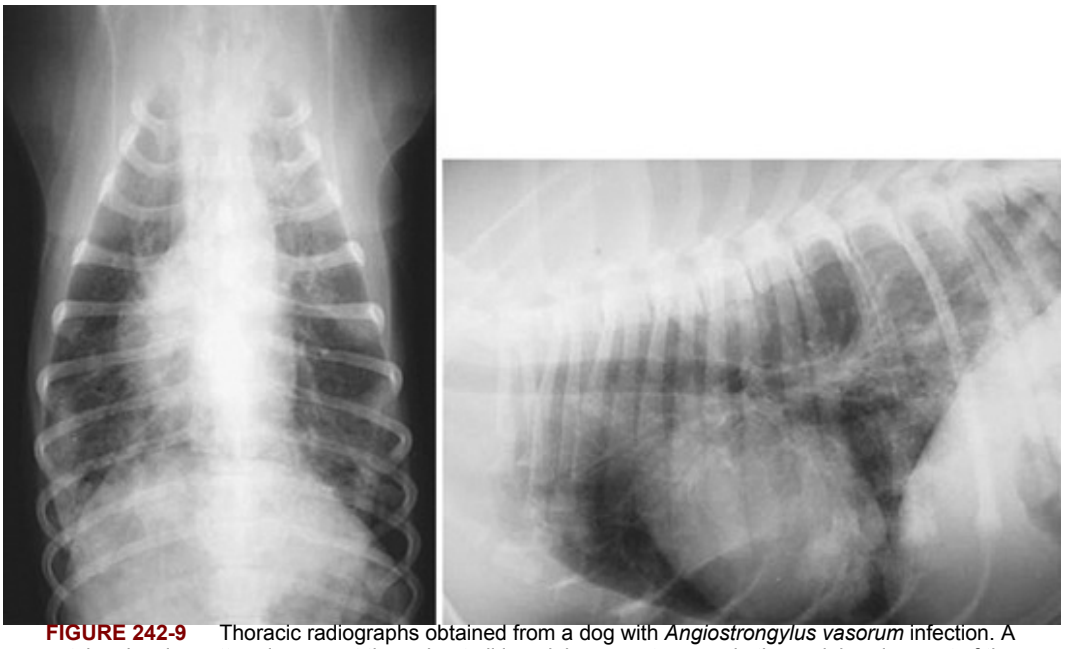


FIGURE 242-9 Thoracic radiographs obtained from a dog with *Angiostrongylus vasorum* infection. A patchy alveolar pattern is present throughout all lung lobes, most severe in the peripheral aspect of the right caudal lung lobe, caudal aspect of the cranial segment of the left cranial lung lobe, and throughout the left caudal lung lobe. A mild degree of peribronchial thickening is also present throughout all lung lobes. Both the cardiac silhouette and pulmonary vasculature remain unremarkable. (Courtesy Dr. Harriet Syme, Royal Veterinary College.)

Appropriate diagnosis and treatment generally are associated with a good prognosis for recovery.[83] As for many pulmonary parasites, Baermann fecal examination (see E-Figure 242-3) is the diagnostic standard and parasites also can be identified on airway lavage.[98] More recently, sensitive and specific serologic and molecular detection tests have been described.[81,98,99] The drug of choice for treatment of *A. vasorum* is fenbendazole (25-50 mg/kg PO q 24 h for 10-20 days), although other effective treatments (e.g., ivermectin [0.2 mg/kg SC each week for two doses], milbemycin oxime [0.5 mg/kg PO each week for 4 weeks], imidacloprid 10%/moxidectin 2.5% spot-on solution, levamisole) have been described.[70,81,100] Treatment with spinosad and milbemycin oxime can be used as a once-monthly prophylactic regimen.[101] Despite recovery of most dogs after treatment, post-treatment reactions including dyspnea, ascites, and sudden death have been observed.[102]

Bacterial Pneumonia

Bacterial pneumonia encompasses a wide spectrum of disease from acute to chronic, unilobar or multilobar, clinically silent infection to fatal infection. There are multiple potential routes of pulmonary exposure to potentially pathogenic bacteria. Bacteria can be inhaled or aspirated into the lung, they can reach the lung through direct extension from the pleural space or intrathoracic structures, or they can gain access to the lung hematogenously. Most bacteria that cause pneumonia are secondary pathogens and only cause disease when allowed the opportunity (e.g., immune suppression, aspiration). Bacterial pneumonia often is the result of mixed flora infections, and obligate anaerobes could account for as many as a quarter of pathogens involved.[103-106] The bacteria most commonly implicated include enteric pathogens (e.g., *Escherichia coli, Klebsiella*), *Pasteurella* spp., coagulase-positive staphylococci, streptococci, *Mycoplasma* spp., and *Bordetella bronchiseptica* (Table 242-3).[5,65,103-111] It is unusual for healthy adult pets, especially cats, to develop bacterial pneumonia. With the exception of infections caused by primary bacterial respiratory pathogens (e.g., *Bordetella bronchiseptica*), most animals with bacterial pneumonia have been compromised in some fashion. The diagnosis of bacterial pneumonia should prompt the clinician to search for a predisposing cause.

TABLE 242-3

Commonly Isolated Bacterial Pathogens Involved in Lower Respiratory Infection/Pneumonia

BACTERIAL GENERA AND SPECIES	ISOLATES FROM DOGS[104-106,108,109]	ISOLATES FROM CATS[5,65,110,111]
Escherichia coli	132	7
Pasteurella spp.	104	22
Bordetella bronchiseptica	105	15
Streptococcus spp.	149	12
Coagulase (+) *Staphylococcus* spp.	101	1
Klebsiella spp.	45	
Enterococcus spp.	15	1
Pseudomonas aeruginosa	66	3
Mycoplasma spp.	95	34

Presentation

Dogs develop bacterial pneumonia more often than do cats.[5,23,104,112,113] Many pets with bacterial pneumonia have a predisposing factor for infection, including extremes of age, debilitation, immunocompromise, or preexisting respiratory disease (Box 242-5).[107,112,114-119] Occasionally, bacterial pneumonia is accompanied by only minor clinical signs or physical examination abnormalities, especially when it is regionally limited to involve a single lung lobe. Commonly, clinical signs include cough (often soft and productive), nasal discharge, exercise intolerance, or respiratory distress. Anorexia and lethargy also are commonplace. Fever is inconsistent at best, and normothermia does not rule out bacterial pneumonia. Loss of body condition, tachypnea, increased (or when consolidation is present, decreased) bronchovesicular lung sounds, inspiratory crackles, sinus arrhythmia, and cyanosis can be identified.

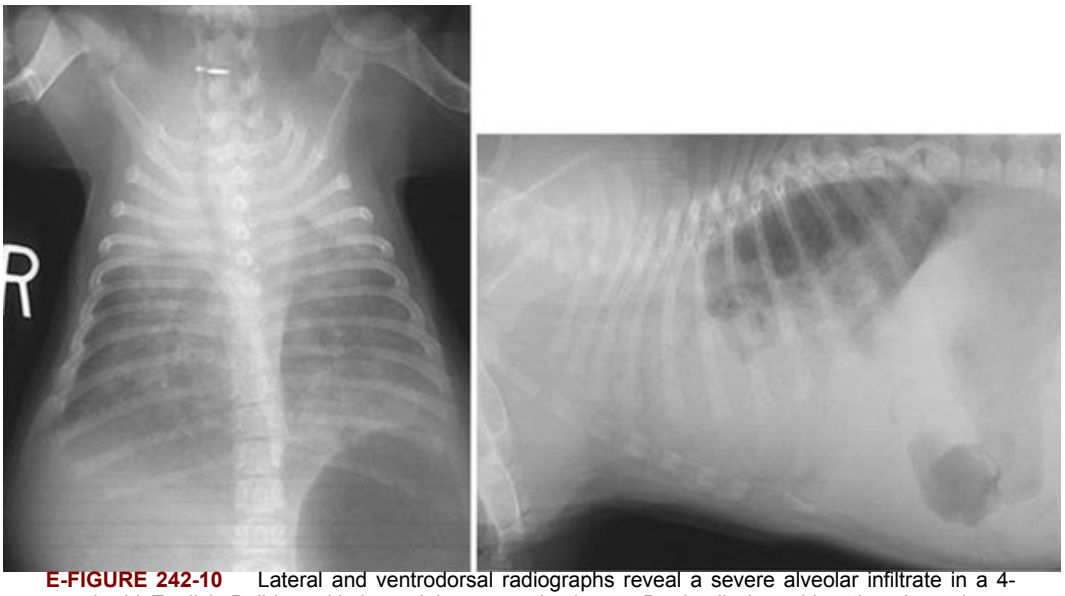
Box 242-5

Factors That Predispose to Development of Bacterial Pneumonia

- Debilitation
- Prolonged recumbency
- Systemic immunosuppression
  - Drug-related (e.g., corticosteroids, chemotherapy)
  - Infection (e.g., feline leukemia virus, feline immunodeficiency virus)
  - Endocrine disorders (e.g., hyperadrenocorticism, diabetes mellitus)
- Immunodeficiency states
  - Extremes of age
  - Congenital immunodeficiency (e.g., breed-related syndromes, severe combined immunodeficiency disease, phagocytic defects)
- Defective respiratory defenses
  - Primary ciliary dyskinesia
  - IgA deficiency
- Damage to respiratory epithelium
  - Smoke inhalation
  - Drowning
  - Viral, parasitic, protozoal, or fungal infection
  - Neoplasia
  - Acute respiratory distress syndrome
- Aspiration (see Box 242-11)
- Pleural/mediastinal/airway infection
- Penetrating thoracic injury
- Airway obstruction (functional or structural)
- Bronchiectasis
- Sepsis/bacteremia

Diagnostic Evaluation

Diagnostic screening tests for animals with suspected bacterial pneumonia include thoracic radiographs, CBC, and arterial blood gas or pulse oximetry measurement. Ideally, a serum biochemical profile, urinalysis, and fecal examination also are performed because they provide potentially valuable information regarding the animal's overall health and sometimes provide clues as to the presence of a systemic disease that might predispose to development of pneumonia. Neutrophilia (± left shift), lymphopenia, and mild anemia are inconsistent but common findings on CBC. Hypoxemia is common but depends on severity of functional lung impairment.[105,120] The classic radiographic appearance of bacterial pneumonia is an alveolar pulmonary pattern with a predominantly ventral distribution.[112,121,122] Sometimes, only a single lung lobe is involved (particularly following foreign body inhalation or aspiration). Dorsocaudal involvement may predominate after hematogenous bacterial exposure, and all lung fields can be involved in cases of severe pneumonia (E-Figure 242-10). In less severe pneumonia or early in the disease course, only an interstitial pattern might be identified. Occasionally, complications such as abscessation, pleural effusion, or pneumothorax are identified concurrently.[121]



E-FIGURE 242-10 Lateral and ventrodorsal radiographs reveal a severe alveolar infiltrate in a 4-month-old English Bulldog with bacterial pneumonia due to *Bordetella bronchiseptica*. A moderate bronchointerstitial pattern is present in the caudodorsal lung lobes, while an alveolar pattern is found in the remainder of the lung lobes.

A specific diagnosis of bacterial pneumonia is confirmed by identification of pulmonary sepsis. Airway lavage provides material for cytologic examination, as well as culture and sensitivity testing. In a recent study from the Ryan Veterinary Hospital at the University of Pennsylvania, the empiric choice of antimicrobial selected for the treatment of pneumonia was found to be inappropriate for the pathogens identified on culture and susceptibility in 26% of dogs.[106] Even more worrisome, for dogs that had received antimicrobials during the preceding 4 weeks for any reason, there was resistence to the empiric antimicrobial choice in 64.7% of dogs with community-acquired pneumonia, underlining the importance of gathering materials for culture and susceptibility prior to initiation of treatment.[106]

Treatment is likely to be prolonged, and culture and sensitivity allow the identification of the safest, most economical, and correctly targeted antimicrobial drugs. However, once the samples have been obtained, antimicrobials should not be withheld pending susceptibility results. It must be recognized that prior antibiotic therapy, incorrect sample handling, or infection with fastidious organisms can result in negative culture even in the face of bacterial pneumonia.[108,123,123a] Because bacterial pneumonia often results in a productive cough, lavage of the large airways (e.g., transtracheal or transoral wash) can be safe, inexpensive, and useful (see ch. 101 and 240).[103] BAL also can be used for obtaining samples for cytology and culture.[107,108] In severe bacterial pneumonia, foreign body pneumonia, aspiration pneumonia, or when areas of pulmonary consolidation are present, anaerobic culture should be requested in addition to routine aerobic

culture.[112,124] Because some *Mycoplasma* spp. might be primary bacterial pathogens of the airways but are difficult to culture using routine methods, specific *Mycoplasma* PCR can be considered as well.[113,125] The airways are not sterile even in health, and noninfectious respiratory disease can be associated with secondary bacterial infection. Therefore, the diagnosis of bacterial pneumonia must be based on integration of all clinical and radiographic findings, ideally in conjunction with cytologically demonstrated neutrophilic airway inflammation and intracellular bacteria in addition to a positive bacterial culture.

Treatment

Bacterial pneumonia should be treated with antimicrobial drugs.[106,124] Initial empiric treatment can be adjusted later, based on results of bacterial culture and susceptibility testing. Initial therapy can be guided in part by cytologic morphology and staining characteristics of microbes recovered from airway lavage.[107,109] For severely affected or unstable animals, initial therapy must include antimicrobials with Gram-positive, Gram-negative, aerobic and anaerobic efficacy. Most often, this approach involves combination therapy administered parenterally (Box 242-6); the author often begins with a combination of ampicillin and enrofloxacin while the recent recommendations of the International Society of Companion Animal Infectious Disease (ISCAID) recommend an initial combination of a fluoroquinolone with either ampicillin or clindamycin.[124] Animals with mild to moderate disease may be treated initially with orally administered antimicrobials with a more limited spectrum of activity (see Box 242-6). Although many antimicrobials (including beta-lactam antibacterials) do not readily penetrate the airway's blood-bronchus barrier, this is less of a concern with pneumonia, which is a parenchymal tissue infection rather than an airway infection. While aerosolized administration of antimicrobials could have an (unproven) benefit in the treatment of certain animals with bacterial pneumonia, aerosol delivery should only be considered as an adjuvant therapy and never as a replacement for systemic antimicrobials.[123,126] Historically in veterinary medicine, the recommended duration of antimicrobial therapy was 1 week past radiographic resolution, typically a minimum of 3 to 4 weeks. This is in extreme excess compared to the duration of therapy recommended for treatment of pneumonia in humans[127,128] and likely longer than is required for pets. Newly developed ISCAID guidelines for respiratory infections suggest reevaluation of animals 10-14 days after treatment has begun, with antimicrobial use extended, altered, or halted on the basis of clinical response.[124]

Box 242-6

Empiric Antimicrobial Choices for the Initial Treatment of Bacterial Pneumonia

Severe, Unstable Disease

Monotherapy:
- Meropenem or imipenem-cilastatin or ticarcillin

Combination therapy:
- Beta-lactam (e.g., ampicillin, amoxicillin/clavulanate, second- or third-generation cephalosporin) or clindamycin
- AND EITHER
- Fluoroquinolone (e.g., enrofloxacin, marbofloxacin, orbifloxacin)
- OR
- Aminoglycoside (e.g., amikacin, gentamicin)

Moderate, Stable Disease

Monotherapy:
- Amoxicillin/clavulanate or trimethoprim-sulfonamide

Combination therapy:
- Beta-lactam AND fluoroquinolone
- OR
- Clindamycin AND fluoroquinolone

Mild, Stable Disease

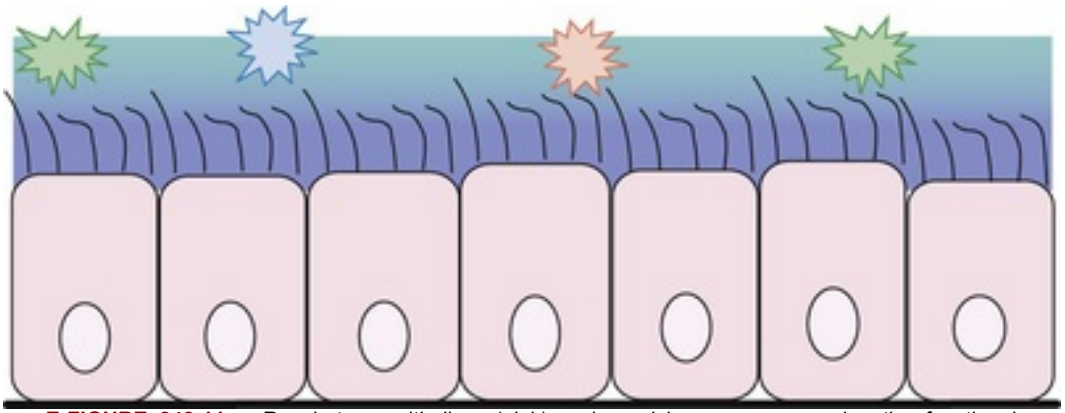
Monotherapy:

Amoxicillin/clavulanate or fluoroquinolone or trimethoprim-sulfonamide

Note: Initial, empiric choice of antimicrobials should be adjusted based on results of microbial culture and sensitivity. The more severe the initial disease is, the more important it is for therapy to provide broad-spectrum coverage.

Dogs with severe bacterial pneumonia often are hypoxemic.[120] Ideally, PaO_2 is determined via arterial blood gas analysis (see ch. 128) but SpO_2 can be used as a rough correlate (see ch. 98). In animals with acute hypoxemia, oxygen supplementation should be provided when PaO_2 is <80 mm Hg or SpO_2 is <94%. The most practical means of delivery include placement of nasal cannula or oxygen cages (see ch. 131). Oxygen should be humidified prior to delivery to prevent drying of the airways with resultant impaired mucociliary clearance. Persistent hypoxemia or continued marked respiratory effort despite oxygen supplementation indicates the need for mechanical ventilation. Unfortunately, the prognosis for recovery of dogs and cats with underlying respiratory disease severe enough to warrant mechanical ventilation is poor.[129] In part, this might be related to the presence of more antimicrobial resistant pathogens in patients with respiratory failure due to pneumonia.[130]

Fluid therapy is indicated for the treatment of animals with severe bacterial pneumonia (see ch. 129). Dehydration is common in weak, depressed, anorexic, febrile, and tachypneic animals. In addition to the systemic effects of hypovolemia, dehydration impairs mucociliary respiratory defenses. Airway mucus functions to trap bacteria and inhaled particulates. The respiratory epithelial cilia propel entrapped particulates craniad to the oropharynx, where they can be expelled through coughing or swallowing.[131] The mucus itself is made of two layers—the watery sol layer through which the cilia move and the overlying gel layer that traps the particulates (E-Figure 242-11). If the sol layer becomes dehydrated, the cilia themselves become entrapped in the gel layer, effectively inhibiting the mucociliary escalator. Crystalloid fluids should be provided at a rate to attain and maintain hydration. Overly aggressive fluid therapy can lead to iatrogenic pulmonary edema and worsen respiratory compromise. Nebulization of sterile saline can enhance mucus fluidity and more effective mucociliary function, although this benefit has not been documented in pets. Saline nebulization 3 to 4 times a day seems to improve breathing in many animals with pneumonia (E-Box 242-7).



E-FIGURE 242-11 Respiratory epithelium (pink) and overlying mucus comprise the functional mucociliary escalator. The apical surface of the respiratory epithelium is covered with a layer of mucus. The mucus layer is not uniform but includes the less viscous sol layer in closest contact with the epithelial surface (purple), as well as a more tenacious, viscous gel layer on top of the sol (teal). Particulates (starbursts) become entrapped in the gel layer, while the respiratory cilia move in a coordinated fashion predominantly in the sol layer. Ciliary movement propels the gel layer with entrapped particulate craniad for expulsion from the respiratory tract. Dehydration of the sol layer impedes ciliary movement and therefore impedes the mucociliary escalator.

E-Box 242-7

Nebulization in Pet Animals

Nebulization creates extremely small fluid particles for inhalation. The site of deposition of these particles depends on their size, charge, hygroscopy, and other parameters. Humidifiers create larger droplets that do not reach lower airways, whereas nebulizers create smaller particles (0.5 to 3 micrometers) that penetrate more deeply into the respiratory tract.

The basic nebulizer types include jet nebulizers and ultrasonic nebulizers. Modifications of these (e.g., spinning disc nebulizers, vibrating mesh nebulizers) exist to improve delivery or modulate particle size. Nebulizers are available in portable sizes at a modest price, certainly suitable for use in veterinary hospitals and even practical for at-home use by owners. In general, jet nebulizers are more bulky but more sturdy, whereas ultrasonic nebulizers are small and portable but prone to malfunction. Ultrasonic nebulizers efficiently deliver small liquid volumes, which can be advantageous when administering expensive medications.

Nebulized liquids can be delivered to dogs and cats via face mask, or the animal can be placed in a closed tent or aquarium-type container. Nebulized aerosols also can be administered via tracheostomy tube. In general, the more removed the particle generator is from the respiratory tract, the more drug is lost outside the respiratory tract. Therefore, while tent/tank nebulization could be adequate for saline nebulization, medications should be administered via mask.

In small animal medicine, nebulizers most often are used for the treatment of respiratory infection. Simple saline nebulization could improve mucus fluidity and therefore function of the mucociliary escalator, but no proof of such efficacy exists in the veterinary literature. The author often treats animals with pneumonia with saline nebulization from one to four times daily. Nebulization also can be used for delivering medications including antimicrobial drugs, bronchodilators, glucocorticoids, or mucolytics agents (caution—not all liquid drug forms are suitable for nebulization!). Administration of drugs not specifically developed for inhalational delivery can be associated with adverse reactions including severe bronchoconstriction and with damage to the equipment. Antimicrobials designed for inhalational delivery (e.g., tobramycin [Tobi]) are prohibitively expensive for veterinary use. Aminoglycosides designed for intravenous administration often are used instead. Specific dosage recommendations have not been developed for nebulized antimicrobials. The author has used gentamicin 6 to 8 mg/kg, qs 5 to 10 mL in saline, via nebulization for animals with susceptible airway pathogens once daily as an adjunct to systemic antimicrobial administration. Bronchodilators and glucocorticoids for inhalational use are readily available for a reasonable price. Nebulization of mucolytic agents results in bronchoconstriction and thus is not routinely advocated. Pretreatment with bronchodilators might improve lower airway delivery of inhaled medications.

When nebulizers are used in the treatment of pets with contagious respiratory disease, the device itself must be kept meticulously clean to avoid iatrogenic transmission of respiratory infection. Nebulization of nosocomial pathogens could have devastating consequences for an animal with compromised respiratory function.

Cough is encouraged in animals with bacterial pneumonia, and cough suppressants are contraindicated. Coupage (i.e., thoracic physical therapy) is a simple technique of thoracic percussion that aids mobilization of airway secretions and encourages cough (Figure 242-12). Although not documented to be particulary efficacious in adult humans with pneumonia, it has been useful in other settings such as pneumonia associated with cystic fibrosis.[132] As far as the author is aware, there are no studies documenting efficacy of the technique in dogs or cats. Coupage should follow saline nebulization when both are used. Animals should be encouraged to move, and recumbent animals should be repositioned frequently, to aid in mobilization of respiratory secretions.

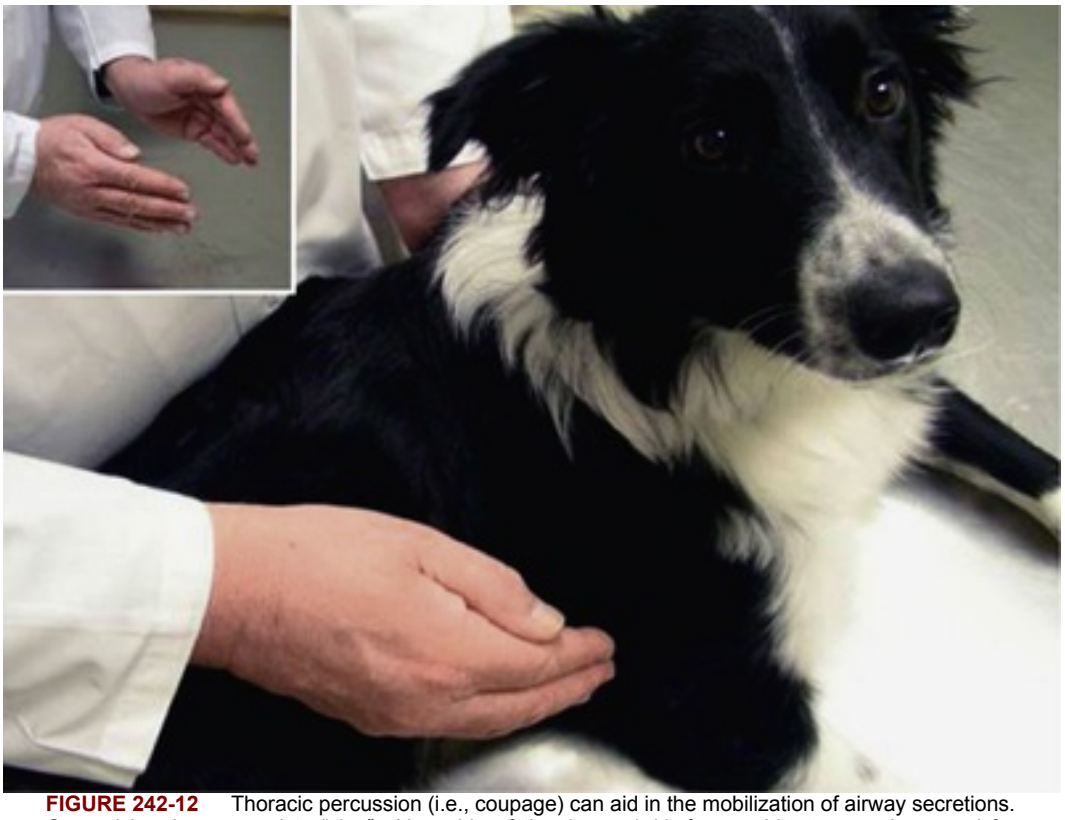
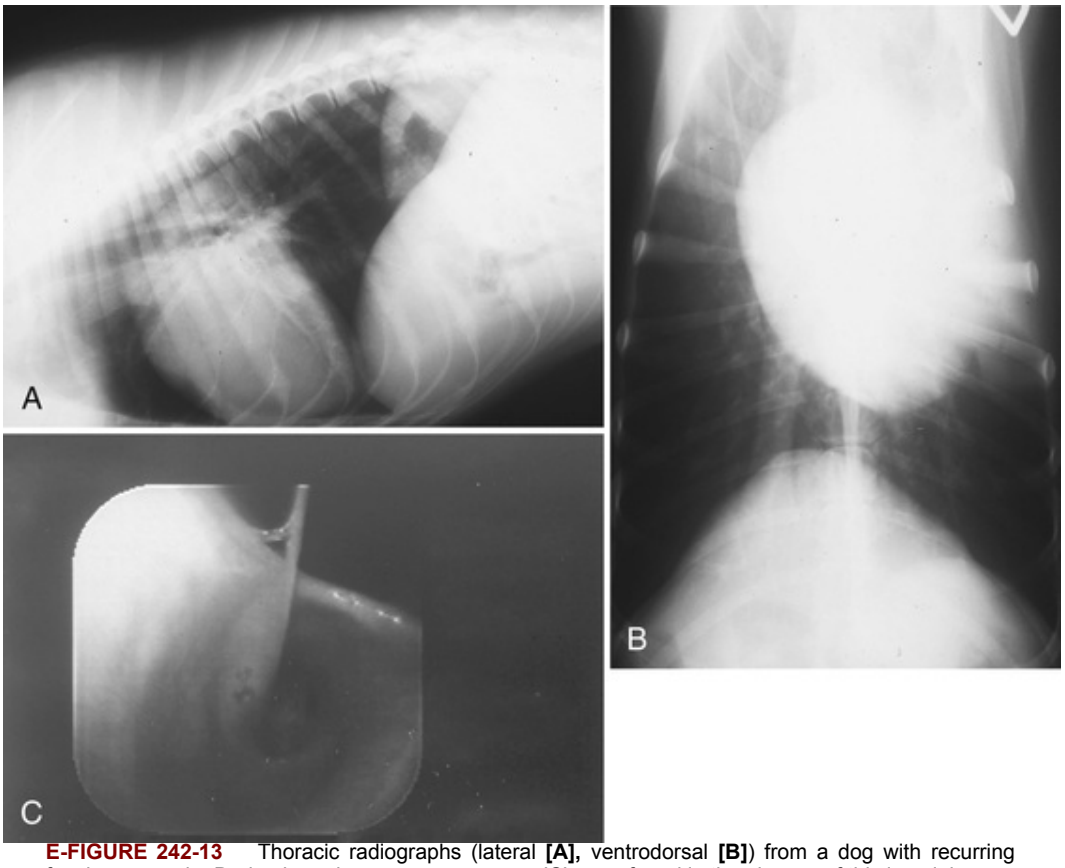


FIGURE 242-12 Thoracic percussion (i.e., coupage) can aid in the mobilization of airway secretions. Cupped hands are used to "clap" either side of the thorax (with force a bit stronger than used for applause) in a repeated fashion. Saline nebulization prior to coupage can further improve mobilization of secretions.

Additional therapeutic considerations for animals with pneumonia include bronchodilators, mucolytics, and nutritional and supportive care. Bronchodilators are not used routinely for the treatment of bacterial pneumonia. Either inhaled albuterol or oral methylxanthine bronchodilators (e.g., theophylline) are considered in animals that remain hypoxemic despite supplemental oxygen administration, when there is concurrent bronchoconstriction (especially likely in cats), or prior to administration of inhalant drug therapy. Bacterial pneumonia can result in the production of copious quantities of thick, tenacious mucus. Theoretically, liquefaction of mucus can result in more effective mucociliary clearance. Simple maintenance of systemic hydration and airway humidification typically are adequate, but mucolytic drugs sometimes are advocated. The mucolytic N-acetylcysteine (NAC) reduces viscosity by breaking mucin disulfide bonds, but unfortunately nebulization of NAC causes bronchoconstriction.[133] Oral administration of NAC has not been investigated in pets with naturally occurring pneumonia but in other species has demonstrated at least some utility in the treatment of both infectious and noninfectious airway disease associated with excessive mucus secretion.[134-136] The author has used oral NAC (available through health food stores) in animals with excessive mucus accumulation due to pneumonia at a dosage of 125 mg up to 600 mg PO q 8-12 h, to seemingly good effect. Animals with pneumonia might be reluctant to eat, and nutritional support must not be neglected.

Lung lobectomy occasionally is indicated for treatment when pneumonia fails to resolve with appropriate antimicrobial therapy.[137-139] Residual infection in a single lobe can be related to an underlying physical problem such as a bronchial foreign body, abscess, or tumor (E-Figure 242-13). Removal of the lobe can result in cure in such cases. Occasionally, failure to respond to appropriate antimicrobial therapy is the result of an incorrect diagnosis. Any lung tissue removed surgically should be submitted both for tissue culture and for histopathologic analysis.



E-FIGURE 242-13 Thoracic radiographs (lateral **[A],** ventrodorsal **[B]**) from a dog with recurring focal pneumonia. During bronchoscopy, grass awns **(C)** were found in the airways of this lung lobe.

Unique Pathogens Causing Bacterial Pneumonia

Bordetella bronchiseptica

B. bronchiseptica is a primary respiratory pathogen. Essentially, it creates its own opportunity to cause infection via secretion of exotoxins that result in dysfunction of the mucociliary escalator.[140,141] Bordetellosis is contagious; both dogs and cats are susceptible but disease is more common in dogs.[142,143] Infection usually results in tracheobronchitis but can cause severe pneumonia in immunocompromised or young animals (see E-Figure 242-10). In a retrospective study of community-acquired pneumonia in dogs <1 year of age, *B. bronchiseptica* accounted for nearly half of all cases.[105] These infections can be difficult to eliminate despite the use of antimicrobials with demonstrated *in vitro* susceptibility. Pneumonia has been demonstrated in *Bordetella*-infected puppies treated with amoxicillin or amoxicillin-clavulanate even though *Bordetella*'s susceptibility to these antimicrobials had been shown *in vitro.*[105] The addition of nebulized aminoglycosides to systemic antimicrobials has been proposed, but documentation of efficacy in treating *Bordetella* pneumonia is lacking. The use of inhaled antimicrobials should never replace systemic antimicrobial administration for the treatment of pneumonia. For more information, see ch. 97.

Streptococcus equi Subspecies Zooepidemicus

Streptococcus equi subspecies zooepidemicus can cause necrotizing hemorrhagic pneumonia in dogs and recently has been recognized to affect cats also.[144-146] Unlike other causes of contagious canine infectious respiratory disease complex, illness rapidly can become life-threatening.[147-150] The pathogen is particularly likely to cause severe and even fatal hemorrhagic pneumonia in kenneled dogs, including those in shelters and research colonies. As with other types of bacterial pneumonia, airway lavage can be used for identifying infection and guiding appropriate antimicrobial therapy. Dogs dying acutely, or with evidence of pneumonia, in a kennel setting should undergo necropsy with bacterial culture to confirm infection.

Mycoplasma

Mycoplasma species, fastidious microbes that lack a cell wall, include pathogenic (e.g., *Mycoplasma pneumoniae* in humans, *Mycoplasma hyopneumoniae* in swine) and commensal organisms. As many as 15 different species of *Mycoplasma* have been isolated from dogs, and many have been isolated from cats as well.[151] However, because these organisms are difficult to grow and difficult to speciate, their exact role in canine and feline respiratory disease is not well defined.

Mycoplasma species are found commonly in the upper airways and occasionally in the lower airways of healthy dogs and cats.[152-154] Experimental inoculation of some mycoplasmas causes pneumonia, and naturally occurring pneumonia in both dogs and cats occasionally has been attributed to *Mycoplasma* spp. (especially *Mycoplasma cynos*).[153,155-161] However, in a study of 93 dogs with bacterial pneumonia specifically tested for mycoplasmas, *Mycoplasma* species were recovered from only 7 dogs as the sole bacterium and from 58 dogs with additional non-*Mycoplasma* bacteria.[104] This, combined with a favorable clinical outcome even when antimicrobial therapy was not directed at *Mycoplasma* spp., suggests that *Mycoplasma* bacteria primarily were opportunists. Nonetheless, they might contribute to morbidity when present as coinfection with other respiratory pathogens.[151,157]

Special culture or PCR must be requested to identify *Mycoplasma* spp. Compared with culture, PCR identification of mycoplasma from respiratory specimens provided a sensitivity of detection of 81.8% with specificity of 78.9%.[125] *Mycoplasma* spp. usually respond well to macrolides, tetracyclines, chloramphenicol, and fluoroquinolone antimicrobials but do not respond to antimicrobials that interfere with cell-wall synthesis (e.g., beta-lactams), which this genus lacks.

Mycobacterial Pneumonia

Cats and dogs occasionally are diagnosed with mycobacterial pneumonia. Both tuberculosis (i.e., *Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium microti*) and nontuberculosis-type (e.g., *Mycobacterium avium* complex, *Mycobacterium fortuitum*) mycobacterial infections cause pneumonia in pets.[162-174] Pneumonia can occur as the primary manifestation of mycobacterial infection or as a component of disseminated infection. Pneumonia due to mycobacteria often is granulomatous, and radiographs can demonstrate lymphadenomegaly and pleural effusion in addition to interstitial to alveolar pulmonary

infiltrates. Mixed pulmonary patterns are common, frequently including bronchial, alveolar, nodular structured interstitial, or unstructured interstitial components.[174] Organisms are found in low numbers, if at all, in samples retrieved by BAL or FNA, or aspiration of lymph nodes. Because they do not take up routinely-used stains, these acid-fast inclusions show up as negatively staining ("empty") rods on routine cytologic examination.[169,170,175] Both culture and PCR have been used for confirming the presence of mycobacterial species from dogs and cats, but tuberculosis-type mycobacteria are notoriously slow growing.[169,170,176,177] *M. tuberculosis* primarily is a human pathogen; when identified in dogs, it is considered a reverse zoonosis.[170,178] With such cases, the local health department should be contacted and owners of infected pets should be instructed to contact their physician. The public health implications of attempting treatment for tuberculosis-type mycobacterial infections must be thoroughly considered. Both tuberculosis and nontuberculosis mycobacterial infections require prolonged, multiple drug treatment regimens to achieve control. For more information on mycobacterial infection, refer to ch. 212.

Yersinia Pestis Pneumonia (Plague)

Practitioners in the midwestern and far-western United States, especially New Mexico and Colorado, must consider plague as a differential diagnosis in any cat with pneumonia. Although infection is relatively rare, its importance relates to zoonotic potential. Dogs are resistant to plague and seldom develop respiratory signs (although zoonotic transmission from dogs has also been reported).[179,180] Plague in domestic cats, on the other hand, has a mortality approaching 50% and can be spread to humans through contact or inhalation of aerosolized droplets.[181-183] Rodents (e.g., prairie dogs and squirrels) are the natural reservoir of the Gram-negative coccobacillus *Yersinia pestis.* Cats can be infected either by ingestion of bacteremic rodents or rabbits, or via the bite of infected fleas. Most commonly, cats that consume infected rodents develop suppurative lymphadenitis (buboes) initially in the submandibular and cervical nodes.[181] This bubonic form can develop into either a septicemic or secondary pneumonic form. Humans can develop primary pneumonic plague after inhalation of infected droplets from coughing cats. Untreated, pneumonic plague is uniformly fatal. In endemic regions, any cat with pneumonia should be strictly isolated and handled with extreme caution. Cytologic examination of exudate or lymph node aspirates typically reveals bipolar, safety-pin-shaped Gram-negative rods. The Centers for Disease Control and Prevention should be contacted if the diagnosis is suspected; confirmation relies on fluorescent antibody testing, culture, or rising antibody titer. Pending diagnosis, cats should be treated for fleas and antimicrobials should be begun immediately. Aminoglycosides, fluoroquinolones, chloramphenicol, and tetracyclines all have been used for the treatment of *Y. pestis.*

Viral Pneumonia

As opposed to bacterial respiratory infection, viral respiratory disease is caused predominantly by primary pathogens and is usually contagious. Some viral pathogens that cause pneumonia target the respiratory tract specifically (e.g., influenza), whereas other viruses are polysystemic (e.g., distemper virus, feline infectious peritonitis). Viral infections implicated as potential causes of pneumonia are listed in Box 242-8. Effective vaccines minimize morbidity associated with many potential causes of viral pneumonia. Although bacterial pneumonia is easily confirmed by routine cytology and culture of airway lavage, there is no single simple test with which to confirm viral pneumonia. Often, infection is merely presumed. Specifically targeted serologic or PCR tests are used for confirming infection more often than is viral isolation. Many of the viruses that cause pneumonia are pathogens of Canine Infectious Respiratory Disease Complex (i.e., CIRDC; see ch. 227) or also cause feline upper respiratory infections (see ch. 229).[184,185] Panels of PCR tests for many of these pathogens are available from many laboratories.

Box 242-8

Viral Infections Implicated in Infectious Pneumonia of Dogs or Cats

Avian influenza (rare)
Canine distemper virus
Canine herpesvirus
Canine infectious hepatitis
Canine influenza (H3N8 and H3N2)

Canine parainfluenza virus
Canine respiratory coronavirus
Feline calicivirus
Feline herpesvirus
Feline infectious peritonitis/coronavirus

Note: Feline leukemia virus and feline immunodeficiency virus lead to immunosuppression and secondary infectious pneumonia but do not directly result in viral pneumonia.

In many respects, bacterial and viral pneumonia are similar. In fact, much of the mortality associated with viral pneumonia results from opportunistic bacterial infections. Because there are few specific antiviral therapies, and little evidence to support the use of these expensive medications when they do exist, treatment of viral pneumonia is largely supportive. Dogs suspected of having viral pneumonia should be isolated due to the contagious nature of these infections. Additional information on viruses relevant to the respiratory health of dogs and cats can be found in ch. 227-230.

Influenza Virus

Until recently, influenza viruses were not thought to infect dogs or cats. In 2004, an outbreak of respiratory disease in a kennel of racing Greyhound dogs was found to be caused by H3N8 influenza virus.[186,187] Since that time, a number of other influenza type A viruses has been recognized to cause sporadic or experimental cross-species infection in dogs and cats.[188-191] Most have not resulted in sustained transmission within the species for which infection is newly recognized. However, H3N2 influenza, like H3N8, has developed the ability to spread from dog-to-dog, resulting in epidemics in Asia and the United States[188,192] (https://ahdc.vet.cornell.edu/news/civchicago.cfm; accessed July 20, 2015). Influenza viruses are RNA viruses adept at mutation either through spontaneous mutations or when one host is simultaneously infected with two viruses that become intermixed.[188,190,193] The H3N8 canine virus apparently originated as an equine influenza virus, while H3N2 seems to be of avian origin. Both of these viruses are highly contagious between dogs. Less is known about the course of disease in dogs infected with H3N2 than H3N8. For both, an acute onset of cough, fever, and lethargy are typical (E-Box 242-9). Morbidity is marked but mortality is uncommon. When fatalities occur, they often are related to opportunistic bacterial pneumonia. It does not appear that H3N8 is zoonotic, but the possibility of multiple reassortment events means that veterinarians must remain vigilant to this eventuality.[192,194] Although specific antiinfluenza drugs are available commercially (e.g., oseltamivir phosphate [Tamiflu]), their use is not encouraged. These costly drugs have not been evaluated in canine influenza. Even when used as labeled for human influenza, they must be administered within 48 hours of illness and result in only minor reductions in disease duration and severity. Inactivated canine influenza vaccines directed at H3N8 or H3N2 are available. Protection from canine influenza currently requires administration of each vaccine type as there is no combined canine influenza vaccine.

E-Box 242-9

Diagnosis of Canine Influenza Virus (CIV) H3N8 and H3N2

1. Serologic diagnosis
   Unvaccinated dogs are assumed to be naïve to CIV, so recognition of antibodies to CIV strongly supports infection. However, antibody formation lags behind clinical signs, resulting in false-negative tests early in the disease course. Therefore, although a single positive titer can be used for confirming infection, it cannot be used for ruling out infection during illness. When both acute and convalescent titers are obtained, serologic testing is the most sensitive means of CIV diagnosis. Hemagglutination inhibition tests that are specific to each virus subtype are offered commercially and may be combined as part of a testing panel (e.g., Cornell Animal Health Diagnostic Center).
2. Antigen identification
   The influenza A nucleoprotein is shared between CIV and human influenza infections, allowing the use of human point-of-care enzyme-linked immunosorbent assay influenza tests in dogs. Samples from nasal or nasopharyngeal swabs or lavage may be used in these kits (e.g., QuickVue Quidel, Directigen Flu-A test by Becton-Dickinson). Unfortunately, these tests are only positive during viral shedding. Shedding occurs early in the disease (peaking at 2-3 days post-infection) and is

inconsistent, resulting in frequent false-negative tests.

3. Virus isolation
   Virus isolation is the gold standard method of testing for viral infection and has the advantage of being able to potentially detect any subtype of influenza. Sampling requirements vary by laboratory. Virus isolation depends on the presence of virus in the submitted sample, so false-negative results are possible because influenza is shed only for the first several days of illness.
4. Polymerase chain reaction (PCR) identification
   Real-time PCR testing can be conducted on samples from nasal or pharyngeal swabs to identify nucleic acid sequences. Often, individual PCR tests are combined into a panel of tests for a variety of respiratory pathogens. Here too, testing will only be positive during viral shedding, which can lead to false-negative test results. The specificity of PCR depends on primers used for the reaction. Most commercial laboratories now use primers that will detect either H3N8 or H3N2, but PCR might miss other subtypes of influenza.

   Antigen detection, virus isolation, and PCR identification of CIV are all prone to false-negative results. During an outbreak in a kennel, sampling multiple dogs (10% to 30% of those affected) and sampling as early as possible in the course of disease will improve diagnostic accuracy.

Influenza is recognized less frequently in cats than in dogs, but cats are susceptible to natural and experimental infection with several types of influenza A.[195-197] Cats have been infected with virulent avian influenza H5N1 both from consumption of infected poultry and through direct cat-to-cat transmission, and the resultant illness often is life-threatening.[197-201] Veterinarians should be vigilant for possible influenza virus infection in pets, both because of the resultant illness in the examined animal, and also because of the potential for contagion to other pets and zoonotic infection of in-contact humans (E-Box 242-10).[196,200]

E-Box 242-10

Feline Influenza

Until recently, cats were not thought to be susceptible to influenza virus.[443] We now know that cats are susceptible to both experimental and natural infection with several different strains of influenza A, resulting in manifestations ranging from subclinical infection to severe illness or even death.[192,198,199,444-450] Fortunately, sustained transmission of influenza from cat-to-cat remains rare.

During the 2005-2006 epidemic of highly pathogenic avian influenza H5N1 in Asia, the virus was documented to infect domestic cats via experimental inoculation, by feeding on infected birds, and importantly, by direct transmission between cats.[201,444] Although many cats develop subclinical infection, others develop extensive pulmonary damage and multifocal organ hemorrhage and necrosis. Neurologic signs including ataxia and seizure in naturally infected cats likely result from nonsuppurative encephalitis. More common signs include fever, depression, elevation of the third eyelids, conjunctivitis, increased respiratory effort, nasal discharge, and icterus. Sudden death can occur within days of infection.[201,444,451]

Domestic cats also are susceptible to the 2009 pandemic seasonal human H1N1 influenza virus, as well as other types of human seasonal influenza.[197,452-454] Although experimental infections produce only minimal to mild disease, there are reports of naturally infected cats with moderate to severe respiratory illness.[197,454,455] In serosurveys from the USA and northeastern China, as many as one third of tested pet cats demonstrated antibodies to seasonal H1N1 influenza.[449,453,454]

There are many other causes of an acute onset of respiratory signs in cats (e.g., herpesvirus, calicivirus, bacterial pneumonia) that are more likely than feline influenza infection, but veterinarians must be vigilant to this possibility. Besides H5N1 and H1N1, cats are susceptible to many other influenza subtypes, including canine influenza.[188,450,454,456-460] Documented influenza infections in birds in the area, respiratory illness in human household contacts, and/or high fever should increase the index of suspicion for influenza in ill cats. Viral isolation from oropharyngeal or rectal swabs, necropsy specimens, or RT-PCR are typical methods of confirmation. Immunohistochemistry can be used on infected organs. Serologic diagnosis using hemagglutination inhibition also is possible. Treatment would be largely supportive. Thus far, transmission of any influenza from infected cats to humans has not been

documented.[200,448]

Protozoal Pneumonia

Protozoal pneumonia is not common among dogs or cats. Of the protozoal pathogens that do cause pneumonia, toxoplasmosis is the most frequently encountered. Cats are the reservoir host for *Toxoplasma gondii* and often are infected without displaying clinical illness.[202] When illness does occur, it can involve the gastrointestinal tract, the central nervous system, the abdominal viscera, heart, eyes, or the respiratory tract. Respiratory manifestations of interstitial pneumonia, either acute or slowly progressive, are among the most common.[203,204] Results of routine laboratory testing vary with organ involvement. Serologic identification of specific IgM supports active disease, but both false-positive and false-negative tests occur.[205] Occasionally, *T. gondii* tachyzoites are identified in airway lavage from animals with pneumonia.[204,206,207] Rapid response to treatment with potentiated sulfonamides or clindamycin is expected, but recurrence is possible. More information on *T. gondii* can be found in ch. 221.

Mycotic Pneumonia

A variety of systemic fungi (especially *Blastomyces dermatitidis, Histoplasma capsulatum,* and *Coccidioides immitis*) can cause mycotic pneumonia in dogs and cats.[208-210] Slowly progressive lower respiratory disease can be the primary manifestation, but extrathoracic manifestations including weight loss and lymphadenopathy also are common (E-Table 242-4). Radiographic changes associated with mycotic pneumonia vary greatly (E-Figures 242-14 to 242-16) and often include nodular or miliary nodular interstitial lung patterns and hilar lymphadenopathy. Treatment is expensive and potentially toxic; therefore, a definitive rather than a presumptive diagnosis is important. Because interstitial mycotic infections do not result in early exfoliation of fungal elements into the airways, airway lavage is not a sensitive technique for identification of fungal elements. Diagnosis often is confirmed from other sites (e.g., lymph node aspirates, impression smears of dermal lesions). Recently, relatively sensitive and specific urine fungal antigen tests have become available to aid in the diagnosis and therapeutic monitoring of mycotic pneumonia.[211-213] Please see ch. 162 and 231-236 for more detail.

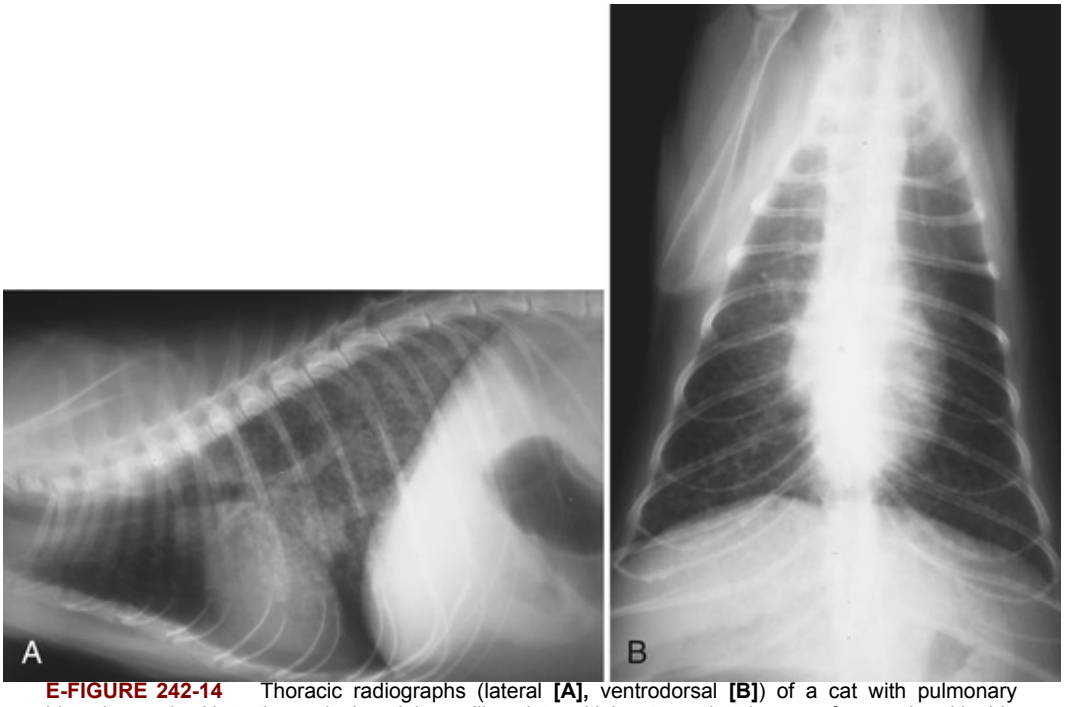
E-TABLE 242-4

Most Common Systemic Mycoses of Dogs and Cats

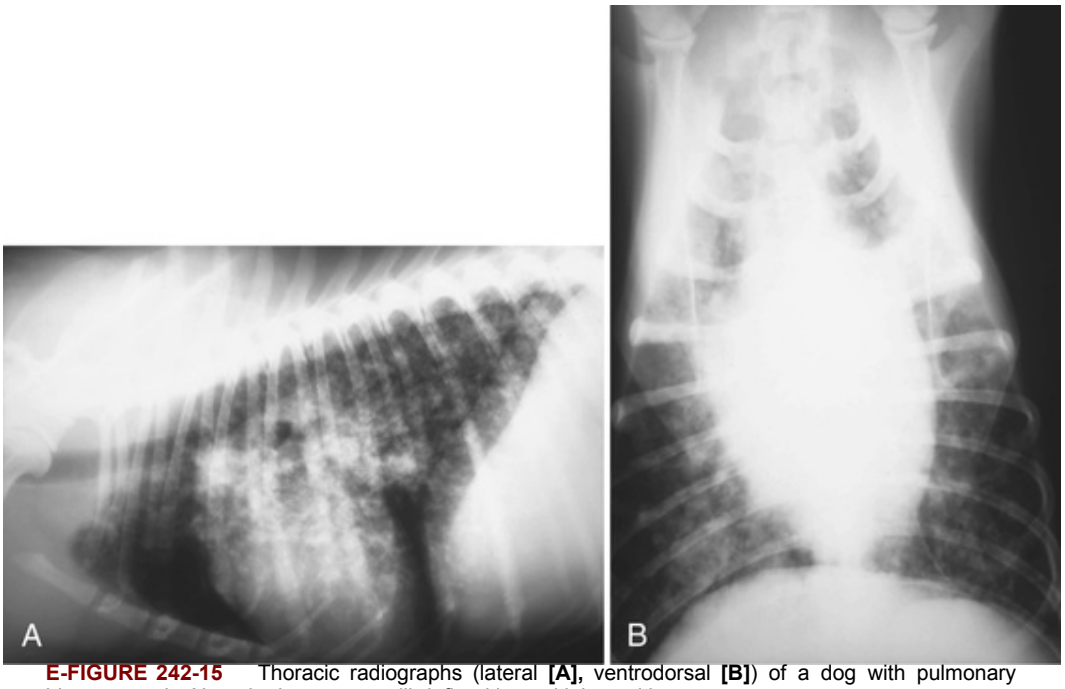
	GEOGRAPHIC DISTRIBUTION	COMMON SITES OF EXTRAPULMONARY INFECTION	CYTOLOGIC MORPHOLOGY	SPECIES AFFECTED
Blastomycosis	Mississippi, Missouri, and Ohio River Valleys; mid-Atlantic states; Canadian provinces of Alberta, Quebec, Manitoba, and Ontario; Africa; and Central America	Lymph nodes, skin, bones, eyes	Thick-walled, broad-based budding yeast (7-15 micron diameter)	Dogs > cats
Histoplasmosis	Mississippi, Missouri, and Ohio River Valleys, Central and South America	Gastrointestinal tract (especially dog), eyes, bone marrow (especially cats), liver and spleen	Multiple round bodies (2-4 micron diameter) with basophilic center and clear, thin outer rim contained within phagocytic cells, narrow-based budding	Cats = dogs
Coccidioidomycosis	Southwestern United States, Mexico, Central and South America	Perihilar lymph nodes, bones, CNS, heart/pericardium, skin, eyes	Very small numbers of organisms found. Round, double-walled spherules (2-200 micron diameter) containing endospores (1 micron diameter).	Dogs > cats

Systemic aspergillosis	Worldwide distribution	Bone, spine, lymph nodes, kidney, spleen, pancreas, liver	Septate hyphae (2-3 micron wide) with parallel walls and dichotomous branching	Dogs > cats
Cryptococcosis	Worldwide distribution	Nasal cavity (cats) CNS and eyes (dogs)	Round to oval yeast (4-10 micron diameter) with thick clear capsule; narrow-based budding can be seen	Cats > dogs

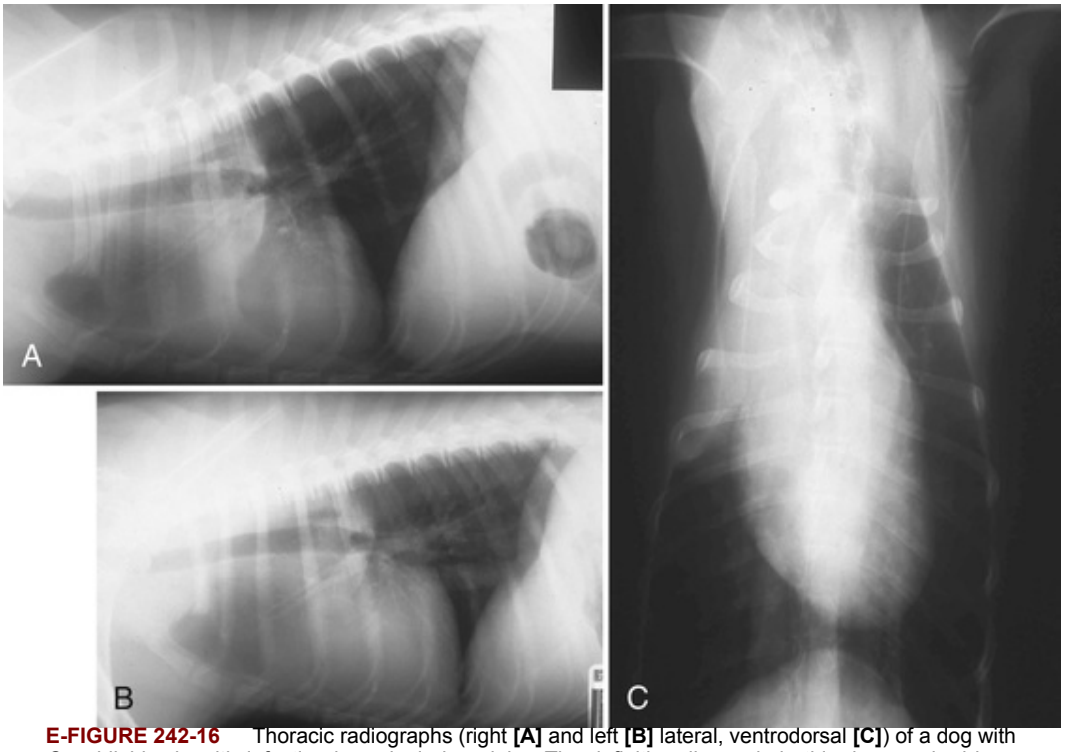
CNS, Central nervous system.



E-FIGURE 242-14 Thoracic radiographs (lateral **[A],** ventrodorsal **[B]**) of a cat with pulmonary histoplasmosis. Note the typical nodular, miliary interstitial pattern that is seen frequently with this infection. (Courtesy Dru Forrester, Blacksburg, VA.)



E-FIGURE 242-15 Thoracic radiographs (lateral **[A],** ventrodorsal **[B]**) of a dog with pulmonary blastomycosis. Note the larger, more ill-defined interstitial opacities.



E-FIGURE 242-16 Thoracic radiographs (right **[A]** and left **[B]** lateral, ventrodorsal **[C]**) of a dog with *Coccidioides immitis* infection in a single lung lobe. The definitive diagnosis in this dog required lung lobectomy and histologic assessment of the excised tissue.

Pneumocystis carinii (also known as *Pneumocystis jerovici*) was originally classified as a protozoon but now is considered a fungus. Although this widely distributed saprophyte is not highly virulent, in immunocompromised hosts of many species it can result in severe morbidity with high mortality due to pneumonia. Infection has been described in several small-breed dogs with presumed immunocompromise, but it is overwhelmingly most common in Miniature Dachshunds and Cavalier King Charles Spaniels.[214-220]

A unique immunodeficiency in each breed (common variable immunodeficiency in Dachshunds and in Pomeranians; IgG deficiency in Cavaliers) has been suggested.[216,220,221] Most infected dogs are young, and most are presented for veterinary attention due to progressive lower respiratory disease signs. Although there are no unique physical, radiographic, or laboratory signs, absence of fever despite severe pneumonia is a clue to this type of infection.[221] The diagnosis is complicated because the pathogens are not recovered easily by airway lavage, and special stains such as Grocott-Gomori methenamine silver stain may be required to visualize the organism when it is present.[222] Potentiated sulfonamides appear to be the most effective therapy when administered early in the disease course. Although *Pneumocystis* pneumonia is important in immunocompromised people (e.g., during HIV infection), dogs are not thought to harbor the same strain and thus should pose little zoonotic risk.[223]

Aspiration Pneumonia

Aspiration pneumonitis and pneumonia result from inhalation of materials into the lower respiratory tract. Often, the aspirated material consists of stomach contents with or without solid particulate matter. Iatrogenic aspiration can occur as a result of forced feedings, oral administration of substances such as barium or mineral oil, or inappropriate induction of emesis after oral intoxications (e.g., with petroleum distillates) (see ch. 151; E-Figure 242-17). Depending on the volume of material aspirated, as well as the physical properties of the material (e.g., pH, tonicity, bacterial contamination, particulate volume and size), the result can range from minimal change to fulminant pulmonary edema, necrosis, and hemorrhage. Irritating chemicals (including stomach acid) result in pneumonitis, while aspiration of larger volumes of a more benign fluid can result in a "drowning" event. Aspiration of polyethylene glycol bowel-cleansing solutions can be especially harmful as these substances draw interstitial fluid into the lungs.[224,225] Aspiration of large particulates can result in acute airway obstruction. Because of the low bacterial burden of stomach content, infection seldom is an important initial component of aspiration. However, the damage done to the respiratory tract by acid or other irritants predisposes to secondary bacterial infection. Aspiration injury occurs in phases beginning with an acute airway response, followed by lung inflammation, and often culminating in opportunistic bacterial infection.

E-FIGURE 242-17 Lateral thoracic radiograph of a cat with severe barium aspiration.

A variety of conditions can predispose animals to aspiration (Box 242-11), and many of these are found in

animals hospitalized for diverse reasons. Unwitnessed aspiration should be suspected in any hospitalized animal with a new onset of lower respiratory signs. Although general anesthesia is a risk for aspiration, in a recent multicenter study, the incidence of postanesthetic aspiration pneumonia was only 0.17%; several factors were identified that increased this risk.[226] In retrospective studies of 88 or 120 dogs with aspiration pneumonia, fewer than half were febrile (31% and 43%, respectively).[227,228] Panting or tachypnea were common but inconsistent findings. Most had cough and either harsh/loud, adventitial, or diminished lung sounds on auscultation.[227,228] Leukocytosis, with or without a left shift, was a common but inconsistent finding.[227,228] The classic radiographic appearance of aspiration pneumonia is that of a patchy or focal alveolar infiltrate (Figure 242-18), but one quarter of affected dogs in a retrospective study demonstrated a predominantly interstitial pattern.[227] Radiographic changes can lag behind aspiration because fluid accumulation lags behind chemical lung injury. Radiographs should include both lateral views to improve recognition of pneumonia. The left lateral view is especially important to improve recognition of an alveolar pattern in the right middle lung lobe, a lobe that is largely silhouetted against the cardiac shadow. Because aspiration of liquids is gravity-dependent, the most commonly affected lung lobes are the right middle, right cranial, and caudal portion of the left cranial; however, the lobe affected depends on the position of the animal at the time of aspiration.[227-229] In one study, the prognosis was worse for animals with more than a single involved lung lobe, and more than one third of all dogs had radiographic evidence that 2 or more lung lobes were affected.[228] Airway lavage can be used diagnostically when there is no clear history of aspiration nor any known predisposition to aspiration. Neutrophilic inflammation is expected, and lipid-laden macrophages or debris (e.g., foodstuffs) can be identified. Measurement of pepsin concentration has been used in humans to confirm aspiration.[230] Polymicrobial and anaerobic infections are common but delayed complications of aspiration.

Box 242-11

Conditions That Predispose to Aspiration

Impaired conscious protection of the airways (e.g., general anesthesia, heavy sedation, seizures, coma)
Impaired unconscious protection of the airways (e.g., laryngeal paralysis, surgical alteration of laryngeal anatomy [tie-back], myasthenia gravis)
Impaired swallowing (e.g., achalasia, cranial nerve V deficits, rabies)
Regurgitation (e.g., megaesophagus, motility disorder, esophageal diverticulum)
Gastric overdistention (e.g., overfeeding, ileus, gastrointestinal obstruction)
Vomiting (e.g., primary gastrointestinal disease, pancreatic disease, uremia, hepatic disease)
Forced feeding or administration of oral medications

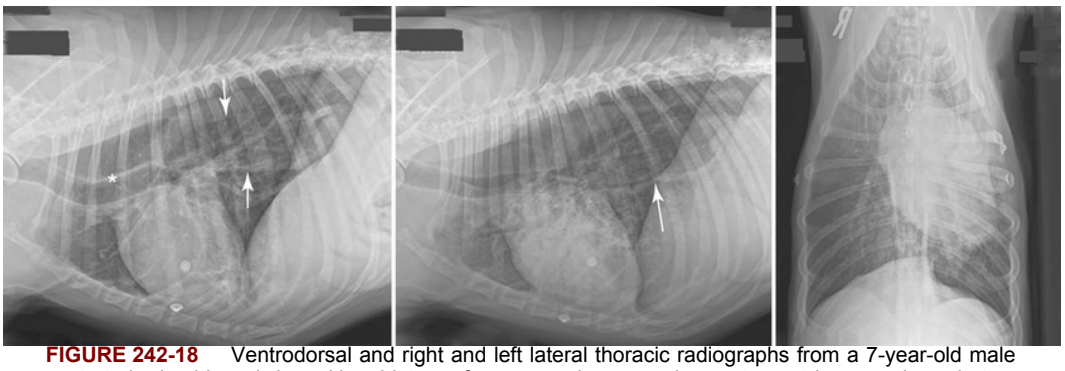


FIGURE 242-18 Ventrodorsal and right and left lateral thoracic radiographs from a 7-year-old male castrated mixed-breed dog with a history of megaesophagus and recent-onset increased respiratory effort. Megaesophagus is evident (arrows; the visible dorsal margin of the trachea [asterisk] suggests highlighting against an air-filled esophagus), and an alveolar pattern consistent with aspiration pneumonia is most seen in both the right middle and the caudal portion of the left cranial lung lobes. The cardiac shadow has shifted into the left hemithorax.

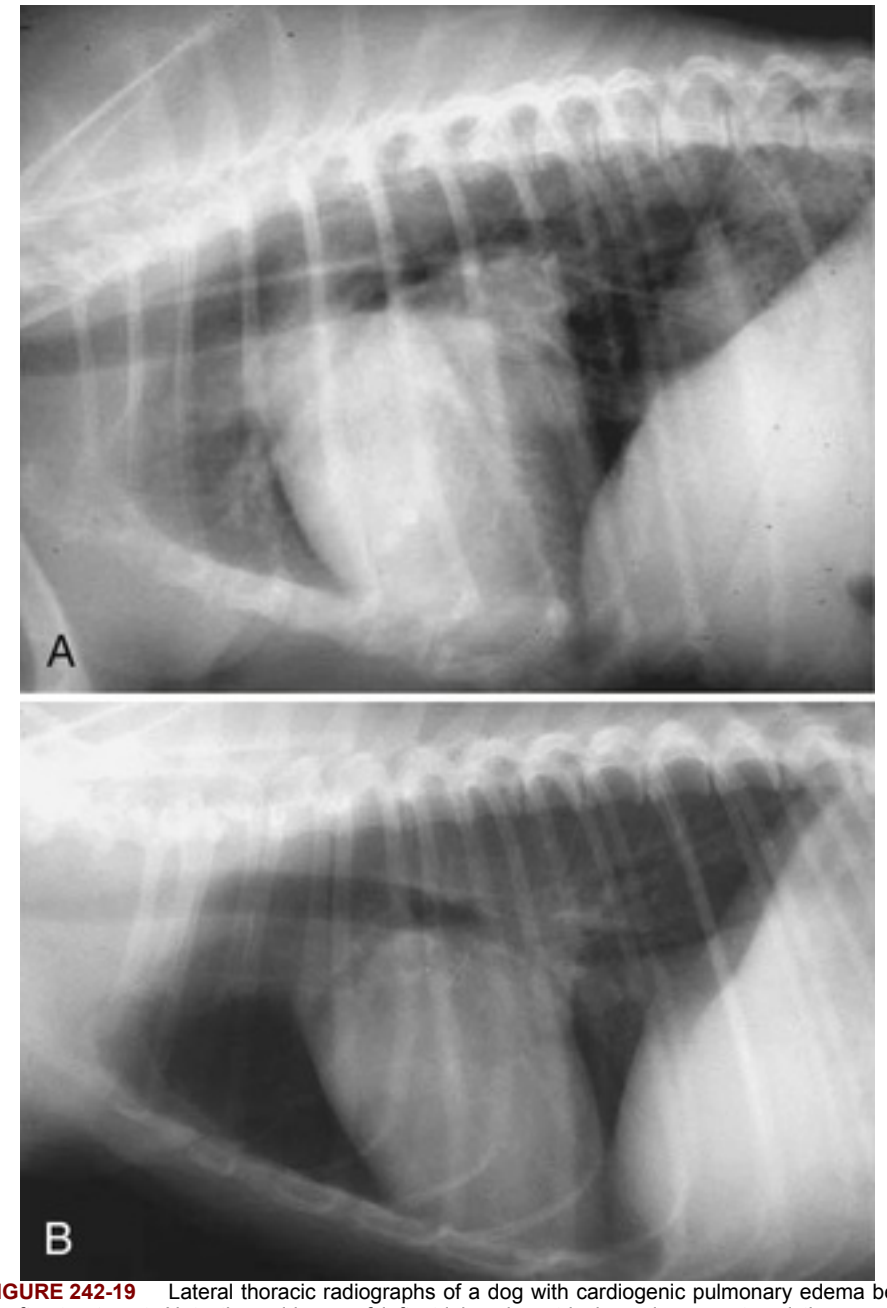
Treatment of aspiration largely is supportive. Efforts should be made to prevent aspiration when possible,

ideally via correction of predisposing factors (see Box 242-11). Animals should be fasted prior to anesthesia and insufflated endotracheal cuffs used when appropriate. For conscious animals with frequent regurgitation or vomiting, or when airway protection is impaired, oral intake should be minimized. Feeding pets with megaesophagus from elevated bowls and keeping the pet upright after feeding are common practices, but efficacy of these techniques to prevent aspiration is unknown. For animals with frequent regurgitation due to megaesophagus, the placement of a gastrostomy tube can facilitate feeding while minimizing risk of aspiration (see ch. 82). Administration of H2 receptor antagonists or proton pump inhibitors increases the pH of stomach content and could lessen chemical lung injury due to aspiration but might also increase gastric bacterial content.[231] Prokinetic drugs such as metoclopramide promote gastric emptying and tighten the lower esophageal sphincter, which might diminish the risk of aspiration of gastric content.[232-234] Unfortunately, neither morbidity nor mortality is decreased in humans given prokinetic or antacid drugs. When aspiration is witnessed (for instance, during anesthesia), physical clearing of the airways may be attempted. Airway lavage also has been used therapeutically to "rinse" irritating substances from the airways following a known aspiration event.[235] Following known aspiration, baseline thoracic radiographs should be obtained and oxygenation monitored. If dyspnea occurs after aspiration, bronchodilators could ameliorate acute bronchospasm. Oxygen supplementation should be employed and adjusted as needed (see ch. 131); overly aggressive oxygen supplementation could worsen oxidative lung injury associated with chemical pneumonitis, however. Secondary bacterial infection could require treatment with appropriate antimicrobial therapy. The prognosis for recovery generally is good, but it cannot be predicted by severity of radiographic changes alone.[236]

Pulmonary Edema

Pulmonary edema is not a disease but is a consequence of disease. As a result of increased hydrostatic pressure, decreased oncotic pressure, impaired lymphatic drainage, or increased vascular permeability (see ch. 18), fluid accumulates in the interstitium and then the alveoli at a rate faster than it can be reabsorbed. Fluid accumulation in the alveolar space leads to ventilation-perfusion mismatching and hypoxemia. Fortunately, the lungs are relatively resistant to edema formation compared with other tissues.

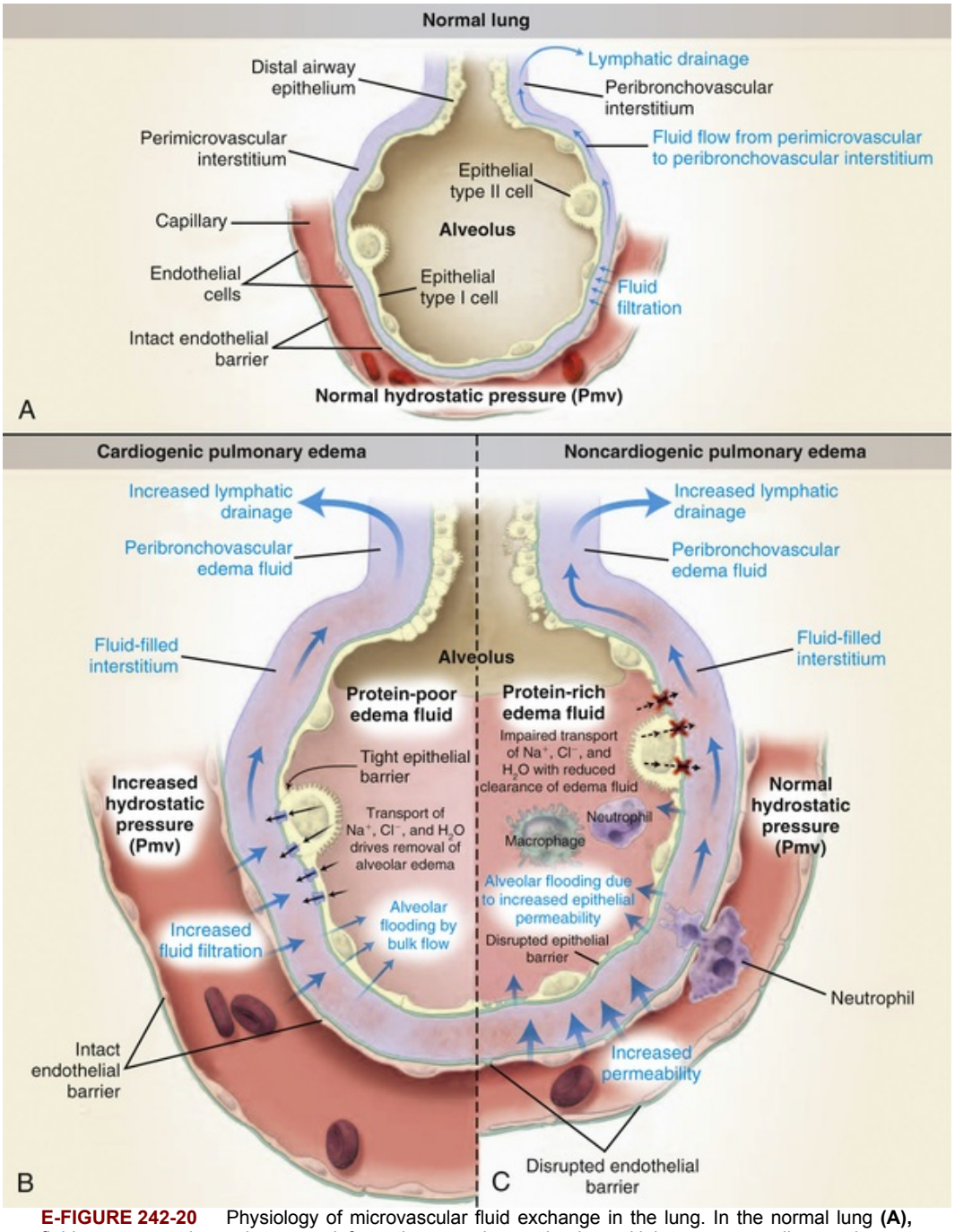
Pulmonary edema is described as either "cardiogenic" or "noncardiogenic." Differentiation is crucial because the conditions are treated differently. Cardiogenic edema, which follows increased venous pulmonary hydrostatic pressure associated with left-sided heart failure, is treated via diuretic administration, afterload reduction, and any specific therapy aimed at the cause of congestive heart failure (E-Figure 242-19). Cardiogenic pulmonary edema and its treatment are discussed in detail in ch. 246 and 247. This section focuses on the noncardiogenic causes of pulmonary edema.



E-FIGURE 242-19 Lateral thoracic radiographs of a dog with cardiogenic pulmonary edema before and after treatment. Note the evidence of left atrial and ventricular enlargement and the engorged pulmonary veins, especially left cranial lobar vein. **A,** There is an interstitial and alveolar pattern present in the pretreatment radiograph not evident in the posttreatment film, **B.**

It is useful to have a basic understanding of microvascular fluid movement in the lung (E-Figure 242-20).[237] In health, minute quantities of fluid and solutes leak from gaps between the capillary endothelial cells and enter the interstitial space. Tight junctions between alveolar epithelial cells prevent the fluid from entering the alveoli. Instead, interstitial fluid moves into the peribronchovascular space, where it is removed by lymphatics and returned to the circulation. Starling's equation for filtration across a semipermeable membrane describes the factors that determine the amount of vascular leakage (see ch. 18) (E-Box 242-12). In congestive heart failure or intravascular volume overload, increased microvascular hydrostatic pressure leads to increased transvascular fluid filtration and pulmonary edema. Because capillary endothelial permeability is unchanged, this edema fluid contains little protein. On the other hand, most noncardiogenic pulmonary edema occurs when vascular permeability increases as a result of direct or indirect lung injury. In contrast to cardiogenic edema, noncardiogenic edema fluid is relatively rich in protein. The protein-rich fluid modifies oncotic pressure gradients, which further alters fluid flux. In both cardiogenic and noncardiogenic edema,

accumulation of alveolar fluid, combined with decreased lung compliance and airway compression resulting from edema, all act to increase pulmonary vascular resistance. Hypoxemia is the consequence of ventilation-perfusion mismatching resulting from each of these factors. Spontaneous removal of alveolar fluid depends on active transport of sodium and chloride from the luminal surface through the epithelial cell and across the basolateral membrane. Water movement passively follows salt movement. Because fluid removal requires active salt transport across the epithelium, injury to the epithelial cells not only leads to edema formation but impedes the lung's ability to resolve edema. As a result of these mechanisms of causation and resolution, noncardiogenic pulmonary edema is more refractory to treatment than is cardiogenic edema.



E-FIGURE 242-20 Physiology of microvascular fluid exchange in the lung. In the normal lung **(A),** fluid moves continuously outward from the vascular to the interstitial space according to the net difference between hydrostatic and protein osmotic pressures, as well as to the permeability of the capillary membrane. The Starling equation for filtration of fluid across a semipermeable membrane describes the factors that determine the amount of fluid leaving the vascular space: Q = K[(Pmv − Ppmv) − (mv − pmv)], where *Q* is the net transvascular flow of fluid, *K* is the membrane permeability, *Pmv* is the hydrostatic pressure in the microvessels, *Ppmv* is the hydrostatic pressure in the

perimicrovascular interstitium, *mv* is the plasma protein osmotic pressure in the circulation, and *pmv* is the protein osmotic pressure in the perimicrovascular interstitium. When hydrostatic pressure increases in the microcirculation, the rate of transvascular fluid filtration rises **(B).** When lung interstitial pressure exceeds pleural pressure, fluid moves across the visceral pleura, creating pleural effusion. Because the permeability of the capillary endothelium remains normal, the filtered edema fluid leaving the circulation has a low protein content. The spontaneous removal of edema fluid from the airspaces of the lung depends on active transport of sodium and chloride across the alveolar epithelial barrier. The primary sites of sodium and chloride reabsorption are the epithelial ion channels located on the apical membrane of alveolar epithelial type I and II cells and distal airway epithelia. Sodium is extruded actively into the interstitial space by means of the Na^+/K^+-ATPase located on the basolateral membrane of type II cells. Water follows passively, probably through aquaporins, which are water channels that are found predominantly on alveolar epithelial type I cells. Noncardiogenic pulmonary edema **(C)** occurs when the permeability of the microvascular membrane increases because of direct or indirect lung injury (including the acute respiratory distress syndrome), resulting in a marked increase in the amount of fluid and protein leaving the vascular space. Noncardiogenic pulmonary edema has a high protein content because the more permeable microvascular membrane has a reduced capacity to restrict the outward movement of larger molecules such as plasma proteins. The degree of alveolar flooding depends on the extent of interstitial edema, the presence or absence of injury to the alveolar epithelium, and the capacity of the alveolar epithelium to actively remove alveolar edema fluid. In edema due to acute lung injury, alveolar epithelial injury commonly causes a decrease in the capacity for the removal of alveolar fluid, delaying the resolution of pulmonary edema. (Reprinted with permission from Ware LB, Matthay MA: Acute pulmonary edema. *N Engl J Med* 353:2788, 2005.)

E-Box 242-12

Starling's Equation for Filtration Across a Semipermeable Membrane

$$Q = K[(Pmv - Ppmv) - (pmv - ppmv)]$$

where Q = net transvascular flow of fluid, K = membrane permeability, Pmv = hydrostatic pressure in the microvessels, $Ppmv$ = hydrostatic pressure in the perimicrovascular interstitium, pmv = plasma protein osmotic pressure in the circulation, and $ppmv$ = protein osmotic pressure in the perimicrovascular interstitium.

There are myriad potential causes of noncardiogenic pulmonary edema (Box 242-13). Severe hypoalbuminemia (<1.5 g/dL) is correlated with diminished vascular colloid oncotic pressure. Although hypoalbuminemia can contribute to pulmonary edema, pulmonary lymphatics are very efficient at fluid removal from the interstitial space. Therefore, animals with low oncotic pressure are far more likely to be presented for ascites, peripheral edema, or even pleural effusion than for pulmonary edema.[238] Nevertheless, hypoalbuminemia will potentiate pulmonary edema in the face of vascular permeability changes or the overzealous administration of crystalloid fluids.[239] Similarly, although lymphatic drainage is an important key to normal interstitial fluid balance, impairment of thoracic lymphatic drainage (e.g., granuloma or neoplasia, lymphangitis) is more likely to result in chylous effusion than in pulmonary edema. Electrical shock or acute insult to the central nervous system can lead to a unique neurogenic form of noncardiogenic pulmonary edema. Although the mechanisms causing neurogenic edema are incompletely understood, both intense pulmonary vasoconstriction (and resultant increased pulmonary hydrostatic pressure) and an inflammatory mechanism are hypothesized to increase pulmonary capillary permeability.[240] Noncardiogenic edema most commonly is related to (direct or indirect) pulmonary epithelial injury. Acute pulmonary inflammation and edema from a variety of initial insults resulting in respiratory compromise may be termed acute respiratory distress syndrome (ARDS).[241,242] These can be direct insults to the lung (e.g., pneumonia, aspiration, smoke inhalation) or indirect injuries (e.g., pancreatitis, uremia, sepsis, major trauma).[243,244] The most recent working veterinary definitions related to this syndrome were developed in 2007 and are no longer in line with the more recent definitions developed for use in humans.[241] For humans, a consensus panel developed a set of definitions related to ARDS known as the "Berlin Definition."[245] In this new system of nomenclature, the term "acute lung injury" has been discarded; ARDS itself is now characterized as mild, moderate, or severe; and specific diagnostic criteria for ARDS have been developed. By these criteria, ARDS is

defined as having a characteristic time of onset (within 1 week of the inciting event or onset/worsening of respiratory signs), thoracic radiographic and/or CT findings (bilateral opacities beyond those expected with effusions, atelectasis, or mass lesions), and noncardiogenic origin (exclusion of heart disease of sufficient severity to cause cardiogenic pulmonary edema).[245] ARDS is characterized as mild (PaO_2/FiO_2 = 200 to 300 mm Hg with positive end-expiratory pressure [PEEP] or continuous positive airway pressure [CPAP] ≥ 5 cm H_2O), moderate (PaO_2/FiO_2 = 100 to 200 mm Hg with PEEP ≥ 5 cm H_2O), or severe (PaO_2/FiO_2 = <100 mm Hg with PEEP ≥ 5 cm H_2O), and these categories of severity have predictive value in regards to outcome of lung injury in humans.[244,245] It is very likely that veterinary medicine will follow the lead of human medicine and revise definitions related to ARDS.

Box 242-13

Predisposing Factors for the Development of Noncardiogenic Pulmonary Edema

Neurogenic pulmonary edema (e.g., seizures, electrocution, head trauma)
Postobstructive pulmonary edema (e.g., strangulation, laryngeal paralysis, pulmonary reexpansion)
Systemic disease predisposing to acute respiratory distress syndrome (e.g., sepsis, shock, severe pancreatitis, virulent babesiosis, paraquat poisoning, envenomation, gastric/splenic/mesenteric torsion, parvoviral enteritis, uremia)
Direct pulmonary injury (e.g., aspiration pneumonia, bacterial pneumonia, lung lobe torsion, smoke inhalation, parasitic pneumonitis, pulmonary contusion, hyperoxia)
Profound hypoalbuminemia (e.g., protein-losing nephropathy, lymphangiectasia, liver failure)
Impaired lymphatic drainage (e.g., lymphangitis, lymphatic neoplasia)
Miscellaneous causes (e.g., vasculitis, drowning, high altitude, air embolus, pheochromocytoma)

Presentation

Regardless of cause, the clinical presentation of animals with noncardiogenic pulmonary edema is similar. Clinical signs can follow rapidly or can be delayed for as much as 72 hours after the inciting insult. The severity of signs depends on the degree of pulmonary injury and amount of fluid accumulation; early signs include exercise intolerance and tachypnea. A moist cough can produce frothy foam. Respiratory distress and orthopnea can be observed, and animals can demonstrate cyanosis and/or hemoptysis. Harsh, loud bronchovesicular sounds are expected, and inspiratory and/or end-expiratory crackles auscultated. Occasionally, lung sounds are quiet when edema is severe. Animals with cardiogenic edema usually have an audible heart murmur or dysrhythmia, but these findings are also possible in animals with noncardiogenic edema; therefore, their *absence* is strongly suggestive of a noncardiogenic mechanism, but the presence of a murmur and/or arrhythmia is nonspecific. Sinus tachycardia is common in animals with cardiogenic edema, whereas vagal stimulation associated with lung disease often causes respiratory sinus arrhythmia. Other abnormalities on physical examination can be associated with the underlying disease process (e.g., fever, pain).

Diagnostic Evaluation

Because animals with pulmonary edema are fragile, thorough diagnostic investigation must follow medical stabilization (see treatment, later). Abnormalities on CBC, serum biochemical profile, and urinalysis depend almost entirely on the underlying disease process. Likewise, radiographic changes vary, depending on both the underlying condition and the degree of edema. An unstructured interstitial and/or peribronchial radiographic pattern that progresses with severity of edema produces an alveolar pattern; patchy infiltrates are common in ARDS. The caudodorsal lung fields often are the most severely affected, but depending on the source of lung injury, the predominant location may be elsewhere (e.g., edema associated with aspiration would be most severe in the affected lobes). Cardiomegaly (especially left atrial enlargement) or pulmonary venous engorgement suggests cardiogenic rather than noncardiogenic edema. Hypoxemia is expected, and typically the alveolar to arterial oxygen gradient (see E-Box 242-1) is increased as a result of ventilation-perfusion mismatching (see ch. 128).

Treatment

Treatment of noncardiogenic pulmonary edema should include measures to address the underlying disorder. In certain cases, it might be impossible to correct the instigating cause (e.g., electrocution) or doing so might require time (e.g., pancreatitis). Treatment must address hypoxemia. When respiratory distress is apparent, or if PaO_2 is <80 mm Hg or the SpO_2 is <94% (see ch. 98), supplemental oxygen should be provided in the least stressful manner possible (see ch. 131). Because animals with hypoxemia often are distressed, judicious use of sedatives (e.g., morphine sulfate or acepromazine IV) could be warranted. Caution must be used because sedatives can depress respiration. Animals in respiratory distress should be allowed to position themselves for comfort, but if recumbent, they should be either supported in a sternal position or placed with the more severely affected lung in the dependent position. Animals with ARDS often have critical respiratory compromise; if stabilization is not possible with less invasive measures, intubation and ventilatory support might be required. Positive pressure ventilation (PPV) should be considered if initial therapy is unable to maintain $SpO_2 \geq 90\%$, $PaO_2 \geq 60$ mm Hg, and $PaCO_2 < 60$ mm Hg; PPV also can be indicated to relieve sustained respiratory effort, which might result in respiratory muscle fatigue.

Diuretic administration is more effective in the resolution of cardiogenic or intravascular volume overload-associated edema than noncardiogenic edema. Neurogenic pulmonary edema results from both increased hydrostatic pressure and vascular permeability changes. Therefore, diuretics such as furosemide could be of some benefit in this condition. Neurogenic pulmonary edema usually resolves without specific treatment, assuming that neurologic and respiratory function can be preserved for 48 to 72 hours after the initiating insult.[240] Alpha-adrenergic blockade and dobutamine have been suggested to be of benefit in the treatment of neurogenic pulmonary edema. Drugs that result in cerebral vasodilation should be avoided. Noncardiogenic edema that results from or is exacerbated by hypoalbuminemia can be addressed with colloidal support. Plasma transfusion is impractical to replenish colloid oncotic pressure due to both the large associated fluid volume required and the high costs of massive plasma transfusion.[246] Instead, synthetic colloids or albumin transfusion should be considered in animals with pulmonary edema resulting from decreased colloid oncotic pressure (see ch. 130). Unfortunately, adverse effects can be associated with either synthetic colloids administration or xenoalbumin transfusion.[247-249] As an additional complication of colloid administration, any increase in pulmonary vascular permeability can lead to colloid leakage into the alveolar space. This may in turn actually worsen edema. The balance between these limitations and the benefits of treatment must be considered on a case-by-case basis.

Medical treatment of ARDS, like the medical treatment of the systemic inflammatory response syndrome (SIRS; see ch. 132) that often accompanies ARDS, is complex. A variety of drugs that inhibit inflammation, alter production of cytokines or enzymes, or act in any of a dozen other ways has been used in the treatment of ARDS, with variable (usually minor) success.[242,250] Intravenous fluid administration could be required for the appropriate treatment of the underlying disease processes (e.g., uremia), but it must be used judiciously to avoid worsening edema via increased pulmonary hydrostatic pressure.[251] Conversely, reduction of hydrostatic pressure via furosemide, which may also cause bronchodilation and improve lymphatic flow, can be considered in well-hydrated animals but will not have the profound effects often observed by resolution of cardiogenic pulmonary edema. Despite the fact that mechanical ventilation can actually exacerbate functional and structural lung alterations, it often is necessary in the treatment of humans with ARDS.[244] The same could be true in animals.[252-254] The treatment of ARDS largely is dependent on supporting oxygenation and treating the underlying disease while allowing the lungs to heal themselves.[244]

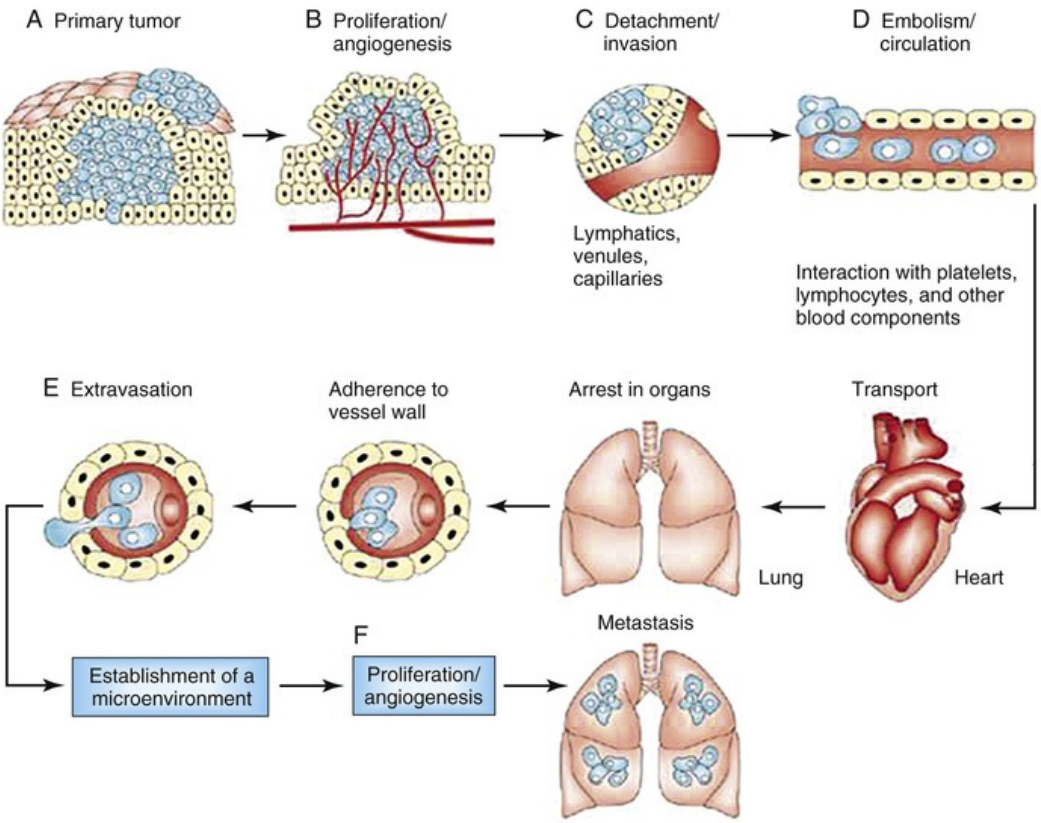
Lung Cancer

Both primary respiratory neoplasia and metastasis of nonrespiratory cancers occur in the lung. Differentiating less-common primary lung tumors from the more common metastatic variety is important because the diagnosis, treatment, and prognosis of primary lung tumors differ from those of metastatic cancer. Animals with lung cancer can be presented for cough, hemoptysis, panting, or other signs of respiratory dysfunction. Often, lung cancers are identified radiographically in animals without respiratory signs during evaluation for nonspecific signs such as weight loss or extrathoracic neoplasia. Occasionally, animals with lung tumors are presented for investigation of paraneoplastic conditions such as hypertrophic osteopathy or polyneuropathy.

Metastatic and Special Lung Cancers

Normally, the pulmonary vascular bed receives the entire output of the right ventricle during each cardiac cycle. The blood passes through numerous small-diameter, well-oxygenated capillary beds, making the lung

an ideal location for metastasis. The "seed and soil" hypothesis describes detached tumor cells as seeds that can only flourish in suitable soil (tissue).[255] Besides simple mechanics, the lung might be targeted specifically by certain tumors as a preferential site of metastasis. Cancer metastasis is complex; cancer cells must detach from the primary tumor, gain access into blood or lymph vessels to be carried to distant sites, migrate from the vessels into the tissues, adhere and then grow in the new site (see ch. 338; E-Figure 242-21).[255] Virtually any neoplasm may metastasize to the lungs, but several that are particularly likely to do so include oral and nail bed melanoma, thyroid carcinoma, osteosarcoma, hemangiosarcoma, and mammary carcinoma.



E-FIGURE 242-21 Pulmonary metastasis. The main steps in the formation of a metastasis (also see ch. 338). **A,** Cellular transformation and tumor growth. Growth of neoplastic cells must be progressive, with nutrients for the expanding tumor mass initially supplied by simple diffusion. **B,** Extensive vascularization must occur if a tumor mass is to exceed 1-2 mm in diameter. The synthesis and secretion of angiogenic factors establish a capillary network from the surrounding host tissue. **C,** Local invasion of the host stroma by some tumor cells occurs by several parallel mechanisms. Thin-walled vessels, such as lymphatic channels, offer very little resistance to penetration by tumor cells and provide the most common route for tumor-cell entry into the circulation. **D,** Detachment and embolization of single tumor cells or aggregates occur next, with most circulating tumor cells being rapidly destroyed. After the tumor cells have survived the circulation, they become trapped in the capillary beds of distant organs by adhering either to capillary endothelial cells or to subendothelial basement membrane that might be exposed. **E,** Extravasation occurs next, probably by mechanisms similar to those that operate during invasion. **F,** Proliferation within the organ parenchyma completes the metastatic process. To continue growing, the micrometastasis must develop a vascular network and evade destruction by host defenses. The cells then can invade blood vessels, enter the circulation, and produce additional metastases. (Reprinted with permission from Fidler IJ: The pathogenesis of cancer metastasis: the "seed and soil" hypothesis revisited. *Nat Rev Can* 3(6):453-458, 2003.)

Presentation and Diagnostic Evaluation

Often, animals with metastatic lung cancer have few respiratory signs despite a large tumor burden. Pulmonary metastasis usually is identified via screening thoracic radiographs. Radiographic screening for metastasis should include a combination of images obtained in dorsal, ventral, right lateral and left lateral recumbencies, because the mild atelectasis that occurs in the dependent lung can obscure identification of tumors (E-Figure 242-22). The radiographic appearance of metastatic cancer varies widely, typically with few

to many interstitial nodules of varying size distributed throughout the lungs (Figure 242-23). However, metastasis can appear as a single nodule, an interstitial or alveolar lung pattern, a miliary interstitial pattern, or even as multiple cysts (Figure 242-24).[257-260] Even with appropriate positioning, summation artifact can make identification of tumors that are <8 to 9 mm in diameter difficult.[17] Although inverse display of digital thoracic radiographs has been postulated to improve ability to detect pulomonary nodules, this was not corroborated in a recent small study.[261] Thoracic CT is a more sensitive means of imaging small tumors (E-Figure 242-25), but the need for anesthesia or sedation, equipment, and financial resources prevent CT scan from serving as a routine screening test.[17,256,260,262] Because there is no pathognomonic radiographic appearance of pulmonary metastasis, animals should not be condemned based on thoracic radiographs alone when a primary tumor has not been definitively identified. Instead, the neoplastic nature of lung disease should be confirmed or refuted via aspirate, lavage, or biopsy techniques (see ch. 240).

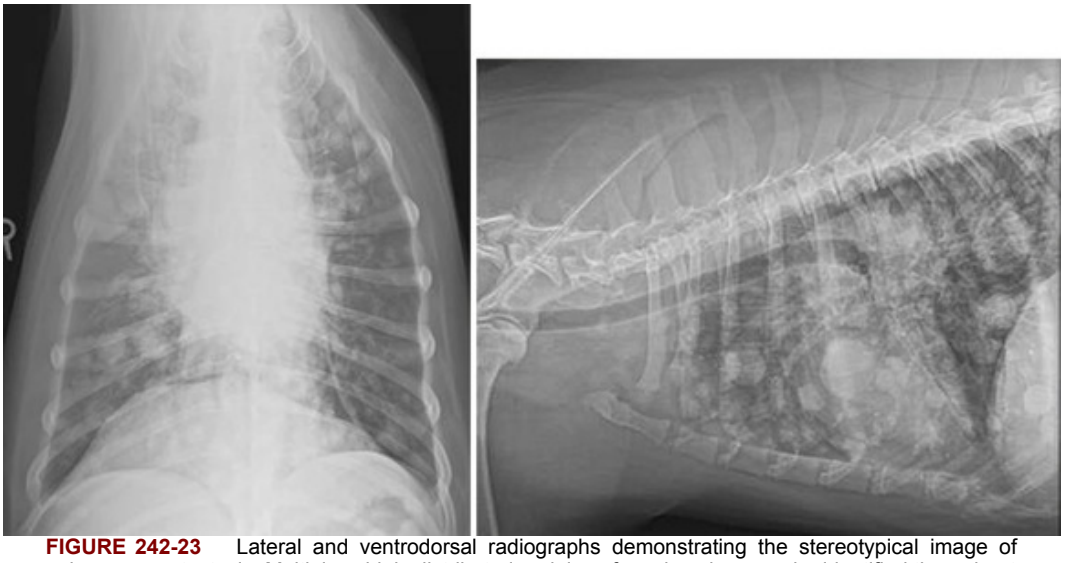


FIGURE 242-23 Lateral and ventrodorsal radiographs demonstrating the stereotypical image of pulmonary metastasis. Multiple, widely distributed nodules of varying sizes can be identified throughout the lung fields.

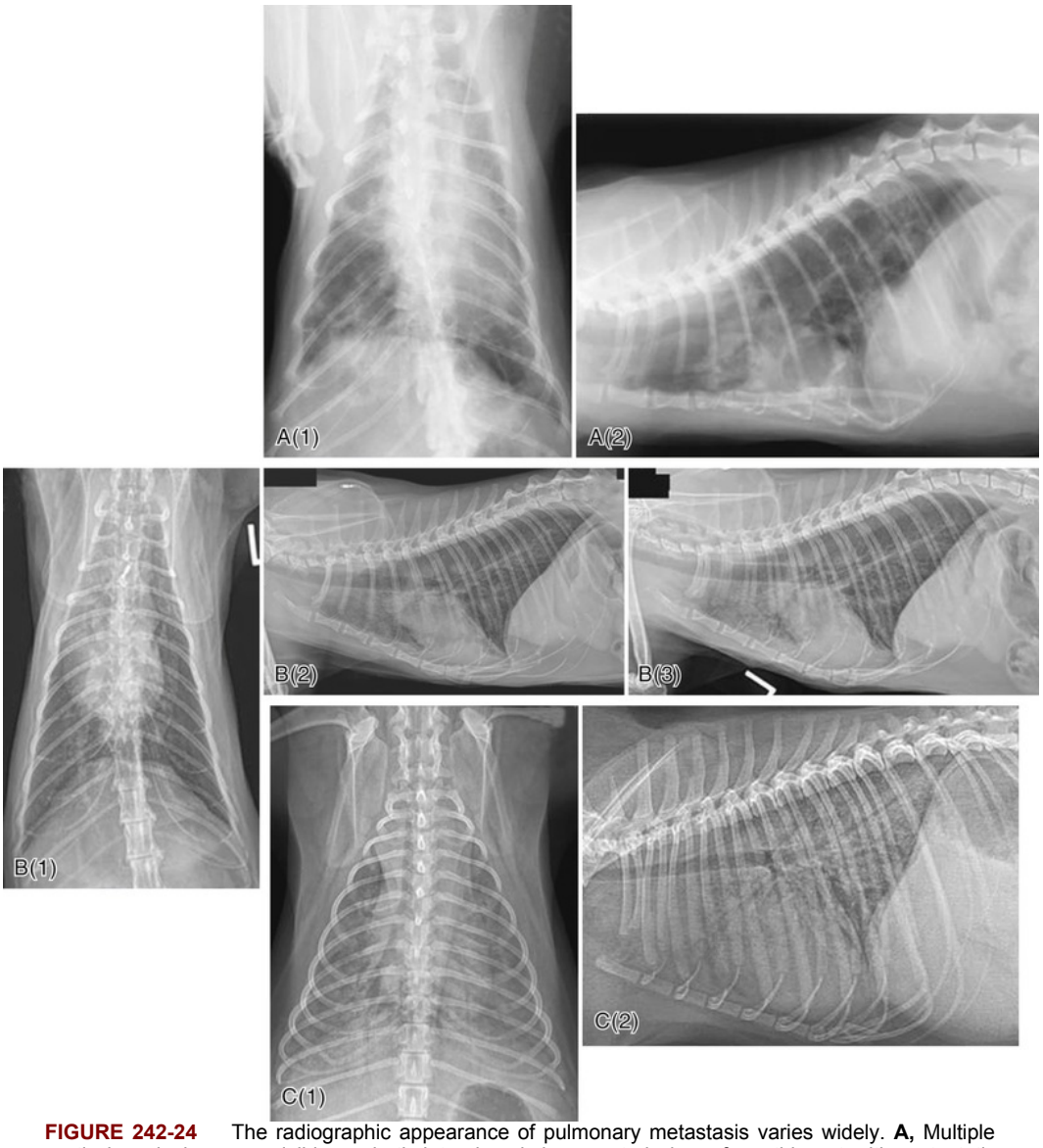
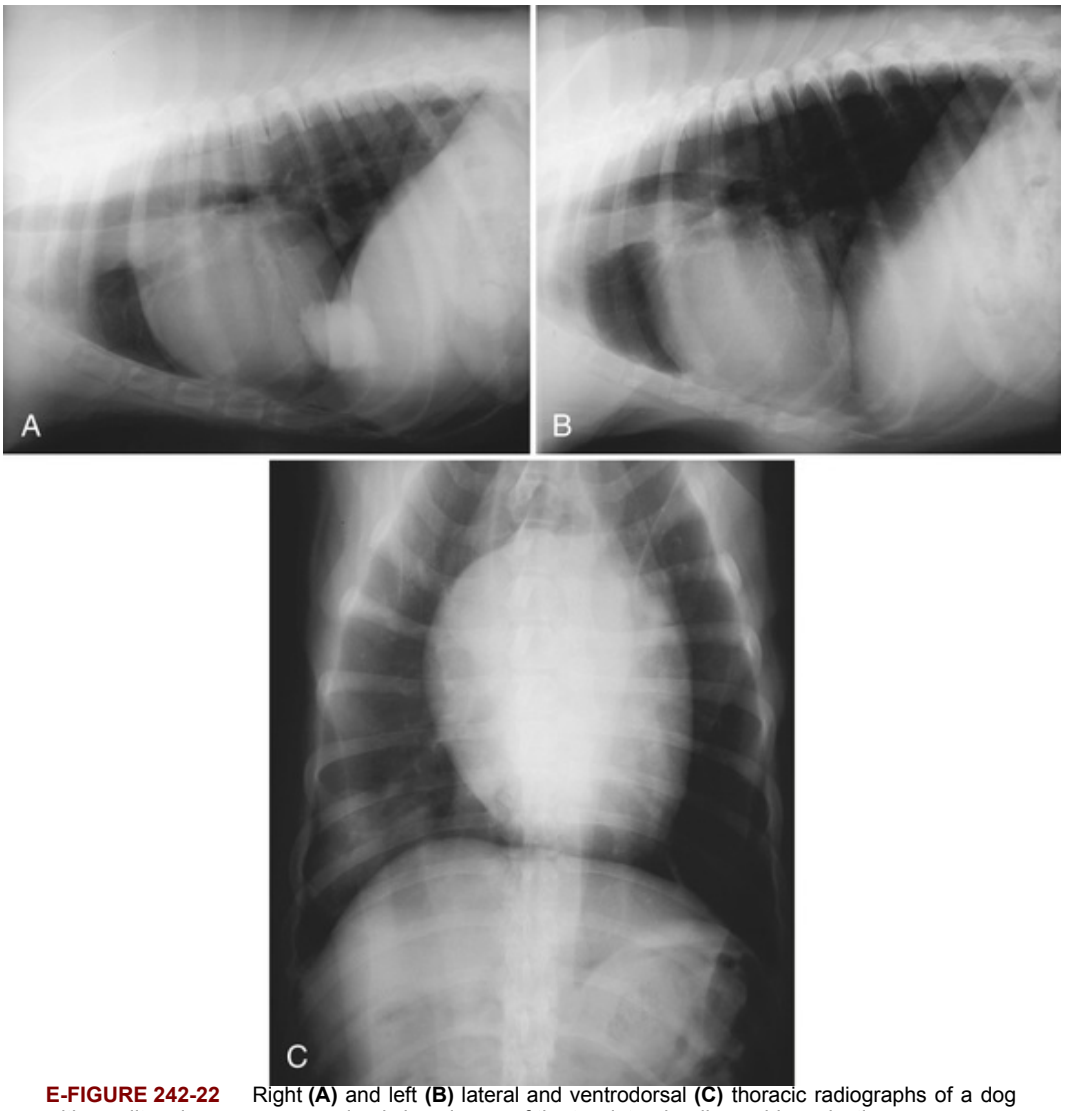
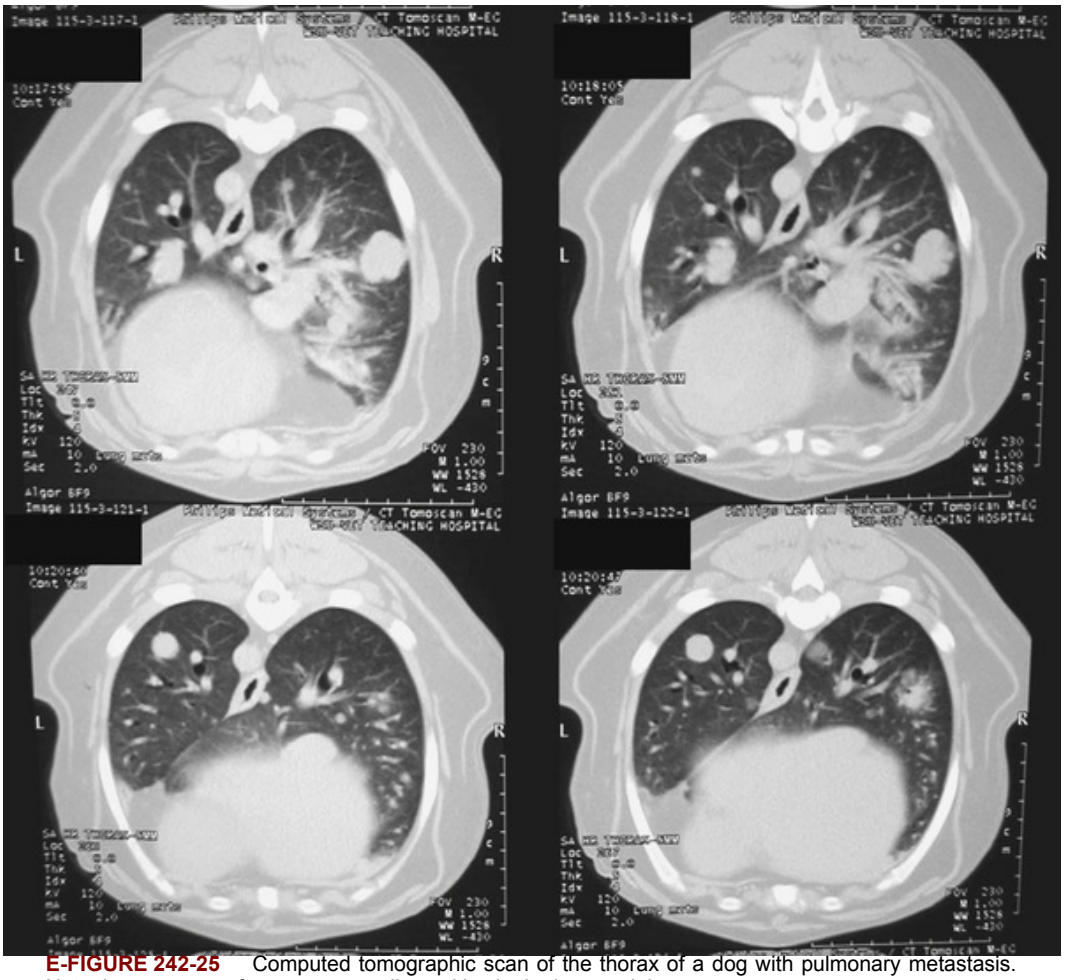


FIGURE 242-24 The radiographic appearance of pulmonary metastasis varies widely. **A,** Multiple cystic lung lesions are visible on both lateral and dorsoventral views from this cat with metastatic squamous cell carcinoma. **B,** A single nodule dorsal to the tracheal bifurcation is visible on the right lateral view, and both alveolar and interstitial patterns are identified in this cat with metastatic mammary carcinoma. **C,** A widespread interstitial to alveolar pattern is present in this dog with disseminated lymphoma.



E-FIGURE 242-22 Right **(A)** and left **(B)** lateral and ventrodorsal **(C)** thoracic radiographs of a dog with a solitary lung mass seen clearly in only one of the two lateral radiographic projections.



E-FIGURE 242-25 Computed tomographic scan of the thorax of a dog with pulmonary metastasis. Note the presence of numerous small opacities in the lung periphery.

Treatment

Unfortunately, treatment of metastatic lung cancer is seldom of long-term benefit. Treatment with tyrosine kinase inhibitors could have limited efficacy.[263] In those cases where only a single or few pulmonary nodules is/are present, surgical resection via thoracoscopy or thoracotomy (± adjunctive chemotherapy) may be an option.[264-266] Metastasectomy particularly can be useful in cases where metastasis occurs long after treatment of the primary tumor.[267] Inhalant therapies with chemotherapy drugs, immunologic molecules (i.e., liposomal interleukin-2), and gene therapy resulting in production of immunogenic molecules have been described for the treatment of both primary and metastatic pulmonary neoplasia.[268-273] As of yet, such therapy is not well established or readily available for pet animals.

Pulmonary Lymphoma

Lymphoma can affect the lungs of both dogs and cats, either in conjunction with lymphoid and solid organs or, rarely, without additional tumor burden. Interstitial, alveolar, and mixed pulmonary infiltrative patterns are observed on thoracic radiographs with or without concurrent hilar and mediastinal lymphadenopathy. When lymphoma is confirmed in other tissues and other inciting causes (e.g., advanced heart disease) are absent, radiographic pulmonary infiltrates can be attributed presumptively to lymphoma. FNA, BAL, or lung biopsy may be used for confirming isolated pulmonary lymphoma. A more complete discussion of lymphoma and its treatment can be found in ch. 344.

Pulmonary Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis (LG) is a rare lymphoproliferative cancer in which atypical lymphoid cells infiltrate around and destroy blood vessels. In humans, LG is regarded as a low-grade precursor to T-cell

lymphoma. Immunophenotyping of several canine tumors has demonstrated the presence of T-cell markers and sometimes B-cell markers.[274,275] Although pulmonary involvement is reported most often, other sites including lymph nodes, abdominal organs, and the dermis can be involved. Dogs of any age or gender can be affected, but there are few case reports in cats.[274-281] Leukocytosis with eosinophilia and/or basophilia has been documented in several affected dogs, but concurrent parasite infection was present in some of these animals. Thoracic radiographs typically demonstrate either pulmonary masses and/or lobar consolidation. Interstitial and alveolar infiltrates also are common, as is tracheobronchial lymphadenopathy. Although FNA or airway lavage can be suggestive of lymphoma, pulmonary biopsy is required to achieve a diagnosis because the unique relationship between the granulomatous lymphoid infiltrates and the vasculature defines the disease. Utility of the less-invasive tests is largely to rule out more common causes for pulmonary consolidation. Supportive care might be necessary for hypoxemic animals, but definitive treatment relies on chemotherapy. Protocols used for treatment are identical to those used to treat lymphoma (see ch. 344). Treatment often results in durable remission, but recurrence of pulmonary involvement or development of lymphoma in other organ systems can occur months to years after apparently successful treatment.

Malignant Histiocytosis

Malignant histiocytosis (disseminated histocytic sarcoma) is one of several histiocytic diseases that occur more commonly in dogs than cats (see ch. 350). The condition was first recognized in Bernese Mountain Dogs, a breed for which a genetic basis with a polygenic mode of inheritance is suspected.[282,283] Other breeds overrepresented among those diagnosed with this condition include Flat-Coated Retrievers, Golden Retrievers and Rottweilers. As with lymphoma, malignant histiocytosis can affect any combination of organs, including the bone marrow, central nervous system, abdominal viscera, and lungs.[283,284] Atypical histiocytic cells (a mononuclear cell lineage) accumulate within the affected organs, resulting in dysfunction. Clinical presentation often involves nonspecific signs such as lethargy and anorexia; cough and/or dyspnea are common.[284-287] When pulmonary involvement exists, radiographs can demonstrate thoracic lymphadenopathy (tracheobronchial and sternal nodes, especially); pulmonary nodules (often quite large, and most often found in the right middle lung lobe) or an interstitial infiltrate; and sometimes pleural effusion.[288] On CT scan, most masses are mildly to moderately enhancing and heterogeneous, poorly marginated, and bronchocentric.[288] Diagnosis usually is based on histopathologic assessment of involved tissue or suggestive clinical findings and supportive bone marrow cytologic features. To date, most chemotherapeutic regimens have been largely ineffective and the prognosis remains guarded to grave.

Recently, another histiocytic lung disease, feline pulmonary Langerhans cell histiocytosis, was described in seven cats.[283,289] All were older adults with progressive respiratory failure. Radiographs demonstrated a diffuse bronchointerstitial pattern with miliary to nodular opacities, and all were diagnosed at necropsy.

Primary Lung Cancer

Primary lung cancer is uncommon in dogs and even less common in cats. A relationship between accumulation of inhaled dust (i.e., anthracosis) and primary lung cancers has been proposed, but no definitive link to living with smokers or an urban environment has been confirmed in pets.[290,291] When primary lung tumors do occur in pets, they usually are malignant. Adenocarcinomas predominate, with most other tumors morphologically classified as carcinoma, squamous cell carcinoma, or anaplastic carcinoma.[292-297] Primary mesenchymal lung tumors are exceedingly rare.

Presentation

Most primary lung tumors in small animal medicine are identified in older animals. Just over half of dogs with primary pulmonary neoplasia are presented for evaluation of a chronic, nonproductive cough.[291,294,295,298] Although other respiratory signs can occur as well, as many as one third of dogs with primary lung tumors display no respiratory clinical signs.[294,295,298] Similarly, respiratory signs often are absent in cats with primary lung tumors: Only 20% to 40% of cats with primary lung tumors present with dyspnea.[292,299] Cough, tachypnea, cyanosis, and hemoptysis occur occasionally in dogs or cats. Affected animals of either species can be brought to veterinary attention due to weight loss, lethargy, and diminished appetite with or without concurrent respiratory signs. Animals with primary pulmonary neoplasia also are presented for evaluation of lameness due to either paraneoplastic osteopathy or, in cats, metastasis of the pulmonary neoplasm to the phalanges (lung-digit syndrome).[291,300] Other presenting problems might include

edema of the head and neck, ascites resulting from tumor obstruction of flow through veins or lymphatics, vomiting, and diarrhea. Sometimes, pleural effusion or spontaneous pneumothorax leads to an acute onset of respiratory distress.

Diagnostic Evaluation

Although essentially any radiographic pattern is possible in animals with primary lung cancer, rare or solitary parenchymal masses often are observed.[293,299,301,302] Solitary nodular tumors, other than histiocytic tumors, are identified most frequently in the caudal lung lobes (Figure 242-26).[293,299] On CT scan, primary lung tumors often are well-circumscribed, bronchocentric masses with internal air bronchograms; up to one quarter of these tumors demonstrate metastasis at the time of diagnosis.[301] As with pulmonary metastasis, the radiographic pattern cannot be considered pathognomonic and the differential diagnosis for solitary or multifocal pulmonary nodules must be considered (Box 242-14).

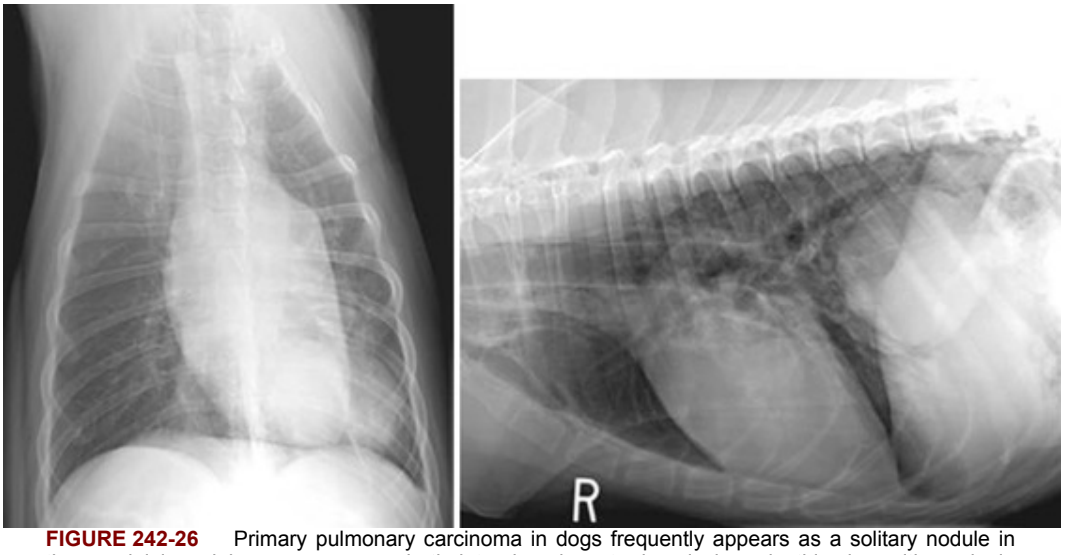


FIGURE 242-26 Primary pulmonary carcinoma in dogs frequently appears as a solitary nodule in the caudal lung lobes, as seen on both lateral and ventrodorsal views in this dog with a single radiographically visible mass in the left caudal lung lobe.

Box 242-14

Differential Diagnoses for Solitary or Multifocal Pulmonary Nodules

Arteriovenous malformation
Atelectasis
Eosinophilic pneumonia (also called pulmonary infiltrates with eosinophilia, eosinophilic bronchopneumopathy, eosinophilic granuloma)
Fluid-filled bullae
Focal pneumonia
Focal bronchiectasis with mucus filling
Fungal granuloma
Foreign body granuloma
Hematoma
Metastatic pulmonary neoplasia
Mucoid impaction
Parasite granuloma
Primary pulmonary neoplasia (usually carcinoma)
Pulmonary abscess
Pulmonary cysts

Pulmonary parasites
Pulmonary thromboembolism
Tuberculosis

Diagnosis must be confirmed by microscopic examination of cells for criteria of malignancy. Samples obtained by BAL or tracheal lavage (see ch. 101) help rule out nonneoplastic disease and rarely demonstrate cells with neoplastic morphology. Radiographic localization of nodules can be used for estimating needle placement for FNA, or aspirates may be obtained with fluoroscopic or CT guidance.[16,26] Nonaerated solid masses located near the edge of the lung could be amenable to ultrasound-guided needle aspiration, but there is a minimal risk of needle-tract seeding.[303,304] Percutaneous lung biopsy should be obtained only with imaging guidance due to the risk of complications (i.e., pneumothorax, hemothorax).[26] Although good correlation has been found between the diagnosis obtained by FNA and percutaneous biopsy, results of FNA are less likely to provide a conclusive diagnosis.[25,26] Other lung biopsy techniques include thoracoscopy, keyhole biopsy, and limited or full thoracotomy.[305-307] Depending on tumor size and location, these techniques also offer the opportunity to completely excise the lung tumor.

Because metastasis greatly affects prognosis, tumor staging should be attempted before lung lobectomy. Reasonable efforts must be made to identify distant tumors because single lung nodules can be either metastatic or primary tumors. Thorough physical examination (including prostate, mammary glands, and long bones), as well as abdominal radiographs and ultrasonographic imaging, are indicated. Ideally, thoracic CT should be performed prior to any planned surgical intervention to identify small masses in other lung lobes that might otherwise be missed; canine primary lung tumors typically appear radiographically as a well-circumscribed solitary mass in the periphery of a caudal lung lobe, but up to one third of primary lung tumors affect multiple lobes.[292,293,295,301] Additionally, CT improves the ability to detect involvement of tracheobronchial lymph nodes, impacting the prognosis.[297,301]

Treatment

Excision is the treatment of choice for primary lung tumors confined to one lobe. Because lymph node involvement negatively impacts prognosis, even normal-sized nodes should be examined histologically.[296-298] Favorable prognostic findings include complete tumor removal, the presence of a single tumor without metastasis, a lack of clinical signs referable to the lung tumor, lower histologic grade or more well-differentiated tumor, peripherally located tumor, and absence of pleural effusion.[292,294,296,298,299,308] Postoperative survival times vary widely but can be up to 2 years. Large reports of traditional radiation or chemotherapy for the treatment of primary lung tumors in dogs and cats are not available. Damage to intrathoracic structures and constant movement of the target associated with respiration have limited the use of traditional radiation therapy in the treatment of lung tumors, but intensity-modulated radiation therapy could offer effective treatment with few adverse effects.[309] Vinorelbine, a mitotic inhibitor that achieves far higher pulmonary concentrations than other vinca alkaloids, has been used with some success to treat two dogs with bronchoalveolar carcinoma.[310,311] Piroxicam, a nonsteroidal antiinflammatory drug that has antitumor effects, also has been speculated to be useful in the treatment of pulmonary carcinoma.[312] Intracavitary chemotherapy occasionally has been utilized to good effect in dogs with malignant pleural effusion, carcinomatosis, sarcomatosis, or mesothelioma.[313,314] Several reports document the potential utility of inhalational chemotherapy or inhalational delivery of biologic response modifiers in the treatment of either metastatic or primary lung cancer.[268-273]

Interstitial Lung Disease

Interstitial lung diseases (ILDs) are a heterogeneous group of noninfectious, nonmalignant respiratory tract disorders that can be definitively diagnosed only with histopathologic examination of lung tissue.[315] Tissue changes center on the space between the basement membrane of the alveolar epithelial cells and the capillary endothelial cells (i.e., the pulmonary interstitium) plus adjacent vasculature and lymphatics. These relatively rare disorders are characterized by inflammation, fibrosis, and/or abnormal accumulations of protein or lipid that restrict effective lung volume and diminish pulmonary compliance. Although recognition of ILDs is increasing, they remain poorly characterized and likely are underdiagnosed in dogs and cats.

As expected for a heterogeneous group of diseases, the causes of ILD are many. Inhalation of toxicants, allergens, and irritants (e.g., mineral fibers) could cause alveolar epithelial inflammation and subsequent reaction, leading to ILD. Tissue damage also can result from systemic exposure to drugs or toxins, or via hypersensitivity reactions. Unfortunately, many ILDs remain idiopathic. Many ILDs have been recognized in dogs and cats, including eosinophilic pneumonia, idiopathic pulmonary fibrosis (IPF), lymphocytic interstitial pneumonitis (LIP), bronchiolitis obliterans with organizing pneumonia (BOOP), endogenous lipid pneumonia, pulmonary alveolar proteinosis, silicosis, and asbestosis (E-Box 242-15).[1,2,316-329] Most ILDs are described as single case reports or small case series.

E-Box 242-15

Uncommon Interstitial Lung Diseases of Dogs or Cats

Numerous interstitial lung diseases (ILDs) have been reported in humans, but far fewer are described in dogs and cats. These disorders often are divided into (1) idiopathic interstitial pneumonia (e.g., idiopathic pulmonary fibrosis [IPF], desquamative interstitial pneumonia, cryptogenic organizing pneumonia); (2) environmental and occupational diseases (e.g., asbestosis, silicosis, extrinsic allergic alveolitis); and (3) multisystem disorders (e.g., sarcoidosis, systemic sclerosis, granulomatosis with polyangiitis [formerly Wegener's granulomatosis]).[461] In addition to IPF, eosinophilic pneumonia, and lipid pneumonia, the following ILDs have been rarely reported in dogs or cats:

Bronchiolitis Obliterans with Organizing Pneumonia (BOOP)

Well-known in humans, both naturally occurring (3 dogs, 1 cat) and experimentally induced BOOPs have been described in pet animals.[155,321,328,462,463] The condition can be idiopathic or secondary. Bronchioles become plugged with connective tissue, leading to a downstream organizing pneumonia.

Familial Acute Respiratory Distress Syndrome

A form of "familial ARDS" has been described in 12 related Dalmatian dogs (3 adult dogs and 9 pups between 5 and 10 months).[464] Unlike the more typical ARDS associated with direct or indirect lung injury, these related dogs developed acute, progressive respiratory distress independently of any recognizable insult. Marked histopathologic changes suggestive of acute interstitial pneumonia characterize this poorly understood interstitial lung disorder.

Lymphocytic Interstitial Pneumonitis (LIP)

Described in feline immunodeficiency virus–infected cats and HIV-infected humans, LIP likely occurs when lentivirus-infected alveolar macrophage and T-cells become activated.[319]

Pulmonary Alveolar Proteinosis (PAP)

Dysfunctional alveolar macrophages and impaired surfactant clearance and alveolar macrophage dysfunction are believed to cause PAP in humans.[343] A similar disorder has been reported in two dogs.[324,326]

Sjögren's Syndrome

An immune-mediated connective tissue disorder characterized primarily by xerophthalmia and xerostomia, Sjögren's syndrome also has a component of ILD.[465] Although not histologically confirmed, a cat presenting with a Sjögren's-like disorder additionally had tachypnea and radiographic pulmonary infiltrates.[466]

Silicosis and Asbestosis

Silicosis and asbestosis develop after exposure to inhaled particulates. Granulomatous interstitial pneumonia with fibrosis follows chronic exposure. Both disorders rarely have been reported as causes of disease in dogs.[322,467] Special studies such as electron microscopy and x-ray diffraction analysis are required to characterize the type of crystalline particles observed on histopathologic examination.

Eosinophilic Pneumonia

Many names have been used for describing eosinophilic diseases of the terminal bronchioles, alveoli, and blood vessels in dogs and cats (see also ch. 241). Variably called eosinophilic pneumonia, pulmonary infiltrates with eosinophilia/eosinophils (PIEs), eosinophilic bronchopneumopathy, pulmonary hypersensitivity, eosinophilic granulomatous pneumonia, pulmonary eosinophilic granulomatosis, hypereosinophilic syndrome, and eosinophilic pneumonitis, there is little agreement on classification of eosinophilic lung disorders.[327,330-336] In humans, eosinophilic pneumonia can be broadly categorized as being of either determined or undetermined origin and either acute or chronic. Eosinophilic pneumonia of determined origin can be caused by parasitic, fungal, or other infectious agents, or by drug administration or toxin exposure.[337] Eosinophilic pneumonia (EP) of undetermined origin in humans is subdivided into systemic disease with pulmonary involvement (i.e., hypereosinophilic syndrome; HES) or isolated eosinophilic pneumonia.

Although reactive eosinophilic airway disease (i.e., asthma) is more common in cats, EP of undetermined origin is more common in dogs. Eosinophilic pneumonia most often is identified in young adult dogs, and more often in females than in males.[338] A predisposition has been reported in Siberian Husky, Alaskan Malamute, and Rottweiler breeds, but dogs of any breed can be affected.[336,338,339] The clinical course of disease can be acute or chronic. Cough is the most consistent clinical finding, but gagging, retching, respiratory effort, and nonrespiratory signs such as weight loss sometimes are identified (particularly in association with systemic infection, neoplasia, or HES). A diffuse bronchointerstitial pulmonary radiographic pattern most commonly is identified in dogs with EP, but alveolar patterns also are recognized (Figure 242-27). Dense infiltrates easily can be mistaken for pulmonary neoplasia (Figure 242-28). EP is one of the most common diseases associated with bronchiectasis in dogs.[339] Although peripheral eosinophilia is identified in ≈50% to 60% of affected dogs, absence of eosinophilia does not rule out EP. BAL fluid from dogs with EP demonstrates increased cellularity (>200 to 400 cells/mcL) with a marked increase in eosinophil percentage (Figure 242-29). Lavage fluid from dogs with suspected EP should be examined carefully for the presence of neoplastic cells (e.g., mast cells, lymphoma), fungal elements, or pulmonary parasites and should be cultured. In dogs with eosinophilic airway lavage, parasitic infections should be ruled out through repeated fecal testing (i.e., zinc sulfate centrifugation-flotation and Baermann sedimentation) and/or deworming, as well as heartworm antigen testing.

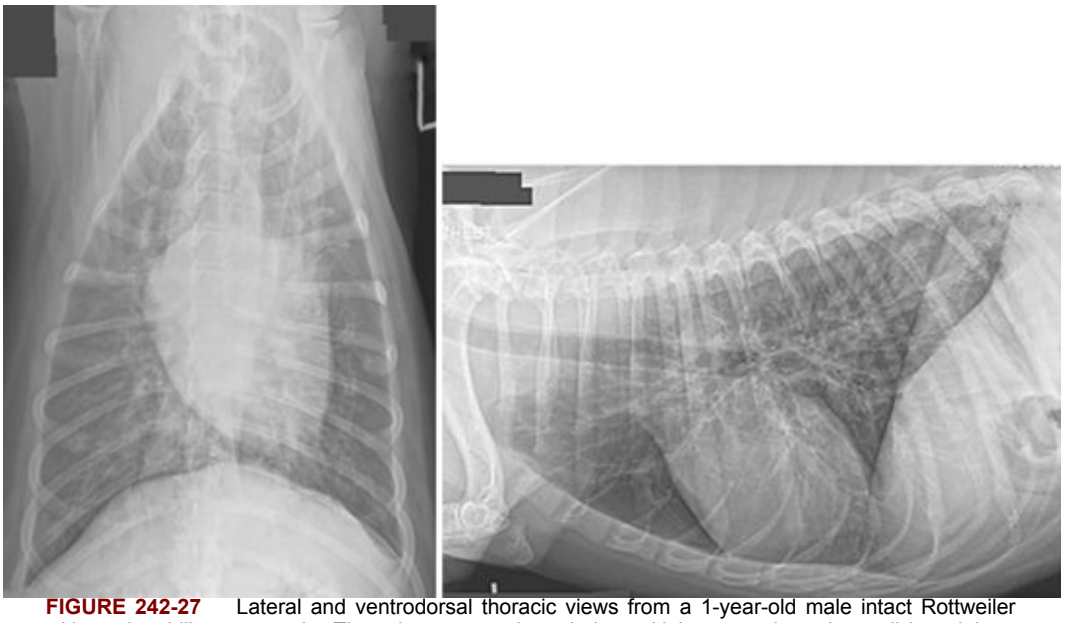


FIGURE 242-27 Lateral and ventrodorsal thoracic views from a 1-year-old male intact Rottweiler with eosinophilic pneumonia. There is a severe bronchointerstitial pattern throughout all lung lobes, and multiple pleural fissure lines are best identified on the ventrodorsal view. Focal patchy alveolar infiltrates are seen over the cardiac apex.

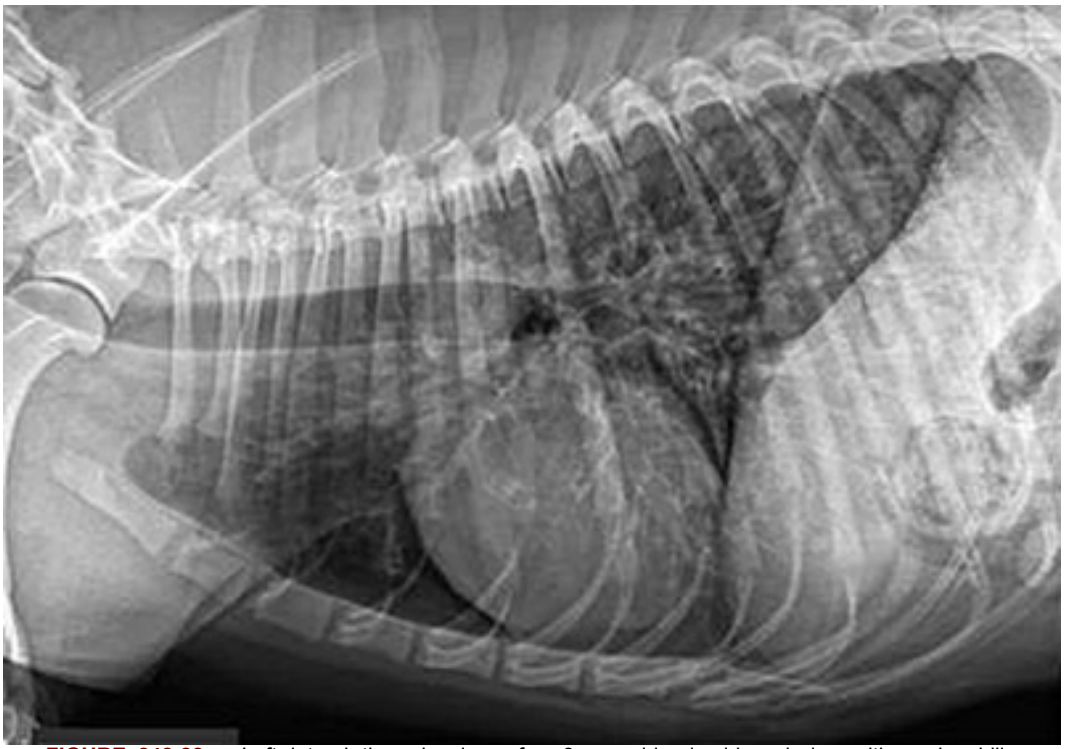


FIGURE 242-28 Left lateral thoracic view of a 3-year-old mixed-breed dog with eosinophilic pneumonia. A marked bronchointerstitial pattern is seen. Dense pulmonary infiltrates easily could be mistaken for pulmonary neoplasia.

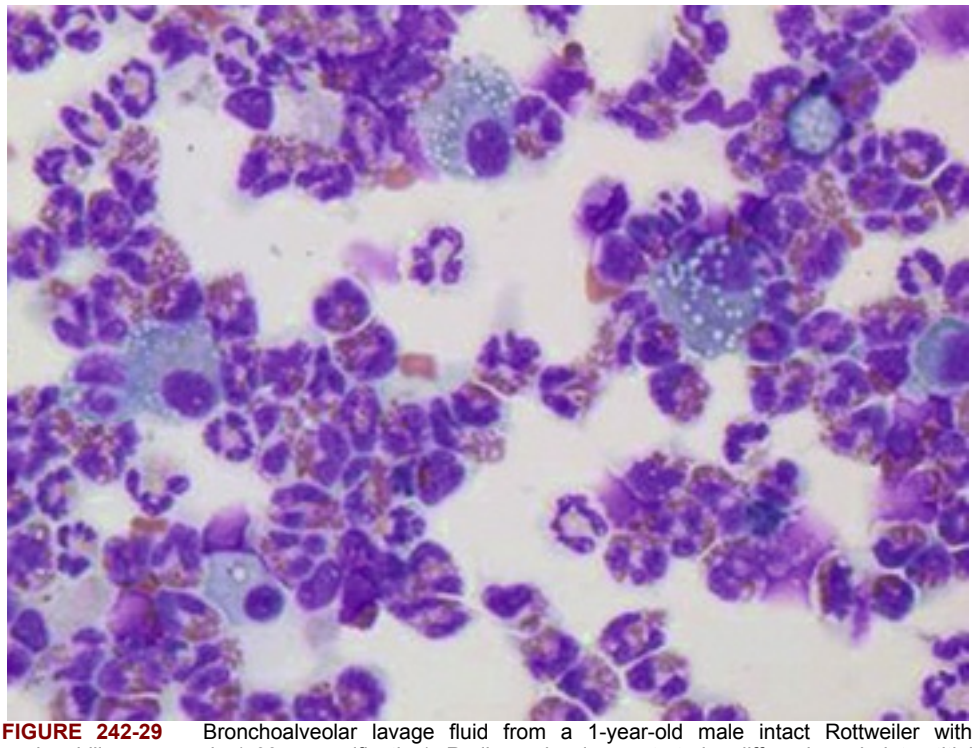


FIGURE 242-29 Bronchoalveolar lavage fluid from a 1-year-old male intact Rottweiler with eosinophilic pneumonia (500× magnification). Radiographs demonstrated a diffuse bronchointerstitial pattern with diffuse alveolar infiltrates (see Figure 242-27). The highly cellular fluid recovered by bronchoalveolar lavage demonstrates 90% to 95% eosinophils with lesser numbers of alveolar macrophages. No organisms or neoplastic cells were identified. (Courtesy Dr. Linda Berent, University of Missouri.)

After underlying infectious, neoplastic, or drug-related causes have been ruled out, treatment of idiopathic EP primarily relies on a tapering course of corticosteroids (e.g., prednis(ol)one 1 to 2 mg/kg PO q 24 h starting dosage). Prognosis for recovery from idiopathic EP is fair to excellent, unless severe bronchiectasis is demonstrated.[327,331,336,338,339] Dogs with isolated pulmonary involvement have a better prognosis than those with other organ infiltrates (i.e., HES).

Lipid Pneumonia

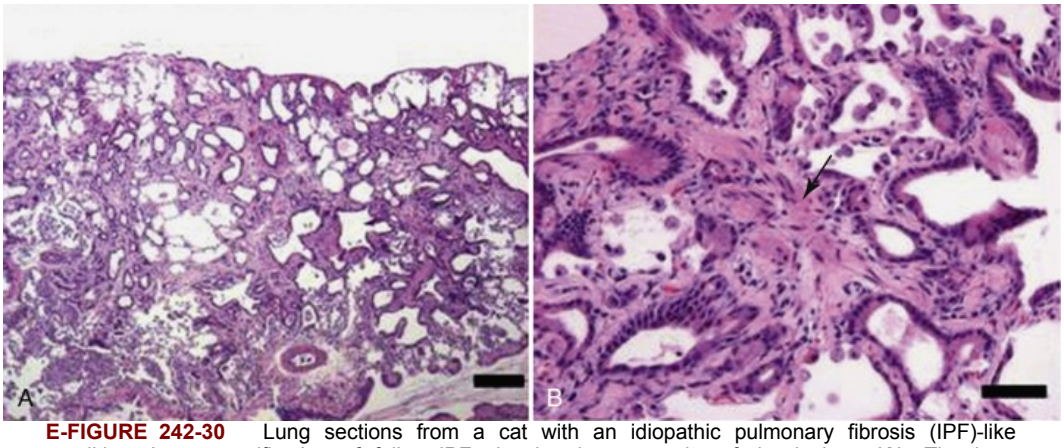
Lipid pneumonia results from an inflammatory response to accumulated globules of lipid in the alveolar airspaces.[2,325] Exogenous lipid pneumonia follows aspiration of lipid—for instance, after the aspiration of mineral oil– or petroleum-based products used for treating constipation or hairballs.[340-342] Endogenous lipid pneumonia (EnLP) is unassociated with aspiration. Although uncommon, EnLP has been reported in a variety of animal species including cats and dogs.[2,3,323,325,329,343] Pneumocyte injury associated with obstructive pulmonary disease, including diseases related to pulmonary neoplasia, has been associated with EnLP.[343,344] Pneumocyte injury leads to cellular degeneration with release of cholesterol and overproduction of cholesterol-rich surfactant.[2] Lipids then are phagocytosed by pulmonary macrophages; these foamy macrophages accumulate in the alveoli. Endogenous lipid also is involved in the pathogenesis of certain infectious pneumonias, such as atypical mycobacterial pneumonia in cats.[167] In other instances, no underlying pulmonary disorder can be identified in association with EnLP.[345]

Endogenous lipid pneumonia is rare enough that no meaningful statements can be made regarding the typical signalment. In a series of 24 cats found to have EnLP on necropsy, ages ranged from 1 to 15 years with a median age of 8.4 years.[2] Cats were presented for veterinary attention due to a variety of nonspecific signs including lethargy, anorexia, and weight loss. Only 16 of 24 had respiratory signs such as dyspnea (11/24; 46%) or cough (8/24; 33%). Serum lipemia was not detected in any of these cats. Radiographic abnormalities were variable and nonspecific. Because animals with EnLP often have additional lung disease (e.g., heartworms, neoplasia, bacterial infection), it is impossible to determine which lesions are most related to EnLP and which to concurrent disease.[2,325,346] BAL in animals with EnLP can be normal, can be suggestive of concurrent respiratory disease, or can demonstrate foamy, lipid-filled macrophages.[345] Necropsy most often

has been used for achieving the diagnosis of EnLP in veterinary patients, meaning there is little information on potential treatment options or prognosis.[2,247,251,325,329] When a specific concurrent lung disease is identified in animals with EnLP, that disease should be addressed directly. In humans, idiopathic EnLP has been reported to respond to corticosteroids.[346a]

Idiopathic Pulmonary Fibrosis

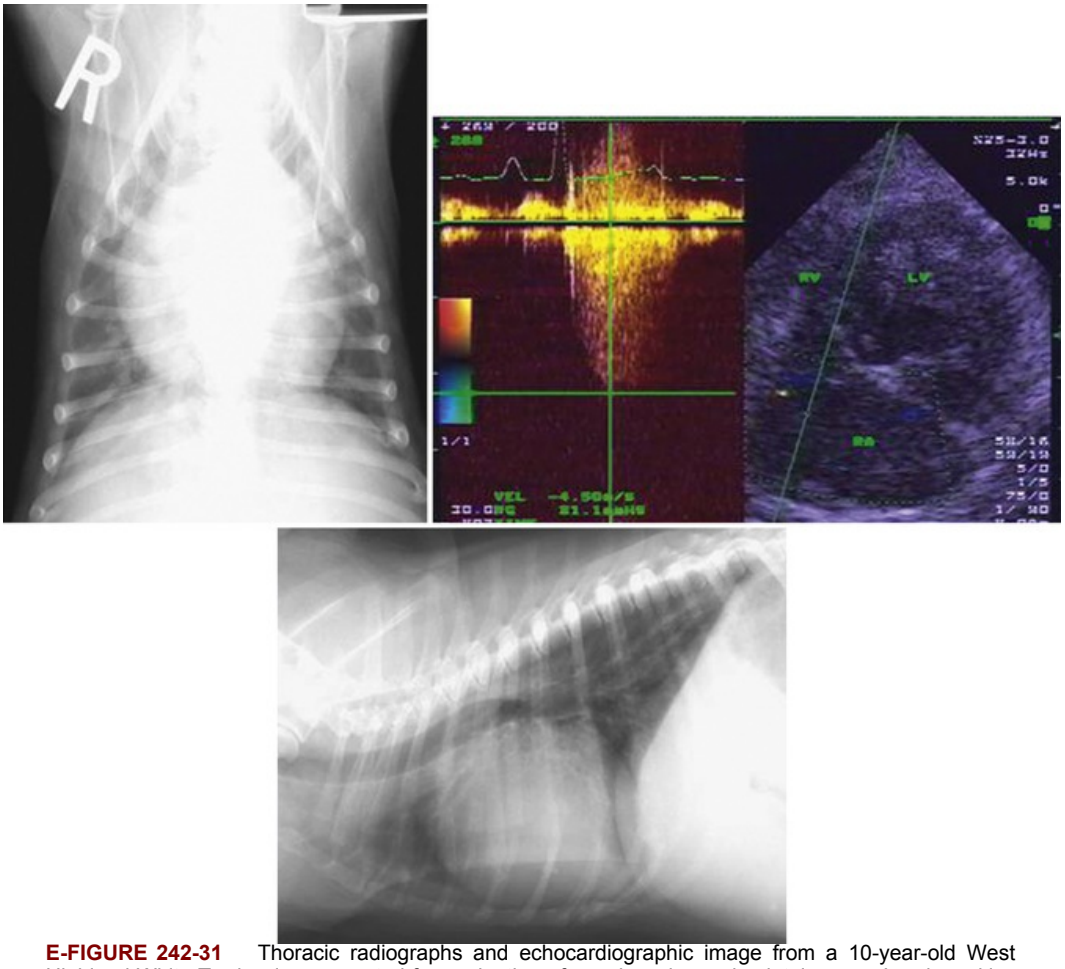
Pulmonary fibrosis can occur as a reaction to lung injury or as a primary disease process of unknown etiology (i.e., IPF).[347] IPF has been recognized in both dogs and cats. The condition in cats shares the histologic features of usual interstitial pneumonia (UIP), which characterizes IPF in humans.[348] These features include interstitial fibrosis, fibroblast and myofibroblast proliferation, enlarged airspaces lined by prominent epithelium (so-called honeycombing), and relatively mild inflammatory changes (E-Figure 242-30). The lungs are heterogeneously affected with areas of normal lung admixed with diseased tissue. Lesions from dogs with IPF contain some histopathologic features of UIP, but even more so those of another common type of human interstitial pneumonia known as "nonspecific interstitial pneumonia."[316,320,349,350]



E-FIGURE 242-30 Lung sections from a cat with an idiopathic pulmonary fibrosis (IPF)-like condition. Low magnification of feline IPF showing heterogeneity of the lesions **(A).** The lung remodeling is patchy, with adjacent affected and unaffected areas present. Honeycomb epithelial metaplasia in feline IPF **(B).** Note the enlarged airspaces lined by cuboidal to columnar epithelial cells with intervening interstitial fibrosis and distinct bundles of smooth muscle present (arrow). Bar (A) = 200 microns, Bar (B) = 50 microns. (Courtesy Dr. K.J. Williams, Michigan State University College of Veterinary Medicine.)

Presentation

Breed predispositions are well described for canine but not feline IPF, with West Highland White and Staffordshire Bull Terriers overrepresented. In terrier dogs, IPF occurs predominantly in older dogs (mean age 8 years) and manifests initially as cough with exercise intolerance. Respiratory distress occurs later in the disease process.[317,318,320,351-354] As opposed to dogs, cats of any age and either gender can be affected with IPF. Because cats are adept at hiding clinical signs of lung disease, they can present with what appears to be a very acute onset of respiratory distress or even sudden death rather than with cough or insidious increase in respiratory effort.[1,354] Adventitial lung sounds commonly are identified in animals with IPF. In dogs especially, prominent inspiratory crackles are ausculted in all lung fields. A systolic heart murmur of tricuspid regurgitation can be noted, especially in dogs that have pulmonary hypertension/cor pulmonale. Cyanosis is a common finding in dogs (but not cats) with IPF late in the disease process. There are no specific changes on routine blood or urine testing suggestive of IPF, but in the later stages of disease, hypoxemia might result in polycythemia and/or increased serum alkaline phosphatase concentration.[350] Radiographic findings in cats with IPF vary widely and include bronchiolar, interstitial, and alveolar patterns; because this disease commonly is accompanied by pulmonary neoplasia, even lung nodules can be identified in affected cats.[1,354,355] In dogs, bronchointerstitial infiltrates are the most commonly recognized pulmonary radiographic pattern but these changes are neither sensitive nor specific (E-Figure 242-31).



E-FIGURE 242-31 Thoracic radiographs and echocardiographic image from a 10-year-old West Highland White Terrier dog presented for evaluation of cough and exercise intolerance. Loud crackles were heard throughout the thorax, and a grade 2/6 systolic heart murmur was loudest in the tricuspid region. These radiographs reveal a diffuse interstitial lung pattern and predominantly right-sided cardiomegaly. Doppler echocardiographic estimation of the pulmonary artery systolic pressure is increased at 83 mm Hg, compatible with pulmonary hypertension. The presumptive diagnosis was idiopathic pulmonary fibrosis, although confirmatory lung biopsy was not performed.

The identification of loud inspiratory crackles in the absence of an alveolar lung pattern can be an excellent clue to the presence of IPF in dogs.[315,350,351] High-resolution CT is used for supporting a diagnosis of IPF in the absence of histologic tissue examination in humans and has been used similarly in dogs.[350,356,357] The few reports of thoracic CT in cats with IPF describe focally increased soft tissue attenuation, masses, and areas of consolidation.[354] Echocardiography can be used for ruling out congestive heart failure as a cause of clinical signs if no cardiac lesion of sufficient severity is identified to explain the patient's signs; primary heart disease can coexist independently in the same patient population as those affected with IPF, and in such cases, determining whether the pulmonary disease or the heart disease is responsible for clinical signs can be challenging (and worthy of referral to an internist and a cardiologist). Measurement of tricuspid regurgitant velocity can be used for estimating pulmonary artery pressure, a useful measure because pulmonary hypertension frequently is associated with IPF in dogs and can respond to medical treatment (see ch. 243).[350,358] Serologic titers, bronchoscopy, BAL, and similar diagnostic studies help rule out respiratory diseases other than IPF. Several potential biomarkers have been investigated for IPF in dogs, but so far no one such finding can confirm the diagnosis.[351,359-365] No technique other than histologic examination of lung tissue can confirm a diagnosis of IPF, and even when pulmonary fibrosis is documented by biopsy, a diagnosis of IPF depends on ruling out known causes of lung injury that might result in secondary fibrosis.

Treatment and Prognosis

Generally, the long-term prognosis for IPF is poor; however, dogs with pulmonary hypertension who respond well to treatment and/or dogs whose owners are content with calmer pets can live a length and

quality life that approach normal for the dog's age. Most reported cats have survived only days to weeks.[1] In dogs, the disease progresses more slowly with median survival, from onset of signs, of 32 months or less.[351,353] While there are no controlled trials for treatment of IPF in dogs or cats, in humans glucocorticoids, cytotoxic agents, and N-acetylcyseine have not been demonstrated to improve survival or quality of life. Very recently, some efficacy has been demonstrated in treatment of humans with IPF using the tyrosine kinase inhibitor nintedanib or the oral antifibrotic pirfenidone, but these have not been investigated in pets and are financially impractical.[366,367] Because cough can be a prominent component of the disease in dogs, pharmacologic suppression of severe cough can improve the quality of life for the dog and pet owner. Pulmonary hypertension can be a severe complication of IPF, which might benefit from directed therapy. Adequate pharmacologic control of pulmonary hypertension without causing systemic hypotension can be difficult. Treatment with phosphodiesterase-5 inhibitors (e.g., sildenafil 1 mg/kg PO q 8 h; tadalafil) has been shown to significantly improve clinical signs in dogs with naturally occurring pulmonary hypertension.[368-371]

Physical Lung Injury

Physical injury to the lungs may be minor or profound, nonsymptomatic or fatal, depending on severity of injury. The most common means of injury include blunt thoracic trauma, drowning, and smoke inhalation. These conditions seldom pose a diagnostic dilemma because historical circumstances and concurrent wounds typically make the cause of injury apparent.

Thoracic Trauma

Automotive injury and fight wounds are the most common causes of thoracic trauma in small animals (see ch. 149). Regardless of the specific cause, trauma can result in serious concurrent injury including hemorrhage and shock. Thorough examination of the entire patient is warranted not only because additional injuries directly affect therapy, but because the discovery of serious coincident injury (e.g., spinal injury, bladder rupture) can have a substantial impact on extent of treatment, prognosis, and the owner's decision as to whether to embark on treatment (see ch. 147). Trauma can result in airway rupture (see ch. 139 and 241), rib fracture, flail chest, diaphragmatic hernia (see ch. 245), pneumothorax (see ch. 102 and 244), and/or pulmonary contusion, any of which can result in tachypnea and respiratory distress.

Pulmonary contusion results from bleeding into the lung interstitium and alveoli. Occasionally, contusion occurs as the result of coagulopathy rather than thoracic trauma. Respiratory distress occurs as a result of ventilation-perfusion mismatching due to flooding of a large number of alveoli with blood. Crushing lung injury, airway and chest wall injury, and pain often worsen respiratory distress. Although crackles and/or diminished bronchovesicular sounds can be heard, their presence does not confirm contusion and their absence does not rule it out. Hemoptysis (see ch. 29) is uncommon following thoracic trauma but does suggest the presence of pulmonary hemorrhage.[372] Thoracic radiographs are vital to evaluate the extrapulmonary structures (e.g., ribs, diaphragm, pleural space) and the pulmonary parenchyma. Intrapulmonary hemorrhage can be evident as either interstitial or alveolar radiographic lung patterns, or as a combination of the two. Radiographic changes in the pulmonary parenchyma often are delayed by up to 24 hours. Therefore, radiographs taken soon after the injury can underestimate the severity of lung injury. Electrocardiographic monitoring can demonstrate premature ventricular complexes as a result of traumatic myocarditis after substantial thoracic trauma (see ch. 141 and 248).

Animals presenting with tachypnea or respiratory distress after thoracic trauma should receive immediate supplemental oxygen during all diagnostic procedures (see ch. 131 and 149). Many animals with pulmonary contusion have mild to moderate injury and respond well to supplemental oxygen and supportive care. However, when hypoxemia and/or dyspnea persists despite oxygen supplementation, intubation and mechanical ventilation (ideally using positive pressure ventilation) is required.[373]

Specific treatment of traumatic pulmonary contusion is not possible, but therapy for concurrent traumatic injury and its complications (e.g., shock, hypovolemia) is vital. In animals with contusion due to bite wounds, surgical exploration of the wound and thoracic cavity can improve outcome.[374] When pulmonary contusions are due to coagulopathy rather than trauma, specific treatment of coagulopathy is indicated. Because rodenticide intoxication is the most likely nontraumatic cause of pulmonary hemorrhage, administration of fresh or fresh frozen plasma, or fresh whole blood and vitamin K, is indicated if prothrombin time is prolonged in animals with pulmonary contusion (see ch. 152). Antimicrobial drugs are not indicated for pulmonary contusion in the absence of other indications for such therapy (e.g., penetrating trauma). Although fluid therapy can be a vital aspect of treatment for animals with trauma, it should be carefully

monitored to avoid pulmonary edema and worsened lung function.[251] Complications such as cavitary lung lesions or abscessation occur rarely, and most animals that survive the first several hours to a day after pulmonary contusion recover completely from lung injury. The prognosis worsens when pulmonary compromise is sufficient to require mechanical ventilation and is worse in smaller animals than in larger animals.[373]

Drowning

Drowning occurs when submersion or immersion in liquid causes a primary respiratory impairment.[375,376] All drowning (fatal or not) involves aspiration of liquid. Although older literature referred to laryngospasm during or after submersion as "dry drowning," this phenomenon is now believed to be very rare and inappropriately described as drowning.[375,377] The pathophysiology of drowning differs somewhat when hypotonic freshwater is aspirated as compared with hypertonic saltwater. Regardless of minor differences in systemic and pulmonary vascular volumes and electrolyte alterations, the most important immediate consequences of either type of drowning relate to hypoxemia.[376,378,379] Alveoli filling with fluid, diluted and dysfunctional surfactant allowing alveolar collapse, and intrapulmonary vascular shunting all result in ventilation-perfusion mismatching and subsequent hypoxemia. Diminished pulmonary compliance and pulmonary inflammation resulting in noncardiogenic pulmonary edema due to ARDS further contribute to hypoxemia. Hypoxemia leads to lactic acidosis, and hypercapnia due to pulmonary compromise can result in respiratory and metabolic acidosis. Pulmonary injury can be worsened by aspiration of chemicals or bacteria in the water.[379] Rarely, invasive systemic fungal or bacterial infection follows nonlethal drowning.[379-382]

Drowning is far more common in dogs than cats, probably because cats are less likely to enter water than dogs.[383] Because dogs often are strong swimmers, drowning and near-drowning occur most often when circumstances prevent their egress from water (e.g., a swimming pool with steep sides and no steps, falling into an ice-covered pond, strong currents), when medical circumstances prevent their normal airway protective reflexes from working appropriately (e.g., laryngeal paralysis or laryngeal tie-back), or when they lose consciousness while swimming (e.g., seizure).[383] A larger-than-expected proportion of dogs presented for near drowning is young (age <4 months). Typically, drowning victims are presented for care following rescue from the water. Common presentations include respiratory arrest, respiratory distress, cough, altered mental status, or loss of consciousness. Circulatory shock (see ch. 127) and hypothermia (see ch. 49) often are identified concurrently. Thoracic auscultation can reveal either diminished bronchovesicular sounds or a combination of crackles and wheezes. Assessment of oxygenation and acid-base status should be conducted, ideally via arterial blood gas analysis (see ch. 75 and 128). Radiographs typically demonstrate a diffuse interstitial to alveolar pattern, but as with pulmonary contusion, radiographic changes can underestimate the severity of lung injury because radiographic changes often progress following rescue due to development of ARDS. The radiographic appearance of "sand bronchograms" (radiopaque material in the airways) is a poor prognostic indicator. Other poor prognostic indicators include the need for cardiopulmonary resuscitation or mechanical ventilation, and acidosis with a blood pH of <7.0. Level of consciousness at admission was not associated with outcome in a retrospective review of freshwater drowning with full recovery, even of animals presenting in a coma.[383] Supplemental oxygen should be administered immediately (see ch. 131). Often, hypoxemia persists despite delivery of supplemental oxygen. Mechanical ventilation, ideally with continuous positive airway pressure or positive end-expiratory pressure, should be administered if the animal is unable to maintain PaO_2 of >60 mm Hg with an F_IO_2 of >50%.[129,379] Even animals who remain normoxemic following rescue can develop ARDS and should therefore be observed for at least 24 hours. Hypothermic animals should be warmed, and shock directly addressed. There can be a difficult balance between fluid administration to address shock and overhydration in the face of lung injury. Continuous hemodynamic monitoring is indicated, and inotropic support could be necessary. Severe acidosis (pH < 7.1) or electrolyte imbalances can require treatment. Despite the potential occurrence of bacterial pneumonia after drowning, prophylactic antibiotics have not been shown to reduce the risk in humans or animals.[129,379,382-384] If evidence of bacterial pneumonia develops later, airway lavage cytology and culture should guide the choice of antimicrobials. Corticosteroids are not indicated because they neither improve oxygenation nor increase survival.[379,385] Although as yet untested clinically, a recent study demonstrated that pentoxifylline (a nonspecific phosphodiesterase inhibitor) administered by constant infusion after freshwater drowning reduced subsequent lung injury due to ARDS.[386]

Smoke Inhalation

Despite the frequency with which house fires occur, there is limited information on smoke inhalation injury in pet animals.[387-392] Smoke inhalation does not always follow every exposure to fire, but when inhalation occurs, often it results in serious respiratory injury. Upper airway obstruction related to bronchospasm and laryngeal swelling can result from thermal and chemical injury; such obstruction typically peaks within the first 24 hours.[390] Inhalation of soot and noxious gases released through combustion of household components (e.g., hydrogen cyanide, ammonia, aldehydes, acrolein), inflammation of airways and airspaces, systemic inflammatory mediators, inactivation of surfactant, reflex bronchoconstriction, atelectasis, airway edema, and ARDS all can contribute to lung injury in this context.[388,390-393] Carbon monoxide and cyanide exposure further compromise oxygen delivery and utilization by tissues. Exfoliation of dying epithelial cells and soot can result in delayed lower airway obstruction even days after the event, meaning that respiratory compromise from smoke inhalation remains dynamic for up to a week after the inciting event. As a further concern, impaired local and systemic defense mechanisms markedly predispose to secondary bacterial pneumonia.

Animals rescued from fire can be presented for care in apparent good health or with severe injury. Common clinical findings include cough and gag, hyperemic mucous membranes, tachypnea, increased respiratory effort, harsh bronchovesicular or adventitial lung sounds, upper airway noise, nasal discharge, and burns or lacerations.[388,391,392] Additionally, neurologic abnormalities can be identified (e.g., ataxia, stupor) as a result of CNS hypoxia, or such abnormalities can occur days later due to leukoencephalomalacia.[254,394,395] Oxygenation ideally is measured via arterial blood gas analysis (see ch. 75 and 128). Because these patients usually are being provided supplemental oxygen, assessment of PaO_2:F_IO_2 ratio is more useful than simple assessment of PaO_2; a ratio <300 signifies marked respiratory compromise. Only dissolved oxygen is measured via blood gas analysis, so it must be remembered that tissue hypoxia may be profound in animals with carbon monoxide intoxication despite a normal PaO_2. Although carbon monoxide interferes with hemoglobin-oxygen saturation, pulse oximetry cannot distinguish oxyhemoglobin from carboxyhemoglobin. Thus, oximetry can provide an overestimation of the blood's oxygen-carrying capacity in carbon monoxide intoxication cases.[396] If available, a cooximeter can be used for measuring carboxyhemoglobin concentration. On thoracic radiographs, dogs frequently demonstrate an alveolar pulmonary pattern, whereas interstitial and alveolar patterns were identified nearly equally in smoke-exposed cats.[388,392]

Supplemental oxygen should be administered at least until initial assessment is complete; administration of supplemental oxygen (ideally beginning at rescue) can result in rapid clinical improvement (see ch. 131).[388] Supplemental oxygen is useful for treatment of hypoxemia and also facilitates the pulmonary elimination of carbon monoxide. The role of hyperbaric oxygen therapy remains controversial and has limited availability for most veterinarians (see ch. 84).[391,397] Persistent hypoxemia in the face of supplemental oxygen delivery could necessitate mechanical ventilation. Occasionally, upper airway swelling requires either intubation or tracheostomy. Crystalloid fluid therapy certainly is required for animals presenting with burns or in shock. Aggressive fluid therapy could contribute to respiratory edema, however, requiring careful monitoring of both fluid dosage and patient response.[389,391] The use of both colloids and hypertonic saline in humans with burns (which can accompany smoke inhalation) is controversial and should be undertaken with caution.[391] Prophylactic antimicrobial therapy has no proven benefit in humans but has not been evaluated in pets with smoke inhalation injury.[388,392,396] Although some corticosteroid preparations have been beneficial in certain rodent models of smoke inhalation, they were not effective in a clinical study using a dog model and are neither proven effective nor routinely used in humans with inhalation injury.[396,397a] Other therapies sometimes employed to treat animals with smoke inhalation include bronchodilators, saline nebulization and coupage, ocular lubricants, and treatment of concurrent burns (including analgesia). Because ARDS can develop and worsen after initial smoke exposure, monitoring through the first 24 hours is suggested even when animals appear well. Improvement in respiratory status during the first day after rescue is a strong positive prognostic indicator.[388,392] Respiratory deterioration past the first day of hospitalization, the presence of concurrent burns, and the need for mechanical ventilation all are negative prognostic indications.

Miscellaneous Lung Diseases

Atelectasis

Pulmonary atelectasis is simply noninflated or underinflated lung. The term can be used for describing newborn lungs that have not yet inflated, lungs that have collapsed as a result of mechanical compression (including compression associated with recumbency), areas of alveolar collapse resulting from alveolar filling, or areas of alveolar collapse resulting from airway obstruction with resorption of trapped air. Atelectasis is not a primary disease state but a consequence of disease.

Cavitary Lung Lesions

Cavitary lung lesions can vary in size, shape, wall thickness, number, location, and content. There is a multitude of potential causes for cystic or cavitary lung lesions (Box 242-16).[398] A few specific causes are addressed next.

Box 242-16

Potential Causes of Cavitary or Cystic Lung Lesions*

Abscess (partially air filled)
Bronchiectasis
Bullae
Congenital cysts
Hydatid disease (rare)
Idiopathic fibrosis with honeycombing
Metastatic neoplasia
Mycotic granuloma (e.g., *Aspergillus*)
Parasites (especially *Paragonimus*)
Pneumatoceles
Pneumocystis carinii pneumonia
Postaspiration injury
Primary pulmonary neoplasia (e.g., bronchogenic carcinoma)
Pulmonary infarct
Traumatic cysts

*References 41, 121, 258, 259, 341, 342, 403, 413, 441, 442.

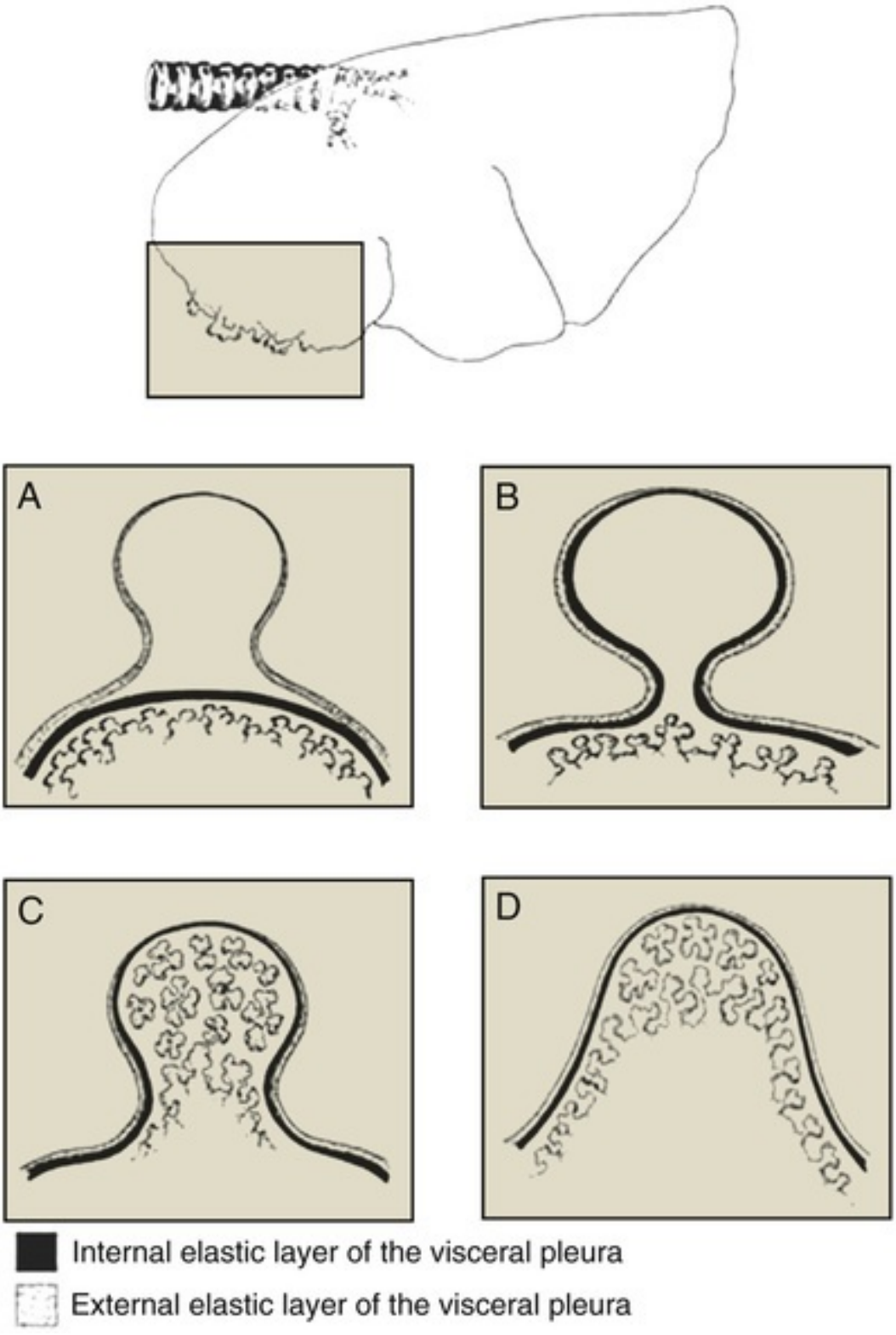
Abscesses

Pulmonary abscessation is an uncommon diagnosis in dogs and cats. An abscess can predominantly be air filled or can have a nodular soft-tissue radiographic appearance due to fluid accumulation; a fluid line can be visible when both air and fluid are present, specifically on horizontal-beam projections. Typically, abscesses occur in areas of otherwise diseased lung (e.g., pneumonic regions, bronchiectasis) and have a thick wall or capsule with an irregular inner margin.[399,400] In humans, lung abscess formation especially is likely as a sequela of aspiration pneumonia with secondary bacterial infection, or when there is obstruction of distal airways as a result of malignancy, inflammation, foreign material (see E-Figure 242-13), or inspissated mucus plugging.[401] Respiratory signs or signs of systemic infection can be identified in dogs with pulmonary abscesses, as might evidence of hypertrophic osteopathy (see E-Figure 242-1).[399,400,402-405] When only a single lung lobe is involved, surgical excision is preferred to antimicrobial therapy alone. The excised lung can be cultured and examined histologically. Sometimes, an underlying cause of abscessation such as foreign material or neoplasia is identified.[137,406] Surgical lobectomy also minimizes the risk of pneumothorax and pyothorax due to abscess rupture.[405] When surgery is not possible, antimicrobial therapy ideally is guided by culture and sensitivity results, but acquiring a specimen carries possible risks: rupture of an abscess during needle aspiration could lead to empyema or pneumothorax, while airway lavage might result in rupture of an air-filled abscess pocket.

Pulmonary Blebs, Bullae, and Emphysema

Bullae are air pockets within the pulmonary parenchyma; they result from destruction of alveolar walls with confluence of adjacent alveoli and are not lined by epithelium as are pulmonary cysts. Bullae have been

classified into several subtypes depending on size and connectivity with surrounding lung tissue. Bullae can be large or small and can occur near the lung surface or deep within the parenchyma.[407] Pulmonary blebs are accumulations of air formed when air escaped from the lung becomes trapped inside the visceral pleura; blebs always are found on the lung surface (E-Figure 242-32).[407] The term *bullous emphysema* sometimes is used for describing bullae.[408] Bullae formation very often is idiopathic, but it can result from lung damage due to parasitic, neoplastic, infectious, or other disease conditions in either dogs or cats. Bullae can be related to congenital disease including bronchopulmonary dysplasia.[409-411] Idiopathic bullae occur predominantly in otherwise healthy deep-chested or large-breed, middle-aged dogs. Idiopathic bullae usually are discovered as a consequence of rupture with resultant spontaneous pneumothorax.[407,408,412] Bullae can be identified radiographically as an incidental finding in dogs or cats with underlying lung disease.[41,259,413,414] Unfortunately, thoracic radiography is insensitive (<5 to 50% detection) for bullae and blebs.[407,408,412,415,416] CT scanning improves detection (up to 75%) but still is imperfect.[408,412] Once significant pneumothorax has occurred, partial lung lobectomy to remove affected lung tissue is recommended whenever possible.[407,408,415,416] Additional information on spontaneous pneumothorax can be found in ch. 244.



E-FIGURE 242-32 Pulmonary bullae and blebs. Line drawings illustrating the apex of the lung (shaded box in top drawing) and a pulmonary bleb **(A),** type 1 bulla **(B),** type 2 bulla **(C),** and type 3 bulla **(D).** Note the accumulation of air between the layers of the visceral pleura in the pulmonary bleb and the different connections to the underlying pulmonary parenchyma in **B, C,** and **D.** (Reprinted with permission from Lipscomb VJ, Hardie RJ, Dubielzig RR: Spontaneous pneumothorax caused by pulmonary blebs and bullae in 12 dogs. *J Am Anim Hosp Assoc* 39:435, 2003.)

Emphysema is any lung condition marked by distention and eventual rupture of alveoli with resultant loss of pulmonary elasticity and lung function. In humans, emphysema most commonly is found in conjunction

with chronic obstructive pulmonary disease (COPD) and often is a consequence of long-term exposure to cigarette smoke or pollution.[417] This form of emphysema is exceedingly rare in pet animals. However, lobar emphysema has been reported in a number of young dogs.[410,418-424] Unlike emphysema of adult humans, congenital lobar emphysema is a condition of infants and young dogs in which a lung lobe becomes overexpanded. The condition can be idiopathic or may result from bronchial obstruction, defect, or compression.[418,424] The enlarged, emphysematous lobe causes compression of the more normal lobes, and increased alveolar pressure in the affected lobe results in progressive emphysema with development of blebs and/or bullae.[420] Radiographic findings usually include lobar hyperinflation with pulmonary blood vessels extending to the lobe margin, contralateral mediastinal shift, caudal displacement of the diaphragm (unilateral or bilateral), thoracic cavity enlargement, atelectasis of unaffected lobes, and possibly pneumothorax.[410,418,419,421,422,424,425] Comparison of inspiratory and expiratory films can be useful because the emphysematous lung will not deflate on expiration. Successful surgical removal of the affected lung has been reported.[411,418,419,422,424]

Lung Lobe Torsion

Lung lobe torsion is uncommon in dogs and rare in cats.[426-430] The lobe usually rotates on the long axis, resulting in occlusion of both the bronchus and pulmonary vasculature at the hilus.[429,431] Because the muscular pulmonary artery continues to allow the passage of small amounts of blood while the thin-walled pulmonary vein collapses completely, the affected lobe becomes congested and consolidated. Eventually, fluid leaves the lobe surface and enters the pleural space resulting in effusion. Although torsion results in pleural effusion, effusion might also predispose to torsion. Torsion can occur spontaneously or can be associated with thoracic neoplasia or trauma.

Presentation

Although torsion can occur in any breed, Afghan Hounds and Pugs are overrepresented.[427,428,432-436] Most affected dogs are young to middle-aged.[427,428] The most common historic complaints are lethargy, anorexia, and increased respiratory effort and rate, although some animals present with little in the way of respiratory signs.[436] Cough, hemoptysis, and collapse also can be presenting complaints. Common physical abnormalities include fever, diminished bronchovesicular lung sounds, and muffled heart sounds. Cyanosis, tachycardia, prolonged capillary refill time, and poor or bounding pulses sometimes are identified.

Diagnostic Evaluation

Peripheral neutrophilia (with or without left shift) is common. Thoracic radiographs often reveal pleural effusion; if so, they should be repeated after thoracocentesis (see ch. 102) to facilitate recognition of lung lobe consolidation (Figure 242-33). Abnormal positioning of the bronchus is inconsistently identified, and a narrowed proximal bronchus can be seen.[427,429,437] When identified, a vesicular gas pattern (small, scattered bubbles) in the affected lobe is strongly suggestive of torsion.[429,437] Thoracic CT (with or without reconstructed "virtual bronchoscopy") is more sensitive and specific than are radiographs for detection of lung lobe torsion.[429] Ultrasonography can be used for further imaging suspected lung lobe torsion.[20,427,428,437] Though seldom necessary, bronchoscopy (see ch. 101) can confirm lung lobe torsion.[438] Evaluation of pleural effusion often reveals a blood-tinged modified transudate with high numbers of neutrophils and lymphocytes, but chylous effusion occurs in some affected dogs and cats.[427,430] Chylous effusions often are identified in Afghan Hounds both with and without lung lobe torsion, making it especially unclear in this breed if effusion leads to torsion, torsion leads to effusion, or some of each occurs.[427,432,433,439,440] Reactive mesothelial cells frequently are identified but seldom indicate mesothelioma. Bacterial culture of effusion or lung tissue from 26 dogs with lung lobe torsion was positive in 8 dogs (*Pseudomonas* spp., *E. coli, Enterococcus* spp., *Proteus* spp., *Staphylococcus* spp., *Enterobacter* spp., and *Serratia* spp.).[42]

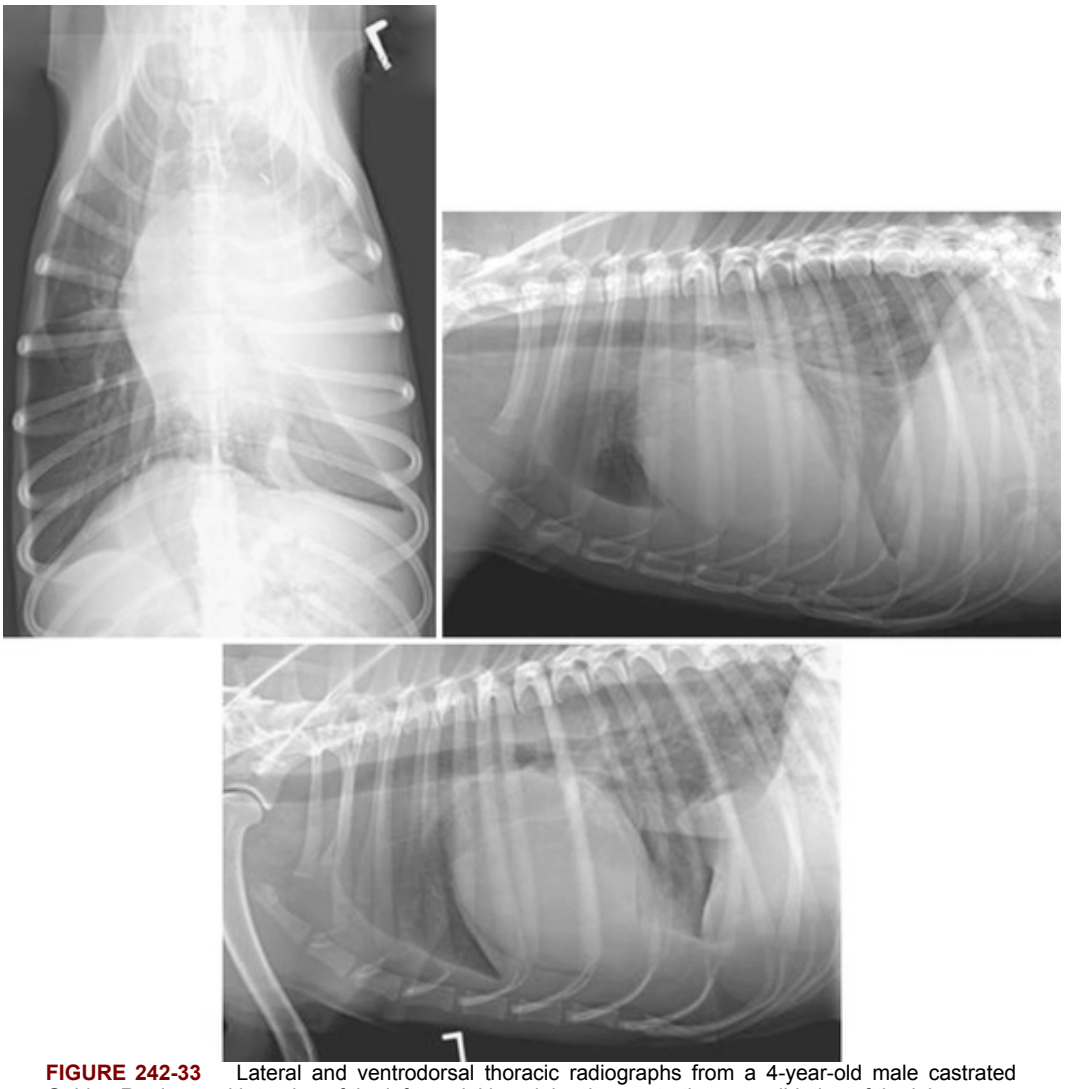


FIGURE 242-33 Lateral and ventrodorsal thoracic radiographs from a 4-year-old male castrated Golden Retriever with torsion of the left cranial lung lobe demonstrating consolidation of the lobe.

Treatment

Once recognized, removal of the affected lobe is the only appropriate treatment for lung lobe torsion. Torsion can occur in any lobe(s). Of 58 dogs described in 3 case series, torsion occurred in the left cranial lobe (n = 37), right middle lobe (34), right cranial lobe (11), right caudal lobe (2), and left caudal lobe (1).[427,428,437] Approximately 60% of dogs recover fully after surgery, with perhaps a better prognosis for complete recovery in pugs.[427,428] Substantial delayed morbidity including pneumothorax, chylous effusion, and torsion of additional lung lobes has been reported in a small proportion of dogs surviving surgery.[427,435]

Pulmonary Thromboembolism

Pulmonary thromboembolism, an occlusion of pulmonary vasculature to aerated sections of lung, results in ventilation-perfusion mismatching and subsequent hypoxemia. For details see ch. 243.

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CHAPTER 243

Pulmonary Hypertension and Pulmonary Thromboembolism

Justin G. Williams

Client Information Sheet: Pulmonary Hypertension

Pulmonary Hypertension

Pulmonary hypertension (PH) can be defined as a pulmonary arterial systolic pressure > 30 mm Hg and/or diastolic pressure > 19 mm Hg as estimated by echocardiographic measurements of the tricuspid or pulmonic regurgitation gradients.[1-5] The normal mean pulmonary arterial (PA) pressure is 14 mm Hg.[6] An increased appreciation for the etiologies, symptoms, and treatments of PH has led to improved quality of life and survival.

Pulmonary Physiology & Pathophysiology

The pulmonary vascular bed is a low-pressure, low-resistance, high-capacitance system. Blood flows from the right ventricle (RV) through the PA into a network of thin-walled arteries, capillaries and veins, before returning to the left atrium via the pulmonary veins. Pulmonary arterial pressure (PAP) is determined by RV cardiac output (or pulmonary blood flow), pulmonary vascular resistance (PVR) and pulmonary venous pressure. Pulmonary hypertension develops when there is an imbalance between the factors that control pulmonary artery vasoconstriction, vasodilation, platelet activation and smooth muscle cell proliferation.

Inducers of pulmonary vasoconstriction include alveolar hypoxia, endothelin-1 and serotonin. Hypoxia-induced vasoconstriction is likely a physiologic response that results in deoxygenated blood shunting to better-ventilated areas of the lung. While this might be beneficial acutely, in chronic conditions this may lead to PH. Endothelin-1 (ET-1) is a peptide released from the vascular endothelium in response to changes in blood flow, vascular stretch and thrombin concentrations. ET-1 causes vasoconstriction, stimulates smooth muscle growth, increases collagen synthesis, promotes vascular remodeling, and is increased in people with PH.[7-9] Canines have elevations in ET-1 in diseases linked to PH, such as heartworm[10] and acquired left heart disease.[11]

Prostacyclin and thromboxane A_2 are arachidonic acid metabolites of PA vascular cells with opposing effects on PA vascular tone. Prostacyclin is a potent vasodilator, inhibits platelet activation and has antiproliferative properties.[7] Conversely, thromboxane A_2 is a vasoconstrictor and platelet agonist. In people with PH, thromboxane A_2 predominates, resulting in PA vasoconstriction, thrombosis, and cellular proliferation.[12] Platelet-derived growth factor (PDGF) induces proliferation and migration of PA smooth muscle cells. Expression of PDGF and its receptor are increased in people with idiopathic PH.[13,14]

Nitric oxide (NO) is a vasodilator, inhibitor of platelet activation, and inhibitor of vascular smooth muscle proliferation. It is synthesized from L-arginine and oxygen by NO synthase enzymes in the PA endothelium. Once formed, NO activates cyclic guanosine monophosphate (cGMP), which causes pulmonary vasodilation. This vasodilation is limited by inactivation of cGMP by the phosphodiesterase 5 (PDE5) isoenzyme.[7]

Classification of Pulmonary Hypertension

Pulmonary hypertension can be simply classified based on anatomical location as *pre-* or *postcapillary*, or classified as a five-group system based on the underlying pathological process. Developed for people, this

group system has been amended for veterinary etiologies (Box 243-1). The five groups of PH are: pulmonary arterial hypertension due to arteriolar vascular disease (Group I); pulmonary venous hypertension due to left heart disease (Group II); pulmonary hypertension with chronic lung disease and/or hypoxia (Group III); chronic thromboembolic pulmonary hypertension (Group IV); and pulmonary hypertension from unclear or multifactorial mechanisms (Group V).[15]

Box 243-1

Classification of Pulmonary Hypertension[1-5,15,17-19,21,30-33,35-37,39-50,53,60,62,71,89-96]

I. Pulmonary arterial hypertension (PAH) due to pulmonary arteriolar vascular disease
- Pulmonary vascular parasitic disease
  - *Angiostrongylus vasorum* (French heartworm)
  - *Dirofilaria immitis* (heartworm disease)
- Congenital systemic-to-pulmonary shunts
  - Atrial septal defect (ASD)
  - Patent ductus arteriosus (PDA)
  - Ventricular septal defect (VSD)
- Necrotizing vasculitis/arteritis
- Idiopathic

II. Pulmonary hypertension with left heart disease (pulmonary venous hypertension)
- Mitral valve disease
- Myocardial disease
- Miscellaneous left-sided heart disease

III. Pulmonary hypertension with pulmonary disease/hypoxemia
- Chronic obstructive pulmonary disease
- High-altitude disease
- Interstitial pulmonary fibrosis
- Neoplasia
- Reactive pulmonary artery vasoconstriction (from pulmonary edema and hypoxemia)
- Tracheobronchial disease

IV. Pulmonary hypertension due to thrombotic and/or embolic disease
- Thromboembolism
  - Cardiac disease
  - Corticosteroid administration
  - Disseminated intravascular coagulation
  - Endocarditis (pulmonic/tricuspid valve)
  - Hyperadrenocorticism
  - Immune-mediated hemolytic anemia
  - Indwelling venous catheters
  - Neoplasia
  - Pancreatitis
  - Protein-losing disease (nephropathy or enteropathy)
  - Sepsis
  - Surgery
  - Trauma
- *Dirofilaria immitis* (heartworm disease)

V. Miscellaneous
- Compressive mass lesions (neoplasia, granuloma)

Group I PH includes pulmonary arterial hypertension (PAH) due to pulmonary arteriolar vascular disease. This group includes congenital systemic-to-pulmonary shunts and heartworm disease *(Dirofilaria immitis).* Heartworm disease causes PH via vascular damage, resulting in lesions of medial hypertrophy and intimal proliferation and fibrosis (see ch. 255).[16] *Angiostrongylus vasorum,* also known as French heartworm, is

associated with PAH in dogs (see ch. 241).[17-21] Systemic-to-pulmonary cardiac shunts have low pulmonary resistance and high pulmonary flow causing stress to the pulmonary arterial endothelial lining and leading to PH.[22] Eisenmenger syndrome involves large intra- or extra-cardiac defects that begin as left-to-right shunts but ultimately lead to significantly increased PVR and reversal of shunt flow or bidirectional shunting.[15,23]

Group I also includes genetic or familial PH in people.[15] Polymorphisms of PDE5 have been associated with variable responses to sildenafil and NO, as well as progression of PH in people.[24-26] In dogs, a polymorphism in PDE5 is associated with a reduced expression of cGMP.[27] While this suggests a possible predisposition to PH, a study of dogs infected with *A. vasorum* did not reveal differences in the frequency of the polymorphism between PH and non-PH dogs.[17]

Group II PH involves pulmonary venous hypertension (PVH) due to left heart disease, such as degenerative mitral valve disease (MVD), dilated cardiomyopathy, or any left atrial or left ventricular heart disease. Left-sided heart disease may result in PH via a combination of elevated left atrial pressure and PVH, as well as reactive pulmonary arterial vasoconstriction. These cardiovascular effects are due to acute or chronic hypoxemia, decreased NO availability, elevated endothelin-1 expression, and desensitization to natriuretic peptides.[28,29] Group II has been suggested to be the most common cause of PH in dogs, as MVD may be the cause of PH in 30-74% of naturally occurring PH cases.[1-4,30-32]

Group III PH occurs secondary to pulmonary disease or chronic hypoxemia. In dogs, Group III PH is associated with pulmonary fibrosis, pneumonia, tracheobronchial disease and neoplasia.[4,5] Up to 40% of West Highland White Terriers with chronic interstitial pulmonary disease have some degree of PH.[5]

Group IV PH includes pulmonary hypertension caused by thrombotic or embolic disease. Heartworm disease is again included as it can cause PH by worm embolization and direct obstruction of the pulmonary artery lumen.

Group V PH is a grouping of diseases with multifactorial or unclear mechanisms. This grouping includes myeloproliferative diseases (such a primary polycythemia vera), granulomatous diseases, chronic immune mediated hemolytic anemia, and tumor obstruction.[15,33]

Evidence of feline pulmonary hypertension is limited to case reports. Feline PH has been associated with pulmonary thromboembolism,[34-36] right-to-left shunting patent ductus arteriosus,[37] heartworm disease,[38,39] chronic upper airway obstruction,[40] and *Aelurostrongylus abstrusus* (feline lungworm) infection.[41] A cat with Eisenmenger's syndrome and an atrial septal defect was treated with sildenafil for 10 months.[41a]

Signalment

Most canine patients with PH are small breed and middle- to older-aged, which coincides with the signalment of predisposing etiologies such as degenerative mitral valve disease and chronic pulmonary disease.[2,4,42-46] Terrier breeds may be overrepresented given their predisposition to chronic pulmonary diseases such as interstitial pulmonary fibrosis.[5,42,47]

Clinical Signs and Physical Examination

Since PH causes impaired oxygen transport and reduced cardiac output, clients most often note exercise intolerance, cough (see ch. 26), dyspnea (see ch. 28) and syncope (see ch. 30) in dogs with PH.[3,4,32] Patients may also present with specific clinical signs associated with the underlying cause. A physical exam may reveal abnormal lung sounds, cyanosis (see ch. 52) and/or ascites (see ch. 17).[2-4,42] Respiratory auscultation often reveals pulmonary crackles, wheezes, and harsh or increased respiratory sounds.[4,32,42,48,49] Left- or right-sided murmurs are auscultated in the majority of dogs with PH.[2,32,43,50] A split or abnormally loud second heart sound (S2) may be noted (see ch. 55). Clinical and physical exam signs of feline PH include dyspnea, jugular venous distension and a right-sided systolic heart murmur.[34-37,40,41]

Diagnostics

Echocardiography (ECHO) is the primary means of diagnosing PH in veterinary medicine. While right heart catheterization and direct measurement of the PA pressure is the gold standard in human medicine,[51,52] its use in veterinary patients is often precluded by cost, availability, and requirement of anesthesia in an often unstable patient.

Doppler ECHO provides a noninvasive method of estimating PA pressures in conscious animals. Peak regurgitant flow velocity of tricuspid regurgitation (TR) or pulmonic insufficiency (PI) can diagnose PH (Figure 243-1, *A*). In the absence of pulmonic stenosis, the regurgitant velocity allows estimation of PA pressures by using the modified Bernoulli equation (pressure gradient = 4 × (peak velocity)^2). However, the accuracy of the predicted pressures depends upon operator skill, degree of TR, and patient tolerability of examination, as well as physiological factors such as RV systolic function. A peak TR velocity > 2.8 m/s (peak TR pressure gradient > 31 mm Hg) or a peak PI velocity > 2.2 m/s (peak PI pressure gradient > 19 mm Hg) strongly suggests PH.[2,4,5] PH can be categorized as mild PH (31 mm Hg to 50 mm Hg), moderate PH (51 to 75 mm Hg), and severe PH (>75 mm Hg).[2,5,49,53,54] If known, the right atrial pressure added to the TR pressure gradient theoretically offers the most accurate prediction of pulmonary systolic pressure. Right atrial (RA) pressure has been estimated off ECHO as 5 mm Hg in dogs with a non-dilated RA, 10 mm Hg if the RA is enlarged but without right-sided heart failure, and 15 mm Hg during clinical signs of right-sided heart failure.[30,32,55] Echocardiographic and direct invasive measurements of PH have a moderate correlation but wide variability.[55] In a study of experimental, acute embolic PH in anesthetized dogs, ECHO had a tendency to underestimate direct PH measurements; however, both under- and overestimation was observed.[55]

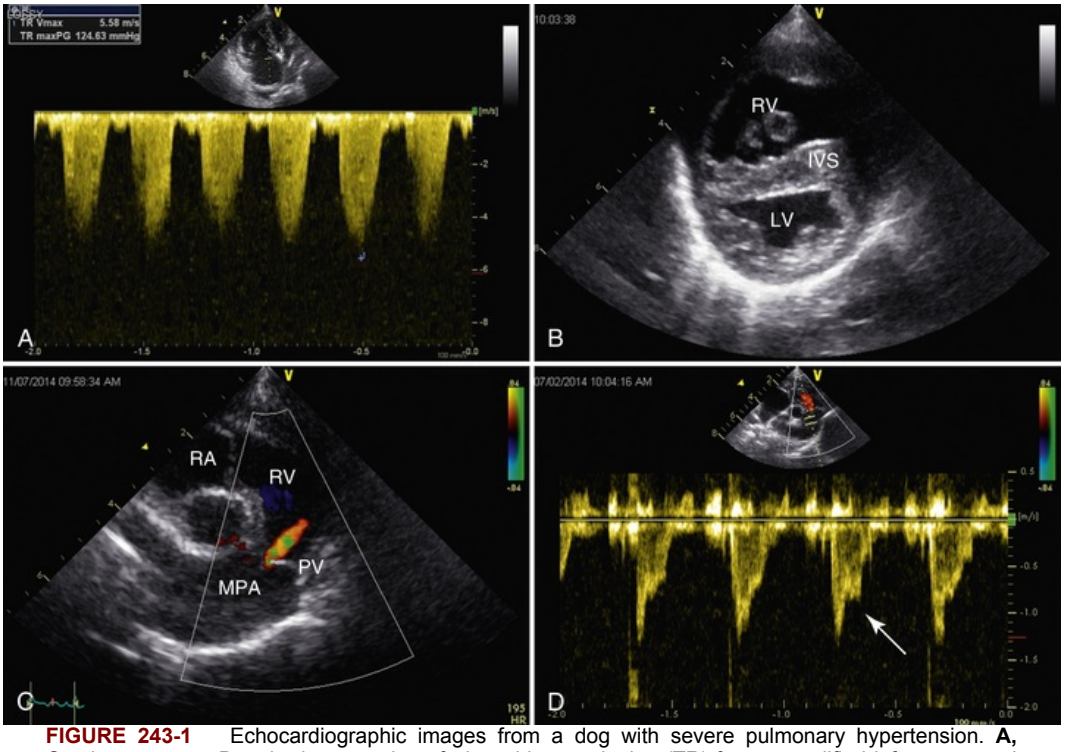

FIGURE 243-1 Echocardiographic images from a dog with severe pulmonary hypertension. **A,** Continuous wave Doppler interrogation of tricuspid regurgitation (TR) from a modified left parasternal four-chamber view. The TR velocity is 5.58 m/sec and the gradient is 124.63 mm Hg, as calculated from the modified Bernoulli equation (pressure gradient = 4 × velocity^2). In the absence of pulmonic stenosis and high right atrial pressures, the TR gradient represents systolic pulmonary artery pressure. **B,** Interventricular septal flattening and right ventricular free wall hypertrophy and chamber dilation. **C,** Obtained from the right parasternal short axis view at the heart base. The image depicts severe dilation of the main pulmonary artery and mild pulmonic insufficiency. **D,** Spectral Doppler across the pulmonic valve from the right parasternal short-axis view. There is an early peak and decrease in velocity with a slight reversal of flow in late systole (indicated by arrow). This pulmonary artery velocity profile is type III, and supports the diagnosis of severe pulmonary hypertension. *IVS,* Interventricular septum; *LV,* left ventricle; *MPA,* main pulmonary artery; *PV,* pulmonic valve; *RA,* right atrium; *RV,* right ventricle.

In the absence of TR or PI, other ECHO findings can be helpful in diagnosing PH. Two-dimensional ECHO can reveal RV concentric hypertrophy or RV eccentric hypertrophy, RA enlargement, septal flattening, and potentially RV systolic dysfunction caused by moderate to severe PH (Figure 243-1, *B* and *C* and Video 243-1).[2,4,5,53,56,57]

Spectral Doppler profiles of the pulmonic valve flow potentially aid in the diagnosis and categorization of

the severity of the PH (Figure 243-1, *D*).[2,4,5,31,32,45,49] Other ECHO measurements supporting a diagnosis of PH in dogs include tricuspid annular plane systolic excursion (TAPSE),[56] right ventricular systolic time intervals,[5,49] right-sided tissue Doppler imaging (TDI),[31,58] main pulmonary artery-to-aorta ratios,[31] the Tei index of myocardial performance (Tei),[31,32,58] and right pulmonary artery distensibility index (RPAD).[59]

While not specific for PH, thoracic radiographs may demonstrate findings supportive of PH. Based on the underlying cause of PH, right-sided heart enlargement, pulmonary artery dilation and/or pulmonary infiltrates may be evident (Figure 243-2). A retrospective study of MVD patients (<15 kg) demonstrated a vertebral heart scale short axis of >5.2 vertebrae (v) and a length of sternal contact > 3.3 v had a predictive accuracy of 85.9% for the detection of PH.[54]

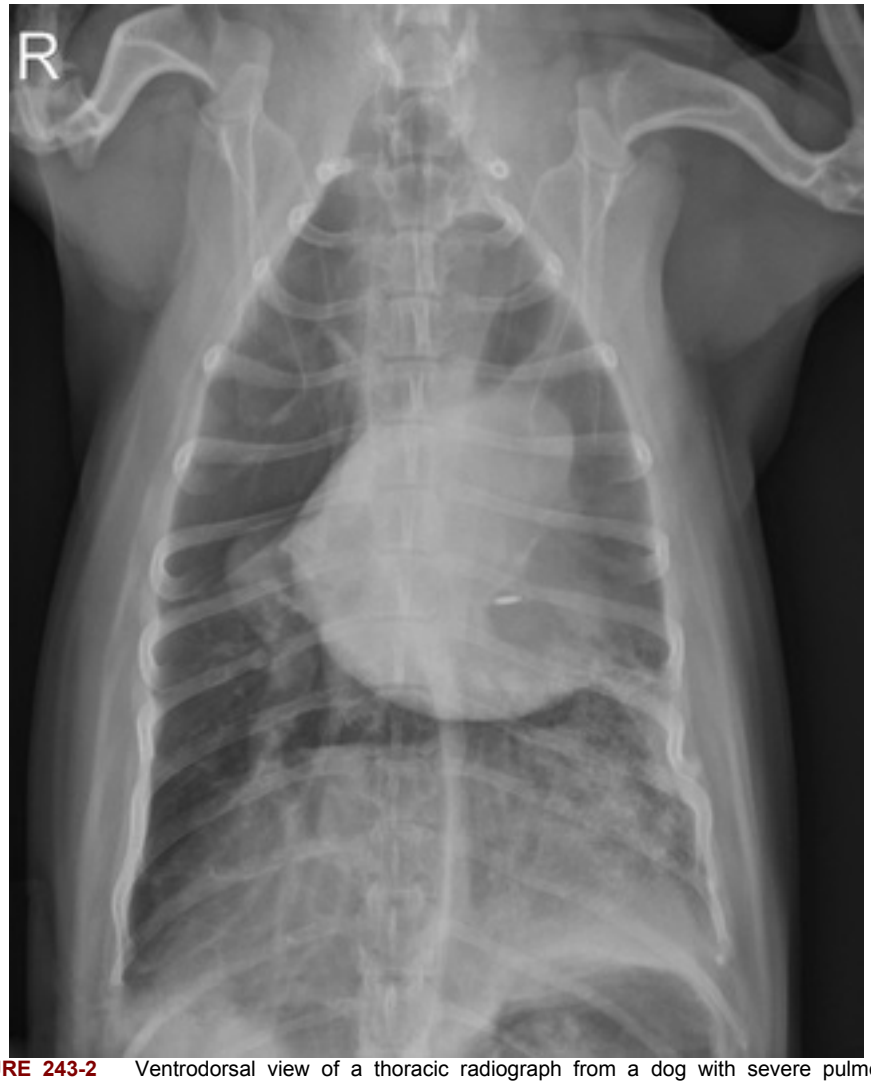

FIGURE 243-2 Ventrodorsal view of a thoracic radiograph from a dog with severe pulmonary hypertension and a one-year history of exercise intolerance, increased expiratory effort, progressive panting and episodes of syncope. Note the severe dilation of the main pulmonary artery and right caudal lobar pulmonary artery with pulmonary infiltrates in the left caudal lung field.

Biomarkers such as NT-pro-B-type natriuretic peptide (NT-proBNP) or cardiac troponins may be useful in the diagnosis of PH. NT-proBNP is a peptide that is released from the ventricular myocardium in response to stress or strain. Traditionally, NT-proBNP has been used to screen for the presence of heart disease, as well as differentiate between cardiac and respiratory diseases.[60,61] However, NT-proBNP can be elevated in dogs with pre- and post-capillary PH.[45,60,62] Dogs with respiratory disease and PH (i.e., Group III PH) have higher median serum NT-proBNP concentrations compared to dogs with respiratory disease but no PH.[60,62] Furthermore, NT-proBNP may correlate with peak TR gradient.[62] However, NT-proBNP is not specific

enough to discriminate between dogs with MVD and those with MVD plus PH.[54] Overall, NT-proBNP elevations increase the suspicion for PH but cannot discriminate between PH and primary cardiac disease.

Cardiac troponin I (cTnI) concentration is a measure of myocardial injury. Pre- and post-capillary PH dogs have been associated with a significant increase in cTnI compared to normal dogs.[30] However, cTnI was not different between dogs with respiratory disease and PH versus those with respiratory disease without PH.[62]

Treatment

Pulmonary hypertension develops from a heterogeneous group of diseases with numerous subgroups. Consequently, treatment should be aimed at the underlying etiologies (see Treatment sections of ch. 241, 242, 247, and 255) as well as direct reduction of PH to improve quality of life. Once labeled the "kingdom of the near dead,"[63] pulmonary hypertension can be treated with a number of therapeutic agents in human medicine. Endothelin antagonists (i.e., bosentan, ambrisentan, macitentan) and prostacyclin analogs (i.e., beraprost, epoprostenol, iloprost) are cost-prohibitive, and often require continuous subcutaneous or inhaled administration, which greatly limits their application in veterinary patients. The value of endothelin antagonists or prostacyclin analogs has yet to be confirmed in canine PH patients. However, phosphodiesterase type V inhibitors (PDE5-I) are commonly prescribed for PH in dogs.

PDE5-I medications, such as sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra), cause vasodilation by increasing pulmonary vascular concentrations of cGMP. This increase subsequently results in increased endogenous NO concentrations.[2,3,64] In addition to directly improving PH via PA vasodilation, PDE5-I medications reduce cardiac remodeling, apoptosis, fibrosis, ventricular hypertrophy, and improve left-heart function in people.[64] Sildenafil is a short acting PDE5-I. In veterinary medicine, sildenafil has been shown to decrease clinical signs of PH and improve quality of life.[2,3,46] A measureable reduction in TR pressure gradients has been found in some studies[3,46] but not in others.[2] Nevertheless, studies demonstrate clinical improvement in dogs receiving sildenafil independent of any change in estimated PH. Sildenafil is well tolerated in dogs at 1-2 mg/kg PO q 8-12 h.[2,3,46] While no consensus exists regarding the use of sildenafil in dogs, one potential clinical decision-making process for Group II and III PH is provided in Figure 243-3. Sildenafil has anecdotally been used in cats, including a case report of a cat with PH from a left-to-right PDA.[65] No clinical trials have been published in cats.

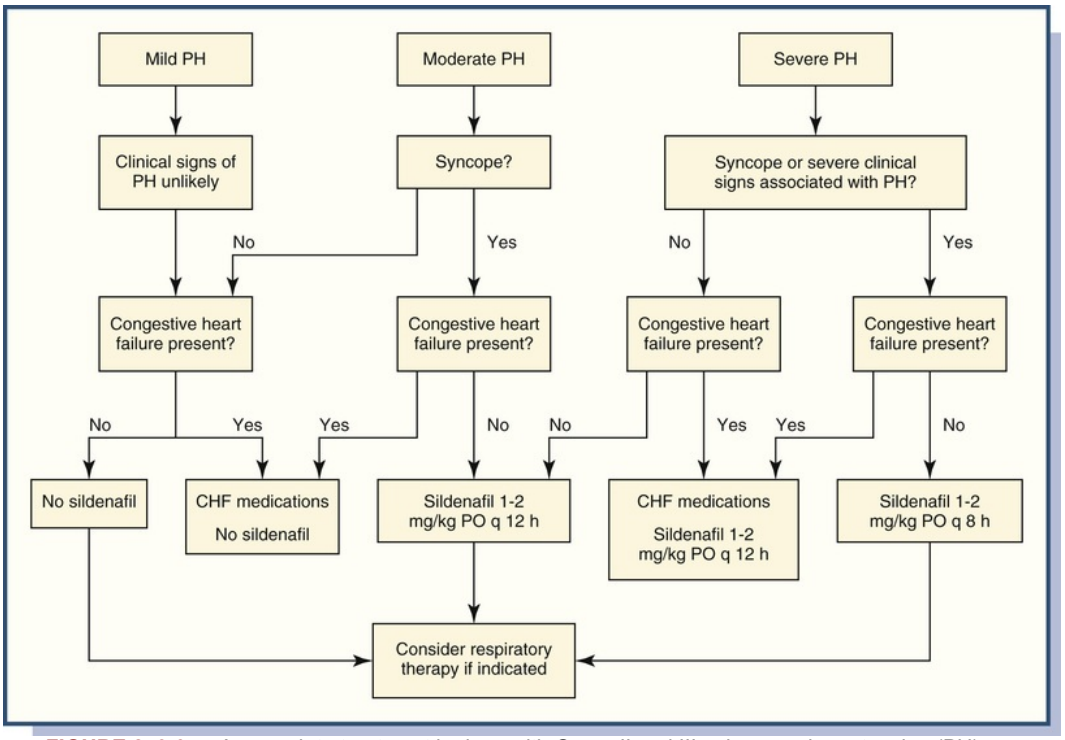

FIGURE 243-3 Approach to treatment in dogs with Group II and III pulmonary hypertension (PH).

Tadalafil is a long-acting PDE5 inhibitor. A single published case study exists of a dog with idiopathic PH treated with tadalafil (1 mg/kg PO q 48 h).[66] This dog demonstrated a decrease in PAP and improved clinical signs. Oral and injectable tadalafil has been shown to reduce experimentally-induced PH in dogs.[67] Vardenafil, another long acting PDE5-I, has yet to be studied in canine PH.

Pimobendan (Vetmedin) is a phosphodiesterase 3 (PDE3) inhibitor and calcium sensitizer. Treatment of PVH (Group II PH) with pimobendan in dogs with MVD reduced NT-proBNP levels. Furthermore, this therapy improved quality of life in the short term, while maintaining a reduction in measureable PVH in the long term.[45]

Considering that *in situ* thrombosis and increased thromboxane A_2 synthesis occurs in people with idiopathic PH, aspirin or clopidogrel have been used.[68] Some veterinary clinicians use antiplatelet therapy in dogs with idiopathic PH; however, its indication and effectiveness are unknown.

Newer therapies are emerging in human medicine, some of which have already been evaluated in dogs. Imatinib (Gleevec) inhibits the activation of platelet-derived growth factor (PDGF) and also inhibits the PDGF receptor. Six dogs with congestive heart failure and PH from MVD or heartworm were treated with imatinib at a 3 mg/kg dosage PO q 24 h for 30 days. These dogs demonstrated improvement in maximum TR velocity, left atrial size and plasma atrial natriuretic peptide concentration.[69]

Outcome

The prognosis for canine PH is quite variable, and often depends upon the underlying cause. Severe PH carries a poor long-term prognosis. Prior to the availability of sildenafil, canine PH was associated with survival only days past diagnosis.[4] With the introduction of sildenafil, published survival has increased to 91 days[3], with some patients surviving almost two years.[2,3] Well-defined prognostic indicators are lacking in veterinary medicine. In people, the degree of PH-induced clinical symptoms as well as achievement of treatment goals (improvement in RV function, NT-proBNP levels and in 6 minute walk distances) are the most predictive long-term prognostic indicators.[70]

Pulmonary Thromboembolism

Etiology/Pathophysiology

Pulmonary thromboembolism (PTE) is the partial or complete obstruction of the PA or its branches by thrombi secondary to other disease processes. Diseases associated with thromboembolic disease are listed in Box 243-1 under Group IV. The pathogenesis of PTE is based on endothelial damage, blood flow stasis and hypercoagulable states (see ch. 197).[71] PTE results in hypoxemia, bronchoconstriction, ventilation-perfusion mismatch, and hyperventilation. Hemodynamic complications associated with PTE depend on the extent of pulmonary vasculature occlusion and pre-existing cardiac and pulmonary dysfunction. Over time, further complications arise such as atelectasis, pulmonary edema, and pleural effusion.

Clinical Signs and Diagnostics

Clinical signs of PTE are highly variable and nonspecific. The most common signs of PTE are dyspnea, tachypnea and lethargy.[71-74]

Antemortem diagnosis of PTE in veterinary medicine is difficult to achieve due to a lack of a feasible and available gold standard diagnostic test. Thoracic radiographs are indicated but findings are often nonspecific, ranging from focal pulmonary infiltrates to normal findings.[73,75] Arterial blood gas abnormalities may increase the index of suspicion, but is not sufficiently specific enough to confirm PTE. The most common blood gas changes associated with PTE include hypoxemia, hypocapnia and increased alveolar-arterial oxygen tension gradient (see ch. 75 and 128).[71,73] Since PTE is a sequela of other disease, broad diagnostics such as a complete blood count, serum chemistry, urinalysis, and heartworm test may identify predisposing factors. PTE is generally suspected in patients in whom no cardiopulmonary disease can be confirmed and the patient is known to have a predisposition to thrombosis. Thromboelastography (TEG) provides a global evaluation of coagulation and fibrinolysis with the potential to identify hypercoagulable states and increase the suspicion of PTE (see ch. 196).[71,75] Unfortunately, antemortem confirmation of PTE is rarely obtained in veterinary medicine.

In people, computed tomography (CT), selective pulmonary angiography and radionuclide

ventilation/perfusion scans are used for screening and confirmation of thromboembolic disease.[51,71] Selective angiography is difficult in unstable veterinary patients considering the need for general anesthesia. However, a small prospective study in dogs demonstrated thoracic CT with simultaneous bolus injection of contrast (i.e., CT pulmonary angiography) was possible under sedation in patients with respiratory clinical signs, and useful toward confirming/refuting PTE.[75]

Since CT angiography availability and associated expertise are limited, the use of widely available blood tests such as D-dimers is appealing. D-dimer is the byproduct of cross-linked fibrin degradation by plasmin and is reflective of fibrinolysis (see ch. 196). While D-dimer is not specific to PTE, a normal or low D-dimer concentration is highly sensitive in ruling out acute PTE in dogs.[76-80] D-dimers should be measured within 1 to 2 hours of a suspected PTE, as levels peak rapidly and can return to baseline within 24-48 hours.[81]

Treatment

The goal of therapy is typically to limit thrombus growth and prevent recurrence.[71] Anticoagulants, antiplatelet therapy and thrombolytics have been used; however, an evidence-based approach or consensus regarding treatment is lacking. Thrombolytic therapy using streptokinase, urokinase or tissue plasminogen activator is particularly controversial therapy and without clinical trials evaluating its use in veterinary PTE. Catheter-directed, local infusion of thrombolytics to a thrombus has been described and may result in a decreased risk for systemic bleeding complications.[82,83] Unfractionated heparin (100 to 300 IU/kg per dose SC q 6-8 h, adjusting the dosage to keep activated partial thromboplastin time [aPTT] at 1.5 to 2 times baseline)[84,85] or low molecular weight heparin (dalteparin 100-150 IU/kg q 8 h in dogs[84] and 100-180 IU/kg SC q 8-24 h in cats[84,86]) has been suggested for initial in-hospital therapy. Supportive care with oxygen (see ch. 131), judicious IV fluids (see ch. 129), sildenafil and bronchodilators can be beneficial (see ch. 139).[71] Successful treatment of acute PTE should be bridged to long-term antiplatelet or anticoagulation therapy. Aspirin is beneficial for thromboprophylaxis in immune mediated hemolytic anemia and protein-losing nephropathy.[71,85] Commonly used aspirin dosages are 0.5 mg/kg PO q 24 h in dogs and 5-81 mg/dose PO q 3 days in cats.[71,84,85,87] Clopidogrel is also often used with suggested dosages of 2-3 mg/kg PO q 24 h in dogs and 18.75 mg/dose PO q 24 h in cats.[85,88]

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CHAPTER 244

Diseases of the Pleural Space

Elizabeth Rozanski

Client Information Sheets:
Pleural Effusion
Pneumothorax

Anatomy

The pleural space is defined as the area or potential space between the lungs and the chest wall. Normally, there are no soft tissue structures or free air present in this space. A very small amount (1-5 mL) of fluid, which is undetectable on radiographs or ultrasound, can be present within the thoracic cavity. The pleural cavity is lined by the visceral and parietal pleura, which covers the lungs and the thoracic wall, respectively. In small animals, the two hemithoraces are incompletely separated, which results in pleural effusions being generally divided between the right and left side. In longstanding effusions, fibrous adhesions can result in the presence of unilateral disease, but as a general rule in dogs and cats, the mediastinum is incomplete. As throughout the body, fluid movement reflects Starling's forces, as well as the tissue permeability and lymphatic drainage.[1] In animals with longstanding effusion, the rate of lymphatic drainage can be increased.

Physiology

Adequate lung function is dependent on adequate oxygenation and ventilation, which, in turn, is dependent on lung mechanics and ease of lung expansion. The normal intrathoracic pressure is subatmospheric, with an average pressure of −5 cm H_2O (−3.7 mm Hg). Negative intrathoracic pressure in conjunction with surfactant acts to keep the lungs inflated, which reduces the work of breathing.

Pleural effusion affects lung function by creating a restrictive defect with decreased total lung capacity (TLC) and functional residual capacity (FRC). In advanced cases, there will be increasing ventilation-perfusion mismatch and, left untreated, severe pleural effusion will result in decreased cardiac output and ultimately cardiac arrest.[2] This phenomenon is more common with pneumothorax, where tension pneumothorax can arise quickly, in contrast to pleural effusions, which tend to develop more slowly.

As pleural effusion forms, there is gradual collapse of the lung parenchyma, and also an *increase* in intrathoracic pressure. In the presence of marked effusion, the intrapleural pressure will be positive. While typically it is assumed that removal of isolated pleural effusion will result in immediate improvement in lung function, this is not always the case. In people, two separate categories of non-recruitable lung associated with pleural effusion are recognized. The first is termed *lung entrapment*, which is a disorder that develops in association with active pleural inflammation or neoplasia.[3] Immature fibrin and overlying inflammation prevent re-expansion, and contribute to the failure to recruit lung after thoracocentesis. During longer-standing effusions, there is thickening and constriction of the visceral pleura and thickening of the parietal pleura. This may lead to the development of *trapped lung*, or lung that is tightly constricted by overlying visceral pleura, and cannot adequately re-expand, even in the presence of negative intrathoracic pressure.[3] Trapped lung likely is more common in veterinary patients, as most effusions are associated with more active inflammation. However, the non-recruitable lung has been much less evaluated in dogs and cats than people, but could particularly be associated with the development of thoracocentesis-associated pneumothorax (see below).

Physical Examination

Clinical signs of pleural space disease can include tachypnea, orthopnea, or overt difficulty breathing, with classically rapid/shallow breathing considered the most common manifestation (Video 244-1). Some animals have marked abdominal effort. Physical examination findings can include respiratory distress, use of accessory muscles in respiration, and diffusely (pneumothorax or pleural effusion) or dependently (pleural effusion) muffled heart/lung sounds; occasionally, lung sounds can appear normal. It can be possible to percuss a ventral dullness on the thorax in patients with pleural effusion. Other clinical findings can reflect the underlying disease process (e.g., cardiac gallop sound, intrathoracic mass lesion, fever, trauma). Identification of a pleural space abnormality should be considered a strong clinical sign, but not a final diagnosis. Overall, the prognosis for a patient with pleural effusion is guarded, although many cases respond well to therapy, at least in the short term.

Initial Diagnostic Evaluation

Diagnosis of pleural effusion or pneumothorax can be made either through thoracocentesis, or diagnostic imaging. Radiography has classically been the most common imaging technique to identify either disorder, but ultrasonography is widely used in emergency and general practices (Figure 244-1), especially for detecting pleural effusion but increasingly for detecting pneumothorax (see below). Computed tomography and magnetic resonance imaging also can demonstrate pleural effusions and pneumothorax, but are used less commonly as the initial diagnostic imaging modality (Figure 244-2).

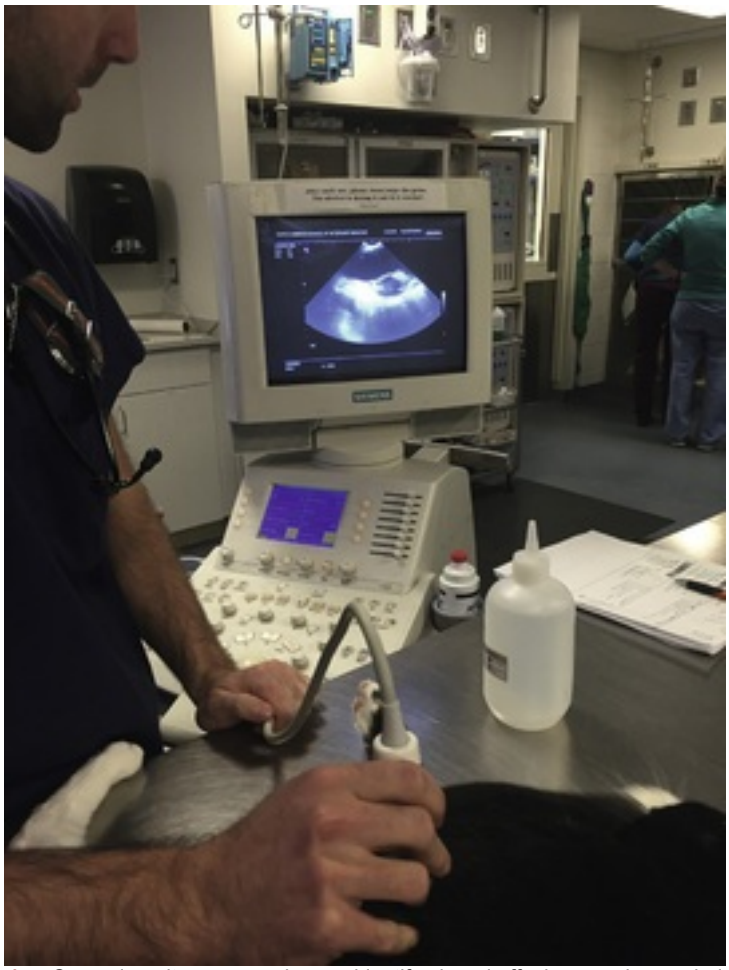

FIGURE 244-1 Screening ultrasonography can identify pleural effusion as a hypoechoic or anechoic space. While advanced ultrasonography skills are needed for specific identification of many diseases, most clinicians can relatively quickly gain the skills required to identify fluid.

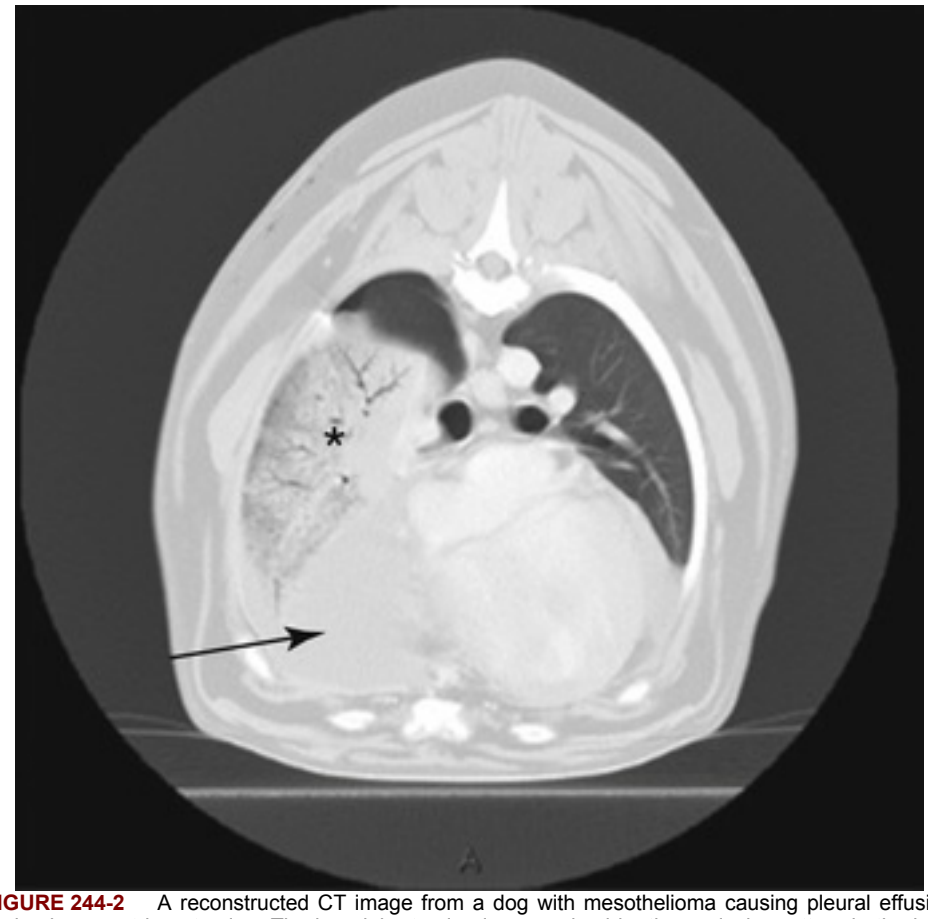

FIGURE 244-2 A reconstructed CT image from a dog with mesothelioma causing pleural effusion and subsequent lung torsion. The lung lobe torsion is recognized by the vesicular pattern in the lobe (asterisk), while fluid is gray (arrow).

Radiographic signs of pleural effusion include decreased detail ("whiteout"), scalloping of the ventral lung borders, fissure lines between lung lobes and an obscured cardiac silhouette. A dorsoventral (DV) radiograph is helpful to confirm the presence of pleural effusion with minimal stress on the patient. If available, horizontal beam radiographs also are very useful.[4] Chronic pleural effusions can result in the radiographic appearance of "rounded" lung margins representing pleural fibrosis. On ultrasonography, pleural effusion is recognized as an echo-free area, appearing black.[5,6]

Thoracocentesis (see ch. 102)

Therapy of pleural space disease is directed at both improving respiratory status by removing fluid/air, and at identifying the underlying cause. Thoracocentesis is performed by clipping and aseptically preparing an area between the seventh and ninth rib near the costochondral junction (Videos 244-2A and 244-2B). Occasionally, the site can be more ventral or more dorsal based on suspicion of fluid or air, respectively. The animal should be gently restrained in a sternal or standing position. Typically, in cats and small dogs, a butterfly catheter, stopcock and 5-30 mL syringe are used. In bigger cats and most dogs, a longer needle is required. In dogs, with an expected large volume (> 1 liter) of effusion, an IV catheter and suction may be used for more rapid removal of effusion, often with less stress for the patient as well as potentially less risk of iatrogenic pneumothorax.

Aseptic technique is recommended, and supplemental oxygen may be provided (see ch. 131). A local block (9 : 1 2% lidocaine: 8.4% bicarbonate) or mild sedation may be considered. Fractious patients, whether resisting due to temperament or respiratory distress, may require heavy sedation or anesthesia (see ch. 138); however, the clinical team should be prepared to intubate and ventilate if necessary, as sedation will reduce respiratory drive. A distinct "pop" is felt upon entering the pleural cavity with the needle tip, although junior clinicians may less commonly appreciate this. Volumes of fluid and air retrieved should be recorded; in general 5-30 mL/kg are required to improve ventilatory mechanics; however, a smaller amount can be useful

for diagnostic purposes. As the mediastinum is typically incomplete, the hemithorax chosen as the site of entry (i.e., right or left side) is less important. As much effusion should be removed as possible. The presence of fibrin or loculated effusion can make thoracocentesis more challenging. If thoracocentesis is unsuccessful, the presence of effusion should be re-confirmed, ideally with ultrasound. If the fluid is present, a longer needle could be required to reach the pleural space or a different location can be attempted.

Complications of thoracocentesis are uncommon but can occur. The most significant complication is iatrogenic pneumothorax, which can occur either from damage to thickened/fibrotic visceral pleural and lung parenchyma or from marked drops in intrathoracic pressure which result in the formation of spontaneous tears in the lung/pleura and subsequent creation of a pulmonary-pleural fistula. Small volume iatrogenic pneumothorax can resolve without treatment, but large or ongoing leaks could require placement of a thoracostomy tube or even surgery. Other potential complications include hemorrhage if a great vessel or the heart inadvertently is punctured, or subcutaneous leakage of infected pleural effusion.

Thoracostomy Tubes (see ch. 100)

Thoracostomy tubes (chest tubes) can be required for the management of pleural effusion or pneumothorax in cases with large volume effusion or air that is recurring quickly, in cases of infectious effusion, or post-operatively. Red rubber catheters may be used as chest tubes, but more commonly, either trocar-style catheters or small-bore catheters (e.g., Mila International) are placed. Continuous suction units may be applied to help with fluid and air removal, and are more commonly used in cases of persistent pneumothorax than in pleural effusion. In pneumothorax, as the rate of air accumulation may be quite rapid, chest tubes may be required in order to facilitate the timely removal of air. In animals with trauma, either an unending pneumothorax or recurrence after thoracocentesis should prompt placement of a thoracostomy tube. As with pleural effusion, a variety of options for tube choice exists. Continuous suction units can be particularly useful for preventing reaccumulation of air, and promoting healing of damaged parenchyma.

Fluid Analysis

Fluid analysis should be performed to help characterize pleural effusions (see ch. 74). The gross appearance of the fluid can be purulent, chylous (milky), hemorrhagic, serous or serosanguineous, or icteric. Most effusions are serous or serosanguineous. Pleural effusion associated with pyothorax can be associated with a foul odor (anaerobic bacteria) as well as appearing grossly purulent (Figure 244-3). Fluid should be characterized as a transudate, modified transudate, or exudate based on the protein level and cell count (Table 244-1). After assessing the gross appearance, protein level and cell counts, the cytologic assessment of the effusion often is very helpful in reaching a final diagnosis. Other cytologic findings include the presence of neoplastic cells (carcinoma, lymphoma), small lymphocytes, neutrophils, bacteria, red blood cells, macrophages and mesothelial cells. In rare cases, other cell types can be appreciated, such as melanoma cells (Figure 244-4). In longstanding effusions, mesothelial cells can assume bizarre cytological appearances, which may make distinction from neoplastic cells more difficult.

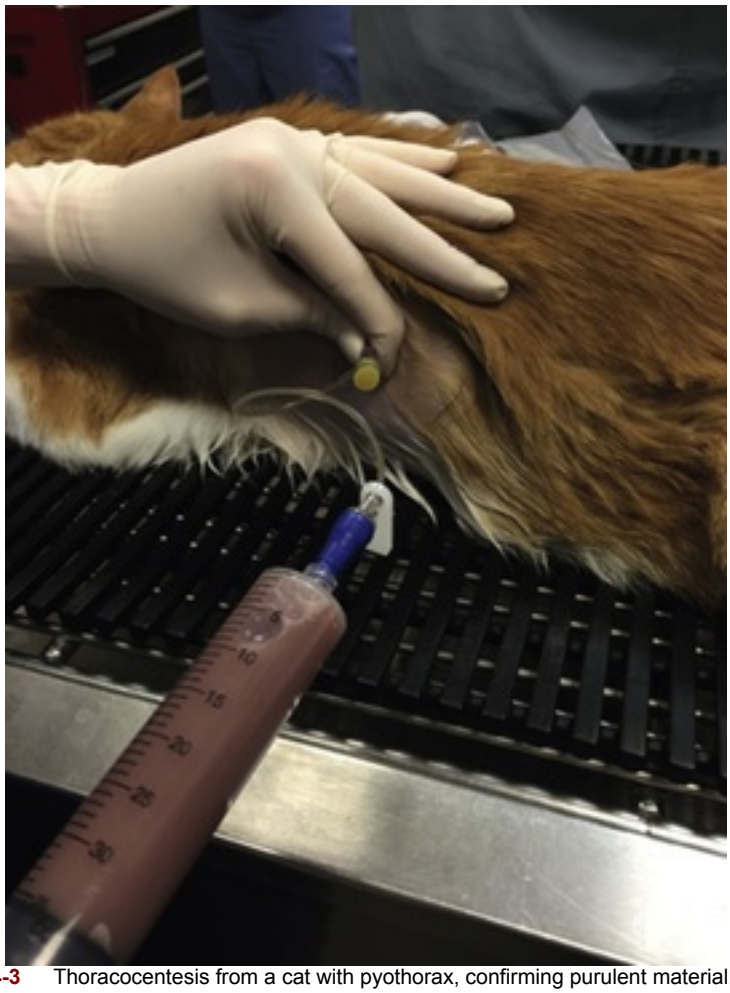

FIGURE 244-3 Thoracocentesis from a cat with pyothorax, confirming purulent material.

TABLE 244-1

Characteristics of Pleural Effusion

	TOTAL PROTEIN	CELLULARITY	CELL TYPES	DISEASE EXAMPLE
Transudate	<2.5 g/dL	<2500 cells/mcL	Nondegenerative neutrophils, macrophages, mesothelial cells	Low albumin (e.g., protein-losing enteropathy)
Modified transudate	2.5-7.0 g/dL	1000-7000 cells/mcL	Nondegenerative neutrophils, macrophages, mesothelial cells, neoplastic cells, lymphocytes	Congestive heart failure (CHF), neoplasia, chyle
Exudate	>7.0 g/dL	>7000 cells/mcL	Varies	Pyothorax

Modified transudates are the most common cause of effusion. The underlying cause of the effusion is the most important predictor of long-term outcome of the pleural effusion patient.

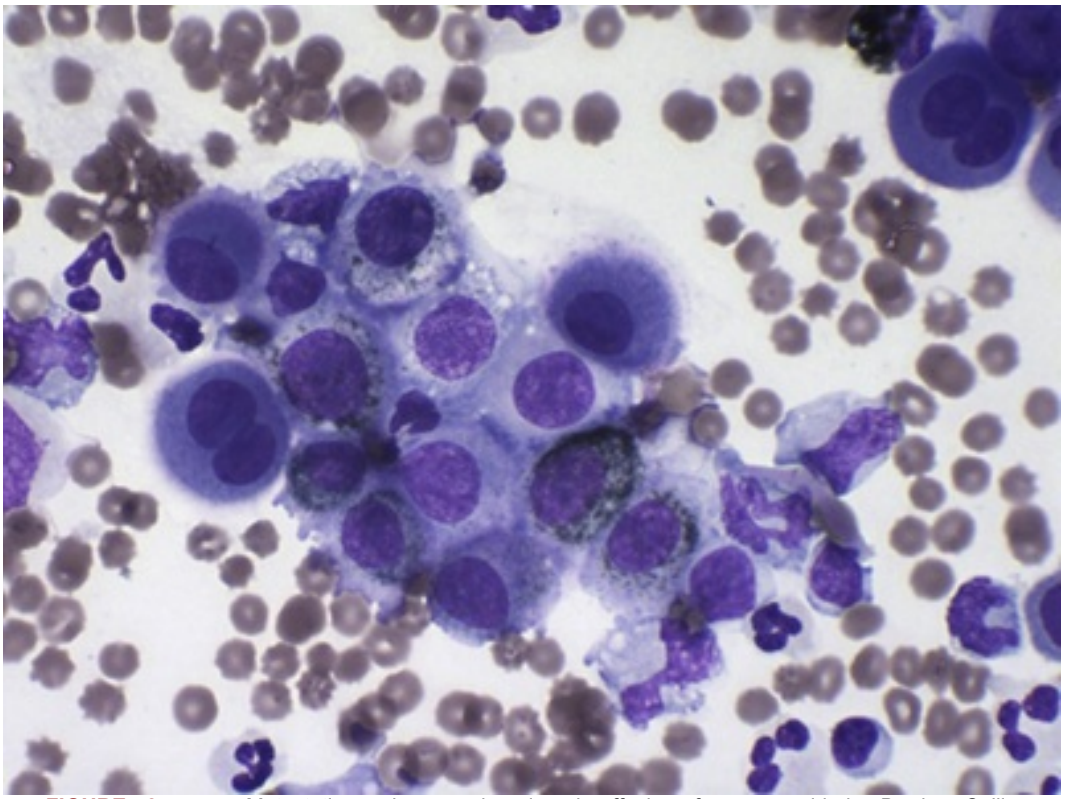

FIGURE 244-4 Metastatic melanoma in pleural effusion from an elderly Border Collie cross. (Photomicrograph courtesy Joyce Knoll, VMD, PhD, DAVCP.)

Biochemical assessment of pleural effusion is useful in some cases. In human medicine, Light's criteria are widely applied to pleural effusion, and recently have been described in cats.[7] Briefly, Light's criteria evaluate the ratio of effusion protein to serum protein, as well as lactate dehydrogenase (LDH) levels; exudates have higher ratios (>0.5) and higher levels of LDH.[8] In people, biochemical analysis of pleural effusion is pursued more commonly than it is in dogs and cats. Biochemical properties of pleural effusion include pH and concentrations of glucose, amylase, creatinine or BUN, cholesterol, triglycerides, and a variety of other substances. In people, pleural fluid amylase concentration has been used for confirming esophageal perforation, for example, but dogs and cats do not produce amylase in their saliva.[9] Biochemical analysis of pleural effusion in dogs and cats has been limited. Lower glucose levels are not as consistently associated with a septic pleural effusion as they are with a septic abdominal effusion.

The NT pro-BNP concentration in pleural effusion is high in cats with congestive heart failure.[10] A pleural fluid NT-proBNP concentration >322.3 pmol/mL was associated with a sensitivity of 100% and a specificity of 94% for differentiating cardiogenic from noncardiogenic pleural effusion in one feline case series.[10] Further studies of biochemical properties of pleural effusion could eventually add useful information to individual case evaluation.

Bacterial culture and sensitivity testing is warranted in cases with suspected infection or with neutrophilic effusions. Recurrent thoracocentesis can predispose a patient to iatrogenic infections. Bacterial culture is most frequently employed for evaluating for aerobic organisms, although pyothorax often is due to anaerobic infections. Anaerobic bacterial cultures can be hard to perform, and limited sensitivity data could be gained. More fastidious organisms might require special culture media and a dedicated microbiological laboratory. Viral infection can result in pleural effusion.[11] PCR testing also is very useful for identification of infectious organisms, and may be pursued, especially for atypical infections.[12]

Further Diagnostic Testing

Other diagnostic testing in patients with pleural effusion should be guided by signalment, physical examination findings, and results of fluid analysis. Routine laboratory testing, including a complete blood count, serum biochemistry profile, and urinalysis are advised to look for systemic disease. Thyroid testing in

cats (see ch. 301), and heartworm testing in endemic areas (see ch. 255) also are recommended.

Thoracic radiographs after removal of pleural effusion often are useful to evaluate for mass lesions, diaphragmatic hernia, or an enlarged cardiac silhouette. Echocardiography is essential to look for evidence of right-sided heart disease or pericardial effusion. Thoracic ultrasound can be useful to identify and biopsy mass lesions and to evaluate the integrity of the diaphragm. Computed tomography also is helpful to evaluate for the underlying cause of effusion.

Exploratory thoracotomy or thoracoscopy may be used to more completely evaluate the thoracic cavity, especially with recurrent or intractable pneumothorax, and to obtain biopsies if indicated.

Types of Effusions (see ch. 74)

Pure Transudate

This type of effusion usually develops in hospitalized pets or in animals with chronic protein-losing conditions. Grossly, the fluid appears similar to water and cellularity is low. Yorkshire Terriers with lymphangiectasia appear particularly likely to develop pleural effusions. Treatment includes thoracocentesis (see ch. 102), possibly colloid support (e.g., plasma, or synthetic colloids; see ch. 129), diuretics, and specific therapy for the underlying condition.

Modified Transudate

These effusions are the most common type observed in dogs and cats. The most common causes include the following diseases.

Congestive Heart Failure (CHF)

Right-sided heart failure can result in substantial accumulations of pleural fluid (see ch. 246 and 247). CHF is a particularly common cause of pleural effusion in cats. Right-sided heart failure can develop in association with chronic valvular diseases, or certain congenital malformations (e.g., tricuspid valve dysplasia). Physical examination typically shows other signs consistent with heart failure, such as abnormal heart sounds, tachycardia, and/or jugular venous distension. Gookin and Atkins described that moderate- to large-volume pleural effusion (≥17-22 mL/kg) will increase central venous pressure (CVP) by a mean of 4.5 cm H_2O (range 0-7 cm H_2O), causing misdiagnosis of pleural effusion as being cardiogenic in a small proportion of cats in one study.[13] Diagnosis of heart failure is based upon echocardiographic demonstration of a cardiac lesion of sufficient severity to be consistent with CHF. Elevations in NT pro-BNP also are supportive of CHF, both in plasma[6,14] and serum.[14] The recent addition of a feline point-of-care SNAP NT pro-BNP test improves the real-time availability of this test (IDEXX Laboratories, Westbrook, ME). Cytologic findings in pleural effusion associated with CHF include mild inflammation, while some animals, particularly cats, have chylous effusion. Treatment of pleural effusion associated with CHF is individualized and ideally is based on an evaluation by a veterinary cardiologist, typically including diuretics, pimobendan, and angiotensin-converting enzyme inhibitors. Medical management is more useful to delay the return of pleural effusion than clearing the effusion; therefore, initial thoracocentesis to remove as much fluid as safely possible is advised (see ch. 102).

Pericardial Disease

Pericardial effusion can result in the development of pleural effusion and ascites due to cardiac tamponade (see ch. 254). Pleural effusion associated with cardiac tamponade commonly will resolve following pericardiocentesis (see ch. 102). The presence of ascites with pericardial effusion suggests a more chronic course, and has been associated with a better prognosis than acute cardiac tamponade without secondary ascites.[14] Constrictive pericarditis also can be associated with the development of pleural effusion.

Malignant

Neoplasia is a common cause of pleural effusion. Some neoplasms exfoliate well (lymphoma, some carcinomas) while in others, cytologic criteria of malignancy are lacking. As stated earlier, longstanding effusions can be associated with reactive mesothelial cells that can be difficult to distinguish from mesothelioma. The lack of cytologic criteria for malignancy does *not* exclude neoplasia from the differential list. Therapy for neoplastic effusions can include periodic thoracocentesis, intracavitary therapy (e.g., cisplatin, bleomycin, carboplatin) or shunting of neoplastic fluid. In animals with pulmonary masses thought

to be associated with a malignant effusion, thoracotomy and resection of the mass rarely will be beneficial, and may be associated with significant morbidity or even mortality.

Exudate

Infectious

Pleural effusions can be infectious in origin. Affected animals often have systemic signs of sepsis (lethargy, fever, leukocytosis or leukopenia; see ch. 132). Cytologic evaluation of infectious effusions demonstrates degenerative neutrophils, and possibly intra- and extracellular bacteria. Infections can be aerobic or anaerobic; anaerobic infections can produce particularly foul-smelling exudates, but precautions must be taken not to expose personnel to infectious agents through inhalation. In cats, bite wounds are considered the most common source of infection, while in dogs, bite wounds and penetrating foreign bodies (sticks/plant awns) frequently are responsible. Occasionally, pleural effusions are identified secondary to bacterial pneumonia (i.e., parapneumonic effusions), but these are quite rare in dogs and cats compared to in people and horses. Other less common infectious causes of pleural effusion include *Bartonella* spp., *Mycobacterium* spp., and viral infections.

Therapy for pyothorax involves drainage (usually via thoracostomy tube; see ch. 100) and antibiotics based on culture and sensitivity. Some animals can require surgical intervention for resection and drainage of affected tissues. The prognosis for pyothorax frequently is good if the pet does not present in a moribund condition. Pyothorax is one of the few pleural effusions that can be cured.

Feline infectious peritonitis (FIP) can cause pleural effusion (see ch. 224). Affected cats usually are young, and usually will have elevated total globulin levels in their plasma and also a high protein level in the pleural effusion (usually >6.0 g/dL). Cytologically, reactive macrophages and neutrophils are present, but in small number. There is no effective therapy for FIP to date.

Hemorrhage

Hemothorax can result from anticoagulant rodenticide intoxication (e.g., brodifacoum; see ch. 152), trauma, lung lobe torsion, or neoplasia.[15] In hemothorax, by definition the hematocrit of pleural effusion is >20%, or is >50% of the patient's peripheral hematocrit. Clinical signs of hemothorax more commonly reflect hypovolemia than the presence of pleural effusion. In dogs with anemia and pleural effusion, it is prudent to check coagulation status prior to thoracocentesis in order to exclude coagulopathy. Therapy of hemothorax is dependent on the underlying cause and can include plasma transfusion, vitamin K therapy, surgery, or rest. Rib tumors can result in hemothorax, with resection required to control hemorrhage. Small-volume traumatic or toxic hemothoraces that are not affecting ventilation and where the underlying cause is controlled may be left alone to resorb.

Chylothorax

Chylous effusion appears milky white or pinkish and, cytologically, it contains high concentrations of small lymphocytes. There are many potential causes of chylous effusion, with idiopathic disease accounting for about 50% of cases. Evaluation of a patient with chylous effusion includes a careful search for an underlying cause, such as cardiac disease, cranial vena caval thrombus or mass, heartworm disease, or neoplasia. Post-surgical chylothorax has been described.[16] Idiopathic chylous effusion is associated with dilation of the lymphatics (lymphangiectasia), but the mechanism remains elusive. Diagnosis is made by identifying a high triglyceride value in the pleural fluid relative to the serum. If a specific cause is found, therapy may be directed against that. In idiopathic effusion, treatment may include periodic thoracentesis (see ch. 102) or surgical intervention. A multitude of different surgical techniques has been proposed to palliate chylous effusion, but no therapy is routinely successful, with cure rate hovering around 50-70%. The best surgical outcome appears to be associated with a meticulous and experienced surgeon.

Idiopathic

In some dogs and cats, despite a concerted effort, no specific cause is identified for pleural effusion. Treatment in this case is directed at ameliorating clinical signs. A search for atypical infections is warranted before initiating any immunosuppressive therapy if immune-mediated disease is suspected.

Miscellaneous

A variety of causes intermittently can be associated with the development of pleural effusion, including lung lobe torsion (see Figure 244-2), pancreatitis, immune-mediated diseases, chronic diaphragmatic hernia, pulmonary thromboembolism, gunshot injuries[17] or recent abdominal or thoracic surgeries. Cats seem particularly predisposed to the postoperative development of pleural effusion.

Chronic Effusions

Chronic pleural effusions may occur secondary to a wide variety of diseases, but are seen most commonly with idiopathic effusions, chylothorax, some congenital heart diseases, and mesothelioma. Survival times with chronic effusions depend on the underlying disease, as well as patient and pet owner characteristics. Some dogs with chronic effusions may be managed for months to years with intermittent thoracocentesis, particularly if their quality of life is otherwise good, there is limited formation of adhesions, and the owner has emotional and financial resources for chronic disease management. Importantly, animals with chronic effusions are much more likely to develop pneumothorax following thoracocentesis, and could develop infected fluid (pyothorax).

Pneumothorax also is a common iatrogenic complication of thoracocentesis in animals with chronic pleural effusion when the effusion results in thickening of the pleura and possibly trapped lung. In this context, pneumothorax can be a devastating complication, as the pleura is unlikely to heal spontaneously. Pleural ports (Figure 244-5) may be placed to permit thoracocentesis without the risk of inadvertent laceration of the pleura.[18] In larger dogs, the size (20 g) of the Huber needle could result in long times required to drain the effusion. Additionally, iatrogenic infections can occur with such a system, particularly if drainage is performed by lay individuals that have not been properly trained. Omentalization also has been described for treatment of chronic effusion.[19]

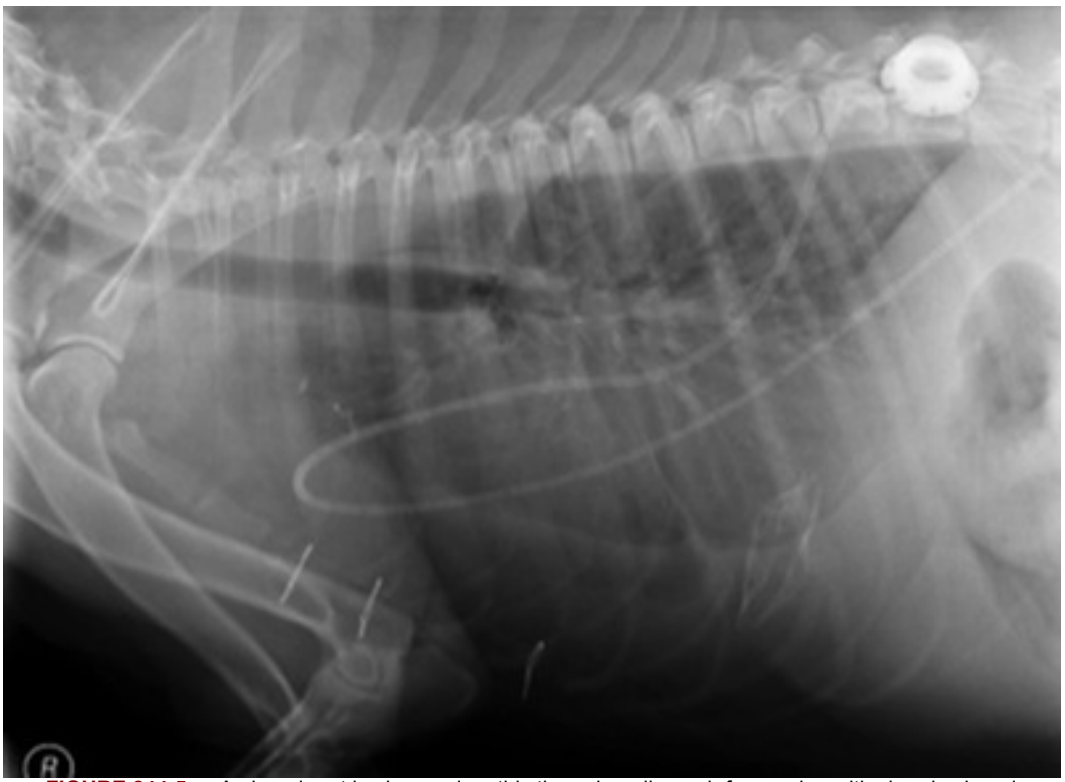

FIGURE 244-5 A pleural port is observed on this thoracic radiograph from a dog with chronic pleural effusion of unclear cause.

Pleural Pressure Measurement

Pleural pressure determinations potentially are useful in the intensive care unit and emergency department, and may be considered as point-of-care evaluations of physiologic responses to critical illness or injury. Pleural manometry often is recommended in people with pleural effusion, and may be performed easily in animals.[20] Pleural pressure may be monitored during thoracocentesis for pleural effusion or pneumothorax, or continuously if a thoracostomy tube is in place.

Pleural manometry was designed to monitor the pleural cavity for signs of non-recruitable lung, as evidenced by large decreases in intrapleural pressures that subsequently could lead to pain or spontaneous pneumothorax. Iatrogenic pneumothorax is of particular interest, as in veterinary medicine, iatrogenic pneumothorax associated with thoracocentesis is most commonly thought to be associated with inadvertent laceration of the lung. The concept of non-recruitable lung is compelling, as larger increases (e.g., more negative) in pleural pressures might be associated with spontaneous pneumothorax as well, via tearing of the visceral pleura in response to markedly negative pressures. A pilot evaluation of pleural manometry in our hospital, performed by Kendra LaFaunci, DVM, showed findings as illustrated below (Figure 244-6). Interestingly, in Cat 2B, iatrogenic pneumothorax developed after thoracocentesis, potentially associated with trapped lung, and substantially negative intrathoracic pressure. Additionally, the use of pleural manometry is also able to identify whether the needle or catheter is still in the pleural space following re-positioning, patient movement, or apparent completion of the procedure, which in animals is perhaps the most useful insight that can be gained.

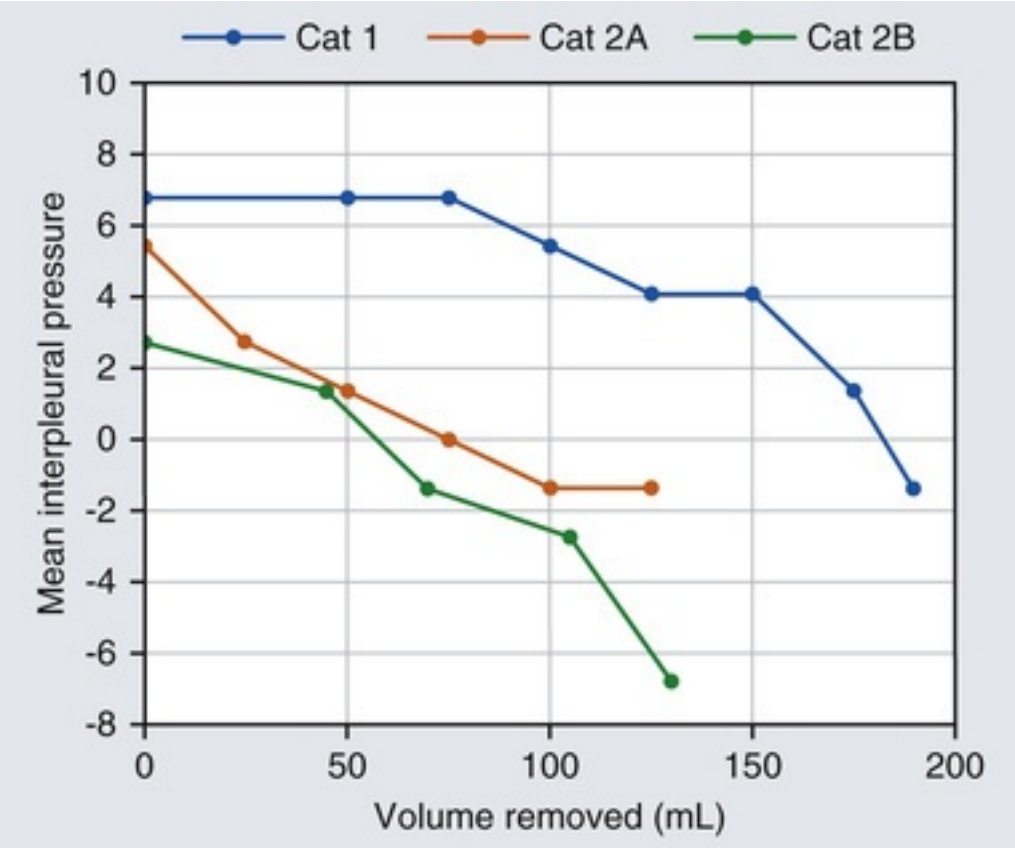

FIGURE 244-6 The graph represents the fall in pleural pressure associated with removal of pleural effusion. The curve for Cat 2B shows pleural pressure readings when thoracocentesis was performed for the second time. A more negative pressure developed in association with the same volume of effusion being removed; this cat subsequently developed pneumothorax, potentially associated with a non-recruitable lung.

Pleural Effusion Summary (Box 244-1)

Pleural effusion is a clinical disorder but not a final diagnosis. Many different conditions can result in the formation of pleural effusion; therapy is more likely to result in their resolution if it is specific to the inciting

cause. Comprehensive diagnostics could be required to reach an answer, and in some cases, the etiology remains elusive.

Box 244-1

Summary of Pleural Effusion

1. Detection of pleural effusion should prompt a thorough search for the underlying cause.
2. Many cases of pleural effusion can be palliated successfully, but true cure is unlikely except with infection, trauma, or intoxication.
3. Iatrogenic air leak can accompany thoracocentesis, particularly in chronic effusions.
4. Cytologic evaluation is warranted with every thoracocentesis, even "repeat offenders."

Pneumothorax

Pneumothorax is defined as free air in the pleural space. It can be characterized as traumatic, spontaneous, or iatrogenic, and as open or closed[21] (Box 244-2). *Tension pneumothorax* is a pneumothorax severe enough to affect cardiac output and, if not promptly evacuated, will result in the death of the patient. A tension pneumothorax can result from any type of pneumothorax, although it almost always is a closed pneumothorax (Figure 244-7).

Box 244-2

Summary of Pneumothorax

1. Pneumothorax can be traumatic, spontaneous, or iatrogenic.
2. Thoracostomy tubes can be required if large volumes of air are accumulating (see ch. 100).
3. Pneumothorax caused by blunt trauma should resolve with supportive care.
4. Pneumothorax caused by penetrating trauma could require surgery to prevent infection and to repair devitalized tissues.
5. Spontaneous pneumothorax in dogs should prompt surgical exploration.
6. Spontaneous pneumothorax in cats should be treated individually.
7. Iatrogenic pneumothorax should be treated on a case-by-case basis.

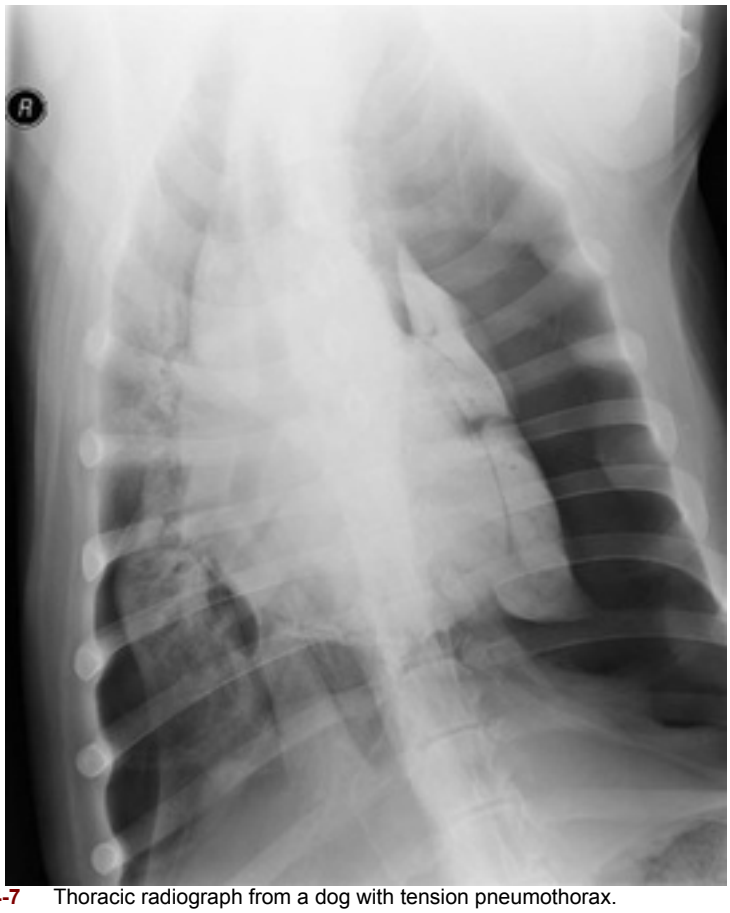

FIGURE 244-7 Thoracic radiograph from a dog with tension pneumothorax.

Traumatic Pneumothorax

Traumatic pneumothorax results from injury to the thorax. It is divided into *open*, where there is an open wound connecting the pleural space and the outside air, and *closed*, where the air leak is occurring from damaged lung tissue. It is suspected that trauma is the most common etiology of pneumothorax in dogs. Traumatic wounds can be blunt (e.g., hit by car) or penetrating (e.g., bite wounds). Treatment of traumatic pneumothorax reflects the severity of clinical signs, with a principal recommendation being to treat the patient, not any radiographic abnormalities.

As animals with traumatic pneumothorax often have pulmonary contusions or rib fractures concurrently, it can be challenging to determine the contribution of pneumothorax to respiratory distress. If in doubt clinically, diagnostic thoracocentesis (see ch. 102) is advised to avoid missing an opportunity to treat a "treatable" condition.

Identification of traumatic pneumothorax may be made through diagnostic thoracocentesis, thoracic radiographs, or ultrasonography. A negative diagnostic thoracocentesis can be truly negative, or might reflect an inadequate length of needle/catheter or pocketing of the air. A thoracic focused assessment with ultrasound (T-FAST) may be used as a point of care diagnostic test for pneumothorax (see ch. 149), but the clinician is advised that it may be more difficult for the less experienced clinician to identify pneumothorax than pleural effusion with ultrasonography.

Treatment of traumatic pneumothorax reflects the severity of the pneumothorax, and the mechanism of the development of pneumothorax (blunt versus penetrating trauma). Most blunt traumatic pneumothoraces will heal rapidly (1-4 days) with supportive care, and rarely require surgery to control air leak. The prognosis for blunt traumatic pneumothorax is good, with the majority of cases requiring only a short hospital stay. It is important to evaluate the patient fully for other wounds, because injuries such as spinal fractures can be present and can impact the patient's healing and the prognosis.

Penetrating thoracic wounds generally are considered worthy of surgical exploration, as bite wounds can bring fur and other debris into the thoracic cavity. Specifically, in bite wounds, the clinician should recall that

the site of the skin puncture wound can be far removed (several centimeters) from the site of penetration into the thorax. In small breed dogs (e.g., Yorkshire Terriers) that are grabbed and shaken by large dogs, it is very uncommon for a bite wound over the thorax to not actually penetrate the thoracic cavity. Small disruptions in the chest wall (rib fractures or intercostal tears) can be visualized as a paradoxical motion of the chest wall or palpated as a divot (see ch. 149). A flail chest, which is defined as the presence of two or more fractures in 2 or more adjacent ribs, also can occur in conjunction with blunt or penetrating trauma. While surgical stabilization may be considered in association with penetrating wounds, in blunt trauma, rest and pain relief should be adequate to permit healing and normalization of lung mechanics.

Spontaneous Pneumothorax

Spontaneous pneumothorax (SP) is a pneumothorax that occurs atraumatically. Spontaneous pneumothorax is termed primary if there is no underlying lung disease, and secondary if it is due to an underlying pulmonary disorder. Spontaneous pneumothorax is more common in dogs than in cats; the rupture of pulmonary blebs or bullae results in primary spontaneous pneumothorax. Large-breed dogs appear to be affected more commonly. Clinical signs reflect a restrictive breathing pattern, and include restlessness, respiratory distress, and tachypnea. Owners of dogs with suspected SP should be queried as if trauma is a possible cause, because SP in dogs is considered a surgical disease, with prompt surgical intervention and resection of affected lung tissue associated with a better outcome, while blunt traumatic pneumothorax typically is treated conservatively.[22] Preoperative diagnostics should include three-view thoracic radiographs, and baseline laboratory testing. Other testing may be performed at the discretion of the managing clinician. When surgical exploration is undertaken, it typically is done via median sternotomy, which permits for exploration of both hemithoraces. In some cases, despite an open surgical approach, it has been difficult to identify the source of the air leak. In such cases, it can be helpful, while exploring the thorax, to intermittently provide positive pressure ventilation (e.g., inflating the lungs to a pressure of 15-20 cm H_2O) while the thorax is filled with sterile saline; this submerges the lungs and allows the surgeon to watch for bubbles that signify air leak. In cats, primary spontaneous pneumothorax is very rare.

Secondary spontaneous pneumothorax develops without trauma but due to pre-existing lung disease. It has been reported in dogs secondary to neoplasia, pulmonary thromboembolism, and rarely to pneumonia. In cats, the most likely cause is thought to be asthma/lower airway disease or heartworm disease. Patients with small volumes of air can be treated conservatively (medically), although large volumes or those associated with a mass lesion should be treated surgically. The prognosis for spontaneous pneumothorax generally is good with treatment, with the exception of neoplastic lesions.

Iatrogenic Pneumothorax

Iatrogenic pneumothorax is pneumothorax created during the treatment of a patient. The most common causes are thoracocentesis of a pet with chronic effusion, or in association with intermittent positive pressure ventilation associated with high inspiratory pressures.

Treatment of iatrogenic pneumothorax can be difficult, as the pre-existing chronic effusion might preclude thoracotomy or increase the risks associated with surgical intervention. Small volumes (5-20 mL) of air removed during thoracocentesis should trigger careful monitoring of the patient, while larger volumes should prompt more urgent interventions. Blood "patching" has been advised for treating an ongoing air leak.[23] The major benefits of blood patching are that it is easy to perform, and that the patient's blood is readily available. Blood patching recently has been described in a population of eight dogs, with overall results that were encouraging.[24] The most common complication of blood patching seen in people is infection, although tension pneumothorax due to blood clotting in the thoracostomy tube also is possible. Typically, 50 mL of whole blood without anticoagulant is collected and placed into the thorax via a thoracostomy tube. Further investigation of blood patching in dogs and cats is ongoing.

Other Pleural Space Diseases

Other diseases also can affect the pleural space and result in respiratory distress. These conditions are covered more completely in other chapters (see ch. 139, 149, 240, 245, and 273). It is wise to consider whether these could be part of the patient's distress. These conditions include thoracic wall masses, diaphragmatic hernia, mediastinal masses, and esophageal masses or foreign bodies. Thoracic wall masses can arise from the ribs, and the most common causes are osteosarcoma, chrondosarcoma, or fibrosarcoma (see ch. 245). These masses

can be associated with severe hemothorax and can be hard to visualize with radiography if large amounts of effusion are present.[15] Surgical resection can be palliative and even curative in low-grade tumors. Computed tomography (Figure 244-8) can be very useful to help elucidate the extent of such masses.

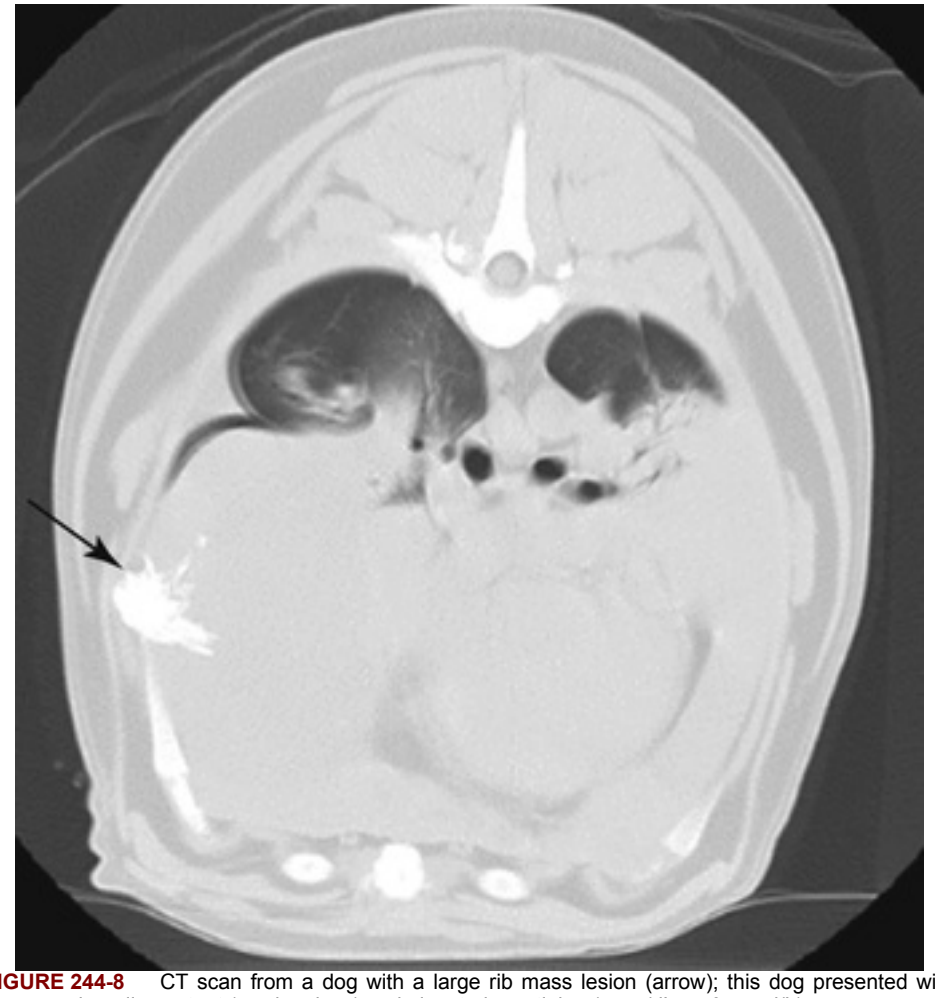

FIGURE 244-8 CT scan from a dog with a large rib mass lesion (arrow); this dog presented with decreased cardiac output (weak pulses) and elevated creatinine (5 mg/dL; 440 mmol/L).

Diaphragmatic hernias (DH; see ch. 245) are most commonly associated with blunt trauma, and may be identified by the loss of the continuity of the diaphragm or by the presence of abdominal contents within the chest cavity. While some DH are easily identified on routine thoracic imaging, in other cases documentation of the lesion can be more challenging. Ultrasound, computed tomography or rarely exploratory surgery may be used to help confirm a diagnosis. Surgical correction should be performed promptly, and on an emergency basis if the patient is unstable or the stomach has herniated into the chest.

Mediastinal masses (see ch. 245 and 344) typically result in respiratory distress through the development of pleural effusion. However, very large masses (e.g., certain thymomas) can result in compression of intrathoracic structures or concurrent myasthenia gravis can result in neuromuscular weakness and subsequent respiratory distress.

Esophageal disease (see ch. 273) usually will result in regurgitation and difficulty swallowing, but in some cases (Figure 244-9), apparent respiratory distress is present. Esophageal perforation may also result in the development of pleural effusion.

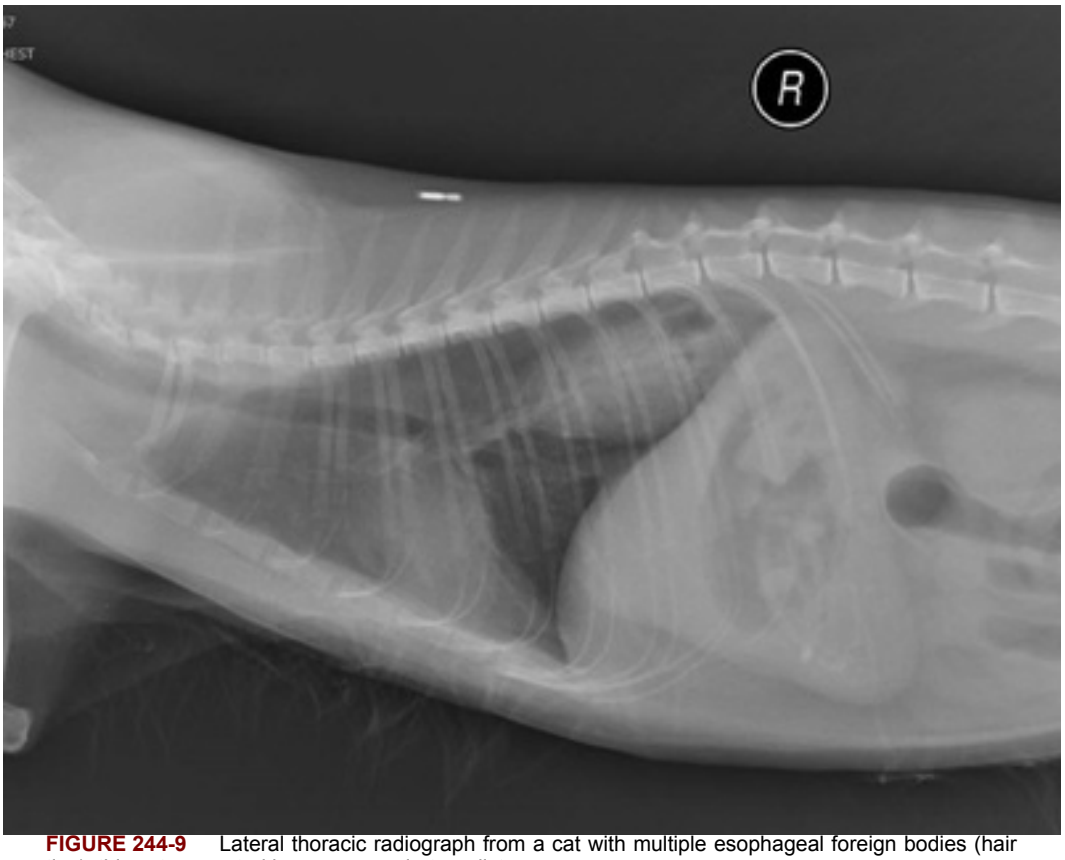

FIGURE 244-9 Lateral thoracic radiograph from a cat with multiple esophageal foreign bodies (hair ties); this cat presented in severe respiratory distress.

Summary

Pleural space disease may be characterized as effusion, pneumothorax, or as a space-occupying lesion. Prompt identification of pleural space disease is vital from a diagnostic standpoint, because an important component of therapy is addressing the underlying cause. Many causes of pleural effusion are associated with chronic disease, and could require long-term management, while pneumothorax can be treated more successfully. Mass lesions can be curable (DH) or could be palliated with appropriate therapy.

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CHAPTER 245

Diseases of the Mediastinum, Chest Wall, and Diaphragm

Martha Moon Larson, David S. Biller

The Mediastinum

Anatomy

The mediastinum is a true space created by pleural reflections, and lies between the right and left pleural cavities.[1,2] It is located primarily on the midline of the thorax, although it deviates slightly to the left to accommodate extension of the right cranial and accessory lung lobes. The mediastinum contains and encloses the heart, trachea, esophagus, thymus, thoracic lymph nodes, thoracic duct, vagus nerves, aorta, cranial and caudal vena cava, and all other vessels that enter or leave the heart. The mediastinal space extends dorsally to the longus coli ventral to the thoracic spine, and ventrally to the sternum, and from thoracic inlet to diaphragm. It is not a closed space, but communicates with the cervical soft tissues via the thoracic inlet, and with the retroperitoneal space via the aortic hiatus. Therefore, disease in any of these compartments can spread and communicate. For example, subcutaneous emphysema in the cervical soft tissues can extend into the mediastinum creating a pneumomediastinum, and from there into the retroperitoneal space. The mediastinum is separate from the pleural space, but mediastinal fenestrations allow pleural air and fluid to communicate between thoracic cavities. The mediastinum is divided into 5 compartments: cranioventral, craniodorsal, middle, caudoventral, and caudodorsal.

Three sets of lymph nodes are located within the mediastinum, but are not typically visualized unless enlarged.[3-5] The cranial mediastinal lymph nodes are located along the cranial vena cava, just ventral to the trachea, and cranial to the heart. They vary in number, and receive afferent lymphatics from the trachea, esophagus, heart, pericardium, and pleura, as well as muscles of the neck, thorax, and abdomen, scapula, last six cervical vertebrae, thoracic vertebrae, ribs, thyroid, thymus, and mediastinum. The tracheobronchial (hilar) lymph nodes are paired, with one pair located inside the bifurcation of the mainstem bronchi (carina), just dorsal to the left atrium. They are located slightly more cranially in the cat compared to the dog. Additional tracheobronchial nodes are located lateral to the carina. These nodes receive afferent lymphatics from the lungs and bronchi. The sternal lymph nodes lie along the ventral aspect of the cranial mediastinum, just dorsal to the second and third sternebrae. The feline sternal lymph nodes are located slightly more caudally on the sternum compared to those of the dog. Sternal lymph nodes receive afferents from the diaphragm, pericardium, ventral thoracic and abdominal walls and peritoneal cavity.

Diagnostic Evaluation

The mediastinum is not easily accessible for clinical evaluation due to its location within the thorax, and there are no blood tests that are specific for mediastinal disease. On physical exam, a large cranial mediastinal mass can be suspected, particularly in cats, if the cranial thorax is noncompliant during gentle compression. Loss of normal breath sounds on auscultation also can suggest a mass lesion; pneumothorax is an important differential diagnosis. Imaging of the mediastinum (radiology, ultrasound [US], computed tomography [CT], magnetic resonance imaging [MRI], or nuclear medicine) is essential for noninvasive evaluation.

Survey Radiography

The mediastinum is seen as a soft tissue opacity only in the cranial thorax, ventral to the trachea. This opacity is created by border effacement of several mediastinal structures, including esophagus, cranial vena cava, left subclavian artery, brachiocephalic trunk, and cranial mediastinal lymph nodes. These structures are seen

individually only when air is present in the mediastinum to act as a negative contrast. On the ventrodorsal (VD) or dorsoventral (DV) view, the mediastinum is superimposed over the spine, and should be no more than twice the spinal thickness, although fat deposits in the mediastinum can cause nonpathologic thickening. Thickening due to fat should result in smooth straight margins. In young animals, the thymus may be visualized as a triangular, sail-shaped soft tissue opaque structure in the cranioventral aspect of the mediastinum, just to the left of midline, and cranial to the heart.

Survey radiography is ideal as the first step for localizing mediastinal disease, and can assess size, shape, opacity, and position of abnormalities. In general, mediastinal lesions include mediastinal shift, pneumomediastinum, and increased size and/or opacity of the mediastinum (mediastinal mass).

A mediastinal shift occurs when there is a decrease in volume of one or more lung lobes on one side. The mediastinum will shift towards the affected side to compensate for the loss of volume. The heart is the largest organ in the mediastinum, and a deviation to one side (on a properly positioned VD or DV view) is indicative of a mediastinal shift. The diaphragm on the affected side also can shift cranially to compensate. Alternatively, the mediastinum shifts towards the normal hemithorax when the opposite side has increased in volume, secondary to a large volume of unilateral pleural effusion, or a very large pulmonary mass.

Increased mediastinal size may be due to a mediastinal mass, esophageal enlargement, or fluid in the mediastinum. These diseases will be manifested radiographically as diffuse or focal enlargement of the mediastinum. Diffuse soft-tissue widening can be caused by the accumulation of fluid secondary to inflammation or hemorrhage. Focal mediastinal widening is usually the result of a mass lesion. Masses in the cranial mediastinum are most common, and if large enough, can result in border effacement of the cranial margin of the heart, elevation of the trachea and caudal displacement of the carina (normally located at the sixth intercostal space) and heart. Cranial widening of the mediastinum on VD/DV views is present. Middle mediastinal masses are most commonly due to enlarged hilar lymph nodes. These create a mass effect at the base of the heart, with ventral deviation of the carina and stem bronchi (lateral view), and lateral deviation of the stem bronchi (DV/VD view). Caudal mediastinal masses may be due to esophageal disease, abscess, granuloma, or tumor.

Ultrasonography

Ultrasound of the thoracic cavity is limited in its efficacy for imaging the normal mediastinum, as air in adjacent lung lobes prevents transmission of the sound waves. However, sonographic evaluation may provide useful information in animals with pleural effusion (which creates a window to the mediastinum) or with cranial mediastinal disease.[6-9] Ultrasonography allows visualization of most cranial mediastinal masses. Placing the transducer in a cranial parasternal position or using the heart as an acoustic window may be necessary for adequate evaluation of smaller masses. Ultrasonography is especially helpful in defining the internal architecture of masses as solid or cystic, and providing localization of vascular structures relative to the mass. Although the ultrasound appearance of a mass is not specific for the exact tissue of origin, it can be used for directing needle placement for fine needle aspirate (FNA) or tissue core biopsy.[10] Transesophageal ultrasonography provides excellent visualization of the heart base, major cranial mediastinal vessels, descending aorta, and part of the azygos vein (see ch. 104).[11-13] This modality eliminates imaging difficulties due to obesity, poor intercostal windows, and lung air interference.

Computed Tomography

Computed tomography of the thorax provides more detailed information regarding presence, location, and extent of disease. It provides better contrast discrimination than survey radiographs do, allowing distinction between solid, fatty, or cystic structures.[14] The cross-sectional imaging format eliminates the issue of superimposed anatomy. The ability to do multiplanar reconstruction is an additional advantage. Contrast enhancement after intravenous administration of an iodinated contrast agent provides added information regarding perfusion of soft tissues and vascular anomalies.[14-19] Especially in the presence of pleural effusion, CT is superior to thoracic radiographs in locating mass lesions to the mediastinum, determining their character (cystic versus solid), and determining extent of disease, including regional vascular invasion. This is critical information for determination of surgical resectability of a mass. Computed tomographic angiography is necessary to more reliably evaluate vascular invasion. To control respiratory motion, general anesthesia is usually necessary for thoracic CT examination.

Further Diagnostic Evaluation

Thyroid scintigraphy using technetium 99m or iodine 131 can be used for identifying ectopic or metastatic functional thyroid tissue within the mediastinum.[20,21]

Diseases of the Mediastinum

Pneumomediastinum

Pneumomediastinum is the abnormal accumulation of air within the mediastinum and it can be caused by a variety of mechanisms.[22-25] Tracheal disruption can leak air into the mediastinum, and has been reported with cervical trauma, mechanical ventilation, transtracheal aspiration, tracheostomy, tracheal intubation and overinflation, or central venous catheter placement (see ch. 241).[23,26] General anesthesia with endotracheal intubation and positive pressure ventilation (possible barotrauma and tracheal rupture), followed by trauma and tracheal foreign bodies, were reported as the most common causes of pneumomediastinum in cats.[25,27] Similar to tracheal trauma, esophageal or pharyngeal rupture can result in pneumomediastinum.[28,29] Subcutaneous emphysema from any location can eventually enter the mediastinum via the cervical soft tissues and thoracic inlet. Lung trauma or overdistension and rupture of alveoli can result in free alveolar air dissecting along the pulmonary interstitium and bronchovascular sheath, into the mediastinal space (Macklin effect).[30] This can occur completely separately from lung trauma that results in pneumothorax. Severe pulmonary lesions or preexisting respiratory disease can lead to bronchial or alveolar rupture with subsequent pneumomediastinum.[31,32] Less commonly, air can enter the mediastinum from gas accumulation in the retroperitoneal space. In some cases, the cause of pneumomediastinum is not determined (spontaneous pneumomediastinum).[24,25]

The presence of air in the mediastinum creates enhanced contrast and detail, allowing radiographic visualization of individual mediastinal structures (best seen on lateral images), including cranial vena cava, brachiocephalic trunk and left subclavian artery, esophagus, and azygos vein (Figure 245-1). Visualization of the tracheal wall is enhanced due to the presence of both intraluminal and extraluminal air. Mediastinal air can communicate with the retroperitoneal space via the aortic hiatus, resulting in secondary pneumoretroperitoneum. Pneumomediastinum does not occur secondary to pneumothorax. However, a severe pneumomediastinum has the potential to cause a secondary pneumothorax.

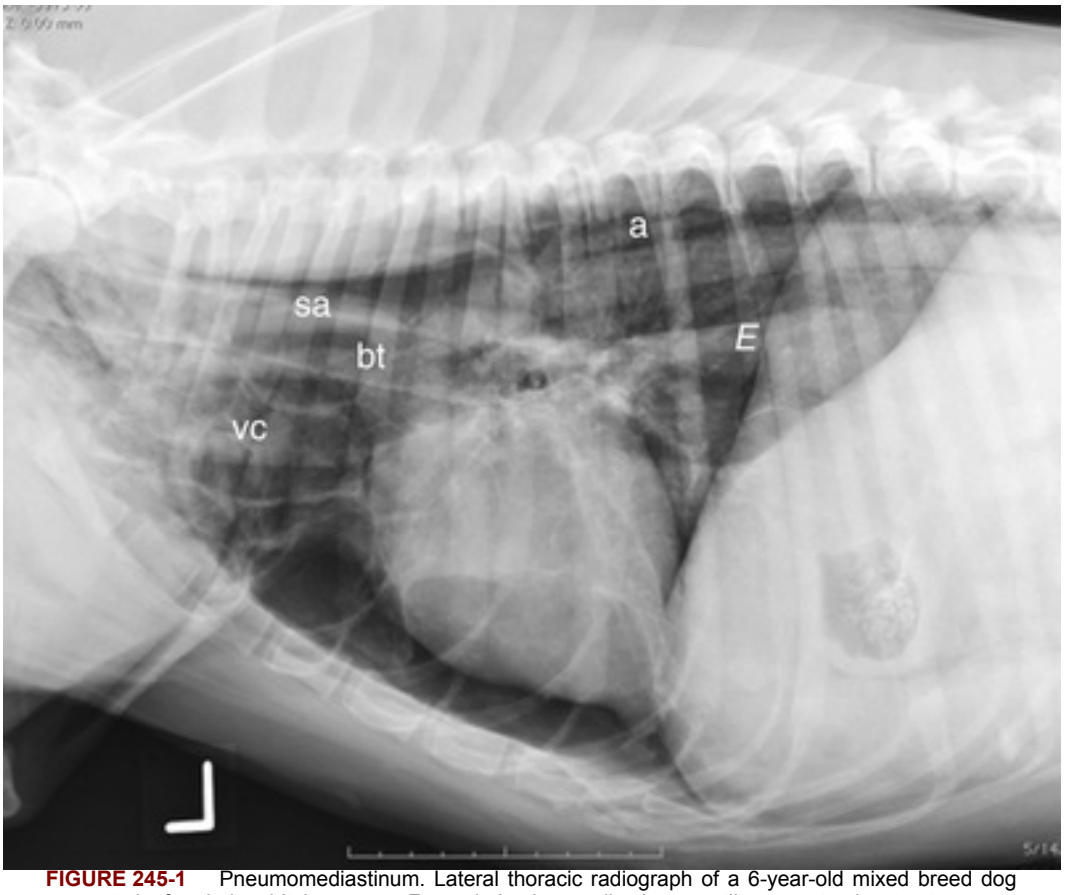

FIGURE 245-1 Pneumomediastinum. Lateral thoracic radiograph of a 6-year-old mixed breed dog presented after being hit by a car. Free air in the mediastinum outlines anatomic structures not normally seen, including cranial vena cava (vc), esophagus (E), inner and outer tracheal walls, brachiocephalic trunk (bt), left subclavian artery (sa), and azygos vein (a).

While pneumomediastinum can create dramatic radiographic changes, respiratory distress typically is absent unless concurrent pleural or pulmonary disease is present. If pneumomediastinum progresses to pneumothorax, tachypnea and dyspnea often are seen (see ch. 244). Animals with pneumomediastinum associated with esophageal rupture present with signs associated with esophageal disease, such as regurgitation, pain, and dysphagia (see ch. 273). The air trapped within the mediastinum does not require treatment and will spontaneously resolve within 2 weeks if there is no ongoing source of air leakage.

Mediastinitis

Clinical signs associated with mediastinitis include tachypnea (likely related to thoracic pain), dyspnea, cough, head and/or neck edema, and regurgitation. Voice changes may occur secondary to recurrent laryngeal nerve involvement. Physical examination may also reveal head and/or neck edema, fever, and decreased lung sounds if pneumothorax or pleural effusion is also present.

Mediastinal inflammation is manifested radiographically as either focal or diffuse widening of the mediastinum. Mediastinal pleural thickening, mediastinal air and fluid, mediastinal lymph node enlargement, and mediastinal mass lesions have been reported with CT.[33,34] These changes may result from esophageal or tracheal perforation, deep cervical soft tissue infections extending along fascial planes into the mediastinum, or extension of infection from the pericardium, pulmonary parenchyma, or pleural space.[35] Migrating intrathoracic grass awns have been reported as a cause of mediastinitis.[33] Chronic granulomatous mediastinitis may be caused by fungal organisms, such as *Histoplasma* or *Cryptococcus* spp., or bacterial organisms, such as *Actinomyces* or *Nocardia* spp.[36,37] Mediastinitis has been documented secondary to spirocercosis in dogs.[38,39] Abscessation of the mediastinum may result from progression of chronic infectious or neoplastic mediastinal disorders.[35] Both mediastinal abscesses and granulomas typically appear on radiographs as mediastinal masses and thus may be mistaken for neoplasia.

Therapy involves resolving the underlying disorder. Esophageal perforation may require surgical repair

and mediastinal masses may require surgical resection and/or drainage, along with appropriate antimicrobial therapy and supportive care.[35,37,39] Mediastinitis without a mass lesion may respond to antimicrobial therapy and supportive care alone.

Mediastinal Hemorrhage

Hemorrhage into the mediastinum usually results from either trauma or coagulopathy.[40-42] The clinical signs associated with mediastinal hemorrhage are related to the effects of acute blood loss. Dyspnea may occur if mediastinal hemorrhage progresses to hemothorax, or if the trachea is compressed by surrounding mediastinal hemorrhage. Radiographic signs include widening of the mediastinum with soft tissue opacity on both lateral and VD/DV views. Tracheal diameter may be narrowed due to compression, or wall thickening may occur due to submucosal hemorrhage (Figure 245-2).[41] Treatment is aimed at resolution of the underlying cause, such as plasma and vitamin K_1 therapy for anticoagulant rodenticide intoxication, along with supportive care (see ch. 152). Mild mediastinal hemorrhage usually does not need specific treatment.

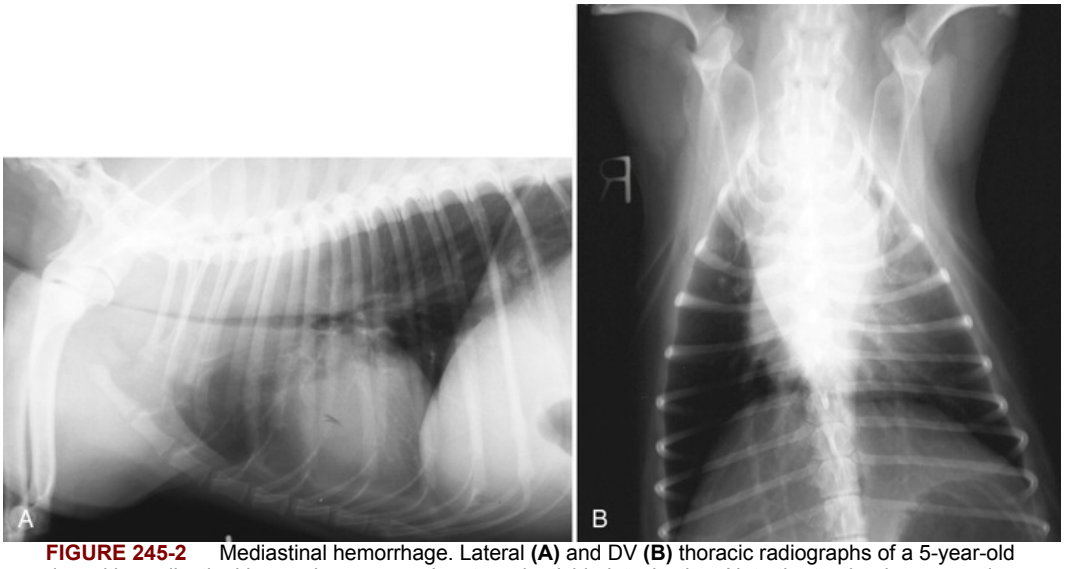

FIGURE 245-2 Mediastinal hemorrhage. Lateral **(A)** and DV **(B)** thoracic radiographs of a 5-year-old dog with mediastinal hemorrhage secondary to rodenticide intoxication. Note the tracheal compression due to surrounding mediastinal hemorrhage (lateral) and widened mediastinum (DV view).

Mediastinal Masses

Mediastinal masses frequently are classified by location (Table 245-1).

TABLE 245-1

Differential Diagnoses for Lesions Associated with Focal Mediastinal Enlargement

REGION	DISEASES
Cranioventral	Lymphadenopathy; abscess; thymic mass; ectopic thyroid; hematoma; granuloma; obesity; vascular mass (aorta, cranial vena cava); esophageal mass, foreign body, or dilatation; tracheal mass
Craniodorsal	Esophageal mass, foreign body, or dilatation; heart base mass; neurogenic tumor; paraspinal or spinal mass; hematoma; lymphadenopathy; aortic stenosis; patent ductus arteriosus; abscess; tracheal mass
Perihilar	Lymphadenopathy; left atrial enlargement; esophageal mass, foreign body, or dilatation; main pulmonary artery mass (poststenotic dilatation); heart base or right atrial mass; spinal or paraspinal mass
Caudodorsal	Esophageal mass, foreign body, or dilatation; hiatal hernia; diaphragmatic hernia or mass; spirocercosis; spinal or paraspinal mass; aortic aneurysm; gastroesophageal intussusception

Caudoventral	Diaphragmatic hernia; peritoneopericardial diaphragmatic hernia; abscess; granuloma; hematoma

Mediastinal Cysts

Benign cranial mediastinal cysts can originate from different anatomic structures (parathyroid cyst, thyroglossal cyst, thymic branchial cyst, and pleural cyst), and are identified most commonly in older cats.[43,44] Radiographically, they appear as focal soft-tissue masses located in the cranioventral mediastinum, often more caudal than other mediastinal masses (Figure 245-3). Ultrasound or CT can be used to demonstrate the fluid contents, and differentiate from solid mass lesions. On ultrasound exam, mediastinal cysts are ovoid/bilobed, thin-walled, contain anechoic fluid, and usually are accompanied by distal enhancement. Solid neoplasms, abscesses, or granulomas may have cystic components and must be differentiated from a simple cyst. Fine needle aspiration with ultrasound guidance is the diagnostic test of choice. Aspirated fluid is typically clear, colorless, and minimally cellular. Mediastinal cysts often are incidental findings that produce no clinical signs unless they are large enough to compress adjacent structures such as the trachea.

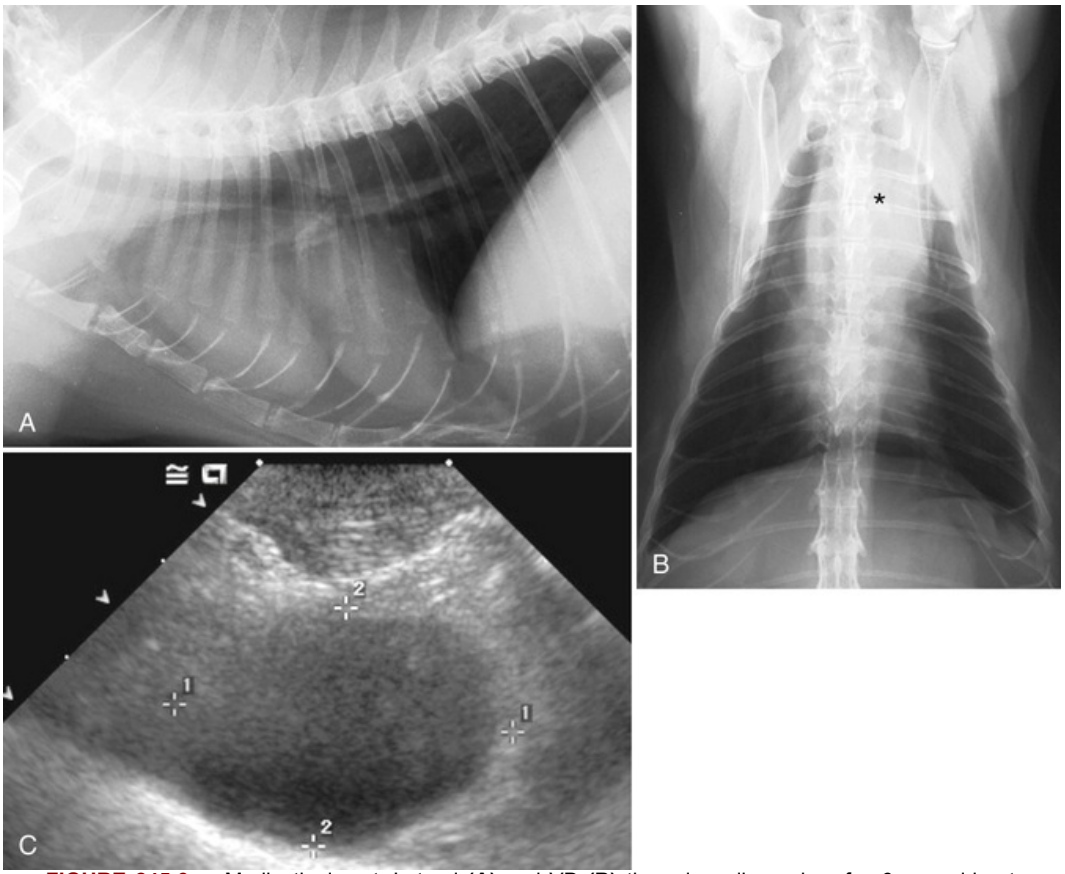

FIGURE 245-3 Mediastinal cyst. Lateral **(A)** and VD **(B)** thoracic radiographs of a 6-year-old cat presented for evaluation of vomiting. A well-marginated, soft-tissue mass is present in the cranial mediastinum just cranial to the heart. The mediastinum is widened on the VD view (*). **C,** Ultrasound image of the cranial mediastinal mass of the same cat. The mass is anechoic and fluid-filled, consistent with a benign mediastinal cyst.

Mediastinal Lymphadenopathy

Mediastinal lymph node enlargement is caused by a variety of diseases. Hilar (tracheobronchial) lymph nodes enlarge most commonly secondary to lymphoma or fungal pneumonia (histoplasmosis, blastomycosis, coccidioidomycosis)[45] (Figure 245-4). Additional causes include histiocytic sarcoma complex, metastatic adenocarcinoma (hepatocellular, anal sac, pancreatic), mycobacterial infections, eosinophilic bronchopneumopathy, eosinophilic pulmonary granulomatosis, and lymphomatoid granulomatosis.[45-55]

There does not appear to be a correlation between the size of the tracheobronchial lymph nodes and the type of disease. Cranial mediastinal lymph nodes receive afferents from the head/neck (see Anatomy section, above), and may enlarge with diseases of these areas. Lymphoma likely is the most common cause of visible enlargement. Sternal lymphadenopathy can be identified early on radiographs, as these nodes are relatively isolated from other soft tissue structures, making enlargement more readily visible. Since these nodes receive afferent drainage from the peritoneal cavity, enlargement should prompt investigation of abdominal disease.

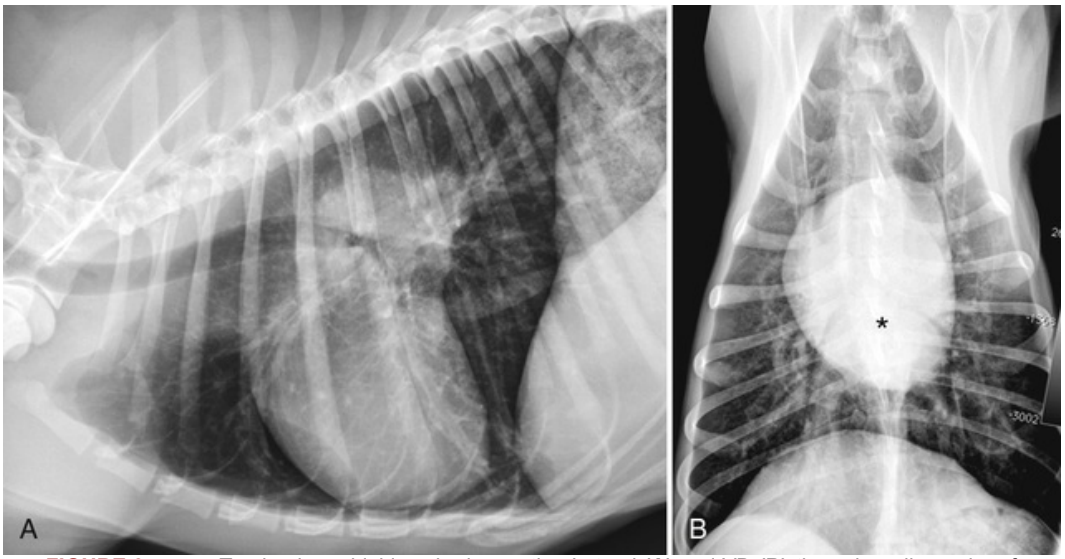

FIGURE 245-4 Tracheobronchial lymphadenopathy. Lateral **(A)** and VD **(B)** thoracic radiographs of a 3-year-old dog presented for coughing. The tracheobronchial lymph nodes are enlarged, and create a mass effect just dorsal to the carina resulting in ventral deviation of the caudal stem bronchi (lateral view). On the VD view, the enlarged tracheobronchial nodes (*) create an increased opacity over the base of the heart, and cause lateral deviation of the caudal stem bronchi.

Mediastinal Neoplasia

Mediastinal tumors can originate from any structure in the mediastinum (lymph nodes, thymus, great vessels, trachea, esophagus, or ectopic thyroid or parathyroid tissue) or from extension of neoplastic lesions in adjacent tissues.[56-59] Mediastinal neoplasms may also be metastatic lesions or components of a multicentric neoplastic process.[59-61] Benign tumors have been documented.[62]

Clinical signs associated with mediastinal tumors are usually caused by compression or invasion of structures such as the great vessels, thoracic duct, esophagus, and trachea, or due to associated pleural effusion. Signs include coughing, dyspnea, dysphagia, regurgitation, and edema of the head, neck, and/or forelimbs. Signs caused by peripheral nerve entrapment are less common and include laryngeal paralysis, vocalization changes, or Horner's syndrome. Signs associated with multicentric disease may reflect other sites of neoplastic involvement or may be related to paraneoplastic syndromes. These signs include anorexia, weight loss, regurgitation, vomiting, diarrhea, and polyuria/polydipsia.

Mediastinal lymphoma originates from either lymph node or thymic tissue in the cranial mediastinum (Figure 245-5 and Video 245-1), and is more common in the cat than the dog.[56,58] It typically occurs in younger cats (2-4 years of age), and they are often feline leukemia virus-positive.[56,58,61] Mediastinal lymphoma is often associated with pleural effusion, which may obscure radiographic visualization of the mediastinal mass. The diagnosis of mediastinal lymphoma can usually be confirmed by cytologic identification of neoplastic lymphocytes in either a sample of pleural fluid or a sample obtained directly from the mediastinal mass via fine needle aspiration (see ch. 74). In dogs, mediastinal lymphoma may be associated with hypercalcemia.[62,63]

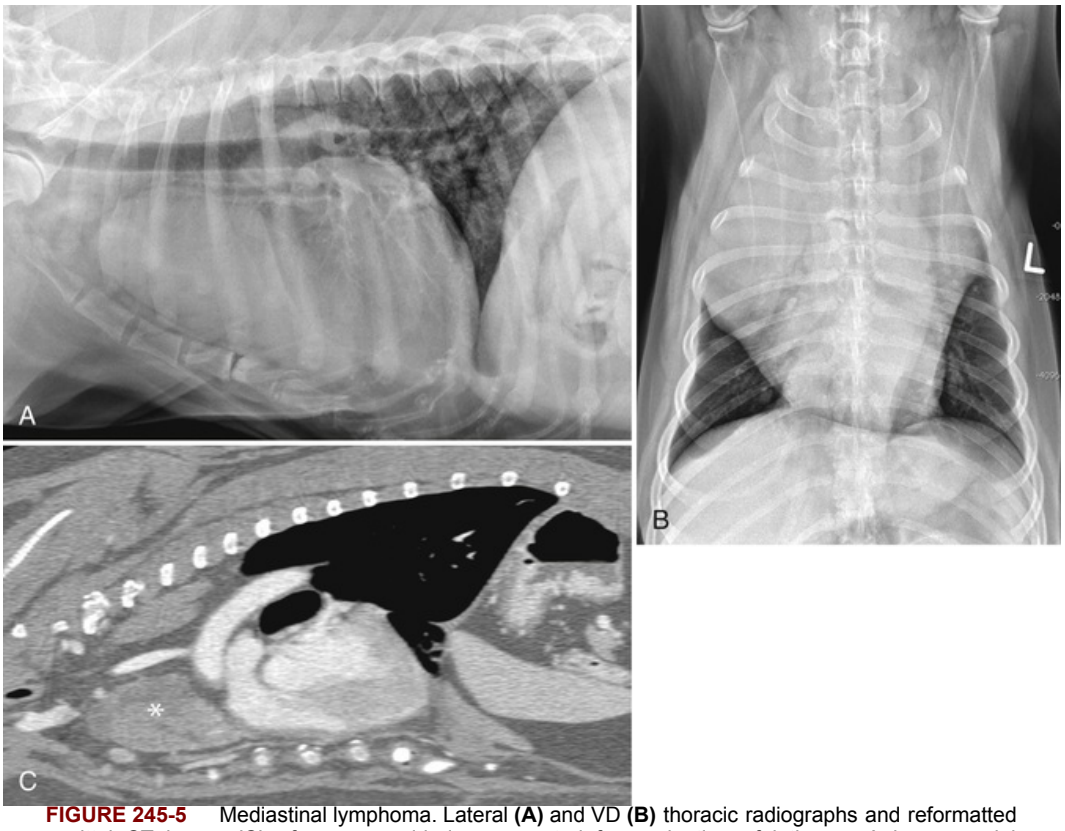

FIGURE 245-5 Mediastinal lymphoma. Lateral **(A)** and VD **(B)** thoracic radiographs and reformatted sagittal CT image **(C)** of a 7-year-old dog presented for evaluation of lethargy. A large cranial mediastinal mass is present. On the lateral view, the trachea is dorsally displaced, and there is border effacement with the cranial margin of the heart. On the VD view, the mass is centralized and cranial to the heart, but extends bilaterally. The CT image shows the cranial mediastinal mass (*). Lymphoma was diagnosed using ultrasound-guided fine needle aspiration, and it was subsequently removed surgically.

Chemodectomas, which are usually aortic or carotid body tumors, are most often identified as heart base masses (see ch. 254) (Figure 245-6).

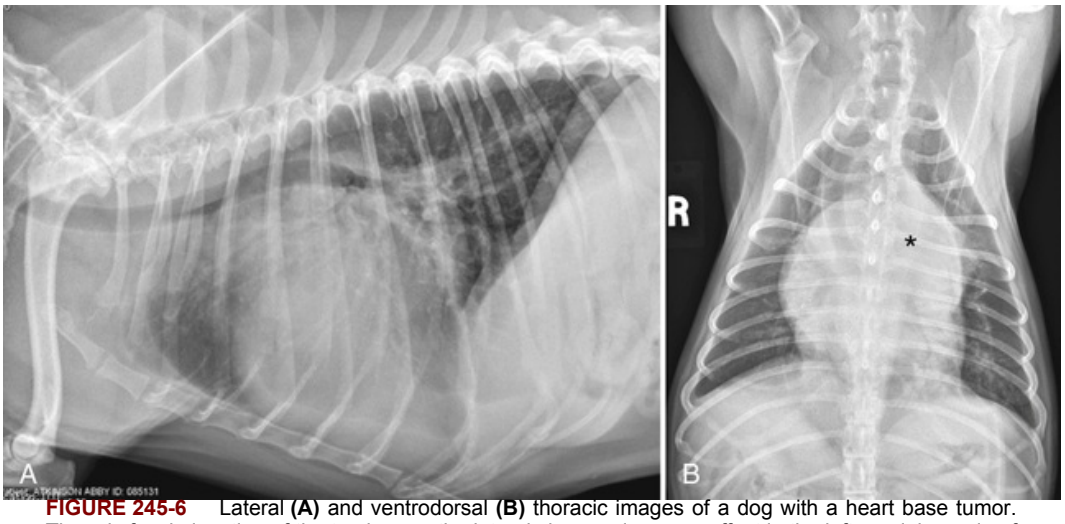

FIGURE 245-6 Lateral **(A)** and ventrodorsal **(B)** thoracic images of a dog with a heart base tumor. There is focal elevation of the trachea on the lateral view, and a mass effect in the left cranial margin of the heart on the VD view (*).

Other less common neoplastic mediastinal masses include ectopic thyroid carcinoma, neuroendocrine carcinoma, and anaplastic carcinoma.[59] The tumor type of a mediastinal mass cannot be determined on

radiographic signs alone. However, it is critical to identify this information, as the recommended treatment for cranial mediastinal tumors other than lymphoma is surgical resection. Computed tomography is invaluable in aiding in a more detailed evaluation of mass location, morphology, involvement with adjacent vessels, and identification of pulmonary metastasis.[64]

Diseases of the Thymus

The thymus extends from the thoracic inlet caudally to the fifth rib in the dog and the sixth rib in the cat. Dorsally, it lies next to the phrenic nerves and cranial lung lobes. Thymic involution in small animals occurs concurrently with the onset of sexual maturity and the loss of deciduous teeth.[65] The thymus atrophies and is gradually replaced by connective tissue and fat, but remnants persist into old age.[65]

Thymic Hemorrhage

An uncommon disease consisting of spontaneous thymic hemorrhage has been described in dogs and one cat.[56,66,67] Although not uniformly fatal, most animals documented with this syndrome have died. Most affected animals are <2 years of age; thus, it appears to be associated with thymic involution. Clinical signs include lethargy, signs of thoracic pain, increased respiratory effort, and dyspnea. Physical examination findings are attributable to acute blood loss/hypovolemia and pleural effusion. Signs include pale mucous membranes, prolonged capillary refill time, tachycardia, tachypnea, and muffled lung sounds. Thoracic radiographs demonstrate a mediastinal mass (hemorrhage, hematoma) usually associated with pleural effusion. Treatment is supportive and involves intravascular volume support (see ch. 129), blood replacement (see ch. 130), and thoracocentesis as needed (see ch. 102).

Thymoma

Thymomas are well-recognized but uncommon tumors in the dog and cat. Thymomas arise from the epithelial cells of the thymus, and can be benign or malignant.[56,57,61,68-71] This assessment appears to be based on invasiveness and resectability rather than histopathologic characteristics.[57] Malignancy is associated with invasiveness, vascular infiltration, and local or distant metastasis. Radiographically, a thymoma appears as a soft-tissue opacity in the cranioventral, or occasionally craniolateral aspect of the thorax (within the mediastinum). Tracheal deviation or compression, pleural effusion, or in some cases, megaesophagus and evidence of aspiration pneumonia, can be seen. Sonographically, thymomas can appear as solid, cystic, or both. Cytologic examination of FNA samples reveals a variable number of mature lymphocytes, which makes cytologic differentiation of thymoma from mediastinal lymphoma difficult. Mast cells also are frequently identified in cytologic samples from thymomas. Surgical or ultrasound-guided percutaneous biopsy is required for a definitive diagnosis. Paraneoplastic syndromes are common with thymoma in both dogs and cats,[68,72] notably myasthenia gravis (see ch. 269), which is often associated with megaesophagus (see ch. 273) in dogs with thymoma (Figure 245-7).[68] Also see ch. 352. Surgical resection is the treatment of choice for thymoma, but recurrence and metastasis have been reported.

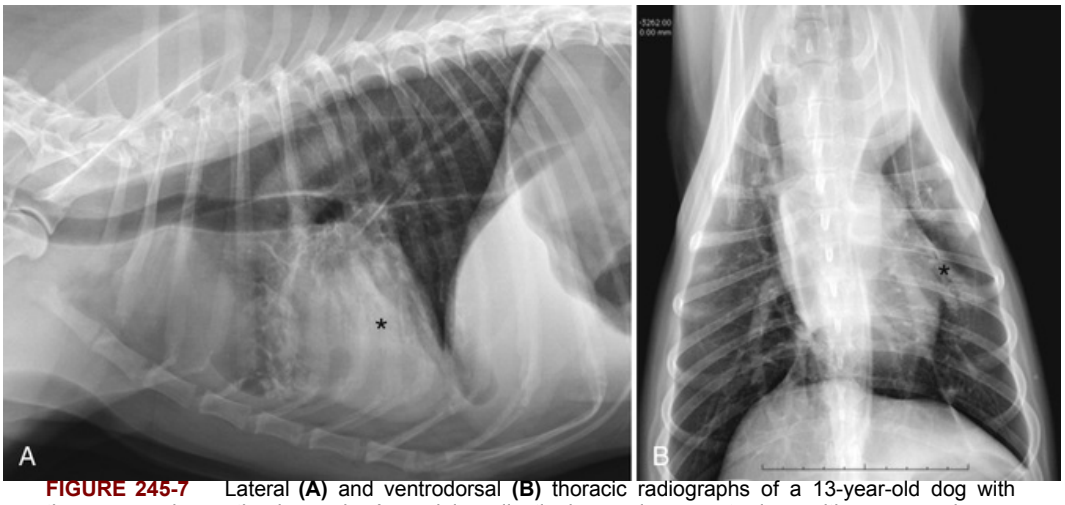

FIGURE 245-7 Lateral **(A)** and ventrodorsal **(B)** thoracic radiographs of a 13-year-old dog with thymoma and myasthenia gravis. A cranial mediastinal mass is present, along with megaesophagus. An alveolar lung pattern consistent with aspiration pneumonia is noted in the cranial subsegment of the left cranial lung lobe (*).

The Chest Wall and Diaphragm

Anatomy of the Chest Wall

The sternum and ribs surround and protect the thorax laterally and ventrally. Thirteen pairs of ribs and 8 sternebrae are normal. However, congenital abnormalities in numbers are common, and typically of no clinical significance. The last set of ribs (13th) may be smaller than normal, or even absent. Sternebrae may be fused or decreased in number. Lesions involving these structures are best evaluated on radiographs or CT scans of the thorax.

Diseases of the Ribs

Rib fractures commonly are associated with trauma, and should be carefully assessed on thoracic images taken after a traumatic incident. Flail chest occurs when at least 2 consecutive ribs are fractured both dorsally and ventrally, resulting in an independent wall segment. This segment demonstrates paradoxical movement with respiration, moving inward with inspiration, and outward with expiration. Mechanical failure secondary to chronic respiratory distress/coughing can result in nontraumatic rib fractures in cats with chronic airway disease.[73,74] These are usually the more caudal ribs (9-13), and involve the midportion.

Tumors involving the ribs, most commonly osteosarcoma and chondrosarcoma, can create an extrapleural mass lesion (a broad-based mass arising peripheral to the parietal pleura, creating a convex margin facing the lungs) and may result in a secondary pleural effusion (Figure 245-8). The ribs should be evaluated with care in patients with pleural effusion of unknown etiology. Computed tomography is an excellent imaging modality for a more detailed evaluation of the ribs and pleural space in these cases.

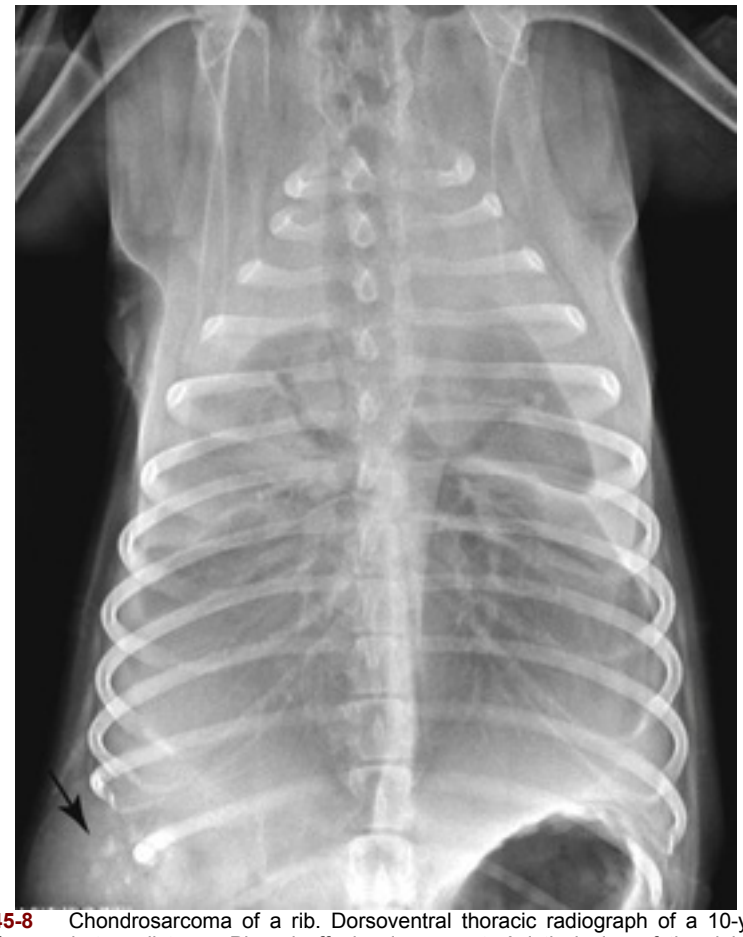

FIGURE 245-8 Chondrosarcoma of a rib. Dorsoventral thoracic radiograph of a 10-year-old dog presented for respiratory distress. Pleural effusion is present. A lytic lesion of the right 12th rib is present (arrow). Chondrosarcoma was diagnosed.

Diseases of the Sternum

Pectus excavatum is a deformity of the sternum and associated costal cartilages characterized by dorsal deviation of the sternebrae (usually the caudal sternebrae) and a dorsal to ventral compression of the thorax (Figure 245-9).[75-78] This is most often a congenital defect, but acquired pectus excavatum has been described secondary to chronic upper airway resistance, with increased inspiratory effort.[75] Clinical signs are dependent on the severity of the deformity, and are secondary to compression of the heart and lungs. While some patients have no clinical signs, others exhibit exercise intolerance, tachypnea, cyanosis, respiratory distress, and cardiac murmur. The murmur may be functional, secondary to cardiac malposition, or may be due to congenital heart defect concurrent with the pectus excavatum. Clinical signs can be progressive, and in some cases, life-threatening. A mild to severe dorsal deviation of the caudal sternebrae with deviation of the cardiac silhouette are the most common radiographic changes. Treatment is dependent on the severity of the deformity and associated signs, and ranges from conservative management to surgical repair.

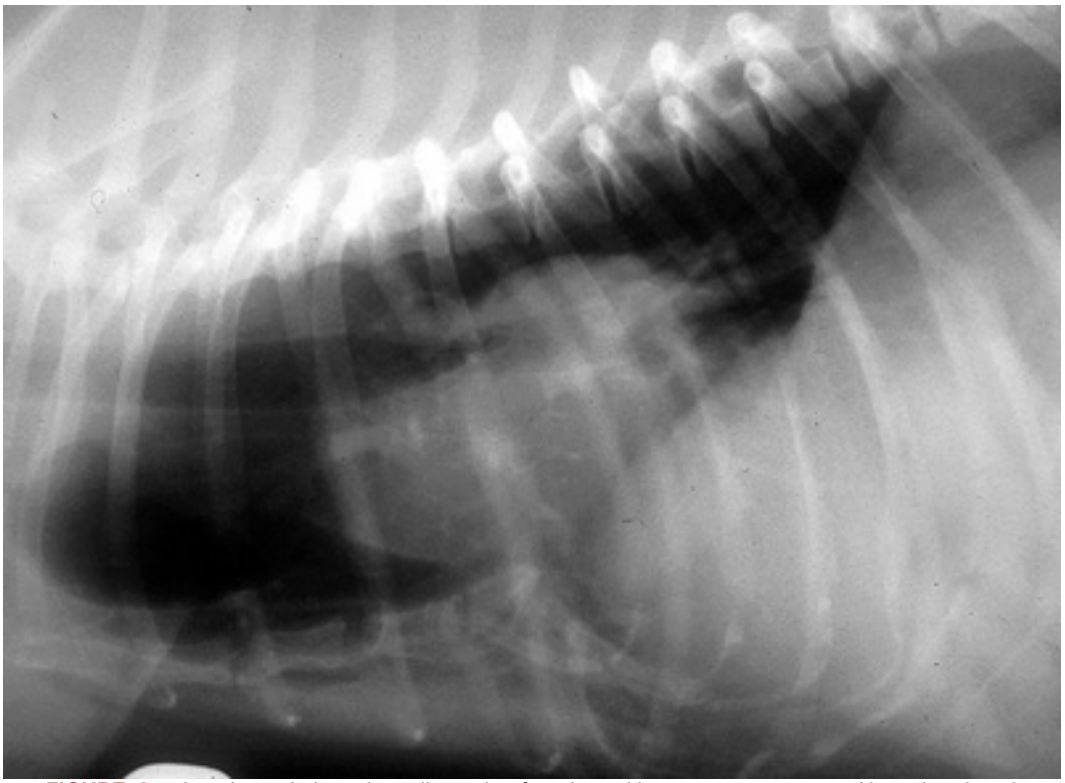

FIGURE 245-9 Lateral thoracic radiograph of a dog with pectus excavatum. Note the dorsal deviation of the caudal aspect of the sternum.

Diaphragm

Anatomy

The diaphragm is the musculotendinous partition between the thoracic and abdominal cavities.[79] The muscular portion is composed of the pars lumbalis, attaching to the ventral aspect of the third and fourth lumbar vertebrae (forming the left and right crura), the pars costalis, which attaches to ribs 8-13, and the pars sternalis, attaching to the xiphoid cartilage of the sternum.

Diaphragmatic Hernia (Traumatic)

The most common disease of the diaphragm is traumatic rupture, often secondary to vehicular trauma or falls. With rupture, varying amounts of abdominal viscera become displaced cranial to the diaphragm; the most frequently herniated organ in the cat is the liver, followed by small intestine, stomach, omentum, spleen, pancreas, and large intestine.[80] A similar order of organ herniation is present in reports in the dog (liver, small bowel, stomach, spleen, omentum).[81,82] Clinical signs of acute diaphragmatic hernia most often are related to respiratory compromise, and include dyspnea, coughing, exercise intolerance, or lethargy. On thoracic radiographs, herniated organs may be visualized cranial to the diaphragm, especially if gas-filled, such as the stomach or intestines (Figure 245-10). The displaced liver or spleen (solid organs) may be difficult to differentiate from pleural effusion or pulmonary consolidation. Cranial displacement of abdominal organs, or absence of visualization in their normal location, may be noted. Occasionally, the herniated viscera have a focal appearance, mimicking a pulmonary mass.[83] Pleural effusion often is present, especially with chronic diaphragmatic hernias.[82] Not all diaphragmatic hernias are recognized immediately, likely due to minimal clinical signs, poorly defined radiographic changes, or lack of awareness of a traumatic incident. Clinical signs of chronic hernias may be nonspecific, and include anorexia, lethargy, vomiting, or weight loss. Not all patients have respiratory signs. Ultrasound and CT are beneficial as adjunct imaging modalities for the detection of abdominal viscera cranial to the diaphragm, especially when pleural effusion obscures visualization on thoracic radiographs.

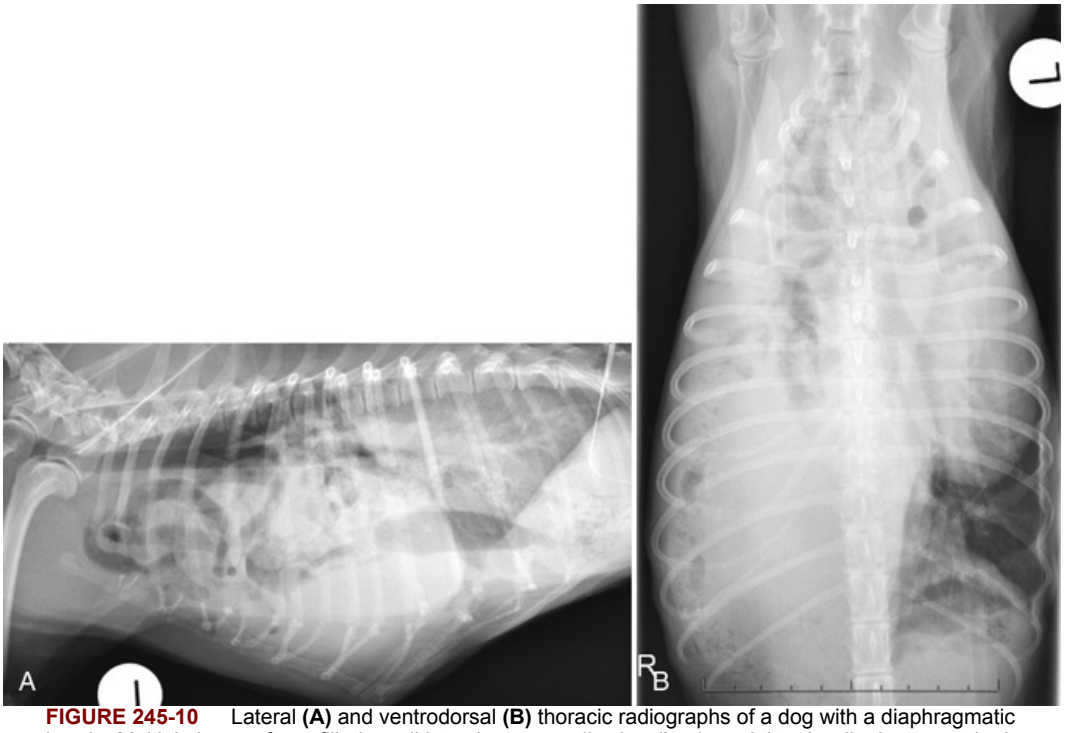

FIGURE 245-10 Lateral **(A)** and ventrodorsal **(B)** thoracic radiographs of a dog with a diaphragmatic hernia. Multiple loops of gas-filled small intestine are easily visualized cranial to the diaphragm on both views. The liver was also herniated.

Peritoneopericardial Diaphragmatic Hernia

Peritoneopericardial diaphragmatic hernia (PPDH) is discussed with pericardial diseases, ch. 254.

Hiatal Hernia

Hiatal hernias (Figure 245-11) are discussed with disorders of the esophagus, ch. 273.

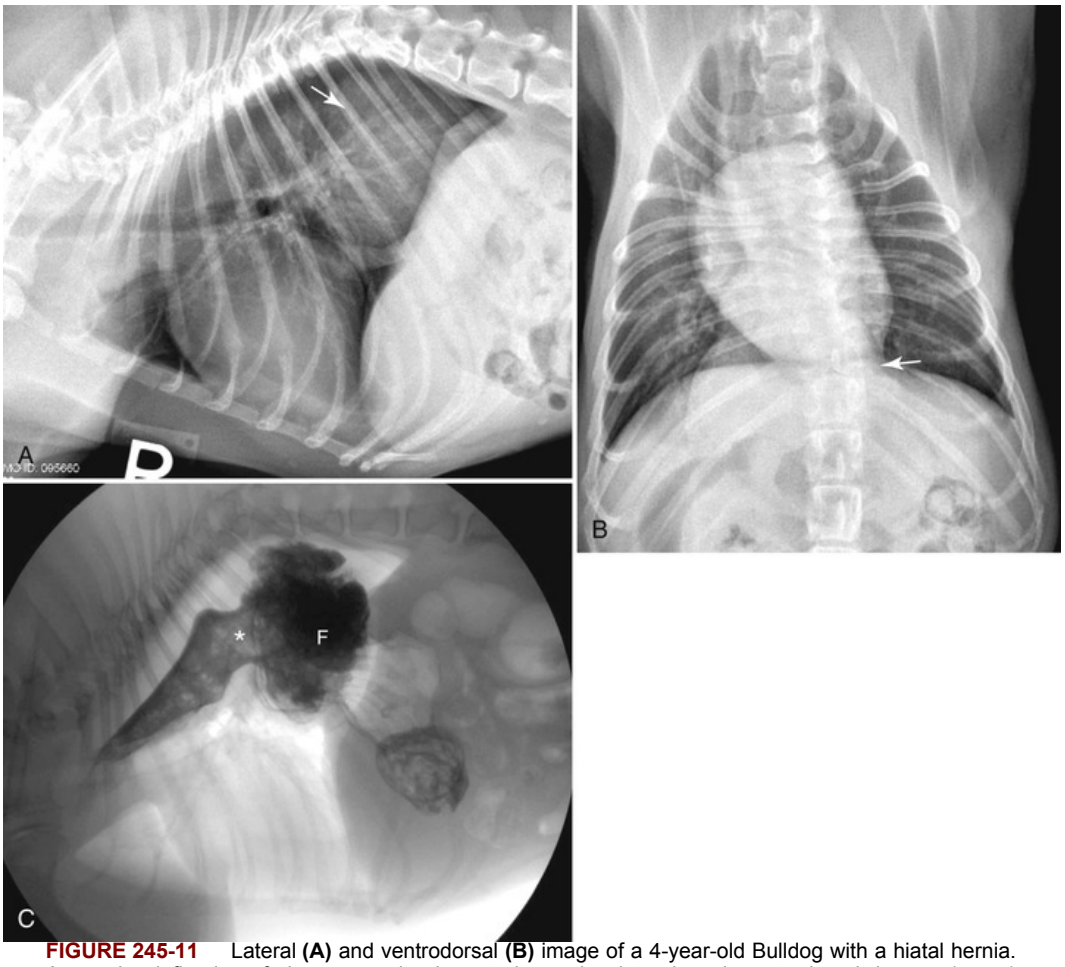

FIGURE 245-11 Lateral **(A)** and ventrodorsal **(B)** image of a 4-year-old Bulldog with a hiatal hernia. A poorly defined, soft-tissue opacity is noted on the lateral and ventrodorsal image (arrow) representing the hernia. A lateral fluoroscopic image **(C)** taken after barium contrast administration shows the cranial displacement of the gastroesophageal junction (*) and fundic portion of the stomach (F).

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SECTION XVI

Cardiovascular Disease

OUTLINE

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CHAPTER 246

Pathophysiology of Heart Failure

Katherine F. Scollan, D. David Sisson

The heart has two fundamental mechanical functions that are essential for operation of the circulatory system. One is to eject enough blood into the aorta and pulmonary arteries with sufficient force to meet the perfusion requirements of the metabolizing tissues. The other essential function of the heart is to receive blood from the pulmonary and systemic veins in a manner that provides adequate drainage of the pulmonary and systemic capillary beds and maintains an appropriate distribution of the circulating blood pool. Mean arterial pressure in the systemic arterial tree approximates 90 to 100 mm Hg in healthy dogs and cats, ensuring adequate distribution of blood through the multitude of vascular beds in this high-resistance circuit. Mean arterial pressure in the low-resistance pulmonary circuit averages around 20 mm Hg.

Cardiac failure can be defined as the pathophysiologic state wherein the heart is impaired in its ability to eject or receive blood, and this impairment becomes severe enough to overwhelm the compensatory mechanisms of the cardiovascular system.[1] Heart disease is defined as the presence of any cardiac finding outside the accepted limits of normality, including a cardiac murmur, abnormal cardiac rhythm on electrocardiogram (ECG), or reduced contractility noted on echocardiogram. The presence of identifiable heart disease does not inherently imply that heart failure is currently present or will ever manifest as a clinical problem. Heart failure is present when abnormal cardiac function results in either the retention of sodium and water and elevated venous and capillary pressures *(congestive heart failure or backward failure)* or inadequate cardiac output *(low-output heart failure* or *forward failure)*.

Heart failure can result from functional impairment of the myocardium, heart valves, or pericardium, or as a consequence of increased resistance to ejection. Myocardial failure is defined as a decrease in myocardial contractility and is not synonymous with heart failure. Although myocardial failure is common in patients with heart failure, some patients suffer heart failure even though myocardial function is preserved. Relevant examples include patients that experience massive pulmonary thromboembolism, acute valvular insufficiency, or cardiac tamponade. It is helpful for the practicing clinician to be mindful that normal circulatory function is dependent on the overall functional integrity of the heart, the vascular bed, and the blood, together with its regular mass of circulating red blood cells.[2] Signs of circulatory failure develop with serious compromise of any one of these components of this integrated system. Thus, although all patients with heart failure evidence signs of circulatory failure, the converse is not necessarily true.

Pathogenesis

Heart failure is a progressive disorder that begins with an initial insult or event that perturbs myocyte or myocardial function. It is clinically helpful to characterize patients with heart failure based on the main or the most obvious functional consequences of their underlying disease (Box 246-1). Accordingly, some patients develop signs of heart failure primarily as a consequence of impaired cardiac filling due to restrictive pericardial diseases, mitral and tricuspid valvular stenoses, cor triatriatum, or primary myocardial disorders that reduce ventricular compliance including hypertrophic and restrictive cardiomyopathy. Patients that develop heart failure from these diseases are often appropriately described as suffering from *diastolic heart failure* due to the primary effect of reduced diastolic filling. The concept of ventricular compliance is best explained by a graphic display of the ventricle's end-diastolic pressure-volume relationship, the slope of which defines compliance at any given level of preload (Figure 246-1).[3] Distensibility is closely related to compliance and refers to the pressure that is required to fill the ventricle to a specified volume. Given the same end-diastolic volume, end-diastolic pressure will be higher if the ventricle is stiffer (less distensible and less compliant) than normal.

Box 246-1

Functional Classification of Heart Failure

Heart Failure Resulting from Impeded Cardiac Filling

Pericardial Disease with Restricted Filling
Pericardial effusion with tamponade
Constrictive pericarditis

Valvular Inflow Obstruction
Atrioventricular valve stenosis
Other anatomic obstructions
  Cor triatriatum
  Neoplasms, granulomas

Intrinsic Myocardial Disease with Impaired Diastolic Function
Hypertrophic cardiomyopathy
Restrictive cardiomyopathy

Heart Failure Resulting from Increased Resistance to Ejection

Increased Resistance to the Ejection of Blood (Afterload)
Discrete outflow tract obstruction
  Pulmonic and (subvalvular) aortic stenosis
  Hypertrophy *obstructive* cardiomyopathy
Thromboembolism of the great vessels
Pulmonary hypertension

Heart Failure Resulting from Impaired Ejection or Volume Overload

Primary and Secondary Myocardial Disease with Impaired Systolic Function
Dilated cardiomyopathy
Ischemic, infectious, nutritional, and toxic myocardial disorders

Misdirected Blood Flow Resulting in Volume Overload
Valvular insufficiency
Left-to-right shunts, arteriovenous fistulas

Chronic High-Output States
Thyrotoxicosis, chronic anemia

Heart Failure Resulting from Arrhythmias and Conduction Disorders

Sustained Tachyarrhythmias
Supraventricular tachycardia
Atrial fibrillation

Chronic Bradyarrhythmias
Complete heart block

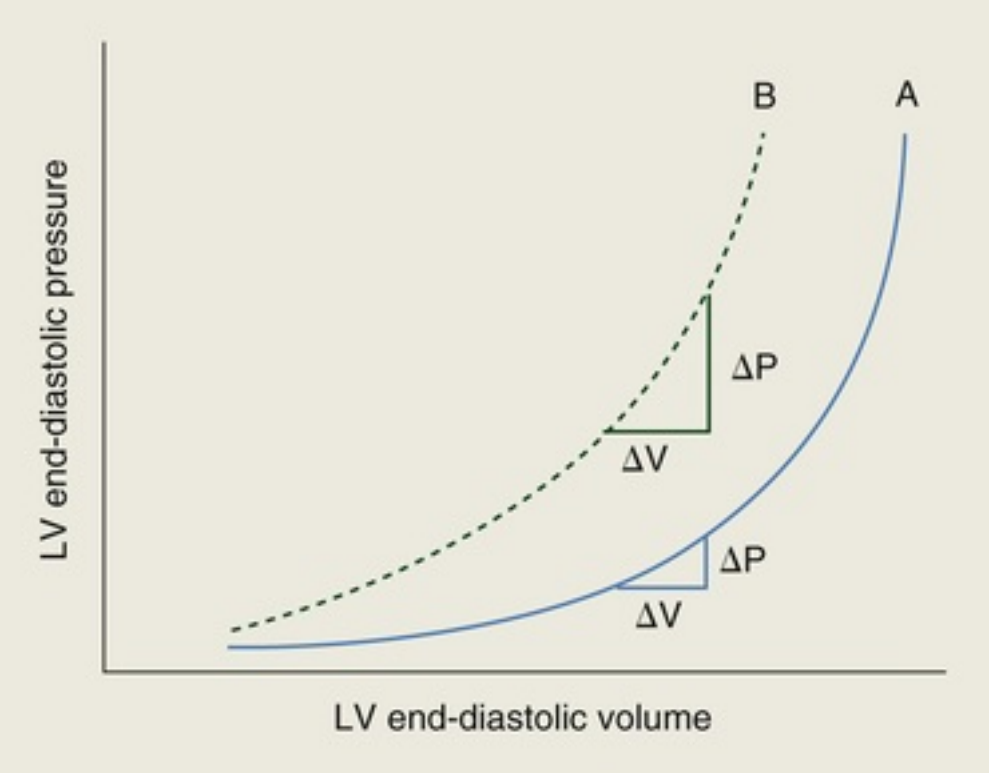

FIGURE 246-1 Ventricular compliance is the reciprocal of stiffness and is determined by the volume and geometry of the chamber, as well as the thickness and tissue characteristics of its walls. This graphic displays the relationship of ventricular end-diastolic pressure to the volume of the ventricle for a healthy subject **(A)** and a patient with reduced ventricular compliance **(B),** defined as the slope of the diastolic pressure-volume relationship. At any given volume, patients with reduced ventricular compliance will have a higher end-diastolic pressure compared with a healthy subject. *LV,* Left ventricle.

In other patients, heart failure results from dramatically increased afterload that impedes ventricular ejection including aortic or pulmonic stenosis, acute pulmonary thromboembolism, and chronic systemic or pulmonary hypertension. Afterload represents the sum of all those forces that oppose the ejection of blood from the ventricle into the circulation and is often expressed as the systolic tension or wall stress experienced by the ventricles during the period of ejection.[4] Afterload is determined mainly by the peripheral (systemic) vascular resistance (SVR), the physical properties (compliance) of the arterial tree, and the volume of blood in the ventricle at the onset of systole.

Volume overload, whether the result of a left to right shunt or valvular insufficiency, is a commonly encountered cause of heart failure wherein ventricular systolic performance is impaired due to the combined influence of misdirected blood flow and a progressive decline in myocardial contractility. Conversely, patients with primary myocardial failure, including dilated and ischemic cardiomyopathy, secondarily develop volume overload due to decreased contractility and altered chamber geometry. Inasmuch as the diastolic and systolic functions of the heart are interrelated, both tend to be concurrently compromised in animals with many heart diseases. It is nonetheless clinically useful to distinguish those patients with reduced systolic pump function from those with compromised diastolic function and normal or nearly normal systolic function.

Cardiac arrhythmias and conduction disturbances may exert adverse effects on systolic or diastolic function depending on the type and duration of the rhythm disturbance (see ch. 248). In some clinical situations, it can be quite difficult to determine if a specific arrhythmia is the cause of the observed functional deficit or an unfortunate complication of pre-existing heart disease. Patients with severe chronic anemia, arteriovenous fistulas, or hyperthyroidism may experience signs of heart failure even though their cardiac output equals or exceeds that of normal animals, termed *high-output heart failure.*[5] In these circumstances, cardiac output after the onset of heart failure is always less than it was prior to the onset of heart failure, indicating that the heart can no longer meet the increased blood flow requirements imposed by the underlying disorder.

Regardless of the inciting abnormality, many patients with heart disease remain asymptomatic for a period of time, likely due to the activation of a number of compensatory mechanisms. Ultimately, sustained

activation of these neurohormonal and cytokine compensatory mechanisms leads to end organ changes and cardiac remodeling, and thus precipitate the progression of heart failure.[2]

Progression of Heart Disease to Heart Failure

Neurohormonal Alterations

There is evidence that suggests that heart failure develops as a result of the overexpression of biologically active agents that are capable of exerting deleterious effects on the heart and circulation.[6] Neuroendocrine responses to developing heart failure have been well documented in human patients wherein there is a demonstrable increase in the activity of the adrenergic nervous system, activation of the renin-angiotensin-aldosterone system, overexpression of atrial and brain natriuretic peptides, augmented synthesis and release of adrenomedullin, endothelin and arginine vasopressin, and amplified expression of a number of proinflammatory cytokines such as tumor necrosis factor-alpha, interleukin-1, and interleukin-6.[7] More recently conducted studies in dogs and cats with heart disease indicate the operation of qualitatively similar neuroendocrine responses.[8] Understanding these complex systems is vital to understanding the pathogenesis of heart failure and the rationale of modern treatment strategies. Based on the neuroendocrine hypothesis that the progression of heart failure is a consequence of the excessive operation of certain maladaptive neuroendocrine responses, such as the adrenergic and renin-angiotensin-aldosterone systems, much investigation has been directed at treatment strategies that blunt or otherwise modify these responses. Familiarity with the mediators of these adaptive responses aids the astute observer in that plasma concentrations of certain neurohormones, such as NT-proBNP, are able to serve as valuable biomarkers that can be used to more accurately establish a diagnosis of heart failure.

Sympathetic Nervous System Activation

Early in the progression of heart failure, increased heart rate and contractility, through the activation of the sympathetic nervous system (SNS), are the dominant compensatory mechanisms employed to combat declining cardiac performance.[2] The primary determinants of stroke volume and cardiac output include preload, afterload, heart rate, myocardial contractility, and ventricular synchrony. Resting cardiac output is often restored to nearly normal levels in patients with heart failure by a moderate increase in heart rate. Sympathetic activation increases heart rate by affecting the rate of SA nodal depolarization. Stimulation of beta-adrenergic receptors increases the firing rate of SA nodal cells by increasing the slow inward calcium current, I_{CaL}. Additionally, SNS activation shifts the activation curve of the inward pacemaker current, I_f, to more positive voltages via G_s-dependent stimulation of adenylyl cyclase. The precise effect of heart rate on cardiac output has immense clinical relevance. Cardiac output increases linearly with heart rate up to a certain threshold value; thereafter, the shortened diastolic interval causes a reduction in stroke volume blunting the slope of this curve (Figure 246-2).[9] At very fast heart rates, stroke volume is diminished to the extent that cardiac output begins to decline. It is noteworthy that stroke volume begins to decline at a lower heart rate and to a greater extent in heart failure patients than in normal individuals. This imposes a very real limitation on this adaptive response and contributes to the dismal performance of heart failure patients attempting to exercise.

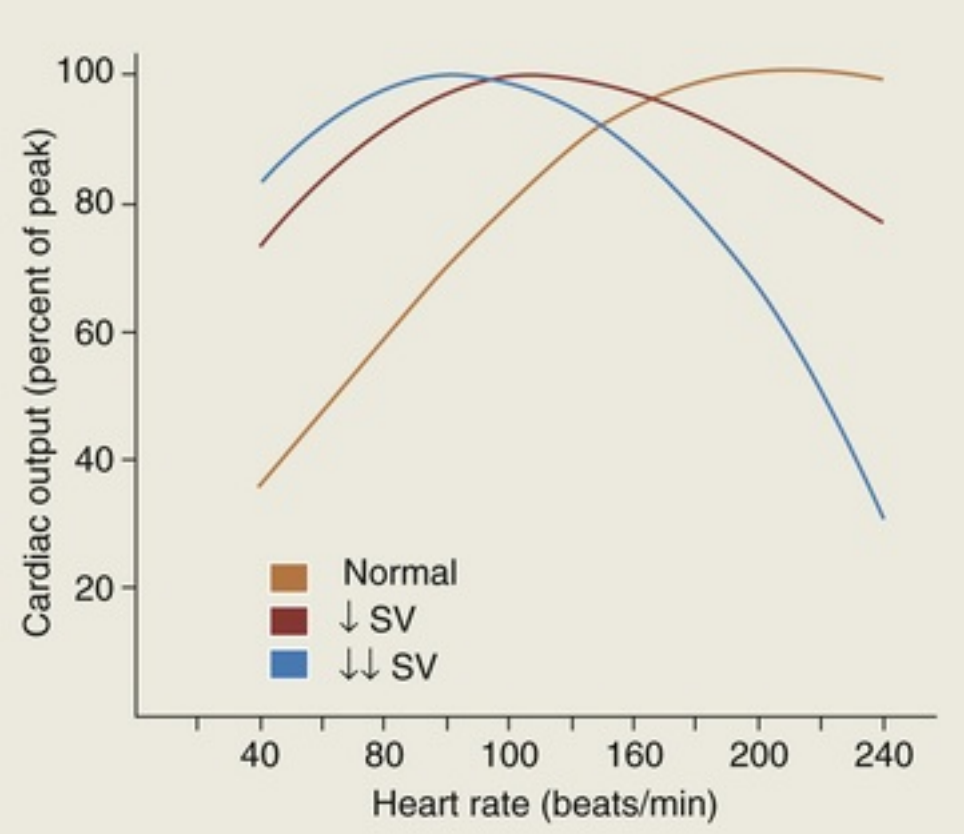

FIGURE 246-2 In dogs with heart disease, maximal cardiac output is achieved at a lower heart rate than in healthy dogs. When ventricular function is compromised, excessive heart rates lead to a substantial decline in stroke volume (SV) and a reduction in cardiac output. It should be noted that it is very difficult to determine optimal heart rate in an individual patient.

Myocardial contractility, the intrinsic force of contraction of the myocardium independent of loading conditions, is increased by adrenergic nervous stimulation, circulating catecholamines, heart rate, and to some extent, afterload. In the early stages of myocardial failure, declining contractility is concealed by adrenergic activation. Through the action of the stimulatory G_s protein, beta-adrenergic stimulation leads to the activation of adenylyl cyclase, and the formation of cyclic AMP (cAMP), which then activates protein kinase A (PKA).[10,11] Activated PKA phosphorylates a number of key proteins (such as the L-type calcium channels, ryanodine, phospholamban, and SERCA2) that facilitate calcium transport across the sarcolemma, augment calcium-induced calcium release by the sarcoplasmic reticulum (SR), and increase calcium reuptake by the SR.[10,11] Protein kinase A also increases the activity of a variety of other proteins that augment the rate and force of contraction of the myofilaments (troponin I and myosin-binding protein C).

Adrenergic venous constriction in patients with heart failure results in an immediate increase in venous return (preload). Increased preload induces a more forceful cardiac contraction and a corresponding increase in stroke volume as described by the Frank-Starling law of the heart (Figure 246-3). Increased diastolic stretch of myocardial fibers increases the sensitivity of the contractile elements to cytosolic calcium, a process that is sometimes referred to as *length-dependent activation*.[12]

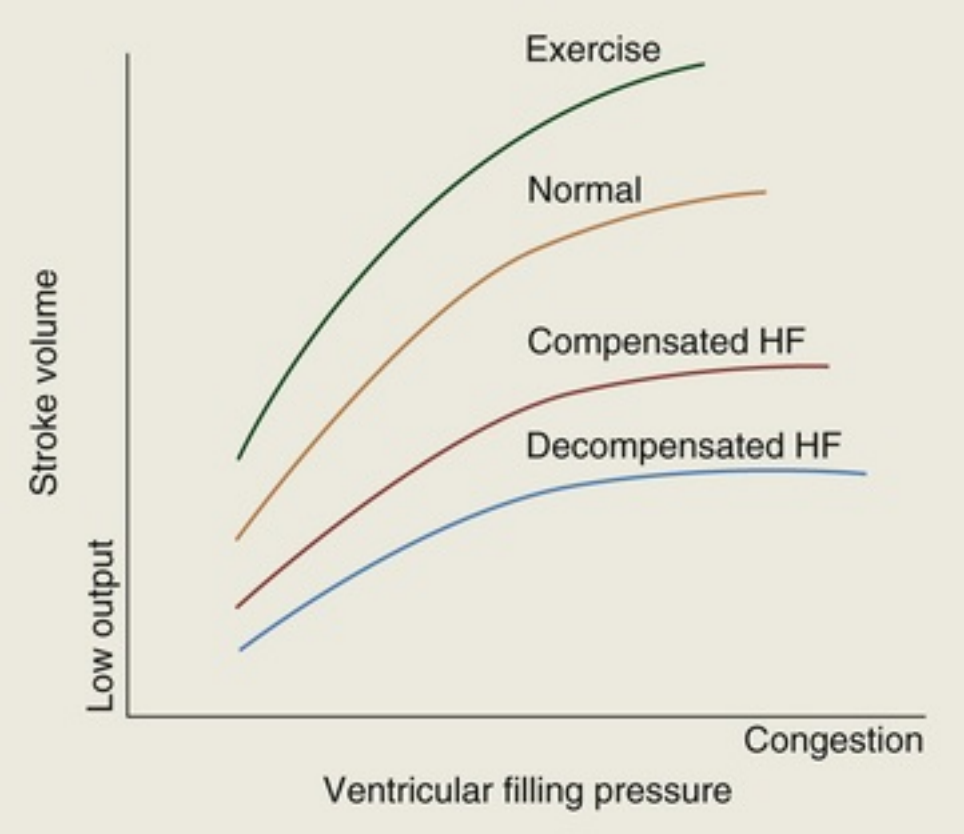

FIGURE 246-3 In normal subjects, ventricular stroke volume increases as venous return and ventricular filling pressures increase. This becomes most dramatic with exercise when increased contractility and reduced afterload augment the Frank-Starling mechanism. In patients with heart failure (HF), the Frank-Starling mechanism is compromised by the combination of reduced contractility, increased afterload, and, in some patients, reduced ventricular diastolic function.

The activation of the SNS provides a short-term mechanism to support cardiac performance, although chronic exposure to high norepinephrine (NE) levels becomes maladaptive. Myocardial performance in patients with diminished contractile reserves may be negatively impacted by the resulting mismatch of afterload to contractility. This consequence is also exaggerated in patients with chronic heart failure wherein downregulation and uncoupling of cardiac beta$_1$-receptors further diminishes the contractile response. Depletion of myocardial norepinephrine stores also augments mismatching as it renders the heart overly reliant on circulating levels of catecholamines. The process of downregulation is accomplished by reduced transcription of mRNA and this mechanism is well established for the beta$_1$-receptor.[6,13] By a distinctly different process, increased myocardial expression of beta-receptor kinase (βARK) facilitates uncoupling of cardiac beta$_1$- and beta$_2$-receptors from G proteins, via the action of beta arrestin, thereby reducing the subsequent production of cyclic AMP.[14] The result of all these perturbations is a diminished increase in heart rate and myocardial contractility in response to adrenergic stimulation.

The adrenal medulla synthesizes and stores both NE and epinephrine (EPI) and releases them into the circulation in response to acute stress. Unlike the adrenal gland, peripheral nerves lack the enzyme phenylethanolamine N-methyltransferase and do not synthesize or release epinephrine. Thus, NE, not epinephrine, plays a central role as a neurotransmitter and is constantly released from terminal sympathetic nerve endings. Despite reuptake and inactivation of most of the NE released in this fashion, a small portion leaks into the circulating blood so that plasma levels of NE, measured at rest, can serve as a useful index of sympathetic nervous system activity. Plasma NE concentrations in human congestive heart failure (CHF) patients correlate with the severity of heart failure and are inversely related to survival.[15] Furthermore, rising concentrations of NE in human patients treated for CHF correlate with a decline in clinical status.[16] Importantly, catecholamine plasma concentrations are known to rise in many circumstances other than heart failure, including emotional stress and physical exertion, emphasizing the rather poor specificity of such measures. For these reasons, interpretation of plasma catecholamine levels in individual patients will always

be problematic.

The estimation of adrenergic activity in dogs and cats in a clinical setting is challenging and there are large variations of such plasma catecholamines even in patients appropriately categorized according to the severity of underlying heart disease. Ware and colleagues[17] first reported significantly elevated plasma NE levels in small numbers of dogs with naturally-occurring heart failure due to dilated cardiomyopathy (DCM) and chronic degenerative valve disease (CDVD) compared with normal dogs. Plasma concentrations of NE correlated directly with the severity of heart failure and they tended to be higher in dogs with DCM compared with dogs with CDVD. Plasma EPI levels in dogs with heart failure were also slightly higher than those measured in control dogs, but the difference was not statistically significant. In a larger study,[18] Sisson et al found that plasma EPI and NE concentrations averaged 133 pg/mL and 254 pg/mL, respectively, when healthy client-owned dogs were sampled by jugular venipuncture. In dogs with heart failure due to CDVD, both EPI and NE were significantly elevated to 314 pg/mL and 314 pg/mL, respectively; and in dogs with DCM, EPI and NE increased to 211 pg/mL and 631 pg/mL, significantly different from controls but not significantly different from the dogs with heart failure due to CDVD. Less dramatic, but still significant, elevations of EPI (290 pg/mL) and NE (445 pg/mL) were identified in dogs with CDVD that had not yet evidenced signs of congestive heart failure. In cats with congestive heart failure or systemic thromboembolism due to hypertrophic and restrictive cardiomyopathy, we found plasma EPI and NE concentrations above 2000 pg/mL and 2500 pg/mL, compared with 250 pg/mL and 1000 pg/mL, respectively, in healthy cats sampled by jugular venipuncture.[19] In healthy, relaxed cats with preplaced jugular catheters we measured EPI and NE concentrations at 221 pg/mL and 424 pg/mL, respectively. In cats with hypertrophic or restrictive cardiomyopathy that were not in heart failure, we found plasma EPI and NE concentrations above 1500 pg/mL and 1700 pg/mL, respectively. These results convincingly establish that sympathetic nervous system activity is increased in dogs and cats with naturally-occurring heart disease, not unlike that observed in human patients.[16,20]

RAAS Activation

Reduced cardiac output and activation of the SNS in heart failure leads to activation of the renin-angiotensin-aldosterone system (RAAS). The components of the RAAS are activated later in HF compared to the SNS. The major stimuli for the release of renin from the juxtaglomerular cells of the kidney include decreased effective renal perfusion, reduced sodium reabsorption by the renal tubules, and beta$_1$-adrenergic stimulation.[21,22] Not surprisingly, low-sodium diets, dehydration, blood loss, and vigorous exercise all stimulate renin release from the juxtaglomerular apparatus. The main action of renin is to accelerate the conversion of the large prohormone angiotensinogen to the decapeptide angiotensin I, which is subsequently converted to the octapeptide, angiotensin II (AT II), by angiotensin-converting enzyme (ACE). Angiotensinogen is a globular glycoprotein produced in the liver and released into the circulating plasma, which serves as the primary storage reservoir.[21] Angiotensin II inhibits renin formation, exemplifying the phenomenon of classic feedback inhibition.

When first discovered, the RAAS was thought to act almost exclusively within the confines of the vascular bed. Now, the vast majority of ACE in the body is known to reside in the tissues, with less than 10% in the circulation.[23] Moreover, all of the various components of RAAS can be found in a variety of tissues including the brain, myocardium, vasculature, adrenal gland, and kidney, and many investigators believe that tissue RAAS is activated at an earlier stage of heart failure than the circulating components.[24] It is likely that the role of the tissue RAAS varies in different circumstances and in accordance with the nature of the underlying disease. Angiotensin II, derived from cardiomyocytes and fibroblasts, plays a particularly substantive role in the development of certain types of pathologic remodeling, acting via G_q and the operation of multiple mitogen activated protein kinases (MAPKs). ACE is a dipeptidyl carboxypeptidase and it acts by cleaving terminal dipeptides from the C-terminus of substrate peptides. The selectivity of ACE is such that it cleaves any substrate peptide, R1-R2-R3-OH, where R1 is a protected L–amino acid, R2 is any L–amino acid except proline, and R3 is any L–amino acid with a free carboxy-terminal. Thus, ACE converts angiotensin I to active angiotensin II and also inactivates the potent vasodilator, bradykinin. The conversion of angiotensin I to angiotensin II can be accomplished by enzymes other than ACE including cathepsin G, elastase, tissue plasminogen activator, chymase, and chymostatin-sensitive AII-generating enzyme (CAGE).[25,26] The importance of these alternate pathways is species-dependent, and several reports suggest that tissue chymase is more active than ACE in the myocardium and extracellular matrix of dog and cats.[26,27] Sequential actions of aminopeptidase and ACE acting on angiotensin I produces angiotensin III, a 7–amino acid peptide

(heptapeptide) that has actions similar to but less potent than angiotensin II.[25,28]

The physiologic actions of AT II have been thoroughly explored and all of its important physiologic effects appear to be mediated by AT_1 receptors, which are abundantly located in blood vessels, the kidney, liver, heart, pituitary, and adrenal glands.[21,28] The half-life of circulating AT II is on the order of 1 or 2 minutes as it is rapidly hydrolyzed to inactive peptide fragments by circulating and tissue angiotensinases. In addition to its role as a potent vasoconstrictor, AT II promotes sodium and water retention via direct effects on the renal tubules and indirectly by stimulating aldosterone production and release from the adrenal glands. Angiotensin II and aldosterone play essential roles regulating sodium and water balance and maintaining vascular pressure when the circulating blood volume is reduced by hemorrhage or salt and water deprivation. Reactive oxygen species (ROS), generated as a consequence of increased AT II and aldosterone expression, are central to the development of myocardial hypertrophy and the detrimental vascular and ventricular remodeling processes observed in patients with chronic heart failure.[25,29,30]

Major stimuli for aldosterone production and release include AT II, elevated potassium levels, and corticotropin (ACTH) (see ch. 308). Other messengers, including plasma catecholamines, endothelin-1, and arginine vasopressin, are also known to promote the production and release of aldosterone into the tissues and blood.[25,30] The main physiologic effects of aldosterone have traditionally been attributed to its effects on the kidney, where it exerts sodium-conserving effects. In this regard, aldosterone acts on epithelial cells of the distal collecting ducts, where it diffuses into the cytoplasm and binds to cytoplasmic mineralocorticoid receptors (MRs).[21,25,30] Following their entry into the nucleus, activated MRs induce a cascade of events that ultimately increase absorption of sodium ions and excretion of potassium. Aldosterone production is not confined to the adrenal gland and mineralocorticoid receptors are more widely distributed than previously realized. In patients with heart failure, aldosterone contributes to baroreceptor dysfunction, enhancing the activity of the sympathetic and diminishing the actions of the parasympathetic nervous systems. Aldosterone also contributes to generalized vasoconstriction via mineralocorticoid receptor-mediated stimulation of sympathetic nervous system activity, via inhibition of NE uptake and degradation in the periphery, and via other complex actions contributing to endothelial cell dysfunction.[21,29,31] Of particular interest is the emerging role of aldosterone as a mediator of inflammation, fibrosis, and other biologic processes, such as oxidative stress, involved in pathologic remodeling in the vasculature, kidney, and heart.[29-31] Aldosterone-induced cytokine synthesis is an important component of these pathologic remodeling processes. Many of the advances in the treatment of heart failure and systemic hypertension realized in the recent past have resulted from the use of compounds that prevent the formation of AT II via inhibition of ACE, that block the interaction of angiotensin II with AT_1 receptors (ARBs), or that antagonize the actions of aldosterone.

Substantial elevations of plasma renin activity and serum aldosterone levels have been identified in dogs with overt congestive heart failure due to mitral regurgitation (MR) and dilated cardiomyopathy (DCM), as well as in cats with hypertrophic or restrictive cardiomyopathy (HCM, RCM). Activation of RAAS is particularly marked in dogs and cats with acquired heart disease when furosemide is used to alleviate congestive signs. There is some disagreement about the role of RAAS in patients with less severe heart disease. Several investigators have noted that plasma renin activity and aldosterone concentrations are within the normal range or only slightly elevated in dogs and cats with heart disease prior to the onset of overt heart failure.[32,33] It is also noteworthy that plasma renin activity and aldosterone concentrations are not always elevated in patients with overt congestive heart failure.[34,35] Given that the physiologic effects of RAAS activation include volume expansion and vasoconstriction, both of which serve to diminish renin production, the activity of this system tends to be phasic and to conceal its activation. Thus, while there is unanimity of opinion regarding the activation of RAAS in dogs and cats with overt congestive heart failure, there is uncertainty regarding the precise point of its upregulation in patients with less severe heart disease.

Neurohormonal Alterations of Renal Function

In heart failure, several mechanisms result in the renal retention of sodium and water.[36] Despite overall volume expansion in the setting of heart failure, inadequate cardiac output results in a decreased effective arterial blood volume. This is sensed by arterial baroreceptors and leads to the sustained activation of the SNS and RAAS. Decreased renal perfusion and increased renal sympathetic nerve-mediated vasoconstriction cause decreased renal blood flow and increased sodium and water retention. Angiotensin II causes increased thirst and stimulates the release of aldosterone and arginine vasopressin (antidiuretic hormone, ADH), both of which cause further water retention. Moreover, norepinephrine augments the activity of the RAAS and

stimulates the synthesis and release of ADH. Blunting of the renal response to natriuretic peptides further tips the imbalance of competing mechanisms from vasodilatory/natriuretic to vasoconstrictive/sodium retention.[37] The eventual results of these alterations include diminished and redistributed renal blood flow, a concomitant reduction in sodium excretion, and elevated plasma levels of arginine vasopressin with retention of solute-free water. The continued sodium and water retention in the setting of heart failure ultimately leads to excessively elevated venous pressures and the development of edema and effusion.

Natriuretic Peptides

Atrial and brain (B-type) natriuretic peptides, ANP and BNP, released from the heart, and C-type natriuretic peptide, located mainly in the vasculature, play important regulatory roles in the circulation and provide balance to the vasoconstrictive and sodium retaining agents. In healthy humans, cats, and dogs, circulating forms of BNP and ANP are probably derived mainly from the atria, where they are stored as precursor molecules, proANP and proBNP, in membrane-bound granules for later release.[38-41] The third natriuretic peptide, C-type or CNP, is located primarily in the vascular endothelium. Circulating levels of CNP are much lower than those of ANP and BNP in healthy animals and humans, suggesting that it acts in a paracrine fashion inducing local relaxation of vascular smooth muscle and inhibiting vascular remodeling. Sudden rises in plasma ANP and BNP levels are accomplished by their release from atrial storage granules mainly by the stimulus of atrial stretch. Sustained increases in circulating ANP and BNP, as seen in patients with heart disease, are accomplished by increased m-RNA expression in different regions of the heart.[42] In patients with myocardial disease, plasma BNP concentrations rise dramatically and often surpass ANP levels as the major site of BNP production switches from the atria to the ventricles.[43,44] In cats with hypertrophic cardiomyopathy, there are marked increases in the expression of BNP in both the atria and ventricles.[45] Others, studying dogs with experimental, pacing-induced heart failure, reported that ventricular BNP expression remains rather modest and that the atria remain the predominant source of most circulating BNP.[46]

The physiologic actions of ANP and BNP generally oppose those exerted by the RAAS.[47,48] Atrial and B-type natriuretic peptides act via the A-type natriuretic peptide receptor, NPR-A, to induce natriuresis and diuresis by inhibiting tubular sodium transport in the inner medullary collecting duct of the kidney. This same receptor type mediates vasorelaxation of systemic and pulmonary arterioles, thereby decreasing systemic and pulmonary vascular resistance. Additional actions of ANP and BNP mediated by NPR-A include direct inhibition of the release of renin by the kidney and aldosterone from the adrenal cortex. A second receptor, NPR-B, responds to ANP and BNP but preferentially mediates vasodilation from locally-produced CNP. The NPR-C receptor acts to clear mature ANP and BNP from the circulation. ANP and BNP are also cleared by the action of membrane-bound neutral endopeptidase, which cleaves them into inactive peptide fragments. Neutral endopeptidase and NPR-C show greater affinity for ANP than BNP, offering an explanation for the longer plasma half-life of BNP.[47-49] N-terminal fragments of proANP and proBNP are thought to be removed more slowly from the circulation than their C-terminal counterparts because clearance of these peptides is more dependent on renal excretion. As a result, NT-proANP and NT-proBNP plasma levels are higher than and not as labile as their C-terminal counterparts. Both N-terminal peptides are sensitive markers of heart disease in humans and their levels tend to correlate closely with the severity of any underlying heart disease.[50,51]

Measurements of plasma natriuretic peptide concentrations, especially BNP, are helpful for discriminating human patients with dyspnea due to heart failure from those with pulmonary disease or other disorders.[51-55] The mean BNP concentrations of human patients with NYHA class III and IV heart failure was eightfold to tenfold higher than the cutoff value for subjects without heart failure.[56] In recently reported studies in cats with myocardial disease, measures of plasma BNP levels appear to have similar diagnostic potential.[57,58] Plasma BNP levels, elevated more than tenfold, distinguished cats with heart failure from control cats better than plasma ANP levels, which were increased fourfold to fivefold. The diagnostic potential of plasma BNP levels does not appear quite as promising in dogs where the magnitude of the change is less dramatic than that observed in cats and humans,[59,60] although a few studies have shown that BNP levels can differentiate between cardiac and noncardiac causes of respiratory distress.[61-63] The recent development of a point-of-care NT-proBNP assay for feline plasma should offer several advantages to the use of BNP as a cardiac biomarker in cats including results being available in-house within ten minutes.[64]

Arginine Vasopressin (AVP)/Antidiuretic Hormone (ADH)

Arginine vasopressin (AVP), often referred to as antidiuretic hormone (ADH) in the veterinary literature, is a nonapeptide with the amino acid, arginine, at the 8 position (see ch. 296).[65,66] The amino acid sequence of the mature peptide is highly conserved in most mammals and is identical in humans, dogs, and cats.[67] Provasopressin, derived from preprovasopressin, is produced by neurons whose cell bodies are located in the hypothalamus. Subsequently, provasopressin is processed into the mature peptide, vasopressin, in vesicles that are transported along the length of the axon to the posterior pituitary, where they become secretory granules containing the active peptide within the nerve endings.[65] Stimuli for release of vasopressin from the neurohypophysis into the circulation include increased plasma osmolality or hypovolemia. When plasma volume is reduced, stretch receptors in the atria and large veins decrease their firing rate, stimulating release of AVP.[65] Sympathetic stimulation and AT II also stimulate AVP release. Following its release, vasopressin reacts with V1A receptors in the vasculature and heart, mediating vasoconstrictive and inotropic actions, and with V2 receptors in the kidney, stimulating water reabsorption.[66,68] This latter effect is accomplished via regulation of the number of aquaporin-2 water channels inserted into the luminal membrane of cells in the renal collecting ducts.[66,68] Baroreceptor V2 receptors respond to elevated plasma AVP levels by augmenting baroreceptor reflexes, which lower the heart rate in order to maintain arterial blood pressure in the normal range.

In dogs with heart failure induced by rapid pacing, plasma levels of arginine vasopressin rise prior to the development of congestive signs in association with activation of the RAA system. Marked increases are observed with the onset of congestive signs. Elevated plasma AVP levels are detectable in some human patients with CHF, particularly those with severe heart failure and dilutional hyponatremia.[65,69] The paradox of increased AVP release in the face of reduced plasma osmolality and high filling pressures may be due to baroreceptor signaling caused by low arterial blood pressure.[70] Whatever the mechanism, selective V2 or combined V1A/V2 receptor antagonists have been shown to normalize plasma sodium concentrations and to alleviate congestive signs in affected patients.[66,71,72] These agents are sometimes referred to as aquaretics because they cause the elimination of free-water without changing urinary excretion of sodium or potassium. Conivaptan, a combined V1A/V2 blocker, has shown efficacy in dogs with experimentally-induced heart failure and in human patients with severe symptomatic CHF.[73,74] Tolvaptan is a more selective orally-active vasopressin V2 receptor antagonist also being evaluated in clinical trials.[75] Increased levels of circulating AVP have been documented in dogs with dilated cardiomyopathy[76,77] and chronic degenerative valve disease,[77] but no observations have yet been reported in cats.

Neurohormonal Alterations of Peripheral Vasculature

Operation of the systemic circulation requires relatively high pressures, and maintenance of systemic blood pressure is a mandated physiologic priority in all patients with heart failure. This involves input from both the autonomic nervous system and local autoregulatory mediators. When cardiac output falls, systemic blood flow is preferentially directed to certain vital centers by a variety of adaptive responses increasing the tone of the resistance vessels supplying less vital regions. The adrenergic nervous system plays a predominant role in redirecting blood flow in patients with heart failure to vital centers (brain and heart), causing much of the observed increase in peripheral vascular resistance.[6] Other influential changes altering the functional and structural properties of the vascular wall include downregulation of parasympathetic tone, upregulation of the RAAS, increased expression and release of endothelin and AVP, and alterations in the processes that autoregulate blood flow to specific vascular beds.

Norepinephrine, angiotensin II, endothelin, and AVP effect vasoconstriction via specific smooth muscle membrane receptors linked to the G protein, Gq, leading to activation of phospholipase C and the inositol triphosphate (IP3) signaling system.[78] The IP3 system regulates calcium ion release via the IP3 receptor (a calcium release channel) in the sarcoplasmic reticulum of smooth muscle cells, thereby stimulating calcium-mediated vasoconstriction. With chronic IP3 signaling, diacylglycerol activates protein kinase C (PKC), initiating a cascade of intracellular signals that initiate smooth muscle hypertrophy and replication, as well as a plethora of associated changes in the extracellular matrix (vascular remodeling).[79] Reduced activity of the parasympathetic limb of the autonomic nervous system contributes to generalized vasoconstriction by withdrawal of its vasodilatory influence. The parasympathetic muscarinic receptors, stimulated by acetylcholine, activate guanylyl cyclase, causing the formation of cyclic GMP, which inhibits calcium entry

into the cell and decreases intracellular calcium concentrations. The increased sympathetic activity and increased circulating vasoconstrictors in heart failure maintain arterial pressure and also increase venous return and cardiac filling via peripheral venoconstriction. Unfortunately, the affiliated increase in afterload stimulates cardiac remodeling and further contributes to cardiac dysfunction.

Endothelin

Vascular tone is modulated by the endothelium-derived vasodilators, nitric oxide and prostacyclin, and by the complex actions of the potent endothelium-derived vasoconstricting peptide, endothelin.[80] Three related peptides, endothelin-1, endothelin-2, and endothelin-3, comprise the endothelin family.[81] Circulating endothelins are derived from larger peptides produced by vascular endothelial cells (myocytes and a variety of other cells) in a sequence of steps analogous to that described for natriuretic peptides.[81-83] Thus, preproendothelin gives rise to biologically inactive proendothelin, also termed big endothelin, which is subsequently cleaved at the N-terminus by endothelial-converting enzyme (ECE) to yield the active mature peptide, endothelin-1 (ET-1). Endothelin-1 mRNA expression and ET-1 production are stimulated by hypoxia and mechanical factors, including stretch and low shear stress; by vasoactive substances such as ATII, AVP, NE, and bradykinin; and by growth factors and cytokines including transforming growth factor beta, tumor necrosis factor alpha, and interleukin-1.[82,83]

Endothelin-1 acts via two receptors, ETA and ETB, to exert complex biologic effects serving to maintain normal vascular tone.[82-85] Vasoconstriction of smooth muscle, increases in myocardial contractility, and aldosterone secretion are among the more prominent effects mediated by ETA receptor stimulation. Chronic stimulation of ETA receptors and persistently elevated ET-1 levels cause proliferation and hypertrophy of vascular smooth muscle and myocardial hypertrophy. In addition to its direct vasoconstricting effects in heart failure, ET-1 inhibits the endogenous nitric oxide (NO) synthase inhibitor, asymmetric dimethylarginine (ADMA), and this effect can be blocked by ETA receptor antagonists.[83] Vasodilation, mediated by increased NO production, and aldosterone secretion results from stimulation of endothelial cell ETB receptors, providing an elegant and complex means of balancing vascular tone. Increased NO levels, in turn, inhibit ET-1 synthesis, exemplifying a negative feedback mechanism. Following intravenous injection of ET-1, blood pressure first declines transiently and then increases, reflecting the action of these two receptor subtypes. The interactions of endothelin and RAAS are complex, but the net effect is suppression of renin production and stimulation of aldosterone secretion.[86] Therapeutic strategies based on blocking ET receptors and inhibition of endothelin-converting enzyme have not produced convincing clinical benefits.

In healthy people and animals, most circulating ET-1 is derived from the vasculature and ET-1 levels are very low, reflecting its paracrine role in the maintenance of normal vascular tone. Myocardial production of ET-1 is thought to contribute to the increased plasma concentrations of ET-1 observed in humans, dogs, and cats with heart failure. It is noteworthy that the magnitude of elevation of ET-1 in heart failure is not as dramatic as that seen with the natriuretic peptides. Plasma ET-1 levels more than double in dogs with CHF due to CDVD or DCM and increase more than threefold in cats with cardiomyopathy and CHF or systemic thromboembolism.[84,85] Significant but more modest elevations are observed in dogs and cats with less severe disease. In a study of dogs presented for dyspnea, plasma ET-1 levels were less accurate than plasma NT-proANP for distinguishing dogs with CHF from those with dyspnea from other causes.[87] Endothelin-1 concentrations are also consistently elevated in patients with pulmonary hypertension and some forms of renal disease, but, interestingly, not in patients with systemic hypertension.[88,89]

NO and Adrenomedullin

Nitric oxide, produced in endothelial cells from L-arginine via the action of endothelial nitric oxide synthase (eNOS), diffuses into smooth muscle cells and contributes to vasodilation by several different mechanisms.[90] Nitric oxide increases intracellular cGMP levels in vascular smooth muscle cells by activating soluble guanylate cyclase and directly activates potassium channels, leading to hyperpolarization of the cell and vasodilation. In patients with heart failure, impaired endothelial cell function causes decreased NO synthesis, contributing further to excessive vasoconstriction.[91]

Adrenomedullin (ADM) is a potent natriuretic and vasodilating 52–amino acid peptide with positive inotropic properties. Adrenomedullin has been detected in a variety of tissues, including the adrenal medulla, heart, lung, and kidney.[92,93] Plasma levels of ADM are increased in human heart failure patients and in dogs

with pacing-induced experimental heart failure. Recent studies indicate that AT II stimulates ADM production and secretion from cardiac myocytes and fibroblasts and that ACE inhibition can block this response. Thus, ADM appears to have endocrine, autocrine, and paracrine effects.[93] Interestingly, ADM serves as a marker of ventricular hypertrophy but acts to attenuate myocardial hypertrophy and collagen production. Adrenomedullin has received little attention in dogs or cats with naturally-occurring heart disease. This is likely to change because there is increasing interest in ADM as a possible therapeutic agent.

Cytokine and Integrin Signaling

Cytokines, more appropriately referred to as protein regulatory factors, are small water-soluble signaling proteins or glycoproteins produced by a wide variety of cell types that are used extensively in cellular communication.[94] Cytokines exhibit a combination of endocrine, paracrine, and autocrine actions via membrane-bound receptors that up- and down-regulate the expression of groups of genes and their transcription factors, thereby acting as potent modifiers of protein synthesis. Increased production and elevated plasma concentrations of proinflammatory cytokines, including interleukin-1, interleukin-6, and tumor necrosis factor alpha (TNF-alpha), have been identified in human patients with chronic heart failure and are regarded as important negative prognostic indicators.[95] Increased TNF-alpha levels act to depress myocardial function, and chronic elevations of TNF-alpha promote apoptosis.[96] Unfortunately, clinical trials of agents blocking the actions of TNF-alpha in human subjects were disappointing.[97]

Cardiac Remodeling

Chronic perturbations in the circulation and pathologic insults to the heart elicit anatomic and morphologic changes in the heart that are broadly referred to as cardiac remodeling. While the maladaptive neurohormonal responses to heart failure explain part of its progressive nature, cardiac remodeling further affects and often exacerbates cardiac dysfunction. The concept of cardiac remodeling does not only affect the size of the cardiac myocytes; cardiac remodeling involves the volume of myocyte and nonmyocyte components, the anatomy and biology of cardiac myocytes, and the geometry of the cardiac chambers.

Myocyte and Nonmyocyte Alterations

Cardiac hypertrophy, the increase in myocyte size, is the foundation of the remodeling response given the extremely limited ability of the heart to add new cardiomyocytes. When the heart is healthy, cardiomyocytes occupy about three fourths of the volume of the heart and comprise about one third of the total number of cells.[98] These muscle cells are embedded in a collagen-rich extracellular matrix produced by large numbers of fibroblasts, and both components are nourished by an extensive network of coronary vessels lined by endothelial cells and richly endowed with smooth muscle cells. Noncellular constituents of the extracellular matrix include mainly type I and type III collagens, a rich soup of proteoglycans and a large variety of signaling peptides and extracellular proteases.[99] Interstitial collagen is organized in a complex fashion that serves to connect and bundle the myofibers in a sophisticated weave that facilitates the primary function of collagen, which is the transmission of force. Endomysial collagen surrounds individual myocytes, giving rise to collagen struts that connect to neighboring myocytes and to capillaries. Perimysial collagen fibers form a complex weave of collagen surrounding groups of myocytes and joining adjacent groups of myocytes to one another. Epimysial collagen forms a sheath that encompasses muscle bundles and is connected to the perimysium by strong, tendonlike cables.[100] From this perspective, the heart can be viewed as a collagen fiber–reinforced composite material that is designed to support the working cardiomyocytes during diastolic filling and systolic ejection. Since the interstitium and myocardium are inextricably linked, changes in either one alter the biologic responses and remodeling processes of the other.

In humans, heart weight can decline by as much as 25% to 30% during prolonged bed rest or weightlessness and can increase to an extreme of 50% to 60% with extreme exercise.[101] Mechanical stress, growth factors, and neurohormonal stimuli act in concert to elicit paracrine and autocrine signaling mechanisms integral to these physiologic remodeling processes. Reorganization of the interstitium is appropriately coordinated with the symmetric growth of myocardial cells, and these changes are reversible once the physiologic challenge is resolved, as in exercise- or pregnancy-induced cardiac hypertrophy. Reverse remodeling is accomplished by deactivation of pro–growth signaling pathways and activation of other signaling pathways that disassemble the adaptive constructs of the hypertrophied heart. The number of

myocytes in the mature heart declines with age and the remaining myocytes must, by necessity, remodel as they assume a greater percentage of the hemodynamic burden.

Pathologic cardiac remodeling shares many of the adaptive processes and signaling pathways of physiologic remodeling, but the end result is often irreversible remodeling, reduced systolic or diastolic performance, and eventual cardiac decompensation. Forty years ago, Meerson and colleagues[102] identified three phases of the hypertrophic response: (1) an initial stage wherein hypertrophy develops in response to increased wall stress, (2) a compensated stage wherein wall stress has been normalized by the hypertrophic response, and (3) an exhaustion phase characterized by the death of cardiomyocytes, development of myocardial fibrosis, ventricular dilation, and reduced cardiac output. Compensatory and adaptive remodeling processes are transformed when the hemodynamic stresses are prolonged in duration or excessive in magnitude, when physiologic patterns of neurohormonal activation are excessively modified (RAAS, NE, ET-1), and when vascular remodeling exerts its toll on myocardial perfusion.

The law of Laplace emphasizes that any increase in chamber size should be accompanied by a proportional increase in wall thickness if normal wall stress is to be maintained. The law states:

$$\text{Wall stress} = \text{pressure} \times \text{radius}/2 \times \text{wall thickness}$$

This relationship provides a rationale for observed changes in cardiac architecture when an abnormal hemodynamic burden is chronically imposed on the heart (Figure 246-4). Hence, pressure overloads are compensated for (wall stress is normalized) by increases in wall thickness with little or no changes in chamber size. Despite this compensation, the total work of the pressure-overloaded heart is increased relative to normal, imposing a persistent requirement for increased energy production and oxygen delivery. Volume overload, in turn, is characterized by an enlarged chamber and only a modest increase in wall thickness, sufficient to normalize wall stress. In this fashion, the workload is redistributed appropriately to the cardiomyocytes, forward stroke volume is normalized, and the patient's functional capacity is, at least theoretically, normalized. The total work of the volume-overloaded heart is increased relative to the normal heart but substantially less than is observed in a pressure-overloaded heart.[10]

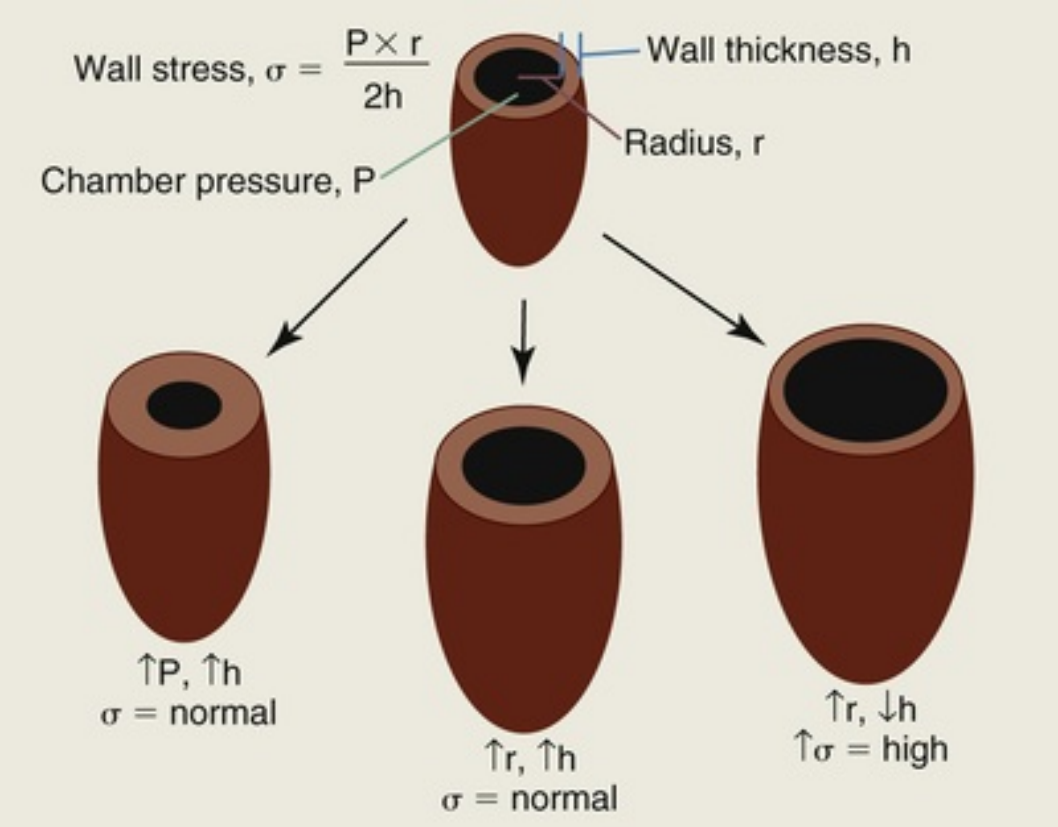

FIGURE 246-4 The heart responds to hemodynamic challenges in a predictable fashion as described by Laplace's equation (top). In response to chronic pressure overload, ventricular wall thickness increases to normalize wall stress (left). Chamber diameter and wall thickness increase proportionally during athletic training and pregnancy to maintain normal wall stress (center). Wall stress is increased in patients with heart failure due to dilated cardiomyopathy as the chamber dimensions increase disproportionately to wall thickness (right).

Abrupt increases in systolic wall stress, such as that caused by experimentally created aortic stenosis, induce an abrupt increase in LV end-systolic volume and a concomitant decrease in stroke volume. During this phase, the size and number of mitochondria increase to meet the increased demands for energy.[103,104] Over time, the myocardium responds to pressure overload through the process of *concentric hypertrophy*, wherein the sarcomeres replicate in parallel (side to side), causing the muscle fibers to thicken, increasing left ventricular and septal wall thickness. The radius of the ventricle is unchanged or may even decrease slightly due to encroachment by the thickened ventricular walls. In this fashion, systolic wall stress is normalized and the patient experiences little or no functional compromise. Fibroblasts in the interstitium also experience the increased pressure load and elevated levels of locally generated transforming growth factor beta-1, AT II, and aldosterone. They respond to these stimuli by proliferating and by increasing the synthesis and deposition of collagen, mediated at least in part by reduced expression of adaptor molecule DOC-2 in activated fibroblasts. In the interstitium, the breakdown of collagen is reduced due to increased expression of tissue inhibitor of metalloproteinase-1 (TIMP-1) and the corresponding reduced activity of the matrix metalloproteinases, MMP-1 and MMP-9.[105]

When the initiating insult is mild, long-term cardiac compensation is achieved with minimal functional compromise, as evidenced by the long survival time of dogs with mild to moderate outflow tract obstructions. However, when pressure overload is sufficiently severe, myocardial function is compromised. Capillary density and myocardial perfusion do not keep pace in proportion to large increases in wall thickness, and chronic myocardial hypoxia results in premature death of myocardial cells and more extensive myocardial fibrosis. Not surprisingly, the most common consequence of severe subvalvular aortic stenosis in dogs is sudden death from ventricular arrhythmia, presumably as a result of myocardial ischemia and its sequelae. In some patients, severe concentric hypertrophy and ischemia-induced myocardial fibrosis act to compromise left ventricular compliance, precipitating diastolic heart failure. On occasion, global systolic pump failure develops as a consequence of terminal remodeling processes culminating in myocardial fiber elongation, myofibrillar lysis, and death of cardiomyocytes. During the exhaustion phase, the rate of collagen breakdown exceeds the rate of synthesis and the hypertrophied ventricle begins to dilate and fail.

The response of the heart to volume overload differs substantially from that observed in pressure overload. Common causes of volume overload include valvular insufficiency and congenital left-to-right shunting lesions, such as patent ductus arteriosus and ventricular septal defect. Pure volume overload is characterized by increased diastolic wall stress to which cardiomyocytes respond by replicating new sarcomeres in series (end to end). The ventricle becomes more spherical and the diameter of the chamber becomes larger in a process referred to as *eccentric hypertrophy*. Wall thickness increases only modestly so as to maintain a normal ratio of wall thickness to radius, thereby normalizing wall stress. The closest clinically relevant model of volume overload is mitral regurgitation wherein the additional volume load is ejected into a low-pressure reservoir, the left atrium. Other forms of volume overload, such as aortic valve insufficiency and patent ductus arteriosus, represent examples of combined volume and pressure overload wherein an additional volume of blood is ejected into a high-pressure reservoir, the aorta. When examining the mechanisms of volume overload, it is useful to focus attention on mitral regurgitation rather than on disorders where cardiac adaptation represents a combination of volume and pressure overload.

Compared with pressure overload, volume overload induces a relatively modest increase in heart weight and protein synthesis.[106] Interestingly, the increase in heart weight occurring secondary to mitral regurgitation results mainly from a reduced rate of protein degradation. This observation reinforces the concept that signals mediating volume overload differ from those elicited by pressure overload and that there must be a corresponding difference in the pattern of gene activation. Myocytes from volume-overloaded hearts are elongated relative to normal or pressure-overloaded hearts.[107] It is presumed that differences in mechanoreceptor signaling are largely responsible for the remodeling differences between pressure and volume overload inasmuch as increased levels of norepinephrine, cardiotrophin-1, and AT II are common to the pathogenesis of both forms of hypertrophy. Nonetheless, the integrated operation of these signaling pathways is still poorly understood and other factors, not apparent at this time, may be responsible for some of the observed differences. The extracellular matrix is drastically altered in the hearts of dogs with experimentally induced mitral regurgitation.[108,109] This change is characterized by a loss of collagen and

disappearance of the elaborate collagen scaffold tethering the cardiomyocytes. Collagen synthesis in cardiac fibroblasts is substantially reduced in dogs with mitral regurgitation, paralleling the observed reduction in sarcomeric protein synthesis. The rate of collagen degradation is augmented by the increased activities of MMP-1 and MMP-9, in absolute terms and relative to MMP tissue inhibitor levels. The population of mast cells in the interstitium increases in dogs with mitral regurgitation.[108] In addition, tissue expression of transforming growth factor-beta-1 is reduced together with downregulation of cell-matrix scaffolding genes controlled by the transformng growth factor-beta-1 pathway. These alterations are most obvious early in the course of volume overload; they tend to normalize during the compensated phase only to reactivate again in the late stages of the disorder.

The remodeling processes of ischemic myocardial disease and dilated cardiomyopathy differ qualitatively and quantitatively from those described for pressure or volume overload. In the compensated phase of ischemic cardiomyopathy, the adaptive responses are more similar to those observed in pressure overload due to the chronic operation of potent neuroendocrine adaptive responses. However, in the decompensated phase, cardiomyocytes begin to elongate, the collagen matrix begins to disintegrate, and the chamber dilates, indicating a shift in intracellular signaling. The hearts of dogs with dilated cardiomyopathy (DCM) show a mixed remodeling pattern as well, but the eccentric hypertrophy phenotype predominates.

Myocyte Biology Alterations

In addition to myocardial hypertrophy, heart failure also results in structural and functional alterations in excitation-contraction coupling components, contractile and regulatory proteins, cytoskeletal proteins, apoptotic signaling mediators, and energy metabolism.[110,111] Calcium cycling is abnormal in most patients with heart failure and these alterations contribute substantially to systolic and diastolic dysfunction.[112,113] Importantly, the total amount of calcium stored in the sarcoplasmic reticulum is reduced in heart failure patients. This reduction has been linked to (1) lowered SERCA levels or reduced SERCA ATPase activity, (2) increased removal of intracellular calcium by the sodium-calcium exchanger, and (3) alterations in calcium release via the ryanodine receptor.[112,114] As a direct consequence, the onset of the peak calcium transient in working cardiomyocytes is delayed and the time to return to baseline is prolonged.[115] Enhanced activity of the sodium-calcium exchanger compensates for diminished reuptake via SERCA to some extent, but eventually the rate of Ca^{++} removal during diastole is reduced.[116] These perturbations in calcium handling predispose the cardiomyocyte to early and delayed afterdepolarizations, increasing the likelihood of serious ventricular arrhythmias and increasing the risk of sudden death.

Myocardial contractility is further impaired by reduced myofibrillar ATPase activity observed in association with altered patterns of troponin I phosphorylation resulting from increased PKC and reduced PKA mediated processes.[117] Different isoforms of the contractile proteins and associated regulatory proteins also may contribute to declining contractility depending on the species and underlying cause of heart failure.[118] Such changes relate to reduced expression of adult isoforms and increased expression of isoforms that were expressed during embryonic development and is sometimes referred to as the fetal gene program.[119,120] The pathways and processes regulating gene expression, protein transcription, myocardial hypertrophy, as well as necrosis and apoptosis are complex with considerable cross-talk between them. They are mediated, in part, through alpha-adrenergic receptor-linked Gq activation of phospholipase C, subsequent translocation and activation of PKC, and activation of extracellular signal-related kinase, ERK1/2.[121] Extracellular signal-related kinase 1/2 is one of four known mitogen-activated protein kinase (MAPK) pathways operating in the heart to regulate protein transcription and gene expression.[13] Additional MAPK pathways, including c-Jun N-terminal protein kinases (JNKs) and the p38 pathway involved in cell differentiation and apoptosis, and other cellular processes modifying gene expression such as the calcineurin–nuclear factor of activated T cells (NFAT) pathway and the Phosphoinositide 3-Kinase/Akt/Glycogen Synthase Kinase-3 (PI3/Akt/GSK-3-beta) signaling system are also involved.[122] This is an understandable if unpardonable oversimplification of processes that orchestrate different responses to differing stimuli and the interested reader is directed to several excellent reviews of these complex systems for further detail.[120,123]

Prior to the onset of heart failure, cardiomyocytes performing additional external work generate more energy and recycle more calcium than do cells that are not similarly burdened. As more energy is produced, more heat is produced and the cell experiences greater oxidative stress. As a result, more energy must also be dedicated to cell maintenance and repair. Thus, it is not surprising that one of the first responses of overworked cells is to increase the number of mitochondria to address the need for energy.[104] Additional

energy must be devoted to the construction and maintenance of the pathways used to store and distribute energy as well. These adaptive processes eventually fall short, resulting in abnormalities of calcium cycling, systolic and diastolic dysfunction, and cell death. In patients with heart failure, there is a switch in substrate utilization from fatty acids to carbohydrates and a decrease in aerobic ATP production.[124] The amount of ATP in failing cardiomyocytes is not altered, but the rate of use and rate of replenishment of ATP are reduced as the capacity of the mitochondria to produce ATP becomes limited.[125] Heart failure is characterized by declining levels of creatine phosphokinase in the cytosol and mitochondria and a correspondingly reduced creatine phosphate/ATP ratio. This alteration has been described in explanted hearts from human patients with end-stage heart failure, in dogs with experimentally created mitral regurgitation, and in dogs with spontaneously occurring DCM.[126,127] O'Brien and colleagues[128] found reduced mRNA content and enzyme activity for markers of calcium cycling, glycolysis, and oxidative phosphorylation in dogs with DCM. More recently, Oyama and Chittur[129] reported reduced expression of genes involved in glycolysis and oxidative phosphorylation. Lopes and colleagues[130,131] reported similar patterns of altered energy production reflected in the protein expression profiles of mitochondria from dogs with pacing-induced and naturally occurring cardiomyopathy.

These functional changes are reflected in structural alterations of the mitochondria, which become smaller and more numerous.[104] These changes are accompanied by alterations and disruption of the internal cristae. In context, there is also a breakdown in the architecture of other cellular constituents with dissolution of the myofilaments and disorganization of cytoskeletal elements. Ischemia is a rather obvious cause of diminished energy production and is of paramount importance in human patients with atherosclerosis. Regional ischemia, associated with vascular remodeling, is a likely cause of altered energy production and cell death in some of our animal patients, most notably in cats with hypertrophic cardiomyopathy and dogs with subaortic stenosis wherein the remodeling of intramyocardial coronary arterioles is often quite marked. These vascular lesions are commonly associated with focal myocardial scars completely devoid of functioning myocytes.

Clinical Signs of Heart Failure

Ultimately, the mechanisms activated to compensate for heart disease including the neurohormonal alterations and cardiac remodeling initiate a vicious circle of inappropriate sodium and water retention and decreasing cardiac function. Most, but not all, patients with cardiac failure develop systemic or pulmonary congestion and are classified as having either right- or left-sided CHF, respectively. This categorization is not comprehensive because some patients experience both systemic and pulmonary congestion, and congestive signs are sometimes absent when heart failure develops suddenly and plasma volume is normal or reduced.

Patients with heart failure are most clearly distinguished from healthy individuals by their limited ability to increase cardiac output in response to exercise. Indeed, most of the clinical schemes devised to categorize the severity of heart failure are based on exercise capacity. Cardiac output at rest is only modestly reduced in most patients with heart failure due to the actions of the adaptive responses acting to augment preload, heart rate, and contractility. Only when heart failure is severe is cardiac output markedly reduced at rest.

Pulmonary or systemic congestion develops in most animals with heart failure as a consequence of excessive elevation of venous pressure caused by the combined effects of increased plasma volume (sodium and water retention) and decreased venous capacitance (venoconstriction). With functional impairment of the left side of the heart, pulmonary venous pressure increases, resulting in pulmonary edema and signs of respiratory distress (Figure 246-5, *A*). Congestive signs, such as cough or labored breathing, are likely to be observed when mean pulmonary capillary wedge pressure (PCWP) exceeds 25 mm Hg (normal < 10 mm Hg). With impairment of the right side of the heart, systemic venous pressures rise, resulting in hepatomegaly and ascites, which usually become apparent when central venous pressure exceeds 15 mm Hg (normal < 5 mm Hg) (Figure 246-5, *B*). Patients with gradually developing heart failure are more tolerant of elevated filling pressures because of adaptive changes in the capacity of lymphatic flow.[132] Filling pressures are often monitored in patients with heart failure to determine if they are responding appropriately to various treatment interventions. This prudent exercise is useful only if attention is focused on the appropriate variable. A common mistake made in clinical practice is to measure central venous pressure (CVP) as a guide to fluid administration in patients with compromised left heart function. The capacitance of the splanchnic veins, where 70% of the circulating blood resides, is much larger than that of the pulmonary circulation and is complemented by an extensive network of systemic lymphatic channels. As a result, pressure rises slowly in the systemic capillary beds when blood volume increases and the manifestations of right-sided congestion tend to develop slowly. Because the capacitance of the pulmonary veins is small, relatively small changes in

blood volume or its distribution can cause a rapid rise in pulmonary venous pressure and pulmonary edema. Sudden increases in sympathetic tone (fear, anxiety, exercise) cause constriction of the splanchnic veins, causing a shift of the circulating blood volume from the systemic to the pulmonary venous reservoir. This can precipitate the rapid onset of pulmonary edema in patients prone to left heart failure.

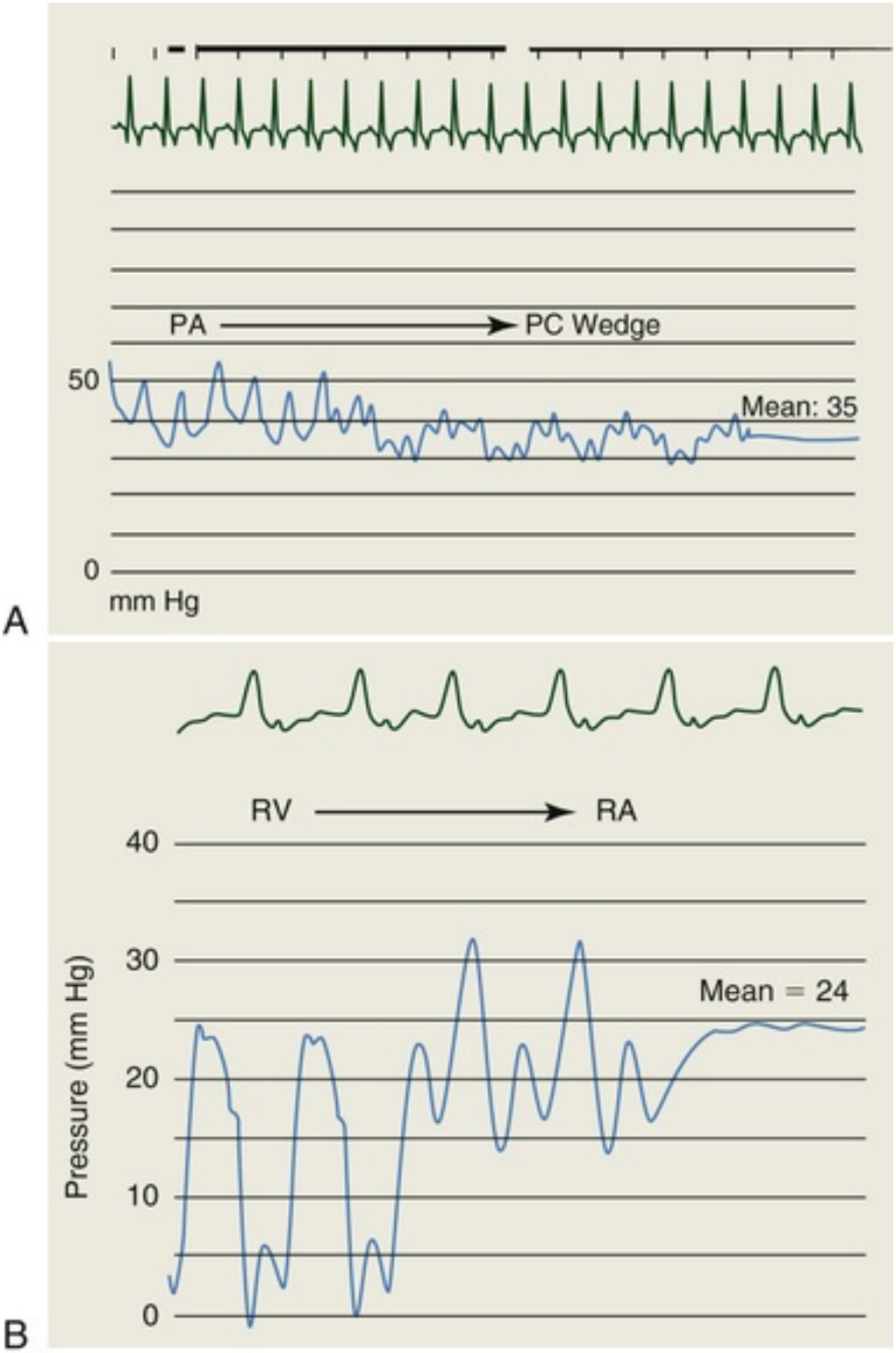

FIGURE 246-5 Pulmonary congestion is likely to develop whenever mean pulmonary capillary (PC) wedge pressure exceeds 25 mm Hg, as shown in this dog with dilated cardiomyopathy **(A).** Systemic congestion is likely to develop when mean right atrial pressure exceeds 15 mm Hg, as shown in this dog with tricuspid valve stenosis **(B).** *PA,* Pulmonary artery; *RA,* right atrium; *RV,* right ventricle.

The pulmonary and systemic circulations operate in series and are, as a direct consequence, interdependent. Dysfunction of either circuit will necessarily impact the operation of the other. Hence, a rise in left atrial pressure, as occurs with mitral regurgitation, results in a corresponding increase in pulmonary artery pressure and the work performed by the right heart. In most instances, this pressure increase is quite modest; however, profound pulmonary vasoconstriction can be induced when the oxygen saturation of the blood is reduced as a consequence of pulmonary congestion, resulting in the development of debilitating pulmonary hypertension and right heart failure. The feline pulmonary vascular bed is more reactive to hypoxemia than that of dogs and, as a result, cats may be more prone to the development of serious pulmonary hypertension as a consequence of left heart failure.[133] The complex relationship between the systemic and pulmonary circulations is also evidenced by the pattern of congestion that develops when both ventricles fail simultaneously. Pleural effusion, which is uncommon with isolated right- or left-sided heart failure, develops frequently when systemic and pulmonary venous pressures are concurrently elevated.[134] In this circumstance, fluid accumulates in the pleural space because lymphatic drainage, derived from both circulations, cannot keep pace with the rate of pleural fluid formation.

Summary

The evolution of treatment of heart failure (see ch. 247) parallels the evolution of our understanding of the pathophysiology of this complex clinical syndrome. Emphasis on the mechanisms of congestion and fluid retention led to the development of effective diuretics. Focus on the hemodynamic alterations in heart failure and the mechanisms of reduced contractility led to the development of positive inotropic drugs and vasodilators. Recognition of the reactive neurohormonal alterations in heart failure provided the rationale for treatment with ACE inhibitors, aldosterone antagonists, and beta-blockers. Understanding of the fundamental processes involved in excitation and contraction, energy production and utilization, and remodeling will undoubtedly lead to a variety of new therapeutic approaches and preventive strategies.

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CHAPTER 247

Heart Failure

Clinical Management

Adrian Boswood

Client Information Sheet: Diuretic Therapy for Heart Failure

Introduction

Veterinarians frequently encounter patients with heart failure that require appropriate management to alleviate their clinical signs and improve their quality of life. The most effective treatment of these patients will be provided if the attending clinician approaches management in a systematic manner, cognizant of the type of clinical signs the patient is showing and pathophysiologic mechanisms that are likely to underlie those signs. Not all patients with clinically detectable heart disease will be showing signs of heart failure; many common diseases have lengthy preclinical ("asymptomatic") phases during which the patient is completely free of any clinical signs. It is common for older patients with heart disease to suffer from comorbidities; therefore, not all signs shown by patients with heart disease will be due to their having heart failure.

What Is Heart Failure?

Heart failure can be said to be present when, as a consequence of an abnormality of the heart, patients demonstrate clinical signs because of an inability to sustain a cardiac output sufficient to provide for their metabolic requirements at normal cardiac filling pressures (see ch. 246). Patients therefore can show signs of inadequate cardiac output with normal filling pressures (forward failure); can have clinical signs as a consequence of excessive cardiac filling pressures but a normal cardiac output (backward or congestive failure); or, as is often the case in patients with an emergency presentation, they both can have signs brought about by excessive cardiac filling pressures and concurrently demonstrate signs associated with an inadequate cardiac output. Typical clinical signs of inadequacy of cardiac output include exercise intolerance, syncope (see ch. 30), pallor, cold extremities, and manifestations of hypotension (see ch. 159) such as lethargy and depression. Signs indicating that a patient has excessive cardiac filling pressures typically occur as a consequence of congestion of the venous circulation and include tachypnea and dyspnea due to pulmonary congestion and edema (see ch. 28); abdominal distension due to ascites (see ch. 17); and tachypnea and dyspnea due to pleural effusion (see ch. 244). Occasionally, excessive cardiac filling pressures can be indicated by the development of subcutaneous edema (see ch. 18) but this is a rare presentation in canine and feline patients.

How Do We Decide When Heart Failure Is Definitely Present?

In order to confirm that a patient has heart failure, two things need to be established: first, that *the patient has evidence of heart disease* and second, that the patient *is showing clinical signs as a consequence of that heart disease.*

If a patient only has clinical findings suggestive of heart disease, such as a murmur or an arrhythmia, but is not showing any clinical signs as a consequence of that disease, then that patient is not (yet) in heart failure. The treatment of patients with acquired heart disease that do not yet have signs of heart failure is controversial, and evidence for and against the treatment during the preclinical phase of different heart diseases is covered in specific chapters (see ch. 251-253).

A confounding factor that often complicates diagnosing the presence of heart failure is that patients may

have clinical evidence of heart disease and be showing clinical signs; however, those signs are caused by another condition with which the patient is suffering concurrently. For example, dogs with heart disease can be exercise intolerant due to concurrent osteoarthritis or dyspneic due to laryngeal paralysis. To conclude that a patient has heart failure, one must therefore establish that the patient has heart disease *of sufficient severity to be likely to be the cause of the signs* and *evidence that those signs directly relate to the patient's heart disease.*

A diagnosis of heart failure therefore is usually made on the basis of a combination of a history of clinical signs indicative of heart failure, physical examination findings indicative of the presence of heart disease, and the results of ancillary diagnostic tests that help to establish that the observed signs are a consequence of the patient's heart disease.

In a patient presenting with increased respiratory rate and effort (see Video 252-6), the most useful diagnostic test to establish whether or not those signs are cardiac in origin is usually thoracic radiography. The demonstration of abnormalities of the shape and size of the cardiac silhouette in conjunction with findings consistent with heart failure, such as pulmonary venous congestion and an alveolar pattern is usually considered the gold-standard for establishing a diagnosis of heart failure. Figure 247-1 is a lateral thoracic radiograph that demonstrates characteristic findings taken from a dog with left-sided congestive heart failure secondary to degenerative valvular disease. Thoracic radiographs can be more difficult to interpret if the cardiac silhouette is obscured by the presence of pleural effusion. In such cases, establishing the presence of substantial atrial enlargement with echocardiography can help to rule in (or, when absent, to rule out) heart disease as the cause of the effusion (see ch. 104). In patients presenting with ascites as a possible manifestation of right-sided congestive heart failure, evidence supporting a cardiovascular cause for the ascites would include demonstration of hepatic venous congestion on abdominal ultrasound and/or evidence of substantial right-sided cardiac disease or pericardial effusion on echocardiography. Examples of characteristic findings from the history, physical examination, and supportive results from diagnostic imaging are shown in Table 247-1.

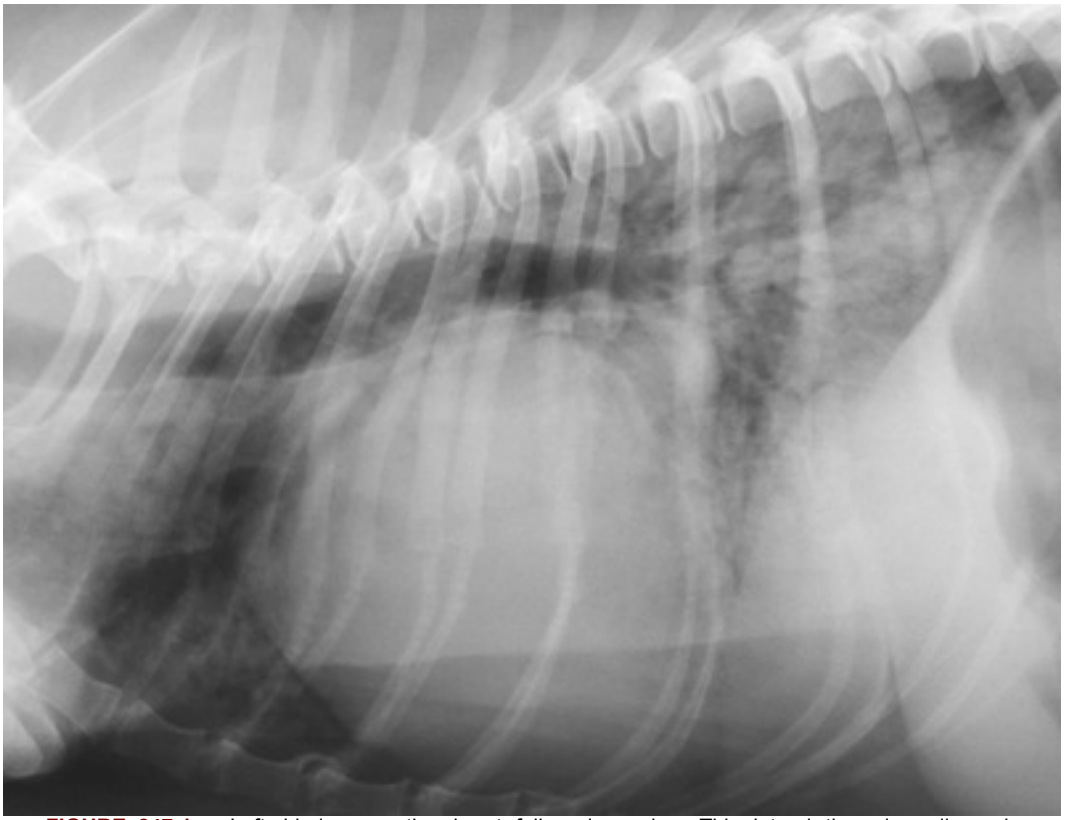

FIGURE 247-1 Left-sided congestive heart failure in a dog. This lateral thoracic radiograph illustrates some of the classic radiographic findings associated with left-sided congestive heart failure. There is marked enlargement of the cardiac silhouette with a widespread opacification of the pulmonary parenchyma consistent with pulmonary edema.

TABLE 247-1

Historical, Physical Examination and Ancillary Diagnostic Testing Findings Consistent with the Presence of Heart Failure

HISTORICAL SIGNS CONSISTENT WITH THE PRESENCE OF HEART FAILURE	PHYSICAL EXAMINATION FINDINGS INDICATIVE OF THE PRESENCE OF *HEART DISEASE*	PHYSICAL EXAMINATION FINDINGS THAT MAY INDICATE THE PRESENCE OF *HEART FAILURE*	ANCILLARY DIAGNOSTIC FINDINGS SUPPORTIVE OF A CARDIAC CAUSE FOR THE PHYSICAL EXAM FINDINGS
Tachypnea, dyspnea, and/or respiratory distress Exercise intolerance Cyanosis Dullness and depression Weakness and lethargy Inappetence	A heart murmur A cardiac arrhythmia An audible gallop sound	Increased respiratory rate and effort with or without audible pulmonary crackles	Thoracic radiographic evidence of cardiomegaly with pulmonary venous congestion and evidence of an alveolar/interstitial pattern in the lung parenchyma
		Increased respiratory rate and effort with ventral dullness on auscultation or percussion	Thoracic radiographic evidence of a pleural effusion with evidence of an abnormal cardiac silhouette (if visible) Ultrasonographic confirmation of pleural effusion with evidence of atrial enlargement
		Abdominal distension with a palpable fluid wave, particularly if accompanied by jugular venous distension and/or hepatojugular reflux	Evidence of hepatic venous congestion on abdominal ultrasound or evidence of significant right-sided heart disease or pericardial effusion on echocardiography
		Pallor and cold periphery	Hypotension that is not attributable to another cause

In order to establish with reasonable confidence that a patient's signs are due to heart failure, the patient should have historical signs consistent with heart failure, physical examination abnormalities suggestive of heart disease and heart failure, in addition to supportive results from ancillary diagnostic tests. For differential diagnosis of some of the signs described here, readers are referred to ch. 26-30.

Measurement of concentrations of circulating cardiac biomarkers such as N-terminal B-type natriuretic peptide (NT-proBNP) can assist in establishing a cardiac cause for observed clinical signs (see ch. 246). Numerous studies in dogs and cats have shown that patients demonstrating signs that could be a consequence of congestive heart failure (e.g., dyspnea) and that have high circulating concentrations of NT-proBNP are more likely to have a cardiac cause for their signs; that is, the likelihood of the patient's signs being due to heart failure is increased considerably when that patient has increased circulating concentrations of NT-proBNP.[1] A recent study has also demonstrated that high NT-proBNP concentrations in the pleural fluid of cats with pleural effusion helps to differentiate those with a cardiac cause of the effusion from those with other causes.[2]

Once a clinician is satisfied that a patient's signs are likely to be a consequence of heart failure, then the clinician should consider how best to manage those signs. In some patients presenting as emergencies with severe and potentially life-threatening clinical signs, it might be impossible to carry out ancillary diagnostic tests without risk to the patient. In these circumstances, the clinician may need to treat the patient on the basis of the most likely underlying condition and then perform appropriate diagnostic tests later, when the patient is more stable and more likely to tolerate them.

Management of Heart Failure

There are four important steps in the management of patients with heart disease causing heart failure:

1. Correct identification of the underlying disease process
2. Staging of the severity of disease
3. Applying "evidence-based medicine" (see ch. 5).
4. In the absence of "best-evidence," making an informed and rational decision, on the basis of the clinical findings, regarding the type of therapy that will be most effective.

These steps ideally should be followed in all cases showing clinical signs of heart failure; however, in some cases, particularly those with acute presentations and severe clinical signs, it may be necessary to initially stabilize the patient prior to performing steps 1-3. The characteristic diagnostic findings of each condition that can result in heart failure are presented in detail in ch. 250-255, as are the most appropriate evidence-based therapy supporting treatment of specific conditions at specific stages. The remainder of this chapter will therefore consider the following points: How can we choose the most effective therapy for a heart failure patient and which clinical findings should guide us in our treatment choices?

Almost all veterinary patients with signs of heart failure will require medical management to resolve their clinical signs. However, there are some exceptions to this generalization—most notably patients with pericardial effusions (see ch. 102 and 254). For some patients, medical management will be the sole intervention required, whereas for others, medical management can be part of a treatment regimen that includes other interventions such as thoracocentesis (see ch. 102) and supplementation of inspired oxygen (see ch. 131).

Some patients may have developed heart failure secondary to a condition that can be surgically managed such as a patent ductus arteriosus. In patients such as these, medical management may be used for stabilizing the patient prior to a more definitive treatment being provided.

Pathophysiological Rationale for Administration of Medications

Patients presenting with signs of heart failure will have abnormalities consisting of one or more of the following:

- Abnormalities of preload
  - Preload can be thought of as cardiac wall stress at end-diastole. This is predominantly determined by the pressure with which blood returns to the heart from the venous circulation (although it is also influenced by the size of the ventricle). Many of the adaptive mechanisms stimulated in patients with heart disease lead to retention of fluid. This causes an increase in filling of the venous circulation and therefore preload. Preload is excessive in patients showing signs of congestion and is primarily modified by drugs that reduce circulating fluid volume **(diuretics)** and dilate veins **(venodilators).**
- Abnormalities of afterload
  - Afterload can be thought of as the force resisting contraction of the myocardium. The main determinant of afterload (in the absence of a ventricular outflow tract obstruction) is the resistance in the vascular bed into which the ventricle is ejecting, i.e., systemic vascular resistance for the left ventricle and pulmonary vascular resistance for the right ventricle. The pathophysiologic response to heart disease is characterized by stimulation of several mechanisms that increase afterload, including the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS). Increased afterload will inhibit ventricular ejection, tend to reduce cardiac output, increase myocardial work and may result in signs of poor perfusion. **Vasodilators** are drugs that reduce systemic or pulmonary vascular resistance and they can be used to modify afterload.
- Abnormalities of myocardial contractility
  - Myocardial contractility is one of the main determinants of cardiac output. Primary or secondary impairment of contractility is present, although difficult to quantify, in many patients with signs of heart failure and may underlie signs of inadequate cardiac output. **Positive inotropic drugs** lead to an increase in contractility.
- Abnormalities of cardiac filling
  - In order to fill adequately, the heart must have enough time to fill and the myocardium must be sufficiently flexible to allow adequate venous return to enter the ventricles during diastole. Diseases that cause the myocardium to be excessively stiff, that impair relaxation (impair lusitropy), or that give the heart insufficient time or space to fill, can compromise filling. This necessitates an increase in preload to maintain an adequate output or leads to a reduction in output. Various types of drugs can directly or indirectly influence the ability of the heart to fill. Drugs that directly influence the ability of the myocardium to relax are referred to as lusitropic drugs; these include sympathomimetic agents and calcium channel blockers. Filling can be improved indirectly by modifying heart rate and rhythm such that there is more time for effective ventricular relaxation and filling.
- Abnormalities of heart rate and rhythm
  - Patients with signs of heart failure frequently have changes in heart rate and rhythm. It is quite

appropriate for many patients with heart failure to be tachycardic—to the extent that a mild to moderate sinus tachycardia is to be expected in many patients with heart failure; however some abnormalities of cardiac rhythm cause sufficient impairment of cardiac function to result in the development of heart failure (e.g., third-degree atrioventricular block or tachycardia-mediated cardiomyopathy), or contribute to the worsening of signs of heart failure in patients with pre-existing heart disease. Patients with bradycardia have a drop in cardiac output due to a drop in heart rate. Patients with marked tachycardia have a drop in cardiac output due to insufficient time for the ventricles to fill and, in some cases, a loss of the normal coordinated pattern of ventricular contraction (ventricular dyssynchrony).

Since some or all of the pathophysiological abnormalities outlined above are likely to be present in patients with signs of heart failure, it is easy to understand that drugs which influence these factors are likely to be those which will be effective in the treatment of patients with heart failure. Thus we can categorize drugs used for the treatment of heart failure into those that decrease preload, decrease afterload, enhance systolic function, improve cardiac filling, or optimize cardiac rate and rhythm.

Drugs Used in the Treatment of Heart Failure

Drugs That Decrease Preload

Indications for Preload Reduction

The clinical signs most likely to be present in a patient with excessive preload are those associated with signs of congestion. Excessive preload will be associated with elevated ventricular filling pressure, elevated atrial pressure, elevated venous pressure, and congestion of the vascular beds that drain into the affected side of the heart. A patient requiring preload reduction is therefore likely to have one or more of the following: pulmonary edema, pleural effusion, or ascites.

The two most effective types of drug for the reduction of preload are diuretics and venodilators. Diuretics will reduce a patient's circulating fluid volume, thereby reducing venous filling pressures (Figure 247-2, *A-C*). Venodilators will reduce pressure within the veins by increasing their diameter (Figure 247-2, *D*).

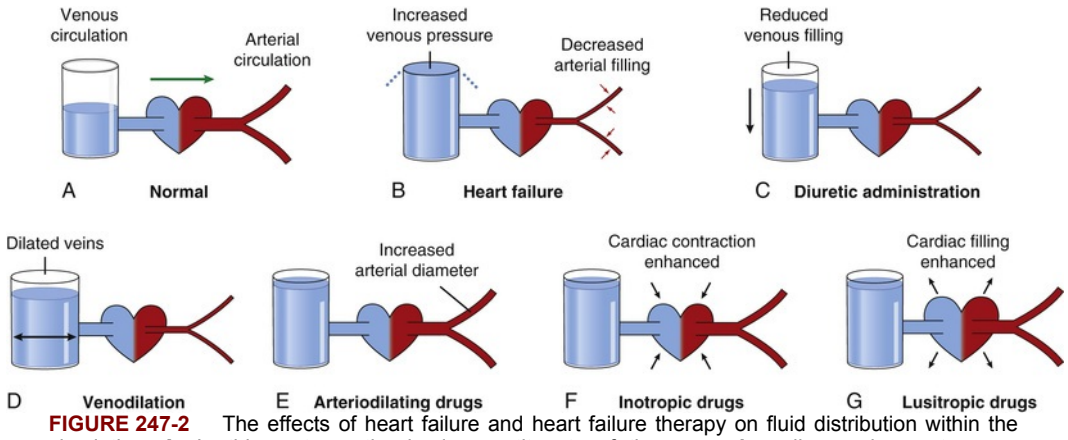

FIGURE 247-2 The effects of heart failure and heart failure therapy on fluid distribution within the circulation. **A,** In this cartoon, the basic constituents of the ***normal*** cardiovascular system are illustrated. The vertically orientated cylinder on the left of the image indicates the venous circulation. The level of blood in this cylinder reflects the pressure within the venous circulation. The heart is in the middle of the cartoon and to the right of the heart is the arterial circulation, indicated by the branching cylinders. The diameter and size of these "arteries" indicates the adequacy of filling of the arterial circulation. The green arrow at the top of the image indicates the direction of flow within the circulation, from the venous circulation through the heart into the arterial circulation. **B,** Illustrates the consequence of ***heart failure.*** Fluid retention has led to increased filling of the venous reservoir, leading to higher venous pressure. Eventually pressure increases to such an extent that fluid begins to leak out of the venous circulation into either tissues or body cavities, leading to "congestive" or "backward" failure. The arterial circulation is underfilled due to reduced cardiac output leading to "output" or "forward" failure. **C,** Illustrates the effect of ***diuretic administration:*** a reduction in circulating fluid volume. This results in reduced venous filling, lowering pressure in the venous circulation below the level at which fluid leaks out, and thus relieving signs of congestion. Diuretic administration alone will have, at best, no effect on cardiac output; therefore, arterial filling is unchanged. **D,** Illustrates the effect of ***venodilation.*** Dilating veins will reduce the pressure within the venous circulation without a change in circulating fluid volume. This is due to the greater capacity of the veins to hold the volume of fluid present. This will have the effect of reducing pressure within the venous circulation below the level at which fluid leaks out. Therefore, the primary effect will be the reduction of signs of congestion and the effect on arterial filling will be, at best, neutral. **E,** Illustrates the effect of administration of ***arteriodilating drugs.*** Decreasing

the resistance to ejection of blood from the ventricle will have the effect of improving delivery of blood into the arterial circulation; therefore, arterial filling will be improved, although this might come with the drawback of a reduction in blood pressure. This may also help to reduce the pressure within the venous circulation by allowing the heart to maintain the same output at a lower preload. **F,** Illustrates the effect of ***inotropic drugs.*** If the force of contraction is increased, the heart will be able to sustain a greater cardiac output, improving arterial filling. The heart may also be able to achieve this output with lower filling pressures, leading to a reduction in venous pressures and improving signs of congestion. **G,** Illustrates the effect of ***lusitropic drugs.*** Improving the capacity of the heart to fill during diastole allows cardiac output to be maintained at lower venous filling pressures. Thus, venous pressures can be reduced and/or cardiac output and arterial filling improved.

Diuretics

Diuretics are, for good reason, the most frequently used medication in patients with congestive heart failure. All diuretics used for the treatment of heart failure patients have a mechanism of action that results in an increase in the excretion of sodium by the patient. If sodium excretion is increased (provided there is not a corresponding increase in intake) there will be a reduction in a patient's extracellular fluid volume. This will result in lower circulating fluid volume and a reduction in preload. A reduction of preload is likely to lead to a rapid improvement in a patient's clinical signs if those signs are a consequence of excessive cardiac filling pressures.

There are several classes of diuretic that increase excretion of sodium by different mechanisms within the nephron (Table 247-2 and Figure 247-3). The relative potency of a diuretic can be expressed by the extent to which it increases the fractional excretion of sodium—the proportion of sodium filtered at the glomerulus that is excreted in the urine (see ch. 73). By this measure, the most potent class of diuretic is the loop diuretics.

TABLE 247-2

Classes of Diuretic, Their Site and Mechanism of Action, and Their Relative Potencies

CLASS OF DIURETIC	EXAMPLES	PRINCIPAL MECHANISM OF ACTION	SITE OF ACTION IN NEPHRON	RELATIVE POTENCY EXPRESSED AS THE MAXIMUM FRACTIONAL EXCRETION OF SODIUM THAT CAN BE ACHIEVED[15]
"Loop diuretic"	Furosemide Torsemide	Blockade of Na+/K+/2Cl− cotransporter	Loop of Henle	Up to 25%
Thiazide	Hydrochlorothiazide	Blockade of Na+/Cl− carrier	Distal tubule and connecting segment	Up to 5%
Potassium-sparing	Spironolactone	Blockade of aldosterone receptors	Cortical collecting tubule	Up to 2%

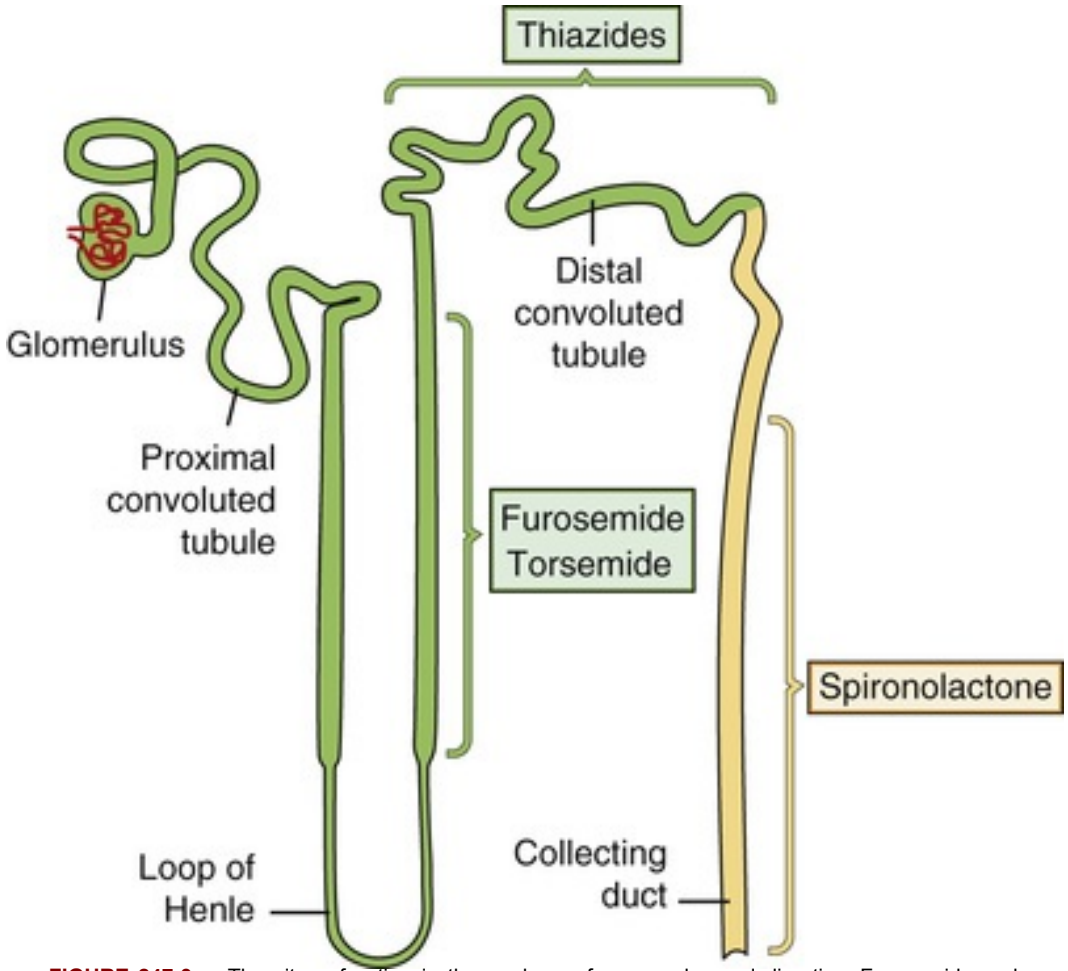

FIGURE 247-3 The sites of action in the nephron of commonly used diuretics. Furosemide and torsemide are loop diuretics and have their principal site of action in the ascending limb of the loop of Henle. Thiazide diuretics act predominantly in the distal convoluted tubule. Spironolactone acts on the collecting duct. Administration of combinations of diuretics with actions at more than one site in the nephron is known as "sequential nephron blockade," which can lead to more potent diuresis.

Three of the most frequently used diuretic agents are furosemide, spironolactone, and torsemide. Thiazide diuretics are also used but usually in combination with loop diuretics to control signs of congestion in patients with more advanced signs of heart failure.

Furosemide should be regarded as first line therapy for any patient requiring medical treatment to relieve clinical signs brought about by congestion. This includes patients that present with dyspnea due to pulmonary edema and pleural effusion, although in the latter case it is likely that the patient will also benefit from thoracocentesis (see ch. 102). Patients with ascites or (rarely) subcutaneous edema due to heart disease will also require diuresis to relieve their clinical signs. If a patient has a large volume of ascites that is causing respiratory compromise, abdominocentesis (see ch. 90) can be indicated to obtain rapid relief of clinical signs but diuretic treatment will still be required to inhibit the redevelopment of the abdominal effusion. Furosemide can be administered by multiple routes including orally, by bolus injection, and by constant rate infusion.[3] Patients that have not previously encountered the diuretic are likely to experience a profound diuresis when the drug is first administered. Patients that have already chronically received furosemide can become refractory to the drug and are likely to have a less profound response to diuresis and in order to achieve control of their clinical signs may require either higher dosages of furosemide or the additional administration of different types of diuretic that act at different sites in the nephron. In dogs refractory to the administration of furosemide, it appears that the administration of torsemide can result in improved diuresis and it has been associated with a sustained resolution of otherwise refractory clinical signs in some cases.[4,5] Initial oral doses of furosemide administered to a canine or feline patient should be in the region of 1-2 mg/kg q 12 h. Doses can be escalated to as high as 4 mg/kg three times a day (up to 12 mg/kg/day). If patients are receiving near to the maximal dosage of furosemide and their signs of congestion are proving

refractory to therapy, rather than further escalation of the dose of furosemide, it is likely that they will benefit more from the co-administration of a second diuretic such as spironolactone, a thiazide, or the administration of torsemide. In cases where patients are apparently refractory to diuretic therapy given at home, it is important to establish that the medication is being administered appropriately. This may require tactfully exploring with the owners their understanding of, and adherence to, the treatment regime prescribed. It is also worth taking a detailed dietary history to determine whether a high-sodium intake is partly responsible for the observed resistance to diuretic therapy (see ch. 183).

Spironolactone is a potassium-sparing diuretic that acts through the inhibition of aldosterone receptors. Benefits demonstrated in human patients with heart failure[6] imply an action independent of the diuretic effect of the agent. This agent should therefore be regarded more broadly as an aldosterone receptor antagonist. Evidence of its effectiveness in the management of canine patients with acquired valvular disease[7] has led to its frequent administration to canine patients with heart failure. Although it has been administered for its diuretic effect, and other putative benefits, in cats with heart disease and heart failure one study in a small number of cats suggested that there may be concern over the development of cutaneous adverse drug reactions.[8] This may have limited the frequency with which it is administered to this species.

In dogs, the effective dosage of spironolactone has been shown to be 2 mg/kg PO q 24 h.[9] In contrast to furosemide, there is little evidence that improved control of clinical signs will be obtained by higher dosages or more frequent administration.

Spironolactone does not have sufficient natriuretic potency to be used as the sole diuretic in patients requiring medical management of signs of congestion. It is better, therefore, to regard it as an agent to be administered alongside other diuretics, particularly loop diuretics, to potentiate their effect. The other argument for its administration is that the benefits associated with its administration are thought to extend beyond diuretic effects. Aldosterone receptor blockade is thought to be of benefit through blocking detrimental effects of aldosterone on the vasculature and cardiac remodeling.

Torsemide (torasemide) is a loop diuretic similar to furosemide that has been used as a salvage agent in patients that have become refractory to high dosages of furosemide during chronic treatment for heart failure. There are several theoretical advantages to the administration of torsemide, including a decreased likelihood of patients becoming refractory to its administration[10] and also possible anti-aldosterone effects,[11] in addition to the effects in the loop of Henle. In patients with refractory signs of congestive failure, torsemide is substituted for the furosemide in the treatment regime and furosemide therapy is ceased. This substitution can take place abruptly with the first torsemide dose administered when the next furosemide dose would have been given. The recommended method of administration is to initiate treatment with a total daily torsemide dose (split into two doses administered at ≈12 hour intervals) that is approximately one-tenth of the total daily furosemide dose the patient was receiving[5] (Box 247-1).

Box 247-1

An Example of a Dosage Conversion from Furosemide to Torsemide

An 11 kg dog currently receives 40 mg of furosemide three times a day and has evidence of ascites that is refractory to current treatment. What dosage of torsemide should be substituted for the current furosemide treatment?

- The current total daily dose of furosemide is 120 mg per day (=10.9 mg/kg/day).
- The total daily torsemide dose therefore should be 120 mg/10 (i.e., 12 mg per day).
- This should be administered as two equal doses approximately 12 hours apart.
- Therefore the dose of torsemide should be 6 mg PO q 12 h.

Thiazide diuretics represent another class of diuretic that is widely used in human patients, particularly those with systemic hypertension. They are also used in canine heart failure patients, especially those with signs of congestion that are refractory to furosemide and spironolactone. Thiazides predominantly act by inhibition of sodium reuptake in the distal convoluted tubule; therefore, when used with a loop diuretic and a potassium-sparing diuretic, this combination produces "sequential nephron blockade," where greater diuresis can be achieved through inhibiting sodium reabsorption at numerous sites in the nephron (see Figure 247-3). Hydrochlorothiazide is a thiazide diuretic agent that can be used in this situation.

Complications of Diuretic Treatment

Although widely used and generally well-tolerated, there are numerous possible complications and side-effects of diuretic administration that warrant the careful monitoring of patients receiving them chronically. The most obvious "side-effect" of diuretics, from the perspective of the animal's owner, is the polyuria and polydipsia that will result from their administration. Owners should always be warned that this is an expected effect of the treatment the pet will be receiving.

All of the most commonly observed complications are direct consequences of the drugs' mechanisms of action and the patient's adaptation to their administration. These include volume depletion and reduction in cardiac output, and electrolyte abnormalities.

Volume Depletion and Reduction in Cardiac Output

The intended effect of diuretic administration is to reduce the patient's circulating fluid volume appropriately. The goal is for the volume to be reduced sufficiently to relieve signs of congestion while allowing the patient to maintain adequate perfusion. If, as a consequence of treatment, the circulating fluid volume is reduced excessively, or if the patient is especially dependent on having a high ventricular filling pressure to maintain an adequate cardiac output (which is particularly likely in patients with predominantly diastolic heart failure, e.g., cats with hypertrophic cardiomyopathy) then there could be a fall in cardiac output and perfusion may be compromised following diuresis. This can manifest in a number of ways, including the patient's becoming hypotensive or azotemic. If a patient does demonstrate these signs after diuresis, it may be necessary to consider one or both of the following:

- Reducing of the intensity of diuretic treatment
- Introducing a more balanced heart failure treatment regime that counteracts the drop in cardiac output by other means, e.g., vasodilation or the administration of inotropic drugs.

One common misapprehension is that a patient showing these signs is "dehydrated" and will therefore benefit from the administration of intravenous fluids. Heart failure—as explained above—is a problem of inappropriate distribution of fluid. In a patient with a normal heart, the administration of fluid into the venous circulation is likely to improve cardiac output and will therefore improve signs of low cardiac output and poor perfusion. In a patient with heart failure, particularly one with signs of congestion, there is already more than enough fluid in the venous circulation; the problem is that the heart is unable to adequately transfer that fluid into the arterial circulation. Adding more fluid into the venous circulation is likely to worsen signs of congestion and is unlikely to improve the signs of poor perfusion. Recently, it has been shown in human patients that intravenous fluid therapy during an episode of acute decompensated heart failure worsens rather than improves outcome.[12] Intravenous fluid therapy is usually contraindicated in patients with signs of congestive heart failure.

Electrolyte abnormalities also commonly occur as a complication of diuretic treatment. The normal physiologic response to increased sodium and water loss is the stimulation of homeostatic mechanisms that attempt to more vigorously retain sodium and water. Predominant among these mechanisms is the RAAS. Less commonly—although significantly—vasopressin release is sometimes also stimulated by a marked fall in blood pressure secondary to heart disease or diuretic treatment. One of the effects of the stimulation of these homeostatic mechanisms is altered handling of electrolytes. Increased activity of aldosterone will tend to favor sodium retention and potassium loss in the distal nephron. This leads to one of the more commonly observed consequences of loop diuretic administration: hypokalemia. Hypokalemia is less likely to be observed in patients if they are concurrently receiving treatments that tend to counteract the RAAS.[13] More widespread use of angiotensin-converting enzyme inhibitors (ACEIs; see below) and spironolactone, in addition to loop diuretics, mean that hypokalemia now is seen less frequently. The situation in which it is now probably most likely to be encountered is during the emergency stabilization of patients where they are likely to receive large doses of furosemide and might not yet have been started on other agents.

Where substantial hypotension arises as a consequence of either severe cardiac disease or vigorous diuretic treatment, vasopressin release can be stimulated. Vasopressin mediates the renal retention of free water. Free water retention will lead to expansion of circulating fluid volume but with the drawback of a reduction in sodium concentration. Thus, severe, advanced heart disease and vigorous diuretic treatment can be associated with the development of hyponatremia.[13] In human studies, the presence of hyponatremia in heart failure patients is associated with a worse prognosis.[14]

After a few days of diuretic administration, a patient will have physiologically adapted to the increased sodium and water loss and reached a new steady state whereby increased sodium loss has been balanced by

more vigorous sodium retention.[15] In this new steady state, sodium intake will equal sodium loss, but crucially this new steady state will have been achieved following a reduction in the patient's circulating fluid volume. After 10-14 days of diuretic treatment, a patient will be in a new equilibrium but with a lower circulating fluid volume. This lower circulating volume will be maintained, and signs of congestion will remain controlled, as long as the patient continues to receive (and respond to) the same diuretic dosage, the sodium intake is consistent, and the heart disease does not significantly worsen. The period during which this new equilibrium develops is the period in which the patient is most likely to develop complications of diuretic treatment; therefore, signs of excessive volume depletion and electrolyte abnormalities are more likely to occur in the 10-14 days following the introduction or modification of a diuretic regime.

Given the frequency with which abnormalities of volume homeostasis, perfusion, and blood electrolyte concentrations occur in patients receiving diuretics, it is good practice to evaluate indicators of renal function and blood electrolyte concentrations before and after the initiation or substantial modification of diuretic treatment. Re-checking serum urea, creatinine, sodium, potassium and chloride concentrations 10-14 days after initiation or alteration of a diuretic regime will allow early detection of abnormalities and necessary adjustments of treatment can be made.

For hospitalized patients with acute heart failure receiving intensive heart failure therapy and frequent dosage adjustments, it is prudent to check serum electrolyte concentrations and indicators of renal function regularly: ideally at least once in every 24 hour period and more frequently in patients experiencing complications.

Venodilators

Venodilators are agents that dilate the systemic veins. Many vasodilators act on both veins and arteries and are described as "balanced" vasodilators (these will be considered further below under afterload reduction). Some vasodilators act predominantly on veins and therefore primarily reduce preload. By dilating veins, these agents increase the volume of the capacitance vessels within the circulation, decreasing the pressure within veins and therefore reducing the pressure at which blood returns to the heart. This will reduce the hydrostatic pressure in the veins and in the capillaries which drain into them—thus tending to reduce signs of congestion that a patient is showing (see Figure 247-2, *D*). Since the two main determinants of the venous hydrostatic pressure are the volume of fluid in the veins and the extent to which those veins are dilated, one can understand how venodilators will tend to act in a complementary way with diuretics in the reduction of preload: Diuretics reduce the volume of blood in the veins and venodilators increase the venous capacity to hold that volume of blood at relatively lower pressures. The class of vasodilators that act predominantly on the veins is nitrate vasodilators and the agent of this class most often administered to veterinary patients is nitroglycerin (glyceryl trinitrate). Some nitrate vasodilators, particularly nitroprusside, have effects on afterload and preload and will be considered with balanced vasodilators, below.

Venodilators tend to be administered in situations where preload reduction is required acutely, i.e., in the management of patients with severe signs of congestion that require emergency management. Nitroglycerin is typically administered as a cutaneous ointment that requires percutaneous absorption in order to be effective. The method of administration and rapid development of tachyphylaxis (tolerance and rapid loss of efficacy) limit the use of nitroglycerin to short periods of administration in hospitalized patients.

There is some evidence of favorable effects of nitrate vasodilators in human patients in the acute setting, but the evidence that exists is relatively weak and does not demonstrate superiority of nitrates over other methods of controlling clinical signs.[16] Long-term, controlled studies of these agents have not been conducted in veterinary patients. Studies in anesthetized normal dogs have demonstrated that splenic volume—and therefore, by inference, capacitance vessel volume—increases in response to transdermal administration of nitroglycerin.[17] In contrast, in a separate study the oral administration of the nitrate vasodilator isosorbide dinitrate was found not to be associated with a redistribution of blood volume between body cavities,[18] implying that this nitrate compound may not be an effective venodilator in dogs.

Drugs That Decrease Afterload

Heart failure is brought about by the chronic stimulation of a number of homeostatic mechanisms responding to a perceived drop in pressure within the arterial circulation (see ch. 246). Many of the systems stimulated in heart failure—including the sympathetic nervous system, the RAAS and the vasopressin system—result in an increase in systemic vascular resistance. This is in an effort to restore blood pressure to a more normal level. Although beneficial as an acute response to a fall in blood pressure, chronic vasoconstriction has a

detrimental effect on cardiac function. Increased vascular resistance will either impair cardiac output or necessitate an increase in cardiac work to maintain an adequate cardiac output. Increased cardiac work will increase myocardial oxygen consumption and, if cardiac work is chronically increased, lead to further deterioration in cardiac function, hastening the further decline of the already failing heart. In the patient with mitral regurgitation, systemic arterial vasoconstriction will resist the ejection of blood from the left ventricle into the aorta and can favor the backward flow of blood through the incompetent valve into the left atrium. The path by which blood leaves the left ventricle in the presence of mitral regurgitation is determined by the relative resistance to ejection into the aorta or back into the left atrium. Reduction of resistance to ejection into the aorta (through reduced systemic vascular resistance) will tend to favor blood leaving the ventricle this way and reduce the magnitude of the regurgitant jet. If the resistance to ejection is reduced, it is also possible that a similar cardiac output will be able to be maintained with a lower ventricular preload—thus, agents that reduce systemic vascular resistance may indirectly bring about preload reduction.

The hypothetical advantages of vasodilators are easy to understand: They should lead to an improvement in cardiac output or alternatively the maintenance of the same cardiac output but with reduced myocardial work (Figure 247-2, *E*).

Clear clinical evidence of the advantages of vasodilation was established in a number of groundbreaking studies in human heart failure patients including the V-HeFT study[19] and the CONSENSUS study.[20] These studies demonstrated improvement in survival of heart failure patients when vasodilators were administered.

There are various classes of drugs that are administered to heart failure patients that act either entirely or partly through a vasodilator effect; these include the nitrates, ACEIs, pimobendan, and calcium channel blockers. Other classes of vasodilator have historically been used in dogs, such as hydralazine[21] and prazosin, but their use has fallen out of favor as evidence to support the use of other agents has strengthened.

A potential disadvantage of vasodilator administration is that reduction in vascular resistance in a patient with already impaired cardiac function could lead to a fall in blood pressure, resulting in signs of hypotension such as syncope, weakness, and hypoperfusion. Patients with certain underlying cardiac diseases might be less able to increase their cardiac output following afterload reduction as a consequence of the type of cardiac disease by which they are affected, and therefore at greater risk of the development of these complications. Patients particularly at risk of this complication are those with outflow tract obstructions and with diseases causing predominantly diastolic dysfunction, such as hypertrophic cardiomyopathy in cats. Despite these valid concerns, the wide variety of benefits, beyond simple reduction in vascular resistance, that are associated with administration of agents such as ACEIs, means that in practice they are frequently given to patients with such underlying diseases. In such cases, more cautious introduction and careful monitoring is warranted.

Nitroprusside

Nitroprusside is a rapidly acting, intravenously administered nitrate vasodilator. It has a balanced effect, meaning that it can achieve preload reduction through venodilation and afterload reduction through arteriodilation. It is rapid acting with profound effects and requires careful administration by constant rate infusion. In an intensive care unit, where blood pressure can be carefully monitored (see ch. 99), it can be a very useful adjunct to other treatments in the acute management of a patient requiring intensive preload and afterload reduction. Administration of nitroprusside in the primary care setting is probably not practicable. Nitroprusside is awkward to administer as it must be protected from light during infusion. As with nitroglycerin, above, patients rapidly become refractory to nitroprusside, which limits its value for chronic administration. It is also metabolized to cyanide, which limits its cumulative use.

Angiotensin Converting Enzyme Inhibitors (ACEIs)

As a class, the ACEIs are one of the most widely used types of agent in the management of veterinary patients with heart failure. There are numerous agents with similar pharmacodynamic effects; these include *enalapril, benazepril, ramipril* and *imidapril,* among others. The effectiveness of ACEIs for the treatment of canine patients with heart failure was established in a number of studies in the 1990s.[22,23] Since then, ACEIs have become, with good reason, a standard part of the chronic therapy for most patients with heart failure. The evidence for their effectiveness in feline patients with heart failure is less well established. One study's preliminary results did suggest that ACEIs were superior to beta-blockers in the treatment of heart failure secondary to myocardial disease in cats.[24] Due to their theoretical (rather than proven) benefits, they are also frequently used as a mainstay of therapy in cats with heart failure.

Through the inhibition of angiotensin converting enzyme, ACEIs tend to both bring about vasodilation and

inhibit fluid retention (see ch. 246). Their interference in this pathway is particularly beneficial in patients that are also receiving diuretics. As described above, diuretic administration leads to sodium loss and RAAS stimulation. It is advantageous to inhibit the pathway by which the patient attempts to circumvent the sodium-wasting effects of diuresis. This complementary effect of the two types of agent is frequently used as an argument for their routine co-administration. Generally ACEIs are administered to most patients with heart failure that require chronic diuresis unless there is a contraindication to their administration. In practice this means that most dogs and cats receiving therapy for heart failure will receive an ACEI. The dosages of some of these agents are outlined in Box 247-2.

Box 247-2

Drugs Commonly Administered for the Treatment of Heart Failure in Dogs and Cats, Including Their Rationale for Administration and Mechanism of Action

Preload Reduction

Diuretics

- Furosemide
  - Oral: 1-4 mg/kg q 8-12 h
  - IV: In the emergency setting, 1-4 mg/kg as a bolus injection; repeat at intervals of 4 hours (or less if signs severe) until clinical signs improve
  - IV CRI: 0.5-1 mg/kg/h until signs improve
  - Total daily doses >12 mg/kg/day should be avoided if possible. Failure of a patient to show improvement after multiple intravenous doses or a CRI for >4 hours should lead to re-evaluation of the diagnosis and modification of the treatment regime.
- Spironolactone
  - Oral: 2 mg/kg q 24 h
- Torsemide
  - Calculate dosage on the basis of the furosemide dose to be replaced (see Box 247-1)
- Hydrochlorothiazide
  - Oral: 0.5-4 mg/kg q 12-24 h. Use lower end of the dosage range when in combination with other diuretics.

Venodilators

- Nitroglycerin
  - Administered as percutaneous ointment
  - 2.5 cm of 2% transdermal ointment per 10 kg body weight

Afterload Reduction

Vasodilators

- Enalapril
  - Oral: 0.5 mg/kg q 12-24 h
- Benazepril
  - Oral: 0.25-0.5 mg/kg q 24 h
- Ramipril
  - Oral: 0.125 mg/kg q 24 h
- Imidapril
  - Oral: 0.25 mg/kg q 24 h
- Amlodipine
  - For heart failure treatment in dogs
  - Oral: 0.05-0.1 mg/kg q 24 h
- Nitroprusside
  - IV CRI: 1-5 mcg/kg/min
  - Start at low dose, titrate up, and monitor blood pressure

Right Ventricular Afterload Reduction

Pulmonary Vasodilator

- Sildenafil
  - Oral: Wide dosage ranges reported from 0.25 mg/kg q 12 h up to 2 mg/kg q 8 h
  - Start low and increase gradually

Improved Cardiac Filling

Lusitropic Agents

- Diltiazem
  - Oral: 10 mg/cat q 8 h
  - Various slow-release preparations are also used, but pharmacokinetics are less well established

Enhanced Cardiac Contractility

Inotropic Agents

- Dobutamine
  - IV CRI: Start at low end of dosage range. Titrate to effect while monitoring for signs of toxicosis, especially arrhythmias.
  - Dog: 2-15 mcg/kg/min
  - Cat: 1-5 mcg/kg/min
- Pimobendan
  - Dog
  - Oral: 0.1-0.3 mg/kg q 12 h (similar dosages have been used empirically in cats)
  - IV: Bolus injection (available in Europe): 0.15 mg/kg

CRI, Constant rate infusion; *IV,* intravenous.

ACEIs are not particularly profound vasodilators and their benefits are more likely to be associated with chronic rather than acute administration. For this reason they are more likely to constitute a part of a chronic treatment regime than be an agent to be administered in the acute heart failure setting.

Much controversy has surrounded whether or not ACEIs have a beneficial effect in preclinical heart disease. Two prospective placebo-controlled studies in dogs with preclinical mitral valve disease[25,26] failed to conclusively demonstrate a prolongation of the time to the onset of congestive heart failure. A retrospective study in dogs with dilated cardiomyopathy[27] suggested that benazepril could be associated with improved outcome, but a prospective placebo-controlled study of these agents has yet to be undertaken in the preclinical stage of this disease. No conclusive evidence currently supports their use at the preclinical stage of feline myocardial disease.

The best evidence, and the majority of expert opinion, support the use of ACEI in most patients with signs of heart failure requiring chronic diuretic administration.

Pimobendan

Pimobendan is described as an "inodilator": an agent with both inotropic and vasodilatory effects. It is impossible to separate these two effects and therefore somewhat artificial to consider the drug as either an "inotrope" or a "vasodilator" here; however, further description of the mechanism of action of, and indications for, this drug will be found below under inotropes.

Calcium Channel Blockers

As a class, the calcium channel blockers have numerous and varied cardiac electrophysiological and vascular effects. The calcium channel blocker most widely administered to veterinary patients for its vasodilator effect is *amlodipine.* It is most frequently used as an antihypertensive agent in cats with systemic hypertension (see ch. 158); however, its marked effects as an arteriodilator have led some to advocate its use as a vasodilator in dogs with heart failure. It may be of particular benefit when that heart failure is secondary to mitral valve disease, for reasons outlined above. Experimental studies have shown a reduction in left atrial pressure in dogs with mitral regurgitation associated with the administration of amlodipine, which suggests a pathophysiological rationale for its administration in dogs with heart failure secondary to this condition;[28] however, a prospective study of the effect of this drug on clinically meaningful outcomes in dogs (or cats) with heart failure has yet to be published.

Therefore, amlodipine could be considered for administration to dogs with heart failure, particularly when secondary to mitral regurgitation, but should probably be given as a second or third line vasodilator to patients that are already receiving pimobendan and ACEI and have refractory signs of heart failure despite receiving such treatment.

Diltiazem is also a calcium channel blocking agent that has been advocated for use in both canine and feline patients with heart failure. In dogs it is widely used as an antiarrhythmic agent and in cats as a possible positive lusitrope so it is considered further for those effects below, and in ch. 248.

Pulmonary Vasodilators

The vasodilators described above act either predominantly or exclusively on the systemic arterial vasculature. Some agents act principally or partially on the pulmonary circulation. In patients with right-sided congestive heart failure, clinical signs can be improved by reduction of the pulmonary vascular resistance. This can improve output from the right side of the heart (and therefore result in an overall improvement in cardiac output) and can also result in a reduction in systemic venous pressures due to more effective transfer of blood from the systemic veins through the pulmonary arteries. Pulmonary vasodilation is most likely to improve a patient's clinical signs when these are, at least in part, a consequence of increased pulmonary vascular resistance, i.e., where the patient has pulmonary hypertension as either the primary cause or a secondary complication of cardiac disease.

Sildenafil is a phosphodiesterase V inhibitor that is widely used with the aim of reducing pulmonary vascular resistance and improving clinical signs in patients with signs of heart failure secondary to increased pulmonary vascular resistance (see ch. 243). Case series have been published describing improvements in clinical signs associated with the administration of this agent in dogs.[29,30] One prospective blinded crossover study suggested that sildenafil, when administered to dogs with heart failure and pulmonary arterial hypertension secondary to degenerative mitral valve disease, is associated with a reduction in pulmonary artery pressures, improved exercise tolerance and quality of life.[31] This agent is most likely to be indicated in patients with heart failure due to causes such as pulmonary vascular parasitic disease or chronic pulmonary diseases. It is also advocated for administration to dogs in the later stages of myxomatous mitral valve disease where right-sided heart failure may develop secondary to the development of pulmonary hypertension (see ch. 251).

Pimobendan may also have pulmonary vasodilatory properties in addition to its systemic vasodilating effects and could therefore also be effective in controlling clinical signs of right-sided heart failure in dogs with more advanced mitral valve disease.

There are occasional reports of the administration of endothelin receptor antagonists (e.g., *bosentan*) to dogs with pulmonary hypertension but there is insufficient evidence currently available to make recommendations regarding their effectiveness. They are also prohibitively expensive.

Drugs That Enhance Inotropic Function

One of the primary determinants of a patient's cardiac output is myocardial contractility. If myocardial contractility is physiologically or pharmacologically enhanced, then a greater cardiac output will be achieved with the same cardiac filling (preload), or the same cardiac output can be achieved with lower cardiac filling pressures. Drugs that enhance contractility therefore have the capacity to increase cardiac output or indirectly decrease preload, by allowing patients to sustain a similar cardiac output at lower filling pressures (Figure 247-2, *F*).

Myocardial contractility is frequently impaired in patients with heart failure. Impairment of contractility can be the primary abnormality causing a patient to have heart failure, e.g., in patients with dilated cardiomyopathy, or may be secondarily impaired due to chronic changes in load imposed upon the heart by other conditions such as valvular heart disease or hypertension. Enhancement of cardiac contractility has the capacity to improve the clinical signs of many patients with heart failure. Patients with signs of forward failure are particularly likely to benefit from improved cardiac output. Indirect reduction of preload can also improve signs of congestion.

Inotropes can be administered in the hospitalized patient with an acute onset of heart failure (or a patient with an acute deterioration of chronic heart failure) or may be chronically administered to patients being managed at home. The inotropic agent most commonly administered to heart failure patients in the acute setting is *dobutamine.* The agent with inotropic properties most commonly administered chronically is *pimobendan.* Other agents with inotropic effects used in the treatment of canine patients include digoxin and milrinone. The former is still frequently administered to dogs but principally because of its

parasympathomimetic effects in dogs with supraventricular arrhythmias (see ch. 248). The latter, a phosphodiesterase inhibitor, is not used commonly.

Dobutamine

Dobutamine is a sympathomimetic agent that acts primarily through stimulation of beta-1 receptors. It therefore enhances both the force of myocardial contraction and the rate at which the myocardium relaxes; i.e., both inotropic and lusitropic effects, respectively. It can only be administered by constant rate intravenous infusion. This means it can only be administered to hospitalized patients. There is a very marked dose-response relationship and higher dosages are more likely to be associated with side-effects such as the induction of arrhythmias. For these reasons, it is an agent that is most safely administered in an intensive care setting where accurate dosing and careful monitoring can be ensured.

Dobutamine is most likely to be indicated in those patients with acute signs of heart failure complicated by either hypotension or primary failure of myocardial contractility (i.e., dilated cardiomyopathy). It is also of value as a "rescue" agent in the treatment of patients with an acute crisis that are already receiving chronic treatment for congestive heart failure of any cause, e.g., dogs with mitral valve disease presenting with signs of heart failure refractory to oral medication.

Due to the restrictions on dobutamine's use imposed by the method of administration, it is inevitable that it will be given for short periods of time—at most a few days—and it should therefore be regarded as a bridge to the development of an effective chronic treatment regime.

Pimobendan

Pimobendan is a widely used agent with both inotropic and vasodilatory properties. These are brought about by phosphodiesterase inhibition and calcium sensitization. Since these effects are inseparable, it is impossible to determine which of pimobendan's effects are brought about through which mechanism and broadly regarding the drug as an "Inodilator" is probably most helpful. Due to effects outlined above, these inodilatory effects will lead to enhancement of cardiac output through reduction of systemic vascular resistance and improved myocardial contractility. It is argued that these combined effects overcome some of the disadvantages of purely inotropic agents, enabling cardiac output to be improved without a substantial increase in myocardial work, due to the simultaneous reduction in afterload.

These hypothetical benefits of pimobendan are supported by a wealth of data from prospective randomized clinical trials demonstrating improved outcomes in dogs with heart failure secondary to both myocardial and valvular heart diseases.[32-34] Although strictly outside the scope of a chapter on the treatment of heart failure, there is also more recent evidence to suggest a potential benefit of pimobendan in delaying the onset of clinical signs of heart failure in dogs with dilated cardiomyopathy[35] and preclinical degenerative mitral valve disease.[35a]

Pimobendan is indicated for chronic administration to all dogs with heart failure secondary to degenerative mitral valve disease or dilated cardiomyopathy, the two most common causes of acquired heart failure in the dog. Although evidence for a benefit of its administration in canine patients with heart failure secondary to other causes is less strong, it can be regarded as indicated in most canine patients unless medical treatment is not appropriate (e.g., in dogs with pericardial effusion causing cardiac tamponade) or where its administration might be contraindicated (e.g., in dogs with a left ventricular outflow tract obstruction).

Pimobendan is usually administered orally; however, an intravenous preparation is available in Europe for administration in the emergency setting.

The benefits of pimobendan in cats suffering from heart failure seem intuitively less obvious in light of the types of diseases that most commonly lead to heart failure in this species. It is more difficult to formulate a pathophysiological rationale for the benefits of an inodilator in patients with hypertrophic cardiomyopathy, since the primary underlying disease process is not one that is conventionally believed to be associated with impaired contractility. Nevertheless, several case series[36,37] and one case-control study[38] have now demonstrated that pimobendan is tolerated, probably safe, and may be associated with improved outcomes in cats with heart failure, even those where the primary underlying disease process is hypertrophic cardiomyopathy. Pimobendan can therefore be considered to be indicated in some cats with heart failure. It is usually administered to cats in addition to an ACEI and diuretic. It is particularly indicated in those presenting with signs of poor cardiac output, in conjunction with signs of congestion and in those already refractory to the more conventional combination of a diuretic and an ACEI.

Drugs That Inhibit Inotropic Function

Beta-Blockade

Some patients with heart disease can have clinical signs precipitated by increased sympathetic stimulation, which increases cardiac contractility and heart rate. This is particularly thought to be the case in cats with hypertrophic obstructive cardiomyopathy, where increased contractility can be associated with worsening of outflow tract obstruction and increased heart rate may further impair already compromised diastolic ventricular filling. Therefore, it has been argued that there could be a benefit of administering drugs that reduce contractility and heart rate to these patients—particularly drugs that inhibit the increase in contractility associated with sympathetic stimulation. For many years, cardiologists advocated the use of beta-blockers such as *atenolol* in the treatment of cats with hypertrophic cardiomyopathy, particularly those with evidence of dynamic left ventricular outflow tract obstruction. More recently, studies have suggested a possible detrimental effect of beta-blockers on outcome in cats with heart failure secondary to myocardial disease[24] and a neutral effect of atenolol on the outcome of cats with preclinical myocardial disease.[39] As a result, the use of beta-blockers in cats with myocardial disease is now falling out of favor.

Studies have been conducted to evaluate the effect of beta-blockade in dogs with dilated cardiomyopathy[40] and mitral valve disease.[41,42] The rationale for these studies has been based on the extrapolation of favorable outcomes associated with beta-blocker administration in human patients with heart failure. None of these studies has demonstrated a clear improvement in clinical status of patients receiving these drugs, nor an improvement in a clinically meaningful outcome, such as survival. Currently, there is insufficient evidence to advocate their administration to dogs with preclinical cardiac disease, and some evidence to suggest that their administration to dogs with overt clinical evidence of heart failure is contraindicated.

The only remaining uncontroversial indication for beta-blocker administration to canine and feline patients with heart failure is due to their effects on cardiac rate and rhythm in patients where arrhythmias are contributing to their clinical signs (see ch. 248).

Improving Cardiac Filling

In order to maintain a normal cardiac output at normal intracardiac filling pressures, the heart must be able to fill normally between contractions. In order to do this, myocardial relaxation must be normal and the myocardium must be compliant. Cardiac filling can be impaired in many ways; there could be inadequate time for the heart to fill if heart rate is excessive, the myocardium might be excessively stiff due to fibrosis or hypertrophy, and normal physiological mechanisms that reduce wall tension at the onset of diastole (principally mechanisms that lead to a reduction in intracellular calcium concentrations) might be impaired.

Heart failure therapy can either directly or indirectly influence cardiac filling. Indirectly, interventions that reduce sympathetic tone and improve oxygenation are likely to result in reduced heart rate and improved myocardial diastolic function. Drugs that directly improve myocardial relaxation are called "lusitropic" agents (Figure 247-2, *G*). Part of the rationale underlying the administration of diltiazem to cats with hypertrophic cardiomyopathy was based on a positive lusitropic effect of the drug. Only weak evidence of a benefit of administering diltiazem to cats with hypertrophic cardiomyopathy has been shown[43] and no peer-reviewed published evidence of superiority of diltiazem over other methods of treatment, such as using ACEI, is available. As such, diltiazem treatment of feline hypertrophic cardiomyopathy is now no longer widely advocated.

Optimizing Cardiac Rate and Rhythm

Patients with heart failure often have abnormalities of cardiac rate and rhythm. Cardiac output is the product of heart rate and stroke volume. Bradyarrhythmias compromise cardiac output due to the reduction in heart rate. Tachyarrhythmias compromise output due to a reduction in stroke volume. Stroke volume is reduced at high heart rates because of reduced time available during diastole for the heart to fill. Some tachyarrhythmias also cause loss of atrioventricular synchrony and/or abnormalities of the sequence of activation of the ventricular myocardium, both of which can further impair stroke volume.

Those patients with signs of heart failure directly attributable to a cardiac arrhythmia, such as those with rapid persistent supraventricular tachycardia or those with bradyarrhythmias like third-degree atrioventricular block, will be substantially improved through control of the arrhythmia. In patients where signs of heart failure are exacerbated by a concurrent arrhythmia, although the arrhythmia may not be the primary cause of the signs, appropriate management of that arrhythmia should also be a specific aim of the

treatment, alongside other attempts to control signs of congestion and poor output (see ch. 248 and 249).

Restoration of a more normal heart rate, by either a reduction or an increase in the heart rate where appropriate, is likely to improve cardiac output. However, it should be borne in mind that many patients with heart failure will have a moderately elevated heart rate and sinus tachycardia. In these patients it can be appropriate, during an acute episode of heart failure, to have a heart rate higher than would be expected in a normal dog. Reduction of heart rate in these patients should be achieved by better control of signs of heart failure rather than by direct administration of negatively chronotropic (heart-rate–reducing) agents such as beta-blockers. Restoration of synchronous atrial and ventricular activation, secondary to abolition of ventricular arrhythmias, is also likely to improve output when such arrhythmias are present.

Monitoring and Adjustment of Heart Failure Therapy

The two main purposes of monitoring patients receiving heart failure therapy are to establish whether the initial aims of treatment have been achieved, and whether any adverse reactions have developed in response to the administration of treatment (Figure 247-4).

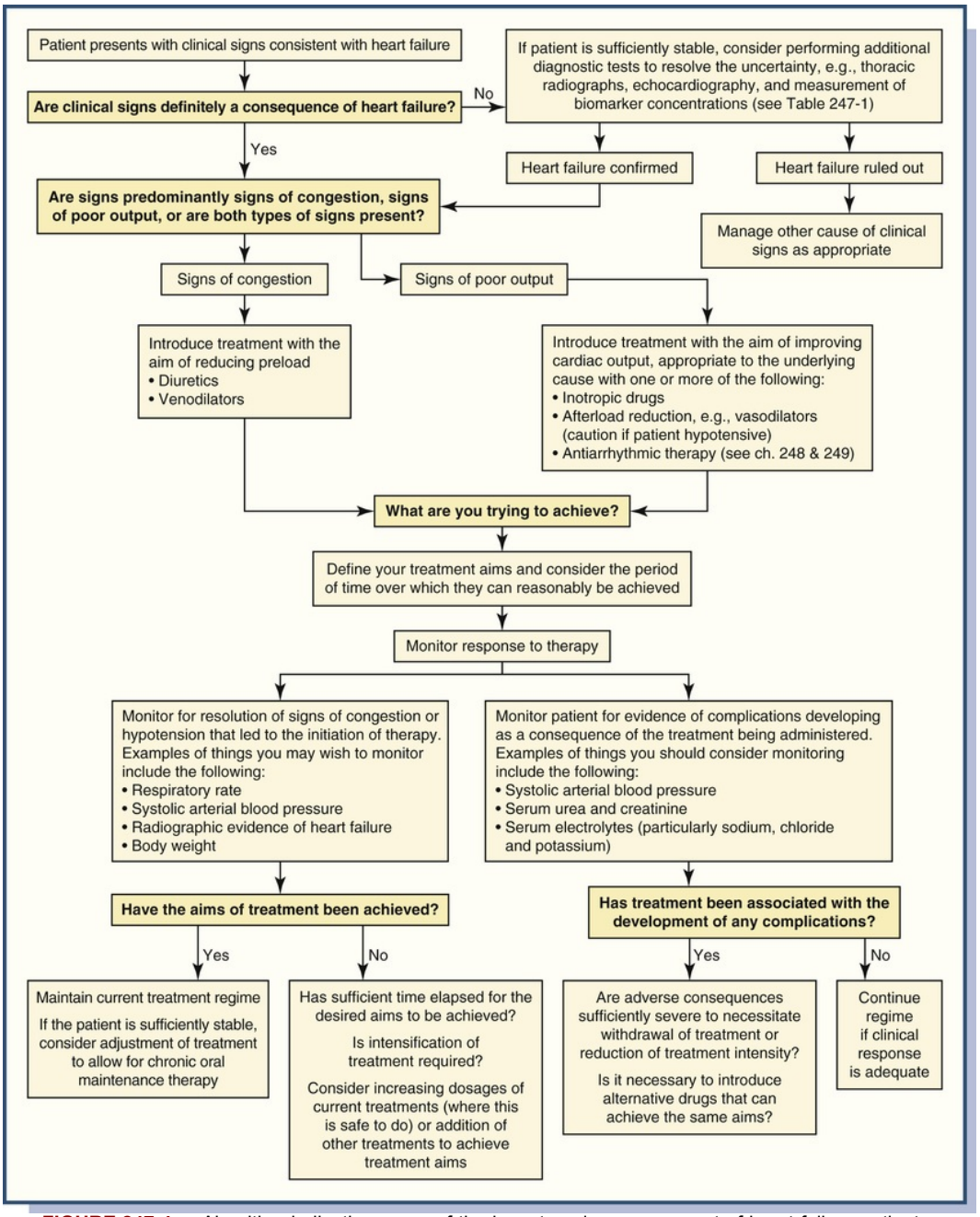

FIGURE 247-4 Algorithm indicating some of the key steps in management of heart failure patients. Boxes highlighted and with boldface font indicate the important questions that a clinician must ask in order to make appropriate therapeutic and monitoring choices.

Complications of diuretic treatment—specifically, their detection and management—are outlined above in the section on diuretics.

The success of therapy will be demonstrated by a resolution of the clinical signs and/or diagnostic findings that necessitated the introduction of treatment. If a patient required treatment because of the presence of pleural effusion leading to dyspnea, then successful treatment would be visible as the resolution of the pleural effusion and restoration of a more normal respiratory rate and effort. Similarly, if the main indication for treatment was dyspnea confirmed radiographically to be secondary to pulmonary edema, successful treatment would be apparent as restoration of normal respiratory rate and effort in conjunction with radiographic resolution of the pulmonary edema.

In a patient hospitalized for the initial management of congestive heart failure, successful treatment ideally would result in an improvement in respiratory rate and effort within the first few hours of treatment. Radiographically detectable improvement of pulmonary edema usually lags behind any improvement in

clinical signs and may take longer to achieve, perhaps 24-48 hours. If clinical indications of congestive heart failure, such as respiratory rate, are not improving, there is probably little point in re-radiographing a patient unless there is doubt over the initial diagnosis of cardiogenic pulmonary edema and alternative explanations for the patient's signs are being sought. The purpose of repeating radiographs therefore is often to confirm and document improvement in the signs of heart failure in a patient already showing clinical evidence of improvement.

In patients that present with clinical signs of poor perfusion, resolution of those signs is likely to indicate successful treatment. If a patient was hypotensive on presentation, then an improvement in blood pressure would be an indication of a favorable response to treatment. Evidence of improved perfusion can be indicated by a patient having warmer extremities. In patients with cardiac disease that present with prerenal azotemia, improved perfusion can result in improvement of the azotemia.

Monitoring of Resting Respiratory Rate

One of the most effective means of chronically monitoring the successful resolution of clinical signs of congestive heart failure appears to be owner measurement of home resting respiratory rate. One study showed that, in dogs receiving heart failure treatment, a resting respiratory rate of <40 breaths per minute was highly predictive of that patient having adequate heart failure control.[44] Similar values are also valid to guide the adequacy of heart failure control in cats. One study showed that normal cats and cats with subclinical heart disease rarely have respiratory rates higher than 30 breaths per minute.[45]

Most owners are able to measure their pet's resting respiratory rate and there is a range of smartphone apps available to facilitate this. Owners can be given, or can themselves establish, ranges of respiratory rates that represent good control of heart failure, and values which would be a cause for concern. In an individual patient, after a period of monitoring, owners can develop a good idea of their own pet's normal range for resting respiratory rate. Owners can then alert their veterinarian if their pet's respiratory rate increases. Some owners can even be given instructions as to how to titrate their pet's diuretic dosage according the respiratory rate; this approach is particularly useful in unstable patients that require frequent adjustment of heart failure therapy, or feline patients that get very stressed when visiting the veterinary hospital.

Adjustment of Chronic Home Therapy

The intensity of a patient's heart failure therapy may be increased or decreased. An intensification of treatment is usually indicated because of poor control of signs of heart failure. Although the majority of patients respond well to the introduction of heart failure therapy, in almost all cases clinical signs of heart failure redevelop after a variable period of time. In the QUEST study, which followed a population of dogs with ACVIM stage C degenerative mitral valve disease, it was common for heart failure therapy to require adjustment and most dogs that had adjustment of their therapy required treatment modification within the first three months of treatment.[46]

The nature of the necessary treatment change is usually indicated by the type of clinical signs the patient is showing. The adjustment most frequently made to treatment is an intensification of diuretic treatment due to the redevelopment of signs of congestion (e.g., tachypnea or dyspnea). In cases where this happens, increasing dosages of furosemide can be administered until the patient's clinical signs are refractory to treatment despite doses of up to 4 mg/kg PO q 8 h. As has been explained above, this often necessitates the administration of multiple diuretics or the substitution of torsemide instead of furosemide.

Occasionally, after a prolonged period of clinical stability, it may be possible to consider reduction of a patient's diuretic dose. This can be done with a sequential reduction in the dosage administered. Every time the diuretic dosage or frequency is changed, the patient should be monitored for a change in respiratory rate. If the respiratory rate remains stable despite the reduction in the diuretic dose, then further dose reduction can be attempted until the lowest dose that continues to adequately control the clinical signs is found.

If a patient redevelops clinical signs of poor cardiac output, then the intensification of therapy aimed at improvement of cardiac output could be required. Depending on the nature of the patient's underlying disease, this may require modification of the dosage of drugs already being administered (such as optimization of the pimobendan dose) or improved control of a patient's arrhythmia.

Outcome of Heart Failure Therapy

Most canine and feline patients can enjoy many months, and in some cases more than a year, of good quality

life as a consequence of successful pharmacological management of their signs. Unfortunately, it remains the case that the most common outcome following the development of signs of heart failure is for the patient, despite treatment, to eventually succumb to their heart disease. Studies in dogs[32,47] and cats[48] with heart disease and heart failure show that the majority of patients with heart failure die of their heart disease within one year of diagnosis. For dogs with dilated cardiomyopathy the median survival time is less than six months.[47]

It is a realistic and laudable aim of therapy to relieve patients' clinical signs, and prolong their life where that life remains of a good quality. It should also be the responsibility of the veterinarian to counsel the owner of the patient about the likelihood of the pet's death and a realistic time frame in which this will probably occur. Although initially hearing about this guarded prognosis can be difficult and distressing for owners, many then feel better prepared for the death of their pet when it eventually occurs.

Eventually, despite the best therapy, patients will succumb to their heart disease. Prioritizing a patient's welfare during end of life care is also of great importance during this phase of their disease.

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CHAPTER 248

Cardiac Arrhythmias

Etienne Côté, Stephen J. Ettinger

Well over 100 years after its invention, the electrocardiogram (ECG, EKG) remains the diagnostic test of choice for the clinical evaluation of patients with cardiac arrhythmias.[1-5] The ECG also has valuable applications in monitoring patients with systemic abnormalities, including electrolyte disturbances and hypoxemia. Additionally, abnormalities in the dimensions of various components of the ECG can serve as an approximate guide for evaluating structural heart disease. These ECG morphologic criteria are rarely based on controlled studies identifying specificity and sensitivity, however, and ECG parameters for dogs or cats by breed, body type, age, and sex are not comprehensively established. An abnormal heart may have a normal ECG and vice versa. Therefore the ECG, like a blood count, is not always an absolute indicator of normalcy or disease, and patterns emerging from serial tracings, or additional clinical information, are essential for understanding the true meaning of most patients' ECGs. The technical aspects of electrocardiography, and reference intervals, are presented in ch. 103.

Cardiac Conduction System and Electrocardiography

Each component of an ECG tracing reflects an electrical event occurring in a specific part of the heart.[1,2,5] The sequence of electrical events follows specific anatomic pathways within the heart, and in health, does so precisely and consistently. This has been the subject of a recent and insightful review.[6]

Initiation of the normal heartbeat occurs in the sinoatrial (SA) node. The SA node is located in the subepicardial tissues of the terminal crest in the dorsolateral right atrium (RA), at the junction of the cranial vena cava and right atrium and directly adjacent to the crista terminalis.[7,8] It is perfused by the SA node artery, a branch of the right coronary artery,[9] and has extensive collateral circulation. In the dog, the heartbeat originates from the middle or cranial regions of the node[10] except under high parasympathetic tone when the more ventral portions of the node, and adjacent extranodal tissues, are the site of origin of the heartbeat.[11] This change in site of impulse formation explains the variation in P wave morphology sometimes observed on the ECGs of dogs (and rarely cats) during changes in autonomic tone and is called the *wandering pacemaker*.

Why does the heart continue to beat? Within the pacemaker cells of the SA node, the heartbeat is born of several ionic shifts, especially the predominantly sodium-carrying (but also potassium-carrying) inward current, I_f.[6,12-14] This "funny current" is so named because of its unusual characteristic of being activated by hyperpolarization rather than depolarization (the hyperpolarization-activated, cyclic nucleotide-gated channel, HCN4, being the channel that gives rise to I_f). This activation begins the process of spontaneous depolarization; a time-dependent decay in the repolarizing potassium currents I_{Kr} and I_{Ks}, the effect of transmembrane I_{NCX} exchanging sarcoplasmic reticulum-derived cytosolic calcium for extracellular sodium, and local (cytosolic) calcium releases,[12] also play important roles in raising the SA nodal cell membrane potential to a less negative value between heartbeats. This process of spontaneous, or phase 4, diastolic depolarization is the hallmark of a normal pacemaker cell. The resulting increase in cell membrane potential leads to the crossing of a threshold level, at which point a combination of transient ($I_{Ca\text{-}T}$, T-type) and long-lasting ($I_{Ca\text{-}L}$, L-type) inward calcium currents cause depolarization of the cell. Depolarization ends when the repolarizing potassium currents, including the transient outward, fast delayed rectifier, and slow delayed rectifier currents (I_{to}, $I_{K,r}$, and $I_{K,s}$, respectively), are activated, evacuating potassium ions from the cell. Overall, this entire panoply of depolarizing and repolarizing currents, which form the cornerstone of initiation of the heartbeat, recently have been grouped together within the SA node's membrane clock and calcium clock paradigm (Figure 248-1).[6,12]

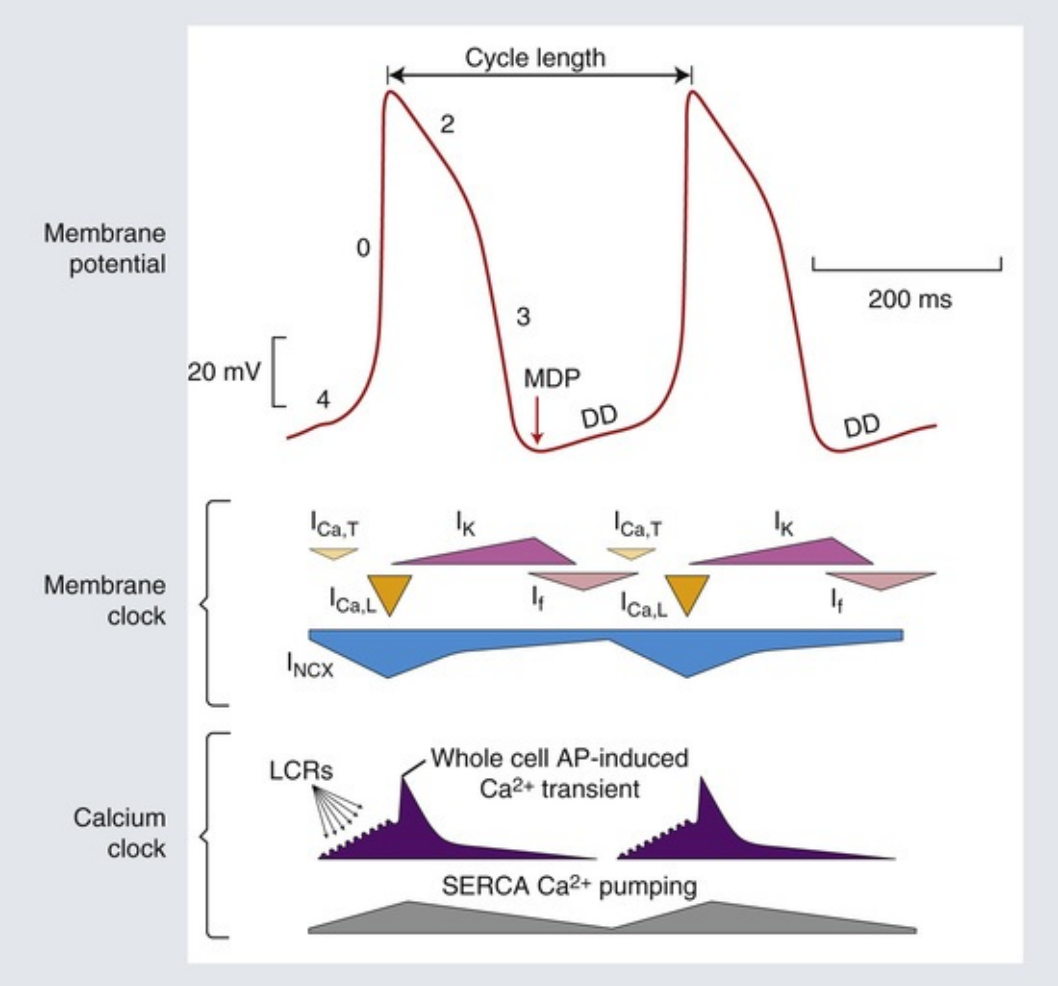

FIGURE 248-1 Components of the membrane clock and calcium clock that are responsible for sinoatrial node depolarization. *DD,* Diastolic depolarization; $I_{Ca,L}$, L-type voltage-dependent Ca^{2+} current; $I_{Ca,T}$, T-type voltage-dependent Ca^{2+} current; I_f, funny current; I_K, delayed rectifier potassium current; I_{NCX}, sodium-calcium exchange current; *LCRs,* local Ca^{2+} releases; *MDP,* maximum diastolic potential; *SERCA,* sarco-endoplasmic reticulum ATPase. (From Monfredi O, Maltsev VA, and Lakatta EG. Modern concepts concerning the origin of the heartbeat. *Physiology (Bethesda)* 28:74-92, 2013. Reproduced with permission.)

The impulse thus formed spreads from the SA node through both atria, forming the P wave on the ECG (Figure 248-2). Specifically, part of the impulse that propagates from the SA node travels along three sets of specialized fibers in the atria called the *internodal pathways or tracts,* consisting of the paired ventral (anterior) pathways, which carry electrical activity directly to the atrioventricular (AV) node, and the dorsal (posterior) pathway called Bachmann's bundle, which is responsible for left atrial activation.[15,16] All three converge on the AV node in the floor of the RA.[7,17] Thus the outward movement of electrical activity from the SA node both triggers the muscular contraction of the atria and carries a sequence of electrical activity to be transmitted to the ventricles.

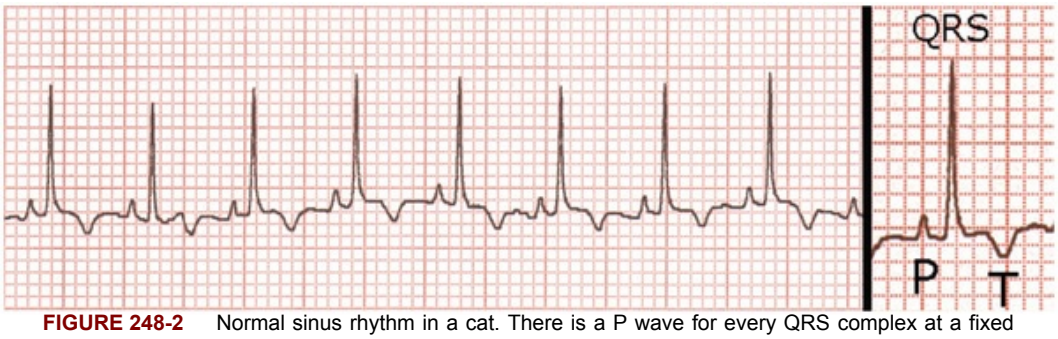

FIGURE 248-2 Normal sinus rhythm in a cat. There is a P wave for every QRS complex at a fixed PR interval, and the P wave and QRS complex morphologies do not change. The R waves are slightly taller than normal, consistent with left ventricular hypertrophy in this cat with hypertrophic cardiomyopathy (R wave height; 1.0 mV; feline reference range: <0.9 mV). The heart rate is 155 beats/min. Lead II, 25 mm/sec, 1 cm = 1 mV.

At the level of the AV node, the electrical impulse depolarizing the heart is purposefully delayed due to a low concentration of gap junctions between cells, which slows intercellular conduction.[9] This delay is a normal process and indeed, failure of the impulse to pause in the AV node is an abnormality called preexcitation (see Macroreentrant Syndromes, later). The purpose of this delay is to optimize ventricular filling by allowing the atria to finish contracting. The period of relative electrical quiescence during which the impulse slowly passes through the AV node is reflected on the ECG as a flat segment between the P wave and QRS complex, the PR segment; in terms of nomenclature, the PR *interval* consists of the PR segment plus the P wave (see later). In addition to transmitting impulses from the atria to the ventricles, the healthy AV node acts as a gatekeeper, blocking unwanted atrial impulses from crossing to and activating the ventricles, such as when these impulses are premature or excessive (e.g., atrial fibrillation [AFib]). This characteristic depends on the refractory period of AV nodal cells and varies among individuals, and even within individuals depending on autonomic inputs. In normal individuals, the unidirectionally conducting fibers of the AV node–His bundle complex make up the only electrical connection between the atria and the ventricles.

The AV node is sometimes considered to have three components: the atrionodal (AN), nodal (N), and nodal-His (NH) regions, from proximal (furthest from the ventricles) to distal (closest to the ventricles), respectively.[18] This division is based on experimental demonstration of differences in action potentials of the three regions and is of limited clinical significance. Of importance is the automaticity of the N region, an ability to form impulses spontaneously much in the same way as the SA node normally does, but at a slower rate. In this manner, the AV node usually is overridden (and its pacemaking ability suppressed) during normal sinus rhythm by normal sinus impulses, which pass through—and reset—the latent pacemaker cells in the AV node before they have had a chance to depolarize. This normal phenomenon prevents the AV node from competing with the SA node as the natural pacemaker for the heart. Still, the N region of the AV node can assume the role of pacemaker for the heart if sinus impulses do not reach it—a failsafe mechanism that is activated only when the need occurs, and which is called an *escape mechanism* or *escape rhythm.* Specifically, an escape rhythm originating from the N region is termed a *junctional escape rhythm*, highlighting that it originates from the AV junction rather than the His-Purkinje system in the ventricles. Because the N region is in the center of the AV node, it can be seen that AV block (such as that caused by AV nodal fibrosis) affecting the proximal (AN) region would allow a junctional escape rhythm to emerge, whereas with AV block occurring in the N or NH regions, the ability for a junctional escape rhythm to exist would be lost, and a generally slower His-Purkinje/ventricular escape mechanism would become activated instead.

Having crossed through the AV node, the electrical impulse of a normal heartbeat travels rapidly and uniformly through the ventricles via the His-Purkinje system.[9,16] This network of conductive fibers ensures that the impulse is carried quickly and distributed uniformly, such that the ventricles depolarize, and can then contract, in a synchronized fashion.[19] The fibers begin as a thick cable, the His bundle, that accepts transmission from the AV node and crosses through the endocardial cushion to the ventricles. The His bundle quickly divides into right and left bundle branches (RBB and LBB), directed to their respective ventricles, and the left bundle in turn divides into left anterior, left posterior, and septal fascicles of highly variable shape and pattern of arborization.[16] The clinical relevance of this division into bundles relates to interruptions of electrical conduction through the bundles, which can occur under various pathologic, and occasionally normal, conditions (see Bundle Branch Blocks, later). Overall, depolarization of the ventricles is apparent on the ECG as the QRS complex. When the ventricles have completely finished depolarizing, a sequence of

repolarization returns the myocardial cells to their resting state. This repolarization sequence, which follows in the wake of the depolarization sequence, is seen as the T wave on the ECG.

Repolarization of the ventricles occurs transmurally: epicardial myocytes repolarize first, creating the ascending limb of the T wave. The T wave's amplitude is limited by the onset of repolarization in endocardial myocytes, which then contributes to the descending limb of the T wave. Repolarization is complete when the last population of midmural ventricular myocytes, called M ("midmyocardial") cells, is repolarized.[20] Alterations in this complex process can be pathologic, producing changes such as "J" or Osborn waves in hypothermic patients, or can be normal variants, such as the T wave of healthy dogs, which can be positive or negative. It should be noted that the atria also repolarize, but the amount of electrical activity involved in this process is generally directed in an orientation that registers a trivial deflection, if any, in most leads of the ECG, and whatever deflection occurs can routinely be masked by the subsequent QRS complex.[21,22] Severe atrial repolarization changes occasionally may be observed as an atrial T wave, or T_a wave, and these tiny deflections may be more apparent in the presence of AV block, when the post-P wave ECG is unfettered by an ensuing QRS complex.[21,22]

The heart rate is constantly governed by autonomic influences. A dog of medium body size without autonomic control of the heartbeat has an intrinsic heart rate of 142 beats/min, as shown with simultaneous parasympathetic and sympathetic antagonism, instead of a normal resting heart rate of approximately 100 beats/min.[23] Holter studies support the large moment-by-moment variability of autonomic inputs to the heart: over a 24-hour cycle, the heart rate varies from 55 to 243 beats/min in healthy Beagles[24] and 77 to 282 in healthy cats.[25,26]

Diagnostic Manipulations with Electrocardiography

Vagal Maneuver

Artificially increasing a patient's vagal tone has potential value both diagnostically and therapeutically. Diagnostically, slowing the heart rate and increasing AV nodal refractoriness through vagal maneuvers may slow a rapid tachycardia, allowing some of its features to be more apparent and facilitating the ECG diagnosis (Figure 248-3). Therapeutically, an increase in vagal tone that interrupts macroreentrant circuits occasionally can terminate such arrhythmias as AV nodal reentrant tachycardia and orthodromic AV reciprocating tachycardia (see Pre-excitation/Macroreentrant Syndromes, later).

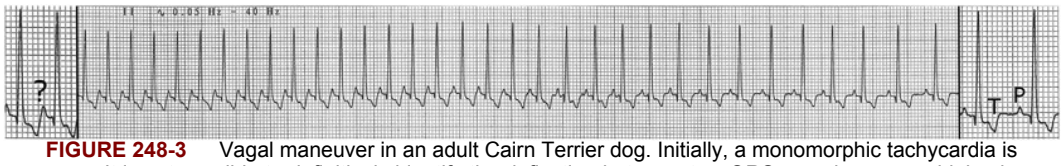

FIGURE 248-3 Vagal maneuver in an adult Cairn Terrier dog. Initially, a monomorphic tachycardia is seen. It is not possible to definitively identify the deflection between two QRS complexes as a biphasic T wave, summated T and P waves, or T waves and flutter waves (left inset, "?"). Carotid sinus massage was begun 5 seconds earlier; by the end of the tracing, P waves and T waves are clearly separated (right inset), allowing the diagnosis of sinus tachycardia. Lead II, 25 mm/sec, 1 cm/mV.

Carotid sinus massage is one type of vagal maneuver. It involves the simple application of gentle, sustained digital pressure by the clinician to one or both of the patient's carotid sinuses, located just caudal to the dorsal aspect of the larynx (sometimes to the point of eliciting a gag reflex), for 5 to 10 seconds, while the ECG tracing is being recorded. The patient should tolerate such a maneuver, and signs of discomfort, resentment, or a marked change in heart rate warrant immediate termination of the maneuver. Because dogs and cats very rarely suffer from carotid artery atherosclerosis, concern for thromboembolic consequences of carotid sinus massage as expressed in human cardiology is unlikely to be relevant to small animal practice. Ocular pressure over closed eyelids is another form of vagal maneuver. It consists of applying firm but controlled gentle digital pressure to both globes through closed eyelids. The distance of retropulsion of the globes depends on the shape of the orbit, and subjectively, the amount of pressure applied is the best guide; it should not exceed the digital pressure one would place on a ripe grape without rupturing it. Ocular pressure is contraindicated in patients with ocular problems. There appears to be interindividual variation in response to vagal maneuvers, with some individuals demonstrating a stronger effect during carotid sinus massage and others ocular pressure. Another simple method of eliciting a vagal response without inflicting pressure on a body

part is to immerse the patient's face or distal limb into a small bucket of ice water for a short period.[27] In the awake dog or cat, this usually will rapidly evoke a vagally mediated decrease in sinus heart rate.

Atropine Response Test

Administration of atropine sulfate 0.04 mg/kg IV can be used diagnostically to evaluate bradycardias.[3] It allows the differentiation between physiologic bradycardias that are purely of vagal origin (atropine increases the heart rate) and pathologic bradycardias that are caused by intrinsic disturbances of impulse formation or conduction (atropine has no effect). The response occurs within seconds to minutes (within 15 minutes) after injection.[3] A positive response to atropine is poorly predictive of a beneficial effect of oral vagolytic drugs such as hyoscyamine or propantheline in dogs with AV block,[28] but is associated with a beneficial effect of medical treatment of sinus node dysfunction (sick sinus syndrome, SSS).[28a]

Cardiac Rhythm Disturbances

The terms "dysrhythmia" and "arrhythmia" are used interchangeably, although "arrhythmia" is preferred.[29] For evaluation and management of patients with cardiac arrhythmias, a useful and practical classification scheme is one that separates arrhythmias into three groups: (1) disturbances of impulse formation (cardiac excitability), (2) disturbances of impulse transmission (cardiac conduction), and (3) complex disturbances involving abnormalities both of excitation and conduction. Some rhythm disturbances fit poorly into any category. Some disturbances of cardiac excitability are secondary to conduction disturbances (e.g., junctional or ventricular escape rhythms). Disturbances are presented in this chapter according to the anatomic level of their origin (i.e., atrial, junctional, or ventricular).

Excitation disturbances can cause either excessive or inadequate functioning of the heart or its parts. Increased excitability produces extrasystoles if intermittent, and tachycardia if sustained. Ectopy is the term that describes spontaneous production of impulses anywhere in the heart other than the SA node. Decreased excitability replaces impulse formation with electrical quiescence, resulting in bradycardia or asystole.

Conduction disturbances within the heart are called *blocks*. Their categorization depends on the anatomic location of the block and its extent or degree (see below). Block can occur at the SA node (rarely identified), the AV node, or in branches of the His bundle (bundle branch blocks, BBBs).

Finally, disturbances combining excitability and conduction abnormalities also are clinically relevant. Serum electrolyte abnormalities commonly have repercussions on the rhythm of the heartbeat, which can involve alterations in excitation, conduction, or both. In preexcitation and macroreentrant syndromes, accessory conduction pathways bypass part of the normal AV conduction pathway. Sinus node dysfunction, also called *sick sinus syndrome* (SSS), generally involves periods of bradycardia and tachycardia caused by dysfunction of the SA node and supraventricular and ventricular conductive tissues.

Clinical Impact of Rhythm Disturbances

The rhythm disturbances discussed above carry varying degrees of clinical importance. Their clinical impact can range from harmless (some are benign variations of normal) to severely detrimental (life-threatening). In cats, ventricular extrasystoles, preexcitation, and isorhythmic AV dissociation have been associated with feline cardiomyopathies. In the dog, disturbances of excitability, especially extrasystoles and AFib, are more common than are disturbances of conduction, the majority of which are AV blocks.[1,2,30]

A cardiac arrhythmia's impact on the patient—the hemodynamic consequences—depends on at least eight factors: (1) the ventricular rate, (2) the duration of the abnormal rhythm, (3) the temporal relationship between the atria and ventricles, (4) the sequence of ventricular activation, (5) inherent myocardial and valvular function, (6) cycle length irregularity, (7) drug therapy, and (8) extracardiac influences.[1-3] Ultimately, the sum of these factors—not just the appearance of the ECG—determines the impact of the arrhythmia on the patient. This is the reason that some animals with ventricular tachycardia (VT) appear overtly normal, whereas others are moribund, for example.

Identification of Rhythm Disturbances

Today, most clinical electrocardiography in veterinary medicine relies on single-lead, in-hospital ECGs. Multilead ECGs provide an additional level of information that is sometimes indispensable (see Figure 248-13).

Rhythm disturbances are identified on the ECG using a methodical, five-point examination. First, a rapid, cursory evaluation from left to right of the entire tracing gives a general idea of the cardiac rate and rhythm and an initial diagnostic orientation. This step reveals whether a single rhythm or many rhythms exist. (Are all QRS complexes of the same morphology? Are the R-R intervals, or *coupling interval*, the same, or do they vary? If so, does the variation occur in a predictable manner?) One grossly assesses the heart rate (slow, normal, or fast), whether the rhythm is regular or irregular (R-R intervals the same, or variable, respectively), and detects premature or delayed complexes.

Second, the R-R intervals are evaluated in representative sections of the entire tracing. In cats in the clinical setting, variability of the R-R interval is not normally seen and is considered pathologic.[31] In dogs, a cyclical (i.e., rhythmic, patterned, "regularly irregular") variation of the R-R interval, respiratory sinus arrhythmia, is normal (Figure 248-4). Patternless, irregularly irregular R-R intervals are always abnormal in both species.

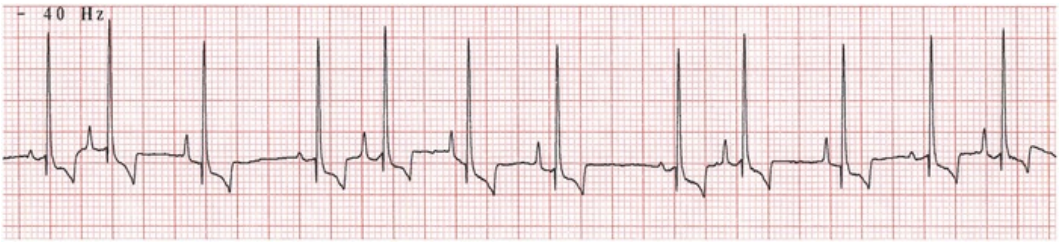

FIGURE 248-4 Respiratory sinus arrhythmia and wandering pacemaker in a dog. Lead II, 25 mm/sec, 1 cm/mV.

Third, the examination of individual QRS complexes consists of determining whether they are narrow or wide. Narrow QRSs generally identify normal ventricular depolarization (i.e., of supraventricular origin) (see Figures 248-2 to 248-4). Wide QRSs represent the asynchronous depolarization of the two ventricles, which may be due to the ventricular origin of a depolarization, to BBB, or to preexcitation/macroreentry (see later). Because repolarization follows directly in the wake of depolarization, a QRS complex of abnormal shape should also have a T wave of abnormal or different shape. If the T wave is normal, the possibility of artifact, rather than a truly abnormal QRS, should be considered as the explanation for a wide, bizarre deflection.

Fourth, examination of the P waves (present, absent; positive, negative) provides information on the depolarization of the atria. Examination of the P-R interval (1) determines if a P wave exists for every QRS complex and a QRS complex for every P wave (to assess AV synchrony) and (2) assesses AV nodal conduction, which is confirmed by a constant P-R interval duration.

Finally, the basic underlying rhythm and any additional or secondary rhythms that are superimposed are identified. Normally, a P wave exists for every QRS complex (an atrial depolarization for every ventricular depolarization). Abnormalities causing more than one P wave for each QRS complex include second- and third-degree AV blocks, and abnormalities producing QRS complexes without P waves include ventricular arrhythmias, AFib, and atrial standstill.

Disturbances of Excitability

An important subdivision involves classifying disturbances of excitability broadly as disturbances of supraventricular excitability,[32,33] including STach, premature atrial complexes (PACs), atrial tachycardias, atrial flutter, and AFib; or as disturbances of ventricular excitability, including ventricular extrasystoles (PVCs, VPCs), VT, torsade de pointes (TdP), ventricular flutter, and VF. Proper classification is clinically important: the inciting factors that produce the arrhythmias in these two subgroups often are specific to the subgroup, and antiarrhythmic treatment is also usually different between the two subgroups.

Disturbances and Alterations of Sinus Excitability

These arrhythmias are variations of sinus rhythm, and are most commonly linked to normal or excessive autonomic inputs.

Respiratory (Normal) Sinus Arrhythmia

Even in the hospital setting, the balance between the sympathetic and parasympathetic inputs to the heart generally tilts in favor of the parasympathetic system in most resting dogs.[23] In the veterinary clinic, this

characteristic is in contrast to the average cat. Vagal predominance in the dog produces two particular features of sinus rhythm on the canine ECG: respiratory sinus arrhythmia (RSA) and wandering pacemaker (WP).

RSA is the result of vagal and hemodynamic effects that occur within the thorax during each respiratory cycle (see Figure 248-4). In dogs, it is a normal physiologic phenomenon requiring no treatment. The result is a correlation between heart rate and respiratory rate, with slowing of the heart rate during expiration and acceleration of the heart rate during inspiration. The repeating, cyclic nature of this arrhythmia is its hallmark. RSA is first noted in the puppy after 4 weeks of age,[1] generally disappears when the heart rate exceeds 150 beats/min at any age (because sympathetic tone overtakes parasympathetic tone in most situations that produce such rapid heart rates),[1,2] and can be enhanced when severe dyspnea is present (pneumothorax, pulmonary fibrosis, emphysema, upper airway obstruction) due to exaggerated changes in intrathoracic pressure.[1] In cats, respiratory sinus arrhythmia occurs commonly during sleep[34] and in the home environment in general,[25] but an adrenergic surge brought about by the clinical environment likely explains its rarity in the hospital setting. In dogs, the presence of RSA can constitute a valuable diagnostic clue in a common clinical situation, namely in the coughing, small- to medium-breed adult dog. It is common for these dogs to have concurrent myxomatous/degenerative mitral valvular heart disease (DMVD; typical murmur is ausculted) and a primary respiratory disorder such as chronic sterile bronchitis. It might be difficult to pinpoint whether congestive heart failure (CHF) or a primary respiratory problem is responsible for the animal's respiratory signs, yet the need for immediate and long-term treatment and the prognosis both depend on knowing which disease process predominates. The presence of RSA makes decompensated DMVD as the sole cause of respiratory signs unlikely because the cardiogenic pulmonary edema of CHF would almost invariably be associated with increased sympathetic tone and loss of RSA.

Successful treatment of CHF can bring about the reappearance of RSA in a patient previously with sinus or other supraventricular tachycardia, particularly if treatment includes digoxin. This return of RSA is due to the reduction of sympathetic tone associated with resolving CHF; an additional benefit of digitalization, albeit a theoretical one in veterinary practice, is reactivation of baroreceptors, which otherwise remain downregulated ("exhausted") by the ongoing sympathetic stimulation of CHF.

Ventriculophasic Sinus Arrhythmia

Ventriculophasic sinus arrhythmia refers to an uncommon phenomenon consisting of variation in the P-P interval in patients with high-grade second-degree, or third-degree, AV block.[35,36] Specifically, the P-P interval that flanks the QRS complex is shorter than the P-P interval during block (see Figure 248-22). Since the sinus rate should be constant during AV block, this cyclical, repeating variation in P-P interval is unusual, and can be explained either by an increase in SA nodal arterial perfusion after ventricular contraction, or triggering of the Bainbridge reflex with atrial filling. There is no clinical importance specific to the finding of ventriculophasic sinus arrhythmia other than to not mistake it for an atrial arrhythmia.

Wandering Pacemaker

WP is a normal, physiologic phenomenon in dogs that is not associated with pathologic conditions and requires no treatment (see Figure 248-4). As discussed previously, the origin of depolarization in the canine heart is not fixed but can move within the RA, or even between the SA node and the AV node. On the ECG, the result is variation in the P wave amplitude, with a constant P-R interval and QRS complexes that retain a normal, supraventricular appearance. This variability in the P wave is often cyclic and often associated with RSA (see Figure 235-3). In this situation the amplitude of the P wave increases with an increased heart rate (inspiration) and decreases with decreased heart rate (expiration), sometimes to the point of disappearance (isoelectric P wave) or, rarely, negativity of the P wave in leads II, III, and aVF.[1,2] The ECG differential diagnosis for WP includes morphologic abnormalities (e.g., P pulmonale) and supraventricular extrasystoles. In some individuals with marked resting vagal tone (e.g., brachycephalic dogs), an exaggerated but normal RSA and WP can be difficult to differentiate from a pathologic arrhythmia, namely PACs (supraventricular extrasystoles). Both PACs and the combination of WP and RSA produce a P wave of different morphology, a shorter R-R interval, and QRS complexes of normal morphology. Differentiation rests on the degree of prematurity (WP and RSA should not occur so prematurely as to produce a P wave inside the preceding T wave), heart rate (WP and RSA do not occur at a rate above 150/min), P wave morphology (as described above, RSA produces P waves that are taller, not shorter, when the heart rate is faster, whereas with PACs the P wave can be taller or shorter than the normal P wave), and the appearance of a series or "paroxysm" of such beats closely coupled to each other (corresponding to multiple supraventricular extrasystoles [i.e.,

supraventricular tachycardia], not RSA). If none of these characteristics is apparent, a Holter monitor can be used for assessing a large number of heartbeats.

Sinus Bradycardia

Sinus bradycardia (SB) is a sinus rhythm in which the heart rate is abnormally low (Figure 248-5). A 1 : 1 ratio of normal-appearing QRS complexes and P waves exists, with a constant P-R interval. Although some approximate normal ranges of heart rate exist for dogs and cats (e.g., 70-160 beats/min for dogs, and 140-220 beats/min for cats; see ch. 103), the notion of bradycardia varies according to species, age, breed, and especially environment; older or brachycephalic dogs tend to have slower heart rates than average, and both dogs and cats have normal heart rates that can be markedly influenced by environmental stimuli.

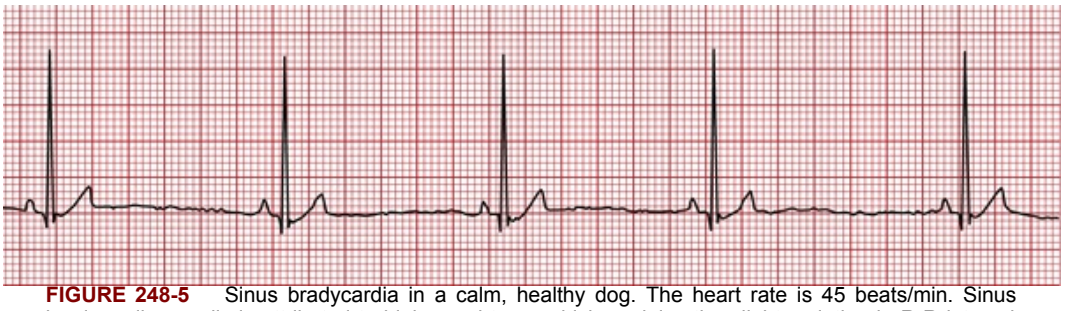

FIGURE 248-5 Sinus bradycardia in a calm, healthy dog. The heart rate is 45 beats/min. Sinus bradycardia usually is attributed to high vagal tone, which explains the slight variation in R-R interval (respiratory sinus arrhythmia). Lead II, 25 mm/sec, 1 cm = 1 mV.

SB generally indicates the physiologic (e.g., brachycephalic, athletic individual, sleep) or pathologic (e.g., systemic intoxication) predominance of the parasympathetic system. A diagnostic aid is the response to an intravenous injection of atropine (see previous discussion), which should convert physiologic SB into normal sinus rhythm or sinus tachycardia.[37] As a general concept, severe bradycardias directly linked to overt clinical signs (syncope, malaise, seizures) warrant specific treatment with drugs or pacemaker implantation, and SB is almost never the cause of such clinical manifestations. SB may occur as the cardiac manifestation of asphyxiation (e.g., upper airway obstruction due to foreign body, neoplasm, nasopharyngeal polyp, or elongated soft palate; closed pop-off valve in an intubated patient) and in such a situation, treatment of SB with atropine (e.g., 0.04 mg/kg IV) or low-dosage epinephrine (e.g., 0.01 mg/kg IV) can be appropriate if immediate relief of the airway obstruction is not possible or, if accomplished, fails to immediately raise the heart rate. In virtually all instances, SB is the effect, rather than the cause, of a patient's problem. Hypothermia, an excessively deep anesthetic plane, and high vagal tone of any origin (gastrointestinal [GI], respiratory, neurologic, ophthalmic) are common causes of SB, and treatment of the bradycardia mainly consists of treating the underlying cause first. Perhaps the only exception is the occurrence of SB as part of sinus node dysfunction/SSS, where indeed SB can be a primary, pathologic bradycardia, in which case it is typically accompanied by AV block and/or extrasystoles (see sinus node dysfunction/SSS, later). Finally, a potentially dangerous situation is the instantaneous transition from a tachycardia to SB (or other bradycardia [e.g., ventricular escape rhythm]; see ventricular escape rhythm) in a debilitated, unstable, often unconscious patient. Such a rapid change can herald an upcoming cardiac arrest and should be addressed with immediate assessment of the patient for underlying causes and preparation for cardiopulmonary resuscitation (see ch. 140 and 141).[38]

Sinus Tachycardia

STach is a sinus rhythm that occurs at an elevated rate (Figure 248-6). The wide range of resting heart rates in normal cats and dogs makes the cut-off between NSR and STach an approximate one. In dogs, STach is defined as a heart rate greater than 160 beats/min but of SA nodal origin (i.e., P-QRS-T complexes of normal shape and sequence). Diagnosing this arrhythmia on the ECG can be difficult when the heart rate is extremely elevated, causing T and P waves to blend together. A vagal maneuver, which temporarily slows the heart rate, separates the P and T waves and clarifies that the tachycardia is of sinus origin (see Figure 248-3).

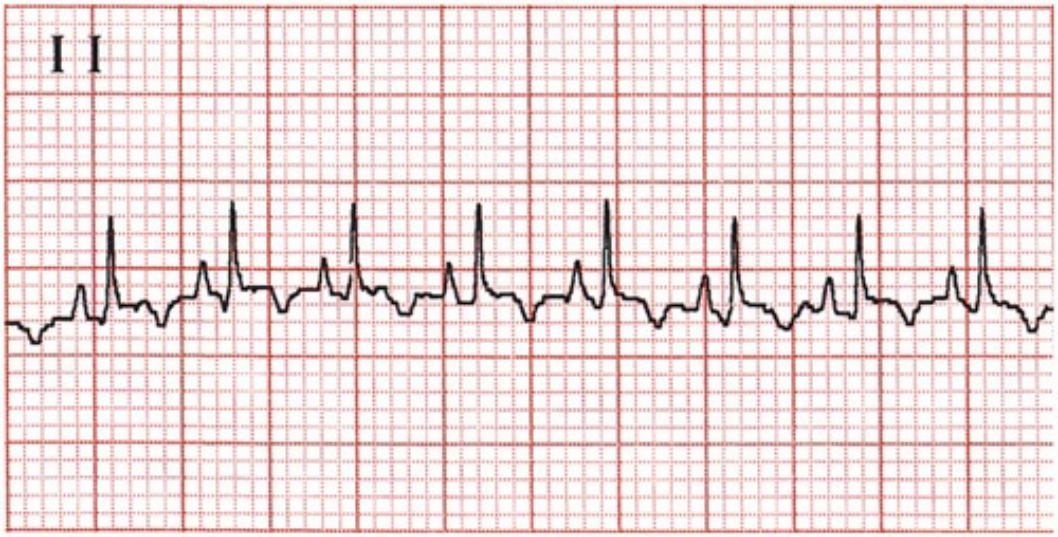

FIGURE 248-6 Sinus tachycardia in a cat with cardiomyopathy. The heart rate is 210 beats/min. Lead II, 25 mm/sec, 1 cm = 1 mV.

The causes of STach are diverse and are all marked by sympathetic predominance over parasympathetic inputs. STach is almost invariably a result of, rather than a cause of, a patient's problems. Therefore, it can be expected to resolve (return to NSR) when the causative disorder, such as hypovolemia, CHF, anemia, or pain, has been treated appropriately. Deliberate suppression of STach in an attempt to restore a more normal heart rate, especially in an acutely ill patient, can be (and has been) catastrophic, because in many instances, STach is a compensatory response. In these cases, suppression of STach using beta-blockers or calcium-channel blockers reduces an essential component of adequate cardiac output (heart rate) and can cause hypotension, circulatory collapse, and cardiac arrest. Therefore, treatment of STach consists of identifying the underlying cause and addressing the cause appropriately.

An important aspect of cardiovascular treatment is the prevention of STach in patients with structural heart disease.[14,39] The rationale is intuitive: tachycardia increases myocardial oxygen consumption, and also reduces the duration of diastole, the part of the cardiac cycle during which most coronary perfusion of the myocardium occurs. Therefore, tachycardia could force the heart to do more with less, which can be especially detrimental in patients with heart disease. To avoid this situation, tachycardia can be limited in dogs and cats with heart disease through lifestyle management: replacing periods of intense, off-leash running in dogs with lower-intensity leash walks, or avoiding chasing and intense game play with cats. Even so, experience in humans with heart disease indicates that prevention of tachycardia through pharmacologic means can increase survival.[39] In preclinical (compensated, "asymptomatic") heart disease in small animals, such an approach has involved beta-blockers, calcium-channel blockers, and Na^+/K^+ funny-current blockers. None has proven to prolong survival, however. Atenolol can be given safely to cats with subclinical (occult) hypertrophic cardiomyopathy (see ch. 253),[40] and to dogs with subclinical (occult) subaortic stenosis (see ch. 250);[41] no difference in outcome has been observed between treated animals and untreated control animals, but a uniform benefit also was not observed. Dogs with DMVD[42] or with dilated cardiomyopathy[43] that were treated with carvedilol did not have better outcomes than control animals. Importantly, only one of all of these studies was prospective,[43] meaning that the low strength of evidence of retrospective studies leaves room for additional evaluation of heart rate modulation, using beta-blockers or other drugs,[44] in dogs and cats with heart disease.

Disturbances of Atrial Excitability

Disturbances of atrial excitability are common, especially in the dog. Indeed, in the most common forms of heart disease in dogs (DMVD, cardiomyopathy, many congenital malformations), atrial distension leads to pathologic alterations of the atrial tissue, which can then generate ectopic atrial impulses. Such changes also have been noted with natural aging.[44a,44b]

Premature Atrial Complexes

PACs (synonyms: premature atrial contractions, atrial premature complexes or contractions [APCs], atrial premature depolarizations or extrasystoles, supraventricular [or atrial] premature beats]) are premature depolarizations that originate in an ectopic atrial focus (Figure 248-7).

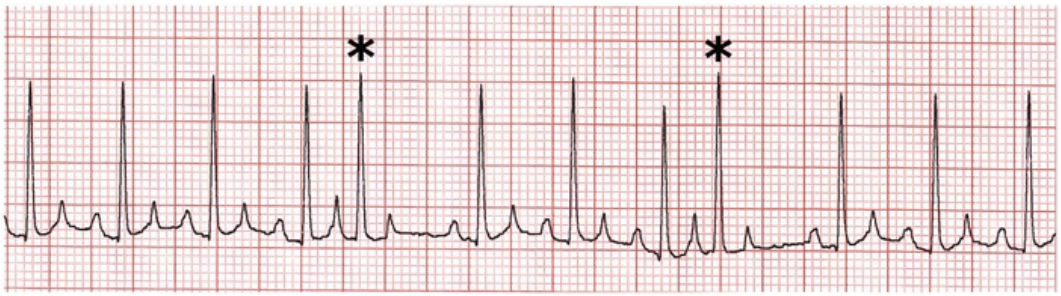

FIGURE 248-7 Premature atrial complexes (PACs) in a 3-year-old Newfoundland dog; the arrhythmia was an incidental finding. Note the normal sinus rhythm that is interrupted twice by beats that have QRS complexes with a morphology similar to sinus QRS complexes (i.e., PACs [asterisks]). There is superimposition of the premature P wave on top of the preceding sinus T wave; this can be inferred by noting the PR interval of the sinus beats and counting back to the expected location of the P wave of each PAC. Both PACs are followed by resetting with pause (see Figure 248-8). Lead II, 25 mm/sec, 1 cm = 1 mV.

Identification of PACs is based on a combination of the first two, and often all five, of the following ECG features: (1) prematurity of the P-QRS-T sequence; (2) QRS complexes that have a supraventricular appearance, in that they are narrow and comparable in shape to the sinus QRS complexes (uncommonly, QRS complexes can be absent or widened in cases of PACs that are exceptionally early and thus occur during the total or partial refractory period, respectively); (3) a P wave of different amplitude than sinus P waves, including negative, biphasic, or positive P waves, but always preceding the QRS complex; (4) a P-R interval that may be slightly different from the sinus P-R interval, be it shorter or longer;[2] and (5) a postextrasystolic pause that most often is noncompensatory (Figure 248-8).

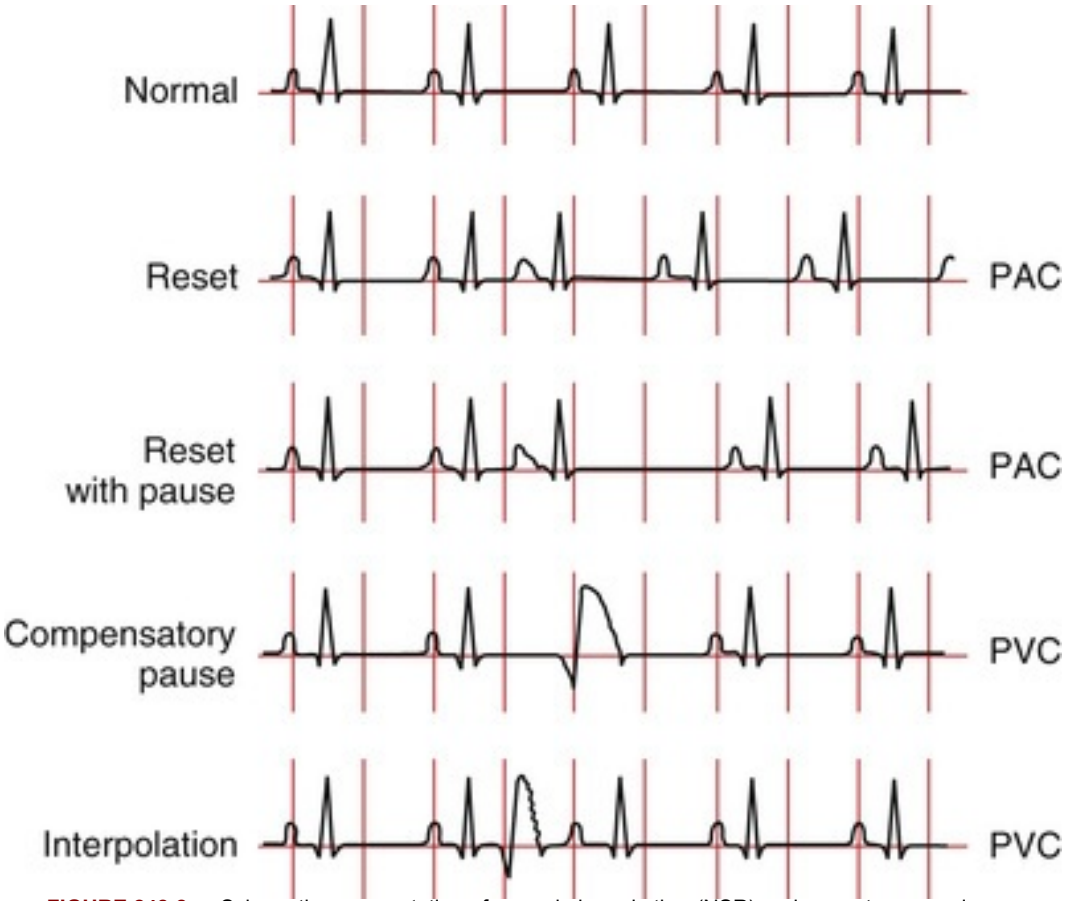

FIGURE 248-8 Schematic representation of normal sinus rhythm (NSR) and premature complexes. **Normal:** The heart rate remains constant, and the intervals from P to P and from R to R do not change. **Resetting:** A premature atrial complex (PAC; beat 3) resets the sinus rhythm so that the period from the beginning of the premature P wave to the next normal P wave is equal to exactly one P-P interval. **Resetting with pause:** The PAC (beat 3) is followed by a pause greater than one P-P interval but less than two P-P intervals. Both resetting and resetting with pause are examples of noncompensatory pauses (the rhythm of the SA node is affected by the premature beat, which alters the SA node's ability to provide a normally timed, "compensatory" beat after the premature beat). **Compensatory pause:** The premature ventricular complex (PVC; beat 3) is followed by a compensatory pause; that is, the period from the normal P wave in the beat preceding the PVC to the normal P wave of the beat after the PVC is equal to exactly two P-P intervals. During the PVC, the sinus P wave occurs on time, but it is not conducted through the atrioventricular (AV) node to the ventricles, which are in a refractory state due to the PVC. **Interpolation:** A PVC (beat 3) occurs between two normal sinus complexes without disrupting the normal sinus rhythm. Concealed conduction of the PVC into the AV node can be inferred to have occurred: interpolated PVCs commonly delay AV nodal transmission of the next beat, which manifests as prolongation of the P-R interval for the heartbeat that follows the interpolated PVC. This characteristic is useful for differentiating interpolated PVCs from motion artifact.

The pathogenesis of PACs most commonly is related to a structural cardiac (atrial) lesion. Distension of the atria is the main cause of these ectopic foci, but atrial tumors (hemangiosarcoma), hyperthyroidism in the cat, digitalis toxicosis, and other systemic disturbances also are recognized causes.[3,5]

Clinical repercussions of PACs are minor, except in cases of multiple repeated bursts (see Supraventricular Tachycardias, later), and the main interest in identifying PACs on an ECG is to raise the suspicion of atrial disease. Therefore, treatment for PACs first is aimed at addressing the underlying cause rather than resorting to antiarrhythmic drugs.

Atrial Tachycardias

Supraventricular tachycardias are defined broadly as any tachycardia originating from the SA node, atrial myocardium, AV node/junction, or veins entering the atria.[45] Specifically included are sinus tachycardia, sinus node reentrant tachycardia, automatic atrial tachycardia, intraatrial reentrant tachycardia, atrial flutter, atrial fibrillation, AV nodal reentrant tachycardia (AVNRT), orthodromic atrioventricular reciprocating tachycardia (OAVRT), and automatic junctional tachycardia.[46] Sinus tachycardia has been discussed (earlier),

and atrial flutter and atrial fibrillation are presented separately (see later), as are AVNRT and OAVRT, both forms of macroreentrant arrhythmias (see Macroreentrant Syndromes, later). The remaining arrhythmias are generally grouped in the broad category of "atrial tachycardias." This simplification is excessive for the occasional patient whose tachycardia can be cured with radiofrequency catheter ablation,[47] and indeed the 12-lead ECG provides important clues for localizing the ectopic focus in dogs, as it does in humans.[48] Still, this regrouping of sinus node reentrant tachycardia, automatic atrial tachycardia, intraatrial reentrant tachycardia, and junctional tachycardia into one basic category called atrial tachycardias is adequate for practical purposes in most veterinary clinical settings. An atrial tachycardia may be defined as a series of three or more consecutive PACs occurring at a rate greater than the sinus rate (Figure 248-9).

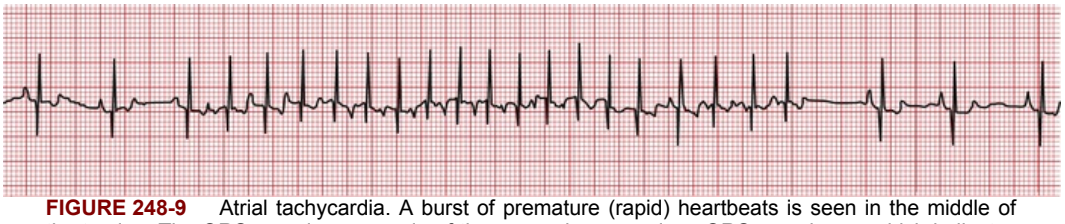

FIGURE 248-9 Atrial tachycardia. A burst of premature (rapid) heartbeats is seen in the middle of the tracing. The QRS complexes remain of the same shape as sinus QRS complexes, which indicates a supraventricular origin. During much of the tachycardia, P and T waves are not clearly seen; however, because the QRS complexes are unchanged in shape, so too must the T waves be of the same shape. Therefore, the negative deflections between QRS complexes (middle of the tracing) must be a superimposition of normal T waves and very different, deeply negative P waves, indicating an ectopic atrial focus of origin for the tachycardia. No clinical signs were present in this older Golden Retriever dog, either at admission or during follow-up, and an echocardiogram was unremarkable. Lead II, 25 mm/sec, 1 cm = 1 mV.

Atrial tachycardias can be intermittent or continuous, and the impulses all can be transmitted to the ventricles or physiologic AV block can occur as a protective mechanism if the rate of the atrial impulses is excessively high and the patient's AV node is suitably discriminating. The mechanism of atrial tachycardias can involve microreentry (e.g., sinus node reentrant tachycardia, intraatrial reentrant tachycardia) or spontaneous automaticity of an ectopic atrial focus (e.g., automatic atrial tachycardia, automatic junctional tachycardia).[32,46] Identifying intermittent atrial tachycardias usually is straightforward: The ECG shows a burst of PACs (see Figure 248-9). Establishing a diagnosis of atrial tachycardia when it is sustained can be difficult, however, because P waves might not be clearly evident, each one potentially being buried within the previous QRS complex or T wave. Differentiation between sustained atrial tachycardia and "high" ventricular (i.e., originating near the AV node) tachycardia therefore can be helped by exteriorizing the P waves, which can be elicited with a vagal maneuver (see previous discussion) and subsequent slowing of the tachycardia or even sinus capture (i.e., resumption of sinus rhythm) (see Figure 248-3).

The same short-term goal also can be reached pharmacologically using graded doses of an intravenous agent. Intravenous treatment is reserved for dogs or cats with very rapid atrial tachycardias (e.g., sustained heart rate >200/min in dogs, >260/min in cats). Treatment options include diltiazem (0.05-0.1 mg/kg slow IV boluses, repeated to effect or to cumulative maximal dosage of 0.25-0.35 mg/kg),[46,49] propranolol (0.02 mg/kg IV PRN, typically q 2-10 min; 3 doses over 2 hours in 1 case report),[27] esmolol (25 mcg/kg/min IV CRI,[50] with reports of up to 100-500 mcg/kg/min IV CRI[51] or 500 mcg/kg IV bolus over 1 minute[46]), edrophonium (0.05-0.1 mg/kg IV; have atropine and endotracheal tube available),[52] or phenylephrine (0.004-0.01 mg/kg IV).[52] These treatments require the patient to have normal systolic and diastolic function and no evidence of CHF, which could make the dosages listed above dangerous (hemodynamically compromising). Intravenous adenosine used for this purpose subjectively appears to be much less effective in dogs than in humans,[46] probably at least in part because of the rare occurrence of AVNRT in dogs compared with people.[53] Long-term oral treatment is discussed below.

Causes for atrial tachycardias are the same as those listed for PACs (see previous discussion). A significantly higher incidence of atrial tachycardias has been noted in association with age: in one study of dogs monitored for 1 week after undergoing pneumonectomy, 7/8 dogs that were ≥8 years old developed episodes of atrial tachycardia compared to 0/7 dogs <4 years old that underwent the same procedure.[54] Two important findings were that the older dogs had a progressive increase in sinus heart rate beginning 15 minutes before the onset of atrial tachycardia, and that the older dogs had evidence of atrial fibrosis and

inflammation that the younger dogs did not.[54]

The clinical impact of an atrial tachycardia depends on its duration, rate, and underlying cardiac lesions. With rapid atrial tachycardias, intermittent AV block can limit the ventricular rate, allowing for improved diastolic ventricular filling and a lessened clinical impact. When atrial tachycardia produces a persistently elevated heart rate (and/or syncope), as described above, treatment is necessary to avoid such long-term complications as tachycardia-mediated cardiomyopathy.[49,55] Such oral treatment is initiated at the low end of the dosage range, and only after any signs of CHF have been resolved (e.g., eliminating pulmonary edema with diuretics). Treatment options include a beta-blocker (e.g., atenolol 0.3-1.5 mg/kg PO q 12 h, or metoprolol 0.2-0.4 mg/kg PO q 12 h, or carvedilol 0.2-0.3 mg/kg PO q 12 h), a calcium channel blocker (e.g., diltiazem regular [not sustained-release] 0.8-1.5 mg/kg PO q 8 h),[49] digoxin (0.005 mg/kg PO q 12 h), or a combination of these if monotherapy is ineffective. Up-titration of the dosage can be undertaken to achieve the desired effect, which requires Holter monitoring for obtaining the optimal heart rate (whether through producing AV block to a degree that results in an appropriate ventricular rate, or suppressing the atrial tachycardia to a degree that the dominant rhythm is NSR). Atrial tachycardias often precede the development of AFib, probably in large part because of a common disease substrate (atrial enlargement and interstitial fibrosis).[56] Treatment of the underlying disease is an essential part of managing these arrhythmias.

Atrial Flutter

Atrial flutter classically is characterized by a rapid and regular series of atrial depolarizations, without a rest phase between them (Figure 248-10 and Video 248-1).[32,46] The time-honored ECG characteristics are (1) rapid, rhythmic waves of atrial electrical activity referred to as *flutter (F) waves*, usually occurring at a very high rate (280 to 400/min); (2) absence of a return to baseline between F waves, giving a "sawtooth" baseline appearance; (3) QRS complexes of a normal, supraventricular appearance; and (4) a variable, irregularly irregular R-R interval if some atrial impulses are blocked, as is often the case.

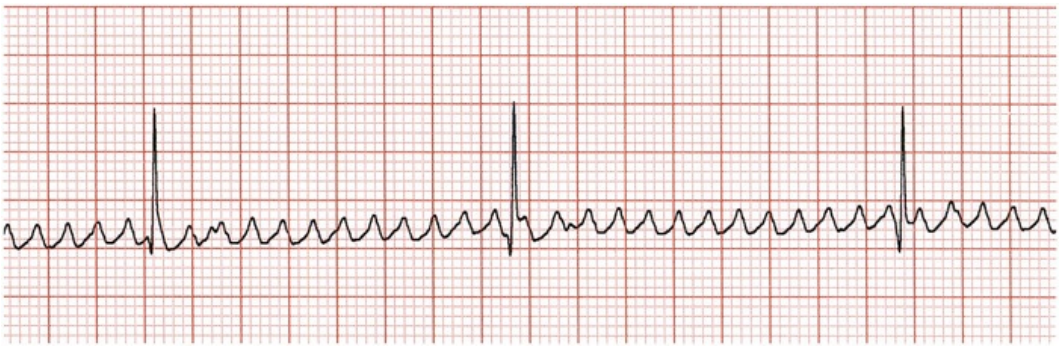

FIGURE 248-10 Atrial flutter. Atrial depolarizations occur in a distinct and organized fashion (F waves), without a return to baseline between each, in this 10-year-old Cocker spaniel. This produces the characteristic sawtooth baseline of atrial flutter. In this dog, the resulting heart rate is slow (approximately 40 beats/min), which is unusual for atrial flutter and which suggests concurrent AV nodal disease. Lead II, 25 mm/sec, 1 cm = 1 mV.

Atrial flutter occurs as a result of impulse propagation through a macroreentrant circuit; that is, self-perpetuating electrical conduction that occurs along a preexisting, closed loop of rapidly conductive tissue in the right atrium.[32,46] Termination of atrial flutter sometimes can occur spontaneously; more often, treatment is necessary when most or all of the flutter waves are conducted because of the resulting markedly elevated heart rate (risk of tachycardia-mediated cardiomyopathy if a heart rate of >240/min persists incessantly in a dog for >3 weeks).[49]

The diagnosis of atrial flutter can be very challenging when each flutter wave is transmitted through the AV node to the ventricles. Such 1 : 1 conduction leaves the F waves buried in the preceding QRS complexes or T waves, making the diagnosis difficult and usually requiring a vagal maneuver to induce transient AV block and reveal the F waves (see above). Intracardiac electrophysiologic assessment in dogs with atrial tachycardias has shown that the classic features of atrial flutter are not always apparent on the surface ECG.[57] This insight is important when minimally invasive therapies are being considered as a cure for an atrial tachycardia. However, all pharmacologic treatment choices for atrial flutter remain the same as those of atrial fibrillation (see below). Permanent abolition of atrial flutter is achieved with radiofrequency catheter–based

interruption of the flutter circuit.[57,58]

Atrial Fibrillation

AFib is a common and important arrhythmia. It represents 14% of all canine arrhythmias, including a 50% prevalence in cases of dilated cardiomyopathy in dogs, and it can trigger clinically overt hemodynamic changes requiring specific treatment.[32,59,60] A prevalence of AFib in up to 2% of the human population is estimated,[60] but a similar statistic is not available in veterinary medicine. AFib is characterized by complete electrical disorganization at the atrial level, leading to a chaotic, rapid series of atrial depolarizations (400 to 1200 per minute) (Figures 248-11 to 248-14).[61]

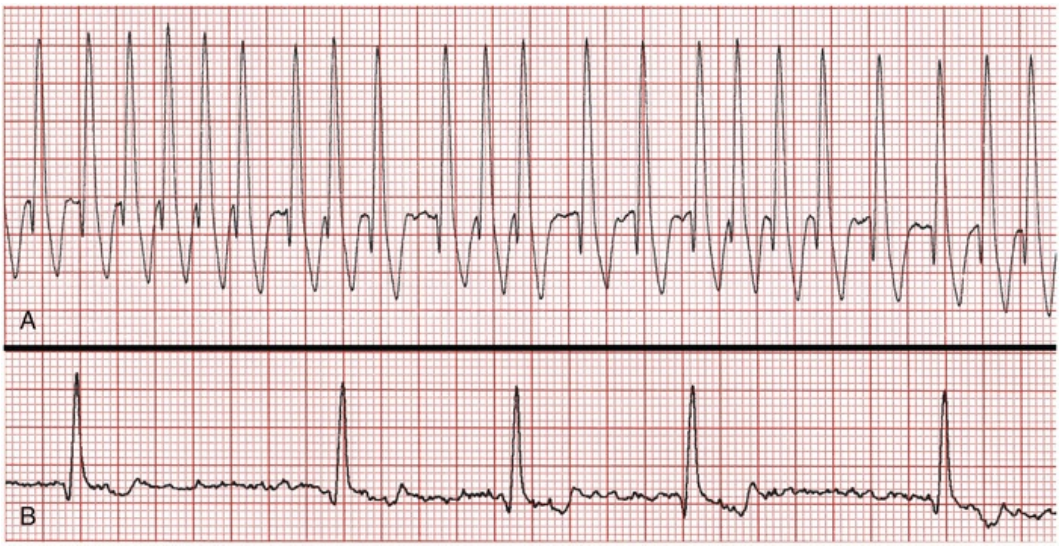

FIGURE 248-11 Atrial fibrillation in 2 dogs: poorly-controlled **(A)** and well-controlled **(B).** Both tracings show the characteristic features of atrial fibrillation: irregularly irregular R-R interval, absence of P waves, and a fine, undulating baseline (f waves). These features are clearer in the dog in panel **B,** because this ECG was made when the patient was stable. The heart rate (ventricular response rate) is 115 beats/min. Gradual up-titration of diltiazem with digoxin achieved this result. The heart rate in panel **A** is 240 beats/min. The dog in panel **A** had the ECG obtained on initial presentation, and such rapid ventricular response rates make the irregularity of the rhythm much less obvious in atrial fibrillation. Panel **A** also shows left bundle branch block (QRS duration = 0.08 second, with positive QRS in lead II), consistent with the dog's underlying dilated cardiomyopathy. **(A),** Lead II, 25 mm/sec, 1 cm = 1 mV. **(B),** Lead II, 50 mm/sec, 1 cm = 1 mV.

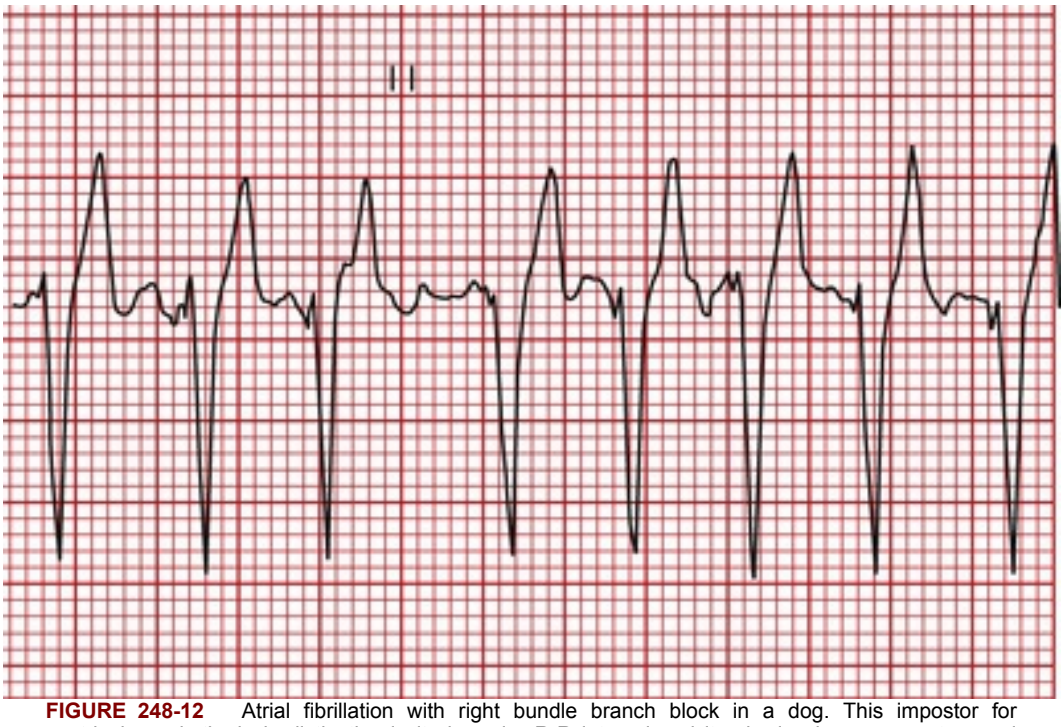

FIGURE 248-12 Atrial fibrillation with right bundle branch block in a dog. This impostor for ventricular arrhythmia is distinctive in its irregular R-R interval and its slowing in response to vagal maneuvers. Lead II, 25 mm/sec, 1 cm = 1 mV.

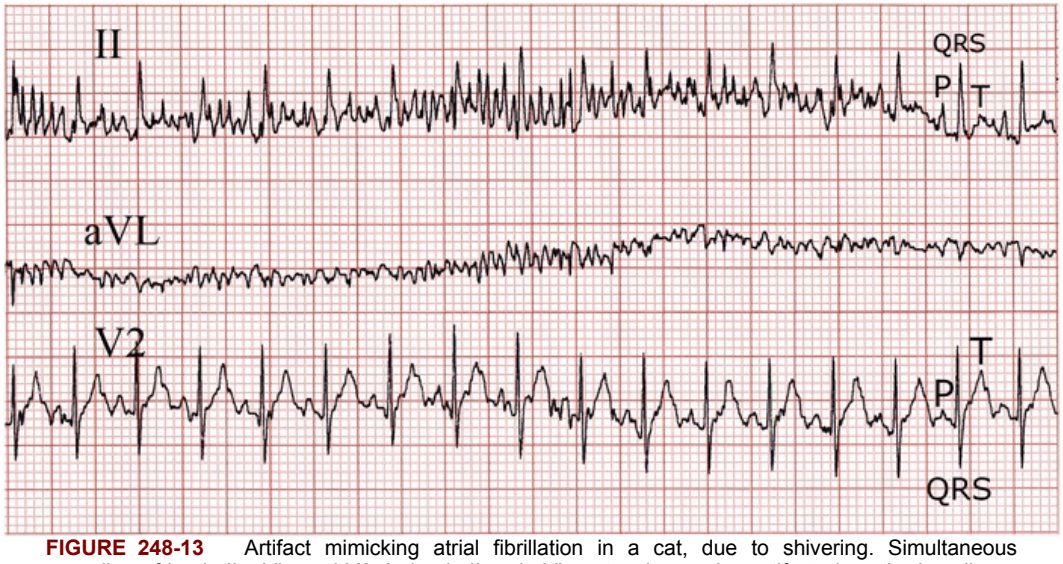

FIGURE 248-13 Artifact mimicking atrial fibrillation in a cat, due to shivering. Simultaneous recording of leads II, aVL, and V2. In leads II and aVL, extensive motion artifact gives the baseline a coarse undulating appearance. The rhythm is normal sinus rhythm, which is more clearly apparent when the animal stops shivering (last 3 heartbeats) and throughout the entire tracing in lead V2. This ECG shows the advantage of recording multiple leads simultaneously, because artifact often can affect one or more leads but not all of them. 25 mm/sec, 1 cm = 1 mV.

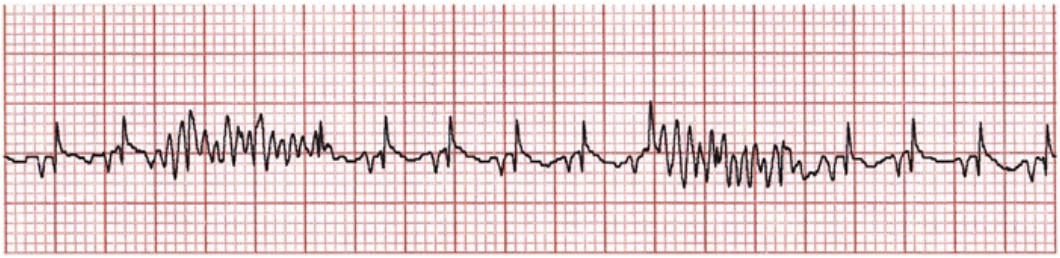

FIGURE 248-14 Artifact mimicking atrial fibrillation in a cat, due to purring. The beginning, middle, and end of this tracing show sinus tachycardia. In between them, two instances of purring artifact produce a coarse undulation of the baseline. Lead I, 25 mm/sec, 2 cm = 1 mV.

In contrast to atrial flutter, the fibrillatory impulses of AFib appear on the ECG as tiny deflections of highly variable—essentially random—shapes that cannot be identified as organized atrial electrical activity. The AV node acts as a "gatekeeper" for this chaotic electrical activity, allowing only those electrical depolarizations with optimal intensity, timing, and orientation to pass through to the ventricles and thus controlling the ventricular rate to some extent.

The three ECG characteristics of AFib are (1) supraventricular-appearing QRS complexes (narrow, upright, and of only slightly variable amplitude in lead II, unless ventricular aberrancy/BBB is concurrent); (2) an irregularly irregular rhythm, meaning a variable R-R interval, with a ventricular rate that can be low, normal, or most commonly without treatment, high; and (3) no visible P waves (replaced by a fine undulation of the isoelectric line, termed *f waves*) (see Figures 248-11 and 248-12, and Video 248-2). During diastole, ventricular filling is optimized by atrial contraction, which can account for up to 30% of total ventricular filling. Therefore, its absence can reduce ventricular volume to suboptimal levels, producing overt clinical signs during peaks of cardiac activity like intense physical exercise. Furthermore, the rapid overall ventricular rate commonly resulting from AFib can limit diastolic filling when insufficient time has occurred during diastole before the ventricles are triggered to depolarize again. For these reasons, some contractions intermittently can be ineffective, and one or more ausculted heartbeat(s) can occur without a corresponding palpable arterial pulse (i.e., a pulse deficit). AFib is one of the few arrhythmias that may be suspected from the moment of auscultation and palpation during the physical examination, based on the chaotic irregularity of the cardiac rhythm on auscultation and palpation of the chest, together with pulse deficits. Polymorphic VT, atrial tachycardias, and frequent PVCs or PACs, however, should be included in the differential diagnosis of this physical examination finding (see following).

An uncommon but important diagnostic impostor on ECG is the combination of AFib and BBB (see Figure 248-12), which produces wide QRS complexes and therefore can appear to mimic VT, but without P waves to conclusively indicate AV association (BBB) or dissociation (VT). In such a situation, a vagal maneuver can be performed (see previous), and its effect on the AV node could reduce the ventricular rate with AFib + right bundle branch block (RBBB) but not with VT. In addition, sustained, monomorphic VT is generally characterized by regular R-R intervals, whereas AFib with BBB is not.

AFib in dogs most often occurs in association with primary, underlying cardiac disease involving atrial enlargement.[62] However, AFib also can occur in individuals with structurally normal hearts ("lone AFib") in association with anesthesia (especially with opiates)[63]; hypothyroidism; rapid, large-volume pericardiocentesis; GI disease; and volume overload causing atrial stretch, if those hearts contain sufficient atrial myocardial mass to perpetuate fibrillation (i.e., medium- to large-breed dogs).[62] In giant-breed dogs, lone AFib is recognized commonly.[62,64,65] Lone AFib carries a better prognosis than does AFib associated with structural heart lesions, perhaps because it also is associated with a slower ventricular rate (mean: 120 beats/min) compared to AFib in dogs with subclinical structural heart disease (mean heart rate: 155 beats/min) or with structural heart disease and CHF (mean heart rate: 203 beats/min).[64] It remains to be determined whether those patients with AFib and structurally normal hearts that progress to dilated cardiomyopathy do so because of their arrhythmia, or whether, conversely, AFib is only the arrhythmic prelude to a disease that inherently involves subsequent cardiac chamber dilation and systolic dysfunction.

In cats, AFib occurs less commonly than in dogs and is virtually always associated with structural heart disease causing atrial enlargement.[66] Feline AFib is an incidental finding in 20% to 25% of cases. AFib does not necessarily confer a worse prognosis than the underlying heart disease: more than half of cats with AFib live for 6 months or longer (6 to 12 months: 21%; 1 year or more: 33%).[66,67]

AFib usually is a persistent, permanent arrhythmia. It can occur paroxysmally in the dog[68,69] and very

rarely does so in the cat. Paroxysmal AFib usually is of short duration and often will resolve spontaneously in <4 days if inciting triggers causing high vagal tone (e.g., GI disturbances, opiate drugs) are eliminated. In some dogs with structurally normal atria, and nearly all dogs with severe atrial enlargement, paroxysmal AFib progresses to persistent (permanent) AFib.

The onset of AFib carries prognostic implications in medium- to large-breed dogs with DMVD and CHF and probably other disease groups too. Those with AFib live a median of 142 days (range: 9-478 days) after the onset of CHF, compared to those without AFib (median: 234 days; range 13-879 days).[70] This difference could be due to deleterious effects caused by AFib, or to AFib's role as a marker of DMVD that is more advanced or more rapidly progressive.

In most cases of AFib, two goals of treatment exist: (1) managing the underlying heart disease and (2) maximizing cardiac output by controlling (slowing) the rate of conduction through the AV node if needed (see Figure 248-11). In small animal medicine, the ideal ventricular rate varies for each patient depending on many factors, including presence or absence of CHF and body weight. One substantiated guideline suggests that treatment should target a ventricular rate for dogs with AFib weighing 20 to 25 kg of approximately 130 to 145 beats/min.[71] A practical approach used by this chapter's authors is to aim for a ventricular response rate that corresponds approximately to the expected sinus rate under the environmental conditions (physical location, state of arousal, etc.) at the time the ECG/Holter is recorded. Ideally, Holter monitoring is used for assessing baseline and again for response to therapy, since the influence of autonomic variability is very substantial from one patient to another, and within the same patient in different environments. Specifically, in-hospital ECG has overestimated the ventricular response rate in dogs with AFib by an average of 26 beats/min (range 3-48 beats/min) when compared with Holter monitoring.[72] Auscultation alone for measuring the heart rate in atrial fibrillation also is suboptimal: in one study, the level of accuracy of auscultation compared to ECG ranged from 64% to as low as 12% for veterinary students and some veterinarians.[73]

Treatment of atrial fibrillation can involve conversion to NSR (rhythm control) or acceptance that AFib will persist and a focus on optimizing the resultant ventricular/heart rate if it is too rapid (rate control).[60,74-76] The latter approach has been validated in humans[60,74,77] and is the more widely used treatment strategy in canine and feline AFib. The medications of choice are sustained-release diltiazem (3 mg/kg PO q 12 h) and digoxin (0.005 mg/kg PO q 12 h) given together.[78] The exact dosage needs to be adjusted to produce an optimal ventricular response rate (heart rate), as described above; adjustments generally involve changing the diltiazem dosage and keeping a fixed digoxin dosage, unless there are signs of digoxin toxicosis (lethargy, inappetence, vomiting, diarrhea), which would warrant decreasing the digoxin. The duration of treatment usually is indefinite, unless spontaneous conversion to NSR occurs. In dogs with AFib, the combination of digoxin and diltiazem produces better heart rate control (median heart rate: 126 beats/min, from 194 beats/min pre-treatment) compared to digoxin alone (164 beats/min) or diltiazem alone (158 beats/min).[78] Beta-blockers, notably atenolol, have been less successful at reducing the ventricular rate in dogs with AF compared to digoxin + diltiazem.[70] Adequate heart rate control is important because it is associated with improved survival: in a study of medium- and large-breed dogs with DMVD and CHF, digoxin + diltiazem produced a median heart rate of 144 beats/min and a median survival time of 130 days, compared to a median survival time of only 35 days (and median heart rate of 180 beats/min) with diltiazem alone.[70] Initial, low-dose treatment to begin to reduce the ventricular response rate is undertaken at the same time as initiation of diuretics in patients with new-onset rapid AFib; medication uptitration to achieve heart rate control more precisely is undertaken once the patient's clinical signs of CHF are eliminated with ongoing diuretic treatment, and the patient is stable (alert, eating).

In dogs with AFib, improved defibrillation technology has renewed interest in converting AFib electrically to NSR.[79-82] Biphasic defibrillation converted 36/39 dogs (92.3%) in one study, with a median duration of NSR of 120 days thereafter (postcardioversion treatment: amiodarone 12-15 mg/kg PO q 12 h × 2 weeks, then 5-7 mg/kg PO q 24 h; hematologic and serum biochemical monitoring q 6 months).[79] Recent-onset AFib and absence of structural heart disease were associated with longer maintenance of NSR.[80] Ranolazine 22 mg/kg PO q 12 h, added to amiodarone and initiated after successful cardioversion of AF, is under investigation for efficacy and safety in dogs with naturally-occurring atrial fibrillation (Dr. Janice Bright, personal communication, 2016). Acute AFib has been converted pharmacologically in dogs using intravenous amiodarone (0.33-0.5 mg/kg/min IV infusion to effect; 3.78-8.3 mg/kg cumulative dose to convert AFib to NSR in 2 reported cases),[83] procainamide (14.3 mg/kg slow IV bolus; conversion to NSR 12 minutes after end of bolus in 1 case),[84] or lidocaine (for AFib associated with high vagal tone [e.g., laryngeal paralysis, opiate

drugs]: 2 mg/kg single IV bolus; can be repeated once if ineffective; conversion is expected in 20-90 seconds).[85,86] In an experimental model, ranolazine (3.2 mg/kg IV bolus, then 0.17 mg/kg/min) terminated AFib in 3/4 episodes (75%) in dogs; safety and efficacy in clinical veterinary patients is unknown.[87] Overall, treatment of most canine AFib patients at the present time involves medications for ventricular rate control.

Atrial Dissociation

The occurrence of two organized but independent atrial rhythms, one of which traverses the AV node normally and triggers ventricular activity while the other is constantly confined to the atria, is referred to as *atrial dissociation.* This uncommon, apparently benign, incidental finding is characterized electrocardiographically by two populations of P waves, one of which (generally the larger P waves) is followed consistently by QRS complexes, and the other of which shows exit block—the smaller P waves (called *P' waves*) do not activate the ventricles. The resulting appearance is a superimposition of normal sinus rhythm and an independent atrial rhythm, either of which may or may not be influenced by autonomic inputs (altering the P-P and/or P'-P' intervals). No disease link is known to exist between atrial dissociation and any other cardiac disorder, and no treatment or intervention is required.[88,89]

Disturbances of Ventricular Excitability

Disturbances of ventricular excitability are important because they involve the main element in the cardiac pump and may therefore produce severe hemodynamic and clinical repercussions. However, it must be recognized that ventricular arrhythmias have very diverse mechanisms and causes (especially noncardiac), such that severity, treatment, and prognosis depend on more than ECG findings alone.

Ventricular Extrasystoles or Premature Ventricular Complexes

Ventricular extrasystoles (synonyms: premature ventricular contractions, beats, or depolarizations [PVC; VPB, VPC, VPD, ventricular ectopy]) are premature depolarizations generated by an ectopic focus located in the ventricular tissue.[1-5] These arrhythmias are the most common of all pathologic rhythm disturbances in dogs and cats.[59,90] Hallmarks on the ECG are a short R-R interval (i.e., prematurity), and a wide QRS complex, which has a different morphology (shape) than normal sinus QRS complexes. Most ventricular extrasystoles have a wide, often bizarre-appearing QRS complex (>0.07 second in dogs), without an associated P wave, and a different (often very large) associated T wave (Figure 248-15).

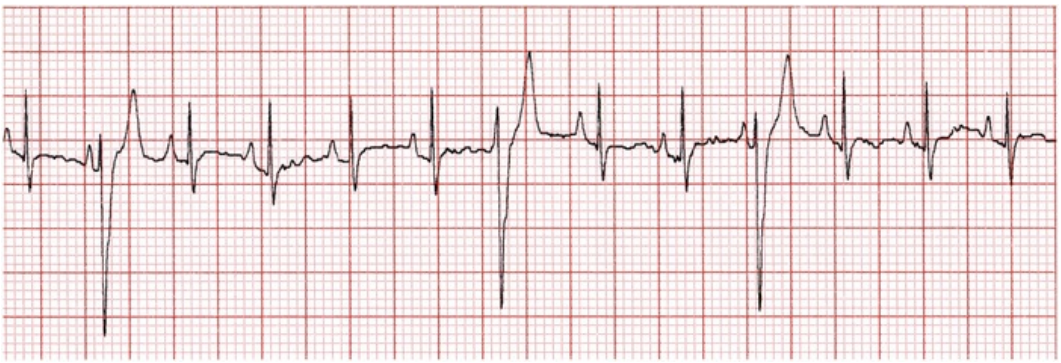

FIGURE 248-15 Premature ventricular complexes (PVCs) in a 10-year-old domestic shorthaired cat with cardiomyopathy. The rhythm is normal sinus rhythm, with 3 monomorphic (same-shaped) PVCs apparent as wide, bizarre, premature deflections. Note that atrial function is undisturbed: P waves are still apparent, but are not responsible for the wide, bizarre QRS complexes because the PR interval between the P waves and the PVCs is too short to be consistent with AV nodal transit time as shown in the PR interval of the sinus beats. That is, the PVCs are, by definition, premature depolarizations that preempted the normal SA node/atria/AV node/ventricles sequence. PVCs do not alter SA nodal function; therefore, the pause that follows each one is compensatory (see Figure 248-8). Lead II, 25 mm/sec, 2 cm = 1 mV.

Single PVCs usually are followed by a compensatory pause (see Figure 248-8) but can be interpolated instead. 1 : 1 alternation between sinus beats and PVCs is referred to as ventricular bigeminy; multiples of two PVCs are referred to as a pair; and three or more PVCs in a row constitutes ventricular tachycardia (VT; see following).

For purposes of identifying an underlying cause and for accurate therapy, it is important to differentiate ventricular extrasystoles from PACs. It is also essential to differentiate ventricular extrasystoles from the other major causes of altered QRS morphology: (1) changes due to cardiomegaly and axis shift; (2) intraventricular conduction disturbances within the bundle branches (see Figures 248-24 and 248-25); (3) abrupt motion or other artifact (see Figure 248-19); (4) the wide but nonpremature QRS complexes of ventricular escape beats (see Figure 248-23); and (5) QRS morphology changes caused by severe hyperkalemia. These five causes for wide QRSs are not ventricular arrhythmias, do not involve a pathologic focus in the ventricle, and therefore are not treated with antiarrhythmic drugs (Figure 248-16)

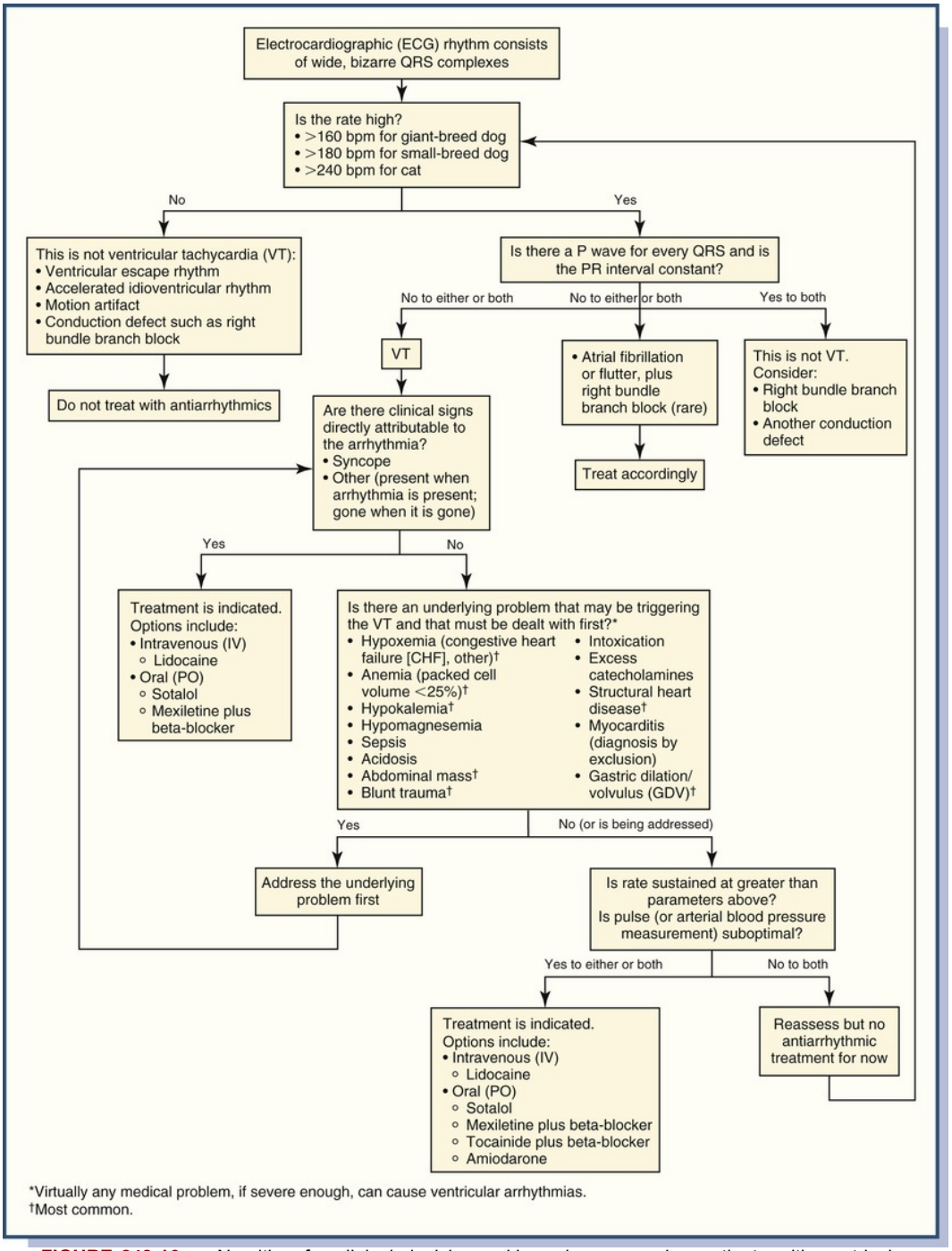

FIGURE 248-16 Algorithm for clinical decision-making when managing patients with ventricular arrhythmias.

Causes of ventricular extrasystoles include virtually any cardiac or systemic disorder, with the most

common of these including such primary cardiac diseases as cardiomyopathy,[91-93] valvular heart disease, congenital heart disease, and endocarditis[94] and such systemic problems as hypokalemia, anemia, hypoxemia, blunt trauma,[95] gastric dilatation-volvulus,[96,97] abdominal masses (commonly splenic or hepatic),[98-100] intoxication, and acidosis. Normal dogs commonly have up to 24 PVCs daily as recorded on Holter studies.[24,101] In cats, ventricular extrasystoles are associated predominantly with myocardial disease. In a retrospective study of 106 cats with ventricular extrasystoles, a significantly higher proportion of cats with ventricular extrasystoles had an abnormal echocardiogram (102/106, 96%) compared with an equivalent cohort of dogs with ventricular extrasystoles (95/138, 69%; $p < 0.001$), suggesting that ventricular extrasystoles more often coexist with structural heart disease in cats than in dogs.[93] The most challenging aspects of managing ventricular extrasystoles remain the evaluation of their severity and the assessment of the need for treatment. Treatment options and approaches are discussed below (see Ventricular Tachycardia).

Two specific heart diseases of dogs are almost exclusively arrhythmogenic: they produce PVCs and VT, and often overt clinical manifestations of acute arrhythmia (malaise, syncope, hypoxic/anoxic seizures, or sudden death) as the chief abnormality. The first, arrhythmogenic right ventricular cardiomyopathy (ARVC, familial ventricular arrhythmia of Boxer dogs, Boxer cardiomyopathy, arrhythmogenic RV dysplasia) causes ventricular extrasystoles and VT, and is described in ch. 252. The second is inherited sudden cardiac death of German Shepherd dogs. This disorder can exist in a latent state or may produce overt clinical signs.[102,103] The disease occurs rarely but is international in distribution and has affected several generations.[102] The predominant abnormality is paroxysmal, rapid VT. Dogs with this disease often develop clinical signs early in life, and these include both syncope and a high prevalence of sudden death. Therefore, the disease causes clinical manifestations mainly in puppies or young adult dogs (mean age: approximately 1 year; age range: 4 to 30 months). As a rule the arrhythmia does not coexist with structural cardiac changes, and thoracic radiographic and echocardiographic results are expected to be normal in affected dogs. A myocardial repolarization defect appears to be the cause of the arrhythmia.[104] Although treatments that limit bradycardia (e.g., vagolytic drugs, ventricular pacing) reduce the occurrence of arrhythmia, no definitive treatment exists for the disorder at this time. Most commonly, affected dogs that survive the first year of life outgrow the disease and live normal lives thereafter.

Accelerated Idioventricular Rhythm

Accelerated idioventricular rhythm (AIVR) is a ventricular rhythm of intermediate rate. AIVRs have the same ECG characteristics as VT except rate, which is slightly below that of VT. Therefore AIVR clinically is considered as a slower subset of VT, and indeed it was given the logical but oxymoronic name "slow VT" at first. On the ECG, AV dissociation, wide and bizarre QRS complexes, and the possibility of capture beats and fusion beats, are seen, just as in VT. However, in a typical medium-size dog, the rate of AIVR by definition is between 70 and 160 beats/min, which places it between idioventricular (i.e., escape) rhythms (<70 beats/min) and true VT in terms of rate. The causes of AIVRs are similar to those of ventricular extrasystoles, but the lower ventricular rate is less compromising of diastolic ventricular filling time; as a result, AIVRs are generally well-tolerated.[105] Treatment therefore is directed at the underlying cause; antiarrhythmic medications are not considered unless management of the underlying cause is ineffective at abolishing the arrhythmia and the rate increases to the point that the criteria for VT are met.

Ventricular Tachycardia

VT is a series of three or more ventricular extrasystoles occurring at a high rate (Figure 248-17 and Video 248-3). It can be continuous (sustained) or intermittent (paroxysmal). Causes are the same as those listed for ventricular extrasystoles (PVCs; see previous discussion). Clinical manifestations are frequent (weakness, syncope, hypoxic/anoxic seizures) but their occurrence depends directly on the hemodynamic consequences of the rhythm. An increasingly rapid VT, for example, will cross a threshold of ventricular rate beyond which a greater number of beats will not translate into greater cardiac output. This "point of diminishing returns," which varies according to the variables described previously, exists because diastolic filling time is most compromised at high heart rates. Thus, very rapid VT, like any other very rapid tachycardia, can produce overt clinical signs of reduced cardiac output.

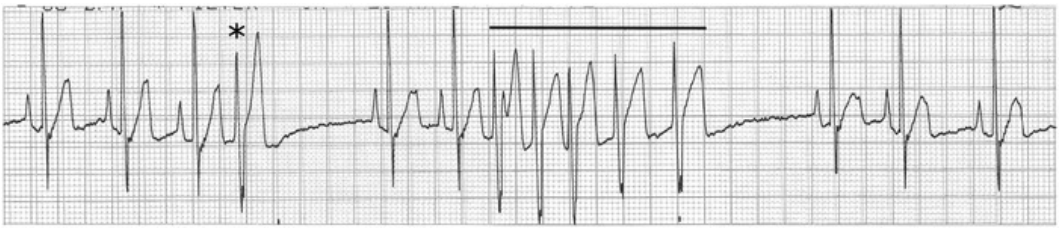

FIGURE 248-17 Ventricular tachycardia in a 5-month-old puppy immediately after thoracotomy and patent ductus arteriosus ligation. Normal sinus rhythm/respiratory sinus arrhythmia is interrupted by one premature ventricular complex (asterisk), and then a series of 5 monomorphic (same-shaped) PVCs, i.e., a run of ventricular tachycardia. The arrhythmia resolved with management of inciting factors (see Figure 248-16). 25 mm/sec, 1 cm = 1 mV.

The identification of VT is easier when the VT is intermittent. The typical appearance is one or several series of QRS complexes that are wide (>0.07 second in the dog, >0.04 second in the cat), do not resemble the sinus QRS complexes, are associated with different-looking, often giant T waves, are not linked to P waves, and may include a capture beat (the first normal sinus P-QRS complex after a paroxysm of VT) and fusion beats (QRS complexes with a morphology that is intermediate, between sinus QRS complexes and ectopic QRS complexes due to intraventricular electrical collision between a normal sinus beat and a PVC); the latter 2 are diagnostic of VT. In VT, P waves are present (the atria depolarize, but the impulse is blocked at or just after the AV node because the more rapid rhythm [VT] dominates the ventricles) but are often engulfed by the wide, bizarre QRS complexes and T waves. Thus the presence of P waves at regular intervals but not fixedly associated with QRS complexes is consistent with VT (see Figure 248-17)—the atria are not "aware" of VT. The ECG diagnosis can become more challenging when VT is continuous, particularly if it is of septal or RV origin and thus produces QRS complexes that are fairly narrow and that could resemble supraventricular complexes. Wide QRS complexes caused by other factors (see previous discussion of ventricular extrasystoles) must not be mistaken for VT.

Treatment of VT begins with confirmation of the ECG diagnosis (i.e., ruling out other causes of wide, bizarre QRS complexes) and identification and treatment of the underlying cause. Given the risk of proarrhythmia with any antiarrhythmic treatment, and the lack of evidence that elimination of VT significantly reduces the risk of death in affected dogs or cats, elimination of the inciting factors responsible for the VT should be considered the first and most definitive form of treatment.[106] When elimination of the cause is not possible, the presence or absence of overt clinical signs caused by VT (especially syncope, or presyncope—episodic stumbling and disorientation without loss of consciousness) justifies antiarrhythmic treatment. In the absence of such signs, antiarrhythmic drugs should be given if the VT is hemodynamically severe; in turn, this generally depends on the heart rate (ventricular rate) caused by the VT. A step-by-step approach, and drug dosages and applications, are shown in algorithmic form in Figure 248-16.

Ventricular Flutter

Ventricular flutter is a very rapid, often prefibrillatory stage of VT. The ECG appearance of this rhythm is a series of identical, tight, tall sinusoidal waves in which it is impossible to separate QRS complexes and T waves (Figure 248-18). This intermediate stage between VT and VF is rare, brief, and either improves (slows to VT ± converts to NSR) or worsens to VF and cardiac arrest. It must be differentiated from motion artifact. Artifact masquerading as ventricular flutter still shows evidence of coordinated ventricular activity (normal QRS complexes within the "flutter" impostors) on close inspection (Figure 248-19). Ventricular flutter is considered a severe ventricular arrhythmia and warrants immediate correction of predisposing causes, intravenous antiarrhythmic treatment (beginning with lidocaine 2 mg/kg IV bolus), and possibly electrical defibrillation (see ch. 140 and 141).

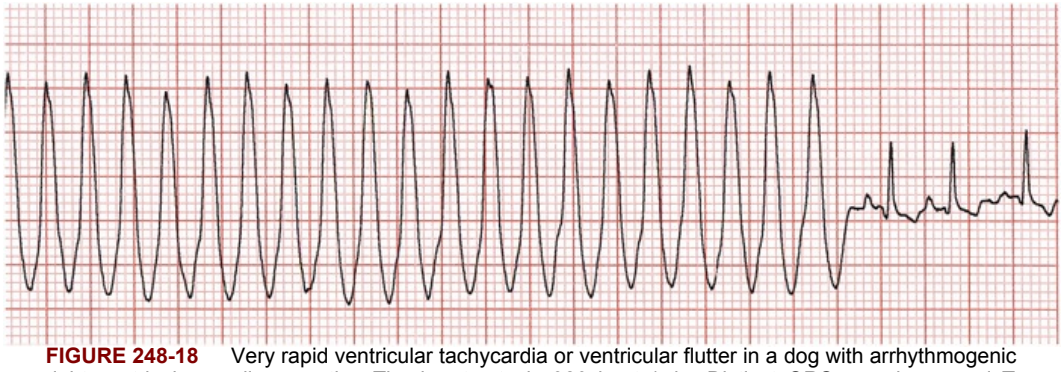

FIGURE 248-18 Very rapid ventricular tachycardia or ventricular flutter in a dog with arrhythmogenic right ventricular cardiomyopathy. The heart rate is 320 beats/min. Distinct QRS complexes and T waves are not seen until the last 3 heartbeats when the rhythm converts to sinus tachycardia at a rate of 180 beats/min. A tachycardia that is this rapid can be expected to markedly reduce diastolic filling of the ventricles, decreasing cardiac output and often producing such clinical signs as syncope or sudden death (Video 248-3). 25 mm/sec, 1 cm = 1 mV.

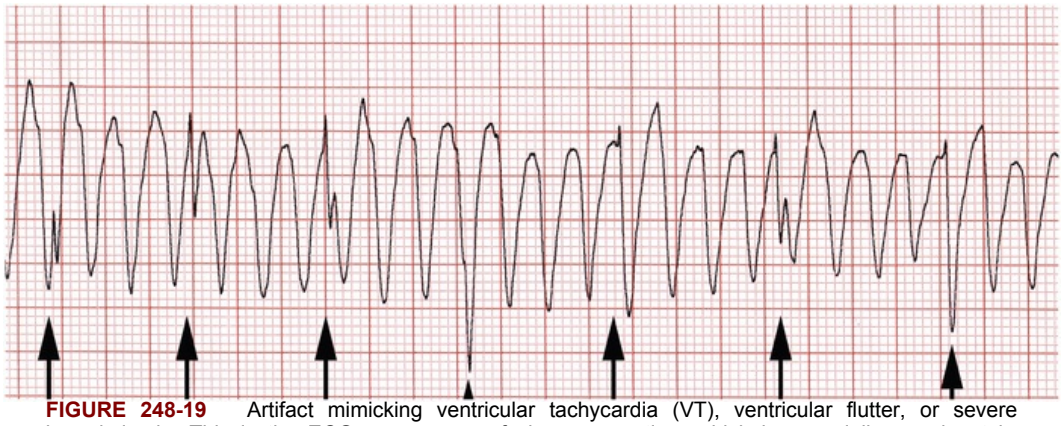

FIGURE 248-19 Artifact mimicking ventricular tachycardia (VT), ventricular flutter, or severe hyperkalemia. This is the ECG appearance of vigorous panting, which is especially prominent in precordial leads like this one. The rhythm is normal sinus rhythm. Close inspection shows evenly-spaced, narrow, positive upstrokes (arrows) that represent the normal sinus QRS complexes emerging through the artifact. This would not be apparent in true VT, ventricular flutter, or hyperkalemia. Lead V2, 25 mm/sec, 1 cm = 1 mV.

Ventricular Fibrillation

VF is a terminal (fatal), disorganized, chaotic pattern of ventricular depolarizations involving complete desynchronization of ventricular electrical activity. Hemodynamically, it produces circulatory collapse and arrest. Therefore it is a preagonal state leading to death within seconds to minutes. Indeed, the cardiac rhythms that define cardiac arrest are VF, asystole, and pulseless electrical activity (notably pulseless VT), not just asystole.[107] The ECG appearance of VF consists of erratic, patternless waves of variable morphology, amplitude, and frequency (Figure 248-20).

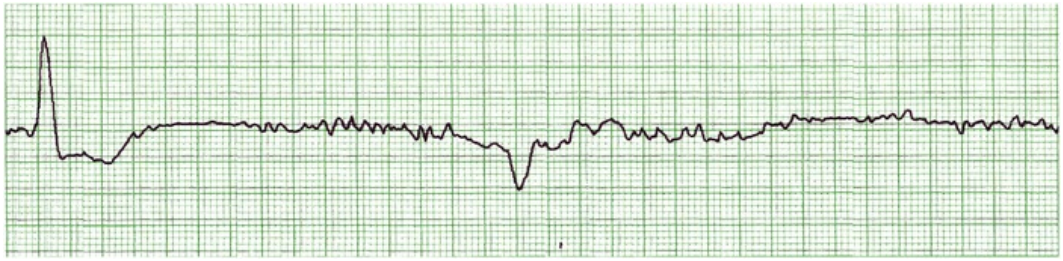

FIGURE 248-20 Ventricular fibrillation in a cat with syncope caused by severe hypertrophic cardiomyopathy. After the final QRS complex, the ventricles fibrillate, producing a fine undulation of the

baseline and no synchronized ventricular or atrial activity. This rhythm signifies cardiac arrest and requires electrical defibrillation or withholding of resuscitation for a humane death. External movement artifact explains the wider deflection in the middle of the tracing. 25 mm/sec, 1 cm = 1 mV.

The underlying cause is by definition a severe disorder, such as myocardial trauma, anoxia, severe electrolyte disturbance, and advanced states of shock. If VF is suspected on ECG, artifact must immediately be ruled out; poor electrical connection between the patient and the ECG leads can mimic VF. Rapid confirmation of VF consists of (1) applying isopropyl alcohol to the skin-ECG lead interface to improve conductivity (help rule out artifact); (2) assessing that the arrhythmia is present in multiple leads, not just lead II; (3) feeling for the arterial pulse (any palpable pulse rules out VF); and (4) noting that the patient is unconscious, because VF is inconsistent with adequate cerebral perfusion. VF is often preceded, and therefore heralded, by ventricular extrasystoles (possibly demonstrating the R-on-T phenomenon), then sustained VT, then possibly ventricular flutter.[2] Unfortunately, treatment of PVCs/VT with antiarrhythmic drugs does not reliably reduce the risk of VF,[106] and rather, the underlying cause and other inciting factors that can be arrhythmogenic (hypokalemia, anemia, etc.) must be addressed. When the rhythm has reached VF, treatment (cardiopulmonary resuscitation), though often unrewarding, must be instituted immediately and generally involves electrical defibrillation if available (see ch. 140 and 141). Prevention of initial VF or of VF recurrence can be pursued through surgical placement of an implantable cardioverter-defibrillator. This form of therapy, which is vastly more effective and safer that antiarrhythmic medications in human patients, is gaining interest in veterinary medicine.[108,109]

Torsade de Pointes

Torsade de pointes (TdP) is a ventricular arrhythmia that arises from prolongation of the Q-T interval.[110,111] The rotation of the peaks of the QRS complexes on the horizontal axis of the ECG is due to the ever-changing geometry of the reentry circuit, which oscillates within the ventricles. The diagnosis of TdP is based on the following criteria: (1) the rhythm immediately prior to onset of TdP is slow, and the Q-T interval is prolonged (>0.25 second in the dog); (2) the onset of TdP involves an R-on-T ventricular extrasystole (e.g., depolarization [R wave] occurs during the vulnerable part of the T wave); (3) the ensuing rapid (>180 beats/min) ventricular rhythm has QRS complexes that are more regular than in VF but that are continuously changing in amplitude and polarity.

The total duration of a self-resolving paroxysm of TdP usually is very brief (5 to 10 seconds), but it can persist for longer; in those instances it often evolves lethally into VF. TdP is not commonly recognized in the dog but can be caused by any disorder that prolongs the Q-T interval[111]: congenital long QT syndrome (Dalmatian), hypokalemia, hypocalcemia, and overdose or toxicosis due to antiarrhythmic drugs, particularly class 1A antiarrhythmics such as quinidine. The treatment is highly specific and requires discontinuation of all antiarrhythmic drugs and institution of intravenous magnesium sulfate (20-60 mg/kg slow IV bolus).[111]

Ventricular Parasystole

Ventricular parasystole ("two hearts beat as one") is a complex arrhythmia that results from the concurrent and independent activity of two pacemakers, one being a normal supraventricular pacemaker and the other existing in a protected site in a ventricle.[112] By definition, parasystole has (1) a ventricular focus with independent, abnormal automaticity and a rate that is greater than an escape focus and (2) a unidirectional (entry) block that shields this focus from sinus depolarizations. Parasystole is most often benign, does not warrant antiarrhythmic treatment, and regardless is usually refractory to antiarrhythmic therapy.

Isorhythmic Atrioventricular Dissociation (IAVD)

Isorhythmic atrioventricular dissociation (IAVD) is a rhythm disturbance in which atria and ventricles are driven by independent pacemakers at equal or nearly equal rates. It has been identified in a group of 11 Labrador Retrievers, possibly correlated to focal junctional tachycardia.[113] The authors of this chapter have seen it disproportionately more often in Samoyed dogs, usually as an incidental finding (Figure 248-21). The characteristic ECG finding is of P waves that drift into the QRS complex and even precede it (IAVD with type I synchronization). This can occur periodically, with periods of identical atrial and ventricular rate ("accrochage") giving the appearance of AV synchrony.[113] The clinical implications of IAVD are not known to be harmful: there is no proven association with progressive heart disease, and at the present time, IAVD is considered an incidental electrocardiographic finding.

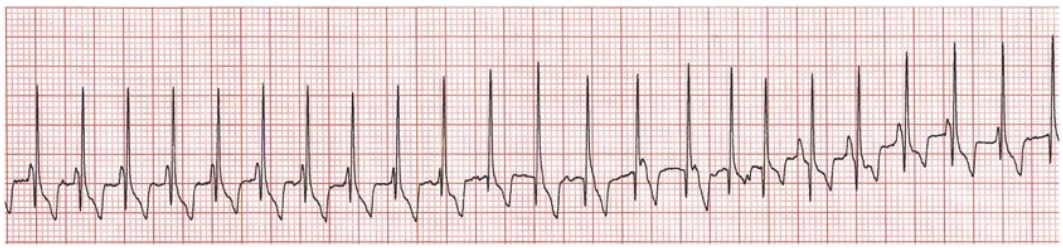

FIGURE 248-21 Isorhythmic atrioventricular dissociation in a Samoyed dog. P waves and QRS complexes are closely associated but the drifting of P waves into and out of QRS complexes indicates lack of atrioventricular synchrony. Hallmarks of this arrhythmia are a supraventricular-appearing (narrow, positive in lead II) QRS complex and similar, but not perfectly identical, atrial and ventricular rates. Lead II, 25 mms/sec, 1 cm = 1 mV.

Disorders of Conduction

Disorders arising from faulty intracardiac electrical conduction are simply referred to as *blocks*. Blocks are grouped according to anatomic and functional criteria. Anatomic criteria separate them depending on their level of physical location: SA blocks, AV blocks, BBBs, and fascicular blocks. Functional criteria characterize blocks according to their degree of severity. First-degree block produces a delay in conduction; second-degree block causes complete but intermittent block; and third-degree block causes complete, sustained block.

Atrioventricular Block

In a healthy heart, the AV node serves an important gatekeeper function that introduces a normal delay with each sinus beat, allowing the atria to finish contracting. The AV node also prevents excessive atrial impulses from reaching the ventricles in supraventricular tachycardias (see Atrial Fibrillation, previously). This normal and vital electrical filtering function helps preserve a more normal heart rate when supraventricular tachycardias occur, and this effect can be enhanced if needed using negative dromotropic (AV nodal conduction-delaying) medications, as described above for the treatment of AFib. However, the function of the AV node may be excessive or extreme, hindering the passage of normal sinus impulses. Failure of normal AV nodal conduction from the atria to the ventricles is called *AV block* and its clinical significance depends on the characteristics described below.

First-degree AV block

First-degree AV block is simply a delay in AV conduction. Conduction through the AV node is slower than normal, but every impulse crosses the node successfully. It can be permanent or transient and can arise from a structural lesion or simply be functional. The ECG diagnosis is based on normal, sinus-appearing QRS complexes and a prolonged PR interval. The clinical manifestations are nil; first-degree AV block is an ECG finding only and it neither produces overt clinical signs nor warrants treatment. It should draw the clinician's attention to possible causes of high vagal tone, which generally are physiologic but occasionally can be toxic (e.g., digitalis glycoside toxicosis). First-degree AV block does not progress to second-or third-degree AV block except in cases of drug toxicosis.

Second-degree AV block

Second-degree AV blocks involve the complete (but transient) interruption of AV conduction. Therefore, a P wave exists for every QRS complex, but a QRS complex does not exist for every P wave. Two important subtypes of second-degree AV block exist.[28] The first, Mobitz type I second-degree AV block, is characterized by a progressive lengthening of the P-R interval until ultimately a P wave is blocked (P wave without QRS complex), an entity known as the *Wenckebach phenomenon.* Anatomically, Mobitz type I second-degree AV block originates high in the AV node and is said to carry a good prognosis because it is closely related to first-degree AV block and virtually never causes clinical signs (Figure 248-22).

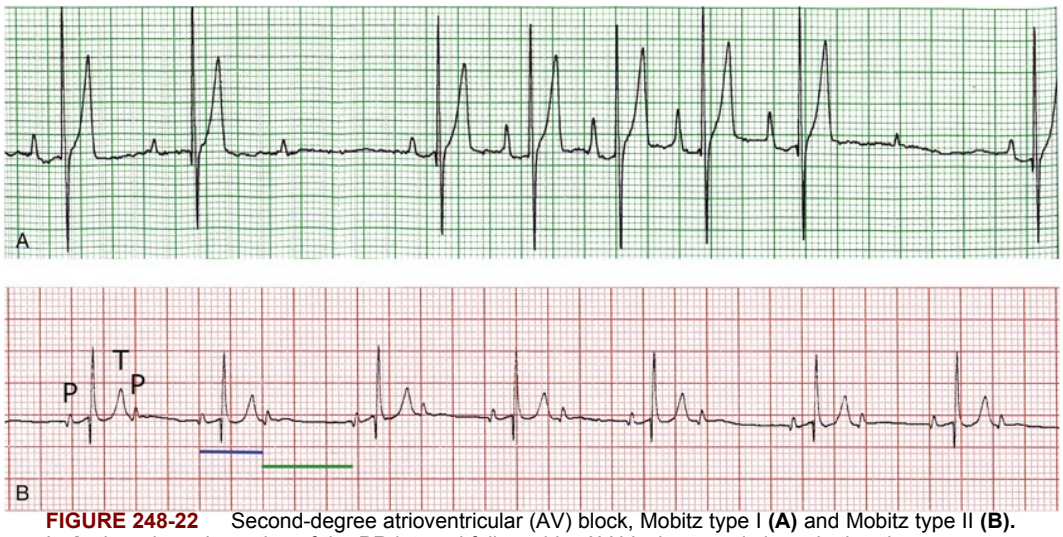

FIGURE 248-22 Second-degree atrioventricular (AV) block, Mobitz type I **(A)** and Mobitz type II **(B).** In **A,** there is prolongation of the PR interval followed by AV block; normal sinus rhythm then resumes, with a normal PR interval, until prolongation and block occurs again. This is considered a harmless physiological variant (i.e., manifestation of high vagal tone). The change in P wave height reflects a wandering pacemaker (see Figure 248-4), which is another manifestation of high vagal tone. In **B,** the atrial impulse is blocked with no lengthening of the preceding PR interval. Specifically, this is 2 : 1 block; there are two P waves for each one that is conducted. Causes include pharmacologic (e.g., alpha-2 agonist drugs), physiologic (less commonly), and pathologic (e.g., AV node fibrosis) etiologies. The resulting ventricular rate is 70 beats/min. Depending on progression—especially to 3 : 1, 4 : 1, or higher grades of block—and presence of clinical signs, such patients can require pacemaker implantation. Note that ventriculophasic sinus arrhythmia is an incidental finding: instead of a constant P-P interval throughout the tracing, the P-P interval that flanks the QRS complexes (blue line) is shorter than the P-P interval during block (green line). Lead II, 25 mm/sec, 1 cm = 1 mV.

The second, Mobitz type II second-degree AV block, by contrast, demonstrates perfectly regular P-R intervals, until one or more P waves is/are blocked (see Figure 248-22). Mobitz type II second-degree AV block arises from the AV bundle and is said to carry a more guarded to poor prognosis because it more closely resembles third-degree AV block. However, objective evidence is lacking to support this extrapolation of severity in Mobitz types I and II from human cardiology to veterinary patients. In "simple" Mobitz type II second-degree AV block, more conducted P waves occur than blocked P waves, whereas in "advanced" or "high-grade" Mobitz type II second-degree AV block (as in Figure 248-22), more blocked P waves occur than conducted P waves. The presence or absence of clinical signs appears to be related to the ventricular rate. Specifically, dogs with high-grade Mobitz type II second-degree AV block have an expected survival that is no different than that of dogs with third-degree AV block, and pacemaker implantation significantly improves survival in both groups, regardless of the presence or absence of bradycardia-associated clinical signs.[28]

Therefore, Mobitz type I and simple Mobitz type II second-degree AV blocks rarely produce clinical manifestations such as exercise intolerance, whereas the more advanced Mobitz type II second-degree AV blocks, by virtue of blocking more impulses in the AV node and resulting in a lower ventricular rate, commonly produce clinical signs that are similar to those of third-degree AV block: weakness, lethargy, syncope, and Stokes-Adams hypoxic-anoxic seizures (true convulsions caused by critical, bradycardia-induced cerebral hypoperfusion)[114] even with minimal exertion. The presence of such clinical signs, and the ventricular rate, are principal determinants of whether the patient requires treatment (pacemaker implantation; see ch. 249).

Third-degree AV block

Third-degree, or complete, AV block is a complete and sustained interruption of AV conduction. The ventricles depolarize according to a slow, regular, independent rhythm, called an *escape rhythm* (junctional or ventricular; see following) (Figure 248-23 and Video 248-4). It is important to recognize the lifesaving salvage function of a ventricular escape rhythm because it prevents asystole. Therefore, even though ventricular escape QRS complexes are wide and bizarre, ventricular antiarrhythmic therapy is absolutely contraindicated.

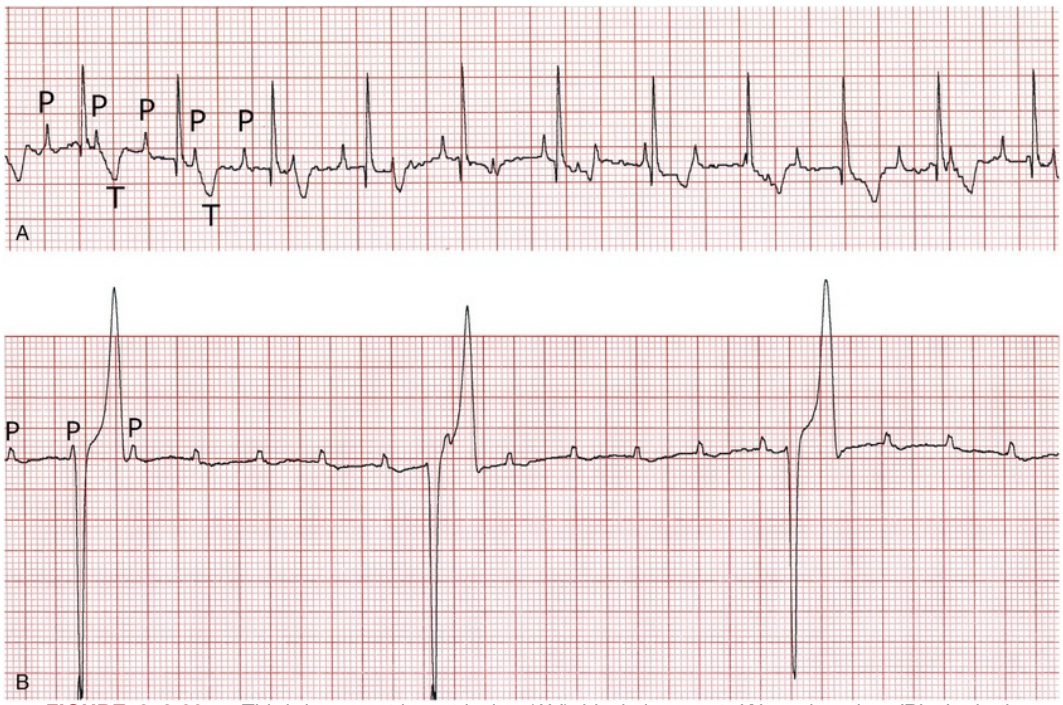

FIGURE 248-23 Third-degree atrioventricular (AV) block in a cat **(A)** and a dog **(B).** In both instances, the atria and ventricles depolarize independently. In each tracing, the P-P interval is constant and the R-R interval (escape rhythm) is constant. The main difference is in ventricular escape rate. As is often noted in cats with third-degree AV block, the ventricular rate is rapid for an escape rhythm (**A,** 120 beats/min), whereas in dogs, it often is much slower (**B,** 30 beats/min). Both tracings: lead II, 25 mm/sec, 1 cm = 1 mV.

In third-degree AV block, electrical communication between the atria and ventricles is nonexistent (complete AV dissociation). Therefore, the ECG diagnosis is based on the complete absence of P wave conduction (P waves occur with a constant P-P interval but are not followed immediately and consistently by QRS complexes; no repeatable PR interval) and slow, regular (constant R-R interval) ventricular rhythm, where the QRS complexes are usually of a uniform, but wide, bizarre morphology. Third-degree AV blocks typically produce marked exercise intolerance, weakness, and syncope. Even so, it is possible to encounter older animals, not very active by nature, that have "asymptomatic" third-degree AV block; pacemaker implantation may reveal the extent and duration of clinical signs restrospectively, when the patient shows a substantial improvement in exercise tolerance and vigor at home postoperatively. In cats, especially, third-degree AV block can exist with a ventricular escape rhythm that is only minimally less than the normal sinus heart rate at home (e.g., 110-140 beats/min) and the block is an incidental finding (see Figure 248-23).[3,5,115]

The causes of AV blocks are diverse. First-degree AV and Mobitz type I second-degree AV blocks often are functional (high vagal tone in healthy individuals; negative dromotropic effects of digitalis, antiarrhythmics, or alpha 2–stimulating sedatives) and thus are normal physiologic variants or resolve with drug discontinuation. Rarely, cardiac disease with atrial dilation and AV nodal lesions can be present as a cause of first-degree or Mobitz type I second-degree AV block. Mobitz type II second-degree AV block and third-degree AV block sometimes are functional (hyperkalemia, digitalis toxicosis, alpha 2–receptor agonists like dexmedetomidine) but are more commonly associated with a structural lesion, be it inflammatory (endocarditis, Lyme myocarditis, traumatic myocarditis) or degenerative (physical disruption of the AV node arising from cardiomyopathy, endocardiosis, or fibrosis).[116-118] In dogs, third-degree AV block usually is considered irreversible but it has been shown to return spontaneously to NSR in 7% of cases and to second-degree AVB in 5% of cases.[119]

Treatment of AV block is aimed at the underlying cause when possible. In clinically overt, advanced, Mobitz type II second-degree AV blocks or third-degree AV blocks, response to parasympatholytic or sympathomimetic drugs tends to be disappointing because these agents do not reverse the disease process in the AV node, nor do they typically overcome the AV block to a clinically meaningful degree.[28] Pacemaker implantation (see ch. 249 and Video 248-4) is more effective and it leads to significantly longer survival: the one-year survival rate for dogs with high-grade second-degree AV block or third-degree AV block that receive a pacemaker is 80-85% compared to 50-55% for those that do not, and the 2-year survival rate is 70-

75% versus 30-35%, respectively.[28]

It is important to note that the decision to implant a pacemaker can be a dilemma for owners who question whether an older dog is reaching the end of its natural lifespan because the dog "has been showing signs of getting older lately." Such owners should understand that these signs often were the progressive manifestations of the bradycardia, not of aging, and that pacemaker implantation—while not a panacea—can produce a quality of life that owners had not seen in their dogs for months or years. Therefore, comorbidities (e.g., chronic kidney disease), nonspecific signs, and an advanced age, while relevant to the patient, should be seen as factors that pacemaker implantation could help, rather than reasons to automatically forgo the procedure.

Cats with third-degree AV block have distinct features that are clinically important. Many (11/18, 61% in one case series)[115] have such underlying structural heart diseases as cardiomyopathy, which will not be reversed by pacemaker implantation. Ventricular escape rates approximate NSR (80-140, median 120 beats/min in one case series),[115] such that third-degree AV block can be an incidental finding in cats. Survival without a pacemaker can be surprisingly long (median 386 days; range, 1-2013 days in one case series),[115] regardless of presenting signs.

Bundle Branch Blocks

BBBs are slowings or interruptions of conduction involving one or more of the ventricular branches of the His bundle. Blocks can be functional (transient interruptions due to a depolarization's occurring during the refractory period) or structural (permanent interruptions due to a physical disturbance). The ECG diagnosis of BBBs is based on the abnormal shape of the QRS complexes, which become widened due to the desynchronization of the two ventricles. BBBs cannot be considered arrhythmias because they do not alter the rhythm of the heartbeat; therefore, the ECG diagnosis is stated as "rhythm" (e.g., normal sinus rhythm) "with [right or left] bundle branch block" (or "BBB pattern"). The duration of the QRS complexes is >0.07 second in dogs with BBB (>0.04 second in cats with BBB), and the polarity is positive in lead II for left BBBs and negative in lead II for RBB blocks[111] (Figures 248-24 and 248-25).

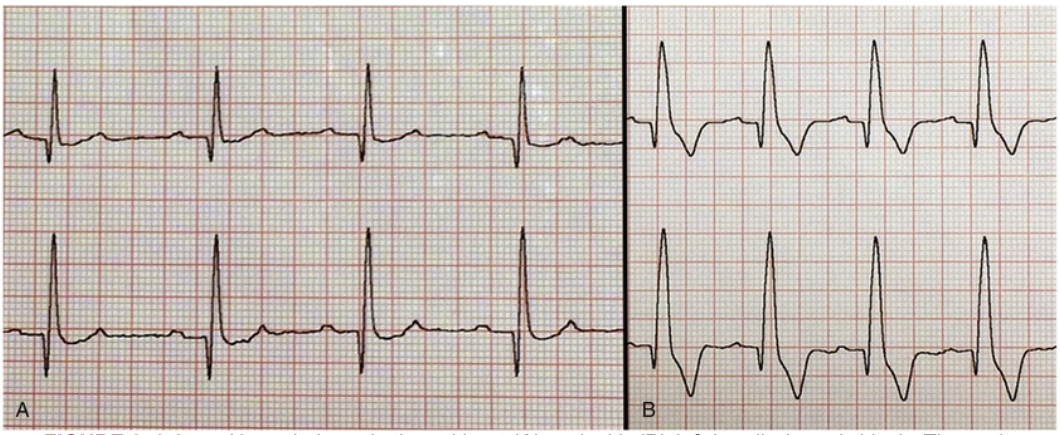

FIGURE 248-24 Normal sinus rhythm without **(A)** and with **(B)** left bundle branch block. The main difference is in the width of the QRS complexes (0.09 second in panel **B**), which exceeds the normal range for dogs (up to 0.06 second). Panel **A** was obtained before doxorubicin treatment for this dog's neoplasia. Panel **B** was obtained after a lifetime cumulative dose of 150 mg/m^2, an amount that sometimes can be associated with cardiotoxicosis. Both tracings: leads I and II, 25 mm/sec, 1 cm = 1 mV. (Courtesy Dr. Glenna Mauldin, Animal Cancer Centre, Western Veterinary Specialist and Emergency Centre, Calgary, AB, Canada.)

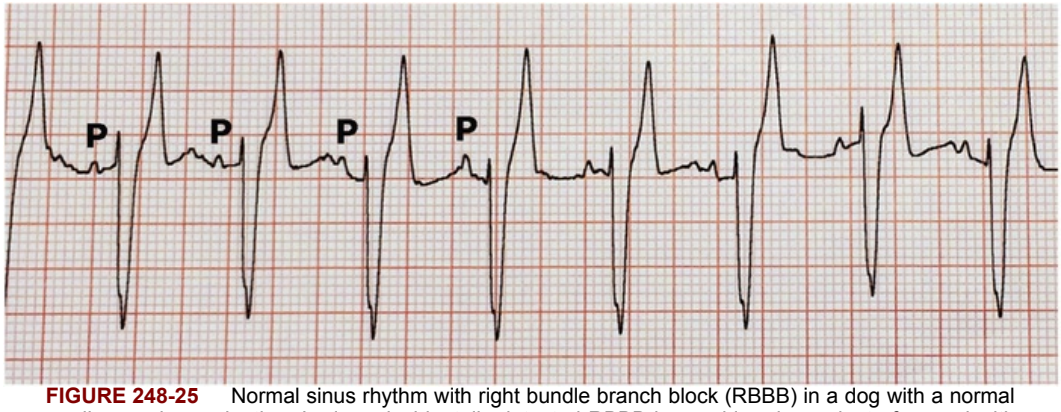

FIGURE 248-25 Normal sinus rhythm with right bundle branch block (RBBB) in a dog with a normal cardiovascular evaluation. In dogs, incidentally detected RBBB is considered a variant of normal with no clinically significant consequences. The wide, bizarre QRS complexes can be misinterpreted as PVCs if the association between a P wave and each QRS complex, at a constant PR interval, is overlooked. Lead II, 25 mm/sec, 1 cm = 1 mV. (Courtesy Dr. Glenna Mauldin, Animal Cancer Centre, Western Veterinary Specialist and Emergency Centre, Calgary, AB, Canada.)

If BBBs occur during sinus rhythm, the ECG diagnosis is straightforward because other than the very abnormal appearance of the QRS complexes, the P-QRS-T sequence throughout the ECG is normal: A P wave occurs before each QRS and the PR interval is fixed and normal. Still, care must be taken to properly identify the rhythm as normal sinus rhythm and avoid misdiagnosis of VT based on wide, bizarre QRS complexes alone. If the block occurs concurrently with a nonsinus rhythm, such as AFib, establishing a diagnosis in BBB can be much more challenging (see Figure 248-12). A BBB together with AFib mimics ventricular extrasystoles or VT, which may misdirect therapeutic decisions (see previous discussion of atrial fibrillation). Cats with heart disease (especially cardiomyopathy) are classically described as being prone to developing block in a subdivision of the LBB known as the *left anterior fascicle* (LAF).[5] This electrocardiographic observation is supported by the histologic finding in 63 cardiomyopathic feline hearts that 54 left bundles (86%) showed degeneration, fibrosis, osseous metaplasia, and other lesions, compared to 20 right bundles (32%).[121] LAF block produces a tall R wave in lead I and aVL and a deep S wave in leads II, III, and aVF, and therefore, a left-axis deviation.[122]

The causes of BBB are many, because BBBs can be due to a variety of pathologic changes including concentric hypertrophy (as seen in hypertrophic cardiomyopathy),[121] dilation (as seen in dilated cardiomyopathy), and inflammation (endocarditis, traumatic myocarditis). In the dog, RBB block usually is a completely normal, unnecessarily worrisome ECG finding. Conversely, LBBB almost always is associated with left ventricular enlargement (see Figure 248-24). Clinical manifestations of BBBs alone generally do not occur.[120,122] These disturbances therefore do not warrant specific treatment beyond that of their underlying problem if one exists. The importance of recognizing BBB lies in the fact that LBBB could be the first indicator of underlying cardiac disease, which itself warrants further diagnosis and treatment; and that they can—and should not—be misinterpreted as ventricular arrhythmias.

Atrial Standstill (Silent Atrium)

This rhythm disturbance is characterized by the total absence of atrial depolarization (Figure 248-26). The three differential diagnoses for atrial standstill are (1) moderate to marked hyperkalemia ($K^+ > 7.5$ mEq/L; see later discussion), (2) atrial myopathy, and (3) ECG artifact (P waves too small, or isoelectric, preventing them from being seen properly). Although hyperkalemia is the most common cause of atrial standstill (and the only reversible one), atrial standstill can occur due to marked atrial stretch,[123] as occurs particularly in cats with various forms of cardiomyopathy, or atrial parenchymal hypoplasia, as is seen in association with a dystrophic form of neuromyopathy, particularly in the Springer Spaniel. Regardless of cause, the ECG appearance is of a regular rhythm (constant R-R interval), usually with QRS complexes that are of a supraventricular appearance, and with a low or normal rate but without detectable P waves in any lead on the ECG. Differentiating between the two main causes of this rhythm using the ECG alone is difficult, and immediate measurement of serum potassium concentration is warranted.

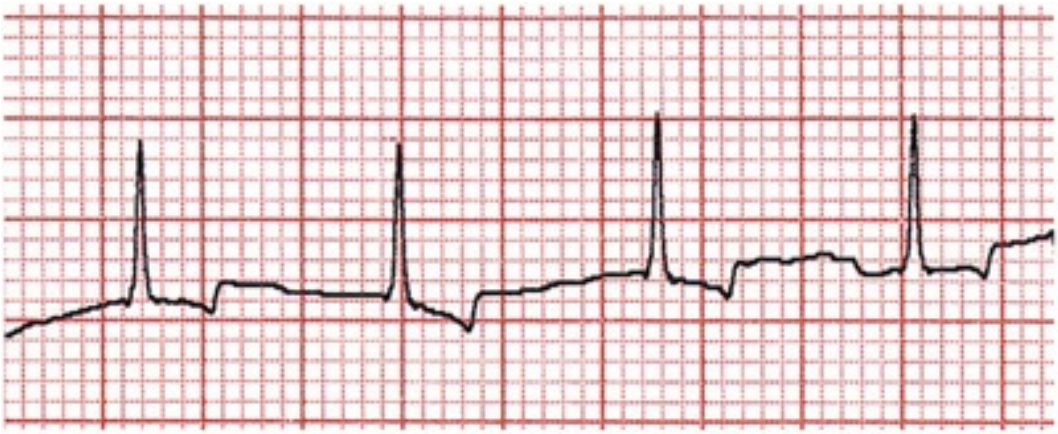

FIGURE 248-26 Atrial standstill in a 10-year-old Labrador Retriever dog. No P waves are seen on this lead, nor were they present in any other lead. The rhythm is regular, at a rate of 120 beats/min. The most important possible cause is hyperkalemia, which can be life-threatening, but which was ruled out with a normal serum potassium concentration in this dog. Therefore, the diagnosis by exclusion is atrial myopathy. Lead II, 25 mm/sec, 1 cm = 1 mV.

Electromechanical Dissociation

Electromechanical dissociation (EMD) is not, strictly speaking, an abnormality of cardiac rhythm. EMD refers to the failure of conversion of an electrical rhythm into the mechanical forces of systole and diastole.[124,125] The ECG therefore can show virtually any rhythm, and the diagnosis rests on the combination of a hemodynamically collapsed patient with an ECG that shows any rhythm but asystole. The arterial pulse usually is barely perceptible or absent, the patient typically is unconscious, and EMD most commonly is a prearrest or terminal condition. Treatment requires correction of underlying causes if possible and then is aimed at increasing circulation to improve myocardial perfusion (see ch. 140 and 141). Because EMD generally indicates profound myocardial hypoxia, the prognosis is grave irrespective of treatment.

Complex Disorders Involving Abnormalities of Both Excitability and Conduction

Cardiac Effects of Systemic Potassium and Calcium Abnormalities

Because cardiac activity depends fundamentally on transmembrane movements of ions, pathologically high or low systemic concentrations of potassium and calcium can lead to disturbances in cardiac function. Such disturbances can have important effects on the heart's rhythm.

Hypokalemia

Serum potassium concentrations are most accurate if measured on blood drawn into lithium heparin (green top) tubes. Purple top tubes contain tripotassium EDTA, which produces an artifactually high test result incompatible with life, and red top tubes allow coagulation, a process that, during platelet activation and aggregation, releases potassium and can artifactually raise the measurement by small but clinically significant levels.

A low serum potassium concentration produces two major effects in cardiomyocytes. First, it makes the resting membrane potential increasingly negative (Figure 248-27),[126,127] which decreases myocyte excitability. This effect is a result of the greater difference between intracellular and extracellular potassium concentrations in hypokalemia compared with normokalemia (hyperpolarization) and in cardiomyocytes is generally mild and transient. Second, hypokalemia prolongs repolarization, increasing action potential duration.[126,127] Myocyte repolarization depends principally on the activity of potassium currents, notably the delayed rectifiers $I_{k,r}$ and $I_{k,s}$. With hypokalemia, these currents function more slowly. This prolongation of repolarization lengthens the normally very brief period of repolarization during which the diastolic membrane potential is near the threshold potential. Therefore, hypokalemia-induced prolongation of repolarization opens a window of increased excitability during which spontaneous ectopic activity (such as atrial or ventricular extrasystoles) can occur based on the threshold being reached after the absolute refractory period by a slowly repolarizing cell. Clinically, the second (arrhythmogenic) effect predominates over the first

(suppressive), and the dominant cardiovascular effect of a serum potassium concentration <3.5 mEq/L in dogs and cats is an increased risk of spontaneous depolarizations, notably ventricular extrasystoles (PVCs). Other ECG manifestations of hypokalemia can include evidence of prolonged, abnormal repolarization in the form of U waves, Q-T interval prolongation, and AV dissociation.[128]

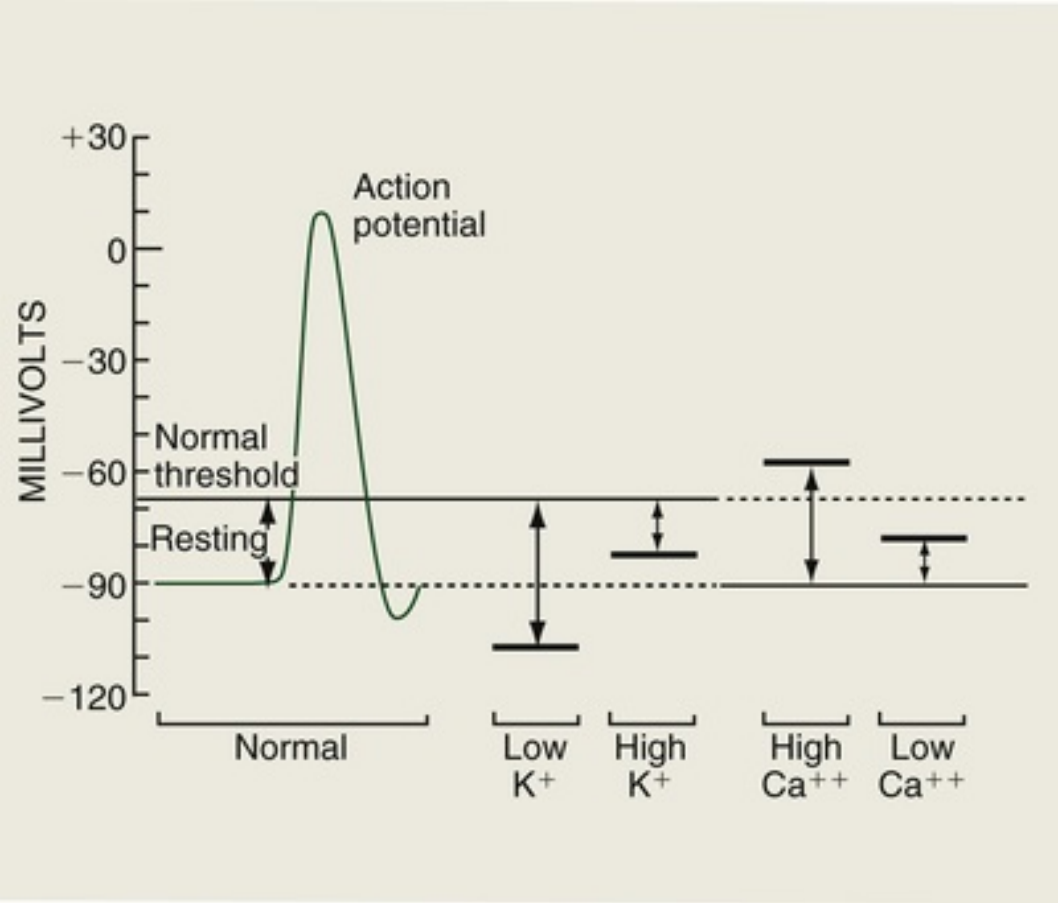

FIGURE 248-27 Effects of abnormal serum calcium and potassium concentrations on cell membrane characteristics in excitable tissues. The concentration of potassium in extracellular fluids affects the resting potential, whereas the concentration of calcium in extracellular fluids affects the threshold potential. Equally or more important, though not shown here, are the effects of these abnormalities on repolarization. (Reproduced with permission from Leaf A, Cotran R: *Renal pathophysiology*, New York, 1976, Oxford University Press, p 116.)

Because class I antiarrhythmics (e.g., lidocaine, mexiletine, quinidine) act on sodium channels that require normal serum potassium concentrations to function, hypokalemia also is important as a cause of antiarrhythmic drug refractoriness: a patient whose PVCs are caused by hypokalemia generally will return to normal sinus rhythm with potassium supplementation alone, whereas treatment with lidocaine during hypokalemia is unlikely to alter the ventricular arrhythmia but still can cause lidocaine toxicosis (neurologic disturbances such as seizures) if dosing is readministered repeatedly for lack of conversion to sinus rhythm. This important observation has wide-ranging implications in patients with dilutional hypokalemia (e.g., gastric dilatation-volvulus patient with large-volume fluid resuscitation) or potassium-wasting metabolic illness (e.g., chronic kidney disease) when PVCs/VTs occur and the question "When should I treat this arrhythmia with an antiarrhythmic?" arises. An important initial step toward answering this question should always be to ensure that normokalemia is present before considering antiarrhythmic therapy. The maximum safe rate of IV potassium chloride infusion is 0.5 mEq/kg/h (see ch. 68).

Hyperkalemia

Mildly elevated serum potassium levels (5.6 to 6.5 mEq/L) are associated with greater cell membrane permeability to potassium during repolarization. These repolarization effects predominate over depolarization effects shown in Figure 248-27, and such mild hyperkalemia has been described as a rhythm-

stabilizing condition. Thus, mild hyperkalemia in dogs can be reflected on the ECG as faster ventricular repolarization (i.e., a shorter than normal Q-T interval and an abnormally narrow, often peaked or "tented" T wave).[126,127,129,129a] It is a common but serious mistake to think that tented T waves must always equal hyperkalemia: in a case series of 205 dogs with hypoadrenocorticism, many were hyperkalemic but only 15% of these hyperkalemic dogs had "tented" (tall, narrow) T waves.[130] Similarly, of 37 dogs or cats with naturally occurring hyperkalemia, only 2 (5%) had tall T waves,[131] and both were more hyperkalemic than expected with this ECG finding (serum $[K^+]$ = 7 − 9.99 mEq/L). The reverse also can be a pitfall: many normal, healthy dogs may have T wave parameters that exceed the normal range. Therefore T wave amplitude abnormalities are insensitive and nonspecific and, particularly in cases of hypoadrenocorticism, should be taken with a grain of salt.

Sinus bradycardia can occur (33% of hyperkalemic dogs with hypoadrenocorticism) because hyperkalemia decreases the activity of normal pacemaker tissue. Specifically, it decreases the slope of phase 4 of diastolic depolarization,[126] which slows the heart rate. However, naturally-occurring hyperkalemia also routinely coexists with abnormalities in acid-base status or other serum electrolytes, pain, fear, sepsis, hypovolemia, and other disorders, all of which tend to cause the opposite—sinus tachycardia. The routine observation that many cats and dogs with even severe hyperkalemia have elevated heart rates makes heart rate unreliable for inferring a patient's serum $[K^+]$.[131,132]

Mild to moderate increases in serum potassium (6.6 to 7.5 mEq/L) can begin to interfere with cell-to-cell transmission velocity in the ventricles. In dogs that are hyperkalemic due to hypoadrenocorticism, wide QRS complexes are observed in 32% of cases.[130] A decrease in R-wave amplitude has been reported in 47% of these same dogs.

Moderate to severe hyperkalemia (7.0 to >8.5 mEq/L) can cause P-R interval prolongation (45%) or absence of P waves altogether (47%, for a total of 92% of hyperkalemic dogs with hypoadrenocorticism), which are probably the most characteristic ECG findings for hyperkalemia.[130] The atria are more sensitive to hyperkalemia than are the ventricles, and within the atria, the myocardium is more sensitive to the effects of hyperkalemia than are the internodal tracts. The result when severe hyperkalemia occurs is a *sinoventricular rhythm*, so named because the heartbeat originates in the SA node as usual, crosses the atria through the internodal tracts (but the impulse does not spread outward—no atrial activation, no P wave), and then passes through the AV node and His-Purkinje system in the usual sequence. The ECG appearance is a regular rhythm with normal or slightly widened QRS complexes and no P waves in any lead.

Very high serum potassium concentrations (>8.5 mEq/L) can be lethal. So many other factors influence the rhythm in these catastrophically ill patients that an exact cutoff for lethality cannot be established for serum potassium concentration alone. With rising concentrations comes further widening of the QRS complex and of the T wave, and these can blend into a sine-wave type of regular but poorly functional or nonfunctional rhythm, or a ventricular-type of escape rhythm at a very low rate (both likely preagonal rhythms). If not corrected immediately, critical hyperkalemia that has produced these dramatic ECG changes can cause cardiac arrest (ventricular fibrillation, escape rhythm with electromechanical dissociation) within minutes (see ch. 140 and 141).

Hypocalcemia

Low serum calcium concentrations have modest and often clinically insignificant cardiac effects; instead, the skeletal muscle effects dominate the clinical picture. Altered calcium concentrations affect the threshold of a myocyte's action potential rather than the resting membrane potential (see Figure 248-27). Hypocalcemia lowers the threshold, facilitating depolarization. The clinical expression is fine skeletal muscle fasciculations progressing to generalized tremors if calcium is not normalized. This effect is minimal in cardiomyocytes. Hypocalcemia also prolongs the initial phase of ventricular repolarization, which can manifest as a prolongation of the Q-T interval on the ECG.[126]

These effects help explain why intravenous calcium infusions are considered "cardioprotective" in severe hyperkalemia, even though they do not change the circulating potassium concentration. Hyperkalemia raises the resting membrane potential (see Figure 248-27), and providing additional calcium raises the threshold for depolarization, re-establishing a more normal ionic gradient across the cell membrane. Considering that 75% of cats with urethral obstruction concurrently have mild, moderate, or severe hypocalcemia,[133] IV calcium gluconate (50 mg/kg slow IV over 10-30 minute period, given to effect) is a logical first-line treatment for severe hyperkalemia in these patients.

When infusing calcium intravenously (always as a slow infusion and with ongoing ECG monitoring), the

ECG parameters sometimes attributed to hypercalcemia can be used as markers of excessively rapid infusion. A sudden slowing of the heart rate, shortening of the Q-T interval, or appearance of ventricular extrasystoles are grounds for stopping the infusion and resuming later if necessary. Here, as with hyperkalemia, the ECG is particularly valuable because ECG recordings are obtained at admission, and it is possible to determine whether the patient's parameters are changing during treatment compared with his or her own baseline.

Hypercalcemia

Similarly, hypercalcemia generally is of greater concern for its extracardiac effects than for any alterations in cardiac rhythm. Severe hypercalcemia raises the threshold of the cardiomyocyte, which should hinder depolarization. It also shortens early ventricular repolarization, making the Q-T interval shorter.[126,134] These consequences of severe hypercalcemia are of secondary concern compared with dystrophic mineralization of the kidneys and other soft tissues, for example.

Preexcitation and Macroreentrant Syndromes

In preexcitation, the normal impulse originating from the SA node is split at the end of atrial depolarization, with part of the impulse traveling normally through the AV node and another part of the impulse traveling simultaneously through an abnormal segment of rapidly conductive fibers that links the atria and the ventricles (the *accessory pathway* or *bypass tract*), thus bypassing the AV node. The result is partial, premature, immediate activation of the ventricles through the bypass tract, without the benefit of a pause in the AV node —i.e., preexcitation. With one major exception (see later), the effect of this abnormal pattern of activation is minimal because only a part of the atrial contribution to ventricular filling is lost. The ECG demonstrates that the normal delay through the AV node was preempted by conduction through the bypass tract (little or no segment separates the P wave from the QRS complex) and that conduction through the bypass tract caused asynchronous activation of the ventricles (the bypass tract and the normal AV nodal conduction ultimately each activates its share of the ventricles), resulting in a notched QRS complex. The size and location of the QRS complex's notch, the *delta wave*, depends on the distance that separates the bypass tract and the AV node in the individual's heart (Figure 248-28). Bypass tracts usually are single but can be multiple, and most originate in the right atrium, rather than the left, in dogs.[135] This makes them more readily accessible for radiofrequency ablation.

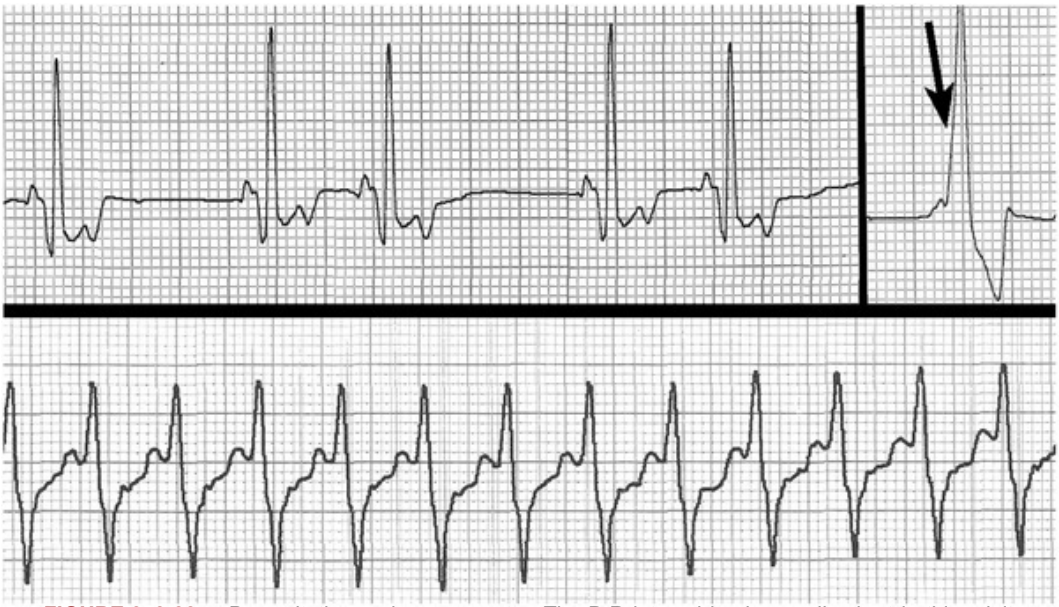

FIGURE 248-28 Preexcitation and macroreentry. The P-R interval is abnormally short in this adult Golden Retriever (upper tracing). A delta wave also is present, seen best in lead V2 (upper tracing inset, which also shows the PR interval shortening more clearly). The diagnosis is respiratory sinus arrhythmia with evidence of ventricular preexcitation. The heart rate is 90 beats/min. Lead II, 25 mm/sec, 1 cm = 1 mV. The same dog was hospitalized due to a sudden onset of severe tachycardia detected by the owner (lower tracing). The tracing shows a wide-complex monomorphic tachycardia at a rate of 330 beats/min. Together with the baseline ECG finding of preexcitation, the most likely diagnosis is macroreentrant tachycardia. The short PR interval during the tachycardia is unusual for the Wolff-Parkinson-White syndrome (orthodromic atrioventricular reentrant tachycardia). Modified

precordial lead (intensive care monitoring), 50 mm/sec, 1 cm = 1 mv.

Under usual circumstances, preexcitation is an incidental, clinically silent finding. However, in individuals with preexcitation, a premature depolarization can initiate a macroreentrant cycle that can produce extremely rapid, persistent tachycardias. Although bypass tracts conduct impulses rapidly, their refractory period typically is longer than that of the AV node. Therefore, the timing of a premature supraventricular depolarization can fail to conduct through the bypass tract but be able to conduct through the AV node, depolarizing the ventricles normally. As the impulse completes the depolarization of the ventricles, the bypass tract has repolarized and is able to conduct. Bypass tracts often can conduct impulses in either direction, such that the ventricular impulse conducts retrograde through the bypass tract to the atria, then again through the AV node in the normal direction and again through the bypass tract, initiating an endless loop. This type of self-perpetuating cycle is a macroreentrant circuit, and it can produce a potentially very rapid and clinically overt (apparent discomfort, gastrointestinal signs, exercise intolerance, lethargy, syncope)[53] tachycardia called *orthodromic* (the impulse travels in a normal, "normograde" direction through the AV node) AV reentrant tachycardia (OAVRT), the main form of clinically manifested ventriculoatrial macroreentry, or *Wolff-Parkinson-White syndrome,* in the dog.[32,46,53,136] Dogs with this syndrome can have unrelenting heart rates >300 beats/min. Initial treatment can involve vagal maneuvers that, through slowing of AV conduction (i.e., negative dromotropic action), break the cycle of reentry (see Figure 248-3). More definitive treatment is achieved using IV diltiazem or esmolol as described for atrial tachycardias, above.

Sinus Node Dysfunction/Sick Sinus Syndrome

Sinus node dysfunction (sick sinus syndrome [SSS], bradycardia-tachycardia syndrome) is a well-recognized cardiac arrhythmic syndrome that is the second-most frequent indication for pacemaker implantation in dogs (after AV block).[28a,137-139] It involves a complex disturbance of the cardiac conductive tissues, producing simultaneous defects in sinus activity (SB and sinus arrest), AV conduction disturbances (first-degree and second-degree AV blocks), and disturbances in supraventricular and ventricular excitability (Figure 248-29). Therefore, the disturbance is not a problem involving only the SA node, as the name SSS suggests, but rather is an illness that affects cardiac pacemaking and conductive tissues at all levels.

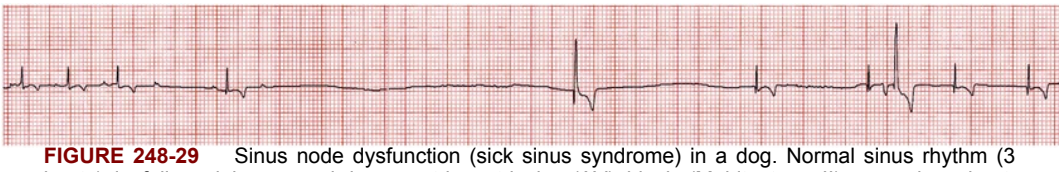

FIGURE 248-29 Sinus node dysfunction (sick sinus syndrome) in a dog. Normal sinus rhythm (3 beats) is followed by second-degree atrioventricular (AV) block (Mobitz type II), one sinus beat, another instance of Mobitz type II second-degree AV block, and a period of asystole lasting 3.5 seconds. Asystole terminates with a wide, bizarre-appearing ventricular escape beat, followed by asystole for 2 seconds, a junctional escape beat, a premature ventricular complex (PVC), and two junctional escape beats. This highly varied mixture of bradycardic rhythms and tachycardia (PVC) is characteristic of sinus node dysfunction. Lead II, 25 mm/sec, 1 cm = 1 mV.

The cause of SSS is unknown. Some human beings with SSS have autoantibodies directed at SA nodal tissue or at cholinergic receptors,[140,141] and such mechanisms bear investigating in veterinary medicine because they could explain the panoply of arrhythmias noted in dogs with this disorder. Certain epidemiologic features stand out from cases reported in the veterinary literature. The disease is recognized almost exclusively in dogs, and the stereotypical breed predilection for female Miniature Schnauzers is not exclusive. Many other breeds, notably Cocker Spaniels,[137,138] West Highland White Terriers,[137,142] and mixed breed dogs, represent an ever-increasing proportion of patients with this disorder.[28a] The spectrum of disease described as SSS likely regroups more than one distinct disorder that future research will categorize into separate entities.

The age of onset typically is mid- to late adulthood (6 to 10 years), and the association with DMVD is common but not obligatory. Histopathologically, depletion of SA nodal cells is seen with fibrous/fibrofatty replacement causing effacement between the SA node and atrial myocardium.[143] The ECG diagnosis often requires repeated and sufficiently long (2- to 3-minute) tracings, to convincingly demonstrate some or all of the aspects of SSS:SB (often with first- or second-degree AV block), prolonged sinus pauses with variable

escape beats, and bursts of supraventricular tachycardia or ventricular extrasystoles at various rates (see Figure 248-29). In some cases, only SB occurs. Because these features occur intermittently, the diagnosis often is only made by obtaining an ECG during an episode of syncope, stumbling, or ataxia (near syncope), which are the most common overt clinical manifestations of this arrhythmia. Ambulatory ECG, especially cardiac event recording, is ideally suited for establishing the diagnosis of SSS when the in-hospital ECG is unhelpful (see ch. 103). Such technology has identified that episodes occur during bradycardia rather than tachycardia. An atropine response test (see above) can confirm the heart's ability to respond to vagolytic treatment, and such a response has recently been shown to translate into long-term response to vagolytic drugs in many affected dogs.[28a] Such drugs (e.g., propantheline 0.5-3 mg/kg PO q 8 h[142] or hyoscyamine 0.005 mg/kg PO q 8 h[144] or aminophylline/theophylline 10 mg/kg PO q 8 h)[145] can improve the situation by reducing the impact of bradycardia episodes and pauses; 54% of dogs with sinus node dysfunction were controlled with pharmacologic treatment according to a recent retrospective.[28a] Definitive treatment when episodes are recurrent generally requires the implantation of a pacemaker (see ch. 249).

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CHAPTER 249

Cardiac Pacing

Amara H. Estrada

Client Information Sheet: Cardiac Pacing

Indications for Pacing

Bradycardia causing overt clinical signs remains the most compelling indication for pacemaker therapy in dogs and cats. Detailed classification schemes are established for pacing in people, where categories of "generally indicated," "may be indicated," and "not indicated" guide treatment decisions. In veterinary medicine, the indications are similar and cardiac pacing is most commonly performed in dogs with complete (third-degree) atrioventricular (AV) block or sinus node dysfunction (Figure 249-1). Less commonly, pacemakers are placed in veterinary patients with persistent atrial standstill (not associated with hyperkalemia) and high-grade second-degree AV block.

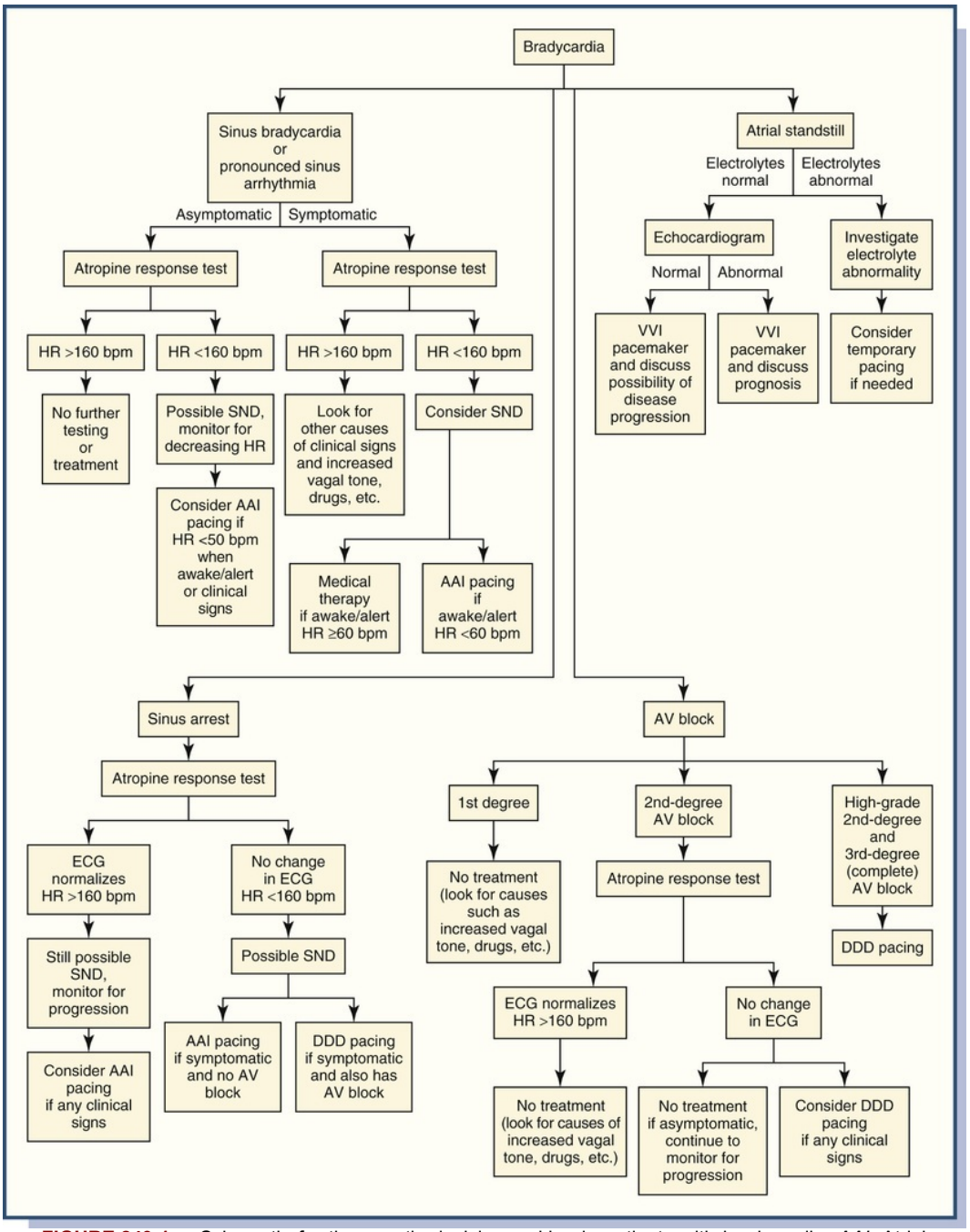


FIGURE 249-1 Schematic for therapeutic decision making in patients with bradycardia. *AAI,* Atrial pace, atrial sense, inhibit; *AV,* atrioventricular; *DDD,* dual chamber pace, dual chamber sense, inhibit; *ECG,* electrocardiogram; *HR,* heart rate; *SND,* sinus node dysfunction; *VVI,* ventricular pace, ventricular sense, inhibit.

Atrioventricular Block (see ch. 248)

Dogs with high-grade second degree or complete AV block should almost always be considered candidates for permanent pacemaker therapy (see ch. 30). Even escape rhythm rates > 50 beats/minute (bpm) have the potential to decrease over time. Cats differ in terms of their escape rhythm rates when AV block develops, typically having a faster ventricular escape rhythm (90-120 bpm) such that they do not frequently require cardiac pacing. Occasionally, cats with cardiomyopathy develop bradycardias with escape rhythms that are slow enough to require pacemaker therapy to either keep them out of congestive heart failure or, if physical activity is affected, to improve quality of life.

Sinus Node Dysfunction (SND; "Sick Sinus Syndrome"; see ch. 248)

Patients with sinus node dysfunction that is causing overt signs such as syncope represent a definite indication for pacing (see ch. 30). Patients with ECG findings compatible with SND but whom the owners feel are not showing clinical signs represent a dilemma. Many of these patients are older and clinical signs may exist but be mistaken for "slowing down due to old age." The degree of bradycardia at which pacing should be considered is controversial even in human medicine, and each patient should be considered individually. It is the author's opinion that sinus rates consistently <50 bpm during alert/awake periods are an indication for pacing. Additionally, sinus pauses >3 seconds during alert/awake times should also be considered abnormal and warrant pacing if the patient has signs of exercise intolerance or lethargy. Pauses that occur during sleep (usually detected during Holter monitoring or inpatient telemetry) are less of a concern. Some dogs with SND exhibit an excessive response to enhanced vagal tone. This is likely because there is an autonomic component that contributes to the disease process. Administration of an anticholinergic drug such as atropine may allow for a higher sinus rate and elimination of sinus pauses, but that does not mean that the sinus node dysfunction is benign and pacemaker therapy should still be considered in these cases, especially if there are clinical signs that could be attributed to the bradycardia.

Atrial Standstill

Persistent atrial standstill is an uncommon arrhythmia associated with atrial myocarditis causing the atria to be unable to depolarize from a sinus-initiated impulse. Although the sinus node continues to fire, it is ineffective in depolarizing the atria and penetrating the AV node. P waves are absent on the ECG and a junctional or ventricular escape rhythm is usually present. Pacemaker implantation is indicated in this disease, as increasing the heart rate can both improve clinical signs of exercise intolerance or syncope and assist in the management of congestive heart failure if it is present. The prognosis following pacing depends on the severity or presence of underlying myocardial disease and often is not as favorable as pacing for SND and AV block. Temporary atrial standstill caused by hyperkalemia is discussed further in ch. 248 and 309, and is not an indication for permanent cardiac pacing.

Less Common Uses for Pacing Therapy

There is still controversy regarding cardiac pacing for *vasovagal syncope* (see ch. 30) when medical therapy fails. It has been shown in human clinical trials[1,2] that vasovagal syncope can be aborted or blunted with dual-chamber pacing, and even if syncope does occur, pacing can prolong consciousness to avoid injury. Newer pacing algorithms are currently being investigated in a clinical trial specifically for people with vasovagal syncope. Enrollment in this clinical trial is complete and the study is ongoing.[3]

Pacing for *tachyarrhythmias* is not commonly used in veterinary medicine at this time. However, chronic supraventricular tachyarrhythmias (such as atrial fibrillation, re-entrant atrial arrhythmias, atrial tachycardia) that are refractory to medical management have become an indication for permanent pacing in people. Various techniques have been used, including the so-called "ablate and pace" for chronic atrial fibrillation wherein the AV node is radiofrequency-ablated and a pacemaker inserted within the ventricle to achieve heart rate control. Another approach has been aimed at the prevention of atrial fibrillation in patients with refractory atrial tachyarrhythmias involving biatrial synchronous pacing.[4-6] This "dual site" atrial pacing has been shown to decrease the number of episodes of paroxysmal atrial fibrillation and flutter.[7] In addition to these alternate pacing techniques, pacing algorithms have been incorporated into pacemakers in an effort to decrease the number of premature atrial complexes and maintain consistent atrial pacing. Another common indication for permanent pacemaker implantation in people is for refractory ventricular tachycardia, especially for disorders such as long QT syndrome known to have a high incidence of sudden death due to degeneration of ventricular tachycardia to ventricular fibrillation. Many trials have identified a clear benefit of dual chamber pacemakers/intracardiac defibrillators (ICDs) over medical therapy alone in the prevention of sudden death.[8-11] There are now several reports in the veterinary literature on the successful use of ICD therapy.[12-14]

More than 25 years ago, dual chamber pacing was promoted as a specific treatment remedy for patients with *hypertrophic obstructive cardiomyopathy,* in the absence of conduction system disease. The hypothesis was that by shortening the AV interval to prevent normal conduction through the AV node, "pure" right ventricular apical (RVA) pacing could be guaranteed. With this approach there would then be delayed contraction of the basal portion of the interventricular septum with resultant reduction or elimination of

outflow tract obstruction.[15-18] This approach has now been abandoned because of lack of efficacy[19,20] and concern regarding the negative effects of long-term RVA pacing.

Cardiac resynchronization therapy (CRT) is the term applied to reestablishing synchronous contraction between the left ventricular (LV) free wall and the ventricular septum by simultaneous or near simultaneous pacing of the right ventricular apex and the LV free wall (BiV pacing). This type of pacing therapy is now an accepted and cost-effective treatment for human patients with advanced heart failure, impaired LV function, and a wide QRS complex.[21] This therapy is now also a realistic option for patients with mild heart failure and may ultimately replace RVA pacing as a more physiologic means of cardiac pacing. For now, devices are expensive and only obtainable through donation to veterinary patients, and lead placement, and subsequent programming of devices, take considerable practice for the clinician to become proficient.[22]

Types of Pacemakers and Hemodynamics of Pacing

Once an indication for pacing has been identified, consideration should be given to selecting the most appropriate pacing mode for the patient. Factors that should be considered include: (1) the underlying rhythm disturbance; (2) overall physical condition of the patient and any associated medical problems; (3) exercise/activity capacity of the patient; (4) chronotropic response to exercise/excitement; (5) effect of pacing on long-term morbidity and mortality.

Pacing Nomenclature

Pacemaker nomenclature is labeled using Roman numerals I-V. Position I refers to the chamber or chambers being paced: *A* = atrium; *V* = ventricle; *D* = dual chamber, meaning both A and V. Position II refers to the chamber or chambers in which sensing occurs. The letter options are the same as in the first position. The designation *O* refers to absent sensing (and thus refers to fixed, asynchronous pacing). Position III refers to the device's response to sensed events. An *I* represents the inhibited mode, meaning that when an event is sensed, the device will be inhibited from further pacing; this is the most common form of sensing. *T* indicates a triggered response. When the pacemaker senses an event and is programmed in this mode, it will trigger the device to deliver a pacing stimulus. *D* means that both *T* and *I* responses can occur. In single-chamber pacing situations, the sensed event and triggered impulse occur within the same chamber so this function is never used in single-chamber pacing. In dual-chamber application, however, an atrial-sensed event inhibits atrial stimulation and triggers the delivery of a ventricular stimulus with an AV interval delay programmed to be similar to that of a normal PR interval. Position IV indicates programmability and rate modulation. In practice, *R* is the only indicator commonly used in this position and indicates that the pacemaker incorporates a sensor to modulate the rate independently of intrinsic cardiac activity. Position V is used to indicate whether multisite pacing is present in none of the cardiac chambers *(O),* one or both atria *(A),* one or both ventricles *(V),* or any combination of atria and ventricles *(D).* For instance, to describe a patient with a dual-chamber rate adaptive pacemaker with biventricular stimulation, the code would be DDDRBiV.

Single Chamber

From a practical standpoint, there are essentially only two forms of single-chamber pacing: VVI and AAI, with the former being the most common in veterinary medicine.[23] Rate modulation is an option in both of these pacing configurations (VVIR or AAIR).

Ventricular-Inhibited Pacing (VVI)

VVI pacemakers have one pacing lead placed within the ventricle and are capable of pacing only in the ventricle (V in the first position of the pacemaker code), sensing only in the ventricle (V in the second position), and, if a native ventricular beat is sensed, the pacemaker is inhibited from firing (I in the third position) (Figure 249-2). Although VVI pacing protects the patient from lethal bradycardias, it is substantially limited because it does not restore or maintain AV synchrony and, compared to VVIR pacing, does not provide rate responsiveness in the chronotropically incompetent patient—that is, in the patient in whom the spontaneous sinus heart rate does not increase in response to a physiological demand. In addition, some patients with VVI pacing experience the onset, or worsening, of clinical signs during ventricular pacing. Adverse hemodynamic effects associated with a normally functioning pacing system are referred to as "pacemaker syndrome." This term is used to refer to a complex of clinical signs and symptoms related to the adverse hemodynamic and electrophysiologic consequences of ventricular pacing. Neurologic signs or those

suggesting low cardiac output or congestive heart failure are the clinical signs indicative of the pacemaker syndrome. In a study of human patients with dual chamber pacemakers (DDD) who were randomized to DDD or VVI pacing mode, some degree of pacemaker syndrome was thought to be present in 83 percent of the patients implanted with VVI pacing systems.[24] Key concepts identified as causes of the pacemaker syndrome included: (1) improper sequencing of atrial and ventricular contraction and (2) no ability to allow for physiologic rate modulation, and such effects may underlie the pacemaker syndrome observed in dogs as well.

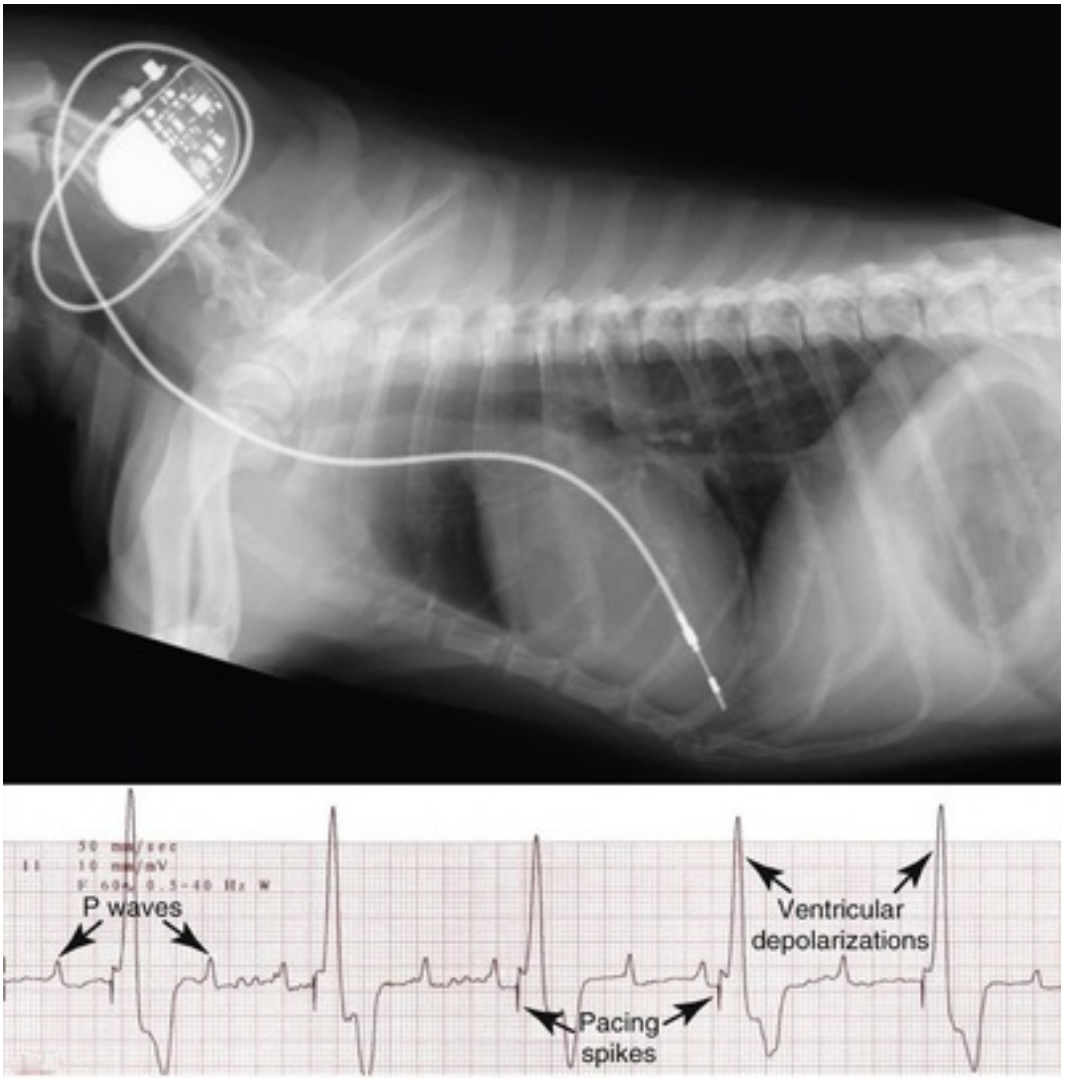


FIGURE 249-2 Lateral thoracic and cervical radiograph and ECG from a patient with complete heart block implanted with a permanent transvenous VVI pacemaker. Note the dissociation between the P waves and QRS complexes. Each QRS complex is preceded by a pacing spike generated by the pacemaker and transmitted through the lead in the right ventricular apex.

Atrial-Inhibited Pacing (AAI)

Single-chamber atrial pacing is selected only for patients in whom the bradyarrhythmia is a sinus mechanism and AV block is not a problem. In this situation, a lead is placed only within the atrium (right auricular appendage or atrial septum). Pacing occurs only in the atrium (A in the first position of the pacemaker code) if there is lack of native activity sensed within the atrium (A in the second position) at or below a specific programmed lower rate limit. If a native atrial/sinus beat is sensed within the atrium, then the pacemaker is inhibited from firing (I in the third position). Such pacing is appropriate for patients that have SND with normal AV conduction (Figure 249-3). The obvious disadvantage of AAI pacing is lack of ventricular support should AV block occur. If the patient with SND is assessed carefully for AV nodal disease at the time of

pacemaker implantation, the occurrence of *clinically significant* AV nodal disease in the future is rare.[25] Assessment of AV nodal function before use of an AAI system should include incremental atrial pacing at the time of pacemaker implantation. The criterion used at the author's institution is that the patient should be capable of 1 : 1 AV nodal conduction up to rates of 120 bpm while under anesthesia. If AV block occurs at lower rates, dual chamber pacing systems are utilized. The benefit of AAI pacing in a patient with SND lies not only in the maintenance of AV synchrony, but also in the maintenance of the normal activation pattern in the heart (via the AV node). Moreover, retrograde conduction of impulses through the AV node is common in dogs paced with ventricular-based pacing systems, often resulting in retrograde conduction and echo beats. It is therefore important that when VVI pacing is used in dogs with SND, the pacemaker is programmed at a low rate and functions only as a "backup" for periods of bradycardia, in order to retain as much AV nodal conduction as possible.

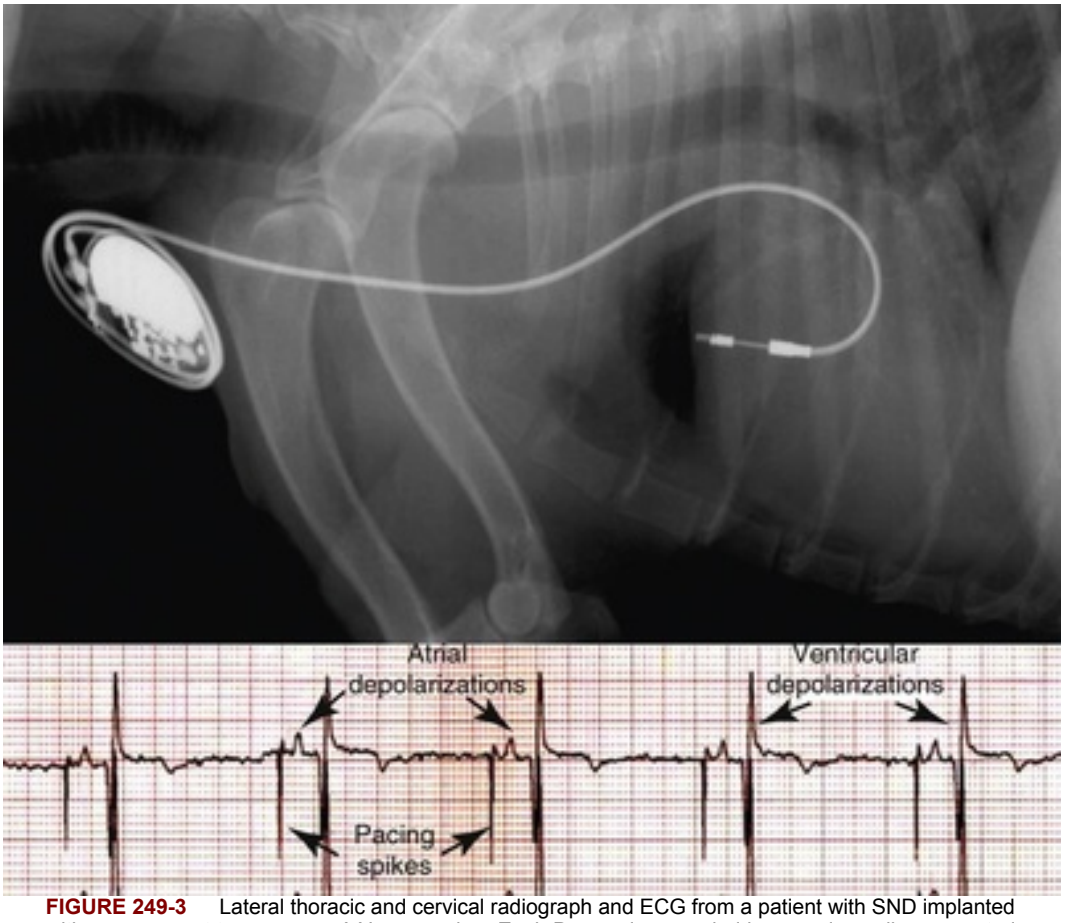


FIGURE 249-3 Lateral thoracic and cervical radiograph and ECG from a patient with SND implanted with a permanent transvenous AAI pacemaker. Each P wave is preceded by a pacing spike generated by the lead in the right auricular appendage.

Dual Chamber

Maintenance of AV synchrony (physiologic pacing) provides substantial beneficial effects on hemodynamics and patient mortality. For this reason, physiologic pacing for AV block must involve a system that "replaces" the AV node's ability to conduct atrial depolarizations to the ventricular myocardium. Currently, the most widely used dual chamber pacing systems are VDD, DDD or DDDR pacing with mode switching (discussed below).

Atrial Synchronous Pacing (VDD)

This mode paces only in the ventricle (V in the first position of the pacemaker code), senses in both chambers (D in the second position), and can respond by either inhibition of ventricular output if intrinsic ventricular

activity is sensed, or by triggering a response in the ventricle if atrial activity is sensed (D in the third position). This mode of pacing is termed atrial synchronous pacing as it "tracks" native (sinus) P waves. This mode of pacing allows for maintenance of AV synchrony and the ventricular rate is modulated by the inherent autonomic tone of the patient as it is driven by the patient's own sinus rate. If there is a sinus pause and no atrial event is sensed, the pacemaker is able to escape with a paced ventricular event at the lower programmed rate. That is, the pacemaker will display VVI activity in the absence of a sensed atrial event. VDD pacing is appropriate for the patient with normal sinus node function and conduction disease of the AV node. This atrial synchronous, ventricular inhibited (VDD) pacemaker utilizes one pacing lead which incorporates both a pacing electrode within the right ventricle and a floating atrial electrode in the intra-atrial portion of the ventricular lead to sense P waves propagated through the blood. These native P waves are sensed by the pacemaker, and then following an appropriately programmed AV delay, the system delivers a ventricular pacing impulse (Figure 249-4). The set distance between the floating atrial electrode and ventricular pacing tip often prevents its use in small dogs.

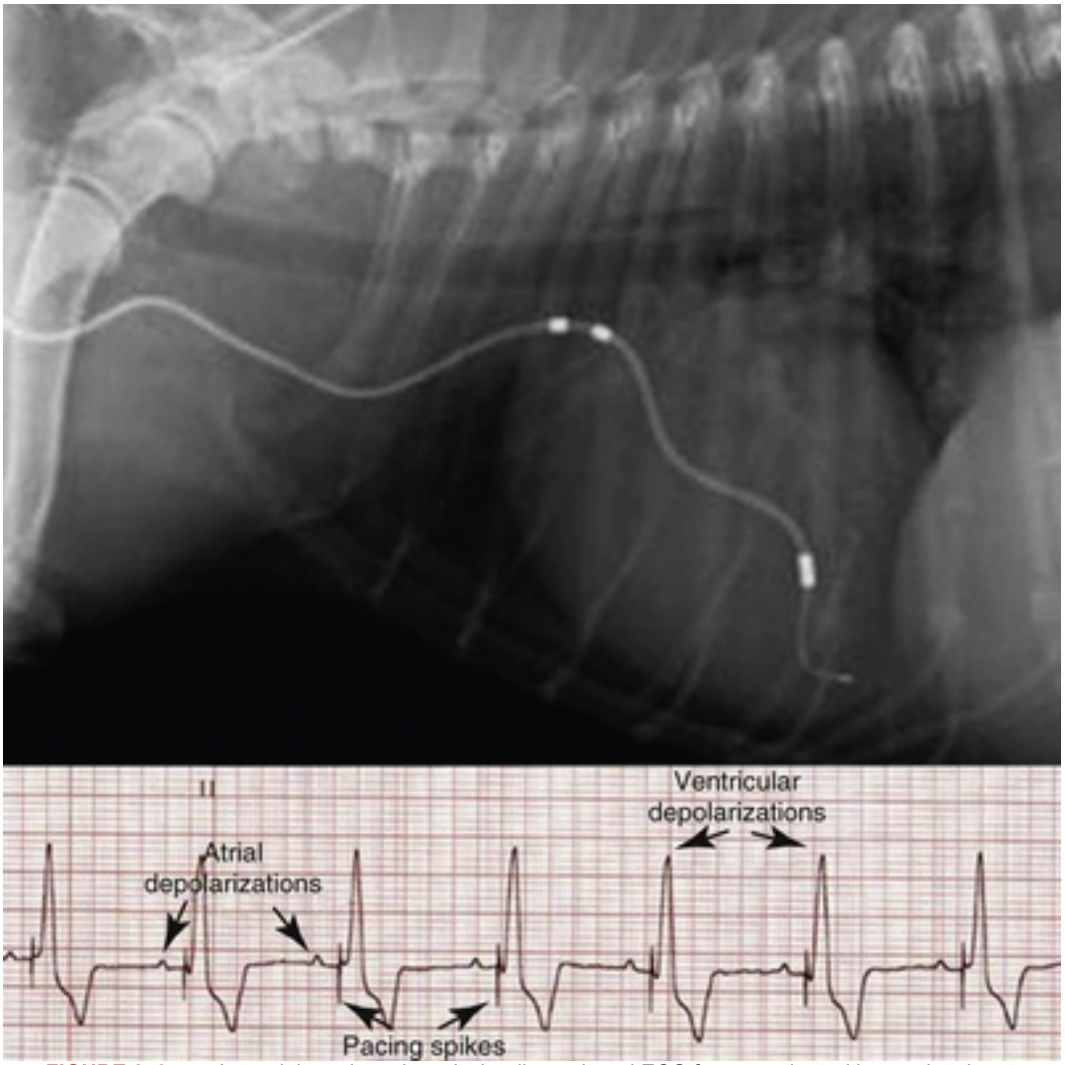
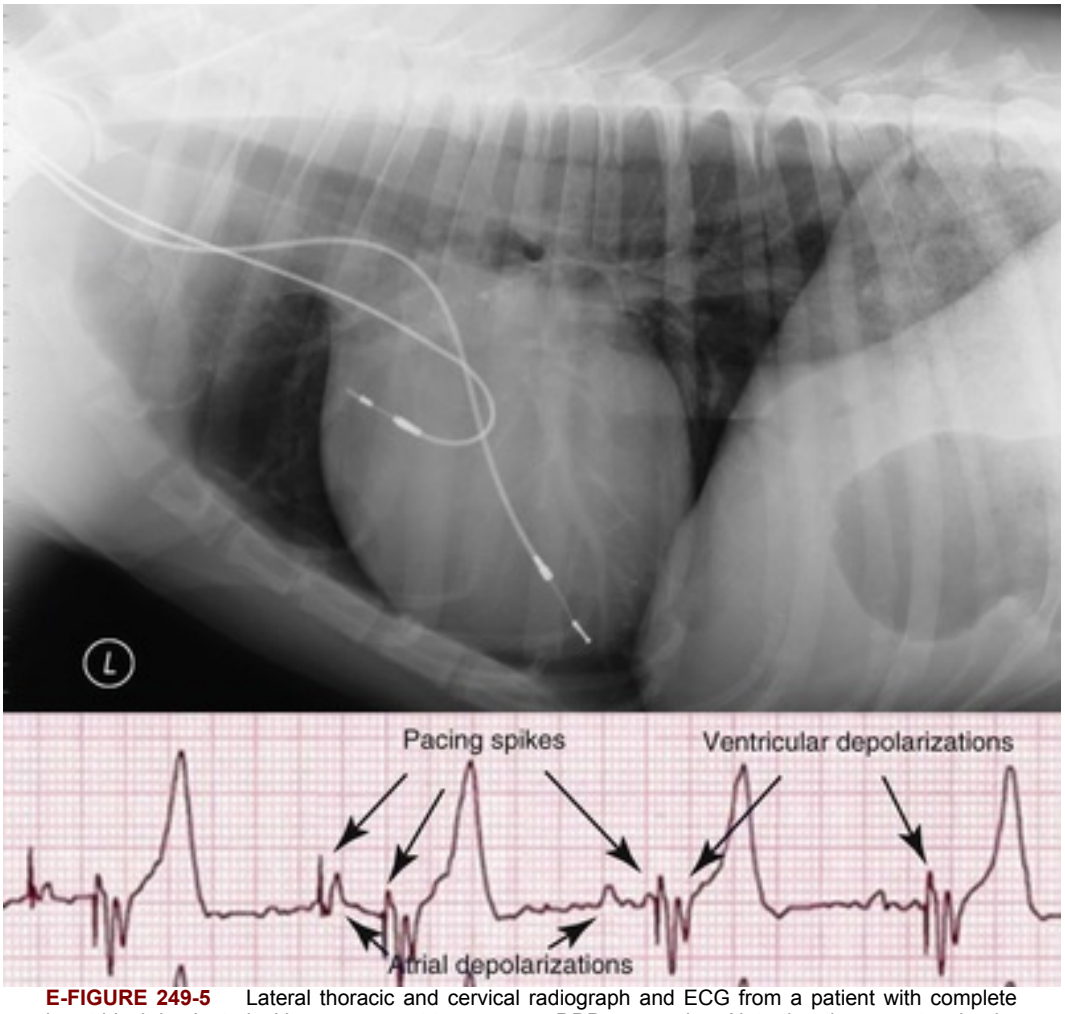


FIGURE 249-4 Lateral thoracic and cervical radiograph and ECG from a patient with complete heart block implanted with a permanent transvenous VDD pacemaker. Note the floating atrial electrode within the right atrium. This electrode senses the native P waves generated by the sinus node and a ventricular pacing spike is then delivered by the lead positioned within the right ventricular apex to cause a ventricular depolarization.

Dual-Chamber Pacing and Sensing with Inhibition and Tracking (DDD)

Known as the "fully automatic pacemaker," DDD pacing is capable of sensing and pacing in both the atrium

and the ventricle. This type of pacing mode would be appropriate for patients with SND where there is also AV block, or for patients with complete or high-grade second-degree AV block. Because it is capable of performing dual functions in both chambers, normal DDD function can appear electrocardiographically as (1) normal sinus rhythm, (2) atrial pacing only, (3) AV sequential pacing, or (4) atrial synchronous pacing (E-Figure 249-5).



E-FIGURE 249-5 Lateral thoracic and cervical radiograph and ECG from a patient with complete heart block implanted with a permanent transvenous DDD pacemaker. Note that there are two leads: one in the right auricular appendage capable of sensing and pacing the atrium; and another lead in the right ventricular apex also capable of sensing and pacing. On the ECG, there are periods where both the atrium and ventricle are paced but there are also periods where native P waves are sensed and then a ventricular impulse is delivered.

Previously, it has been suggested that dual-chamber pacing systems, particularly those with 2 leads, are more difficult and more time-consuming to place and require more complex programming. Thus, it has been assumed that implantation of dual-chamber pacemakers would produce higher complication rates both initially and in the long term. Recently published data show that while multiple-lead implantation (Figure 249-6) does prolong anesthesia and procedural time, dogs do not have any increased incidence of either short-term or long-term complications.[26]

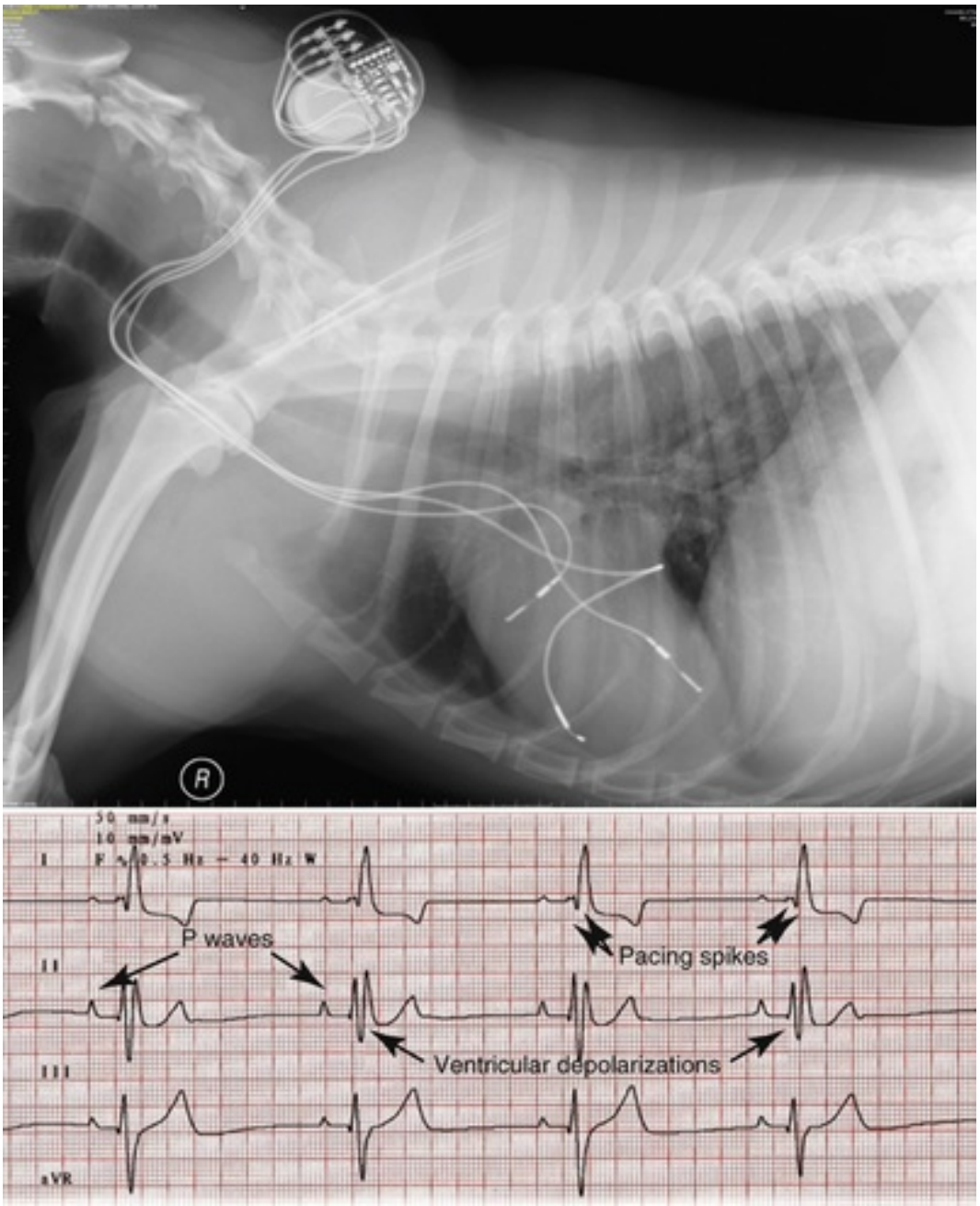


FIGURE 249-6 Lateral thoracic and cervical radiograph and ECG from a patient implanted with a CRT system. There is one lead in the right auricular appendage, one lead within the coronary sinus and down a lateral coronary vein for pacing of the left ventricular free wall, and a third lead placed in a standard right ventricular apical position.

Transvenous Pacemaker Implantation

Temporary Pacing

For patients with bradyarrhythmias, the safest way to implant a permanent pacemaker is after some method of temporary pacing has been implemented (Video 249-1). This allows for a normal heart rate, more stable patient, and less rushed surgical procedure during permanent pacemaker implantation. Temporary pacing can be accomplished transvenously, transthoracically or transesophageally, with pros and cons for each technique.[27-32]

Implantation of Permanent Pacemaker

The procedure is shown in Video 249-1; detailed descriptions of the implantation procedure also are available elsewhere.[33] The majority of permanent pacemakers are placed transvenously through a jugular approach. Exceptions to this are patients who repeatedly dislodge transvenous leads, patients with a risk of hypercoagulability, or, for some clinicians, in cats and smaller breed dogs, where epicardial placement of leads is desired. There have been reports of cranial vena caval obstruction[34] and resultant development of chylothorax[35] with transvenous pacing, and thus most cardiologists choose to place an epicardial lead on the left ventricular apex through an abdominal/transdiaphragmatic approach in cats and in dogs < 2.2 kg if pacing is required. There are, however, small diameter leads (4.1 French, Medtronic SelectSecure Model 3830) that may be suitable to use in small patients, but thus far the veterinary experience with this lead model is minimal.[36]

Pacemaker Programming

Pacemakers can be programmed and evaluated noninvasively to adjust and fine-tune the pacing parameters. Programming and interrogation of pacemakers will typically occur in the immediate (24-hour) post-operative period, at a 4-6 week recheck, at 3 and 6 months, and then yearly to assess function and battery life. Pacemaker programmers are not interchangeable and a specific pacemaker will require a certain programmer. Programmers can either be borrowed for use or donated to veterinary institutions by pacing manufacturers. Some local sales representatives will also come to a specific institution for recheck evaluations of patients. A detailed description of pacemaker programming is beyond the scope of this text but a few of the most critical parameters merit mention here.

Pulse Width and Voltage Amplitude Programmability

There are two aspects of energy output that can be programmed: the *voltage*, or amplitude of the impulse; and the *pulse width*, or how long this voltage is applied to the myocardium. The combination of these make up the output delivered to the myocardium. The output must be high enough to trigger depolarization plus allow an adequate pacing margin of safety but should also be programmed with the intent of maximizing pacemaker longevity. To determine appropriate output settings, first, the pulse width is left constant and the voltage is gradually decreased until a loss of capture is seen on the ECG. The opposite is next performed where the voltage is left constant and the pulse width is gradually decreased. A strength duration curve is generated, which allows determination of appropriate values to ensure an adequate safety margin. Values are usually set at either twice the voltage amplitude or three times the pulse width, at threshold. The less output used, the longer the battery will last. Some pacemakers will automatically determine output parameters and others continually do surveillance of the capture threshold (termed capture management) and automatically adjust output on a day-to-day basis. Thresholds for pacing do not remain static and can change throughout the day rapidly, which is the reason for programming with a margin of safety. Time produces probably the most important change in threshold. A pacing lead usually has its lowest threshold at the time of implantation. Over a period of 2 to 6 weeks, the threshold rises to its highest level ("matures") and then falls to a chronic threshold that is usually stable at approximately two or three times the acute level.

Rate Programmability

Rate-adaptive programming can be programmed into all currently manufactured pacemakers in most pacing modes (e.g., AAIR, VVIR, DDDR). A typical programmable rate is 30 to 180 bpm with some pacemakers capable of pacing as fast as 220 bpm. Sensors that detect physical movement and minute ventilation allow patients to have slower paced rates when sleeping or resting and higher rates when exercising. Lowering the rate when a higher rate is not needed also preserves the battery life of the pacemaker. Pacing algorithms are incorporated to tell the pacemaker when to speed up and when to slow down. While these algorithms work very well for people and long-term reliability is excellent, it is unknown whether they function as well for veterinary patients, especially those that pant or scratch frequently!

Sensitivity

Sensing is the pacemaker's ability to recognize the intrinsic activity of the heart. Sensing is vital to a pacemaker because it allows the pacemaker's internal computer to respond to the heart's own activity, which

means that it will inhibit pacing when it is not needed and the pacing will not compete or interfere with the patient's own rhythm. In dogs with complete heart block and a dual chamber device, sensitivity is important for tracking of native P waves and delivering a ventricular impulse in response. In dogs with SND, it is important that the system recognize normal beats and only pace when necessary. All patients with pacemakers could potentially have arrhythmias such as atrial or ventricular premature complexes (APCs or VPCs) that must be "seen" by the pacing system to ensure that pacing during the vulnerable period in the T wave does not occur.

The two main challenges to sensing are *oversensing* (i.e., sensing events that are not really there or that should not be sensed) like motion artifact, and *undersensing*, which refers to not sensing events that ought to have been sensed. Oversensing is usually seen on an ECG as inappropriately long pauses between pacing spikes and can be definitively diagnosed by watching a programming marker channel. Undersensing occurs when there is an intrinsic event (P wave or QRS complex) that the pacemaker ought to have detected, but somehow missed. An ECG with undersensing will show intrinsic activity followed too closely by a pacing spike.

Sensitivity is a programmable parameter measured in millivolts (mV). Although it may seem counterintuitive initially, increasing the sensitivity (making the device more sensitive) means decreasing the mV setting, while decreasing sensitivity means increasing the mV setting.

Refractory Period

The refractory period is a brief period where the pacemaker's sensing function is turned off or ignored after either a sensed QRS signal or a pacemaker spike. It is programmed to the patient's QT interval as measured on the surface ECG. The advantage of a refractory period is that it does not allow the pacemaker to sense either the T wave of the preceding QRS complex or the pacemaker after-potential, which is residual electric activity occurring after a paced beat. The disadvantage is that early VPCs or APCs may not be sensed. The refractory period can be lengthened to eliminate inappropriate sensing of a QRS signal, T wave, or after-potential. It can also be shortened to allow frequent VPCs or APCs to be sensed and thus reduce the risk of pacing within the T wave of the premature beat.

Special Features

Pacemaker technology has evolved to such a degree that it is impossible to incorporate a discussion of all the special features available in one book chapter. Different companies use different terminology and the programming might work a little differently with each device. When working with pacemakers, it is advisable to have device manuals on hand for reference or to take advantage of training materials from the various manufacturers. Regional technicians or technical support lines can also be helpful in programming and interpreting/trouble shooting during evaluations.

Pacemaker Complications

Complications following pacemaker implantation have been shown to be directly related to the experience of the implanter in both veterinary and human medicine.[37-39] Development of a seroma is a fairly common occurrence but can be easily managed with wrapping of the neck with gentle pressure. Some cardiologists also empirically treat with antibiotics to reduce the risk of infection. It is important to note that drainage of fluid surrounding the generator, with a needle and syringe, not be performed because of the risk of introduction of bacteria to the site and also for concern of damage to the leads and generator within the pocket.

Partial or silent venous thrombosis of the jugular vein likely is common following transvenous lead placement but does not typically cause clinical signs. Thrombus adherence/formation on the lead also is sometimes visualized on recheck echocardiograms without clinical signs having been noted by the owner. In the author's experience, these types of thrombi do not typically dislodge or grow bigger over time. It is advisable, however, to treat patients with antithrombotic agents such as low-dose aspirin or clopidogrel if a thrombus is recognized.

Atrial or ventricular perforation by a lead is a possible, although rare, occurrence.[36,37] Cardiac tamponade is the most dramatic outcome from perforation but lack of clinical signs is common. In fact, the only signs of perforation may be a rising stimulation threshold, a change in depolarization pattern on surface ECG, or diaphragmatic contraction with each output stimulus.

The most common complication, especially in the immediate post-operative period, is lead dislodgment or malposition of the lead causing loss of capture. Loss of capture appears on ECG as pacing spikes that are not followed by electrical capture of the appropriate chamber. To minimize the risk of this complication, it is important that patients are rested and not allowed to run or jump following implantation. At the author's institution, sedation is given prior to recovery from anesthesia, and upon discharge from the hospital, owners are instructed to keep the pet quiet and restricted in activity with leash walks only for the first 6 weeks. Following this time period, patients are allowed to resume normal activity.

Arrhythmias occurring as a result of the inflammation and irritation associated with lead placement can be safely treated if needed with antiarrhythmic agents (see ch. 248) and will typically resolve in a couple of days following implantation.

Sometimes, dogs will have contraction of the neck or diaphragm with each pacing stimulus ("pacemaker twitch"; Video 249-2). This is usually due to either high voltage output or phrenic nerve stimulation and can be avoided by lowering the voltage output. Pacemakers that are donated from pacing manufacturers often have etching on the back to indicate they are not for use in humans. This can sometimes lead to voltage leak around the generator and it should be implanted with the etched side down in attempt to avoid contraction of the overlying musculature.

Pulse generators have a life span of 10 to 12 years when manufactured. Most generators implanted in veterinary medicine have not been used previously but remaining battery life at implant is variable and can be assessed using a programmer prior to implantation. Various programming changes can increase or decrease the life span of the pulse generator. When a generator is close to, or near, the end of its battery life, an *end of life* or *elective replacement indicator* (EOL or ERI) is turned on. Most commonly, this is signaled by a gradual decrease in pacing rate, thus giving ample time to replace the generator prior to complete failure of the generator.

Infections

In veterinary medicine, the incidence of infection following pacemaker implantation is reported to be 5-10 percent,[40] which is much higher than in human medicine with an incidence of <2 percent.[41,42] Careful attention to surgical detail and sterile procedure is of extreme importance in avoiding pacemaker site infection. At the author's institution, implantation is delayed (if possible) if there are signs of more than mild skin infection or urinary tract infections, and urinalysis with culture and sensitivity is routinely performed prior to implantation. Prophylactic use of antibiotics before implantation and in the immediate post-operative period remains controversial but is routinely performed.[43] Most human studies do not show any significant difference in the rate of infection between patients who have had prophylactic antibiotics and those who have not. The optimal treatment of an infected pacemaker (Figure 249-7) is removal of the entire system (lead and generator) if possible, appropriate long-term antibiotic therapy (via culture and sensitivity) and replacement of the pacing system on the opposite side of the neck if delay is not feasible.[44] Treatment with antibiotic therapy alone is rarely associated with eradication of the infection.[40-42]

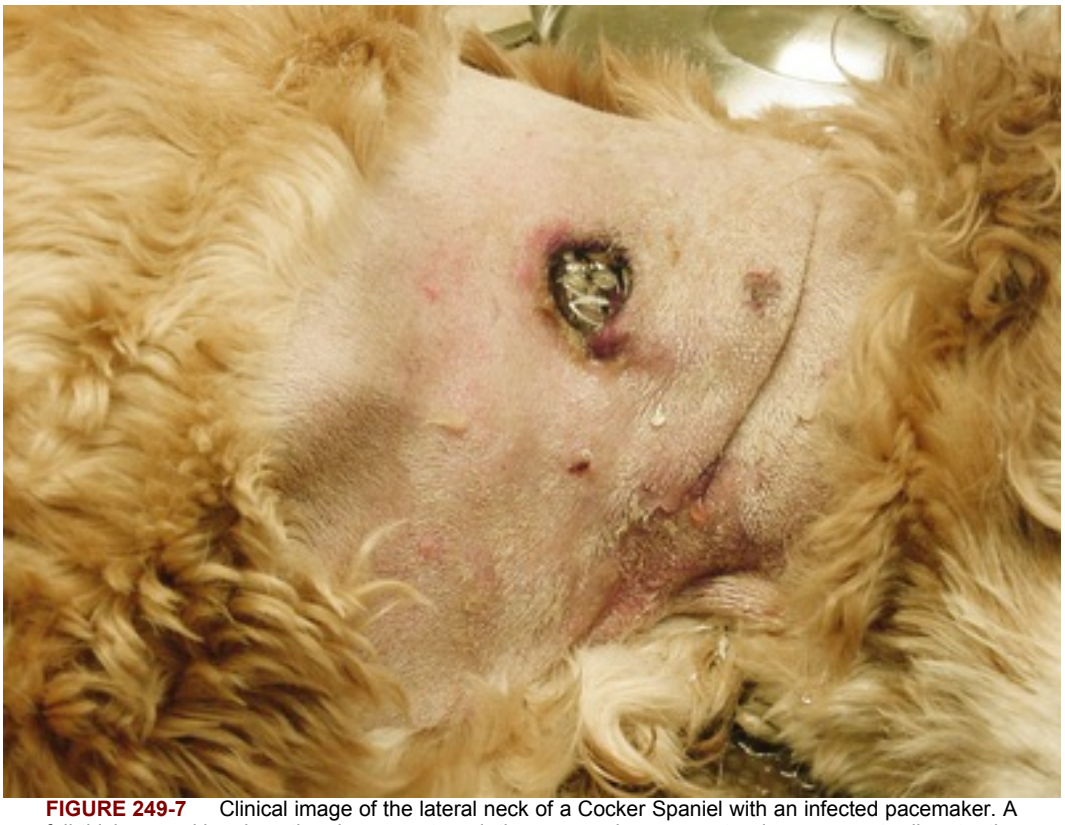


FIGURE 249-7 Clinical image of the lateral neck of a Cocker Spaniel with an infected pacemaker. A full-thickness skin ulceration is present and the pacemaker generator is seen protruding to the surface. (Courtesy Drs. Etienne Côté and Nancy Laste, Angell Animal Medical Center.)

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CHAPTER 250

Congenital Heart Disease

Niek J. Beijerink, Mark A. Oyama, John D. Bonagura

Client Information Sheets:
Congenital Heart Disease: General Considerations
Patent Ductus Arteriosus
Subvalvular Aortic Stenosis (Subaortic Stenosis)
Pulmonic Stenosis
Ventricular Septal Defect
Cyanotic Congenital Heart Disease

Introduction

The term congenital heart disease (CHD) encompasses a large number of morphologic and functional abnormalities of the heart and contiguous blood vessels that are present at birth. These malformations generally arise from some altered or arrested development of the embryonic heart triggered by genetic or environmental factors. The severity of CHD can range from trivial to life-threatening, and clinical signs might manifest anytime from the neonatal period—before the first veterinary examination—to relatively late in life. Although some types of CHD are well-tolerated, severe functional consequences can occur, including congestive heart failure (CHF), hypoxemia, cardiac arrhythmia, or sudden cardiac death. This chapter provides an overview of CHD in dogs and cats along with principles of diagnosis and management of commonly encountered defects. The reader is also referred to ch. 122 for a description of interventional techniques used for correcting congenital heart defects, ch. 257 that addresses some forms of venous vascular anomalies and to ch. 273 for additional consideration about the diagnosis and management of esophageal obstruction caused by vascular ring malformations.

In most cases, successful management of CHD begins with the prompt recognition of a cardiac disorder by the family veterinarian, followed by referral to a cardiologist for detailed evaluation. In most situations, a definitive diagnosis of CHD can be attained noninvasively following a complete echocardiographic examination. However, precise definition of some complex forms of CHD—as well as certain vascular malformations—can demand advanced imaging techniques, as discussed later. The prognosis for any CHD relates to the type and the severity of the underlying malformation. Some forms of CHD require no treatment and carry a favorable prognosis. Other defects are amenable to definitive therapy or to some form of palliative treatment.

Etiology

Congenital cardiac malformations can be caused by genetic or environmental factors, and in most cases a single causative agent cannot be conclusively identified. The potential interaction of toxicologic, nutritional, infectious, and genetic factors makes it difficult to determine a definitive cause. The observation that certain congenital defects display a species or breed predilection[1-4] strongly suggests a heritable basis in many cases (Table 250-1). This hypothesis has been demonstrated for several specific defects in certain canine breeds.[1,5-12] A number of studies indicates a simple Mendelian basis for transmission, supporting the concept that identifiable genetic factors contribute to development of the embryonic heart and relate to specific types of CHD. Other genes can demonstrate additive or modifying effects and produce a discrete phenotype once a Mendelian trait has been inherited, including variability in the penetrance of that characteristic.[13-17]

TABLE 250-1

Canine Breed Predilections for Congenital Heart Disease

BREED	DEFECTS
Basset Hound	PS
Beagle	PS
Bichon Frisé	PDA
Boxer	SAS, PS, ASD
Boykin Spaniel	PS
Bull Terrier	MVD, AS
Chihuahua	PDA, PS
Chow Chow	PS, CTD
Cocker Spaniel	PDA, PS
Collie	PDA
Doberman Pinscher	ASD
English Bulldog	PS, VSD, ToF
English Springer Spaniel	PDA, VSD
German Shepherd Dog	SAS, PDA, TVD, MVD
German Shorthaired Pointer	SAS
Golden Retriever	SAS, TVD, MVD
Great Dane	TVD, MVD, SAS
Keeshond	ToF, PDA
Labrador Retriever	TVD, PDA, PS
Maltese	PDA
Mastiff	PS, MVD
Newfoundland	SAS, MVD, PS
Pomeranian	PDA
Poodle	PDA
Rottweiler	SAS
Samoyed	PS, SAS, ASD
Schnauzer	PS
Shetland Sheepdog	PDA
Terrier breeds	PS
Weimaraner	TVD, PPDH
Welsh Corgi	PDA
West Highland White Terrier	PS, VSD
Yorkshire Terrier	PDA

AS, Aortic stenosis; *ASD*, atrial septal defect; *CTD*, cor triatriatum dexter; *MVD*, mitral valve dysplasia; *PDA*, patent ductus arteriosus; *PPDH*, peritoneopericardial diaphragmatic hernia; *PS*, pulmonic stenosis; *SAS*, subaortic stenosis; *ToF*, tetralogy of Fallot; *TVD*, tricuspid valve dysplasia; *VSD*, ventricular septal defect.

The complexity and uncertainty surrounding the exact mode of inheritance of many cardiac defects hamper the counseling of owners who want to use individual dogs for breeding. Although cardiologists often attempt to identify CHD in breeding animals during screening clinics, these efforts are confounded by the limited sensitivity and specificity of the available diagnostic studies. Certainly, a normal physical examination does not equate with genetic normalcy. Moreover, many soft murmurs are difficult to interpret,[18-20] and echocardiographic screenings often yield equivocal findings in the absence of true, gold-standard criteria for

the diagnosis of mild disease. Even with careful attention to pedigree and the results of breeding trials, it can be very difficult to influence the overall prevalence of a specific defect in the larger population. Progress in this regard hinges on the development of economical genetic tests that can detect the presence of the genetic mutations responsible for specific malformations.

The situation in cats is even more complicated and there are no detailed genetic studies of cats with CHD. A number of possible breed predispositions has been reported, such as tricuspid valve dysplasia (TVD) and atrial septal defect (ASD) in the Chartreux cat,[21,22] and older reports link endocardial fibroelastosis and supravalvular mitral stenosis to Siamese cats. Other feline breed predispositions are listed below under specific defects.

Prevalence

In surveys of dogs from the 1960s conducted by Patterson and Detweiler,[23,24] the prevalence of CHD in dogs was approximately 0.56% of hospital cases. Subsequent studies have indicated an overall prevalence of CHD in dogs between 0.46% and 0.85% of hospital admissions with Buchanan reporting a prevalence of approximately 0.68% for all dogs examined at the University of Pennsylvania.[25] Most studies have stemmed from university hospitals, and these surveys likely encompassed a significant number of cases referred for cardiac evaluation. By contrast, in a recently published study from a shelter population, Schrope reported a comparably lower prevalence of CHD of 0.13% in 76,301 mixed-breed dogs (screened by shelter veterinarians and subsequently evaluated by a cardiologist).[26]

Despite these differences in prevalence, the most common cardiac malformations in dogs have been largely unchanged for the last half-century.[2-4,24-27] Patent ductus arteriosus (PDA), subaortic stenosis (SAS), and pulmonic stenosis (PS) have topped the list of most surveys. In the studies of Patterson and Detweiler[23,24] the reported frequencies of diagnoses were approximately 28% for PDA, 20% for PS, 14% for SAS/aortic stenosis (AS), 8% for persistent right aortic arch, 7% for ventricular septal defect (VSD), and less than 5% for tetralogy of Fallot (ToF), persistent left cranial vena cava, and ASD. The report by Buchanan,[25] which included prevalence information from a North American database of over 1300 cases, indicated that PDA was most frequently reported (31.7% of cases), followed by SAS (22.1%) and PS (18.3%). However, in the aforementioned study of CHD in mixed-breed shelter dogs, the most common malformations were PS (31% of CHD cases), PDA (17%), SAS (15%), and VSD (14%).[26] European studies have indicated a higher prevalence of SAS and PS compared to PDA, with the largest retrospective study of 976 dogs reporting a prevalence of approximately 32% for PS, 27% for SAS/valvular AS, and 21% for PDA. The shifting popularity of some dog breeds over time certainly influences the regional prevalence of a particular defect. For example, Golden Retrievers, Labrador Retrievers, and Bull Terriers have likely increased the number of dogs diagnosed with SAS, TVD, and mitral valve dysplasia (MVD),[28] respectively. Scansen and colleagues[29] have tabulated 4,694 reported malformations from the literature and calculated the relative distribution of specific defects. As shown in Table 250-2, *A*, PDA, SAS/AS, and PS are the most common overall cardiac malformations affecting dogs.

TABLE 250-2

A, Congenital Heart Disease in Dogs: Data from Combined Studies[1,3,4,25,28,167,341-345]

DEFECT	NUMBER	PERCENTAGE
Patent ductus arteriosus (PDA)	1207	25.7
Subaortic stenosis (SAS)	1102	23.5
Pulmonic valve stenosis (PS)	1039	22.1
Ventricular septal defect (VSD)	413	8.8
Tricuspid valve dysplasia (TVD)	216	4.6
Mitral valve dysplasia (MVD)	204	4.3
Other defects	160	3.4
Persistent right aortic arch or other vascular ring anomaly (PRAA)	155	3.3

Tetralogy of Fallot (ToF)	110	2.3
Atrial septal defect (ASD)	89	1.9
Total	4694	100

Reprinted from Scansen BA, Cober RE, Bonagura JD: Congenital heart disease. In Bonagura JD, Twedt DC, editors: *Kirk's current veterinary therapy XV*, ed 15, St Louis, 2014, Elsevier/Saunders, pp 756-761.

B, Congenital Heart Disease in Cats: Data from Combined Studies[28,33-35,344]

DEFECT	NUMBER	PERCENTAGE
Ventricular septal defect (VSD)	80	18.4
Patent ductus arteriosus (PDA)	49	11.3
Tricuspid valve dysplasia (TVD)	47	10.8
Mitral valve dysplasia (MVD)	44	10.1
Atrioventricular septal defects (AVSD)	42	9.7
Aortic stenosis (AS)	31	7.1
Tetralogy of Fallot (ToF)	30	6.9
Atrial septal defect (ASD)	26	6.0
Persistent right aortic arch (PRAA)	23	5.3
Endocardial fibroelastosis (EFE)	21	4.8
Pulmonic stenosis (PS)	17	3.9
Other malformation	11	2.5
Double outlet right ventricle (DORV)	7	1.6
Cor triatriatum sinister	7	1.6
Total	435	100

Reprinted from Scansen BA, Cober RE, Bonagura JD: Congenital heart disease. In Bonagura JD, Twedt DC, editors: *Kirk's current veterinary therapy XV*, ed 15, St Louis, 2014, Elsevier/Saunders, pp 756-761.

Several surveys of CHD in cats have been reported.[30-36] The largest series stem from urban centers and include the Animal Medical Center (New York) and Angell Memorial Animal Hospital (Boston). The prevalence of CHD in cats worldwide is uncertain. The two largest surveys indicated a prevalence of 0.02% to 0.1% of hospital admissions and 1.95 to 2.9% of autopsies, as summarized by Harpster and Zook and by Liu and colleagues.[32-34] In a smaller autopsy study, 3.5% of 368 kittens were identified with CHD.[31] The study of 57,025 mixed-breed cats from a shelter population reported an overall prevalence of 0.14%.[26]

In terms of specific feline cardiac malformations, there are notable differences across surveys, which might represent sampling methods or true geographical differences.[37] Scansen and colleagues[29] have tabulated the results of the larger surveys (Table 250-2, *B*). The most commonly diagnosed defects in the combined surveys were VSD (18.4%), PDA (11.3%), TVD (10.8%), MVD (10.1%), atrioventricular (AV) septal defects (9.7%) and AS (7.1%). Some surveys showed a male predilection. In a retrospective study of mixed-breed shelter cats,[26] VSD was most common (21%) with SAS and valvular AS combining for 17% of the feline CHD diagnoses. Obstructions across the span of the right ventricular outflow tract (RVOT) also were relatively common in this population.

Classification

While a number of schemes has been devised to classify CHD, the standard in human pediatrics today is for a sequential segmental analysis that models the heart as three major segments: atria, ventricles, and great arteries. The relationships between these segments—atrioventricular and ventriculoarterial—are also critical to the scheme. In segmental analysis, the atria and ventricles are not defined by their venous, arterial, or other connections, but by their morphology. The position (situs) of each atrium is also relevant to the classification system. This approach is especially appealing for complex CHD and the interested reader is referred to the writings of Richard Van Praagh and Robert Anderson,[38,39] the two major (though sometimes opposing) forces who have redefined the anatomy of CHD. An example of this scheme applied to cats has recently been

published.[37]

Older and simpler organizational schemes are still relevant to veterinary medicine, and these include classifying lesions as anomalies of the cardiac valves; obstructions to ventricular outflow; and defects allowing left-to-right, right-to-left, or bidirectional shunting. Other types of malformations can involve the cardiac position or situs (as with ectopia cordis and situs inversus)[37]; defects or cysts affecting the pericardium (see ch. 254) and a number of vascular anomalies involving or connecting to the heart (see ch. 257).

Clinical Approach

While assembling the history, it is important to note the species and breed, as many congenital diseases have a suspected or proven genetic basis, and most canine cardiac malformations show breed predilections (see Table 250-1). Whenever possible, the health records of the sire, dam, and any siblings should be reviewed. The clinical diagnosis of CHD is usually stimulated not by clinical signs but by the identification of a cardiac murmur during a routine examination or health clinic. Most young animals with CHD are asymptomatic when first examined. Even those dogs and cats with hemodynamically severe regurgitant, obstructive, or shunting defects seem completely normal to many owners, especially during the first 6 to 12 months of life. The clinician should not necessarily conclude from an unremarkable history that the underlying defect is mild. A useful rule-of-thumb is that when a dog or cat with CHD does exhibit clinical signs of heart disease, the patient is at high risk of death unless some therapy can be instituted relatively soon.

There are no specific historical features or clinical signs of CHD. When respiratory signs such as tachypnea are attributed to heart disease, the potential for CHD should at least be entertained, especially in younger animals. The authors have evaluated many patients in which clinical signs of CHD manifested during middle age or even later in life. Sometimes an arrhythmia, such as ventricular tachycardia or atrial fibrillation, will supervene and incite syncope or CHF. Clinical signs of significant CHD can include exercise intolerance, exertional collapse or syncope, sudden cardiac death, or clinical signs of CHF. The occasional cat is presented for arterial thromboembolism, especially when there is LA dilatation secondary to obstruction of the mitral valve inlet.[40]

Physical Examination

A cardiac murmur is a hallmark feature of CHD (see ch. 55); however, a significant number of murmurs are missed in clinical practice. Intractability, panting and purring, rapid heart rates, cardiac rotation, and closely spaced auscultatory areas typical of puppies and cats pose challenges to auscultation. Additionally, a failure to auscult over the left, craniodorsal cardiac base (for PDA) and over the tricuspid valve area (for tricuspid regurgitation) are common examination errors. Soft murmurs are common in puppies and in kittens, and in most instances are benign (functional) in origin.[18,20,41-43] Unfortunately, there are no specific auscultatory findings distinguishing a functional murmur from that associated with mild CHD. The systolic murmur that is soft, brief, and musical or vibratory is more likely to represent a functional (innocent) murmur, but these characteristics are not absolute. Even murmurs that come and go can be associated with malformations, as with MVD with dynamic left ventricular outflow tract (LVOT) obstruction. Especially problematic is the diagnosis of trivial-to-mild SAS and AS in dogs, especially in breeds prone to those diseases. There are simply no gold standards for the diagnosis of clinically insignificant, but potentially heritable conditions (see later). In contrast, a moderate to loud systolic murmur or a murmur with a palpable thrill will be indicative of CHD in a young animal. These should be promptly investigated by Doppler echocardiography,[20] remembering that the intensity of a murmur can but might not correlate with the severity of the lesion. The typical characteristics of the heart murmurs associated with the most common congenital defects are discussed under specific malformations.

Most healthy puppies and kittens with faint or soft murmurs—especially those not intended for breeding—can reasonably be followed with repeated physical examination during the vaccine sequence. Physiologic reasons for murmurs, such as fever, infections, and anemia,[43] should be excluded. Many functional murmurs fade during the vaccination period, but those murmurs that increase in intensity or duration, especially in larger-breed dogs prone to SAS or TVD, should be further evaluated with echocardiography. A client should probably be offered echocardiography for the pet when a soft murmur persists. Early detection of CHD allows definitive treatment when applicable (see ch. 122). Accepting that most people quickly develop a bond with their pets, the early detection of CHD is valuable to that pet owner who is willing to accept a healthy

replacement for one affected by a cardiac malformation.

Murmur intensity and duration do correlate with the severity of some lesions, especially with SAS and PS. Conversely, a murmur can be inconspicuous in some cases of serious CHD. In theory, a large VSD might have only a soft murmur due to equilibration of ventricular pressures, but practically, most cases have at least a moderately loud murmur unless there is concurrent pulmonary hypertension. In the setting of severe pulmonary hypertension, as with reversed PDA, murmurs can be completely absent and only a tympanic- or split second heart sound identified. Secondary erythrocytosis in right-to-left shunting also reduces the likelihood of turbulence associated with murmurs. The murmur associated with severe AV valve dysplasia can be faint, especially in the setting of pure AV valve stenosis.

Ancillary physical examination findings are sometimes useful in the differential diagnosis and clinical assessment. Palpation for a ventricular heave (a prominent apical impulse indicating ventricular enlargement) or a precordial thrill (indicating the point of maximal intensity of a loud cardiac murmur) can be instructive regarding the underlying lesion. Arterial and venous pulses can also offer insight about the underlying defect; however, the rapid heart rates and small sizes of many patients diminish the sensitivity and specificity of physical diagnosis, especially for inexperienced examiners. Hyperkinetic ("waterhammer") arterial pulses are characteristic of lesions causing abnormal diastolic run-off of aortic blood flow and low arterial diastolic pressure; classic causes are PDA and severe aortic regurgitation. Hypokinetic or late-rising arterial pulses are typical of moderate to severe LVOT obstruction (i.e., SAS) or severe defects accompanied by low left ventricular (LV) output. A prominent jugular venous pulse or jugular venous distension indicates an abnormality of the right side of the heart, as occurs with TVD or PS.

The finding of cyanosis in a young animal, especially in the absence of dyspnea or overt pulmonary disease should strongly signal consideration for a cardiac malformation and "cyanotic heart disease." (see ch. 52) The term "cyanotic congenital heart disease" is used for categorizing those congenital defects causing admixture of venous and arterial blood, such as tetralogy of Fallot (ToF). Right-to-left shunting refers to situations wherein desaturated blood flows into the systemic arteries allowing admixture of desaturated and oxygenated blood, leading to hypoxemia. This can occur as a result of defects such as transposition of the great vessels or a combination of a communicating defect connecting the two sides of the circulation and some mechanism elevating pressures on the right side as with ToF. Reversed shunting has been observed with PDA, aorticopulmonary window, VSD, ASD and PS or TVD with patent foramen ovale. Visible cyanosis develops when the partial pressure of arterial oxygen falls below ≈45 mm Hg and desaturated arterial hemoglobin reaches 5 g/dL. Differential cyanosis is typical of a reversed PDA (see below).

Physiology of Right-to-Left Shunting

The term Eisenmenger's syndrome (physiology) is invoked to describe those circumstances wherein increased pulmonary vascular resistance causes reversal of a left-to-right shunt and causes cyanotic heart disease.[44-46] The factors underlying the development of Eisenmenger's syndrome are incompletely understood but are most likely related to shear stresses caused by the high flow rates in the pulmonary vasculature and proliferative changes within the vessel wall.[44,46-49] Eisenmenger's syndrome usually develops rapidly in affected dogs and almost always before 6 months of age. Development of pulmonary vascular disease in cats can be more gradual. Pulmonary arterial intimal thickening, medial hypertrophy, and plexiform lesions of dogs and cats with Eisenmenger's physiology are similar to those of humans as described by Edwards and Heath and amended by Roberts.[50] In some cases, a component of increased pulmonary vascular resistance is related to arterial vasoconstriction. These patients can respond clinically to phosphodiesterase V inhibitors such as sildenafil that function as pulmonary vasodilators. However, plexiform lesions are generally considered irreversible. Surgical closure of the shunt pathway forces the right ventricle (RV) to work against a tremendous pulmonary resistance, resulting in outcomes that can include RV failure, circulatory collapse, and death.

Systemic responses to arterial hypoxemia include an increase in red blood cell mass in an attempt to improve systemic oxygen delivery. Hypoxia of the renal tissue incites erythropoietin release and induces secondary erythrocytosis. As packed cell volume (PCV) increases, the high viscosity of the blood predisposes patients to thrombosis and microvascular complications.[44,47] This hyperviscosity syndrome, which typically occurs once the PCV exceeds 68%, is the primary cause of morbidity and mortality in affected animals rather than CHF, which is rare. Clinical manifestations include weakness, hemostatic deficiencies, renal dysfunction, metabolic acidosis, iron deficiency, cerebrovascular events, syncope, and seizures.[51-54]

The direction of blood flow across shunting lesions depends on the relative resistances of the systemic and pulmonary circulations. Exercise promotes systemic arteriolar vasodilation and decreases systemic resistance,

thereby increasing the magnitude of right-to-left shunting. In cases of RV hypertrophy and VSD, tachycardia or elevated sympathetic tone can increase the magnitude of right-to-left shunting by exacerbation of dynamic infundibular obstruction and increased resistance to RV ejection.[55] Nonspecific beta-adrenergic blocking drugs are sometimes used to blunt or prevent this phenomenon, particularly in patients with ToF.[53,56] Beta-blockers also tend to limit exercise, offering another explanation for their efficacy in some patients. Anemia, absolute or relative, reduces the ratio of systemic to pulmonary resistance when pulmonary resistance is fixed.[52] By this mechanism, overzealous phlebotomy can increase the severity of arterial hypoxemia as it decreases the oxygen carrying capacity of blood.

Right-to-left shunting leads to compensatory increases in nutritive systemic blood flow to the lung via the bronchial arteries. These systemic collateral vessels are easily recognized at angiography. While uncommon, it is possible for these vessels to rupture, leading to hemoptysis. Paradoxical embolization is another potential complication of right-to-left shunting defects. Normally, the pulmonary vasculature filters systemic venous emboli before they can reach the left side of the circulation. With reversed shunting, the possibility of a venous embolus reaching the coronary, cerebral, or other systemic arteries must be considered, particularly when intravenous catheters are present. By this mechanism, a thrombus, infectious agents, or air might gain access to vital systemic organs. Animals with cyanotic heart disease sometimes experience adverse reactions (particularly bradycardia) to sedatives and tranquilizers.

Diagnostic Studies

The diagnostic workup in the patient with suspected CHD centers today on echocardiography with Doppler studies. Additional examinations including radiography, electrocardiography, and clinical laboratory tests can be contributory, but rarely definitive, in terms of a diagnosis. Advanced imaging such as computed tomography (CT) with contrast (CT angiography) or magnetic resonance angiography is most useful for the diagnosis of complex CHD or vascular anomalies. Cardiac catheterization with angiography[30,57-60] is still a gold-standard method for diagnosis but is rarely undertaken except during catheter-delivered therapies (see ch. 122).

Thoracic radiographs should be obtained in all cases with respiratory signs. In addition to recognizing CHF, radiographs can also help stage severity of disease, especially in volume-overload states caused by AV valve malformation or left-to-right shunts.[61-64] Key features include identification of specific chamber enlargements, dilation of the great vessels, and pulmonary circulation. However, concentric hypertrophy will be underestimated by radiography, and might only be recognized by apex elevation (for the RV) or mild cardiac elongation (for the LV). Dilation of the main pulmonary artery is suggestive of PS, left-to-right shunt, or pulmonary hypertension. Dilation of the aorta is observed with SAS, aortopathies,[65] and PDA. Increased pulmonary vascularity is compatible with a significant left-to-right shunt, whereas scant vascular markings are often found with right-to-left shunts or with pulmonary hypertension.

In the absence of a cardiac arrhythmia, the value of the multiple-lead electrocardiogram (ECG; see ch. 103) recording is lower in the era of Doppler echocardiography. A normal ECG does not exclude a diagnosis of CHD. Nevertheless, the ECG can often identify moderate to severe atrial or ventricular enlargement or conduction disturbances that might be suggestive of one or more specific disorders.[66,67] As examples, increased QRS voltages in caudal and left precordial leads are typical of PDA, a right axis deviation is common with moderate to severe PS, and splintered QRS complexes are reported with TVD.[68] The frequent finding of a cranial frontal axis often mitigates the value of the standard limb leads in cats. Importantly, the principal indication for an ECG in CHD is the identification of arrhythmias or evidence of myocardial ischemia that might indicate a more complicated form of CHD. An ambulatory (Holter) ECG can be useful to detect exercise-induced arrhythmias or ischemia that might prompt treatment. It should be noted that some heart rhythm disorders should be considered a form of CHD: in particular, accessory pathways associated with ventricular pre-excitation and re-entrant supraventricular tachycardias (see ch. 248). These have been observed in Labrador Retrievers with TVD.

Aside from a PCV, routine laboratory tests are of little consequence except in cases complicated by CHF, arterial thromboembolism, or other comorbidities. Hypoxemia can be verified by pulse oximetry or arterial blood gas analysis, but these tests are rarely needed.

Echocardiography

Echocardiography with Doppler studies (see ch. 104) has largely supplanted cardiac catheterization and angiography for the diagnosis and assessment of most congenital heart lesions. This diagnostic study is

described in detail in ch. 104 and in many examples and references within the present chapter.[69-85] Saline contrast echocardiography is sometimes performed to identify right-to-left shunting, especially across a patent foramen ovale (PFO), ASD or VSD.

The major outcomes of the echocardiographic study in CHD can be summarized as follows: (1) identifying morphologic lesions such as septal defects, PDA, valvular malformations, and outflow tract obstructions using 2D and 3D imaging; (2) characterizing secondary responses such as dilation of cardiac chambers and great vessels and identifying myocardial hypertrophy using 2D, 3D, and M-mode studies; (3) delineating abnormal blood flow such as shunts and valvular dysfunction using color- and spectral-Doppler methods; (4) quantifying systolic and diastolic ventricular function using multiple modalities; and (5) assessing pressures, flow, and resistances using mostly Doppler methods. These detailed evaluations generally require an examiner with specialty training because many evaluations have to be modified during the examination based on contemporary findings. Transesophageal echocardiography is also highly relevant to CHD, not only for the diagnosis of some lesions, but also for guidance during interventional catheterization procedures.[86] Epicardial echocardiography is also used during so-called hybrid procedures—those combining surgical and catheter-based techniques—for guidance of devices delivered transmurally across the atrial or ventricular wall.

Both qualitative (subjective interpretation) and quantitative aspects of echocardiography are relevant to the diagnosis and assessment of CHD. Owing to differences in body size and growth, it can be difficult to quantify cardiac size relative to a breed or body weight standard. This is a challenge, but most experienced examiners can subjectively assess moderate to severe chamber enlargements in CHD. Important aspects of this modality, such as the modified Bernoulli equation, are presented in detail in ch. 104 and are illustrated with examples in the present chapter.

Cardiac Catheterization

Cardiac catheterization is an invasive hemodynamic and angiographic procedure performed for diagnostic or therapeutic reasons. Most catheterization procedures involve measurement of hemodynamics—mainly intracardiac and intravascular pressures (Figure 250-1)—along with angiography and some form of catheter-based intervention. Owing to anesthetic effects, hemodynamic measurements, especially blood pressures and cardiac output, are markedly depressed compared to the awake or lightly tranquilized states and will not correspond to Doppler-derived measurements unless they are performed under the same conditions.[75] Today, cardiac catheterization is mainly reserved for procedures designed to repair or palliate CHD. Specific examples include balloon valvuloplasty for PS, delivery of an occluding device to close a PDA or an ASD, and an electrophysiologic study used to identify and then ablate an accessory electrical pathway. Principles and examples of interventional catheterization procedures are discussed more fully in ch. 122.

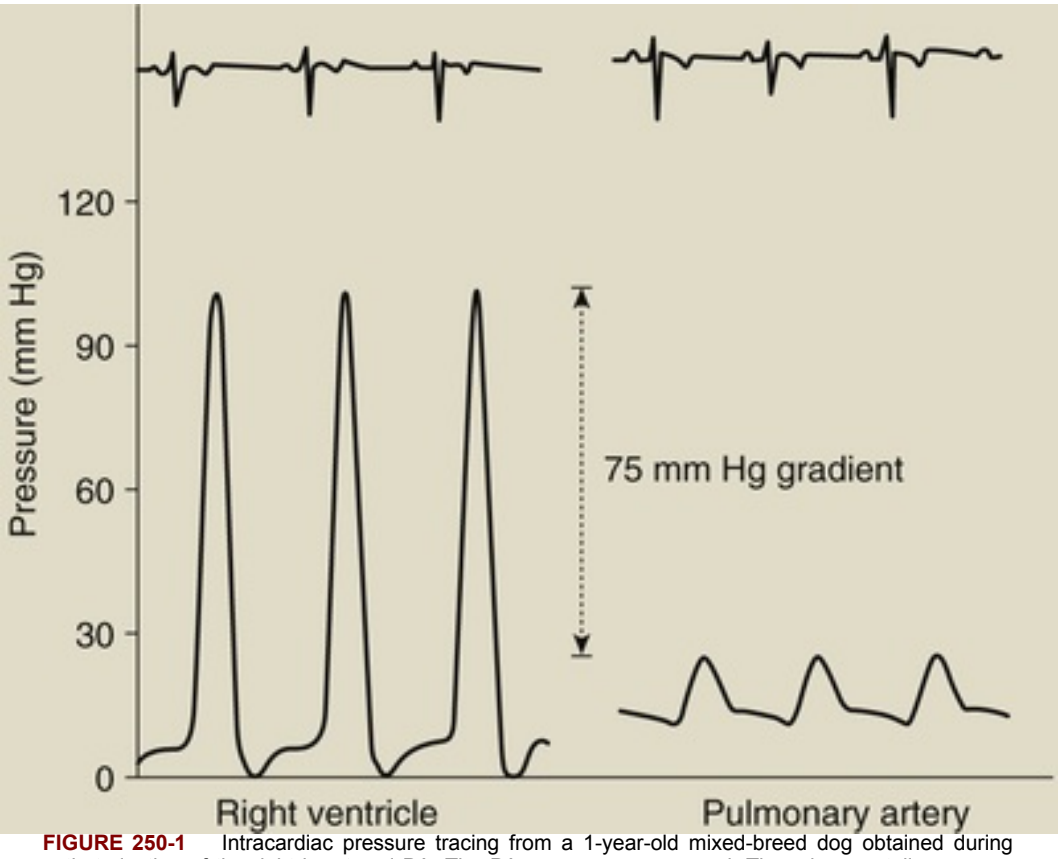

FIGURE 250-1 Intracardiac pressure tracing from a 1-year-old mixed-breed dog obtained during catheterization of the right heart and PA. The PA pressures are normal. There is a systolic pressure gradient of 75 mm Hg between the RV and PA, indicating the presence of an obstruction to RV outflow (in this case, valvular pulmonic stenosis [PS]). There is also a small diastolic pressure gradient between the PA and RV, which is caused by the diastolic closure of the pulmonic valve, and is a normal finding. The ECG displays a deep S wave, which is often found in animals with PS and secondary RV hypertrophy.

Patent Ductus Arteriosus

The ductus arteriosus develops from the embryonic left sixth aortic arch. This vital fetal structure shunts unoxygenated blood from the pulmonary artery through the descending aorta to the placenta where the blood is oxygenated, thereby diverting the majority of the RV output away from the nonfunctional fetal lungs. Following parturition and the onset of breathing, pulmonary vascular resistance falls, flow in the ductus reverses, and the resulting rise in arterial oxygen tension inhibits local prostaglandin release. These processes lead to constriction of the vascular smooth muscle within the vessel wall and functional closure of the ductus arteriosus. While the ductus may be probe-patent in puppies less than 4 days of age, it is usually closed securely by 7 to 10 days after birth.[2,87,88] Persistence of an opened ductus arteriosus beyond the early neonatal period is called PDA and is the first or second most commonly diagnosed congenital cardiac defect in dogs, depending on the survey. Cats are also affected but much less commonly than dogs.

Pathogenesis

Failed ductal closure in dogs and cats results from distinct histologic abnormalities within the ductal wall. The normal fetal ductal wall contains a loose branching pattern of circumferential smooth muscle fibers throughout its length, whereas in prenatal puppies bred to have a high probability of PDA, varying portions of the ductal wall are comprised of elastic fibers only. Increased prevalence of PDA in many breeds (see Table 250-1) indicates that genetic factors are likely involved in the pathogenesis. A mixed-breed, Poodle line of dogs with hereditary PDA has been extensively investigated, and a polygenic pattern of inheritance has been suggested.[89] Increasing genetic liability to PDA results in "extension of the noncontractile wall structure of the aorta to an increasing segment of the ductus arteriosus, progressively impairing its capacity to undergo

physiologic closure."[2] In humans, abnormalities in the genes that interfere with the remodeling of vascular smooth muscle cells of the ductal media, the putative cause of PDA, have been identified.[90] It is likely that similar genetic defects might be operational in the vascular smooth muscle of dogs with PDA.

In its mildest, clinically silent form, the ductus closes completely at the pulmonary arterial end and a blind, funnel-shaped pocket in the ventral aspect of the aorta, known as a ductus diverticulum, develops. This type of PDA, characterized by incomplete ductal closure (the *forme fruste* of the disease) can only be diagnosed by angiography or necropsy, but indicates that the dog carries a genetic liability for this defect.[2,89] Echocardiographic diagnosis of a ductus diverticulum has not been reported in dogs or other animals. Increasing genetic liability results in a tapering, funnel-shaped ductus arteriosus that remains patent after the early postnatal period and allows blood to flow from the aorta to the pulmonary artery, where intravascular pressures are lower (Figure 250-2, *A* and *B*). This is the most common form of PDA observed in dogs.[91] The most severe, but relatively uncommon, form is the cylindrical, nontapering ductus with persistent postnatal pulmonary hypertension (Eisenmenger syndrome or reaction) and bidirectional or right-to-left shunting (Figure 250-2, *C* and *D*). PDA may also be identified in animals with complex forms of CHD. For additional information regarding the morphology and pathogenesis of PDA, the reader is referred to several outstanding reviews of the subject.[92-94]

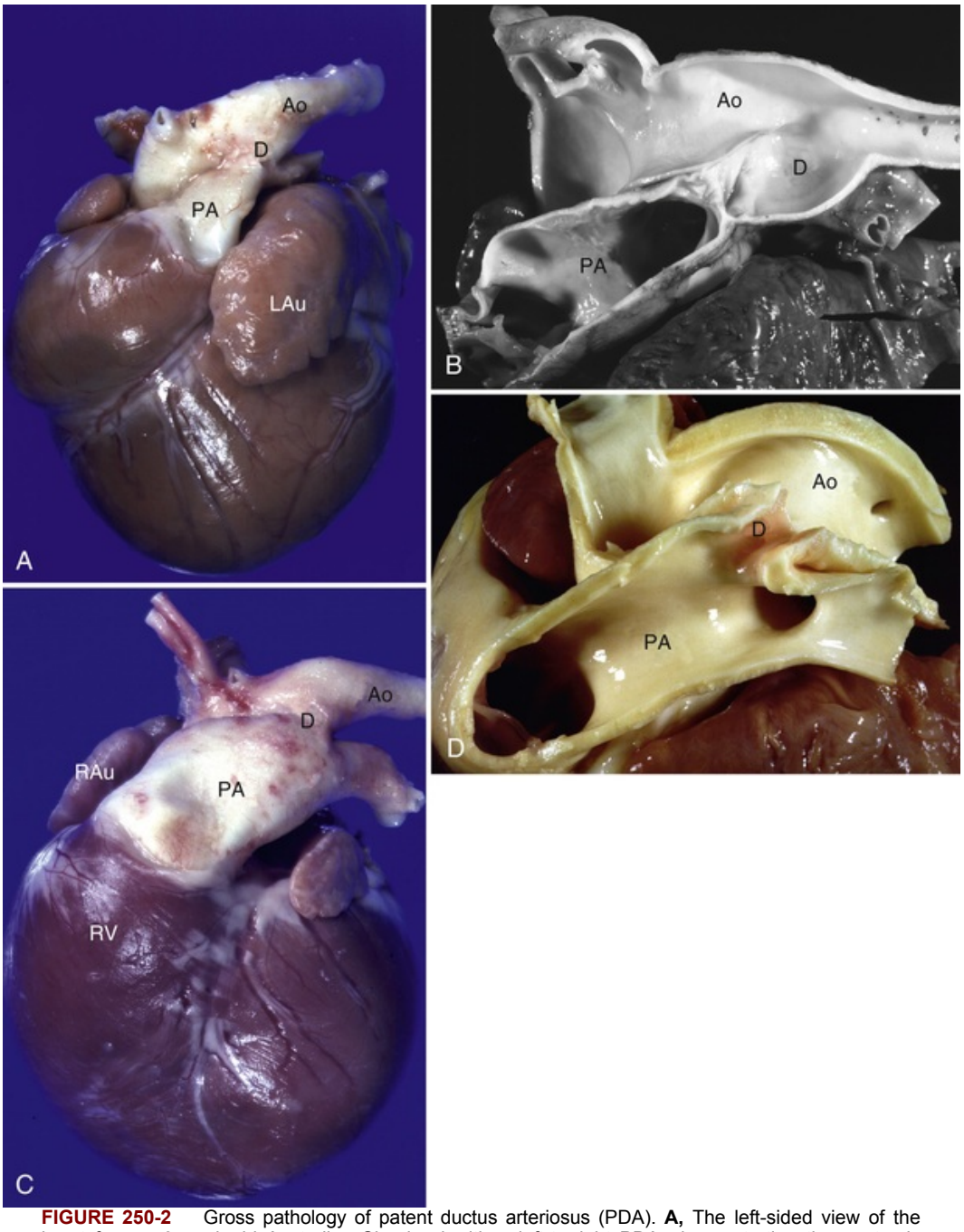

FIGURE 250-2 Gross pathology of patent ductus arteriosus (PDA). **A,** The left-sided view of the heart from a 9-week-old Australian Shepherd with a left-to-right PDA, demonstrating the anatomic location of the ductus (D) between the descending aorta (Ao) and main pulmonary artery (PA). The left auricle (LAu) is enlarged. **B,** Cut-away view of a left-to-right PDA in a dog. The ductus is funnel shaped, tapering toward the PA end. **C,** The left-sided view of the heart from a dog with a right-to-left shunting PDA. Note the enlargement of the right ventricle (RV) and right auricle (RAu). The pulmonary artery (PA) is enlarged. **D,** Cut-away view of a right-to-left shunting PDA in a dog. Note the cylindrical nature of the ductus (D) and the fact that the anatomic location of the ductus is distal to the aortic branches that supply the cranial portion of the body.

Pathophysiology

The direction of blood flow through a PDA is determined by the relative resistances of the pulmonary and systemic vascular beds, and in the vast majority of cases it proceeds from left to right (i.e., from the aorta to the pulmonary artery). The extent of shunting is determined by the relative pressure gradient between the systemic and pulmonary circulation, as well as the level of resistance within the PDA. Most often, the flow-

limiting region is at the level of the pulmonary ostium, where the ductus is at its narrowest. Flow through the PDA results in pulmonary overcirculation as blood is shunted from the aorta to the pulmonary artery. Higher LV stroke volume resulting from an increase in pulmonary venous return and end-diastolic volume associated with eccentric hypertrophy contributes to a rise in systolic aortic pressure. In diastole, rapid run-off of blood from the aorta to the lower-pressure pulmonary artery via the PDA causes a reduction in aortic diastolic pressures. The resultant pressure difference between systolic and diastolic blood pressures creates the hyperkinetic (waterhammer) arterial pulse detected in dogs with substantial shunts (see ch. 56). Since blood shunts continuously across the PDA during both systole and diastole, a continuous murmur arises, and is typically loudest near the time of the second heart sound (see ch. 55). All vascular structures involved in the transport of the shunted blood enlarge to accommodate the extra volume flow, with dilation of the proximal aorta, main pulmonary artery, and pulmonary vasculature. Dilation of the left atrium (LA) and eccentric hypertrophy of the LV develop in proportion to the volume of flow across the shunt. This mechanism permits compensation of the volume overloaded state for a variable period of time; if the shunt is large, however, myocardial failure (cardiomyopathy of volume overload) develops together with progressive elevation of LV end-diastolic pressure and overt pulmonary edema. Because the left-to-right shunt occurs at the level of the great vessels, the RV and RA are not directly exposed to the shunted blood, and these structures remain normal unless pulmonary hypertension develops.

In a small percentage of canine cases, the lumen of the PDA remains wide without tapering at the pulmonary ostium. The absence of a restrictive ductal orifice allows aortic pressures to be transmitted to the pulmonary circulation without impedance, thus precluding the normal postnatal decline in pulmonary vascular resistance. In this circumstance, the aortic and pulmonary arterial pressures equilibrate, the RV remains concentrically hypertrophied after birth, and reversal of flow through the shunt might develop. In Patterson's colony of dogs, this pattern of pulmonary hypertension and reversed (right-to-left) shunting developed within the first few weeks of life.[89] These observations fit the usual clinical presentation of most dogs diagnosed with a (reversed) PDA, in which there is usually no history of a continuous murmur and no evidence of LV enlargement or large left-to-right shunt earlier in life. Most dogs with reversed PDA flow exhibit diminished pulmonary blood flow, a normal to small LV, and marked concentric hypertrophy of the RV. On rare occasions, dogs with a moderate to large left-to-right shunting PDA will experience a sudden increase in pulmonary resistance due to necrotizing pulmonary vasculitis. Equally rare to detect is the gradual reversal of the direction of shunting, typically at several months to several years of age following a history of left-sided CHF.[49] Substantial residual LV enlargement is evident on thoracic radiographs and by echocardiography. Pulmonary blood flow is reduced but RV hypertrophy is less pronounced than in dogs that reverse the direction of shunting at an early age. The precise pathogenesis of pulmonary hypertension is not completely understood, but anatomic descriptions of the pulmonary vasculature are similar in humans and animals. Histologic changes within small pulmonary arteries include hypertrophy of the media, thickening of the intima and reduction of lumen dimensions, and development of plexiform lesions of the vessel wall.[49,50,95] Most of these changes are considered to be irreversible, precluding surgical correction of the reversed PDA, except possibly in rare cases where pulmonary arterial pressures remain subsystemic, something observed in cats with PDA and less often in dogs.[96]

Clinical Findings

PDA is the only congenital cardiac defect where there is a published sex predisposition for females (2.49/1000 in females versus 1.45/1000 in males).[1] Many breed predilections for PDA have been reported (see Table 250-1). Severely affected pups and kittens might develop stunting, poor body condition, or tachypnea from left-sided CHF, and it is likely that some puppies die from heart failure prior to the first veterinary examination that typically occurs at 6 to 8 weeks of life. Most puppies are reported to be asymptomatic with normal physical development at the time of diagnosis.

Left-to-Right Shunting PDA

A thorough physical examination usually suffices to suggest the initial diagnosis. Usually, the arterial pulses are hyperkinetic. Mucous membranes are pink unless severe left-sided CHF is present. The precordial impulse is often exaggerated and covers a larger area across the thoracic wall than normal because of LV enlargement. A thrill is commonly palpated craniodorsally in the left axillary region, and a classic continuous murmur is best heard in the same location (Figure 250-3 and see ch. 55). The murmur's point of maximal intensity is located over the main pulmonary artery at the craniodorsal left heart base, and it may radiate

cranially to the thoracic inlet and to the right base, where it is almost always softer.[89,97,98] Frequently, only a systolic murmur is audible over the mitral area. This murmur may result from radiation of the loudest portion of the continuous murmur from the heart base or may be due to secondary mitral regurgitation which has developed as a consequence of severe LV dilation. In cats, the continuous murmur of a PDA may be heard best somewhat more caudoventrally than in affected dogs and the murmur is often confused with a "long" systolic murmur, especially if pulmonary hypertension is developing. Other differential diagnoses for this presentation with a continuous murmur as a hallmark include aortopulmonary shunts, coronary arteriovenous fistula, rupture of sinus of Valsalva aneurysm, aorticopulmonary window, anomalous left coronary artery and arteriovenous shunts, although these are relatively rare compared with the prevalence of PDA.[99-102]

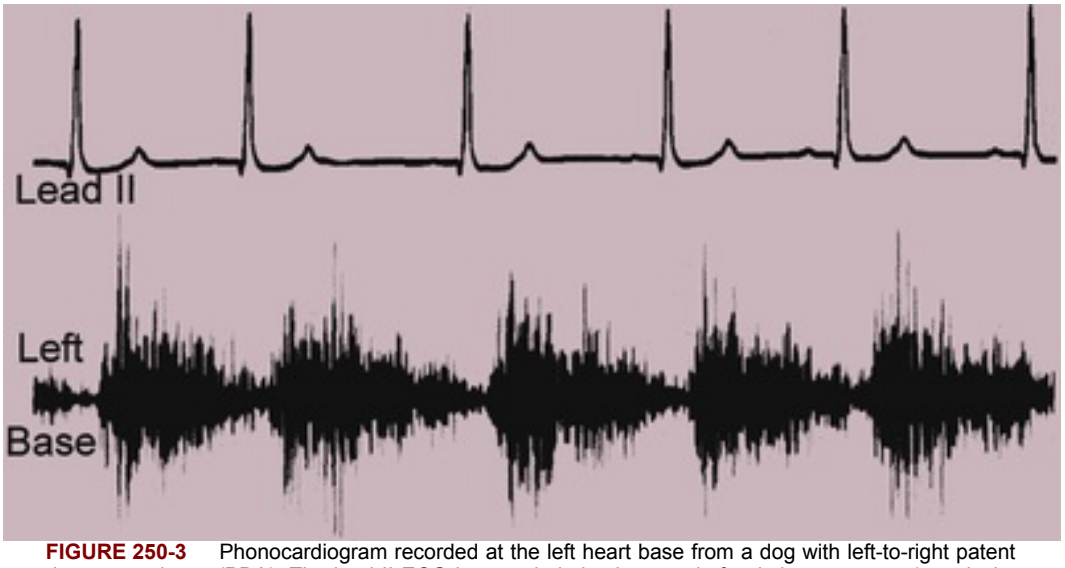

FIGURE 250-3 Phonocardiogram recorded at the left heart base from a dog with left-to-right patent ductus arteriosus (PDA). The lead II ECG is recorded simultaneously for timing purposes (ventricular mechanical systole is approximately the period from the middle of the QRS complex to the end of the T wave; the remainder of the time is diastole). The recorded murmur is continuous, increasing in intensity during systole, peaking near the end of systole, and decreasing in intensity during diastole.

Thoracic radiographs indicate left heart enlargement and pulmonary overcirculation in proportion to the magnitude of the left-to-right shunt (Figure 250-4). On the dorsoventral projection, the aortic arch, left auricle, and main pulmonary artery may be abnormally prominent. The most specific radiographic finding is the appearance of an aortic bulge ("ductus bump"), which is caused by abrupt narrowing of the descending aorta just caudal to the origin of the ductus, aneurysmal dilatation of the aorta, and/or the ductus itself (see Figure 250-4). Moderate to severe LV enlargement sometimes causes the cardiac apex to shift to the right (common in cats). Pulmonary edema is present following the onset of CHF.

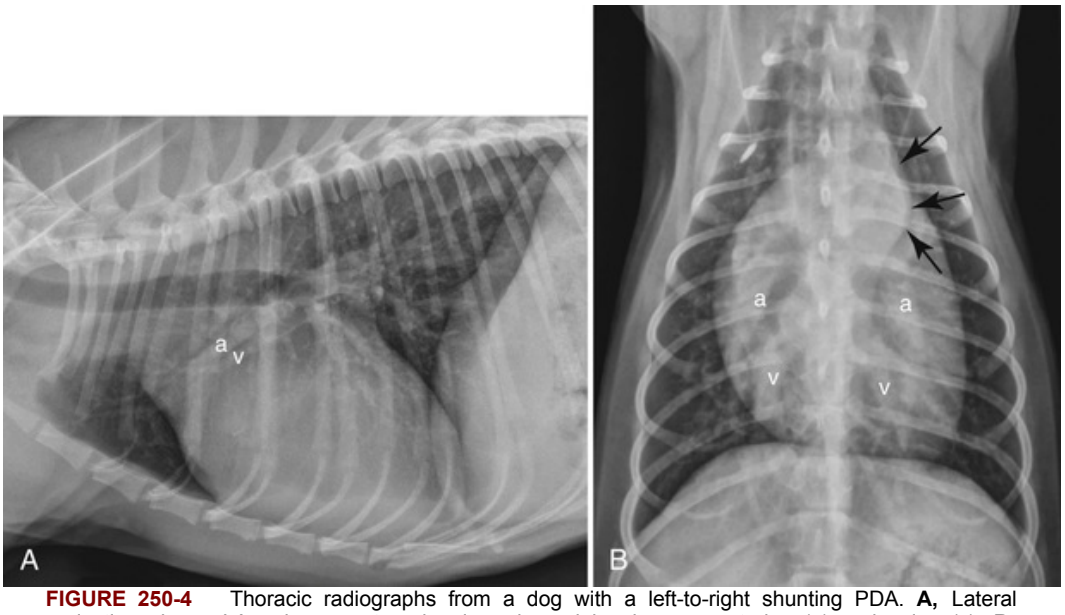

FIGURE 250-4 Thoracic radiographs from a dog with a left-to-right shunting PDA. **A,** Lateral projection shows LA enlargement and enlarged cranial pulmonary arteries (a) and veins (v). **B,** Dorsoventral projection shows moderate cardiomegaly, a characteristic bulge in the descending aorta (arrows) and dilation of the main pulmonary artery. The pulmonary vasculature is prominent.

When the rhythm is normal, the ECG contributes little to the overall diagnosis. Indications of LV enlargement (increased Q wave and R wave voltages in leads II, III, aVF and in the left precordial leads, V2 and V4) and LA enlargement (widened P waves) may be found. An arrhythmia is the principal indication for recording an ECG, and in dogs with long-standing PDA, atrial fibrillation, as well as supraventricular and ventricular premature complexes, may develop (see ch. 248).

The diagnosis of a PDA can be confirmed by a complete Doppler echocardiographic study in almost all cases. 2D and M-mode echocardiography demonstrate eccentric LV hypertrophy and dilatation of the LA, ascending aorta, and pulmonary artery (Figure 250-5, *A* and Videos 250-1 and 250-2). Reduced ventricular systolic function might be observed, and is suggested by findings of reduced fractional shortening, increased E-point to septal separation, and/or increased LV end-systolic volume. The ductus may be imaged and its size estimated from the left cranial parasternal view (Figure 250-5, *B* and Video 250-3).[103] Doppler interrogation of the main pulmonary artery demonstrates high-velocity, continuous ductal flow directed towards the pulmonic valve (Figure 250-5, *C* and Video 250-4). In the typical case, the peak velocity of this jet is at least 4.5 to 5.0 m/s and occurs at end-systole (Figure 250-5, *D*). Other common echocardiographic findings include mildly increased LV outflow velocity (1.8 to 2.3 m/s, but sometimes higher) and mild secondary mitral (Video 250-5), aortic, and pulmonic valve insufficiency, although in some dogs, moderate to severe mitral regurgitation might be identified. In dogs with PDA, associated cardiac defects are uncommon; nonetheless, it is still worthwhile to exclude, via a carefully performed echocardiographic examination, the presence of concurrent congenital defects such as PS. Owing to increased ejection volume and flow velocity across the LVOT, the diagnosis of mild SAS/AS can be difficult to achieve, and in the setting of overt SAS, its severity might not be evident until the ductus is closed. In animals that develop pulmonary hypertension, RV concentric hypertrophy may also be present, along with marked PA dilatation. Transesophageal echocardiographic techniques have also been described and may provide enhanced visualization of the ductal anatomy.[86,104] Cardiac catheterization and angiocardiography are usually not required to confirm a diagnosis of PDA (Video 250-6) and are not advised unless the Doppler echocardiographic evaluation is ambiguous or additional congenital malformations are suspected.

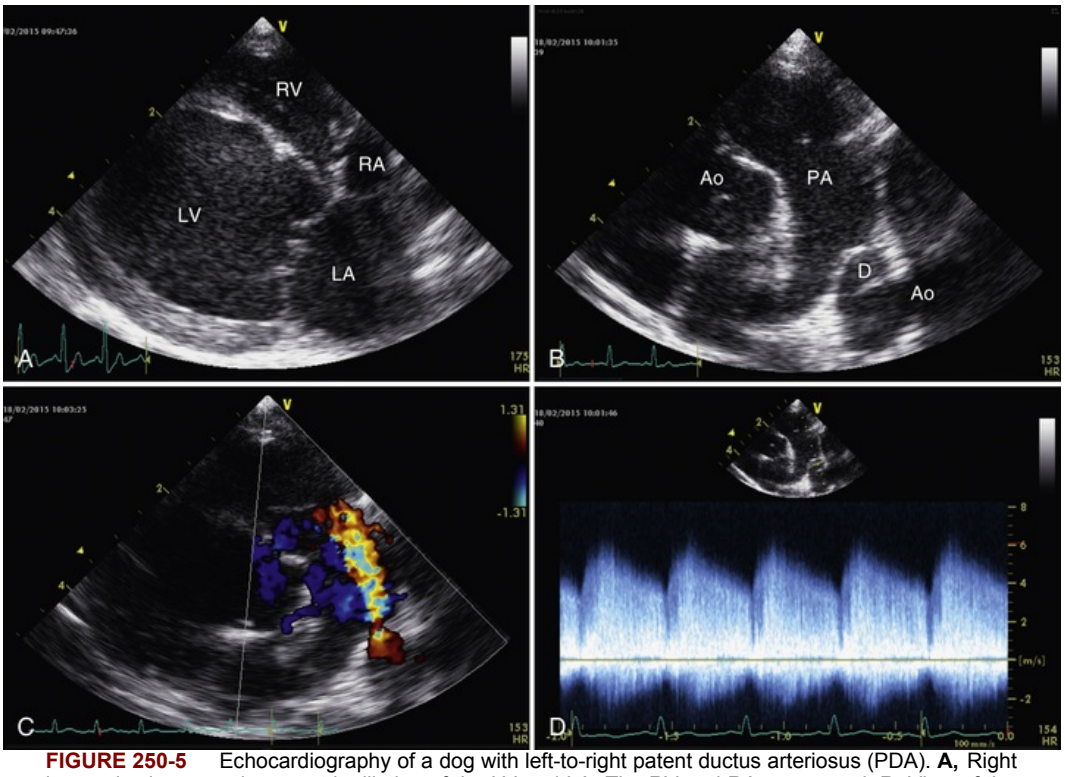

FIGURE 250-5 Echocardiography of a dog with left-to-right patent ductus arteriosus (PDA). **A,** Right long-axis view reveals eccentric dilation of the LV and LA. The RV and RA are normal. **B,** View of the ductus (D) imaged from the left heart base. The typical left-to-right ductus is widest at the aortic (Ao) end and tapers near the main pulmonary artery (PA). **C,** Color flow Doppler imaging applied to the echocardiographic view in **B,** demonstrating turbulent left-to-right blood flow through the ductus. **D,** Continuous wave Doppler tracing of the PDA jet obtained from the left heart base demonstrating continuous flow and a peak velocity of around 6.0 m/s.

PDA with Pulmonary Hypertension (Right-to-Left Shunting PDA)

High pulmonary vascular resistance causing right-to-left shunting through a PDA defines the clinical syndrome commonly referred to as a "reversed PDA."[49,51,89,95,105-109] Right-to-left shunting is observed in a very small minority of dogs with a PDA, but the prevalence of this phenomenon is probably underestimated and may be increased in dogs living at altitudes greater than 5000 feet (1500 meters) above sea level. Clinical signs are usually evident during the first year of life, but many owners do not recognize clinical signs in their pets during the first 6 to 12 months of life, and some animals are not diagnosed until 3 to 4 years of age or later. Reported signs include exertional fatigue, hind limb weakness, shortness of breath, hyperpnea, differential cyanosis, and, more rarely, seizures. Clinical examination is very different from the more common left-to-right PDA. Right-to-left flow through a wide PDA exhibits little turbulence and physical examination reveals either no murmur or only a soft, systolic murmur at the left base. The most common auscultatory finding is an accentuated and split second heart sound. Differential cyanosis (cyanosis of the caudal mucous membranes with pink cranial membranes) may be observed, but recognition may require examination after exercise. Differential cyanosis is caused by the location of the PDA, which shunts right-to-left from the pulmonary artery into the descending aorta (see Figure 250-2, *C* and *D*) but spares the proximal branches of the aorta, which provide normal oxygen delivery to the cranial portion of the body. Perfusion of the kidneys with hypoxemic blood triggers elaboration of erythropoietin and secondary erythrocytosis and hyperviscosity as the PCV gradually increases to 65% or greater.[51] Erythrocytosis may occur during the first year of life, but often does not become severe until 18 to 24 months of age.

The ECG of dogs with a reversed PDA virtually always reveals evidence of RV hypertrophy (right axis deviation, increased S wave amplitude in leads I, II, III, and the left precordial leads, V2 and V4). Thoracic radiographs indicate right heart enlargement, dilatation of the main pulmonary artery, a visible "ductus bump" and variable appearance of the lobar and peripheral arteries. Echocardiography demonstrates RV concentric hypertrophy and a dilated main pulmonary artery (Figure 250-6). In some cases, a wide and cylindrical ductus may be imaged (see Figure 250-6). Pulmonary hypertension can be verified in some cases

by Doppler interrogation of tricuspid or pulmonic insufficiency jets (see Figure 250-6). Contrast echocardiography, nuclear scintigraphy, oximetry, or angiography can be used to demonstrate the presence of right-to-left shunting should Doppler interrogation prove inadequate. Contrast echocardiography (see ch. 104) is performed by injecting air-agitated saline into a cephalic or saphenous vein, thereby opacifying the right heart, pulmonary artery, and the descending aorta (best observed by imaging of the abdominal aorta dorsal to the bladder). Cardiac catheterization can demonstrate pulmonary artery hypertension with equilibration of RV and LV and aortic systolic pressures; oximetry verifies decreased oxygen saturation distal to the entrance of the PDA in the descending aorta, and RV angiography demonstrates RV hypertrophy and usually outlines a wide PDA that appears to continue distally as the descending aorta (Figure 250-7). The lobar pulmonary arteries may appear normal angiographically, especially during the first year of life, or may show increased tortuosity. Aortic or LV contrast injections permit visualization of an often extensive bronchoesophageal collateral circulation (see Figure 250-7).

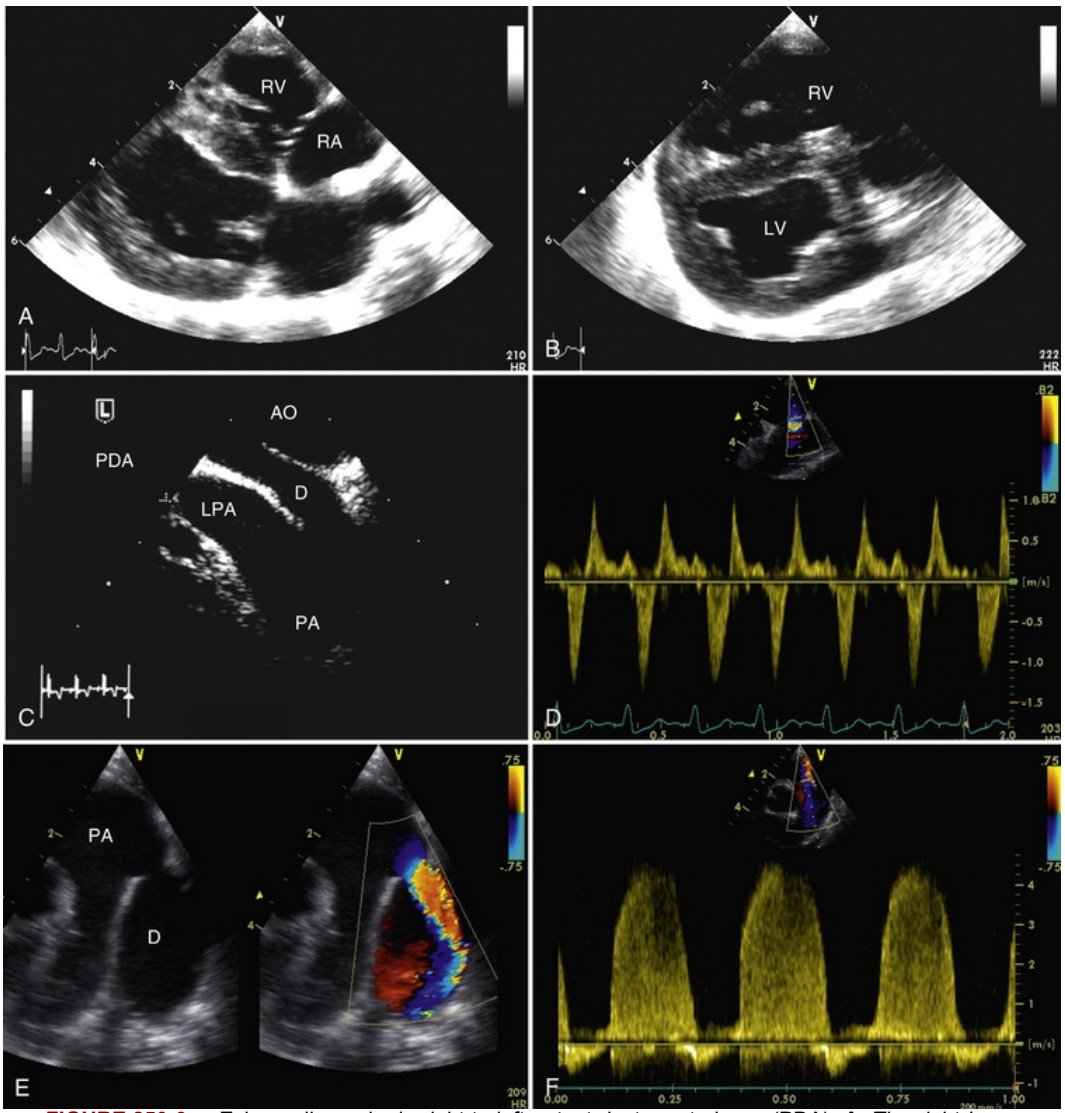

FIGURE 250-6 Echocardiography in right-to-left patent ductus arteriosus (PDA). **A,** The right long-axis view from an American Eskimo dog shows enlargement of the RV and RA. **B,** The right short-axis view shows enlargement of the RV and flattening of the interventricular septum toward the LV. This finding is highly suspicious for pressure overload of the RV. **C,** Transesophageal echocardiogram of a dog with a right-to-left PDA. The ductus (D) connects the aorta (Ao) with the pulmonary artery (PA), and is wide and cylindrical in shape. Both the PA and left pulmonary artery (LPA) are enlarged. **D,** Continuous wave Doppler study of the dog in **A** showing bidirectional flow through the ductus. Right-to-left flow (below the baseline) occurs during systole, while left-to-right flow (above the baseline) occurs during diastole. **E,** Simultaneous two-dimensional and color flow Doppler study of the dog in **A.** Flow from the pulmonary artery (PA) can be seen moving right-to-left into the large ductus (D). **F,** Continuous wave Doppler study of pulmonic insufficiency from the dog in **A.** The peak velocity of

insufficiency is 4.5 m/s, indicating a pulmonary artery diastolic pressure of approximately 80 mm Hg. This finding is consistent with a diagnosis of pulmonary arterial hypertension and the presence of a right-to-left shunt.

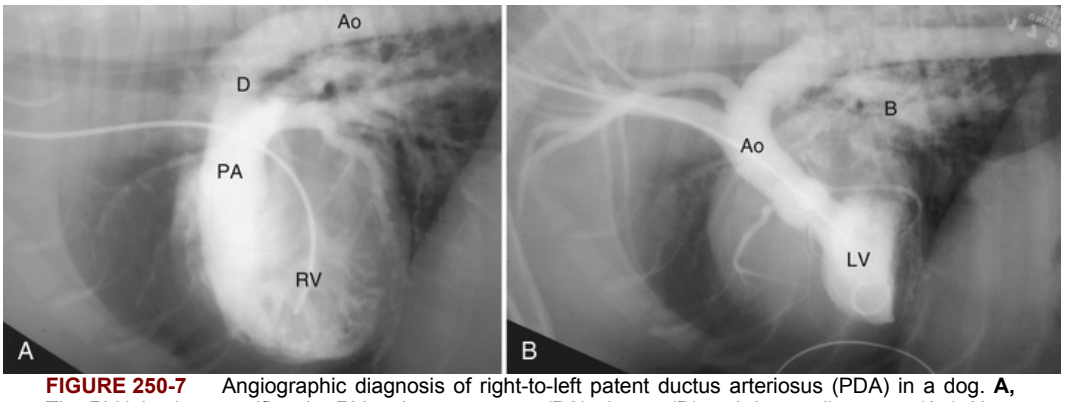

FIGURE 250-7 Angiographic diagnosis of right-to-left patent ductus arteriosus (PDA) in a dog. **A,** The RV injection opacifies the RV, pulmonary artery (PA), ductus (D) and descending aorta (Ao). Note that the systemic arteries to the cranial portion of the dog are not opacified. **B,** An LV injection of the same dog opacifies the LV, aorta (Ao), and prominent collateral bronchoesophageal circulation (B).

Natural History

Puppies and kittens with PDA are frequently clinically unaffected by their defect at the time of diagnosis. However, if left uncorrected, PDA typically leads to complications related to chronic left-to-right shunting (i.e., left-sided cardiomegaly, mitral valve regurgitation, arrhythmias, left-sided CHF, and death). The natural progression of untreated PDA in small animals is limited to a single study of 100 sequential cases in which the defect was not occluded in 14 affected dogs; 64% of these 14 dogs died within a year of examination.[110] While these numbers are relatively small, they provide a clear recommendation for most cases of PDA to receive a closure device or surgery. Pulmonary artery dissection is a recently recognized potential complication of uncorrected PDA in the dog. Dogs with this complication are more likely to present at an older age than the typical dog diagnosed with PDA.[111] In cats, literature regarding the natural history of PDA is scarce. Cats may develop significant pulmonary hypertension from left-to-right shunting more frequently than dogs do.[109,112-114] Importantly, pulmonary hypertension due to PDA can develop more slowly and might be arrested with prompt intervention.[113,114] When persistent pulmonary hypertension in the neonate leads to reversed shunting, clinical signs result from hypoxemia, erythrocytosis, hyperviscosity, and cardiac arrhythmias. CHF almost never develops but sudden death and complications from hyperviscosity are common. Dogs and cats with milder forms of PDA often survive to maturity and may live beyond 10 years of age.[115,116]

Clinical Management

Correction of uncomplicated PDA is considered to be curative. Furthermore, PDA closure results in an immediate decrease in left-sided volume overload, gradual reversal of LV eccentric hypertrophy over time,[117] and an excellent prognosis.[118] Correction may not be warranted in older pets if the shunt volume is small and cardiomegaly is minimal or absent. Generally, closure of PDA is an elective procedure that should be scheduled immediately when the diagnosis is made, and at the earliest age possible to prevent the condition from acutely deteriorating. If the patient presents in CHF with LV myocardial failure, the patient should be stabilized for a short period of time with medications for CHF (furosemide, pimobendan, ACE inhibitors) before considering anesthesia. Medical therapies for CHF are often continued for several months following repair in these animals. In some cases with atrial fibrillation, consideration can be given to electrocardioversion at the time of ductal closure or later; however, chronic medical management (digoxin and diltiazem, with or without beta-blocker; see ch. 248) might be needed.

Closure of reversed (right-to-left) PDA is generally accepted to be contraindicated due to case-based evidence of poor outcomes. Closure of left-to-right PDA with concurrent pulmonary hypertension of varying

severity has been reported to be successful in both dogs[96] and cats.[113,114] Treatment with prostaglandin inhibitors is not effective in dogs and cats, most likely because of the absence of smooth muscle in the ductal wall. Some dogs have shown clinical benefit to treatment with sildenafil citrate (1-3 mg/kg PO q 8-12 h), and this should be tried for at least 3-4 weeks to gauge clinical response.

The typical PDA can be surgically ligated, or closed by transcatheter techniques using thrombogenic coils or an occluder such as the Amplatz Canine Duct Occluder (ACDO). The latter transcatheter approaches represent the most important advance in PDA management over the past two decades and are widely employed today. These interventional catheterization procedures for PDA are discussed in ch. 122. Despite the substantial advances in transcatheter techniques, surgical ligation by means of a left thoracotomy remains a very successful method for PDA occlusion and should not be viewed as an inferior approach. Determining the appropriate treatment is dependent on ductal morphology, patient size, operator experience, and owner preference. Some advantages of per-catheter PDA occlusion over thoracotomy and surgical ligation include lower morbidity, shorter hospitalization, and faster recovery. In a large retrospective study comparing surgical ligation and transcatheter coil occlusion for treatment of PDA, surgical ligation was associated with a higher risk of major complications, whereas transcatheter occlusion using coils was associated with a lower initial success rate which was due to inability to stabilize coils, coil migration, and significant residual flow after appropriate coil placement.[119] In the current era of the ACDO, it is difficult to know how to compare transcatheter and surgical methods without a suitable prospective study. There are some disadvantages of catheter-based approaches, including: the need for fluoroscopy and radiation exposure; the requirement for specialized catheterization equipment and operator training; the inability to safely close cylindrical lesions lacking a tapering morphology; and, in some situations, the longer duration of the procedure (considering highly experienced surgeons can accomplish closure in less than 40 minutes). The inability currently to deliver an ACDO into very small patients (<2 to 2.5 kg) might be overcome by the availability of low-profile ACDOs.[120] In light of these points, the greatest advantage of surgical ligation is that it can be performed in animals with all ductal morphologies and body weights, and is therefore the method of choice for very small dogs and cats, as well as animals with a type III (nontapering) ductal morphology. Recovery is usually rapid with contemporary pain management. Complications of surgical PDA repair in dogs include intraoperative hemorrhage (11-15% of cases), infection, pneumothorax, cardiac arrhythmias, cardiac arrest, and heart failure, and perioperative mortality rates between 0-5.6% have been reported.[98,119,121]

After ductal closure, most dogs experience an uneventful recovery. Although overall cardiac size decreases after surgery, in many dogs some left-sided heart enlargement persists.[122-125] Postoperative Doppler examination may indicate a small residual shunt,[98,126] although the continuous murmur is usually absent and the clinical outcomes are very good. A soft left apical systolic murmur, usually from residual secondary mitral regurgitation, is often heard for a variable period after ductus ligation.[97] Postoperative ductal recanalization has been reported but is uncommon, occurring in less than 2% of cases and most commonly associated with an infection.[92] Postoperative fever and pulmonary infiltrates may indicate infection at the surgical site and hematogenous pneumonia.[127]

Animals with reversed PDA have irreversible obstructive pulmonary vascular disease. Morbidity and mortality are usually the result of complications related to erythrocytosis and chronic hypoxemia rather than CHF. Treatment of these patients consists of exercise restriction, avoidance of stress, preventing dehydration, and maintenance of the PCV between 58% and 65% by periodic phlebotomy.[94] As mentioned above, treatment with sildenafil citrate can also improve clinical signs. Long-term management by these techniques is possible.[128] Phlebotomy should be performed cautiously to avoid weakness or collapse, and intravascular volume may be supported during phlebotomy by administration of crystalloid solutions. Attempts to reduce the red cell volume of reversed PDA cases using drug therapy (e.g., hydroxyurea) have been reported and may be an alternative to repeated phlebotomy.[129] Activity restriction is usually advised, as exercise-induced systemic vasodilation increases the degree of right-to-left shunting and predisposes to hind limb paresis or collapse and cyanosis. Closure of reversed PDA is strongly contraindicated, as it invariably leads to late operative or early postoperative acute right heart failure and death.

Atrial and Ventricular Septal Defects

During cardiac embryonic development, the atria and ventricles begin as a common chamber. The heart is subsequently partitioned into the normal four-chambered heart by the growth of cardiac septa and AV valves. The atria are partitioned by a wall formed mainly from two septa: the septum primum, which forms

first, and the septum secundum, which develops to the right of the septum primum. The foramen ovale, a slit-like passageway which persists between these septa, permits right-to-left atrial shunting in the fetus, but functionally and anatomically closes in the neonate once the lungs expand and LA pressures rise. The major portion of the ventricular septum forms by inward growth from the ventricular walls. The area of AV confluence, including the upper ventricular septum, lower atrial septum, and AV valves, is formed primarily by growth and differentiation of the endocardial cushions. The AV valves normally insert at different levels of the ventricular septum, with the tricuspid valve connecting slightly apically to the mitral valve. The resultant offset, defined as the AV septum, essentially forms an atrial septum on the right and a ventricular septum on the left.[130]

Defects in the development of the embryonic ventricular septum, the primum or secundum atrial septa, or the endocardial cushions, can result in a VSD, an ASD, or both lesions, respectively, along with malformations in the AV valves. Congenital septal defects are common in both dogs and cats as isolated lesions or as components of more complex lesions such as complete AV septal defects (AVSD) and ToF.[22]

Pathogenesis of the Septal Defects

Except for the proven genetic basis of VSD in the Keeshond with so-called conotruncal malformations,[11] there are no data on the cause(s) of spontaneous septal defects in dogs or cats. ASDs are usually classified based on the anatomic region of the malformation. Defects at or near the foramen ovale are most common and are referred to as ostium (or septum) secundum defects (Figure 250-8). Defects of the lower atrial septum are called ostium primum defects and can occur in isolation or as a component of partial or complete AVSD. The rarely observed sinus venosus ASD is most often found dorsocranial to the fossa ovalis near the entrance of the cranial vena cava[131] and often involves the entry of a pulmonary vein into the RA. Since the endocardial cushions are largely responsible for partitioning the lowermost atrial septum, defects in the region immediately adjacent to the AV valves (septum primum) have been called "endocardial cushion defects"; however, this term is less preferred today. A defect in this area can also involve anomalous development of the AV valves. These can range from a "cleft" in the septal leaflet of the mitral valve to a common AV septal leaflet that bridges across the two sides of the heart. A complete AVSD (endocardial cushion defect) consists of a large defect of the lower atrial septum, an inlet VSD (ventral to the septal tricuspid valve leaflet), and a common (bridging) AV valve that includes a cleft in the septal mitral leaflet. Older terminologies for these severe malformations include a common AV canal defect, since the embryonic AV canal area never partitions and there is communication between all four cardiac chambers. Partial and complete AVSDs are more commonly detected in cats[132,133] and can cause left-sided or bilateral CHF; conversely, AVSDs are comparably rare in dogs.[134,135] Patent foramen ovale is not a true ASD inasmuch as the atrial septum forms normally, but the walls bordering the foramen are pushed apart. Most often, a PFO is due to conditions that increase RA pressure; however, severe LA dilation can also lead to persistent patency of the foramen ovale. A PFO usually achieves clinical significance when it allows right-to-left shunting, as might occur with severe PS[136] or TVD.

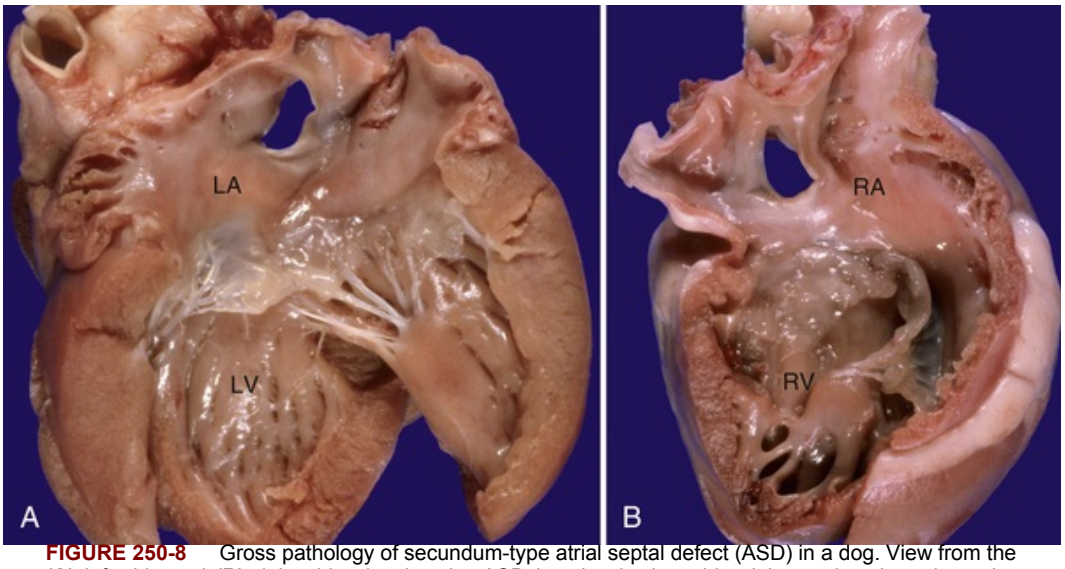

FIGURE 250-8 Gross pathology of secundum-type atrial septal defect (ASD) in a dog. View from the **(A)** left side and **(B)** right side showing the ASD location in the mid-atrial septal region where the foramen ovale would exist.

Most VSDs are located within or adjacent to the membranous portion of the upper ventricular septum, just below the aortic valve and cranial to the septal tricuspid leaflet (Figure 250-9, *A*).[137] These are variously termed "membranous," "perimembranous," and "paramembranous" defects by different authors and "infracristal" defects in older literature. Membranous ventricular septal aneurysm with or without a small, patent perimembranous VSD has also been described by echocardiography in both dogs and cats.[138]

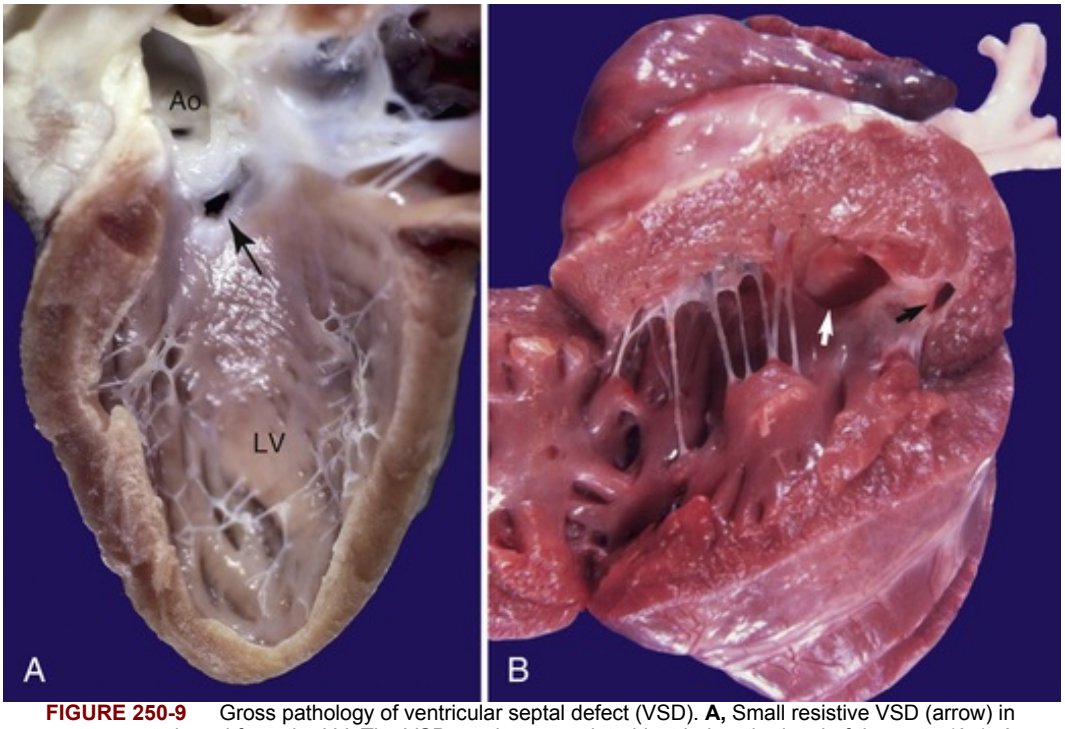

FIGURE 250-9 Gross pathology of ventricular septal defect (VSD). **A,** Small resistive VSD (arrow) in a young cat viewed from the LV. The VSD can be appreciated just below the level of the aorta (Ao). A fine network of excessive moderator bands/false tendons is an unrelated finding. **B,** Large, nonresistive VSD in a young dog with ToF, viewed from the RV. The large defect (white arrow) is located just cranial to the tricuspid valve apparatus. The RV is markedly thickened and a narrow subvalvular fibrous ring of subvalvular PS is present (black arrow).

The typical membranous VSD, when viewed from the left side of the ventricular septum, is located just

below the aortic valve, most often centered between the right coronary and noncoronary cusps. On the right side of the septum, the opening is often described by its position relative to the supraventricular crest (crista supraventricularis), the muscular ridge that separates the inflow from the outflow tracts. Membranous defects are subcristal (infracristal), whereas subarterial defects are located in a supracristal position just below the pulmonic valve. Large membranous defects can obliterate the crista and these are often associated with additional defects such as ToF (Figure 250-9, *B*). The right side of the root of the aorta, including the right coronary and noncoronary cusps, can be displaced to the right (dextropositioned) so that the aorta straddles the defect, creating a "malalignment" VSD. Extreme cranial and rightward deviations of the aortic root are observed in the spectrum of ToF-pulmonary atresia-double outlet right ventricle. However, the altered geometry of the aortic root that accompanies many VSDs can result in substantial aortic valve regurgitation without involving these severe malformations. Defects in the muscular ventricular septum are rare in dogs and cats and can be located dorsally or apically. Inlet VSDs were mentioned previously under AVSD.

Pathophysiology

Shunting across small (resistive or restrictive) defects depends primarily on the size of the defect and the pressure difference between the two chambers, while shunting across large (nonresistive) defects depends primarily on relative resistances within the systemic and pulmonary vasculature.[137,139-141] In the absence of other abnormalities, left heart pressures exceed those on the right and the direction of shunting is left-to-right. With left-to-right shunts, cardiac chambers in the circuit of the shunt enlarge to accommodate the excess blood volume, and the pulmonary vasculature becomes overcirculated. Large-volume left-to-right shunts can eventually result in myocardial failure, elevated filling pressures, and the development of overt CHF. Right-to-left shunting occurs via a septal defect when PS, tricuspid dysplasia (ASD), or pulmonary hypertension raises pressures on the right side of the heart. The consequences of "reversed" shunting include cyanosis from arterial hypoxemia, erythrocytosis, hyperviscosity, and sudden death (see Physiology of Right-to-Left Shunting, above).

Atrial Septal Defect

Flow across an ASD occurs primarily during ventricular diastole. The pressure difference across the defect is low and the direction and magnitude of the shunt is determined mainly by the defect size and relative diastolic resistance to inflow for each ventricle. Normally, the RV is more compliant than the left and offers little resistance to filling, causing blood to preferentially shunt from the LA into the RA and RV. The result is dilation of the RA, eccentric hypertrophy of the RV, and pulmonary overcirculation. At cardiac catheterization, oxygen saturation in the right heart and pulmonary arteries is increased. The LA receives the shunted blood, but most of the increased pulmonary venous return is shunted immediately into the RA, resulting in minimal LA dilation. If considerable LA enlargement is observed in an animal with an ASD, an AVSD with mitral regurgitation should be suspected.

The flow across an ASD does not usually generate an audible heart murmur because the pressure gradient and flow velocity across the defect are both low. When the shunted blood joins with blood entering from the vena cava, the volume and velocity of flow through the right heart is increased, resulting in a murmur of relative PS (common) or tricuspid stenosis (uncommon). Delayed closure of the pulmonic valve (and early closure of the aortic valve) causes splitting of the second heart sound.[139,142] Since the volume overload affects the RV and not the LV, large shunts culminate in the development of right heart failure or pulmonary vascular injury with clinical signs related to pulmonary hypertension and right-to-left shunting.

Ventricular Septal Defect

Flow across a VSD occurs primarily during ventricular systole. In the absence of other cardiovascular defects, peak LV systolic pressure is about five times that of the RV, and flow proceeds from the LV to the RV. The magnitude of left-to-right shunting with small (resistive) defects is mainly determined by the diameter of the defect and the systolic pressure difference (gradient) between the ventricles. The peak pressure difference across the defect can be estimated noninvasively with Doppler echocardiography (see ch. 104). A resistive defect with relatively normal RV and LV pressures (approximately 20-25 mm Hg and 100-120 mm Hg, respectively) is expected to have a peak jet velocity through the defect >4.5 m/s, corresponding to a peak pressure gradient >80 mm Hg. This high-velocity flow creates a prominent systolic murmur. If the peak velocity is lower than predicted, RV systolic pressure is most likely increased, caused either by the presence of PS or increased pulmonary artery pressure that can stem from high pulmonary flow, left heart failure, or

increased vascular resistance.

When a small VSD is located high in the membranous septum, blood is ejected by the LV directly towards the RVOT and out the main pulmonary artery; the right heart experiences only a modest volume overload and right heart enlargement is minimal. Right heart enlargement is more prominent when the VSD is large or is located in the muscular portion of the interventricular septum (IVS). In the setting of a membranous or subarterial VSD, cardiac catheterization shows oxygen saturation in the RVOT and pulmonary artery that is higher than that measured within the RA or apex of the RV. Large shunts (pulmonary to systemic flow ratio >3 : 1) can overload the left heart enough to increase ventricular diastolic pressures and cause signs of left-sided CHF. Very large, nonresistive VSDs cause the pressures in both ventricles to equilibrate, and the two ventricles behave as a common pumping chamber. Unless a stenotic pulmonic valve protects the pulmonary circulation, the development of CHF or pulmonary hypertension is unavoidable. With both small and large malalignment VSDs, aortic regurgitation can occur because of prolapse of the right aortic valve cusp into the VSD during diastole. This can increase LV wall stress, and predispose to CHF.

Clinical Findings

Atrial Septal Defect

Canine breed predispositions for ASD are presented in Table 250-1. In cats with ASD, one study found an overrepresentation of domestic shorthair, Persian, and Chartreux breeds.[22] Clinical findings of the typical left-to-right ASD include a soft, grade 2-3/6, systolic ejection murmur over the left heart base and splitting of the second heart sound (Figure 250-10).[22,143] The murmur is often misinterpreted as one arising from mild PS or as an innocent murmur. A low-frequency, right-sided diastolic murmur of relative tricuspid stenosis may occur, but this it is usually inaudible, especially in smaller patients. Cyanosis is absent unless there is an additional defect such as PS or TVD,[144] or the infrequent complication of pulmonary hypertension, to cause right-to-left shunting.[22] Signs of right-sided CHF may be present in dogs or cats with large defects.

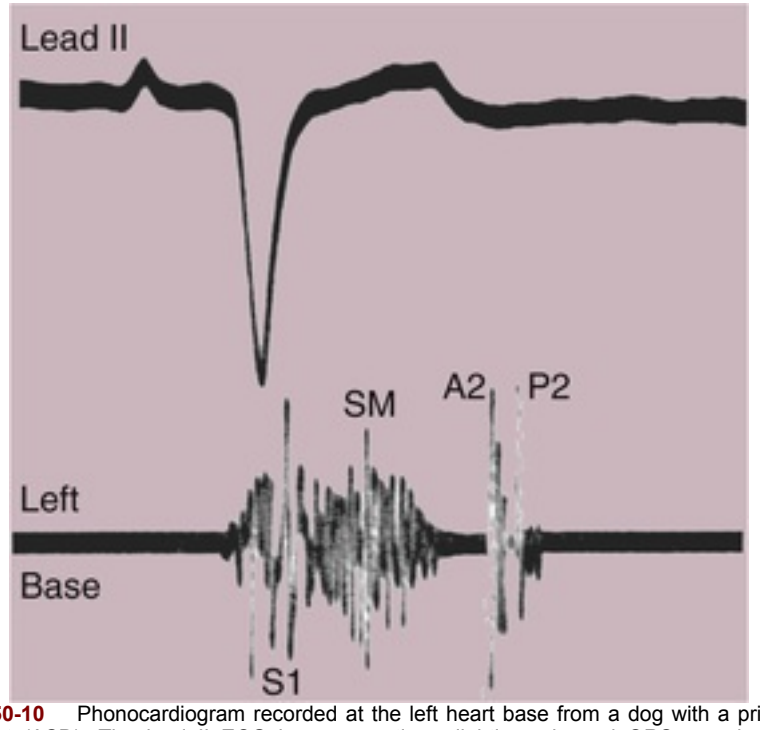

FIGURE 250-10 Phonocardiogram recorded at the left heart base from a dog with a primum atrial sepal defect (ASD). The lead II ECG has a negative, slightly prolonged QRS complex, which is indicative of an RV conduction disorder (partial or incomplete right bundle branch block). The phonocardiogram shows a systolic ejection murmur (SM) that ends well before the second heart sound, which is widely split. *S1,* First heart sound; *A2,* aortic component of the second heart sound; *P2,* pulmonic component of the second heart sound.

The main cardiac structural changes caused by an ASD include dilation of the RA and eccentric

hypertrophy of the RV. The ECG may indicate RV enlargement (right axis shift, increased S wave depth in leads I, II, III), but intraventricular conduction disturbances, especially partial or complete right bundle branch block, are also seen, especially with ostium primum defects or AVSD.[2,133] The latter can also exhibit a left-cranial axis deviation in the frontal axis. Thoracic radiographs show enlargement of the right heart, main pulmonary artery, and pulmonary hypervascularity proportional to the magnitude of the shunt (Figure 250-11). The LA is only modestly enlarged unless there is concurrent mitral regurgitation from a mitral valve malformation or an AVSD. 2D echocardiography permits direct imaging of ASD,[22] but false positive impressions of an ASD are common because of imaging artifacts caused by beam orientation and the thinness of some portions of the normal interatrial septum. Doppler evidence of transatrial shunting is more reliable and typically shows laminar or mildly turbulent diastolic flow through the ASD (Figure 250-12 and Video 250-7), and increased RVOT and pulmonary artery velocities. Doppler studies are also helpful for demonstrating associated problems such as mitral regurgitation or other associated defects.[145] One pitfall is confusing normal venous return from the caudal vena cava for left to right atrial shunting, as this flow enters along the atrial septum in the parasternal long-axis view. Additionally, in short axis image planes, the atrial septum can be foreshortened, confusing the location of a secundum ASD with that of a primum defect. Contrast echocardiography is helpful (see ch. 104), particularly when the defect is large or when elevated right heart pressures cause reversed flow across the defect. Cardiac catheterization of animals with an ASD might be helpful for evaluating the magnitude and direction of shunting and pulmonary vascular resistance. In cases of left-to-right shunting, oximetry samples from the vena cava, RA, and RV indicate an increase in oxygen saturation between the vena cava and the atrium and/or ventricle, and the magnitude of systemic to pulmonary shunting can be estimated. Central venous and RV diastolic pressures are elevated when CHF is present or imminent. Increased systolic flow across the pulmonic valve may result in "relative" PS, identified by a mild systolic pressure gradient (5 to 15 mm Hg) between the RV and pulmonary artery.[142] Flow through the ASD can be demonstrated by angiocardiography. When introduced via a femoral vein, a catheter can often be easily passed from the RA through an ASD or PFO into the LA to perform a contrast study for visualization of left-to-right shunting. Alternatively, contrast injection into the pulmonary artery will outline left-to-right shunting defects during the left-sided phase of the study. Following pulmonary venous return, the atrial septum usually can be seen between the LA and aorta on the lateral projection. Passage of contrast from the LA into the RA and vena cava confirms the presence of the defect. When a more extensive endocardial cushion defect is suspected, a contrast injection into the LV can be performed to demonstrate the VSD, mitral regurgitation, and occasionally, left ventricular-to-right atrial shunting through the ASD.

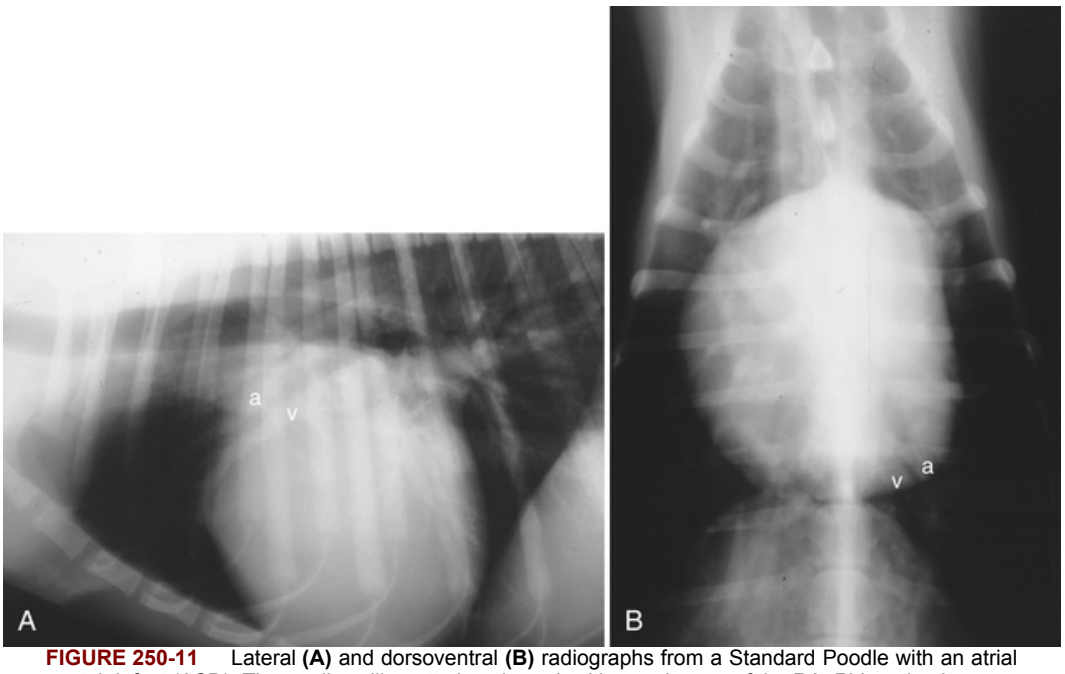

FIGURE 250-11 Lateral **(A)** and dorsoventral **(B)** radiographs from a Standard Poodle with an atrial septal defect (ASD). The cardiac silhouette is enlarged, with prominence of the RA, RV, and pulmonary arteries (a) and veins (v).

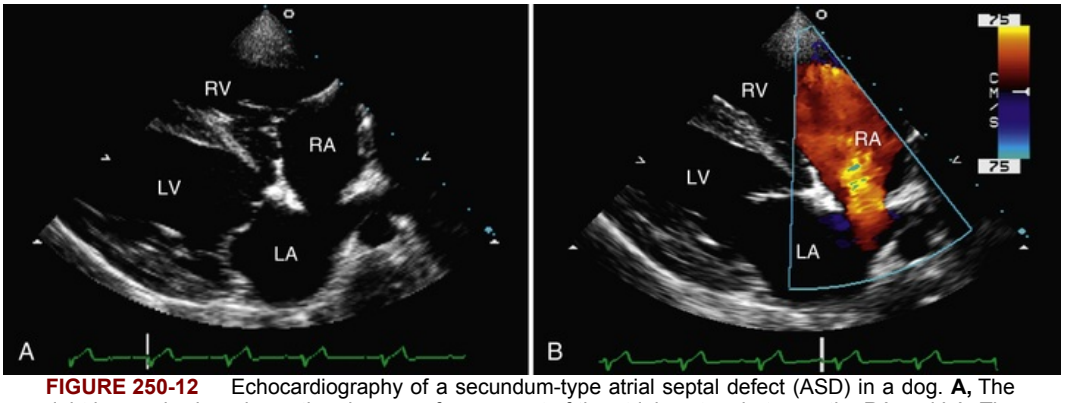

FIGURE 250-12 Echocardiography of a secundum-type atrial septal defect (ASD) in a dog. **A,** The right long-axis view shows the absence of a segment of the atrial septum between the RA and LA. The RA and RV are moderately enlarged. **B,** Color flow Doppler study indicates low velocity left-to-right flow through the ASD.

Ventricular Septal Defect

Canine breed predispositions for VSD are indicated in Table 250-1. VSD is one of the most frequent congenital anomalies in cats,[36] and no known breed predispositions have been reported, although clinical experience suggests they are relatively common in the Maine Coon cat. In contrast, certain breeds of dogs including English Springer Spaniels, West Highland White Terriers and Lakeland Terriers have been reported to be predisposed to VSDs. The clinical features of VSD depend on the magnitude of the shunt and presence of complications or other defects. Animals with a typical small, membranous VSD are asymptomatic and they present with a harsh, holosystolic murmur that is heard best over the right, ventral, mid- to cranial precordium.[137,146,147] In rare cases of subarterial VSD, the defect opens just under the pulmonic valve, and the systolic murmur is heard best at the left heart base. Splitting of the second heart sound can occur but is often unrecognized because of the superimposition of the murmur on the second heart sound. If distortion of the aortic root causes significant aortic regurgitation, a blowing, decrescendo diastolic murmur can be evident over the LV outflow area. This results in a combination of systolic and diastolic murmurs that can be readily confused with a PDA. Aortic regurgitation can also flow into the RV to produce a diastolic murmur best heard on the right hemithorax. Systolic murmurs over the AV valves may also be detected if a VSD is part of a complete AVSD.

ECG findings in animals with a VSD are variable. With moderate or large left-to-right shunts, there is often evidence of LA or LV enlargement, but RV conduction defects also can occur. Frontal plane leads may demonstrate a subtle abnormality in early ventricular septal activation, characterized by a Q wave that is wide or contains high-frequency notching.[148] Right axis deviation and a narrow QRS complex in a dog with VSD usually indicate RV hypertrophy and a more complex lesion, such as VSD with PS or pulmonary hypertension. Thoracic radiographs are very useful in assessing the magnitude of left-to-right shunting VSDs. Pulmonary hypervascularity and LA and LV enlargement are observed in proportion to shunt magnitude (Figure 250-13).[61] The main, lobar, and peripheral pulmonary arteries are usually prominent. In animals with small defects, thoracic radiographs may appear entirely normal. With large defects, the RV may also enlarge. A large pulmonary artery segment, underperfused lungs, and scant peripheral pulmonary vasculature suggest the possibility of PS or pulmonary hypertension and right-to-left shunting.

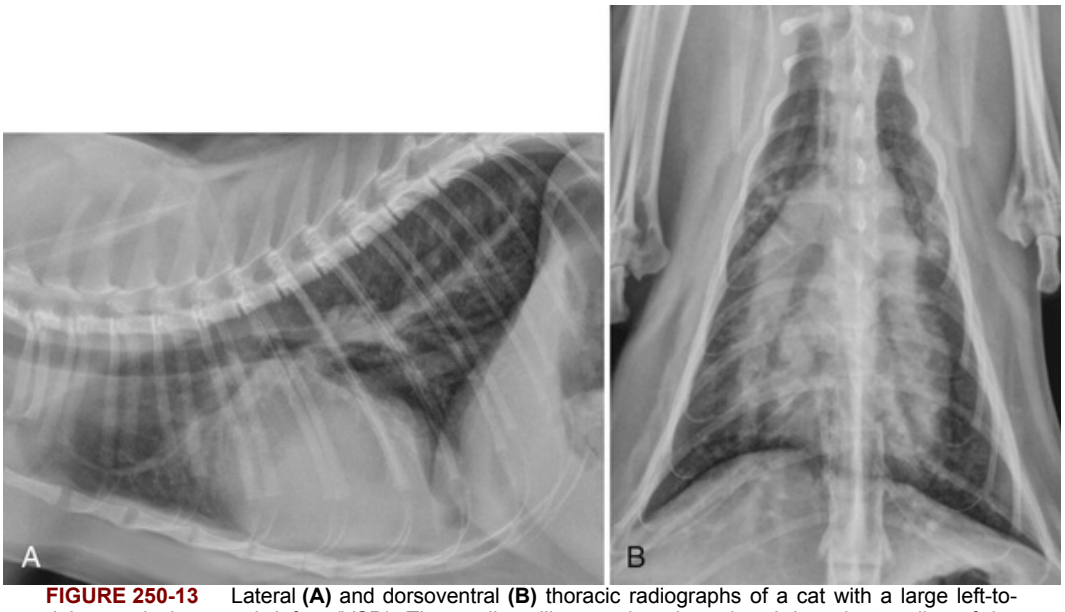

FIGURE 250-13 Lateral **(A)** and dorsoventral **(B)** thoracic radiographs of a cat with a large left-to-right ventricular septal defect (VSD). The cardiac silhouette is enlarged and there is rounding of the cranial border of the heart on the lateral view. The pulmonary arteries and veins are enlarged on the dorsoventral view.

On echocardiography, LA and LV enlargements of variable degrees are observed. With moderate to large VSDs, right heart enlargement may also be present. Two-dimensional echocardiography from the right thorax is most often utilized to identify the membranous VSD, located just below the aortic valve (Figure 250-14, *A*) and found adjacent to the cranioventral edge of the septal tricuspid leaflet. The rare subarterial VSD is best identified on short axis images at the level of the aorta that include the RV inlet and RV outlet into the pulmonary artery. Off-angle views are often needed. The left apical four-chamber image is best for visualizing an AVSD. As a general rule, when the maximal diameter of the VSD is <40% of the aortic root diameter, the lesion is likely to be restrictive/resistive and often well tolerated as long as there is no aortic regurgitation. Small aneurysms of membrane-like tissue may occasionally be seen protruding into the RV from the margins of the VSD.[138] As for ASDs, Doppler studies of VSDs should be performed to confirm the presence of the shunt, and color Doppler is particularly useful for identification of small lesions. For a perimembranous defect, a jet of blood moving toward the transducer can be observed in the long- or short-axis views from the right side (Figure 250-14, *B* and *C* and Videos 250-8 and 250-9). Continuous-wave (CW) spectral Doppler studies are useful to quantify the high-velocity jet through small, resistive VSDs, as previously mentioned (Figure 250-14, *D*). The larger the VSD, the smaller the pressure difference between the ventricles, and the lower the velocity of blood flow through the VSD. Thus, the peak velocity of blood flow through the VSD on CW Doppler can also be used for helping to define the size of the defect. The region of the aortic valve should also be interrogated for aortic regurgitation. Contrast echocardiography may also be used for identifying flow through the defect, but it is usually not necessary if careful 2D and Doppler examinations have been performed.

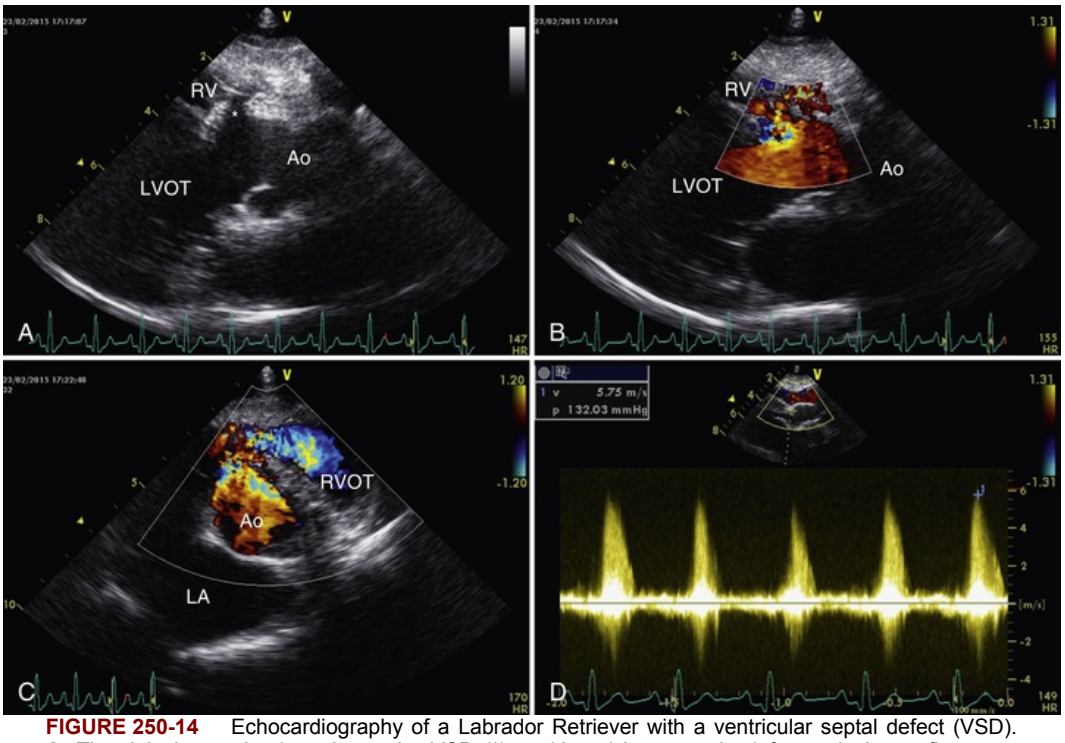

FIGURE 250-14 Echocardiography of a Labrador Retriever with a ventricular septal defect (VSD). **A,** The right long-axis view shows the VSD (*) positioned between the left ventricular outflow tract (LVOT) and aorta (Ao) and opening into the RV. Note the proximity of the VSD to the root of the Ao and origin of the aortic valve. **B,** The right long-axis color flow Doppler study reveals systolic left-to-right shunting across the VSD into the RV. **C,** The right parasternal short-axis color flow Doppler study reveals systolic left-to-right shunting across the VSD into the right ventricular outflow tract (RVOT). **D,** Spectral Doppler recording through the VSD, showing turbulent high-velocity left-to-right flow in systole (QRS complex to T wave).

Today, cardiac catheterization is rarely conducted to diagnose VSD. However, if a patient is considered a surgical candidate, catheterization allows further delineation of the anatomic defect and estimation of the degree of shunting.[146] Additionally, catheter-based methods are now available to occlude some VSDs (see ch. 122). At catheterization, oximetry samples demonstrate a "step-up" in oxygen content between the RA and pulmonary artery. Intracardiac and pulmonic artery pressures are usually normal in dogs and cats with a small VSD. RV pressures are often elevated 5 to 15 mm Hg above the pressure in the pulmonary artery. More dramatic increases in RV systolic pressure indicate pulmonary hypertension or concurrent PS, and the development of elevated end-diastolic ventricular pressures and central venous pressure herald the onset of CHF. Bidirectional or right-to-left shunting is observed when RV systolic pressure reaches and exceeds LV systolic pressure. Anatomic changes of the semilunar valves or great vessels, especially of the aortic root, are best visualized by injection of contrast in the proximal aorta, which is also the preferred location to determine the presence and severity of aortic regurgitation.

Atrioventricular Septal Defect

A partial defect with a primum ASD and relatively normal AV valvular function should behave like an isolated ASD. When an AVSD includes significant AV valve malformation, there can be substantial valvular regurgitation, including mitral regurgitation, tricuspid regurgitation, and mitral regurgitation into the RA across the ASD. The classic appearance of a complete AVSD on echocardiography includes an ASD, inlet VSD, and a "floating," bridging AV valvular leaflet that serves both ventricles. Outcomes can include clinical signs of CHF or of pulmonary hypertension due to secondary pulmonary vascular disease. Some of these details have been described elsewhere.[132] One unique manifestation of an AVSD is the so-called double outlet right atrium (see below).

Natural History

The morbidity and mortality associated with ASDs and VSDs depend on defect size and location, magnitude and direction of shunt flow, and the presence of additional lesions. Spontaneous closure of small VSDs often

occurs in children, but this is seemingly an uncommon occurrence in cats and dogs.[149] Animals with uncomplicated and small defects that result in only modest shunting usually live a normal lifespan without ever developing recognizable clinical signs. Larger shunts causing moderate to severe cardiomegaly can lead to intractable CHF, although it is likely that most of these cases die once pulmonary vascular resistance falls and the animal is never seen by a veterinarian. Moderate to severe aortic regurgitation, an uncommon complication of VSD, presents a very substantial risk of left heart failure and shortened survival, although it might take more than five years for CHF to supervene. When VSD is associated with obstruction to RV outflow—from a double-chambered right ventricle, infundibular stenosis, or obstruction near the valvular level—right-to-left shunting can lead to signs similar to those of ToF. It is often difficult to predict outcome in very young animals with a VSD until they grow closer to adult size at 6 to 12 months of age. Cats with severe AVSD often develop marked cardiomegaly and biventricular CHF. Some will succumb at an early age (<2 years), while others survive much longer.[132] Animals that develop pulmonary hypertension (Eisenmenger's syndrome) have a guarded short-term and very guarded to poor long-term prognosis, although survival beyond 7 years is possible.

Clinical Management

Medical therapy, surgery, and catheter-based treatments are possible but rarely needed for small isolated ASDs or VSDs. Patients with CHF (unilateral or biventricular) should be treated as any other patients with volume-overloaded hearts, using furosemide, an angiotensin-converting enzyme (ACE) inhibitor, spironolactone, and pimobendan (see ch. 247). These patients are also candidates for palliative or definitive repair, although these procedures are not widely available to veterinary patients.

Closure is the definitive treatment for all atrial and ventricular septal defects. Open-heart correction is uncommonly attempted in animals because of the requirement for cardiopulmonary bypass or other techniques to arrest and perfuse the heart.[135,142,150-156] Palliative surgical treatment of a large VSD can be considered without bypass by applying a constrictive band around the main pulmonary artery. This technique creates a supravalvular PS and increases the RV systolic pressure, thereby reducing the magnitude of left-to-right shunting.[157] This procedure is recommended for dogs and cats showing signs of rapidly progressive cardiomegaly and overt or impending CHF. Overaggressive banding should be avoided, because it is often unnecessary, and if too tight, the band can result in pressure overload, acute right heart failure or, in surviving animals, right-to-left shunting. Alternatively, systemic arterial vasodilators can be administered to reduce systemic vascular resistance and the magnitude of left-to-right shunting.[158] Successful closure of both ASDs[159,160] and VSDs[161-164] can be accomplished using percutaneous closure devices that have been developed over the last decade as well (see ch. 122). Hybrid procedures involving thoracotomy and transmural cardiac delivery of the device with ultrasound guidance also have been reported.[165,166] As noted for reversed PDA, surgical correction of animals with Eisenmenger's syndrome should not be attempted. Restricted physical activity is probably the most prudent and effective strategy in such cases. Sildenafil citrate treatment can also improve clinical signs. Periodic phlebotomy may be useful in some patients developing extreme erythrocytosis. Maintenance of the PCV at 58% to 65% is recommended.

Valvular Dysplasia

Pulmonic and Aortic Valve Regurgitation

Pulmonic Regurgitation

While inconsequential pulmonic regurgitation is a common finding in dogs and cats of all ages,[167] primary congenital pulmonic regurgitation (PR) is an uncommon abnormality resulting from abnormal development of valve leaflets or dilation of the pulmonary artery annulus.[168] PR causes RV volume overload and eccentric hypertrophy. The main and proximal branches of the right and left pulmonary arteries enlarge to accommodate the concomitant increase in RV stroke volume. Isolated PR is often well tolerated. Congenital PR is more likely to cause CHF if pulmonary vascular resistance subsequently increases as a result of severe pulmonary parenchymal or vascular disease or if the tricuspid valve is also diseased. Trivial PR is often observed in dogs with a PDA, presumably from dilation of the main pulmonary artery. Most dogs with PS have mild valvular insufficiency, but severe concurrent PR is sometimes observed. PR of varying degrees of severity usually occurs as a result of surgery or balloon dilation to relieve PS. PR is a potential consequence of any disorder prompting the development of pulmonary hypertension.

Clinical features of PR include variable systolic (caused by increased outflow or another lesion) and diastolic murmurs best heard at the left heart base. This "to-and-fro" murmur should not be confused with the continuous murmur of PDA. ECGs from dogs with congenital PR may be normal or reflective of RV enlargement. Thoracic radiographs in severe, isolated PR usually show enlargement of the main pulmonary artery and RV, giving the erroneous impression of PS. Contrast injection into the main pulmonary artery using a small diameter catheter documents valvular insufficiency. Slow clearance of contrast from the dilated and thin-walled RV also supports a diagnosis of PR. Color flow Doppler echocardiography can elegantly demonstrate these same features noninvasively and permit visualization of the rudimentary or misshapen valve leaflets (see ch. 104). Furthermore, Doppler studies also aid in the recognition of pulmonary hypertension. When the velocity of the pulmonary regurgitant jet exceeds 2 m/s, pulmonary hypertension is the likely cause of the arterial dilation and valvular insufficiency. Treatment for congenital PR has not been described in companion animals. In dogs suffering from CHF, conventional medical therapy with diuretics, ACE inhibitors and pimobendan is a reasonable palliative approach (see ch. 247).

Aortic Regurgitation

Isolated congenital aortic regurgitation (AR, aortic insufficiency) is a rare disorder. It is occasionally detected in young or older dogs with idiopathic dilation of the aorta (annuloaortic ectasia). Mild to moderate AR has also been reported in dogs with bicuspid[169] or quadricuspid aortic valves[170,171] (Figure 250-15, *A* and *B* and Videos 250-10, 250-11, and 250-12). Because of the increasing application of Doppler echocardiography, AR is being recognized with increasing frequency as a complication of other cardiac malformations.[172,173] AR often accompanies SAS and has been observed with VSD, ToF, and following balloon catheter dilation for AS/SAS. The potential mechanisms for aortic valvular insufficiency in these conditions have been reviewed.[173] As in congenital PR, the murmur resulting from AR can be both systolic and diastolic (to-and-fro) and is best heard over the left hemithorax. However, many dogs with AR do not have an audible murmur. In contrast, when AR is audible, the valvular incompetency is generally severe. The diagnosis of clinically significant AR is supported by palpation of a hyperkinetic arterial pulse resulting from the combination of higher stroke volume and reduced diastolic pressures owing to diastolic run-off of aortic blood back into the LV. Eccentric to mixed hypertrophy of the LV develops in proportion to the severity of the insufficiency. Severe AR commonly results in left-sided CHF. Documentation of AR and estimation of its severity requires angiocardiography or, more practically, Doppler echocardiography. Definitive repair requires cardiac bypass surgery and valve replacement. Use of arterial vasodilators can reduce the regurgitant volume and may delay the onset of CHF but at the risk of reducing coronary perfusion. Treatment with diuretics, ACE inhibitors, and pimobendan are indicated if CHF is present (see ch. 247).

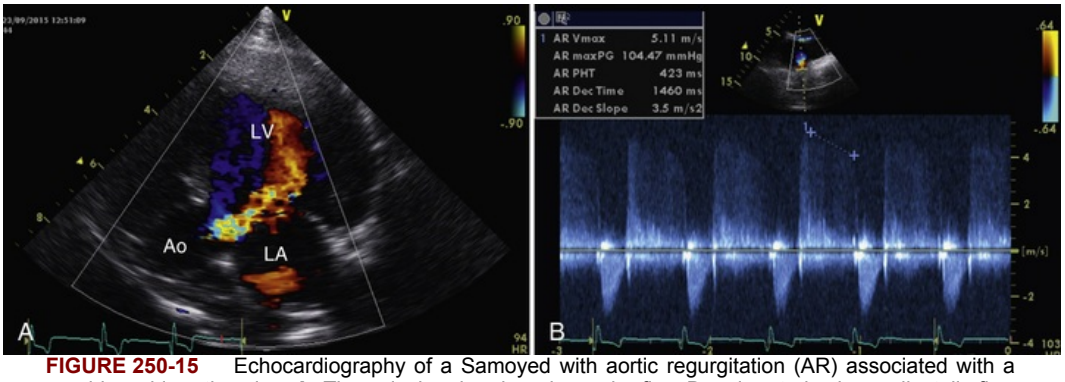

FIGURE 250-15 Echocardiography of a Samoyed with aortic regurgitation (AR) associated with a quadricuspid aortic valve. **A,** The apical 5-chamber view color flow Doppler study shows diastolic flow from the aorta into the LV. **B,** Spectral Doppler recording of the aortic insufficiency jet, demonstrating diastolic flow and a peak velocity of 5.11 m/s and a pressure half-time (PHT) of 423 ms.

Atrioventricular Valve Dysplasia

Congenital malformations of the mitral and tricuspid valves are reported in both cats and dogs. In cats, mitral valve dysplasia (MVD) is one of the most common congenital anomalies described. Consequences of these malformations include (1) mitral or tricuspid valve regurgitation (most common); (2) inflow obstruction (i.e.,

mitral or tricuspid valve stenosis); and (3) dynamic obstruction of the LVOT via inappropriate, systolic displacement of the mitral valve into the LVOT. Fixed obstruction of the LVOT has also been described from mitral malformation.[174] The pathophysiology and clinical course of congenital mitral regurgitation are similar to that described in acquired degenerative valvular disease in the dog (see ch. 251). Ebstein's anomaly is a congenital defect reported in dogs related to TVD, whereby the origins of the tricuspid valve leaflets are apically displaced into the RV.[21,175,176] It may or may not be associated with leaflet dysplasia.

Systolic anterior motion (SAM) of the mitral valve apparatus and dynamic LVOT obstruction in cats and dogs, long regarded solely as a manifestation of hypertrophic cardiomyopathy (see ch. 252 and 253), may be caused primarily by architectural changes in the mitral valve apparatus in some animals. When the primary disorder is valve dysplasia, concentric LV hypertrophy often resolves if the obstruction is abolished by treatment (beta-receptor blocking drugs).[177-179]

Pathogenesis

TVD has been shown to have a genetic basis in some of the most commonly afflicted breeds,[9,10,180] and in Labrador Retrievers an autosomal dominant mutation with incomplete penetrance has been mapped to chromosome 9.[10] A wide spectrum of congenital morphologic abnormalities of the mitral and tricuspid valves has been described, including shortening, rolling, notching, and thickening of the valve leaflets; incomplete separation of valve components from the ventricular or septal wall (failure of delamination); elongation, shortening, fusion, and thickening of the chordae tendineae; direct insertion of the valve edge into a papillary muscle; and atrophy, hypertrophy, fusion, and malpositioning of the papillary muscles and chordae tendineae.[175,181-185] The usual consequence of these changes is valvular insufficiency. Examples of mitral and tricuspid valve dysplasia are shown in Figures 250-16 and 250-17. Some dogs and cats with mitral or tricuspid dysplasia have a PFO or a concurrent ASD, resulting in left-to-right or right-to-left shunting.

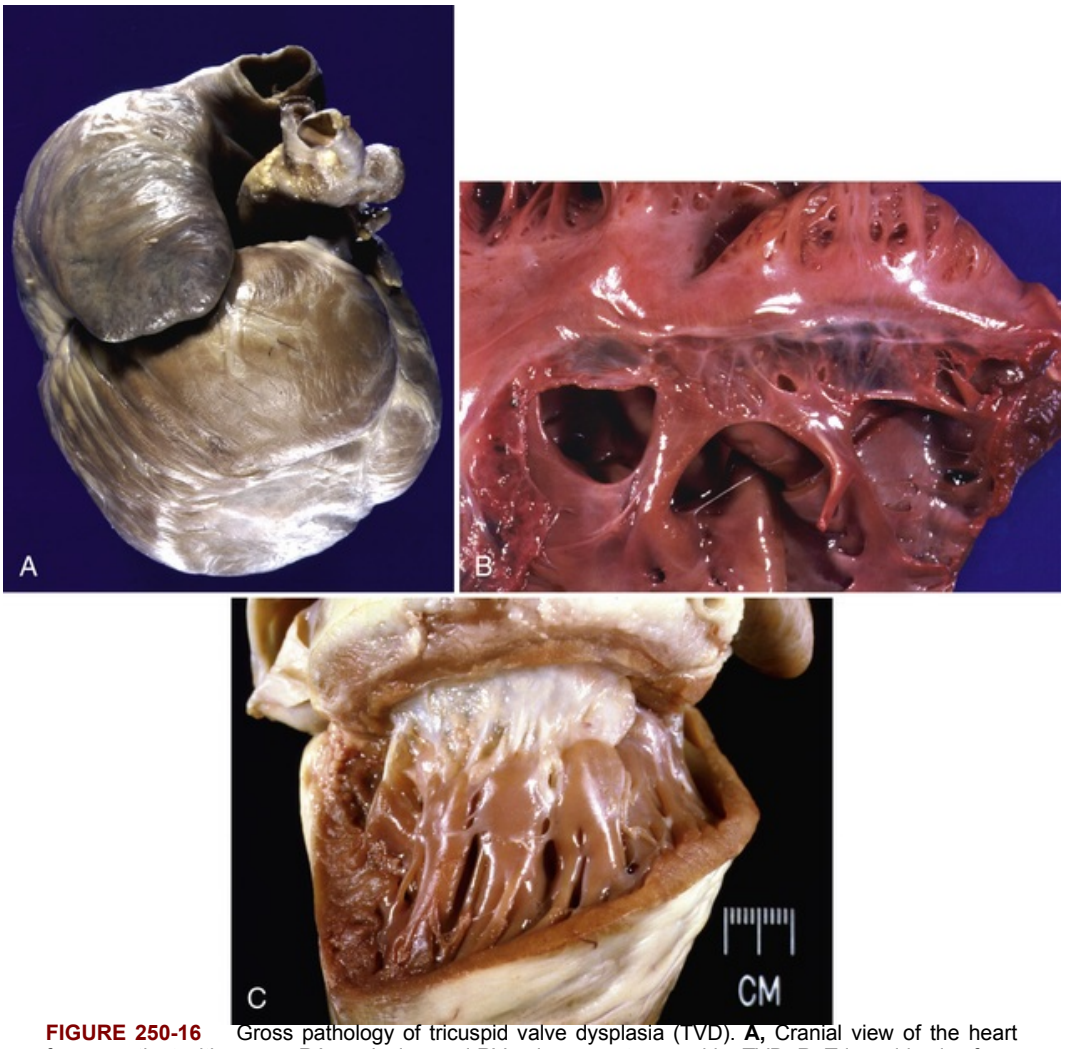

FIGURE 250-16 Gross pathology of tricuspid valve dysplasia (TVD). **A,** Cranial view of the heart from a patient with severe RA, auricular, and RV enlargement caused by TVD. **B,** Tricuspid valve from a 2-year-old Labrador with severe TVD. The edges of the valve leaflets insert directly into the papillary muscles and there is conspicuous absence and shortening of the chordae tendineae. The RA and RV are dilated. **C,** Curtainlike deformity of the tricuspid valve from a 2-year-old Samoyed with TVD and tricuspid stenosis. The tricuspid valve is thickened and opaque. There are multiple large and fused papillary muscles with short chordae tendineae.

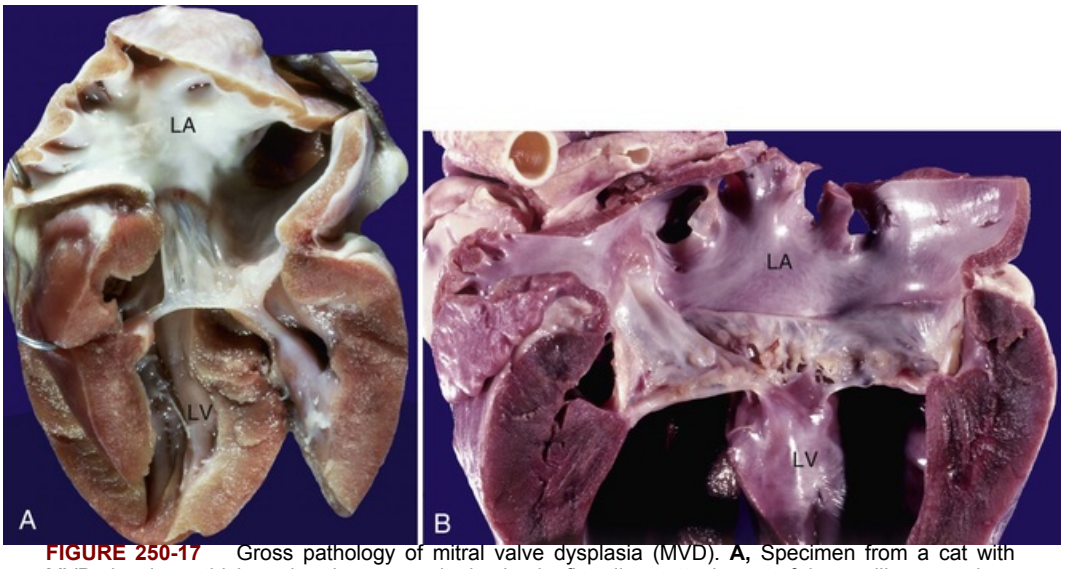

FIGURE 250-17 Gross pathology of mitral valve dysplasia (MVD). **A,** Specimen from a cat with MVD showing a thickened and opaque mitral valve leaflet, direct attachment of the papillary muscle to the leaflet edge, and LA enlargement. **B,** Specimen from a dog with MVD showing short chordal attachments from the LV papillary muscle to the leaflet edge, a thickened and nodular mitral valve leaflet, and marked LA enlargement.

Pathophysiology

The fundamental pathophysiologic abnormality of AV valve malformations is valvular insufficiency that produces volume overload and manifests as atrial dilation and eccentric hypertrophy of the affected ventricle. Some dogs and cats have survived for 8 years or more with relatively severe AV valve malformations, but more often CHF develops at a young age, especially with MVD. The development of atrial fibrillation is especially destabilizing to patients with these lesions. In some cases of TVD, cyanosis is observed as a consequence of right-to-left shunting across a PFO or ASD. Severe AV valve stenosis limits cardiac output so that hypotension, syncope, or collapse with exertion can be observed. Tachycardia abbreviates diastole and increases the transvalvular diastolic gradient further, explaining exercise intolerance. Pulmonary hypertension and right-sided CHF frequently develop secondary to severe mitral stenosis as a consequence of chronic elevations in LA pressure; this is more common in cats. As a result, some patients initially presenting with signs of left-sided CHF from mitral stenosis can re-present months later with signs of right-sided CHF. As indicated above, dogs and cats with AV valvular dysplasia are predisposed to atrial fibrillation as well as paroxysmal or sustained supraventricular tachycardias (see ch. 248); their onset typically results in sudden clinical deterioration.

Clinical Findings

Increased prevalence of MVD and TVD in several breeds (see Table 250-1) indicates that genetic factors are likely involved in the pathogenesis. Mitral valve stenosis, in particular, is common in Bull Terriers, where it often occurs together with valvular aortic stenosis.[186] Cats of all breeds, Great Danes, German Shepherds, Bull Terriers, Golden Retrievers, Newfoundlands, Dalmatians, and Mastiffs are predisposed to MVD.[182,187,188] Although TVD has been described in cats, it appears to occur most commonly in large male dogs and especially in the Labrador Retriever breed.[189]

Dogs and cats with valvular dysplasia can appear clinically well. Clinical signs arise from exertional fatigue, or right-sided, left-sided, or biventricular CHF, pulmonary hypertension, or right-to-left shunting. Hemoptysis can occur with mitral stenosis. The hallmark of valvular insufficiency is a holosystolic murmur heard best over the affected valve area. A loud gallop may also be detected.[187] A soft, late diastolic murmur and opening "snap" is sometimes auscultated in dogs or cats with valvular stenosis, but this finding is often absent or missed. In cases of TVD, murmur intensity may not always reflect the severity of disease. In severe cases, a murmur may be very soft or absent as the valve offers no resistance to regurgitant blood flow. Jugular venous distension and pulsations are common findings in cases of TVD, and hepatomegaly and ascites are present in dogs that present with right-sided CHF. Animals with right-sided CHF often have a poor body

condition.

Splintered QRS complexes (e.g., Rr′, RR′, rR′, rr′) are a distinctive and common ECG finding in dogs and cats with TVD (Figure 250-18).[68] Right heart enlargement patterns may also manifest. Tall or wide P waves are observed with all types of valvular dysplasia, but ventricular enlargement patterns are mainly limited to animals with regurgitant physiology and are not observed with isolated valve stenosis, except when pulmonary hypertension develops secondary to mitral stenosis. Atrial arrhythmias, including atrial premature complexes, atrial tachycardia, and atrial fibrillation (see Figure 250-18), are often recorded. The pattern of chamber enlargement on thoracic radiographs generally reflects the involvement of the affected valve and resulting physiologic consequences (Figure 250-19). In cases of TVD, the degree of cardiomegaly is often impressive, and may resemble the globoid appearance of pericardial effusion. The possibility of valvular stenosis should be considered whenever the atrium is markedly dilated without enlargement of the ipsilateral ventricle.

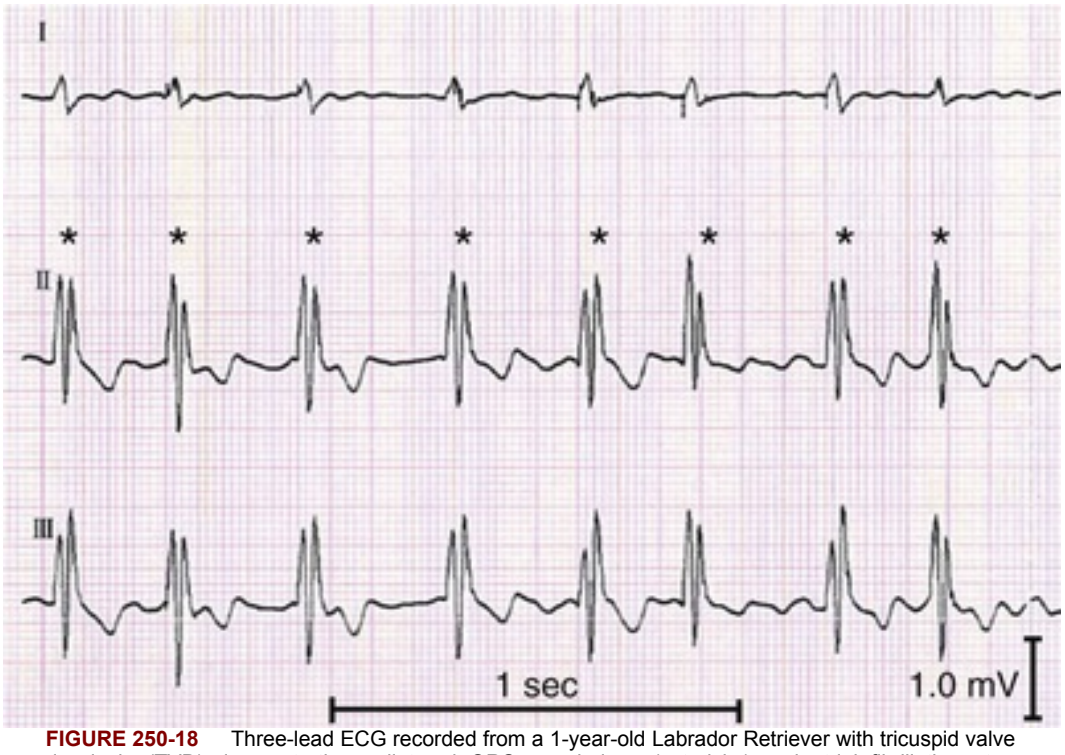

FIGURE 250-18 Three-lead ECG recorded from a 1-year-old Labrador Retriever with tricuspid valve dysplasia (TVD) demonstrating splintered QRS morphology (asterisks) and atrial fibrillation at a ventricular rate of 200 depolarizations per minute. Sensitivity 10 mm/mV at a paper speed of 50 mm/sec.

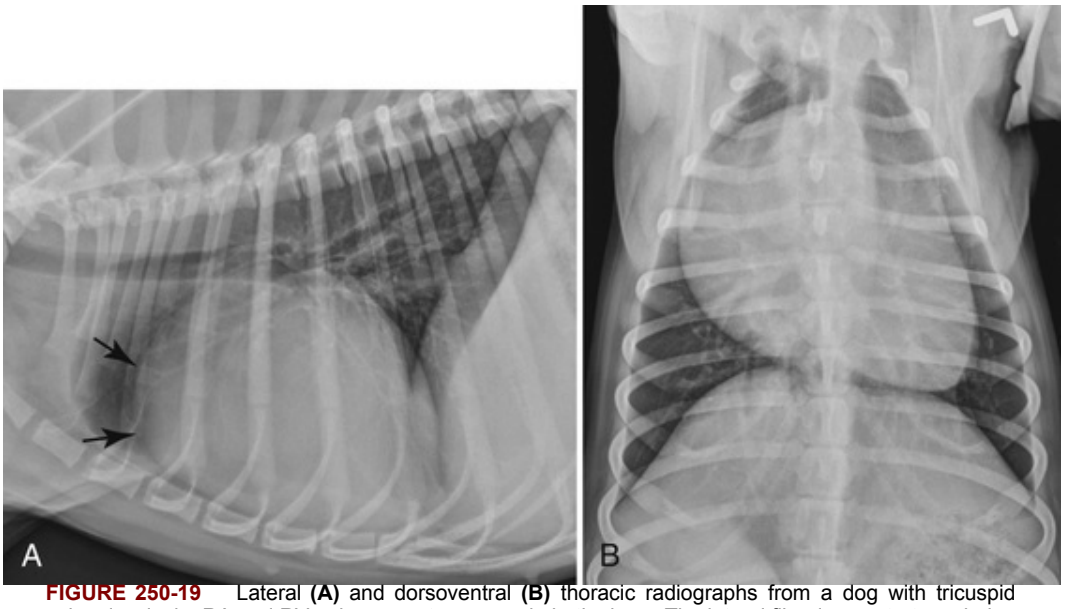

FIGURE 250-19 Lateral **(A)** and dorsoventral **(B)** thoracic radiographs from a dog with tricuspid valve dysplasia. RA and RV enlargement are seen in both views. The lateral film demonstrates a bulge in the cranial waist (arrows), most likely caused by right auricular enlargement.

Definitive diagnosis of AV valve malformation requires echocardiography (see ch. 104). Abnormal location, shape, motion, or attachment of the valve apparatus is easily observed with this technique (Figure 250-20, *A-D* and Videos 250-13 and 250-14). With valve insufficiency, volume overloading of the respective atrium and ventricle can be seen, and Doppler studies demonstrate regurgitant jets streaming from the ventricle into the atrium through the incompetent valve (Video 250-15). With isolated valve stenosis, the ventricle appears small and the atrium enlarged, and the thickened valve leaflets can be observed to "dome" into the ventricle during diastole. Color flow Doppler studies in AV stenosis show a high-velocity jet (often >2.0 m/sec) entering the LV or RV during early diastole, and a prolonged pressure halftime, as determined by measurement along an abnormally shallow E-F slope. With MVD and dynamic LVOT obstruction, variable degrees of concentric LV hypertrophy (see Figure 250-20, *A*), and high-velocity turbulent flow within the LVOT accompanied by a posterolaterally directed jet of mitral valve insufficiency can be seen. Continuous wave Doppler interrogation of the LVOT in such cases will display a dynamic and labile pressure gradient secondary to SAM of the mitral valve (see Figure 250-20, *B*). TVD is identified by a marked apical dislocation of the tricuspid valve insertions (see Figure 250-20, *C* and *D*). In human Ebstein's anomaly, apical dislocation with atrialization of the proximal part of the RV is observed. However, the diagnosis of apical dislocation should be made with caution as the normal insertion point of the tricuspid valves is slightly more apical than the normal insertion point of the mitral valve and the reason for apical displacement is typically a failure of the valve to delaminate from the walls. Confirmation of Ebstein's anomaly is best made at cardiac catheterization, where a ventricular electrogram is recorded along with an atrial pressure tracing within the supravalvular chamber.

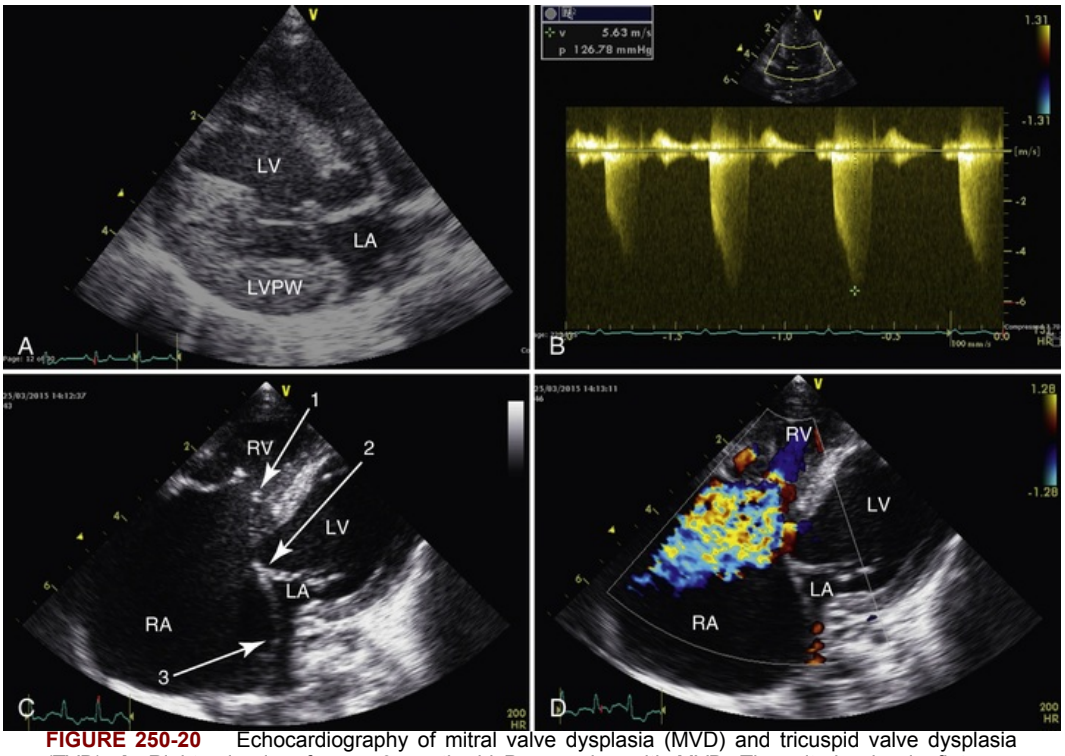

FIGURE 250-20 Echocardiography of mitral valve dysplasia (MVD) and tricuspid valve dysplasia (TVD). **A,** Right-axis view from a 6-month-old Pomeranian with MVD. The mitral valve leaflets are markedly thickened and the chordae tendineae are shortened. The LV (especially the LV posterior wall) is concentrically hypertrophied. **B,** Continuous wave Doppler study from the same dog demonstrating dynamic LVOT obstruction. The cursor is aligned along a systolic signal that abruptly increases in velocity at the time of systolic anterior motion of the mitral valve. **C,** The left apical view from a dog with tricuspid valve dysplasia. The origin of the tricuspid valve is displaced apically and the septal leaflet is fused to the interventricular septum (1). The origin of the mitral valve leaflet (2) is shown for comparison. The atrial septum is bulging severely to the left (3). **D,** The left apical color flow Doppler study from a dog with severe tricuspid regurgitation caused by TVD.

Although echocardiography is diagnostic, cardiac catheterization and angiography can also be performed, especially if some intervention is planned. Diastolic pressure gradients (valve stenosis) and varying degrees of ventricularization of atrial waveforms (from severe valve insufficiency) can be recorded. Angiographic visualization of valvular insufficiency is best appreciated by ventricular injections of contrast, while valve stenosis is best demonstrated following an atrial injection, which in the case of mitral stenosis often requires a transseptal puncture.

Natural History

The morbidity and mortality associated with mitral or tricuspid dysplasia depend on the form and severity of valvular dysfunction, and the presence of additional lesions. Animals with small insufficiencies usually live a normal lifespan without ever developing recognizable clinical signs. Large insufficiencies and/or severely stenotic valves causing moderate to severe cardiomegaly often lead to atrial arrhythmias and intractable CHF. These outcomes are not invariable, however, and survival to six or eight years of age is not uncommon, especially with TVD.

Clinical Management

Repair of the affected valve has been performed, and surgical replacement of dysplastic AV valves has been successfully accomplished in dogs with mitral[190-192] or tricuspid dysplasia.[193] Cardiac bypass is required for these infrequently performed procedures. Balloon valvuloplasty has been described in dogs with mitral[194,195] and tricuspid[196,197] stenosis, and is further discussed in ch. 122. Medical treatment is instituted once heart failure develops; treatment of CHF caused by valvular insufficiency largely consists of diuretics, ACE inhibitors, and pimobendan (see ch. 247). The value of any "preventative" therapy is unknown. In dogs with TVD and refractory heart failure, periodic paracentesis despite concurrent medical therapy is often needed (see ch. 90 and 102). Inasmuch as tachycardia is poorly tolerated in AV valve stenosis patients, every effort should be made to avoid stress and to restrict exercise. Administration of beta-blockers, calcium channel blockers, and/or digoxin is helpful in some cases for the management of atrial fibrillation or other supraventricular tachyarrhythmias (see ch. 248). Animals with significant LVOT obstruction secondary to SAM of the mitral valve, regardless of the presence or absence of clinical signs, are commonly treated with beta-blockers (such as atenolol), which has been reported to successfully alleviate the dynamic LVOT obstruction.[177-179] Some patients tolerate serious defects surprisingly well for many years. In other cases, there is rapid progression to heart failure and death.

Ventricular Outflow Obstructions

Pulmonic Stenosis

Pulmonic stenosis is the third most common congenital heart defect in dogs (see Table 250-2)[3,167] and it is occasionally recognized in cats.[198-202] PS occurs in the majority of cases as an isolated heart defect, but it is also frequently accompanied by additional cardiac anomalies, such as TVD. Congenital outflow tract obstructions of the right heart can develop in the subvalvular and supravalvular regions, but primary malformation of the pulmonic valve (dysplasia) is the most frequently observed defect in dogs. Patterson and associates, who studied the heritability and pathology of pulmonic valve dysplasia in the Beagle, initially suggested a polygenic mode of transmission for this defect.[203] These breeding studies did not, however, exclude the possibility of a single gene mechanism with variable penetrance. The pattern of inheritance of PS has not been studied in other predisposed dog breeds or in cats.

Pathology

Valvular lesions consist of varying degrees of valve thickening, leaflet fusion, and hypoplasia of the valve annulus components. While some dogs manifest a thin, dome-shaped valve with a central orifice (Figure 250-21), many dogs have more complicated lesions resembling atypical PS in children.[47,203,204] The valve leaflets are often thickened, misshapen, or fused (see Figure 250-21). In addition to thickening and commissural fusion, the distal edges of the leaflets can be tethered to the pulmonary arterial wall, mimicking a supravalvular obstruction. The annulus of the pulmonic valve is hypoplastic in some dogs, further narrowing the area available for RV ejection. Histologic abnormalities include thickening of the valve spongiosa and the presence of bands of fusiform cells in a dense collagen network. These changes are thought to represent overproduction of normal valve elements or a failure of conversion of the cushion-like embryonic valve primordia. Some dogs with valve dysplasia also have a fibrous ring just below the valve leaflets accompanying the valvular changes. In other dogs and cats[198] the obstructive lesion occurs in the infundibular region of the RVOT. On occasion, the RVOT is partitioned from the body (inflow region) of the RV by a well-developed, fibromuscular ridge, resulting in an anomaly referred to as double- or dual-

chambered right ventricle or primary infundibular stenosis.[205,206] The distinction between infundibular PS and double-chambered right ventricle is not always clear, especially in cats.[198] Supravalvular PS is uncommon, and in the authors' experience, is most often observed in Giant Schnauzers. Subvalvular PS has been associated with anomalous development of the coronary arteries, especially in English Bulldogs and in Boxers.[207,208] In this condition, the coronary circulation is derived from a single ostium located in the right aortic sinus of Valsalva, and both left and right coronary arteries branch from a single large coronary artery (Figure 250-22). From this location, the anomalous left coronary artery encircles the RVOT just below the pulmonic valve. Whether this lesion contributes to the subvalvular component of this malformation or is simply a comorbidity is undecided as it has been observed in Bulldogs without PS. Regardless, it is clinically relevant because vigorous balloon valvuloplasty of the subvalvular lesion has been associated with sudden death (see Figure 250-22).

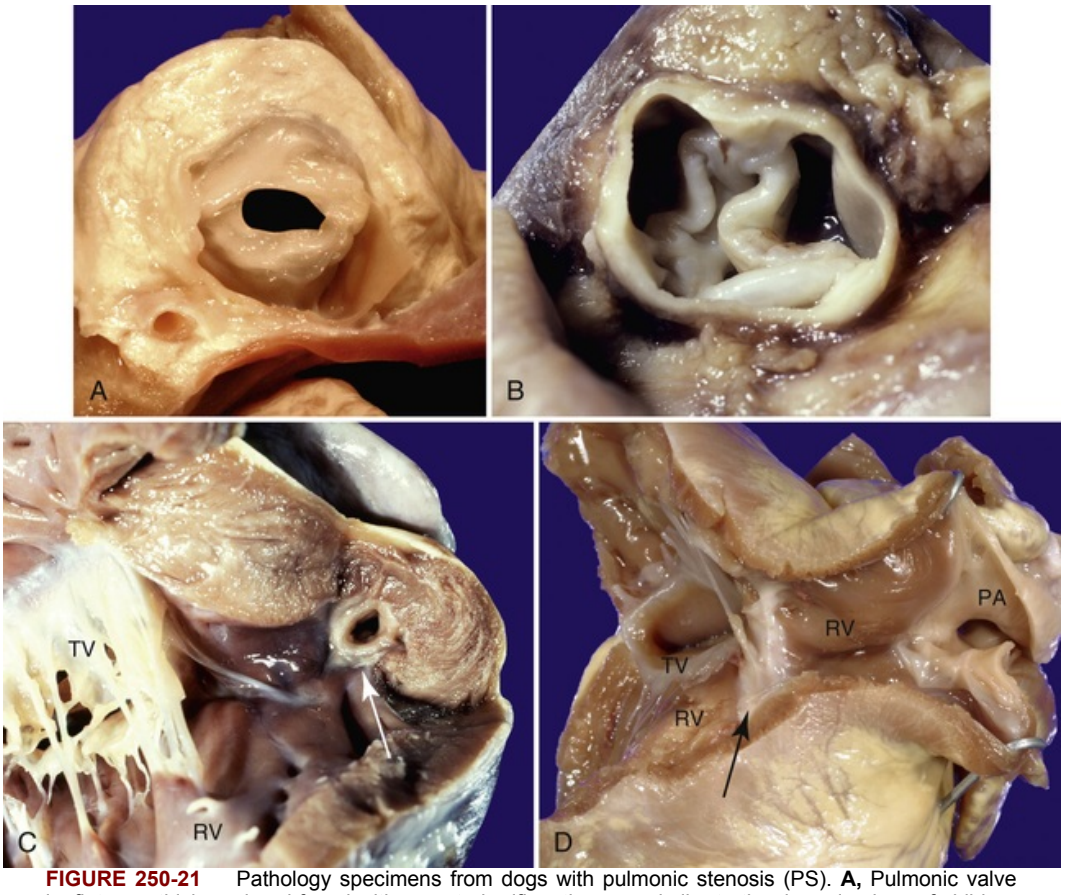

FIGURE 250-21 Pathology specimens from dogs with pulmonic stenosis (PS). **A,** Pulmonic valve leaflets are thickened and fused with a central orifice; they are similar to the domed valves of children with PS. **B,** Very thick (dysplastic) valve cusps in a dog with PS. **C,** Fibrous ring of subvalvular PS (arrow). **D,** Fibrous ring (arrow) in the infundibular area of the RV several centimeters below the pulmonic valve and pulmonary artery (PA). *TV,* Tricuspid valve.

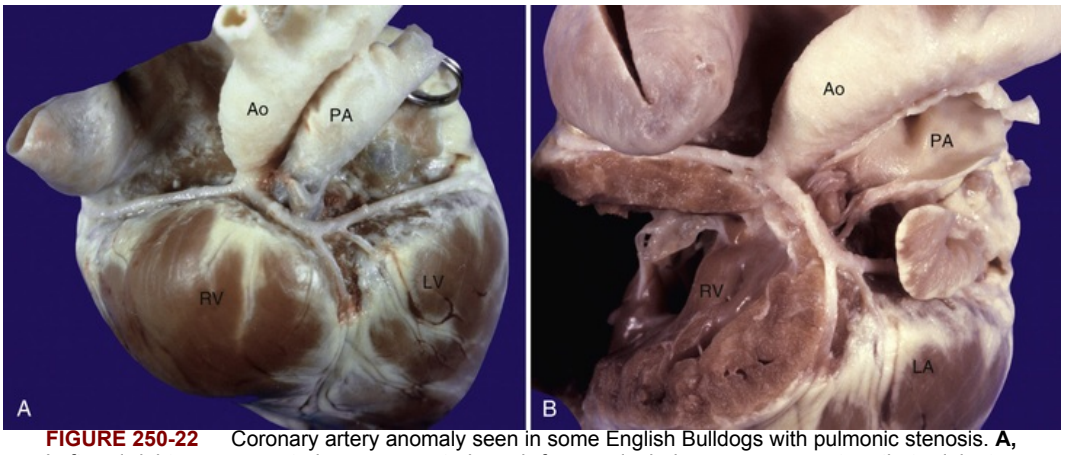

FIGURE 250-22 Coronary artery anomaly seen in some English Bulldogs with pulmonic stenosis. **A,** Left and right coronary arteries are seen to branch from a single large coronary artery that originates from the right aortic sinus of Valsalva. From this location, the left coronary artery encircles the RVOT just below the level of the pulmonic valve. **B,** Anterior walls of the pulmonary artery and RV have been removed to show the hypoplastic annulus, the diminutive proximal pulmonic artery (PA), and the crowded and thickened pulmonary valve leaflets. *Ao,* Aorta.

Increased resistance to systolic ejection results in concentric RV hypertrophy, which likely begins *in utero* and develops in proportion to the severity of the obstructing defect. While this compensatory response serves to normalize wall stress, it can have deleterious consequences on RV diastolic function as well as myocardial oxygen supply and demand. In some dogs with PS, secondary hypertrophy of the infundibular region of the RVOT contributes to a mainly dynamic outflow tract obstruction, particularly evident during exercise or stress. The presence of this additional mechanism of obstruction can complicate the clinical outcomes of surgical valvotomy or interventional balloon valvuloplasty. Other cardiac defects can complicate the physiology and alter the clinical presentation and prognosis of patients with PS. For example, PS and TVD can be a particularly injurious combination. Insofar as the volume of tricuspid regurgitation is a function of the size of the regurgitant orifice (severity of dysplasia) and the RV pressure (severity of PS), severe tricuspid regurgitation tends to develop in affected dogs, leading to intractable right-sided heart failure. Atrial fibrillation can also destabilize the patient with PS.

Meticulous ultrasonic examination, often using contrast echocardiography, will reveal that patent connections between the right and left heart occur in a substantial percentage of dogs with PS, and some dogs with severe PS become cyanotic as a result of right-to-left shunting through an ASD, PFO, or VSD. Some of these defects and consequences are discussed more thoroughly under the heading of ToF.

Pathophysiology

Obstruction to RV outflow increases resistance to ejection, causing a proportional increase in ventricular systolic pressure. Concentric hypertrophy of the RV develops in an attempt to normalize wall stress. During systole, blood ejected from the RV accelerates as it traverses the obstructive orifice. Blood flow velocity increases and becomes turbulent distal to the obstruction. A poststenotic dilation develops in the main pulmonary artery as the turbulent jet of blood decelerates and expends some of its kinetic energy against the vessel wall.

Concentric hypertrophy reduces RV diastolic compliance, impairs ventricular filling, and often results in elevated RA pressure. Tricuspid regurgitation from progressive ventricular dilation, valvular dysplasia, or a combination of these factors, can contribute to further increases in atrial pressure. As RA pressure approaches 15 mm Hg, jugular distension, ascites, pleural effusion, and other signs of right-sided CHF develop. Syncope secondary to transient hypotension is presumed to develop as a consequence of reduced cardiac output (secondary to bradycardia or worsening of a dynamic infundibular obstruction) and in combination with peripheral arteriolar vasodilation (especially with or in anticipation of exercise). Stimulation of mechanoreceptors in the pressure-overloaded RV might also trigger reflex bradycardia and vasodilation. Reduced right coronary blood flow has been documented in some dogs with PS and may contribute to the development of syncope due to arrhythmias, exercise intolerance, and myocardial failure. On rare occasions, severe septal hypertrophy and diminished LV size caused by PS results in dynamic LV outflow tract obstruction.[209]

Clinical Findings

PS is common in certain breeds of dogs including Beagles, Samoyeds, Chihuahuas, English Bulldogs, Miniature Schnauzers, Cocker Spaniels, Boykin Spaniels, Labrador Retrievers, Mastiffs, Chow Chows, Newfoundlands, Basset Hounds, and other terrier and spaniel breeds (see Table 250-1).[25,105,108,210] Miniature Doberman Pinschers also seem predisposed. Most dogs with PS are asymptomatic during the first year of life when the condition is usually discovered via detection of a heart murmur. Approximately 35% of dogs with severe disease demonstrate clinical signs, which can include exertional fatigue, syncope, or ascites.[211] Signs of right-sided CHF, such as ascites, are most often reported in dogs that are older.[204] In cats with severe PS, exertional dyspnea and lethargy may be present.[199] Cyanosis may be noted when PS is complicated by right-to-left shunting across a PFO or coexisting ASD or VSD.

The most prominent physical examination finding of PS is a systolic ejection murmur that is best heard over the left heart base and that often radiates dorsally. In some cases the murmur is heard well on the right cranial thorax. In dogs with concurrent severe pulmonic valvular insufficiency, the systolic ejection murmur is accompanied by a soft decrescendo diastolic murmur heard best just ventral to the pulmonic valve region. Less often a systolic ejection click is detected which presumably indicates a fused but mobile valve. A holosystolic murmur of tricuspid regurgitation may be noted over the right hemithorax. Large-amplitude jugular pulses may result either from a giant a wave caused by atrial contraction into the stiff RV or from cv waves indicating significant tricuspid regurgitation. Jugular venous distension and prominent jugular pulses are evident in most dogs with right heart failure and ascites. Peripheral arterial pulses are usually normal.

Evidence of RV enlargement is usually present on the ECG unless the lesion is very mild.[66,212,213] Right axis deviation, and deep S waves in leads I, II, III, aVF, and the lower left precordial chest leads (V2, V4) are common indicators of right heart enlargement (Figure 250-23). Thoracic radiographs typically show a prominent right heart and poststenotic dilation of the main pulmonary artery (Figure 250-24).[61,105,204,214] These changes are usually most evident on the dorsoventral view. Additional and more variable findings include dilation of the proximal left pulmonary artery, diminished size of the pulmonary vasculature, and enlargement of the caudal vena cava.

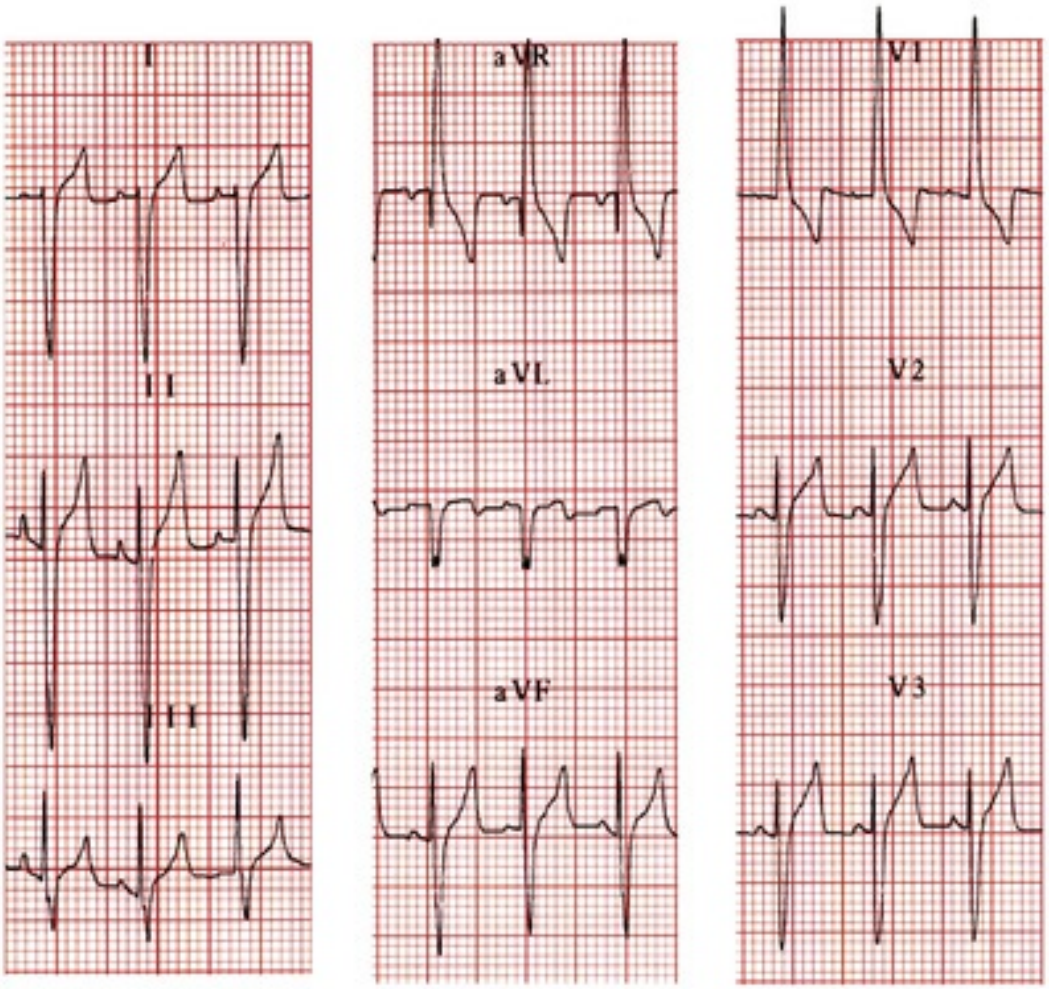

FIGURE 250-23 ECG from a dog with pulmonic stenosis showing a typical RV enlargement pattern. The mean electrical axis is shifted to the right (−130°), and there are prominent S waves in leads I, II, aVF, V2, and V3 (V4).

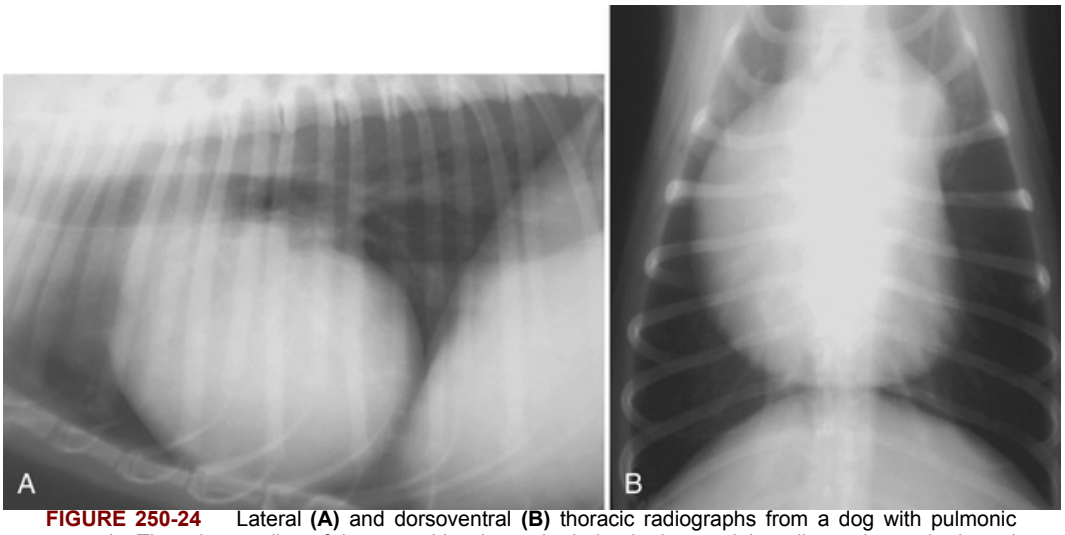

FIGURE 250-24 Lateral **(A)** and dorsoventral **(B)** thoracic radiographs from a dog with pulmonic stenosis. There is rounding of the sternal border and a bulge in the cranial cardiac waist on the lateral view. There is right heart enlargement and a bulge in the main PA segment on the dorsoventral view. The pulmonary vessels are diminished even in the absence of a right-to-left shunt.

Echocardiography is the most commonly used method for confirming a diagnosis of PS. M-mode and 2D imaging typically show concentric hypertrophy of the RV, increased prominence of the papillary muscles, deformity in the region of the obstruction(s), narrowing of the RVOT, varying degrees of RA enlargement, and poststenotic dilation of the main pulmonary artery (Figure 250-25).[76,215] Of the four cardiac valves, the pulmonic valve is usually the most difficult to visualize clearly by transthoracic echocardiography. Thus, it might be impossible to visualize the exact location and nature of the obstruction in some dogs without additional imaging modalities such as transesophageal echocardiography. It is often particularly difficult to identify a discrete subvalvular obstruction in close proximity to the pulmonic valve. The pulmonic valve leaflets are typically thickened, often fused, and appear to dome upwards into the pulmonary artery during systole (see Figure 250-25). The distal edges of the leaflets can appear partially tethered to the pulmonary artery wall, creating an hourglass appearance relative to the sinuses. This is not supravalvular stenosis *per se*, but does indicate a supravalvular component to the stenotic, dysplastic valve. In comparison, isolated supravalvular obstruction with otherwise-normal pulmonic valves is considered rare. When present, hypoplasia of the pulmonic valve annulus can further obscure the valve anatomy and confound the treatment. Color flow Doppler echocardiography is useful in establishing the anatomic location of the obstruction, as a region of flow acceleration changes to a turbulent, high-velocity jet that can usually be seen emerging just distal to the obstructive orifice (see Figure 250-25). Careful inspection of the coronary artery anatomy, especially as these vessels arise from the aortic sinuses, can help identify cases of coronary artery anomalies. This is particularly important with subvalvular PS in Boxers and English Bulldogs (Figure 250-26). Mild to moderate pulmonic valve insufficiency is also apparent in many dogs affected with valvular PS.

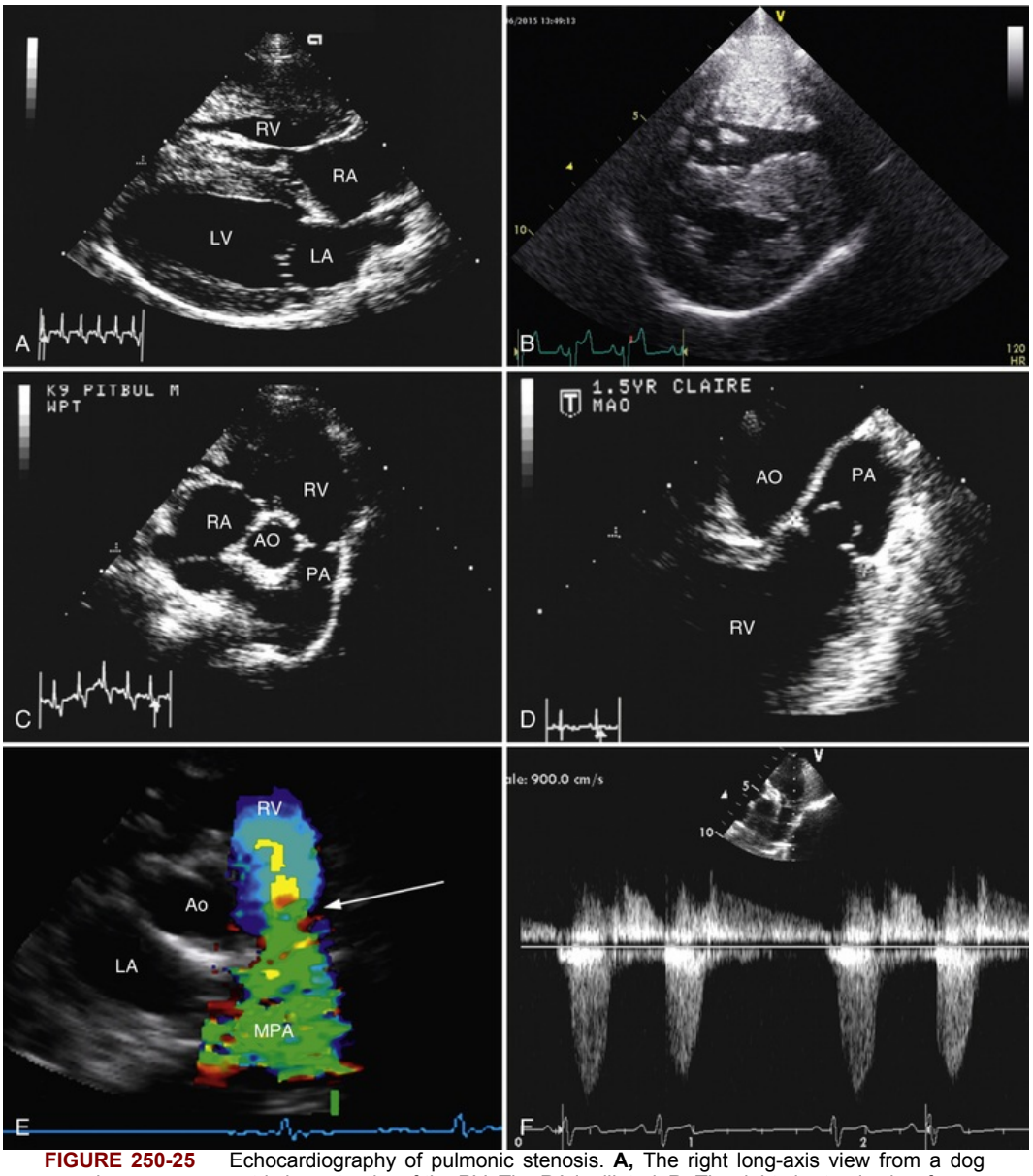

FIGURE 250-25 Echocardiography of pulmonic stenosis. **A,** The right long-axis view from a dog reveals severe concentric hypertrophy of the RV. The RA is dilated. **B,** The right short-axis view from a dog shows flattening of the interventricular septum and RV concentric hypertrophy caused by pressure overload. **C,** The right short-axis view of the heart base from a dog with valvular PS shows thickened pulmonic valves. There is a poststenotic dilation of the pulmonary artery (PA). **D,** Transesophageal ultrasound of a young Rottweiler with valvular PS. The pulmonic valve leaflets can be seen doming into the PA during systole. **E,** The color flow Doppler study in a dog shows high velocity and turbulent blood flow moving from the RV through the stenosis (arrow) and into the main pulmonary artery (MPA). **F,** A continuous-wave Doppler tracing obtained from a view similar to **E** shows high-velocity (5.0 m/s) systolic flow through the obstruction. The presence of pulmonic insufficiency is also noted during diastole. *Ao,* Aorta; *RA,* right atrium; *RV,* right ventricle.

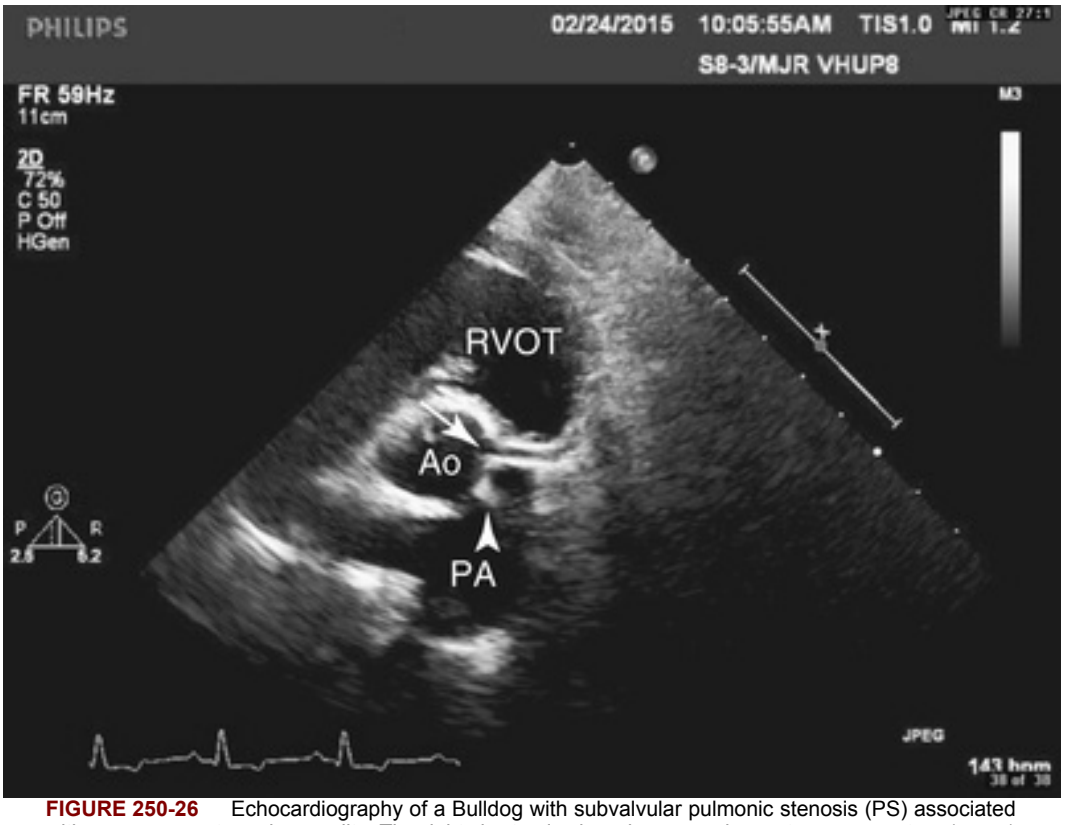

FIGURE 250-26 Echocardiography of a Bulldog with subvalvular pulmonic stenosis (PS) associated with a coronary artery abnormality. The right short-axis view shows an aberrant coronary artery (arrow) arising from the aorta (Ao) and extending along the subvalvular region of the right ventricular outflow tract (RVOT) just below the pulmonic valve (arrowhead). The main pulmonary artery (PA) shows a poststenotic dilation.

To accurately quantify the severity of the obstruction, the peak velocity of the blood flow jet must be recorded on a spectral Doppler tracing acquired with the continuous-wave Doppler beam in parallel alignment with the direction of flow (see Figure 250-25 and ch. 104). As a general rule, Doppler-derived gradients are 40% to 50% higher than the gradient measured during cardiac catheterization in an individual dog, mainly due to general anesthesia needed for the latter procedure.[216] In addition, hemodynamic studies typically indicate the severity of obstruction as a peak-to-peak pressure gradient, and such measures are almost always lower than the instantaneous peak pressure gradient calculated from Doppler measures of peak flow velocity.[75] Underestimation of the gradient in the awake patient is usually caused by excessive angle of incidence between the ultrasound beam and the pathologic flow pattern. Overestimation might be more common and is due to spectral recordings that are overpowered during ultrasound transmit and overgained during the receiving phase. The RV systolic pressure can be estimated by subtracting a normal PA systolic pressure (20 to 25 mm Hg) from the pressure gradient as PA pressure is invariably normal in cases of isolated PS. In dogs with both dynamic (infundibular) and fixed (valvular) stenosis, Doppler interrogation of the outflow tract and pulmonary artery can produce a tracing that displays the temporal and velocity relationship between the two components of the stenosis. Doppler interrogation of the right heart can also identify any coexisting tricuspid valve insufficiency, and RV systolic pressure can also be estimated using the Bernoulli relationship and assuming the RA pressure is 0 to 5 mm Hg (in dogs without CHF). This approach offers a quality control on the estimate obtained from RV outflow tract signal. Measuring the velocity of this regurgitant jet is particularly helpful for assessing the severity of the PS obstruction when it is not possible to attain proper alignment with flow through the outflow tract.

Angiocardiography is often performed just before balloon valvuloplasty (Video 250-16) or to clarify right heart anatomy in anticipation of surgery (see ch. 122). Such studies clearly demonstrate the anatomic location of the obstruction(s), the degree of RV hypertrophy, presence of tricuspid regurgitation, and the poststenotic dilation of the pulmonary artery. The angiographic features of valvular stenosis consist of any combination of the following: narrowing at the immediate base of the valve sinuses, asymmetrical valve sinuses, hypoplasia of the annulus or a valve sinus, thickening of individual valve leaflets producing a lucent filling defect,

narrowing of the contrast column with a central or asymmetric jet of contrast observed within a narrowed valve orifice, systolic doming of the valve (indicating fusion of the commissures), or supravalvular leaflet tethering (Figure 250-27).[203,204] Dynamic muscular obstruction of the RV infundibulum is often visible in dogs with PS (Figure 250-28). The term double-chambered right ventricle is applied when the RV is divided into a low-pressure region (the infundibulum) and a region of high pressure (the apex and inlet portion of the RV) by a muscular or fibromuscular ridge deep in the infundibulum (Figure 250-29). Some confusion can develop between this lesion and a subvalvular PS that is not immediately adjacent to the valve leaflets. LV angiography or coronary arteriography should be performed when abnormalities of the left heart or coronary circulation are suspected. Such studies must be performed whenever surgery or balloon valvuloplasty is contemplated in an English Bulldog or Boxer dog. Even in breeds at lower risk for coronary anomalies, the "follow through" levophase of the right ventriculogram can be instructive by identifying discrete right and left coronary arteries. Enlargement of the right coronary artery is an expected finding in all dogs with PS and well-developed RV hypertrophy.

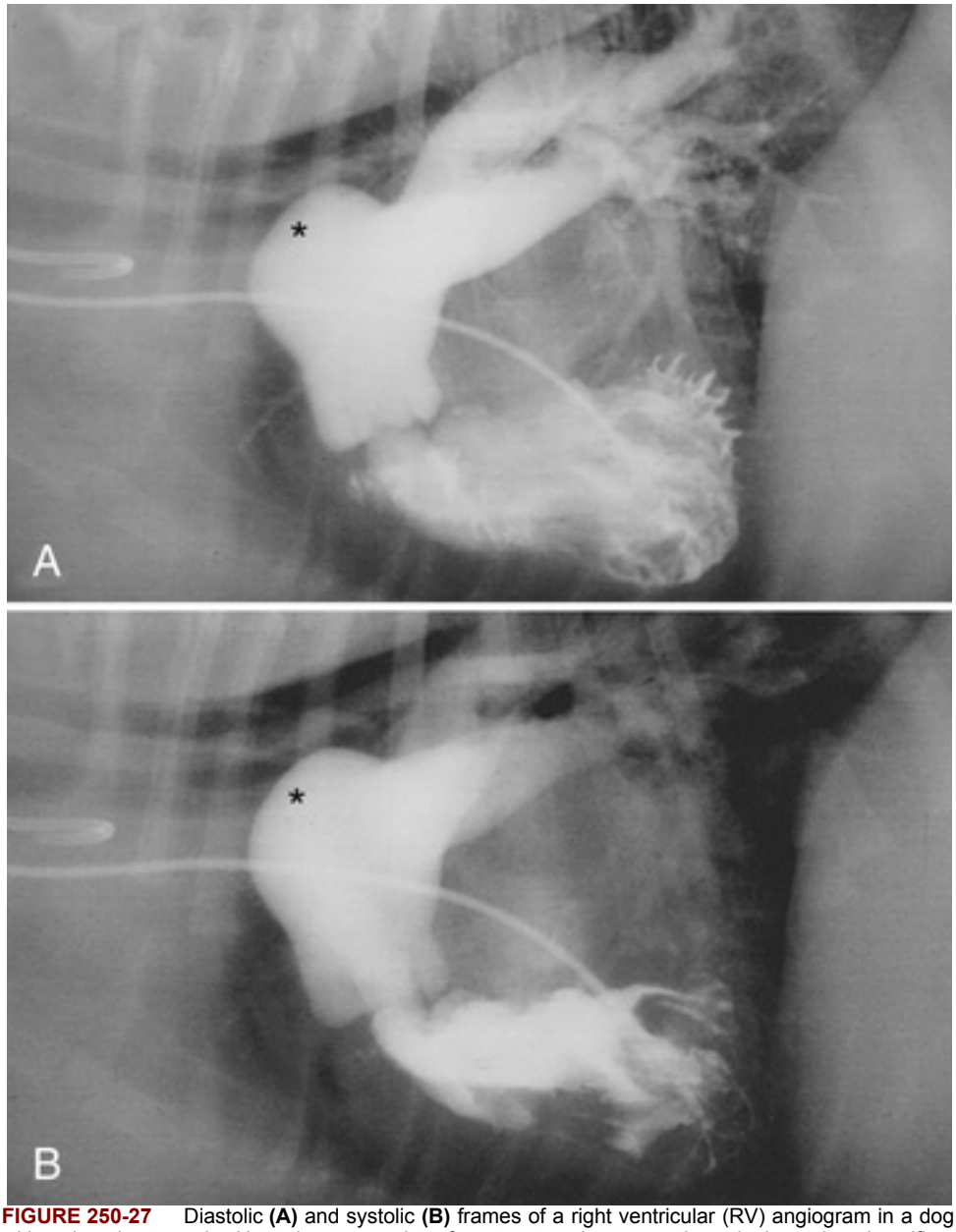

FIGURE 250-27 Diastolic **(A)** and systolic **(B)** frames of a right ventricular (RV) angiogram in a dog with pulmonic stenosis. Note the narrow jet of contrast as it passes through the pulmonic orifice. Poststenotic dilatation (asterisk) of the pulmonary artery is visible in both frames, as is hypertrophy of the RV wall and papillary muscles.

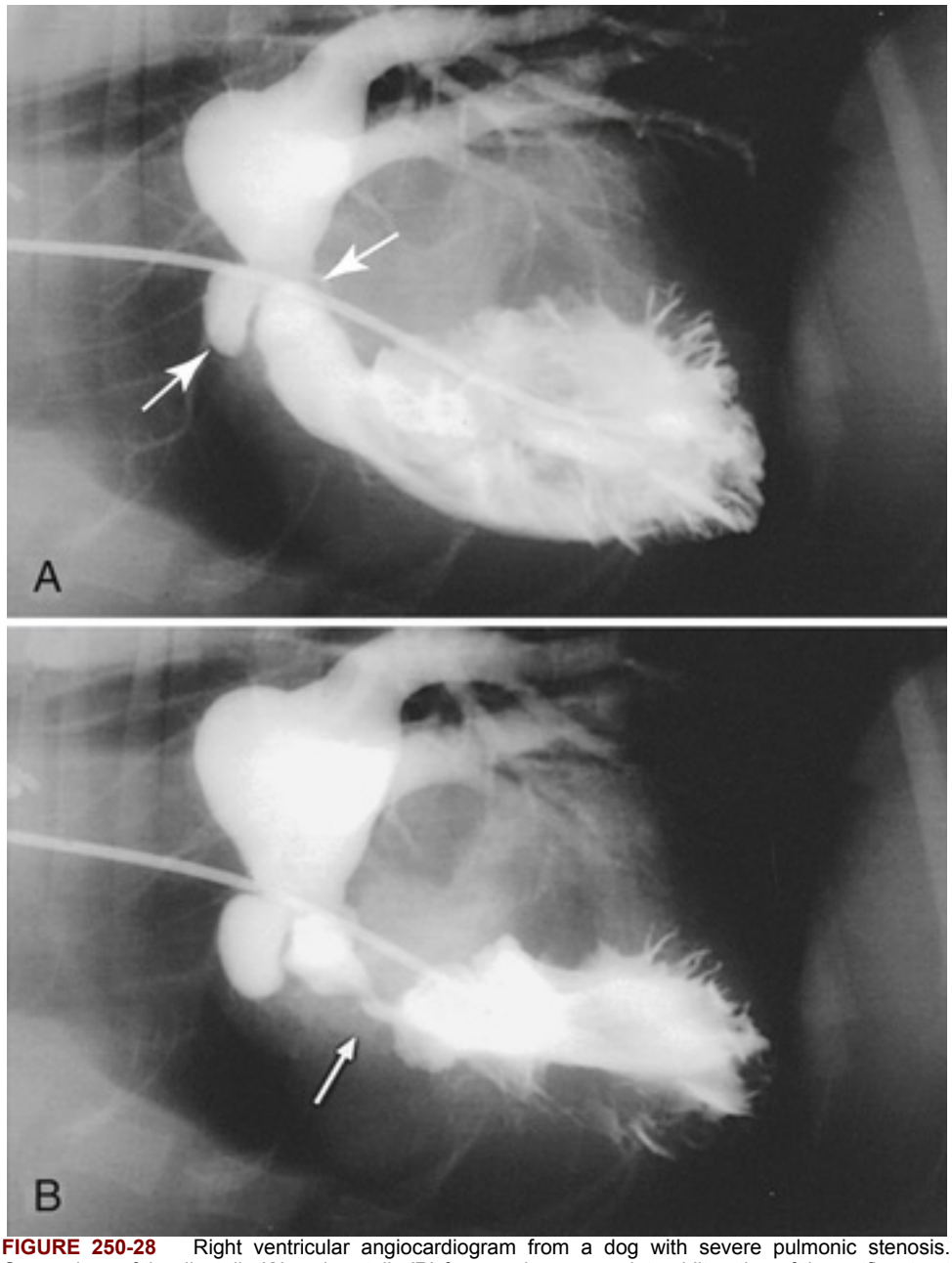

FIGURE 250-28 Right ventricular angiocardiogram from a dog with severe pulmonic stenosis. Comparison of the diastolic **(A)** and systolic **(B)** frames shows complete obliteration of the outflow tract caused by vigorous contraction of the hypertrophied infundibulum (arrow in frame B). Compare with Figure 250-27. Also note the distortion of the pulmonic valve sinuses (arrows in frame A).

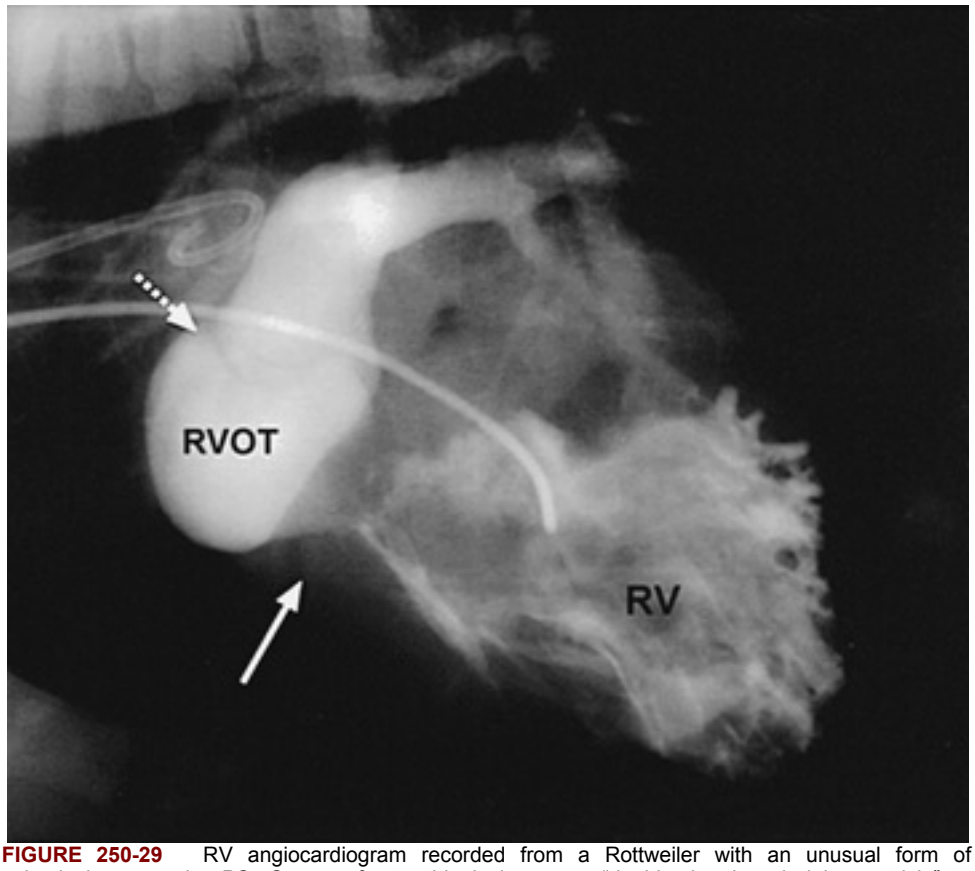

FIGURE 250-29 RV angiocardiogram recorded from a Rottweiler with an unusual form of subvalvular muscular PS. Some refer to this lesion as a "double-chambered right ventricle" to distinguish it from dynamic collapse of the hypertrophied infundibulum (see Figure 250-28). Others use the term only when the lesion is deeper within the RV, and some avoid the term altogether. Solid arrow indicates the muscular obstructing lesion in the RVOT. Dashed arrow indicates the location of the pulmonic valve.

Hemodynamic confirmation of outflow tract obstruction is accomplished by measuring a systolic pressure gradient across the lesion (see Figure 250-1). The severity of the obstruction is usually defined as the difference in peak systolic pressures measured above and below the obstruction (peak-to-peak pressure gradient). Inasmuch as the recorded gradient varies with the rate of flow across the obstruction, this measurement is greatly affected by myocardial contractility and the anesthetic regimen selected. Despite these limitations, the systolic pressure gradient has been used for dividing patients with PS into mild (<50 mm Hg), moderate (50 to 80 mm Hg) or severe (>80 mm Hg) categories.[204,217,218] A more accurate approach requires the measurement of cardiac output and calculation of the functional area of the constricted orifice (see ch. 104). Additional potential catheterization findings include a giant a wave in the RA, giant c-v wave in the setting of severe tricuspid regurgitation, or increased RV end-diastolic pressure due to vigorous RA contraction or development of RV failure.

Natural History

Precise criteria for establishing an accurate prognosis have not been developed for dogs and cats with PS. Clinical experience indicates that most dogs with mild and even moderate PS (Doppler derived gradient < 80 mm Hg) usually live normal or nearly normal lives, especially if no clinical signs are evident.[219] This generalization does not encompass those dogs with other complicating defects. The problem of concurrent TVD and its relation to developing heart failure has already been discussed. While systolic pressure gradients are not always predictive of clinical outcome, there appears to be a general correlation between pressure gradient and survival. Dogs with Doppler-derived RV-PA gradients > 125 mm Hg frequently develop secondary tricuspid regurgitation, heart failure, exertional syncope, or a serious cardiac arrhythmia (e.g., atrial fibrillation). When an ASD, PFO, or VSD coexists with PS, there is the potential for right-to-left shunting. If that shunting is pronounced, consequences include arterial hypoxemia, erythrocytosis, and serious debilitation. Sudden death occurs in some dogs with severe PS, but this occurrence is uncommon.

Clinical Management

Patients with uncomplicated and asymptomatic PS of mild or moderate severity usually do not require treatment. Serial echocardiographic examinations can be performed to monitor the degree of ventricular hypertrophy, development of secondary infundibular stenosis, and development of tricuspid regurgitation. Exercise restriction is usually unnecessary. Some dogs will develop more severe obstruction over time. Dogs with severe or symptomatic disease are candidates for surgery or balloon valvuloplasty (see ch. 122). No prospective trials investigating the effect of balloon valvuloplasty on survival have been performed. Data from retrospective studies suggest that balloon valvuloplasty in dogs with severe disease is associated with reduced risk for cardiac-related death.[219-221] The exact pressure gradient warranting intervention cannot be stated with certainty. Dogs with a Doppler gradient exceeding 100 to 125 mm Hg should be considered candidates for balloon valvuloplasty or surgery. Dogs with lesser gradients are also candidates for these procedures if they are symptomatic or have a large amount of tricuspid regurgitation. Intervention at a young age should be encouraged, as the development of overt CHF substantially lessens the chance for a successful outcome, regardless of the method of repair or palliation. Because of a high likelihood of heritability, even mildly affected dogs should not be bred.

The goals of intervention in dogs with severe PS are to abolish the systolic pressure gradient or reduce it to the mild range and to provide symptomatic relief in dogs experiencing clinical signs. For many years, surgery was the only available option for treating PS, and several surgical techniques have been advocated, including valve dilation, patch grafting, or the placement of a conduit from the RV to the pulmonary artery.[217,218,222-228] The open patch-graft technique, while challenging to perform, is a particularly versatile and cost-effective method for treating dogs with PS, particularly when there is a substantial subvalvular obstruction.[226-228] This technique is well-suited to the treatment of some defects not amenable to balloon valvuloplasty (e.g., dogs with muscular RVOT obstructions, double-chambered right ventricle, or severe hypoplasia of the pulmonic annulus). The patch-graft technique should not be performed in dogs with subvalvular PS associated with an anomalous coronary artery as severing of the artery will result in death.

Catheter-based percutaneous balloon valvuloplasty is a preferred alternative to surgery and should be recommended for dogs with valvular PS. This interventional catheterization procedure for PS is discussed in ch. 122. Successful reduction of the obstructive gradient by 50% or more has been reported in 75% to 80% of the dogs treated with this technique.[211,221,229,230] Retrospective analysis of 40 dogs that underwent balloon valvuloplasty indicated a 53% reduction in mortality as compared with 41 dogs that did not undergo the procedure.[220] Dogs with hypoplasia of the pulmonary annulus or anomalous development of the coronary arteries and subvalvular PS are at particular risk for serious complications of balloon valvuloplasty, including avulsion of the coronary artery or rupture of the pulmonary annulus.[231] Conservative balloon valvuloplasty using balloon sizes 0.6-1.0 times the diameter of the pulmonic valve annulus is reported in a small number of such cases, with variable results.[232]

Aortic Stenosis

Subvalvular aortic stenosis (SAS) is the most common congenital cardiac malformation in large breed dogs.[4,172,173,233-242] Most cases of SAS result from a fixed ridge or ring of fibrous tissue located in the LVOT, just below the aortic valve. SAS is a problematic disorder for several reasons. It is very difficult to diagnose in mildly affected dogs and it is difficult to treat when it is severe. The phenomenon of dynamic SAS is also being recognized with increasing frequency in dogs and cats with a variety of cardiac disorders, including fixed SAS, MVD, hypertrophic cardiomyopathy, and other conditions causing hypertrophy of the interventricular septum and reduced LV size (i.e., PS, ToF).[243] Bull Terriers are predisposed to valvular aortic stenosis wherein the leaflets are thickened and the aortic valve annulus is mildly hypoplastic. Normal Boxers also demonstrate aortic annulus diameters that are smaller than those of other breeds of dogs, and this confounds diagnosis of mild disease in this breed.[244] Mild AS caused by a bicuspid valve occurs on rare occasions.[169] Fixed aortic stenosis has been described in a small number of cats,[32-34,245] including one case of supravalvular stenosis.[246]

Pathology and Pathogenesis

SAS has been most extensively studied in the Newfoundland dog. Breeding studies in this and other breeds have established a genetic basis for the perpetuation of SAS.[2,247-249] An autosomal dominant abnormality in

the PICALM gene has been associated with SAS in Newfoundland dogs,[12] although these data might require further validation.[250] An autosomal recessive mode of inheritance is reported in the Dogue de Bordeaux.[180] Thus, it is likely that SAS in the dog can be the result of different genetic abnormalities. The breeding colony studies of Pyle and Patterson further indicate that the obstruction may not be present at birth, but instead develops during the first 4 to 8 weeks of life.[2,235-237,247] This progression has particular significance relative to the identification of cardiac murmurs in pups of breeds known to be at risk for SAS. Recent work in Golden Retriever dogs has suggested that an aortopathy or narrow, abnormal septal-aortic angle might play a role in the development or progression of SAS in dogs, a situation previously reported in children.[251]

The lesions of SAS in Newfoundlands have been described in postmortem studies as mild (grade 1), consisting of "small, whitish, slightly raised nodules on the endocardial surface of the ventricular septum immediately below the aortic valve"; moderate (grade 2), consisting of a "narrow ridge of whitish, thickened endocardium" extending partially about the LVOT; and severe (grade 3), consisting of "a fibrous band, ridge, or collar completely encircling the LVOT just below the aortic valve."[2,247] This ring is raised above the endocardium, extends to—and may involve—the cranioventral leaflet of the mitral valve and the base of the aortic valves (Figure 250-30). The stenotic ring consists of loosely arranged reticular fibers, mucopolysaccharide ground substance, and elastic fibers. Discrete bundles of collagen and even cartilage are found in advanced lesions.[247] Cardiac catheterization of dogs with grade 1 lesions failed to reliably detect the lesion that is visible at postmortem, whereas grade 2 lesions often were associated with soft cardiac murmurs and minimal systolic pressure gradients. As evidenced by these studies and discussed below, clinical detection of mild SAS is often quite difficult, and genetic counseling may be fraught with error. A variety of cardiac abnormalities can accompany SAS, most notably MVD, PDA, and a host of aortic arch abnormalities. The valvular lesions seen in Bull Terrier dogs, including myxomatous degeneration and cartilaginous metaplasia of the valve leaflets, resemble those in humans with calcific valvular stenosis.[252] Most dogs with SAS exhibit some degree of aortic dilation distal to the stenosis. This poststenotic dilation can range from trivial to severe and can extend into the arch vessels. The degree of poststenotic dilatation is often greater with severe obstructions, but this relationship is quite variable.

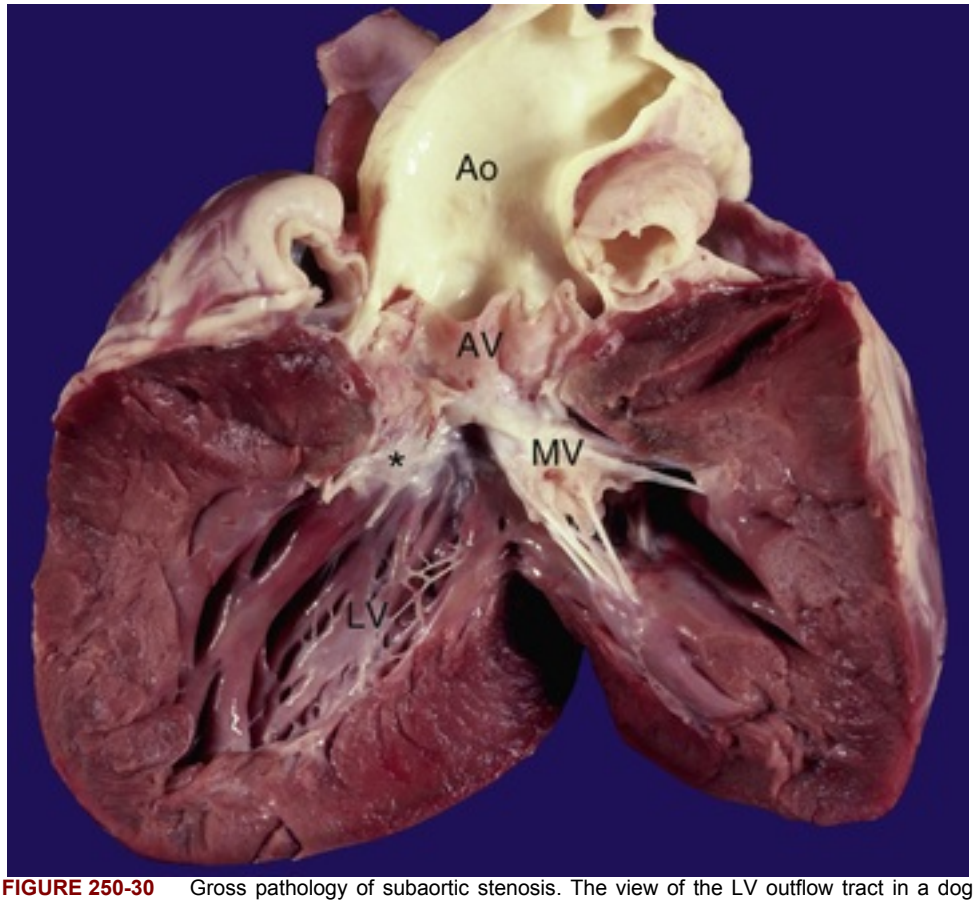

FIGURE 250-30 Gross pathology of subaortic stenosis. The view of the LV outflow tract in a dog

shows the presence of a circumferential ring of fibrous tissue directly below the aortic valve (AV). A ridge of thick fibrous tissue is seen just below the aortic valve and extending onto the ventricular septum (asterisk). The ventricular walls are markedly thickened. A thickened anterior mitral valve (MV) leaflet and associated chordae tendineae are seen to the right of the lesion. A poststenotic dilation of the proximal portion of the aorta (Ao) is noted.

In some affected dogs, the pathologic findings diverge from the classical description. The anterior mitral valve leaflet is thickened in apposition to a septal plaque of endocardial fibrosis where the mitral leaflet impacts the IVS as a consequence of dynamic obstruction.[253] Instead of a fibrous collar, the septum is uniformly hypertrophied or a broad fibromuscular ridge, arising from the base of the interventricular septum, protrudes into the LVOT. Malformed, malpositioned, or misaligned papillary muscles, thickened chordae tendineae, and elongated or distorted mitral leaflets contribute to the development of obstruction.[254] Mitral valve malformations are also associated with SAS in cats, although the disorder is relatively rare in this species.[245,255] In some cats, relatively long, tunnel-like obstructions have been observed.

Concentric hypertrophy of the LV develops in dogs with valvular, fixed, or dynamic SAS more or less in proportion to the severity of the outflow obstruction, albeit that the correlation between wall thickness and the magnitude of the measured gradient is often poor.[77] Structural and functional abnormalities of the LV[78] and coronary circulation are well documented in dogs with SAS.[235,237] Abnormal coronary flow has also been measured in the larger, extramural arteries with diminished baseline diastolic flow and reversal of coronary flow during systole.[105,237] Focal areas of myocardial infarction and fibrosis are commonly observed in the papillary muscles and subendocardium of dogs with severe SAS, often in association with abnormal intramural coronary arteries. Histologic changes of the intramural coronary arteries in these locations include intimal proliferation of connective tissue and smooth muscle, and medial degeneration. These changes are presumably related to the high wall tension found in this condition, and their genesis may be related to the elaboration of angiotensin II or other biochemical mediators of hypertrophy and remodeling.[256-258] Moreover, these arterial lesions may be important in the genesis of malignant ventricular arrhythmias and sudden death.

Pathophysiology

Obstruction to LV outflow causes an increase in LV systolic pressure and concentric hypertrophy. Consequent to fixed obstruction, the rate of LV ejection is delayed, causing a diminished and late-rising arterial pulse (parvus et tardus). High velocity and turbulent flow across the stenotic area produces the systolic ejection murmur and contributes to poststenotic dilation usually involving the ascending aorta, aortic arch, and brachiocephalic artery. Left atrial hypertrophy develops as a consequence of impaired relaxation and reduced compliance of the hypertrophied LV. Mild aortic regurgitation is commonly present, presumably because of thickening of the valve leaflets or dilation of the ascending aorta. Damage to the aortic valvular endothelium (jet lesions) predisposes dogs with SAS to infective endocarditis.[259,260] Dogs with severe SAS can develop left-sided CHF from myocardial failure, diastolic dysfunction, mitral regurgitation, atrial fibrillation, or a combination of these factors. More often, exertional syncope or sudden death is reported, presumably as a result of myocardial ischemia and the development of malignant ventricular arrhythmias. Congruous with this finding is that exercise ECGs can reveal significant, labile ST-segment depression. In some dogs, exertional collapse might be caused by hypotension precipitated by exercise-induced increases in LV pressure, activation of ventricular mechanoreceptors, and inappropriate bradycardia or vasodilation.[261]

Clinical Findings

Congenital SAS is common in many canine breeds (see Table 250-1), especially in Newfoundlands, Boxers, Rottweilers, Golden Retrievers, and German Shepherd Dogs.[167,262] Valvular AS is common only in Bull Terriers. The clinical findings of SAS vary with the severity of the obstruction and the presence of concurrent cardiac defects. Clinical findings in pups with mild SAS are often subtle and easily overlooked. Asymptomatic dogs have a soft to moderately intense ejection murmur that can easily be confused with an innocent or functional heart murmur.[263] More sophisticated time-frequency or heart rate turbulence analysis of soft murmurs may provide clues as to which murmurs are associated with mild disease.[264,265] Insofar as the lesions of SAS can develop during the postnatal period, the murmur may become increasingly prominent during the first 6 months of life. In rapidly growing breeds, such as the Newfoundland, the grading of SAS severity in a puppy should be reserved until the dog has attained nearly full maturity, because progression

from mild to severe has been observed during this interval.[247,251,266] Severely affected dogs can present with exertional fatigue, syncope, or left-sided CHF, but the vast majority of dogs are asymptomatic. In dogs with severe disease, a common client observation is that the affected dog is smaller than its healthy littermates. Sudden death, without premonitory signs, is common in severely affected dogs aged 1-3 years.[260]

Recognition of severe SAS is not difficult, as the systolic murmur generally becomes louder and later-peaking-to-holosystolic when the obstruction is more severe.[267] The murmur of severe SAS is usually best heard at the left heart base, recognizing that in some dogs, the systolic murmur is equally loud or louder at the right cardiac base, presumably from radiation into the ascending aorta. The murmur of aortic stenosis often radiates up the carotid arteries and can be auscultated over the ventral cervical region. Frequently, the murmur projects towards the apex and can be confused with mitral regurgitation. In fact, a substantial percentage of dogs with SAS also have mitral regurgitation, but these murmurs are usually difficult to separate given their similar timing and overlapping areas of maximal intensity. Despite the frequent occurrence of aortic regurgitation captured by Doppler echocardiography, a soft diastolic murmur secondary to aortic valve insufficiency is infrequently detected. Other physical abnormalities detected in moderately to severely affected dogs include a diminished and late rising arterial pulse and a prominent LV precordial impulse arising from the hypertrophied LV.

The ECG is often normal, but may, in severe cases, indicate LV hypertrophy (increased R wave amplitude in leads II, III, aVF, V2, V4). Depression of the ST segment and T wave changes suggest secondary repolarization changes or myocardial ischemia; the latter is especially likely when ST changes are precipitated by exercise or occur in the company of ventricular ectopia (Figure 250-31). Compared with the resting ECG, 24-hour ambulatory (Holter) ECG recordings offer a more sensitive method of detecting intermittent or exercise-induced ventricular arrhythmia and ST segment changes. The severity of arrhythmias detected in this fashion often corresponds to the severity of disease.[268]

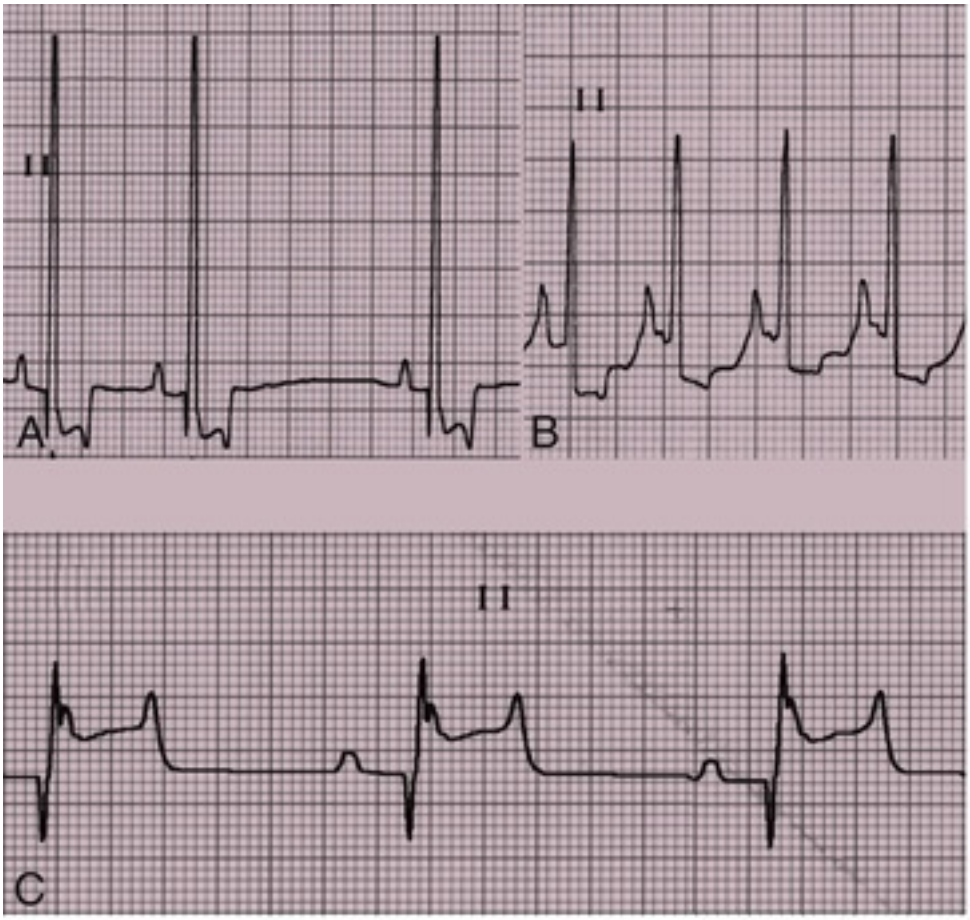

FIGURE 250-31 ECGs demonstrating ST segment depression **(A, B)** and elevation **(C)** in three dogs with severe SAS are suggestive of myocardial ischemia. Sensitivity, 10 mm/mV. **A,** Tracing from a 1-year-old Golden Retriever at 25 mm/sec. **B,** This 6-month-old Newfoundland dog collapsed and died suddenly 1 hour after the ECG was performed, 25 mm/sec. **C,** Tracing from a 1-year-old Golden

Retriever, 50 mm/sec.

Thoracic radiographs can be normal or may indicate LV hypertrophy.[61,105,214] Poststenotic dilation of the horizontally inclined ascending aorta causes loss of the cranial waist on the lateral radiograph and widening of the mediastinum on the dorsoventral radiograph in severe cases (Figure 250-32). Mild LA enlargement is common in dogs with moderate or severe SAS but marked LA enlargement suggests concurrent mitral regurgitation, LV failure or concurrent left-to-right shunt. Although unnecessary for the diagnosis, angiocardiography is useful for delineating the site and geometry of obstruction, which is usually most evident in the ventral aspect of the outflow tract when viewed on the lateral projection (Figure 250-33 and Video 250-17). Other angiographic findings include poststenotic dilation of the ascending aorta, enlargement of the left coronary artery and its extramural branches, a small LV cavity, and hypertrophy of the papillary muscles and LV wall. Supravalvular aortic injections can be performed to identify insufficiency of the aortic valve, but Doppler echocardiography is a more sensitive technique. Hemodynamic recordings document the presence and severity of a systolic pressure gradient across the obstruction (Figure 250-34). Such recordings are also useful for detecting elevated LV end-diastolic pressure and impending CHF.[105,269] Pressure gradients recorded from dogs with SAS are depressed by general anesthesia to approximately 40% to 50% of those measured in the unanesthetized state as a result of diminished flow (stroke volume).[270]

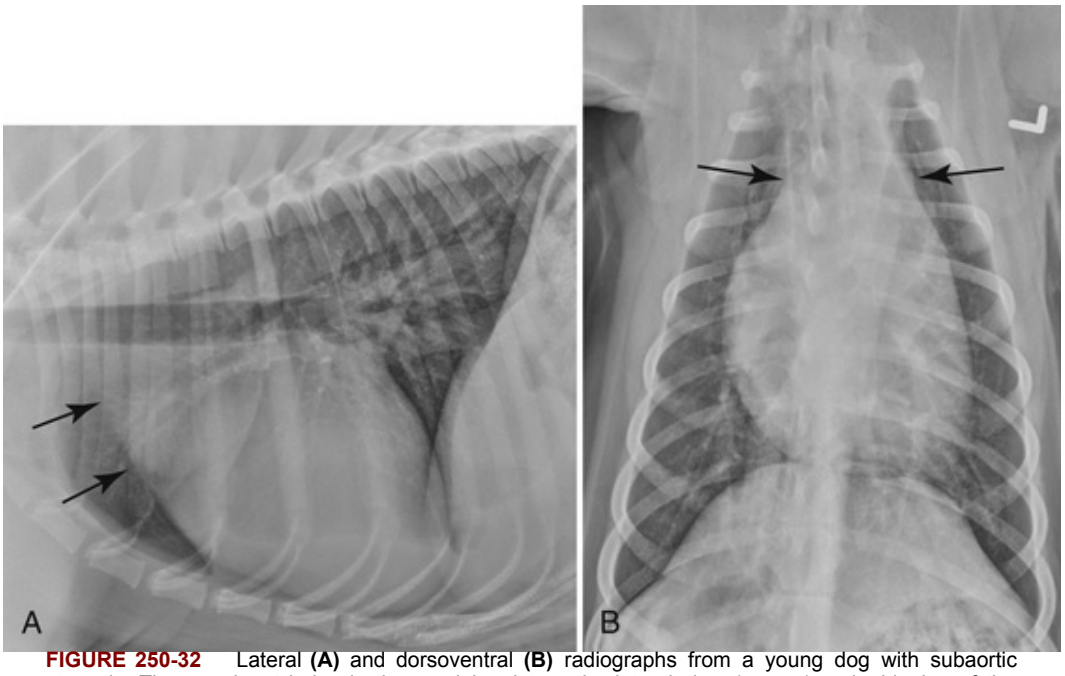

FIGURE 250-32 Lateral **(A)** and dorsoventral **(B)** radiographs from a young dog with subaortic stenosis. The prominent bulge in the cranial waist on the lateral view (arrows) and widening of the cranial mediastinum on the dorsoventral view (arrows) are consistent with a poststenotic dilation of the ascending aorta.

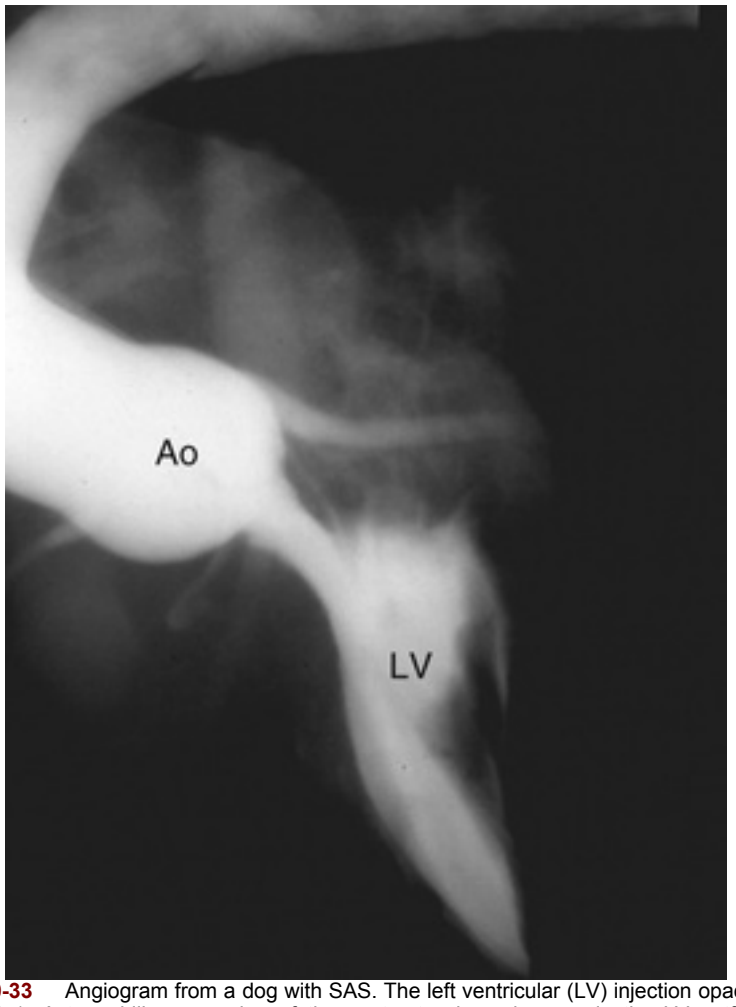

FIGURE 250-33 Angiogram from a dog with SAS. The left ventricular (LV) injection opacifies the LV and aorta (Ao). A tunnel-like narrowing of the contrast column is seen in the LV outflow tract. A prominent left circumflex coronary artery is also seen.

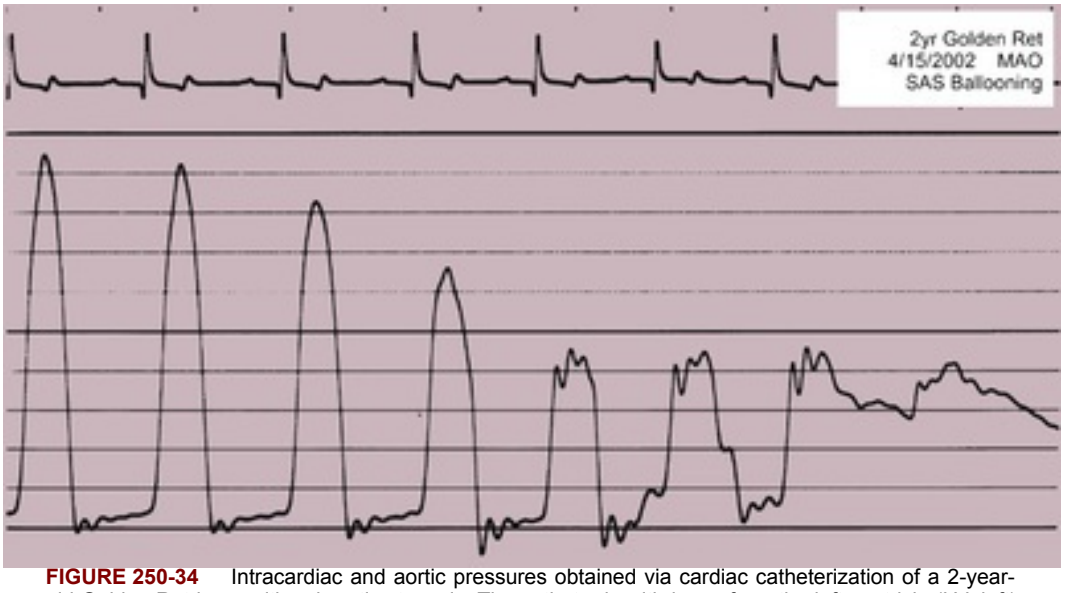

FIGURE 250-34 Intracardiac and aortic pressures obtained via cardiac catheterization of a 2-year-old Golden Retriever with subaortic stenosis. The catheter is withdrawn from the left ventricle (LV; left) into the left ventricular outflow tract (LVOT; center) and into the ascending aorta (right). A 100 mm Hg systolic pressure gradient is demonstrated between the LV and LVOT, indicating the subvalvular

location of the obstruction. (Catheter motion artifact superimposed on the outflow tract and aortic recordings.)

Moderate to severe SAS is easily confirmed by 2D and Doppler echocardiography (see ch. 104). Typical findings include concentric LV hypertrophy, a subvalvular obstructing lesion, reduced LV orifice area, and poststenotic dilation of the aorta (Figure 250-35).[71,76,201,215,239] In Golden Retriever dogs, a more acute angle between the ascending aorta and IVS (aortoseptal angle) has been associated with increased LV outflow tract velocities and development of SAS (Figure 250-36).[251] The papillary muscles and endocardial surface of the ventricular myocardium often appear hyperechoic in severe disease, presumably as a result of myocardial ischemia and replacement fibrosis or calcification. Structural changes in the mitral valve can often be appreciated and abnormal motion of the mitral valve (systolic anterior motion, SAM) is evident in those cases with coexisting mitral valve dysplasia and dynamic obstruction.[253] Spectral Doppler interrogation of the LVOT is used to assess disease severity by measuring the peak velocity of flow in the LVOT.[271] Such measures show excellent correlation with invasive measures (see Figure 250-35).[75] Doppler measurements can be made from a variety of parasternal or subcostal imaging windows, although velocities obtained from the subcostal position generally display the highest values.[272] While Doppler-estimated pressure gradients between 80 and 100 mm Hg (peak flow velocities ranging from 4.5 to 5.0 m/s) are used for indicating moderate LVOT obstruction, and higher velocities used for indicating severe obstructions, these designations are somewhat arbitrary. Doppler-derived pressure gradients are affected by the amount of flow (stroke volume) crossing the obstructive orifice, and may either overestimate the severity of obstruction if cardiac output is high (e.g., in dogs that are stressed or excited, or affected with a PDA), or underestimate the severity if flow is subnormal (e.g., in dogs under anesthesia or with concurrent myocardial failure). In these cases, indexing the gradient to stroke volume or some related measure or simple estimation of the two-dimensional orifice area may provide a better estimate of disease severity.[77,201,273] Color flow Doppler recordings are valuable for detecting and estimating the severity of coexisting aortic or mitral valve insufficiency, although focusing solely on jet area is likely to result in overestimation of severity.[202]

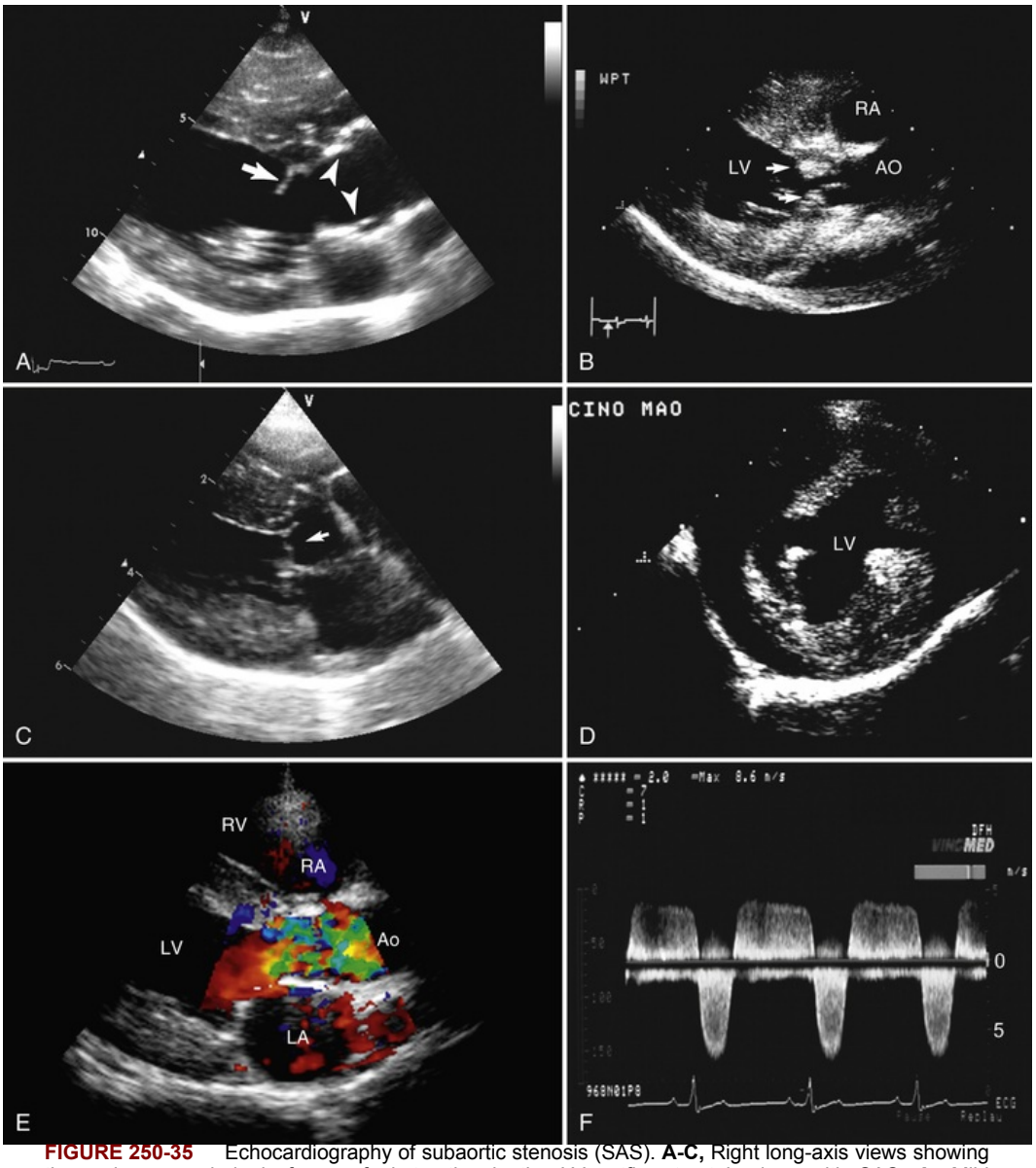

FIGURE 250-35 Echocardiography of subaortic stenosis (SAS). **A-C,** Right long-axis views showing the various morphologic forms of obstruction in the LV outflow tract in dogs with SAS. **A,** Mild membranous SAS in a 5-year-old Rottweiler. A thin membranous flap of tissue extends from the interventricular septum. No appreciable LV concentric hypertrophy is noted. The open aortic valve leaflets are indicated by the arrowheads. **B,** Severe tunnel-like SAS in a 4-year-old Golden Retriever. Two ridges of hyperechoic tissue are present at the base of the aortic valve (arrows). The LV is hypertrophied, with a hyperechoic endocardial surface. **C,** Dynamic SAS in a Poodle. Systolic anterior motion of the mitral valve is seen projecting into the left ventricular outflow tract (arrow). The LV shows concentric hypertrophy. The blood flow velocity across the obstruction was in excess of 5.5 m/s, indicating a severe degree of pressure overload to the LV. **D,** The right short-axis view from a 3-month-old mixed-breed dog shows LV concentric hypertrophy and marked hyperechogenicity of the subendocardial tissue and papillary muscles. This finding is thought to represent areas of myocardial ischemia and replacement fibrosis. **E,** The right long-axis color flow Doppler study from a dog with SAS reveals high velocity and turbulent blood flow in the LVOT and aorta (Ao). **F,** The continuous wave Doppler tracing from the left apical view in a dog with severe SAS shows a peak systolic velocity of 6.5 m/s, indicating a pressure gradient of 169 mm Hg across the obstruction. The presence of aortic insufficiency is also detected.

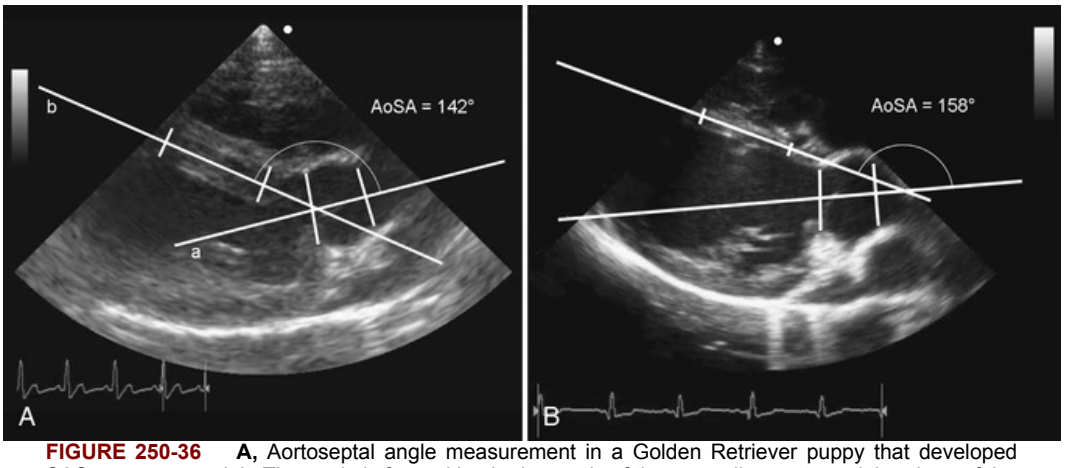

FIGURE 250-36 **A,** Aortoseptal angle measurement in a Golden Retriever puppy that developed SAS as a young adult. The angle is formed by the long axis of the ascending aorta and the plane of the IVS. The midline axis of the aortic root is constructed by bisecting the aortic root at the level of the annulus and above the sinotubular junction (line a). The midline axis of the IVS is constructed by bisecting the septum at the level of the mitral leaflet tips and 2 cm apically from that point (line b). AoSA = 142°. **B,** Aortoseptal angle measurement in a normal Golden Retriever puppy. AoSA = 158°. *AoSA,* Aortoseptal angle; *IVS,* interventricular septum; *SAS,* subaortic stenosis. (From Belanger MC, Cote E, Beauchamp G: Association between aortoseptal angle in Golden Retriever puppies and subaortic stenosis in adulthood. *J Vet Intern Med* 28:1498-1503, 2014.)

Antemortem detection of the mildest forms of SAS by auscultation, angiography, or echocardiography is often not achievable and the precise outflow velocity at which the diagnosis of AS becomes both sensitive and specific is controversial and undefined by any gold standard. Dogs with subtle abnormalities (i.e., grade 1 lesions as described previously), escape detection by even the most accomplished examiners. Even in dogs with grade 2 lesions, segregation from normal dogs solely on the basis of LV velocities is problematic. An upper limit for aortic velocity in normal dogs has been reported but is not well established for differing breeds and examination conditions.[274] The averaged, maximum pulsed-wave aortic velocity in the authors' laboratory for healthy dogs without any cardiac murmur is 1.7 m/s, and this is similar to values reported in a study of healthy dogs without cardiac murmurs in which maximal LVOT velocities were <1.8 m/s when measured from the left apex (upper limit of the 95% confidence interval).[275] Velocities recorded using CW Doppler from the subcostal position are minimally faster but generally <2 m/sec in dogs without murmurs. However, LVOT ejection velocities in excess of these values are often recorded in dogs with soft ejection murmurs but with no 2D evidence of discrete outflow tract obstruction. Such velocities are especially common in breeds characterized by slightly diminished outflow tract dimensions (Boxers and Bull Terriers). A diagnosis of mild SAS is more secure once averaged maximal velocity measurements exceed 2.3 to 2.4 m/s and are accompanied by other findings, particularly: disturbed flow on PW Doppler; an anatomic lesion on 2D imaging; holodiastolic aortic regurgitation; and when flow velocity abruptly accelerates over a discrete region in the LVOT. Some investigators consider an echocardiographic LV outflow tract area indexed to body surface area <1.46 cm/m^2 or aortoseptal angle <145° as indicators of mild or developing SAS in Golden Retriever pups.[201,251] The inability to reliably detect mild SAS is a great source of frustration when attempting to provide genetic counseling to breeders, who are interested in reducing the incidence of disease.

Natural History

Severe SAS is a discouraging condition, since many affected dogs die prematurely. In a retrospective survey of 96 dogs with SAS, 21 died suddenly, most often during the first 3 years of life.[260] Eleven dogs developed endocarditis and/or CHF, and 32 dogs evidenced exercise intolerance or syncope. Dogs with minimal ventricular hypertrophy, mild ventricular outflow obstruction, and a maximal Doppler pressure gradient <50 mm Hg are more likely to live normal lives, whereas dogs with pressure gradients >125-130 mm Hg are very likely to develop serious complications or to experience sudden death.[276] Complicating factors that contribute to an adverse outcome include: progressive LV diastolic and systolic dysfunction, mitral regurgitation, aortic regurgitation, aortic valve endocarditis, and atrial fibrillation.[266,277,278] Sudden death is most likely to occur during or shortly after vigorous activity.

Clinical Management

Dogs with mild SAS are not treated other than administration of prophylactic antibiotics during periods of anticipated bacteremia, such as during dental procedures, surgery, or whenever a concurrent infectious disease is suspected. This practice remains common despite the fact that the efficacy of prophylactic antibiotics for reducing the risk of infective endocarditis in dogs with SAS has not been definitively established.[278] A number of treatment options can be considered for dogs with moderate to severe SAS, but most are of uncertain value. Open resection of the obstructing lesion during cardiopulmonary bypass clearly offers the best opportunity to substantially and permanently reduce the systolic pressure gradient[279,280]; however, an otherwise successful procedure does not appear to substantially alter the prevalence of sudden death.[280] Other surgical procedures employed to dilate or bypass the obstruction have either failed to achieve a sustained reduction of the systolic pressure gradient or they entail an unacceptable risk of complications.[281,282] Moreover, these remedies are usually limited in their availability and prohibitively expensive to be considered practical options.

Balloon dilation of SAS has been attempted in dogs as an alternative to surgery or lifelong medical therapy. On average, catheter-based balloon dilation is able to reduce the severity of SAS obstruction in dogs by 50%[283]; however, this short-term benefit is attenuated in some (and perhaps a majority) of dogs over time,[271] and balloon valvuloplasty has not been shown to improve survival versus medical therapy with atenolol.[284] The use of "cutting" balloons that score or lacerate the stenotic lesion followed by dilation with high-pressure balloons has been described (see ch. 122) but whether this procedure produces superior outcomes over traditional balloon dilation is thus far unknown.[285] Balloon dilation of SAS is more challenging than balloon valvuloplasty of PS. Life-threatening complications of ballooning include fatal arrhythmia, development of aortic valve endocarditis, rupture of the aortic annulus, and avulsion of the brachiocephalic artery during balloon withdrawal. Moreover, the inability of surgical resection to prevent sudden death suggests that effective treatment requires more than reduction of the pressure gradient.

The authors typically recommend avoidance of prolonged vigorous exercise, recognizing that in young and otherwise healthy dogs, even this conservative recommendation is not always practical. Based on clinical and pathologic evidence of myocardial ischemia, the authors also consider administration of beta-adrenergic receptor blockers to dogs with high gradients or a history of syncope. Beta-blockers (such as atenolol) reduce maximal heart rate, decrease myocardial oxygen consumption, and increase the time for diastolic coronary artery flow, thereby offering a theoretic protective benefit to the myocardium against ischemia and the development of arrhythmias. Moreover, dogs receiving high dosages of beta-blockers seem less willing (or are less able) to indulge in prolonged vigorous exercise. Despite these theoretic advantages, a retrospective study found no survival benefit of atenolol in dogs with SAS (Figure 250-37).[276] In theory, treatment with calcium channel blockers or angiotensin-converting enzyme inhibitors may also be of value in dogs with SAS; however, none of these medical strategies has been evaluated in placebo-controlled clinical trials.

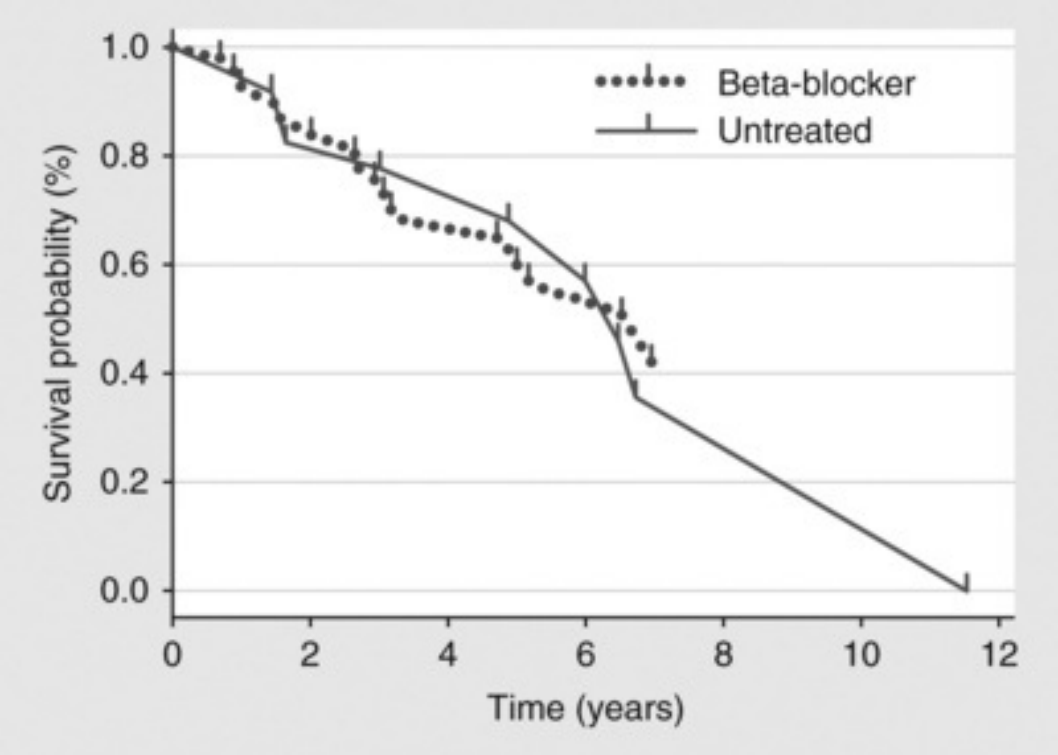

FIGURE 250-37 Cox-adjusted survival curve of cardiac-related death in dogs with severe SAS receiving beta-blocker therapy (n = 27) versus untreated (n = 23). There was no significant difference in survival function between groups (P = 0.97). (From Eason BD, Fine DM, Leeder D, et al: Influence of beta blockers on survival in dogs with severe subaortic stenosis. *J Vet Intern Med* 28:857-862, 2014.)

Tetralogy of Fallot

The defining anatomic features of ToF are RV outflow obstruction due to infundibular obstruction, secondary RV hypertrophy, a typically large perimembranous VSD, and a rightward-positioned aorta (dextroaorta) (Figure 250-38). The pulmonic valve is often hypoplastic in ToF and can contribute to RVOT obstruction in addition to, or instead of, purely valvular PS. Valvular PS occurring in combination with an isolated VSD produces similar pathophysiology and clinical findings of ToF; however, the infundibular septum is not malaligned, the aorta is normally positioned, and the infundibulum of the RV is not narrowed.[286] In children, pulmonary atresia is considered the extreme variant of ToF.

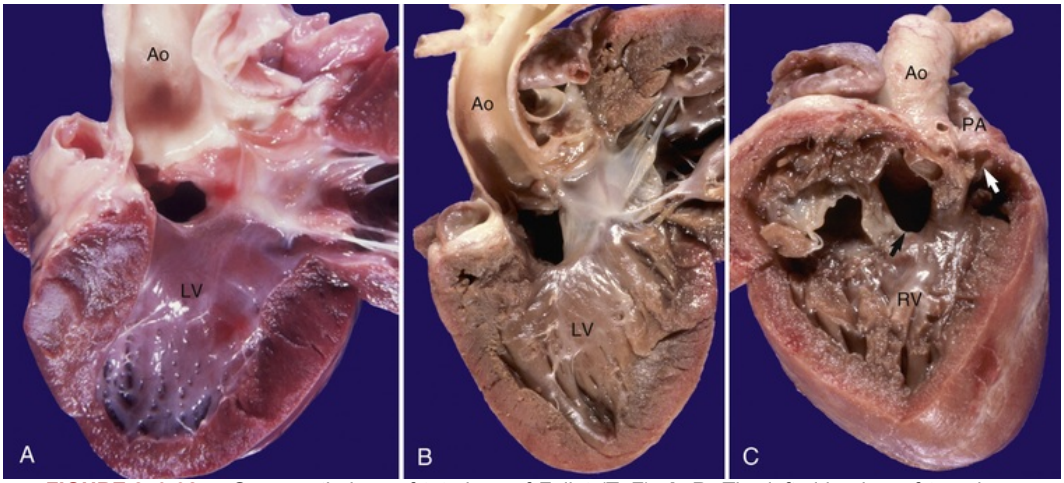

FIGURE 250-38 Gross pathology of tetralogy of Fallot (ToF). **A, B,** The left-side view of two dogs with ToF shows a large nonresistive ventricular septal defect (VSD) located between the aorta (Ao) and LV. Note the close proximity to the root of the aorta and the possibility for prolapse of an aortic

valve leaflet into the VSD. **C,** Right-side view of the dog from **B** showing the large VSD (black arrow), PS (white arrow), and hypertrophy of the RV. *PA*, Pulmonary artery.

Pathogenesis

ToF has been extensively studied in Keeshond breeding colonies and is likely oligogenic in etiology.[11] The pathogenesis of this malformation likely relates to ventrocranial deviation of the ventricular outlet septum.[287] In veterinary medicine, the term "conotruncal septal defects" has persisted. Regardless of the terminology, a spectrum of lesions, ranging from the subclinical to the clinically complicated, has been identified.[6,288-291] Patterson et al. graded the conotruncal defects as follows: grade 1—subclinical malformations involving persistence of the conus septum fusion line, aneurysm of the ventricular septum, and absence of the papillary muscle of the conus; grade 2—PS or VSD in addition to the grade 1 lesions; and grade 3—ToF: PS, VSD, and dextropositioned aorta (with secondary RV hypertrophy).[6] Additional abnormalities found in some dogs included a dilated and tortuous ascending aorta, pulmonary atresia, hypoplasia of the supraventricular crest, and anomalies of the aortic arch system. Based on extensive breeding studies and sophisticated genetic analysis, conotruncal defects have been shown to be an inherited autosomal recessive trait with variable expression.[8]

Pathophysiology

The predominant components of ToF are severe subvalvular RVOT obstruction and a VSD. As a result of the outflow obstruction and elevated RV systolic pressure, desaturated blood shunts from the right heart through the septal defect to mix with oxygenated blood coming from the LV.[292,293] Pulmonary arterial blood flow and pulmonary venous return are reduced, and the LA and LV are small and underdeveloped. The addition of desaturated blood from the RV to the systemic side of the circulation causes arterial hypoxemia, decreased hemoglobin oxygen saturation, cyanosis, and secondary erythrocytosis. Systemic collateral circulation to the lung increases via the bronchial arterial system. These vessels supply blood to the capillaries of the pulmonary parenchyma either directly or via anastomosing connections with a larger pulmonary artery. A substantial portion of this blood can participate in pulmonary gas exchange. Other aspects of clinical pathophysiology have been previously described.

Clinical Findings

ToF is common in the Keeshond, English Bulldog, and in some families of other breeds.[167] It has also been recognized in the cat.[108] Presenting complaints and clinical signs are as previously described for cyanotic heart disease. In most cases, the murmur of ToF is produced by high-velocity, turbulent blood flow through the obstructed RVOT.[286] Exercise or excitement may induce or enhance detection of peripheral cyanosis by accentuating right-to-left shunting. Radiography usually reveals a small or normal-sized heart with rounding of the RV border (Figure 250-39). The main pulmonary artery is not enlarged on survey radiographs, in contrast to the usual case of PS with intact ventricular septum. The pulmonary vasculature is diminished and the left auricle may be inconspicuous as a consequence of decreased venous return. The ECG typically exhibits criteria for right heart enlargement including right axis deviation, although left- or cranially directed vectors may be found in some cats.[294] Echocardiographic findings include RV hypertrophy, increased RV chamber dimensions, reduced LA and LV dimensions, a large perimembranous-outlet VSD, and RV outflow obstruction (Figure 250-40). Echocardiographic saline contrast or angiography can be employed to document right-to-left shunting at the ventricular outflow level.[76,295] On Doppler studies, shunting is usually bidirectional but predominantly right-to-left and of low-velocity owing to the small pressure gradient across the ventricles.

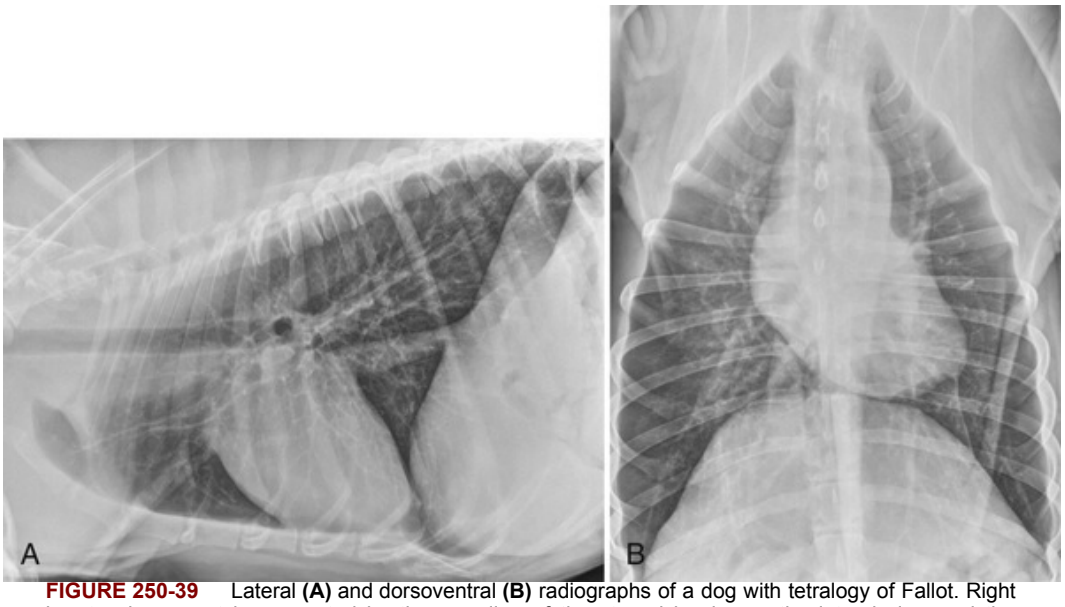

FIGURE 250-39 Lateral **(A)** and dorsoventral **(B)** radiographs of a dog with tetralogy of Fallot. Right heart enlargement is suggested by the rounding of the sternal border on the lateral view and the reverse D appearance on the dorsoventral view. The main pulmonary artery and peripheral pulmonary vessels are diminished.

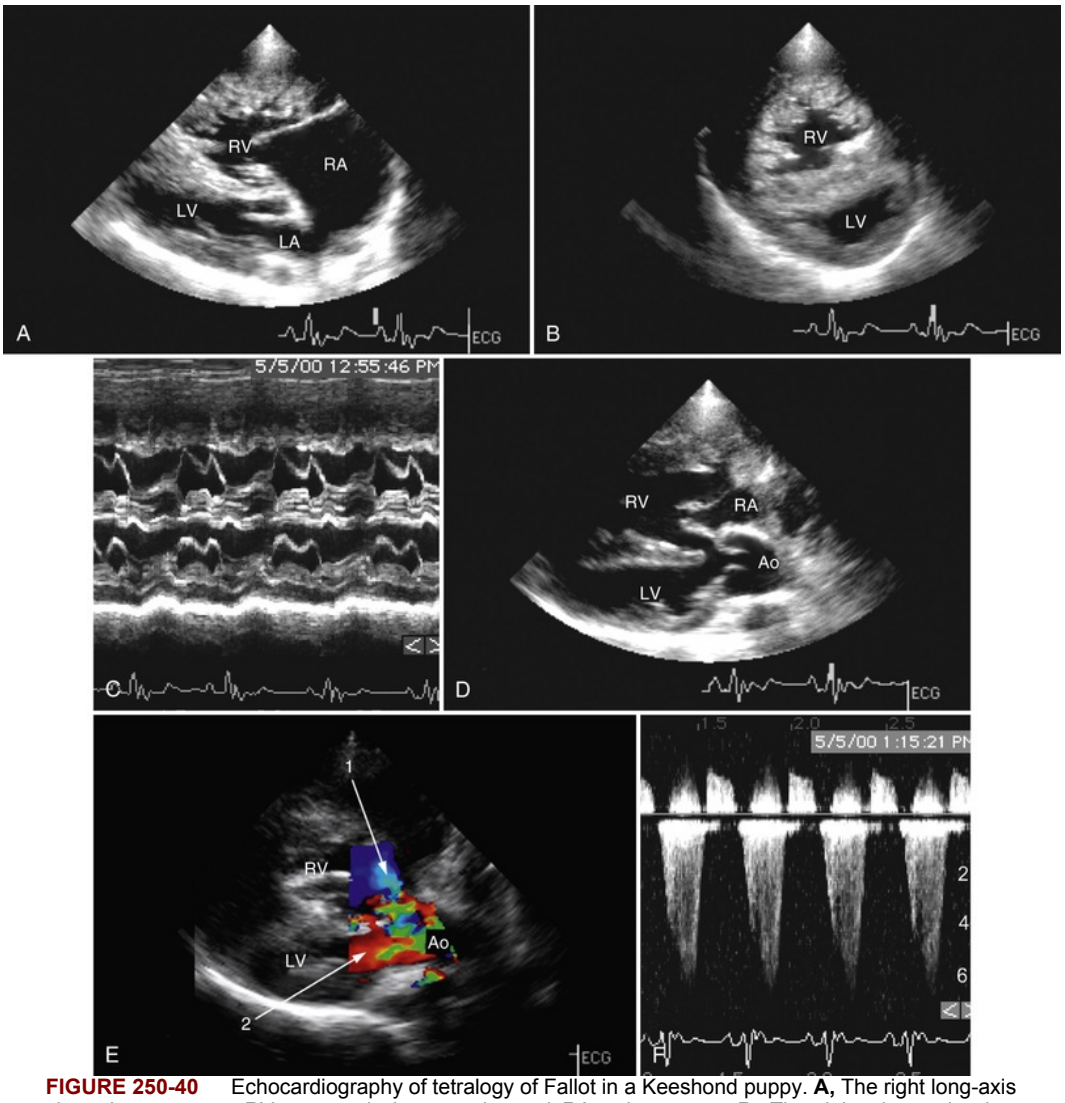

FIGURE 250-40 Echocardiography of tetralogy of Fallot in a Keeshond puppy. **A,** The right long-axis view shows severe RV concentric hypertrophy and RA enlargement. **B,** The right short-axis view shows severe RV concentric hypertrophy, flattening of the interventricular septum, a small underloaded LV, and hyperechogenicity of the RV subendocardium. **C,** The M-mode study shows enlargement of the RV as compared with the LV. The tricuspid and mitral valves are seen moving in the center of their respective ventricles. There appears to be paradoxical septal motion toward the RV during systole. **D,** The right long-axis view shows the VSD and rightward (dextropositioned) displacement of the aortic root and aorta (Ao). **E,** The color flow Doppler study of an image similar to that in **D** shows right-to-left shunting of blood from the RV (1), across the VSD, and merging with blood from the LV (2) into the Ao. **F,** The continuous wave Doppler study from the left heart base across the pulmonic valve indicates the presence of high-velocity blood flow caused by PS.

Cardiac catheterization demonstrates equilibration of LV and RV systolic pressures, compatible with RVOT obstruction and a large nonrestrictive (nonresistive) VSD.[291] Oximetry samples reveal a step-down at the LV outflow level and the aortic blood is relatively desaturated. Angiocardiography reveals both morphologic features and functional consequences of the malformation, including: RV hypertrophy; narrowing of the RV infundibulum; PS (typically from a hypoplastic pulmonary valve); minimal poststenotic dilatation of the pulmonary artery; varying degrees of pulmonary artery hypoplasia; a large perimembranous VSD; a small, dorsally displaced LV; enlarged, cranioventrally displaced and rightward-positioned aorta; and prominent bronchial circulation (Figure 250-41).[6,288-291] Bidirectional shunting across the VSD is common. In cases of pulmonary atresia, the pulmonary blood flow will be derived from the ductus arteriosus, bronchial arteries, or systemic collaterals. Cardiac catheterization is rarely needed for diagnosis but if performed anticoagulation therapy (e.g., heparin) should be considered to prevent systemic embolization during and immediately after the procedure.

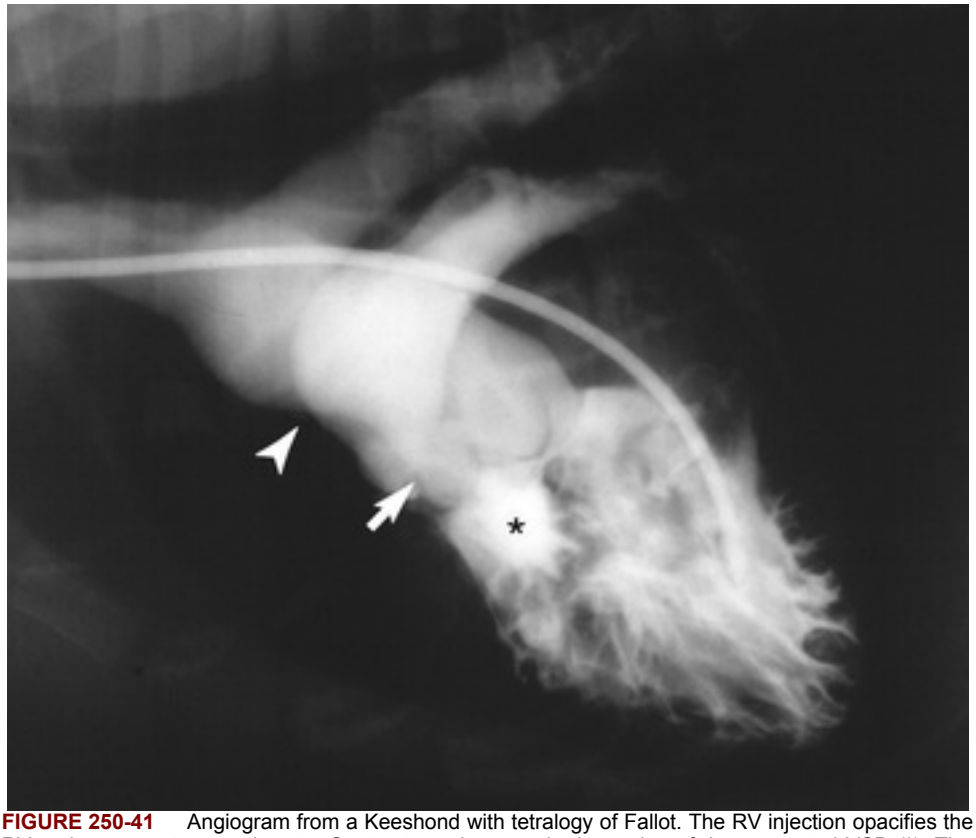

FIGURE 250-41 Angiogram from a Keeshond with tetralogy of Fallot. The RV injection opacifies the RV, pulmonary artery, and aorta. Contrast can be seen in the region of the suspected VSD (*). The contrast column narrows in the RV outflow tract and region of the pulmonic valve (arrow). There is a large poststenotic dilation of the main pulmonary artery (arrowhead). A wide and rightward-positioned aorta can be appreciated.

Clinical Management

The natural history and survival times of dogs and cats with ToF are not well characterized. Like other cyanotic heart diseases, ToF can be tolerated for years, provided pulmonary blood flow is maintained and hyperviscosity is controlled.[128] Most affected animals have severely limited exercise capacity. Sudden death is common because of the combined consequences of hypoxemia, hyperviscosity, or cardiac arrhythmia. Unlike PS with intact ventricular septum, CHF is an unusual outcome in ToF.

Options for treating animals with ToF include medical and surgical approaches. Definitive correction of the defect (closing the VSD and removing or bypassing the stenosis) can be done under cardiopulmonary bypass, but such surgery is rarely performed in animals.[296,297] As a general rule, the stenosis should not be completely relieved if the VSD cannot be closed because the loss of RV pressure results in marked left-to-right shunting with subsequent left-sided CHF.[291,298] Some dogs have been treated with "gentle" ballooning of the RVOT to increase pulmonary blood flow. As an alternative to definitive correction, surgical palliation through the creation of a systemic-to-pulmonary shunt can be quite rewarding.[291,299-301] Some variant of the subclavian to pulmonary artery shunt (Blalock-Thomas-Taussig) has been created most often in dogs and cats. Some surgeons prefer to use a graft instead of turning down the subclavian artery. By creating a left-to-right shunt distal to the cyanotic defect, pulmonary perfusion is increased and there is a greater contribution of oxygenated blood to the systemic circulation. The size of the accessory shunt must be controlled to prevent overloading of the diminutive LV and subsequent pulmonary edema. The extent to which these shunts remain patent over long periods of time in veterinary patients has not been reported, but one of us followed a dog with a Blalock-Thomas-Taussig shunt that remained patent for over a decade. Another option, if a ductus arteriosus is still patent, is catheter-based stenting of the PDA to maintain or increase pulmonary blood flow.

Maintenance of hydration is important. Periodic phlebotomy, performed to maintain the PCV between 62% and 68%, produces a satisfactory result in many cases.[128] Excessive withdrawal of blood should be avoided, and the blood volume withdrawn should be replaced with crystalloid fluids to maintain cardiac output and

tissue oxygen delivery.[52] Some children with ToF benefit from nonspecific beta-blockade with propranolol to reduce hyperdynamic contraction of the RV that can increase outflow obstruction; however, controlled studies of the clinical efficacy of this treatment in animals are lacking.[53,56] Severe hypoxemic spells should be treated with cage rest, oxygen, IV fluids, and sodium bicarbonate (if metabolic acidosis is evident). Treatment with vasoconstrictive agents such as phenylephrine can also help reduce the amount of right-to-left shunting in an urgent situation. Drugs with marked systemic vasodilating properties, including acetylpromazine, should be avoided.

Other Causes of Cyanotic Congenital Heart Disease

Valvular Atresia

Pulmonary atresia with a VSD is the exaggerated form of ToF (Figure 250-42). All of the blood ejected from the right heart is shunted right-to-left across a large VSD and into an enlarged aorta. The tricuspid valve is usually normal. The term "pseudotruncus arteriosus" has been used for describing this defect. It differs from a true truncus arteriosus because the pulmonary arteries do not arise from the truncus and at necropsy careful dissection reveals an imperforate pulmonic valve and a vestigial pulmonary trunk connecting to the left and right pulmonary arteries. On occasion, both the pulmonic and tricuspid valves are atretic (see Figure 250-42). The RV is small or hypoplastic and blood returning to the RA shunts through a PFO or ASD to produce cyanosis. The lungs are supplied via a PDA or an extensive bronchoesophageal collateral circulation.

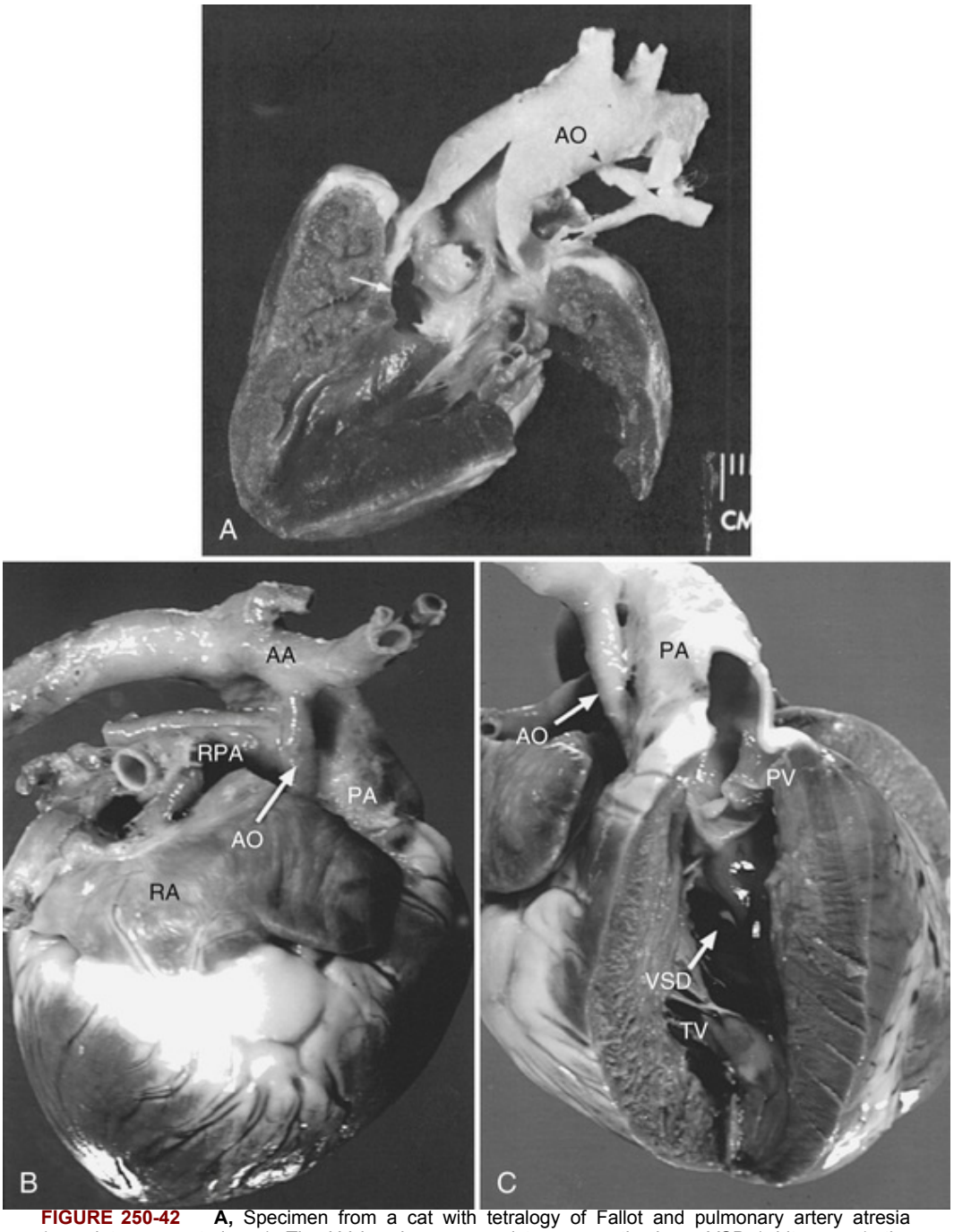

FIGURE 250-42 **A,** Specimen from a cat with tetralogy of Fallot and pulmonary artery atresia (pseudotruncus arteriosus). The LV has been opened to expose the large VSD (white arrow), the hypoplastic pulmonary artery (small black arrow), and the dilated aorta (AO). Pulmonary flow was through the ductus arteriosus, the origin and termination of which are shown by arrowheads. Although the lobar pulmonary arteries were patent, almost no blood was found in the main pulmonary artery. **B,** Specimen from a dog that exhibited severe cyanosis from birth. The proximal aorta is hypoplastic, and an aortic opening (valve) could not be identified (aortic valve atresia). A huge pulmonary artery (PA) gives origin to the right and left pulmonary branches, and a large patent ductal segment connects to the aortic arch (AA), supplying the brachiocephalic vessels, the descending aorta, and the hypoplastic aorta. **C,** Same dog as in **B.** Note the marked hypertrophy of the opened right ventricle, as well as the ventricular septal defect (VSD), which received blood from the underdeveloped left heart. *PV,* Pulmonic valve; *RA,* right atrium; *RPA,* right pulmonary artery; *TV,* tricuspid valve.

Aortic atresia with a hypoplastic left heart is a rare form of cyanotic heart disease in dogs. The aortic orifice is often imperforate and the ascending aorta is hypoplastic and the mitral valve is usually atretic or hypoplastic. In the absence of a VSD, the LV is very small; when a VSD is present, the LV is better developed. The right heart supplies the entire pulmonary and systemic circulations, resulting in profound cyanosis and, in most cases, early death.

Double Outlet Right Ventricle

Double outlet right ventricle (DORV) describes a heterogeneous group of malformations in which both great vessels exit from the RV. This has been reported in both dogs and cats (Figure 250-43).[302,303] A VSD provides the LV an avenue for outflow into the great vessels. Depending on the location of the VSD in relation of the origin of the great vessels, DORV can manifest as either pulmonary overcirculation or as a form of cyanotic heart disease. Concurrent abnormalities such as PS, pulmonary hypertension, and coarctation of the aorta can also affect the development of clinical signs. Surgical correction of this condition in dogs has been attempted.

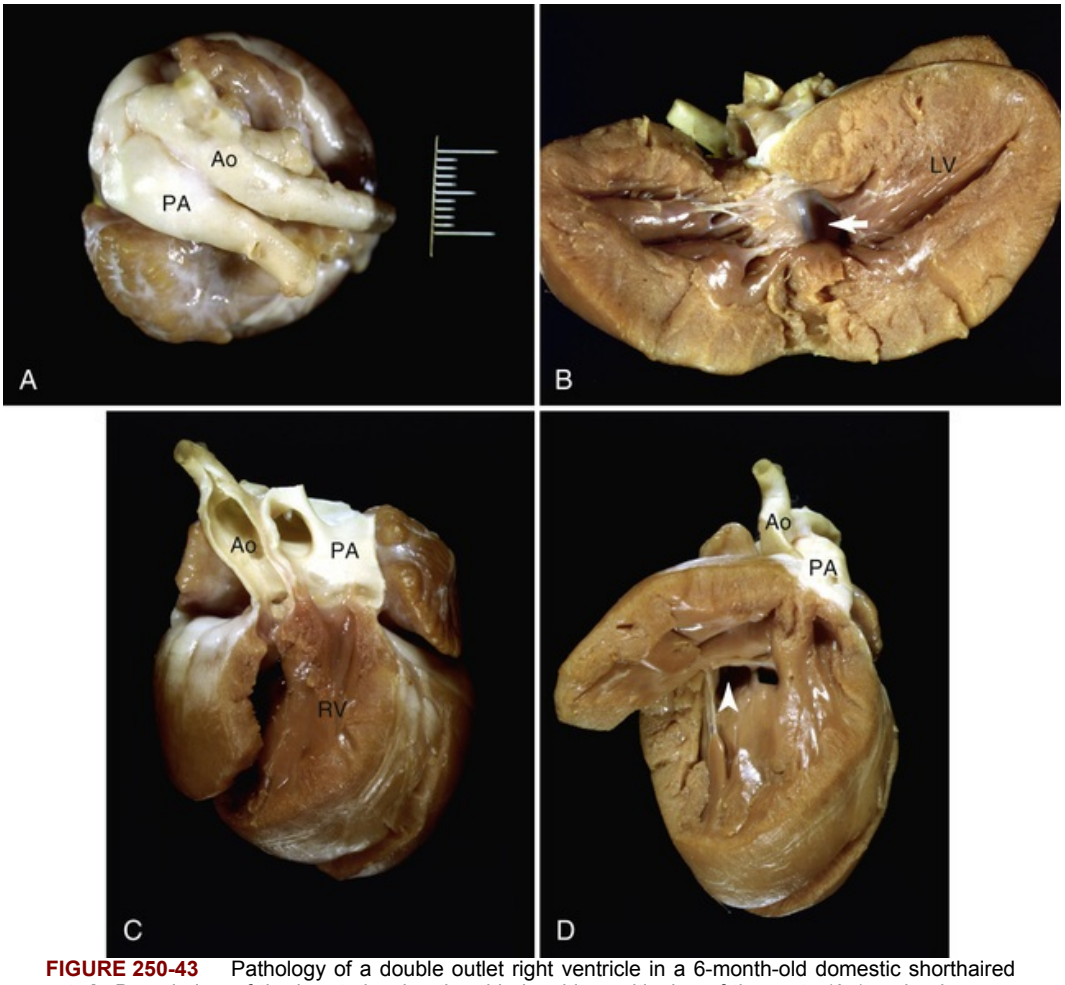

FIGURE 250-43 Pathology of a double outlet right ventricle in a 6-month-old domestic shorthaired cat. **A,** Dorsal view of the heart showing the side-by-side positioning of the aorta (Ao) and pulmonary artery (PA) at the cranial right edge of the heart. **B,** View of the VSD (arrow) from the LV side. Note the absence of an LVOT and aorta originating from the LV, and the discontinuity between the mitral valve apparatus and the missing aorta. **C,** View from the right cranial aspect showing the origin of the Ao and PA from the RV. The opening of the VSD into the RV is below the crista supraventricularis and is not easily seen in this view. **D,** The view of the right side of the interventricular septum reveals the location of the VSD (arrowhead) near the origin of the aorta (aortic-committed double outlet right ventricle). (Courtesy Dr. Richard Kienle).

Transposition of the Great Arteries

In D-transposition of the great arteries, the aorta originates from the RV and the pulmonary trunk from the LV.[47,304] In the pure and fatal case, two independent circulations coexist and the systemic arteries never receive oxygenated blood. Survival of an animal with D-transposition depends on the presence (or development) of shunts between the two circulations to allow for mixing of blood to prevent fatal hypoxemia. These defects are complex, generally lethal, and most likely underdiagnosed in animals, relative to children, since most animals probably die undiagnosed at a very young age.

Miscellaneous Cardiac Defects

The potential for variations in cardiac situs, for abnormalities in venoatrial, atrioventricular, and ventriculoarterial connections, and for malformation of the individual cardiac chambers, septa, and valves is tremendous.[38,39] It is beyond the scope of this chapter to discuss the spectrum of all potential or reported cardiac malformations in animals. It should be noted that ectopia cordis is extremely rare in cats and dogs in comparison to the situation in cattle. More often encountered are congenital abnormalities of the sternum. Some of these occur with some congenital heart defects, including peritoneopericardial diaphragmatic hernia (see ch. 254).

Atrial Malformations

Congenital heart defects affecting the atria include the previously mentioned forms of ASD along with defects that are more complex. These latter malformations include cor triatriatum sinister (CTS), cor triatriatum dexter (CTD), supravalvular mitral ring, and double outlet right atrium. As implied by the name, cor triatriatum refers to a partitioning of the left (sinister) or right (dexter) atrium into two chambers creating "three atria." Cor triatriatum is characterized relative to blood flow by a proximal (usually caudal) chamber in continuity with venous return and a distal chamber in continuity with the atrioventricular valve. The intra-atrial membrane obstructs venous return from the proximal chamber leading to venous congestion behind the affected side of the heart. Partitioning of the LA appears quite rare in veterinary medicine and is more often observed in cats while CTD (see below) is seemingly more common in dogs. With CTS, the left auricle is located distal to the obstructing membrane. One important differential diagnosis for CTS is supravalvular mitral stenosis or supramitral ring. This is a form of mitral stenosis characterized by an obstructive membrane between the mitral valve and the LA.[40,305] The left auricle is incorporated in the proximal, high-pressure chamber of the LA and the mitral valve can be normal or malformed. Both of these obstructions to pulmonary venous return are more often reported in cats and lead to clinical signs of pulmonary congestion. Management options are limited but one successful hybrid (surgical-catheter) procedure has been reported.[306] The differential diagnosis of obstructed pulmonary venous return must also include the so-called double-outlet right atrium. This malformation is characterized by extreme leftward deviation of the ventral atrial septum with insertion of the membrane dorsolateral to the mitral valve. Pulmonary venous return enters the LA and crosses a primum ASD into the RA, which connects to both atrioventricular valves. There are variations of this defect that can lead to clinical signs of pulmonary venous congestion or to desaturation and signs of cyanotic heart disease.[307]

Of the complex atrial malformations, CTD is most often reported and appears to occur mainly in dogs.[308-316] This condition involves an intra-atrial obstruction that impedes venous return from the caudal vena cava and coronary sinus. The distal (cranial) part of the RA includes the right auricle, which receives cranial venous return normally. This defect can develop in isolation or as part of a more general hypoplasia or obstruction within the right heart. Tricuspid valvular or supravalvular stenosis,[316] hypoplastic RV, and PS have all been observed in dogs with CTD. The typical case of isolated CTD leads to posthepatic venous obstruction with the clinical presentation of ascites most common. The degree of inflow obstruction varies and presumably can worsen over time, as some cases present after two years of age. In most cases, cranial vena caval blood drains normally into the cranial chamber and tricuspid orifice. The absence of a murmur can lead to an erroneous diagnosis of hepatic or intra-abdominal disease. Echocardiography is diagnostic. Both catheter-based and surgical interventions have been used to successfully manage CTD in dogs.

Ventricular Malformations

In addition to VSD and double-chambered right ventricle discussed previously, there are several relatively rare disorders of the ventricles reported in dogs and cats. The near absence of RV myocardium with replacement by fibrous tissue and fat (similar to Uhl's disease in humans) has been reported in cats and perhaps one dog.[317-319] The condition should be considered in the differential diagnosis of RV dilation and failure.

Endocardial fibroelastosis (EFE) has been reported in dogs and cats[3,320,321] and was believed to be familial in some lines of Burmese and Siamese cats. It is a rare diagnosis today and must be distinguished from secondary endocardial thickening associated with chronic LV dilation. Inasmuch as some of the gross and clinical features of the disease are similar to those of taurine deficiency in cats, there is speculation that some

of the previously reported feline cases might have been dilated cardiomyopathy with secondary EFE. The gross anatomic findings of primary EFE include LV and LA dilatation, with severe endocardial thickening characterized grossly by diffuse, white, opaque thickening of the luminal surface (Figure 250-44). Obstruction or abnormalities of lymphatic drainage of the myocardium is a suggested cause. Affected dogs can also have thickening of the mitral valve leaflets. Histologic lesions in well-studied feline cases include diffuse hypocellular, fibroelastic thickening of the endocardium with layering of thin, randomly organized collagen and elastic fibers. Edema of the endocardium with dilation of lymphatics is prominent, and there is no evidence of myocardial inflammation or necrosis. The clinical features of EFE include early development of left-sided or biventricular failure, generally before 6 months of age. Mitral regurgitation might be detected. Left ventricular and atrial dilation are evident on radiographs, ECG, and echocardiography. The clinical and necropsy differential diagnoses include MVD, AS/SAS, restrictive and dilated cardiomyopathy, and myocarditis with secondary EFE. Affected animals fail to thrive. Medical treatment of CHF (see ch. 247) might prolong life, but recovery is unlikely.

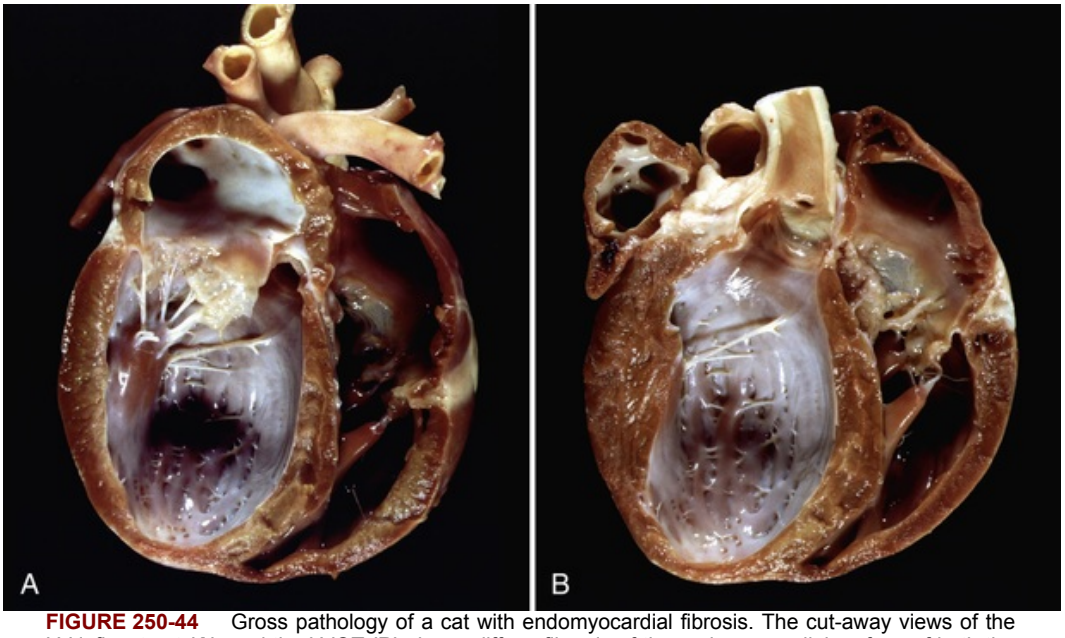

FIGURE 250-44 Gross pathology of a cat with endomyocardial fibrosis. The cut-away views of the LV inflow tract **(A),** and the LVOT **(B)** shows diffuse fibrosis of the endomyocardial surface of both the atrium and ventricle.

Vascular Anomalies

Arterial and venous vascular anomalies can be classified based on their location within the vascular system as systemic, pulmonary, or coronary. A number of vascular malformations has been reported, of which PDA represents the most important and has been previously discussed. Peripheral vascular disorders, including abnormal abdominal and hepatic venous drainage and arteriovenous fistulas, are detailed in ch. 284 and 257, respectively.

Arterial Anomalies

Malformations of the fetal truncus include persistent truncus arteriosus and aorticopulmonary septal defect (window). Truncus arteriosus communis is caused by failure of septation in the fetal truncus arteriosus and is characterized by a large VSD, a single great vessel exiting the heart, and is further classified by the origin and number of pulmonary artery branches originating from the truncus. The condition has been observed rarely in dogs and in cats,[322-325] and clinical signs depend largely on whether pulmonary blood flow is increased (i.e., left-to-right shunt) or restricted (in which case cyanosis is likely). An aorticopulmonary septal defect is caused by failure of the truncus arteriosus to fully differentiate, causing a common opening between the aorta and pulmonary artery, and shunting between the left and right sides of the circulation.[100] While a clinical

condition similar to that of PDA can develop, in other cases pulmonary hypertension develops during the first year of life and clinical signs are then similar to dogs that develop Eisenmenger's physiology associated with other defects. Management is similar to that for a reversed PDA. Surgery is difficult without cardiopulmonary bypass and should not be attempted if pulmonary vascular resistance is markedly elevated.

Coronary arteries can develop anomalously, but rarely cause documented clinical disease except in cases of single right coronary ostium with prepulmonary passage of the left branch of the coronary artery. This is most common in English bulldogs and was discussed previously under PS. However, coronary malformations also can be observed in the absence of PS in some dogs (including English Bulldogs) and other coronary variations are recognized in dogs with PS. For example, single left coronary ostium has been reported in English Bulldogs with valvular PS.[326] Rarely, shunting has been reported involving coronary arterial connections to the pulmonary arteries or to the heart.[327,328] The authors have observed other coronary malformations during angiography, including cameral fistulas and abnormal connections of coronary vessels to other systemic arteries.

Aortic abnormalities are often associated with SAS. As mentioned previously, these aortic dilations or aneurysms can occur in the absence of overt SAS and might represent aortopathies in some affected breeds including Rottweilers, Golden Retrievers, and Leonberger dogs.[65] Coarctation of the aorta, a shelf-like narrowing near the ductus arteriosus, and more extreme examples of aortic obstruction such as tubular hypoplasia or interruption of the aorta are rarely observed in dogs and cats (two cases are reported in English Bulldogs).[329,330]

In veterinary medicine, vascular ring anomalies refer to malformations that entrap the esophagus leading to regurgitation in weanlings. Persistence of the right aortic arch, as opposed to the left fourth aortic arch, is the most commonly reported. Vascular ring anomalies include this common malformation along with other total or partial ring anomalies. These include esophageal compression formed by retroesophageal subclavian arteries, double aortic arch, or left aortic arch with right-sided ligamentum arteriosum.[4,25,29,37,331-334] Such disorders are relatively common in German Shepherd dogs and have been recognized in many other canine breeds including Irish Setters, Great Danes and German Pinschers. Vascular ring anomalies are less common in cats but have been seen.[37,102,331,334] Occasionally, other cardiac defects are present, including PDA and persistent left cranial vena cava (Figure 250-45). Diagnosis of persistent right aortic arch can usually be made from the history and by inspecting a VD or DV radiograph that shows leftward deviation of the trachea at the heart base.[335] More complicated lesions require CT, MRI, or standard angiography. These conditions are described more fully in ch. 273 and in the references.[29,37]

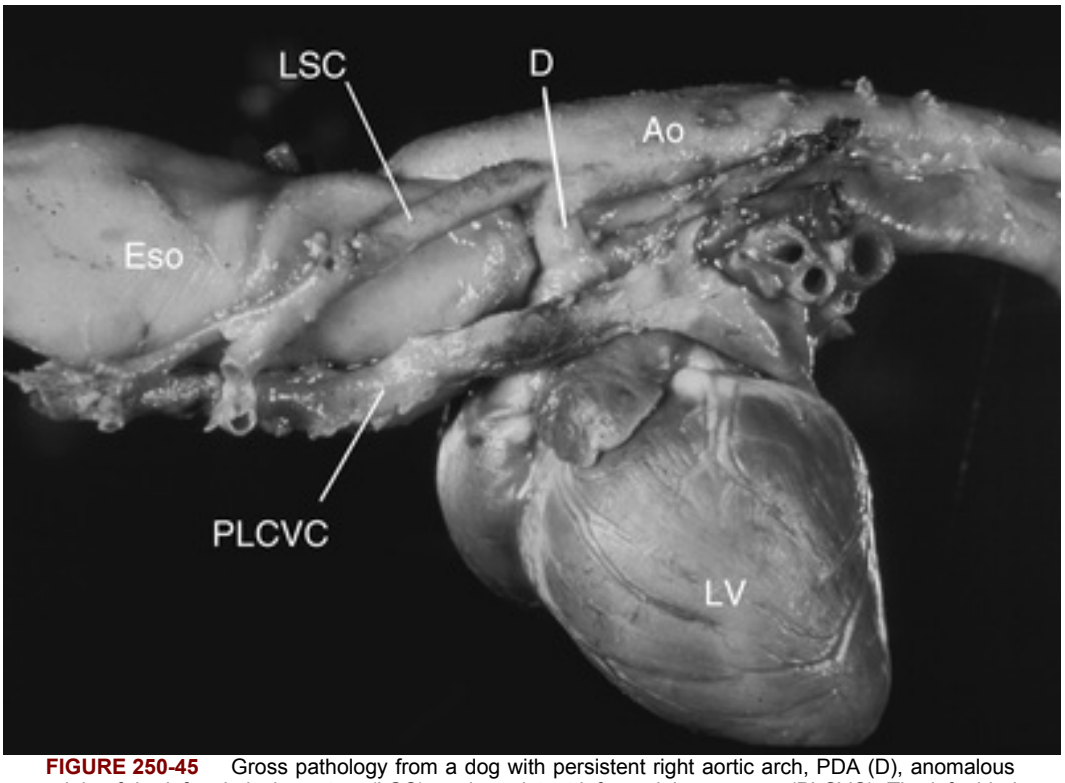

FIGURE 250-45 Gross pathology from a dog with persistent right aortic arch, PDA (D), anomalous origin of the left subclavian artery (LSC), and persistent left cranial vena cava (PLCVC). The left-sided view of the heart, great vessels, and esophagus (Eso) shows the entrapment and cranial dilation of the esophagus by the vascular ring. The origin of the left subclavian artery is moved distal from its usual location and is dorsal to the esophagus. The PLCVC can be seen extending laterally alongside the esophagus and left heart base, and coursing around the caudal waist of the heart. *Ao,* Aorta.

Abnormalities of the pulmonary arteries can be observed under a number of conditions. Unilateral atresia or hypoplasia of a pulmonary artery has been recognized in cats. Pulmonary artery dissection is reported as a complication of PDA in dogs.[111] An overlooked diagnosis is that of systemic-to-pulmonary arterial vascular malformations.[102,336,337] These arteriovenous malformations are typically multiple, and can connect the aorta, brachiocephalic artery, or other systemic arteries to the pulmonary arterial system. The result is volume overloading of the left side of the heart. Murmurs are often difficult to detect, but can include continuous murmurs related to the shunts or systolic murmurs due to functional mitral regurgitation from LV dilation and increased aortic blood flow. The diagnosis can be suspected from color Doppler imaging of the pulmonary artery and failure to identify a typical ductus arteriosus. CT angiography or contrast angiography are diagnostic. Management can include surgical intervention or coil occlusion of the vascular malformation; however, the clinician should always suspect multiple shunts and the potential for opening of new arteriovenous malformations with the closure of others.

Venous Anomalies

Venous anomalies, especially those unrelated to the heart, are discussed more fully in ch. 257. Venous malformations rarely cause cardiac problems in small animals. Total or partial anomalous pulmonary venous return has been reported rarely, and it behaves functionally as a left-to-right shunt at the atrial level. This is most commonly associated with a sinus venosus–type ASD with partial anomalous venous drainage into the right atrium across the ASD. Abnormalities of abdominal venous drainage, such as patent ductus venosus, can induce hepatic encephalopathy (see ch. 284).

A relatively common venous abnormality of clinical significance during thoracic surgery or cardiac catheterization is the persistent left cranial vena cava (Figure 250-46).[70,338-340] This structure, normally present in the fetus as part of the left cardinal venous system, can persist and drain into the embryonically related coronary sinus in the caudal aspect of the RA. Diagnosis is straightforward in most cases and can be made using 2D echocardiography by recognizing a dilated coronary sinus near the atrioventricular groove. The diagnosis can be confirmed by contrast (saline) echocardiography, CT angiography, or contrast angiography

(see ch. 104). A persistent left cranial vena cava can interfere with surgical exposure, particularly during surgical treatment of persistent right fourth aortic arch, or confound cardiac catheterization, but otherwise it is of no known functional significance (Figure 250-47). As with persistence of the right fourth aortic arch, this vascular anomaly is common in German Shepherd dogs, and has been reported in other canine breeds as well as in cats. Division of this vessel generally poses no clinical problem provided the normal right cranial vena cava is also present (see Figure 250-47).

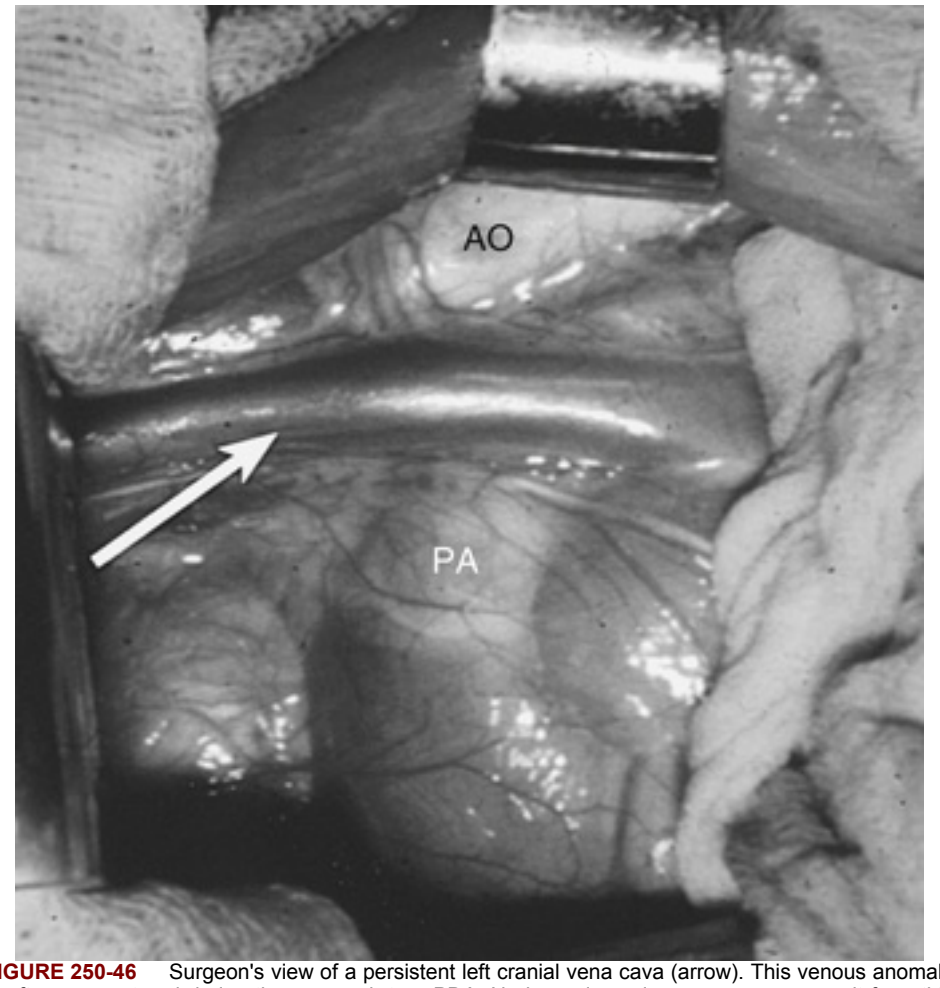

FIGURE 250-46 Surgeon's view of a persistent left cranial vena cava (arrow). This venous anomaly is often encountered during the approach to a PDA. No hemodynamic consequences result from this anomaly. *AO*, Aorta; *PA*, pulmonary artery.

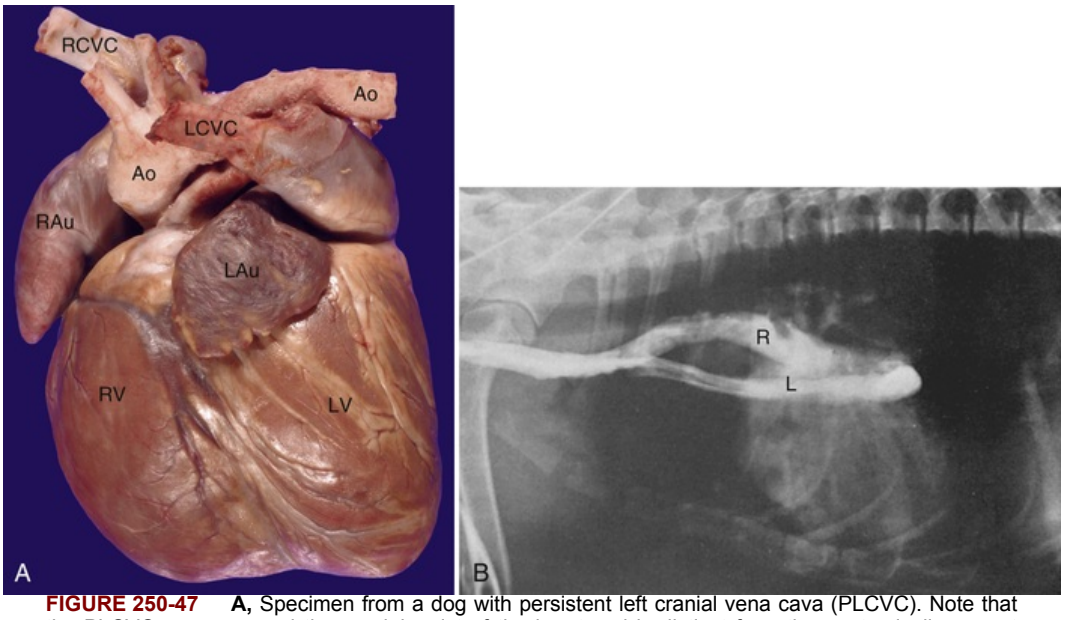

FIGURE 250-47 **A,** Specimen from a dog with persistent left cranial vena cava (PLCVC). Note that the PLCVC wraps around the caudal waist of the heart and is distinct from the anatomically correct right cranial vena cava (RCVC). **B,** Nonselective angiogram from a dog. Contrast is injected into the right and left jugular veins. The normal right cranial vena cava (R) is evident, as is the PLCVC (L). Note that the PLCVC wraps around the caudal aspect of the heart and enters into the caudal portion of the RA. *Ao,* Aorta; *LAu,* left auricle; *RAu,* right auricular appendage.

Acknowledgments

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CHAPTER 251

Adult-Onset Valvular Heart Disease

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Client Information Sheet: Myxomatous Mitral Valve Disease

Myxomatous Mitral Valve Disease

Myxomatous mitral valve disease (MMVD) is characterized by a slow progressive myxomatous degeneration of the mitral valve apparatus with subsequent left atrial (LA) and ventricular (LV) dilatation.[1-4] Although the myxomatous degeneration most commonly affects the mitral valve, any of the four intracardiac valves can be affected. However, the pulmonary and aortic valves (the semilunar valves) rarely develop pronounced degenerative changes.[2,3,5] The condition has been given many names, such as chronic valvular disease, degenerative mitral valve disease, mitral valve disease, endocardiosis, and more recently myxomatous mitral valve disease. The term "myxomatous" describes a characteristic histologic feature of this disease and excludes most, if not all, other forms of mitral valve disease, but MMVD does not necessarily exclude involvement of other valves. Thus, MMVD accurately and succinctly defines the pathophenotype of this condition.

Occurrence

MMVD is the most prevalent cardiac disease in dogs, and has been estimated to account for 75% to 80% of canine cardiac diseases.[1,6-9] MMVD is encountered in all breeds, but the highest prevalence is seen in small to medium-sized dog breeds, such as Cavalier King Charles Spaniel (CKCS), Dachshunds, miniature Poodles, and Yorkshire Terriers.[8-13] Affected dogs have no signs of valve abnormalities at birth, but develop MMVD later in life. The prevalence increases with age and is, at a given age, higher in males.[1,2,6,7,9,12] The prevalence of MMVD in cats without primary myocardial disease is unknown, but seems to be low. Similar changes of the mitral valve are also seen in humans, horses, and pigs.[14-16]

Inheritance and Breeding

The etiology of MMVD has not been ascertained but heredity has long been suspected to play a major role; owing to the strong association of this disease with certain small to medium-sized breeds. Studies of families of CKCS and families of Dachshunds provide evidence that genetic factors play a large role in the etiology.[17-19] These studies suggest that the disease has a polygenic inheritance; that is, multiple genes influence the trait and a certain threshold has to be reached before MMVD develops.[17,18] The polygenic mode of inheritance means that a combination of a sire and a dam, that both have an early onset of MMVD, will give offspring that have, on average, an early onset of MMVD (and CHF). A combination of dogs with late onset will give offspring that manifest the disease at old age or never. Males have a lower threshold than females, which means that males will develop the disease at a younger age than females within a family of dogs in which the offspring on average have the same genotype. Two loci, located on chromosomes 13 and 14, have been shown to be associated with an early onset of MMVD in CKCS dogs.[20] This finding is likely to herald causative mutations in the future, and such discovery will clearly increase the knowledge of disease pathways, and may lead to genetic tests, but no such tests are currently available. The major role played by genetic factors implies that other factors, such as level of exercise, degree of obesity, and diet, have minor influence on disease development. Breeding programs aimed at reducing the prevalence of MMVD have been launched in Europe and North America and elsewhere for CKCS and Dachshunds. In the absence of reliable genetic tests, these

breeding programs use auscultation to identify the presence of a heart murmur, and/or echocardiography to detect and quantify mitral valve degeneration and/or mitral regurgitation (MR). Dogs that are under a specific age and have developed a certain degree of heart murmur or echocardiographic findings consistent with MMVD are not allowed to breed within the programs. Some programs are also partly based on assessments of MMVD status of the parents. The age limit for potential breeding dogs and parents is very important: The age limit should be set at an age at which dogs with an early onset of MMVD are excluded, but not too high because this may impoverish the breeding population and reduce it to unacceptable low numbers.[21] A recent evaluation of a breeding shows a reduction in prevalence of heart murmurs and severity of mitral valve lesions assessed by echocardiography.[22]

Pathology

Macroscopic appearance of myxomatous degeneration depends on at which stage of disease the valve is examined, and macroscopic findings in cases of mild myxomatous degeneration might be overlooked if not investigated thoroughly.

The changes begin in the area of apposition of the leaflets and are usually most pronounced in sections where chordae tendineae insert. The free edges of the leaflets, which normally are thin, translucent and soft, become thickened and irregular, with areas showing bulging/ballooning towards the LA side (Figure 251-1, *A* and *B*).[1-3,23,24] The chordae tendineae themselves might also become affected by the myxomatous degeneration.[3,13,23] With progression, the bulging becomes worse, and the lesions spread into other parts of the leaflets (Figure 251-2, *B*). In late stages, fibrosis can cause marked thickening and contraction of leaflets and chordae tendineae. The chordae tendineae might rupture, which leads to an unattached free edge. Atrial endocardial lesions (fibrosis) opposite the mitral orifice (i.e., "jet lesions") might be observed. In severe cases, varying degrees of atrial rupture, such as endomyocardial splits, ruptured pectinate muscles in the atrial appendage, acquired atrial septal defect, and hemopericardium might be seen (see ch. 254).[2,25]

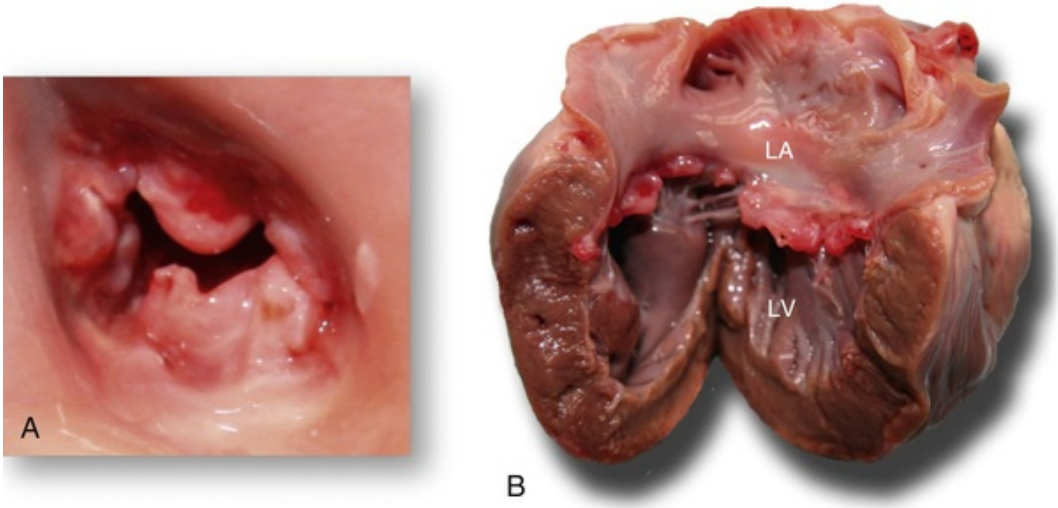

FIGURE 251-1 Postmortem specimen of a dog that suffered from severe myxomatous mitral valve disease (MMVD) viewed from the atrial **(A),** and lateral side **(B)** with the left atrium (LA) and ventricle (LV) opened. The mitral valve leaflets are thickened and contracted, with nodules rolling in the free edges and with areas bulging/prolapsing towards the left atrial side. Chordal rupture, particularly of lesser-order chordae, is a common finding. A jet lesion, which is present on the atrial wall, is a result of the high velocity regurgitant stream of blood from the LV striking the atrial wall.

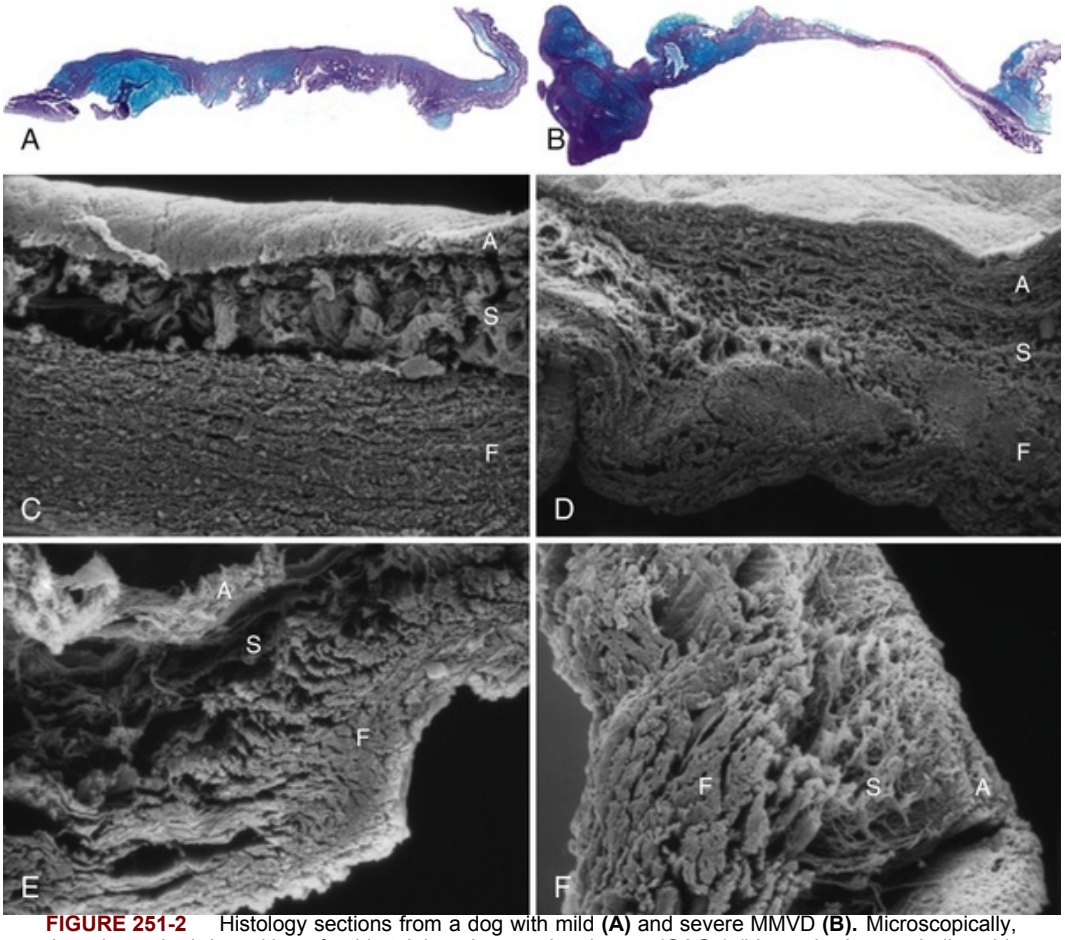

FIGURE 251-2 Histology sections from a dog with mild **(A)** and severe MMVD **(B).** Microscopically, there is marked deposition of acid-staining glycosaminoglycans (GAGs) (blue color in a periodic acid-Schiff [PAS] reaction/alcian blue staining) in the spongiosa and fibrosa layers of the leaflets. Scanning electron micrographs of a cell-macerated abnormal canine mitral valve at the level of the mid-zone **(C-F).** The images illustrate the damage to the valve leaflet that occurs as the disease progresses through the different Whitney grades (micrographs **C-F** corresponding to Whitney grades 1-4).[5] There is a loss and distortion of the layered structure with advancing disease and concurrent reduction in collagen density in all three layers. *A,* Atrialis layer; *S,* spongiosa layer; *F,* fibrosa layer. (**A** and **B,** Courtesy Lisbeth Höier Olsen, University of Copenhagen, Denmark. **C-F,** From Han RI, Impoco G, Culshaw G, et al: Cell maceration scanning electron microscopy and computer-derived porosity measurements in assessment of connective tissue microstructure changes in the canine myxomatous mitral valve. *Vet J* 197:502-505, 2013. Published with permission from the publisher.)

Histopathological findings in the valve leaflets include myxomatous degeneration (Figure 251-2, *A* and *B*), which refers to a characteristic pathological weakening and disturbance in the organization of the connective tissue in which the spongiosa component is unusually prominent, and the collagen fibers are disorganized in the fibrosa layer (Figure 251-2, *C-F*).[26,27] Increased amounts of mucopolysaccharides, and glycosaminoglycans are commonly seen within affected valves.[3,27,28] Characteristic findings of endothelial cells covering the valve surface include pleomorphism and damage to the cell lining. The endothelial damage, which is most commonly evident near the edges of the valve leaflets, can cause regional loss of endothelial cells, hence exposing underlying basement membranes or subendothelial matrix.[23]

Histopathological findings in the left heart chambers include changes in composition and structure of both the extracellular matrix (ECM) and the myocytes, but the underlying cellular and molecular bases for these changes remain poorly understood. Both myocardial fibrosis and intramyocardial arteriosclerosis, especially in the papillary muscles, have been described in dogs with advanced stages of MMVD.[29,30]

Pathogenesis

Little is known about the pathogenesis of the progressive thickening and degeneration of the leaflets. Probably, one or more primary inciting factors increase(s) the risk of disease in predisposed dogs as not all

dogs develop atrioventricular valve myxomatous degeneration.

It likely plays an important role for the progression of the disease that the endothelium is damaged or even missing in diseased areas,[23,24,31] because endothelial cells are known to communicate extensively with subendothelial cells (e.g., valvular interstitial cells, VICs). Endothelial damage induces release of vasoactive peptides, such as endothelin-1, which potentially is involved in transforming subendothelial VICs from a predominantly fibroblast phenotype into more active myofibroblast and smooth muscle cell phenotypes.[23,26,32] The transformation of VICs has also been suggested to be initiated by serotonin (5-HT),[33-35] and serum concentrations of 5-HT have been shown to be higher in CKCS dogs compared to dogs of some other breeds,[33,36] and also increased in mitral valve and left ventricular (LV) myocardial tissue in MMVD dogs.[37] Likewise, expression of 5-HT receptors and extracellular matrix signaling molecules are altered in diseased mitral leaflets.[34,38,39] Proteolytic enzymes, such as the matrix metalloproteinases (MMPs), might also be involved in the degenerative processes, leading to atypical organization of connective tissue components.[38,40-42]

Pathophysiology

Mitral Regurgitation Caused by Myxomatous Mitral Valve Disease

Distortion of the valve architecture and the corresponding chordae tendineae leads to systolic atrial displacement of the mitral valve leaflets (i.e., mitral valve prolapse),[43] and abnormal coaptation of the mitral valve leaflets during ventricular systole. Thus, a percentage of the LV stroke volume is ejected backwards into the LA. Elongation and potentially rupture of the chordae tendineae structures worsens MR by causing leaflets to partially or completely prolapse (valve flail) into the LA.[13]

The MR volume has been described to depend on the mitral valve orifice area, and the systolic pressure gradient between the LA and the LV,[44,45] of which the latter is influenced by the intra-atrial pressure, LV function, as well as the systemic arterial blood pressure. The myxomatous degeneration of the mitral valve apparatus causes an abnormal leaflet apposition, and hence primary MR, whereas left-sided cardiac dilation exaggerates the abnormality in valve apposition, leading to secondary MR.[2,46] Consequently, regurgitation begets regurgitation. Most commonly, dogs with MMVD have a laterally directed MR jet, presumably because the anterior leaflet is longer and has a greater mobility than the posterior leaflet (as described in dogs and people),[46,47] and hence, is more likely to prolapse than the posterior leaflet. However, the spatial orientation of the jet is not constant, particularly not in mild cases of MR, probably due to changes in the shape and orientation of the mitral orifice area during LV contraction.[48]

Primary MR of lesser degree does not induce any apparent change in indices of cardiac size or function. The forward stroke volume is maintained, and the small regurgitant volume is easily accepted by the LA. With progression of the valve lesions, the regurgitant part of the total LV stroke volume increases, but several cardiac and non-cardiac (e.g., renal, neurohumoral, and vascular) compensatory mechanisms contribute to maintain the forward stroke volume.[49] Expansion of the LA, buffers the increasing MR volume, thereby allowing the intra-atrial pressure to remain comparably low, and blood can easily be ejected into the LA during ventricular systole, even in dogs with severe MMVD. More than 75% of the total LV stroke volume has been reported to be ejected into the LA during systole in dogs with severe MMVD.[50] The severity of left-sided cardiac dilation is linked to MR severity, suggesting that MR volume is the major determinant factor for the degree of left-sided cardiac dilation.[50,51]

The extra pathway (into the LA) for stroke volume ejection reduces the LV afterload (the resistance to LV emptying), whereas the increased volume load leads to an increased preload.[52] The retrograde ejection of LV stroke volume starts in early systole, leading to a short isovolumetric contraction period (defined as the interval between closing of the atrioventricular valves and opening of the semilunar valves).[53,54] The LA has an important function by allowing the regurgitant volume to be absorbed within the atrial cavity, and it protects the pulmonary vascular bed from hypertension.[55] Increased LA pressure results in pulmonary venous congestion and edema. The effect of regurgitant volume on LA pressure and volume, and consequently pulmonary capillary pressure, depends on the LA size, as well as on the compliance of the LA wall. Consequently, LA compliance is determined by the rate of increase in regurgitant volume, which itself is determined by the rate of progression of MMVD, and by remodeling in response to the volume overload. In cases with slowly progressing MMVD, there is often a drastic enlargement of the LA, whereas pulmonary congestion and pulmonary edema develop late. The edema is also delayed by the development of a more

effective lymphatic drainage of the pulmonary interstitium in chronic pulmonary congestion.[56] In cases with acutely increased MR, as in rupture of a first order, or several, chordae tendineae, the LA is unable to adapt, which results in a rapid elevation of LA and pulmonary capillary pressure, and consequently rapid development of pulmonary congestion and edema.

The passive back-transmission of increased LV filling pressure to the pulmonary capillaries can furthermore lead to development of pulmonary hypertension, and dogs with more severe MR, and therefore higher LA pressure, have an increased risk of developing pulmonary hypertension.[57]

The LV compensates for the loss of forward stroke volume by increasing the end diastolic volume, and in order to accommodate the increased filling pressure (preload), the LV undergoes various compensatory responses (see ch. 246). The volume overload triggers an unnatural growth—so-called eccentric hypertrophy, which is characterized by chamber enlargement but with maintained relative wall thickness. This is sufficient to normalize pressure in the volume-overloaded LV and maintain an adequate forward stroke volume.[58-60] Myocardial hypertrophy has also been suggested to be stimulated by increased neurohormonal activation, such as by increased formation of angiotensin II (AII),[61] although circulating levels of AII appear comparably unchanged during progression from mild MMVD to overt CHF.[62] However, the canine myocardium is most likely capable of forming AII locally in the heart in response to hemodynamic wall stress: Angiotensin converting enzyme (ACE), chymase and cathepsin D have all been reported capable of promoting tissue AII formation in the volume-overloaded canine heart.[61,63]

Although both long- and short-axis dimensions increase in response to chronic volume overload, the short-axis dimension increases more, which leads to a change in LV shape from elliptical to more globular.[64] The increase in global LV sphericity might allow myocardial adaptation to abnormal regional wall stress. A more globular LV shape might contribute to a further increase in volume overload by stimulating secondary MR due to disruption of normal mitral annular geometry.[49]

The compensatory mechanisms, such as LV hypertrophy, dilation, and enhanced activity of the neurohormonal system, are all initially considered beneficial in order to provide the hemodynamic support needed to maintain sufficient cardiac output despite MR. However, with progression of disease, these mechanisms themselves become factors leading to deterioration of the failing heart, such as by myocyte injury and accumulation of collagen fibers (i.e., myocardial fibrosis).[49,60]

The cardiac remodeling by chronic volume overload in MMVD dogs will, in turn, impact mechanical function of the heart. The increased preload causes an increased force of contraction according to the Frank-Starling mechanism.[65] Depending on severity of MR, these changes lead to normal to hyperdynamic LV contraction (hyperkinesia), even in the presence of intrinsic myocardial dysfunction. Although myocardial systolic function declines with progression of disease, the remodeling process allows the LV to retain a relatively well-preserved forward cardiac pump function even in advanced MMVD.[49,66] Nevertheless, because of chronic volume overload and the fact that the hypertrophy, while necessary, is a pathologic remodeling, myocardial contractility decreases slowly, but progressively and inexorably, even in clinically compensated dogs.[67-69] An increased amount of myocardial fibrosis has been suggested to influence the Frank-Starling mechanism in heart failure dogs,[65] and thereby disable an optimal transduction of contractile force generated by the myocytes in systole. However, increased pulmonary blood volume, and not decreased forward stroke volume, has been shown to be the main cause of abnormal cardiopulmonary function in dogs with MMVD.[51] This finding corresponds with the clinical observation that dogs with severe MR suffer more commonly from pulmonary congestion and edema (which cause respiratory signs) than signs caused by reduced forward cardiac output (lethargy, weakness, exercise intolerance).[70]

Tricuspid Regurgitation Caused by Myxomatous Valve Disease

Tricuspid regurgitation (TR) is a common incidental finding in dogs and cats.[71] Tricuspid regurgitation commonly occurs concomitantly with myxomatous degeneration of the mitral valve as a consequence of primary valvular changes, and/or secondary to pulmonary hypertension due to left-sided myxomatous degeneration. The degenerative changes of the tricuspid valve apparatus are identical to those found when the mitral valve is affected (see Pathology section).[72]

Myxomatous degeneration of the tricuspid valve commonly leads to TR of mild to moderate degree. Tricuspid regurgitation, in the absence of concurrent obstruction of the pulmonary valve or pulmonary artery hypertension, is comparably well tolerated.[73] However, because the right ventricle (RV) is designed to contract against a low-pressure artery, it is vulnerable to increases in pressure. It responds poorly to the

increased work; even relatively small acute increases in pulmonary artery pressure cause sharp decreases in RV stroke volume.[74] Thus, TR is of significance if pulmonary hypertension is present. In addition to the RV dilatation, right atrial (RA) enlargement develops and adds to the tricuspid annular dilatation and TR. Enlargement of the RA may result in atrial tachyarrhythmias, such as atrial fibrillation and supraventricular tachycardia. As a consequence of increased RA pressure, ascites, pleural effusion (especially in cats), pericardial effusion, hepatomegaly, and splenomegaly may develop.

Clinical Signs

Mild to moderate MMVD (ACVIM Stages A and B) is usually not associated with any signs of disease. Most dogs with MMVD are free of clinical signs for most of the time they have a murmur, although exercise intolerance might be noted. Cough is a common presenting complaint in MMVD. Although this sign is not specific for heart disease it should merit further evaluation (see ch. 26). Dogs with left mainstem bronchial compression, but without pulmonary congestion or edema, may have coughing spells at any time during the day, especially during physical exercise or excitement. Otherwise, mild to moderate MMVD dogs do not demonstrate clinical signs of heart disease.

The first clinical signs of decompensated CHF (ACVIM Stage C) are usually mild but may be aggravated within days or sometimes weeks (see ch. 246). Since these signs are vague and not specific for decompensated CHF, the differential diagnostic challenge in MMVD is commonly not to establish whether the disease is present, but whether or not MMVD is responsible for the clinical signs. The signs relate to the presence and degree of one or several of the following pathophysiologic events, listed in order of their relative importance: (1) increased LA and pulmonary venous pressure, which might result in respiratory distress and cough due to pulmonary edema and mainstem bronchial compression; (2) reduced LV or RV forward flow, which might result in weakness and reduced stamina; (3) increased RA and systemic venous pressures, which might result in pleural effusion and ascites; and (4) acute decompensation due to rupture of chordae tendineae, atrial rupture, or ventricular fibrillation, which might cause sudden death.

Tachypnea and dyspnea are present when pulmonary congestion and edema have developed.[75] Coughing is also commonly observed, and in the case of advanced MMVD, the cough may be caused by pressure of the LA on the left mainstem bronchus, by pulmonary congestion and edema or, most commonly, a combination.[76] Dogs in decompensated CHF are often anxious and restless during the night, and they commonly prefer lying in sternal recumbency. Abnormal respiratory sounds, such as wheezes may be audible. Dogs in decompensated CHF are often inactive and have varying degrees of inappetence. Cardiac cachexia may develop, although loss of body weight may be masked by concurrent fluid retention and edema.

Syncope (see ch. 30) is encountered in some dogs with MMVD. Syncope may be associated with a tachyarrhythmia, but the character of these events often resembles vasovagal syncope.[77-79] The frequency of the syncope varies from occasional spells to several attacks per day. Other causes of syncope include tussive fainting that may occur in conjunction with paroxysms of coughing or exercise in the presence of pulmonary hypertension (see ch. 243).[76]

Isolated TR in the absence of pulmonary hypertension rarely results in clinical signs of disease.[72,76,80] Evidence of reduced exercise tolerance, weakness, or syncope occurs mainly in instances with pulmonary hypertension, developing as a consequence of longstanding severe MR, or tachyarrhythmia. It is common for these animals to show signs of right-sided CHF that may include respiratory distress due to pleural effusion; abdominal distention due to ascites, hepatomegaly, or splenomegaly; or gastrointestinal signs such as diarrhea, vomiting, and anorexia.

Although myxomatous degeneration is sometimes evident at postmortem on one or both semilunar valves,[72,76,80] myxomatous degeneration of these valves rarely results in significant leakages associated with clinical signs.

Physical Examination

A mid-systolic click might be encountered in early stages of MMVD (Audio 251-5),[81,82] but a systolic heart murmur is a more prominent clinical finding when performing cardiac auscultation on dogs affected by MMVD (Figure 251-3). However, lack of an audible murmur cannot rule out mild regurgitation.[83] The sound begins as a soft systolic murmur with the point of maximal intensity over the mitral valve area on the left side of the thorax, and may be intermittent (Audio 251-1).[84,85] In the early stages of MMVD, the murmur can

often be augmented by physical maneuvers, such as a short run.[81] A soft murmur in a small-breed dog with MMVD is indicative that disease severity is mild and that CHF is unlikely.[85] With further disease progression, a murmur of "harsher" and more intense quality, and longer duration (holosystolic) develops (Audios 251-2 and 251-3; see Figure 251-3).[21,82,83,86,87] Moderate to severe murmurs radiate over to the other puncta maxima of the left and right side of the thorax, and loud heart murmurs are also accompanied with a palpable thrill on the left thoracic surface (cardiac apical area; see ch. 55). Dogs presenting with a precordial thrill rarely have mild disease, and are at higher risk of developing CHF and/or pulmonary hypertension.[85] Musical murmurs (whoop sounds) of high intensity occur less frequently, and murmurs of such character do not necessarily reflect the severity of MMVD (Audio 251-4).[82] Trivial, physiologic TR is common in dogs and this regurgitation is usually silent to auscultation. Pathological TR can be characterized by a systolic murmur with varying intensity and with the point of maximal intensity over the tricuspid area.

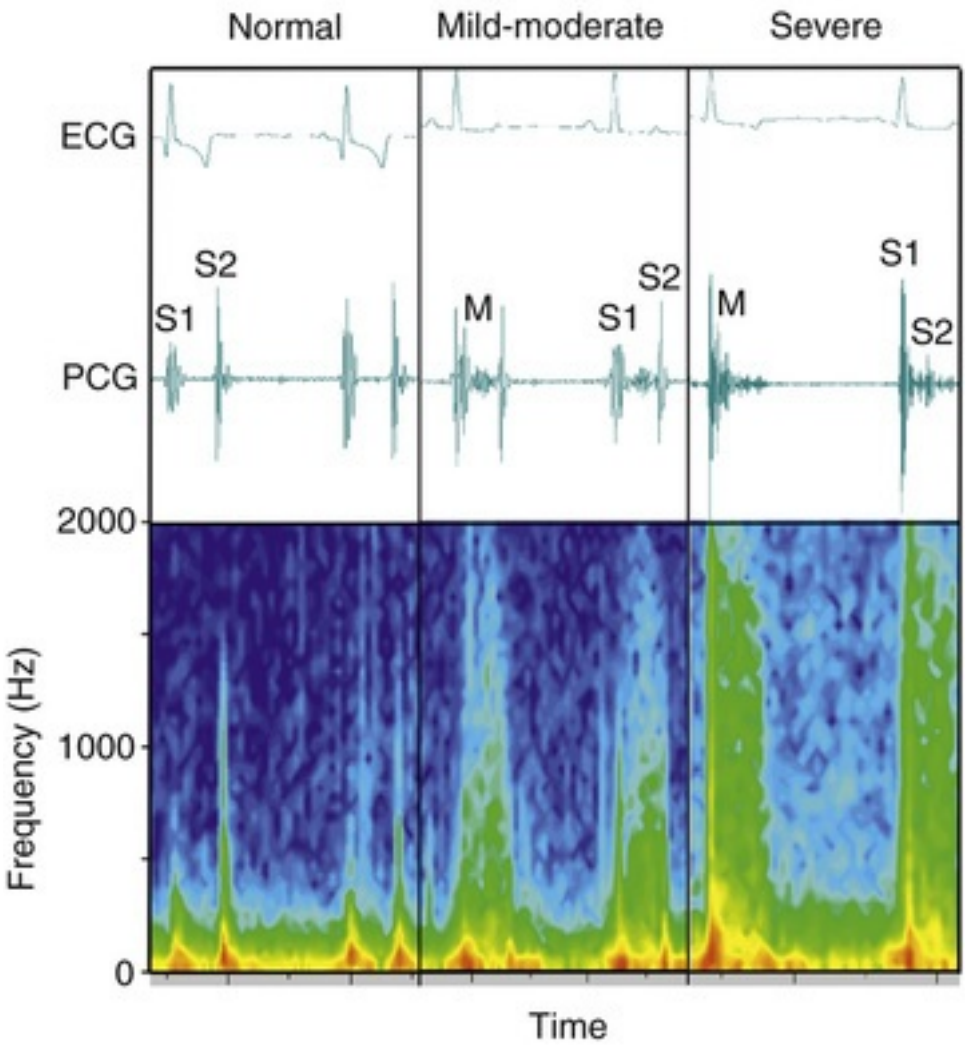

FIGURE 251-3 Phonocardiogram (PCG) in dogs with different stages of myxomatous mitral valve disease (MMVD). The recording is displayed in two modes, which are timed with respect to each other: The upper mode shows synchronous electrocardiographic (ECG Lead II) and phonocardiographic (PCG) traces; and the lower mode shows a time-frequency graph where different frequencies are displayed according to intensity, with high-intensity frequencies in red and low-intensity frequencies in blue. A holosystolic murmur (M) is present on the phonocardiograms from the dogs with mild-moderate and severe disease. Note that the frequency components of the murmur changes with disease severity. *S1,* First heart sound; *S2,* second heart sound.

Merging of the first heart sound (S1) with the forceful murmur might give an impression of increased intensity of the S1 when subjectively assessed by cardiac auscultation. However, advanced signal analysis has

shown that intensity of S1 remains comparably unchanged with increasing MR severity.[83] The sound intensity of S2 has been found to decrease with increasing disease severity (see Figure 251-3).[83,86] The intensity of S2 is considered to primarily depend on the rate of change in the pressure gradient across the aortic valve at closure,[88] and a decreased forward stroke volume[51] might explain why the intensity of the S2 decreases with increasing MMVD severity. A low-intensity third heart sound might be present, but this sound is often difficult to detect by standard auscultation.[82,86,87] The presence of a clearly audible third (gallop) sound is a strong indicator for myocardial failure.[82]

In dogs with MMVD without signs of CHF, the lung sounds and respiratory rates at rest are expected to be normal.[75] In dogs with more severe MMVD that show signs of CHF, the pulmonary sounds are usually more pronounced, and crackles, snaps, and popping sounds, best heard at end of inspiration, may be detected. Similar abnormal sounds are common in dogs with small airway disease,[89] and if occurring concurrently it may be a diagnostic challenge to determine the cause of the clinical signs. In the case of pulmonary congestion and edema, respiratory rates at rest or sleep are expected to be increased (i.e., >30 breaths/min).[75,90]

Mucous membranes are usually normal, even in dogs with CHF, but may occasionally be cyanotic, grayish, or ashen in advanced cases of CHF. Weak pulses may be noted in CHF. Weak and variable pulses with deficits can also be observed with rhythm disturbances (see ch. 248). If tamponade occurs, owing to pericardial hemorrhage due to a tear in the LA, the femoral pulse will be weak, and jugular venous distention may be present (see ch. 254).

Ascites in isolated MMVD is uncommon, but progressive MMVD often tends to involve the right side of the heart as a consequence of pulmonary hypertension and/or advanced myxomatous degeneration of the tricuspid valve, or due to development of a tachyarrhythmia. In these dogs, signs of right-sided CHF such as venous distention with signs of hepatomegaly and/or splenomegaly, pulsations in the jugular veins, in addition to ascites, may be present. The heart sounds may be muffled by pleural effusion.

Electrocardiographic Findings

Most ECG abnormalities associated with MMVD are the result of accentuations of the normal ECG. Electrocardiographic findings in MMVD vary from normal tracings to marked abnormalities in rate, rhythm, or configuration of complexes. With the exception to document and classify a certain arrhythmia, the ECG is of limited use in the diagnosis or management of MMVD.

Sinus arrhythmia is usually preserved early in the course of MMVD (see ch. 248). In dogs with CHF, sinus tachycardia and a loss of sinus arrhythmia are common. Supraventricular premature beats are commonly seen in MMVD dogs,[79,91] but this finding is of little hemodynamic significance in most dogs. Atrial fibrillation, paroxysmal supraventricular tachycardia, atrioventricular dissociation, ventricular premature beats, and ventricular tachycardia are less common. These arrhythmias are most often encountered in advanced cases and hence often indicate a poor prognosis.

ECG is an insensitive indicator of cardiac enlargement and cannot detect CHF (see ch. 103 and 248). The mean electrical axis in the frontal plane often remains within the normal range throughout the progression of the disease. In cases with significant LA enlargement, the P wave may be prolonged. In cases of significant LV enlargement, the QRS complex may be prolonged and the R wave amplitude in lead II increased.[92]

In significant TR with pulmonary hypertension, the ECG changes may include evidence of RA enlargement (tall P wave), an RV enlargement pattern, and a right deviation of the mean electrical axis.[92] However, even in severe cases of TR and pulmonary hypertension secondary to MMVD, these signs may not be obvious because of the concurrent changes to the left side of the heart. In these cases, the recording may only show evidence of left-sided involvement.[72,76]

Radiographic Findings

Left-Side Cardiac Chambers

The value of radiography is in assessment of the hemodynamic consequences of MMVD (global cardiac size and presence of pulmonary congestion and edema). Furthermore, radiography helps to exclude other possible causes for the clinical signs. In dogs with MMVD, important structures to evaluate are the LA, the LV, the mainstem bronchi, the pulmonary vessels, and the lung field. Dogs with mild MMVD usually have a normal heart size, normal lung fields, and normal vascular markings.

LA enlargement is one of the earliest and most consistent radiographic features of MMVD. The LA and LV

continue to enlarge with progression of the disease. Heart chamber enlargement, assessed by vertebral heart score (VHS), has been characterized by a slow phase of steadily progressing MMVD until about 6 to 12 months before onset of CHF, when the rate of change of enlargement is fast.[93] Signs of LA and LV enlargement on the lateral projection include dorsal elevation of the caudal portion of the trachea and carina, dorsal displacement of the left mainstem bronchus, and visible prominence of the LA causing the caudal border of the heart to appear straight or bulge dorsocaudally (Figure 251-4, *B*). In the dorsoventral (or ventrodorsal) projection, the enlarged LA appendage may be identified as a bulge in the left cranial part of the cardiac border (between the 2 and 3 o'clock positions). The border of the enlarged LV appears rounded and there may be a shift of the cardiac apex to the left or right.

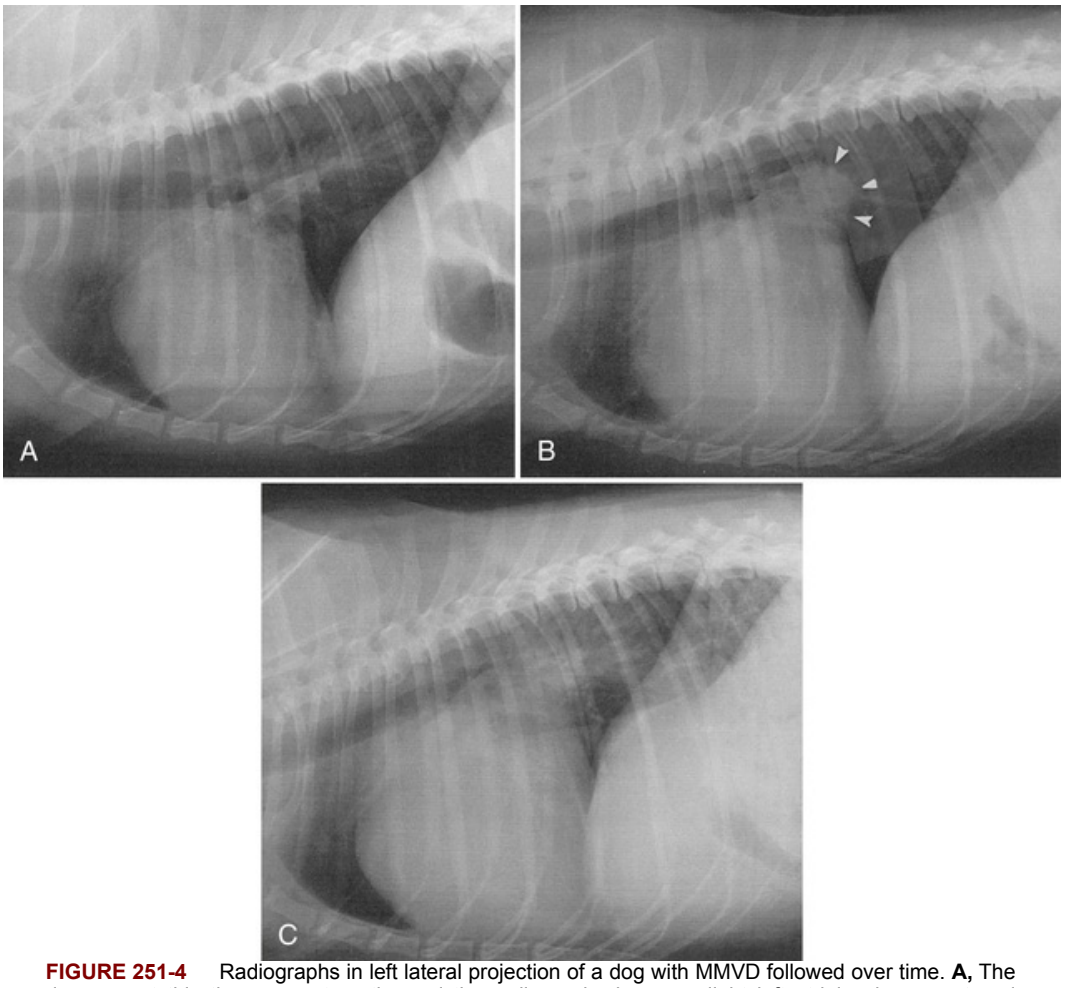

FIGURE 251-4 Radiographs in left lateral projection of a dog with MMVD followed over time. **A,** The dog was at this time asymptomatic, and the radiograph shows a slight left atrial enlargement and normal vascular perfusion. **B,** Radiograph of the same dog 4 years later. The dog had developed exercise intolerance and persistent cough. Marked left atrial (white arrowheads) and left ventricular enlargement, and elevation and slight compression of the left mainstem bronchus are visible, whereas the vascular markings are within normal limits. **C,** Six months later the dog had also developed dyspnea and had suffered episodes of syncope. In addition to the findings in the previous radiograph **(B),** there is a more obvious compression of the left mainstem bronchus and evidence of pulmonary congestion and interstitial edema. (Courtesy Kerstin Hansson, Uppsala, Sweden.)

During the progression of MMVD, radiographic signs of pulmonary congestion and edema may develop (Figure 251-4, *C*). Pulmonary congestion and edema are more likely to be present in a dog with significant heart enlargement (indicating advanced MMVD) than in a dog with normal or slightly increased heart size. However, the degree of cardiac enlargement is poorly related to the severity of pulmonary congestion and edema. Pulmonary venous distension, when present, is an early indication of pulmonary congestion; the diameter of the veins is greater than that of the corresponding pulmonary arteries and they often become tortuous (especially in cats). However, venous distention is not a consistent finding even in dogs with pulmonary edema, and in some dogs, the outlining of the distended vein is indistinct as interstitial edema

partially obscures the pulmonary vessels. In dogs, pulmonary edema is often first detected in the perihilar region and the dorsal parts of the caudal lung lobes, sometimes more prominent on the right side, but acute edema may involve the cranial lobes. In cats, the location of cardiogenic pulmonary edema is not as predictable as in MMVD dogs. It commonly has an ill-defined, patchy appearance.

Pulmonary findings may be inconclusive, as early radiographic changes of pulmonary interstitial edema and bronchial pattern resemble the radiographic appearance of chronic airway disease, and the tendency is to overdiagnose pulmonary edema when investigating radiographs from dogs with signs of cardiac enlargement.

Right-Side Cardiac Chambers

Mild RA and RV enlargement are usually not associated with detectable radiographic signs. Signs of moderate to severe RA enlargement on a lateral projection include bulging of the RA in the craniodorsal direction. This causes the cranial border of the heart to appear straight rather than convex and elevates the trachea as it courses dorsally over the RA. In addition to elevation of the trachea and dilation of caudal vena cava, signs of RV enlargement include increased sternal contact and rounding of the right heart border. In the dorsoventral (or ventrodorsal) projection, the enlarged RA may be identified as a bulge in the right cranial part of the cardiac border (in the 9 to 12 o'clock position). The border of the enlarged RV appears rounded and, if severely enlarged, it may resemble an inverted letter "D". There is a shift of the cardiac apex to the left. Signs of right-sided CHF may be observed, including pleural effusion, abdominal effusion, hepatomegaly, and splenomegaly. If biventricular failure occurs, the global cardiac size will be increased and signs of both left and right CHF may be present.

Echocardiographic Findings (see ch. 104)

Mitral Valve and Left-Side Cardiac Chambers

Echocardiography is useful for obtaining a diagnosis of MMVD, and thereafter to monitor the condition. Although some echocardiographic variables have been suggested to be useful for predicting the presence of CHF,[94] none of these variables has been shown to be more accurate and sensitive than other clinical tests, such as respiratory rate. Two-dimensional echocardiography allows the ultrasonographer to evaluate the anatomy of the mitral valve and to identify leaflet thickening and systolic leaflet protrusion (mitral valve prolapse) of one or both leaflets into the atrial side of the mitral annulus (Figure 251-5, *B*). Transthoracic real-time three-dimensional (RT3D) echocardiography has been reported to provide a more precise, extensive, non-invasive, *in vivo* evaluation of valvular anatomy in human cardiac patients (Video 251-16 and Figure 251-5, *C* and *D*),[95] and its potential in canine patients is currently under evaluation. Mitral valve prolapse is an early indication of MMVD and it might be present in dogs with or without MR (Videos 251-1, 251-2, 251-3, and 251-4).[96,97] The presence and severity of protrusion of the leaflets may be measured in the right parasternal long-axis view, and the degree of displacement is reported to correlate well with the severity of MR.[18,97,98] The gross pathologic changes of the two leaflets (anterior and posterior) are often equally severe at postmortem examination, but the degenerative changes commonly appear more prominent on the anterior leaflet in the right parasternal long axis view on the echocardiogram.[99] With progression, the degenerative changes become more prominent (Videos 251-5, 251-6, 251-7, 251-8, 251-9, 251-10, 251-11, 251-12, 251-13, 251-14, 251-15, and 251-16) and the leaflets often have a "club-like" appearance with greatest thickening at the tip (see Figure 251-5, *B* and *C*). Chordal thickening or a valve flail may be identified (Video 251-17; see Figure 251-5, *B* and *C*).[100,101] Valve flail is said to be present when the edge of a leaflet or, in severe cases, a complete leaflet moves into the LA in systole, and indicates rupture of one or more chordae tendineae, which may occasionally be identified in the LA or in the LV.[100-102]

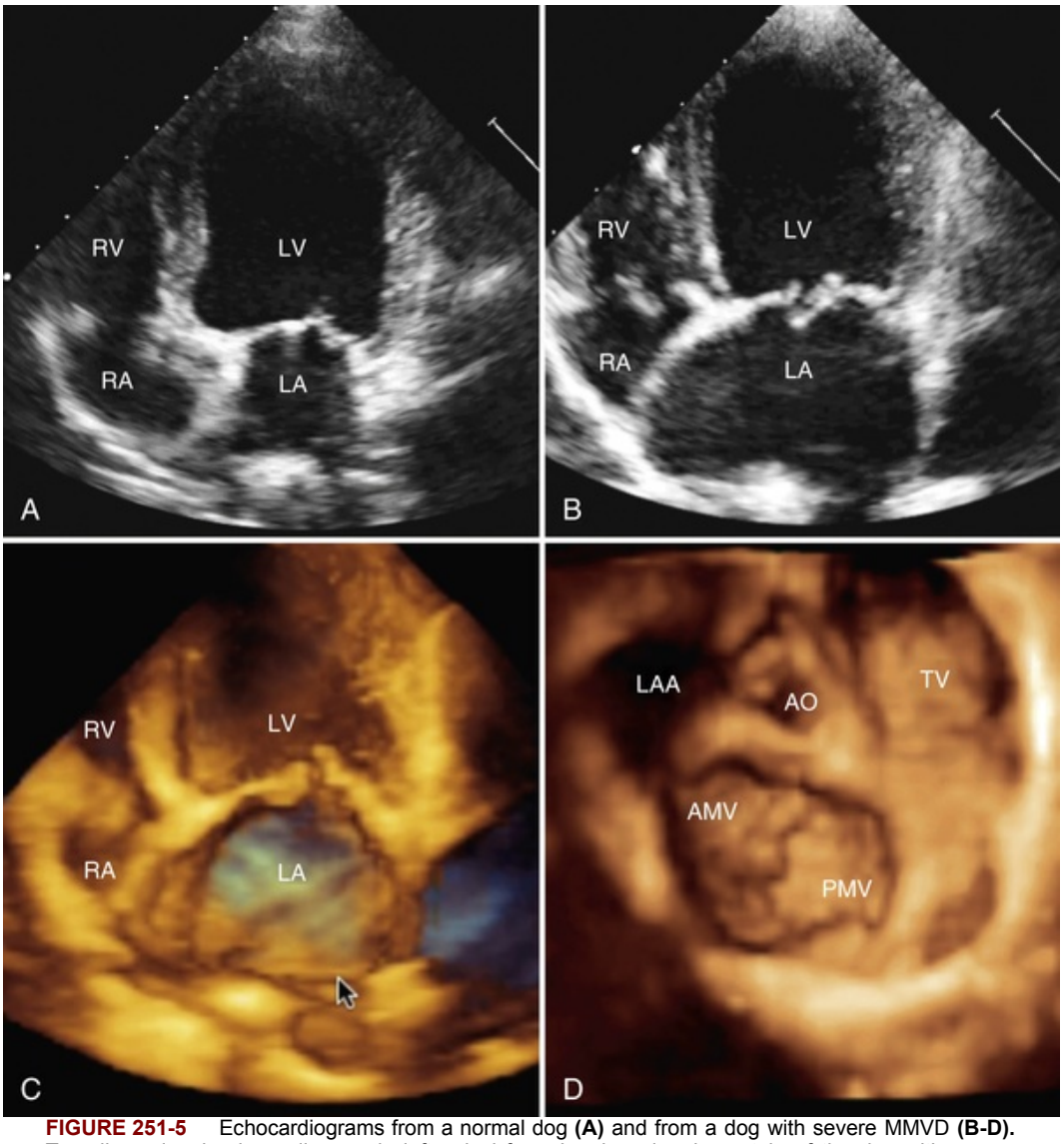

FIGURE 251-5 Echocardiograms from a normal dog **(A)** and from a dog with severe MMVD **(B-D).** Two-dimensional echocardiogram in left apical four-chamber view in systole of the dog with severe MMVD **(B)** shows bilateral prolapse of the mitral valve leaflets, prolapse of the tricuspid valve leaflet and left atrial and ventricular dilatation. Three-dimensional (3D) echocardiogram from the same dog in the same view in late diastole **(C),** and the mitral valve viewed *en face* in a 3D echocardiogram from the atrial side **(D)** during systole. Prolapse is evident at several locations on both leaflets. *Ao,* Aorta; *AMV,* anterior mitral valve leaflet; *LA,* left atrium; *LAA,* left atrial appendage; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle; *PMV,* posterior mitral valve leaflet; *TV,* tricuspid valve.

The LA is an important structure to evaluate in dogs with MMVD because its size reflects disease severity.[50] Although the LA may be examined from several views, the view of choice is the right parasternal short axis view with the aortic root, the LA body and the auricle in view. The most useful information from this view is the LA size because it can be compared with the size of the aortic root, which is relatively constant for a given dog size. In dogs with MMVD, the diameter of the LA body may be considerably greater than that of the LA appendage.[103] Early cases of MMVD with a small degree of MR have no echocardiographic signs of LA enlargement. With progression of MMVD, the LA dimension increases and dogs in CHF often have an LA to aortic root ratio (LA/Ao) of 2 or greater.[104] Real time 3D echocardiography allows for more accurate volume estimations of the LA, and the potential of LA volume assessment by RT3D echocardiography has recently been demonstrated in MMVD dogs.[105] However, a shortcoming of the RT3D technique is that it is more time-consuming compared to traditional echocardiographic techniques, and a normal reference range for LA volume is currently not available.

LV anatomical dimensions, volume and function can be assessed subjectively or by using various echocardiographic quantitative techniques. Traditional clinical echocardiographic assessments of the LV rely

on dimension estimates from 1-dimensional (M-mode) and/or two-dimensional (2D) images. However, LV size can also be evaluated using volume estimates based on either 2D (Simpson's modified disc method) or 3D imaging techniques (Figure 251-6, *A*).[106] The potential of LV volume assessment has been demonstrated in MMVD dogs,[64,107] but normal reference range for LV volumes is currently only available for a few breeds. Normal LV size, or only a mildly enlarged LV is seen in dogs with mild MMVD. With progression, the LV end-diastolic short axis dimension and volume increase, whereas the end-systolic measurements do not increase at the same rate.[64,93] The rate of change increases and is highest when the dogs are in close proximity to CHF (Figure 251-6, *B* and *C*).[93] The LV wall thickness is usually within normal limits. The increased size of the LV combined with a normal wall thickness indicates presence of volume overload and eccentric hypertrophy.

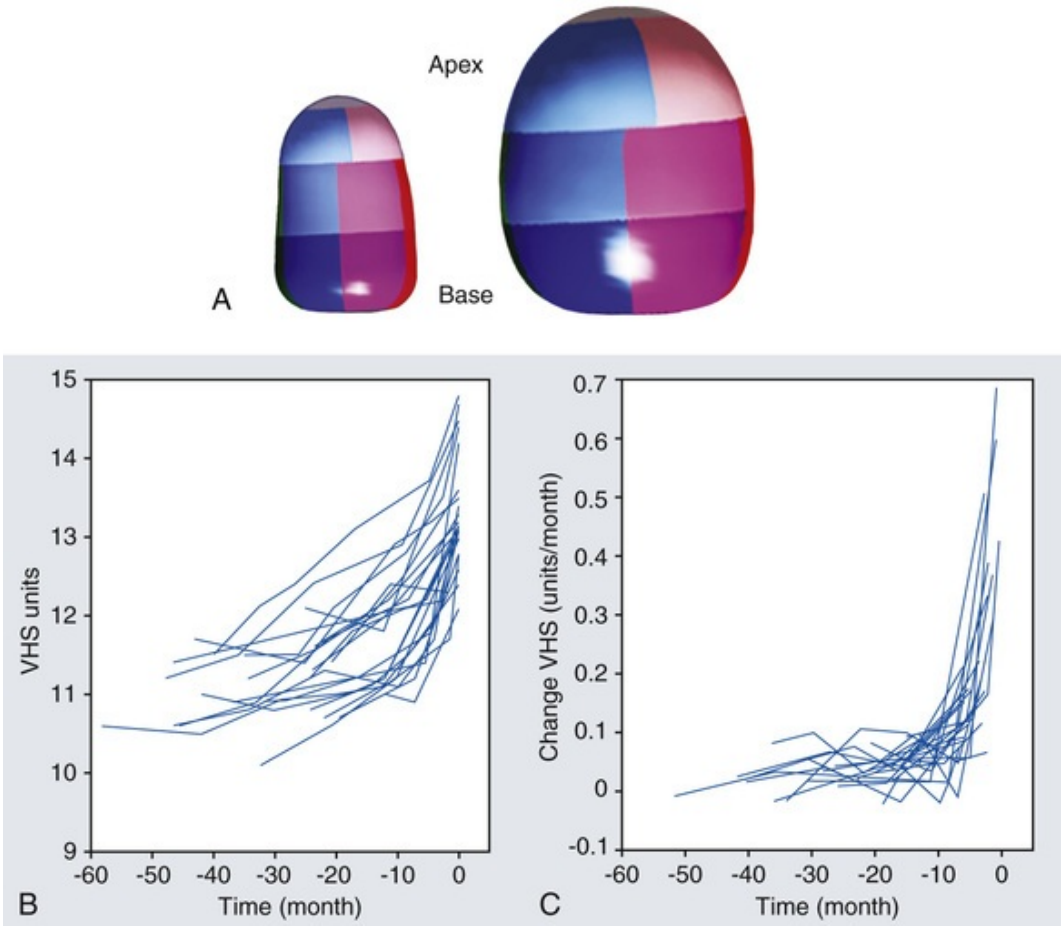

FIGURE 251-6 **A,** Left ventricular (LV) casts obtained from the 3D dataset of a healthy dog (left) and a dog with severe MMVD (right). The LV cast is automatically divided into 17 segments. The LV volume is clearly increased in the diseased dog, and the shape is changed from an elliptical to a more globular form (increased sphericity) in response to the increasing volume overload. Plots of radiographic vertebral heart score (VHS) **(B)** rate of change of VHS and **(C)** against time in ACVIM stage B dogs progressing into CHF (time 0). During the progression of MMVD, heart size is characterized by a slow rise until about 6 to 12 months before the onset of CHF, after which the rate of change increases as the dogs are progressing into CHF. (**B** and **C,** From Lord P, Hansson K, Kvart C, et al: Rate of change of heart size before congestive heart failure in dogs with mitral regurgitation. *J Small Anim Pract* 51:210-218, 2010. Published with permission from the publisher.)

Changes in LV shape, accompanying LV dilation, can be evaluated using a sphericity index, either on 2D or 3D echocardiographic images.[64] A RT3D echocardiographically derived sphericity index, which can be obtained by dividing the end-diastolic volume by the volume of a sphere, has been demonstrated as an earlier and more accurate predictor of remodeling compared to other echocardiographic variables in people.[108] The sphericity index is usually not included in the routine echocardiographic protocol when assessing LV remodeling in MMVD dogs, but this index might be useful for evaluation of LV remodeling progression in

dogs.[64]

Although myocardial systolic function declines with progression of MMVD, the remodeling process allows the LV to maintain a relatively well-preserved forward cardiac pump function even in advanced MMVD.[51,66] Identification of systolic dysfunction using echocardiographic modalities is challenging in dogs with MMVD.[109] Many of the commonly used echocardiographic indices for evaluating systolic function, such as the ejection phase indices (e.g., LV fractional shortening, ejection fraction, and mean velocity of circumferential shortening) are, besides being dependent on intrinsic contractility, also known to be influenced by hemodynamic load and sympathetic tone, thereby potentially masking significant myocardial dysfunction in dogs with MR.[109] In dogs with mild MMVD, values of ejection phase indices are often normal, whereas the values can be greater than normal in dogs with moderate to severe MMVD. Therefore, in the setting of moderate or severe MMVD, a normal fractional shortening commonly represents a reduction of myocardial contractility. Assessment of LV end-systolic dimension or volume has been suggested to better reflect systolic dysfunction in the presence of MR.[66,110] The end-systolic dimension or volume increases as the systolic function declines, despite increasing retrograde LV stroke volume into the low resistance LA.[66] But if the LV contractile function is preserved, the fully compensated LV will shorten to an almost normal end-systolic dimension.[109] The end-systolic volume indices have been shown to increase in dogs with more severe MMVD, indicating systolic dysfunction.[64,110] The more recently introduced tissue Doppler imaging (TDI) and speckle tracking techniques have been considered comparably independent of loading conditions, but studies suggest that these techniques are affected by loading conditions and sympathetic tone activity to a greater extent than previously expected. Similar to fractional shortening, LV strain and strain rate values appear to be increased in moderate-to-severe MMVD, but the values can decrease (return to values found in normal dogs) at more advanced stages, indicating myocardial failure.[111] This might limit the additional informative value obtained from this technique, compared to when using end-systolic volume indices in MMVD dogs.

Valvular regurgitations can be detected and quantified by spectral and color-flow Doppler (Figure 251-7, *A*).[81] Ideally, the regurgitant flow should be aligned with the ultrasound beam and this is most often achieved in the left apical four-chamber view. As the flow direction depends on the orientation of the regurgitant orifice, which in turn depends on the leaflet morphology, other views may also give good alignment.

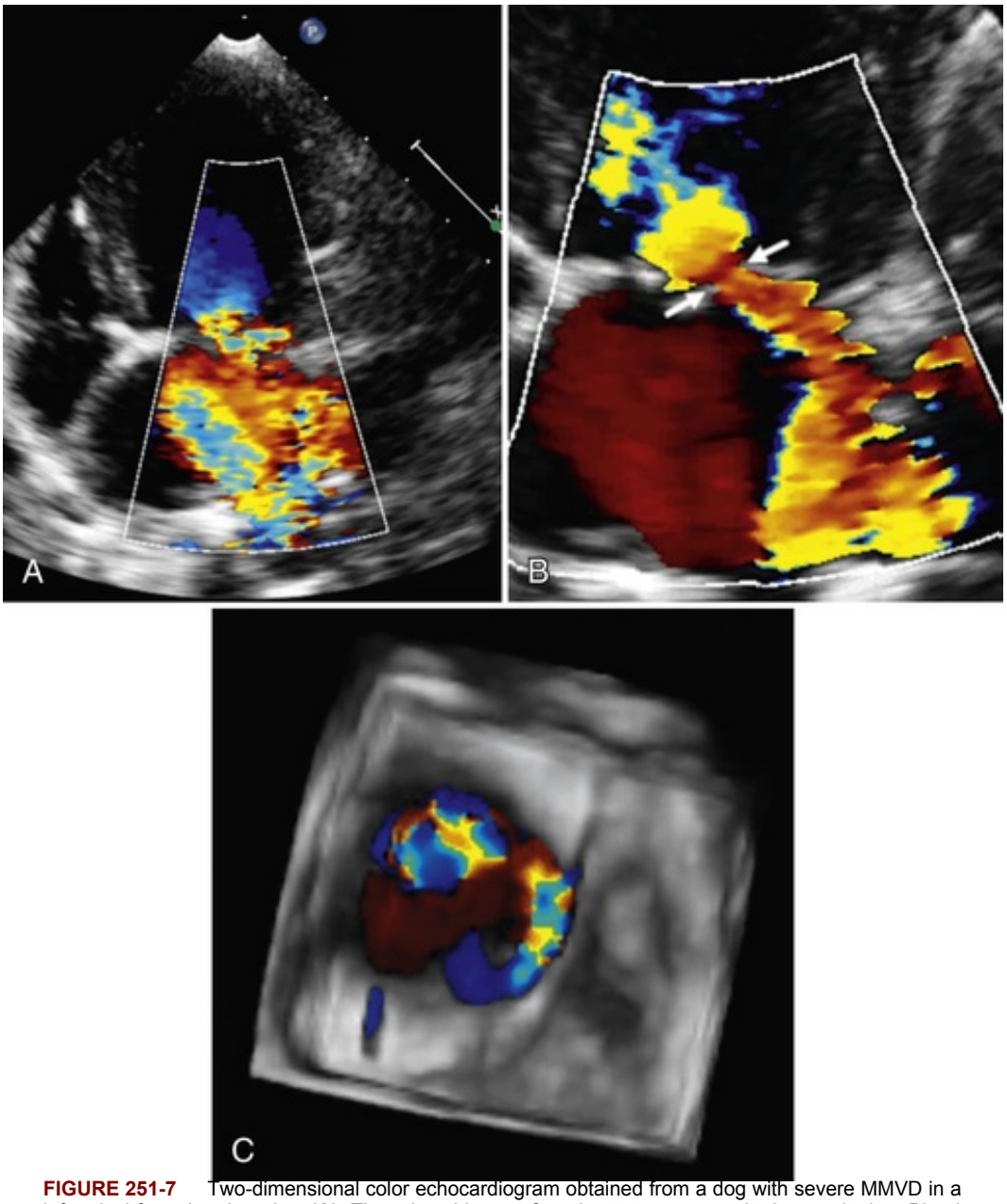

FIGURE 251-7 Two-dimensional color echocardiogram obtained from a dog with severe MMVD in a left apical four-chamber view **(A).** There is evidence of moderate to severe mitral regurgitation. Blood accelerates on the ventricular side towards the regurgitant orifice of the valve, and there is a laterally directed jet and turbulent flow in the left atrium. Severity of mitral valve regurgitation may be assessed by relating the area of the jet to the left atrial area, or by using the radius of the hemicircle created when the blood flow converges on the ventricular side before it passes the regurgitant orifice (proximal isovelocity surface area [PISA] method; see text for details), or as illustrated in a zoomed color Doppler echocardiogram in **(B),** by measuring the diameter of the vena contracta, which is the narrowest central flow region of a jet that occurs at, or just downstream to, the orifice of the regurgitant valve (arrows). The area of the vena contracta, which is approximately the same as the effective regurgitant orifice, may be assessed using color Doppler 3D echocardiography as illustrated in **C,** where the mitral valve is inspected from the atrial side and mitral regurgitation is evident at two sites.

Color-flow Doppler echocardiography confirms the presence of a regurgitant jet, and the size of the jet can be compared with the size of the LA (see Videos 251-2, 251-4, 251-6, 251-8, 251-11, 251-13, and 251-15, and ch. 104). This measurement is dependent on the ultrasound system settings, and is semiquantitative in dogs and cats. A small jet rules out moderate to severe MR, but it is often difficult to clearly discriminate between moderate and severe regurgitation based on information from the jet size. Small jets in the vicinity of the mitral valve should not be over-interpreted in dogs without any other valve abnormality, as trivial regurgitations may often be detected in normal dogs.

Spectral Doppler gives information of the velocity of the regurgitant jet and velocity time tracings may help

in estimating regurgitant volume (see ch. 104). The systolic transmitral pressure gradient can be estimated by calculating the peak MR gradient using the simplified Bernoulli equation: Peak MR pressure gradient = 4 × (MR velocity)^2. Typically, dogs with MMVD without significant myocardial failure have a velocity of the regurgitant jet of 5 to 6 m/sec.[80] However, the velocity may be increased in individuals with systemic hypertension, and decreased in individuals with hypotension, significantly increased LA pressure and/or myocardial failure. Accordingly, the velocity of the regurgitant jet is typically below 5 m/sec in dogs with acute fulminant CHF.

Regurgitant fraction is the percent of total LV stroke volume that flows back into the LA chamber. Measurements of regurgitant fraction in dogs with moderate to severe MR indicate that they can eject more than 75% of the total stroke volume into the LA.[50] There are several ways to estimate regurgitant volume and fraction. The MR stroke volume may be estimated indirectly using the volumetric method by calculating the difference between total stroke volume and forward stroke volume into the aorta. The total stroke volume may be estimated using 2D based disc summation method (modified Simpsons' rule) of LV volume, and the forward stroke volume may be estimated by multiplying the aortic cross-sectional area with the velocity time integral obtained from the spectral Doppler tracing of the aortic flow (see ch. 104). Alternatively, the total stroke volume may be estimated by multiplying the annular cross-sectional area of the mitral valve obtained from the two-dimensional mode with the velocity time integral obtained from the spectral Doppler tracing of the diastolic flow over the valve. Both these methods involve multiple measurements, each with its own errors, which means that they will only provide estimates of regurgitant volume. Regurgitant fraction is calculated by dividing the regurgitant stroke volume by the total LV stroke volume.

The regurgitant fraction may also be quantified with use of the proximal isovelocity surface area (PISA) color-flow method in dogs with MR (Figure 251-7, *B*).[50,112] In MR, blood flow converges on the ventricular side of the mitral valve orifice before it passes the regurgitant orifice, and this area is characterized on the color Doppler echocardiogram as a hemisphere. Based on the values of the radius of this hemisphere, the aliasing velocity, the maximal velocity of the regurgitant jet, and the velocity time integral of the regurgitant flow (the latter two are obtained from spectral Doppler measurements), the regurgitant stroke volume may be calculated. The regurgitant fraction is obtained by dividing the regurgitant volume with the sum of the forward and regurgitant stroke volumes. Although this method has significant advantages compared to other methods of measuring regurgitant fraction, it has several practical limitations and may not be readily applicable in all cases of MR. Furthermore, none of the Doppler methods has been shown to be more reliable indicators of disease severity than LA size in dogs and cats with MR.

Another, more straightforward method to assess severity of MR is to measure the diameter of the vena contracta on the color echocardiogram, a method that has been applied in dogs.[101,113] The vena contracta is defined as the narrowest central flow region of a jet that occurs at, or just downstream to, the orifice of a regurgitant valve, and where the blood velocity is highest (see Figure 251-7, *B*).[114] The vena contracta in MR or TR is usually measured on the 2D color echocardiogram as a diameter in the left apical four-chamber view, but 3D color echocardiography can provide measurements of vena contracta area, which may provide a more accurate estimate of effective regurgitant orifice. In fact, the vena contracta area in MR or TR is not a circle; it is more spherical owing to regurgitation occurring along the line of leaflet coaptation (Figure 251-7, *C*). Regardless of whether the vena contracta diameter or area is measured, the method has shown good agreement with angiocardiographic grade of MR and regurgitant volume in people.[114]

Spectral Doppler may also be used to study the transmitral flow during diastole. Significant MR is usually associated with increased diastolic filling velocities as a consequence of increased diastolic transmitral flow.[115] Furthermore, abnormal diastolic ventricular function, as a consequence of severe volume overload, may be detected. It is important to time the events when evaluating the transmitral flow to separate systolic regurgitation from diastolic flow to avoid a false-positive diagnosis of clinically significant MR. Diastolic regurgitation is common in cases with bradycardia (and second-degree AV block), or arrhythmias, and probably indicates small reverse pressure gradients during cardiac filling.[116]

Tricuspid Valve and Right-Side Cardiac Chambers

The echocardiographic appearance of the tricuspid valve affected by myxomatous degeneration is similar in two-dimensional mode to the myxomatous lesions on the mitral valve already described. With the use of color-flow Doppler, TR may be detected and semiquantified. The RA is, however, not as easily accessible as the LA owing to the anatomy, and the orientation of TR jets is not consistent. Pulmonary hypertension is a common complication in dogs with MMVD, and echocardiography is the standard veterinary non-invasive

technique for diagnosing the condition (see ch. 243).[57] Spectral Doppler may be used to estimate RV stroke volume and to identify pulmonary hypertension by estimation of RV systolic pressure and pulmonary arterial systolic and diastolic pressures.[80] The pressure gradient between the RA and RV may be calculated with use of the peak velocity of the regurgitant jet and the modified Bernoulli equation as outlined above.[57,117] The RV systolic pressure is obtained by adding an estimate of the RA pressure to the calculated pressure gradient over the AV valve. It is arbitrarily considered to be 5 mm Hg in the absence of RA dilatation, 10 mm Hg in the presence of RA dilatation but no sign of right-sided CHF, and 15 mm Hg in dogs with right-sided CHF.[117]

Similarly, the peak velocity of a pulmonic valve regurgitation and an estimate of RV diastolic pressure may be used to predict pulmonary artery diastolic pressure.[118]

Pulmonary hypertension can be diagnosed if the peak TR velocity is >3 m/sec corresponding to a peak TR gradient >36 mm Hg.[57] Lack of TR on an echocardiogram cannot preclude a diagnosis of pulmonary hypertension in MMVD dogs. Additional echocardiographic findings indicating pulmonary hypertension include signs of hypertrophy and dilatation of the RV, dilatation of the pulmonary artery, and flattening or paradoxical motion of the interventricular septum.[57]

Significance and Progression

Myxomatous mitral valve disease accounts, in comparison to many other canine diseases, for a high morbidity and mortality in affected breeds, and the disease has been reported to account for 75% of the cases of CHF in dogs,[70] a proportion of which is considerably higher in affected breeds.[12,21,119] Progression of the disease varies between individuals, but affected dogs can usually compensate the MR for a very long time. The progression of MMVD from the detection of a soft heart murmur to end-stage disease is often a matter of years in small dogs, but some large dogs appear to be less tolerant to MMVD: In these dogs, the disease has a more drastic progression with more severe clinical signs than in small dogs.[120] It is important to stage the severity of disease for risk assessment, for treatment decisions and for establishing prognosis. In 2009, an ACVIM Consensus statement was published and it was recommended to stage dogs with MMVD into four groups of dogs: From Stage A to D (Table 251-1).[121]

TABLE 251-1

ACVIM Consensus Recommends Staging MMVD Dogs Into Four Classes (A to D)[121]

<table>
<tr><th>STAGE A</th><th colspan="2">STAGE B</th><th>STAGE C</th><th>STAGE D</th></tr>
<tr><td rowspan="2">Dogs at risk for developing heart disease but that currently have no identifiable structural disorder of the heart (e.g., Cavalier King Charles Spaniels without heart murmur)</td><td colspan="2">Dogs without clinical signs, but presenting with a systolic click (early stage) and/or systolic heart murmur</td><td rowspan="2">Dogs with past or current clinical signs of CHF associated with structural heart disease. Severity of clinical signs of CHF range from mild to severe, the latter requiring aggressive therapy that more typically would be reserved for those with refractory disease (see Stage D).</td><td rowspan="2">Dogs with end-stage disease presenting clinical signs of heart failure caused by AV valve regurgitation that are refractory to standard CHF therapy. Such patients require advanced or specialized treatment strategies in order to remain clinically comfortable with their disease.</td></tr>
<tr><td>B1</td><td>B2</td></tr>
<tr><td></td><td>Dogs presenting with evidence of mild MR (heart murmur and echocardiographic signs of AV valve regurgitation) but no signs of cardiomegaly</td><td>Asymptomatic dogs that have hemodynamically significant AV valve regurgitation, as evidenced by radiographic or echocardiographic findings of cardiomegaly</td><td></td><td></td></tr>
</table>

Although a risk exists for future development of CHF, many affected dogs will never develop clinical signs from the disease during their lifetime.[87,99,121,122] Risk factors for progression from mild to severe MMVD include age, sex, breed, severity of valve lesion, severity of MR, LA and LV dilatation, heart rate, circulating concentrations of N-terminal pro-B-type natriuretic peptide (NT-pro BNP) and cardiac-specific troponin I (cTnI), arrhythmias and syncope.[4,21,70,87,98,99,101,123-128]

Differential Diagnosis

Mitral Regurgitation

Although the usual cause for MR is myxomatous degeneration, other causes of MR are noteworthy: dilated cardiomyopathy and other myocardial diseases; bacterial endocarditis of the mitral valve; or previously undiscovered congenital heart disease, such as mitral valve dysplasia or patent ductus arteriosus (PDA). However, the signalment, clinical signs, and physical examination findings are often of such character that they strongly suggest MMVD. Early cases of MMVD may have a mild and early-systolic heart murmur that may be confused with physiologic flow murmur or murmurs due to congenital heart disease, such as mild aortic or pulmonic stenosis. However, dogs with physiologic flow murmurs or aortic or pulmonic stenosis are usually young and have a murmur with maximal intensity over the heart base, whereas dogs with mild MMVD are usually older and have a murmur with maximal intensity over the mitral area. However, the age of onset of MMVD is variable and an echocardiographic examination should always be performed to confirm the diagnosis. The exclusion of dilated cardiomyopathy and hypertrophic cardiomyopathy also requires an echocardiographic examination.

The echocardiographic appearance of a mitral valve affected with endocarditis may appear very similar to nodular thickening of valve leaflets characteristic for myxomatous degeneration. However, lesions of endocarditis may be more echogenic and more isolated. Furthermore, bacterial endocarditis patients often have a history of fever, arthritis, systemic disease, a recently developed heart murmur, and clinical signs that may indicate thromboembolic disease,[129] whereas dogs with MMVD often have had a heart murmur for years, and do not have fever or other signs of systemic disease.

Tricuspid Regurgitation

Secondary or functional TR may occur as a consequence of RV dilatation in all conditions associated with an acquired increase in RV pressure. These include heartworm disease, pulmonary thromboembolism, pulmonary hypertension secondary to left heart disease, and idiopathic pulmonary hypertension. In addition, secondary TR occurs in biventricular or dilated cardiomyopathy and in congenital pulmonic stenosis. It is unusual for the tricuspid valve to be affected by infective endocarditis or chordal rupture.[72,80] Tricuspid regurgitation can be seen in cats with cardiomyopathy and hyperthyroidism.[130]

Nonspecific Clinical Signs

Although MMVD may readily be diagnosed in a patient with clinical signs, the true diagnostic challenge lies in determining if decompensated CHF is the underlying cause of the clinical signs present. Most dogs with MMVD are older, small to medium-sized, and many of these dogs have rather minor demands on daily exercise level. Thus, exercise intolerance may be difficult to identify. Furthermore, the clinical hallmarks of left-sided CHF, such as coughing, dyspnea and tachypnea, may be caused by several conditions, such as small airway disease (see ch. 241), tracheal instability (see ch. 241), pulmonary fibrosis (see ch. 242), neoplasia (see ch. 242), heartworm disease (see ch. 255), and pneumonia (see ch. 242). Many of these differential diagnoses can be excluded by different clinical tests, particularly radiography, but in some cases, the results may be inconclusive. This includes measurement of natriuretic peptides, which may aid in distinguishing mild from severe MMVD, and distinguishing dyspnea from primary respiratory disease from dyspnea caused by CHF.[131,132] Dogs may present with a combination of significant MMVD and primary respiratory disease, and the additional value of natriuretic peptides is limited in this setting. In these inconclusive cases, a 48- to 72-hour diuretic therapy trial followed by evaluation of respiratory rate (respiratory rate is then compared with values prior to initiation of diuretics) and repeat radiographs may help to identify the underlying etiology.

Management

Ideally, the therapy of MMVD should halt the progression of the valvular degeneration, or improve valvular function. No therapy is currently known to inhibit or prevent the valvular degeneration, whereas surgical repair or valve replacement has the potential to improve valvular function. Case series with comparably good outcomes have been reported for surgical mitral valve repair,[133] but this procedure is only available at very few sites in the world, and, therefore, not technically, economically, or ethically possible for most canine and feline patients. The management of MMVD is therefore mainly concerned with improving quality of life, by prolonging the preclinical (asymptomatic) phase, ameliorating the clinical signs, and improving survival. This

usually means that therapy is tailored for the individual patient, owner, and practitioner, and often involves concurrent treatment with two or more drugs once signs of CHF are evident. Management of MMVD will be discussed in four groups of patients: (1) dogs without signs of CHF (ACVIM Stage B); (2) dogs with mild to moderate signs of CHF (ACVIM Stage C); (3) dogs with recurrent CHF (ACVIM Stages C or D); and (4) dogs with severe and life-threatening (fulminant) CHF (ACVIM Stages C or D).[121] Possible complications are discussed separately. It is unusual to treat cases of isolated MMVD in cats and details of drug dosages for cats are therefore not included in this section.

Dogs without Signs of CHF (ACVIM Stage B)

Dogs belonging to ACVIM stage B are a comparably heterogeneous group of dogs ranging from dogs having only mild MR and normal heart size (ACVIM Stage B1) to dogs having severe MR and significant LA and LV dilatation (ACVIM Stage B2). This dilemma leads to the questions of when to start therapy, and if therapy before the onset of decompensated CHF is beneficial, ineffective or harmful. ACE inhibitors are frequently prescribed to dogs with MMVD before the onset of CHF, even to dogs in ACVIM Stage B1. At present, however, there is no evidence that ACE-inhibitor therapy has a preventive effect on development and progression of clinical signs of CHF, or improves survival in ACVIM Stage B MMVD dogs. Two large placebo-controlled multicenter trials, the SVEP and the VETPROOF trials,[87,122] have been conducted to study the effect of monotherapy of the ACE inhibitor enalapril on the progression of clinical signs in asymptomatic MMVD in dogs. Both failed to show a significant difference between the placebo and the treatment groups in time from onset of therapy to confirmed CHF,[87,122] regardless of whether the dogs were in ACVIM Stage B1 or B2.[87] Beta-receptor antagonists have shown to have some beneficial effects in experimental MR by improving the hemodynamic situation and myocardial contractility.[134] There are, however, very few studies of the effect of beta-receptor antagonists in naturally occurring MMVD,[135,136] and there is currently no conclusive evidence that these drugs have a preventive effect in asymptomatic MMVD. Indeed, a large, prospective, placebo-controlled clinical trial including ACVIM Stage B MMVD dogs was terminated prematurely because of lack of efficacy. Arterial vasodilators, such as amlodipine, have been suggested to be beneficial in stage B2 MMVD, because a reduction of aortic impedance may theoretically reduce MR. Amlodipine has been studied at a dosage of 0.57 mg/kg PO q 12 h in dogs.[137] The clinical documentation of amlodipine is scarce, but it has been assessed in a non-blinded echocardiographic study of dogs with MMVD, where a significant improvement in regurgitant stroke volume and regurgitant orifice area, as well as blood pressure reduction (10%) was reported.[138] The inodilator (a combined calcium sensitizer/phosphodiesterase III inhibitor) pimobendan has, in addition to its inotropic effect, arterial vasodilatory effects in dogs.[139,140] Pimobendan has been shown to decrease cardiac size in MMVD dogs, both in the short and long term,[141,142] an effect which potentially could delay the onset of signs of CHF in ACVIM Stage B2 dogs. The EPIC trial is a large prospective placebo controlled multicenter trial including ACVIM Stage B2 MMVD dogs and was designed to compare the effectiveness of pimobendan to placebo in the prevention of the onset of signs of CHF. In 2015, the trial was terminated prematurely because an interim analysis concluded that there was clear evidence of benefit of pimobendan administration in prolonging the time to development of left-sided CHF, or death presumed to be cardiac in origin. The interim analysis did not raise any concern over the safety of pimobendan administration. Full and final results of the EPIC trial were not yet available at the time of writing this chapter.

Disease progression may be monitored at regular rechecks at 3 to 12 months if cardiomegaly is present. Milder cases do not warrant as frequent monitoring (see Significance and Progression). Owners of dogs with asymptomatic MMVD should be instructed about signs of developing CHF and, in case of breeding, about the fact that the disease is significantly influenced by genetic factors. Owners should be instructed to count sleeping/resting respiratory rates at home, and be informed that a respiratory rate consistently >30 breaths/minute is abnormal and warrants further investigation as this can be an indication of CHF.[75]

At present, there is little evidence-based information concerning the effects of exercise and diet on the progression of MMVD in dogs. Dogs with mild MMVD do not need any dietary or exercise restriction, and it is our experience that dogs with advanced asymptomatic MMVD usually tolerate comparably long walks at their own pace, have a better quality of life with this type of exercise, and do better if obesity is avoided. However, from a pathophysiological standpoint, strenuous exercise or diets with high sodium content should be avoided in advanced MMVD Stage B2 dogs as this may promote pulmonary edema.

Dogs with Mild to Moderate Signs of CHF (ACVIM Stage C)

The stage when a patient starts to show clinical signs of MMVD (i.e., has developed decompensated CHF) is the end of a process started much earlier with the onset of valve leakage. Considering the pathophysiology of MMVD, therapy should be directed toward: (1) reducing the venous pressures to alleviate edema and effusions, (2) maintaining adequate cardiac output to prevent signs of weakness, lethargy and prerenal azotemia, (3) reducing the cardiac workload and valvular regurgitation, and (4) protecting the heart from negative long-term effects of neurohormones.

Dogs with mild to moderate pulmonary edema can often be managed on an outpatient basis with regular re-examinations. Cases with moderate to severe pulmonary edema may need intensive care, including cage-rest and sometimes oxygen supplementation (see ch. 131 and 141). The cornerstone of the CHF therapy is a diuretic, most often furosemide, and drugs with other modes of action are added to the diuretic agent (see ch. 247). A commonly used combination of drugs in this setting includes triple therapy of a loop diuretic (furosemide or torsemide), pimobendan and an ACE inhibitor. Spironolactone and/or digoxin are also frequently used.

The dosage of furosemide should preferably be based on clinical signs rather than radiographic findings. A patient may breathe with ease even in the presence of radiographic signs of interstitial edema, or vice versa. The usual course of treatment of a case with mild to moderate CHF is an initial intensive treatment with furosemide (2-4 mg/kg IV, IM, SC q 8-12 h) for two to three days, after which the dosage of diuretic is decreased to a maintenance level, such as 1-2 mg/kg PO q 12-48 h or lower. More severe cases of CHF may require higher dosages. It is important to use an appropriate dosage of diuretic to relieve clinical signs, but avoid an unnecessary high maintenance dosage. Overzealous use of diuretics may lead to weakness, hypotension, syncope, aggravation of prerenal azotemia and acid-base and electrolyte imbalances. Accordingly, the lowest dosage of diuretics possible, that can keep the dog free from clinical signs of CHF, should always be used. The owner should be informed about the need for regular contact with the veterinarian for an optimized treatment strategy for the individual dog. Oftentimes, the owner can be instructed to vary the dosage, within a fixed dose range, according to the need of the dog. Torsemide is an alternative to furosemide. It is also a loop diuretic, but with longer duration of action, decreased susceptibility to diuretic resistance, and adjunctive aldosterone antagonist properties compared with furosemide.[143] The recommended dosage of torsemide is 1/10 of the furosemide dosage.[143]

Several clinical trials indicate that pimobendan is indicated as first-line treatment in dogs with CHF caused by MMVD. Indeed, pimobendan is now approved for veterinary use in dogs with DCM or MMVD in many countries at a dosage of 0.25 mg/kg PO q 12 h. Data from two multicenter controlled clinical trials (the VetSCOPE and the QUEST trials)[124,144] and one single-center clinical study[145] concerning the efficacy of pimobendan in dogs with CHF caused by MMVD are available. The results show that dogs with CHF caused by MMVD receiving pimobendan as adjunct therapy to diuretics show less severe signs of CHF and have a longer survival time (as indicated by a prolonged time from onset of therapy to a composite endpoint of death/euthanasia from a cardiac cause or a treatment failure) than those receiving an ACE inhibitor and diuretics.[124,144,145] Indeed, pimobendan therapy was shown in the QUEST trial to prolong survival (measured as time from onset of therapy to the composite endpoint) by 91%, and a 32% overall risk reduction to reach the composite endpoint first, as compared with the positive control (benazepril).[124] The median survival times were 267 days in the pimobendan group and 140 days in the benazepril group, and the maximum difference between the two treatments (>20% difference in risk reduction) was found between approximately 150 to 330 days, indicating that the beneficial effect of pimobendan was not only occurring early in the trial.

The benefit of pimobendan on outcome in MMVD dogs is probably mediated through the combination of vasodilatation and increased contractility, which reduce MR by decreasing the size of the LV and the mitral valve annulus through an improved forward stroke volume. Indeed, clinical trials report a decreased cardiac size in dogs receiving pimobendan in comparison to a positive control.[141,142,144] The results from the pimobendan clinical trials indicate that the risk of this type of therapy to promote increased MR (due to the increased systolic pressure gradient across the mitral valve) or to promote chordal rupture is comparably small. Other beneficial effects of pimobendan in treating MMVD dogs in ACVIM stage C include a reduction in heart rate and pulmonary transit times,[142] and a reduced tendency for retention of free water in comparison to a positive control.[141]

ACE inhibitors are indicated in combination with diuretics in advanced MMVD with CHF, because dogs in large placebo-controlled clinical trials receiving an ACE inhibitor have been shown to have less severe clinical signs of disease, better exercise tolerance,[146,147] and to live longer than those not receiving an ACE inhibitor.[148,149] However, it is currently not known if the combination of pimobendan and ACE inhibitor

confers a better outcome compared to pimobendan alone, when either is added to ongoing diuretic therapy. The dosage of ACE inhibitor (e.g., enalapril, benazepril, lisinopril, ramipril and imidapril) is usually fixed and depends on the specific ACE inhibitor used. In the dose range that is recommended for use in dogs and cats, the vasodilating actions of the drugs are not prominent and side-effects associated with hypotension, such as fainting and syncope, are rare.[87,122,146,147,150] A reason for this may be that the short-term effects of ACE inhibitors on the circulation are dependent on the activity of the RAAS prior to administration of the drug: The higher activity, the more pronounced effect of the drug.[151] In combination with diuretics, such as furosemide, the ACE inhibitors have a synergistic effect with the diuretic by counteracting the reflex stimulation of RAAS that occurs in diuretic therapy. Thus, ACE inhibitors decrease the tendency for fluid retention and counteract peripheral vasoconstriction and other negative effects on the heart.

Spironolactone, which is an aldosterone antagonist and a potassium-sparing agent, is currently approved within the European Union with the indication of adjunct therapy with other ongoing CHF therapy in dogs with MMVD. This approval was based on registration trials, which showed that spironolactone, when added to other CHF therapy, reduced the risk of reaching the primary endpoint of the study, which was a composite of cardiac related death, euthanasia or worsening of CHF.[152] This suggests that it might be more advantageous to initiate spironolactone therapy at an earlier stage than previously practiced (see recurrent CHF). This trial also showed that spironolactone therapy in dogs is comparably safe and that the risk for hyperkalemia is low.

Digoxin is controversial in treating dogs with MMVD. There is a general lack of scientific evidence supporting the use of digoxin. Some cardiologists, however, initiate digoxin therapy when signs of CHF first appear. Digoxin is a comparably weak positive inotrope, compared to pimobendan, but has a place by reducing reflex tachycardia, by normalizing baroreceptor activity and by reducing central sympathetic activity.[153] Thus, digoxin may be useful to slow sinus tachycardia, or to treat supraventricular tachycardia such as atrial fibrillation, and to abolish or limit the frequency of syncopal episodes (see above).

The way dogs with mild to moderate CHF are managed after initiation of therapy varies. Regular contacts with the owner by phone or email should be maintained when the dog is managed on an outpatient basis in order to monitor therapeutic outcome and to establish a suitable maintenance dosage of diuretic. Re-examinations should be scheduled after one to two weeks of therapy, and thereafter every 3 to 6 months. More severe cases may require more frequent monitoring of the disease. The owner should be instructed to count sleeping respiratory rates at multiple times (preferably it should be <30/min), and also be informed about complications that may develop in the future. In areas with a seasonal climate, it may be valuable to re-examine the dog before the temperature increases and instruct the owner to avoid high ambient temperatures for the dog if possible. The use of low-sodium diets as complementary therapy in CHF patients is controversial. Currently, there are no clinical studies to support that they are beneficial in managing CHF in dogs and cats. However, dogs with symptomatic MMVD should avoid excessive intake of sodium. Dogs that are stable on their heart failure therapy usually tolerate walks at their own pace, but strenuous exercise should be avoided.

Dogs with Recurrent CHF (ACVIM Stages C or D; see ch. 247)

The maintenance dosage of diuretic (furosemide) in a MMVD patient usually has to gradually be increased over weeks or years to prevent clinical signs of CHF from recurring. Reasons for increasing the dosage often include recurrent dyspnea caused by pulmonary edema or, less commonly, development of ascites. Severe ascites, which compromises respiration, may require abdominocentesis (see ch. 90). However, many MMVD cases with less severe ascites respond to increased dosages of diuretics. Even in cases requiring abdominocentesis, the diuretic dosage should be increased, as the ascites will re-occur without a change in medication after evacuation. When the dosage of furosemide has reached a level of approximately 4-5 mg/kg PO q 8-12 h, a switch from furosemide to torsemide may be considered. Furthermore, sequential blocking of the nephron should be considered by adding another diuretic. The drug of choice is spironolactone (1-3 mg/kg PO q 12-24 h) (see above under mild to moderate CHF). However, a thiazide such as hydrochlorothiazide (2-4 mg/kg PO q 12 h) or triamterene (1-2 mg/kg PO q 12 h) or amiloride (0.1-0.3 mg/kg PO q 24 h) may be considered. The documentation of triamterene and amiloride in veterinary medicine is limited. Because furosemide treatment precedes and is used concomitantly with these drugs, the risk of hyperkalemia is low, even when they are added to a patient that is currently treated with an ACE inhibitor. The risk of inducing prerenal azotemia, hypotension and acid-base and electrolyte imbalances increases with the intensity of the diuretic treatment. However, the practitioner usually has to accept some degree of such disturbances when treating a patient with CHF and although such disturbances might occur, they seldom

result in clinical problems.

Dogs with Severe and Life-Threatening (Fulminant) CHF (ACVIM Stages C or D)

Causes of acute severe CHF often include undertreatment of existing CHF, a ruptured major tendinous chord, development of atrial fibrillation, or intense physical activity, such as chasing birds or cats, in the presence of significant MMVD. Patients with severe CHF have radiographic evidence of severe interstitial and/or alveolar edema, and have significant clinical signs of CHF at rest. They are often severely dyspneic and tachypneic and have respiratory rates in the range of 40 to 90. They may cough white or pink froth, which is edema fluid. These dogs require immediate hospitalization and aggressive treatment. It is important not to stress dogs with severe or fulminant CHF as stress may lead to death. A light sedation, in order to calm the dog, may be indicated in dogs struggling to breathe (see ch. 138). A commonly used sedative in this setting is butorphanol (0.25 mg/kg IM, IV, repeated in 30 to 60 minutes) or combinations of buprenorphine (0.0075-0.01 IM mg/kg) and acepromazine (0.01-0.03 mg/kg IV, IM, or SC). Furthermore, thoracic radiographs and other diagnostic procedures may have to wait until the dog has become more stabilized as a result of furosemide therapy. Dogs with significant dyspnea benefit from intravenous injections of furosemide at a dose of 1-4 mg/kg IV q 2-6 h or higher (see ch. 141).[121,154] The furosemide may be administered intramuscularly should placement of an intravenous catheter not be impossible. The exact dosage of furosemide depends not only on severity of clinical signs but also on whether or not the dog is already on oral furosemide treatment. Should the initial response to a furosemide bolus be poor, with failure of dyspnea and respiratory rate to improve over 2 hours, furosemide may be administered as an IV constant rate infusion (CRI) at a dosage of 1 mg/kg/h IV after the initial bolus.[121,154] Pimobendan treatment may be considered, administered either as a single IV dose at 0.15 mg/kg and continued after 12 h by pimobendan PO at a dosage of 0.25-0.3 mg/kg q 12 h, or as PO administration only.[121] The clinical documentation of pimobendan's efficacy in severe acute CHF is limited, but its use here is supported by its hemodynamic actions,[155,156] experimental studies (pacing model) in dogs,[157] and clinical experience.

Oxygen therapy is always beneficial in hypoxemic patients and it can preferably be administered using an oxygen cage provided that the temperature can be controlled inside the cage (see ch. 131). Nasal insufflation or a facial mask may also be used provided that the animal accepts them without struggle.

For the most critically ill patients, an arterial vasodilator and/or a venodilator may be considered, to reduce afterload and stabilize the CHF (see ch. 247). Commonly used vasodilating agents in this setting are the venodilator nitroglycerin ointment (4-12 mg topically q 12 h), which acts to unload the heart, and arterial vasodilators such as amlodipine PO, hydralazine PO, or intravenous nitroprusside to reduce afterload. Dosages of arterial vasodilator may need adjustment in dogs already on an ACE inhibitor. Amlodipine is administered at 0.1 mg/kg q 24 h, and it has been shown to reduce LA pressure in dogs with experimental MR,[158] and MR severity in dogs with MMVD.[138] Hydralazine has been used in patients with MMVD at an initial dosage of 0.5-2 mg/kg PO q 12 h, but should be used with caution because of potential adverse reactions. Furthermore, the dosage is increased at daily to weekly intervals to an appropriate maintenance dose of 1-2 mg/kg PO q 12 h, or until hypotension develops, detected either by blood pressure measurements or by clinical signs. Reflex tachycardia may develop in response to hypotension, and gastrointestinal problems are sometimes observed. In dogs judged to be too sick to wait for the effects of oral afterload reduction or inotropic support (e.g., pimobendan with or without hydralazine or amlodipine), nitroprusside (for afterload reduction in life-threatening pulmonary edema) or dobutamine (for inotropic support of the hypotensive patient) must be administered by IV CRI (see ch. 141). Both drugs can be administered at dosages of 0.5-1 mcg/kg/min and up-titrated every 15-30 minutes to a maximum of approximately 10 mcg/kg/min. These drugs, either separately or in combination, can be used for 12-48 hours to improve hemodynamic status and control refractory cardiogenic pulmonary edema. Continuous electrocardiographic and blood pressure monitoring is recommended to minimize the potential risks of this therapy (see ch. 99 and 103).

Patients with severe or fulminant CHF need frequent initial monitoring of the respiratory rate because it reflects the clinical response to the furosemide treatment. Significantly decreased respiratory rate within the first hours indicates successful therapy, whereas absence of change indicates that furosemide is required at a higher dose or more frequent administration. Once the respiratory rate has decreased, the dosage of furosemide may be reduced according to the status of the dog and clinical judgment. Abnormal laboratory findings such as prerenal azotemia, electrolyte imbalances, and dehydration are common after high dosages of furosemide. Again, these abnormalities are seldom a clinical problem and the laboratory values often tend to shift towards normal with clinical improvement and as the dog starts to eat and drink. Dehydration is usually not severe even after intensive furosemide treatment and intravenous rehydration should be

performed slowly and with caution in cases where it is needed, as the volume challenge may produce pulmonary edema.

From an ethical standpoint, euthanasia should also be considered in dogs in severe or fulminant CHF if the dog is already on high dosages of diuretics and other heart failure therapies, owing to a poor long-term prognosis, an increased risk of unresponsiveness to further intensification of CHF therapy, and/or increased likelihood of adverse side-effects.

Prognosis after the Onset of CHF

Some clinical variables have been shown to provide prognostic information after the onset of CHF in dogs with MMVD. It has been shown that the type of adjunct therapy influences the survival (increased survival shown in dogs treated with pimobendan and the ACE inhibitors enalapril and benazepril).[124,148,149] Furthermore, the expected survival time decreases with higher maintenance dosages of furosemide, with worsening exercise tolerance, with severity of mitral valve prolapse, with increased cardiac size and severity of MR (VHS score, LA size [LA/AO], LV end-diastolic dimension, and diastolic E wave velocity), with worsening systolic function (increased LV end-systolic dimension), and with decreasing serum creatinine concentration (indicating cardiac cachexia in development).[4,101,124,148] There are some indications that breed also affects the outcome after the onset of CHF, but the results are currently not conclusive. Finally, the development of a complication (see below) may be associated with a worse clinical outcome.

Complications Associated with MMVD

Coughing Due to Left Mainstem Bronchial Compression

Severe LA enlargement may produce coughing even in the absence of pulmonary congestion and edema by compressing the left mainstem bronchus, which may be identified on the lateral radiograph. However, coughing due to other respiratory problems, such as tracheal instability, is also commonly seen in breeds frequently affected by MMVD. The severity of coughing may range from a few coughs per day to constant coughing. Mild occasional coughing does not necessitate daily medication owing to the effort of giving medication and potential adverse side-effects. Furthermore, very little evidence is available concerning effect of the types of drugs at hand to alleviate or reduce coughing. With significant coughing likely caused by left mainstem bronchial compression, therapy is aimed at suppressing the cough reflex or reducing the influence of the underlying cause for the compression, the LA enlargement. Cough suppressants such as hydrocodone bitartrate (2.5 to 10 mg/dog PO q 6-12 h), butorphanol (0.55 to 1.1 mg/kg PO q 6-12 h), or dextromethorphan (0.5 to 2 mg/kg PO q 6-8 h) may alleviate coughing in some cases. Dogs with evidence of concurrent tracheal instability or chronic small airway disease may improve with a bronchodilator, or a brief course of glucocorticoids. Different xanthine derivatives, such as aminophylline (8-11 mg/kg PO q 6-8 h), theophylline (sustained duration) 20 mg/kg PO q 12 h, and oxitriphylline (sustained action) 25-30 mg/kg PO q 12 h, are commonly used bronchodilators, although the efficacy of these drugs varies considerably between individuals. Beta-2 receptor agonists such as terbutaline and albuterol should be used with caution in MMVD dogs, as these drugs may produce unwanted elevations in heart rate and contractility as a consequence of myocardial beta-2 receptor stimulation.

Theoretically, coughing due to left mainstem bronchial compression could improve by reducing LA and LV size. This may be achieved either by reducing the MR or by reducing pulmonary venous pressure, or a combination of both. The actual clinical benefit from such treatments on severity of coughing is currently unknown. Drugs with a potential to reduce the MR, by reducing afterload, include the arterial vasodilators amlodipine and hydralazine, and to a lesser extent ACE inhibitors (see above under Severe and Life-Threatening [Fulminant] CHF [ACVIM Stages C or D]). Furthermore, the inodilator pimobendan has been shown to reduce cardiac size in MMVD dogs, both in the short and long term.[141,142] Diuretic monotherapy may be considered to decrease the MR by contracting the blood volume and thereby the LV size. However, diuretics activate the renin-angiotensin-aldosterone system (RAAS),[159] and in the long term may cause electrolyte disturbances. Accordingly, diuretics should be reserved for patients with signs of pulmonary congestion and edema or patients where cough suppressants, glucocorticoids, and vasodilators have failed to alleviate more severe clinical signs of coughing.

Right-Sided CHF Due to Pulmonary Hypertension

Many patients with longstanding history of MMVD develop right-sided CHF. It is presumed that this condition develops as a consequence of concurrent chronic TR attributable to myxomatous degeneration, or

development of pulmonary hypertension, or a combination of both (Figure 251-8). In MMVD, the pulmonary hypertension is thought to develop secondary to the persistent elevation of the LA and pulmonary venous pressures, but concurrent chronic airway disease may also contribute. Individuals with pulmonary hypertension are sensitive to exercise, with signs of weakness or collapse even at mild exercise. A physical examination may reveal evidence of right-sided CHF, such as ascites, pleural effusion, hepatic and splenic congestion, and distention of the jugular veins with abnormal pulsations. The presence and degree of pulmonary hypertension may be indirectly quantified by Doppler echocardiography (see ch. 104 and 243). A pressure gradient > 55 mm Hg has recently been shown to be an independent negative predictor of outcome.[57]

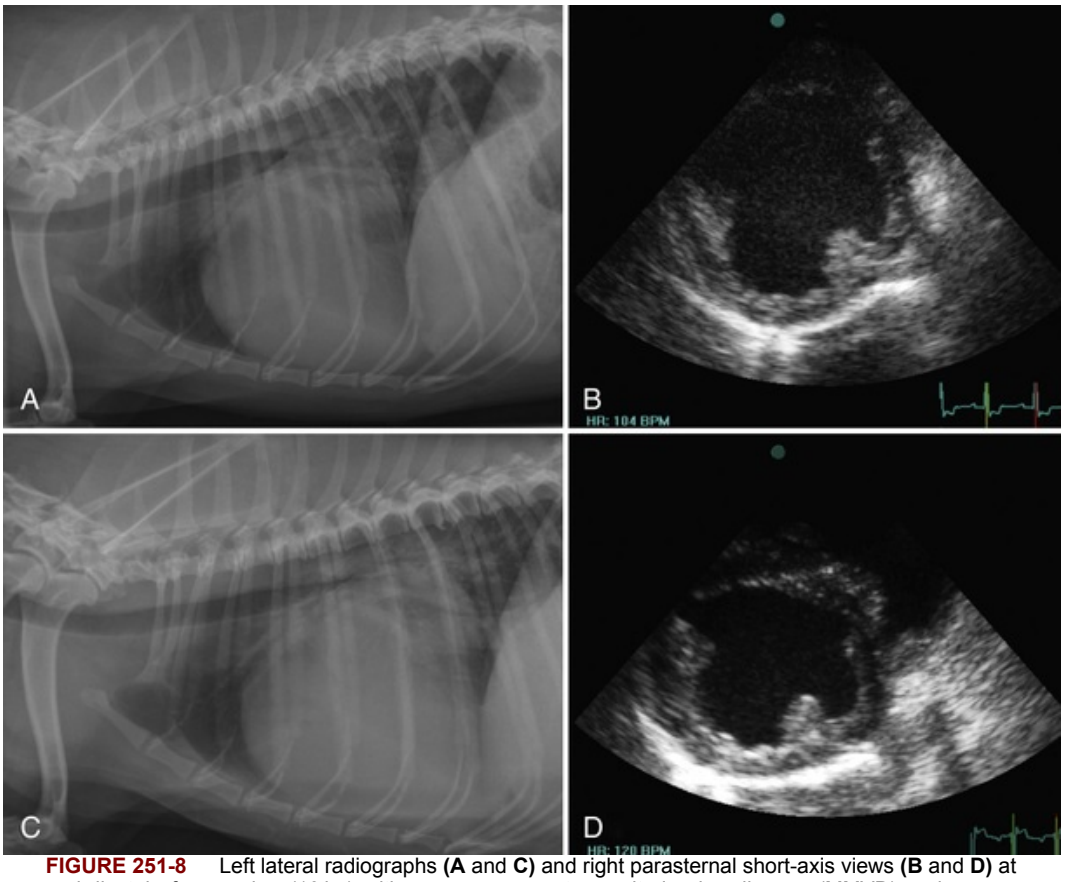

FIGURE 251-8 Left lateral radiographs **(A** and **C)** and right parasternal short-axis views **(B** and **D)** at end-diastole from a dog (10 kg) with severe myxomatous mitral valve disease (MMVD) and severe cardiac enlargement showing development of pulmonary hypertension. The dog had developed CHF but was stabilized on heart failure therapy when images **A** and **B** were obtained. Images **C** and **D** were obtained one year later when the dog had developed more pronounced exercise intolerance and evidence of right-sided CHF. At this stage, the radiographic cardiac size had increased from vertebral heart scale of 13.8 in **A** to 15.0 in **C,** but the left ventricular end diastolic diameter had decreased from 5.5 cm in **B** to 4.0 cm in **D,** and the left ventricle was displaced further away from the transducer owing to right ventricular enlargement. There is also evidence of septal flattening, and the systolic tricuspid regurgitation pressure gradient was 64 mm Hg.

Dogs with pulmonary hypertension may be difficult to manage. The goal of therapy is to eliminate contributing factors and restrict exercise. Oxygen supplementation is indicated in cases of acute collapse (see ch. 131). Since persistently increased pulmonary venous pressures are in large part responsible for the condition, therapy should be directed as for MMVD with pulmonary congestion (see Management). In addition, sildenafil at a dosage of 0.5-2 mg/kg q 8-24 h (2-3 mg/kg PO q 12 h may be required in some cases) is a commonly used pulmonary arterial vasodilator.[160,161] Published case series of sildenafil treatment in dogs are available, in which many of the included dogs had pulmonary hypertension due to longstanding severe MMVD.[160,161] A major disadvantage of this drug is that it is comparably expensive. A less expensive alternative to sildenafil therapy to treat pulmonary hypertension in this setting is pimobendan. This drug has been shown to decrease pulmonary arterial pressure in experimental dogs, mediated through its suppression

of phosphodiesterase III,[139] and in a short-term crossover study in MMVD dogs.[162] Thus, dogs with MMVD and longstanding CHF that have developed pulmonary hypertension probably benefit from this therapy if not yet already receiving it. Bronchodilator therapy may also be indicated, and methylxanthines and beta-2 selective agonists may be considered, but the latter should be used with caution in MMVD dogs. Aggressive diuretic treatment may be required to resolve ascites, if present. Physically draining the abdomen of fluid will also provide temporary relief from the ascites, giving the medications prescribed additional time to take effect (see ch. 90).

Development of Arrhythmia Leading to Syncopal Events and/or Acute Exacerbation of Signs of CHF

With advancing MMVD, it is not uncommon that episodes of syncope develop (see Clinical Signs and ch. 30). In dogs with MMVD with syncopal events, it is important to ascertain that the patient is actually fainting and not suffering from neurological or other disease. Furthermore, it is important to rule out the presence of CHF, pulmonary hypertension, or bradyarrhythmias such as third-degree AV block or sustained tachyarrhythmia such as atrial fibrillation. An enlarged LA predisposes to supraventricular premature beats, atrial fibrillation, and supraventricular tachycardia (see ch. 248).[91] Although ventricular tachyarrhythmias do occur in MMVD dogs, usually at advanced stages of the disease, intermittent supraventricular tachyarrhythmia is far more common.[79,91] Typically, the 24 hour (Holter) ECG shows episodes of a rapid supraventricular rhythm immediately followed by a bradycardia during which the dog faints.[79,91] Dogs developing sustained atrial fibrillation or supraventricular tachycardia often have a longstanding history of MMVD, with an acute onset of pulmonary edema. In addition to other characteristic findings in MMVD, these cases have a change in cardiac rhythm. The goal of therapy is to relieve the pulmonary edema, as described earlier under management, and to reduce heart rate to an acceptable rate for improving cardiac output. Diliazem and/or digoxin are the drugs of choice in dogs with supraventricular tachycardia.

Management of dogs with syncopal events, outlined above, or sustained atrial fibrillation/supraventricular tachycardia often includes digoxin (0.22 mg/m^2 or less, PO q 12 h) to control the supraventricular tachyarrhythmia. Should this fail to control frequency and duration of intermittent tachycardia (and syncopal events), or, in the case of atrial fibrillation with a high ventricular rate, diltiazem (0.5-2 mg/kg PO q 8 h) or a beta-1 receptor antagonist such as atenolol (0.25-2 mg/kg PO q 12-24 h) or metoprolol (0.5-1 mg/kg PO q 8-12 h) could be added. See ch. 248. It should be noted that individuals with MMVD usually are sensitive to negative inotropic drugs, such as beta-receptor antagonists, and they should be avoided in dogs with acute CHF. Therefore, these drugs should be initiated at the lowest possible dosage and then gradually increased with careful monitoring. In cases of CHF, another goal of therapy is to relieve the pulmonary edema, as described earlier under management.

Acute Exacerbation of Pulmonary Congestion and Edema Due to Ruptured Chordae Tendineae

Ruptured chordae tendineae may be suspected in all dogs suffering from MMVD with acute development of pulmonary congestion and edema (see Video 251-17), whereas it is a rare finding in cats. The most important ruptures involve those of first order chordae that are attached to the septal leaflet, and these patients are expected to die rapidly from acute volume overload and fulminant pulmonary edema. Ruptures of lesser order chordae or perhaps first order chordae that are attached to the free wall leaflet may result in minor clinical signs or none at all.[100] Significant chordae tendineae rupture causes acutely increased MR, and the clinical findings may differ from those encountered in chronic MR. Due to the acute increase in MR, there may be a marked increase in LA and pulmonary venous pressures, leading to acute pulmonary edema, pulmonary hypertension and right heart failure.[55,67] The physical examination of these patients often reveals a heart murmur of lower intensity than that of chronic MMVD, an S_3 gallop is more likely to be present (see ch. 55), and jugular venous distention is more likely to be present with pulsations than in chronic MMVD. The radiographic and echocardiographic findings of cardiac size vary, depending on how far the MMVD had progressed before the onset of ruptured chordae tendineae. Doppler echocardiography shows severe MR, and a flail segment of the mitral valve leaflet may be detected using 2D views. Thoracic radiographs show a markedly increased interstitial and alveolar pattern with distention of the pulmonary veins. These patients require intensive care to stabilize the condition, and thereafter maintenance therapy for MMVD (see under Management section and ch. 141). As long as a first order chorda attaching to the septal leaflet has not ruptured, many of these cases may be sustained with the aid of appropriate medication.

Left Atrial Rupture and Cardiac Tamponade

As a consequence of the dilatation in MMVD, the LA becomes thin-walled and more vulnerable to increases

in pressure. Endocardial splitting is a frequent postmortem finding in dogs with a history of longstanding MMVD (Video 251-18).[72] The significance of this finding is that it may progress to rupture of the LA with the sudden development of hemopericardium, cardiac tamponade and sudden death (Video 251-19). Most cases with atrial rupture and cardiac tamponade are expected to die suddenly. There is often a history of trauma, excitement or physical exercise preceding the atrial rupture and sudden death. For those dogs surviving the initial event, clinical signs of cardiac tamponade together with signs of MMVD can be found. Acute development of ascites, collapse, or marked exercise intolerance is to be expected. The physical examination may reveal signs of pericardial effusion (see ch. 254). Echocardiography is required for a definitive diagnosis by identifying the presence of significant pericardial effusion in combination with MMVD, whereas the tear often is difficult to detect on an echocardiogram. Treatment of atrial rupture with hemopericardium and cardiac tamponade is usually futile. Immediate pericardiocentesis is indicated (see ch. 102), and pericardial fluid should be removed to alleviate the tamponade without removing so much that further bleeding is stimulated. If the bleeding continues after pericardiocentesis, the final option is emergency thoracotomy with pericardiectomy and closure of the tear, but the prognosis for this procedure is very guarded.

Infective Endocarditis

Infective endocarditis (IE) is a life-threatening disorder caused by microorganisms colonizing the endocardium, commonly resulting in proliferative or erosive lesions of the valve and other cardiac structures, and, consequently, valve leakage (Figure 251-9, *A*). Vegetation may cause thromboembolism or metastatic infections involving multiple body organs, producing a large variety of clinical signs, which makes diagnosis difficult.

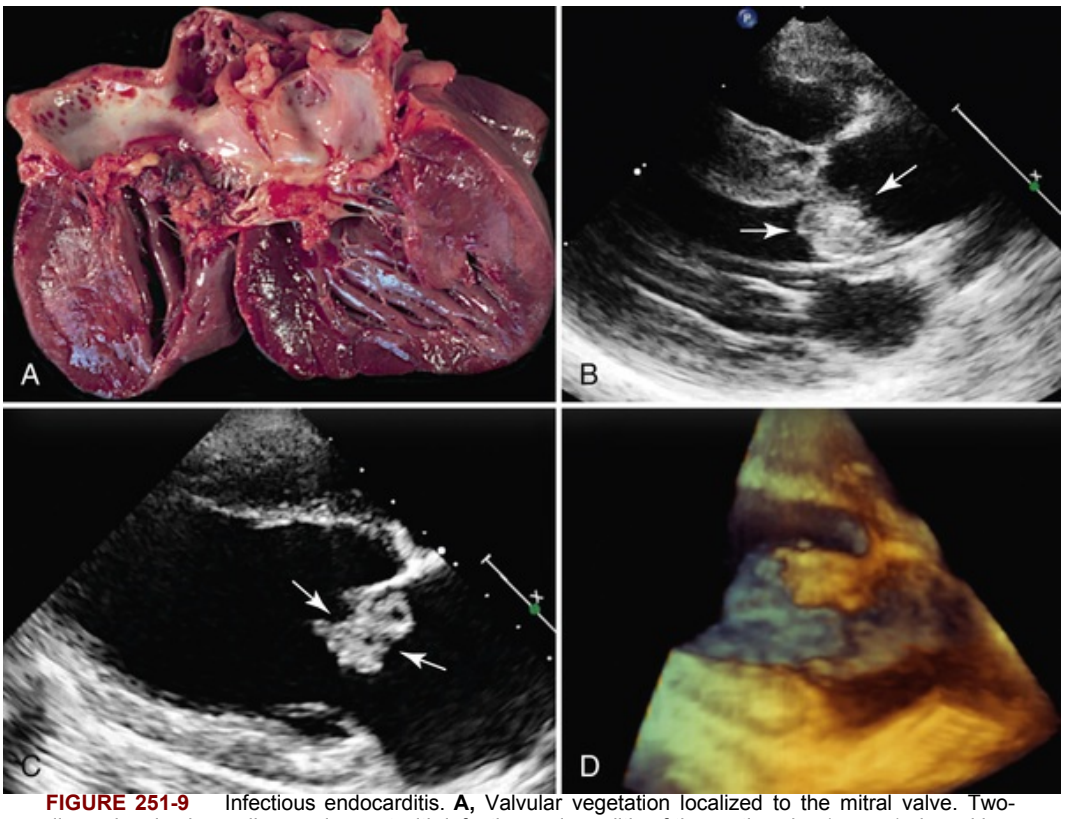

FIGURE 251-9 Infectious endocarditis. **A,** Valvular vegetation localized to the mitral valve. Two-dimensional echocardiogram in a cat with infective endocarditis of the aortic valve (arrows) viewed in a right parasternal long axis view **(B).** Infectious endocarditis affecting the mitral valve (arrows) viewed in a right parasternal long axis view **(C).** 3D echocardiogram from the same dog as in **(C),** but the view is slightly rotated to allow inspection of the mitral valve from the atrial side **(D).** Notice the size of the irregular-shaped echogenic mass attached to the septal mitral valve leaflet. *LA,* Left atrial chamber; *LV,* left ventricular chamber. (**A,** Courtesy Páll S. Leifsson, University of Copenhagen, Denmark.)

Occurrence

The prevalence of infective endocarditis in necropsied dogs has been reported to range from 0.09 to 6.6%.[163] Evaluation of data from dogs referred to a veterinary teaching hospital indicates that IE is a comparably rare clinical condition with prevalences ranging from 0.04 to 0.13 percent.[164,165] However, given the difficulty in diagnosing the condition, the non-specific clinical signs, and the comparably low proportion of dogs undergoing necropsy, the true incidence is presumably considerably higher. Medium to large breeds, mainly purebred, middle-aged male dogs are reported to be at higher risk for developing endocarditis.[166,167] The prevalence in cats, based on clinical experience, is considered to be 7 to 10 times lower than in dogs.[165,168,169] Animals with congenital heart disease have a low incidence of IE,[129] but associations have been reported with subaortic stenosis,[170] and with PDA.[171] IE has not been found to have any association with MMVD in dogs, despite dental procedures and other causes of bacteremia.[129]

Etiology and Pathogenesis

Transient or persistent bacteremia is a prerequisite for the development of IE. The origin of the bacteremia may be active infection localized somewhere within the body. A proportion of cases with IE has no clinically detectable source of infection.[172,173] Possible routes for bacteria to reach and infect the endocardium are by direct contact with the surface endothelium via the bloodstream or from capillaries within the valve (vasculitis).[174] Most bacteria require predisposing factors to cause IE, such as depression of the immune system or endothelial tissue damage,[129] sometimes associated with depositions of platelet-fibrin complexes, to adhere to the valve and create IE.[175] Extracellular matrix proteins, thromboplastin, and tissue factor all trigger coagulation. Coagulum forms on the damaged endothelium and inflammatory factors are activated. The inflammatory process together with enzymes released from the bacteria both contribute to the degradation of valve tissue.

A large number of bacteria has been identified in dogs with bacteremia[176] (see section on Blood Culture below), and some are known to cause IE.[172,173] Organisms that commonly cause IE are indeed those with the greatest ability to adhere to damaged valves, and they include *Staphylococcus* and *Streptococcus* spp. Bacteria such as *Staphylococcus aureus* and *Bartonella* may become internalized within the endothelial and other cells and remain undiscovered by the immune system. Furthermore, the bacteria are also protected from the immune system and from antibiotic substances by being embedded within the coagulum.

The consequences of IE depend on several factors: virulence of the infective agent; site of infection; degree of valvular destruction; influence of vegetation on valvular function; production of exo- or endotoxins; interaction with the immune system with the formation of immunocomplexes; and development of thromboembolism and metastatic infections. Gram-negative bacteremia often results in a peracute or acute clinical manifestations, while Gram-positive bacteremia typically results in a subacute or chronic condition. Necrosis and destruction of the valve stroma and/or chordae tendineae proceed rapidly in peracute or acute IE, causing valvular insufficiency and cardiac failure. Deposition of immunocomplexes in different organs may cause glomerulonephritis, myositis, or polyarthritis.[177] Thromboembolic complications as a cause of clinical signs have been reported in approximately 30-40% of dogs with IE,[129,167] and the lungs have been shown to be the most common site for embolization followed by the kidneys and the distal part of aorta.[129]

Pathology

Vegetation associated with IE mainly affects the left heart, with a higher prevalence of lesions involving the mitral valve compared to the aortic.[129,167] Mural endocardial involvement may be present, with or without concurrent valvular lesions,[129] but right heart involvement is uncommon.[129] Pathological findings vary and depend on the virulence of the infecting organism, the duration of infection and the immunological response. An intracardiac vegetation consists of different layers of fibrin, platelets, bacteria, red and white cells, and is often covered by an intact endothelium. Bacteria may continue to grow despite antibiotic therapy, owing to the location deep within the vegetation and a slow metabolic rate.[175]

History and Clinical Signs

The diagnosis of IE can easily be overlooked because the case history and clinical signs are not specific and

there may be an absence of predisposing factors to raise the suspicion of IE. Predisposing factors that, in combination with clinical signs, should raise the suspicion of IE are: immunosuppressive drug therapy such as corticosteroids,[129,166] non-oral surgery within 3 months, trauma to mucosal surfaces in the oral or genital tract and infections in these body regions, indwelling catheters, infected wounds, abscesses, or pyoderma.[129,178]

Clinical signs are variable and occur in different combinations. Lameness has been described as the most frequent presenting complaint in dogs with IE, followed by non-specific signs such as lethargy, anorexia, respiratory abnormalities, weakness, fever (often recurrent), weight loss, and GI disturbances.[166,167] Stiffness and pain originating from joints or muscles may be caused by immunomediated responses, and abdominal pain may be caused by secondary renal or splenic infarction, septic embolization, or abscess formation. If the condition leads to severe valvular damage, signs of CHF and syncope from arrhythmias may occur. Arrhythmias, primarily ventricular, have been reported in 62% of dogs with aortic IE.[172,173]

Physical Examination

Most clinical signs lack specificity for IE. However, fever, heart murmur (particularly if newly developed), and lameness are considered classical signs.[129] Fever is reported to occur in 50 to 90% in dogs with IE.[166,167] Absence of fever is reported to be more common in cases with aortic valve involvement,[167,172] a finding which may be attributable to *Bartonella* infections. *Bartonella* infections have been reported to be more frequently afebrile,[167] but this finding may also be attributed to treatment already initiated with antibiotics. Because severe aortic insufficiency is otherwise uncommon in dogs, the finding of a diastolic murmur and bounding peripheral pulse should raise the suspicion of IE of the aortic valve. Systolic murmurs may be caused by destruction of the mitral valve, resulting in MR, or by vegetations obstructing the aortic outflow tract leading to stenosis (Audio 251-6).[166] It should be noted that 26% of dogs with IE are reported to lack audible murmurs.[166] Lameness is also an inconsistent finding in IE with an incidence of 34% in one study.[163] A range of other physical findings may be present, depending on which organs are affected by circulating immunocomplexes or septic embolization. Possible findings are pain reactions from muscles or abdomen (spleen, intestines or kidneys), cold extremities, cyanosis and skin necrosis from severe embolization, and a variety of neurological disturbances if the central nervous system is affected.

Diagnostic Testing

Echocardiographic Findings

Echocardiography significantly improves the possibilities for diagnosing and monitoring animals with IE.[178] Valvular vegetations may be detected using 2D echocardiography. The valvular vegetations appear hyperechoic (Videos 251-20 and 251-21 and Figure 251-9, *B-D*), are often irregularly outlined, and often move independently of the valve. Some of these smaller lesions may be very difficult to distinguish from myxomatous lesions. Erosive lesions may be more difficult to identify on the echocardiogram, but the presence of moderate to severe aortic regurgitation, identified on the color echocardiogram, should raise the suspicion of aortic IE. Other causes that are associated with aortic regurgitation include congenital valvular or subvalvular stenosis, myxomatous lesions (usually only mild aortic regurgitation), severe systemic hypertension and quadricuspid aortic valve (a very uncommon congenital malformation). The aortic valve needs to be viewed from several planes to help exclude the differential diagnoses and to identify the erosive lesion. Mitral or aortic regurgitation may be detected using continuous or color-flow Doppler echocardiography. The severity of aortic regurgitation may be estimated in the left apical five-chamber view either by assessing the slope of the regurgitant flow tracing by continuous wave Doppler (steeper slope indicates more severe insufficiency), or by assessing the size of the regurgitant jet on the color echocardiogram, which gives a semiquantitative estimate. Assessment of severity of MR is described elsewhere in this chapter and in ch. 104. Likewise, secondary LA and LV dilatation may be identified using 2D, 3D, or M-mode echocardiography as previously described. In cases where the clinical suspicion of IE is great, but no valve lesion may be identified by transthoracic echocardiography, transesophageal echocardiography may be considered to obtain a more detailed evaluation of the aortic and mitral valves.

Electrocardiographic Findings

Arrhythmia is reported to occur in 50 to 75% of dogs with IE.[166,167,172] Ventricular premature beats and

ventricular tachyarrhythmias are the most commonly encountered arrhythmias, but they are usually not life-threatening. Deviation in the ST-segment might suggest myocardial hypoxia and may indicate coronary artery embolism or myocardial ischemia of other etiologies.[92] Evidence of chamber enlargement may occur in chronic IE. All the mentioned ECG abnormalities are, however, non-specific.

Radiographic Findings

Radiography often does not add any information specific for IE. In cases of chronic IE with aortic or mitral insufficiency, left-sided cardiac enlargement may be detected. Approximately 50% of dogs with IE were reported to present with CHF, as indicated by perihilar and caudodorsal pulmonary infiltrates, with no difference between those with IE of the mitral valve or aortic valve.[164,167] Surprisingly, significant LA enlargement was reported absent in a comparably large proportion of the dogs with CHF, presumably indicating an acute onset of severe valve leakage and CHF.[164,176]

Blood Culture

Positive blood cultures are essential for establishing a diagnosis of IE and for selecting appropriate antimicrobial treatment. Unfortunately, 60-70% of obtained blood cultures in dogs with IE have been reported to be negative.[164,172] The high proportion of dogs receiving antimicrobial therapy prior to the time of sampling presumably contributes to the lack of bacterial growth.[164] Other causes for negative blood cultures include chronic "encapsulated" infections, non-infectious IE (only platelets and fibrin in vegetation) or failure to grow organisms from samples. Some bacteria may grow slowly and samples should not be regarded as definitely negative until they have been cultured for 10 days (*Bartonella* requires culture for up to 4 weeks). In those cultures that are positive, 90% will be so within 72 h of incubation.[179] PCR methodology may be used to amplify and identify bacterial nucleic acid in blood, and thereby potentially increase the likelihood of detecting bacteremia. However, it appears that this method is not more sensitive than blood culture for detection of bacteremia in dogs with suspected endocarditis.[180] The risk of negative cultures is reduced when collection and handling of samples is conducted properly.[175] The time for sampling is probably not critical, but avoiding sample contamination is. The technique for obtaining samples aseptically and anaerobically is important and described in detail below. In cases of positive blood culture, it is important to evaluate if the microorganism is consistent with the diagnosis of IE. Microorganisms known to cause IE in dogs are *Staphylococcus* spp. (*S. aureus, S. intermedius,* coagulase-positive and coagulase-negative), *Streptococcus* spp. (*S. canis, S. bovis,* and beta-hemolytic), *Bartonella* spp., *Escherichia coli, Pseudomonas aeruginosa, Corynebacterium* spp., and *Erysipelothrix rhusiopathiae.*[164,172,177] *Bartonella vinsonii* and related proteobacteria *(B. henselae, B. clarridgeiae, B. washoensis)* have been recognized as potential causes for endocarditis in dogs.[164] In a study comprising dogs from California, *Bartonella* spp. were the cause for IE in 28% of the cases, and in 45% of the IE cases with negative blood cultures.[164] *Bartonella* is also a potential cause for IE in cats.[169] Epidemiological studies suggest that ticks and fleas may be vectors for *Bartonella.* Indeed, concurrent seroreactivity to *Ehrlichia canis, Anaplasma phagocytophilum* and *Rickettsia rickettsii* is common in dogs with IE caused by *Bartonella* spp.[164] (see ch. 215 and 216).

Obtaining Blood Cultures

The reference laboratory should ideally be contacted concerning the preferred type of vials before obtaining a sample. To avoid contamination, strict aseptic sampling should be observed. Three or four samples of approximately 5-10 mL each (the likelihood for a positive blood culture increases with increasing blood volume) should be collected aseptically from different puncture sites at least 30 minutes to 1 hour apart. Samples should be submitted for aerobic and anaerobic culture. Lysis centrifugation tubes may increase diagnostic yield. Sampling through indwelling catheters should be avoided but may be used as a last option. For culture of *Bartonella* spp., 2 mL EDTA blood collected aseptically is frozen at −70°C until cultured.[173] The samples are cultured on a special culture medium for *Bartonella* for up to 4 weeks (see ch. 215 and 216).

Other Laboratory Findings

Mild regenerative anemia is found in 50 to 60% of cases with IE.[129,166,167,172] The anemia implies chronic inflammation, usually being normocytic and normochromic. Leukocytosis is found in about 80% of dogs with IE, usually due to neutrophilia and monocytosis (left shift). Other findings that may be encountered include elevated blood urea nitrogen (BUN) or creatinine concentrations due to embolization, metastatic infection,

CHF or immune-mediated disease. Elevated serum alkaline phosphatase and hypoalbuminemia are probably caused by circulating endotoxins and reduced hepatic function.[163,178] Serum glucose concentration may be decreased and serological tests for immune-mediated disease, such as Coombs' test, may be positive.[178] Urinalysis may reveal hemoglobinuria, hematuria, pyuria, bacteriuria and/or proteinuria. Urine culture (preferably performed by cystocentesis) should always be obtained in dogs with a suspicion of IE in attempt to isolate the infective microorganism.

Diagnosis

Since the clinical signs of IE are often a result of complications, rather than reflecting the intracardiac infection, the diagnosis may easily be overlooked. Although IE may be suspected in many dogs, definite diagnosis of IE requires pathologic examination of tissue, which is not possible in the living dog. The diagnosis of IE is often established by identification of more major and minor criteria for IE. A scoring system, adapted from the modified Duke criteria for IE in people,[181] has been proposed to determine a possible clinical diagnosis of IE in dogs (Table 251-2).[173]

TABLE 251-2

Suggested Criteria for Diagnosis of Infective Endocarditis in Dogs

MAJOR CRITERIA	MINOR CRITERIA	DIAGNOSIS
Positive echocardiogram: Vegetative or erosive lesion, or abscess **New valvular insufficiency:** >Mild aortic insufficiency without subaortic stenosis or annuloaortic ectasia **Positive blood culture:** ≥2 positive blood cultures, or ≥3 if common skin contaminant	**Fever** **Medium to large dog (>15 kg)** **Subaortic stenosis** **Thromboembolic disease** **Immune-mediated disease: polyarthritis glomerulonephritis** **Positive blood culture not meeting major criteria listed in this table** ***Bartonella serology ≥ 1 : 1024**	**Definite** Histopathology of valve 2 major criteria 1 major and 2 minor criteria **Possible** 1 major and 1 minor criteria 3 minor criteria **Rejected** Other disease diagnosed Resolution of regurgitation or valvular abnormality within 4 days of treatment No pathologic evidence endocarditis on postmortem examination

*Not officially accepted yet as a criterion in veterinary medicine.

The veterinary criteria are modified from the Modified Duke criteria used in human medicine for the diagnosis of endocarditis.[181,184]

Modified from MacDonald KA: Infective endocarditis. In Bonagura JD, Twedt D, editors: *Kirk's current veterinary therapy XV,* Philadelphia, 2015, WB Saunders, p 786.

Management

The goal of therapy is to eradicate the infective microorganism and to treat all secondary complications. A successful outcome of therapy is based on early diagnosis and immediate and aggressive treatment. A blood culture (see section above) and an antibiotic sensitivity profile should be obtained. A blood sample for serology is indicated in cases where *Bartonella* can be suspected to be the cause for IE. While waiting for results from cultures and sensitivity tests, intravenous treatment should commence using a bactericidal broad-spectrum antibiotic IV (e.g., beta-lactam antibiotics [such as timentin, which is a combination of ticarcillin and clavulanate] 50 mg/kg IV q 6 h or imipenem 10 mg/kg IV q 8 h).[173] The aminoglycoside amikacin 20 mg/kg q 24 h can be combined with either of the above mentioned beta-lactam antibiotics to obtain a more complete spectrum.[173] The initial treatment is similar for dogs with suspected IE caused by *Bartonella.* Aminoglycosides are potentially nephrotoxic and are only recommended for limited time usage. Patients receiving aminoglycoside therapy IV should be supported with IV fluids. Concurrent furosemide therapy is contraindicated because it can enhance the nephrotoxicity. This limits the use of aminoglycosides

in dogs with IE and CHF. An alternative to an aminoglycoside is enrofloxacin for suspected Gram-negative IE, but the resistance to this antibiotic for different bacteria appears to be variable at different geographic sites. A significant resistance pattern in the local geographic area may limit the use of enrofloxacin as a first-line antibiotic. The choice of antibiotic is also dependent on the site of infection as organ distribution and tissue penetration of antibiotics differ. The primary source of the infection should be sought and treated as aggressively as possibly (e.g., using surgical drainage or debridement).[182] It is important to identify possible secondary problems, such as CHF or kidney injury, which may affect the choice of an antibiotic, or may need specific therapy, or may indicate a poorer prognosis. Dogs in CHF and/or with arrhythmia require treatment as outlined above and in ch. 247 and 248. When results are available from blood cultures, the appropriate antibiotics should be selected and aggressive IV treatment might be continued for 1 to 2 weeks, whilst the patient is closely monitored, in particular with respect to renal function. If results from cultures are negative, the decision to continue antibiotic therapy should be based on clinical improvement. Depending on the early outcome of therapy, subcutaneous administration may, replace IV treatment after 1-2 weeks, and later, oral preparations. The duration of therapy should be at least 6 weeks on the effective antibiotic. In patients with positive blood cultures, it is recommended to obtain a new blood culture 1-2 weeks after initiation and 1-2 weeks after the termination of the antibiotic therapy. Repeat echocardiographic examinations, blood panels, and urinalyses are recommended during and after the antibiotic therapy to monitor the therapeutic success and identify possible complications. Dogs diagnosed with IE caused by *Bartonella* may be monitored with repeat serology 1 month after the initiation of antibiotic therapy.[173] A significantly reduced titer indicates effective treatment; an increased titer suggests ineffective treatment and indicates that a change of antibiotic is needed (see ch. 215 and 216).

Prognosis

Factors that may indicate a poor prognosis include: late diagnosis and late start of therapy, aortic valve involvement,[184] valvular vegetation,[183] *Bartonella* infections (leads most commonly to aortic IE),[176] Gram-negative infections, heart or renal complications that do not respond to therapy, septic embolization or metastatic infection, thrombocytopenia,[167] elevation of serum alkaline phosphatase and hypoalbuminemia (70% mortality is reported if this is found in cases with IE),[163] concurrent treatment with corticosteroids, regardless if antibiotics are given simultaneously,[167] treatment with bacteriostatic antibiotics or premature termination of antibiotic therapy. Factors that have been reported to indicate a more favorable prognosis include: mitral valve involvement only (median survival time of 476 days in one study),[164] Gram-positive infections, infection originating from the skin, abscesses, cellulitis, or wound infections.[178]

Prevention

Prophylactic antibiotics may be indicated 1-2 hours before and 6 hours after cardiovascular procedures in cases where turbulent blood flow is suspected to have damaged the endothelium (e.g., aortic stenosis, PDA or VSD). In these cases, early treatment of all infections is important to avoid bacteremia and reduce the risk for IE. Amoxicillin may be the first choice, but other antibiotics, such as clindamycin, may also be considered depending on the organ system involved and site of infection.[175] Finally, it is very uncommon that dogs with MMVD develop IE as a consequence of dental procedures, which indicates that prophylactic treatment of these dogs is redundant.[129]

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CHAPTER 252

Myocardial Disease

Canine

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Client Information Sheet: Myocardial Disease in Dogs

Canine myocardial disease is one of the most common forms of acquired heart disease in the dog.[1] The most common form of myocardial disease in the dog is dilated cardiomyopathy, but arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy and myocarditis, among others, are also reported.

Canine Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is a primary myocardial disease characterized by cardiac enlargement and impaired systolic function of one or both ventricles (Figure 252-1). Diastolic dysfunction may also be observed.[2] An increased understanding of the etiology of both the human and canine disease has led to the development of the theory that DCM is the final result of a variety of myocardial insults including viral, nutritional, toxic and genetic.[3] In human beings, the disease has been shown to be familial in at least 30-50% of the cases and causative mutations have been identified in more than forty genes.[4,5] The etiology remains undetermined in many cases and they are thus considered idiopathic.

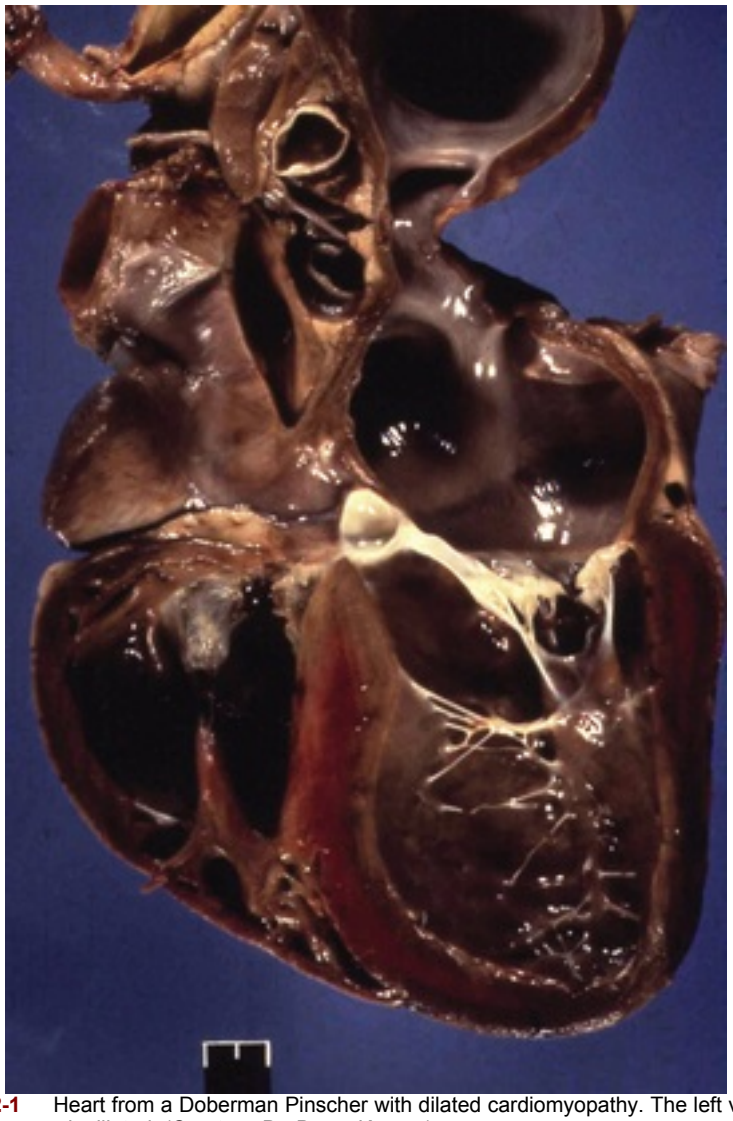

FIGURE 252-1 Heart from a Doberman Pinscher with dilated cardiomyopathy. The left ventricle and left atrium are grossly dilated. (Courtesy Dr. Bruce Keene.)

Although canine DCM is described as one disease, significant variation in the presenting complaint, clinical evaluation and rate of progression has been observed depending on the breed of dog and underlying etiology.[6-12]

Generally DCM is a disease of large and medium sized dog breeds. Some breeds are clearly overrepresented, particularly in specific geographical regions. Surveys in North American publications find an increased incidence in the Doberman Pinscher, Irish Wolfhound, Great Dane and Cocker Spaniel.[13,14] European sources suggest an increased incidence of the Airedale Terrier, Doberman Pinscher, Newfoundland and English Cocker Spaniel.[15] The differences in breed prevalence between the canine populations may suggest an influence of environmental factors on the development of DCM, but more likely is related to the strong genetic influences of certain popular dog breeds within an area. This population stratification is seen when genetic studies of the same disease in a single breed identify regionally specific results. To date, two genetic mutations associated with the development of DCM are reported in dogs and are detailed under the breed-specific sections below.[16,17]

Clinical Presentation

Dilated cardiomyopathy is an adult-onset disease, with the exceptions of the Portuguese Water Dog and Toy Manchester Terrier in which it is most frequently diagnosed before one year of age.[12,18]

There appear to be two stages of DCM: an "asymptomatic" stage, referred to as occult, which may be

detected by careful screening; and a stage at which clinical signs appear, referred to as overt. Clinical signs may include coughing, dyspnea, tachypnea, syncope, exercise intolerance and occasionally, ascites.

Physical Examination

A soft systolic murmur consistent with mitral valve regurgitation and/or a gallop sound (S_3) may be ausculted at the left apex (see ch. 55). A tachyarrhythmia of ventricular or atrial origin may be noted. In some cases, these may be the first signs of the occult form of disease and should not be overlooked. Since primary valvular disease is relatively uncommon in large breed dogs (see ch. 251), and the detection of DCM before the development of congestive heart failure (CHF) may be beneficial in the long-term management of the case, identification of a new murmur, gallop or tachyarrhythmia in suspect breeds may warrant a thorough cardiac work-up. Although canine DCM is predominantly a left ventricular disease, biventricular involvement and heart failure with jugular venous distension and ascites is frequently noted, particularly in the giant breeds.

Diagnostic Testing

Electrocardiography

Many dogs with DCM have normal electrocardiograms but atrial and/or ventricular enlargement patterns may be observed (see ch. 103). Additionally, tachyarrhythmias, particularly atrial fibrillation and/or ventricular tachyarrhythmias, are common (see ch. 248). Sinus tachycardia may be observed, particularly in the face of CHF.

Radiography

Dilated cardiomyopathy is a progressive myocardial disease. If the disease is diagnosed in the early stages, radiographic findings may be subtle. Therefore, depending on the stage of the disease, thoracic radiographs may be within normal limits or may indicate atrial and ventricular enlargement (typically left) with or without pulmonary venous distension and pulmonary edema. In some cases, biatrial and biventricular enlargement may be noted, particularly with more advanced disease and in conjunction with tachyarrhythmias.

Echocardiography

Echocardiography is the diagnostic test of choice for diagnosing canine DCM and is also an important test for occult disease (see ch. 104). Echocardiographic findings in the patient with overt disease should include left and sometimes right atrial and ventricular dilation as quantified by M-mode and two-dimensional measurements (Figure 252-2, *A* and *B* and Video 252-2, *A* and *B*). The measurements should be compared to the normal values for that particular breed or size (body surface area) of dog. In some cases, the ventricular wall thickness may appear thin during diastole, but generally when it is measured it is found to be within normal limits as DCM is characterized by eccentric hypertrophy. An important part of the diagnosis is usually concurrent left ventricular systolic dysfunction based upon decreased fractional shortening (FS%), ejection fraction (EF%) or shortening area, and increased end-systolic volume. Many dogs may demonstrate diastolic dysfunction as well, as determined by evaluation of transmitral flow, tissue Doppler and pulmonary venous flow.[2] Doppler echocardiography may be used to document a central jet of mitral regurgitation that may be associated with dilation of the ventricle. A differential diagnosis for DCM is severe atrioventricular (AV) valve disease (see ch. 251) since severe ventricular dilation and systolic dysfunction may be occasionally observed in these cases. Consideration of the breed of dog may be helpful in differentiating between DCM and AV valve disease since it is uncommon for many of the large breed dogs to develop significant primary valve disease. Additionally, DCM is supported in cases that lack the typical AV valve thickening associated with classic AV valve degeneration. An exception to this may be the Cocker Spaniel, a breed that has a high incidence of primary valve disease, and also is at increased risk of DCM.

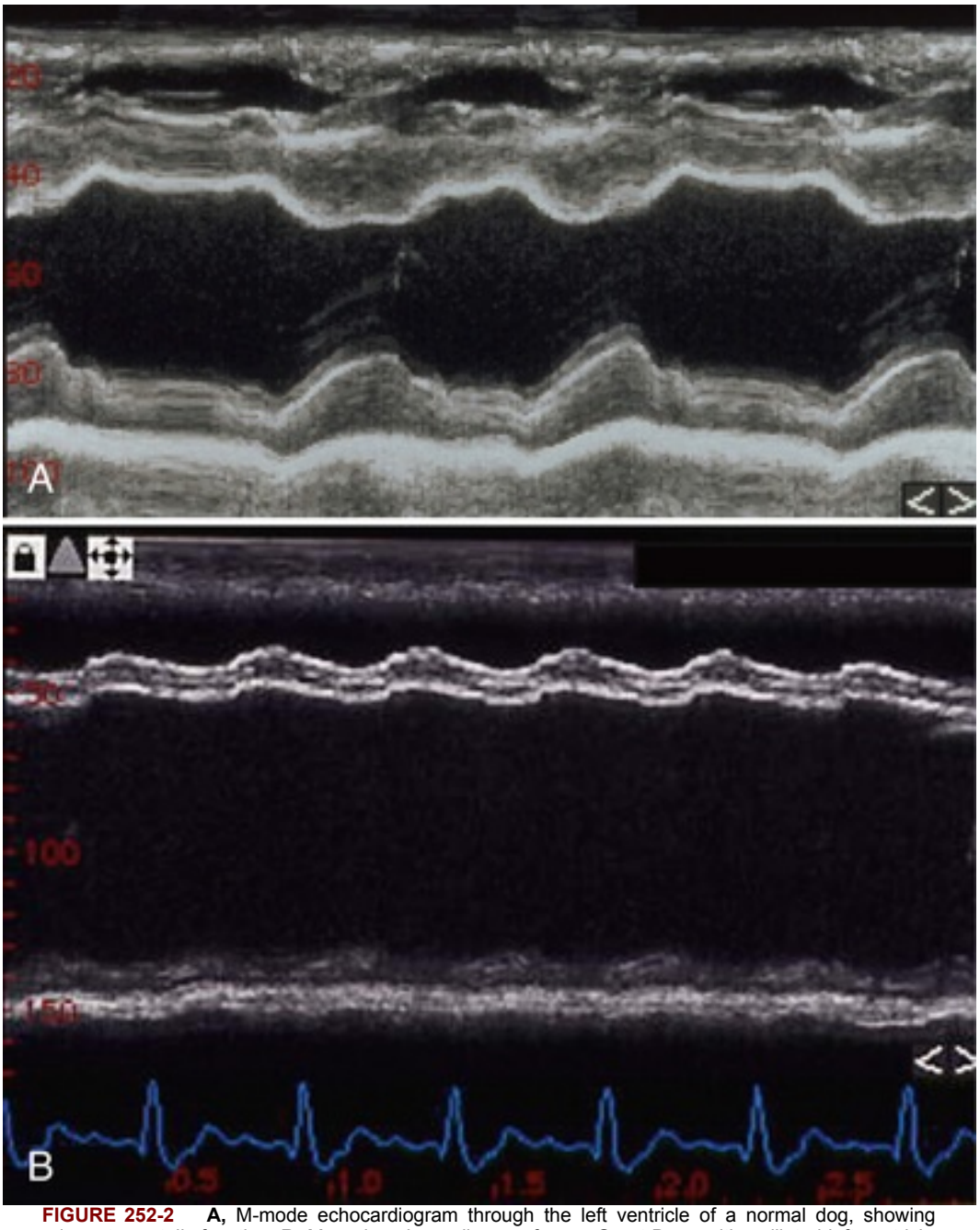

FIGURE 252-2 **A,** M-mode echocardiogram through the left ventricle of a normal dog, showing adequate systolic function. **B,** M-mode echocardiogram from a Great Dane with a dilated left ventricle with a markedly decreased systolic function.

Unfortunately, the diagnosis of the occult stage of DCM is much more difficult. In some cases, dilation of the ventricle precedes the development of systolic dysfunction and is an early indicator of DCM.[20] However, this is not always the case and systolic dysfunction may precede dilation. Annual two-dimensional and M-mode echocardiography is recommended for adult dogs of at-risk breeds or if early signs (heart murmur, gallop, tachyarrhythmias) are detected. Additional studies that have been suggested for additive information when evaluating borderline cases include measurement of the mitral valve annulus motion, sphericity index, E-point-to-septal-separation, systolic time intervals, Simpson's method of disc functional assessment, systolic and diastolic performance index and stress echocardiography.[21-25] Because desirable breeding age may precede the age of onset for DCM, early identification of disease is of paramount importance for reducing the prevalence of this disease in the population.

Biomarkers

Cardiac biomarkers are biological substances of cardiac stress and myocyte injury (see ch. 246).[26] Atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and troponin I (cTnI) are biomarkers shown to be important in the evaluation of cardiac disease in the dog.[21-31]

Atrial natriuretic peptide, a peptide released in response to increased atrial pressure and stretch, has been shown to be significantly increased in both occult and overt dilated cardiomyopathy in the Doberman Pinscher.[28] However, an additional study of dogs of various breeds with DCM found that ANP was not specific or sensitive enough to be useful as a screening tool for the occult stage of DCM.[27] The ability of ANP to suggest the presence of cardiac disease is likely dependent on the stage of the disease, with earlier cases still having normal levels.

Cardiac troponin-I (cTnI) is also a marker of myocardial injury. Plasma cTnI levels were found to be increased in Doberman Pinschers with overt DCM.[29] Cardiac troponin-I levels were also observed to be increased in dogs with occult DCM; however, cTnI levels appeared to lack the sensitivity and specificity to be used as a marker of early DCM in this group of dogs.[27] High sensitivity assays for cTnI have recently become available. Their utility in evaluating occult DCM is not yet reported.

B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are cleaved from a pre-prohormone BNP that is synthesized in the myocytes (see ch. 246). Prohormone BNP is released when the ventricles are dilated, hypertrophic or subjected to increased wall tension and cleaved into the two polypeptides.[26] Levels of BNP have been shown be increased in dogs with congestive heart failure and can be used to help diagnose or exclude a diagnosis of heart failure in dogs that presented for cough or dyspnea.[30] A more recent study measured NT-proBNP in dogs with dilated cardiomyopathy and determined that NT-proBNP levels were significantly higher in affected dogs.[31] BNP screening was quite sensitive even for dogs in the occult stage of disease. Doberman Pinschers were shown to have elevated plasma concentrations of NT-proBNP when affected with DCM and up to 1.5 years prior to the development of DCM.[32] Therefore, it would appear that BNP may be the most useful biomarker for both the occult and overt stages of the disease, although additional studies are needed.

Pathology

Gross pathology of DCM typically demonstrates dilation of both left and right atria and ventricles, although in some cases, the left side is more affected than the right.[33-35] Myocardial eccentric hypertrophy should also be evident by an increased heart to body weight ratio.

Histopathologic findings may vary and are generally fairly nonspecific. Common findings can include attenuated wavy myofibers, fibrosis, vacuolization of myocytes, necrosis and in some cases fatty infiltration.[33,35]

Etiology

The term *cardiomyopathy* can be used to define myocardial diseases caused by a variety of factors including genetic, viral and nutritional, among others (see ch. 253).[3] In many canine cases, the cause is unknown. It is clear that several breeds appear to be overrepresented and some breeds seem to have unique characteristics of the disease that may suggest that this is a unique disease for their breed. A familial form of DCM has now been identified in several breeds and is suspected in others.[9,17,18,36,37] Occasionally, atypical breeds of dogs develop DCM. The etiology of the disease in these cases is unknown and external factors that can insult the myocardium, including infectious organisms or nutritional imbalances, should be considered.[38-44]

Breed-Specific Dilated Cardiomyopathy

Cocker Spaniels

Dilated cardiomyopathy has been reported in both American and English Cocker Spaniels.[1,6,45] An association between the development of DCM and low plasma taurine levels has been reported in some American Cocker Spaniels.[6] American Cocker Spaniels with low taurine levels that were provided taurine and L-carnitine supplementation showed an increase in FS% and a decrease in left ventricular end diastolic and end systolic diameter over a 4-month period, although myocardial function did not return to normal.[46] This study suggested that at least some American Cocker Spaniels with DCM may benefit from

supplementation with taurine and, perhaps, L-carnitine.

Taurine levels may be assessed by evaluation of blood or plasma taurine levels, although blood levels are less affected by sample handling and recent feedings compared to plasma levels. American Cocker Spaniels with DCM should have blood or plasma levels of taurine measured and should be treated with 500 mg of taurine and 1 gram of L-carnitine PO q 12 h.[46] Additional treatment should be given as needed to address any other complications of the disease, including congestive heart failure and arrhythmias. In many cases, supportive cardiovascular medications can be gradually withdrawn after the left ventricular fractional shortening increases to at least 20% (usually after 3-4 months of supplementation). Supplementation with taurine, and L-carnitine if possible, should be continued for life.

In some cases of Cocker Spaniel DCM, taurine deficiency is not identified. The prognosis is generally poorer in these cases.

English Cocker Spaniels also get a form of DCM but a relationship to taurine or carnitine levels has not been identified. Many reported dogs were from the same kennel, which may suggest a heritable component.[47,48] Evidence of profound left ventricular enlargement on the electrocardiogram with R wave amplitudes > 3.0 mV in lead II was frequently observed.[45] Some of the reported dogs died suddenly, but many have a prolonged, fairly asymptomatic course of disease, or a long survival (years) with medical management.[47]

Dalmatians

Dalmatians are occasionally diagnosed with DCM, although not as commonly as some of the other breeds such as Doberman Pinschers, Great Danes and Irish Wolfhounds.[1] Male dogs appear to be overrepresented in Dalmatian DCM, although large studies have not been performed.[7] All dogs had adult-onset disease and presented for signs consistent with left heart failure (cough, dyspnea) or syncope. None of the dogs had evidence of biventricular heart failure. Electrocardiography frequently demonstrated sinus rhythm or sinus tachycardia with occasional ventricular ectopy. Atrial fibrillation was not observed in any of the dogs. Duration of survival ranged from 1.5 to 30 months with euthanasia due to refractory CHF. None of the dogs died suddenly. Interestingly, the majority (8/9) of reported dogs had been fed a low protein diet for all or part of their lives for prevention or treatment of urate stones. The low protein diet may have resulted in an imbalance that could have led to the possible development of dilated cardiomyopathy; however, in the dogs that were tested, there was no evidence of L-carnitine or taurine deficiency. The cause and effect of these diets on the development of DCM is not known, but Dalmatians that develop DCM that are being fed a low protein diet should be switched to a more balanced diet if possible.

Occasionally Dalmatians develop acquired AV valve disease so this should be considered as an important differential diagnosis (see ch. 251).

Doberman Pinschers

The Doberman Pinscher is one of the most commonly reported breeds of dogs to be diagnosed with DCM in North America.[8,14,49,50] It is an adult onset disease that results in the development of left and/or biventricular failure, often with atrial fibrillation or sudden cardiac death.[51] The occult stage can be characterized by infrequent ventricular premature complexes, mild ventricular dilation and/or systolic dysfunction.[51] Diastolic function is often present.[2] The overt stage is often characterized by atrial fibrillation, ventricular premature complexes and congestive heart failure. Many affected dogs will first present for symptoms from their ventricular tachyarrhythmias including syncope and sometimes, sudden cardiac death.[52,53] Although, syncope is often associated with the presence of ventricular tachyarrhythmias, bradycardia associated episodic weakness and syncope has also been observed in cardiomyopathic Doberman Pinschers.[53] Therefore, every attempt should be made to determine the cause of the syncopal episodes with a Holter or event monitor before treatment is started.

Pathologic evaluation of the hearts of affected Doberman Pinschers identified a variety of nonspecific findings. Moderate to severe dilatation of all four cardiac chambers was often observed, although the left side was typically worse than the right. Heart weight to body weight ratios are often increased (11.5 +/− 2.4 g/kg; normal = 6.6 +/− 0.3 g/kg, p <0.001).[53b] Histologic lesions have been characterized by marked myofiber degeneration and atrophy, myocardial replacement by thick bands of collagen fibers, interstitial fibrosis, aggregates of fat, multifocal myocytolysis and myocardial necrosis.

Dilated cardiomyopathy in the Doberman Pinscher appears to be familial. An autosomal dominant mode of inheritance has been defined by the appearance of the disease in multiple generations, equal gender

representation and evidence of male-to-male transmission[36] (Figure 252-3). In North American Doberman Pinschers, a splice-site mutation in the pyruvate dehydrogenase kinase 4 (*PDK4*) gene has been identified and associated with development of DCM. A mutation test is available and may be utilized to inform breeding decisions. This mutation is incompletely penetrant, meaning that not all dogs with the mutation will develop disease and the expression of disease is variable.[16] Ongoing studies in Europe aim to identify a second mutation in Doberman Pinschers, as the PDK4 gene does not appear to be the only cause of US Doberman DCM, it was not associated with a European cohort of DCM Dobermans, and a different chromosomal region of interest was identified by genome-wide association analysis in European dogs.[54,55]

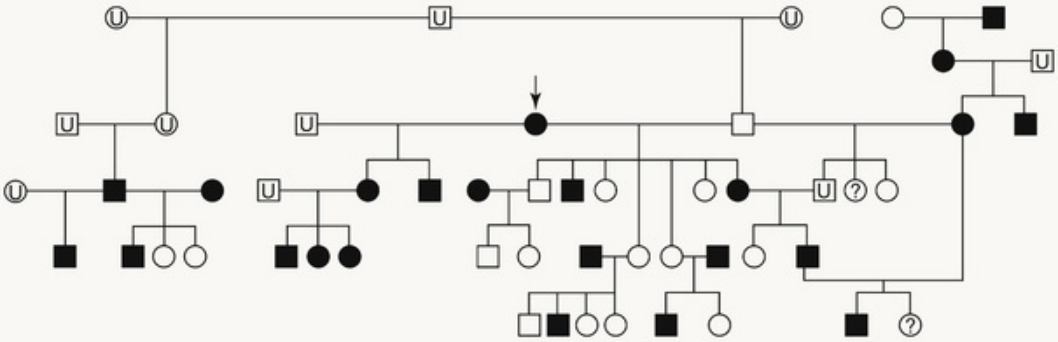

FIGURE 252-3 Pedigree from a Doberman Pinscher family with dilated cardiomyopathy and an autosomal dominant mode of inheritance. The proband is indicated by an arrow. Circles represent female dogs; squares represent male dogs. Solid black symbols represent affected animals; a U in the symbol represents dogs classified as indeterminate; solid white symbols represent unaffected animals; a question mark in the symbol represents animals not available for evaluation. (Previously published in Meurs KM, Fox PR, Norgard M, et al: A prospective genetic evaluation of familial dilated cardiomyopathy in the Doberman pinscher. *J Vet Intern Med* 21:1016-1020, 2007.)

Evidence that the disease is familial and the suggestion that early intervention may increase survival has led to significant interest in screening asymptomatic dogs for signs of occult disease. Annual echocardiography and ambulatory electrocardiography (Holter monitoring) are believed to be the best predictors of early DCM.[50,56] Criteria that are believed to be indicators of occult disease include an echocardiographically determined left ventricular end diastolic diameter greater than 4.6 cm and a left ventricular end systolic diameter greater than 3.8 cm, even in the absence of systolic dysfunction.[22] These numbers are based on average sized DCM dogs and may be less valid for very large dogs (Videos 252-1 and 252-3). Annual Holter monitoring has also been recommended to detect Doberman Pinschers that may develop ventricular arrhythmias before ventricular dilation and systolic dysfunction (Figure 252-4). Adult Doberman Pinschers with greater than 50 ventricular premature complexes (VPCs) per 24 hours, or with couplets or triplets are suspect for the development of DCM.[56] Measurement of circulating BNP or NT-proBNP may also be useful for early detection of disease.[27,32] Genetic testing for the associated PDK4 mutation may aid in the development of screening protocols.[16] Owners should be advised that since this is an adult-onset disease with variability in the age of onset, screening tests should be performed annually.

FIGURE 252-4 Adult Doberman Pinscher with a Holter monitor used for screening for occult disease.

Great Danes

Dilated cardiomyopathy in the Great Dane appears to be a familial disease.[9] In one study, affected male dogs were overrepresented, suggesting an X-linked pattern of inheritance in at least some families.[9] If this is true, sons of affected females are at high risk of developing the disease; daughters of affected fathers are likely to be silent carriers. Affected Great Danes presented most commonly for weight loss and/or coughing. Left-sided heart murmurs, a gallop and ascites were frequently observed. The most common electrocardiographic findings included atrial fibrillation with an occasional ventricular premature complex. In some cases, atrial fibrillation developed before any other evidence of underlying myocardial disease (chamber enlargement or systolic dysfunction). Therefore, dogs with atrial fibrillation should be carefully evaluated for early DCM and should be followed annually to monitor for possible development of disease.

Irish Wolfhounds

Dilated cardiomyopathy appears to be a familial trait in the Irish Wolfhound.[37,57] The mode of inheritance is autosomal recessive with sex-specific alleles. Male dogs may be overrepresented.[10] As in the Great Dane, atrial fibrillation frequently preceded the development of a heart murmur, clinical signs and CHF. Atrial fibrillation was present in the majority of Irish Wolfhounds by the time they developed DCM.[10,58] The progression of the disease is not well understood but appears to be slow, with the development of atrial fibrillation preceding the development of CHF by an average of 24 months.[10] Occasionally, additional electrocardiographic abnormalities have been described including ventricular premature complexes and left anterior fascicular block patterns. Affected Irish Wolfhounds occasionally died suddenly, but more commonly were euthanized due to heart failure, most commonly biventricular, and sometimes with chylothorax.[58,59] Low whole blood taurine levels are occasionally encountered in Irish Wolfhounds, but no clear relationship between taurine levels and DCM can be established in this breed.[60]

Newfoundlands

Adult-onset DCM without a gender predisposition has been reported in the Newfoundland.[11,23] Clinical presentation included dyspnea, cough, inappetence and ascites with left or biventricular heart failure. Interestingly, a heart murmur was auscultable in only a very small percentage of the dogs (4/37).[11] The most common electrical abnormality was atrial fibrillation, but isolated ventricular premature complexes were also observed.

Portuguese Water Dogs

A juvenile form of familial DCM has been reported in the Portuguese Water Dog and is thought to be inherited as an autosomal recessive trait that is linked to a region on canine chromosome 8.[12,61] Affected puppies were from seemingly unaffected parents and typically died between 2 and 32 weeks of age, either from sudden collapse and death without any preceding signs or the development of congestive heart failure.[61]

Standard Schnauzers

Familial DCM in the standard Schnauzer has been reported and recently a deletion and frame-shift mutation in the RNA binding motif protein 20 *(RBM20)* gene was identified. This mutation is inherited in an autosomal recessive pattern. Although clinical reports of this disease and mutation in the breed are currently lacking, a genetic mutation test is available and may be used to inform breeding decisions.[17]

Toy Manchester Terriers

A rapidly progressive juvenile form of familial DCM has been reported in the Toy Manchester Terrier and is clinically similar to the Portuguese Water Dog with DCM. Most affected dogs are less than 1 year of age and typically die suddenly without signs of overt congestive heart failure.[18]

Nutritional Cardiomyopathy

Taurine Related Cardiomyopathy

The development of dilated cardiomyopathy due to low taurine is much less common in the dog than in the cat since dogs have a much greater ability to synthesize taurine than cats. However, as mentioned above, a relationship between taurine and L-carnitine abnormalities and DCM has been previously described in the Cocker Spaniel.[6,46] There have now been additional reports of the development of DCM in the dog in which low blood or plasma levels of taurine have been documented.[43,44] The dogs were all adult at the time of onset and were breeds that would be considered to be in the large breed dog groups. A common factor observed in several dogs that developed DCM and were determined to have low taurine was the feeding of a diet of a dry dog food with lamb meal, rice or both as the primary ingredient.[44] It has been hypothesized that rice bran or whole rice products may result in decreased taurine levels in some dogs. However, there is also a report of a family of Golden Retrievers with an apparent familial taurine deficiency and dilated cardiomyopathy. In a separate study of plasma taurine concentrations in dogs with heart disease, 4 out of 6 Golden Retrievers with DCM had low taurine levels.[43] These findings suggest that there may be some breed variations in taurine handling that could result in the development of DCM in certain breeds.

A blood level of less than 150 nmol/mL or plasma levels less than 40 nmol/mL indicates a diagnosis of taurine deficiency. If taurine deficiency is suspected, taurine supplementation should be started while waiting for the results of the blood or plasma levels. Published dosages for taurine supplementation appear to vary slightly, although 1000 mg/day (PO, divided or once a day) appears to be a consistent recommendation.[43,44] Additional cardiac medications should be provided as needed including inotropic support such as pimobendan and treatment of heart failure if needed (see ch. 247). Taurine-deficient dogs with dilated cardiomyopathy appear to respond to supplementation fairly rapidly and improvement in echocardiographic measurement should be observed in 3-6 months. Ideally, blood levels of taurine should be reevaluated in 1-2 months to confirm that the levels have increased.[43]

Treatment

Treatment of the Dog with Dilated Cardiomyopathy

The ideal treatment for dilated cardiomyopathy would be directed at the primary insult to the myocardium. Unfortunately, in the majority of cases, the underlying cause is not known and treatment should be directed

to the identified cardiac abnormalities—for example, systolic dysfunction, presence of heart failure (see ch. 247) or arrhythmias (see ch. 248).

Treatment of the Dog with Occult Dilated Cardiomyopathy

There are very few studies that have evaluated the benefit of medical therapy for dogs diagnosed in the occult stage of the disease; however, this area is likely to expand with our increasing ability to diagnose the disease early. Administration of angiotensin converting enzyme (ACE) inhibitors may have some benefit for the dog with early ventricular dilation, with or without systolic dysfunction. The use of ACE inhibitors in the Doberman Pinscher with ventricular dilation was associated with a longer period of time before the onset of CHF.[19] Although this study was limited to evaluation of Doberman Pinschers and was retrospective in nature, the use of ACE inhibitors for other breeds of dogs with occult DCM should be considered.

Administration of beta-blockers to the dog in the occult stage of DCM for a cardioprotective effect is still being evaluated. The addition of low-dose beta-blockers to the treatment of human patients with DCM and stable heart failure has demonstrated a reduction in both mortality and morbidity.[63] However, many human patients with DCM cannot tolerate even very low dosages of beta-blockers and demonstrate rapid cardiac decompensation. One prospective, placebo-controlled canine study that looked at the effect of three months of the beta-blocker carvedilol at a gradually increasing dosage did not identify any differences between the beta-blocker and placebo effect in echocardiographic indices of left ventricular size or function, neurohormonal activation, radiographic heart size, heart rate or owner perceived quality of life.[64] It is possible that a greater effect might be observed if the medication was given over a longer period of time or at a higher dosage. Overall, the use of beta-blockers for the canine patient with DCM has not yet been well studied and a consensus opinion on use of these drugs for the canine patient is not yet available. Beta-blockers might be considered for the patient with occult disease, but such patients should be very carefully monitored and the beta-blocker should not be given if there is evidence of heart failure until it is very well stabilized. It cannot be over-emphasized that the addition of beta-blockers in canine DCM patients should be done very cautiously with gradual increases in dosing after a two-week period and careful monitoring of heart rate, blood pressure and clinical signs.

Administration of pimobendan, an inodilator, with calcium-sensitizing and phosphodiesterase inhibition effects, is widely utilized in the treatment of canine congestive heart failure (see ch. 247).[65] The PROTECT study, a multicenter double-blinded placebo-controlled evaluation, identified a clear survival benefit in Doberman Pinschers given pimobendan during the occult phase of their disease process. The median time to onset of congestive heart failure or sudden cardiac death was found to be significantly longer (718 days versus 441 days) for Dobermans with occult DCM that received standard doses of twice-daily pimobendan.[66] Although this study was limited to the evaluation of Doberman Pinschers, the use of pimobendan for other breeds of dogs with occult DCM should be considered.

Treatment of the Dog with Dilated Cardiomyopathy and Congestive Heart Failure

Dogs with DCM and heart failure will benefit from inotropic support. Ideally, this would be with pimobendan, a phosphodiesterase III and V inhibitor with calcium-sensitizing properties that acts as a positive inotrope as well as vasodilator (inodilator).[65] Pimobendan has balanced vasodilatation and positive inotropic effects and has been shown to increase survival (median of 130 days versus a median of 14 days for the placebo in one study) in Doberman Pinschers with DCM when given at a dosage of approximately 0.25 mg/kg PO q 12 h[62,65] (Video 252-6, *A* and *B*).

Additional medications for heart failure such as ACE inhibitors and diuretics should be started as needed (see ch. 247). Nonspecific treatments including nutritional supplementation with compounds like taurine should be considered in dogs that may be suspected of having low levels until proven otherwise.[67] Supplementation with fatty acids may be considered for patients with cachexia (see ch. 177 and 183). Treatment of confounding supraventricular or ventricular arrhythmias must be considered (see ch. 248). The use of digoxin and/or diltiazem is frequently utilized in the co-management of atrial fibrillation and congestive heart failure.

Treatment of the Dog with Ventricular Arrhythmias

There is little consensus for the decision of when and how to treat ventricular arrhythmias in the dog with DCM. Rapid ventricular tachycardia, complex ventricular arrhythmias or the combination of ventricular arrhythmias, ventricular dilation and systolic dysfunction are thought to be associated with a higher risk of

sudden cardiac death and to be indications for treatment, but this has not been well studied. Additionally, some dogs die suddenly without having any of these arrhythmias documented. If treatment is warranted, consideration might be given to the use of one of several ventricular antiarrhythmics (see ch. 248). Sotalol, a combination beta-blocker and potassium channel blocker, may be beneficial in some cases, but should be used a bit more cautiously (low-dose) if systolic dysfunction is present. Mexiletine at a dosage of 5-6 mg/kg PO q 8 h can be very effective at decreasing the arrhythmia. In a small number of cases it can cause nausea but this can be significantly reduced if it is given with at least a small meal, so it should never be given on an empty stomach. Amiodarone has been studied in the affected Doberman Pinscher at a dosage of 10 mg/kg PO q 12 h for 5 days and then 5 mg/kg q 24 h. Careful evaluation of serum drug concentrations, complete blood counts (neutropenia has been reported) and serum liver enzyme activities on a monthly basis is suggested.[51] Although the goals of treatment include decreasing the number of ventricular premature complexes, decreasing clinical signs and decreasing the risk of sudden death, the ability of any antiarrhythmic to reach these goals has not been well studied.

Prognosis for the Dog with Dilated Cardiomyopathy

Prognosis is likely to be dependent on the underlying cause, which is generally not known. However, for the canine population with DCM, certain negative predictors of survival have been identified including age of onset of clinical signs, pleural effusion, pulmonary edema, ascites, atrial fibrillation, end systolic volume index, ejection fraction and a restrictive pattern of transmitral flow.[68,69]

Arrhythmogenic Right Ventricular Cardiomyopathy in the Boxer

Since the early 1980s, the term Boxer cardiomyopathy has been used to describe adult Boxer dogs that present with ventricular arrhythmias, and sometimes, syncope.[70] Recent studies have demonstrated that the disease has many similarities to a human disease called arrhythmogenic right ventricular cardiomyopathy (ARVC). The similarities between the diseases include clinical presentation, etiology and a fairly unique histopathology that includes a fibrous fatty infiltrate of the right ventricular free wall[71] (Figure 252-5). The disease is most commonly characterized by ventricular arrhythmias, syncope and sudden death. However, systolic dysfunction and ventricular dilation are seen in a small percentage of cases.

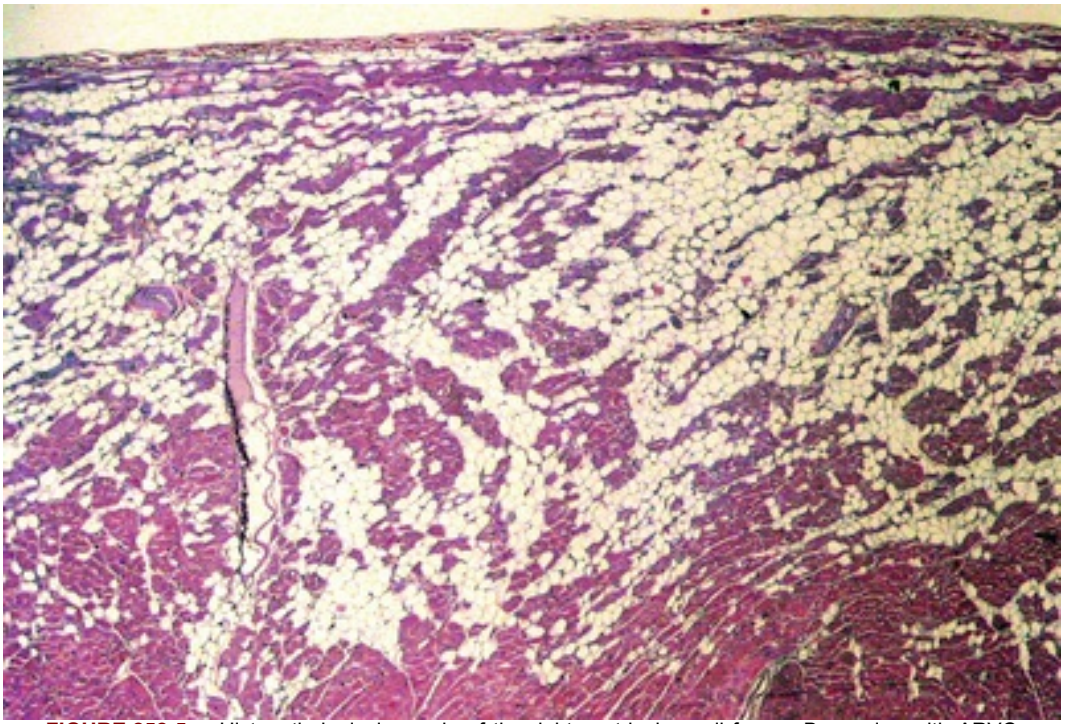

FIGURE 252-5 Histopathological sample of the right ventricular wall from a Boxer dog with ARVC demonstrates multifocal myocyte vacuolization, myocyte loss, and significant fatty infiltration. 20× magnification, hematoxylin and eosin stain.

Arrhythmogenic right ventricular cardiomyopathy is a familial disease in the Boxer and appears to be inherited as an autosomal dominant trait.[72] Unfortunately, the disease also appears to be a disease of variable genetic penetrance and affected dogs can have many different presentations including asymptomatic, syncope, sudden death and systolic dysfunction with CHF. A genetic deletion mutation in the gene striatin was found to be associated with development of ARVC in Boxers. This mutation is inherited in an autosomal dominant pattern with incomplete penetrance. Importantly, homozygous mutant dogs exhibit more severe forms of ARVC including higher number of ventricular arrhythmias, sudden death events and the rare structural heart disease variety of this condition, termed type III ARVC.[73,74]

Diagnosis

The most common presenting complaint is one of syncope (see ch. 30). Episodes of syncope may be associated with a period of exercise or excitement, but are not always. Some dogs present for exercise intolerance or lethargy and others die suddenly without ever developing symptoms. Infrequently (approximately 10% of affected dogs), a dog may present with signs of left or biventricular heart failure.

Most affected Boxers have a completely normal physical examination. However, a tachyarrhythmia may be ausculted. In the small percentage of cases with ventricular dilation and systolic dysfunction, termed type III ARVC, a systolic murmur and/or gallop (S_3) may be ausculted at the left apex. Infrequently, signs of right heart failure (ascites and jugular venous distension) may be observed. The Boxer breed also has a very high incidence of left basilar systolic murmurs. These murmurs may be associated with aortic stenosis, or potentially may be physiologic. Many Boxers with ARVC have these murmurs in addition to their arrhythmic disease, but left basilar systolic heart murmurs are not an indication of Boxer ARVC.

Biomarkers appear to be of variable value in the diagnosis of Boxer ARVC. Cardiac troponin I has been shown to be significantly elevated in Boxers with ARVC and correlated with both VPC number and grade, or complexity, of the arrhythmia[75] (Figure 252-6). However, some affected dogs had lower levels of cTnI that overlapped with normal Boxers. Therefore, although measurement of cTnI may provide supportive information in a dog in which a diagnosis of ARVC is suspected, further study is needed before it can be an independent screening test. B-type natriuretic peptide measurement in similar groups of Boxers did not identify a difference in affected dogs in comparison to normal Boxers and normal unaffected boxers; therefore, BNP does not appear to be a useful indicator of disease.[76]

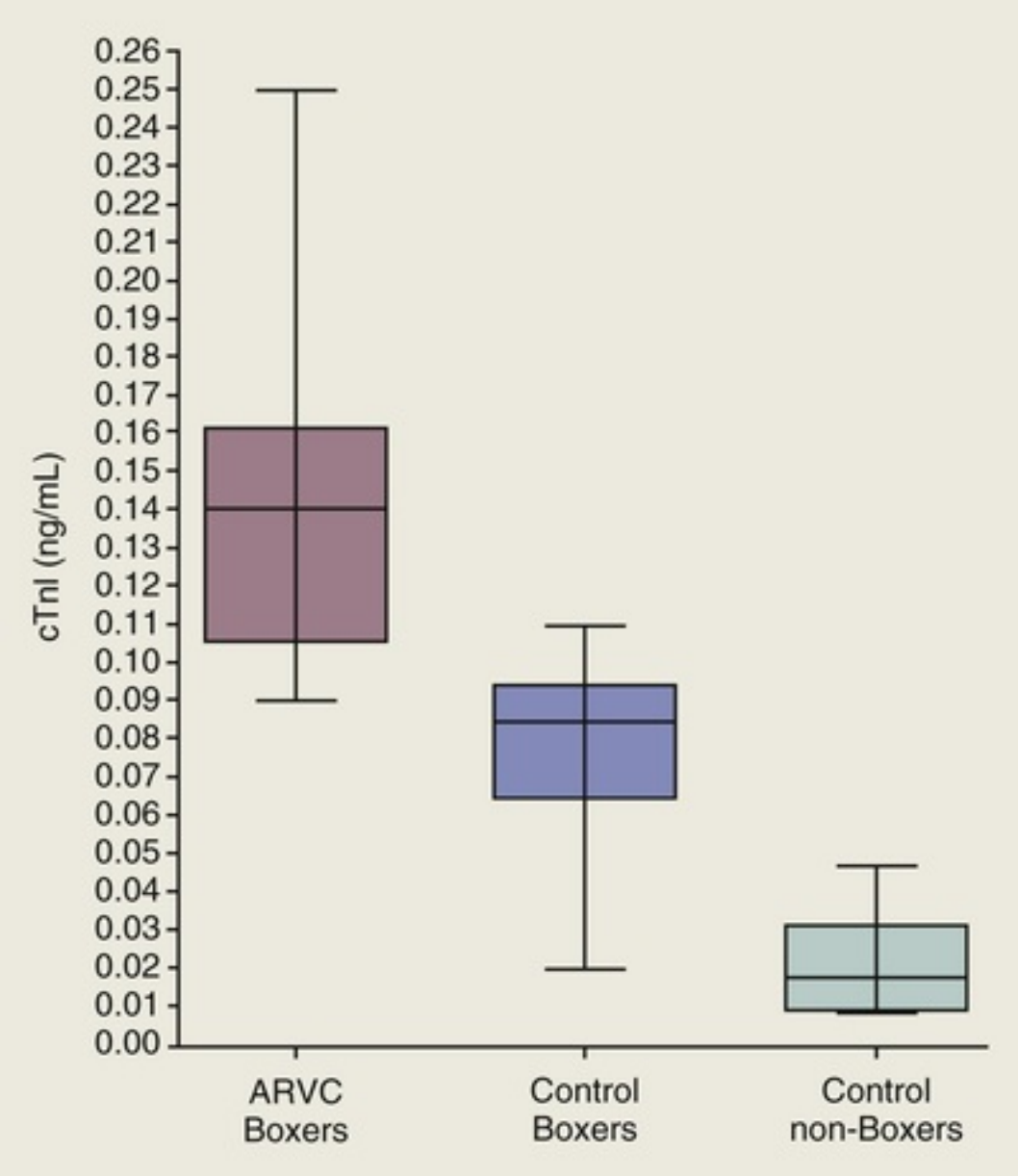

FIGURE 252-6 Box plot of serum cTnI concentrations obtained from ARVC Boxers (n = 10), control Boxers (10), and control non-Boxers (10). Troponin I was significantly elevated in ARVC Boxers. Solid horizontal lines within boxes represent mean values. Each box represents 95% confidence intervals. Whiskers represent the range of values. (Previously published in Baumwart RD, Orvalho J, Meurs KM: Evaluation of serum cardiac troponin I concentration in Boxers with arrhythmogenic right ventricular cardiomyopathy. *Am J Vet Res* 68:524-528, 2007.)

A 2-5 minute electrocardiogram (see ch. 103) is frequently normal in the affected Boxer; however, ventricular premature complexes may be present singly, in pairs and in runs of paroxysmal ventricular tachycardia (Figure 252-7). The ventricular premature complexes typically have a left bundle branch block morphology in leads I, II, III, and AVF, consistent with the right ventricular origin of this arrhythmia.[77] In some cases, the ventricular arrhythmias that cause syncope may not be observed on the electrocardiogram and a 24-hour Holter monitor should be performed to evaluate for arrhythmias.

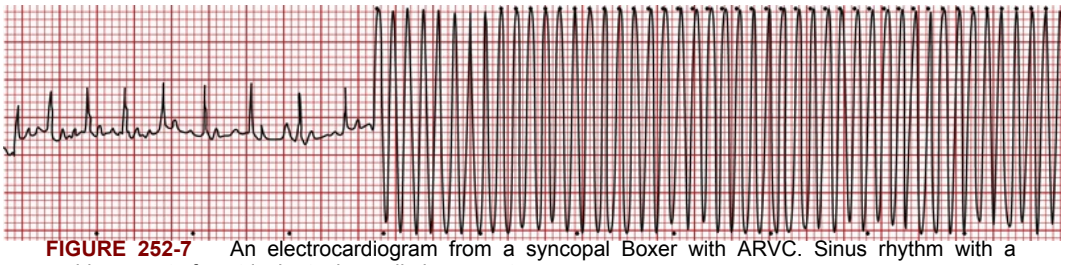

FIGURE 252-7 An electrocardiogram from a syncopal Boxer with ARVC. Sinus rhythm with a sudden onset of ventricular tachycardia is present.

Interpretation of the Holter results can sometimes be challenging because strict criteria for this diagnosis do not exist. However, since it is unusual for a normal dog to have any VPCs in a 24-hour period, the observation of >100 VPCs, or periods of couplets, triplets or runs of ventricular tachycardia are abnormal and may be diagnostic in a dog with clinical signs.[78] Supraventricular premature complexes may also be observed, particularly in Boxers with ventricular dilation and systolic dysfunction.

Thoracic radiographs are usually within normal limits. However, in the small number of cases with left ventricular dilation and systolic dysfunction (Type III ARVC), generalized cardiomegaly with pulmonary edema and/or pleural effusion may be noted (Video 252-5).

Echocardiography is an important part of the evaluation because ventricular dilation and systolic dysfunction may occur, but in most cases affected dogs have normal chamber sizes and systolic function. In some cases, careful evaluation will allow the identification of right ventricular enlargement (Video 252-4).

The familial etiology of ARVC has led to a widespread interest in screening dogs before selecting them as breeding animals. Genetic mutation testing for the striatin mutation is available and may be used to guide breeding decisions and make recommendations for reevaluation schedules.[73,74] However, since ARVC-positive Boxers have been identified without the striatin mutation, it is prudent that continued clinical screening be carried out, as at least one other cause of ARVC exists.

Since ARVC presents as an electrical abnormality more often than one of myocardial dysfunction, screening efforts should be based on annual Holter monitoring as well as annual echocardiography. Unfortunately, clear criteria for the diagnosis of occult ARVC do not exist. However, dogs that are symptomatic show clinical signs (syncope, heart failure) or have evidence of ventricular tachycardia on a Holter should not be used for breeding. Additionally, dogs that have over 100 left bundle branch block morphology VPCs/24 hours are probably highly suspicious of being affected. However, not all affected dogs will ever develop clinical signs and many may live a normal lifespan. It is likely that there are multiple factors that may influence which dogs develop overt clinical signs of the disease. To help decrease the risk of making an error when adding or removing a dog from a breeding program, owners should be encouraged to screen annually rather than putting significant emphasis on a single Holter monitor reading. Since the disease is adult in onset and an increase in VPCs has been observed with age in affected animals, an animal that is clear at the age of two is not guaranteed to stay clear. Additionally, an animal with a few hundred VPCs at the age of two years may have more, fewer, or the same number the next year. Until a greater understanding of disease inheritance and disease progression exists, caution should be used when advising breeders to remove dogs from breeding programs. Overzealous removal of animals based on the results of a single Holter monitor may have a significant negative impact on the breed.

Treatment

If an arrhythmia is detected on routine examination in an asymptomatic dog, a Holter monitor should be performed to evaluate for the frequency and complexity of the arrhythmia. Although a strict relationship between the development of clinical signs and the number of VPCs does not exist, treatment is generally started if >1000 VPCs/24 hours, runs of ventricular tachycardia, or evidence of the R on T phenomenon exist. One may consider an earlier treatment intervention in Boxer dogs known to be homozygous positive for the striatin mutation as they have been shown to have more severe disease.[74] Owners should be advised that ventricular antiarrhythmics have the potential for proarrhythmic effects and that treatment is not known to decrease risk of sudden death. At this time, there is no evidence that treatment will significantly alter the outcome for affected dogs. However, treatment has been shown to decrease the number of ventricular premature complexes as well as syncopal episodes.[79]

Dogs with syncope and ventricular arrhythmias are generally started on treatment. There are two choices

for treatment that are well tolerated and have been shown to decrease VPC number and complexity: sotalol 1.5-3.5 mg/kg PO q 12 h or mexiletine 5-6 mg/kg PO q 8 h.[79] In some cases, the combination of sotalol and mexiletine at the dosages stated above is indicated for optimal control of the arrhythmia. It is likely that there is individual variation for drug response and if a poor response is observed with one drug, a different one or the combination of the two may prove to be more effective. Ideally, a Holter monitor would be placed before starting therapy and repeated two to three weeks after starting therapy to monitor the effect of the medication. Significant day-to-day variation in VPC number exists but a therapeutic effect is likely to exist if at least an 85% reduction in VPC number is observed after starting medication.[80]

In one study, fish oils (780 mg EPA and 497 mg DHA PO per day) given orally for six weeks were shown to decrease the number of VPCs but not to a degree that was beyond what might be due to day-to-day variation. Thus, antiarrhythmics are still indicated for management, perhaps in combination with fish-oil supplementation.[81]

If echocardiography demonstrates systolic dysfunction and ventricular dilation, treatment for DCM (pimobendan, ACE inhibitors, diuretics) may be warranted. Additionally, supplementation with L-carnitine might be considered at a dosage of 50 mg/kg PO q 8-12 h, since a small number of affected Boxers have demonstrated improvement in systolic function and prognosis after supplementation.[41]

Prognosis

Dogs with ARVC are always at risk of dying of sudden cardiac death. However, many dogs may live for years on antiarrhythmics without clinical signs, but some of these may eventually develop ventricular dilation and systolic dysfunction. Boxers without systolic dysfunction and ventricular dilation maintain a prognosis that is comparable to that of non-ARVC Boxers, with a median survival age of 11 years.[82]

Myocarditis

Myocarditis is a form of myocardial disease characterized by the presence of myocardial necrosis or degeneration and inflammation. A variety of physical, chemical and infectious agents can damage the myocardial tissue and evoke an inflammatory response, which may result in chamber enlargement, myocardial dysfunction similar to that observed in DCM and a variety of tachyarrhythmias and bradyarrhythmias.[83,84] Plasma cardiac troponin I (cTnI) levels are often elevated, suggesting myocardial injury. In the dog, protozoal and viral organisms are reported most commonly.

Chagas' disease, caused by the protozoan parasite *Trypanosoma cruzi*, is common in the dog, particularly in the southern part of North America. Three stages of infection have been described: acute, latent and chronic. The acute stage is characterized by lethargy, generalized lymphadenopathy, pale mucous membranes, increased capillary refill time and hepato-splenomegaly.[85] This stage is associated with a variety of electrocardiographic abnormalities including sinus tachycardia, prolonged PR interval, decreased R wave amplitude, axis shifts and conduction disturbances.[86] Sudden death may be observed. Dogs that survive the acute stage may enter a prolonged latent period during which the clinical signs appear to regress.[86] The chronic stage of Chagas' disease is associated with signs of progressive right-sided cardiac dysfunction, ascites, pleural effusion, hepatomegaly and jugular venous distention. Occasional ventricular tachycardias have been reported.[86] In one study, almost half of the dogs diagnosed histopathologically with Chagasic myocarditis at necropsy were dogs that died suddenly and fifty percent of those dogs were less than 1 year of age.[84] The diagnosis of Chagas' disease is most commonly performed by serology, and the acute form can sometimes be diagnosed by the presence of circulating trypomastigotes on thick blood smears. In general, treatment of Chagas' disease is directed at palliation of clinical signs, since destruction of the intracellular form of the parasite may result in severe exacerbation of the host inflammatory response. However, there is some preliminary work in dogs which suggests that a cysteine protease inhibitor may be very effective for reducing the severity of the cardiac aspects of the disease.[81]

Leishmania are protozoal organisms that are endemic in certain geographical regions including the Mediterranean basin (see ch. 221).[87] Clinical signs of the myocarditis associated with *Leishmania* are thought to be a result of direct action of the parasite within the myocardium as well as intense inflammation in response to the parasite. Cardiac arrhythmias including first degree AV block have been observed, and both epicarditis and myocarditis have been identified at necropsy. Additional protozoan parasites that have been associated with the development of myocarditis include *Neospora caninum* and *Toxoplasma gondii*.[88-90]

Parvovirus myocarditis is an uncommon form of myocardial disease (also see ch. 225). It may present with a peracute form that affects puppies between 3 and 8 weeks of age. Puppies present with acute dyspnea consistent with severe left heart failure and die within hours.[39] At necropsy, the hearts are found to be dilated with multifocal myofiber necrosis, mononuclear cell infiltrate and intranuclear inclusion bodies in the myocardial nuclei.[39,91] A second form of the disease affects juvenile dogs (generally less than 1 year of age) and has a clinical presentation similar to that of DCM.[39,40]

West Nile virus has been observed uncommonly in the dog and clinical signs are often vague and include lethargy, inappetence, neurologic signs, arrhythmias and fever.[92,93] Severe lymphocytic, neutrophilic myocarditis and vasculitis have been observed with focally extensive hemorrhage and myonecrosis. The diagnosis can be confirmed in a variety of ways including immunohistochemistry, reverse-transcriptase polymerase chain reaction testing, virus isolation and serology.[92]

Fungal myocarditis due to *Blastomyces* has been reported, although this does not appear to be a common form of this fungal infection (see ch. 233).[94] Three dogs presented for syncope, one for sudden death and three had newly diagnosed heart murmurs. Cardiac findings included sinus tachycardia as well as one dog with ST segment elevation and one dog with third degree AV block. Two dogs had cardiac compression due to an extracardiac granuloma while others had myocardial, epicardial, pericardial or valvular involvement. Although only a small number of cases have been reported, generally the dogs with cardiac involvement with blastomycosis had a poor prognosis.

Infrequently, infectious organisms including bacteria, *Bacillus piliformis, Citrobacter koseri* and the spirochete, *Borrelia burgdorferi* have been associated with the development of myocarditis.[95,96]

Atrial Myocarditis

A form of myocarditis limited to the atria has been reported.[97-99] Unexplained atrial arrhythmias including atrial fibrillation have been associated with inflammation or infectious organisms in the atria. Multifocal myocarditis of both atria was observed at necropsy in a case with atrial fibrillation.[97] Intermittent asystole with syncope was observed in a dog with lymphocytes, macrophages, and neutrophils throughout the right, and to a lesser extent, the left atrium.[98] One case of atrial myocarditis was associated with a concurrent diagnosis of polymyositis.[99] The dog had significant right atrial dilation, atrial premature complexes and increased troponin levels. Histopathologic analysis identified right atrial lymphocytic infiltration.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a primary myocardial disease characterized by concentric hypertrophy of the interventricular septum and left ventricular free wall (see ch. 253). Hypertrophic cardiomyopathy and the variant hypertrophic obstructive cardiomyopathy are infrequent forms of canine myocardial disease (Video 252-7). There appear to be significant differences between the canine disease and the disease more commonly observed in cats and human beings with regard to etiology and pathological findings.[100,101] An inheritable form of hypertrophic obstructive cardiomyopathy has been observed in the Pointer dog, but most canine cases appear to be sporadic.[100-103] Because of the relative infrequency that hypertrophic and hypertrophic obstructive cardiomyopathy are observed in the dog, suspect patients should be carefully evaluated for other causes of concentric hypertrophy of the left ventricle including the much more common left ventricular outflow tract obstruction observed with subvalvular and valvular aortic stenosis.

Hypothyroidism

Some dogs with hypothyroidism have been observed to have a reduction in left ventricular fractional shortening percentage and an increase in left ventricular dimensions; however, the values had significant overlap with normal dogs.[104] Thus, although evaluation of thyroid levels might be considered in dogs that have minor echocardiographic changes in addition to other signs of hypothyroidism, it should not be considered a common cause of myocardial dysfunction nor ventricular dilation.[105] Despite many investigations into hypothyroidism of Doberman Pinschers, a recent study identified no role of hypothyroidism in the etiology or progression of Doberman Pinschers DCM.[106]

Myocardial Infarction

Acute myocardial infarctions are an uncommon form of myocardial disease in dogs and appear to be most commonly associated with concurrent systemic or cardiac disease that has led to a thromboembolic state. These conditions might include endocarditis, neoplasia, renal disease, immune-mediated hemolytic anemia and pancreatic disease. Dogs with infarcts were very rarely diagnosed with atherosclerosis as opposed to human beings, who have a high incidence of infarcts associated with atherosclerosis.[107]

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CHAPTER 253

Feline Myocardial Diseases

Valérie Chetboul

Client Information Sheets:
Feline Myocardial Diseases—General Presentation
Focus on Feline Hypertrophic Cardiomyopathy

Introduction: Classification (Nosological Considerations) and Prevalence

Myocardial diseases refer to a broad spectrum of heterogeneous diseases of the heart muscle, and are by far the most common cardiac disorders in the cat.[1-5] Over the last 4 decades, several classifications of human myocardial diseases have been proposed and modified, due to the increased knowledge of their various underlying causes, molecular and genetic basis and complex pathophysiological features as well as the discovery of new pathological entities.[6-14] In 1980, the World Health Organization (WHO) identified "*heart muscle diseases of unknown cause*" as cardiomyopathies, which were differentiated from specific heart muscle diseases (of known cause).[6] In 1995, the next WHO classification redefined cardiomyopathies as "*diseases of myocardium associated with cardiac dysfunction*" and added two newly recognized myocardial diseases to the list[7], i.e., arrhythmogenic right ventricular cardiomyopathy (ARVC) and restrictive cardiomyopathy (RCM), both described several years later in the cat.[15-17] Cardiomyopathies were thus classified into 5 groups according to their dominant pathophysiology, i.e., dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), RCM, ARVC, and unclassified cardiomyopathies (UCM) including cases that did not fit into the 4 other phenotypes.[7] An additional group named "specific cardiomyopathies" was also recognized, including myocardial diseases associated with specific cardiac or systemic disorders (e.g., ischemic, valvular, hypertensive, inflammatory, metabolic, toxic cardiomyopathies, and myocardial disorders associated with neuromuscular or general system diseases). In 2006, an expert committee of the American Heart Association (AHA) defined cardiomyopathies as "*a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilation and are due to a variety of causes that frequently are genetic.*"[8] The AHA 2006 expert consensus panel excluded all pathological myocardial processes secondary to other cardiovascular abnormalities from this definition and proposed a new classification of cardiomyopathies with 2 major groups (primary *vs* secondary) based on predominant organ involvement: primary cardiomyopathies (genetic, non-genetic, or mixed) are those solely or predominantly confined to the myocardium, whereas secondary cardiomyopathies show myocardial involvement as part of numerous generalized systemic or multiorgan disorders.[8] In 2008, the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases proposed an updated classification of cardiomyopathies mainly based on the 5 phenotypes of the 1995 WHO classification (i.e., HCM, DCM, ARVC, RCM and UCM), and each myocardial phenotype was then subdivided into familial/genetic and non-familial/non-genetic forms.[11] However, the nosological approach to myocardial diseases still remains debated[18,19] as a given etiology may be associated with a spectrum of myocardial phenotypes, morphological and functional phenotypes can overlap and even evolve over time, while our etiological knowledge of previously named idiopathic cardiomyopathies continues to improve. To avoid confusion and be clearer for the reader, this chapter on feline myocardial diseases will refer to the following "combined" classification system better suited to practical use in feline cardiology. As proposed in the AHA 2006 classification system,[8] cardiomyopathies will refer to heart muscle disorders non-secondary to other cardiovascular disorders, and primary cardiomyopathies will be distinguished from secondary cardiomyopathies of systemic origins. Primary cardiomyopathies will be

further subdivided into the 5 1995 WHO phenotypes (Figure 253-1).[7] The primary cardiomyopathies are the most common feline heart diseases, and therefore constitute the central part of this chapter. In a study of 287 cardiac cats, HCM was the most common diagnosed heart disease (68%), whereas congenital disorders only accounted for 12% of the recruited cases.[20] Similarly, in a report focusing on HCM, RCM and secondary cardiomyopathies, HCM represented 53% of the included cases *vs* 15% and 32% for RCM and secondary cardiomyopathies, respectively.[21] In another study on primary cardiomyopathies,[22] HCM was also by far the most common disease (58%), followed by RCM (21%), DCM (10%) and UCM (10%), with no reported case of ARVC (the rarest feline primary cardiomyopathy).[1,20] In the latter report, one cat showed echocardiographic changes compatible with so-called moderator band "cardiomyopathy." Left ventricular (LV) moderator bands, also named false tendons, are cord-like structures of varying length stretching across the LV cavity, attached to the interventricular septum (IVS), LV free wall (LVFW), and/or LV papillary muscles and apex,[23-25] and composed of varying amounts of Purkinje fibers, collagenous fibers, myocardial and fibrous connective tissue, adipose tissue, and blood vessels covered with endothelium.[23-27] As in people,[23-25,28] false tendons are common incidental echocardiographic findings in cats, with no consequence on cardiac morphology and function (Figure 253-2, *A* and *B*).[29,30] However, similar to people,[23] excessive networks of LV moderator bands have been reported in the cat, with various secondary deleterious effects, such as LV myocardial dysfunction and LV remodeling, arrhythmias, congestive heart failure (CHF), and arterial thromboembolism (ATE), potentially leading to death even in kittens (Figure 253-2, *C* and *D* and Videos 253-1 and 253-2).[1,26,27] Because LV moderator bands are of congenital origin, the term "moderator band cardiomyopathy" is commonly used to define this diseased state and does not fit into the AHA definition of cardiomyopathies.[8] Nevertheless, the prevalence of false tendons in the LV outflow tract (LVOT) is higher in cats with obstructive HCM (OHCM, also called hypertrophic obstructive cardiomyopathy or HOCM), as compared to healthy cats and cats with non-obstructive HCM, which suggests a possible role of false tendons in the pathogenesis of dynamic LVOT obstruction (LVOTO, Figure 253-2, *E*).[29]

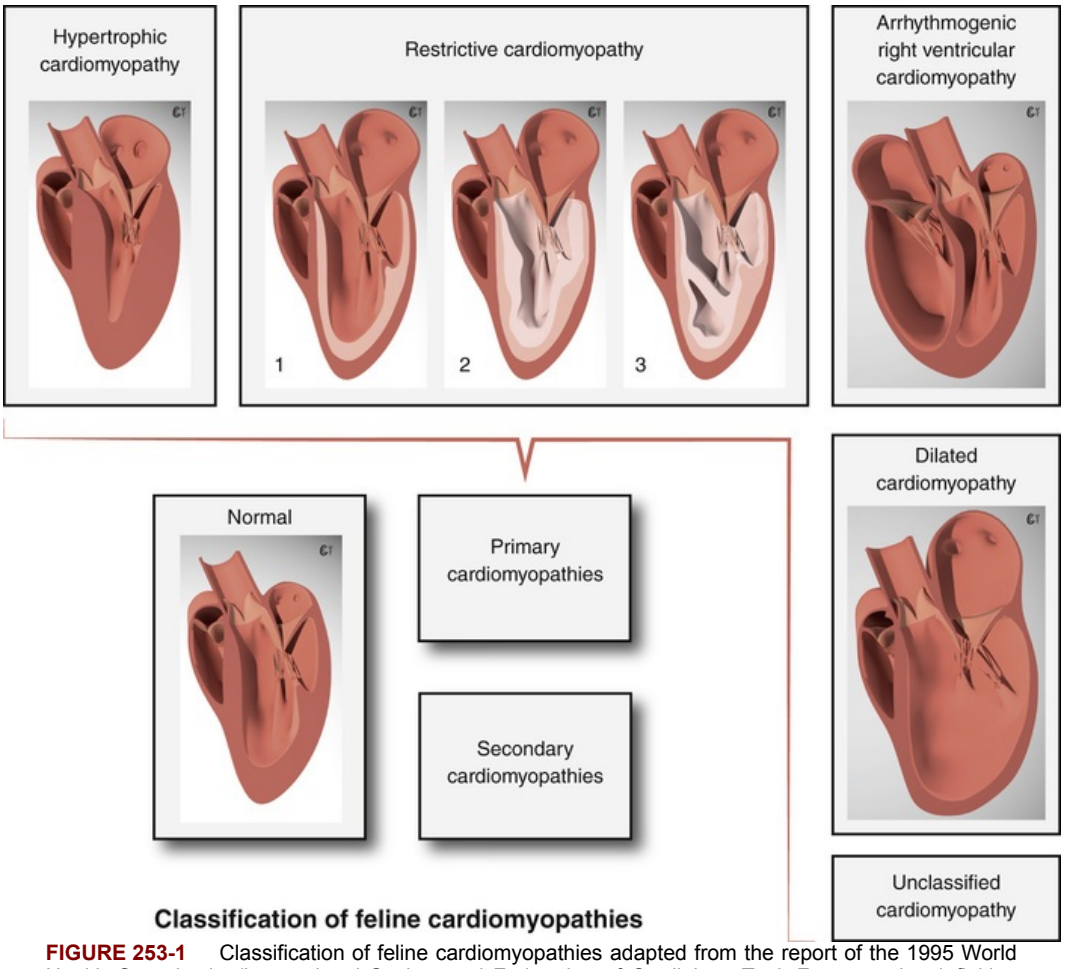


FIGURE 253-1 Classification of feline cardiomyopathies adapted from the report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies.[7] Primary cardiomyopathies encompass hypertrophic cardiomyopathy, restrictive cardiomyopathy (RCM), dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and unclassified cardiomyopathy (which includes cases that do not fit into any other group). Hypertrophic cardiomyopathy consists of left (or left and right) ventricular hypertrophy. Restrictive cardiomyopathy is characterized by restrictive filling and reduced diastolic volume of either ventricle (mainly left ventricle) or both, with normal or near-normal systolic function and wall thicknesses. Two basic RCM forms have been identified in the cat[16], i.e., myocardial RCM (the most common, n°1) and endomyocardial RCM (also known as endomyocardial fibrosis) with either a diffuse endomyocardial scar reducing the left ventricular cavity (n°2) or exuberant bridging scar connecting the interventricular septum and the left ventricular free wall (n°3). Dilated cardiomyopathy is characterized by dilation and impaired contraction of the left ventricle or both ventricles. Lastly, arrhythmogenic right ventricular cardiomyopathy consists of progressive fibrofatty replacement of the right ventricular myocardium, global right enlargement (and also potential left ventricular involvement). (Illustrations: execution and conception by Dr. Charlotte Taton and Prof. Valérie Chetboul.)

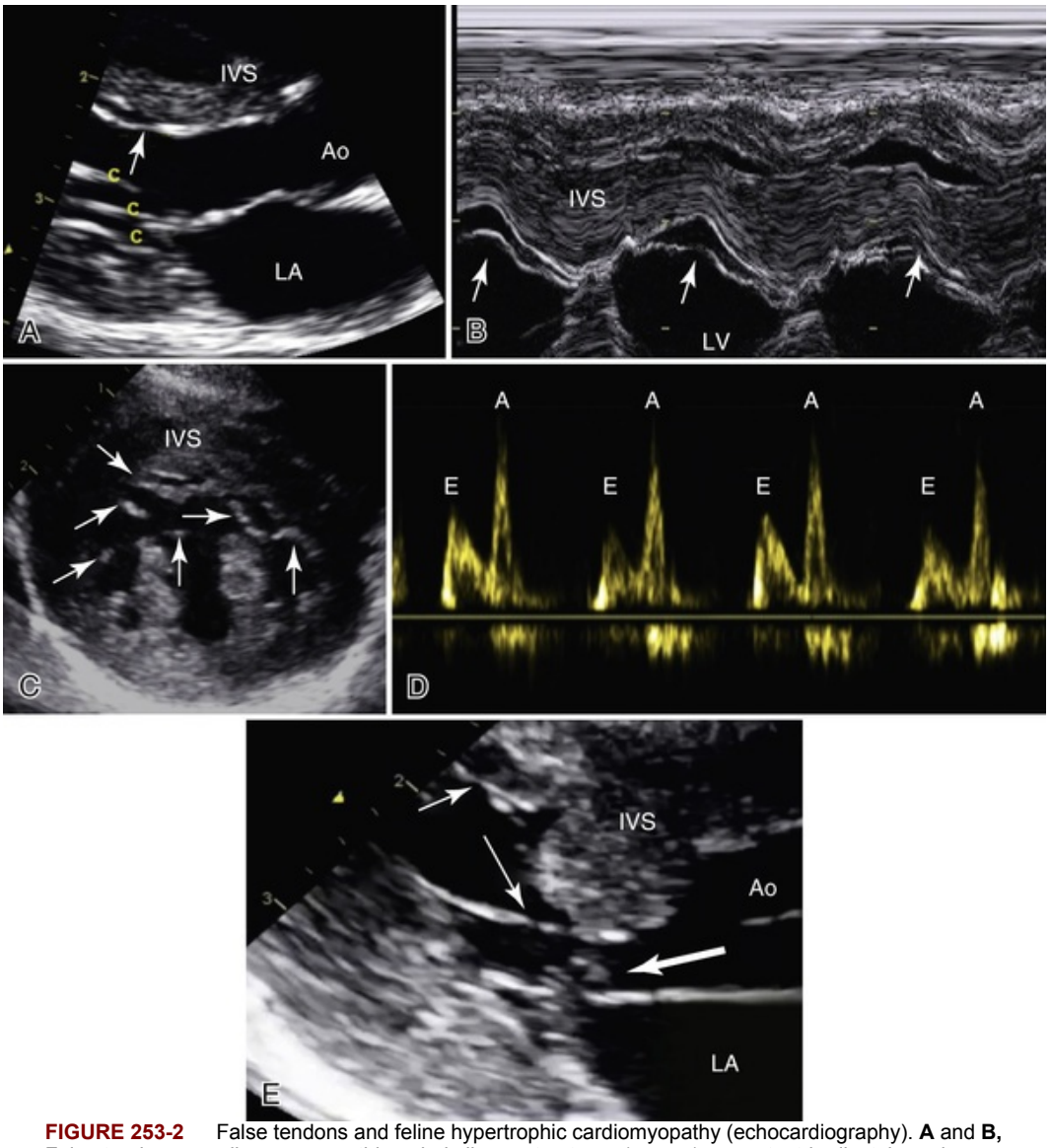


FIGURE 253-2 False tendons and feline hypertrophic cardiomyopathy (echocardiography). **A** and **B,** False tendons usually appear as thin echoic linear structures (arrows), more taut in diastole and more lax in systole, here incidentally found along the interventricular septum (IVS) in a healthy cat on the two-dimensional echocardiogram (right parasternal 5-chamber view, **A**) and on the M-mode echocardiogram **(B).** *Ao,* Aorta; *C,* chordae tendineae; *LA,* left atrium; *LV,* left ventricle. **C** and **D,** Transventricular short-axis view showing excessive network of false tendons (arrows) in an 8-month Bengal cat **(C),** resulting in diastolic alteration as confirmed by pulsed-wave Doppler assessment of mitral inflow velocity **(D).** An impaired relaxation pattern characterized by an early (E) to late filling wave (A) ratio <1 (E : A = 0.66) associated with a prolonged (>100 ms) E deceleration time (132 ms) is observed.[66] **E,** Right parasternal 5-chamber view obtained at end-systole from a cat with severe obstructive hypertrophic cardiomyopathy. The IVS bulges into the left ventricular outflow tract. Note the presence of false tendons (thin arrows) including one attached to the subaortic IVS as well as the systolic anterior motion of the mitral valve (large arrow), both contributing to worsen obstruction of the left ventricular outflow tract.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is phenotypically characterized by increased cardiac mass due to a hypertrophied non-dilated LV in the absence of an obvious cause of LV hypertrophy (LVH), such as pressure overload (e.g., systemic arterial hypertension) or hormonal stimulation (e.g., hyperthyroidism).[1,31]

Left Ventricular Hypertrophic Patterns, Gross Pathology and Histopathology

As in people, feline HCM is characterized by marked phenotypic variability, including mild to severe, diffuse or segmental, concentric LVH (Figures 253-3 and 253-4).[31-34] In most cats with HCM (up to two thirds), LVH is diffuse, involving portions or all of both the IVS and the LVFW, with hypertrophy of the LV papillary muscles and a consequently reduced LV cavity (see Video 253-3).[31,34] Diffuse LVH can be symmetric or asymmetric with predominant thickening of the IVS or LVFW. In about one third of cases, LVH is confined to only one segment, i.e., usually the basal IVS and less commonly the apex.[31,34] In some cases, the thickened basal IVS protrudes into the LVOT, resulting in mild to severe LVOTO, thus defining OHCM forms (see Videos 253-4, 253-5, and 253-6). Marked combined LVH and hypertrophy of the papillary muscles can result in systolic mid-ventricular cavity obstruction, associated with the presence of endocardial contact plaques.[2,35] Although rare, myocardial infarction of the LVFW may also occur (see Video 253-12).[31] Such varied geometric patterns are also revealed by two-dimensional (2D) and M-mode echocardiography (see ch. 104), with breed variations.[36,37] In one study, Persians and Chartreux showed significantly more OHCM (44%) than other cats (18%), whereas almost half of Maine Coons had diffuse symmetric LVH (see Figure 253-4).[37]

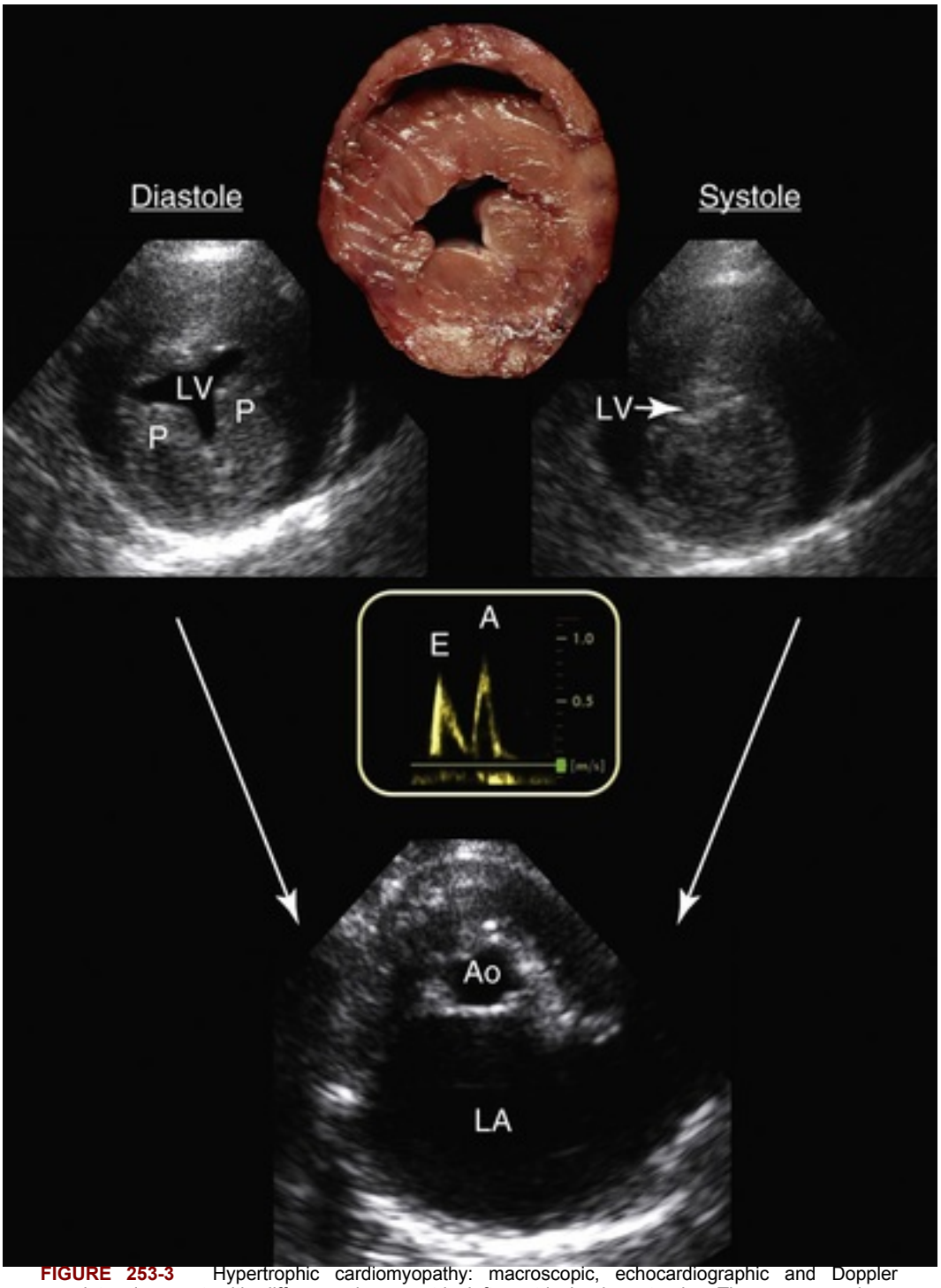


FIGURE 253-3 Hypertrophic cardiomyopathy: macroscopic, echocardiographic and Doppler correlates in a cat with diffuse and symmetric left ventricular hypertrophy. The gross specimen sectioned transversely and the right parasternal short-axis views (top figures) both show severe left ventricular hypertrophy, resulting in a reduced lumen of the left ventricle (LV), with a secondary markedly enlarged left atrium (LA), as observed on the right parasternal transaortic view (bottom figure; end-diastolic LA : Ao ratio of 3.7; values obtained from a population of 100 healthy cats: 0.5 to 1.2).[78] Note the disappearance of the LV cavity at end-systole. Transmitral pulsed-wave Doppler examination obtained from the left apical 4-chamber view (central figure) reveals an impaired LV relaxation pattern characterized by a reversed (<1) E : A ratio (E and A, peak velocities of early and late diastolic transmitral flow, respectively), confirming both decreased early LV filling due to impaired relaxation and a greater LA contribution to LV filling (with LA contraction).[66] *Ao,* Aorta; *P,* LV papillary muscles. (Pathology: courtesy Prof. Jean-Jacques Fontaine, Pathology Department, National Veterinary School of Alfort, France.)

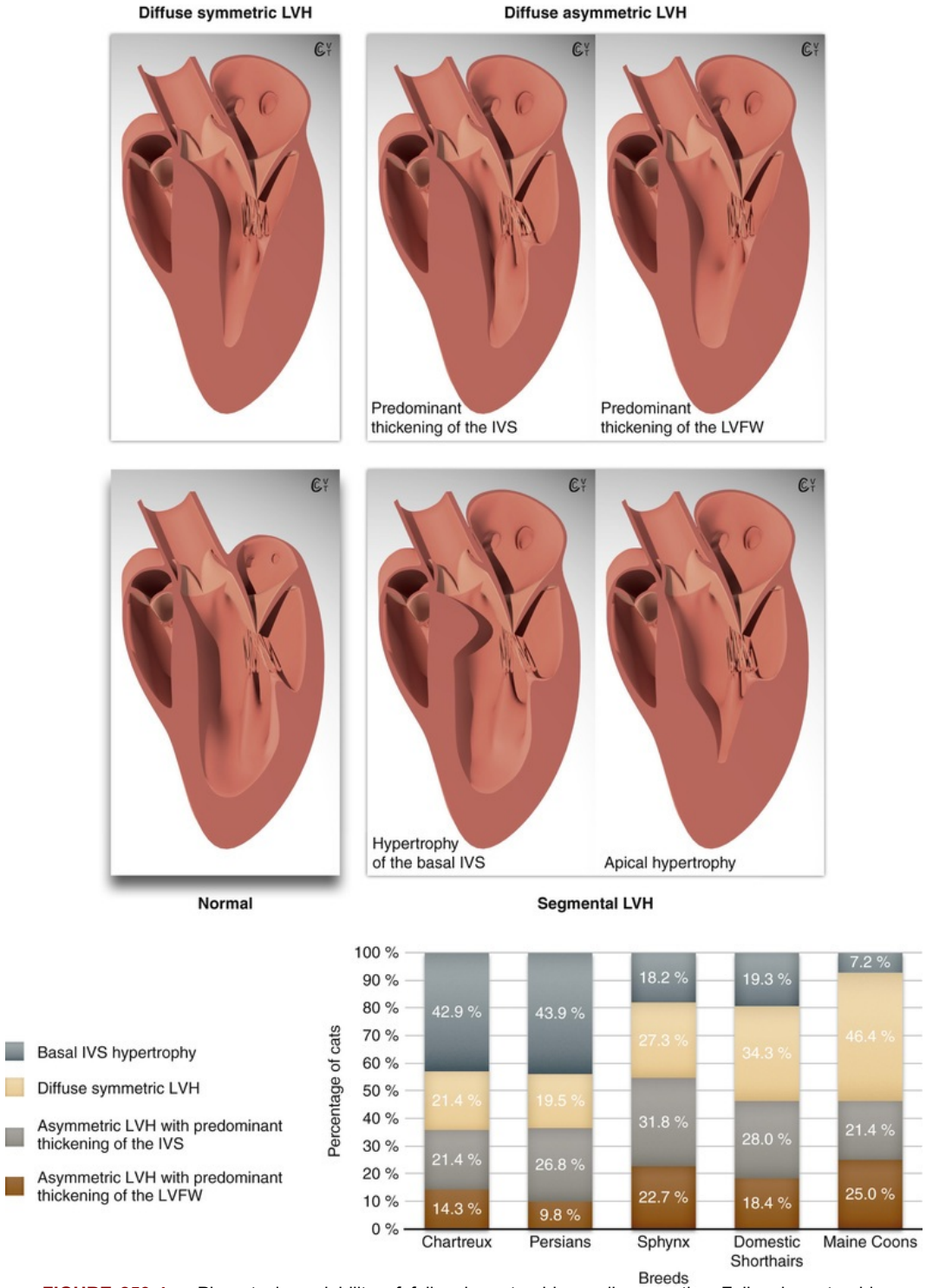


FIGURE 253-4 Phenotypic variability of feline hypertrophic cardiomyopathy. Feline hypertrophic cardiomyopathy is characterized by various left ventricular (LV) geometric patterns, including diffuse symmetric and asymmetric LV hypertrophy (LVH) with predominant thickening of the interventricular septum (IVS) or the LV free wall (LVFW), and segmental LVH (e.g., apical or subaortic IVS hypertrophy). Subaortic IVS hypertrophy can be either isolated or associated with LV diffuse geometric patterns. Hypertrophy of the LV papillary muscles is often present. All these forms can lead to left atrial enlargement and congestion of the pulmonary veins as shown here. Below: histograms representing distribution of the LV geometric patterns by breed assessed by echocardiography in a population of 344 cats with hypertrophic cardiomyopathy, including 239 Domestic Shorthairs, 41 Persians, 22 Sphynx, 28 Maine Coons, and 14 Chartreux (values on the bars represent the percentage of cats).[37] (Illustrations: execution and conception by Dr. Charlotte Taton and Prof. Valérie Chetboul.)

In cases of mild to moderate LVH, the left atrium (LA) is usually normal.[2] Severe LVH is often associated

with mild to severe LA enlargement (LAE; see Figure 253-3 and Videos 253-7 and 256-2).[31] Right ventricular (RV) hypertrophy may also be present, associated or not with right atrial (RA) enlargement.

Histopathology

As in people,[33] histological features of feline HCM include various degrees of myocardial fiber disarray within the LV myocardium (less commonly the RV myocardium), associated with mild to severe arteriosclerosis of intramural coronary arteries, interstitial myocardial fibrosis and replacement fibrosis (Figure 253-5).[2,31,32,34] In one report, disorganized cardiac muscle cells were identified in the IVS of 30% of HCM cats. Disorganized architecture of the LVFW was less common (14%) and systematically associated with IVS disorganization.[32] Such histological differences impact regional diastolic myocardial function, as observed using tissue Doppler imaging (TDI).[38,39] In both people and cats, myocardial fiber disorganization can also be observed in non-severely thickened, even in non-hypertrophied, LV myocardial segments,[2] which from a practical point of view, explains why TDI can detect regional myocardial dysfunction in apparently normal myocardial segments of HCM cats (Figure 253-6).[38] In OHCM forms, a LVOT fibrous contact plaque can be observed on the IVS surface due to systolic apposition of the mitral valve leaflets to the IVS. Increased myocardial collagen deposition, associated with neutrophilic and lymphocytic infiltrates, has also been found in the myocardium of cats with pre-clinical HCM, suggesting the possible contribution of an early inflammatory process to myocardial fibrosis (e.g., [involving] inflammatory cytokines), which will require further investigation.[40]

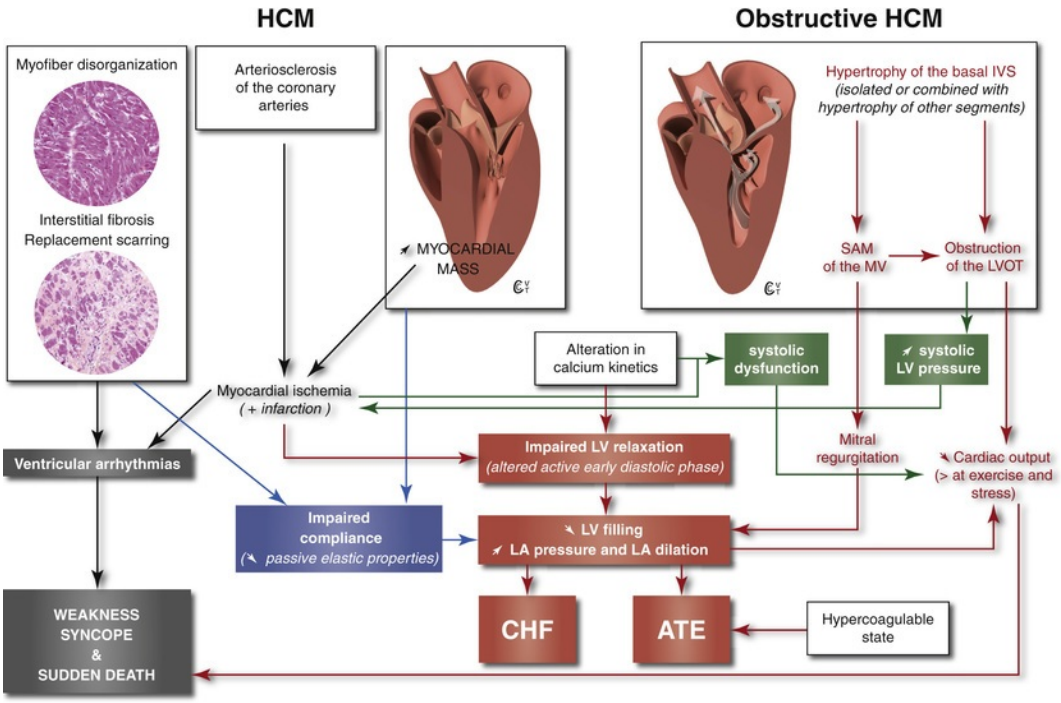


FIGURE 253-5 Main pathophysiological consequences of feline hypertrophic cardiomyopathy (HCM): myocardial dysfunction, arrhythmias and left ventricular outflow tract obstruction. (1) Diastolic dysfunction typically refers to abnormalities of active myocardial relaxation and passive compliance, leading to abnormal left ventricular (LV) filling with decreased end-diastolic volume or adequate end-diastolic volume only at the expense of increased filling pressures.[66] In the case of HCM, relaxation and compliance are both altered, but relaxation abnormalities dominate and occur early, thus affecting the early rapid LV filling phase. The rate and volume of early LV filling are decreased, resulting in a compensatory increase in the contribution of left atrial (LA) contraction to LV filling, associated first with an elevation of LA pressure at end-diastole.[66] Reduced LV compliance, resulting from several factors (LV hypertrophy *per se,* interstitial fibrosis, replacement scarring, and disorganized myocardial cells), also contributes to increased LV diastolic pressure and subsequent increase in LA pressure. The latter worsens with disease progression, which in turn leads to LA dilation, and is finally transmitted back into the pulmonary vascular system leading to venous congestion and congestive heart failure (CHF). Left atrial dilation also predisposes to blood stasis and arterial thromboembolism (ATE), especially as a systemic hypercoagulable state has been evidenced in cats with HCM, even without concurrent CHF and ATE.[70,71] (2) Although not predominant, systolic dysfunction resulting from myocardial ischemia,

alteration in calcium kinetics, increased matrix connective tissue and regional myocardial asynchrony, can contribute to the decrease in cardiac output, particularly at end-stages of the disease and/or in the case of obstructive HCM.[38,39,72] (3) Histopathological lesions associated with HCM also represent an electrically unstable substrate for reentrant ventricular tachyarrhythmias, responsible for weakness, syncope, and sudden death. (4) In obstructive forms of HCM, dynamic left ventricular outflow tract (LVOT) obstruction may produce high systolic intraventricular pressure gradients (even >100 mm Hg) with several deleterious consequences, including decreased cardiac output and worsening of both myocardial hypertrophy and ischemia (by increasing myocardial wall stress and oxygen demand). In these particular HCM forms, the subaortic obstruction results from both protrusion of the thickened basal interventricular septum (IVS) into the LVOT and systolic anterior motion of the mitral valve (SAM), characterized by abnormal mid- to late systolic IVS contact (see also Figure 253-8). In human patients with obstructive hypertrophic cardiomyopathy, the longer the mitral-IVS contact duration, the greater the severity of LVOT obstruction.[33,73] The presence of SAM may also result in loss of coaptation of the mitral leaflets, leading to a postero-laterally directed mitral valve regurgitation, that potentially contributes to increased LA pressure.[33,73] *MV,* Mitral valve. (Illustrations: execution and conception by Dr. Charlotte Taton and Prof. Valérie Chetboul. Histopathology: courtesy Prof. Jean-Jacques Fontaine, Pathology Department, National Veterinary School of Alfort, France.)

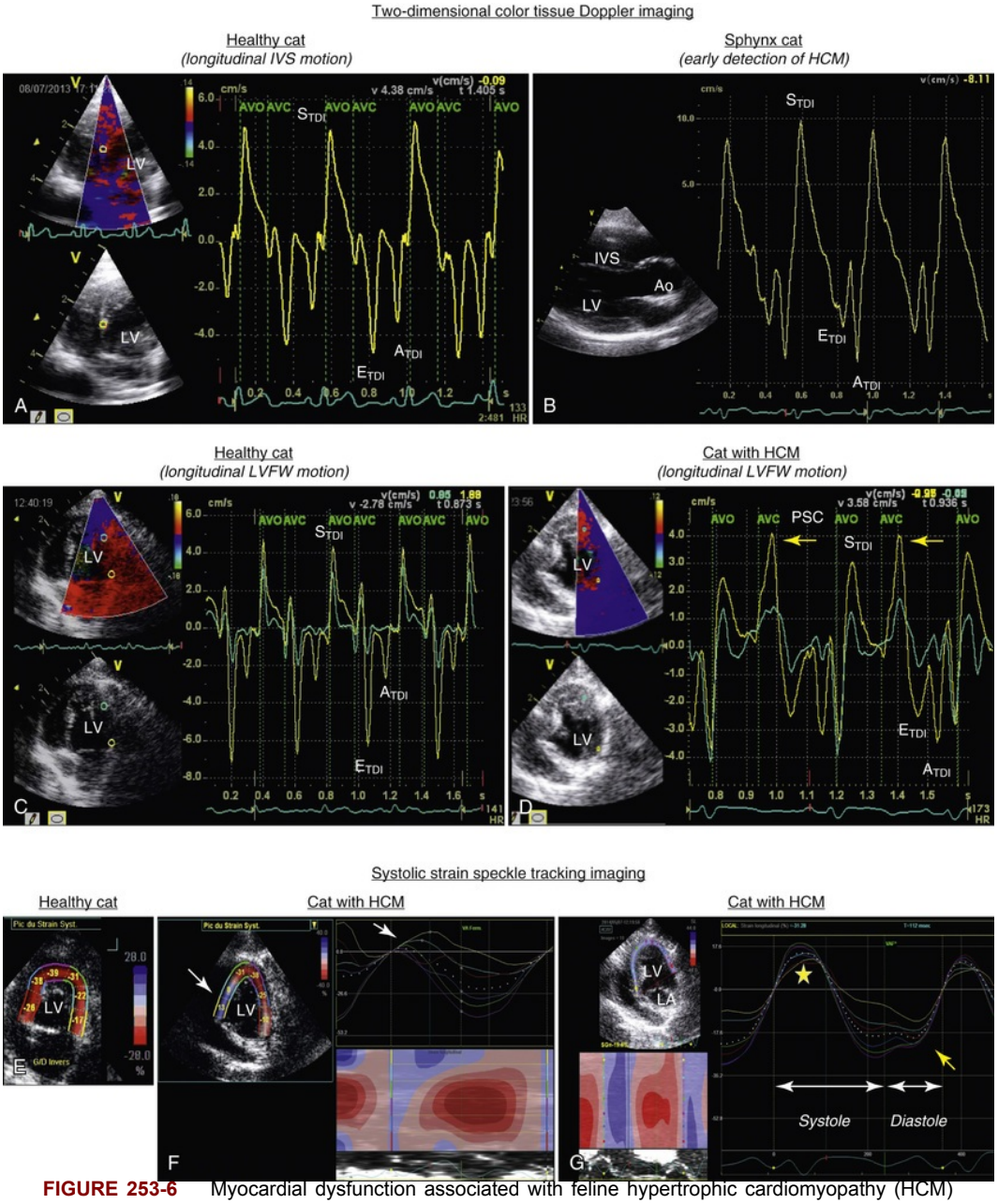


FIGURE 253-6 Myocardial dysfunction associated with feline hypertrophic cardiomyopathy (HCM)

using two-dimensional color tissue Doppler imaging (TDI, **A-D**) and speckle tracking imaging **(E-G). A-D** show longitudinal myocardial velocity profiles of the interventricular septum (IVS, **A** and **B**) and the left ventricular free wall (LVFW, **C** and **D**), obtained from left parasternal long-axis views. S_{TDI}, E_{TDI}, and A_{TDI} are peak myocardial velocities recorded during systole, early diastole, and late diastole, respectively. **A** and **B,** As compared with the healthy cat **(A),** the velocity profile recorded at the IVS base in the Sphynx cat **(B)** shows a typical diastolic alteration; i.e., an inverted $E_{TDI} : A_{TDI}$ ratio ($E_{TDI} : A_{TDI}$ <1), despite the absence of myocardial hypertrophy on two-dimensional and M-mode echocardiography (as shown here by the right-parasternal 5-chamber view). Six months later, this cat developed moderate subaortic IVS hypertrophy followed by diffuse asymmetric obstructive HCM. *Ao,* Aorta; *AVO* and *AVC,* aortic valve opening and closure, respectively; *IVS,* interventricular septum; *LV,* left ventricle. **C** and **D,** As compared with the healthy cat **(C),** longitudinal velocity profiles recorded simultaneously at the base and apex of the LVFW (yellow and green curves, respectively) in the cat with HCM **(D)** show several signs of regional diastolic dysfunction: (1) an inverted $E_{TDI} : A_{TDI}$ ratio at the base and (2) the presence of post-systolic contraction waves (PSC, yellow arrows), occurring after S_{TDI} waves (and after AVC) and greater than the latter, particularly at the base. This marked PSC motion, which was confirmed by using strain imaging (data not shown), delays the two subsequent diastolic events (E_{TDI} and A_{TDI} waves). **E-G** show several longitudinal systolic strain recordings using speckle tracking echocardiography from the left parasternal 4-chamber view. Strain represents the deformation of a myocardial segment over time and is expressed as the percentage of change from its original dimension. In these 3 examples, longitudinal systolic strain was recorded in 6 myocardial segments of the left ventricle (LV), 3 within the IVS and 3 within the LVFW. **E,** In this healthy cat, all segments undergo a systolic regional shortening. The systolic strain is therefore negative and homogeneously encoded in red (peak values are superimposed on the two-dimensional color-coded view). **F,** In this cat with segmental hypertrophy of the IVS, the affected septal segments undergo an abnormal lengthening at early systole (arrow) and are therefore encoded in blue (left panel). The right panel shows the six corresponding LV longitudinal strain *vs* time curves, confirming an abnormal positive strain for these two abnormal IVS segments (arrow). **G,** In this cat with diffuse HCM, note the presence of PSC (yellow arrow), occurring during the diastolic phase. Note also that all myocardial segments undergo an abnormal lengthening at early systole (yellow star).

Epidemiology

In large HCM populations, males are overrepresented (70% to 79%), with a predominance of Domestic Shorthairs (65% to 70%), followed by Domestic Longhairs (9% to 22%) and Persians (3% to 12%).[37,41,42] Other commonly reported breeds vary according to studies (British Shorthair, Chartreux, Himalayan, Maine Coon, Sphynx, Ragdoll).[37,41-43] Burmese, Siamese, Oriental Shorthairs and Abyssinians are less commonly affected.[1,37,41,42] Most HCM cats are middle-aged at diagnosis (median age: 5 to 7 years), but with wide age ranges ([0.5-19], [0.2-18.3], and [0.2-16.7] years in 3 reports involving 127 to 344 HCM cats)[37,41,42] and breed variations: In one report, Maine Coon and Sphynx cats were younger at diagnosis than other cats (Figure 253-7, *A*).[37] In another, Ragdoll cats were younger (2.5 [0.5-4.5] years) than others (5.0 [0.2-16.7] years).[42]

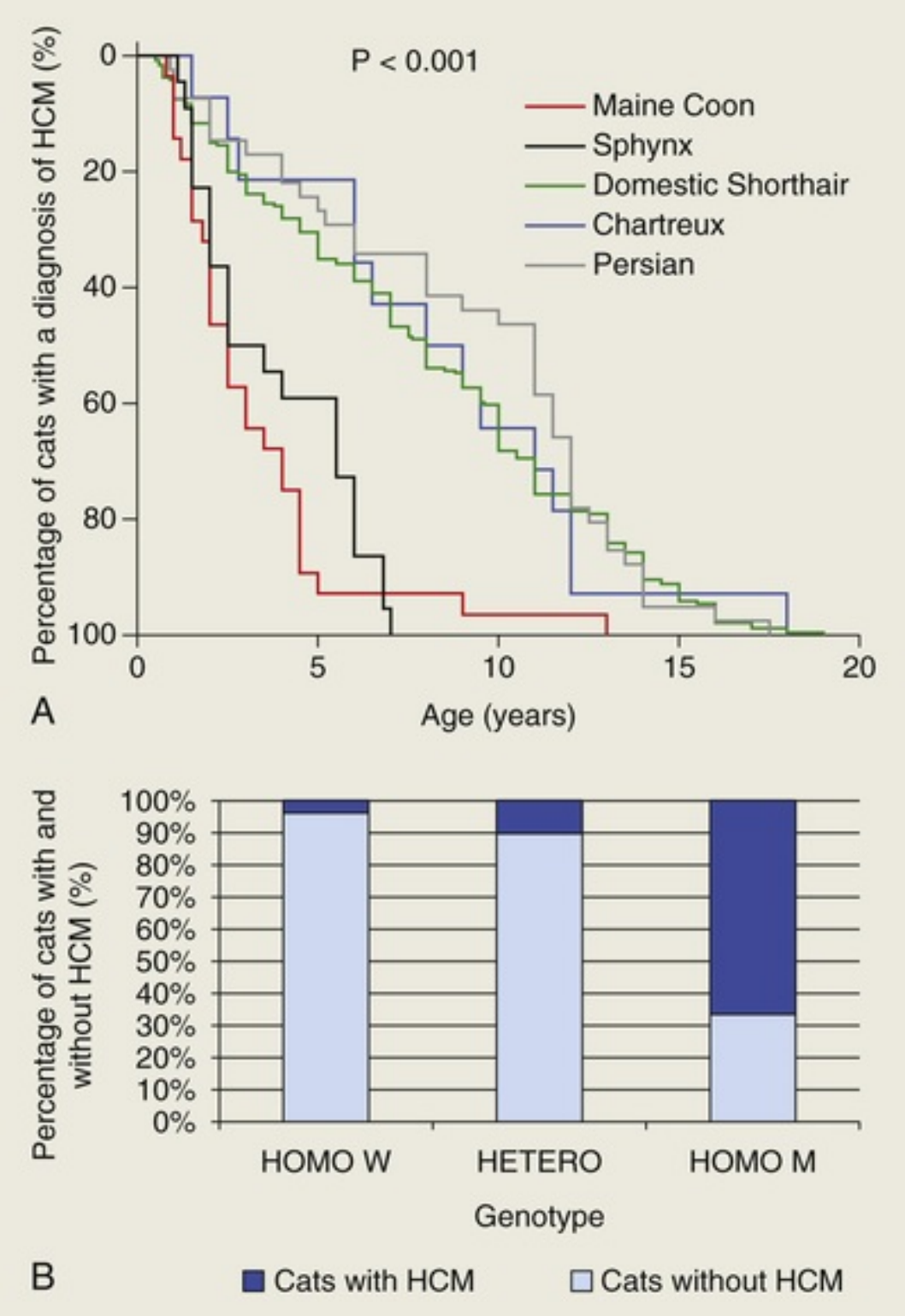


FIGURE 253-7 Feline hypertrophic cardiomyopathy (HCM) and breed specificities. **A,** Age at the time of HCM diagnosis in a population of 344 cats affected by HCM, including 239 Domestic Shorthairs, 41 Persians, 22 Sphynx, 28 Maine Coons, and 14 Chartreux. Kaplan-Meier curves show the percentages of cats with a diagnosis of HCM, according to age.[37] **B,** Distribution of a Maine Coon cat population (n = 96) according to the genotype (Homo WT, Hetero, Homo M) and phenotype (presence or absence of HCM).[39] HOMO W group: homozygous wild-type cats (i.e., without the *MyBPC3*-A31P mutation). HETERO and HOMO M groups, respectively, heterozygous and homozygous mutated cats.

Genetic Basis: Relationship Between Genotype and Phenotype

Human HCM

Human HCM is a familial disease in at least 50% to 60% of cases, with autosomal dominant inheritance most commonly identified.[44,45] Hypertrophic cardiomyopathy was the first human heart disease for which a molecular genetic cause was demonstrated, and the gene responsible (*MYH7*, coding for the beta-myosin heavy chain protein) identified in 1990.[46] At the time of writing, more than 1400 mutations associated with HCM have been identified, with most implicated genes encoding for proteins of the myofilaments or Z-discs of the sarcomeres.[44,45]

Maine Coon Breed

A causative mutation in the cardiac Myosin Binding Protein C sarcomeric gene *(MyBPC3)* for inherited HCM, with autosomal dominant inheritance, was similarly identified in the Maine Coon breed in 2005.[47] This report was the first to demonstrate a spontaneous mutation causing HCM in a non-human species.[47] The *MyBPC3* gene was shown to be mutated in exon 3, with a single base pair change (guanine to cytosine) causing an alteration of the protein structure owing to the replacement of one conservative amino acid (i.e., alanine (A) in the 31st codon) by proline (P).[47] In one study (n = 3310 cats of 17 different breeds from Asia, Europe, Australia, and North America with 3238 Maine Coon cats), the latter accounted for 100% of all cats positive for the *MyBPC3*-A31P mutation.[48] In one European report (n = 3757 cats of 17 different breeds including 2744 Maine Coons), the mutation was only found in Maine Coon cats and one British Longhair.[49] Thus the *MyBPC3*-A31P substitution mutation appears to be specific to the Maine Coon breed, although potential marginal events may occur.[48,49] The prevalence of the mutation in this breed is high, ranging from 31% (Asia, North America) to 42% (Europe) and 46% (Australia), with a marked predominance (up to 92%) of the heterozygous status.[48-50] The prevalence of the HCM phenotype varies from 7 to 10%, increases with age and is strongly dependent on the genetic status (Figure 253-7, *B*).[49,50] The *MyBPC3*-A31P mutation is associated with an increased risk of HCM and the risk is much higher for homozygous cats (relative risk = 9.9 and 35.5, respectively), with incomplete penetrance for heterozygous cats at least at middle age.[49,50] In one study, more than 80% of the heterozygous cats remained healthy at least until 4 years of age.[50] Inversely, some homozygous wild-type Maine Coon cats may develop HCM, suggesting involvement of other causes or mutations.[39,50,51]

Other Feline Breeds

A second substitution mutation in *MyBPC3* associated with HCM has been identified in the Ragdoll breed.[52] This *MyBPC3* R820W mutation is also characterized by a single base pair change (cytosine to thymine in codon 820), with secondary change of one amino acid (arginine to tryptophan).[52] In a survey of 236 Ragdoll cats, the prevalence of the mutation was 34%, with marked predominance of the heterozygous status (85%).[53] Familial forms of HCM have also been reported or suggested in several other breeds, including British Shorthairs,[42] Sphynx,[54,55] Norwegian Forest cats,[56] and non-pedigree cats.[57,58] An autosomal dominant inheritance pattern with incomplete penetrance was shown in the Sphynx breed.[55]

Pathophysiological Consequences (See Detailed Explanations in Figure 253-5)

Ventricular arrhythmias, myocardial dysfunction and dynamic LVOTO are the main pathophysiological consequences of HCM. Diastolic dysfunction, which is considered the major mechanism explaining the development of CHF,[33,34,59-62] occurs early in the course of HCM, even before detectable chamber remodeling as confirmed by TDI studies (see Figure 253-6).[33,38,39,61-66] It results in progressively increased LA pressure with secondary LAE, and CHF (pulmonary edema). Because visceral pleural veins drain into the LA in cats, increases in LA pressure can also lead to pleural effusion due to a decrease in visceral pleural venous drainage.[67] As confirmed by decreased blood velocities in the LA appendage,[68] blood stasis is another common complication of LAE, predisposing to thrombus formation and ATE (see ch. 256 and Videos 253-10 and 253-11).[69-71] Regional and, more rarely, global systolic dysfunction of various causes may also be

present (see Figure 253-6).[38,39,72] Lastly, an abnormal motion of the mitral valve (systolic anterior motion, SAM; see Figures 253-5 and 253-8) contributing to both LVOTO with decreased cardiac output and mitral valve regurgitation, is frequently reported in cats with HCM (29% to 67%).[29,34,41,42,60,62,73] The length of the anterior mitral valve leaflet and prevalence of false tendons in the LVOT are higher in cats with OHCM than in cats with non-obstructive HCM forms (41% *vs* 22%), suggesting a possible role of these abnormalities in LVOTO (see Figure 253-2).[29]

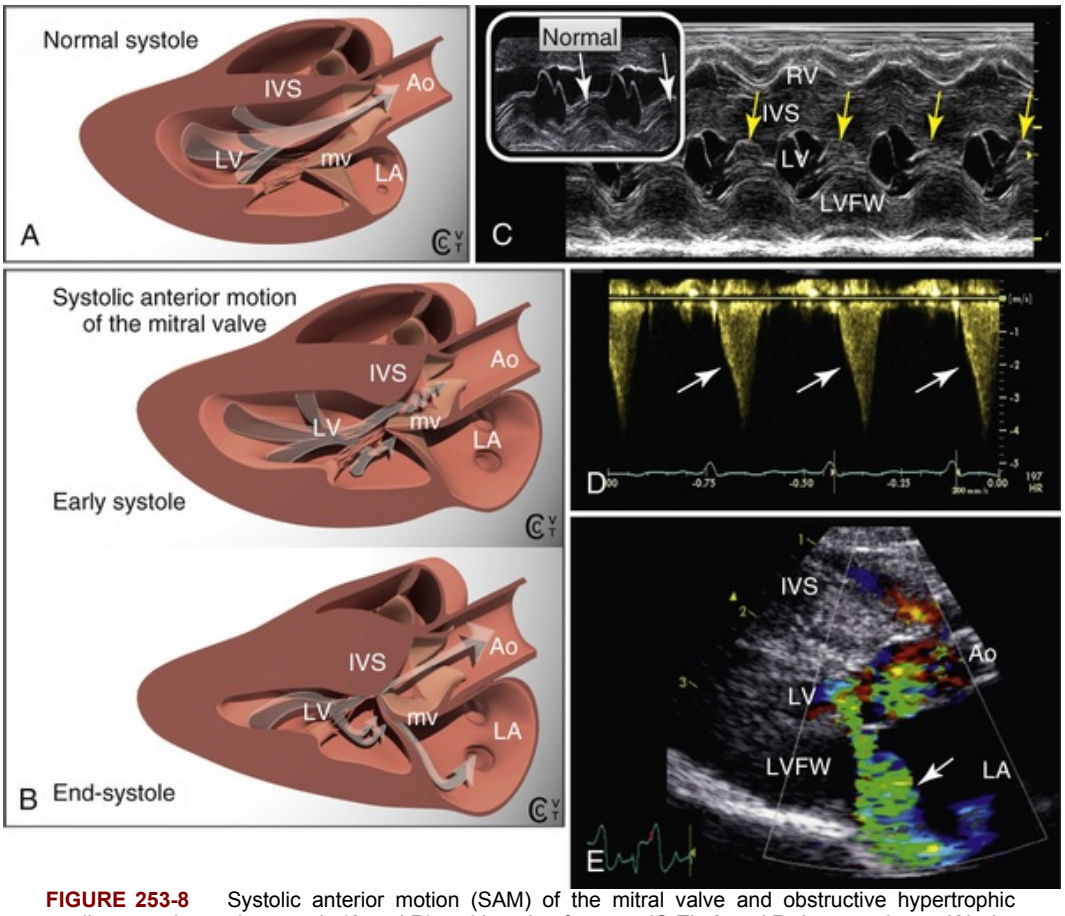


FIGURE 253-8 Systolic anterior motion (SAM) of the mitral valve and obstructive hypertrophic cardiomyopathy: pathogenesis (**A** and **B**) and imaging features **(C-E). A** and **B,** In normal cats **(A),** the mitral valve does not protrude into the left ventricular outflow tract (LVOT) during systole. Obstructive hypertrophic cardiomyopathy (OHCM) is characterized by a dynamic LVOT obstruction, resulting from hypertrophy of the basal interventricular septum (IVS) and/or SAM of the mitral valve, which is an abnormal motion of the mitral valve towards the LVOT during systole **(B),** with a mid- to late systolic contact between the mitral valve and the IVS. The nature of the hydrodynamic systolic forces responsible for SAM of the mitral valve has been debated.[29,33,73] A Venturi mechanism, whereby high velocity flow in the left ventricular outflow tract lifts the mitral valve toward the IVS, was first proposed, but more recent echocardiographic and Doppler studies in humans with OHCM support the hypothesis that drag, the pushing force of flow, is the dominant hydrodynamic force that initiates SAM of the mitral valve, as shown here.[73] In the case of OHCM the systolic LV flow is able to push the underside of both mitral valve leaflets towards the IVS, owing to the abnormally increased "angle of attack" between the flow direction and mitral valve leaflets at early systole. This increase in the angle of attack results from 2 combined mechanisms: (1) local changes in intra-LV flow direction (coming closer to the mitral valve) owing to the IVS bulge; (2) protruding mitral valve leaflets (with the mitral leaflet coaptation point closer to the IVS than normal) owing to hypertrophy of the papillary muscles, also contributing to increased chordal mobility.[73] As shown here, systolic protrusion of the chordae tendineae in the LVOT, either isolated (14%) or combined with SAM of the mitral valve (45%), is reported in 59% of OHCM cases (*vs* 16% and 56% in healthy cats and cats with non-obstructive HCM, respectively).[29] *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *LVFW,* left ventricular free wall; *mv,* mitral valve; *RV,* right ventricle. **C,** M-mode tracing obtained from a cat with OHCM showing marked SAM of the mitral valve, characterized by a prolonged systolic contact (yellow arrows) between the anterior mitral valve leaflet and the thickened IVS, which is not the case for the healthy cat (left upper panel, white arrows). **D,** Continuous-wave Doppler recording in a cat with OHCM and SAM of the mitral valve, showing an increased peak systolic aortic velocity (4 m/s; normal maximal value of 1.9 m/s)[78] and a

late peaking flow profile, characterized by a typical concave asymmetrically-shaped waveform, owing to a sudden flow acceleration at mid-systole (arrows). This confirms dynamic LVOT obstruction. Using the modified Bernoulli equation, the corresponding pressure gradient is 64 mm Hg, indicating a moderate LVOT obstruction. **E,** (Same cat as in Figure C.) The color-flow Doppler mode applied to the right parasternal 5-chamber view confirms a double systolic turbulent jet, including an aliased ejection flow within the abnormally narrowed LVOT and a typical aliased mitral regurgitation jet within the enlarged LA. As commonly observed in the case of SAM of the mitral valve and also illustrated in Figure **B** (bottom figure), the mitral regurgitation jet originates from the mitral valve–IVS contact point, follows the posterior mitral valve leaflet direction (arrow), and then reaches the posterior part of the LA wall. (Illustrations: execution and conception by Dr. Charlotte Taton and Prof. Valérie Chetboul.)

Clinical Presentation at Diagnosis

Clinical Signs

Many cats with HCM show no clinical signs at the time of diagnosis (33% to 77%).[37,41,42,60,74] These cats are usually referred because of an abnormal cardiac auscultation detected on routine examination, for screening purposes before mating, or for cardiovascular evaluation before anesthesia. Most symptomatic cats (70% to 80%) with HCM show clinical signs of CHF (i.e., mainly tachypnea and dyspnea related to pulmonary edema and/or pleural effusion, reported in 18% to 46% of HCM cats at presentation; see Videos 253-8 and 253-9).[37,41,42,74] Coughing is more rarely reported than in dogs.[1] Ascites related to right-sided CHF is also rare.[37] Anorexia and lethargy are common in cats with CHF and can even precede the onset of CHF by 24-72 hours. An antecedent event that may have precipitated decompensation is reported in 14% to 50% of cases, 7 to 15 days prior to CHF onset (e.g., intravenous [IV] fluid therapy, recent anesthesia, surgery or corticosteroid administration, and trauma).[37,41] The second most common clinical signs are related to ATE, detected in 4 to 17% of HCM cats at diagnosis with or without concomitant CHF, and mainly characterized by acute bilateral and painful hindlimb paresis, and less commonly, forelimb paresis (see ch. 256).[37,41,42,60] Other clinical signs include syncope and weakness observed in 1 to 6% of HCM cats at diagnosis.[37,41,60] Lastly, open-mouth breathing and dyspnea despite the absence of radiographic and echocardiographic signs of CHF are reported in HCM cats.[42] One possible explanation is that these cats are suffering from angina-like chest pains, similar to those reported in human patients with HCM.[42]

Cardiac Auscultation

Cardiac auscultation is abnormal in most HCM cats (78% to 92%).[37,41,42] The commonest abnormalities are systolic heart murmurs (64% to 89% of HCM cats) heard best over the left apex or the cranial sternum, and respectively resulting from mitral regurgitation and LVOTO (see ch. 55).[37,41] These murmurs are often dynamic (i.e., of variable grade, increasing with heart rate) and more commonly found in asymptomatic (89% to 92%) than in symptomatic cats (77%).[37,42] This may be explained by the fact that heart murmurs are one of the main reasons why practitioners refer asymptomatic animals for echocardiography. A gallop rhythm and arrhythmias are detected in up to 33% and 6 to 10% of HCM cats, respectively.[37,41,42] Unlike heart murmurs, both are uncommon in cats with subclinical HCM (<10% and ≤5%, respectively), probably because they reflect severe myocardial lesions.[37,42]

Electrocardiographic Findings

Various nonspecific morphological electrocardiographic (ECG; see ch. 103) alterations are associated with feline HCM, resulting from LVH (QRS amplitude >0.9 mV) and LAE (P wave duration >0.04 seconds, PR interval >0.09 seconds).[1,75] The latter P wave-related ECG indices have low sensitivity (12% to 60%) but high specificity (81% to 100%) for predicting LAE in cats with cardiomyopathy.[75] A left axis deviation suggestive of left anterior fascicular block is reported in 11% to 33% of HCM cats, more commonly than in those suffering from other cardiomyopathies.[1] Arrhythmias are also frequently diagnosed (in about one third of HCM cats in one report, with a predominant proportion of ventricular premature complexes: 65%; see ch. 248).[60,76] Myocardial diseases, predominantly HCM, represent the most common cause of ventricular arrhythmias in cats.[77] Other reported arrhythmias include supraventricular premature complexes, atrioventricular blocks or atrioventricular dissociation (1%), and atrial fibrillation (0.5%).[1,37,60] Use of 24-hour Holter monitoring, which is more sensitive than "in-clinic ECG" for arrhythmia detection, showed that cats

with asymptomatic HCM had more frequent and complex ventricular and supraventricular arrhythmias than normal cats, despite similar heart rates.[76] All asymptomatic cats had ventricular arrhythmias, with 82% exhibiting complex arrhythmias *vs* 20% for normal cats, and 87% had supraventricular arrhythmias with 23% exhibiting complexity *vs* respectively 60% and 13% for normal cats.[76] Whether such arrhythmias are associated with an increased risk of sudden cardiac death or a shorter life span requires further investigation.

Clinical Course and Prognosis

Survival time of HCM cats is highly variable. Some live for years, even have a normal life expectancy, and die from non-cardiac causes, whereas others die several days after diagnosis or even die suddenly before an *ante-mortem* diagnosis of HCM can be established. For example, an overall median survival time of 709 days with a wide range (2-4418 days) was reported for HCM cats that survived >24 hours.[41] This highly variable survival time was also shown in another study (1276 days, 0-3617 days).[42] Cardiac deaths related to HCM mainly include spontaneous deaths or euthanasia either secondary to ATE or CHF (each representing about 33% to 50% of all cardiac deaths), and also sudden death (10% to 25% of all HCM-related deaths).[37,41,60] Various clinical, breed, genetic and imaging risk factors associated with cardiac death have been identified.[37,41,42,53,60]

Clinical Signs

The reported percentage of HCM cats dying for cardiac reasons varies from 37% to 81%, depending on the proportion of cats presenting with clinical signs at diagnosis.[21,37,41,42,60] Much longer survival times have been reported for asymptomatic cats than those of symptomatic cats, depending strongly on the types of clinical signs that occur, but with wide ranges of lifespans for each clinical status category.[37,41,42,74] In the report by Rush et al, cats with occult HCM lived the longest (median = 1129 days), followed by cats presenting with syncope (654 days), CHF (563 days), and ATE (184 days).[41] Payne et al also found that cats without CHF (>3617 days) survived longer than those with CHF (194 days),[42] and Trehiou-Sechi et al showed that 80% of asymptomatic cats at diagnosis died from non-cardiac related causes, whereas 80% of symptomatic cats died for cardiac reasons.[37] Other negative clinical predictors of cardiac death include age, presence of a gallop sound and arrhythmia at diagnosis.[60]

Breed

Ragdolls have shorter survival times than other cats (median survival, 19 days *vs* 1297 days respectively).[42] In one study with no Ragdolls, the age at first cardiac event (CHF, ATE, syncope, sudden death) was lower in Maine Coon cats (median age, 2.5 years) than in other cats (7.0 years), with half of the Maine Coon deaths attributed to cardiac causes whereas most (>75%) deaths of Chartreux and Persian cats were attributed to non-cardiac causes.[37]

Genetic Status

Ragdoll cats homozygous for the *MyBPC3* R820W mutation are more likely to die from cardiac causes and have a shorter time to cardiac death than do heterozygous and wild-type cats (median age at cardiac death of 5.7 years *vs* >16.7 years and >15.2 years, respectively).[53]

Imaging Variables

Left atrial enlargement, assessed using several methods,[66,78] is consistently negatively associated with survival time in both occult and overt HCM.[21,41,42,60,62] Median survival of HCM cats with normal LA size (>3617 days) is thus greater than that of HCM cats with LAE (229 days).[42] Other imaging predictors of increased risk of cardiac death include severe LVH (≥9.0 mm), decreased systolic function (fractional shortening [FS%] ≤30%), decreased LA function (assessed by LA-FS%), RV enlargement, regional wall hypokinesia, spontaneous echo-contrast/thrombus or both, and a restrictive diastolic filling pattern.[21,41,42,60,79]

Restrictive Cardiomyopathy

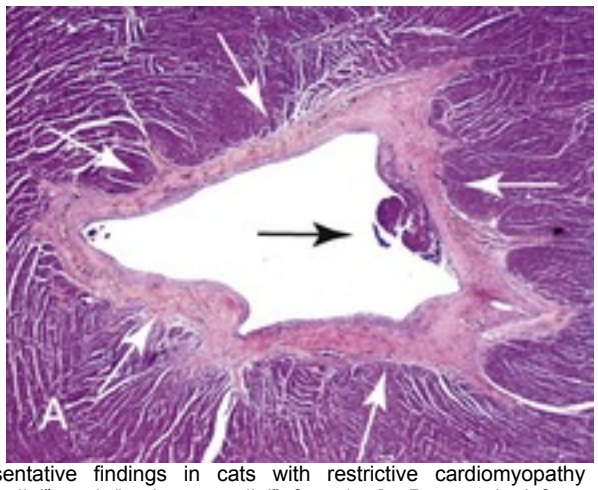
Definition: Pathological Lesions

Human RCM

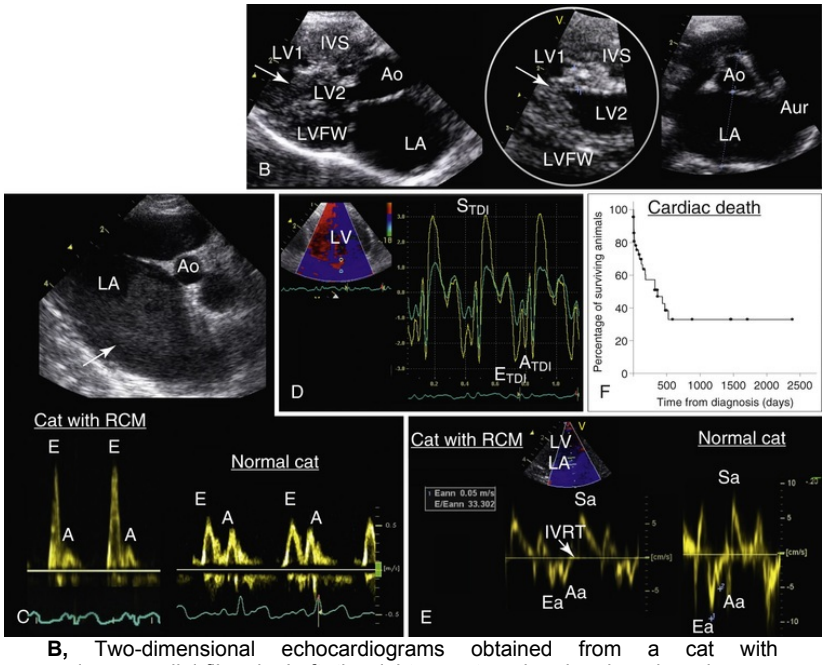
Human RCM is an uncommon heart muscle disease primarily characterized by impaired ventricular filling due to increased myocardial stiffness (or reduced ventricular compliance) of either ventricle (mainly LV) or both, with normal or near-normal systolic function and wall thicknesses.[7,80-83] The reduced ventricular compliance restricts ventricular filling (hence the term "restrictive"), with secondary increased end-diastolic ventricular filling pressure, resulting in marked LA or biatrial enlargement. In the early stages, global systolic function is normal, but altered systolic function is usually observed as the disease progresses.[11,83] Human RCM actually represents a heterogeneous group of heart disorders subdivided into primary and secondary RCM.[11,82,83] Causes of secondary RCM are various including infiltrative diseases (e.g., amyloidosis, sarcoidosis, Gaucher and Hurler diseases) and storage diseases (e.g., hemochromatosis, glycogen storage disorders, and Fabry disease). Secondary RCM, especially endomyocardial fibrosis, is also reported in the hypereosinophilic syndrome and as an iatrogenic complication (radiation, drugs).[80,83] Primary human RCM is characterized by patchy to diffuse interstitial myocardial fibrosis with possible fibrosis of the sinus and atrioventricular nodes resulting in atrioventricular blocks.[80] Endomyocardial fibrosis is a specific form of primary RCM, characterized by marked endocardial fibrosis in addition to myocardial fibrosis.[84,85] Similarly to HCM, familial forms of primary RCM are reported, with most identified genes encoding for sarcomere or Z-disk proteins (e.g., cardiac troponin genes and *MYH7*).[86-88] Interestingly, in addition to these genetic similarities, "overlap" or "crossover" phenotypes of RCM and HCM have been observed in families with mutations in sarcomeric genes, suggesting that some RCM cases may be considered as "minimally hypertrophic" HCM phenotypes.[83]

Feline RCM

"Myocardial RCM" and "endomyocardial fibrosis RCM," similar to human forms of primary RCM, have been identified in the cat,[1,16,17,89] with greater frequency than reported in humans[17] as RCM is currently the second most common feline primary cardiomyopathy (Figure 253-9).[22] At the time of writing, no causal mutations for either feline RCM form have been identified. Nevertheless and interestingly, Fox et al reported that histopathological features of feline HCM (e.g., myocyte disarray, abnormal intramural coronary arterioles, patchy replacement scarring) are found in most cats with RCM, thus suggesting that feline RCM could be the phenotypic expression of sarcomere mutations.[17] The hallmark feature of feline endomyocardial fibrosis is severe endomyocardial scar commonly appearing as a distinct "tubular" lesion bridging the IVS and LVFW, that may result in mid- to apical intra-cavity stenosis (see Figure 253-9, *B*).[16] The less common form of feline endomyocardial fibrosis is characterized by diffuse endomyocardial scar resulting in reduction or obliteration of the LV cavity (see Figure 253-9, *A*). In both endomyocardial forms, endocardial thickening may also involve atrial chambers, the RV (rarely), and is associated with myocardial interstitial fibrosis, various degrees of myocyte hypertrophy and necrosis, intramural coronary arteriosclerosis and inflammatory infiltrates.[16] Such inflammatory infiltrates are also described in the feline "myocardial RCM" form, suggesting a possible role of viral infection and/or immune-mediated induced lesions.[90] In one report, interstitial pneumonia was found in >25% of RCM cats and a question raised by the authors was whether the same agent or process could affect both the heart and lungs.[89]



Representative findings in cats with restrictive cardiomyopathy (RCM, "myocardial" and "endomyocardial" forms). **A,** Panoramic left ventricular cross-sectional view demonstrating a severe and diffuse circumferential left ventricular endocardial scar (white arrows) in a cat with endomyocardial fibrosis that died suddenly. A mural thrombus is also present (black arrow). (Hematoxylin-Eosin-Saffron stain). (Courtesy Prof. Jean-Jacques Fontaine, Pathology Department, National Veterinary School of Alfort, France.)



B, Two-dimensional echocardiograms obtained from a cat with endomyocardial fibrosis. Left: the right parasternal 5-chamber view shows a large heterogeneous bridging scar (arrow) connecting the interventricular septum (IVS) and the left ventricular free wall (LVFW), thus dividing the left ventricular cavity into two apical (LV1) and basal (LV2) parts, with secondary dilation of the left atrium (LA) as compared to the aorta (Ao). Center: zoomed view of the bridging scar (arrow) with focal hyperechoic areas (fibrosis). Right: right parasternal transaortic short-axis view demonstrating marked auricular (Aur) and LA enlargement (end-diastolic LA : Ao ratio = 2.2; values obtained from a population of 100 healthy cats: 0.5 to 1.2).[78] **C,** Echocardiography and Doppler features in a cat with RCM. Top figure: the severely enlarged LA (end-diastolic LA : Ao ratio = 3.7) contains smoke-like echoes (arrow) indicative of blood stasis. Bottom figures: as compared with a normal cat (right), transmitral pulsed-wave Doppler examination of the cat

with RCM (left) obtained from the left apical 4-chamber view reveals a typical restrictive filling pattern characterized by an increased ratio (>2)[66] between the peak velocities of early (E wave, m/s) and late (A wave, m/s) diastolic flow resulting from both increased LA pressure and reduced ventricular compliance with secondary elevated LV diastolic pressure (i.e., E : A = 4.6 *vs* 1.4 [0.65 : 0.45] for the normal cat). Decreased LA function may also contribute to the small A wave amplitude. The cat with RCM also shows a short E-wave deceleration time because of rapid equalization of LA and LV pressures after early diastolic filling (30 ms *vs* 92 ms for the normal cat; values obtained in 41 healthy cats: 54 to 192 ms).[17] **D,** Radial diastolic dysfunction diagnosed in a cat with RCM using two-dimensional color tissue Doppler imaging (TDI, right parasternal short-axis view). The radial velocity profiles are recorded simultaneously in 2 LVFW segments, i.e., subendocardium (yellow) and the subepicardium (green). The diastolic dysfunction is characterized by low diastolic waves, especially in the subendocardium (e.g., subendocardial E_{TDI} wave of 2.6 cm/s; normal values recorded in a population of 100 healthy cats: 5.7 ±1.5 cm/s [3.5-10.8]).[78] A_{TDI}, peak myocardial velocity during late diastole; E_{TDI}, peak myocardial velocity during early diastole; *LV,* left ventricle; S_{TDI}, peak myocardial velocity during systole. **E,** Pulsed-wave TDI recording from the lateral mitral annulus in a cat with RCM (left) showing markedly reduced diastolic velocities (Ea and Aa, cm/s), reflecting a diminished velocity of longitudinal diastolic motion, as compared with the normal cat (right, same animal as in **C**). The peak annular velocity during early diastole (Ea) is only 5 cm/s (*vs* 9.8 cm/s for the normal cat; normal values >6 cm/s).[66] Additionally, in the diseased cat, the ratio between mitral E wave (1.66 m/s, data not shown) and Ea is high (33 *vs* 0.65 : 0.098 = 6.6 for the normal cat; normal values <12).[66] By combining peak mitral E wave (mainly determined by LV filling pressure and relaxation) with Ea (which mainly depends on relaxation) the E : Ea ratio is an index reflecting LV filling pressure (as the effect of relaxation on E is minimized),[66] although prospective studies involving the use of this ratio in cats with RCM are missing. *Aa* and *Sa,* Peak annular velocities during late diastole and systole, respectively. **F,** Kaplan-Meier curve illustrating the time to cardiac death after the initial diagnosis of RCM at the Alfort Cardiology Unit in 73 cats with an available follow-up and that survived >24 hours after the initial examination. Median survival time was 364 days (range, 2-525). (Figure from Prof. R Tissier, INSERM U955 and Pharmacology-Toxicology Unit, National Veterinary School of Alfort, France.)

FIGURE 253-9

Epidemiology: Clinical Presentation at Diagnosis

In the report by Fox et al on 35 RCM cats, mean age at diagnosis was 10 ±4 years with a wide range (1.5-17.1).[17] Similarly, in a retrospective study performed at the Alfort Cardiology Unit (UCA) on 112 RCM cats (2000-2011), age at diagnosis was 10.0 ±4.8 years (0.1-18.9) with only 10% of animals >12 years old. In a case series of 22 RCM cats, most were females (73%).[22] However most were males (71%) in the report by Fox et al,[17] whereas males (52%) and females (48%) were equally represented in the UCA population. In all 3 studies, different breeds were affected (e.g., Burmese, Siamese, Persian, Birman, Maine Coon), with a predominance of Domestic Shorthairs (59 to 78%), but no reported familial link.

Almost all cats with RCM show clinical signs at the time of diagnosis, predominantly related to CHF.[17,21,22] In the report on 35 RCM cats, 91% presented with CHF, 6% with lethargy and 3% with syncope and transient paresis.[17] Similarly, most of the 112 RCM cats (94/112, 84%) recruited at the UCA were symptomatic at diagnosis, with 76% presenting at least 2 clinical signs. The remaining cats (16%) were referred for echocardiography owing to the presence of heart murmurs or arrhythmias detected during routine cardiac auscultation. The most common clinical signs detected in the 94 symptomatic RCM cats were dyspnea (76%), followed by non-specific signs (lethargy, weakness, hypothermia, anorexia [56%], ascites [17%], and paresis/paralysis related to ATE [10%]). Dyspnea was related to pleural effusion for most cats (71%) and to pulmonary edema for others. A heart murmur (left apical systolic heart murmur in 90% of cases) and a gallop rhythm were respectively reported in 66% and 31% of RCM cats (see ch. 55).

Electrocardiographic Findings

Various arrhythmias are commonly associated with feline RCM, predominantly including ventricular premature complexes (23% to 29%) and supraventricular tachycardia (9% to 23%) (see ch. 103 and 248).[17,22] Atrial fibrillation is much less common. Six of the 112 RCM cats diagnosed at the UCA presented with atrial fibrillation (5%), and all showed severe LAE (LA: Ao ratio = 2.5 ±0.7).

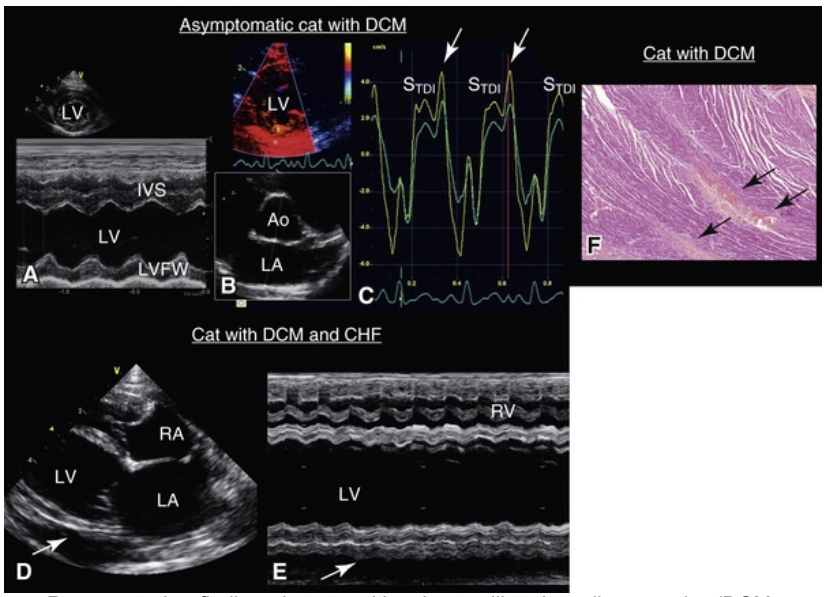
Clinical Course and Prognosis

The overall prognosis of human RCM is poor, with most patients requiring cardiac transplantation.[91] Feline RCM is similarly associated with a poor prognosis, with most animals dying from cardiac-related causes (60% to 86%).[17,21,22] Median survival times of 132 days and 273 days were reported in 16 and 14 RCM cats.[21,22] Spontaneous death or euthanasia for refractory CHF (associated with ATE in >25% of cases) and sudden death were reported in 51% and 9% of 35 RCM cats, respectively, with a median survival of 3.4 months (0.1-52).[17] Similarly, 47/87 cats in the UCA population with an available follow-up died during the study period, i.e., 14 (30%) from non-cardiac-related causes and 33 (70%) from cardiac-related causes (including 9% of sudden death), with one third of the latter occurring within the first 24 hours after diagnosis (spontaneous death or euthanasia for acute CHF). Excluding cats that survived less than 24 hours (n = 14, including 11 that died suddenly), the median survival time was 364 days (2-525) considering cardiac death (see Figure 253-9, *F*).

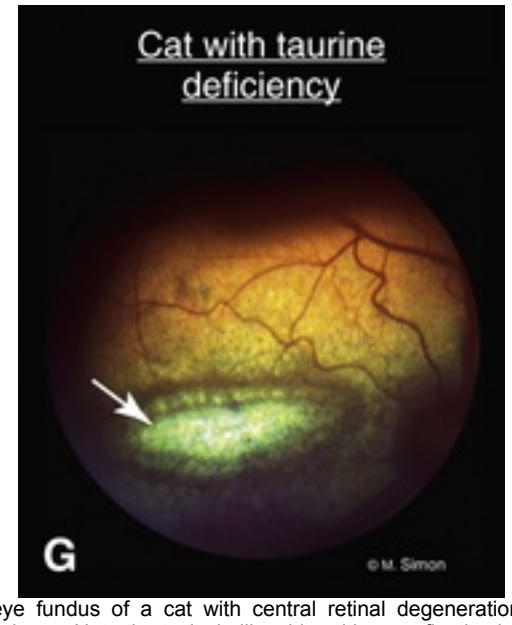
Dilated Cardiomyopathy

Definition and Prevalence

Dilated cardiomyopathy, a primary cardiomyopathy characterized by a dilated LV with systolic dysfunction (Figure 253-10 and Video 253-15),[8,83] was previously recognized as the second most common feline heart disease.[1] However, since the demonstration by Pion et al in 1987 that most cases of feline DCM were actually not "primary" but instead related to taurine deficiency, and that they could be reversible and preventable with oral supplementation of taurine,[92-100] commercial cat foods have been subsequently supplemented with taurine (Box 253-1). Other causes of DCM phenotypes such as sustained tachycardia are also reported.[101] The prevalence of what was initially thought to be a primary myocardial failure has thus decreased markedly, and DCM currently represents only 5% to 10% of primary cardiomyopathies.[20,22] A large number of genetic causes of DCM has been recognized in humans, with most of the implicated genes encoding sarcomere, Z-disk, or cytoskeleton proteins.[83] A mutation in the gene encoding for a mitochondrial protein (PDK4) is similarly associated with the development of DCM in the Doberman Pinscher.[102] However, at the time of writing, no causal mutation has been identified for feline DCM, although a genetic involvement with complex pattern of inheritance was evidenced in a large colony of Domestic Shorthairs.[103]



Representative findings in cats with primary dilated cardiomyopathy (DCM, **A-F**) and taurine deficiency-induced myocardial failure **(G). A** and **B,** M-mode **(A)** and two-dimensional **(B)** echocardiograms from an asymptomatic Maine Coon cat with DCM referred for echocardiographic examination before mating. Myocardial failure is confirmed by a mildly decreased fractional shortening (27%; values obtained from a population of 100 healthy cats: 33 to 66%).[78] The left atrium (LA) is still normal (end-diastolic LA : Ao ratio = 1; values obtained from a population of 100 healthy cats: 0.5 to 1.2).[78] *Ao,* Aorta; *IVS,* interventricular septum; *LV,* left ventricle; *LVFW,* left ventricular free wall. **C,** (Same cat as in **A** and **B.**) Radial myocardial velocity profiles of the LVFW obtained from a right parasternal short-axis view using two-dimensional color tissue Doppler imaging. The simultaneous recording of myocardial velocities in a subendocardial (yellow) and subepicardial (green) segment shows that the subendocardium is moving more rapidly than the subepicardium in systole and also in diastole, thus defining systolic and diastolic radial myocardial velocity gradients. However, the mean systolic gradient is here within low normal ranges (0.9 cm/s; values obtained in a population of 100 healthy cats: 2.2 ±0.7 cm/s).[78] Post-systolic contraction waves (arrows), occurring after S_{TDI} waves and greater than the latter (particularly in the subendocardium) are also seen. Radial post-systolic contraction waves, defined as abnormally delayed radial myocardial contractions occurring during the early diastolic phase (rather than during the systolic phase), were not observed in a population of 100 healthy cats.[78] *S_{TDI},* Peak myocardial velocities recorded during systole. **D** and **E,** Echocardiograms obtained from a cat with DCM and pleural effusion (arrows) related to congestive heart failure. Dilation of the 4 cardiac chambers is observed on the right parasternal 4-chamber view **(D).** A poor LV function is confirmed by the low fractional shortening value (15%) and hypokinesia of both the IVS and the LVFW on the M-mode echocardiogram **(E).** *RA,* Right atrium; *RV,* right ventricle. **F,** Broad bands of fibrosis (arrows) replacing myocardial fibers associated with diffuse interstitial fibrosis in a cat with DCM that died suddenly (Hematoxylin-Eosin-saffron stain, ×25). (Courtesy Dr. Nathalie Cordonnier, Pathology Department, National Veterinary School of Alfort, France.)



G, Right eye fundus of a cat with central retinal degeneration related to taurine deficiency. Note the typical ellipsoid and hyperreflective lesion (arrow) with a pigmented border in the area centralis (i.e., lateral to the optic disc). (Courtesy Dr. Marc Simon, Paris, France.)

FIGURE 253-10

Box 253-1

The Particular Case of Taurine Deficiency-Induced Myocardial Failure, an Example of Nutritional Secondary Cardiomyopathy

Taurine (or 2-aminoethanesulfonic acid) is a sulfonic acid that was first identified in bull bile (hence the name, from the Latin word *Taurus,* meaning bull).[151,152] Taurine is widely distributed in animal tissues, with highest concentrations found in heart, retina, skeletal muscles, and central nervous system.[151-153] It has many different biological actions including conjugation of bile acids, normal retinal and myocardial function, and development and function of central nervous system and skeletal muscles.[96,151-155]

Why Taurine Deficiency in Cats?

Cats can synthesize a limited amount of taurine from cysteine owing to low tissue concentrations of cysteine-sulfinic acid decarboxylase, a key enzyme required for its synthesis.[96,156] Additionally, even when dietary taurine is restricted, cats exclusively use taurine for bile acid conjugation rather than using the alternate glycine conjugation.[157] Taurine loss in the feces as bile acids together with a low synthetic ability predisposes the cat to becoming taurine deficient, particularly when dietary intake of taurine is restricted.[96,157,158] Owing to the various roles of taurine, its deficiency results in a wide range of organ and clinical alterations, which can be prevented and/or reversed with adequate dietary taurine. These include retinal central degeneration, reproductive abnormalities (e.g., infertility, increased incidence of fetal resorptions and abortions, low birth weight), compromised immune function, and myocardial failure as discovered by Pion et al in 1987 (see Videos 253-17, 253-18, and 253-19).[92,96,153,156] However, not all taurine-deficient cats develop overt myocardial failure (about 25%), thus suggesting the influence of other undetermined factors.[96]

Diagnostic Issues Regarding Taurine Deficiency-Induced Myocardial Failure

Routine supplementation of commercial feline diets with taurine has led to a dramatic decrease in the prevalence of taurine deficiency-induced myocardial failure, which is currently rarely diagnosed in cats, except in particular conditions, e.g., use of vegetarian and vegan diets (see Videos 253-17, 253-18, and 253-19).[4,96] However, it is highly likely that a small number of cases continues to be the result of

commercial feline foods containing inadequate amounts of taurine.[96,159] Therefore, the diagnosis of taurine deficiency in cats with echocardiographic DCM phenotype relies mainly on the dietary history together with low plasma and/or whole blood taurine concentration, and systemic evidence of taurine deficiency (e.g., retinal central degeneration; Figure 253-10, *G*).[95,96] Plasma and whole blood taurine concentrations are not affected by age or body weight of cats,[160] and the best clinical method to evaluate the taurine status in cats is ideally the determination and interpretation of both plasma and whole blood taurine concentrations,[155] with whole blood taurine concentration being less subject to change than plasma taurine concentration during the postprandial period or with food deprivation.[95] Normal plasma and whole blood taurine concentrations are usually >60 and >200 nmol/mL, respectively, and risk of developing taurine deficiency–induced myocardial failure occurs for values <30 and <100 nmol/mL, respectively.[96] However, 24 hours of fasting can result in low plasma taurine concentration values, leading to "false positive taurine deficiency" results. Inversely, diet-induced taurine deficiency may be misdiagnosed in some cats with myocardial failure as (1) taurine deficient diets may be difficult to identify as taurine bioavailability may decrease with heat processing (during the canning process), potassium depletion, acidification, and rice bran or whole rice content,[100,161,162] (2) false negative results (i.e., normal taurine concentrations) can be found in several situations (postprandial sampling, recent ATE or dietary changes), and (3) central retinal degeneration is inconsistently found in cats with taurine deficiency–induced myocardial failure (about one third) and does not provide proof of current taurine deficiency (as it may also be the sign of past taurine deficiency).[92,94-96] Assessment of the response to taurine supplementation can therefore be an additional indirect method to help identify taurine deficiency in cats with a DCM phenotype, and taurine supplementation is recommended for all of them regardless of the taurine concentration values.[93,96,105]

Taurine Supplementation, Other Treatments and Prognosis

Therapy of taurine deficiency–induced myocardial failure includes taurine supplementation (250 mg PO q 12 h) together with standard treatment of CHF (e.g., diuretic and ACE inhibitors; see paragraph on treatment). Hypothermia and ATE are associated with an increased risk of early death, which occurs within the first month in more than one third of cats.[93] However, nearly all cats that survive more than 1 month show both marked clinical and echocardiographic improvement. Clinical improvement including the cat's demeanor and appetite is usually observed within 2 weeks and, for most cats, evidence of progressive echocardiographic improvement (firstly a decreased LV systolic diameter and increased FS%) is reported 3 to 9 weeks after beginning taurine supplementation.[93,98] Treatment of CHF can be progressively discontinued when signs of CHF resolve and taurine supplementation can also be stopped once echocardiographic values normalize (usually within 4 months) if adequate taurine intake is ensured by food, which should be confirmed by periodic monitoring of plasma and/or whole blood taurine concentrations.[96] Even if most cats undergo a complete reversal of the myocardial disease, others may show persistent mild myocardial failure (FS% between 25 to 30%) despite taurine supplementation.[96] However these animals are usually asymptomatic and do not require specific therapy except for taurine.[96]

Pathophysiological Consequences

As in humans and dogs,[83,104] feline DCM is characterized by degenerative myocardial lesions of the LV or both ventricles, with various degrees of myocytolysis, fibrosis, coronary arteriosclerosis and some inflammatory infiltrates.[1,90] These lesions are responsible for decreased systolic function, with secondary systolic and then diastolic dilation of affected ventricles. Dilation of the ventricular cavities commonly results in enlargement of the corresponding atrioventricular valve annulus, with secondary valve insufficiency potentially contributing to atrial dilation, subsequent CHF, and increased risk of ATE.[22,105] In one report, valve insufficiency was evidenced in 69% of 32 DCM cats, with mitral and tricuspid valves concomitantly affected in half of the cases and spontaneous echo contrast in the LA of 9% of the cases.[105]

Epidemiology: Clinical Presentation at Diagnosis

A higher proportion of females (73%) with a mean age of 9.1 years (range 2-15.5 years) was reported in one

case series of 11 DCM cats, whereas a higher proportion of males (two thirds) of similar age (10 years, range: 3-16 years) was reported in 32 DCM cats, without any breed predisposition.[22,105] Most DCM cats present with clinical signs of CHF at diagnosis,[22,105] predominantly dyspnea resulting from pleural effusion and/or pulmonary edema (diagnosed in 69% and 34% of cases, respectively)[105] and ascites (6 cases in a series of 11 DCM cats).[22] Signs of systemic hypotension (e.g., weakness) are reported (55%),[22] as well as ATE (9%) and collapse (3%).[105] Feline DCM can also be incidentally diagnosed in asymptomatic animals (see Figure 253-10, *A-C*), indicating the evidence of an occult phase of the disease, but this is currently not as well characterized as that of canine DCM.[104] Cardiac auscultation abnormalities are detected in most DCM cats (97%), including gallop sound (72%), systolic heart murmur (34%), muffled heart sounds (3%) and arrhythmias (28%).[105]

Electrocardiographic Findings

Most ECG tracings from cats with DCM are abnormal (8/11 DCM cats with ECG tracings in two case series) (see ch. 103).[20,22] Non-specific morphological ECG alterations resulting from cardiac chamber enlargement are commonly found.[20,22] Various arrhythmias are also frequently diagnosed, predominantly including ventricular premature complexes and supraventricular tachycardia (see ch. 248).[105] Atrial fibrillation is much less common (only 1 out of 11 DCM cats in one case series).[20]

Clinical Course and Prognosis

Among cats with primary cardiomyopathies, those with DCM have one of the shortest survival times. A median survival time of 11 days was reported in a case series of 11 DCM cats.[22] Similarly in a recent report, survival of cats with DCM was short despite addition of inotropic therapy (pimobendan) to standard therapy (furosemide, taurine, ACE inhibitor, and/or digoxin), (i.e., 49 days [1 to >502 days] *vs* 12 days [1-244 days] for cats receiving the standard therapy alone). In most cases, death was due to euthanasia for refractory CHF (42%) or ATE (19%), and a high proportion of sudden death was also reported (36%; see Figure 253-10, *F*).[105] Hypothermia at presentation and a FS% <20% were both associated with reduced survival.[105]

Arrhythmogenic Right Ventricular Cardiomyopathy

Definitions: Comparative Knowledge in Humans and Small Animals

Humans

ARVC is predominantly a rare genetically determined cardiomyopathy, primarily affecting the RV and pathologically characterized by fibrofatty replacement of RV myocytes, leading to RV dysfunction and failure, ventricular tachyarrhythmias, and increased risk of sudden cardiac death.[106-116] In early stages of the disease, structural myocardial changes are mild and confined to localized RV areas.[110,112] At a later stage, RV myocardial fibrofatty lesions become diffuse, with potential involvement of the LV.[112] Besides this "classic right-dominant form" of the disease, two less common forms are reported: a biventricular form and a left-dominant form characterized by early occurrence of LV involvement, while RV remains preserved.[112,114] Owing to these biventricular and left-dominant subtypes, the term ARVC does not strictly reflect actual myocardial lesions, explaining why the broader term "arrhythmogenic ventricular cardiomyopathy" has been proposed.[111] Interestingly, ARVC was first described by French cardiologists in 1978,[106] and the term "ARV dysplasia" initially chosen for the disease, as myocardial lesions were thought to result from embryological aberrations.[106-108] Nowadays ARVC is known as an acquired heart disease with a causal mutation in genes encoding proteins of the intercalated disk, mainly desmosomal proteins (e.g., plakoglobin, desmoplakin, desmocollin-2, plakophilin-2, and desmoglein-2) in more than 60% of patients.[109,110,112] The cardiac desmosome plays various important roles: it supports structural stability of the myocardium, maintains proper electrical stability and conductivity through regulation of gap junctions and calcium homeostasis, and regulates transcription of genes involved in adipogenesis and apoptosis.[110] The ARVC genetically determined disruption of desmosomal integrity therefore results in myocyte detachment, apoptosis, and necrosis, with inflammatory infiltration (as a reactive process to cardiac death), and subsequent fibrofatty replacement (presumed to represent a "reparative" myocardial process).[110,112] These lesions result in atrophy of the RV

myocardial wall, with secondary RV hypokinesia and dilation, potentially leading to tricuspid regurgitation, RA enlargement, and right-sided CHF. Disruption of desmosomal integrity also promotes ventricular arrhythmias at early stages of the disease, owing to electrical instability and alteration in myocyte electrical coupling.[112,115] Myocardial inflammation associated with ARVC could also represent immune or infectious mechanisms. A predisposition of human patients with ARVC to viral or bacterial myocarditis has been suggested, and myocarditis is known to potentially mimic ARVC lesions. However, the link between myocarditis and ARVC remains to be clarified.[112,116]

Small Animals

Spontaneous AVRC is reported in the dog,[117-124] and is a familial disease in the Boxer breed (autosomal dominant trait, incomplete and age-related penetrance; see ch. 252) frequently associated with a deletion in the striatin gene on chromosome 17.[120,121] Striatin is localized at the intercalated disc region of cardiomyocytes and co-localized with other desmosomal proteins involved in the pathogenesis of human ARVC.[109,110,112] In the cat, ARVC is a recently-recognized cardiomyopathy, accounting for <5% of all myocardial diseases (Figure 253-11).[1,20,125] A series of 12 cases of feline ARVC was extensively described in 2000.[15] Since then, a few sporadic cases have been reported.[126-128] At the time of writing, unlike human and canine ARVC, no genetic transmission has been identified in association with feline ARVC, which remains, therefore, of uncertain origin. In the series of 12 ARVC cats,[15] morphological lesions were similar to those described in humans, including diffuse (7/12) or segmental (5/12) thinning of the RV wall, RV aneurysms of various importance and RA enlargement in 6/12 and 7/12 cats, respectively (see Video 253-16). Histological lesions were also similar to human ARVC, including marked RV myocardial atrophy with fibrous or fibrofatty (9/12) and fatty (3/12) replacement in all cats, apoptosis and focal or multifocal myocarditis in 9/12 and 10/12 cats, respectively. As described in humans and dogs,[112,117] similar lesions were observed in the LV of most cats (10/12), with even severe LV involvement reported.[127]

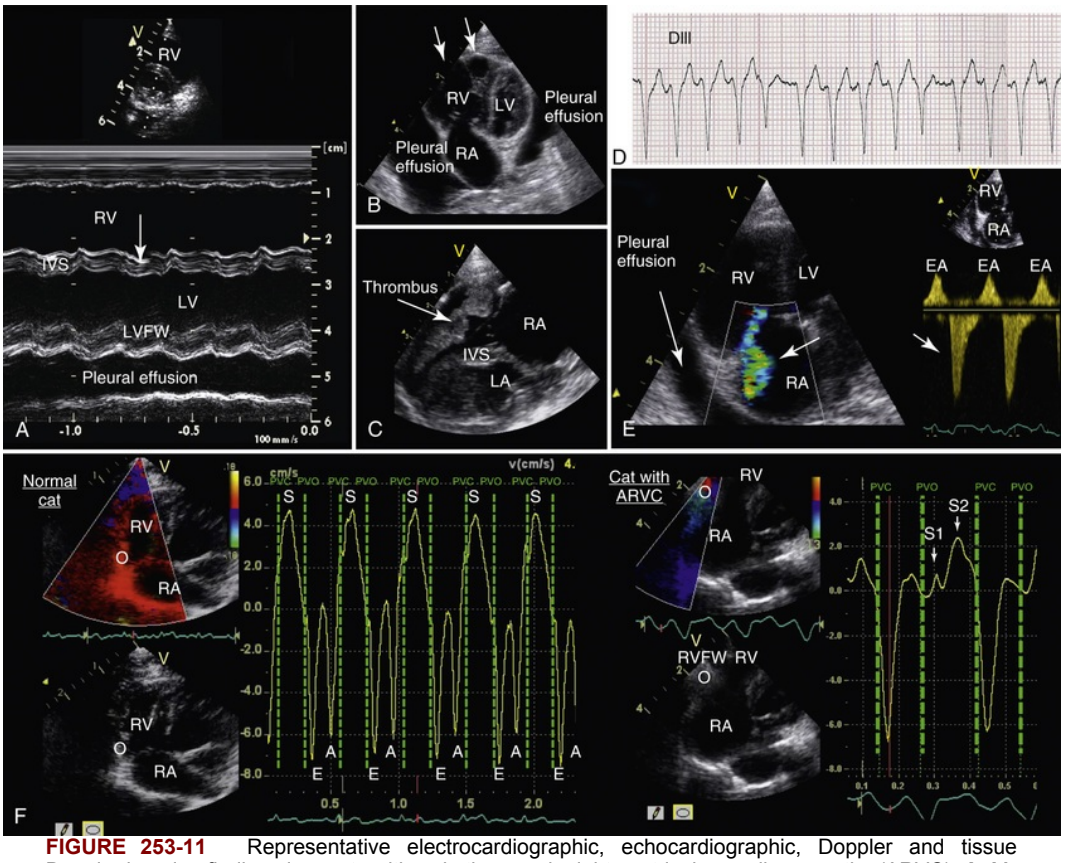


FIGURE 253-11 Representative electrocardiographic, echocardiographic, Doppler and tissue Doppler imaging findings in 4 cats with arrhythmogenic right ventricular cardiomyopathy (ARVC). **A,** M-mode echocardiogram confirming a severe dilation of the right ventricle (RV) with a paradoxical motion (arrow) of the interventricular septum (IVS). Note also the presence of pleural effusion as a sign of

congestive heart failure. *LV,* Left ventricle; *LVFW,* left ventricular free wall. **B,** Two-dimensional echocardiogram obtained from another cat with ARVC (left apical view) showing severe aneurismal RV dilation (arrows), associated with enlargement of the right atrium (RA), and pleural effusion as well. **C,** Two-dimensional echocardiogram obtained from a third cat with ARVC (right parasternal 4-chamber view) showing severe dilation of both right cardiac chambers with a voluminous thrombus in the RV cavity. *LA,* Left atrium. **D,** Atrial fibrillation with right bundle branch block configuration in a cat with severe ARVC (same animal as in **A**). Lead III, paper speed = 25 mm/s, 2 cm = 1 mV. **E,** Tricuspid insufficiency (arrows) documented with color-flow (left panel) and continuous-wave (right panel) Doppler modes from the left apical 4-chamber view in a fourth cat with ARVC. No heart murmur could be heard because of muffled heart sounds owing to the presence of pleural effusion. Note the markedly enlarged right cardiac chambers. *EA,* Fused early (E) and late (A) diastolic tricuspid waves. **F,** Severe right myocardial systolic dysfunction assessed by two-dimensional color tissue Doppler imaging in a cat with ARVC (right panel, same animal as in **B**) compared to a normal cat (left panel). In the diseased cat, recording of longitudinal velocities in a basal segment of the right ventricular free wall (RVFW) shows an abnormal double systolic wave (S1 and S2), with a decreased and delayed peak systolic wave (S2) occurring at end-systole, instead of mid-systole (S) for the normal cat. *S, E,* and *A,* Peak velocities of the right myocardial wall during systole, early diastole, and late diastole, respectively; *PVC* and *PVO,* pulmonic valve closure and opening, respectively.

Epidemiology: Clinical Presentation at Diagnosis

Most ARVC cats are middle-aged at diagnosis (mean age = 7.3 years),[15] even though the age range is wide (1 to 20 years).[15,126,127] No breed or sex predisposition has been reported. The familial aspect of the disease has been evoked, but not demonstrated.[125] Most ARVC cats show clinical signs of right-sided CHF at presentation (see Figure 253-11).[15,126,127] Syncope related to ventricular tachyarrhythmias is a less common clinical expression.[15,125] As in humans and dogs, ARVC cats may remain asymptomatic for a variable period of time. The disease can thus be diagnosed in apparently healthy cats referred for echocardiography, mainly because of an abnormal cardiac auscultation (heart murmur and/or arrhythmias).[125,128] A soft right apical systolic heart murmur consistent with tricuspid regurgitation is detected in most ARVC cats (8/12 cats in the series by Fox et al).[15,125] Arrhythmias may also be detected. However, cardiac sounds may be muffled in cases of pericardial or pleural effusion.[125,126] Nonspecific general signs (e.g., lethargy, anorexia) are also reported in ARVC cats, even in those without evidence of CHF.[15,125]

Electrocardiographic Findings

As reported in humans and dogs, cats with ARVC display a large variety of ECG alterations, including ventricular premature complexes/tachycardia of RV and LV origin (particularly with LV involvement), atrial fibrillation, supraventricular tachycardia, right bundle branch block, and first- and third-degree atrioventricular blocks (see Figure 253-11, *D*, and ch. 248).[15,125,126]

Clinical Course and Prognosis

Although cats with ARVC may remain asymptomatic for an unknown duration, the prognosis of overt ARVC is usually poor. Most cats with ARVC-related CHF soon die of cardiac causes (spontaneous death or euthanasia due to worsening or unresponsive CHF and/or ATE despite therapy), several days or weeks after the initial diagnosis.[15,126,127] In the report by Fox et al, 6 of the 12 ARVC cats died of CHF 2 days to 4 months after clinical onset (median = 1 month).[15]

Unclassified Cardiomyopathies

This category is reserved for cardiomyopathies that do not fit under other headings (HCM, RCM, DCM, and ARVC).[7] In other words, UCM does not characterize a single distinct myocardial disease, but instead encompasses the uncommon primary cardiomyopathies whose echocardiographic changes do not correspond to the typical features of the 4 above well-defined cardiomyopathies. In cats, echocardiographic examination most commonly reveals a mix of alterations including segmental LVH, regional hypokinesia, and marked LAE.[4] In humans, primary UCM also include other forms of cardiomyopathies (e.g., myocardial non-compaction).[11,129] Although of unclear pathogenesis, at least some UCM could represent specific forms or stages of other cardiomyopathies, in particular HCM, as a result of more or less extensive areas of myocardial ischemia and/or infarction (secondary to coronary arteriosclerosis, decreased coronary blood flow secondary

to increased LV filling pressure, functional coronary constriction, inadequate capillary density related to increased myocardial mass, and/or coronary vascular thromboembolism).[130-133] The follow-up of human and feline HCM patients has thus highlighted a "dilated" HCM stage characterized by LV dilation, relative thinning of LV myocardial walls, diffuse or regional decreased contractility, and usually severe LAE.[131-134] In addition to the role of myocardial ischemia and/or infarction, apoptosis and genetic mutations have been evoked to explain this phenotypic HCM evolution in humans.[135,136] These particular HCM forms are also characterized by multifocal myocardial scarring with large regions of replacement fibrosis that can mimic RCM lesions.[133] Therefore, the diagnosis of UCM should be established with caution and the hypothesis of evolution of another primary cardiomyopathy, in particular HCM or RCM, should first be ruled out. However, a differential diagnosis may be difficult to establish in the absence of previous sequential echocardiographic examinations. In one study, UCM represented only 10% of 106 primary cardiomyopathies.[22] Most affected cats were adult females, with a mean age of 8.8 ± 4.8 (0.8-15 years) and more than half presented with signs of CHF. Surprisingly, a greater survival time was observed for cats with UCM (925 days) as compared with HCM (492 days), RCM (132 days) and DCM (11 days).

Secondary Cardiomyopathies

The final diagnosis of any primary cardiomyopathy should be established after exclusion of secondary cardiomyopathies and other heart diseases characterized by similar echocardiographic phenotypes. Although sometimes difficult, the differential diagnosis should for instance include hyperthyroidism particularly in elderly cats,[137-140] infiltrative tumor (lymphoma) or myocarditis, muscular dystrophy,[141,142] acromegaly,[143,144] steroid-induced cardiomyopathy,[145] and cardiovascular causes of LVH (e.g., aortic stenosis and systemic arterial hypertension)[146-149] in cases of the HCM phenotype,[150] as well as taurine deficiency (see Box 253-1),[92-99,151-162] drug toxicosis (e.g., doxorubicin), or sustained tachyarrhythmia in cases of the DCM phenotype.[4,92-99,101]

Diagnostic Approach to Feline Primary Cardiomyopathies

Thoracic Radiography

Cardiomegaly

Cardiomegaly is the most common radiographic abnormality associated with feline cardiomyopathies (Figure 253-12).[41,163-165] As in dogs, the vertebral heart score (VHS) may be used to objectively assess and compare heart size in sequential radiographs, with normal values of 7.5 ±0.3 vertebrae (v) on lateral radiographs, very few breed variations (unlike dogs), and usually accepted upper limits of ≤8.1 and 9 v on lateral and dorsoventral or ventrodorsal views, respectively.[165-167] However, thoracic radiographs present some diagnostic limitations. Asymptomatic HCM cats with mild to moderate LVH and no LAE do not show any radiographic alteration, and similarly to dogs, pulmonary edema or pleural effusion can obscure margins of the cardiac silhouette, precluding accurate evaluation of heart size and shape. Guglielmini et al demonstrated that VHS is relatively specific but not sensitive to predict cardiac enlargement in cats.[165] For example, with a VHS cut-off >8.2 v on lateral views, the specificity for predicting any degree of LAE was 92%, but the sensitivity ranged from 63% to 78% in cats with mild to severe LAE, respectively. With the same cut-off, the specificity for distinguishing cats with left-sided heart diseases from healthy cats was 100%, but the sensitivity was only 52%.[165] Nevertheless, VHS remains a useful tool to help differentiate cardiac from non-cardiac causes of respiratory distress in emergency situations when echocardiography is not immediately available or technically achievable: In cases of acute dyspnea, a VHS >9.3 v on lateral radiographs is highly specific for presence of an underlying heart disease.[168]

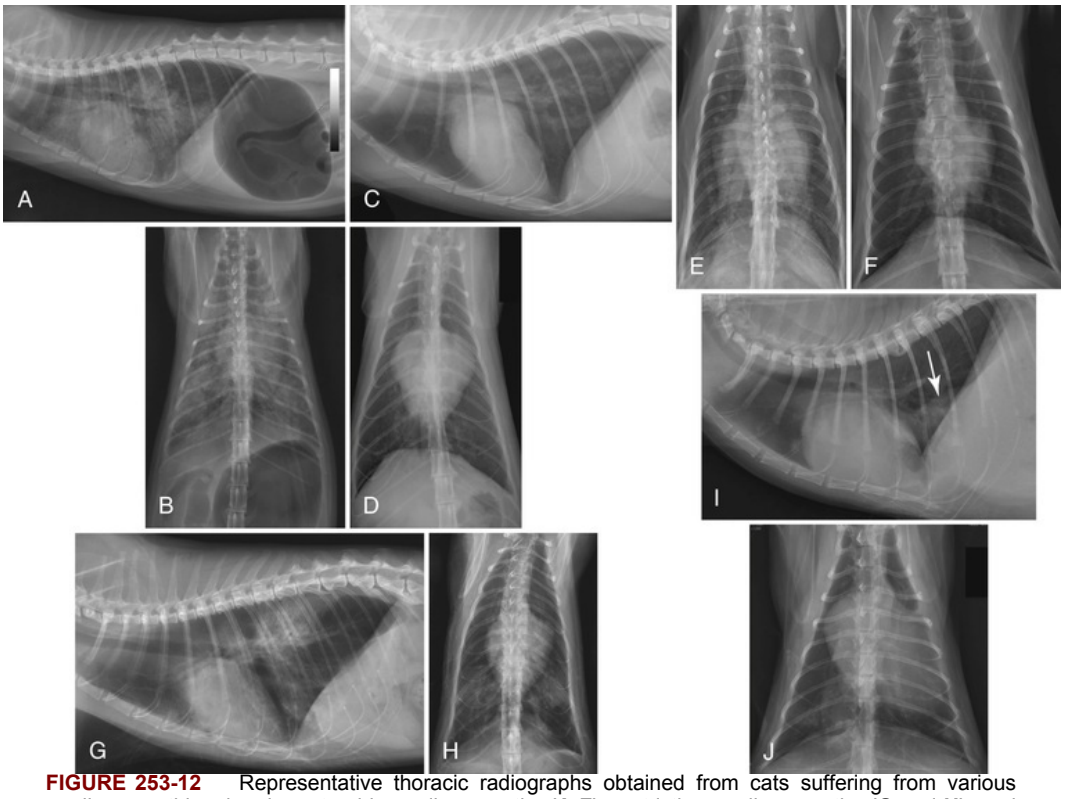


FIGURE 253-12 Representative thoracic radiographs obtained from cats suffering from various cardiomyopathies, i.e., hypertrophic cardiomyopathy **(A-F),** restrictive cardiomyopathy **(G** and **H),** and arrhythmogenic right ventricular cardiomyopathy **(I** and **J). A** and **B,** These right lateral and dorsoventral projections show marked cardiomegaly with a vertebral heart score (VHS) of 8.9 on the lateral projection and a valentine-shaped heart on the dorsoventral projection. The echocardiographic examination confirmed a severely enlarged left atrium without any right atrial enlargement. Note the alveolar lung pattern with symmetrical mainly cranioventral and caudoventral distribution. A severe gaseous distension of the stomach secondary to respiratory distress is also seen. **C** and **D,** These right lateral and ventrodorsal projections show severe cardiomegaly (VHS = 9.4 on the lateral projection) and a valentine-shaped heart on the ventrodorsal projection. The echocardiographic examination confirmed a severely enlarged left atrium (end-diastolic left atrium : aorta ratio = 2.2; normal maximal value = 1.2)[78] without any right atrial enlargement. Pulmonary edema is here characterized by a diffuse uniform unstructured interstitial lung pattern. **E,** This dorsoventral projection obtained from a Maine Coon cat with hypertrophic cardiomyopathy shows a marked enlargement of the pulmonary vessels in comparison with the thickness of the ninth rib where they cross each other. Note the severely increased width of the cardiac silhouette (>2/3 of that of the thoracic cage), without identification of a valentine-shaped heart. Cardiogenic pulmonary edema is characterized by a marked diffuse unstructured interstitial lung pattern. **F,** (Same cat as in **E.**) The ventrodorsal projection obtained the following day after treatment with furosemide shows regression of the pulmonary edema, decreased size of the cardiac silhouette, but persistent enlargement of the pulmonary vessels. **G** and **H,** These right lateral and ventrodorsal projections obtained from a cat with restrictive cardiomyopathy show severe cardiomegaly (VHS of 9.2 on the lateral projection) and a valentine-shaped heart on the ventrodorsal projection. On echocardiography, severe enlargement of only the left atrium was documented (end-diastolic left atrium : aorta ratio = 1.7). Note also the multifocal alveolar patches in the cranioventral and caudodorsal lung fields consistent with pulmonary edema. There is no perihilar distribution as seen in the dog. **I** and **J,** These right lateral and ventrodorsal projections obtained from a cat with arrhythmogenic right ventricular cardiomyopathy show an increased contact between the cardiac silhouette and the sternum and a left cardiac shift consistent with right-sided cardiomegaly, with a VHS of 9.0. A marked enlargement of the caudal vena cava (arrow) is also seen (twice the height of the thoracic aorta). Note also the presence of two alveolar patches in the caudal lung lobes. Differentials to consider include pulmonary edema or pulmonary thromboembolism. (Courtesy Dr. Pascaline Pey, Diagnostic Imaging Department, National Veterinary School of Alfort, France.)

Cardiac Shape

Until recently,[169,170] the typical valentine-shaped heart, assessed on dorsoventral or ventrodorsal views (see Figure 253-12, *D*), was considered to be related to biatrial enlargement and relatively specific to feline HCM.[1,164] However, a strong positive correlation between LA size and severity of the valentine shape was recently demonstrated, without any effect of RA size on the latter, except when concurrent with severe LAE.[170] Similarly, in a recent report, the majority (83%) of cats with a valentine-shaped heart were suffering

from cardiomyopathies, but only 32% had HCM (RCM and UCM accounting for 17% and 34% of the remaining cases; see Figure 253-12, *H*), with biatrial enlargement confirmed in only one third of cats.[169] In both reports, 10% to 19% of cats with a valentine-shaped heart were diagnosed with conditions other than cardiomyopathies (e.g., congenital heart diseases and volume overload), and up to 7% did not even show any echocardiographic abnormality.[169,170] The valentine-shaped heart should therefore no longer be considered as a specific feature of feline HCM. Neither does it predict the presence of biatrial enlargement, as its primary cause is LAE alone.[169,170] In the particular case of ARVC, thoracic radiographs typically show enlargement of the cardiac silhouette related to RV and RA dilation, frequently associated with a dilated caudal vena cava (see Figure 253-12, *I* and *J*).[1,15,125] Global heart enlargement can also be seen in cases of pericardial effusion and/or dilation of the left cavities.

Signs of CHF

As in dogs, radiographic signs of CHF include vascular enlargement, pulmonary edema, and/or pleural effusion. Thoracic radiographs usually show pleural effusion in cats with decompensated ARVC, whereas pulmonary edema is more commonly diagnosed than pleural effusion in cats with decompensated HCM (66% *vs* 34%; see Figure 253-12, *A-E*).[41] Unlike dogs, the perihilar to caudodorsal distribution of cardiogenic pulmonary edema does not predominate in cats. Pulmonary edema related to CHF is instead characterized by an increased opacity with a range of mixed patterns of variable distribution. In one study of 23 cats with CHF, diffuse (uniform or non-uniform) distribution was the most common, and all cats had evidence of a reticular or granular interstitial pattern.[171] Diffuse interstitial patterns may be similar to those associated with chronic bronchitis (see Figure 253-12, *C* and *D*), which can be confusing. A ventral distribution is also common (see Figure 253-12, *A*), mimicking pulmonary opacities related to bronchopneumonia, and leading, therefore, to another risk of misdiagnosis.[171]

Echocardiographic and Doppler Examination (Table 253-1 and ch. 104)

Two-Dimensional and M-Mode Echocardiography

Two-dimensional and M-mode echocardiography combined with Doppler examination (Videos 253-3, 253-4, 253-5, 253-6, 253-7, 253-8, 253-9, 253-10, 253-11, 253-12, 253-13, 253-14, 253-15, 253-16, 253-17, 253-18, and 253-19) is the most accurate non-invasive tool to identify myocardial diseases and assess myocardial phenotypes (HCM, RCM, DCM, or UCM). However, the following basic principles should be considered to limit the risk of misdiagnosis:

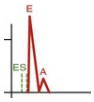
1. If technically possible, complete echocardiographic examinations should always be performed. For example, HCM is characterized by a wide spectrum of LVH patterns of variable severity. Multiple 2D imaging views (long-axis and short-axis views from the base to the apex) are therefore needed to confirm LVH and accurately assess its distribution and severity. The presence of spontaneous echo contrast, more specifically in the LA and LA appendage, should also be systematically and thoroughly sought to determine cats at high risk for ATE (see Videos 253-9, 253-10, 253-11 and 253-13).
2. Volume depletion can induce several changes, e.g., increased IVS and LVFW thicknesses, decreased LV diameters with possible end-systolic cavity obliteration, potentially leading to an erroneous HCM diagnosis.[172] Conversely, IV fluid administration can increase diastolic LV diameter, FS% or LA : Ao ratio above normal limits, with even the appearance of systolic heart murmurs. Thus, the hydration status and ongoing diuretic treatment should always be taken into account when interpreting echocardiographic measurements in cats.
3. The influence of the observer's experience on the variability of echocardiographic measurements in cats has been demonstrated, with a higher variability for less skilled observers and a frequent tendency of the latter to overestimate myocardial wall thicknesses (up to 2 mm), with a subsequent risk to "over-diagnose" HCM of which practitioners should be aware.[173]
4. A breed and body weight effect has been demonstrated for some echocardiographic measurements (e.g., end-diastolic LV diameter, LVFW and IVS thicknesses).[55,78] For example, the end-diastolic cut-off value commonly used to define LVH is ≥6 mm, but lower cut-offs (e.g., 5.0 mm and 5.5 mm) should be used in Sphynx cats weighing <4 kg and ≥4 kg, respectively.[55]
5. Left atrial measurement is of great importance as LAE is considered as the structural expression of chronicity and severity of diastolic dysfunction in HCM and RCM cats, with a high prognostic

value.[34,42,60,62,66] Guidelines on the optimal technique for LA size estimation in cats are currently not available.[66] Some cardiologists measure the LA diameter, parallel to the mitral valve plane, from the middle layer of the atrial septum to the blood-tissue interface of the posterior LA wall, and a diameter of <16 mm is considered as normal in most cats, with ranges between 16 mm to <20 mm, 20 mm to <25 mm, and >25 mm used to categorize LAE as mild, moderate, and severe, respectively.[66] The LA : Ao ratio is also commonly used to assess LAE (see Figure 253-9, *B*). In the author's lab, LA : Ao is preferentially measured at end-diastole (when LA is minimal) from 2D short-axis images, as it is highly reproducible, with no body weight, breed, or gender effect, and likely more closely reflects the LV end-diastolic pressure than early-systolic measurement (normal values = 0.5-1.2).[66,78,173] When measuring LA at end-systole or early diastole (first diastolic frame in which aortic valve closure is evident), a LA : Ao >1.5 is consistent with LAE (2D and M-mode methods, respectively).[174] Nevertheless, a systematic subjective evaluation of LA size as compared with other adjacent structures (aorta, atrial septum) is recommended.[66]

TABLE 253-1

Echocardiographic Diagnostic Criteria for the 4 Main Primary Cardiomyopathies (see also Figures 253-3, 253-6, and 253-8 through 253-11)*

		HYPERTROPHIC CARDIOMYOPATHY	RESTRICTIVE CARDIOMYOPATHY	DILATED CARDIOMYO
Echocardiography (2D and M-Mode)	Most common features & specific forms	• Diffuse or segmental, symmetric or asymmetric concentric LV hypertrophy with end-diastolic LVFW and/or IVS ≥ 6 mm† • Hypertrophy of papillary muscles • Possible obliteration of the LV cavity at end-systole • Normal to increased systolic function • LA dilation • *OHCM:* specific form with hypertrophy of the subaortic IVS and SAM of the mitral valve and/or the chordae tendineae resulting in dynamic LVOT obstruction	• Severe LA or biatrial enlargement • Normal LVFW and IVS thicknesses (or within upper reference ranges) • Normal FS% (or within lower reference ranges) • Focal or diffuse hyperechoic myocardial and endocardial areas (fibrosis) • *EMF:* specific form with bridging scar between the LVFW and the IVS and/or diffuse circumferential hyperechoic endocardial thickening with reduced LV cavity	• Increased and systol (≥12 mm)[1] diameters • Decreased (<30%)[1] • Thinning LVFW, the and/or pap muscles • Increased valve M-m point to se separation • LA enlarg
	Other potential findings	• RVMW hypertrophy • RA dilation • Myocardial infarction (thin and akinetic myocardial wall)	• Mildly decreased systolic function during disease progression • Mild to moderate LV hypertrophy in the case of severe myocardial fibrosis	RA and RV enl
Pulsed-Wave Doppler Mode	Mitral inflow	Relaxation pattern: inversed E : A ratio (<1), prolonged E DT‡ and IVRT (>60 ms)§,‖	Restrictive pattern: increased E : A ratio (>2) with increased E wave and decreased A wave, shortened	Variable patter depending filling press

			E DT‡ and IVRT (<34 ms)§,‖ 	loading con Restrictive p possible at e stages of the with high L. pressure
	Pulmonary vein inflow	Systolic-dominant flow pattern with a prominent AR wave (and Adur : ARdur ratio >1 if LV filling pressure still normal) 	S : D reversal (diastolic-dominant flow pattern) with a small or absent AR wave (and Adur : ARdur ratio <1) predictive of poor LA contraction 	
Mitral Annulus Pulsed-Wave Tissue-Doppler Imaging (TDI)		Low diastolic waves (with Ea <6 cm/s) but mitral E : Ea ratio normal (<12) if LV filling pressures not yet elevated (if elevated, E : Ea ≥12)[66] 	Low diastolic waves,[66] i.e., Ea <6 cm/s, with inversed (<1) or normal (>1) Ea : Aa ratio associated with E : Ea ratio >12 	
Color-Flow Doppler Mode		• Mitral regurgitation • *OHCM:* 2 turbulent systolic jets (aliased ejection jet in the LVOT and posterior-directed aliased jet of mitral regurgitation)		

• Mitral regurgitation • *EMF with bridging scar:* systolic obstruction of the mid LV cavity	Mild to moderate mitral and/or tricuspid regurgitation owing to dilation of the corresponding annulus	Mild to moderate tricuspid regurgitation			
Continuous-Wave Doppler Mode		• *OHCM:* late peaking ventricular outflow profiles (typical concave asymmetric shaped waveform) and high mitral regurgitation velocities • Doppler signs of pulmonary arterial hypertension	• Doppler signs of pulmonary arterial hypertension • *EMF with bridging scar:* increased blood flow velocity in the mid LV cavity	Doppler signs of pulmonary arterial hypertension	Moderate to severe increased velocity of tricuspid regurgitation owing to increased RV pressure
2D Color TDI Examination of Radial and Longitudinal Myocardial Motion		• Early signs of diastolic dysfunction (may be present before overt LV hypertrophy): inversed longitudinal E_{TDI} : A_{TDI} ratio (<1)[38,39] with PSC waves (>50% of cases) in the LVFW and the IVS, and prolonged longitudinal regional TDI IVRT; earlier IVS diastolic dysfunction for some cats (e.g., Maine Coon cats)[39] • Later stages: inversed radial E_{TDI} : A_{TDI} ratio (<1)[38,39] • Decreased S_{TDI} (mainly for the longitudinal LVFW and IVS motions)[38,39]	• Low radial and longitudinal diastolic LVFW and IVS waves (E_{TDI} and A_{TDI})[¶] • Low radial and longitudinal S_{TDI} in severe forms of the disease[¶]	• Decreased radial systolic MVG mainly due to decreased subendocardial S_{TDI}; radial and/or longitudinal PSC waves; myocardial regional dyssynchrony[¶] • Decreased longitudinal S_{TDI} in the LVFW and IVS[¶] • Less commonly: inversed radial and/or longitudinal E_{TDI} : A_{TDI} ratio[¶]	• Delayed, low (usually <3 cm/s) and/or biphasic S_{TDI} for the longitudinal motion of the RVMW at the base[¶] • ± Inversed E_{TDI} : A_{TDI} ratio (<1) of the RVMW at the base[¶]

[*] **Other ultrasound imaging features include signs of congestive heart failure (e.g., pleural and pericardial effusion, dilatation of the caudal vena cava and ascites), and spontaneous echo contrast or thrombus in dilated atrial chambers. The definitive diagnosis of primary cardiomyopathy should never be based solely on these imaging criteria. Secondary cardiomyopathies characterized by the same phenotype should always be excluded first.**

[†] Lower cut-off values should be used according to body weight and breeds.[55,78] See text for explanation.

[‡] Various reference intervals of E DT have been reported (most often <100 ms, but ranging from 45 to 192 ms, thus rendering this variable less reliable in clinical decision-making).[17,66]

[§] The lower and upper range of the reference interval for IVRT assessed in 100 healthy awake cats of various breeds was 34 ms and 56 ms, respectively,[78] with a lower minimal IVRT cut-off value (28 ms) in the Sphynx breed.[55] An upper IVRT cut-off of 60 ms is often used in practice.[66]

[‖] In late stages of hypertrophic cardiomyopathy, a restrictive pattern (E : A ratio >2 with shortened E DT and IVRT) preceded by a "pseudonormal" pattern may be observed whereas in early stages of restrictive cardiomyopathy, an abnormal relaxation mitral inflow

pattern (E : A ratio <1 with prolonged E DT and IVRT) may be found.

¶Unpublished data (Cardiology Unit of Alfort).

2D, Two-dimensional; *A,* peak velocity of late diastolic transmitral flow; *Aa,* peak velocity of late diastolic mitral annular motion as assessed by pulsed-wave TDI; *Adur,* duration of mitral A wave; *AR,* peak velocity of pulmonary vein flow reversal at atrial contraction; *ARdur,* duration of the AR wave; *ATDI,* peak myocardial velocity assessed by 2D color TDI during late diastole; *D,* peak velocity of diastolic pulmonary vein flow; *E,* peak velocity of early diastolic transmitral flow; *Ea,* peak velocity of early diastolic mitral annular motion as assessed by pulsed-wave TDI; *E DT,* mitral E wave deceleration time; *EMF,* endomyocardial form of restrictive cardiomyopathy; *ES,* end-systole; *ETDI,* peak myocardial velocity assessed by 2D color TDI during early diastole; *FS%,* fractional shortening of the left ventricle; *IVRT,* isovolumic relaxation time; *IVS,* interventricular septum; *LA,* left atrium; *LV,* left ventricle; *LVFW,* left ventricular free wall; *LVOT,* left ventricular outflow tract; *MVG,* myocardial velocity gradients assessed by 2D color TDI and defined as differences between subendocardial and subepicardial velocities (radial MVG) or between basal and apical velocities (longitudinal MVG); *OHCM,* obstructive hypertrophic cardiomyopathy; *PSC,* post-systolic contraction; *RA,* right atrium; *RV,* right ventricle; *RVMW,* right ventricular myocardial (free) wall; *S,* peak velocity of systolic pulmonary vein flow; *SAM,* systolic anterior motion; *STDI,* peak myocardial velocity assessed by 2D color TDI during systole.

Pulsed-Wave Doppler Mode

Pulsed-wave Doppler mode provides surrogate measures of LV diastolic function (e.g., mitral inflow velocities, deceleration time of early transmitral flow [E], isovolumic relaxation time) which are commonly used in cats with HCM and RCM together with mitral annular velocities assessed by pulsed-wave TDI (see Figure 253-9),[66,175] because early mitral annular velocity (Ea) and the E : Ea ratio are considered as surrogate measures of LV relaxation and filling pressure (see Table 253-1).[66] Lastly, **continuous-wave and color-flow Doppler modes** are used to assess dynamic LVOTO and atrioventricular valve regurgitations (see Table 253-1 and Figure 253-8).

Tissue Doppler Imaging for Assessment of Myocardial Motion (See Table 253-1)

Tissue Doppler imaging quantifies myocardial velocities in real time and offers a sensitive and quantitative analysis of regional myocardial function.[176,177] Several studies have demonstrated the ability of the 2D color TDI mode to analyze LV myocardial function in awake healthy cats[78,178,179] and in awake cats with HCM.[38,39] Other TDI modes (pulsed-wave mode and color M-mode) may also be used, although velocity measurements are then limited to a single segment or line, respectively, which decreases the diagnostic abilities of the technique.[63,64,72,180] Another drawback of the pulsed-wave TDI mode is the impossibility of changing the position and size of the region of interest within the myocardium with post-processing.

Radial and longitudinal diastolic LVFW and IVS motions assessed by 2D color TDI are similarly altered in HCM cats (Videos 253-20 and 253-21) and cats with LVH due to systemic arterial hypertension.[38] Longitudinal regional systolic dysfunction is an additional component of HCM-associated myocardial alteration characterized by a decrease in systolic myocardial velocities and gradients as well as TDI systolic strain despite normal or increased FS%.[38,181] Most importantly, the 2D color TDI mode has been shown to be more sensitive than conventional echocardiography in detecting regional myocardial dysfunction in both feline HCM and a feline HCM model before occurrence of or in the absence of overt myocardial hypertrophy.[38,39,65,142] However, it is important to emphasize that to optimize the abilities of TDI to detect early myocardial dysfunction, the 2D color TDI mode should be preferred for the above-mentioned reasons. Cats should not be sedated, and the use of summated early and late diastolic velocities should be avoided. As performed in the author's lab, calm animal handling in a relaxing environment with minimal restraint by performing ultrasound examinations with the cat standing is highly recommended to reduce stress, thus avoiding fusion of diastolic waves in about 90% of cats.[66,78] The TDI technique is also commonly used to differentiate constrictive pericarditis from RCM in humans.[182] However, TDI data on feline RCM are currently lacking.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (cMRI), which has emerged as a powerful tool in human patients with cardiomyopathies, providing data on cardiac volumes and function and on tissue characterization (fibrosis and fatty infiltration).[183] It has been used in Maine Coon cats with moderate to severe HCM, but no difference in the cMRI indices of diastolic function was found between control and HCM cats, whereas TDI could detect diastolic dysfunction in all HCM cats.[184-186]

Other Diagnostic Tools (Genetic Tests for HCM and Biomarkers)

Genetic Tests

Genetic tests (from blood or buccal swab samples) are available to identify the *MyBPC3*-A31P and *MyBPC3* R820W mutations for Maine Coon and Ragdoll cats, respectively, which is useful for breeding programs and to determine the risk of a given cat developing and dying from HCM.

Biomarkers (see ch. 246)[187-197]

Serum/plasma cardiac troponins I and T (cTnI and cTnT) are highly sensitive and specific indicators of acute myocardial cell injury, and should be assayed in cases of echocardiographic suspicion of myocardial infarction, a rare HCM complication.[31,133] Feline HCM is associated with elevated cTnI and cTnT, with cTnI revealing a higher percentage of cats with myocardial injury (67%) than cTnT (28%).[188-190] Both are also predictors of death, but with low sensitivity and specificity, and without correlation between concentration changes and LV thicknesses over time.[188] cTnI is higher in cats with CHF-related dyspnea than in cats with non-cardiac dyspnea, but with a marked overlap between the two.[191] Conversely, plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP), which primarily increases in response to myocardial wall stress, distinguishes CHF from primary respiratory diseases in cats with respiratory signs with approximately 90% diagnostic accuracy, and its use in addition to conventional diagnostic tests significantly increases the accuracy of differential diagnosis for general practitioners.[194,195] NT-proBNP also reliably discriminates normal cats from cats with occult cardiomyopathy (specificity and sensitivity of 100% and 70.8%, respectively, for a >99 pmol/L cut-off, with a positive correlation between NT-proBNP and LV thicknesses or LA : Ao ratio).[196,197]

Management of Feline Primary Cardiomyopathies

Medical Therapy of Feline Cardiomyopathies: An Attempt at an Evidence-Based Approach

Both evidence-based human and veterinary medicine rely on current evidence,[198-201] and ranking such evidence after critical appraisal of the literature is pivotal.[202-205] Different systems have been developed to stratify evidence in human medicine.[206] As few clinical trials are reported in cardiac cats, a simplified 3-level classification of evidence strength seems more suitable in this species:[207] **level 1** (i.e., best evidence), based on data from at least one prospective randomized controlled clinical trial (PRCT); **level 2,** based on data from at least one well-designed clinical trial without randomization, cohort or case-controlled analytic studies, studies using acceptable laboratory models or simulations in target species, or dramatic results in uncontrolled experiments; and **level 3,** based on opinions of respected authorities from their clinical experience, descriptive studies (case reports, cases series), studies in other species, pathophysiologic justification, or reports of expert committees. The American College of Cardiology (ACC)/AHA classification used in the consensus statement on chronic canine valvular disease may also be applied to feline heart diseases to clarify the different therapeutic situations:[208,209] **stage A** corresponds to cats at risk for developing heart disease but with no currently identifiable structural heart disease (no treatment indicated, as no disease present); **stage B** includes cats with structural heart disease, but that have never developed clinical signs caused by the latter; **stage C** refers to cats with past or current mild to moderate clinical signs (e.g., dyspnea due to CHF) related to a structural heart disease; and lastly **stage D** applies to cats with severe clinical signs due to end-stage heart disease.

Medical Therapy of Feline Hypertrophic Cardiomyopathy (Stages B to D; Table 253-2)

Therapeutic Goals: Main Drug Classes

The general goal in stages C and D is to relieve clinical signs or prevent their recurrence in order to improve quality of life and survival. Ideally, the specific therapeutic goal should be to decrease myocardial lesions (remodeling and ischemia) and counteract the main pathophysiological events (diastolic dysfunction and dynamic LVOTO), to improve LV filling and increase cardiac output. Beta-blockers, ivabradine, calcium channel blockers, ACE inhibitors, and spironolactone may be indicated for this purpose. The potentially

beneficial effects of beta-blockers on HCM are mainly attributable to their negative chronotropic and inotropic effects, with subsequent prolongation of the diastolic phase and reduced LVOTO, respectively, both resulting in reduced myocardial oxygen demand (i.e., reduced ischemia), associated with antiarrhythmic properties.[210-212] Atenolol, a beta 1–selective beta-blocker, is usually preferred to non-selective agents (e.g., propranolol) because of the reduced risk of bronchospasm.[5] The potentially beneficial effect of ivabradine relies on its negative chronotropic effect through inhibition of the I_f current in the sinoatrial node (see ch. 248).[213,214] Ivabradine improves diastolic function in healthy cats (level 1 evidence),[61] but its benefit in feline HCM needs further assessment. The rationale for using calcium channel blockers includes negative chronotropic and inotropic effects, direct LV relaxation improvement, coronary vasodilation, and antiarrhythmic properties.[210,215-219] Owing to their potent vasodilatory effects, dihydropyridine calcium channel blockers (e.g., amlodipine) may be deleterious in human OHCM,[210] and should also be avoided in feline OHCM (level 3 evidence). Diltiazem (a benzothiazepine calcium channel blocker) is more commonly used in cats than phenylalkylamine calcium channel blockers (verapamil), because of its less potent negative inotropic and vasodilatory effects.[1,5,218,219] Lastly, there are various level 3 evidence data for using antagonists of the renin-angiotensin-aldosterone system (RAAS) (e.g., ACE inhibitors and spironolactone) in feline HCM. Angiotensin II and aldosterone can induce myocardial hypertrophy and fibrosis *in vitro* and *in vivo*, and in LVH animal models, spironolactone and angiotensin II blockers may reverse such lesions and improve diastolic function, with additional vasodilatory effects for ACE inhibitors.[220-226]

TABLE 253-2

Drugs Most Commonly Used for Treatment of Feline Cardiomyopathies*

DRUGS		PHARMACOLOGICAL ACTION OF INTEREST	REPORTED ROUTES AND DOSAGES	INDICATIONS	CONTRAI
Aldosterone Antagonist	***Spironolactone***	Selective aldosterone receptor antagonist, thus potassium-sparing diuretic action and potential reduction of cardiac remodeling and hypertrophy	≤2 mg/kg PO q 24 h or 0.5 to 1 mg/kg PO q 12 h	CHF refractory to standard therapy	Hyperkale
Drugs Used as Antiarrhythmic Agents	***Digoxin***	Antiarrhythmic properties with mild positive inotropic action	0.007 mg/kg PO q 24 h q 2 d or 0.03 mg/cat q 24 h each day (cats > 4 kg) or q 2 d (cats < 4 kg)	• Supraventricular tachyarrhythmias including atrial fibrillation • Myocardial failure (e.g., DCM)	Ventricula tachya
	Esmolol	Short-acting beta-blocker	50-200 mcg/kg/min IV CRI or 50 to 200 (up to 500) mcg/kg/min IV bolus every 5 min	Acute management of supraventricular and ventricular tachyarrhythmias refractory to lidocaine	• Hypo • Sever failur

	Ivabradine	Selective funny current (I_f) inhibitor in the sinus node (negative chronotropic effects)	0.3 mg/kg PO q 12 h	CM with sinus tachycardia	Bradycard
	Lidocaine	Class Ib antiarrhythmic	10-30 mcg/kg/min IV CRI or 0.2-0.75 mg/kg slow bolus (over 5 minutes), repeat 1 to 2 times only	Initial emergency treatment of ventricular tachyarrhythmias	• Hypo • Sever failur
	Sotalol	Beta-blocker with class III antiarrhythmic properties	10 mg/cat PO q 12 h or 2 mg/kg PO q 12 h	Chronic oral treatment of ventricular tachyarrhythmias	• Hypo • Sever failur
Antiplatelet Drugs	***Aspirin***	Nonsteroidal anti-inflammatory drug with inhibition effect on platelet aggregation	5 to 81 mg/cat PO q 3 d or 5 mg/cat to 5 mg/kg q 3 d administered with food	Prevention of ATE: • Mild to moderate LAE and/or spontaneous echo contrast at echocardiographic examination • History of ATE	• Dehy • Hypo • Gastr signs • Bleed
	Clopidogrel	Thienopyridine derivative (inhibitor effect on platelet aggregation induced by adenosine diphosphate, ADP)	18.75 mg/cat PO q 24 h		• Gastr symp • Bleed
ACE Inhibitors	***Benazepril***	• RAAS inhibition; thus venous and arterial vasodilatory effects (reduced ventricular preload and afterload & decreased	0.25 to 0.5 mg/kg PO q 24 h to q 12 h	• CHF in association with furosemide • Myocardial remodeling associated with HCM and RCM	• Dehy • Acut injur • Hypo
	Enalapril		0.25 to 0.5 mg/kg PO q 24 h to q 12 h each day or q 2 d		
	Imidapril		0.25 to 0.5 mg/kg PO		

		myocardial ischemia), decreased water and Na retention, potential reduction of cardiac remodeling and hypertrophy • Renal protective effect	q 24 h (increase the dose if given with food)		
	Ramipril		0.25 to 0.5 mg/kg PO q 24 h		
Beta-Blocker (Other Than Esmolol and Sotalol; see above)	*Atenolol*	Beta-blocker (with relatively selective beta-1 antagonist activity): • Improves diastolic function through negative inotropic (resulting also in decreased LVOTO) and chronotropic effects • Antiarrhythmic properties (supraventricular and ventricular tachyarrhythmias)	6.25 to 12.5 mg/cat PO q 24 h to q 12 h	Mainly indicated in cats with stage B OHCM or with stage B HCM with ventricular tachyarrhythmias	Severe my
Calcium Channel Blockers (Benzothiazepine)	*Diltiazem*	• Improves diastolic function through negative inotropic and chronotropic effects, and dilation of coronary arteries • Directly improves relaxation • Antiarrhythmic properties	1 to 3 mg/kg PO q 8 h For emergency treatment of supraventricular arrhythmias: 0.1 to 0.2 mg/kg IV bolus and then 2-6 mcg/kg/min IV	• Diastolic dysfunction (HCM, RCM) • Supraventricular arrhythmias	• Brad • AV b • Hyp • Hepa • Myo (e.g.,
Diuretics	*Furosemide*	Highly efficient diuretic effect (loop diuretic)	Emergency: 1 to 4 mg/kg IV/IM/SC to be adapted according to RR	CHF (first-line treatment)	Stage B ca with n cavitie

			(maximum 8 mg/kg/day) Chronic therapy: usually 0.5-2 mg/kg PO q 24 h to q 8 h		
	Hydrochlorothiazide	Diuretic effect	1 to 2 mg/kg PO q 24 h to q 12 h	CHF refractory to furosemide	Same as al
Inotropes	***Dobutamine***	Adrenergic agonist (positive inotropic properties)	1-5 mcg/kg/min CRI	Acute management of myocardial failure	Severe ver tachya
	Pimobendan	Inodilator (calcium sensitizer and PDE III inhibitor)	0.1-0.25 mg/kg PO q 12 h 1 h before food	• DCM • Systolic dysfunction as complication of any other CM except OHCM • CHF refractory to standard therapy	OHCM
Sedative/Analgesic Agent	***Butorphanol***	Synthetically-derived opiate Kappa agonist-Mu opioid antagonist	0.1-0.4 mg/kg slow IV or IM (repeat if needed every 1 to 4 hours)	Decreased stress (acute CHF)	Depressed
Taurine		2-aminoethanesulfonic acid (sulfonic acid)	250 mg/cat PO q 12 h	• Taurine-deficient myocardial failure • DCM • Systolic dysfunction as complication of any other CM	

*For treatment of arterial thromboembolism; see ch. 256.

ACE, Angiotensin converting enzyme; *ARVC,* arrhythmogenic right ventricular cardiomyopathy; *ATE,* arterial thromboembolism; *AV,* atrioventricular block; *CHF,* congestive heart failure; *CM,* cardiomyopathy; *CRI,* constant rate infusion; *DCM,* dilated cardiomyopathy; *GI,* gastrointestinal; *HCM,* hypertrophic cardiomyopathy; *IM,* intramuscular route; *IV,* intravenous route; *LAE,* left atrial enlargement; *LVOTO,* left ventricular outflow tract obstruction; *OHCM,* obstructive HCM; *PDE,* phosphodiesterase; *PO,* orally; *q 2 d,* every 2 days; *q 3 d,* every 3 days; *RAAS,* renin-angiotensin-aldosterone system; *RCM,* restrictive cardiomyopathy; *RR,* respiratory rate; *SC,* subcutaneous route.

Stage B

Asymptomatic HCM cats may live years and most (80%) die from non-cardiac causes.[37,41,42] Thus, as in people, prophylactic therapy to prevent or delay onset of clinical signs remains a subject of debate. According to the ACC/ESC Clinical Expert Consensus on human HCM, some cases at particularly high risk of sudden death should receive medical treatment at that stage.[210] If this document is applied to cats (level 3 evidence), it would be prudent to similarly consider "risk categories" of cats with stage B HCM that could require medical treatment (e.g., homozygous mutated Ragdoll or Maine Coon cats, cats with ventricular tachyarrhythmias, severe LVOTO or LVH, and cats with LAE [a risk factor of cardiac death and ATE,[21,41,42,60] even at stage B[62]]). However, data supporting the clinical or functional benefit of such early treatment are currently lacking. A prospective, observational, open-label, clinical cohort study failed to demonstrate an effect of atenolol on 5-year survival in cats with stage B HCM (level 1 evidence).[62] Nor did atenolol decrease

biomarkers in 6 Maine Coon cats with stage B HCM, thus suggesting a lack of beneficial effect on myocardial ischemia and myocyte death (level 2 evidence).[227] Lastly, atenolol decreases LA function and flow velocity in the left auricle of healthy cats, two known risk factors for LAE and ATE, raising the issue of potential deleterious effects if used in feline HCM.[61] Thus, if the treatment option is chosen rather than "watchful waiting," many clinicians now favor calcium channel blockers or RAAS antagonists (mainly ACE inhibitors) over atenolol in stage B feline HCM, except in cases of severe LVOTO and/or ventricular tachyarrhythmias. However, no benefit on survival or onset of clinical signs has been evidenced for either therapeutic class, and their effects on diastolic function remain unclear. A double-blinded randomized prospective study in cats with stage B HCM (level 1 evidence), revealed an increased mitral E : A ratio in the benazepril group but not the diltiazem group; but without any difference between the two at the end of the study.[228] Ramipril or spironolactone did not improve diastolic function in Maine Coon cats with stage B HCM assessed by a hybrid pulsed-wave TDI index in a non-myocardial location (based on Ea for some cats, summated Ea and late annular velocities for others).[186,229] Further studies are therefore required to accurately assess the effect of RAAS antagonists on myocardial function in occult HCM, using various non-hybrid diastolic indices from different imaging techniques (conventional Doppler combined with pulsed-wave TDI as well as 2D color TDI applied in several myocardial segments) in cats of various breeds. In one report, ulcerative facial dermatitis was found in 31% cats about 2.5 months after starting spironolactone treatment (2 mg/kg PO q 12 h).[229] This adverse skin reaction (level 1 evidence),[229] reversible after drug discontinuation, suggests that lower spironolactone doses should be used in cats (≤2 mg/kg PO q 24 h, level 3 evidence). Cats with LAE or spontaneous echo contrast could also benefit from antiplatelet therapy, although its prophylactic efficacy at that stage has not been demonstrated.

Stage C

The first-line agent for controlling CHF signs is furosemide (loop diuretic).[230,231] In acute CHF, hospital-based therapy typically includes parenteral administration of furosemide, oxygen (see ch. 131), sedation to minimize stress (e.g., butorphanol; see ch. 138), thoracocentesis in cats with severe pleural effusion (see ch. 102), and cage rest (level 3 evidence).[231] As furosemide has potential deleterious effects on renal perfusion and electrolytes, the initial emergency dosage should be reduced as soon as CHF signs have improved, with re-evaluation of renal parameters and electrolytes (Na, K) within the first week of discharge for outpatients.[231] Once initiated, furosemide is maintained at the lowest effective dose every day for the rest of the cat's life (q 8-24 h) or every 2 to 3 days in very rare cases of CHF related to stressful events. Antiplatelet drugs are also prescribed owing to the risk of ATE (see ch. 256). A "specific" treatment (most commonly ACE inhibitors)[232] is usually added to furosemide, although beneficial effects on long-term survival warrant further investigation. As shown with enalapril,[233] diltiazem therapy in cats with stage C HCM was associated with improved clinical signs and several imaging variables (e.g., isovolumic relaxation time), with 94% survival at 6 months in a non-placebo controlled prospective study (level 2 evidence).[218] In a non-blinded non-placebo prospective trial, addition of benazepril to long-acting diltiazem was well tolerated with some beneficial effects on clinical signs and LVH (level 2 evidence), but no reported survival data.[234] Lastly, the interim results of the Multicenter Feline Chronic Heart Failure Study (level 1 evidence) for cats with CHF treated with furosemide (including 80% HCM cats), showed that survival rate was highest in those receiving enalapril (median survival = 920 days), similar in cats treated with diltiazem (227 days) or placebo (235 days), and lowest for the atenolol group (72 days).[235] However, the differences between treatment groups were not statistically significant, partly due to the few cats/group (personal communication from Dr. Philip Fox).

Stage D

In cases of medical-refractory pleural effusion, periodic pleurocentesis is needed (see ch. 102). Spironolactone can also be used (level 3 evidence). In some severe cases, the daily furosemide dosage can be greatly increased (e.g., cumulative daily dose of 6-12 mg/kg or even more for some authors) if the cats continue to eat and drink (level 3 evidence), although dehydration and azotemia are common at these dosage and concomitant ACE inhibitors should be used with much caution.[232,236] Another diuretic (hydrochlorothiazide) can be cautiously added to furosemide (level 3 evidence).[232] Lastly, pimobendan, a potent inodilator licensed for the treatment of canine CHF, can be prescribed in cats with refractory CHF and/or echocardiographically identified LV systolic dysfunction and renal insufficiency, at similar dosages as in dogs (level 2 evidence), although data from PRCT are still lacking at the time of writing.[231,237-240] Pimobendan is not recommended in OHCM

owing to its positive inotropic action potentially worsening LVOTO with subsequent systemic hypotension, as already reported (level 3 evidence).[239] Because of the potential cardiac remodeling effects of pimobendan shown in other species (level 3 evidence for cats),[241-243] an echocardiographic follow-up of treated HCM cats is recommended.

Other Primary Cardiomyopathies

No PRCT has been specifically conducted in cats with RCM. Management of feline RCM and HCM is therefore similar, as both diseases are pathophysiologically characterized by diastolic dysfunction with subsequent CHF (level 3 evidence).

Owing to the limitations regarding identification of cats with taurine deficiency–induced myocardial failure, taurine supplementation is recommended in all cats with echocardiographic DCM phenotype (level 1 evidence), regardless of blood/plasma taurine concentrations (see Box 253-1).[92,93,96,105] Positive inotropic therapy is also indicated whereas negative inotropic agents (e.g., diltiazem, atenolol) should be avoided. Digoxin is a weak inotrope agent, and therefore it is mainly prescribed for its antiarrhythmic properties (in cases of supraventricular tachycardia).[244] Pimobendan is therefore preferred for treating DCM cats. Added to standard therapy (furosemide, taurine, ACE inhibitor, with or without digoxin) pimobendan improves survival in cats with non-taurine responsive DCM although the prognosis remains poor (median survival time = 49 days, level 2 evidence).[105]

Management of feline ARVC is similar to that of DCM (level 3 evidence). Antiplatelet therapy is usually prescribed due to the risk of ATE related to marked RA enlargement. Refractory cases of symptomatic ventricular tachycardia can be treated with lidocaine IV or esmolol IV. Sotalol may be prescribed for long-term oral treatment but its negative inotropic effects can be problematic.[125,219]

Management of feline UCM is aimed at controlling CHF if present and also based on the predominant myocardial phenotype (i.e., medical treatment of predominant diastolic or systolic dysfunction being similar to that of HCM or DCM, respectively [level 3 evidence]).

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CHAPTER 254

Pericardial Diseases

Kristin MacDonald

Client Information Sheet: Pericardial Effusion

Introduction

Pericardial effusion is the most common pericardial abnormality in dogs and cats. When it causes cardiac tamponade, it is a common cause of right-sided congestive heart failure in dogs, yet the treatment is very different from most other causes of right heart failure. Pericardial effusion is a multi-etiologic disorder, including infectious, inflammatory, and neoplastic causes, with a wide spectrum of prognoses ranging from good to grave.[2] Congenital defects including peritoneal pericardial diaphragmatic hernia (PPDH), pericardial defects, or pericardial cysts are less commonly diagnosed in dogs and cats. Constrictive pericarditis is an uncommon acquired pericardial disease in dogs and is extremely rare in cats.

Pericardial Anatomy and Physiology

The pericardium is formed by two membranes: an outer, fibrous, parietal membrane, and an inner, serous, visceral membrane that forms the epicardium. The base of the fibrous pericardium is continued on the great arteries and veins that leave and enter the heart and blends with the adventitia of these vessels. The apex of the fibrous pericardium is continued to the ventral part of the diaphragm as the phrenicopericardiac ligament or caudomedial mediastinal reflection.[7-9] The parietal and visceral membranes join at the cardiac base, and the space around the heart between the two membranes is the pericardial cavity. A small volume of fluid (0.3-1 mL) is normally present in the pericardial cavity, and it serves to lessen friction between the two membranes.

The parietal membrane is composed of mesothelial cells and connective tissue including compactly arranged collagen fibers in a multi-layered orientation, interspersed with less abundant elastin fibers. This structure provides fibroelastic properties, so that it is easily distensible at low volumes but less distensible with large volumes of pericardial fluid. In the presence of chronic increases in pericardial volume, the pericardium stretches to increase the intrapericardial volume and thereby shift to a more distensible, compliant part of the pressure volume curve (see Pericardial Effusion—Pathophysiology, below). The intrapericardial pressure is normally subatmospheric through most of the cardiac cycle (with a nadir at ventricular ejection), and parallels the intrapleural pressure. The visceral pericardium is composed of mesothelial cells that overlie connective tissue and elastin.

Although the pericardium has several functions for the heart, it is not a vital requirement to maintain normal cardiovascular function, and surgical removal or congenital agenesis is not associated with deleterious effects. The pericardium functions to provide restraint to prohibit cardiac overdilation, protects the heart from infection and forming adhesions to surrounding tissue, maintains the heart in a fixed position within the thorax, regulates the interrelationship between stroke volumes of the two ventricles, and prevents tricuspid regurgitation when ventricular diastolic pressure is increased. The lubricant effect of pericardial fluid allows the heart to move easily within the pericardial sac during systole and diastole.[10]

Congenital Pericardial Disorders

Peritoneopericardial Diaphragmatic Hernia (PPDH)

A PPDH is a congenital defect that causes a communication between the pericardial and peritoneal cavities, allowing abdominal organs to enter the pericardial space while keeping the pleural space intact. A PPDH

forms when there is abnormal embryologic development of the ventral aspect of the diaphragm due to abnormal fusion of the septum transversum with the pleuroperitoneal folds.[3] The most commonly herniated organs are liver and gallbladder, followed by small intestine, omentum, spleen, stomach, and omentum.[4-6] PPDH is an uncommon defect, with prevalence ranging from 0.02 to 0.15% in dogs and 0.05 to 0.59% in cats.[5-7] Medium- and long-haired cats are overrepresented (24/31 cats in one study), and predisposed breeds include Maine Coon cats (prevalence 12.9%), Himalayans (2.2%), domestic long hair cats (2.2%), and Persians (1%).[6] Weimaraner dogs also are predisposed.[5,6]

Clinical Signs

Clinical signs with PPDH vary depending on the herniated organs or tissue. Approximately half of dogs and cats in a case series had no clinical signs and PPDH was an incidental finding.[5] In symptomatic animals, signs referable to the respiratory and gastrointestinal (GI) systems predominate: tachypnea, respiratory distress, vomiting, and anorexia are common. Other signs can include lethargy, weight loss, diarrhea, exercise intolerance, and coughing.

Diagnosis

Physical examination abnormalities in affected dogs and cats most frequently include muffled heart sounds, a displaced or absent apical beat, muffled lung sounds, tachypnea, and thin body condition. Other less common abnormalities include presence of a heart murmur, fever, thoracic borborygmus, an empty abdomen on palpation, or a full, painful abdomen on palpation.[5,6,10] Common associated abnormalities in dogs include sternal malformations (incomplete xiphoid; pectus excavatum; and absent, deformed, or fused sternebrae), cranioventral abdominal hernias, and other congenital heart defects (pulmonic stenosis, ventricular septal defect). Associated abnormalities in cats are less common and usually are limited to sternal malformations and cranioventral abdominal hernias.

Thoracic radiographs typically are diagnostic for PPDH (Figure 254-1).[5,10] Abnormalities consistent with PPDH include increased size of the cardiac silhouette and a loss of distinction between the heart and the diaphragm, with superimposed soft tissue opacity. The cardiac silhouette often contains gas-filled bowel loops and structures of differing radiopacities (see Figure 254-1). The hepatic silhouette can be small or absent in the cranial abdomen, causing a cranial shift in the gastric axis. Various other organs (small intestine, spleen) can be absent from the abdomen. In cats, a dorsal peritoneopericardial mesothelial remnant, which represents the dorsal border of the hernia, may be recognized on the lateral view as a curvilinear opacity between the cardiac silhouette and the diaphragm, either ventral to, or superimposed over, the caudal vena cava.[4-6] The use of standard thoracic radiographs and echocardiography have eliminated the need for performing upper GI barium series to diagnose PPDHs.

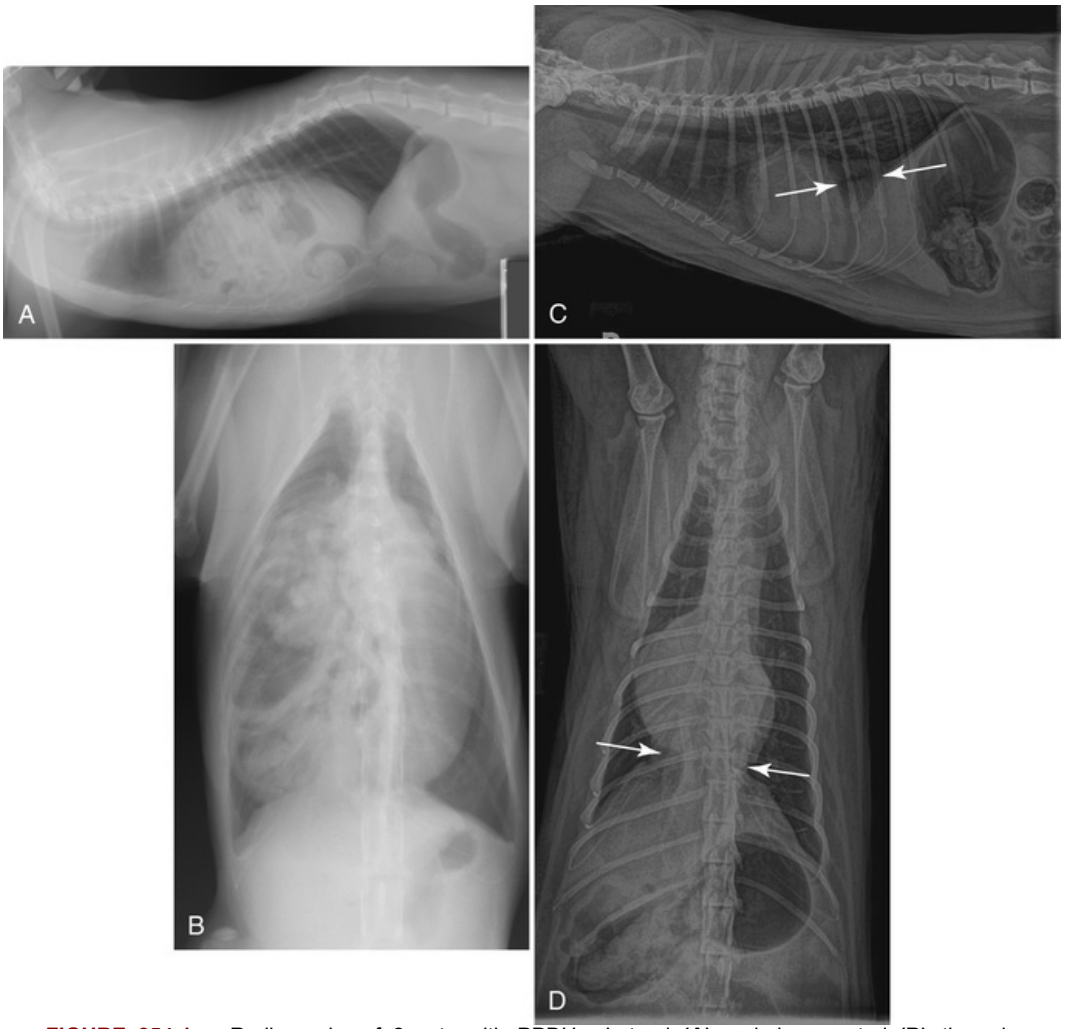


FIGURE 254-1 Radiographs of 2 cats with PPDHs. Lateral **(A)** and dorsoventral **(B)** thoracic radiographs of a cat with a large PPDH. The cardiac silhouette is severely enlarged, and the pericardial space contains differential opacities and gas-filled bowel loops. Most of the abdominal contents, including the liver and small intestines, are displaced into the pericardial sac. Lateral **(C)** and dorsoventral **(D)** radiographs of a different cat with PPDH. While abnormalities are less striking, the lateral view clearly shows a persistence of the dorsal mesothelial remnant (arrows).

Echocardiography serves as a confirmatory test for the diagnosis of PPDH, where abdominal organs (most commonly liver) can be visualized adjacent to the heart within the pericardial space (Figure 254-2; Video 254-1). An important differential diagnosis is consolidation (hepatization) of the accessory lung lobe; thoracic radiographic findings help differentiate this from PPDH. Mild pericardial effusion can be present, but severe pericardial effusion and cardiac tamponade are uncommon. Electrocardiograms can be normal or show low-voltage complexes and abnormal orientation of the mean electrical axis. Complete blood count and serum biochemistry profile results often are unremarkable, and the most common abnormalities include elevated serum alanine aminotransferase activity in dogs (n = 10/26 dogs), and an elevated serum calcium concentration in cats (9/29).[6]

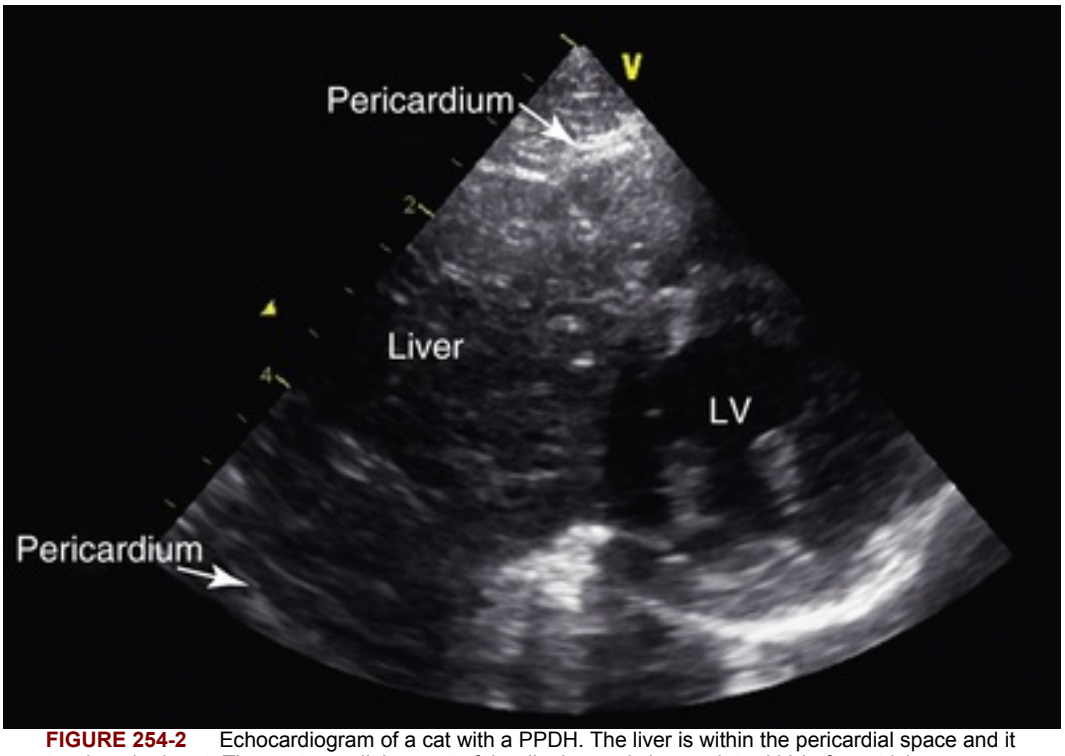


FIGURE 254-2 Echocardiogram of a cat with a PPDH. The liver is within the pericardial space and it touches the heart. The ventromedial aspect of the diaphragm is incomplete. *LV,* Left ventricle.

Treatment

Surgical correction of the PPDH is indicated for animals showing clinical signs (Figure 254-3). Presence of clinical signs or small intestines within the pericardial space was significantly associated with surgical treatment in a group of 34 dogs and cats with PPDH. Prognosis with successful surgery is excellent, with postoperative mortality rates ranging from 5-14%.[6,10] Intraoperative complications arose in 38% of 37 cats in one case series, and postoperative complications within 3 days of surgery and between 3 days-6 months were seen in 78% and 41% of cats, respectively, most being classified as mild.[10] Resolution of clinical signs is seen in 75-85% of cases with surgical repair, yet one case series reported no difference in long-term survival between surgically and nonsurgically treated animals.[5,10] Adhesions between herniated organs and the pericardium can complicate or preclude PPDH reduction in older animals. Consequently, in an asymptomatic older animal where PPDH is an incidental finding, it may be prudent to recommend continued observation rather than surgical repair.

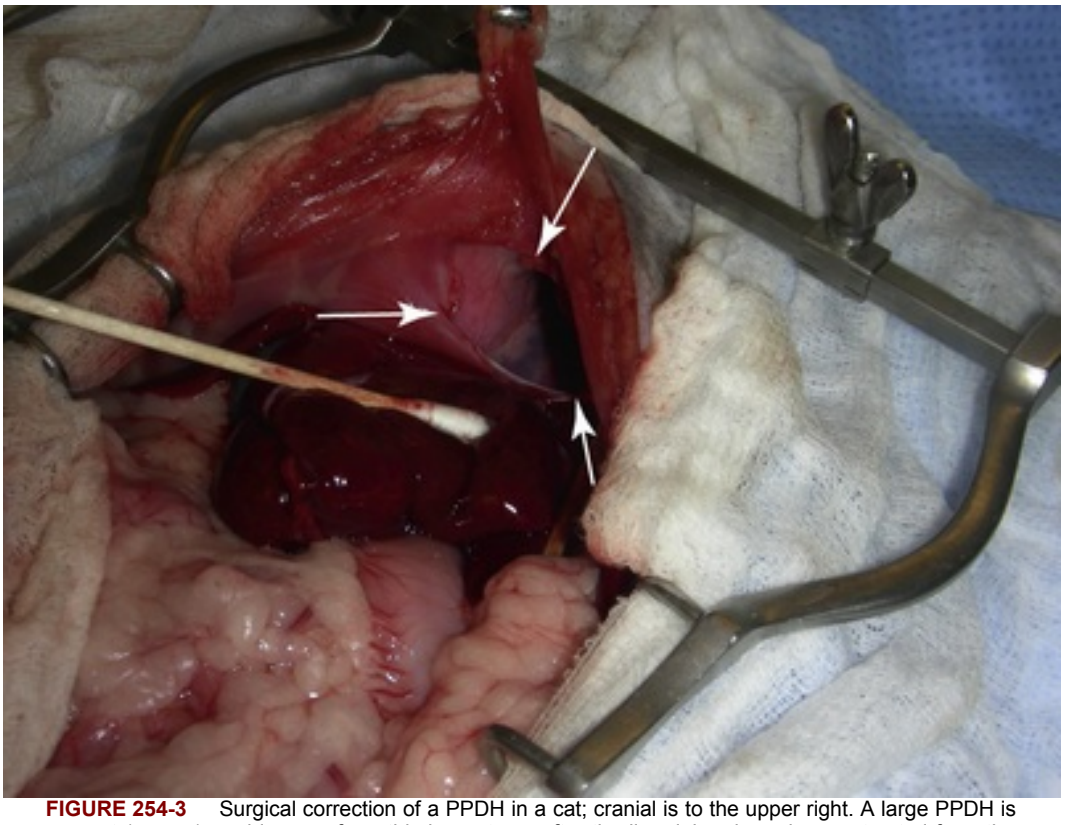


FIGURE 254-3 Surgical correction of a PPDH in a cat; cranial is to the upper right. A large PPDH is present (arrows), and is seen from this laparotomy after the liver lobes have been retracted from the pericardial space into the abdominal cavity.

Pericardial Cysts

Pericardial cysts are rare in dogs and have not been reported in cats. In humans, pericardial cysts may arise from anomalous pericardial development, lymphatic elements, bronchial cysts, and teratomas. In dogs, pericardial cysts appear to resemble cystic hematomas. Since they are mostly seen in young dogs, this suggests a congenital or developmental anomaly. Characteristic pathologic abnormalities include encapsulation of cysts within adipose tissue, with extensive hemorrhage and necrosis, or organizing cystic hematomas. In some cases, the benign intrapericardial cyst is associated with a small PPDH. In other cases, the cyst is attached by a pedicle to the apex of the pericardium; the pedicle results from prenatal herniation of omentum or falciform fat from the peritoneum into the pericardium and subsequent closure of a PPDH. Vascular obstruction of the herniated tissue and repeated trauma from the beating heart lead to cyst formation.[19,20] Intrapericardial cysts cause cardiac tamponade by direct cardiac compression and associated pericardial effusion in some cases. Treatment involves surgical removal of the cyst and its associated pedicle, pericardectomy, and herniorrhaphy in cases with a PPDH.

Pericardial Defects

Pericardial defects are rare in dogs and have not been reported in cats. They can be congenital or acquired secondary to trauma, and range from partial to complete absence of the pericardium.[11] Left- and right-sided defects appear to be equally represented based on literature review of 15 dogs (left-sided, n = 7; right-sided, n = 6; left- and right-sided, n = 1; and complete absence of pericardium, n = 1).[11-14] Until recently, most cases were discovered incidentally on necropsy or during thoracic surgery for unrelated causes. Herniation with incarceration of the left or right auricle can lead to severe clinical consequences of collapse or syncope.[13,14]

The most common diagnostic finding in pericardial defects is an unusual shape of the cardiac silhouette on thoracic radiographs, due to an abnormal bulge of the left or right auricle. This bulge can be mistaken for a cardiac mass or atrial dilation secondary to atrioventricular (AV) valve disease. Echocardiography is necessary to distinguish the cause of the abnormal cardiac silhouette, and it can show disproportionate

dilation of the auricle compared to the atrium and possible constriction of the atrium/auricle by a ring-like fibrotic orifice of the pericardial defect. Treatment of pericardial defects in symptomatic animals includes either pericardial repair if the defect is small, or pericardectomy for larger defects.

Acquired Pericardial Disorders

Pericardial Effusion

Pericardial effusion is the most common pericardial disease in dogs and cats, and, overall, is a fairly common acquired cardiac condition in dogs. Prevalence has been reported to be 0.43% (1 dog/233 cases) for dogs examined at a referral veterinary hospital, and it accounts for approximately 7% of dogs with clinical signs of cardiac disease.[1] It is a multiple-etiologic disorder, with a wide spectrum of prognoses that range from good to grave depending on the cause.[2] The most common causes of pericardial effusion in dogs include hemangiosarcoma (HSA; see also ch. 347), idiopathic pericarditis, mesothelioma, and chemodectoma.[3-5] Determination of the cause of pericardial effusion provides valuable information regarding appropriate treatment, clinical progression, and prognosis.

Pathophysiology

Pericardial effusion increases the intrapericardial pressure, which is transmitted equally to all cardiac chambers during diastole and systole. However, the thinner-walled, more compliant right heart bears the brunt of the effects of increased intrapericardial pressure, and this leads to cardiac tamponade. Cardiac tamponade is defined as the impairment of ventricular filling due to accumulation of fluid within the pericardial space, leading to reduction in stroke volume and cardiac output. Cardiac tamponade has different pathophysiologic characteristics based on the rate of increase in the intrapericardial pressure, and is divided into acute cardiac tamponade and chronic cardiac tamponade.

In acute cardiac tamponade, rapid accumulation of pericardial effusion leads to rapid increase in the intrapericardial pressure, at volumes as low as 50-150 mL (for a 20 kg dog) (E-Figure 254-4).[15] If additional fluid accumulates chronically, it stretches the pericardium to accommodate several hundred milliliters of fluid without clinically relevant increases in intrapericardial pressure (Figure 254-5).[16] Collapse of the right atrium and ventricle increases right atrial and ventricular diastolic pressures. Diastolic collapse of the right heart decreases right ventricular filling and right ventricular stroke volume, thereby reducing venous return to the left heart. Left ventricular stroke volume is decreased (seen as decreased LV diastolic diameter on echocardiography), which decreases cardiac output and causes arterial hypotension and cardiogenic shock. Diastolic collapse of the right atrial and ventricular chambers occurs early in this process, typically when the cardiac output has decreased by approximately 20%, and prior to a reduction in arterial blood pressure.[17] In an experimental canine model of acute cardiac tamponade, mean arterial pressure was maintained until intrapericardial volume had increased to approximately 100 mL, and intrapericardial pressure was approximately 10 mm Hg. Left ventricular systolic function is maintained in acute cardiac tamponade and is not the cause of the arterial hypotension; rather, decreased left ventricular diastolic filling is the cause of the low cardiac output.[18] Increased sympathetic activity in response to arterial hypotension in cardiac tamponade is differentially controlled: Based on an experimental canine model of cardiac tamponade, it is increased to the heart, adrenal gland, and liver, but is inhibited to the kidneys, reducing urinary output in attempts to maintain blood volume.[19]

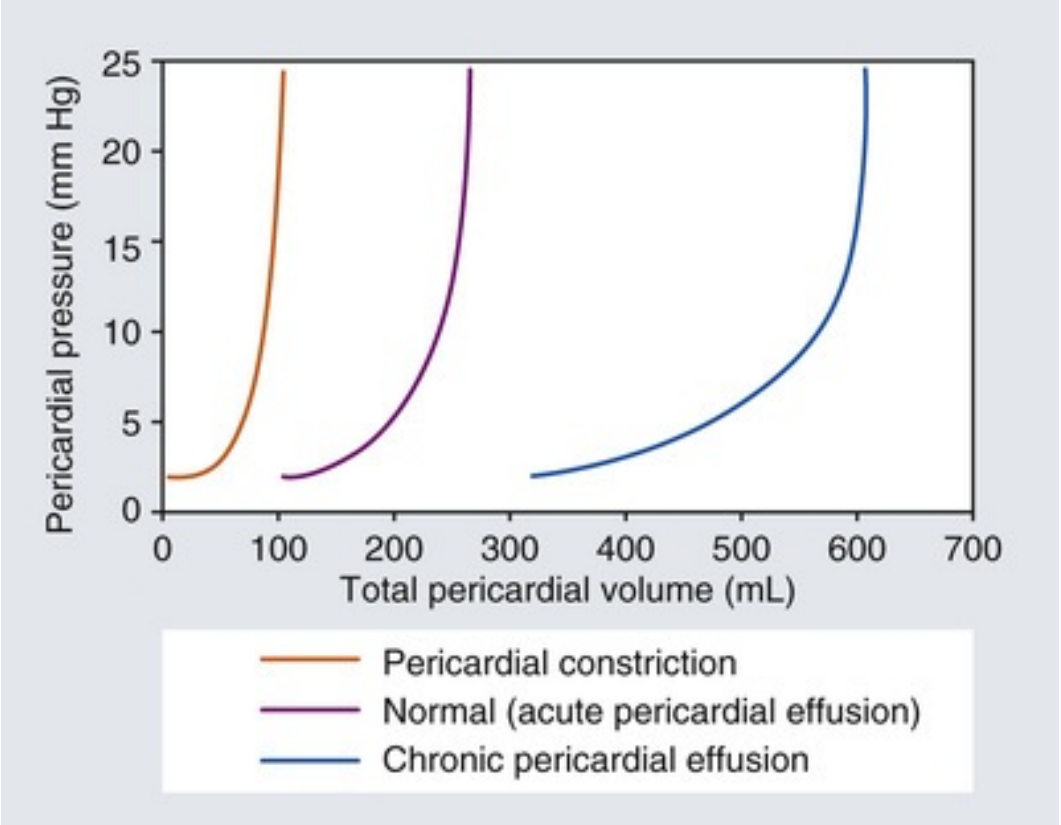
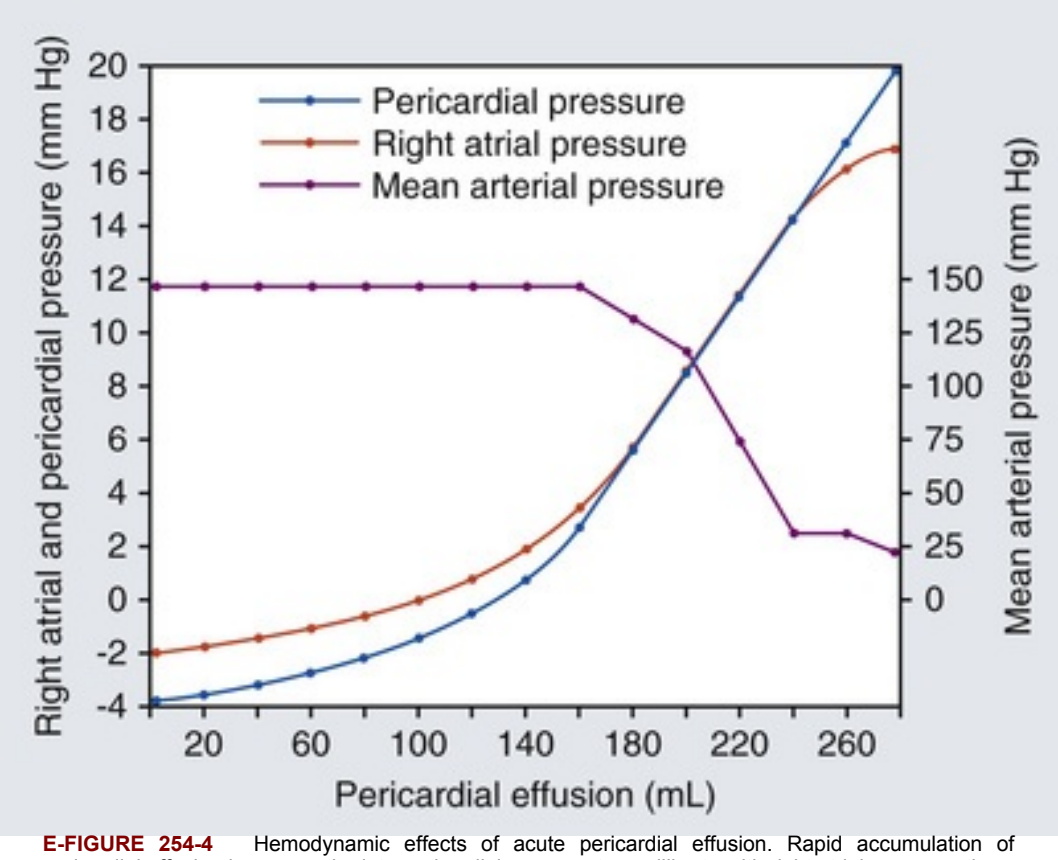


FIGURE 254-5 Effects of acute pericardial effusion, chronic pericardial effusion, and constrictive pericarditis on intrapericardial pressure. Intrapericardial pressure increases dramatically with only 50-150 mL of pericardial effusion in the acute setting. During chronic, slow accumulation of large volumes of pericardial effusion, the pressure volume curve is shifted to the right due to pericardial stretching and pericardial hypertrophy to accommodate large volume of fluid without a marked increase in pressure. Conversely, in constrictive pericarditis, the pressure volume curve is shifted to the left, due to the noncompliant, stiff pericardium, which operates on a steep curve of dramatic increases in pericardial pressure for slight increases in pericardial volume. (Obtained with permission from Kittleson MD, Kienle RD: *Small animal cardiovascular medicine*, St Louis, 1998, Mosby, Chapter 25, p 414.)



E-FIGURE 254-4 Hemodynamic effects of acute pericardial effusion. Rapid accumulation of pericardial effusion increases the intrapericardial pressure to equilibrate with right atrial pressure; then, both rise steeply, leading to arterial hypotension and cardiogenic shock. (Obtained with permission from Kittleson MD, Kienle RD: *Small animal cardiovascular medicine*, St Louis, 1998, Mosby, Chapter 25, p 414.)

Chronic cardiac tamponade is manifested as elevated right heart diastolic pressures and right-sided congestive heart failure. Although all cardiac chambers are subjected to the same increased intrapericardial pressure, the increase in diastolic pressure required to cause leaking of systemic capillaries is much lower (10-15 mm Hg) than it is for pulmonary capillaries (25-30 mm Hg), so right heart failure is seen rather than a combination of left and right heart failure. Chronic, slow accumulation of pericardial effusion causes the pericardium to stretch to accommodate often hundreds of milliliters of fluid without a clinically significant increase in pressure (see Figure 254-5). The precise mechanisms of pericardial expansion are uncertain and could include slipping of the layers of collagen followed by stretching of the wavy collagen fibers, or possibly fibroblast proliferation with new connective tissue deposition.[20] Based on the viscoelastic properties of pericardium, initial stretching of the pericardium causes straightening of the wavy collagen bundles with concomitant stretching of the elastin fibers, but when it is stretched further, there is an inextensibility due to the inelasticity of the straightened collagen fibers.

Neurohormonal activation in cardiac tamponade occurs in response to decreased cardiac output. This includes activation of the sympathetic nervous system and the renin angiotensin aldosterone system, in efforts to increase cardiac output. However, unlike other forms of cardiac disease with elevated diastolic filling pressures, atrial natriuretic peptide does not increase in cardiac tamponade, which limits natriuresis and sustains volume overload and elevated venous pressure.[21,56,57] Consequently, with chronic pericardial effusion, signs of increased systemic venous pressure predominate and manifest primarily as right-sided congestive heart failure.

Pulsus Paradoxus

Pulsus paradoxus is defined as a fall of systolic arterial blood pressure >10 mm Hg during the inspiratory phase of normal breathing (Figure 254-6).[22] The paradox described by Adolf Kussmaul in 1873 was a "pulse simultaneously slight and irregular, disappearing during inspiration and returning upon expiration," despite the continued presence of the cardiac impulse during both respiratory phases.[22] Pulsus paradoxus is an

accentuation of the normal small decline of left ventricular stroke volume and systemic arterial blood pressure that occurs with inspiration. Normally during inspiration, intrathoracic pressure decreases and blood flows preferentially into the low pressure, highly compliant vena cavae, pulmonary veins, right atrium, and right ventricle. Blood pooling in the right heart and pulmonary veins reduces preload to the left heart and consequently reduces left ventricular stroke volume. In humans, left ventricular stroke volume normally decreases by an average of 7% during inspiration, and this is associated with a 3% drop in systolic arterial blood pressure. Right ventricular stroke volume, on the other hand, increases during inspiration due to increased right-sided filling.

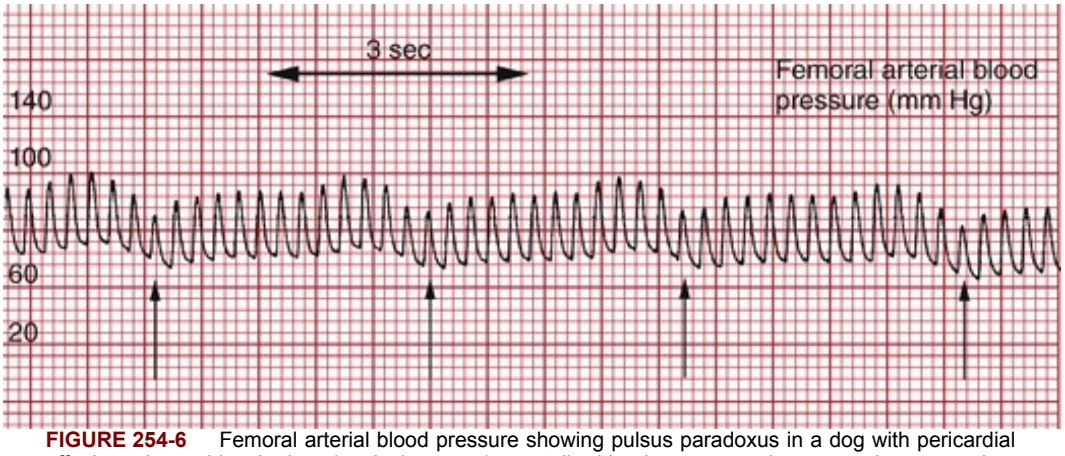


FIGURE 254-6 Femoral arterial blood pressure showing pulsus paradoxus in a dog with pericardial effusion. At end-inspiration (vertical arrows), systolic blood pressure decreases by more than 10 mm Hg and pulse pressure narrows.

Reciprocal and phasic changes with respiration in left and right ventricular filling and stroke volume are exaggerated in the presence of pericardial effusion. Outward expansion of the ventricles is limited in the face of pericardial effusion, and any increase in the volume of one ventricle can only occur at the expense of the other, a process called ventricular interdependence. Thus, greater right ventricular filling during inspiration increases the pressure within the pericardial sac and pushes the interventricular septum leftward, both of which reduce the left ventricular chamber size, reducing left ventricular filling. This interaction between the ventricles is superimposed upon the normal decrease in left ventricular stroke volume that occurs during inspiration, and leads to pulsus paradoxus. In the clinical veterinary setting, pulsus paradoxus can be challenging to identify, especially when intrathoracic pressures change rapidly, as they do with panting.

Etiology

Pericardial effusion is caused by a wide spectrum of disorders, including neoplastic, infectious, metabolic and toxic, cardiovascular, traumatic, and idiopathic.[23-26] In a case series of 107 dogs with pericardial effusion, the following etiologies were identified: HSA (33.6%; n = 36/107), idiopathic pericarditis (19.6%; n = 21/107), mesothelioma (14.0%; n = 15/107), chemodectoma (8.4%; n = 9/107), thyroid gland adenocarcinoma (5.6%; n = 6/107), infective pericarditis (4.7%; n = 5/107), lymphoma (2.8%; n = 3/107), sarcoma (1.8%; n = 2/107), and carcinomatosis, ruptured left atrium secondary to severe mitral valve regurgitation, sterile foreign body, and granuloma (each 0.9% and each n = 1/107).[23]

Neoplasia

Neoplastic disease is the most common cause of pericardial effusion in dogs. In a case series of 107 dogs with pericardial effusion, 71% of cases were caused by neoplastic disease.[23] HSA is the most common neoplastic cause of pericardial effusion, and it has a predilection for the right atrium (88% of right atrial masses were HSA[23]; Figure 254-7), and uncommonly occurs at the heart base (13% of heart base masses were HSA[23]).

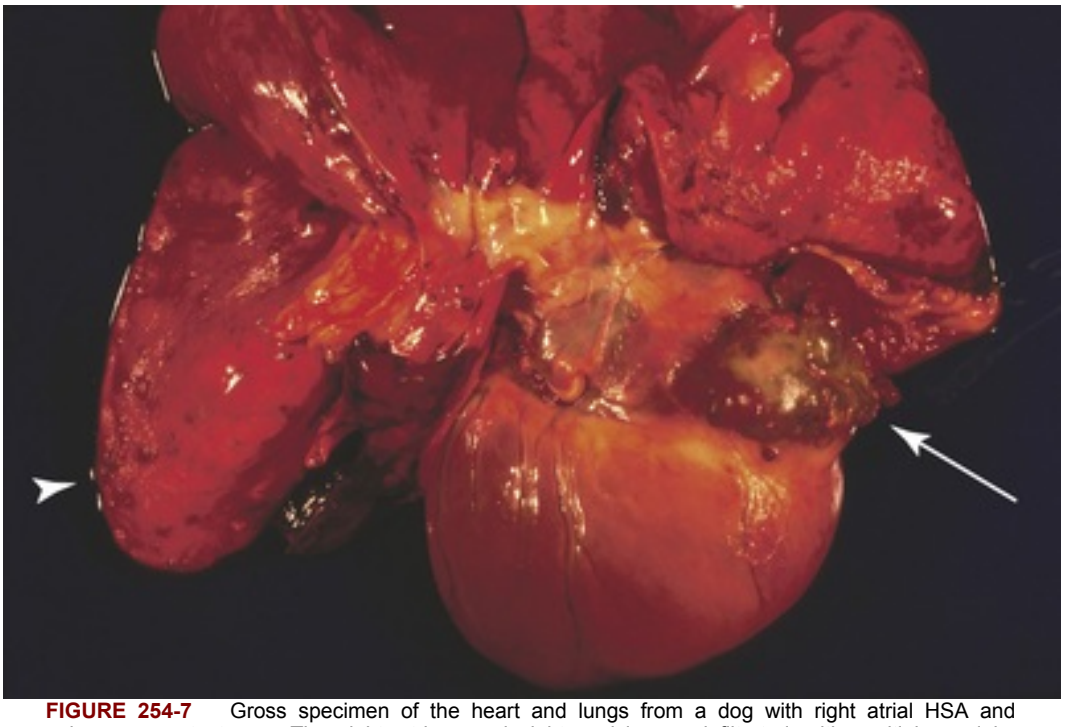


FIGURE 254-7 Gross specimen of the heart and lungs from a dog with right atrial HSA and pulmonary metastases. The right atrium and right auricle are infiltrated with multiple nodular hemorrhagic masses (arrow), characteristic of cardiac HSA. There are many small metastatic nodules throughout the pulmonary parenchyma (arrowhead), which were not visible on thoracic radiographs.

Heart base masses are characterized by a mass growing on the ascending aorta at the aortic body (Figure 254-8), and are caused by an array of neoplastic etiologies, including neuroendocrine tumors (chemoreceptor cell tumors including aortic body tumor, chemodectoma, non-chromaffin paragangliomas; 9/23 [39.1%]), thyroid gland adenocarcinoma (6/23 [26.1%]), mesothelioma (5/23 [21.7%]), and HSA (3/23 [13%]).[23] Mesothelioma typically causes a neoplastic seeding of the serosal surfaces of the pericardium and often pleura, without causing a discrete cardiac or pericardial mass, although discrete masses can be seen with mesothelioma at the heart base or rarely the right atrium. Other less common neoplastic causes of pericardial effusion are lymphoma and sarcomas (e.g., undifferentiated, rhabdomyosarcoma, fibrosarcoma).[23]

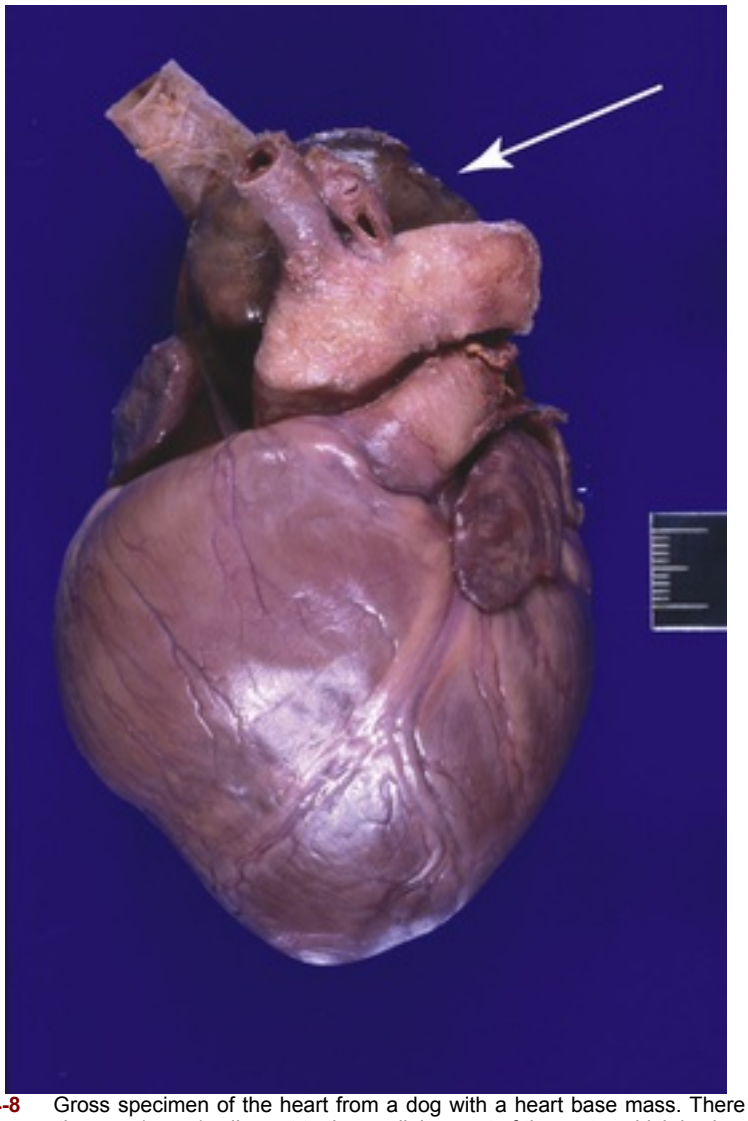


FIGURE 254-8 Gross specimen of the heart from a dog with a heart base mass. There is a large, well-defined, smooth mass (arrow) adherent to the medial aspect of the aorta, which is characteristic of a heart base mass.

Metastasis of cardiac tumors is common, and appears equally common among different neoplastic etiologies: HSA (67.9%; n = 19/28), mesothelioma (55.6%; n = 5/9]), thyroid gland adenocarcinoma (50%; n = 2/3), and chemodectoma (66.7%; n = 4/6).[23] Concurrent splenic HSA occurs in approximately 30% of dogs with cardiac HSA based on 2 different case series.[23,27] The lungs are the most common site of metastasis for the combined group of all neoplastic etiologies (30.5%; n = 18/59). In dogs with cardiac HSA, the most common sites of metastasis include the lungs (42.8%; n = 12/28), spleen (28.6%; n = 8/28), liver (28.6%; n = 8/28), and kidneys (14.3%; n = 4/28).[23] The most common sites of metastasis in dogs with mesothelioma include the intrathoracic lymph nodes (66.7%; n = 6/9), lungs (22%; n = 2/9), and pleura (22%; n = 2/9).[23] In dogs with neuroendocrine tumors, 50% of dogs (n = 3/6) had metastases involving the lungs, followed by the spleen (16.7%; n = 1/6) and liver (16.7%; n = 1/6).[23] The most common site of metastasis for dogs with thyroid gland adenocarcinoma was the pericardium (66.7%; n = 2/3), followed by the lungs (33.3%; n = 1/3), transcoelomic (33.3%; n = 1/3 dogs), and myocardium (33.3%; n = 1/3).[23]

Idiopathic Pericarditis

Second to HSA, idiopathic (hemorrhagic) pericarditis is the next-most-common cause of pericardial effusion in dogs (etiology in 20-75% of cases).[23,28,29] True to the name, the cause of idiopathic pericarditis is unknown, but is postulated to be pericardial inflammation secondary to viral or immune-mediated disease. Inflammation from mononuclear cell infiltration and fibrosis appear to target the pericardial blood vessels

and lymphatics.[30] Damaged pericardial blood vessels are the likely source of the hemorrhagic pericardial effusion. The effusion typically accumulates slowly, making a common clinical presentation of chronic cardiac tamponade. This process may spontaneously resolve after pericardiocentesis in approximately half of cases, and the remaining half suffer from recurrent pericardial effusion within days to a couple of years and require a subtotal pericardectomy. Constrictive pericarditis is a possible chronic sequela to idiopathic pericarditis.

Infective Pericarditis

Infective pericarditis is an uncommon cause of pericardial effusion in dogs, and was reported in only 4.7% of 107 dogs with pericardial effusion.[23] A common nidus of infection is migrating grass awns (3/5 dogs in that case series) or other intrapericardial penetrating foreign body. The pericardial effusion typically appears flocculent and suppurative grossly, which is different from the typically dark, hemorrhagic effusion of other causes, and pericardial fluid analysis typically distinguishes infective pericarditis from other causes of pericardial effusion (see below). Bacterial or fungal agents that have been reported most commonly include: *Bacteroides* spp., *Actinomyces* spp., *Streptococcus canis*, *Pasteurella* spp., *Peptostreptococcus* spp., and *Coccidioides immitis.*

Cardiovascular Causes

A less common cause of pericardial effusion is rupture of the left atrium in dogs with severe mitral regurgitation from myxomatous mitral valve disease. Endocardial tears can occur in dogs with severely elevated left atrial pressure and dilation, accompanied by jet lesions from the high velocity mitral regurgitation jet hitting the left atrial wall. The clinical scenario is one of acute cardiac tamponade, weakness, cardiogenic shock, and often acute death. Small breed dogs with severe mitral valve degeneration are at greatest risk for left atrial tear, with Shetland Sheepdogs, male Poodles, Dachshunds, and Cocker Spaniels appearing to have a higher predilection for left atrial rupture.[31,32]

Pericardial effusion is frequently detected in dogs and cats with congestive heart failure, but seldom in sufficient quantity (and essentially never with sufficiently high intrapericardial pressure) to cause significant hemodynamic compromise.

Metabolic and Toxic

Metabolic and toxic causes of pericardial effusion are rare. They include pericardial effusion secondary to uremia and cholesterol-based pericardial effusion associated with hypothyroidism.[33] Coagulation disorders leading to pericardial effusions occasionally occur with anticoagulant rodenticide intoxication and secondary to disseminated intravascular coagulation, warfarin intoxication, and other coagulopathies.[4,34] Although a bleeding disorder is an uncommon cause of pericardial effusion, assessment of bleeding status (blood clotting times, platelet count) is necessary prior to pericardiocentesis.

Patient History and Clinical Characteristics

Two different clinical scenarios exist in patients with pericardial effusion causing overt clinical signs: acute cardiac tamponade and chronic cardiac tamponade. Patients with acute cardiac tamponade typically have a rapid onset of weakness or collapse, prompting an emergency visit, with little prior history of abnormalities. Patients with chronic cardiac tamponade often have a vague history of inappetence, lethargy, exercise intolerance, progressive abdominal distension, and respiratory abnormalities such as tachypnea or dyspnea.

Male, medium- to large-breed dogs, particularly Golden Retrievers, are overrepresented in dogs that develop pericardial effusion. However, any size, sex, or breed of dog may develop pericardial effusion. As expected, dogs with cardiac masses are typically older (mean, 9.7 years) than dogs without masses (mean, 7.9 years).[23] Middle-aged to older English Bulldogs, Boxers, and Boston Terriers are predisposed to neuroendocrine tumors of the heart base (chemodectomas), but these tumors also occur in nonbrachycephalic breeds. Chronic hypoxia-induced hyperplasia and neoplasia of chemoreceptors may explain the predisposition of brachycephalic dogs to aortic body tumors.[35]

Physical Examination Abnormalities

Muffled heart sounds, a weak pulse, tachycardia, and pale mucous membranes are the hallmark physical abnormalities of acute cardiac tamponade. In addition to muffled heart ± lung sounds, signs of right heart failure, such as distended jugular veins or jugular pulsation, a positive hepatojugular reflux test,

hepatomegaly, and ascites with a ballottable fluid wave (see ch. 17) are typical abnormalities in animals with chronic cardiac tamponade. In a case series of 107 dogs with pericardial effusion, 67 dogs (62.6%) had evidence of right heart failure.[23] More than half of dogs with right heart failure (36/107 [33.6%]) had concurrent pleural effusion and ascites, while fewer had isolated ascites (17/107 dogs [15.9%]) or pleural effusion (14/107 dogs [13.0%]).[23] There was no difference between dogs with neoplastic or non-neoplastic causes with regard to presence of bicavitary effusion, pleural effusion, or ascites.[23] Cardiac arrhythmias may be auscultated in some cases, the most common being sinus tachycardia due to cardiogenic shock. A left apical systolic murmur should be present in dogs with left atrial rupture, and is typically softer in intensity compared to previous examinations. Pulsus paradoxus, though uncommon (10-20% of cases), may be identified in dogs with cardiac tamponade and a regular slow respiratory pattern (i.e., not panting).

Diagnosis

Echocardiography is the essential diagnostic test to diagnose pericardial effusion, and to help differentiate etiologies of pericardial effusion. Radiographs and electrocardiograms are insensitive and nonspecific, but may increase suspicion for pericardial disease in some cases.

Thoracic Radiographs

Although the quintessential thoracic radiographic abnormalities of globoid cardiomegaly with crisp cardiac margins are classic for pericardial effusion (Figure 254-9), the reality is that radiographs are both insensitive and nonspecific for pericardial effusion. In fact, radiographic appearance of globoid cardiac silhouette was only 41.9% sensitive and 40% specific for diagnosis of cardiac tamponade and pericardial effusion in 50 dogs in one series, and was present in approximately half of 107 dogs in another study.[23,36] Cardiomegaly, defined as vertebral heart size >10.7, also was insensitive (sensitivity = 77.6%) and nonspecific (specificity = 47.8%) for cardiac tamponade, likely due to rapid accumulations of small volume pericardial effusion in acute tamponade.[36] Pulmonary hypoperfusion and diminished caudal vena caval size are common in dogs with cardiogenic shock from acute cardiac tamponade. Conversely, dilated caudal vena cava, loss of abdominal detail, and pleural effusion may be seen with more chronic cardiac tamponade, and often are accompanied by the more classical globoid cardiomegaly appearance. Identification of a cardiac mass on radiographs (see Figure 254-9) is insensitive but specific (100% in one study), and was identified in 10 of 63 dogs with cardiac masses.[23] Pulmonary metastases commonly occur (see Figure 254-9), but radiographs have a low detection rate of only 1/3 of cases with pulmonary metastases confirmed at necropsy or thoracotomy.[23]

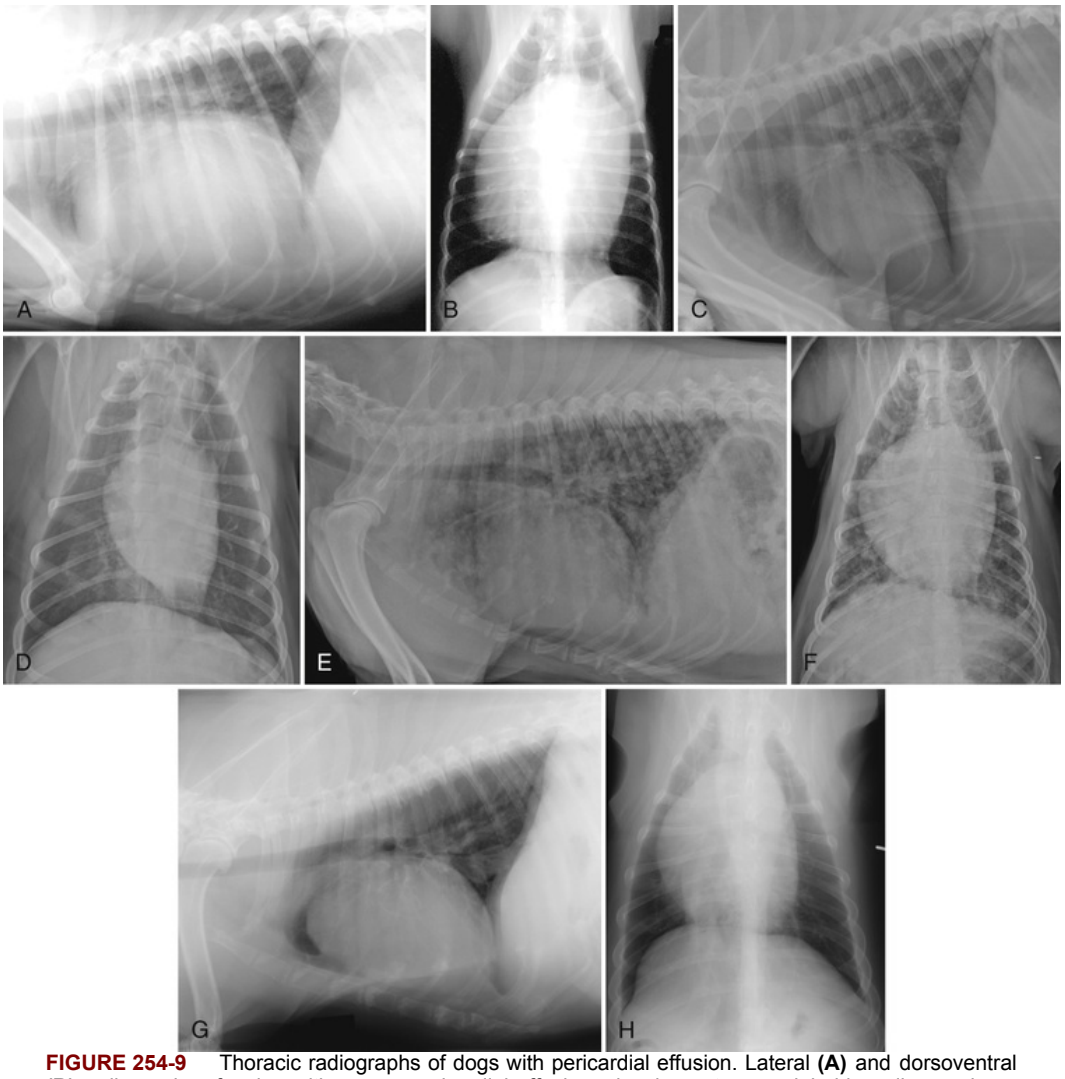


FIGURE 254-9 Thoracic radiographs of dogs with pericardial effusion. Lateral **(A)** and dorsoventral **(B)** radiographs of a dog with severe pericardial effusion, showing extreme, globoid cardiomegaly as well as crisp cardiac margins supportive of the diagnosis of pericardial effusion. There is loss of abdominal detail suggestive of ascites. Radiographs obtained post-pericardiocentesis show normalization of cardiac silhouette **(C** and **D).** Radiographs from another dog with pericardial effusion show mild globoid cardiomegaly due to acute pericardial tamponade and presence of a diffuse nodular pulmonary pattern consistent with pulmonary metastases (**E** and **F**); see Video 254-4 for echocardiogram. Radiographs from a dog with a large heart base mass (**G** and **H**) show a bulge at the cranial cardiac waist at the heart base on the lateral view, with less obvious changes on the DV view, and mild globoid cardiomegaly is present.

Tomographic Imaging

The use of multidetector computed tomography increases the diagnostic sensitivity for detection of pulmonary metastases compared to thoracic radiography, but does not increase the diagnostic yield for detection of cardiac masses compared to transthoracic echocardiography.[37] Likewise, cardiac magnetic resonance imaging (MRI) does not increase diagnostic yield for detection of cardiac masses in dogs with pericardial effusion compared to echocardiography, but may provide descriptive information on extent of disease, location, and tumor characteristics if performed by specialists with extensive additional training in cardiac MRI.[38]

Electrocardiography

An electrocardiogram is indicated for any patient with an arrhythmia auscultated on physical examination, but is not an accurate diagnostic test for pericardial effusion (see ch. 103). Abnormalities are variably present, and in a series of 107 dogs included, in order of occurrence: electrical alternans (30/107 dogs [28.0%]), sinus tachycardia (30/107 dogs [28.0%]), dampened QRS voltage (R wave < 1 mV) (26 dogs [24.3%]), and ventricular

arrhythmia (14/107 dogs [13.1%]).[23] Electrical alternans is the beat-to-beat variation in QRS amplitude caused by the heart swinging back and forth in a large volume of pericardial effusion, and is rather specific for pericardial effusion in dogs (Figure 254-10). Dampening of the QRS voltages is due to pericardial effusion insulating the electrical signal from being transmitted to the body surface, and it also may occur with pleural effusion, obesity, large thoracic masses, or hypothyroidism. Other less common electrocardiographic abnormalities in dogs with pericardial effusion can include supraventricular tachycardia (3/107 dogs [2.8%]), premature atrial complexes (2/107 dogs [1.9%]), atrial fibrillation (2/107 dogs [1.9%]), and ST segment changes (2/107 dog [1.9%]).[23]

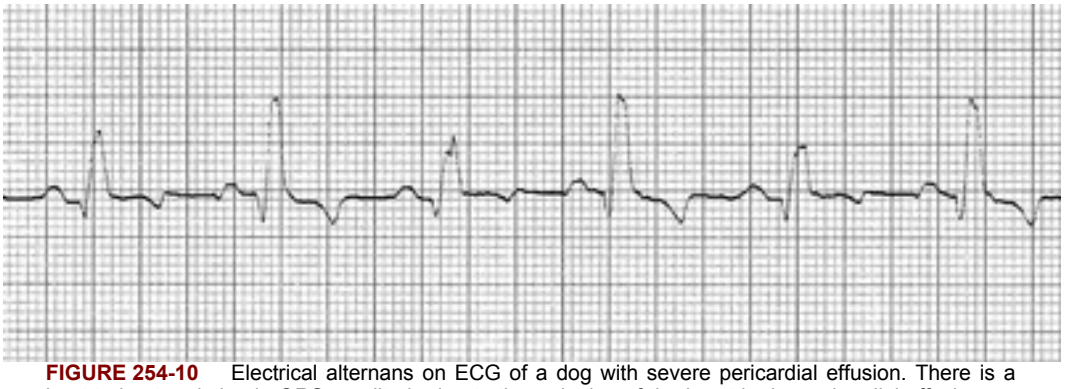
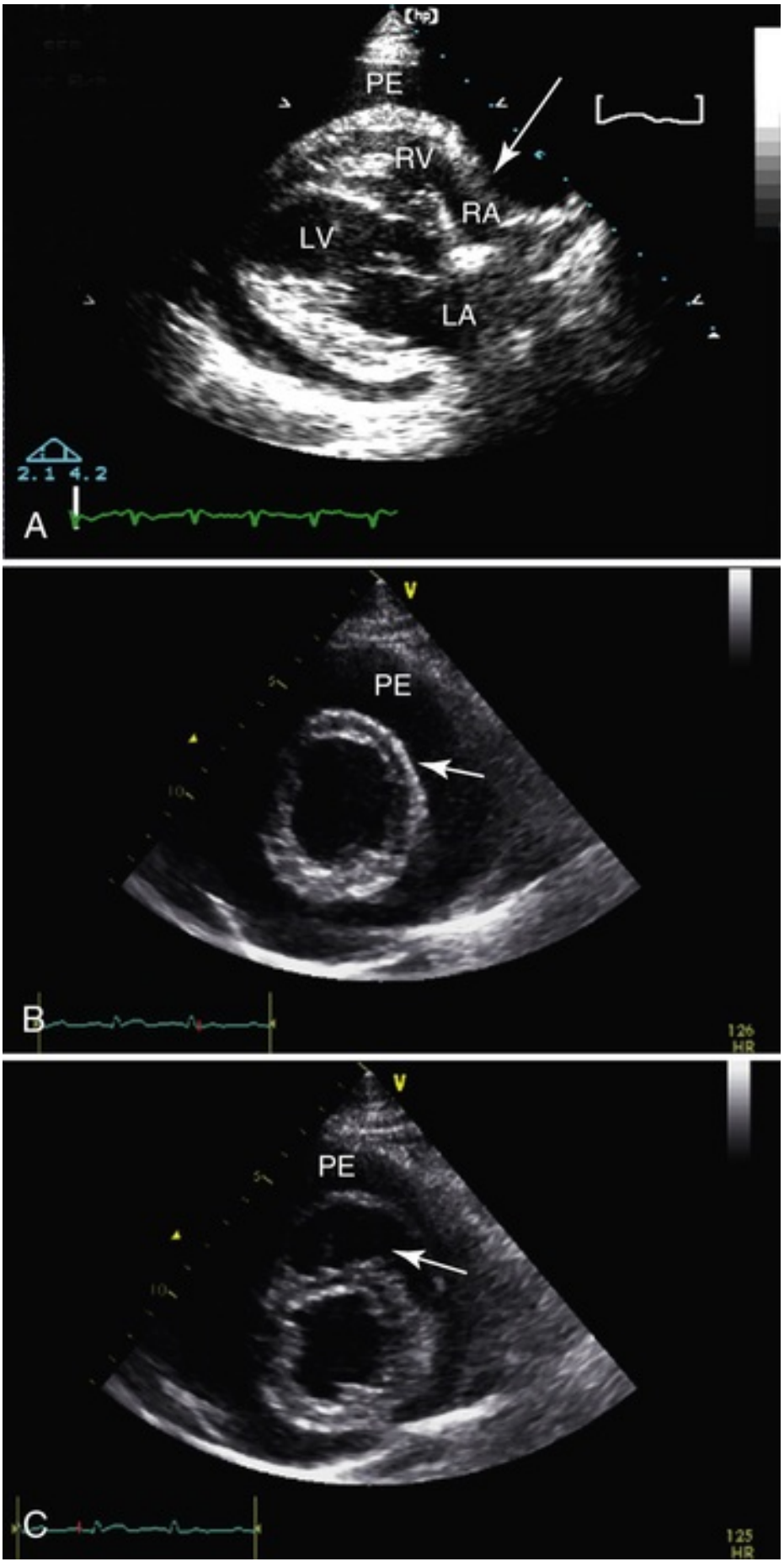


FIGURE 254-10 Electrical alternans on ECG of a dog with severe pericardial effusion. There is a beat to beat variation in QRS amplitude due to the swinging of the heart in the pericardial effusion, as well as dampened QRS complexes (<1 mV). 50 mm/sec; 1 cm = 1 mV.

Echocardiography

Echocardiography is the essential test not only to confirm the diagnosis of pericardial effusion on a triage-level scan, but, using higher level scans, to provide additional information on possible etiology of the effusion, whether pericardiocentesis is needed, and if there is underlying structural or functional cardiac disease (see ch. 104). Echocardiographic detection of a cardiac mass is sensitive (82%) and specific (100%) when performed by a cardiologist, which is similar whether the mass is right atrial (82% and 99%, respectively) or heart base (74% and 98%, respectively).[23] Repeat echocardiographic evaluation within weeks to months increases sensitivity (88%) for detection of cardiac masses.[23]

Pericardial effusion appears as an anechoic space surrounding the heart, within the pericardial space. The pericardium is seen external to the anechoic fluid, and is often highlighted by the concurrent presence of pleural effusion. Along with characteristic physical examination findings, echocardiographic diagnosis of cardiac tamponade is important to help define treatment strategies and timing of pericardiocentesis. A relatively low pericardial fluid volume can cause acute tamponade if it occurs very quickly, as may be seen in acute hemorrhage from HSA. Conversely, in cases of slowly accumulating pericardial effusion, there may be an extremely large volume of pericardial effusion that ultimately causes chronic tamponade and right heart failure. Echocardiographic evidence of cardiac tamponade includes diastolic compression of the right atrium with concave bowing of the wall inward into the right atrial chamber, and often right ventricular compression or collapse seen as an inward bowing of the right ventricular free wall or right ventricular chamber obliteration in severe tamponade (E-Figure 254-11; Video 254-2). The left ventricle appears underloaded, with a reduced chamber size, especially in cases of acute cardiac tamponade. Chronic tamponade also often causes hepatic venous distension, generalized hepatomegaly, ascites, and pleural effusion. Pulsus paradoxus may be diagnosed echocardiographically using pulsed wave Doppler interrogation of the aortic blood flow velocity, which, as described above, shows a cyclical reduction in aortic blood flow velocity during inspiration and increase in velocity during expiration (and the converse for pulmonic blood flow velocities).


PE
RV
RA
LV
LA
2.1 4.2
A
PE
B
126
HR
PE
C
125
HR

E-FIGURE 254-11 Echocardiogram of a dog with cardiac tamponade. This right parasternal long-axis view **(A)** shows pericardial effusion and collapse of the right atrial free wall (arrow) consistent with cardiac tamponade. The right parasternal short-axis view **(B)** shows severe compression and obliteration of the right ventricle (arrow) during diastole, due to cardiac tamponade, but the right ventricular chamber (arrow) is visible during systole **(C)** when intracardiac pressures are higher than intrapericardial pressure. *LA*, Left atrium; *LV*, left ventricle; *PE*, pericardial effusion; *RA*, right atrium; *RV*, right ventricle.

Careful examination of all chambers, with particular focus on the heart base and right atrium/auricle, is needed to evaluate for cardiac masses. Masses typically are characterized as heart base, right atrial/auricular, or other. The reason for this characterization is that there is a predilection of tumor types for anatomic locations in the heart and there is a different biologic behavior for each of the different neoplastic etiologies. For example, 88% of right atrial masses in a case series were HSA, whereas heart base masses are more likely to be neuroendocrine tumors (40%) or thyroid adenocarcinoma (25%).[23] Despite the generalization of tumor predilections for right atrium and heart base, there is an overlap of tumor etiologies at each location. For example, right atrial masses other than HSA include the following (each accounting for 2.5% of cases): neuroendocrine tumor, thyroid adenocarcinoma, mesothelioma, lymphoma, and sarcoma.[23] Similarly, heart base tumors other than neuroendocrine tumors or thyroid adenocarcinoma include mesothelioma (20%) and HSA (15%).[23]

The echocardiographic tissue characteristics of right atrial or auricular HSA consist of an irregular, heterogeneous mass that moves with the chamber, and has intratumoral hypoechoic or cavitary spaces consistent with hemorrhage. The mass may be localized to the right auricle, which must be visualized using the left cranial parasternal long-axis view (Figure 254-12; Videos 254-3 and 254-4), or more commonly may extend along the right atrial wall and/or right atrioventricular groove (Videos 254-3 and 254-5). Sometimes, there are concurrent right atrial and heart base masses, most likely from spread of the primary mass but rarely from two different neoplastic causes. Sometimes, right atrial masses penetrate into the right atrial lumen, and can obstruct venous return to the right atrium or impair right ventricular filling (see Videos 254-3 and 254-5; see also ch. 122).

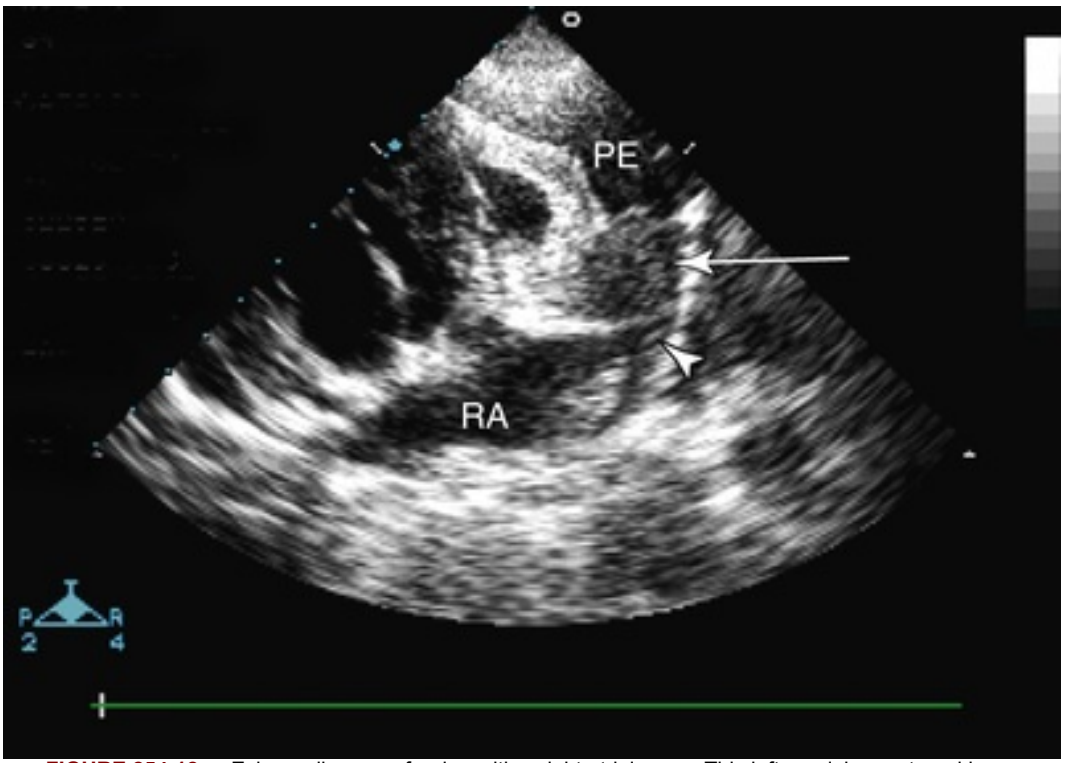


FIGURE 254-12 Echocardiogram of a dog with a right atrial mass. This left cranial parasternal long-axis view shows a heterogeneous, mottled right auricular mass (arrow) as well as pericardial effusion (PE). Arrowhead indicates the right auricle. *RA*, Right atrium.

Heart base masses that are neuroendocrine tumors usually are homogeneous, encapsulated masses growing from the ascending aorta, adjacent to but separate from either the left atrium or right atrium (Figure 254-13; Video 254-6). Since heart base masses comprise a variety of neoplastic etiologies, echocardiographic characteristics also may vary. Some heart base masses are small and easy to overlook unless the ascending aorta is carefully examined in the right parasternal long-axis left ventricular outflow tract view as well as short-axis views along the base of the heart. Other heart base masses can be so large that the site of origin is challenging to determine. Large heart base masses may externally compress the right ventricular outflow tract or pulmonary artery in some cases. Sometimes, heart base masses do not cause pericardial effusion, and are incidentally diagnosed based on suspicion of a heart base mass on radiographs or during workup of a heart murmur.

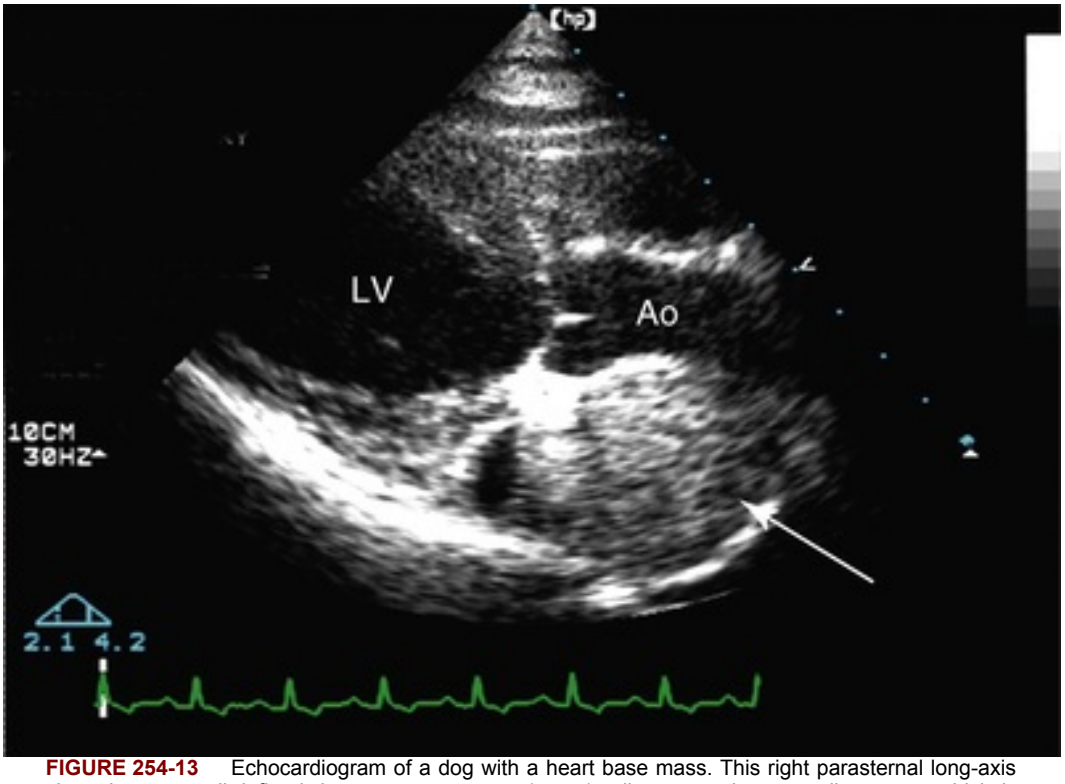


FIGURE 254-13 Echocardiogram of a dog with a heart base mass. This right parasternal long-axis view shows a well-defined, homogeneous mass (arrow) adherent to the ascending aorta, which is characteristic of a heart base mass. *Ao*, Aorta; *LV*, left ventricle.

The presence of pericardial effusion greatly facilitates the detection of intrapericardial masses, especially cardiac HSA and heart base tumors, because fluid forms an anechoic zone around the right atrium and auricle, as well as the ascending aorta. Consequently, if the clinical condition permits, pericardiocentesis should be deferred until a thorough echocardiographic examination has been completed. However, in dogs with cardiac tamponade and cardiovascular collapse, pericardiocentesis should not be delayed as it is a lifesaving procedure.

Pericardial effusion secondary to left atrial rupture accompanies echocardiographic evidence of myxomatous mitral valve disease and severe left atrial dilation (see ch. 251). An elongated hyperechoic thrombus usually is visualized extending from the epicardial surface of the left atrium into the pericardial space (Video 254-7).

In cases where no mass is seen, the main differential diagnoses include idiopathic pericarditis, mesothelioma, infective pericarditis, or a mass that is too small or too remote to be imaged. It is impossible to distinguish between idiopathic pericarditis and mesothelioma by echocardiography. Diagnosis requires histopathologic and immunohistochemical evaluation of the pericardium to help differentiate these two diseases in dogs with recurrent pericardial effusion that undergo pericardectomy. Sometimes, a definitive diagnosis of mesothelioma is impossible, but the suspicion is increased in dogs with recurrent pleural effusion within 4 to 6 months of subtotal pericardectomy.

Pericardial Fluid Analysis

Pericardial fluid analysis with cytologic evaluation typically is nonspecific,[39] and the fluid usually is characterized as hemorrhagic. Nevertheless, fluid analysis remains an essential diagnostic step to diagnose infective pericarditis and certain neoplastic causes such as lymphoma. Pericardial fluid may be characterized as hemorrhagic (40/47 [85%]), suppurative inflammatory (6/47 [12.7%]), pyogranulomatous inflammatory (4/47 [8.5%]), modified transudative (2/47 [4.2%]), or chylous (1/47 [2.1%]). Pericardial cytology has been found to be nondiagnostic in 87-92.3% of dogs, yet was able to identify a specific neoplastic etiology in 4.6% of 250 dogs (n = 7 round cell neoplasia, n = 3 atypical epithelioid cells, n = 1 hemic neoplasia) and all cases of infective pericarditis (n = 8; 3.1%).[23,40] Therefore, despite a low diagnostic yield, it is essential to submit pericardial fluid for analysis. Mesothelial reactivity was identified in 25 of 47 (53.2%) dogs, and is not typically helpful to differentiate idiopathic pericarditis from mesothelioma. Since hyperreactive mesothelial cells may be inadvertently mischaracterized as mesothelioma, the diagnosis of mesothelioma is made by histopathologic evaluation of the pericardium after pericardectomy or on necropsy. Among cardiac tumors, cardiac lymphoma is unique because cytologic evaluation of the pericardial fluid establishes the diagnosis in many cases (11/12 dogs [88%] in one case series) and the tumor may be amenable to combination chemotherapy.[35,38,55] Aerobic and anaerobic culture of pericardial effusion should be submitted in cases with gross evidence of flocculent light-colored fluid, and/or when fluid is characterized as an exudate on fluid analysis. Serologic testing for *C. immitis* is indicated in dogs with inflammatory pericardial effusion that live in endemic areas (see ch. 232). Pericardial fluid pH has a wide overlap between neoplastic and non-neoplastic etiologies, and its measurement is not considered reliable.[41,42] Measurement of serum cardiac troponin I (cTn-I) has produced different results in different studies. Serum (cTn-I) is consistently higher in dogs with pericardial effusion than in normal dogs, but some results identify a higher level in dogs with HSA compared to dogs with other tumors or to non-neoplastic disorders, whereas other results do not demonstrate such a difference.[43-45]

Treatment

In patients with cardiac tamponade and hemodynamic compromise, pericardiocentesis and rapid intravenous fluid resuscitation are immediately lifesaving (see ch. 102). The timing of pericardiocentesis depends on the severity of cardiovascular compromise, and should not be delayed if cardiogenic shock is present. In stable patients, pericardiocentesis should be delayed if a high-level echocardiogram is possible, then performed after the echocardiogram. Abdominocentesis (see ch. 90) ± thoracocentesis (see ch. 102) may be palliative in patients with chronic cardiac tamponade and ascites or pleural effusion, respectively.

Approximately 50% of idiopathic pericarditis cases have recurrent pericardial effusion, which requires subtotal pericardectomy. In cases of recurrent pericardial effusion without an identifiable mass, subtotal pericardectomy is necessary, and histopathologic evaluation of the pericardium should be performed (often with special immunohistochemical stains) for differentiation of idiopathic pericarditis from mesothelioma. Subtotal pericardectomy is curative for idiopathic pericarditis: dogs with idiopathic pericarditis treated with subtotal pericardectomy never reached a median survival time during a 3 year study (100% survival rate), yet dogs with idiopathic pericarditis undergoing thoracoscopic pericardial window did much more poorly, with a disease-free interval of 11.6 months and a median survival time of 13.1 months.[46]

Mesothelioma may be clinically suspected during thoracotomy by the gross appearance of abnormal serosal surfaces of the pleura and pericardium, which mandates biopsy of pleura and lymph nodes. The median survival time of patients with mesothelioma undergoing subtotal pericardectomy was 10.3 months, and not significantly different from pericardial window (median survival time of 8.6 months). Intracavitary infusions of carboplatin have been used for treatment of mesothelioma, with sparse clinical reports published. A case report documented one dog that was disease-free 27 months after treatment with intrathoracic carboplatin and intravenous doxorubicin.[47] Another case report documented two dogs with peritoneal mesothelioma treated with intracavitary carboplatin and daily piroxicam who lived for 8 months and >3 years.[47,48]

Partial pericardectomy is indicated for dogs with heart base masses, as it relieves cardiac tamponade and is associated with a significant prolongation of survival time (median survival time of 730 days with pericardectomy versus 42 days without pericardectomy).[49] In that study of 24 dogs with aortic body tumors, only pericardectomy, and not other treatments including chemotherapy, was found to increase survival time.[49] A second study showed similar results.[50] Other additional treatments have not been assessed for efficacy. Three-dimensional conformal radiation therapy was performed in a dog with histopathologically

confirmed chemodectoma; there was >50% reduction in tumor volume 25 months after therapy, and the dog was still alive 42 months after therapy (after undergoing pericardectomy for recurrent pericardial effusion).[51]

Pericardectomy is controversial for dogs with presumptive HSA, unless it is combined with mass resection, which is rarely possible. In one study, partial or subtotal pericardectomy in dogs with all neoplastic causes combined resulted in disappointing survival rates of 2.7 and 3.8 months respectively.[46] In dogs with isolated right auricular HSA, surgical resection is a feasible option, followed by chemotherapy, yet results still remain underwhelming. In a small study of 23 dogs with surgically resected right atrial or right auricular HSA, administration of chemotherapy increased survival time (median survival time with chemotherapy and surgery 175 days versus 42 days with surgery alone).[52] A retrospective study evaluating 64 dogs with presumptive HSA (i.e., right atrial/auricular masses with a characteristic heterogeneous appearance) treated with doxorubicin compared to 76 dogs without doxorubicin showed an extension in overall survival time with doxorubicin treatment (116 days vs. 12 days, respectively), yet dogs in the doxorubicin treatment group underwent more pericardiocenteses and owners could have been more motivated to continue therapy than those in the no-treatment group.[53] Only 14% of doxorubicin-treated dogs had a probability of surviving >6 months. Neither group underwent pericardectomy or mass resection. Presence of metastases was not related to overall survival, but mass size and thrombocytopenia were negative prognostic indicators. Lastly, a retrospective study of dogs without surgical resection of cardiac HSA that were treated with doxorubicin ± other chemotherapies reported a median survival time of 139.5 days (range 2-302 days), yet no control group was evaluated for comparative purposes.[54] In the author's experience, recurrent acute hemorrhage and cardiac tamponade is common in dogs with cardiac HSA, and usually is lethal before the animal succumbs to metastatic disease.

Cardiac lymphoma is classified as stage V, substage b. Dogs with stage III lymphoma or higher and clinical signs (substage b) have a poor prognosis for remission and survival. In a retrospective study of 12 dogs with cardiac lymphoma and pericardial effusion that were treated with various combinations of pericardiocentesis, pericardectomy, and chemotherapy, median survival time was 41 days. However, three dogs were still alive 328 days after the initial diagnosis, suggesting that cardiac lymphoma does not always warrant a poor prognosis.[55]

Subtotal pericardectomy, postoperative chest tube drainage, and long-term (at least 6 months) antibiotic therapy is the treatment of choice for infective pericarditis. The prognosis is good for dogs undergoing pericardectomy and receiving long-term antibiotics.[56] Long-term antifungal treatment for many months to years may be necessary in dogs with *C. immitis* infections (see ch. 232).

Constrictive Pericarditis

Constrictive pericarditis occurs when the parietal pericardium, the visceral pericardium, or both develop(s) fibrosis, with or without fusion of the parietal and visceral layers to each other. This process decreases compliance and possibly intrapericardial volume (Figure 254-14). The fibrotic pericardium constricts the cardiac chambers and increases atrial and diastolic ventricular pressures. A small volume of pericardial fluid sometimes is present, in a process called constrictive-effusive pericarditis, such that for any mild increase in pericardial effusion volume, there is a dramatic increase in intrapericardial pressure. The pathophysiologic consequence of pericardial constraint is similar to chronic cardiac tamponade. Ascites is a consistent feature, and jugular venous distension is common.[57] Pulsus paradoxus is an uncommon finding in constrictive pericarditis, probably because the rigid, stiff pericardium does not transmit the respiratory variations of intrathoracic pressures to the heart as a structurally normal pericardium would. Causes of constrictive pericarditis are unclear, but case reports cite the following causes: previous idiopathic pericarditis, previous infective pericarditis (especially *C. immitis* infections), intrapericardial foreign body, osseous metaplasia of the pericardium, or idiopathic disease.[57-59] Medium- to large-breed dogs are most commonly affected.

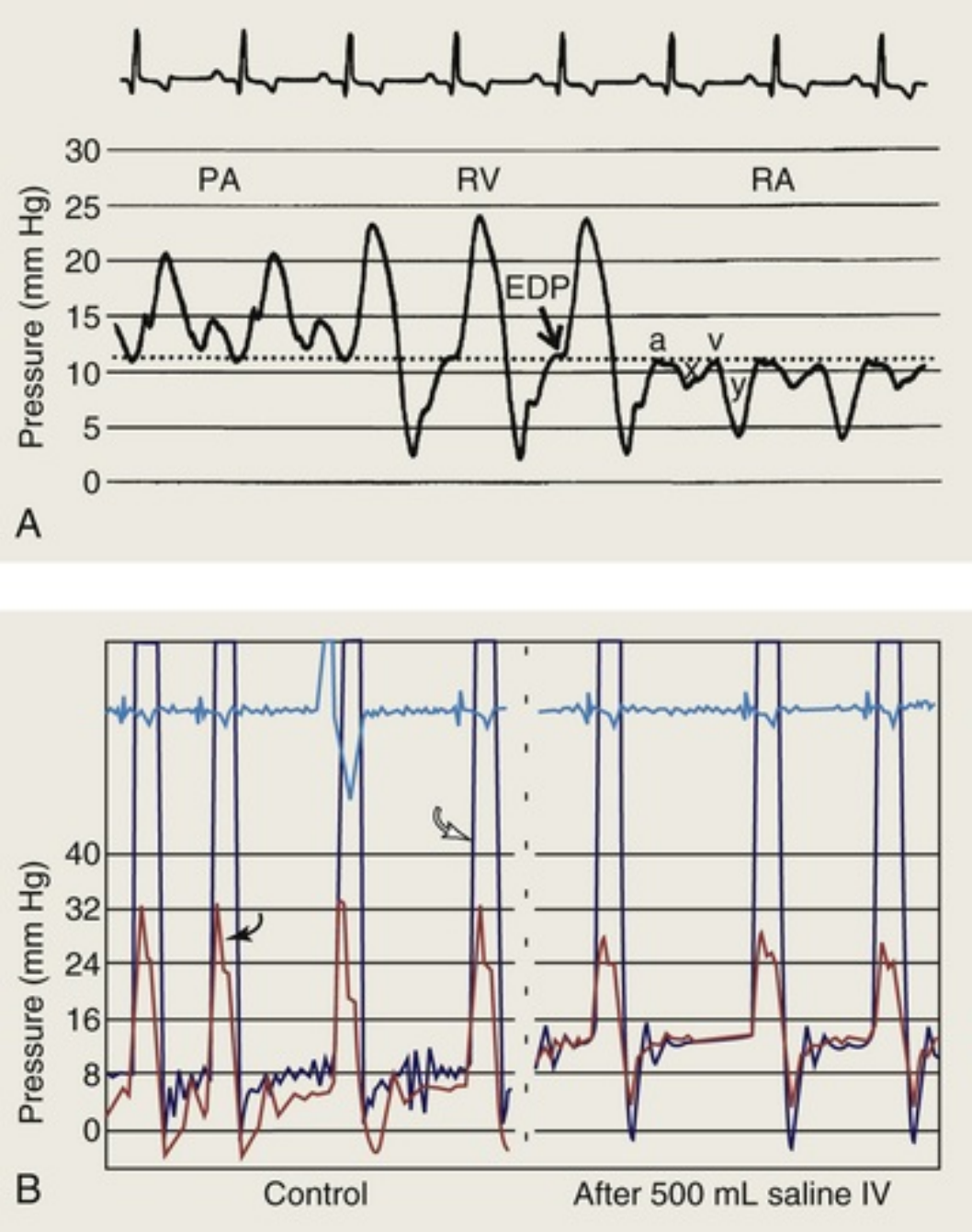


FIGURE 254-14 Hemodynamic abnormalities associated with constrictive pericarditis. **A,** Elevation and equilibration of end-diastolic pressure (EDP) in pulmonary artery (PA), right ventricle (RV), and right atrium (RA). Right atrial pressure waveform has an M-shaped pattern due to a reduced X descent and a prominent Y descent. **B,** Simultaneous recordings of left ventricular (open arrow) and right ventricular (solid arrow) pressures before and after saline infusion. Under control conditions, the pressure waveforms show slight elevations in end-diastolic pressures. Unmasking of pathognomic constrictive physiology occurs after rapid intravenous infusion of 500 mL saline, resulting in elevation and equilibration of left and right ventricular diastolic pressure, and emergence of the dip-and-plateau diastolic filling pattern. (From Sisson D, Thomas WP: Pericardial diseases and cardiac tumors. In Fox PR, et al, editors: *Textbook of canine and feline cardiology*, ed 2, Philadelphia, 1999, Saunders, pp 697-698.)

In contrast to other forms of pericardial disease, echocardiography is not sufficient to provide a diagnosis, and typically it shows minimal or no pericardial effusion and no right atrial and ventricular collapse, yet there is usually evidence of hepatic venous distension and ascites.

Diagnosis of constrictive pericarditis requires right heart catheterization. Pericardial constriction does not limit early active diastolic filling, but limits diastolic filling in mid-diastole as the heart is confined by the stiff

pericardium. This results in a characteristic "dip and plateau" pressure waveform (the square root sign) when measuring right ventricular diastolic pressures during cardiac catheterization (see Figure 254-14). The dip portion of the pressure tracing is the enhanced rapid early diastolic filling of the heart operating in low volumes not limited by the pericardial constraint. The plateau occurs once the chamber volume expands to be limited by the pericardial constriction, which creates a rapid increase in filling pressure in mid- to late diastole and cessation of diastolic filling, which may be more obvious during rapid saline intravenous infusion. A characteristic W- or M-shaped right atrial diastolic pressure tracing also is present in constrictive pericarditis, where there is accentuated early diastolic filling after ventricular systole (y descent), and a rapid decrease in RA pressure after atrial systole (x descent) (see Figure 254-14).

Treatment for constrictive pericarditis requires subtotal pericardectomy and removal of the constricting pericardium from the underlying myocardium if possible (Figure 254-15). Overall prognosis depends on whether the process is limited to the parietal pericardium (better prognosis) or if it extends to the visceral pericardium which may become adhered to the epicardial surface (grave prognosis). In a case series of 13 dogs, 8 dogs had parietal pericardial constriction, 5 dogs had visceral pericardial constriction, and parietal pericardectomy was successful in relieving the syndrome in 6 of 10 dogs.[57] Perioperative mortality was most often due to pulmonary thromboembolism in those cases. In cases where constrictive pericarditis is a complication of systemic *C. immitis* infection, adjunctive long-term antifungal therapy is necessary. In a retrospective study of 17 dogs with constrictive pericarditis from *C. immitis,* perioperative mortality was high (23.5%). However, surgery was successful in relieving clinical signs in some dogs for >2 years.[58]

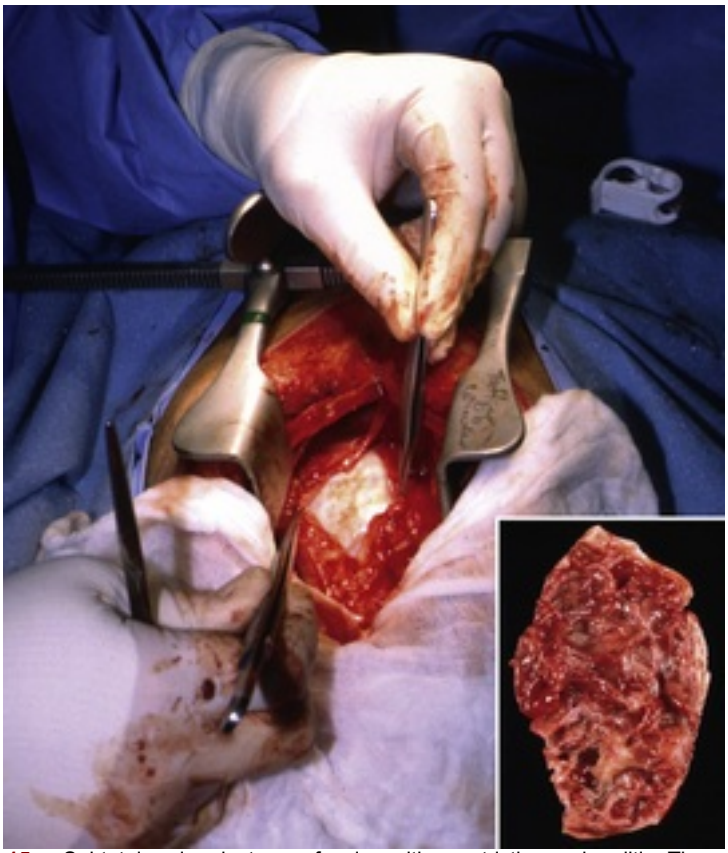


FIGURE 254-15 Subtotal pericardectomy of a dog with constrictive pericarditis. The pericardium is markedly thickened, irregular, constrictive, and fibrotic. Although the epicardial surface was pale, there was no visceral pericardial constriction, and a subtotal parietal pericardectomy was performed. Inset: gross specimen of resected, thickened pericardium.

Feline Pericardial Effusion

Pericardial effusion is the most common type of pericardial abnormality in cats, and is present in approximately 6% of feline cardiology patients.[60] Most cases are mild and not caused by pericardial disease

but by elevated intracardiac filling pressures secondary to congestive heart failure (44-75% of feline cases of pericardial effusion) through the same pathophysiologic mechanism as pleural effusion development in heart failure.[60,61] Unlike dogs, cats rarely develop pericardial effusion that is severe enough to cause cardiac tamponade or clinical signs, or require pericardiocentesis.[61,62] After congestive heart failure, neoplasia is the second most common cause of pericardial effusion in cats (19% of 83 cases, including lymphoma, adenocarcinoma, thymoma, and mesothelioma).[61] Cardiac neoplasia is a rare cause of pericardial effusion in cats, and reports include chemodectoma and rhabdomyosarcoma. Pericarditis is also rare in cats, and was only found in 3 of 83 cats in that case series.[61] Likewise, infective pericarditis is rare in cats, and reported causes of infection are *E. coli, Staphylococcus aureus, Enterococcus*, and *Actinomyces.* Other uncommon causes include: peritoneopericardial diaphragmatic hernia, feline infectious peritonitis, hypoalbuminemia, systemic infection and inflammation, and disseminated intravascular coagulation.

Pericardiocentesis (see ch. 102) is necessary in cats with echocardiographic evidence of cardiac tamponade. The pericardial fluid usually has a gross appearance similar to pleural effusion, and, unlike in dogs, is rarely hemorrhagic. Fluid analysis and cytologic evaluation ± microbial culture should be submitted to evaluate for infectious, neoplastic, or inflammatory etiologies.

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CHAPTER 255

Canine and Feline Heartworm Disease

Clarke Atkins

Client Information Sheets:
Ferreting Out Heartworm Prevention
Battling Boredom: Tips for Surviving Cage Rest
The Truth About Cats and Dogs
5 Facts About Heartworm Disease
Heartworm Treatment Guidelines for the Pet Owner
Heartworm Incidence 2013
American Heartworm Society Resistance Statement

Canine Heartworm Disease

Heartworm infection (HWI, dirofilariasis, dirofilarosis), caused by *Dirofilaria immitis,* primarily affects members of the family Canidae. Dirofilarosis is widely distributed, being recognized in northern and southern temperate zones, in the tropics, and in the subtropics. Infections are recognized in most of the United States, although the distribution favors the Southeast and Mississippi River Valley (Figure 255-1). In some endemic areas in the United States, infection rates approach 45%, and in some hyper-endemic tropical regions, virtually all dogs are infected. Dirofilarosis is generally infrequent in Canada, but there are endemic areas of concern in southern Ontario. A 2001 survey of veterinarians indicated that there were approximately 240,000 cases diagnosed in the United States, but realistic estimates put the prevalence at >1,000,000 cases.[1]

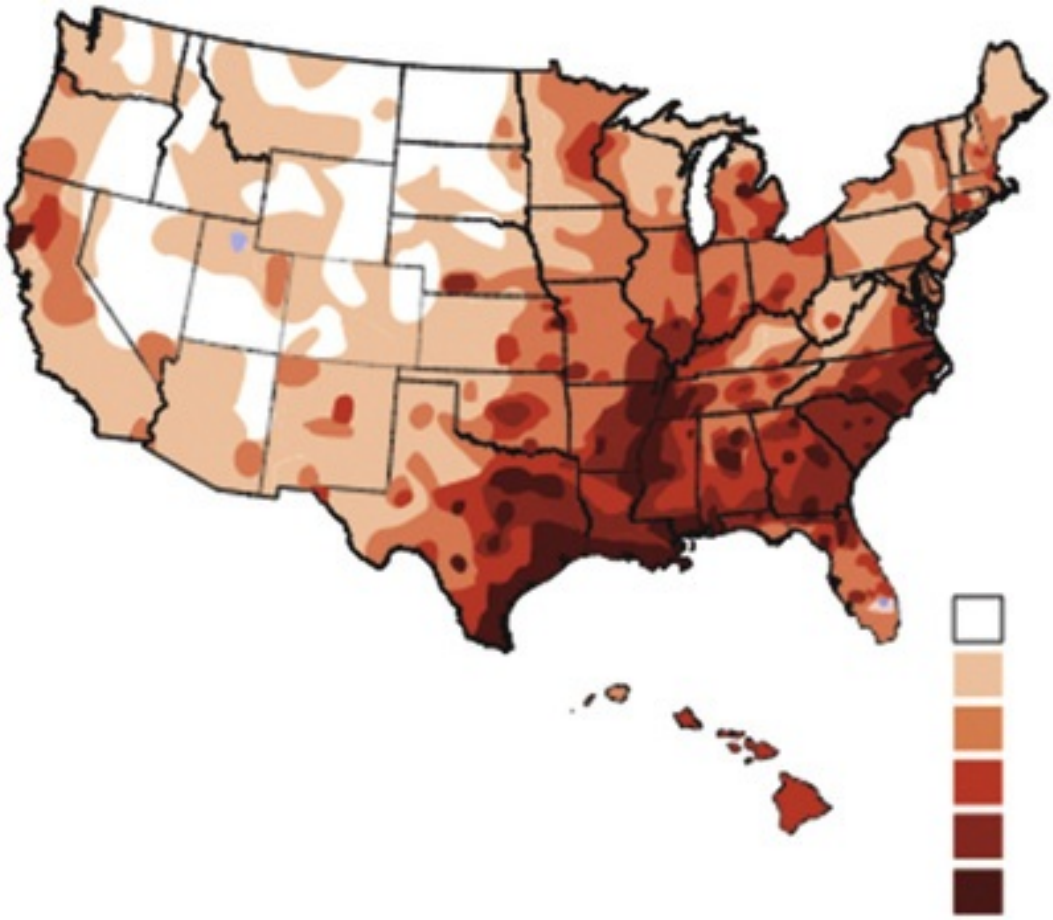


FIGURE 255-1 American Heartworm Society map, demonstrating relative prevalence of heartworm infection in the United States in 2013, based on practice surveys. (Courtesy the American Heartworm Society.)

Species known to have been infected with *D. immitis* include the domestic dog, wolves, foxes, coyotes, domestic cats, ferrets, muskrats, sea lions, nondomestic cats, coatimundi, and humans. The species of greatest interest to the practicing veterinarian include the dog and domestic cat. Because the consequences, treatment, and prognoses differ between the two species, clinical aspects of canine and feline heartworm disease (HWD) are discussed separately.

When HWI is severe or prolonged, it may result in the pathologic process called *heartworm disease (HWD).* This may vary from asymptomatic (radiographic lesions only) to severe, life-threatening, chronic pulmonary artery, lung, and cardiac disease. In chronic HWI, glomerulonephritis, anemia, and thrombocytopenia may also be recognized. Severe dirofilarosis may, in addition, produce acute and fulminant multi-systemic presentations, such as caval syndrome (CS) and disseminated intravascular coagulation (DIC).

Life Cycle

D. immitis is transmitted by over 70 species of mosquitoes, although important mosquito vectors probably number fewer than fifteen. Understanding the complex life cycle of *D. immitis* is imperative for veterinary practitioners in heartworm endemic areas (Figure 255-2). The terminology for the larval stages can be confusing. For the final heartworm stage, *L5* (last stage or 5th larval stage) is no longer the preferred term. The nomenclature has been updated, because, although far smaller than a mature adult, this stage does not molt again so is not a larval stage. Preferred terminology for this pre-cardiac stage includes immature Stage 5 ([S5], immature or juvenile adult). For the purposes of this chapter, *L5, Stage 5, juvenile, juvenile adult, immature adult,* and *mature adult* are terms used to describe the final stage in the heartworm development. Additionally, the term *L1* (1st larval stage) refers to the 1st stage larvae after ingestion by the female mosquito, while prior to this, in the host, these earliest HWs are termed *microfilariae.*

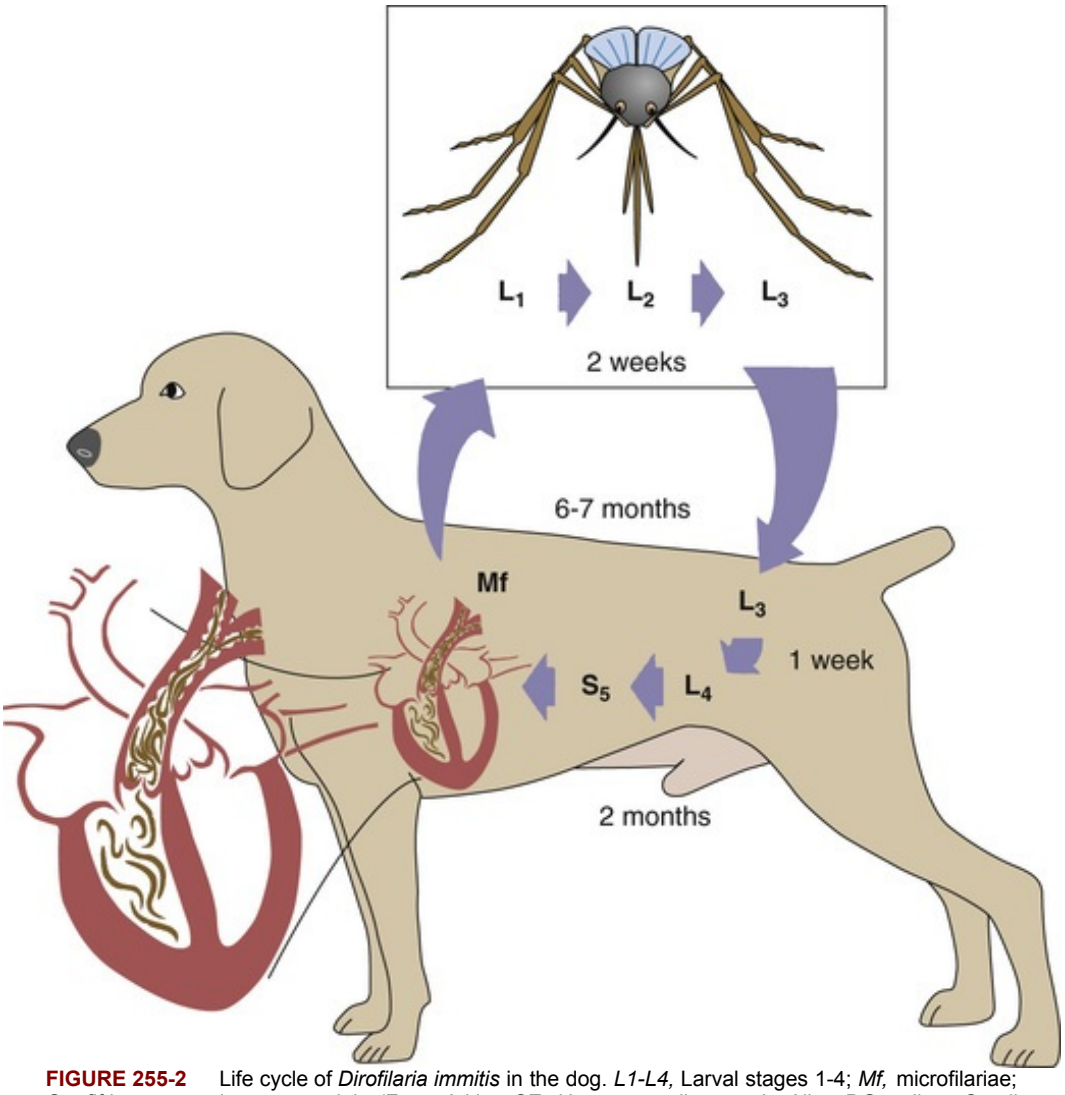


FIGURE 255-2 Life cycle of *Dirofilaria immitis* in the dog. *L1-L4,* Larval stages 1-4; *Mf,* microfilariae; *S5,* fifth stage or immature adult. (From Atkins CE: Heartworm disease. In Allen DG, editor: *Small animal medicine*, Philadelphia, 1991, JB Lippincott, pp 341-363.)

Adult heartworms reside in the pulmonary arteries and, to a lesser extent (in heavy infections), the right ventricle. After mating, microfilariae (Mf; first stage larvae) are produced by mature adult female heartworms (mature S5) and are released into the circulation. These Mf are ingested by feeding female mosquitoes and undergo two molts (L1 to L2 to L3) over an 8- to 17-day period. It is important to note that this process is temperature-dependent; in times of the year when insufficient numbers of days occur in which the ambient temperature is adequate, molting in the mosquito does not occur during the lifetime of the female mosquito and transmission cannot occur.[2,3] Larval molts and maturation are also dependent on the presence of an intracellular symbiotic bacterium, *Wolbachia pipientis*.[4] The resultant L3 is infective and is transmitted by the feeding mosquito to the original or another host, most often a male dog. Another molt to L4 occurs in the subcutaneous, adipose, and skeletal muscular tissues shortly after infection (1 to 12 days), with a final molt to S5 (immature adult) occurring 2 to 3 months (50 to 68 days) after infection.

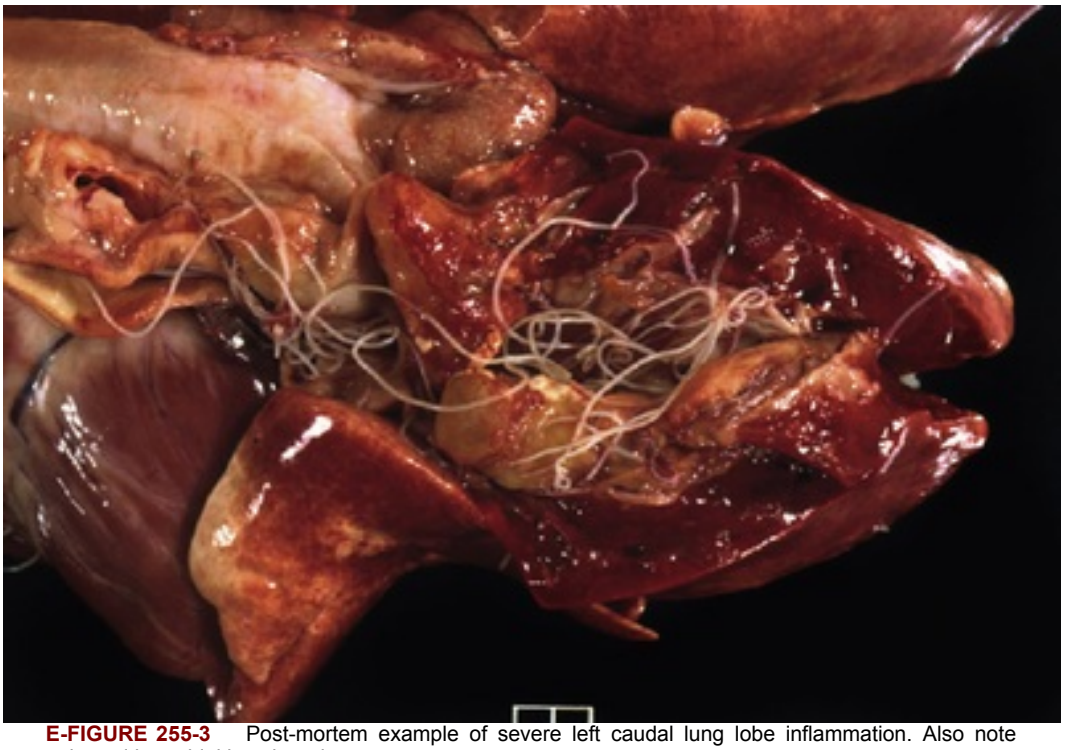
This immature adult (1 to 2 cm in length) soon enters the vascular system, migrating to the heart and lungs, where final maturation (mature male adults range from 15 to 18 cm and females from 25 to 30 cm) and mating occur. Under optimum conditions, completion of the life cycle takes 184 to 210 days. The canine host becomes microfilaremic as early as 6, but typically by 7 to 9 months after infection. Microfilariae, which are variably present in infected dogs, show both seasonal and diurnal periodicity, with greatest numbers appearing in the peripheral blood during the evening hours and during the summer. Adult heartworms in dogs are known to live 5 to 7 years and Mf up to 30 months. Dillon has emphasized that the disease process in HWD begins with the molt to S5 (as soon as 2 to 3 months post-infection), at which time these immature adults enter the vascular system, initiating vascular and possibly lung disease, with eosinophilia and eosinophilic infiltrates

and signs of respiratory disease.[5] It is important to note that this antedates the profession's current ability to diagnose HWI.

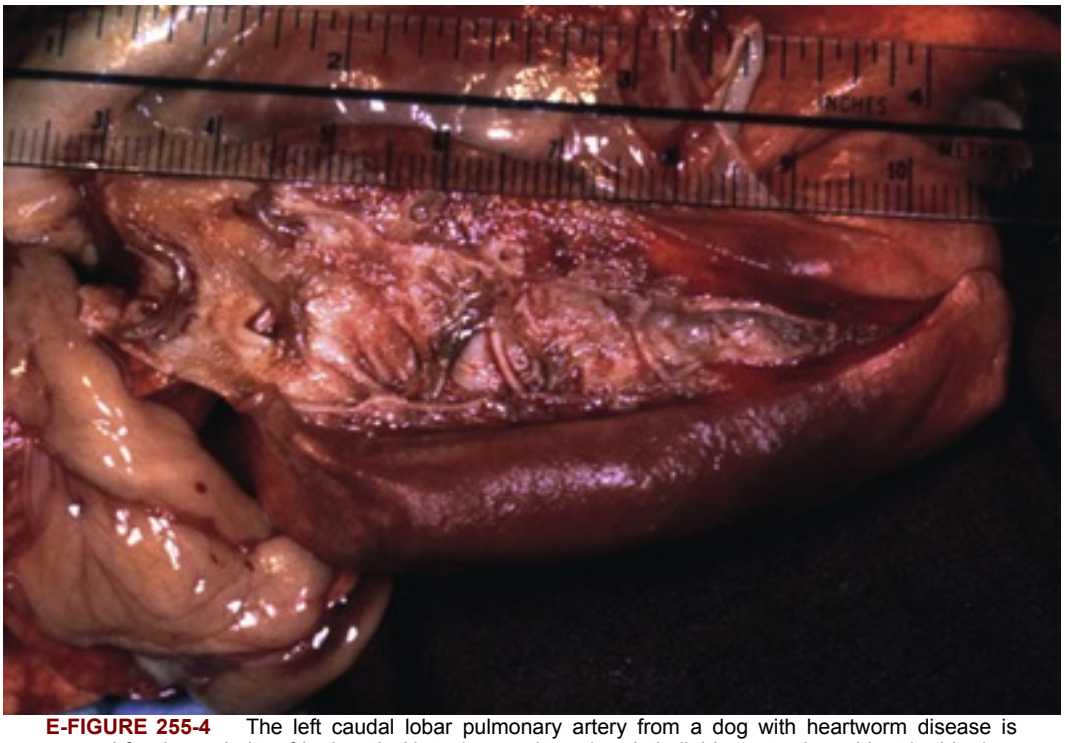
Pathophysiology

Heartworm is a misnomer because the adult actually resides in the pulmonary arterial system for the most part, and the primary insult to the health of the host is a manifestation of damage to the pulmonary arteries and lung. The severity of the lesions and hence clinical ramifications are related to the relative number of worms (ranging from one to >250), the duration of infection, and the host and parasite interaction. Immature and mature adult heartworms reside primarily in the caudal pulmonary vascular tree, occasionally migrating into the main pulmonary arteries, the right heart, and even the great veins in heavy infections.

Obstruction of pulmonary vessels by living worms is of little clinical significance, unless worm burdens are high or the patient small. The major effect on the pulmonary arteries is produced by worm-induced (toxic substances, immunological response, and physical trauma) villous myointimal proliferation, inflammation, pulmonary hypertension (PHT; see ch. 243), disruption of vascular integrity, and fibrosis (E-Figures 255-3 and 255-4). This may be complicated by arterial obstruction and vasoconstriction caused by live worms,[6] dead worm thromboemboli and HW products.[7] Pulmonary vascular lesions begin to develop within days of worm arrival (as early as 3 months post-infection), with endothelial damage and sloughing, villous proliferation, and activation and attraction of leukocytes and platelets. The immigration of such cells and the release of trophic factors induce smooth muscle cell proliferation and migration, with collagen accumulation and fibrosis. Proliferative lesions eventually encroach upon and even occlude vascular lumina. Endothelial swelling with altered intracellular junctions increases the permeability of the pulmonary vasculature. Worms, which have died naturally or have been killed, elicit an even more severe reaction, inciting thrombosis, granulomatous inflammation, and rugous villous inflammation. Grossly, the pulmonary arteries are enlarged, thick-walled, and tortuous, with roughened endothelial surfaces. These changes are at least partially reversible.[7]



E-FIGURE 255-3 Post-mortem example of severe left caudal lung lobe inflammation. Also note enlarged bronchial lymph node.



E-FIGURE 255-4 The left caudal lobar pulmonary artery from a dog with heartworm disease is opened for the majority of its length. Note the roughened endothelial hypertrophy evident in this dog. This demonstrates the extensive damage produced by heartworms.

Although the role of exercise in exacerbation of the signs of thromboembolic HWD is accepted, its role in the development of pulmonary vascular disease and PHT is less clear. While Rawlings[8] was unable to show an effect of 2.5 months' controlled treadmill exercise on PHT in heavily infected dogs, Dillon[9] showed more severe PHT in lightly infected, mildly exercised dogs than in more heavily infected but unexercised dogs. Clinical observation suggests that outdoor dogs, particularly hunting dogs, have more severe lesions and PHT, possibly related to exercise, but the role of increased exposure and worm burden must also be considered.

Diseased pulmonary arteries are thrombosed, thickened, dilated, tortuous, noncompliant, and functionally incompetent, thereby resisting recruitment during increased demand; hence, exercise capacity is diminished. Vessels to the caudal lung lobes are most severely affected. Pulmonary vasoconstriction results secondary to vasoactive substances likely released from heartworms, as well as endothelin-1 produced in excess by vascular endothelial cells[10] and vasoconstrictive substances, such as serotonin, adenosine diphosphate (ADP), and thromboxane A_2, produced by activated platelets. Furthermore, hypoxia (induced by ventilation-perfusion mismatching secondary to pulmonary thromboembolism [PTE; see ch. 243], eosinophilic pneumonitis, pulmonary consolidation, or all three) further contributes to vasoconstriction. The result is PHT, increased right ventricular afterload, and compromised cardiac output.[9-11] PHT is exacerbated by exercise or other states of increased cardiac output. The right heart, which is an efficient volume pump but does not withstand pressure overload, first compensates by eccentric hypertrophy (dilatation and wall thickening) and, in severe infections, decompensation (right heart failure). In addition, hemodynamic stresses, geometric changes, and cardiac remodeling may contribute to secondary tricuspid insufficiency, thereby complicating or precipitating cardiac decompensation. Further compromise occurs with the advent of cardiac arrhythmia (see ch. 248). Pulmonary infarction is uncommon because of the extensive collateral circulation provided the lung and because of the gradual nature of vascular occlusion. Because of increased pulmonary vascular permeability, perivascular edema may develop. Although, along with an inflammatory infiltrate, this fluid accumulation may be evident radiographically as increased interstitial and even alveolar density, in and of itself, it is seemingly of minimal clinical significance and certainly does not indicate left heart failure (in other words, it is not cardiogenic pulmonary edema and furosemide is not indicated).

Spontaneous or post-adulticidal PTE with dead worms may precipitate or worsen clinical signs, producing or aggravating PHT, right heart failure or, in rare instances, pulmonary infarction. Dying and disintegrating worms worsen vascular damage and enhance coagulation. Pulmonary blood flow is further compromised

and consolidation of affected lung lobes may occur. With acute and massive worm death, this insult may be profound, particularly if associated with exercise. Exacerbation by exercise likely reflects increased pulmonary artery flow with escape of inflammatory mediators into the lung parenchyma through badly damaged and permeable pulmonary arteries (see Figure 255-12). Dillon has suggested that the lung injury is similar to that seen in adult respiratory distress syndrome (ARDS; see ch. 242).[9]

Pulmonary parenchymal lesions also result by mechanisms other than post-thromboembolic consolidation. Eosinophilic pneumonitis is most often reported in true occult HWD, in which immune-mediated destruction of Mf in the pulmonary microcirculation produces amicrofilaremia. This syndrome results when antibody-coated Mf, entrapped in the pulmonary circulation, incite an inflammatory reaction (eosinophilic pneumonitis).[12] A more sinister, but rare form of parenchymal lung disease, termed *pulmonary eosinophilic granulomatosis,* has been associated with HWD. The exact cause and pathogenesis are unknown, but it is felt to be similar to HWD-related eosinophilic pneumonitis.[13] It is postulated that Mf trapped in the lungs are surrounded by neutrophils and eosinophils, eventually forming granulomas and associated bronchial lymphadenopathy.

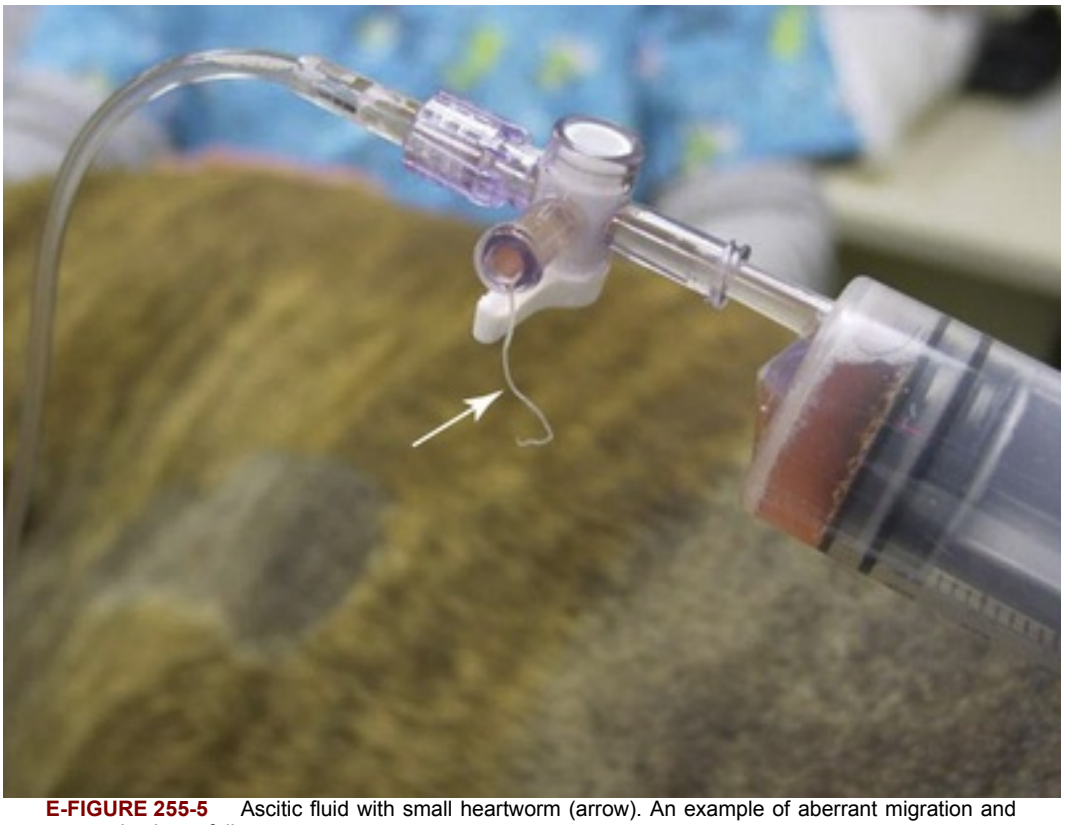
Antigen-antibody complexes, formed in response to heartworm antigens, can produce glomerulonephritis in heartworm-infected dogs (see ch. 325).[14] The result is proteinuria (albuminuria), uncommonly associated with renal failure.

Heartworms may also produce disease by aberrant migration. This uncommon phenomenon has been associated with neuromuscular and ocular manifestations because worms have been described in tissues such as muscle, brain, spinal cord, and anterior chamber of the eye. In addition, systemic arterial thrombosis with S5 has been observed when worms migrate aberrantly to the aortic bifurcation or more distally in the digital arteries (see ch. 256).[15] Adult heartworms may also passively "migrate" in a retrograde manner from the pulmonary arteries to the right heart and venae cavae, producing caval syndrome (CS), a devastating complication, described later.[16]

It has been recently been recognized as important that the bacterium *W. pipientis* inhabits filarid parasites, including *D. immitis.* Importantly, these bacteria live in a symbiotic relationship with the filarid parasites, being necessary for molts within the mosquito and the canine host (L3-L4, L4-S5). The exact role of *Wolbachia* in the pathogenesis of HWD is unclear, but *Wolbachia* proteins (*Wolbachia* surface proteins [WSP]) have been identified in the glomerulus and lung of heartworm-infected dogs.[17,18] In addition, proteins produced by the bacteria are thought to contribute to the hosts' inflammatory reaction to worm death.

Clinical Signs

The clinical signs of chronic HWD depend on the severity and duration of infection and, in most chronic cases, reflect the effects of the parasite on the pulmonary arteries and lungs and, secondarily, the heart. It is important to point out that the vast majority of dogs with HWI are asymptomatic. Historical findings in affected dogs variably include weight loss, diminished exercise tolerance, lethargy, poor condition, cough, dyspnea, syncope, and abdominal distension (ascites). Physical examination (see ch. 2) may reveal evidence of weight loss, split-second heart sound (13%), right-sided heart murmur of tricuspid insufficiency (13%), and cardiac gallop (see ch. 55).[19] If right heart failure is present, jugular venous distension and pulsation typically accompanies hepatosplenomegaly and ascites (E-Figures 255-5 and 255-6). Cardiac arrhythmias and conduction disturbances are uncommon in chronic HWD (<10%). With pulmonary parenchymal manifestations of HWD, cough and pulmonary crackles may be noted and, with granulomatosis (a rare occurrence), muffled lung sounds, dyspnea, and cyanosis are also reported. When massive PTE occurs (see ch. 243), the additional signs of dyspnea, fever, and hemoptysis may be present.



E-FIGURE 255-5 Ascitic fluid with small heartworm (arrow). An example of aberrant migration and congestive heart failure.

E-FIGURE 255-6 Jugular venous distension apparent in a dog with heartworm disease and jugular venous distension.

Diagnosis

Microfilarial Detection

Ideally, the diagnosis is made by routine evaluation prior to the onset of clinical signs (i.e., HWD). Dogs in areas in which heartworms are endemic should undergo a heartworm test yearly, particularly if not receiving heartworm preventive. This was accomplished most commonly in the past by the microscopic identification of Mf on a direct blood smear, above the buffy coat in a microhematocrit tube, using the modified Knott test, or after millipore filtration. The accuracy of these tests, typically used for routine screening and for the diagnosis of suspected HWI, is improved by multiple testing. The modified Knott test and millipore filtration are more sensitive because they concentrate Mf, improving chances of diagnosis. The direct smear technique allows examination of larval motion, helping in the distinction of *D. immitis* from *Dipetalonema reconditum* (now termed *Acanthocheilonema reconditum*); other useful diagnostic criteria are included in Table 255-1. This distinction is important because the presence of the latter parasite does not require expensive and potentially harmful arsenical therapy, as does *D. immitis*. None of these tests can rule out HWI conclusively because of the potential for amicrofilaremic infections (reported to be 5% to 67% of cases, with 10-20% being generally accepted[20]) and the fact that false-negative results may occur, particularly if microfilarial numbers are small, a small amount of blood is collected, or direct smears are relied upon. The number of circulating Mf in the peripheral blood does not correlate well with the number of adult heartworms and therefore cannot be used to determine the severity of infection. In most practices, microfilarial testing has been largely supplanted by immunodiagnostic antigen testing (i.e., enzyme-linked immunosorbent assay [ELISA], lateral flow immunoassay, and rapid immunomigration techniques; Table 255-2). The modified Knott test, millipore filter test, or wet mount direct smear should *always* be performed, however, in antigen-positive dogs to determine microfilarial status. The reasons for this include knowing if large numbers are present, which allows pre-treatment or a scheduled observation time after the first dose of a macrocyclic lactone (ML). Secondly, there is concern that HW resistance to ML may be favored when these drugs are administered to HW-positive, microfilaremic dogs. Some veterinarians choose to combine the antigen and microfilarial tests. This practice is most useful in dogs receiving no preventive (MLs typically render the dog amicrofilaremic). The generally accepted 1% of infected dogs that are Mf positive and antigen negative[20] may be an underestimate, based on new information about antibody-antigen complexing in HWI.[21-23]

TABLE 255-1

Differentiating Characteristics of *Dipetalonema reconditum* and *Dirofilaria immitis*

	NUMBER IN BLOOD	MOTION	SHAPE	LENGTH (MODIFIED KNOTT TEST)
D. reconditum	Usually few	Progressive	Curved body Blunt head Curved or "buttonhook" tail	263 microns (250-288 microns)
D. immitis	Usually many	Stationary	Straight body and tail Tapered head	308 microns (295-325 microns)

TABLE 255-2

Commercial Antigen and Antibody Test Kits for Heartworm Diagnosis in Dogs and Cats*

MANUFACTURER	PRODUCT	FORMAT	TEST TYPE	SAMPLE	SPECIES	RUN TIME	STEPS
Heska	Solo Step CH	M	LFI	P, S, WB	Canine	10 (WB), 5 (S, P)	1
Heska	Solo Step CH Batch Test Strips	M	LFI	P, S	Canine	5	1
Heska	Solo Step FH (antibody)	M	LFI	P, S	Feline	5	1

IDEXX	PetCheck Heartworm Antigen PF	MW	E	P, S, WB	Canine and feline	20	9 or 10
IDEXX	SNAP Heartworm Antigen Kit	M	E	P, S, WB	Canine	8	4
IDEXX	SNAP 3Dx, 4Dx	M	E	P, S, WB	Canine	8	4
IDEXX	SNAP Feline Heartworm Antigen Kit	M	E	P, S, WB	Feline	10	4
IDEXX	SNAP Feline Triple Antigen Kit	M	E	P, S, WB	Feline	10	4
Synbiotics	Witness HW	M	RIM	P, S, WB	Canine and feline	10	2
Synbiotics	DiroCHEK	MW	E	P, S	Canine and feline	15	4

*Tests listed in alphabetic order by manufacturer.

E, ELISA; *LFI*, lateral flow immunoassay; *M*, membrane; *MW*, microwell; *P*, plasma; *RIM*, rapid immunomigration; *S*, serum; *W*, well; *WB*, whole blood.

Immunodiagnostic Antigen Tests

In dogs not having received ML preventive therapies, the prevalence of amicrofilaremic infections is typically 10% to 20%.[24] This may be observed in prepatent (young) infections, in single-sex infections, with immune-mediated destruction of Mf, and with drug-induced amicrofilaremia. Dogs receiving ML preventives are typically amicrofilaremic. Hence, immunodiagnostic tests are now regularly used for both screening and in suspected HWI. These tests are popular because of their high sensitivity and specificity and ease of performance (see Table 255-2).[25-28] The weakness of these tests is that they detect antigen from adult female heartworms and hence will produce negative results during the first ≈6 (5 to 8) months of any infection, in all-male infections, and in infections with low female worm burdens. In fact, in a study of the performance of three commercial test kits in detecting low worm burden (≤4 females), naturally acquired infections demonstrated an overall (median for three test kits) sensitivity of 79% and a median specificity of 97%.[29] The sensitivity was relatively low (64%) for infections of only one female worm but improved with increasing female worm burden (median of 85%, 88%, and 89% for two, three, and four female worms, respectively). Of course, with higher worm burdens, better sensitivity is experienced. Nevertheless, despite overall excellent results in detection of small worm burdens, false-negative results do occur (Figure 255-7).[29]

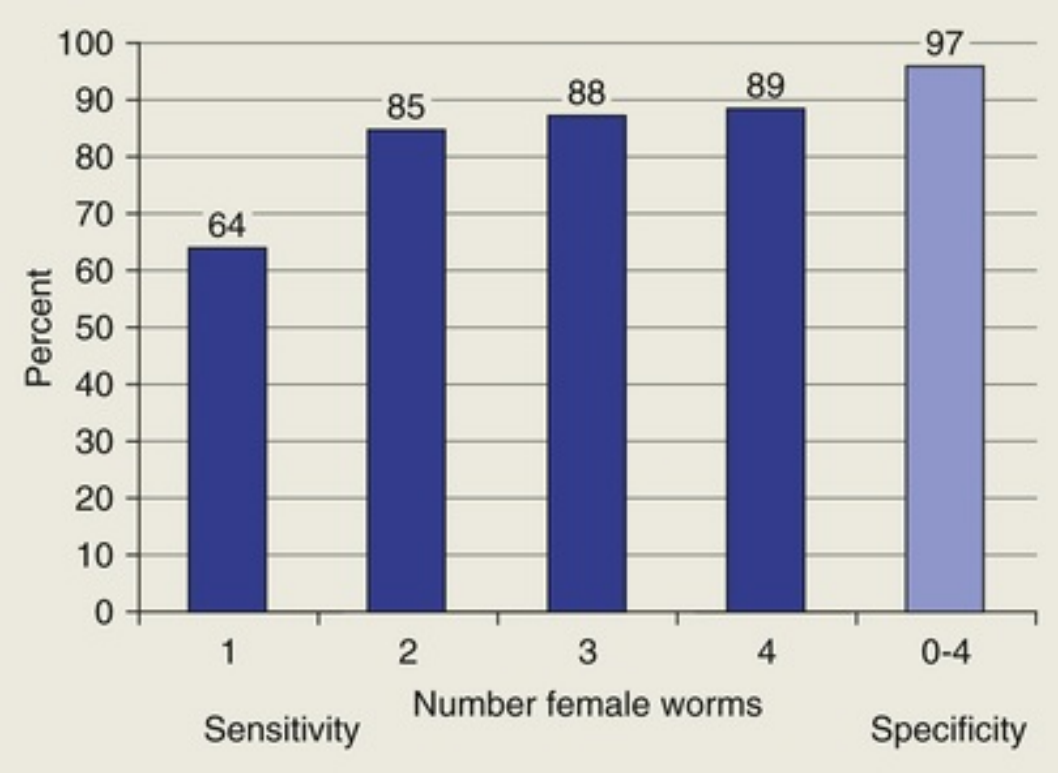


FIGURE 255-7 Comparison of sensitivity and specificity of three commercial heartworm test kits on known sera from naturally infected dogs with low worm burdens (zero to four adult female heartworms). Dark blue bars represent median sensitivity of the three tests for sera of dogs with one, two, three, and four adult female heartworms. Light blue bar represents the median specificity of the three tests for sera from dogs infected with zero to four adult female heartworms. (Data from Atkins CE: Comparison of results of three commercial heartworm antigen tests in dogs with low heartworm burdens. *J Am Vet Med Assoc* 222:1221-1223, 2003.)

Certain ELISA antigen tests are designed to quantitatively predict worm burdens, based on antigen concentrations. Semiquantitative ELISA (SNAP Canine Heartworm PF) has been used to successfully predict antigen load and hence approximate worm burden. Rawlings and colleagues[30] have shown this to be useful in predicting thromboembolic complications, with dogs bearing greater worm burdens being more likely to experience such complications after adulticide. This application is most useful, however, in instances of low antigen concentration (suggesting low worm burden) because high antigen concentrations might be recognized when all or most worms are dead, having released a large amount of antigen into the circulation. ELISA technology also allows determination of the efficacy of adulticide therapy. ELISA antigen concentration typically falls to undetectable levels 8 to 12 weeks after successful adulticide therapy, so a positive test persisting beyond 12 weeks post-therapy has been suggested to indicate persistent infection.[31] However, antigen tests may remain positive for longer periods, and this author does not assume a failure in adulticidal therapy unless the antigen test is positive >6 months after adulticidal therapy and does not advocate routine retesting until 8-12 months post-treatment.

The American Heartworm Society (AHS) now prefers "no antigen detected" to the term "negative," when referring to antigen test results that are not positive. This is to emphasize the fact that negative tests do not rule out immature, small, or all-male HWI.

As previously suggested, ML therapy with either ivermectin, milbemycin oxime, moxidectin, or selamectin results in clearance of Mf within 6 to 8 months.[31-36] In addition, embryostasis may be permanent. Thus the sole use of direct smears, the modified Knott test, or the millipore filter test (i.e., microfilarial tests) in dogs receiving ML heartworm preventives is inappropriate, though they certainly play a supplemental role. The only routinely effective testing modality in dogs receiving monthly preventive is the use of antigen assays. A general approach to the diagnosis of HWI is demonstrated in Figure 255-8.

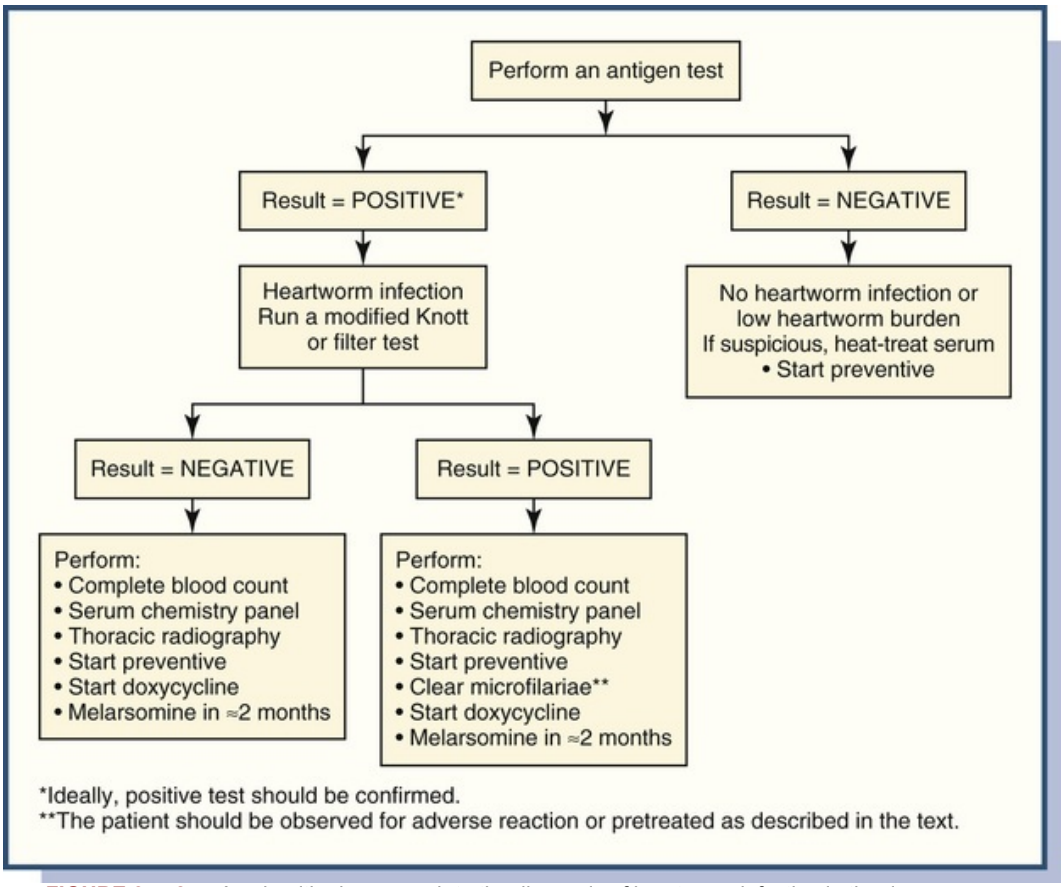


FIGURE 255-8 An algorithmic approach to the diagnosis of heartworm infection in the dog.

Radiography

Although not an effective screening test for HWI, thoracic radiography offers an excellent method for detecting HWD, for determining its severity, for evaluating pulmonary parenchymal changes, and for discovery of differential diagnoses. Radiographic abnormalities, which develop relatively early in the disease course, are present in approximately 85% of cases. According to the study of 200 heartworm-infected dogs by Losonsky and colleagues,[37] radiographic features (Figure 255-9) include right ventricular enlargement (60%), increased prominence of the main pulmonary artery segment (70%), increased size and density of the pulmonary arteries (50%), and pulmonary artery tortuosity and "pruning" (50%). If heart failure is present, enlargement of the caudal vena cava, liver, and spleen, as well as pleural effusion, ascites, or both, may be evident. Thrall and Calvert[38] suggested that pleural effusion is uncommon in heart failure due to HWD, demonstrating that marked enlargement of the cranial lobar pulmonary artery was a more sensitive indicator of HWD-associated heart failure than enlargement of the caudal vena cava.

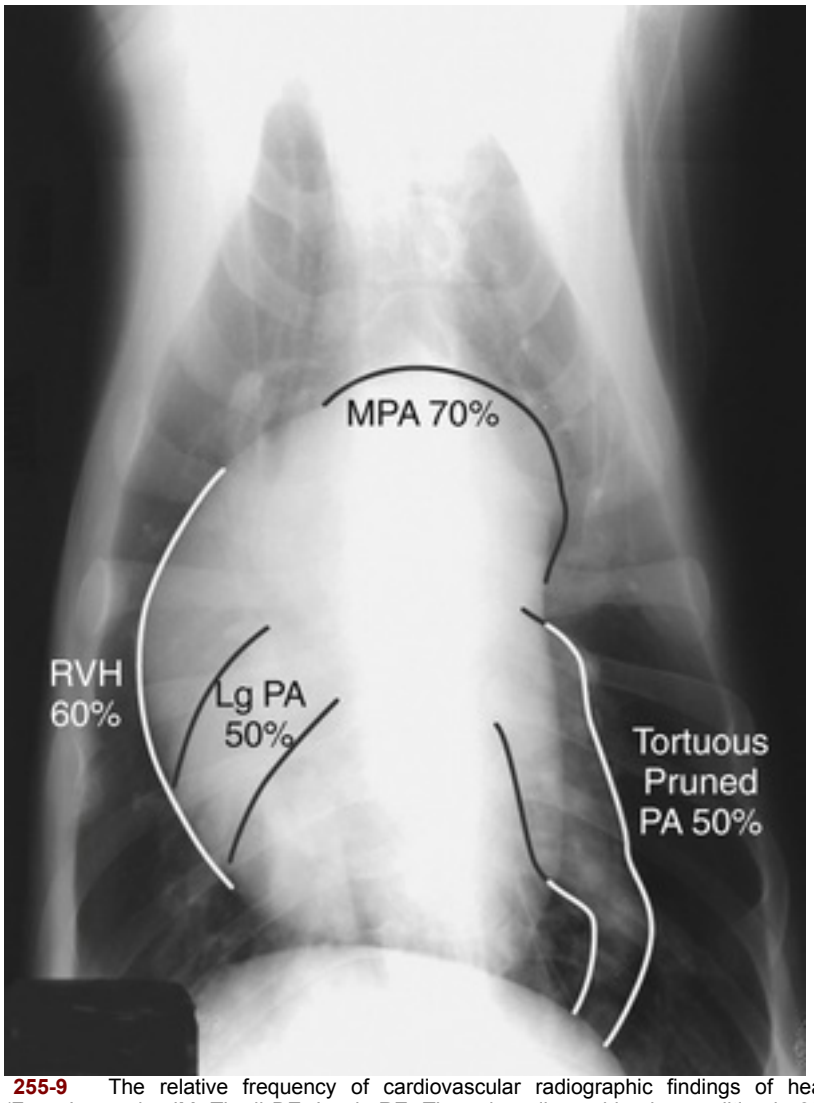


FIGURE 255-9 The relative frequency of cardiovascular radiographic findings of heartworm disease. (From Losonsky JM, Thrall DE, Lewis RE: Thoracic radiographic abnormalities in 200 dogs with heartworm infestation. *Vet Radiol* 24:120-123, 1983.)

Thoracic radiographs obtained in the ventrodorsal projection are preferable for cardiac silhouette evaluation and ease, and they often minimize patient stress. However, the dorsoventral projection is superior for the evaluation of the caudal lobar pulmonary vessels, which are considered abnormal if larger than the diameter of the ninth rib where the rib and artery intersect (Figures 255-9 and 255-10). The cranial pulmonary artery is best evaluated in the lateral projection and should normally not be larger than its accompanying vein or the proximal one third of the fourth rib (Figure 255-11).

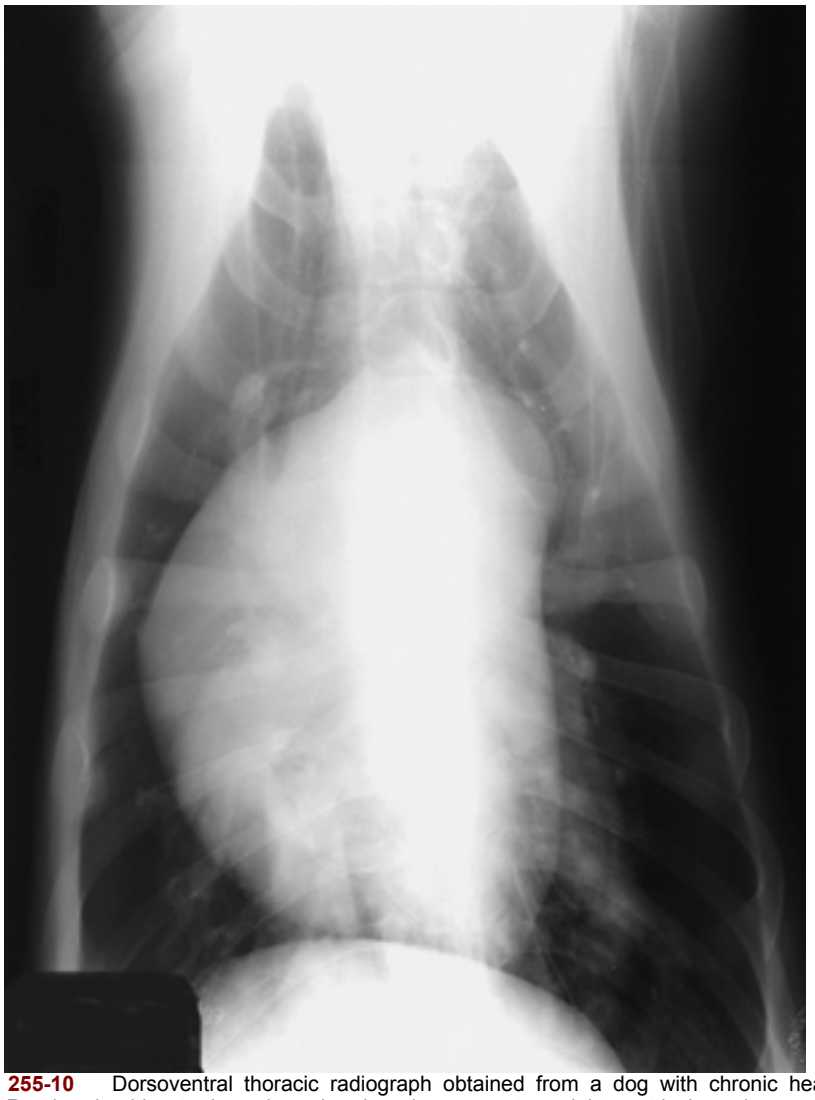


FIGURE 255-10 Dorsoventral thoracic radiograph obtained from a dog with chronic heartworm disease. Reader should note the enlarged main pulmonary artery, right ventricular enlargement, and enlarged, tortuous caudal lobar pulmonary arteries. (See Figure 255-9 for schematic of radiographic abnormalities.)

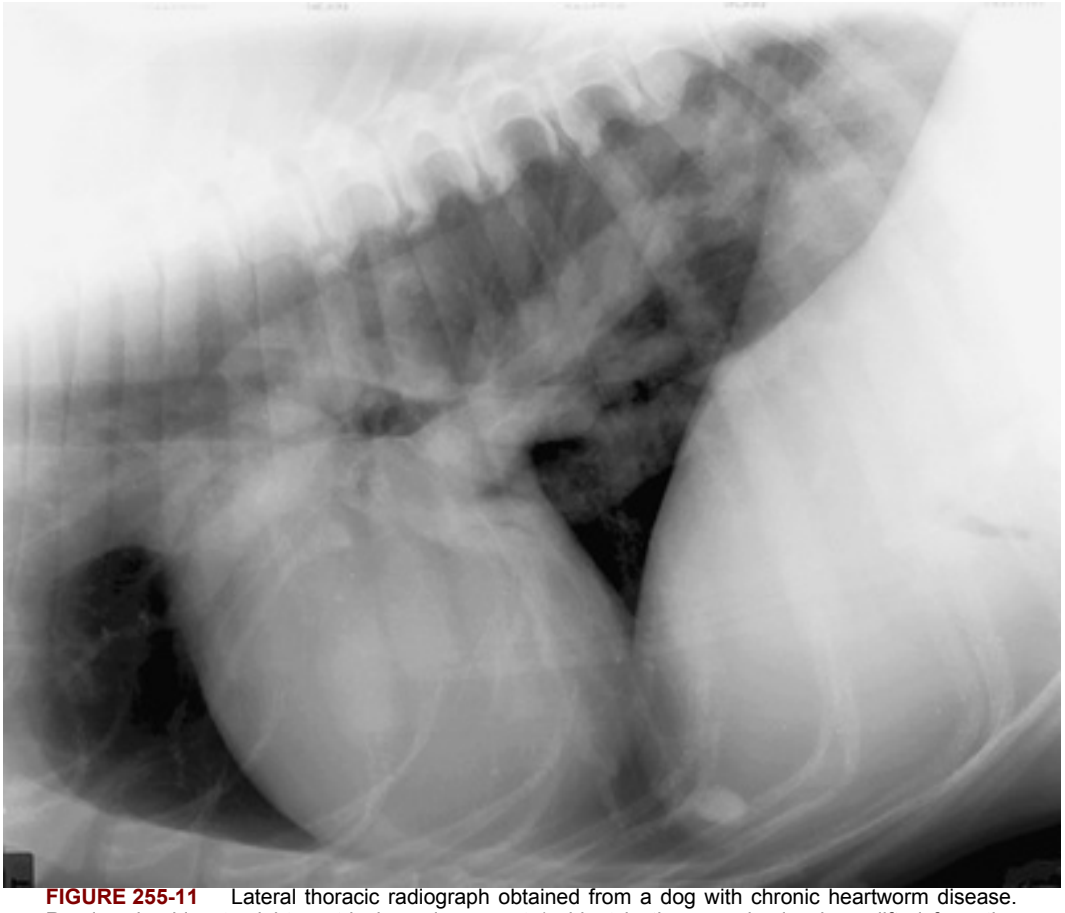


FIGURE 255-11 Lateral thoracic radiograph obtained from a dog with chronic heartworm disease. Reader should note right ventricular enlargement (evident in the apex having been lifted from the sternum), enlarged apical pulmonary artery, and an interstitial infiltrate in the caudal lung lobes.

The pulmonary parenchyma can best be evaluated radiographically. With pneumonitis, the findings include a mixed interstitial to alveolar density, which is typically most severe in the caudal lung lobes (Figure 255-12). In eosinophilic nodular pulmonary granulomatosis, the inflammatory process is arranged into the interstitial nodules, associated with bronchial lymphadenopathy and, occasionally, pleural effusion. With PTE, the radiographic findings of coalescing interstitial and alveolar infiltrates, particularly in the caudal lung lobes, reflect the increased pulmonary vascular permeability and inflammation described previously (see Figure 255-17). Consolidation may accompany massive embolization, pulmonary infarction, or both.

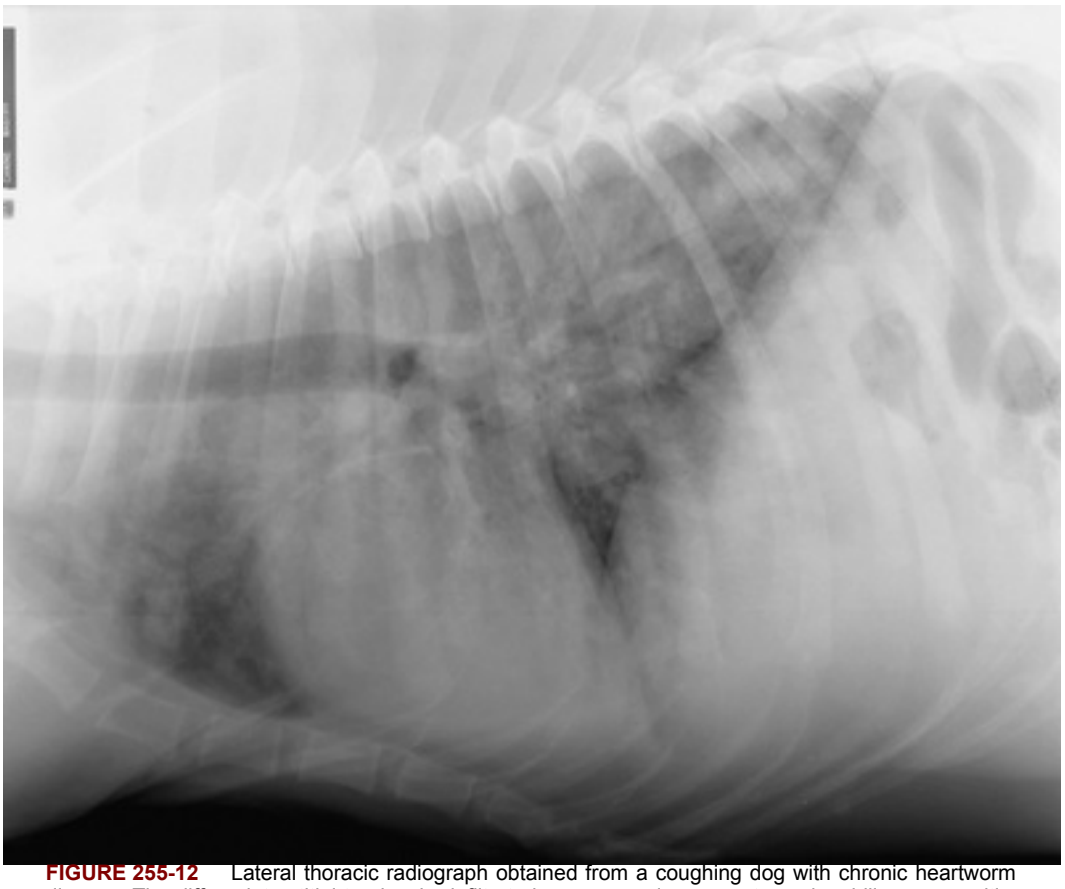


FIGURE 255-12 Lateral thoracic radiograph obtained from a coughing dog with chronic heartworm disease. The diffuse interstitial to alveolar infiltrate is severe and represents eosinophilic pneumonitis. Cardiac and pulmonary arterial changes are less severe than seen in Figures 255-10, 255-11, and 255-17.

Electrocardiography

Electrocardiography is useful in detecting arrhythmias but is generally insensitive in detection of cardiac chamber enlargement in HWD, when compared with radiography and echocardiography. If radiography does not suggest HWD, it is unlikely that the electrocardiogram (ECG) will be useful in the absence of arrhythmias. With the exception of CS and heart failure, arrhythmias are rare (2% to 4%).[39,40] Nevertheless, the finding of a right ventricular enlargement pattern (see ch. 248) is supportive evidence for HWD. Lombard and Ackerman[39] demonstrated that ECG abnormalities were present in 38% to 62% of dogs with moderate and severe echocardiographic changes of HWD, while Calvert and Rawlings[41] found that only 6% of 276 dogs with dirofilarosis had ECG changes suggestive of right ventricular enlargement. These investigators[41] also showed that the most sensitive ECG parameters for detection of HWD are lead II S waves deeper than 0.8 mv, mean electrical axis greater than 103 degrees, and greater than three ECG parameters of right heart enlargement. The latter ECG finding (more than three criteria) is considered to be the most accurate. P-pulmonale (tall P waves, indicative of right atrial enlargement) is unusual in HWD.

Echocardiography

Echocardiography is relatively sensitive in the detection of right heart enlargement because the right ventricular end-diastolic dimension and septal and right ventricular free wall thicknesses are all increased (Figure 255-13). Lombard reported abnormal (paradoxical) septal motion in 4 of 10 dogs with HWD.[42] The ratio of left-to-right ventricular internal dimensions is a useful calculation, being reduced from a normal value of 3 to 4 to a mean value of 0.7 in dogs with HWD. In some instances, two-dimensional echocardiography can be used to demonstrate worms in the pulmonary artery (see Figure 255-30). Although heartworms can occasionally be demonstrated in the right ventricle, this method is insensitive except in dogs with CS or very heavy worm burdens, because the worms infrequently inhabit this location.[42]

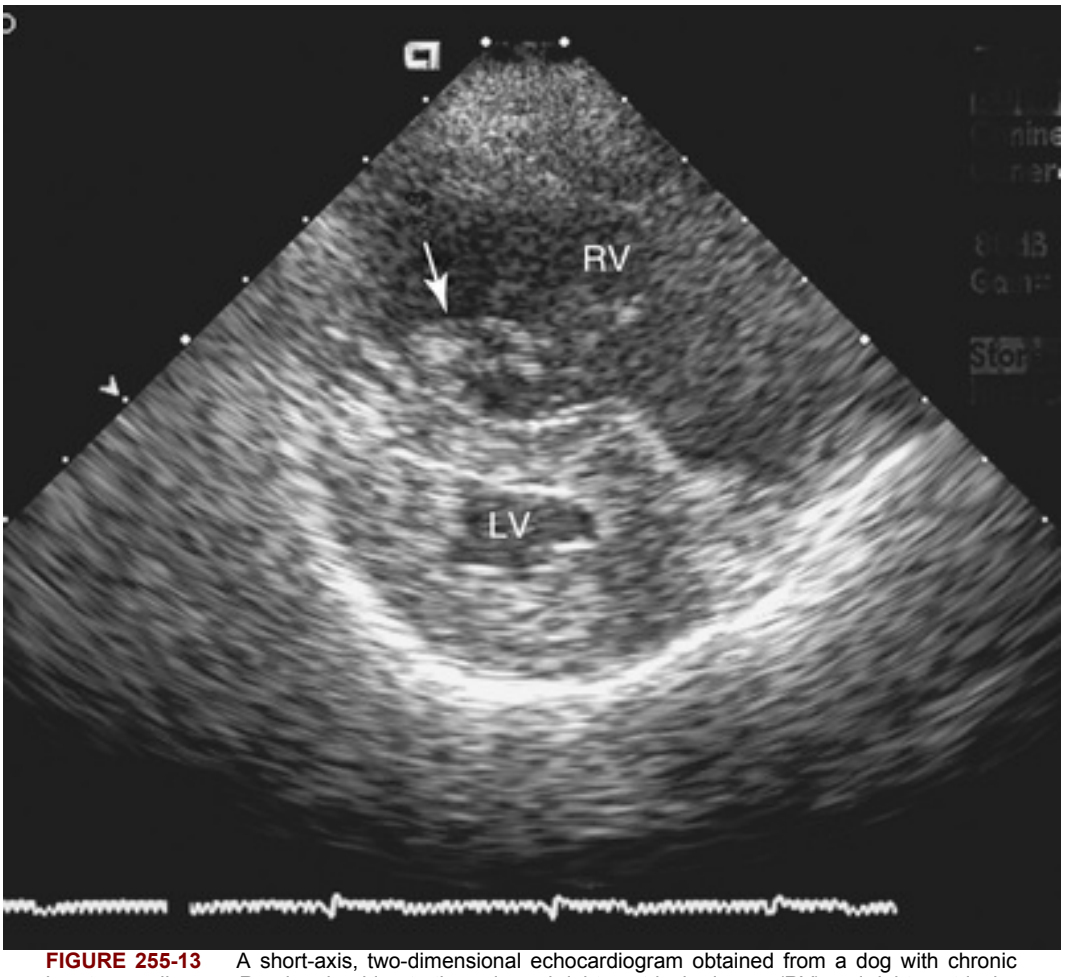


FIGURE 255-13 A short-axis, two-dimensional echocardiogram obtained from a dog with chronic heartworm disease. Reader should note the enlarged right ventricular lumen (RV) and right ventricular papillary muscle (arrow). The septum is flattened and bows toward the small left ventricle (LV). The electrocardiogram at the bottom of the figure demonstrates that this is a diastolic frame.

Clinical Pathology

Hematologic and serum chemical abnormalities, although of limited use in making a diagnosis of HWD, are frequently useful in providing supportive evidence and for evaluating concurrent disease processes that may or may not be related to HWD. Calvert and Rawlings[41] report that the dog with HWD in Georgia is typically found to have a low-grade, nonregenerative anemia (present in 10% of mildly to moderately affected dogs and up to 60% of severely affected dogs), neutrophilia (20% to 80% of cases), eosinophilia (≈85% of cases), and basophilia (≈60% of cases). Thrombocytopenia, which may be noted in chronic HWD, CS, and DIC, is most common 1 to 2 weeks after arsenical therapy. In severe HWD, especially if heart failure is present, liver enzyme activities may be increased (10% of cases) and occasionally hyperbilirubinemia is noted. Azotemia, seen in only 5% of cases, may be prerenal in origin if dehydration or heart failure is present or may be secondary to glomerulonephritis. In 10% to 30% of cases, albuminuria is noted. If glomerular disease is severe, hypoproteinemia (hypoalbuminemia) has the potential to complicate the clinical picture. Not surprisingly, the most severe clinicopathologic findings are associated with the most severe clinical findings.

Evaluation of tracheobronchial cytology (see ch. 101) is at times useful, particularly in the coughing dog with pneumonitis, occult HWD, and minimal radiographic evidence of HWD. Microscopic examination reveals evidence of an eosinophilic infiltrate. In microfilaremic dogs, Mf may occasionally be detected in this manner. Abdominal fluid analysis in cases of congestive heart failure (CHF) typically reveals a modified transudate. Dogs with HWD and right heart failure have central venous pressure (CVP; see ch. 76) that ranges from 12 to more than 20 cm H_2O, but ascites may develop at lower CVPs if hypoalbuminemia is present.

Only recently has the use of biomarkers been evaluated expressly for HWI/HWD. Venco et al[43] reported on C-reactive protein (CRP), which binds to dead and dying cells in response to increased cytokine plasma

concentrations. The CRP level in serum of dogs with and without HWI/HWD was shown to be higher in HWD than in controls and correlated to degree of pulmonary artery damage and PTE. The hope is that this biomarker, which rises and falls quickly with disease and its resolution, respectively, may be useful in staging HWI, monitoring therapy, and evaluating therapeutic outcome. Carreton et al have shown that D-dimer, cardiac troponin I and myoglobin, are abnormally elevated in HWD, indicating PTE and myocardial damage, respectively.[41,44,45] While the results of these preliminary studies are encouraging, the exact clinical use of biomarkers in diagnosis and evaluation of HWI/HWD requires further study.

Medical Management

The medical management of HWI is complex because of the complicated parasite life cycle, the marked variability in clinical manifestations and severity of HWD, prophylactic considerations, adulticidal and microfilaricidal considerations, and the relative toxicity and complications associated with adulticidal therapy. For these reasons, the diagnosis, prevention, and treatment of HWI remain a challenge.

Prevention of Heartworm Disease

Prevention of HWD in pets is an obvious and attainable goal for the veterinary profession. Prevention failure results from ignorance or misunderstanding on the part of owners as to the presence or potential severity of HWI, lack of owner compliance, or from inadequate instruction on preventive measures by the attending veterinarian.[1,46-48] Studies of owner compliance have revealed that approximately 55% of dog owners using veterinary care purchase heartworm preventive, and enough medication is dispensed only to meet the needs of approximately 56% of those dogs. Hence the proportion of "cared for" dogs in the population that receive adequate heartworm prophylaxis is less than one third.[47] If one takes into consideration doses purchased but not administered and dogs that are never taken to a veterinarian, the percentage of protected dogs falls drastically. The latter point was emphasized in North Carolina in 1999, when Hurricane Floyd caused extensive flooding and disruption in the poorest part of the state. Of dogs rescued from the floodwaters, 67% were infected with heartworms (personal communication, Dr. Kelli Ferris, North Carolina State University, 2003). In addition, evidence suggests that the veterinary profession is falling short in client education. A survey of veterinary clients purchasing ML preventives found that 38% did not realize that their prescribed drug's spectrum was broader than solely preventing HWI.[49] Another study utilized "client-actors" with pets to probe the role of veterinarians in compliance failure and found that only 60% of dog owners and ≈25% of cat owners received HW mention, questions, or medication during their scheduled visit.[50]

Macrocyclic Lactone Antibiotics

The 1987 introduction of the ML ivermectin was followed by the development and release of milbemycin oxime, selamectin, and moxidectin. MLs include the avermectins (ivermectin, doramectin, eprinomectin, and selamectin) and milbemycins (milbemycin oxime and moxidectin) and are derived from soil microorganisms belonging to the genus *Streptomyces.* This drug class has provided the veterinary profession with highly effective heartworm preventives in a variety of formulations, drug combinations, spectra, and modes of administration. These agents, because they terminate tissue stage larval development (L3 and L4) during the first 2 months after infection, have a large temporal window of efficacy, and are administered orally or topically monthly or by injection every 6 or 12 months (12-month product not available in the USA), thereby being very convenient. Additionally, they produce less severe reactions than previously experienced with diethylcarbamazine[51] when inadvertently given to microfilaremic dogs. They also variably allow a grace period ("reach-back," "retroactive efficacy," or "safety net") for inadvertent lapses in administration, being at least partially effective with treatment lapses of up to 2 to 3 months, when used continuously for the next 12 months.[52] Additionally, they have a dual role as microfilaricides[28,52-54] and some MLs have adulticidal activity, if used continuously for prolonged periods.[54-57] It bears emphasizing that, at the time of this writing, HWs have shown resistance to this class of drugs (all molecules and formulations) and reach-back and continuous systemic ML presence,[58] while offering potential advantages in making up for failures in purchase, administration, or absorption, *should not be relied upon.* Regardless, if MLs are administered without interruption (i.e., every month or every 6 months, depending on product), these advantages accrue.

Ivermectin

Ivermectin, a ML derived from avermectin B_1 that is obtained from *Streptomyces* spp., is effective against a

range of endoparasites and ectoparasites and is marketed as a once-monthly heartworm preventive. It is also marketed in a form combined with pyrantel pamoate (hookworms and roundworms) and one with pyrantel pamoate and praziquantel (hookworms, roundworms, and tapeworms) to improve efficacy against intestinal helminths (Table 255-3). These combination products are safe in puppies as young as 6 weeks of age. The ML provides a wide window of efficacy and provides some protection when lapses in therapy occur ("reach-back"). Ivermectin is effective as a prophylactic with lapses of up to 2 months. Protection in experimental infections is extended, with continuous 12-month administration post-exposure, with lapses of 3 months (98% efficacy) and of 4 months (95% efficacy).[52] As stated previously, ivermectin is microfilaricidal at preventive dosages (6 to 12 mcg/kg/month), resulting in a gradual decline in microfilarial numbers. Despite this gradual microfilarial destruction, generally mild, adverse reactions (transient diarrhea) can occur if administered to microfilaremic dogs.[52] Individuals with the *ABCB1* (aka, multidrug resistance 1 *[MDR1]* and P-glycoprotein 1 *[PGP1]*) gene mutation (most often, but not exclusively Collies, Shetland Sheepdogs, and other herding breeds) are susceptible to ivermectin (and other ML) toxicosis at *high, extra-label* dosages that can lead to neurologic signs.[59] This has typically occurred with the use of concentrated livestock preparations, with clinical signs recognized with doses greater than 16 times the recommended dosage.[36] For this reason, only preparations designed for pet use should be administered to dogs. When used appropriately, ivermectin is very effective in preventing HWI. Additionally, it has been shown to have adulticidal properties when used continuously for 16 months[55] and to be 95% effective with continuous administration for 30 months[56] (see Controversies). This adulticidal feature is enhanced with the addition of a 30-day course of doxycycline therapy. Ivermectin and doxycycline appear to be synergistic in a number of ways related to HWI (see Anti-*Wolbachia* Therapy).

TABLE 255-3

Spectra of Macrocyclic Lactones in Dogs

DRUG	HW/MF	ROUNDWORMS	HOOKWORMS	WHIPS/TAPES	TICKS	FLEAS	MITES
Iver/Pyrantel	+	+	+				
Iver/PP/Prazi	+	+	+	T			
Milbe-Lufen	+	+	+	W		+	
Milbe-Spino	+	+	+	W		+	
Milbemycin	+	+	+				
Moxi Inject	+		+				
Moxi-Imida	+/+	+	+	W		+	
Selamectin	+		*		+	+	+

*Selamectin has label claim for hookworms in Canada.

HW, Heartworms; *Iver,* ivermectin; *MF,* microfilariae; *Milbe-lufen,* milbemycin lufenuron; *Milbe-spino,* milbemycin-spinosad; *Moxi-imida,* moxidectin-imidacloprid; *Moxi inject,* moxidectin injection; *PP,* pyrantel pamoate; *Prazi,* praziquantel; *T,* tapeworms; *W,* whipworms.

Milbemycin Oxime

Milbemycin oxime is a non-macrolide member of a family of milbemycin ML antibiotics and is derived from a different species of *Streptomyces.* At 0.5 to 1 mg/kg, it has efficacy against developing L3 and L4 larval stages, stopping development in the first 6 weeks. It can therefore be given at monthly intervals with a "reach-back" effect of 2 months when doses are inadvertently delayed. With 12 months' continuous treatment post-exposure, this "safety net" can be extended to 3 months (97% efficacy), falling to 41% with lapses of 4 months.[52] At the preventive dosage, milbemycin oxime is a broad-spectrum parasiticide, being also effective against certain hookworms, roundworms, and whipworms (see Table 255-3) and can be initiated in puppies as young as 2 months of age. In microfilaremic dogs, milbemycin oxime has potential for adverse reactions because it is an excellent microfilaricide at the preventive dosage.[32,33] Rare adverse reactions, similar to those observed with ivermectin at microfilaricidal dosages, may be observed in microfilaremic dogs receiving milbemycin oxime at preventive dosages.[33] Based on the fact that label claims of marketed ML, regarding Mf

death and reactions, are very similar, the importance of this phenomenon has been questioned.[35] As with microfilaricidal dosages (50 mcg/kg) of ivermectin, diphenhydramine (2 mg/kg IM) and dexamethasone (0.25 mg/kg IV) may be administered prior to milbemycin oxime to eliminate the possibility of adverse reactions in Mf-positive dogs, particularly in those with high Mf counts. Milbemycin oxime, like other MLs, is safe for use in dogs with the *ABCB1* mutation at the preventive dosage. With appropriate use, milbemycin oxime is highly efficacious as a heartworm prophylactic. Today, milbemycin oxime is available as a single agent and combined with lufenuron or spinosad, to expand its spectrum to include ectoparasites (see Table 255-3).

Moxidectin

Moxidectin was originally marketed as an oral, narrow-spectrum (heartworm and hookworm) heartworm preventive. It has been shown to be safe and effective at 3 mcg/kg PO, given monthly up to 2 months post-infection.[60,61] Oral moxidectin (currently not marketed in the U.S., but it and a topical formulation are Federal Drug Administration–Center for Veterinary Medicine [FDA-CVM] approved) is gradually microfilaricidal at this dosage, and did not produce adverse reactions in a small number of microfilaremic dogs treated with the prophylactic dosage.[53] At 15 mcg/kg, 98% reduction in Mf numbers was documented 2 months post-treatment. Moxidectin is safe in Collies and other breeds with the *ABCB1* mutation,[62] but cannot be administered orally to dogs <6 months of age or to cats.

A parenteral, narrow-spectrum (HWs and hookworms) liposomal formulation of moxidectin, which provides the potential to improve owner compliance, gives 6 months' protection with one subcutaneous injection. With 12 months' (two injections) continuous treatment, injectable moxidectin is 97% effective at preventing infection after a 4-month lapse in preventive therapy but, surprisingly, appears to have limited adulticidal properties.[61] It cannot be administered to dogs <6 months of age or to cats of any age.

Most recently, moxidectin (2.5% for dogs and 1% for cats) has been combined with imidacloprid (10%) and marketed as a broad-spectrum topical product (see Table 255-3).[63,64] This combination product produces high and sustained concentrations of moxidectin in the body and has increased endoparasitic and ectoparasitic efficacy. It is safe, has excellent reach-back capabilities, and is highly efficacious for heartworm prevention when applied monthly at approximately 2.5 to 6.8 mg/kg moxidectin for dogs (1 to 2.5 mg/kg for cats). At the recommended dosage, this preventive is also effective at preventing and killing fleas; treatment and control of hookworms, roundworms, and whipworms; as well as eliminating heartworm Mf and sarcoptic mange. Bathing twice, as soon as 90 minutes after application, does not alter efficacy. Safety has been shown at three-fold and five-fold topical doses in ivermectin-sensitive collies. This product can be administered to puppies at 7 and kittens at 9 weeks of age.

Selamectin

Selamectin is a semisynthetic ML. It is unique in that a single molecule provides broad-spectrum protection with once-monthly topical use (see Table 255-3). Its efficacy against HWI is similar to that of other MLs in both dogs and cats.[66] At 6 to 12 mg/kg topically, this preventive is effective against heartworms and kills fleas and flea eggs, sarcoptic mange mites, ticks, and ear mites.[46] Bathing and swimming, as soon as 2 hours after application, does not alter efficacy. Safety has been shown at tenfold topical doses, with oral consumption of single doses and, in ivermectin-sensitive Collies, at recommended dosages and five-fold overdosing for 3 months.[67] Like other MLs, selamectin has at least a 2-month reach-back effect and, with 12 months' continuous administration, is 99% protective after 3-month lapses in prophylaxis.[66,68] Selamectin has slow microfilaricidal activity similar to other MLs.[68] Selamectin can be administered to puppies as young as 6 weeks of age. Chronic, continuous selamectin administration has adulticidal efficacy, although no published data indicate that it is as effective in this role as ivermectin.

Eprinomectin

Eprinomectin, the amino-avermectin derived from avermectin B_1 (modified terminal oleandrose moiety called 4(OO)-epiacetylamino-4(OO)-deoxy-avermectin B_1) was originally used as a highly effective topical formulation against internal and external parasites of cattle. This ML is also formulated in a combination pharmaceutical for cats[69] with excellent bioavailability, distribution, and systemic activity following topical application.[70] After topical application, the average eprinomectin maximum plasma concentration was reached 24 h after topical dosing in the majority of the cats, with an average bioavailability of 31%. The

average terminal half-life is 114 hours, due to slow absorption, compared to the rapid mean elimination half-life of 23 hours, following intravenous administration.[70] The combination product (BROADLINE; fipronil, (S)-methoprene, eprinomectin, and praziquantel) has been approved in Europe for the treatment/prevention of *D. immitis, Aelurostrongylus,* tapeworms, hookworms, *T. cati,* and fleas. Multiple studies have shown this product to be an efficacious and safe topical HW preventive at the minimum intended dosage of 0.5 mg/kg monthly.[70]

In summary, the ML class offers a convenient, effective, and safe method of heartworm prophylaxis with varying spectra and modes of administration (see Table 255-3). All are safe in Collies and other breeds with the *ABCB1* mutation, when used as directed, at preventive dosages. They all have microfilaricidal efficacy, although only the imidacloprid-moxidectin topical formulation has FDA-CVM approval for this use, and are thought to render female heartworms sterile. Hence, Mf testing for HWI cannot be reliably used in dogs receiving these products. Prophylaxis should be commenced no later than 6 to 8 weeks of age in endemic areas or as soon thereafter as climatic conditions dictate.[27,71] Although safer than diethylcarbamazine (the original daily HW preventive, eventually replaced by the ML) in microfilaremic dogs, there is a variable risk when MLs are administered to these dogs. Before first-time administration, any dog older than 6 months of age and at risk of infection should be tested (antigen test, followed by a Mf test, if antigen positive; or ideally, in all cases) and tested a second time in 7-8 months.

Understanding the "reach-back" capability of this class of drugs is important because it is an advantage unto these molecules, but it should not be considered in the routine preventive protocol. Even though protective in experimental situations for at least 8 weeks post-exposure, MLs should be administered *precisely* as indicated by the manufacturer. MLs can, however, be used to "rescue" dogs that have experienced lapses in preventive administration.[27,71] If accidental lapses of more than 6-8 weeks occur (depending on location and time of year), the preventive should be reinstituted at the recommended dosage and maintained for at least 12 consecutive months to attain reach-back and adulticidal benefits.[36] In the event of a lapse in preventive administration during a time of known exposure risk, an antigen heartworm test should be performed 7 to 8 months after the last possible exposure to determine if infection has occurred.

Both the AHS (https://www.heartwormsociety.org) and the Companion Animal Parasite Council ([CAPC], www.CAPCvet.org) advocate yearlong prevention, regardless of geographic location.[72] This stance remains controversial as it is known that HWs are not transmitted all year long, other than in sites in the very southern tip of the U.S. Because many veterinarians and pet owners in northern climes still use a seasonal approach to HW prophylaxis, the AHS recommends beginning ML HW preventives within 1 month of the anticipation of transmission season[36] and continuing 1 month beyond the transmission season.[27,71] This author advocates yearlong prevention, at the very least, below the Mason-Dixon line in North America (see Controversies [addendum in electronic edition at ExpertConsult.com]).

In the last decade, concern of HW resistance to MLs has surfaced (see Controversies [addendum in electronic edition at ExpertConsult.com]). While this is important, the ML class is still largely effective in preventing HWI, and the use of these products should continue.

Blocking Agents: Repellent Insecticides

Permethrin, a third-generation pyrethroid, is an insecticide which has a rapid knockdown effect against a variety of species of insects. This molecule is currently found in an oral form in at least 2 repellents that have utility against mosquitoes and, thereby, heartworms. One has been shown to provide month-long repellence and lethality to 3 heartworm vectors *(A. aegypti* and *albopictus* and *C. pipiens).*[73] The second has been shown to repel and kill *A. aegypti* mosquitoes allowed to feed on dogs infected with JYD-34 HW strain.[74] Feedings on untreated control dogs yielded ≈80-95% engorgement rate, with 95% of mosquitoes harboring L1. However, only 2% of mosquitoes became engorged on treated dogs 28 days after the medication was applied. The implication from these studies is that a monthly application of permethrin can repel and kill mosquitoes, effectively eliminating HW transfer to and from the feeding victims, also reducing the discomfort of mosquito bites and local mosquito populations. This approach is also effective for protecting against ML-resistant HW and promises to be an effective adjunct to current preventive measures.

Adulticidal Therapy

Melarsomine

In most cases of HWD, it is imperative to rid the patient of the offending parasite. Thiacetarsamide

(Caparsolate), for decades the only drug approved for this purpose, is no longer marketed, though some stockpiles exist. It has been replaced by melarsomine (Immiticide), an organoarsenical, superior in safety and efficacy to thiacetarsamide.[75,76] In a study of 382 dogs with HWI receiving melarsomine, none required cessation of therapy due to hepatorenal toxicosis (as compared with 15% to 30% with thiacetarsamide), and no case of severe PTE was observed.[77]

Melarsomine has a mean retention time five times longer than thiacetarsamide, and its metabolites are free in the plasma (on which heartworms feed).[75,76] Hence, it has superior efficacy. With two doses (2.5 mg/kg IM q 24 h for two treatments), the efficacy approximates 90%, with 99% efficacy achievable with repeated two-dose therapy in 4 months or with the split dosage described later. It is important to realize that a 90% worm kill does not translate into 90% of treated dogs being cleared of infection. Estimates are that only 70% of dogs are cleared with the 2-injection protocol, even though their worm burden is drastically reduced.[76]

Despite the enhanced safety of this product, adverse reactions are still noted.[19,24,78,80] In fact, successful pharmacologic adulticidal therapy, by definition, dictates thromboembolic events. The clinician can diminish the severity of this complication by restricting exercise after melarsomine administration. Perhaps the drug's biggest asset is the possibility of flexible dosing ("split-dose"—1 injection, followed in no less than 30 days, by 2 injections, the latter spaced by 24 hours), allowing the potential for a safer 50% initial worm kill, followed by subsequent injections to approach 100% efficacy. Studies have shown that patients treated with the split-dose regimen have a higher seroconversion to a negative antigen status than patients previously treated with either Caparsolate or with the standard melarsomine dosing regimen.[81,82]

A split-dose protocol can be used in severely afflicted individuals or in those in which PTE is anticipated (Table 255-4). This method allows for destruction of only one-half the worms initially (one injection of 2.5 mg/kg IM), thereby lessening the chance for embolic complications. This single dose is followed by a two-dose regimen in 1 month, if clinical conditions permit; the author has waited as long as 3 months when there was significant adversity with the first injection. Although the manufacturer recommends this protocol for severely affected dogs, the author uses it for all cases, unless financial constraint or underlying concern for arsenic toxicosis exists (e.g., pre-existent severe renal or hepatic disease; Figure 255-14).[78] Disadvantages to the split-dose method include additional expense, increased total arsenic administration, and the need for 2 months' exercise restriction.

TABLE 255-4

Manufacturer's Recommendations for the Use of Melarsomine Dihydrochloride, Based on Patient Status

CLASS 1	CLASS 2	CLASS 3	CLASS 4
Heartworm infection (asymptomatic, no radiographic lesions)	**Symptomatic heartworm disease (mild to moderate signs)**	**Symptomatic heartworm disease (severe signs)**	**Caval syndrome**
Two doses melarsomine 24 hours apart (2.5 mg/kg IM)	Two doses melarsomine 24 hours apart (2.5 mg/kg IM)	One dose melarsomine (2.5 mg/kg IM), followed in approximately 1 month with 2 injections 24 hours apart	Melarsomine not indicated for acute care

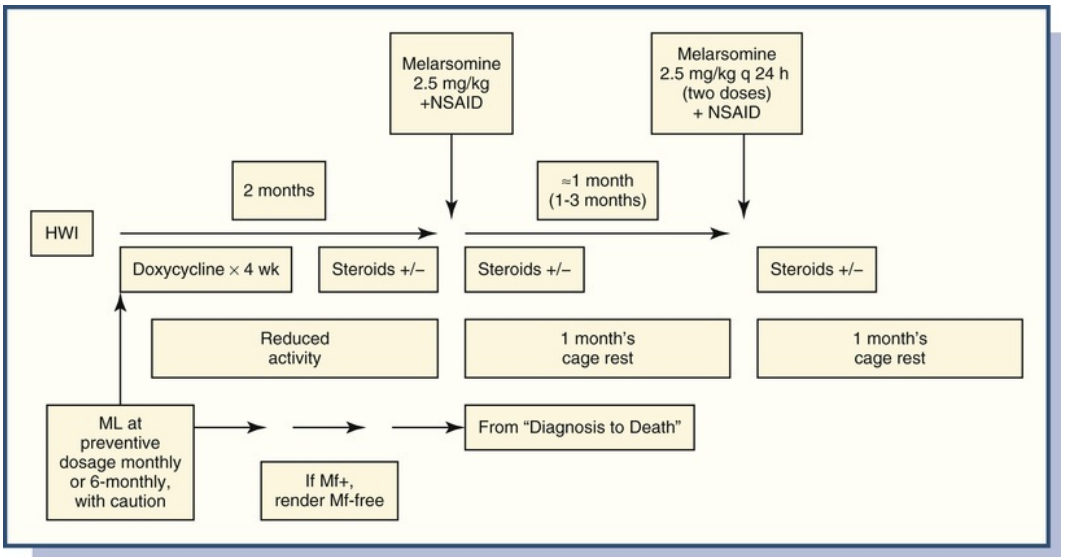


FIGURE 255-14 An approach to the management of heartworm infection in the dog. *HWI*, Heartworm infection; *Mf*, microfilariae; *ML*, macrocyclic lactone preventive drug; *NSAID*, nonsteroidal anti-inflammatory drug. (Adapted from Atkins CE, Miller M: Is there a better way to administer heartworm adulticidal therapy? *Vet Med* 98:310-317, 2003.)

In 55 dogs with severe HWD that were treated in this manner, 96% had a good or very good outcome with more than 98% negative for antigenemia 90 days post-therapy.[77] Of the 55 severely affected dogs, 31% had "mild or moderate PTE," but no fatalities resulted. The most common sign was fever, cough, and anorexia 5 to 7 days post-treatment. This was associated with mild perivascular caudal lobar pulmonary radiographic opacities and subsided spontaneously or after corticosteroid therapy. A recent small study demonstrated reduced biomarker evidence of lung and cardiac damage with the split-dosage protocol, as compared to the standard 2-dose method.[82] Furthermore, the split-dose protocol provided better resolution of proteinuria.

It is now known that administration of doxycycline therapy and monthly ivermectin, for a month prior to administration of melarsomine, reduces the severity of lung lesions in dogs with heartworms, as well as providing other benefits (see Doxycycline).[83]

At the time of diagnosis (usually by positive heartworm antigen test), a minimum database is completed. This includes a Mf test, chemistry panel, complete blood count (CBC), urinalysis, and thoracic radiographic evaluation. If liver disease is suspected from clinical and laboratory findings, serum bile acid determination may be useful in evaluating liver function. At this time, a ML preventive is prescribed (see Figure 255-14).[78] This approach, which has been adopted by the AHS,[84] is used to prevent further infection, to reduce or eliminate Mf (chronic therapy renders the dog less dangerous to itself or other dogs and cats), and to destroy developing L4 (not yet susceptible to adulticidal therapy). Today, concerns around HW resistance to MLs dictate that Mf must be cleared more rapidly than occurs with dosages as preventive agents. The Mf may be dispatched more quickly, though not always completely, with imidacloprid-moxidectin, doxycycline + ivermectin, milbemycin oxime, or high-dose ivermectin (50 mcg/kg; not advised). The addition of doxycycline to this protocol offers numerous advantages discussed below. In microfilaremic dogs, the first ML dose is administered in the hospital or at home with observation, so an adverse reaction might be recognized and treated promptly. Corticosteroids with or without antihistamines (dexamethasone at 0.25 mg/kg IV and diphenhydramine at 2 mg/kg IM; or prednisolone 1 mg/kg PO 1 hour before ±6 hours after administration of the first dose of preventive) may be administered to reduce the potential for adverse reaction in highly microfilaremic patients. It is important to emphasize that adverse reactions are unusual with MLs at preventive dosages but caution should be exercised, particularly with milbemycin oxime.

Depending on the time of year, up to 2 to 3 months has traditionally been allowed to lapse before adulticidal therapy is administered.[78] While initiation of ML administration prevents further infection, this delay allows larval maturation to adulthood, ensuring that the only stage of the life cycle present is the adult, the stage vulnerable to melarsomine therapy. This is more important if the diagnosis is made during or at the end of a mosquito exposure season. If the diagnosis is made in the spring or late winter, when infective larvae have matured, adulticidal therapy may be commenced (see Figure 255-14). This window to possible HW larval escape is also largely closed with 30 days' pre-treatment with doxycycline (98-100% larval kill-rate, if

administered during first 60 days post-infection, and 70%, if given on days 65-94 post-infection; see Doxycycline).[85]

Adulticidal Procedure

Approximately 60 days after diagnosis, including 30 days' treatment with doxycycline (10 mg/kg PO q 12 h), 2 monthly treatments or 1 injection of ML, adulticidal therapy is begun. The second month of waiting is optional, but, while there are no supportive data, it is logical that in killing *Wolbachia* and degrading the HW, an extra 30 days is thought to further lessen the worms' biomass and potential protein release upon their demise.

In the author's clinic, a nonsteroidal anti-inflammatory drug (NSAID) is given the morning before the injection and continued for a total of 4-5 days, in most cases. The first injection of melarsomine is administered by deep intramuscular injection (2.5 mg/kg) in the lumbar musculature (as described in the package insert) and the injection site recorded. Before injection, the needle is changed and care is taken to inject deep into the muscle and nowhere else. Some in the author's practice employ sedation and surgical preparation of the injection site. Care is taken to ensure that the dog does not move during the injection and we accomplish this by supporting the hindquarters to prevent sitting/collapsing, potentially misdirecting the injection. Patients are typically, but not necessarily, hospitalized for the day. The need for exercise restriction for 1 month is *strongly emphasized,* and sedation is provided if necessary. Owners are also advised as to adverse reactions (fever, local inflammation, lassitude, inappetence, cough, dyspnea, collapse), to call if they have concerns, and to return for a second series of two injections in approximately 1 month.

If serious systemic reaction results, the second stage of the adulticidal treatment is delayed or occasionally even cancelled. Typically, however, even with severe reactions, the entire treatment protocol is completed within 2 to 3 months (see Figure 255-14). After a minimum of 1 month, the melarsomine injection procedure is repeated, again with a record of the injection site. If significant local reaction was noted after the first injection, dexamethasone or oral NSAIDs to minimize pain at the injection site accompany subsequent injections. The next day (approximately 24 hours after the first injection) the process is repeated with melarsomine injection into the opposite lumbar area. Client instructions are similar to those previously given, with reemphasis of the need for 1 month's strict restriction of exercise. Antigen testing is repeated 8-12 months after the second series of injections, with a positive test result indicating incomplete adulticidal efficacy. It is emphasized that despite the proven efficacy of melarsomine, not all worms are killed in every patient. The worm burden is typically markedly reduced, but if as few as one to three adult female worms remain, positive antigen tests are likely. Whether to repeat adulticidal therapy, under these circumstances, is decided on a case-by-case basis, with input from the owners.

Macrocyclic Lactones as Adulticides

It is now known that certain MLs have adulticidal properties.[54-56] When these drugs are used to clear a dog of adult HW, the terms *soft-kill* and *slow-kill* are used to describe the approach. Ivermectin has been most studied and is most used for this practice, which should generally be avoided (see Controversies). In this chapter, the terms *soft-* and *slow-kill* are used interchangeably.

Ivermectin, when administered monthly for 31 consecutive months, has ≈95% adulticidal efficacy in young HWIs.[56] Selamectin, when administered continuously for 18 months, killed approximately 40% of transplanted worms.[54] Monthly imidacloprid-moxidectin coupled with 30 days' doxycycline therapy (10 mg/kg q 12 h) is effective at eliminating 5-month-old experimental infections.[57] Milbemycin oxime and sustained-release injectable moxidectin appear to have minimal adulticidal efficacy.[55,61] Although there may be a role for this therapeutic strategy in cases in which financial constraints or concurrent medical problems prohibit melarsomine therapy, the current recommendations are that MLs not be adopted as the primary adulticidal approach (see Controversies).

Exercise Restriction

Cage rest is an important aspect of the management of HWD after adulticidal therapy, after PTE, or during therapy of heart failure. This can often be best, or only, accomplished in the veterinary clinic. If financial constraints preclude this, crating or housing in the bathroom or garage at home, with or without tranquilization, and allowing only gentle leash walks is a useful alternative solution. Nevertheless, some owners do not or cannot restrict exercise, resulting in or worsening thromboembolic complications. In the author's opinion, failure to restrict exercise post-adulticide is the major association with severe thromboembolic complication.

Surgical Therapy

Sasaki, Kitagawa, and Ishihara[86] have described a method of mechanical worm removal using a flexible alligator forceps (Figure 255-15 and Video 255-1). This method was 90% effective in 36 dogs with mild and severe HWD. Only two of the severely affected dogs (n = 9) died of heart and renal failure over 90 days post-operatively. These data suggest that, in skilled hands, the technique is safe. Subsequent studies by Morini and colleagues[87] demonstrated superior results as compared with melarsomine, producing less PTE and CS. It is important to note that the majority of dogs treated surgically required subsequent melarsomine administration to effect a cure. Advantages to this technique include its diminished potential for arsenic complications (subsequent adulticidal therapy would be administered to an asymptomatic dog, using just 2 doses) and relative freedom from thromboembolic complication. Disadvantages include the need for general anesthesia, required operator skill and fluoroscopy, potential for anesthetic or surgical misadventure, and incomplete HW eradication. Nevertheless, it remains a potential alternative for the management of high-risk patients.

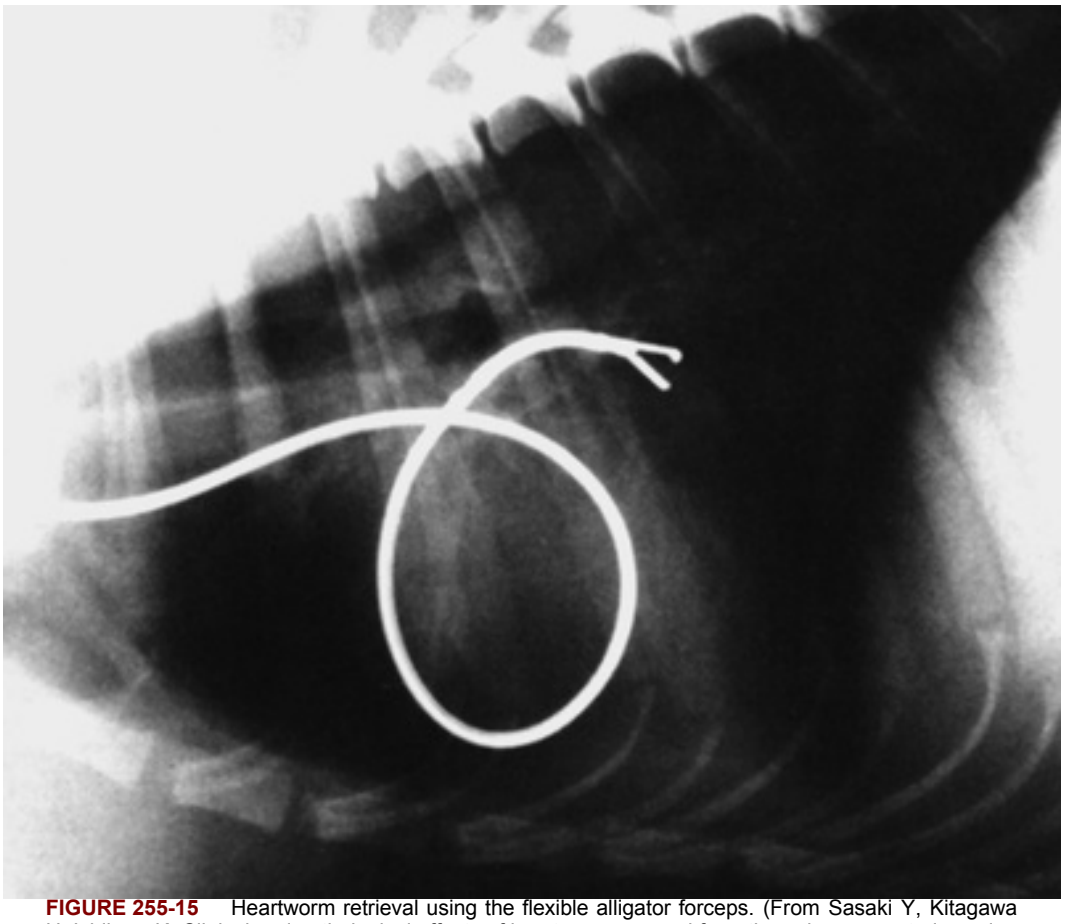


FIGURE 255-15 Heartworm retrieval using the flexible alligator forceps. (From Sasaki Y, Kitagawa H, Ishihara K: Clinical and pathological effects of heartworm removal from the pulmonary arteries using flexible alligator forceps. In Otto GF, editor: *Proceedings of the 1989 American Heartworm Symposium*, Batavia, IL, 1990, American Heartworm Society, p 45.)

Ancillary Therapy

Corticosteroids

The anti-inflammatory and immunosuppressive effects inherent to corticosteroids are useful for treatment of some aspects of HWD. Prednisone, the steroid most often advocated, reduces pulmonary arteritis but actually worsens the proliferative vascular lesions of HWD, diminishes pulmonary arterial flow, and reduces the effectiveness of thiacetarsamide (there are no data to reflect this effect on melarsomine). For these reasons,

corticosteroids are indicated in HWD only in the face of pulmonary parenchymal complications (eosinophilic pneumonitis, eosinophilic granulomas, and PTE), to treat or prevent adverse reactions to microfilaricides, and possibly to minimize tissue reaction to melarsomine. For pneumonitis, prednisone (1 mg/kg/day) is administered orally for 3 to 5 days and discontinued or tapered as indicated.[12,24] The response is generally favorable. Prednisone has also been advocated, along with cage rest, for the management of PTE at 1 to 2 mg/kg/day PO, continued until radiographic and clinical improvement is noted.[24] Because of the potential for steroid-induced fluid retention, such therapy should be used cautiously in the face of heart failure. In addition, caution is warranted because early studies demonstrated that corticosteroid therapy reduced pulmonary blood flow and worsened intimal disease in a model of HWI[88] and corticosteroids are also procoagulant.[24] As mentioned with adulticidal (previously discussed) and microfilaricidal (discussed below) therapies, corticosteroids may be used to minimize potential adverse reactions to melarsomine and to MLs given to rapidly kill Mf.

Aspirin

Antithrombotic agents have received a good deal of attention in the management of HWD[88-92] and the subject has recently been reviewed.[93] Potential benefits include reduction in severity of vascular lesions, reduction in thromboxane-induced pulmonary arterial vasoconstriction and PHT, and minimization of post-adulticidal PTE.[90] Aspirin has shown success in diminishing the vascular damage caused by segments of dead worms,[90] reducing the extent and severity of myointimal proliferation caused by implanted living worms,[91] and in improving pulmonary parenchymal disease and intimal proliferation in dogs with implanted worms, receiving thiacetarsamide.[88] More recent studies, however, have produced controversial results. Four dogs with implanted heartworms, receiving adulticide and aspirin, showed no improvement in pulmonary angiographic lesions, and treated dogs had more severe vascular tortuosity than did controls and dogs receiving heparin.[89] Boudreau and colleagues[92] demonstrated that the aspirin dosage required to decrease platelet reactivity by at least 50% was increased by nearly 70%, with HWI (implantation model) and by nearly 200% with a model (dead worm implantation) of PTE. There were not significant differences in severity of pulmonary vascular lesions in aspirin-treated versus control dogs. For these reasons, the AHS does not endorse antithrombotic therapy for routine treatment of HWD.[28] Calvert and colleagues[24] have, however, successfully used the combination of aspirin and strict cage confinement with adulticidal therapy for severe HWD. If used, aspirin (5-7 mg/kg) is administered PO daily beginning 1 to 3 weeks prior to and continued for 4 to 6 weeks after adulticide administration. With protracted aspirin therapy, packed cell volume (PCV) and serum total protein should be monitored periodically. Aspirin is avoided or discontinued in the face of concurrent corticosteroid therapy, gastrointestinal bleeding (melena or falling PCV), persistent emesis, thrombocytopenia (<50,000/mm^3), and hemoptysis.[24] Clopidogrel (Plavix) has not been evaluated in HWD.

Heparin Therapy

Low-dose calcium heparin has been studied in canine HWD and shown to reduce the adverse reactions associated with thiacetarsamide in dogs with severe clinical signs, including heart failure.[94] In this study, calcium heparin, administered at 50 to 100 IU/kg SC q 8-12 h for 1 to 2 weeks before and 3 to 6 weeks after adulticidal therapy, reduced thromboembolic complications and improved survival, as compared with aspirin and indobufen. Dogs in both groups also received prednisone at 1 mg/kg/day. It is emphasized that this therapy has not been studied with melarsomine adulticidal therapy. Calvert and colleagues[24] advocate sodium heparin (50 to 70 U/kg) in dogs with thrombocytopenia, DIC, or both, continuing until the platelet count is greater than 150,000/mm,[3] for at least 7 days, and possibly for weeks.

Doxycycline

Wolbachia pipientis, first recognized in the 1920s in mosquitoes, is now known to be an endosymbiont in filarid and other parasites, including *D. immitis.* It is essential for the filarids' development, reproduction, infectivity, well-being and survival. Kramer and Genchi have published an excellent review of the relationship between *Wolbachia* and *D. immitis.*[18] With the relatively recent realization that *Wolbachia* may contribute to the pathogenesis of HWI and the adverse reactions to spontaneous and pharmacologically-induced worm death, methods to clear *Wolbachia* have come under study.[17,18,57,83,85,95-100] While doxycycline has many benefits in managing and preventing HWI, ivermectin and doxycycline appear to work synergistically in this regard. In

experimental infections (jugular adult worm transplantation), it has been shown that a complex regimen of ivermectin (weekly at preventive dosages [i.e., four times typical dosage]) and doxycycline (10 mg/kg/day in an interrupted treatment regimen for 14 of 36 weeks) for 36 weeks reduced/eliminated *Wolbachia* in HW, produced parasite uterine involution, eliminated Mf within 8 weeks, reduced PTE after melarsomine therapy, and reduced heartworm burden with ivermectin in a soft-kill protocol, compared with that of control dogs by 78% after 9 months' therapy.[17,18,83,96-98] It should be recognized that this treatment regimen is preliminary, proof of concept, off-label, complex, and impractical. It does, however, demonstrate a potential role for wolbachicidal therapy with doxycycline or other drugs in HWI. Also, the PTE-protective characteristic was not lost in a study of ivermectin monthly at recommended dosage and 30 days' doxycycline therapy. A more practical protocol, employing ivermectin at preventive dosage two times per week for 6 months and 30 days' doxycycline (10 mg/kg/day), hastened slow-kill heart worm therapy, with 73% of experimentally-infected dogs converting to antigen negative status by day 300 post-infection.[100] Additionally, at 10 mg/kg q 12 h, doxycycline monotherapy has demonstrated efficacy in destroying developing tissue stage larvae, as mentioned above.[85,99] Combination therapy with doxycycline and ivermectin renders all host stages "*Wolbachia*-free" and subsequent mosquito-borne L3 non-infectious.[97,99] Doxycycline monotherapy at 10 mg/kg q 12 h for 30 days has also been shown to have negative effects on HWs at all stages of development.[97,99] This is particularly important because it breaks the HW transmission cycle, thereby reducing/eliminating subsequent infections from the treated host and lessening chances of resistant HW isolates being propagated in down-stream hosts. The data at hand indicate that doxycycline or other wolbachiostat is indicated in all dogs with HWI.

Microfilaricidal Therapy

Despite the fact that, prior to 2014, no agent was approved by the FDA-CVM for the elimination of Mf, microfilaricidal therapy has traditionally been instituted 3 to 6 weeks after adulticide administration.[24,36] The MLs offer a safe and effective alternative to previously used levamisole and dithiazanine. Microfilariae are rapidly cleared with ivermectin at 50 mcg/kg (approximately eight times the preventive dosage) or milbemycin oxime at 0.5 mg/kg (preventive dosage), although this represents an extra-label use. Adverse reactions, the severity of which is likely related to microfilarial numbers and the rate at which they are cleared, were observed in 6% of 126 dogs receiving ivermectin at the microfilaricidal dosage.[101] Signs included shock, depression, hypothermia, and vomiting. With fluid and corticosteroid (dexamethasone at 2 to 4 mg/kg IV) therapy, all dogs recovered within 12 hours. One fatality, however, was observed 4 days after microfilaricidal therapy. Similar, but less severe, findings and frequency have been reported with milbemycin oxime at the preventive dosage.[33] Dogs so treated should be hospitalized and carefully observed for the day. Dogs weighing less than 16 kg, harboring more than 10,000 Mf per milliliter of blood, are more apt to suffer adverse reactions.[101] Diphenhydramine (2 mg/kg IM) and dexamethasone (0.25 mg/kg IV) can be administered to prevent adverse reactions to microfilaricidal dosages of ML.

A slower microfilarial kill rate is achieved with ivermectin, selamectin, and topical imidacloprid-moxidectin at preventive dosages.[31,32,53,54,65,66,101,102] Using either the more rapid or slower approach rids the patient of most Mf and sterilizes the female heartworm. The only drug with an FDA-CVM label claim as a microfilaricide is imidacloprid-moxidectin.[102] Doxycycline with ivermectin (or, possibly, another ML) also eliminates Mf promptly and safely. There is currently neither need nor reason to use the bovine ivermectin product to eliminate Mf in dogs.

This author chooses an alternative approach (see Figures 255-8 and 255-14), beginning the administration of ML and doxycycline at the time of diagnosis, often days to weeks prior to adulticidal therapy.[78] This approach is simpler, safer, and invokes immediate protection from further HWI. With the slower-acting microfilaricides (ivermectin, moxidectin, or selamectin *at preventive dosages*), little chance exists of an adverse reaction. However, in treating microfilaremic dogs, the owner should be warned of the possibility and advised to administer the medication (1) on a day when he or she will be at home, (2) in the hospital, or (3) with pre-treatment, as described below. If milbemycin oxime preventive is used, while reactions seem to be rare, the first dose is administered in the hospital and/or may be preceded by administration of dexamethasone and diphenhydramine, when large microfilarial burdens are recognized (see Adulticidal Therapy).

Complications and Specific Syndromes

Asymptomatic Heartworm Infection

Most dogs with HWI are asymptomatic, even though many of these have HWD (radiographic and pathologic lesions). Treatment is as described previously, using melarsomine in the split-dose regimen, along with a ML preventive. Asymptomatic dogs may, however, become symptomatic after adulticidal therapy due to PTE and lung injury (as described elsewhere in this chapter). The risk of PTE can be imperfectly predicted by semi-quantitation of the worm burden, using certain antigen tests, and by the severity of radiographic lesions.[30] Clearly a dog with severe radiographic lesions will not tolerate thromboembolic complications well, but not all dogs with radiographic signs have heavy worm burdens. For example, a dog with moderate to severe radiographic lesions and high antigenemia may not be at high risk for post-adulticidal PTE, because it is possible that the worms have died, explaining both the antigenemia (release from dead worms) and radiographic abnormalities (chronic HWD). This conclusion might also be valid in the dogs with severe radiographic lesions and negative or low antigenemia (assumes most or all worms have died, and antigen has been cleared). Alternatively, antigenic evidence of a heavy worm burden in a dog with minimal radiographic signs might still portend a severe reaction after melarsomine because the findings are compatible with large worm numbers but without natural worm attrition (i.e., a relatively young infection with minimal disease). Of course, low worm burden and minimal radiographic lesions would suggest the least risk of an adverse reaction to adulticide.

It bears emphasis that with each scenario, some guesswork is involved and precautions should be taken. When the risk of PTE is greatest, a 10-14 day tapering dosage of prednisone initially at 5 to 7 mg/kg/day PO at diagnosis and after each melarsomine treatment or clopidogrel (18.75 mg/kg/day PO; no data available for HW) is sometimes employed. Corticosteroids or even heparin are advocated by some.[24] Forced exercise restriction is most important. The owners should be educated as to the risk, the signs suggestive of PTE, and the importance of prompt veterinary assistance in case of an adverse reaction.

Glomerulonephritis

The majority of dogs suffering from chronic HWI have glomerulonephritis, which can be severe (Figure 255-16 and ch. 325).[14] Therefore, when a dog demonstrates glomerular disease, HWI should be considered as a differential diagnosis. Although it is generally felt that the glomerular lesions produced by HWI are unlikely to produce renal failure, a therapeutic dilemma results when a dog is presented with proteinuria, azotemia, and HWI. Logic suggests that adulticidal therapy is indicated because HWI contributes to glomerular disease, but it likewise carries risks. The approach embraced by this author is to hospitalize the patient and to administer intravenous fluids (lactated Ringer's solution at 2 to 3 mL/kg/h; see ch. 129) for 48 hours (beginning 12 hours prior to the first melarsomine dose in the split-dose protocol). The patient is then released, and a 48-hour recheck appointment for blood urea nitrogen (BUN) and creatinine determination is advised. The second and third injections are tentatively scheduled for 1 to 3 months, with the treatment decision based on age, general health, renal function and the patient response to initial adulticidal therapy.

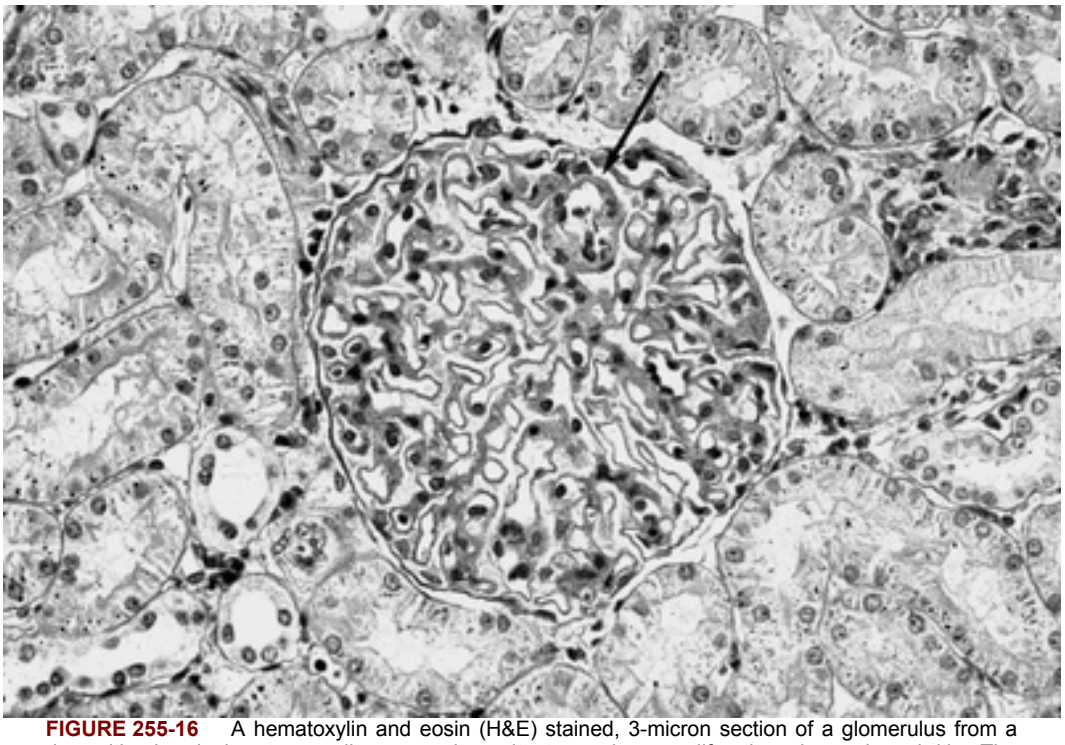


FIGURE 255-16 A hematoxylin and eosin (H&E) stained, 3-micron section of a glomerulus from a dog with chronic heartworm disease and resultant membranoproliferative glomerulonephritis. The capillary walls are thickened, and an overall increase in cellularity is seen. The reader should note a thick-walled capillary containing intraluminal microfilariae (arrow). (Courtesy Dr. Greg Grauer.)

Eosinophilic Pneumonitis

Eosinophilic pneumonitis, which is reported to affect 14% of dogs with HWD, is a relatively early development in the disease course.[12,24] In fact, the pathogenesis probably involves immunologic reaction to dying Mf in the pulmonary capillaries. Clinical signs include cough and sometimes dyspnea and other typical signs of HWD, such as weight loss and exercise intolerance. Specific physical examination findings may be absent or may include dyspnea and audible crackles in more severe cases. Radiographic findings include those typical of HWD with an interstitial to alveolar infiltrate, often worse in the caudal lung lobes (see Figure 255-12). Eosinophils and basophils may be found in excess in peripheral blood and in airway samples.

Corticosteroid therapy (prednisone or prednisolone at 1 to 2 mg/kg/day PO) results in rapid attenuation of clinical signs, with radiographic clearing in less than a week. The drug can then be stopped in 3 to 5 days if clinical signs subside. Although microfilaricidal therapy is typically not indicated because infections are often occult, ML prophylaxis is indicated to avoid further infection. Adulticidal therapy can be employed after clinical improvement.

Eosinophilic Granulomatosis

A more serious, but rare, manifestation, pulmonary eosinophilic granulomatosis, responds less favorably. This syndrome is characterized by a more organized, nodular inflammatory process, associated with bronchial lymphadenopathy and, occasionally, pleural effusion. With pulmonary granulomatosis, cough, wheezes, and pulmonary crackles are often audible; when very severe, lung sounds may be muffled and associated with dyspnea and cyanosis. Treatment with prednisone at twice the dosage used in pneumonitis is reported to induce partial or complete remission in 1 to 2 weeks. The prognosis remains guarded because recurrence within several weeks is common. Prednisone may be combined with cyclophosphamide or azathioprine in an effort to heighten the immunosuppressive effect (see ch. 165). The latter combination appears to be the most effective. Adulticide therapy should be delayed until remission is attained. Because the prognosis for medical success is guarded, surgical excision of lobar lesions has been advocated.[103]

Pulmonary Embolism

Spontaneous thrombosis or PTE associated with dead and dying worms (the most important heartworm complication) may precipitate or worsen clinical signs, producing or aggravating PHT, right heart failure or, in rare instances, hemoptysis and pulmonary infarction (see ch. 243). Acute fatalities may result from fulminant respiratory failure, exsanguination, or DIC (see ch. 197), or they may be unexplained and sudden (arrhythmia or massive pulmonary embolism). The most common presentation, however, is a sudden onset of lethargy, anorexia, and cough 7 to 10 days after adulticidal therapy, often after failure to restrict exercise. Dyspnea, fever, mucous membrane pallor, and adventitial lung sounds (crackles) may be noted on physical examination.

Thoracic radiographs (Figure 255-17) reveal significant pulmonary infiltrates, most severe in the caudal lung lobes. Severity, as compared with pre-treatment radiographs, is typically dramatic. The infiltrate, usually alveolar, is most severe in the caudal lobes, and occasionally areas of consolidation are noted. Laboratory abnormalities vary with the severity of signs but may include leukocytosis, left shift, monocytosis, eosinophilia, and thrombocytopenia. The degree of thrombocytopenia may provide prognostic information.

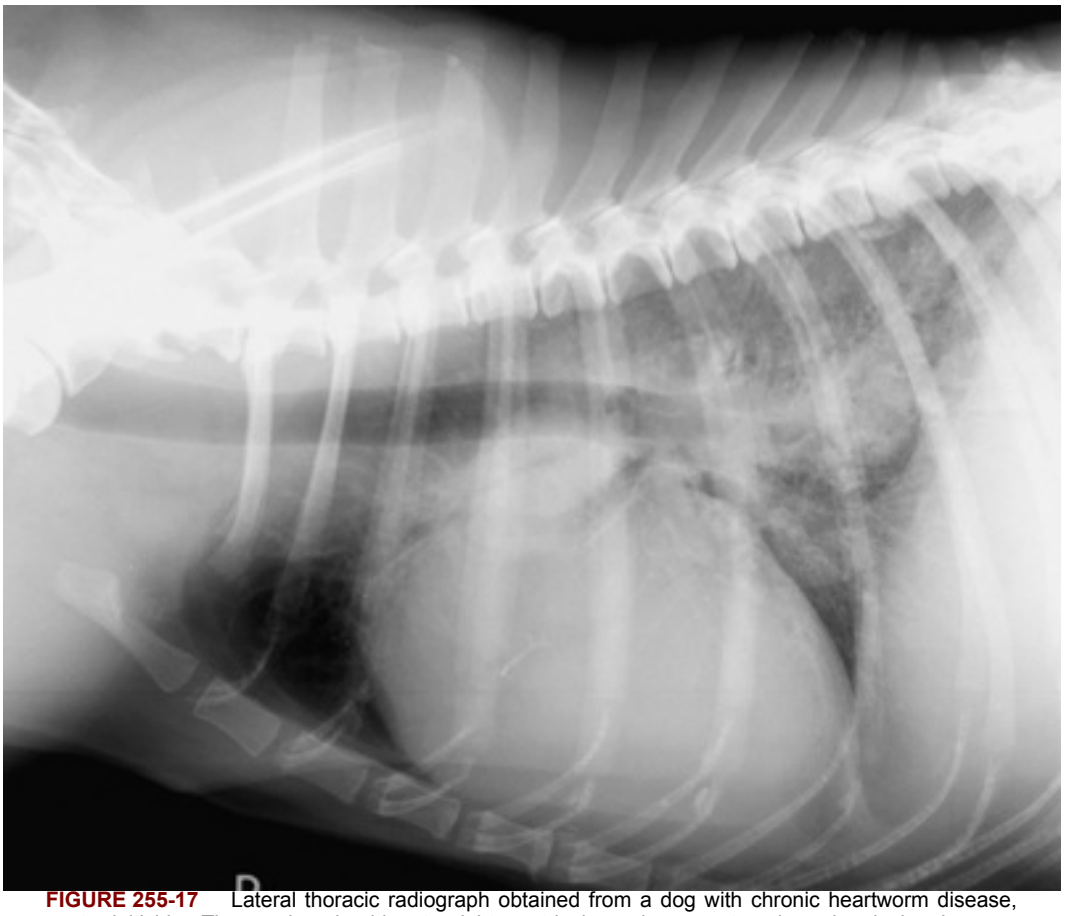


FIGURE 255-17 Lateral thoracic radiograph obtained from a dog with chronic heartworm disease, post-adulticide. The reader should note right ventricular enlargement, enlarged apical pulmonary arteries partially obscured by pulmonary infiltrate, and an interstitial and alveolar infiltrate, most severe in the caudal lung lobes.

Medical management of thromboembolic lung disease is largely empiric and without general agreement. It is generally agreed that strict cage confinement, oxygen administration via oxygen cage or nasal insufflation (50 to 100 mL/kg/min; see ch. 131), and prednisone (1 mg/kg/day for 3 to 7 days) are indicated in the most severe cases.[19,24,104] Some advocate careful fluid therapy (see Caval Syndrome) to maximize tissue perfusion and combat dehydration.[104] The use of heparin (75 IU/kg SC three times a day until platelet count has normalized [5 to 7 days]) and aspirin (5 to 7 mg/kg/day) has been advocated by some[41] but remains controversial.[5,88-93]

Other therapeutic strategies might include cough suppressants, antibiotics (if fever is unresponsive), and, although speculative at this time, vasodilators (amlodipine, sildenafil, hydralazine, diltiazem; see discussion of heart failure below and in more depth in ch. 247).[105,106] If vasodilator therapy is employed, one must monitor blood pressure because hypotension (see ch. 159) is a potential side effect. Clinical improvement may be rapid, with possible release from the hospital after several days' treatment. For less severely affected dogs, careful confinement and prednisone at home are often adequate.

Congestive Heart Failure

Right heart failure results from increased right ventricular afterload (secondary to chronic pulmonary arterial disease and thromboemboli with resultant PHT; see ch. 246). When severe and chronic, PHT may be complicated by secondary tricuspid regurgitation and right heart failure. Congestive signs (ascites) are worsened in the face of hypoproteinemia (Figure 255-18). Calvert suggests that up to 50% of dogs with severe pulmonary vascular complication to HWD will develop heart failure.[24] Clinical signs (see Figure 255-18) variably include weight loss, exercise intolerance, ashen mucous membranes with prolonged capillary refill time, ascites, dyspnea, jugular venous distension and pulsation (Video 255-2), arrhythmias with pulse deficits, and adventitial lung sounds (crackles and possibly wheezes). Dyspnea may be due to pulmonary

infiltrates with eosinophils (PIE) or PTE, but *not* cardiogenic pulmonary edema; abdominal distension; or pleural effusion.

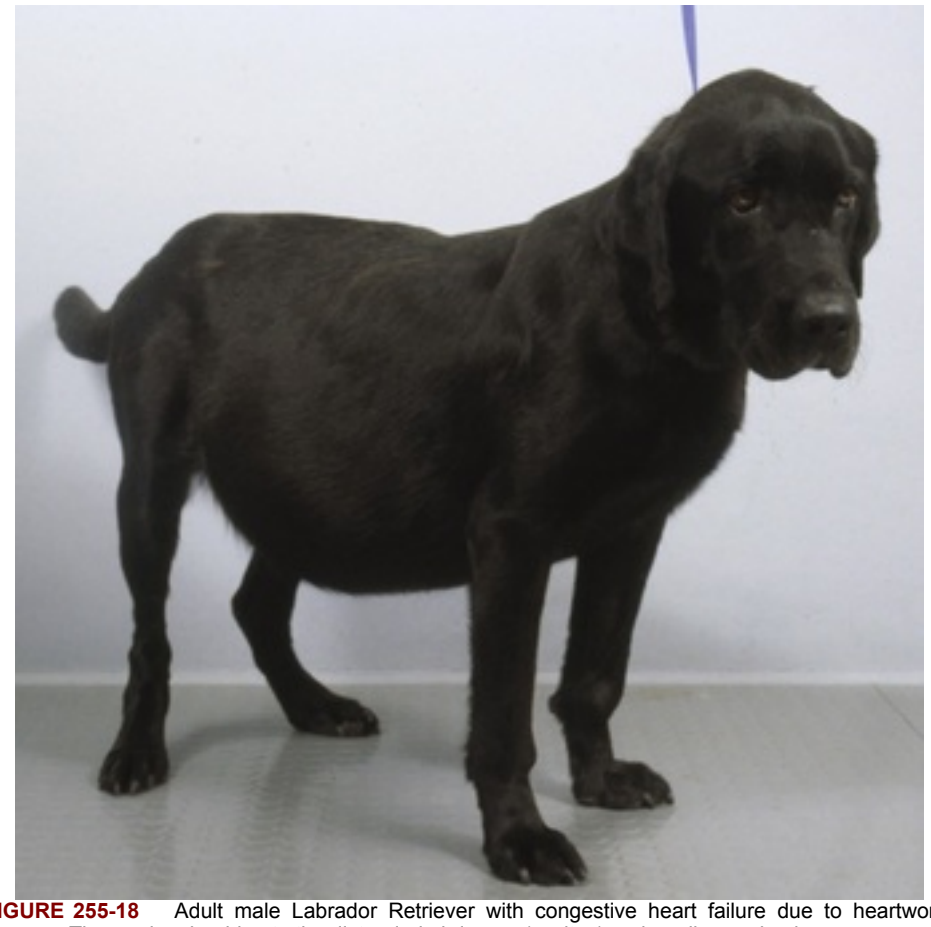


FIGURE 255-18 Adult male Labrador Retriever with congestive heart failure due to heartworm disease. The reader should note the distended abdomen (ascites) and cardiac cachexia.

Adulticide therapy is delayed until clinical improvement is noted. Treatment involves dietary, pharmacologic, and procedural interventions. Specific aims include reduction in signs of congestion (diuretics, sodium restriction, and paracentesis), reducing PHT (vasodilator therapy, ideally with sildenafil and/or pimobendan; see ch. 243), improving cardiac output (reducing afterload and improving systolic function with inotropic therapy [pimobendan]); and blunting the neurohumoral response to a fall in cardiac output (renin-angiotensin-aldosterone system [RAAS] and sympathetic nervous system with angiotensin-converting enzyme [ACE] inhibitors and mineralocorticoid receptor blockers [spironolactone]).

Moderate salt restriction is logical and probably useful in diminishing diuretic needs. To achieve this, the author chooses a diet designed for senior patients or early heart failure. Diuretics may be useful in preventing recurrence of ascites but are typically not able to mobilize large fluid accumulations effectively. This then requires periodic abdominal and/or thoracic paracentesis when discomfort is apparent (see ch. 102). Furosemide is typically used at 2 to 6 mg/kg/day, depending on severity and patient response. Additional diuretics, which provide a supplemental effect by using differing parts of the nephron, include spironolactone (2 mg/kg/day PO), and hydrochlorothiazide (1 to 2 mg/kg PO q 12-48 h). Torsemide, a more potent loop diuretic, can be used to replace furosemide at 10% of its current dosage (see ch. 247).[107]

The ACE inhibitors (e.g., enalapril, benazepril, lisinopril, ramipril), by their effect on the RAAS, may be of use as mixed vasodilators, in blunting pathologic cardiac remodeling and in reducing fluid retention, particularly cases of refractory ascites. The arterial vasodilator, hydralazine, has been shown by Lombard[105] to improve cardiac output in a small number of dogs with HWD and heart failure. It has also been demonstrated to reduce pulmonary artery pressure and vascular resistance, right ventricular work, and aortic pressure without changing cardiac output or heart rate in dogs with experimental, severe HWD (but without heart failure).[106]

Clinical experience suggests that, in order of preference, pimobendan, sildenafil, hydralazine, amlodipine, and diltiazem might all have a role in this setting. Further studies are necessary. In heart failure, the author's first choice is the combination of pimobendan (0.25 mg/kg PO q 12 h) and sildenafil (0.5-1 mg/kg PO q 8-12 h). If finances play an important role in drug choice, hydralazine at 0.5 to 2 mg/kg PO q 12 h, amlodipine at 0.1-0.25 mg/kg PO q 24 h, or diltiazem at 0.5 to 1.5 mg/kg PO q 8 h or a long-acting formulation up-titrated to 2 to 4 mg/kg PO q 12-24 h, may be substituted. The risk of hypotension with these therapies must be realized and blood pressure monitored. In the author's practice, the inodilator pimobendan is employed under these circumstances, either alone or with sildenafil, to provide pulmonary artery vasodilation and inotropic support to reduce the chances of hypotension.

Because of the risk of toxicity and pulmonary vasoconstriction associated with the use of digoxin, it is not routinely utilized by the author in the management of HWD-induced heart failure. However, digoxin accompanied by diltiazem may be beneficial in the management of atrial fibrillation, by controlling the ventricular response rate.

Aspirin or clopidogrel, theoretically useful because of their ability to ameliorate some pulmonary vascular lesions and platelet-induced vasoconstriction, may be used at 5 and 2-3 mg/kg/day PO, respectively. Strict exercise restriction of indefinite duration is strongly advised.

Often, heart failure follows adulticidal therapy, but if it is present prior to adulticidal therapy, the difficult question arises as to when (or whether) to administer melarsomine. If clinical response to heart failure management is good, adulticidal therapy may be offered in 4 to 12 weeks, as conditions allow. Melarsomine is generally avoided if heart failure is refractory, with reliance on a slow-kill approach (ivermectin and 30 days' doxycycline therapy).

Caval Syndrome

Heartworm CS is a relatively uncommon, but severe variant or complication of HWD. Most studies have shown a marked sex predilection, with 75% to 90% of CS dogs being male. It is characterized by heavy worm burden (usually >60, with the majority of the worms residing in the right atrium and venae cavae) and a poor prognosis.[26] Studies performed in the author's laboratory indicate that retrograde migration of adult heartworms to the cava and right atrium, from 5 to 17 months after infection, produces partial inflow obstruction to the right heart and, by interfering with the valve apparatus, tricuspid insufficiency (with resultant systolic murmur, jugular pulse, and CVP increase).[108] Affected dogs also exhibit preexistent heartworm-induced PHT, which markedly increases the adverse hemodynamic effects of tricuspid regurgitation. These combined effects substantially reduce left ventricular preload and hence, cardiac output. Cardiac arrhythmias may further compromise cardiac function (Figure 255-19).

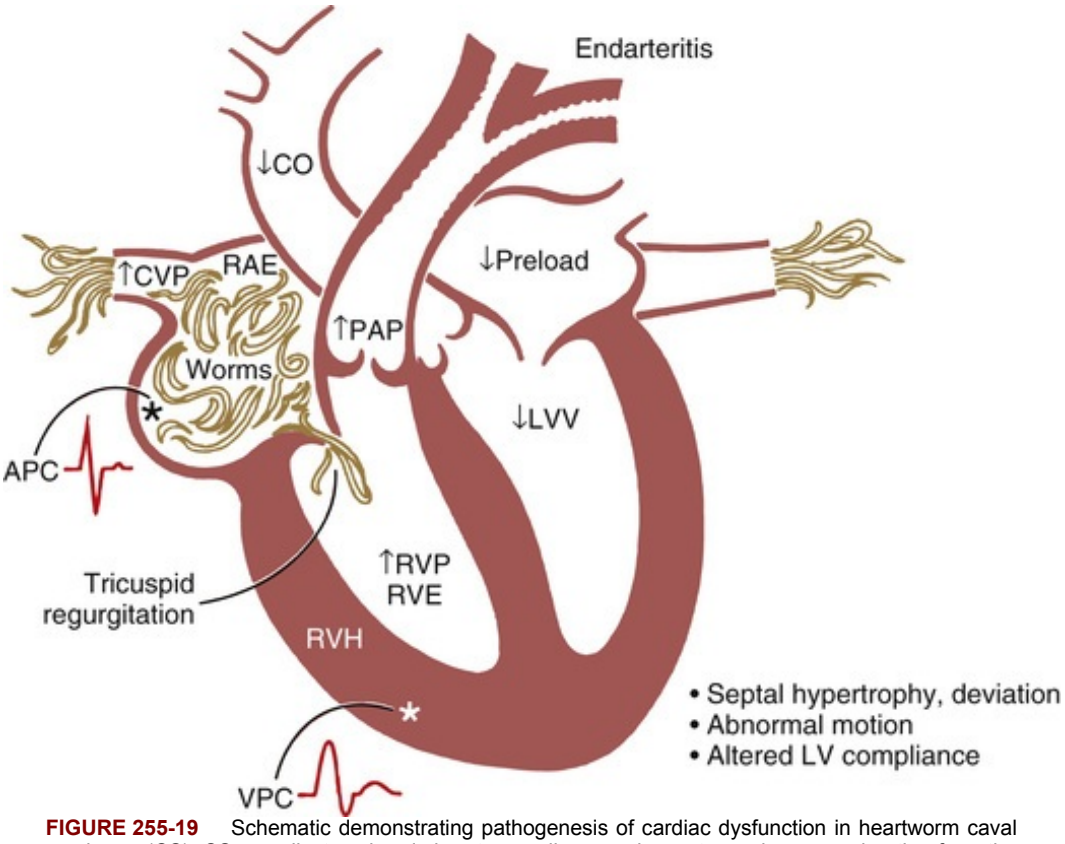


FIGURE 255-19 Schematic demonstrating pathogenesis of cardiac dysfunction in heartworm caval syndrome (CS). CS complicates chronic heartworm disease when retrograde worm migration from the pulmonary arteries occurs, with the majority of worms relocating in the venae cavae and right atrium. Tricuspid valvular function is altered, resulting in incompetence. Tricuspid regurgitation is superimposed on pulmonary hypertension. Left ventricular preload is diminished. Congestive and low-output heart failure ensues. Septal deviation to the left and abnormal, rightward septal motion contributes to preload starvation of the left ventricle. Right ventricular inflow obstruction due to heartworms and cardiac arrhythmias may further contribute to cardiac dysfunction but are probably less important. *APC,* Atrial premature complex; *CO,* cardiac output; *CVP,* central venous pressure; *LVV,* left ventricular volume; *PAP,* pulmonary artery pressure; *RAE,* right atrial enlargement; *RVE,* right ventricular enlargement; *RVH,* right ventricular hypertrophy; *RVP,* right ventricular pressure; *VPC,* ventricular premature complex; *arrows,* increased or decreased. (From Atkins CE: Pathophysiology of heartworm caval syndrome: recent advances. In Otto GF, editor: *Proceedings of the 1989 American Heartworm Symposium*, Batavia, IL, 1990, American Heartworm Society, pp 27-31.)

This constellation of events precipitates a sudden onset of clinical signs, including hemolytic anemia (see ch. 198) caused by trauma to red blood cells (RBCs) as they pass through a sieve of heartworms occupying the right atrium and venae cavae, as well as through fibrin strands in capillaries if DIC has developed. Intravascular hemolysis, metabolic acidosis, and diminished hepatic function with impaired removal of circulating procoagulants contribute to the development of DIC. The effect of this traumatic insult to the erythron is magnified by increased RBC fragility, due to alterations in the RBC membrane in dogs with HWD. Hemoglobinemia, hemoglobinuria, and hepatic and renal dysfunction also are observed in many dogs. The cause of hepatorenal dysfunction is not clear, but it probably results from the combined effects of passive congestion, diminished perfusion, and the deleterious effects of the products of hemolysis. Without treatment, death frequently ensues within 24 to 72 hours due to cardiogenic shock, complicated by anemia, metabolic acidosis, and DIC. A sudden onset of anorexia, depression, weakness, and occasionally coughing are accompanied in most dogs by dyspnea and hemoglobinuria. Hemoglobinuria has been considered pathognomonic for this syndrome. Physical examination reveals mucous membrane pallor, prolonged capillary refill time, weak pulses, jugular distension and pulsation, hepatosplenomegaly, and dyspnea. Thoracic auscultation may disclose adventitial lung sounds; a systolic heart murmur of tricuspid insufficiency (87% of cases); loud, split S2 (67%); and cardiac gallop (20%) (see ch. 55). Other reported findings include ascites (29%), jaundice (19%), and hemoptysis (6%). Body temperature varies from subnormal to mildly elevated.[18]

Hemoglobinemia and microfilaremia are present in 85% of dogs suffering from CS.[26] Moderate (mean PCV,

28%) regenerative anemia characterized by the presence of reticulocytes, nucleated RBC, and increased mean corpuscular volume (MCV) is seen in the majority of cases. This normochromic, macrocytic anemia has been associated with the presence of target cells, schistocytes, spur cells, and spherocytes. Leukocytosis (mean white blood cell [WBC] count, approximately 20,000 cells/mm^3) with neutrophilia, eosinophilia, and left shift has been described. Dogs affected with DIC (see ch. 197) are characterized by the presence of thrombocytopenia and hypofibrinogenemia, as well as prolonged one-stage prothrombin time (PT), partial thromboplastin time (PTT), activated coagulation time (ACT), and high fibrin degradation product concentrations. Serum chemistry analysis typically discloses increases in liver enzymes, bilirubin, and indices of renal function. Urine analysis reveals high bilirubin and protein concentrations in 50% of cases and, more frequently, hemoglobinuria. CVP is high in 80% to 90% of cases (mean, 11.4 cm H_2O; normal, <5 cm H_2O; see ch. 76). Electrocardiographic abnormalities include sinus tachycardia in 33% of cases and atrial and ventricular premature complexes in 28% and 6%, respectively (see ch. 248). The mean electrical axis tends to rotate rightward (mean, +129 degrees), with an S1,2,3 pattern evident in 38% of cases. The S wave depth in CV6LU (V_4), the most reliable indicator of right ventricular enlargement (>0.8 mv), is present in 56% of cases. Thoracic radiography reveals signs of severe HWD with cardiomegaly, main pulmonary arterial enlargement, increased pulmonary vascularity, and pulmonary arterial tortuosity, recognized in descending order of frequency (see Figures 255-9 to 255-11). Massive worm inhabitation of the right atrium with movement into the right ventricle during diastole is evident echocardiographically (Video 255-3). This finding on M-mode and two-dimensional echocardiograms is pathognomonic for CS in the appropriate clinical setting (Figure 255-20). The right ventricular lumen is enlarged and the left diminished in size, suggesting PHT accompanied by reduced left ventricular loading. Paradoxical septal motion, caused by high right ventricular pressure, is commonly observed. No echocardiographic evidence of left ventricular dysfunction exists. Cardiac catheterization documents pulmonary, right atrial, and right ventricular hypertension and reduced cardiac output.

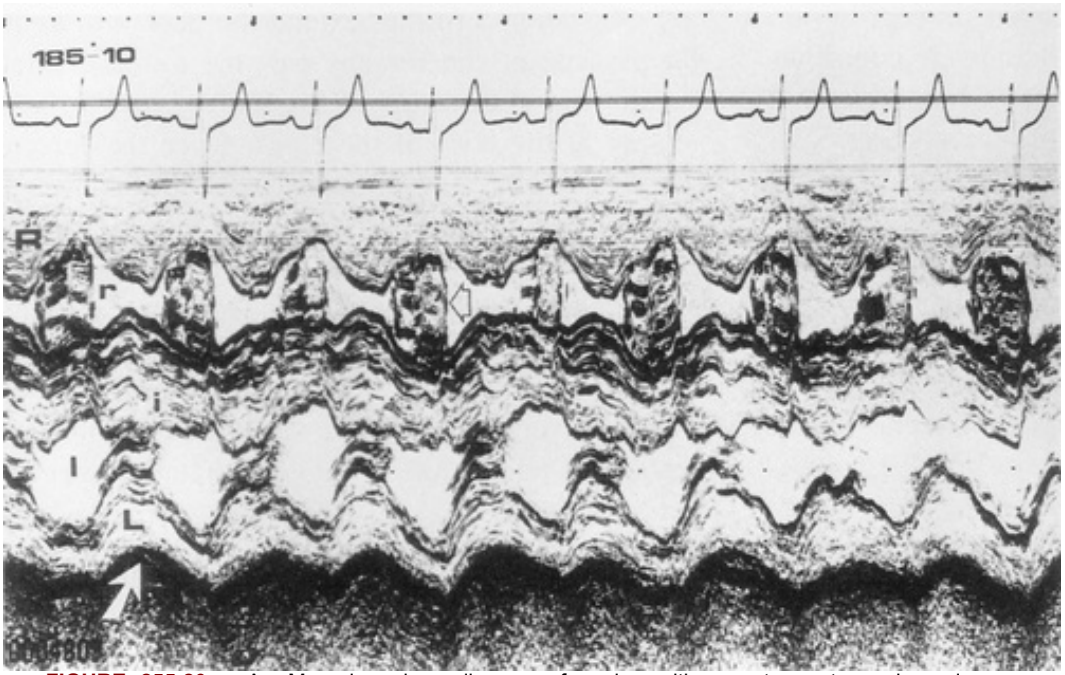


FIGURE 255-20 An M-mode echocardiogram of a dog with recent onset caval syndrome, demonstrating thickening of the right ventricular and intraventricular septal walls, right ventricular eccentric hypertrophy, and a small left ventricle. An echogenic mass (upper arrow) of heartworms can be seen "falling" into the right ventricle with each diastole. Paradoxical septal motion is evident. The lower arrow denotes the pericardium. *i,* Intraventricular septum; *l,* left ventricular lumen; *L,* left ventricular posterior wall; *r,* right ventricular lumen; *R,* right ventricular wall. (From Atkins CE: Heartworm caval syndrome. *Semin Vet Med Surg* 2:64-71, 1987.)

Prognosis is poor unless the cause of the crisis—the right atrial and caval heartworms—is removed. Even with this treatment, mortality can approximate 40% or more. In a retrospective study of 21 dogs with CS,

perioperative mortality (6) or retrieval failure (1) occurred in 33%.[109] All 14 dogs which underwent successful worm removal were discharged from the hospital, with 10 surviving 18 months or longer.

Fluid therapy (see ch. 127) is necessary to improve cardiac output and tissue perfusion, to prevent or help to reverse DIC, to prevent hemoglobin nephropathy, and to aid in the correction of metabolic acidosis. Over-exuberant fluid therapy, however, may worsen or precipitate signs of CHF. In the author's clinic, a left jugular catheter is placed (see ch. 76) and intravenous fluid therapy instituted with 5% dextrose in water or one-half strength saline and 2.5% dextrose. The catheter should not enter the cranial vena cava because it will interfere with worm embolectomy. A cephalic catheter may be substituted for the somewhat inconvenient jugular catheter, but this does not allow monitoring of CVP. The intravenous infusion rate for fluids is dependent on the condition of the animal. A useful guideline is to infuse as rapidly as possible (up to 1 cardiovascular volume during the first hour) without raising the CVP or without raising it above 10 cm H_2O if it was normal or near normal at the outset. Initial therapy (see ch. 127 and 129) should be aggressive (10 to 20 mL/kg for the first hour) if shock is accompanied by a normal CVP (<5 cm H_2O), and it should be curtailed to approximately 1 to 2 mL/kg/h if CVP is 10 to 20 cm H_2O. Whole blood transfusion is not indicated in most cases because anemia usually is not severe, and transfused coagulation factors may worsen DIC. Sodium bicarbonate is not indicated unless metabolic acidosis is severe (pH 7.15 to 7.20). Broad-spectrum antibiotics and aspirin (5 mg/kg daily) may be administered. Treatment for DIC is described elsewhere (see ch. 197) in this text.

Jackson developed the technique for surgical removal of caval and atrial heartworms.[110] This procedure should be undertaken as early in the course of therapy as is practical. Sedation may not be necessary in the moribund patient, in which case, the procedure can be accomplished with only local anesthesia. To facilitate the procedure and maintain aseptic technique, general anesthesia is typically employed in the author's practice. The dog is restrained or laid in left lateral recumbency after surgical clipping and preparation. The jugular vein is isolated distally. A ligature is placed loosely around the cranial aspect of the vein until it is incised, after which the ligature is tied. Alligator forceps (20 to 40 cm, preferably of small diameter) are guided gently down the vein while being held loosely between the thumb and forefinger. The jugular vein can be temporarily occluded with umbilical tape. If difficulty is encountered in passage of the forceps, gentle manipulation of the dog by assistants to further extend the neck will assist in passage of the forceps past the thoracic inlet; medial direction of the forceps may be necessary at the base of the heart. Once the forceps have been placed, the jaws are opened, the forceps are advanced slightly, the jaws are closed, and worms are removed. One to four worms are usually removed with each pass. This process is repeated until five to six successive attempts are unsuccessful. An effort should be made to remove 35 to 50 worms. Care should be taken not to fracture heartworm during extraction. After worm removal, the jugular vein is ligated distally, and subcutaneous and skin sutures are placed routinely. Other catheters, such as urethral stone basket catheters, horsehair brushes, snares and flexible alligator forceps, have also been used.[111] Fluoroscopic guidance, when available, is useful in this procedure. Successful worm retrieval is associated with a reduction in the intensity of the cardiac murmur and jugular pulsations, absence of HW echo shadows on ultrasound examination, rapid clearing of hemoglobinemia and hemoglobinuria, and normalization of serum enzymatic aberrations. Immediate and latent improvement in cardiac function occurs over the next 24 hours. It is important to realize that removal of worms does not adequately reduce right ventricular afterload (PHT), and hence fluid therapy must be monitored carefully before and after surgery to avoid precipitation or worsening of right heart failure. Cage rest should be enforced for a period of time, dependent on patient progress.

Worm embolectomy through a jugular venotomy is frequently successful in stabilizing the animal, allowing adulticide therapy to be instituted to destroy remaining heartworms in a minimum of 1 month. Careful scrutiny of BUN, creatinine and serum liver enzyme concentrations should precede the latter treatment. If aspirin or other anticoagulant therapy is employed, it is continued for 3 to 4 weeks after adulticide therapy. Substantial improvement in anemia should not be expected for 2 to 4 weeks after worm embolectomy. ML preventive therapy, as described previously, is administered at the time of release from the hospital.

Aberrant Migration

Although heartworms in the dog typically inhabit the pulmonary arteries of the caudal lung lobes, they may find their way to the right ventricle, and rarely (see Caval Syndrome) the right atrium and venae cavae. Much less frequently, immature S5 aberrantly migrate to other sites, including the brain, spinal cord, epidural space, anterior chamber of the eye, the vitreous, the subcutis, scrotum, and the peritoneal cavity. In addition, the worms may inhabit the systemic circulation, producing systemic thromboembolic disease.[15] Treatment of aberrantly migrating heartworms requires either nothing (e.g., peritoneal cavity), surgical excision of the offending parasite, adulticidal therapy, or symptomatic treatment (e.g., seizure control with brain migration).

The method for surgical removal from internal iliac and femoral arteries has been described.[15]

Prognosis

The prognosis for asymptomatic HWI is generally good and, although the prognosis for severe HWD is guarded, a large percentage of such cases can be successfully managed.[112] Once the initial crisis has passed and adulticidal therapy has been successful, resolution of underlying manifestations of chronic HWD begins. The prognosis is poorest with severe DIC, CS, massive pulmonary embolism, eosinophilic granulomatosis, severe pulmonary artery disease, and heart failure. After adulticidal therapy, intimal lesions regress rapidly, though not completely, based on their severity.[113-115] Improvement is noted as early as 4 weeks post-treatment in the main pulmonary artery, with all pulmonary arteries having undergone marked resolution within 1 year. Radiographic and arteriographic lesions of HWD begin to resolve within 3 to 4 weeks, and PHT is reduced within months and may be normal within 6 months of adulticide therapy. Pulmonary parenchymal changes are worsened during the 6 months after adulticidal therapy and then begin to lessen in severity, with marked resolution within the next 2 to 3 months. Persistence of such lesions is suggestive of ongoing infection. Corticosteroid therapy hastens the resolution of these lesions. Likewise, irreversible renal disease is uncommon, with glomerular lesions resolving within months of successful adulticidal therapy. Signs of heart failure are also reversible with symptomatic therapy, cage rest, and successful clearing of infection.

Controversies and Areas of Concern

Yearly Testing

The remarkable efficacy of ML preventives and the reduced danger of Mf-induced reactions with their use (see Preventives) have caused some to question the need for yearly testing.[75] Most or all experts, however, currently advocate this practice, including the AHS and the CAPC. In fact, the majority of practicing veterinarians advocate this but experience some client resistance. The issue of yearly testing is clearly important because it deals with financial and ethical, in addition to medical, issues. The veterinary profession must walk the fine line between adequate testing, by which we protect the public, and excessive testing, by which the public may feel "gouged." This is difficult because only sparse scientific detail exists to answer this question, and the answer likely differs by geographic region and even within regions, based on socioeconomic strata and client compliance. That said, the revelation about resistance has changed the dynamics, making the arguments for yearly testing more compelling.

Arguments can be put forth both for and against yearly testing.[26] Proponents might argue that this practice gets animals into the clinic yearly (vaccination no longer does [see ch. 208]), thereby ensuring yearly examination and resultant health benefits and income, and provides inexpensive insurance against unrecognized infection caused by poor compliance, resistance, or dogs that surreptitiously expectorate orally administered medications. In addition, yearly antigen testing is very specific (i.e., little risk of false-positive results), prevents long-term infections from becoming established during the period between heartworm checks, and would seem to limit liability to the practicing veterinarian. They might well also point out that recent reports have demonstrated poor compliance for heartworm prophylaxis nationwide,[46-48] and even though ML preventives provide the safety net of the so-called reach-back effect (retroactive efficacy, safety net), discussed elsewhere, this benefit is realized only with lapses of less than 3 to 4 months, varies between products, and requires continuous administration for 1 year after the lapse.[56] Finally, yearly testing for heartworm antigen is useful to pick up latent (infections that have progressed too far to be eliminated with preventive, but are not patent at the time that preventive was prescribed), incompletely eradicated infections, and product failure.

On the other hand, the opponent of yearly testing might point out that if as a profession we emphasize the efficacy and importance of preventive agents, we may lose credibility by also promoting yearly testing. Additionally, the ML preventives are very efficacious, possessing reach-back potential in the hands of conscientious clients, and the risk of severe adverse reactions in dogs with undisclosed infections, which receive ML, is small. The reason that adverse reactions are less likely is that an infected dog on preventive is rendered either amicrofilaremic or is left with a small microfilarial burden. In addition, the reactions to ML in microfilaremic dogs are less severe than previously encountered with the use of diethylcarbamazine. Furthermore, the argument can be made that the small worm burdens, most likely to result when preventive lapses are brief, will be minimally harmful and might even escape detection by immunologic tests, and that

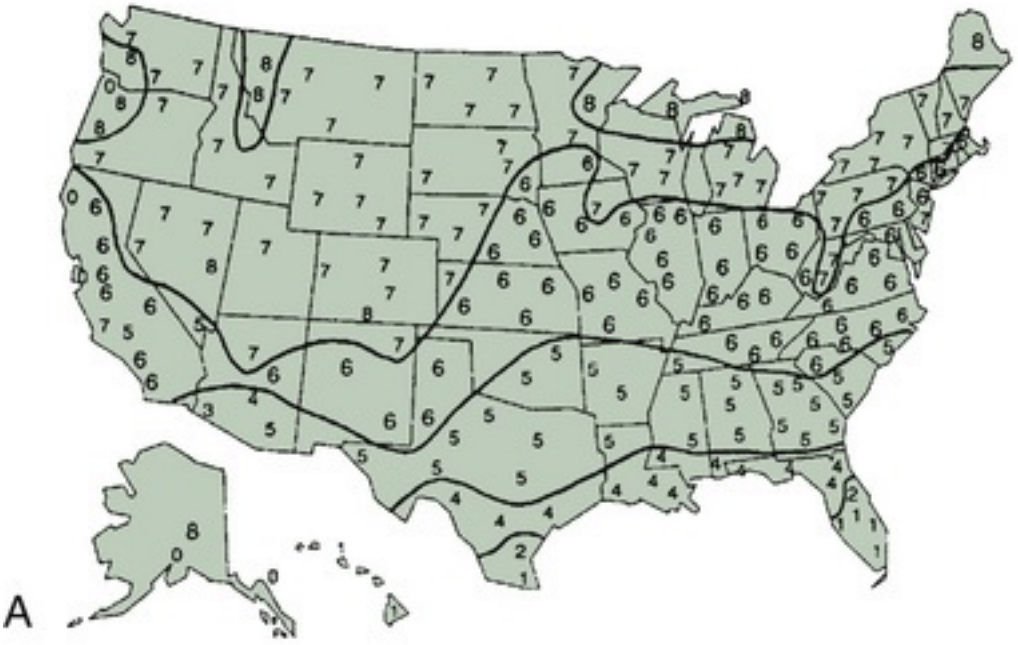
the chances of false-positive tests increase with low prevalence (as would be expected in a population of pets receiving preventive and yearly evaluation).

The AHS addressed this question in 1995.[116] It stated "after the initial retest, if it appears that monthly chemoprophylaxis is being given as prescribed, retesting at intervals greater than 1 year may be sufficient. However, reasonable doubt that administration has been adequate would justify retesting at shorter intervals, perhaps on an annual basis." Unfortunately, existing data on owner compliance are alarming. Cummings and colleagues[47] surveyed dispensing records of 50 veterinary practices in heartworm-endemic areas in the United States and found that, based on the practices' own recommendations, only enough medication was dispensed to adequately protect 41% of the canine clients. This was largely due to the fact that medication was dispensed for less than 50% of the dogs in the practices. It is important to add that this study did not identify compliance failure in which dispensed medications were not administered or in which administered medication was not applied or was not swallowed. These data suggest that the majority of our canine patients *should* undergo yearly testing. Positive test results in this population should be carefully scrutinized, however. In 2005, the AHS stated, "As lack of efficacy has been reported for all macrocyclic lactones (MLs), annual retesting is an integral part of ensuring that prophylaxis is achieved and maintained" and today, both the AHS and the CAPC recommend annual testing.[79]

Yearlong Prevention

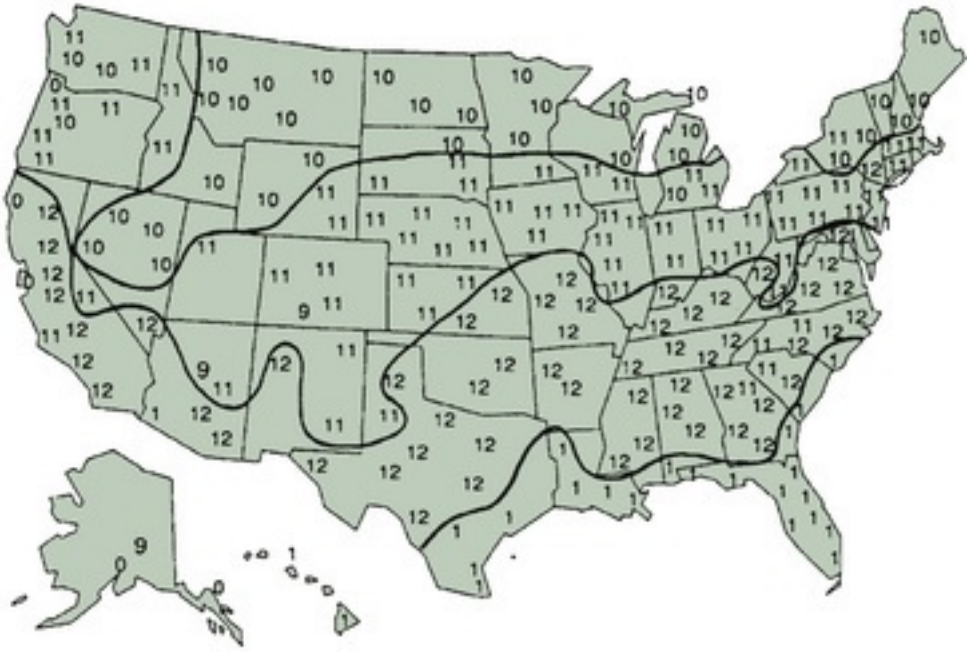
Because of the necessity of the mosquito as an intermediate host for HWI, it has been logical and accepted practice to discontinue preventives during the winter months in the more northern climates. In warmer climates, where mosquitoes may be encountered 12 months of the year, yearlong prophylaxis has been the practice. With the advent of monthly, very effective prophylactic agents, and with improved understanding of the temperature dependence of heartworm transmission by mosquitoes, this yearlong practice has been called into question.[3] Although no supportive data exist, it might be assumed that the ease of administration of monthly preventives may improve owner compliance and that the reach-back effect will make up for short lapses in therapy or unexpected exposures at the beginning or end of the transmission season, thereby making the effective period of prevention longer. More importantly, studies have shown that transmission, even in the most heartworm-endemic areas, does not occur during the final quarter of the year.[2] This is because the mosquito, which is generally assumed to live 30 days, requires a minimum average daily ambient temperature to allow larval development to the infectious (L3) stage. This requirement is defined in heartworm development units (HDUs). An HDU is the degree days (in °C) that the average ambient temperature surpasses the developmental threshold of 14° C (57° F).[2] Restated, for each day that the average ambient temperature exceeds the threshold, an HDU is attained; if the average temperature is 16° C for 1 day, for example, then 2 HDUs are attained. For development of infective larvae, 130 HDUs must be attained and, to be effective, these must be attained in the lifetime of the female mosquito (≈30 days). If the average temperature is 16° C, for example, it would take 65 days for L3 to develop, thereby making transmission impossible. On the other hand, a 24° C average temperature would allow the molt to L3 to occur in 13 days, well within the mosquito's life expectancy. In a very innovative approach to this question, Knight and Lok[3] surveyed temperature extremes in 200 weather stations over a 30-year period and calculated the worst-case scenario for transmission of heartworms. The resultant isotherm maps (E-Figure 255-21) constructed from this information indicate the month to begin and to cease heartworm preventive therapy by geographic region. In only Hawaii, southern Florida, and the southern tip of Texas is yearlong preventive deemed necessary, using this model.

Macrolide heartworm chemoprophylaxis
estimated timing of first monthly dose
first day of month administration



A

Macrolide heartworm chemoprophylaxis
estimated timing of last monthly dose
first day of month administration



B

E-FIGURE 255-21 Isotherm maps demonstrating the month to begin **(A)** and stop **(B)** heartworm monthly preventative therapy based on data from nearly 200 weather stations (see text for detailed description). A zero (0) indicates no preventative necessary. (From Knight DH, Lok JB: *Seasonal timing of heartworm chemoprophylaxis in the United States. Proceedings of the 1995 American Heartworm Symposium*, Batavia, IL, 1996, American Heartworm Society, pp 37-42.)

Arguments may be drawn against this theory and in support of yearlong prevention, or at least for a longer prevention season than indicated by the isotherm maps, published by Knight and Lok.[3] First, though fascinating and backed by scientific fact, this approach represents only a theory, and one that can never be proven. It cannot be proven because this would require testing the hypothesis in every locale in the country in an infinite number of years and seasonal variation. Second, some aspects of the HDU model fall under question:

- Do all female mosquitoes really live only 30 days?
- Do not some mosquito species live longer than others?
- Are there not other climatic factors such as humidity that play a role in larval development?
- Are there not microclimates within isotherm regions that might allow more HDUs to be attained?
- Might not mosquitoes seek microclimates (indoors perhaps) with temperatures to allow heartworm larval development?
- Climate change is not taken into consideration in this scheme.

Recent work indicates that HDUs calculated on an hourly, rather than daily basis, are more accurate and that the method used for the Lok-Knight maps may underestimate the risk of HWI.[117] Third, owner compliance has been shown to be far less than optimal, making any compromise in HW prevention questionable.[46-48] Fourth, the ML reach-back benefit, which protects dogs for which compliance is imperfect, falls after a maximum 4-month lapse in therapy, varies among preventives, and requires 12 to 14 months of continuous therapy after the lapse to be effective, which does not happen with seasonal prevention programs.[52,55,56] Additionally, should an adult infection be present, ML adulticidal efficacy requires at least 2 years' continuous therapy.[56] Fifth, sometimes significant differences exist in adjacent isotherm regions, rendering decision making confusing and potentially hazardous. For example, in Florida, the model describes adjacent regions exist which require 10 or 12 months of preventive treatment. How, in this instance, does an owner or veterinarian know which protocol to use? Furthermore, in some areas, the change from current recommendations to those based on the isotherm maps is minimal. For example, in Wisconsin, current seasonal recommendations would dictate starting heartworm preventive in May and continuing through November, whereas the isotherm map suggests July through October, a difference of two doses. Sixth, animals travel, often to warmer climates during winter. Seventh, because some ML and ML combination products have broad spectra, their use in other parasite control might argue for their use for longer than just the projected heartworm transmission season. Eighth, the savings to clients is relatively small. If a client in North Carolina (June 2015) changes from yearlong prevention to the Knight-Lok recommendation (12-month administration to 7-month administration), the savings for 40-lb and 20-lb dogs is about $35 and $24 per year, respectively. Ninth, most clients do not want to take a chance when the risks/options are carefully and thoughtfully explained to them. Tenth, and most importantly, the Knight-Lok recommendations were made prior to the discovery of ML-resistant strains. This knowledge makes the prospect of altering policy to that which increases the risk potential for HWI to be harbored and spread very questionable, indeed.

The Knight-Lok model provided novel and useful information, indicating that the risk in other than prime heartworm season is less than previously believed, and that in some instances heartworm prophylaxis might be excessive. The Knight-Lok model should stand as a suggestion for planning the timing of seasonal prophylaxis, with practice erring to the conservative. This means extending the isotherm map suggestion 1 month in either direction and taking the earliest implementation date and the latest cessation date surrounding one's geographic region. As a profession, we are faced with the dilemma of providing the best care with fiscal responsibility. We now have the information to decide what is best in a given geographical area and recommendations from two organizations advising year-round HW prevention. Once explained honestly, it then falls upon the shoulders of the client to determine if the risk of possible, but generally unlikely, infection is worth the savings.

Macrocyclic Lactones as Adulticides

It is now proven that ivermectin and probably selamectin have adulticidal efficacy that can approach 100%

with prolonged, continuous administration.[55,56,68] Ivermectin was demonstrated to be 95% successful as an adulticide in experimental, young infections with 31 months' continuous administration.[55] A more recent study by the same investigator demonstrated less optimistic results (only 71% in 24 months).[118] The exact role of MLs in the management of HWI, other than as preventives, is unclear and likely will continue to stir controversy for years to come.

The appeal of MLs for this use is that it takes the veterinarian out of the "complication loop." Complications might indeed still occur but would not as likely to be temporally linked to the ML administration (as they are to arsenical use). In addition, reduced cost, patient discomfort, and inconvenience are appealing. Lastly, and importantly, ivermectin coupled with 30 days' doxycycline therapy has been shown to shorten the time to worm death, while ridding the patient of microfilariae, thereby lessening the concern that this protocol lends itself to the development of ML resistance.[100]

Arguments against the use of ivermectin in this way include the following:

- Represents an off-label use of ivermectin
- Requires continuous compliance from a client who often has allowed HWI to occur—most often by poor compliance
- Lack of knowledge about the timing and degree of exercise restriction necessary; safe use might require >31 months of continuous exercise restriction
- Absence of a controlled kill as seen with melarsomine, reducing the ability to effectively monitor for adverse effects
- Lack of knowledge as to the effect of chronic antigen release from slowly dying adult heartworms on the kidneys and lungs
- Knowledge that ML "slow adulticidal therapy" does not stop progression of lung disease associated with HWI and that lung disease progresses as long as worms are present[119]
- Proven efficacy is only in young (<8 months old) experimental HWI[56]; however, efficacy may vary with different ages of HW
- More recent studies in natural infections showed only 71% efficacy at 24 months, based on positive antigen tests[118]
- McCall, instrumental in discovering the adulticidal efficacy of MLs, based on worsening of clinical parameters in dogs with natural HWD, now states "monthly administration of IVM to dogs with clinical, radiographic or echocardiographic evidence of heartworm disease is ill-advised and such treatment of even the asymptomatic dog should be done only with much caution and frequent monitoring"[118]
- Concern that this approach predisposes to heartworm resistance to ML[120,122,149]

In 2001, prior to knowledge of doxycycline's use in HW control, at the American Heartworm Symposium, the audience and a panel of experts were polled by this author as to their beliefs regarding the role of ivermectin as an adulticide in their own practices.[123] Five percent of the audience and none of the expert panelists used *only* ivermectin for adulticidal therapy. Approximately one third of both groups did not, or would not, use ivermectin as an adulticide, under any circumstances. Finally, approximately 70% of the expert panel and 50% of the audience stated that they would use ivermectin for this purpose only under mitigating circumstances of financial or medical constraint. An unpublished survey of veterinarians attending heartworm seminars at the North American Veterinary Conference in 2012 showed that while 18% of attendees used the slow-kill approach as their primary method of HW treatment, only 7% used this approach *without* doxycycline.

The author recommends that melarsomine be the primary adulticidal tool and recommends or accepts the *limited* use of ivermectin in instances where a preventive is necessary in a heartworm-positive dog and the owner cannot afford arsenic therapy or in which medical conditions preclude its use; in the event of residual infection after appropriate treatment with melarsomine (assumes low worm burden); and, obviously, in unrecognized infections. In addition, whenever slow-kill methodology is intentionally utilized, it should be accompanied by 30 days' doxycycline therapy to reduce microfilarial numbers and propagation efficiency, thereby reducing the risks of development of resistance (see Anti-*Wolbachia* Therapy, below).

Anti-*Wolbachia* Therapy

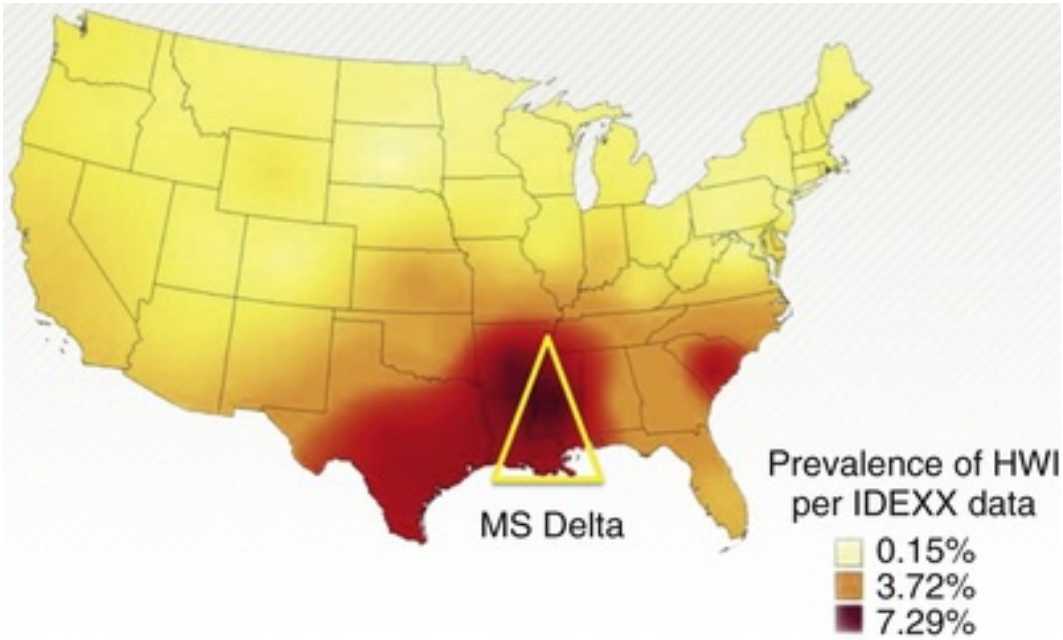
The interactions of *Wolbachia*, filarid parasites, and their hosts, as well as the use of doxycycline therapy, has been reviewed and is covered above in the Treatment section.[4,18] The use of doxycycline to destroy *Wolbachia*,

which lives in a symbiotic relationship within the HW, is logical as there is evidence that the HWs are debilitated or killed, that larval development is inhibited, that HW fertility and transmission are lessened, that adulticidal efficacy of ivermectin is enhanced, that immune-mediated processes (e.g., glomerulonephritis) might be reduced, and that the pathology produced by living or dead/dying worms and *Wolbachia* is lessened. Published evidence of the efficacy of doxycycline in the treatment of natural HWI is still rather sparse, the ideal protocol is far from understood, and doxycycline is not without side effects.[124,125] This author, nevertheless, combines doxycycline (20 mg/kg/day, divided into 2 doses × 30 days) with monthly ivermectin for soft-kill (when used because of lack of an alternative) to hasten worm demise, kill developing tissue stages of *D. immitis,* and rid the patient of Mf. When adulticidal therapy is chosen, this author employs doxycycline (along with ivermectin) in an attempt to reduce melarsomine-associated PTE, eliminate Mf, and kill tissue larval stages (see Figure 255-14).[4,18]

Heartworm Resistance to Macrocyclic Lactones

Prevention failure most often results from a lack of understanding on the part of owners as to the risk of HWI, a lack of owner compliance, or from inadequate instruction on preventive measures by the attending veterinarian.[1,46-48] Another potential source of prevention failure is the very real and frightening prospect of HW drug resistance, with the potential loss of this important drug class from the armamentarium of the practicing veterinarian.

Since the earliest part of this century, there has been growing concern that heartworms are becoming resistant to the ML class. This concern is based on reports from the field of increasing instances of drug failure to prevent HWI, termed LOEs (lack of efficacy reports). These reports have largely emanated from a region termed the Mississippi Delta (MS Delta), including parts of Tennessee, Arkansas, Louisiana, and Mississippi. Veterinarians in this area (E-Figure 255-22) have reported increased drug failure in dogs considered to have received adequate ML preventives and an increase in the difficulty with which Mf are cleared, using this class of drugs.



E-FIGURE 255-22 Map showing the Mississippi (MS) Delta, as the term is used in the context of heartworm infection. Landmarks include Memphis, TN and Jonesboro, AR at the northern borders and Gulfport, LA and Port Charles, MS as the southern borders. *HWI*, Heartworm infection. (Courtesy Auburn University and Novartis Animal Health.)

Based on the growing number of veterinary reports, the FDA-CVM formally reported this concern in 2005, subsequently requiring that manufacturers remove product claims of 100% efficacy.[126] During the next decade, millions of dollars have been spent to explore the validity and suspected mechanisms behind LOE.[127-149] *In vivo* microfilarial resistance to MLs was documented in a Hurricane Katrina canine survivor,

which could not be cleared of Mf, regardless of dosage and combination of MLs (but not doxycycline) utilized.[127]

Other early studies focused on a handful of dogs with medical records supporting claims of good preventive compliance and a history of difficulty in clearing Mf with ML.[128] Using an *in vitro* assay, Mf isolated from 4 of these dogs were subsequently demonstrated to be less susceptible to all currently marketed ML molecules, as compared to Mf from control dogs. Subsequent genetic analysis showed a close relationship between these Mf isolates, with a particularly high degree of homozygosity in the *P-gp* gene.[129] Importantly, in three isolates studied, there was a significant negative correlation between the susceptibility of the Mf to MLs and the percentage of homozygous (GG-GG) P-gp genes.[129]

Independent of these findings, a HW isolate (MP3) from Athens, Georgia, produced infection, despite treatment with either ivermectin or milbemycin oxime in the FDA-CVM (1-dose, 30 days post-infection) test of efficacy, the first ever recorded.[130] Expanding our understanding of the breadth of the problem and its therapeutic variability, Blagburn used a heavy MP3 challenge (100 L3) to demonstrate failure of one dose of ivermectin, milbemycin oxime, and selamectin, while topical imidacloprid-moxidectin experienced no failures in preventing HWI.[131] The infection rate was high (7/8 dogs in each group), but the worm burden of infected dogs was small. Subsequent tests showed that milbemycin oxime, given for 3 consecutive monthly doses, was 100% protective, temporarily alleviating some, but not all concern.[132] Furthermore, 2 of the aforementioned Blagburn isolates (Td2008 and Jd2009) and 2 separate LA isolates (LSU10 and LSU13) were used to challenge dogs receiving ivermectin.[133,134] All were successful in creating infection, as was Jd-2009 in dogs having received moxidectin in the six-month injectable formulation.[135]

Finally, and most concerning, is the isolate JYD-34, whose L3 produced infection in 7 of 8 dogs (worm burdens 1/3 to 1/2 that of control group) per group, despite *3 monthly doses* of ivermectin, milbemycin oxime, or selamectin,[136] while topical imidacloprid-moxidectin, with high and prolonged tissue levels, protected against JYD-34 in the FDA-CVM *one-dose* protocol.[136] It is noteworthy that, in a separate 1-dose study of JYD-34, 1 of 8 dogs was infected with 2 worms, despite having received imidacloprid-moxidectin.[136]

Importantly, resistance to ML in HW-challenge was proven in all 6 isolates referred to above. Also, the MP3 strain is considered by some to be only partially resistant because it can be prevented with traditional preventive molecules, administered for *3* consecutive months after exposure.[122] The JYD strain is highly resistant to all ML molecules, but only partially resistant to topical imidacloprid-moxidectin.

At the time of this writing, the concept of *hereditary* HW resistance to ML in certain isolates or biotypes is well accepted by clinicians and HW researchers.[122,127-142] It also is now clearly apparent that Mf exist which have reduced or absent susceptibility to this drug class.[127,128]

Other areas remain controversial, unclear, or both. At least one expert believes that the off-label use of ML as a "slow-kill" HW adulticide has produced this resistance, with the MS Delta LOE explosion being the result (Dwight Bowman, personal communication, 2014). Bowman, who has long warned against use of the soft-kill technique and long predicted the development of resistance, succinctly explains the hypothesized role treating microfilaremic dogs with ML. "The concern with the extended presence of microfilariae in dogs on a long-term preventive regimen … [is that] … these microfilariae are persisting in the presence of the macrocyclic lactones. The worry is that these microfilariae have been selected for resistance to these molecules, and the mosquitoes have the ability to transfer worms that have already been selected for their ability to survive in the presence of these products."

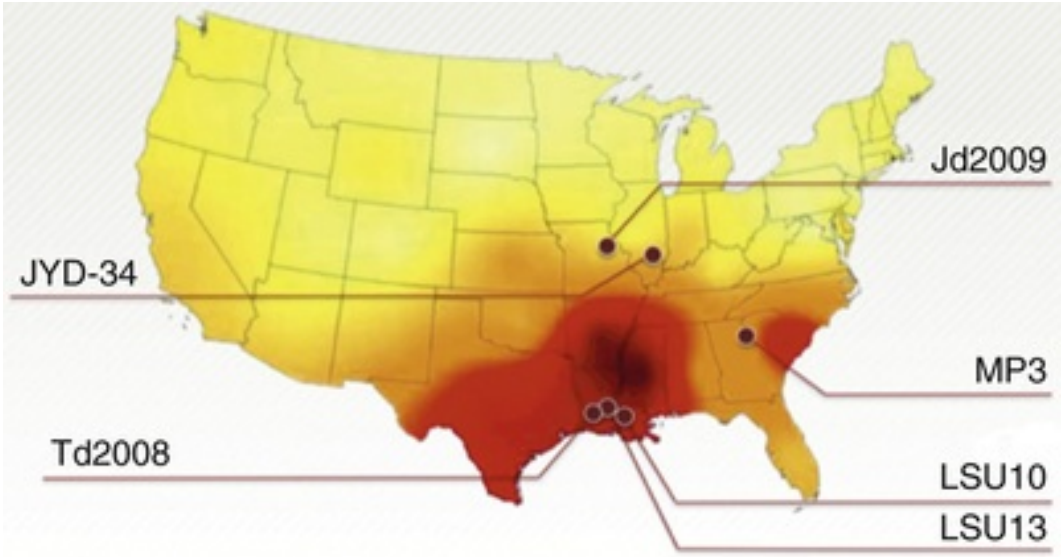
Some parasitologists, veterinarians, and laypeople also believe, or are concerned, that the problem is not just wide-spread, but also spreading north from the Delta.[139-142] While believing in the existence of HW resistance and *advocating against* the use of the slow-kill approach, this author takes a somewhat less alarmist perspective on the range and immediate danger of resistance. This is based on published and unpublished data and personal observation. Importantly, however, he does *strongly advocate* for careful surveillance and taking appropriate steps to do what we can to prevent further resistance development and spread, which at its worst, has the potential to render this class of drugs useless to us for HW control (see What Do We Do?).

While it is accepted that there are HW biotypes that are resistant or less susceptible to MLs, when compared to our historical perspective, there is an alternative to the "man-made resistance" explanation. This is the possibility that a bell-shaped curve of susceptibility, due to spontaneous mutation,[122,137] naturally exists, with HW biotypes being variably susceptible to MLs. This possibility is supported by experts on resistance and by the fact that early (1980s) range-finding studies of ivermectin showed that some heartworms were able to break through at a dosage of 3 mcg/kg (one-half the recommended dosage), even

though the majority of infections were prevented.[134] Indeed, it is at least conceivable, since no one had ever looked for resistant biotypes until circa 2005, that less susceptible HWs have always been there. If true, this neither reduces the risk nor diminishes the importance of these recently discovered resistant HWs.

While not an advocate of the soft- or slow-kill adulticidal approach, this author does *not* feel that the LOE rise reported from the Delta is likely due solely to resistance arising from off-label use of MLs as adulticides. First, the validity of the vast majority of such claims has been called into question. In a study carried out by the author and colleagues, 301 cases of HWI in 271 proven HW-infected dogs from 19 Delta practices expressing concern regarding resistance were scrutinized.[143] Each of the dogs evaluated was the source of an owner satisfaction guarantee claim to the pharmaceutical company making the heartworm preventive in question. Computerized analysis (Window of Infection Tool, Merial, Ltd.) of the medical records from the dogs involved in the claims revealed that *only* 1.7% of the 301 infections had a perfect purchase history (no lapses in purchasing HW preventive >45 days in duration), evident in the medical record. Another 19% of claims, while they did not have purchase gaps >45 days, within the window of infection, were associated with multiple HWIs per dog, sporadic purchase histories, and significant (often prolonged and multiple) purchase gaps outside the window of infection, casting aspersions on the reliability of the preventive care provided to these dogs. Nearly 80% of the claims were invalidated by careful investigation of the owners' purchase histories and over 98% drawn into question. Several conclusions can be drawn from these data. First, compliance is a problem. Second, the majority of claims are invalid and the vast majority are, at the very least, questionable. And third, the LOE problem has been vastly over-reported.

Still another argument against slow-kill driven resistance being the cause of the Delta "epidemic" is that in 10 years' exploration, only 6 dogs have been discovered from which Mf have been able to develop into proven resistant L3.[130,133,134,136] The origin of these dogs has been varied and somewhat scattered (E-Figure 255-23), only 3 of which were isolated from the Delta. It is difficult to look at this number and distribution and conclude resistance is widespread, with "scattered" and "sporadic" being more appropriate adjectives. Furthermore, 2 of the 6 (MP3 and JYD-34) were found in geographical sites without resistance concerns and far from the MS Delta (Illinois and Georgia).



E-FIGURE 255-23 Sites of discovery of macrocyclic lactone–resistant heartworm isolates. (Courtesy Auburn University and Novartis Animal Health.)

That the MS Delta's increase in LOEs is resistance-driven is also challenged by the fact that the three major tenets of resistance have not been met.[122,144-147] These tenets are:

1. Resistance does not develop where there is a large refugia (susceptible animals not receiving preventive). The Delta has likely the largest refugia in the nation, with wildlife, a high percentage of unprotected pets, a low per capita income, and a massive mosquito population with a high infection rate.[144-146,148]
2. Resistance spreads rapidly.[122,147] The *lack of spread* of "resistance" beyond the Delta over the last 10 years is impressive, with cities 1-2 hours' drive beyond its boundaries (e.g., Tupelo, MS; Mobile, AL; and

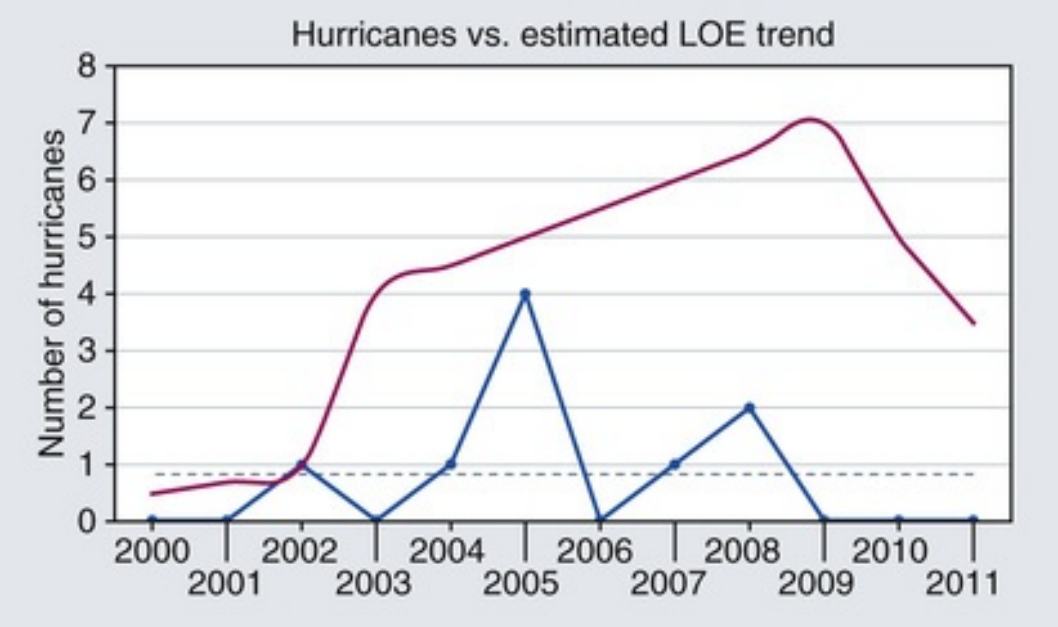
Pensacola, FL) voicing little concern over escalating LOE (Atkins, personal observation). Furthermore, while most of the "resistant" isolates are similar in that they share the GG-GG P-gp genotype, two isolates (MP3 and JYD34), which came from dogs far from the Delta and from areas with no current resistance concerns, do not exhibit this polymorphism, arguing that these isolates did not originate in the Delta. Three of 4 remaining "resistant" isolates had the P-gp genotype and were found in the Delta, supporting the viewpoint that "resistance" has been largely static and is not spreading.

3. Resistance is forever.[147] Since peaking in 2009, the number of Delta LOE claims made to manufacturers has dropped substantially, according to industry sources. Pulaski has confirmed this in Louisiana, where the peak was in 2009.[134] This decline is not consistent with drug resistance being the primary driver of LOE claims.[122]

The Delta LOE spike appears to meet none of these three "necessary" criteria needed to support ascribing this increase in LOE solely to resistance. There are, however, potential alternative explanations for failure of these tenets to hold true for HW resistance in the MS Delta.[122] Certainly, while resistance *does* indeed exist, the possibility that it might *not* be the sole, or even major, reason for the rise in Delta LOEs, must at least be entertained.

If the Delta LOE dilemma is not entirely due to resistance, as has been suggested herein, then what other factors have contributed?

1. As stated above, compliance failure is the biggest association/causative factor, explaining the vast majority of Delta LOEs.[143]
2. Also, for maintaining owner satisfaction guarantees, yearly heartworm tests are required. It only stands to reason that if we test more frequently, we will find more heartworms.
3. Another important factor, in the author's opinion, is that the climatic disasters that hit the Gulf Coast, and particularly ravaged the MS Delta, contributed to the HWI "explosion." The tremendous rise in the number of LOEs from 2004 to 2009 occurred during the heaviest Gulf Coast hurricane incidence in recorded history. During 2004-2008, the time of ramping up of LOE reports, there were 8 hurricanes, 2.2/year (nearly 3 times the average of 0.83/year).[150] Between 2009 and 2011, there were no hurricanes in the Gulf. The peak in LOE reports was in 2009, with a steady decline since then, through 2013 (E-Figure 255-24). Though, clearly circumstantial, the relationship in timing between the major storms and a marked increase in LOEs suggests a cause and effect. There are several explanations as to how this might occur. First, major storms leave broken trees, debris, and water in their wake to act as breeding grounds for mosquitoes. Second, mosquito populations may change after storms, with repopulation by different species, potentially increasing (or lowering) possible heartworm vectors. Finally (and possibly most importantly), the resultant devastation of storms such as Katrina leaves lost and abandoned animals (250,000 in New Orleans, alone) in a heavy heartworm endemic area without veterinary care, including heartworm preventive. This scenario is quite plausible as a (major) contributor to the upswing in LOE reports between 2000 and 2009. A recent study by the author demonstrates that a large HW epidemic began circa 2002 and peaked in 2011. This epidemic dwarfed and preceded the LOE epidemic by 3 years. Between 1997 and 2015, HW prevalence was significantly associated with MS Gulf hurricane numbers (Atkins C, et al, unpublished data, 2016).



E-FIGURE 255-24 The number of hurricanes striking Gulf Coast from 2000-2011 (blue line) and a unitless estimate of LOE claims filed (red line) during the same time period.[126,134,150]

4. Lastly, if there is a reward for filing an owner satisfaction claim for failure of a ML, there will be more claims submitted. LOEs have been grossly over-reported.[143] As was shown in a study of over 300 canine HWIs, for which whose owners and veterinarians filed for reimbursement for product failure, between 80% and 98% could not be justified with careful examination of the purchase history.[143]

The previous points are not intended to deny the existence of heartworm resistance, nor do they infer that resistance is an unimportant threat to our patients, clients and profession. But they offer evidence that heartworm resistance alone cannot explain the rise in LOEs in the MS Delta and that resistance likely cannot be ascribed to a single factor such as the overuse or misuse of slow-kill methodology.

What Do We Do?

There are numerous ways in which the practicing veterinarian can help slow the spread of resistance.

- The most important step that veterinarians can take is to ensure that MLs are used appropriately, year-round, at adequate dosage, and without lapses in administration. This effort should be buttressed by efforts to ensure compliance for those clients who purchase preventive, both in refilling and administering preventive. This can be done in a number of ways, including reminders using smart phone apps, the telephone, and postcard mailers. If compliance is an impossibility, consideration should be given to the use of 6-month injectable moxidectin.
- In addition, yearly testing is imperative because if a drug or an owner fails, the resultant HW continues to be exposed to ML, which has been shown to change the genetic make-up of the Mf, with greater expression of genetic markers associated with resistance.[149] In addition, this testing practice will reveal infected dogs so that adulticide can be administered, rather than allowing unrecognized HWI to progress into HWD. The unwanted results of this being the ultimate development of clinical signs, with the conditions for potential spread of HW, rendered less ML-susceptible, after having been exposed to ML.
- Adulticidal therapy with melarsomine (after 30 days' doxycycline and monthly ivermectin) should be administered as soon after diagnosis as is medically and logistically possible.
- Because administration of ML to microfilaremic dogs risks pushing HW toward ML resistance, all HW antigen-positive dogs should be tested for Mf and, when present, Mf should be eliminated. This can be accomplished with either doxycycline and ivermectin or with imidacloprid-moxidectin. While the AHS recommends either a modified Knott or millipore filter test, the less arduous direct smear also gives valuable information as to the presence and numbers of Mf. Knowledge of the presence of Mf is important in the fight against resistance and the numbers are important in assessing if precautions need be employed to avoid an adverse reaction.

- Slow-kill approach to HWI eradication *should be avoided*! If mitigating circumstances dictate otherwise, doxycycline should be administered and eradication of Mf confirmed (see Macrocyclic Lactones as Adulticides in Controversies).
- The use of doxycycline in antigen-positive dogs plays another role in reducing infectivity of L3 by eliminating *Wolbachia* from all HW stages. This, of course, reduces not only the potential of resistant HW being propagated, but reduces the spread of HWI in general.
- Puppies should be started on preventive as early as drug label claims allow, and kept indoors or in screened enclosures prior to institution of preventive therapy. Doing this alone has the potential to eliminate nearly 15% of the MS Delta LOE reports, as was shown in the study by Atkins et al, described above.[143] Ancillary measures include topical or oral repellents/insecticides, mosquito abatement programs, avoiding walking dogs at dawn and dusk, and keeping dogs indoors or in screened enclosures at night.
- The profession could also lobby to require negative microfilarial status for health certificates, needed for interstate travel or relocation.
- Research into the incidence and spread of resistance should continue to be studied and the development of genetic markers of resistance in Mf, as is being done at McGill University, should be encouraged.[138]
- Finally, in practices experiencing true LOEs, changing to a preventive with the best spectrum for known resistant biotypes is logical, as is emphasizing reduced mosquito exposure through changes in housing or via permethrin-containing, knock-down repellants.[73,74]

Treatment of Heartworm Infection When Finances Are of Concern

HWI is strongly and inversely correlated to the per capita income.[148] Clinicians are well aware of the fact that HWI is more common in lower socioeconomic strata of the country. This dictates that a "one-size fits all" approach will be doomed to failure and alternatives are presented in E-Table 255-5. The approach advocated in this chapter and by the AHS is considered to be the ideal approach, sparing no expense. Many cannot afford this approach and this is why many veterinarians advocate the soft-kill method, while others reluctantly choose it when finances dictate that there is no alternative.

E-TABLE 255-5

Guide to Choosing Heartworm Therapeutic Protocol

	PROTOCOL	ADVANTAGES	DISADVANTAGES	UTILITY*
1	Split-Dose (3 Inj.) Melarsomine Doxycycline Thoracic radiographs Lab (CBC, UA, Chem, Coag)	Incr. efficacy Decr. PTE risk Safety of phased HW kill No resistance concern	$$$$ 2 months' exercise restriction	Appropriate for all Best approach for severe heartworm disease
2	Std. Dose (2 inj.) Melarsomine Doxycycline Thoracic radiographs Lab (CBC, UA, Chem, Coag)	Reduced cost Decr. PTE risk (vs. std. dose) Only 1 month's rest No resistance concern	$$$ Incr. PTE risk (vs. split-dose) Decr. kill efficacy (vs. split-dose)	Appropriate when financial constraints and mild-moderate heartworm disease
3	Std. Dose (2 inj.) Melarsomine	Reduced cost Only 1 month's rest Easier for shelters No resistance concern	$$ Incr. PTE risk (vs. std. dose) Decr. kill efficacy (vs. split-dose) Cage rest is imperative!	Appropriate when financial constraints and mild heartworm disease
4	Slow-kill with ivermectin	Reduced cost Easy, no inj.	$ Incr. risk of resistance	Appropriate only when severe financial or other constraints

	Doxycycline	Appeals to shelters No hospitalization Shorter Rx duration than slow-kill	Not AHS-approved ≈12-month course Lung disease progression Time of HW death unknown	
5	Slow-Kill with ivermectin	Inexpensive Easy, no injections Appeals to shelters	Incr. risk of resistance 30-month course Lung disease progression Time of HW death unknown	This approach should be avoided

*None of these is appropriate for initial management of caval syndrome but may be used to complete therapy after worm removal.

AHS, American Heartworm Society; *CBC*, complete blood count; *Chem*, chemistry panel; *Coag*, coagulation profile; *Decr.*, decrease; *HW*, heartworm; *Incr.*, increase; *Inj.*, injection; *Lab*, laboratory; *PTE*, pulmonary thromboembolism; *Std.*, standard; *UA*, urinalysis; *X-Ray*, radiographs; *$*, relative cost.

The classical 2-dose melarsomine approach is still a viable alternative if finances dictate a compromise, and when coupled with doxycycline, ivermectin, and strict exercise restriction post-treatment makes sense when administered to asymptomatic, young and otherwise healthy patients. While the safety advantage of "split-" or 3-dose therapy (killing approximately 50% of the worms with the first and 50% with the second and third injections) is lost, the reduction in pathology with doxycycline/ivermectin and careful attention to exercise restriction makes it reasonably safe. It is much cheaper than the split-dose approach and requires one, rather than two months' exercise restriction. It is ethically superior to the slow-kill approach in terms of resistance concerns and is medically superior in that heartworms are eliminated much more quickly without ongoing, progressive lung damage over the months-to-years of slow-kill.

There are clients who cannot afford any adulticide therapy at all. In this instance, the soft-kill approach is the only option, though arguments to the contrary can be put forth to clients and, if persuasive, may open alternative treatment avenues.[121] If clients cannot be convinced, assuring that Mf are eradicated and that prevention efforts are redoubled largely removes resistance concerns. Ideally, 30 days' doxycycline therapy should be administered to minimize lung damage as HWs expire. While the soft-kill approach cannot be advocated, this modification is preferable to owners "giving up" and deciding to just settle for a heartworm-infected pet, which in addition to being a major health compromise, increases the risk of other unprotected dogs and of resistance development. If veterinarians find themselves in the latter position, doxycycline and ivermectin therapies should be advocated to lessen infectivity of the current HWI and to lessen host response to dying worms.

Feline Heartworm Disease

Life Cycle

The life cycle of *D. immitis* is similar in the cat and the dog (see Figure 255-2). Heartworm infection differs in cats, in that they are not generally the preferred target for feeding mosquitoes; that to be an effective vector for cats, a mosquito has to have first fed on a canid; and that, as an unnatural host, cats are inherently resistant to HWI. Infections in cats therefore tend to be relatively infrequent and small. In addition, the life cycle takes longer in the cat, such that patency (noted in <20% of cats) does not occur until 7 to 8 months post-infection. Lastly, the cat is subject to pulmonary and pulmonary vascular pathology, even if an infection never matures.

This phenomenon, called heartworm-associated respiratory disease or HARD,[152,153] has produced confusion in the nomenclature regarding HW infection vs. exposure. In most infectious and parasitic disease, the presence of antibodies without an established (mature) infection is termed "exposure," meaning the host was either exposed and rejected the infection or was (or currently is) infected. But in HWI, because antibody-positive status occurs when HW larvae enter the host and molt twice, with potential of ultimately producing disease, some now refer to this as "infection," *even if the infection is aborted*, prior to the parasites' maturation. In this section of the chapter, the author will use the term "mature HWI" for mature adult infections (or HWD, being due to mature HWI, with identifiable pathology), and will refer to those infections, that are ultimately aborted, as "immature infections" for individual cats or "exposure" when referring to populations, with the acknowledgment that an estimated 50% of such cats may develop lung disease from their exposure

(HARD).[152,153]

Pathophysiology

The domestic cat, though an atypical host, can be parasitized by *D. immitis,* with resultant HWD. The clinical manifestations of the disease are different and often more severe in this species, but if one considers mature infections only, the infection rate is only 5% to 20% of that of the dog.[154] Experimental infection of the cat is more difficult to establish than in the dog, with less than 25% of L3 reaching adulthood.[155] This resistance is also reflected in natural infections, in which feline heartworm burdens are almost always less than 10 and typically only 1 to 4 worms.[154] Other indications of cats' inherent resistance to this parasite are a shortened period of worm patency, high frequency of amicrofilaremia and low Mf counts, and shortened life span of adult heartworms (generally thought to be 2 to 3 years, with new evidence suggesting that it may be longer in natural infections—up to 4 years).[156] Nevertheless, studies have shown a mature HWI prevalence as high as 14% in shelter cats[154] and a study performed on well-cared-for cats in Texas and North Carolina revealed mature HWD in 9 of 100 cats with cardiorespiratory signs.[157] Furthermore, antibody testing showed 26% of these cats had been "exposed" to HWI.[157] Recent studies have failed to support the belief that males were at greater risk for natural HWI, although in experimental infections, males harbor greater worm burdens.[157,159] Aberrant worm migration has been suggested as being a more frequent occurrence in cats than in dogs.

At the risk of repetition, it is important to clarify the distinction between mature HWI (adult HW living in pulmonary arteries, or elsewhere) and aborted infections ("exposure" without parasite maturation). The death of immature adults (immature or juvenile S5, immature or juvenile adults, or juveniles) may create pulmonary and pulmonary vascular lesions in cats, prior to maturation. Uniquely, the disease process develops *even in cats that ultimately resist the mature infection,* and clinical signs and disease antedate clinicians' ability to diagnose the disease through conventional means. Studies have shown that pulmonary anatomical and radiographic lesions develop in experimentally-infected cats,[152,153,160] and that pulmonary vascular lesions are documented in naturally-infected cats[151] in which maturation of immature adults *does not* occur. Furthermore, experimental infections, pharmacologically aborted before HW maturation, have recently been shown to produce not only proliferative and inflammatory pulmonary arterial lesions, but proliferative and inflammatory disease of bronchioles and lung parenchyma as well.[152,153] Presumably, these findings are associated with the respiratory signs often seen in cats without mature HWI and have been called HARD.[152,153] These important studies showed that cats "exposed" (infected without allowing full HW maturation) to HW develop respiratory lesions and clinical signs of HWD. These findings are important in that they not only demonstrate that HWI that is ultimately rejected often produces asthma-like clinical signs, but that many more cats develop signs of HWD than was previously believed. This is because 38% to 74% of cats with mature HWI develop clinical signs, as do an estimated 50% of those that abort the infection (HARD, estimated to be 5 to 10 times more common than mature infections).[156,160] This distinction is also important in communicating to the pet owner that the cat with HARD will likely recover, while the cat with mature HWI has the potential to die from the disease.

The exact clinical importance of HARD, however, is difficult to gauge because it is a diagnosis of exclusion and the inherent suspicion of veterinarians for feline HWI is low. Thereby, it is likely that a large percentage of cases are not recognized. Also, the experimental model used a very high infection rate (100 L3 per cat), far higher than a cat would acquire naturally. So it is difficult to directly transfer our knowledge of experimental HARD to the naturally infected cat.

The pulmonary arterial response to mature adult heartworms is more severe in cats than in dogs (due, in part, to the presence of pulmonary intravascular macrophages [PIMs][162]), although PHT has infrequently been reported. Dillon[5] demonstrated pulmonary enlargement within 1 week of transplantation of adults, suggesting an intense host-parasite interaction. This has been confirmed by post-mortem examination, which revealed a severe endarteritis with villous intimal hyperplasia.[158] Such severe myointimal and eosinophilic response produces pulmonary vascular narrowing and tortuosity, thrombosis, and possibly PHT (Figure 255-25).[163,164] Maia et al demonstrated diffuse pulmonary arterial inflammation and hypertrophy, bronchiolar lesions, and intense interstitial pneumonitis, within 6 weeks of introducing 2 adult HWs via the jugular vein.[164] Type II pneumocyte hyperplasia was evident, using scanning electron microscopy, indicative of pulmonary parenchymal damage. Because the feline pulmonary artery tree is smaller than that of the dog and has less collateral circulation, embolization, even with small numbers of worms, produces disastrous results

with infarction and even death. Although uncommon, cor pulmonale and right heart failure can be associated with chronic feline HWD and is manifested by pleural effusion (hydrothorax or chylothorax), ascites, or both.

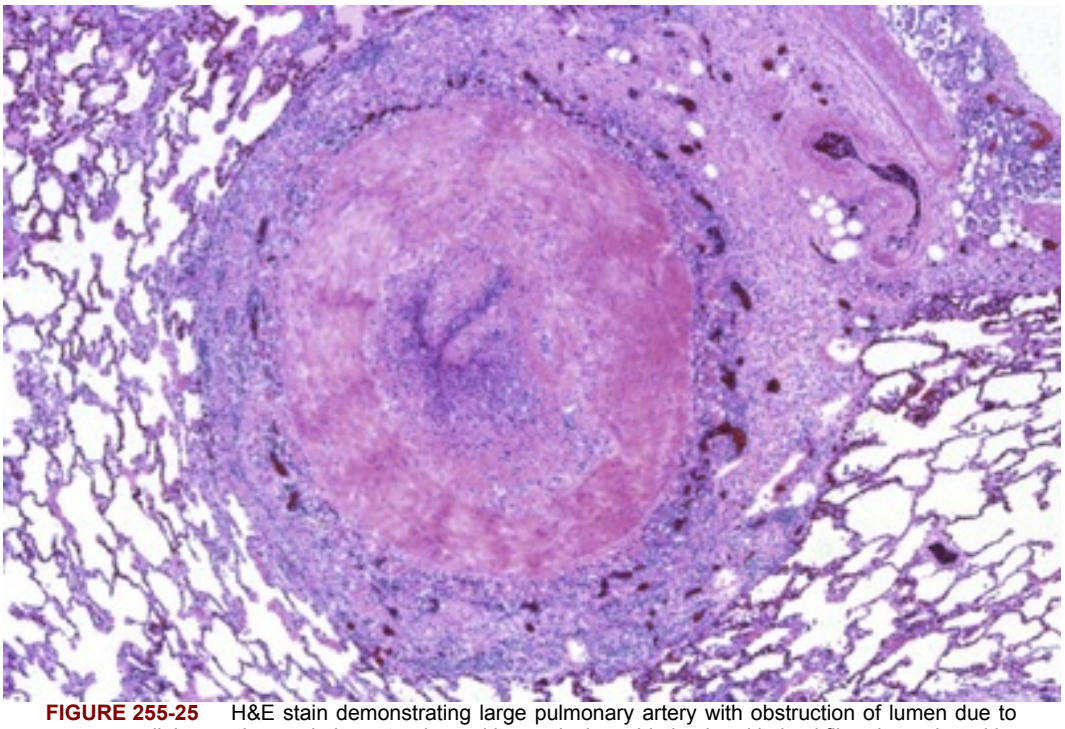


FIGURE 255-25 H&E stain demonstrating large pulmonary artery with obstruction of lumen due to severe medial smooth muscle hypertrophy and hyperplasia, subintimal and intimal fibrosis, endarteritis, and possibly thrombosis. The reader should also note the periarterial interstitial (probably eosinophilic) pneumonia.

The lung *per se* is also insulted by HWI, with eosinophilic infiltrates in the lung parenchyma (pneumonitis) and pulmonary arteries (Figure 255-26). The pulmonary vessels may leak plasma, producing pulmonary edema (possibly acute respiratory distress syndrome). Also, PIM-induced type II cell proliferation is recognized. Together, this combination of insults to the respiratory system alters O_2 diffusion, producing hypoxemia.[162] In addition, radiographic findings suggest air trapping, compatible with bronchoconstriction.[158,160]

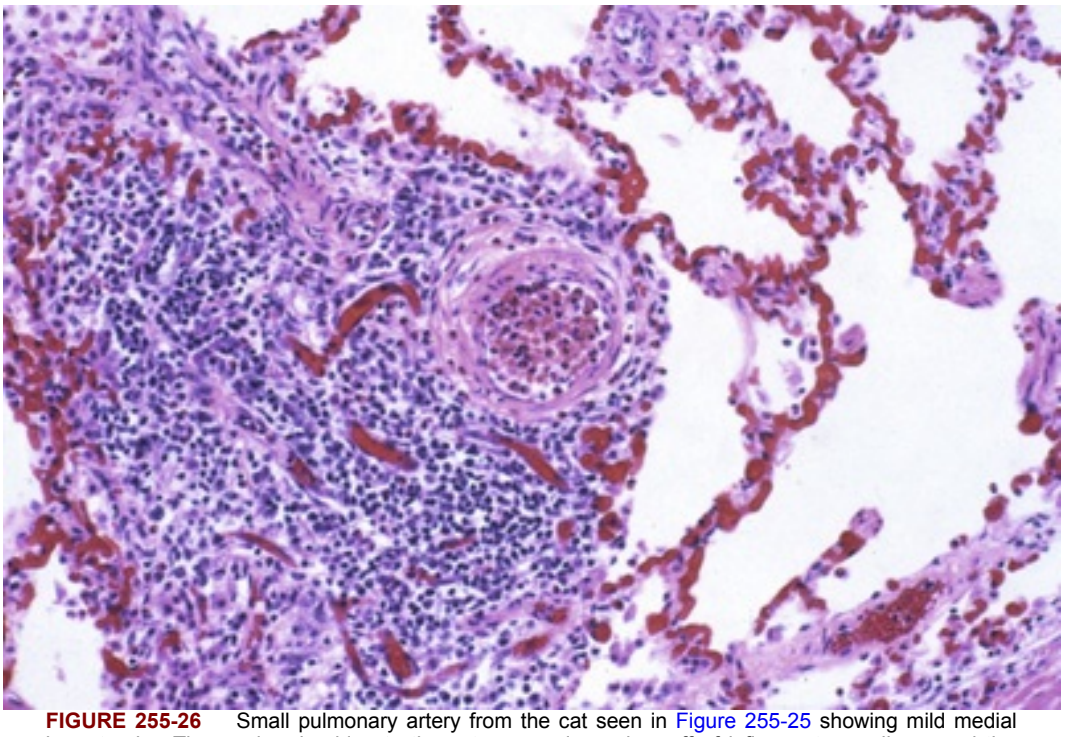


FIGURE 255-26 Small pulmonary artery from the cat seen in Figure 255-25 showing mild medial hypertrophy. The reader should note the extreme perivascular cuff of inflammatory cells around the vessel, representing an eosinophilic infiltrate.

The actual role of bronchoconstriction in this process is unclear, and experimental studies have led to differing conclusions. Studies have concentrated on aspects of both mature HWI and HARD, using mature and immature experimental infections, *Wolbachia* antigen-positive and antigen-negative natural infections, HW obtained from dogs having received doxycycline and from those which had not, and infusions of HW homogenate.[166-170] While an in-depth review of these manuscripts is not possible, salient findings are summarized below.

Despite increased bronchiolar wall thickness in heartworm-infected cats, a hyperreactive response of the bronchiolar smooth muscle does not appear to be the primary mechanism of respiratory tract clinical signs. The recognized attenuated response of the airway to isoproterenol may, however, indicate refractoriness to catecholamine-induced bronchiolar relaxation in heartworm-infected cats.[165] Possibly contradictory results have been obtained using plethysmography to evaluate airway function in symptomatic cats with serologic evidence of HWI. There were significant differences in several *in vivo* indicators of bronchoconstriction between cats with HWD and normal controls.[166] Subsequent studies, using this technique to compare *Wolbachia* specific protein-positive to WSP-negative cats, demonstrated significant abnormalities in indices of bronchoconstriction in antibody-positive, symptomatic cats.[167] This indicates the possibility of a role for *Wolbachia* or, more likely its proteins, in the pathogenesis of bronchoconstriction in feline HWD. On the other hand, a study of normal cats receiving 18 days' intravenous injection of HW homogenate demonstrated no difference in pulmonary lesions or indicators of bronchoconstriction, whether the HW used had been harvested from doxycycline-treated dogs or those which had not been so treated.[168] This study also revealed that homogenate infusion produced interstitial and peribronchial smooth muscle and myofibrocyte proliferation, apparently caused by a humoral substance, as lesions were not clearly related to areas in which HWs are typically found.

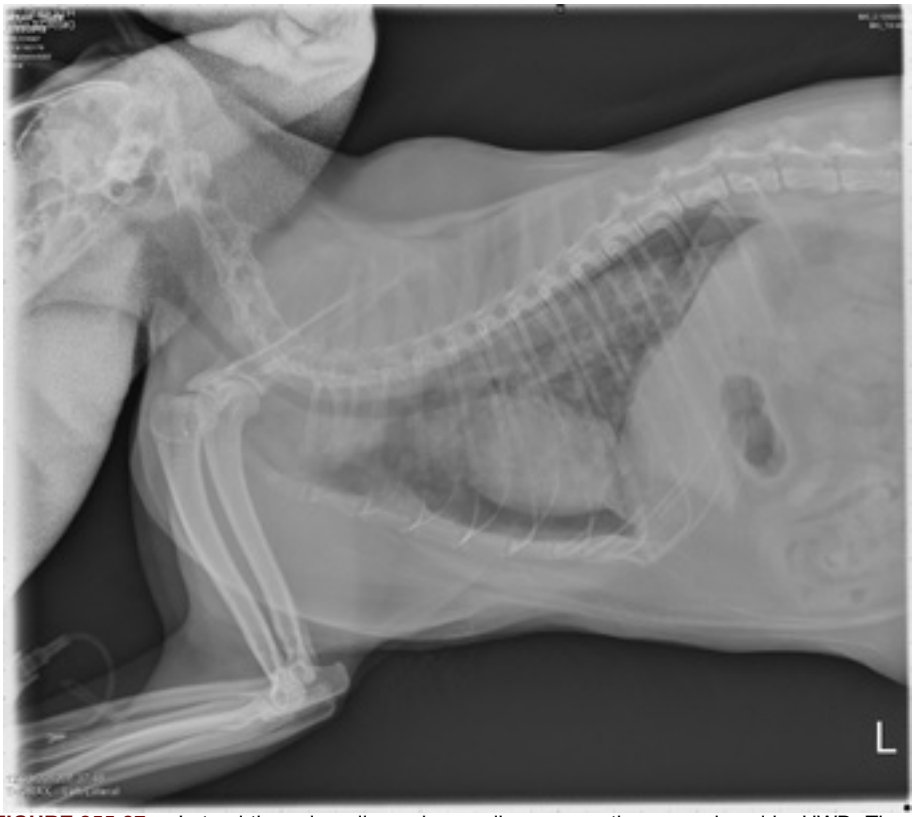
Inflammatory mediators (eicosanoids) appear to contribute to the lesions associated with HWD. Morchon et al demonstrated that naturally infected cats showed significantly higher serum levels of prostaglandin E_2 (PGE_2), thromboxane B_2 (TXB_2) and leukotriene B_4 (LTB_4) than uninfected cats.[170] In experimentally-infected cats, followed sequentially for 180 days, PGE_2 increased significantly during the first 60 days post-infection, then progressively decreased until day 180 post-infection, while TXB_2 and LTB_4 increased progressively, reaching maximum levels 180 days post-infection. This suggests that PGE_2 may be related to immature S5 parasite death (HARD), while TXB_2 and LTB_4 may be involved in reaction to mature HW.

The end result of this multifaceted insult is diminished pulmonary function, hypoxemia, dyspnea, cough, and even death. Sudden death in heartworm-infected cats may involve an anaphylactic-like reaction to dying worms with or without ARDS.[171] It appears unlikely to be due to WSP antigen.[169]

Clinical Signs

Clinical manifestations of HWD in cats may be peracute,[171] acute, or chronic.[157,158,173-175] However, in a retrospective study, 28% of cats with mature HWI, seen at a referral center, were presented for signs not referable to HWI.[174] Furthermore, newer, prospectively derived data from two Italian studies of 77 cats seen in general practice, revealed that only 58% of asymptomatic cats ultimately developed clinical signs of HWD, with one third of these being fatal.[156,161]

Acute or peracute presentation is usually due to worm death and/or embolization or aberrant migration, and signs variably include salivation, tachycardia, shock, dyspnea, hemoptysis, vomiting and diarrhea, syncope, dementia, ataxia, circling, head tilt, blindness, seizures, and death. Post-mortem examination often reveals pulmonary infarction with congestion and edema. More commonly, the onset of signs is less acute (chronic form). Reported historical findings in chronic feline HWD include anorexia, weight loss, lethargy, exercise intolerance, signs of right heart failure (pleural effusion; uncommon), cough, dyspnea, and vomiting. The author and colleagues have found dyspnea and cough to be relatively consistent findings and, when present, should cause suspicion of HWD in endemic areas.[174] Chylothorax, pneumothorax, and CS have also been recognized as uncommon manifestations of feline HWD (E-Figure 255-27).



E-FIGURE 255-27 Lateral thoracic radiograph revealing pneumothorax produced by HWD. There is probable atelectasis, as is seen in the increased opacity in the dorsocaudal lung fields. There is likely pulmonary disease as well.

In a report of 50 natural cases of feline HWI in North Carolina, presenting signs were most commonly related to the respiratory system (32 cats; 64%), with dyspnea (24 cats; 48%) being most often noted, followed by cough (19 cats; 38%) and wheezing (Figure 255-28).[174] Vomiting was reported in 17 (38%) cats and was noted frequently in 8 (16%). Five (10%) heartworm-infected cats were reported to have exhibited vomiting without concurrent respiratory signs and vomiting was a presenting sign in seven (14%). Neurologic signs

(including collapse or syncope [10%]) were reported in seven (14%) cats. Five (10%) of the cats were dead at the time of presentation. Murmurs were infrequently noted in cats that did not have concurrent heart disease, independent of HWI. Heart failure was present in one cat, but it had concurrent hypertrophic cardiomyopathy. HWI was considered to be an incidental finding in 14 (28%) of the cats in this study. It is noteworthy that studies of natural asymptomatic feline HW infections in a hyper-endemic region in Italy revealed that approximately 80% of infected cats self-cured.[156,161]

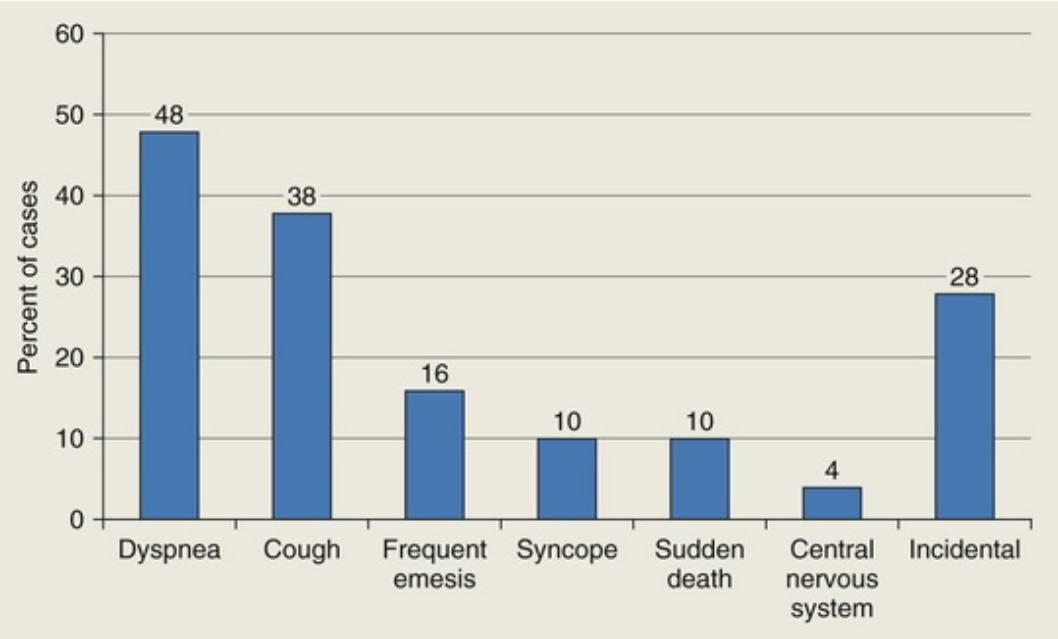


FIGURE 255-28 Clinical signs recorded in 50 cats with proven heartworm infection. (Data from Atkins CE et al: Heartworm infection in cats: 50 cases [1985-1997]. *J Am Vet Med Assoc* 217:355-358, 2000.)

Physical examination is often unrewarding, although a murmur, gallop, or diminished or adventitial lung sounds (or a combination of these findings) may be noted (see ch. 55). In addition, cats may be thin, dyspneic, or both. If heart failure is present, jugular venous distension, dyspnea, and rarely ascites are detected.

Diagnosis

The diagnosis of HWI in cats poses a unique and problematic set of issues.[5] First, clinical signs are often absent, and when present, quite different from those of the dog. In addition, the overall HWI incidence in cats is low, so suspicion is lessened; eosinophilia is transient or absent; immunologic tests are often falsely negative; electrocardiographic findings are minimal; radiographic signs are inconsistent and may be transient; and most cats are amicrofilaremic. Finally, the clinician must understand that antigen-positive cats nearly always have mature HWI and antibody-positive (antigen-negative) cats typically do not have mature HWI. However, approximately 50% of antibody positive/antigen negative cats develop pulmonary lesions of HARD. The diagnosis of HARD is one of exclusion and requires a high index of suspicion (Table 255-6).

TABLE 255-6

Comparison of Heartworm-Associated Respiratory Disease (HARD) Produced by Death of Immature Adult Heartworms in the Pulmonary Vasculature and Feline Heartworm Disease Produced by Mature Adult Heartworms

PARAMETER	HARD	CHRONIC HEARTWORM DISEASE
Onset of clinical signs after infection	≈3 months	>7 months

Etiology	Arrival and death of immature heartworms in pulmonary arteries	Pulmonary vascular, parenchymal, and cardiac response to the presence, death, and deterioration of adult heartworms
Clinical signs	Dyspnea, coughing, wheezing	Dyspnea, coughing, hemoptysis, collapse, vomiting, neurological signs, heart failure, sudden death
Serological test results		
Antigen	Negative	Positive or negative
Antibody	Often positive	Often positive
Microfilaremia	Absent	Occasionally present
Radiographic findings	Bronchointerstitial pattern	Variably bronchointerstitial pattern, pulmonary artery enlargement, and pulmonary hyperinflation; less commonly pleural effusion or pulmonary consolidation
Echocardiographic findings	Normal (no heartworm discernible)	Heartworm(s) often found in pulmonary artery, right atrium, or right ventricle; possible pulmonary hypertension

From Lee ACY, Atkins CE: Understanding feline heartworm infection: disease, diagnosis, and treatment. *Top Companion Anim Med* 25:224-230, 2010.

No compelling medical reasons exist to screen cats for HWI prior to administration of ML preventives because the risk of adverse reactions associated with microfilarial death is small (cats are amicrofilaremic or have small microfilarial numbers, and adverse reactions are minimized with ML preventives). Nevertheless, screening allows the clinician to alert pet owners if their cats have been exposed (antibody positive) so that they might choose to pursue confirmation of the diagnosis of mature HWI. It also minimizes public relations difficulties if the cat develops HWI, while on preventive. In addition, routine screening allows the clinician to understand the risk of heartworm pressure in his or her own practice area. The author's approach to routine screening of cats for heartworms differs somewhat from that when suspicion of infection exists (Figure 255-29).

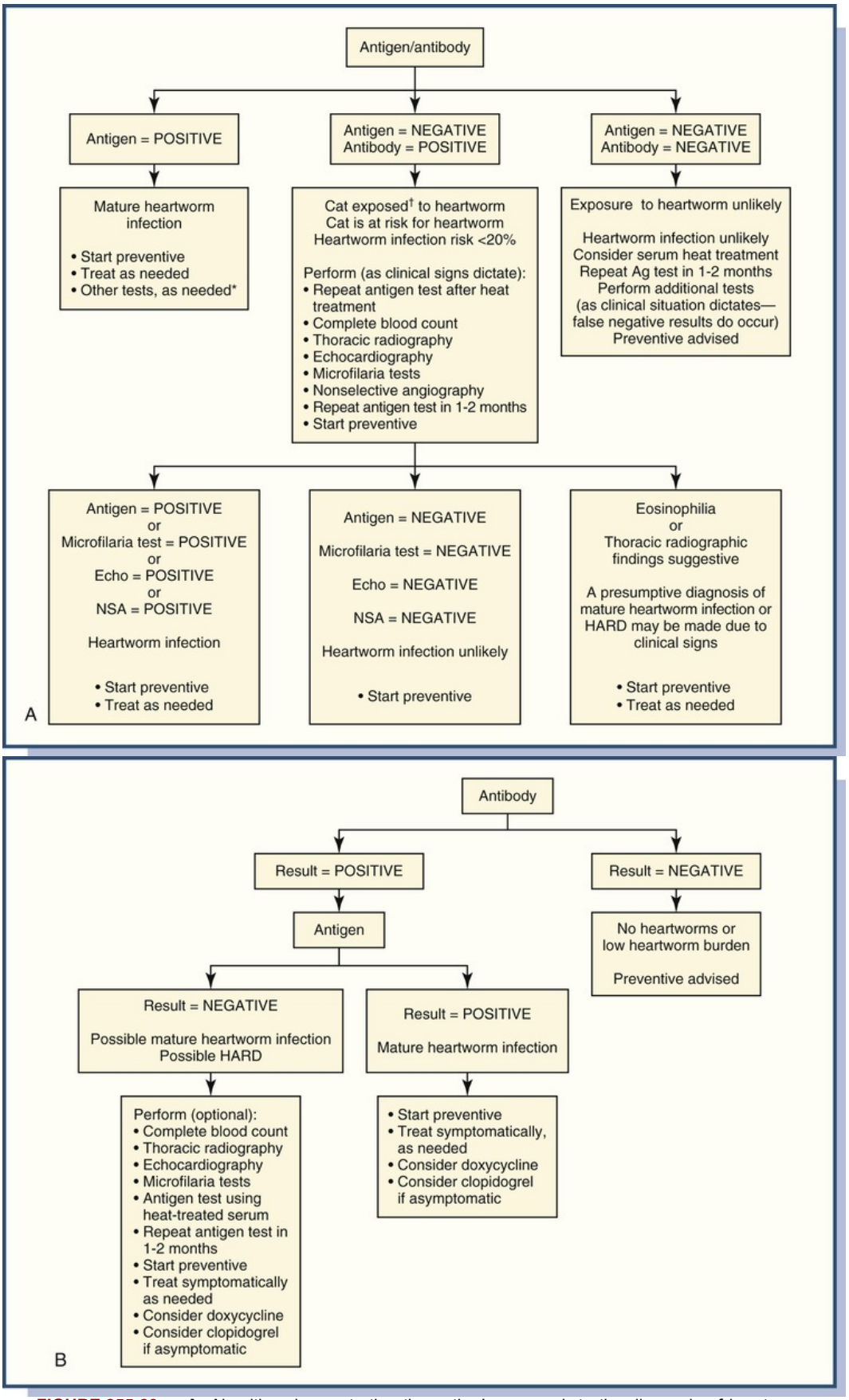


FIGURE 255-29 **A,** Algorithm demonstrating the author's approach to the diagnosis of heartworm infection in cats in which infection is suspected. **B,** Algorithm demonstrating the author's approach to screening cats for heartworm infection. *HARD,* Heartworm-associated respiratory disease; *NSA,*

nonselective angiography. *Thoracic radiographs and blood tests; †, *exposure* means that cat was exposed and allowed development to L4 stage, but may or may not have allowed parasite maturation. Some prefer to refer to this cat as *infected*, since the infection was probably eliminated at the immature S5 stage and clinical signs may be present.

Immunodiagnostic methods (see Table 255-2) are imperfect in cats because of the low worm burdens and hence, antigenic load.[175] In one study, ELISA antigen tests performed on sera from experimentally infected cats were positive on sera from 36% to 93% of 31 cats harboring 1 to 7 female heartworms, with sensitivity increasing as female worm burden increased.[176] Cats with only a male worm or only male worms were not detected as positive. Therefore false-negative tests occur frequently, depending on test used, maturity and gender of worms, and worm burden. All tests were, however, virtually 100% specific. It is important to realize that infection with signs may be present prior to the presence of detectable antigen (from adult females). McCall and colleagues[177] report that, in natural infections, the antigen test detects less than 50% of proven cases, while Snyder and colleagues[178] present differing data (from natural infections in which blood was obtained as long as 2 hours post-euthanasia) that show that the antigen test is more sensitive (74%) than previously reported. Also, because antigen tests continue to improve, their exact sensitivity is somewhat obfuscated, but is estimated to be 50% to 75% in *natural* mature infections.

Antigen tests detect 0% of cats afflicted with HARD, but the antibody tests are routinely positive in such cats (see Table 255-6).[175] An antigen test (IDEXX's SNAP Feline Heartworm Antigen Test) has been marketed for cats and is part of the snap platform for feline infectious diseases. This is an adaptation of the canine test, with a reported increase in sensitivity of 15% over conventional antigen tests.

Although less specific for mature infections, heartworm antibody tests are of use in the detection of feline HWI, even when antigen tests are negative. In a study of 257 HW antibody-positive cats, only 13.1% were antigen positive.[179] The antibody test also serves as a marker for exposure to and risk of HWI (even if the cat never develops a mature infection) and for the possibility of HARD. An in-clinic feline heartworm antibody test is also available (HESKA: Solo Step FH). It is important to emphasize that it is estimated that half of antibody-positive, antigen-negative cats have post-mortem manifestations of HWD and that, in these cats, the antibody-positive state may wane with time. Often, the antibody test is used in conjunction with the antigen test; each is available in a cage-side and send-off format.

Recently, the utility of detecting *Wolbachia* antigens (WSP, *Wolbachia*-specific proteins) and the use of PCR to disclose *Wolbachia* DNA have shown promise in diagnosing feline HWI[180,181] and it has been demonstrated that heat treatment of serum may increase the sensitivity of the antigen test.[22] In 6 cats with experimental infections, testing false-negative on 4 commercial antigen tests, treatment of the serum at 103° F for 10 minutes, rendered the serum derived from the resultant coagulum to give positive results in 5 of 6 cats. This has potential to be a needed boost in our ability to definitively diagnose HWI in cats; it is unlikely that it will disclose all-male infections.

Thoracic radiographs are useful in diagnosing HWD (or other diseases mimicking HWD). However, asymptomatic cats rarely have radiographic lesions, so this modality is not ideal for screening purposes.[161,182] The most sensitive radiographic criterion (left caudal pulmonary artery greater than 1.6 times the ninth rib at the ninth intercostal space on the ventrodorsal projection) was only detected in 53% of cases. Furthermore, even though most cats with clinical signs have some radiographic abnormality, the findings are not specific to HWD. In addition, a study by Selcer and colleagues[160] demonstrated that radiographic findings were often transient, and radiographic abnormalities were found in cats that ultimately resisted heartworm maturation and were negative on post-mortem examination, therefore likely having suffered what later became known as HARD. Radiographic findings include enlarged caudal pulmonary arteries (Figure 255-30), often with ill-defined margins, pulmonary parenchymal changes that include focal or diffuse infiltrates (interstitial, bronchointerstitial, or even alveolar), perivascular density, and occasionally, atelectasis (Figures 255-31 and 255-32). Pulmonary hyperinflation may also be evident, and the misdiagnosis of feline bronchial disease can easily be made (see Figures 255-25, *A* and 255-26, *A*). Pulmonary angiography has also been used to demonstrate radiolucent linear intravascular foreign bodies and enlarged, tortuous, and blunted pulmonary arteries (Figure 255-33).

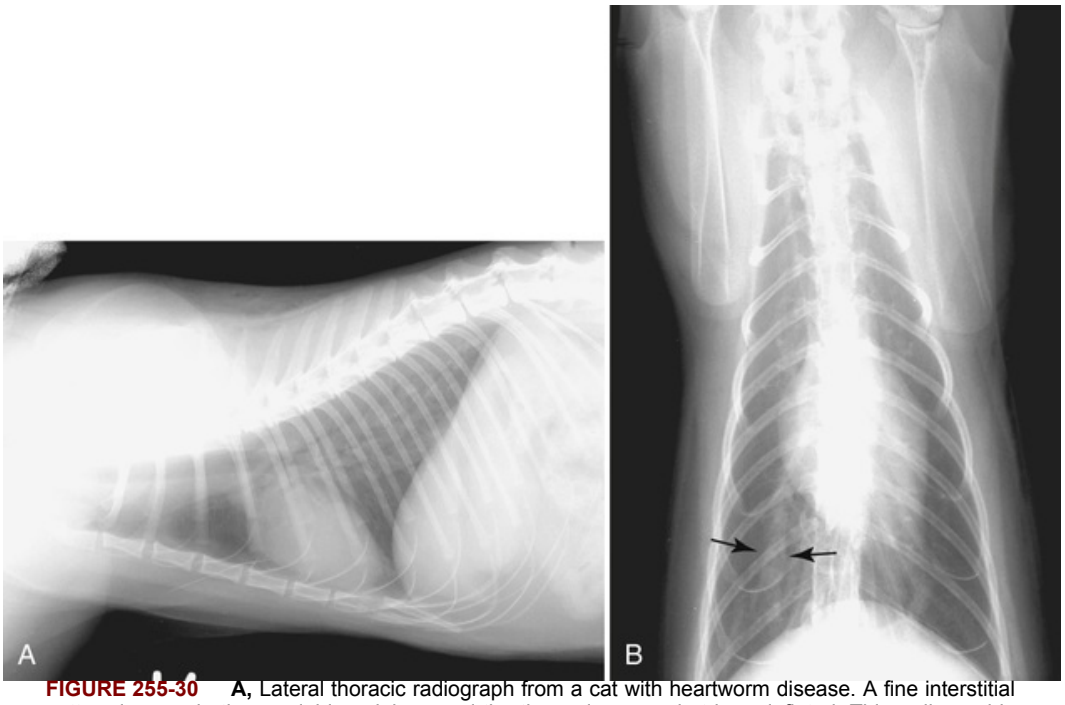


FIGURE 255-30 **A,** Lateral thoracic radiograph from a cat with heartworm disease. A fine interstitial pattern is seen in the caudal lung lobes, and the thorax is somewhat hyperinflated. This radiographic pattern is similar to—and hence confused with—that of feline bronchial disease. **B,** Dorsoventral thoracic radiograph from the same cat shown in **A.** Again, the changes are not dramatic, but the right caudal lobar pulmonary artery is enlarged (>1.6 times the ninth rib at the ninth intercostal space; arrows). The opposite pulmonary artery can be seen to be somewhat tortuous.

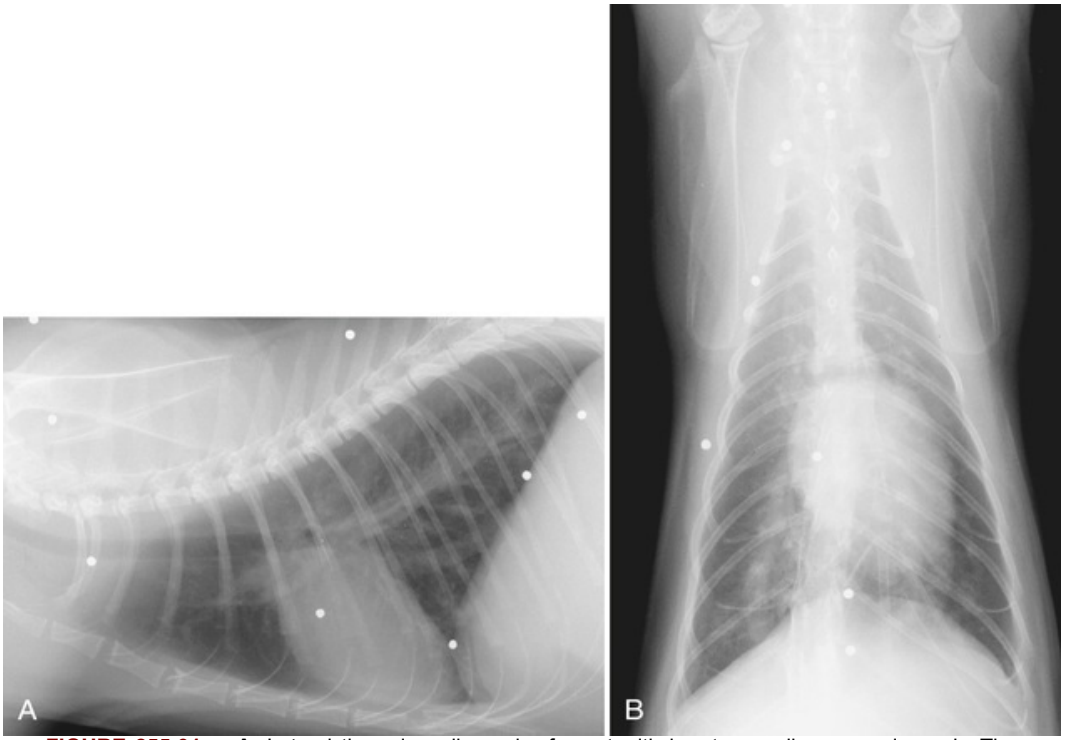


FIGURE 255-31 **A,** Lateral thoracic radiograph of a cat with heartworm disease and cough. The reader should note the hyperinflated chest, flat diaphragm, and moderate interstitial pulmonary infiltrate. The right ventricle is mildly enlarged. **B,** Dorsoventral thoracic radiograph from the same cat shown in **A.** The pulmonary infiltrate is more readily appreciated in this view in the right caudal lung lobe. The reader should note the enlarged right caudal lobar pulmonary artery.

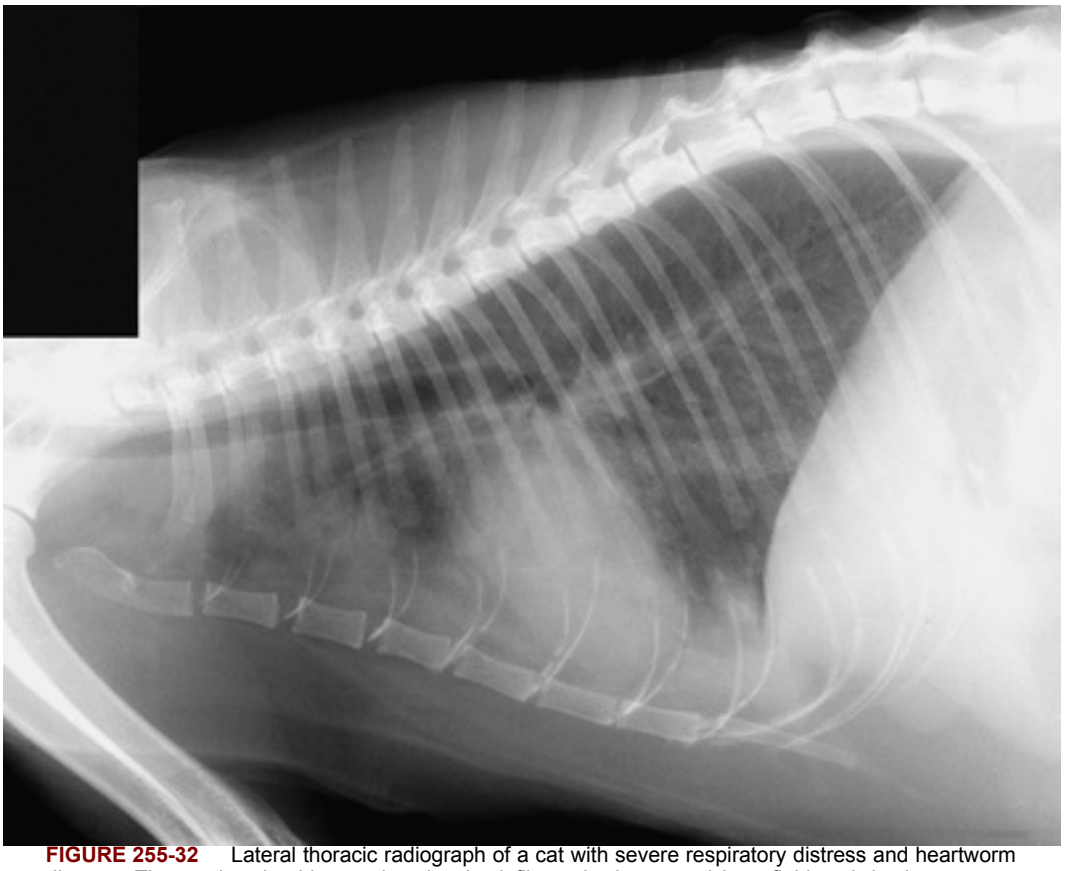


FIGURE 255-32 Lateral thoracic radiograph of a cat with severe respiratory distress and heartworm disease. The reader should note the alveolar infiltrate in the ventral lung field and the less severe interstitial infiltrate more dorsally in caudal lung lobes. This severe lung disease is probably due to heartworm death and may represent acute respiratory distress syndrome.

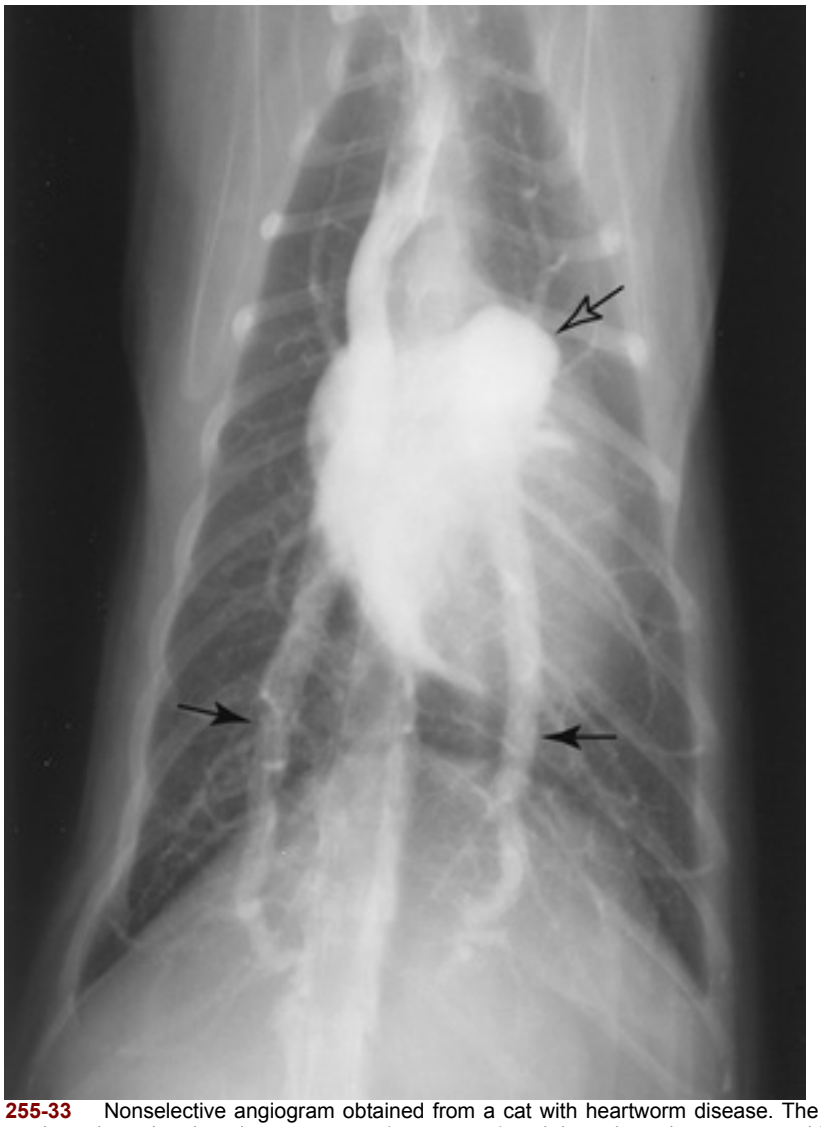


FIGURE 255-33 Nonselective angiogram obtained from a cat with heartworm disease. The reader should note the enlarged main pulmonary artery (open arrow) and the enlarged, tortuous, and blunted caudal pulmonary arteries (arrows). Careful scrutiny reveals linear radiolucencies in the right caudal pulmonary artery. (Courtesy Dr. Kathy Spaulding. From Atkins CE: Heartworm disease. In Allen DG, editor: *Small animal medicine*, Philadelphia, 1991, JB Lippincott, pp 341-363.)

Echocardiography, in the author's experience, is more sensitive in cats than in dogs.[157,183,184] Typically, a double-lined echodensity is evident in the main pulmonary artery, one of its branches, the right ventricle, or occasionally at the right atrioventricular (AV) junction (Figure 255-34 and Video 255-4). Atkins et al[157] visualized heartworms via echocardiography in 78% of nine clinical cases, as did Selcer and colleagues[160] in 16 experimental infections.

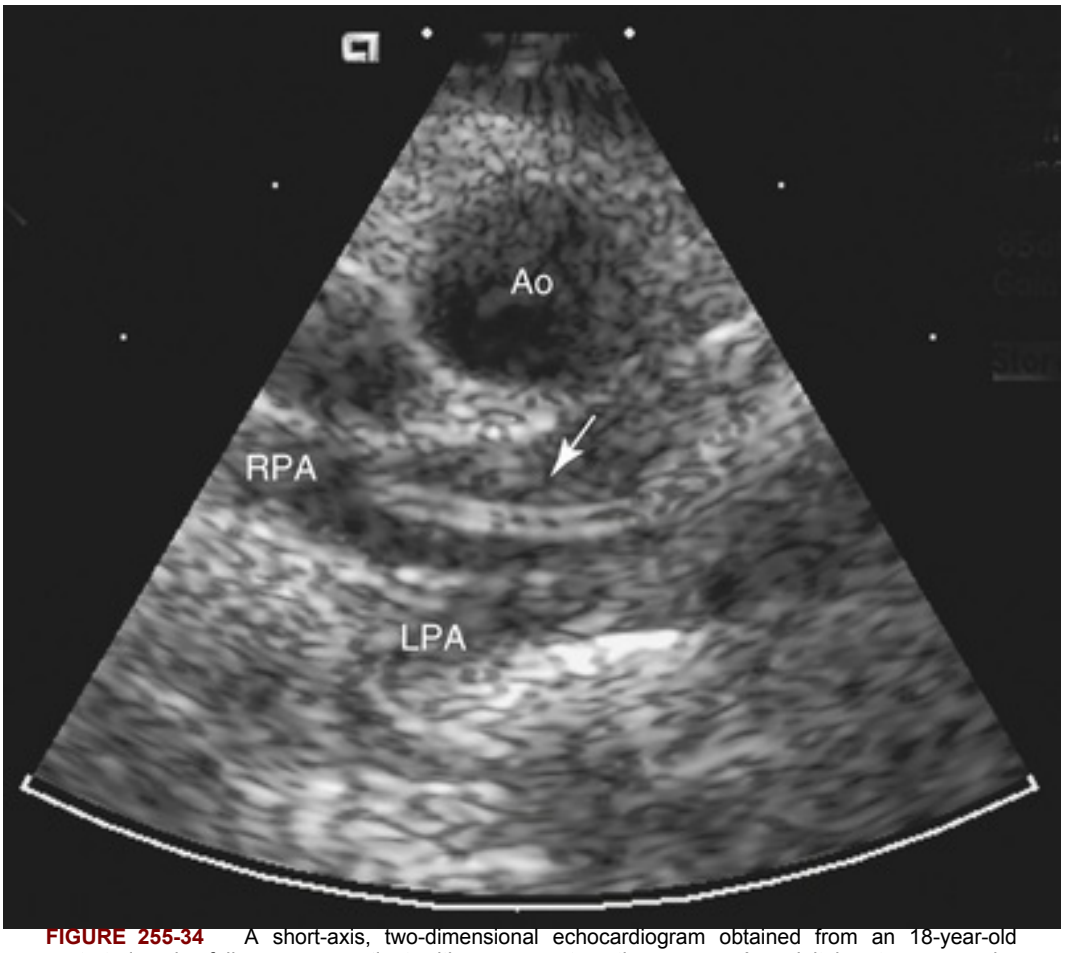


FIGURE 255-34 A short-axis, two-dimensional echocardiogram obtained from an 18-year-old castrated male, feline cancer patient with an asymptomatic murmur. An adult heartworm can be identified by two echo-dense parallel lines, in the right pulmonary artery (arrow). *Ao,* Aorta; *LPA,* left pulmonary artery; *RPA,* right pulmonary artery.

Treatment and Prevention

The question arises as to whether heartworm prophylaxis is warranted for cats because they are not the natural host and because the incidence is low. Necropsy studies of feline HWI in the Southeast have yielded a mature HWI prevalence of 2.5% to 14%, with a median of approximately 5% (Figure 255-35).[154] When considering the question of institution of prophylaxis, it is worth considering that this prevalence approximates or even exceeds that of feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) infections. A 1998 nationwide antibody survey of over 2000 largely asymptomatic cats revealed an exposure prevalence of nearly 12% (Figure 255-36)[185] and has been suggested as being as high as 16%,[186] though other estimates have been lower (1% to 8%).[187] If one assumes that a 12% antibody-positive rate indicates a prevalence of mature HWI of 1% to 2% and of 5% to 6% for HARD, then a nationwide feline morbidity (mature cases and HARD cases) associated with HWI might be expected to approach 6% to 8%. It is also noteworthy that, based on owners' information, nearly one third of cats diagnosed with HWD at NCSU were housed solely indoors.[174] Lastly, the consequences of feline HWD are potentially dire, with no clear therapeutic solutions. Therefore the author advocates preventive therapy in cats in endemic areas—anywhere dogs are on preventive.

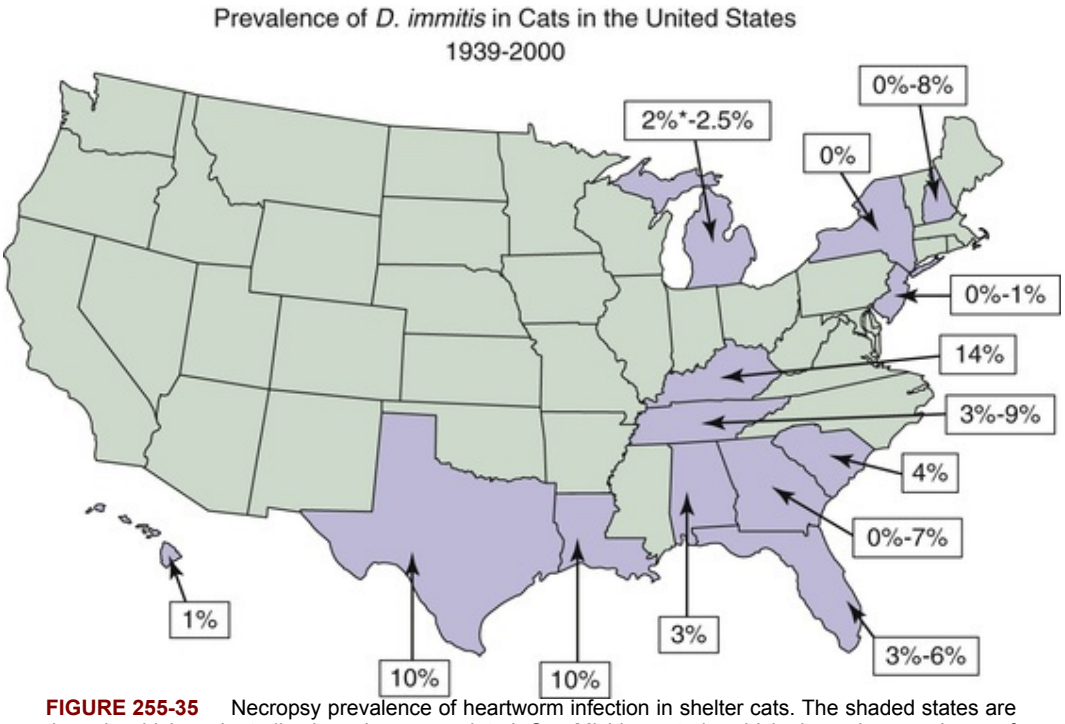


FIGURE 255-35 Necropsy prevalence of heartworm infection in shelter cats. The shaded states are those in which such studies have been completed. One Michigan study, which showed a prevalence of 2%, was an antigen study. *, This number represents antigen test positives, not necropsy-based positives, as are all the others. (Adapted from Ryan WG, Newcomb KM: Prevalence of feline heartworm disease—a global review. In Soll MD, Knight DH, editors: *Proceedings of the 1995 American Heartworm Symposium*, Batavia, IL, 1996, American Heartworm Society.)

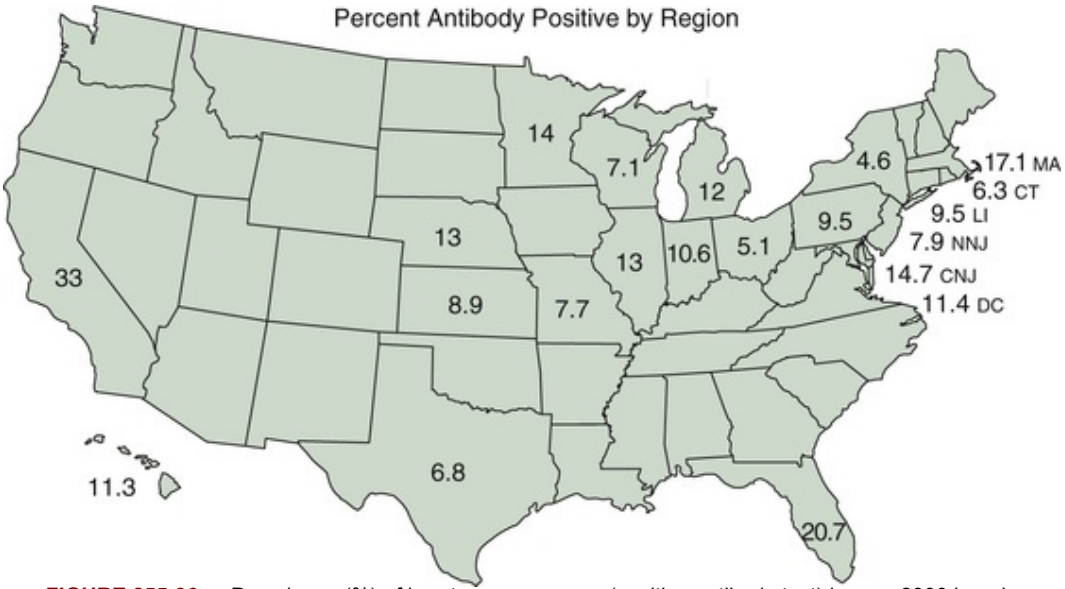


FIGURE 255-36 Prevalence (%) of heartworm exposure (positive antibody test) in over 2000 largely asymptomatic cats in 19 states (21 regions). *CNJ,* Central New Jersey; *LI,* Long Island, New York; *NNJ,* Northern New Jersey. (Adapted from Miller MW, Atkins CE, Stemme K, et al: Prevalence of exposure to *Dirofilaria immitis* in cats from multiple areas of the United States. In Soll MD, Knight DH, editors: *Proceedings of the 1998 American Heartworm Symposium*, Batavia, IL, 1998, American Heartworm Society, pp 161-166.)

Five broad-spectrum endo- and ecto-parasiticides, with FDA-CVM approval, are marketed (or will be) for use in cats in the U.S. (Table 255-7). Ivermectin is provided in a chewable formulation, milbemycin oxime as a flavored tablet, and selamectin, moxidectin/imidacloprid, and eprinomectin/fipronil/praziquantel come in

topical formulations. The spectrum and the formulation of these products vary; hence the clients' individual needs are easily met in most cases.

TABLE 255-7

Heartworm (HW) Preventive Agents for Cats Available in the U.S., with Spectra

DRUG	HW	HOOKWORMS	WHIPWORMS	ROUNDWORMS	TAPEWORMS	FLEAS & EGGS	TICKS
Ivermectin (Chewable) Heartgard for Cats	+	+					
Milbemycin-oxime (Flavored tablet) Interceptor	+	+		+			
Selamectin (Topical) Revolution	+	+		+		+/+	
Moxidectin/Imidacloprid (Topical) Advantage Multi	+	+		+		+/−	
Eprinomectin/Fipronil/Praziquantel* (Topical) BROADLINE	+	+			+	+	

*Not currently marketed in U.S.; label claims are for Europe and anticipated in the U.S. European label claim also includes *Aelurostrongylus abstrusus*.

Because the vast majority of cats are amicrofilaremic, microfilaricidal therapy is unnecessary in this species. The use of arsenical adulticides is problematic. Thiacetarsamide (sodium caparsolate), if available, poses risks even in normal cats. Turner et al reported death due to pulmonary edema and respiratory failure in 3 of 14 normal cats given thiacetarsamide (2.2 mg/kg, given twice, 24 hours apart).[188] Dillon and colleagues[189] could not confirm this acute pulmonary reaction in 12 normal cats receiving thiacetarsamide, but one cat did die after the final injection. More importantly, a significant, though unquantified, percentage of cats with HWI develop PTE after adulticidal therapy.[172-174] This occurs several days to 1 week after therapy and is often fatal. In 50 cats with HWI, seen at NCSU, 11 received thiacetarsamide. There was no significant difference in survival between those receiving thiacetarsamide and those receiving symptomatic therapy.[174]

Data on melarsomine in experimental (transplanted) HWI in cats are limited and contradictory. Although an abstract report exists in which one injection (2.5 mg/kg; one half the recommended canine dosage) of melarsomine was used in experimentally infected cats without treatment-related mortality, the worm burdens after treatment were not significantly different from those found in untreated control cats.[190] Diarrhea and heart murmurs were frequently noted in treated cats. A second abstract report, using either the standard canine protocol (2.5 mg/kg, given twice, 24 hours apart) or the split-dose (one injection, followed by two injections, 24 hours apart, in 1 month) gave more favorable results.[191] The standard treatment and split-dose regimens resulted in 79% and 86% reduction in worm burdens, respectively, and there were no adverse reactions. Although promising, these unpublished data need to be interpreted with caution because the transplanted worms were young (<8 months old and more susceptible), and the control cats experienced a 53% worm mortality (average worm burden was reduced by 53% by the act of transplantation). Additionally, the clinical experience in naturally infected cats has been generally unfavorable, with an unacceptable mortality. Because of the inherent risk, lack of clear benefit, and the short life expectancy of heartworms in this species, this author does not advocate adulticidal therapy in cats.

Surgical removal of heartworms has been successful and is attractive because it minimizes the risk of thromboemboli. The mortality seen in the only published case series was, unfortunately, unacceptable (two of five cats).[192] We have recently had success in cats with HWD-associated heart failure, using a nitinol snare to remove worms via the jugular vein.[193] Even with its advantages, this approach is still impractical for the vast majority of cases. Cats with HWI should be placed on a monthly preventive and short-term corticosteroid therapy (prednisolone 1 to 2 mg/kg SC 8-48 h) to manage respiratory signs. If signs recur, alternate-day steroid therapy (at the lowest dose that controls signs) can be continued indefinitely. For embolic

emergencies, oxygen, corticosteroids (dexamethasone 1 mg/kg IV or IM, or prednisolone sodium succinate 50 to 100 mg/cat IV), and bronchodilators (aminophylline 6.6 mg/kg IM q 12 h, theophylline sustained release 15 to 20 mg/kg PO q 24 h, or terbutaline 0.01 mg/kg SC) may be used. Bronchodilators have logic, based on the ability of agents, such as the xanthines (aminophylline and theophylline), to improve function of fatigued respiratory muscles. In addition, the finding of hyperinflation of lung fields may indicate bronchoconstriction, a condition for which bronchodilation would be indicated. Nevertheless, this author does not routinely use bronchodilators in feline HWD.

The use of aspirin has been questioned because vascular changes associated with HWI consume platelets, increasing their turnover rate and effectually diminishing the antithrombotic effects of the drug. The conventional dosage of aspirin did not prevent angiographically detected vascular lesions in experimental HWI.[194] Aspirin dosages required to produce even limited histologic benefit approached the toxic range. Because the quoted studies were based on relatively insensitive estimates of platelet function and pulmonary arterial disease (thereby possibly missing subtle benefits), because therapeutic options are limited, and because at conventional dosages (40 to 80 mg PO q 72 h), aspirin is generally harmless, inexpensive, and convenient, the author continues to advocate aspirin for cats with HWI. Aspirin is not, however, prescribed with concurrent corticosteroid therapy. Recent data on systemic arterial thromboembolism show that clopidogrel is a better anti-platelet drug than aspirin in the cat, as in man.[195] Although clopidogrel (18.75 mg/cat q 24 h) has not been studied in feline HWI, it would appear to be a better, though more expensive, choice for cats with HWI than is aspirin. Management of other signs of HWD in cats is largely symptomatic.

Prognosis

In the aforementioned study of 50 cats with natural HWI, at least 12 cats died of causes other than HWD. Seven of these and two living cats were considered to have survived HWD (lived >1000 days).[174] The median survival for all heartworm-infected cats, living beyond the day of diagnosis, was 1460 days (4 years; range, 2 to 4015 days), whereas the median survival of all cats (n = 48 with adequate follow-up) was 540 days (1.5 years; range, zero to 4015 days). Survival of 11 cats treated with sodium caparsolate (mean, 1669 days) was not significantly different from that of the 30 managed without adulticide (mean, 1107 days). Likewise, youth (<3 years of age), presence of dyspnea, cough, ELISA-positivity for heartworm antigen, presence of echocardiographically identifiable worms, or gender of the cat did not appear to affect survival.[174] Recent aforementioned data indicate that approximately 40% to 75% of infected cats may be asymptomatic and that as many as 80% of these cats may self-cure.[156,161] This is interpreted as indicating that HWI in cats is probably much more common than currently appreciated and that the adverse effects may be less dire than currently believed. The effect of HWI on survival has been compared with that of other cardiovascular diseases (Figure 255-37).[196]

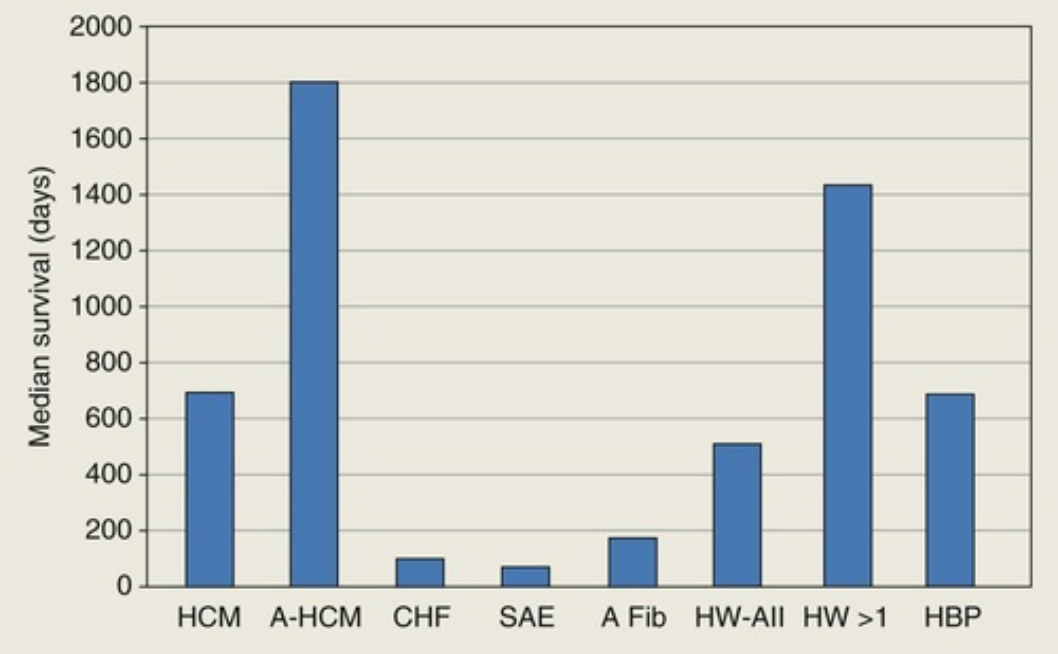


FIGURE 255-37 Median survival from four previous reports for cats with varying cardiovascular diseases. Median survival shown as 5 years was actually more than 5 years. *A Fib,* Atrial fibrillation; *A-HCM*,* asymptomatic hypertrophic cardiomyopathy; *CHF,* hypertrophic cardiomyopathy with heart failure; *HBP,* high blood pressure; *HCM,* hypertrophic cardiomyopathy; *HW-All,* heartworm infection, all cases; *HW>1,* heartworm infection with survival beyond day 1; *SAE,* hypertrophic cardiomyopathy with systemic embolism. (From Atkins CE, Côté E, DeFrancesco TC, et al: Prognosis in feline heartworm infection: comparison to other cardiovascular disease. In Seward LR, Knight DH, editors: *Proceedings of the 2001 American Heartworm Symposium*, Batavia, IL, 2003, American Heartworm Society, pp 41-44.)

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CHAPTER 256

Arterial Thromboembolic Disease

Daniel F. Hogan

Background

Arterial thromboembolism (ATE) is defined as the infarction of one or more arterial beds by embolic material usually derived from a thrombus at a site distant to the infarcted arterial bed. It is important to differentiate ATE from arterial thrombosis for multiple reasons. First, the underlying lesion usually is very different. The endothelial surface of the infarcted vessel is normal in cases of ATE, while disruptions to the vascular endothelium and/or vascular wall are hallmarks of arterial thrombosis. Second, ATE usually is associated with stagnant flow or blood stasis while arterial thrombosis is associated with high shear flow within a narrowed blood vessel. Third, ATE occurs commonly in veterinary patients while true arterial thrombosis is exceedingly rare.

In some instances, the site of the initiating thrombus is either known or reliably suspected. With cardiogenic embolism (CE), thrombi most often are found within a dilated left atrium or auricle. The heart also is the source of emboli that develop with endocarditis (see ch. 251). However, many times the source of the thrombus cannot be determined and these include conditions such as neoplasia and protein-losing nephropathy. Some have suggested that deep venous thrombi are the source of the embolic material, but this would not explain the arterial location of the embolus in the absence of a right-to-left shunting cardiovascular defect. *Paradoxical embolism,* which is an arterial thromboembolic stroke resulting from deep venous thrombosis, occurs in humans and is usually associated with an interatrial communication such as a persistent foramen ovale that allows passage of an embolus from venous to arterial circulation. This has been reported in veterinary medicine[1] and could be the situation for many more of our domestic animal species as a recent study suggests that atrial septal defects are much more common in the dog than originally suspected.[2] Pulmonary neoplasia is unique in that thrombosis within a pulmonary vein could generate an embolus that enters the systemic arterial circulation.

Pathogenesis

In the normal healthy state, there is an equilibrium between thrombus formation and thrombus dissolution. This delicate balance allows for continuous repair of endothelial injury while preventing unregulated thrombus development. Primary hemostasis begins with the exposure of subendothelial collagen and is characterized by adhesion of platelets to the subendothelial site. Platelet activation and aggregation follow, with release of agents exhibiting pro-aggregating and vasoconstrictive properties. These substances, in conjunction with circulating factors within the plasma, initiate the coagulation cascade, resulting in secondary hemostasis. As the hemostatic plug is formed and endothelial healing is taking place, profibrinolytic mechanisms are activated to break down the developing hemostatic plug, thereby preventing excessive thrombus formation. Pathologic thrombosis happens when the balance between thrombus formation and fibrinolysis is deranged in favor of the former.

The development of pathologic thrombosis classically has been described through Virchow's triad: endothelial injury, blood stasis, and the presence of a hypercoagulable state. Endothelial injury could result from a dilated left atrium in a cat with hypertrophic cardiomyopathy, damaged aortic valve in a dog with subaortic stenosis, or tumor invasion of the arterial tree. Blood stasis can be associated with dilated cardiac chambers (Video 256-1) or restricted blood flow from tumor growth. The presence of a hypercoagulable state is much more difficult to identify specifically, especially in our domestic animal species. Known hypercoagulable states in humans include inherited abnormalities in the procoagulant factors IIa (thrombin), Va, and VIIIa, and the antithrombotic proteins antithrombin (AT), protein C, and protein S.[3-7] Additional hypercoagulable states have been associated with platelet hypersensitivity, and increases in homocysteine,

lipoprotein(a), plasminogen activator inhibitor (PAI-1), and thrombin-activatable fibrinolysis inhibitor (TAFI). Clinical thrombosis in dogs and cats has been associated with increased platelet hypersensitivity, decreased AT and protein C activity, and increases in factors II, V, VII, VIII, IX, X, XII, and fibrinogen.[8-14] It seems prudent to view the development of pathologic thrombosis through the concept of cumulative risk, where each arm of Virchow's triad can contribute to an increased risk of thrombosis.

Early pathologic thrombus composition is platelet-rich but progressively becomes more fibrin-rich as the thrombus continues to grow. As the thrombus matures, it will become lamellated, where superficial portions can break off, forming emboli that infarct distant arterial beds. The level of infarction depends on the size and stability of the embolus, as obstruction occurs where the size of the embolus reliably exceeds vessel diameter.

Clinical Signs

Clinical signs attributable to ATE depend on the degree of infarction and the location of the infarcted vascular bed. The severity of clinical signs is inversely proportional to the amount of arterial blood flow. Many organs have a collateral network that can be recruited to provide blood flow around a site of obstruction to a major artery. However, these networks develop more fully with gradual loss of blood flow and there is strong evidence that the acute infarction caused by ATE is associated with an impaired development of these networks.[15,16]

Renal infarction has been associated with signs of renal pain and acute kidney injury while mesenteric infarction can result in evidence of abdominal pain, vomiting, and diarrhea. Splenic infarction can be associated with lethargy, anorexia, vomiting and diarrhea.[17] Profound neurologic deficits and seizures have been associated with cerebral infarctions as well as sudden death in severe cases.[1]

Although cerebral, renal and splanchnic infarction occurs occasionally, infarction of the aortic trifurcation accounts for the majority of ATE cases in dogs and cats.[18] Infarction of the aortic trifurcation (classic saddle embolus) results in a loss of blood flow to the pelvic limbs and causes ischemic neuromyopathy (INM) (Figure 256-1). Clinical signs of INM include paresis or paralysis of the pelvic limbs with absence of segmental reflexes, firm and painful pelvic limb musculature, and cold and pulseless limbs with cyanotic nail beds (Video 256-2). The changes can be bilaterally symmetrical or asymmetrical, or unilateral, depending on the degree of arterial obstruction and collateral vessel development. Clinical signs develop acutely and can worsen but usually remain stagnant or improve over the next several days to 3 weeks. A major contributing factor to the development of INM appears to be the release of vasoactive substances from activated platelets, reducing collateral flow around the site of obstruction. Similar pathophysiologic changes have been identified in humans suffering from thrombotic stroke, cardiogenic embolism, cardiogenic thromboembolic stroke, and pulmonary embolism.[19-22] With experimental aortic obstruction, blood flow in cats is maintained through an extensive collateral circulation in the vertebral system and epaxial muscles (E-Figure 256-2 and Video 256-3).[15,16,23] However, this collateral circulation is lost to varying degrees with the presence of a thrombus in the aortic segment and clinical signs of INM are evident. Serotonin, released from activated platelets, appears to be at least one major factor for this finding. Research models have demonstrated that the presence of serotonin in an isolated aortic segment results in loss of the collateral network and signs of INM while pretreatment with serotonin antagonists prevents these changes.[16,24]

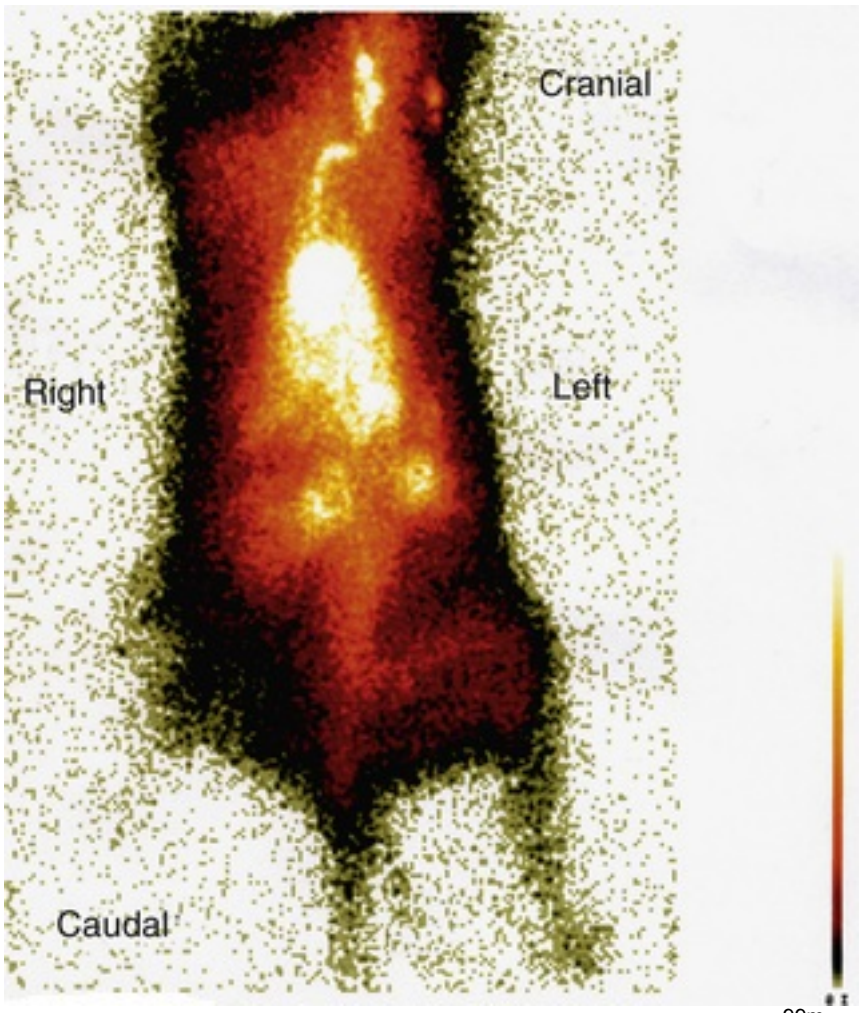
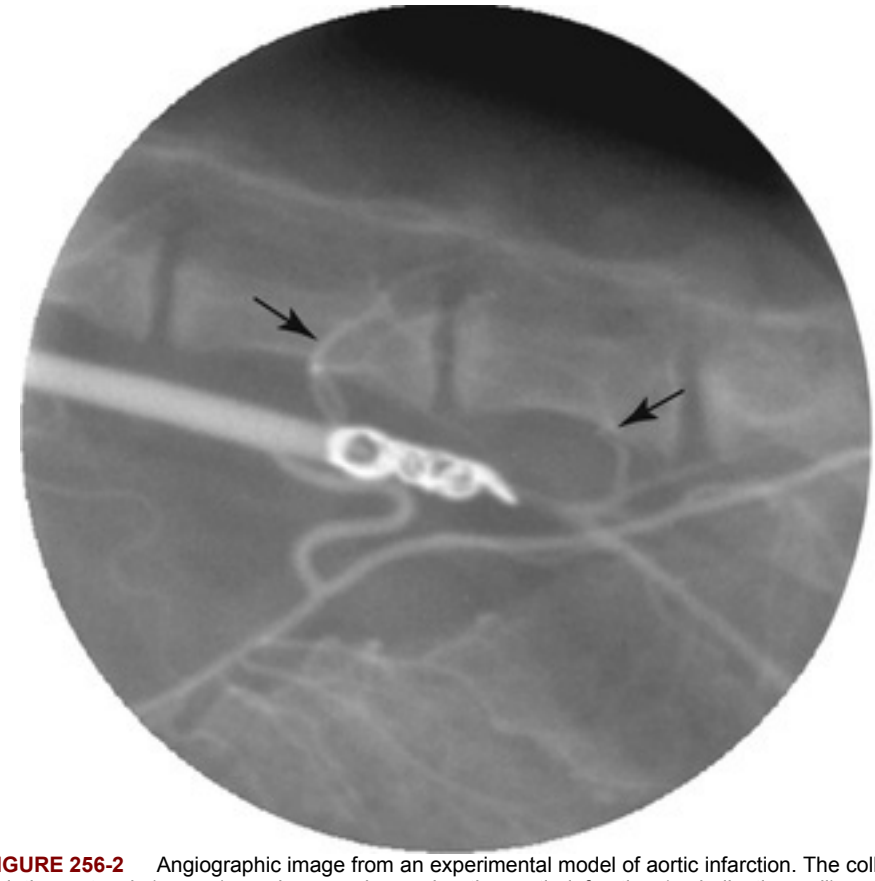


FIGURE 256-1 Nuclear perfusion scan in a cat with asymmetric ATE using unbound ^{99m}Tc. There is a dramatic reduction in perfusion of the right pelvic limb and below the stifle in the left pelvic limb.



E-FIGURE 256-2 Angiographic image from an experimental model of aortic infarction. The collateral circulation network (arrows) can be seen bypassing the aortic infarction (embolization coil) providing blood flow distal to the site of infarction.

Infarction of the right subclavian artery is the second most common site of ATE in cats with underlying cardiac disease. The clinical signs associated with infarction of this site are essentially identical to those for infarction of the aortic trifurcation, although the signs are confined to the right forelimb.[25]

In addition to the clinical signs associated with the infarcted vascular bed, additional clinical signs related to the underlying disease can be present. These could include fever, depression and dyspnea with sepsis; depression, tachypnea and pallor with immune-mediated hemolytic anemia (IMHA); depression and ascites or peripheral edema with nephrotic syndrome; tachypnea, weakness and polyuria/polydipsia with hyperadrenocorticism; dyspnea, and cardiac murmur or gallop sounds with underlying cardiac disease. In cats with cardiogenic embolism, concurrent congestive heart failure (CHF) has been reported in 44%-66% of cases.[18,26,27]

Treatment

Key elements in the acute management of ATE include preventing continued thrombus formation associated with the embolus, improving blood flow to the infarcted organ, pain management when appropriate, treating concurrent clinical conditions, and supportive care.

Reduce Thrombus Formation

Unfractionated heparin (UH) is a group of heterogeneous molecules with a mean molecular weight of ≈15,000 Daltons (range of 3,000 to 30,000 Daltons). Due to variability in molecular size, pharmacokinetic and anticoagulant properties can vary. Heparin molecules contain a pentasaccharide sequence that binds to AT, facilitating the inhibition of IIa, Xa, IXa and XIIa. There is also an inhibition of thrombin-catalyzed activation of factors V and VIII. Unfractionated heparin also exhibits an antiplatelet effect in normal humans by inhibiting thrombin-induced platelet aggregation, and binding to and inhibiting von Willebrand factor (vWF). The most common adverse effect of heparin therapy in humans is bleeding, while heparin-induced thrombocytopenia can develop in up to 10% of patients. Objective studies evaluating the bleeding risk in dogs

and cats receiving heparin therapy do not exist although bleeding has certainly been reported. To the author's knowledge, there is no clinical report of heparin-induced thrombocytopenia in dogs or cats. Ideally, a bleeding profile including platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), and possibly thromboelastography (TEG) should be submitted prior to heparin therapy (see ch. 196). This determines baseline coagulation function and identifies bleeding disorders, such as disseminated intravascular coagulation, that could be associated with the ATE or its underlying cause. Adequate dosing of heparin in dogs and cats has been shown to be quite variable and dosing requirements can change over time due to a decrease in circulating AT levels.[28-30a] Reasonable dosing regimens include 250-375 IU/kg IV initially followed by 150-250 IU/kg SC q 6-8 h for cats and 200-300 IU/kg IV initially followed by 200-250 IU/kg SC q 6-8 h for dogs. Historically, serial measurement of the aPTT has been used to monitor heparin therapy with a target of 1.5-2.0 times the baseline value, and this methodology is readily available.[29] However, one study in cats suggests that aPTT does not correlate well with plasma UH levels.[28] Therefore, anti-Xa monitoring may be considered, although assays have not been evaluated with regard to effective inhibition of thrombus growth.[31]

The low-molecular-weight heparins (LMWH) are smaller in size than UH and could be used in lieu of UH. The cost for these agents is much higher than UH (approximately $3-$5/dose) but they can be administered SC q 12 h in humans for acute management of thrombotic conditions. Dalteparin and enoxaparin have been used in dogs and cats at 100 IU/kg SC q 24-12 h and 1-1.5 mg/kg SC q 24-12 h, respectively.[32,33] However, clinical trials evaluating inhibition of thrombus growth with these agents do not exist in veterinary medicine so the exact dosage and clinical response are unknown at this time.

Improve Blood Flow

Arterial Flow—Thrombolytic Therapy

An ideal goal with infarction is to re-establish arterial flow to the infarcted organ. This requires removal of the embolus either through embolectomy or dissolution with thrombolytic drugs. Thrombolytic drugs have been used in dogs and cats to dissolve emboli and re-establish arterial flow.[34-39] Ideally, they should be administered as soon as possible after the embolic event but effective dissolution has been noted as late as 18 hours after initial clinical signs.[34] Severe adverse effects can be associated with thrombolytic therapy; therefore, caution should be exercised when considering these drugs. The sudden resumption of arterial flow to infarcted organs can result in the rapid development of life-threatening hyperkalemia and severe metabolic acidosis. This is *reperfusion injury,* and it is most likely to occur with terminal aortic infarction. The frequency of reperfusion injury following thrombolytic therapy in cats with CE is 40-70%.[34-36] Reperfusion injury represents the most common cause of death in cats receiving pharmacologic thrombolytic therapy with survival rates reported from 0% to 43%.[34-36] Due to potential adverse effects and cost, thrombolytic therapy should not be used in all cases of ATE. However, thrombolytic therapy should be strongly considered in cases of cerebral, splanchnic or renal infarction, as the re-establishment of arterial flow is of principal importance.

Streptokinase

Streptokinase (SK) combines with plasminogen to form an activator complex that converts plasminogen to the proteolytic enzyme plasmin. Plasmin degrades fibrin, fibrinogen, plasminogen, coagulation factors and SK. The SK-plasminogen complex converts circulating and fibrin-bound plasminogen and is therefore considered a nonspecific activator of plasmin. Streptokinase is produced by streptococci, which can lead to antigenic stimulation, especially with repeated administrations. These anti-SK antibodies also can reduce the efficacy of the drug. Streptokinase typically is administered by giving 90,000 IU IV over 1 hour followed by an infusion of 45,000 IU/hour for up to 12 hours in dogs and cats. In one study, all eight treated cats experienced respiratory distress and died suddenly during the maintenance phase.[36] In a second study, ≈50% of 46 cats with CE had a return of femoral pulses within 24 hours of initiating SK[35]; motor function returned in 30%, most (80% of these) within 24 hours. Cats with single limb infarction did dramatically better, with 100% regaining pulses and 80% regaining motor function. Spontaneous bleeding occurred from oral, rectal, or catheter sites in 24% of cats and reperfusion injury in ≈40%. Bleeding was severe enough to require transfusions in 27% of the cats, with only 18% of these cats surviving SK therapy. The overall survival rate was 33% during hospitalization. There is one published report of three dogs treated with SK for ATE.[37] Partial resolution of the thrombus was noted in one dog while the other 2 had complete resolution after 1-3 doses of SK. All three experienced partial or complete resolution of clinical signs with only minor bleeding

that resolved with discontinuation of SK infusion. There was no evidence of reperfusion injury in any of the dogs. Streptokinase is no longer available in the United States, although there is some limited availability in a small number of other countries.

Urokinase

Urokinase (UK) is similar in activity to streptokinase but is considered more fibrin-specific due to the physical characteristics of the compound. Commercial preparations consist of both high-molecular-weight (HMW) and low-molecular-weight (LMW) fractions. There is a much higher concentration of HMW molecules in the commercial solution but they are quickly and continuously converted to the LMW form in the circulation. The LMW molecules bind with greater affinity to the lysine-plasminogen form of plasminogen, which preferentially accumulates within thrombi. This confers some of the fibrin-specificity of UK. Urokinase has been administered IV to cats and dogs for ATE with a 4,400 IU/kg loading dose given over 10 minutes followed by 4,400 IU/kg/h for 12 hours.[38,39] Of 12 cats treated with UK, 56% regained motor function while only 27% regained pulses. No bleeding was seen, but evidence of reperfusion injury was noted in 25% of treated cats. Overall, 5/12 (42%) survived treatment.[38] The clinical experience was much less rewarding in dogs where the mortality rate was 100% in UK treated dogs.[39] Urokinase is no longer available in the United States.

Tissue Plasminogen Activator

Tissue-plasminogen activator (t-PA) is the primary activator of plasmin *in vivo;* however, it does not readily bind circulating plasminogen. Plasminogen and t-PA both have a high affinity for fibrin, thereby forming an intimate relationship within thrombi, resulting in a fibrin-specific conversion of plasminogen to plasmin. However, the fibrin specificity is relative and when t-PA is administered at high dosages, a systemic proteolytic state and bleeding can be seen.[40]

There is very little clinical experience with human recombinant t-PA in dogs and cats with spontaneous ATE.[34,41,42] The drug has been administered IV either as a constant rate infusion in cats (0.25-1 mg/kg/h IV for a total dose of 1-10 mg/kg) or multiple bolus therapy in dogs (1 mg/kg IV). In two dogs treated for arterial thromboembolism, one had gradual return of femoral arterial pulses[43] after multiple boluses of t-PA while the other dog showed no response.[41] There has been one reported clinical trial of t-PA therapy in six cats with CE.[34] Complications included minor hemorrhage from catheter sites (50%), fever (33%) and reperfusion injury (33%). The acute survival rate was 50%, with deaths attributed to reperfusion injury and cardiogenic shock. Of the cats that survived, 100% had infarction of both limbs. Perfusion was restored within 36 hours and motor function returned within 48 hours in 100% of surviving cats. Tissue plasminogen activator currently is the only pharmacologic thrombolytic approved for human use in the United States.

Improve Collateral Flow

If dissolution of the embolus is unsuccessful or not attempted, then increasing perfusion to the infarcted organ can be attempted by increasing flow through the collateral network. The use of vasodilators, such as acepromazine, generally has been unsuccessful and clinical hypotension may result, further reducing perfusion. The platelet release products serotonin and thromboxane have been implicated as potential agents responsible for loss of collateral flow associated with aortic infarction. Therefore, antiplatelet agents might help improve collateral flow by reducing the amount of vasoactive substances released from platelets. Aspirin reduced the amount of thromboxane released from activated cat platelets and improved collateral flow in an experimental cat model of aortic infarction, but a very high dosage of aspirin (associated with toxicosis in clinical cases) was used.[44] Clopidogrel has been shown to reduce serotonin release from activated platelets in cats while studies in other species have demonstrated reduced production of thromboxane.[45,46] There is also evidence that clopidogrel exerts an *ex vivo* vasomodulating effect (reduced vasoconstriction) in rats, rabbits, and dogs[47,48] and a similar effect experimentally in cats *in vivo,* including a significant reduction in clinical signs.[49] While maximal antithrombotic effects of clopidogrel are achieved within 72 hours of daily administration of 2-4 mg/kg PO in dogs and cats,[45,50] an oral loading dose of ≈10 mg/kg given to dogs resulted in comparable antithrombotic effects within 90 minutes with no adverse effects.[50] Additionally, daily administration of 75 mg PO to cats (≈15 mg/kg) has been well-tolerated and not associated with adverse effects. Therefore, while there are no objective data to support this assertion, the acute administration of clopidogrel on presentation for ATE could be helpful in improving collateral flow and should not be

associated with adverse effects.

Pain Management

Arterial thromboembolism can result in severe pain and controlling this pain is a critically important aspect of acute ATE treatment (see ch. 126). Narcotic agents are most commonly used and they work very well. Butorphanol (0.1-0.4 mg/kg SC, IM, IV q 1-4 h; dogs and cats), hydromorphone (0.08-0.3 mg/kg SC, IM, IV q 2-6 h; dogs and cats), buprenorphine (0.005-0.02 mg/kg SC, IM, IV q 6-12 h; dogs and cats), or oxymorphone (0.05-0.2 mg/kg SC, IM, IV q 1-3 h; dogs and cats) have been widely used and appear to provide good analgesia with few adverse effects. In severe or refractory cases, fentanyl (4-10 mcg/kg IV bolus followed by 4-10 mcg/kg/h IV infusion; dogs and cats) can be used. Injections should be given cranial to the diaphragm to assure adequate absorption.

Survival

Reported survival rates for initial CE events in cats are remarkably similar whether conservative (35%-39%)[18,26,27] or thrombolytic (33%)[35] therapy is used. Cats with single pelvic limb infarction do dramatically better (68%-93%)[18,26,27,35] than do cats with bilateral pelvic limb infarction (15%-36%) regardless of therapy used.[18,26,27,35] Nonsurvival rates range from 61%-67% with natural death rates (28%-40%) similar to euthanasia rates (25%-35%).[18,26,27,35] Nonsurvival has been significantly associated with hypothermia,[18,35] reduced heart rate[18] and absence of motor function.[18] Reported long-term median survival times following the initial CE event have ranged from 51 days to 345 days.[18,26,27,35,51,52]

Prevention

Primary prevention of ATE is defined as therapy that reduces the risk of the first thromboembolic event in an animal at risk for ATE. While primary prevention would be an ideal and logical goal, there is a poor understanding of thrombotic risk in our patients. We do know that some underlying conditions are associated with ATE but we cannot accurately predict which animals will actually go on to develop ATE. The greatest body of evidence is associated with CE in cats. Cats appear to be at a greater risk for ATE if they have larger left atrial size or evidence of systolic dysfunction.[52] Similar patterns have been identified in humans. These findings combined with clinical experience have led to the recommendation that prophylactic antithrombotic therapy be considered in cats with echocardiographic measurements of an end-systolic left atrial diameter >1.7 cm or left atrium-to-aortic ratio (LA/Ao) >2.0.[53] Prophylactic antithrombotic therapy is also indicated in cats with spontaneous contrast in the left atrium on echocardiography (see Video 256-1).[53]

Secondary prevention has received more attention in veterinary medicine and is defined as preventing a subsequent ATE event in an animal with a history of ATE. Again, the largest body of evidence in veterinary medicine is related to CE in cats. The reported recurrence rates from non-controlled, retrospective studies for cats receiving some antithrombotic agent range from 17% to 75%[18,26,27,34,35] with a 1 year recurrence rate of 25% to 50%.[27,35] Recently, the first prospective study evaluating secondary prevention of CE in cats was published.[54] The Feline Arterial Thromboembolism; Clopidogrel versus Aspirin Trial (FAT CAT) was a double-blind, randomized, and positive-controlled multicenter study that enrolled 75 cats after they survived a CE event. Clopidogrel 18.75 mg/cat PO q 24 h was associated with a significantly reduced likelihood of recurrent CE compared to aspirin and a longer median time to recurrence (443 days vs. 192 days). Clopidogrel also was associated with a significantly reduced likelihood of the composite endpoint of recurrent CE or cardiac death with a longer median time to event (346 days vs. 128 days).

Antithrombotic Drugs

Due to their direct effect on thrombus formation, antithrombotic agents have become a mainstay for primary and secondary prevention of ATE in dogs and cats. However, it should be emphasized that a goal of complete prevention of recurrent embolic events in animals with chronic diseases such as cardiac disease or nephrotic syndrome probably is not realistic. The goal should be to delay the time to the next ATE event or to reduce the clinical signs associated with the event.

Antiplatelet Agents

These agents inhibit some aspect of platelet adhesion, aggregation, or release reaction, and impair the formation of the initial platelet-rich thrombus at the injured endothelial site. Some of these agents also exhibit some vasomodulating effects by interfering with vasoactive substances such as serotonin and thromboxane.

Aspirin

Aspirin is the most used and studied antiplatelet agent available today. It irreversibly acetylates platelet cyclooxygenase, preventing the formation of thromboxane A_2, which has potent pro-aggregating and vasoconstrictive properties. Aspirin is considered a modest and indirect antiplatelet agent that inhibits secondary but not primary platelet aggregation. Aspirin exerts a similar effect on cyclooxygenase in endothelial cells, reducing the production of prostacyclin, a substance that exhibits anti-aggregating and vasodilating properties. However, endothelial cells are able to overcome this inhibition, unlike platelets, so antithrombotic properties predominate in the clinical setting. The pharmacologic, analgesic, and antiplatelet effects of aspirin have been evaluated in the dog and cat.[55-58] Recurrence rates in retrospective studies range from 17% to 75%.[18,26,27,34] Adverse effects are typically gastrointestinal (GI; e.g., anorexia, vomiting) and have been reported in up to 22% of treated cats.[18] One study evaluating a low-dosage aspirin protocol did not identify a significant difference in recurrence rates compared to a standard aspirin dosage but there was a reduced rate of adverse GI events.[18] There was only one case of reported adverse GI effects associated with aspirin in the FAT CAT study, although one additional cat that died from a recurrent CE event had a large gastric ulcer on necropsy.[54] The FAT CAT study protocol required that the study drugs be administered in a gelatin capsule, and this may have resulted in less gastric irritation.

There is very little published clinical evidence regarding the use of aspirin for the prevention of thrombosis in dogs. One study reported greater survival in dogs with IMHA that received a low dosage of aspirin in addition to immunosuppressive therapy.[59] Additionally there is a retrospective study of thrombosis treatment in dogs where 3/9 (33%) experienced improvement or resolution of the thrombus.[59a] Healthy dogs receiving aspirin have been reported to have uniformly developed moderate gastroduodenal endoscopic lesions including erosions and submucosal hemorrhages, although at dosages considerably higher than those used clinically.[60] In that study, vomiting was noted in approximately 7% of the dogs during the treatment period with no evidence of diarrhea.

Clopidogrel

Clopidogrel is a second-generation thienopyridine that induces specific and irreversible antagonism of the ADP_{2Y12} receptor along the platelet membrane. It inhibits both primary and secondary platelet aggregation in response to multiple agonists. These effects are more potent than those induced by aspirin. The ADP-induced conformational change of the glycoprotein IIb/IIIa complex also is inhibited, which reduces binding of fibrinogen and von Willebrand factor.[61] It also impairs the platelet release reaction, decreasing the release of pro-aggregating and vasoconstrictive agents such as serotonin and ADP.[46] Vasomodulating effects also have been seen *in vitro* and *in vivo*.[48,49] The parent compound does not possess antiplatelet effects; it must undergo hepatic biotransformation to form an active metabolite. Unlike aspirin, clopidogrel is not associated with gastroduodenal ulceration. In normal cats given 18.75 mg/cat PO q 24 h, maximal antiplatelet effects occur after 3 days of drug administration and are lost within 7 days after drug discontinuation[45]; similar results have been noted in dogs treated with 1-3 mg/kg PO q 24 h.[50,62] Stimulation of the hepatic P450 enzyme system in dogs results in antiplatelet effects at lower dosages, presumably due to an increase in the biotransformation of the parent molecule. No adverse effects were noted during either study, but there are anecdotal reports of sporadic vomiting in cats receiving clopidogrel clinically, which could be due to the extreme bitterness of the drug. Regarding thromboprophylaxis, one small study compared 90-day survival in dogs with IMHA that received clopidogrel, ultralow-dose aspirin, or both.[63] Most of the dogs in all groups survived the first 90 days with very small numbers experiencing clinically suspicious thrombosis and none experienced bleeding complications. Platelet aggregation was not monitored with either drug so it is not known if there was an actual pharmacodynamic effect from aspirin or clopidogrel. In cats, clopidogrel is associated with a significantly reduced likelihood of recurrent CE compared to aspirin in cats (see Aspirin, above). To date, there are no reported cases in dogs or cats of agranulocytosis or thrombotic thrombocytopenic purpura (TTP), possible adverse effects in humans receiving clopidogrel.

Anticoagulant Agents

This group of drugs inhibits the coagulation cascade by interfering with the formation of one or more active coagulation factors. Some of these drugs also exhibit minor antiplatelet effects.

Warfarin

Warfarin inhibits the formation of the vitamin K–dependent coagulation factors II, VII, IX and X as well as the anticoagulant proteins C and S. After warfarin administration in humans, circulating levels of protein C fall prior to the decrease in coagulation factors, theoretically resulting in a hypercoagulable state for 4-6 days. For this reason, UH typically is administered during this period. Warfarin is indicated in many diseases in humans with a risk for ATE including atrial fibrillation and prosthetic heart valves. Numerous studies have demonstrated the efficacy of warfarin for primary and secondary prevention of CE with atrial fibrillation, even when lower-intensity anticoagulation protocols are used. Bleeding is the most common complication in humans.[64] Warfarin has numerous interactions with other medications that could increase or decrease the anticoagulation effect. In humans, warfarin therapy is adjusted by monitoring a parameter that is normalized for different thromboplastin reagents in different laboratories, the international normalized ratio (INR). Medium anticoagulation intensity (INR of 2-3) is recommended for most conditions in humans.

Pharmacokinetic and pharmacodynamic studies in dogs and cats[65,66] have demonstrated that absorption after oral administration is rapid. Enterohepatic recirculation occurs, which could contribute to the known widely variable inter- and intra-individual anticoagulant response.[66] Warfarin is not evenly distributed throughout the tablet so the tablet should be crushed and compounded by a pharmacist rather than split. Close and careful monitoring is required, and owners should be aware of this prior to beginning therapy as it requires dedication and expense for the owner. It has been recommended that adjustments to warfarin dosing should be done by changing the total weekly dose and not daily dose in response to INR monitoring.[67] While unsubstantiated, an INR of 2-3 has been considered an indicator of adequate anticoagulation in dogs and cats. Objective clinical trials evaluating the efficacy of warfarin for the prevention of thrombotic events in dogs and cats do not exist. Published CE recurrence rates for cats receiving warfarin range from 42% to 53% in retrospective studies, with estimated mean survival times from 210 to 471 days.[26,35] Bleeding (both major and minor) is the most common complication, seen in 13-20% of cats, and with fatal hemorrhage reported in up to 13% of cats.[26,33,35]

Low-Molecular-Weight Heparins

The low-molecular-weight heparins (LMWHs) are smaller in size (4,000 to 5,000 Daltons) compared to UH but they maintain the pentasaccharide sequence that binds to AT, inhibiting factor Xa, with a greatly reduced inhibition of IIa. The reduced anti-IIa activity translates into a negligible effect on the aPTT and thromboelastography (TEG) with LMWH therapy.[68] For this reason, monitoring of LMWH treatment has been performed through measurement of anti-Xa activity.[69,70] In humans with active thrombosis, enoxaparin therapy can produce peak anti-Xa levels of 0.6-1.0 U/mL at 4 hours and these levels are correlated with reduced thrombotic events.[69,71] There is not a commonly accepted therapeutic range of anti-Xa activity with once daily thromboprophylactic LMWH therapy in humans although a mean peak (4 hours) activity of 0.42 IU/mL and median trough (24 hours) activity of 0.03 IU/mL (0.00-0.188 IU/mL) has been reported.[72] The most common human adverse effect of LMWH is minor (5-27%) or major (0-6.5%) bleeding, which is similar to UH.

In healthy cats,[32,68] dalteparin and enoxaparin have produced similar results: peak anti-Xa levels at 4 hours that decrease below the limit of detection at 8 hours.[32,68] These results might suggest the need for a short interdose interval; however, as mentioned previously, peak anti-Xa levels in humans are not meant to be maintained throughout the entire dosing period. Indeed, in a modified venous stasis model in healthy cats, enoxaparin (1 mg/kg SC q 12 h) resulted in 100% thrombus inhibition at 4 hours and 91.4% thrombus inhibition at 12 hours after drug administration. There was a poor correlation between the antithrombotic effect of enoxaparin and the anti-Xa level, however, as there was no measurable anti-Xa activity 12 hours after drug administration.[73] In the author's opinion, enoxaparin exhibits an antithrombotic effect at the currently reported dosing regimen of 1 mg/kg SC q 12-24 h, and peak anti-Xa levels need to be correlated to reduced thrombotic events through clinical trials before dosing regimens that are more accurate can be recommended.

In a similar study of enoxaparin in dogs, pharmacokinetic modeling was used for determining whether anti-Xa levels were maintained throughout the dosing period.[75] As this is not the goal of LMWH therapy, current dose recommendations of 1 mg/kg SC q 12-24 h could be followed until clinical trials provide accurate dosing information.

A retrospective study comparing dalteparin to warfarin for the prevention of recurrent CE in cats demonstrated a comparable recurrence rate and median survival time between treatment groups.[33] None of the cats receiving dalteparin experienced bleeding complications, and infrequent bleeding was noted with dalteparin therapy in another study in cats.[74]

Newer Anticoagulants

Recently, new anticoagulant drugs developed for the human market have been designed with excellent efficacy; they generally do not require monitoring and have relatively low bleeding risks. The first drug to challenge the clinical dominance of warfarin was the direct thrombin inhibitor dabigatran, which was noninferior to warfarin for preventing CE associated with atrial fibrillation.[76] There is no known published study on the clinical use of dabigatran in dogs or cats.

A larger class of drugs is the Xa inhibitors. As suggested by the name, these drugs inhibit factor Xa either directly or through the potentiation of antithrombin. They, too, have been shown to be noninferior to warfarin for preventing CE associated with atrial fibrillation.[77,78] The most common adverse effect is bleeding, occurring with a similar frequency as with the LMWHs. These drugs have not been critically evaluated in dogs or cats to date, but basic pharmacologic data are accumulating. Fondaparinux is a synthetic Xa inhibitor that potentiates antithrombin activity. In a small number of healthy cats, fondaparinux (0.06 mg/kg SC q 12 h) produced anti-Xa activities that approximated therapeutic levels in humans.[79] Currently, this protocol is more expensive than LMWH, and since a superior clinical response is not expected, fondaparinux cannot be strongly supported for clinical use. Rivaroxaban and apixaban are oral, direct Xa inhibitors that are approved for use in humans. Both of these agents exert a dose-dependent *in vitro* effect on coagulation assays in cats.[80,81] Additionally, apixaban has been used in experimental dogs for the prevention of thrombosis associated with an implantable heart valve.[82]

The Xa inhibitor class of drugs is likely to have a major impact on clinical prophylaxis over the next 5-10 years. A therapeutic option that can be administered orally, does not require monitoring, has a low risk of bleeding, and is cost-effective would dramatically improve the clinical management of dogs and cats at risk for thrombosis.

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CHAPTER 257

Venous and Lymphatic Disorders

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Client Information Sheet: Venous and Lymphatic Disorders

Clinical signs resulting from disorders of the peripheral veins or lymphatics are uncommonly encountered in veterinary practice. However, diseases of these vessels should be considered in the differential diagnosis of the dog or cat with swelling of the extremities (including the head and neck), in patients with cavitary effusions, or in cases of unexplained edema (see ch. 18). Changes in the microcirculation that alter venous hydrostatic or oncotic pressures, increase vascular or lymphatic permeability, or impede venous or lymphatic drainage can underpin such clinical signs. These disorders can be primary, including developmental anomalies or inherited syndromes, or be secondary to compression, inflammation, or infiltration of venous or lymphatic vessels. This chapter briefly reviews systemic venous and lymphatic physiology, imaging techniques for evaluation of these vascular beds, and finally considers selected conditions associated with abnormalities of systemic veins or lymphatics (Box 257-1).

Box 257-1

Venous and Lymphatic Disorders

Diseases of Veins

Phlebectasia
Varicosis
Phlebitis and thrombophlebitis
Venous thrombosis
Venous malformations

Diseases of Lymphatics

Lymphangitis
Lymphedema
Lymphangiectasia
Lymphatic hypoplasia, aplasia, hyperplasia
Lymphangioma, lymphocysts
Lymphangiosarcoma

Tumors of Peripheral Blood Vessels

Angioma, hemangioma, hemangiosarcoma

Physiology of Systemic Venous and Lymphatic Flow

The systemic veins serve as a low-pressure, compliant reservoir for the intravascular volume, with approximately 60% of blood volume contained within these vessels.[1] Systemic venous return is controlled by a number of forces. These include the positive intravascular pressures behind *(vis a tergo)* and the more negative intracardiac pressures ahead *(vis a fronte)* of a column of venous blood; lateral forces *(vis a latre),* especially the alternating contraction and relaxation of skeletal muscles; gravity and posture; vascular resistance modulated by autonomic traffic, hormones, and local vasoactive mediators; and changes in

intrathoracic pressures operative during both spontaneous ventilation and mechanical ventilation. In health these forces drive systemic blood back towards the right atrium, assisted by one-way venous valves that prevent backflow.[2] Dysfunction or insufficiency of the systemic veins is common in humans related to abnormalities in the venous valves, dysfunction of muscular pumps, venous reflux, venous dilatation, venous thrombosis, or venous outflow obstruction.[2] Similar conditions in small animals are rarely recognized, though thrombotic conditions do occur, particularly with indwelling central venous catheters. Venous insufficiency and outflow obstruction can also develop secondary to extraluminal compression or from intraluminal narrowing, phlebitis, and thrombosis.

The lymphatic system plays a critical role in regulating body cavity and interstitial fluid volumes. Lymphatics also assist in the removal of inorganic material from subcutaneous tissues and the modulation of fat absorption in the gastrointestinal tract, while contributing to antigen transport and immune surveillance.[3] Additionally, the lymphatic system is the preferred metastatic route for many forms of cancer. This diversity of function highlights the pivotal role played by the lymphatic system in both health and disease.

Lymphatics originate within the interstitium as specialized endothelial-lined capillaries transporting fluid, solutes, and macromolecular particles back into the venous system. Fluid, protein, cells, and macromolecular particles from the interstitial space empty into the initial lymphatics that are composed of a series of small lymphatic capillaries beginning blindly in the tissues. The lymph then flows through a system of lymphatic vessels, which progressively increase in diameter. As lymph flows centrally it passes through at least one lymph node before emptying into larger lymphatic trunks.[4] The deep trunks unite to form two major lymphatic vessels: the thoracic and right lymphatic ducts. The thoracic duct drains most of the body and returns lymphatic fluid into the venous system at the brachycephalic vein or the left subclavian vein. The right lymphatic duct drains the right side of the head and neck and right forelimb.

Lymphatic vessels contain many junctions between individual endothelial cells, which are connected to the surrounding extracellular matrix by reticular fibers and collagen. These junctions open when tissue hydrostatic pressure becomes elevated and the anchoring filaments stretch, allowing fluid to move into the vessel.[5] As the fluid is cleared from the interstitium, the connecting fibers contract and the junctions between the endothelial cells close. The opening and closing of these junctions allow them to act as inlet valves preventing the backflow of lymph into the interstitium. The larger vessels of the lymphatic system have progressively fewer open junctions, increasingly muscular walls, and frequent intra-lymphatic valves that also prevent backflow of lymph. The action of external muscular contraction along with intrinsic contractility of the lymphatic vessels aids in the movement of lymph through the lymphatic system and lymph nodes. While in the lymph node, the lymph is in contact with the blood circulation and approximately half of the fluid is drained before leaving into the larger lymphatic ducts.[4] In addition to its transport function, the lymph system plays a major role in the immunologic responses to infectious agents.[3] It serves as a filtering system to impede the spread of microorganisms and neoplastic cells. The cellular components, in particular the lymphocytes, are indispensable for immunologic reactions and antibody formation.[3,5]

Techniques Used to Evaluate Venous and Lymphatic Disease

Angiography

Angiography is the traditional diagnostic test for evaluating peripheral vascular diseases due to its ability to characterize and visualize normal and abnormal vascular anatomy. Diagnostic outcome requires careful attention to three important elements: selection of radiopaque contrast agent, technique for vascular delivery of contrast material, and high-quality radiographic imaging.

As discussed in ch. 122, iodine-based particles are almost singularly used as contrast agents in the vascular system. Today, second-(iohexol, iopamidol) and third-(iodixanol) generation contrast agents are administered due to a greater safety profile than first-generation agents. Factors to be considered when selecting a contrast agent include patient safety, image quality, and cost. For animals with renal impairment, conservative administration of contrast agents should be employed and concurrent fluid diuresis performed.

Venography is far easier to accomplish than lymphangiography and is generally less challenging than arterial angiography owing to easier vascular access and the lower pressures of the venous system. A small gauge intravenous catheter can be placed in a superficial vein distal to the site of the suspected vascular lesion and contrast material injected. Images are acquired during and following the injection to evaluate anatomy and rate of venous clearance. Venography may be used to detect venous thrombi or vascular invasion by a neoplasm (each appearing as vascular filling defects), venous stenosis (Figure 257-1; Video 257-1), or

complete obstruction. With fluoroscopic cine imaging, venous insufficiency can also be appreciated. The presence of prolific collateral vasculature suggests chronic obstruction.

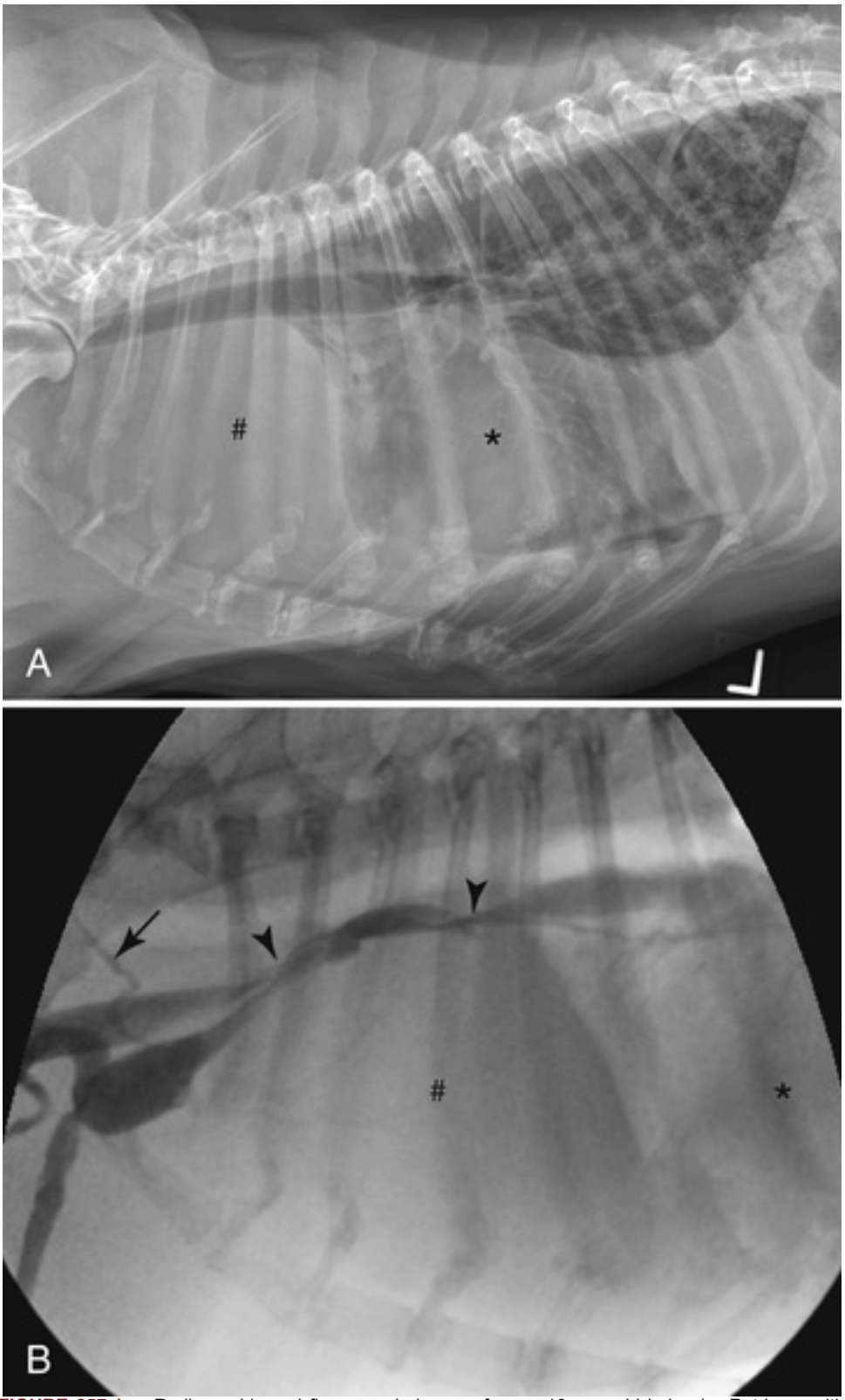

FIGURE 257-1 Radiographic and fluoroscopic images from a 10-year-old Labrador Retriever with thymoma. A large soft tissue mass (#) is present cranial to the heart (*) on the lateral thoracic radiograph in panel **A** with mild pleural effusion apparent. Nonselective venography via a cephalic catheter is shown in panel **B,** revealing a narrowed and extraluminally compressed cranial vena cava

(arrowheads) and development of collateral venous varicosities (arrow).

Lymphangiography facilitates regional assessment of the lymphatic system. The technique of indirect lymphangiography relies on a contrast agent, infused into tissue, to be selectively absorbed and transported through lymphatic channels.[6] Direct lymphangiography is more challenging (unless lymphangiectases have formed) but provides superior results when successfully performed (Video 257-2). Selective lymphatic cannulation requires aseptic cut-down over the lymphatic region of interest (note—the identification of lymphangiectases may be facilitated by subcutaneous injection of vital dyes [e.g., 3% Evans blue dye or 11% patent blue violet] into the toe web or consumption of a high fat meal for intestinal lymphatics). The lymphatic vessel is then cannulated with a 27- or 30-gauge needle or a special lymphatic cannula.[6] An iodine-containing soluble contrast medium as discussed above is then injected slowly into the vessel. Because water-soluble contrast media rapidly diffuse through lymphatic walls into surrounding tissues, the radiographic detail is blurred unless radiographs are taken shortly after contrast injection. Alternatively, oily iodine-containing contrast agents (e.g., Lipiodol) are used, reducing leakage of contrast from the lymphatic vessels. The oily contrast agents are sequestered within the lymphatics and lymph nodes along the draining pathways; some human reports suggest lymphangiography with this agent can even be curative for chylous leaks.[7] During lymphangiography, patency of the lymphatic channels can be appreciated in addition to the size of regional lymph nodes. Metastatic disease to the lymph nodes or granulomas appears as filling defects within the contrast-filled node. Lymphangiography can also be used to identify the location of lymphatic leakage or thoracic duct localization in small animals with chylous effusion.[8-10]

Diagnostic Ultrasound

Ultrasound imaging provides a direct, noninvasive technique for assessing venous abnormalities, patency, and function.[11,12] Ultrasound can aid in the diagnosis of venous thrombosis, aneurysms, traumatic vascular disease, and compression of vascular structures from local disease processes (Figure 257-2). Specialized ultrasound methods have been used in people to image the venous entry of the thoracic duct, but these have not been reported in dogs or cats.

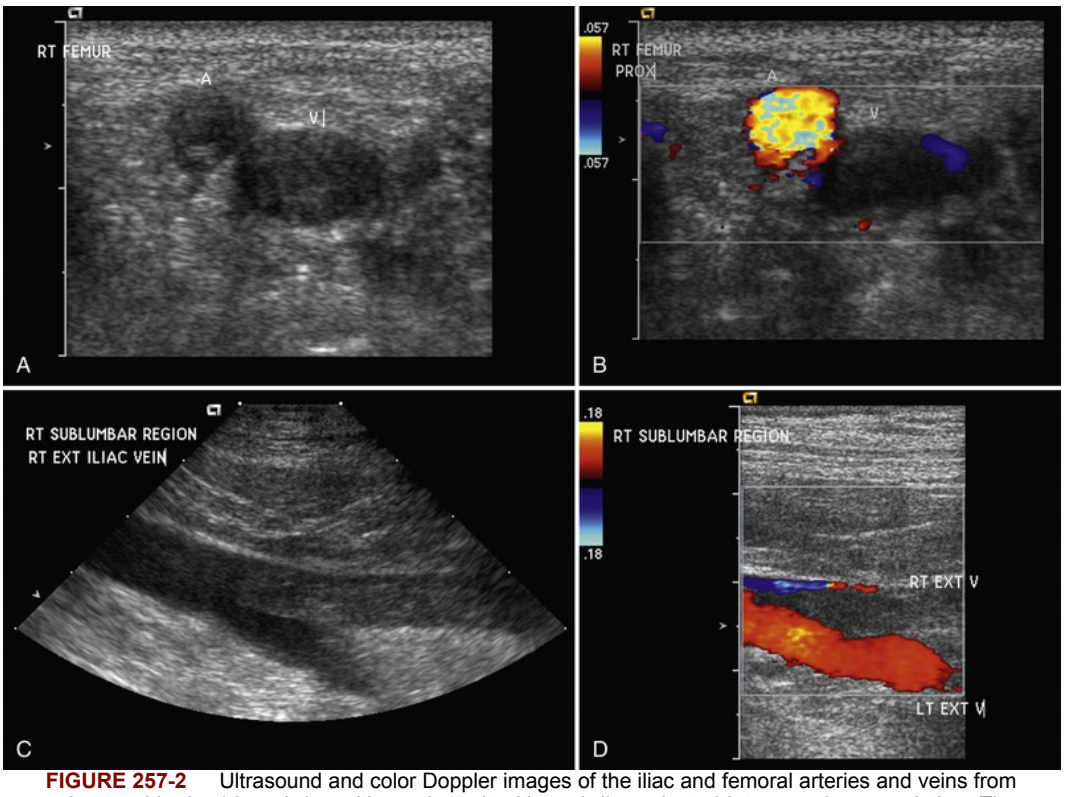

FIGURE 257-2 Ultrasound and color Doppler images of the iliac and femoral arteries and veins from a 9-year-old mixed breed dog with septic peritonitis and disseminated intravascular coagulation. The cross-sectional image in panel **A** shows that the lumen of the right (RT) femoral vein (V) is filled with a

hyperechoic thrombus and is noncompressible, while panel **B** shows normal color Doppler flow in the proximal (PROX) femoral artery (A), but nearly absent flow in the vein (V). Panels **C** and **D** show sagittal images of the external (EXT) iliac veins with hyperechoic thrombus and obstructed flow in the right external iliac vein (RT EXT V), compared to a patent lumen and flow in the left external iliac vein (LT EXT V).

Duplex ultrasonography incorporates grayscale two-dimensional imaging, coupled with simultaneous pulsed and color flow Doppler techniques.[12,13] Thrombi, foreign bodies, compression, and abnormal vascular anatomy can be identified with two-dimensional imaging.[13] Color Doppler superimposed on the two-dimensional image can further define anatomy and identify turbulence associated with vascular malformation and stenotic lesions.[11] Failure of a vein to compress with pressure from the ultrasound probe is a marker of partial or complete thrombosis.[13] Ultrasound assessment of venous flow reversal duration following the Valsalva maneuver or calf muscle compression and release are diagnostic tests for venous insufficiency in people, but are challenging if not impossible to adapt to animals.[14]

Lymphoscintigraphy

Lymphoscintigraphy involves injection of a radioactive tracer, monitored by a gamma camera. Although commonly employed in human medicine for evaluation of lymphatic drainage and oncologic staging,[15] it is not routinely utilized in veterinary medicine. Lymphoscintigraphy to evaluate lymphatic drainage from the mammary glands of dogs has been described.[16]

Cross-Sectional Imaging

Three-dimensional imaging of vascular structures is now possible using computed tomography angiography (CTA) or magnetic resonance angiography (MRA). Both CTA (Figure 257-3) and MRA (Figure 257-4) have been employed to evaluate vascular structures in animals.[17-19] The benefit of cross-sectional imaging such as CTA or MRA is the avoidance of selective central catheterization since only peripheral venous access is required for these techniques. Most of the published literature on these modalities has focused on anatomic delineation of portosystemic shunts,[17,20,21] though these methods can be used to investigate any vascular structure. Respiratory gating, or subjecting the animal to a breath-hold or apneic period during the scan, is preferred to avoid movement during scan acquisition, particularly if the abdominal or thoracic veins are being evaluated; this may not be required for CTA of the limb vasculature.

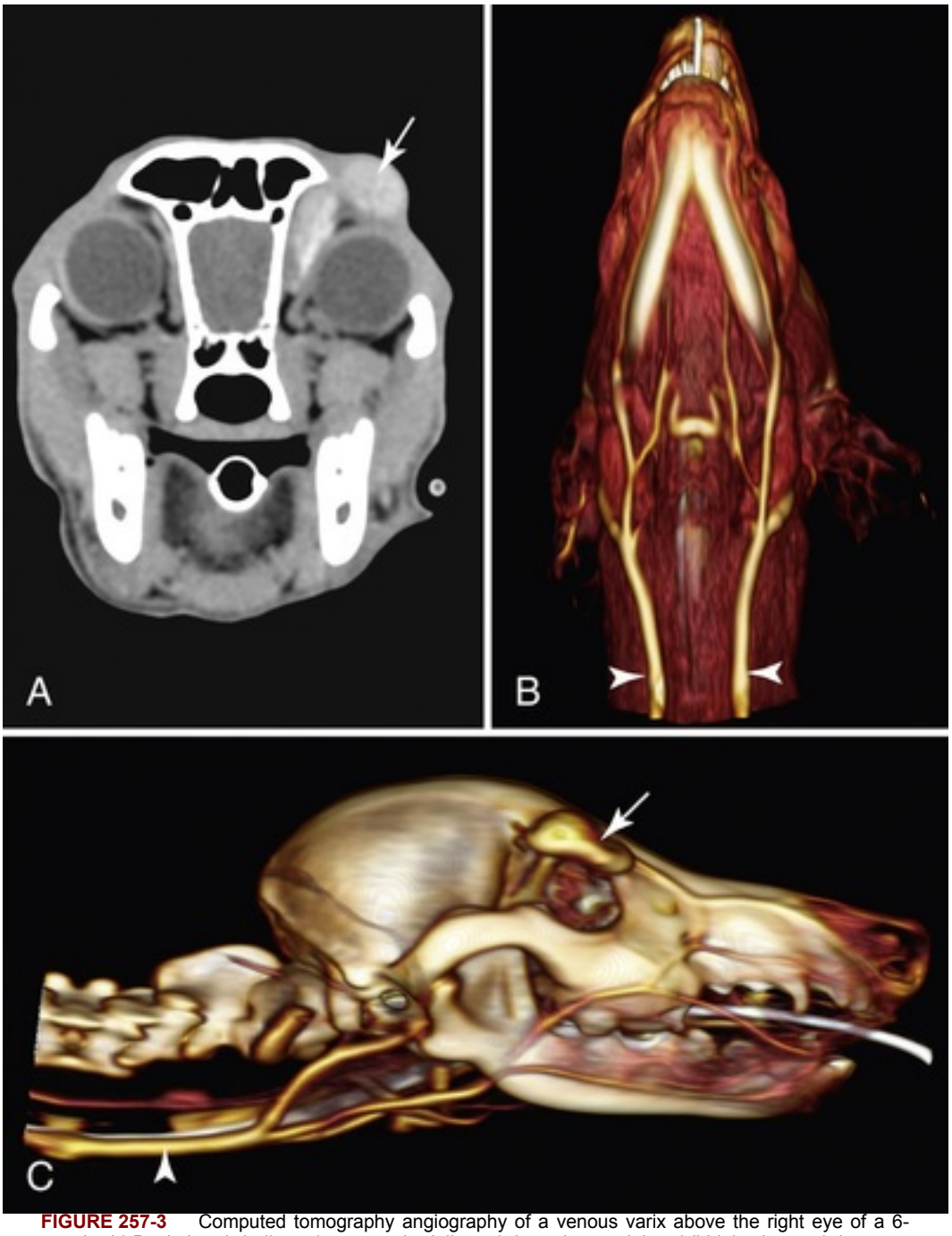

FIGURE 257-3 Computed tomography angiography of a venous varix above the right eye of a 6-month-old Dachshund. Iodinated contrast is delivered through a peripheral IV injection and the scan timed to the arrival of contrast at the lesion of interest. In this case, the transverse image in panel **A** shows an axial view of the head with a large venous structure (arrow) above and medial to the right orbit. Three-dimensional reconstructions in the ventral **(B)** and lateral **(C)** projection show the venous anatomy overlying musculoskeletal structures with the external jugular veins denoted by arrowheads and the varix denoted by the arrow.

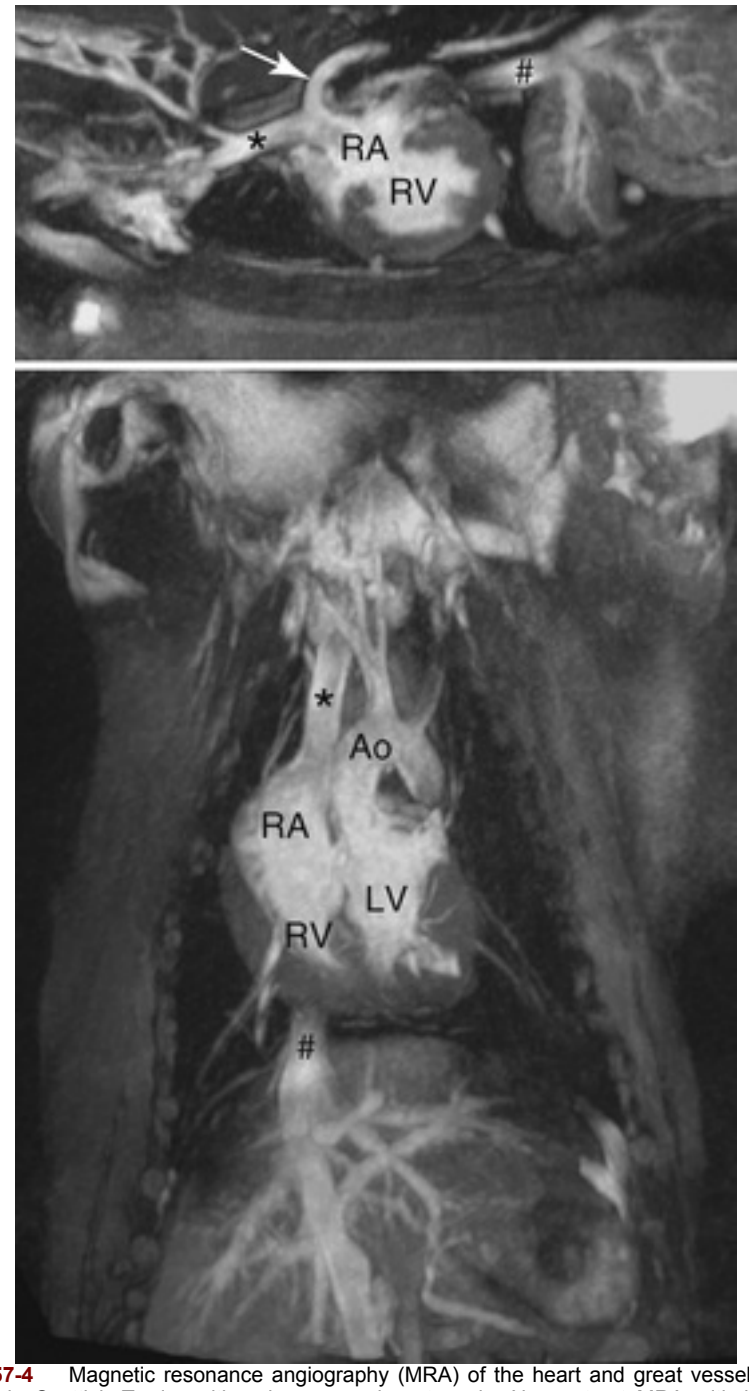

FIGURE 257-4 Magnetic resonance angiography (MRA) of the heart and great vessels from a 2-year-old male Scottish Terrier with pulmonary valve stenosis. Noncontrast MRA with bright blood imaging highlights both venous and arterial anatomy allowing visualization of the cranial (*) and caudal (#) vena cava, azygous vein (arrow), right atrium (RA), right ventricle (RV), left ventricle (LV), and aortic arch (Ao).

In addition to gating or breath holding, the method of processing and viewing images obtained during a CTA or MRA can dramatically enhance the information gained from the study. Viewers that support maximum intensity projections (MIP), minimum intensity projections, and three-dimensional volume rendering with the ability to stack images can improve image interpretation—particularly for vascular studies. The MIP is a technique whereby the image viewing software creates a single image by projecting the voxel with the highest attenuation value on a series of images, or slab, onto a two-dimensional image. When stacks of images are processed in this manner, the entire course of a vessel and its relationship to surrounding structures can be more clearly appreciated. Three-dimensional volume rendering of a CTA allows for the full spatial relationship of the vasculature to be realized and can greatly enhance surgical or interventional

planning.

Unique to MRA, imaging techniques are available to visualize blood clearly on the image without the administration of contrast (see Figure 257-4). Contrast agents may still be used and are preferred for some studies (such as perfusion scans), but may not be necessary for anatomic delineation of blood vessels.

Computed tomography lymphangiography is commonly employed in people to evaluate lymphatic structures, and has been applied to canine imaging (Figure 257-5), particularly for evaluation of thoracic duct anatomy prior to surgery for idiopathic chylothorax (Video 257-3).[9,22,23] Improved identification of lymphatic branches and digital subtraction of superimposing anatomic structures are two benefits seen with CT lymphangiography over radiographic lymphangiography in dogs.[9] Magnetic resonance lymphangiography is now performed in humans,[24,25] with preliminary work suggesting similar utility in veterinary medicine.

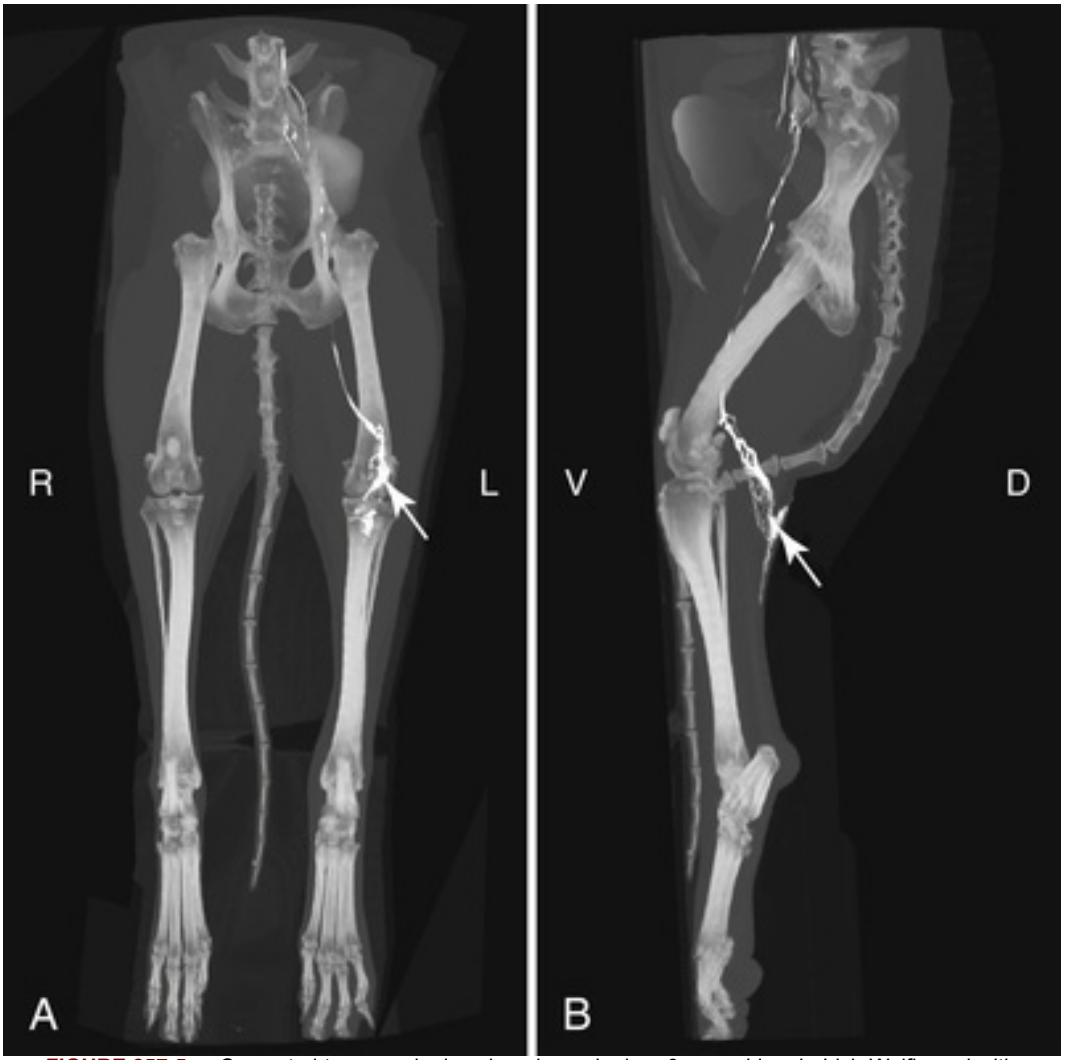

FIGURE 257-5 Computed tomography lymphangiography in a 6-year-old male Irish Wolfhound with lymphedema of the left pelvic limb. Three-dimensional maximum intensity projection images of the rear limbs and pelvis in a dorsal **(A)** and sagittal **(B)** perspective highlight normal lymphatic drainage within the left rear limb after injection of iodinated contrast into the left popliteal lymph node (arrow). Note mild soft tissue swelling of the left distal limb consistent with lymphedema of uncertain etiology. *D*, Dorsal; *L*, left; *R*, right; *V*, ventral.

Diseases of Veins

Diseases of the venous system seldom result in significant morbidity in small animals, despite the fact that trauma, thromboembolism, edema, local inflammation, tumor invasion, and septic processes commonly affect

veins. Many conditions, however, go unrecognized. Venous disorders include traumatic injuries, superficial and deep phlebitis and thrombosis (thrombophlebitis), catheter embolization, venous aneurysms, venous compression syndromes, and varices.

Venous thrombi form in the venous circulation under low blood flow conditions and are composed of fibrin and erythrocytes. Venous thrombi are understood to develop secondary to the classic components of Virchow's triad—flow stasis, endothelial disruption, and a hypercoagulable state.[26] Venous thrombosis causes fewer overt clinical abnormalities than arterial thrombosis and, consequently, is often undetected. Deep venous thrombosis is a major risk factor for pulmonary embolism in humans, but is not known to be a risk factor for pulmonary thromboembolism in animals. Pulmonary thromboembolism (PTE) is a common and often life-threatening complication associated with a variety of systemic and metabolic diseases. A thrombus that is formed in the peripheral veins, vena cavae, or right heart may embolize to the pulmonary arterial vasculature. Development of PTE can occur in several prothrombotic disease states including the nephrotic syndrome, hyperadrenocorticism, immune-mediated hemolytic anemia, thrombocytosis, cardiac disease, sepsis, disseminated intravascular coagulation, heartworm disease, and neoplasia.[27-35] Antithrombin (AT) deficiency may be involved in thrombogenesis in a number of these diseases by altering intravascular blood chemistry and increasing the risk for thrombosis. In immune-mediated hemolytic anemia, for example, destruction of red blood cells releases thrombogenic substances.[34] Thrombin and other clotting factors are inhibited by AT such that even mild reduction in AT can result in thrombosis or thromboembolism. The presence of multiple concurrent disorders in animals with thromboembolism is common. For example, 47% of cats with necropsy confirmed PTE had multiple predisposing disorders.[36] Massive pulmonary thrombi may also occur *in situ* and have been described primarily in the Cavalier King Charles Spaniel[37] (Figure 257-6) or in dogs or cats with heartworm disease (see ch. 255). Pulmonary thromboembolism is covered in detail in ch. 243.

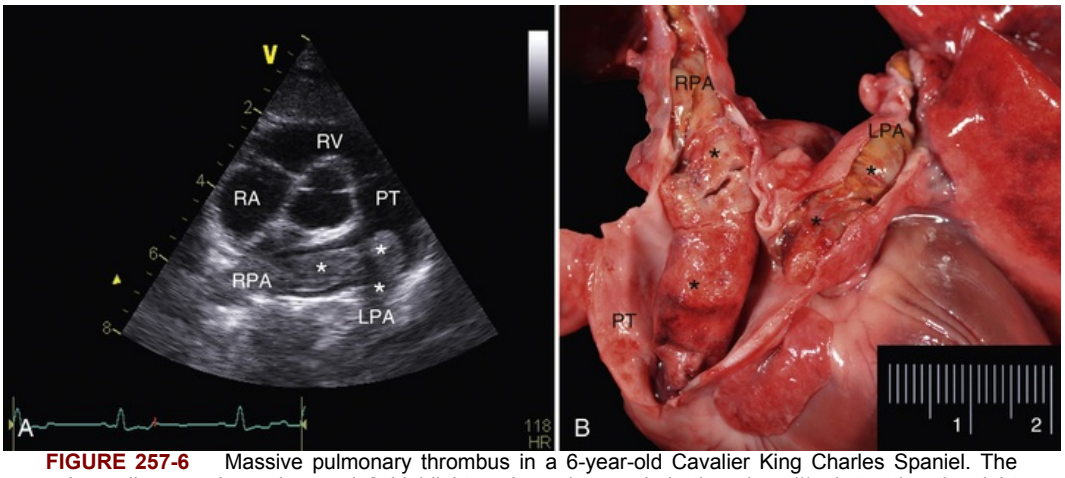

FIGURE 257-6 Massive pulmonary thrombus in a 6-year-old Cavalier King Charles Spaniel. The echocardiogram shown in panel **A** highlights a large hyperechoic thrombus (*) obstructing the right (RPA) and left (LPA) pulmonary arteries and extending into the pulmonary trunk (PT). Panel **B** is the autopsy image from the same dog revealing organized thrombus (*) throughout the PT and branch pulmonary arteries. *RA*, Right atrium; *RV*, right ventricle.

Venous varicosis, a condition of tortuous and dilated veins, is rare in dogs and cats (Figure 257-7). When detected, venous varices may accompany arteriovenous fistulae[38] or develop as a consequence of chronic venous obstruction (see Figure 257-1), with a recent review categorizing four pathways for collateral venous flow in the setting of caudal vena caval obstruction in dogs.[39] Cutaneous phlebectasia is a benign lesion sometimes erroneously called telangiectasis. It is reported almost exclusively in dogs with spontaneous or iatrogenic Cushing's syndrome (see ch. 306).[40] Phlebectasia is an abnormal dilatation, extension, or reduplication of veins or capillaries or a combination of these changes.

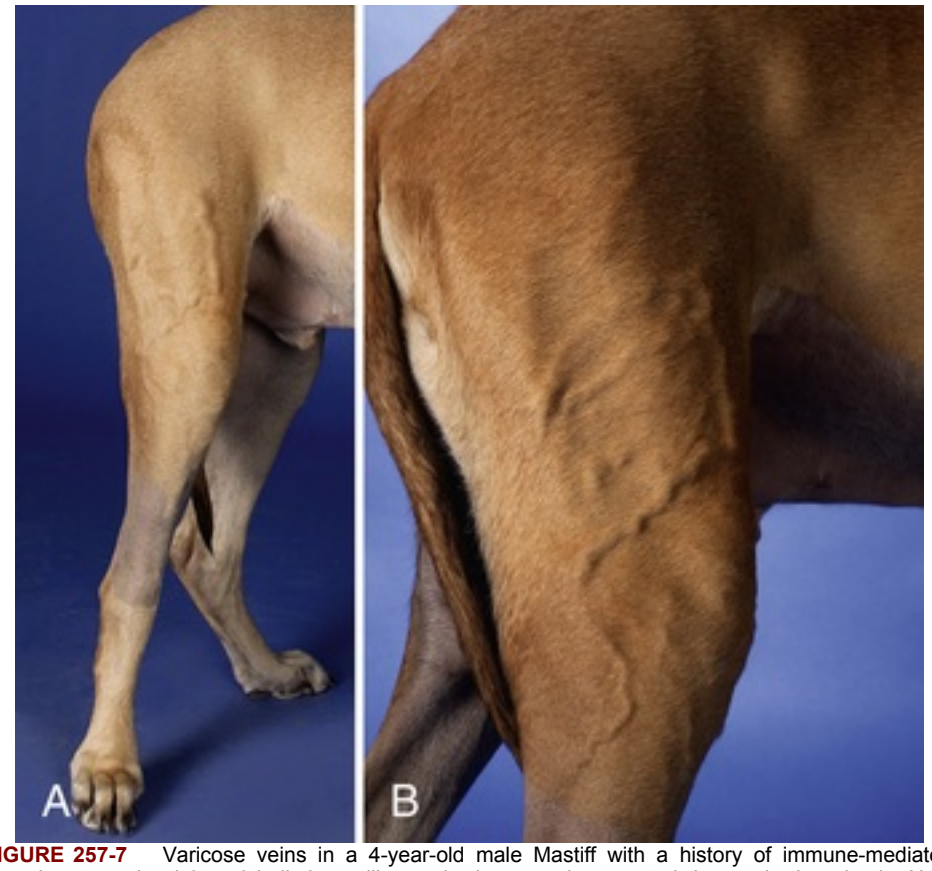

FIGURE 257-7 Varicose veins in a 4-year-old male Mastiff with a history of immune-mediated thrombocytopenia, right pelvic limb swelling and edema, and suspected deep vein thrombosis. Note the distended and tortuous superficial veins that have developed to provide collateral drainage as seen from the cranial **(A)** and lateral **(B)** perspective.

Venous perforation or blunt trauma to veins is usually well tolerated because rapid clotting results in venous occlusion and prevents serious hemorrhage. When venous occlusion is severe, resultant edema and cyanosis are usually temporary because of collateral circulation. If all veins draining an area are compromised, marked edema and necrosis can ensue. Blunt trauma has been associated with caudal vena caval obstruction or kinking of the intrathoracic caudal vena cava and subsequent ascites.[41-43]

Venous malformations are often incidental findings and may occur as duplication, interruption, transposition, or as an anomalous connection; persistence of the left cranial vena cava is noteworthy.[44] Dogs and cats normally have a right-sided cranial vena cava. When the embryologic left anterior cardinal vein fails to regress in these species, a persistent left cranial vena cava occurs (see ch. 250). The left cranial vena cava may occur singularly or, more often, both left and right cranial cava are present (Figures 257-8, 250-45, and 250-46). Buchanan described two types of persistent left cranial vena cava in the dog—complete and incomplete.[45] The left cranial vena cava enters the caudoventral aspect of the right atrium at the coronary sinus, in contrast to the entrance of the right cranial vena cava at the cranial aspect of the heart. The persistent left cranial vena cava generally poses no clinical problem for the animal, although a case report of an incomplete persistent left cranial vena cava in a Brittany Spaniel did suggest the possibility of this structure causing megaesophagus if it is partially atretic.[46] Transpositional venous anomalies are common in animals with transpositional arterial anomalies such as persistent right aortic arch. Reports of pacemaker implantation and heartworm extraction through a persistent left cranial vena cava can be found,[47,48] although this approach is technically more challenging than the standard route.

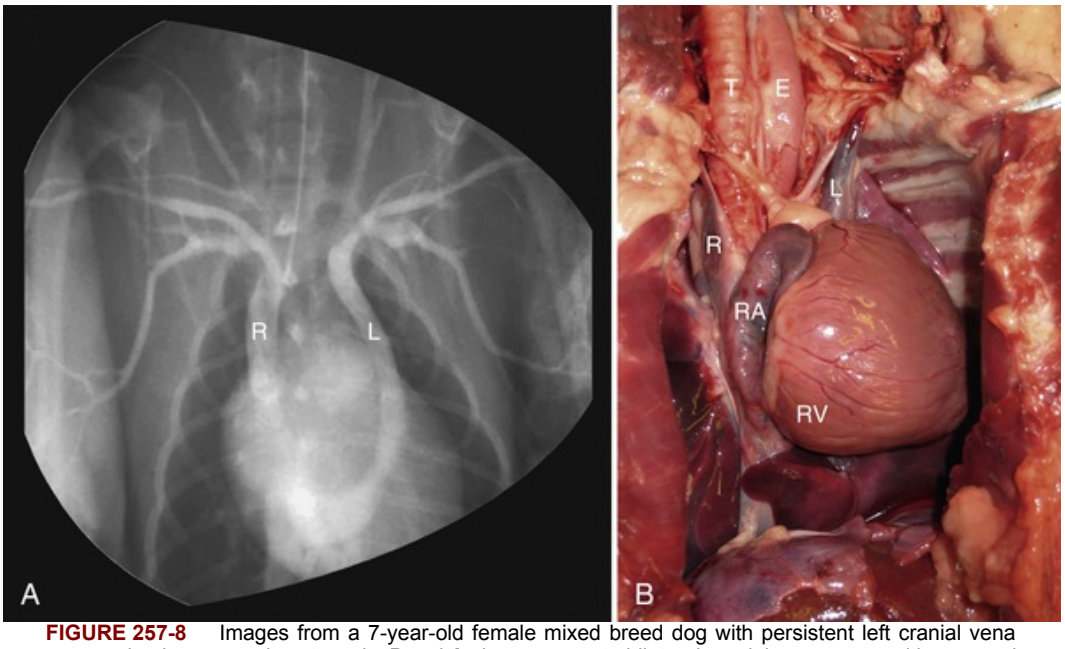

FIGURE 257-8 Images from a 7-year-old female mixed breed dog with persistent left cranial vena cava and pulmonary valve stenosis. Panel **A** shows separate bilateral cranial vena cavae with a normal right cranial vena cava (R) and a persistent left cranial vena cava (L); note the entrance of the persistent left cranial vena cava into the coronary sinus at the caudal aspect of the right atrium. Panel **B** shows an autopsy image of the same dog with both vena cava apparent. *E,* Esophagus; *RA,* right atrium; *RV,* right ventricle; *T,* trachea.

Additional venous anomalies have been reported. Notably, unilateral absence of the left external jugular vein has been described in the cat[49] and the author has observed absence of the right external jugular vein in two English Bulldogs.[50] A left azygous vein is present in some species, but is typically absent in the dog and cat. If present, it is a remnant of the left supracardinal system, which also enters the coronary sinus. Case reports of left azygous vein have been reported in the dog, occasionally as the sole source of caudal venous return if concurrent with interruption of the caudal vena cava.[51,52] Numerous abnormalities of the caudal vena cava have been reported in animals.[18,53-63] The caudal vena cava may display duplication, leftward transposition, or interruption with azygous continuation; these malformations are sometimes associated with portosystemic shunts (see ch. 284). Most of these malformations cause no clinical signs (unless concurrent with portocaval shunting), but might appear during surgical exploration or diagnostic imaging studies and should therefore be appreciated. Venous malformations, or venous hemangiomas, may be considered benign vascular growths that may develop locally or extensively, falling within a spectrum of abnormalities that are anatomically categorized into capillary, lymphatic, venous, or arteriovenous malformations.[64,65] The veterinary literature has not fully defined a categorization scheme or standardized nomenclature for these lesions in animals, although a histopathologic review of vascular tumors suggested parallels to human schemes.[66] Arteriovenous malformations are covered in more detail in ch. 284.

Cystic dilation of veins may also occur; venous dilation or aneurysm generally permits only low-velocity blood flow and small lesions are asymptomatic. Expansion of the lesion may occur, however, especially following trauma. Thrombosis can result from sluggish blood flow, resulting in localized swelling and tenderness. Larger lesions in dependent areas may enlarge, causing significant vascular dilation, potentially causing changes in skin color, dermal ulceration, and hemorrhage. Affected areas appear as a warm, soft, compressible mass. No thrills or bruits are present due to the low flow. Pain may result from pressure exerted on deep tissues and nerves. Diagnosis is made using history, physical examination, and ultrasound. Venography or cross-sectional imaging such as CTA or MRA may be necessary to define the lesion, particularly for intraabdominal aneurysms.[67] Symptomatic therapy using light, compressive wraps is sometimes helpful for acute management. Surgical excision of affected vessels is occasionally required, but complete resection is difficult and local recurrence is common.

Venous aneurysms are rarely recognized in veterinary medicine. Aneurysms of the external jugular, linguofacial, and maxillary veins, as well as the cranial vena cava have been reported.[68-70] In these cases, the lesions were considered to be congenital vascular anomalies and not associated with an obstructive or

traumatic process. The author has recognized caudal vena caval aneurysms in association with caudal vena caval interruption and azygous continuation in a dog (Figure 257-9). Fifteen cases of portal venous aneurysms were described in a CTA review of over 3000 dogs; none of the dogs of this study showed clinical signs, though portal venous thrombosis at the site of an aneurysm was described in one case.[67]

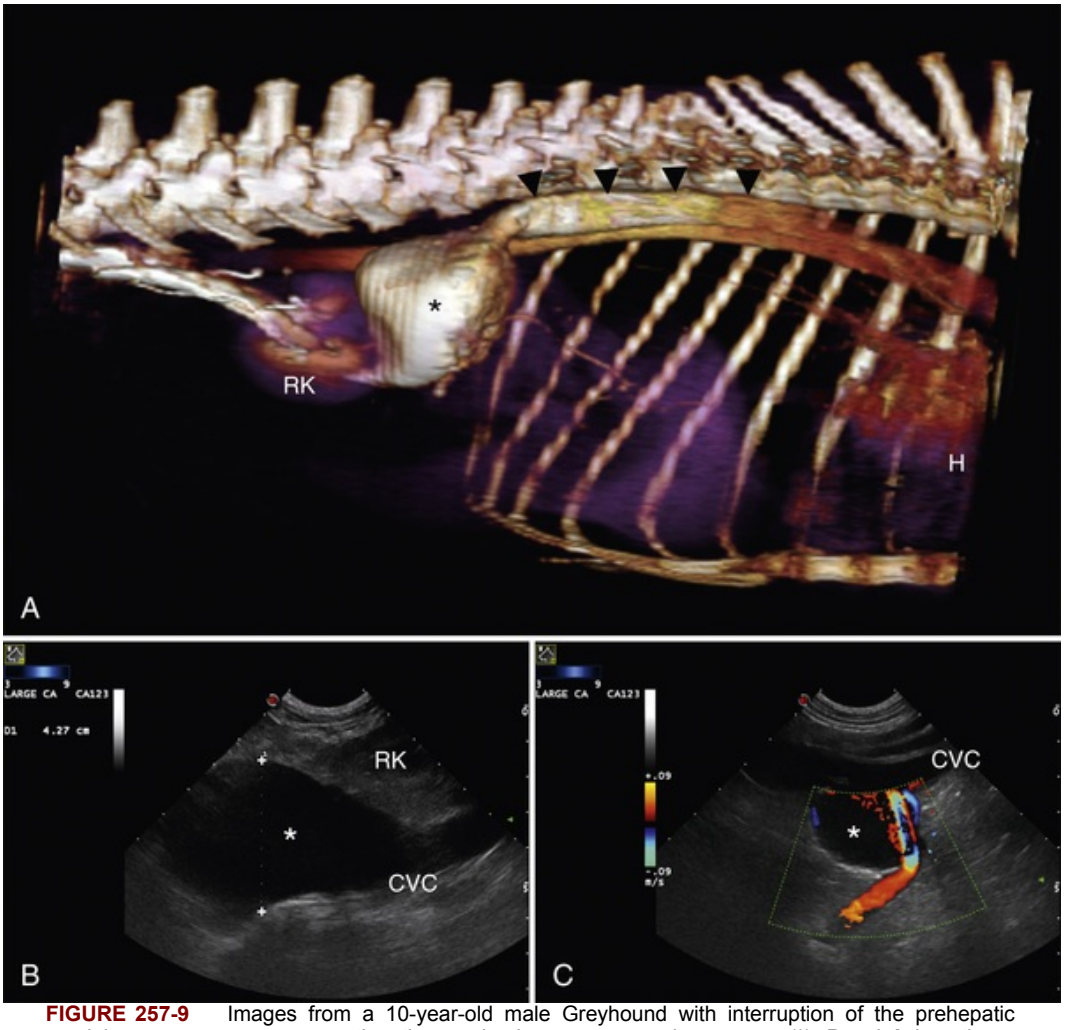

FIGURE 257-9 Images from a 10-year-old male Greyhound with interruption of the prehepatic caudal vena cava, azygous continuation, and a large vena caval aneurysm (*). Panel **A** is a three-dimensional sagittal reconstruction from a computed tomography angiography scan showing the large aneurysmal dilation of the caudal vena cava and continuation through the azygous vein (arrowheads). Panels **B** and **C** represent grayscale **(B)** and color Doppler **(C)** ultrasound images of the aneurysm, which measures about 4.3 cm in diameter. *CVC*, Caudal vena cava; *H*, heart; *RK*, right kidney.

Embolization of severed intravascular catheter fragments is an occasional complication of intravenous catheter placement.[71-73] In humans, reported complications of catheter embolization include perforation of cardiac walls, endocarditis, pulmonary embolism, and severe arrhythmias.[74,75] Therefore, it is generally considered prudent to remove catheter fragments. Nonsurgical, transvenous removal of catheter fragments using loop-snare catheters, forceps, and basket catheters have been described in animals.[72,73] Whenever possible, steps should be taken to avoid situations predisposing to catheter fragmentation including inadequate restraint during catheter placement, withdrawal of catheters through their placement needles during repositioning, failure to properly secure catheter to the patient, inadvertent severing of catheters during bandage changes, and the use of resterilized but damaged cardiac catheters.

Phlebitis can occur from a local inflammatory process extending to the veins or can originate from a venous intimal lesion. Common causes of venous intimal lesions are perivenous or intravenous injection of irritating drugs, infusion of large amounts of fluid, and long-term placement of intravenous catheters. Infusion-related phlebitis occurs in three forms: (1) chemical (injury to vein by irritating drugs), (2) physical (trauma to the

intima by catheters, needles, hypertonicity or particulate matter in infused fluids), and (3) microbial (infected fluids, skin, or catheter tip). Either sterile or septic thrombophlebitis may result. Thrombophlebitis is typically localized and is characterized by pain, swelling, and exudation (Figure 257-10). Patients with serious illnesses or compromised immune systems, however, may develop sepsis, thromboembolic pneumonia, or endocarditis.

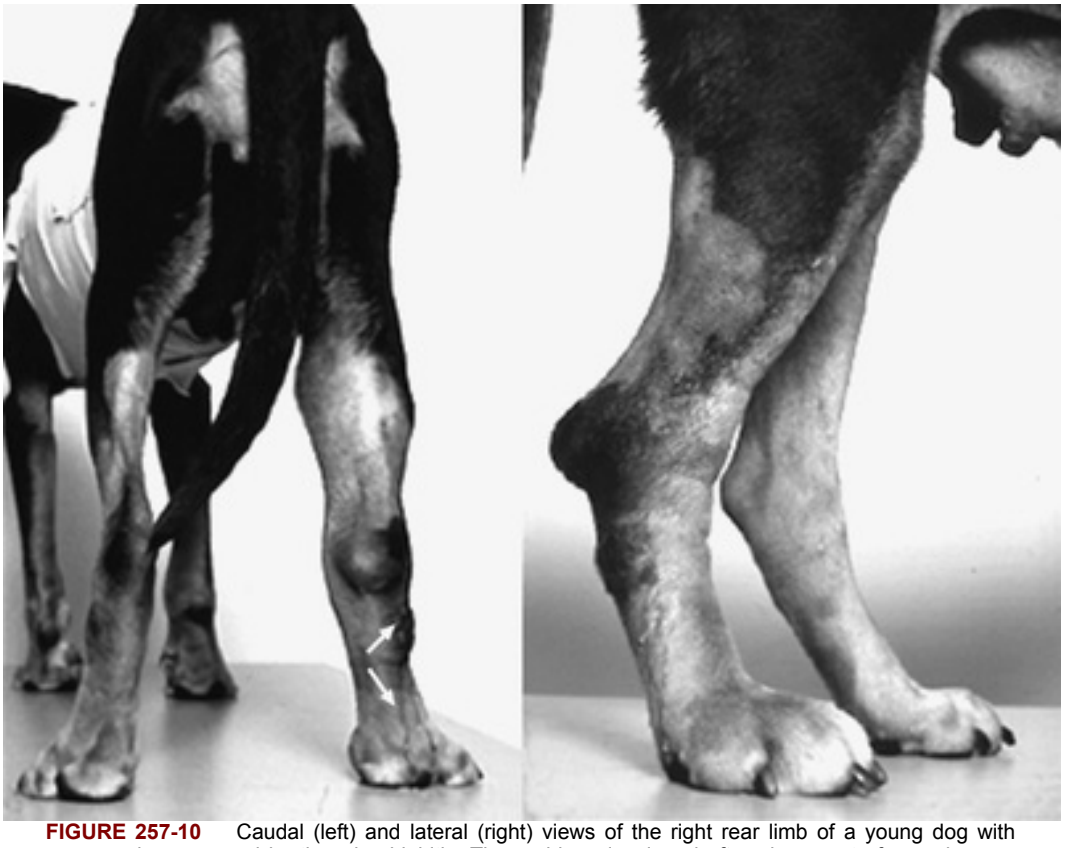

FIGURE 257-10 Caudal (left) and lateral (right) views of the right rear limb of a young dog with severe edema caused by thrombophlebitis. The problem developed after placement of a saphenous vein catheter. The limb is markedly swollen and edema fluid (arrows) is leaking through a small ulcer in the skin. Thrombosis of the vein prevents venous drainage and increases lymphatic fluid formation.

Phlebitis is a major cause of intimal damage leading to venous thrombosis. The thrombosis is usually of little local consequence if localized to smaller vessels. However, emboli may be carried to the lung and cause PTE. In most animals, blood clots carried to the lung are rapidly lysed and cause no complications. However, when inflammatory disease, dehydration, or circulatory failure occurs, thrombus formation may continue in the pulmonary vessels and lead to vascular occlusion, dyspnea, pain, and death.[31] In infectious thrombophlebitis, bacterial emboli may be carried to the lungs and cause thromboembolic pneumonia. Spontaneous venous thrombosis is rare, although thrombosis of the portal venous system including the splenic veins is occasionally diagnosed in dogs (Figure 257-11).[76] In the majority of cases, underlying hepatic disease or conditions associated with a prothrombotic state (protein-losing nephropathy, immune-mediated hemolytic anemia, or hyperadrenocorticism) or compression (splenic torsion) are identified.[76] Clinical signs include ascites, abdominal pain, acquired portosystemic shunting, and hypovolemic shock.[76]

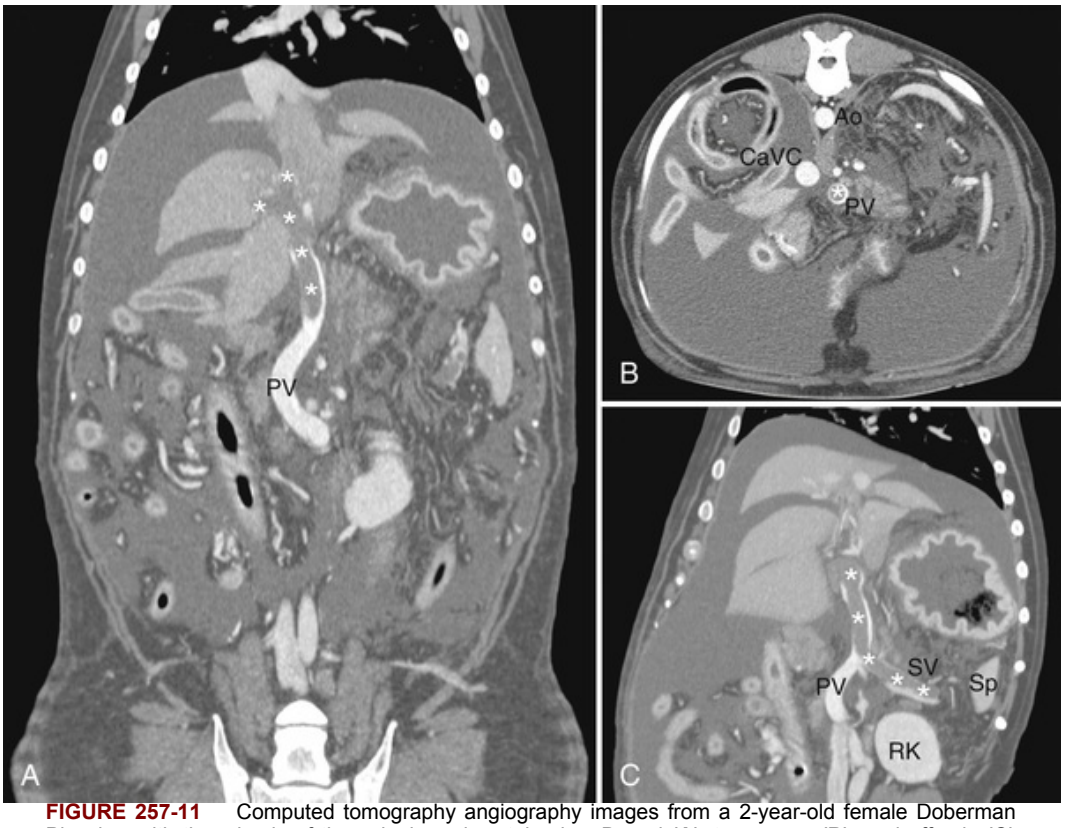

FIGURE 257-11 Computed tomography angiography images from a 2-year-old female Doberman Pinscher with thrombosis of the splenic and portal veins. Dorsal **(A),** transverse **(B),** and off-axis **(C)** maximal intensity projection reconstructions show a hypoattenuating structure consistent with thrombus (*) within the splenic vein and extending into the portal trunk and intrahepatic branches. Moderate ascites is also apparent. *Ao*, Aorta; *CaVC*, caudal vena cava; *PV*, portal vein; *RK*, right kidney; *Sp*, spleen; *SV*, splenic vein.

In cases of venous occlusion, clinical signs depend on the anatomic location, extent, and duration of the obstruction. Acute obstruction of centrally located, deep systemic veins causes edema, cyanosis, discomfort, and venous dilatation distal to the obstruction site. Obstruction of the cranial vena cava causes edema in the neck, head, front limbs, and dependent portions of the cranial thorax (Figure 257-12; see ch. 18). Pleural effusion commonly results from central venous obstruction. Common causes of cranial vena caval obstruction include cranial mediastinal masses, indwelling central venous catheters, and transvenous pacemaker leads.[77-85] Clinical disorders resulting in kinking, compression, neoplastic obstruction, or thrombosis of the intrathoracic caudal vena cava have also been reported with animals showing signs of ascites and subcutaneous edema (Figure 257-13).[41,86-89] Obstructions of the intraabdominal or pelvic venous systems cause edema of the hindlimbs and the scrotum. Clinical signs depend upon collateral vessel reserve and capacity of regional lymphatics to drain interstitial and serous cavity fluid. In addition to thrombosis, causes of venous obstruction include invasive malignant processes and venous compression by abscesses, hematomas, tumors, and lymphadenopathy. Several tumors have a tendency for venous invasion, including chemodectomas, adrenal tumors such as pheochromocytoma, and hemangiosarcomas (Figure 257-14). Angiography may indicate the occlusive or compressive lesion or highlight increased collateral circulation (see Figure 257-1). Diagnostic ultrasonography is useful to detect masses or flow disturbances; CTA or MRA can define the three-dimensional anatomy of the obstruction and evaluate extraluminal causes (see Figure 257-14). The prognosis and therapy of venous obstruction depends on the primary disease. These are discussed in various chapters throughout this book.

FIGURE 257-12 Cranial vena cava syndrome in a dog associated with a mediastinal mass and compression of the cranial vena cava. Severe peripheral edema of the cranial extremities is present.

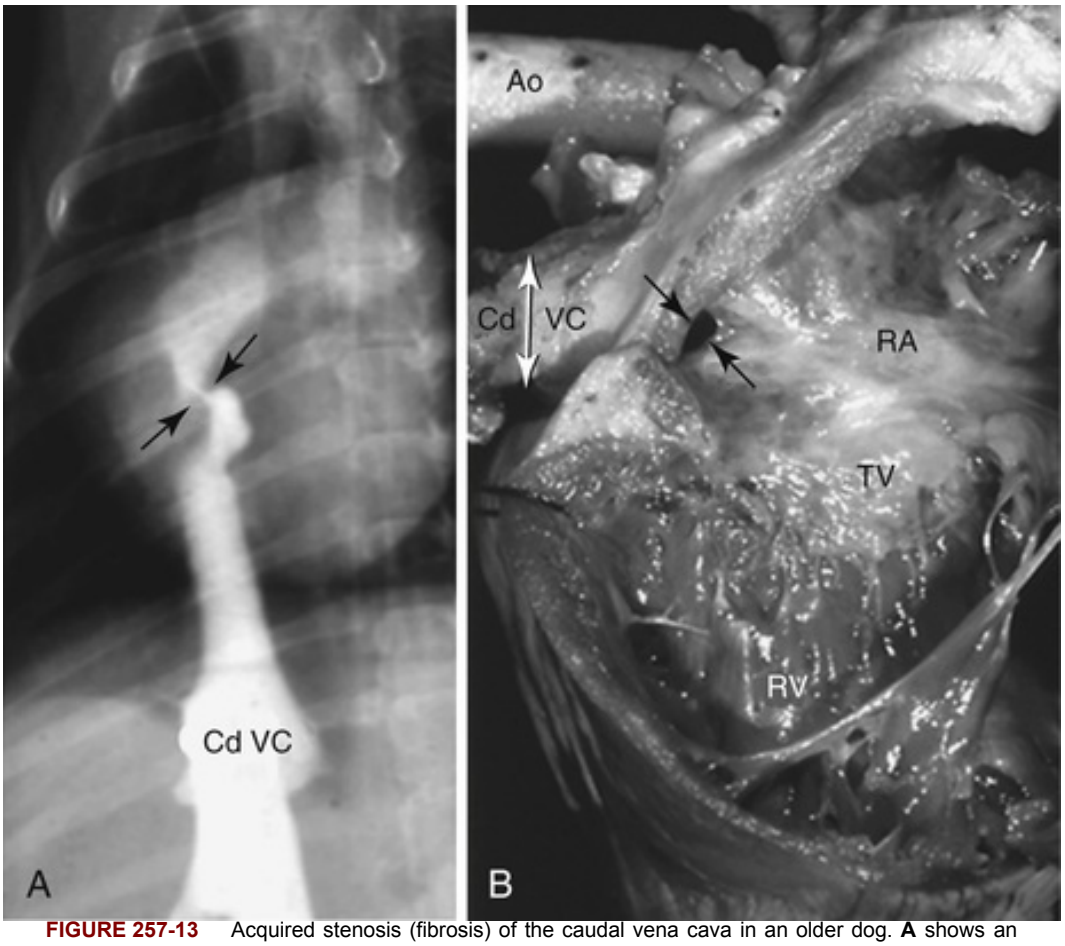

FIGURE 257-13 Acquired stenosis (fibrosis) of the caudal vena cava in an older dog. **A** shows an

angiogram of the caudal vena cava (Cd VC), which demonstrates a severe narrowing of the dye column (arrows) at the venous entry into the caudal right atrium. **B** is a postmortem view of the heart taken from the right lateral perspective. The right atrial and ventricular walls have been retracted to demonstrate the stenotic, caval orifice (small arrows). The reader should compare this opening with the diameter of the caudal vena cava (to the left, vertical double arrow). The right ventricle (RV), tricuspid valve (TV), right atrium (RA), and descending aorta (Ao) are shown.

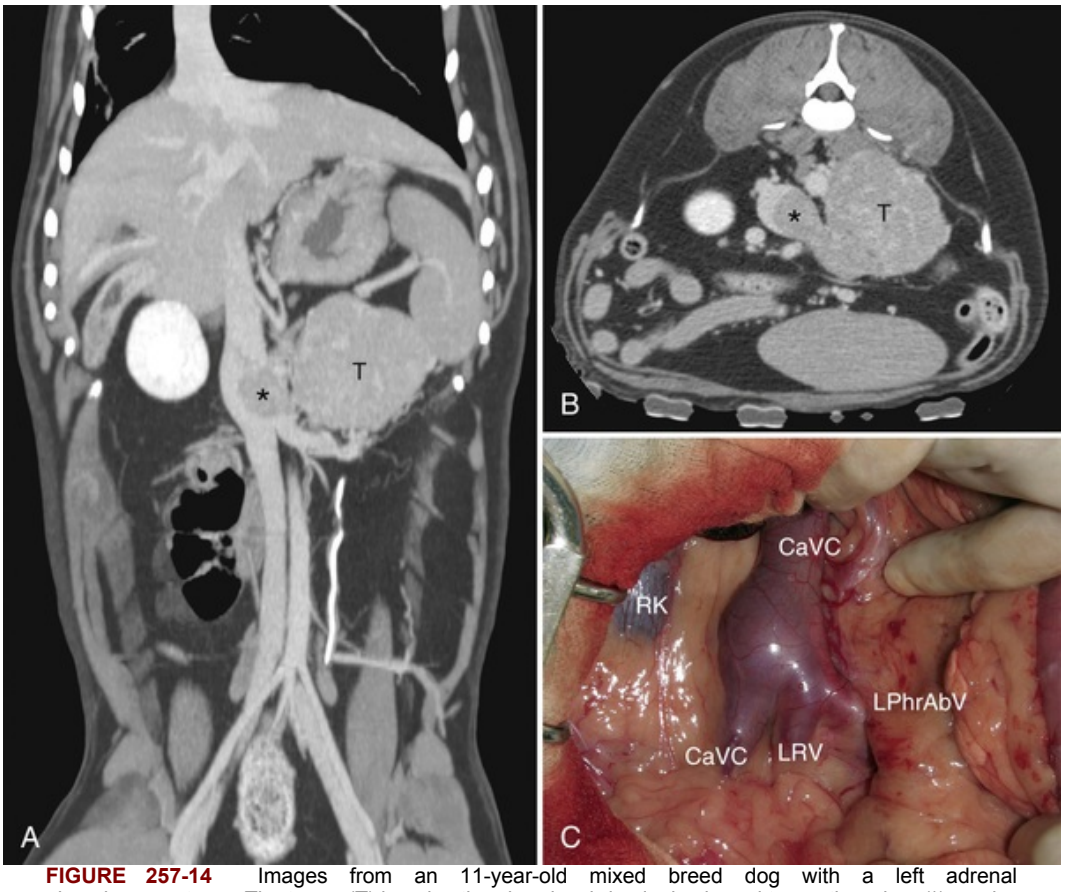

FIGURE 257-14 Images from an 11-year-old mixed breed dog with a left adrenal pheochromocytoma. The tumor (T) invades the phrenicoabdominal vein and tumor thrombus (*) can be seen extending into the lumen of the caudal vena cava. Surgical exposure of the same dog is seen in panel **C,** highlighting the anatomy of the caudal vena cava (CaVC), left renal vein (LRV), left phrenicoabdominal vein (LPhrAbV), and right kidney (RK). The tumor and left kidney are not visible, obscured by omentum. (Surgical image courtesy Kathleen Ham, DACVS.)

Diseases of the Peripheral Lymphatics

Lymphatic disorders can be subdivided into those of internal organs, such as intestinal lymphangiectasis, and peripheral lymphatic disorders. Several lymphatic diseases including lymphedema, intestinal lymphangiectasia, chylothorax, lymphadenitis, lymphocysts, lymphoma, lymphangioma, and lymphangiosarcoma have been recognized in animals. Types and causes of peripheral lymphatic disorders are summarized in Box 257-2.

Box 257-2

Causes of Peripheral Lymphatic Disorders

Lymphangitis, lymphedema, lymphadenitis, lymphadenopathy
- Infection
- Neoplasia
- Reactive hyperplasia

- Granuloma
- Lymphedema
  - Primary—developmental abnormality of lymphatics
    - Hypoplasia
    - Aplasia
    - Lymphangiectasia
    - Hyperplasia
  - Secondary—acquired abnormalities of lymphatics
    - Surgical excision of lymphatics or lymph nodes
    - Posttraumatic lymphangiopathy
    - Neoplastic invasion
    - Extrinsic compression of lymph vessels or tissue
    - Acute obstructive lymphadenitis
    - Chronic sclerosing lymphadenitis/lymphangitis
    - Lymphatic atrophy with interstitial fibrosis
    - Radiation therapy
  - Lymphocysts
- Cystic hygroma, lymphoceles, pseudocyst
- Lymphangiomas
- Lymphangiosarcomas

Inflammatory Lymphatic Disorders (Lymphangitis and Lymphadenitis)

Lymphangitis and lymphadenitis often occur secondary to local inflammation, particularly involving the skin, mucous membranes, and subcutaneous tissues. Lymphangitis can also result from bacterial or fungal infection or adjacent neoplastic and inflammatory disease. Lymphatics may be affected and occluded as they drain inflammatory agents and their by-products from tissue spaces. In lymph nodes, microorganisms are phagocytized and inactivated or killed by humoral and cellular mechanisms. During this process, lymph nodes may become obstructed, enlarged, warm, and painful. Affected limbs may be locally swollen and lameness can result. Pyrexia, anorexia, and depression are common and leukocytosis may be present with acute, severe lymphangitis.

Lymphangitis may become chronic when associated with a granulomatous or static lesion such as a foreign body or with unsuccessfully treated acute inflammation. Lymphangitis has been associated with cutaneous coccidioidomycosis in a dog and cat, intestinal lymphadenitis secondary to bite wounds, sporotrichosis, and chronic lipogranulomatous lymphangitis in chronic protein-losing intestinal disease (see ch. 276).[90-94] Persistence of inflammatory edema in cutaneous infections results in mesenchymal cell proliferation, which in turn can cause irreversible thickening of the skin and subcutis. The prognosis is variable depending on the cause and in general more favorable with early treatment. Therapy consists of moist, warm, local compresses or soaks, which reduce swelling and promote drainage. Aggressive local and systemic antibiotic therapy usually promotes recovery in animals with fever and anorexia. Bacterial culture and sensitivity testing and cytologic examination of regional lymph nodes should be performed if acute lymphangitis fails to respond to treatment and in cases of chronic lymphangitis. Contrast studies and surgical exploration may be indicated if fistulous tracts or abscesses are present, or if a foreign body is suspected.

Lymphedema

Pathologic fluid accumulation occurs in the interstitium when the microvascular filtration rate exceeds lymphatic drainage.[3] Starling's forces conceptualize the interplay of oncotic and hydrostatic pressure, coupled with vascular permeability, which drive microvascular filtration.[5] In the microvascular bed, there is a net movement of ultrafiltrate to the interstitium such that in states of inadequate or impaired lymphatic flow, the ultrafiltrate accumulates leading to lymphedema. Lymphedema specifically refers to an accumulation of fluid in the interstitial space resulting from abnormal lymphatic drainage.[4] This term should not be used for other forms of edema, such as edema related to venous obstruction or generalized edema related to hypoproteinemia. The protein-rich fluid of lymphedema (2 to 5 g/dL) causes a high osmotic gradient and exacerbates fluid accumulation.[95] Numerous classification schemes have been used to categorize lymphedema. Commonly used etiologic categories of lymphedema include overload, inadequate collection

into lymphatic capillaries, abnormal lymphatic contractility, insufficient lymphatics, lymph node obstruction, and main lymphatic ductal defects.

Traditionally, clinical effort is undertaken to differentiate primary versus secondary lymphedema. Primary lymphedema refers to an abnormality of the lymphatic vessels or lymph nodes. Secondary lymphedema refers to disease in the lymphatic vessels or lymph nodes due to a different pathologic process. Secondary lymphedema can occur as a result of neoplasia, surgery, trauma, parasites, radiation therapy, or infection and is more common than primary lymphedema. Distinguishing between primary and secondary lymphedema is often difficult. A disease process involving a lymph node can result in fibrosis and obstruction with secondary lymphedema developing.

Primary Lymphedema

Primary lymphedema can result from three principal morphologic and functional abnormalities including (1) abnormalities of large vessels such as aplasia or hypoplasia of the thoracic duct and cisterna chyli, (2) aplasia of the peripheral lymphatics or congenital valvular incompetence, and (3) lymph node fibrosis or a deficient lymph node size and number.[96]

Lymphedema caused by aplasia, hypoplasia, or dysplasia of proximal lymph channels or lymph nodes occurs most often in the hindlimbs of young dogs (Figure 257-15). The edema can be transient, observed only during the juvenile period, or permanent. Mild cases are restricted to the hindlimbs, whereas severe cases may progress to whole-body edema.[97-101] Although the condition is frequently bilateral, one limb is often more swollen than the other. A number of cases of suspected congenital lymphedema have been reported, though nearly all represent single case reports from decades ago.[100-102] A small series of dogs with familial primary lymphedema was described and studies of this family suggested an autosomal dominant mode of inheritance, variable severity of symptoms, and a high rate of mortality in severely affected dogs.[97,103] Reported breeds include Bulldogs, Poodles, Old English Sheepdogs, and Labrador Retrievers, although it is not clear whether these breeds are at increased risk.

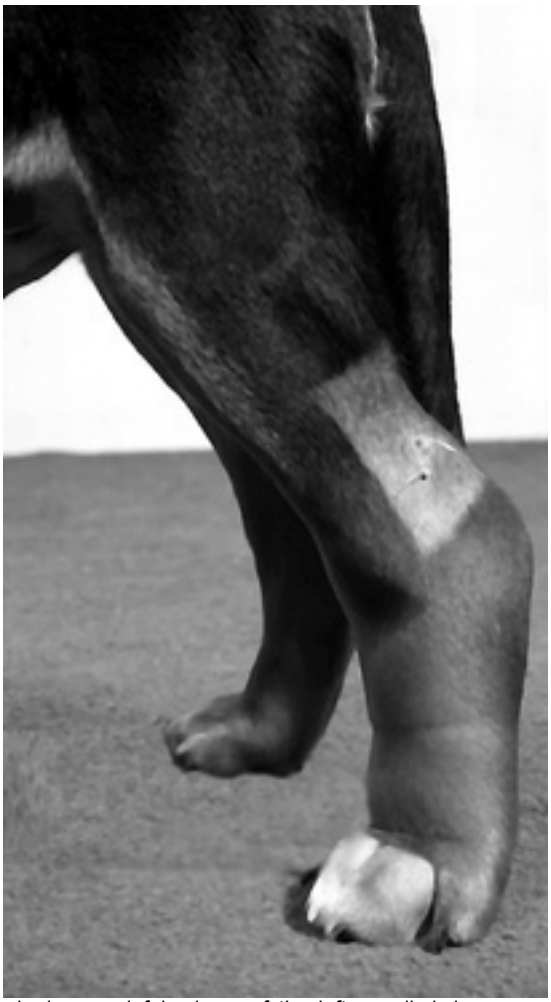

FIGURE 257-15 Marked, nonpainful edema of the left rear limb in a young dog with congenital lymphatic dysplasia.

The history may identify chronic limb swelling since birth or edema appearing later in life. The swelling represents a pitting edema of varying magnitude that is neither warm nor cold (see ch. 18 and Video 18-1). The edema is not usually accompanied by lameness or pain unless there is massive enlargement or cellulitis. Growth and activity are usually normal but rest and limb massage do not typically reduce the severity of edema. Regional lymph nodes, normally prominent in growing puppies, are sometimes difficult to identify. Total plasma protein, serum protein electrophoresis, hemogram, and blood chemistry are generally unremarkable. The diagnosis of primary lymphedema is based on history (age of onset, disease progression, affected limbs, and distribution of edema) and clinical signs. Previous surgery, trauma, or infections should also be noted. Radiographic lymphangiography may be necessary to confirm the diagnosis in subtle cases and is helpful in determining morphology of anomalous lymphatic systems (Figure 257-16).

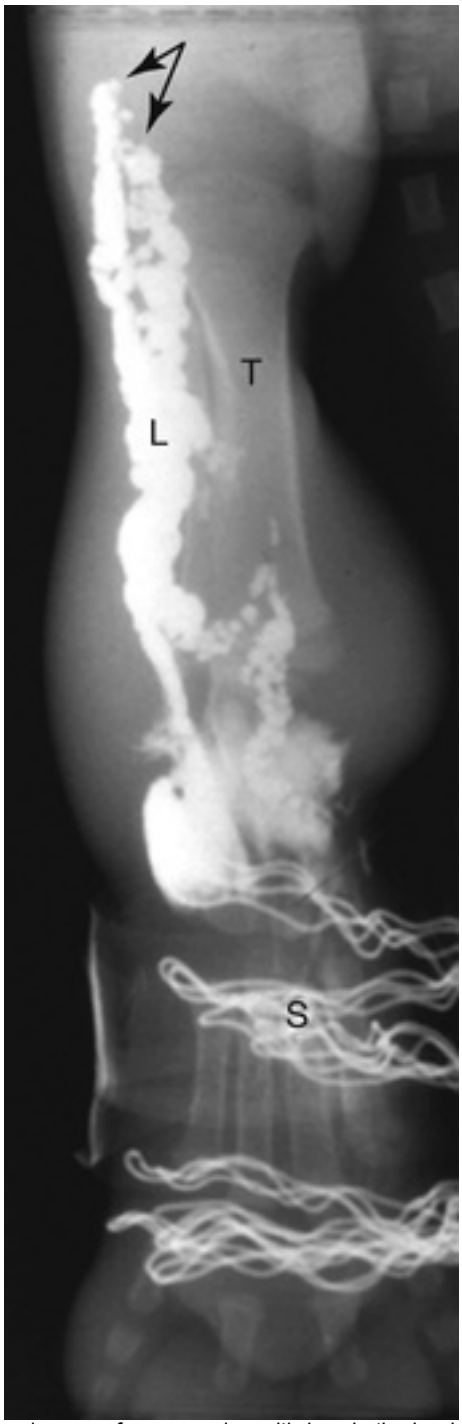

FIGURE 257-16 Lymphangiogram of a young dog with lymphatic dysplasia. After cannulation of a distal lymphatic vessel, contrast medium was infused into the lymphatic system. The reader should note the dilated, tortuous, lymphatic channels (L) that end blindly at the stifle (arrows). *S,* Radiopaque surgical sponges; *T,* tibia.

The prognosis for resolution of congenital lymphedema is guarded and depends on the etiology. Some dogs that develop hindlimb edema during the neonatal period improve spontaneously. Dogs with severe edema of the limbs and trunk are more likely to succumb during the first few weeks after birth.[97,98] Chronic lymphatic vessel dilation leads to permanent lymphatic valvular dysfunction. Metabolic by-products accumulate and lead to collagen deposition and fibrosis. Complications such as abrasions and recurrent infection often develop. Dogs with primary lymphedema should not be used for breeding—as noted above, test matings of dogs with congenital lymphedema support the hypothesis of autosomal dominant inheritance with variable expression.[97]

Secondary Lymphedema

Persistent lymphedema occurs only after destruction or blockage of a considerable number of major lymph channels or several sequential lymph nodes with their afferent or efferent lymphatics.[95] Factors that can delay or prevent edema formation include opening of collateral vessels, rerouting of lymph flow through peripheral lymphaticovenous anastomoses and perilymphatic routes of lymph drainage, and increased venous fluid uptake. Secondary lymphedema is often related to a combination of lymphatic and venous obstruction.[104] Inhibited venous return increases lymphatic flow by altering Starling's forces toward increased tissue fluid accumulation. This overloads the lymphatic capillaries and results in the accumulation of fluid in the interstitial space.[95] Distal lymphatics may become more distended, causing loss of valvar competency, stagnation of lymph flow, mural insufficiency, and further accumulation of proteinaceous fluid in subcutaneous tissues. Other common etiologies include posttraumatic, postradiation therapy, or postsurgical interruption of lymphatics; lymph node excision; and blockage of lymph nodes and lymph vessels by compression or invasive neoplasms.[105-108] Lymphedema resulting from local neoplasia is usually a sign of a widely disseminated and highly invasive malignant process.

Clinical signs associated with secondary lymphedema vary depending on the underlying cause and any systemic response and overlap with clinical signs of systemic venous obstruction. Accordingly, physical diagnosis and appropriate imaging should assess both systems. Lymphedema may be localized to the periphery of an extremity (Figure 257-17) or extend proximally to the subcutaneous tissues.[105] The location and severity of obstruction determine the extent of edema formation. For example, sublumbar or intrapelvic obstruction induces bilateral hindlimb edema and edema of the thighs and external genitalia. Mediastinal masses and thrombosis of the cranial vena cava induce bilateral edema of the front limbs and tissues of the ventral thorax, neck, and head. The clinician must palpate all lymph nodes carefully for enlargement and pain. With bilateral hindlimb edema, it is important to perform rectal or abdominal palpation to assess sublumbar lymph nodes. The prostate and anal region or mammary glands and vaginal area should be carefully inspected for neoplasms, which can lead to obstructive intrapelvic processes. Intrapelvic masses should be suspected in all dogs with hindlimb edema and vague signs of sublumbar pain, discomfort during ambulation, or difficulties with defecation or urination. Depending on the type and extent of underlying systemic illness, limb edema may be the only detectable abnormality or may be accompanied by fever, anorexia, and weight loss. Clinicopathologic findings depend on the underlying primary disorder.

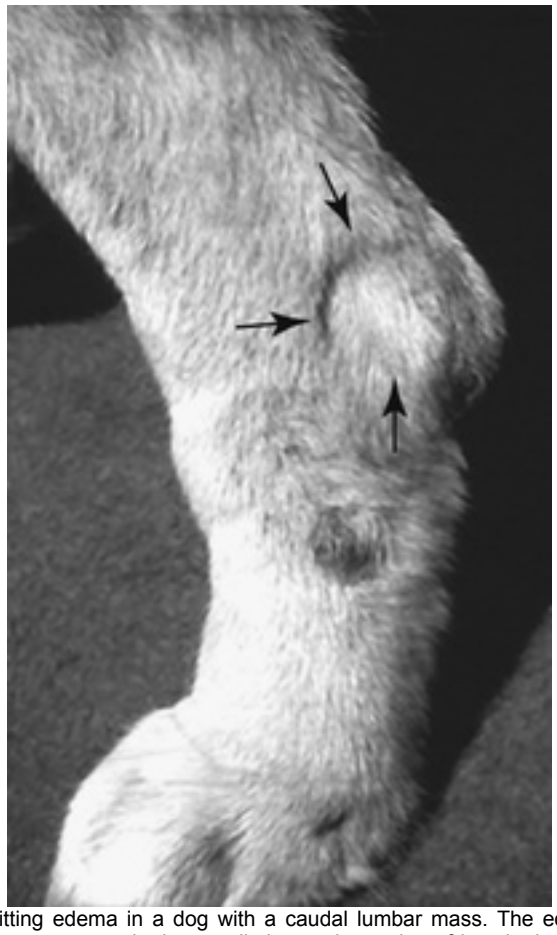

FIGURE 257-17 Pitting edema in a dog with a caudal lumbar mass. The edema was caused by either obstruction of venous return in the rear limbs or obstruction of lymphatic drainage. Tissue fluid was deformed by light digital pressure, resulting in a visible subcutaneous pit in the rear limb (arrows).

The diagnosis of lymphedema is based largely on history and physical examination and is facilitated by diagnostic imaging and the ruling out of venous obstruction. Survey radiographs should be taken of suspicious areas, which often include the pelvis or cranial thorax. In a substantial number of cases, soft tissue masses or destructive bony lesions can be detected. Occasionally, the identification of subclinical pleural effusions in cases of peripheral edema suggests a more generalized lymphatic disorder. Ultrasonography can provide information about soft tissue masses and readily identifies enlarged lymph nodes and other structures, both peripherally and within the abdomen. Duplex imaging, as described previously, should be used to exclude venous thrombosis or obstruction. Lymphangiography, lymphoscintigraphy, venography, or CTA may be indicated to evaluate venous and lymphatic anatomy and luminal integrity if the diagnosis remains unclear. Lymphangiography was traditionally relied upon for definitive diagnosis of lymphatic disorders. In some cases, the lymphatics are hypoplastic throughout their course. When aplastic, lymphatics suitable for cannulation and injection of radiocontrast agent may not be found. Failure to outline a lymph node after lymphography is not absolute proof of its absence.[6] Lymphangiographic features of primary lymphedema include lymph node aplasia and small lymphatics that end blindly or anastomose into collateral vessels around (instead of into) the locations where lymph nodes would normally be found.

Differential diagnoses for dogs with edema confined to one limb include inflammation, trauma, vascular obstruction, hemorrhage, cellulitis, phlebitis, and AV fistula (see ch. 18). Diagnostic considerations for dogs with edema involving both forelimbs include thrombosis or compression or invasion of the cranial cava by a mediastinal mass. With the latter, edema usually involves the head and neck regions, as well as the limbs. Causes of only bilateral hindlimb edema include obstruction of sublumbar lymph nodes by neoplastic infiltration, right-sided congestive heart failure, and pericardial effusion, accepting that in some dogs no cause is ever identified—in the authors' experience, the Irish Wolfhound appears overrepresented in cases of idiopathic lymphedema (see Figure 257-5). If all four limbs are involved, the differential diagnoses should include hypoproteinemia, congestive heart failure, renal failure, portal hypertension, or a lymphatic neoplasm (lymphangiosarcoma). As noted earlier, the close association of lymphatic and venous structures

can make it difficult to distinguish between lymphatic and venous obstruction, and both can occur at the same time. Ulceration, dermatitis, cyanosis, weeping varices, or fat necrosis are signs of venous obstruction rather than lymph stasis.

Therapy is usually unrewarding unless the edema is due to an underlying cause of elevated venous pressure (as opposed to true lymphedema). In the early stages of lymphedema, medical management is directed to maintaining the animal's comfort and reducing swelling. Infectious disorders require long-term antimicrobial therapy. Some neoplastic conditions may benefit from chemotherapy or radiation therapy. Long-term heavy bandage application (comparable to compression stockings in people) and physical therapy may encourage lymphatic flow and reduce subcutaneous lymph accumulation (see ch. 355).[109] Local topical skin care and intermittent antibiotic therapy are helpful in reducing secondary cellulitis. With the exception of isolated cases, pharmacologic therapies are generally unrewarding. The benzopyrones (e.g., rutin) are a group of drugs that have been advocated to reduce high-protein lymphedema by stimulating macrophages, promoting proteolysis, and enhancing absorption of protein fragments, though proof of efficacy in the treatment of lymphedema is lacking.[110,111] Long-term diuretic administration is considered as contraindicated because reduction of interstitial fluid will concentrate proteins in the residual interstitial space, which may promote tissue injury.[6] Surgical options may include (1) procedures to facilitate lymph drainage from affected limbs (lymphangioplasty, bridging procedures, shunts, omental transposition) and (2) procedures to excise abnormal tissue. Surgical excision of the subcutaneous edematous tissue should be staged to decrease devascularization.[6] Short-term administration of anti-inflammatory agents, bandaging, and physical therapy may be helpful in cases of traumatic or postsurgical lymphedema.

Lymphangioma, Lymphangiosarcoma

Lymphangiomas are benign tumors of small-caliber lymphatic vessels and are thought to develop when primitive lymphatic sacs fail to establish venous communication.[112] In a 5-year survey of 221 vascular tumors of dogs, only one case of lymphangioma was definitively identified, suggesting these are rare lesions.[66] Lymphangiomas can be classified into three categories based on their histologic appearance: (1) capillary lymphangiomas composed of a network of capillary-sized lymphatic channels, (2) cavernous lymphangiomas composed of dilated lymphatics that infiltrate the surrounding tissue, and (3) cystic hygromas (unilocular or multilocular, cystic masses lined by a single layer of endothelium supported by a connective tissue stroma and containing a straw-colored, proteinaceous [1.3 to 4.5 g/dL] fluid).[113] The lesions present as large, fluctuant masses in the subcutaneous, fascial, mediastinal, hepatic, lymph nodes, and retroperitoneal spaces.[114-117] Lymphangiomas have also been diagnosed on the extremities, metacarpal pads, nasopharynx, axilla, inguinal and mammary region, retroperitoneal space, and skin of dogs.[112,118-120] Clinical signs are related to the size, location, and extent of the lymphangioma. They can exert pressure on surrounding structures and may interfere with muscle function, breathing (compression of the trachea), urination, or intestinal function. Lymph may ooze to the skin surface through single or multiple fistulous tracts. Differential diagnoses include other space-occupying masses such as abscesses, enlarged lymph nodes, neoplasms, and congenital cysts of nonlymphogenic origin. The prognosis can be good after appropriate surgical excision, marsupialization, or radiation therapy.[121] Risk of recurrence is high due to inherent inability to identify distinct boundaries.

Lymphangiosarcoma originates from lymphatic endothelial cells.[122] It is a rare malignant tumor in dogs and cats, although it is frequently reported secondary to chronic lymphedema in humans.[123-125] The diagnosis can be challenging by light microscopy with hematoxylin and eosin staining, as features of the neoplasm are shared with hemangiosarcoma. Prior reports suggest hemangiosarcoma and lymphangiosarcoma can be distinguished by a lack of erythrocytes in the vascular spaces of lymphangiosarcoma.[122] Newer immunohistochemical stains appear to better characterize these neoplasms.[66,122] A breed or sex predisposition has not been detected, but medium to large breeds may be at highest risk, and both young and older animals are affected.[107,122,126-131] Metastasis occurs commonly in dogs and cats, estimated to be present in a third to half of cases at diagnosis.[122,129,132] Clinical signs include pitting edema of the extremities, inguinal region, axilla, and head and neck.

In a report of 12 cats with lymphangiosarcoma, 9 presented with fast-growing, noncircumscribed subcutaneous masses and the others presented with a thoracic or abdominal mass.[129] In all cats affected, the tumor was invasive and complete surgical resection was not possible.[129] The presenting complaints were similar in a series of 12 dogs with lymphangiosarcoma in which 10 of the cases were presented for swelling of

the neck, ventral abdomen, or limbs—nearly all with serosanguineous discharge from the overlying tissue.[122] Associated chylous effusions (pleural, abdominal, subcutaneous) have been reported.[133-135] Pulmonary lymphangiosarcoma was diagnosed in one dog presenting with a chylous thoracic effusion.[136] Cytology of the mass or swelling is unrewarding, with most cytologic reports finding mild inflammation without signs of malignancy.[122] Diagnosis is confirmed by obtaining a biopsy specimen. Histologically, tumors of lymphatic endothelial origin are characterized by a neoplastic proliferation of endothelial cells. Immunocytochemical stains, such as prospero-related homeobox gene 1, have been used to confirm the diagnosis in dogs and cats.[122,137,138] The prognosis with lymphangiosarcoma is guarded to poor, with a high rate of local recurrence and metastasis. In early reports, most animals were euthanized or died due to severe lymphedema, pleural effusion, or distant metastases. In one case report, lack of recurrence and absence of metastatic disease was documented over 9 months following mass resection and doxorubicin treatment.[139] In the case series of 12 dogs,[122] variable treatment strategies were employed with incomplete surgical excision in 5 dogs having a mean survival time of 513 days, chemotherapy alone having a survival time of 182 days in 1 dog, prednisone alone in 1 dog having a survival time of 90 days, combination therapy (surgery, chemotherapy, +/− radiation therapy) having survival of 574 days in one dog and more than 248 days in another. The three dogs that did not receive therapy had a mean survival of 368 days.[122] Currently, the optimal therapy for lymphangiosarcoma in dogs and cats is unknown.

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SECTION XVII

Neurologic Disease

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CHAPTER 258

Neurophysiology

Dennis P. O'Brien, Joan R. Coates

Nervous system function is based on excitable membranes. The potential to pass excitation on to other neurons begins with the resting membrane potential, the rechargeable battery that powers the process. Fluctuating conductance of voltage-gated Na^+ and K^+ channels in the axon will transmit the excitation on as the action potential. This transmission is facilitated by the insulating myelin sheath, which permits saltatory propagation to jump rapidly down the axon. The action potential ends at the nerve terminal, opening voltage-gated Ca^{++} channels that trigger a cascade of synaptic docking proteins and release a neurotransmitter. The neurotransmitter binds with a post-synaptic receptor and then is terminated by specific reuptake proteins or enzymatic inactivation. The neurotransmitter affects the post-synaptic neuron, either short term or long term, making it more or less likely to pass that excitation on. The graded excitatory and inhibitory inputs to a neuron summate at the axon hillock, where the "decision" is made to stop any further signal or begin the process again with a new action potential. This basic process of excitation and inhibition plays out in the complex anatomy of the nervous system to generate attention, perception, motivation, and action.

Excitable Membranes: Resting Membrane Potential and Ion Channels

At rest, an excitable cell like a neuron has an electrical charge across the membrane with the inside of the cell negative relative to the outside: the resting membrane potential. This potential is created by the active transport of ions across the membrane resulting in concentration differences inside and outside the cell. Na^+/K^+ ATPase utilizes energy from ATP to pump 3 Na^+ ions out of the cell in exchange for 2 K^+ ions. This creates a concentration gradient with sodium concentrations [Na^+] much greater outside the cell and potassium concentrations [K^+] much greater inside the cell. Since one more Na^+ is pumped out than K^+ pumped in, an electrical gradient is also established. Negatively charged anions such as proteins and amino acids, which cannot diffuse through the membrane, maintain the negative charge on the inside of the membrane. For neurons, this potential difference is about −65 to −70 mV. A disease process such as hypoglycemia will impair the ability of neurons to supply enough ATP to the Na^+/K^+ ATPase. When the cell cannot maintain the resting membrane potential, it will decay toward a more depolarized state, which can trigger seizures or progress to coma.

The permeability of the membrane to an ion is determined by the state of channels in the membrane, which are selectively permeable to different ions. The degree and direction of flow will depend on the concentration gradients and the charge of the membrane. When, for example, a K^+ channel opens, the ion will diffuse down the concentration gradient: in the case of K^+, from inside the cell to outside. Balancing this force, however, is the difference in electrical charge. The negatively charged anions inside the cell attract the positively charged K^+ and oppose their diffusion out of the cell (Figure 258-1). The voltage difference across the membrane at which these forces are in balance and no diffusion occurs is the equilibrium potential (E_k). This depends on the concentration differences driving diffusion ($[K^+]_{out}/[K^+]_{in}$) and is calculated by multiplying the log of that quotient by a constant (the Nernst equation).

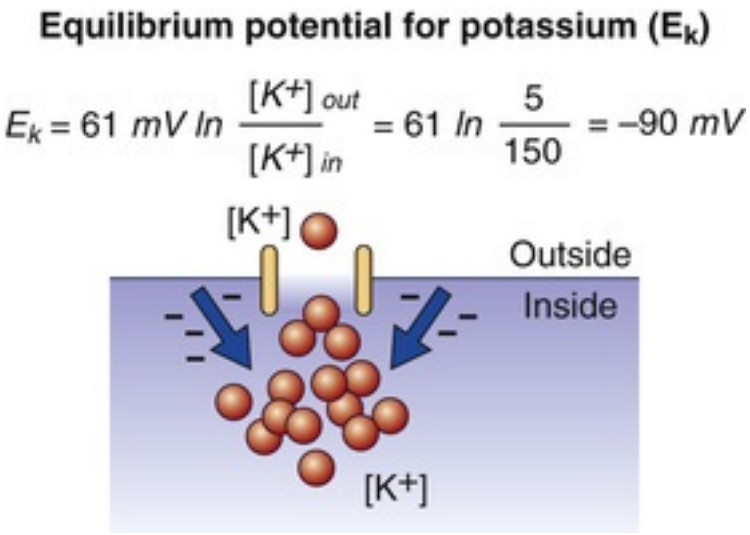

FIGURE 258-1 The higher concentration of K^+ inside the cell encourages diffusion from the cell. This force is opposed by the negative charge inside the membrane, which attracts the positively charged K^+. The membrane voltage where these two forces are in balance is the equilibrium potential *(E_K)* calculated by the Nernst equation. Thus, when the membrane is at −90 mV, there will be no diffusion of K^+. (From O'Brien, D.P. Vet Med 8415: Advanced Veterinary Neurology, http://bblearn.missouri.edu, 2015. Used with permission.)

Opening and closing of these ion channels is regulated by the membrane voltage or by a neurotransmitter binding to a receptor linked to the channel. When the channel is open, the ion that it is permeable to will diffuse to reach the equilibrium potential. If a K^+ channel opens, K^+ would diffuse out of the cell down the concentration gradient until the inside of the cell reached the equilibrium potential of −90 mV when the forces of voltage and diffusion would be in balance. Thus, this would make the cell more negative (hyperpolarized). On the other hand, $[Na^+]$ outside the cell is much greater than $[Na^+]$ inside and the electrical gradient favors diffusion into the cell. The cell is very impermeable to Na^+ at rest, but when a sodium channel opens, Na^+ will diffuse into the cell until its equilibrium potential is reached at 59 mV, depolarizing the cell. The other ion critical to the resting potential is Cl^-. It has its own active transport mechanisms that create a gradient with the $[Cl^-]$ outside the cell much greater than inside, giving an E_{Cl} of −70 mV.

The concentration gradients and the resting permeability of the neuronal membrane for these different ions all contribute to the resting membrane potential. The Goldman, Hodgkin, Katz equation predicts the membrane potential based on the balance of these variables. At rest, the $[Na^+]$ and $[Cl^-]$ are large outside the cell compared to inside and the opposite is true for $[K^+]$. The resting permeability for K^+ (P_K) is large, as numerous "leak" channels are open at that voltage. The P_{Cl} is much less while the P_{Na} is even less still. The summation of all these factors gives rise to the potential of the membrane at rest of about −65 mV for neurons.

Channelopathies are diseases that affect ion channel function and alter the excitability of the neuronal membrane. Cats with complex partial seizures have antibodies against voltage-gated potassium channels and dogs with a mutation in the gene that codes for a portion of this potassium channel complex have benign familial juvenile epilepsy.[1,2] These diseases alter P_k and thus the excitability of the cell membrane, predisposing to excessive neuronal activity and seizures.

Transmitting Excitation: the Action Potential

When a neuron depolarizes past a threshold (−55 mV), voltage-gated Na^+ channels in the axon will open, beginning the action potential that will transmit that signal on to other neurons (Figure 258-2, *A*). The amount of Na^+ that diffuses into the cell through a permeable channel is expressed as conductance (g_{Na}). As Na^+ diffuses into the cell, it further depolarizes the membrane until it approaches the equilibrium potential for Na^+ (E_{Na}) of 59 mV. Na^+ channels have a secondary gating mechanism, the inactivation gate, which closes the channel preventing further diffusion of sodium through that channel for a brief period of time (Figure 258-2, *B*). Voltage-gated K^+ channels will open in response to the depolarization produced by the g_{Na}. K^+ now

diffuses through these ion channels toward its equilibrium potential of −90 mV. Since this is below the normal resting membrane potential of −65 mV, there is an after-hyperpolarization of the membrane until the normal resting conductances bring the voltage back to rest. Antiepileptic drugs such as phenytoin enhance inactivation of sodium channels, making it less likely that an action potential will be propagated.[3] Toxins such as pyrethrins block sodium channel inactivation, increasing action potential generation and causing tremors and seizures (see ch. 152).[4]

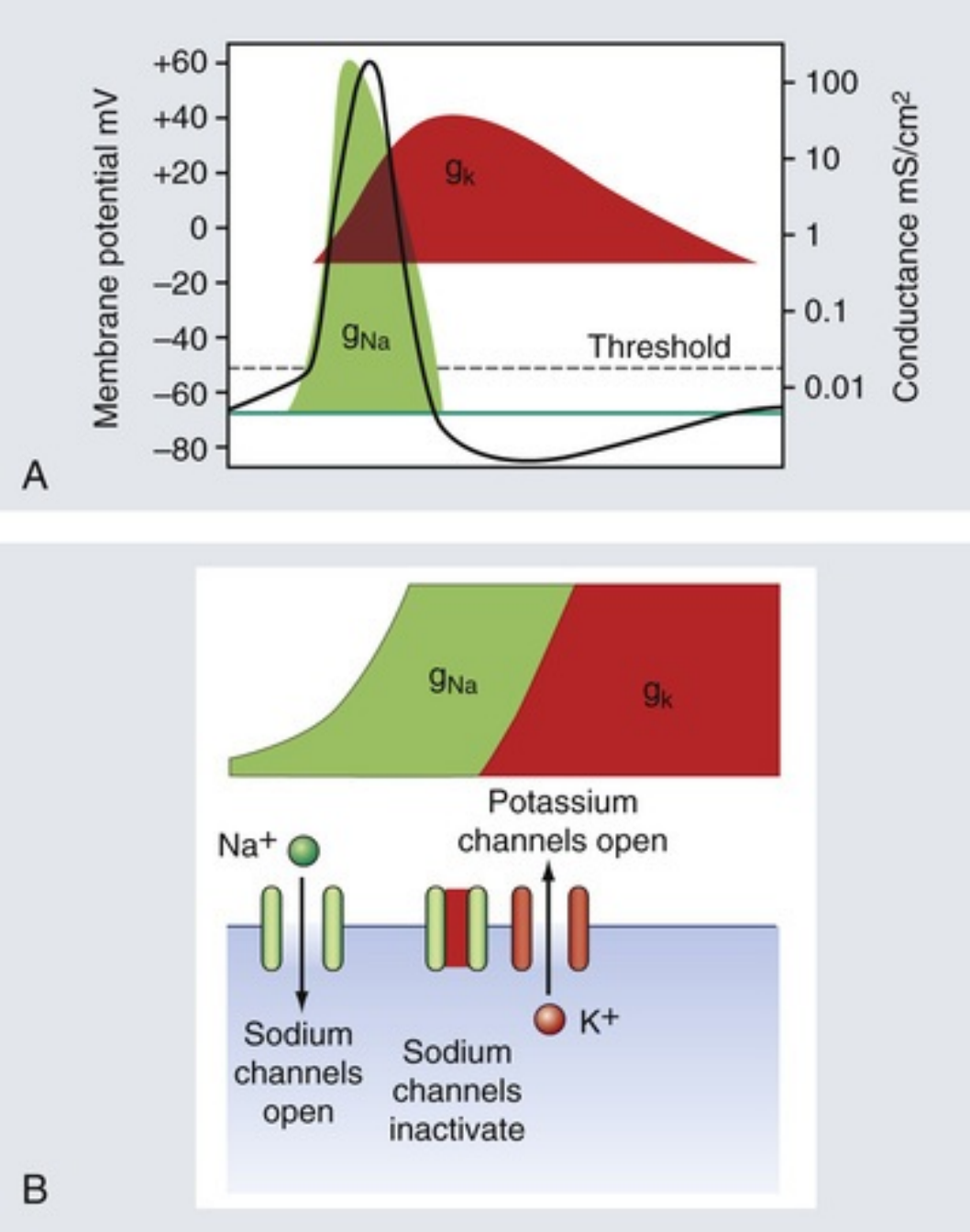

FIGURE 258-2 **A,** The action potential (black line) is generated by changes in the conductance of Na^+ (g_{Na} in green) and K^+ (g_K in red). When the cell depolarizes past a threshold of −55 mV, Na^+ channels open **(B)** and Na^+ diffuse into the cell until it reaches the equilibrium potential of 59 mV. Na^+ channels inactivate, preventing any further diffusion of that ion. Voltage-gated K^+ channels open with depolarization, permitting K^+ to diffuse out of the cell until its equilibrium potential of −90 mV is reached. (From O'Brien, D.P. Vet Med 8415: Advanced Veterinary Neurology, http://bblearn.missouri.edu, 2015. Used with permission.)

Two factors influence the speed at which the action potential travels down an axon: axonal diameter and myelin. Increasing the diameter of the axon increases the number of ions available for currents to flow (i.e., it decreases the resistance to ion flows). At the same time, however, it increases the surface area where the difference in charge between the inside and outside is stored (i.e., it increases the capacitance which resists ion flow). Adding an insulating layer of myelin decreases the ability of the membrane in that area to store a charge (decreases the capacitance) without affecting resistance to ion flows within the axon, and permits the ions to flow between the unmyelinated areas (nodes of Ranvier) in a saltatory fashion. Demyelinating diseases such as polyradiculoneuritis (see ch. 268) increase the capacitance of the axonal membrane, thus slowing the conduction velocity and potentially blocking propagation of the action potential.

Communication Between Neurons: the Synapse

Neurons communicate with each other via synapses. While some synapses permit a direct flow of ions between neurons (electrical synapses or gap junctions), most utilize chemical signals via neurotransmitters. Neurotransmitters are packaged into vesicles stored in the nerve terminal. When the action potential depolarizes the nerve terminal, voltage-gated calcium channels open, allowing Ca^{++} to flow into the cell. The Ca^{++} activates a series of synaptic vesicle proteins that dock the vesicle to the presynaptic membrane where it fuses with the cell membrane, releasing the neurotransmitter into the synaptic cleft. Botulism toxin binds to one of the vesicle docking proteins, preventing release of acetylcholine at the neuromuscular junction (see ch. 214).[5]

The neurotransmitter diffuses across the synaptic cleft and binds to a receptor on the membrane of the post-synaptic cell, which can be another neuron, a muscle or another effector like an endocrine cell. Receptors can be divided into ionotropic receptors which regulate ion channels and metabotropic which act through second messengers. The effects of the neurotransmitter will be terminated by diffusion from the synapse, enzymatic degradation, or an active uptake mechanism.

The classic ionotropic receptors have subunits composed of membrane spanning domains that form a central pore, which is selectively permeable to certain ions. Several structural molecules are important in adhering the pre- and post-synaptic zones together as well as anchoring the ion channels, docking protein, receptors and various second messengers to the membrane in those zones. When the neurotransmitter binds to an extracellular ligand binding site, it alters the conformation and the permeability of the pore. The three families of ionotropic receptors are (1) nicotinic acetylcholine (ACh), gamma-amino butyric acid (GABA) and glycine, (2) glutamate, and (3) ATP or purine P2X receptors.[6] The effects on the post-synaptic cell can be either excitatory or inhibitory depending on which ion diffuses through the open pore.

When ACh binds to the nicotinic receptor, the pore becomes permeable to cations.[6] At a resting membrane potential, Na^{+} will be the major ion to diffuse into the cell, depolarizing the post-synaptic membrane. When recording the membrane potential in the post-synaptic cell, this depolarization appears as an excitatory post-synaptic potential (EPSP) (Figure 258-3). Acetylcholinesterase in the synaptic cleft breaks down ACh to choline and acetic acid, which are taken up into the presynaptic terminal and used to resynthesize ACh. In myasthenia gravis, autoantibodies directed against the alpha1 subunit partially block the ACh receptor in the neuromuscular junction (see ch. 269).[7] This makes it more difficult for ACh to open the channel and produces the fatigue that is the hallmark of the disease. Acetylcholinesterase inhibitors prolong the interaction of ACh with the receptor and reverse the clinical signs.

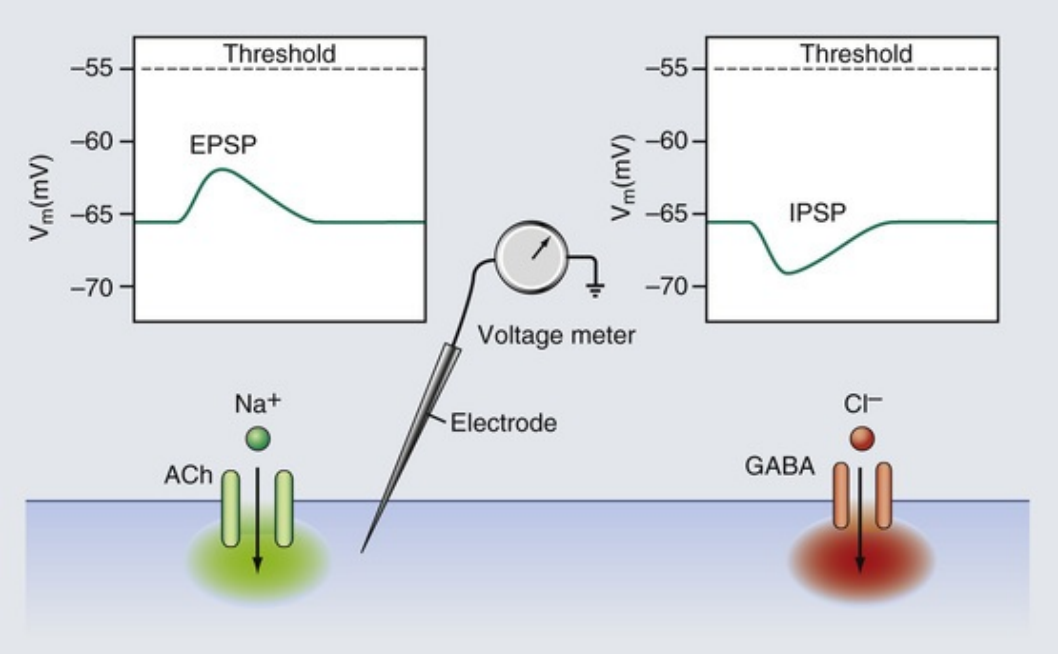

FIGURE 258-3 When the nicotinic ACh channel opens and Na^+ diffuses into the cell, a subthreshold depolarization of the membrane can be recorded as an excitatory post-synaptic potential (EPSP). When an inhibitory neurotransmitter like gamma-amino butyric acid (GABA) binds to its receptor, the influx of Cl^- further polarizes the cell and is recorded as an inhibitor post-synaptic potential (IPSP). (From O'Brien, D.P. Vet Med 8415: Advanced Veterinary Neurology, http://bblearn.missouri.edu, 2015. Used with permission.)

GABA is the major inhibitory neurotransmitter. The GABA-A receptor and the closely related glycine receptor have a similar structure to the ACh receptor, but the ion channel is only permeable to the anion Cl^-.[6] When channel opens, Cl^- can diffuse into the cell, creating an inhibitory post-synaptic potential (IPSP) that hyperpolarizes the cell (see Figure 258-3). Since the resting membrane potential in many neurons is close to the equilibrium potential for Cl^-, there may not be much movement of Cl^- across the membrane when the ion channel opens. Nonetheless, the open channel makes it less likely that the post-synaptic cell will reach threshold to generate an action potential since any depolarization will shift the balance towards diffusion of Cl^- into the cell. Commonly used antiepileptic drugs such as diazepam and phenobarbital bind to extracellular sites on the GABA-A receptor. They do not open the ion channel, but they alter the kinetics of the channel, increasing the time the pore is open when GABA binds to its receptor.[8]

The function of the major excitatory neurotransmitter in the central nervous system, glutamate, is more complicated.[6,9] There are two subtypes of ionotropic glutamate receptors named for the drugs which were first used to differentiate them, the AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) and the NMDA (N-methyl-D-aspartate) receptors, which are often found in close proximity. Glutamate must bind to both receptors to produce an effect. Binding to the AMPA receptor partially depolarizes the membrane, releasing a Mg^{++} ion which blocks the NMDA channel. Binding to the NMDA receptor can then allow additional Na^+ conductance, which enhances the EPSP produced by activation of the AMPA receptor. The NMDA channel is permeable to Ca^{++} as well. The increase in intracellular Ca^{++} that results can trigger second messenger systems that have more prolonged effects on the synapse, as discussed below. With excessive NMDA receptor activation, the accumulation of intracellular Ca^{++} can trigger cell death, a process called excitotoxicity.[10]

The second class of neurotransmitter receptors, the metabotropic receptors, includes muscarinic acetylcholine receptors, metabotropic glutamate receptors, GABA-B receptors, and most serotonin receptors, as well as receptors for norepinephrine, epinephrine, histamine, dopamine, neuropeptides and endocannabinoids.[6,9] These receptors act through second messenger systems such as G-proteins and produce more prolonged influences on function. Sometimes these systems indirectly affect ion channel conductance and the same neurotransmitter can have opposite effects depending on the receptor. When ACh binds to the M2 muscarinic ACh receptor, a G-protein binds GTP and dissociates a subunit that then binds to the G-

protein–coupled inward-rectifying potassium channel (GIRK). This opens the ion channel and permits K^+ to diffuse from the cell, hyperpolarizing the membrane. In contrast, M1 receptor activation closes the M-type K^+ channel, producing a prolonged EPSP.[9]

Metabotropic receptors can also mediate long-term changes in synaptic function. For example, the metabotropic glutamate receptor mGluR1 is found in high concentration on Purkinje cells in the cerebellum. When glutamate binds to this receptor, it activates a G-protein, which works through a series of other second messengers to ultimately activate a protein kinase C (Figure 258-4). This removes a phosphate from the AMPA receptor, causing internalization and degradation of the receptor. This makes that synapse less responsive to excitatory glutamatergic stimulation, a process termed long-term depression, which is an essential part of learning and memory. Coton de Tulear dogs with a mutation in the mGluR1 gene *(GRM1)* cannot make these changes as they develop. Thus they have impaired motor learning and severe cerebellar ataxia (Video 258-1).[11] Other metabotropic neurotransmitters will produce long-term potentiation of synaptic strength.

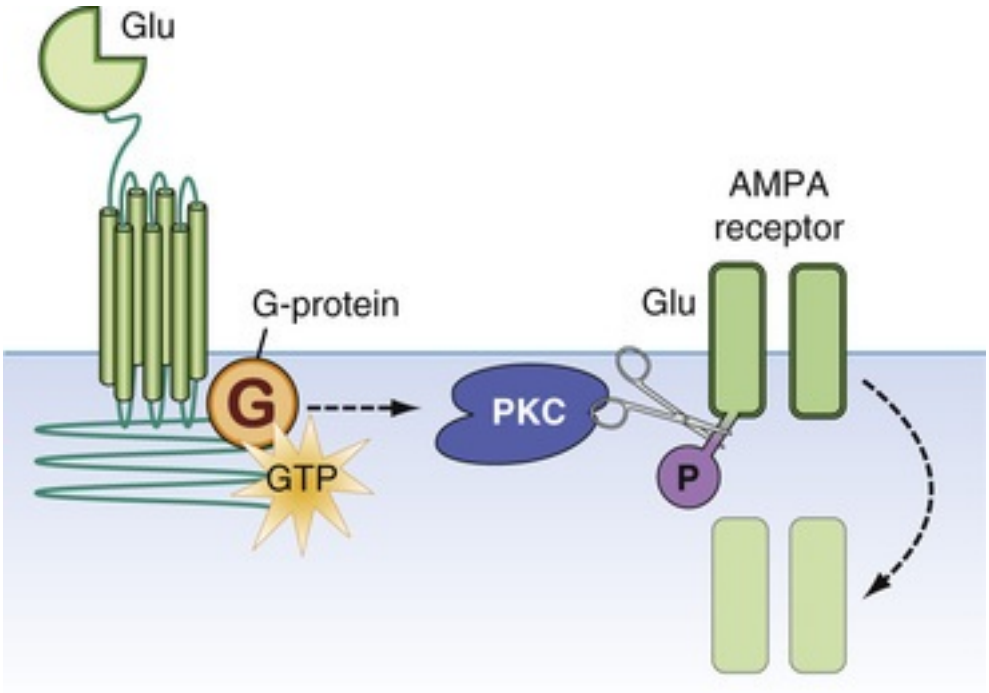

FIGURE 258-4 Activation of the metabotropic glutamate receptor mGluR1 produces long-term changes in synaptic function. Through a series of intermediate steps, the G-protein activates a protein kinase C (PKC), which removes a phosphate from the AMPA receptor. This leads to internalization and degradation of the receptor, weakening the strength of the synapse. This long-term depression of synaptic function is one of the building blocks of synaptic plasticity and learning. (From O'Brien, D.P. Vet Med 8415: Advanced Veterinary Neurology, http://bblearn.missouri.edu, 2015. Used with permission.)

Another class of neurotransmitters that work through metabotropic receptors are the monoamines such as dopamine or serotonin. Dopamine and adenosine act through separate receptors to affect cyclic AMP activity. Stimulating the D2 dopamine receptor decreases cyclic AMP levels and increases arousal. Stimulating the adenosine receptor increases cyclic AMP levels and decreases arousal. Drugs like caffeine block adenosine receptors, leaving dopaminergic activity unopposed and thus increasing arousal.[12]

Serotonin is an important neurotransmitter in the regulation of mood, and deficiency of serotonin activity is thought to be responsible for clinical depression. The activity of serotonin on its post-synaptic receptor is terminated by reuptake of serotonin into the presynaptic terminal by the serotonin transporter. Drugs like fluoxetine selectively block serotonin transporters with fewer effects on the other related monoamine transporters. Such drugs are used to treat separation anxiety and compulsive behaviors in dogs.[13,14]

Maintaining the Machinery: Axonal Transport

All the proteins are synthesized near the nucleus and must be transported through the cytoplasm to the place they are needed. Neurons differ from other cells in that the proteins, vesicles and mitochondria must be transported down the length of the axon, which in an animal like a horse may be meters in length. Damaged proteins and other byproducts must then be transported back to the cell body for degradation and recycling. Thus, a system of axonal transport has evolved to accomplish this task. The cellular railway along which this cargo is transported is composed of microtubules, which run the length of the axon. Two separate molecular engines carry the cargo along the microtubules: kinesins for transporting from the cell body to the nerve terminals (anterograde transport) and dyneins for transporting from the nerve terminal back to the cell body (retrograde transport). These motors utilize ATP to undergo conformational changes and "walk" down the microtubules. Vesicular cargoes move at a consistent, rapid speed. Cytosolic proteins, cytoskeletal proteins and mitochondria were originally thought to move more slowly. Recent research, however, has shown they travel at the same speed but make frequent stops along the way.[15] Toxins or mutations that disrupt axonal transport can result in an accumulation of material in the form of spheroids at the cell body or in the nerve terminal. Failure to supply the nerve terminal adequately can result in dying-back of the longest axons.[16]

Simple Circuitry in the Nervous System

The basic process of excitation and inhibition permits simple circuitry, which can be layered to produce the complex processes of nervous system function. When a single action potential releases an excitatory neurotransmitter, the EPSP produced typically does not reach the threshold to generate another action potential in the post-synaptic neuron. EPSPs from a run of several action potentials can summate to depolarize the post-synaptic membrane above threshold, the process of temporal summation. Alternatively, axons from multiple pre-synaptic neurons may converge on a single neuron. When more than one action potential converges on the neuron simultaneously, the EPSPs can also summate to depolarize the post-synaptic neuron above threshold in the process of spatial summation. In contrast, one excitatory neuron may branch and synapse on many post-synaptic neurons. Such divergent circuits allow for the spread of a signal through multiple second order neurons.

Inhibitory neurons typically function as interneurons in circuits to control excitation. They often synapse closer to the cell body where they can block the propagation of the EPSP to the axon hillock where the action potential would be generated. The Renshaw cell in the spinal cord is an example of an inhibitory interneuron. An excitatory impulse to a motor neuron will also activate the Renshaw cell. The Renshaw cell then inhibits surrounding motor neurons in a process of collateral inhibition. Tetanus toxin blocks glycine release, resulting in excessive excitation of the motor neurons and the classic clinical sign of tetany (see ch. 214).

The inhibition can also be directed at the origin of the excitation. The large pyramidal cells in the cerebral cortex are excitatory, glutaminergic neurons that send long projection fibers from the cortex. A branch of this axon synapses on GABAergic interneurons within the cortex that then synapse back on the pyramidal cell. This feedback inhibition helps prevent excessive firing of the pyramidal cells and a failure of this inhibition may underlie some seizure activity.[17]

Sensory Processing

Combining some of these simple circuits illustrates how the nervous system processes information (Figure 258-5). A sensory stimulus such as touch or light will activate receptors immediately beneath the stimulus more strongly than surrounding receptors. The more strongly stimulated receptors will generate more action potentials than those on the periphery. Divergent innervation from each of these receptors will innervate a number of adjacent post-synaptic cells. Axon branches from both the highly excited central receptors and the less excited peripheral receptors converge on the central, second order neuron. The combination of temporal and spatial summation ensures that the second order neuron reaches threshold to generate an action potential. Branches off this second order neuron's axon synapse on inhibitory interneurons that project to the surrounding second order neurons: lateral inhibition. Though these neurons receive some excitatory inputs, these inputs are much weaker and the lateral inhibition prevents these neurons from reaching threshold. This focuses the excitation on the center of the stimulus while inhibiting the surrounding neuron. When this center-surround programming is spread across whole populations of sensory circuits, it can be used to detect edges and shapes. When combined with the duration and timing of activation of adjacent areas, movement is detected.

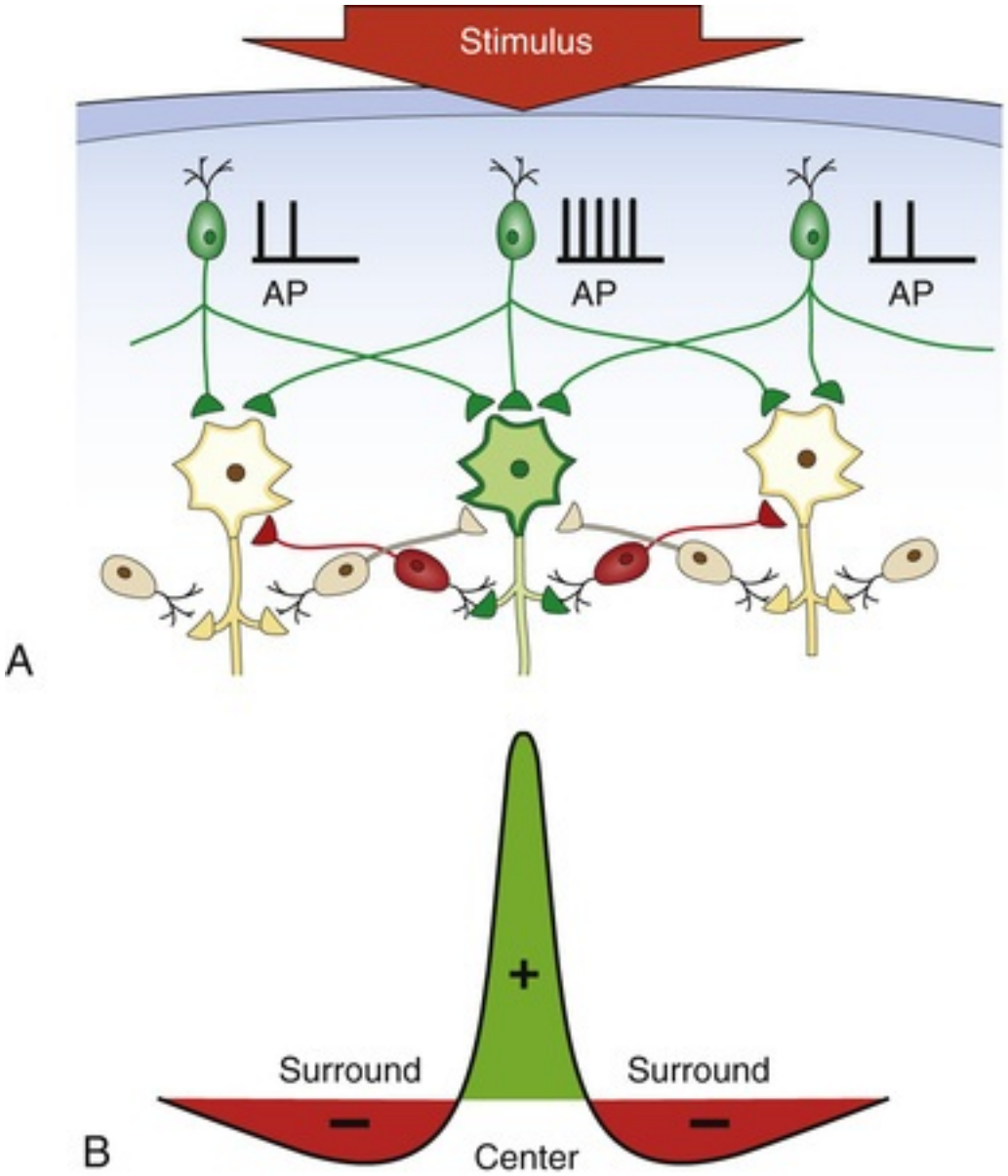

FIGURE 258-5 In sensory systems, the stronger the stimulus on a receptor, the greater the number of action potentials (AP) generated. Convergence of strong and weak excitation from adjacent receptors activates second order neurons at the center of the stimulus **(A).** Lateral inhibition of surrounding second order neurons creates a halo of inhibition that focuses the response to a select group of second order neurons **(B).** (From O'Brien, D.P. Vet Med 8415: Advanced Veterinary Neurology, http://bblearn.missouri.edu, 2015. Used with permission.)

Cognitive Function, Attention and Motivation

In the cerebral cortex and subcortical areas, sensory information is acted upon based on the level of arousal, motivational state, and past experiences of the animal. Arousal of the brain is essential for consciousness and attention. This process is largely mediated by projections to the forebrain from monoaminergic (primarily norepinephrine, dopamine, serotonin and histamine) and cholinergic neurons in the brainstem and basal forebrain,[9] a system sometimes referred to as the reticular activating system. Large lesions within these projection pathways can produce stupor and coma while more selective lesions can affect different aspects of attention or motivation without loss of consciousness.

Motor Control

As in the sensory system, understanding the function of the motor system begins with simple circuits. When a

muscle is stretched, receptors in the muscle spindle are stimulated. The action potentials generated by the stimulus travel to the spinal cord where they synapse directly on the motor neuron that innervates that muscle, producing a contraction. This stretch or myotatic reflex is part of a circuit designed to regulate muscle length and tension but it is also an essential tool of the neurologic examination (see ch. 259). The withdrawal or flexor reflex, another important reflex in the neurologic examination, has a more complex circuitry. When an animal steps on a thorn or the clinician pinches a toe, pain afferents will synapse on interneurons within the spinal cord as well as project to the cerebral cortex, where the pain will be perceived. Completely independent of any perception, however, reflex circuits will respond to protect the limb. Excitatory interneurons within the spinal cord will synapse on the motor neurons to the flexor muscles of the limb, withdrawing it from the noxious stimulus. This sudden flexion of one limb shifts additional weight to the opposite limb. To provide the support needed for that shift, another interneuron crosses over to the opposite side of the spinal cord and excites motor neurons to the extensor of the contralateral limb (Figure 258-6). In normal animals, the crossed-extension component of the reflex will be inhibited by descending motor controls if the animal is in lateral recumbency, and there will be only the withdrawal. If that descending control is abolished by a lesion affecting the upper motor neurons, the crossed-extension reflex is released from inhibition and it occurs when withdrawal is induced. Taking this crosstalk between neurons to another level, central pattern generators can generate rhythmic activities such as walking. Some pattern generators are composed of cells that undergo spontaneous burst firing, but patterns can also be generated through a system of reciprocal inhibition called a half-center.[9] The descending upper motor neuron system facilitates or inhibits these local pattern generators through neuromodulatory inputs to produce normal walking rhythm, which is further modified at the spinal cord level based on sensory feedback. If the normal upper motor neuron control of this process is lost due to a spinal cord lesion, these spinal pattern generators can function spontaneously, resulting in "spinal walking" (Video 258-2).

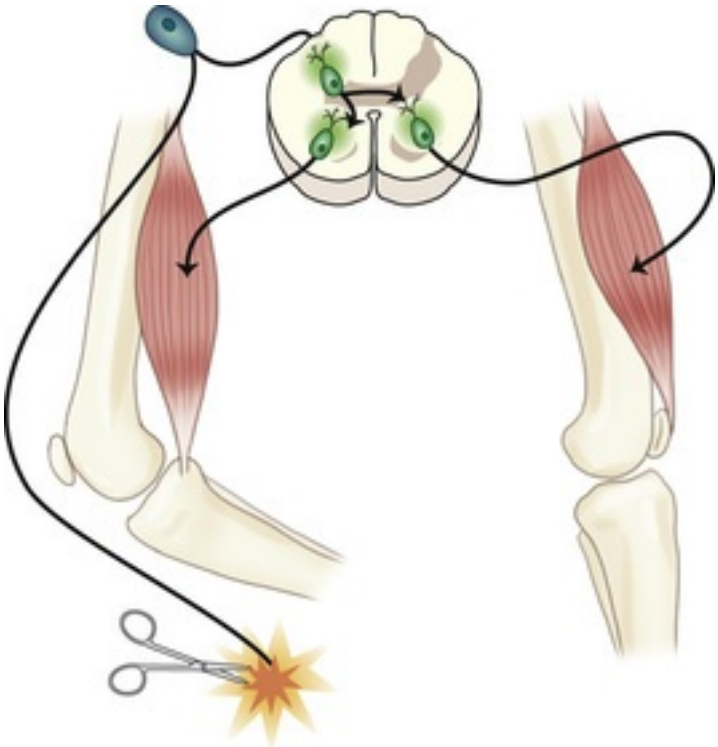

FIGURE 258-6 A painful stimulus to the paw elicits two reflex responses: withdrawal and crossed extension. Pain afferents synapse on an interneuron that excites motor neurons innervating the flexors of the limb. This withdrawal is a reflex independent of conscious perception. Other interneuron fibers cross to the contralateral side and synapse on extensors to bear the increased weight shifted to that side by the withdrawal. The crossed extension component is only seen when there is loss of UMN inhibition of the reflexes. (From O'Brien, D.P. Vet Med 8415: Advanced Veterinary Neurology, http://bblearn.missouri.edu, 2015. Used with permission.)

This hierarchy of control of movement is continued centrally. The position of the head and neck influence

the tone of extensors and flexors in the limbs through tonic neck reflexes, preparing the body for movements based on where the head and neck are directing attention. Different modulatory signals to the spinal pattern generators will produce different gaits. The brainstem locomotor areas that generate these modulatory signals are in turn directed by the cortical and basal nuclear motor systems. These systems are regulated by past experiences through the monoaminergic projections that mediate motivation and arousal.

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CHAPTER 259

Neurologic Examination and Neuroanatomic Diagnosis

Scott J. Schatzberg

A precise *neuroanatomic diagnosis* remains indispensable for the generation of an appropriate differential diagnosis. The differential diagnosis allows the clinician to, in turn, interpret neurodiagnostic tests correctly. This chapter is meant to provide the clinician with the basic, functional neuroanatomy and clinical examination skills necessary to make an accurate neuroanatomic diagnosis. It is modeled heavily upon the examination recommended by de Lahunta.[1] Video clips for this chapter demonstrate various components of the neurologic examination and show the salient abnormalities associated with the most common neuroanatomic diagnoses.

The past 15 years have been marked by a dramatic increase in the availability of advanced, neurodiagnostic testing for veterinary patients. Magnetic resonance imaging (MRI), in particular, has enhanced our ability to diagnose complex and elusive neurologic disorders. The "downside" to such advances is that clinicians have developed a natural tendency to rely heavily (or exclusively!) on advanced imaging in patients with neurologic disorders. Although MRI and computed tomography (CT) scans are sensitive for the identification of abnormalities of the central and peripheral nervous systems (CNS and PNS), both imaging modalities lack specificity and may be misleading when interpreted outside the context of the neuroanatomic and differential diagnosis. Despite the exceptional availability of cross sectional imaging, the clinician's ability to successfully diagnose, prognosticate and treat patients with neurological disease remains critically reliant on the neurological examination.

Neurologic Examination

The neurologic examination can be divided into five parts. These include evaluation of (1) sensorium and behavior; (2) posture and gait; (3) postural reactions; (4) muscle mass, tone, spinal reflexes, and cutaneous sensation; and (5) cranial nerves. The order in which the neurologic examination is performed is not critical, but the clinician should develop a consistent routine for evaluating each dog or cat.

Sensorium and Behavior

The owner is often the best judge of changes in a pet's mental attitude and behavior and should be questioned carefully. Examples of behavioral changes include docile pets that have become aggressive (and vice versa) or pets that have forgotten learned habits. Procurement of an accurate history may prove to be critical because behavioral changes may be secondary to intracranial lesions that otherwise have no impact on the neurological examination (also see ch. 9 and 13).

Sensorium should be assessed carefully in recumbent pets. Recumbency may be associated with brainstem, cervical spinal cord, or diffuse neuromuscular disorder (NMDs). Of the three localizations, only brainstem lesions should affect the sensorium. An alteration in sensorium is typically due to a disturbance in the ascending reticular activating system (ARAS) and/or limbic system components of the cerebrum or rostral brainstem (diencephalon). Numerous terms have been used to describe changes in sensorium and/or behavior and include: depression, lethargy, unresponsiveness, stupor, coma, anxiety, disorientation, hyperactivity, hysteria, propulsion, and aggression. Also see ch. 148.

Posture and Gait

Posture

The clinician should evaluate posture when the pet is standing and walking. The patient should be assessed for a head tilt (e.g., vestibular disease); a head or body turn (e.g., rostral brainstem or cerebral disease); neck position (e.g., lowered with cervical spinal cord or diffuse neuromuscular disease); hock angle (e.g., plantigrade with peripheral neuropathies); evidence of trembling (e.g., neuromuscular disease) and tail position (e.g., flaccid with lumbosacral disease). The clinician also should recognize breed-specific alterations in posture such as sunken tarsi in German Shepherd Dogs.

Severe intracranial lesions may lead to two separate opisthotonic postures: *decerebrate* or *decerebellate rigidity*. Decerebrate rigidity is characterized by opisthotonus with rigid extension of the neck and all four limbs, and is typically associated with midbrain or rostral cerebellar lesions. Decerebellate rigidity results from severe cerebellar lesions and is characterized by opisthotonus with extensor rigidity of the limbs, but with the hips flexed.

Pleurothotonus refers to the deviation of the head and neck to one side and may be present with mid to rostral brainstem or cerebral lesions.

Gait

Strength and coordination are the key gait components to be evaluated. Gait should be assessed in an area where the pet may move with or without a leash (if possible), and always on a non-slippery surface. Pattern recognition of gait abnormalities is a key component of the neuroanatomic diagnosis.

Paresis

Paresis refers to an inability to support weight or a deficiency in the ability to generate a gait. In neurologic patients, paresis may result from a lesion in the lower motor neuron (LMN)/neuromuscular system, the upper motor neuron (UMN) system, or both.

Animals with "LMN paresis" manifest a wide variation in their ability to support weight. Thoracic or pelvic limbs (or both sets of limbs with diffuse LMN disease) may be affected. A dog with a mild to moderate NMD may be ambulatory with a "short and choppy" stilted gait (Videos 259-1 and 259-41), whereas a patient with a severe NMD actually may be tetraplegic. Some ambulatory pets with LMN disease advance both pelvic limbs simultaneously, but this also may occur with orthopedic and spinal cord disorders.

Animals with "UMN paresis" also may have considerable variation in their ability to generate a gait. Depending on the location of a spinal cord or mid-to-caudal brainstem lesion, thoracic and/or pelvic limbs may be affected with UMN signs. Ambulatory pets with UMN paresis walk with a long-strided, spastic gait that is typically accompanied by *general proprioceptive (GP) ataxia* (Videos 259-2 and 259-39). The latter occurs because the majority of the key UMN pathways (reticulospinal and rubrospinal tracts) that function in gait generation are anatomically adjacent to GP pathways (spinocerebellar tracts and conscious proprioceptive pathways). Spinal cord and mid- to caudal brainstem lesions disrupt descending UMN pathways and ascending GP pathways, resulting in variable degrees of paresis and ataxia.

Some clinicians utilize a grading scheme for spinal cord lesions to help prognosticate and monitor treatment response. Such grading schemes evaluate the gait with respect to strength and proprioception. Grading schemes typically are on a 0 to 5 scale but are somewhat inconsistent; some utilize grade 0 as normal, whereas others are reversed (e.g., grade 5 is normal). If a grading scheme is utilized, clinicians should qualify the grade with descriptors of strength, proprioception, and nociception (in recumbent pets) to avoid confusion. For spinal cord lesions, the degree of dysfunction recently has been classified using a modified Frankel score.[2,3]

Grade 0: tetraplegia or paraplegia with no deep nociception
Grade 1: tetraplegia or paraplegia with no superficial nociception
Grade 2: tetraplegia or paraplegia with nociception
Grade 3: nonambulatory tetraparesis or paraparesis
Grade 4: ambulatory tetraparesis or paraparesis and GP ataxia
Grade 5: spinal hyperesthesia only (grade 5) or no dysfunction

Ataxia

Three clinical forms of ataxia (incoordination) exist: (1) GP ataxia, (2) vestibular ataxia, and (3) cerebellar ataxia.

GP ataxia previously was mentioned in relation to UMN paresis because the two typically occur simultaneously. GP ataxia results from disruption of the ascending long tracts that relay the spatial location and the degree of muscle contraction of the limbs, trunk, and neck. When ascending GP information fails to

reach the brain, incoordination results. This incoordination may include crossing the limbs, scuffing or dragging of the digits, standing or landing on the dorsal aspect of the paws, and sometimes a delay in the swing phase of the gait. Together with the UMN signs, this produces a relatively characteristic gait that reflects both UMN paresis and GP ataxia (see Videos 259-2 and 259-39).

Vestibular ataxia results from a loss of orientation of the head with respect to the eyes, neck, limbs, and trunk. Pets with vestibular disease may lose their balance and have a tendency to drift, lean, or fall in one direction (Video 259-3). A head tilt and abnormal nystagmus commonly accompany vestibular ataxia (Video 259-28). With peripheral vestibular lesions, pets maintain normal strength and proprioception, but with central vestibular lesions, UMN tetraparesis and GP deficits typically are present (Video 259-34).

Cerebellar ataxia is characterized by a hypermetric gait with sudden bursts of motor activity (Video 259-4). Cerebellar hypermetria may be differentiated from a UMN gait by a marked *overflexion* of the limbs on protraction; occasionally, this differentiation is challenging. Because of the close connection between cerebellum and vestibular systems, a head tilt, loss of balance, and abnormal nystagmus may be seen with cerebellar lesions (Video 259-35).

Postural Reactions

Following the gait observation, postural reactions should be evaluated to identify subtle deficits of strength and coordination. A pet's ability to perform postural reactions requires that all major sensory (GP) and motor (UMN and LMN) components of the central nervous system (CNS) and peripheral nervous system (PNS) be intact. Although many clinicians use postural reactions to assess conscious proprioception, or "CP," this is a misnomer because all postural reactions rely on both the motor and proprioceptive systems. Furthermore, when assessing postural reactions, both the conscious and unconscious sensory pathways are tested; deficiencies in these two key components of GP cannot be separated practically.[1]

The clinician should be cautious when interpreting postural reaction deficits because they are not of localizing value when performed without other components of the neurologic examination (Figure 259-1). For example, a recumbent dog or cat with a severe and diffuse NMD *or* one with a severe cervical spinal cord lesion may have delayed (to absent) postural reactions in all four limbs. Close assessment of spinal reflexes, as well as muscle mass and tone, is necessary to differentiate between these two localizations. Another example would be that of a patient with unilateral postural reaction deficits, which has several possible localizations including a unilateral lesion of the prosencephalon (cerebrum and/or thalamus), brainstem, or spinal cord. Unilateral prosencephalic lesions typically result in *contralateral* postural reaction deficits with a normal gait (and potentially accompanied by a contralateral menace deficit, contralateral sensory deficits, and changes in sensorium) (Video 259-33). Unilateral (caudal) brainstem or spinal cord lesions cause *ipsilateral* postural reaction deficits. The presence of cranial nerve abnormalities and/or changes in sensorium may help to differentiate between the two localizations and suggest brainstem dysfunction.

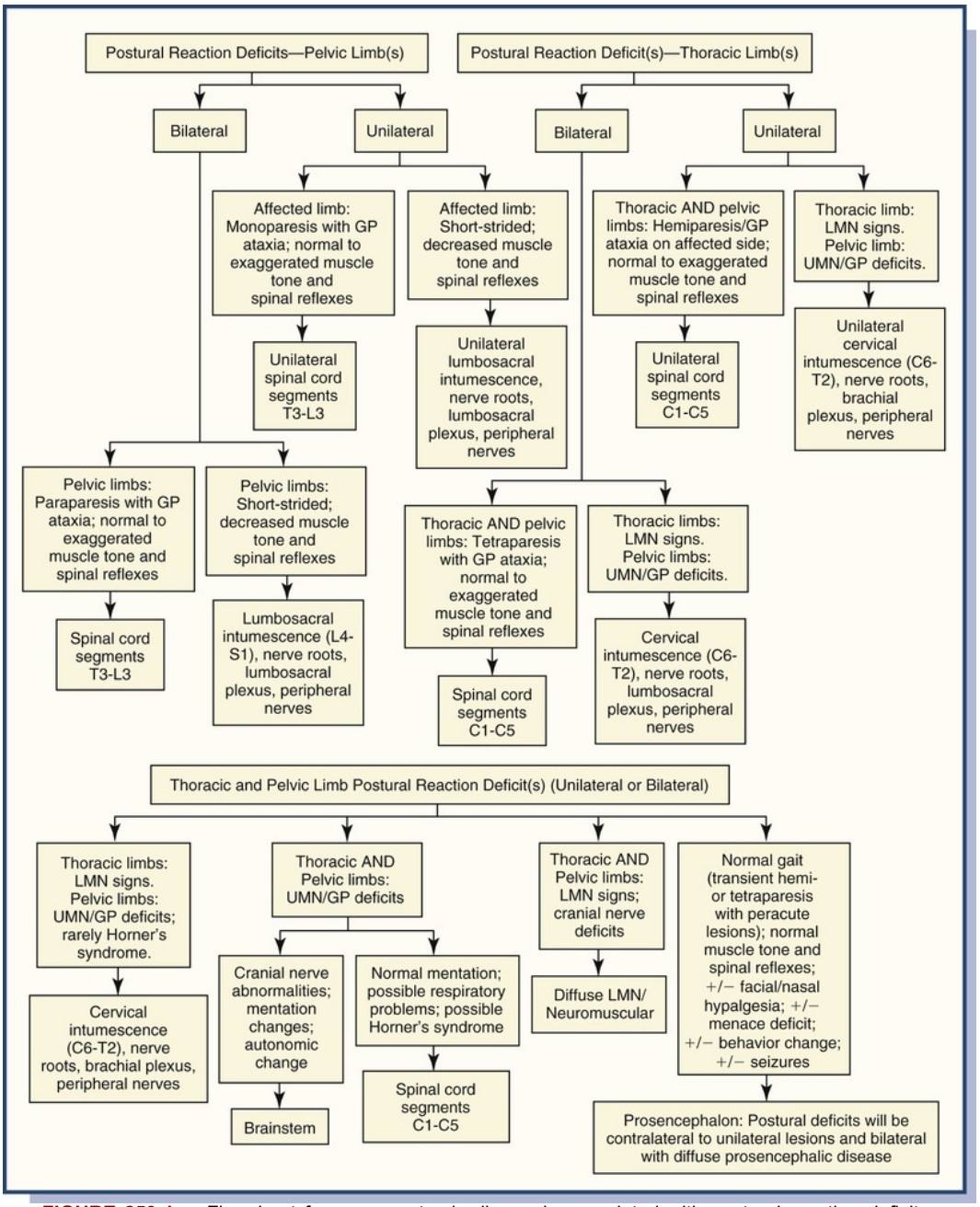

FIGURE 259-1 Flowsheet for neuroanatomic diagnosis associated with postural reaction deficits. *GP,* General proprioceptive; *LMN,* upper motor neuron; *UMN,* upper motor neuron.

In recumbent patients, postural reaction testing may help to differentiate between UMN and LMN tetraparesis. A dog with "pure" LMN disease that maintains some voluntary movement should have relatively normal postural reactions (if most of the body weight is supported) (see Video 259-41). This is because the GP system is unaffected by pure LMN disease. Conversely, a recumbent pet with a brainstem or spinal cord lesion will have delayed to absent postural reactions in all four limbs.

Hopping and placing responses are the most useful postural reactions (Videos 259-5, 259-6, and 259-7). However, additional testing (e.g., wheelbarrowing, extensor postural thrust) may prove useful when these responses are equivocal.

Postural Reaction Tests

Hopping

While supporting the pelvic limbs, the pet should be hopped on one thoracic limb while the other thoracic

limb is held off the ground. The pet should be moved laterally. Limb strength and coordination should be observed in comparison with one another (see Video 259-5). The clinician should observe the lateral aspect of the thoracic limb being tested; the limb should move as soon as the shoulder is moved laterally over the paw. Any delay, irregularity, or exaggeration in this response is abnormal. Delayed hopping (symmetric or asymmetric) may occur with a motor (UMN or LMN) or sensory (GP) lesions. Commonly, both the UMN and GP systems (e.g., brainstem and spinal cord diseases) are affected simultaneously and the abnormal hopping response is a reflection of both (e.g., UMN/GP deficits). Lesions in the GP system or cerebellum may produce exaggerated responses (see Video 259-6).

Hopping responses in the pelvic limbs should be evaluated similarly. While supporting the chest and thoracic limbs, one pelvic limb should be held up and the dog or cat hopped laterally on the supporting limb. The pelvic limb hopping responses should be compared with one another (not to thoracic limbs) (see Video 259-6). Typically, pelvic limb hopping responses are more spastic, with a slightly larger excursion than the thoracic limbs.

Paw Replacement, Tactile Placing Responses

Paw replacement responses assess whether the dog or cat corrects its paw position after it has been flexed so that weight is borne on its dorsal surface (see Video 259-7). Normal pets quickly return their paw to the normal anatomic position. Paw replacement responses should be performed on both thoracic and pelvic limbs individually. The clinician should support most of the pet's weight during the test. Although some clinicians attribute a delay in paw replacement response to diminished CP (e.g., "CP deficit"), this is a misinterpretation of the test for three reasons: (1) A severely paretic animal with a pure LMN disease (e.g., myasthenia gravis) may have delayed (or even absent) paw replacement, despite having no lesion in the CP system (e.g., the dog may be too weak to return its paw to the normal anatomical position); (2) paw replacement responses do *not* isolate the CP pathways from the other afferent sensory pathways (e.g., spinocerebellar tracts) of the PNS and CNS; and (3) rarely (and inexplicably!) some pets without neurologic disease have delayed paw replacement responses.

Tactile placing responses typically are performed in cats or small dogs. The pet should be supported off the ground and its thoracic limbs should be brought to the edge of a table so that the dorsal surface of the paws makes contact (Video 259-8). The pet should step quickly onto the table with the correct anatomic position. The test should be performed on the thoracic limbs simultaneously and individually. It may help to cover the pet's eyes because vision may compensate for sense of position when the GP system is abnormal.

Extensor Postural Thrust

Although this test is performed only occasionally, it may be helpful in patients with subtle pelvic limb signs. The pet should be held off the ground and supported caudal to the scapulae, lowered to the ground, and allowed to extend its pelvic limbs to support its weight. Moving the pet forward and backward tests symmetry of pelvic limb strength and coordination (Video 259-9).

Hemiwalking

This postural reaction is not performed routinely but it may be useful in large dogs. On one side of the body, the thoracic and pelvic limbs should be held off the ground and the dog then forced to walk forward or to the side. Healthy dogs hop smoothly on both thoracic and pelvic limbs (Video 259-10).

Wheelbarrowing

This postural reaction also is performed rarely, but it may be helpful in patients with subtle thoracic limb deficits. The pet should be supported under the abdomen so that the pelvic limbs are held off the ground and then walked on its thoracic limbs (Video 259-11). With this posture, vision is compromised and the animal relies heavily on GP. With the head extended in normal position, dogs and cats should walk with symmetric movements of both thoracic limbs. With severe lesions, patients may carry their head flexed with the nose oriented close to the ground for support.

Muscle Mass, Tone, Spinal Reflexes, and Cutaneous Sensation

Muscle mass and tone, spinal reflexes, and cutaneous sensation should be evaluated when a dog or cat is relaxed, preferably in lateral recumbency. It is helpful to evaluate responses to noxious stimuli last, to maintain cooperation.

Muscle Mass and Tone

The head, neck, and thoracolumbar epaxial muscles should be evaluated for symmetry and any evidence of atrophy. Each thoracic and pelvic limb should be assessed similarly, from proximal to distal. Muscle tone should be evaluated by passive range of motion of each limb. Degree of resistance should be assessed as normal, hypotonic, or hypertonic/spastic. Degree of hypertonicity/spasticity may vary from mild to marked, with the latter occasionally associated with a "clasp knife" response ("clasp knife" refers to attempts made to flex the limb that actually *increase* the degree of extension of the limb until it suddenly gives way to complete flexion without resistance).

Hypertonia or spasticity typically results from lesions in the UMN pathways (although it also may be seen with myotonic disorders) (Videos 259-12 and 259-15). The UMN normally influences activity of the LMN to facilitate voluntary motor activity and to maintain muscle tone, supporting the body against gravity. Lesions disrupting the UMN pathways may "release" the LMNs from inhibition, leading to overactivity of the facilitatory mechanism (see ch. 258).

Conversely, hypotonia is associated with LMN/neuromuscular disease (Video 259-13). The functional integrity of the complete "LMN unit" (cell body, nerve root, peripheral nerve, neuromuscular junction, and muscle) is necessary to produce muscle cell contraction and to effectively maintain muscle tone. When the LMN unit is diseased, one consequence is a loss of muscle tone. With LMN disease, denervation also may lead to muscle cell degeneration and neurogenic atrophy may be appreciable.

Tetraplegic dogs should be supported in a standing position, and the clinician should evaluate limb muscle tone and voluntary responses. Dogs with cervical spinal cord disease often have hypertonic limbs while the trunk and limbs may feel spastic. Occasionally, the hypertonia associated with cervical spinal cord disease is so profound that the pet can maintain a standing position even when unsupported. Conversely, tetraplegic dogs with diffuse LMN/neuromuscular disease typically are hypotonic (or atonic) and collapse when the clinician attempts to support them in a standing position. It is critical to differentiate between UMN and LMN tetraplegia because the differential diagnoses are markedly different, as are diagnostics, management, and treatment recommendations.

Spinal Reflexes

Although most neurology textbooks describe numerous tendon and muscle reflexes, the majority are of limited use because they are not present in all normal small animals. The most reliable reflexes are the patellar reflex and withdrawal-flexor reflexes described later. The other spinal reflexes are considered briefly.

Patellar Reflex

The most reliable tendon reflex is the patellar reflex, which is mediated by the femoral nerve through spinal cord segments L4-L7. With the limb held in partial flexion, the clinician should elicit this reflex by lightly tapping the patellar tendon with a plexor or pediatric hammer (Video 259-14). This reflex should be tested with the pet in *both* lateral recumbencies. For inexplicable reasons, this reflex commonly is elicited more easily in the limb adjacent to the floor. It is noteworthy that one or both patellar reflexes may be absent in older dogs with no other neurologic signs.[4] Responses are typically graded as absent (0), hyporeflexive (+1), normal (+2), hyperreflexive (+3), or clonic (+4). An absent or hyporeflexive reflex occurs when there is a disease of a portion of the reflex arc (most commonly in the LMN unit). Hyperreflexia or clonus may be present in UMN diseases (see Video 259-15).

Biceps and Triceps Reflexes

In the thoracic limb, the biceps and triceps reflexes often can be elicited in relaxed pets that are in lateral recumbency. The clinician should place a finger on and tap the distal ends of both biceps and brachialis muscles at the level of the elbow. A normal response is slight flexion of the elbow. The musculocutaneous nerve mediates the biceps reflex through spinal cord segments C6-C8. The triceps reflex is elicited by lightly tapping the tendon of insertion of the triceps muscle proximal to the olecranon. This causes slight extension of the elbow. The radial nerve mediates the triceps reflex through spinal cord segments C7-T2.

Withdrawal-Flexor Reflexes—Thoracic and Pelvic Limbs

Withdrawal-flexor reflexes assess the integrity of the thoracic and pelvic limb withdrawal reflex arcs. They are elicited by applying pressure to the base of the toenail with a firm, manual pinch or with hemostats (Videos 259-16 and 259-17). A normal response is an immediate, strong withdrawal of the limb with complete

flexion of all joints. Animals with reduced withdrawal-flexor reflexes occasionally extend or kick the limb in response to the noxious stimulus (Videos 259-18 and 259-19). In the thoracic limb, the thoracodorsal, axillary, musculocutaneous, median, ulnar, and radial nerves are responsible for flexion of the shoulder, elbow, carpus, and digits. The nerves responsible for this reflex arise from spinal cord segments C6-T2. The specific sensory nerve stimulated depends on the location of the noxious stimulus. The median and ulnar nerves innervate the skin of the palmar surface of the paw; the radial nerve innervates the dorsal surface and the cranial and lateral surfaces of the antebrachium. The ulnar and musculocutaneous nerves innervate the caudal and medial surfaces, respectively. One must be cautious not to overinterpret the autonomous zones because there is some overlap of the cutaneous innervation supplied by these nerves and a degree of individual patient variation.

Deficiencies in the thoracic limb withdrawal-flexor reflex (see Videos 259-18, 259-39, 259-41, and 259-42) suggest a C6-T2 lesion (spinal cord segments, nerve roots, brachial plexus, peripheral nerves) or potentially a more diffuse LMN/NMD (the latter would be accompanied by reduced pelvic limb reflexes, reduced tone, and other neuromuscular signs). It has been suggested that dogs with C1-C5 spinal cord lesions may *mislocalize* to C6-T2 because of reduced withdrawal reflexes that may be present in the thoracic limbs.[5] The explanation for this phenomenon is unclear.

In the pelvic limb, the withdrawal-flexor reflex is mediated by the sciatic nerve through spinal cord segments L6-S1. Lesions of the motor component of the sciatic nerve (distal to the pelvis) may result in hypotonia, atrophy, and paralysis of the flexors of the stifle, tarsus, and digits, as well as of the extensors of the hip, tarsus, and digits. With sciatic lesions, pelvic limb withdrawal-flexor reflexes will be reduced to absent (see Video 259-19). Dogs and cats can walk with sciatic nerve paralysis, but the tarsus is typically "dropped," or closer to the ground than normal, on the affected side (tibial dysfunction) and the paw is often misplaced on the dorsal surface (peroneal dysfunction); however, the limb can support weight if the femoral nerve is intact.

Sensory branches of the peroneal and tibial nerves innervate the dorsal and plantar surfaces of the pelvic limb paw, respectively. The saphenous nerve (branch of the femoral entering the spinal cord at L4-L6) innervates the medial aspect. Therefore, animals with a severely contused sciatic nerve typically maintain sensation to the medial aspect of the paw. If the medial surface of the paw is stimulated in a pet with a pure sciatic injury, the animal will flex the hip because of intact innervation of the iliopsoas muscle, but the stifle, tarsus, and digits will *not* flex. Therefore, both the medial and lateral surfaces of the pelvic limb paw should be tested for the withdrawal-flexor reflex and also for nociception (see later).

Crossed Extensor Reflex

Recumbent pets with lesions of the UMN pathways may have a crossed extensor reflex when the withdrawal-flexor reflex is evaluated. Reflex extension may occur in the opposite limb to that being tested. Although typically abnormal and indicative of UMN disease, normal dogs occasionally have crossed extensor reflexes. To avoid voluntary extension of the contralateral limb as a response to the noxious stimulus, the withdrawal-flexor reflex should be elicited with a *mild* pinch while the opposite limb is observed.

Perineal Reflex

The perineal reflex is elicited by stimulation of the anus with a mild, noxious stimulus. The anal sphincter and tail should be observed for contraction and flexion, respectively. The perineal reflex is mediated by branches of the sacral and caudal segments of the spinal cord through the pudendal nerve.

Cutaneous Trunci Reflex

This reflex is observed as a contraction of the cutaneous trunci muscle in response to mild stimulation of the dorsal skin of the trunk. It can be elicited from the thoracic and most of the lumbar region. Regional segmental spinal nerves carry sensory impulses (Video 259-20) into the spinal cord, where they are relayed cranially to spinal cord segment C8. At this level, a synapse occurs on the LMNs of *both* lateral thoracic nerves that innervate the cutaneous trunci muscle. This reflex may require multiple attempts to elicit; rarely, normal dogs and cats manifest no reflex. This reflex may be particularly useful in diagnosing the level of a transverse thoracolumbar spinal cord lesion or for monitoring a progressive spinal cord injury (e.g., ascending or descending myelomalacia). Typically, the reflex is preserved for one to two vertebral bodies caudal to the level of the spinal cord lesion.

Nociception (Pain Perception)

In recumbent animals, the clinician may apply a noxious stimulus to a digit (Video 259-21). This generates afferent impulses that enter the spinal cord via peripheral nerves and associated dorsal nerve roots that are relayed to bilateral tracts in the lateral funiculi of the spinal cord. These tracts ascend the spinal cord and continue through the medulla, pons, and midbrain to specific nuclei in the thalamus for relay to somatic sensory areas of the cerebral cortex. A positive response is evidenced by vocalization, turning of the head, or dilation of the pupils when the impulses reach the thalamus or cerebrum.

Although several grading schemes for spinal cord injury differentiate between superficial and deep pain perception, this can be extremely challenging and is not typically necessary. However, it is *critical* to differentiate nociception from the withdrawal component of the withdrawal-flexor reflex (see earlier). *Animals with transverse spinal cord lesions maintain the withdrawal reflex and this should* ***not*** *be mistaken for intact nociception*.

Cranial Nerves

It is important to develop a systematic method for evaluation of the cranial nerves. This component of the neurologic examination is ideally performed with a dog or cat that is cooperative. This section offers a stepwise approach for evaluation of the cranial nerves by assessment of (1) vision and pupillary light responses (PLRs), (2) palpebral fissure and third eyelid symmetry, (3) eyeball position and movement, (4) vestibular function, (5) facial and trigeminal function, and (6) tongue and laryngeal-pharyngeal function. The clinical signs associated with cranial nerve dysfunction are summarized in Table 259-1.

TABLE 259-1

Function, Testing, and Clinical Signs Associated with Cranial Nerve Dysfunction

CRANIAL NERVE	FUNCTION	TEST	CLINICAL SIGNS OF DYSFUNCTION
CN I Olfactory	Smell	Not routinely tested	Anosmia; hyposmia
CN II Optic	Vision; response to light	Menace response; PLR; obstacle course; tracking moving objects	Blindness; dilated or unresponsive pupils
CN III Oculomotor	Motor to extraocular muscles; parasympathetic to pupil	Physiologic nystagmus; resting eyeball position; pupillary light responses	Ventrolateral strabismus; ptosis; dilated pupils; diminished to absent PLRs
CN IV Trochlear	Motor to dorsal oblique muscle	Resting eyeball position (cat); fundic examination (dog)	Dorsomedial strabismus (cat); lateral deviation of retinal vein (dog)
CN V Trigeminal	Motor to muscles of mastication (mandibular); sensory to face (ophthalmic and maxillary)	Jaw tone; muscle bulk; sensation to face, cornea, and nasal mucosa	Masticatory muscle atrophy; dropped jaw if bilateral; decreased or absent facial/nasal sensation
CN VI Abducent	Motor to lateral rectus and retractor bulbi	Physiologic nystagmus; resting eyeball position	Medial strabismus
CN VII Facial	Motor to muscles of facial expression; parasympathetic to lacrimal glands; sensory (taste) to rostral tongue	Menace response; palpebral reflex; lip retraction; ear movement; Schirmer tear test	Inability to close eyelid, move ear, or retract lip; hemifacial tetany; deviation of nasal philtrum (contralateral); dry eye
CN VIII Vestibulocochlear	Balance; hearing	Body and head posture; gait; eye movement and position; hearing	Head tilt; vestibular ataxia; nystagmus; positional strabismus; deafness
CN IX Glossopharyngeal	Sensory and motor to pharynx	Gag reflex; ability to swallow	Diminished gag reflex; dysphagia
CN X Vagus	Sensory and motor to pharynx, larynx, and viscera	Gag reflex; oculocardiac reflex	Diminished gag reflex; dysphagia; laryngeal paralysis; megaesophagus

CN XI Accessory	Motor to trapezius	Evaluation of muscle mass	Atrophy of trapezius
CN XII Hypoglossal	Motor to tongue muscles	Evaluation of tongue	Atrophy of tongue; inability to retract tongue if bilateral

PLR, Pupillary light response.

Vision and Pupillary Light Responses (II, III, VII)

The menace response is the most reliable test for vision assessment in animals. It is a learned response that may not be present until 10 to 12 weeks of age in puppies and kittens (tracking of moving objects may be helpful in such young animals). The menace response requires a functional optic nerve, optic tract (diencephalon), and optic radiation up to the occipital cortex, as well as the efferent pathway that includes the facial neurons. Although the exact mechanism is unknown, a functional cerebellum also is required for the menace response.[1] The majority of the visual pathway caudal to the optic chiasm is contralateral to the eye being tested. With one pet eye covered, the clinician should make a menacing gesture toward the open eye (with careful attention not to touch or stimulate the pet with air currents!) (Video 259-22).

A normal menace response is manifested as complete eyelid closure. Eyelid closure is dependent on normal facial nerve innervation of the orbicularis oculi muscle. If the menace is absent or delayed, the eyelids must be assessed for their ability to close by eliciting the palpebral reflex (Video 259-23). If facial paralysis is present, eyeball retraction, elevation of the third eyelid, and head retraction may help in the assessment of vision (Video 259-29). Alternatively, the patient's ability to navigate an obstacle course can be evaluated.

Following the menace responses, the clinician should evaluate pupil size and PLRs (Video 259-24). Pupils should be assessed for symmetry in ambient light and a dark room. A bright light source should then be directed into each eye individually (Video 259-25). Normal pets have rapid constriction of the pupil into which the light is directed (direct PLR) and the opposite pupil also should constrict (indirect or consensual PLR). The indirect response occurs because the majority of the optic nerve fibers cross at the optic chiasm and again at the level of the pretectal nucleus, stimulating the parasympathetic oculomotor nuclei bilaterally.

In addition to optic and oculomotor nerve lesions, there are several possible localizations for PLR deficits (Table 259-2). If a direct PLR is not elicited in one eye, the clinician should direct the light as close to that eye as possible and move the light to all aspects of the ocular fundus. If no response is present, the clinician should swing the light to the responsive pupil and the nonresponsive pupil should be assessed for constriction. If nonresponse is the result of an ocular or optic nerve lesion, it will constrict when light is directed into the contralateral eye (e.g., positive indirect PLR). Such testing may need to be repeated multiple times to differentiate between an ocular/optic and oculomotor nerve problem.

TABLE 259-2

Lesion Locations (Right-Sided Lesions Only, as an Example) and Associated Resting Pupil Size, Pupillary Light Responses (PLRs), and Menace Responses

	LESION LOCATION				
RESTING PUPIL SIZE, PLRs, MENACE	**RIGHT CN II *(OPTIC NERVE)***	**RIGHT CN III *(OCULOMOTOR NERVE)***	**RIGHT RETROBULBAR**	**RIGHT OPTIC TRACT *(THALAMUS)***	**RIGHT OCCIPITAL CORTEX**
Left Pupil					
Resting size	Normal size	Normal size	Normal size	Normal size	Normal size
PLRs	Light in left eye, both pupils constrict	Light in left eye, only left pupil constricts	Light in left eye, only left pupil constricts	Light in left eye, both pupils constrict	Light in left eye, both pupils constrict
Left menace	Positive	Positive	Positive	Severe deficit	Severe deficit
Right Pupil					
Resting size	Normal to partial dilation	Complete dilation	Complete dilation	Normal size	Normal size

PLRs	Light in right eye, neither pupil constricts	Light in right eye, only left pupil constricts	Light in right eye, neither pupil constricts	Light in right eye, both pupils constrict	Light in right eye, both pupils constrict
Right menace	Negative	Positive	Negative	Mild deficit	Mild deficit

Palpebral Fissure and Third Eyelid Symmetry (III, V, Sympathetic Nerves)

The clinician should observe the palpebral fissures for size and symmetry. A reduced fissure size (ptosis) may be due to dysfunction of cranial nerve III (oculomotor) with secondary paresis of the levator palpebrae superioris muscle, dysfunction of cranial nerve V (mandibular branch of trigeminal nerve) with secondary atrophy of the masticatory muscles (Video 259-26), or sympathetic dysfunction with loss of orbitalis smooth muscle tone. Atrophy of the masticatory muscles or sympathetic dysfunction both may result in third eyelid elevation.

Eyeball Position and Movement (III, IV, VI, VIII)

While examining the head, the clinician should assess whether or not each eye is in a central position within the orbit, which requires normal function of the peripheral and central components of the vestibular system; cranial nerves III (oculomotor), IV (trochlear), and VI (abducent); and the extraocular muscles that they innervate. Ventrolateral strabismus is associated with oculomotor nerve dysfunction, a medial strabismus with abducent nerve dysfunction, and eyeball extorsion with trochlear nerve dysfunction. Trochlear dysfunction in cats causes a lateral rotation of the dorsal aspect of the pupil, which cannot be recognized on external ocular examination in dogs because their pupils are round. In dogs, fundic examination is required and would show lateral deviation of the retinal vein.

Vestibular Function (VIII)

Physiologic nystagmus (oculocephalic or oculovestibular responses) is evaluated by moving the head in a horizontal plane from side to side (Video 259-27). This stimulates cranial nerve VIII to relay impulses to the brainstem, on to the vestibular nuclei and the medial longitudinal fasciculus, and finally to abducent and oculomotor neurons for abduction and adduction of the eyeball, respectively.

Strabismus and nystagmus commonly are associated with dysfunction of the vestibular system. A positional, ventrolateral strabismus commonly is associated with vestibular disease. Nystagmus is an involuntary oscillation of the eyeball (see Video 259-28). Resting or spontaneous nystagmus is continual and observed when the head is in any position, whereas positional nystagmus is seen only when the head is held in certain positions. The latter often is seen in patients that have accommodated for lesions in the vestibular system. Occasionally, positional nystagmus can be elicited in compensated patients placed on their backs with their head and neck extended. Utility of nystagmus for vestibular lesion localization is reviewed in the Neuroanatomic Diagnosis section of this chapter.

Facial and Trigeminal Nerve Function (V, VII)

The clinician should evaluate the palpebral reflex by gently touching the medial and lateral canthi of the eye (see Videos 259-23 and 259-29). A normal response is an immediate, complete closure of the palpebral fissure. Sensory branches (ophthalmic—medially, maxillary—laterally) of the trigeminal nerve mediate the afferent arm of the palpebral reflex, and the palpebral branch of the facial nerve mediates the efferent motor arm. The clinician also should assess the symmetry of the face. A lip or ear droop (see Video 259-29) or unilateral salivation suggests facial nerve dysfunction. Occasionally, the nasal philtrum will be deviated toward overstimulated facial muscles due to facial tetany.

To evaluate the mandibular branch of the trigeminal nerve, the clinician should evaluate the temporalis and masseter muscles for size and symmetry. With unilateral mandibular nerve dysfunction (e.g., trigeminal nerve sheath neoplasm), no loss of jaw function will be appreciable but profound muscle atrophy may be present (see Video 259-26). With bilateral mandibular nerve dysfunction (e.g., idiopathic trigeminal neuritis), the patient may have a dropped jaw and drool excessively (Video 259-30). Mandibular paralysis may be accompanied by facial hypalgesia depending on the extent of involvement of the ophthalmic and maxillary sensory nerves.

Trigeminal sensory function is most easily evaluated by testing nasal sensation. The clinician should gently touch the medial aspect of the nasal mucosa with the tip of a pen or closed hemostats (Video 259-31).

Normal patients will quickly pull their head away (stoic patients occasionally will not object). This test evaluates two neural pathways. First, it tests the ipsilateral branch of the ophthalmic nerve that innervates the nasal mucosa. It also tests the nociceptive pathways that project to the contralateral thalamus and somesthetic cerebral cortex. Therefore, nasal hypalgesia must be interpreted in light of the remainder of the neurological examination. It may indicate an *ipsilateral* trigeminal nerve lesion or a *contralateral* prosencephalic lesion (see Video 259-33).

Tongue and Laryngeal-Pharyngeal Function (IX, X, XII)

The clinician may use the "gag-reflex" to simultaneously evaluate the glossopharyngeal, vagus, and hypoglossal cranial nerves. Upon opening the patient's mouth, the tongue first should be evaluated for atrophy and movement to assess hypoglossal function. Depending on patient cooperation, the clinician then may insert a finger through the oral cavity into the oropharynx and laryngopharynx. The muscle tone and gag should be evaluated to assess pharyngeal branches of glossopharyngeal and vagal nerves. Clinical utility of this test is limited due to the variability in normal responses. Dysphagia (see ch. 38 and 273) is a more reliable indicator of cranial nerve IX and X dysfunction.

Neuroanatomic Diagnosis

After performing the complete neurologic examination, the clinician should attempt to make a neuroanatomic diagnosis to one of five major regions of the nervous system: (1) prosencephalon (cerebrum and/or thalamus); (2) mid- to caudal brainstem (midbrain, medulla, pons); (3) cerebellum; (4) spinal cord; and (5) LMN/neuromuscular system. Neurologic signs associated with lesions in each of these regions are tabulated (Tables 259-3 through 259-6); key neurologic deficits and examination patterns are expanded for each region.

TABLE 259-3

Neurologic Signs That May Be Associated with Prosencephalic Disease

NEUROLOGIC TEST	POSSIBLE ABNORMALITIES
Sensorium/behavior	Seizures; abnormal behavior; propulsive activity; depression to coma
Posture/gait	Head turn, ***normal gait*** (unless peracute lesion); propulsive circling (usually ipsilateral to lesion) or pacing; aimless wandering; head pressing; movement disorders (rare)
Postural reactions	*Contralateral* deficits
Muscle mass/tone	Normal
Spinal reflexes	Normal
Cutaneous sensation	*Contralateral* (often facial/nasal) hypalgesia
Cranial nerves	*Contralateral* menace deficits with normal (optic radiation and occipital cortex) or abnormal (optic chiasm, optic tracts) PLRs; facial; tongue or pharyngeal weakness (rare)
Other	Abnormalities in thirst, appetite, thermoregulation

PLRs, Pupillary light responses.

TABLE 259-4

Neurologic Signs That May Be Associated with Mid- to Caudal Brainstem Disease

NEUROLOGIC TEST	POSSIBLE ABNORMALITIES
Sensorium/behavior	Depression—coma
Posture/gait	UMN tetraparesis (or tetraplegia) and GP deficits; vestibular ataxia (pontine or medullary lesions); opisthotonus (midbrain lesions)

Postural reactions	Ipsilateral deficits (pons and medulla), contralateral deficits (rostral midbrain)
Muscle mass/tone	Normal to increased (all four limbs)
Spinal reflexes	Normal to increased (all four limbs)
Cutaneous sensation	Hypalgesia of trunk and limbs may be present (rare)
Cranial nerves	Anisocoria (III, sympathetics); dropped jaw (V bilateral); atrophy of muscles of mastication (V); facial hypalgesia (V); head tilt (VIII); resting or positional nystagmus (VIII); abnormal physiologic nystagmus (III, IV, VI, VIII); resting or positional strabismus (III, IV, VI, VIII); facial paresis or paralysis (VII); dysphagia (IX, X); tongue paresis or paralysis (XII)
Other	Respiratory or cardiac abnormalities

GP, General proprioceptive; *UMN,* upper motor neuron.

TABLE 259-5

Neurologic Signs That May Be Associated with Cerebellar Disease

NEUROLOGIC TEST	POSSIBLE ABNORMALITIES
Sensorium/behavior	Unaffected
Posture/gait	Intention tremor of head, neck or eyes; opisthotonus and extensory rigidity of all limbs with hips flexed (severe, rostral lesions); truncal sway; head tilt; hypermetric/spastic gait with *strength preserved;* loss of balance
Postural reactions	Delayed and then exaggerated in all limbs with diffuse disease or in ipsilateral limb with unilateral lesions
Muscle mass/tone	Muscle tone may be exaggerated
Spinal reflexes	Normal to exaggerated
Cutaneous sensation	Unaffected
Cranial nerves	Menace deficit (ipsilateral); anisocoria (rare)

TABLE 259-6

Thoracic and Pelvic Limb Signs Associated with Spinal Cord Lesions

LESION LOCATION	THORACIC LIMBS	PELVIC LIMBS	SEVERE LESIONS
C1-C5	UMN paresis; GP deficits; normal withdrawal reflexes* and muscle tone	UMN paresis; GP deficits; normal to exaggerated spinal reflexes and muscle tone	Spastic tetraplegia; potential respiratory complications; UMN Horner's syndrome
C6-T2	LMN paresis (short and choppy gait); reduced withdrawal reflexes and muscle tone	UMN paresis; GP deficits; long-strided gait; normal to exaggerated spinal reflexes and muscle tone	Flaccid LMN paralysis in thoracic limbs, spastic paraplegia in pelvic limbs; potential respiratory complications; Horner's syndrome (T1-T3)
T3-L3	Normal	UMN paresis; GP deficits; long-strided gait; normal to exaggerated spinal reflexes and muscle tone	Spastic paraplegia; Schiff-Sherrington may occur in thoracic limbs; possible paradoxical LMN signs (spinal shock) in pelvic limbs
L4-S3	Normal	LMN paresis (short and choppy gait); GP deficits (white matter); reduced patellar reflexes (L4-L6) or withdrawal reflexes (L6-S1)	Flaccid paraplegia in pelvic limbs that may include flaccid anus and tail with reduced to absent sensation of perineum

*C1-C5 lesions may be associated with reduced thoracic limb withdrawal reflexes.[5]

GP, General proprioceptive; *LMN*, lower motor neuron; *UMN*, upper motor neuron.

The clinician initially should attempt to reconcile all neurologic deficits with a single lesion. If a single lesion cannot explain all signs, the neuroanatomic diagnosis is likely to be multifocal or diffuse (see later). After localizing the lesion to one of the five major regions of the CNS or PNS, a more precise localization should be determined (e.g., side of lesion; specific anatomic segments affected: C1-C5, C6-T2, etc.). As mentioned previously, an accurate neuroanatomic diagnosis provides critical information for establishing an appropriate differential diagnosis and for selecting and interpreting neurodiagnostic tests.

Prosencephalon

Although commonly used as an embryologic term to denote the area of brain composed of the telencephalon (cerebral hemispheres) and diencephalon (epithalamus, thalamus, and hypothalamus), this large region is a key neuroanatomic diagnosis. Because of overlap in clinical signs associated with cerebral and thalamic disease, lesions affecting the two areas cannot be reliably differentiated. When neurologic signs suggest cerebro-thalamic ("forebrain") disease, a prosencephalic neuroanatomic diagnosis is made.

Animals with prosencephalic disease often have a history of generalized or partial seizures and/or abnormal behavior (see Table 259-3). Typical behavior changes include depression (due to lesions of the ARAS), lethargy, disorientation, loss of training, increased aggression or docility, irritability, hysterical or maniacal behavior, head pressing, propulsive pacing or circling (Video 259-32). Abnormalities in autonomic and endocrine function (thirst, appetite, temperature, electrolyte and water balance) and sleep patterns also may be present.

Although seizures, behavioral, and autonomic/endocrine changes support a prosencephalic neuroanatomic diagnosis, these abnormalities rarely help to lateralize the lesion to one side of the cerebrum or thalamus. Animals with prosencephalic lesions commonly manifest visual, sensory (facial/nasal hypalgesia), and postural reaction deficits, all contralateral to the side of the lesion (see Video 259-33). Despite having postural reaction deficits (a true "CP" deficit), animals with prosencephalic disease typically have a normal gait (a transient gait deficit may be present with peracute lesions such as a cerebrovascular accident). The gait is normal with prosencephalic lesions because the critical UMNs responsible for gait generation in domestic species (rubrospinal and reticulospinal tracts) are spared, being located more caudally in the midbrain, pons, and medulla.

An unusual phenomenon known as the *adversive (hemi-neglect or hemi-inattention) syndrome* occurs sometimes with unilateral prosencephalic lesions. With this syndrome, the pet "ignores" all sensory input perceived from its environment that is contralateral to the prosencephalic lesion. The pet may circle propulsively or eat out of one side of a bowl (ipsilateral to the lesion). Table 259-3 summarizes the potential clinical signs associated with prosencephalic disease.

Brainstem

The brainstem is ventral to the two cerebral hemispheres and the cerebellum. Although anatomically the diencephalon is the rostral extent of the brainstem, it is considered part of the prosencephalic localization (above). A neuroanatomic diagnosis of "brainstem" is used to denote lesions that include the midbrain, pons, and medulla oblongata. Functionally, the brainstem contains the paired cranial nerve nuclei, the regulatory centers for consciousness (ARAS) and respiration, and descending motor and ascending sensory pathways. Thus, cranial nerve abnormalities, behavioral changes, loss of key autonomic functions, and a loss of strength and coordination may be present with brainstem disease (see Table 259-4).

The brainstem connects the cerebral hemispheres to the spinal cord via ascending sensory (GP) and descending motor pathways (UMNs). As with C1-C5 spinal cord lesions, UMN tetraparesis (through tetraplegia) and GP deficits may accompany brainstem disease. Because of the presence of vestibular nuclei in the pons and medulla, vestibular ataxia may be present and superimposed upon GP ataxia (see Video 259-34).

Depending on the region of the mid- to caudal brainstem affected, dysfunction of cranial nerves III-XII may be present. The neurologic examination allows for assessment of the diverse motor and sensory functions of the cranial nerves (see Tables 259-1 and 259-4). Lesions affecting the cranial nerves in the caudal brainstem typically cause ipsilateral postural reaction deficits because of their impact on the UMN and GP systems. The presence of cranial nerve abnormalities and normal postural reactions suggests a peripheral (cranial) neuropathy; however, an early or slowly compressive brainstem lesion cannot be excluded. If there is

ambiguity in postural reaction testing, a neurodiagnostic workup should be considered.

Vestibular Disease

A head tilt, vestibular ataxia, nystagmus, and strabismus are seen commonly with vestibular disease (see Videos 259-28, 259-34, and 259-35). However, these neurologic signs rarely help the clinician to differentiate between central and peripheral vestibular disease. The key differentiating feature between central and peripheral vestibular disease is the presence or absence of postural reaction deficits. With vestibular lesions involving the caudal brainstem, ipsilateral postural reaction deficits will be present due to involvement of the UMN/GP pathways (see Video 259-34). Conversely, postural reactions will be normal with peripheral vestibular lesions because there is no involvement of the UMN/GP pathways.

Lesions affecting the peripheral vestibular nerve result in a head tilt that is ipsilateral (lower ear is on the side of the lesion) to the lesion; this is less predictable with brainstem lesions. Although most pets with central vestibular disease have an ipsilateral head tilt, those with brainstem lesions involving the caudal cerebellar peduncle (or flocculonodular lobules of the cerebellum) may manifest a contralateral, or so-called paradoxical head tilt (see Video 259-35).

Resting or positional nystagmus commonly accompany both central and peripheral vestibular disease (see Video 259-28). The direction of nystagmus is defined by the fast phase of the jerk of the eyeball. The plane of rotation may be *rotatory, horizontal,* or *vertical.* Typically, vertical nystagmus is associated with central vestibular lesions (see Video 259-34), whereas rotatory or horizontal nystagmus may be present with *either* central or peripheral lesions. With peripheral vestibular lesions, the fast phase of the nystagmus is away from the lesion; this is not reliable with central disease and may be in either direction. Moreover, the fast phase of nystagmus occasionally changes direction with brainstem lesions.

Additional cranial nerve deficits commonly accompany vestibular disorders. Facial nerve disorders are the most common and may be seen with *both* peripheral and central vestibular disease. Occasionally, Horner's syndrome accompanies peripheral vestibular lesions because the sympathetic fibers pass through the middle ear en route to the orbit. Rarely, a Horner's syndrome may be associated with a brainstem lesion because of involvement of the UMN (hypothalamo-tecto-tegmental) sympathetic pathway; this typically requires a severe brainstem lesion and usually the pet is tetraplegic with marked mentation changes. Sensorium is unaffected with peripheral vestibular lesions, whereas animals with central vestibular disease may be dull to comatose depending on the extent of involvement of the ARAS.

Cerebellum

The cerebellum functions as a *regulator* rather than a primary initiator of motor activity. It functions to coordinate movements in relation to the animal's posture providing synergy of muscular activity. Cerebellar disease produces a unique *dysmetria* characterized by an inability to regulate the rate, range, and force of a movement (see Video 259-4). Although a dog or cat with cerebellar disease may be incapacitated and unable to stand, voluntary movements should be elicited with normal strength.

Ambulatory animals with cerebellar ataxia typically manifest "bursty" hypermetric movements in all ranges of motion. Voluntary movements typically are delayed in onset and, once initiated, exaggerated. When walking, the limbs usually are raised excessively and returned forcefully to the ground with each step. Muscle tone commonly is increased, and spinal reflexes may be normal to exaggerated. Although CP is unaffected with cerebellar disease, postural reactions typically are delayed and exaggerated. When the head of a pet with cerebellar disease is extended and then support is withdrawn suddenly, a *rebound phenomenon* may be present in which the head drops excessively in a ventral direction.

Because of the close connection to the vestibular system, a head tilt (usually paradoxical) and other vestibular signs may accompany cerebellar disease (see Video 259-35). Commonly, a mild *intention tremor* of the head, neck, or eyes is present with cerebellar diseases (Video 259-37). This should not be confused with generalized, whole body tremors that are associated with diffuse CNS disorders (Video 259-38). Finally, it is noteworthy that cerebellar disease may be associated with an ipsilateral (bilateral with diffuse cerebellar disease) menace deficit. Although the cerebellum most commonly is affected diffusely (e.g., cerebellar hypoplasia or abiotrophy), occasionally unilateral or focal cerebellar lesions (cerebellar infarction or neoplasm) produce ipsilateral cerebellar signs (see Videos 259-35 and 259-36). Table 259-5 summarizes the potential clinical signs associated with cerebellar dysfunction.

Spinal Cord

A spinal cord segment is defined as a portion of the spinal cord, which gives rise to one pair of spinal nerves. There are 8 cervical, 13 thoracic, 7 lumbar, 3 sacral, and at least 2 caudal spinal cord segments in dogs and cats. Functionally, the spinal cord can be divided in four neuroanatomic regions: cranial cervical (C1-C5), cervico-thoracic (C6-T2), thoracolumbar (T3-L3), and lumbosacral (L4-S3).

The LMN cell bodies for the thoracic and pelvic limbs are located within the ventral gray matter of the cervico-thoracic (C6-T2) and lumbosacral (L4-S3) intumescences, respectively. The ascending (sensory) and descending (motor) pathways comprise the white matter of the spinal cord and are located more superficially. With rare exceptions, spinal cord lesions predictably result in a sequential loss of general proprioception, motor and bladder function, and nociception. Recovery of function typically occurs in the reverse direction.

As discussed in the gait and posture section, spinal cord lesions typically produce a combination of UMN and GP deficits in the limbs caudal to the level of the lesion (see Videos 259-2 and 259-39). If the spinal cord lesion is in the cervical or lumbar intumescence, it will produce LMN signs in the corresponding thoracic or pelvic limbs. Spinal cord lesions may produce a combination of UMN and LMN signs in thoracic or pelvic limbs (see Video 259-39). For example, a herniated disk at the C6/C7 intervertebral disk space may cause a long-strided thoracic limb gait (UMN sign) but reduced thoracic limb withdrawal reflexes (LMN sign). Ambulatory patients with C6-T2 lesions typically have a disconnected, "two-engine" gait in which the thoracic limbs are "short and choppy" (LMN sign) and pelvic limbs are long strided (UMN sign) with GP ataxia[1] (Video 259-40).

Establishing a neuroanatomic diagnosis to one of the four spinal cord segments typically is straightforward and is based upon four potential combinations of normal, LMN, and UMN signs that may be present in the thoracic and pelvic limbs (Tables 259-7 through 259-10; see Figure 259-1 and Table 259-6). However, there are a few clinical scenarios that may create confusion with T3-L3 spinal cord disease. These situations are considered below.

TABLE 259-7

Neurologic Abnormalities Associated with C1-C5 Spinal Cord Dysfunction

NEUROLOGIC TEST	POSSIBLE ABNORMALITIES
Sensorium/behavior	Normal
Posture/gait	Variable: ranges from UMN tetraparesis/GP ataxia through spastic tetraplegia
Postural reactions	Delayed to absent in all four limbs
Muscle mass/tone	Normal muscle mass (mild atrophy due to disuse in chronic disease), normal to exaggerated muscle tone in all four limbs; possible UMN bladder
Spinal reflexes	Normal to increased in all four limbs, occasionally reduced withdrawal reflexes in thoracic limbs*
Cutaneous sensation	Hypalgesia caudal to a focal lesion (rare)
Cranial nerves	Ipsilateral miosis (rare due to UMN Horner's syndrome)
Other	A focal, severe lesion between these segments may result in death due to respiratory dysfunction

*C1-C5 lesions may be associated with reduced thoracic limb withdrawal reflexes.[5]

GP, General proprioceptive; *UMN*, upper motor neuron.

TABLE 259-8

Neurologic Abnormalities Associated with C6-T2 Spinal Cord Dysfunction

NEUROLOGIC TEST	POSSIBLE ABNORMALITIES
Sensorium/behavior	Normal
Posture/gait	Variable: LMN gait in thoracic limbs, UMN paresis/GP ataxia in pelvic limbs through spastic tetraplegia

Postural reactions	Delayed to absent in all four limbs
Muscle mass/tone	Thoracic limb neurogenic atrophy (chronic lesions); reduced tone in thoracic limbs; normal to exaggerated tone in pelvic limbs; possible UMN bladder
Spinal reflexes	Normal to reduced withdrawal reflexes in thoracic limbs; normal to exaggerated patellar and withdrawal-flexor reflexes in pelvic limbs
Cutaneous sensation	Hypalgesia or normal in all four limbs or hypalgesia in thoracic limbs only
Cranial nerves	Ipsilateral Horner's syndrome (T1-T3 lesions)
Other	A focal, severe lesion between these segments may result in death due to respiratory dysfunction

GP, General proprioceptive; *LMN*, lower motor neuron; *UMN*, upper motor neuron.

TABLE 259-9

Neurologic Abnormalities Associated with T3-L3 Spinal Cord Dysfunction

NEUROLOGIC TEST	POSSIBLE ABNORMALITIES
Sensorium/behavior	Normal
Posture/gait	Variable: UMN paresis/GP ataxia in pelvic limbs through spastic paraplegia
Postural reactions	Normal in thoracic limbs; delayed to absent in pelvic limbs
Muscle mass/tone	Normal tone in thoracic limbs (unless Schiff-Sherrington spasticity in thoracic limbs); normal to exaggerated tone in pelvic limbs; normal muscle mass unless disuse atrophy in pelvic limbs; possible UMN bladder
Spinal reflexes	Normal withdrawal reflex in thoracic limbs; normal to exaggerated patellar and withdrawal reflexes in pelvic limbs; cutaneous trunci "cut-off" may be present slightly caudal to the lesion
Cutaneous sensation	Normal in thoracic limbs; hypalgesia, analgesia, or normal in pelvic limbs
Cranial nerves	Normal
Other	L4-L7 lesions of the *white matter* may produce similar signs

GP, General proprioceptive; *UMN*, upper motor neuron.

TABLE 259-10

Neurologic Abnormalities Associated with L4-S3 Spinal Cord Dysfunction

NEUROLOGIC TEST	POSSIBLE ABNORMALITIES
Sensorium/behavior	Normal
Posture/gait	Variable: flaccid paraparesis and GP ataxia in pelvic limbs through flaccid paraplegia
Postural reactions	Delayed to absent in pelvic limbs
Muscle mass/tone	Normal tone in thoracic limbs; reduced tone in pelvic limbs, reduced muscle mass in pelvic limbs (chronic); UMN (rare) or LMN bladder
Spinal reflexes	Hyporeflexia through areflexia of patellar (L4-L6), withdrawal (L7-S1), and perineal reflexes (S1-S3)
Cutaneous sensation	Normal in thoracic limbs; normal, hypalgesia or analgesia in pelvic limbs, tail, perineum, anus (penis)
Cranial nerves	Normal
Other	L4-L7 *(white matter)* lesions may produce signs that mimic T3-L3

GP, General proprioceptive; *LMN*, lower motor neuron; *UMN*, upper motor neuron.

Thoracolumbar (T3-L3) spinal cord lesions typically spare the thoracic limbs and cause a combination of UMN signs and GP deficits in the pelvic limbs (see Video 259-2). However, peracute T3-L3 lesions may produce a marked spasticity in the thoracic limbs referred to as the *Schiff-Sherrington syndrome.* This phenomenon results from disruption of *ascending* inhibitory axons arising from interneurons (border cells) located in the dorsolateral border of the ventral gray column of spinal cord segments L1-L7.[1] These ascending interneurons exert an inhibitory influence on the LMNs of the cervical intumescence, which may be lost with peracute, transverse T3-L3 lesions. Postural reaction testing will discriminate between a severe C1-C5 lesion and Schiff-Sherrington syndrome. Postural reactions will be delayed in the former because of the involvement of the UMN and GP pathways, but it will be normal in the latter despite the presence of spasticity.

A second challenging clinical scenario is associated with acute T3-L3 lesions that produce contradictory LMN signs (reduced spinal reflexes and hypotonia) in the pelvic limbs. This situation commonly is accompanied by Schiff-Sherrington syndrome, and the LMN signs in the pelvic limbs have been referred to as *spinal shock.* It is thought to be secondary to a transient disconnection between the descending UMNs and the LMNs of the lumbosacral intumescence.[6] Although spinal shock can persist for weeks in humans, it generally is transient (hours to days) in dogs and cats.

Occasionally, T3-L3 lesions produce LMN signs in the pelvic limbs that are *not* accompanied by the Schiff-Sherrington syndrome. This is most common with fibrocartilaginous embolic myelopathy (FCEM) and rarely occurs with intervertebral disk disease.[7] For hours, upwards of days, contradictory LMN signs may be appreciated in the pelvic limbs with such T3-L3 lesions. It has been hypothesized that this also represents a variation of spinal shock.[6]

A third challenging situation relates to L4-L7 lesions that may produce UMN signs and GP ataxia, rather than the predicted LMN signs, in the pelvic limbs. This may result from lesions affecting predominantly the white matter of the spinal cord at this level.

Peripheral Nervous System

Lower Motor Neuron/Neuromuscular System

The LMN unit consists of the nerve cell body in the ventral gray matter of the CNS, ventral nerve root, peripheral nerve, and muscle. Disease of any component of this unit will produce LMN signs. Normal strength depends not only on functional LMN unit, but also on effective neuromuscular transmission via acetylcholine (ACh) across the neuromuscular junction (NMJ). Diseases affecting neuromuscular transmission (e.g., myasthenia gravis, tick paralysis), so-called junctionopathies, may produce LMN signs that are indistinguishable from neuropathies and myopathies.

Because NMDs may mimic one another, the neurologic examination rarely confirms the exact component of the LMN unit that is affected. The clinician may require ancillary tests (serum creatine kinase [see ch. 66] and aspartate aminotransferase [see ch. 65], edrophonium testing, acetylcholine receptor antibody titer [see ch. 269], electrodiagnostics [see ch. 117], nerve and muscle biopsies [see ch. 116]) to further localize the problem to the nerve, muscle, or NMJ. The LMN unit may be affected diffusely or individual peripheral or cranial nerves may be affected. When cranial nerve deficits (e.g., facial paresis) are present, these must be interpreted with other neurologic findings in order to differentiate neuromuscular disease from a brainstem disorder.

Neuromuscular weakness is characterized by flaccidity and depressed or absent spinal reflexes. Postural reactions typically are normal with pure NMDs (no sensory nerve involvement) (see Video 259-41), although the patient must be well supported or may fail postural testing on account of weakness. Ambulatory patients with pure NMDs typically have a "short and choppy" gait *without* ataxia because GP is unaffected (see Videos 259-1 and 259-41). Exercise intolerance may be the only abnormality present in some patients with NMDs.

An important exception to the classic "short and choppy" pattern of neuromuscular disease is the pelvic limb gait associated with sciatic dysfunction in dogs and cats that have polyneuropathies. Because sciatic dysfunction does not affect weight bearing, the pelvic limb gait is not short-strided. Despite being a LMN problem, an exaggerated pelvic limb gait is present in which the pet repeatedly initiates the gait from a plantigrade position and "flings" its pelvic limbs forward (see Video 259-42). This should not be confused with T3-L3 or cerebellar hypermetria. Hip flexion is exaggerated due to the lack of antagonistic contraction of the caudal thigh muscles. Patients with polyneuropathies also may have delayed postural reactions because of involvement of the sensory nerve fibers in the peripheral neuropathy.

In some NMDs (e.g., polyneuropathies), involvement of the recurrent laryngeal nerve may lead to a change in, or loss of, voice (dysphonia) and increased inspiratory noise (stridor). The development of megaesophagus

in various NMDs may cause regurgitation, often with accompanying aspiration pneumonia. The NMDs also carry the risk of hypoventilation due to involvement of the respiratory muscles. Finally, changes in muscle mass may vary from severe neurogenic atrophy (e.g., brachial plexus avulsion) to "pseudohypertrophy," which accompanies myopathies (e.g., muscular dystrophy) (Table 259-11).

TABLE 259-11

Neurologic Abnormalities Associated with LMN/Neuromuscular Dysfunction

NEUROLOGIC TEST	POSSIBLE ABNORMALITIES
Sensorium/behavior	Normal
Posture/gait	Variable: flaccid paresis in affected limb(s) through flaccid paralysis of affected limb(s); exercise may exacerbate the paresis
Postural reactions	Delayed to absent in affected limb(s); normal in "pure" LMN disease if patient maintains some voluntary motor function
Muscle mass/tone	Decreased tone of affected limb(s); neurogenic atrophy may be severe; pseudohypertrophy in certain myopathies; possible LMN bladder
Spinal reflexes	Variable: hyporeflexia through areflexia of affected limb(s); possibly reduced perineal reflexes (S1-S3)
Cutaneous sensation	Normal in "pure" LMN disease (but if a polyneuropathy with a sensory component, hypalgesia may be present)
Cranial nerves	Variable: multiple cranial nerves may be affected
Other	Laryngeal paralysis, dysphagia, megaesophagus common with LMN disease

LMN, Lower motor neuron.

Peripheral Sensory Nerves

Sensory afferent nerve fibers run together with the LMNs within the peripheral nerves. Sensory axons have a cell body in the dorsal nerve root ganglion or in homologous ganglia of cranial nerves. A cutaneous region innervated by afferent nerve fibers from a single spinal or cranial nerve is called a *dermatome.* Diseases exclusively affecting the sensory system are rare (e.g., sensory neuropathies, ganglioradiculoneuritis) and they are characterized by variable sensory deficits ranging from hypalgesia to analgesia of various body parts.

Multifocal Localizations and Diffuse Central Nervous System Disorders

With various neurologic disorders, the deficits cannot be explained by a single lesion. For example, a Pug with necrotizing meningoencephalitis might manifest both prosencephalic (seizures) and vestibular (head tilt, vestibular ataxia) signs. In this scenario, a multifocal, intracranial localization is made.

Multifocal localizations are not analogous to disorders that affect the CNS diffusely, in which the majority of the neural axis is affected. The most common neurologic sign associated with diffuse CNS disease is a fine, whole body tremor (see Video 259-38). Whole body tremors should not be confused with the brief, intentional tremors of the head, neck, or torso that may be present with cerebellar disease (see Video 259-37). The differential list for a diffuse CNS localization is relatively narrow and includes dysmyelinogenesis, diffuse meningitis (idiopathic tremor syndrome, disseminated granulomatous meningoencephalomyelitis, infectious meningitis) and various toxicoses (e.g., molds, algae, ethylene glycol).

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CHAPTER 260

Brain Diseases

Degenerative, Anomalous, Metabolic, Neoplasia, Idiopathic Epilepsy, and Vascular

Joan R. Coates, Dennis P. O'Brien

"All the most acute, most powerful, and most deadly diseases and those most difficult to be understood…fall upon the brain."

Hippocrates

Client Information Sheets:
Brain Tumors in Dogs
Idiopathic Epilepsy in Dogs
Hydrocephalus

Response of the Brain to Injury

General Responses and Their Results

The nervous system has relatively few responses to damage and the complexity of neurologic signs in response to trauma depends upon the location of the injury (Table 260-1). Because neurons are excitable cells, one potential response to disease is excessive discharge; its most dramatic example would be seizure activity. If a condition destroys the neurons of a system, it will lose function. For example, destruction of a cranial nerve nucleus in the brainstem will lead to paralysis of the muscles innervated by that nerve. If the system lost is an inhibitory pathway, then the system that is no longer inhibited may show an exaggerated response. The classic example of such disinhibition is the exaggerated reflexes seen with upper motor neuron (UMN) loss. When dealing with higher brain functions, such responses can be complex. For example, paradoxical aggression sometimes seen in dogs given benzodiazepines or barbiturates may represent a disinhibition of aggressive behavior. The nervous system is especially sensitive to genetic mutations since many genes are only expressed for brief periods during development. Few neurons are capable of reproducing after maturity because the initial systematic and complex construction process cannot be duplicated. Mutations which interfere with the ability of cells to respond to insults such as oxidative stress or enzyme deficiencies can lead to accumulated damage and early or late onset of degeneration.

TABLE 260-1

Summary of Pathophysiologic Mechanisms Associated with Categories of Brain Diseases

DEGENERATIVE	ANOMALOUS	METABOLIC	NEOPLASTIC	INFLAMMATORY	TRAUMA	TOXIC
Specific neuronal degeneration and loss (cell body, axon) Axonopathy Myelinopathy	Genetic and environmental factors (virus, toxin) causing abnormal neuron migration or	Genetic and environmental factors Secondary due to systemic disease Loss of enzyme	Tissue destruction Compression Vasogenic edema Vessel obstruction	Tissue destruction Compression Vasogenic and cytotoxic edema CSF obstruction	Tissue injury Compression, concussion Hemorrhage Ischemic injury Neuro-inflammation	Ene d Iml e a ir Dir

Spongy degeneration Neuro-inflammation Astrocytosis Genetic mutations causing premature cell death, channelopathy, etc.	loss, neural development, axonal guidance and transport Tissue destruction Congenital hydrocephalus	function causing storage product accumulation (See also Toxic) Encephalomalacia	CSF obstruction Neuro-inflammation Astrocytosis Spread along neuraxis ("drop metastasis")	Inflammatory mediators causing vascular compromise, altered neural function and conductance, astrocytosis		tc n An ir Ion ir Cy e My e

Increased Intracranial Pressure

In addition to local effects, a disease process in the brain can produce generalized effects secondary to increased intracranial pressure. Because the calvarium is a bony globe, the three major components within it (brain, cerebrospinal fluid [CSF], and blood) are confined to a fixed space. Any increase in one of these components would then have to be accompanied by a decrease in one of the others (the Monro-Kellie doctrine). A gradual increase in volume of one component, such as slowly progressive hydrocephalus, can be compensated for, to some extent, by atrophy of brain tissue. Acute disease does not allow time for compensatory atrophy, and even chronic disease (brain tumor) will eventually exceed the ability to compensate, and increased intracranial pressure results. With increasing intracranial pressure, generalized forebrain signs develop, even if the inciting cause is a localized process such as neoplasia. Systemic blood pressure increases to maintain cerebral perfusion which can cause reflex increase in vagal tone and decrease in heart and respiratory rates (the Cushing's phenomenon). Vomiting may also occur.

Continued increases in intracranial pressure will lead to herniation. Brain tissue can either herniate laterally under the falx cerebri or caudally under the tentorium or through the foramen magnum.[1] Tentorial herniation leads to a progressive rostral-caudal deterioration of neurologic status when the midbrain, pons, and terminally the medulla are compressed. Resulting brainstem compression causes pupillary changes, and disruption of UMN and respiratory pathways. The progression can be rapid or can evolve slowly over a matter of hours or even days. Herniation is most commonly associated with forebrain lesions, such as neoplasia or trauma. Increased pressure arising below the tentorium (e.g., a cerebellar tumor) will cause herniation of the cerebellum through the foramen magnum, mimicking the terminal events of tentorial herniation without any of the earlier signs.

Brain Edema

Three types of brain edema (cytotoxic, vasogenic, interstitial), a common response to insults, can coexist. Cytotoxic edema results from fluid accumulation in neurons. Energy depletion due to failure of the ATP-dependent Na^+/K^+ ATPase pump and other ion channels results in intracellular translocation of extracellular water. Cytotoxic edema usually occurs as a result of ischemia or processes that alter the cellular membrane. Vasogenic edema results from physical or functional disruption of the vascular endothelium, often in association with the blood-brain barrier (BBB). Fluid accumulation is extracellular and preferentially distributed within the white matter because its myelinated neuronal fibers are diffusely distributed within a matrix of glia and capillaries. Interstitial edema often accompanies obstructive hydrocephalus, causing compartmentalized CSF to cross ependymal linings and creating extracellular periventricular interstitial brain edema. Determining edema type allows for the most appropriate treatment. Cytotoxic and interstitial edemas are managed by treating the underlying cause, whereas vasogenic edema can be treated using osmotic and corticosteroid therapies.

In addition to primary CNS inflammatory diseases, neuroinflammation plays a role in the pathophysiology of many brain conditions in animals.[2] It is characterized by a broad range of immune responses, differing from peripheral inflammation primarily in the principal cells involved, most notably the astrocytes and microglia.[3] The BBB (including the blood–spinal cord barrier) refers to the flow of cells and macromolecules from the systemic circulation to the CNS being protected.[4] This selectively permeable barrier is composed of endothelial cells, basement membranes, and neighboring perivascular pericytes, glial cells (astrocytes, microglia) and neurons. Together, they temper the intensity of CNS inflammatory responses.[4-6] However,

although the CNS traditionally has been considered "immunologically privileged," current data confirm that the CNS is immunocompetent and actively interacts with the peripheral immune system.[7] Peripheral inflammation can trigger a neuroinflammatory response involving BBB endothelia, glia and neurons through inflammatory mediators and cytokines.[2]

Localizing the Lesion

One aim of the neurologic examination is to localize the lesion into one of four areas within the brain: (1) forebrain (cerebrum and diencephalon), (2) midbrain, (3) pons and medulla, or (4) cerebellum (Table 260-2). While one may further localize a lesion within one area, correctly placing a lesion in one of the broad divisions is sufficient to have a reasonable list of differential diagnoses and a diagnostic plan (see ch. 259 and Video 260-1). When localizing the lesion, the first question the clinician must answer is whether the signs reflect focal, diffuse, or multifocal disease. Focal lesions are suspected if signs exhibited are strongly lateralizing (e.g., circling, focal onset seizures, lateralized cranial nerve deficits). A focal lesion is most suggestive of a neoplasm, vascular disease, or localized infection. Usually, degenerative processes or a metabolic or toxic insult are expected to affect the brain more generally and not preferentially affect one side. Although symmetric forebrain signs suggest a diffuse disease process, they do not rule out focal disease. Focal disease can produce diffuse signs through mechanisms like obstructive hydrocephalus, diffuse edema and increased intracranial pressure. Every effort should be made to explain the clinical signs on the basis of a single lesion. If a single lesion cannot explain all signs, multifocal disease is suspected. For example, a single lesion cannot explain an animal that has both seizures (cerebral cortex) and unilateral facial palsy (medulla or facial nerve).

TABLE 260-2

Clinical Signs Associated with Intracranial Localization

LOCALIZATION SITE	CLINICAL SIGNS
Cerebrum	Seizure, abnormal behavior and mentation, normal gait, propulsive gait, ipsilateral circling and head turn, contralateral postural reaction deficits, and contralateral menace response and facial sensory deficits
Diencephalon	Abnormal behavior and mentation, circling either direction, normal gait, postural reaction deficits, anorexia or polyphagia, temperature dysautoregulation, endocrine abnormalities, visual deficits
Midbrain	Abnormal mentation, circling and turning, postural reaction deficits, hemi- or tetraparesis, GP ataxia, CN III deficits
Brainstem	Normal to abnormal mentation, ipsilateral head tilt and circling, vestibular ataxia, ipsilateral postural reaction deficits, hemi- or tetraparesis, ipsilateral CN V-XII deficits
Cerebellum	Normal mentation, wide-base stance, paradoxical vestibular dysfunction, decerebellate posture, intention tremor, cerebellar ataxia, may see ipsilateral menace response deficit

CN, Cranial nerve; *GP*, general proprioceptive.

Differential Diagnoses

Age, Gender, Breed

Once a lesion has been localized, a list of differential diagnoses can be generated and a diagnostic plan developed. Most diseases in veterinary medicine are categorized by their clinical presentation and/or pathologic changes, but clinical signs can be nonspecific. Signalment often provides the first clue to a diagnosis. Congenital and hereditary diseases are most common in young purebred animals. Congenital anomaly refers to any malformation present at birth, including both genetic conditions and those resulting from external influences during gestation, such as toxin, malnutrition or infection. Many hereditary neurologic diseases will be congenital or at least apparent at an early age, but there are notable exceptions. Some lysosomal storage diseases require time for accumulation of byproducts. Animals with hereditary cerebellar ataxia (abiotrophy) may be normal clinically and histologically for an unpredictable time period

until clinical signs follow the death of Purkinje neurons. Finally some conditions (idiopathic epilepsy or neuronal ceroid lipofuscinosis) will not cause signs until early or even late adulthood. While infection, trauma, and intoxication can occur anytime, young animals are more likely to be affected. With increasing age, neoplasia, metabolic encephalopathies, and degenerative diseases become increasingly common.

Onset, Progression, and Type of Signs

Onset and progression of signs can provide important clues in prioritizing a differential diagnosis list. Congenital malformations are present from birth and relatively static. However, conditions like hydrocephalus could progress over time. Acute onset of signs is most likely with vascular disease, trauma, most toxins, and many infectious/inflammatory or metabolic diseases. Waxing and waning signs can be characteristic of inflammatory and metabolic diseases. Some infectious/inflammatory, metabolic, cancerous and degenerative conditions are chronic and progressive. Episodic onset is characteristic for epilepsy, some disorders associated with abnormal movements and channelopathies.

Results of the neurologic examination may suggest the type of disease process (see ch. 259). Some diseases will have a predilection for specific regions of the brain. Generally, lateralizing signs (circling, hemiparesis, or unilateral cranial nerve deficits) suggest a localized disease process such as an infection, vascular disease, neoplasia, or traumatic injury. Likewise, focal onset seizures would suggest localized cortical damage, although idiopathic epilepsy can produce focal seizures.[8,9] Of these, infectious/inflammatory, vascular, or metastatic neoplasia would be the most likely to produce multifocal signs. Metabolic or toxic insults usually do not cause focal or asymmetric signs. Because the cerebral cortex is the most metabolically demanding area of the brain, forebrain signs tend to predominate. However, localized disease processes can result in diffuse forebrain signs through increased intracranial pressure. The clinician should have a high index of suspicion of hereditary diseases in cases of young, pure-breed animals with diffuse, symmetrical signs of brain disease when toxic, routine metabolic and infectious etiologies have been ruled out. Breed tables can be consulted for specific diseases that have been reported.[10-12]

Diagnostic Approach to Brain Disease

Routine Laboratory Assessment

When considering the diagnostic approach to diseases affecting the brain (Figure 260-1), clinicians should consider cost, imaging availability, risks, and potential yield. The value of a thorough history and neurologic examination should never be underestimated (see ch. 259). Even if advanced imaging reveals a clear lesion, if that lesion does not correspond to results of the neurologic examination, its significance needs to be questioned. Routine clinical pathology can provide critically important information, and is readily available, cost-effective and not invasive. Even with apparently focal disease, reviewing the minimum database on any ill animal is essential. Complete blood count (CBC) may suggest infectious/inflammatory etiologies as well as provide clues to other causes. Serum biochemistry profile and urinalysis will be essential to rule out energy deficiencies, electrolyte disturbances, or accumulation of endogenous toxins. Pets with diffuse forebrain signs or seizures should have liver function assessed with bile acids or ammonia tolerance (see ch. 284). If inborn errors of metabolism are suspected, urine assays for abnormal metabolites may be necessary. Assays for specific exogenous toxins, such as lead or organophosphate, may be indicated if signs and history are suggestive (see ch. 152). Screening for all possible neurotoxins is not feasible. Since hypothyroidism (see ch. 299), hyperadrenocorticism (see ch. 306), insulin secreting tumors (see ch. 303) and other endocrine conditions can be accompanied by neurologic signs, endocrine testing should be considered if indicated by gathered information. Thoracic and abdominal imaging will be important, particularly in geriatric patients, to rule out metastatic and co-existing diseases.[13,14]

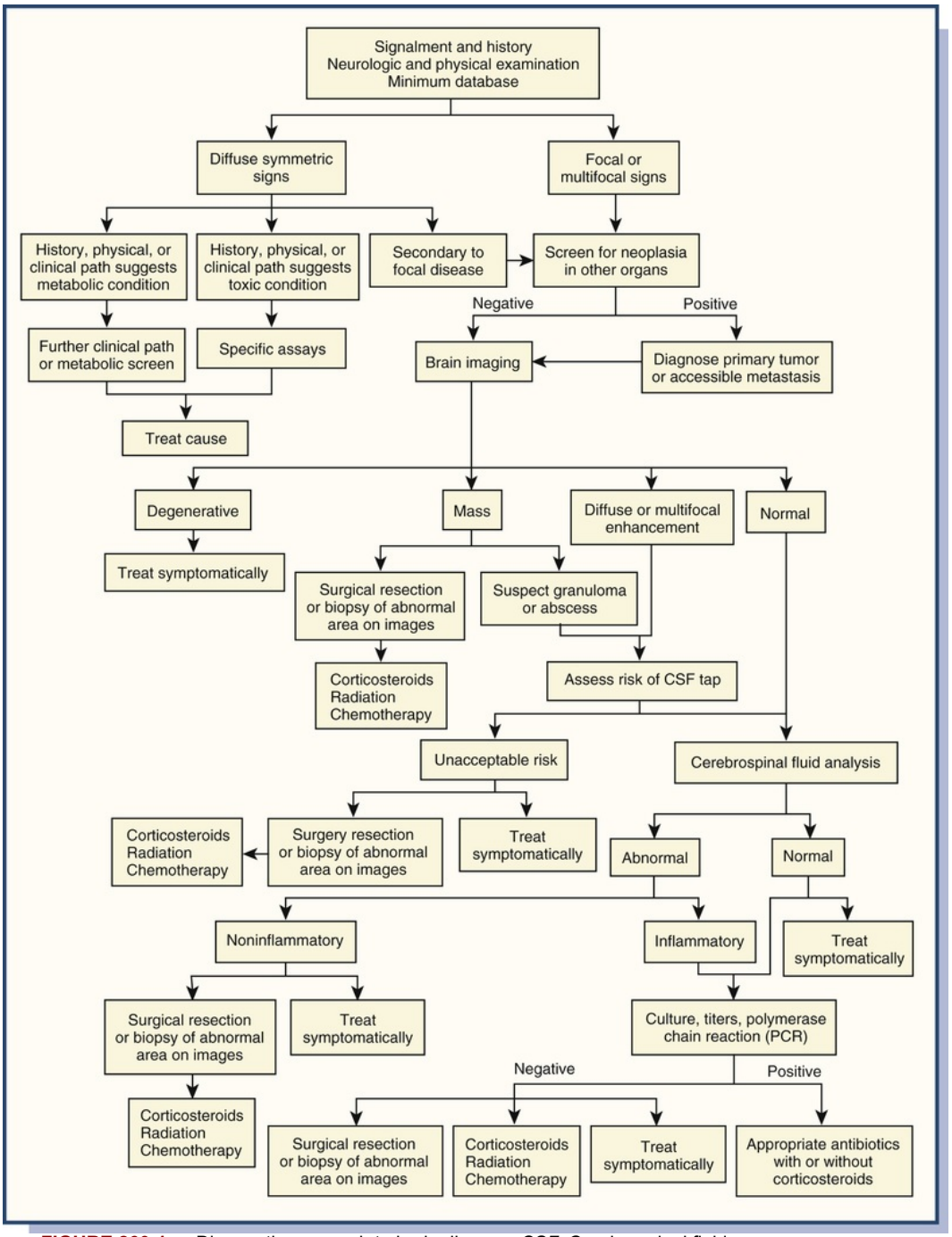


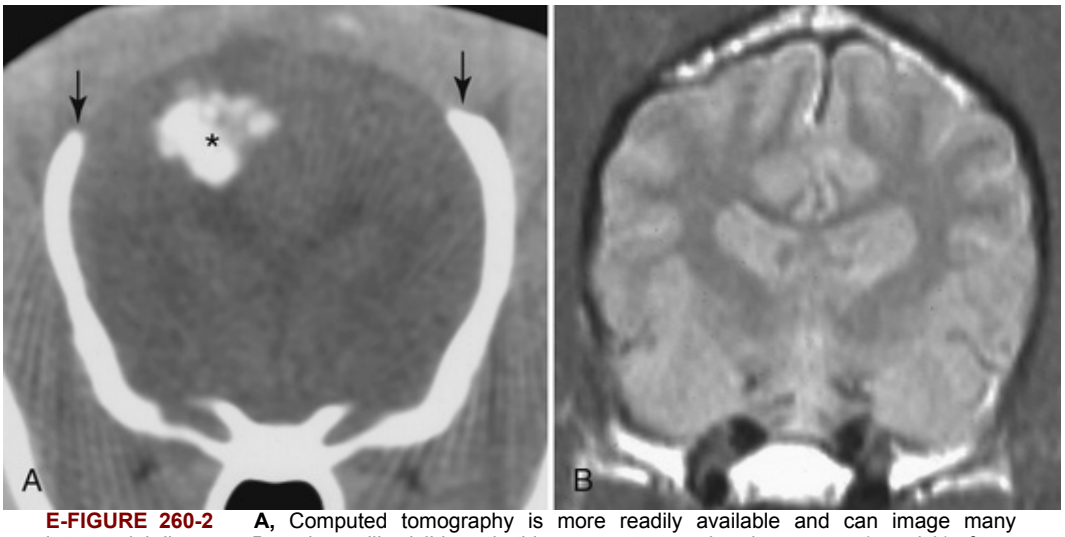
FIGURE 260-1 Diagnostic approach to brain disease. *CSF*, Cerebrospinal fluid.

Brain Imaging

Overview

The availability of computerized tomography (CT) or magnetic resonance imaging (MRI) scans for animals with brain disease has revolutionized neurology. While expensive, information gained usually justifies the investment. Routine skull radiographs are of little value in diagnosing brain disease because only the skull can be imaged without contrast studies or angiography and superimposition of structures makes interpretation difficult. Ultrasound (US) imaging of the brain, while useful, is only an option when an open fontanelle or craniotomy provides an acoustic window. Cross-sectional imaging with a CT or MRI scan allows detection of structural changes within the brain.[15,16] CT and MRI scans produce images that are slice oriented,

thereby eliminating the summation effects associated with conventional radiography. MRI scans provide better contrast resolution of nervous tissues whereas CT provides better spatial resolution and rapid imaging (E-Figure 260-2). With CT scans, reconstruction of sagittal and dorsal plane images from the transverse causes inferior spatial resolution. The direct multiplanar images acquired by MRI result in better spatial resolution of each plane, although the scans are more time-consuming. The shorter time needed to acquire CT images may be advantageous in post-trauma patients. MRI cannot be used when metal implants or cardiac pacemakers are present. Sometimes even identification microchips can interfere with MRI scans.



E-FIGURE 260-2 **A,** Computed tomography is more readily available and can image many intracranial diseases. Bone is readily visible as in this recurrent osteochondrosarcoma (asterisk) after a prior craniectomy (arrows). **B,** Magnetic resonance imaging provides much greater detail of brain parenchymal lesions. This proton density image of normal brain clearly delineates gray and white matter.

Computed Tomography

CT relies on traditional radiographic principles. A shade of gray assigned to a pixel by the computer, normalized to the absorption characteristics of water, is assigned a number referred to as a Hounsfield unit (HU; Table 260-3). Only cross-sectional images are acquired, although computer reconstructions can generate images in a sagittal plane, dorsal plane, or in three dimensions. CT has the advantage of being able to image bone, which is useful in detection of mineralization and hemorrhage. The ventricular system is readily appreciated on CT, but fine anatomical detail of parenchymal lesions is often not visible. Edema may be visible as a reduced density of the parenchyma, while hemorrhage or calcification produces increased density. CT resolution is limited by X-ray attenuation by the skull. The density of petrosal bones at the base of the skull limits CT image quality to the tentorium cerebelli. The attenuation of the X-rays will be similar to that of the gamma rays used in radiation therapy, so CT images can be used to calculate dose delivery.

TABLE 260-3

Hounsfield Units for Various Intracranial Tissues

TISSUE	HOUNSFIELD UNIT (HU)
Air	−1000
Fat	−50 to −100
Water	0
CSF	0 to 15
Brain	25 to 50
Hyperacute to acute blood	60 to 100

Mineral and bone	100 to >1000
Metal (e.g., metallic iodine contrast)	Variable on dilution, 100 to >3000

Magnetic Resonance Imaging

MRI orients hydrogen atoms, with their unpaired electron, in alignment based on their magnetic properties. When energy—a radiofrequency pulse—is applied, there are changes in the alignment of the atoms and when the pulse is removed, the realigned atoms return to their previous orientation, while releasing energy back into the environment. It is this energy release that helps form images. The rate at which energy is released is based on inherent tissue characteristics. Two time constants, termed T1 and T2, describe this process. A series of images, called a pulse sequence, can be acquired based or "weighted" on the T1 or T2 properties, referred to as T1-weighted (T1W) or T2-weighted (T2W) images. The resultant images are gray-scale images in which the degree of relative brightness is referred to as intensity (Table 260-4). T1W images are characterized by bright fat and dark water and T2W images are characterized by bright water and dark fat. Edema is readily apparent as increased signals on T2W images. Proton density is an in-between sequence that characterizes areas with high proton density (bright) and areas with low proton density (dark). The contrast decreases between the ventricles and the brain, but increases between gray and white matter, revealing fine anatomic detail. Several sequences have been developed to suppress the signal of certain tissues, e.g., CSF and fat. The fluid attenuated inversion recovery (FLAIR) sequence suppresses signal from fluid with low or no protein (i.e., CSF) so that it is hypointense and allows improved identification of pathologies (tissue edema) and lesions near the ventricles. Short-tau inversion recovery (STIR) sequences allow for fat suppression. Gradient echo (GRE) T2W imaging (T2*) is used to detect artifact from blood products that are formed in hemorrhage.

TABLE 260-4

Commonly Used MRI Sequences to Define Tissue Intensity* and Indications

	T2W	FLAIR (T2W)	T1W	STIR	GRE (T2*)
Fat	Hypo	Hyper	Hyper	Hypo	Hyper
CSF	Hyper	Hypo	Hypo	Hyper	Hyper
Edema	Hyper	Hyper	Hypo	Hyper	Hyper
Indications for Selected Sequence	Allows distinction between fluid and tissue; perform on every MRI study	Suppression (nulling) of low-protein fluid (i.e., CSF), allowing for visualization of periventricular lesions	Comparison of pre- and post-contrast images to assess for tissue vascular supply and BBB disruption	Allows for suppression of hyperintense fat signal	Most sensitive for detecting signal void on hemorrhage, bone, mineralization

*Tissue intensity appearance on sequence compared to brain cortex (gray matter).

FLAIR, Fluid attenuated inversion recovery; *GRE*, gradient echo; *STIR*, short-tau inversion recovery.

More advanced MRI techniques can be used to investigate functional disturbances in the CNS. MR spectroscopy (MRS) evaluates brain chemistry and metabolism (molecular content of tissues) that can be altered in disease and provide chemical signatures for pathologic processes as in neoplasia and inflammation. Diffusion weighted imaging (DWI) depends on the molecular motion or diffusion of water, altered in many disease processes. Accompanied by calculated "apparent diffusion coefficients" (ADC), DWI can aid in identifying issues like cytotoxic edema associated with ischemic infarction. Diffusion tensor imaging (DTI), also known as fiber tracking, evaluates the direction of diffusion (anisotropy) in white matter to provide more information on neuronal connectivity. MR angiography (MRA) uses gradient echo sequences to detect signal changes of flowing blood (vessels) in tissues.

Lesion Description for Cross-Sectional Imaging

For both CT and MRI, a standard approach is used to characterize primary and secondary structural abnormalities. Primary lesion descriptions are based on their number (single or multiple) and density/intensity (hypo-dense, hyper-dense, iso-dense) (Table 260-5) with respect to the adjacent normal area,

its distribution (homo- or heterogeneous), borders, anatomic location, and location in reference to the CNS (extra-axial, intra-axial) and meninges (intradural, extradural, intraparenchymal). Secondary effects on the surrounding anatomy are also described to include extent and type of edema, and mass effect causing a shift of midline structures, tissue herniation or distortion of the ventricles. Alterations of CSF flow may cause periventricular edema, obstructive hydrocephalus or ventriculomegaly and syringohydromyelia.

TABLE 260-5

Pathologies with Increased CT Density or MRI Intensity

CT DENSITY	T1W INTENSITY	T2W INTENSITY
Bone proliferations Mineralized tissue Hemorrhage (hyperacute, acute) Iodine-enhanced lesion Tissues of high cellular density (fibrous) Metallic object	Fat Methemoglobin stage in hemorrhage Mucinous fluid Cortical laminar necrosis Gadolinium-enhanced lesion Melanin Iron deposition	CSF and other fluids Edema Necrosis Demyelination Cellular changes (gliosis, inflammation, neoplasia)

Contrast agents can be employed with either CT or MRI scans to improve tissue resolution for detection of pathologic processes. Images can be obtained immediately after IV contrast to evaluate vasculature or they can be delayed several minutes to evaluate tissue uptake. Contrast agents used for CT are iodinated and alter X-ray attenuation, whereas contrast agents used for MRI are paramagnetic and function by changing the relaxation rates of protons. Lesions are characterized on the degree and distribution of contrast enhancement. Following IV administration, the BBB would normally exclude such agents. The presence or absence of contrast enhancement with CNS disease depends upon the degree of BBB disruption or presence of vasodilation or neovascularization and, as such, is a nonspecific finding associated with a variety of CNS diseases.[17-19] Breakdown of this barrier by neoplasia or inflammation will result in accumulation and contrast enhancement of the lesion, thereby increasing the ability to identify primary lesion(s).

Other Imaging Modalities

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are functional imaging techniques that allow for qualitative and quantitative measurements of tissue metabolism and are gaining utility in veterinary medicine.[20] Major uses include defining metabolically active areas for biopsy versus inactive ischemic lesions. Images produced from PET are co-registered with CT or MRI to obtain anatomic relationships. PET imaging has been evaluated on normal canine brains and in dogs with intracranial disease.[21-24]

Brain Biopsy

While advanced imaging provides excellent views of the nervous system, it cannot provide definitive diagnoses which, for many brain diseases, is based on histology. Antemortem brain biopsy may yield a more definitive diagnosis to guide treatment approaches, although such procedures are dependent upon obtaining biopsy material from representative portions of the lesion. Image-guided biopsy techniques decrease morbidity and increase availability. Minimally invasive techniques such as CT or MRI-guided stereotactic systems, free-handed techniques that utilize US, CT, or MRI, and endoscopic-guided biopsy have been developed for brain biopsy in dogs.[25-35] Diagnostic yield for biopsy of brain lesions may be influenced by sample size and difficulty in distinguishing between the primary lesion and secondary lesion changes such as edema and necrosis. Intraoperative cytologic evaluation of a biopsy sample may improve diagnostic accuracy.[36,37] In addition to limitations in accuracy of diagnosis from biopsy, there are also risks that cannot be overlooked; a recent study on dogs with encephalitis suggested mortality and morbidity rates of 6 and 29%, respectively.[34] Modern neuro-navigation may further refine biopsy techniques and decrease morbidity.[31,38,39] Combined use of rigidly fixed external markers for landmarks within and outside the cranial vault and labeled surgical instruments provide real-time feedback during the procedure.

CSF Analysis

Because a mass lesion producing increased intracranial pressure significantly increases the risk of complications, imaging should precede CSF collection. CSF is most useful for identifying inflammatory disease, but can provide other clues (increased protein with neoplasia). In some, CSF analysis can be diagnostic. In cryptococcosis (see ch. 231), for example, organisms may be seen on examination. More commonly, CSF analysis simply confirms inflammation or presence of disease. Further tests are necessary to make a definitive diagnosis. Culture of CSF has low yield. Microbial culture of blood or urine may be considered with suspected bacterial infection.

CSF, serum or both can be analyzed for antibodies to infectious diseases, most notably *Neospora caninum, Toxoplasma gondii, Ehrlichia* spp., *Anaplasma* spp., *Rickettsia rickettsia,* and *Coccidioides immitis*. Prevalence varies with geographic location. Infection by *Cryptococcus* spp. is usually detected by antigen testing. Other microbial DNA or RNA can be detected by the highly sensitive and specific polymerase chain reaction (PCR) assays.[40-42] Results should be interpreted carefully to avoid false positives and rigorous negative controls must be evaluated in parallel (see ch. 207). A negative PCR result may indicate that undetectable levels of nucleic acid are present, an agent may be in neural tissue but not in CSF, or that the disorder may have been triggered by an agent no longer present.[41] Other analyses on CSF have been studied for CNS diseases but lack disease specificity. CSF protein composition can be further defined by semiquantitative electrophoretic techniques and abnormalities have been reported to be useful in identification of inflammatory, neoplastic and degenerative disease.[43-45] Flow cytometry and immunophenotyping, used to identify mononuclear cells in CSF inflammatory disorders[46] and lineage identification of neoplastic cells, is not practical because of the need for large volumes (4 to 5 mL) of CSF unless the cell count is very high.

Electroencephalogram (EEG), Genomics, Response to Therapy, and Other Diagnostics

The EEG is used primarily to confirm epileptic activity in brains of suspected seizure patients. It is particularly useful in status epilepticus to confirm that seizure activity has been stopped. The brainstem auditory evoked response (BAER) is used primarily to assess cochlear function, but latter wave intervals can also evaluate brainstem conduction.[47,48] Somatosensory and visual evoked potentials can assess function of these systems.

Advances in animal genomics have allowed identification of disease-causing mutations and development of DNA tests to detect mutant alleles. This has simplified diagnosis of many hereditary brain diseases, most of which in dogs and cats are autosomal recessive traits or the result of a complex inheritance. Dominant traits can be eliminated from a breed by not breeding affected animals. Familial diseases are not necessarily genetic, however, because families may share the same diet, environment, infection exposure, and so on. Breed predilection for a disease suggests a genetic contribution, but again, could reflect other factors such as the typical use of a particular breed or administration of supplements in vogue. Ultimately the hereditary nature of some disorders will be classified on the gene or its product that is altered. Many websites are now available to identify laboratories performing these tests. However, the clinician must be able to select the test and interpret results appropriately.[49-51] This requires an understanding of the terminology used, the types of genetic tests available and appreciating the potential pitfalls of DNA testing (see ch. 4).

Response to therapy can be important diagnostically, particularly when financial or other factors limit testing. Therapy for the most likely condition can be started and response monitored. For example, dramatic improvement with a tetracycline would support a presumption of tick-borne disease. While corticosteroids play an important role in treating brain disease, the risk of side effects, including exacerbation of an infectious disease, need to be weighed carefully. Dramatic improvement with corticosteroids would be consistent with a neoplasia or infectious/noninfectious inflammatory disease. Improvement with neoplasia is usually short-lived, while some noninfectious inflammatory disease may be kept in remission with prolonged treatment. Infectious diseases may also often respond dramatically to corticosteroids, only to worsen if appropriate antibiotics are not also instituted. Response to antiepileptic drugs (AEDs) helps to confirm a seizure disorder, but does not rule out an underlying cause to the seizures.

Specific Brain Diseases

The brain is the most metabolically demanding organ in the body. A large portion of the body's energy is reserved for maintaining resting membrane potentials and neurotransmission. The nervous system has more

limited energy metabolism pathways than other tissues, and is thus more sensitive to disturbances of glucose or oxygen supply. The brain is also sensitive to exogenous or endogenous toxins, with the highest centers most sensitive to metabolic insults. Therefore, forebrain signs are a common manifestation of systemic diseases (see ch. 12). The disorders will be described according to the DAMNITV (*d* = degenerative, *a* = anomalous, *m* = metabolic, *n* = neoplastic and nutritional, *i* = idiopathic epilepsy and inflammatory, *t* = traumatic, *v* = vascular) classification scheme. Inflammatory disease processes, most of which are multifocal, and head trauma are discussed in ch. 148 and 261, respectively.

Primary Brain Degenerative Diseases (E-Box 260-1)

E-Box 260-1

Degenerative Primary Brain Diseases and Brain Anomalies

Degenerative

Central Myelinopathy

Many of the central myelinopathies manifest with signs of spinal cord dysfunction but also cause encephalopathy.[52,53] Disorders of myelin development may not be apparent until the animal relies on adequate myelination for walking. Some disorders cause severe destruction of the central or peripheral myelin and lead to axon loss. Primary CNS myelin degenerative disorders can be classified as myelin dysgenesis (hypomyelination, dysmyelination), the leukodystrophies (necrotizing encephalomyelopathy and leukoencephalomyelopathy), and spongy degeneration.[52-54] Diagnosis is based on clinical signs in a breed at risk, DNA testing for some, and confirmation at necropsy based on disease pattern.

In hypo- and dysmyelinogenesis, numbers of oligodendrocytes are decreased or are unable or retarded in producing functional myelin.[53] Typically, myelin throughout the CNS is affected but peripheral nerves are spared. Reflexes are normal or exaggerated. These disorders clinically manifest with whole body tremors, dysmetria noticeable from the first attempts at walking and nystagmus. Breeds documented with this disorder include the Dalmatian, Springer Spaniel, Samoyed, Chow Chow, Weimaraner, Lurcher and Bernese Mountain Dog.[55-62] In some breeds like the Chow Chow, improvement occurs with time, but others, like the Springer Spaniel, are permanently disabled. Both X-linked and autosomal recessive forms have been described and a mutation of one of the myelin proteolipid proteins (PLP) has been identified in the Springer Spaniel.[52,54,63] In the autosomal recessive demyelinating disorder of Weimaraner pups, a mutation was found in the folliculin interacting protein 2 gene *(FNIP2),* which may be responsible for a delay in migration or differentiation of a subpopulation of oligodendrocyte progenitor cells.[64] Toy Fox and Rat Terriers affected by congenital hypothyroidism with goiter (see ch. 299) have regional CNS hypomyelination, most evident in the corpus callosum. In Rat Terriers, this is associated with a mutation in the thyroid peroxidase gene.[65]

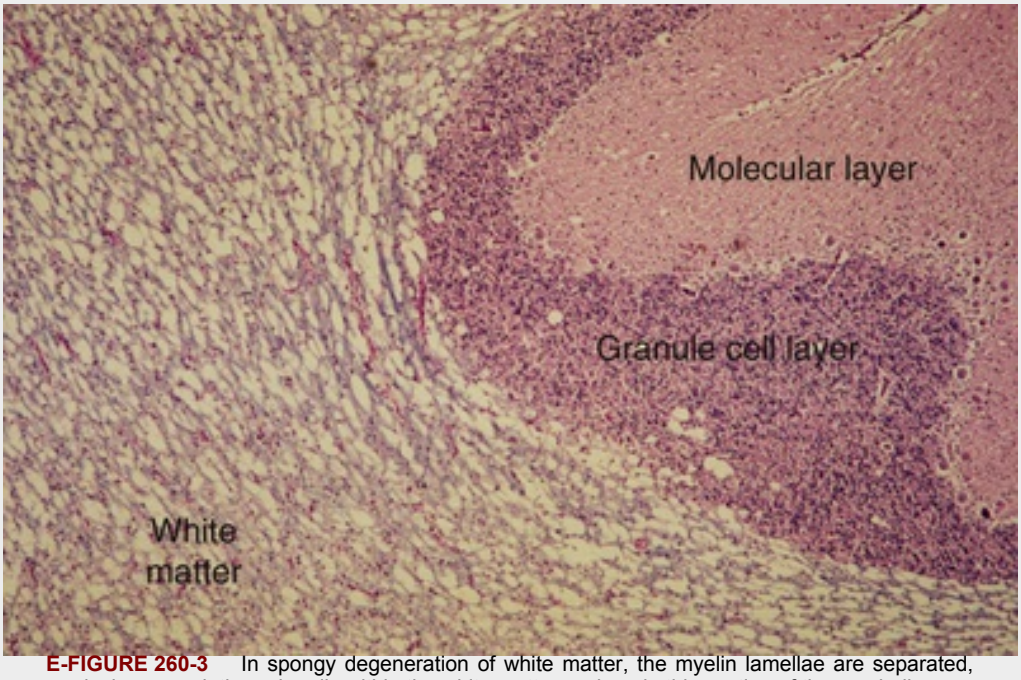
The leukodystrophies are a broadly classified group of diseases that include varieties of leukodystrophies, necrotizing encephalomyelopathies and leukoencephalomyelopathies.[53] Often conditions are inherited and diagnosed in younger animals with defective myelin synthesis. Myelin is formed early in life followed by a bilaterally symmetrical destruction of myelin with eventual loss of axons in some. Alexander's disease (fibrinoid leukodystrophy) has been reported as a sporadic occurrence in several breeds. Leukodystrophies have been reported in 3- to 6-month-old Dalmatians, Labrador Retrievers, Scottish Terriers, Bull Mastiffs, Shetland Sheepdogs, and Miniature Poodles.[66-72] Clinical signs initially manifest as general proprioceptive (GP) ataxia and upper motor neuron (UMN) paraparesis, which progress to tetraparesis. Signs of cerebellar involvement and seizures may occur. Histopathology reveals myelin degeneration without producing vacuolation, that is replaced by severe astrogliosis or Rosenthal fibers (astrocytic processes) and is widespread throughout the brain and spinal cord.

Myelinolysis is characterized by disintegration of initially normally formed myelin. These disorders are presumed due to an autosomal recessive inheritance and have been described in the Afghan Hound, Miniature Poodle, and Dutch Kooiker.[73-77] Age at onset varies from weeks to a few years and the paraparesis is acute. There is bilateral and symmetrical loss of myelin and there are cavitations that are most severe in all spinal cord funiculi with tapering extension into the brainstem. Myelin is

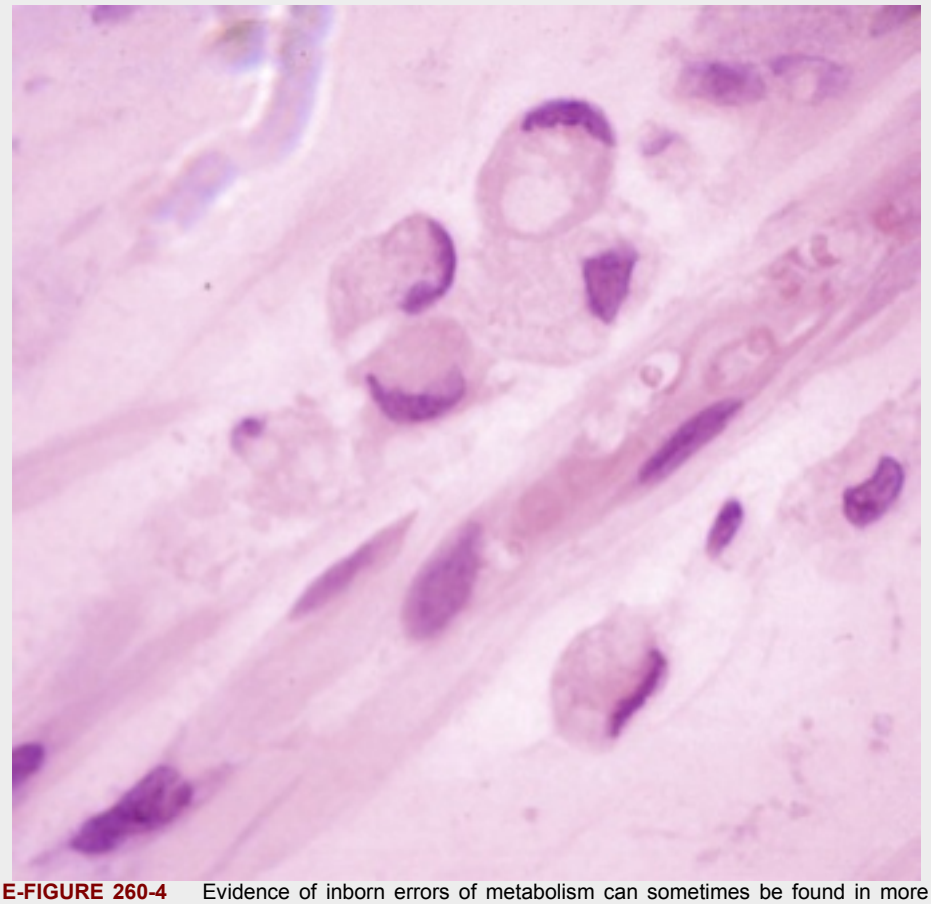
predominantly affected but the axons are usually spared in the Afghan Hound myelopathy, indicating primary myelinopathy, whereas prominent Wallerian degeneration in the Dutch Kooiker is more indicative of axonopathy. If the type of myelin degeneration cannot be determined, a more general term for inherited or acquired conditions, leukoencephalomyelopathy, is used. Specific leukoencephalomyelopathies have been documented in the Rottweiler, and Leonberger.[78-80] Myelin and axons are affected and there may be evidence of active remyelination. The age at onset of signs is within a few months to over 3 years and disease progression is slow and insidious.

Spongy Degeneration Involving Myelin

Spongy degeneration is a nonspecific term used to denote affected tissue vacuolation, seen in disorders that involve separation of the myelin sheath or that involve the neuronal cell body, as in the prion diseases, transmissible spongiform encephalopathy (TSE). Spongy white matter degeneration, similar to Canavan's disease of humans, has been reported sporadically in breeds of dogs and cats.[81] Spongiform leukoencephalomyelopathies have been reported in the Border Terrier, Silky Terrier and Labrador Retriever.[82-85] Onset of signs occurs within 1 to 9 months of age and the signs are progressive. Clinical signs manifest as cerebellar ataxia, seizures and opisthotonus. At necropsy in the Labrador Retrievers, splitting of the myelin resulted in vacuolation of the white matter throughout the brain (E-Figure 260-3) and to lesser extent the spinal cord.[84,85] Some lysosomal storage diseases (globoid cell leukodystrophy) cause vacuolar-like demyelination (E-Figure 260-4) by accumulating psychosine, a metabolite toxic to myelin-forming oligodendrocytes and Schwann cells.[86,87]



E-FIGURE 260-3 In spongy degeneration of white matter, the myelin lamellae are separated, producing vacuolation primarily within the white matter such as in this section of the cerebellum.



E-FIGURE 260-4 Evidence of inborn errors of metabolism can sometimes be found in more accessible tissues such as white blood cells, liver, or peripheral nerve. Macrophages with lysosomal storage product in vacuoles (globoid cells) were found in this peripheral nerve of a Cairn Terrier with globoid cell leukodystrophy.

Central Axonopathy

Axonal degeneration results from disease within the neuronal cell body or the axon itself. Central axonopathy usually consists of bilateral and symmetrical degeneration of both axon and myelin, affecting spinal cord sensory and motor tracts with the longest fibers being the most vulnerable.[88] Lesions appear as diffuse myelinated fiber loss of varying severity in the cerebellar white matter and/or in the dorsal funiculi and pyramidal tracts in the spinal cord that extend into the brainstem. Clinical signs can manifest as GP or cerebellar ataxia and UMN paresis. Breeds at risk include Jack Russell Terriers, Smooth Fox Terriers, Scottish Terriers, and Labrador Retrievers.[89-95] Jack Russell Terriers and related breeds manifest a spinocerebellar ataxia that varies in onset, early or late, and is progressively insidious. Histopathologic changes of neuronal fiber loss and astrogliosis are most severe in the spinal cord and brainstem. Signs of early onset spinocerebellar ataxia are observed by about 3 months of age and has included myokymia, seizures or both. A missense mutation in the gene coding for the inwardly rectifying potassium channel Kir4.1 *(KCNJ10)* was significantly associated with the disease.[96] "Late-onset ataxia," with clinical signs limited to spinocerebellar ataxia, usually begins by 6-12 months of age. A missense mutation in *CAPN1* that encodes for a cysteine-related protease mutation was strongly associated with the late-onset spinocerebellar ataxia in Parson Russell Terriers.[97]

The axonal degenerative diseases that selectively involve axons in the long tracts of the CNS and in the nerve fibers of PNS are as described in central-peripheral distal axonopathy. Segmental spinal reflex abnormalities reflect the PNS involvement. Disease with clinical signs and lesions limited to the PNS are classified as neuropathies.[98,99] Central-peripheral axonopathy of young dogs has been described in the Ibizan Hound, Alaskan Husky, Boxer, Pyrenean Mountain dog and New Zealand Huntaway.[81,100-104] Canine degenerative myelopathy associated with mutations in the superoxide dismutase-1 gene *(SOD1)* is a central-peripheral axonopathy of older-aged dogs seen in many breeds.[105,106] A sensory central-peripheral axonopathy of maternal inheritance has been described in Golden Retrievers. Onset of signs,

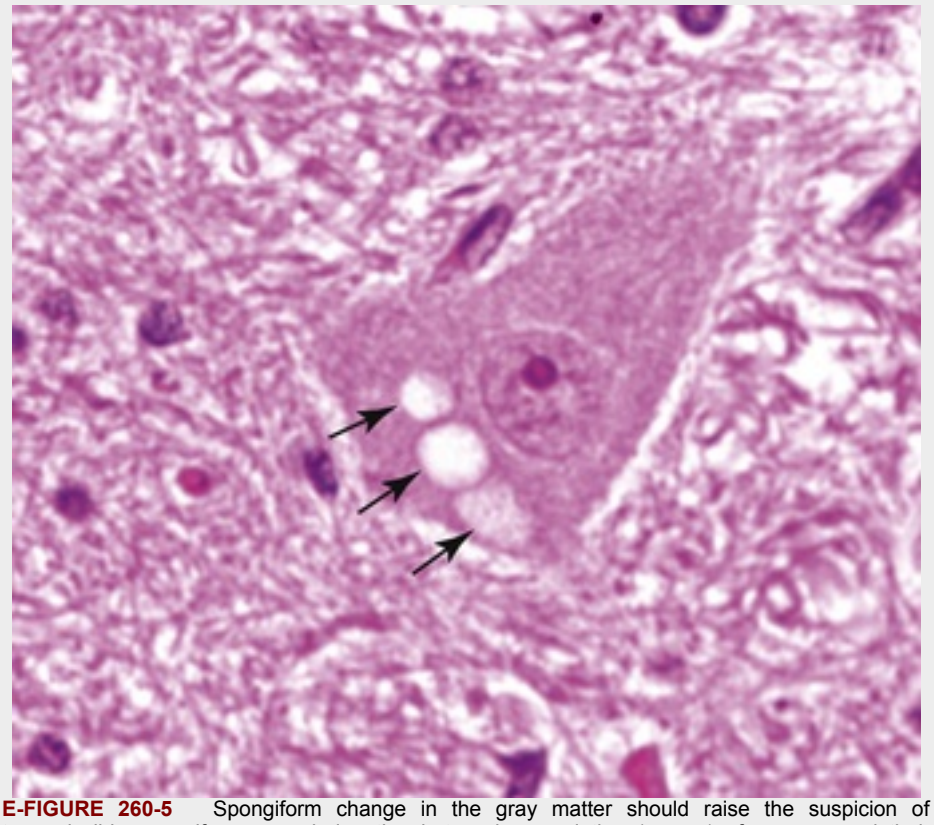
ataxia and dysmetria, is seen at 2-8 months of age.[107] The causative mutation has been found in the *MT-TY* gene *(tRNA-Tyr)* that impairs respiratory chain enzyme activity.[108] A central-peripheral axopathy has been reported in Birman cats.[109]

Neuroaxonal Dystrophy

Neuroaxonal dystrophies are primary disorders of axonal transport, characterized by swellings within the axons. These "spheroids" may be indicative of disordered cytoskeletal element trafficking, which accumulate in axons or synaptic terminals and represent the histologic abnormality necessary to be categorized in this group.[81] Because longer axons have farther to transport such elements, spheroids are most prominent in the termination of long proprioception tracts in brainstem nuclei (i.e., nuclei gracilis and cuneatus). If peripheral nerves are involved, the disease can be diagnosed by nerve biopsy (see ch. 116). Afflicted dogs (<1 year of age) usually have progressive cerebellar ataxia and tetraparesis. In dogs, neuroaxonal dystrophy has been described in the Rottweiler, Chihuahua, Working Collie Sheepdog, Jack Russell Terrier, German Shepherd Dog, and Papillion.[110-117] Neuroaxonal dystrophy has been sporadically described in cats.[118-120] A family of Scottish Terrier pups developed progressive tremors, ataxia, and paraparesis beginning at 10-12 weeks of age. They differed from the neuroaxonal dystrophies previously described in that their axons were diffusely swollen rather than concentrated in spheroids.[94] A fetal-onset neuroaxonal dystrophy (FNAD) has been reported in a colony of Giant Schnauzer-Beagle cross dogs.[121] Affected pups have a constellation of gross abnormalities, including joint contracture, scoliosis, cerebellar hypoplasia and respiratory failure. Neuronal lesions are present throughout the cerebellum, brainstem, spinal cord and peripheral nerves affecting specific nuclei. A mutation was found in the mitofusin 2 gene *(MFN2),* which is a multifunctional, membrane-bound GTPase of mitochondria and endoplasmic reticulum.[122]

Spongiform Polioencephalopathies

Spongiform degenerative conditions are subdivided into those with vacuolation within white matter myelin sheaths (leukoencephalopathies) or within neuronal gray matter (E-Figure 260-5). The spongiform polioencephalopathies encompass a heterogeneous group of diseases associated with neuronal spongiform changes at necropsy.[123] Some lysosomal storage diseases (see below) may also be characterized by vacuolation of neurons, but in those conditions, vacuoles are lysosomes distended with storage products. In the spongiform polioencephalopathies, vacuoles appear empty, and if intraneuronal, they are not membrane-bound. Large intraneuronal vacuoles are an uncommon pathologic finding seen in relatively few diseases including transmissible spongiform encephalopathies (prion diseases), some metabolic encephalopathies and a few viral infections such as human immunodeficiency virus or rabies.[124] Some reference sources reserve the term spongiform encephalopathy for the transmissible spongiform encephalopathies (TSEs), caused by an enigmatic agent, the prion.[53] Scrapie was the first TSE described. The outbreak of bovine spongiform encephalopathy (BSE) in England, and the subsequent recognition that this disease may be spread to cats and humans by ingestion of meat products from affected cows, has made these diseases of general interest.[125,126] The prion is unique in that it is not a nucleic-acid-based organism, but rather a rogue protein isoform (the prion protein). An alpha-helical isoform of the prion protein is found in normal neurons. The disease isoform (the "scrapie isoform") of the protein forms a beta-sheet similar to amyloid, which renders it resistant to degradation by proteases. Abnormal prions then accumulate in neurons as scrapie-associated fibrils that interfere with cell function and produce intraneuronal vacuolation. The scrapie isoform apparently propagates by inducing, via unknown processes, conversion of normal isoforms to the beta-sheet conformation.[127] A long latency period characterizes the TSEs. Cats affected with feline spongiform encephalopathy (FSE) show signs reminiscent of BSE: ataxia, behavioral changes, and hyperesthesia to touch or sound. At necropsy, the TSEs are characterized by vacuolation of nerve processes and to a lesser extent their cell bodies. In cats, such lesions occur throughout brain gray matter.[126] Control of BSE may decrease concerns of TSEs in dogs and cats, but future outbreaks are possible. Maintaining an index of suspicion will permit early recognition of the disease.[128]



E-FIGURE 260-5 Spongiform change in the gray matter should raise the suspicion of transmissible spongiform encephalopathy, but such vacuolation (arrows) of neurons and their processes can be seen in hereditary diseases such as hereditary spongiform encephalopathy in this Rottweiler dog.

Hereditary or Metabolic Encephalopathies

Hereditary spongiform polioencephalopathy has been identified in the Rottweiler, Black Russian Terrier, Australian Cattle Dog, Shetland Sheepdog, Lagotto Romagnolo, and an Egyptian Mau cat.[129-134] A maternal inheritance pattern has been determined in Australian cattle dogs and Shetland sheepdogs. The first signs recognized in affected <1-year-old dogs were seizures. After variable periods, progressive ataxia, vestibular signs, thoracic limb atrophy and muscle rigidity was noted, ultimately causing recumbency[71,131,135] Symmetrical increased signal was apparent on T2W MRI in the cerebellar, vestibular, and other brainstem nuclei.[135] At necropsy, there is vacuolar degeneration in the neuropil, astrocytes and myelin within the ventral horns of the spinal cord, cerebellar and brainstem nuclei. A mutation was found in mitochondrial encoded cytochrome *b (CYTB).*[136] In Rottweilers and Black Russian Terriers, beginning at 6-8 weeks of age, affected pups develop progressive laryngeal paralysis, tetraparesis and proprioception deficits most prominent in the pelvic limbs, and cerebellar ataxia.[129] No abnormal prion proteins were detected in these dogs,[129] and mutations have not been found in the prion protein gene. Malinois Shepherd crosses and Malinois with congenital generalized tremors have been reported with diffuse vacuolation of the cerebellar nuclei, and Bull Mastiffs with hydrocephalus and cerebellar ataxia have cerebellar roof nuclei spongiform changes.[137-139] While these conditions are rare, it is important to differentiate them from TSEs, with their public health implications.

Polioencephalomyelopathies

Because neurons have a high metabolic demand, they are particularly susceptible to disturbances of energy metabolism and involvement of gray matter suggests a metabolic deficit that creates dysfunction in neurons or glia. The clinical signs of polioencephalopathies vary widely, but because neurons of the cerebral cortex are often affected, seizures and behavior changes are common, as are cerebellar ataxia, and sensory or motor deficits. Thiamine deficiency has propensity to involve the periventricular gray matter, lateral geniculate nuclei, caudal colliculi and vestibular nuclei.[140-143] Polioencephalomyelopathy, associated with altered mitochondrial metabolism, has characteristic bilaterally symmetrical cavitating lesions of necrosis and spongy degenerative changes in the neuropil of the thalamus, basal nuclei

midbrain and brainstem. These changes are characteristic of subacute necrotizing encephalopathy, also referred to as Leigh or Leigh-like syndrome in people. Subacute necrotizing encephalopathy has been described in several breeds of dogs including Australian Cattle Dogs, Alaskan Huskies, Yorkshire Terriers, and American Staffordshire Bull Terriers.[145-149] Please see the "inborn errors of metabolism" section of this chapter for additional discussion.

Brain Neuronal Degeneration

Multisystem neuronal degeneration involves CNS axonopathies, neuronopathies and, in some, neuropathies. These disorders can resemble the motor neuron diseases.[150] A diffuse multisystemic chromatolytic neuronopathy, involving loss of Nissl bodies in motor neurons without neuron loss in the spinal cord, brainstem and thalamus has been reported in the Cairn Terrier.[151-153] Cocker Spaniels present with abnormal gait, tremors and thalamocortical dysfunction.[154] A central-peripheral axonopathy with motor neuron depletion has been reported in the Golden Retriever.[155]

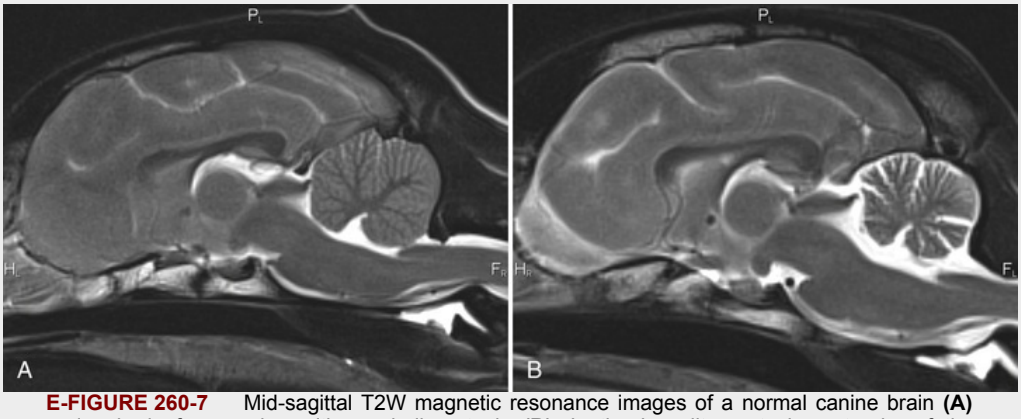
Multiple Systems Degenerations

When the cerebellum and basal ganglia are involved in a disease process, the conditions are referred to as multiple systems degenerations. The basal ganglia, such as the caudate nucleus and substantia nigra, are important in movement and are affected in Huntington's and Parkinson's disease in humans. The best characterized syndrome of this type in animals is the disease of Kerry Blue Terriers and Chinese Crested dogs called progressive neuronal abiotrophy (PNA) by breeders.[156-159] In these dogs, cerebellar ataxia begins at 8-12 weeks of age, but is followed at 6-12 months of age by degeneration of the basal ganglia. As the basal ganglia degenerate, affected dogs have increasing difficulty initiating movements and maintaining balance. Some exhibit "festinating locomotion" in which the dog begins to lose balance and then runs that direction to keep from falling (E-Figure 260-6). The degeneration of the basal ganglia is visible on MRI as an increased T2 signal. Severe motor difficulties are usually noted before 1-2 years of age.[159]

E-FIGURE 260-6 As Chinese Crested dogs with multiple system degeneration progress from cerebellar ataxia to basal ganglia degeneration, they develop difficulty initiating movements. They may shift weight forward until they begin to fall, and then they are able to move forward.

Cerebellar Degenerations

Cerebellar degeneration, in dogs, is in the hereditary ataxia subgroup, a heterogeneous group of neurodegenerative diseases characterized by symmetrical cerebellar ataxia.[160] Primary cerebellar cortical degeneration can be further subdivided into diseases that primarily affect the Purkinje and/or granular neurons. Numerous descriptions of different cerebellar degenerations have been reported in purebred dogs and cats. Signs may manifest as neonatal, juvenile or adult onsets and are progressive. Routine laboratory testing and CSF analysis are normal and will rule out other acquired causes. MRI can reveal atrophy of the cerebellum (E-Figure 260-7).[161] Genetic tests for some of these disorders have been developed and enable a definitive diagnosis.[160]

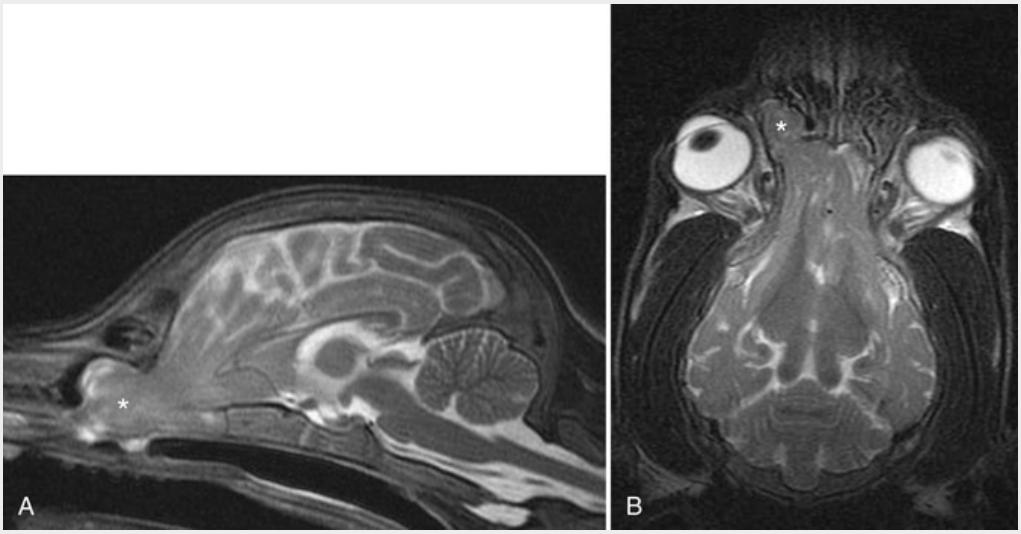


E-FIGURE 260-7 Mid-sagittal T2W magnetic resonance images of a normal canine brain **(A)** and a brain from a dog with cerebellar ataxia **(B).** In the hereditary ataxias, atrophy of the cerebellar cortex may be apparent as shrinkage and flattening of the cerebellum with an increased space between the folia **(B).**

Anomalies

Disorders of Mesoderm Induction

The calvaria develops from axial mesoderm induced by development of brain parenchyma.[162] Typically, cranial mesodermal defects are most apparent in midline structures. In some, concurrent malformation of overlying tissues allows protrusion of meningeal (meningocele) or brain tissue (meningoencephalocele; E-Figure 260-8).[53,164] Some cranial defects can be surgically treated.[165,166] Craniofacial malformations in Burmese cats, selected for a brachycephalic facial appearance, have an autosomal dominant inheritance pattern.[167] The genetic defect causes abnormal migration of neural crest cells (neuroectoderm) secondarily causing varying severities of meningoencephalocele and hydrocephalus.[168]



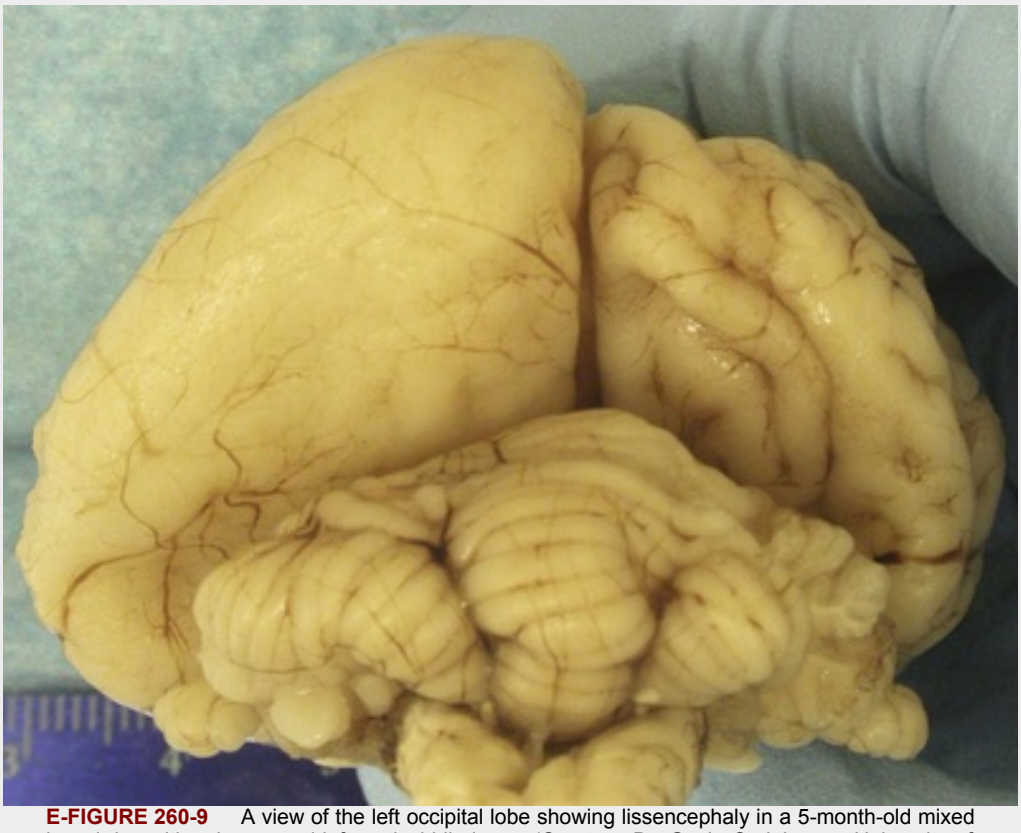
E-FIGURE 260-8 Mid-sagittal **(A)** and dorsal **(B)** T2-W magnetic resonance images of a unilateral ethmoidal meningoencephalocele in a 6-month-old Rottweiler with seizures. A portion of the olfactory bulb (asterisk) is herniated into the left caudal nasal cavity.

Disorders of Forebrain Induction

Forebrain developmental disorders include holoprosencephaly, arrhinencephaly and cyclopia. In holoprosencephaly, the cerebrum and other midline structures fail to separate and there may be incomplete formation of other midline areas. Agenesis of the corpus callosum usually is accompanied by other defects but can be a distinct malformation. The most common presenting clinical sign identified in association with corpus callosum agenesis was hypodipsia/adipsia that led to episodes of hypernatremia.[169]

Disorders of Neuronal Migration

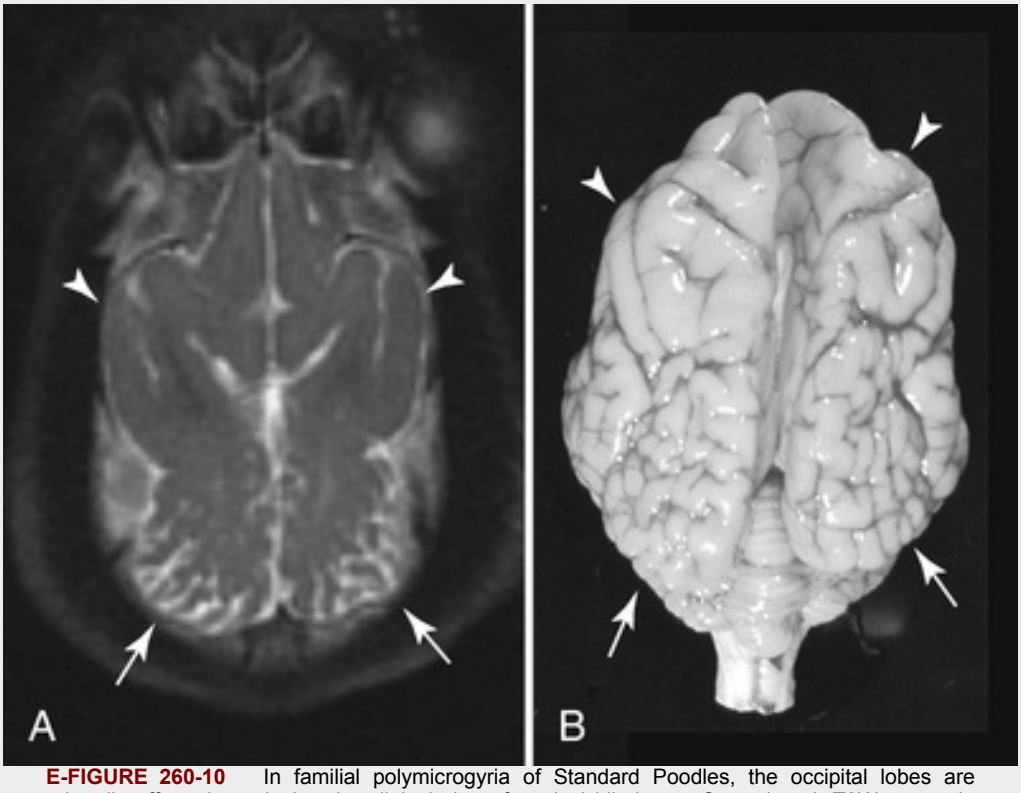
Once the neural tube has formed, differentiation of various brain components occurs which can be disrupted by genetic or environmental influences. Migration of neurons within the cerebral cortex leads to the characteristic sulci and gyri and the normal laminar arrangement of neurons within the cortex. Brain malformations can be caused by abnormalities in neuronal migration. In lissencephaly, some or the entire surface of the cortex is smooth (agyria; E-Figure 260-9) and reflected by microscopic thickening of the cortical laminae, which can be visualized on MRI in dogs.[163,170] In humans, a variety of mutations has been associated with lissencephaly and a genetic etiology is suspected in dogs because it has been recognized primarily in purebreds, including the Lhasa Apso, Irish Setter, Wire Fox Terrier and Samoyed.[164,170,171] Affected dogs showed behavioral changes, vision deficits and seizures.



E-FIGURE 260-9 A view of the left occipital lobe showing lissencephaly in a 5-month-old mixed breed dog with seizures and left cortical blindness. (Courtesy Dr. Gayle C. Johnson, University of Missouri.)

Polymicrogyria is a disorder of cerebrocortical development resulting in excessive production of small gyri and often accompanied by hydrocephalus. It has been reported as a familial disease of Standard Poodles (E-Figure 260-10). The occipital lobes are preferentially affected, with cortical blindness being the primary clinical sign.[172,173] In other conditions such as heterotopia, the gross structure of the brain is

normal, but the laminar arrangement of neurons and white matter within the cortex is disrupted, leading to abnormally placed nests or rows of neurons. Such dysplasia has been observed in the cerebellar cortex but was associated with severe motor problems suggesting that more than cerebellar function was disrupted even though dysplasia was not apparent in other areas.[174]



E-FIGURE 260-10 In familial polymicrogyria of Standard Poodles, the occipital lobes are primarily affected, producing the clinical sign of cortical blindness. On a dorsal, T2W magnetic resonance image **(A)** or necropsy **(B)** the multiple, small gyri can be seen (arrows) in contrast to the more normal gyri in the frontal lobes (arrowheads).

Cerebellar hypoplasia is seen most commonly in cats following *in utero* or early neonatal infection with the feline panleukopenia virus (see ch. 225). The rapidly multiplying granule cells of the cerebellum are sensitive to damage by the virus at this stage of development.[53,175] Though apparently much less common, there is now evidence that canine parvovirus infection can produce similar damage to the developing cerebellum.[176] Cerebellar aplasia or hypoplasia can also occur as an isolated malformation without evidence of infection, or as part of a more generalized brain development abnormality. The Dandy-Walker syndrome of humans is characterized by agenesis of the cerebellar vermis and hydrocephalus. A similar malformation has been described in dogs and cats.[53,164,177-180] Recently a mutation in *VLDR,* encoding the very low density lipoprotein receptor, was found to underlie a Dandy-Walker malformation in the Eurasier dog.[181,182]

Hydrocephalus

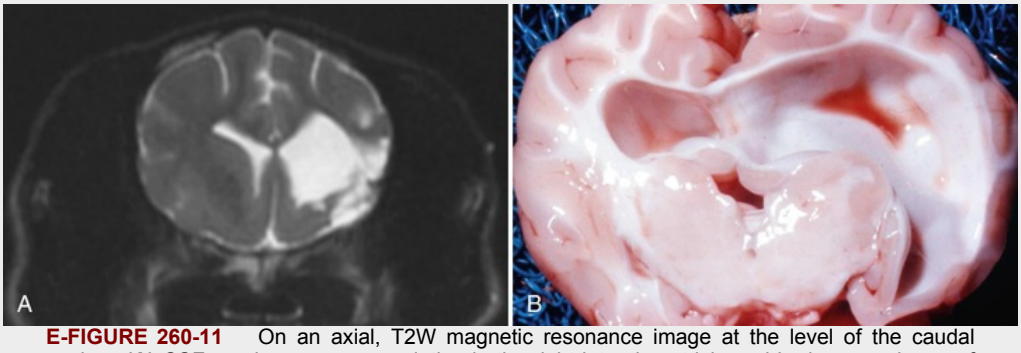
Definitions

Hydrocephalus is broadly defined as an active distension of the ventricular system of the brain related to inadequate passage of CSF from its point of production within the ventricular system to its point of absorption into the systemic circulation.[183] An animal diagnosed as being hydrocephalic has clinical signs of neurologic dysfunction related to the dilated ventricles. The term "ventriculomegaly" is used to describe an incidental imaging finding in animals with subjectively dilated lateral ventricles and no clinical signs of dysfunction caused by the enlargement. Hydrocephalus can be classified as communicating or noncommunicating based on its involvement with the ventricular system and subarachnoid space.

Hydrocephalus is further classified as intraventricular and extraventricular obstructive

hydrocephalus.[183,184] In intraventricular obstructive hydrocephalus, the blockage of CSF flow through the ventricular system is most commonly seen at recognized bottle-necks: the connection between the lateral ventricle and the third ventricle (the interventricular foramen) or most commonly, the connection between the third and fourth ventricle (the mesencephalic aqueduct). Obstruction of one interventricular foramen will result in unilateral dilation of the lateral ventricle. With obstruction of the mesencephalic aqueduct, both lateral ventricles and the third ventricle will dilate. Obstruction at the lateral apertures usually shows marked enlargement of the 4th ventricular and to a lesser degree the rostral aspects of the ventricular system. Diffuse dilation can be seen when absorption of CSF from the subarachnoid space into the venous drainage is impeded—for example, by inflammation or neoplastic infiltrates of the arachnoid villi or in the subarachnoid space.

Extraventricular hydrocephalus occurs with obstruction at the level of the subarachnoid space or arachnoid villi and the entire ventricular system and subarachnoid space dilate. Ventricles also dilate in response to atrophy or necrotic processes of surrounding brain tissue, called compensatory hydrocephalus or hydrocephalus *ex vacuo* (E-Figure 260-11). Rarely, fluid can accumulate outside the ventricular system. External hydrocephalus results from CSF accumulating in the subarachnoid space, presumably due to obstruction of flow secondary to inflammation.[185] Another common site of fluid accumulation is in the quadrigeminal cistern between the cerebellum and cerebrum that has been recognized as an intracranial intraarachnoid cyst or quadrigeminal cyst.[186-189] This can be an incidental finding but will produce clinical signs if causing excessive compression, particularly on the cerebrum and cerebellum.[187,190]



E-FIGURE 260-11 On an axial, T2W magnetic resonance image at the level of the caudal nucleus **(A)** CSF can be seen accumulating in the right lateral ventricle and brain parenchyma of the parietal and temporal lobes. On necropsy at the level of the thalamus **(B),** hydrocephalus *ex-vacuo* was confirmed in a Pug dog with right persistent circling and central blindness.

Causes of Hydrocephalus

Causes of obstructive hydrocephalus are classified as congenital or acquired. Acquired hydrocephalus usually occurs when a disease process such as neoplasia, hemorrhage or inflammation occludes the flow of CSF. Neoplasia can cause compression of a segment of the ventricular system or ventricular occlusion by drop metastasis that impedes CSF flow. Brain injury from hydrocephalus is due to effects of tissue compression or indirectly caused by damage to the blood vasculature.[184] The intraventricular increase in CSF pressure may eventually lead to focal destruction of the ependymal lining, compromise of cerebral vessels and damage to the periventricular white matter.[191-193] The resulting interstitial edema in severe cases leads to neuronal injury and neuronal loss in the cerebral cortex.

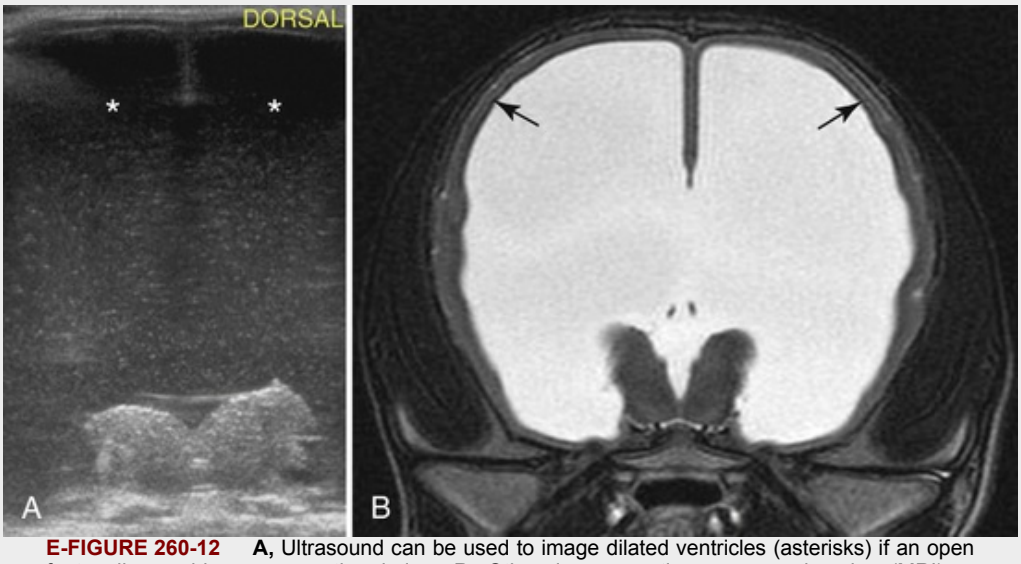
Congenital hydrocephalus is a common and defined entity in some toy and brachycephalic breeds but there is little published research on the condition.[194] It is occasionally seen in conjunction with other congenital problems such as Chiari-like malformations, polymicrogyria or cerebellar ataxia in Bull Mastiffs.[139,173,195] A commonly identified cause in predisposed breeds is stenosis or absence of the mesencephalic aqueduct associated with fusion of the rostral colliculi.[53,164,196] Neonatal infections, such as parainfluenza virus in dogs, can result in stenosis without leaving any trace of the etiology once the initial ependymitis has resolved.[197,198] The strong breed predilection, however, suggests a hereditary basis. Presence of an open fontanelle is common in many toy breeds (e.g., Chihuahua), but does not necessarily indicate presence of hydrocephalus.

Onset of signs and their rate of progression is variable in dogs and cats with congenital hydrocephalus.

A retrospective study showed that 30% of dogs were >2 years of age.[194] Clinical signs of hydrocephalus include behavioral changes, ataxia, visual deficits and seizures. Physical features may include an enlarged and dome-shaped calvaria, persistent cranial sutures and fontanelle. Ventrolateral strabismus is common in congenital hydrocephalus, but it is not clear whether this is due to oculomotor nerve damage, brainstem compromise, or orbital malformation. Lateralized signs (circling) are evident with obstruction of the intraventricular foramen causing dilation of one lateral ventricle. Even in congenital cases, the disease may follow a waxing and waning course. Sometimes dramatic hydrocephalus may be present and the owners report few clinical signs other than learning deficits.[199] Increased intracranial pressure can lead to tentorial herniation, particularly in acute, obstructive hydrocephalus.

Diagnosis

Hydrocephalus can be diagnosed with electrophysiologic and imaging studies. EEG may show a characteristic pattern of high voltage synchronous activity, but imaging the dilated ventricles is necessary to confirm the diagnosis. If a persistent fontanelle is present, the ventricles can often be adequately imaged with ultrasound. If not, cross-sectional imaging of the dilated ventricles is necessary to rule out obstructive disease or another congenital anomaly (E-Figure 260-12). Criteria of clinical relevance, based on MRI findings of canine brains, were suggested for supporting diagnosis of symptomatic internal hydrocephalus.[200] The ventricle/brain-index was significantly higher in dogs with clinical signs of hydrocephalus and a threshold value of 0.6 was specified to differentiate between internal hydrocephalus and ventriculomegaly.[200,201] Other anatomic findings indicative of clinical hydrocephalus included elevation of the corpus callosum, flattening of the interthalamic adhesion, periventricular edema, dilation of the olfactory recesses, effacement of the cortical sulci, attenuation of the subarachnoid space and disruption of the internal capsule.[200]



E-FIGURE 260-12 **A,** Ultrasound can be used to image dilated ventricles (asterisks) if an open fontanelle provides an acoustic window. **B,** Otherwise magnetic resonance imaging (MRI) or computed tomography (CT) is necessary. On axial T2W MRI for the dog in **B,** only a rim margin of brain parenchyma (arrows) at the level of the thalamus was evident. The chief complaints from the owners was their dog's irritability on restraint and inability to become house-trained.

Treatment

The choice of treatment is guided by the patient's neurologic and physical status and age, and the underlying cause. Medical management of hydrocephalus is largely directed at reducing intracranial pressure, CSF production, and seizure activity.[184] Anti-seizure drugs are administered as needed and diuretics (e.g., furosemide), carbonic anhydrase inhibitors (e.g., acetazolamide) or proton pump inhibitors (e.g., omeprazole) in combination with corticosteroids or corticosteroids alone are used to decrease CSF production. Mannitol can be administered for acute decompensation, but benefits are transient. While medical therapy may ameliorate the signs, hydrocephalus tends to be a progressive disease.

Surgical treatment involves either resection of the mass lesions causing the ventricular obstruction or

shunting of CSF away from the obstructed regions of the ventricular system. Surgical treatment is reserved for animals with worsening neurologic signs that do not respond or become refractory to medical therapy. Contraindications include infection of the shunt placement sites and the procedure's inability to change the outcome with respect to severity of brain atrophy and presumptive neuronal injury, based on clinical signs.[184] Placement of a drainage device (shunt) diverts CSF from the lateral ventricle through a one-way ultra-low pressure valve and reservoir to another site such as the peritoneal space, atrium of the heart or SC space.[202-204] A pressure valve is necessary to prevent excessive drainage of CSF which could collapse the overlying cerebrum and cause subarachnoid hemorrhage, and to prevent pressure in the abdomen during coughing or exertion from being transmitted to the ventricles.

Prognosis

Prognosis for severe congenital hydrocephalus is usually guarded as clinical signs are often severe at presentation. In a retrospective study of 30 dogs and 6 cats with congenital hydrocephalus and ventriculoperitoneal shunt placement, 72% had improvement of clinical signs within a median time of 4 months.[203] Based on retrospective studies, the rate of complications varies from 22 to 30%.[203-205] Complications are most likely to develop within the first 3 months after surgery and include shunt migration from the calvaria, mechanical failure, infection and occlusion of the shunt.[203-205]

Chiari-Like Malformations and Syringohydromyelias

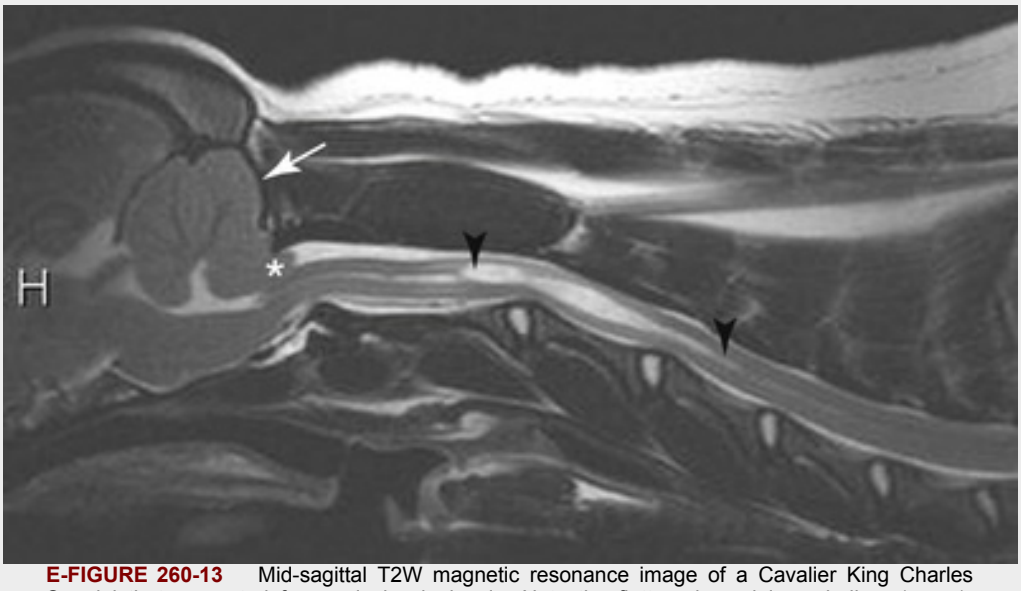
Chiari-like malformations (CM) and syringohydromyelias are recognized in small breed dogs, especially the Cavalier King Charles Spaniel (CKCS) and Brussel Griffon,[206-210] and the terminology is adopted from similar disorders in humans. In dogs, CM is characterized by herniation of the cerebellar vermis and medulla into or through the foramen magnum and indention of the cerebellum by the occipital bone.[211] In the CKCS, CM has been associated with premature closure of the spheno-occipital synchondrosis that may contribute the brachycephalic skull conformation and CM.[212,213] Additionally, a failed communication between mesodermal cartilaginous precursors of the occipital bone and neural tube closure could lead to reduce capacity of the caudal cranial fossa to contain the brain parenchyma.[206,214]

Thus, the pathophysiology of CM involves mismatch between the caudal cranial fossa volume and contained brain parenchyma leading to cerebellar herniation, medullary kinking, hydrocephalus, obstruction of the dorsal craniocervical subarachnoid space, and/or alteration of CSF flow.[214-218] A sequela of CM is development of syringohydromyelia: formation of fluid-filled cavities within the spinal cord, most commonly the cervical cord, but they can form in multiple locations.[219] In the CKCS there is an association between increased cerebellar volume and syringohydromyelia.[214] The development of syrinxes and association between CM and syringohydromyelia is complex, but it is suspected to be multifactorial including obstruction of the subarachnoid space and abnormal CSF dynamics.[220-222] There are significant associations between medullary elevation (i.e., medullary kinking), dorsal compressive atlantoaxial bands, and the presence of syringohydromyelia.[223,224] Development of hydrocephalus is likely related to reduced craniospinal compliance due to failed CSF absorption into the venous sinuses.[225] Syringohydromyelia secondary to CM in the CKCS is considered to have a complex inheritance pattern.[226-229]

In addition to signs caused by hydrocephalus or cerebellar compression, clinical signs of syringohydromyelia secondary to CM include thoracic and pelvic limb general proprioceptive ataxia, postural reaction deficits and neuropathic pain. Excessive scratching of the ear, neck, or shoulder, vocalization and facial rubbing may be the chief complaint reported by the owner.[195,230-232] Size (diameter) and asymmetry of the syrinx are the strongest predictors of pain.[231,233] The mechanisms by which syringohydromyelia leads to neuropathic pain may involve the anatomic distortion of dorsal horn resulting in abnormal processing of sensory information.[232,233] Recent studies have demonstrated decreased expression of substance P and interleukin-6 in CSF and spinal cord tissue of CKCSs with syringomyelia and persistent pain; interestingly, expression of these same mediators was increased caudal to the syringomyelia.[234,235]

Management of syringomyelia is based on an imaging diagnosis combined with severity of clinical signs. Chiari-like malformation and syringohydromyelia are readily diagnosed on midsagittal MRI on which the herniation of the cerebellum and any concurrent hydrocephalus or syringomyelia can be identified (E-Figure 260-13). Dogs exhibiting pain, neurologic deficits or with progressive signs can be

treated medically or surgically, but clinical signs can be frustrating to treat given the variability in disease progression. Initial medical therapy involves use of analgesics, including gabapentin for neuropathic pain and drugs to reduce CSF production. Surgical treatment of CM in dogs may have importance in restoring craniospinal compliance but there is limited information regarding patient selection or other criteria on which to base decisions. With improved CSF dynamics after decompressive surgery, clinical signs may resolve but recurrence is common and neuropathic pain may persist.[236-238]



E-FIGURE 260-13 Mid-sagittal T2W magnetic resonance image of a Cavalier King Charles Spaniel that presented for cervical spinal pain. Note the flattened caudal cerebellum (arrow), herniated cerebellar vermis (asterisk), brainstem medullary kinking and extensive syringohydromyelia (arrowheads) extending from C2 to C4 vertebrae.

Neurodegenerative brain diseases have a progressive course and are usually diagnosed in quite young or geriatric pets (also see ch. 263). Degenerative encephalomyelopathies can be selective, diffuse, or multifocal since the neuron or myelin often involve both brain and spinal cord (E-Table 260-6). Thalamocortical, brainstem, spinal cord and/or cerebellar signs may predominate. Findings on brain MRI may show bilateral and symmetrical selective lesions in the gray or white matter that can have a regional or diffuse distribution. Additionally, MRI findings of brain atrophy can also be regional or diffuse. However, a definite diagnosis for many of these disorders is made on biopsy or necropsy. DNA testing may be of use. Currently, there is no effective treatment for most of the neurodegenerative diseases. Genetic discoveries have enabled better understanding of the underlying disease-causing pathways that can provide targeted therapeutic studies. These therapeutic strategies include somatic gene transfer therapy, enzyme replacement therapy, heterologous cell transplantation, and RNA silencing. They hold promise and clinical trials on several disease models of dogs and cats are underway.

E-TABLE 260-6

Classification of Degenerative Encephalopathies/Encephalomyelopathies

NEUROANATOMIC PATHOLOGY	SPECIFIC DESCRIPTION
Myelinopathy	Hypo- or dysmyelogenesis
	Leukodystrophy
	Myelinolysis
	Leukoencephalomyelopathy
	Spongy degeneration involving myelin

Spongy degeneration	Neuronal vacuolation
	Myelin vacuolation
Axonopathy—Wallerian degeneration, distal axonopathy (dying-back neuropathy), segmental degeneration	Central-peripheral axonopathy
	Central-peripheral distal axonopathy
	Neuroaxonal dystrophy
Spongiform polioencephalopathy	Transmissible spongiform encephalopathy
	Spongy degeneration involving gray matter (neuronal vacuolation)
Polioencephalopathy	Necrotizing encephalopathy
Brain neuronal degeneration (neuronopathy and involving axonopathy)	Multisystem neuronal degeneration
Multiple systems degeneration	Cerebellar and basal neuron (ganglia) degeneration
Cerebellar degenerations	Primary cerebellar cortical degeneration involving primary Purkinje and/or granular neuron degeneration

Brain Anomalies (see E-Box 260-1)

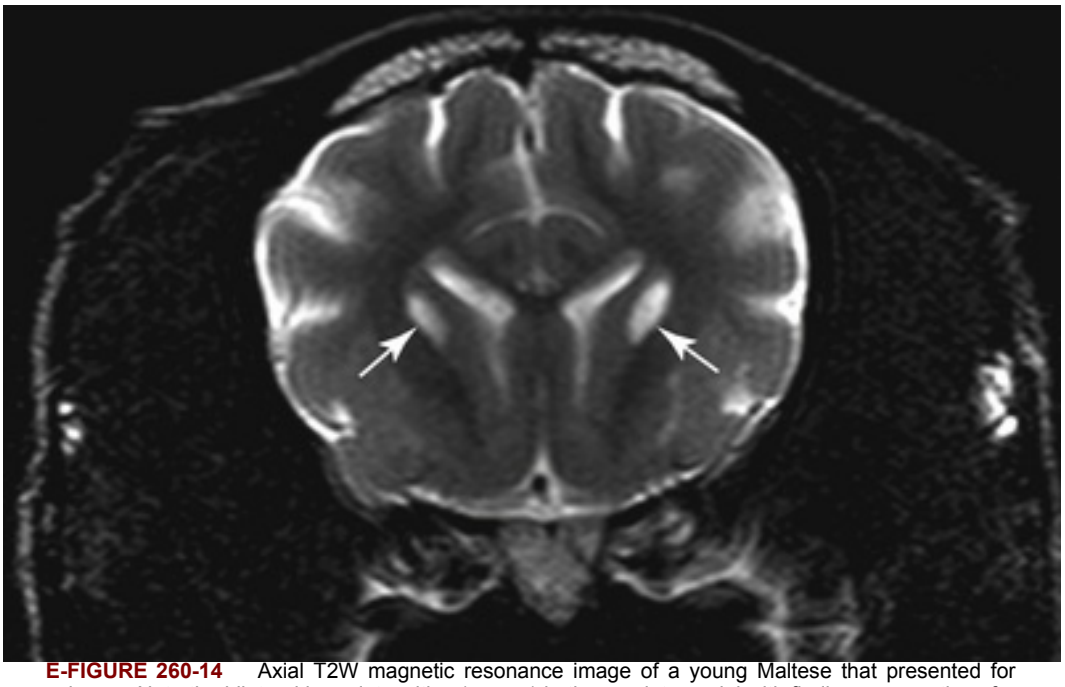
Congenital malformations of the brain would typically be present from birth and nonprogressive. A few exceptions, such as congenital hydrocephalus, can manifest later in life with progressive signs. The nervous system originates from a plate on the dorsal surface of the embryo, which folds in to form the neural tube, beginning in the thoracic area and extending rostrally and caudally. Genetic defects and *in utero* infection, intoxication, or malnutrition may cause failure of normal closure of the neural tube, typically seen at the rostral or caudal ends of the developing nervous system. Cranial neural crest cells are required for folding the tube and become the mesenchyme of the face and base of the calvaria.[162] Neural tube closure defects of the brain can vary in severity, the most severe being anencephaly with complete lack of brain development and no induction of the calvaria formation.

Severe malformations are apparent on physical examination and brain imaging.[163] Post-mortem examination may be necessary to detect more subtle deficits. Brain anomalies may accompany other defects such as cleft palate or cardiac anomalies. For most congenital malformations, treatment is symptomatic and prognosis depends on severity of the condition. History and serology can help rule out treatable toxic or infectious etiologies. Genetic, vaccine and nutritional counseling may help prevent future occurrences in breeding facilities.

Metabolic Encephalopathy

Inborn Errors of Metabolism

Inborn errors of metabolism interfere with function at a biochemical level or lead to premature neuronal death. Often signs manifest as waxing and waning diffuse and symmetric encephalopathy in neonates or the young. The earliest and most consistent signs are abnormal mentation and seizures. Neonatal encephalopathy with seizures (NEWS), for example, is a hereditary disease of standard poodles characterized by developmental delay with seizures and death before weaning with few biochemical or histological clues as to cause. A mutation in a major transcription factor (ATF2) has been identified which affects the normal programming of neuronal development.[239] Other neurologic signs vary with the regional distribution of lesions and severity of metabolic disturbance. Some diseases show characteristic bilateral and symmetric signal changes on brain MRI (E-Figure 260-14). Diet may influence severity of signs.



E-FIGURE 260-14 Axial T2W magnetic resonance image of a young Maltese that presented for seizures. Note the bilateral hyperintensities (arrows) in the caudate nuclei with findings suggestive of a metabolic encephalopathy that was diagnosed as malonic aciduria.

Some inborn errors of metabolism may be apparent on laboratory testing. Deficiencies in urea cycle enzymes increase blood ammonia concentrations while ketonuria or acidosis, without a clear underlying cause like diabetes mellitus, may reflect errors in mitochondrial metabolism. If there is accumulation of an abnormal metabolite, that product can sometimes be detected, such as blood lactate and pyruvate abnormalities in mitochondrial disorders. Identification of abnormal concentrations of certain metabolites in urine can be an ideal diagnostic aid, since metabolites may be excreted via the kidneys in high concentrations and sufficient urine volumes for assays can be collected, even from neonates. Simple urine screening tests are available for some inborn errors of metabolism, but most require testing at specialized laboratories. Serum or CSF may need to be assayed for metabolites that are not detected in urine while other tests measure specific enzyme activities.

Bilaterally symmetrical CNS lesions may be either manifestations of selective susceptibility of cellular populations to altered metabolisms or be determined by vascular anatomy (ischemia). Many inborn errors of metabolism affect other organs evaluated more readily than the brain. If peripheral nerves are involved, a nerve biopsy may yield clues—e.g., the presence of vacuolated macrophages in globoid cell leukodystrophy (see E-Figure 260-4). Occasionally such vacuolated cells may be visible on routine blood smears or CSF analysis. Because muscle also has a high metabolic demand, diseases affecting energy metabolism may show changes on muscle biopsy. If there is hepatomegaly or lymphadenopathy accompanying neurologic signs, a biopsy of one of these more accessible organs may reveal storage products.[240,241]

Mitochondrial Encephalopathy

Subacute necrotizing encephalopathy, known as Leigh syndrome or Leigh-like syndrome in people, consists of defects of the mitochondrial respiratory chain or pyruvate metabolism. Lesions are attributed to vascular congestion, caused by lactic acidosis resulting in hypoxemia and necrosis. Clinical signs include ataxia, paresis, movement disorders, cognitive deficits, nystagmus and seizures. Mitochondrial encephalopathy has been recognized as acute proprioceptive ataxia, seizures, behavior changes, central blindness, tetraparesis, and/or facial sensation deficits in Alaskan Huskies <1 year of age. Cavitating and spongiform lesions of the gray matter are seen symmetrically in the thalamus and striatum and junctional gray and white matter in the cerebral cortex, brainstem and cerebellar vermis.[145-147] These lesions are clearly visible on MRI as T2W hyperintensity.[147,242] A mutation in *SLC19A3*, encoding a thiamine transporter protein, was determined to play a role in Alaskan Husky encephalopathy.[146,242] Subacute necrotizing encephalopathy associated with combined respiratory chain defects also has been reported in Yorkshire Terriers and American Staffordshire Bull Terriers.[148,149,243]

Organic Acidurias

These diseases are characterized by abnormal organic acids due to errors in a metabolic pathway. While relatively few have been described in veterinary medicine, they are common in humans and probably occur on occasion in some purebred dogs. They can be diagnosed by urine organic acid screens and have the potential for therapeutic intervention if the deficient pathway can be bypassed. Cellular malonic acid levels regulate use of carbohydrates or fatty acids as energy sources in fed versus fasted states, respectively. A Maltese dog from a family with malonic aciduria developed seizures, stupor, hypoglycemia, acidosis, and ketonuria after a brief period of anorexia. Frequently feeding a high-carbohydrate, low-fat diet eliminated the need to rely on fatty acids as an energy source and ameliorated the clinical signs.[244]

Cobalamin (vitamin B12) is a necessary cofactor in the conversion of methylmalonyl CoA to succinyl CoA, a significant step in the Krebs cycle. Hereditary selective cobalamin malabsorption has been reported in Giant Schnauzers, Beagles, Border Collies and Australian Shepherd dogs.[245-247] Mutations in either the amnionless gene *(AMN)* or cubulin gene *(CUBN)* lead to Imerslund-Grasbeck syndrome (IGS) or selective cobalamin malabsorption. Genetic studies in dogs have demonstrated mutations in *AMN* in Giant Schnauzers and Australian Shepherds and *CUBN* in Beagles and Border Collies.[248-251] Typical clinical signs include altered mentation, inappetence and seizures associated with hyperammonemia and blood dyscrasias. Identifying high urinary methylmalonic acid (MMA) and low serum cobalamin concentrations confirms the diagnosis. Urea cycle dysfunction is a consequence of MMA accumulation. Clinical signs resolve with parenteral administration of cyanocobalamin. Cobalamin deficiency has been associated with elevated urine MMA and neurologic signs in cats, presumably due to a deficiency of intrinsic factor necessary for absorption of vitamin B12 (cyanocobalamin).[252] Gastrointestinal disease in cats can also interfere with cobalamin absorption in cats.[253,254] Cats with gastrointestinal disease can also develop a D-lactic acidosis, presumably due to excessive bacterial production of the D isoform in the intestines.[255] D-lactate is not detected by most routine lactate assays which are designed to detect the L isoform produced by mammals, but is much more likely to produce an encephalopathy.[256]

Increased concentrations of methylmalonic and malonic acids, as well as other intermediary metabolites, were found in the urine of a 12-week-old Labrador Retriever pup with progressive neurologic signs. The pup was not ketoacidotic or hyperammonemic, and cobalamin levels were normal. Diffuse atrophy of the CNS was found at necropsy, but no specific metabolic defect identified.[257] Staffordshire Bull Terriers and Yorkshire Terriers with hereditary L-2-hydroxyglutaric aciduria develop seizures, ataxia and altered behavior, usually between 4 and 5 years of age. On T2W MRI, diffuse hyperintensity is seen in the cerebral, cerebellar, thalamic, and brainstem gray matter.[258] L-2-hydroxyglutaric acid levels were elevated in urine, CSF and plasma from affected dogs.[258,259] Mutations in the dehydrogenase *(L2HGDH)* that metabolizes the organic acid have been described in Staffordshire Bull Terriers and Yorkshire Terriers.[259-261]

Lysosomal Storage Diseases

Definitions

Lysosomal storage diseases are characterized by accumulation of metabolic byproducts within lysosomes, the cellular organelle responsible for breakdown of complex macromolecules. Lysosomes maintain an acidic pH and substrates for catabolism that include sphingolipids (a major component of myelin), oligosaccharides, mucopolysaccharides, glycoproteins, and proteins (Table 260-7). The storage diseases are caused by key enzyme deficiencies, resulting in a failure to break down molecules and substrate accumulation. Most syndromes are named for the accumulated product. Proteases are less substrate-specific and single protease deficiencies are uncommon and less likely to produce problems, although ceroid lipofuscinosis may be one such defect.[240,241,262,263] Some defects interfere with cells' ability to utilize a normal enzyme. In I-cell disease (mucolipidosis) of cats, for example, there appears to be a disorder in trafficking enzymes into the lysosome, with multiple enzymes affected.[264] Some substrates must be engulfed into a double wall organelle, the autophagosome, and then delivered to the lysosome for degradation. Mutations in genes that would disrupt this process (autophagy) have recently been associated with neurodegenerative diseases in dogs. Hereditary cerebellar ataxia in Gordon Setters and Old English Sheepdogs and a neurodegenerative disease in Lagotto Romagnolos characterized by cerebellar ataxia, personality changes and neuronal vacuolation have been associated with mutations in the autophagy genes *RAB24* and *ATG4D*, respectively.[133,265] Recent reviews of storage diseases in animals are available.[240,241,262,263,266,267] Accumulation of storage products occurs over

time and onset of signs is delayed with most storage diseases despite enzyme deficiency since birth. Age of onset and severity can depend on residual enzyme function and on systems affected, since some storage diseases affect multiple organs and others only affect the nervous system. How accumulated storage products produce neurologic disease is not clear. In globoid cell leukodystrophy, one of the storage products is clearly toxic to oligodendroglia. In others, spheroid formation may be related to neuronal death.[240,241,263,268]

TABLE 260-7

Classification of Canine and Feline Lysosomal Storage Diseases

STORAGE DISEASE (HUMAN DISEASE)	ENZYME/PROTEIN DEFICIENCY (*MUTATED GENE*)	SPECIES—BREED	CLINICAL SIGNS
Glycoproteinoses			
Fucosidosis	Alpha-L-fucosidase *(FUCA1)*	C-*English Springer Spaniel*	Cerebellar ataxia, behavioral change, dysphonia, dysphagia, seizures
Mannosidosis (alpha-mannosidosis)	Alpha-D-mannosidase *(MANB)*	F-DSH, DLH, *Persian*	Cerebellar ataxia, tremor, corneal opacity, skeletal anomalies, neuropathy
Lafora's disease	Alpha-glucosidase *(EPM2A)*	C-Beagle, Basset Hound, Poodle, *wirehaired Dachshund;* F-DSH	Myoclonic epilepsy, dullness
Oligosaccharidoses/Glycogenoses			
GSD type 1 (von Gierke disease)	Glucose-6-phosphatase *(M121I)*	C-Silky Terrier, *Maltese,* other toy breeds; F-DSH	Weakness, seizures, stupor
GSD type 2 (Pompe disease)	Acid alpha-glucosidase *(GAA)*	C-Lapphund dog; F-DSH	Ataxia, muscle weakness
GSD type 3 (Cori disease)	Amylo-1,6-glucosidase *(AGL)*	C-Akita, German Shepherd, *Curly-Coated Retriever (IIIA)*	Lethargy, exercise intolerance, organomegaly
GSD type 4 (Andersen disease)	Glycogen branching enzyme *(GBE1)*	F-*Norwegian Forest cat*	Cerebellar ataxia, tremor, neuromuscular, organomegaly
GSD type7 (Tarui disease)	Phosphofructokinase *(PFKM)*	C-*English Springer Spaniel, American Cocker Spaniels, Whippets, mixed breeds, Wachtelhund Dog*	Exercise intolerance, rhabdomyolysis
Mucolipidosis			
Mucolipidosis II (I-cell disease)	N-acetylglucosamine-1-phosphotransferase *(GNPTA)*	F-*DSH*	Facial dysmorphism, dullness, retinal, ataxia
Sphingolipidoses			
GM1-gangliosidosis type 1 (Norman-Landing disease)	Beta-D-galactosidase *(GLB1)*	C-Beagle cross, *Portuguese Water Dog,* English Springer Spaniel, *Siberian Husky, Shiba dog;* F-*DSH, Siamese, Korat*	Cerebellar ataxia, corneal clouding, tremor, seizures, paralysis, skeletal facial dysmorphism
GM2-gangliosidosis (Tay-Sachs disease) (variant B)	Beta-N-acetyl hexosaminidase A (alpha subunit) *(HEXA)*	C-German Shorthair Pointer; *Japanese Chin*	Cerebellar ataxia
GM2-gangliosidosis (Sandhoff disease)	Beta-N-acetyl hexosaminidase B	C-Golden Retriever, *Toy Poodles;* F-*DSH-Japan, Korat, Burmese-Europe*	Cerebellar ataxia

(variant O)	(beta subunit) *(HEXB)*		
GM2AB-gangliosidosis (Bernheimer-Seitelberger disease) (variant AB)	GM2 activator protein deficiency *(GM2A)*	F-*DSH*	Cerebellar ataxia
Galactosialidosis	Galactosialidosis with alpha-neuraminidase	C-Schipperke (5 yr)	Cerebellar ataxia
Glucocerebrosidosis (Gaucher's disease)	Beta-D-gluco cerebrosidase	C-Sydney Silky dog	Cerebellar ataxia
Globoid cell leukodystrophy (Krabbe's disease)	Beta-D-galactosyl ceramidase *(GALC)*	C-*West Highland White Terrier, Cairn Terrier, Beagle, Poodle,* Australian Kelpie; Basset Hound, Blue Tick Hound, Pomeranian, *Irish Setter;* F-DSH, DLH	Cerebellar ataxia, tremor, paraparesis, neuropathy
Metachromatic leukodystrophy	Arylsulfatase A	F-DSH	Progressive motor dysfunction, seizures, opisthotonus, neuropathy
Sphingomyelinosis (Niemann-Pick disease type A)	Sphingomyelinase	C-Miniature Poodle; F-Balinese, Siamese	Cerebellar ataxia, tremor, paraparesis, neuropathy; biopsy
(Niemann-Pick disease type C)	Cholesterol esterification deficiency *(NPC1, NPC2)*	C-Boxer; F-*DSH*	C-cerebellar ataxia, hepatomegaly, neuropathy; F-cerebellar ataxia
Mucopolysaccharidoses			
MPS I (Hurler's syndrome)	Alpha-L-iduronidase *(IDUA)*	C-*Plott Hound,* Rottweiler, mixed breed; F-*DSH*	Growth retardation, facial deformity, lameness, corneal opacity
MPS II	Iduronate-2-sulfate sulfatase	C-Labrador Retriever	Cerebellar ataxia, exercise intolerance, corneal opacity, facial dysmorphism
MPS III (A, B, E)	A: Heparin sulphamidase *(SGSH)* B: N-acetyl-alpha-D-glucosaminidase *(NAGLU)* E: Arylsulfatase G *(ARSG)*	C-*Huntaway dog* (IIIA), wirehaired Dachshund (IIIA) *Schipperke* (IIIB) *American Staffordshire Terrier* (IIIE)	Cerebellar ataxia, tremor, retinal degeneration, corneal opacity
MPS VI (Maroteaux-Lamy disease)	N-acetylgalactosamine 4-sulfase (Arylsulfatase B) *(ARSB)*	C-Miniature Pinscher, Miniature Schnauzer, *Miniature Poodle,* Welsh Corgi; F-*Siamese cat,* DSH	Growth retardation, facial deformity, corneal opacity, spinal proliferations
MPS VII (Sly syndrome)	Beta-D-glucuronidase *(GUSB)*	C-mixed breed; F-*DSH*	C-paraparesis, cardiac; F-growth

			retardation, facial deformity, corneal opacity, spinal proliferations
Neuronal Ceroid Lipofuscinoses (Batten's Disease)			
CLN 1	Palmitoyl protein thioesterase 1 *(PPT1)*	C-*Miniature Dachshund*	Visual deficits, cerebellar ataxia, cognitive impairment, myoclonus, seizure
CLN 2	Tripeptidyl-peptidase *(TPP1)*	C-*Longhaired Dachshund*	Same
CLN 5	Soluble lysosomal protein CLN5 *(CLN5)*	C-*Border Collie; Golden Retriever*	Same
CLN 6	Transmembrane protein CLN6 *(CLN6)*	C-*Australian Shepherd*	Same
CLN 7	Major facilitator superfamily domain MFSD8 *(MFSD8)*	C-*Chinese Crested dog*	Same
CLN 8	Transmembrane protein CLN8 *(CLN8)*	C-*English Setter; Australian Shepherd Mix*	Same
CLN 10	Cathepsin D *(CTSD)*	C-*American Bulldog*	Same
CLN 12	P-type ATPase *(ATP13A2)*	C-*Tibetan Terrier*	Same
Others	Unknown gene mutation	C-Australian Shepherd, Chihuahua, Cocker Spaniel, Collie, Dachshund, Dalmatian, Golden Retriever, Japanese Retriever, Labrador Retriever, Miniature, Poodle, Polish Lowland Sheepdog, Saluki, Spitz, Welsh Corgi; F-Siamese cat, Japanese DSH, European DSH	

Breeds in *italics* signify gene mutation discovered.

C, Canine; *CLN*, ceroid lipofuscinosis; *DLH*, domestic longhaired cat; *DSH*, domestic shorthaired cat; *F*, feline; *GSD*, glycogen storage disease; *MPS*, mucopolysaccharidosis.

Signs

Cerebellar signs of dysmetria, truncal ataxia, and nystagmus are often the first signs of storage diseases.[241] The cerebellum, dependent on fast conduction for sensory feedback during movement, is quite sensitive to disorders affecting myelin or information processing and even subtle deficits may cause signs. More profound learning or mentation deficits may be necessary in other conditions to reach a threshold for signs, which often progress to UMN weakness, behavioral abnormalities, and seizures.[241] Some diseases (e.g., neuronal ceroid lipofuscinosis) cause forebrain and visual dysfunctions before cerebellar dysfunction is noted.[269] Peripheral nerves are involved in some conditions such as globoid cell leukodystrophy, fucosidosis, glycogenosis type IV, mannosidosis and Niemann-Pick disease.[98,270] In some lysosomal storage diseases, signs of other organ involvement may be apparent. Visible retinal or cataract formation may be seen (see ch. 11). Bony and connective tissue abnormalities frequently characterize the mucopolysaccharidoses, mucolipidosis and alpha-mannosidosis, whereby radiographic examination reveals dysmorphic bony malformations of the spine and/or face. Cardiac, hepatic, splenic or lymph node enlargement may accompany the neurologic signs.

Diagnosis

The multisystemic distribution of lysosomal storage disease abnormalities affords the ability to obtain a diagnosis from extraneural tissues. Storage vacuoles may be apparent in white cells on a peripheral blood smear or, in globoid cell leukodystrophy or fucosidosis, on CSF analysis. Lymph nodes (see ch. 95), liver (see

ch. 89 and 91), spleen or muscle (see ch. 116) can be biopsied or aspirated to reveal storage vacuoles. With some lysosomal storage diseases, cross-sectional imaging using MRI can show various hyperintensities and brain atrophy.[241,267] Necropsy may be necessary to demonstrate accumulated storage products when only the nervous system is involved. Electron microscopy can demonstrate storage material contained within lysosomes. Abnormal metabolites may be detectable in urine with some of the storage diseases. Definitive diagnosis is based on molecular testing for the known mutation (see Table 260-7) and/or demonstration of deficient enzyme activity in affected tissues, leukocytes or cultured fibroblasts.

Neuronal Ceroid Lipofuscinosis (NCLs)

Definitions

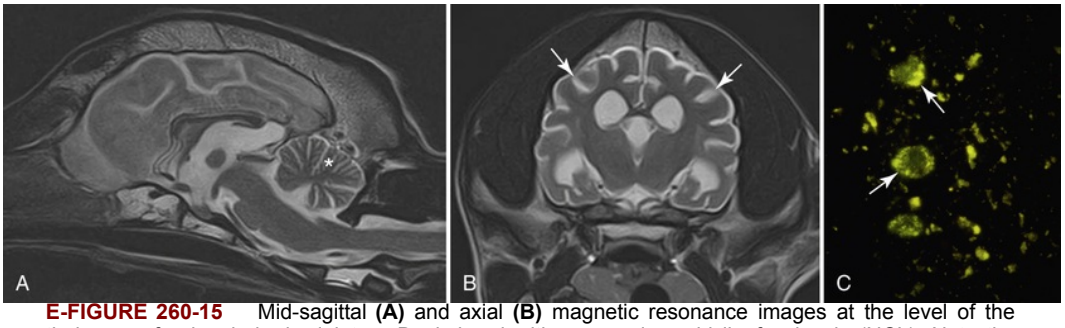
NCLs, also known as Batten disease, are a subset of lysosomal storage diseases in which the storage products are proteins with characteristic autofluorescence, similar to ceroid and lipofuscin pigments which accumulate normally with aging. The storage products in NCLs are subunit c of mitochondrial ATP or sphingolipid activator proteins (saposins A and D), due to deficient soluble enzymes. Membrane proteins are located in the lysosome, endoplasmic reticulum, or in synaptic vesicle-associated-proteins.[271,272]

Signs

Clinical signs due to NCLs include progressive visual impairments (usually the first sign, especially in dim light), decline in cognition and motor functions, seizures, generalized brain atrophy and death in young to middle age. Behavior changes become prominent with disease progression and include timidness, hyperesthesia, confusion, unprovoked aggression, seizures, jaw chomping, bruxism, and myoclonus. General proprioceptive and cerebellar ataxia tend to be later manifestations in many breeds although they are the most prominent sign in American Bulldogs with cathepsin D deficiency.[273,274]

Diagnosis and Treatment

Generalized brain atrophy can be seen on cross-sectional imaging in later stages of the disease but definitive diagnosis requires recognition of autofluorescent material in the brain or other tissues (E-Figure 260-15). Mutations responsible for many of the canine NCLs have been identified and DNA tests are available (see Table 260-7). Genetic mutations of the canine NCLs include *CLN1* (Dachshund), *CLN2* (longhaired Dachshund), *CLN4* (American Staffordshire Terrier), *CLN5* (Border Collie, Golden Retriever), *CLN6* (Australian Shepherd), *CLN7* (Chinese Crested Dog), *CLN8* (English Setter, Australian Shepherd mix), *CLN10* (American Bulldog), *CLN12* (Tibetan Terrier).[274-285] These tests assist with confirming a diagnosis and assist dog breeders in efforts to reduce the incidence of NCL in the breeds. There is no effective therapy for the storage diseases. Gene therapy, stem cell therapy and enzyme replacement therapy hold promise.[262,266,267] Symptomatic therapy for seizure control and behavior altering drugs can help ameliorate some of the signs.



E-FIGURE 260-15 Mid-sagittal **(A)** and axial **(B)** magnetic resonance images at the level of the thalamus of a longhaired miniature Dachshund with neuronal ceroid lipofuscinosis (NCL). Note the generalized brain atrophy with increased CSF hyperintensity between the gyri (arrows) of the cerebrum and folia (asterisk) of cerebellum, and ventriculomegaly. A diagnosis of NCL was based on the autofluorescent material (arrows) in neurons **(C).** (Courtesy Martin L. Katz, University of Missouri.)

Neoplasia

Intracranial neoplasia is a common condition in dogs and cats. Reviews highlight diagnosis, treatment,

imaging, and histology.[17,286-290] Tumors in brain tissue are broadly classified as primary or secondary. Primary intracranial neoplasms (Table 260-8) include tumors derived from neural, glial, or meningeal tissues, whereas secondary intracranial neoplasms are extraneural and locally invade or spread to neural tissues from a distant site.

TABLE 260-8

Primary Intracranial Neoplasms

TYPE	HISTOLOGIC EXAMPLES
Tumors of Neuroepithelial Tissue	
Astrocytic tumors	Pilocytic, subependymal giant cell, pleomorphic xanthoastrocytoma, diffuse (fibrillary, gemistocytic, protoplasmic), anaplastic, gliobastoma, gliomatosis cerebri
Oligodendroglial tumors	Oligodendroglioma, anaplastic oligodendroglioma
Oligoastrocytic tumors	Oligoastrocytoma, anaplastic oligoastrocytoma
Ependymal tumors	Subependymoma, myxopapillary, ependymoma (cellular, papillary, clear cell tanycytic), anaplastic ependymoma
Choroid plexus tumors	Choroid plexus papilloma, atypical choroid plexus papilloma, choroid plexus carcinoma
Other neuroepithelial tumors	Astroblastoma, choroid glioma, angiocentric glioma
Neuronal and mixed neuronal-glial tumors	Dysplastic gangliocytoma of the cerebellum, desmoplastic infantile astrocytoma, dysembryoplastic neuroepithelial tumor, gangliocytoma, ganglioglioma, anaplastic ganglioglioma, central neurocytoma, extraventricular neurocytoma, cerebellar liponeurocytoma, papillary glioneuronal tumor, rosette-forming glioneuronal tumor of the 4th ventricle, paraganglioma
Tumors of the pineal region	Pineocytoma, pineal parenchymal tumor of intermediate differentiation, pineoblastoma, papillary tumor of the pineal region
Embryonal tumors	Medulloblastoma (desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity, anaplastic medulloblastoma, large cell medulloblastoma), CNS primitive neuroectodermal tumor (CNS neuroblastoma, CNS ganglioneuroblastoma, medulloepithelioma ependymoblastoma), atypical teratoid/rhabdoid tumor
Tumors of the Meninges	
Tumors of meningothelial cells	Meningioma (meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte, metaplastic, chordoid, clear cell, atypical papillary, rhabdoid, anaplastic)
Mensenchymal tumors	Lipoma, angiolipoma, hibernoma, liposarcoma, solitary fibrous tumor, fibrosarcoma, malignant fibrous histiocytoma, leiomyoma, leiomyosarcoma, rhabdomyoma, rhabdomyosarcoma, chondroma, chondrosarcoma, osteoma, osteosarcoma, osteochondroma, hemangioma, epithelioid, hemangiopericytoma, anaplastic hemangiopericytoma, angiosarcoma, Kaposi sarcoma, Ewing sarcoma
Primary melanocytic lesions	Diffuse melanocytosis, melanocytoma, malignant melanoma, meningeal melanomatosis
Other neoplasms related to meninges	Hemangioblastoma
Lymphoma and Hematopoietic Neoplasms	Malignant lymphomas, plasmacytoma, granulocytic sarcoma
Germ Cell Tumors	Germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, teratoma (mature, immature, with malignant transformation), mixed germ cell tumor

Tumors of the Sellar Region	Craniopharyngioma (adamantinomatous, papillary), granular cell tumor, pituicytoma, spindle cell oncocytoma of the adenohypophysis

Adapted from the World Health Organization Classification System.

From Louis DN, Ohgaki H, Wiestler OD, et al: The 2007 WHO Classification of tumors of the central nervous system. *Acta Neuropathol* 114:97-109, 2007.

Primary Brain Tumors

Types, Metastasis, Incidence

Meningiomas comprise about 50% of primary brain tumors in dogs, gliomas 30-40% and choroid plexus tumors are less common (Table 260-9).[291-293] Primary brain tumors also include histiocytic sarcoma, granular cell tumors, lymphoma and primitive neuroectodermal tumors (PNETs). In cats, meningiomas represent about 60% of all tumor types with gliomas occurring at lower frequency.[294,295] Rarely, primary intracranial neoplasms can disseminate throughout the CNS by hematogenous or CSF ("drop metastasis") routes. Tumors with potential for extraneural spread include meningiomas, PNETs, and malignant gliomas, histiocytic tumors, and choroid plexus tumors. Narrowed ventricular system areas are predisposed to obstructive hydrocephalus and its clinical signs. Olfactory meningiomas of dogs may invade the brain through the cribriform plate.[296] Rarely, meningioma may metastasize outside the CNS to lung or pancreas.[297,298] Glial tumors rarely metastasize unless there is ventricular involvement. Ependymomas and choroid plexus tumors have the potential to implant along CSF pathways and seed to distant spinal cord tissue.[299-301] The incidence for primary CNS tumors has been reported as 14.5 in 100,000 dogs (similar to people) and 3.5 in 100,000 cats.[302-304] The prevalence of intracranial neoplasia in dogs based on necropsy data has been reported to be 2-4.5% with a prevalence of primary neoplasms at 2.3% of total population (2.8% in dogs > 1 year) and secondary neoplasms at 2.2% (2.6% in dogs > 1 year).[291]

TABLE 260-9

Magnetic Resonance Imaging Scan Features of Common Canine and Feline Brain Tumors

TUMOR TYPE	ANATOMIC LOCATION	MR SIGNAL CHARACTERISTICS*	CONTRAST ENHANCEMENT	TUMOR MARGINATION AND EDEMA
Tumors of Neuroepithelial Origin (Intra-Axial)				
Astrocytoma Histologic origin: astrocytes	Rostrotentorial (frontal, periform, temporal lobes); thalamus in higher grade; infratentorial can occur; ventricular contact but do not invade	T1W-mild to moderate hypointense; T2W-moderate hyperintense	Variable; low grade-minimal to mild; higher grade-moderate to marked, nonuniform or peripheral (ring) enhancement	Distinct to indistinct margins; peritumoral edema is variable; high grade tumors may contain hemorrhage; may contain cystic regions
Oligodendroglioma Histologic origin: oligodendrocyte	Usually rostrotentorial (frontal, piriform, temporal lobes); can have surface and ventricular contact, drop metastasis	T1W-moderate hypointense; T2W-hyperintense, marked when mucinous	Variable; low grade-minimal to mild; higher grade-moderate to marked, nonuniform or peripheral (ring) enhancement	Distinct to indistinct margins, globular; tend to have less peritumoral edema than astrocytomas; high grade tumors may contain hemorrhage; may contain cystic regions
Gliomatosis cerebri Histologic origin: most	Focal or multifocal lesions, spread down white	T1W-iso- to hypointense; T2W-hyperintense;	Minimally or nonenhancing;	Indistinct margins; minimal

astrocytic; oligodendroglial?	matter, periventricular, subpial lesions or diffuse meningeal lesions; histologic origin as oligodendroglial or astrocytic	no detection	meningeal lesions can enhance	peritumoral edema; no mass effect
Medulloblastoma/primitive neuroectodermal tumors (PNETs) Histologic origin: Embryonic neuronal tumor	Medulloblastoma-cerebellum; PNETs-olfactory/ frontoparietal lobes	T1W-iso- to hypointense; T2W-hyperintense	None to mildly heterogeneous; PNETs can have marked enhancement	Distinct to indistinct margins
Ependymoma Histologic origin: ependymal lining cells of ventricular system	Common in lateral, 3rd and 4th ventricles; suprasellar region; less common than CPTs	T1W- hypo- to slight hyperintense; T2W-moderate to hyperintense	Variable; none to marked heterogeneous enhancement	Usually distinct conforming to shape of ventricle; absent to minimal peritumoral edema; may contain cysts or hemorrhage; cause ventriculomegaly
Choroid plexus tumor (CPT) Histologic origin: choroid plexus epithelium	Lateral, 3rd and 4th ventricles and lateral apertures; most occur in 4th ventricle; drop metastasis	T1W-hypo-, iso- or hyperintense; T2W-hyperintense; can appear heterogeneous when hemorrhage	Marked, homogeneous enhancement	Usually distinct conforming to shape of ventricle with invasion into tissue; absent to minimal peritumoral edema; may contain cysts or hemorrhage; cause ventriculomegaly
Tumors of the Meninges (Extra-Axial)				
Meningioma (dogs) Histologic origin: leptomeninges or cells forming arachnoid granulations	Most common in meninges of olfactory bulbs and frontal lobes and then cerebral, cerebellar convexities associated with basilar, tentorial, falcine and suprasellar; can penetrate cribriform plate	T1W-usually isointense, heterogeneous; T2W-hyperintense	Usually marked, homogeneous enhancement, can be heterogeneous	Distinct margins, globoid, dural tail, plaque-like, broad base; peritumoral edema; cysts are common
Meningioma (cats) Histologic origin: leptomeninges or cells forming arachnoid granulations	Most common in meninges of cerebral convexity-parietal common, cerebellum; can be multiple	T1W-iso- to hypointense; T2W- hyperintense; signal void from ossification in tumor and hyperostosis of calvaria	Marked, uniform enhancement; can be heterogeneous	Distinct margins with smooth or irregular borders; peritumoral edema; cysts are common
Granular cell tumor Histologic origin: unknown, meningeal origin is suspected	Plaque-like mass extending along meninges of cerebral convexity and floor, falx, suprasellar	T1W-moderate hyperintense; T2W hyperintense	Marked, homogeneous enhancement; meningeal involvement	Irregular but defined margins, plaque-like; peritumoral edema
Lymphoma and Hematopoietic Tumors				
Lymphoma (primary or metastatic) Histologic origin: B or T cell;	Intra- or extra-axial; primary-rostrotentorial,	T1W-iso- to hypointense; T2W-iso-to hyperintense	Variable; homo- to heterogeneous enhancement;	Indistinct margins; minimal to moderate

Dog-B cell, Cat-B or T cell	suprasellar, often near ventricle; metastatic—often meninges with parenchymal invasion; focal or multifocal		diffuse meningeal enhancement	peritumoral edema
Histiocytic sarcoma Histologic origin: arise from interstitial dendritic cells of meninges	Usually extra-axial but can be intra-axial; restricted to meninges and choroid plexus near olfactory, cerebral convexity, cerebellum; focal or diffuse	T1W-iso- to hypointense; T2W-iso-, hypo- to heterogeneous intensity	Moderate, homo- to heterogeneous enhancement; mild to marked, diffuse meningeal enhancement	Indistinct to distinct margins, dural tail, plaque-like; mild to marked peritumoral edema
Sellar Region Tumors				
Pituitary tumors	Most arise from the adenohypophysis into sellar region (>10 mm)	T1W-isointense; T2W-mild hyperintense	Marked homogeneous enhancement	Distinct margins; mild to moderate peritumoral edema when large; may be cystic or hemorrhagic
Metastatic Tumors				
Metastasis	Usually multifocal lesions; gray-white matter interface cerebrum	T1W-mixed intensity; T2W-mixed intensity	Variable contrast enhancement; peripheral (rim) enhancement	Indistinct margins; marked peritumoral edema; some tumors (e.g., hemangiosarcoma) have hemorrhage and cysts

*Compared to gray matter.

References 17, 288, 289, 301, 305, 334, 337, 338, 343, and 344.

Age, Gender, Breed and Risk Factors

Primary brain tumors typically affect older dogs, with no sex predilection and a median age of 9 years (range, 4 to 13 years); 95% are older than 5 years.[292,293] The median age for dogs with meningiomas, gliomas (astrocytoma, oligodendroglioma) and choroid plexus tumors is reported as 10-14 years, 8 years, and 5-6 years, respectively.[291,293,301,305] Primary brain tumors, particularly gliomas, can be seen in younger dogs.[291,306] The Boxer, Boston Terrier, Golden Retriever, French Bulldog and Rat Terrier have increased risk of primary intracranial neoplasia.[291] Dolichocephalic breeds may be at increased risk for meningiomas, whereas brachycephalic breeds may have increased risk for gliomas.[291,293] Certain breeds were found to be at a significantly increased risk for specific primary intracranial neoplasms, including Golden Retrievers, mixed breed, Miniature Schnauzers, Rat Terriers for meningiomas; English Toy Spaniels, Boston Terriers, French Bulldogs, Boxers, English Bulldogs and Bullmastiffs for gliomas; and Dalmatians and English Setters for choroid plexus neoplasms/ependymomas.[291] Dogs >15 kg had increased risk of meningioma.[291] Doberman Pinschers and Cocker Spaniels were found to have a significantly decreased risk of primary intracranial neoplasms.[291]

Cats with brain tumors are older, with a median age of approximately 12 years old.[294] In feline meningiomas, male cats are affected more than female cats.[294,307] The Domestic Shorthair cat is the most common breed identified.[294] Definitive risk factors for development of brain tumors are unknown for dogs and cats. Genetics may have a role in some breeds of dogs since meningiomas (like in people) have similar phenotypes and may share similar genetic alterations leading to tumorigenesis.[308] The marked breed association of specific tumors such as gliomas with brachycephaly may provide an opportunity to decrease incidence by selective breeding.[291,309] Young cats with mucopolysaccharidosis type I have a high incidence of meningiomas, providing suspicion for a genetic basis.[310] Hormones such as estrogen and progesterone can

influence tumorigenesis.[311,312] Overexpression of vascular endothelial growth factor (VEGF) appears to be common in primary brain tumors of dogs and may correlate with tumor malignancy.[313,314]

Secondary Brain Tumors

Types

Secondary intracranial neoplasia can follow metastasis into the brain parenchyma from a distant primary site or by direct extension from adjacent tissues. Nasal tumors are the most common to spread by direct extension through the cribriform plate.[315-317] Tumor types that invade by direct extension include otic squamous cell carcinoma, pituitary tumors, calvarial tumors (osteochondrosarcomas, chondrosarcoma, multilobular osteochondrosarcomas), and nerve sheath tumors (cranial nerve V tumors). Intracranial metastasis usually occurs by the hematogenous route in dogs, with embolization at the gray-white junction or "watershed" distributions of the intracranial vasculature in the cerebral cortex and cerebellum.[13] Leptomeningeal metastasis can occur when tumor cells enter the arachnoid space hematogenously through leptomeningeal and diploic veins or the choroid plexus, or by perineural spread along peripheral and cranial nerves. Although rare, a diffuse or multifocal infiltration of leptomeninges with carcinoma cells can cause meningeal carcinomatosis.[299,318,319]

Dogs

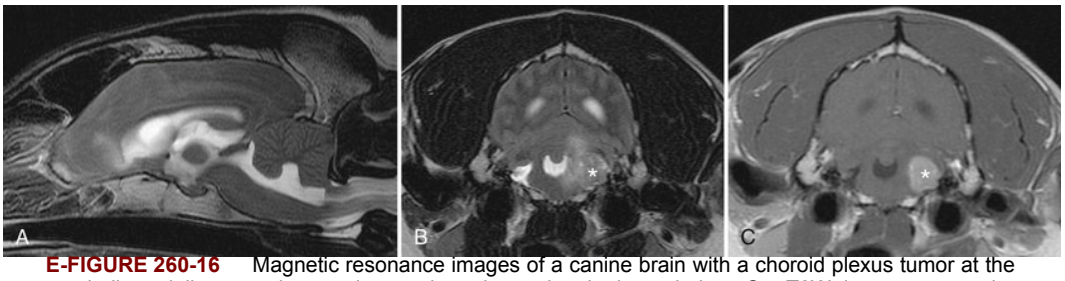
Secondary neoplasia accounts for approximately 50% of all canine intracranial tumors. In two large groups of dogs, hemangiosarcoma (29, 35%), pituitary tumors (11, 25%), lymphoma (12, 20%), metastatic carcinomas (12, 19%) extension of nasal neoplasms (6%), malignant melanoma (3%) and histiocytic sarcoma (3%) were the most common intracranial tumors.[13,291] Nerve sheath tumors (0.9%) and poorly differentiated round cell neoplasms (0.48%) were not common.[291] Metastases more often affect the cerebrum.[13,289] Secondary pituitary tumors may consist of lymphoma, carcinomas, or less commonly histiocytic sarcoma or melanoma.[13,320-322] Imaging for identification of intracranial metastases accounts for increased awareness of some cancers. Use of imaging has led to better treatment regimens for many conditions resulting in increased longevity and more time for metastasis to occur. Multifocal distribution of secondary brain tumors occurs in only 30% and concurrent unrelated neoplasms in about 18% of dogs.[13,293]

Cats

Prevalence of secondary intracranial neoplasms in cats is about 22% of brain tumors; the most common are lymphoma and pituitary tumors.[294,295,303,323] Primary renal lymphomas often spread to the CNS and the meninges may be a site for lymphoma.[324] Spread by the hematogenous route (pulmonary adenocarcinoma is most common) in cats is seen in about 6%.[294] Other secondary tumor types in cats include adenocarcinoma, squamous cell carcinoma, fibrosarcoma, malignant fibrous histiocytoma, sarcoma, and hemangiosarcoma.[294]

Clinical Signs

Clinical signs reflect the location of the intracranial tumor. Regardless of the tissue origin, focal intracranial neoplasms cause typical signs in dogs due to compression of surrounding brain tissue by the expanding mass or peritumoral edema compromising blood flow or obstructive hydrocephalus (E-Figure 260-16). Intracranial tumors may cause brain vasogenic edema, preferentially distributed in peritumoral extracellular space of white matter. As a condition progresses, clinical signs may evolve and reflect further damage due to rising intracranial pressure that causes shifts in intracranial contents. Additional damage and clinical signs can result from expansion of the tumor into nonneural tissues, such as the nasal cavity, periorbita, or the surrounding calvarium. Common neurologic signs observed in animals with brain tumors include altered mentation (e.g., obtundation, stupor, coma), seizures, ataxia, circling, and behavioral changes. Seizure (45%-51%) is most common, but circling (23%), ataxia (21%), and head tilt (13%) occur.[292,293] Dogs with intracranial neoplasia that are at higher risk for seizures from tumors that affect the frontal lobe, enhance markedly with gadolinium or cause subfalcine and subtentorial herniation.[325] Brain neoplasia should be considered as a disease differential when a dog has its first seizure after 4 years of age.[292]



E-FIGURE 260-16 Magnetic resonance images of a canine brain with a choroid plexus tumor at the cerebellomedullary pontine angle causing obstructive hydrocephalus. On T2W images, note the enlargement of the entire ventricular system **(A)** and the hyperintense mass (asterisk) at the right cerebellomedullary pontine angle **(B)** causing mass effect and edema of the medulla. On the T1W image **(C)** after intravenous gadolinium contrast administration, note the homogeneous hyperintensity of the mass (asterisk).

Clinical signs in cats are similar but often are vague or nonspecific with anorexia and lethargy being most common. In 160 cats, their most common neurologic signs were altered mentation (26%), circling (22.5%) and seizures (22.5%).[294] Cats with nonspecific neurologic signs were common (21%).[294] Behavioral changes were noted in 81% of 121 cats with meningioma.[307]

Diagnosis

Baseline Testing

When intracranial neoplasia is suspected, neuroimaging is of fundamental value, but when used alone may only prioritize a differential diagnosis. CBC, biochemical analysis, and urinalysis may be useful for identifying underlying metabolic, inflammatory, or toxic disorders that can mimic intracranial neoplasm. Thoracic and abdominal radiography and abdominal ultrasound (US) are useful screening tools to rule out metastatic disease and comorbidities that may alter treatment plans.[326] In a retrospective study of 177 dogs with secondary intracranial neoplasm, 76% had pulmonary metastasis on post-mortem examination and 39% had evidence of metastatic disease on thoracic radiography.[13] US examination of the abdomen should be included in the evaluation of any dog with CNS signs.[14]

Cross-Sectional Imaging

Cross-sectional imaging with MRI or CT is usually needed for tentative diagnosis and for identifying an area for acquisition of tissue. Biopsy requires special equipment or surgery. CT abnormalities in intracranial neoplasia consist of multifocal or focal distributions, mass effect associated with edema and neoplastic mass and ventricular asymmetry. Lesions may be difficult to detect with CT if located in the caudal fossa due to interference by the surrounding petrous temporal bone or a lack of contrast enhancement. CT is necessary for radiation planning because bony structure radiation attenuation is used in calculations.

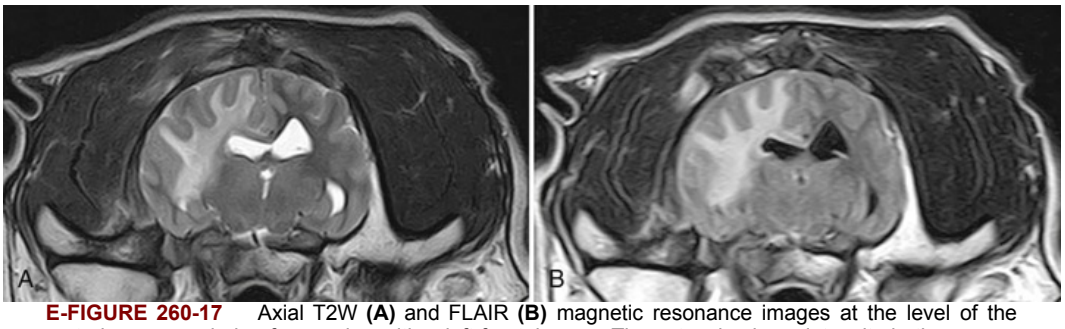
MRI Scans Are Preferred

MRI is the preferred technique for antemortem diagnosis of intracranial neoplasms. Image acquisition in multiple planes is especially useful for surgical planning. MRI can provide detail regarding tumor size, margination, tissue properties and anatomic location. MRI scans may identify secondary pathologic effects (e.g., edema, obstructive hydrocephalus) caused by a tumor.[17,289] Extra-axial masses arise from outside the brain (e.g., meninges, calvaria, ventricles) and intra-axial from within brain parenchyma. MRI features of intracranial neoplasms are often used to prioritize the differential diagnosis.[17-19,288,289,305,327] MRI patterns have been described for extra-axial meningeal and ventricular masses, intra-axial enhancing lesions, intra-axial mildly or nonenhancing lesions, and multifocal lesions in dogs. Features of each may provide suspicion for a particular tumor type (see Table 260-9).[288]

Primary Brain Tumor MRI

Based on MRI scans, the majority of primary brain neoplasms are solitary. Meningiomas, gliomas, and choroid plexus tumors can be multifocal.[293,305,311,328-332] Brain tumors are often hypo- to isointense on T1W imaging and hyperintense on T2W imaging. Mass effect (midline shift, distortion of ventricles and adjacent parenchyma and brain herniations) may be identified. Mass effect can also be caused by peritumoral edema that tends to follow the white matter (corona radiata) and is evident by hyperintensity on T2W and FLAIR

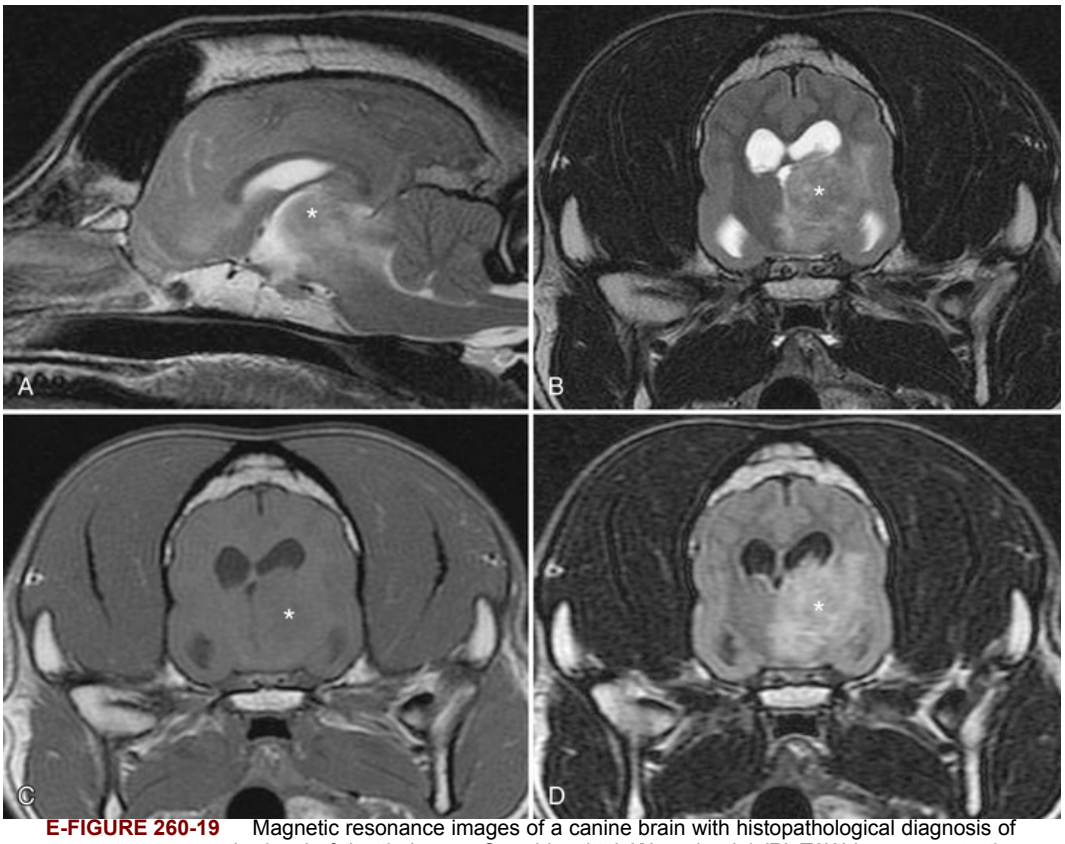
images (E-Figure 260-17). Diffuse edema is reported in 52% of canine meningiomas.[305] Most meningeal masses (e.g., meningioma, histiocytic sarcoma, granular cell tumor, meningeal carcinomatosis, lymphoma) tend to have broad-base dural contact and sometimes a "dural tail" sign.[288,289,329,333,334] A distinct border with the neuroparenchyma helps in distinguishing meningioma from extra-axial meningioma.[305] However, smaller granulomas and other intradural masses could have similar locations, a dural tail, marked and homogeneous contrast enhancement, perilesional edema and T2-hyperintensity.[293,305,323,329,335] As intra-axial masses, gliomas, including oligodendroglioma and astrocytoma vary widely in their appearance on MRI and may be confused with an embolus or inflammatory disease.[289,336] Tumor margins often appear indistinct on MRI.[337,338] There are no MRI features that reliably distinguish astrocytoma from oligodendroglioma.[338]



E-FIGURE 260-17 Axial T2W **(A)** and FLAIR **(B)** magnetic resonance images at the level of the rostral mesencephalon from a dog with a left frontal mass. The extensive hyperintensity in the corona radiata both on T2W and FLAIR images is consistent with high protein fluid content suggestive of vasogenic edema. Note the signal null in the lateral ventricles, which represents the low protein content of CSF. A mass effect is also recognized by deviation of the falx cerebri to the right and compression of the left lateral ventricle.

Many primary brain tumors on MRI demonstrate contrast enhancement after gadolinium-based contrast agents are given.[13,17,19,288,289,293,301,305,323] Contrast enhancement, well-defined margins, and regular shape are key features of neoplasia on MRI as compared with inflammatory or vascular diseases.[19,339] Peripheral ring contrast enhancement is a nonspecific finding consistent with central necrosis associated with neoplastic and nonneoplastic brain diseases.[17,288,289,340] Since the pachymeninges lie outside the BBB, most tumors (e.g., meningioma, histiocytic sarcoma, granular cell tumor, meningeal carcinomatosis, lymphoma) and granulomas that arise from this area will contrast enhance (E-Figure 260-18).[299,305,334,341-344] Of the ventricular masses, choroid plexus tumors tend to strongly contrast enhance,[301] whereas enhancement of ependymomas is more variable.[335,345] The characteristic contrast enhancement of gliomas on MRI is that of a diffuse, variable or ring-like enhancing mass compared to hypointense to isointense on pre-contrast T1W images (E-Figure 260-19).[288,293,337] This type of enhancement pattern can overlap with MRI features of intra-axial lymphoma and granuloma.[19,293,294,335] Low-grade gliomas tend to have mild to no enhancement more commonly than high-grade gliomas.[337,338] Gliomas that are classified as high-grade on histopathology tend to have moderate or marked enhancement after IV contrast administration.[293,337,338,346] However, minimal to no contrast enhancement is an imaging characteristic of gliomatosis cerebri.[347]

E-FIGURE 260-18 Magnetic resonance images of a canine brain with a histopathologically diagnosed meningioma (asterisk) at the level of the right frontal lobe. Note the broad-base proximity to the dura, heterogeneous intensity on the mid-sagittal **(A)** and axial **(B)** T2W images. Compared to the isointensity on the pre-contrast axial T1W images **(C),** the mass has a homogeneously hyperintense and well-demarcated enhancement pattern after gadolinium contrast administration on T1W images **(D).**

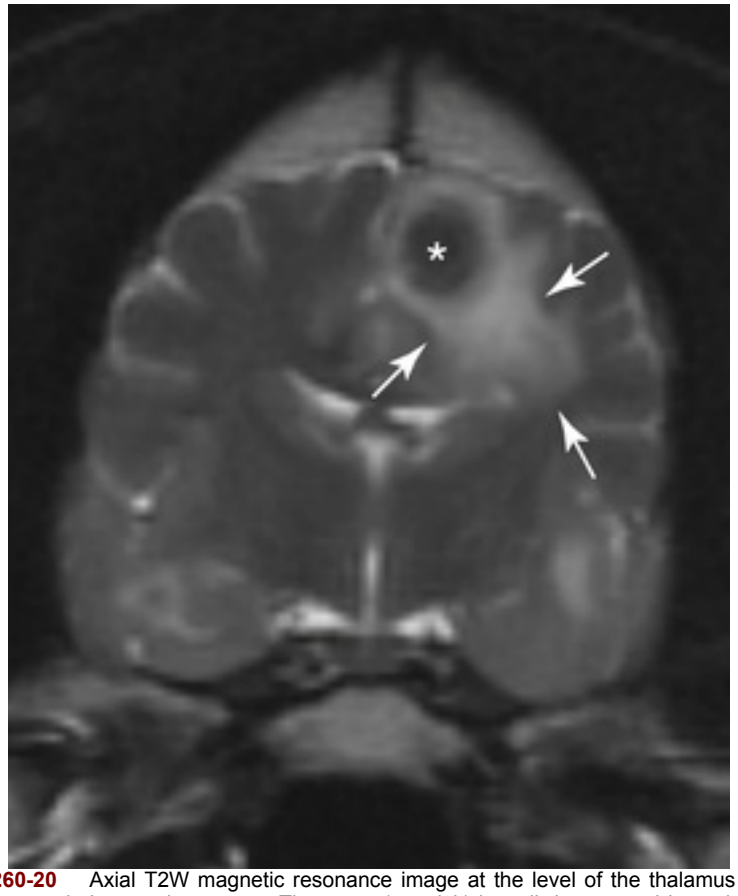


E-FIGURE 260-19 Magnetic resonance images of a canine brain with histopathological diagnosis of an astrocytoma at the level of the thalamus. On midsagittal **(A)** and axial **(B)** T2W images, note the intra-axial location, and heterogeneous hyperintensity with presumed peritumoral edema extending into

the midbrain and right corona radiata. Compared to the isointensity on pre-contrast T1W images **(C),** the enhancement pattern of the mass is heterogeneous and poorly demarcated **(D)**.

Metastatic Tumor MRI

Metastatic tumors on MRI are usually multifocal lesions in the brain parenchyma or meninges.[13,17,288] Multiple small mass lesions are usually present although solitary lesions can occur. Hematogenous metastatic brain tumors on MRI appear as ovoid to spherical lesions at the gray-white matter interface, while embolism is likely to occur in the cortical arterioles (E-Figure 260-20). Other characteristic MRI features of metastatic CNS tumors include multiple hyperintense lesions on T2W images surrounded by marked edema and variably contrast enhance or have peripheral enhancement on post-contrast T1W images.[13,17,288]



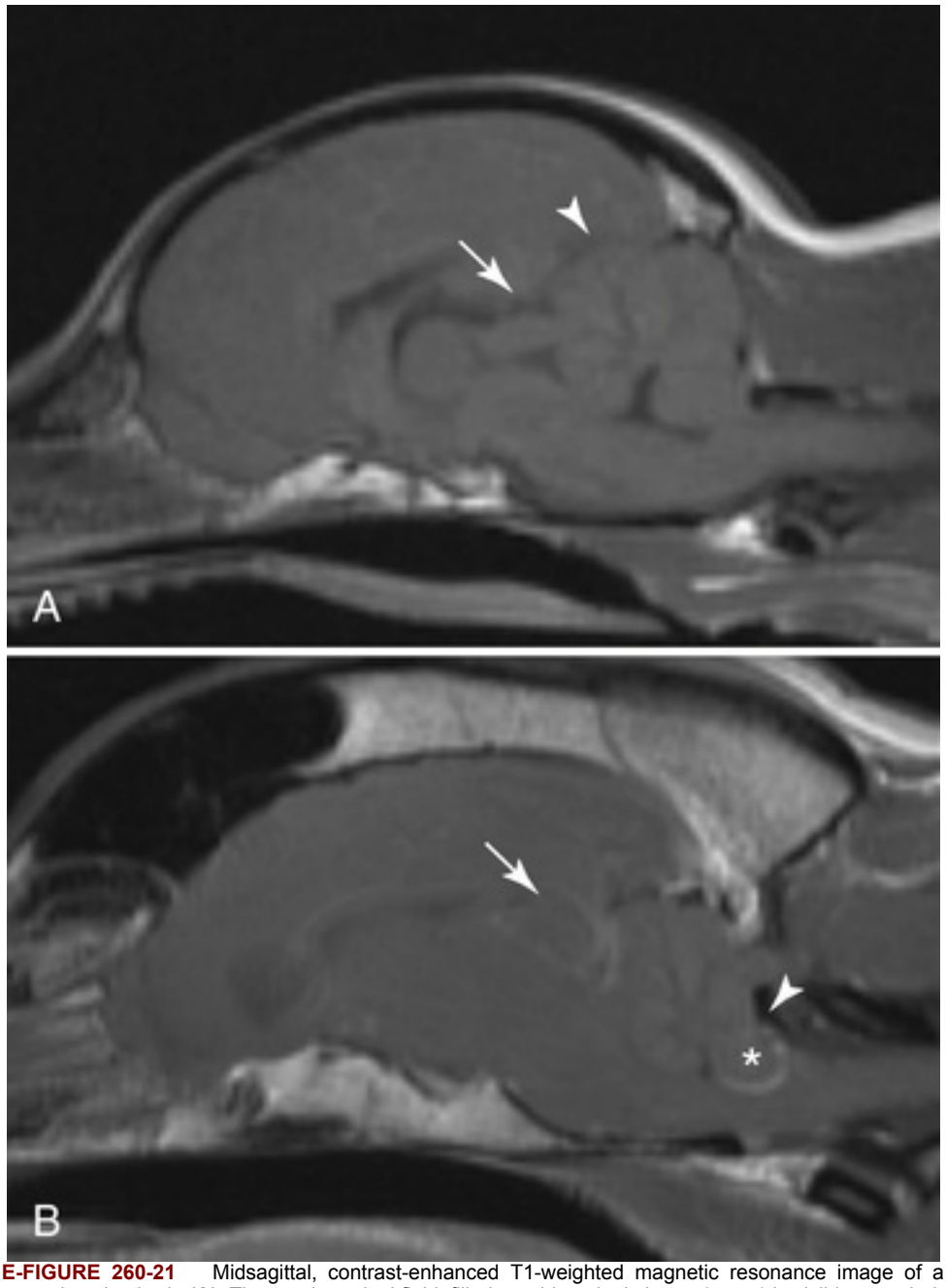
E-FIGURE 260-20 Axial T2W magnetic resonance image at the level of the thalamus of a canine brain with metastatic hemangiosarcoma. The mass (asterisk) is well demarcated by a ring-pattern of edema that has extended (arrows) into the adjacent white matter.

Other Imaging Aids

Metabolic and physiologic MRI techniques, combined with structural data gleaned from traditional MRI or CT, are more commonly used for identification and monitoring intracranial neoplasms and other CNS diseases.[286,348] Specifically, positron emission tomography (PET) using 2-deoxy-2 [^{18}F] fluoro-D-glucose (FDG), which reflects increased glucose metabolism in brain tumors is gaining use for defining the best areas to biopsy.[23,24] Diffusion-weighted imaging based on the ADC image and MRS have been described in brain tumors of dogs but lacked specificity in determining the histological type of intracranial disease.[349] Metabolite alterations using MRS have been used to differentiate inflammatory from neoplastic lesions; neoplastic lesions tend to have lower N-acetylaspartate (NAA) and higher choline concentrations.[350]

Cerebrospinal Fluid Analysis

Analysis of CSF can aid in diagnosis and ruling out overt inflammatory disease and may be beneficial as a screening test (see ch. 115).[351,352] Collection of CSF should be avoided due to risk of herniation when increased intracranial pressure is suspected based on clinical signs and imaging (deviation of the falx cerebri, compression of the ventricles or quadrigeminal cistern, or obstructive hydrocephalus) (E-Figure 260-21). Increased protein concentration and a normal to mild increase in total nucleated cell count (albuminocytologic disassociation) are typical for an intracranial neoplasm.[353-355] Choroid plexus tumors are associated with the most marked elevations in CSF total protein, and in others, CSF may have increased white blood cell numbers, increased total protein, but cytology is usually a mixed nonspecific cell pleocytosis.[293,353,354,356] Similar findings are reported for cats.[294,357] Rarely, neoplastic cells can be found in CSF in association with neoplasms in close proximity to the ventricular system or meninges such as choroid plexus tumor, lymphoma, glioma, ependymoma, neurocytoma, and histiocytic sarcoma.[293,301,333,358-361] CSF protein composition can be further defined by semiquantitative electrophoretic techniques and abnormalities have been reported to be useful in identification of inflammatory, neoplastic and degenerative disease.[43,352] Studies defining biomarkers from dogs with brain neoplasms (matrix metalloproteases [MMP], uric acid, fibrinolytic activity) for determining tumor burden and type have limitations in specificity and sensitivity.[362-365]



E-FIGURE 260-21 Midsagittal, contrast-enhanced T1-weighted magnetic resonance image of a normal canine brain **(A)**. The cerebrospinal fluid–filled quadrigeminal cistern (arrow) is visible as a dark area below the osseous tentorium (arrowhead). With increased intracranial pressure due to a forebrain mass **(B),** herniation under the tentorium (arrow) has compressed the quadrigeminal cistern. Herniation of the cerebellum (asterisk) through the foramen magnum (arrowhead) is also compressing the medulla, usually the terminal event of herniation. Note also the rim of enhancement around the herniated tissues.

Brain Biopsy and Histopathology

Development of improved imaging techniques permits a higher degree of lesion definition from anatomic and pathologic characteristics. Brain biopsy is particularly useful when lesions are small, deep-seated, or in a surgically inaccessible area. Choice of biopsy site depends on the suspected diagnosis and lesion extent. Tissue heterogeneity on imaging should be taken into account by adequate sampling of different areas, including the interface between tumor and adjacent brain. Sampling areas of necrosis is to be avoided as it is usually unrewarding. Diagnostic yield is considered highest when biopsy targets include both the noncontrast- (necrotic) and contrast-enhancing areas of the tumor.[366] Tru-cut biopsy is considered more

reliable than fine needle aspirates in determining the specific type of tumor.[366] Cytologic evaluation of brain tumor crush preparations can be performed within minutes of biopsy collection.[37] Diagnostic yield is generally >90% for neoplastic lesions.[286] Early studies of brain biopsy report morbidity and mortality rates ranging from 7 to 27%.[25,28]

Definitive diagnosis of intracranial neoplasia and of tumor subtype and grade is by histologic examination of tissue.[52,53] Immunohistochemistry is being used to more accurately identify cell phenotype using cell-specific antigenic markers to further classify intracranial neoplasms.[290] Molecular and genetic characterization of neoplasia is becoming more common in veterinary neuropathology and neuro-oncology.[286,313,367,368]

Treatment

Goals

Goals for treatment of brain tumors are complete tumor removal or size reduction and control of secondary effects (edema, increased intracranial pressure).[286,287] Treatment options depend on tumor type and location, onset of clinical signs, costs, and associated morbidity/mortality.[286,287] Treatment guidelines for specific types of brain tumors consist of palliative and definitive therapies. Surgical resection and fractionated radiotherapy are the common definitive methods used to treat canine and feline brain tumors. Other contemporary therapeutic advancements for brain tumor in animals include stereotactic radiosurgery, convection enhanced delivery and immunotherapy.[287]

Palliative Therapy

Palliative therapy consists of controlling tumor-caused secondary effects and minimizing clinical signs. For animals with brain tumors, palliative therapy has focused on controlling vasogenic edema and seizures. Corticosteroid treatment counters the secondary effects of peritumoral edema and obstructive hydrocephalus and reduces intracranial pressure. Anti-inflammatory doses of corticosteroids may be used and adjusted on clinical response. Osmotherapy such as mannitol is useful to control acute increases in intracranial pressure.[369] Mannitol is most widely used at a 25% solution administered as an IV bolus (0.5 to 2 g/kg). Furosemide (0.7 mg/kg IV) may have a synergistic effect in rapidly reducing vasogenic edema.[370] Single doses have brief effect and may need to be repeated. Clinical signs of mass-associated ventricular obstruction may be ameliorated with a ventricular shunting procedure.[204] Antiepileptic drug therapy for acute (e.g., diazepam) and maintenance seizure control is indicated for tumor-associated seizures.

Surgery

Surgery alone can be curative when complete resection is achieved, but is often limited by anatomy and extent of disease. Surgery can achieve cytoreduction, yield a definitive diagnosis, and provide prognostic information for adjunctive treatment planning. Craniectomy can relieve signs due to secondary increases in intracranial pressure.[371] Criteria for successful surgery include that the tumor mass is solitary, noninvasive, located near the brain surface in the cerebral hemisphere, and removal will cause minimal neurologic impairment. Surgery has been most common for forebrain meningiomas, but carries a poorer prognosis in dogs than in cats because they are more invasive and often atypical in dogs.[328,372-375] Dogs with surgically excised meningiomas have had a median survival of about 7 months while the median survival in cats is about 36 months.[307,328,372,373] Surgical treatment incorporating ultrasonic aspiration and endoscopic techniques has increased access to tumors located deep within the brain parenchyma.[35,374] Irreversible electroporation (IRE) is a novel nonthermal tissue ablation technique that involves electrodes and delivery of electrical pulses.[376] Safe and feasible use of IRE delivered stereotactically with a NanoKnife system was reported for treating canine gliomas.[377]

Radiation Therapy

Radiation therapy has become a mainstay in management of malignant and benign CNS tumors in animals. Radiation therapy can be delivered in multiple treatments (fractionated radiotherapy) or in a single treatment (radiosurgery) (see ch. 340).[286,287] Fractionated radiotherapy is beneficial in the treatment of brain tumors as a sole therapy or as an adjuvant to surgical resection.[328,378,379] Studies investigating presumptively diagnosed

brain tumor varieties in dogs with fractionated radiotherapy reported median survival times that ranged from 5 to 24 months.[378-383] When censoring death from causes unrelated to the brain tumor and using survival based on deaths attributable to worsening of neurologic signs, a median overall survival time was 39 months for radiotherapy alone on extra-axial, intra-axial and pituitary brain tumors combined.[378] Radiation as the sole therapy has produced median survival times of 11.5 to 19 months in dogs with a histologic diagnosis of meningioma.[378,379]

Recurrent deterioration of neurologic signs due to either recurrent disease or necrosis is usually the cause of death or reason for euthanasia of dogs with brain tumors treated with radiation.[328,378-380] The risk of CNS necrosis increases as the radiation dose increases.[384] Acute adverse effects of radiation include cerebral edema linked to BBB disturbance, which may result in demyelination and responds to corticosteroid therapy.[385,386] Delayed complications include focal CNS radiation necrosis and severe vascular lesions.[385] As technology has continued to evolve, computer generated treatment plans and more accurate methods for patient positioning have contributed to better dose homogeneity and reduced toxicosis to normal brain tissue.[378,387-389] Three-dimensional conformal radiation therapy has shown a median survival of 19 months in treated dogs with meningioma, which was increased to 30 months when censoring patients that died of causes unrelated to meningioma.[330] At a few veterinary centers, stereotactic radiosurgery (e.g., linear accelerator, GammaKnife, CyberKnife) for brain tumors is being used to administer a single large radiation dose to a defined target. Stereotactic radiosurgery involves use of convergent ionizing radiation to intersect at the treatment target. A single-dose therapy session delivers a precise high dose (>10 gray) causing significant vascular damage and hypoxia to tumor tissue while sparing surrounding normal tissue. Meningiomas have been the most commonly reported tumor treated by stereotactic radiosurgery. Median survival time in dogs was 13.3 months for all brain tumors and for meningiomas.[390,391] Thus, radiosurgery alone has shown promise in the treatment of brain tumors in dogs with fewer acute adverse effects than conventional radiation therapy.

Chemotherapy

Systemically administered chemotherapeutics for treatment of brain tumors in veterinary medicine is primarily anecdotal. The BBB has been considered a major hindrance to the use of chemotherapy for brain tumors, even if it can be iatrogenically disrupted with mannitol administration prior to administration of agents.[392] Hydroxyurea has been advocated as chemotherapy in dogs with meningioma.[393] Intrathecal cytosine arabinoside and methotrexate have been evaluated for short-term safety in dogs with CNS disease, including neoplasia.[394] A recent study failed to demonstrate a difference in median survival in dogs with brain tumors treated with palliative prednisone and AEDs compared with those that received palliative therapy and lomustine.[395]

Novel Therapies

The recognition of canine brain tumors as a translational disease model has created collaborative opportunities for novel treatment methods.[286,287] Convection-enhanced delivery (CED) circumvents the BBB, resulting in high intratumoral drug concentrations with minimal systemic toxicosis. The technique involves targeted local delivery of macromolecules by bulk flow using low pressure microinfusion with specifically designed catheters. In dogs with gliomas, CED has been performed as a single therapeutic modality prior to and after surgical resection.[396] Use of CED in delivery of liposomal CPT-11 and cetuximab bioconjugated magnetic iron oxide nanoparticles has been shown to have efficacy in canine gliomas.[397,398] During CED, infusions can be monitored with real-time MRI and gadolinium based tracers.[287,399]

Immunotherapies, in oncology, consist of using the host immune response to kill tumors (see ch. 341). In active immunotherapy, patients are treated with a combination of tumor antigens or antigen-presenting cells with a stimulatory agent such as a cytokine or immunoadjuvant that is often combined with another definitive therapy.[287] This combination immunotherapy has been used in dogs with brain tumors.[400,401] In these studies, it was demonstrated that vaccines induced antibodies systemically and locally at the tumor site.

Prognosis and Survival

Except for feline and canine meningiomas, the prognosis for other brain tumor types is quite variable. Survival times for gliomas after imaging diagnosis tend to be short with a median <80 days.[338] The prognosis for dogs with palliative-treated brain tumors is poor. Dogs with brain tumors definitively diagnosed at necropsy had a median survival of 2 months after diagnosis with brain imaging.[402] Longer survival times may occur depending on tumor size, type, location, severity of clinical signs and owner decision to continue therapy. Supratentorial tumors tend to have a longer median survival time compared to infratentorial tumors.[402] Metastatic brain tumors have a median duration of clinical signs to death of 21 days.[13]

Prognostic conclusions from definitive therapies of brain tumors in animals are limited by small case numbers, retrospective study design, lack of definitive histopathologic diagnoses and lack of easily monitored objective criteria.[286,287] Median survival times for all tumor types reported in dogs after surgery alone vary from 2 to 7 months.[328,380] Usually within the first 30 days after surgery, animals with infratentorial tumors are at a significantly higher risk of mortality compared with those with supratentorial tumors.[403] A common devastating perioperative complication is aspiration pneumonia (see ch. 242). As previously described in dogs with brain tumors, surgery combined with radiation therapy resulted in the longest survival times. Median survival times for dogs with brain meningiomas treated by combination surgical excision and radiation therapy have been reported between 11 and 28 months in previous studies.[311,328,379,381] Since cats have meningiomas that can be completely removed by surgery, their overall survival prognosis is better than dogs. A recent large retrospective study of meningiomas after surgical excision reported a median survival time of 37 months (95% confidence interval of 28-54 months).[307]

Goals of molecular characterization of canine brain tumors have been directed toward obtaining information regarding prognosis. Aberrant expression of tumor-specific genes, receptors, cytokines and cellular proteins have been identified in canine and feline brain tumors, including progesterone receptors, proliferating cell nuclear antigen, vascular endothelial growth factor (VEGF) and a proliferative marker Ki-67.[312,313,404-407] Progesterone receptors have been identified in canine meningiomas and loss of receptors may be associated with higher tumor proliferative fractions, which may indirectly affect prognosis.[311,312] A positive association may exist between degree of malignancy and an angiogenic factor, VEGF[312,406] in canine meningiomas but may not correlate with outcome.[405] In dogs, tumors with a high proliferative fraction index measured by immunohistochemical techniques to detect proliferating cell nuclear antigen have been associated with lower survival rates.[311,408] The increased recognition of epidemiologic, neuropathologic, molecular biologic and genetic similarities between canine and human brain tumors will continue to drive the use of canine brain tumors as translational disease models.[286,287,396,409]

Idiopathic Epilepsy

Consensus Statements

In 2014, the International Veterinary Epilepsy Task Force (IVETF) was founded and it developed a series of consensus reports based on published understanding of epilepsy.[410] The consensus reports focused on definition, classification, terminology, breeds, diagnosis, treatment, outcome measures of therapeutic trials, neuroimaging and neuropathology.[410-417] In 2015, an ACVIM Small Animal Consensus Statement was established to focus on canine seizure management based on literature and complementary clinical expertise.[418] Both consensus statements provide a platform for ongoing and future research of epilepsy in veterinary medicine that will improve our understanding of epilepsy and its management.[410,418]

Primary and Syndromic Epilepsy

Definitions

Epileptic seizures are defined as transient signs due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy refers to at least 2 unprovoked seizures >24 hours apart (also see ch. 35).[419,420] The term idiopathic means a disease of unknown cause, but to be meaningful, the term must clearly define an entity.[421] In people, many epilepsies previously classified as "idiopathic" have been associated with specific mutations. This led to the recommendation that the prior International League Against Epilepsy (ILAE) classification

system of idiopathic, symptomatic and cryptogenic be replaced with genetic, structural/metabolic, and unknown.[422] Until the genetics of epilepsy in animals is better defined, however, there is still utility in using the well-recognized term idiopathic epilepsy (IE) for pets in whom a structural or metabolic cause of the seizures has not been identified.[411,423]

Incidence

The incidence of epilepsy from all causes in dogs has been estimated at 0.62-0.75%, comparable to the estimated incidence in people (0.22-4.1%).[424-426] Most dogs with epilepsy have idiopathic disease, whereas only 0-22% of epileptic cats have idiopathic disease.[427-430] Male dogs are more commonly affected than females at a ratio of about 1.4 : 1 while no sex bias has been found in cats.[424,425,430,431] The majority of epileptic dogs have their first seizure between 1 and 5 years of age and those are more likely to be diagnosed as idiopathic. About one-third of dogs 1-5 years of age are diagnosed with a structural or metabolic seizure cause. Dogs of any age may not have a cause for their seizure identified.[431-435] The median age of onset of idiopathic epilepsy in cats was 3.8 years in one study while each cat with familial epilepsy had its first seizure when <1 year of age.[430,436] Epileptic dogs are more likely to be diagnosed as idiopathic if the time between the first and second seizures is >4 weeks.[431] Seizures in IE can be either generalized or focal in onset, even when a genetic cause is suspected.[8,9,431,437-441]

Cause

There is strong evidence that IE is genetic in many dog breeds. The prevalence of epilepsy is significantly greater in purebred dogs versus mixed-breed dogs.[442] Offspring of an epileptic dogs have a significantly greater chance of having seizures and an earlier age of onset.[434] Specific genetic studies in numerous breeds show a genetic basis with an incidence of up to 33% in some breeds.[9,434,435,437-439,441,443-456] Where calculated, heritability runs as high as 0.87, suggesting a significant role of genetics in the risk of epilepsy. In contrast, only one family of cats with genetic epilepsy has been reported.[436] In spite of this strong evidence for a genetic cause, the association of specific genetic variants with epilepsy in most breeds has remained elusive.[457]

Specific mutations have been identified in a number of diseases where recurrent seizures are a part of a broader syndrome. For example, the progressive myoclonic epilepsies have other progressive neurologic signs.[458] In dogs, mutations have been identified in the malin gene *(EPM2b* or *NHCLRC1)* in Dachshunds with Lafora disease and in several of the neuronal ceroid lipofuscinosis genes associated with progressive myoclonic epilepsy (*TPP1* and *PPT1* genes in Dachshunds) or other seizure syndrome (*CLN5* in Border Collies, *CLN8* in cattle dogs and English Setter, and *ATP13A2* in Tibetan Terriers) (see Table 260-7).[278-283,459,460] In all these diseases, other signs such as ataxia, blindness or cognitive decline are also present. Other examples of syndromic epilepsy would include mutations in ion channels such as the potassium channel *KCNJ10* in spinocerebellar ataxia with myokymia and seizures in Jack Russell Terriers[96] or mutations in transcription factors *ATF2* in neonatal encephalopathy with seizures in Standard Poodles.[239]

The only mutation associated with IE in dogs is in the *LGI2* gene in Lagotto Romagnolo dogs with remitting focal epilepsy.[461] Variants in the *ADAM23* gene have been linked with an increased risk of seizures in Belgian Shepherd dogs.[462] *LGI2* and *ADAM23* form part of a pre-synaptic, voltage-gated potassium channel complex, and antibodies against this complex have been demonstrated in cats with temporal lobe epilepsy.[463,464] These cats show evidence of hippocampal necrosis, which would classify them as structural/metabolic seizures, but they illustrate that there can be causes of IE other than genetic predispositions.

Diagnosis Using IVETF Criteria

Traditionally, the clinical diagnosis of IE is one of exclusion following diagnostic testing for causes of reactive seizures and structural epilepsy. The IVETF established a three-tier system of confidence criteria for the diagnosis of idiopathic epilepsy.[413] Tier I confidence for the diagnosis of IE is based on a history of two or more unprovoked epileptic seizures occurring at least 24 hours apart, first noted between 6 months and 6 years of age, unremarkable interictal physical and neurologic examinations, and no significant abnormalities on minimum database bloodwork and urinalysis. Tier II confidence for the diagnosis of IE is based on tier I factors plus unremarkable fasting and post-prandial bile acids, MRI of the brain and CSF analysis. Tier III

confidence level is based on tier I and II factors plus identification of EEG abnormalities characteristic for seizure. Use of advanced imaging and CSF were preferable but not essential for the diagnosis of IE. The IVETF recommends performing brain MRI and CSF analysis after exclusion of reactive seizures in dogs with one of the following: (1) age at epileptic seizure onset <6 months or >6 years; (2) interictal neurologic abnormalities consistent with intracranial localization; (3) status epilepticus or cluster seizure; and (4) previous diagnosis of IE and drug resistance to a single AED titrated to highest tolerable dosage.[413]

Imaging and CSF Analysis

Epileptic seizure activity, itself, can cause changes on MRI scans and in the CSF. Brain histopathology of epileptic dogs and cats can reveal evidence of neuronal injury and loss in susceptible brain areas, such as piriform/temporal lobes, cingulate gyrus, hippocampus and cerebral cortex.[465-468] Signal changes on MRI can be localized unilaterally or bilaterally in those susceptible brain areas and are characterized by varying degrees of hyperintensity on T2W, FLAIR and post-contrast T1W imaging (E-Figure 260-22).[467,469] These signal changes have been shown to partially or completely resolve on repeated MRI 10-16 weeks later after seizure control, indicating vasogenic or cytotoxic edema due to seizure activity.[467] Hippocampal atrophy also can be a component of MRI findings in dogs and cats with chronic epilepsy.[436,470] If MRI abnormalities are compatible with seizure-associated changes, the IVETF recommends repeating the MRI 16 weeks after seizure control.[413] CSF abnormalities reflected sometimes by a mild pleocytosis with an increased protein concentration can occur as a result of epileptic seizure activity.[471] The longer the time interval after the seizure, the lower the CSF white blood cell count.[471] If CSF abnormalities are present, infectious disease should be ruled out; it has been recommended to repeat the CSF analysis following a seizure-free interval.[413]

E-FIGURE 260-22 Midsagittal **(A)** and axial T2-weighted magnetic resonance images at the level of the thalamus **(B)** and caudal midbrain **(C)** from a dog with idiopathic epilepsy 24 hours after cluster seizures. Note the hyperintensity in the cingulate gyrus (arrowheads) and in the temporal lobes and hippocampus (asterisks), indicating cytotoxic and vasogenic edema.

Treatment

Treatment Goals

The goals of therapy are to decrease seizure frequency, severity and duration with few acceptable side-effects and no adverse effects, while taking into account that complete elimination of seizures is not a realistic goal in dogs. Use of antiepileptic drugs (AEDs) has been the mainstay of therapy for epilepsy in dogs and cats. However, lack of uniform and scientifically based guidelines on AED treatment has posed challenges in appropriate decision-making. When deciding on AED therapy, clinicians should follow a treatment approach taking into account: (1) when to start AED treatment; (2) selecting the most appropriate AED and dosage; (3) monitoring the AED and adjusting treatment; (4) knowing when to add or change AED; and (5) promoting owner compliance.[414,472-475]

Antiepileptic Drug Therapy Initiation

The decision to start AED treatment is based on a number of factors, including etiology, risk of recurrence, seizure type and tolerability.[475] Clinicians should also consider the general health of the pet, owner lifestyle, financial limitations, and ability to comply with any proposed regimen.[472] In people, there is no benefit to starting AED therapy after a single unprovoked seizure, but there is evidence to support early seizure control after a second.[476-478] In dogs, long-term seizure management is thought to be most successful if AED therapy is initiated soon after onset, especially in dogs with frequent seizures and in breeds known to have severe epilepsy.[437,438,479,480] To summarize, the IVETF and ACVIM consensus statements recommend initiation of

long-term treatment in animals with epilepsy when any one of the following criteria is present: (1) identifiable structural lesion or prior history of brain disease or injury; (2) acute repetitive seizures (status epilepticus) has occurred; (3) interictal period is < 6 months (i.e., 2 or more seizures within 6 month period); (4) prolonged, severe or unusual post-ictal periods; and (5) epileptic seizure frequency and/or duration is increasing and/or seizure severity is worse over three interictal periods.[414,418]

Overview of Medical Choices

A variety of AEDs can be used for management of epileptic dogs and cats, but no evidence-based guidelines are available to aid in choosing a first-line AED for long-term management of seizure control in dogs and cats. Most seizures in dogs with IE can be controlled with monotherapy. After the first systematic review in veterinary medicine to evaluate drug efficacy in treatment of IE, most data are derived from retrospective studies and open-label trials.[481] A meta-analysis of three randomized controlled drug trials on epileptic dogs revealed that 30% of dogs experienced a 50% or greater reduction in seizures with placebo, a consideration when evaluating retrospective or open-label studies, especially those that involve a small number of animals, as reported results might be overstated.[482] Due to ethical issues of a placebo-controlled study, which are of relevance to epileptic dogs and their owners, there is general consensus that clinical trials of AEDs in veterinary patients should be conducted in a controlled, blinded and randomized manner in order to achieve a high level of evidence and to adjust for the placebo effects.[415,481]

In principle, administration of a single AED is preferred because it avoids drug-to-drug interactions and improves owner compliance. Other factors to consider when choosing an AED include mechanism of action, efficacy, adverse effects, potential drug interactions, frequency of administration based on pharmacokinetic properties and cost.[472] Mechanisms of action for many AEDs include increase in inhibitory effects of the GABA-activated chloride channels, modulation of membrane associated cation (sodium and calcium) channels, and reduction in excitatory neurotransmission. The most commonly used AEDs in veterinary medicine mechanistically enhance inhibition in the brain.[475] In general, AEDs are initiated at the low end of the dosage range and then tailored to individual needs based on seizure control, adverse effects and serum drug concentrations. A number of AEDs with improved tolerability, fewer side-effects, and fewer drug-drug interactions have been developed for treating people with epilepsy and several (e.g., levetiracetam, zonisamide, gabapentin, pregabalin) have been used in dogs and cats. Currently, these drugs are being used as first-line AED or as add-on in dogs with refractory epilepsy; however, efficacies for either use still remain to be established. Table 35-2 (ch. 35) lists the commonly used AEDs with reported adverse effects in the treatment of seizures in dogs and cats. Other current reviews exist on properties and usage recommendations of AEDs in dogs and cats.[414,418,472,475]

Until recently, phenobarbital (PB) and potassium bromide (KBr) were the first-choice sole AEDs for long-term treatment of IE in dogs based on their history, availability, and cost.[483-486] The meta-analysis review of AED efficacy reported a better level of evidence supporting use of oral PB as compared with oral KBr.[481] In a randomized clinical trial comparing PB to KBr as first-line AEDs in dogs with presumptive IE, 85% of dogs given PB became seizure-free for 6 months compared with 52% of dogs given KBr, and PB was better tolerated.[486] In 2013, imepitoin was approved in Europe as a first-line AED in dogs with IE, based on randomized controlled trials that demonstrated antiepileptic drug efficacy, high tolerability and safety. The evidence for recommending use of imepitoin as sole AED in dogs with epileptic seizures is good.[481,487-489] In a randomized controlled study, the efficacy of imepitoin was similar to PB, with fewer side-effects.[489] The ACVIM consensus panel provides high recommendation and established treatment efficacy for PB and imepitoin as first-line AEDs in dogs with IE.[418]

Therapeutic Monitoring

Once AED therapy is started, it is important to systematically monitor seizure control, systemic drug effects, and serum drug concentrations with goals of seizure control with minimal adverse effects.[472] Epilepsy management depends on accurate owner observation when assessing efficacy of therapy.[472] Owners should be instructed to maintain a logbook to document seizure occurrences and changes in medication administration. Objectives of monitoring serum concentrations include determining: effective drug levels after therapy initiation; if drug failure is due to pharmacokinetic factors (metabolic tolerance) or pharmacodynamic factors (functional tolerance) regarding a change of drugs; if treatment failure is due to poor compliance or inadequate drug level; prevent toxic effects from occurring; and aid with

individualization of therapy.[418] Measurement of drug concentrations takes place after establishment of a steady-state concentration based on 5 elimination half-lives. Peak and trough levels are recommended for drugs with short elimination half-lives and when seizures are not well controlled.[490] Serum drug concentrations are available for some medications to determine whether or not the target range has been reached. A 20% or greater drop in the trough serum concentration is often an indicator of poor administration compliance.[475] Therapeutic serum concentrations are based on studies evaluating the concentration at which the majority (population) of dogs with IE experience seizure control. However, few AEDs (i.e., PB, KBr) in veterinary medicine have established therapeutic concentrations and dose adjustments are based on the seizure control, serum drug concentrations, and side effects. It is important to have regular assessment of serum concentrations even at times when seizures are well controlled in order to monitor for toxic levels, especially for drugs with a narrow therapeutic window (i.e., PB and KBr), to monitor for serum concentration fluctuations and to have awareness when there is a need to make changes in therapy (see ch. 35).

Combination Therapies

Not all epileptic patients can be controlled with a single AED and such patients may require add-on medications for seizure control. Approximately 30% of dogs with IE require two or more AEDs to control seizures.[481,483,484] Moreover, approximately half of all epileptic dogs are able to maintain a seizure-free status without experiencing adverse effects from the medication.[491] Before initiating a second drug, sufficient time must be allotted to determine effects of the first drug and to assure that adequate serum concentrations have been achieved before assuming lack of efficacy. A drug should not be considered a failure until maximum dosage or target serum concentrations have been attained or unacceptable side effects or adverse effects occur.

Refractory Epilepsy

The term refractory or drug-resistant epilepsy is utilized in veterinary medicine to describe a condition in which an animal with epilepsy fails to attain satisfactory seizure control or suffers intolerable side-effects despite appropriate therapy with conventional AEDs.[473,474] Although drug resistance is a serious problem for some dogs with IE, it is less frequent in cats. Factors for refractory IE can be related to three variables: disease-related, drug-related and patient-related issues.[475] Disease-related factors are attributed to underlying brain disease such as cortical malformation, prior traumatic brain injury or another active disease process. Drug-related mechanisms include metabolic or functional tolerance, known as pharmaco- or drug resistance, which has two theories on pathogenesis: the target hypothesis which proposes genetic or disease-related alterations in cellular targets of AEDs and the transporter hypothesis which postulates altered transport of drugs across the BBB.[492,493] Metabolic tolerance occurs when increasing the drug dosage does not result in a parallel increase in serum drug concentration. As the genetics of canine and feline epilepsy become better understood, patient-related issues may become more relevant with respect to treatment response.[412] Evidence for predicting pharmacoresistance in dogs is limited, although seizure density (multiple seizures within a short time period) was an influential predictor of pharmacoresistance.[494]

Criteria for decision-making on starting a second or third AED are lacking in veterinary medicine. Several factors should be considered when deciding on a second AED: selecting an AED with a different mechanism of action, minimizing drug-drug interactions, limiting additive toxicity, determining risk versus benefit of polytherapy, and effects on quality of life for the pet and pet owner.[418] The ACVIM consensus panel recommended PB, KBr, levetiracetam, zonisamide, and imepitoin (Europe) be considered for drug resistant epileptics.[418,473,485,495-499] The only published clinical trial in cats with refractory epilepsy evaluated the use of levetiracetam; 7/10 cats had a favorable response to treatment and tolerated the drug well.[500]

Prognosis

Based on a consensus by the IVETF, *seizure freedom* is the primary treatment goal in the therapeutic management of canine and feline epilepsy.[415] Seizure freedom was defined as extending the interseizure interval to three times longer than the pretreatment interval after a minimum of 3 months of therapy. Partial therapeutic success is defined as preventing cluster seizures or status epilepticus, relevant reduction of seizure frequency while considering the pretreatment seizure frequency and reduction in seizure severity.[415] Evaluation of treatment efficacy of AEDs has often been assessed by the proportion of dogs in a study population that had a reduction in seizure frequency. When >50% reduction in seizure frequency is used as an

outcome measure, about two-thirds of dogs achieved this goal.[494] Factors associated with reduction in seizures included female gender, neutering, no history of cluster seizures and older age at onset. In people, factors associated with remaining seizure free include no structural brain lesion, short duration of epilepsy, few seizures before pharmacologic control and AED monotherapy.[478]

Dogs and cats with epilepsy can experience debilitating recurrent epileptic seizures, which can lead to behavior changes, other clinical effects and reduced quality of life.[501,502] Moreover, the quality of life is also impacted for a pet owner of an epileptic pet.[503-505] In one study, 60% of owners reported that their dog's epilepsy had a negative impact on their quality of life.[501] Several studies have shown a normal life expectancy for dogs with idiopathic epilepsy while others have shown up to a 2-year decrease in life expectancy.[444,501,506,507] A median survival time of 1.5 years for canine epilepsy after diagnosis has been reported in a large cohort study of epileptic dogs.[424] This same study found that breeds kept solely for companionship lived longer after diagnosis than those with dual purpose, such as hunting and working breeds.[424] The breeds least likely to go into remission or have a >50% in seizure reduction were the Border Collie, German Shepherd Dog and Staffordshire Terrier.[494] Many pets are euthanized because of the severity of seizures or because of severe drug-induced side-effects.[485,501,508]

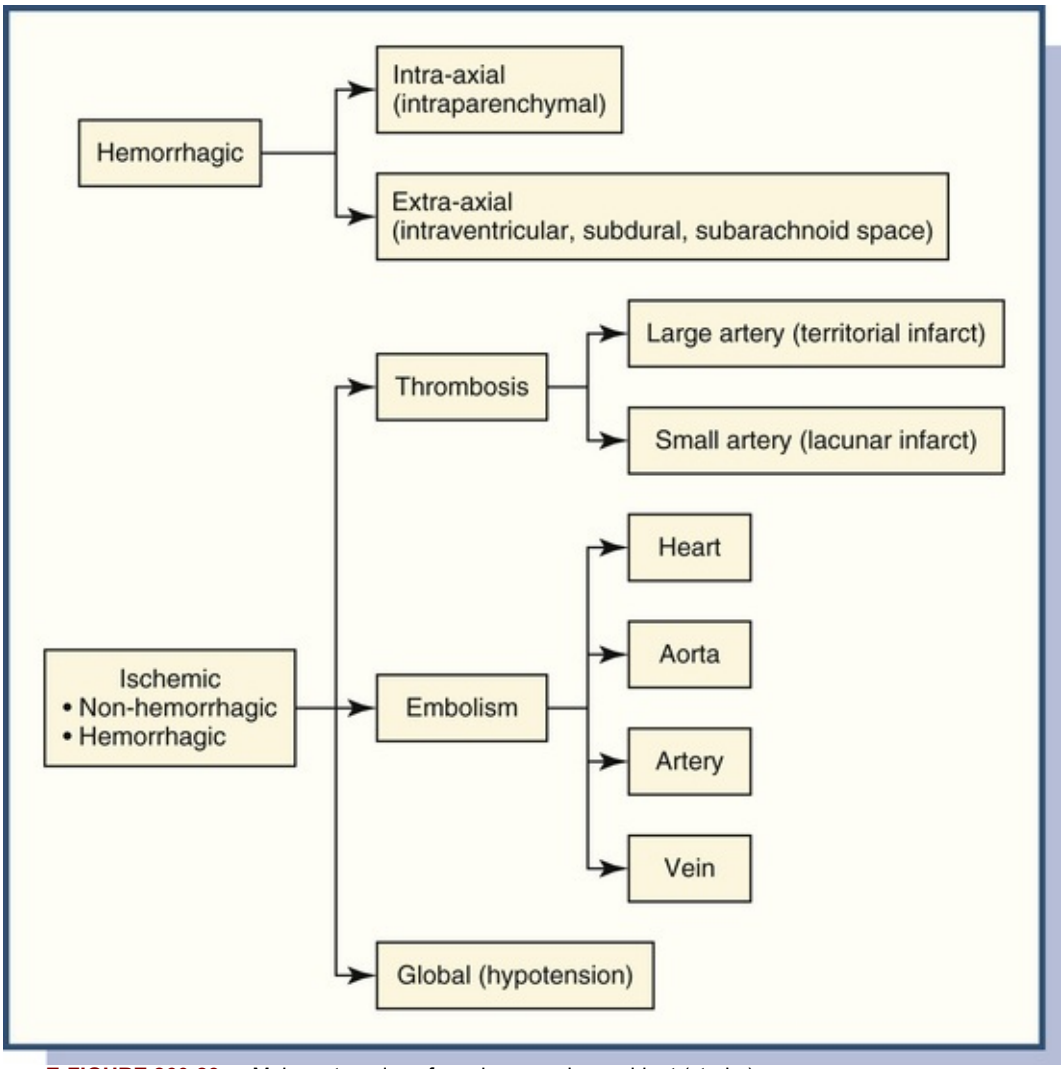
Risk factors for euthanasia include younger age of onset, high initial seizure frequency, poor seizure control, and episodes of status epilepticus.[437,479,506,507] Approximately 40-60% of dogs with epilepsy have one or more episodes of cluster seizures or status epilepticus and a mean lifespan of 8 years compared to 11 years for those with epilepsy and no status epilepticus.[428,507-510] Dogs that have had cluster seizures are significantly less likely to achieve remission with any AED treatment.[494] Though life expectancy of the pet may not be affected, the odds of an epileptic going into complete remission and not requiring ongoing therapy are low: 6-8% in dogs[438,479,501] and 17% in cats.[430] Thus, epilepsy in companion animals usually requires lifelong therapy and commitment from the owner. A balance between quality of life and therapeutic success is often key for an owner's commitment to the pet's therapy.[503]

Although AED treatment should be considered lifelong, discontinuation of AEDs may be considered in pets with seizure remission. The decision to gradually taper the dosage of AED should be on an individual basis, but seizure remission of at least 1 to 2 years is advised.[414,474] There is little information on seizure recurrence and owners must be aware that seizures could recur anytime. It is advised to decrease the AED dosage by 20% or less on a monthly basis.[414] Only in the case of life-threatening adverse effects should the AED be immediately discontinued. In this situation, the animal is under close observation and an AED that has a different metabolism is simultaneously administered as a loading dose.

Vascular Brain Disease

Classification

The high metabolic demand of brain tissue necessitates adequate blood supply. Reduced blood supply causes lack of oxygen and/or glucose, leading to neuronal ischemia and death. Cerebrovascular disease is defined as any abnormality of the brain resulting from a pathologic process affecting its blood supply.[511] Vascular diseases of the brain may result from excessive blood flow through the cerebral vasculature (hypertension), rupture of vasculature (bleed) or a reduction of blood flow (infarction).[53,175] Cerebrovascular accident (CVA), also known as stroke, is the clinical manifestation of cerebrovascular disease resulting from brain ischemia *(ischemic stroke)* and less commonly brain hemorrhage (*hemorrhagic stroke;* E-Figure 260-23).



E-FIGURE 260-23 Major categories of cerebrovascular accident (stroke).

Clinical signs must be present for ≥24 hours to be considered a stroke.[512] If signs of a CVA resolve within 24 hours, the term used is *transient ischemic attack*. *Global ischemia* refers to hypoxia/anoxia of the entire brain and bilaterally symmetrical death in selectively vulnerable neuronal populations (e.g., cerebral cortex, hippocampus, cerebellar cortex, basal nuclei and thalamus).[53]

Brain infarction can result from disruption of the vasculature leading to a hemorrhagic infarction or by vascular occlusion causing ischemic infarction.[513] A thrombus or embolus causes a focal occlusion but, less commonly, it can be multifocal. Ischemic infarcts that have secondary hemorrhage are termed *hemorrhagic infarcts*, whereas when hemorrhage is not present, infarcts are termed *nonhemorrhagic infarcts*. Based on size of the vessel, infarcts can be a consequence of small vessel disease, which gives rise to lacunar infarcts, or of large vessel disease, which gives rise to a territorial infarct. Territorial infarcts tend to occur in the cerebellum and cerebrum. Nontraumatic hemorrhagic stroke follows rupture of a brain vessel and development of a hematoma. Hemorrhage can be localized as intra-axial in the brain parenchyma or extra-axial such as in the intraventricular, subdural or subarachnoid space and CSF.[514] Subarachnoid hemorrhage can produce cerebral vasospasm, a temporary constriction of an intracranial artery causing transient regional ischemia. Vasospasm is difficult to determine clinically in animals but has been associated with subarachnoid hemorrhage in dogs.[515]

Pathophysiology

Ischemic Stroke

An infarct is an area of compromised brain parenchyma that is the result of focal vascular occlusion by

thrombosis or embolism. In thromboembolic-related stroke, the occlusion is due to an embolic source (septic, parasitic, metastatic, atherosclerotic) that has traveled from another vascular bed or from the heart.[512,516] The area of infarcted brain consists of an ischemic core with permanent loss of blood flow and irreversible neuronal injury surrounded by a penumbra, where blood flow is decreased but still-viable neurons are at risk for irreversible injury. Therapy is targeted at reversing this pathologic process as in 4-6 hours the ischemic cascade and vasogenic edema may progress within the penumbra and continue over 24-48 hours.[512,516]

Nonhemorrhagic ischemic infarcts are the most common CVA recognized in dogs.[517,518] Common sites for ischemic stroke in dogs include the cerebellum, striatocapsular region, and thalamus.[517-521] No underlying antemortem cause is detected for about 50% of dog CVAs.[522] No age or sex related factor has been identified and incidence is unknown.[512] Cavalier King Charles Spaniels and Greyhounds appear overrepresented.[517,518,522] Greyhounds appear more predisposed to ischemic stroke than all other breeds combined, with hypertension a possible contributing factor.[523] Cerebellar territorial infarcts are more likely in small breed dogs, especially in Cavalier King Charles Spaniels, and lacunar thalamic/midbrain infarcts occur more often in large breed dogs.[518,522] Miniature Schnauzers may be at increased risk possibly related to hyperlipidemia.[524]

Various etiologies have been associated with ischemic stroke in dogs and cats, including sepsis, atherosclerosis associated with primary hypothyroidism and Miniature Schnauzers with primary hyperlipidemia, aberrant parasite migration, thromboembolic disease, and neoplasia.[512-529] Diseases that predispose to nonhemorrhagic ischemic stroke include metabolic disorders (hypothyroidism, pheochromocytoma, hypertension) or hypercoagulopathy (diabetes mellitus, hyperadrenocorticism, renal disease, protein-losing nephropathy).[512-531] Hemorrhagic brain infarcts may follow venous thrombosis or vascular damage with leakage of blood when reperfusion occurs in focal ischemia.[53] Various conditions underlie hemorrhagic ischemic stroke (coagulopathy, hypertension, sepsis, inflammation, and metastasis (hemangiosarcoma).[512,531,532]

Hemorrhagic Stroke

Bleeding can injure the neighboring tissues by interrupting vital pathways, by exerting local pressure on surrounding brain structures and by causing ischemia of adjacent tissues. Hematomas may be large enough to increase intracranial pressure, causing shift and herniation of brain tissue. Nontraumatic intracranial hemorrhage results from blood vessel rupture or bleeding disorder and may be primary or secondary. Multiple hemorrhages may indicate bleeding disorder, toxin, trauma or metastatic vascular tumors.[53] Incidence of hemorrhagic stroke in dogs and cats is unknown. Intracranial hemorrhage occurs most commonly secondary to head trauma.[514] In a study of 75 dogs with nontraumatic intracranial hemorrhage, lesions were intraparenchymal (n = 72), subdural (n = 2) or intraventricular (n = 1); 33 of the dogs had a concurrent condition including *Angiostrongylus vasorum* infection, hypertension, metastatic hemangiosarcoma, chronic kidney disease, hyperadrenocorticism, intracranial lymphoma, meningothelial meningioma, sepsis and hypothyroidism.[533] Bleeding disorder associated with *A. vasorum* infection likely predisposes to intracranial hemorrhage.[534] Concurrent conditions most commonly associated with multiple lesions <5 mm (cerebral microbleeds) were endocrinopathies and hypertension.[533] Pituitary adenoma infarction or hemorrhage (pituitary apoplexy) can cause sudden onset seizures, behavior changes or vision loss.[535]

Less is known about CVAs in cats but hemorrhagic and ischemic strokes have been reported.[532] Feline ischemic encephalopathy, a cerebral infarction syndrome, usually involves the middle cerebral artery. Some cases have been associated with aberrant migration of *Cuterebra* spp. larvae into the brain.[528,536] Since not all have obvious vascular lesions, vasospasm may be the result of hemorrhage in the subarachnoid space caused by the migrating larva or the results of a larval produced toxin.[196] Hemorrhagic infarcts should be suspected in cats with liver disease and central vestibular signs.[532]

Global Ischemia

Global brain ischemia is a differential in dogs and cats with peracute neurologic dysfunction after anesthesia or post-cardiopulmonary resuscitation.[537,538] Watershed infarction develops when cerebral blood flow is lowered below the point of compensation by cerebral autoregulatory mechanisms, causing widespread

bilateral brain dysfunction. Use of ketamine and the brachycephalic breeds predispose for global ischemia.[537] Use of mouth gags in cats has been associated as a potential risk factor for development of cerebral ischemia, hearing loss and blindness.[538] If the mouth is opened maximally, blood flow through the maxillary arteries is occluded in some cats.[539,540] Additional findings suggest that vision and hearing deficits might not only be the results of reduced perfusion to the brain, but could also result from disrupted blood flow directly to the retina or inner ear.[539] Smaller mouth gags were not associated with abnormalities on retinal function tests or MRI angiography and still provided sufficient opening while minimizing the risks of reductions in maxillary artery blood flow.[541]

Clinical Signs

Onset of neurologic signs is peracute to acute and usually nonprogressive after 24 hours.[512] Common signs noted by owners include altered mentation, hemiparesis, seizures and vestibular dysfunction. Neurologic deficits in dogs with CVAs usually have a focal anatomic localization and reflect the site and lesion extension of the vascular insult.[512,517,521,522,531,542] Infarction of a specific brain region is associated with specific clinical signs (i.e., forebrain, thalamus, midbrain, pons, medulla, cerebellum).[517,542] In 38 dogs with brain infarctions, locations involved were the cerebrum (29%), thalamus/midbrain (21%), cerebellum (47%) and multifocal in 7%. Ischemic stroke in 27 dogs involved the middle cerebral artery in 70% of dogs.[542]

Motor dysfunction and general proprioceptive ataxia were reported in 78%, including signs of sensory hemi-neglect and contralateral motor deficits as a result of middle cerebral artery infarction. One study reported seizures in 50% of dogs after ischemic stroke,[542] but another study reported seizures in only 1 dog. Onset of ischemic stroke is usually acute to peracute. Typically, deterioration occurs after the insult, presumably due to edema, but then becomes static or improves after the first 24 hours. In hemorrhagic stroke, often the territory affected involves more than one artery and secondary signs ensue from increased intracranial pressure. If the hemorrhage is associated with mass effect, deterioration may be a result of edema formation or hematoma enlargement.

Diagnosis

Initially, other acute brain diseases such as metabolic, neoplastic, inflammatory and trauma must be considered. It is important to determine presence of underlying extraneural disorders (Figure 260-24). Dogs and cats with ischemic and hemorrhagic stroke should be evaluated for hypertension, endocrine disease, renal disease, cardiac disease and metastatic disease.[522,530] Along with physical (see ch. 2) and neurologic (see ch. 259) examinations, a retinal examination (see ch. 11) should be considered and changes may reveal evidence of tortuous vessels suggestive of hypertension (see ch. 157) and hemorrhage that may suggest a bleeding disorder or hypertension. A CBC allows identification of abnormal red blood cell indices or platelet abnormalities. Serum biochemistry profile and urinalysis should be used to evaluate for hypercoagulability or other underlying systemic disease. Specific coagulation testing is recommended (see ch. 196). Serial blood pressure monitoring can detect underlying hypertension (se ch. 99). Hypertensive encephalopathy can be observed with acute (>30 mm Hg from resting level) or sustained (>180 mm Hg) increases in systolic arterial blood pressure (see ch. 157).[543] Other adjunctive testing includes thoracic, abdominal and cardiac imaging, and endocrine testing for adrenal (see ch. 306) and thyroid (see ch. 299) diseases.

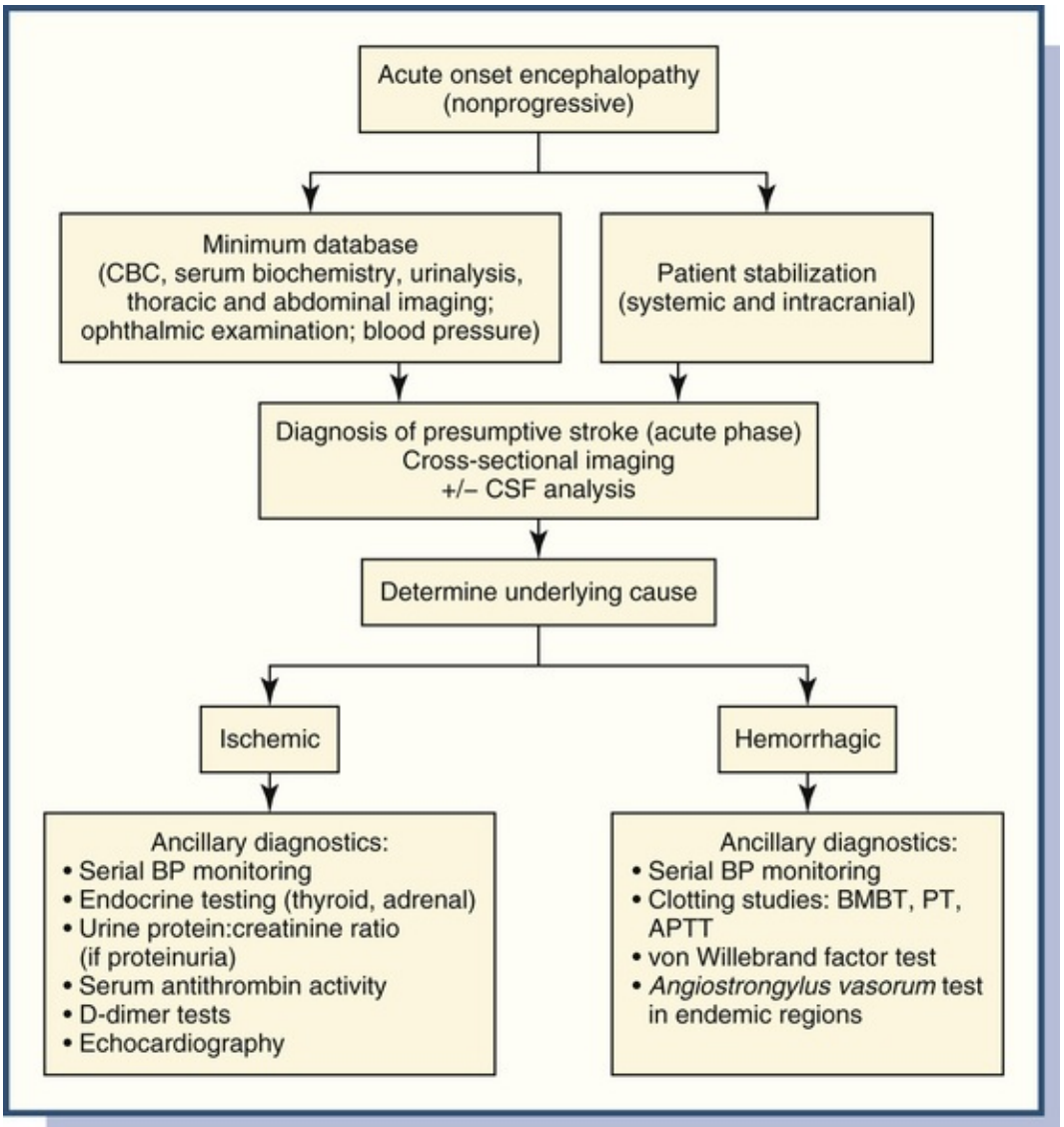
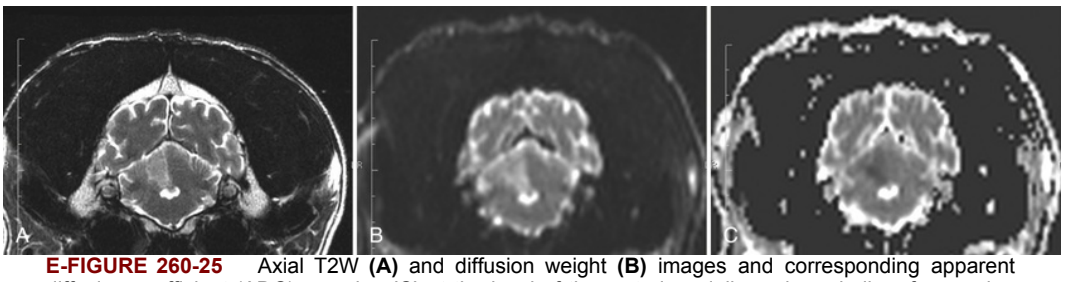


FIGURE 260-24 Algorithm of diagnostic approach to suspected cerebrovascular accident. *APTT*, Activated partial thromboplastin time; *BMBT*, buccal mucosal bleeding time; *BP*, arterial blood pressure; *CBC*, complete blood count; *CSF*, cerebrospinal fluid; *PT*, prothrombin time.

Definitive diagnosis of stroke requires histology via biopsy or necropsy. Imaging studies are necessary to make a presumptive diagnosis, determine the lesion extent and distinguish between ischemic and hemorrhagic stroke.[512,531] Moreover, recognizing infarction and/or hemorrhage assists with appropriate patient management. CT images are frequently normal during the acute phase of ischemia; thus, a diagnosis relies on exclusion of other mimicking diseases. Early signs of ischemic injury on CT include parenchymal hypodensity, loss of gray-white matter distinction, subtle effacement of cortical sulci and local mass effect from edema.[512,531] MRI is considered more sensitive than CT for detecting acute ischemic lesions.[513] Characteristic MR imaging findings associated with ischemic infarction include well demarcated, wedge-shaped lesions, with minimal mass effect. The intra-axial lesion is hyperintense on T2W and FLAIR sequences and hypointense on T1W sequences with minimal enhancement.[336,513,517] Lesion distribution should correlate with its loss of territorial arterial supply.[336,517,518,542] Chronic CVA lesions tend to weakly contrast enhance for days after onset,[517,518,531,544] which can be confused with neoplasia and inflammation.[19,336]

Difficulty in differentiating acute from chronic ischemic lesions using MRI can be overcome with functional MRI techniques. Diffusion weighted imaging (DWI) complements other conventional MR sequences with its sensitivity to cytotoxic edema, especially in early ischemia, and in assessing temporal evolution in acute versus chronic ischemic stroke.[513,545] Tissue contrast on DWI reflects Brownian motion of water molecules. Peracute (hours to 4 days) ischemic infarction appears as hyperintense on DWI that corresponds with

hypointensity on ADC maps, consistent with cytotoxic edema and reduced Brownian motion of water molecules (E-Figure 260-25). With time vasogenic edema develops and on DWI and corresponding ADC mapping, the signal becomes hyperintense as the diffusion becomes higher due to increased extracellular water. MR angiography (MRA) can be useful for identify underlying vascular occlusion or malformation.



E-FIGURE 260-25 Axial T2W **(A)** and diffusion weight **(B)** images and corresponding apparent diffusion coefficient (ADC) mapping **(C)** at the level of the rostral medulla and cerebellum from a dog with an ischemic infarct in the left cerebellar hemisphere. Note the wedge-shaped hyperintensity on the T2W image **(A)** and the hyperintensity on the diffusion weighted image. The lesion appears hypointense on ADC mapping, indicating restricted diffusion associated with cytotoxic edema after a hyperacute ischemic injury. (Courtesy Fred A. Wininger, Veterinary Surgical Specialist, St Louis, MO.)

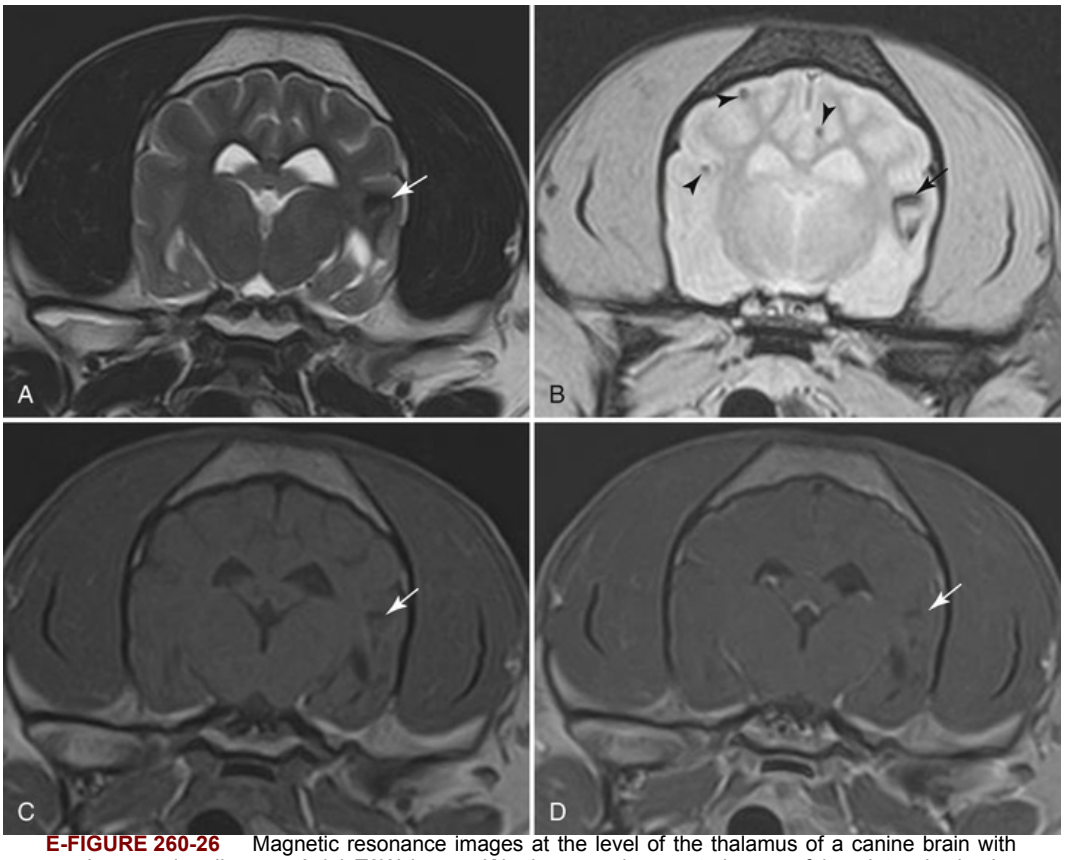
Recognition of hemorrhage is important in diagnosis and appropriate management. CT is considered highly sensitive for detection of acute hemorrhage, which appears hyperdense due to attenuation of X-rays by the globin portion of hemoglobin (Table 260-10). Over days to weeks, hematomas eventually become isodense with variable contrast enhancement. On MRI, acute and subacute hemorrhagic lesions often are associated with surrounding vasogenic edema, which appears as hyperintense on T2W and FLAIR sequences. There are distinct stages of MRI appearance of intracranial hemorrhage lesions due to RBC breakdown and various forms of hemoglobin that create various patterns of signal intensities on defined sequences (see Table 260-10).[546-548] Gradient-echo sequences (T2*) are recommended for visualization of hemorrhage. The T2*W sequence takes advantage of the magnetic properties of hemosiderin, oxy-, deoxy-, and methemoglobin to identify areas of blood product accumulation and temporal evolution of intracranial hemorrhage. The paramagnetic properties of deoxyhemoglobin in acute hemorrhage cause a susceptibility artifact on T2*W, which is visualized as a signal void (dark; E-Figure 260-26). Sometimes the T2*W sequence can improve conspicuity of microbleeds (<4 mm) that are not readily seen on a T2W sequence.[549]

TABLE 260-10

Timing of Hemorrhage and MRI/CT Description

	<24 HOURS	1-3 DAYS	>3 DAYS	>7 DAYS	>1 MONTH
Clinical Stage	Hyperacute	Acute	Early subacute	Subacute to chronic	Chronic
State of Hemoglobin (Hb)	OxyHb	DeoxyHb	MetHb	MetHb	Hemosiderin and ferritin
Cellular Location in RBCs	Intra	Intra	Intra	Extra	—
T1W Signal Intensity	Iso	Iso to hypo	Hyper	Hyper	Iso to hypo
T2W/FLAIR Signal Intensity	Slightly hyper	Hypo	Hypo	Hyper	Hypo
T2* (GRE) Signal Intensity Loss (Signal Void)	Present (rim)	Present	Present	Present	Present
CT Density	Hyper	Hyper	Hyper	Iso	Iso to hypo

GRE, Gradient echo; *RBC*, red blood cell.



E-FIGURE 260-26 Magnetic resonance images at the level of the thalamus of a canine brain with cerebrovascular disease. Axial T2W image **(A)** shows a demarcated area of hypointensity in the corona radiata (arrow). On T2*W **(B)** of the same area, a signal void is recognized along with additional other smaller focal lesions (arrowheads) of signal void that were not conspicuous on T2W imaging. The lesion was T1-hypointense **(C)** with no contrast enhancement **(D).**

Treatment

Management of CVAs is largely supportive: controlling seizures and intracranial pressure, and treating any underlying cause such as vasculitis or hypertension.[512] After an ischemic stroke, recovery often occurs within several weeks with supportive care. Treatment includes correcting of physiologic abnormalities, minimizing effects of the ischemic cascade and improving cerebral blood flow. Based on development of the penumbra in human stroke patients, the "window of opportunity" for instituting these therapies is within 6 hours.[516]

Principles of acute treatment for stroke include monitoring of vital parameters (airway, breathing, circulation), intracranial stabilization and investigating underlying causes. Intracranial stabilization focuses on reducing cerebral edema, optimizing cerebral blood flow and if indicated, removal of the space-occupying hematoma. Cerebral perfusion is optimized with management of systemic blood pressure and elevated intracranial pressure. In hemorrhagic stroke, benefits likely outweigh the risks when considering administration of an osmotic agent, such as mannitol. Thrombolytic agents (i.e., tissue plasminogen activator, streptokinase) during acute treatment are infrequently used because of expense, rarity of blood clots associated with infarction in dogs and cats, and failure to administer these agents within the 6 hour window.[512,516] Although unproven to be beneficial, long-term antithrombotics (e.g., aspirin) may be considered in thromboembolic disease to reduce risk of another infarction. Long-term, the patient should be serially monitored for signs of recurrence of stroke and progression of the underlying condition.

Prognosis

Prognosis depends on the type and localization of the CVA, severity of neurologic dysfunction, occurrence of deterioration or complications and the underlying cause.[522] Survival studies of CVAs are difficult because dogs often have severe neurologic signs that prompt owners to elect euthanasia. In ischemic stroke, most

dogs recover within weeks after onset of signs.[517,518,522] In a study of 20 dogs with ischemic stroke, prognosis was good if they survived the initial 30 days post-stroke, but there is risk of recurrence.[550] Recurrence has been based on a repeated episode of acute neurologic dysfunction.[522,542] Dogs with a concurrent medical condition causing ischemic stroke have shorter survival times than dogs with no identified underlying condition.[522] In a study of 75 dogs with nontraumatic intracranial hemorrhage, 61% had a good to excellent long-term outcome.[533] However, hemorrhagic stroke in the cerebellum is associated with higher mortality.[518] Identification of hypertension in dogs with nontraumatic intracranial hemorrhage is a poor prognostic indicator.[533] In dogs with intracranial hemorrhage and multiple lesions >5 mm, *A. vasorum* (see ch. 242) was the only concurrent condition with a good outcome.[533]

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CHAPTER 261

Inflammatory, Infectious, and Other Multifocal Brain Diseases

Chelsie Estey, Curtis W. Dewey

Client Information Sheet: Granulomatous Meningoencephalitis

Disorders of the brain in which the neurologic examination reveals multifocal or diffuse involvement are relatively common in clinical practice. Multifocal or diffuse involvement of the brain refers to clinical evidence that more than one functional division of the brain is affected by a disease process. For example, a dog with both forebrain and cerebellar dysfunction would be considered to have multifocal or diffuse involvement of the brain. Whether to call a neurologic localization multifocal or diffuse is somewhat a matter of semantics, but *diffuse* suggests a more generalized and symmetric constellation of deficits, whereas *multifocal* connotes a more asymmetric group of abnormalities. There are several implications of multifocal/diffuse localization in a patient with signs of encephalopathy; for example, the type of disorder more likely to present with such a neurolocalization. In general, inflammatory disorders, metabolic disorders, multifocal/metastatic neoplasia and toxins are highest on the differential diagnosis list for dogs and cats with multifocal/diffuse encephalopathy. However, it is important to note that these implications are sometimes inaccurate. Patients with metabolic or toxic disorders causing brain disease are more likely to exhibit symmetric neurologic deficits (i.e., resulting from a diffuse encephalopathy), but this is not an absolute. The clinician should be aware that focal brain lesions can lead to multifocal signs of encephalopathy due to several mechanisms: (1) an extensive mass that invades more than one region of the brain; (2) edema surrounding a focal mass, producing a mass effect; (3) obstruction by a brain lesion of normal cerebrospinal fluid (CSF) flow, leading to accumulations of ventricular CSF (e.g., obstructive hydrocephalus associated with a caudal fossa lesion); and (4) lesions affecting one area of the brain that has influence over a separate region of the brain (e.g., flocculonodular lobe or caudal cerebellar peduncle).

This chapter reviews salient clinical features of the more common multifocal/diffuse brain disorders encountered in dogs and cats. Disorders that commonly lead to multifocal/diffuse brain dysfunction are summarized according to the DAMNIT (*d*egenerative, *a*nomalous, *m*etabolic, *n*eoplastic, *n*utritional, *i*nflammatory [noninfectious], *i*nfectious, *t*oxins, *t*rauma) scheme in Box 261-1. Not all of these disorders are discussed in detail, and some are not discussed at all because they appear elsewhere in this textbook. Emphasis is placed on the noninfectious inflammatory brain disorders of dogs due to their frequent occurrence in clinical practice and propensity to cause multifocal brain dysfunction.

Box 261-1

Disorders That May Cause Multifocal or Diffuse Brain Dysfunction

Degenerative

Lysosomal storage disease* (also see ch. 260)
Cognitive dysfunction syndrome (also see ch. 263)
Leukodystrophy/spongy degeneration (also see ch. 260)
Neuronal vacuolation and spinocerebellar degeneration in Rottweilers and Boxer dogs

Anomalous

Caudal occipital malformation syndrome (also see ch. 260)
Intracranial arachnoid cyst

Congenital hydrocephalus (also see ch. 260)
Neuronal migration disorders
Atlanto-occipital overlap
Dandy-Walker syndrome (also see ch. 260)

Metabolic

Hepatic encephalopathy (also see ch. 281 and 284)
Hypoglycemic encephalopathy (also see ch. 303)
Electrolyte-associated encephalopathy
Endocrine-related encephalopathy (e.g., hypothyroidism [see ch. 299], hyperthyroidism [see ch. 301])
Renal-associated encephalopathy (also see ch. 322)
Kernicterus
Mitochondrial encephalopathy
Organic acidurias

Neoplastic

Primary brain tumors (also see ch. 260)
Metastatic/multifocal brain tumors (e.g., lymphoma; also see ch. 260)

Nutritional

Thiamine deficiency (see ch. 12)
Cobalamin deficiency (Border Collies) (also see ch. 292)

Inflammatory, Noninfectious

Granulomatous meningoencephalomyelitis
Necrotizing encephalitis
Eosinophilic meningoencephalitis

Infectious

Bacterial
Fungal
Viral
Rickettsial
Protozoal
Verminous
Hydrocephalus with periventricular encephalitis

Toxins

Bromethalin (see ch. 152)
Marijuana (see ch. 154)
Metaldehyde (see ch. 152)
Tricyclic antidepressants (see ch. 153)
Brunfelsia (see ch. 155)
Lead
Methylxanthine overdose
Nicotine (see ch. 155)
Salt intoxication (paintballs; see ch. 13 and 152)

Trauma (see **ch. 148**)

Intracranial hemorrhage
Edema
Diffuse axonal injury

*These disorders can also be considered metabolic in nature.

Inflammatory, Noninfectious Disorders of the Brain

The terminology associated with these disorders can be confusing. An important concept to remember is that these terms are based upon histopathologic descriptions, rather than known etiologies. In addition, it has been estimated that approximately one-third of all inflammatory canine brain disorders do not achieve a specific diagnosis. The two most commonly recognized disorders in this disease category are granulomatous meningoencephalomyelitis (GME) and necrotizing encephalitis (NE). Necrotizing encephalitis is often subdivided into two forms: necrotizing meningoencephalitis (NME) and necrotizing leukoencephalitis (NLE). The authors have encountered a number of patients with features of both GME and NE. Because of this phenomenon and the lack of specific identifiable causes for these disorders, the "umbrella" term *meningoencephalitis of unknown etiology* (MUE) has been suggested.[1] Although such a term does have some clinical utility, clinical features and response to therapy do tend to differ between "classic" GME and NE cases. Because of this, the authors feel it is important to consider these as separate clinical entities when it is possible to use clinical and/or diagnostic information to help differentiate between the two disease processes.

Granulomatous Meningoencephalomyelitis

This is a common and enigmatic idiopathic inflammatory disease of the central nervous system (CNS) in dogs and is considered extremely rare in cats. GME is diagnosed definitively via histologic features, typified by perivascular infiltrates of primarily mononuclear cells (lymphocytes, macrophages, and plasma cells) in the brain and/or spinal cord. Characteristic perivascular cellular infiltrates of GME both define the disease syndrome and are responsible for the observed neurologic deficits. The underlying cause of this disease remains a mystery, but it is widely believed that GME is an autoimmune disorder, specifically a delayed-type (T cell–mediated) hypersensitivity reaction. Lesions predominate in the white matter. Autoantibodies directed against astrocytes have been demonstrated in GME cases, further supporting the suspicion that this is an autoimmune brain disorder. It is, however, unclear whether these anti-astrocytic antibodies represent a primary or secondary immune response. Recent polymerase chain reaction (PCR) studies have failed to detect viral genetic material in brain tissue from dogs with GME. There are three recognized clinical forms of GME: focal, multifocal (disseminated), and ocular. The ocular form is the least common form. In the experience of the authors, multifocal GME is the most common form of the disorder.

GME can affect any breed of dog of any age and either sex. However, young to middle-aged (median age of 5 years) female dogs of small breeds (e.g., Poodles, Terriers) appear to be predisposed. Seizures, cerebellovestibular dysfunction, and cervical hyperesthesia are common features of multifocal GME. Patients with GME may occasionally be febrile upon presentation. There are reports of biopsy-confirmed cases of GME in dogs, but the vast majority of confirmed GME cases have been diagnosed at necropsy. A presumptive antemortem diagnosis of GME is based upon characteristic signalment and historical and clinical findings in addition to results of diagnostic testing. CSF evaluation (see ch. 115) usually provides the most important information in the antemortem diagnosis of GME. A mainly mononuclear pleocytosis, with a variable percentage of neutrophils and elevated protein level, is typical of GME. Results of imaging studies are highly variable in dogs with GME. In most cases, however, computed tomography/magnetic resonance (CT/MR) images of the brain in GME patients show solitary or (more commonly) multiple (Figure 261-1) lesions, or they may reveal areas of contrast enhancement with indistinct margins.

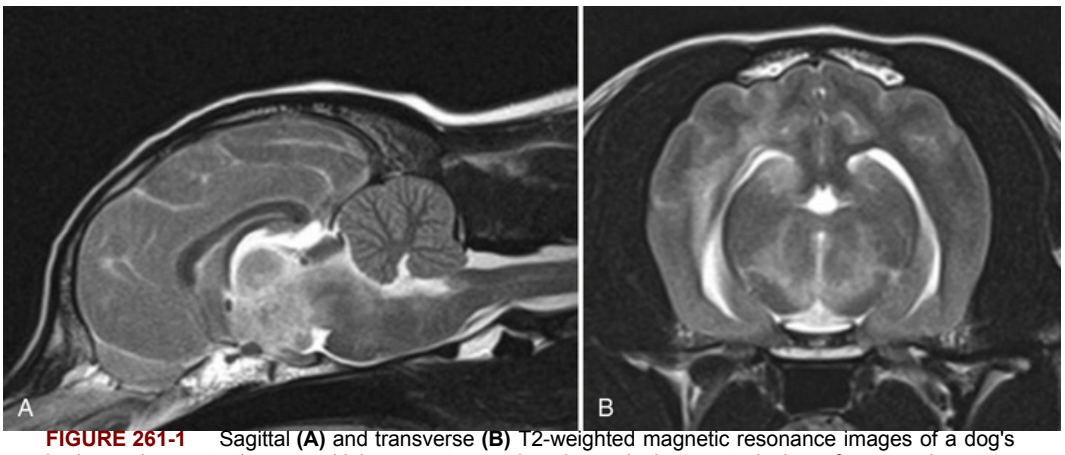

FIGURE 261-1 Sagittal **(A)** and transverse **(B)** T2-weighted magnetic resonance images of a dog's brain, demonstrating multiple contrast-enhancing lesions typical of granulomatous

meningoencephalomyelitis.

Immunosuppressive glucocorticoid therapy (e.g., oral prednisone, 1 to 2 mg/kg q 12 h; also see ch. 165) has long been considered the standard treatment protocol for GME, despite a high rate of clinical failure. The dosage may be slowly reduced over time if the patient exhibits a clinical response to treatment. However, GME patients typically require lifelong immunosuppressive therapy. The prognosis for GME remains guarded, but has improved dramatically in recent years, due to new treatment protocols for the disease. In one study, the median survival time of dogs with multifocal GME treated with glucocorticoid therapy was 8 days.[2] Several alternative immunosuppressive drugs have been evaluated as adjunctive treatment options for GME patients. The three most promising drug options include procarbazine, cytosine arabinoside, and cyclosporine.[3-6] Survival times exceeding 12 months have been reported for each of these three drugs. In addition, the use of these drugs appears to allow for successive decreases in glucocorticoid dosages, thereby minimizing adverse side effects associated with steroid use. Procarbazine is an antineoplastic drug that crosses the blood-brain barrier (BBB) and has some specificity for T cells. The cytotoxic effects of procarbazine are thought to be primarily via methylation of DNA bases. In one study of presumptive GME dogs, the use of procarbazine as an adjunct to prednisone was associated with a median survival time of 14 months, regardless of the clinical form of GME (the majority were multifocal). The dosage used by the authors is 25 mg/m^2 PO q 24 h. Myelosuppression is the most likely adverse effect, although hemorrhagic gastroenteritis may also occur. A complete blood count (CBC) should be checked weekly for the first month, then monthly thereafter to monitor for myelosuppression.[3] Cytosine arabinoside is a synthetic nucleoside analog that crosses the BBB. This drug inserts itself into DNA molecules after enzymatic activation, causing premature chain termination in mitotically active cells. The protocol used for dogs with GME is a continuous rate IV infusion (CRI) (400 mg/m^2) administered over 24 hours. The IV CRI is the authors' preferred route of administration since the steady state achieved via this route may allow for a more prolonged exposure of cytarabine at cytotoxic levels in plasma.[7] A subcutaneous injection of 50 mg/m^2 q 12 h for 2 subsequent days is less effective than the CRI due to the cell-cycle–specific nature of this medication. Drug administration should be repeated initially every 3 weeks, with the interval gradually extending over time. The drug should be diluted 2 : 1 with sterile saline (to prevent tissue irritation) prior to injection, and gloves should be worn when handling cytosine arabinoside. Because myelosuppression is a potential side effect of this drug, a CBC should be checked weekly for the first month and a CBC and serum biochemistry profile should be checked prior to every subsequent treatment. Myelosuppression appears to be very infrequent with this protocol. In one report of 10 dogs with noninfectious encephalitis of undetermined etiology, cytosine arabinoside treatment was associated with a median survival time of approximately 1.5 years. In two of these dogs, tertiary treatment (procarbazine, leflunomide) was also administered.[4] Cyclosporine (cyclosporine A) is a lipophilic peptide that does not readily cross the BBB. Despite this, it is thought that the drug may become trapped in endothelial cells in the CNS, and that the inflammatory nature of GME may allow more cyclosporine to cross the BBB than would occur in the absence of inflammation. The mode of action of cyclosporine is blocking of transcription of genes in activated T cells that lead to the production of inflammatory cytokines. There have been several clinical reports of cyclosporine use in the treatment of GME in dogs; the drug appears to be successful, with a median survival time of 2.5 years in one report of 10 dogs.[5] Several dosage regimens have been suggested. The authors use 3 to 5 mg/kg PO q 12 h. Reported side effects attributable to cyclosporine use in dogs include vomiting, diarrhea, anorexia, weight loss, gingival hyperplasia, papillomatosis, hypertrichosis, and excessive shedding.[5] There has been one report describing the use of leflunomide, a pyrimidine analogue, for noninfectious inflammatory brain disease in three dogs. The dogs responded favorably to leflunomide and were still alive more than 12 months after starting therapy.[8] The specific inflammatory brain disease(s) affecting these dogs were not determined in this report. In recent years, the authors have been combining the three newer drugs to treat suspected GME patients, most commonly using prednisone, cyclosporine and cytosine arabinoside. Results are preliminary, but responses have been favorable and side effects minimal.

Necrotizing Encephalitis

This disease subcategory includes NME and NLE. As with GME, these are suspected to be autoimmune disorders. Both necrotizing disorders are similar in that they are characterized by multiple cavitary necrotic nonsuppurative inflammatory brain lesions that involve both gray and white matter (Figure 261-2). In NME, these lesions are typically found in the cerebrum, with consistent meningeal involvement. Extensive cerebral

cavitations with a loss of demarcation between gray and white matter are often found in NME images. NLE exhibits similar lesions that often involve the brainstem in addition to the cerebrum, with less consistent involvement of the meninges and cerebral cortex (i.e., mainly white matter). Early reports of these disorders in predisposed breeds led to the terms *Pug encephalitis* or *Pug/Maltese encephalitis* for NME and *Yorkshire Terrier encephalitis* for NLE. Pug and Maltese dogs are commonly affected by NME, but other breeds have been reported with this disorder, including Chihuahua, Shih Tzu, Pekingese, Papillion, Yorkshire Terrier, Coton de Tulear, Brussels Griffon and Staffordshire Terrier mixed breed dog.[9,10] Yorkshire Terriers seem to be the most common breed afflicted by NLE, but this disease may also affect other small-breed dogs, such as the French Bulldog. It is very possible that NME and NLE represent variants of the same disease process. It is expected that more breeds will be reported with idiopathic NE. PCR tests have failed to identify viral DNA associated with these disorders. As with GME, the necrotic lesions observed on brain histopathology both account for the clinical signs of dysfunction and define the disease syndrome.

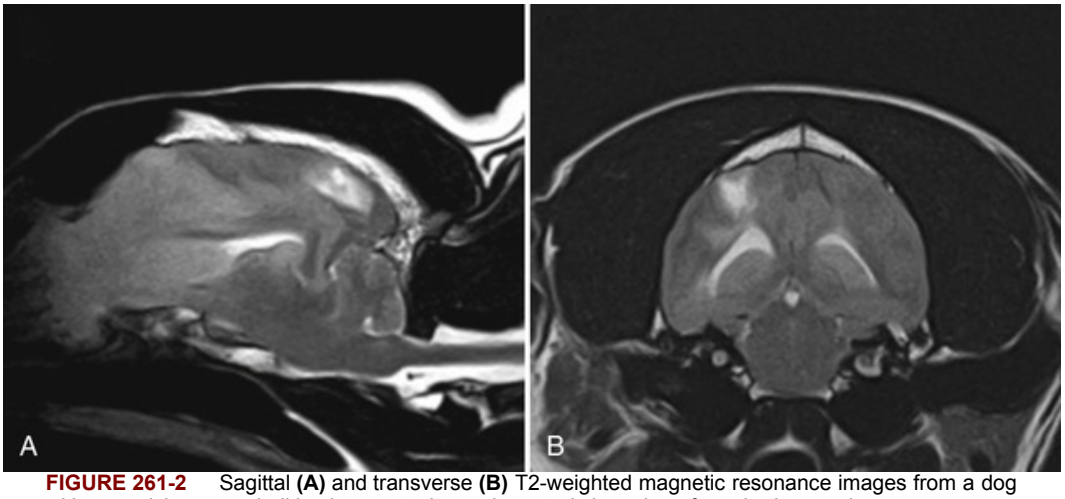

FIGURE 261-2 Sagittal **(A)** and transverse **(B)** T2-weighted magnetic resonance images from a dog with necrotizing encephalitis, demonstrating a characteristic region of cerebral necrosis.

NE tends to occur in young, small-breed dogs, but a wide age range has been reported. Clinical signs (see ch. 259) typically correspond to the distribution of brain lesions. Seizure activity is frequent with NE, often being the primary clinical complaint. Pug and Maltese dogs with NME have varying ages at presentation—between 6 months and 7 years. The onset and progression of clinical signs of neurologic dysfunction may be acute (disease course of 2 weeks or less) or chronic (disease course of 4 to 6 months). Clinical signs of forebrain dysfunction (seizures, circling, obtunded mental status, visual deficits with normal pupillary light reflexes, head-pressing, etc.) predominate. Neck pain is a common feature and may be due to the meningitis and/or forebrain disease. Yorkshire Terriers with NLE have been reported between the ages of 1 and 10 years. These dogs commonly display a chronic, progressive worsening of neurologic dysfunction over several months. In addition to clinical signs of forebrain dysfunction and neck pain, Yorkshire Terriers with NLE often show clinical signs of brainstem dysfunction (e.g., central vestibular disease). The definitive diagnosis of NE is based upon characteristic histopathologic brain lesions observed at necropsy. A tentative diagnosis is based primarily upon signalment, history, and findings of the neurologic examination. Bloodwork results are characteristically normal. CSF findings (see ch. 115) are often abnormal; most commonly, a predominantly or exclusively mononuclear pleocytosis with elevated protein levels is found. The mononuclear cells in NME are usually primarily lymphocytic, whereas a mixture of lymphocytes and monocytes is usually seen in the CSF of NLE patients. MRI and CT findings have been described in several cases of NE. Lesions on MRI are usually isointense or hypointense on T1-weighted images, hyperintense on T2-weighted and FLAIR images, and inconsistently and nonuniformly contrast enhancing. Asymmetric ventricular dilation and areas of hypointensity in the brain (corresponding to malacic brain parenchyma), sometimes appearing continuous with the lateral ventricles, are consistent findings.

Treatment of suspected NE patients with glucocorticoids and anticonvulsant drugs (if seizures are occurring) should be attempted but often has little to no appreciable clinical effect. The prognosis for NME is poor to grave. The majority of dogs die or are euthanized due to progressive neurologic dysfunction within 6 months of onset of neurologic deficits. The same drug protocols used in recent years for GME have been

suggested for use in cases of NE. Due to lower case numbers compared with GME, as well as lack of distinction in some reports between GME and NE, it is unclear whether these drugs are effective for NE or not. In the authors' experience, procarbazine does not appear to be as effective in suspected NE cases, as compared with GME cases. The prognosis for this group of disorders remains poor. The authors and colleagues have had anecdotal success treating several suspected NME patients with mycophenolate mofetil (see ch. 165).

Eosinophilic Meningoencephalitis

Eosinophilic meningoencephalitis (EME) is an uncommonly diagnosed cause of canine intracranial disease. It is characterized primarily by meningeal inflammation and an eosinophilic pleocytosis with a greater than 10% eosinophil count in the cerebrospinal fluid (CSF) of affected animals, independent of circulating blood eosinophil levels. In veterinary medicine, EME is frequently idiopathic in nature, although infectious EME can be caused by agents such as *Cryptococcus neoformans* (see ch. 231), *Neospora caninum* (see ch. 221), and *Baylisascaris procyonis* (see ch. 210). In one retrospective study, an infectious cause for EME was only identified in 17% of cases, while 70% were determined to be idiopathic.[11] In contrast to other canine encephalitides, such as granulomatous meningoencephalitis and necrotizing meningo- and leukoencephalitis, to which toy and small-breed dogs are predisposed, idiopathic EME is most commonly diagnosed in larger breeds. Specifically, the Rottweiler, Golden Retriever and Belgian Tervuren appear over-represented for this condition.[12-14] Idiopathic EME has been reported to occur in only a handful of small-breed dogs, including the Yorkshire Terrier, Beagle, Pug dog and Miniature Pinscher. A diagnosis can be made based on clinical findings, MRI appearance and an eosinophilic pleocytosis on CSF analysis (see ch. 115). A wide range of MRI appearances is seen in canine idiopathic EME, including normal scans.[11] The same drug protocols used for treatment of GME and NE have also been used with success by the authors.

Greyhound Nonsuppurative Meningoencephalitis

Greyhound nonsuppurative meningoencephalitis is a breed-associated disorder with a unique lesion distribution. This disease process affects young Greyhounds that are typically less than 12 months of age. A genetic risk factor is assumed because the disease has been shown in siblings and a causative infectious agent has yet to be identified. An association between dog leukocyte antigen class II haplotype and Greyhound meningoencephalitis has been found.[15] Reported clinical signs are varied and can include forebrain signs (mentation and behavior changes, blindness) and brainstem signs (head tilt, circling, ataxia).[16] MRI abnormalities show a predilection for the rostroventral portions of the cerebrum, particularly the olfactory lobes and bulbs.[17] Histopathologic examination reveals severe gliosis and gemistocytosis with mononuclear cell perivascular cuffing in the caudate nucleus and cortical gray matter of the cerebrum and in the periventricular gray matter of the rostral portion of the brainstem. Milder lesions are also found in the molecular layer of the cerebellum, the caudal brainstem, and the cranial cervical spinal cord.[18]

Infectious Disorders of the Brain

Infections of the brain may result in neurologic dysfunction by producing a mass effect (i.e., organized abscess) or release of toxins and inflammatory mediators. A major cause of neurologic deficits is thought to be the secondary inflammatory response induced by the organisms. Infectious brain disorders are far less commonly encountered in dogs and cats compared with noninfectious disorders. However, the dogmatic assumption that these disorders are rare, combined with the often rapid clinical progression of such diseases, may place an affected patient at undue risk of not receiving timely and appropriate therapy. This is, of course, a specific concern for those infectious diseases that may respond to antimicrobial agents. In some cases, surgical decompression and brain abscess or granuloma removal may also be indicated on an emergency basis.

Bacterial Meningoencephalitis

Bacteria can gain access to the brain via the hematogenous route or by extension of infection from a neighboring focus (e.g., extension of otitis interna). The BBB and absence of a lymphatic system in the CNS help protect it from microbial invasion. However, once an infectious agent has successfully breached the BBB, the immunologically privileged nature of the CNS represents an advantage to the invading organism and a

detriment to the host. Commonly implicated organisms in canine and feline bacterial meningoencephalitis include *Staphylococcus* and *Streptococcus* species, *Pasteurella multocida* (especially cats), *Actinomyces* and *Nocardia* species, as well as anaerobes (e.g., *Bacteroides, Peptostreptococcus, Fusobacterium, Eubacterium*). In one report of canine bacterial meningoencephalitis, the most common causative organisms were *Escherichia coli, Streptococcus* species, and *Klebsiella* species. Gram-negative infections were most common, and single-versus multiple-organism infections were equally likely.[19]

Dogs and cats of any age, breed, or sex may develop bacterial meningoencephalitis, but it is more common in young to middle-aged animals (e.g., 1 to 7 years). Clinical signs of neurologic dysfunction are often acute and rapidly progressive. Fever and cervical hyperesthesia are considered classical features of bacterial meningoencephalitis but may not be evident. A tentative diagnosis of bacterial meningoencephalitis is based upon historical and clinical data, as well as results of laboratory tests. A positive response to antibiotic drugs also supports the diagnosis. CBC results may indicate a systemic inflammatory response, but this is often not the case. Abnormalities on serum chemistry profiles (e.g., elevated ALT and SAP levels, hypoglycemia, hyperglycemia) are apparent in the majority of cases. Advanced imaging (CT, MRI) may be helpful in diagnosing mass lesions (Figure 261-3) or obstructive hydrocephalus. The most valuable information is obtained from CSF analysis (see ch. 115), which is usually abnormal. With acute bacterial meningoencephalitis, a suppurative CSF pattern, often with degenerate and toxic-appearing neutrophils, is common. Protein levels are also often elevated. The presence of intracellular bacteria in the CSF sample confirms the diagnosis. Extracellular bacteria may represent causative agents but may also be contaminants. Positive CSF, blood, and/or urine culture results also support the diagnosis of bacterial meningoencephalitis, but these are often falsely negative (see ch. 221).

FIGURE 261-3 Axial T1-weighted (with contrast) brain magnetic resonance image of a cat with a cerebral abscess. (Reprinted with permission from Dewey CW: Encephalopathies: disorders of the brain. In Dewey CW, editor: *A practical guide to canine and feline neurology*, ed 2, Hoboken, NJ, 2008, Wiley-Blackwell.)

Antibiotic treatment of bacterial meningoencephalitis is ideally based upon culture/sensitivity results of the causative organism. Because this is often not obtainable, antibiotic therapy is often based on Gram stain results of organisms seen on CSF analysis, or on the most likely pathogen(s), if organisms are not observed. Appropriate antibiotics for bacterial meningoencephalitis should ideally be bactericidal, have a low-level protein binding, and be able to cross the BBB. Intravenous therapy is recommended for at least the initial 3 to 5 days of therapy. High intravenous dosages of ampicillin (e.g., 22 mg/kg q 6 h) have been recommended as an appropriate therapeutic choice for most cases of canine and feline bacterial meningoencephalitis.

Ampicillin crosses the inflamed BBB relatively well and is bactericidal. If a Gram-negative infection is suspected or confirmed, enrofloxacin (e.g., 10 mg/kg IV q 12 h in dogs) or a third-generation cephalosporin (e.g., cefotaxime at 25-50 mg/kg IV q 8 h) are good choices. Metronidazole (10 mg/kg IV slowly q 8 h) is an excellent antibiotic choice for most anaerobic infections. Intravenous metronidazole should be administered over 30 to 40 minutes because rapid infusion can lead to hypotension.

In severe cases of bacterial meningoencephalitis, it may be prudent to institute combination antimicrobial therapy while awaiting CSF laboratory results (Gram stain, culture results). Based on information concerning causative agents in canine bacterial meningoencephalitis, inclusion of antibiotics with strong activity against Gram-negative bacteria is highly recommended. Once a positive response to intravenous antibiotic therapy is achieved, the patient can be switched to oral therapy. Trimethoprim-sulfonamide (15 mg/kg PO q 12 h) is broad and bactericidal, and it readily penetrates the BBB, even when the BBB is not inflamed. Oral formulations of enrofloxacin and metronidazole are also available. Recommendations for the length of oral antibiotic therapy vary. Discontinuation of antibiotic therapy is ideally based both on clinical signs as well as normal follow-up CSF tap results. However, the latter-mentioned information is often not available. Antibiotic therapy should be administered for 10 to 14 days after resolution of clinical signs of disease. Glucocorticoid use in the face of infection is theoretically contraindicated, but there is evidence that transient (maximum of 4 days), anti-inflammatory doses of glucocorticoids improve outcomes in people with bacterial meningitis.[9] Such therapy should be considered for dogs and cats with this disorder. If CT or MR imaging localizes a surgically accessible abscess, surgical intervention may play an important role in the management of bacterial meningoencephalitis. Unfortunately, there are no reports describing large groups of dogs or cats treated appropriately for confirmed bacterial meningoencephalitis.

The sparse information available suggests a poor prognosis overall. Similar to human bacterial CNS infections, the key to successfully treating dogs and cats with bacterial meningoencephalitis is early diagnosis and rapid, aggressive therapy.

Fungal Meningoencephalitis

There is a wide variety of fungal organisms that may invade the CNS, including *Cryptococcus* (see ch. 231), *Coccidioides* (see ch. 232), *Blastomyces* (see ch. 233), *Histoplasma* (see ch. 233), *Aspergillus* (see ch. 234 and 235), and the phaeohyphomycoses (e.g., *Cladosporium*; see ch. 236). *Cryptococcus neoformans* is by far the most common fungal organism associated with meningoencephalitis in dogs and cats. Meningoencephalitis due to coccidioidomycosis has been reported in 36 dogs.[20] Fungal disease is typically contracted by dogs and cats via inhalation of fungal spores. Infection of the CNS can occur via local extension (e.g., nasal/frontal sinus) or hematogenously. Similar to bacterial meningoencephalitis, dogs and cats with fungal meningoencephalitis are often young to middle-aged. Although clinical signs of neurologic dysfunction may be acute in onset and rapidly progressive, fungal meningoencephalitis is often characterized by slow progression (weeks to months) of neurologic dysfunction, often preceded by a period of nonspecific illness (e.g., lethargy, anorexia). Clinical evidence of extraneural fungal infection is common in cases of fungal meningoencephalitis. With cryptococcosis, extraneural infection around the head region (eyes, nasal and frontal sinuses) is most likely. With coccidioidomycosis, initial infection of the pulmonary system is typical.

The diagnosis of fungal meningoencephalitis is based upon identifying the presence of a fungal organism in a patient displaying signs of encephalopathy. Finding a fungal organism in an extraneural site in a patient with brain dysfunction is strong evidence for fungal meningoencephalitis. Brain imaging (preferably MRI) is likely to demonstrate intraaxial lesions that strongly contrast enhance (Figure 261-4). These fungal granulomas often have evidence of substantial perilesional edema. Identifying the organism in a CSF sample is the strongest evidence to support the diagnosis, and this is more likely to occur with *Cryptococcus* infections than with other fungal infections (see ch. 115). Special stains are available to help identify specific fungi on cytology specimens. CNS fungal infections typically cause a mixed-cell pleocytosis with elevation of protein on CSF examination. The nature of the pleocytosis is highly variable but usually includes a large proportion of both mononuclear cells as well as neutrophils, typical of a granulomatous disease. In the report of dogs with intracranial coccidioidomycosis, mononuclear pleocytosis was most commonly demonstrated, followed by mixed-cell pleocytosis. Eosinophils may also constitute a large proportion of CSF white blood cells in fungal meningoencephalitis patients. Testing of CSF and/or serum for antibodies to fungal antigens can also be performed. These tests are very reliable for *Cryptococcus*, *Coccidioides*, and *Blastomyces* infections, less so for *Aspergillus* infections, and unreliable for *Histoplasma* infections. No such tests are available for the phaeohyphomycoses. The various fungi can also be cultured from bodily fluids, using special growth media; this can be hazardous to human health in the case of blastomycosis, coccidioidomycosis and histoplasmosis.

Bloodwork abnormalities are variable and nonspecific. Fungal elements may be identifiable in urine samples. Ophthalmic examination may show evidence of inflammatory disease (e.g., uveitis, chorioretinitis; see ch. 11). Pulmonary lesions may be identifiable in some cases (e.g., *Histoplasma, Blastomyces, Coccidioides*) on thoracic radiographs. Cats with suspected or confirmed fungal meningoencephalitis should be tested for feline leukemia virus (see ch. 223) and feline immunodeficiency virus (FIV; see ch. 222).

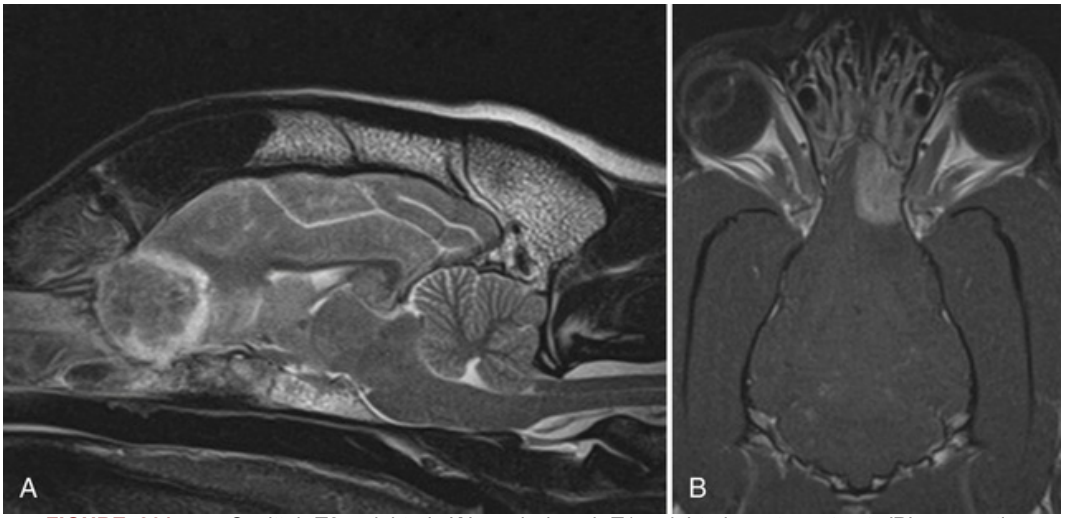

FIGURE 261-4 Sagittal T2-weighted **(A)** and dorsal T1-weighted post contrast **(B)** magnetic resonance images of a dog with a cryptococcal granuloma.

Treatment and prognosis for canine and feline fungal meningoencephalitis are poorly defined. Although antifungal drugs constitute the mainstay of treatment for these cases, surgical removal/debulking of large intracranial granulomas may sometimes be indicated. Similar to bacterial meningoencephalitis, data describing large numbers of dogs and cats with CNS fungal disease treated with appropriate antifungal agents are lacking. Meningoencephalitis caused by *Aspergillus* or phaeohyphomycosis species is likely to be fatal. Few antifungal drugs are able to cross the BBB effectively, even when inflamed. Flucytosine (5-fluorocytosine) and the triazole drug fluconazole are two antifungal drugs that readily cross the BBB. There are several reports of sustained remissions or cures in CNS cryptococcosis patients treated with drug combinations that included flucytosine and/or the newer triazole drugs (itraconazole and fluconazole). Flucytosine use alone may lead to the development of drug resistance. In a report of 36 dogs with intracranial coccidioidomycosis, 84% of dogs improved or resolved with fluconazole therapy.[20] Once clinical signs of disease are controlled, most patients with fungal meningoencephalitis will require long-term antifungal therapy (months). In the author's experience, fluconazole therapy for fungal meningoencephalitis cases may need to be very prolonged. In the report of 36 dogs with coccidioidomycosis meningoencephalitis, the minimum treatment time was one year.[20] The decision of when to discontinue antifungal therapy should be based upon clinical signs, repeat CSF results, and CSF/serum titers for the organism (if appropriate). Because fluconazole penetrates the BBB well and itraconazole does not, fluconazole for CNS fungal infection is the preferred antifungal agent (5 mg/kg PO q 12 h). The main drawback of fluconazole use is the high cost of the drug. Although controversial, it may be beneficial to administer low dosages of oral prednisone (e.g., 0.5 mg/kg q 12 h) in the early treatment period (1 to 2 weeks), in order to combat perilesional edema.

Viral Meningoencephalitis

The most frequently encountered viral infections of the brain in dogs and cats in clinical practice are canine distemper (paramyxovirus; see ch. 228) virus and feline infectious peritonitis (FIP-coronavirus; see ch. 224) virus, respectively. Other, less common causes of viral meningoencephalitides include rabies virus (dogs and cats; see ch. 226), FIV (a lentivirus; see ch. 222), canine herpesvirus (see ch. 228), feline parvovirus (panleukopenia virus; see ch. 225), feline Borna disease virus (BDV; see ch. 270), pseudorabies (dogs and cats, caused by a porcine herpesvirus; see ch. 228), and West Nile virus (a mosquito-borne flavivirus; see ch. 228). CNS involvement is rarely reported in association with canine adenovirus (infectious canine hepatitis virus), canine parainfluenza virus (also a paramyxovirus), and canine parvovirus. There are multiple routes of viral

infection, but inhalation is most common. Rabies is typically contracted via bite wounds from infected animals, and pseudorabies from ingestion of infected raw pork meat. FIV may be spread via bite wounds. Viruses can damage brain parenchyma via both direct (e.g., cytolytic) and indirect (e.g., immune-mediated) effects. Some viruses have a predilection for neuronal and glial cells and are termed "neurotropic." Such viruses include the causative agents of canine distemper, rabies, pseudorabies, and feline Borna disease.

As with other CNS infectious diseases, affected animals are often young to middle-aged. Viral CNS infections typically run an acute to subacute course but may be peracute (e.g., pseudorabies) or insidious (FIP) in onset and progression. Clinical signs of multifocal encephalopathy are common. Extraneural signs (e.g., fever, ophthalmic disease, respiratory disease) of viral infections may or may not be present. In canine distemper meningoencephalitis, historical or clinical evidence of gastrointestinal and/or respiratory disease prior to or concurrent with neurologic dysfunction are classic findings supportive of the diagnosis. Hyperkeratosis, or "hard pad," affecting the footpads and/or planum nasale is another classic yet inconsistent indicator of canine distemper infection. Other extraneural manifestations of distemper virus infection in dogs include mucopurulent conjunctivitis, mucopurulent rhinitis, and chorioretinitis (see ch. 11). Extraneural involvement can be either nonexistent or subclinical and therefore may not be appreciated. Myoclonus (repetitive, rhythmic muscular contraction) involving one or more limbs and/or muscles of the head is a relatively specific and common clinical finding in canine CNS distemper infection (see ch. 31). Myoclonus is thought to be due to abnormal pacemaker activity in neurons damaged by the virus. "Chewing gum fits"—rhythmic jaw movements displayed by some dogs with CNS distemper—may represent a form of myoclonus or focal seizure activity. FIP (coronavirus) infection of the CNS is typically associated with the noneffusive form of the disease. Historical and clinical signs of systemic disease (e.g., fever, weight loss) are common in cats with coronavirus meningoencephalitis. Multifocal encephalopathy is common, often with brainstem and cerebellar dysfunction.

A poor to nonexistent vaccination history in an acutely encephalopathic dog or cat with possible exposure to wildlife or other nonvaccinated dogs or cats should alert the clinician to consider rabies (see ch. 226). The typical "furious" and "paralytic" forms of rabies have been described. The furious form is more common in cats and is characterized by apprehension and aggression, suggesting primarily forebrain dysfunction. The paralytic form, encountered more frequently in dogs, is characterized by lower motor neuron dysfunction of brainstem nuclei, leading to a dropped jaw (cranial nerve [CN] V) and swallowing difficulty with attendant ptyalism (CNs IX to XI). Respiratory difficulty and gait abnormalities may also be apparent. Focal and/or generalized seizure activity may occur with either form of rabies. Dogs and cats with rabies may present with a wide variety of clinical signs of neurologic dysfunction, and the previously mentioned forms of rabies should be viewed as very rough guidelines.

Diagnosis of viral meningoencephalitis is usually made at necropsy. Identification of causative virus in brain parenchyma through various methods (e.g., visualizing inclusion bodies, immunocytochemistry, viral isolation) and the appearance of characteristic histologic patterns (e.g., pyogranulomas in FIP, demyelinating brainstem lesions in canine distemper) help confirm a diagnosis of a specific viral-induced encephalopathy. In the case of an unvaccinated dog or cat that has died or was euthanized because of brain disease (of recent onset) and has had exposure to people (especially bite wounds), examination of the brain (e.g., direct fluorescent antibody test) for rabies is mandatory. The antemortem diagnosis of viral meningoencephalitis is often difficult and relies on combining characteristic historical and clinical findings with several diagnostic tests. Specific and reliable diagnostic tests for viral meningoencephalitis are lacking. Intuitively, identifying the presence of a viral agent in a patient displaying encephalopathic signs would support that virus as being the causative factor. However, identifying virus or viral antigen in body tissues or fluids is usually unsuccessful. The indirect fluorescent antibody test for canine distemper, usually performed on conjunctival scrapings, buffy coat smears, and/or urine sediment, may produce too many false-negative and false-positive results to be of much clinical use. Identification of circulating antibody against various viruses in the blood and CSF can be readily accomplished. Because the patient may have been exposed naturally or intentionally (vaccination) to a suspect viral pathogen in the past, a positive serum antibody titer often has little clinical meaning. Similarly, in a patient previously immunized for a specific viral disease, demonstrating a positive titer in the CSF for that viral agent has little meaning. If the BBB is disrupted for any reason, the serum antibodies can passively move to the CSF. Demonstrating a gradient of titers (i.e., CSF titer for an antiviral antibody higher than the serum titer) is more definitive evidence of that virus as the causative agent.

More recently, the use of a one-step, reverse transcriptase-polymerase chain reaction (RT-PCR) test to amplify canine distemper virus–specific RNA products in serum and CSF has been described. This PCR procedure appears to be a specific antemortem test for canine distemper virus infection. The authors have had a number of positive RT-PCR results for coronavirus from CSF procured from cats with suspected or proven

neurologic FIP. The sensitivity and specificity of RT-PCR for CSF in neurologic FIP are currently unknown, but it is likely that this test is sensitive but not specific for neurologic FIP. Some basic laboratory tests may provide supportive evidence for specific viral infections, if abnormal. Lymphopenia may occur with canine distemper infections (see ch. 228), and hyperglobulinemia is common with FIP infections (see ch. 224). Ophthalmic examination may provide valuable clinical evidence in some diseases (e.g., hyperreflective retinal lesions in canine distemper; see ch. 11).

CSF values are often abnormal with viral meningoencephalitis. Immature dogs with distemper affecting primarily gray matter may have normal CSF results. The characteristic CSF analysis results of a patient with CNS viral disease consist of predominantly mononuclear (lymphocytic) pleocytosis with elevated protein. The exception to this rule is CSF from FIP patients. The coronavirus tends to induce an intense immune response in this disease, and the predominant cell type in FIP meningoencephalitis is usually the neutrophil, with variable numbers of lymphocytes and macrophages (a pyogranulomatous response). CSF IgG titers to feline coronavirus are probably not diagnostically useful.

Advanced imaging (CT/MRI) may demonstrate brain lesions (e.g., contrast-enhancing regions of inflammatory foci) in some cases of viral meningoencephalitis. Although brain imaging is unlikely to reveal specific characteristic abnormalities in most cases, it may be useful to rule out other diseases (e.g., intracranial intraarachnoid cysts in young dogs and cats). Hydrocephalus may be a common sequela to FIP meningoencephalitis that can be appreciated on a CT or MR image. Periventricular contrast enhancement has also been described in MR brain images of cats with FIP meningoencephalitis. Cats with confirmed FIP meningoencephalitis may have normal MR brain images.

There are no effective antiviral agents available for viral meningoencephalitis, and the prognosis for these diseases is generally poor to grave for survival. Rabies and pseudorabies are rapidly progressive and invariably fatal (often from respiratory failure) within 1 week and 48 hours of the onset of clinical signs, respectively. FIP typically progresses over several weeks and is also invariably fatal. Most dogs with CNS distemper infections die or are euthanized due to progressive neurologic dysfunction. However, clinical signs of disease may remain static or improve in some dogs, and survival is possible with proper nursing care. Anti-inflammatory doses of prednisone are often prescribed to lessen the secondary effects of viral infection on CNS tissue in these cases. FIV-associated encephalopathy appears to have a chronic course without progression of clinical signs in many cases.

Other Infectious Diseases

Other infectious organisms that may lead to multifocal encephalopathy in dogs and cats include rickettsial (e.g., ehrlichiosis, Rocky Mountain spotted fever [RMSF] in dogs; see ch. 218), protozoal (e.g., *Toxoplasma* in dogs and cats, *Neospora* in dogs; see ch. 221), and verminous (e.g., *Cuterebra* in cats) agents. *Toxoplasma gondii* and *Neospora caninum* are protozoal agents known to occasionally cause meningoencephalitis in dogs. *Toxoplasma* has also been reported to cause meningoencephalitis in cats. Experimental infection of cats with *Neospora* may lead to meningoencephalitis, but no naturally occurring cases have been reported. Canine and feline meningoencephalitis due to an organism that appears to be *Sarcocystis* has also been reported.

For rickettsial and protozoal infections, antemortem diagnosis is usually based upon serologic testing for the presence of the offending organism (i.e., rising antibody titers), in conjunction with other supporting evidence (e.g., thrombocytopenia in a dog with RMSF infection). Unfortunately, diagnosis of verminous meningoencephalitis requires identification of the parasite, which is often not possible. Advanced imaging (preferably MRI) may demonstrate contrast-enhancing brain lesions with these infections, and CSF results are likely to be abnormal. Varying distributions of cell types have been reported for CSF analyses from patients with these infectious disorders.

Drugs used to treat dogs with rickettsial meningoencephalitis include doxycycline, chloramphenicol, and enrofloxacin. Clindamycin or sulfonamides combined with trimethoprim or pyrimethamine are recommended for protozoal meningoencephalitis. In suspected cases of CNS cuterebriasis in cats, ivermectin treatment is recommended. These cats should be pretreated with diphenhydramine and glucocorticoids in order to ameliorate allergic reactions to dead and dying intracranial larvae. In addition, it is recommended to treat these cats for 2 weeks with antibiotics (e.g., amoxicillin/clavulanic acid) after ivermectin treatment, to minimize the likelihood of secondary bacterial meningoencephalitis.

Degenerative and Anomalous Disorders of the Brain (see also ch. 260)

Degenerative brain disorders that may cause multifocal or diffuse encephalopathy are numerous and include

lysosomal storage diseases, mitochondrial encephalopathies, and organic acidurias. These categories of degenerative diseases comprise a wide variety of inherited (primarily autosomal recessive) abnormalities, which have in common the intracellular accumulation of one or more products of an interrupted degradative metabolic pathway. The metabolic defect is responsible for the development of intracranial disease, typically via an accumulation of by-product(s) that will lead to cellular dysfunction, presumably due to cellular swelling, a toxic effect of the accumulated material(s), or both. In general, diagnosis of these diseases requires either identifying the specific enzymatic defect, an accumulation or storage product, and/or a defective gene responsible for the abnormality. At present, treatments are limited for these disorders and the prognosis is often guarded to poor. There are a number of anomalous brain disorders that can lead to multifocal or diffuse clinical signs of brain dysfunction. These include caudal occipital malformation syndrome (COMS, also known as *Chiari type I malformation* and *occipital bone hypoplasia*), intracranial arachnoid cysts, and congenital hydrocephalus. These disorders are best diagnosed with MR imaging and treated with a combination of surgical and medical management (Figure 261-5).

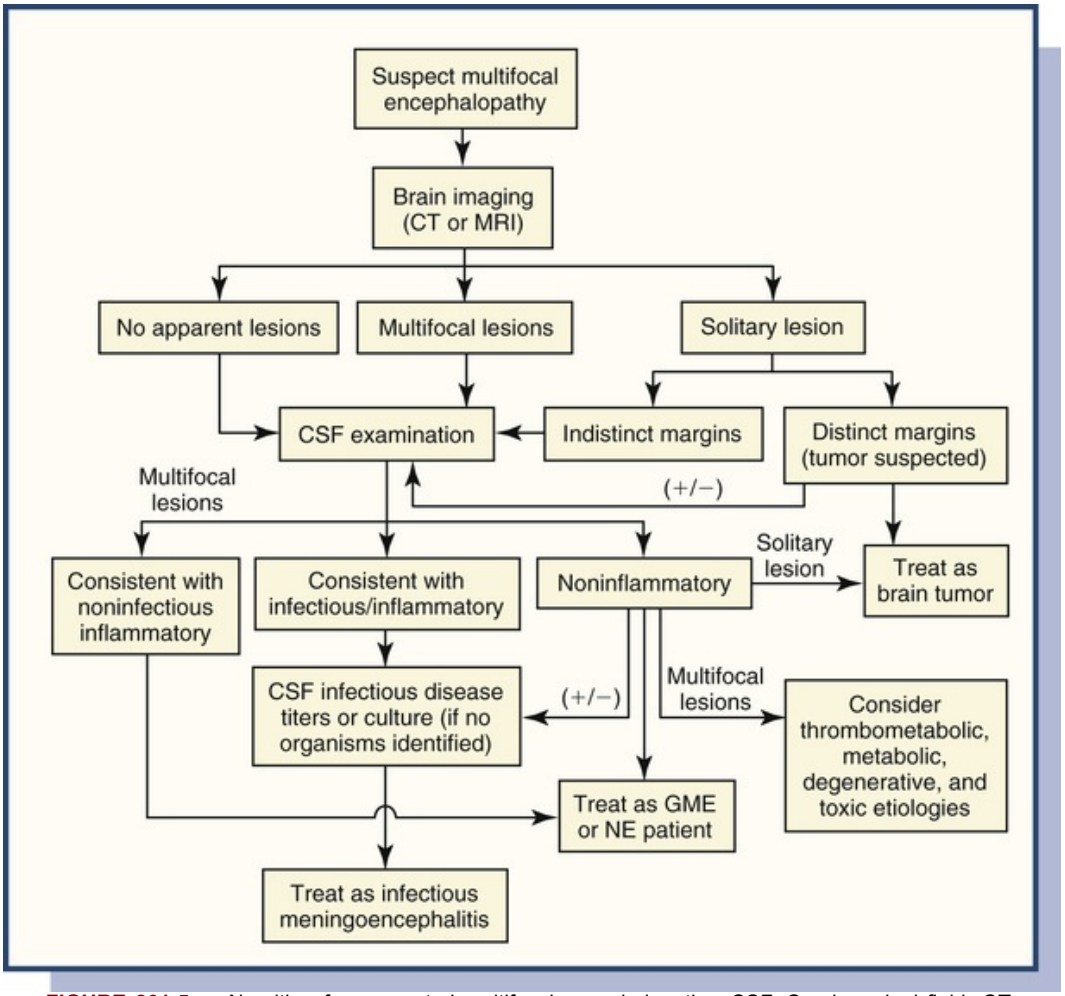

FIGURE 261-5 Algorithm for suspected multifocal encephalopathy. *CSF,* Cerebrospinal fluid; *CT,* computed tomography; *GME,* granulomatous meningoencephalomyelitis; *MRI,* magnetic resonance imaging; *NE,* necrotizing encephalitis.

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CHAPTER 262

Sleep Disorders

Brian M. Zanghi

Client Information Sheet: Sleep Disorders of Dogs and Cats

Sleep is a complex physiological process driven by an active neurobehavioral state maintained by the central nervous system. Ultimately, sleep plays an essential restorative function for both physical and cognitive purposes, and is an indispensable function of a healthy life. Naturally occurring sleep disorders are relatively uncommon in cats and dogs. In all types of sleep disorders, the condition can vary from subtle to severe, but may also indicate another underlying neurological disease. Having some familiarity with both normal and abnormal sleep will assist in diagnosing sleep-associated abnormalities.

Normal Sleep

Sleep is not a passive resting state, but is a dynamic physiology that is controlled by very active neurological processes.[1] Peak hours of "normal" locomotor activity or sleep in healthy cats and dogs are influenced by feeding frequency,[2-4] age,[2,3,5] housing (indoor and/or outdoor),[6] and daily schedule of the pet-owner.[7,8] In addition, activity during wakefulness, and rest during periods of sleep, can be influenced by many other factors including environmental light, temperature, presence of other animals, and/or hunger. Therefore, considering a pet's home environment, age, feeding pattern, and owner's schedule will assist in assessing the individual pet's "normal" sleep pattern and influencing factors, and thus assist in evaluating an intrinsic sleep disorder or extrinsic sleep disturbance prior to conducting a more thorough diagnostic evaluation.

The chronobiology and characteristics of sleep have been well documented in humans and rodents over the past several decades.[9-15] In addition, an understanding of the normal characteristics of electroencephalography (EEG)-measured sleep in dogs[16-19] and cats[20-23] exists. Normal sleep consists of rapid eye movement (REM) and non-REM (or slow wave sleep; SWS) sleep states, which all mammalian species experience. The process of sleep begins with transition into SWS, followed by REM sleep, then a brief state of wakefulness before re-entering the cycle and re-initiating SWS.[16,18] SWS stages and REM sleep are best determined by polysomnography (PSG) that allows for the simultaneous generation of EEG, electro-oculogram (EOG), and/or electromyography (EMG) data, that are summarized to generate a hypnogram (Figure 262-1). Although PSG is considered to be the "gold standard" in determining sleep/wake status, it is difficult to conduct in a normal clinical setting because it is time consuming, expensive, and requires attachment of multiple electrodes in a manner that prevents dislodgement. Consequently, PSG is largely limited to experimental use and not offered clinically.

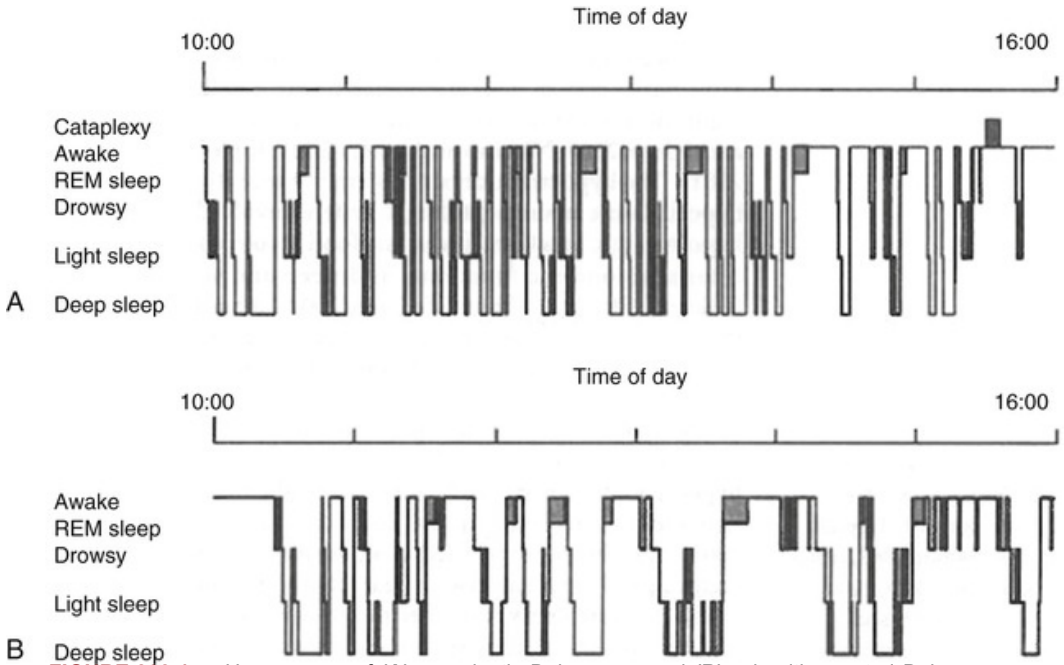

FIGURE 262-1 Hypnograms of **(A)** narcoleptic Dobermann and **(B)** a healthy control Dobermann. The recordings were carried out by cortical electroencephalography (EEG) and neck muscle electromyography (EMG) monitoring with chronically implanted electrodes (Shelton and coworkers, 1995). Sleep was scored on the basis of the EEG and EMG signals and each 30-second period was classified as wake, drowsy, light sleep, deep sleep, or rapid eye movement (REM) sleep (or cataplexy for the narcoleptic dog). (Used with permission from Tonokura M, Fujita K, Nishino S: Review of pathophysiology and clinical management of narcolepsy in dogs. *Vet Rec* 161:375-380, 2007.)

The relative proportions of different sleep and wake states observed in kennel-housed dogs are generally similar across multiple studies.[16-19] Wakefulness of adult dogs predominates during the day, comprising 7-8 hours of the 12-hour day[19,24] compared to ≈5 hours during the night. In contrast to dogs, cats housed with 12-hour light/dark cycles exhibit typical nocturnal behavior (awake/drowsy state 42% of light phase versus 53% during the dark phase).[23]

Geriatric Changes in Sleep and Circadian Rhythm

As in humans,[25,26] age-related changes in PSG-measured sleep/wake rhythms occur in the dog,[27] and awareness by dog-owners that activity declines with advancing age has been reported.[28-30] Senior dogs (>9 years) can experience lower locomotor activity, more daytime sleep, decreased REM sleep, fragmented sleep during the day (more naps, not longer naps), and increased night-time PSG-wakefulness.[3,27,31] However, it is undefined if night-time sleep disruptions reported by pet-owners are related to increased night-time PSG-wakefulness or are a symptom of other age-related behavioral/physical change.

Age-related sleep changes in people are linked to circadian rhythm disruptions,[25,26,32,33] which is also linked to cognitive dysfunction, such as in Alzheimer's patients, who experience significantly more daytime sleep, disrupted nocturnal sleep,[34] and exaggerated hyper- and hypoactivity.[35,36] Cognitively impaired dogs[31] also experienced a delay in peak activity (circadian rhythm shift), but in the absence of cognitive dysfunction, this does not appear to occur as a consequence of advanced age.[2] The relationship between advanced age, behavioral sleep/activity patterns, and cognitive impairment has only been initially explored in dogs.[31,37,38] In addition, age-related (9-15 years old) hyperactivity appears associated with a progression of multiple cognitive domain dysfunction,[31,37] but not single domain,[38] and if severe, may be best treated through addressing the underlying cognitive impairment. (See ch. 263, cognitive dysfunction syndrome [CDS] in dogs).

Diagnostic Approach

Sleep disorders are either primary or secondary. Secondary sleep disorders may result from encephalitis,

intracranial masses, trauma, drug administration, or other disease processes. In addition to a thorough history, physical and neurologic examination (see ch. 2 and 259), an owner video of the event is invaluable if it occurs during sleep, since most animals will not relax enough to sleep at the veterinarian's office. Information about the time of onset of the event after sleep, duration, and whether the animal can be roused from it will help the veterinarian determine whether this is likely to be a sleep disorder. The possibility of a true seizure must be ruled out, since most animals have the onset of epileptic seizures during sleep. Conversely, a sleep disorder should be considered a possibility in an animal treated for suspected epilepsy with minimal or no response to appropriate doses of anticonvulsant medication.

Systemic screening with blood work and radiographs of the thorax and abdomen or abdominal ultrasound will rule out other diseases. Abnormalities on neurologic examination should increase suspicion for primary CNS disease, but intracranial imaging with magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis are necessary to rule out structural brain disease or infectious or inflammatory disease. If intracranial disease is identified in a patient with a sleep disorder, treatment of the primary disease should be attempted, if possible, prior to any specific treatment of the sleep disorder, as it may be secondary to underlying brain disease.

REM Sleep Behavior Disorder

During REM sleep, normal inhibition of motor neurons causes most muscles to become atonic. Exceptions exist with minor and/or random contractile activity of diaphragm, intercostals and small distal muscles of the face, paws, larynx and tail.[39-42] This localized muscular activity results in the hallmark twitching of the eyes, as well as face, larynx, and paws, with minor coordinated contraction sometimes leading to a paddling of all four limbs (paddling not in cats)[39,41] representing a "dreaming" state. In REM Sleep Behavior Disorder (RBD), no muscle atonia is present and significant coordinated movement occurs. Movements often result in violent limb movements,[39,41,43] but can also present as chewing and teeth grinding, biting at air or bedding, and/or attacking the owner or another dog.[43]

In people, the diagnosis of suspected RBD is based on both clinical and PSG criteria,[44] which requires (1) the PSG-determined REM sleep without atonia, (2) documented PSG abnormality during REM sleep (elevated EMG tone and/or excessive phasic limb twitching), and (3) absence of an EEG epileptiform activity during REM sleep. Because of the rarity of RBD in veterinary medicine, little need exists to use PSG in cases with suspected RBD. Therefore, the diagnosis of RBD in the majority of veterinary cases has relied on (1) a description of the clinical signs that are characteristic of RBD behaviors and (2) examination of video recordings of the sleep events.

Reports provided by pet-owners revealed that in 93% of RBD dogs (13 of 14 cases) the RBD events were unsuccessfully treated with melatonin, gabapentin, diazepam, diphenhydramine, acepromazine, clonazepam, or phenobarbital.[41,43] However, dose and frequency of these medication treatments were not reported by clients during the study review survey.[43] Potassium bromide (44 mg/kg/day) decreased the severity and frequency of client reported RBD events in 78% of the dogs (11 of 14 cases).[43] In addition, longer-term (6-month) reduction of RBD episode severity during night-time sleep was observed with clomipramine starting at 1 mg/kg PO q 12 h and progressively increasing dosage to 4 mg/kg PO q 12 h by 12 weeks.[45]

Sleep-Disordered Breathing or Sleep Apnea

Sleep apnea is a common problem in humans. The characteristics of sleep-disordered breathing (SDB) include normal arterial oxygen saturation when awake, but disordered respiration and episodes of oxygen desaturation when asleep, particularly in REM sleep, frequently causing awakening. Hypersomnolence, or excessive daytime sleepiness, is also present, likely a result of continually interrupted sleep. The brachycephalic conformation has anatomic features (stenotic nares, elongated soft palate, hypoplastic trachea) that will increase upper airway resistance and can cause an obstructive breathing pattern (see ch. 238). Clinically, the respiration of a brachycephalic dog can be exacerbated by excitement or exertion (increased passage of air), or when the pharyngeal region is relaxed (anesthesia, sedation, sleep).

The English Bulldog has been proposed as a natural model of SDB. Bulldogs demonstrated marked oxygen desaturation in REM sleep, paradoxical breathing patterns (unsynchronized thoracic and abdominal movements), and awakening from events of apnea.[46,47] These dogs also fell asleep faster than control dogs, suggesting hypersomnolence. Clinical improvement of the hypersomnolence was noted in one dog in which upper airway surgery was performed to alleviate clinical signs.[46] Bulldogs were also used to evaluate

effectiveness of various experimental drug therapies with serotonergics.[48-50]

Narcolepsy (Narcolepsy-Cataplexy)

Narcolepsy occurs in animals and humans, and is a chronic sleep disorder of neurological origin characterized in dogs by excessive daytime sleepiness and/or very pronounced cataplexic attacks (sudden loss of muscle tone). Because affected dogs share very similar clinical characteristics to humans with narcolepsy/cataplexy, a great deal of research has been conducted with affected dogs to determine the underlying pathology, which has facilitated criteria for positive diagnosis of primary narcolepsy for both animals and humans.

Forms of Primary Narcolepsy and Pathophysiology

Primary canine narcolepsy exists as familial or sporadic, and is estimated to have a very low prevalence in dogs (less than 0.2%).[51] The sporadic form is the most common and has been observed in over 17 breeds[51,52] with initial onset occurring over a wide range of ages (7 weeks to 7 years). For familial affected dogs, onset occurs before 6 months of age[53,54] and is a result of a mutation in the hypocretin-receptor-2 gene *(Hcrtr 2)* that is heritable through classic Mendelian genetics. Etiology of both forms is associated with a deficit in hypocretin neurotransmission.[52,55]

Clinical Signs of Narcolepsy

The diagnosis of narcolepsy in dogs is mainly focused on the occurrence of cataplexy that can manifest as a mild loss of skeletal muscle tone or muscle weakness, likely observed as a buckling of both hind legs and possibly accompanied by a drooping of the neck. In mild conditions, the dog may appear drowsy or struggling to resist "sleepiness," whereas more severe attacks can be a complete paralysis and collapse lasting from a few seconds to a few minutes. Excessive salivation and incontinence are not observed during a cataplectic attack, as in seizures. Because narcolepsy is a sleep disorder, dogs experiencing prolonged cataplectic attacks may experience characteristics of REM sleep. Following a cataplectic attack, dogs will get up and resume normal activity, or possibly go into normal sleep.

Diagnosis

For proper diagnosis, it is important to rule out cataplectic attacks resulting from other episodic disturbances like seizures or syncope.[56] Owner-reported information about previous attacks and age of onset is also helpful to evaluate how and when the attacks occur.

Because cataplectic attacks can be triggered by positive emotional experiences, an attack can be elicited by engaging play or being offered a favorite food reward. Therefore, cataplexy can be clinically assessed by using the food-elicited cataplexy test (FECT).[57] However, if the dog is nervous during the examination it may not exhibit the attacks, thus in-home testing with video recording would be beneficial. Video clips of typical cataplexy attacks and FECT are included (Videos 262-1 and 262-2), as well as available online through the Stanford School of Medicine, Center for Narcolepsy website at http://med.stanford.edu/psychiatry/narcolepsy (2014).

Measuring the concentration of hypocretin-1 peptide (<80 pg/mL; normal = 250 to 350 pg/mL) in the CSF is the most specific and sensitive diagnostic tool for diagnosing the sporadic form of narcolepsy.[55] Cases with the familial form that results from a mutation in *Hcrtr 2* receptor gene have "normal" CSF hypocretin concentrations, and thus does not exclude a diagnosis of narcolepsy.[55]

If a mild form of narcolepsy/cataplexy is suspected, a drug challenge may be useful for diagnosing dogs and is well tolerated. Increased cholinergic activity for triggering REM sleep has been established[57] and centrally active acetylcholinesterase inhibitors (physostigmine salicylate; 0.025-0.1 mg/kg IV) increase the frequency of cataplectic attacks within 15 min in narcoleptic dogs, but have no effect on normal, non-narcoleptic dogs. Starting with the lower dosage range is recommended because of possible adverse effects of salivation and diarrhea.

Treatment and Prognosis

The treatment of narcolepsy in animals is aimed primarily at reducing the frequency and duration of cataplectic attacks. Dogs with mild to moderate cataplectic attacks may be best treated by avoiding the inciting cause, thus limiting the play experiences or behaviors that trigger a cataplectic episode. For multiple-dog households, feeding narcoleptic dogs in a separate location and/or time from other dogs may reduce episodes. Efficacy at reducing, but not curing, cataplectic episodes has been demonstrated with both a change in routine and oral administration of various drugs (Table 262-1). Activation of the adrenergic systems that inhibits cataplexy is the main form of treatment.[57] Recording the frequency of cataplectic attacks and the time to finish a meal when attacks occur is useful for judging the efficacy of the treatment and daily dosage.

TABLE 262-1

Anticataplectic Drugs for Treating Narcolepsy in Dogs

DRUG TYPE	COMPOUND	DAILY DOSAGE (mg/kg PO)	HALF-LIFE (hours)	SIDE EFFECTS (class)	COMMENTS	REFERENCES
Tricyclic antidepressant	Imipramine	1.5-3	5-30	Vomiting, anorexia, lethargy, diarrhea, anticholinergic, antihistaminergic	Care should be taken if the dog has epilepsy	57-59
	Clomipramine	3-6	15-60			57
	Desipramine	3 twice daily	10-30			57, 61
Serotonin/noradrenaline uptake inhibitor	Venlafaxine	6-12	4*	No anticholinergic side effects		62
Alpha-2 adrenergic antagonist	Yohimbine	0.045 twice daily†	<1	Seizures, excitement, muscle tremor, ptyalism		61

*Active metabolite is O-desmethylvenlafaxine, which has an 11 hour half-life.

†Tolerance may develop and clinical signs are moderately well controlled with altering monthly regimen between yohimbine and desipramine.

Canine narcolepsy is neither progressive nor life-threatening, but requires proper care by the pet-owner throughout the life of the pet. The pet's quality of life can be maintained with understanding by the pet-owner about the disease so that provisions can be made to the pet's environment to improve safety. Care should include the use of unbreakable food bowls, elevated water bowl (possibly at shoulder level) should the pet experience a cataplectic attack near the bowl or while drinking, and possibly also restricting access to stairs.

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CHAPTER 263

Cognitive Dysfunction in Aged Dogs and Cats

Gary Landsberg

Client Information Sheet: Cognitive Dysfunction in Aged Dogs and Cats

Advanced age in dogs and cats can be associated with a variety of behavioral changes, including an increase in, or the onset of, fears, phobias and anxiety, increasing irritability and aggression, repetitive disorders, night waking and vocalization, and housesoiling.[1,2] Such signs are consistent with manifestations of pathologic brain aging. However, some of these behaviors instead can be attributable to underlying medical conditions (including other neurologic disorders) and some can be due to primary behavior problems arising from changes in the household. In addition, senior pets can be more stressed and less able to adapt to change than younger ones. Therefore, to determine whether such clinical signs are related to pathologic brain aging, these other medical and behavioral causes first must be ruled out (see ch. 9).

Clinical Signs

Cognitive dysfunction syndrome (CDS) is a neurodegenerative disorder of senior dogs and cats that is characterized by behavioral changes in an array of domains, which are believed to be cognitively based, and is associated with the development of distinct patterns of brain lesions. CDS is not an inevitable consequence of aging in dogs and cats, and individual differences are more likely the rule than the exception. Some aged animals show only mild behavioral signs, while others develop severe or multiple signs, which can include a decline in awareness, altered response to stimuli, and deficits in learning and memory, all of which can disrupt normal function and dramatically reduce quality of life. Clinical signs of CDS in dogs have been described by the acronym DISHA, which refers to *D*isorientation, altered *I*nteractions with owners or other pets, *S*leep-wake cycle alterations, *H*ousesoiling, and *A*ctivity changes (which might be increased, repetitive, or reduced).[1-4] Additional signs also can include: increasing agitation and anxiety; altered responsiveness to stimuli (i.e., heightened or reduced); altered interest in appetite and/or self-hygiene (i.e., increased or reduced); and decreased ability to perform previously trained commands or tasks. This same constellation of signs also applies to CDS in cats, although prevalence of individual signs can differ.[5,6]

Early detection and intervention might slow further decline, prevent complications, increase longevity, and address the pet's welfare. Signs of CDS often go unreported because veterinarians might not solicit the necessary information and because pet owners can consider the behavioral signs insignificant or untreatable.

The prevalence of CDS has been assessed in a number of survey-based studies. In one, ≈48% of owners of 150 dogs reported that their senior dogs (≥7 years old) exhibited at least one clinical sign of CDS. However, only 17% of these owners reported these signs to their veterinarians (proprietary data, 1999, Pfizer Animal Health). In another study, 180 owners of aged dogs with no identifiable medical problems reported at least one sign consistent with CDS in 28% (aged 11-12 years) to 68% (aged 15-16 years) of dogs.[4] Prevalences of 22.5%[7] and of 5% (10-12 year old dogs) to 41% (dogs >14 years of age) have been reported more recently.[7,8] While overall prevalence was 14.2% (68/479) in the latter study, a diagnosis of CDS was made in only 1.9% (9/479) of all dogs or 13% (9/68) of affected dogs.[8] Further, CDS is a progressive disease with prevalence and severity increasing with age.[7,9] In some studies, females and neutered males have been reported to be more affected than males and intact dogs, respectively.[7,10] However, while females might live longer if spayed, a longer lifespan was not associated with neutering in males, except in giant breeds, which are less likely to reach an age at which CDS would become a clinical concern.[11,12] In a study of cats >11 years old, 35% were diagnosed with CDS (28% of 95 cats aged 11-15 years and 50% of 46 cats >15 years old).[5,6]

The high prevalence and underdiagnosis of CDS make it essential for veterinarians and staff to inform

clients of the importance of reporting these signs for early identification of CDS. Veterinarians should be proactive in asking owners if there has been any change in behavior or any signs that might be indicative of CDS. A behavioral questionnaire should include questions eliciting information about (a) disorientation or confusion, (b) decreased interest in social interactions (e.g., petting, play), (c) altered sleep/waking at night, (d) housesoiling, (e) repetitive activities such as pacing or circling, (f) a decrease in activity or apathy about feeding or self-hygiene, (g) increasing anxiety or irritability, (h) altered response to stimuli (sights, sounds, odors) and (i) decreased responsiveness to previously learned commands.

Laboratory Studies

Questionnaire-based tools used for identifying cats and dogs with CDS provide evidence of global brain dysfunction, but are likely to be insensitive to early and subtle changes in learning and memory associated with pathologic brain aging.[1,5,13] Cognitive dysfunction is most accurately evaluated with the use of neuropsychological tests designed to provide quantitative measures of cognitive function using a standardized test apparatus (Toronto General Testing Apparatus; Figure 263-1). These tests are systematic, standardized, objective, and provide a quantitative measure of age-related cognitive decline.[14-18] In fact, while signs of CDS might not be recognized until ≥11 years of age, neuropsychological tests can identify age-related deficits in learning and memory in dogs and cats as early as 6 years of age.[8,15,18,19] Similarly, functional changes in the neurons of the caudate nucleus result in impairments in information processing in cats as young as 6 years of age.[19] Several cognitive functions assayed with these laboratory-based tasks are also likely to be contributors to the clinical signs that might be noted by pet owners.[20,21] Although these tests generally are too lengthy and complex to be applicable for clinical use, recently researchers have demonstrated that these tasks might be used in a clinical environment to identify cognitive deficits in pet dogs.[22-25]

FIGURE 263-1 Toronto General Test Apparatus (TGTA). This apparatus and computer software are the feline version of the test apparatus for learning and memory tasks. In the discrimination task, the cat would first learn to displace one of the two objects (e.g., yellow circle), randomly placed in one of the two locations, for a food reward. Once the cat can consistently displace the correct object for food, the food is then placed under the opposite object (blue square) until the cat learns to displace the new object consistently (reversal task). (Photograph used with permission of CanCog Technologies.)

In laboratory studies using a battery of reward-motivated neuropsychological tests, several cognitive

domains or functions can be evaluated independently in aged dogs and cats.[18-26] These tests involve simple learning problems such as discrimination tasks in which the animal is presented with two objects that are different in appearance, and one is associated with a food reward (see Figure 263-1 and Video 263-1). Aged dogs and cats can learn these problems, and may not differ from younger animals in rate of learning.[17,27,28] Once dogs and cats have learned a visual discrimination problem, the object-reward contingency can be switched, such that the previously incorrect object becomes the rewarded object. This is called *reversal learning*, a type of cognitive ability that depends upon the intact function of the prefrontal cortex[27,28] (see Video 263-1). Aged dogs and cats, compared to young counterparts, are impaired in their ability to switch to selecting the previously incorrect object, suggesting a lack of ability to modify learned behaviors.[17,26-28] Other behavioral changes that are likely to be associated with prefrontal cortex dysfunction include stereotypical behaviors (such as pacing); changes in personality, including increasing fearfulness, irritability, or aggression; and an inability to inhibit previously learned behaviors (e.g., housesoiling).

The aging process also can affect memory significantly. Spatial memory is measured by the ability of dogs to remember where they last obtained a hidden food reward and is compromised in a subset of aged animals[14-18,26,29,30] (Figure 263-2). Functionally, this type of memory impairment can present clinically in companion animals as disorientation, wandering, and getting lost. Dogs also show age-dependent impairments in their ability to recognize objects seen previously.[14] This type of dysfunction may be reflected in decreased recognition of familiar people or animals. In a laboratory study evaluating feline performance in a holeboard task, aging did not significantly affect spatial learning but memory errors were increased.[30]

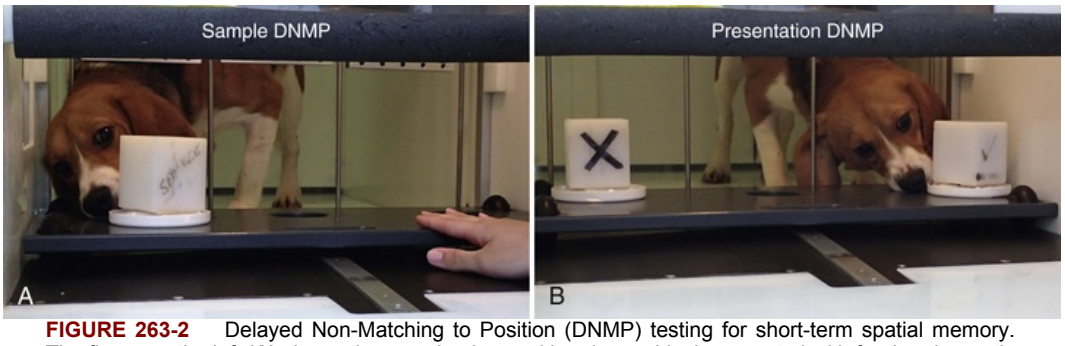

FIGURE 263-2 Delayed Non-Matching to Position (DNMP) testing for short-term spatial memory. The figure on the left **(A)** shows the sample phase with only one block presented with food underneath. The object is withdrawn and this is followed by the presentation phase. During this phase, two identical objects then are displayed, with the non-matching object covering the food. In the figure on the right **(B),** food is located under the new (right) object. Memory can be assessed by increasing the delay between withdrawing the initial object (sample) and offering the two objects (presentation). (Photograph used with permission of CanCog Technologies.)

Age-related behavioral differences also have been demonstrated in reactivity tests.[20,21,31] The curiosity test, for example, allows dogs to examine and play with a variety of toys to assess an animal's reaction and attention to objects. In this 10-minute test, young dogs show significantly more exploration and contact with novel objects than do old dogs, with cognitively impaired aged dogs showing the least object contact.[21] Further, cognitively impaired aged dogs show higher levels of locomotion than do their age-matched unimpaired peers, which could be linked to stereotypy or wandering behavior.[21,31] Measures of exploratory behavior might be more amenable to clinical assessment because they require brief testing sessions and a small test area, suggesting that they may be a useful clinical screen for aged animals with CDS.[21,31]

Neurobiologic Basis

Gross morphologic changes in the aging canine brain include decreased brain mass particularly in the frontal cortex, increased ventricular volume, and meningeal thickening.[27,32] Additional changes can include accumulation of lipofuscin, emergence of apoptic bodies, neuroaxonal degeneration, a reduction in neurons, and demyelination.[32-34]

Aged dogs show neuron loss in the hippocampus, a brain region that plays a critical role in memory.[35] Interestingly, providing aged dogs with behavioral enrichment (outdoor walks, social interaction, play toys,

cognitive training) can lead to maintenance of hippocampal neurons.[35] Aged dogs also lose their ability to generate new hippocampal neurons (i.e., neurogenesis), which is linked to a loss of learning and memory ability.[36] Magnetic resonance spectroscopy studies also have identified an age-related decline in neuronal health.[37]

Aged cats also demonstrate cerebral atrophy, neuronal loss, widening of the sulci, a decrease in gray and white matter volumes, and increased lateral ventricular volumes, although these may not be as marked as in the dog.[6,19,38-40] Changes in the pyriform lobe could be associated with cognitive decline, and a reduction in cerebellar Purkinje cells might be associated with information processing and motor deficits.[5,6,38,40]

At the biochemical level, several changes have been reported in canine aging, including a reduction in cholinergic function and oxidative damage; feline aging is associated with marked atrophy of the cholinergic system in the locus coeruleus.[39-45] The role of oxidative damage is supported by the finding that a diet rich in antioxidants and mitochondrial cofactors can significantly improve cognitive function in aged dogs and cats.[18,46]

Amyloid-beta (A-beta) accumulation in the human brain is one of the earliest pathologic features in the development of Alzheimer's disease and is thought to precede synaptic and neuronal dysfunction, neuronal loss, brain atrophy, and symptoms.[47] The A-beta change in dogs is strikingly similar to that seen in human Alzheimer's disease patients in its peptide sequence, temporal distribution, and biochemistry,[48,49] and cognitive impairment in dogs is correlated with increased A-beta deposition (Figure 263-3).[35,50,51] By contrast, cats >10 years old demonstrate more diffuse A-beta plaques and predominantly a shorter species of the protein.[7,9,48,51-54] Although some studies in cats demonstrate an association between CDS and A-beta lesions, others do not.[51,53,54] In contrast to human Alzheimer's patients, neither dogs nor cats demonstrate neurofibrillary tangles, although hyperphosphorylated tau is reported in both species and it could represent pre-tangle abnormalities.[53-56] Cerebrovascular and perivascular changes, including A-beta accumulation, and periventricular microhemorrhage, or infarcts, also can cause some of the clinical signs associated with cognitive dysfunction in senior pets[2,6,27,32,34,48,50,51,53] (see Figure 263-3). Vascular A-beta may contribute to cerebral hypoperfusion.[57]

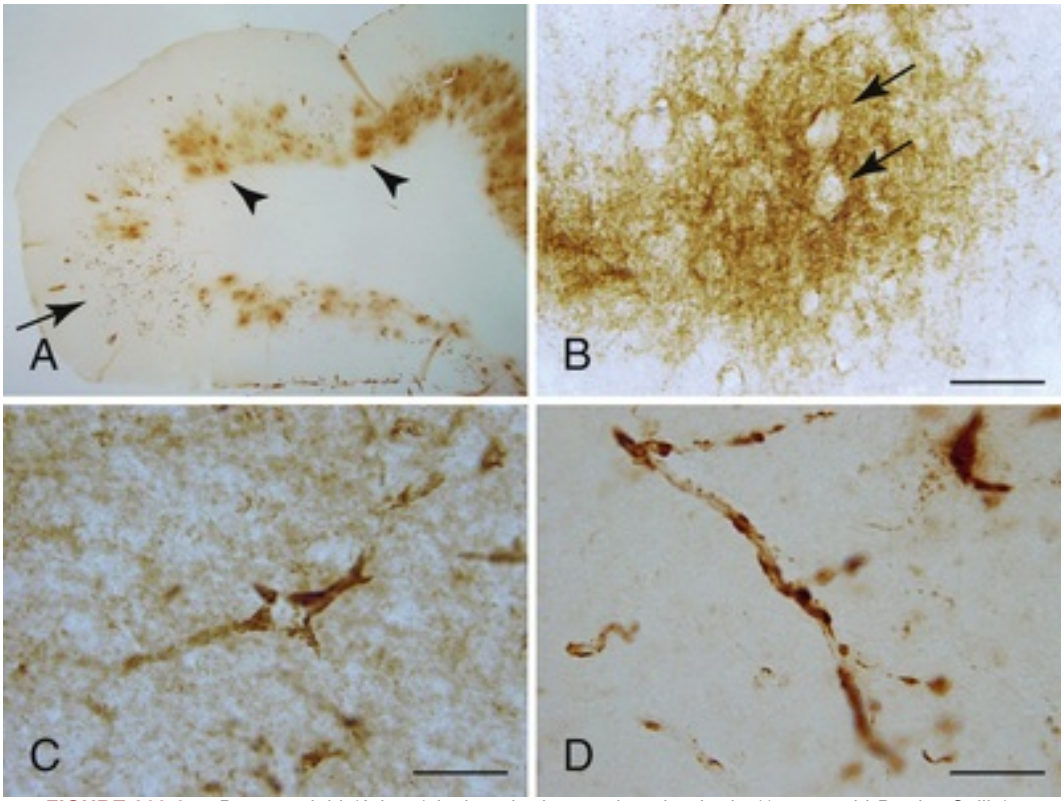

FIGURE 263-3 Beta-amyloid (A-beta) lesions in the aged canine brain (15-year-old Border Collie). **A,** A-beta accumulates extensively in the temporal cortex as both diffuse deposits (arrowheads) or in

the cerebrovasculature (arrow). **B,** A higher magnification of a diffuse A-beta plaque shows small fibrils accumulating in the space between neurons (arrows). **C,** A-beta also can be observed on the membranes of neurons. **D,** Blood vessels within the parenchyma of the brain also can accumulate A-beta. All sections immunostained with anti-Abeta1-42 antibody. Bars in **B-D** = 20 microns. (Brain tissue kindly provided by Carolyn Wilki.)

Treatment Options

Diet, drugs or supplements all might be effective in improving signs and slowing the progress of CDS. Canine studies have demonstrated that mental stimulation in the form of training, play, exercise, and use of manipulation toys can help to maintain quality of life as well as cognitive function, but are most effective together with an appropriate nutritional base.[58,59] This is consistent with studies in humans in which education, and brain and physical exercise, have been found to delay the onset of dementia.

Currently there is one pharmaceutical in North America, selegiline (Anipryl, Zoetis Animal Health), that is approved for the treatment of CDS in aged dogs. Selegiline hydrochloride is a selective reversible monoamine oxidase B inhibitor, which was found to significantly improve cognitive signs in aged dogs.[60,61] In the canine brain, selegiline increases 2-phenylethylamine, a neuromodulator that enhances dopamine and catecholamine function. Its metabolites l-amphetamine and l-methamphetamine could further enhance cognitive function and improve behavior. Selegiline also might contribute to a decrease in free radical load in the brain.

Propentofylline, a xanthine derivative, is licensed in Europe and Australia for the treatment of dullness, lethargy, and depressed demeanor in old dogs. It could increase blood flow and inhibit platelet aggregation and thrombus formation. In a laboratory trial with aged Beagle dogs, it had no effect on behavioral activity.[62]

Since the elderly are particularly susceptible to the effects of anticholinergic drugs, it is prudent to avoid medications with anticholinergic effects in such patients.[41] In fact, drugs or natural products that enhance cholinergic transmission might have potential benefits for improving signs of CDS in dogs and cats, but more research is required to find safe and effective drugs and dosages.[63]

No drugs are approved for treatment of CDS in cats; however, both selegiline and propentofylline have been reported anecdotally to be useful.[1,5,6]

Another therapeutic strategy for cognitive dysfunction in dogs, cats, and humans is diets and natural supplements that might reduce the risk factors that contribute to brain aging and cognitive decline. It is likely that an integrative approach is required to achieve and maintain brain health, such as diets supplemented with polyunsaturated fatty acids, antioxidants, and mitochondrial co-factors.[64-66] Two veterinary therapeutic diets that have been developed for the management of CDS have been demonstrated in laboratory studies to improve learning and memory in dogs. A diet from Hills Pet Nutrition (Canine b/d) is supplemented with fatty acids, antioxidants (vitamins C and E, beta carotene, selenium, flavonoids, carotenoids), and dl-alpha-lipoic acid and l-carnitine to enhance mitochondrial function.[58,59,67] When the diet was combined with environmental enrichment, the greatest level of improvement was achieved.[58,59] In a clinical trial, significant effects were obtained from the diet alone.[68] A diet from Nestle Purina Research (Purina Pro Plan Bright Minds) is supplemented with botanic oils containing medium chain triglycerides to provide ketone bodies as an alternate source of energy for aging neurons.[69] A dietary supplement from Nestle Purina (not yet commercially available) with antioxidants, (vitamins E and C, and selenium), arginine, B vitamins, and fish oil significantly improved learning and memory tasks in cats aged 5.5 to 8.7 years.[18]

A number of nutritional supplements also might be effective in the management of CDS based on laboratory and/or clinical studies. Senilife (CEVA Animal Health), which contains phosphatidylserine (a membrane phospholipid) and *Gingko biloba,* vitamins E and B6, and resveratrol, is labeled for both dogs and cats but only has been evaluated in canine studies to date.[70,71] Activait (Vet Plus Ltd), which contains phosphatidylserine, omega-3 fatty acids, vitamins E and C, l-carnitine, alpha-lipoic acid, coenzyme Q, and selenium, has been evaluated in a canine clinical trial.[72] A feline product also is available with alpha-lipoic acid removed. S-adenosyl-l-methionine (Novifit, Virbac Animal Health) might help to maintain cell membrane fluidity and receptor function, regulate neurotransmitter levels, and increase production of glutathione.[73,74] Apoaequorin (Neutricks, Neutricks, LLC), is a calcium-buffering protein found in jellyfish that improved learning and attention in dogs in laboratory trials.[75] Immunotherapy has also been evaluated in aged dogs, involving the vaccination of aged animals against the A-beta protein. Although the study was not successful in reversing cognitive deficits, this approach might have future treatment potential.[76]

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CHAPTER 264

Cranial Neuropathies

John Henry Rossmeisl Jr.

Client Information Sheet: Cranial Neuropathies

The term cranial neuropathy refers to any condition that causes dysfunction of a cranial nerve (CN) anywhere along its anatomic course.[1] Cranial neuropathies most often affect a single CN (mononeuropathy), but can involve multiple CNs, or appear in association with generalized polyneuropathies.[2-5] A thorough neurologic examination is necessary (see ch. 259) to correctly localize the level of CN dysfunction, with particular emphasis on identification of involvement of the central or peripheral components of the affected CN in order to best formulate differential diagnoses and a management plan (Table 264-1).[1] For example, identification of deficits involving two or more CNs usually indicates the lesion involves the anatomic region in which the nerves are in close proximity, as would be the case for signs of Horner's syndrome, facial paresis, and peripheral vestibular dysfunction caused by disease of the middle and inner ear.[6] Common etiologies of cranial neuropathies include degenerative, idiopathic, inflammatory, metabolic, and neoplastic diseases.[1-6] By convention, an idiopathic cranial neuropathy is diagnosed only following exclusion of structural and metabolic causes of disease with the propensity to affect the dysfunctional CN, which can be challenging in the living patient. Idiopathic mononeuropathies affect CNs more frequently than other peripheral nerves, and many of these idiopathic cranial neuropathic syndromes are self-limiting.[2,3,5]

TABLE 264-1

Cranial Nerves: Names, Functions, and Manifestations of Dysfunction

NUMBER	NAME	MAJOR FUNCTIONS	CLINICAL SIGNS OF DISEASE
I	Olfactory	Smell	Inability to smell
II	Optic	Vision	Blindness
III	Oculomotor	Movement of the eye and constriction of the pupil	Abnormal eye position, pupil size, or pupil reactivity to light
IV	Trochlear	Movement of the eye	Abnormal eye position
V	Trigeminal	Sensation to the eye and face, movement of the jaw	Rubbing or pawing of the face Loss of muscle mass on the head Dropped jaw—flaccid inability to close the mouth
VI	Abducent	Movement of the eye	Abnormal eye position
VII	Facial	Movement of facial muscles Taste Tear and saliva production	Drooping of the ear or cheek, deviation of the nose, drooling Dry eye
VIII	Vestibulocochlear	Balance and hearing	Abnormal head position, abnormal eye movements, vertigo Deafness
IX	Glossopharyngeal	Sensation and movement of throat muscles Taste	Difficulty eating or swallowing
X	Vagus	Movement of throat muscles	Loss of voice, coughing, regurgitating

XI	Accessory	Movement of neck and shoulder muscles	Difficult to appreciate in small animals
XII	Hypoglossal	Movement of the tongue	Tongue deviation or paralysis, difficulty eating

Optic Nerve (Cn II)—Optic Neuritis

Optic neuritis is characterized by an acute onset of vision loss, which is typically bilateral and associated with mydriatic and unresponsive pupils (see ch. 11).[7] Frequently, there are visible changes in the posterior segment of the eye, such as optic disc swelling (Figure 264-1), vascular congestion, hemorrhage, and peripapillary neuroretinitis, although the ophthalmic examination can be normal in cases of retrobulbar disease.[7,8] If optic disc swelling is visible, differential diagnoses include papilledema or optic nerve edema that can accompany uveitis or glaucoma. These conditions usually can be differentiated based on the collective findings of the clinical examination.[7] Papilledema is non-inflammatory disc edema resulting from intracranial hypertension that does not cause acute vision loss.

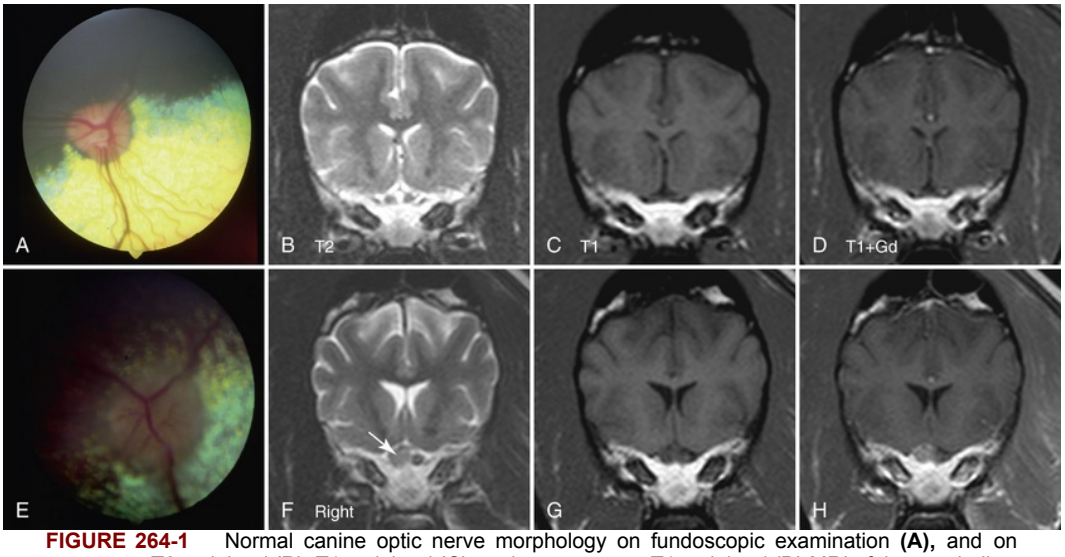

FIGURE 264-1 Normal canine optic nerve morphology on fundoscopic examination **(A),** and on transverse T2-weighted **(B),** T1-weighted **(C),** and post-contrast T1-weighted **(D)** MRI of the retrobulbar region. Optic neuritis associated with fundoscopic evidence of a swollen optic disc **(E),** caused by optic nerve astrocytoma, which appears as unilateral enlargement of the right optic nerve on transverse MRI **(F** [arrow], **G, H).**

Potential etiologies of optic neuritis include infectious (e.g., canine distemper viral, mycotic, and protozoal) and immune-mediated (e.g., granulomatous meningoencephalitis) meningoencephalitides, and neoplasms (see Figure 264-1) that infiltrate or compress (e.g., meningioma, glioma, pituitary tumors) the optic nerves or chiasm.[7-10] Thus, magnetic resonance imaging (MRI) examinations of the brain (see ch. 260 and 261), cerebrospinal fluid analysis (see ch. 115), and serologic assays are diagnostics recommended in cases of optic neuritis.[8-10] The management of meningoencephalitis is reviewed in ch. 261. Electroretinography (ERG) is normal in patients with optic neuritis. In many dogs with optic neuritis, no underlying cause is identified, the disease is presumed to be idiopathic, and systemic therapy with immunosuppressive dosages of prednisone is attempted (see ch. 165).[7] In dogs, sudden acquired retinal degeneration syndrome (SARDS) is another cause of bilateral acute blindness associated with mydriatic pupils.[10,11] However, many dogs with SARDS will have sluggish and incomplete pupillary light reflexes, the fundic examination is initially normal, and the ERG will be extinguished.[10,11] The prognosis for complete visual recovery with optic neuritis is guarded to poor.[7]

Oculomotor (CN III), Trochlear (CN IV), And Abducent (CN VI) Nerves

Collectively, these nerves innervate the extraocular muscles. They participate in ocular position and coordinated and conjugate movement of the eyes, along with the vestibular and cervical proprioceptive systems.[12] The parasympathetic portion of CN III is responsible for pupillary constriction. Clinical signs of

dysfunction of these nerves or their associated vestibular projections include strabismus, abnormal physiological nystagmus due to external ophthalmoplegia, pathological nystagmus if the lesion involves the vestibular system, and internal ophthalmoplegia (i.e., a mydriatic and fixed pupil) if the lesion affects the parasympathetic portion of CN III.[12-14]

Cavernous sinus (CSS) and orbital fissure (OFS) syndromes are defined by clinical dysfunction of two or more of the following CNs: III, IV, and VI, and the ophthalmic or maxillary branches of CN V.[13,14] The axons of these CNs course in intimate anatomic association with each other along the floor of the skull adjacent to the cavernous sinus prior to exiting the skull through the orbital fissure. Clinical signs frequently observed with these syndromes include external and internal ophthalmoplegia, reduced corneal sensitivity, neurotrophic keratitis, and ptosis.[13,14] Differentiation of CSS from OFS requires demonstration of the anatomic level of the lesion with diagnostic imaging. The most common causes of CSS and OFS are primary or metastatic neoplasms, although infectious causes have been reported, particularly in cats.[13,14]

Trigeminal Nerve (CN V)—Trigeminal Neuropathy

The trigeminal nerve consists of three primary branches that provide sensation to the face (i.e., ophthalmic, maxillary, and mandibular nerves) and motor function to the muscles of mastication (i.e., mandibular nerve).[1,2] Common clinical presentations of trigeminal mononeuropathies involve mandibular motor dysfunction; cases of isolated trigeminal sensory dysfunction are rare.[15] The first is an acute onset of a flaccid bilateral paresis of the mandibular nerves resulting in a dropped jaw and inability to close the mouth (Video 264-1).[2] This clinical presentation can result from disorders affecting mechanical jaw function (e.g., temporomandibular joint fracture or avulsion), diseases resulting in pain associated with jaw movement (e.g., masticatory muscle myositis, retrobulbar mass lesions), and inflammatory (e.g., *Neospora, Toxoplasma, Cryptococcus,* rabies), idiopathic, or neoplastic (e.g., hematopoietic neoplasia, nerve sheath tumor [NST]) trigeminal nerve lesions.[2,16-18] Animals with clinical signs limited to an acutely dropped jaw usually have disease of the peripheral portions of the trigeminal nerve, because a bilateral lesion in the pontine trigeminal motor nuclei would be expected to be associated with additional and severe clinical signs of pontomedullary syndrome, which often include central vestibular dysfunction, a depressed level of consciousness, and/or CN VI-XII deficits.[1]

Idiopathic trigeminal neuritis (ITN) is the most common cause of dropped jaw in dogs (see Video 264-1). ITN mainly impairs masticatory muscle motor function, although trigeminal sensory deficits can accompany ITN in approximately one-third of dogs, and concurrent facial nerve paralysis, masticatory muscle atrophy, or Horner's syndrome occasionally also can be observed.[2] Treatment includes supportive care with assisted feeding (see ch. 82). Affected dogs usually recover within 2-4 weeks. MRI of the brain of animals with trigeminal neuropathy provides the best, non-invasive method to differentiate etiologies of trigeminal neuropathy. On MRI, both normal and abnormal trigeminal nerves will demonstrate contrast enhancement.[19] ITN may be associated with normal nerve signal characteristics and morphology, or diffusely enlarged and T2-hyperintense nerves.[20]

Another presentation of trigeminal neuropathy is an acute onset of unilateral, and often severe, atrophy of the muscles of mastication ipsilateral to the dysfunctional mandibular nerve. Trigeminal NST are a common etiology of unilateral neurogenic masticatory muscle atrophy (Figure 264-2).[20] Facial hypalgesia or paresthesia, manifesting as facial rubbing, itching, or pain, in addition to Horner's syndrome, also can be seen. NST are locally invasive and slow to metastasize. Treatment options for NST include surgical debulking, radiotherapy, or supportive care with glucocorticoids.[20,21] The prognosis is guarded, although a median overall survival of 881 days was reported in 4 dogs with trigeminal NST treated with stereotactic radiosurgery.[21]

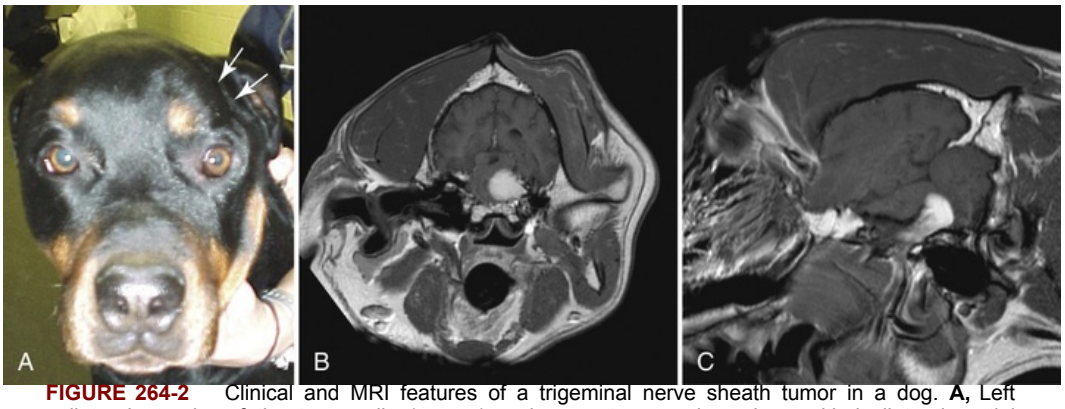

FIGURE 264-2 Clinical and MRI features of a trigeminal nerve sheath tumor in a dog. **A,** Left unilateral atrophy of the temporalis (arrows) and masseter muscles, along with ipsilateral partial Horner's syndrome. Transverse **(B)** and left parasagittal **(C)** post-contrast T1-weighted MRI demonstrating lobular, contrast-enhancing extra-axial mass involving the trigeminal nerve resulting in mesencephalic compression and loss of muscle mass (**B;** left temporalis).

Facial Nerve (CN VII)—Facial Neuropathy/Paralysis

Facial paralysis is characterized by an acute inability to close the palpebral fissure, a drooping of the ear and lip and drooling on the affected side.[1] Causes of peripheral facial nerve paralysis include otitis media-interna, iatrogenic surgical injury (e.g., bulla osteotomy), idiopathic disease, metabolic disease (e.g., hypothyroidism), otic neoplasms, trauma, and sulfonamide hypersensitivity.[3,6,22,23] Due to the close anatomic relationships of the vestibulocochlear and facial nerves in both the medulla and petrous temporal bone, vestibular signs can accompany both peripheral and central (e.g., neoplasia, meningoencephalitis) etiologies of facial paralysis.[6,24] Facial paresis also can be a feature of generalized neuropathies or neuromuscular diseases, such as acute canine polyradiculoneuritis, tick paralysis, and myasthenia gravis.[25-27] Facial paralysis is reported to be idiopathic in 75% of dogs and 25% of cats with facial neuropathy.[3] Approximately 60% of cases of idiopathic disease present with unilateral signs and 40% with bilateral signs (Video 264-2).[28] Idiopathic facial paralysis is commonly associated with various segments of facial nerve enhancement on MRI examinations.[28,29] Spontaneous recovery from idiopathic facial nerve paralysis is possible. In dogs, contrast enhancement of the nerve on MRI can provide prognostic information, with one study indicating that recovery of facial nerve function is less likely to occur or may be prolonged in cases demonstrating enhancement.[29] Animals that recover usually do so within 3 to 8 weeks.[3,29]

Vestibulocochlear Nerve (CN VIII)

The vestibular branch of CN VIII participates in maintenance of balance and posture, and disorders affecting the vestibular system are reviewed in ch. 265.[1,12] Dysfunction of the cochlear branch results in deafness that can be classified as conductive (e.g., otitis externa/media) or sensorineural in origin.[30] The most common cause of deafness is congenital hereditary sensorineural associated with a white coat color and the piebald and merle genes.[30,31] In dogs and cats, acquired sensorineural deafness can occur secondary to progressive age-related cochlear degeneration (i.e., presbycusis) or ototoxic drug therapy (e.g., aminoglycosides).[30] Deafness is diagnosed via brainstem auditory evoked response testing.[30,31]

Glossopharyngeal (CN IX), Vagus, (CN X), And Accessory (CN XI) Nerves —Dysphagia, Megaesophagus, and Laryngeal Paralysis

The glossopharyngeal, vagus, and accessory nerves are important for function of the pharynx, larynx, and esophagus.[1] In the dysphagic patient, it is important to differentiate neurogenic prehensile problems that imply dysfunction of the jaw (CN V), lips (CN VII) and/or tongue (CN XII) from neurogenic deglutition problems. Prehensile and oropharyngeal dysphagic disorders can be identified with a physical examination, including observation of eating, while characterization and diagnosis of disorders of the pharyngeal, cricopharyngeal, and/or esophageal phases of swallowing often requires diagnostic imaging examinations

including contrast radiography or videofluoroscopy (see ch. 38).[32] Dysphagia can be associated with clinical signs of gagging, coughing after drinking or eating, pharyngeal accumulation of saliva or food, and an abnormal gag reflex. Neurologic diseases that commonly cause dysphagia include primary myopathies (see ch. 354), polyneuropathies (see ch. 268), neuromuscular junctional disorders (e.g., myasthenia gravis, botulism; see ch. 269), and caudal brainstem lesions (e.g., encephalitis and neoplasia; see ch. 260 and 261).[25,27,33,34]

The esophagus is innervated by the vagus and internal branch of the accessory nerves.[1] Megaesophagus is characterized by generalized dilation and abnormal peristalsis of the esophagus (see ch. 273).[35,36] Regurgitation is the primary clinical sign observed, and secondary aspiration pneumonia is common (see ch. 242). Megaesophagus is more common in dogs than in cats, and can be congenital or acquired, although most canine cases are acquired and idiopathic.[35] Although megaesophagus can be identified readily with thoracic radiography, a thorough history and ancillary diagnostics are required to establish the etiology.[32] Acquired megaesophagus can be caused by polyneuropathies, polymyopathies, myasthenia gravis, endocrinopathies (e.g., hypoadrenocorticism, hypothyroidism), intoxications (e.g., lead, organophosphate, thallium), that must be ruled out to make a diagnosis of idiopathic megaesophagus.[25,27,32,33,35-40] Treatment is directed at the underlying cause, when present, and various assisted feeding procedures (e.g., Bailey chair, gastrostomy tube). The prognosis associated with megaesophagus is highly variable and dependent on the underlying etiology (see ch. 273).[35-39]

The larynx is innervated by branches of the vagus nerve.[1] The recurrent laryngeal nerve innervates the abductor muscles of the larynx. Lesions affecting the recurrent laryngeal nerve can result in dysphonia, inspiratory stridor, and respiratory distress.[4] Congenital laryngeal paralysis has been described in several breeds.[25,41,42] Acquired laryngeal paralysis has been associated with metabolic disease (e.g., hypothyroidism), trauma to the recurrent laryngeal nerve, neoplasia (e.g., squamous cell carcinoma, thyroid carcinoma), intoxications (e.g., lead), and brainstem disease (e.g., neoplasia, encephalitis).[25,42-44] In older, large-breed dogs, laryngeal paralysis is often the initial clinical manifestation of a progressive, degenerative polyneuropathy (see ch. 239).[4,25,42]

Horner's Syndrome

Horner's syndrome (HS) results from lesions affecting any portion of the three-neuron oculosympathetic pathway.[5,45] Clinical signs consist of miosis, ptosis, protrusion of the third eyelid, and enophthalmos. First order (i.e., upper motor neuron or central) neurons originate in the rostral brainstem, travel down the cervical spinal cord to synapse on second order (i.e., preganglionic) neurons, which have their cell bodies in the T1-T3 spinal segments. Second order axons course up the vagosympathetic trunk to synapse on third order (i.e., post-ganglionic) neurons in the cranial cervical ganglion, which then project to the eye and adnexa.[5,46] Topical phenylephrine testing can aid in lesion localization along this pathway.[5] Observation of mydriasis within 20 minutes of the application of phenylephrine indicates a post-ganglionic lesion, whereas mydriasis occurring after 20 minutes suggests a pre-ganglionic lesion.[5] HS can be caused by degenerative, inflammatory, ischemic, metabolic, neoplastic, or traumatic lesions at any site in the oculosympathetic system, although in the majority of HS cases no etiology is found and the condition is presumptively idiopathic.[5,46] Golden Retrievers are predisposed to developing idiopathic HS.[45,46] Recent data indicate idiopathic HS is post-ganglionic in the majority of cases, which contradicts results of earlier reports.[45,46] Idiopathic HS is mainly an aesthetic problem, as vision is not impaired unless the problem is bilateral, and the condition will resolve in many dogs within 3-4 months.[45,46]

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CHAPTER 265

Vestibular Disease

Veronique Sammut

Client Information Sheet: Vestibular Disease

Head tilt and nystagmus are clinical manifestations of vestibular diseases and are a common neurologic problem in small animals. Patients with vestibular diseases can have a dramatic clinical presentation. Vestibular dysfunction can originate from the peripheral or central vestibular system.

Functional Neuroanatomy

The vestibular system is the sensory system responsible for maintaining the head and body posture, balance, and tone in relation to gravitational forces and movement. It is divided into peripheral and central components (Figure 265-1). The peripheral vestibular system is located primarily in the petrosal portion of the temporal bone and includes the membranous labyrinth and the vestibular portion of the vestibulocochlear nerve (cranial nerve [CN] VIII). The membranous labyrinth is a series of fluid-filled structures consisting of three semicircular canals, the utricle, and the saccule, which are responsible for the vestibular function.

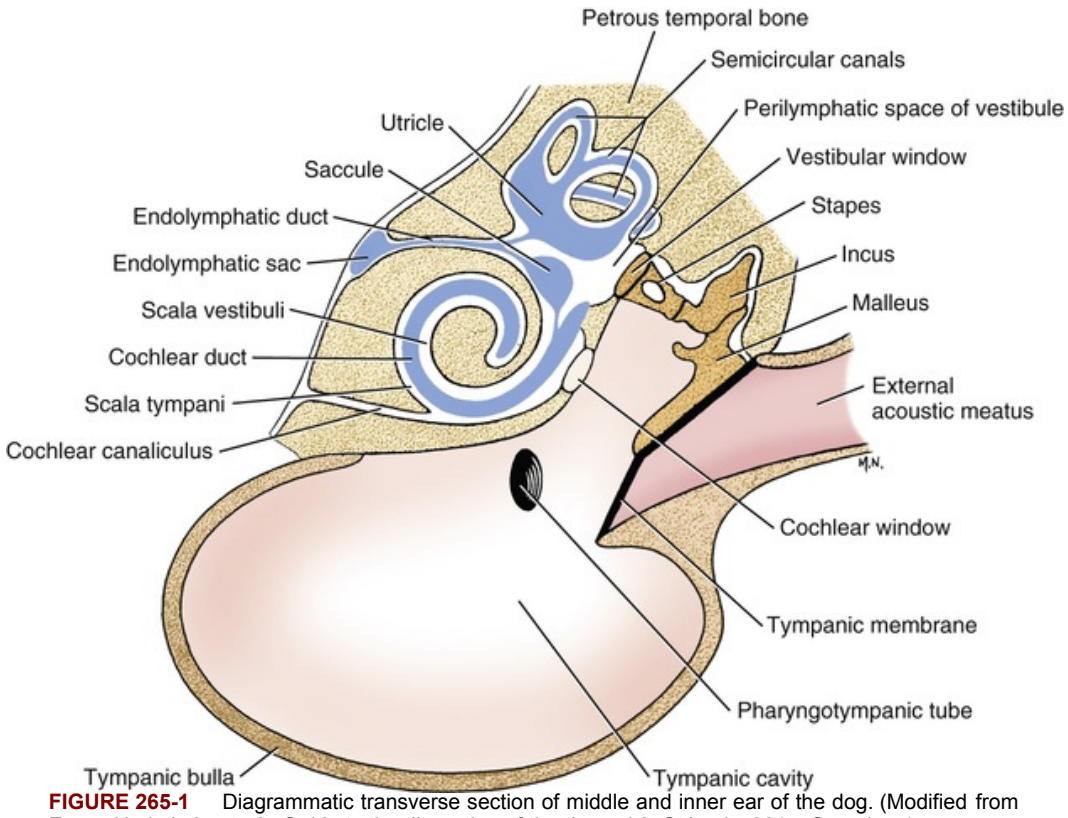

FIGURE 265-1 Diagrammatic transverse section of middle and inner ear of the dog. (Modified from Evans H, de Lahunta A: *Guide to the dissection of the dog,* ed 8, St Louis, 2017, Saunders.)

The central vestibular components include the four pairs of vestibular nuclei adjacent to the wall of the

fourth ventricle on the dorsal part of the pons and medulla, and the fastigial nucleus and flocculonodular lobe of the cerebellum. From CN VIII, some axons synapse in one of the vestibular nuclei, whereas others will ascend directly to the cerebellum via the caudal cerebellar peduncle. Most axons from the vestibular nuclei project to the spinal cord via the ipsilateral lateral vestibulospinal tract to influence extensor tone by facilitation on the ipsilateral extensor muscles and inhibition on the ipsilateral flexor muscles and to the medial longitudinal fasciculus (MLF) which synapses in the nuclei of CN III, IV, and VI, to adjust the position of the eyes in relation to the position and movement of the head. A few axons will project to the vomiting center in the reticular formation of the medulla (playing a role in motion sickness), whereas others will ascend to the cerebral cortex (forebrain) for conscious perception of position via a relay through the thalamic nuclei. For this reason, vestibular disease can sometimes be seen with thalamic lesions. The cerebellum provides an inhibitory effect on the vestibular nuclei, preventing excessive extensor tone.

Clinical Signs

A vestibular lesion will cause a lack of facilitation of the extensor muscles on one side, leading to imbalance with the normal side "pushing" the body and head toward the abnormal side. Because most disease processes are unilateral or asymmetrical, loss of balance and head tilt to one side is usually seen. However, bilateral involvement is possible as well.

Head Tilt

A head tilt is the most common and most consistent sign of a unilateral or asymmetrical vestibular disorder. It is characterized by a rotation of the head on the median plane bringing one ear lower than the other. It is important to differentiate a head tilt from a head turn or torticolli from a forebrain lesion, in which both ears and eyes are parallel to the ground but the nose is turned toward one side of the body. Patients with bilateral vestibular involvement may not have a head tilt unless one side is more affected than the other but tend to have wide head excursions from side to side. With cerebellar involvement, the head may be tilted to the opposite side of the lesion (see Paradoxical Syndrome).

Vestibular Ataxia

Vestibular ataxia is characterized by a wide-based stance and loss of balance on the side of the lesion. The head and body can sway and the animal will often lean, fall, or even roll to one side. The animal may walk in circles (vestibular circling) and the circles are typically erratic and of small diameter (Video 265-1). This must be differentiated from compulsive circling secondary to a forebrain lesion where the circles are typically large, regular and nicely shaped. The presence of paresis and/or general proprioceptive (GP) deficits indicates a central lesion affecting the descending motor pathways and the ascending proprioceptive tracts. However, evaluation of GP can be difficult initially if the patient is severely affected.

With bilateral disturbance, the animal will typically stand crouched and low to the ground and may lose balance on both sides.

Nystagmus

Nystagmus is a rhythmic, involuntary movement of the eyes. It can have equal movement on both sides (pendular nystagmus) or most commonly has a fast phase and a slow phase (jerk nystagmus). It can be physiologic or pathologic. By convention, the direction of the nystagmus is described in regards to its fast phase and can further be characterized as horizontal, vertical, or rotary.

Pendular nystagmus is not a sign of vestibular dysfunction and is mainly recognized in Siamese, Himalayan, Birman, and crosses of these breeds.

Physiologic

Physiologic nystagmus is the conjugated eye movement occurring during head movement in order to stabilize images on the retina. It can be elicited in normal patients with movement of the head from side to side (oculovestibular reflex). In vestibular diseases, the physiologic nystagmus may be reduced in both eyes when the head is turned toward the side of the lesion. In cases of bilateral involvement, the physiologic (and pathologic) nystagmus may be completely absent because of lack of vestibular activation on both sides.

Pathologic

Pathologic nystagmus is frequently, but not always, present in vestibular disease. It can be spontaneous, which occurs when the head is in the normal position, or positional, which is visible only when the head is placed in an unusual position (e.g., in complete extension or with the animal in dorsal recumbency). The pathologic nystagmus is described by the orientation of the plane in which the eyeballs are moving (vertical, rotary or horizontal) and, by convention, by the direction of the fast phase (left or right) (Videos 265-2 and 265-3). With vestibular disturbance, the eyes will tend to "drift" in the direction of the lesion (slow phase) and will quickly reset to their original position through a brainstem reflex (fast phase). This makes the fast phase of the nystagmus away from the lesion. Spontaneous nystagmus is often present in acute lesions and can disappear within a few days because of central compensation. For this reason, and because the presence of pathologic nystagmus (either spontaneous or positional) is always abnormal and indicative of vestibular disease, it is important to attempt to elicit positional nystagmus.

In peripheral vestibular disease, the pathologic nystagmus can be horizontal or rotary and the fast phase is always away from the lesion. In central disease the pathologic nystagmus can be in any plane (including vertical), can change direction with different positions of the head, and the fast phase can be toward the lesion. Therefore, identification of a vertical nystagmus or a nystagmus with the fast phase toward the lesion is an indication of central involvement. However, caution should be exerted when labeling a patient with central disease based on vertical nystagmus alone since it is easy to confound nystagmus with a slight rotary component with vertical nystagmus. One comparative clinical study also suggested that the number of beats of the resting nystagmus was significantly higher in peripheral vs. central disease. A resting nystagmus rate of more than 66 beats per minute was found to be very specific (95%) and sensitive (85%) of peripheral disease.[2]

Strabismus

Vestibular strabismus is characterized by a ventral deviation of the ocular globe on the side of the lesion when the head is in extension (positional strabismus). However, the eye can move normally from side to side because there is no paralysis of any of the extraocular muscles. This type of strabismus can be seen with a peripheral or central vestibular lesion.

Cranial Nerve Deficits

Although not exactly part of the vestibular syndrome, other CN deficits can be seen along with vestibular signs. In the brainstem, the facial nerve (CN VII) is close to the vestibulocochlear nerve and travels close to the inner ear as well. For this reason, facial nerve paralysis may be noticed with both peripheral and central diseases. The sympathetic innervation of the eye also travels close to the inner ear and Horner's syndrome can occur from peripheral disease but is seen rarely in central diseases. Any other CN involvement indicates a central origin of the disease.

Nausea and Vomiting

Nausea and vomiting are frequently seen with vestibular disease and can be related to motion sickness or the result of a problem in the pathways between the vestibular nuclei and the vomiting center in the brainstem. Nausea and vomiting can be seen with both peripheral and central diseases, although vomiting might be more common with peripheral diseases.[1]

Change in Mentation

Patients with vestibular disease are often very anxious and quite disoriented by the lack of balance. However, this should be differentiated from central depression or obtundation, which indicates brainstem involvement. Some degree of mental depression usually occurs with central diseases because the vestibular nuclei are in close proximity to the diffuse ascending reticular activating system (ARAS) responsible for normal alertness.

Paradoxical Syndrome

The cerebellum is inhibitory to the ipsilateral vestibular nuclei. With a lack of inhibition from a cerebellar lesion, the vestibular nuclei will appear "hyper" on that side. This will cause excess in extensor tone on the

side of the lesion, which will "push" the head and the body on the other side. This causes the head to be tilted away from the lesion. The side of the lesion can be identified by the presence of concomitant deficits (ipsilateral GP deficit, paresis, hypermetria, or CN deficits).

Paradoxical vestibular syndrome can be seen with lesions in the flocculonodular lobe of the cerebellum, the caudal cerebellar peduncle, and the rostral and medial vestibular nuclei in the medulla.[3]

Neurolocalization

The most important aspect in evaluating a patient with vestibular disease is to localize the lesion to either the peripheral vestibular system or to a central origin (Table 265-1). A good history, physical examination, and careful and thorough neurologic examination are essential (see ch. 1, 2, and 259).

TABLE 265-1

Clinical Signs Associated with Peripheral and Central Diseases

CLINICAL SIGNS	PERIPHERAL	CENTRAL
Nystagmus	Horizontal or rotary Fast phase away from the lesion	Horizontal, rotary, or vertical Fast phase away or toward the lesion
Positional strabismus	Possible	Possible, real strabismus also possible (from CN III, IV, VI)
Cranial nerve (CN) deficits	CN VII only (except in case of polyneuropathy)	Any CN possible (mostly CN V to XII)
Horner's syndrome	Possible	Rare
Mental status	Alert, may be anxious or disoriented	Altered May be obtunded, stuporous, comatose, and disoriented
General proprioception deficit and/or paresis	No	Possible, usually ipsilateral
Hypermetria	No	Possible if cerebellar lesion (ipsilateral)

To diagnose central involvement, identification of deficits that cannot be attributed to the peripheral components such as GP deficits, paresis, altered mentation or CN deficits (other than CN VII) is necessary. The presence of vertical nystagmus without rotary component or of nystagmus with the fast phase toward the lesion is also suggestive of a central involvement. The presence of Horner's syndrome suggests a lesion in the middle/inner ear. Although it may seem like a straightforward distinction between peripheral and central diseases, clinical signs often overlap.

Diagnostic Procedures

In the assessment of peripheral vestibular diseases, diagnostic tests should include an otoscopic examination (ideally under sedation or anesthesia), imaging of the tympanic bullae with radiographs or ideally, advanced imaging (computed tomography [CT] or magnetic resonance imaging [MRI]), myringotomy for cytology (see ch. 33, 85, and 259) and culture, and thyroid evaluation. CT is more sensitive than radiographs even with otitis media (84% vs. 75%, respectively) but MRI has even greater sensitivity and can detect otitis interna as well.[53]

Diagnosis of central diseases (Figure 265-2) often requires advanced imaging of the brain with CT or MRI, cerebrospinal fluid (CSF) analysis, and titers for infectious diseases. MRI is preferred over CT because it provides better soft tissue details and because the bone-hardening artifact in CT renders the evaluation of the vestibular component in the caudal fossa more difficult. MRI also allows visualization of the inner ear structures as well as CSF, meninges and brain parenchyma (Figure 265-3).[4] Other potentially useful diagnostic procedures include a fundic examination to evaluate for lesions of chorioretinitis or retinal hemorrhages (ch. 11) and a brainstem auditory evoked response (BAER) test because the latter also evaluates the brainstem component of hearing.

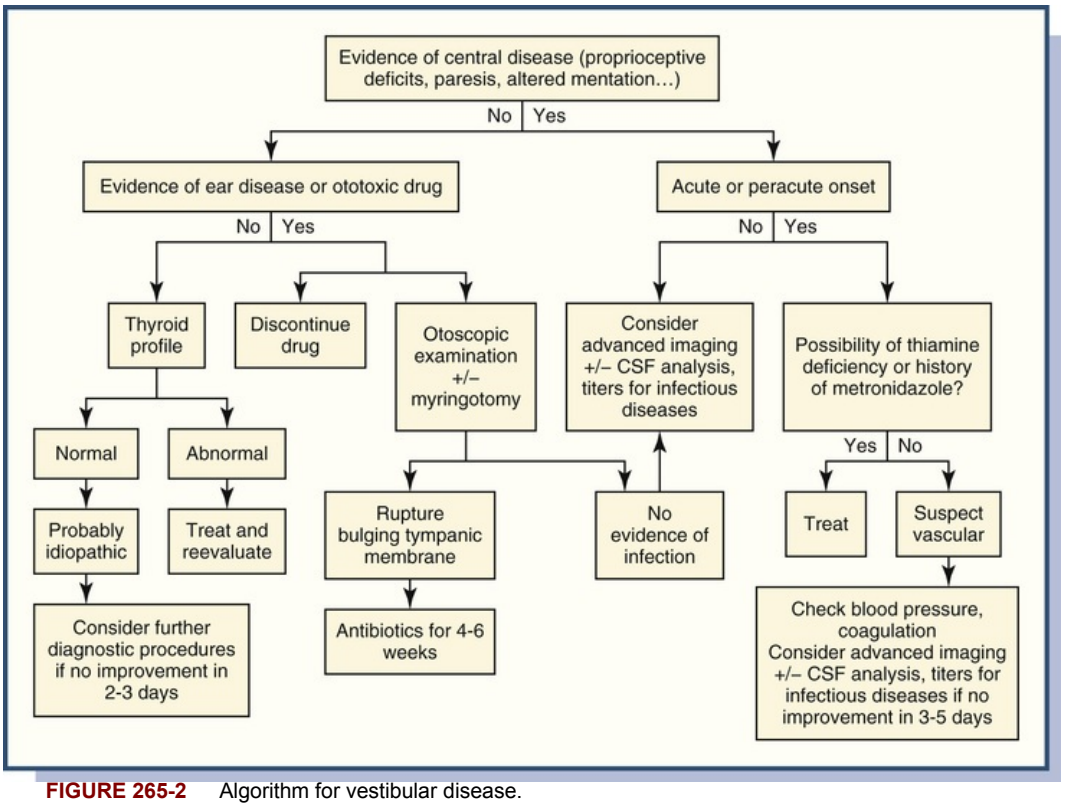

FIGURE 265-2 Algorithm for vestibular disease.

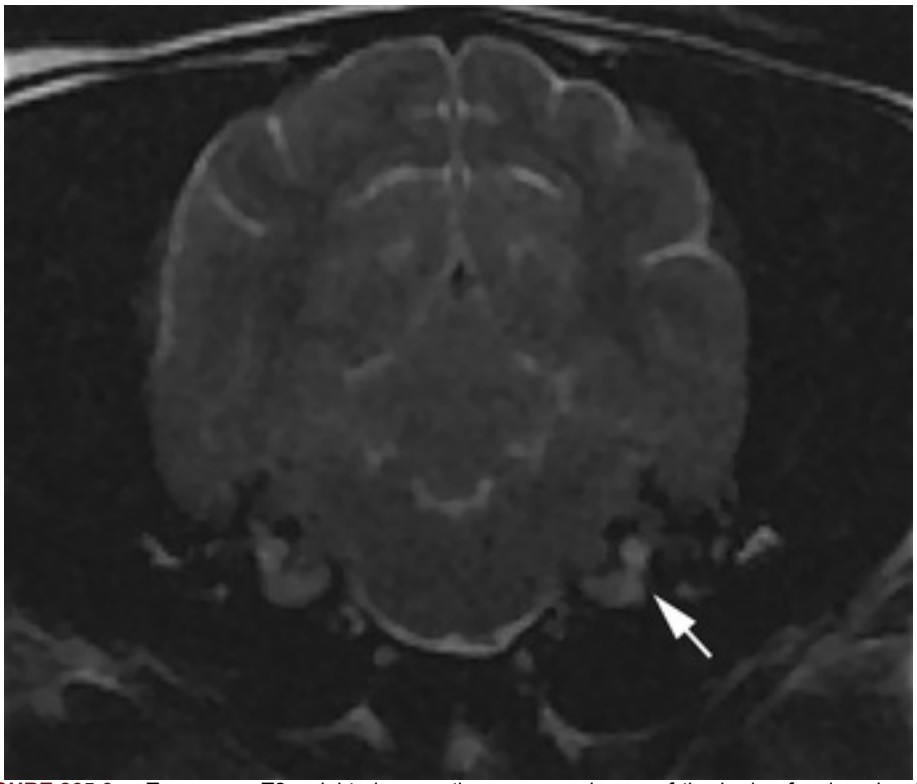

FIGURE 265-3 Transverse T2-weighted magnetic resonance image of the brain of a dog showing the hyperintense fluid in the normal inner ears (arrow).

SUPPORTIVE Treatment and Compensation in Vestibular Diseases

The central vestibular system has a great potential of compensation for even extremely severe vestibular signs. Patients with vestibular disease will benefit from general therapy aimed at reducing some clinical signs such as vomiting and motion sickness. Promoting normal activity and physical therapy will also speed up the recovery in most cases. Correction of the vestibular deficits by the central nervous system (CNS) requires that the patient move in order to provide the somatosensory feedbacks necessary for compensation.

Antiemetics and fluid therapy (ch. 39 and 129) might be necessary if the patient is vomiting and/or dehydrated. Meclizine (12.5 to 25 mg per pet PO q 24 h) has antiemetics and antivertigo properties.[5] It likely helps through its weak antihistamine, CNS depressant properties and anticholinergic effects. Maropitant (1 mg/kg SC q 24 h or 2-8 mg/kg PO q 24 h in dogs and 1 mg/kg PO q 24 h in cats) is a neurokinin-1 inhibitor, which blocks the action of substance P to the final common pathway in the emetic center in the brain. However, maropitant does not seem to possess any antivertigo effect and therefore, meclizine might be beneficial even in conjunction with maropitant.

Peripheral Vestibular Diseases

Otitis Interna/Media

Otitis interna/media (OIM) is a common cause of peripheral vestibular disease in dogs and cats (Video 265-4). Facial nerve involvement and Horner's syndrome are often present as well. The etiology is most commonly an extension of otitis externa in dogs, but an ascending infection from the nasopharynx (via the Eustachian tube) seems more common in cats.[8] Hematogenous spread is also possible. The most common bacteria are *Staphylococcus* species, *Streptococcus, Pseudomonas, Proteus,* and the yeast *Malassezia pachydermatis.* The diagnosis is usually made by otoscopic examination, imaging of the bullae, and myringotomy for culture and sensitivity. The entire eardrum might not be visualized with standard otoscopy and an intact tympanic membrane does not rule out a diagnosis of OIM. If material is present in the middle ear, samples should be obtained if possible for cytology and culture. Radiographs are normal in up to 25% to 33% of confirmed cases, whereas CT results are falsely negative in about 17%.[9,10] Treatment of OIM consists of antibiotic therapy based on the results of the culture and sensitivity for a minimum of 4 to 6 weeks. In the absence of a culture, an antibiotic effective against the most common causative organisms with good boney penetration should be chosen (e.g., amoxicillin/clavulanate or a fluoroquinolone) (ch. 161 and 162). In some cases, a bulla osteotomy may be required in order to control the infection or to confirm the diagnosis. The prognosis is good for resolution of the infection.[12] However, a mild permanent head tilt is possible and the damage on the facial nerve may be irreversible. Occasionally, the infection can extend into the cranial cavity causing an otogenic meningoencephalitis, epidural empyema or a brain abscess which can be life threatening (Figure 265-4). Treatment should be aggressive and consists of surgical drainage of the tympanic cavity with antibiotic therapy but the prognosis is usually favorable.[6,11]

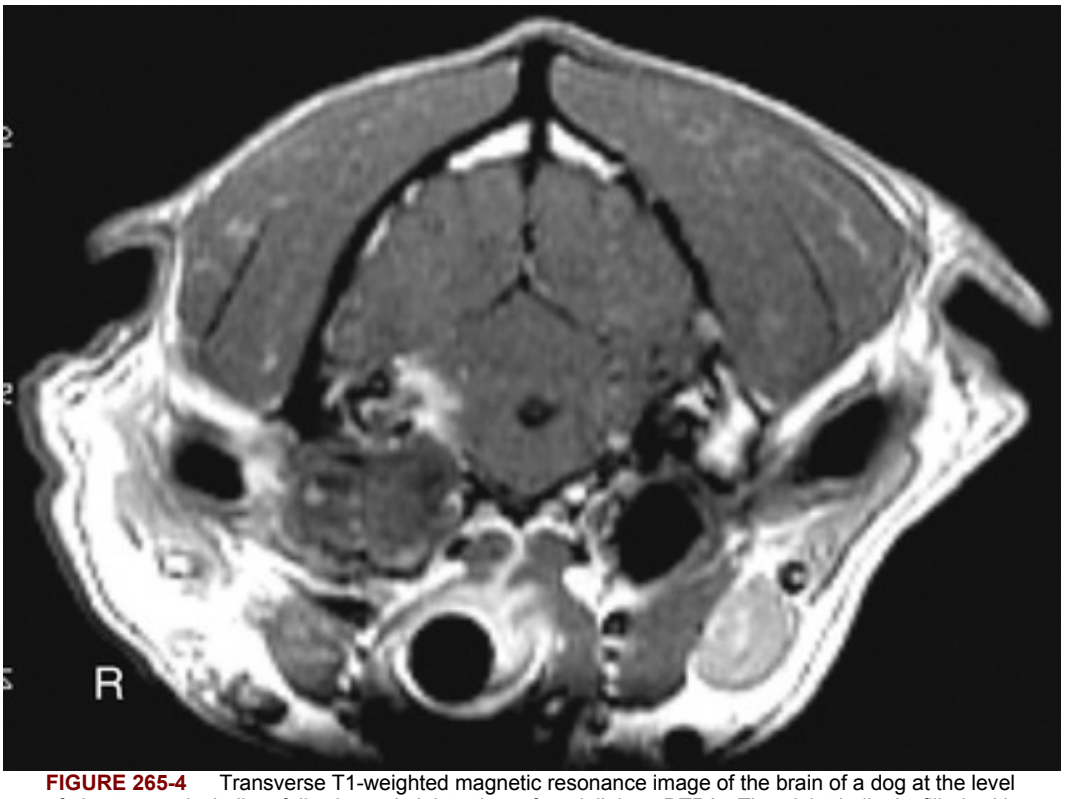

FIGURE 265-4 Transverse T1-weighted magnetic resonance image of the brain of a dog at the level of the tympanic bullae following administration of gadolinium–DTPA. The right bulla is filled with isointense material and there is contrast enhancement in the brainstem at the same level. The diagnosis of middle/inner ear infection was confirmed in surgery.

Nasopharyngeal Polyps

Nasopharyngeal polyps are pedunculated growths resulting from chronic inflammation (see ch. 238). In cats, they may be congenital.[13] They originate from the auditory tube, the nasopharynx, or the lining of the tympanic bulla. Young cats between 1 and 5 years old are most commonly affected, but this can occur in dogs as well (Figure 265-5).[15] In addition to causing signs of middle/inner ear disease, they can cause upper respiratory signs (sneezing, stridor) or pharyngeal signs (gagging, dysphagia). Treatment involves removal of the polyp. This can be done by a simple traction-avulsion, but recurrence is possible in 30% to 50% of cases.[13,14] When there is middle ear involvement, a bulla osteotomy is often necessary to prevent recurrence. A recent retrospective study of per-endoscopic trans-tympanic traction of polyps in 37 cats suggested a resolution in 94% of cases with fewer complications than bulla osteotomy and simple traction (8% vs. 57-81% vs. 43%, respectively).[54]

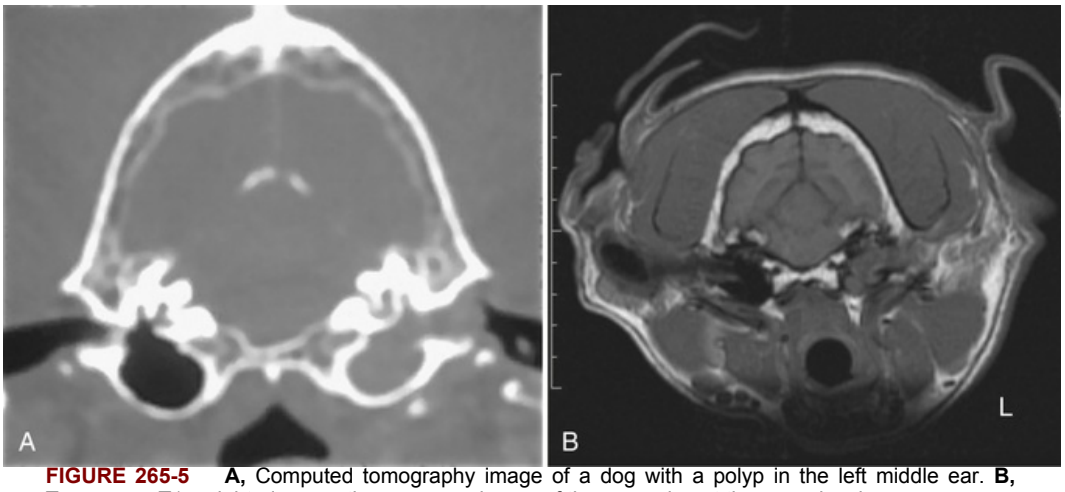

FIGURE 265-5 **A,** Computed tomography image of a dog with a polyp in the left middle ear. **B,** Transverse T1-weighted magnetic resonance image of the same dog at the same level.

Idiopathic Vestibular Disease

This is a common condition seen in cats of all ages and in older dogs, which is why it is sometimes called "old dog vestibular disease" or "canine geriatric vestibular disease."[16,17] The condition is characterized by an acute or peracute onset of peripheral vestibular signs. Unilateral signs are more common but bilateral disease is sometimes seen, especially in cats. It can easily be misinterpreted as a stroke or a seizure. The vestibular signs can be mild but are usually quite severe to the extent that the patient is severely incapacitated, making a complete neurologic examination difficult initially. Nausea and vomiting are common as well as anxiety but there is no sign of central involvement or middle ear disease (i.e., no facial paralysis or Horner's syndrome). The etiology is unknown but could be an abnormality in the endolymph flow. In cats, the condition is more common in the northeastern part of the United States and Canada in the summer and early fall and may be caused by the migration of small *Cuterebra* larvae through the ear canal.[18] A similar presentation is seen in the southeastern part of the United States in cats ingesting the tail of the blue tail lizard.[1,19] The diagnosis is one of exclusion and most patients improve significantly within 72 hours, although complete recovery may take 2 to 3 weeks. Treatment is directed toward the nausea and vomiting and supportive care only. Despite the often dramatic presentation, the prognosis is very good but mild residual deficits are possible. Treatment directed toward *Cuterebra* in cats is usually neither necessary nor recommended.

Hypothyroidism

Vestibular disease secondary to hypothyroidism is mainly recognized in middle-aged to older dogs (see ch. 299).[20] The vestibular signs are usually mild to moderate and can be unilateral or bilateral and may result from a deficit in energy metabolism with disturbance in axonal transport and possible segmental demyelination.[21] There may be concomitant facial nerve involvement and the patient may be lethargic, which makes differentiation from central disease difficult.[22] Definitive diagnosis is made with thyroid testing and resolution or improvement of the clinical signs is expected within 2 months of adequate thyroid hormone supplementation.

Ototoxicosis and Iatrogenic Trauma

A list of ototoxic agents has been compiled mainly from extrapolation from the human literature or from anecdotal reports. These include aminoglycosides, loop diuretics, chlorhexidine and cisplatin.[23,24] Among those, aminoglycosides (mostly streptomycin) and chlorhexidine are probably most common. Because of the potential for ototoxicosis, these should never be used topically if the tympanic membrane cannot be visualized.

Iatrogenic trauma during ear cleaning is probably more common than true ototoxicosis. Iatrogenic rupture of the tympanic membrane during ear cleaning will allow entry of material in the bulla which can lead to a severe inflammatory otitis media.[8,26] Facial nerve paralysis and/or Horner's syndrome can be seen

concomitantly.

Others

Congenital

Congenital unilateral vestibular disease has been reported in a few dog breeds including German Shepherds, English Cocker Spaniels, Dobermans, and Smooth Haired Fox Terriers and cat breeds including Siamese, Burmese, and Tonkinese.[25,27-29] Bilateral congenital disease has been reported in Akitas and Beagles.[25] The etiology can be either a malformation or degeneration of the inner ear structures. Clinical signs are usually noticed when the animal first starts to ambulate and include vestibular ataxia and head tilt unless the condition is bilateral. Pathologic nystagmus is usually not a feature of the condition but some patients also have hearing impairment. There is no treatment but the vestibular signs usually improve because of compensation.

Neoplasia

Tumors of the ear canal or middle ear are not common and tend to be aggressive, especially in cats. They include ceruminous gland adenocarcinoma, squamous cell carcinoma, fibrosarcoma, osteosarcoma or chondrosarcoma, and lymphoma (cats mainly). Overall, most of these tend to have a very guarded to poor prognosis.

Because of the proximity of the trigeminal nerve (CN V) to the CN VIII, dogs with a trigeminal nerve–sheath tumor can present with vestibular signs.

Central Vestibular Diseases

Any disease process that can affect the brain has the potential to cause a vestibular syndrome. However, some conditions and diseases tend to affect the vestibular components preferentially.

Inflammatory Diseases

Inflammatory diseases of the brain (encephalitis), either infectious or noninfectious, can affect any part of the CNS and often produce multifocal signs. They are a common cause of vestibular disturbance. Some diseases tend to cause vestibular signs more often and are discussed briefly here. The reader is referred to ch. 261 for a more complete discussion of inflammatory diseases.

Infectious Diseases

Canine distemper virus commonly causes cerebellar and vestibular signs, which can progress to tetraparesis. In older dogs, systemic signs and myoclonus are often lacking, making the diagnosis difficult.[30,31] The diagnosis can be made by direct immunofluorescence assay (IFA) of a conjunctival scraping or CSF, but this is often unrewarding in chronic cases. Polymerase chain reaction (PCR) analysis of either urine or CSF has proven most useful in the antemortem diagnosis of CNS distemper.[30,32] There is no specific treatment and the prognosis is guarded to poor. However, some dogs may recover although residual neurological deficits are common (see ch. 228).

In cats, vestibular signs can be seen with feline infectious peritonitis (FIP). Neurologic signs are reported in one fourth to one third of cats with the dry form of FIP.[33] Cats affected are often younger than 3 years old and from multiple-cat homes or shelters. The FIP virus induces a pyogranulomatous and immune complex–mediated vasculitis. Antemortem diagnosis is difficult. The prognosis is poor, and the disease is usually fatal (see ch. 224).

Rocky Mountain spotted fever (RMSF) and ehrlichiosis are reported to cause neurologic signs in about 40% and 20% of cases, respectively, and vestibular dysfunction is a common manifestation especially for RMSF.[7,34] The presence of typical laboratory findings (thrombocytopenia, anemia, leukocytosis) should raise the suspicion of these diseases even if there is no history of tick exposure.[31,35] Fungal diseases, in particular cryptococcosis, can lead to vestibular dysfunction. Bacterial diseases are rare and mainly result from extension of middle ear diseases. *Toxoplasma gondii* infection in dogs and cats and *Neospora caninum* in dogs can also be seen. Rabies has been reported to cause rapidly progressive vestibular signs (see ch. 226 and 231).[31,36-40]

Noninfectious Diseases

Noninfectious inflammatory diseases of the brain are also called meningoencephalitis of unknown etiology (MUE) or steroid-responsive encephalitis (see ch. 261). These diseases affect dogs and much less commonly cats. Included in these are the granulomatous meningoencephalitis (GME) and some breed-specific encephalitides (e.g., necrotizing leukoencephalitis of Yorkshire Terriers, necrotizing encephalitis of Pugs), which carry a guarded to poor prognosis. Clinical signs may be acute or insidious and signs are usually progressive. Definitive diagnosis requires histopathology (see ch. 261), but a presumptive diagnosis can be made based on the results of advanced imaging (CT or ideally MRI), CSF analysis, and negative titers for infectious diseases. Treatment consists of steroids (e.g., prednisone 1 to 2 mg/kg/day PO) along with other immunosuppressive drugs (e.g., cytosine arabinoside, lomustine, procarbazine, cyclosporine) or radiation therapy. Most patients improve with therapy but relapses are common. The prognosis is guarded but extremely variable and with aggressive therapy, it is now considered better than previously reported.

Neoplasia

Primary or secondary tumors can affect the brainstem and cerebellum. They are a common cause of central vestibular disorders. The reader is referred to ch. 260 for a more detailed discussion on brain tumors. The most common primary tumors affecting the vestibular components of the CNS in dogs are meningioma, nerve-sheath tumor of the trigeminal nerve (affecting the brainstem or CN VIII by extension), and choroid plexus tumor in the fourth ventricle. In cats, meningioma and lymphoma are most often diagnosed. Clinical signs can be acute or insidious and the condition is usually progressive over a period of weeks to months (Video 265-5). Diagnosis requires advanced imaging of the brain (CT or ideally MRI). CSF analysis might be useful in attempting to rule out the possibility of inflammatory diseases but is seldom diagnostic of a tumor process (Figure 265-6). Treatment can be palliative with glucocorticosteroids or directed toward the tumor process (surgical excision, chemotherapy, radiation therapy). The prognosis is usually guarded to poor.

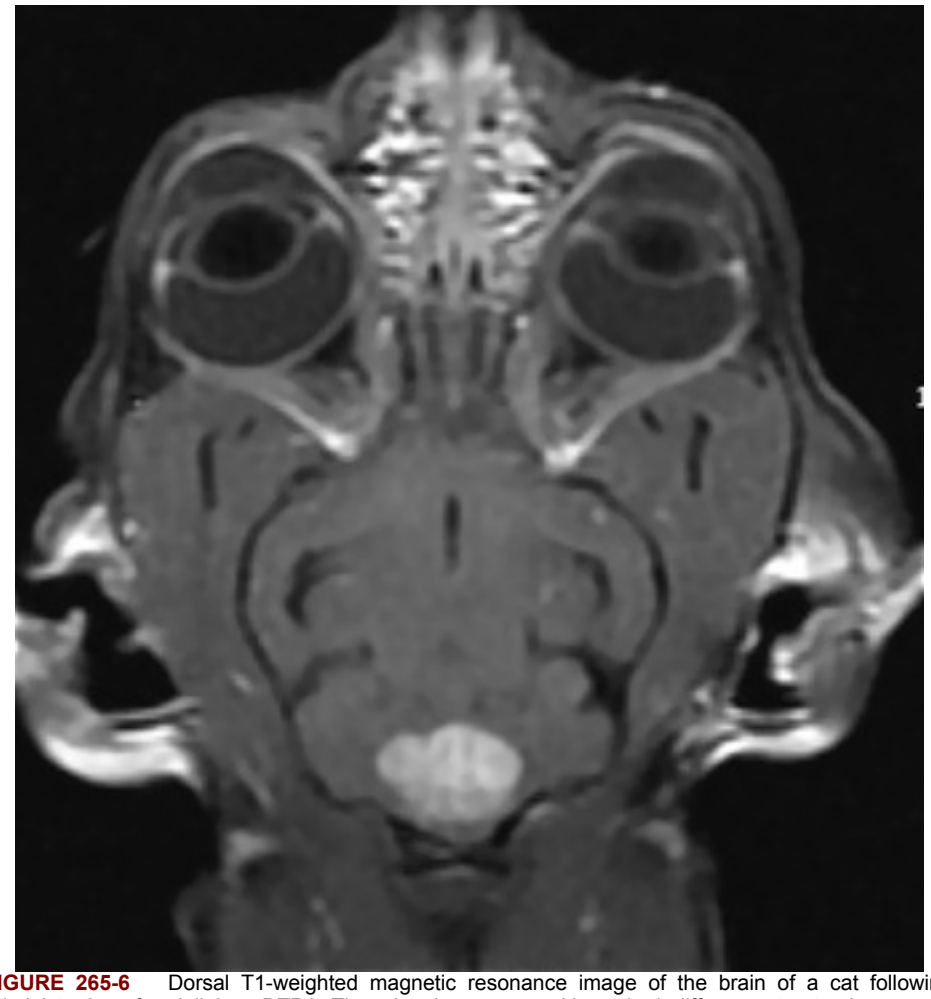

FIGURE 265-6 Dorsal T1-weighted magnetic resonance image of the brain of a cat following administration of gadolinium–DTPA. There is a large mass with marked, diffuse contrast enhancement in the cerebellum. The presumptive diagnosis was a primary brain tumor. However, *Cryptococcus* organisms were identified on cerebrospinal fluid analysis and the cat responded to fluconazole.

Vascular

A cerebrovascular accident (CVA) or stroke is characterized by a sudden onset of nonprogressive focal signs of brain dysfunction (see ch. 260). It occurs when the blood flow to a region of the brain is obstructed by an infarct (thrombus or embolism), a hemorrhage, or an arterial spasm and may result in death of brain tissue. It was previously believed to be uncommon in dogs and cats but is now recognized with increased frequency with the use of MRI.[41,42] The most common location for CVA in dogs is the cerebellum, in areas supplied by the rostral cerebellar artery.[42] Most CVA result from nonhemorrhagic infarcts but a hemorrhagic component is present in some cases.[43] The etiology of the CVA cannot be determined in many cases.[45] However, concurrent medical conditions such as chronic renal failure or hyperadrenocorticism are present in a little more than 50% of cases. Cats with hemorrhagic infarcts often have a liver pathology and/or nephritis. The diagnosis is made with the history (peracute onset of nonprogressive neurological deficits) and MRI findings. Typical MRI findings include a well-defined lesion with sharp demarcation that is hyperintense in T2-weighted images and fluid-attenuated inversion recovery (FLAIR) sequences and has minimal to no mass effect (Figure 265-7) and minimal peripheral or no contrast enhancement. The sensitivity and specificity of MRI in the diagnosis of CVA is improved with the use of newer functional studies like the diffusion-weighted imaging, but its use is not widely available in veterinary medicine.[42] Gradient echo images (T2* or T2-GRE) are helpful in identifying hemorrhagic infarcts, as hemorrhages will appear hypointense on this sequence no matter the age of the hemorrhage. Evaluation of coagulation can be helpful in the diagnosis of hemorrhagic infarcts. Thromboelastography (TEG), which evaluates clot formation and lysis, can detect a hypercoagulable state. Unfortunately, this test has very limited availability at this time. If a hypercoagulable state is confirmed

or suspected, treatment with clopidogrel (1-3 mg/kg PO q 24 h), an ADP-receptor antagonist, can help reduce platelet aggregation.

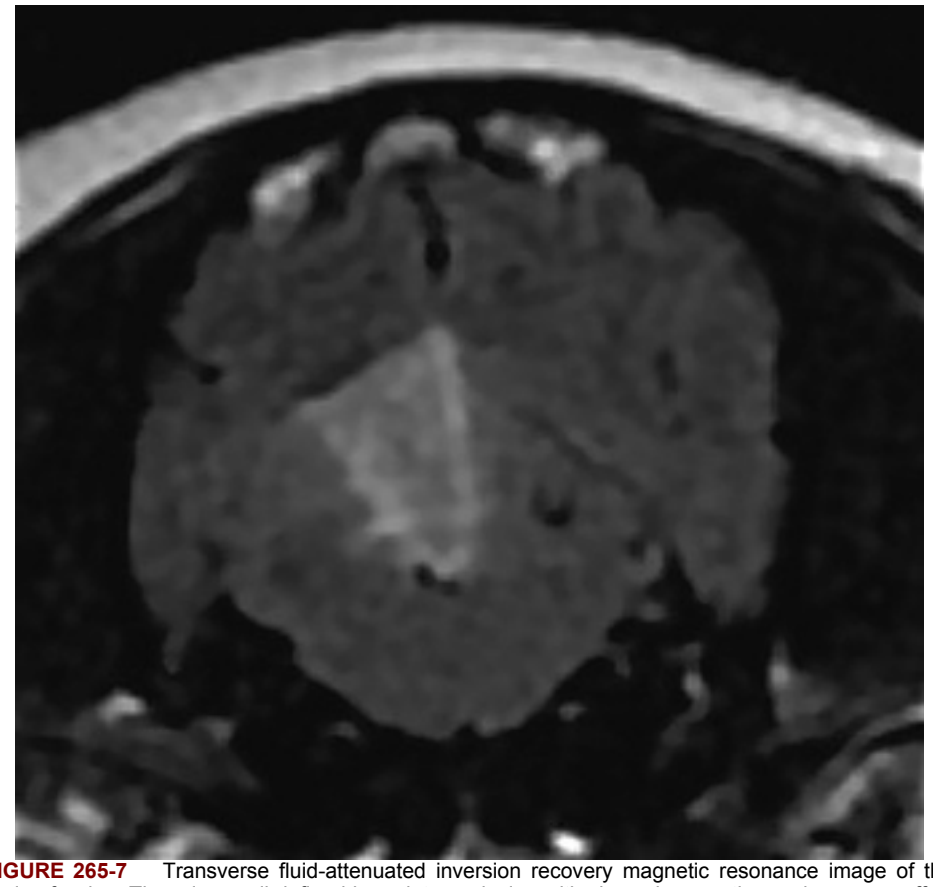

FIGURE 265-7 Transverse fluid-attenuated inversion recovery magnetic resonance image of the brain of a dog. There is a well-defined hyperintense lesion with sharp demarcation and no mass effect in the cerebellum compatible with a vascular accident (rostral cerebellar artery).

Treatment is mainly supportive and attention should be made to ensure good hydration, blood pressure, and oxygenation (Video 265-6). The prognosis is guarded to good, but dogs with a concurrent disease have a shorter survival and an increased risk of relapse.[44] A retrospective study of 23 dogs with ischemic stroke reported a mortality rate of 23% within 30 days but a mean survival of 505 days.[55] Sometimes, episodes of paroxysmal neurologic events are seen prior to the presentation (sometimes described as seizures because of their short duration) and these could represent transient ischemic attacks (TIAs).[42] TIAs are episodes of brief, focal neurologic deficit secondary to embolism, vascular constriction, or spasms that resolve within 24 hours with most of them resolving within minutes to few hours.[46] In humans, TIAs precede cerebellar infarcts in 26% to 41% of cases. TIAs are poorly recognized and understood in veterinary medicine.

Toxicosis

Metronidazole toxicity in dogs causes acute to subacute bilateral central vestibular signs usually accompanied by cerebellar signs (intention tremors, hypermetria) (Video 265-7). Resting or positional vertical nystagmus is a common finding. Anorexia and vomiting often precede the vestibular signs. The exact mechanism of toxicity is unknown but metronidazole seems to interact with the GABA receptors in the cerebellum and vestibular nuclei. Toxicosis is usually seen with daily administration of more than 60 mg/kg/day for 3 to 14 days but has been reported in dogs receiving as little as 33 mg/kg/day.[47] Recovery usually occurs in 1 to 2 weeks after stopping the metronidazole with supportive care. The addition of diazepam (0.5 mg/kg IV followed by 0.5 mg/kg PO q 8 h) to the treatment fastens the recovery to about 1 to 3 days because of its effect on GABA receptors.[47] In cats, metronidazole toxicosis tends to cause forebrain disturbance (seizures,

blindness, ataxia) instead of vestibular signs.[48]

Others

Thiamine Deficiency

Thiamine (vitamin B_1) deficiency causes bilateral necrosis and hemorrhage in susceptible brain nuclei (also see ch. 12). In cats, the vestibular and ocular nuclei are often affected, leading to vestibular signs and dilated, unresponsive pupils, often with profound ventroflexion of the head and neck. Thiamine deficiency can occur in patients fed a diet rich in thiaminase (raw fish) or canned food subjected to excessive heat (>100° C or 212° F).[50] Sulfur dioxide used as a preservative can destroy thiamine in food. Diagnosis is based on history, typical MRI findings and blood thiamine level.[57] Treatment consists of thiamine administration (12.5 to 50 mg per patient per day, IM, SC, or PO) and the prognosis is usually good if the disease is recognized and treated rapidly.

Anomaly

Some malformations and congenital anomalies can cause vestibular signs. Among those, the caudal occipital malformation syndrome common in Cavalier King Charles Spaniels and sometimes seen in other small-breed dogs is probably the most common. An arachnoid cyst, especially in the quadrigeminal cistern, can also cause cerebellar deficits.

Trauma

Head trauma can cause vestibular signs because of cerebellar and/or brainstem involvement. If the brainstem is affected, obtundation and even stupor or coma is likely. The prognosis for head trauma is fair for a cerebellar lesion and very guarded with brainstem involvement.

Degenerative Diseases

Storage disease, abiotrophy, and cerebellar hypoplasia among others can cause vestibular signs. These diseases are usually progressive and the prognosis is guarded to poor.

Postanesthetic Vestibular Syndrome in Cats

The author and other veterinarians from the province of Quebec, Canada, have seen and reported cases of acute vestibular syndrome following anesthesia in young cats. In a retrospective study, 18 cases have been evaluated over a period of 4 years.[51] In this study, 90% of the cats were between 3 and 6 months with 72% being between 3 and 4 months. These cats recovered normally from the anesthesia with no observed deficits and the vestibular signs appeared 2 to 24 hours after the recovery. Most cats were alert, although salivation and nausea were occasionally reported. No ear cleaning was performed during the procedure in any of the cats. Recovery took 48 hours to 10 weeks with the vast majority being back to normal within a week. The cause of the condition is unknown and no anesthetic complications were reported in any of the cases. Not a single drug or combination of drugs or technique was identified to be common to every case (Video 265-9).

Episodic

Episodic vestibular disturbance is sometimes seen, mostly in dogs (Video 265-8). The episodes may last a few seconds to a few minutes and are characterized by a head tilt, loss of balance, and nystagmus. In some patients, the episodes seem to be induced by excitement or certain activities or movements. The etiology of these "vestibular episodes" is probably varied. Some cases may represent TIAs, while others are likely secondary to hypertensive encephalopathy and therefore, serial blood pressure evaluations should be considered in these cases. Hypertensive encephalopathy has been reported with both acute and sustained elevation in systolic blood pressure (see ch. 99 and 157). The clinical signs are often reversible with normalization of the blood pressure.[56] However, the etiology remains undetermined in many cases despite an extensive diagnostic workup. It is possible that some seizures may present with vestibular signs. In humans, temporal lobe epilepsy can cause dizziness and vertigo.[52] Two conditions tend to cause episodic vestibular disturbance in humans: benign paroxysmal positional vertigo (BPPV) and Meniere's disease. With BPPV, the episodes are usually triggered by certain head positions. They last a few seconds and the condition can

resolve in a few months.[52] Although these conditions have not been reported in veterinary medicine, the episodic vestibular syndrome could represent one of these.

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CHAPTER 266

Spinal Cord Diseases

Congenital (Developmental), Inflammatory, and Degenerative Disorders

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Client Information Sheets:
Intervertebral Disc Disease in Dogs
Wobbler Syndrome

Cervical Spondylomyelopathy

Etiology and Pathogenesis

Cervical spondylomyelopathy (CSM) is the most common disease of the cervical vertebral column of large- and giant-breed dogs. Fifteen names have been used to describe this disease (wobbler syndrome, cervical vertebral instability, cervical malformation-malarticulation syndrome, among others) reflecting the limited understanding of the disease's pathogenesis.[1-4]

The cause of CSM remains unresolved. Genetic, congenital, body conformation, and nutritional factors have been proposed; however, both body conformation and nutrition do not appear to be significant.[5,6] Current evidence supports a congenital etiology with a genetic basis. This has been documented in Dobermans as an autosomal dominant trait with variable penetrance.[7]

There are two forms of CSM, which despite some degree of overlap, can be broadly divided into osseous-associated compression and disc-associated compression.[1,8,9] Disc-associated compression typically is seen in middle-aged large-breed dogs (mostly Dobermans). It is caused by intervertebral disc protrusion with or without hypertrophy of the dorsal longitudinal ligament or ligamentum flavum (Figure 266-1, *A*). The vast majority of these compressions affect the C5-6 and C6-7 discs. The pathophysiology of the osseous form is different. This form is seen predominantly in young adult giant-breed dogs, especially Great Danes. Giant breeds usually have spinal cord compression secondary to proliferation of the vertebral arch (dorsally), articular processes (dorsolaterally), or articular processes and pedicles (laterally) (Figure 266-1, *B*). The cause of the compression appears to be a combination of vertebral malformation and osteoarthritic-osteoarthrotic changes affecting the articular processes.[1]

FIGURE 266-1 **A:** Disc-associated cervical spondylomyelopathy. *Top:* Ventral spinal cord compression and nerve root compression at C5-6 caused by intervertebral disc protrusion. Dorsally, hypertrophy of the ligamentum flavum causes mild spinal cord compression. **a,** Transverse section at the level of the C4-5 disc region showing normal spinal cord and vertebral canal. **b,** Ventral compression at the C5-6 region caused by intervertebral disc protrusion and hypertrophy of the dorsal longitudinal ligament and ligamentum flavum (leading to mild dorsal compression). **c,** Asymmetric intervertebral disc protrusion at C6-7 causing spinal cord and nerve root compression. **B:** Osseous cervical spondylomyelopathy. **a,** Severe dorsolateral spinal cord compression at C2-3 caused by osseous malformation and osteoarthritic changes. **b,** Normal C3-4 disc region. **c,** Bilateral compression at C4-5 caused by osteoarthritic changes and medial proliferation of the facets resulting in absolute vertebral canal stenosis and foraminal stenosis, which lead to spinal cord and nerve root compression, respectively. *Bottom:* Dorsal spinal cord compression at C3-4 caused by lamina malformation and hypertrophy of the ligamentum flavum. Osteoarthritic changes also are shown at C2-3. (From da Costa RC: Cervical spondylomyelopathy (wobbler syndrome) in dogs. *Vet Clin North Am Small Anim Pract* 40(5):881-913, 2010.)

Clinical Findings

Dogs with CSM will typically present with a longstanding history of chronic and progressive gait deficits affecting mainly the pelvic limbs. The main neurological abnormality is proprioceptive ataxia leading to a "wobbly" gait (thus the name "wobblers"), along with variable degrees of weakness affecting the pelvic limbs or all four limbs. Since most lesions are located in the caudal cervical region, many dogs present with the so-called "two-engine gait," where the thoracic limb gait can appear choppy and short-strided, whereas the pelvic limb gait is often wide-based (abducted), with a longer stride length, and markedly uncoordinated (Video 266-1). Postural reaction deficits (proprioceptive positioning deficits) are usually seen, but may not be evident in those with a chronic history despite the presence of proprioceptive ataxia, thus reinforcing the importance of a careful gait evaluation (see ch. 259). Spinal reflexes in the thoracic limbs will usually reveal decreased flexor (withdrawal) reflex with normal to increased extensor tone. The pelvic limb reflexes will be normal to increased. Palpation of the cervical spine may reveal pain; however, cervical hyperesthesia is not a prominent feature of this disease. Forceful manipulations of the cervical spine are unnecessary and can lead to severe neurologic decompensation.

Diagnosis

Definitive diagnosis should be made using advanced imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) or myelography. Survey radiographs cannot be used as the only criteria for diagnosis. Radiographs can be used as a screening test to rule out other differential diagnoses and for a presumptive diagnosis. Radiographic findings seen in the disc-associated form are primarily changes in the shape of the vertebral body, narrowing of the intervertebral disc space, and vertebral canal stenosis. Osteoarthritic, sclerotic changes of the articular processes are the radiographic hallmarks in giant-breed dogs with osseous compressions, and can be seen on lateral and ventrodorsal projections.[10] Myelography is no longer the method of choice to diagnose CSM. It can be used if CT and MRI are not available. CT is a rapid test that allows visualization of transverse sections of the cervical spine. It has to be combined with myelography to identify the exact location of the compressive lesion(s). It provides superior visualization of the direction and severity of the spinal cord compression compared with myelography.[11] MRI is the gold standard test for diagnostic evaluation and has been shown to be superior to myelography and complementary to CT.[12-14] The main advantage of MRI is that it detects spinal cord signal changes (seen in approximately 50% of affected dogs), allowing precise identification of the site(s) most severely affected.[15]

Treatment

Ideally the *natural history* of a disease should be understood so that treatment recommendations and prognosis can be based on this knowledge. Unfortunately, the natural history of CSM has not been defined. It appears that the disease progresses slowly in many dogs with both forms of CSM.[4,16] The two broad options for treatment are medical (conservative) or surgical. Conservative management is a viable option for many dogs, primarily those giant-breed dogs with multiple compressive lesions affecting the lateral aspect of the spinal cord. It may also be appropriate to start dogs on medical management initially to evaluate the improvement obtained with it, and to give owners the opportunity to decide on surgery. The response to medical management can be used to indirectly evaluate the degree of reversibility of spinal cord lesions. The most important component of medical management is exercise restriction to minimize the dynamic component of spinal cord injury.[1,17] Dogs can be leash-walked, but free, unsupervised activity is strongly discouraged. A body harness should be worn instead of a neck collar. Corticosteroids appear to benefit dogs with CSM, and anti-inflammatory dosages of prednisone often are used (0.5 to 1 mg/kg PO q 12 to 24 h) progressively tapering it over the course of 2 to 4 weeks. Proposed mechanisms of actions for corticosteroids are reduction of vasogenic edema, protection from glutamate toxicity, and reduction of neuronal and oligodendroglial apoptosis.[18-20] Surviving demyelinated axons may also remyelinate with treatment. Due to the possibility of gastrointestinal complications, omeprazole or famotidine is often used in conjunction with corticosteroid therapy. Approximately 50% of dogs improve with medical management.[16,21-23]

Surgery is generally assumed to represent the treatment of choice for most dogs with CSM.[2,24] Because most affected dogs have spinal cord compression, decompressing the spinal cord in theory provides the definitive treatment. It is important, however, to consider several factors such as severity of neurological signs, type and severity of compressive lesion(s), response (or lack of response) to medical management,

short- and long-term expectations of the owner, and presence of other concurrent neurological, orthopedic, systemic or cardiac diseases such as dilated cardiomyopathy that would affect the long-term outcome. This is also one of the most controversial topics regarding this disease. Twenty-seven surgical techniques have been proposed to treat CSM.[24,25] They can be broadly divided into direct decompression (e.g., ventral slot or dorsal laminectomy), indirect decompression (e.g., distraction techniques with polymethyl methacrylate plug), and motion-preserving techniques (disc replacement).[24-28] Currently no technique is clearly superior. Approximately 70-80% of dogs improve with surgical treatment, although many deteriorate 2-3 years after surgery. Extensive discussion on surgical options is beyond the scope of this chapter.

Degenerative Lumbosacral Stenosis

Etiology and Pathogenesis

Degenerative lumbosacral stenosis is a common disease of adult large-breed dogs. Several terms have been used to describe it, such as cauda equina syndrome, cauda equina compression, lumbosacral stenosis or disease, lumbosacral instability, and degenerative lumbosacral stenosis.[29-31] These terms all encompass a syndrome characterized by stenosis (narrowing) of the lumbosacral region frequently caused by intervertebral disc protrusion (Figure 266-2). The basic pathophysiology involves chronic progressive intervertebral disc degeneration, with subsequent protrusion of the L7-S1 intervertebral disc into the vertebral canal along with proliferation of the soft tissues surrounding the cauda equina, such as hypertrophy of the interarcuate ligament (ligamentum flavum), the joint capsule, and epidural fibrosis.[29,32,33]

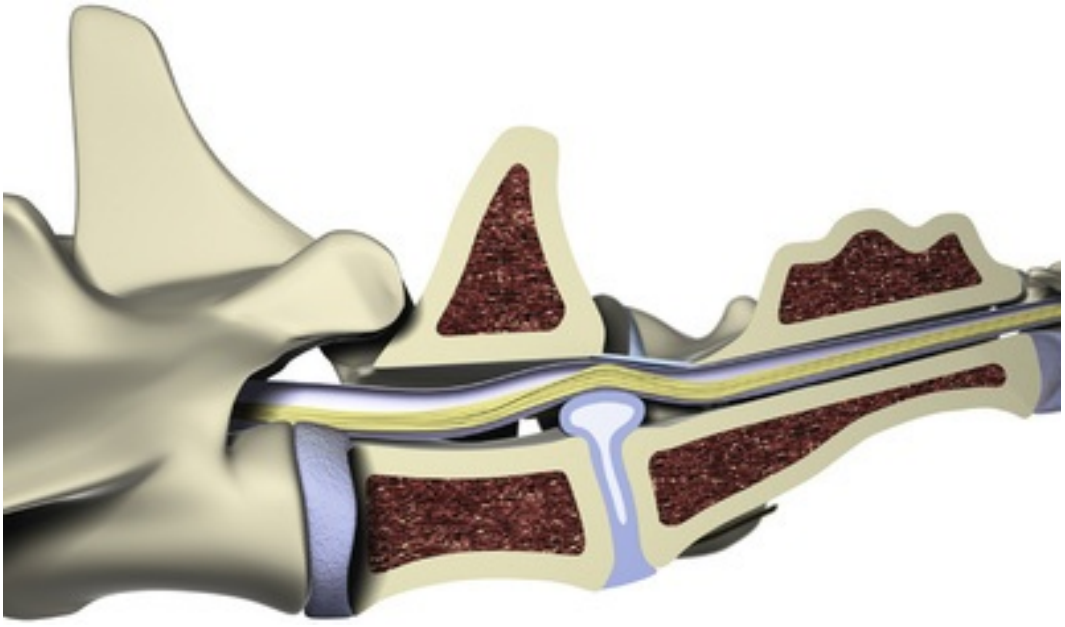

FIGURE 266-2 Schematic illustration of intervertebral disc protrusion at L7-S1 compressing the cauda equina. (From Dewey CW, da Costa RC: *Practical guide to canine and feline neurology*, ed 3, Ames, IA, 2015, Wiley.)

The specific causes for the high incidence of this degenerative process in the lumbosacral region are unknown. A genetic basis was proposed recently in German Shepherds.[34] It appears that the presence of transitional vertebrae or sacral osteochondrosis at the lumbosacral junction in German Shepherd Dogs as well as other large-breed dogs is associated with development of degenerative lumbosacral stenosis.[34-37] German Shepherds have also been shown to have vertebral canal stenosis and a higher step between L7-S1 compared to other breeds.[34]

Clinical Signs

The signs reflect compression of the spinal nerves and nerve roots at the lumbosacral region. The main

clinical sign is lumbosacral pain. Patients will come with a history suggestive of pain, such as difficulty or reluctance to sit, jump, go up stairs and lameness. Careful palpation of the lumbosacral area, including lordosing the caudal spine while pressing on the lumbosacral area, elevation of the tail, or rectal palpation, should cause pain. It is important to always perform rectal examination in these dogs as neoplasms in the pelvic canal can extend dorsally, causing signs of cauda equina dysfunction.[29]

Gait examination of affected dogs reveals pelvic limb weakness (without proprioceptive ataxia), and often a "stiff" gait. In some cases, the only sign is uni- or bilateral lameness, which can be misinterpreted as a sign of orthopedic disease. Many large dogs also have concurrent orthopedic diseases, highlighting the importance of a good neurologic evaluation (see ch. 259) and spinal palpation. Most dogs will have deficits on proprioceptive positioning tests of the pelvic limbs, with a decreased flexor reflex (primarily poor hock flexion), and a normal patellar reflex (sometimes with "pseudohyperreflexia"). In the latter stages of the disease, patients may show urinary and/or fecal incontinence.

Diagnosis

Diagnosis of degenerative lumbosacral stenosis is based upon signalment (mostly middle-aged to older large-breed dogs), historical and clinical findings, and results of imaging tests of the lumbosacral region. Radiographic examination should always be the initial imaging test. It is rarely diagnostic by itself, but can be used to rule out discospondylitis, osseous spinal neoplasms and traumatic lesions. Common radiographic findings are collapse of the intervertebral disc space, sclerosis of the vertebral endplates, malalignment of the sacrum with the L7 vertebra, narrowing of the cranial foramina of the sacrum, and spondylosis.

A number of procedures have been proposed to definitively diagnose degenerative lumbosacral stenosis, but it is clear that CT and MRI (primarily MRI) provide the most detailed structural information regarding the cauda equina, including information concerning the L7-S1 intervertebral foramina and L7 nerve roots.[32,38-43] It is important to bear in mind that clinically normal dogs (mainly older dogs) can have compression of the lumbosacral region without associated clinical signs, and that the degree of cauda equina compression seen on imaging does not correlate with presence of disease or its severity.[42,44] This is one of the challenges associated with the diagnosis of lumbosacral stenosis.[45]

Treatment

Treatment of the patient with degenerative lumbosacral stenosis may be non-surgical or surgical. Treatment decisions are based primarily on severity of clinical signs, age of the patient, and concurrent diseases (neurologic and non-neurologic). Non-surgical therapy consists of enforced rest initially for a few weeks, followed by a period of regular short walks to maintain muscle mass. Additionally, anti-inflammatory medication (either non-steroidal drugs or prednisone, not both; see ch. 164), analgesics (such as gabapentin; see ch. 126, 166, and 356), and body weight reduction (see ch. 176) are recommended.[29,33] Non-surgical or conservative treatment is a reasonable initial option, primarily in older patients with multiple orthopedic or systemic diseases. A recent retrospective study evaluated the short- and long-term follow-up of 31 dogs treated medically, and found a successful outcome in 55% of cases (17 out 31 dogs).[46] Epidural steroids are a popular therapeutic approach in people for lumbar and lumbosacral disc herniations compressing nerve roots.[47] A retrospective study evaluated the use of fluoroscopic-guided epidural steroid injections and found an improved outcome in 79% of dogs.[48]

Surgical treatment is elected when the patient's signs are severe or refractory to medical management. Surgery usually consists of a dorsal laminectomy over the L7-S1 interspace, often combined with removal of hypertrophied soft tissue. Lateral extension of the decompression (facetectomy) may be necessary depending on the lesion. Stabilization may also be necessary in some cases. In cases of lateralized foraminal stenosis, as opposed to vertebral canal stenosis, foraminotomy (surgical enlargement of the foramen) may need to be performed.[49] The prognosis for functional recovery from this disorder is generally good to excellent with surgical intervention. Successful outcomes after surgery range from 66.7% to 95% of cases.[50-52] Surgical treatment is less successful in dogs with fecal or urinary incontinence, with a report indicating failure of resolution of incontinence in 55% to 87% of cases.[29,33,50-52]

Extradural Synovial Cysts

Etiology and Pathogenesis

Extradural synovial cysts (ESC) or extradural intraspinal cysts are cysts arising from periarticular joint tissue. They can be divided into two cyst types: synovial and ganglion cysts. Synovial cysts have a synovial lining containing fluid, and ganglion cysts contain myxoid material with no specific lining. These are pathological differences that may indeed reflect different stages of the same disease.[53] Considering that both types of cysts occur in close proximity with the intervertebral joints, the term *juxtafacet cysts* has been coined to encompass both cysts.[53] The pathophysiology of these cysts is not well established. It is thought that degeneration of the zygapophyseal joint (osteoarthritic changes) causes protrusion of the synovial membrane through defects of the joint capsule. Protrusion of the synovial membrane will cause the formation of a para-articular cavity filled with synovial fluid, which leads to extradural compressions.[53,54] Other proposed mechanisms are proliferation of pluripotent mesenchymal cells, myxoid degeneration with cyst formation in collagen tissue, and increased production of hyaluronic acid by fibroblasts.[54] Some of the affected dogs with lumbosacral cysts had transitional vertebrae, and this may be a risk factor.[55]

Clinical Findings

The clinical signs of synovial cysts will reflect their location in the vertebral column, with the two most frequent locations being the lumbosacral and cervical regions. Clinical signs of cervical cysts are those of a cervical myelopathy with proprioceptive ataxia and tetraparesis, whereas pelvic limb lameness or weakness, with or without pain on palpation, can be seen with lumbosacral cysts.[54,55]

Diagnosis

The majority of reported dogs with lumbosacral/caudal lumbar synovial cysts were large-breed, middle-aged or older dogs (median age 8 years).[53] Cervical synovial cysts are relatively common in association with the osseous form of CSM in young, giant-breed dogs.[3,56,57] Two MRI studies indicate that they occur in 20% of dogs with CSM.[3,56,57]

Diagnosis of synovial cysts is best done with MRI (Figure 266-3). In human beings, MRI is reported to have a sensitivity of 90% for the diagnosis of ESC, compared with 70% with CT.[58] Both soft tissue and bone windows have to be used to increase accuracy of CT to detect these cysts. MRI in dogs reveals the cysts as well-circumscribed extradural masses on one or both sides of the vertebral canal. They are hyperintense in T2-weighted images, with variable characteristics on T1-weighted images.[55,56,59] Radiographic changes are non-specific and will only indicate degenerative joint disease in the affected sites. Myelographic changes may be suggestive but are not diagnostic. Changes in the lateral projection are dorsal extradural compression(s), and in the ventrodorsal view, uni- or bilateral axial compressions.[54] Cerebrospinal fluid (CSF) typically reveals albuminocytologic dissociation but mild mononuclear pleocytosis may also be seen.[53,54]

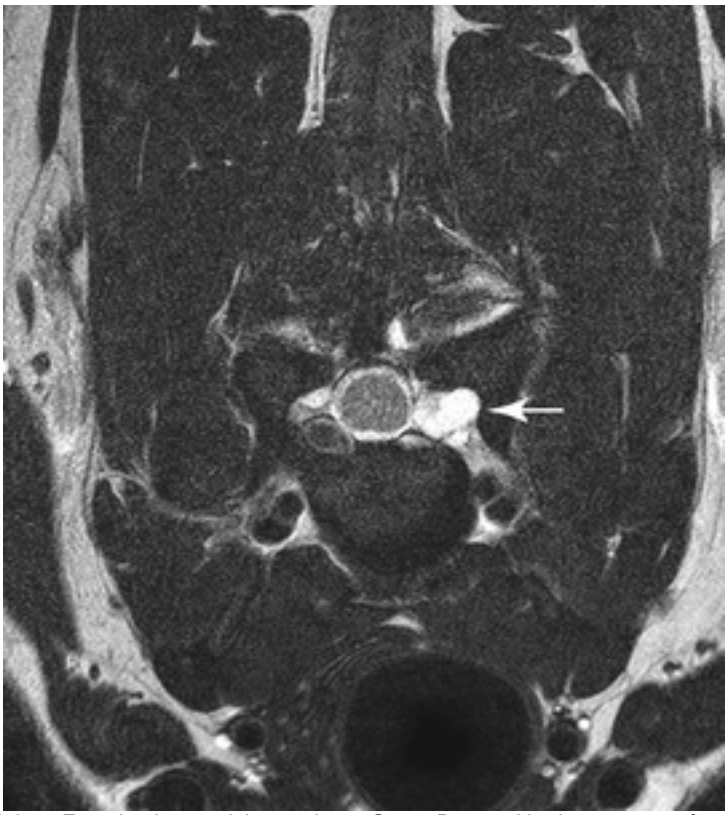

FIGURE 266-3 Extradural synovial cyst in a Great Dane with the osseous form of cervical spondylomyelopathy (arrow).

Treatment

Treatment of these cysts is typically surgical, many times done at the same time as the decompressive surgery (dorsal laminectomy) for CSM or degenerative lumbosacral stenosis. In humans, however, many of these cysts are asymptomatic, and in many cases may be incidental findings.[60] The same may be true for dogs. Therefore, attempting medical management with activity restriction and anti-inflammatories is recommended initially. All reported cases of surgical treatment of synovial cysts had positive outcomes.[53]

Spinal Arachnoid Diverticula (Cysts)

Etiology and Pathogenesis

Spinal arachnoid diverticula are focal dilations of the subarachnoid space, which can lead to a progressive, compressive myelopathy. These diverticula were previously called arachnoid cysts, but this is a misnomer because they are not closed epithelial lined cavities.[53,61,62] They have also been called intra-arachnoid or subarachnoid cysts, meningeal cysts, leptomeningeal cysts, and pseudocysts.[63-65] Currently, it appears that these diverticula are being recognized more frequently with the widespread use of MRI. In people, cyst-like structures of the meninges have been classified into three types, with type III (intradural forms) best fitting the diverticula described in dogs.[53,61]

The etiology of these cysts is not fully understood. A recent report indicated a genetic predisposition in Pugs.[62] It appears that a congenital etiology is likely in the cases seen in young dogs. Other proposed causes are the presence of concurrent diseases. A large, recent case series indicated that 21.3% of dogs had concurrent diseases (e.g., intervertebral disc disease, vertebral malformations, myelitis) in close proximity with the diverticula, which might have influenced their development.[66]

Two recent studies reviewed 215 cases of arachnoid diverticula.[53,66] These studies revealed that approximately 55% of these diverticula occur in the cervical region, whereas 45% are seen in the thoracolumbar region. The most common specific sites were C2 and C3, and T9 to T13. Large-breed dogs have

a predilection for cervical diverticula, whereas small-breed dogs have a tendency to have thoracolumbar diverticula.[53,66] Approximately 88% of the diverticula appear to be located in the dorsal aspect of the spinal cord, 8% in the ventral region, and the remainder in the lateral or circumferential regions.

Clinical Signs

Clinical signs reflect the location of the myelopathy. This disease is primarily characterized by proprioceptive ataxia with various degrees of tetraparesis or paraparesis, without obvious spinal pain. Some dogs with cervical diverticula will display more severe signs in the thoracic limbs, suggesting an intramedullary lesion. A common feature is a severely spastic gait in the thoracic limbs, giving the appearance of "pseudo-hypermetria."[67] Spinal hyperpathia is not a prominent sign, but has been reported in 18.9% of dogs in a large case series (although a good proportion of dogs had concurrent diseases, thus making it difficult to know the exact source of pain).[66] Urinary and fecal incontinence have been reported in approximately 8% of dogs, primarily with thoracolumbar diverticula.

Diagnosis

Two breeds are overrepresented: Rottweilers and Pugs. French Bulldogs are also predisposed to thoracolumbar diverticula. Overall, a male predisposition is clear, with a male-to-female ratio ranging from 2 : 1 to 3 : 1 in large case series. Median age of affected dogs is 2.5 years, ranging from 2.5 months to 13 years. Pugs tend to be affected at an older age (median 59 months).[53,66]

Myelography, CT-myelography or MRI are required to diagnose this disorder (Figure 266-4). Myelography and post-myelographic CT demonstrate these diverticula as contrast-filled teardrop shaped expansions of the subarachnoid space.[53,63] It may also reveal a block of the subarachnoid contrast column without filling of the subarachnoid diverticula. MRI is generally considered the imaging modality of choice to evaluate these diverticula because it also allows assessment of the spinal cord parenchyma and detection of comorbidities, such as syringohydromyelia. It is important to use MR myelogram sequences (heavy T2-weighted images) to facilitate visualization of the diverticulum.[68] CSF analysis is typically normal in the majority of cases. Approximately 20% of dogs show albuminocytologic dissociation and 10% can show mild mononuclear pleocytosis.[53,63]

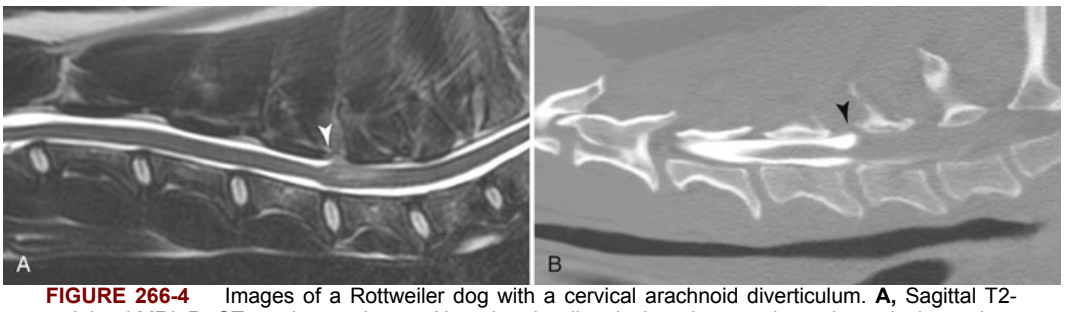

FIGURE 266-4 Images of a Rottweiler dog with a cervical arachnoid diverticulum. **A,** Sagittal T2-weighted MRI. **B,** CT-myelogram image. Note that the diverticulum does not have the typical tear-drop appearance on MRI (white arrowhead). CT-myelography facilitates visualization (black arrowhead) and confirmation. (From Dewey CW, da Costa RC: *Practical guide to canine and feline neurology*, ed 3, Ames, IA, 2015, Wiley.)

Treatment

Medical management (i.e., glucocorticoid therapy) may be attempted initially. In a few cases the signs can be managed for long periods and the disease appears to become stable. Surgical management is typically the treatment of choice. Surgical techniques described involved fenestration with durotomy or durectomy, and marsupialization of the diverticulum. In cases where vertebral instability may be present, stabilization is recommended. From the limited data available, surgical treatment of spinal arachnoid cysts appears to have a good prognosis. It appears that 65-80% of cases have good outcomes.[53,65] It is not clear how many dogs have recurrence because the follow-up of reported cases is variable, but it appears that at least 10-20% of cases have

recurrence of signs. Factors associated with a better outcome were age (younger than 3 years) and duration of clinical signs (less than 4 months).[65]

Spondylosis Deformans

Etiology and Pathogenesis

Spondylosis is a very common degenerative process of the vertebral column, with essentially no clinical significance by itself.[69] It is characterized by the formation of exostoses or bone proliferations around the ventral (and sometimes lateral) vertebral endplate margins, which could result in a bony bridge between adjacent vertebrae.[70] This is a non-inflammatory condition believed to be associated with degenerative changes in the annulus fibrosus of the intervertebral discs in an effort to stabilize the disc region. Osteophytes vary from small spurs to bone bridges across the disc space, leaving at least part of the ventral surface of the vertebral body unaffected. A recent retrospective study of 2041 dogs found spondylosis in 367 (18.1%) of dogs.[70] Spondylosis commonly affects the thoracic, lumbar and lumbosacral regions.

Clinical Signs

It is very tempting to attribute signs of spinal cord disease such as paresis, paralysis or proprioceptive ataxia to spondylosis but such association has never been documented (in spite of the high prevalence of spondylosis). A study suggested that spondylosis may predispose dogs to adjacent segment disease, making them susceptible to the development of intervertebral disc protrusion (type II) in the segments cranial or caudal to the fused disc spaces.[71] Thus, the presence of neurologic deficits should indicate the possibility of concurrent neurologic diseases. The only sign reported to occur in working dogs is a reduction of activity level secondary to the diminished flexibility of the vertebral column.[70] Nerve root compression (leading to pain and lameness) has been documented in dogs with diffuse idiopathic skeletal hyperostosis. It is possible that it could also occur rarely in cases of spondylosis with severe lateralized bony proliferation causing intervertebral foraminal stenosis.[72]

Diagnosis

Spondylosis can be seen in adult animals of various sizes and ages, but is more prominent in middle-aged to older, medium- to giant-breed dogs. Boxers, German Shepherds and Flat-Coated Retrievers seem to be primarily predisposed.[70,73] Diagnosis is established based on the radiographic appearance of vertebral osteophytes arising from the periphery of the endplate, along with sclerotic endplates, and preservation of central portion of the vertebral bodies.[70] It is important to differentiate spondylosis from discospondylitis and disseminated idiopathic skeletal hyperostosis (DISH). As previously stated, spondylosis by itself does not cause neurological signs, so in patients with obvious neurologic signs, further diagnostic work-up with myelography, CT, MRI and CSF is recommended to definitively diagnose the cause of signs (see ch. 115).

Treatment

Spondylosis has no clinical significance in the vast majority of dogs, and treatment is not necessary.[69] In the cases where it can be documented to cause nerve root compression, treatment with analgesics such as gabapentin or surgical decompression of nerve roots may be necessary.[72]

Disseminated Idiopathic Skeletal Hyperostosis (DISH)

Etiology and Pathogenesis

DISH is a systemic disorder characterized by fibrocartilaginous proliferation followed by endochondral ossification within soft tissues of the axial and appendicular skeleton. Ossification of DISH appears to affect an area rather than specific anatomic structures. DISH in dogs is mostly characterized by generalized new bone formation that appears as flowing ossification along the ventral and lateral aspects of the vertebral column.[70]

Initially thought to be a rare condition, a recent report described DISH in 78 dogs (3.8% of 20,141 dogs). Among these 78 dogs, 53 (67.9%) also had spondylosis. The most common locations for DISH were T6-T10

and L2-L6 vertebral regions.[70]

Clinical Signs

Similar to spondylosis, DISH is typically a radiographic finding with little clinical significance. It can cause spinal stiffness and limited performance in working dogs.[70] Spinal pain may be seen, although is probably quite uncommon. It has been shown to cause foraminal stenosis leading to pain and pelvic limb lameness (nerve root signature).[72] As DISH can predispose dogs to adjacent segment disease, any dog with clear neurologic deficits should be thoroughly investigated.[67]

Diagnosis

DISH is seen primarily in older (mean age 8 years), large-breed dogs, with Boxers being overrepresented. The characteristic radiographic appearance is "flowing" ossification primarily at the ventrolateral aspect of the vertebral column, extending for at least four contiguous vertebrae (Figure 266-5).[70,74] The osseous proliferation does not invade the vertebral canal and as such does not cause spinal cord compression or neurologic deficits. There may also be ossification of the interspinous ligaments dorsally, which might be quite extensive.[75,76] It is important to differentiate DISH from spondylosis deformans.[70] Lesions of spondylosis typically spare at least part of the ventral surfaces of adjacent vertebral bodies, and that is the most important radiographic difference with DISH.

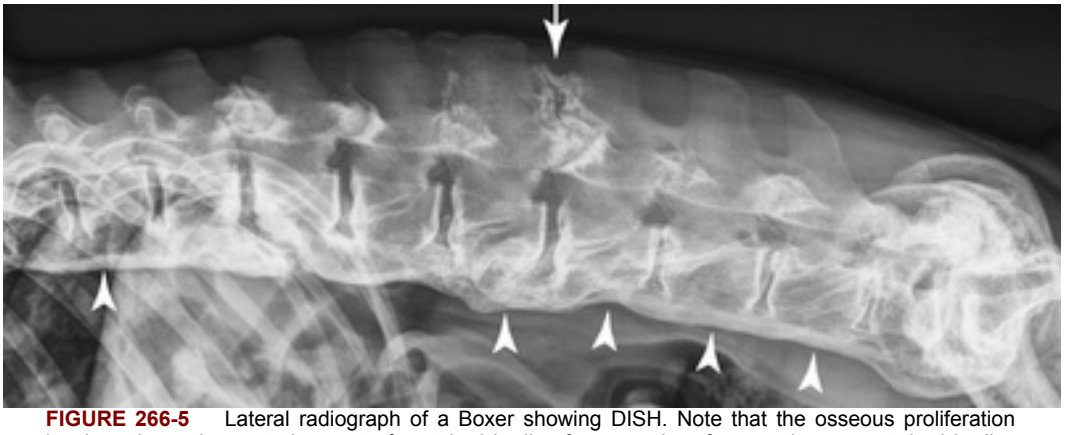

FIGURE 266-5 Lateral radiograph of a Boxer showing DISH. Note that the osseous proliferation involves the entire ventral aspect of vertebral bodies for more than four contiguous vertebral bodies (arrowheads). Osseous proliferation is also seen in the dorsal aspect of the vertebral column at L3-4 (arrow).

An MRI study revealed the signal intensity of the proliferative bone lesions to be of equal intensity to the vertebral bone marrow (on both T1- and T2-weighted sequences). In contrast, in dogs with spondylosis, the signal from osteophytes was hypointense compared to the bone marrow signal on both T1- and T2-weighted images.[77]

Treatment

Similar to spondylosis, the vast majority of dogs with DISH do not display signs secondary to the disease's bone proliferation. If nerve root compression is documented as the source of pain, treatment with analgesics or surgical decompression of nerve roots may be necessary.[72]

Degenerative Myelopathy

Etiology and Pathogenesis

Degenerative myelopathy is a degenerative disease that affects primarily the thoracolumbar spinal cord of medium- to large-breed dogs.[78,79] It has also been called degenerative radiculomyelopathy because of nerve

root involvement.[80]

Immunologic, inflammatory, metabolic, nutritional, oxidative stress, excitotoxic and genetic mechanisms have been explored as underlying the pathogenesis of degenerative myelopathy (DM).[79,81-87] Definitive causal evidence is lacking for most of these mechanisms. An incompletely penetrant autosomal mode of inheritance has been proposed after the identification of a mutation in the superoxide dismutase 1 *(SOD1)* gene in some affected dogs.[85] Familial degenerative myelopathy has been reported in Boxers and Rhodesian Ridgebacks.

Degenerative myelopathy is a primary central axonopathy restricted to the spinal cord that begins in the thoracic spinal cord and ascends and descends along the spinal cord. Axon and myelin degeneration of the spinal cord occurs in all funiculi but primarily in the dorsal aspect of the lateral funiculi and dorsal funiculi. Hence the lesion description is best denoted as a segmental degeneration of the axon and associated myelin rather than Wallerian degeneration.[88,89]

Clinical Signs

The clinical signs are those of chronic thoracolumbar (T3-L3) myelopathy (Video 266-2). Signs start with mild proprioceptive ataxia and paraparesis that slowly progresses, leading to more severe paresis until dogs are non-ambulatory. This progression usually takes 6-12 months in large-breed dogs.[78,79] Lack of spinal hyperesthesia is a typical feature and greatly assists in the differential diagnosis with other compressive myelopathies that occur in older large-breed dogs (such as intervertebral disc protrusion and spinal neoplasia). Proprioceptive deficits are commonly seen in the early disease stages. Spinal reflexes in the pelvic limbs are typically normal to hyperreflexive. Decreased to absent patellar reflexes are found in approximately 10%-15% of patients. This does not necessarily indicate a lower motor neuron lesion, but instead may reflect selective damage to dorsal (sensory) lumbar nerve roots in these dogs. The extensor tone of these dogs is always increased in the earlier phase of the disease, which suggests that the patellar areflexia or hyporeflexia is a sensory, rather than lower motor neuron disturbance. The disease relentlessly progresses, and if the dogs are kept alive it will progress to involve the lumbar and cervical spinal cord regions, as well as the brainstem, causing lower motor neuron deficits, tetraparesis and eventually dysphonia and dysphagia.

Diagnosis

Several large breeds of dogs can be affected with degenerative myelopathy but German Shepherds and Boxers are the most commonly affected breeds. Age of onset of neurologic signs is usually 5 years or older with a mean age of 9 years in large dog breeds. The mean age of affected Pembroke Welsh Corgis was 11.2 years in one study.[84] There appears to be a female predominance (1.6:1) for the disease in Corgis but not in other breeds.[79]

The diagnosis is based primarily on the exclusion of other myelopathies. Spinal imaging (myelogram, MRI, CT) is typically normal, but some dogs may have concurrent mild disc protrusions. The clinician must then consider the duration of clinical signs as well as the findings of the neurological examination to determine the significance of these lesions. MRI is the imaging modality of choice to ensure that all other differentials are ruled out, including intramedullary lesions such as neoplasms.[90] Patients with degenerative myelopathy typically have normal CSF results, or increased protein levels with a normal cell count.[84] A DNA test based on the *SOD1* mutation is commercially available. Dogs that are homozygous for the mutation are at risk for developing DM and will contribute one chromosome with the mutant allele to all of their offspring. The heterozygotes are DM carriers that are unlikely to develop clinical DM but could pass on a chromosome with the mutant allele to half of their offspring.[78] Corticosteroids can be used to assist in the differential diagnosis of this disease. Corticosteroids will typically lead to improvement in dogs with chronic compressive myelopathies (such as intervertebral disc protrusion) but will not benefit dogs with degenerative myelopathy. This strategy might be useful to convince pet owners to pursue advance imaging.[67]

Treatment

No pharmacological therapy has been shown to alter the course of degenerative myelopathy. Vitamin supplementation, glucocorticoid administration, aminocaproic acid, and *N*-acetylcysteine have all been used, but none of these medications showed beneficial effects.[91] The only treatment that has been shown to alter the

long-term course of the disease is physical therapy (see ch. 355).[92] In one retrospective study, dogs with confirmed and suspected degenerative myelopathy had controlled physical therapy, including walking, passive range of motion of the pelvic limbs, massage of pelvic limb and paraspinal muscles, and hydrotherapy. Dogs that were treated with a more intense physical therapy regimen had a mean survival time of 255 days, compared with dogs receiving a moderate regimen (130 days) or no physical therapy (55 days).[92] The long-term prognosis is poor, and most dogs are euthanized due to severe pelvic limb dysfunction within 6-12 months. In the study of Pembroke Welsh Corgis, the average time from diagnosis to death was 1.25 years.[93]

Intervertebral Disc Disease (IVDD)

Etiology and Pathogenesis

The intervertebral discs are interposed in every intervertebral space (except between C1 and C2), uniting the bodies of the adjacent vertebrae.[94,95] Each intervertebral disc consists of an outer laminated fibrous ring (annulus fibrosus) and a central, amorphous, gelatinous center (nucleus pulposus).[96] The nucleus pulposus is highly hydrated gelatinous mesodermal remnant of the notochord.[95] Chondrodystrophic breeds show progressive collagenation and calcification in the nucleus pulposus and inner annulus fibrosus at an early age.[95] The annulus fibrosus consists of bands of parallel fibers that run obliquely from one vertebral body to the next. They provide a means for the transmission of stresses and strains that are required by all lateral and upward movements.[96]

Intervertebral disc degeneration or disease leads to extrusion or protrusion (both termed *herniation*) of disc material into the spinal canal resulting in clinical signs due to spinal cord compression and/or contusion.[94,97] The pathophysiology of the resulting spinal cord injury, which has been well described elsewhere,[97] doesn't always explain the degree of associated neurological dysfunction.[98] IVDD is classified as Hansen type I and type II.[99] Type I IVDD is herniation of the nucleus pulposus through the annular fibers and extrusion of nuclear material into the spinal canal. It is typically associated with chondroid disc degeneration but sometimes a hydrated nucleus pulposus extrusion can be responsible for spinal cord dysfunction.[100,101] The disc extrudes through the dorsal annulus causing ventral, ventrolateral or circumferential compression of the spinal cord. Type I IVDD typically affects chondrodystrophic breeds and has an acute onset. However, large non-chondrodystrophic breeds of dog such as the Doberman Pinscher and Labrador Retriever, may also be affected,[102] particularly when subsequent to trauma.[103] Congenital vertebral malformations result in early degeneration of adjacent intervertebral discs,[104] although clinical disc disease at these sites may not be as common as elsewhere in the spinal column.[105] Long backs, miniaturization and being overweight also increases the risk of type I IVDD.[106] Hansen type II IVDD is annular protrusion caused by shifting of central nuclear material and is commonly associated with fibroid disc degeneration. The annulus fibrosus slowly protrudes into the spinal canal to cause spinal cord compression. The chronic compression can lead to focal ischemic and other microvascular derangements of the spinal cord. Type II IVDD usually occurs at the mobile points of the spinal column and is more common in older, non-chondrodystrophic breeds of dog. It is not uncommon to identify multiple affected disc spaces. Chronic spinal instability may be an underlying predisposition to type II IVDD.

Cervical Disc Disease

Clinical Findings

Most dogs with cervical disc disease, which accounts for 14% to 25% of intervertebral disc disorders in dogs,[107,108] have disc extrusion rather than protrusion.[109] Chondrodystrophoid and other small breeds are at the greatest risk. Dachshunds, Toy Poodles and Beagles have been documented to account for the majority of cases[110]; however, large-breed dogs such as Labrador Retrievers, Dalmatians and Dobermans can be affected with cervical disc extrusions, accounting for up to 24% of all cases.[94,109,111,112] Most affected dogs are between 4 and 8 years of age when they present with clinical signs with a mean age ranging from 6.3 years to 8.6 years; it is extremely rare for dogs less than 2 years of age to be affected.[109-113] Males and females are evenly affected.[110] When large-breed dogs are affected by acute or chronic cervical disc disease, an underlying concurrent malformation and/or instability as part of a CSM syndrome should always be considered (see

CSM section). Most cases of cervical disc disease in chondrodystrophoid dogs occur in the cranial cervical spine, with 80% affecting C2-C4 spaces and 44%-59% affecting C2-C3 alone[107,108]; however, most large-breed dogs are affected at the C6-C7 intervertebral disc space and most protrusions versus extrusions are more caudally located.[109,113]

Approximately 45% of dogs with cervical disc extrusion will have an acute onset of signs, with 55% experiencing a slower onset of signs, whether the dogs are large non-chondrodystrophoid or small breeds.[109] The predominant clinical sign is neck pain, which can be seen in up to 60% of dogs with no neurological deficits and nearly 90% of affected dogs overall.[109,114] Neck pain, evident from the animal's posture or from palpation of the spine and muscles of the neck, can be extreme, unremitting and refractory to medication, which is apparently less likely with hydrated nucleus pulposus extrusions than with other disc-related disease.[101] Nerve "root signature" is another frequent finding with cervical disc disease and can be seen in 22-50% of dogs.[108,114] Neurological deficits may be restricted to one thoracic limb or the animal may show hemiparesis, tetraparesis or even tetraplegia with hypoventilation. Ambulatory tetraparesis is seen in up to 42% of dogs and 11-22% exhibit non-ambulatory tetraparesis.[109,114,115] Tetraplegia is uncommon and has been described in 2-7% of cases.[109] Neurological deficits are more common with lesions at C4-C5 to C6-C7 inclusive, which may reflect the greater degree of space in the cranial vertebral canal compared to more caudally.[116] The reduction or loss of thoracic limb reflexes usually implies a C6-T2 spinal cord lesion; however, 36% of dogs with reduced to absent thoracic limb reflexes actually have a C1-C5 spinal cord lesion.[112]

Diagnosis

Survey radiographs can help to rule out discospondylitis, neoplasia and anatomic malformations, which may be considerations given the clinical signs.[117] Although radiographic signs such as narrowing of the intervertebral disc space and dorsal displacement of mineralized disc material may be highly suggestive of disc extrusion, myelography, CT or MRI is essential for a definitive diagnosis.[117] The overall accuracy rate for correct identification of the site(s) of disc extrusion with radiography is 35%.[117] CSF analysis should be considered to rule out inflammatory disease (see ch. 115). Deviation of the ventral contrast column is the most common myelographic finding of cervical disc disease; oblique views can help with lateralized or foraminal localizations.[118,119] CT performed after myelography can provide more detailed information on the localization of the compressive lesion (Figure 266-6), particularly for lateralized discs and intradural discs.[120,121] MRI is the best method for evaluation of the cervical spinal cord and provides a safe and non-invasive method for obtaining high-resolution images (see Figure 266-6).[122,123] This imaging modality can provide detailed information on the structure of the intervertebral discs and spinal cord and may help with prognosis.[124,125]

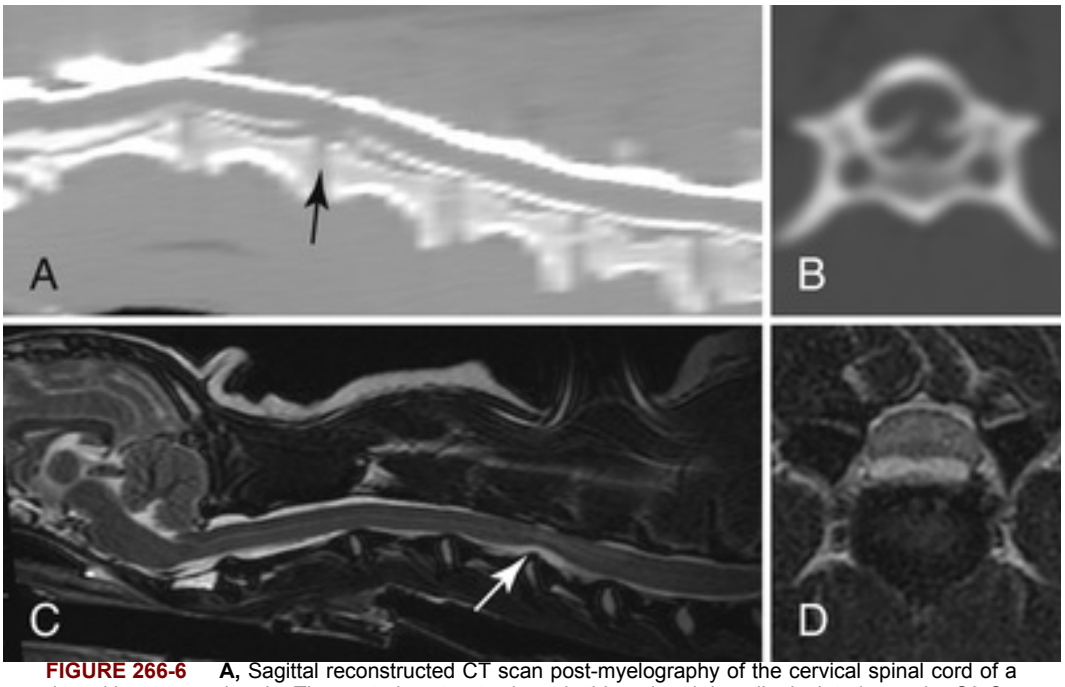

FIGURE 266-6 **A,** Sagittal reconstructed CT scan post-myelography of the cervical spinal cord of a dog with acute neck pain. The ventral contrast column is thinned and dorsally deviated over the C3-C4 disc space (arrow) due to a disc extrusion (type I disease). **B,** The transverse CT-myelographic image at the level of the C3-C4 disc space confirms ventral cord compression. **C,** A sagittal T2-weighted MRI of the cervical spinal cord of a dog with acute tetraparesis. Ventral cord compression can be identified above the C4-C5 disc space due to a hyperintense lesion (arrow). **D,** A transverse T2-weighted MRI at the C4-C5 disc space confirms that the cord is ventrally compressed by a hyperintense structure, which is compatible with acute hydrated nucleus pulposus extrusion.

Treatment

Strict cage rest for 4-6 weeks is the most important aspect of a conservative approach to cervical disc disease. This can be followed by restricted and gradual incremental exercise over the next month using a body harness rather than a collar and leash. The protracted period of rest enables resolution of the inflammation and stabilization of the ruptured disc by fibrosis, preventing further herniation.[94] The use of anti-inflammatory medications such as corticosteroids or non-steroidal analgesics can be recommended for a few days to accompany the rest (see ch. 164). Analgesic medications may be necessary in some dogs in addition or in place of the anti-inflammatory medications (see ch. 126, 166, and 356). The use of acupuncture in dogs with cervical disc disease has been described and was reported to be associated with an initial recovery in 69% of cases (see ch. 356).[126] Muscle relaxants such as diazepam and methocarbamol are useful adjunctive medications in dogs with neck pain related to disc disease. Signs of nerve root involvement such as nerve root signature, or foraminal herniation identified on advanced imaging, may be treated with gabapentin (10-20 mg/kg PO q 8 h). Recurrence rates of 33-36% or more have been reported with conservative approaches.[126-128] A study evaluating 88 dogs with conservatively managed presumptive cervical intervertebral disc herniation found that 49% of cases had a successful outcome, 33% recurred and 18% had therapeutic failure.[128] More chronic disease duration and more severe neurological deficits may result in less success when managed conservatively, as is the case with thoracolumbar disc disease.[128]

The decision to treat surgically is often based on multiple factors. Pertinent criteria include neurological severity, chronicity, whether the signs represent a recurrence, response to medical treatment, systemic health of the patient and owner finances. Symptomatic patients can be divided into three groups: group I, first episode involving neck pain only; group II, repeated episodes of neck pain only; and group III, neck pain and concurrent neurological deficits.[94] Medical therapy can often be recommended for group I dogs. Surgical decompression is most appropriate for group II dogs and is necessary for group III dogs.

When treated with ventral slot decompression alone, complete recovery is observed in up to 90% of dogs at 1 month and 98% of dogs at 12 months following surgery.[114] Long-term follow-up (6 months to 4 years) for ventral slot decompression for caudal cervical disc protrusion in large-breed dogs revealed only a 66%

success rate, and it was concluded that dynamic compressive lesions may need a stabilization procedure.[129] The recurrence rate following surgery for cervical disc disease has been suggested to be approximately 5 to 10%, with a mean time to recurrence being 91 days for all dogs.[109,127] Several significant adverse events have been reported in up to 10% of dogs undergoing ventral slot surgery, which include deterioration in neurologic status, respiratory difficulty, intraoperative hemorrhage and persistent pain.[130]

Thoracolumbar Disc Disease

Clinical Findings

Hansen type I IVDD most commonly occurs within the thoracolumbar region of chondrodystrophic breeds. The thoracolumbar junction (T12-T13 to L1-L2) accounts for the highest incidence of all disc lesions.[131] The incidence of thoracolumbar IVDD progressively decreases from T12-T13 caudally. The most common site for Hansen type I IVDD in large, non-chondrodystrophic breeds is the interspace between L1 and L2[102]; however, German Shepherd Dogs particularly can be affected by discs between T1-T5.[132,133] Onset of neurological signs may be peracute (<1 hour), acute (<24 hours) or gradual (>24 hours). Dogs presenting with peracute or acute thoracolumbar disc extrusions may manifest clinical signs of spinal shock or Schiff-Sherrington postures.[131] These indicate acute and severe spinal cord injury but do not determine prognosis. The degree of neurological dysfunction is variable and affects prognosis. Clinical signs vary from spinal hyperesthesia only to paraplegia with or without pain perception. The incidence rate of focal and ascending/descending myelomalacia has been reported to be as high as 10% in dogs with acute thoracolumbar IVDD and loss of nociception[131,134,135]; the risk of developing this condition may be higher in certain breeds such as French Bulldogs.[105] Severe neurologic dysfunction function is also not an uncommon scenario with acute non-compressive nucleus pulposus extrusions (Hansen type III IVDD, traumatic disc extrusion, high-velocity low-volume disc extrusion) where the extruded nucleus spreads along the epidural space and may completely surround or penetrate the dura mater (Figure 266-7).[136,137] Clinically significant intervertebral disc extrusion has been reported in cats <5 years of age but is more common in middle-aged to older cats.[138,139] Clinical signs due to disc disease in cats may reflect a painful transverse myelopathy at any region of the spinal cord but the probability of clinically significant disc extrusion seems to be higher in the thoracolumbar and lumbar area. Onset of type I IVDD in cats is usually acute.[138]

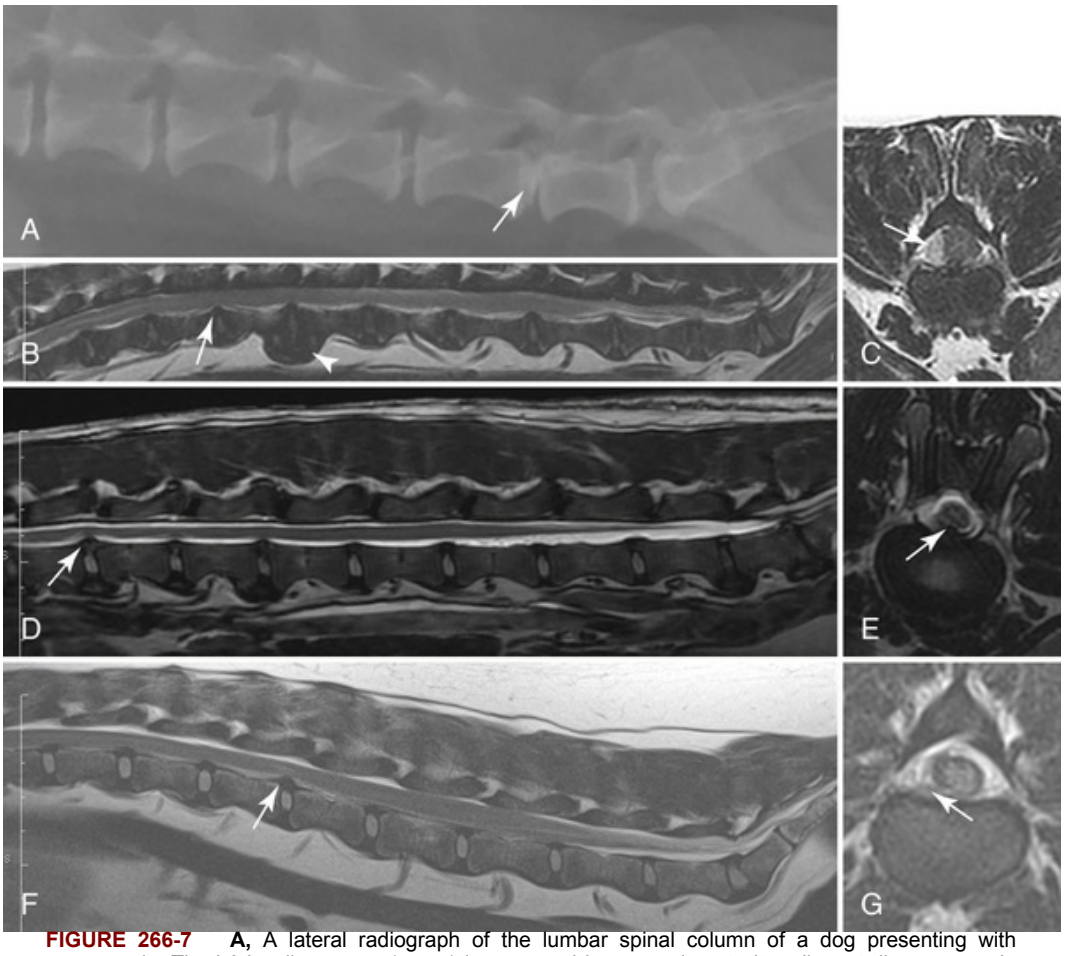

FIGURE 266-7 **A,** A lateral radiograph of the lumbar spinal column of a dog presenting with paraparesis. The L6-L7 disc space (arrow) is narrowed in comparison to its adjacent disc spaces. In addition, the disc appears calcified *in situ* and there is opacity in the intervertebral foramen. All of these characteristics are compatible with intervertebral disc extrusion at this site. **B,** A T2-weighted sagittal MRI of the thoracolumbar spinal column of a dog with acute onset back pain and paraparesis. There is moderate ventral vertebral body bridging spondylosis at L1-L2 (arrowhead). In addition, there is mild ventral deviation of the spinal cord at T13-L1 (arrow), which is not convincing of a lesion that would require surgery. However, marked lateral cord compression can be seen at this site (arrow) on the transverse T2-weighted MRI **(C),** which was due to an acute disc extrusion. **D,** A T2-weighted sagittal MRI of the thoracolumbar spinal column of a large-breed dog with mild paraparesis and ataxia. Ventral cord deviation can be identified at T12-T13 due to annular protrusion compatible with a type II disc lesion. The mild cord deviation can be seen on the transverse T2-weighted MRI **(E),** due to the ventrolateral annular protrusion (arrow). In **(F)** a sagittal T2-weighted MRI of a large-breed dog with acute paralysis again reveals a mild lesion ventral to the cord at L2-L3 (arrow) which appears to be similar to Figure 266-2, *D*. However on transverse T2-weighted imaging at this site **(G),** abnormal signal is present within the epidural pace (arrow) and the cord appears heterogeneously hyperintense. The lesion inside the cord was due to an acute non-compressive nucleus extrusion, often itself associated with trauma.

Diagnosis

The initial diagnosis of thoracolumbar IVDD is obtained from the signalment, history and neurological examination. Survey spinal radiography can help to determine the diagnosis and site of a thoracolumbar disc extrusion if radiographic signs are well-defined and consistent with neuroanatomical localization (see Figure 266-7).[140,141] Studies of dogs with surgically confirmed thoracolumbar IVDD showed that when identifying the site of disc extrusion, survey radiography had an accuracy of 68-72%; but the percentage accuracy was higher with myelography.[131] Longitudinal lesion localization by myelography for thoracolumbar IVDD varies in accuracy from 40% to 97%, but is usually close to 90%.[131] CT or MRI are used alone or as an adjunct to myelography to more completely delineate lateralization of extruded disc material and lesion extent.[97] CT alone has been shown to be more accurate than myelography at identifying the major site of disc herniation and has the advantage of being a more rapid test with fewer side effects than myelography.[142,143] Mineralized

disc material and acute hemorrhage can be identified in the vertebral canal using non-contrast-enhanced CT. Acutely extruded disc material typically is recognized as a heterogeneous hyper-attenuating extradural mass compressing the spinal cord,[144,145] and chronically extruded disc material has a more homogeneous hyper-attenuating appearance. MRI provides a more sensitive technique in recognition of spinal cord pathology, e.g., edema and hemorrhage and three-dimensional delineation of the spinal cord compression allowing for an accurate surgical approach and determining the extent of surgical decompression required (see Figure 266-7).[146] MRI is considered the best method for early recognition of *in situ* disc degeneration based on a decrease in signal intensity within the nucleus pulposus on T2-weighted images and for determining localization and extent of extruded disc material within the epidural space.[147,148] MRI has also been demonstrated to be superior for the assessment of recurrent IVDD.[149]

Treatment

Indications for non-surgical treatment of thoracolumbar IVDD include a first-time incident of spinal pain only, mild to moderate paraparesis and the financial constraints of the client. The latter is the only reason for non-surgical treatment of a recumbent patient, which should always be considered a surgical candidate. Dogs can be managed with strict cage rest for 4-6 weeks combined with pain relief using anti-inflammatory drugs, opioids and muscle relaxants (see ch. 356). Acupuncture also has been advocated as a treatment for pain management. Dogs should be monitored closely for deterioration of neurological status. If pain persists or the neurological status worsens, surgical management is recommended. Studies have shown that recovery rates in non-ambulatory dogs are lower and recurrence rates higher following conservative rather than surgical treatment. Success rates for conservative management of ambulatory dogs with pain only or mild paresis range from 82% to 100%.[131] More recent retrospective studies of conservatively managed dogs with thoracolumbar disc disease documented 30% to 50% recurrence rates in dogs with minimally affected ambulatory status.[131,150] Recurrence of spinal pain in dogs with thoracolumbar IVDD that are conservatively managed usually occurs within 6 months to 1 year from onset of the initial clinical signs. Indications for surgical management of thoracolumbar IVDD include spinal pain or paresis unresponsive to medical therapy, recurrence or progression of clinical signs, paraplegia with intact pain perception and paraplegia without pain perception for <24-48 hours. Prolonged loss of pain perception (>48 hours) carries a poor prognosis and owners should be made aware of this prior to surgery. Surgery includes spinal cord decompression by removal of extruded disc material. Differences in recovery rates of non-ambulatory dogs vary according to the severity of neurological dysfunction (neurological grade), time interval from initial clinical signs to surgery and speed of onset of signs.[131] In ambulatory dogs, an increasing degree of deficits pre-operatively is significantly associated with longer recovery times.[151] Administration of corticosteroids or high-dose methylprednisolone sodium succinate appears to not improve outcome in dogs undergoing surgery for intervertebral disc extrusion but instead has been associated with higher prevalence of gastrointestinal and urinary tract complications, increased hospital stay and owner expense.[97,150] Pain perception is considered the most important prognostic indicator for a functional recovery. In general, the majority of dogs with intact pain perception have an excellent prognosis particularly if treated surgically.[152] Dogs with loss of pain perception for more than 24-48 hours prior to surgery have a poorer prognosis for return of function. A study of 87 dogs with loss of deep pain perception reported 58% of the animals regained deep pain perception and the ability to walk.[134] In general, the prognosis is poor if pain perception does not return within 2 to 4 weeks from time of surgery.[131,134,135] Recurrence of clinical signs after decompressive surgery in dogs with thoracolumbar IVDD is a common clinical entity with incidence rates reported from 2% to 42%.[131] The time for recurrence usually occurs between 1 month and 2 years after surgery. Recurrence of clinical signs within 1 month after surgery is likely related to the original herniated disc space; later recurrence of longer than 1 month after surgery is caused by a disc herniation at a site distinct from the initial extrusion.[131]

Atlantoaxial Instability

Etiology and Pathogenesis

Atlantoaxial (AA) joint instability leads to compression and concussion of the cervical spinal cord resulting from displacement of the vertebrae (subluxation) into the vertebral canal[153]; atlantoaxial subluxation results from a ligamentous and/or osseous abnormality between the atlas (first cervical vertebra) and the axis (second cervical vertebra). The axis has a cranioventral peglike projection called the dens or odontoid process. The

dens lies within the vertebral foramen of the atlas, held down by the transverse ligament, which prevents its movement into the spinal canal but still allows rotational movement. The dens is also attached to the foramen magnum by the apical ligament and to the occipital condyles by bilateral alar ligaments. There is also a dorsal atlantoaxial ligament joining the dorsal arch of the atlas and the craniodorsal spine of the axis.

Atlantoaxial subluxation was first reported in dogs in 1967.[154] Since this time, several congenital and developmental deformities of the AA joint have been documented to cause instability of the vertebral column predisposing to AA subluxation particularly in young, small-breed dogs.[155-158] Possible congenital or developmental anomalies of the AA joint include dysplasia (34% of dogs), hypoplasia or aplasia (46% of dogs), dorsal angulation, and separation of the dens, as well as absence of the transverse ligament.[155,156,159,160] Any abnormality of the dens will predispose to instability of the AA joint due to its important role in the normal stability of this joint; however, up to approximately 24% of dogs with AA subluxation will have a normal dens.[160]

Small breeds of dogs including Yorkshire Terriers, Chihuahuas, miniature Poodles, Pomeranians, and Pekingese are most often affected by the congenital and developmental anomalies that predispose to AA instability and potential subluxation.[159,161,162] This is mainly because the dens is prone to maldevelopment in miniature breeds due to aberrations of physeal growth plate closure. However, atlantoaxial subluxation due to congenital vertebral anomalies has also been reported in large-breed dogs.[163,164] Atlantoaxial subluxation due to congenital vertebral anomalies in cats is very rare.[165-167] Traumatic AA subluxation can occur in any breed and age of dog. Traumatic AA subluxation results from forceful over-flexion of the head, which may tear the ligaments or cause a fracture of the dens or dorsal arch of the axis.[159] Considerable impact may be required to cause such injuries in a normal AA joint and so many times even traumatic AA luxations are associated with an underlying congenital defect and instability of the joint.[159,160]

Clinical Findings

Neck pain is the most common sign associated with AA subluxation, being seen in most dogs with traumatic lesions and 30-60% of dogs with congenital lesions.[159,160,162,168] The associated neurological deficits (see ch. 259) are determined by the degree of damage present in the spinal cord following both the concussion and residual compression. The neurological deficits can range from mild postural reaction abnormalities (56%) to tetraplegia (10%); overall, gait dysfunction has been reported in up to 94% of dogs.[160,168,169] These deficits can appear asymmetrical in addition to appearing worse in either the pelvic limbs or the thoracic limbs. In the rare cases which present with tetraplegia, progression of the clinical signs to a state of clinical respiratory compromise and even arrest is possible.[159]

Diagnosis

Atlantoaxial subluxation can be diagnosed from survey radiographs of the cervical spine although extreme care must be taken when restraining and moving dogs in which this disease is suspected. On lateral radiographs, an increased space can be seen between the dorsal lamina of the atlas and the dorsal spinous process of the axis (Figure 266-8).[153] In severe cases, malalignment of the bodies of the atlas and axis is clearly visible. The presence and size of the dens can be evaluated most accurately on ventrodorsal views; this can also be evaluated well on oblique radiographs.[170] These views are preferable to open mouth views, which place the patient at severe risk of spinal cord trauma. If there is no evidence of subluxation on the lateral views, the neck can be carefully flexed to see if there is instability (the space between the dorsal lamina of the atlas and the dorsal spinous process of the axis should be evaluated). It is preferable to do this with fluoroscopy so that the movement can be monitored to prevent accidental iatrogenic subluxation; this can provide a rapid diagnosis in a conscious dog. CT and MRI can add vital information, which helps with decision making regarding treatment of the individual patient.[171-173] CT can assist with identification of dens conformation, dens or vertebral fracture presence and surgical implant placing.[171,173] Three-dimensional CT reconstruction of the AA joint can add an extra level of understanding to the diagnosis which can assist with surgical decision making. An MRI can provide additional information regarding spinal cord pathology such as hemorrhage or edema and syringohydromyelia that might be important for prognosis (see Figure 266-8).[173,174]

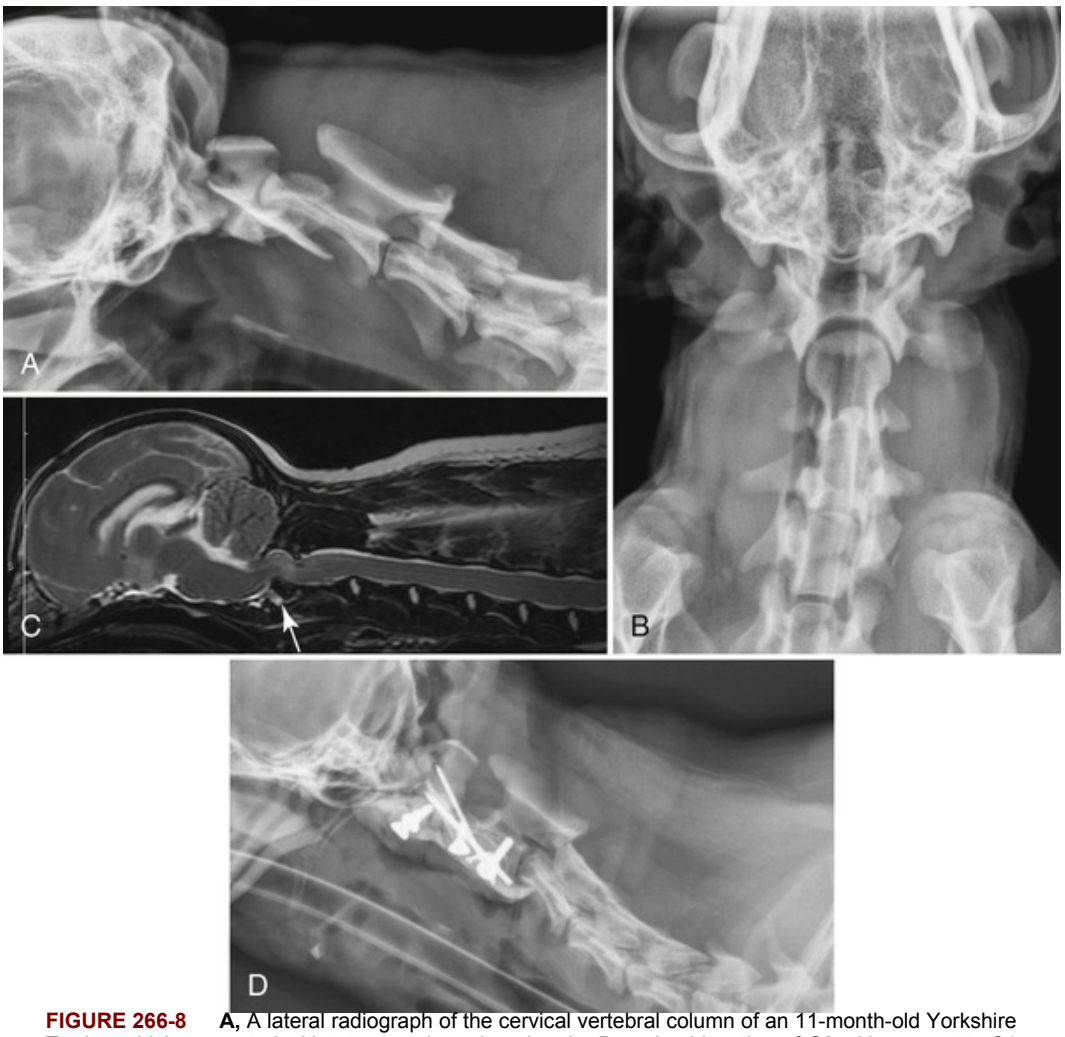

FIGURE 266-8 **A,** A lateral radiograph of the cervical vertebral column of an 11-month-old Yorkshire Terrier, which presented with tetraparesis and neck pain. Dorsal subluxation of C2 with respect to C1 causes an increased space between the dorsal lamina of C1 and dorsal arch of C2. **B,** A ventrodorsal radiograph of the cervical vertebral column of the dog in Figure 266-3, *A*. The joint space between the first and second cervical vertebrae is enlarged and there is no evidence of a dens, a predisposing factor for atlantoaxial subluxation. **C,** A sagittal T2-weighted MRI of the cervical vertebral column of a dog with atlantoaxial subluxation identifies the spinal cord compression associated with the vertebral lesion and an enlarged atlantoaxial joint space (arrow). **D,** A lateral postoperative radiograph of a dog with surgical fixation of the atlantoaxial joint using transarticular pins, vertebral body screws and methylmethacrylate cement.

Treatment

The goal of conservative treatment is to stabilize the AA joint while the ligamentous structures heal.[161] Non-surgical treatment of AA subluxation, including strict cage confinement for 6 weeks, analgesia and a rigid cervical brace, has been successful in some patients; however, non-surgical or conservative approaches are likely to result in recurrent or progressive clinical signs.[161,175,176] The splint must immobilize the AA junction and so the entire wrap must come over the head cranial to the ears and go back to the level of the chest. Complications associated with the use of a splint and neck wrap include recurrence of disease, corneal ulcers, migration of the splint to become ineffective, moist dermatitis and decubital ulcers, hyperthermia, respiratory compromise (dyspnea, aspiration), anorexia, otitis externa and the accumulation of food between the splint and mandible.[161] A good long-term outcome has been documented in 10 of 26 (38%) cases managed conservatively.[161,175,176] Dogs that were affected for less than 30 days were significantly more likely to have a good long-term outcome when managed conservatively, compared with dogs affected >30 days.[161] The goal of surgical treatment is to stabilize the AA joint, thereby preventing further spinal cord damage (see Figure 266-8). Although the surgery will by design reduce the compressive component of the disease, it will not

address any underlying parenchymal disease resulting from the concussion associated with this disease. Surgery should be considered in all dogs as it holds the potential to fuse the AA joint permanently and reduces the chance of catastrophic recurrence. Perioperative mortality rate associated with AA fixation has been reported to be between 10-30%.[160,162] Risk factors affecting surgical outcome in dogs have been identified.[160] Age of onset (<24 months) was significantly associated with greater odds of a successful first surgery and final outcome.[160] Duration (<10 months) and severity of clinical signs was significantly associated with greater odds of a successful final outcome[160]; despite the guarded prognosis for dogs with severe neurological deficits, many dogs that are unable to walk before surgery have a good outcome.[162] Whether a dorsal or ventral procedure is performed does not seem to change the odds of a successful outcome.[160]

Congenital Spinal Column Malformations

Incidental, congenital malformations of the vertebrae are described commonly in several dog breeds such as the Bulldog, and occasionally in cats.[177-179] The defects may be associated with structural abnormalities of the spinal cord, both of which may arise during embryonic or fetal development. Embryonic developmental abnormalities primarily affect formation of the vertebral bodies (e.g., butterfly and hemivertebra predominantly causing scoliosis) while fetal anomalies are more commonly segmentation defects (e.g., block vertebrae and centrum defects predominantly causing kyphosis), but there can be cross-over.[178] Survey radiographs can often detect a vertebral anomaly but advanced imaging such as MRI is necessary to evaluate for associated spinal cord compression or concurrent disease (Figure 266-9). A modified human radiographic classification scheme has been proposed to assist in describing these anomalies,[180,181] while the degree of radiographically calculated spinal curvature has been shown to be associated with the presence of neurological deficits.[182,183] Three-dimensional CT reconstructions can assist with a greater understanding of the vertebral anomaly present in the individual case and in humans CT serves to help classify the underlying anomaly (see Figure 266-9).[178,184]

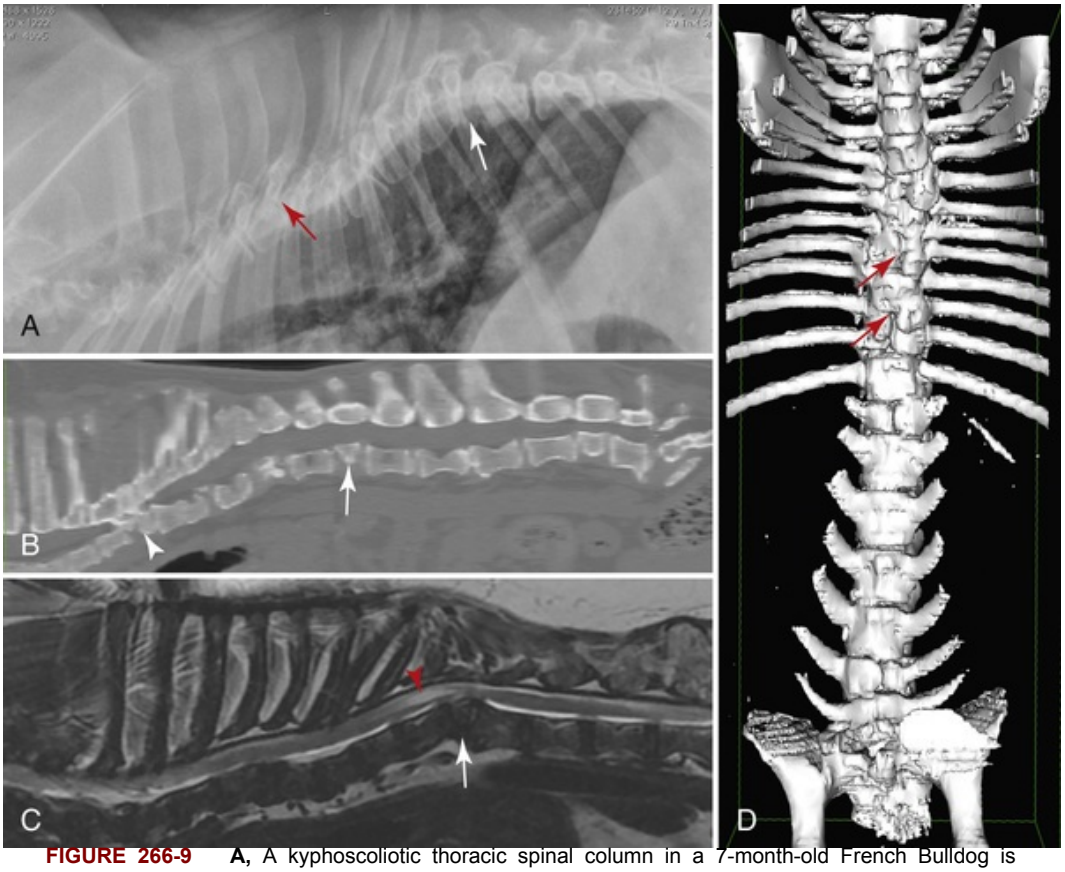

FIGURE 266-9 **A,** A kyphoscoliotic thoracic spinal column in a 7-month-old French Bulldog is

demonstrated on this lateral radiograph, which is due to the vertebral malformations present. The most severe vertebral body abnormalities, compatible with centrum hypoplasia, can be seen to be affecting T10 (white arrow) and T5 (red arrow). **B,** A sagittal CT scan of the thoracolumbar vertebral column of a different French Bulldog makes it easier to discern the shape of the vertebral bodies and infer how they may be affecting the spinal canal. The anomaly affecting L1 (arrow) does not seem to be associated with canal stenosis. The anomalies affecting the cranial thoracic vertebral column (arrowhead) are associated with a significant stenosis. **C,** A sagittal T2-weighted MRI of the thoracolumbar vertebral column of a Pug Dog demonstrates the effect that a vertebral body anomaly (arrow) associated stenosis has on the spinal cord causing compression and a syrinx (red arrowhead) cranial to the lesion. **D,** A three-dimensional reconstructed CT scan of the vertebral column of a French Bulldog helps to identify multiple vertebral body anomalies (arrows).

Butterfly Vertebrae

So named because of their ventrodorsal appearance on a radiograph, they result from failure of formation of the ventral and central portions of the vertebral body.[178,185] These anomalies are most often seen in brachycephalic, screw-tailed breeds and although are often clinically insignificant, they may result in deviation of the column.[178]

Hemivertebrae

These anomalies arise due to the failure of one sagittal half of the vertebra to develop, possibly due to congenital absence of vascularization, and result in a laterally wedged vertebra and scoliotic angulation.[178] They are most commonly described in French and English Bulldogs and Boston Terriers, although other breeds can be affected.[183] They are thought to be heritable in English Bulldogs, Yorkshire Terriers and German Shorthaired Pointers as an autosomal recessive abnormality.[186] Most affected vertebrae are located between T5-T9 but they could arise in any location.[183,187] Hemivertebrae are not associated with severe canal stenosis; spinal cord compression, however, results more from associated kyphosis and subluxation.[183] In addition, at the site of the anomaly it is not uncommon to find concurrent disc herniation and/or an arachnoid diverticulum, both of which could be responsible for neurological signs. Although hemivertebrae may be clinically insignificant, when they are associated with clinical signs, the signs are referable to their neuroanatomical location and occur at a very young age or late into adulthood.[183,187] Surgical realignment and stabilization rather than a dorsal laminectomy alone has been advised in clinical cases with the prognosis being good to guarded.[183,188]

Centrum Hypoplasia

Centrum hypoplasia or aplasia results in variable (bilateral or unilateral) loss of the vertebral body, resulting in a degree of scoliosis.[178] The degree of spinal column deviation that results is related to the severity of the defect and the number of vertebrae affected. This defect is said to be distinct from a hemivertebra, albeit potentially appearing similar on a radiograph and resulting from the same hypothetical etiologies in the same screw-tailed breeds. Although these defects are present at birth, associated clinical signs may not be apparent until 10 months of age,[189] at which time they can appear acute or chronic in onset; clinical signs at a later stage in life may be due to an association with a concurrent condition such as disc disease.[178]

Block Vertebrae

This defect results from partial or total fusion of two vertebrae at any point. They may be associated with angulation of the spinal column, atlantoaxial subluxation and or disc disease.[158,190]

Articular Facet Aplasia

Abnormalities of the articular process or facet of the vertebrae may result from dysgenesis of the two neural arch ossification centers or abnormal development of secondary ossification centers.[191] Frequently located between T1-T9 and asymptomatic, they have been occasionally reported caudal to this region and associated with vertebral canal stenosis.[191-193]

Transitional Vertebrae

Found at the junction between two structural divisions of the spinal column (e.g., thoracolumbar and lumbosacral), transitional vertebrae are congenital vertebral anomalies that share characteristics of both divisions. The most common abnormality is the presence or absence of a costa or transverse process, often asymptomatic and described in both dogs and cats.[178] Similar to block vertebrae, these anomalies can be associated with disc disease, which has been well described at the lumbosacral junction in German Shepherd Dogs.[194-196]

Meningomyelitis

Meningomyelitis is defined as inflammation of the spinal cord parenchyma and surrounding meninges. It is relatively uncommon for it to be present without encephalitis; a retrospective review of 220 dogs with inflammatory central nervous system (CNS) diseases revealed that only 41 had focal spinal cord involvement.[197] Canine distemper virus (see ch. 228) and protozoa (see ch. 221) have been the most commonly identified infectious causes, while steroid-responsive meningitis-arteritis is often the most frequently recognized probable non-infectious inflammatory disease process.[197] Rickettsiae, fungi, bacteria, helminths and meningitides of unknown etiology (MUE) such as granulomatous meningoencephalomyelitis are other reported causes of meningomyelitis in dogs.[198-204] However, in many cases the underlying disease process remains undetermined. A review of 28 dogs with meningomyelitis revealed that MUE was the most common diagnosis and that hound and toy breed dogs less than or equal to 3 years of age had a 13 times higher odds of meningomyelitis compared with other breeds.[205]

The clinical signs associated with meningomyelitis reflect the region of the CNS involved and can include paraspinal hyperesthesia, general proprioceptive ataxia and limb paresis or paralysis. Definitive diagnosis of inflammatory CNS disease requires histopathology but can be presumptively diagnosed using a combination of CSF analysis (see ch. 115), advanced imaging and infectious disease testing (see ch. 207). The prognosis is presumed to be specific to the underlying disease process and severity of clinical signs.[205] For a more detailed description of inflammatory CNS diseases, the reader is referred to ch. 261.

Steroid-Responsive Meningitis-Arteritis (SRMA)

Etiology and Pathogenesis

An immunological cause of this disease is suspected, resulting in a vasculitis, although no specific trigger factors have been identified.[206,207] Notably, increased levels of CSF and serum immunoglobulin A (IgA), increased CSF and blood B-cell/T-cell ratios, and CSF interleukin (IL)-6 and IL-8 levels are all thought to be compatible with immune system stimulation.[208-210] High CD11a expression on polymorphonuclear cells appears to be an important factor in the pathogenesis of SRMA and may be involved in the enhanced passage of neutrophils into the subarachnoid space, leading to meningitis and clinical signs.[211] Matrix metalloproteinase (MMP)-2 seems to also be involved in the neutrophilic invasion into the subarachnoid space.[212] Involvement of such molecular markers provides a potential therapeutic target. With chronic progression of the lesions, rupture and hemorrhage of the weakened vasculature may be present accompanied by thickened leptomeninges with less severe inflammation.

Clinical Findings

SRMA, also termed necrotizing vasculitis, juvenile polyarteritis syndrome, corticosteroid-responsive meningitis/meningomyelitis, aseptic suppurative meningitis, panarteritis and pain syndrome, is reported in Beagles, Bernese Mountain Dogs, Boxers, German Shorthaired Pointers, Border Collies, Jack Russell Terriers, Weimaraners and Nova Scotia Duck Tolling Retrievers,[207,213,214] but is noted and probably occurs in other medium to large dog breeds. Affected dogs are often young adults (8-18 months old) but may be of any age, and are usually febrile and hyperesthetic, with cervical rigidity and anorexia. Neurological deficits can be seen in the chronic form of this disease and rarely severe motor dysfunction may result from spontaneous bleeding into the subarachnoid space.[213] Some dogs (up to 46%) with immune-mediated polyarthritis (see ch. 203), especially Bernese Mountain Dogs, Boxers and Akitas, may show similar clinical signs to dogs with SRMA and have concurrent meningitis (see ch. 261).[215]

Diagnosis

A marked peripheral neutrophilia with a left shift may be seen at the time of the clinical signs. CSF (see ch. 115) often reveals a marked neutrophilic pleocytosis and protein elevation; cell counts of >100 cells/mcL are common. Neutrophils are non-degenerative, unlike bacterial meningitis. In the majority of dogs with either acute or chronic disease, there are elevations of IgA levels in the CSF and the serum, although this is not specific for this disease. IgA CSF concentrations are significantly higher in dogs with SRMA compared to other disease categories, with the exception of inflammatory CNS disease, and so are considered nonspecific. The sensitivity for IgA concentrations in serum and CSF was 91% with a specificity of only 78% when evaluated in 311 dogs with SRMA.[216] C-reactive protein (CRP) is the primary major canine acute phase protein (APP) and has been shown to be immediately responsive to both inflammation and its resolution; other APPs include serum amyloid-A (SAA), haptoglobin and alpha-1-acid glycoprotein (AGP). Serum CRP has been shown to be significantly higher in dogs with SRMA in comparison to dogs with other neurological diseases.[217] Results of a recent study of 9 dogs with SRMA demonstrated a significant increase of all serum APPs above normal concentrations, which all decreased, apart from haptoglobin, in response to corticosteroid treatment.[218] Serum CRP and SAA were also found to be consistently elevated in all patients exhibiting signs consistent with a relapse during treatment in the presence of normal CSF and leucograms. However, much like IgA, elevations of CRP are considered to be nonspecific, are elevated in sepsis, and so can only be used as a supportive diagnostic test.[219]

Treatment

The prognosis can be good if dogs are treated early and aggressively with immunosuppressive doses of corticosteroids (see ch. 165), with up to 80% of cases going into a long-term remission.[220,221] Infectious diseases should be ruled out before this treatment is initiated. The treatment is long-term, and has been reported to be required for over 2 years in some dogs; however, after this time, serum and CSF IgA levels were still elevated in some dogs so these titers are not considered valuable for disease monitoring.[221] Monitoring of CSF cell count in dogs with this condition is a sensitive indicator of success of treatment. In refractory cases or in patients having steroid-related side-effects, alternative immunomodulation therapy should be considered, such as azathioprine.

Discospondylitis

Etiology and Pathogenesis

Discospondylitis is due to infection of the intervertebral disc and adjacent vertebral endplates; if the infection is confined to the vertebral body, it is called vertebral osteomyelitis or spondylitis.[222] Coagulase-positive *Staphylococcus* spp. (*S. pseudintermedius* or *S. aureus*) is the most common etiological agent associated with canine discospondylitis[213]; other less commonly identified organisms include *Streptococcus* spp., *Escherichia coli, Actinomyces* spp. and *Brucella canis,* as well as *Aspergillus* spp. Young German Shepherd bitches seem to be predisposed to aspergillosis (see ch. 234),[223] whereas young Basset Hounds contract discospondylitis due to systemic tuberculosis (see ch. 212).[224] Hematogenous spread from distant foci of infection (urogenital tract, skin, dental disease), penetrating wounds, surgery,[225] or plant material migration can cause direct infection of the disc space or vertebrae, the latter of which is usually seen at the level of L2-4 at the insertion of the diaphragmatic crus. The most commonly affected sites are L7-S1, caudal cervical, mid-thoracic, and thoracolumbar spine.[213] The infection is usually slowly progressive but can result in acute signs due to secondary pathological vertebral fractures and intervertebral disc disease. An association with empyema has been documented in several dogs, which may represent an extension of the disease and should be considered when selecting diagnostic tests and/or when dealing with a refractory case.[226-228]

Clinical Findings

Spinal pain is the most common initial clinical sign in this disease, which is most frequently seen in large intact male young to middle-aged dogs.[229] With proliferation of inflammatory tissue, compression of neural tissue can lead to ataxia, paresis and occasionally paralysis dependent on where the lesion is located. Approximately 30% of dogs have signs of systemic illness such as fever and weight loss.

Diagnosis

Hematological changes are usually not present unless there are concurrent conditions such as endocarditis (see ch. 251). Urine cytology may reveal bacterial or fungal agents (see ch. 72). Blood and urine cultures should be performed in all suspected cases and are positive in up to 75% and 50% of cases, respectively (see ch. 207).[213,222] Ideally these should be performed prior to initiating antibiotic therapy. Serology for brucellosis should also be performed, especially in view of its zoonotic potential (see ch. 213); this has been reported to be positive in up to 10% of cases. Definitive diagnosis is usually made with spinal radiographs (Figure 266-10), although radiographic change may not be evident in the first 2-4 weeks of infection. The most commonly affected site is L7-S1, but other frequently affected sites include the caudal cervical/cranial thoracic vertebrae and the thoracolumbar junction. As this can be a multifocal disease, the entire spine should be radiographed. Radiographic evidence of disease includes narrowing of the disc space, accompanied by subtle irregularity of both endplates through to gross lysis and osseous proliferation of the adjacent vertebral bone and even fractures. Radiography can also be used to monitor the response to treatment or the progression of the disease,[230] although clinical progression is equally important, as radiographic change can lag behind clinical improvement. Myelography used to be recommended in patients with substantial neurological deficits to rule out concurrent disc disease and subluxation affecting the neural tissue; however, this should be reserved for when neither CT nor MRI is available. A study of 27 dogs with discospondylitis found that contrast-enhanced radiographs revealed only a 5% median cord compression in the dogs that was not related to clinical signs or outcome.[231] CT can identify subtle endplate erosion and paravertebral soft-tissue swelling more readily than radiography. Post-myelogram CT clearly defines compression of the neural tissues by infected tissues, as does MRI. Discospondylitis appears to have increased signal intensity on T2-weighted images and decreased signal intensity on T1-weighted images, changes also seen in the paravertebral tissues in all cases.[232,233] Contrast enhancement was seen in the endplates of affected vertebrae in 15 of 17 (88%) of sites in one study as was endplate erosion and T2-hypointense bone marrow. MRI can also highlight the inflammation in the surrounding muscles (see Figure 266-10).

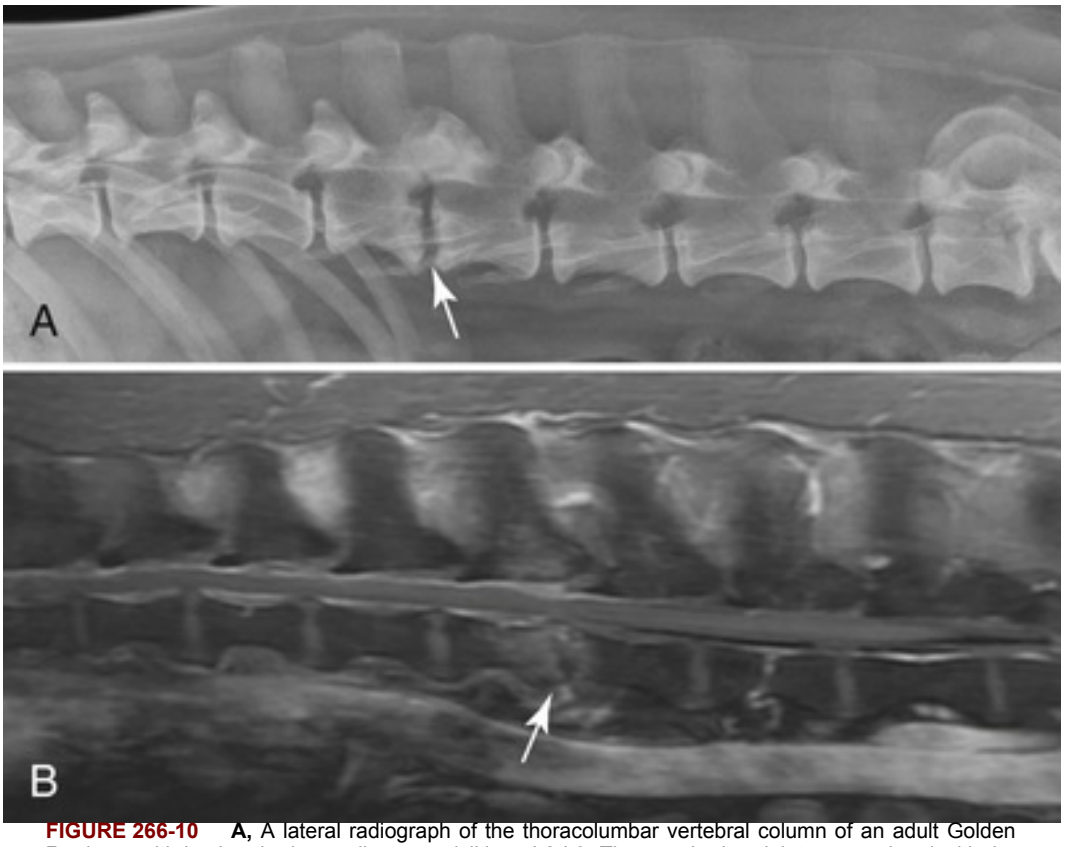

FIGURE 266-10 **A,** A lateral radiograph of the thoracolumbar vertebral column of an adult Golden Retriever with back pain due to discospondylitis at L2-L3. The vertebral endplates associated with the L2-L3 intervertebral disc space (arrow) are irregular due to lysis and osseous proliferation. **B,** A sagittal T1-weighted post-contrast MRI of the thoracolumbar vertebral column depicted in Figure 266-5, *A*

reveals contrast uptake (hyperintensity) within the vertebral body and dorsal spinous process of L1 and associated with the endplates of L1 and L2 (arrow). Soft-tissue proliferation and spread of infection into the epidural space secondary to the discospondylitis is associated with a slight narrowing of the spinal cord above the disc space.

Treatment

The initial treatment of discospondylitis consists of antibiotics (potentiated amoxicillin or cephalexin), cage rest and analgesics. Intravenous antibiotics should be considered if severe neurological compromise or signs of sepsis are present; otherwise, oral antibiotics are acceptable. However quickly the patient improves, continuation of the antibiotics for 8-16 weeks is recommended, although one study evaluating 513 cases noted a mean duration of treatment as 54 weeks.[213,222,229] Resolution of clinical signs, such as pain and fever, should be expected within 5 days of initiating therapy; however, complete neurological resolution may take 2-3 months. Residual deficits may remain, but persistent pain indicates an active disease, and these patients should be treated with an additional antibiotic and considered for further diagnostics as they may have a potential fungal infection or surgical lesion. Discospondylitis associated with *Aspergillus* spp. has been treated with itraconazole (5 mg/kg of body weight, PO, q 24 h) although long-term reports of success are lacking with the belief being that chronic recurrence and progression is likely (see ch. 234). The prognosis for this disease is generally very good unless the etiology is fungal, there are multiple lesions, vertebral fracture or subluxation occurs or there is endocarditis; the potential for recurrence should be considered, especially if brucellosis has been diagnosed or an underlying immunosuppressive condition is present.

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CHAPTER 267

Spinal Cord Diseases

Traumatic, Vascular, and Neoplastic Disorders

Nicholas Jeffery

Client Information Sheet: Fibrocartilaginous Embolization

Mechanisms of Spinal Cord Dysfunction

Traumatic, vascular and neoplastic disorders may seem unrelated, but each causes spinal cord dysfunction primarily by impairing blood flow. Acute impact trauma and vascular interruption cause instantaneous compromise of blood flow that triggers a secondary series of autodestructive events within the spinal cord, forming a sharp contrast to the slow, progressive, compression of blood vessels and attenuation of circulation generally associated with neoplastic lesions. Pure impact injury may cause little immediate damage to the spinal cord, such as a few severed axons and focal hemorrhage, but this cannot be used to predict the severity of subsequent destructive events.[1]

Functional consequences of impact injury usually arise because trauma initiates a cascade of molecular reactions culminating in severe microcirculatory impairment that causes cellular apoptosis, tissue necrosis and progressive damage over 3-7 days.[2,3] Almost complete cross-sectional destruction can occur, although the extent of damage is clearly related to severity of the initial injury.[4,5] Extent of injury is mediated in large part by inflammatory mediators. The loss of circulation leads to secondary consequences caused by lack of oxygen and lack of glucose. Ultimately, the depolarization of neurons and axons allows accumulation of calcium as a key secondary messenger that will activate many autodestructive enzymes, notably calpains, caspases and xanthine oxidase.[2] Similar events follow primary vascular lesions, but usually with more limited spatial effects because affected vessels are often of narrow diameter with small regions of distribution. They also differ in that external trauma can be associated with prolonged compression. For example, displaced vertebral fractures may further compromise blood flow.

The mechanisms underlying the tissue destruction associated with chronic compression of the spinal cord are less well understood. There is evidence of impaired microcirculation.[6,7] Neoplastic lesions usually cause progressive compression of the spinal cord over a period of weeks to months. Initially, blood flow remains sufficient to preserve adequate spinal cord function but, eventually, a "tipping point" is reached, at which the compression becomes too severe to allow compensation and clinical signs then rapidly progress.

Diagnosis of Spinal Cord Lesions

Introduction

The initial approach to nervous system disease is to attempt to localize the problem using the physical neurologic examination (see ch. 259). With this information, one can then consider the possible causes of a lesion at that site in the context of the signalment and history. The rate of onset and degree of progression or regression of clinical signs is important. This approach is used for localizing traumatic, vascular or neoplastic spinal cord diseases. Crucially, either traumatic or neoplastic disease can be associated with spinal pain without evidence of neurologic deficits. In such cases, careful observation and gentle palpation may aid in localizing the lesion site, although observations can be misleading in anxious or stoic animals. Sometimes an accurate assessment can be assisted by in-clinic observation during a period of 24 hours or longer.

History

Listening carefully and evaluating owner observations can be critically important for developing an "index of suspicion" for specific types of spinal cord lesions. Historical and signalment information are crucial.[8] In people, it has been estimated that ≈80% of diagnoses are derived from history alone, although the species aspect of "signalment" is a given in humans.[9]

Differential Diagnosis

In general, traumatic lesions may have few differential diagnoses. Clinical signs in pets with vascular lesions are usually highly obvious.

Diagnostic Testing

Most traumatic, vascular and neoplastic diseases require imaging to confirm localization and suggest an etiology, although the precise diagnosis is usually dependent upon histologic examination. Inflammatory disease can be identified using cerebrospinal fluid (CSF) analysis, but it is rare for this to be a reasonable first diagnostic test because of associated risks (e.g., exacerbated hemorrhage, spread of tumor cells) and images are often required to aid interpretation of the results. For instance, raised CSF protein is a non-specific finding that is commonly, but not invariably, associated with spinal cord compression.[10,11] Radiography and computed tomography (CT) are excellent modalities for diagnosing lesions affecting vertebrae but provide poor detail of the spinal cord itself. Magnetic resonance imaging (MRI) scans are preferred for diagnosis of spinal cord lesions and MRI can also be used in detecting ligamentous injuries. MRI has the drawback of providing relatively poor bone detail, and can be expensive and time-consuming. CT and MRI scans can be regarded as complementary, but in veterinary medicine one is often selected dependent on whether the lesion is suspected to be bony or soft-tissue (especially affecting the spinal cord). This decision is usually made bearing in mind the nature of the inciting injury (e.g., external trauma), the severity of the lesion, the need to diagnose a lesion for subsequent surgical intervention and whether the animal shows evidence of pain (which tends to suggest skeletal involvement). Animals in which a vascular lesion is suspected would be initially imaged with MRI because such lesions are not visible using other modalities (Table 267-1).

TABLE 267-1

Ability of Imaging Modalities to Detect Lesions of the Spinal Cord and Vertebral Column

LESION TYPE	RADIOGRAPHS	CT	MRI
Traumatic			
Fracture-luxation	+	++	+
Disc extrusion	−	±	++
Vascular (any type)	−	−	++
Neoplasia			
Extradural	±	±	++
Intradural/extramedullary	−	−	++
Intramedullary	−	−	++

CT, Computed tomography; *MRI*, magnetic resonance imaging.

Treatment

Overview

Categories of disease in this chapter have extremely varied etiologies and prognoses. For instance, traumatic lesions may require demanding surgical stabilization (e.g., unstable fracture-luxations; Figure 267-1), but conservative (e.g., stable fractures) or non-specific (e.g., peracute disc extrusion) supportive care, such as cage rest, is sometimes recommended. Primary vascular lesions that cause spinal cord damage are generally not

responsive to therapy by the time affected animals are diagnosed. This does not imply a hopeless prognosis because many injuries are incomplete and those animals recover function as inflammation resolves and plastic alterations in circuitry supervene.[12] Neoplastic lesions also show extreme variability in prognosis; some cases are hopeless with or without treatment (e.g., disseminated metastases of hemangiosarcoma), whereas other affected animals may be expected to live for several years (e.g., multiple myeloma[13]).

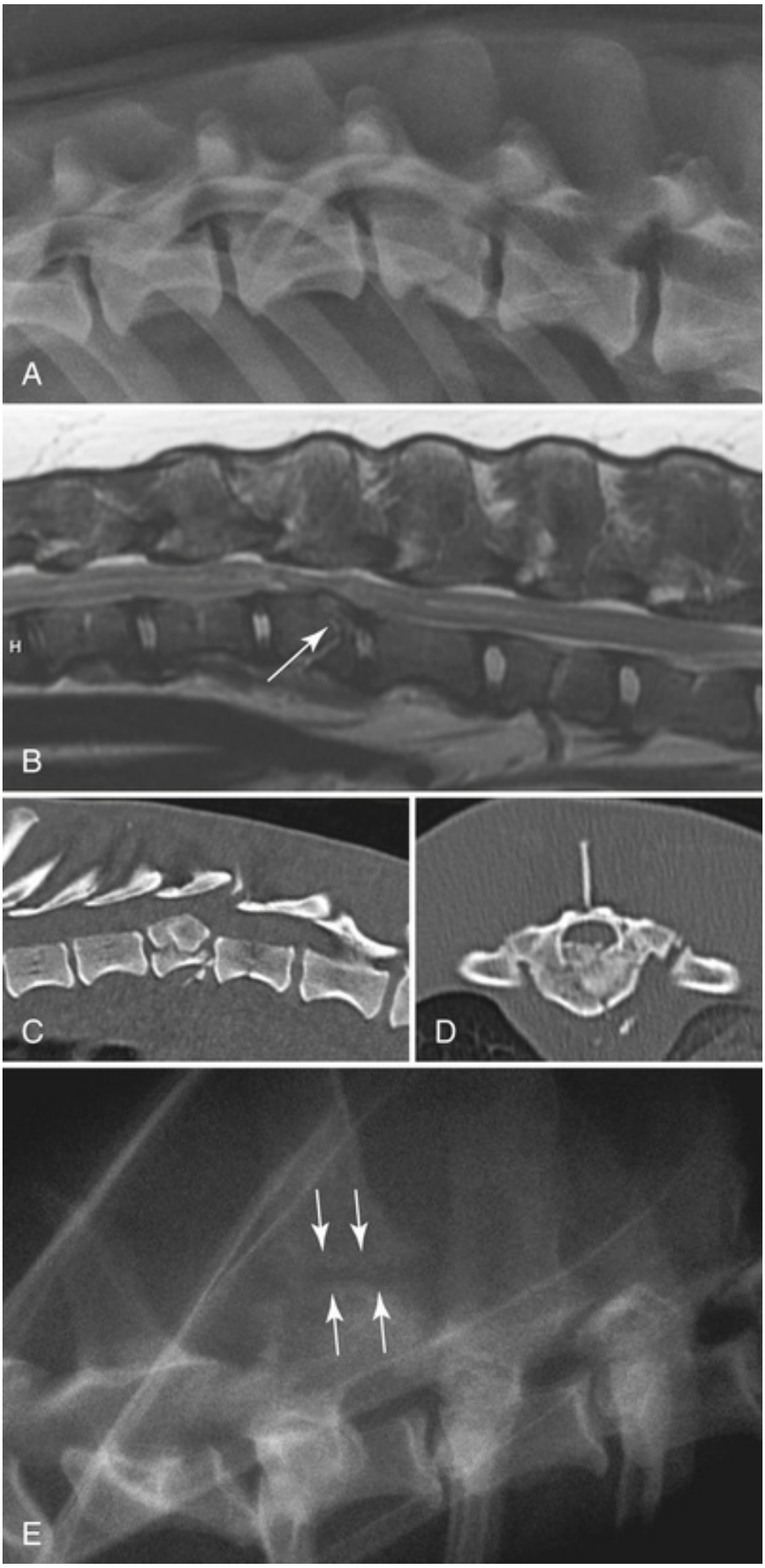

A
B
C
D
E

FIGURE 267-1 Thoracolumbar vertebral fracture-luxations frequently cause instability that threatens spinal cord integrity and often requires surgical stabilization. **A,** Fracture of caudal aspect of L1 vertebra clearly visible using radiography alone. **B,** T2-weighted sagittal MRI scan also shows the fracture (arrow) and reveals detail of the spinal cord injury. **C,** Sagittal reconstructed CT scan reveals excellent detail of a T13 vertebral fracture in another dog. **D,** Corresponding transverse CT image reveals the extent of vertebral canal compromise associated with this "burst" fracture, probably resulting from compression along the long axis of the vertebral column. **E,** Pathological fracture of the spinous process of T1 vertebra (arrows). This lesion did not cause neurologic deficits but was associated with severe pain.

Corticosteroids

The role of corticosteroid therapy in traumatic and vascular spinal cord lesions is a source of persistent controversy.[14] For decades, physicians and veterinarians have used corticosteroids, often at high dosages, to reduce the functional and pathologic consequences of acute spinal cord insults. Despite the positive effects of corticosteroids that are sometimes reported in laboratory research, positive results have not been duplicated in clinical studies.[15] Initial reports on the use of high-dose methylprednisolone sodium succinate in human spinal cord injury suggested a benefit,[16] but this has since been disputed and the current consensus is that corticosteroids are not helpful in ameliorating acute spinal cord insults.[17] Further, corticosteroid use is detrimental in head trauma, perhaps because it reduces muscle mass and is immunosuppressive.[18]

However, corticosteroids often have a dramatic alleviating effect on the neurologic deficits associated with (prolonged) central nervous system (CNS) compression by reducing blood vessel permeability and reducing edema in the vicinity of the compressive lesion.[14] Although this can be helpful from the perspective of an owner and the pet, steroids may obscure both functional and imaging information. Indiscriminate corticosteroid administration can also expose animals to an unnecessary risk of detrimental side effects such as immunosuppression.

Traumatic Diseases

Signalment and History

No specific signalment need be associated with traumatic injury, but it is well-recognized that young, especially male, animals tend to be overrepresented. The history may be of greatest value in raising suspicion of traumatic lesions. There is almost always an acute onset of clinical signs and often the traumatic event has been witnessed. The exceptions are few, but animals that sustain vertebral fracture-luxations occasionally do not exhibit neurologic signs immediately after the incident but, with time, vertebrae in the affected region may become displaced, producing signs of neurologic deterioration and pain. This seems to be particularly prevalent in association with lesions of the upper cervical region, specifically the atlanto-axial region, and at L7/S1 (although lesions at this level do not affect the spinal cord). Although external trauma causing symptomatic spinal lesions is usually severe, some animals develop signs of spinal cord injury after what was considered minor trauma; e.g., dogs with congenital atlanto-axial subluxation who develop clinical signs after trivial trauma, such as hitting their head on the underside of furniture when rising from recumbency.

Presentation and Immediate Management

Vehicular impact or falls from height are the most common causes of vertebral column traumatic lesions that cause obvious neurologic deficits. However, some pets only have signs of poorly localized pain. Importantly, some animals may present in circulatory shock so that neurologic examination is not immediately reliable because poor CNS perfusion can cause temporary neurologic deficits. For this reason, it is imperative to re-examine affected animals at frequent intervals to determine whether neurologic status is changing. When first examined, it may be tempting to attend to striking neurologic injuries first, but it is important to prioritize treatment according to the ABC (airway, breathing, circulation) system (see ch. 147).[19] On the other hand, it is crucial to be cognizant of the possibility of neurologic injury, specifically fracture-luxation. This is especially true of animals that have nonspecific pain, because careless handling can lead to inadvertent further injury. It is important not to move animals more than absolutely needed if presented recumbent after major external trauma. It is often sensible to take radiographs of the vertebral column at an early stage, even sometimes prior to full neurologic examination, so as to identify sites which may be at risk of iatrogenic injury. In animals in which a single spinal fracture-luxation has been identified, it is essential to consider the possibility that there

could be additional lesions in the vertebral column which may not be producing such obvious clinical signs.[20] Therefore, it is frequently prudent to obtain radiographs or, better still, CT images, of the entire vertebral column.

Diagnostic Testing

For almost all pets known to have suffered trauma, imaging results are a critical decision-maker. Thoracic radiographs are always indicated because pneumothorax (see ch. 149 and 244) and pulmonary hemorrhage (see ch. 149 and 242) are common. Plain radiographs of the vertebral column function best as "rule-in" rather than "rule-out" tests, because many traumatic lesions, even those affecting the vertebrae or, indeed, the vertebral canal itself, can be overlooked. CT is indicated in animals in which a lesion of the skeletal structures is still suspected—for instance those exhibiting severe spinal pain despite negative findings on radiography. However, some traumatic lesions may not be apparent despite use of CT. MRI scans are excellent for detecting traumatic lesions within the spinal cord, although they provide less precise definition of bone contours.

Specific Diseases

Differential Diagnosis

Traumatic lesions have few differential diagnoses, particularly if the trauma was observed. Trauma should also be considered as a possible explanation for any animal with acute clinical signs indicative of spinal cord injury, whose major differential diagnoses are intervertebral disc herniation or vascular lesions of the spinal cord. Although inflammatory disease can theoretically cause acute clinical signs, it is not common for them to develop as quickly as occurs after trauma. Trauma may be overlooked as a possible cause, especially in animals with acute signs of lethargy or obtundation (which may indicate pain).

Vertebral Fracture-Luxation

The most commonly observed result of external trauma is fracture or luxation of vertebrae.[21] Unless such lesions affect the vertebral canal they will not cause clinical signs indicative of *spinal cord* injury (although spinal *nerves* may be affected). All patients exhibit pain. In most cases, subluxation is caused by part of a vertebra fracturing, but there can be simple subluxations resulting from ligamentous injury alone, most notably in the cranial cervical region (Figure 267-2). Treatment of vertebral fracture-luxations depends largely upon the severity of the clinical signs, an estimate of "stability," and lesion location.[21] It is critical to determine if the "deep pain" response is intact, because this provides the most accurate prognostic information (see ch. 259). It is important to remember that animals in circulatory shock may have temporarily dulled pain responses.

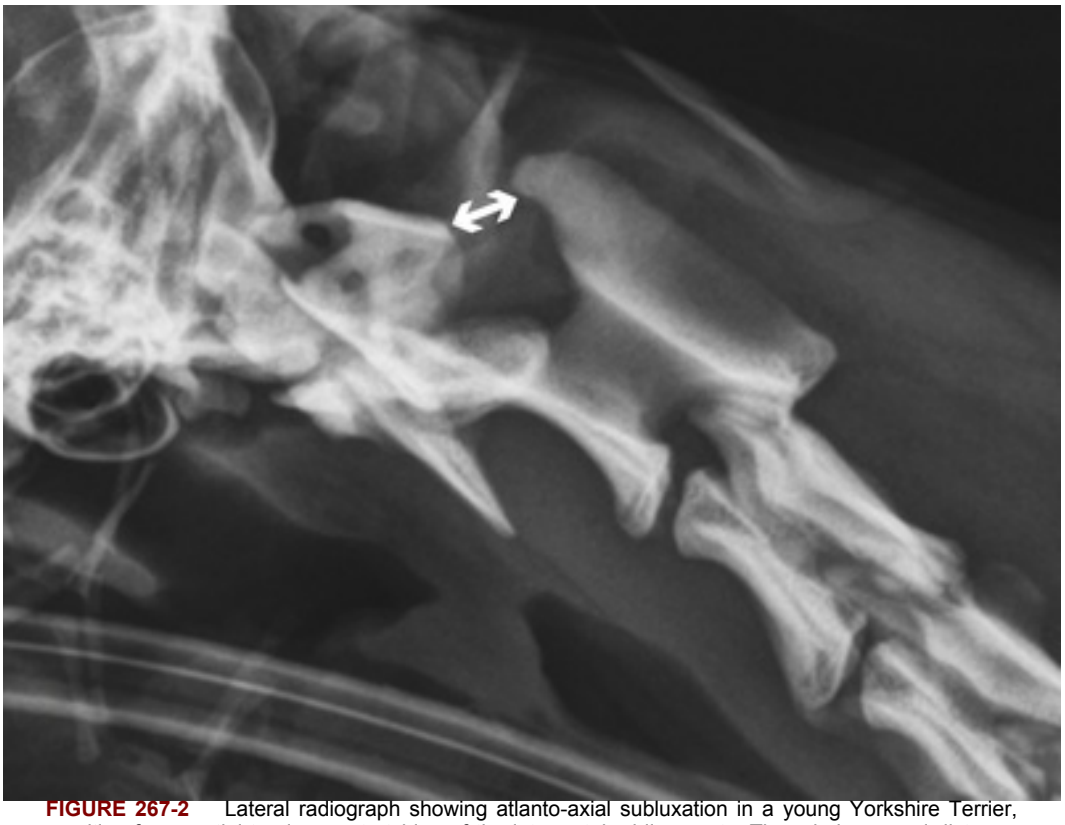


FIGURE 267-2 Lateral radiograph showing atlanto-axial subluxation in a young Yorkshire Terrier, resulting from partial tearing or stretching of the intervertebral ligaments. There is increased distance between the arch of the atlas and the cranial tip of the spinous process of the axis (arrows). This sign must be interpreted with caution because it can also be observed to some extent in apparently normal dogs.

Treatment options for spinal fracture-luxations can vary greatly. For instance, ambulatory animals displaying mild neurologic deficits in the pelvic limbs associated with inherently stable fractures of the thoracic vertebrae may not require surgical intervention and may recover with simple restriction of exercise while the lesion heals. In contrast, an animal with paraplegia (but intact pain sensation) caused by a fracture of a lumbar vertebral body would be a good candidate for surgical stabilization. Treatment of vertebral fracture-luxations is the subject of many reviews.[21] Decision-making can be aided by thinking of the vertebral column as a series of three sagittal columns running through its entire length. If two of the three columns are interrupted by the lesion it suggests instability, providing a strong indication for internal fixation. The magnitude of subluxation at the injury site is not often a good guide to prognosis because the position of the skeletal elements during imaging may not adequately reflect the extent of motion during the injury process.

Traumatic Disc Extrusion

Occasionally, animals (especially dogs) that have suffered external trauma to the vertebral column will have signs of severe spinal cord injury yet no obvious evidence of vertebral fracture-luxation. In some, there will be apparent intervertebral disc space narrowing. With use of MRI, many of these patients can be demonstrated to have collapsed disc spaces associated with escape and dorsally-directed extrusion of the nucleus pulposus.[22,23] Almost invariably, this disc extrusion is not of a diseased nucleus, as commonly occurs in type I disc herniation in chondrodystrophic dogs (see ch. 266). Rather, the escape of a normal nucleus is via an annulus that has been torn.[24] Forceful extrusion of a small volume of nucleus creates a spinal cord lesion due to a contusion that does not cause persistent compression (Figure 267-3). Clinical signs are often lateralized because the disc herniates to one side of the midline dorsal longitudinal ligament. Signs may resemble those of fibrocartilaginous embolism (FCE). Postmortem examination of such cases has suggested that the extruded nucleus may sometimes actually pass through the spinal cord substance.[25] The resultant spinal cord lesion cannot be seen on images other than MRI.

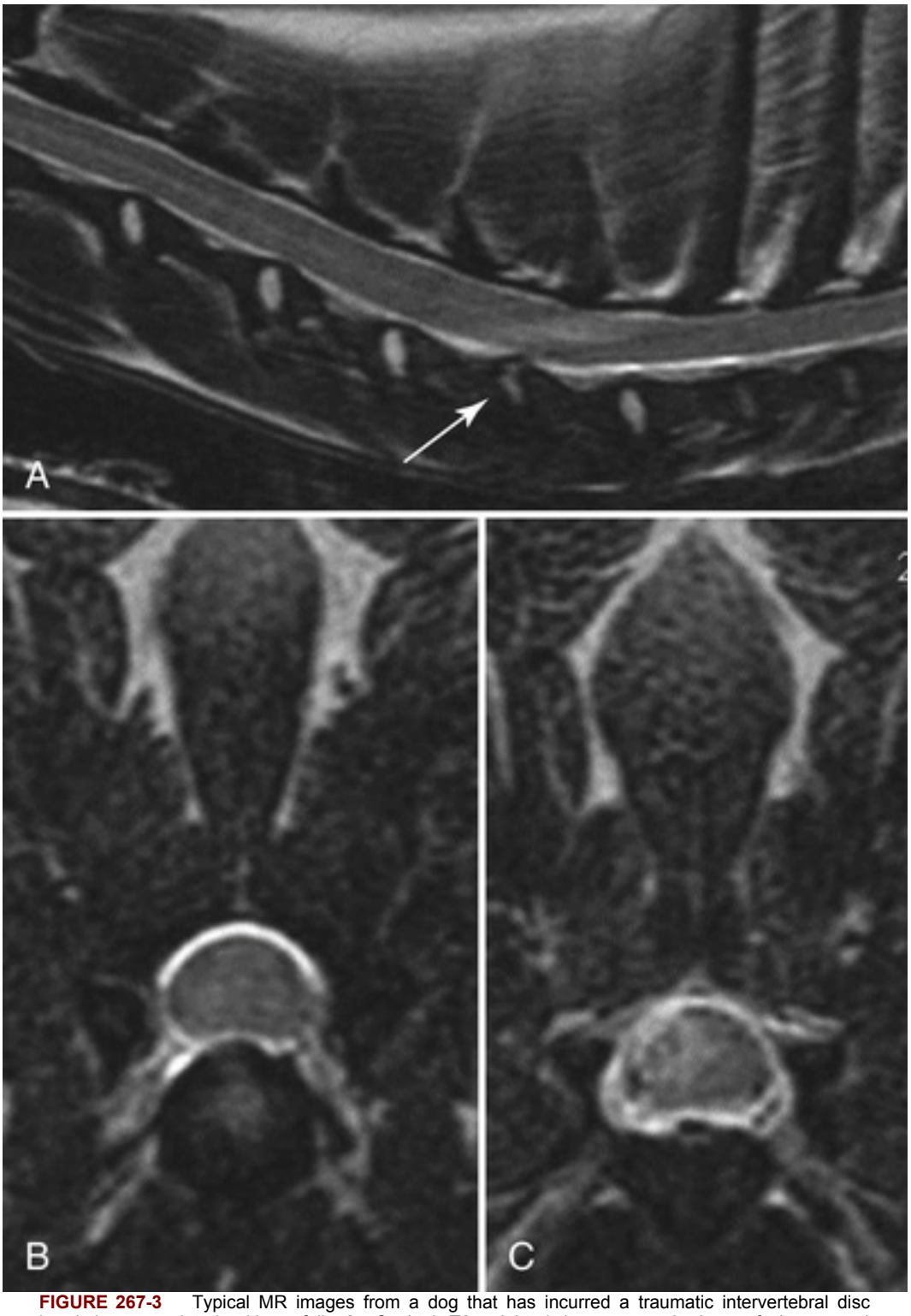


FIGURE 267-3 Typical MR images from a dog that has incurred a traumatic intervertebral disc herniation associated with a fall. **A,** Sagittal T2-weighted image reveals loss of the normal hyperintensity of the nucleus of the intervertebral disc between C6 and C7 vertebrae (arrow), plus hyperintensity of the immediately adjacent spinal cord, suggestive of edema. **B,** Transverse T2-weighted image at the mid-portion of the C6 vertebra illustrates normal intensity of spinal cord parenchyma. **C,** Transverse T2-weighted image at the mid-portion of the C7 vertebral body reveals abnormal hyperintensity within the spinal cord.

Microchip Trauma

There are several reports of inadvertent introduction of identifying microchips into the spinal canal.[25a]

Reports suggest that very small dogs might be at heightened risk for this type of injury, which can occur immediately following implantation or develop after properly placed microchips migrate.[26,27]

Prognosis

The prognosis for traumatic lesions of the spinal cord is, of course, dependent upon the severity of injury, but is often surprisingly good. The best available prognostic indicator remains "deep pain" sensation. When it is present, most animals will (eventually) recover enough locomotor ability to live normal, or near-normal, lives. Animals with cervical lesions almost always retain deep pain sensation—those that don't, usually die of respiratory compromise.[28] Loss of deep pain sensation after external thoracolumbar trauma is indicative of an extremely guarded prognosis, at best. Few such pets recover to walk again. Animals with thoracolumbar injury and intact pain sensation usually recover remarkably good function.

Recovery after serious traumatic spinal cord injury can be a long process—animals will frequently require at least 10 days before demonstrating *ANY* change at all. Full recovery may take three months or more. After severe spinal cord injury, a "scar" develops within the spinal cord consisting mainly of astrocytic processes and a secreted proteoglycan matrix. Both can inhibit axonal regeneration.[29] More familiar fibroblastic scarring can also develop in the subarachnoid space and impair CSF flow. The end result of such scarring may lead to accumulation of fluid within the spinal cord, sometimes sufficiently severe to be recognized as syringomyelia (see ch. 266). These secondary lesions may give rise to pain syndromes in people that are uncommonly recognized in dogs and cats. Loss of fecal continence may occur (see ch. 42).[30]

Vascular Diseases

Introduction

A wide range of circulatory disorders could lead to spinal cord dysfunction. This includes any cause of reduced blood pressure (see ch. 159). However, other clinical signs are likely to predominate in conditions (e.g., heart failure) severe enough to cause such systemic circulatory disturbances. Nevertheless, it may be prudent to measure blood pressure in cases with no obvious cause for spinal cord dysfunction (see ch. 99). Signs associated with aortic thrombosis (see ch. 256), peripheral nerve disease (see ch. 268) or muscle diseases (see ch. 354) also may be consistent with spinal cord disease. Blood pressure measurement may provide a straightforward rule-in/rule-out test.[31] Similarly, systemic diseases that affect blood clotting (see ch. 197), including both hypercoagulable states such as hyperadrenocorticism and hypocoagulable states such as thrombocytopenia, might cause spinal cord lesions and should be considered during physical examination (see ch. 196). Most pets with spinal cord damage due to a vascular lesion have a regionally-specific disease, and those are discussed below.

Signalment

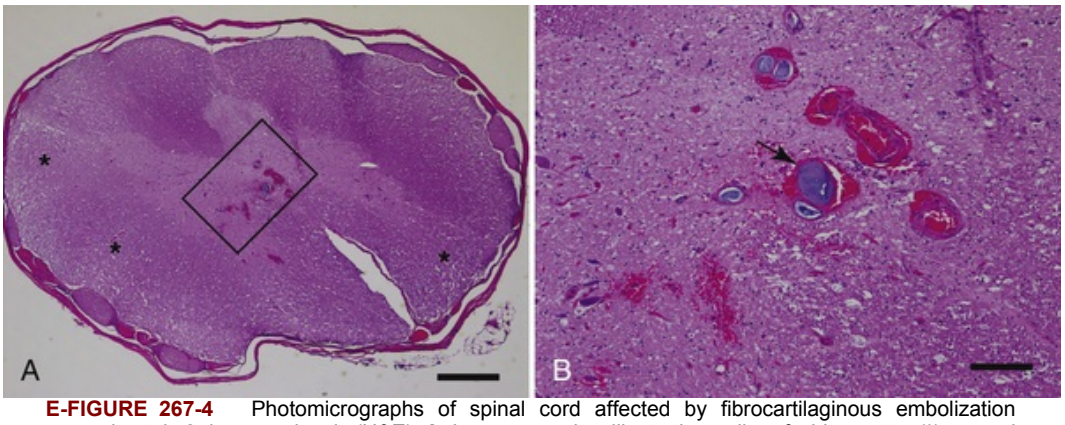
Spinal cord vascular lesions are, in general, more common in middle-aged to older animals. Fibrocartilaginous embolization, specifically, occurs more commonly in non-chondrodystrophic breeds and, perhaps, the Miniature Schnauzer is at increased risk.[32] In general, signalment is not especially suggestive of this specific type of lesion and, indeed, spinal infarctions have been documented in animals that are relatively young.[33]

History

Vascular-origin spinal cord lesions have an instantaneous onset, during which the animal may exhibit signs of pain. Most often, the animal is exercising and then suddenly cries out or simply collapses and is already neurologically impaired.[34] By the time the animal is seen by the veterinarian, there is usually no evidence of pain (but beware of anxious and stoic patients; see ch. 126). Over the course of several subsequent days (if the animal is not seen for that long) there is often gradual regression of neurologic signs. Animals with vascular lesions of the spinal cord are not thought to show pain when examined after a delay. This history, especially combined with other typical signs, can be so characteristic of vascular lesions they are almost pathognomonic.

Presentation

Spinal cord vascular lesions frequently have a highly stereotypical presentation. The underlying cause can be obstruction of the vasculature (thrombosis or embolism); rupture of a (often abnormal) blood vessel is less common. In either case, the vessel is usually small, and signs are almost always strongly lateralized. Therefore, the typical presentation is a peracute onset of neurologic signs which are often highly lateralized (Video 267-1). However, alternative presentations do occur; for instance, animals in which the ventral spinal artery is compromised will show evidence of severe bilateral disease. The typical progression after the immediate presentation is of gradual recovery of lost function. The rapidity of recovery depends on the precise localization and severity of the lesion. Animals with lesions that do not affect the lower motor neurons (which lie within the C5-T2 and L4-S3 spinal cord segments) typically will recover rapidly if the lesion is insufficiently severe to cause loss of deep pain sensation. The occasional animal with an extremely severe vascular lesion usually does not survive. At necropsy, severe or widespread thrombosis is usually identified (E-Figure 267-4). Animals in which the lower motor neuron regions are affected are especially at risk for needing prolonged recovery time or failure to recover.



E-FIGURE 267-4 Photomicrographs of spinal cord affected by fibrocartilaginous embolization approximately 2 days previously (H&E). **A,** Low-power view illustrating pallor of white matter (*) caused by widespread axonal destruction. Scale bar = 500 microns. **B,** High-power view of the region contained within the box in **A,** illustrating chondroid material obstructing the lumen of several arteries (example is arrowed). Scale bar = 100 microns. (Photomicrograph courtesy Dr. Jodi Smith, College of Veterinary Medicine, Iowa State University.)

Differential Diagnosis

Typical signs of vascular lesions are highly suggestive of the etiology. Nevertheless, intervertebral disc herniation (see ch. 266) and traumatic spinal cord injury should be considered. Each differential diagnosis requires MRI scanning to confirm the etiology.

Diagnostic Testing

Apparent lack of spinal pain, plus the stereotypical lateralization, often strongly suggests a vascular origin. Such a suspicion leads to an MRI scan as the only modality that can reveal disease within the spinal cord parenchyma. Other imaging modalities cannot rule out this diagnosis. Only if there is doubt about other diagnoses is it worth using other imaging modalities.

Specific Diseases

Fibrocartilaginous Embolism (FCE)

This condition is well described in the veterinary literature and can occur in dogs or cats. The inciting lesion is an occlusion of the spinal cord arterial supply by chondroid material that obliterates the vessel lumen. This causes the equivalent of a "stroke" in the spinal cord. The dependent spinal cord region after infarction is devitalized and non-functional immediately. It later becomes necrotic.[35] In the hours following the initial insult, edema may accumulate within the surrounding spinal cord parenchyma, leading to mild worsening of clinical signs that may be visible to the owner and veterinarian. The source of the chondroid material is not known. It has been suggested that it is derived from an intervertebral disc (nucleus) and then ends up in the

arterial supply.[36] However, there are no satisfactory explanations for the eventual location of the material. Alternative explanations include blood vessel walls undergoing chondroid metaplasia with that material ending up either detaching and lodging further downstream or, perhaps, inducing a thrombus at the original site.

FCE is suspected in animals which exhibit typical clinical signs with the typical lesion observed on MRI scan, but definitive diagnosis can only be made at postmortem examination. Classic FCE lesions are small, often localized to one quadrant of the spinal cord, hyperintense to normal gray matter on T2-weighted scans, and iso- or hypointense on T1-weighted scans.[37] However, many dogs suspected of having FCE display large regions of hyperintensity on T2-weighted and STIR MRI scans (Figure 267-5).[38] Since many recover naturally, the diagnosis is not definitively confirmed and the precise nature of the lesion remains speculative. For this reason, the term *ischemic myelopathy* is sometimes used to more accurately reflect the lack of a precise diagnosis.[39] Before widespread access to MRI, FCE was suspected in a larger proportion of cases. With use of MRI, some cases have been shown to have one of several types of peracute intervertebral disc herniation (see Figure 267-3; see ch. 266). Most dogs suspected of having FCE exhibit mild to moderately severe, lateralized signs that show considerable improvement within a period of about 48 hours. Others, however, can have devastating functional deficits from which spontaneous improvement cannot occur. Of course, the only lesions that are definitively diagnosed are those (unusual) cases that are found at postmortem examination, therefore providing a possibly biased view of the nature of the disease. Risk factors for this condition are not established but it may be prudent to analyze the clotting status of affected animals (see ch. 196).

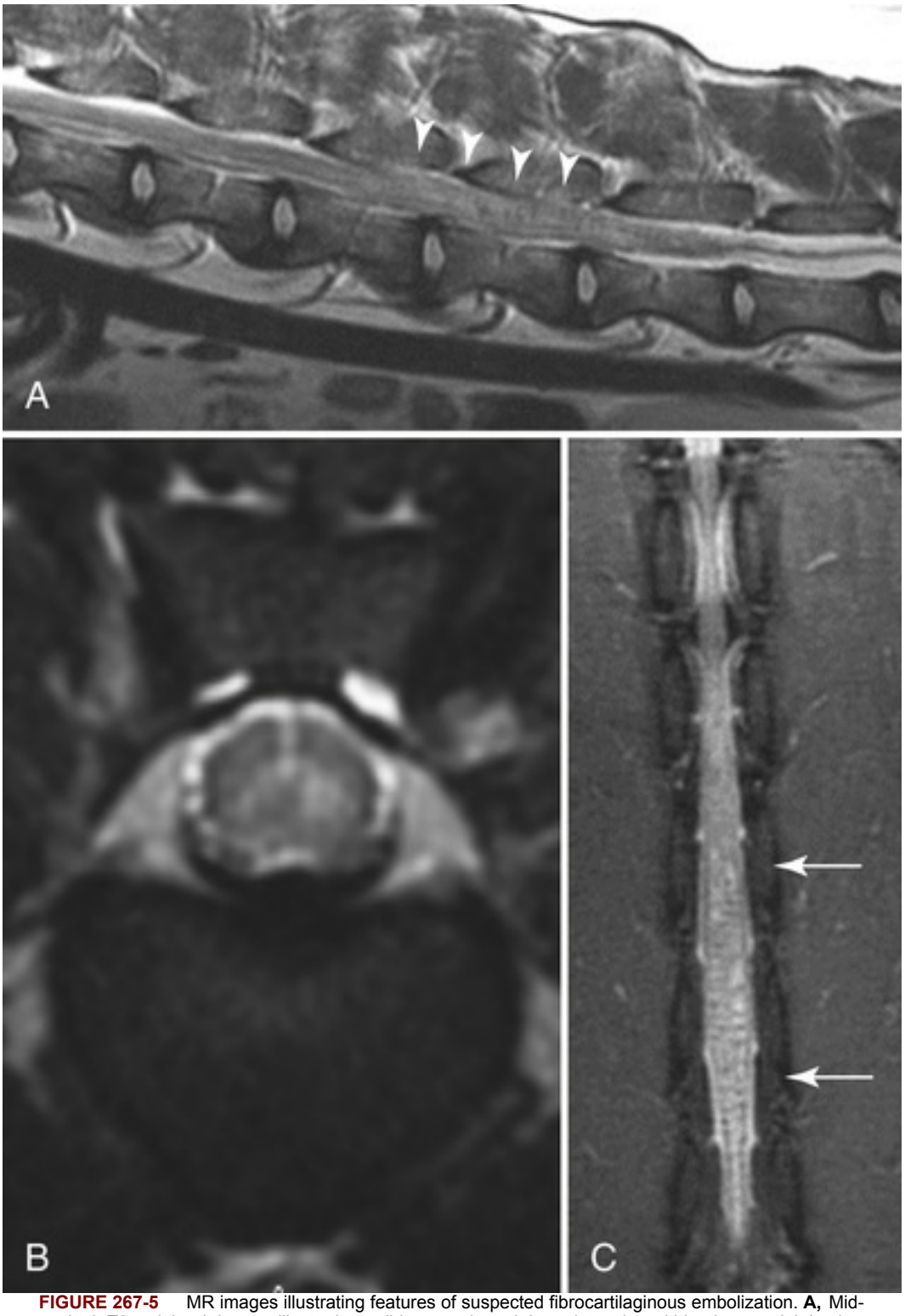


FIGURE 267-5 MR images illustrating features of suspected fibrocartilaginous embolization. **A,** Mid-sagittal T2-weighted image illustrating mild parenchymal hyperintensity within the caudal lumbar vertebrae (arrowheads). Note the normal size, shape and intensity of the intervertebral disc nuclei, indicating that disc herniation is not a likely cause. **B,** Transverse T2-weighted image at mid-lesion level illustrating asymmetric hyperintensity of the gray matter. **C,** Dorsal STIR image of the caudal lumbar region. This scan sequence is often sensitive to vascular lesions and reveals characteristic patchy parenchymal hyperintensity (see region between arrows).

Prognosis is dependent on severity and location of the initial lesion. In general, animals with lesions in the T3-L3 or C1-C5 regions of the spinal cord have a good prognosis if their deep pain sensation is intact (see ch. 259). Animals that have lost deep pain or that have large lesions affecting the spinal cord intumescences (i.e.,

C6-T2 or L4-S3) have a more guarded prognosis because there is less scope for plastic responses to ameliorate the functional deficits if those gray matter regions have been destroyed. Lesions that affect the sacral spinal cord can be particularly troublesome because fecal and/or urinary incontinence are common and difficult-to-manage long-term issues. No treatment is required but, similar to the prognosis for traumatic lesions, a period of up to three months or more must be allowed to appreciate the full extent of recovery.

Blood Vessel Rupture/Hematomyelia

A small number of cases with a hematoma within the substance of the spinal cord have been reported.[40] Many of these cases have been young animals and the assumption has been that the hematoma developed because of rupture of an anomalous vessel. Indeed, anomalous vessels have been described within the spinal cord in some cases, supporting this assumption. Risk factors for this condition are not known but it would be presumed to occur more frequently during periods of raised systemic blood pressure, although this has not been documented. Trauma has not been associated with this condition. Although one might expect such lesions to occur acutely, there is evidence in many that bleeding accumulates over a period of several weeks. The severity of clinical signs varies considerably. The definitively diagnosed cases have tended to be quite severe, but this might reflect the implicit need for diagnosis in such cases.

Diagnosis of this intraparenchymal lesion relies on MR imaging. Blood accumulations in the spinal cord undergo a series of changes in imaging characteristics over time, which can aid in identifying its duration. However, changes can be unreliable and vary considerably depending upon the field strength of the magnet and various other factors (e.g., precise timing of image acquisitions).[41] Small hematomas within the spinal cord are suspected fairly frequently, but when associated with relatively mild clinical signs that have developed acutely, the affected animals are often treated conservatively. Thus, a definitive diagnosis is not achieved because they often recover uneventfully. Severely affected cases that have large intraparenchymal masses require emergency surgical intervention. If left unchecked, the expanding hematoma will cause progressive damage to the spinal cord that may cause irreversible clinical deficits. Surgical intervention aims to drain the hematoma via incision through the pia and superficial parts of the spinal cord parenchyma.[40] Anomalous blood vessels can be identified and biopsied if present. The prognosis for surgical treatment depends mainly upon the severity of the clinical signs.

Extradural Hematoma

Extradural hematomas are commonly found in association with acute disc herniations and occasionally with disorders of hemostasis. Rarely, dogs are presented with acute or chronic progressive neurologic signs, often associated with pain, for which the underlying cause is an idiopathic hematoma.[42] Surgical decompression is associated with a good to excellent prognosis. It is important to recognize that such patients exist, because the imaging appearance is also consistent with extradural neoplasia, which has a far worse prognosis.

Vascular Anomalies

Vascular anomalies are often incriminated in the development of intraparenchymal hemorrhage.[43] They can also sometimes form mass lesions which can be detected on MRI scans and might be candidates for surgical removal.[44]

Systemic Disease Associated with Bleeding and Thrombosis Into the Spinal Cord

Bleeding into the spinal cord parenchyma may also arise from systemic disease that causes hypocoagulable states. Disorders of blood clotting, such as hemophilia, are rare causes of spinal lesions in dogs (see ch. 197).[45] However, there are various clotting disorders that can be associated with spinal dysfunction, including von Willebrand disease and, rarely, immune-mediated thrombocytopenia (see ch. 201).[46,47] Vascular fragility associated with inflammation (vasculitis) can also be a cause of hemorrhage into or around the spinal cord. Recognized causes in dogs include *Angiostrongylus vasorum* infection (see ch. 242) and leishmaniasis (see ch. 221).[48-50] Conversely, vasculitis can also lead to spinal cord lesions by causing thrombosis rather than hemorrhage.[51]

Neoplastic Lesions

Signalment

Neoplastic lesions of the spinal cord or vertebral column have definite breed associations. Large dogs are more susceptible to osteosarcoma, a common spinal tumor.[52,53] Golden Retrievers in the United States are thought to be at risk for hemangiosarcoma, another common spinal neoplasm.[52] Older age (≈4 years old for giant dogs) is a recognized risk factor for any neoplastic condition, although younger dogs (often ≈12 months old) are susceptible to nephroblastoma, an intramedullary spinal tumor.[54] Age should not be used as a rule-out for neoplastic disease. Nephroblastoma may be more common in German Shepherd Dogs, although not all studies concur.[53-55] Lymphoma is a common spinal lesion in cats and dogs (see ch. 344). It is the leading cause of spinal lesions in adult cats.[56] Metastatic lesions of the spinal cord occur occasionally,[57] so it is worth considering that possibility during the clinical examination, especially in cachexic animals.

History

Animals with neoplastic disease commonly have an insidious onset of clinical signs, as the lesion gradually enlarges. However, some animals with spinal tumors have an acute onset of clinical signs. This can arise through two main mechanisms: (1) development of pathologic fracture, in which a progressively weakened bone finally fractures and causes immediate spinal cord injury; and (2) acute vascular injury associated with tumor embolization or with compression and thrombosis associated with prolonged or excessive pressure. Thus, it is important to consider the possibility of a tumor in any older dog that has evidence of spinal cord dysfunction, even if the onset is acute.

Presentation

Most animals bearing spinal neoplasms have a slow onset of progressive neurologic deficits and spinal pain. However, clinical signs vary depending on the nature of the tumor. Extradural neoplasia is typically painful, probably because it distorts the spinal cord meninges or nerves, or because of damage to the skeletal elements. Lesions inside the dura are not typically associated with signs of pain until the later stages, but some recent data on intramedullary lesions suggest this may not be accurate.[57] Rate of tumor growth is highly variable. Similar tumors may grow differently depending on the spinal cord site, although the progression of signs can be misleading because lesions may become quite large before any clinical signs are noted (Figure 267-6). On the whole, clinical signs associated with intradural lesions progress slowly, and some animals may have clinical signs for many months or even years prior to presentation.[58] On the other hand, animals that have clinical signs associated with extradural lesions typically show rapid (days to weeks) progression.

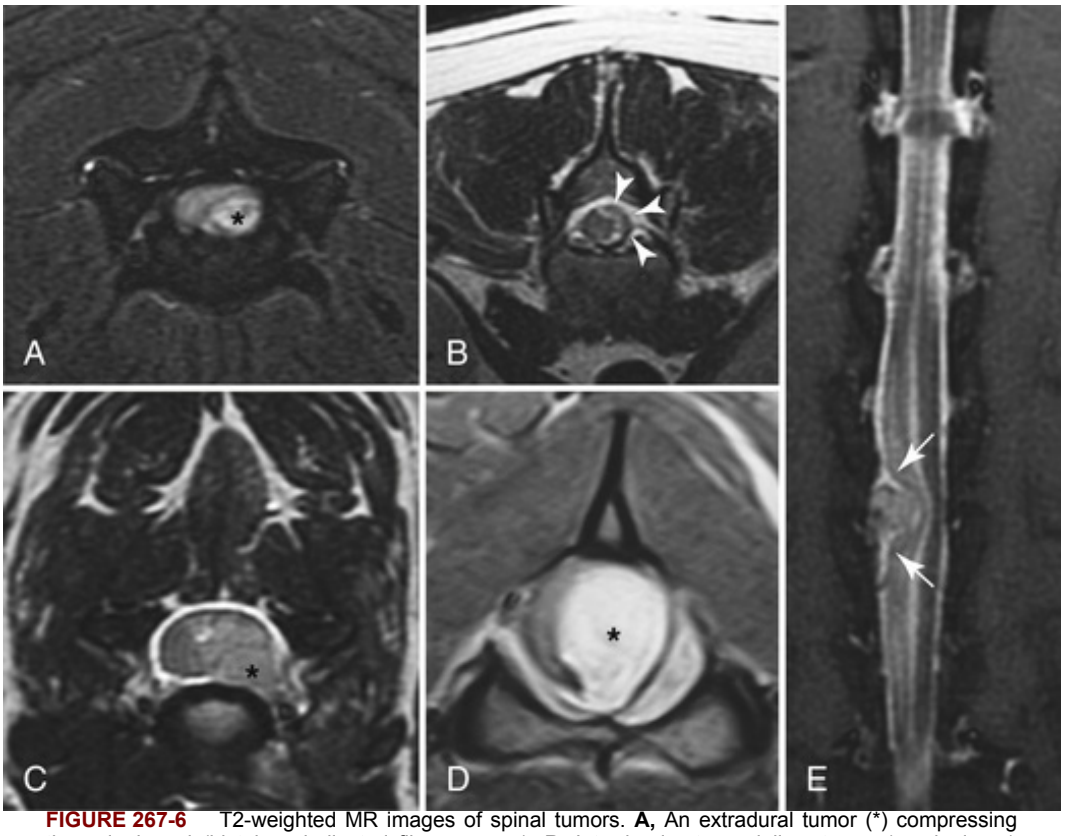


FIGURE 267-6 T2-weighted MR images of spinal tumors. **A,** An extradural tumor (*) compressing the spinal cord (histology indicated fibrosarcoma). **B,** Intradural-extramedullary tumor (meningioma) (arrowheads). **C,** Nerve sheath tumor (intradural-extramedullary to intramedullary) (*). **D,** This large extradural tumor (*) was diagnosed in a dog that was ambulatory at the time of presentation. **E,** Cervical meningioma illustrating the typical "golf tee" appearance created by the surrounding CSF (arrows).

Differential Diagnosis

Chronic progressive spinal cord dysfunction is most often associated with neoplasia or chronic disc herniations (usually type II). However, there is a reasonably wide possible differential diagnosis that would also include inflammatory or infectious diseases such as discospondylitis and meningoencephalomyelitis of unknown origin.[60] In older animals, degenerative diseases are often a consideration, most notably degenerative myelopathy, especially in corgis and German Shepherd Dogs[61] (see ch. 266). Congenital,[62] post-traumatic or adhesion-associated syringomyelia (accumulation of fluid within the spinal cord parenchyma) can produce similar clinical signs in some cases, especially in small dogs.[30] In addition, there are many non-neoplastic masses or anomalies that can be associated with gradually progressive spinal cord progression and neural deficits, such as dermoid sinus, calcinosis circumscripta, hematomas (see above), cartilaginous exostosis, lipoma, bony proliferation associated with inborn errors of metabolism, and poorly-classified disorders such as meningioangiomatosis.[63-68] This wide differential diagnosis list, including many benign lesions, implies the need for precise diagnosis to avoid assumptions of poor prognosis. For animals with acute spinal cord dysfunction the main differential diagnosis is acute disc herniation (even in large-breed dogs) and the traumatic and vascular lesions discussed above. Many, but not all, cases of acute spinal cord injury associated with neoplastic lesions exhibit signs of pain.

Diagnostic Testing

As for most conditions of the central nervous system, after a lesion has been localized, the usual next diagnostic step is to image the affected area. Frequently it is helpful to commence with radiographs, because a reasonable proportion of affected animals will have lesions of the skeletal elements that can be identified (see Figure 267-1). However, it is important to recognize that only a proportion of spinal neoplasia will cause sufficient bone loss or bone proliferation to be recognizable on plain radiographs. Lesions within the dura

usually will not change bone density and not even all epidural neoplasia is associated with bone change. Therefore, radiography is a good "rule-in" but poor "rule-out" test. The next step is usually an MRI scan (see Figure 267-6). MRI is excellent for detecting lesions, regardless of location outside or within the spinal cord parenchyma. CT is limited to detection of radio-opaque lesions or those that cause changes in bone density, although this can be extremely useful for specific lesion types (Figure 267-7).

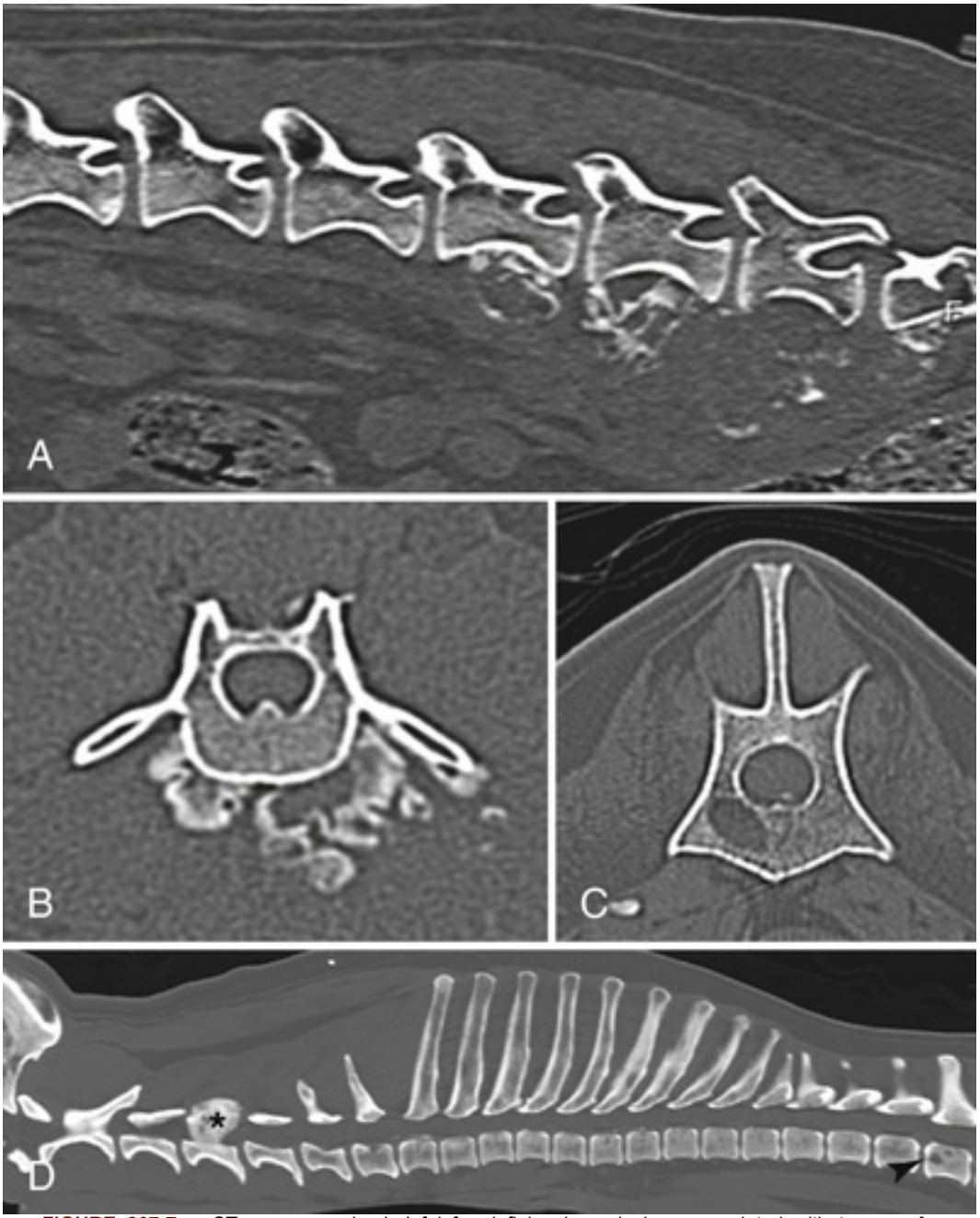


FIGURE 267-7 CT scans can be helpful for defining bone lesions associated with tumors. **A,** Sagittal reconstructed image illustrating extensive bone proliferation along the ventral aspect of the caudal lumbar vertebrae, associated with a metastatic prostatic tumor. **B,** Transverse image of the same lesion. **C,** Transverse image illustrating a lytic lesion within the L2 vertebral body caused by multiple myeloma. **D,** Sagittal reconstructed CT image illustrating a primary lesion in the C4 vertebra (*) and suspected metastatic lesion in the L1 vertebral body (arrowhead).

Specific Diseases

Overview

Neoplastic disease of the spinal cord is best categorized according to the location of the lesion in relation to the meninges surrounding the cord. Thus the clinical (and pathologic) divisions are extradural, intradural/extramedullary and intramedullary. Of these, the most common are thought to be extradural, with intradural/extramedullary types probably being the next most common.[53,58,59]

Extradural Tumors

These lesions lie within the epidural space, normally filled by fat. In line with their site of origin, neoplasms arising here usually are tumors of bone or various types of soft-tissue sarcoma, such as osteosarcoma, hemangiosarcoma, fibrosarcoma, lymphoma, liposarcoma, and multiple myeloma. Rare benign tumors in this location include lipomas.[66] Most epidural tumors are malignant and often cause secondary bone damage leading to bone weakening and, commonly, pathological fractures. Many such cancers (e.g., hemangiosarcoma, osteosarcoma) have metastasized by the time of diagnosis and it is common to observe metastatic lesions at other sites in the skeleton or within the lungs (see Figure 267-7). Importantly, many dogs affected by extradural spinal neoplasia appear to experience considerable pain, which can aid in suspecting these types of lesions versus other tumor types described below.

Intradural/Extramedullary Tumors

These are lesions of tissue that lines or projects through the subarachnoid space, such as the meninges and nerve roots. Both meningiomas and nerve sheath tumors tend to be slow-growing, producing clinical signs over a period of months to years.[58] Nerve sheath tumors appear to be more common at spinal cord intumescences, although this may also reflect the greater likelihood of diagnosis of lesions at sites that cause lameness. Meningiomas can occur at any site but appear to be especially common at the C1/C2 space in dogs, with a possible predisposition in Boxer dogs. Although both nerve sheath tumors and meningiomas are generally regarded as relatively benign histologically, each typically invades locally into normal tissue and can be difficult to excise in their entirety. Some nerve sheath tumors appear to be associated with neuropathic pain syndromes, including generalized depression and behavior changes.[58]

Intramedullary Tumors

These tumors are not common.[57] They arise from elements of the neuropil, such as glial cells (of various types) and (rarely) the neurons. Common tumor types in this category include astrocytoma and ependymoma. They can vary considerably in their histologic behavior: some are well-circumscribed by a capsule and can be excised, while others are highly invasive and aggressive. Typically they have a slowly progressive course over a period of several months. Nephroblastoma is an example of a neoplasm found in this compartment, although it may also cross into the extramedullary/intradural space. This tumor appears to develop close to the thoracolumbar junction of juvenile dogs as a consequence of an error during embryogenesis, in which a small number of kidney progenitor cells are incorporated into the developing neural tube and later become neoplastic.[55] This type of tumor often has a benign histologic phenotype but can be locally invasive.

Diagnosis of Spinal Tumor Type

Bearing in mind the extreme variability in tumor behavior and, therefore, prognosis, it is highly desirable to be able to make a specific diagnosis without traditional open surgery. Analysis of CSF may also be of assistance occasionally, in that cancer cells may exfoliate into the fluid and be detected or, alternatively, the fluid may reveal evidence of an infectious condition (see ch. 115).[69,70] Blood and/or bone marrow aspirate analysis (see ch. 92) may be helpful in some cases, such as those with suspected multiple myeloma (see ch. 344).[13] Similarly, it may be useful to obtain aspirates from enlarged lymph nodes to identify cases of multifocal lymphoma or lung aspirates from lesions suspected to be metastases. If a mass lesion has been identified on images, it may be possible to obtain biopsy samples from within or outside the spinal cord parenchyma without open surgery.[71,72] Ultrasound, fluoroscopic or CT-guided biopsies can be obtained using needles, TruCut biopsy tools or Jamshidi needles. There are obvious and serious potential hazards. For lesions within the spinal cord itself, it may be possible to place a needle into the spinal cord and obtain biopsy through judicious aspiration.[71] Such biopsies may be useful to rule out other differential diagnoses such as fungal granulomas or benign mass lesions. Despite a multitude of methods, it can be difficult to diagnose

cancer percutaneously unless it exfoliates easily. Most spinal tumors are suspected on imaging but not confirmed until histology is performed. Extradural masses should not be assumed to be neoplastic because affected animals may be inappropriately euthanatized.

Treatment and Prognosis

Neoplastic disease affecting the spinal cord has a wide range of treatments and prognoses, depending upon the nature of the lesion. For instance, meningiomas can often be surgically excised, although they will frequently regrow over a period of months to years. Nerve sheath tumors can theoretically be excised in their entirety but, because they often are close to the spinal cord and require large margins for total excision, this is rarely achieved when they lie within the spinal canal. Nevertheless, long-term (>12 month) disease-free interval can be achieved by surgical resection alone. Some other neoplastic lesions have a hopeless prognosis, such as hemangiosarcoma that has already metastasized. Others have an intermediate prognosis and may occasionally be responsive to chemotherapy (e.g., multiple myeloma).[13] Although radiation-induced myelitis is a potentially devastating sequel to radiotherapy directed at the spinal cord, careful planning can produce gratifying outcomes.[73,74] Radiotherapy is most notably an option for adjuvant therapy for cases in which there is recurrence of a previously excised tumor, or in which there has been incomplete primary extirpation.[55]

In general, the prognosis for most epidural tumors is poor, mainly because they are often malignant and may well have already metastasized at the time of diagnosis. Surgical debulking can provide rapid and effective relief of compression, which is often associated with rapid recovery of much lost function. Unfortunately the results, especially for sarcomas, are often short-lived, with recurrence of clinical signs within a few weeks to months. Intradural/extramedullary tumors are amenable to surgical excision and this is the major treatment modality. The outcome can be quite gratifying for meningiomas, because they are frequently slow-growing and the clinical signs can be alleviated for ≈12 months. In contrast nerve sheath tumors tend to have a worse prognosis because of the difficulty in removing the tumor in its entirety. Intramedullary tumors often are of benign types and may even be encapsulated, meaning that they can potentially be excised. This of course entails incising the spinal cord parenchyma and using microdissection techniques, but the results can be quite gratifying,[55,75] although recurrence of clinical signs has been reported in some of the (very small) number of cases reported in the veterinary literature.

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CHAPTER 268

Peripheral Neuropathies

Christopher L. Mariani

Client Information Sheet: Peripheral Neuropathies

The peripheral nervous system (PNS) includes all nerve structures outside the central nervous system (CNS; i.e., the brain and spinal cord). The PNS is comprised of motor nerve fibers innervating skeletal muscle, sensory nerve fibers carrying touch, pain and proprioceptive position information from the skin, joints and muscles, afferent fibers carrying special sense information (e.g., auditory and vestibular systems), and autonomic fibers innervating the thoracic and abdominal viscera as well as other structures (e.g., salivary glands, irises, baroreceptors). The autonomic system is further divided into the sympathetic and parasympathetic systems. Peripheral nerve fibers may arise from the ventral horn of the spinal cord, exiting via the ventral root (motor and sympathetic fibers), from the dorsal root ganglion adjacent to the spinal cord, entering the cord via the dorsal root (sensory fibers), or from the brainstem or adjacent ganglia (motor and parasympathetic fibers), entering or exiting in cranial nerves. Although some nerves carry purely motor or sensory information, most nerves are comprised of a combination of motor and sensory fibers. A neuropathy refers to peripheral nerve disease (either spinal or cranial nerves [see ch. 264]) while polyneuropathies affect multiple peripheral nerves, often in a diffuse manner.

Clinical Signs

Most recognized peripheral nerve disorders in veterinary medicine have a clinical presentation dominated by dysfunction of the motor nerves, although sensory and autonomic signs are seen with some conditions. Characteristic clinical signs include paresis, hypotonia, muscle atrophy, and depressed or absent segmental spinal reflexes (Video 268-1). The paresis may involve all limbs, or may manifest as paraparesis, and often results in a short-strided gait. Dysphonia, dysphagia, inspiratory stridor, megaesophagus, and reduced or absent gag and palpebral reflexes may be seen due to involvement of the recurrent laryngeal, glossopharyngeal, vagus and facial nerves (see ch. 259).[1-3] Disorders of the neuromuscular junction (see ch. 269) and muscle (see ch. 354) can result in many of the same signs, and can be difficult to distinguish from peripheral nerve disease based on clinical examination alone. Signs of sensory dysfunction include ataxia, loss of proprioceptive positioning, reduced or absent spinal reflexes and paresthesia or anesthesia, potentially resulting in self-mutilation. Autonomic dysfunction may result in vomiting or regurgitation, diarrhea, ileus, urinary retention, incontinence, impaired lacrimation and salivation, and pupillary dysfunction. These disorders may exhibit acute and progressive, or occasionally episodic signs, but more often display a chronic, progressive course.

Diagnostic Plan

A complete blood count, serum biochemical evaluation and urinalysis are indicated to identify metabolic disorders responsible for nerve dysfunction (e.g., diabetes mellitus, hypothyroidism), comorbid disease, and to assess the suitability of patients for general anesthesia. Additional metabolic testing, including thyroid evaluation (see ch. 299-302) and serum fructosamine (see ch. 304 and 305), may also be considered. Serum creatine kinase (see ch. 66), carnitine, and pre- and post-exercise pyruvate, lactate (see ch. 70), and blood gas evaluation (see ch. 128) may be useful to identify certain muscle disorders. Imaging of the thoracic and abdominal cavities is often indicated to identify neoplastic disease. Serum titers or polymerase chain reaction (PCR)–based testing for infectious disease (see ch. 207), such as toxoplasmosis or neosporosis (see ch. 221), may also be appropriate.

More advanced diagnostic imaging (magnetic resonance imaging [MRI] or computed tomography [CT]) is occasionally useful to demonstrate neoplastic, inflammatory or other disease processes affecting specific nerves or nerve roots, or for diseases also displaying CNS lesions. However, these modalities typically play a larger role in ruling out other disorders on the differential diagnosis list. Similarly, cerebrospinal fluid (CSF) evaluation (see ch. 115) is most useful to eliminate other disease processes, but is occasionally abnormal in peripheral nerve disorders involving the nerve roots or those with both CNS and PNS involvement.

The most useful diagnostic tests for peripheral nerve disorders are electrodiagnostics (see ch. 117) and histopathology of muscle and nerve biopsies (see ch. 116). Electrodiagnostic testing includes electromyography (EMG), motor and sensory nerve conduction velocities (MNCV, SNCV), F wave evaluation, cord dorsum potentials, H reflex evaluation, magnetic stimulation and brainstem auditory evoked response (BAER).[4,5] Together, EMG and MNCV are useful to confirm dysfunction of the neuromuscular system, to differentiate peripheral nerve disease from muscle disease, and to distinguish axonal disease from demyelination. F wave evaluation allows investigation of the proximal nerve and ventral nerve roots, while SNCV and cord dorsum testing evaluates sensory nerves and dorsal nerve roots. However, electrodiagnostic testing rarely allows the diagnosis of a specific etiology. Histopathologic examinations of muscle and nerve biopsies are helpful to confirm and further define abnormalities detected with electrodiagnostic testing and are more likely to identify a specific etiology.[6,7] Electrophysiologic testing and muscle and nerve biopsy are described in more detail elsewhere (see ch. 116 and 117). Specific tests for autonomic dysfunction may also be useful to identify animals with involvement of this part of the nervous system.[8,9]

Degenerative Disorders

There are several degenerative neuropathic disorders that affect specific breeds of dog and cat and thus, appear to be heritable in nature. These disorders are quite rare, and a detailed discussion is beyond the scope of this chapter. The reader is referred to more comprehensive reviews of this topic.[10-16]

Metabolic Disorders

Diabetes Mellitus

Diabetic neuropathy is one of the most common causes of peripheral nerve dysfunction in human patients,[17] but appears to occur with much less frequency in veterinary medicine. Clinical signs are primarily noted in cats (see ch. 305) while overt disease is rarely recognized in dogs (see ch. 304). The pathophysiology of diabetic neuropathy has been intensely studied, with a number of causative theories proposed.[18-20] Clinical signs include paraparesis, progressing in some cases to tetraparesis, pelvic limb ataxia (see Video 305-2), difficulty in jumping, reduced postural reactions and segmental spinal reflexes, and distal muscle atrophy.[12,18-24] A plantigrade stance is frequently seen in cats (see Video 305-3). Although poorly recognized, sensory nerve dysfunction resulting in paresthesias, hyperesthesia and irritability likely occurs with some frequency in this disorder.[12,19,22,23,25] Cranial nerve and autonomic signs are common in humans, but are rarely reported in animals.[19,26] However, subclinical nerve dysfunction appears to occur with some frequency.[27-30]

The diagnosis is strongly suspected with demonstration of hyperglycemia and glucosuria in an animal with consistent clinical signs. Serum fructosamine may also be of some utility, as neuropathy is more common in poorly regulated patients. Electrodiagnostic testing may reveal spontaneous activity within affected muscles with reduced motor and sensory nerve conduction velocities, although these changes may be subtle and patchy.[12,18,21,24,26,28] However, consistent abnormalities are detectable in MNCV, SNCV, F wave and cord dorsum evaluation, even when EMG abnormalities are subtle or absent.[22] Evidence of conduction block has also been noted in dogs.[28] Together, these findings suggest that demyelination predominates over axonal changes, which is supported by histopathology of muscle and nerve biopsies,[22,27,31] although at least one report documents the contribution of axonal injury to the disease process.[23] Microscopic and ultrastructural evidence of perineurial abnormalities and microvascular lesions has also been documented in diabetic dogs and cats.[32,33]

Therapy is primarily directed at control of the underlying diabetic disorder, and improved glycemic control typically results in improvement or resolution of signs.[18,20,21] There are few reports of additional therapy in veterinary medicine. Acetyl-L-carnitine has multiple potential beneficial mechanisms of action, and has

demonstrated efficacy in experimental models and human patients.[34] It has been used in cats with diabetic neuropathy with anecdotal success.[35] The author has noted dramatic improvement of signs in some feline patients after antioxidant therapy with vitamin E and N-acetylcysteine.

Hypothyroidism

Signs of neuromuscular dysfunction have been frequently associated with hypothyroidism in both canine and human patients (see ch. 299).[18,20,36,37] The underlying pathophysiology of this association remains poorly characterized but potentially involves both peripheral nerve and muscle. Thyroid hormone deficiency appears to lead to both axonal damage and demyelination, based on electrophysiological studies.[36-39] Accumulation of glycosaminoglycans and glycogen within Schwann cells may be responsible for cellular dysfunction and resultant demyelinating change. There is also experimental evidence of a role for thyroid hormone in microtubule assembly and normal axonal transport, which may result in axonopathies when impaired.[18] Altered sodium-potassium ATPase activity, with impaired axonal transport, is another potential mechanism.[39-41] In human patients, mononeuropathies (particularly carpal tunnel syndrome) are common, and are attributed to mucinous deposits in the soft tissue structures causing a compressive neuropathy.[42] It has been suggested that a similar process may be responsible for the compression of cranial nerves in veterinary patients.[18]

Animals may present with paresis or rarely lameness involving a single limb, two limbs or all four limbs.[41,43,44] Cranial nerve deficits, including facial paresis, vestibular signs and trigeminal nerve dysfunction are frequently recognized, are often unilateral, and commonly affect multiple nerves (see ch. 264).[18,45-48] These signs may occur secondary to a peripheral neuropathy, or in other cases may be related to CNS involvement.[49] An association has also been made between hypothyroidism and both megaesophagus (see ch. 273) and laryngeal paralysis (see ch. 239),[41,50] although a causal role is tenuous and remains to be proven.[45,51-53] Affected animals may or may not have classical clinical signs such as lethargy, weight gain, alopecia, and seborrhea. Complete blood count and serum biochemistry profile may show a mild nonregenerative anemia, hypercholesterolemia, or an elevated creatine kinase level. The diagnosis is confirmed by the demonstration of a reduced free and total serum thyroxine (T_4) level with an elevated thyroid stimulating hormone level (see ch. 299).[54] Analysis of CSF may show an increased protein without concurrent pleocytosis.[40,46] Electrophysiological testing shows denervation potentials on EMG, with reductions in MNCV and SNCV.[41,43,44] BAERs may also be abnormal.[41,46] Muscle biopsy shows type I and II fiber atrophy consistent with neuropathic change, or a selective type II fiber atrophy suggestive of a myopathy. Nerve biopsy may show mixed changes characteristic of both axonal degeneration and demyelination.[12,15,41,43] In many cases, the diagnosis is partly based on the administration of levothyroxine and demonstration of a clinical response, which often begins within several days and is complete by 3-8 weeks.[45] Cranial nerve deficits, megaesophagus and laryngeal paralysis may be less likely to improve.[18,41,45,50]

Neoplastic Disorders

Peripheral nerve dysfunction due to neoplasia may result from compression of nerve tissue due to a nerve or nerve sheath tumor,[55-57] from adjacent neoplastic tissue,[58-62] or may occur as a paraneoplastic process. Nerve sheath tumors frequently display malignant characteristics, based on histopathology and their tendency to be locally invasive, growing proximally up nerves or nerve roots.[15,56,63-67] These tumors may occur in any small animal patient (Video 268-2), although they are most common in large-breed dogs and are rare in cats.[57,65,66,68] They commonly arise from the brachial plexus. Lameness and muscle atrophy are the most common and often the only clinical signs for extended periods before additional signs such as paresis, postural reaction or reflex deficits occur.[56,57,65,66,69] The tumor may eventually invade the spinal cord, leading to ataxia, paresis, and postural reaction deficits caudal to the site of invasion. Pain may be elicited with manipulation of the limb or with palpation of the axilla or inguinal region.[56] Horner's syndrome may be present with involvement of the caudal brachial plexus.[56,69] Trigeminal nerve sheath tumors are the most common cranial nerve neoplasms and typically lead to unilateral masticatory muscle atrophy.[70] Tumors involving other cranial nerves are seen less frequently.[71,72]

Diagnosis of peripheral nerve sheath tumors can be challenging. Occasionally, a mass may be palpated in the axilla or via the rectum.[73] MRI or CT may allow visualization of the tumor in many cases.[58,70,74-80] Ultrasonography can also be useful, and can facilitate fine needle aspiration or biopsy of identifiable mass lesions.[58,71,81-85] An EMG examination may be helpful in demonstrating denervation potentials, supporting a neuropathic process in lame patients without an obvious orthopedic cause.[56,65,73] Definitive therapy for peripheral nerve sheath tumors consists of surgical removal of the neoplasm, which can be very difficult. Although tumors involving distal portions of peripheral nerves may be completely resectable, most tumors involve the brachial or lumbar plexus and associated nerve roots.[77,86-89] Surgical intervention for these tumors typically requires amputation of the affected limb, and definitive removal may require laminectomy with sectioning of the nerve roots as close to the spinal cord as possible. Despite such aggressive therapy, many tumors recur, as they have a tendency to grow proximally and invade multiple nerve roots.[56,87] Surgical removal of trigeminal nerve sheath tumors has been reported.[70] Other neoplasms that may involve peripheral nerves include sarcomas,[58,61] carcinomas,[60] and round cell tumors.[59,80,90-94] Lymphoma and other round cell neoplasms may involve single or, in many cases, multiple nerves or nerve roots, leading to focal or multifocal signs.[80,90-93,95,96]

Paraneoplastic Neuropathy

A polyneuropathy associated with cancer in a remote location has been described in a number of dogs and a cat (see ch. 352). This syndrome has been reported most frequently with insulinoma (see ch. 303),[97-104] although a variety of other tumors has also been implicated.[12,105-112] The mechanism of disease is suspected to be primarily immune-mediated, due to antigen mimicry, wherein the immune system generates a response to antigens present within the neoplasm that are shared with the peripheral nerves.[113,114] In patients with insulinoma, hypoglycemia has also been suggested to have a causative role. Sensory, motor and autonomic neuropathies have been described in humans,[115] but motor signs have predominated in veterinary reports. Although infrequently reported, electrophysiological or histological evidence of peripheral nerve dysfunction is present in a large proportion of animals with cancer, and this condition is likely an underrecognized cause of weakness in these patients.[97,116,117] A substantial number of circulating autoantibodies have been associated with specific neoplasms in human patients with paraneoplastic polyneuropathies, often predating the diagnosis through conventional means.[113,114,118] Such autoantibodies have not yet been identified in veterinary patients. Diagnosis consists of documenting appropriate clinical signs (e.g., paresis, hyporeflexia, muscle atrophy), electrophysiologic changes and muscle and nerve biopsy results in an animal with an identified neoplasm, while eliminating other potential etiologies.

Dramatic improvement or resolution of clinical signs has been documented after surgical excision or other therapy for the cancer.[98,102,105,108,119,120] As the underlying mechanism is likely immune-mediated, immunomodulatory therapy has been utilized in human patients, including corticosteroids, plasma exchange, intravenous immunoglobulin, and other immunosuppressive drugs. Such therapy may be ineffective in resolving the neurologic signs if neuronal destruction has already occurred, although stabilization of signs may be seen.[113,121] Immunomodulatory therapy has been infrequently reported in veterinary patients, although dramatic improvement after corticosteroid therapy has been documented in a dog with insulinoma.[98]

Infectious and Inflammatory Disorders

Protozoal Polyradiculoneuritis

Neosporosis has emerged as an important cause of neuromuscular disease in dogs (see ch. 221).[122-124] The responsible protozoal organism, *Neospora caninum*, was first identified in 1988, and the canine species was confirmed to be a definitive host in 1998.[125-129] Many cases of protozoal polyradiculoneuritis previously attributed to *Toxoplasma gondii* were likely caused by *N. caninum*.[123,124,130] These organisms can be distinguished with immunohistochemistry, and occasionally with careful study of cyst structure with light or electron microscopy.[122,131] Both *T. gondii* and *N. caninum* display a predilection for nervous tissue, and can invade peripheral nerves, muscle and the CNS. Clinical signs include paresis involving one or multiple limbs, muscle atrophy, reduced muscle tone, muscle pain, postural reaction deficits, and reduced or absent

segmental spinal reflexes.[132,133] Cranial nerve signs such as head tilt, dysphagia, and tongue paresis have occasionally been reported.[132] A classical presentation of *N. caninum* infection is paraparesis in young puppies, which progressively leads to a non-ambulatory state characterized by rigid extension of the pelvic limbs associated with muscle contractures.[122,134-136] These dogs are infected transplacentally, and 25% or more of puppies from such litters may show clinical signs.[124,130,133,137] Ingestion of raw meat appears to be a risk factor for both *T. gondii* and *N. caninum* infection.[124,133,138]

Serological tests are available for *T. gondii* and *N. caninum* but must be interpreted with care, as exposed animals may seroconvert in the absence of clinical disease.[122,138-141] Paired acute and convalescent titers and evaluation of IgM levels (for *T. gondii*) may help in distinguishing infected from merely exposed animals.[133] However, serum titers for *N. caninum* rarely exceed 1 : 800 in clinically unaffected dogs.[132,139] PCR tests have been developed for these organisms and are now available from a number of laboratories.[142-144] EMG typically shows spontaneous activity in affected limb muscles. Analysis of CSF may show a mixed cell or nonsuppurative pleocytosis with protein elevation.[123,124] Muscle and nerve biopsies often show evidence of inflammatory cell infiltrates and may show protozoal organisms in some cases.[145]

Clindamycin remains the treatment of choice for *T. gondii* infection in both dogs and cats, although other drugs, including sulfonamides, pyrimethamine, doxycycline, and minocycline have some efficacy.[133] For *N. caninum*, therapy with clindamycin or potentiated sulfonamide drugs, with or without pyrimethamine, is often effective and can result in complete resolution of signs.[132,146,147] However, some patients progress in the face of such therapy, and significant improvement is very unlikely if muscle contractures have occurred.[136,148]

Acute Polyradiculoneuritis

Acute polyradiculoneuritis can be seen in both dogs and cats and causes an acute, ascending, flaccid tetraparesis (Video 268-3). Clinical signs typically progress rapidly over several days, although progression may continue for up to 10 days.[18,149-152] Although the pelvic limbs are usually involved first, with subsequent involvement of the thoracic limbs, the latter may be primarily or exclusively involved in rare cases. Severe cases progress to involve the cranial nerves and respiratory musculature, leading to hypoventilation. Segmental spinal reflexes are reduced to absent, but sensation remains intact, and many animals appear hyperesthetic. This disorder was first recognized in dogs approximately 7-10 days after contact with a raccoon and was originally termed coonhound paralysis. However, identical signs are seen in animals without raccoon exposure, and although other precipitating causes such as vaccination or infection may be identified, in many cases the trigger is unknown.[151-153] The evidence strongly suggests that this is an immune-mediated disease with similarities to Guillain-Barré syndrome (GBS) in humans, resulting from shared antigen between the inciting stimulus and peripheral nervous tissue.[18] Inflammatory cell infiltrates occur in and around peripheral nerves and particularly involve the ventral nerve roots.[18,149-151,154] Recently, circulating anti-GM2 ganglioside antibodies have been detected in a subset of dogs with acute polyradiculoneuritis.[155]

The diagnosis is suspected based on characteristic clinical signs, disease course, and potential history of an inciting cause. The main differential diagnoses are tick paralysis, botulism, elapid envenomation, and fulminant myasthenia gravis, which are all diseases of the neuromuscular junction (see ch. 269). Electrophysiologic testing can be helpful in distinguishing acute polyradiculoneuritis from these other diseases (see ch. 117). Spontaneous activity is seen on EMG examination, which may be detectable 1-2 days after disease onset.[156,157] Abnormalities on motor nerve conduction studies include reduced compound muscle action potential (CMAP) amplitudes and temporal dispersion with prolonged CMAP latencies.[4,156] Motor and sensory nerve conduction velocities are relatively preserved. F wave evaluation is particularly sensitive in detection of this condition due to involvement of the ventral nerve roots, and reveals increased F wave latencies, abnormal F ratios or completely absent F waves.[18,156] Analysis of CSF collected from the lumbar cistern (see ch. 115) may reveal an increased protein concentration without pleocytosis.[18] Therapy is mainly supportive in nature, and most animals will recover if given sufficient time (Video 268-4).[151,152] However, recovery time is variable, and may take a few weeks or up to 6 months in rare cases.[18,158] Patients with respiratory muscle involvement may require mechanical ventilation.[159] Despite the immune-mediated nature of the disease, corticosteroid therapy has not been shown to be beneficial, worsens muscle atrophy and

may predispose patients to secondary infections.[149] A recent study suggested that administration of human intravenous immunoglobulin might shorten the recovery time in dogs with acute polyradiculoneuritis,[160] although this and other immunomodulatory therapies such as plasmapheresis require further study in veterinary patients.

Brachial Plexus Neuritis

Brachial plexus neuritis is a rare condition, with only a few case reports in the veterinary literature.[88,161-165] Reported clinical signs include lameness, paresis, muscle atrophy, depressed segmental spinal reflexes, and sensory impairment exclusively affecting the thoracic limbs, typically with a bilateral but asymmetric distribution. Spontaneous activity is noted on EMG, while nerve conduction may be normal or slightly prolonged. Analysis of CSF may also be normal or may show a mild lymphocytic pleocytosis and protein elevation.[164] Diagnostic imaging, particularly MRI, may show thickened nerves and nerve roots suggestive of this condition, but histopathology may be required to differentiate neuritis from neoplastic infiltration of the nerves.[15,88,164] A response to glucocorticoids has been noted in some cases,[164,165] and spontaneous remissions, although often protracted, have been described.[15,158] The cause of this syndrome is uncertain, but an immune-mediated mechanism is likely.

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory neuropathies characterized by demyelination have been described in both dogs and cats using a number of terms, including chronic inflammatory demyelinating polyneuropathy (CIDP), chronic relapsing neuropathy, acquired demyelinating neuropathy, and chronic demyelinating polyradiculoneuritis.[14,18,158,166,167] Parallels have been drawn to the human disease, also termed CIDP.[167,168] The underlying etiology is unknown, but is suspected to be immune-mediated based on endoneurial mononuclear inflammatory cell infiltrates, IgG antibody immunostaining of myelin, the absence of detectable infectious agents, and a positive response to corticosteroid administration.[15,18,158,166] Demyelination is the predominant pathologic finding on examination of nerve biopsies, with axonal degeneration seen less frequently.[15,158] Inflammatory cell infiltrates have a patchy distribution and may not be appreciated in biopsy samples. Skeletal muscle biopsies may show fiber size variation, consistent with denervation.[166,169,170] Clinical signs usually develop insidiously and are slowly progressive, typically involving the pelvic limbs first and then the thoracic limbs.[167] Monoparesis is a less frequent initial manifestation. Some patients display a relapsing-remitting course[167,169,170] and acute onset of signs has also been described.[171] Clinical signs consist of various degrees of paresis, exercise intolerance, muscle wasting, reduced segmental spinal reflexes, and occasionally muscle tremors, lameness, ventroflexion of the neck, facial paralysis, dysphonia, megaesophagus, and laryngeal paralysis (Video 268-5).[15,167,169,170] EMG may be normal or may show patchy spontaneous activity, but MNCV is consistently decreased, often with evidence of conduction block (see ch. 117).[18,167,169,170] Many animals respond to corticosteroid administration at immunosuppressive dosages, although this response is incomplete in some animals.[18,158,167,169] Additional immunosuppressive regimens have not been well studied in veterinary patients, although intravenous immunoglobulin, plasma exchange, azathioprine, cyclophosphamide, and other immunomodulatory drugs have been recommended for human patients.[168,172]

Sensory Polyganglioradiculoneuritis

An inflammatory neuropathy preferentially affecting the sensory nerves, nerve roots and dorsal root ganglia has been described in various breeds of dog from 1.5-9 years of age.[149,173-176] The underlying cause of the condition is unknown, although infectious (viral), immune-mediated, and toxic etiologies have been suggested.[173,176] Similar sensory nerve involvement has been seen with some toxins, including mercury, doxorubicin and the administration of large amounts of pyridoxine (vitamin B_6).[158,177,178] There is a mononuclear inflammatory cell infiltrate into the sensory nerve structures and occasionally into autonomic ganglia predominated by CD3+ lymphocytes.[15,173-176] Clinical signs consist of ataxia, reduced to absent proprioception and segmental spinal reflexes (particularly the patellar reflex), and hypalgesia of the face, trunk or limbs.[149] Dysphagia, regurgitation, megaesophagus, anisocoria, and self-mutilation have been

reported in some cases.[149,173,175] Acute and chronic clinical courses have been noted, and the condition is typically progressive. Limb muscle mass, tone and strength is preserved, although masticatory muscle atrophy has been reported in some cases, and is attributed to damage to motor fibers as they pass through the trigeminal ganglion.[15] EMG and MNCV are typically normal, although SNCV is abnormal and may not be recordable.[173] CSF analysis is usually normal.[173] Histological changes characterized by axonal degeneration may be noted with a nerve biopsy, although care should be taken to biopsy a sensory or mixed function nerve (e.g., caudal cutaneous antebrachial nerve or caudal cutaneous sural nerve).[6,7,179] Inflammatory infiltrates may not be noted unless a dorsal root ganglion is biopsied. Muscle biopsy is usually normal. As the disease is inflammatory and suspected to be immune-mediated, immunosuppressive therapy with corticosteroids and other drugs has been attempted, but has not been successfully reported to date.[158,173] A similar condition has been described in a young cat.[180]

Traumatic Disorders

Trauma to peripheral nerves can occur secondary to a variety of insults, including blunt trauma, laceration injuries (e.g., animal bites, knife wounds), stretching or tearing injuries (e.g., automobile accidents), compression from fractures or swollen compartmentalized tissue, or iatrogenic injury (e.g., injection site injury or surgical trauma). Several terminologies and grading systems have been developed to describe the degree of nerve injury based on disruption of the myelin sheath, axon and supporting tissue.[158,181] The most common injuries are those involving the brachial plexus secondary to a motor vehicle accident (Video 268-6),[165,181] the sciatic nerve secondary to trauma or iatrogenic injury,[181-187] and the caudal nerves secondary to traction injury of the tail.[181,188-190] Femoral nerve dysfunction is also being increasingly recognized secondary to trauma involving the iliopsoas muscle in dogs.[191-193]

The main clinical signs are varying degrees of paresis and disuse of the limb or tail, impaired postural reactions and reflex function, pain with ambulation or limb manipulation and possibly impaired sensation.[181,184,186] The diagnosis is usually obvious based on history and examination. However, assessment of the severity of the injury may be aided with EMG to document denervation or nerve conduction studies to document the presence or absence of conduction past the injured site (see ch. 117).[69,181,183,194-196] Ultrasonography, CT or MRI may be useful in documenting nerve or muscle trauma associated with the injury.[191-193,197,198] Therapy typically centers on supportive care and rehabilitation including passive range of motion, massage and other physiotherapy exercises to help to maintain muscle and joint integrity while awaiting recovery (see ch. 355). Removal of compressive bone fragments or implants is indicated, if present. Some animals may traumatize limbs due to dragging during ambulation or by self-mutilation, and covering the limb with a bandage or bootie may help to avoid this complication.[199] Other potentially useful interventions include analgesics and medications to modulate paresthesias (e.g., gabapentin, pregabalin) and orthotics or braces for limb support.[199-203] Although rarely employed, techniques to surgically reattach partially or fully severed peripheral nerves and the use of nerve grafts have been described in small animals.[184,204-208] Recovery is dependent on the integrity of the endoneurial structures as well as the distance required to re-innervate the target, as axonal regeneration occurs at a rate of approximately 1-2 millimeters per day.[181] A loss of sensation in the limb or tail distal to the injury usually indicates a poor prognosis, although ideally 4-6 weeks should be allowed for potential recovery. Ultimately amputation of the limb or tail is often necessary.

Toxic Disorders

Several toxins, pharmaceuticals and other agents have been reported to cause peripheral neuropathies in small animals, although these are infrequently seen and documented. Such substances include heavy metals (e.g., mercury, thallium, lead), antibiotics (e.g., lasalocid, nitrofurantoin, salinomycin), pesticides (e.g., organophosphates), organic solvents and chemicals (e.g., acrylamide, hexacarbons), vitamins (e.g., pyridoxine), and antineoplastic drugs (e.g., vincristine, vinblastine, cisplatin).[15,18,120,177,178,209-218]

Autonomic Neuropathies

Dysautonomia refers to generalized dysfunction of the autonomic nervous system, and is seen in several

veterinary species.[219-223] Detailed discussion of this condition is beyond the scope of this chapter, and interested readers are referred to more comprehensive reviews of the topic.[9,219,224,225] Autonomic dysfunction can also occur as part of a more generalized peripheral neuropathy, which has been well documented in human patients with a variety of conditions including diabetes mellitus, paraneoplastic polyneuropathy, Guillain-Barré syndrome, and toxic neuropathies.[115,226,227] Reports of such autonomic involvement are infrequent in the veterinary literature, but this component of the disease process may be under-recognized.[26,104,225,228] Selective autonomic lesions have been reported in dogs with myenteric ganglionitis presenting with diarrhea or megacolon,[229,230] a dog with pupillotonia and several cats with Pourfour du Petit syndrome presenting with unilateral mydriasis,[231,232] and are frequently seen in animals with Horner's syndrome or oculomotor nerve lesions due to neoplastic, inflammatory, traumatic, or idiopathic causes.[233]

Miscellaneous Idiopathic Neuropathies

Distal denervating disease is an idiopathic canine polyneuropathy with primarily axonal involvement that affects motor nerves in a distal distribution and usually spontaneously improves in 4-6 weeks.[158,234,235] Other axonopathies with a similar distal distribution, but with chronic, unremitting courses, have also been described and termed distal symmetrical polyneuropathy or chronic axonal degeneration.[18,158,236] Idiopathic neuropathies affecting the trigeminal, facial and vestibular nerves are frequently recognized.[47,158,237-241] Whereas dysfunction of the trigeminal and vestibular nerves is typically self-limiting with spontaneous improvement, facial nerve paralysis often fails to improve, and requires long-term management. Idiopathic laryngeal paralysis occurring in older dogs is likely one manifestation of a more generalized peripheral neuropathy and Labrador Retrievers are overrepresented in reports of this condition (see ch. 239).[242-244]

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CHAPTER 269

Neuromuscular Junction Disorders

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Client Information Sheet: Myasthenia Gravis

Introduction

Definitions

The neuromuscular junction (NMJ) is composed of the pre-synaptic motor nerve terminal, synaptic cleft and post-synaptic muscle end plate (Figure 269-1). It provides unidirectional communication between axon terminal of the motor nerve and the muscle via the neurotransmitter acetylcholine (ACh). The NMJ is one of several components of the motor unit, and patients with disease of the NMJ present with clinical signs consistent with lower motor neuron (LMN) disease (see ch. 268).

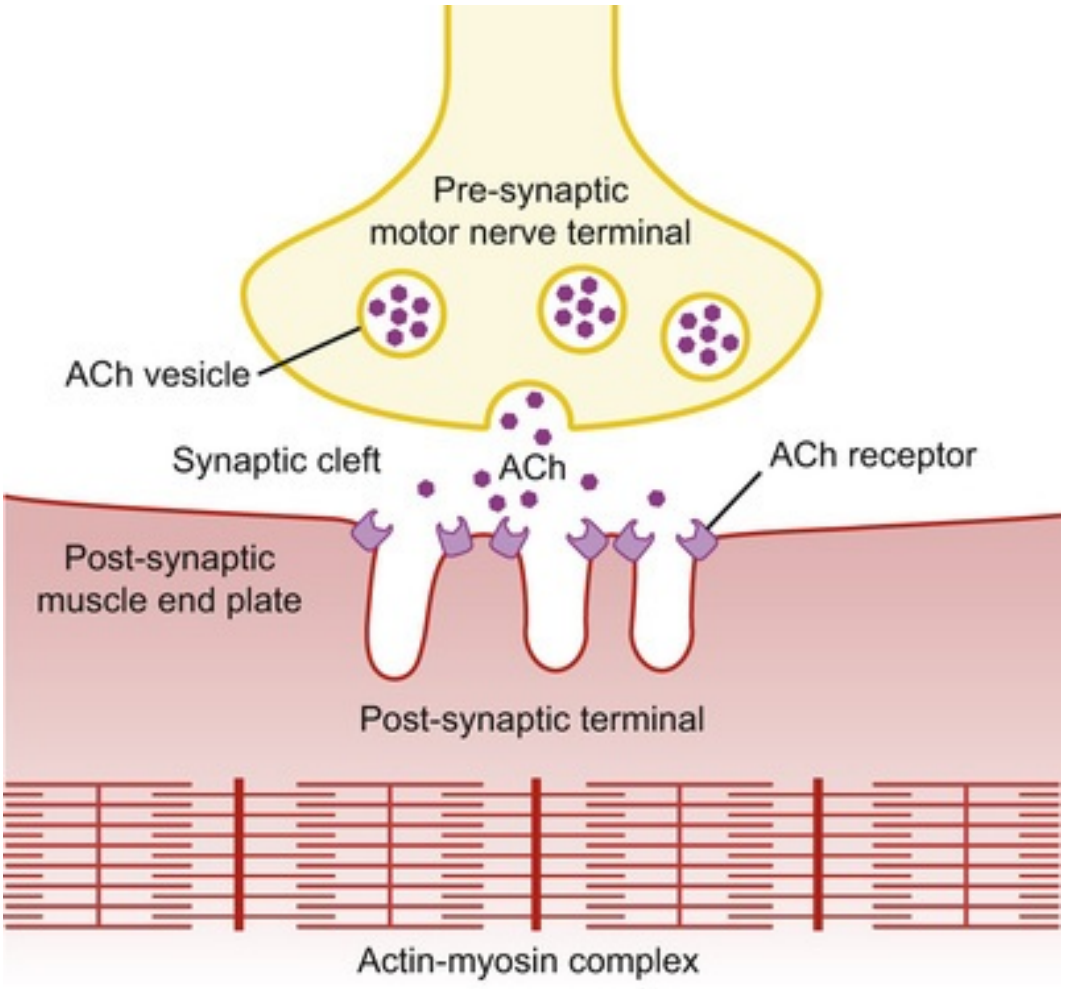

FIGURE 269-1 Schematic representation of the neuromuscular junction. (Reproduced with

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Function

Action potentials originating within the ventral horn motor neurons of the spinal cord are propagated down peripheral motor nerve fibers. Flattened processes of the motor nerve endings (the *pre-synaptic terminal*) form a small indentation in skeletal muscle fibers, called the *synaptic cleft*. A thickened portion of the muscle fiber membrane adjacent to the synaptic cleft constitutes the *post-synaptic terminal*. The pre-synaptic terminal contains a large store of ACh-containing vesicles which are released into the synaptic cleft in response to depolarization of the pre-synaptic nerve terminal. Calcium, an important co-factor in this process, facilitates fusion of ACh vesicles to the pre-synaptic membrane and subsequent exocytosis of ACh into the NMJ. ACh diffuses across the synaptic cleft to bind to ACh receptors (AChR) on the post-synaptic muscle membrane to ultimately result in muscle fiber contraction. Free ACh that persists within the synaptic cleft is broken down by the enzyme acetylcholinesterase (AChE) (see Figure 269-1). In normally-functioning motor units, there is an excess of available ACh and AChR. The muscle membrane potentials produced by nerve depolarization also greatly exceed what is required for muscle fiber contraction. This is known as the *safety factor* of neuromuscular transmission.

Clinical Signs

Disorders affecting the NMJ can be classified as pre-synaptic or post-synaptic in nature. They result from inability to release ACh from the pre-synaptic terminal into the synaptic cleft, or from inability of the post-synaptic muscle membrane to respond to ACh. Either disorder results in impaired neuromuscular transmission. Clinical manifestations of impaired neuromuscular transmission are typically symmetrical in nature, and may include acute tetraparesis or tetraplegia, chronic static or progressive tetraparesis, or episodic weakness that is exacerbated by activity. Pets with clinical signs referable to the NMJ have paresis that is accompanied by decreased muscle tone (flaccid paresis) and they may not be able to hold their head up due to weakness of the cervical musculature. They may also have decreased segmental spinal reflexes, cranial nerve deficits, or autonomic signs. The presence of the latter three abnormalities is disease- and severity-dependent. Patients with disease of the NMJ generally have normal sensory function and a normal level of consciousness.

Pre-Synaptic Diseases of the Neuromuscular Junction

Tick Paralysis

Tick paralysis is most commonly associated with exposure to ticks of *Dermacentor* sp. or *Ixodes* sp.[1,2] Clinical signs of tick paralysis result from a neurotoxin produced in the large salivary glands of female ticks. This neurotoxin is released into circulation after the tick attaches and feeds for several days. The exact cellular mechanism of this salivary neurotoxin has not been defined but it appears to interfere with ACh release from the pre-synaptic nerve terminal via a calcium-mediated mechanism.[1,3,4] Tick paralysis does not cause abnormalities on the complete blood count (CBC), serum biochemical tests, diagnostic imaging, or cerebrospinal fluid (CSF) evaluation.[5] Electrodiagnostic procedures are not typically performed. Clinical signs are present when an engorged tick is attached, and resolve when the offending tick is removed. Diagnosis is presumptive in most cases and is based on identification and removal of an engorged tick (see Video 211-1 in ch. 211).

In North America, *Dermacentor* ticks are most commonly associated with tick paralysis.[1] Dogs are commonly affected, while cats appear resistant. Clinical signs begin 5-9 days after tick attachment.[6] Dogs with tick paralysis have an acute, rapidly progressive, ascending flaccid paresis that can progress to tetraplegia over 12-72 hours. Segmental spinal reflexes are severely diminished to absent in all four limbs, and muscle tone is decreased.[5,7-9] Cranial nerve deficits are uncommon in dogs from North America, but mild facial and masticatory muscle weakness and dysphonia are occasionally observed.[7] Autonomic, sensory, and sphincter abnormalities do not occur in dogs with American tick paralysis. In severe cases, respiratory paralysis may necessitate mechanical ventilation and death due to hypoventilation can occur. Removal of the offending tick results in dramatic improvement in signs, usually within hours.

In Australia tick paralysis is far more severe, and is most often caused by *Ixodes* sp. ticks. Cats as well as

dogs may be affected.[3,6-8] Similar to American tick paralysis, dogs and cats with Australian tick paralysis have an acute, rapidly progressive ascending flaccid paresis that can progress to tetraplegia in hours. Autonomic dysfunction, urinary dysfunction, and congestive heart failure due to diastolic dysfunction can occur.[5,7,8,10] Pupillary dilation is common in cats and often observed in advanced canine cases.[6] Affected animals may develop pulmonary edema, aspiration pneumonia, and progressive hypoventilation.[5,8,10] Unilateral cranial nerve deficits and Horner's syndrome have also been reported.[11] Unlike American tick paralysis, pets with Australian tick paralysis may continue to decline for several days after tick removal.[12]

Tick removal in conjunction with supportive care is the primary treatment for both American and Australian tick paralysis. Pets should be searched carefully for ticks, which may necessitate clipping the hair. Examining the ear canals, perineum, mouth, nasal cavities, and interdigital spaces is also important. If a tick cannot be found, topical acaricides may be applied. In Australian tick paralysis, phenoxybenzamine and acepromazine may be used to treat autonomic signs.[7,8,13] Glucocorticoids are not routinely used to treat tick paralysis, and antibiotic therapy is not helpful.[7,9]

Botulism

Botulism is an acute diffuse lower motor neuron condition resulting from exposure to neurotoxins produced by the bacterium *Clostridium botulinum,* a Gram-positive anaerobe ubiquitous in soil, water, and the gastrointestinal (GI) tracts of mammals and fish. Most pets develop botulism by ingesting the pre-formed botulinum neurotoxin in spoiled or uncooked meat, although rarely botulinum toxin may be produced *in vivo* after liver or GI infection. This latter scenario is referred to as toxico-infection. Eight different types of botulinum toxin have been identified, but the most common in dogs is botulinum neurotoxin type-C (BoNT-C).[15-18] Naturally occurring botulism is extremely rare in cats, but has been reported with BoNT-C.[19]

Botulinum toxin blocks release of ACh at the pre-synaptic terminal of skeletal muscle and cholinergic autonomic synapsis by irreversible enzymatic cleavage of Soluble N-ethylmaleimide-sensitive factor activating protein receptor (SNARE) proteins.[6,15,20,21] SNARE proteins are essential for "docking" synaptic ACh vesicles to pre-synaptic membranes, allowing release of ACh into the synaptic cleft. Impaired ACh release causes an acute onset of progressive tetraparesis accompanied by autonomic signs such as ileus, tachy- or bradycardia, mydriasis, and urinary retention. Cranial nerve deficits such as a decreased palpebral reflex, megaesophagus, and diminished pupillary light reflexes are also common.[15,16,22] The rate of development and severity of clinical signs is dependent on the quantity of toxin ingested, with signs occurring within hours to as long as 6 days after ingestion of contaminated food.[8,10]

A diagnosis of botulism can be made by demonstrating BoNT in blood, feces, stomach contents, or food source of an affected animal. Historically, the gold standard for diagnosing botulism was the mouse inoculation test: instilling a patient sample into the peritoneal cavity of a mouse and observing development of clinical signs.[15,16] In reality, a clinical diagnosis of botulism is often presumptive based on history and clinical examination. Routine bloodwork will not show abnormalities. Electrodiagnostic testing can confirm botulism poisoning by demonstrating incremental increases in compound muscle action potentials (CMAP) with stimulation at high rates.[18] This finding is present in about 60% of adult humans with botulism, but has not been described in the dog.[23]

Treatment for botulism is primarily supportive in nature. Antibiotics are not generally indicated but may be considered if toxico-infection is a possibility or if other indications such as aspiration pneumonia are present. Certain antibiotics such as aminoglycosides and ampicillin may potentiate neuromuscular blockade and should be avoided.[24] Although the administration of antitoxin has been recommended, most available products do not contain antibodies against BoNT-C and are therefore not useful for dogs.[15,22] Antitoxins cannot bind toxin after it has entered nerve terminals, but they may be effective in binding circulating toxin and in partly halting the progression of disease.[15,20] If given, a test injection should be performed, as these products are of equine origin, and anaphylactic reactions are possible (see ch. 137).[20] Recovery from botulism occurs spontaneously over 1 to 4 weeks and the prognosis for most animals is excellent if they can be adequately supported.[8,15]

Elapid Snake Envenomation (see ch. 156)

Elapid snakes include the eastern *(Micrurus fulvius)* and Texas *(Micrurus tener)* coral snakes in North America,

the tiger *(Notechis scutatus)*, brown (*Pseudonaja* spp.) and red-bellied black snakes *(Pseudechis porphyriacus)* in Australia, and a variety from other continents, including cobras, kraits, and mambas.[25-29] Unlike crotalids, elapid snakes have short, rigid, immovable fangs, and an obvious puncture wound may not be present in envenomated animals.[25] Depending on the snake, the venom causes either a postsynaptic nondepolarizing neuromuscular blockade by tightly binding to AChR on the postsynaptic membrane, or it causes a presynaptic inhibition of ACh release.[25,27,30]

Clinical signs occur within hours of envenomation and include flaccid tetraparesis or tetraplegia, hypotonia, reduced or absent segmental spinal reflexes, and hypoventilation.[25-32] Pelvic limb ataxia may also be a prominent clinical sign in some cases.[33-35] Cranial nerve signs—ptyalism, dysphagia, dysphonia, and facial paresis or paralysis—are frequently observed.[28,31,32] Urine discoloration due to hemoglobinuria or myoglobinuria is seen in many dogs, but not as frequently in cats.[26,32,33] This can be useful in diagnosis, as it is not a feature of other NMJ or peripheral nerve diseases. Other abnormalities noted include vomiting, depression, hypotension, hypothermia, bleeding secondary to coagulopathies, and ventricular arrhythmias.[27,31-35] Diagnosis of elapid snake envenomation is typically presumptive, based on clinical signs and history. A CBC may show decreased hematocrit, spherocytosis, and erythrocyte "burring."[32]

Treatment is mainly supportive. The use of a pressure bandage at the site of envenomation can help to prevent circulation of venom through the lymphatics.[27] Fluid diuresis should be considered if hemoglobinuria or myoglobinuria is present (see ch. 129). The administration of antivenin has been advocated and may be beneficial in preventing or reducing the severity of clinical signs.[25,26,29,33-36] Equine-based products carry risks of anaphylaxis, and test injections should be considered. A variety of antivenins is available in Australia and other countries. North American supplies of coral snake antivenin are no longer being manufactured. However, cross-protection with tiger snake and Mexican coral snake antivenins occurs, and this product is used routinely with good results by some clinicians.[37-39] Most animals make a full recovery within 1 to 2 weeks with adequate supportive care.[29,31-33,39]

Post-Synaptic Diseases of the Neuromuscular Junction

Acquired Myasthenia Gravis (MG)

Pathogenesis and Breed Predispositions

Acquired myasthenia gravis (MG) is an autoimmune disorder characterized by production of autoantibodies against nicotinic AChR on the post-synaptic muscle terminal.[40-42] These autoantibodies lead to complement-mediated destruction of the AChR, reduced numbers of functional receptors, and a diminished ability of the muscle to respond to ACh released into the synaptic cleft.[43-47] The result is skeletal muscle weakness that is often exacerbated by activity. There is a bimodal age distribution for developing acquired MG. Dogs are usually <4 or >9 years of age.[44,48,49] Breeds overrepresented include Akitas, German Shorthaired Pointers, Chihuahuas, German Shepherds, Golden Retrievers, and Newfoundlands.[6,50-52] Acquired MG is less common in cats, but predilections for Abyssinian, Somali, and other pure breeds are reported.[48,53,54] Acquired MG can present in one of three forms, the most common being "generalized," but focal and severe fulminant forms are reported.[48]

Generalized MG

Patients with generalized MG generally have a normal neurologic examination at rest (see ch. 259). However, during a bout of exercise or activity-induced weakness, they demonstrate a choppy, stilted gait first noted in the pelvic limbs.[44] If continued activity is encouraged, thoracic limb involvement will become apparent. Some pets demonstrate a diminished or fatigable palpebral reflex, although not consistently present. Segmental spinal reflexes are typically normal. Signs of pharyngeal or laryngeal dysfunction which can manifest as ptyalism (due to difficulty swallowing; see ch. 36) and/or dysphonia are variably present.[44,48] Dogs with generalized MG often have concurrent megaesophagus and a history of regurgitation (see ch. 39 and 273). In cats, megaesophagus is less often noted.[53] Ventroflexion of the neck due to weakness of the cervical muscles is more common in cats than in dogs.[48,54-56]

Fulminant and Focal Forms of MG

Patients with fulminant MG have sudden and rapidly progressive severe diffuse weakness that does not improve with rest. Their condition progresses quickly to nonambulatory tetraparesis and lateral recumbency.[6] Spinal reflexes may be preserved or diminished.[6] Frequent regurgitation of large fluid volumes associated with megaesophagus is typical and aspiration pneumonia common (see ch. 242 and 360).[40] Additional signs include respiratory muscle weakness and urine retention. The prevalence of fulminant myasthenia has been reported to be 16% in dogs and 15% in cats. Thymoma has been associated with the development of this form of the disease in both species.[42,55,57-63]

Focal MG presents as weakness of an isolated muscle group, most commonly the ocular, facial, esophageal, pharyngeal, or laryngeal muscles. Generalized weakness is not observed in these pets and typical presenting complaints include regurgitation, dysphagia, dysphonia, or strabismus.[44,49,64]

Associated Conditions

Several diseases have been associated with MG in dogs and cats. These include thymoma, hypothyroidism, hypoadrenocorticism, polymyositis, and masticatory myositis.[42,63,65,66] In hyperthyroid cats, an association between acquired MG and methimazole treatment has been reported, which resolves with discontinuing the medication.[53,67,68]

Diagnosis

No change on routine CBC or serum biochemistries is pathognomonic for MG. Evidence of inflammation is common in pets with aspiration pneumonia. These tests are valuable in screening for metabolic causes of neuromuscular weakness (hypocalcemia, hypothyroidism, hyperadrenocorticism) and to assess creatinine kinase as an indicator of polymyositis (see ch. 66).[69] Thoracic radiographs or thoracic CT should be obtained to document presence or absence of thymoma and to screen for secondary aspiration pneumonia. Contrast swallowing studies can be used to assess dysphagic pets (see ch. 273), but are contraindicated in megaesophagus and regurgitation. Abdominal ultrasound may also be considered to rule out paraneoplastic causes of acquired MG in older patients (see ch. 88).[70-73]

The gold standard for diagnosis of acquired generalized MG in veterinary patients is demonstration of anti-AChR autoantibodies in serum.[69,73,74] While some cross-reactivity between species does occur, autoantibodies against the AChR are relatively species-specific. For this reason, it is essential to use a canine- or feline-specific assay system.[69] Antibody levels are highly variable between patients and do not correlate well with severity of clinical signs; however, within a specific patient, a decrease in antibody levels correlates well with improvement in clinical signs and can be followed to assess remission of disease.[69] It has been suggested that measurement of species-specific anti-AChR autoantibodies will detect approximately 98% of dogs with generalized acquired MG.[69] Antibodies are reported in a smaller percentage of dogs with focal MG. Antibody titers may be negative early in the course of disease and can be impacted by administration of corticosteroids prior to measurement.[75] Retesting is suggested in patients where either scenario is suspected. A small number of patients may have true seronegative acquired MG. In these cases, a diagnosis can be confirmed by documenting decrements in CMAP in response to repetitive nerve stimulation, and by normalization of limb muscle weakness after anticholinesterase therapy.[75]

Administration of the short-acting anticholinesterase drug edrophonium can be used diagnostically to assess improvements in muscle strength, gait, or the ability to swallow.[42] This drug inhibits AChE, allowing more ACh to remain in the NMJ, thereby improving neuromuscular transmission. Animals will often show improvement within seconds of receiving the drug (Video 269-1). The effect lasts for several minutes, followed by a return of clinical signs. It should be noted that improvement following edrophonium administration is not completely specific to MG, as some animals with other forms of neuromuscular weakness can also show improvement.[43,73,76] In addition, not all animals with MG will improve with edrophonium.[43,73,77] Precipitation of a cholinergic crisis is possible by overstimulation of AChR, leading to aggravation of weakness, salivation, tremors, vomiting, bradycardia, bronchoconstriction, and respiratory distress. Animals must be monitored closely after edrophonium administration. Atropine and equipment to provide intubation and respiratory support must be available and ready for use if necessary.

Long-Term Treatment

Long-term treatment for animals with acquired MG targets two goals: (1) increasing the amount of ACh

available within the synaptic cleft to counteract the deficiency in AChR numbers and (2) reducing autoantibodies produced against the AChR. Anticholinesterase drugs such as pyridostigmine bromide (oral) or neostigmine (IM) are the mainstays of therapy, working by inhibiting AChE so that ACh has a longer duration of action within synaptic clefts.[8,42,78,79] These medications must be carefully titrated to effect. Neostigmine is generally only used in hospitalized patients that are unable to take medications by mouth such as those in acute crisis or with profound and frequent regurgitation. Both medications have a narrow therapeutic window, and significant side effects such as bradycardia, hypersalivation, vomiting, diarrhea, muscle cramping, and weakness can occur.[79] This can be problematic, as the clinical signs associated with excessive anticholinergic drug administration may be difficult to distinguish from those of uncontrolled MG.

Immunosuppressive drugs such as cyclosporine, mycophenalate mofetil (MMF), and azathioprine are also frequently used in the treatment of acquired MG to reduce the levels of circulating autoantibodies by targeting the adaptive immune response while sparing innate immunity and neutrophil function (see ch. 165).[78,80-83] MMF was once the favored immunosuppressive drug for MG based on the human experience; however, a recent study comparing pyridostigmine plus MMF and pyridostigmine alone showed no difference in survival time or remission rates.[83]

Corticosteroids can also be effective in the treatment of MG (see ch. 165), but should be used with caution in patients with aspiration pneumonia (see ch. 242 and 360). Corticosteroids can potentiate muscle weakness and exacerbate clinical signs in some patients, and a gradual increase in steroid dosage is recommended to help avoid this complication.[41,57,73,75,77,78] Other strategies for immunomodulation may also be employed in patients with MG, including therapeutic plasma exchange and IV immune globulin (IVIG).[84-86] Neither technique has been thoroughly evaluated in a large number of dogs with MG, although there is some evidence to support their utility in this and other immune-mediated diseases.[86-91] A long-term spontaneous remission rate as high as 88% has been reported for dogs with non-paraneoplastic causes of acquired MG.[92]

Congenital Myasethenia Gravis

Presumed congenital MG, or myasthenic syndrome, has been reported in Jack Russell Terriers, Smooth Fox Terriers, Springer Spaniels, Samoyeds, smooth-haired Miniature Dachshunds, Gammel Dansk Hønsehund (GDH) dogs, mixed-breed dogs, and cats.[54,93-104] A deficiency of AChR is assumed in most breeds and has been documented in Jack Russell Terriers, Springer Spaniels, and Miniature Dachshunds.[101,105] The disease often affects multiple animals within the same litter and usually becomes evident after 6 to 9 weeks of age. Generalized limb and cervical muscle weakness that worsens with activity is common. Megaesophagus may or may not be present.[98,101] The GDH dogs are unusual because the condition begins at about 4 months of age and is relatively unresponsive to AChE-blocking drugs.[102,106] These dogs are thought to have a pre-synaptic defect in neuromuscular transmission.[106,107] An autosomal-recessive mode inheritance has been demonstrated in Smooth Fox Terriers, Jack Russell Terriers, and GDH dogs.[94,97,108]

A definitive diagnosis of congenital MG can be made by quantification of AChR in a muscle biopsy (see ch. 116), although such testing is not readily available.[101,105] Pyridostigmine or neostigmine are cornerstones of therapy and often cause improvement. However, the long-term response to therapy is variable, and reports in most breeds describe death or euthanasia of affected animals due to difficulty in controlling clinical signs.[98,99] Exceptions to this are congenital MG in Miniature Dachshunds, which spontaneously resolved by 6 months of age, and GDH dogs who remain stable with mild clinical signs.[101,102]

Other

Exercise-Induced Collapse of Labrador Retrievers

Although not a disease of the NMJ, exercise-induced collapse of Laborador Retrievers (EIC) causes fatigue and flaccid para- or tetraparesis during or after strenuous activity. Examination findings are normal at rest. Ataxia, pelvic limb weakness, and collapse develop in association with intense or prolonged field training, hunting, or vigorous play. Clinical signs may progress to involve the thoracic limbs if the animal continues activity. Recovery occurs with rest, and most dogs are clinically normal within 30 minutes; however, severe episodes can result in death.[109-111]

The condition is heritable in Labradors, associated with an autosomal recessively inherited mutation (Arg256Leu) in the gene encoding for the protein dynamin 1 (DNM1).[109,110] The dynamin gene family

encodes for a group of enzymes that maintain synaptic vesicle function during sustained neurotransmission (e.g., during intense physical activity).[109,112] Specifically, DNM1 is expressed at synaptic terminal membranes within the central nervous system and is important in the recycling of synaptic vesicles during high-frequency neurological stimulation. A collapse phenotype is also recognized in other breeds, but association between collapse and the Arg256Leu mutation in variable.[112]

Dogs with DNM1-associated EIC (d-EIC) typically experience their first episode of collapse before 2 years of age.[111] Loss of the patellar reflex is common during an episode, and dogs maintain normal mental status.[111,113] Hyperthermia and elevated plasma lactate often develop during an episode, but are not distinct from what is observed in normal exercising dogs.[113] Serum lactate/pyruvate ratios are normal in dogs with EIC both at rest and during exercise, and muscle biopsies are unremarkable.[113] A genetic test for the *Arg256Leu DNM1* mutation is now commercially available to assist in diagnosis. While there is no cure for EIC, affected dogs have an excellent prognosis if they refrain from intense physical activity known to trigger episodes.[113]

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CHAPTER 270

Unique Feline Neurologic Disorders

Elsa Beltran, Luisa De Risio

Client Information Sheet: Feline Cerebellar Hypoplasia

Central Nervous System (CNS) Diseases

Congenital Malformations

Feline Panleukopenia

Cerebellar hypoplasia caused by perinatal infection with the feline panleukopenia virus (FPV) is the most common diffuse cerebellar disorder in cats.[1] Exposure to FPV during the last 3 weeks of gestation or the first 3 weeks of life may induce destruction of the dividing external germinal layer and cause granuloprival cerebellar hypoplasia in kittens (see also ch. 225).[2,3] Fetal infections before the last 3 weeks of gestation can result in hydranencephaly.[4,5] Vaccination with a modified-live FPV vaccine during pregnancy can result in clinically affected kittens.[5] Clinical signs include cerebellar ataxia, intention tremor, menace response deficits, and nystagmus (Video 270-1). The clinical signs usually remain stable or even improve over time, as some compensation is possible. There are no specific diagnostic tests. Advanced imaging, in particular magnetic resonance imaging (MRI), can reveal cerebellar atrophy. Cerebrospinal fluid (CSF) analysis usually is normal. There is no treatment but these cats may have a good quality of life when their environment is modified to accommodate their disabilities (see online Client Information Sheet). Prevention can be achieved by vaccination of queens before pregnancy.

Inborn Errors of Metabolism

Few are reported uniquely in cats, and these typically also affect the peripheral nervous system (PNS) (Table 270-1).

TABLE 270-1

Inherited Unique Feline CNS and Neuromuscular Diseases

DISEASES, AFFECTED BREED(S), AGE OF ONSET, AND SEX INHERITANCE PATTERN	CLINICAL SIGNS	DIAGNOSTIC TESTS	TREATMENT AND PROGNOSIS
Mannosidosis (alpha-mannosidase deficiency)[74-77] • DSH, DLH, Persian • 7-15 m.o. • AR	Progressive cerebellar dysfunction, abnormal behavior, lethargy, corneal and lens opacification	Genetic test	No treatment Poor prognosis
Glycogen storage disease type IV[78,79] • Norwegian Forest Cat • 5 m.o.	Generalized muscle tremors and weakness that progresses to tetraplegia (PNS and CNS involvement)	Genetic test	No treatment Poor prognosis. Death around 12 m.o.

• AR			
Niemann-Pick disease type A[80-82] • Siamese and Balinese cats • 2-5 m.o., males and females • AR	Progressive tetraparesis, palmi- and plantigrade stance, decreased spinal reflexes	EMG: spontaneous activity Reduced MNCV Enzyme assay in leukocytes and cultured fibroblasts (decreased sphingomyelinase activity)	No treatment Poor prognosis Death around 10 m.o.
Hypokalemic periodic polymyopathy[83-85] • Burmese and Burmese-related breeds • 2 m.o. to 2 y.o., males and females • AR	Episodic and acute onset of passive ventroflexion of the neck, myalgia, head bobbing, stiff gait, weakness. Normal between episodes.	Intermittent hypokalemia (<3.0 mmol/L) and elevated CK Genetic test available	Oral potassium supplementation May improve with time
Muscular dystrophy associated with alpha-dystroglycan deficiency[86,87] • Sphynx and Devon Rex cats • 3-23 w.o., males and females • AR	Inability to jump, passive ventroflexion of the neck, difficulty swallowing, dorsal protrusion of the scapulae, crouching gait, fatigability after short periods of activity	CK: mild to normal values EMG: mild spontaneous activity RNS at 1-3 Hz shows decremental response Muscle biopsy	No treatment Slow progression or can stabilize Death due to aspiration/laryngospasm possible
Polyneuropathy associated with primary hyperchylomicronemia[88,89] • DSH, DLH, Himalaya, Persian, Siamese • 4-8 w.o., females and males • AR	Progressive, focal/multifocal, asymmetric mononeuropathy due to lipid granulomas compressing the peripheral nerves	Reduced LPL activity Mutation in LPL characterized	Low-fat diet could resolve the peripheral neuropathy
Primary hyperoxaluria (L-glyceric aciduria)[90] • DSH • 5-9 m.o., females and males • Suspected AR	Acute onset, weakness, tetraparesis, decreased spinal reflexes, decreased nociception, and abdominal pain	Urine analysis (L-glyceric aciduria) Kidney disease, uremia	Poor prognosis due to acute kidney injury and uremia
Axonal polyneuropathy[91] • Snowshoe cats • 3-6 m.o., males • Suspected inherited	Insidious onset, slightly progressive, intermittent pelvic limb weakness with decreased withdrawal reflex bilaterally	EMG spontaneous activity Reduced MNCV Muscle and nerve biopsies	Supportive treatment Stabilization within 6-12 months, with tendency for remission
Central and peripheral distal axonopathy[92] • Birman cats • 10 w.o., females • Suspect inherited	Slowly progressive palmigrade stance with adduction of the hocks. Hypermetric gait and paraparesis.	EMG: spontaneous activity Reduced MNCV Muscle and nerve biopsies	Supportive treatment Prognosis unknown

AR, Autosomal recessive; *CK*, serum creatine kinase concentration; *CNS*, central nervous system; *DLH*, domestic longhair; *DSH*, domestic shorthair; *EMG*, electromyography; *LPL*, lipoprotein lipase; *m.o.*, months old; *MNCV*, motor nerve conduction velocity; *PNS*, peripheral nervous system; *RNS*, repetitive supramaximal nerve stimulation; *w.o.*, weeks old; *y.o.*, years old.

Prion Disease

Feline spongiform encephalopathy (FSE) is a prion-induced disease affecting the Felidae family.[6-8] Experimental

studies suggest that FSE is caused by the same agent that causes bovine spongiform encephalopathy (BSE) in cattle and new variant Creutzfeldt-Jakob disease in humans.[6,7] Cats are believed to contract the disease by ingestion of BSE-contaminated food. To date, FSE has only been reported in Europe. A recent experimental study demonstrated that chronic wasting disease (transmissible spongiform encephalopathy of mule deer, white-tailed deer, elk, and moose) can be transmitted to the domestic cat, thus raising the issue of potential cervid-to-feline transmission.[9] Clinical disease presents in adult cats and is characterized by chronic progressive clinical signs (from weeks to months), including abnormal behavior, ataxia, muscle tremors, hypersalivation, dilated and unresponsive pupils and hyperesthesia. The diagnosis is based on histopathologic evaluation of the brain.[7,8,10-12] There is no current treatment and the disease is progressive and fatal.

Infectious and Noninfectious Inflammatory CNS Diseases

Viral CNS Diseases

Feline Infectious Peritonitis (FIP)

Feline infectious peritonitis (FIP) is the most common infectious CNS disease in cats.[13-15] Up to 33% of FIP cases show neurological signs, and all three forms (effusive [wet], non-effusive [dry], and mixed) have been associated with CNS involvement; however, the non-effusive form is the most common (see also ch. 224).[14,16,17] FIP usually is seen in purebred cats from multi-cat environments, typically <4 years of age.[14,18-20] The neurologic signs reflect the area of CNS involvement, which often includes the caudal fossa (cerebellum, pons, and medulla oblongata).[17,21] Neurological signs can present alone or in conjunction with systemic signs.[16,18,19] Ophthalmic lesions (iritis, anterior uveitis, and keratitis) have been reported in up to 53% of cases with neurologic FIP (see ch. 11).[16,18,21] The most common neurologic signs are altered mental status, menace response deficits, vestibular syndrome, seizures, ataxia, and paresis (Video 270-2).[16,18,21-25] Seizures occur in up to 33% of cats with neurologic FIP and have been associated with a poor prognosis.[21,24] FIP is the single most common cause of myelopathy in cats younger than 2 years of age (Video 270-3).[23] The general diagnostic evaluation for FIP is described in ch. 224. Current antemortem diagnostic tests for neurologic FIP aim to exclude other conditions that could cause a similar clinical presentation but cannot directly confirm the diagnosis. Advanced imaging findings include obstructive hydrocephalus, ventricular dilation and periventricular, ependymal and meningeal contrast enhancement reflecting the superficial and ventricular nature of the FIP lesions in the CNS (Figure 270-1).[15,18] However, up to 37% of cats with histologically-confirmed neurologic FIP can have normal MRI results.[15] CSF collection should be performed after ruling out the possibility of increased intracranial pressure (ICP), ideally by MRI, because high ICP can increase the morbidity and mortality associated with this procedure in cats with neurologic FIP (see ch. 115).[15,21,26] The most common CSF findings are protein concentration > 2 g/L (>200 mg/dL) and nucleated cell count > 100 cells/mcL with a neutrophilic pleocytosis.[14,16,21,27] Elevated protein concentration in the CSF could cause increased viscosity and therefore CSF may not flow adequately during collection. Coronavirus antibodies have little diagnostic value as negative serum titers or titers <1:400 have been reported in cats with neurologic FIP.[14,18,21] CSF coronavirus antibodies (IgG) are not necessarily more sensitive than serum antibodies.[17] The use of albumin quotient and IgG index has failed to identify a protein pattern specific for neurologic FIP, indicating that disturbance of blood-CSF barrier function and intrathecal IgG synthesis is not a common feature of FIP.[28] A strongly positive reverse-transcriptase polymerase chain reaction (RT-PCR) in CSF supports the diagnosis. However, some cats with histologically-confirmed neurologic FIP have negative RT-PCR.[18] Immunohistochemistry has been used successfully in one cat to identify FIP-infected macrophages in CSF; nonetheless, further studies are needed to assess its sensitivity and specificity.[29] Definitive diagnosis requires a combination of gross and histopathological examination with the demonstration of viral antigen in postmortem CNS samples. There is still no cure nor reliable prevention of FIP (see ch. 224). The prognosis for cats with neurologic FIP is poor: The median survival time has been reported as 6.5 days (range 2 to 330 days) and 21 days (range 7 to 150 days) in two studies.[16,21]

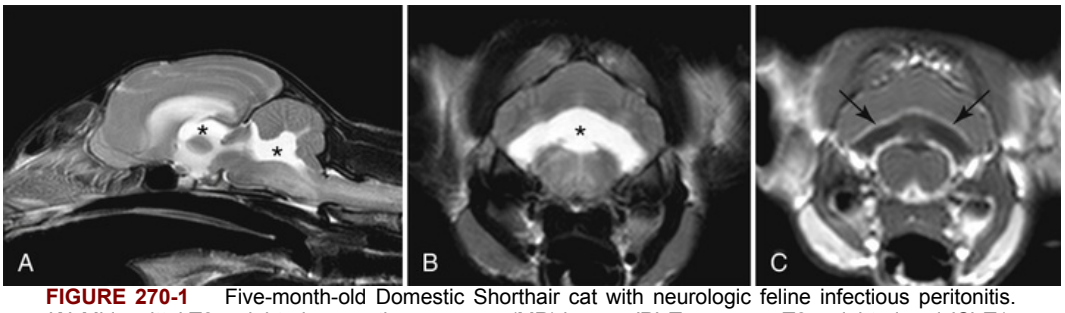

FIGURE 270-1 Five-month-old Domestic Shorthair cat with neurologic feline infectious peritonitis. **(A)** Midsagittal T2-weighted magnetic resonance (MR) image, **(B)** Transverse T2-weighted and **(C)** T1-weighted post contrast MR images at the level of the 4th ventricle showing severe dilation of the ventricular system (asterisks) with marked periventricular enhancement (arrows) after contrast administration.

Feline Immunodeficiency Virus (FIV)

Feline immunodeficiency virus (FIV) is a neurotropic retrovirus that causes acquired immune deficiency syndrome, which can result in opportunistic CNS infections and neoplasms (lymphoma). FIV shares many characteristics with human immunodeficiency virus (HIV) and has been used as an animal model for understanding the neuropathogenesis of HIV (see ch. 222). However, neurologic signs in naturally-infected cats are very uncommon.[30-32] Neurologic signs (insidious onset and progressive course) include abnormal behavior, followed by facial twitching, ataxia, seizures, sleep disorders, and intention tremors.[32,33] Slight elevations in nucleated cell count (mononuclear pleocytosis) and total protein concentration have been reported in CSF.[34] In experimentally-infected cats, MRI showed cortical atrophy and mild ventricular dilation, white matter changes, and increased apparent diffusion coefficients in the white matter, gray matter, and basal nuclei.[35,36] Positive serologic test results and a positive PCR on serum and CSF can support the diagnosis. Treatment is focused on managing opportunistic CNS infections. The prognosis is poor; however, some cats remain asymptomatic for many years.[37]

Feline Leukemia Virus (see ch. 223)

Feline leukemia virus (FeLV) has been associated with a chronic degenerative myelopathy in adult and geriatric cats.[38] There is no breed or sex predilection, and the onset of clinical signs is insidious, with a slowly progressive course. Neurological signs include abnormal behavior, vocalization, hyperesthesia, and paraparesis progressing to paraplegia with urinary incontinence.[38] MRI (brain and spinal cord) and CSF analysis are normal. Positive serologic test results and a positive PCR on serum and CSF can support the diagnosis. This disease is uncommon, and therefore, other concomitant diseases should be considered for FeLV-infected cats with myelopathy. The prognosis is poor and the treatment is supportive.

Feline Borna Disease Virus

Feline staggering disease refers to a meningoencephalomyelitis caused by a negative-stranded RNA virus, Borna disease virus (BDV). It has been reported mainly in Europe but also occurs in other parts of the world, including Asia and Australia.[39-43] The probable reservoirs are birds and rodents; therefore, young adult outdoors cats from rural areas are at increased risk.[44] The most common neurologic signs include unsteady, "staggering" gait (ataxia) and postural reaction deficits followed by abnormal behavior and absent or decreased menace response.[44] Advanced imaging findings usually are unremarkable. CSF can be abnormal in 50-60% of infected cats (mononuclear pleocytosis with increased total protein concentration).[44] Serologic titers and real time RT-PCR in serum and CSF can support but not confirm the diagnosis.[44,45] The disease is progressive, and despite supportive treatment, the majority of affected cats die or are euthanized during the first month after the onset of clinical signs.[44,46]

Parasitic CNS Disease

Gurltia Paralysans

Gurltia paralysans is a neurotropic metastrongylid nematode of domestic cats in South America.[47-51] The life

cycle of *G. paralysans* is unknown. Adult worms and eggs can be found in the thoracolumbar and lumbosacral spinal cord parenchyma and leptomeningeal veins causing chronic and slowly progressive meningomyelitis (feline gurltiosis). There is no breed or sex predilection and young adult cats from rural or periurban areas are generally affected. Clinical signs include pelvic limb proprioceptive ataxia, paraparesis, paraplegia, lumbosacral hyperesthesia, fecal or urinary incontinence and/or tail paralysis (Video 270-4). CT-myelography and MRI show diffuse enlargement of the thoracolumbar and lumbosacral spinal cord.[48] CSF mononuclear pleocytosis has been reported in up to 55% of affected cats.[48] An antemortem presumptive diagnosis of feline gurltiosis is based on neurological signs, epidemiological factors, and the exclusion of other causes of feline myelopathies.[48-51] No larvae or parasite eggs are found on fecal examination. The definitive diagnosis is based on histopathology via detection of adults of *G. paralysans* in the spinal cord (Figure 270-2). PCR of serum and CSF samples is being evaluated as a possible diagnostic tool for *G. paralysans* infection in domestic cats.[52] There is no treatment and the prognosis is poor.

FIGURE 270-2 Pathologic lesions associated with *Gurltia paralysans* infection in an adult cat. **A,** Lumbar spinal cord segments showing marked vascular congestion (asterisk). **B,** Histological section from the spinal cord showing parasite sections inside the vasculature (arrows) within the subarachnoid space and spinal cord parenchyma. (Images courtesy Dr. Marcelo Gomez.)

CNS Disorders of Unknown Origin

Feline hippocampal necrosis (FHN) is a seizure disorder characterized by epileptic events (generalized seizures and/or focal seizures with orofacial involvement) and interictal abnormal behavior.[53-56] There is no breed or sex predilection.[56-61] The age of presentation ranges from 3 months to 14 years of age.[56-58,61,62] The onset of clinical signs is acute with a rapid progression. The seizures have a tendency to become recurrent within days or weeks of onset.[54,56] Two major groups of FHN should be considered: primary or idiopathic FHN, which appears to be the direct cause of the seizures, and secondary FHN, which appears as a consequence of ongoing seizure activity due to a precipitating hippocampal or extrahippocampal forebrain disease (autoimmune feline limbic encephalitis, neoplasia).[54,56,59,60,63] Definitive diagnosis is made histopathologically; however, MRI findings can confirm hippocampal lesions (Figure 270-3).[56] Treatment consists of antiepileptic medications. Immunosuppressive medication also has been recommended in suspected cases of autoimmune feline limbic encephalitis.[56,61,63] The prognosis generally is poor, as the majority of cats become antiepileptic medication-resistant during the acute phase of the disease; however if this phase is overcome, the long-term outcome can be favorable.[54,57,60,61,63]

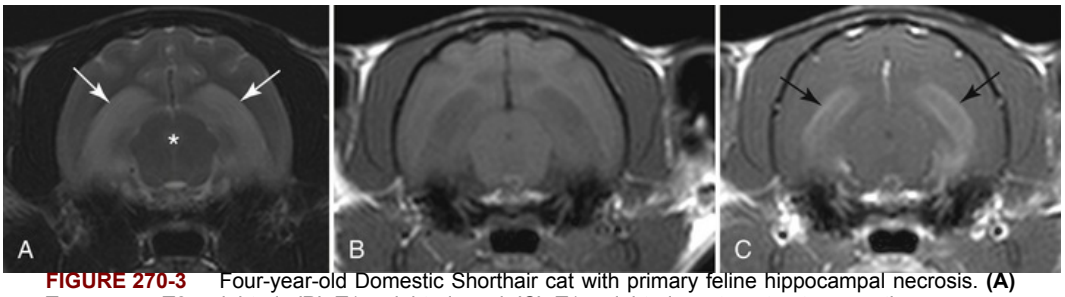

FIGURE 270-3 Four-year-old Domestic Shorthair cat with primary feline hippocampal necrosis. **(A)** Transverse T2-weighted, **(B)** T1-weighted, and **(C)** T1-weighted post-contrast magnetic resonance (MR) images at the level of the mesencephalic aqueduct (**A,** asterisk). There is moderate bilateral hyperintensity on T2-weighted images (**A,** white arrows) and hypointensity to normal gray matter on T1-weighted images of the hippocampal formation **(B).** There is marked enhancement of the hippocampus (**C,** black arrows) on T1-weighted images after contrast administration.

Slowly progressive lymphohistiocytic meningoencephalomyelitis is characterized by a late onset (mean of 9 years old) and slow progression (mean of 11 months).[64] There is no sex or breed predilection and all the reported cases were outdoor cats (active hunters living in northeast Scotland). Neurological signs include an obtunded or disoriented mental status, spastic gait, stiff and extended tail posture, decreased to absent postural reactions in all four limbs, and decreased to absent menace response bilaterally (Video 270-5 ▶). Advanced imaging can show brain atrophy. CSF analysis was normal in one tested cat. Definitive diagnosis is based on histopathologic analysis of brain tissue.[64] The suggested possible causative agents include an infective or environmental immunogenic trigger. There is no treatment and the prognosis is poor.[64]

Feline polioencephalomyelitis is a subacute to chronic nonsuppurative encephalomyelitis with a predominance of pathological changes in the gray matter, mainly affecting the medulla oblongata and the spinal cord.[65,66] Pathological findings are highly suggestive of a viral agent. There is no breed or sex predilection and cats of any age can be affected. The disease is considered rare (prevalence of 1% in cats with myelopathy).[23] Clinical signs include ataxia, paresis, and decreased postural reactions in all four limbs.[65-68] The diagnosis is based on histopathologic analysis of tissue.[65,66,69] There is no treatment, and prognosis can be favorable when neurological signs are mild and non-progressive.[67]

Neuromuscular System Diseases

Inherited Neuromuscular Diseases

Inherited neuromuscular diseases are rare, slowly progressive, and they predominantly affect young kittens (see Table 270-1).

Acquired Neuromuscular Diseases

Motor Polyneuropathy of Unknown Origin in Young Cats

Recurrent or progressive motor polyneuropathy has been reported to affect young cats from 3 to 44 months of age, mainly Bengals (but any breed or sex can be affected).[70,71] Clinical signs include generalized weakness (recurrent or progressive), palmigrade and plantigrade posture, ventroflexion of the neck, and decreased to absent spinal reflexes.[70,71] The diagnosis is based on electrodiagnostic testing (see ch. 117) and histopathologic assessment of muscle and nerve biopsies. Treatment is supportive and the prognosis varies from poor to excellent, which highlights the possible different etiologies.[70,71]

Specific Paroxysmal Disorders of Unknown Origin

Feline orofacial pain syndrome (FOPS) is a pain disorder characterized by acute behavioral signs of oral discomfort with or without tongue mutilation. It is prevalent in Burmese cats; however, cats of any breed, sex or age can be affected.[72,73] FOPS has been hypothesized to be analogous to trigeminal neuralgia in humans. Clinical signs include paroxysmal events of acute onset of exaggerated licking, chewing movements and pawing at the mouth, usually confined to one side of the oral cavity and lips (Video 270-6 ▶). The events last from 5 minutes to 2 hours and the cat typically can be distracted from it. Neurological examination findings

are normal. The diagnosis is based on ruling out other possible causes of oral pain or trigeminal nerve dysfunction. Oral lesions and environmental stress can precipitate these episodes. Some cats can be resistant to traditional analgesics including gabapentin.[73] Adjuvant antiepileptic medications (phenobarbital) could help to control the allodynia effect and environmental stress should be limited.[73] Occasionally, life-long therapy is required; however, remission has been reported in up to 45% of affected cats.[73]

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SECTION XVIII

Gastrointestinal Disease

OUTLINE

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CHAPTER 271

Laboratory Evaluation of the Gastrointestinal Tract

Jörg M. Steiner

Client Information Sheet: Laboratory Evaluation of the Gastrointestinal Tract

Introduction

Signs of gastrointestinal disease are very common in both dogs and cats, but definitive diagnosis can be challenging. There are a wide range of laboratory tests that can help assess patients with suspected gastrointestinal disease. Depending on the clinical signs the patient is presented with (e.g., diarrhea [see ch. 40], vomiting [see ch. 39], weight loss [see ch. 19]), a specific systematic approach should be taken to rule in/out the various causes of the clinical signs. Regardless of the clinical sign(s) observed, the primary goals of the clinician should be (1) to rule out secondary causes of gastrointestinal signs initially, (2) to rule out common causes of gastrointestinal disease before ruling out rare causes, and (3) to use less-invasive and more affordable diagnostic tools before reaching for more-invasive and more expensive ones.

Cytologic evaluation of fine needle aspirates (see ch. 89) or tumor impressions (see ch. 93) and histopathological evaluation of endoscopically- (see ch. 113), laparoscopically- (see ch. 91), or surgically-collected biopsy specimens also belong to the laboratory diagnostic modalities that are important in arriving at a definitive diagnosis, and they are discussed elsewhere (see Section V).

Laboratory Evaluation for Specific Etiologies

Myasthenia Gravis

Megaesophagus describes a loss of motility of the esophagus that leads to an extension of the esophageal diameter, regurgitation, and in many cases aspiration pneumonia. In many patients the underlying cause of megaesophagus cannot be determined, but some patients have a localized form of myasthenia gravis, which can be diagnosed by demonstrating antibodies against acetylcholine receptors in serum from affected dogs, a test which is both highly sensitive and specific for this disease (see ch. 269).[1]

Laboratory Tools to Diagnose Enteropathogens

Helicobacter-Like Organisms

The actual pathogenetic impact of infections with *Helicobacter*-like organisms in dogs and cats is not completely understood. Many healthy dogs and cats show evidence of *Helicobacter*-like organisms in the stomach.[2] However, there is a group of dogs and cats that have evidence of chronic gastritis (i.e., clinical signs of chronic vomiting), have no other identifiable cause of these clinical signs, have evidence of *Helicobacter*-like organisms in the stomach, and respond to triple or quadruple therapy designed for the treatment of *Helicobacter pylori* infections in humans. The presence of *Helicobacter*-like organisms in the gastric mucosa can be determined by using special stains (e.g., Warthin-Starry stain), PCR, or fluorescent *in situ* hybridization (see ch. 275).[3] The organism can also be identified indirectly by a urease test on a gastric biopsy or by ^{13}C-urea blood or urine tests, the latter of which are however currently not commercially available for use in dogs or cats.[3,4]

Parvovirosis

In clinical practice, an in-house ELISA that detects CPV-2 antigen in feces is currently the most frequently used test for parvovirosis in dogs. This test can however be falsely positive in dogs that have recently been

vaccinated.[5] CPV-2 can also be diagnosed by PCR, which is associated with a higher sensitivity, but of course is less optimal in patients with severe peracute disease (see ch. 225).[5]

Salmonella spp.

Salmonella spp. can be harbored by both dogs and cats for a long period of time without causing clinical signs (see ch. 220).[6,7] However, there are dogs and cats that have acute or chronic diarrhea that are positive for *Salmonella* in the feces. Identification of *Salmonella* spp. organisms has traditionally been achieved by specifically culturing for *Salmonella* spp., followed by susceptibility testing. However, in many patients the organism is not consistently shed in the feces (see ch. 40 and 220). Also, *Salmonella* spp. can be diagnosed by an enrichment culture followed by PCR or by a direct PCR.

Pathogenic *Campylobacter* spp.

While there are many different *Campylobacter* spp. that have been identified in the intestinal tract of dogs and cats, only a limited number of these organisms, namely *C. jejuni* and *C. coli,* have been associated with diarrhea (see ch. 40 and 220).[8] These subspecies can be specifically diagnosed by PCR.

Clostridium difficile and *perfringens*

Clostridium difficile has been associated with diarrhea in both dogs and cats (see ch. 220).[9-11] The virulence of *C. difficile* is associated with the presence of genes that encode for various toxins, most notably toxin A (an enterotoxin) and toxin B (a cytotoxin), which can both be detected by ELISA, but positive results do not always correlate with the disease.[9,11]

Clostridium perfringens has commonly been associated with diarrhea in both dogs and cats. The main virulence factor is the *Clostridium perfringens* enterotoxin (CPE), which has been shown to induce mucosal damage, increase intestinal permeability, and reduce water absorption, thus leading to diarrhea.[12] Bacterial culture of feces for *C. perfringens* has little diagnostic value, as *C. perfringens* is a commensal organism that can be detected in up to 80% of fecal samples from dogs and cats.[9,11] Microscopic examination of fecal smears and enumeration of fecal endospores also is not useful for the diagnosis of *C. perfringens*-associated diarrhea.[11,13] The current recommendation for diagnosis of *C. perfringens*-associated diarrhea is the detection of *C. perfringens* enterotoxin by ELISA, but a positive result does not definitively prove a cause-effect relationship.[12]

FISH for Enteroinvasive *E. Coli*

Histiocytic ulcerative colitis is a severe form of colitis that has traditionally most commonly affected Boxer dogs, but it can also be seen in dogs of other breeds (see ch. 40 and 277).[14] Diagnosis is based on histopathologic findings of histiocytic ulcerative colitis on a colonic biopsy sample and the detection of an enteroinvasive *E. coli* by fluorescent *in situ* hybridization.[14,15] This test is based on using a genetic probe directed against a specific section of the DNA of this organism that has been fluorescently labeled.[15] Finding fluorescently labeled organisms in the colonic mucosa confirms the presence of the organism and the disease (see ch. 133 and 277).

Laboratory Tools to Diagnose Endoparasites (see ch. 81)

Fecal Smear

A fecal smear can be used to identify protozoal infections, most commonly *Giardia lamblia* in either dogs or cats or *Tritrichomonas foetus* in cats. However, the sensitivity of a fecal smear for the diagnosis of either infection is rather low and a negative fecal smear does not rule out an infection with a protozoal organism.[16,17] Occasionally, other parasitic infections (e.g., whipworms) can be detected by direct fecal smear evaluation.

Fecal Flotation

Fecal flotation is a great tool for the detection of ova from a wide variety of helminths and *Giardia* cysts in either dogs or cats. There are advanced flotation techniques (i.e., centrifugal flotation, zinc sulfate flotation) that increase the sensitivity of this tool.[18]

Immunofluorescence for *Giardia* and *Cryptosporidium*

Immunofluorescence is an excellent diagnostic technique for the detection of *Giardia* spp. and *Cryptosporidium* spp. in both dogs and cats (see ch. 210 and 221).[19,20] Immunofluorescence uses fluorescently labeled antibodies directed against specific antigens of those protozoal organisms to differentiate these organisms from other fecal matter (Figure 271-1).

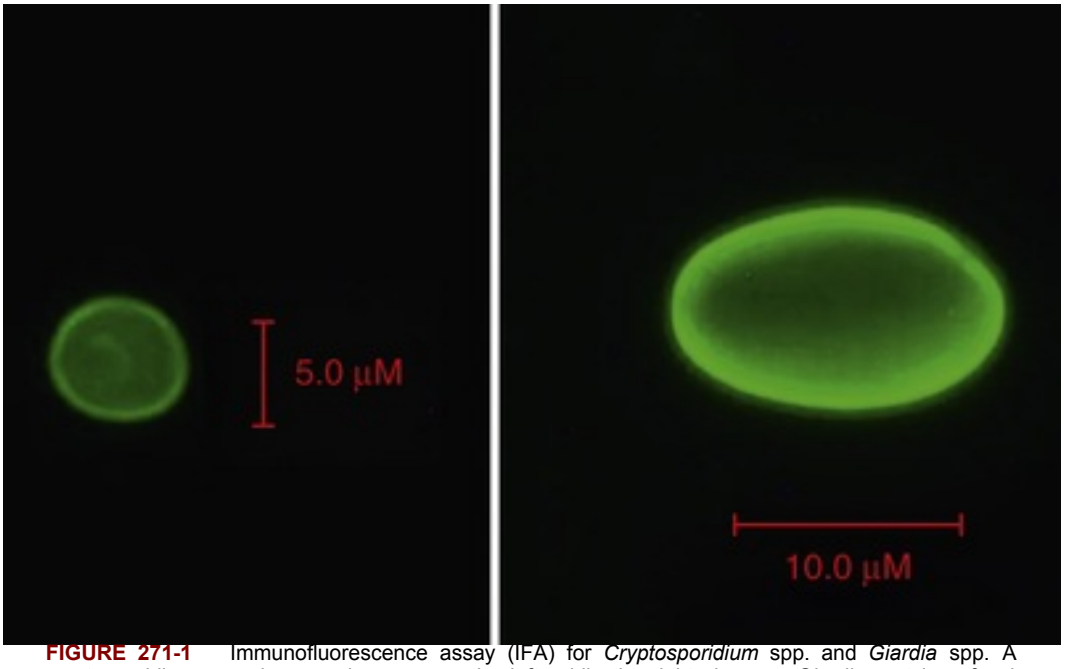

FIGURE 271-1 Immunofluorescence assay (IFA) for *Cryptosporidium* spp. and *Giardia* spp. A cryptosporidium organism can be seen on the left, while the right shows a *Giardia* cyst in a fecal sample from a dog (Magnification ×1000). (Reprinted from The GI Lab Newsletter, Suchodolski, "Update on the diagnosis of enteropathogens," page 3, © 2012, with permission from the Gastrointestinal Laboratory.)

ELISAs for *Giardia lamblia*

There are ELISAs for the detection of antigens from *Giardia* in fecal samples. These ELISAs have been shown to be highly sensitive for the presence of *Giardia,* but the specificity is lower than with immunofluorescence, especially in patients that have recently been treated.[20,21]

PCR for *Tritrichomonas foetus*

Tritrichomonas foetus is one of the most important protozoal infections in cats. In general, *T. foetus* can be diagnosed by direct fecal smear, culture-pouch, or PCR, but only PCR affords an acceptable sensitivity.[22,23] Many laboratories offer PCR testing for this organism. However, there is no generalized standard and some laboratories use real-time PCR while other labs use a more traditional nested PCR. Thus the minimum number of organisms detectable per gram of feces could vary quite dramatically between laboratories. Some cats shed the organism intermittently and a colonic flush (https://www.youtube.com/watch?v=JMfZ9M80V8E) may afford the highest sensitivity.

PCR for *Heterobilharzia americana*

Heterobilharzia americana is a trematode that causes schistosomiasis in dogs and has mainly been described in some areas of Texas and Louisiana. The trematode egg can be identified by sodium chloride sedimentation, which is only performed upon special request. A PCR-based assay for the detection of DNA from the eggs of this organism in feces is available and has been shown to be more sensitive than sodium chloride sedimentation.[24]

Laboratory Tools to Assess Intestinal Function and Disease

Serum Folate Concentration

Folate is a water-soluble B-vitamin (vitamin B_9) that is plentiful in most commercial pet foods. However, folate in the diet is mostly supplied as folate polyglutamate, which cannot be readily absorbed. In the proximal small intestine, folate polyglutamate is deconjugated by folate deconjugase and the resulting folate monoglutamate is absorbed by specific folate carriers in the proximal small intestine (Figure 271-2 and Video 271-1).[25,26] In patients with proximal small intestinal disease, both folate deconjugase and folate carriers can be destroyed, leading to folate malabsorption in patients with severe disease. If the condition is chronic, folate body stores can become depleted and serum folate concentration decreases. The same is true in patients with diffuse small intestinal disease, as long as the proximal small intestine is involved in the disease process.[27,28] Many bacterial species synthesize folate and it is believed that an increased number of certain bacterial species (i.e., small intestinal dysbiosis) can lead to significant increases in serum folate concentrations.[29]

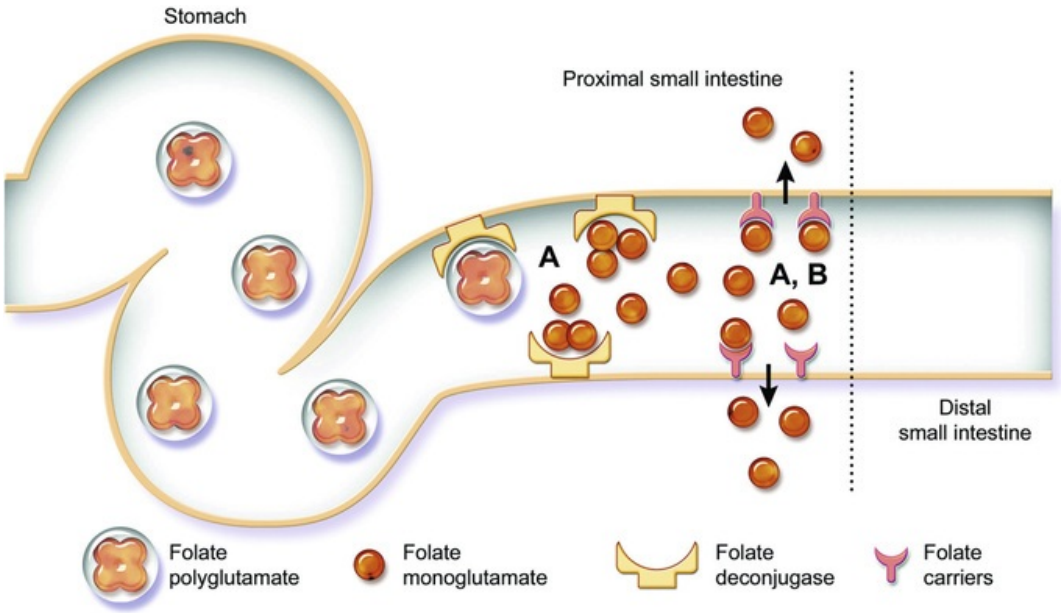

FIGURE 271-2 Folate absorption. Dietary folate enters the gastrointestinal tract predominantly as folate polyglutamate. Folate deconjugase, a brush border enzyme in the cranial small intestine, deconjugates folate polyglutamate to folate monoglutamate. Specific folate carriers on enterocytes located in the cranial small intestine absorb folate monoglutamate. Both the deconjugase and folate carrier molecules are only localized in the cranial small intestine and there is no appreciable absorption of folate in the distal small intestine or the colon. (Reprinted from Clinical Techniques in Small Animal Practice, 18(4): Suchodolski and Steiner, "Laboratory assessment of gastrointestinal function," page 208, © 2003, with permission from Elsevier.)

Serum Cobalamin Concentration

Cobalamin (vitamin B_{12}) is a water-soluble vitamin that is plentiful in most commercial pet foods and dietary deficiencies are thus not very common. However, owners who feed their pets exclusively vegetarian or vegan diets that are not fortified with cobalamin may inadvertently cause cobalamin deficiency in their pets. Dietary cobalamin is bound to animal-based dietary protein and cannot be absorbed. In the stomach dietary protein is digested by pepsin and HCl and cobalamin is released. The free cobalamin is immediately bound by R-protein, which is a cobalamin transporter protein that is synthesized by the gastric mucosa. In the small intestine, R-protein is digested by pancreatic proteases and the free cobalamin is bound by intrinsic factor (Figure 271-3 and Video 271-2).[30] In dogs and cats the vast majority of intrinsic factor is secreted by the exocrine pancreas.[31-33] This is different from humans where the majority of intrinsic factor is secreted by the gastric mucosa.[34] Complexed intrinsic factor/cobalamin is absorbed by specific receptors in the ileum (see Figure 271-3 and Video 271-2).[33] Distal small intestinal disease, if severe, will lead to destruction of cobalamin receptors in the ileum, leading to cobalamin malabsorption. Cobalamin malabsorption will ultimately lead to

depletion of cobalamin body stores and cobalamin deficiency. Diffuse small intestinal disease can also lead to cobalamin malabsorption if the ileum is involved in the disease process.[29,35-39] Exocrine pancreatic insufficiency also commonly leads to cobalamin deficiency.[40,41] Finally, some patients with small intestinal dysbiosis have a decreased serum cobalamin concentration as some intestinal bacteria may compete for the cobalamin available (see ch. 277).[42]

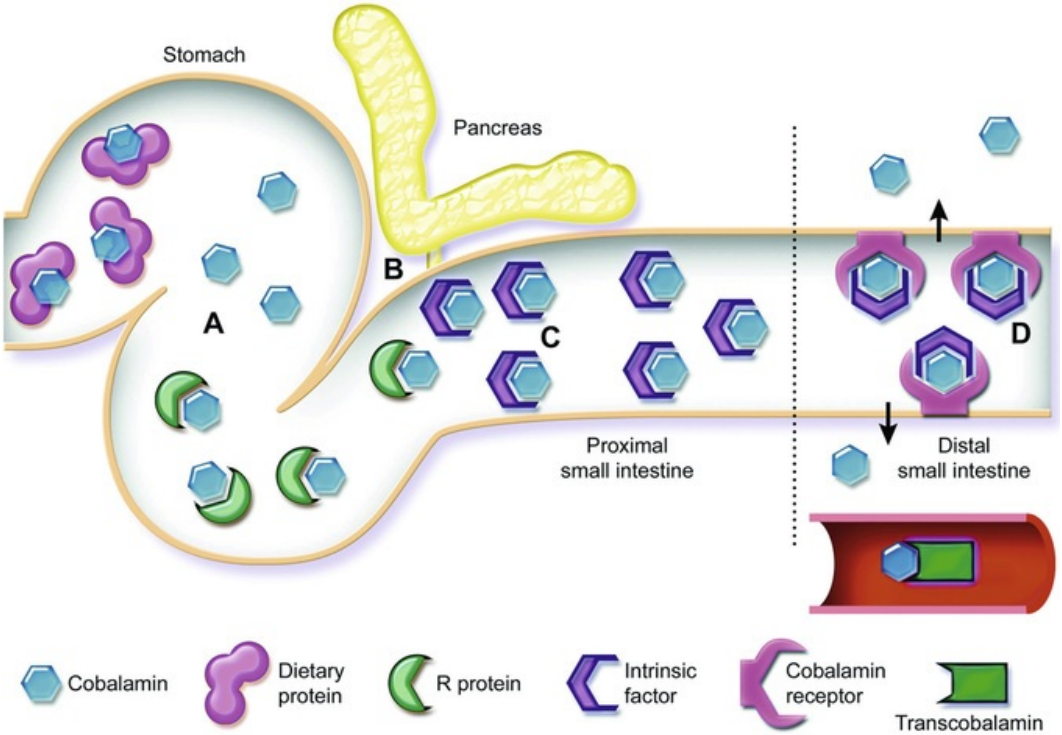

FIGURE 271-3 Cobalamin absorption. Dietary cobalamin is bound to dietary protein. In the stomach, pepsin and hydrochloric acid degrade the dietary protein, releasing cobalamin **(A).** The cobalamin is immediately bound by R-protein, which is produced by the gastric mucosa. In the duodenum, pancreatic proteinases digest the R-protein, releasing cobalamin. Free cobalamin in the duodenum is bound by intrinsic factor **(B).** In dogs and cats intrinsic factor is mostly produced by the exocrine pancreas. Cobalamin remains bound to intrinsic factor during passage through the cranial small intestine **(C).** In the distal small intestine the cobalamin/intrinsic factor complexes are taken up by specific receptors found only on enterocytes in the ileum **(D),** the enterocytes process the intrinsic factor/cobalamin complex and release cobalamin into circulation, where a final set of binding proteins (transcobalamins) complex the vitamin and carry it to the cells. (Reprinted from Clinical Techniques in Small Animal Practice, 18(4): Suchodolski and Steiner, "Laboratory assessment of gastrointestinal function," page 207, © 2003, with permission from Elsevier.)

Fecal Alpha$_1$-Proteinase Inhibitor Concentration

Many gastrointestinal disorders, if severe, can be associated with gastrointestinal protein loss. Alpha$_1$-proteinase inhibitor (alpha$_1$-PI) is synthesized in the liver and inhibits a variety of different proteinases.[43] Alpha$_1$-proteinase inhibitor has a molecular mass of approximately 60,000 Da, which is similar to that of albumin. Thus, when gastrointestinal disease is severe enough to be associated with gastrointestinal loss of albumin, alpha$_1$-PI is lost at approximately the same rate (Figure 271-4).[44] In contrast to albumin, alpha$_1$-PI is not hydrolyzed by digestive and bacterial proteinases in the gastrointestinal lumen.[44] Therefore, fecal alpha$_1$-PI concentration can be used as an estimate for gastrointestinal protein-loss.[45,46] Clinically, fecal alpha$_1$-PI concentration should be evaluated in dogs with hypoalbuminemia that do not have clinical signs of gastrointestinal disease and where an extra-gastrointestinal source of protein loss cannot be identified. Also, dogs belonging to a breed that is associated with a high prevalence of protein-losing enteropathy (e.g., Norwegian Lundehund, Soft Coated Wheaten Terrier, Yorkshire Terrier) that don't have any clinical signs of gastrointestinal disease, but are intended for breeding, should be tested.[45]

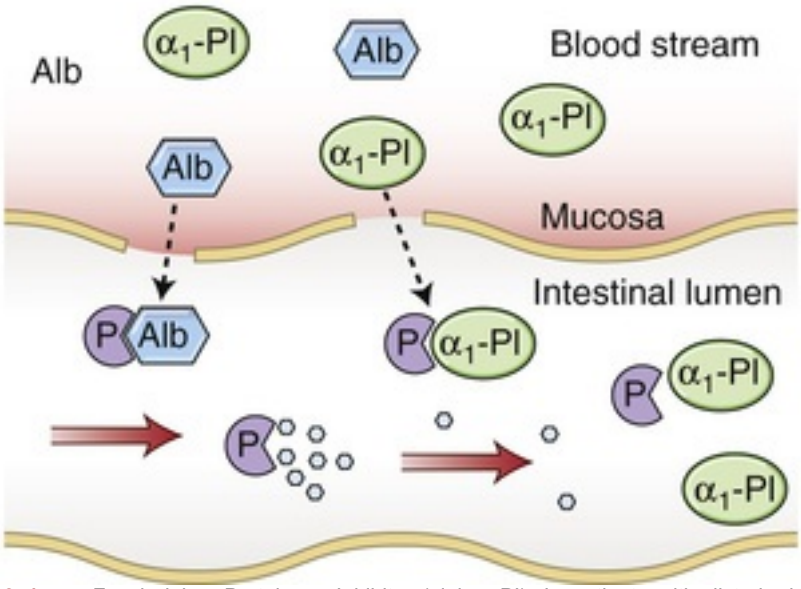

FIGURE 271-4 Fecal alpha$_1$-Proteinase Inhibitor (alpha$_1$-PI). In patients with disturbed mucosal integrity, plasma proteins can be lost into the intestinal lumen. Unlike albumin, which is degraded by digestive and bacterial proteases, alpha$_1$-PI is resistant to proteolytic degradation and can survive intestinal transit. Therefore, alpha$_1$-PI can be measured in feces using an immunoassay. (Reprinted from Veterinary Clinics of North America: Small Animal Practice, 41: Berghoff and Steiner, "Laboratory tests for the diagnosis and management of chronic canine and feline enteropathies," page 321, © 2011, with permission from Elsevier.)

Serum C-Reactive Protein Concentration

C-reactive protein (CRP) is an acute phase reactant that is receiving increasing interest for the assessment of dogs with a variety of inflammatory diseases. C-reactive protein has been reported to be increased in dogs with idiopathic inflammatory bowel disease (IBD), and has also been shown to correlate well with the IBD clinical disease activity index.[47-49] Thus, the greatest clinical utility of this test is for monitoring the response to treatment in dogs with IBD, as effective dietary or medical therapy will be associated with a decrease in serum CRP concentration.[48] A variety of assays for the measurement of CRP in serum are available, but unfortunately not all of them provide reliable results.[50]

Gastrointestinal Permeability Testing

One important property of the gastrointestinal wall is to provide a barrier function against the loss of plasma proteins and against uncontrolled uptake of harmful substances from the gastrointestinal lumen. During intestinal disease the gut wall becomes more leaky and gastrointestinal permeability testing can be used to assess the barrier function. Traditionally, the uptake and/or differential uptake of simple sugars, such as lactulose, rhamnose, and/or lactulose has been used to assess gastrointestinal permeability.[51,52] However, at the moment no assays for routine assessment of gastrointestinal permeability are available. In recent years iohexol has been explored as a new marker for intestinal permeability, but further studies are needed before this test can be suggested for routine use.[53]

Serum or Fecal Concentrations of Inflammatory Markers

Several markers for assessment of gastrointestinal inflammation have recently been described. Calprotectin and S100A12 are markers for neutrophilic inflammation and have been shown to be increased in both serum and feces in some dogs with IBD.[54,55] Methylhistamine is a stable marker of mast cell degranulation, and increased serum and fecal methylhistamine concentrations have been described in some dogs with IBD.[56] Brominated tyrosine is a marker of eosinophil activity and increased serum concentrations have been described in some dogs with IBD.[57] Much more research will be needed before the clinical utility of these markers can be definitively established, but it is an attractive speculation that in the future it may be possible to assess the specific types of inflammatory cells involved in a specific patient with suspected IBD without

intestinal biopsies and determine the optimal therapeutic approach based on a panel of these markers.

Gastrointestinal Endocrinology

The gastrointestinal tract is likely the biggest endocrine organ of the body, yet very little is known about diseases that can occur because of an imbalance of gastrointestinal hormones.[58] Many gastrointestinal hormones cannot even be reliably measured and others show complex cyclical concentrations that make interpretation of a single measurement very difficult. There are validated assays for the measurement of insulin and gastrin in dogs and cats and for the measurement of CCK and motilin in dogs. Measurement of serum gastrin concentration has been shown to be useful for the diagnosis of gastrinoma, but none of the other assays currently play a role in everyday clinical practice.[59,60]

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CHAPTER 272

Oral and Salivary Gland Disorders

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Client Information Sheet: Oral and Salivary Gland Disorders

This chapter will provide information on the importance of recognizing normal anatomical findings of the oral cavity often confused with pathologic lesions. Perioperative considerations are raised, and the judicious use of antibiotics is discussed. Common oral and salivary gland disorders are reviewed, with a focus on their non-surgical management.

Normal Structures Often Confused With Pathologic Lesions

It is not uncommon that dentists and oral surgeons are consulted because of the presence of a normal anatomical finding that could be unpaired and might look larger than expected or is colored differently compared to surrounding tissues (Figure 272-1). The incisive papilla is a rounded eminence of hard palate mucosa situated on the midline caudal to the maxillary first incisors. Occasionally, the papilla may be more or less pigmented compared to surrounding mucosa and then confused with pathologic lesions.

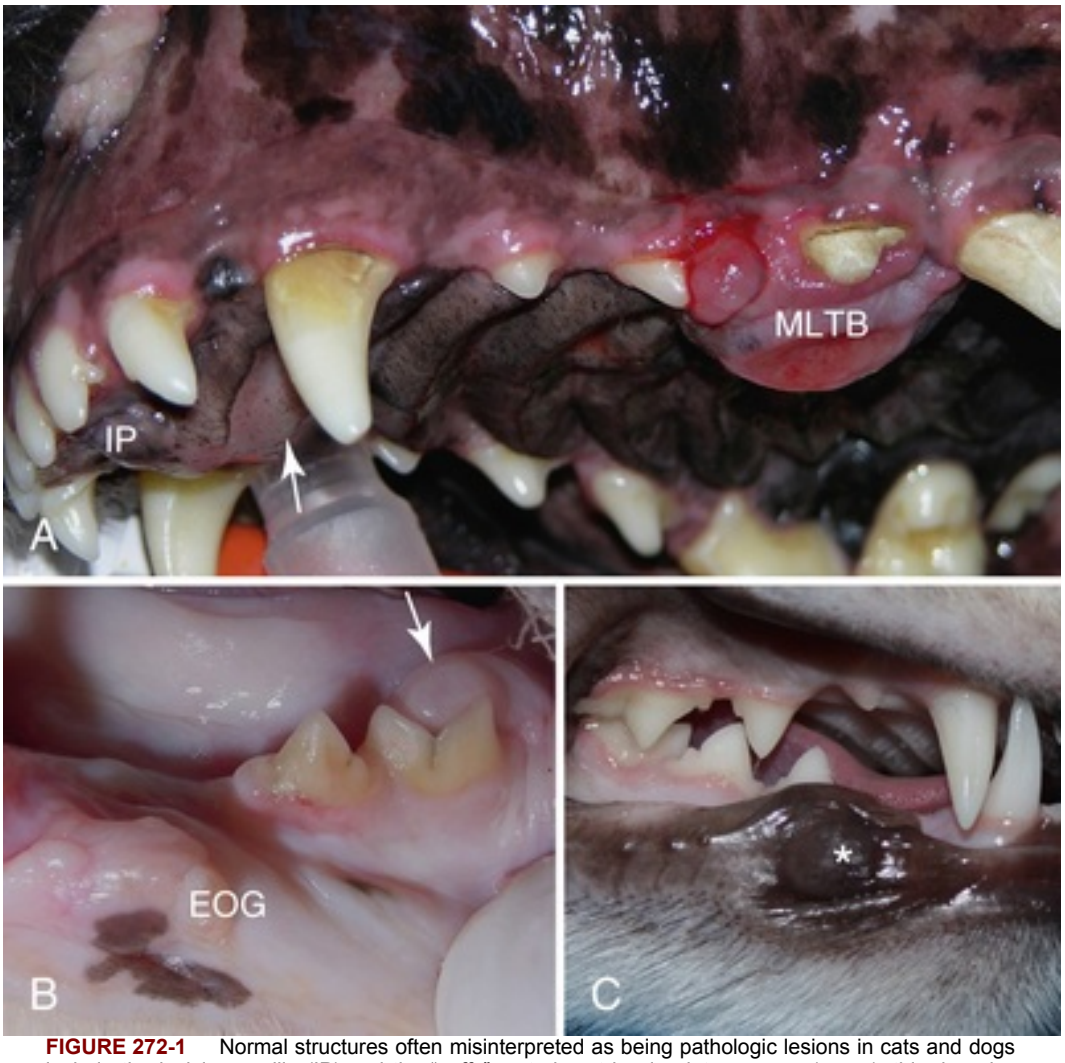

FIGURE 272-1 Normal structures often misinterpreted as being pathologic lesions in cats and dogs include the incisive papilla (IP) and the "puffy" rostralmost hard palate mucosa (arrow); this dog also was diagnosed with a multilobular tumor of bone (MLTB) in its left upper jaw **(A).** The lingual molar gland (arrow) is a small salivary gland situated lingual to the mandibular first molar tooth in the cat; this cat also was diagnosed with eosinophilic granuloma (EOG) at the lower lip margin **(B).** A strong frenulum-like attachment (asterisk) is situated immediately caudal to the mandibular canine tooth in normal cats and dogs **(C).** (Copyright Alexander M. Reiter.)

The mucosa of the most rostral hard palate often appears "puffy," as though sitting on a cushion of air. When a finger presses into this mucosa, it typically feels soft, giving way to the pressure exerted. The apparent swelling returns as soon as the finger is removed. This is normal and due to the presence of an extensive, fine arterial plexus resulting from profuse branching and anastomosing of the major palatine arteries overlying the palatine fissures.

Cats and dogs have four pairs of major salivary glands (parotid, zygomatic, mandibular, and sublingual). Scattered glandular tissue is present submucosally in the lips, the tongue, soft palate, and pharyngeal walls. Cats, but not dogs, have a small gland situated lingually to each mandibular first molar tooth. This lingual molar gland appears as a soft mucosal bulge and should not be confused with an abnormal swelling.

Cats and dogs have very discrete median mucosal folds (frenula) that connect the upper and lower lips to the jaws in the midline. A much stronger and more obvious frenulum-like attachment is situated immediately caudal to each mandibular canine tooth. This lateral lip frenulum sometimes can be more pigmented on one side, giving rise to concern about the presence of a neoplasm.

Oral pigmentation most commonly is associated with melanin produced by melanocytes. While these cells can be involved in the development of pigmented lesions in the mouth, oral mucosa usually shows various presentations of normal pigmentation. Pigmentations suspicious of early malignant melanoma lesions are often slightly raised, whereas normal pigmentation does not alter the mucosal surface.

Perioperative Considerations

Mouth Speculum

Prolonged, wide mouth opening has been reported to reduce maxillary artery blood flow, potentially resulting in temporary or permanent blindness post-anesthesia and/or other neurological deficits in cats.[1] Placing mouth gags and wedge props aids in visualization and allows for access to tissues deep in the oral cavity, pharynx, and larynx. However, the duration of wide mouth opening should be minimized to reduce the risk of masticatory muscle strain and injury to the temporomandibular joints. The wider the mouth of a cat is opened, the tighter the lip and cheek become and the more difficult it will be to deflect these tissues to accomplish procedures such as dental cleaning or tooth extraction. Placing 30 mm or 20 mm plastic gags between maxillary and mandibular canines enables adequate mouth opening for these procedures in cats.[2] Postanesthetic deafness has been reported in dogs and cats following dental and ear cleaning procedures. Geriatric patients could be more prone, and vestibular function also can be compromised. However, this may be temporary, and animals might recover.[3]

Endotracheal Tube Cuff Inflation

In an adult cat, a clinically airtight seal can be obtained by filling the endotracheal tube cuff with 1.6 ± 0.7 mL of air. Overinflation of the cuff can result in tracheal rupture in cats, and this complication has been reported mostly in association with anesthetized dental procedures. Various other causes have been hypothesized, including iatrogenic trauma from endotracheal tube movement during oral manipulations and turning over of the patient.[4] Clinical signs associated with tracheal rupture include palpable evidence of subcutaneous emphysema, coughing, gagging, dyspnea, anorexia, and fever (see ch. 241).

Manipulation of Oral and Adjacent Structures

Overzealous pharyngeal packing, tongue manipulation, excessive elevation of the alveolar mucosa on the lingual aspects of the mandibles and other iatrogenic complications can result in oral edema, which could exacerbate already existing tissue swelling in patients with oral inflammation or trauma.[5] When severe enough, breathing could be compromised during recovery from anesthesia, and such patients could benefit from a single injection of dexamethasone (0.1-0.2 mg/kg IV) at the end of the procedure. The tongue also can be wrapped with a gauze sponge soaked with a hypertonic solution prior to extubation. It is never wrong to be prepared for the potential need of performing an emergency tracheostomy. Gauze sponges used for pharyngeal packing should be counted for safe and complete retrieval at the end of the procedure. Small gauze sponges can have the potential to be displaced into the esophagus. The throat of each patient should be thoroughly inspected with the help of a laryngoscope prior to extubation to ensure that all foreign material has been removed.

Excessive ventral pulling of the tongue in the cat prior to intubation can puncture the sublingual mucosa or mucosa on the underside of the tongue by a very pointed mandibular canine tooth. Owners of dogs with severe periodontal disease should be warned about an increased risk of mandibular fracture, which can occur during relatively routine manipulation (when opening the mouth for intubation, placing a mouth prop or gag, and during tooth extraction). This emphasizes the importance of preoperative dental radiography to determine the health of the jaw bone.

Regular application of eye lubricant or taping the eyelids closed during anesthesia helps prevent corneal injury.[6]

Hypo- and Hyperthermia

Prevention of hypothermia of the patient is of particular importance when water is used for cooling dental power instruments or to rinse debris from the mouth (see ch. 49).[7] Conversely, hyperthermia also is a concern, especially in cats when opiates like hydromorphone, with or without gas anesthesia, ketamine, or both, are used.[8] Cats with postoperative hyperthermia often respond favorably to intravenous fluid administration, removal of blankets in the cage, mechanical cooling methods such as a fan and ice packs, and application of rubbing alcohol to footpads (see ch. 134).

Oral Bleeding and Hemostasis

Severe oral bleeding can be due to injury of larger blood vessels, bleeding dyscrasias (e.g., von Willebrand disease), lingual or palatal injury, oral inflammation, soft tissue trauma, oral neoplasia, or jaw fracture. Intravascular volume replacement is accomplished with crystalloids, colloids and/or blood products.[9] Diffuse bleeding from nasal mucosa (e.g., after maxillectomy or palate surgery) can be stopped by irrigation with a mixture (0.05-0.1 mL/kg in cats; 0.1-0.2 mL/kg in dogs) of 0.25 mL phenylephrine 1% and 50 mL lidocaine 2%,[10] vessel ligation, bone wax, fibrin sealants, and many others.

Subcutaneous or Submucosal Emphysema

Emphysema sometimes occurs after use of air-driven equipment, or blowing air or air/water spray into submucosal tissues, particularly after deep dissection of large mucoperiosteal flaps. In the lower jaw, it is usually subcutaneous, as the air migrates to the intermandibular space and from there to the ventrolateral aspects of the face; submucosal emphysema can happen in either the upper or lower jaw. Emphysema usually resolves within a few days. It can be reduced or prevented effectively with gentle digital pressure applied to the sutured flap for a few minutes to evacuate air bubbles and provide an adhesive seal between soft tissue and bone. Blowing air or air/water spray into alveolar sockets and onto denuded bone or bleeding tissues can cause air emboli and is strongly discouraged.[11]

Incisional Dehiscence

Dehiscence of oral surgical sites usually is a result of tension on suture lines. Other causes include infection or necrosis of hard and/or soft tissues when the surgery was excessively traumatic and/or caused loss of vascular supply to the tissues. Oral wounds may be treated by means of resuturing, or they are left to granulate and epithelialize. Any oral wound that does not seem to be healing for 7 days or longer following surgery should be biopsied to rule out the possibility of neoplasia.

Judicious Use of Antibiotics

The possible transfer of antibiotic-resistant bacteria from cats and dogs to humans recently has been acknowledged as a potential threat to public health,[12,13] and antimicrobial drugs must be used appropriately (see ch. 209). Systemic antibiotics can have a broader range of activity than do topical antibiotics, and can reach all periodontal tissues, but they only achieve a low local concentration. Antibiotics such as amoxicillin-clavulanate (14 mg/kg PO q 12 h), clindamycin hydrochloride (11 mg/kg PO q 12 h) and, for severe osteomyelitis in dogs, metronidazole (30 mg/kg PO q 24 h × 10 days, then 10 mg/kg PO q 24 h × 20 days, in addition to radical surgical debridement) are the drugs of choice against the common periodontopathogens isolated in dogs. When using low-dosage doxycycline (1-2 mg/kg PO q 12 h), the medication's anti-inflammatory features are considered rather than its antibacterial effects. Local application of doxycycline (8.5%) or clindamycin (2%) gel into cleaned periodontal pockets deeper than 4 mm has the advantage of delivering a very high local concentration of drug and results in favorable clinical outcome in dogs.[14,15]

Temporary bacteremia secondary to an oral condition occurs daily in patients with periodontal disease and has been described in cats and dogs during and after dental cleaning and tooth extraction. This is usually short-lived in healthy animals, as the bacteria are eliminated by the host's immune system. Therefore, the expected bacteremia is not an indication for the perioperative use of systemic antibiotics in the otherwise healthy patient. Systemic infection as a result of poorly performed tooth extraction has been reported only anecdotally.[16] Antibiotics could be required in select patients with preexisting conditions that might worsen during or after the dental or oral surgical procedure (e.g., hyperadrenocorticism, diabetes mellitus, renal and hepatic disease, and oncologic patients undergoing chemotherapy). The drug of choice is intravenous ampicillin (22 mg/kg; when working in the mouth only) or cefazolin (20 mg/kg; when the skin outside the mouth is included in the surgery) given at induction and repeated every 2-4 hours during the procedure. In addition to bacteremia in pets with periodontal disease, there is a chronic release of inflammatory mediators, immune complexes, and bacterial and cellular degradation by-products into blood and lymph vessels that can produce direct or immune-mediated distant organ lesions. The systemic effects of periodontal disease are well-documented in humans (heart disease and stroke, diabetes, respiratory disease, and increased risk of premature delivery and low birth weight infants) and are being increasingly investigated in dogs and cats.[17,18]

Oral Inflammation

Most dogs and cats have some degree of periodontal disease. Gingivitis is inflammation of the gingiva, and periodontitis is inflammation of the gingiva, periodontal ligament, alveolar bone, and cementum (Figure 272-2). Periodontopathogens in dental plaque cause periodontal disease, but the host's reaction to bacteria and their toxins also plays a role in inflammatory tissue destruction (gingival recession, attachment loss, periodontal pocketing, alveolar bone resorption, tooth mobility, and tooth loss). Affected teeth are professionally scaled and polished under anesthesia, and various periodontal therapy and surgery options (including extraction) exist. Use of antibiotics for treatment of periodontal disease is not recommended.

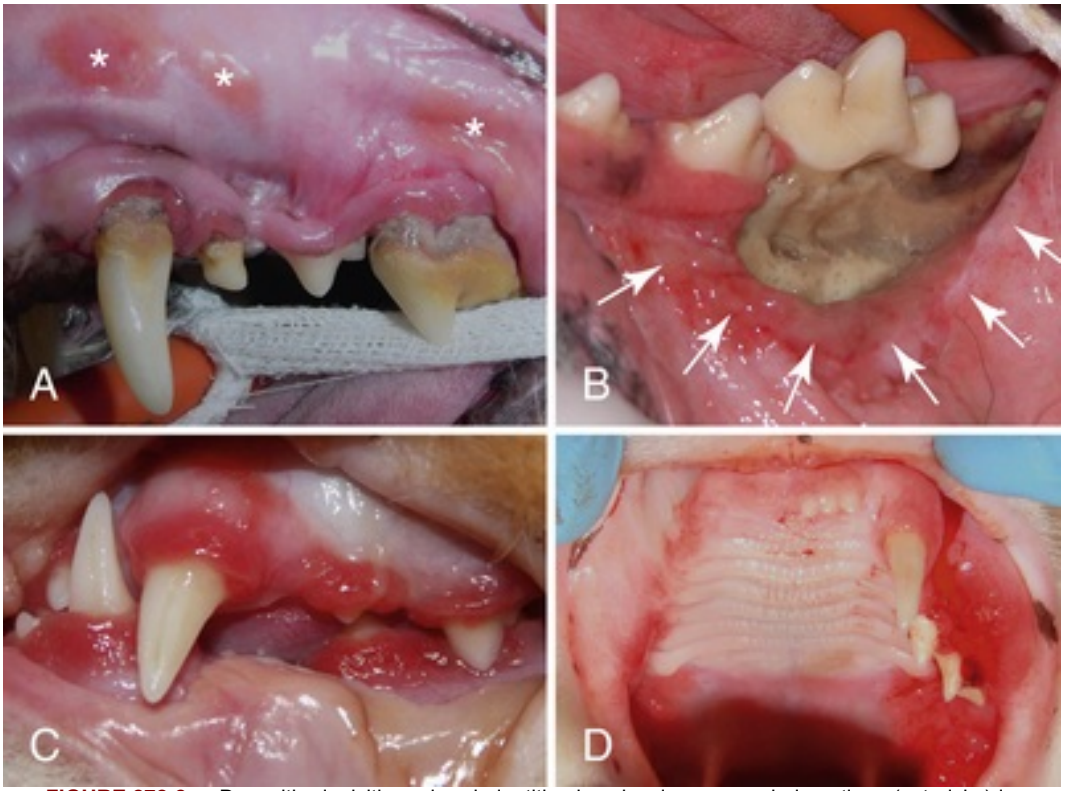

FIGURE 272-2 Dog with gingivitis and periodontitis also showing mucosal ulcerations (asterisks) in the labial and buccal mucosa that contacts the plaque-laden teeth of the left upper jaw **(A).** Dog with idiopathic osteomyelitis and osteonecrosis of the left mandible surrounded by ulceronecrotic oral mucosa (arrows) **(B).** Adolescent cat with juvenile hyperplastic gingivitis **(C).** Adult cat with stomatitis; note that the teeth of the left maxillary quadrant had previously been extracted, resulting in reduction of oral inflammation on that side of the mouth **(D).** (Copyright Alexander M. Reiter.)

Contact Ulcers

In dogs, inflammation beyond periodontal disease tends to be located in oral mucosa facing plaque-laden tooth surfaces. Such lesions commonly are referred to "kissing ulcers" or "contact ulcers." Young adult to middle-aged Cocker Spaniels, Labrador Retrievers, Standard Poodles, Scottish Terrier, Maltese, and Dachshunds sometimes present with severe osteomyelitis and adjacent cellulitis (exposed infected, inflamed, and necrotic bone and tooth roots surrounded by ulceronecrotic oral mucosa) that make them lethargic, febrile, and unwilling to eat and drink due to oral pain. Some of them also have otitis externa, lip fold dermatitis, and pododermatitis. Treatment involves partial- or full-mouth tooth extraction; tissue debridement; pain control; anti-inflammatory, antiseptic, and antibiotic therapy; and nutritional support.[19]

Juvenile Hyperplastic Gingivitis

Juvenile hyperplastic gingivitis can be found in immature, adolescent, and young adult cats that present with enlarged and inflamed gingiva (other oral mucosae are not affected) mostly around their maxillary and

mandibular cheek teeth. Certain medications (e.g., calcium channel blockers, cyclosporines) also can cause gingival hyperplasia. Careful gingivectomy and gingivoplasty should be performed (including histological examination of suspicious lesions), followed by professional dental cleaning. The owners are encouraged to perform daily tooth brushing with an azithromycin-containing dentifrice (8.5%). Azithromycin previously has been shown to reduce the occurrence of gingival enlargement in dogs.[20]

Pyogenic Granuloma

Pyogenic granuloma is a benign ulceroproliferative lesion in cats, resulting from the maxillary fourth premolar tooth traumatizing the gingiva, alveolar and buccal mucosa adjacent to a present or missing mandibular first molar tooth. Surgical excision of the mass plus blunting or extraction of the involved tooth or teeth is the treatment of choice.[21]

Stomatitis

Stomatitis in adult cats usually manifests as inflammation of the mucosal linings of the caudal oral cavity lateral to the palatoglossal folds, extending rostrally into gingiva, alveolar mucosa, buccal and labial mucosa, sublingual mucosa, and occasionally also the ventral and dorsal tongue surface. The etiology is not clear, but feline calicivirus (FCV) and feline herpesvirus-1 (FHV-1) have been implicated (see ch. 229).[22] History and clinical signs of cats with stomatitis include inappetence, weight loss, oral, nasal and ocular discharge, regional lymphadenopathy, and signs of oral pain. In severe cases, the inflamed oral tissues become proliferative and ulcerated, and bleed spontaneously. Various degrees of periodontal disease and tooth resorption can be present. An increase in serum total protein usually is due to elevated gamma globulin concentrations. A biopsy specimen should be obtained to rule out neoplasia or other causes of oral inflammation. A multimodal treatment approach is required, using a combination of surgical and medical therapies. Pain management is imperative (see ch. 356). Plaque control is achieved with professional dental cleaning, topical and systemic antimicrobial therapy, and tooth extraction. Partial and full-mouth tooth extraction still is the gold standard for treatment of feline stomatitis.[23] Corticosteroids often are required to decrease inflammation, reduce pain, and stimulate appetite. Some cats can benefit from periodic subcutaneous or intramuscular injections of methylprednisolone acetate (Depo-Medrol) (4 mg/kg). Others do well with prednisolone ointment (1 mg/kg per 0.1 mL q 12-24 h) that is applied to the pinna of the ears. Cyclosporine (e.g., Neoral) can be useful (starting at 2.5 mg/kg PO q 12 h for 6 weeks before judging effectiveness; monitoring kidney values; whole-blood cyclosporine levels > 300 ng/mL have been associated with significant improvement of oral inflammation). Clinical improvement of stomatitis also was reported with bovine lactoferrin (250 mg PO q 24 h). Low-dosage doxycycline (1 mg/kg PO q 24 h) and interferon omega (5 MU are diluted and divided as necessary to submucosally inject all inflamed areas; the remaining 5 MU are injected into a 100 mL bag of sodium chloride and frozen in ten 10 mL aliquots; the client gives 1 mL PO q 24 h for 100 days; the 10 mL fraction in use is refrigerated and the other aliquots are kept frozen until needed) also have been suggested as medical treatment options for cats with stomatitis.[24] Laser surgery (to remove proliferative tissue and ablate inflamed mucosa) may be used as an adjunct in patients with refractory stomatitis not responding to extractions and medical therapy.[25]

Eosinophilic Granuloma Complex

Eosinophilic granuloma complex includes several conditions of the oral mucosa (dogs and cats) and lips and skin (cats) that are characterized by an eosinophilic infiltrate histopathologically.[26] Lesions are more common in young adult female cats and male dogs. Suggested causes include ectoparasites and other insects, environmental allergens, or dietary hypersensitivity. Clinical signs depend on the location of the lesion, and include dysphagia, ptyalism, and inappetence. In cats, the condition manifests either as nodules (speckled with small, dense, white or yellowish areas) at the dorsal and lateral tongue surfaces, hard and soft palate, palatoglossal folds, and chin, or as well-demarcated ulcers (raised edges surrounding an ulcerated surface) on the upper lip and philtrum (occasionally also the lower lip). In dogs, single or multiple (often confluent) ulcerated lesions can be present on the soft palate and lateral pharyngeal mucosa (typically in Cavalier King Charles Spaniels), or raised, irregular, ulcerated lesions with well-demarcated edges are located on the lateral or ventral tongue (primarily in Siberian Huskies and Alaskan Malamutes). Biopsy with histopathologic evaluation is warranted to rule out differential diagnoses (such as squamous cell carcinoma, lymphoma, and

other skin diseases). In addition to eliminating the underlying cause, the treatment of choice is prednisone or prednisolone (1-2 mg/kg PO q 12 h initially, then tapered to the lowest effective dose) or periodic methylprednisolone acetate injections (4 mg/kg SC or IM). Amoxicillin-clavulanate (14 mg/kg PO q 12 h) also may be attempted. Surgical excision of affected areas rarely is recommended. Untreated lesions can result in major soft tissue loss (upper lip) and oronasal communication (hard palate).[26]

Autoimmune Oral Conditions

Autoimmune diseases causing skin lesions in dogs and cats also can occur at the mucocutaneous junction areas surrounding the mouth and the oral mucosa inside the mouth (lupus erythematosus with autoantibody production against tissue and nuclear proteins; see ch. 204 and 205). Occasionally, they are wholly contained within the oral cavity, as with pemphigus vulgaris and bullous pemphigoid with autoantibody production against specific squamous epithelial structures, or mucous membrane pemphigoid with autoantibody production against tissue proteins. Contrary to stomatitis in cats and contact ulceration in dogs, the hard palate mucosa can be affected. Biopsy of the leading edge of a lesion when an intact blister is not found could be sufficient. Storing the samples in Michel's solution is recommended by some pathologists to preserve tissue antigenicity at ambient temperatures.[27]

Bullae undergo different stages, from bleb (vesicle) formation, to erosion, to ulceration. Vesicles are characteristic, but they might no longer be present at the time of diagnosis and be replaced by scales, crusts, erosions and ulcers. The causative lesion in pemphigus vulgaris is suprabasilar (intercellular clefting) with formation of acanthocytes. The causative lesion in bullous pemphigoid is subepidermal without formation of acanthocytes. Laminin 5 and 6, collagen XVII, and integrin alpha-6/beta-4 have been implicated as autoantigens in mucous membrane pemphigoid in dogs, but only laminin 5 has been recognized in the cat. Treatment approaches are described in ch. 204 and 205.

Hypersensitivity and Metabolic Oral Conditions

Erythema Multiforme and Toxic Epidermal Necrolysis

Erythema multiforme possibly is mediated by deposition of immune complexes in the superficial capillaries of the skin and less often the oral mucosa as a result of an infection or drug exposure.[28,29] Toxic epidermal necrolysis is characterized by full-thickness coagulative necrosis with minimal dermal inflammation[30]; it is an extreme form of drug reaction (see ch. 169), with the animal being depressed, febrile, and inappetent. The underlying cause must preferably be eliminated (e.g., cessation of using a particular drug). Anti-inflammatory, immunosuppressive or immunomodulating therapy is instituted together with nursing care.

Uremia results from retention of uremic wastes after rapid decline in renal function[31] (see ch. 322). A sharp odor of ammonia is present in the breath (see ch. 36), and oral ulcerations occur, especially at the labial and buccal mucosa, lateral margins of the tongue, lateral lip frenula, and lip commissures. Uremic vasculitis and thrombosis can lead to necrosis and sloughing of the mucosa. In severe cases, this may lead to sloughing of the tip of the tongue. The lesions often are painful, contributing to the anorexia already observed in pets with kidney disease. Any condition (e.g., leptospirosis, diabetes mellitus, etc.) that can produce a hypercoagulable state can lead to thrombi formation and subsequent sloughing of the affected areas.[32] Treatment is supportive, until the inciting cause can be removed or resolved, and includes pain management (such as buprenorphine 0.01 mg/kg q 8-12 h, IV), bypassing the mouth with supplemental enteral or parenteral nutrition (see ch. 82), and use of gastric protectants (sucralfate 0.5-1 g PO q 4-6 h). Topical mouthwashes, such as a mixture of diphenhydramine, sucralfate or aluminum and magnesium hydroxide (Maalox, Novartis), and lidocaine can provide some local pain control. Diluted (0.12%) chlorhexidine rinse helps prevent secondary infection of necrotic areas.[31]

Oral Foreign Body

Penetrating foreign bodies can create deep and contaminated wounds in the sublingual area, palatoglossal fold, soft palate, palatine tonsil, floor of the orbit, or pharyngeal wall.[33] They also can be lodged across the hard palate between maxillary cheek teeth (e.g., a wooden stick), entrapped in oral mucosa (e.g., burdock and foxtails) or caught around the tongue and saw their way into the lingual frenulum (e.g., a needle with thread). Affected pets show halitosis, decreased appetite and water intake, pawing at the face, swelling in the intermandibular or neck region, sinus tracts, drooling of clear or blood-tinged saliva, and retching, gagging or

vomiting. Ultrasound, computed tomography, and magnetic resonance imaging are more helpful than radiographs in pinpointing a hidden foreign body's location.[9] Management requires surgical exploration, foreign body removal, wound cleansing and, if appropriate, drain placement and suturing. Microbial sampling is performed and empirical antibiotic therapy is instituted prior to availability of culture and sensitivity results. Intraoral wounds often are closed to prevent entrapment of food, hair, and other debris. If the intraoral point of entry has healed by the time the patient presents with clinical signs, the surgical approach is chosen based on diagnostic findings to determine the most direct and safest route for foreign body retrieval.[9]

Oral Burns (Figure 272-3)

Electric injury usually occurs in young animals that chew on power cords.[24] Life-threatening complications are related to neurogenic pulmonary edema or smoke inhalation (see ch. 242). Affected tissues typically include the lips, cheeks, oral mucosa, tongue, and palate. More extensive burns also affect teeth and bones. The patient initially is stabilized if noncardiogenic pulmonary edema has occurred, then is managed conservatively (wound lavage) at first. Later, once necrotic tissue is evident, conservative debridement may be initiated. Tongue necrosis can cause a large piece of tissue to slough off. Palate necrosis can cause an oronasal defect.

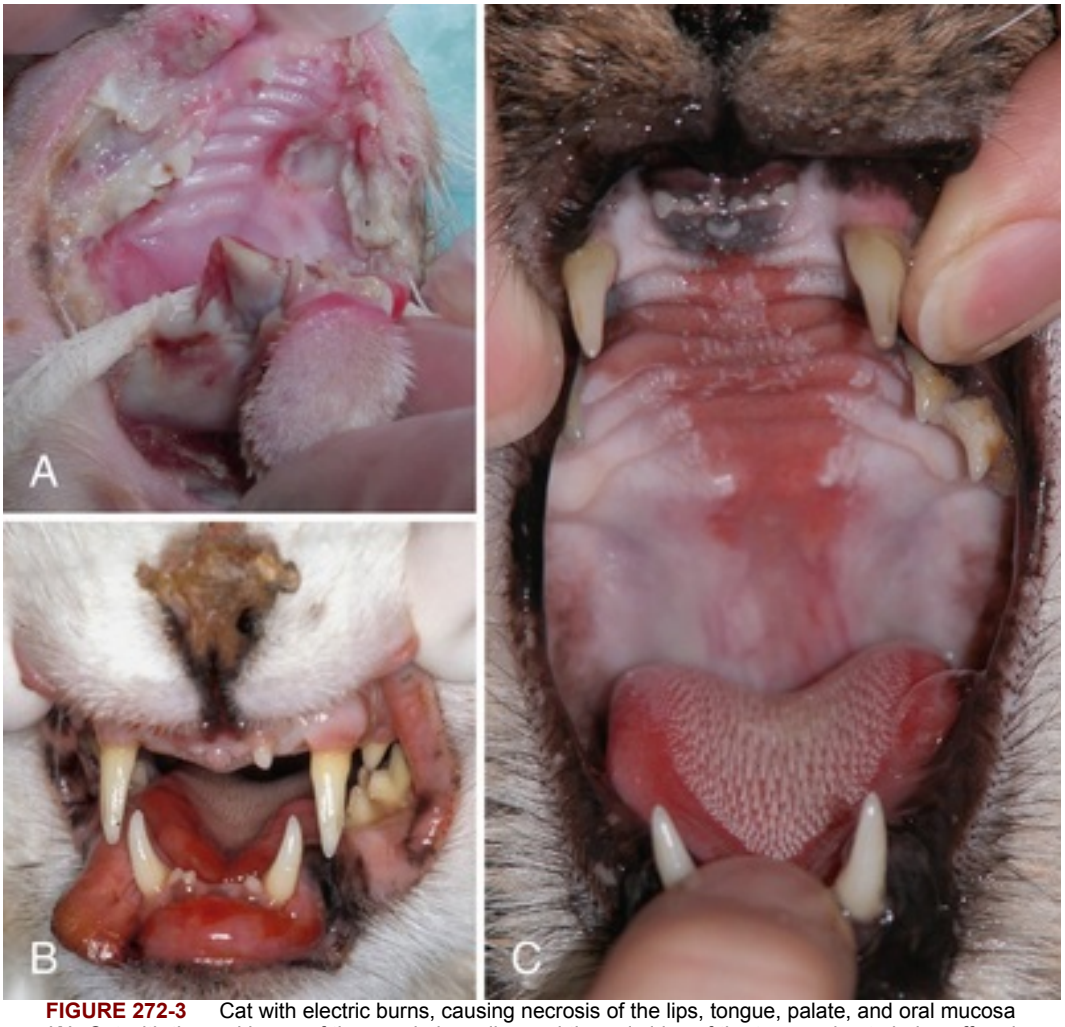

FIGURE 272-3 Cat with electric burns, causing necrosis of the lips, tongue, palate, and oral mucosa **(A).** Cat with thermal burns of the nasal plane, lips and tip and sides of the tongue due to being offered microwaved food **(B).** Cat with chemical burns, resulting in acute-onset erosions of the tip and sides of the tongue and the palate **(C).** (Copyright Alexander M. Reiter.)

Thermal burns resulting from exposure to hot items sometimes are seen on the nasal plane, lips, labial

mucosa, tongue and palate. Owners are advised not to overheat food and liquids when they attempt to make them more palatable in patients with inappetence. Chemical burns present as acute ulcers covered by necrotic debris from exposure to household cleaning products, phenolic compounds, essential oils (e.g., potpourri), heavy metal (thallium), or plant toxins (i.e., *Dieffenbachia*). Initial therapy for thermal and chemical burns is lavage with lactated Ringer's solution, followed by conservative management. The haircoat of an affected pet should be cleansed if there is suspicion that it contains residuals of the agent responsible for a chemical burn.[24]

Masticatory Muscle Myositis

Masticatory muscle myositis (MMM) is an autoimmune disease affecting the temporal, masseter, and medial and lateral pterygoid muscles in dogs (see also ch. 354). Large-breed, young-adult to middle-aged dogs appear to be affected most commonly.[34] An acute stage (painful muscle swelling/inflammation) typically lasts for 2-3 weeks, followed by a latent stage (apparently healthy animal) which is then followed by a chronic stage (muscle atrophy) or a recurrent acute stage. Dogs with acute MMM have a history of decreased activity, lethargy, reluctance to eat, and signs of pain on yawning or when prehending treats and toys. Dogs with chronic MMM usually are bright and alert, but they show progressive atrophy of the masticatory muscles. The acutely affected dog can show fever, regional lymphadenopathy, swelling of temporal and masseter muscles (painful on palpation) and exophthalmos. The dog resists opening of the mouth or is unable to open the mouth fully. The chronically affected dog can show atrophy of masticatory muscles, enophthalmos, and inability to open the mouth fully. Muscle swelling/atrophy can be asymmetric.[34]

The temporal, masseter, and medial and lateral pterygoid muscles possess 2M fibers that differ from the common type 2C fibers of other skeletal muscles. In this disease, autoantibodies target the unique myosin component of type 2M fibers, resulting in muscle inflammation, necrosis, and phagocytosis. A definitive diagnosis of MMM can be made if antibodies against type 2M fibers are identified in serum and/or immune complexes detected in biopsied muscle samples.[35] A serum type 2M fiber antibody titer of <1 : 100 is negative, 1 : 100 is borderline, and >1 : 100 is positive.

Computed tomography (CT) aids in ruling out most differentials of MMM, allows guided fine-needle aspiration of surgically inaccessible pterygoid muscles, shows changes in size (larger due to edema or inflammation; smaller due to atrophy, necrosis or fibrosis), pre-contrast tissue attenuation (hypoattenuated due to edema) and heterogeneous contrast enhancement (due to inflammation) in affected muscles, and the presence of regional lymphadenopathy.[35]

Muscle biopsies are taken from areas of temporal or masseter muscles that show the most obvious contrast enhancement on CT. A 0.5 to 1 cm-diameter specimen of muscle tissue is excised, enveloped in a dry or minimally moistened gauze sponge, and placed into a water-tight container (e.g., a 10 mL red top tube) (see ch. 116). The sample is kept cool and shipped overnight (Comparative Neuromuscular Laboratory, University of California, San Diego, USA or Institut fuer Neuropathologie, Universitaet Duesseldorf, Duesseldorf, Germany). Particular attention should be paid to complete wound closure, because corticosteroids will delay connective tissue healing.[36] Corticosteroid therapy should not be started prior to blood collection and muscle sampling. A dexamethasone injection (1 mg/kg IV once after muscle biopsy) is helpful in the immediate reduction of inflammation in dogs with acute MMM. The patient is discharged with prednisone (1-2 mg/kg PO q 12 h), usually resulting in rapid improvement of clinical signs (reduction of pain and signs of systemic illness, as well as visible improvement of mouth opening, 1-2 days after start of corticosteroid therapy). After 2 to 3 weeks, the dosage can be decreased to 1 mg/kg PO q 24 h for another 3 to 4 weeks before it is slowly tapered to the lowest possible alternate-day effective dosage over a period of 8-12 months. Dogs unable to receive corticosteroids, unresponsive to corticosteroids alone, or showing unacceptable side effects in response to corticosteroids might benefit from administration of azathioprine (1-2 mg/kg PO q 24 h). Follow-up examinations should take place 2 weeks and 1, 2, 6, 9 and 12 months after initiation of corticosteroid therapy and once every 6 to 12 months thereafter, focusing on body weight, degree of muscle atrophy, pain on head palpation, and range of opening the mouth (which is measured with a ruler between the incisal edges of the maxillary and mandibular incisors). Periodic antibody titer tests are important prior to decreasing prednisone dosages, particularly when the dosage already is very low (e.g., 0.1-0.2 mg/kg PO q 48 h). In dogs with relapses, treatment should be reinstituted at the maximum prednisone dosage and slowly tapered to the lowest possible alternate-day effective dosage.[34]

Salivary Gland Conditions

Sialocele (extravasation of saliva into submucosal or subcutaneous spaces) requires surgical treatment, and the reader is referred to surgery textbooks for information on diagnosis and treatment.[37,38]

Sialadenitis, an inflammation of a salivary gland, is seen in middle-aged to older dogs. The zygomatic salivary gland is affected most commonly, and the dog can present with a painful swelling in the orbital/retrobulbar area with exophthalmos. Clinical signs include malaise, inappetence, lymphadenopathy, fever, signs of pain on retropulsion of the eye through the closed eyelid and on opening the mouth, dysphagia, and mucopurulent discharge at the duct opening in the mouth. The soft palate can have an asymmetric appearance from an enlarged, inflamed zygomatic gland. Sialoliths can be a contributing factor. Computed tomography and magnetic resonance imaging should be considered to rule out differential diagnoses. Fine-needle aspiration and cytological evaluation of the zygomatic salivary gland (through the oral mucosa) and regional lymph nodes (see ch. 95), bacterial culture and sensitivity testing (if infection is suspected), and three-view thoracic radiographs (if neoplasia is suspected) may be performed. A definitive diagnosis of sialadenitis requires an incisional biopsy and histopathological evaluation. Intraoral drainage to alleviate mucopurulent fluid accumulation and associated pressure causing discomfort may be attempted. Medical treatment includes management of pain (if present; see ch. 126 and 356) and use of antibiotics (based on culture and sensitivity results of the fluid/tissue aspirate), nonsteroidal anti-inflammatory drugs (NSAIDs), and anti-inflammatory dosages of corticosteroids (see ch. 164).[39]

Sialadenosis is a non-inflammatory enlargement of a salivary gland without obvious cytological or histological abnormalities. *Necrotizing sialometaplasia* (salivary gland necrosis or infarction) is a painful enlargement of a salivary gland with squamous metaplasia of the salivary gland ducts and lobules and lobular ischemic necrosis. Sialadenosis and necrotizing sialometaplasia mostly occur in young adult to middle-aged, small breed dogs. History and clinical signs are less severe with sialadenosis (weight loss, reluctance to exercise, snorting, lip smacking, nasal discharge, hypersalivation, inappetence, depression, retching, and gulping). In addition to those, dogs with necrotizing sialometaplasia often show gagging, regurgitation, chronic vomiting, coughing, tachypnea, dyspnea, reverse sneezing, and abdominal respiratory efforts. Dogs are sensitive on palpation of the pharyngeal region, show signs of pain associated with opening the mouth, and are depressed, nauseated, and anorexic. A neurogenic pathogenetic mechanism is suspected to correlate with abnormalities of the vagus nerve, and conditions associated with necrotizing sialometaplasia include esophageal disorders. In addition to pain management, similar diagnostic and therapeutic attempts as for sialadenitis should be performed. Oral phenobarbital administration (1-2 mg/kg PO q 12 h) has resulted in dramatic improvement in some cases, providing support for a neurogenic mechanism.[39]

Non-Neoplastic Jaw Bone Disorders

Craniomandibular osteopathy is characterized by woven bone proliferation at the body of the mandible, temporomandibular joint, and the tympanic bulla bilaterally in smaller dog breeds. A thickening of the calvarium, tentorium cerebelli, and extremities can be observed.[40] The dog may show signs of pain, unwillingness or inability to fully open the mouth, and reluctance to eat. Hyperthermia can be present, and neurological signs occasionally can be seen. Treatment consists of anti-inflammatory drugs (NSAIDs or corticosteroids; see ch. 164), analgesic drugs (see ch. 126 and 356), and nutritional support (see ch. 82).

Calvarial hyperostosis, primarily seen in young Bullmastiffs, is characterized by irregular, progressive bony proliferation and thickening of the cortical bone of the calvarium. It manifests as a smooth thickening of calvarial bones, making it different from the irregular thickening seen in craniomandibular osteopathy. Clinical signs include painful swelling of the skull, exophthalmos, fever, and lymphadenopathy. In most cases it is self-limiting.[41]

Fibrous osteodystrophy results from a congenital condition associated with primary hyperparathyroidism and nutritional or renal secondary hyperparathyroidism (see ch. 297).[42] There is generalized osteopenia with more pronounced manifestation in the jaw bones, causing tooth mobility, facial swelling, thickened rubbery jaws, and ulcerated oral mucosa. Radiographs display marked, diffuse decrease of bone density, loss of normal trabecular bone structure as well as loss of lamina dura. The teeth usually do not appear to be demineralized and rarely undergo resorption. The prognosis is very poor, except for cases of nutritional secondary hyperparathyroidism that may be treated by feeding an appropriately formulated diet.

Benign Oral Tumors

Papillomas are viral-induced, cauliflower-like whitish lesions at mucous membranes and mucocutaneous

junctions of the mouth in dogs less than one year of age (see ch. 228). They often resolve spontaneously in 1-3 months, unless the patient is immunocompromised; ruling out lymphoma is particularly important in older dogs presenting with severe oral papillomatosis.

Peripheral odontogenic fibromas are mixed odontogenic tumors (common in dogs, rare in cats) and often are located in the gingiva near the incisor, canine, or premolar teeth.[43] The ossifying type (previously called ossifying epulis) is distinguished from the fibromatous type (previously called fibromatous epulis) by its content of varying amounts of bone or dental hard tissue within the tumor's soft tissue. These tumors are excised together with extraction of the involved tooth and thorough curettage of the alveolus. Biopsy will distinguish these tumors from gingival hyperplasia (Figure 272-4).

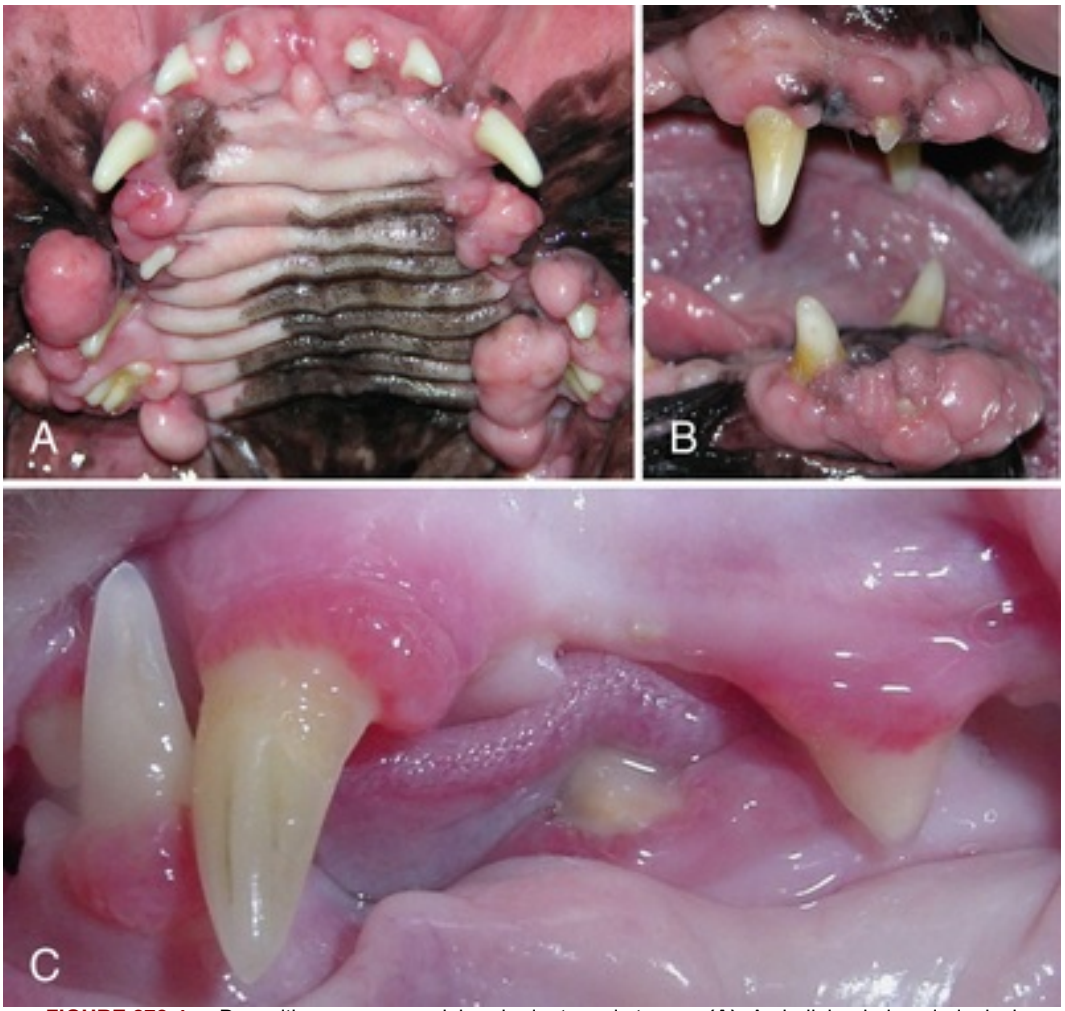

FIGURE 272-4 Dog with numerous peripheral odontogenic tumors **(A).** Amlodipine-induced gingival hyperplasia in a dog **(B).** Cyclosporine-induced gingival hyperplasia in a cat **(C).** (Copyright Alexander M. Reiter.)

Ameloblastomas are epithelial odontogenic tumors. The canine acanthomatous ameloblastoma (previously called acanthomatous epulis) is a locally-invasive tumor causing bone lysis around tooth roots and cystic changes. However, despite this locally aggressive behavior, it does not metastasize and is therefore considered to be benign.[43] Externally, it often has a rough, cauliflower-like surface and sometimes can be similar in appearance to squamous cell carcinoma. It occurs most commonly in the incisor and canine tooth area of the lower or upper jaw, and less commonly in the carnassial tooth area of the lower or upper jaw.

Odontomas are not true neoplasms but, rather, a conglomerate of disorganized, normal tissue cells. Enamel, dentin, cementum, and small tooth-like structures can compose the mass. Lesions with characteristics resembling normal teeth are considered compound odontomas, whereas complex odontomas have a more disorganized arrangement.[44]

Other benign oral tumors that are less common include the cementoma, giant cell granuloma, feline inductive odontogenic tumor, amyloid-producing odontogenic tumor, plasma cell tumor, osteoma, and lipoma.

Malignant Oral Tumors

Malignant melanoma usually occurs in older dogs with oral pigmentation, and it is very rare in cats (see ch. 345). The tumor is pigmented or nonpigmented (amelanotic), often grows rapidly and invades bone early. The tumor surface usually is ulcerated and foul-smelling because of necrosis caused by the lesion outgrowing its blood supply. Typical locations are the gingiva, palate, dorsal surface of the tongue, and mucosal surface and mucocutaneous junctions of the lips and cheeks. Regional and distant metastasis is common at the time of diagnosis.[45]

Nontonsillar *squamous cell carcinoma* typically is a tumor of older cats and dogs, but papillary squamous cell carcinoma also can occur in adolescent and young adult dogs. The tumors most often are found on the gingiva as proliferative and ulcerated lesions and less often on the mucosa of the lips, cheeks, tongue and sublingual area. Bone invasion is common for gingival lesions. If occurring on the upper jaw in cats, the tumor can be less protuberant, while bone invasion is more severe. Use of flea collars, eating canned tuna and canned cat food, and exposure to environmental tobacco smoke have been identified as risk factors for squamous cell carcinoma in cats.[46] Metastasis to regional lymph nodes is common, while distant metastasis can occur late in the disease process. Recent studies of cats with squamous cell carcinoma suggest a rate of metastasis to the mandibular lymph nodes of >30%.[47] Tonsillar and lingual squamous cell carcinoma in dogs are highly metastatic. See ch. 345 for treatment and prognostic information on squamous cell carcinoma.

Fibrosarcoma is the second most common malignant oral tumor in cats and the third most common in dogs. It tends to occur in young adult to middle-aged large-breed dogs and older smaller dogs, affecting the gingiva, lip/cheek mucosa, or the hard and soft palate. Often, it appears as a protuberant, ulcerated lesion. Occasionally, it can arise from the lateral surface of the incisive bone and maxilla, presenting a slowly enlarging, firm mass at the muzzle. Fibrosarcomas are highly invasive. Regional and distant metastasis are less common compared to malignant melanoma and squamous cell carcinoma. Low-grade fibrosarcomas appear benign histologically but are malignant biologically.[48] See ch. 348 for treatment and prognostic information on fibrosarcoma.

Osteosarcoma affects the mandible and, less often, the maxilla, often manifesting as a fleshy, ulcerative or necrotic oral mass with extensive radiographic evidence of bone invasion (bone lysis rather than hard tissue proliferation). Regional and distant metastasis seem to be less common than for limb osteosarcoma.[49] Multilobular tumor of bone is a less aggressive variant of osteosarcoma, manifesting as a hard, well-circumscribed, non-ulcerated mass on the maxilla, palate, ramus of the mandible, zygomatic arch, and calvarium. It appears radiographically as a combination of mineralized and non-mineralized tissue ("popcorn ball" appearance). See ch. 348 for treatment and prognostic information on osteosarcoma.

Peripheral nerve sheath tumors sometimes are misdiagnosed as fibrosarcoma. They tend to grow along major nerves (i.e., infraorbital nerve, inferior alveolar nerve, major palatine nerve) of the face, upper and lower jaw, and palate (see ch. 268).

Other less common, malignant lesions include hemangiosarcoma, lymphoma, mast cell tumor, and anaplastic or undifferentiated tumors.

Approach to Evaluating Oral Masses

The TNM (tumor, node, metastasis) system aids in describing the clinical extent (staging) of neoplastic disease through evaluation of the primary tumor, regional lymph nodes, and distant sites of possible metastasis.[50] Three-view thoracic radiography (and occasionally also an abdominal ultrasound if there is a reason to suspect intraabdominal disease) should be performed prior to placing an oral tumor patient under anesthesia, particularly when a malignant oral lesion is suspected. However, metastatic lesions sized <5 mm in diameter might not be visible on radiographs. Conversely, inclusion of the thorax during computed tomography of the head (to evaluate the primary tumor) and neck (to evaluate lymph nodes) can allow for detection of metastatic lesions <2 mm in diameter.[51] The use of conventional or digital dental radiographs (in particular with size 4 dental films or phosphor plates) is superior to standard medical radiography in the evaluation of quality and extent of bony lesions of upper and lower jaws.

A biopsy preferably is obtained from an area that can be included in the definitive resection. Areas of necrotic tissue can be present in rapidly growing tumors, and such tissue is not helpful diagnostically; viable

tissue should be included in the biopsy sample. Cytological sampling can be performed in the awake or sedated patient. Fine-needle techniques are useful for lesions that exfoliate well, and sampling often is performed with a 22-gauge needle by means of a needle biopsy ("woodpecker method") or needle aspiration (see ch. 93 and 95). Palpation of lymph nodes is neither sensitive nor specific for detecting regional lymph node metastasis.[52] Therefore, cytological examination of lymph node needle biopsies and aspirates should be performed, and this can be adequate for diagnosing metastatic melanoma and squamous cell carcinoma but is less satisfactory for other oral tumors. Impression smears and scrapings obtained from the surface of an epithelialized or ulcerated tumor have no diagnostic value. Impression smears and scrapings can be of much greater value if obtained from the cut surface of an excised tumor (see ch. 86 and 87).

Histological sampling requires general anesthesia and microscopic examination of a formalin-fixed specimen. This is more accurate than cytological sampling. Rongeurs are ideal for bone samples and scalpel blades for incisional and excisional soft tissue sampling. Tissue-damaging instrumentation (e.g., electrocautery) must not be used during the sampling procedure so that a diagnosis is not obscured. Multiple samples should be obtained. Hemostasis is achieved with digital pressure, and biopsy sites of more deeply invading tumors are sutured. For adequate fixation, the specimen is placed in 10% buffered formalin at 1 part tissue to 10 parts fixative. Parotid, mandibular, and medial and lateral retropharyngeal lymph nodes preferably should be evaluated histologically after excision (see ch. 95). A negative lymph node biopsy, however, does not preclude the possibility of regional metastasis, which can occur along perineural or vascular routes, or metastasis to other, less-accessible lymph nodes. If cytological or histological results do not match the clinical findings, a second, deeper, and larger specimen is obtained. A mucosal flap could be raised to access deeper tissue for tumors that are covered by a layer of variably-thick normal tissue.

Outcome and Conclusion

Client communication is extremely important prior to embarking on an involved oral surgical procedure. In general, home care in the immediate postoperative period, long-term home oral hygiene, and the need for periodic reexaminations should be discussed with every client. Considering that general anesthesia is required to assess any dental and oral lesions fully and to perform treatment as needed, the risk of perioperative complications also should be discussed. Additionally, some of the diseases discussed in this chapter require medical treatment for the rest of the patient's life or surgical procedures that could lead to a change in the patient's esthetic appearance or functionality.

A diagnosis of a malignant or locally aggressive oral tumor should lead to an in-depth discussion about the biological behavior of the tumor, possibility of intraoperative complications, expectations in terms of quality of life for the pet, life expectancy after the procedure, life expectancy if surgery is not performed, and non-surgical treatment alternatives (such as radiation therapy, immunotherapy, and chemotherapy). Collaboration with medical and radiation oncologists is helpful to allow the veterinarian and client make an informed decision that fits the pet and its family.

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CHAPTER 273

Diseases of the Pharynx and Esophagus

Stanley Leon Marks

Client Information Sheet: Megaesophagus in Dogs and Cats

Normal Anatomy and Function

The oral cavity, oropharynx, and esophagus can be thought of as a series of expanding and contracting chambers, divided by muscular sphincters. Propulsion of a bolus through this part of the alimentary tract is the result of positive pressure developed behind the bolus, as well as a vacuum or negative pressure developed in front. Any disturbance in the functional or anatomical elements or coordination of this system can result in abnormal transfer of a bolus from the oral cavity to the stomach, resulting in dysphagia (difficulty swallowing). Dysphagia is relatively common in dogs and the list of possible causes is extensive (Box 273-1). Dysphagia is far less common in cats with the exception of structural causes of oropharyngeal dysphagia (OPD) associated with oral tumors, ulcers, and gingivostomatitis.

Box 273-1

Causes of Oropharyngeal and Esophageal Dysphagia in Dogs

Central Nervous System

Cerebrovascular accident
Brainstem tumor

Iatrogenic

Antihistamines
Anticholinergics
Phenothiazines
Chemotherapy
Postsurgical muscular or neurogenic
Radiation
Ingestion of a corrosive substance
Antibiotics (clindamycin, doxycycline)
Nonsteroidal anti-inflammatory drugs

Infectious/Inflammatory

Esophagitis
Botulism
Tetanus
Candidiasis
Rabies
Abscess
Calicivirus infection (cats)
Rhinotracheitis virus infection (cats)

Metabolic

Hyperadrenocorticism

Hypoadrenocorticism
Hypothyroidism (not an important cause in dogs)
Thyrotoxicosis-associated myopathy (people)

Myopathic/Neuropathic

Peripheral neuropathies
Inflammatory myopathies (infectious, immune-mediated, pre-neoplastic)
Dermatomyositis
Muscular dystrophies
Myasthenia gravis
Megaesophagus

Structural

Oropharyngeal or esophageal neoplasia
Cricopharyngeal bar
Proximal esophageal webs
Esophageal tumors
Esophageal stricture
Esophageal fistula
Esophageal diverticulum
Vascular ring anomaly
Foreign body
Congenital anomaly (cleft palate, diverticula)
Hiatal hernia
Gastroesophageal reflux
Gastroesophageal intussusception

The swallowing mechanism is complex, involving 31 pairs of striated muscles and five cranial nerves with nuclei in the brainstem (sensory and motor fibers of the trigeminal, facial, glossopharyngeal, and vagus nerves, and motor fibers of the hypoglossal nerve), and the swallowing center in the reticular formation of the brainstem. The normal swallowing reflex is a four-phase process: oral preparatory, oral, pharyngeal, and esophageal phases.[1] The esophagus transports the bolus from the pharynx into the stomach. The outer coat of esophageal loose connective tissue, the adventitia, is present in the cervical portion but is largely replaced by serosa in the thorax. In dogs, the muscularis of the esophagus is entirely striated from the cricopharyngeus muscle to the gastroesophageal junction. In cats, the striated muscle is replaced by smooth muscle in about one-third of the esophagus. The inner esophageal wall consists of submucosa and mucosa, divided by fenestrated muscularis mucosae, more prominent in the thoracic esophagus. The submucosa contains blood vessels, nerves, and glands. The mucosa is composed of keratinized, stratified squamous epithelium. Innervation of the striated muscle of the esophagus in dogs and cats is provided by special visceral efferent neurons from the bilateral nucleus ambiguus in the medulla oblongata. Axons are carried in the vagus nerves and distributed with the pharyngoesophageal and recurrent laryngeal nerves, and the vagal trunks. The smooth muscle innervations in cats arise from the rostral bilateral nucleus ambiguus via general visceral efferents, and are also distributed via the branches of the bilateral vagus nerve.

Phases of Swallowing

Oral Preparatory, Oral, and Pharyngeal Phases

The *oral preparatory phase* is voluntary and begins as food or liquid enters the mouth. Mastication and lubrication of food are hallmarks of this phase, as the bolus is modified and prepared for swallowing. Abnormalities of the oral preparatory phase are associated with dental disease (see ch. 272), xerostomia, and weakness of the lips (cranial nerves V and VII), tongue (cranial nerve XII), and cheeks (cranial nerves V and VII) (see ch. 264). The *oral phase* consists of the muscular events responsible for movement of the bolus from the tongue to the pharynx, and is facilitated by the tongue, jaw, and hyoid muscle movements. The *pharyngeal phase* begins as the bolus reaches the tonsils, and begins with elevation of the soft palate to prevent the bolus from entering the nasopharynx, elevation and forward movement of the larynx and hyoid, retroflexion of the epiglottis and closure of the vocal folds to close the entrance into the larynx. Then, there is synchronized

contraction of the middle and inferior constrictor muscles of the pharynx together with relaxation of the cricopharyngeus muscle that makes up much of the upper esophageal sphincter (UES). This allows passage of the bolus into the esophagus (Figure 273-1). Respiration is briefly halted (apneic moment) during the pharyngeal phase.[2]

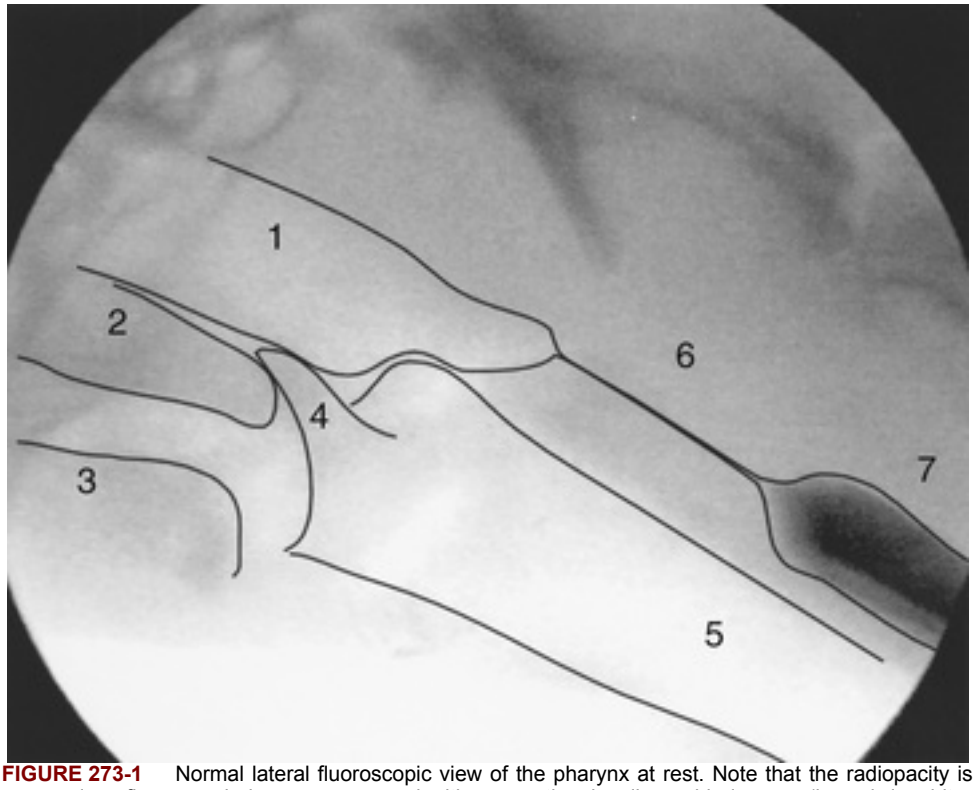


FIGURE 273-1 Normal lateral fluoroscopic view of the pharynx at rest. Note that the radiopacity is reversed on fluoroscopic images compared with conventional radiographic images (i.e., air is white, bone is black). 1. Nasopharynx; 2. Soft palate; 3. Base of tongue; 4. Epiglottis; 5. Trachea; 6. Upper esophageal sphincter; 7. Proximal esophagus with barium in the lumen. (From Pollard RE, Marks SL, Davidson A, et al: Quantitative videofluoroscopic evaluation of pharyngeal function in the dog. *Vet Radiol Ultrasound* 41[5]:409–412, 2000.)

Abnormalities of the pharyngeal phase of swallowing include pharyngeal weakness due to neuropathies or myopathies, pharyngeal tumors or foreign bodies, or obstruction of the UES secondary to hypertrophy of the cricopharyngeus muscle. Synchrony between constriction of the pharyngeal muscles and relaxation of the cricopharyngeus muscle is essential to allow passage of the bolus into the esophagus. Despite the myriad causes of OPD, the pathophysiologic end results fall into one of two inter-related categories: (1) abnormalities of bolus transfer or (2) abnormalities of airway protection. Abnormalities of bolus transfer can be further grouped into those caused by (a) oropharyngeal pump failure (pharyngeal weakness); (b) oropharyngeal and pharyngo-UES asynchrony (neuropathies); and (c) pharyngeal outflow obstruction (cricopharyngeal achalasia, tumors of the pharynx, foreign bodies).

Esophageal Phase

The *esophageal phase* is involuntary, beginning with relaxation of the UES and movement of the bolus into the esophagus. Sensory feedback likely plays a role in regulating the speed and intensity of peristaltic waves, depending on bolus characteristics. Swallow-induced peristalsis is primary peristalsis. Secondary peristalsis occurs in response to distension of the esophageal lumen by a bolus that has failed to be propelled into the stomach. Relaxation of the LES in advance of the propagated pressures permits food to empty into the stomach and once the bolus passes, the LES contracts to prevent reflux of gastric contents into the esophagus.

Diagnostic Approach

Signs

The diagnosis of disorders affecting the oropharyngeal phase of swallowing can be extremely challenging. A history of repetitive swallowing, gagging, and retching associated with meals, nasal regurgitation with meals, swallow-related coughing, food falling from the mouth during swallowing, and recurrent pneumonia should cause suspicion of OPD (Figure 273-2). OPD can cause transient apnea and syncope in some dogs. In contrast, animals with esophageal dysphagia are typically less challenging to diagnose, although some have concurrent disease of the pharynx and esophagus. The hallmark signs of esophageal dysphagia include regurgitation (solids or liquids), odynophagia (painful swallowing), repeated swallowing attempts, and excessive salivation. *Regurgitation of food or water is the most consistent sign of esophageal disease and must be differentiated from the signs of OPD or vomiting.* Pharyngeal or esophageal disease may be part of a systemic disease in animals manifesting signs of dysphagia only, underscoring the importance of a comprehensive systemic evaluation. The assessment of dogs and cats with signs of pharyngeal or esophageal dysphagia include a review of signalment, medication history and asking about any recent anesthesia (Box 273-2). Physical (prefeeding assessment) and neurologic examinations and assessing laboratory tests are valuable before watching swallowing and using imaging studies and endoscopic evaluations.

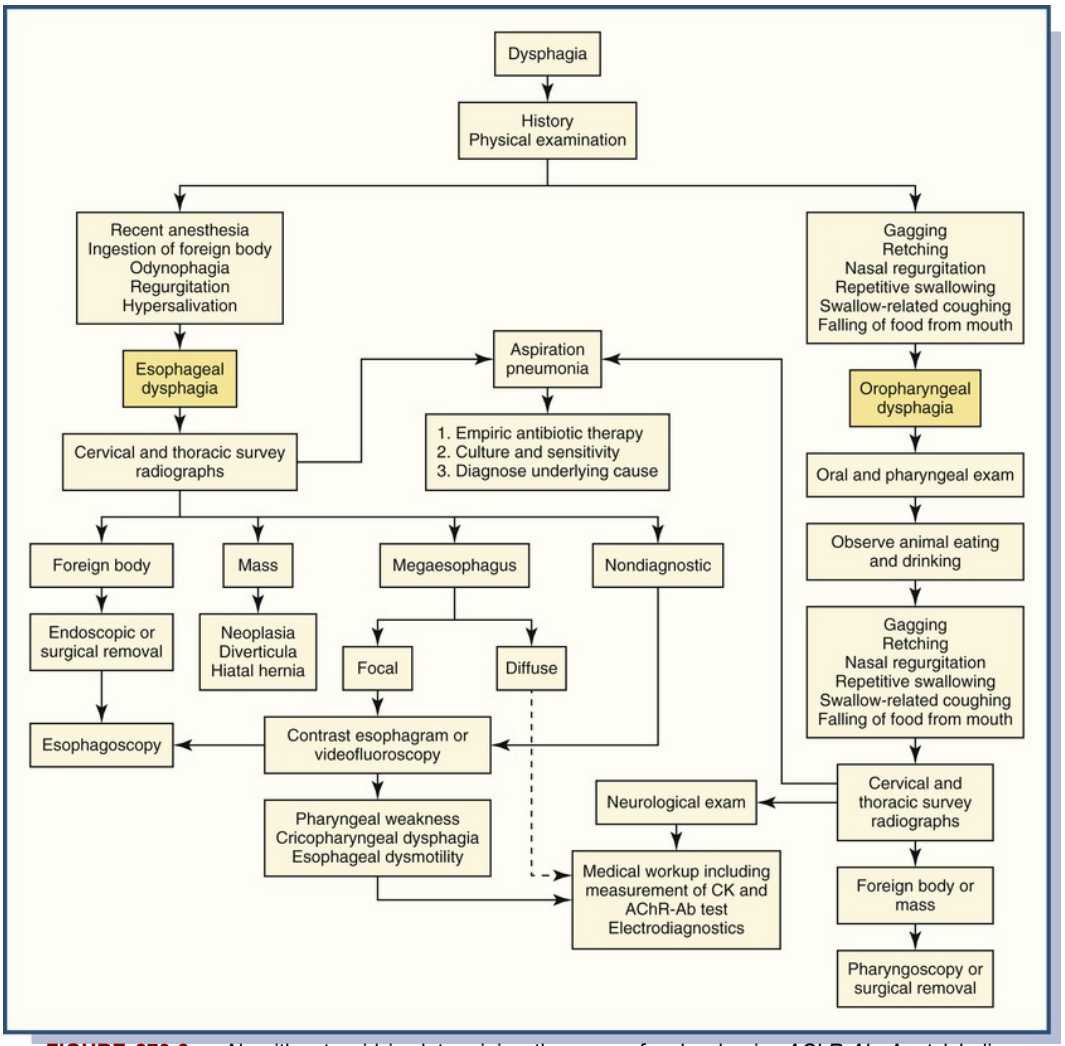


FIGURE 273-2 Algorithm to aid in determining the cause for dysphagia. *AChR-Ab,* Acetylcholine receptor antibody; *CK,* creatine kinase.

Box 273-2

History-Based Evaluation of the Dysphagic Animal

Age of onset?
Sudden onset or gradual onset?
Dysphagia while eating or between meals?
Difficulty with solids or liquids or both?
Intermittent or progressive dysphagia?
Temporal pattern of dysphagia (oropharyngeal dysphagia occurs within seconds following swallowing)
History of coughing?
History of medication administration?
History of dysphonia?
Recent general anesthesia?
History of odynophagia?

Signalment

Causes of OPD in puppies include cleft palate, cricopharyngeal dysphagia, muscular dystrophy, and pharyngeal weakness. Breeds with a hereditary predisposition or high incidence of OPD include the Golden Retriever (pharyngeal weakness),[3] Cocker and Springer Spaniels (cricopharyngeal dysphagia), Bouvier des Flandres and Cavalier King Charles Spaniel (muscular dystrophy)[4] and Boxer and Newfoundland (inflammatory myopathy). Large-breed dogs are predisposed to masticatory muscle disorders. A familial predisposition for congenital megaesophagus has been suggested in the Great Dane, German Shepherd, Labrador Retriever, Irish Setter, Chinese Shar-Pei, Newfoundland, Miniature Schnauzer, and Fox Terrier breeds.[5] Congenital megaesophagus is rare in cats, although Siamese are predisposed. Acquired idiopathic megaesophagus is more commonly recognized in large breed dogs.

Physical and Neurologic Examination

Physical examination of the dysphagic animal includes careful examination of the oropharynx, using sedation or anesthesia if necessary, to help rule out dental disease, foreign bodies, cleft palate, glossal abnormalities, and oropharyngeal tumors. The pharynx and neck should be palpated carefully for masses, asymmetry, or pain and the chest auscultated carefully for evidence of aspiration pneumonia. Evaluation of cranial nerves should include assessment of the tongue, jaw tone, and ability to abduct the arytenoid cartilages with inspiration. Complete physical (see ch. 2) and neurologic (see ch. 259) examinations may reveal evidence of a generalized neuromuscular disorder: muscle atrophy, stiffness, decreased or absent spinal reflexes. The gag reflex should be evaluated by placing a finger in the pharynx; however, presence or absence of a gag reflex does not indicate efficacy of pharyngeal swallowing nor adequacy of deglutitive airway protection.[6]

Observation of Eating and Drinking

The importance of carefully observing the dysphagic animal while eating (kibble and canned food) and drinking cannot be overemphasized. Observations help localize the problem to the oral cavity, pharynx, or esophagus. Dogs with an abnormal oral phase of swallowing typically have difficulty with prehension or aboral transport of a bolus to the tongue base, and these disorders often can be diagnosed by watching the animal eat. OPDs affecting the pharyngeal phase of swallowing can be diagnostically challenging. These dogs often have non-specific signs: gagging, retching, and multiple swallowing attempts before a bolus is moved successfully into the proximal esophagus (Video 273-1). These pets often have abnormal transport of a bolus from the oropharynx to the hypopharynx or from the hypopharynx to the proximal esophagus. Cricopharyngeal dysphagia, with signs similar to those seen with pharyngeal disorders, causes abnormal bolus transport through the UES. Dogs with megaesophagus, esophageal strictures or esophagitis can exhibit evidence of odynophagia and regurgitation seconds to minutes following bolus swallowing.

Laboratory Testing

Comprehensive laboratory testing is warranted in animals with OPD and esophageal dysphagia to provide a minimum neuromuscular data set. Testing should include a complete blood count (CBC), serum chemistry panel (including creatine kinase [CK] and electrolyte concentrations), urinalysis, evaluation of thyroid

function (see ch. 299), and acetylcholine receptor (AChR) antibody titer for acquired myasthenia gravis (see ch. 269). Persistently elevated CK concentrations (2,000-20,000 IU/L) could indicate generalized myositis, whereas marked CK increases (>20,000 IU/L) are more suggestive of necrotizing or dystrophic myopathy (see ch. 354). Normal CK concentrations do not rule out myopathy, particularly when focal (masticatory muscle myositis; see ch. 272) or chronic. Acquired myasthenia gravis is an important neuromuscular cause of OPD causing pharyngeal, esophageal, and/or laryngeal weakness without clinically detectable muscle weakness in the extremities. Pharyngeal weakness as the only clinical sign of myasthenia gravis has been described in 1% of affected dogs.[7] The acetylcholine (AChR) antibody test should be performed in all pets with acquired dysphagia. The gold standard for the diagnosis of acquired myasthenia gravis remains the demonstration of serum autoantibodies against native AChR by immunoprecipitation RIA. Within individuals, AChR antibody levels correlate with disease severity, but antibody levels between patients are highly variable and do not correlate well with severity. This test is not useful for congenital dysphagia in which an immune basis is unlikely.

Cervical and Thoracic Radiography

The pharynx of healthy animals is air filled and easily seen on radiographs. The size of the air-filled space can be decreased by inflammation/edema, neoplasia, or elongation of the soft palate and it can appear increased with pharyngeal or UES dysfunction, chronic respiratory (inspiratory) disease, or chronic severe megaesophagus. The normal esophagus is not visible on survey radiographs except after aerophagia due to excitement, nausea, dyspnea, or anesthesia.

Videofluoroscopic Swallow Study

Contrast videofluoroscopy involves real-time images of the animal swallowing liquid barium or barium-soaked kibble and is one of the most important procedures for assessing the functional integrity of the swallow reflex (see Figures 273-1 and 273-2). Fluoroscopic swallow studies usually involve assessment of 5 swallows of 5-10 mL of liquid barium (60% weight per volume), 5 swallows of canned food and 5 swallows of kibble soaked in barium. Videofluoroscopy is used to determine the sequence of events that make up a swallow and to time these events in relation to one another. Movement of certain anatomic structures can be measured in relation to a fixed point to assess function further. Swallowing events that occur out of sequence, at inappropriate times, or with reduced vigor can cause significant morbidity.

Positioning is not standardized for videofluoroscopy. Alterations in body position (sternal versus lateral recumbency) do not appear to affect measuring pharyngeal constriction ratios or the timing of swallowing in healthy dogs. However, cervical esophageal transit is significantly delayed when dogs are in lateral recumbency.[8] Thus, retaining liquid or kibble boluses in the cervical esophagus may not be considered abnormal when ill dogs are in lateral recumbency during imaging. Swallow studies on dogs in sternal recumbency are significantly more likely to result in generation of primary peristaltic waves for both liquid and kibble boluses.

The timing of the swallow can be determined easily when the swallow video is viewed frame by frame with each frame representing 1/30 of a second in the National Television System Committee (NTSC) system (analog television system used in the United States). The starting point is the frame in which the epiglottis closes over the larynx. The frames are counted until observation of maximal pharyngeal contraction, opening and closing of the UES. The swallow is considered complete when the epiglottis is observed to reopen, usually after 5 or 6 frames in healthy dogs.[9] A contrast videofluoroscopy method for quantifying pharyngeal contractility in dogs has been described.[10] The pharyngeal constriction ratio (PCR) is calculated by dividing the pharyngeal area at maximum contraction by the pharyngeal area at rest. As pharyngeal contractility diminishes, the ratio approaches 1.[10] This simple procedure provides important information regarding the strength of pharyngeal contraction in dysphagic dogs.

Laryngoscopy, Pharyngoscopy, and Esophagoscopy

Thorough laryngeal examination (see ch. 239) is important in all animals with OPD and esophageal dysphagia to rule out laryngeal paralysis associated with a polyneuropathy (see ch. 268). Geriatric large-breed dogs may develop progressive generalized neuropathy with associated pharyngeal weakness, OPD, and esophageal dysmotility.[11] Pharyngoscopy and esophagoscopy provide information about these areas, but both procedures are of limited diagnostic utility for evaluating functional disorders in anesthetized animals.

Esophagoscopy is helpful for diagnosing esophagitis, esophageal strictures (that can be missed on barium swallow studies), and hiatal hernias (see ch. 113).

Electrodiagnostic Testing

Electrodiagnostic evaluation, including electromyography and measurement of motor and sensory nerve conduction velocities, does not provide a specific diagnosis in most cases but can supply important information as to the severity, distribution, and character of a myopathic or neuropathic disease process and assist in selecting the optimal anatomic site for biopsy (see ch. 117). Electrodiagnostic testing should include the pharyngeal muscles and tongue. Health status must be considered because these procedures are performed under general anesthesia.

Muscle and Nerve Biopsies

Muscle and nerve biopsies usually are integral to reaching a specific diagnosis (see ch. 116). Muscle biopsies should be collected early in the course of an evaluation in animals with suspected neuromuscular disease before fibrosis and myofiber loss is extensive but after a negative serum AChR antibody titer has been obtained. If onset of clinical signs is recent and the antibody titer is 0.3 to 0.6 nmoL/L, retesting 4-6 weeks later may be of value, as a significant number of dogs with early clinical signs can have antibody titers in the "gray zone" at initial testing. In dogs with suspected myopathic disease, muscle biopsies are usually obtained from large muscles (the vastus lateralis or the triceps). Biopsies of pharyngeal and cricopharyngeal muscles should be obtained in dogs with OPD.[12] The thin frontalis muscle lies directly under the skin and is commonly biopsied instead of the temporalis muscle in dogs with suspected masticatory muscle myositis (MMM; see ch. 272). The frontalis muscle is not affected in MMM and, if biopsied by mistake, a diagnosis of MMM may be missed.[12] Incise and retract the frontalis muscle and the thick fascia that lies underneath the frontalis and directly over the temporalis muscle to expose the temporalis muscle for biopsy (see ch. 116). Wrap muscle specimens (0.5 × 0.5 × 1.0 cm) in saline dampened (not dripping wet) gauze sponges and place into a dry watertight container and keep cold until shipped. A second smaller biopsy specimen from next to the original biopsy should be placed in 10% buffered formalin. All specimens with cold packs are shipped overnight so the samples arrive at the laboratory within 24-36 h of collection (see ch. 354). Muscle biopsies must remain cold to optimize the condition of the specimens.

Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) Scans

MRI and CT imaging of the head and neck have been used to diagnose inflammatory myopathies, particularly MMM in dogs.[13] Imaging can be used for selecting muscle biopsy sites. Common findings include changes in size (atrophy or swelling) of all masticatory muscles except the digastricus and a predominantly inhomogeneous contrast enhancement seen in the temporalis, masseter, and pterygoid muscles.[13] MRI may also detect neoplasia.

Esophageal Manometry

Esophageal manometry allows the pressures in the esophageal lumen and sphincters to be measured to assess neuromuscular activity. Manometry involves high-resolution (HRM), with up to 36 pressure sensors.[14] Advances in computer processing allow objective pressure data to be presented in real time as a compact, visually intuitive "spatiotemporal plot" of esophageal pressure activity assessing the forces that drive food and fluid from the pharynx to the stomach. This diagnostic test can be employed in fully awake dogs and provides a sensitive functional assessment of the UES, esophagus, and LES.[14]

Esophageal pH/Impedance Testing

Esophageal pH/impedance testing is used to evaluate acid and non-acid reflux in animals with suspected gastroesophageal reflux (GER), unexplained esophagitis, or hiatal hernias. Clinicians have several choices when selecting esophageal pH probes. The catheter-free Bravo pH Monitoring System from Medtronic is the first catheter-free system used to measure esophageal pH in people suspected of having GER. This is revolutionizing esophageal pH testing, because it allows people to maintain their diet and activities during

testing. This system is an alternative to the traditional pH trans-nasal pH catheter that can cause discomfort and is easily dislodged in dogs and cats. The main disadvantages of the Bravo system are that it only records esophageal pH and does not utilize impedance technology that allows more accurate measurement of both acid and non-acid reflux events. Esophageal pH testing has been utilized in awake and anesthetized dogs in an effort to identify risk factors for GER and/or the effects of prokinetic agents on GER.[15,16]

Disorders of the Pharynx

Pharyngitis

Anatomy, Causes, Signs

The pharynx is divided into three regions: nasopharynx, oropharynx, and laryngopharynx. Clinical manifestations vary depending on location and extent of the inflammation, etiology, and involvement of adjacent structures. Pharyngeal inflammation can occur from foreign bodies, obstructive masses (nasopharyngeal polyps, lymphoma, squamous cell carcinoma), infectious disease, ingestion of caustic or irritating substances, and as an extension of stomatitis, rhinitis, or sinusitis. The most common clinical manifestations include dysphonia, snoring, gagging, coughing, dysphagia, hyporexia, and hypersalivation. Tonsillitis is often recognized in association with pharyngitis.

Diagnosis and Treatment

History and oral examination are usually sufficient to confirm this diagnosis, although a comprehensive oral exam under sedation or rhinoscopy with retroflex nasopharyngoscopy may be necessary in select cases. Survey radiographs of the cervical region might be unrewarding unless a radiodense foreign body or pharyngitis secondary to extrapharyngeal disease is present. Removal or treatment of the primary cause is essential. Analgesics, topical antimicrobial rinses, systemic antimicrobials, hydration and nutritional support are important. Nasopharyngeal inflammatory polyps in cats with normal bulla may be removed by traction avulsion. Nasopharyngeal stenosis can be treated by balloon dilation under general anesthesia.

Pharyngeal Weakness

Anatomy, Causes, Signs

Oropharyngeal pump failure (pharyngeal weakness) is a disruption in coordinated transport of food and water from the oropharynx to the hypopharynx, or from the hypopharynx into the esophagus. Pharyngeal weakness can occur secondary to morphologic abnormalities (infection, inflammation, trauma, neoplasia, obstruction to the UES [cricopharyngeal achalasia]) or from functional (neuromuscular disease) causes. Specific neuromuscular disorders that should be considered include myasthenia gravis, muscular dystrophy, polymyositis, hypothyroidism, and cranial nerve neuropathy. Clinical signs commonly include dysphonia, gagging, dysphagia, repeated swallowing attempts of a single bolus, and coughing.

Diagnosis and Treatment

Survey thoracic and cervical radiographs should be obtained in all dogs before completing a videofluoroscopic swallow study. Fluoroscopy can demonstrate absence of aboral pharyngeal contraction, incomplete bolus transport, and occasional nasopharyngeal reflux of barium. Fluoroscopy is pivotal for differentiating pharyngeal weakness from cricopharyngeal dysphagia. A systemic workup (CK level, AChR antibody titer, thyroid hormone testing, electrodiagnostics) is warranted in an effort to rule out systemic disease and an underlying neuropathy or myopathy (see Figures 273-2 and 273-3). Therapy of pharyngeal weakness secondary to underlying neuromuscular disease is mostly palliative, particularly when an underlying cause cannot be identified, and includes enteral nutritional support, alterations in diet and water consistency, and elevated feedings. Dogs with myasthenia gravis should be managed with acetylcholinesterase inhibitors (e.g., pyridostigmine, 1 to 3 mg/kg PO q 8-12 h). Glucocorticoids (e.g., 1 to 2 mg/kg prednisolone or equivalent PO q 12 h with gradual taper over the course of 10-12 weeks depending on response) or cyclosporine (5 mg/kg PO q 12-24 h for 10-12 weeks) are utilized to manage inflammatory polymyopathies (see ch. 354 and 360), and thyroid replacement therapy should be attempted in animals with documented hypothyroidism (see ch. 299).

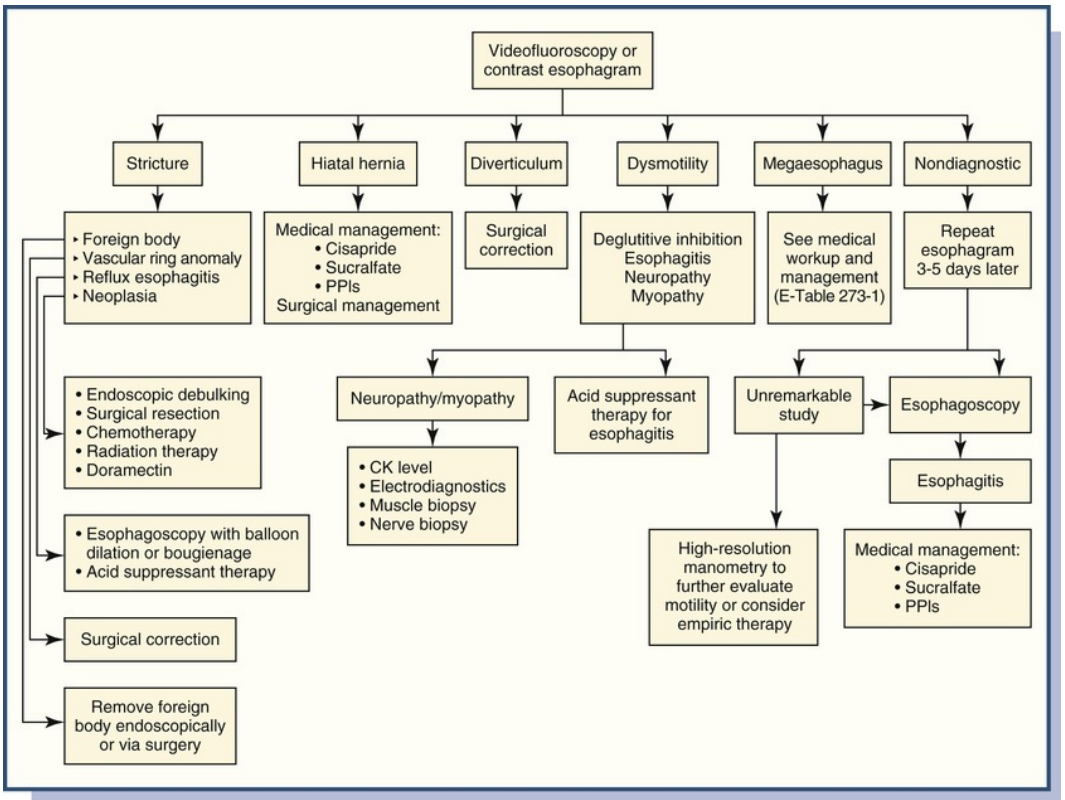


FIGURE 273-3 Algorithm to aid in determining the diagnostic and therapeutic considerations for the most common videofluoroscopic findings in dysphagic dogs. *CK,* Creatine kinase; *PPI,* proton pump inhibitor.

Disorders of the Esophagus

Cricopharyngeal Dysphagia

Definition and Clinical Signs

Cricopharyngeal dysphagia is a congenital or acquired neuromuscular disorder of the UES characterized by failure of the UES to relax *(achalasia)* or a lack of coordination between UES relaxation and pharyngeal contraction *(asynchrony).* Affected dogs have abnormal transport of bolus from the hypopharynx to the proximal esophagus. Cricopharyngeal asynchrony is essentially a "pump problem" whereby the weak pharyngeal muscles are unable to propel the bolus through the UES. The etiology of neither condition is determined, although preliminary studies are supportive of an underlying focal neuropathy. Affected animals demonstrate progressive dysphagia (typically worse when drinking water) at the time of, or shortly after, weaning. Clinical signs are characterized by repeated attempts to swallow, gagging, retching, and nasal regurgitation (see Video 273-1). The clinical signs of dogs with cricopharyngeal achalasia are indistinguishable from cricopharyngeal asynchrony. Physical examination may reveal evidence of aspiration pneumonia (coughing, moist crackles on auscultation, fever).

Diagnosis and Treatment

Dogs suspected of having cricopharyngeal dysphagia should be thoroughly evaluated prior to surgical intervention to ensure that systemic disorders (myopathies [see ch. 354], polyneuropathies [see ch. 259 and 268]) have been ruled out with AChR antibody titers, CK level (see ch. 66), electromyography (EMG; see ch. 117), and muscle biopsy (see ch. 116). In addition, ensure that aspiration pneumonia is properly managed (see Figure 273-1).[17] Thoracic radiographs help rule out structural causes of dysphagia (foreign body, mass); however, a videofluoroscopic swallow study is the diagnostic procedure of choice (Video 273-2). Most affected dogs with cricopharyngeal achalasia have a prominent thickened cricopharyngeus muscle (cricopharyngeal "bar") visible on videofluoroscopy or endoscopy causing severe obstruction to propulsion of the bolus through the UES (Figure 273-4 and E-Figure 273-5). Static contrast radiographs may demonstrate

barium retention in the pharynx or aspiration into the trachea; however, static studies do not allow the functional integrity of the UES or the coordinated contraction of the pharynx and relaxation of the UES to be evaluated.

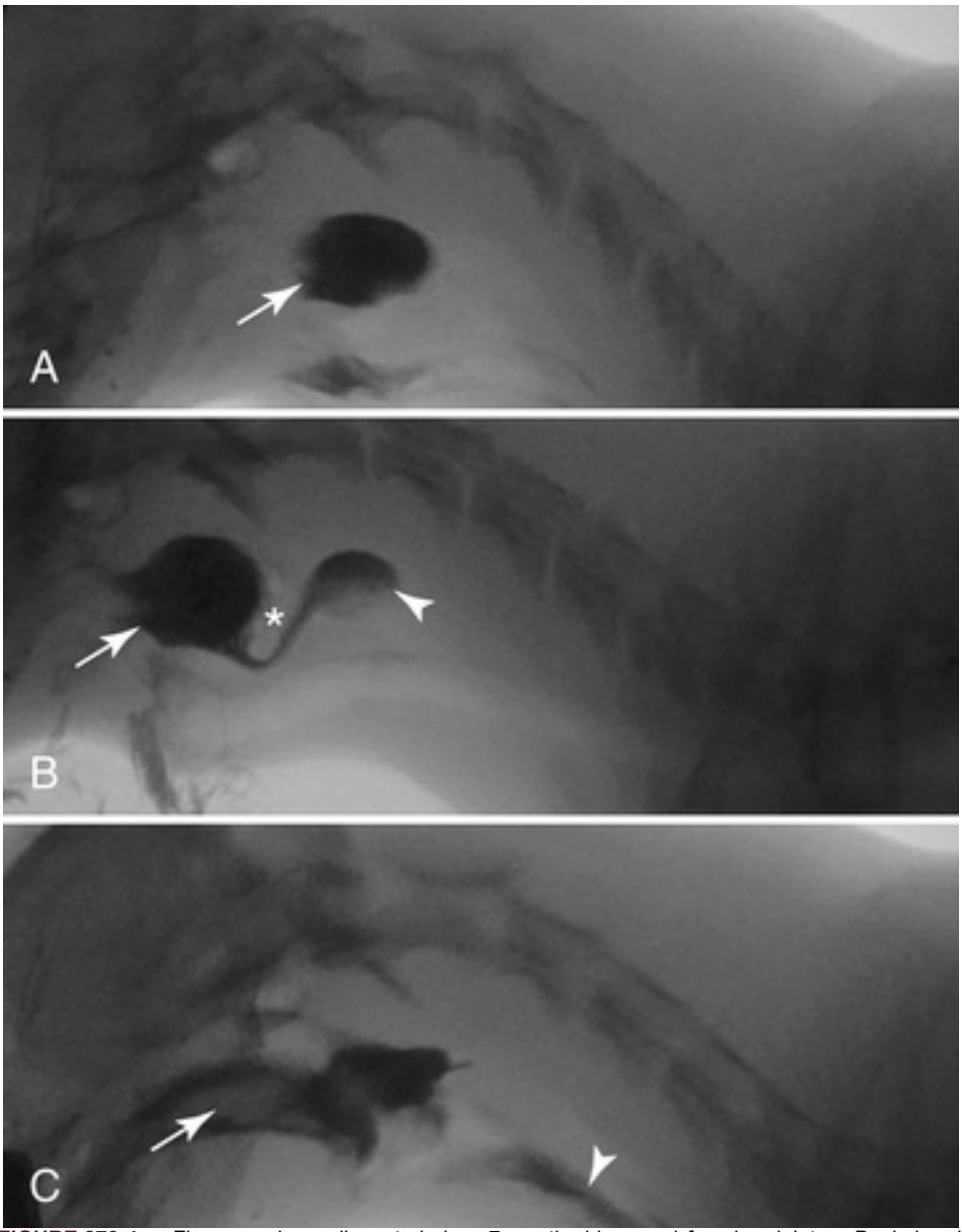
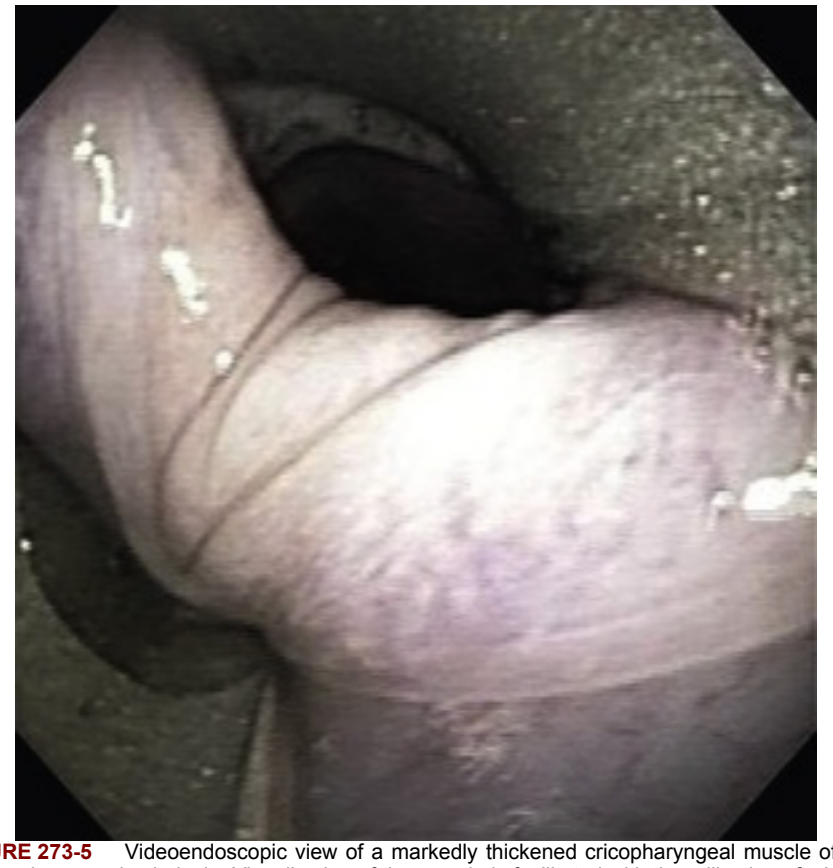
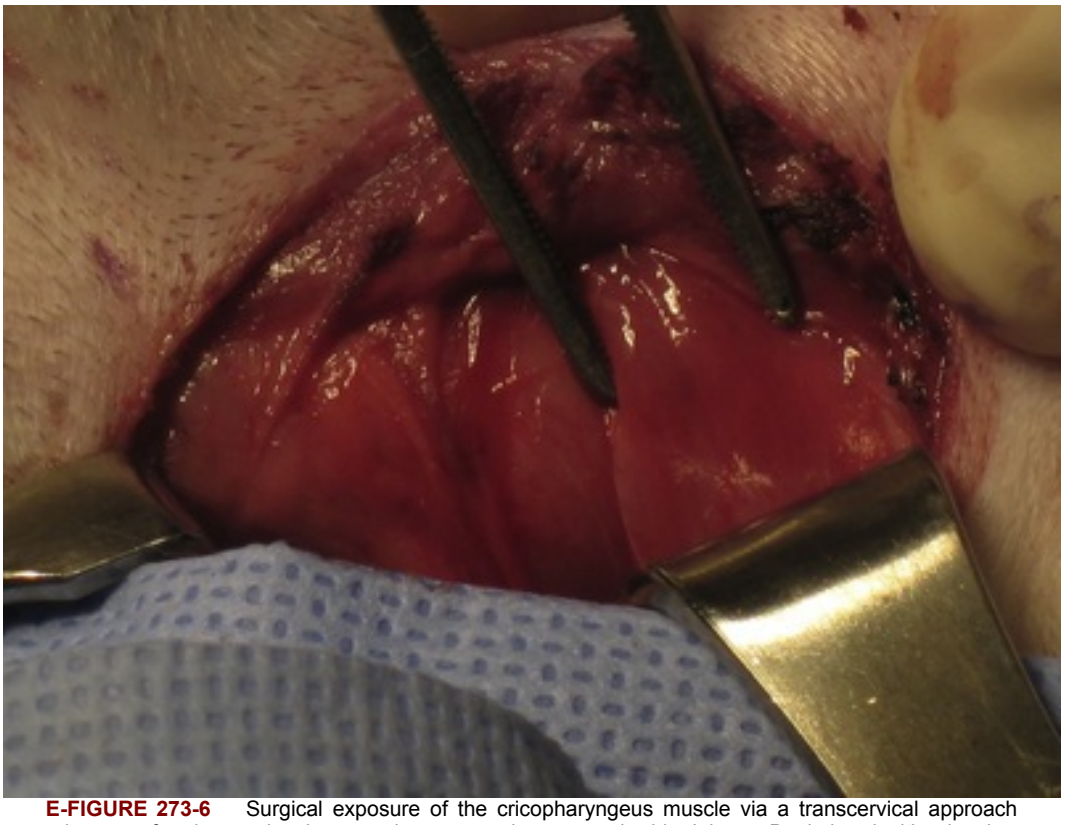


FIGURE 273-4 Fluoroscopic swallow study in a 7-month-old spayed female miniature Dachshund with severe dysphagia secondary to cricopharyngeal achalasia. **A,** The pharynx (arrow) is filled with liquid barium; **B,** hypertrophied cricopharyngeus muscle (cricopharyngeal "bar") (asterisk) obstructing the movement of the bolus from the pharynx (arrow) into the proximal esophagus (arrowhead). Notice the attenuated column of barium being squeezed through the narrow opening of the upper esophageal sphincter (UES); **C,** retrograde movement of liquid barium into the oropharynx (arrow) caused by obstruction of the proximal esophageal sphincter, and subsequent aspiration of barium into the trachea (arrowhead). (From Marks SL: Oropharyngeal dysphagia. In Bonagura JD, Twedt DC: *Kirk's current veterinary therapy XV,* St Louis, 2014, Saunders.)



E-FIGURE 273-5 Videoendoscopic view of a markedly thickened cricopharyngeal muscle of a dog with cricopharyngeal achalasia. Visualization of the muscle is facilitated with the utilization of a Weerda distending diverticuloscope that has been placed in the dog's hypopharynx transorally.

Definitive treatment for cricopharyngeal achalasia involves surgical myotomy or myectomy of the cricopharyngeal muscle (E-Figure 273-6). The cricopharyngeal and thyropharyngeal muscles are approached by standard ventral midline with 180° rotation of the larynx on its longitudinal axis or via a lateral approach with 90° rotation of the larynx.[18] Cricopharyngeal myotomy involves transecting the cricopharyngeal muscle to the level of the pharyngeal mucosa. A closed endoscopic CO_2 laser cricopharyngeal myotomy is being increasingly utilized in people and dogs, with reduced anesthesia time and morbidity compared with the more traditional transcervical cricopharyngeal myotomy.[19]



E-FIGURE 273-6 Surgical exposure of the cricopharyngeus muscle via a transcervical approach prior to performing a cricopharyngeal myectomy in a 5-month-old miniature Dachshund with cricopharyngeal achalasia.

There is less compelling evidence for surgical myectomy of dogs with cricopharyngeal asynchrony; however, one report documented successful bilateral cricopharyngeal myectomy to manage an 8-month-old mixed breed dog with cricopharyngeal asynchrony after initially failing standard unilateral cricopharyngeal myectomy.[20]

A less invasive procedure for the temporary resolution of cricopharyngeal achalasia involves the injection of botulinum toxin into the cricopharyngeus muscle.[21] Botulinum toxin A (BTA), a neurotoxin synthesized from the bacillus *Clostridium botulinum,* acts at the presynaptic cholinergic nerve terminals to block the release of acetylcholine. In a dose-related manner, it weakens contraction when injected into the target muscle and has been successfully used in people and dogs for the temporary management of esophageal achalasia. The toxin is reconstituted shortly before injection with 0.9% sterile saline to a concentration of 25 units/mL and is injected into the cricopharyngeus muscle in 3 sites (10 units per site) using a transbronchial needle. The limited duration of botulinum toxin's effect (about 3-4 months) can be used to help screen dogs that might benefit from a permanent surgical myectomy, because animals that respond favorably to the toxin should do well with surgical myectomy. An effort to identify the optimal consistency of food and water (adding commercial food thickeners such as "Thick-It") for these dogs can be helpful. Some succumb to repeated bouts of aspiration pneumonia and malnutrition. Enteral feeding via a PEG tube is a viable alternative; however, silent aspiration and pneumonia can occur despite the advent of enteral feeding devices.

Esophagitis

Anatomy, Cause, Clinical Signs

Esophagitis is an acute or chronic inflammatory disorder of the esophageal mucosa that occasionally involves the underlying submucosa and muscularis. It may result from a variety of causes, including ingestion of caustic agents, chronic vomiting, esophageal foreign bodies, embrittled nasoesophageal or esophagostomy feeding tubes and gastroesophageal reflux associated with general anesthesia or hiatal hernia. Orally administered doxycycline and clindamycin have caused "pill-induced" esophagitis, particularly in cats.[22] Gastroesophageal reflux during anesthesia preceded development of benign esophageal stricture in 46-65% of cases and represents the most common cause of high-grade esophagitis and stricture formation in dogs.[23]

Relaxation of the LES is mediated by non-adrenergic non-cholinergic pathways and has been shown to occur with the administration of commonly utilized injectable pre-anesthetic and inhalant anesthetic agents.[24,25] The prolonged exposure of the esophageal mucosa to acid is an important cause of esophagitis and potential stricture formation, particularly when pH is <4.0 as the proteolytic pH range for the conversion of pepsinogen to pepsin is between 1.5 and 3.5.[26] In addition, esophagitis decreases LES tone, which leads to more reflux and mucosal inflammation. Disturbances in esophageal motility may occur as a sequela of esophagitis, regardless of cause. The clinical signs of esophagitis are dependent on the severity of inflammation, extent of esophageal involvement, and type of injury. Animals with mild inflammation may exhibit no clinical signs, whereas animals with moderate-to-severe esophagitis may exhibit signs of anorexia, dysphagia, odynophagia, regurgitation, and hypersalivation. Coughing may be observed with concurrent aspiration pneumonia.

Diagnosis and Treatment

Results of CBC, serum biochemistry, and urinalysis are usually unremarkable, and the esophagus appears normal on survey thoracic radiographs. Aspiration pneumonia may be evident in the dependent areas of lung. Segmental or diffuse esophageal dilatation may be seen with severe mucosal inflammation. Videofluoroscopy may confirm irregular esophageal surface, esophageal dysmotility (Video 273-3), or stricture formation (see Figure 273-3). Definitive diagnosis of esophagitis requires endoscopy and esophageal biopsy; however, presumptive diagnosis is often made from the appearance of the esophageal mucosa: erythema and a granular surface with areas of ulceration and active bleeding (Figure 273-7). Mild esophagitis may appear normal on endoscopic examination and mucosal biopsy is necessary to confirm the diagnosis. Lesions are usually most evident in the distal esophagus, adjacent to and including the LES.

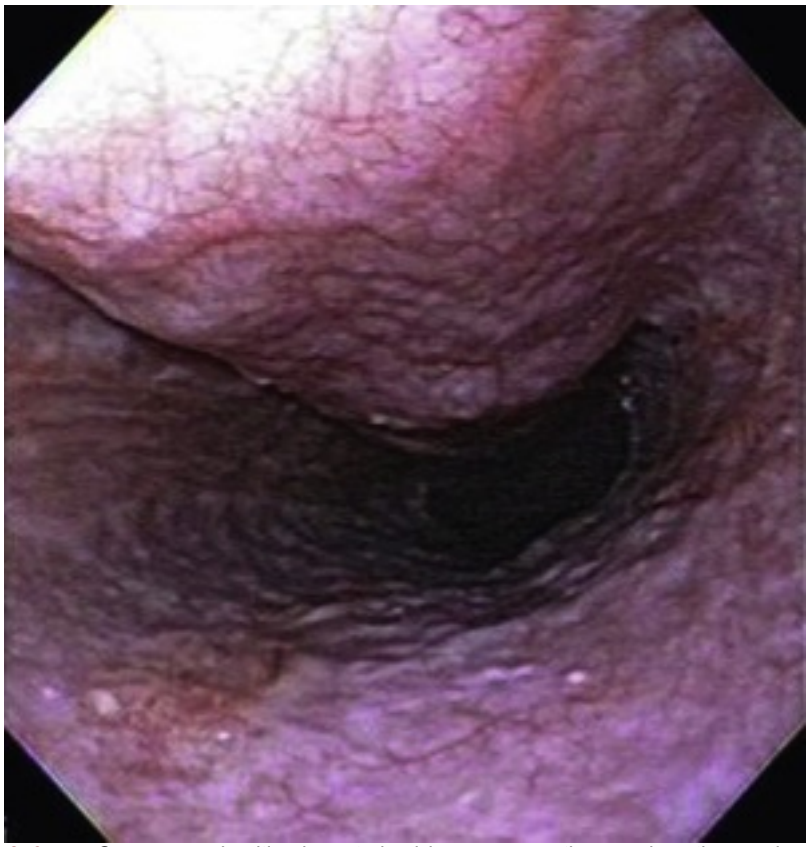


FIGURE 273-7 Severe esophagitis characterized by severe erythema, ulceration, and a granular mucosa in a 3-year-old Labrador Retriever secondary to gastroesophageal reflux during an anesthesia procedure.

Mild esophagitis usually resolves with minimal treatment other than feeding smaller-sized fat-restricted meals frequently to enhance gastric emptying and minimize GER. Animals with moderate to severe

esophagitis or those exhibiting signs of dysphagia, regurgitation, salivation, or anorexia should be managed with gastric acid suppressants and prokinetics. The benefits of proton pump inhibitors (PPIs) such as omeprazole in people with moderate to severe GER are documented and several studies have shown the superior acid suppressive effects of PPIs compared to the H2-receptor antagonists (famotidine, ranitidine).[27,28] The PPIs are administered orally or IV (1 to 1.5 mg/kg q 12 h) and should be gradually tapered over 7-10 days if used for more than 2 weeks. The diffusion-barrier drug sucralfate can be administered as a suspension (0.5 to 1 g PO three times a day) for managing reflux esophagitis. It binds to eroded mucosa and provides effective barrier protection against refluxed barrier contents. Prokinetic agents such as cisapride (0.5 mg/kg PO q 8-12 h) or metoclopramide (0.2 to 0.4 mg/kg SC or IV as a bolus injection q 8 h, or at 1 to 2 mg/kg/24 h as an IV constant rate infusion [CRI]) can be used to increase LES pressure and enhance gastric emptying. Cisapride is a more potent prokinetic than metoclopramide and is more effective at reducing GER in dogs.[14] Broad-spectrum antibiotics are recommended for animals with aspiration pneumonia (see ch. 242). The duration of therapy varies depending on the severity of the esophagitis and clinical signs, but ranges from 5-7 days (mild cases) to 2 to 3 weeks (moderate to severe esophagitis). A combination of cisapride, sucralfate, and omeprazole is an effective combination for the management of severe esophagitis caused by persistent vomiting, GER, or foreign body induced trauma.

Esophageal Stricture

Definition, Anatomy, Clinical Signs

Esophageal stricture, an abnormal narrowing of the esophageal lumen, is most commonly caused by GER during general anesthesia, chemical injury from swallowed substances, esophageal foreign bodies, esophageal surgery, and intraluminal or extraluminal mass lesions (neoplasia or abscess). Cats are particularly susceptible to doxycycline and clindamycin-associated esophagitis and subsequent esophageal stricture.[22] GER during general anesthesia has been reported to have preceded stricture in up to 65% of cases. Clinical signs are seen about 7-8 days post-anesthesia.[29] The incidence of GER in dogs during anesthesia varies from 16-55%, and occurs secondary to a decrease in LES pressure induced by a variety of anesthetic agents, including atropine, morphine, acepromazine, thiopentol, xylazine, and isoflurane.[24,25] Damage to the muscularis layer of the esophagus is associated with fibroblastic proliferation and contraction leading to stricture formation. The clinical signs, progressive regurgitation and dysphagia, are related to the severity and extent of the stricture. Early clinical signs might include a subtle "hard swallow" for a few days that can be easily missed by owners. Progressive clinical signs include dysphagia, odynophagia, regurgitation, salivation, anorexia, coughing, and weight loss.

Diagnosis and Dilation Treatment

Diagnosis of esophageal stricture is often suggested by the history and confirmed with contrast radiographs using liquid barium or barium mixed with canned food (esophagram) or via videofluoroscopic swallow studies (see Figure 273-2 and E-Figure 273-8). Contrast radiographs are helpful for determining the number, location, and length of strictures. Esophagoscopy, the definitive diagnostic procedure, is helpful for differentiating benign from malignant strictures and facilitates balloon-dilation (Figure 273-9). Mechanical dilation of the stricture is best accomplished using balloon dilation or bougienage. The theoretical advantage of balloon dilation (Figure 273-10) is that the forces applied to the stricture are a radial stretch, in contrast to the longitudinal forces applied with the rigid bougienage instrument. However, a retrospective case series in 20 dogs and 8 cats with benign esophageal strictures that underwent bougienage treatment suggested that this procedure was safe and effective for most dogs and cats with benign esophageal strictures, with outcomes similar to balloon dilation.[30] Balloon dilators are available in various diameters (up to 20 mm) and lengths (3 to 8 cm), are made of a rigid plastic material that can withstand a relatively high pressure (up to 147 psi), and are manufactured to either pass through the biopsy channel of the endoscope or alongside the endoscope with the use of a guidewire. If a guidewire is used, it is passed through the channel of the endoscope (or imaged with fluoroscopy) and advanced beyond the stricture into the stomach or caudal esophagus. The scope is removed as the guidewire is advanced through the channel, thus leaving the guidewire near its original position. The balloon catheter is then passed over the guidewire (with the balloon deflated) until it is positioned within the stricture. The position of the balloon is visualized through the endoscope or via fluoroscopy. An inflating device that has a manometric pressure gauge is attached to the balloon and the pressure is slowly increased to the pressure specified by the manufacturer. The balloon is kept inflated for 60-90 seconds and then deflated. Sequentially increasing pressures are applied to dilate the

stricture in 1-2 mm increments without causing excessive tearing or bleeding (Figure 273-11). The procedure is repeated 3-5 days later in an effort to maximally dilate the stricture.

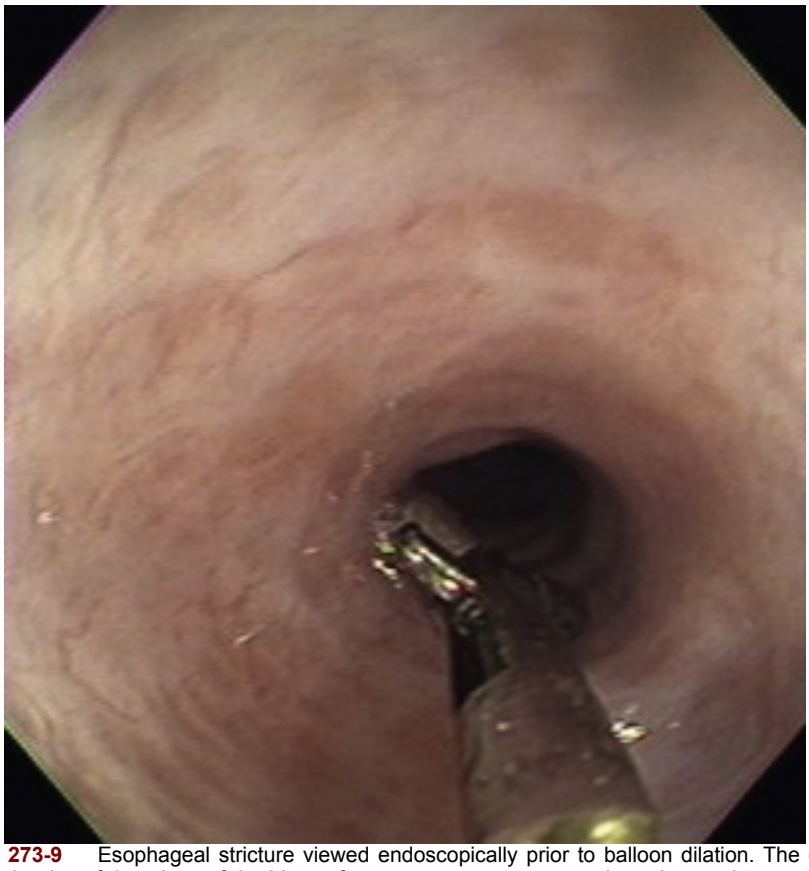


FIGURE 273-9 Esophageal stricture viewed endoscopically prior to balloon dilation. The distance between the tips of the wings of the biopsy forceps measures 5 mm and can be used to measure the diameter of the small stricture.

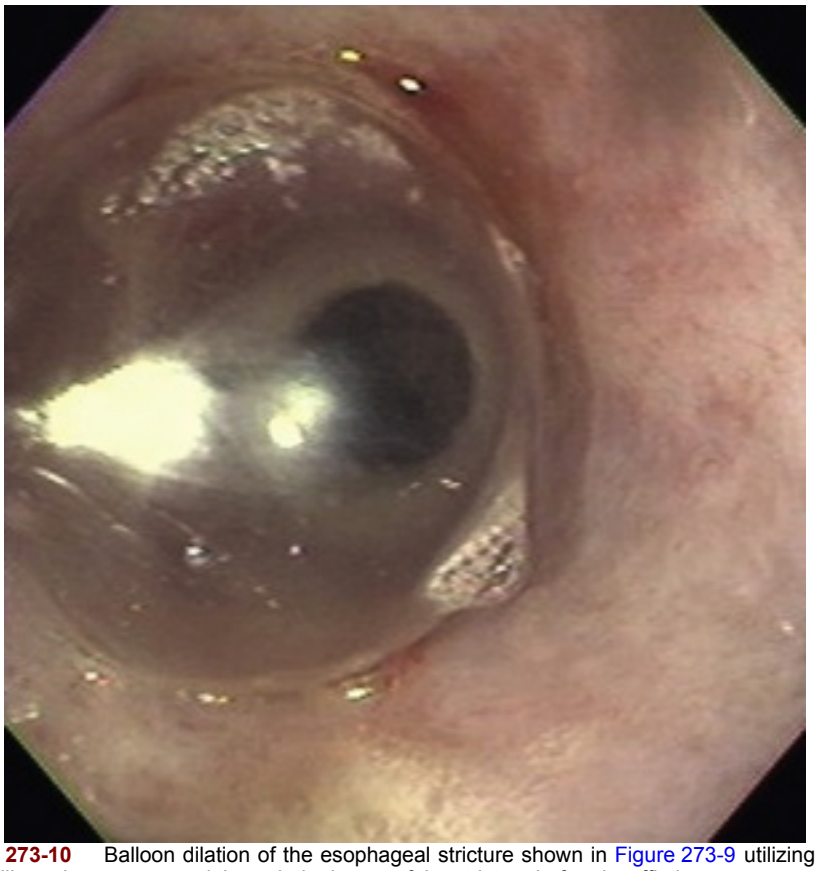


FIGURE 273-10 Balloon dilation of the esophageal stricture shown in Figure 273-9 utilizing a CRE balloon dilator that was passed through the lumen of the stricture before insufflation.

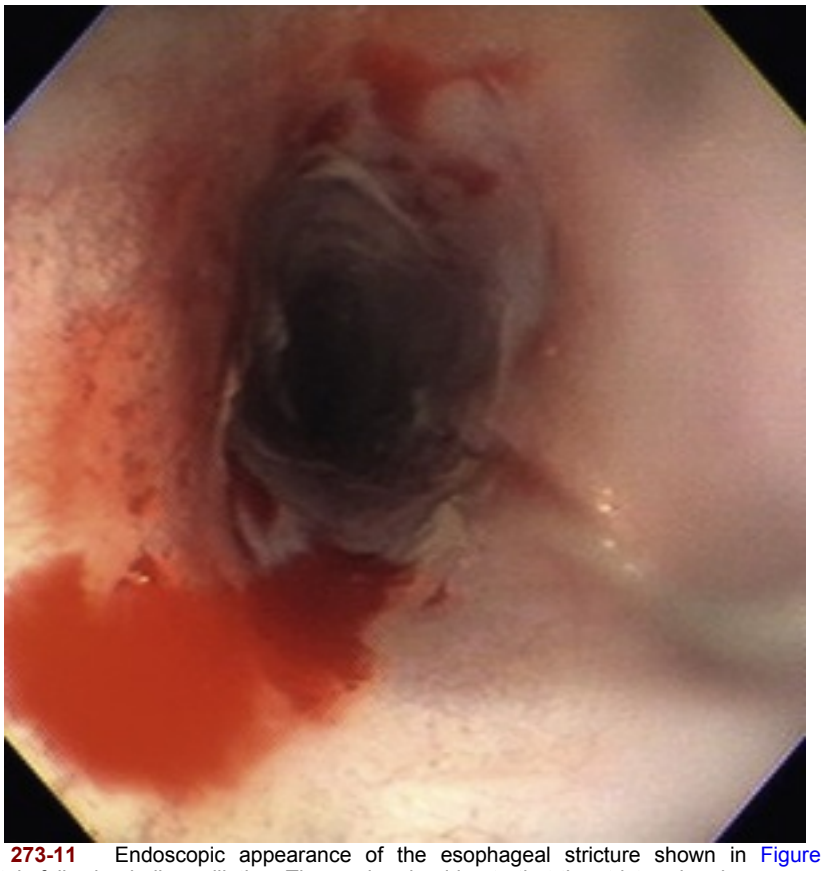
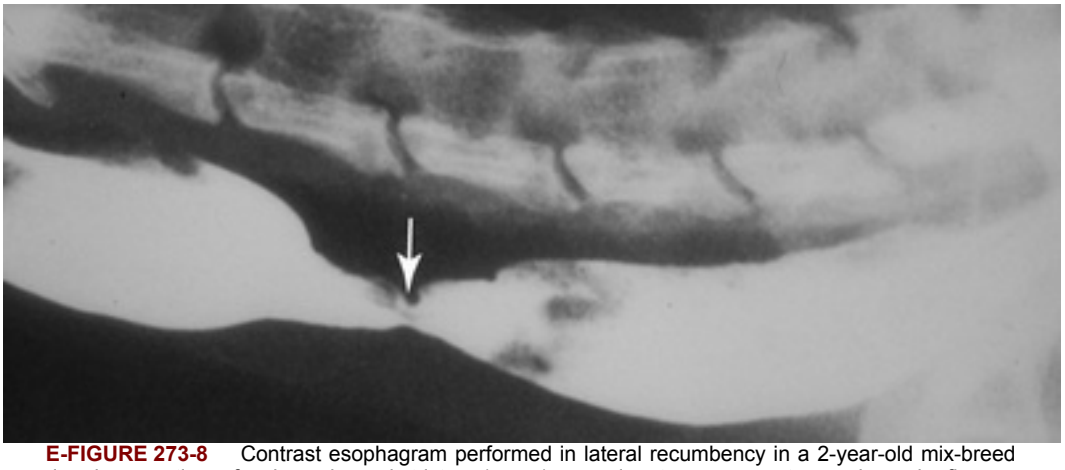


FIGURE 273-11 Endoscopic appearance of the esophageal stricture shown in Figure 273-9 immediately following balloon dilation. The reader should note that the stricture has been successfully broken down; however, the bleeding secondary to the tearing of the stricture at the 7 o'clock position precludes further dilation during this procedure.



E-FIGURE 273-8 Contrast esophagram performed in lateral recumbency in a 2-year-old mix-breed dog documenting a focal esophageal stricture (arrow) secondary to severe gastroesophageal reflux.

Transendoscopic Triamcinolone

The transendoscopic administration of triamcinolone into the submucosa of the stricture site using a four-quadrant approach before the balloon dilation procedure has been associated with a reduced rate of re-stricture formation.[31,32] Approximately 2.5 mg triamcinolone per quadrant is injected using a transbronchial aspiration needle that can be threaded down the biopsy channel of the endoscope. The steroid is generally used for the first 2-3 dilation procedures. Topical mitomycin C (5 mg of mitomycin C using a soaked gauze

sponge that is placed endoscopically at the stricture site for approximately 5 minutes) has also been shown to be beneficial for preventing restricture.[33] The site is rinsed with 60 mL of water after removing the sponge. Continued medical therapy is warranted following balloon dilation using the same medications and dietary alterations as discussed for esophagitis.

Intraluminal Stents

Intraluminal stents can be used in animals that have failed balloon dilation or those with recurrent strictures (see ch. 123).[34] Stents are available both uncovered and covered with polypropylene to prevent growth of tissue within the stent. Available stent materials include Nitinol (nickel plus titanium), Elgiloy (cobalt, nickel, plus chromium), stainless steel, polyester plastic/silicone, or a biodegradable stent (e.g., PDS). Stent selection is based on stricture location, length, and need for removing the stent. Once deployed, stents must be anchored in place or they quickly migrate into the stomach. Stents can be secured using a suturing device (GI Stitch, Pare Surgical) designed to function in a double channel endoscope.

Esophageal Foreign Bodies

Definition and Clinical Signs

Foreign bodies are a common cause of dysphagia in dogs, but less common in cats. The most common esophageal foreign bodies in dogs are bones, fish-hooks (E-Figure 273-12), needles, and sticks, whereas play toys are more commonly seen in cats. Foreign bodies typically lodge at points of minimal esophageal distension: thoracic inlet, heart base, or at the diaphragmatic hiatus. Mucosal abrasion, ulceration, and perforation may occur with sharp or angular objects that are lodged intraluminally.

Severity of esophageal damage and resulting signs are dependent on the foreign body size, shape, edges, and the duration of obstruction. In some cases, the owner observes foreign body ingestion. Onset of clinical signs is often related to degree of esophageal obstruction and type of foreign body ingested. Animals with smaller foreign bodies with a smooth surface causing incomplete obstruction may have had signs for days to weeks' duration, whereas complete obstruction causes acute dysphagia, regurgitation, odynophagia, gagging, and excessive salivation.

Diagnosis and Treatment

Physical examination is variable, ranging from unremarkable to halitosis (tissue necrosis), fever and lethargy. Bone foreign bodies can occasionally be palpated if they become lodged in the cervical esophagus. Definitive diagnosis usually requires radiography. Radiodense foreign bodies can be detected with survey radiography (E-Figures 273-12 and 273-13), but identifying radiolucent foreign bodies requires an esophagram. Survey radiographs are indispensable for detection of aspiration pneumonia or esophageal perforation (pneumomediastinum, emphysema, or mediastinitis; Figure 273-14). A water-soluble positive-contrast agent (iohexol, Gastrografin [diatrizoate]) should be used rather than barium sulfate if esophageal perforation is suspected. Esophagoscopy can be performed to confirm the diagnosis and assess secondary mucosal damage (E-Figure 273-15).

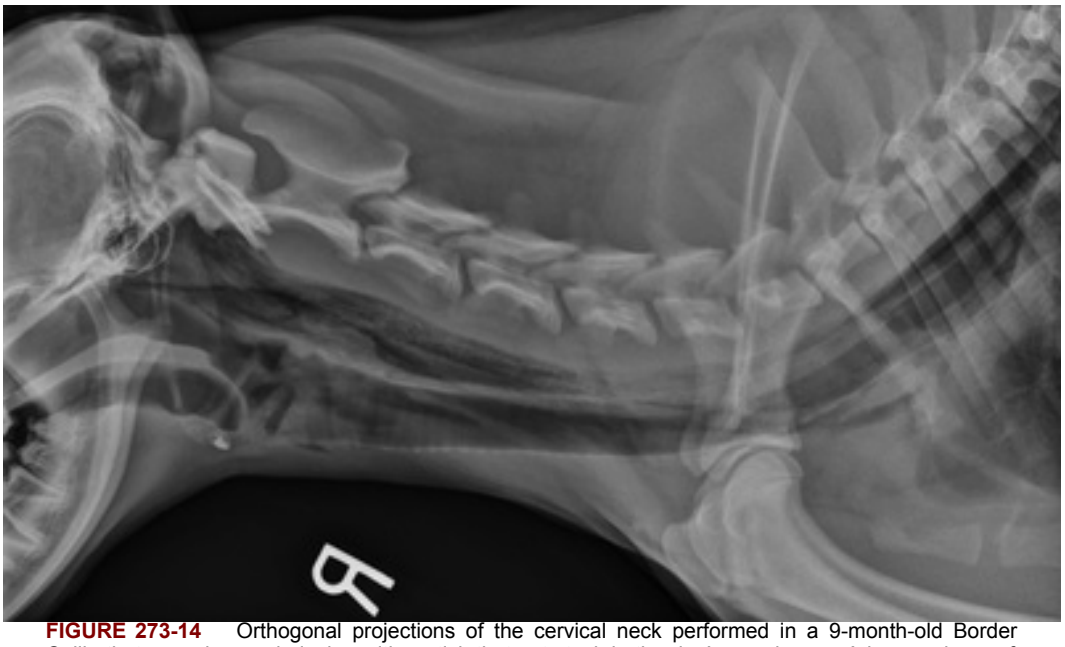
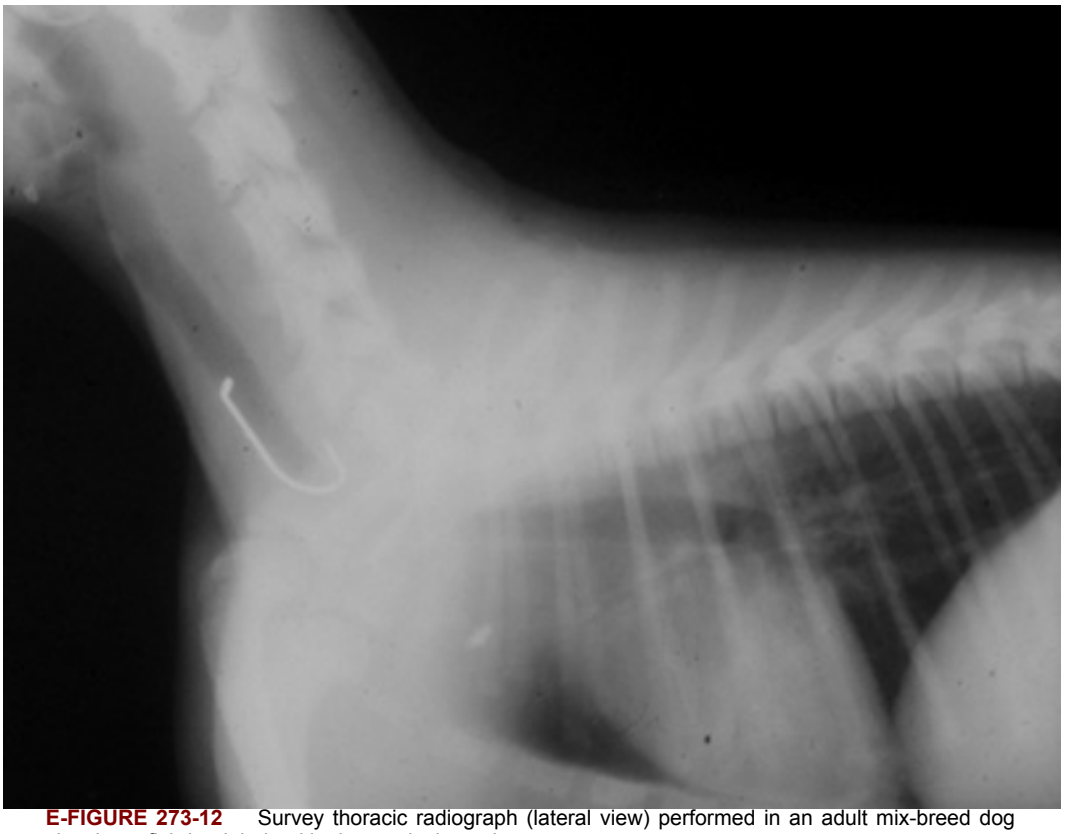
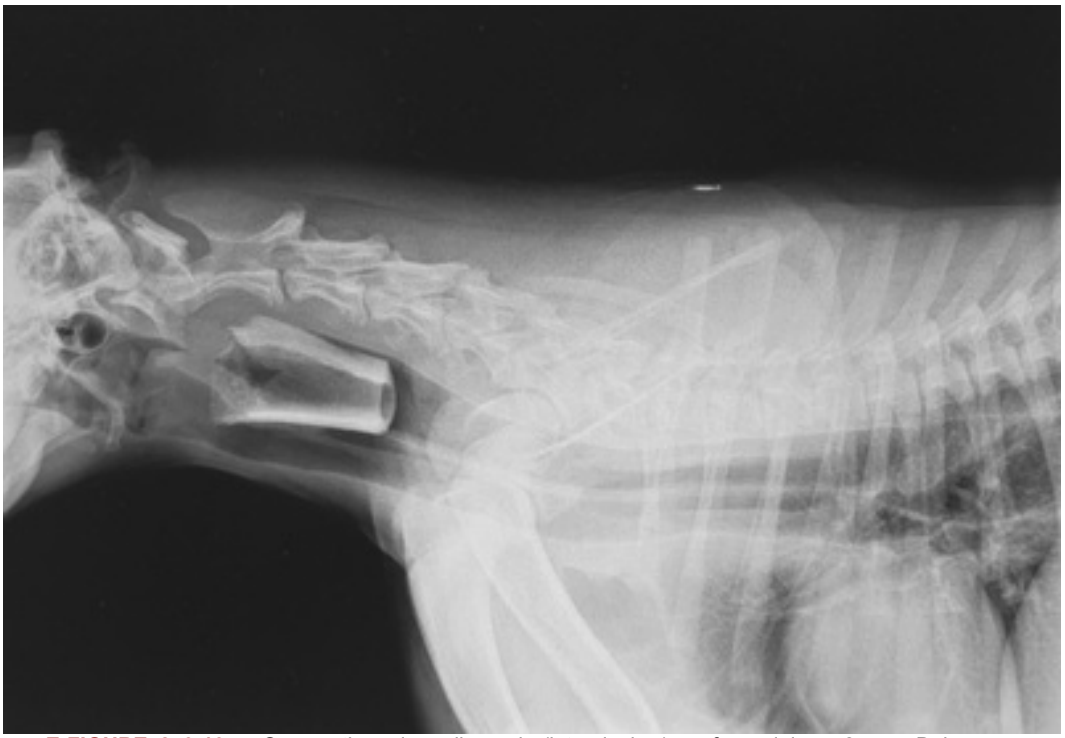


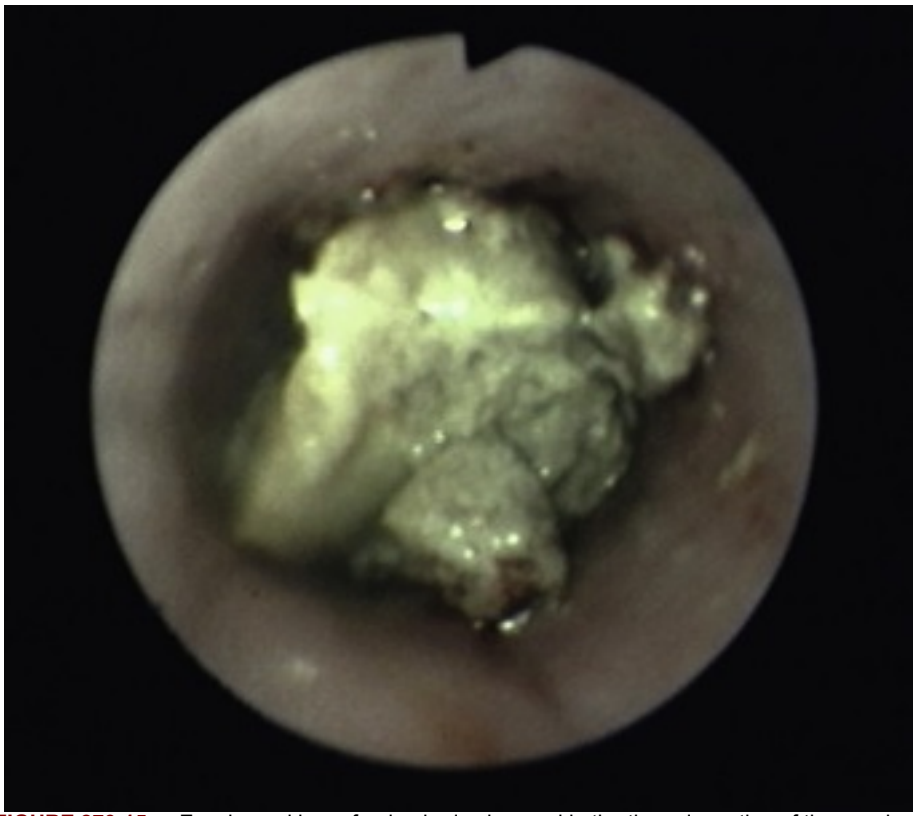
FIGURE 273-14 Orthogonal projections of the cervical neck performed in a 9-month-old Border Collie that was observed playing with a stick that got stuck in the dog's esophagus. A large volume of free gas (emphysema) is seen dorsal to the pharynx dissecting between the retropharyngeal planes, extending caudally into the thoracic inlet and the cranial mediastinum (pneumomediastinum). No radiographic foreign bodies were identified during the study and endoscopic evaluation of the esophagus was recommended.



E-FIGURE 273-12 Survey thoracic radiograph (lateral view) performed in an adult mix-breed dog showing a fish-hook lodged in the cervical esophagus.



E-FIGURE 273-13 Survey thoracic radiograph (lateral view) performed in a 2-year Doberman Pinscher showing a bone foreign body lodged in the cervical esophagus. The bone was ultimately removed transorally using rongeurs with minimal damage to the esophageal mucosa and no delayed stricture formation.



E-FIGURE 273-15 Esophageal bone foreign body observed in the thoracic portion of the esophagus in a 4-year Golden Retriever. The foreign body was ultimately removed using a rigid sigmoidoscope and esophageal foreign body forceps to grasp the foreign body and pull it into the lumen of the sigmoidoscope.

Esophageal foreign bodies should be removed promptly because retention increases risk of esophageal mucosal damage, ulceration, and perforation. Foreign bodies in the proximal esophagus or large bones may be removed with a rigid sigmoidoscope, whereas more distal foreign bodies beyond the reach of a rigid scope should be removed using a flexible endoscope. Large forceps passed through the lumen of the rigid endoscope are used to grasp the foreign body and pull it into the endoscope for safe removal. Distal esophageal foreign bodies can be pushed into the stomach for removal by gastrotomy if not removed through the mouth. Smaller foreign bodies are best removed with a flexible endoscope and basket, biopsy forceps, or snare retrieving forceps. Fish-hooks that are lodged in the proximal to mid-esophagus can be dislodged with the distal end of a rigid endoscope by inserting the open end of the scope between the shaft and hook portion and pushing aborally. Once dislodged from the mucosa, the fish-hook can be pulled into the lumen of the rigid endoscope for safe removal. A flexible endoscope can be used to remove fish-hooks that are lodged beyond the reach of a rigid endoscope.

Animals with esophageal necrosis or ulceration should be fasted for 24-48 hours after foreign body removal. A gastrostomy tube (see ch. 82) can be inserted during foreign body removal in animals with severe esophagitis or necrosis to temporarily bypass the esophagus during feedings. Specific therapy for esophagitis should include sucralfate suspensions and proton pump inhibitors for 7-10 days following removal of the foreign body. Broad-spectrum antibiotics are warranted in animals with severe ulceration or small perforations. Esophagotomy is indicated if endoscopy fails to remove the foreign body; however, it is preferable to attempt to push the foreign body into the stomach for removal via gastrotomy. Surgery is also indicated to repair larger esophageal perforations.

Vascular Ring Anomalies

See Box 273-3.

Box 273-3

Vascular Ring Anomalies

Definitions and Prevalence

Vascular ring anomalies are congenital malformations of the major arteries of the heart that entrap the intrathoracic esophagus and cause esophageal obstruction. Persistent right aortic arch (PRAA) is the most common vascular ring anomaly in dogs and cats and occurs when the embryonic right aortic arch (rather than the left fourth aortic arch) becomes the functional adult aorta. Circular compression of the esophagus occurs by the aorta on the right, the ligamentum arteriosum dorsolaterally on the left, the pulmonary trunk on the left, and the heart base ventrally. This anomaly is considered to be a familial disorder with evidence of a hereditary basis in German Shepherds and Irish Setters.[35] Other less common vascular anomalies include persistent right or left subclavian arteries, double aortic arch, persistent right dorsal aorta, left aortic arch with right ligamentum arteriosum, and aberrant intercostal arteries.

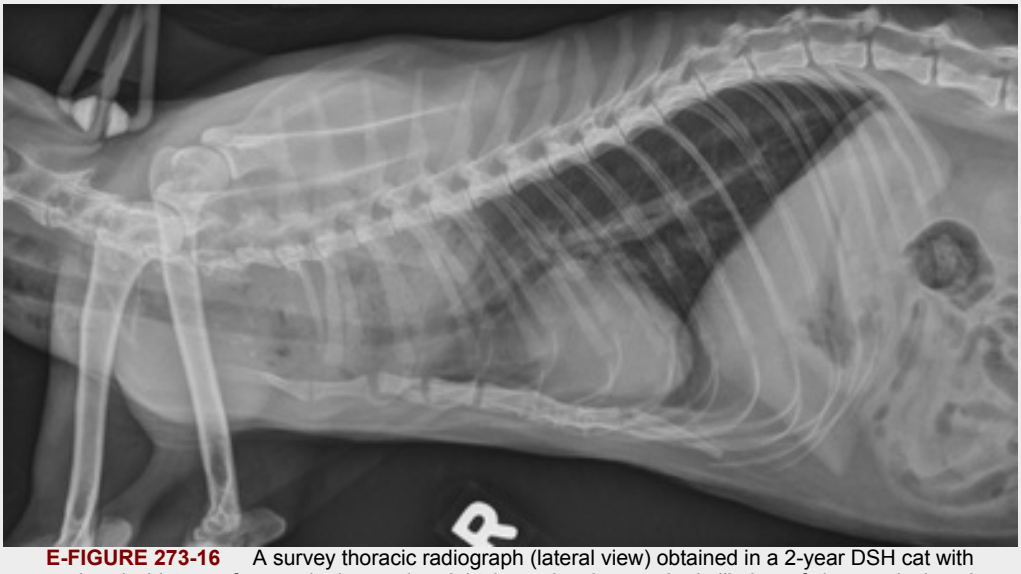
Clinical Signs

Affected puppies and kittens usually present for regurgitation of solid foods at the time of weaning (see ch. 39). Weight loss with failure to thrive despite a good appetite is commonly observed. The presence of a moist cough, dyspnea, and fever suggest aspiration pneumonia (see ch. 242). Physical examination often reveals a thin, stunted animal that is otherwise normal. Occasionally, a dilated esophagus can be observed or palpated in the cervical region.

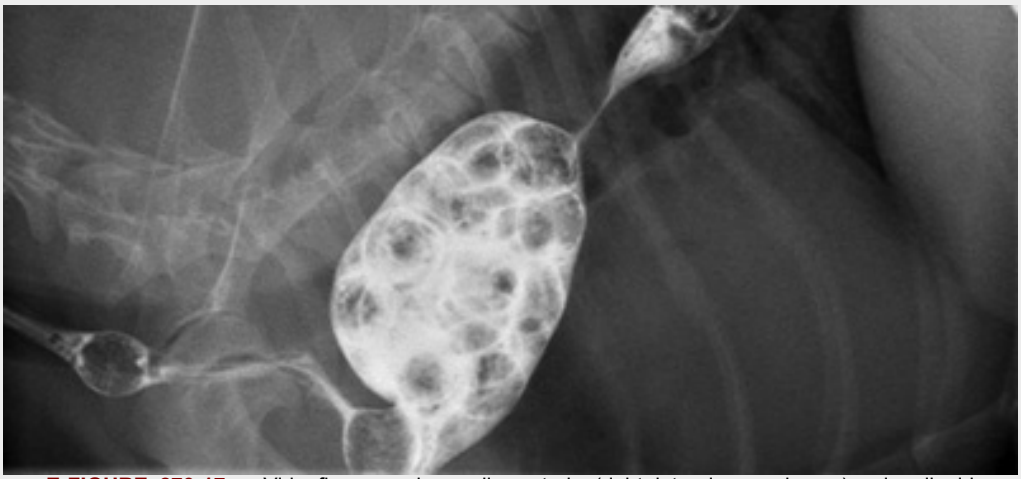
Diagnosis

Vascular ring anomalies should be differentiated from other causes of regurgitation in young animals, such as congenital megaesophagus, esophageal foreign body, and esophageal stricture (see Figure 273-3). The signalment and a compatible history of regurgitation precipitated during weaning are highly supportive of a vascular ring anomaly. Survey thoracic radiographs usually demonstrate esophageal body dilation cranial to the base of the heart (E-Figure 273-16). Focal leftward deviation of the trachea near the cranial border of the heart in dorsoventral or ventrodorsal radiographs is a reliable sign of

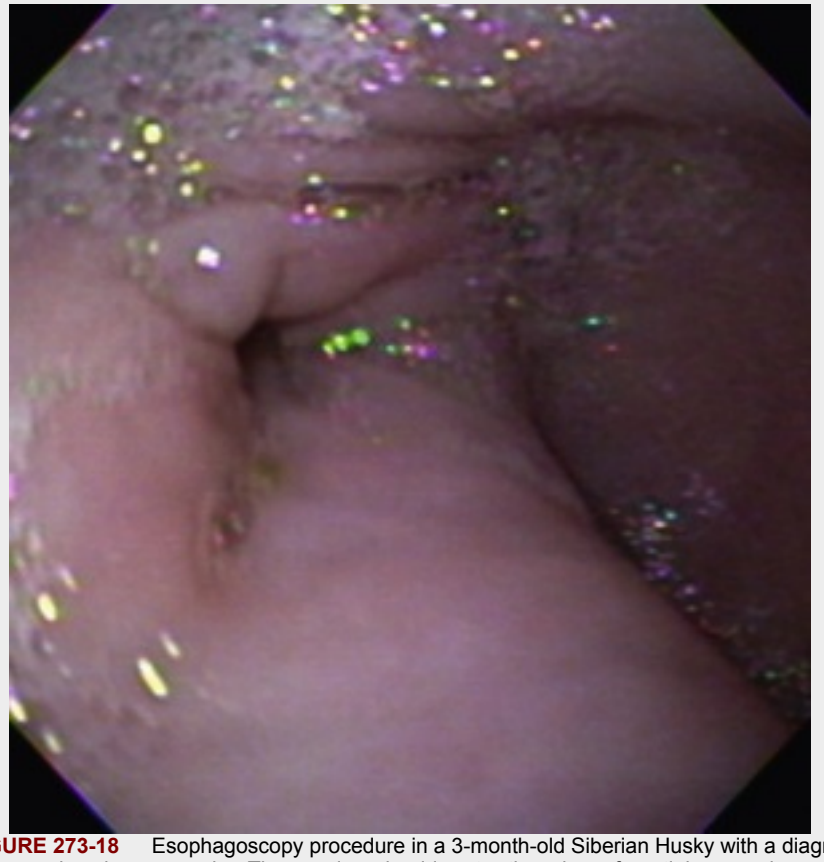
PRAA in young dogs.[36] An esophagram may be performed to confirm the location of esophageal obstruction and the severity of esophageal distension (E-Figure 273-17). Esophagoscopy (see ch. 113) can help differentiate an intraluminal stricture from extraluminal compression (E-Figure 273-18). Strictures appear as distinct intraluminal fibrous rings that remain static when viewed endoscopically, whereas rhythmic pulsations of the major arteries compressing the esophagus externally are observed with a vascular ring anomaly. In addition, vascular ring anomalies occur at the base of the heart, whereas intraluminal strictures can occur in any segment of the esophageal body and are more common in adult animals.



E-FIGURE 273-16 A survey thoracic radiograph (lateral view) obtained in a 2-year DSH cat with a chronic history of regurgitation and weight loss showing marked dilation of the cervical and cranial thoracic esophagus, which is filled with heterogenous soft tissue and gas opaque contents as well as multifocal mineral opacities. The trachea exhibits ventral and rightward deviation in the cranial thorax, and the cardiac silhouette appears mildly enlarged. The primary differentials for this cat included vascular ring anomaly (extraluminal obstruction) or esophageal stricture (intramural obstruction).



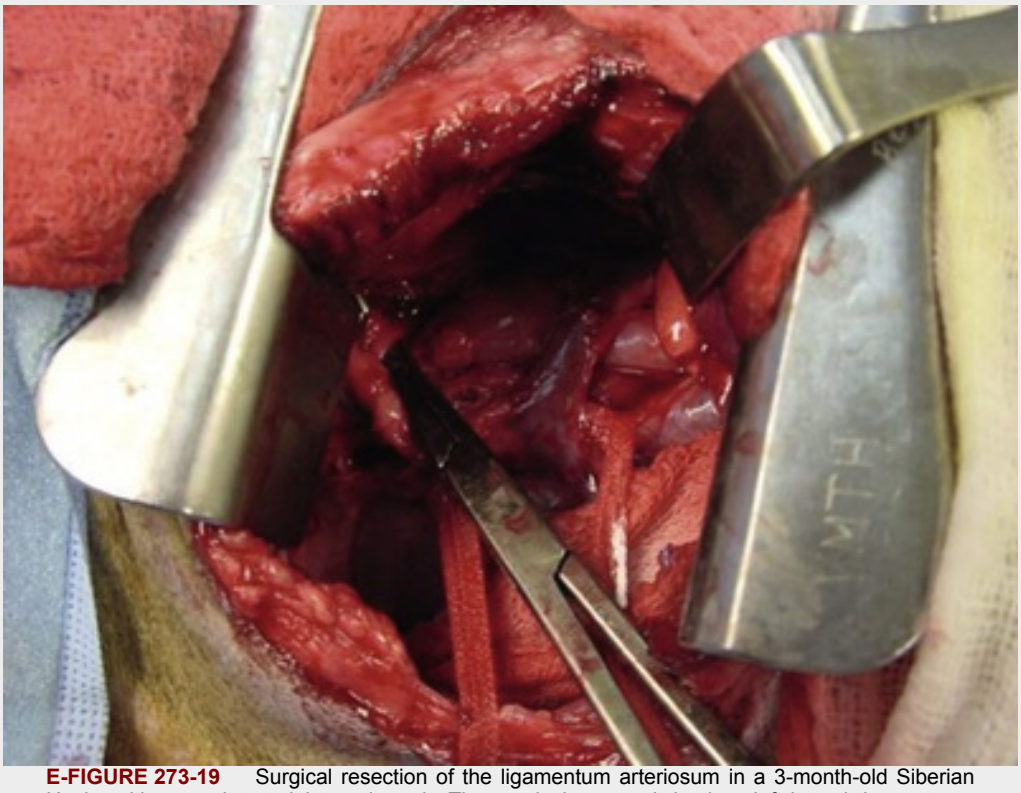
E-FIGURE 273-17 Videofluoroscopic swallow study (right lateral recumbency) using liquid barium mixed with kibble in a 3-year-old miniature Dachshund with a chronic history of regurgitation immediately following the ingestion of food. The dog had no difficulty swallowing water. Barium moved normally through the proximal esophagus but was seen to collect within a distended region of esophagus within the cranial thorax at the level of the first few ribs. The esophagus distal to the distension appears narrowed over the heart base and the trachea was noted to deviate on the dorsoventral view. Thoracic CT confirmed the presence of a vascular ring anomaly.



E-FIGURE 273-18 Esophagoscopy procedure in a 3-month-old Siberian Husky with a diagnosis of a vascular ring anomaly. The reader should note the circumferential narrowing of the esophagus over the base of the dog's heart; the mucosa appears smooth and normal in color in contrast to an intramural stricture in which the mucosa is typically erythematous, granular, and ulcerated and usually has a fibrous band in the strictured region visible on esophagoscopy.

Treatment

Definitive therapy for PRAA is surgical ligation and transection of the ligamentum arteriosum via a left intercostal approach (E-Figure 273-19). During surgery, areas of peri-esophageal fibrosis should be reduced and the strictured site should be dilated with a balloon dilation catheter. Animals with severe debilitation from malnutrition will require enteral nutritional support via gastrostomy tube feedings prior to surgery (see ch. 82). Aspiration pneumonia should be effectively treated with broad-spectrum antibiotics (see ch. 242). Significant clinical improvement usually follows corrective surgery in most patients (>90%); however, esophageal hypomotility and regurgitation may persist, particularly in those animals that have a delay in their surgery. Affected animals may benefit from elevated feedings as described for idiopathic megaesophagus. Unfortunately, there are no drugs to improve motility of esophageal striated muscle.



E-FIGURE 273-19 Surgical resection of the ligamentum arteriosum in a 3-month-old Siberian Husky with a persistent right aortic arch. The surgical approach is via a left lateral thoracotomy between the fourth and fifth ribs.

Esophageal Neoplasia

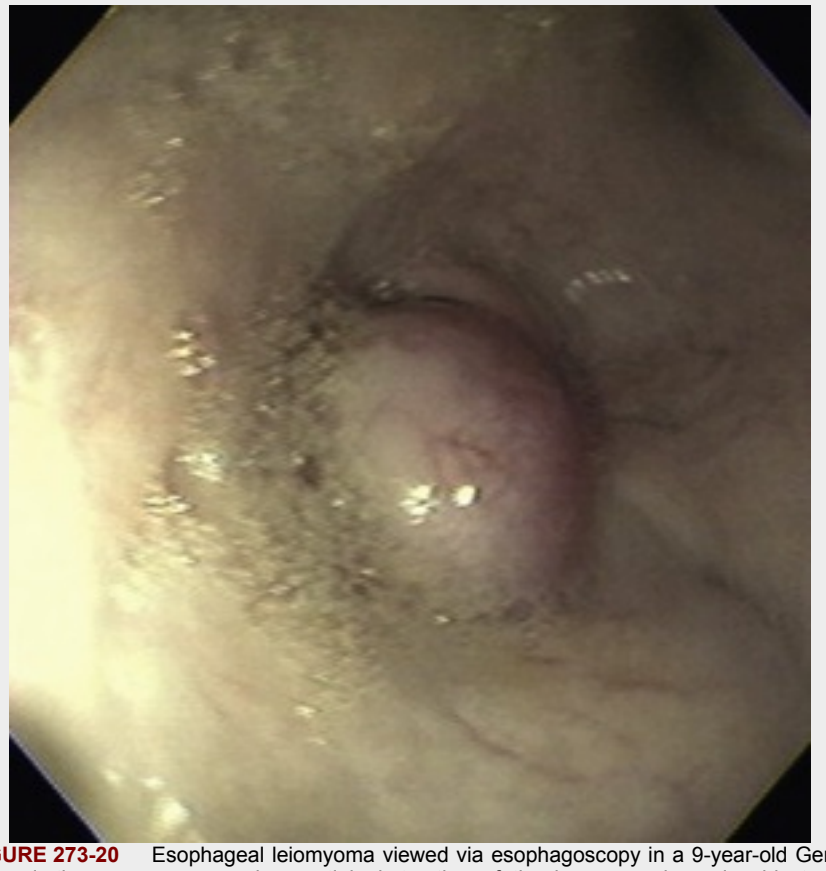
See Box 273-4.

Box 273-4

Esophageal Neoplasia

Definitions and Prevalence

Tumors of the esophagus are relatively rare, accounting for < 0.5% of all cancers in the dog and cat.[37] Tumors may be of primary esophageal, peri-esophageal, or metastatic origin. Esophageal fibrosarcoma and osteosarcoma are the most common malignant tumors in dogs, developing from malignant transformation of esophageal granulomas associated with *Spirocerca lupi* infection.[38,39] Squamous cell carcinoma is the most commonly diagnosed primary esophageal tumor in cats. Other less commonly reported primary esophageal tumors in the dog and cat include leiomyo(sarco)mas (E-Figure 273-20), adenocarcinomas, and undifferentiated carcinomas. Peri-esophageal tumors arising from regional lymph nodes, thyroid, thymus, and heart base cause local esophageal invasion, direct mechanical obstruction, or both. Metastatic lesions (thyroid, pulmonary, and gastric carcinomas) commonly involve the esophagus but are associated with clinical signs of esophageal disease less frequently.



E-FIGURE 273-20 Esophageal leiomyoma viewed via esophagoscopy in a 9-year-old German Shepherd; the mass was causing partial obstruction of the lower esophageal sphincter and subsequent regurgitation following ingestion of meals.

Clinical Signs

Clinical signs develop gradually and reflect progressive esophageal obstruction. The most common clinical signs include regurgitation, dysphagia, odynophagia, ptyalism, and weight loss. Animals with metastatic disease may have general debilitation, anorexia, and signs of pulmonary involvement such as dyspnea and coughing. Physical examination may reveal emaciation, although some peri-esophageal and esophageal tumors involving the cervical esophagus may be palpable.

Diagnosis

Survey thoracic radiographs may be normal or may reveal variable esophageal dilatation, an intraluminal mass, or evidence of a peri-esophageal lesion displacing the esophagus. The lungs should be evaluated for aspiration pneumonia and metastasis. An esophagram usually confirms the presence of an intraluminal mass or obstructive lesion. Esophagoscopy with mucosal biopsy and exfoliative cytology or histopathology is required for definitive diagnosis of esophageal neoplasia. Small pinch biopsies obtained via endoscopy may be superficial and non-representative of the tumor and a double-bite technique should be performed to maximize the diagnostic yield.

Treatment

Chemotherapy, surgical resection, and radiation therapy represent the primary modalities for treatment of malignant esophageal neoplasia; however, radiation therapy may be complicated by acute and chronic injury to adjacent mediastinal structures, while surgical resection is complicated by limited surgical exposure, tension on the anastomosis, and the risk of stricture formation post-operatively. Lymphoma may be managed with chemotherapy (see ch. 344). Slow-growing benign esophageal neoplasms (e.g., leiomyoma) generally have a favorable prognosis with complete surgical resection.[40] Esophageal granulomas associated with *Spirocerca lupi* can be managed with doramectin administered at a dosage of 200 mcg/kg SC at 14-day intervals for three treatments[38] or 500 mcg/kg of the injectable doramectin solution administered orally once a day for 6 weeks. This regimen is repeated for an additional 6 weeks

in dogs exhibiting any evidence of granuloma formation detected via esophagoscopy.[39]

Esophageal Diverticula

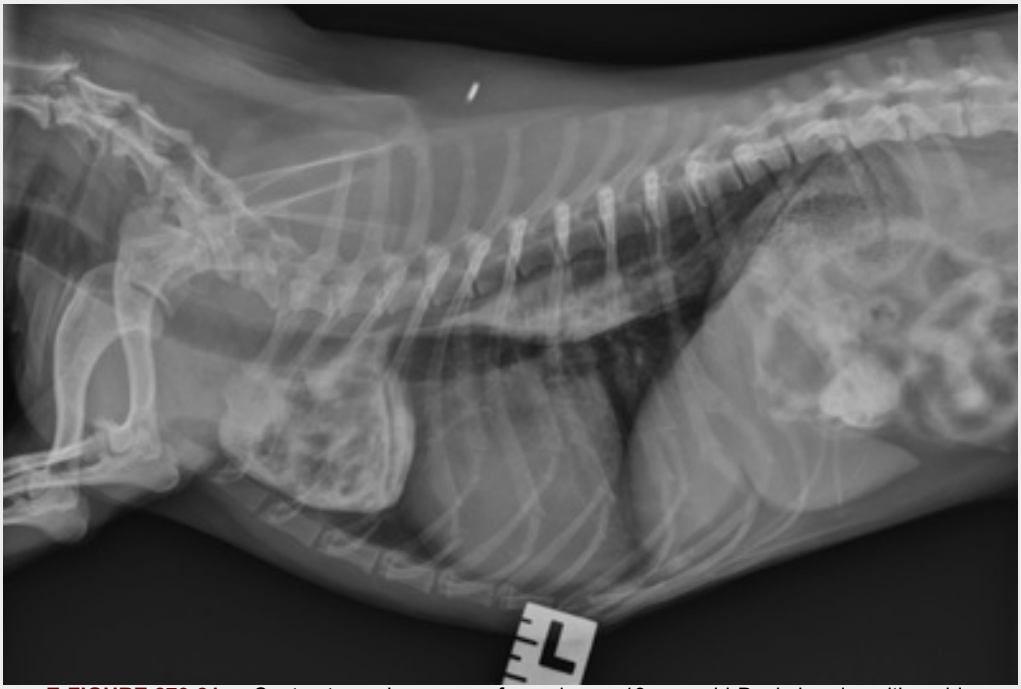
See Box 273-5.

Box 273-5

Esophageal Diverticulum

Definitions and Prevalence

Esophageal diverticula are circumscribed sacculations of the esophageal wall that affect esophageal motility. Congenital diverticula occur secondary to abnormalities in embryological development that permit herniation of the esophageal mucosa through a defect in the muscularis. Acquired diverticula are subdivided into pulsion or traction forms. Pulsion diverticula develop in association with increases in intraluminal pressure secondary to obstruction (stricture or foreign body) or altered motility (E-Figure 273-21).[41] Pulsion diverticula can develop secondary to obstruction from vascular ring anomalies. Traction diverticula result from peri-esophageal inflammation and fibrosis. Adhesions to adjacent tissue (e.g., lung, bronchus, lymph node) distort the esophageal lumen and create sacculations. The development of an abscess from migration of a foreign body (e.g., grass awn migration) is a common cause of traction diverticula in the western United States. The accumulation of ingesta (impaction) within diverticula leads to esophagitis, mechanical obstruction (seen with large diverticula), and esophageal dysmotility.



E-FIGURE 273-21 Contrast esophagram performed on a 13-year-old Dachshund positioned in left lateral recumbency showing a large esophageal diverticulum at the thoracic inlet and irregular filling of the ventral esophagus cranial to the cardiac silhouette. A persistent narrowing (stricture) of the esophageal lumen caudal to the diverticulum was observed. Esophagoscopy of the diverticulum revealed a large amount of blood-tinged fluid in the diverticulum with kibble and a partially chewed raw hide.

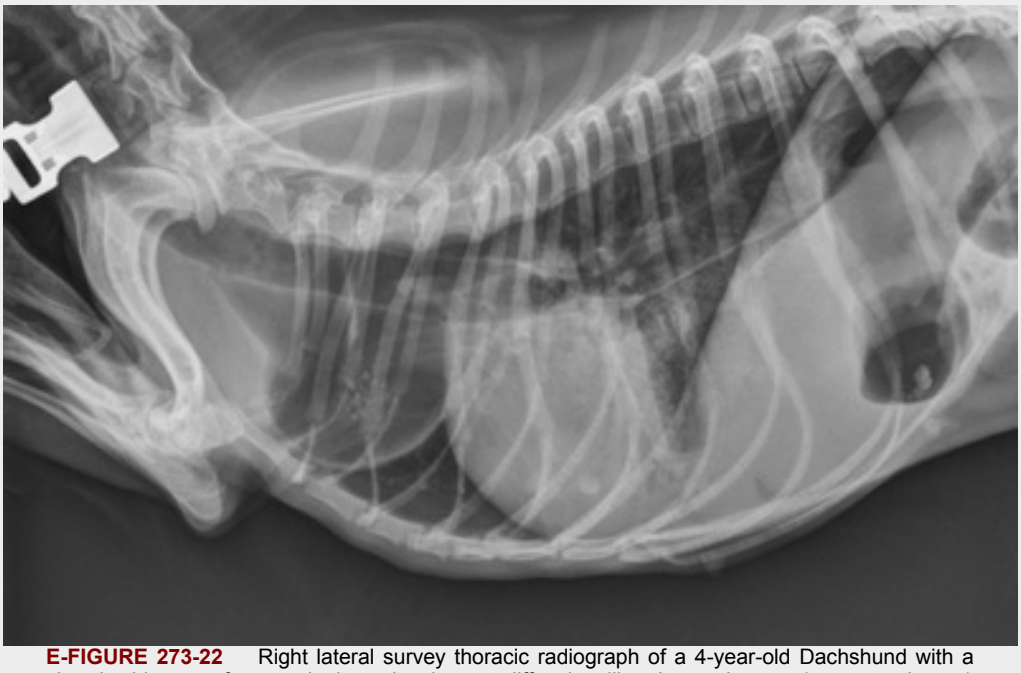
Clinical Signs

The clinical signs of esophageal diverticula are similar to many of the other esophageal disorders and

include regurgitation, odynophagia, and retching. Diverticula can occasionally be an incidental finding in animals with no associated clinical signs. Weakening of the muscularis can occur in rare cases, resulting in perforation of the diverticulum with leakage of food and fluid into the mediastinum and signs of sepsis and respiratory distress.

Diagnosis

Survey thoracic radiographs may reveal an air-filled or soft-tissue opacity adjacent to or involving the esophagus (E-Figure 273-22); however, contrast radiography is necessary to differentiate an esophageal diverticulum from a peri-esophageal, mediastinal, or pulmonary mass. Esophagoscopy (see ch. 113) will confirm the diagnosis, although it may be necessary to suction food and fluid to visualize the diverticulum. Diverticula should not be confused with the normal esophageal redundancy seen in young brachycephalic breeds, Bulldogs and Chinese Shar-Peis. Other differentials for epiphrenic diverticula include hiatal hernia and gastro-esophageal intussusception.



E-FIGURE 273-22 Right lateral survey thoracic radiograph of a 4-year-old Dachshund with a chronic history of regurgitation showing a diffusely dilated esophagus (megaesophagus) throughout the cervical and thoracic regions. There is a large, redundant area of esophagus (diverticulum) at the thoracic inlet that contains some mineral opacity material. There is an alveolar pattern in the left cranial and right middle lung lobes and patchy interstitial to alveolar infiltrates in the left caudal lung lobe. There is poor peritoneal detail due to lack of fat.

Treatment

Diverticulectomy is the preferred therapy, particularly for large diverticula that are a continuous cause of esophageal impaction. Small diverticula in subclinical patients may be left alone or managed medically with smaller-sized, upright feedings of a liquid or semiliquid diet to minimize impaction of ingesta in the diverticulum. Traction diverticula are often managed with broad-spectrum antibiotics, whereas pulsion diverticula are treated for their specific underlying cause (stricture, foreign body, esophagitis). Most cases warrant a guarded prognosis because corrective surgery can induce stricture formation and because segmental hypomotility may persist after surgery.

Esophageal Fistula

See Box 273-6.

Box 273-6

Esophageal Fistula

An esophageal fistula is an abnormal communicating tract between the esophagus and adjacent structures. Most esophageal fistulae involve the lungs or airway structures (e.g., esophagopulmonary, esophagotracheal, and esophagobronchial fistulae; see ch. 242). Both congenital and acquired fistulae have been described, although both forms are rare in the dog and cat.[42,43] Congenital fistulae are rare and result from incomplete separation of the tracheobronchial tree from the digestive tract, from which it is formed during embryological development. Cairn Terriers appear to be predisposed to congenital esophageal fistulae. Acquired esophageal fistulae are usually associated with retained esophageal foreign bodies, especially bones and grass awns that cause esophageal perforation and leakage of esophageal contents into adjacent tissues. Healing leads to development of a communicating tract with resultant airway contamination from esophageal contents. Other less common causes of esophageal fistulae include trauma and neoplasia.

Clinical Signs

Clinical signs are primarily related to the respiratory system and include coughing and dyspnea. Coughing after drinking is a common presenting sign. Regurgitation, dysphagia, lethargy, anorexia, fever, and weight loss are less commonly observed.

Diagnosis

Survey thoracic radiographs usually reveal a localized alveolar, bronchial, or interstitial lung pattern or a combination of these patterns. The right caudal and middle lung lobes in dogs and the left caudal and accessory lobes in cats are most commonly affected.[42,43] Radiopaque foreign bodies may be observed in the esophagus; however, an esophagram is required for definitive diagnosis of esophageal-airway communication. Use of iodinated contrast agents should be avoided because they are hyperosmolar and chemically irritating to the lung. Esophagoscopy or bronchoscopy are of limited value in confirming small fistulae.

Treatment

Surgical excision of the fistula with closure of the esophageal defect is required. Lobectomy of the affected lung lobe may be necessary as a result of pulmonary consolidation or foreign material contained within the airways. Postsurgical therapy includes esophageal rest for 48-72 hours and administration of broad-spectrum antibiotics for infection based on culture and susceptibility testing of involved tissues. A good prognosis is given to animals after successful surgery. The prognosis is guarded if severe complications such as severe pleural effusion, pneumonia, or pulmonary abscessation are present.

Megaesophagus and Esophageal Hypomotility

Congenital Megaesophagus

Megaesophagus, the most common cause of regurgitation in dogs, is characterized by focal or diffuse esophageal dilation and concurrent esophageal dysmotility. Megaesophagus can be a congenital condition or acquired. The acquired form is more common and can be idiopathic or secondary to a recognized disease. Congenital idiopathic megaesophagus is characterized by generalized hypomotility and dilation of the esophagus, causing regurgitation and failure to thrive in puppies shortly after weaning. Familial predisposition has been suggested in the Irish Setter, Great Dane, German Shepherd, Labrador Retriever, Chinese Shar-Pei, Newfoundland, Miniature Schnauzer, and Fox Terrier breeds. Congenital megaesophagus in cats is rare, but Siamese cats may be predisposed. The pathogenesis of the congenital form is poorly understood but may involve a defect in vagal afferent innervation of the esophagus.[44,45]

Acquired Secondary Megaesophagus (ASM)

The underlying cause of ASM is unknown, but a defect in afferent neural response to esophageal distension, similar to congential megaesophagus, is suspected.[46] Myasthenia gravis accounts for 25-30% of ASM in dogs,[47,48] and may involve the esophagus only (focal myasthenia gravis) or, more commonly, involves esophagus and peripheral muscles (see ch. 269). ASM has also been associated with hypoadrenocorticism (see

ch. 309), lupus myositis (see ch. 205), polymyopathies (see ch. 354), polyneuropathies (see ch. 268), dysautonomia, lead poisoning, and severe forms of esophagitis. Dysautonomia, a generalized autonomic neuropathy in which megaesophagus and esophageal hypomotility are consistent findings, is more frequently recognized in cats and is attributed to degenerative lesions involving autonomic ganglia.[49] Other causes of segmental or diffuse esophageal hypomotility include foreign bodies, stricture, vascular ring anomalies, and esophagitis.

Clinical Signs and Diagnosis

Regurgitation is the most frequent clinical sign associated with megaesophagus. Considerable variability exists in the frequency and timing of regurgitation episodes after meal ingestion. Puppies with congenital megaesophagus often begin regurgitating when weaned to solid foods. Affected animals may suffer from malnutrition and aspiration pneumonia (see ch. 242). Additional signs depend on the underlying cause of megaesophagus, and include muscle pain and stiff gait (polymyositis), generalized weakness, exercise intolerance (neuromuscular disease), and GI signs (lead toxicosis, hypoadrenocorticism).

Megaesophagus should be suspected in any animal with a history of regurgitation (see ch. 39). Survey radiographs of the neck and thorax will be diagnostic for most cases of megaesophagus (see Figures 273-2 and 273-23), although contrast radiography (esophagram) can be considered if survey radiographs are equivocal to help exclude a foreign body cause of megaesophagus or to evaluate esophageal motility. Survey radiographs may reveal alveolar opacities consistent with aspiration pneumonia. Routine hematology, serum biochemistry, and urinalysis should be performed to screen for causes of ASM. An AChR antibody titer for acquired MG should be done, even in the absence of generalized muscle weakness, because MG can cause focal megaesophagus. The test should be repeated 4-8 weeks later in all dogs with an initial titer in the "gray-zone" (0.3-0.6 nmol/L), particularly when the onset of megaesophagus has been deemed to be acute in nature. A resting cortisol or ACTH stimulation test should be considered to help rule out hypoadrenocorticism. Additional diagnostic procedures that should be based on the individual case presentation include esophagoscopy (see ch. 113), electromyography, nerve conduction velocity (see ch. 117), and muscle and nerve biopsy (see ch. 116). A clear association with hypothyroidism has not been proven and a low total T4 concentration is more consistent with euthyroid sick syndrome (see ch. 299).

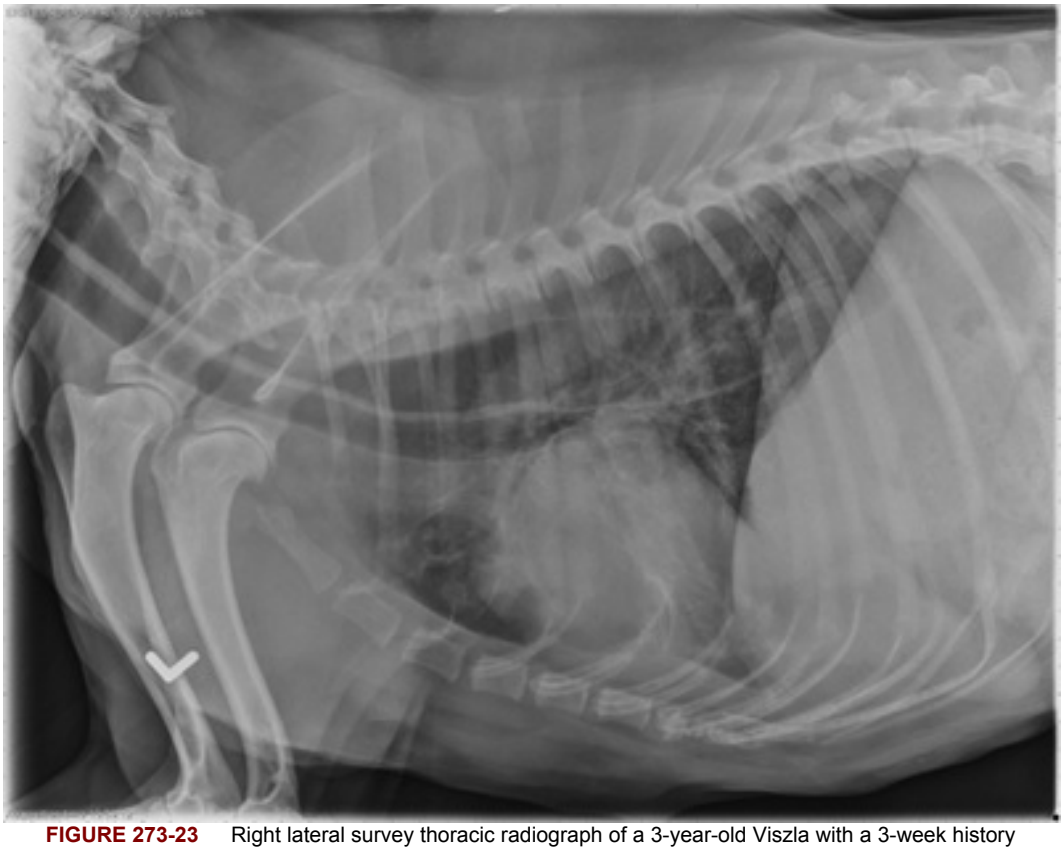


FIGURE 273-23 Right lateral survey thoracic radiograph of a 3-year-old Viszla with a 3-week history

of regurgitation, ptyalism, and dysphonia. The esophagus is diffusely gas-distended and there are ventral interstitial to alveolar infiltrates within the left cranial and right middle lung lobes consistent with aspiration pneumonia. The dog was diagnosed with focal myasthenia gravis and had complete resolution of the megaesophagus and associated clinical signs following administration of pyridostigmine.

Treatment

Animals with ASM should be differentiated from those with acquired idiopathic megaesophagus and their underlying disorder treated (E-Table 273-1). Treatment of idiopathic megaesophagus and those acquired forms that fail to respond to specific medical therapy is supportive and symptomatic. The clinician should recommend small, frequent meals from an elevated or upright position (e.g., Bailey chair) to assist passage of ingesta into the stomach. Food consistency should be varied (liquid, canned meatballs or kibble) to determine which types of food are best tolerated. Severely malnourished animals or animals suffering repeated bouts of aspiration pneumonia should have a temporary or permanent gastrostomy tube placed for enteral nutritional support (see ch. 82). Gastrostomy tube feeding reduces risk of aspiration pneumonia; however, dogs with megaesophagus can still aspirate saliva or ingesta refluxed from the stomach into the esophagus. Broad-spectrum antibiotics should be considered in aspiration pneumonia (see ch. 242). Clients should be counseled that recurrent pneumonia is a common problem necessitating prompt detection and treatment for long-term success.

E-TABLE 273-1

Diagnosis and Treatment of Megaesophagus

CAUSE	DIAGNOSTIC TEST	TREATMENT
Neuromuscular Disease		
Idiopathic	Diagnosis of exclusion	Small, frequent, elevated feedings, alter diet consistency, consider gastrostomy feeding tube in select cases with intractable aspiration
Myasthenia gravis (see ch. 269)	AChR antibody titer, edrophonium response (difficult to assess if only acquired secondary megaesophagus), ± EMG	Pyridostigmine (1-3 mg/kg PO q 12 h; ± prednisone (1-2 mg/kg PO, SC q 12 h)
Systemic lupus erythematosus (see ch. 204)	ANA, skin biopsy	Prednisone (1-2 mg/kg PO, SC q 12 h)
Polymyopathy (see ch. 354)	CK, muscle biopsy, EMG	Prednisone (1-2 mg/kg PO, SC q 12 h) or Cyclosporine 5 mg/kg q 12-24 h
Glycogen storage disease (type II) (see ch. 260)	Muscle or liver biopsy, urine metabolic screening	Supportive care
Dermatomyositis (see ch. 10)	Skin and muscle biopsy	Prednisone (1-2 mg/kg PO q 12 h)
Dysautonomia	Clinical signs	Supportive care
Distemper (see ch. 228)	CSF tap, distemper titer, conjunctival scrape	Supportive care
Tetanus (see ch. 214)	Clinical signs, EMG, serum toxin assay	Supportive care, disinfect site of infection
Esophageal Obstruction		
Neoplasia	Contrast radiography, esophagoscopy and biopsy	Surgical resection, chemotherapy
Vascular ring anomaly	Survey or contrast radiography; CT scan	Surgical correction
Stricture	Esophagram, esophagoscopy	Balloon dilatation, topical triamcinolone

Foreign body	Survey or contrast radiography, esophagoscopy	Endoscopic retrieval, occasionally surgical removal
Toxicoses		
Lead	Hematology, blood lead concentration	Chelation with calcium EDTA
Organophosphate (see ch. 152)	Whole blood cholinesterase activity	Gastric lavage, atropine (0.2 mg/kg SC once), pralidoxime chloride (10-15 mg/kg slow IV), supportive care
Miscellaneous		
Hypoadrenocorticism	ACTH stimulation test	Prednisone (0.1 mg/kg PO q 12 h), fludrocortisone (0.01 mg/kg PO q 12 h) or desoxycorticosterone pivalate (DOCP) at 2 mg/kg (Percorten IM and Zycortal SC) q 25 days initially (dosage is altered based on clinical and electrolyte response)
Hiatal hernia	Contrast radiography, esophagoscopy	Surgical correction for long-term resolution. Medical management (cisapride, omeprazole, sucralfate) can be considered in milder cases or to manage associated esophagitis.
Hypothyroidism (see ch. 309)	Clinical and dermatological findings, thyroid panel, hypercholesterolemia, non-regenerative anemia	Levothyroxine 0.022 mg/kg PO q 12-24 h
Gastric dilatation-volvulus (see ch. 275)	Survey radiography	Surgical correction, supportive care
Esophagitis	Clinical signs, Esophagoscopy (dysmotility may be detected on fluoroscopy)	Sucralfate (0.5-1 g slurry PO q 8 h), Omeprazole 1-1.5 mg/kg PO or IV q 12 h Cisapride 0.5 mg/kg PO q 8-12 h
Thymoma (see ch. 344)	Survey radiography, thymic aspirate	Surgical resection

ACTH, Adrenocorticotropic hormone; *ANA*, antinuclear antibody; *CK*, creatine kinase; *CSF*, cerebrospinal fluid; *CT*, computed tomography; *EDTA*, ethylenediaminetetraacetic acid; *EMG*, electromyography.

Modified from Jergens A. In Ettinger SJ, Feldman EC: *Textbook of veterinary internal medicine*, ed 7, St Louis, 2010, Saunders.

Prokinetic drugs are currently of unproven benefit in the management of idiopathic megaesophagus in dogs. Both metoclopramide and cisapride are smooth muscle prokinetic agents that have no effect on esophageal striated muscle, and could exacerbate clinical signs. Cisapride may be a useful prokinetic agent in cats with distal esophageal motility disturbances affecting the smooth muscle component of the feline esophagus.

Affected animals should be reevaluated at 1- to 2-month intervals to monitor disease progression. Thoracic radiographs should be repeated to assess esophageal dilatation and aspiration pneumonia. Some animals with congenital megaesophagus improve over months with diligent supportive care. The prognosis with acquired idiopathic megaesophagus is generally poor. These animals usually succumb to repeated episodes of aspiration pneumonia or are euthanized because of their irreversible disease. Animals with ASM may respond to resolution of the underlying cause. The prognosis in dogs with megaesophagus caused by acquired MG is favorable, with approximately 50% of dogs responding to supportive therapy.[47]

Hiatal Hernia

Definitions and Incidence

Hiatal hernia is defined as any protrusion of abdominal contents (most commonly a portion of stomach) through the esophageal hiatus of the diaphragm into the thoracic cavity in the presence of an intact phrenico-esophageal ligament. Three types of hiatal hernias have been recognized in dogs and cats: Type I is the sliding hiatal hernia, in which the abdominal segment of the esophagus and parts of the stomach are displaced cranially through the esophageal hiatus. In Type II, the paraesophageal hiatal hernia, the abdominal segment of esophagus and lower esophageal sphincter remain in a fixed position but a portion of the stomach herniates into the mediastinum alongside the thoracic esophagus.[50,51] One case of a type IV esophageal hiatal

hernia has been reported in which the liver, stomach, and small intestine were displaced into the thorax.[52] Type I sliding hiatal hernia is the most common form and may occur as a congenital or acquired lesion in the dog and cat.

Congenital sliding hiatal hernias have been documented in brachycephalic breeds: Chinese Shar-Pei, Chow Chow, English Bulldogs, French Bulldogs, Pugs, and Boston Terriers.[53] Affected animals develop clinical signs shortly after weaning. Acquired hiatal hernia may occur in any dog or cat and may result from sudden increases in intra-abdominal pressure secondary to trauma (via damage to diaphragmatic nerves and muscles resulting in hiatal laxity) or respiratory distress (caused by increased negative intrathoracic pressure seen with intermittent airway obstruction [laryngeal paralysis]). Regardless of cause, hiatal herniation reduces LES pressure and leads to gastroesophageal reflux, esophagitis, and segmental or diffuse esophageal hypomotility.

Clinical Signs and Diagnosis

The most common clinical signs are intermittent regurgitation, vomiting, and hypersalivation, often precipitated by excitement or exercise. The persistent reflux of gastric juice can cause secondary esophagitis with signs of odynophagia. Dyspnea and coughing may occur with severe herniation or aspiration pneumonia. Survey thoracic radiographs should be obtained in all dogs with suspected hiatal hernia and may reveal a caudodorsal, gas-filled, intrathoracic soft-tissue opacity (Figure 273-24). Varying degrees of esophageal dilatation and alveolar opacities consistent with aspiration pneumonia may also be observed. Survey radiographs are relatively insensitive for diagnosing hiatal hernia and a dynamic barium procedure (videofluoroscopy) is far more likely to identify intermittent herniation of the stomach and can allow assessment of esophageal motility (see Video 273-3 and Figures 273-3 and 273-25). A normal videofluoroscopic swallow study does not rule out a hiatal hernia because the problem occurs intermittently and could be missed. Esophagoscopy can be used to diagnose sliding hiatal hernia when the apparent separation between the squamocolumnar junction and the diaphragmatic impression is greater than 2 cm using a J-maneuver.[54] Esophagoscopy is also used to look for evidence of esophagitis. High-resolution manometry (HRM) is a non-invasive tool that can be used for diagnosing hiatal hernias in people and animals.

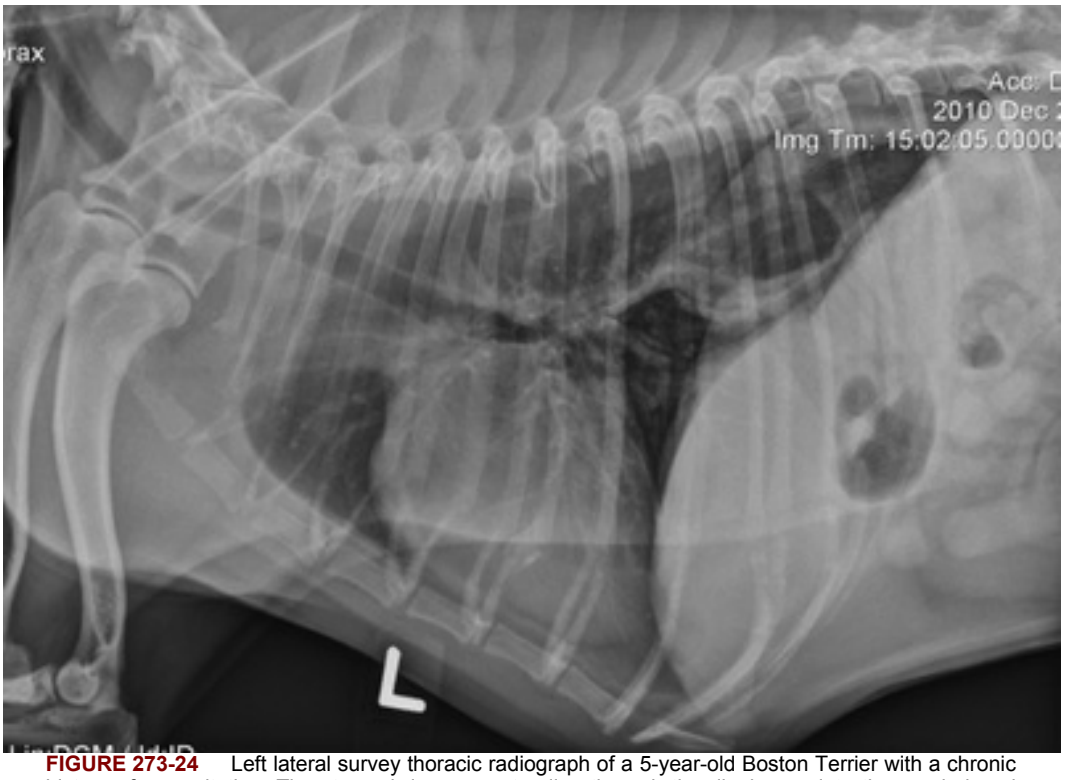


FIGURE 273-24 Left lateral survey thoracic radiograph of a 5-year-old Boston Terrier with a chronic history of regurgitation. The stomach is seen extending through the diaphragm into the craniodorsal thorax on the left lateral projection. It then returns to a more normal location on subsequent projections. These findings are highly supportive of a sliding hiatal hernia.

FIGURE 273-25 Contrast videofluoroscopic swallow study in a 5-year-old Boston Terrier with a chronic history of regurgitation documenting severe gastroesophageal reflux in association with a sliding (type I) hiatal hernia.

Treatment

A sliding hiatal hernia is not always associated with clinical signs, particularly when acquired. Medical therapy should be implemented in animals with clinical signs of severe gastroesophageal reflux (GER), esophagitis, and regurgitation before surgical intervention. Proton pump inhibitors such as omeprazole are superior acid suppressants compared to H2-receptor antagonists and should be administered with sucralfate suspension to afford greater mucosal cytoprotection. Drugs that increase LES tone (cisapride or metoclopramide) can be given with PPIs and sucralfate. Animals failing medical management may benefit from reconstructive surgery, especially for large congenital hiatal hernias. Normal hiatal anatomy can be restored by diaphragmatic crural apposition, esophagopexy, and left fundic tube gastropexy techniques.[40,42] Consideration for surgical management of brachycephalic syndrome in affected dogs with concurrent hiatal hernia is also important because the upper airway obstruction creates an increased negative intrathoracic pressure which can exacerbate herniation. The prognosis for most dogs following surgical correction is generally favorable, although persistent regurgitation is recognized in dogs with concurrent esophageal motility disturbances.

Gastroesophageal Reflux (GER)

Definition and Clinical Signs

GER is associated with reflux of gastric or intestinal fluids or ingesta into the esophagus secondary to the loss of integrity of the gastroesophageal barrier (Figure 273-26). The consequences of GER include varying degrees of esophagitis resulting from prolonged contact of gastric acid, pepsin, trypsin, bile salts and duodenal bicarbonate with the esophageal mucosa. Gastric acid alone produces mild esophagitis; however, the combination of gastric acid with pepsin or trypsin can cause severe esophagitis. The most common causes of GER in dogs and cats include hiatal hernia, general anesthesia induced reductions of LES pressure, chronic vomiting causing a weakening of LES tone, and gastric atony causing GER. The clinical signs of GER are similar to those of esophagitis, and may include regurgitation, hypersalivation, odynophagia, and anorexia. Animals that reflux into their mouth can be seen lip-smacking, panting, or exhibiting a "hard-swallow" immediately following these episodes. Nocturnal reflux occurs more commonly in people and animals because of transient relaxations of the LES during sleep and the loss of the swallow reflex.

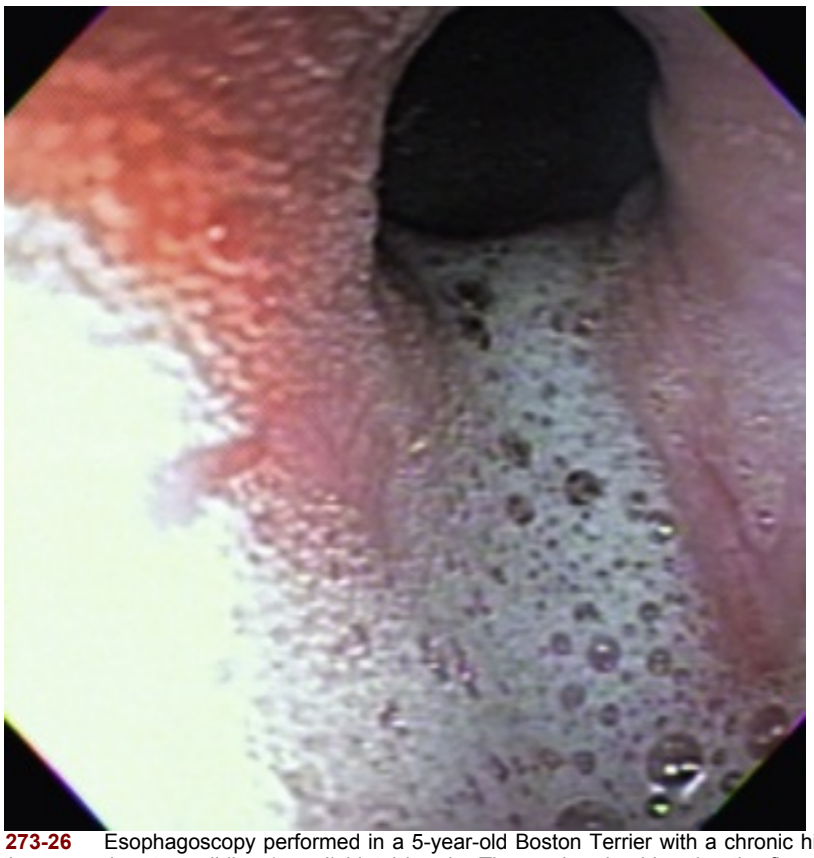


FIGURE 273-26 Esophagoscopy performed in a 5-year-old Boston Terrier with a chronic history of regurgitation secondary to a sliding (type I) hiatal hernia. The reader should notice the flaccid lower esophageal sphincter and evidence of gastroesophageal reflux. The esophageal mucosa at the 9-11 o'clock position appears erythematous secondary to esophagitis.

Diagnosis and Treatment

Diagnosis of GER is suspected on the history (nocturnal panting, hard-swallowing, and lip-smacking), recent general anesthesia, or history of chronic vomiting. Videofluoroscopy may demonstrate intermittent GER; however, intermittent episodes of GER may be observed in animals with normal esophageal function. Esophagoscopy is a useful procedure for documenting mucosal inflammation associated with the GER. Esophageal pH/impedance testing is useful for diagnosing acid and non-acid reflux in people and dogs with suspected GER, unexplained esophagitis, or hiatal hernias (see section: Esophageal pH/Impedance Testing).

Medical therapy is aimed at administering acid suppressants (proton pump inhibitors), diffusion barriers (sucralfate), and prokinetic agents (cisapride, metoclopramide). Cisapride is a superior prokinetic agent to metoclopramide and has been documented to tighten LES tone and enhance gastric emptying in dogs. Animals should be fed a fat-restricted diet because dietary fat delays gastric emptying and can reduce LES pressure. In people with severe GER, anti-reflux surgery is commonly performed laparoscopically and is aimed at reinforcing and repairing the defective barrier through plication of the gastric fundus.[55] Endoscopic anti-reflux therapies are currently being utilized in people, although clinical trials in dogs are lacking.

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CHAPTER 274

Host-Microbiota Interactions in Gastrointestinal Health and Disease

Albert Earl Jergens

Introduction

The gastrointestinal (GI) tract is colonized with a complex community of bacteria, archaea, fungi, protozoa, and viruses that promote immune system development and contribute to host health.[1,2] The total microbial load in the intestines is estimated to range from 10^{12} to 10^{14} organisms, which is approximately 10 times the number of host cells. The pool of microbes inhabiting the gut is known as the intestinal *microbiota* and their collective genomes as the intestinal *microbiome.* These bacteria exert a conditioning effect on intestinal homeostasis by delivering regulatory signals to the epithelium and instructing mucosal immune responses. This habitat is separated from the intestinal milieu by a single layer of epithelial cells and contains hundreds of different bacterial species. The paucity of bacteria in the stomach and proximal small intestine is due to acid, bile, and pancreatic secretions, which kill most ingested bacteria, and because of propulsive motor activity in the distal small intestine, which impedes stable bacterial colonization. However, bacterial density dramatically increases in the distal small bowel and in the large intestine increases to 10^{11}-10^{12} bacteria/g of luminal contents. A large proportion of the fecal mass consists of bacteria (around 60% of fecal solids).[3]

Major functions of the intestinal microbiota that contribute to maintenance of GI health include metabolic activities that cultivate energy and nutrients, important trophic effects on intestinal epithelia and immune structure/function, and protection of the colonized host against invasion by pathogenic microbes (Figure 274-1). Gut microbiota might also be an essential factor in specific pathologic disorders including inflammatory bowel disease, "small intestinal bacterial overgrowth" (SIBO), and infectious causes for gastroenteritis. Furthermore, pro-/prebiotics and synbiotics and fecal microbiota transplantation (FMT) may have a role in the prevention or treatment of some gastrointestinal diseases.

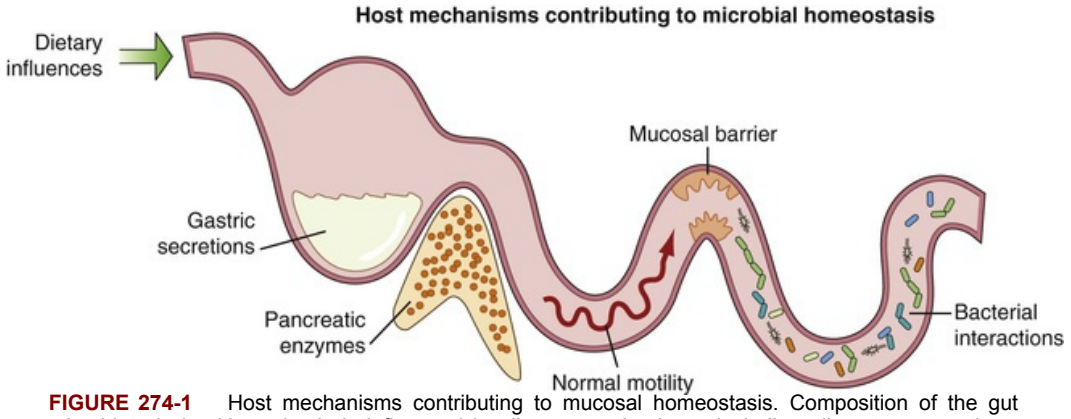

FIGURE 274-1 Host mechanisms contributing to mucosal homeostasis. Composition of the gut microbiota in healthy animals is influenced by diverse mechanisms, including alimentary secretions, gastrointestinal motility, mucosal barrier integrity, the gut-associated lymphoid tissue, and bacterial interactions.

Composition of the Microbiota in Healthy Animals

Colonization of the GI tract starts immediately after birth and occurs within a few days. Commensal bacteria appear to be acquired by opportunistic colonization by particular species as a result of random environmental encounters. These "first chance" bacteria can modulate expression of genes in host epithelial cells and create a favorable habitat for themselves while preventing growth of other bacteria introduced later. Contemporary culture-independent quantitative analyses of the fecal microbiota have shown that anaerobic bacteria outnumber aerobic bacteria by a factor of 100-1000.[1,2] These molecular techniques that focus on the 16S ribosomal RNA (rRNA) genes, which are common to all bacteria but whose precise sequences vary between species, can be used for identifying and classifying bacteria. Examples of this technology include the development of molecular probes for DNA microarrays, high throughput genomic sequencing (i.e., Illumina platform) for microbial abundance, fluorescence *in situ* hybridization (FISH) techniques to assess spatial distributions of mucosal microbiota, and gene chips that identify and enumerate specific bacterial species. Greater than 99% of the human gut microbiota is composed of species within 4 bacterial divisions: *Firmicutes, Bacteriodetes, Proteobacteria,* and *Actinobacteria.*[1,2,4] While the composition of the microbiota within adult humans appears to be relatively stable over time, there is a remarkable degree of inter-individual variation.

It is now realized that the composition of gut flora in healthy dogs and cats is distinctly different. Using traditional bacterial culture, healthy cats have been shown to have a large number of total and anaerobic bacteria in the proximal small intestine.[5,6] The most commonly isolated anaerobic bacteria comprised the genera *Bacteroides, Clostridia, Eubacteria,* and *Fusobacteria,* while *Pasteurella* spp. were the predominant aerobic species. A separate study showed that the canine duodenal microflora typically harbors a bacterial count $>10^5$ CFUs/mL of duodenal juice; however, significantly higher counts have been observed in some breeds and in dogs with no signs of intestinal tract disease.[7,8] Next-generation sequencing studies of the 16S rRNA gene have further defined the canine and feline microbiome, which on higher phylogenetic levels resembles the microbiome of humans and other mammals. On average, 10 different bacterial phyla have been identified in the healthy gut of dogs and cats, with *Firmicutes, Bacteroidetes, Proteobacteria, Fusobacteria,* and *Actinobacteria* comprising the majority of microbes found in feces.[9,10] Importantly, emerging studies now indicate that dietary intake also plays a pivotal role, potentially even greater than host genetics, in shaping intestinal microbial ecology.[11]

Investigation of the canine and feline metagenomes (i.e., shotgun sequencing of genomic DNA) has now provided recent and valuable insight into the functional capacity of the microbiota (Figure 274-2).[12,13] In spite of differences in the microbial populations of dogs and cats, the functional capabilities of these species appear to be highly conserved.

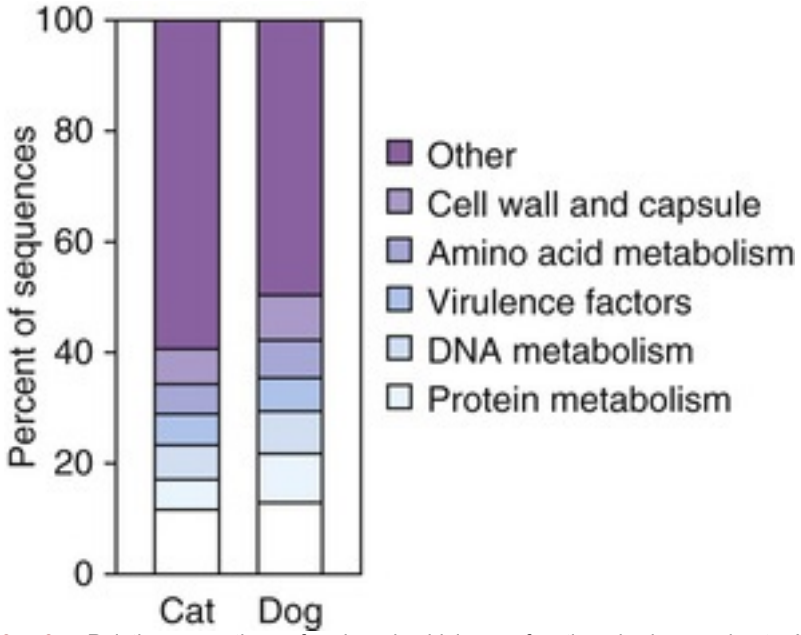

FIGURE 274-2 Relative proportions of major microbial gene functions in dogs and cats. Note that the functional capacity of the microbiota is quite similar between these mammalian species despite variation in their microbial populations. (From Honneffer JB, Minamoto Y, Suchodolski JS: Microbiota alterations in acute and chronic gastrointestinal inflammation of cats and dogs. *World J Gastroenterol*

Physiologic Microbial-Host Interactions

Comparative studies of germ-free and conventionally colonized animals have provided important information about the effect of the gut microbial community on host physiologic mechanisms and disease.

Metabolic Functions

A major metabolic function of the colonic microbiota is the fermentation of non-digestible dietary residues into short-chain fatty acids (SCFA) including acetate, propionate, and butyrate.[14] Butyrate is consumed almost completely by the colonic epithelium, where it serves as a major source of energy for colonocytes. Gene diversity within the microbial community provides the necessary enzymes and biochemical pathways for this purpose and that are distinct from the host's own resources. The outcomes of this complex metabolic activity are recovery of metabolic injury and absorbable substrates for the host, while supplying energy and nutrition for bacterial growth and proliferation. These resident bacteria can break down dietary carcinogens; synthesize biotin, folate, and vitamin K; metabolize bile salts; and assist in the absorption of calcium, magnesium, and iron.[15,16] Colonization increases glucose uptake in the gut, whereas germ-free mice require a greater caloric intake to maintain a normal body weight. It has been proposed that an individual's gut microbiota has a specific metabolic efficiency and differences in microbial composition might regulate energy storage and predispose to obesity in adults.[17]

Trophic and Protective Effects to Epithelium

Enteric bacteria confer numerous and diverse structural and protective effects on the intestinal epithelium.[1,2] Bacterial-induced expression of host genes influences nutrient uptake, metabolism, angiogenesis, mucosal barrier integrity, and the development of the enteric nervous system. Ligands from resident bacteria influence the normal development and function of mucosal immunity.[18,19] These indigenous bacteria educate the mucosal immune system and modulate the fine-tuning/regulation of T-cell repertoires and T-helper cell type 1 (Th1)/Th2 cytokine profiles. Along the epithelium, resident enteric bacteria form a natural barrier (biofilm) against colonization by exogenous microbes. Colonization resistance to pathogenic microbes involves numerous mechanisms including displacement, competition for nutrients and epithelial binding sites, and the production of antimicrobial substances such as lactic acids and bacteriocins.[20] It is noteworthy that the exposure of colonic epithelial cell lines with bacterial ligands enhances ZO-1-associated intestinal barrier integrity.[21]

Host-Microbiota “Cross-Talk” at the Mucosal Surface

Maintenance of mucosal homeostasis requires precise interpretation of the microenvironment to distinguish commensal bacteria from pathogenic microorganisms. Disruption of these processes might lead to inappropriate host immune responses and subsequent intestinal mucosal injury. The interaction between gut-associated lymphoid tissue and microbiota early in life appears to be crucial for appropriate development of complex mucosal and systemic immunoregulatory circuits. Various types of immunosensory cells actively sample commensal bacteria, pathogens, and other luminal antigens. These cells include surface enterocytes, M cells, and dendritic cells (DCs). Surface enterocytes are interconnected by tight junctions and are covered in mucus that promotes antigenic exclusion. They sense danger signals within the luminal microenvironment and respond by secreting defensins, immunoglobulin A, chemokines, and cytokines, which initiate and direct innate and adaptive immune responses.[1,22,23] M cells, which are specialized epithelial cells that overlie lymphoid follicles, sample luminal antigens and deliver their products to DCs and other antigen-presenting cells. Dendritic cells provide further immune surveillance via direct sampling of gut contents by either entering or extending dendrites between surface enterocytes.[24] Furthermore, DCs can ingest and retain live commensal bacteria and transport them to mesenteric lymph nodes, where immune responses to these bacteria might be produced locally.[25] Accordingly, the access of commensal bacteria to the internal host environment is prevented.

Mucosal Recognition of Bacteria

Immunosensory cells must rapidly recognize detrimental pathogenic microbes in the lumen to initiate controlled immune responses but maintain hyporesponsiveness to harmless commensal bacteria (i.e., oral tolerance). This discriminatory process largely is mediated by two major host pattern-recognition receptor (PRR) systems: the family of Toll-like receptors (TLRs) and the nucleotide-binding oligomerization domain (NOD1 and NOD2) molecules.[26] The TLRs comprise a class of transmembrane PRRs that play a key role in microbial recognition, induction of antimicrobial genes, and the control of adaptive immune responses. The NODs are a structurally distinct family of intracellular PRRs that exert antimicrobial activity and prevent pathogenic invasion. Both TLRs and NODs are widely expressed on various cell types of the GI mucosa and participate in host defense against microbial pathogens through: (1) recognition of molecular patterns present on pathogens; (2) expression at the interface with the "environment" of the GI tract; (3) induction of secretion of pro- and anti-inflammatory cytokines and chemokines that link to adaptive immunity; and (4) induction of antimicrobial effector pathways.[23] Thus, TLRs expressed by both non-epithelial cell types (e.g., macrophages, DC) and intestinal epithelial cells (e.g., TLR4 by LPS, and TLR5 by bacterial flagellin) play key functional roles in epithelial cell signaling of innate immune defense.[27]

Different TLRs selectively recognize different PRRs (i.e., each TLR binds specific "molecular signatures" of different classes of microorganisms) and initiates signaling through conserved pathways such as NFkB and mitogen-activated protein kinases (MAPK) signal transduction pathways.[4,26] These downstream effects involve transcriptional activation of genes encoding pro- and anti-inflammatory cytokines and chemokines as well as induction of co-stimulatory molecules.[28] In the healthy gut, TLR/NOD signaling promotes host defense and tissue repair responses, thereby maintaining mucosal as well as commensal homeostasis. This programmed response creates a chemotactic gradient for the entry of neutrophils, monocytes, and T-lymphocytes into the mucosa, which facilitates the clearance of invading pathogens. Conversely, intestinal disease can develop when commensal and/or mucosal homeostasis is/are impaired due to specific genetic (e.g., NOD2/CARD15 mutation in Crohn's disease) or environmental (e.g., dietary constituents, pathogenic infection, use of nonsteroidal anti-inflammatory drugs) triggers.[4,26,29] Therefore, bacterial mis-recognition and mucosal intolerance through aberrant TLR/NOD signaling stimulate exaggerated pro-inflammatory responses, leading to chronic inflammation via cytokine and chemokine production in genetically susceptible hosts.

Microbial Perturbations and Enteric Disease

Idiopathic Inflammatory Bowel Disease

Inflammatory bowel disease is a chronic, immunologically mediated intestinal disorder resulting from the complex interactions between environmental and immunologic factors in genetically susceptible hosts (see ch. 276).[30-32] There is abundant evidence that commensal bacteria are involved in the pathogenesis of human IBD and experimental colitis in animal models. Direct interaction of commensal microflora with the intestinal mucosa stimulates inflammatory activity of the gut lesions in human IBD.[4,30,33] Intestinal lesions also occur in anatomic regions of greatest luminal bacteria concentrations, such as the colon.[34] Flagellin derived from commensal bacteria has been identified as a dominant antigen in humans and dogs, suggesting that TLR5-dependent recognition of flagellin plays a role in immune responses to commensal microbiota observed in IBD.[35] Furthermore, mutations of NOD 2/CARD15 have been strongly associated with the development of Crohn's disease, implicating a role for PRR dysfunction and impaired bacterial sensing in IBD.[4,26,29] Animal models also suggest that the resident microbiota is a causative factor of IBD. In numerous different animal models, colitis and immune activation fail to develop in the absence of commensal bacteria.[1,2,4,30] Multiple animal models also respond to antibiotic therapy for their disease. Moreover, it has been shown that different bacterial species can cause different disease phenotypes in a single host, and that different bacterial species can provide the dominant stimuli for disease expression.[36]

Both clinical and research data indicate that resident microbiota likely play a pivotal role in driving the inflammatory process of companion animal IBD. A role for luminal bacteria is strongly suggested by observations that therapeutic levels of metronidazole and tylosin attenuate clinical disease in cats and dogs, respectively.[32,37] In separate studies, increased lamina propria myeloid/histiocyte antigen-positive macrophages,[38] upregulated epithelial MHC class II molecule expression,[39] and increased antibody reactivity

to components of the normal indigenous bacterial flora[40] have been associated with chronic intestinal inflammation of feline IBD. Furthermore, the numbers of mucosally associated *Enterobacteriaceae* have correlated with abnormalities in duodenal histology, upregulated mucosal cytokine mRNA, and the number of clinical signs in cats with IBD.[41] In separate studies, dogs with IBD have shown distinctly different duodenal microbial communities compared with healthy dogs,[42] and bacteria-responsive TLR2, 4, and 9 were upregulated in the inflamed duodenal and colonic mucosa of diseased dogs.[43] This might lead to increased inflammation through interaction with the commensal bacteria. Granulomatous colitis (GC, formerly histiocytic ulcerative colitis) in dogs now has been recognized to be associated with adherent/invasive *E. coli* (AIEC), wherein affected dogs respond to fluoroquinolone antimicrobial therapy.[44] Detailed phylogenetic studies have confirmed striking similarities between AIEC isolates obtained from Boxer dogs with GC and AIEC isolates derived from ileal tissues of humans with Crohn's disease.[45]

Antibiotic Responsive Diarrhea

Perturbations in the intestinal microbiota and/or dysregulated host responses to its components can cause chronic signs of diarrhea and weight loss (see ch. 276). Canine "small intestinal bacterial overgrowth" (SIBO) traditionally is defined on the basis of increased numbers of total or obligate anaerobic bacteria in duodenal juice, but controversy exists as to which bacterial quantities constitute normal.[46] While the numerical limits of bacteria found within asymptomatic dogs can vary (see above), there is general consensus that SIBO can occur secondary to exocrine pancreatic insufficiency, impaired clearance of bacteria (e.g., intestinal obstruction, motility disorder), or morphologic injury to the mucosa (e.g., infiltrative mucosal disease).[47] Little is known about the etiology of idiopathic SIBO in dogs and the term antibiotic-responsive diarrhea (ARD) has been proposed for antibiotic-responsive enteropathies without an underlying cause.[48,49]

Increased numbers of intestinal bacteria (i.e., SIBO) could cause malabsorption and diarrhea through: (1) competition for nutrients—the bacterial binding of cobalamin which impairs its intestinal absorption; (2) bacterial metabolism of nutrients into secretory products (e.g., hydroxylated fatty acids, deconjugated bile salts) that promote colonic secretions; and (3) biochemical injury to the intestinal brush border, which decreases enzyme activity.[49] Antibiotic-responsive diarrhea can develop secondary to disrupted barrier function, aberrant mucosal immunity, or qualitative changes in the enteric bacterial flora. Studies show that dogs with ARD can have selective IgA deficiency (German Shepherd breed) and increased mucosal CD4+ T cells and IgA plasma cells, which might reflect an underlying immunologic pathogenesis.[50] The microbiota present in ARD generally consists of a mixed population of commensal aerobes and anaerobes that normally inhabit the intestine.

Diagnostic criteria for differentiating SIBO from ARD remain ill-defined. Thorough diagnostic evaluations to eliminate other causes for GI signs should be performed. Due to the limitations of traditional quantitative bacteriology, indirect tests for SIBO/ARD, such as serum folate, cobalamin, and unconjugated bile acids concentrations, have been designed but are unreliable.[46,47] The current diagnostic test of choice for idiopathic ARD is remission of clinical signs following an antibiotic trial.

Infectious Gastroenteritis

Enteropathogenic bacteria can cause diarrhea in young and adult dogs and cats (see ch. 220). The bacteria most frequently incriminated in causing enterocolitis include *Clostridium perfringens, Clostridium difficile, Campylobacter* spp., pathogenic *E. coli,* and *Salmonella* spp.[51] The true prevalence of bacterially mediated diarrhea is confounded by the presence of many of these organisms existing as components of the normal intestinal flora. Nevertheless, diarrhea attributable to perturbation in the intestinal microbiota can result from microbe proliferation, enterotoxin production, and/or mucosal invasion. Information regarding the pathogenesis of *C. perfringens*-associated diarrhea is limited but the mechanism likely involves enterotoxigenic commensal isolates.[51] Administration of antimicrobials prior to admission, and administration of immunosuppressive drugs during hospitalization, were risk factors for hospital-associated colonization with *C. difficile* in one study.[52] Infection with *C. jejuni* is enhanced in crowded, unsanitary environments where its production of cytotoxin and heat-labile toxin promotes mucosal inflammation and fluid secretion, respectively. Much remains to be learned about the role of *Helicobacter* spp. infection in canine and feline chronic gastritis. Studies completed to date indicate that *Helicobacter* spp. are highly prevalent in healthy and sick dogs and cats, and that there is no simple relationship between infection and disease.[53,54]

Probiotics, Prebiotics, and Synbiotics

Bacteria can be used for improving GI health. ***Probiotics*** are living microorganisms that, upon ingestion in sufficient numbers, impart health benefits beyond those of inherent basic nutrition.[55] Lactobacilli and bifidobacteria have been the most commonly used human probiotics, but multi-strain cocktails (e.g., VSL#3), *E. coli* Nissle 1917, and nonbacterial *Saccharomyces boulardii* also have been used for their probiotic effects.[56,57] Probiotic bacteria confer measurable host benefits, including the ability to improve epithelial barrier function, modulate the mucosal immune system, and alter the intestinal microbiota (Figure 274-3). ***Prebiotics*** are non-digestible dietary carbohydrates—lactosucrose, fructo-oligosaccharides (FOS), psyllium, bran—that stimulate the growth and metabolism of endogenous enteric protective bacteria upon consumption.[58] Beneficial effects of prebiotics also are associated with the production of SCFA due to fermentation by colonic bacteria. ***Synbiotics*** are combinations of probiotics and prebiotics that are an emerging therapeutic modality. Increasing evidence supports a therapeutic role for probiotics, prebiotics, and synbiotics in GI diseases of humans, including infectious diarrhea, *H. pylori* infection, irritable bowel syndrome, lactase deficiency, and some forms of IBD.[1,2,59]

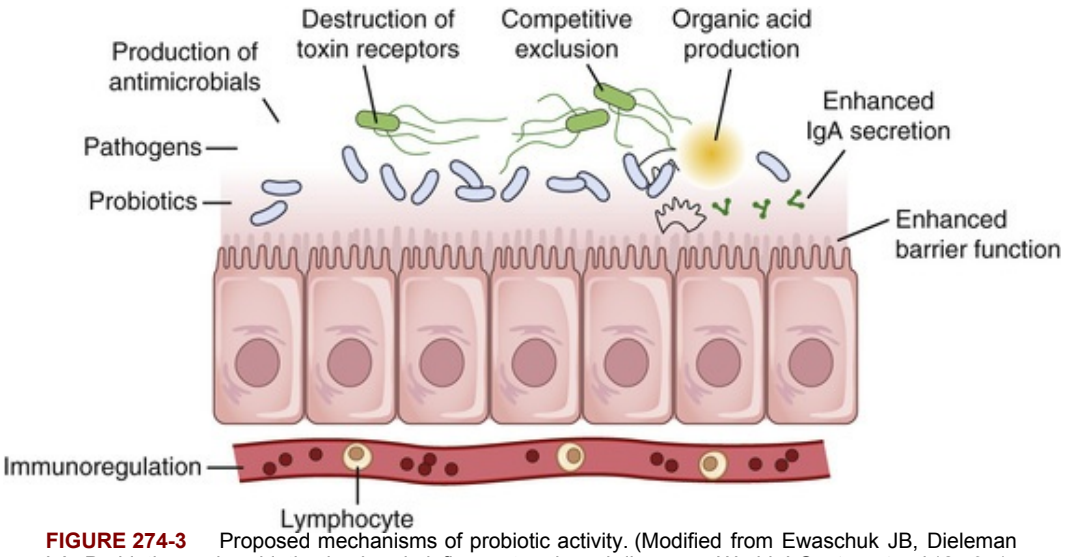

FIGURE 274-3 Proposed mechanisms of probiotic activity. (Modified from Ewaschuk JB, Dieleman LA: Probiotics and prebiotics in chronic inflammatory bowel diseases. *World J Gastroenterol* 12:5941-5950, 2006.)

Scientific studies have investigated the effects of dietary supplementation with prebiotics on the bacterial flora in healthy dogs and cats. In one study, FOS supplemented at 0.75% dry matter produced qualitative and quantitative changes in the fecal flora of healthy cats.[60] Compared with samples from cats fed a basal diet, increased numbers of lactobacilli and *Bacteroides* spp., and decreased numbers of *E. coli,* were associated with the FOS diet. However, bacteriologic examination of the duodenal juice in these same cats showed wide variation in the composition of the duodenal flora, across sampling periods, which was not affected by FOS supplementation.[61] Moreover, healthy Beagle dogs fed a 1% FOS diet in a 3-month trial showed inconsistent fecal excretion of *Lactobacillus* spp. and *Bifidobacterium* spp.[62]

There are only few reports on the use of probiotic bacteria in dogs and cats. Recent *in vitro* studies have confirmed the capacity of a lyophilized probiotic cocktail (e.g., three different *Lactobacillus* spp. strains) to modulate the expression of regulatory versus pro-inflammatory cytokines in dogs with chronic enteropathies.[63] However, a clinical trial using this same probiotic cocktail fed to dogs with food-responsive diarrhea failed to induce consistent patterns of regulatory (e.g., beneficial) cytokine expression despite obvious clinical improvement.[64] One commercially manufactured probiotic (FortiFlora—*Enterococcus faecium* SF68, Nestle Purina) is reported to be of potential benefit in controlling diarrhea and enhancing immune responses in dogs and cats.[65] More recently, human probiotic VSL#3 was shown to enhance clinical remission and reduce histopathologic inflammation in IBD dogs when administered continuously for 8 weeks.[66]

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) describes "the infusion of a fecal suspension from a healthy individual into the GI tract of an individual with colonic disease."[67] The rationale behind FMT includes the reintroduction of a complete, stable microbial community aimed at repairing or replacing the disrupted native microbiota to correct an underlying imbalance. It is assumed that microbiota repair eradicates or hinders pathogens, which could be causing specific GI disease, such as *Clostridium difficile* infection (CDI) colitis in humans.[67,68] Emerging evidence now implicates the intestinal microbiota in the pathogenesis of other non-GI disorders, including obesity, diabetes mellitus, autism, myasthenia gravis, and rheumatoid arthritis in human patients.

Only very sparse clinical data describe the use of FMT to treat chronic GI disease in dogs and cats, including CDI and idiopathic IBD. Formal practice guidelines for performing FMT currently are being designed but should include (1) the clinical indications for use of FMT, (2) proper donor screening procedures, (3) fecal material preparation, and (4) the possible routes of FMT administration (Table 274-1).[67] The link between the intestinal microbiota and GI health is now obvious, and physiologic manipulation of the intestinal microbiota represents an exciting therapeutic strategy for preventing and treating chronic GI inflammation.

TABLE 274-1

Practical Considerations for Fecal Microbiota Transplantation (FMT)

PARAMETER	CONSIDERATION
Donor selection	Breed—GI disease susceptible? Vaccination history Diagnostic screening for infectious agents Recent history of antibiotic use
Recipient preparation	Role of diet? Perform bowel lavage? Perform antibiotic trial prior to FMT?
Donor sample storage	Fresh versus frozen feces
Type of diluent	Saline versus water versus milk
Volume of stool required	≈60 grams feces in 250-300 mL diluent
Route of administration	Nasogastric/enteric versus colonoscopy

Practical guidelines for FMT are under review and have yet to be designed for dogs, cats, or even humans.

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CHAPTER 275

Diseases of the Stomach

Kenneth W. Simpson

Functional Anatomy and Physiology

Overview

The stomach's main function is to act as a reservoir that controls the size and rate of passage of ingesta into the small intestine. The stomach also initiates the digestion of protein and fat and facilitates the absorption of vitamins and minerals.

Anatomically the stomach is composed of four regions: the cardia, fundus, body, and antrum (Figure 275-1). The fundus and body expand to accommodate ingesta. The antrum is thick and muscular and grinds food into small particles that are titrated into the duodenum. The lower esophageal sphincter prevents reflux of ingesta into the esophagus, and the pyloric sphincter controls efflux into the duodenum.

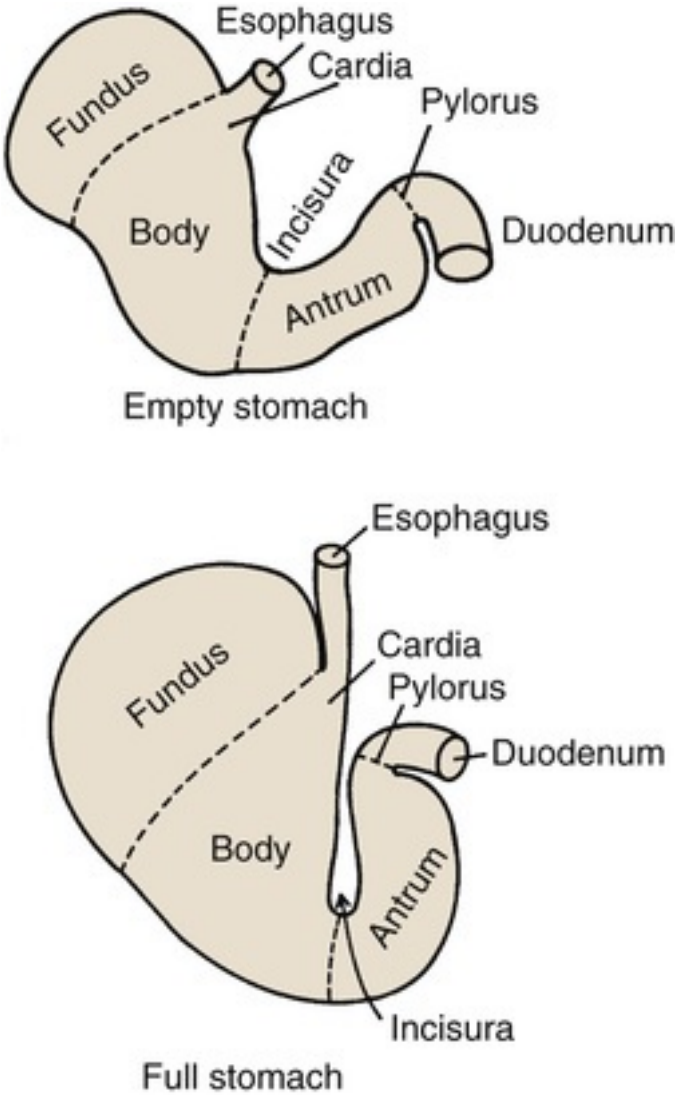

FIGURE 275-1 Gastric anatomy of the empty and full stomach. (From Guilford WG, Strombeck DR: Gastric structure and function. In Guilford WG et al, editors: *Strombeck's small animal gastroenterology*, ed 3, Philadelphia, 1996, Saunders, p 239.)

The gastric wall has three layers: the mucosa, muscularis, and serosa. The mucosa has a superficial epithelium, gastric glands, and an innermost layer of smooth muscle, with fine structure and function varying depending on the gastric region. The mucosa in the cardia and pylorus is thinner and less glandular than in the fundus and body. The mucosa of the body contains mucous neck cells (pepsinogen A, gastric lipase), parietal cells (acid, pepsinogen A, intrinsic factor), and chief cells (pepsinogen A; Figure 275-2).[1-3] A variety of neuroendocrine cells involved with the secretion of gastric acid are interspersed between the glands. The predominant cells are enterochromaffin-like and somatostatin-producing cells in the fundus with gastrin and somatostatin-producing cells in the antrum. Localized small aggregates of lymphoid tissues are observed at the base of the gastric glands. Intertwined among gastric glands is a rich network of blood vessels, lymphatics, and nerves. Beneath the submucosa are two layers of smooth muscle that run perpendicular to each other. The serosa is the outermost layer.

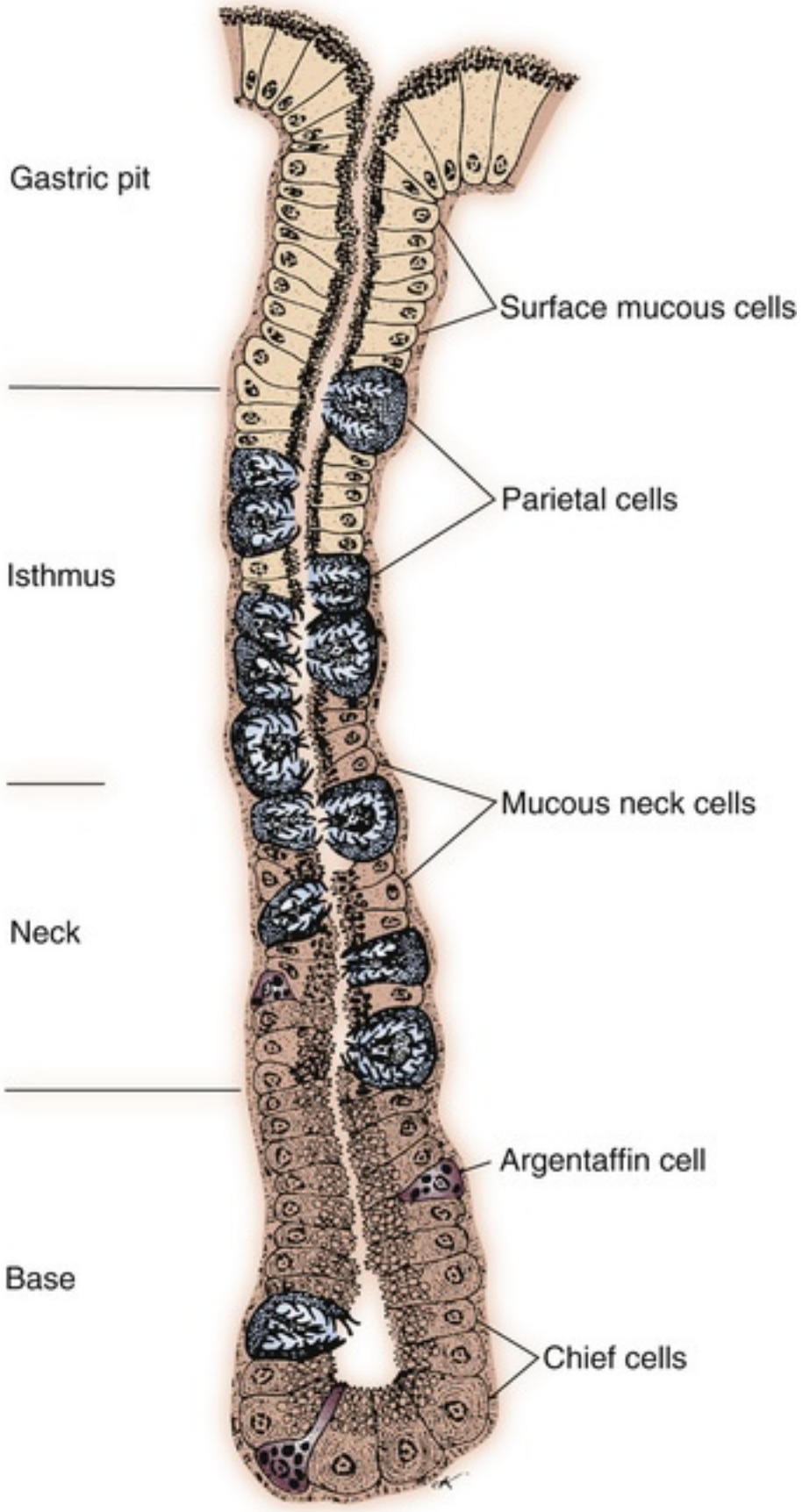

FIGURE 275-2 Histologic appearance of the fundic mucosa. (© Kenneth W. Simpson.)

Regulation of Acid Secretion

Acid secretion is regulated by a variety of neurochemical and neurohumoral stimuli.[4,5] Luminal peptides, digested protein, acetylcholine, and gastrin-releasing peptide stimulate gastrin secretion from G cells and effect histamine release from enterochromaffin-like cells (Figure 275-3). Histamine release from mast cells and binding of acetylcholine and gastrin to parietal cells also contribute to secretion. Somatostatin, released in response to gastric pH levels below 3, decreases gastrin, histamine, and acid secretion.

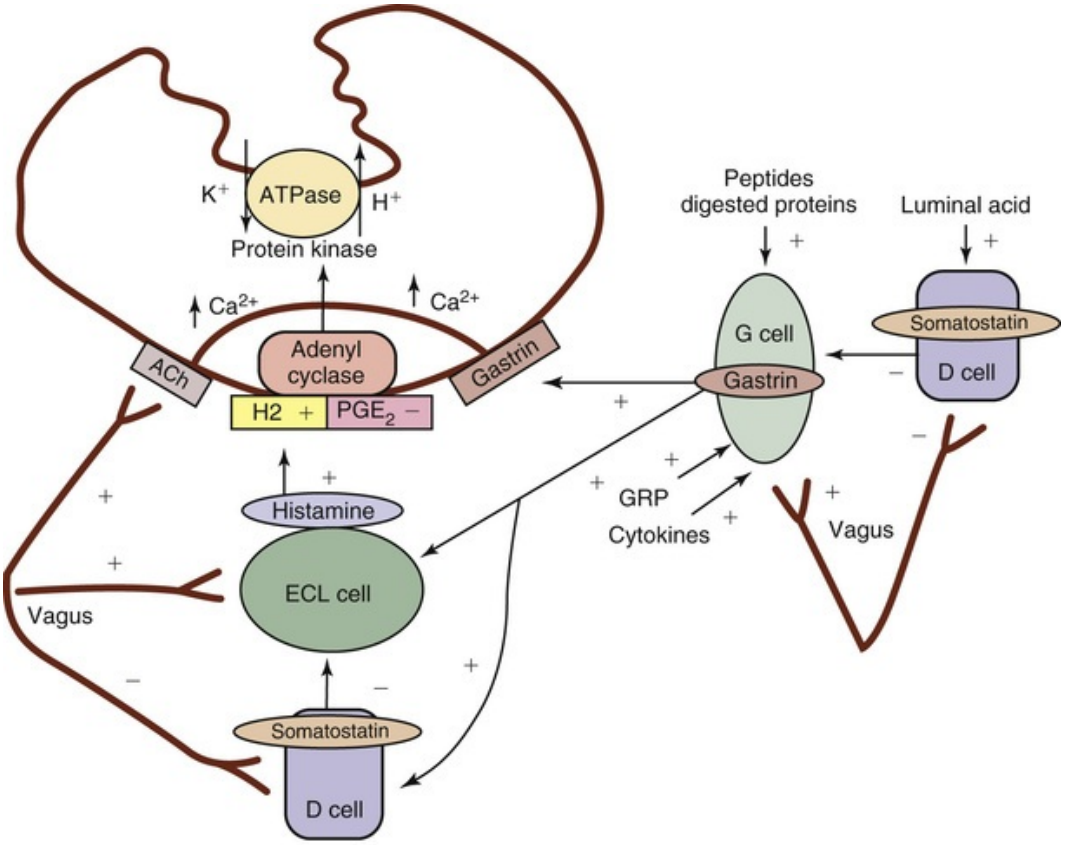

FIGURE 275-3 Regulation of acid secretion. *ACh*, Acetylcholine receptor; *ECL*, enterochromaffin-like cell; *GRP*, gastrin-releasing peptide; *H2*, histamine H2 receptor; *PGE*, prostaglandin E_2 receptor. (Modified from Simpson KW: In DiBartola SP, editor: *Fluid, electrolyte, and acid-base disorders in small animal practice*, ed 4, Philadelphia, 2012, Saunders.)

Unstimulated acid secretion in dogs and cats is minimal (in dogs, <0.04 mmol/kg$^{0.75}$/h)[6] and H^+/K^+-ATPase, "the acid pump," is present in tubulovesicles within the cytoplasm of parietal cells.[7] In the stimulated state, H^+/K^+-ATPase and KCl transporters are incorporated into the parietal cell canalicular membrane; hydrogen ions, derived from the ionization of water within the parietal cells, are transported into the gastric lumen in exchange for K by H^+/K^+-ATPase. Potassium and chloride transporters in the canalicular membrane enable luminal transfer of potassium and chloride. OH^- combines with CO_2, catalyzed by carbonic anhydrase, to form HCO_3^-, which diffuses into the blood (the "alkaline tide"). Stimulation results in a rapid increase in fluid and hydrogen ion secretion, with pH rapidly declining to around 1. The concentrations of K^+ (10 to 20 mmol/L) and Cl^- (approximately 120 to 160 mmol/L) in gastric juice are higher than in plasma.

The stomach is protected from gastric acid by a functional unit known as the *gastric mucosal barrier* (GMB).[8-10] The GMB comprises tightly opposed epithelial cells coated with a layer of bicarbonate-rich mucus and an abundant mucosal blood supply that delivers bicarbonate, oxygen, and nutrients. Local production of

prostaglandins (PGE_2) is important in modulating blood flow, bicarbonate secretion, and epithelial cell renewal. When damage occurs, epithelial cells rapidly migrate over superficial mucosal defects aided by the local production of growth factors such as EGF (epidermal growth factor).

Gastric Motility

Normal gastric motility is the result of the organized interaction of smooth muscle with neural and hormonal stimuli. The rate of gastric emptying is determined by the difference in pressure between the stomach and the duodenum and the resistance to flow across the pylorus. Liquids are expelled more rapidly than solids, and the rate of expulsion of liquids increases with volume. The rate of expulsion of solids depends on caloric density. In dogs, digestible solids <2 mm in size are emptied into the duodenum. Gastric emptying is modulated via intestinal osmoreceptors and chemoreceptors. Carbohydrates, amino acids, and especially fats, retard gastric emptying. The release of cholecystokinin (CCK) in response to fatty acids and amino acids, such as tryptophan, is one factor that slows gastric emptying. Large, undigestible solids are expelled from the stomach in the fasted state by phase III of the migrating motility complex in response to the release of motilin.

Digestion and Assimilation of Nutrients

The stomach has a limited role in the digestion of proteins, fats, and micronutrients. Pepsin, which digests proteins, is secreted as pepsinogen in response to acetylcholine and histamine in tandem with gastric acid. Dog gastric lipase, which digests fat, is secreted in response to pentagastrin, histamine, prostaglandin E_2, and secretin and parallels the secretion of gastric mucus. Although pepsin is active only at acid pH, dog gastric lipase remains active in the small intestine and constitutes up to 30% of total lipase secreted over a 3-hour period.[11] Although gastric lipase and pepsin are not essential for the assimilation of dietary fat and protein, the entry of peptides and fatty acids into the small intestine likely helps to coordinate gastric emptying and pancreatic secretion. Intrinsic factor, necessary for cobalamin (vitamin B_{12}) absorption, is produced by parietal cells and cells at the base of antral glands in the dog but not the cat.[1,12] The importance of gastric intrinsic factor secretion is questionable, as the pancreas is the major site of secretion in both dogs and cats. Gastric acidity may also have an effect on the availability of minerals such as iron and calcium.

Gastric Flora

The concept of gastric contents being sterile was altered when the gastric bacterium *Helicobacter pylori* was isolated from the stomach of people in 1983.[13] The stomach in dogs and cats also harbors a diverse spectrum of large, spiral, acid-tolerant *Helicobacter* species and a variety of aerobes and anaerobes that may play a role in development of gastritis or even cancer (see Chronic Gastritis). A mixed flora of aerobes and anaerobes (approximately 10^6 to 10^7 CFU/mL) is established soon after birth in dogs and colonization with *Helicobacter* spp., which are likely acquired from the dam, has been documented as early as 6 weeks of age.[14] *Helicobacter* spp. are adapted to life in an acid environment and produce urease that catalyzes the formation of ammonia from urea to buffer gastric acidity. Other bacterial species cultured from the canine stomach *(Proteus, Streptococcus, Lactobacillus)* may transiently increase after a meal or after coprophagia.[15] The application of contemporary molecular methods for identifying bacteria has demonstrated the majority of the sequences in healthy Beagle stomachs belong to Proteobacteria (99.6%) with only a few Firmicutes (0.3%). The Proteobacteria included the genus *Helicobacter* (98.6%) in gastric biopsies, consistent with previous *in situ* based analyses.[15-18] Acid secretion and gastric emptying likely regulate much of this transient flora, and bacteria may proliferate in the event of gastric acid hyposecretion due to glandular atrophy or pharmacologic inhibition. Pyrosequencing of 16S rRNA gene amplicons (V1-V3 region) revealed a decrease in *Helicobacter* spp. during omeprazole administration (median 92% of sequences during administration compared to >98% before and after administration; $P = 0.0336$), which was accompanied by higher proportions of Firmicutes and Fusobacteria. Fluorescence in situ hybridization (FISH) confirmed this decrease in gastric *Helicobacter* ($P < 0.0001$) and showed an increase in total bacteria in the duodenum ($P = 0.0033$) during omeprazole administration.[15] From a diagnostic standpoint, it is important to realize that bacteria such as *Escherichia coli* and *Proteus* spp. produce urease that can lead to a false positive test result for *Helicobacter* spp.

Clinical Evaluation of Diseases of the Stomach

Overview

Gastric disease is usually the result of inflammation, ulceration, neoplasia, or obstruction. It manifests clinically as vomiting (see ch. 39), hematemesis, melena (see ch. 41), retching, burping, hypersalivation, abdominal distension (see ch. 17), abdominal pain, or weight loss (see ch. 19). The clinical approach can be simplified by considering gastric diseases as a group of clinical syndromes based on the combination of etiology, pathology, and clinical presentation (Table 275-1). Because a large and varied group of nongastric disorders can cause similar clinical signs, a systematic approach is essential to determine whether primary gastric disease is the cause. The diagnostic approach initially focuses on historical and physical findings, with clinicopathologic testing and diagnostic imaging employed in patients with systemic involvement or chronic signs (Figure 275-4).

TABLE 275-1

Diseases of the Stomach

CLINICAL SYNDROME	PREDOMINANT FEATURES
Acute gastritis	Sudden onset of vomiting
Ulceration or erosion	Vomiting, hematemesis, melena, ± anemia
Gastric dilatation/volvulus	Nonproductive retching, abdominal distension, tachycardia
Chronic gastritis	Chronic vomiting of food or bile
Delayed gastric emptying	Acute to chronic vomiting more than 8-10 hours after feeding
Neoplasia	Chronic vomiting, weight loss, ± anemia

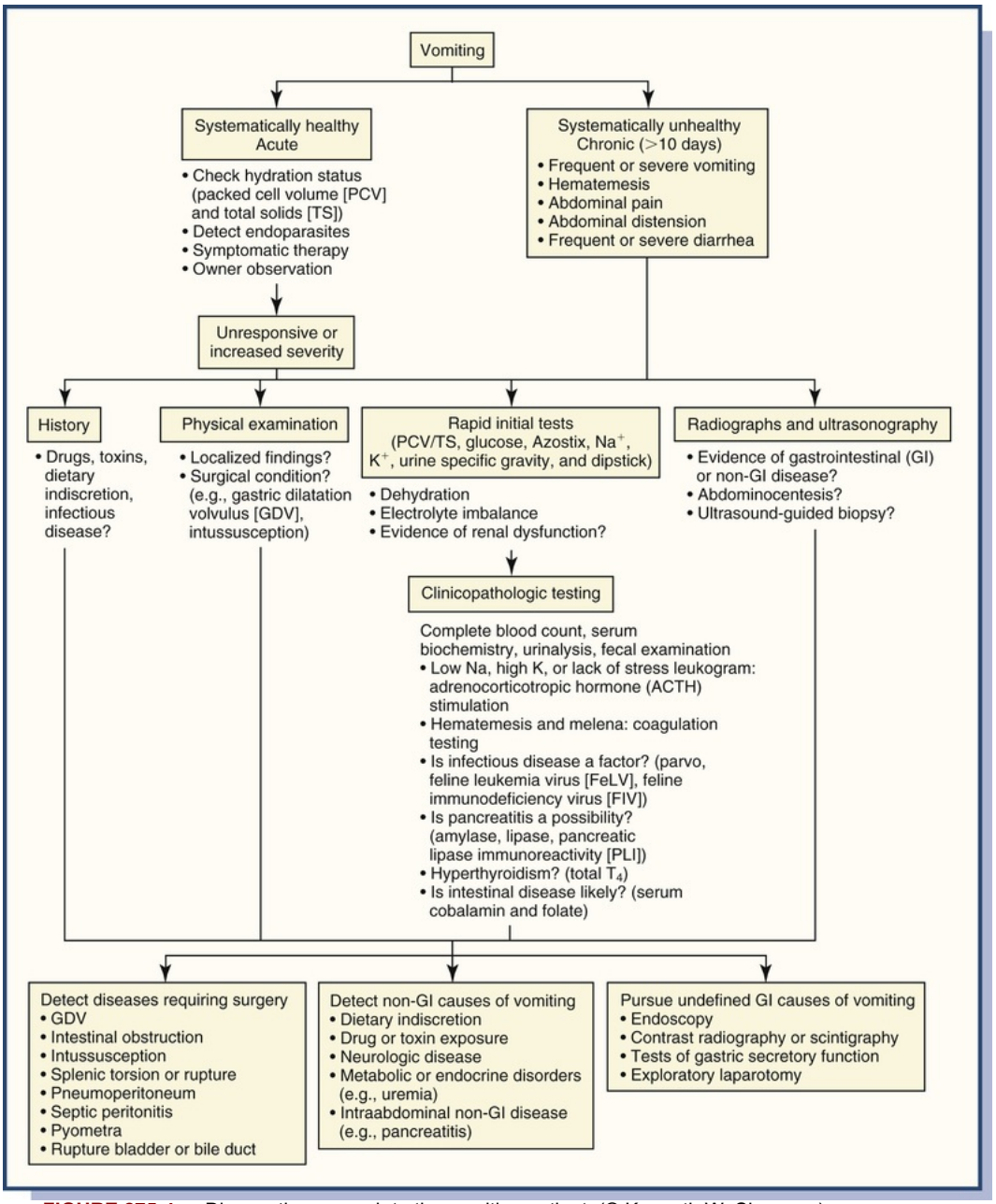

FIGURE 275-4 Diagnostic approach to the vomiting patient. (© Kenneth W. Simpson.)

Signalment, History, and Physical Examination

Age and breed can be helpful in diagnosis of certain gastric disorders. Young dogs are more likely to ingest foreign bodies or to suffer from outflow obstruction caused by *Pythium insidiosum*, whereas gastric cancer is typically encountered in much older dogs and cats. Gastric dilatation and volvulus are typically encountered in giant breeds and dogs with deep chests, such as Great Danes and Irish Setters. There are also breed predispositions to hypertrophic gastropathy (Drentse Patrijshond, Basenji, Shih Tzu), atrophic gastritis (Lundehund), and gastric cancer (e.g., Belgian Shepherd, Rough Collie, Staffordshire Bull Terrier, Beagle, Lundehund). Vomiting is the principal clinical sign of gastric disease (see Table 275-1) and a major objective of the history is to distinguish vomiting from regurgitation (active abdominal effort, presence of bile; see ch. 39). One should attempt to obtain information regarding duration, frequency, contents, color, progression, and relation to eating. Where vomiting cannot be adequately distinguished from regurgitation, it is important to observe episodes. One should request that the owner video episodes at home. Where regurgitation remains a possibility, a video will help. Also, thoracic radiographs can be used to detect esophageal dilatation or

obstruction.

A thorough review of the environment, including whether the animal lives indoors or outdoors, in a single or multi-animal household, with access to foreign bodies, toxins or medications, the vaccination status, body systems (attitude, mentation, presence of polyuria, polydipsia, weight loss, diarrhea, coughing, sneezing, exercise tolerance), past medical history, and physical examination all help to discriminate nongastric from gastric causes of vomiting. Physical examination is often unremarkable in pets with primary gastric disease. Abdominal distension may be detected in animals with gastric dilatation/gastric dilatation and volvulus (GD/GDV) or delayed gastric emptying. Abnormal perfusion, hydration status, temperature, respiratory rate, mucosal pallor, and abdominal pain often accompany diseases such as GD/GDV, gastric outflow obstruction, ulceration, and perforation. Historical and physical findings are integrated to determine whether the patient is systemically well or unwell, and clinical signs may be acute, chronic, mild, or severe (see Figure 275-4).

Non-productive vomiting, retching, and abdominal distension in deep-chested, large-breed dogs are frequently associated with GD/GDV, which requires rapid diagnosis and treatment (see ch. 143 and 144). The presence of fresh or digested blood ("coffee grounds") in vomitus, with or without melena, raises the possibility of gastric ulcers or erosions. Vomiting of food >8-10 hours after ingestion suggests delayed gastric emptying, requiring discrimination of gastric outflow obstruction from defective gastric propulsion. Weight loss is infrequently associated with gastric disease but can accompany cancer, fungal infections, outflow obstruction, and gastropathies that are part of a more generalized disease process, such as Basenji and Lundehund gastroenteropathy. If vomiting is acute and the animal is systemically well, with no historical or physical "red flags," further diagnostic testing is often postponed in favor of symptomatic therapy. If the pet is systemically unwell or has significant historical or physical abnormalities, the emphasis is on efficiently identifying conditions that require surgical intervention, such as gastric dilatation and septic peritonitis, and ruling out nongastrointestinal causes of vomiting before proceeding to more specialized or invasive diagnostic procedures aimed at detecting primary gastric and intestinal disorders (see Figure 275-4).

Clinicopathologic Testing

Clinicopathologic testing helps to differentiate primary gastrointestinal (GI) disease from non-GI disease and to ascertain the metabolic consequences of GI disease (see ch. 39). Blood and urine samples should be obtained prior to treatment. In sick pets, rapid evaluation of microhematocrit (PCV), total solids (TS), blood glucose, blood urea nitrogen (BUN), urine specific gravity, glucose, ketones and protein, and plasma concentrations of sodium (Na) and potassium (K) help detect life-threatening diseases: e.g., renal failure (azotemia, isosthenuria; see ch. 322 and 324) and hypoadrenocorticism (see ch. 309), and to guide initial therapy pending more definitive testing.

Abnormalities in complete blood count (CBC) are infrequent with primary gastric disease. Hemoconcentration as a consequence of dehydration or shock frequently accompanies GDV, gastric perforation, or gastric obstruction. The combination of a hematocrit level greater than 55% and normal or decreased protein concentrations is encountered in dogs with hemorrhagic gastroenteritis, which has recently been associated with the proliferation of *Clostridium* spp. and the elaboration of a necrotizing toxin, netF (see ch. 276).[19,20] Anemia, RBC microcytosis, and thrombocytosis may be present in dogs with chronic gastric bleeding. Drentse Patrijshond dogs can have familial stomatocytosis-hypertrophic gastritis. Basophilic stippling of red cells suggests lead toxicosis. Biochemical abnormalities in primary gastric disease are usually restricted to alterations in electrolytes and acid-base balance, pre-renal increases in creatinine and BUN, and occasionally hypoproteinemia.

Vomiting of gastric and intestinal contents usually involves the loss of chloride (Cl), K, Na, and bicarbonate-containing fluid. Dehydration is variably accompanied by decreases in Na, K, and Cl.[21,22] Determination of acid-base status by assessing total CO_2 or venous blood gas analysis enables recognition of metabolic acidosis or alkalosis (see ch. 128). Metabolic acidosis is generally more common than metabolic alkalosis in dogs with GI disease.[21] Where the gastric outflow tract or proximal duodenum is obstructed, the loss of Cl may exceed that of bicarbonate, with decreases in Cl and K, and alkalosis.[21-23] The metabolic alkalosis is enhanced by retained HCO_3^- due to volume, K and Cl depletion.[24] The net effect is a preferential conservation of volume at the expense of the extracellular pH. The renal reabsorption of almost all filtered bicarbonate and the exchange of sodium for hydrogen in the distal tubule promote an acid urine pH despite an extracellular alkalemia ("paradoxical aciduria").[24,25] Metabolic alkalosis in patients with GI signs is not invariably associated with outflow obstruction and has been encountered in dogs with parvovirus enteritis and acute pancreatitis.[26] Diseases characterized by acid hypersecretion, such as gastrinoma, may also be

associated with metabolic alkalosis and aciduria. Basal gastric acid secretion in two dogs with gastrin-producing tumors (1.7 and 2.7 mmol/h/kg$^{0.75}$ HCl) was maximal in the unstimulated state.[21] In this situation, hypochloremia, hypokalemia, metabolic alkalosis, and dehydration are likely due to the hypersecretion of gastric acid and its loss in vomitus.[27] Venous blood gases and plasma osmolality are often determined in animals suspected of ethylene glycol ingestion, with the findings of metabolic acidosis and a high osmolal gap (calculated by subtracting calculated from measured osmolality) supportive of ingestion (see ch. 152).

Elevated BUN in the absence of elevated creatinine is consistent with gastric bleeding. Low albumin may be detected in Basenji or Lundehund dogs with protein-losing gastroenteropathy, dogs with pythiosis, and dogs or cats with gastric neoplasia. Increased globulin concentrations have been observed in Basenji gastroenteropathy, *Pythium* infection, and gastric plasmacytoma. Elevations in creatinine, urea, calcium (Ca), K, glucose, liver enzymes, bilirubin, cholesterol, triglycerides, and globulin and decreases in Na, Ca, urea, or albumin frequently herald non-GI causes of vomiting.

Urine should be evaluated for specific gravity, pH, glucose, casts, crystals, and bacteria. Thorough urinalysis is important; for example, white cell casts in the urine may be the only evidence that pyelonephritis is the cause of vomiting (see ch. 72). Coagulation testing is indicated in patients with melena or hematemesis to detect underlying coagulopathies and in those with acute abdomen to detect disseminated intravascular coagulopathy (DIC; see ch. 196). Infectious diseases associated with vomiting and diarrhea require fecal examination for diagnosing *Giardia,* endoparasites, *Salmonella* spp., *Campylobacter* spp., and parvovirus (ELISA) or serologic testing (feline leukemia virus [FeLV], feline immunodeficiency virus). Additional tests to confirm hypoadrenocorticism (ACTH stimulation), liver dysfunction (pre- and post-prandial bile acids), hyperthyroidism (T_4), pancreatitis (ultrasound and various tests [see ch. 289-291]), and intestinal disease (serum cobalamin and folate; see ch. 276). In dogs with GDV, assessing serum lactate (see ch. 70 and 144) at the time of admission and its response to therapy may help in determining prognosis and need for aggressive therapy.[28-30]

Imaging

Abdominal Radiography

Survey radiographs are the test of choice when initially evaluating gastric disease, vomiting, or abdominal pain. Radiographs provide information on gastric position and contents that may help to identify GD/GDV, foreign bodies, and gastric outflow obstruction. They also enable evaluating the size and shape of the liver, kidneys, and spleen as well as aiding in detection of intussusception, peritonitis, pneumoperitoneum, and changes suggestive of pancreatitis. Contrast radiographs may provide further information when survey radiographs are inconclusive. However, the combination of ultrasonography (US) and endoscopy is generally more effective for detecting obstructive, inflammatory, and neoplastic GI disorders than contrast radiographs. Use of contrast radiography is often limited to investigating delayed gastric emptying associated with defective propulsion or "functional" intestinal disorders.[31]

Abdominal Ultrasound (US), Contrast Studies, Fluoroscopy

US can be employed to evaluate gastric wall thickness, wall layering and gastric emptying (see ch. 88). US is less accurate than endoscopy for the detection of gastric neoplasia, particularly lymphoma, but it can increase suspicion of gastric lesions and facilitate detection of non-gastric lesions in pets with signs of GI disease.[32,33] When US and endoscopy are not available, distension of the stomach with air (negative contrast) may reveal gastric thickening, masses, or foreign bodies. Positive contrast with barium sulfate can provide further information and is also used to evaluate patency of the gastric outflow tract. The combination of fluoroscopy and positive contrast is helpful for evaluating pyloric patency and gastric emptying. In the absence of endoscopy and US, contrast radiography can be followed by surgical biopsy to achieve a definitive diagnosis.

Endoscopy

Endoscopy (see ch. 113) enables direct visualization and biopsy of the stomach and duodenum and is the best method for diagnosing primary gastric inflammation, ulceration, or neoplasia; removing small foreign bodies; and evaluating patients prior to quantification of gastric emptying. It does not provide good information on submucosal lesions or functional disorders. With mural thickening or gastric masses, endoscopic biopsies are often not deep enough to obtain target tissue and surgical biopsy is required. Recent advances in endoscopic

imaging such as confocal endomicroscopy and chromoendoscopy may help distinguish chronic inflammation from neoplasia.[34] Equipment, its care, techniques, and photographs of a wide range of GI lesions are presented in ch. 83 and 113.[35,36]

The requirement for general anesthesia frequently precludes use of upper GI endoscopy in unstable pets with signs of gastric disease (e.g., hematemesis). The advent of wireless capsule endoscopy has revolutionized non-invasive imaging of the human upper GI tract. Preliminary studies in dogs show it is useful for identifying mucosal lesions in the gastric fundus, pylorus, and small intestine associated with parasitism or gastrointestinal bleeding.[37-39]

Evaluation of Gastric Emptying

Procedures and tools used to evaluate gastric emptying include barium contrast (liquid or mixed with food), barium-impregnated polyspheres, nuclear scintigraphy, the ^{13}C-octanoate and ^{13}C-acetate breath tests, and wireless motility and endoscopy capsules.[37,40-44] Tests of gastric emptying are often used to confirm a suspicion of delayed gastric emptying in patients with normal or equivocal survey radiographs. They are also used where gastric outflow obstruction and obvious causes of defective propulsion have been ruled out prior to and after prokinetic drugs. The limitations and benefits of these approaches are discussed under Delayed Gastric Emptying and Motility Disorders.

Gastric Secretory Testing

Gastric secretory testing is primarily performed in patients with esophagitis, GI ulceration, mucosal hypertrophy, or copious amounts of gastric fluid when acid hypersecretion is suspected. In its simplest form, fasting gastric pH and serum gastrin are measured to determine whether acid hypersecretion is likely (see ch. 273). Anti-secretory therapy should be discontinued for 48 hours prior to testing. Renal and hepatic dysfunction must be ruled out, as either condition can cause increases in circulating gastrin concentrations. The broad range of fasting, unstimulated gastric pH in dogs and cats (pH 1 to 8) makes definitive statements regarding acid production difficult. However, the presence of a gastric pH of <3 with concurrent increases in serum gastrin concentrations rules out the possibility of achlorhydria or mast cell tumor and raises the possibility of gastrinoma.[27] Dogs with mast cell tumors and hyperhistaminemia-induced acid hypersecretion have low serum gastrin concentrations. Dogs with achlorhydria likely have increased gastrin concentrations but a gastric pH >3.[45] Measurement of serum gastrin concentrations after IV infusion of secretin or Ca is used to further investigate the possibility of exogenous gastrin production by pancreatic tumors (gastrinomas; Zollinger-Ellison syndrome; see ch. 310). Basenji dogs with gastroenteropathy and diarrhea have been reported to have enhanced gastrin release in response to secretin stimulation without evidence of gastrinoma.[46] Provocative testing of gastric acid secretion with pentagastrin or bombesin stimulation may be performed to detect achlorhydria in patients with atrophic gastritis, or elevated serum gastrin and gastric pH >3, to determine if achlorhydria is contributing. Pentagastrin-stimulated acid secretion in dogs reaches a peak of 28 mL/kg$^{0.75}$/h, 4.1 mmol HCl/kg$^{0.75}$/h, 0.34 mmol K^+/kg$^{0.75}$/h, and 0.09 Na^+ mmol/kg$^{0.75}$/h.[6] Sedation with oxymorphone and acepromazine is an alternative to anesthesia for secretion studies in dogs.[28] In cats, acid output (mean ± SD) in response to pentagastrin (8 mcg/kg/h) ranges from pH 0.9 to 1.1, with secretion rates (median values) of 1.2 mmol/15 min to 1.4 ± 0.5 mmol/15 min in conscious cats and 1.2 (0.6 to 2.7) mmol/kg$^{0.75}$/h in anesthetized cats.[47] The development of telemetric pH systems may facilitate the non-invasive evaluation of gastric pH in dogs suspected of hypo- and hyper-secretion of gastric acid.[48,49]

Acute Gastritis

Definitions

Acute gastritis is the term applied to the syndrome marked by vomiting of sudden onset presumed to be due to a gastric mucosal insult or inflammation (Box 275-1). In most pets the cause is inferred from the history, such as dietary indiscretion; the diagnosis is rarely confirmed by biopsy, and treatment is symptomatic and supportive (see ch. 39). Animals with acute gastritis associated with drug intoxication, foreign body ingestion, or metabolic disorders frequently have hematemesis, melena, concurrent diarrhea, or other signs of systemic illness, requiring a thorough diagnostic approach to determine the cause and provide optimal care. There is little evidence to support a role of viral infections (parvovirus, distemper, infectious canine hepatitis) in acute

gastritis.

Box 275-1

Causes of Acute Gastritis

Dietary indiscretion or intolerance (nonallergic and allergic)
Foreign bodies (bones, toys, hairballs)
Drugs and toxins (nonsteroidal anti-inflammatory drugs, corticosteroids, heavy metals, antibiotics, plants, cleaners, bleach)
Systemic disease (uremia, liver disease, hypoadrenocorticism)
Parasites (*Ollulanus, Physaloptera* spp.)
Bacteria (bacterial toxins, *Helicobacter*)
Viruses

Clinical Findings and Diagnosis

Vomiting of sudden onset is the principal clinical sign of acute gastritis. In some instances it is accompanied by hematemesis or melena and variable degrees of systemic illness. The history may reveal access to or ingestion of spoiled food, garbage, toxins, medications, or foreign bodies. Signs of toxicosis may be evident, such as jaundice and pallor with zinc ingestion, salivation or defecation with organophosphate toxicosis or mushroom ingestion, and salivation and oral ulceration with chemical ingestion. A diagnosis of acute gastritis is usually based on these clinical findings and response to symptomatic treatment. A specific diagnosis may be sought if the pet had access to foreign objects or toxins, is systemically unwell, or has hematemesis, melena, or vomiting that fails to respond to symptomatic therapy, or other signs of more serious disease. Laboratory testing in most animals with primary acute gastritis reflects mild dehydration and is often not performed in the absence of a suspicion of more serious disease. Abdominal radiographs can be taken to detect foreign objects or GI obstruction. Further diagnostics, such as ultrasonography and endoscopy, are rarely indicated; most animals with simple gastritis respond to symptomatic therapy.

Treatment

Fluid Therapy

Fluid given orally, in small amounts, little and often, can be given to pets who are vomiting, with the volume increasing as vomiting subsides. Giving SC isotonic balanced electrolyte solutions may be sufficient to correct mild fluid deficits (<5%) but is insufficient for moderate to severe dehydration. Pets requiring IV fluids (see ch. 129) should undergo a more extensive diagnostic evaluation.

Dietary Restriction and Modification

When vomiting is acute, oral intake is discontinued for at least 24 hours. Small amounts of a liquid diet can be offered despite vomiting to maintain GI barrier function and to determine whether vomiting has resolved. A homemade non-spicy, fat-restricted, bland diet (e.g., boiled chicken and rice, low-fat cottage cheese, and rice [1 : 3]) or a commercial fat-restricted, rice-based diet can then be introduced, giving little and often with a gradual transition made back to a normal diet over a week or so.

Protectants/Adsorbents

Bismuth subsalicylate, kaolin-pectin, activated charcoal and magnesium, and aluminum- and barium-containing products are often administered to pets with acute vomiting or diarrhea to bind bacteria and their toxins and to coat the GI mucosa. These agents are probably safer and more efficacious than antibiotics or motility modifiers in acute gastroenteritis. Bismuth subsalicylate (Pepto-Bismol 1 mL/5 kg PO q 8 h), bismuth subcitrate, kaolin-pectin (1 to 2 mL/kg PO q 8 h), and sucralfate (0.25 to 1 g PO q 8 h) are often employed. Acid-reducing drugs such as H2-receptor antagonists can be administered but are usually reserved for those with signs of gastric erosion or ulceration (melena, hematemesis) or persistent gastritis as described below. In general, antiemetics should not be given to pets with acute gastritis to avoid masking response to therapy. Patients who continue to vomit require further investigation.

Prognosis

The prognosis for uncomplicated acute gastritis is usually complete recovery.

Gastric Erosion and Ulceration

Definitions and Causes

Gastric erosions and ulcers are associated with a number of primary gastric and non-gastric disorders (Table 275-2). Clinical signs range in duration and severity, from acute to chronic and from mild to life threatening. The pathomechanisms underlying gastric damage can be broadly attributed to impairment of the GMB (defined above) through direct injury, interference with gastroprotective prostaglandins (PGE_2), mucous or bicarbonate, decreased blood flow, and hypersecretion of gastric acid. Perhaps the most predictable cause for gastric erosion and ulceration is use of a nonsteroidal anti-inflammatory drug (NSAID) or a glucocorticoid, either alone or in combination with intervertebral disc disease.[50] NSAIDs cause direct mucosal damage and may interfere with prostaglandin synthesis.[9] Flunixin meglumine, aspirin, and ibuprofen cause gastric erosions and ulcers in healthy dogs (Figure 275-5).[51] Giving anti-inflammatory agents is also considered a significant risk for gastric perforation in dogs and cats.[52,53] High doses of glucocorticoids alone, such as dexamethasone and methylprednisolone, have caused gastric erosions, but the mechanisms by which they induce damage are not clear.[60] Unlike NSAIDs, their effects are not ameliorated by PGE_2 analogs.[61]

TABLE 275-2

Association of Gastric Ulceration and Erosion with Specific Diseases

GASTRIC PROBLEM	RELATED DISEASES
Metabolic/Endocrine	Hypoadrenocorticism, uremia, liver disease, mastocytosis, DIC, hypergastrinemia and other APUDomas
Inflammatory	Gastritis
Neoplastic	Leiomyoma, adenocarcinoma, lymphoma
Drug-induced	Nonsteroidal and steroidal anti-inflammatories
Hypotension	Shock, sepsis
Idiopathic	Stress, spinal surgery, exercise-induced (sled dogs)

DIC, Disseminated intravascular coagulopathy.

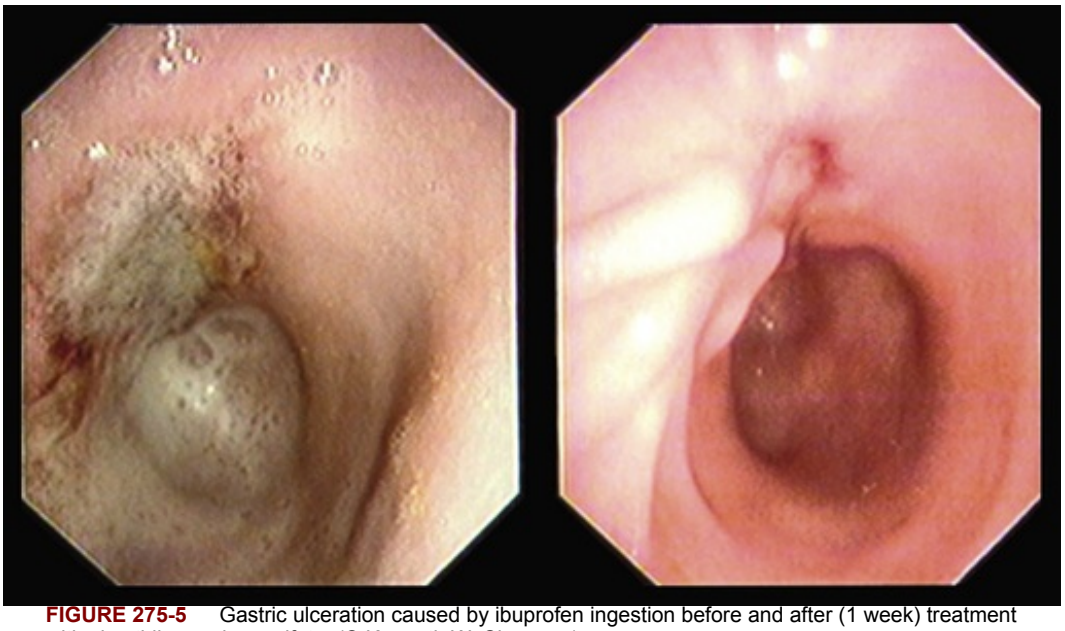

FIGURE 275-5 Gastric ulceration caused by ibuprofen ingestion before and after (1 week) treatment with cimetidine and sucralfate. (© Kenneth W. Simpson.)

To circumvent toxicosis caused by the inhibition of "friendly prostaglandins" (PGE_2), drugs that preferentially block "inducible" cyclooxygenase (COX-2) have been developed. These COX-2 selective agents (e.g., carprofen, meloxicam, deracoxib, etodolac) are less ulcerogenic in dogs.[54,55] However, even COX-2 selective drugs such as meloxicam and deracoxib are ulcerogenic, especially in combination with dexamethasone or other NSAIDs, have been associated with gastric perforation, and their safety in ill pets has not been determined.[51,56-59]

Hypersecretion of gastric acid in response to histamine release from mast cell tumors and gastrin from gastrinomas are clear causes of gastroduodenal ulceration and esophagitis in dogs and cats. Uremia, hepatic failure, hypoadrenocorticism, and hypotension are frequently proposed as risk factors for gastric erosion or ulceration, although few details have been published on pathogenesis, frequency, or severity of gastric damage in these conditions. In a recent study of dogs with chronic kidney disease (CKD), ulceration was present in only 1 of 28 dogs. The predominant findings in these dogs were mucosal edema, vasculopathy, and mineralization that correlated to the degree of azotemia and calcium phosphorus product.[62,63] Similar findings have also been observed in cats with CKD.[63] Sled dogs in the Iditarod race are prone to develop gastric erosions and ulcers (see ch. 173).[64,65] This finding is similar to exercising humans and horses in whom the pathogenesis is not understood but is responsive to acid suppression. Erosions and ulcers are also a sequela of gastric cancer and gastritis and are discussed in this chapter.

Clinical Findings

Vomiting, hematemesis, and melena may be present in patients with gastric erosions or ulcers. Pale mucous membranes, abdominal pain, weakness, inappetence, hypersalivation (potentially associated with esophagitis as a consequence of gastric acid hypersecretion; see ch. 273), and evidence of circulatory compromise are more variably present. Access to toxins and drugs, particularly NSAIDs, should be determined. Testing is directed at identifying current consequences and diseases associated with gastric erosions and ulcers (see Table 275-2). The CBC may reveal anemia that is initially regenerative but can progress to become microcytic, hypochromic, and minimally regenerative. When accompanied by thrombocytosis and decreased iron saturation or low serum ferritin, these findings are characteristic of chronic bleeding and iron deficiency (see ch. 57, 198, and 199). Eosinophilia and lack of a stress leukogram in dogs is consistent with hypoadrenocorticism, dietary allergy (see ch. 186), eosinophilic gastroenteritis, mastocytosis (see ch. 349), or a hypereosinophilic syndrome. A neutrophilic leukocytosis and a left shift may indicate inflammation or possible gastric perforation. Examination of a buffy coat smear may help to detect mastocytosis.

Biochemistry and urinalysis may reveal findings consistent with dehydration (azotemia and hypersthenuria), kidney disease (azotemia and isosthenuria), hepatic disease (increased liver enzymes or

bilirubin; decreased cholesterol, albumin, or BUN), or hypoadrenocorticism (i.e., hyponatremia and/or hyperkalemia). It will also identify electrolyte and acid-base abnormalities associated with vomiting and GI ulceration. The presence of a metabolic alkalosis, hypochloremia, hypokalemia, and acidic urine is consistent with upper GI obstruction (physical or functional) or a hypersecretory state. Testing should be performed to detect abnormalities in primary and secondary hemostasis that may be associated with GI bleeding. Serum gastrin and histamine concentrations can be evaluated where acid hypersecretion is suspected as a cause of ulceration.

Diagnosis

Diagnostic Imaging

Plain radiographs are not usually helpful in diagnosing gastric erosions or ulcers but may help rule out other causes of vomiting, such as foreign bodies, peritonitis, and gastric perforation. Contrast radiographs may reveal filling defects but do not allow detailed mucosal evaluation or sampling. Ultrasonography (see ch. 88) can be used to evaluate the gastric wall for thickening associated with ulcers or masses and also helps to rule out non-gastric causes of vomiting. The information provided by radiography and ultrasound is complementary to endoscopic evaluation, the diagnostic test of choice (Figure 275-6).

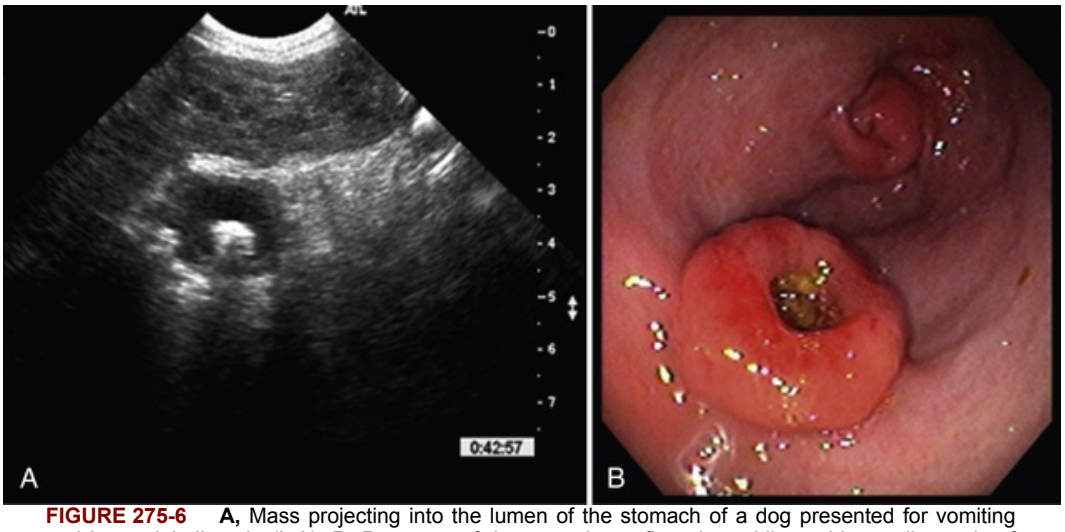

FIGURE 275-6 **A,** Mass projecting into the lumen of the stomach of a dog presented for vomiting and hyperglobulinemia (IgA). **B,** Presence of the mass is confirmed, enabling a biopsy diagnosis of gastric plasmacytoma. (© Kenneth W. Simpson.)

Endoscopy

Endoscopy allows direct evaluation of gastric mucosa and its sampling (see ch. 113). NSAID-associated ulcers tend to be found in the antrum and are not usually associated with marked mucosal thickening or irregular edges (see Figure 275-5). This contrasts with ulcerated tumors that frequently have thickened edges and surrounding mucosa (Figure 275-7). Ulcers should be biopsied at the periphery to avoid perforation. Endoscopically obtained biopsies are not ideal for diagnosing infiltrative gastric neoplasia, but several biopsies from the same site can be taken to enable sampling of deeper tissue. Endoscopic-guided fine needle aspirates that use a needle and tubing in the biopsy channel can also be used to sample deep lesions. Even with this approach, the diagnosis may be missed and surgical biopsy may be required for a definitive diagnosis.

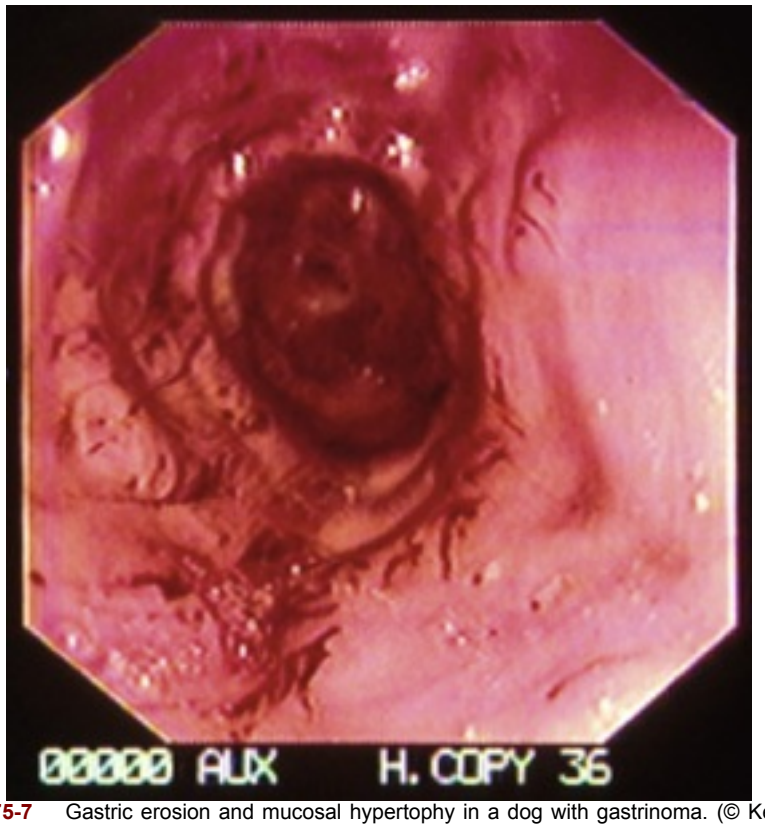

FIGURE 275-7 Gastric erosion and mucosal hypertophy in a dog with gastrinoma. (© Kenneth W. Simpson.)

pH and Serum Gastrin

The combination of mucosal erosion or ulceration, antral mucosal hypertrophy, copious gastric juice, and esophagitis is highly suggestive of gastric hypersecretion (see Figure 275-7). It is prudent to measure gastric pH and serum gastrin in pets with gastric erosion or ulceration not associated with drugs or gastric tumors. Dogs with mast cell tumors and hyperhistaminemia-induced acid hypersecretion have low serum gastrin concentrations.[27] Finding a combination of gastric pH <3 and increased serum gastrin concentrations should prompt further investigation for gastrinoma by secretin stimulation test, US (liver and pancreas), and pentertreotide scintigraphy.[27] The utility of capsule based pH monitoring and endoscopy in detecting gastric acid hypersecretion and associated mucosal abnormalities has not been determined in the clinical setting. The administration of omeprazole or famotidine (both at 1 mg/kg PO q 24 h) to control acid secretion can increase serum gastrin, from 37.2 ng/L to 71.3 ± 19 and 65.5 ± 39.52 ng/L, respectively, within 3 to 7 days.[66] Increased serum gastrin induced by short-term antacid therapy resolved after a 7 day withdrawal period.[66,67] Omeprazole (1.1 mg/kg PO q 12 h for 15 days) has been associated with dramatic increases in gastrin, from a median baseline of 10.0 ng/L (range: 10.0-27.0) to a maximum median of 379.5 ng/L (range: 49.9-566.0) at day 9 of treatment. Serum gastrin remained significantly increased above baseline values from day 6 to day 15 of the treatment, but declined to pre-treatment within three days of cessation.[67]

Treatment

Overview

Treatment of gastric erosions and ulcers is directed at the underlying cause. One should address abnormalities in hydration (see ch. 129), perfusion, electrolytes and/or acid-base (see ch. 128). Blood transfusion may be indicated (see ch. 130). Additional support of the GMB is via enhanced mucosal protection, cytoprotection and decreasing gastric acid secretion. Where vomiting is persistent, antiemetics (see ch. 39) may help to reduce fluid loss, discomfort, and the risk of esophagitis (see ch. 273).

Fluid Therapy

The rate of fluid administration (see ch. 129) depends on the presence or absence of shock (see ch. 127), the degree of dehydration, and the presence of diseases (e.g., cardiac or renal), which predispose to volume overload. Patients with a history of vomiting who are mildly dehydrated are usually responsive to crystalloids (e.g., LRS or 0.9% NaCl) at a rate that will provide maintenance requirements as well as replace deficits and ongoing losses. Potassium depletion is often a consequence of prolonged vomiting or anorexia, and most polyionic replacement fluids contain only small amounts. Therefore KCl is added to parenteral fluids on the basis of serum levels. Central venous pressure monitoring (see ch. 76) and evaluation of urine output (see ch. 322) are necessary in patients with severe GI disease, particularly those complicated by third-space losses of fluid into the gut or peritoneum. Patients in shock require more aggressive support (see ch. 127, 129, and 144).

Reducing Acid Secretion

Pharmacologic inhibition of acid secretion (see Figure 275-3) can be effected by blocking H2 (cimetidine, ranitidine, famotidine), gastrin (proglumide), and acetylcholine (atropine, pirenzipine) receptors and by inhibiting adenyl cyclase (PGE analogs) and H^+/K^+-ATPase (e.g., omeprazole).[68] Long-acting somatostatin analogs, such as octreotide, directly decrease the secretion of gastrin and gastric acid. Decreasing gastric acid secretion with an H2-receptor antagonist has been shown to promote mucosal healing in dogs with a variety of experimentally induced ulcers and erosions (see Figure 275-5). Famotidine is attractive, as it does not inhibit P450 enzymes and can be given once daily. The additional prokinetic activity of ranitidine or nizatidine (mediated by anticholinesterase activity) may make them good choices in cases of delayed gastric emptying associated with defective propulsion.[40] In patients with severe or persistent gastric ulceration refractory to H2 antagonists, more complete inhibition of gastric acid secretion can be achieved with an H^+/K^+-ATPase inhibitor, such as omeprazole (1 mg/kg PO q 24 h [dogs]). Omeprazole is the initial drug of choice in patients with acid hypersecretion secondary to mast cell tumors and gastrinoma (Zollinger-Ellison syndrome). Omeprazole has been shown to have few long-term side effects in dogs (0.7-1 mg/kg PO q 24 h), but it should be used with caution in pets with liver disease and must be reviewed for interactions with drugs such as cisapride. At higher dosages (1.1 mg/kg PO q 12 h) omeprazole has been associated with significant hypergastrinemia and gastric dysbiosis.[67] Sled dogs given omeprazole for exercise-associated gastric hemorrhage had significantly reduced gastric severity scores as compared to placebo. However, the drug caused an increased frequency of diarrhea (omeprazole 54%, placebo 21%).[64] Further investigation is needed on the role of this drug for athletes with gastric ulcers.[64] The combination of omeprazole and the long-acting somatostatin analog octreotide effectively reduced vomiting in a dog with gastrinoma (octreotide 2 to 20 mcg/kg SC q 8 h).[69] Octreotide can also be employed to rapidly decrease gastric acid secretion in pets discovered to have large ulcers at endoscopy, and it has been used to control gastric bleeding in people. Sustained release octreotide acetate (5 mg/IM q 4 weeks) transiently suppressed gastrin secretion in a Shiba Inu with gastrinoma.[70]

Providing Mucosal Protection

The PGE_2 analog misoprostol protects against NSAID-induced gastric erosions in dogs at dosages that do not inhibit acid secretion (3 to 5 mcg/kg PO q 8 h) and may be given to dogs receiving chronic NSAIDs for arthritis.[71,72] The main side effect of misoprostol is diarrhea, and it should not be given to pregnant animals. The mucosal protectant polyaluminum sucrose sulfate (sucralfate) binds to areas denuded of mucosal epithelium, regardless of the underlying cause, and is useful for treating gastric erosions, ulcers, and esophagitis. Sucralfate can be given to patients receiving injectable antacids, but it may compromise absorption of other oral medications and is probably best separated from these by several hours. In contrast to the efficacy of misoprostol and H2 antagonists in preventing NSAID-induced erosions, the prophylactic administration of various combinations of misoprostol, cimetidine, and omeprazole have not been shown to prevent gastric erosions in dogs, with or without intervertebral disc disease, receiving high-dose glucocorticoids.[60,73,74] However, these drugs may speed healing of their gastric lesions. Sucralfate is probably the drug of choice for treating GI ulceration in pets receiving high dosages of glucocorticoids, because it is effective regardless of whether or not acid is causing or delaying healing.

Mast cell tumors (see ch. 349) are also worth considering separately, as gastric ulceration is a frequent and severe complication. Mast cell tumors are thought to cause vomiting via the central effects of histamine on the chemoreceptor trigger zone (CRTZ) and the peripheral effects of histamine on gastric acid secretion, with resultant hyperacidity and ulceration. Treatment of mastocytosis with H1 and H2 histamine antagonists (e.g.,

diphenhydramine and famotidine) should reduce the central and peripheral effects of histamine. Corticosteroids are used to decrease tumor burden. Where acid hypersecretion is present or is suspected, it is likely best managed with proton-pump inhibitors (e.g., omeprazole 1 mg/kg PO q 24 h). Somatostatin analogs may also be useful for controlling refractory gastric acid hypersecretion (e.g., octreotide 2 to 20 mcg/kg SC q 8 h, or octreotide acetate 0.5 mg/kg q 4 weeks).[27,70]

Antiemetics

Antiemetics (see ch. 39) can be used when vomiting is severe and compromising fluid and/or electrolyte balance or causing discomfort.[68] Antiemetics commonly used in dogs include metoclopramide, which antagonizes D_2-dopaminergic and $5HT_3$-serotonergic receptors and has cholinergic effects on smooth muscle (1 mg/kg/24 h CRI IV); phenothiazine derivatives, such as chlorpromazine and prochlorperazine, which are antagonists of $alpha_1$- and $alpha_2$-adrenergic, H1 and H2-histaminergic, and D_2-dopaminergic receptors in the vomiting center and CRTZ; ondansetron (0.5 mg/kg IV), which antagonizes peripheral $5HT_3$ receptors; and maropitant (1 mg/kg IV q 24 h, or 2 mg/kg PO q 24 h, not more than 5 days), which antagonizes neurokinin-1 receptors. Comparing these antiemetics indicates greater efficacy of maropitant and ondansetron for controlling peripheral vomiting induced by ipecac than metoclopramide or chlorpromazine and similar efficacy of maropitant, chlorpromazine, and metoclopramide for controlling centrally mediated vomiting induced by apomorphine.[75] Maropitant has been associated with histologic evidence of bone marrow hypoplasia in puppies and should not be used in dogs <8 weeks or cats <16 weeks of age. Maropitant at 1 mg/kg was effective in preventing xylazine and motion-induced emesis in cats and reduced vomiting (1.1 mg/kg PO daily for 2 weeks) in cats with chronic kidney disease.[76,77] Nonselective cholinergic receptor antagonists such as atropine, scopolamine, aminopentamide, and isopropamide are generally avoided, as they may cause ileus, delayed gastric emptying, and dry mouth.

Antibiotics and Analgesia

Prophylactic antibiotic cover (e.g., cephalosporins, ampicillin) may be warranted for animals in shock with major GI barrier dysfunction. Leukopenia, neutrophilia, fever, and bloody stools are additional indications for prophylactic antibiotics in animals with vomiting or diarrhea. Initial choices in these situations include ampicillin or a cephalosporin (effective against Gram-positive and some Gram-negative and anaerobic bacteria), which can be combined with an aminoglycoside (effective against Gram-negative aerobes) when sepsis is present and hydration status is adequate (see ch. 161). Enrofloxacin is a suitable alternative to an aminoglycoside in skeletally mature patients at risk of nephrotoxicosis from an aminoglycoside. Analgesia can be provided using opioids like buprenorphine (0.0075 to 0.01 mg/kg, IM). Recent studies indicate that the anti-emetic maropitant has analgesic properties during laparoscopic visceral stimulation, but the analagesic effects in other situations remains to be determined.[78] Surgery may be required when the cause of ulceration is unclear or to resect large, non-healing ulcers or those about to perforate. Pyloric perforation has been associated with NSAIDs and mortality rates (about 64%) are similar to perforation at other sites in the GI tract.[52]

Gastric Dilatation and Volvulus

Definitions and Pathogenesis

Gastric dilatation (GD) and gastric dilatation and volvulus (GDV) are characterized by the stomach being dramatically distended with air (see ch. 143 and 144). With volvulus, the stomach twists about its axis, moving dorsally and left of the fundus. Both GD and GDV cause caudal caval obstruction and impair venous return to the heart, resulting in hypovolemic shock that can be exacerbated by devitalization of the gastric wall, splenic torsion or avulsion, congestion of the abdominal viscera, endotoxic shock, and DIC.

No single cause of GD or GDV has been identified. Large-breed dogs with deep chests—such as Akita, Bloodhound, Collie, Great Dane, Irish Setter, Irish Wolfhound, Newfoundland, Rottweiler, Saint Bernard, Standard Poodle, and Weimaraner—are at greater risk. Cumulative incidence of GDV has been estimated at 6% for large-breed and giant-breed dogs. The lifetime risk is influenced by breed, ranging from 3.9% for Rottweilers to 39% in Great Danes.[79] In large-and giant-breed dogs, factors significantly associated with an increased risk of GDV include increasing age, having a first-degree relative with a history of GDV, eating fast, once-daily feeding, a raised feeding bowl, and aerophagia.[80,81] The personality of the dog may also have an

impact, as happier dogs have a decreased incidence.[48] Prior splenectomy does not appear to increase the risk for GDV.[82] Analysis of gastric gas in GD/GDV has been interpreted to support aerophagia as the cause of distension, with dilatation explained by an inability to eructate or empty air into the intestines.[83] However, a recent study found CO_2 composition ranged from 13 to 20%, with one dog having an H2 concentration of 29%.[84] Because the CO_2 content of atmospheric air is less than 1%, these findings suggest that the gaseous gastric distention in GDV is not the result of aerophagia.[84] Likely sources of gas include bacterial fermentation of diet but the specific dietary and microbial factors remain to be determined.[84] Studies in dogs with GDV recovering from gastropexy suggest that abnormal electrical activity and gastric emptying may also be related to the development of GD.[85] The interrelationship of volvulus and gastric distension is unclear, although the length of the hepatogastric ligament may facilitate torsion.

Diagnostic Features

A history of nonproductive retching, salivation, abdominal distention, weakness, or collapse raises the possibility of gastric dilatation or volvulus, particularly in large-breed and deep-chested dogs. Physical findings usually include abdominal distension and tympany, tachycardia, and mucosal pallor. Hypothermia, depression, and coma may be seen when shock is severe. Cardiac arrhythmias, such as ventricular premature beats or ventricular tachycardia, may be detected on the initial examination or may develop up to 72 hours after presentation (see ch. 127 and 144). Radiography is usually performed after fluid support and decompression and helps to distinguish simple dilatation from dilatation and volvulus. Right and left lateral recumbent views are usually required. Dilatation is associated with gas distension, and on a right lateral position, air is present in the fundus (Figure 275-8). With volvulus the pylorus moves dorsally and left, and the stomach is compartmentalized. On a right lateral radiograph, the fundus is viewed as a large ventral compartment with the smaller, gas-filled pylorus located dorsally and separated from the fundus by a band of soft tissue, forming the "Popeye's arm" sign (Figure 275-9). Loss of abdominal contrast may indicate gastric rupture or bleeding from avulsed splenic vessels, whereas increased contrast due to pneumoperitoneum suggests gastric rupture.

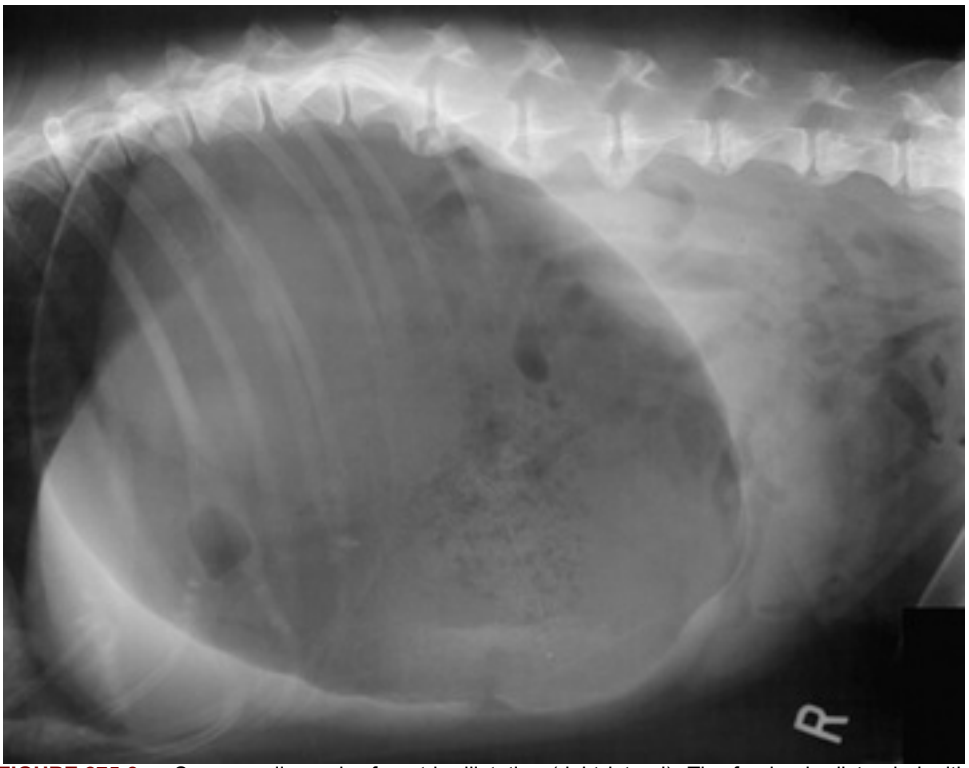

FIGURE 275-8 Survey radiograph of gastric dilatation (right lateral). The fundus is distended with air. (© Kenneth W. Simpson.)

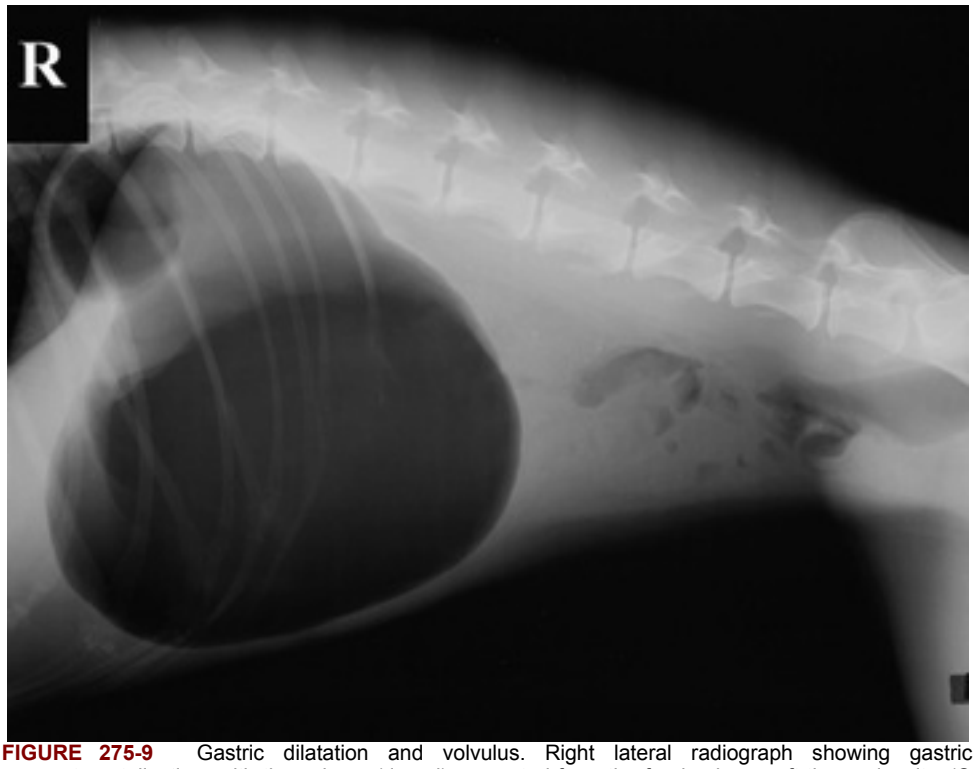

FIGURE 275-9 Gastric dilatation and volvulus. Right lateral radiograph showing gastric compartmentalization, with the pylorus (dorsal) separated from the fundus by a soft tissue density. (© Kenneth W. Simpson.)

Clinicopathologic Findings

Hematologic changes are often restricted to an increase in hematocrit. A variety of acid-base and electrolyte disturbances has been observed in dogs with GDV (see ch. 128).[86,87] Metabolic acidosis and hypokalemia were the most common abnormalities in one study and occurred in 15 and 16 of 57 dogs, respectively.[86] Metabolic acidosis is likely due to tissue hypoperfusion, anaerobic metabolism, and the accumulation of lactic acid (see ch. 70).[86] Metabolic alkalosis may also occur and may be related to the sequestration of gastric acid or vomiting.[86] Measurement of plasma lactate at the time of admission and its response to therapy (>43-50% decrease within 12 h is a good finding) may help in determining the presence of gastric necrosis, prognosis and need for aggressive therapy.[28-30] Respiratory acidosis and alkalosis have been variably observed and reflect hypoventilation or hyperventilation, respectively. The variable nature of acid-base and electrolyte abnormalities in dogs with GDV indicates that fluid therapy should be individualized on the basis of blood gas and electrolyte measurements. Monitoring and correction of acid-base abnormalities are important, because they may predispose to cardiac arrhythmias and muscle weakness. Coagulation abnormalities are usually consistent with DIC (thrombocytopenia, increased D-dimer or FDPs, reduced ATIII, prolongation of the APTT; see ch. 196).

Treatment

Fluids (see ch. 127) and gastric decompression (see ch. 112) are most important.

Fluid Support

Fluid therapy has traditionally consisted of shock doses of LRS (60 to 90 mL/kg/h) given via large-bore catheters into the cephalic or jugular veins (see ch. 127 and 129). Experimental studies comparing crystalloids (60 mL/kg, followed by 0.9% NaCl 20 mL/kg/h) with hypertonic saline (7% NaCl in 6% dextran, 5 mL/kg, followed by 0.9% NaCl 20 mL/kg/h) in dogs with GDV-induced shock indicate that hypertonic saline maintains better myocardial performance, higher heart rate, and lower systemic vascular resistance.[88] The resuscitative dose of hypertonic saline was delivered in 5 to 10 minutes versus an hour for crystalloids. Fluid

therapy should be aggressively monitored by frequent measurement of blood pressure, heart rate, PCV, and total solids and urine output. Potassium and bicarbonate are best administered on the basis of blood gas and electrolyte measurements. Hypokalemia is common after fluid therapy, and 30 to 40 mEq KCl/L should be added to fluids after the initial shock dose, while ensuring that the maximum KCl infusion rate of 0.5 mEq/kg/h is not exceeded (see ch. 324).

Gastric Decompression

Decompression can be performed by orogastric intubation with a well-lubricated stomach tube (see ch. 112), or a 16-g catheter can be used to trocarize the stomach (see ch. 144). Oral decompression can also be performed after trocarization. Decompression should be maintained until surgery. Sedation with butorphanol (0.5 mg/kg IV) or oxymorphone (0.1 mg/kg IV) and diazepam (0.1 mg/kg slow IV) may be necessary to pass a stomach tube.

Adjunct Therapy for Endotoxic Shock and Reperfusion Injury

Adjunct therapy frequently includes prednisolone sodium succinate (10 mg/kg IV) or dexamethasone sodium phosphate for shock and broad-spectrum antibiotics, such as a cephalosporin in combination with a fluroquinolone, to circumvent bacterial translocation and endotoxemia (see ch. 127). Some clinicians advocate flunixin meglumine for endotoxic shock, but the author does not. The administration of agents to decrease lipid peroxidation (U70046F) and chelate iron (desferroxamine) has decreased mortality attributed to reperfusion injury in dogs with experimental GDV.[89,90] These agents are best given before reperfusion occurs, that is, prior to untwisting a torsion.

Cardiac Arrhythmias

Cardiac arrhythmias (e.g., ventricular premature complexes, ventricular tachycardia) are relatively frequent (about 40% of dogs) and may or may not contribute to mortality.[91-94] Arrhythmias can develop up to 72 hours after presentation and are considered a consequence of electrolyte, acid-base, and hemostatic abnormalities, as well as reperfusion injury (see ch. 141 and 248). Arrhythmias should be treated if associated with weakness, syncope, or heart rates >150 beats per minute. Arrhythmias are managed by correcting underlying acid-base, electrolyte, and hemostatic disturbances and administering lidocaine either as a bolus (1 to 2 mg/kg IV) or continuously (up to 50 to 75 mcg/kg/min) and procainamide (10 mg/kg IM q 6 h and then orally if effective) when arrhythmias are persistent (see ch. 141 and 248). It is important that plasma concentrations of K^+ and Mg^{2+} be normalized to enable effective antiarrhythmic therapy. It has been reported that dogs with GDV treated at presentation with lidocaine (2 mg/kg, IV bolus) followed by constant rate infusion (CRI) of 0.05 mg/kg/min IV for 24 h had decreased frequency of arrhythmias, acute kidney injury, and duration of hospitalization.[95]

Surgery

The aims of surgery are to reposition the stomach and spleen and to perform a gastropexy to enable short-term decompression and prevent recurrence. Surgery can be complicated by gastric necrosis, which requires partial gastrectomy, and avulsion or torsion of the spleen, which may require resection or removal.

Prognosis

Mortality rates for dogs with GDV is about 10-15%.[93,94] Dogs with gastric necrosis, gastric resection, splenectomy, pre- or post-operative cardiac arrhythmias, and longer times from presentation until surgery have a higher mortality rate, reaching >30% in some studies.[7,91,93,94] Measurement of plasma lactate at admission (>6 to 9 mmol/L; see ch. 70) and its response to therapy (>43-50% decrease within 12 h is considered a good sign) may help in determining the presence of gastric necrosis, prognosis and need for aggressive therapy (see ch. 127 and 144).[28-30]

Prophylaxis

The recurrence rate of GD/GDV has been estimated at 11% over 3 years in one study, with median survival of 547 days for dogs that had a gastropexy versus 188 days for dogs without.[58] Prophylactic gastropexy in Great Danes, Irish Setters, Rottweilers, Standard Poodles, and Weimaraners reduced mortality from as little as 2.2-

fold in Rottweilers to as much as 29.6-fold in Great Danes.[79] Two recent studies evaluating the effect of prophylactic incisional gastropexy found it completely prevented GDV, with GD reported in 5-11% of 101 cases.[96,97]

Chronic Gastritis

Prevalence and Definitions

Gastritis is common in dogs, with 35% of dogs investigated for chronic vomiting and 26% to 48% of asymptomatic dogs affected.[98,99] The prevalence in cats has not been determined. Diagnosis of chronic gastritis is based on histologic examination of gastric biopsies and is usually sub-classified according to histopathological changes and etiology.

Histopathologic Features of Gastritis

Gastritis in dogs and cats is usually classified according to the nature of the predominant cellular infiltrate (eosinophilic, lymphocytic, plasmacytic, granulomatous, lymphoid follicular), the presence of architectural abnormalities (atrophy, hypertrophy, fibrosis, edema, ulceration, metaplasia), and their subjective severity (mild, moderate, severe). A standardized visual grading scheme has been proposed by Happonen and colleagues and has been adapted for pathologists (Figure 275-10).[99,100] The most common form of gastritis in dogs and cats is mild to moderate superficial lymphoplasmacytic gastritis with concomitant lymphoid follicle hyperplasia (Figure 275-11).[101] Eosinophilic, granulomatous, atrophic, and hyperplastic gastritis are less common.

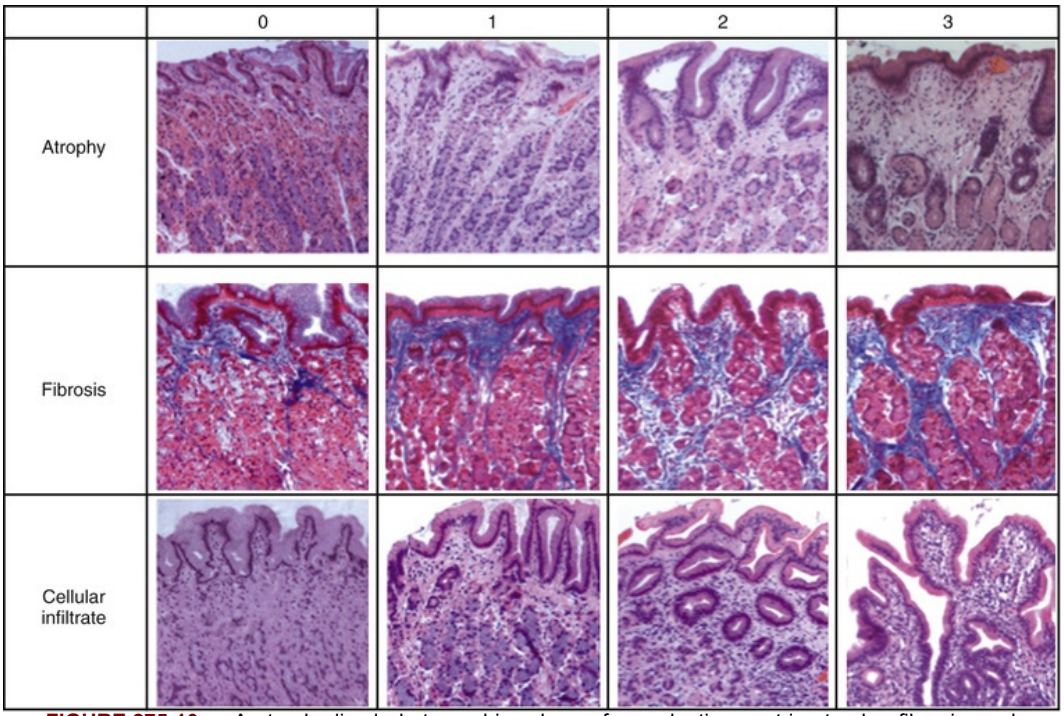

FIGURE 275-10 A standardized photographic scheme for evaluating gastric atrophy, fibrosis, and cellular infiltrates in dogs. (From Wiinberg B, Spohr A, Dietz HH, et al: Quantitative analysis of inflammatory and immune responses in dogs with gastritis and their relationship to *Helicobacter* spp. infection. *J Vet Intern Med* 19[1]:4-14, 2005.)

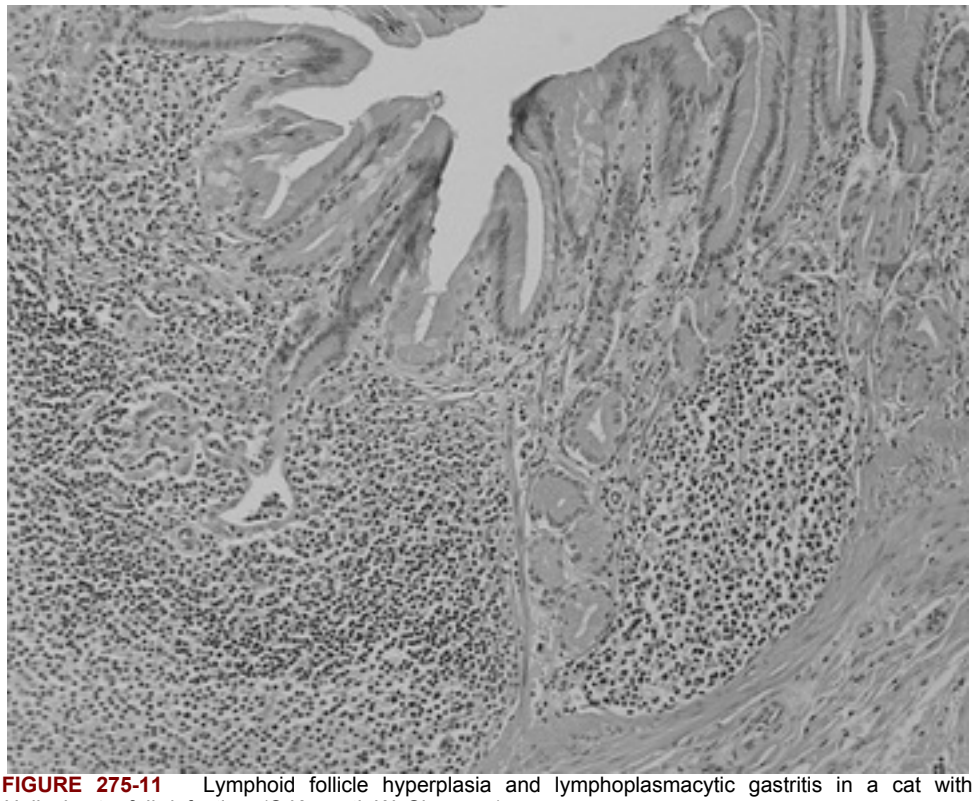

FIGURE 275-11 Lymphoid follicle hyperplasia and lymphoplasmacytic gastritis in a cat with *Helicobacter felis* infection. (© Kenneth W. Simpson.)

Etiology

Overview of the Inflammatory Condition

Despite the high prevalence of gastritis, an underlying cause is rarely identified. In the absence of systemic disease, ulcerogenic or irritant drugs, gastric foreign objects, parasites (*Physaloptera* and *Ollulanus* spp.), and in rare instances fungal infections (*Pythium insidiosum, Histoplasma* spp.), gastritis is usually attributed to dietary allergy or intolerance, occult parasitism, a reaction to bacterial antigens, or unknown pathogens. Treatment is often empirical but can serve to define the cause of gastritis, such as diet responsive (see ch. 178), antibiotic responsive, steroid responsive, or parasitic.

Although the basis of the immunologic response in canine and feline gastritis is unknown, recent studies in experimental animals have shed light on the immunologic environment in the GI tract to reveal a complex interplay between GI microflora, the epithelium, immune effector cells (e.g., lymphocytes and macrophages), and soluble mediators (e.g., chemokines and cytokines).[100,102] In health, this system avoids active inflammation by antigen exclusion and induced immune tolerance. The development of intestinal inflammation in mice lacking the cytokines interleukin (IL)-10, transforming growth factor-beta (TGF-beta), or IL-2 indicates their central importance in damping down mucosal inflammation. In murine models, GI inflammation only develops in the presence of indigenous intestinal microflora, leading to the hypothesis that spontaneous mucosal inflammation may be the result of a loss of tolerance to indigenous GI microflora. The role of these mechanisms in outbred species, such as the dog and cat, remains to be determined, but clearly loss of tolerance to bacterial or dietary antigens should be considered.

The role of epithelial cells in the inflammatory response is being elucidated, with gram-negative or pathogenic bacteria inducing proinflammatory cytokine (e.g., IL-8, IL-1-beta) secretion from epithelial cells, whereas commensal or bacteria such as *Streptococcus faecium* or *Lactobacillus* spp. induce the production of the immunomodulatory cytokines TGF-beta or IL-10.[63] The proinflammatory cytokines produced by epithelial cells are modulated by the production of IL-10 from macrophages and potentially by the epithelial cells themselves.[103] In this context, dogs with lymphoplasmacytic gastritis of undetermined etiology showed a correlation between the expression of the immunomodulatory cytokine IL-10 and proinflammatory cytokines (IFN-alpha, IL-1-beta, IL-8).[16] Simultaneous expression of IL-10 and IFN-alpha mRNA has also been observed

in the intestines of Beagles, in the lamina propria cells and the intestinal epithelium, despite luminal bacterial flora that were more numerous than in control dogs.[104] Thus it is tempting to visualize a "homeostatic loop" consisting of proinflammatory stimuli and responses countered by immunomodulation and repair, with an imbalance in either of these arms manifested as gastritis.

Role of Pathogens

The importance of unknown pathogens in development of inflammation in the mucosa is best demonstrated by the gastric *H. pylori,* a Gram-negative bacterium that chronically infects more than half of all people worldwide.[13] This infection is characterized by infiltration of polymorphonuclear and mononuclear cells and upregulation of proinflammatory cytokines and the chemokine IL-8. Mucosal T cells in infected individuals are polarized toward production of interferon-gamma (IFN-gamma), rather than IL-4 or IL-5, indicating a strong bias toward a Th1 type response.[105,106] Sustained gastric inflammatory and immune responses to infection appears to be pivotal for the development of peptic ulcers and gastric cancer in people.

Helicobacter Prevalence

There is a high prevalence of gastric *Helicobacter* spp. infection in 67% to 100% of healthy pet dogs, 74% to 90% of vomiting dogs, 100% of laboratory Beagles and 40% to 100% of healthy and sick cats.[107-109] Dogs and cats are colonized by a variety of large spiral organisms (5 to 12 microns; Figure 275-12). In cats from Switzerland, the United States, and Germany, *H. heilmannii* is the predominant species, with *H. bizzozeronii* and *H. felis* being much less frequent. Cats can also be colonized by *H. pylori* (2 to 5 microns), but infection has been limited to a closed colony of laboratory cats.[110] In dogs from Finland, Switzerland, the United States, and Denmark, *H. bizzozeronii* and *H. salomonis* are most common, followed by *H. heilmannii* and *H. felis; H. bilis* and *Flexispira rappini* have also been described. These gastric *Helicobacter* spp. are distinct from enterohepatic *Helicobacter* spp. that colonize the distal small intestine and colon.[18] Ownership of dogs and cats has been correlated with an increased risk of infection of *H. heilmannii* in people.[111] Recent studies clearly confirm that dogs and cats harbor *H. heilmannii,* but the subtypes of *H. heilmannii* present in dogs and cats, types 2 and 4, are of minor importance in people (about 15% of cases), who are predominantly colonized by *H. heilmannii* type 1—the predominant *Helicobacter* spp. in pigs.[17] The transmission of a variety of non-*H.pylori Helicobacter* spp., including *H. felis, H. salomonis, H. bizzozeronii,* from animals and pets to man appears more common than was initially appreciated.[112]

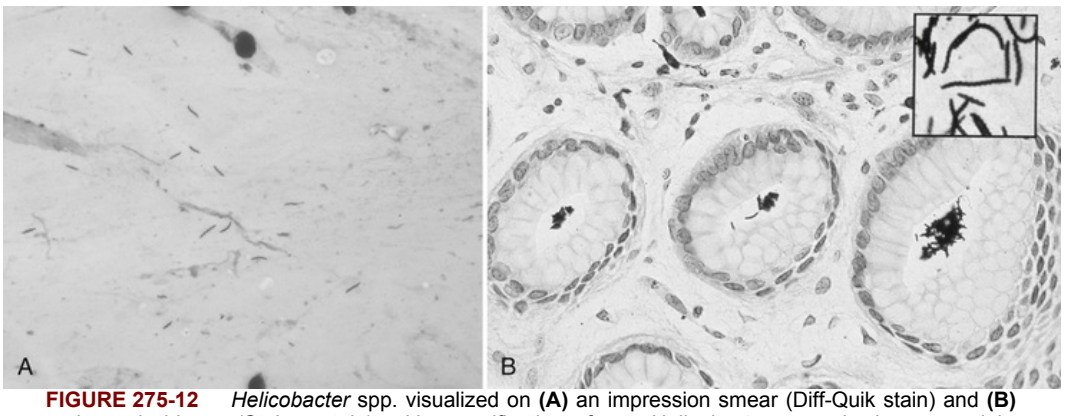

FIGURE 275-12 *Helicobacter* spp. visualized on **(A)** an impression smear (Diff-Quik stain) and **(B)** endoscopic biopsy (Steiner stain), with magnification of one *Helicobacter* group in the upper right corner. (© Kenneth W. Simpson.)

Helicobacter Treatment

The effect of eradicating *Helicobacter* spp. on gastritis and clinical signs in people, the main form of evidence supporting the pathogenic role of *H. pylori,* has not been thoroughly investigated in dogs or cats. An uncontrolled treatment trial of dogs and cats with gastritis and *Helicobacter* spp. infection showed that clinical signs in 57 of 63 dogs and cats responded to a combination of metronidazole, amoxicillin, and famotidine. 14 of 19 animals re-endoscoped had resolution of gastritis and no evidence of *Helicobacter* spp. in gastric

biopsies.[113] A controlled trial of amoxicillin, metronidaziole, and bismuth ± famotidine in 24 dogs found a similar decrease in vomiting (86.4%) but only 43% clearance of *Helicobacter* at 6 months.[114] This study also found that gastritis scores in dogs that were *Helicobacter* negative at 6 months decreased, whereas those in *Helicobacter*-positive dogs increased. The reason for the much higher apparent recrudescence or reinfection rate in dogs and cats than people (1% to 2% per year observed after treatment of *H. pylori*) has not been determined. With such limited information from eradication trials, most current knowledge about the pathogenicity of *Helicobacter* spp. for dogs and cats comes from the evaluation of animals with and without infections and clinical signs and a small number of experimental infections.

The large *Helicobacter* species found in dogs and cats do not attach to the epithelium but colonize the superficial mucous and gastric glands, particularly of the fundus and cardia, and may also be observed intracellularly.[107,109] Degeneration of gastric glands with vacuolation, pyknosis, and necrosis of parietal cells is more common in infected than uninfected animals. Inflammation is generally mononuclear in nature and ranges from mild to moderate in severity. Gastric lymphoid hyperplasia is common and can be extensive in dogs and cats infected with *Helicobacter* spp., particularly when full-thickness gastric biopsies are evaluated. In addition to this local gastric immune response, a systemic response characterized by increased circulating anti-*Helicobacter* IgG has been detected in sera from naturally infected dogs and cats. However, the gastritis observed in dogs and cats infected with large spiral bacteria is generally less severe than observed in *H. pylori*–infected humans. Gastrointestinal ulcers, gastric neoplasia, or changes in serum gastrin or acid secretion have not been associated with *Helicobacter* spp. infection in dogs or cats.

Differences between people, dogs, and cats may be attributed to differences in the virulence of the infecting *Helicobacter* spp. or in the host response. Studies that address this issue indicate that *H. pylori* evokes a more severe proinflammatory cytokine and cellular response in dogs and cats than natural or experimental infection with large *Helicobacter* spp.[110,115] The limited mucosal inflammatory response and absence of clinical signs in most dogs and cats infected with non–*H. pylori Helicobacter* spp., despite significant antigenic stimulation proved by seroconversion and lymphoid follicle hyperplasia, suggests that large gastric *Helicobacter* spp. are more commensal than pathogenic. It is interesting to speculate that it is the loss of tolerance to gastric *Helicobacter* spp., rather than the innate pathogenicity of these bacteria, that explains the development of gastritis and clinical signs in some dogs and cats.

Clinical Findings

The major clinical sign of chronic gastritis is vomiting of food or bile. Decreased appetite, weight loss, melena, or hematemesis is variably encountered. The concurrent presence of dermatologic and GI signs raises the likelihood of dietary sensitivity.[116] Dietary practices and access to toxins, medications, and foreign bodies should be thoroughly reviewed. Signalment is important, as it may increase the probability that chronic gastritis is the cause of vomiting. Hypertrophy of the fundic mucosa is frequently associated with a severe enteropathy in Basenjis and with stomatocytosis, hemolytic anemia, icterus, and polyneuropathy in Drentse Patrijshonds.[117,118] Hypertrophy of the pyloric mucosa is observed in small, brachycephalic dogs such as the Lhasa Apso, associated with gastric outflow obstruction (see Delayed Gastric Emptying and Motility Disorders, below). Atrophy of the gastric mucosa that may progress to adenocarcinoma has been reported in Lundehunds with protein-losing gastroenteropathy.[119] Young, large-breed male dogs in the Gulf states of the United States may have granulomatous gastritis caused by *Pythium* spp. with infection more prevalent in fall, winter, and spring.[120] Physical examination is often unremarkable. Abdominal distension may be related to delayed gastric emptying caused by obstruction or defective propulsion. Abdominal masses, lymphadenopathy, or ocular changes may be encountered in dogs with gastric fungal infections.

Diagnosis

Laboratory Testing

A biochemical profile, CBC, urinalysis, and T_4 (for cats >5 years old) should be performed as a basic screening for metabolic, endocrine, infectious, and other non-GI causes of vomiting, as well as for the acid-base and electrolyte changes associated with vomiting, outflow obstruction, or acid hypersecretion. Test results are often normal in pets with chronic gastritis. Eosinophilia may prompt the consideration of gastritis associated with dietary hypersensitivity, endoparasites, or mast cell tumors. Hyperglobulinemia and hypoalbuminemia may be present in Basenjis with gastropathy or enteropathy or in dogs with gastric pythiosis. Panhypoproteinemia is a feature of gastroenteropathy in Lundehunds, moderate to severe generalized

inflammatory bowel disease, GI lymphoma, and GI histoplasmosis. More specific testing, such as an ACTH stimulation test or serology for *Pythium insidiosum,* is performed based on the results of these initial tests. Determination of food-specific IgE has not been shown to be useful in the diagnosis of dietary sensitivity in dogs or cats. The utility of noninvasive tests, such as serum pepsinogen and gastric permeability to sucrose, used to diagnose gastritis in people has not been determined in dogs and cats.

Imaging

Abdominal radiographs are frequently normal in dogs and cats with gastritis. Gastric distention or delayed gastric emptying (food retained more than 12 hours after a meal) may be noted. Contrast radiography may reveal ulcers or thickening of the gastric rugae or wall but has largely been superseded by the combination of ultrasonography (US) for detection of mural abnormalities and endoscopy to observe and sample the gastric mucosa.[31]

Endoscopy

Endoscopic examination (see ch. 113) enables the visualization of foreign bodies, erosion, ulceration, hemorrhage, rugal thickening, lymphoid follicle hyperplasia (evident as mucosal pock marks), increased mucus or fluid (clear or bile stained), and increased or decreased mucosal friability (see ch. 113). Discrete focal or multifocal mucosal nodules may be observed with *Ollulanus* spp. infection. Gastric phycomycosis can be associated with irregular masses in the pyloric outflow tract and may prompt serologic testing by ELISA, Western blotting, and culture of fresh gastric biopsies. Parasites such as *Physaloptera* spp. may be observed as 1- to 4-cm long worms. Excess bile-stained fluid is suggestive of duodenogastric reflux-associated gastritis, whereas excess clear fluid may indicate hypersecretion of gastric acid. Gastric fluid can be aspirated for cytology (*Helicobacter* spp., parasite ova or larvae) and pH measurement. Impression smears of gastric biopsies are an effective way of identifying *Helicobacter* spp. (5- to 12-micron spirals) and are more sensitive than the biopsy urease test (*Helicobacter* spp. produce urease; see Figure 275-12, *A*). Serum gastrin should be measured if unexplained gastric erosions, ulcers, fluid accumulation, or mucosal hypertrophy is seen.

Dribbling of Antigens and Biopsy

The endoscopic procedure of dribbling dietary antigens onto the gastric mucosa to ascertain the presence of food allergy has not been useful in dogs or cats: It is highly subjective, detects only immediate hypersensitivity, and does not correlate with the results of dietary elimination trials.[116] The stomach should be biopsied even when it looks grossly normal (usually three biopsies from each region: pylorus, fundus, and cardia). Thickened rugae may require multiple biopsies and a full-thickness biopsy is often required to differentiate gastritis from neoplasia or fungal infection and to diagnose submucosal or muscular hypertrophy. The results of gastric US can help predict these possibilities and complement the endoscopic findings (see Figure 275-6).

Gastric sections should be stained with H&E for evaluation of cellularity and architecture and modified Steiner stain for gastric spiral bacteria (see Figure 275-12, *B*). Further special stains, such as Gomori's methenamine silver, are indicated if pyogranulomatous inflammation is present, to detect fungi. Masson's trichrome can be used to highlight gastric fibrosis, whereas sirius red and alcian blue help to reveal eosinophils and mast cells, respectively. Immunocytochemistry can be employed to help distinguish lymphoma from severe lymphocytic gastritis. Mucin staining has been performed in Lundehunds with gastric atrophy and showed an abnormal presence of mucous neck cells and pseudopyloric metaplasia.[121]

Biopsy findings are often used to guide treatment. For example, mild lymphoplasmacytic gastritis may be treated with a change in diet, whereas moderate lymphoplasmacytic gastritis without *Helicobacter* spp. infection, that fails to respond to diet change, may benefit from treatment with corticosteroids. Because the histologic evaluation of gastric biopsies is not uniform among pathologists, even when a standardized scoring scheme is used (see Figure 275-10), the prudent clinician should carefully review histologic sections to get a feel for the pathologist's interpretation.[16] Even with optimum evaluation, similar histologic changes can be observed in patients with different underlying etiologies, so well-structured treatment trials often form the basis of an etiologic diagnosis.

Treatment

Treatment of gastritis initially centers on the detection and treatment of underlying metabolic disorders and the removal of drugs, toxins, foreign bodies, parasites, and fungal infections.

Parasitic Gastritis

Ollulanus Tricuspis

Ollulanus tricuspis is a microscopic worm (0.7 to 1 mm long, 0.04 mm wide) that infects feline stomachs. Its predominant cat-to-cat transmission is through ingestion of vomitus. It can also undergo internal autoinfection, with worm burdens reaching up to 11,000 per stomach. Mucosal abnormalities range from none to rugal hyperplasia and nodular (2 to 3 mm) gastritis. Histologic findings include lymphoplasmacytic infiltrates, lymphoid follicular hyperplasia, fibrosis, and up to 100/hpf globular leukocytes. *Ollulanus* spp. are not detected by fecal examination and require evaluation of gastric juice, vomitus, or histologic sections for larvae or worms. Gastric lavage and xylazine-induced emesis have been described to aid diagnosis. Treatment with fenbendazole (10 mg/kg PO q 24 h 2d) may be effective.

Physaloptera spp.

Physaloptera spp. are about 2- to 6-cm long worms that are sporadically detected in the stomachs of dogs and cats. *Physaloptera rara* are most commonly described and appear to be primarily a parasite of coyotes. Diagnosis is difficult as worm burden is often low and the eggs are transparent and difficult to see in sugar flotation. Treatment with pyrantel pamoate (5 mg/kg PO: dogs, single dose; cats, two doses, 14 days apart) may be effective. Control of infection may be difficult due to the ingestion of intermediate hosts, such as cockroaches and beetles, and paratenic hosts, such as lizards and hedgehogs. Given the difficult diagnosis of *Ollulanus* and *Physaloptera* spp., empirical therapy with an anthelmintic such as fenbendazole may be warranted in dogs and cats with unexplained gastritis.

Other Parasites

Gastric infection with *Gnathostoma* spp. (cats), *Spirocerca* spp. (dogs), and *Aonchotheca* spp. (cats) has been associated with gastric nodules that have been treated by surgical resection of affected gastric tissue.[122]

Gastric Pythiosis

The presence of transmural thickening of the gastric outflow tract (Figure 275-13) and histology that indicates pyogranulomatous inflammation raise the possibility of infection with fungi such as *Pythium insidiosum* (see ch. 236).[120] Special staining (Gomori's methenamine silver), culture, serology, and PCR of infected tissues can be used to help confirm the diagnosis. Treatment consists of aggressive surgical resection combined with itraconazole (10 mg/kg PO q 24 h) and terbinafine (5 to 10 mg/kg PO q 24 h) for 2 to 3 months postsurgery. ELISA titers of pretreatment and posttreatment samples may show a marked drop during successful treatment, and drugs can be stopped. Medical therapy is continued for another 2 to 3 months if titers remain elevated. The prognosis is poor, as <25% of afflicted animals are cured with medical therapy alone.[120,123]

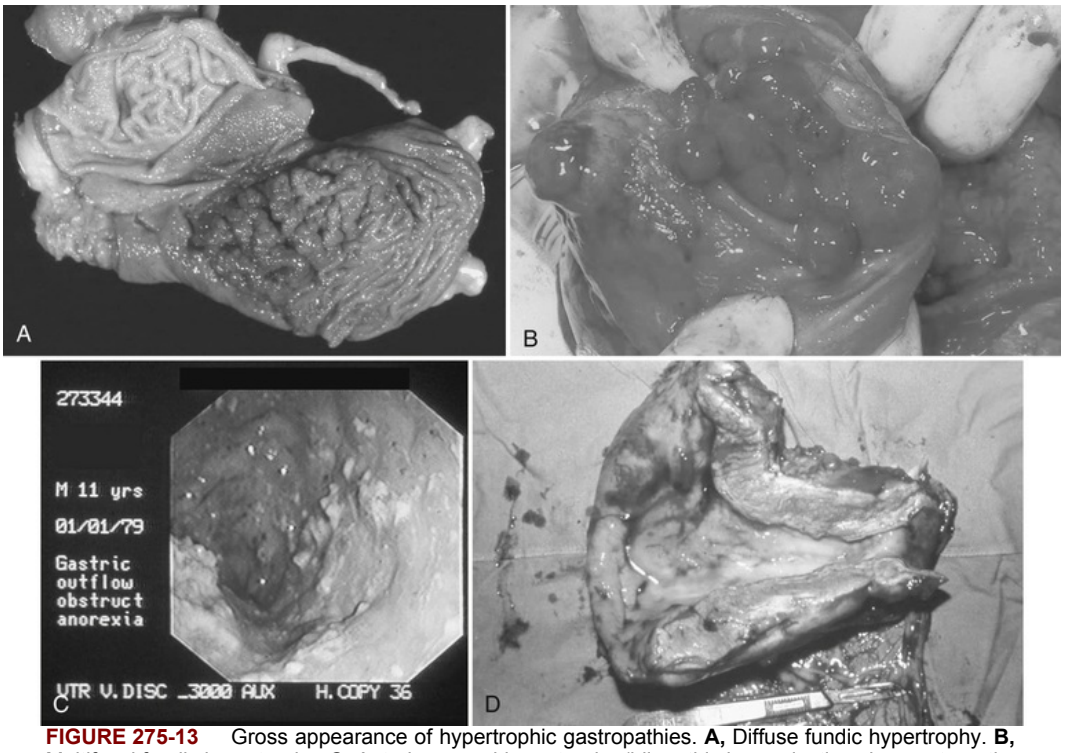

FIGURE 275-13 Gross appearance of hypertrophic gastropathies. **A,** Diffuse fundic hypertrophy. **B,** Multifocal fundic hypertrophy. **C,** Antral mucosal hypertrophy (idiopathic hyperplastic pylorogastropathy in a brachycephalic dog). **D,** Thickening of the pyloric outflow tract due to *Pythium* spp. (**A, B,** and **D,** Courtesy Cornell University; **C,** Courtesy The Ohio State University.) (© Kenneth W. Simpson.)

Helicobacter-Associated Gastritis

The general lack of knowledge of the pathogenicity of gastric *Helicobacter* spp. has meant that veterinarians are faced with the dilemma of either treating or ignoring spiral bacteria observed in biopsies from patients with chronic vomiting and gastritis. In light of their pathogenicity in humans, ferrets, cheetahs, and mice, it would seem prudent that eradication of gastric *Helicobacter* spp. be attempted prior to initiating treatment with immunosuppressive agents to control gastritis. However, this must be decided on an individual basis. For example, in the patient with a lymphoplasmacytic infiltrate of the stomach and small intestine with a concomitant gastric *Helicobacter* spp. infection, should one treat for inflammatory bowel disease, *Helicobacter,* or both?

The author recommends treating only symptomatic patients that have biopsy-confirmed *Helicobacter* spp. infection *and* gastritis. Current treatment protocols are based on those found to be effective in humans infected with *H. pylori.* An uncontrolled treatment trial of dogs and cats with gastritis and *Helicobacter* spp. infection showed that clinical signs in 90% of 63 dogs and cats responded to treatment with a combination of metronidazole, amoxicillin, and famotidine, and that 74% of 19 animals reendoscoped had no evidence of *Helicobacter* spp. in gastric biopsies.[113] A recent controlled trial of amoxicillin (15 mg/kg PO q 12 h for 14 days), metronidazole (10 mg/kg PO q 12 h for 14 days) and bismuth ± famotidine in 24 dogs found a similar decrease in vomiting (86.4%) and reduced gastritis scores in dogs that were *Helicobacter* negative at 6 months. The use of famotidine did not improve resolution of clinical signs or eradication of *Helicobacter.* Unfortunately, only 43% of dogs were free from *Helicobacter* at 6 months,[114] which echoes the results of controlled studies in asymptomatic *Helicobacter*-infected dogs and cats. Treatment combinations evaluated in these asymptomatic animals include (1) amoxicillin (20 mg/kg PO q 12 h for 14 days), metronidazole (20 mg/kg PO q 12 h for 14 days), and famotidine (0.5 mg/kg PO q 12 h for 14 days) in dogs;[124] (2) clarithromycin (30 mg PO q 12 h for 4 days), metronidazole (30 mg PO q 12 h for 4 days), ranitidine (10 mg PO q 12 h for 4 days), and bismuth (20 mg PO q 12 h for 4 days; CMRB) in *H. heilmannii*–infected cats;[125] and (3) azithromycin (30 mg PO q 24 h for 4 days), tinidazole (100 mg PO q 24 h for 4 days), ranitidine (20 mg PO q 24 h for 4 days), and bismuth (40 mg PO q 24 h for 4 days; ATRB) in *H. heilmannii*–infected cats.[125] Re-evaluation of infection status at 3 days (dogs) or 10 days (cats) after treatment revealed 6 of 8 dogs, 11 of 11

CMRB-treated cats, and 4 of 6 ATRB-treated cats to be *Helicobacter*-free on the basis of histology and urease testing (dogs) or ^{13}C-urea breath test (dogs and cats).[125,126] However, at 28 days (dogs) or 42 days (cats) after completing antimicrobial therapy, 8 of 8 dogs, 4 of 11 cats that received CMRB, and 5 of 6 cats that received ATRB were found to be reinfected. A transient effect of combination therapy (amoxicillin 20 mg/kg PO q 8 h for 21 days, metronidazole 20 mg/kg PO q 8 h for 21 days, and omeprazole 0.7 mg PO q 24 h for 21 days) on bacterial colonization has also been observed in 6 cats with *H. pylori* infection.

Further analysis of gastric biopsies from asymptomatic infected dogs and cats and *H. pylori*–infected cats using PCR and *Helicobacter*-specific primers revealed persistence of *Helicobacter* DNA in gastric biopsies that appeared negative on histology and urease testing.[127] These studies suggest that antibiotic regimens that are effective against *H. pylori* in people may only cause transient suppression, rather than eradication, of gastric *Helicobacter* spp. in dogs and cats.

A recent study that gave metronidazole (11 to 15 mg/kg PO q 12 h), amoxicillin (22 mg/kg PO q 12 h), and bismuth subsalicylate (0.22 mL/kg PO q 8 h) to five *Helicobacter*–infected animals (three dogs and two cats) for 21 days documented resolution of vomiting and long-term eradication of *Helicobacter* (9 to 38 months) in all animals.[128] The author has employed the combination of amoxicillin (20 mg/kg PO q 12 h), clarithromycin (7.5 mg/kg PO q 12 h), and metronidazole (10 mg/kg PO q 12 h) for 14 days to successfully eradicate *H. pylori* infection in cats. A similar combination of antibiotics plus omeprazole transiently suppressed *Helicobacter* in 4/13 asymptomatic adult stray cats.[127] These studies suggest that a longer duration of treatment (21 days) or the use of antibiotics that can eradicate intracellular *Helicobacter* (clarithromycin) can improve eradication, but further studies are required before clear guidelines regarding the treatment of gastric *Helicobacter* spp. in dogs and cats can be made.

Chronic Gastritis of Unknown Cause

Lymphocytic-plasmacytic gastritis of unknown cause is common in dogs and cats. It may be associated with similar infiltrates in the intestines.[101] Cats with lymphoplasmacytic gastritis and enteritis should also be evaluated for the presence of concurrent pancreatic and biliary disease, "triaditis."[129] The cellular infiltrate varies widely in severity, and it may be accompanied by mucosal atrophy or fibrosis and less commonly by hyperplasia. Patients with mild lymphoplasmacytic gastritis that lack follicular hyperplasia and evidence of HLO are initially treated with diet. The diet is usually restricted in antigens to which the patient has been previously exposed, such as a lamb-based diet if the patient has previously been fed chicken and beef, or it contains hydrolyzed proteins (usually chicken or soy) that may be less allergenic than intact proteins. Many of these diets are also high in carbohydrates and restricted in fat, which facilitates gastric emptying, and they may contain other substances, such as menhaden fish oil or antioxidants that may alter inflammation. The test diet is fed exclusively for a period of about 2 weeks, and vomiting episodes are recorded.[116] If signs improve, a challenge with the original diet is required to confirm a diagnosis of food intolerance. The introduction of a specific dietary component, such as beef, to the test diet is required to confirm dietary sensitivity. If vomiting is unresponsive, the patient may be placed on a different diet for another 2 weeks, usually the limit of client tolerance, or the patient may be started on prednisolone (1 to 2 mg/kg/day PO, tapered to every other day at the lowest dosage that maintains remission over 8 to 12 weeks).

Patients with moderate to severe lymphoplasmacytic gastritis that are HLO-free may be started on a combination of a test diet and prednisolone. If patients go into remission, they are maintained on the test diet while prednisolone is tapered and discontinued if possible. Antacids and mucosal protectants are added to the therapeutic regimen if ulcers or erosion are detected at endoscopy or if hematemesis or melena are noted. If gastritis is unresponsive to diet, prednisolone, and antacids, additional immunosuppression may be indicated, but this is not often required. Gastric biopsies should be carefully re-evaluated for evidence of lymphoma. In dogs, immunosuppression is usually increased with azathioprine (2 mg/kg PO q 24 h for 5d, then q 48 h on alternating days with prednisolone). Chlorambucil is a safer alternative to azathioprine in cats (PO) and has been successfully employed in the management of inflammatory bowel disease and small-cell lymphoma (see below). Prokinetic agents such as metoclopramide, cisapride, and erythromycin can be used as an adjunct where delayed gastric emptying is present. These are discussed below.

Diffuse eosinophilic gastritis of undefined etiology is usually approached in a similar fashion to lymphoplasmacytic gastritis. The presence of eosinophilia, dermatologic changes, and eosinophilic infiltrates may be even more suggestive of dietary sensitivity. In cats, it should be determined whether it is part of a hypereosinophilic syndrome. Treatment for occult parasites, dietary trials, and immunosuppression can be carried out as described above. Focal eosinophilic granulomas can be associated with parasites or fungal

infection that should be excluded prior to immunosuppression with corticosteroids.

Atrophic Gastritis

See E-Box 275-2.

E-Box 275-2

Atrophic Gastritis

Atrophic gastritis in dogs and cats is often associated with a marked cellular infiltrate (see Figure 275-10). In people, atrophy is associated with *Helicobacter* spp. infection, inflammation, and immune-mediated destruction.[130] Gastric disease is often not discovered until the patient presents with pernicious anemia secondary to cobalamin deficiency caused by a lack of gastric intrinsic factor. In people, atrophic gastritis, intestinal metaplasia of the gastric mucosa, hypergastrinemia, and hypochlorhydria are thought to precede the development of gastric cancer.[131] The host inflammatory response is also thought to contribute to the development of atrophy. Proinflammatory IL-1-beta and IL-10 gene polymorphisms in people are associated with increased inflammation, gastric atrophy, hypochlorhydria, and gastric cancer.[132,133]

Atrophic gastritis has been infrequently described in dogs and cats but does share some similarities with people. Atrophic gastritis characterized by reduction in parietal cells and hyperplasia of neuroendocrine cells has been associated with gastric adenocarcinoma in Lundehunds.[134] Some of the adenocarcinomas displayed enterochromaffin-like cell differentiation, suggesting that hypergastrinemia secondary to fundic atrophy may be important in carcinogenesis. In dogs with lymphoplasmacytic gastritis of undetermined cause, gastric atrophy correlates with the expression of mRNA for IL-1-beta and IL-10 and the presence of neutrophils.[16] However, with the exception of the Lundehund, clear evidence that gastritis progresses to atrophy and gastric cancer in dogs or cats[135] and the role of *Helicobacter* spp. or antigastric antibodies in the development of atrophy in dogs and cats remain to be determined.

In contrast to humans, dogs and cats with atrophic gastritis have not been reported to develop cobalamin deficiency. This is likely because the pancreas, rather than the stomach, is the main source of intrinsic factor in these species. Achlorhydria has been described in dogs and may enable the proliferation of bacteria in the stomach and upper small intestine, although this has not been proven. The use of omeprazole at doses of 1.1 mg/kg PO q 12 h has been associated with hypergastrinemia and dysbiosis of the gastric microflora.[15] The treatment of atrophic gastritis has received limited attention, but *Helicobacter* spp. eradication and immunosuppression have been effective in subsets of people.

Hypertrophic Gastritis

See E-Box 275-3.

E-Box 275-3

Hypertrophic Gastritis

Hypertrophy in the fundic mucosa is uncommon and is often part of breed-specific gastropathies or other gastroenteropathies (see Figure 275-13). Concurrent hypergastrinemia should prompt consideration of underlying hepatic or renal disease, achlorhydria, or gastrin-producing tumors, which should be pursued appropriately. Basenji gastroenteropathy is variably associated with fasting hypergastrinemia and exaggerated secretin-stimulated gastrin, and anecdotal reports suggest that affected Basenjis may respond to antimicrobial therapy. Antral hypertrophy of brachycephalic dogs causes outflow obstruction and is treated with surgery (see later).

Delayed Gastric Emptying and Motility Disorders

Definitions

Disorders of gastric motility can disrupt the storage and mixing of food and its expulsion into the duodenum.[40] Normal gastric motility is the result of the organized interaction of smooth muscle, neural, and hormonal stimuli. Delayed gastric emptying is the most commonly recognized manifestation of gastric motility disorders. Rapid gastric emptying and motility disorders associated with retrograde transit of bile or ingesta are less well defined. Delayed gastric emptying is caused by outflow obstruction or defective propulsion (Box 275-4) and is usually suspected when a pet vomits food at least 8 and often 10 to 16 hours after a meal.

Box 275-4

Causes of Delayed Gastric Emptying

Outflow Obstruction

Congenital stenosis
Foreign bodies
Hypertrophy of pyloric mucosa
Granuloma
Polyps
Neoplasia
Extra-gastric masses

Defective Propulsion

Gastric disorders
Gastritis
Ulcers
Neoplasia
Gastroenteritis
Peritonitis
Pancreatitis
Metabolic (hypokalemia, hypocalcemia, hypoadrenocorticism)
Nervous inhibition (trauma, pain, stress)
Dysautonomia
Gastric dilatation and volvulus
Surgery
Drugs (anticholinergics, narcotics)
Idiopathic

Signalment, History, Physical Examination

Vomiting food 8 to 10 hours after ingestion is the most common sign. Vomiting may be projectile with pyloric stenosis. Abdominal distension, weight loss, melena, abdominal discomfort, distension, bloating, and anorexia are more variably present. Signalment and history may be helpful in prioritizing diagnoses. Vomiting noted at weaning raises the possibility of pyloric stenosis. Access to foreign bodies, bones, and medications is of obvious relevance to outflow obstruction. Brachycephalic, middle-aged, small-breed dogs such as Shih Tzus seem predisposed to a syndrome of vomiting secondary to pyloric outflow obstruction caused by hypertrophy of the pyloric mucosa and/or muscularis.[136,137] Gastric neoplasia is usually detected in older animals with weight loss, hematemesis, and pallor. Gastric pythiosis (see ch. 336) is more prevalent in young large-breed dogs in the Gulf states of the United States. Large-breed, deep-chested dogs are more prone to GDV that may have an underlying problem with gastric emptying (see GD/GDV above). A thorough physical examination is performed to detect causes of vomiting: string foreign bodies; intestinal masses or thickenings; non-GI causes, including thyroid (nodules in cats), liver (jaundice, hepatomegaly), or kidney disease (abnormal on palpation); and the systemic effects of vomiting, such as dehydration and weakness.

Laboratory Assessments

Hematology (CBC), serum biochemistry, urinalysis, fecal analysis (parasites [see ch. 81], parvovirus [see ch. 225]), and serology (FeLV; see ch. 223) are employed to detect non-GI causes of vomiting or delayed gastric emptying and to determine the consequences of vomiting. Laboratory findings vary depending on the severity of vomiting, completeness of pyloric obstruction, and the presence of disorders associated with blood loss or inflammation. The CBC is often normal, but anemia may accompany gastric ulcers or neoplasia. Hyperglobulinemia may be present where outflow obstruction is secondary to fungal granuloma. The presence of hypochloremia, hypokalemia, and metabolic alkalosis, with or without aciduria, should increase suspicion of an upper GI obstruction or potential hypersecretion of gastric acid.

Diagnosis: Imaging, Endoscopy, Gastric pH Testing, Scintigraphic Techniques

Radiographs are essential for diagnosing retention of food or fluid in the stomach longer than 8 hours after a meal and to detect extra-gastric disorders such as peritonitis (see ch. 279). US (see ch. 88) may detect mural thickening or irregularity of the stomach suggestive of neoplasia, granuloma, hypertrophy, a radiolucent foreign object, or detect non-gastric causes of delayed emptying, e.g., pancreatitis. Contrast radiography can be used to detect mural abnormalities and to confirm suspicion of gastric obstruction when plain radiographs are inconclusive (Figure 275-14).

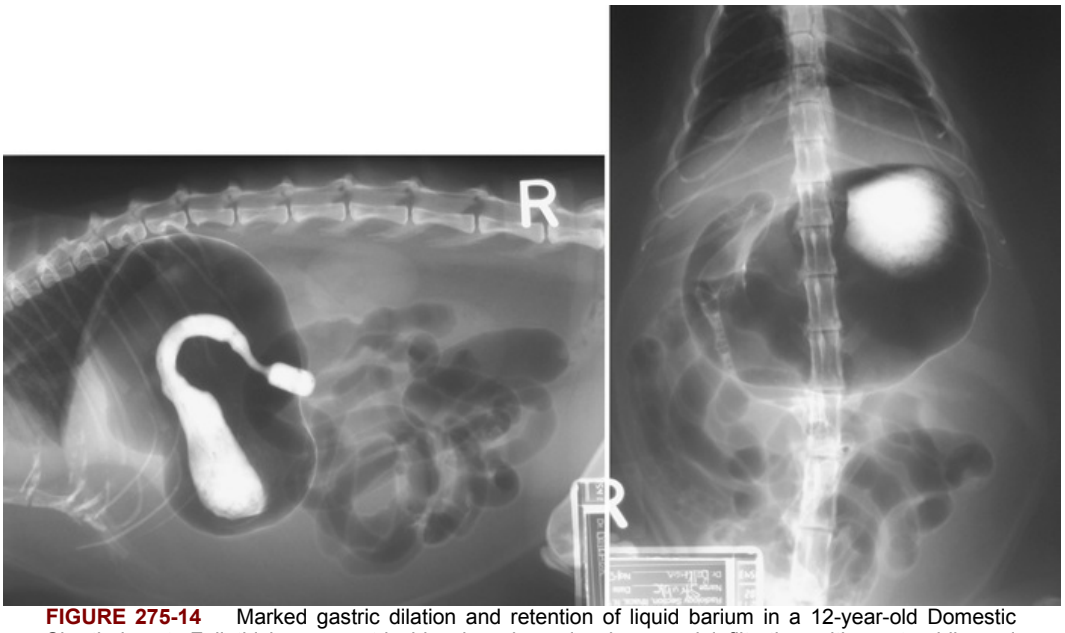

FIGURE 275-14 Marked gastric dilation and retention of liquid barium in a 12-year-old Domestic Shorthair cat. Full thickness gastric biopsies showed submucosal infiltration with neutrophils and lymphocytes. (Courtesy Cornell University. © Kenneth W. Simpson.)

Endoscopy (see ch. 113) is usually favored over radiographic procedures for confirming gastric outflow obstruction or gastric/duodenal causes of decreased propulsion (e.g., ulcers, gastritis; see Figure 275-13). Endoscopy can be hampered by recent administration of barium, so it is often performed first. Endoscopic biopsy is limited to the superficial mucosa, and surgical biopsy is frequently required to achieve a definitive diagnosis of granulomatous, neoplastic, or hypertrophic conditions. Measurement of gastric pH and serum gastrin can help to differentiate idiopathic hypertrophic pylorogastropathy from hypertrophy associated with hypergastrinemia. Pancreatic polypeptide-producing tumors may also be associated with mucosal hypertrophy.

More sophisticated procedures can be used to directly evaluate gastric emptying, motility, and to optimize prokinetic therapy (E-Table 275-3).[40,41] These include barium contrast (liquid or mixed with food), barium-impregnated polyspheres, sonography, nuclear scintigraphy, the ^{13}C-octanoate and ^{13}C-acetate breath tests, and wireless motility capsules.[40-44,49] Radiographic contrast procedures are readily available but are hampered by the wide variability in emptying times for barium in liquid or meal form. Giving barium-impregnated polyspheres is a simplified contrast procedure suited to routine clinical practice, requires far

fewer radiographs than a traditional barium series, and test performance/interpretation are standardized. Its utility in pets remains to be determined. Ultrasound can be useful for detecting gastric wall abnormalities and measuring contractile activity, with standardized measurement of a motility index considered comparable to ^{13}C-octanoate.[138]

E-TABLE 275-3

Review of Methods for Assessment of the Rate of Gastric Emptying in the Dog and Cat[41]

GASTRIC HALF METHOD	SPECIES	TEST MEAL	N	EMPTYING TIME ($T_{1/2}$)*
Radioscintigraphy	Dog	Eggs, starch + glucose	27	66 min (median), 45-227 min (95% CI)
		Beef baby food + kibble	6	4.9 ± 1.96 h (mean ± sd)
		Liver	4	About 2 h
		Canned dog food + egg	6 (18 tests)	172 ± 17 min (mean ± se)
		Canned dog food + egg	7 (14 tests)	285 ± 34 min (mean ± sd); 294 ± 39 min (mean ± sd)
		Canned dog food	6	77 min (mean)
	Cat	Dry cat food	10	2.47 ± 0.71 h (mean ± sd)
		Liver + cream	6 (15 tests)	163 ± 11 min (mean ± se)
		Canned cat food	20	2.69 ± 0.25 h (mean ± sd)
		Dry cat food	20	3.86 ± 0.24 h (mean ± sd)
		Eggs	10	330 min (median), 210-769 min (range)
Radiography		Dry dog food + radiopaque solids	10	3.5 h (median), 1-6 h (range)
		Canned dog food + egg + BIPS	6 (18 tests)	Small BIPS = 416 ± 81 min (mean ± se)
	Dog	Canned dog food + BIPS	20	Small BIPS = 6.05 ± 2.99 h (mean ± sd)
				Large BIPS = 7.11 ± 3.60 h (mean ± sd)
		Kibble + BIPS	8	Small BIPS = 8.29 ± 1.62 h (70% of dogs ± se)
				Large BIPS = 29.21 ± 18.31 h (70% of dogs ± se)
		Kibble + liquid barium	9 (27 tests)	Total gastric emptying time = 7-15 h (range)
		Kibble + liquid barium	4	Total gastric emptying time = 7.6 ± 1.98 h (mean ± se)
	Cat	Canned cat food + BIPS	10	Small BIPS = 6.43 ± 2.59 h (mean ± sd)
				Large BIPS = 7.49 ± 4.09 h (mean ± sd)
		Canned cat food + BIPS	6	Small BIPS = 7.7 h (median), 3.5-10.9 h (range)
				Large BIPS = 8.1 h (median), 5-19.6 h (range)
		Canned cat food + BIPS	10	Small BIPS = 5.36 h (median)
				Large BIPS = 6.31 h (median)
		Cat food + liquid barium	8	Gastric emptying time = 11.6 ± 0.9 h (mean ± sd)
Gastric emptying	Cat	Canned cat food	6	Peak 13C-excretion = 56.7 ± 9.8 min (mean ± sd)
Breath test	Dog	Bread, egg + margarine	6 (18 tests)	3.43 ± 0.50 h (mean ± sd)

*Gastric emptying rate is expressed as gastric half emptying time unless otherwise stated.

BIPS, Barium-impregnated polyspheres.

Reproduced with permission from Wyse CA, McLellan J, Dickie AM, et al: A review of methods for assessment of the rate of gastric emptying in the dog and cat: 1898-2002. *J Vet Intern Med* 17:609, 2003.

Scintigraphic techniques have traditionally been considered the most accurate way to evaluate emptying, but these involve radioactivity and are restricted to specialized facilities. Tests employing non-radioactive ^{13}C-octanoate and ^{13}C-acetate have been evaluated in people and dogs and have been found to reflect gastric emptying (the values are longer than scintigraphy as ^{13}C-substrates have to be absorbed and metabolized before $^{13}CO_2$ is liberated). Wireless capsule telemetry has recently been shown to provide accurate measurement of gastric emptying, with mean coefficients of variation (8%) similar to those of scintigraphy (11%), with emptying times considerably longer than scintigraphy.[43,44] Wireless capsule endoscopy enables simultaneous visualization of the pyloric outflow tract and measurement of gastric emptying time.[37]

Treatment

Direct Management

Treatment of gastric-emptying disorders is directed at the underlying cause. Gastric ulcers, erosions, and inflammation should be investigated and managed medically, as described. Foreign bodies should be removed either endoscopically or surgically. Pyloric stenosis, polyps, and hypertrophic gastropathy that is not associated with hypergastrinemia are managed surgically. When hypertrophic gastropathy, ulcers or erosions, or excessive gastric juice are encountered at endoscopy, IV H2-antagonists can be given during the procedure to try to prevent postoperative perforation or esophagitis. Neoplasia, polyps, and granulomas may require extensive gastric resection and Billroth procedures.

Dietary Modifications

Dietary modification to facilitate gastric emptying may be beneficial regardless of cause. Small amounts of semiliquid, protein- and fat-restricted diets fed at frequent intervals may facilitate emptying, such as an "intestinal-disease diet" blended with water and mixed with an equal volume of boiled rice (see ch. 178).

Medications

No controlled trials in dogs and cats have evaluated the efficacy of different prokinetics in different disease states, and treatment is usually based on a best guess/least harmful basis. Where true prokinetic activity is required, cisapride and erythromycin appear to be the most efficacious.[40] Treatment trials with prokinetics should probably be structured to last between 5 and 10 days to determine benefit. A diary of clinical signs and the objective assessment of gastric emptying using the tests described above, before and after therapy, helps to optimize treatment. Combination therapy, such as erythromycin and cisapride, is not recommended due to the potential for adverse drug interactions (see ch. 169). The prognosis for patients with delayed gastric emptying depends on the cause. A suspected motility disorder characterized by duodenogastric reflux is thought to account for the *bilious vomiting syndrome.* Affected dogs usually vomit early in the morning, and remission may be achieved by feeding the animal late at night. Prokinetic agents may also be employed.

In nonobstructive situations, gastric emptying may be enhanced and duodenogastric reflux inhibited by prokinetic agents such as metoclopramide, cisapride, erythromycin, or ranitidine.[40,68,139] The choice of prokinetic depends on whether a central antiemetic effect is required, as with metoclopramide, or a combined antacid prokinetic (ranitidine) is indicated, or if treatment with one agent has been ineffective or has caused adverse effects, such as behavioral changes with metoclopramide. In addition to its prokinetic activity in the stomach and upper GI tract, metoclopramide (0.2 to 0.5 mg/kg PO SC q 8 h) has central antiemetic properties and is an initial choice in patients with underlying metabolic diseases associated with vomiting and delayed gastric emptying. However, metoclopramide may only facilitate the emptying of liquids and is less effective in promoting organized gastroduodenal and intestinal motility than cisapride. Cisapride (0.1 to 0.5 mg/kg PO q 8 h) has no central antiemetic effects, is generally more potent in promotion of the gastric emptying of solids than metoclopramide, has more drug interactions, and its availability is limited. Erythromycin (dog: 0.5 to 1 mg/kg PO q 8 h, between meals) releases motilin, acts at motilin receptors, and mimics phase III of the interdigestive migrating myoelectric complex, promoting the emptying of solids. Nizatidine and ranitidine (0.5-1 mg/kg PO q 8 h) have prokinetic activity in experimental dogs attributed to an organophosphate-like

effect.[140] Ranitidine hydrochloride (75 mg PO q 12 h) was recently found to have no effect on gastric emptying time evaluated by wireless motility capsule.[43]

Gastric Neoplasia

Overview

Gastric tumors represent <1% of all reported canine and feline neoplasms.[141] Malignant tumors are more common than benign and most types of gastric neoplasms have been reported to occur more frequently in males, except adenomas.[142] Gastric malignancies reported are leiomyosarcoma, lymphoma (see ch. 344), fibrosarcoma, rare anaplastic sarcoma, and gastric extramedullary plasmacytoma (Table 275-4).

TABLE 275-4

Characteristics of Gastric Neoplasia in Dogs

TUMOR	MOST COMMON LOCATION	MEDIAN AGE (YEARS)	REPORTED BREED PREDISPOSITION
Adenocarcinoma	Pyloric antrum, lesser curvature	10	Belgian Shepherd Rough Collie Staffordshire Bull Terrier Lundehund Bouvier Groenendael Standard Poodle Norwegian Elkhound
Leiomyoma	Cardia	16	Beagle
Leiomyosarcoma		7	None
Lymphoma	Diffuse	10	None

Benign Tumors

Benign tumors of the stomach include leiomyomas and, less frequently, adenomatous polyps. Canine gastric leiomyomas are seen in old dogs, median age 16 years, with some identified incidentally at necropsy or when seen for GI bleeding and microcytic anemia (Figure 275-15). Adenomatous polyps are rare in dogs but have been reported as either raised, sessile, or pedunculated single or multiple growths in the stomach, usually in the terminal pyloric antrum. Although most are discovered incidentally, they may also cause signs of GI upset with vomiting (Figure 275-16). In humans, adenomatous polyps are generally regarded as possible premalignant lesions, and changes considered focally malignant have been found in dogs. Benign GI neoplasia in the cat occurs at a much lower frequency than in the dog, although up to 36% of all GI neoplasms are reported to be benign.

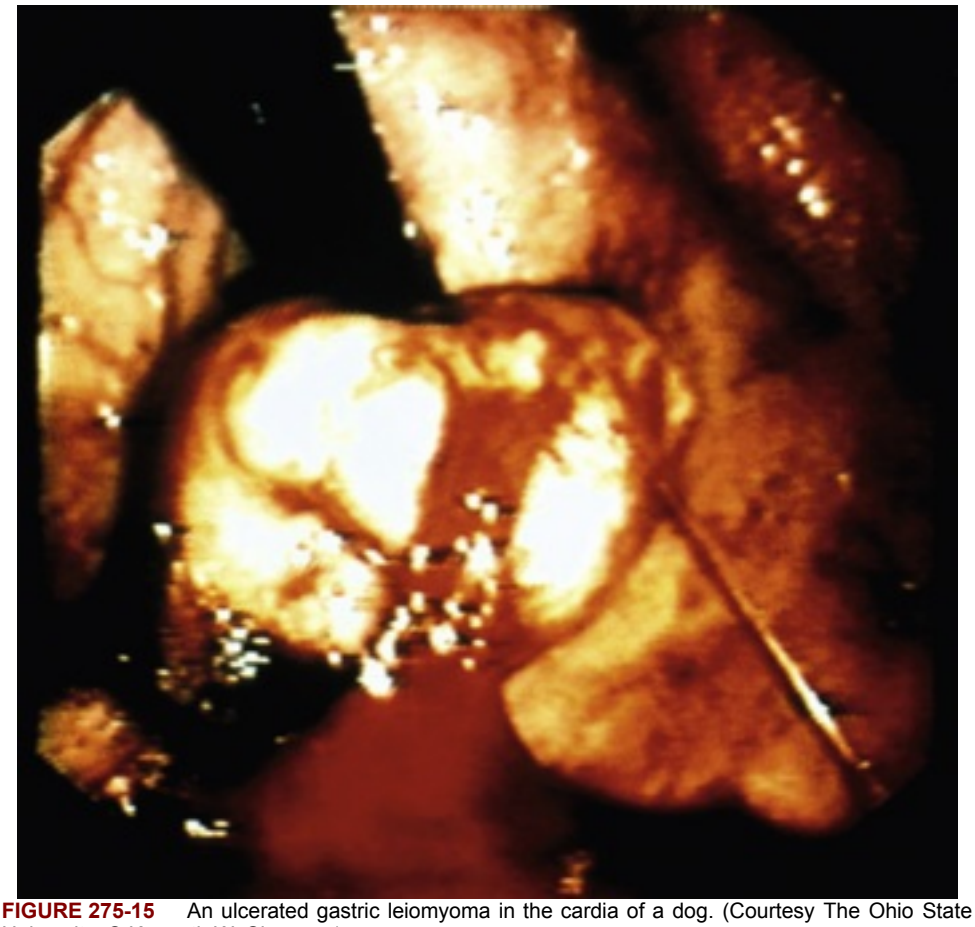

FIGURE 275-15 An ulcerated gastric leiomyoma in the cardia of a dog. (Courtesy The Ohio State University. © Kenneth W. Simpson.)

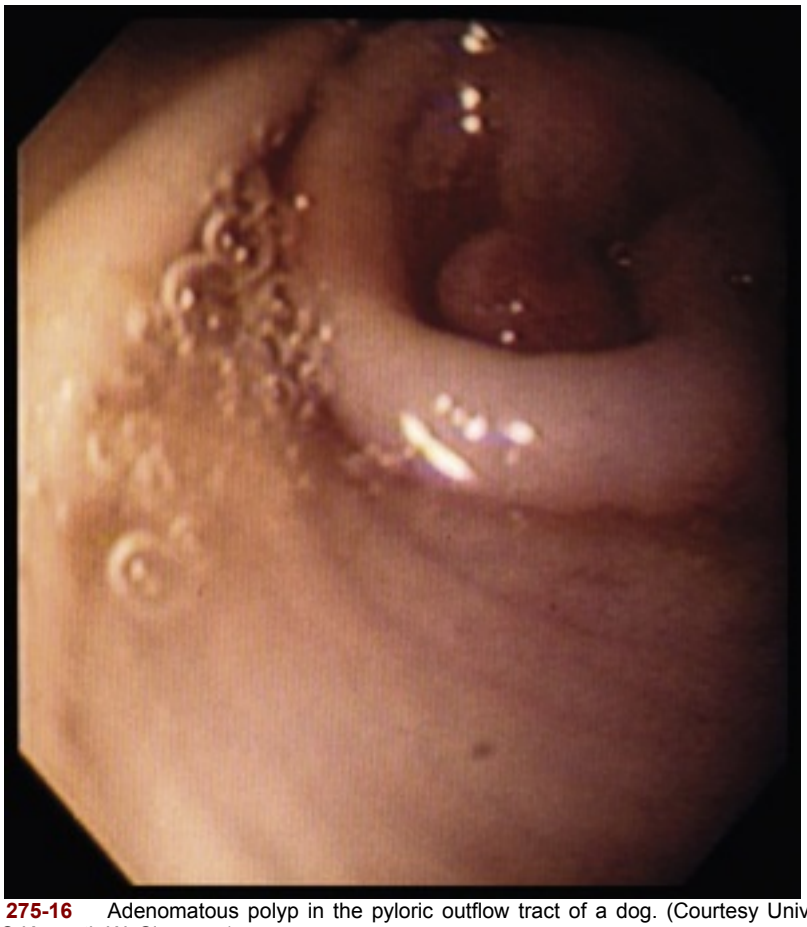

FIGURE 275-16 Adenomatous polyp in the pyloric outflow tract of a dog. (Courtesy University of London. © Kenneth W. Simpson.)

Malignant Tumors

Adenocarcinoma

Malignant adenocarcinoma is the most common gastric neoplasm in dogs, accounting for 47-72% of all canine gastric malignancies.[143-146] Gastric adenocarcinoma is extremely rare in cats. The peak age of dogs with gastric carcinomas has been reported to be from 10 to 12 years with a range of 3 to 13 and an average age of 9 to 10 years. A breed predilection for gastric carcinoma in related Belgian Shepherds, Rough Collies, and Staffordshire Bull Terriers has been suggested, although some studies show no significant breed predilections. The Norwegian Canine Cancer Register indicates that Tervuren/Belgian Shepherd, Bouvier des Flandres, Groenendael, Collie, Standard Poodle, and Norwegian Elkhound had a significantly increased risk of developing gastric carcinoma.[141] Males were more likely to be affected than females. Lundehunds with atrophic gastritis seem overrepresented, and gastric atrophy and inflammation may precede tumorigenesis as it does in humans.[134]

Gastric carcinomas of dogs occur most commonly in the lesser curvature and pyloric region as annular or stenosing lesions, and metastasis is frequent with involvement of lymph nodes, lungs, and liver (Figure 275-17). Carcinomas can be further divided into three morphologic patterns of distribution: (1) diffusely infiltrating, nonulcerating lesions that involve most of the stomach and are consistent with the "leather bottle" appearance described in humans; (2) localized, raised, thickened plaque usually containing a raised, excavating central ulcer; and (3) raised, polypoid, sessile lesion projecting into the lumen of the stomach. Two histologic types of gastric carcinoma have been described in people: (1) *diffuse* and (2) *intestinal* or *tubular.* The diffuse type consists of widespread random infiltrates of neoplastic cells dispersed between stromal elements of the gastric wall. The intestinal type is characterized by a tubular, glandular structure. The diffuse type is more common in dogs.

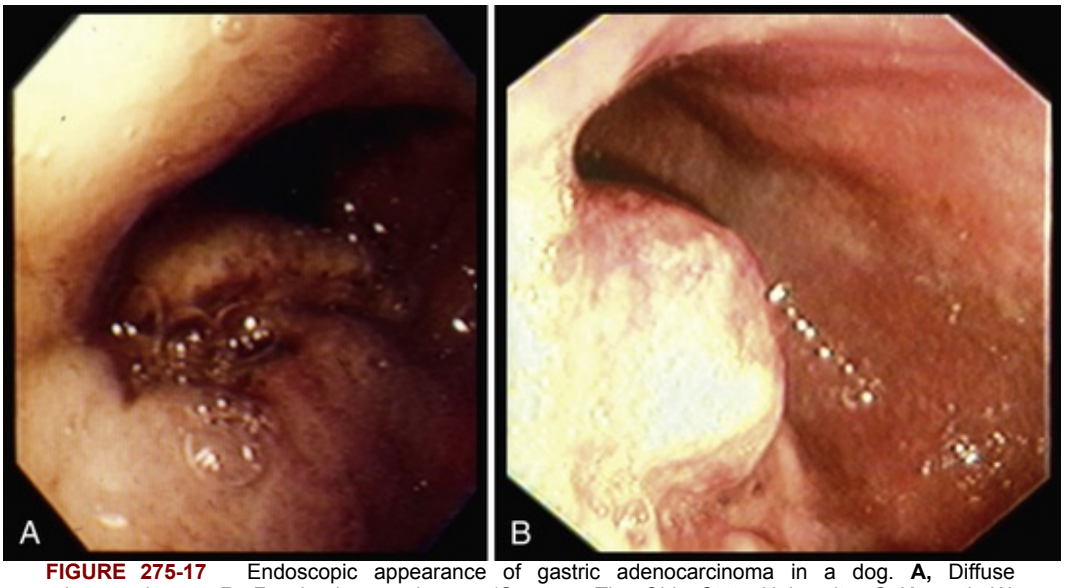

FIGURE 275-17 Endoscopic appearance of gastric adenocarcinoma in a dog. **A,** Diffuse adenocarcinoma. **B,** Focal adenocarcinoma. (Courtesy The Ohio State University. © Kenneth W. Simpson.)

Lymphoma

The most common GI neoplasm in both cats and dogs is lymphoma. In canine lymphoma originating in the gastric submucosa, the process may be described as diffuse or nodular, with the diffuse infiltrate being more common (Figure 275-18). Involvement of the liver, regional lymph nodes, small intestine, and bone marrow is common. Feline gastric lymphoma is not associated with FeLV infection and has been categorized as large cell or small cell, with small-cell lymphoma being more localized to the GI tract and carrying a much better prognosis than large-cell lymphoma.[147,148] In both dogs and cats, lymphocytic-plasmacytic inflammation has been found to precede or coexist with gastric lymphoma. It has been suggested that lymphocytic-plasmacytic inflammation is a prelymphomatous change in the GI tract. The development of gastric lymphoma in response to chronic antigenic stimulation and inflammation is exemplified by gastric MALT lymphoma in people with *H. pylori*–associated gastritis.

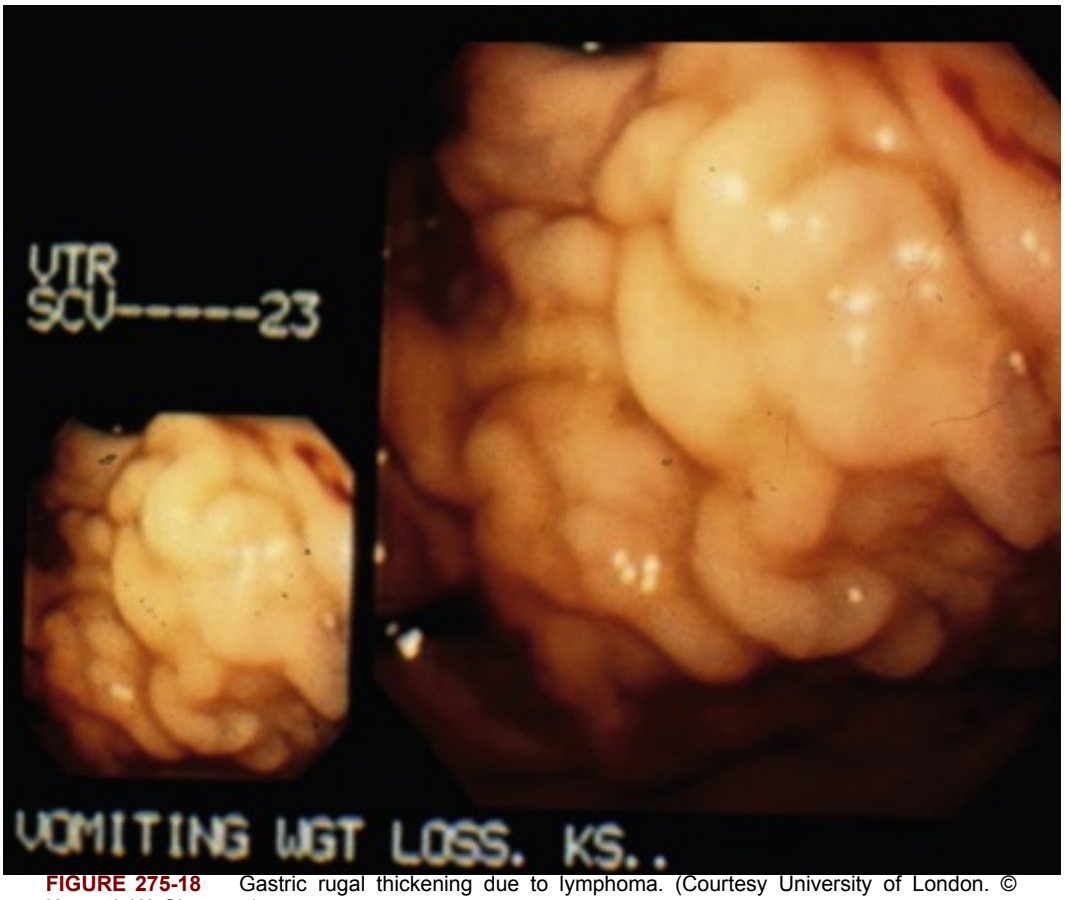

FIGURE 275-18 Gastric rugal thickening due to lymphoma. (Courtesy University of London. © Kenneth W. Simpson.)

Leiomyosarcoma

Leiomyosarcomas are slow growing tumors of smooth-muscle origin. The median age of affected dogs is >10 years. Intestinal leiomyosarcoma has been found to be more common in females and a predilection was reported in the German Shepherd breed. However, neither breed nor sex predilection has been reported for gastric leiomyosarcoma.[149] In one study, dogs with leiomyosarcoma of the spleen, stomach, small intestine, and cecum were grouped together with 79% showing no evidence of metastases at surgery and 64% surviving longer than 2 weeks.[149] Invasion of the gastric wall by leiomyosarcomas and lymphoma is often diffuse. These tumors may cause ulceration grossly resembling adenocarcinomas, or they may appear as discrete masses. The median survival of these dogs was 10 months (range: 1 month to 7 years). Of the stomach/small intestine group, 29% died of leiomyosarcoma eventually. Leiomyosarcoma and leiomyoma have been associated with paraneoplastic hypoglycemia and seizures, presumed due to the production of insulin-like growth factors (see ch. 352).[150]

Clinical Findings

The most common clinical signs associated with gastric neoplasia are chronic vomiting, weight loss, anorexia, diarrhea, and hematemesis, melena, or pallor if ulceration is present. Some dogs have abdominal pain or a distended abdomen. With GI lymphoma, onset of signs is often insidious, gradually increases in severity, and becomes refractory to symptomatic treatment.

Diagnosis

Survey radiographs may be completely normal or may suggest focal gastric wall thickening, an abdominal mass, evidence of peritonitis, splenomegaly, hepatomegaly, or lymphadenopathy. Spontaneous gastrointestinal perforation in cats has been associated with lymphoma.[151] US may reveal mural thickening or

irregularities that may indicate that lesions may be more submucosal or muscular than superficial. Lymphadenopathy or regional metasasis may be evident. US can be employed to evaluate gastric wall thickness and layering, and gastric emptying. US is less accurate than endoscopy for detecting gastric neoplasia, particularly lymphoma, but it can increase suspicion of a gastric lesion and facilitate detection of non-gastric lesions in pets with signs of GI disease.[32,33]

Gastroscopy (see ch. 113) is able to efficiently detect most gastric tumors and has largely replaced contrast radiography. Lymphoma is seen as a diffuse, smooth, or cobblestone-like thickening of the rugae with a mucosa that is pink or white and may have scattered petechial or ecchymotic hemorrhages. Gastric carcinomas tend to be focal, dark pink to red masses that may appear slightly pedunculated. Discolored purple to black areas indicate hemorrhage, whereas yellow to brown foci often represent necrotic ulcers. Some lesions are submucosal and one may gain the impression that something is indenting the stomach, or the wall seems less distensible or thick. Wireless capsule endoscopy may facilitate non-invasive detection of gastric neoplasia.

Several biopsy samples should be taken from suspicious areas, and masses should be biopsied multiple times in the same place to get deeper into tissue, as gastric tumors may have superficial necrosis, inflammation, and ulceration, areas that should be avoided when taking biopsies. Focusing at the periphery helps avoid perforation. Surgical biopsies should be taken where the gross endoscopic appearance does not match the histologic diagnosis, such as a large, focal gastric mass with an endoscopic biopsy result of lymphoplasmacytic gastritis. When endoscopy is not available, contrast radiography may be useful with features of gastric neoplasia, including thickening of the gastric wall, filling defects and derangement of normal rugal pattern, and delayed gastric emptying with retention and irregular pooling of barium. Surgery is then performed to sample the affected area.

Treatment

Except for lymphoma (see ch. 344), surgery is the most common form of treatment for gastric cancer. Resection may be curative if the affected area is localized, or if the tumor is benign. If a widespread area is involved, a partial gastrectomy or antrectomy followed by gastroduodenostomy (Billroth I) may be attempted. However, many patients are at a late stage of disease, and the lesions are often too extensive to resect. Gastric adenocarcinoma often metastasizes, and regional lymph nodes and liver should be inspected and biopsied. Even with surgery, the prognosis for malignant gastric neoplasia is poor, with most pets dying within 6 months from recurrent or metastatic disease. Leiomyosarcoma is an exception and carries a good to excellent prognosis if the mass is surgically resectable. Even if gross metastasis is evident at surgery, a favorable outcome may be achieved, because the tumor is slow growing. Survival in dogs with stomach, small intestinal, splenic, and cecal leiomyosarcoma ranges from 0 to 47 months after surgery, and the median survival is 12.5 months.[149]

GI lymphoma has a poor prognosis in dogs.[152] In cats the prognosis depends on whether the tumor is low or high grade, epitheliotrophic or transmural.[153] Small-T-cell lymphomas (typically epitheliotrophic) achieve substantial remission when treated with chlorambucil and prednisolone.[147,148] Large-cell lymphoma (B or T) is treated with combination cyclical chemotherapy and carries a much poorer prognosis.

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CHAPTER 276

Diseases of the Small Intestine

Edward James Hall, Michael J. Day

Client Information Sheets:
Inflammatory Bowel Disease
Giardia Infection

The conflicting functions of the small intestine (SI), namely nutrient digestion and absorption versus protection of the body from environmental threats, make it the largest and most complex immunologic organ in the body, as well as the main digestive organ. In previous editions of this textbook, the SI diseases chapter initially focused on diseases related to disturbances of its digestive function, and later, on diseases associated with the mucosal immune system.[1,2] The last edition then highlighted how the third major component of the SI, the *microbiome* (formerly the *enteric flora*), interacts with the mucosal immune system as part of the integrated function of the organ.[3] It has now become apparent that the microbiome is important not only in intestinal health but also in disease (see ch. 274). Dysbiosis is a disturbance of the normal microbiome and is involved in intestinal inflammation and even carcinogenesis and death.[4-7] This has led to the emergence of novel therapies such as probiotics, fecal microbial transplants and stem cell therapy for chronic enteropathies.[8-13] Even more remarkable, it is now recognized that the microbiome can affect the whole animal; the gut-brain axis involves two-way communication, with increasing evidence that the microbiome can affect behavior and cognitive function, a phenomenon which will undoubtedly be explored more in future editions.[14-20] But even with our current, improved understanding of its three main elements—mucosa, mucosal immune system, and microbiome—the clinician is better able to understand and treat many SI diseases.

The cardinal sign of these diseases is diarrhea, a significant increase in the frequency, fluidity, or volume of feces (see ch. 40). Yet diarrhea can be a manifestation of disease elsewhere in the gastrointestinal (GI) tract or in other organ systems (Box 276-1). Conversely, diarrhea is not present in all cases of SI disease, and there are many other signs of SI dysfunction, some of which are nonspecific (Box 276-2).

Box 276-1

Causes of Diarrhea

Gastrointestinal Disease

- Diffuse GI disease (e.g., inflammation or lymphoma)
- Gastric disease
  - Achlorhydria*
  - Dumping syndromes*
- Intestinal disease
  - Diet-related (e.g., food poisoning, gluttony, sudden change of diet, toxins)
  - Primary small intestinal disease
    - Dietary
    - Dysbiosis
    - Infectious
    - Inflammatory
    - Neoplastic
    - Toxic

- Primary large intestinal disease (see ch. 277)

Non-gastrointestinal Disease

- Pancreatic disease
  - Exocrine pancreatic insufficiency‡
  - Pancreatitis (acute, chronic)
  - Pancreatic carcinoma‡
  - APUDomas (gastrinoma causing Zollinger-Ellison syndrome)*
- Liver disease
  - Hepatocellular failure
  - Intrahepatic and extrahepatic cholestasis
- Endocrine disease
  - Classical hypoadrenocorticism‡ (see ch. 309)
  - Atypical hypoadrenocorticism‡ (see ch. 309)
  - Hyperthyroidism† (see ch. 301)
  - Hypothyroidism‡ (see ch. 299)
- Renal disease
  - Uremia (see ch. 322)
  - Nephrotic syndrome‡ (see ch. 325)
- Polysystemic infection (e.g., distemper, leptospirosis, infectious canine hepatitis in dogs; FIP, FeLV, FIV in cats)
- Miscellaneous
  - Toxemias (e.g., pyometra, peritonitis)
  - Portal hypertension and right heart failure
  - Autoimmune disease
  - Metastatic neoplasia
  - Various toxins and drugs

APUD, Amine precursor uptake and decarboxylation tumor; *FeLV*, feline leukemia virus; *FIP*, feline infectious peritonitis; *FIV*, feline immunodeficiency virus.

*Rare conditions.
‡Rare in cats only.
†Rare in dogs only.

Box 276-2

Clinical Signs of Small Intestinal Disease

Cardinal Sign

- Diarrhea
  - Increase in frequency, volume, and consistency of stool

Other Signs

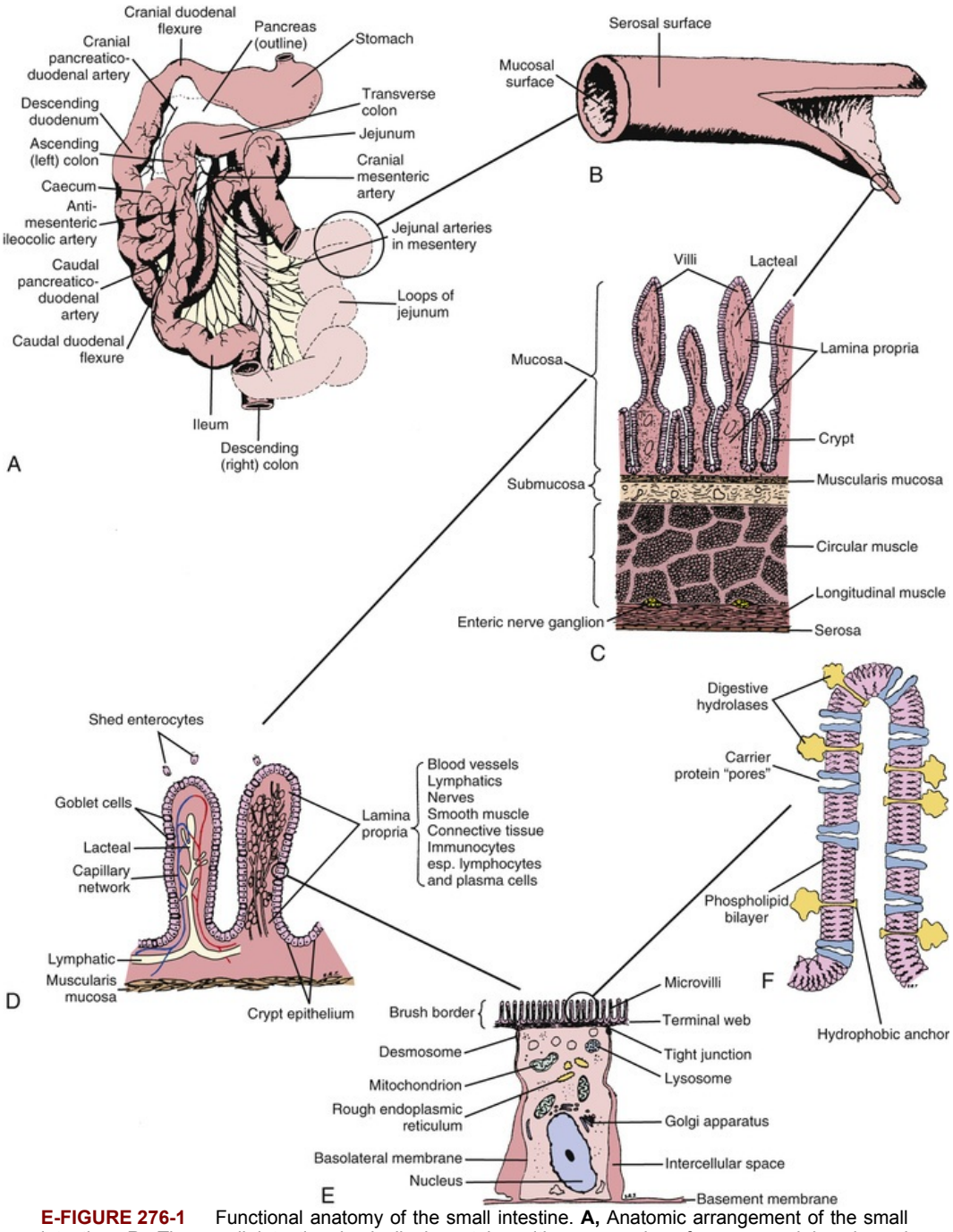
- Vomiting
- Weight loss and/or failure to thrive/stunting
- Hematemesis
- Melena
- Altered appetite
  - Inappetence/dysorexia
  - Anorexia
  - Polyphagia
  - Coprophagia
  - Pica
- Abdominal discomfort, pain

- Abdominal distension: ascites
- Peripheral edema
- Borborygmi and flatus
- Halitosis
- Dehydration
- Polydipsia (compensatory)
- Shock

Functional Anatomy of the Small Intestine

Normal Structure[21-33]

The SI begins at the pylorus of the stomach and ends at the ileocolic valve, being divided arbitrarily into three segments: the duodenum proximally, where the common bile duct and one or more pancreatic ducts enter, then the jejunum, and finally the ileum (E-Figure 276-1, *A*). Blood is supplied by branches of the celiac and cranial mesenteric arteries, and it drains to the liver via the portal vein. Lacteals in the villi drain to mesenteric lymphatic vessels that pass to the cisterna chyli. The autonomic innervation of the SI is from the vagus and splanchnic neves.



E-FIGURE 276-1 Functional anatomy of the small intestine. **A,** Anatomic arrangement of the small intestine. **B,** The small intestine basically is a tube with a serosal surface covered by visceral peritoneum and an inner absorptive and digestive surface, the mucosa. **C,** Beneath the outer serosa, longitudinal and circular muscle layers produce peristaltic and segmental contractions for propelling and mixing the luminal contents. The submucosa is rich in blood and lymphatic vessels. The mucosa comprises the thin muscularis mucosa, the lamina propria, and the columnar epithelium; it is thrown into folds and is covered by fingerlike villi to increase the digestive and absorptive surface area. **D,** Enterocytes, which are shed from the villus tip but are continually replaced through division of crypt cells, are the site of nutrient digestion and absorption. Goblet cells secrete protective mucus. Water-soluble nutrients pass into the rich capillary network of the lamina propria, and fat is passed as chylomicrons into the lacteals. Immunocytes in the lamina propria are involved in maintaining tolerance to luminal antigens. **E,** The luminal membrane of the enterocyte is thrown into processes called microvilli, which increase the luminal surface area. Tight junctions between enterocytes maintain epithelial integrity. Absorbed nutrients are passed from the enterocyte into the intercellular space for distribution to the body. **F,** A schematic representation of a microvillus showing digestive hydrolases anchored in the phospholipid cell membrane and protruding into the intestinal lumen. Carrier proteins in the membrane are believed to act as "pores," shuttling nutrients across the membrane by means of conformational changes in their structure often induced by sodium influx at the expense of energy utilization through Na/K ATPase on the basolateral membrane. (From Hall EJ: Small intestinal disease. In Gorman NT, editor: *Canine medicine and therapeutics,* ed 4, Oxford, 1998, Blackwell Science, p

488.)

The SI is, in essence, a tube ultimately connected to the external environment via the mouth and anus with a basic cross-sectional structure of serosa, muscularis (outer longitudinal and inner circular muscle layers), submucosa, and mucosa around the lumen (E-Figure 276-1, *B*). The inner, mucosal layer is the most important clinically and is responsible for secretory, absorptive, and barrier functions (E-Figure 276-1, *C*). It varies in thickness along the SI, being thinnest distally, and comprises the epithelium and the underlying lamina propria, which contain components of the mucosal immune system. The mucosa is modified by gross folds and finger-like processes, the villi, covered by an epithelial layer of enterocytes and goblet cells that increase its surface area many hundred-fold.

A villus and its feeder crypts comprise the functional unit of the SI (E-Figure 276-1, *D*). Crypt cells are the site of intestinal secretion, and they continually produce undifferentiated epithelial cells. Most develop as enterocytes as they migrate from crypt to villus tip, where they ultimately are shed after approximately three days. Differentiated enterocytes undertake digestive and absorptive processes through digestive enzymes and carrier proteins expressed on the luminal cell membrane, the microvillar membrane (MVM), also called the *brush border* because of its microscopic appearance (E-Figure 276-1, *E* and *F*).

Normal Function[34-38]

Enterocyte function is geared towards production of brush-border proteins for the digestion, absorption, and transfer of simple nutrients and water from the lumen to the blood and lymphatics. Glutamine derived from food is the major energy source for enterocytes, explaining the decline in villus structure and epithelial barrier and immune functions during starvation.

Digestion[39,40]

Major dietary constituents must be hydrolyzed into simple molecules to be transported across the mucosa. This is largely achieved within the SI by bile salt emulsification and luminal enzymatic hydrolysis: the SI merely provides the optimum environment in terms of temperature, pH, and mixing with bile salts and pancreatic digestive enzymes. Only terminal hydrolysis of carbohydrates and proteins is performed by MVM enzymes.

Absorption[41-52]

Simple sugars, amino acids, and oligopeptides are absorbed by active or facilitated carrier-mediated transport; the products of fat digestion and fat-soluble vitamins (A, D, E, and K) are absorbed by passive diffusion into lacteals. Endocytosis of peptides by the adult SI is of no nutritional significance, but neonatal absorption of intact colostral antibodies is crucial.

The absorption of folic acid and vitamin B_{12} is complex (Figure 276-2, *A*) and important clinically because their malabsorption could help determine the site and severity of intestinal disease (Figure 276-2, *B*). Folic acid is absorbed in the proximal SI, while cobalamin (vitamin B_{12}), bound to intrinsic factor, is absorbed in the ileum. Cats and dogs have less capacity to store cobalamin than do humans; cats also lack the binding protein transcobalamin I and rapidly lose cobalamin through enterohepatic recycling. Thus, severe cobalamin malabsorption can deplete cobalamin stores in cats within a month.

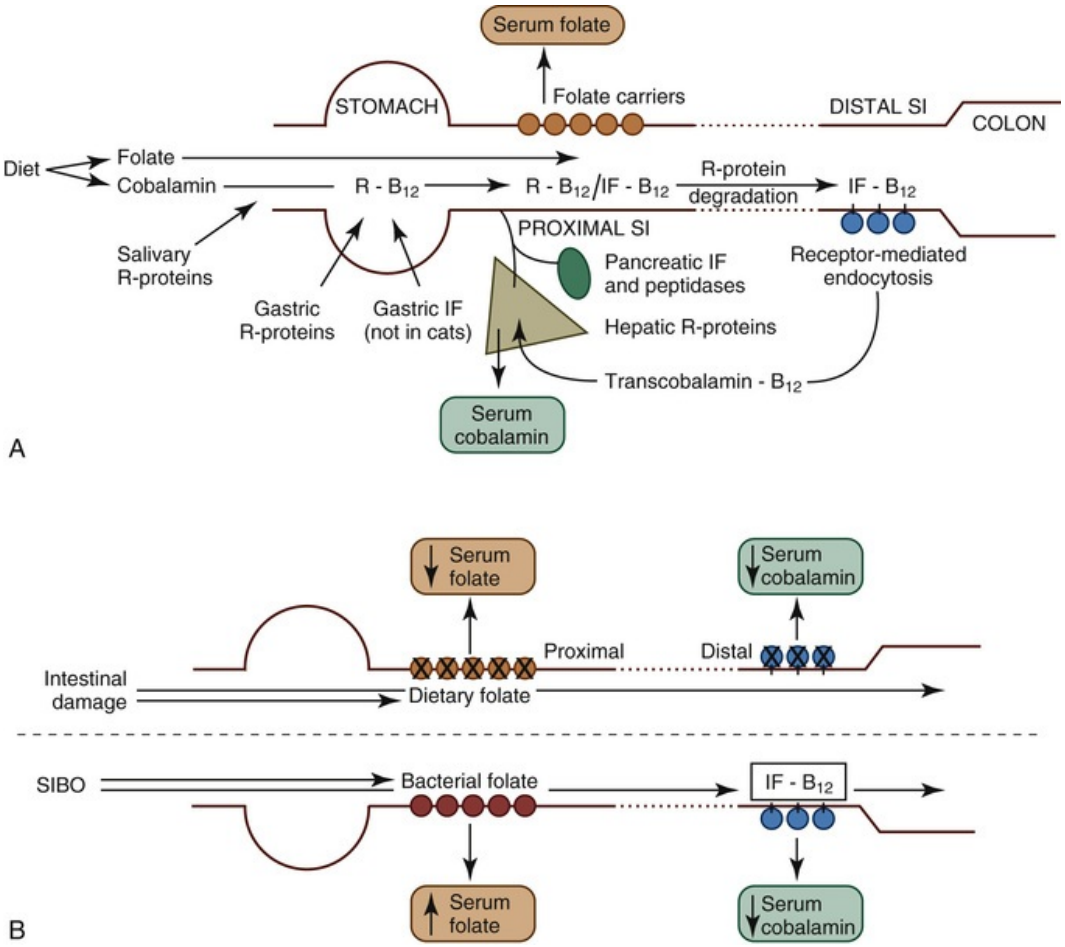


FIGURE 276-2 Diagrammatic representation of the absorption of folate and cobalamin. **A,** In normal intestine, folate is absorbed in the proximal SI by means of carrier-mediated diffusion. Dietary cobalamin initially is protected from digestion by R-proteins and then is absorbed in the ileum through receptor-mediated endocytosis, when bound to intrinsic factor. **B,** In diseased intestine, proximal and distal mucosal damage causes folate and cobalamin malabsorption, respectively. Reduced serum folate and/or cobalamin is/are markers for proximal and/or distal SI damage. Classically, small intestinal bacterial overgrowth (SIBO) causes increased folate uptake because of bacterial folate synthesis and decreased cobalamin uptake because of bacterial incorporation. However, these changes are poorly sensitive and cannot be used for making a diagnosis: they do not correlate with antibiotic-responsiveness. *IF,* Intrinsic factor; *SI,* small intestine.

Motility[53-70]

Slow wave, segmental, and peristaltic contractions of the SI are generated by the coordinated contraction of longitudinal and circular smooth muscle in response to spontaneous electrical activity: interstitial cells of Cajal are the pacemaker cells. Intestinal motility in the fasted state in dogs is characterized by a three-phase cycle: a *quiescent* phase, then *minor contractile activity,* followed by short *migrating myoelectric* (motor) *complexes* (MMCs) that sweep away indigestible material. The MMC "intestinal housekeeper" wave is induced by the hormone motilin, and it can be replicated by low dosages of erythromycin stimulating the motilin receptor. Segmental contractions slow intestinal transit and ensure mixing and digestion of nutrients, until peristalsis propels the ingesta onward. The duration and pattern of contractile activity in the fed state are determined by the nature of the diet, with unabsorbed fats and fiber prolonging activity.

Absorption and Secretion of Water and Electrolytes[71]

The pathophysiology of diarrhea is detailed in ch. 40. Diarrhea is a result of an imbalance between the net amount of fluid and electrolytes secreted and absorbed. Net absorption occurs in health, but the fluxes through the intestine are massive (≈2 liters a day in a 20-kg dog) and net losses result in both diarrhea and severe dehydration. Colonic absorption is important, as it can help compensate for net SI losses, but diarrhea will occur if its reserve capacity is overwhelmed (see ch. 277).

Small Intestinal Microbiome[72-74]

Normal Microbial Population[75-114]

The microbiome comprises bacteria, protozoa, fungi, and viruses, and it is an integral part of the healthy SI. It affects many aspects of SI function—villus size, enterocyte turnover, brush border enzyme turnover, and motility—and the presence of a stable microbiome is important for the development and ongoing balance of the mucosal and systemic immune systems, and for preventing colonization by pathogens. In intestinal disease, the diversity of the bacterial component of the microbiome is reduced and there is a shift to potentially harmful species, while the viral component (the virome) is diversified.

The bacterial flora is the largest component of the microbiome, and it comprises a diverse mixture of aerobic, anaerobic, and facultatively anaerobic bacteria, with more than 200 species present in any individual animal's SI. Many organisms in the microbiome are unculturable, but molecular fingerprinting techniques, using high-throughput 16S rRNA sequencing, can now identify them. The healthy microbiome is relatively resistant to environmental changes but can be modified, both positively and negatively, by dietary changes, antibiotic use, and even lifestyle. Although the effects of antibiotic therapy on the flora often are clinically mild and self-limiting, persistent changes in the microbiome do occur, and therefore, the indiscriminate use of antibiotics in diarrhea is ill-advised, especially as it can also enhance antibiotic resistance; fatal post-antibiotic salmonellosis has been recorded in cats.

Bacterial numbers increase from duodenum to colon: factors maintaining this aboral gradient are luminal patency, motility, substrate availability, bacteriostatic and bactericidal secretions (gastric acid, bile, goblet cell and pancreatic secretions), and an intact ileocolic valve. Quantitative bacterial analysis performed on samples of undiluted intestinal juice from the proximal SI has revealed bacterial counts in healthy dogs and cats ranging from 10^2 to 10^8 colony-forming units (CFUs) of total bacteria/mL. These numbers reach considerably higher than the $<10^5$ CFU/mL reported in healthy humans but which, historically, were extrapolated incorrectly to dogs.

Bacterial-Mucosal Interactions[115-133]

Interactions between bacteria and the mucosa normally are mediated by epithelial surface receptors that are part of the innate immune system. The epithelium uses pattern recognition receptors (PRRs) to recognize conserved elements of bacterial structure (see ch. 274). Originally referred to as "pathogen-associated molecular patterns" (PAMPs) expressed by potentially pathogenic organisms, the alternative terminology "microbe-associated molecular patterns" (MAMPs) encompasses the concept of interaction with normal commensal organisms in addition to pathogens (Figure 276-3).

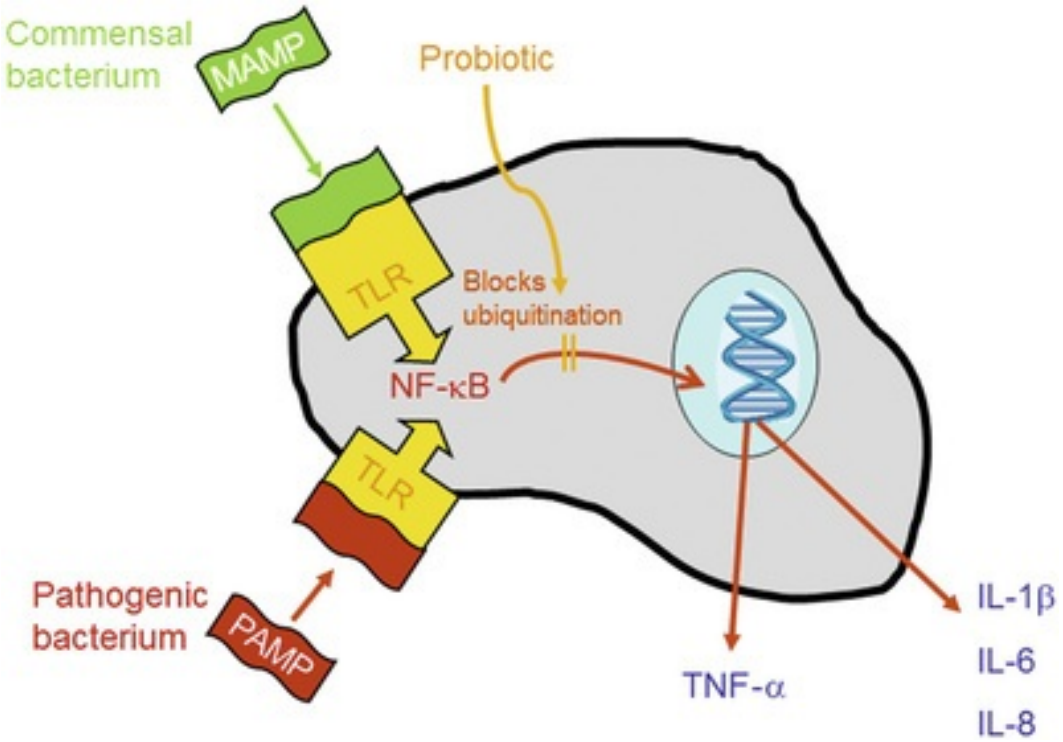


FIGURE 276-3 Recognition of commensal and invading bacteria by mucosal-associated lymphoid tissue. Toll-like receptors (TLRs) are found on endothelial cells, monocytes, macrophages and dendritic cells of the intestinal mucosal-associated lymphoid tissue (MALT), as well as the basolateral surface of enterocytes. The TLRs recognize microbe-associated molecular patterns (MAMPs) expressed by all bacteria and stimulate, via intracellular signalling, the production of the nuclear transcription factor NF-kappa-B. When the cell is exposed to a pathogen-associated molecular pattern (PAMP), NF-kappa-B is ubiquitinated and it can then activate the transcription of the mRNA encoding proinflammatory cytokines such as tumor necrosis factor (TNF-alpha) and various interleukins (ILs), triggering the inflammatory cascade. However, when stimulated by commensal or probiotic organisms, the ubiquitination of NF-kappa-B is blocked. The mechanism of how commensals and pathogens are differentiated is not known.

The enterocyte PRRs include a range of Toll-like receptors (TLRs) and nucleotide oligomerization domain-like receptors (NODs) that can be expressed on the surface membrane or within cytoplasmic compartments. Examples of these molecules include TLR2and TLR4, which, respectively, recognize lipopeptides and lipopolysaccharide found in Gram-negative bacteria; TLR5, which recognizes the bacterial flagella protein (flagellin); and NOD2, which recognizes bacterial lipopolysaccharide.

Gastrointestinal Immune System

The SI mucosa has a general barrier function (E-Box 276-3) and must remain "tolerant" of harmless antigens, such as commensal bacteria and food, while being able to generate a protective immune response against pathogens. The default response of the SI immune system is tolerance, and this is expressed not only within the intestinal tract; tolerance responses at other mucosal surfaces and within the systemic immune system can be induced from interactions within the intestinal tract. Intestinal tolerance responses can be driven by specific subsets of tolerogenic antigen-presenting cells (APCs) that induce antigen-specific regulatory T cells (Tregs) that mediate these effects. Particular elements of the microbiome appear to be responsible for amplifying and maintaining Treg activity to prevent local and systemic immune-mediated diseases.

E-Box 276-3

Components of the Intestinal Mucosal Barrier

- Protein denaturation by gastric acid
- Proteolysis by enzymes and bacteria
- Antimicrobial peptides (e.g., defensins)

- Clearance of waste by peristalsis
- Unstirred water layer
- Surface mucus layer
- Secretory IgA
- Enterocyte microvillus membrane
- Epithelial tight junctions
- Transepithelial electrochemical potential
- Epithelial repair factors (e.g., epidermal growth factor, trefoil peptides)
- Mucosal-associated lymphoid tissue

Functional Anatomy of the Mucosal Immune System[134-138]

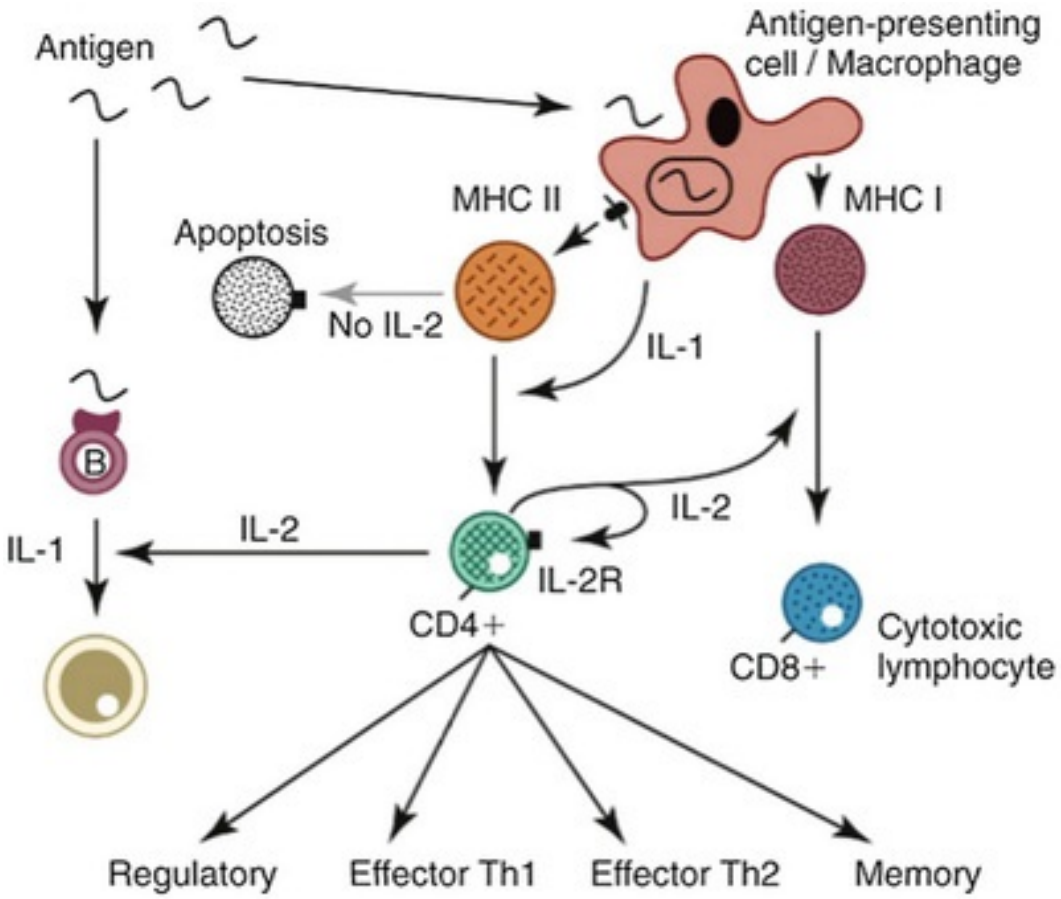
The mucosa-associated lymphoid tissue (MALT) occurs at internal body surfaces; in the intestine, it is termed *gut-associated lymphoid tissue* (GALT) and consists of inductive and effector sites. Inductive sites comprise Peyer's patches (PPs), isolated lymphoid follicles, and the mesenteric lymph nodes (MLNs), whereas effector sites comprise the intestinal lamina propria (LP) and epithelium. Such a distinction is not absolute, however, and the functions of these different sites overlap. The LP consists of a matrix of connective tissue with a prominent mixed, but predominantly lymphoplasmacytic, immune cell component. A large intraepithelial lymphocyte (IEL) population also exists in between enterocytes.

Cells and Molecules of the Mucosal Immune System

Lymphocytes[139-157]

B lymphocytes are present in the follicular region of PPs and the mesenteric lymph nodes. The LP is endowed with a large population of plasma cells, the terminal differentiation stage of an activated B cell. They are predominantly located in the peri-cryptal LP, and most are committed to the production of immunoglobulin (Ig) A. Intestinal T lymphocytes mostly have a T-cell receptor (TCR) formed of an alpha and beta chain and mainly are located within the LP and organized lymphoid tissues; some are IELs. An evolutionarily older T-cell population expressing a TCR comprised of a gamma and delta chain also exists, and these largely are IELs. Because of their location, these cells are considered a primitive first-line defense against pathogens.

T lymphocytes can be subdivided further on the basis of expression of CD4 and CD8 molecules. CD4 T cells (classical "helper" T cells) recognize antigenic peptide presented by major histocompatibility complex class II (MHC II) molecules on APCs, whereas CD8 T cells (usually cytotoxic cells) are MHC class I restricted (E-Figure 276-4). In the canine LP, T cells are most numerous in the upper villus regions and are mostly of the alpha-beta-TCR, CD4 phenotype. However, in the feline LP, CD8 T cells outnumber the CD4 population. There are several functional subsets of the Th population, and these will be described below. Additionally, several subsets of "innate lymphoid cells," which have lymphoid morphology but do not carry classic lymphocyte receptor molecules (see below), now are recognized. Most LP lymphocytes are highly differentiated, which implies that they receive continuous antigenic and mitogenic stimulation, probably from the endogenous microbiome.



E-FIGURE 276-4 Activation of mucosal $CD4^+$ T cells. Antigen presentation in association with major histocompatibility complex (MHC) class II molecules activates mucosal $CD4^+$ T cells. The result is either clonal expansion into memory and effector cells or apoptosis, depending on the synthesis of interleukin-2 receptor (IL-2R) and IL-2. $CD8^+$ T cells are activated by antigen presentation in association with MHC class I molecules and, under the influence of $CD4^+$ T cell–derived cytokines, develop into intraepithelial lymphocytes. Gamma-delta-T cells also form a part of the intraepithelial cell compartment.

Dendritic Cells[118,158-166]

Dendritic cells (DCs) function predominantly as APCs and can be found in both inductive (PP) and effector (LP) tissues. Follicular dendritic cells store antigen to provide continued stimulation to memory B cells. DCs also are prominent in the villus lamina propria, where their main function is antigen sampling. These DCs often are located immediately beneath the enterocyte layer and are able to extend cytoplasmic processes (dendrites) between enterocytes and into the intestinal lumen to sample antigen. In inductive sites, they are responsible for generating active immune responses and tolerogenesis. In rodents, the lamina propria DCs responsible for each of these effects are defined by expression of the CD103 molecule, with those inducing inflammatory responses being $CD103^-$ and those inducing Treg-mediated tolerance being $CD103^+$.

Other Immune Cells[143,145,167-170]

Macrophages are present in the PP and LP, and their functions include phagocytosis, antigen presentation, and immunoregulation. They secrete cytokines, chemokines, and inflammatory mediators, including tumor necrosis factor-alpha (TNF-alpha), eicosanoids, and leukotrienes. Neutrophils are present in small numbers normally, although their numbers increase with mucosal inflammation. Both mast cells (MCs) and eosinophils can be found in the normal LP and can actively produce chemical mediators of inflammation (e.g., histamine, heparin, eicosanoids, and cytokines). Mast cells express the high-affinity IgE receptor (Fc-epsilon-RI), which can bind IgE, causing MC degranulation and release of its inflammatory mediators. In dogs, eosinophils are a prominent population in the LP, especially in the crypts. Eosinophils can have

proinflammatory roles, especially in allergic processes, because they are a rich source of proinflammatory mediators, cytokines, and chemokines. Triangular cross-talk can occur among eosinophils, MCs, and T cells.

Enterocytes[167,171-174]

Enterocytes have important immune functions. First, they exclude antigen. Second, they express surface TLRs, which interact with the enteric flora. Third, they can present antigen through expression of MHC II. In dogs, MHC II is expressed constitutively by enterocytes, but this molecule largely is absent from enterocytes of cats, although it is upregulated in inflammation. Fourth, enterocytes can produce inflammatory mediators, chemokines, and cytokines.

Enteric Neurons[175,176]

Enteric neurons can release immunoactive neuropeptides including substance P, which can cause neurogenic inflammation via neurokinin (NK) receptors. Bidirectional communication also can exist, in which release of mediators by immune cells (e.g., mast cells) can generate axon reflexes and thereby modulate intestinal motility, secretion, and absorption.

Cytokines[177-187]

A large array of cytokines is produced by cells in the SI, and these molecules can be grouped into proinflammatory, immunoregulatory, and chemokinetic types. Different CD4 Th-cell populations have different patterns of cytokine secretion and can differentially regulate distinct arms of the immune system (i.e., humoral and cell-mediated). *In vitro*, two principal populations of $CD4^+$ T cells exist. T helper 1 (Th1) cells produce interleukin-2 (IL-2) and interferon-gamma (IFN-gamma) and mediate cellular immunity involving activation of CD8 cytotoxic T cells and macrophages, classically in response to infection with intracellular pathogens or to cancer. T helper 2 (Th2) cells produce IL-4, IL-5, IL-6 and IL-13 and function to promote B-cell activation and differentiation to antibody-secreting plasma cells. Th2 cells mediate the "immunoglobulin class switch" during B-cell activation, which in the SI is primarily to IgA or IgG. Th17 cells are characterized by production of IL-17, and they function in inflammatory responses, including having a key role in the pathogenesis of inflammatory enteropathies.

Other populations have down-regulatory functions. Th3 cells producing TGF-beta have been identified as effectors of classical "oral tolerance," but the $CD25^+$ $Foxp3^+$ Treg cell (producing IL-10 as a signature cytokine) is the more important "suppressor" population in terms of local intestinal or distant systemic tolerance. Many other cell types also can produce cytokines, and it is the overall local cytokine "milieu" that determines the predominant type of immune response.

The polarized roles of these classical T-cell subsets are mirrored by the complementary activities of recently identified "innate lymphoid cells" (ILCs). Group 1 ILCs, which include the natural killer (NK) cells, produce IFN-gamma akin to Th1 cells. Group 2 ILCs produce IL-5 and IL-13, paralleling the effects of Th2 cells. Group 3 ILCs produce IL-17 and IL-22 and can be either proinflammatory (as for Th17 cells) or in some circumstances have a protective, antiinflammatory effect.

Homing of Lymphocytes in Gut-Associated Lymphoid Tissue[143,149,188-191]

Lymphocytes traffic between inductive and effector sites. Homing pathways are mediated by leukocyte-endothelial interactions through differential expression of "homing receptors" on the surface of the leukocyte interacting with endothelial "vascular addressins." The most important interaction for mucosal lymphocytes occurs between $alpha_4/beta_7$ on the lymphocyte and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) on the endothelial cell. A final factor important to the homing of lymphocytes is the production of chemokines and their receptors. The chemokine milieu of a particular tissue determines which T-helper cell types and other immune cell subsets are recruited from the circulating blood into the tissue.

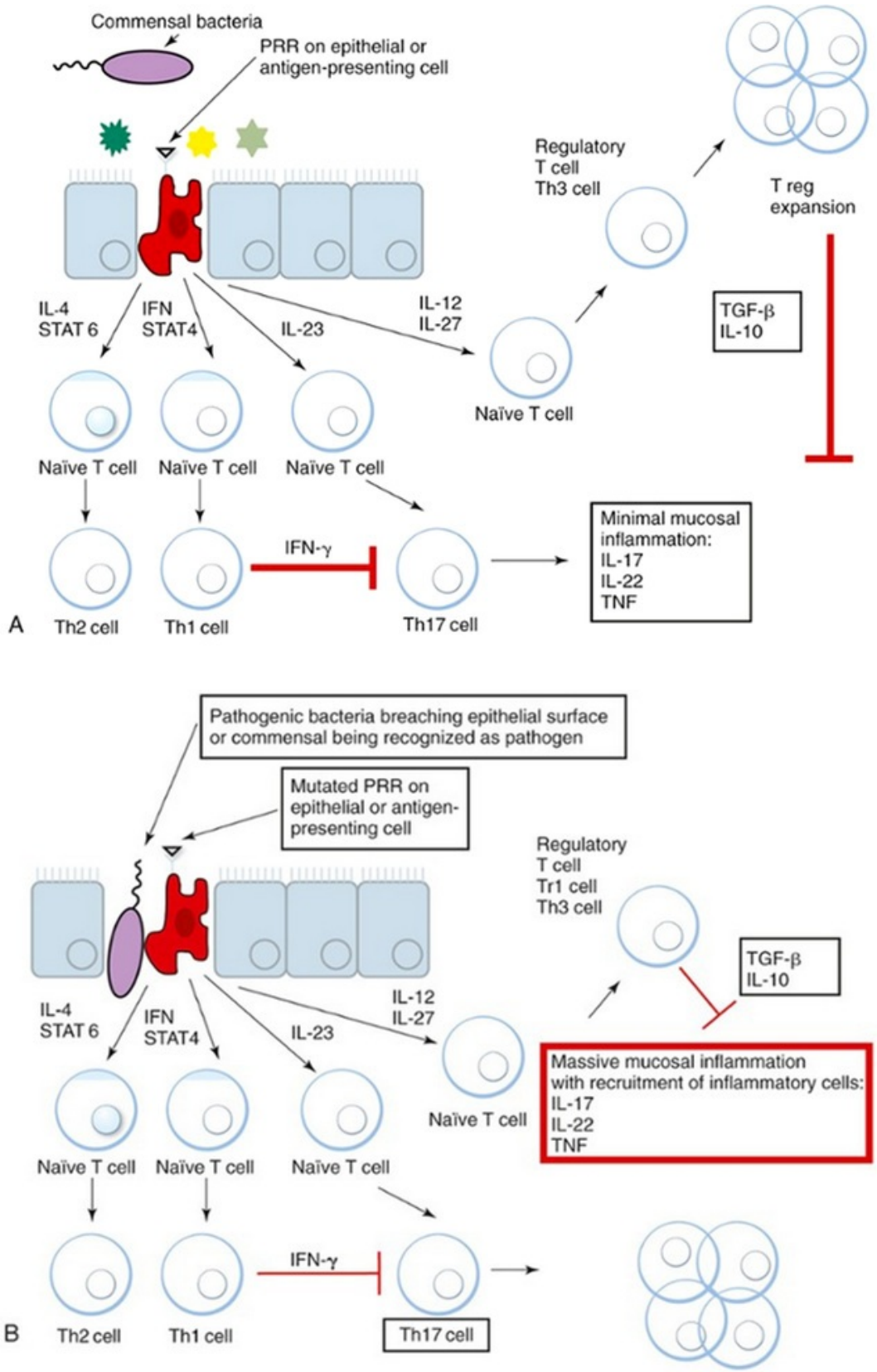
Innate Immune Responses of the SI[192-194]

The innate immune defenses of the SI largely have been described above and include factors such as peristaltic movement, the presence of the intestinal microbiome, the mucus layer and the enterocyte barrier, and the presence and function of innate immune cells (e.g., DCs, macrophages, granulocytes, ILCs and gamma-delta-TCR-expressing IELs). Although poorly defined in the dog and cat, the production of cathelecidin-related antimicrobial peptides (i.e., defensins) by enterocytes (and particularly by cryptal Paneth

cells) is of major importance in other species.

Acquired Immune Responses of Gut-Associated Lymphoid Tissue

Acquired immune responses develop after a series of steps involving antigen uptake, presentation to naïve lymphocytes, costimulation by helper cells, clonal proliferation and differentiation, homing to effector sites, and performance of effector functions (E-Figure 276-5, *A*). The specific mechanisms involved are described in detail elsewhere, but some features unique to the GALT are described here.



E-FIGURE 276-5 A hypothetical model of oral tolerance to commensals and development of inflammatory bowel disease (IBD). **A,** In the healthy intestine, antigen-presenting cells (APCs) continuously sample antigens from the lumen through pattern recognition receptors of microbe-associated molecular patterns (MAMPs) expressed by all bacteria. Depending on both the nature of the antigen and the route by which it is presented (e.g., bacterial, invasive), the APCs drive an adaptive immune response in the appropriate direction. When commensal bacteria are encountered, naïve T cells preferentially differentiate into T-regulatory cells (Treg and Th3), whereas pathogenic bacteria

induce differentiation to Th17 cells to produce proinflammatory interleukin (IL)-17 and IL-22. With exposure to viruses, naïve T cells preferentially differentiate into Th1 cells, which produce cytokines including interferon-gamma (IFN-gamma), thereby recruiting macrophages to kill intracellular viruses and inhibit Th17 differentiation. Parasitic infections drive differentiation to Th2 cells, which recruit eosinophils, basophils, and mast cells to kill or expel the parasite. **B,** In the case of IBD, one or all of 3 factors (dysbiosis, abnormal mucosal permeability, and mutations/polymorphisms in PRRs) lead(s) to the abnormal recognition of commensal bacteria as pathogens, inducing a Th17 response. Proinflammatory cytokines (IL-17, IL-22 and TNF) induce inflammation and epithelial cell injury, allowing more commensal bacterial antigen into the mucosa, such that counterregulation by Tregs fails, and IBD is established. *IFN-gamma,* Interferon gamma; *IL,* interleukin; *PRR,* pattern recognition receptor; *STAT,* signal transducer and activator of transcription protein; *TGF-beta,* transforming growth factor–beta; *Th,* T helper cell; *TNF,* tumor necrosis factor; *Treg,* regulatory T cell.

Antigen Uptake and Presentation[161]

Uptake of particulate antigen occurs through the microfold (M) cells located within the epithelial covering of PPs. M cells transfer luminal antigen to DCs and macrophages within these lymphoid tissues. These APCs process and present antigen to lymphocytes in the context of MHC II molecules (see E-Figure 276-4). Soluble antigens can be absorbed via enterocytes and presented to T cells, and direct luminal antigen sampling by DCs has been described above.

T- and B-Cell Responses[181,195-198]

The role of Th1 and Th17 cells in cytotoxic and inflammatory responses in the intestinal mucosa, and the role of Treg cells in local and systemic tolerance, have been discussed above.

B cells recognize intact conformational antigenic epitopes via their surface membrane B-cell receptor (Ig) (signal 1) and require T cell "help" in the form of direct intercellular molecular interaction (signal 2) and the provision of Th2 cytokine acting on a B-cell cytokine receptor (signal 3). The B-cell "immunoglobulin class switch" enables the differential production of IgA, IgE, or IgG antibodies in response to different classes of antigen. After class switching, B cells undergo further expansion, then traffic to effector sites to differentiate into plasma cells.

IgA synthesis predominates in the healthy intestinal mucosa. Plasma cells in the lamina propria release dimeric IgA molecules, two monomers linked by the joining (J) chain. Dimeric IgA is captured by the polymeric immunoglobulin receptor (pIgR) expressed on the basolateral surface of enterocytes. The complex of receptor and IgA passes through the enterocyte and is delivered across the MVM. On the luminal surface, the pIgR is cleaved to form the secretory component (SC), which remains associated with pIgA, protecting it from enzymatic degradation in the intestinal lumen. The main function of secretory IgA (SIgA) is immune exclusion; that is, to bind its respective antigen and neutralize it. This helps maintain tolerance and protects the mucosa from antigen invasion. Deficiency of SIgA could predispose to intestinal disease.

Responses to parasites involve Th2-determined production of IgE that binds to the Fc-epsilon-RI on mucosal mast cells. When subsequently exposed to antigen, MC degranulation occurs, initiating a local inflammatory reaction, recruitment of tissue eosinophils, and enhanced goblet cell production of mucus. These various effector mechanisms can lead to death of larval forms within the mucosa or expulsion of luminal parasites. Inappropriate IgE responses also can be generated, providing a proposed mechanism for food allergy via a classic type I hypersensitivity response.

Mucosal Tolerance[199-203]

The above descriptions relate to specific immune responses to pathogens, but such responses are the exception rather than the rule, and the default mucosal response to antigens is tolerance. This is not surprising, given that the majority of luminal antigens are derived from innocent dietary components and commensal microflora. Generation of active immune responses to such ubiquitous molecules could be both wasteful and potentially harmful because it could lead to uncontrolled inflammation. Although the mechanisms by which mucosal tolerance actually occurs have been well characterized, the fundamental question of what prompts GALT tolerance or an immune response remains unresolved.

Mucosal tolerance can result either from anergy/deletion (apoptosis) of antigen-specific T cells or from active suppression by antigen-specific suppressor cells. The $CD4^+$ alpha/beta T-cell subsets that mediate active suppression either produce downregulatory cytokines (e.g., TGF-beta, IL-10 or IL-17) or achieve their effect through cell-to-cell interactions (e.g., through CD25, IL-2 receptor). However, any cell capable of producing similar cytokine profiles could play a role and, therefore, tolerance could arise from the effects of $CD8^+$ T cells, macrophages, stromal cells, and enterocytes. Furthermore, because TGF-beta and IL-10 also are

important in IgA production, generation of mucosal tolerance likely occurs in parallel to specific IgA responses, which helps to maintain tolerance through immune exclusion.

Consequences of Inappropriate Immune Activation in the SI[124,132,204-226]

In healthy individuals, the intestinal immune system is maintained in a complex homeostatic balance with a dominant tolerogenic setting. Many of the diseases discussed in this chapter arise when this homeostasis is disturbed by multifactorial influences, including genetic factors, barrier dysfunction and dysbiosis, leading to inappropriate exposure to luminal antigen, induction of tissue inflammation, and alteration in the balance between immune effector and regulatory cells in the mucosa.

If the inappropriate antigenic challenge is contained, the mucosa enters a repair phase, and the normal "tolerogenic" environment returns. However, if the danger persists, either because the mucosal barrier remains breached and/or the pathogenic insult continues unabated, or because of an inherent abnormality in the GALT, a state of chronic inflammation ensues. Inflammation causes increased expression of MHC II molecules and activation of both lymphocytes and endothelial cells, altering the expression of vascular addressins. Enhanced expression of MAdCAM-1 leads to increased recruitment of specific mucosal lymphocytes, whereas expression of other addressins (e.g., E-selectin, P-selectin and peripheral node addressin) can lead to recruitment of a broader range of immunocyte specificities. Extracellular proteolysis by matrix metalloproteinases can lead to architectural changes. Thus, chronic inflammation ultimately leads to histopathologic changes, which are likely to be similar regardless of inciting cause. Furthermore, it has been hypothesized that chronic stimulation of lymphocytes in genetically predisposed patients could ultimately result in expansion of a malignant clone of T-lymphocytes and mucosal lymphoma.

Pathophysiologic Mechanisms in Intestinal Disease

A number of potential pathophysiologic mechanisms can lead to dysfunction of the SI, and one or more of the following can be present in any one specific SI disease.

Luminal Disturbance[227-232]

Lack of pancreatic enzymes in exocrine pancreatic insufficiency (EPI; see ch. 292), or increased destruction of enzymes by acid hypersecretion (e.g., Zollinger-Ellison syndrome; see ch. 275), or bacterial overgrowth, results in failure of digestion. *Dysbiosis* is a better term than overgrowth to describe the disturbance of the normal microbiome that can occur following infection, antibiotic usage, sudden dietary change, or due to underlying mucosal immunoincompetence or inflammation. Some bacteria compete for nutrients and produce metabolites (e.g., deconjugated bile salts, hydroxylated fatty acids) that can stimulate intestinal secretion. Interruption of normal enterohepatic circulation and lack of bile salts result in fat malabsorption. Bile salt deficiency can be caused by marked hepatic dysfunction, bile duct obstruction, bacterial deconjugation, or ileal disease.

Brush Border Membrane Disease[40,47,48,52,233-254]

Primary brush border membrane diseases are biochemical abnormalities that occur in the absence of structural damage. Lack of a key digestive enzyme leads to maldigestion/malabsorption, osmotic diarrhea, and weight loss. Sucrase-isomaltase deficiency is recognized in humans, but it has not yet been described in dogs or cats. Lactase deficiency in man either can be a congenital failure to express the enzyme due to a genetic mutation, or downregulation of expression in adults. Congenital lactase deficiency has not been reported in dogs and cats, but a relative deficiency does occur, particularly in adult cats, as expression is reduced after weaning. Congenital lack of brush border aminopeptidase N has been described in dogs but has no clinical significance as other peptidases compensate.

The mechanism of cobalamin deficiency commonly seen in Chinese Shar-Peis with intestinal disease has not been elucidated yet, but defects in cobalamin–intrinsic factor uptake in the ileum can be due to a mutation in the receptor molecule cubilin. The genetic mutations causing selective cobalamin malabsorption, also known as Imerslund-Gräsbeck syndrome, have been identified in Australian Shepherds, Beagles, Collies, and Giant Schnauzers. All the mutations result in cobalamin deficiency with consequent methylmalonic aciduria and a constellation of clinical signs including one or more of inappetence, failure to thrive, liver degeneration, hepatoencephalopathy, neutropenia, anemia, and proteinuria. Diarrhea can be a feature, as cobalamin-deficient diets result in histologic abnormalities in, and dysfunction of, the SI.

Surgical resection of the ileum (e.g., due to irreducible ileocolic intussusception) and disease affecting the distal SI cause both bile salt and cobalamin malabsorption. However, a congenital deficiency of the ileal bile salt transporter reported in humans, and a cause of severe diarrhea, has not yet been reported in dogs or cats.

Microvillar Membrane Damage[255-260]

The MVM is obviously damaged when overt histologic villus damage can be seen, but even without light microscopic changes, massive impairment of mucosal function can occur if the microvilli are damaged. Such damage is seen with enteropathic *E. coli* infection, carrageenan gum, or lectins, which cause a loss of brush border enzymes and carriers and surface area. Bacterial overgrowth is associated with subtle but specific damage to the membrane, as anaerobes are very effective at degrading membrane glycoproteins and releasing brush border enzymes.

Enterocyte Dysfunction[261,262]

Damage to enterocytes by bacterial toxins but without histologic damage still can interfere with enterocyte function, as well as cause subcellular loss of brush border proteins. Malnutrition and ischemia also impair function and increase epithelial permeability. Abetalipoproteinemia in humans is a failure of transcellular lipid transport resulting in abnormal lipid accumulation within enterocytes. Although this condition has not yet been reported in dogs and cats, the weight loss drug dirlopatide acts by blocking microsomal triglyceride transfer protein within enterocytes and hence fat absorption; diarrhea is a common and predictable side effect of this drug.

Epithelial Barrier Disruption[263-272]

Epithelial integrity is crucial in maintaining oral tolerance and excluding pathogens. In the experimental N-cadherin dominant negative chimeric mouse, where epithelial integrity is disrupted because of a lack of expression of the normal E-cadherin in tight junctions, intestinal inflammation is restricted to regions of the gut where the mutant gene is expressed. In other animal models, malnutrition results in both villus atrophy and increased transepithelial macromolecular absorption, abnormal mucin, and reduced IgA secretion. Natural causes of decreased barrier function include luminal aggressive factors and endogenous inflammatory mediators (E-Box 276-4). Barrier damage can lead to entry of antigens, subsequent allergic and/or inflammatory reactions, and even translocation of bacteria into the circulation. Nonsteroidal anti-inflammatory drugs (NSAIDs) damage the barrier, increasing intestinal permeability, but the presence of soluble fiber (e.g., pectin) is protective. Norepinephrine, which is naturally increased by stress, alters enterocyte tight junction permeability, permitting invasion by *Campylobacter* and recruitment of neutrophils through the induction of IL-8. Leakage of protein-rich tissue fluid in the opposite direction is also of clinical significance, causing a protein-losing enteropathy (PLE).

E-Box 276-4

Examples of Agents That Can Damage the Mucosal Barrier

Luminal Aggressive Factors

- Drugs
  - Cytotoxic drugs
  - Ethanol
  - Nonsteroidal anti-inflammatory drugs
- Endotoxin
- Enteric infections
- Radiation

Endogenous Factors

- Bile salts
- Malnutrition (anorexia, malabsorption)
- Ischemia
- Reperfusion injury

- Nitric oxide
- Remote inflammatory disease and burns

Intestinal Inflammation

- Interferon-gamma
- Mast cell mediators (e.g., histamine, bradykinin)
- Neutrophil migration

Intestinal Neoplasia Leading to Ulceration

- Infiltration causing ischemia
- Crowding out of normal cells

Villus Atrophy[270,273]

Villus atrophy causes loss of intestinal surface area and results in fat malabsorption. Also, carrier-mediated uptake of protein digestion products and of carbohydrate is rate-limited because there are finite numbers of nutrient transporters. Atrophy is caused either by a decrease in the production of enterocytes or an increase in the rate of enterocyte loss. If enterocyte loss outpaces increased proliferation, villus atrophy will result, but if the initiating cause can be removed, the atrophy is completely reversible. However, a persistently increased rate of enterocyte loss can result in a compensatory increase in the crypt cell proliferation rate, such that if the cell loss is matched by the increased proliferation, villus height does not actually decrease. Yet a significant functional effect still occurs because mature enterocytes are replaced by immature, suboptimally functioning enterocytes.

Infectious agents that damage enterocytes can infect the villus tip (e.g., rotavirus) or midvillus (e.g., coronavirus), causing cell loss and a mild to moderate diarrhea. Cytotoxic drugs (e.g., vincristine) and parvovirus infection, which cause crypt arrest and destruction, respectively, can be devastating, causing complete villus and crypt collapse and severe diarrhea. Assuming some stem cells survive the insult, regeneration is possible, but it is likely to take several days.

Disordered Motility[274-282]

Alterations of intestinal motility as a primary cause of SI dysfunction in dogs and cats are poorly characterized. Irritable bowel syndrome (IBS) is a functional disorder with primary changes in motility. Secondary motility alterations occur with intestinal obstruction, pseudo-obstruction, adynamic ileus, or inflammatory and infectious enteropathies. Rapid waves of contractions can be caused by SI ischemia and by enterotoxigenic bacteria. In malabsorption, unabsorbed solutes retain fluid osmotically, causing intestinal distension and reflex hypermotility. Hyperthyroidism in cats decreases transit time and causes diarrhea.

In most instances, however, diarrhea actually is associated with intestinal hypomotility or ileus. Adynamic ileus is a transient and reversible functional obstruction of the intestine with a number of causes (Box 276-5). In enteric viral infections, for example, ileus is common, promoting further diarrhea as stasis allows bacterial fermentation. Postoperative ileus is caused by a combination of surgically induced inflammation and sympathetic inhibition, potentially complicated by peritonitis, opioid administration, or both. Malabsorption leads to the presence of undigested food in the ileum and colon, inhibiting intestinal motility through neurohormonal pathways, and can delay gastric emptying. Hypomotility and constipation are expected with hypothyroidism, but occasionally, antibiotic-responsive diarrhea is found.

Box 276-5

Potential Causes of Ileus

Functional

- Abdominal surgery
- Ischemia
- Irritable bowel syndrome (mixed diarrhea/constipation)

Inflammatory

- Pancreatitis
- Parvovirus

- Peritonitis

Metabolic

- Diabetes mellitus
- Endotoxemia
- Hypokalemia
- Hypocalcemia/hypomagnesemia
- Uremia

Neuromuscular

- Anticholinergic and opioid drugs
- Dysautonomia
- Visceral myopathy
- Visceral neuropathy

Physical

- Intestinal obstruction
  - Foreign body
  - Intussusception
  - Masses—neoplasia, granuloma
  - Mechanical—torsion, volvulus, incarceration, adhesions
- Overdistention by aerophagia

Mucosal Inflammation[283-286]

Inflammation is a cellular and vascular response to a number of inciting causes, including infection, ischemia, trauma, toxins, neoplasia, and immune-mediated reactions. Indeed, anything that disrupts the mucosal barrier is likely to trigger inflammation and tissue damage through the upregulation of matrix metalloproteinases.

Experimental models of GI inflammation in genetically engineered rodents have allowed better understanding of the pathogenesis of mucosal inflammation and the mechanisms that trigger it. Various disruptions of the mucosal immune system can lead to chronic inflammatory responses that are histologically similar. The disruptions can be induced in one of three ways: through disruption of the endogenous microflora, through interference with the mucosal barrier, or through dysregulation of the mucosal immune system. Whether there is mucosal barrier disruption or immune system dysregulation, the presence of an enteric flora is essential for the expression of inflammation. This suggests that healthy individuals are tolerant to their own intestinal microflora, but in patients with idiopathic inflammatory bowel disease (IBD), tolerance is broken (E-Figure 276-5, *B*).

Hypersensitivity[287,288]

Sensitization of a patient to a dietary antigen can provoke an IgE-mediated allergic reaction when the animal is next exposed. The release of numerous mast cell mediators can have generalized systemic effects such as anaphylaxis, remote effects such as pruritus and urticaria, or only local effects on the intestine, inducing rapid changes in absorption and secretion, mucus secretion, epithelial and endothelial permeability, and gut motility.

Neoplasia

Diffuse tumors that infiltrate the mucosa, such as lymphoma, cause SI dysfunction. Malignant cells simply can obstruct blood and lymphatic flow, but enterocyte function is likely to be impaired or the mucosa might show villus atrophy or be ulcerated because of ischemia. Solitary tumors can cause dysfunction, probably through the effects of partial obstruction, with stasis of ingesta and secondary bacterial overgrowth. More typically, solid tumors are associated with signs such as intestinal obstruction, bleeding, and cancer-associated cachexia. Peritonitis can occur if the integrity of the bowel wall is compromised. Cutaneous mast cell tumors can cause histamine-mediated gastric acid hypersecretion leading to gastroduodenal ulceration and even perforation.

Nutrient Delivery Failure[289,290]

After absorption, nutrients are transported via blood and lymph, but only intestinal lymphatic diseases are well described in animals. Primary lymphatic dilatation and dysfunction (lymphangiectasia) that causes malabsorption can be idiopathic or can be associated with lymphangitis. Secondary lymphangiectasia is seen with any condition causing lymphatic obstruction.

Congenital Abnormalities[291-302]

Intestinal stenosis, atresia, nonrotation, and random duplications of segments of both SI and large intestine (LI) in dogs and cats are reported. Duplications are cystlike lesions that rarely cause clinical signs unless they cause an obstruction. Blind-ending diverticula may predispose to foreign body entrapment, bacterial overgrowth, GI bleeding or perforation. Cystic vitelline ducts can occur with umbilical leakage of SI contents if there is a persistent *ductus omphaloentericus.* Arteriovenous fistulae can cause SI hemorrhage.

Clinical Features of Small Intestinal Disease

Diarrhea[303-305]

The cardinal sign of SI dysfunction is diarrhea, which is a significant increase in the frequency, fluidity, or volume of feces caused by an increase in fecal water and/or solid content. Yet it must be remembered that diseases of other organs can cause diarrhea, or that the absence of recognizable diarrhea does not preclude the possibility of significant SI disease; other signs can occur (see Box 276-2).

Diarrhea can be classified in several ways (Box 276-6). These categories are not mutually exclusive, and they allow the problem to be viewed from different perspectives, facilitating the diagnostic approach and the choice of appropriate treatment. A mechanistic approach helps an understanding of why overt diarrhea develops. Most SI diseases have a component of osmotic diarrhea, but even in a situation as simple as lactase deficiency, mixed mechanisms occur (Figure 276-6). Malabsorption typically causes osmotic diarrhea, but bacterial fermentation of unabsorbed solutes can complicate it; fecal pH often is low because of the production of volatile fatty acids, and some products (e.g., hydroxylated fatty acids, unconjugated bile acids) cause colonic secretion. For this reason, signs of LI diarrhea frequently accompany prolonged SI disease. Permeability diarrhea is due to inflammation or neoplastic infiltration causing exudation, and secretory diarrhea is caused by chemical or bacterial toxins (Box 276-7).

Box 276-6

Classification Schemes for Diarrhea

Anatomic
- Extraintestinal
- Small intestinal
- Large intestinal
- Diffuse

Causal
- Exocrine pancreatic insufficiency, salmonellosis, lymphoma, other

Clinical
- Nonfatal, mild, self-limiting
- Protein-losing
- Severe, potentially fatal
- Multisystemic

Etiologic
- Bacterial
- Dietary
- Idiopathic
- Neoplastic
- Parasitic

- Viral

Mechanistic

- Dysmotility
- Osmotic
- Secretory
- Permeability (exudative)
- Mixed

Pathophysiologic

- Allergic
- Biochemical
- Infectious/inflammatory
- Neoplastic
- Vascular/lymphatic

Temporal

- Acute
- Chronic

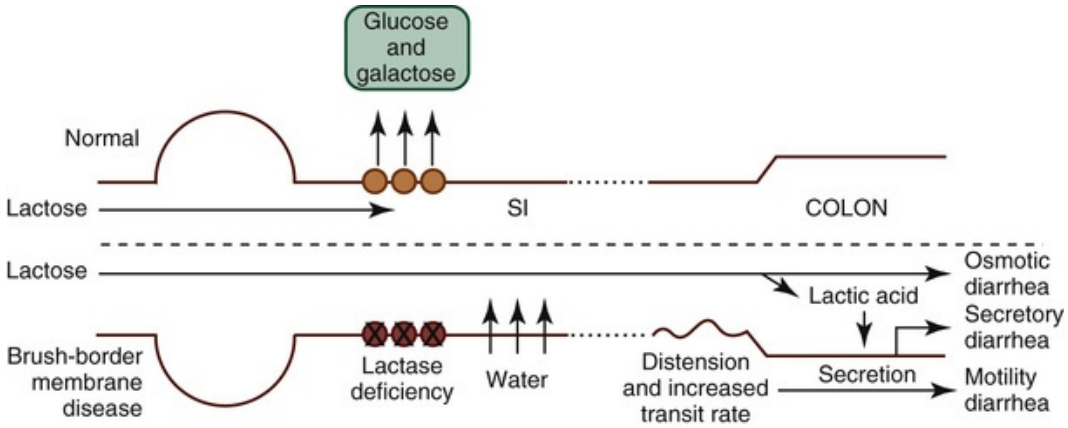


FIGURE 276-6 Lactase deficiency. Diagrammatic representation of the mechanisms of diarrhea caused by lactase deficiency. Absence of the brush border enzyme lactase leads to maldigestion and malabsorption, osmotic diarrrhea, and more rapid transit because of distension with water. Bacterial fermentation of undigested lactose to lactic acid stimulates colonic secretion.

Box 276-7

Causes of Secretory Diarrhea

- Bacterial enterotoxins and endotoxins (e.g., *Clostridium perfringens, Escherichia coli, Salmonella* spp.)
- Hydroxylated fatty acids from bacterial fermentation
- Unconjugated bile acids from bacterial fermentation
- *Giardia* infection
- Stimulant laxatives (e.g., castor oil, dioctyl sodium sulfosuccinate, bisacodyl)
- Cardiac glycosides
- Amine precursor uptake and decarboxylation (APUD) neoplasms (excess vasoactive intestinal polypeptide, serotonin, prostaglandins, substance P)
- Intestinal inflammation

Malabsorption[306-309]

Failure of food assimilation sometimes is classified as either a primary failure to digest (maldigestion) or a primary failure to absorb (malabsorption). However, such a distinction is misleading because failure of absorption is an inevitable consequence of failure to digest. The preferred use of the term malabsorption is to describe defective absorption of a dietary constituent resulting from interference with the digestive and/or absorptive processing of that molecule. The site of the primary abnormality can be found in the luminal, mucosal, or transport phases (Table 276-1). The clinical manifestations of malabsorption—namely diarrhea, weight loss, and altered appetite (polyphagia, coprophagia, pica)—largely are a result of the lack of nutrient uptake and the losses in feces. The reserve capacity of the distal SI and colon can prevent overt diarrhea despite extensive malabsorption and weight loss. Polydipsia is an unusual and peculiar manifestation of excessive appetite. Animals often are systemically healthy but losing weight despite an increased appetite unless an underlying neoplastic or a severe inflammatory condition is present. Only when the patient is severely malnourished or develops hypoproteinemia does he or she appear ill.

TABLE 276-1

Pathophysiologic Mechanisms of Malabsorption

MECHANISM	EXAMPLE
Luminal Phase	
Dysmotility	
Rapid intestinal transit	Hyperthyroidism
Defective Substrate Hydrolysis	
Enzyme inactivation	Gastric hypersection
Lack of pancreatic enzymes	Exocrine pancreatic insufficiency
Impaired release of CCK, secretin	Impairment of pancreatic secretion due to severe small intestine disease
Fat maldigestion	
Decreased bile salt delivery	Cholestatic liver disease, biliary obstruction
Increased bile salt loss	Ileal disease
Bile salt deconjugation	Bacterial overgrowth
Fatty acid hydroxylation	Bacterial overgrowth
Cobalamin Malabsorption	
Intrinsic factor deficiency	Exocrine pancreatic insufficiency
Cobalamin receptor deficiency	Inherited selective cobalamin deficiency (Imerslund-Gräsbeck syndrome)
Competition for cobalamin	Bacterial overgrowth
Mucosal Phase	
Brush Border Enzyme Deficiency	
Congenital	Trehalase (cats) Aminopeptidase N (Beagle)
Acquired	Relative lactase deficiency
Brush Border Transport Protein Deficiency	
Congenital/inherited	Inherited selective cobalamin deficiency
Acquired	Secondary to diffuse SI disease
Enterocyte Defects	
Enterocyte processing defects	Abetalipoproteinemia,* microvillus inclusion disease,* dirlopatide administration
Reduction in surface area	Villus atrophy
Immature enterocytes	Increased enterocyte turnover
Mucosal Inflammation	Inflammatory bowel disease

Transport Phase	
Lymphatic Obstruction	
Primary	Lymphangiectasia
Secondary	Obstruction caused by neoplasia, infection, or inflammation
Vascular Compromise	
Vasculitis	Infection, immune-mediated
Portal hypertension	Hepatopathy, right heart failure, cardiac tamponade

*Human condition, not yet reported in dogs or cats.

CCK, Cholecystokinin.

Melena[310]

The presence of dark, tarry, oxidized blood in feces, a condition called *melena*, reflects either swallowed blood or generalized or localized GI bleeding proximal to the LI (Table 276-2; see ch. 41). It is estimated that the loss of 350 to 500 mg/kg of hemoglobin into the GI tract is required for melena to be visible. As a caveat, medication with ferrous sulfate or bismuth suspensions (e.g., Pepto-Bismol) can also impart a black color to the feces. On the complete blood count, the presence of microcytosis, especially with thrombocytosis, suggests iron deficiency secondary to chronic blood loss. On a serum biochemical profile, an increased blood urea to creatinine ratio (from bacterial digestion of blood) provides supportive evidence. Hypoproteinemia can indicate blood loss or a PLE.

TABLE 276-2

Causes of Melena

Mechanism	Source
Bleeding disorders	Thrombocytopenia, thrombocytopathy, factor deficiencies, DIC
Swallowing of blood	Oral, nasal, pharyngeal, esophageal or pulmonary
Gastrointestinal erosion/ulceration	
Metabolic	Uremia, liver disease
Inflammatory	Gastritis/ulcer, enteritis, HGE
Neoplastic	Leiomyoma, GIST, adenocarcinoma, lymphoma
Paraneoplastic	Mastocytosis, hypergastrinemia (gastrinoma)
Vascular	A-V fistula, aneurysm, angiodysplasia
Ischemia	Hypovolemic shock, hypoadrenocorticism, thrombosis/infarction, reperfusion
Drug-induced	Nonsteroidal anti-inflammatory agents and glucocorticoids
Sharp foreign objects	

A-V, Arteriovenous; *DIC*, disseminated intravascular coagulation; *GIST*, gastrointestinal stromal tumor; *HGE*, hemorrhagic gastroenteritis.

Protein-Losing Enteropathy[289,290,311-315]

When SI disease is severe enough for protein leakage into the gut lumen to exceed plasma protein synthesis, hypoproteinemia develops. Chronic diarrhea associated with panhypoproteinemia usually requires intestinal biopsy to define the cause of the PLE (Table 276-3). Lymphangiectasia, alimentary lymphoma, and IBD are the three most common underlying diseases, although histoplasmosis and pythiosis must be considered in endemic areas. Nonintestinal diseases causing ascites through portal hypertension usually cause ascites before diarrhea. Hypoproteinemia associated with GI disease is much less common in cats than in dogs and, when it occurs, most often is related to GI lymphoma; it results in ascites infrequently in cats.

TABLE 276-3

Protein-Losing Enteropathies

Causes	Examples
Inflammation	Lymphocytic-plasmacytic, eosinophilic, granulomatous
Lymphangiectasia	Primary lymphatic disorder, venous hypertension (e.g., right heart failure, hepatic cirrhosis)
Neoplasia	Lymphoma
Infectious	Parvovirus, salmonellosis, histoplasmosis, phycomycosis
Gastrointestinal hemorrhage	HGE, neoplasia, ulceration
Endoparasites	*Giardia, Ancylostoma* spp.
Structural	Intussusception

HGE, Hemorrhagic gastroenteritis.

Clinical signs associated with PLE include weight loss, diarrhea, vomiting, peripheral edema, ascites, and pleural effusion. Loss of muscle mass frequently is a predominant feature, but diarrhea is not invariably present, particularly with lymphangiectasia and focal intestinal neoplasia, where it can be absent. Physical findings can include pitting edema, ascites, emaciation, thickened intestines, and melena. Thromboembolism secondary to hypoproteinemia is a feature of some cases of PLE because affected patients are hypercoagulable (see ch. 197).

Borborygmi and Flatulence[316]

Borborygmi are abdominal rumbling noises caused by the propulsion of gas in the stomach and through the intestines. Swallowed air and bacterial fermentation of ingesta are the main causes of borborygmi and flatulence and often result in an offensive odor. Feeding a diet that is highly digestible, with a low fiber content (e.g., cottage cheese and rice in a 1:2 ratio), leaves little material in the intestine for bacterial fermentation, and feeding charcoal biscuits can confer a symptomatic benefit in some cases. If borborygmi or flatulence continue despite dietary modification or addition of adsorbents, the animal could be excessively aerophagic or might have malabsorption, especially if diarrhea or weight loss also is present, and investigations for an underlying SI disease should be performed.

Weight Loss or Failure to Thrive

General causes of weight loss are reduced nutrient intake, increased nutrient loss, or increased catabolism (see ch. 19). The history should reveal whether the type and amount of diet fed is adequate and whether anorexia, dysphagia, or vomiting is a potential cause. Weight loss or failure to thrive accompanied by diarrhea often is a feature of malabsorption, and the diagnostic approach is the same as for chronic diarrhea. However, diarrhea does not invariably accompany malabsorption causing weight loss because colonic reserve absorptive capacity can remove the excess water from the feces.

Diagnosis of Small Intestinal Disease

Diagnostic Approach[317-322]

Diarrhea

Most cases of diarrhea are acute, nonfatal, and self-limiting and require only general supportive care and not a specific diagnosis. However, some cases do need definitive diagnosis and management as they can become life-threatening and/or have an infective potential for other animals and/or represent a zoonotic risk. If clinically significant hypovolemia or dehydration is present, fluid and electrolyte deficits must be addressed simultaneously with the diagnostic effort, but the extent of diagnostic investigations required varies. Investigations are necessary if diarrhea is hemorrhagic, accompanied by systemic signs, or unresponsive to nonspecific supportive treatment. By definition, chronic diarrhea is not self-limiting, and an etiologic diagnosis usually is required to allow specific treatment. Diagnostic approaches to acute and chronic diarrhea are discussed in ch. 40 and are outlined in Figures 276-7 and 276-8, respectively.

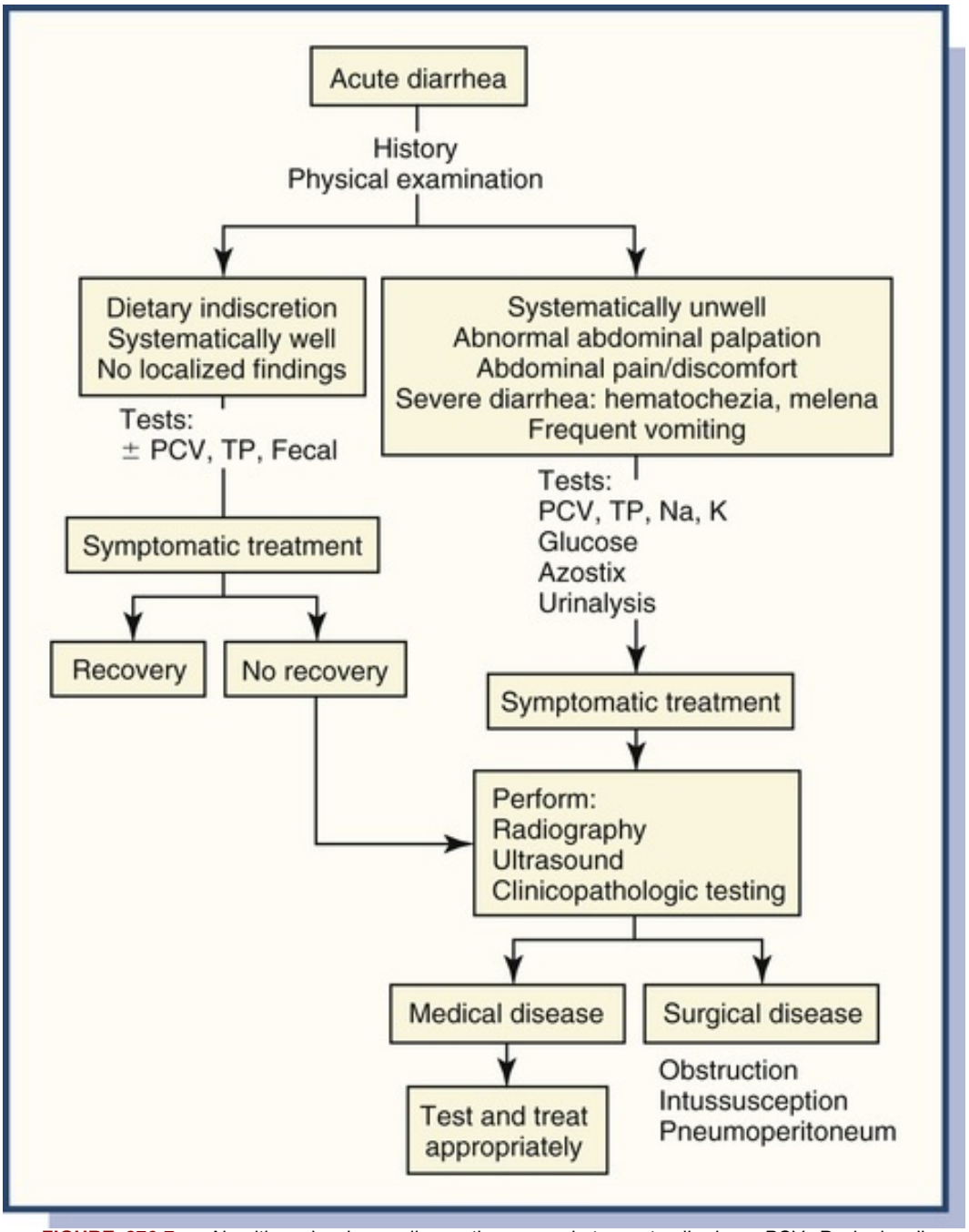
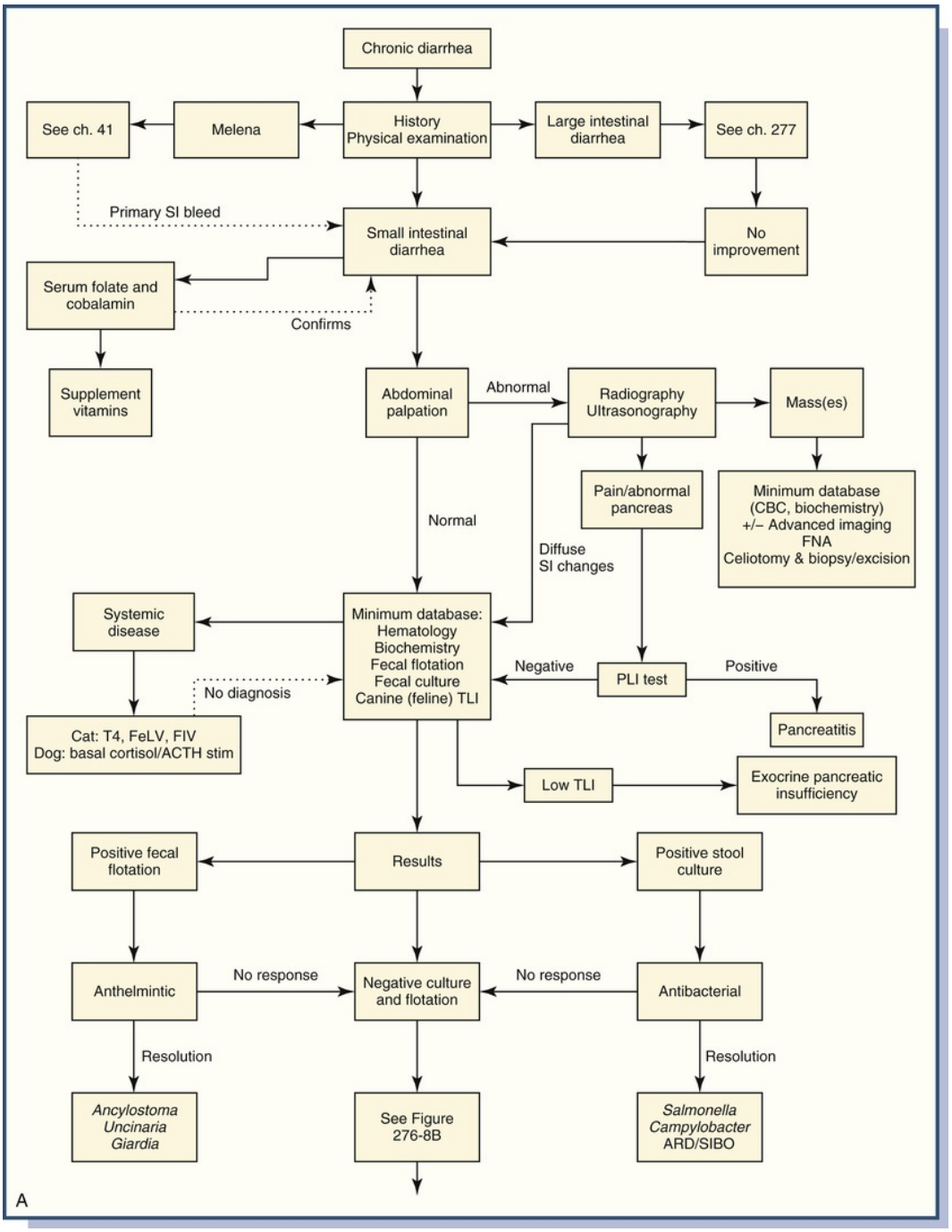


FIGURE 276-7 Algorithm showing a diagnostic approach to acute diarrhea. *PCV,* Packed cell volume; *TP,* total protein.


Chronic diarrhea
History
Physical examination
See ch. 41
Melena
Large intestinal diarrhea
See ch. 277
Primary SI bleed
Small intestinal diarrhea
No improvement
Serum folate and cobalamin
Confirms
Supplement vitamins
Abdominal palpation
Abnormal
Radiography
Ultrasonography
Mass(es)
Pain/abnormal pancreas
Minimum database (CBC, biochemistry) +/– Advanced imaging FNA Celiotomy & biopsy/excision
Normal
Diffuse SI changes
Systemic disease
Minimum database: Hematology Biochemistry Fecal flotation Fecal culture Canine (feline) TLI
Negative
PLI test
Positive
No diagnosis
Cat: T4, FeLV, FIV
Dog: basal cortisol/ACTH stim
Pancreatitis
Low TLI
Exocrine pancreatic insufficiency
Positive fecal flotation
Results
Positive stool culture
Anthelmintic
No response
Negative culture and flotation
No response
Antibacterial
Resolution
Resolution
Ancylostoma
Uncinaria
Giardia
See Figure 276-8B
Salmonella
Campylobacter
ARD/SIBO
A

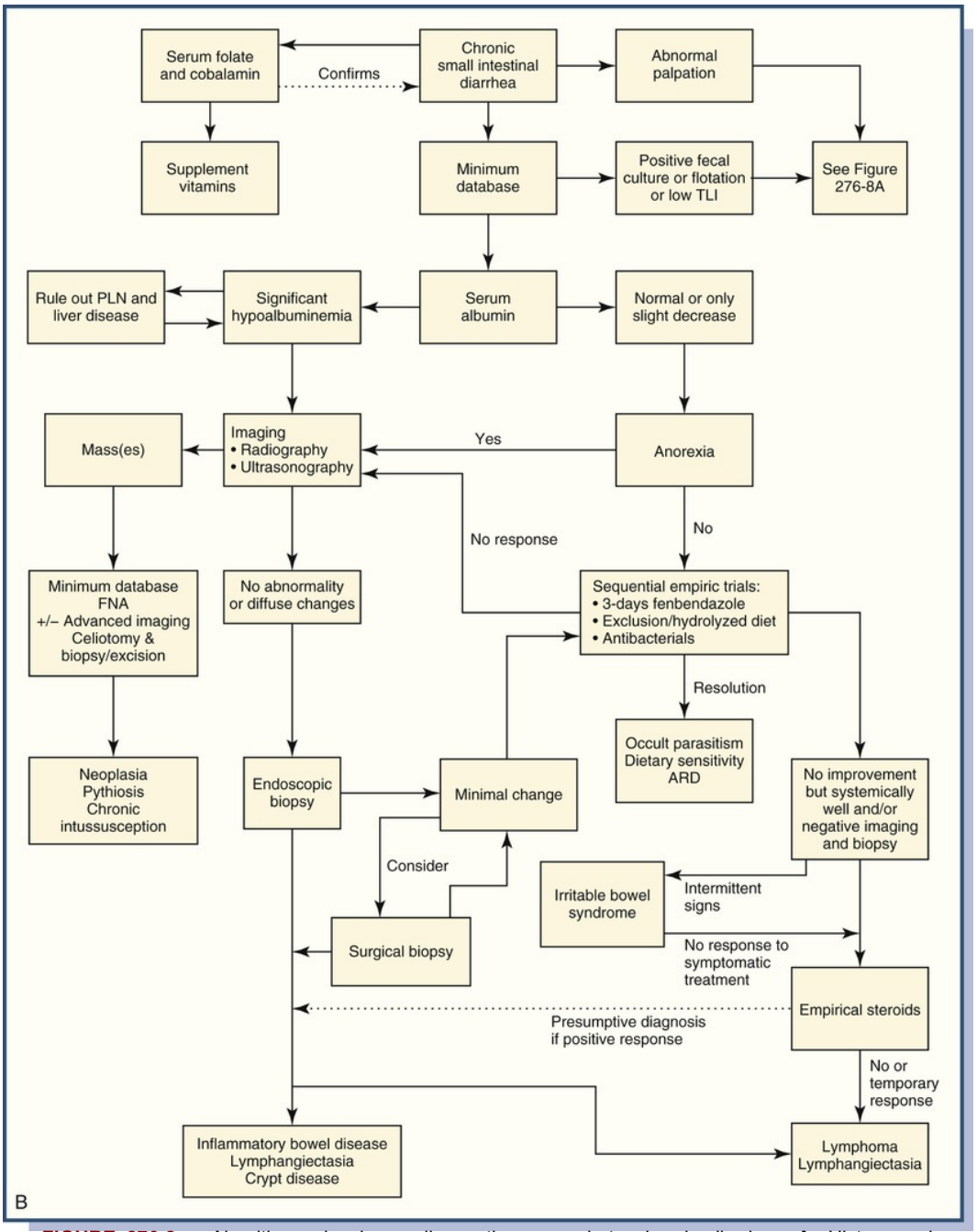


FIGURE 276-8 Algorithms showing a diagnostic approach to chronic diarrhea. **A,** History and physical examination will usually identify a SI problem, but failure of specific therapy for a suspected LI problem should also make the clinician consider SI disease. Abnormal serum folate and cobalamin concentrations can provide more evidence of SI disease and are an indication to supplement. A minimum database can provide evidence of systemic disease, leading the investigation away from the SI, and basal cortisol (or ACTH stimulation test) in dogs and serum T4 in older cats usually are indicated. Abnormal abdominal palpation is an indication for abdominal imaging, but a minimum database of a complete blood count (CBC) and serum biochemistry profile should be performed before investigations that are more invasive. Trypsin-like immunoreactivity (TLI) probably should be measured in all canine cases without abnormalities on abdominal palpation, as the signs of exocrine pancreatic insufficiency are not always typical and serum folate/cobalamin concentrations can be altered. Fecal examination will identify gastrointestinal parasites and pathogenic bacteria, but they could be coincidental findings. **B,** The path taken for further investigations of cases with unremarkable abdominal palpation depends on the serum albumin concentration and the patient's appetite. If albumin is not substantially decreased and the patient is systemically well and eating, sequential empirical trials with fenbendazole, an exclusion or hydrolyzed diet, and with antibacterials such as metronidazole can be undertaken before considering intestinal biopsy. Imaging and endoscopic biopsy are indicated if the patient has evidence of a protein-losing enteropathy or is anorexic. If biopsy results are unremarkable, then surgical biopsy can be considered or empirical trials with glucocorticoids started. *ACTH stim*, Adrenocorticotropic hormone stimulation test; *ARD,* antibiotic-responsive diarrhea; *CBC,* complete blood count; *FeLV*, feline leukemia virus; *FIV*, feline immunodeficiency virus; *FNA*, fine-needle

aspirate; *PLI*, pancreatic lipase immunoreactivity; *PLN*, protein-losing nephropathy; *SIBO*, small intestinal bacterial overgrowth; *TLI*, trypsin-like immunoreactivity.

The aim of the diagnostic approach is to eliminate extraintestinal diseases from consideration and to differentiate SI from LI disease (Table 276-4). The history (Box 276-8 and ch. 1), breed susceptibility (E-Table 276-5), and physical examination (Table 276-6 and ch. 2) are crucial steps toward reaching a diagnosis, and in some cases they can be all that is required. A rectal examination should be performed to confirm diarrhea, identify any unsuspected melena, and obtain samples for rectal cytologic and fecal examinations.

TABLE 276-4

Clinical Signs Associated with Small-Bowel and Large-Bowel Disease

SIGNS	SMALL INTESTINAL DISEASE	LARGE INTESTINAL DISEASE
Feces		
Stool volume	Large	Small
Mucus	Rare	Common
Blood (if present)	Melena	Fresh blood
Fat	Sometimes	Absent
Color	Variable	Normal
Undigested food	Occasionally	Absent
Defecation		
Tenesmus	Rare	Common
Frequency	Two to three times a day	More than three times a day
Urgency	Uncommon	Common
Other Signs		
Vomiting	Sometimes	Uncommon
Gas	Sometimes	Absent
Weight loss	Common	Rare

Box 276-8

Historical Information Useful in the Diagnosis of Small Intestinal Disease

Patient Information

- Age
- Gender
- Species and breed (see E-Table 276-5)

Environmental History

- Indoor versus outdoor
- Free roaming
- Scavenging
- Exposure to parasites
- Contact with infected animals
- Recent change of environment
- Endemic disease area

Past Medical History

- Vaccination status

- Worming status
- Previous abdominal surgery
- Previous excision of cutaneous mast cell tumor
- Drug history

Clinical Signs

- Duration
- Frequency
- Severity
  - Altered appetite
  - Presence of blood
  - Weight loss
- Progression
  - Order of appearance
  - Continuous or intermittent in nature
  - Length of sign-free intervals
- Other signs (e.g., vomiting, ascites)
- Factors that improve or worsen signs (e.g., treatments, diets)

TABLE 276-6

Physical Findings in Animals with Signs of a Small Intestinal Disorder

FINDINGS	INTERPRETATION
General	Rule out other systemic disease
Oropharynx	
Mucous membranes	Hydration status, cardiovascular status, anemia, icterus
Tongue	Linear foreign body
Cervical region	
Thyroid gland	Thyroid nodule (hyperthyroidism)
Abdominal palpation	Effusions, masses, bunching of intestinal loops, foreign bodies, abnormal accumulations of ingesta, associated pain, feces, lymphadenopathy, other systemic disease
Abdominal auscultation	Ileus, borborygmi
Rectal examination	
Digital examination	Masses, foreign bodies, hemostatic disorders, dehydration
Collection of stool sample	Laboratory analysis, identification of melena
Rectal mucosal scrape	Cytology
Cutaneous examination	
Poor coat condition, scale	Malnutrition
Pruritus	Food hypersensitivity
Facial pruritus	Food hypersensitivity
Pedal pruritus	Food hypersensitivity, *Uncinaria stenocephala* infection (larval migration)

E-TABLE 276-5

Some Suspected and Confirmed Breed Susceptibilities to Small Intestinal Disease in Dogs

BREED	CONDITION
Basenji	LPE (also called IPSID)
Beagle	Selective cobalamin malabsorption, aminopeptidase N deficiency
Border Collie	Selective cobalamin malabsorption
German Shepherd Dog	Idiopathic ARD; IBD (lymphoplasmacytic, eosinophilic)
Giant Schnauzer	Selective cobalamin malabsorption
Irish Setter	Gluten-sensitive enteropathy
Lundehund	Lymphangiectasia
Retrievers	Dietary allergy
Rottweiler	Susceptibility to parvovirus, lymphangiectasia
Soft-coated Wheaten Terrier	Protein-losing enteropathy/nephropathy
Chinese Shar-Pei	LPE, cobalamin deficiency
Toy breeds	HGE
West Highland White	Dietary allergy
Yorkshire Terrier	Lymphangiectasia

ARD, Antibiotic-responsive diarrhea; *HGE*, Hemorrhagic gastroenteritis diarrhea; *IPSID*, Immunoproliferative small intestinal disease; *IBD*, Inflammatory bowel disease; *LPE*, Lymphocytic-plasmacytic enteritis.

Preliminary investigations also can include collection of baseline data through a complete blood count (CBC), serum biochemistry profile, urinalysis, and fecal examination. This can identify cases of hypoadrenocorticism, but an abnormal serum sodium to potassium ratio sometimes is seen in primary SI disease, notably salmonellosis and whipworm infection. Diagnostic imaging could be indicated, especially if a disease requiring surgical intervention is suspected from the history and/or physical examination findings (see "Surgical Intestinal Disorders," below). Further investigations in cases of chronic diarrhea include exclusion of EPI, indirect tests of intestinal function (e.g., serum folate and cobalamin) and damage (e.g., fecal alpha$_1$-protease inhibitor, fecal calprotectin) and, ultimately, direct inspection of the SI by endoscopy or surgery with histologic examination of biopsies, but they are rarely necessary in acute disease.

Melena[310,323-334]

The general approach to melena is to rule out generalized bleeding diatheses, ingestion of blood from other lesions (e.g., oral masses), toxicoses (e.g., NSAIDs), and underlying metabolic disorders (e.g., hypoadrenocorticism) before pursuing primary GI causes. Ultrasonography is particularly useful for detecting GI masses and thickening. The next step is endoscopy to identify gastric or duodenal bleeding. Enteroscopy and videocapsule endoscopy can be used for localizing a more distal bleeding site but rarely are available. If the source of GI bleeding still is undetermined, tagged red cell scintigraphy or angiography can be considered, but ultimately exploratory laparotomy can be indicated.

Protein-Losing Enteropathy[289,290,312,314,335-338]

The identification of a PLE is based on finding hypoalbuminemia. Usually in patients with PLE, the serum concentrations of both albumin and globulin are reduced. However, exceptions are hyperglobulinemia with hypoalbuminemia found in both histoplasmosis and immunoproliferative SI disease of the Basenji and occasionally in severe IBD and in alimentary lymphoma. PLE causing substantial hypoalbuminemia is rare in cats, but dog breeds that appear to be predisposed to PLE are the Basenji, Lundehund, Rottweiler, Soft-coated Wheaten Terrier, Yorkshire Terrier, and Chinese Shar-Pei. The breed raises the suspicion in a hypoproteinemic dog even if diarrhea is absent, but renal and hepatic causes of hypoalbuminemia should be eliminated by assay of serum bile acids and urinary protein loss (i.e., urine protein to creatinine ratio), respectively, with the caveat that concurrent PLE and protein-losing nephropathy is seen in Soft-coated

Wheaten Terriers. Hypocholesterolemia and lymphopenia are common in PLE, and ionized hypocalcemia and hypomagnesemia can occur. Measurement of increased fecal alpha$_1$-protease inhibitor can be a sensitive test for PLE before significant hypoalbuminemia develops.

Survey abdominal radiographs are unhelpful in patients with PLE and ascites because of the loss of radiographic contrast, but ultrasound scans can reveal intestinal thickening and/or mesenteric lymphadenopathy, as well as abdominal effusion. Thoracic radiographs can show pleural effusion, metastatic neoplasia, or changes consistent with histoplasmosis. Although intestinal function tests may confirm the presence of malabsorption, they rarely provide a definitive diagnosis and intestinal biopsy is more useful. Because many intestinal causes of PLE are diffuse, endoscopy is the safer way to obtain biopsies, but surgical biopsy could be required to obtain a definitive diagnosis for transmural lymphoma and lymphangiectasia (E-Box 276-9).

E-Box 276-9

Relative Advantages of Endoscopic and Surgical Intestinal Biopsy

Endoscopy

- Advantages
  - Minimally invasive
  - Allows visualization and biopsy of focal lesions
  - Permits multiple biopsies
  - Minimal risk
  - Allows steroids to be started early; no convalescence
- Disadvantages
  - Requires general anesthesia
  - Small risk of perforation
  - Permits reliable access only to duodenum:
    - Proximal jejunum only accessible in cats and small dogs
    - Distal ileum only accessible via colonoscopy
  - Produces only small, superficial (and potentially crushed) biopsies
    - Could miss lymphangiectasia, lymphoma
  - Requires expensive equipment
  - Technically demanding

Laparotomy

- Advantages
  - Allows biopsy of multiple sites
  - Permits large, full-thickness biopsies
  - Allows inspection and biopsy of other abdominal organs
  - Offers potential for corrective surgery
- Disadvantages
  - Requires general anesthesia
  - Surgical risk
  - Postsurgical risk of dehiscence
  - Requires convalescence
  - Requires delay before steroids can be started

Laboratory Examination

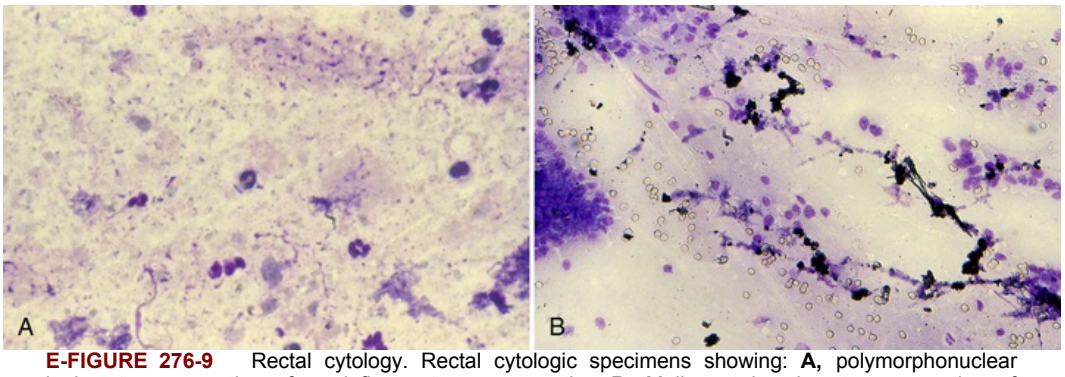
Minimum Database

Preliminary investigations include a complete blood count, serum biochemistry profile, and urinalysis.

Rectal Cytology

At the end of the rectal examination, the gloved finger is rolled on a microscope slide and the smear is stained (E-Figure 276-9). Although the result often is negative or at best more representative of LI disease, an increased number of neutrophils can be suggestive of a bacterial problem, indicating the need for fecal

culture. Fungal elements also can be identified. The test is fast and simple, but in all cases confirmatory tests are indicated.



E-FIGURE 276-9 Rectal cytology. Rectal cytologic specimens showing: **A,** polymorphonuclear leukocytes suggestive of an inflammatory enteropathy. **B,** Malignant lymphocytes suggestive of alimentary lymphoma.

Fecal Examinations

Fecal examinations are an important part of the investigation of SI disease (see ch. 81). Tests such as quantification of fecal fat excretion are unsuitable for practice, and bacterial culture is sometimes of questionable value, but identification of parasites is important.

Direct Smear

Staining of smears for undigested starch granules (Lugol's iodine), fat globules (Sudan stain), and muscle fibers (Wright's or Diff Quik stain) can indicate malabsorption, but findings are nonspecific. The presence of fungal elements and sporulating clostridia is of uncertain significance, but rectal cytology can be helpful to identify an associated neutrophilic inflammation. Very fresh, unstained wet mounts can be used for observing motile protozoal trophozoites. Enterotoxin production by *Clostridium perfringens* is a potential cause of diarrhea; however, the presence of a large number of clostridial endospores (more than 5 per oil immersion field) on Diff Quik–stained smears is no longer considered a reliable indicator, whereas a positive fecal enterotoxin assay (enzyme-linked immunosorbent assay [ELISA]) or reverse passive latex agglutination) is more likely to be significant.

Fecal Concentration Methods[339-345]

For the detection of most intestinal parasites, fecal concentration methods are most rewarding (Figure 276-10; see ch. 81). Examination of three fecal samples by zinc sulfate flotation is recommended to detect *Giardia* oocysts. A direct smear, sedimentation, or the Baermann technique can identify larvae of *Strongyloides* spp.

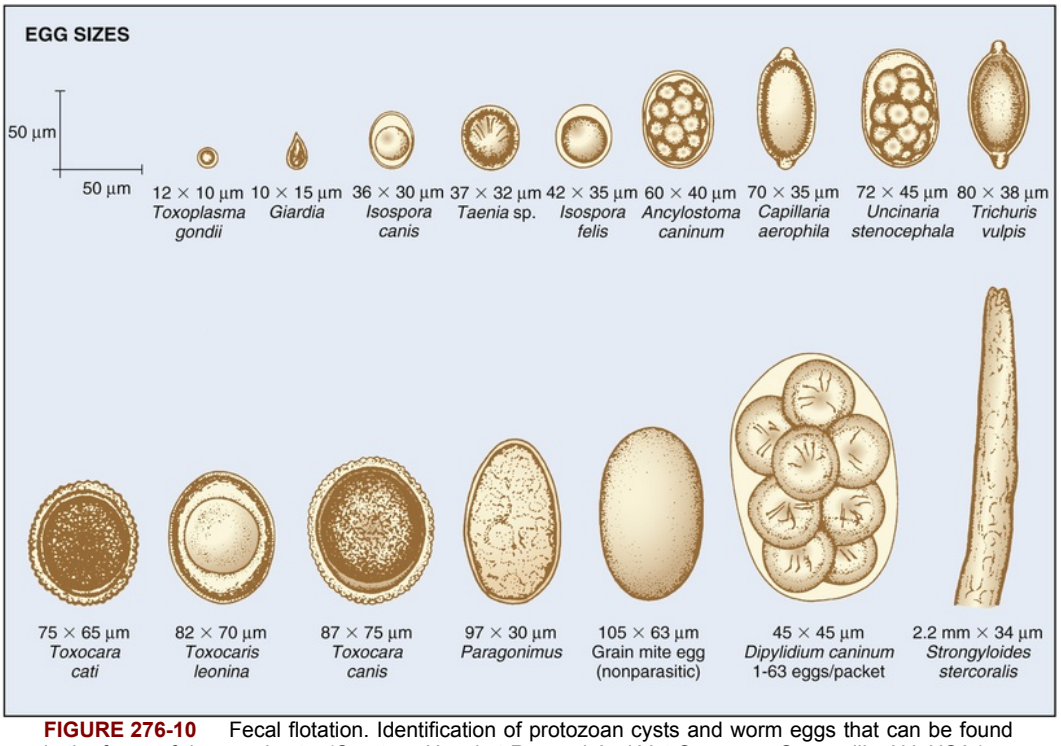


FIGURE 276-10 Fecal flotation. Identification of protozoan cysts and worm eggs that can be found in the feces of dogs and cats. (Courtesy Hoechst-Roussel-Agri Vet Company, Somerville, NJ, USA.)

Antigen Tests[342,346-348]

Copro-antigen tests of feces can be used to detect cestode, trematode and nematode infections, but antigen tests most frequently are used for detecting protozoal or viral infections. Commercially available, point-of care ELISAs can be used for detecting *Giardia* (see ch. 221) and canine parvovirus (see ch. 225) antigen in feces.

Immunofluorescence[348,349]

Imunofluorescent antibody staining of fecal smears is considered one of the most sensitive methods for detecting *Giardia* and *Cryptosporidium* (see ch. 221).

Routine Bacterial Culture[350,351]

Attempting to grow all bacterial species present in a fecal sample is of little value, especially as the fecal flora does not necessarily reflect the SI flora, and many species are unculturable. However, targeted identification of potential pathogens could be helpful. Culture of feces is indicated in animals with hemorrhagic diarrhea or fever, or with an inflammatory leukogram, or with neutrophils on rectal cytology. Identification of *Salmonella* spp., *Campylobacter jejuni,* and *Clostridium difficile* can be helpful, although the significance of a positive isolate should be interpreted in light of the clinical history because these organisms can be present in feces from clinically healthy animals. Feces can be cultured for fungi, such as *Histoplasma capsulatum,* but isolation is difficult and slow.

Fecal Polymerase Chain Reactions (PCR)[352-362]

Although PCR of fecal material can be difficult because of the presence of inhibitors of the reaction, by using specific primers and adequate controls, bacteria and parasites in fecal samples can be identified. PCR potentially is more sensitive than bacterial culture as live organisms need not be present, and speciation also is possible. However, PCR more often is used for classifying organisms after they have been cultured; *E. coli* can be cultured from most fecal samples, but only certain strains are pathogenic, and PCR probes are able to detect molecular pathogenicity genes. PCR is the method of choice for the diagnosis of *Tritrichomonas* infection in cats (see ch. 221 and 277).

Molecular Fingerprinting[72,74,85,104,108,228,363,364]

Many intestinal bacteria are unculturable *in vitro* and can only be identified by gene sequencing of bacterial 16S rRNA. This method is used for looking at the pattern of the flora in intestinal fluid, biopsies, and feces in a population and is unlikely to be helpful in individual patients.

Virologic Examination[365-368]

Viral diarrhea usually is acute and self-limiting and does not require a positive diagnosis. Electron microscopy can be used for identifying characteristic viral particles such as rotavirus, coronavirus, and parvovirus. Fecal ELISA and PCR tests for parvovirus are also available.

Occult Blood[310,369-371]

This test is used for identifying intestinal bleeding from ulcerated mucosa and benign or malignant tumors before melena is seen, but it does not help localize the source. Unfortunately, most assays nonspecifically test for any hemoglobin and are very sensitive, reacting with any dietary meat, as well as patient blood. Therefore the patient must be fed a meat-free or hydrolyzed diet for at least 72 hours for a positive result to have any significance. Immunological tests are too sensitive and they detect hemoglobin from healthy dogs.

Alpha$_1$-Protease Inhibitor[315,372-382]

This test assays the presence in feces of alpha$_1$-protease inhibitor (alpha$_1$-PI), a naturally occurring endogenous serum protein that is resistant to bacterial degradation in the intestinal lumen. It appears to be of value for the diagnosis of PLE, correlating with historical testing by fecal radioactive ^{51}chromium-labeled albumin excretion. It appears to be a more sensitive marker than measurement of serum albumin for the detection of early disease. To improve diagnostic accuracy, three fresh fecal samples should be evaluated. The assay is valid only if used on fecal samples collected after voluntary evacuation because abrasion of the colonic wall during digital evacuation is enough to elevate fecal alpha$_1$-PI concentrations.

Fecal Calprotectin[383-389]

The assay of fecal calprotectin is a proven marker of intestinal inflammation in human IBD, as the molecule that is identified is released with neutrophil elastase activity. A dog-specific assay has been developed, and increased fecal concentrations tend to correlate with intestinal inflammation and the degree of histologic change, but not necessarily with clinical signs.

3-Bromotyrosine and N-Methylhistamine[390-392]

The 3-bromotyrosine molecule (3-BrY) is a stable product of eosinophil peroxidase, and its serum concentration can serve as a marker of eosinophil activation. However, preliminary studies indicate it could be increased in any form of IBD and not just eosinophilic enteritis. Urinary and fecal N-methylhistamine concentrations are poor markers for mast cell activation or clinical disease activity in dogs with chronic enteropathies.

Serum Folate and Cobalamin Concentrations[52,234,237-239,242,377,393-410]

The assay of serum folate and cobalamin concentrations often is performed on the same serum sample taken for the TLI test. This assay has limited value in the diagnosis of specific SI diseases and is *not* recommended for the diagnosis of bacterial overgrowth. Subnormal folate and cobalamin concentrations are primarily markers of GI disease (see Figure 276-2), but also indicators of the need to supplement. Hypercobalaminemia has no significance in dogs or cats with GI disease and could be due to supplementation, but it has been associated with hepatic and neoplastic disease in cats.

Special Indirect Tests[411-414]

In cases of malabsorption, intestinal biopsy usually is necessary to obtain a definitive diagnosis. However, EPI should be ruled out before biopsy because signs of malabsorption are nonspecific and do not permit differentiation of cause. Thus, serum trypsin-like immunoreactivity (TLI) measurement must be performed in all cases (see ch. 292). It also is well recognized that biopsies from up to 50% of patients are considered normal by light microscopy. Therefore, usually before biopsy, a number of indirect tests can be performed to assess for intestinal damage, altered permeability, and dysfunction, although their sensitivity and specificity limit their utility.

Tests of Intestinal Absorption[415-419]

Tests of intestinal function assessing the mediated absorption of numerous substrates—such as lactose, glucose, starch, triglyceride, and vitamin A—are no longer performed because of a lack of sensitivity and specificity. Even the D-xylose test has been abandoned because it is too insensitive in dogs and is nondiscriminatory in cats. The differential absorption of two sugars—xylose/3-O-methyl-D-glucose—eliminates the nonmucosal effects that blight the xylose test, but this assay has not entered routine practice.

Intestinal Permeability[266,416,420-449]

Intestinal permeability is an index of mucosal integrity, and it is assessed by measuring unmediated uptake of nondigestible, nonmetabolizable probe markers in plasma and/or urine. The permeability probe chromium[51]-labeled ethylenediamine tetra-acetic acid (^{51}Cr-EDTA) was used in original studies, but being a gamma-emitter limited its safe use. The lactulose/rhamnose test has become the standard test of SI permeability. Recently, iohexol has been shown to be a useful probe marker, because it is safe and its assay is commercially available. In IBD, there are reductions in E-cadherin and alpha-catenin, which are integral to tight junction structure and function. Consequently intestinal permeability is increased by villus atrophy or epithelial damage or both. NSAIDs also increase intestinal permeability.

Tests for Protein-Losing Enteropathy[315,450,451]

Historically, intestinal protein loss has been detected by measuring the fecal loss of radiolabeled molecules such as ^{51}Cr-labeled albumin and ^{67}Cu-labeled ceruloplasmin. These tests are unpleasant to perform and potentially hazardous and have been discarded, although they remain the standard by which other tests, such as fecal alpha$_1$-PI, are judged.

Breath Tests[405,452-467]

Breath tests are used for assessing bacterial metabolism in the GI tract. Bacteria synthesize a gas, which is absorbed and excreted in breath. Breath hydrogen tests have been used most extensively because mammalian cells cannot produce hydrogen, and therefore any that is measured must be bacterial in origin. Such tests potentially can assess carbohydrate malabsorption, bacterial colonization of the SI, and oro-cecal transit time, but are not widely used.

Unconjugated Bile Salts[468-472]

The hypothesis behind the serum unconjugated bile acids (SUBA) test was that some SI bacterial species can deconjugate bile acids. Unconjugated bile acids then are absorbed passively by the SI and do not undergo enterohepatic recycling. Therefore, in theory, increases in SI bacterial activity might result in an increase in SUBAs. However, results do not correlate with the diagnosis, partly because there is a significant postprandial increase in SUBA in healthy dogs, and the test is no longer recommended.

Miscellaneous Tests of Bacterial Activity[460,472-479]

Several tests for intestinal bacterial metabolites have been devised to detect bacterial metabolic activity, bacterial overgrowth, or to assess oro-cecal transit time. These include the nitrosonaphthol test, urinary indican excretion, serum D-lactate, and bacterial release of sulfapyridine from sulfasalazine or p-amino benzoic acid (PABA) from a bile salt conjugate (PABA-UDCA). Evaluation of the volatile gases emitted by feces can give a profile that is characteristic of specific infections. However, none of these tests is used widely in companion animals.

Indirect Assessment of Intestinal Motility[458,460,479-491]

Intestinal transit time can be assessed directly by barium studies with and without food, ultrasonography (including pulsed-wave Doppler), and scintigraphy. Recording of myoelectrical activity *in vivo* is not practicable in clinical practice, although peristaltic pressure can be measured with the SMART capsule. Indirect assessments of intestinal motility include breath hydrogen following carbohydrate administration, and visual (carmine red dye, chromic oxide) or chemical markers (sulfasalazine, acetaminophen, nitrofurantoin, PABA-UDCA) given orally. Results are variable, and often the methodologies do not correlate well. Many are technically difficult, and the composition of the test diet and stress affect transit rates as much as disease does.

Diagnostic Imaging[492-496]

Historically, imaging of the intestinal tract was limited to plain and contrast radiographs, and now it is complemented by ultrasonography and flexible endoscopy. Scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI) now are rapidly being adopted, and "virtual endoscopy" by helical CT is becoming available.

Plain Radiography[483,497-503]

Survey, plain radiographs are most useful in the investigation of primary vomiting, diarrhea associated with vomiting, evidence of abdominal pain, and palpable abnormalities. Diagnostic yield is improved if both lateral views are taken in addition to an orthogonal view, although a single lateral radiograph may be all that is required if radiography is combined with ultrasonography. Generally the aim is the detection of (acute) surgical disease (foreign bodies, free peritoneal gas, intestinal displacement, masses, obstructions), decreased serosal detail, and ileus (E-Table 276-7).

E-TABLE 276-7

Helpful Survey Abdominal Radiographic Findings in Patients with Intestinal Disease

FINDINGS	INTERPRETATION
Radiopaque foreign bodies	Visible on survey films
Ileus	Either adynamic/paralytic or obstructive (see Box 276-5)
Abnormal soft tissue shadow	Abdominal mass
Displacement of viscera	Abdominal mass, enlargement of intraperitoneal or retroperitoneal organ, rupture, or hernia
Bunching of intestine	Excess intraabdominal fat, large mass, adhesions, linear foreign body
Bowel wall thickness*	Edema, infiltrative (inflammatory, neoplastic) disease
Bowel wall irregularity*	Enteritis, neoplasia, ulcers
Loss of serosal detail	Emaciation and immaturity, peritoneal effusion (ascites in hypoproteinemia and/or portal hypertension, peritonitis, carcinomatosis)

*Requires contrast.

Ileus is an abnormal dilation of an immotile segment of intestine, and the differential diagnosis depends on whether it is localized or generalized and whether an accumulation of gas or fluid is present (Box 276-10). Interpretation should be cautious if the patient has been treated with drugs that can affect the GI tract. Comparisons of the degree of intestinal dilation to bony landmarks to determine if there is an obstruction are not always helpful, and the usefulness of plain radiographs in malabsorption is minimal, especially if ascites is present, as all detail is obscured by fluid.

Box 276-10

Differential Diagnosis of Ileus

Gas Ileus

- Generalized
  - Aerophagia
  - Enteritis
  - Generalized peritonitis
  - Smooth muscle paralyzing drugs (e.g., atropine)
- Localized
  - Disruption of mesenteric arterial supply

- Early-stage bowel obstruction
- Localized peritonitis (e.g., pancreatitis)

Fluid Ileus

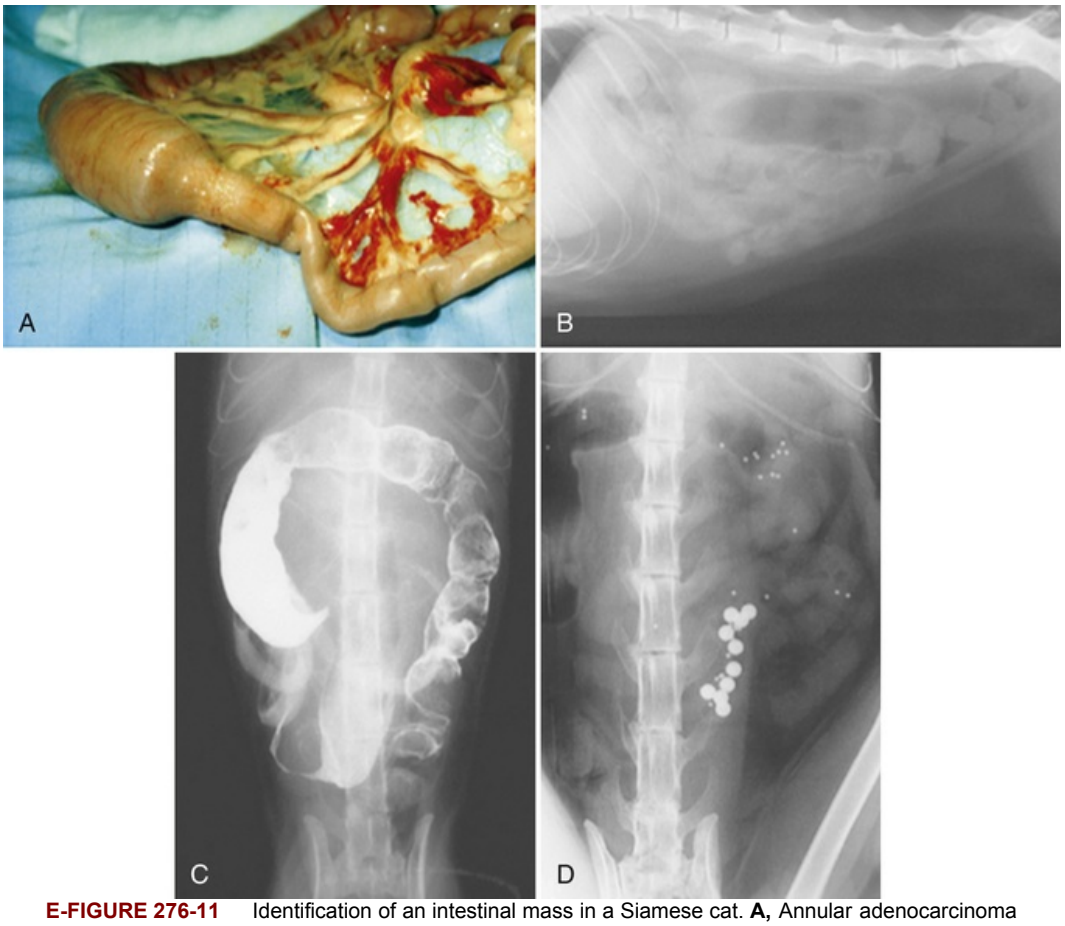
- Generalized
  - Enteritis
  - Diffuse intestinal neoplasia
- Localized
  - Foreign body
  - Intussusception or other mechanical obstruction (e.g., incarceration)
  - Tumor causing obstruction

Contrast Radiography

Since the introduction of abdominal ultrasonography and endoscopy, contrast radiographic studies have had limited value in the assessment of SI disease, but they remain useful for gastroesophageal disease (see ch. 273).

Follow-Through Examinations[504-506]

Studies using microfine barium suspensions can identify ulcers and irregular mucosal detail and could confirm the presence of radiolucent foreign bodies but are insensitive for identifying mural masses and partial obstructions and rarely provide more information than a good-quality survey films (E-Figure 276-11). Administration of barium can delay endoscopy for at least 24 hours. If perforation is suspected, an iodine-based contrast is used. Enteroclysis (deposition of contrast directly into the stomach or intestine via orogastric or orointestinal intubation, for optimal distension) provided more information but is technically demanding and has not been adopted. Although contrast studies allow assessment of the intestinal transit rate of the contrast agent, this is not physiologic and does not correlate closely to movement of ingesta assessed by the gold standard of scintigraphy. Furthermore, evidence of dysmotility provides no etiologic information.



E-FIGURE 276-11 Identification of an intestinal mass in a Siamese cat. **A,** Annular adenocarcinoma in the ileum demonstrated at laparotomy. **B,** Prior plain lateral radiograph showing a dilated loop of bowel associated with this caudal abdominal mass. **C,** Ventrodorsal radiograph after oral administration of barium suspension showing a dilated loop of small intestine on the midline, colonic filling, and narrowing of the intestinal lumen at the site of the mass. **D,** Ventrodorsal radiograph after oral administration of barium-impregnated polyethylene spheres (BIPS) showing accumulation of the larger markers at the site of the partial obstruction caused by the mass. (Courtesy A. H. Sparkes.)

Barium-Impregnated Polyethylene Spheres (BIPS)[491,507-510]

BIPS are solid-phase radiopaque markers that provide information on gastric emptying, intestinal transit, and obstructive disorders (see E-Figure 276-11). Given that the transit time of BIPS is highly variable, their use for transit studies is limited and they are most helpful in the detection of partial obstructions.

Ultrasonography[494,511-562]

Abdominal ultrasound examination of the SI is now a routine part of the investigation of SI disease (see ch. 88 and 89), although its diagnostic utility in chronic diarrhea has been questioned. A conventional examination can detect loss of layering of the SI wall, ulceration, mucosal heterogeneity and striations, evidence of fibrosis, peristalsis, ileus, luminal contents and foreign bodies and can be used for measuring SI wall thickness. Ultrasonography has greater sensitivity than radiography and excellent specificity for the detection of lesions such as intussusceptions, masses, both radiopaque and radiolucent foreign bodies, and intestinal wall thickening and lymphadenopathy in chronic inflammatory, inflammatory, lymphatic, and neoplastic enteropathies (Figure 276-12); even Peyer's patches and sites of previous intestinal surgery can be identified with the appropriate equipment and operator expertise. The development of endoscopic ultrasound now is allowing the mucosal wall and adjacent viscera to be examined in even more detail.

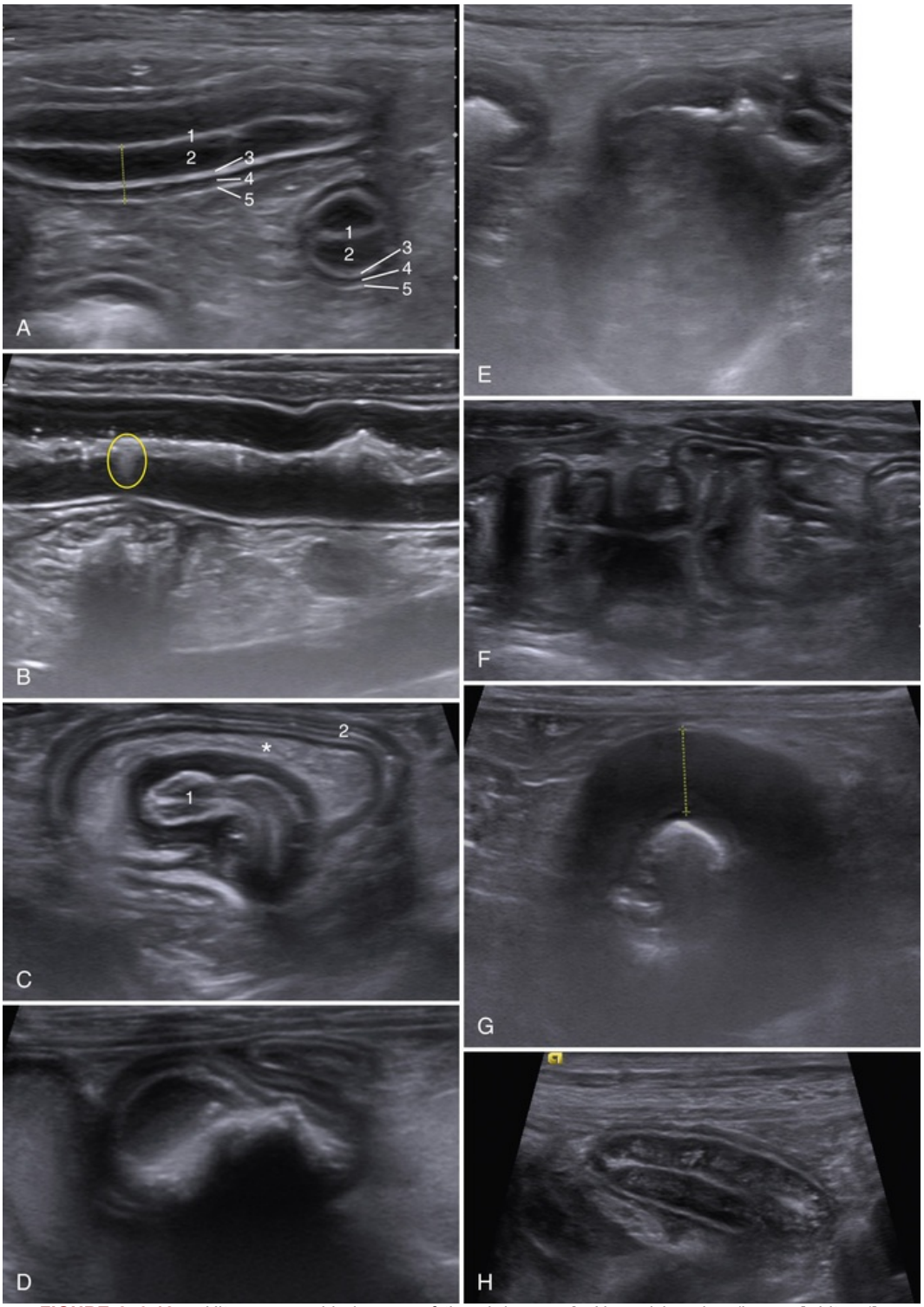
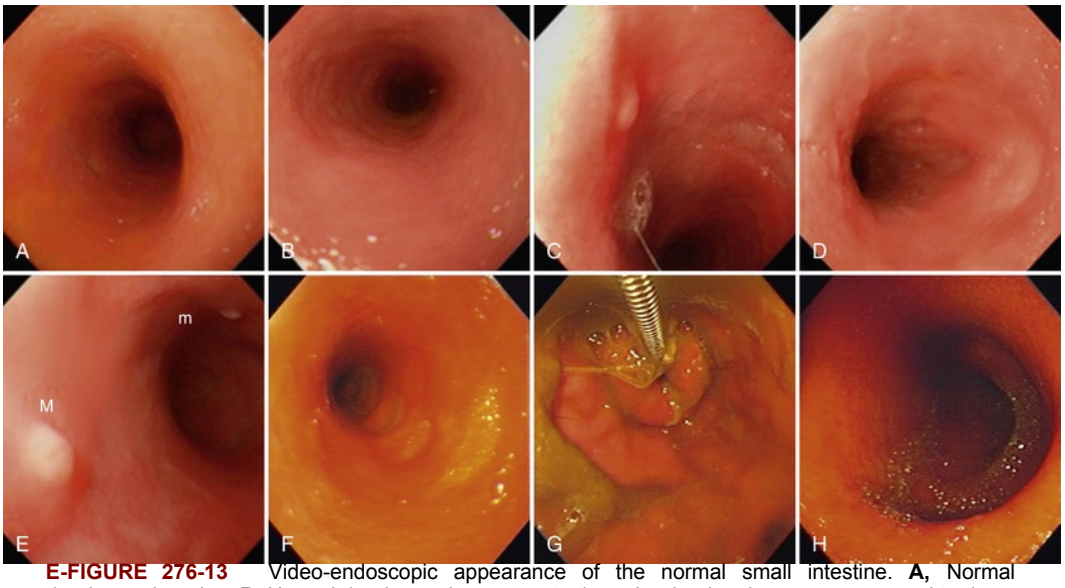


FIGURE 276-12 Ultrasonographic images of the abdomen. **A,** Normal layering (lumen [white; *1*]; mucosa [black; *2*]; submucosa [white; *3*]; muscularis [black; *4*]; serosa [white; *5*]) of loops of jejunum in both longitudinal and transverse section in a dog. **B,** Longitudinal section of canine duodenum with normal layering and a Peyer's patch indenting the mucosa (circled); note that the duodenum is straighter and has a thicker wall than the jejunum. **C,** An intussusception with the classic double-walled structure; the intussusceptum *(1)* is surrounded by ingesta (asterisk) in the intussuscipiens *(2)*. **D,** An intestinal foreign body with acoustic shadowing. **E,** An eccentric mass lesion that would be amenable to fine-needle aspirates or Tru-Cut biopsy. **F,** A linear foreign body with plication of the intestinal loops. **G,** Thickened intestinal wall with loss of layering caused by lymphoma. **H,** Heterogeneous, hyperechoic mottling and striation in the mucosa of a dog with lymphangiectasia (see Figure 276-14, *H*). (Images courtesy Chris Warren-Smith, Langford Veterinary Services.)

Values for normal SI wall thickness have been reported for dogs and cats; thickness decreases from 5-6 mm proximally to 4-5 mm distally but also depends on body size, with the thickest wall being seen in the largest dogs. Intussusceptions usually are recognized in the transverse plane as multiple concentric rings and longitudinally as a thick, multilayered segment. Disruption of the normal five-layered sonographic appearance (mucosal surface, mucosa, submucosa, muscularis, serosa) is typical of neoplasia, whereas wall thickening also can result from other infiltrative disorders and edema, although a thickened muscularis has been associated with lymphoma in cats. Mucosal heterogeneity can be indicative of inflammation or crypt abscessation. Striations reflect lymphatic dilation; administration of corn oil before the examination can improve their identification, although the specificity of the finding is reduced. High-frequency ultrasound can differentiate mucosal lymphoid aggregates. Ultrasound-guided fine-needle aspiration of masses or grossly thickened walls for cytologic examination is possible, and needle biopsy can be possible with larger lesions.

Endoscopy[325,326,331,480,563-586]

Endoscopy allows visualization of the SI mucosa and collection of multiple tissue samples without the need for invasive surgery and the risk of surgical biopsy; complications of bacteremia or perforation are rare. Optimal, well-maintained endoscopic equipment and operator experience are more important than pharmacologic manipulation in achieving successful SI intubation (see ch. 83 and 113). The proximal SI is viewed during gastroduodenoscopy (E-Figure 276-13 and Video 276-1), and the ileum can be sampled by passing the endoscope retrograde through the ileocolic valve during colonoscopy. Therefore only the midjejunum cannot be examined satisfactorily by routine endoscopy. However, given that most cases of malabsorption involve diffuse disease, this limitation might not be significant, although discordance between the findings of paired duodenal and ileal biopsies means that ideally both sites should be sampled.



E-FIGURE 276-13 Video-endoscopic appearance of the normal small intestine. **A,** Normal duodenum in a dog. **B,** Normal duodenum in a cat; note the paler duodenal mucosa compared to dogs. **C,** The major duodenal papilla in the duodenum of the dog is the site of entry of the common bile duct and major pancreatic duct. **D,** Peyer's patches (lymphoid aggregates) in the duodenum appear as pale oval depressions along the antimesenteric border of the descending duodenum. **E,** The minor duodenal papilla (m) is seen in some but not all dogs, distal to the major duodenal papilla (M) and approximately 100 degrees clockwise from it. **F,** Normal canine duodenum with a line of Peyer's patches. **G,** Blind biopsy of the ileum achieved by passing biopsy forceps through the ileocolic valve via colonoscopy. **H,** Normal ileum viewed by successful passage of the endoscope through the ileocolic valve; the mucosa is thinner than in the duodenum and appears more granular due to the presence of multiple small lymphoid follicles. (**A-E,** Reprinted with permission from Lhermette P, Sobel D, editors: *BSAVA manual of canine and feline endoscopy and endosurgery*, Quedgely, Gloucester, England, 2008, BSAVA Publications.)

Currently, flexible endoscopy is the standard diagnostic method, but emerging technologies include capsule endoscopy, enteroscopy, double-balloon endoscopy and confocal endomicroscopy. Enteroscopy uses a much longer, thinner endoscope (with or without a guiding oversleeve) and/or advancement balloons and

could allow examination of most of the jejunum, as does a videoendoscopy capsule that passes from mouth to anus and transmits images by telemetry. The SMART capsule allows collection of physiologic data (pH, pressure) by telemetry but no images. Confocal endomicroscopy allows evaluation of cellular morphology in the SI and the potential for early detection of epithelial dysplasia and neoplasia.

Abnormal findings on gross endoscopic examination include mucosal granularity and friability, erosions/ulcers, retained food, mass lesions, and hyperemia/erythema (Figure 276-14). A milky-white exudate and/or dilated lymphatics is/are suggestive of lymphangiectasia, and the presence of intraluminal parasites can be diagnostic in some cases (Video 276-2), but identification of roundworms usually is an incidental finding. A simple qualitative endoscopic scoring system for IBD has been developed (Table 276-8). However, none of these characteristics is pathognomonic for particular disease conditions, and gross findings frequently do not correlate with histopathological results.

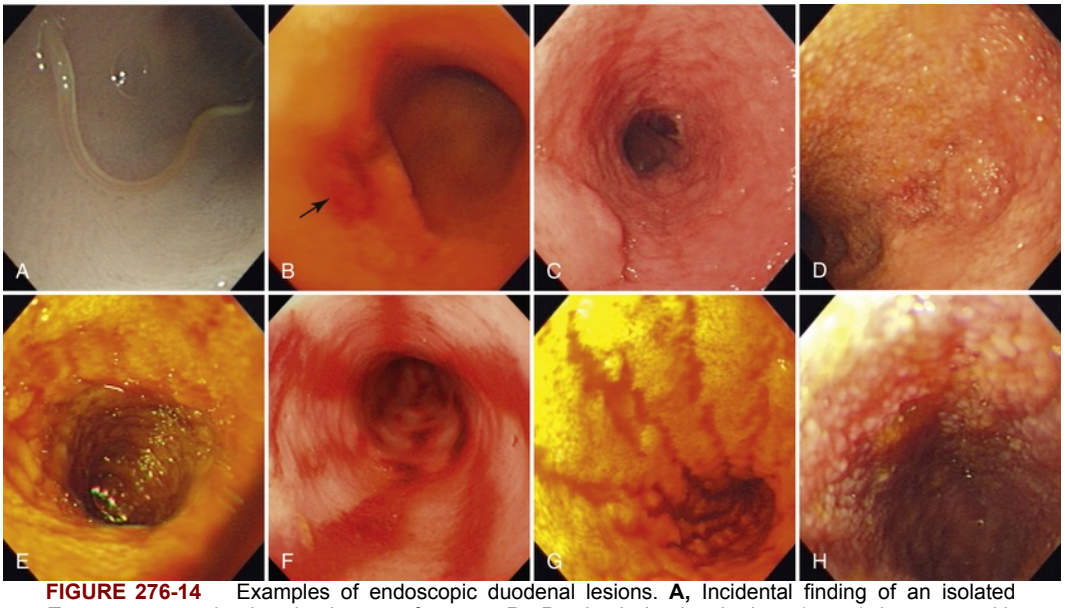


FIGURE 276-14 Examples of endoscopic duodenal lesions. **A,** Incidental finding of an isolated *Toxocara* worm in the duodenum of a cat. **B,** Proximal duodenal ulcer (arrow) in a cat with lymphoplasmacytic enteritis presented because of hematemesis. (Courtesy Natasha Hetzel.) **C,** Mild inflammatory bowel disease: lymphoplasmacytic enteritis; note the irregularity and the major duodenal papilla at approximately 7 o'clock. **D,** Severe inflammatory bowel disease: lymphoplasmacytic enteritis; note the marked granularity, even involving Peyer's patches. **E,** Marked crypt abscessation associated with protein-losing enteropathy in a Chihuahua. (Courtesy Jenny Reeve.) **F,** Inflammatory bowel disease: bleeding associated with eosinophilic enteritis. **G,** Severe inflammatory bowel disease: eosinophilic enteritis. **H,** Lymphangiectasia; note the multiple dilated lacteals containing white lymph.

TABLE 276-8

Quantitative Assessment of Endoscopic Mucosal Appearance

APPEARANCE	SCORE	DESCRIPTION
Friability	0	Absent
	1	Mild bleeding to touch
	2	Marked bleeding to touch
Granularity	0	Normal texture
	1	Texture increased
	2	Markedly increased texture
Erosions	0	Absent
	1	Only few erosions

	2	Diffuse erosions
Lymphatic dilatation	0	Absent
	1	Focal–multifocal white foci
	2	Diffuse white foci

Maximum enteroscopy score = 8.

From Slovak JE, Wang C, Sun Y, et al: Development and validation of an endoscopic activity score for canine inflammatory bowel disease. *Vet J* 203:290-295, 2015.

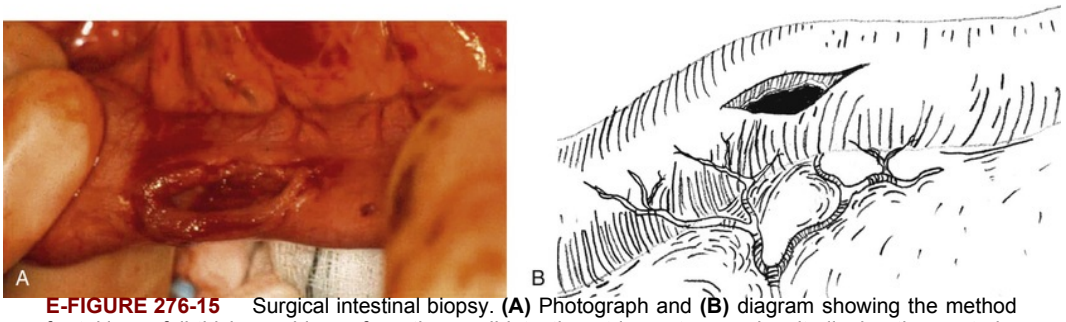
Duodenal Juice[103,469,587-591]

Duodenal juice can be collected during duodenoscopy through a sterile polyethylene tube passed down the biopsy channel or by needle aspiration through the intestinal wall at laparotomy. However, collection of sufficient sample without blood and tissue contamination can be difficult. The sample can be examined for *Giardia* trophozoites, although this has not proven reliable in diagnosis. Alternatively, quantitative and qualitative aerobic and anaerobic cultures can be performed. This was considered the gold standard for diagnosis of bacterial overgrowth, but there are major problems in interpretation and results do not aid in decision-making for cases of GI disease. Therefore, routine bacterial culture of duodenal juice is not recommended.

Intestinal Biopsy[565,577,592-608]

In most cases of acute diarrhea, a tissue diagnosis is not needed, and intestinal biopsy is rarely performed. However, in chronic diarrhea a definitive diagnosis often depends on histologic examination of intestinal tissue, although this does have major limitations. Biopsy specimens are collected either endoscopically or surgically (i.e., laparotomy or laparoscopy).

At laparotomy, full-thickness biopsies usually are taken from at least three sites: the duodenum, the jejunum, and the ileum (E-Figure 276-15). However, the risk of dehiscence after surgical biopsy can be substantial, especially if the patient is malnourished and/or hypoproteinemic, the tissue is neoplastic, or the surgeon inexperienced. Administration of plasma reduces the oncotic effects of hypoproteinemia, but the effect is only transient and only worthwhile to provide oncotic support during the perioperative period; it will not help wound healing.



E-FIGURE 276-15 Surgical intestinal biopsy. **(A)** Photograph and **(B)** diagram showing the method for taking a full-thickness biopsy from the small intestine at laparotomy; a longitudinal antimesenteric, elliptical incision is made and is then closed transversely to prevent stricture formation. (Reprinted with permission from Hall E, Williams D, Simpson J, editors: *BSAVA manual of canine and feline gastroenterology*, ed 2, Quedgely, Gloucester, England, 2005, BSAVA Publications. Part B, Drawn by Ellen Williams and reproduced with her permission.)

The reduced risk of endoscopic biopsy to the patient compared with surgery is balanced by a number of drawbacks (see E-Box 276-9), and the client should always be warned prior to endoscopic biopsy that surgical biopsy might ultimately be required for definitive diagnosis. The duodenum, and proximal jejunum, if possible, are biopsied routinely, and ileal biopsies can be obtained via colonoscopy. It is best practice to perform endoscopic biopsy before contemplating surgery unless there is evidence that the disease is beyond the reach of the endoscope. The surgical option is preferred if there is any possibility of extraintestinal disease or focal intestinal lesions. The size and quality of endoscopic biopsies depends not just on the equipment available but also the pressure exerted by the forceps, which is in part dependent on the operator's experience

and how the biopsies are processed. Biopsies should always be taken, even in the absence of gross abnormalities, because microscopic changes can be present. Multiple specimens (six or more) should be collected because the size of the specimens, crush artifacts, and fragmentation can make interpretation difficult (Figure 276-16).

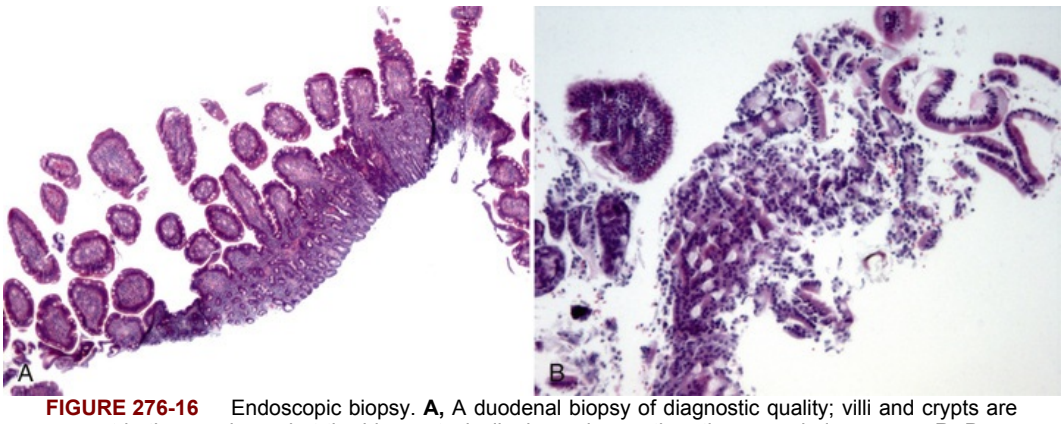


FIGURE 276-16 Endoscopic biopsy. **A,** A duodenal biopsy of diagnostic quality; villi and crypts are present in the specimen, but the biopsy, typically, is no deeper than the muscularis mucosa. **B,** Poor-quality endoscopic biopsy; the tissue is traumatized and disrupted; it is not suitable for making a diagnosis. (Reprinted with permission from Hall E, Williams D, Simpson J, editors: *BSAVA manual of canine and feline gastroenterology,* ed 2, Quedgely, Gloucester, England, 2005, BSAVA Publications.)

Examination of Biopsies[604,609-616]

Histopathology

Although histopathologic assessment of intestinal biopsies remains the supposed gold standard for diagnosis of intestinal disease, it has marked limitations. Many biopsy specimens can be normal by light microscopy, which suggests that many diseases have a functional rather than a morphologic cause (Box 276-11) or that sampling or interpretation problems have occurred. Agreement between histopathologists often is poor, especially when examining endoscopic biopsies, and a standardized approach is required (E-Box 276-12). In one study, some histopathologists made a diagnosis of lymphoma after assessing tissues from healthy dogs, and there was only reasonable agreement between five independent pathologists in about half of the samples examined. Histopathologic scoring schemes and standardized criteria have been suggested by the World Small Animal Veterinary Association (WSAVA) GI Standardization Group as a means of improving agreement. However, Group members also have shown that the experience of the endoscopist, as well as simply the quality and number of biopsies and the quality of processing and staining, all can influence the reliability of the histologic interpretation. As expected, the better the quality of the biopsies, the fewer that are needed to reliably detect architectural changes (i.e., size, depth, and integrity) but more specimens are needed to identify deeper (cryptal) lesions. Ileal biopsies are more likely to show histopathologic changes than are duodenal biopsies. Therefore, the primary clinician should always interpret endoscopic biopsy results cautiously and in light of the clinical presentation; results should be questioned if the tissue diagnosis does not fit the clinical picture or if the response to apparently appropriate therapy is poor. In some cases, repeat biopsy (e.g., by exploratory laparotomy) might be required.

Box 276-11

Causes of Chronic Diarrhea for Which Small Intestinal Biopsy Results Can Be Normal*

- ARD, SIBO
- Brush border membrane disease (e.g., hypolactasia)
- Dietary indiscretion
- Food intolerance
- Intestinal sclerosis (if biopsies are not full-thickness)

- Motility disorder/irritable bowel syndrome
- Patchy mucosal disease not sampled
- Toxigenic/secretory diarrhea
- Type I hypersensitivity to food (if dog is starved before biopsy)
- Undiagnosed EPI or colonic or systemic disease

ARD, Antibiotic-responsive diarrhea; *EPI,* exocrine pancreatic insufficiency; *SIBO,* small intestinal bacterial overgrowth.

*Detection of histologic abnormalities depends on the size and quality of the biopsy, the quality of processing, and the expertise of the pathologist.

E-Box 276-12

WSAVA GI Standardization Group's Histologic Scoring System for Grading Intestinal Inflammation in Endoscopic Biopsies*

Morphologic Features

- Villus stunting
- Epithelial injury
- Crypt distension
- Lacteal dilation
- Mucosal fibrosis

Cellularity in Lamina Propria

- Intraepithelial lymphocytes
- Lymphocytes and plasma cells
- Eosinophils
- Neutrophils
- Other cells

All features graded as normal/mild/moderate/severe.
WSAVA, World Small Animal Veterinary Association.

*Day MJ, Bilzer T, Mansell J, et al: Histopathological standards for the diagnosis of gastrointestinal inflammation in endoscopic biopsy samples from the dog and cat: a report from the World Small Animal Veterinary Association Gastrointestinal Standardization Group. *J Comp Pathol* 138:S1-S40, 2008.

Cytology[617-620]

Cytologic examination of endoscopic biopsy squash preparations or mucosal brushings only are an adjunct to histopathologic examination. Impression smears show the best correlation with histological findings and are most useful for neoplastic masses.

Alternative Examinations[144,621-635]

Other biopsy examinations available include electron microscopy; biochemical assay of brush border enzymes with subcellular fractionation; immunocytochemical characterization of B cells, T cells, and their subsets (e.g., CD4 and CD8 cells) and MHC expression by immunohistochemistry and flow cytometry; cytokine mRNA expression; and assessment of T-cell clonality. These are largely research tools. Fluorescent *in situ* hybridization (FISH) allows identification of organisms in tissues and their spatial arrangement.

Acute Small Intestinal Disease

Diagnosis[320,636-639]

Potential causes of acute diarrhea are listed in Table 276-9, but whether an absolute diagnosis is pursued or

whether supportive, empirical therapy is instituted is a clinical and sometimes economic judgment. Patients that are bright, alert, and not dehydrated might require no further investigation because signs often are self-limiting.

TABLE 276-9

Causes of Acute Diarrhea

CAUSES	EXAMPLES
Anatomic	Intussusception
Dietary	Hypersensitivity (allergy), intolerance, sudden diet change, food poisoning (poor quality, spoiled foods/bacterial)
Infectious	
Bacterial	*Salmonella, Campylobacter jejuni, Clostridium* spp. (?) and *Escherichia coli* (?)
Parasites*	
Helminths	*Ancylostoma caninum, Trichuris vulpis*
Protozoa	Coccidia, *Giardia* spp., *Tritrichomonas foetus*
Viral	
Mild	Adenovirus, Coronavirus, Norovirus, Rotavirus May or may not be FeLV/FIV related
Severe	Parvovirus, Paramyxovirus (distemper)
Metabolic	Hypoadrenocorticism
Toxic	Food or other sources
Pancreatic	Acute pancreatitis

*Often start acutely but become chronic if not treated.

FeLV, feline leukemia virus; *FIV*, feline immunodeficiency virus.

The diagnostic approach to acute diarrhea is discussed in ch. 40 and summarized in Figure 276-7. Nonintestinal causes such as pancreatitis or hypoadrenocorticism are ruled out before focusing on the SI. Further investigation of acute diarrhea is indicated if the patient is dull or depressed, febrile, dehydrated, tachycardic or bradycardic; or has abdominal discomfort, melena, bloody mucoid stools, or frequent vomiting; or has obvious physical abnormalities (e.g., intestinal masses, thickening, or plication) localizing the problem to the SI, and diagnostic imaging (Figure 276-17), noninvasive biopsy, or surgery can define the cause; or has systemic abnormalities as defined by a minimum database and other clinicopathologic tests; or has not responded to general, nonspecific therapy.

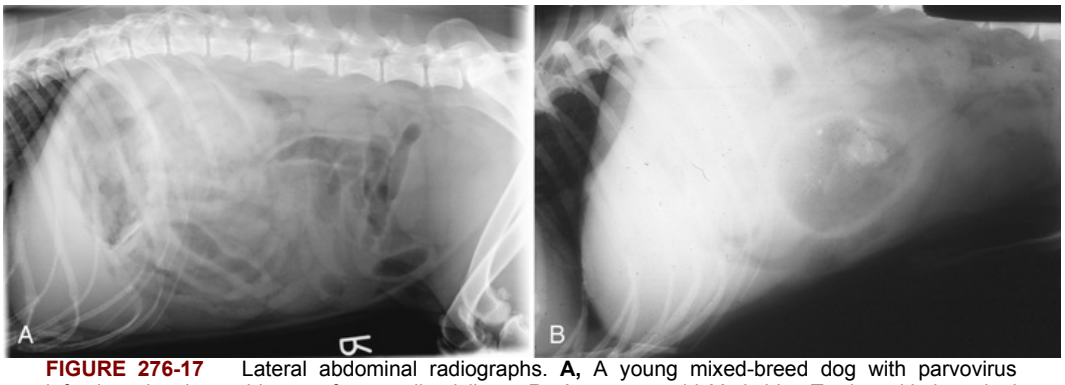


FIGURE 276-17 Lateral abdominal radiographs. **A,** A young mixed-breed dog with parvovirus infection showing evidence of generalized ileus. **B,** A ten-year-old Yorkshire Terrier with intestinal obstruction due to an annular adenocarcinoma. Note the dilated bowel loop proximal to the mass, and the gravel sign (i.e., accumulation of material proximal to the mass).

Treatment of Acute Diarrhea[640-644]

The initial management of acute diarrhea is nonspecific and supportive and is chosen on the basis of clinical findings, especially the presence of dehydration, while the results of the initial database and any further tests are pending. Administration of antiemetics is indicated if the patient is vomiting and an intestinal obstruction has been ruled out. It is important that the patient regularly be reevaluated to monitor the response to therapy and to detect any new criteria of concern that might arise.

Fluid Therapy[645-652]

Oral fluid and electrolyte replacement therapy could be sufficient if acute diarrhea is associated with insignificant or only mild dehydration and if vomiting is infrequent or absent. Solutions containing glucose and electrolytes—sometimes with added glycine, glutamine or peptides (e.g., rice water)—are used, as they promote the osmotic uptake of water (see ch. 189). The inclusion of glutamine, a nutrient utilized preferentially by enterocytes, could promote recovery and decrease bacterial translocation. However, when diarrhea is accompanied by significant vomiting or dehydration, parenteral fluids should be administered, and at a rate that replaces deficits, supplies maintenance needs and compensates for ongoing losses (see ch. 129). Patients with marked hypovolemia require more intensive support. Antiemetics can be beneficial to reduce fluid loss and patient discomfort but could mask signs of intestinal obstruction. The type of fluid and requirement for potassium supplementation is best judged by performing a minimum database and blood gas analysis. Parenteral fluids are best given intravenously; the intraosseous route can be used if venous access is unavailable (see ch. 77), but subcutaneous fluids are unlikely to be adequate.

Diet[644,648,649,653-658]

Current recommendations regarding the role of diet in the treatment of acute diarrhea largely are based on common sense, anecdotal evidence, and extrapolation from management guidelines for treating humans. Best practice generally is considered to be withholding food for 24 to 48 hours to "rest" the gut and then feeding a bland diet, given little and often, for 3 to 5 days. Thereafter, the original diet is gradually reintroduced. Common choices of a bland, fat-restricted diet for dogs are boiled rice with either boiled chicken or white fish or low-fat cottage cheese. Cats have a lower tolerance to dietary starch and could benefit from a diet with a higher protein and fat content. Little attention need be paid to the overall nutritional adequacy of home-prepared bland diets when fed in the short term. Commercial veterinary GI diets are available and more convenient.

The dogma of "intestinal rest" for dogs and cats has been challenged by studies that demonstrate that feeding human infants during infectious, secretory diarrhea promotes recovery and strengthens mucosal immunity. There is some evidence in dogs that feeding speeds recovery from hemorrhagic gastroenteritis (HGE). However, in general, secretory diarrhea is less common in dogs and cats compared to infants, the resultant increased volumes of diarrhea (although over a shorter period) could be cosmetically unacceptable, and the presence of vomiting can preclude this approach anyway.

Theoretically, any intestinal disease can predispose the animal to the development of a food sensitivity. Therefore, feeding of a novel protein source during these periods may preclude the development of sensitivity to the staple diet. However, evidence for this concept of feeding a "sacrificial protein" is circumstantial.

Protectants and Adsorbents[659,660]

Bismuth subsalicylate, kaolin, montmorillonite (a refined form of smectite clay or kaolin), pectin, activated charcoal and magnesium, and aluminum- and barium-containing products often are administered in acute diarrhea to bind bacteria and their toxins and to protect the intestinal mucosa. They also bind water and could be antisecretory. Therapy should not exceed three days if there is no improvement.

Motility- and Secretion-Modifying Agents[661-669]

Anticholinergics and opiates or opioids (loperamide, diphenoxylate) often are used for the nonspecific management of acute diarrhea, but anticholinergic agents can potentiate ileus and are not recommended. Opioid analgesics were thought to exert their effects by stimulating segmental motility, thereby slowing transit, but they actually act mainly by decreasing intestinal secretion and promoting absorption. They are indicated in short-term supportive management of acute diarrhea in dogs; they are contraindicated in cases involving obstruction or an infectious etiology. Loperamide can have central nervous system side effects in

collies and other dogs with the multidrug resistance (MDR-1) gene mutation. Antimuscarinic drugs such as hyoscine (butylscopolamine) generally are not recommended, as they can produce a paralyzed, nonfunctional SI, can predispose to intussusception, and can cause intoxication. However, in mild cases of acute gastroenteritis, their antispasmodic effect could help relieve colic-type pain.

Antimicrobial Therapy[670-675]

Antimicrobials frequently are prescribed for acute diarrhea but are only truly indicated in animals with SI disease with a confirmed bacterial or protozoal infection. The current consensus is that they also are indicated when a widespread breach of intestinal barrier integrity is suspected from evidence of hemorrhagic diarrhea when, consequently, the patient is at risk of sepsis. However, there is no benefit if the patient is not bacteremic or showing signs of sepsis. Leukopenia, neutrophilia with left shift, fever, the presence of blood in the feces, and shock all are potential indications for prophylactic antibiotics in animals with diarrhea. Initial choices in these situations include clavulanate-potentiated amoxicillin or a cephalosporin (effective against Gram-positive and some Gram-negative and anaerobic bacteria). If systemic translocation of enteric bacteria is suspected, antimicrobials effective against anaerobic organisms (e.g., metronidazole or clindamycin) and "difficult" Gram-negative aerobes (e.g., an aminoglycoside or a fluoroquinolone) are indicated. Potentially nephrotoxic aminoglycosides, such as gentamicin, should not be given until the patient is volume-expanded. Intravenous quinolones have been shown to reach therapeutic concentrations in the canine gut lumen and can be effective against enterococci and *E. coli*.

Prebiotics and Probiotics (Synbiotics)[10,676-729]

Prebiotics are selective substrates used by a limited number of "beneficial" microbial species, which therefore cause alterations in the luminal microflora. The most frequently used prebiotics are nondigestible carbohydrates, such as lactulose, inulin, fructo-oligosaccharides (FOS) and mannan-oligosaccharides (MOS), and immunomodulators such as lactoferrin. Their use combined with probiotics is designed to encourage the growth of organism and is termed *synbiosis;* they might also have an effect on the immune system.

Probiotics are defined as "orally administered living organisms that exert health benefits beyond those of basic nutrition." However, what constitutes enteric health is poorly defined, and which features of probiotic activity are beneficial is not clear. For example, probiotics that increase IgA secretion might indicate improved immune exclusion but, conversely, might indicate poorer mucosal barrier function.

In addition to direct antagonistic properties against pathogenic bacteria, probiotics modulate mucosal immune responses (e.g., they can induce Treg cells) and can alter intestinal permeability. There is evidence that the positive effect of probiotics is species-specific and is present only while the probiotic is administered continuously. The traditional practice of feeding live yogurt as a way of repopulating the intestine with beneficial lactobacilli after an acute GI upset or antibiotics is unlikely to work, but probiotics are now available for use in dogs and cats. There is growing evidence of some efficacy in acute diarrhea, and probiotics are a more responsible therapeutic choice than blanket antimicrobial administration in first-opinion cases of gastroenteritis.

Etiologies of Acute Diarrhea[730-732]

In many cases of primary SI disease causing acute diarrhea, an etiologic agent is not identified. The lack of a definitive diagnosis commonly is seen in humans with HGE who survive, and while academically unsatisfying, the lack of a specific diagnosis in dogs and cats does not matter if the problem resolves, does not recur, and does not pose a risk to others. A number of etiologic mechanisms has been described.

Acute Diarrhea Induced by Diet, Drugs, or Toxins[320,733]

Acute, self-limiting diarrhea in dogs most commonly is associated with rapid diet change, dietary indiscretion, dietary intolerance, hypersensitivity, or food poisoning. The history can allow an educated, presumptive diagnosis to be made. However, the exact cause rarely is determined. Sudden diet change quite commonly causes diarrhea, perhaps because it alters the microbiome. Ingestion of drugs (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] or antibacterials) or toxins (e.g., insecticides) also can cause vomiting and diarrhea. The prognosis usually is excellent, and only if the diarrhea does not resolve or the patient's condition deteriorates is further investigation necessary.

Hemorrhagic Gastroenteritis (HGE)[644,674,675,734-749]

There are numerous potential causes of bloody vomiting and diarrhea, but *hemorrhagic gastroenteritis* (HGE) is the name that was given to a syndrome in dogs characterized by acute hemorrhagic diarrhea accompanied by marked hemoconcentration. This condition has recently been renamed acute hemorrhagic diarrhea syndrome (AHDS), but not all reported cases have the characteristic hemoconcentration. The cause of the syndrome is unknown, but the current hypothesis is that it is a consequence of *C. perfringens* enterotoxin production, although that has been refuted. Dysbiosis is present, but it is not clear whether that is a cause or an effect. Indeed, HGE could represent a diet-related type 1 hypersensitivity reaction, as recurrence is noted in some dogs, suggesting repeated exposure to an inciting cause.

Clinical Findings

Small-breed dogs and especially Miniature Schnauzers are affected most frequently, but HGE can affect large breeds too. Dogs present with acute hemorrhagic malodorous diarrhea, sometimes (but not always) preceded by vomiting. Fever is unusual, but depressed mentation and abdominal discomfort are common. The onset can be peracute and can be associated with marked fluid shifts into the SI, leading to severe hypovolemic shock even before classical signs of dehydration (i.e., increased skin tenting) appear (see ch. 127).

Diagnosis

Direct evidence of clostridial invasion has been shown in endoscopic biopsies but rarely is obtained, as endoscopic examination is not normally indicated. Instead, a presumptive diagnosis of HGE is made on the basis of appropriate clinical findings associated with a packed cell volume (PCV) > 60%. Serum total protein concentration often is normal or not as high as would be expected relative to the PCV, probably because of intestinal plasma loss. Radiographs can demonstrate evidence of ileus. The absence of leukopenia and the marked hemoconcentration help distinguish HGE from parvovirus infection, but pancreatitis (see ch. 290) and hypoadrenocorticism (see ch. 309) need to be ruled out.

Treatment

Intravenous crystalloids are essential (see ch. 129); some patients become hypoproteinemic and then require plasma (see ch. 130). Parenteral antibiotics often are administered because of the possible clostridial infection and the high risk of sepsis but might not be necessary and do increase the risk of inducing resistance in the microbiome (see ch. 161). Clinical improvement usually is noted within a few hours, though the diarrhea can take several days to resolve. Once the patient is in the recovery phase, standard supportive therapy for acute diarrhea can be instigated. The prognosis for most animals with HGE is good, although recurrence can occur, but if HGE is complicated by severe hypoproteinemia or sepsis, the prognosis is more guarded.

Infectious and Parasitic Causes[750-753]

Diarrhea caused by infectious and parasitic agents is considered common in animals that are young, immunologically naïve or immunocompromised, housed in large numbers, or housed in unsanitary conditions. Parvovirus (see ch. 225), *Giardia* (see ch. 221), *Tritrichomonas* (see ch. 221), *Salmonella* (see ch. 220), *Campylobacter* spp. (see ch. 220), hookworms, and whipworms (see below) can be significant causes of diarrhea. The importance of coronavirus, *C. perfringens,* and *E. coli* as causes of diarrhea has yet to be defined. Trematodes (flukes) are rare in dog and cats and more likely to cause liver disease, as well as carrying *Neorickettsia* (salmon poisoning; see ch. 218). Intestinal myiasis is a very rare problem.

A zoonotic potential exists for many of these infections, and good hygiene precautions always should be adopted. Specific SI infections are discussed later. Most viral enteritides of dogs and cats cause an acute and usually self-limiting diarrhea, although severe cases in young or immunocompromised patients can be fatal.

Chronic Small Intestinal Disease

Etiologies of Chronic Diarrhea

In many cases of primary SI disease causing chronic diarrhea, mucosal inflammation is present but an etiologic agent is not identified. This situation has been termed *chronic enteropathy,* as it encompasses diet-, antibiotic-, and steroid-responsive diseases. Steroid-responsive disease has been equated with idiopathic IBD, although there are several histologic variations (i.e., lymphoplasmacytic, eosinophilic, neutrophilic, granulomatous) suggesting that even true IBD is not a single disease entity. Known causes of intestinal inflammation include parasites (especially *Giardia*; see ch. 221), bacterial infection (see ch. 220), and food allergy (see below), and only idiopathic inflammation should be termed IBD. Other causes of primary chronic

diarrhea include lymphangiectasia and lymphoma, and structural abnormalities (e.g., chronic intussusception).

Characterization[754-759]

Chronic enteropathies historically have been defined by their histologic appearance. This criterion provides little information as to their etiology, and indeed many cases have no obvious histologic changes. So, more recently, chronic enteropathies have been defined by their response to empirical treatments trialled sequentially. Food-, antibiotic-, and corticosteroid-responsive disease have been compared to dietary sensitivity, bacterial disease, or idiopathic IBD, respectively. Risk-benefit analysis of intestinal biopsy suggests that pursuing a histologic diagnosis before parasiticide treatment and diet and antibiotic trials might not be worthwhile if the patient is still eating and has no evidence of a PLE, and particularly if it is a young animal. Findings of intestinal inflammation still require empiricial trials to be performed in order to reach a presumptive diagnosis, and the response to treatment and the prognosis in older cats is similar whether they have IBD or alimentary lymphoma.

Management of Chronic Inflammatory Enteropathies[760]

If a specific histologic diagnosis is made (e.g., lymphangiectasia, lymphoma), specific treatments can be used. However, in many circumstances there is intestinal inflammation with no identifiable cause because of a lack of specific histopathologic changes. In such cases, it is appropriate to perform empirical treatments sequentially. It is logical and safest to treat with parasiticides first to try to identify occult parasitism, before pursuing a diet trial, followed by an antibacterial trial, before finally attempting immunosuppression. Thus a three-day course of fenbendazole is the most appropriate trial initially, in order to identify or rule out giardiasis and helminthiasis (see ch. 163).

Dietary Management[103,591,654,655,761-778]

Dietary management is a very important treatment modality in the general management of chronic enteropathies (see ch. 178), and anorexia has adverse effects on the immune system. The ideal diet is highly digestible, moderately fat-restricted, lactose free, gluten-free, not markedly hypertonic, nutritionally balanced, and palatable. Hydrolyzed diets are a potential alternative (see below). Feeding the daily nutritional requirement in divided meals (usually between two and four) reduces the load on a compromised intestine. Feeding more frequently is unnecessary because gastric emptying imposes natural trickle-feeding of the SI. Inclusion of moderately fermentable fiber (e.g., psyllium, ispaghula) is known to promote colonic health, and soluble fiber also promotes SI health, but fiber can delay intestinal transit and excess fiber can be contraindicated. Prebiotic supplements such as FOS and MOS alter the fecal flora, but their effect on the SI flora is limited.

Raw meat diets or biologically appropriate foods (BARFs) are currently fashionable, and anecdotal claims of their success in managing chronic enteropathies are made. The concern, however, is that of microbiological safety, as they can be contaminated with *Salmonella, Campylobacter* and *Toxoplasma,* none of which is adequately destroyed by freezing (see ch. 192).

Antibacterials

Antibacterials are indicated for specific conditions in which a bacterial pathogen has been documented, in the treatment of ARD or secondary SIBO, and in other chronic enteropathies, such as IBD, in which modulation of the flora may be desirable. Tylosin, metronidazole, or oxytetracycline is commonly used, but any beneficial effects could go beyond their antibacterial activity, with potential effects on the mucosal immune system (see ch. 161).

Immunosuppression[779]

Immunosuppressive drugs are indicated when evidence of mucosal inflammation is present and no underlying cause is found. However, given the potential for adverse side effects, the diagnosis should be reviewed before institution of such therapy, especially if it was made on the basis of endoscopic biopsy alone, as these are notoriously unreliable. Glucocorticoids are the preferred first choice for immunosuppression, as they are generally effective and have the positive side effect of increasing appetite. However, if such steroids are ineffective or side effects are unacceptable, then other agents, such as azathioprine, chlorambucil, methotrexate, cyclosporine, or mycophenolate, can be used for their steroid-sparing effect (see ch. 165).

Vitamin Supplementation[408,780-783]

Low serum concentrations of folate and cobalamin can be found in cases of malabsorption causing chronic diarrhea and have diagnostic utility. The clinical significance of reduced serum folate is uncertain, and the value of supplementation is unproven. However, hypocobalaminemia is associated with a poorer prognosis. Significant metabolic changes occur with cobalamin deficiency, with accumulation of homocysteine and methylmalonic acid, which can lead to hyperammonemia. The acidemia can cause inappetence, loss of condition, and worsening of the intestinal disease. Cobalamin therefore should be supplemented: weekly parenteral injections are continued for at least 4 weeks and until serum concentrations are high.

Probiotics[718,784]

Most reports of probiotic use in animals concern the treatment of acute diarrhea (see also ch. 167). One report indicated that a symbiotic produced a reduction in feline chronic diarrhea, but there was no evidence for *Enterococcus faecium* SF68 clearing chronic infections such as *Giardia* from dogs.

Adjunctive Treatments[785-787]

Prokinetic agents such as metoclopramide, cisapride, or mosapride could improve well-being and appetite by overcoming the nausea associated with ileus. Mirtazapine often is given to improve appetite, but it also has a prokinetic effect. Loperamide and diphenoxylate slow intestinal transit and reduce the frequency of diarrhea but mostly are useful as cosmetic agents to reduce the likelihood of inappropriate passage of diarrhea. Antidiarrheals such as absorbents and fiber offer general, nonspecific treatment.

Alternative Treatments[788-797]

Acupuncture has been shown to stimulate SI motility, and various herbal preparations (e.g., agrimony, arrowroot, blueberries, chamomile, elm bark, neem bark, and marsh mallow *[Althaea officinalis]*) are recommended for the management of chronic enteropathies. Some bind water, like kaolin, whereas others contain molecules that reduce intestinal secretion. However, there are no blinded, placebo-controlled studies to support their use. Bovine lactoferrin has been proposed as a way of boosting the innate immune system, but there is no positive evidence, and homeopathic remedies have no scientific basis. Beta-1,3/1,6-D-glucan, beta-hydroxy-beta-methyl-butyrate and levamisole have been shown to reduce SI inflammation in IBD, with glucan being the most effective and most rapid in onset. Generic and autogenous enterovaccines have been trialled, but with no proof of efficacy so far.

Management of a PLE

Colloid support or plasma transfusion (see ch. 130) may be indicated during the perioperative period when collecting biopsy specimens but are ineffective at maintaining colloid osmotic pressure in the long term. Diuretics may reduce ascites; spironolactone may be safer (i.e., potassium-sparing and less drastic) and ultimately more effective than furosemide. Specific treatments are discussed later.

Viral Enteritides

Several viral infections of dogs and cats can cause enteritis as an important component of their clinical syndromes. The following are covered in detail in their respective chapters: canine parvovirus infection[365-368,653,798-912] (see ch. 225), feline parvovirus infection/panleukopenia[807,913-926] (see ch. 225), canine and feline coronavirus infections[802,927-955] (see ch. 224), feline immunodeficiency virus[956,957] (see ch. 222), and feline leukemia virus[958] (see ch. 223). Other viruses of generally lower prevalence also can cause enteritis.[959-977] Rotaviruses can infect dogs and cats, but infection usually is so transient that no signs are recognized. Norovirus has been isolated from cats and dogs with enteritis, and there also is serological evidence of widespread infection. A torovirus-like agent has been isolated from the feces of cats afflicted with a characteristic syndrome of chronic diarrhea and third eyelid prolapse, but a clear association with clinical signs was not demonstrated. Circovirus has been isolated from dogs with diarrhea and vasculitis. Bocavirus is a small, nonenveloped virus with a linear ssDNA genome and is a member of the Parvoviridae. Canine strains of bocavirus (minute virus of canines) have been incriminated in causing enteritis in puppies, and a fatal infection was associated with a novel strain, canine bocavirus 2. Many other novel enteric viruses such as Astroviruses (Mamastrovirus 1 and 2), Kobuvirus and Sakobuvirus have been identified, but their pathogenic

roles remain to be elucidated.

Bacterial Enteritides (also see ch. 220)

Relevance of Bacterial Isolation[943,978-982]

Potentially enteroinvasive bacteria, such as *Campylobacter jejuni*, *Salmonella* spp., and *Escherichia coli*, can be pathogenic in dogs and cats and be associated with acute diarrhea. The incidence of infection is greatest in young, kenneled animals and immunocompromised patients, and coinfections probably are common. However, these organisms also can be isolated from healthy animals and from those with chronic diarrhea, so confusion exists about their significance when isolated. Although these organisms still present a zoonotic risk, and care should be taken with pets owned by immunocompromised patients or families with young children (see ch. 210), attempting to eradicate the organisms with antibiotics when the animal is showing no clinical signs can be unhelpful and unnecessary and even could induce a carrier state.

Campylobacter spp.[263,980,983-1020]

Campylobacter organisms (see ch. 220) can be found in the feces of up to 100% of healthy and diarrheic dogs and cats at some point in their lives; eating chicken is a major risk factor for infection. *Campylobacter jejuni*, *C. coli*, *C. helveticus*, *C. lari* and *C. upsaliensis*, identified by molecular analysis of the 16S ribosomal RNA, all have been detected. In humans, all *Campylobacter* species are considered pathogenic, but their presence in the feces of healthy animals begs the question of whether they are pathogenic in dogs and cats. *Campylobacter* organisms attach to intestinal epithelial cells and, under the correct conditions, can invade and cause an ulcerative enterocolitis. Pathogenicity of *C. jejuni* in chickens has been shown to be related to its ability to invade when exposed to norepinephrine and to recruit neutrophils to an inflammatory process. *In vitro* studies using epithelial cell lines have demonstrated activation of NF-kappa-B and production of neutrophil chemokine IL-8 and the ability to induce neutrophil migration via the bacterial production of chemotactic n-formyl peptides.

There is experimental evidence that *C. jejuni* causes enterocolitis in dogs, but it appears to be at its most pathogenic when there is a viral coinfection. *C. coli* infection has been associated with kitten diarrhea and neutrophilic enteritis. It is possible that the most common isolate from dogs, *C. upsaliensis*, is a commensal because longitudinal studies show that it persists in healthy dogs. Thus, many *Campylobacter* infections are asymptomatic, with reported carriage rates in healthy dogs and cats ≥50%; kennelled and younger animals have the highest isolation rates. Clinical signs could depend on the number and species of *Campylobacter* infecting an animal and the animal's condition and can vary widely from mild to severe enterocolitis, with clinical signs of watery, mucoid, or hemorrhagic diarrhea accompanied by vomiting, tenesmus, fever, and anorexia and severe dehydration. Younger animals, with less-developed immune systems and less renal concentrating capability to withstand dehydration, are more likely to be more severely affected.

Diagnosis

The presence of slender, seagull-shaped bacteria on a stained fecal smear yields a presumptive diagnosis. The organism is fragile *in vitro*, and culture of fresh fecal samples, or PCR, is recommended to avoid false negatives. Speciation by biochemical testing of cultured organisms is unreliable, and PCR is preferred.

Treatment[1021]

Whether treatment is necessary depends on the *Campylobacter* species identified, the health status of the pet, and the severity of clinical signs if present. In healthy animals, antimicrobial therapy should be reserved for cases where there could be contact with immunocompromised humans, although the zoonotic risk is small if normal hygiene precautions are taken (see ch. 210). Erythromycin is an effective treatment in dogs and cats (dogs: 20 mg/kg PO q 8 h; cats: 10 mg/kg PO q 8 h), reducing shedding within 48 hours when administered to dogs, but it can cause vomiting. Tylosin and clindamycin are alternatives if antimicrobial therapy is deemed necessary. The organism usually is sensitive to fluoroquinolones, but it is hard to justify their use to eliminate an organism that could either be a commensal or only produces self-limiting signs. Resistance to antibiotics has been reported. Multiple post-treatment cultures to document eradication of *C. jejuni* have been recommended, but unless speciation by PCR is available, this may not be a sensible approach.

Prognosis

The prognosis for recovery usually is good, but persistent colonization, especially by *C. upsaliensis,* may occur.

Salmonella spp.[990,1022-1058]

Salmonella organisms (also see ch. 220) have a zoonotic potential (see ch. 210) and can cause significant clinical signs, although this is unusual and occurs most frequently in young, parasitized, kenneled, or immunocompromised animals. Subclinical carriage is seen more frequently, and *Salmonella* bacteria have been isolated from the feces of up to 30% of healthy dogs and 18% of healthy cats. Isolation rates of ≈2% are reported more commonly, unless the animal is coprophagic or eating raw meat (BARF diets). Rates of *Salmonella* contamination of BARF diets of up to 20% have been reported. Human infection from dogs, cats and their food can occur.

Clinical Findings[1036,1059-1061]

Four scenarios can follow infection: transient subclinical carriage, acute gastroenteritis, bacteremia and endotoxemia, or a carrier state. If infection causes acute diarrhea, the diarrhea ranges from mild to severe and bloody, as well as causing anorexia, fever, abdominal pain, and vomiting. Invasion and then translocation from the gut lumen can result in septicemia, endotoxemia, disseminated intravascular coagulation, and death in susceptible animals (see ch. 132). The receptor for invasion is the cystic fibrosis transmembrane conductance regulator (CFTR) protein expressed by enterocytes, but its expression is modulated by commensal bacteria. Cats with *Salmonella* infection can show only vague signs (e.g., fever, leukocytosis, and conjunctivitis) and no GI signs. A seasonal, acute, febrile illness and diarrhea, known as "songbird fever," has been reported in cats in Mediterranean countries after ingestion of migrating songbirds carrying *S. typhimurium.*

Diagnosis[318,321,354,1062]

Diagnosis is based on the isolation of *Salmonella* organisms from feces, or from blood in septicemic patients, either by cuture on selective media or by PCR. Clinicopathologic features are nonspecific: hyperkalemia and hyponatremia (pseudo-hypoadrenocorticism) can occur.

Treatment[1063]

Antibiotic treatment can promote bacterial resistance and a carrier state, so it is not recommended when *Salmonella* bacteria are isolated from healthy infected animals or stable animals with just diarrhea. In animals with severe hemorrhagic diarrhea, marked depression, shock, persistent fever, or sepsis, parenteral antibiotics need to be given. The choice of antibiotic should be governed by sensitivity testing when possible, but fluoroquinolones appear to be effective against many *Salmonella* spp. and are least likely to induce a carrier state. Therapy should be given for 10 days initially, but prolonged therapy can be required. The feces should be recultured on several occasions to ensure that the infection has been eliminated. However, invading organisms can be seen in SI biopsies by FISH, even when stool culture is negative.

Prognosis

The prognosis for diarrhea associated with *Salmonella* infection in most cases is good. A guarded prognosis should be given in patients with septicemia. Negative prognostic indicators include peracute onset, high fever (>40° C [>104° F]), hypothermia, severe hemorrhagic diarrhea, degenerative left shift, and hypoglycemia.

Clostridium spp.

C. perfringens has been associated with HGE (AHDS; see above and ch. 220). The same organism and *C. difficile* can be part of the resident microflora of dogs but also can cause colitis-like signs (see ch. 277).

Escherichia coli[351,358,1057,1064-1080]

E. coli can be an important cause of acute diarrhea, although the organism often is part of a mixed infection with other pathogens such as parvovirus, while some isolates can cause chronic diarrhea (see ch. 220). Many *E. coli* strains are commensals, but in others, chromosomal and/or plasmid genes encode for pathogenicity mechanisms. Enterotoxigenic, enteropathic (attaching and effacing), and enterohemorrhagic *E. coli* (ETEC, EPEC and EHEC, respectively) can cause both acute and chronic diarrhea. EHECs also have been associated

with hemolytic uremic syndrome, and attaching and invasive *E. coli* (AIEC) with granulomatous colitis (see ch. 277).

ETECs cause SI disease primarily by producing heat-stable and heat-labile toxins that stimulate excess secretion by the SI, whereas EHECs have a tropism for the large intestine (see ch. 277). EPECs, which cause attaching and effacing damage to intestinal epithelial microvilli (Figure 276-18) through intimin expression by the *eae* gene, can damage both the SI and LI. Fatal EPEC infection has been reported in a kitten and an adult cat in which attaching and effacing lesions were found in the ileum and colon. Death of puppies with EPEC infection is believed to be more common, but often there is a mixed infection with distemper virus, parvovirus, and pathogenic protozoa contributing.

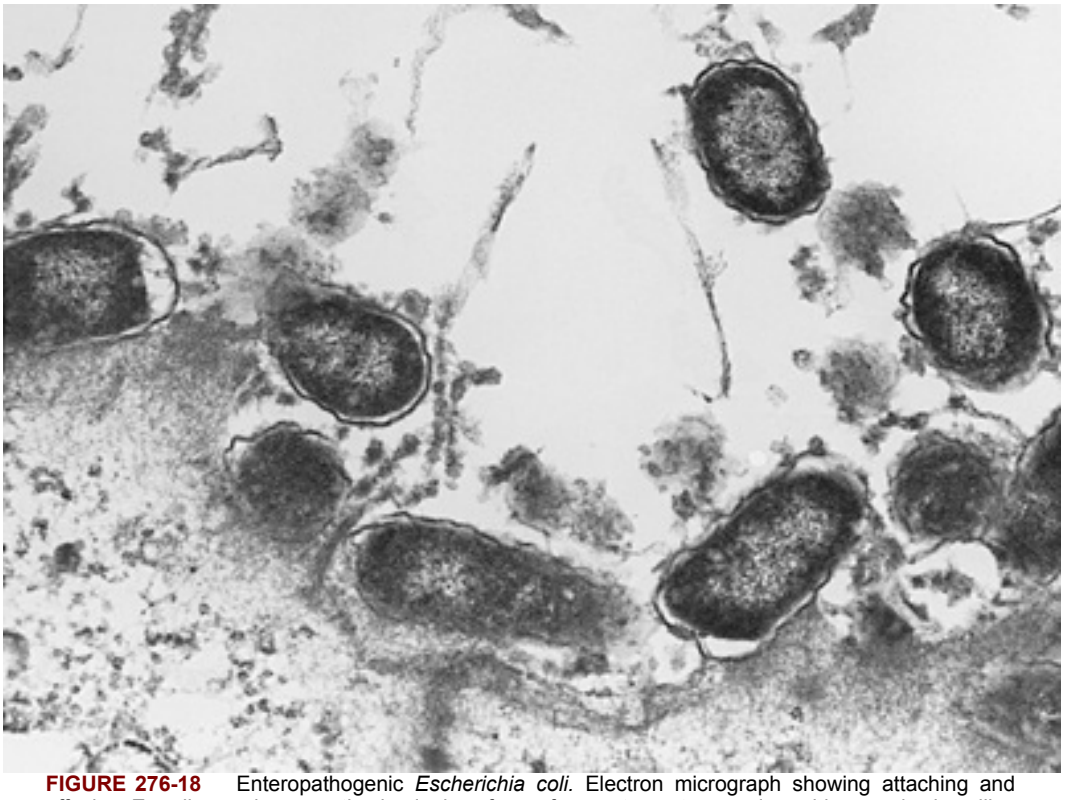


FIGURE 276-18 Enteropathogenic *Escherichia coli.* Electron micrograph showing attaching and effacing *E. coli* organisms on the luminal surface of an enterocyte, causing widespread microvillus damage. (Courtesy R. J. Higgins and G. R. Pearson.)

Identification of pathogenic strains requires specialized assays, such as bioassays for toxins or PCR probes for identification of pathogenicity markers, but even isolation of organisms carrying pathogenic genes does not prove causation. Conventionally, treatment consists of appropriate antibiotics; vaccination and oral immunoglobulins are unproven alternatives that at least do not induce resistance.

Enteroadherent Organisms[1081-1085]

As well as *E. coli*, adherent organisms such as *Streptococcus* spp. have been reported to cause chronic diarrhea in dogs, and *Enterococcus hirae* has been isolated from kittens.

Yersinia pseudotuberculosis[216,1086-1088]

Yersinia pseudotuberculosis can be ingested when cats eat infected rodents or birds. The bacteria infect the GI tract, liver, and lymph nodes, causing marked weight loss, diarrhea, anorexia, lethargy, jaundice, and mesenteric lymphadenopathy. Susceptibility in humans is related to NOD expression. Treatment may be attempted with oxytetracycline or trimethoprim-sulfa, but the disease usually is progressive and fatal. *Yersinia enterocolitica* is predominantly a LI pathogen (see ch. 277).

Tuberculosis[1089]

In dogs and cats, *Mycobacterium* spp. cause multisystemic, granulomatous infections that occasionally involve the GI tract (see ch. 212). Cats can develop SI infection with *M. bovis* from drinking infected cow's milk but more commonly have cutaneous or pulmonary infections. A granulomatous enterocolitis with mesenteric lymphadenopathy associated with *M. avium* infection was reported in five Basset hounds.

Miscellaneous Bacteria[1090-1099]

Many GI bacteria may be opportunistic pathogens or part of a mixed infection, but occasionally clinical signs are related directly to a specific organism, such as *Shigella. Clostridium piliforme* (formerly *Bacillus piliformis*) is a rare infection causing Tyzzer's disease, an acute, fatal diarrhea in puppies and kittens for which no effective treatment has been described. *Providencia alcalifaciens* was reported to cause primary bacterial enteritis in three dogs. *Anaerobiospirillum* has been associated with ileocolitis in cats, but the spirochetes *Brachyspira pilosicoli* and *Serpulina pilosicoli*, although pathogenic and zoonotic, are more likely to cause colitis (see ch. 277).

Rickettsial Diarrhea (Salmon Poisoning; see ch. 218)[1100-1112]

Neorickettsia helminthoeca and *Neorickettsia elokominica* are found in the metacercariae of the fluke *Nanophyetus salmonicola,* which is present in salmon in the western regions of the Cascade Mountains from northern California to central Washington and in Brazil. About a week after ingestion of infected salmon by dogs (and coyotes), the rickettsiae emerge from the mature fluke and cause a disease characterized by high fever, hemorrhagic gastroenteritis, vomiting, lethargy, anorexia, polydipsia, oculonasal discharge, and peripheral lymphadenopathy. Mortality is extremely high in untreated patients. The diagnosis is based on a history of ingestion of raw fish in an endemic area, the detection of operculated fluke eggs in feces, and the presence of intracytoplasmic inclusion bodies in macrophages from lymph node aspirates. Oxytetracycline (7 mg/kg IV q 8 h) is the treatment of choice, and it should be continued for at least 5 days. The trematode vector is eradicated with praziquantel.

Algal Infections[1113-1121]

Toxic algae can lead to acute gastroenteritis and death. Blue-green algal blooms can synthesize an anticholinesterase that induces vomiting, diarrhea, ataxia, and rapid death in dogs that drink contaminated water. *Prototheca* spp. are achlorophyllous algae that cause protothecosis. Typically a cutaneous infection in cats, in dogs it can involve the intestine and the CNS. Fatal disseminated disease affecting the SI has been reported, but LI disease is more common (see ch. 277).

Fungal Infections

Pathogenicity[85,109,1122-1131]

Low numbers of fungi are found in the normal intestinal microbiome by routine culture, but more are identified by molecular fingerprinting techniques. They are generally not considered pathogenic. Increased numbers of fungi can be found in idiopathic IBD, but it is unclear whether this is cause or effect, although empirical benefit of nystatin administration has been reported in intractable diarrhea cases, suggesting a role for fungi. The yeast *Cyniclomyces guttulatus* has been isolated from dogs and cats with chronic diarrhea but is found more frequently in the feces of healthy animals, and probably is not significant unless found in massive numbers. However, under the right circumstances such as immunosuppression, fungi can invade the intestinal mucosa and even disseminate throughout the body. Intestinal aspergillosis (see ch. 234 and 235), mucormycosis (see ch. 236), and cryptococcosis (see ch. 231) occur occasionally, but the incidence of fungal infections varies worldwide; some are ubiquitous (e.g., candidiasis,[840,1130,1132] zygomycosis[1124,1160-1165]; see ch. 236), and some are localized to specific geoclimatic regions (e.g., histoplasmosis[1166-1169]; see ch. 233). Primary intestinal infection with the aquatic oomycete *Pythium* spp. (pythiosis) is by far the most common phycomycosis (i.e., an infection with a poorly septate mold).[1133-1159] GI involvement can be extensive and severe; pythiosis is discussed in ch. 236.

Helminths

Importance[1170-1178]

Helminth infestation is common in dogs and cats (E-Box 276-13). Most infect the SI; *Trichuris* whipworms are a LI infection (see ch. 277). Some species are pathogenic, especially when present in large numbers, others are nonpathogenic except in puppies and kittens but may predispose to other diseases, and some are zoonotic. Regular anthelminthic treatment therefore is important for the health of young animals (see ch. 163) and the protection of humans (see ch. 210). A number of anthelmintics is available (e.g., benzimidazoles [albendazole, fenbendazole, febantel, flubendazole, mebendazole, oxfendazole, thiabendazole], milbemycin oxime, moxidectin, niclosamide, piperazine, pyrantel, selamectin), although their availability can vary geographically.

E-Box 276-13

Intestinal Metazoan Parasites of Dogs and Cats

Helminths

- Roundworms
  - Canine
    - *Toxocara canis*
    - *Toxascaris leonina*
    - *Baylisascaris procyonis*
    - *Strongyloides stercoralis* (rare)
  - Feline
    - *Toxocara cati*
    - *Toxascaris leonina*
    - *Strongyloides* spp. (rare)
- Hookworms
  - Canine
    - *Ancylostoma caninum*
    - *Ancylostoma brasiliense*
    - *Uncinaria stenocephala*
  - Feline
    - *Ancylostoma tubaeforme*
    - *Ancylostoma brasiliense*
    - *Uncinaria stenocephala* (rare)
- Whipworms
  - Canine
    - *Trichuris vulpis*
  - Feline
    - *Trichuris felis*

Cestodes

- Canine
  - *Dipylidium caninum*
  - *Taenia* spp. *(T. crassiceps, T. hydatigena, T. multiceps, T. pisiformis, T. serialis)*
  - *Echinococcus granulosus*
  - *Echinococcus multilocularis*
  - *Diphyllobothrium latum*
  - *Spirometra* spp.
- Feline
  - *Dipylidium caninum*
  - *Taenia taeniaeformis*
  - *Echincoccus multilocularis*
  - *Diphyllobothrium latum*
  - *Spirometra* spp.

Trematodes

- Canine
  - *Nanophyteus salmincola* (carries *Neorickettsia* spp.)

- *Heterobilharzia americana* (mesenteric and hepatic veins)

- Feline
  - *Nanophyteus salmincola*
  - *Platynosomum fastosum* (biliary tree)

Protozoa

- Canine
  - *Giardia*
  - *Cryptosporidium*
  - *Prototheca*
- Feline
  - *Giardia*
  - *Cryptosporidium*
  - *Toxoplasma*
  - *Tritrichomonas*—large intestine

Roundworms[996,1179-1211]

Roundworms are ubiquitous in dogs and cats, with numerous studies showing geographical variations in prevalence, dependent on ownership, economics, and deworming practices. Typically, *Toxocara canis* is found in dogs and *Toxocara cati (T. mystax)* in cats. *Toxascaris leonina* is found less commonly in both dogs and cats. *Baylisascaris procyonis,* the ascarid of racoons, occasionally infects dogs.

Epidemiology[1208,1212-1221]

Adult dogs and cats can be infected by *Toxocara* spp. through ingestion of embryonated eggs or ingestion of paratenic hosts, such as rodents. However, puppies and kittens more commonly are infected because the major route of infection is transplacental transmission for *T. canis* and trans-mammary transmission for both *T. canis* and *T. cati.* Migrating juvenile *T. canis* can cause hepatic, pulmonary, and occasionally ocular damage. The adult nematodes live in the SI.

Clinical Findings[1222,1223]

Roundworms cause disease most often in young animals, and signs of heavy infestation are diarrhea, weight loss, or failure to thrive. A poor haircoat and a potbelly may be evident in puppies or kittens. Intestinal obstruction and rupture have been described in very severe infestations.

Diagnosis[341,342,345,1224]

Almost all puppies can be presumed to have *T. canis* infection. The diagnosis can be confirmed by fecal flotation (see Figure 276-10 and ch. 81) or occasionally on endoscopy (see Figure 276-14, *A*).

Treatment[1213,1225-1235]

A wide range of anthelmintics is effective against roundworms, and any adverse reactions usually are mild or not reported (see ch. 163). Treatment should be repeated at 2- to 3-week intervals in affected animals.

Public Health Concerns[1189,1221,1236-1246]

Infection of humans by *Toxocara* is by ingestion of ova, which, when first shed, are unembryonated and not infective (see also ch. 210). Progression to the embryonated L3 stage is required for infection, so fresh feces are not a zoonotic risk because embryonation takes from two to seven weeks. Humans can be infected by accidental ingestion of contaminated soil or food, or contact with eggs adherent to the animal's coat. *T. canis* presents a substantial public health problem as it can cause visceral, ocular, and neural *larva migrans,* while up to 30% of people are seropositive, indicating exposure. Rates of infection and soil contamination vary widely depending on socioeconomic factors, geography and climate, but children are at greatest risk because of geophagia and pica. Risk is increased threefold if the person owns a dog and fivefold if he or she owns more than one dog.

Young animals should be routinely dewormed at 2, 4, 6, 8, 12, and 16 weeks of age and then at a minimum of 6-month intervals to protect the public, but there are concerns that the lack of antigenic stimulation

provided by endoparasites affects immunocompetence. *T. canis* can be controlled by administering to pregnant bitches either fenbendazole 50 mg/kg PO q 24 h from day 40 of gestation to 2 days after whelping, or two doses of moxidectin.

Strongyloides sp.[1179,1219,1247-1252]

Strongyloides tumefaciens is a parasite of the LI (see ch. 277), but *S. stercoralis* is a small nematode that can cause hemorrhagic enteritis in young puppies. Infective larvae are ingested, transmitted through the dam's milk or through penetration of the skin and, after migration through the lung, they mature in the SI. Fecal evaluation using the Baermann technique or demonstration of motile first-stage larvae in smears of fresh feces (see Figure 276-10) helps differentiate larvae from *Angiostrongylus, Oslerus,* and mature hookworms. Infection can be treated with thiabendazole or possibly fenbendazole or ivermectin (see ch. 163).

Hookworms[1216,1253-1263]

Ancylostoma spp. infections are most common in tropical and subtropical regions and are important zoonoses, causing cutaneous *larva migrans* (see ch. 210). Hookworms have a direct life cycle, and infection can be acquired prenatally, during lactation (not in cats), by ingesting larvae, by migration of larvae through the skin, and by ingestion of a paratenic small rodent host.

Ancylostoma caninum is the most important hookworm of dogs, and it is associated with blood loss and hemorrhagic enteritis. *Ancylostoma braziliense* occurs in dogs in the southern United States and in cats. *Ancylostoma tubaeforme* is the most common hookworm in cats but is rarer and less pathogenic. *Uncinaria stenocephala* is the hookworm of dogs in western Europe, and it does occur in the northern United States and in Canada. Infection most commonly is reported in kennelled dogs, particularly Greyhounds, and very rarely in cats.

Clinical Findings

Diarrhea, vomiting, dehydration, and poor growth are common in puppies with *A. caninum* infection. Weakness and pallor reflect extensive blood loss, and the infection can cause a rapid, potentially fatal anemia or chronic iron deficiency anemia. *U. stenocephala* does not cause anemia, but severe infestations can be associated with diarrhea. Interdigital skin penetration and larval migration of *U. stenocephala* causes pedal pruritus.

Diagnosis[341,342,357,1224,1264,1265]

The diagnosis is made by demonstrating ova in feces (see Figure 276-10 and ch. 81). Hookworms can be seen on endoscopy (see Video 276-2), but infection should be diagnosed or empirically treated before embarking on such a procedure.

Treatment[1225,1264,1266-1269]

For *Ancylostoma* infection in anemic puppies, pyrantel pamoate has been suggested as the treatment of choice because it acts very rapidly and is comparatively safe (see ch. 163). Anemic puppies could require blood transfusion (see ch. 130) and supportive care. Monthly administration of milbemycin or ivermectin plus pyrantel pamoate has been approved for the prevention or control of hookworm in dogs.

Tapeworms[1225,1236,1270-1274]

Dipylidium caninum is the most common tapeworm infecting dogs and cats in the United States and Europe, with fleas as its intermediate host. Usually, there are no clinical signs except motile "rice grains" (proglottids) visible in the perineal area or on feces. Heavy infestations of *D. caninum* only rarely are associated with diarrhea, weight loss, and failure to thrive. A diagnosis of *D. caninum* infection is confirmed by demonstrating characteristic egg capsules, contained in proglottids, obtained from the perineal area or feces (see Figure 276-10).

Various *Taenia* spp. tapeworms are common in dogs and cats, with cattle, sheep, goats, and rabbits the most common intermediate hosts. Dogs are definitive hosts of the small tapeworm *Echinococcus granulosus sensu stricto;* humans and sheep are intermediate hosts. Infection occurs through ingestion of infected raw meat, and sheepdogs typically are infected by ingestion of sheep carcasses. *E. granulosus* infection is not associated with clinical signs in dogs but is an important zoonosis, causing hydatid disease. *Echinococcus multilocularis*

can be carried by dogs and also is an important zoonosis. *Mesocestoides* spp. very rarely causes intestinal disease (PLE), but occasionally causes intraperitoneal infection. The cat is the definitive host of *Spirometra* spp., which rarely causes intestinal signs.

D. caninum, *Echinococcus* spp. and *Taenia* spp. are best controlled by routine administration of praziquantel (alternatives include dichlorophen, epsiprantel, or niclosamide; see ch. 163). Treatment of *D. caninum* infection also involves adequate flea control.

Protozoa

Coccidia generally are considered to be minor pathogens in dogs and cats, causing disease in young or immunosuppressed patients, but *Giardia* infection can be clinically significant. The trichomonads *(Tritrichomonas foetus, Pentatrichomonas hominis, Balantidium coli* and *Entamoeba histolytica)* are colonic inhabitants (see ch. 277).

Isospora spp.[1275-1288]

Isospora spp. (syn, *Cystisospora*) are the most common coccidial parasites of dogs *(I. canis, I. ohioensis)* and cats *(I. felis, I. rivolta).* Transmission occurs by ingestion of ova or paratenic hosts. Sporozoites are liberated in the SI and enter cells to begin development. The prepatent period ranges from 4 to 11 days, depending on the species. Infection with *Isospora* organisms commonly produces no clinical signs. Puppies and kittens kept in unhygienic conditions or immunosuppressed animals can develop heavy infestations, which can be associated with diarrhea that is often mucoid but sometimes bloody. Concurrent infectious agents are common and clinically can be more significant.

Isospora oocysts are found on direct examination of a fecal smear or by flotation. The infection often is self-limiting, but sulfadimethoxine or trimethoprim-sulfa can be used when clinical signs warrant treatment. Coccidiostats, such as toltrazuril and diclazuril, when available, are preferred (see ch. 163 and E-Table 276-10). The prognosis for recovery is good.

E-TABLE 276-10

Oral Treatments for Coccidiosis in Dogs (D) and Cats (C)

DRUG	DOSAGE (SPECIES)
Amprolium	300 to 400 mg (total) q 24 h for 5 days (D); or 110-200 mg (total) q 24 h for 7-12 days (D); or 60-100 mg/kg q 24 h for 7 days; or 1.5 tbsp (23 mL)/gal (sole water source) not to exceed 10 days (D)
Sulfonamides	
Sulfadimethoxine	50-60 mg/kg q 24 h for 5-20 days (D, C)
Sulfadimethoxine/amprolium	150 mg/kg of amprolium and 25 mg/kg of sulfadimethoxine q 24 h for 14 days (D)
Sulfadimethoxine/ormetoprim	55 mg/kg of sulfadimethoxine and 11 mg/kg of ormetaprim q 24 h for 7-23 days (D)
Sulfaguanidine	150 or 200 mg/kg q 24 h for 6 days (D, C); or 100-200 mg/kg q 8 h for 5 days (D, C)
Trimethoprim/sulfonamide	Dosage/duration depends on sulfa; 30-60 mg/kg trimethoprim q 24 h for 6 days in animals > 4 kg; or 15-30 mg/kg trimethoprim q 24 h for 6 days in animals <4 kg
Furazolidone	8-20 mg/kg q 12-24 h for 5 days (D, C)
Quinacrine	10 mg/kg q 24 h for 5 days (C)
Toltrazuril	10-30 mg/kg q 24 h for 1-3 days (D)
Diclazuril	25 mg/kg q 24 h for 1 day (C)
Ponazuril	20 mg/kg q 24 h for 1-3 days (D, C)

Companion Animal Parasite Council Guidelines. Available at: http://www.capcvet.org/capc-recommendations/coccidia/. Accessed August 15, 2016.

Cryptosporidium spp.[349,359,360,844,1287-1322]

The taxonomy of this genus is changing as new molecular genetic information emerges, and these organisms are no longer considered closely related to coccidia. *Cryptosporidium parvum*, a clinically significant pathogen in humans and calves, is now recognized not to be a single species. Over twenty *C. parvum* genotypes have been identified, and they include cat and dog "species," sometimes termed *C. canis* and *C. felis*, respectively (see ch. 221). Dogs can transmit the cattle and murine genotypes to humans, but specific cat and dog genotypes are likely to be zoonotic only to immunocompromised humans (see ch. 210).

C. parvum is an obligate intracellular parasite, with transmission occurring by the fecal-oral route. Infection can be asymptomatic but has been associated with self-limiting diarrhea in cats and rarely in dogs, and with severe hemorrhagic diarrhea in immunocompromised animals and animals with coinfections. Infection is most common in young animals, often with concurrent parasitic infections, but prevalence varies with geography as well. Cats shed more frequently than do dogs, and excretion can be reactivated by corticosteroid administration or surgical stress.

Diagnosis[347,349,359,1307,1315,1323-1325]

Cryptosporidial oocysts are extremely small (approximately 1/10 the size of *Isospora* oocysts) and must be identified by fecal flotation and oil immersion microscopy, direct immunofluorescence and modified acid-fast staining of fecal smears, enzyme immunoassay techniques, or PCR. Organisms can be recognized in intestinal biopsies.

Treatment[1291,1298,1326-1329]

Paromomycin was reported to be effective against *Cryptosporidium* organisms in a cat. However, the drug's efficacy is probably poor and it can cause acute kidney injury and uremia. Tylosin and azithromycin can be tried, but positive effects might be due to treatment of other infectious agents. Nitazoxanide could prove to be as effective as it is in humans but, fortunately, the disease is usually self-limiting in immunocompetent animals and needs no specific treatment.

Giardia sp.

Epidemiology[361,990,1031,1032,1183,1190,1293,1301,1314,1316,1319,1320,1330-1369]

Giardia sp. can infect both dogs and cats (see ch. 221). Previously named *G. lamblia*, molecular epidemiologic studies indicate there are seven genotypes (A-G), but that common assemblages infecting dogs (C and D *[G. canis]*) and cats (F *[G. felis]*) are not those typically found in human infections (A *[G. duodenalis]* and B *[G. enterica]*). Cats and dogs can harbor the zoonotic assemblage A; assemblage B has been found in dogs but not cats.

The parasite usually is transmitted via the fecal-oral route. Ingested oocysts excyst in the upper SI, and trophozoites attach to the intestinal mucosa from the duodenum to the ileum. After multiplication of trophozoites, oocysts are passed in the feces 1-2 weeks after infection.

Prevalence[356,1183,1199,1200,1203,1204,1209,1210,1219,1287,1321,1364,1370-1392]

The prevalence of infection in canine studies depends on geography, diagnostic method, and the age and health status of the animal, ranging from <2% to 100% in kennels. Cats are less commonly infected.

Clinical Findings[1363,1393-1397]

Most infections are asymptomatic, but signs can range from mild, self-limiting, acute diarrhea to severe or chronic small bowel diarrhea associated with weight loss.

Diagnosis[340,342-344,348,412,590,1307,1315,1382,1398-1406]

Giardia organisms can be seen on the surface of intestinal biopsies, but sensitivity is poor as they may be lost during processing; goblet cell numbers are often increased. Infection can also be diagnosed by demonstration of motile trophozoites in duodenal juice or a very fresh fecal smear. Identification of oocysts in feces by zinc sulfate flotation is preferred, but oocyst shedding occurs intermittently, so three fecal analyses within five days are needed for 95% sensitivity (see ch. 81). *Giardia* antigen also can be detected by means of fecal ELISA tests (SNAP *Giardia* Antigen Test Kit, Prospect T *Giardia* Microplate Assay), which have 95% specificity but sensitivities of ≈90% (see ch. 221). This may be the preferred method compared to zinc sulfate flotation performed by an inexperienced technician. Fecal IFA and PCR also are available.

Treatment[714,718,1328,1332,1407-1428]

Metronidazole 25 mg/kg PO q 12 h for 5 days was the drug most commonly used to treat *Giardia* infection in small animals. Ronidazole can be used, but it has side effects. Metronidazole eliminates *Giardia* infection in approximately two thirds of cases, but it can cause neurologic side effects at these high dosages, especially in cats. Efficacy can be increased by supplementing metronidazole with silymarin. Fenbendazole (50 mg/kg PO q 12 h for 3-5 days) generally eliminates *Giardia* infection and can be combined with metronidazole to resolve clinical signs and cyst shedding. Albendazole is not recommended as it is associated with bone marrow toxicosis. The efficacy of febantel (in a combination product with praziquantel and pyrantel) is debated, but nitazoxanide is likely to be effective and secnidazole only needs to be administered once. Decontamination of the patient's coat by bathing and the patient's environment by steam cleaning or cleaning with quaternary ammonium compounds is advised to prevent reinfection. *Giardia* vaccines are no longer available, and administration of probiotics has shown no benefit in clearing infection.

Prognosis

The prognosis is usually good, but some patients might require several treatments to eliminate infection because reinfection is a common problem. Reactivation of latent infection by corticosteroid administration also has been reported.

Adverse Reactions to Food

An adverse reaction to food is a repeatable, deleterious response to a dietary component. It may be a manifestation of either an immunologic reaction to a dietary antigen (i.e., a true food allergy) or a nonimmunologic reaction (i.e., an intolerance). Although food allergy and intolerance differ in their etiopathogeneses, the clinical signs are similar, and the approach to treatment—exclusion of the offending food component—is the same. Food intolerance can be associated with a single ingredient of a prepared food, such as lactose or a preservative, which can be present in immunologically unrelated foods. Conversely, confirmed allergy to a specific food can impart allergy to related foods. In humans, food intolerance is diagnosed more frequently than is hypersensitivity, but its true prevalence in small animals is unknown.

Exclusion diet trials are required to diagnose both food allergy and intolerance but do not distinguish between them.

Food Allergy (Hypersensitivity)[287,288,1429-1437] (see ch. 10, 186, and 191)

Pruritic skin disease is the most commonly reported manifestation of food allergy, but the true prevalence of food allergic intestinal disease is uncertain because no easy, reliable, indirect tests are available, and even a positive response to an exclusion diet is not absolute proof. This is because other causes of GI signs can respond, for nonallergic reasons, to dietary manipulation (Box 276-14). The management of food allergy is simple—feed any food that does not contain the allergen—but the difficulty lies in the initial recognition that food allergy is present, and then the identification of the food(s) that must be excluded (also see ch. 186).

Box 276-14

Conditions That Can Improve Clinically in Response to Dietary Modification

- Chronic gastritis
- Exocrine pancreatic insufficiency
- Food allergy
- Food intolerance
- Gastric emptying disorders
- Gastroesophageal reflux
- Inflammatory bowel disease
- Lymphangiectasia
- Nutritionally inadequate diet
- Pancreatitis

- Portosystemic shunt
- Small intestinal bacterial overgrowth

Mechanisms[1438-1454]

Current hypotheses of food allergy propose one or a combination of mechanisms that lead to breakdown of oral tolerance: an inadequate mucosal barrier, abnormal microbiome, abnormal presentation of dietary antigens to the mucosal immune system, or immune system dysregulation. Such hypotheses could explain both a genetic susceptibility to allergy and its development after a primary GI insult that damages the mucosal barrier, such as viral enteritis, which can damage both the immune system and the mucosal barrier. Active immune responses, rather than tolerance, then can occur directed toward bystander antigens (i.e., sensitization to dietary antigen) and involve a variety of mechanisms, including type I (IgE-mediated, immediate), type III (immune-complex mediated), and type IV (delayed hypersensitivity) reactions. Modulation of the response also depends on the composition of the microbiome. A contemporaneous association between ingestion of a particular food and the onset of signs is suggestive of a type I reaction. In mixed or delayed reactions, the inevitable delay between food ingestion and onset of signs obscures any causative link, particularly if repeated ingestion causes chronic disease.

Clinical Signs[1455-1460]

Clinical signs of food allergy generally involve the skin or the GI tract (Box 276-15); simultaneous skin and GI signs can occur but have been reported infrequently. Systemic signs (anorexia, lethargy) are recorded rarely, and urticaria-angioedema and even anaphylaxis seem rare (see ch. 137). Signs such as abnormal behavior and asthma are largely anedcdotal, but abnormal licking of surfaces (e.g., concrete) has been reported to resolve with the introduction of an exclusion diet (see ch. 9). The major sign of food-allergic skin disease is pruritus; other skin lesions, with the exception of eosinophilic complexes in cats, arise through self-trauma and secondary pyoderma. Signs of food-allergic GI disease are not pathognomonic and include vomiting, diarrhea, abdominal pain, flatulence, borborygmi, and weight loss or failure to thrive (E-Figure 276-19).

Box 276-15

Clinical Signs Recognized as Manifestations of Food Allergy

Systemic Signs
- Anorexia
- Lethargy
- Peripheral lymphadenopathy (cats)
- Urticaria-angioedema
- Anaphylaxis

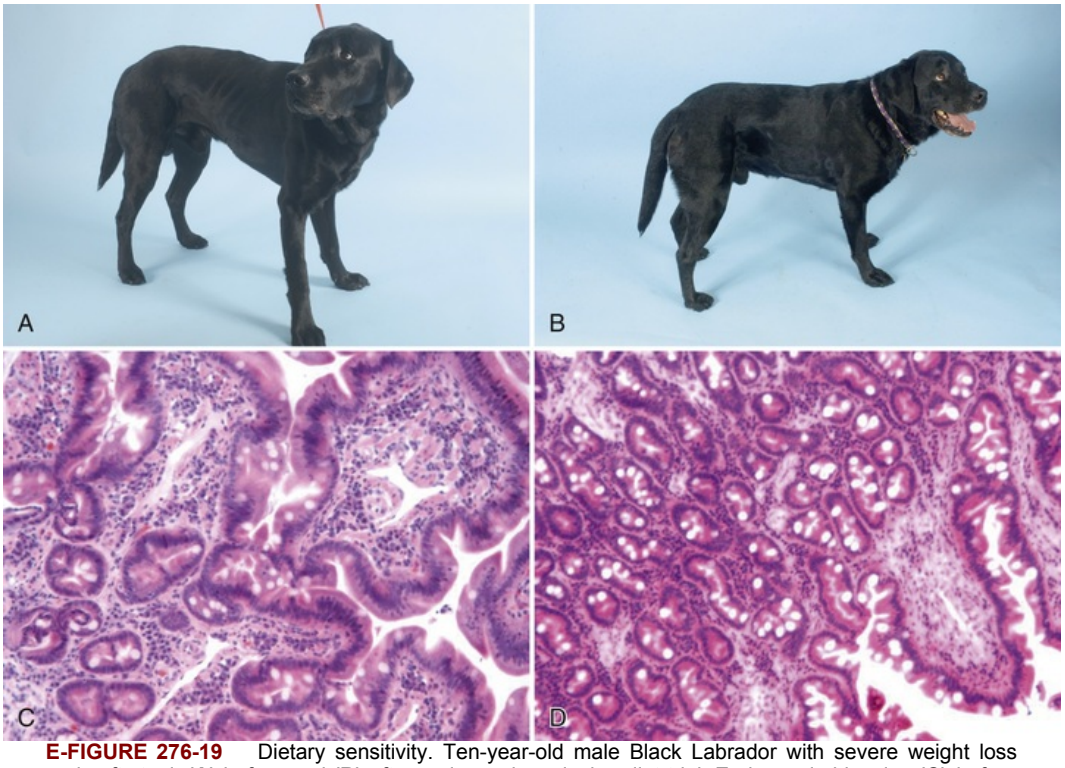
Cutaneous Signs
- Primary papules
- Erythroderma
- Pruritus and self-trauma
  - Secondary pyoderma
  - Scaling
- Otitis externa
- Miliary dermatitis (cats)
- Eosinophilic granuloma complex (cats)

Gastrointestinal Signs
- Abdominal discomfort/pain or "colic"
- Vomiting
- Hematemesis
- Diarrhea
- Small intestinal–like signs
- Colitis-like signs

- Altered appetite
  - Licking surfaces
  - Pica
  - Weight loss and/or stunting

Not Proven

- Asthma
- Behavioral changes
- Lameness



E-FIGURE 276-19 Dietary sensitivity. Ten-year-old male Black Labrador with severe weight loss and soft stool, **(A)** before and **(B)** after a six-week exclusion diet trial. Endoscopic biopsies **(C)** before the trial showing lymphoplasmcytic enteritis and **(D)** resolution of the inflammation after the trial.

Diagnostic Approach[443,525,759,1461-1464]

After negative preliminary investigations (minimum database, fecal examination, imaging) and a fenbendazole trial, the diagnosis of dietary sensitivity is made by the response to dietary manipulation. Although detailed analysis of intestinal biopsies from dogs with food-responsive disease showed a tendency for an increase in mucosal eosinophils, a diet trial is recommended, either before intestinal biopsy in patients that are eating and not hypoproteinemic or after a biopsy that reveals intestinal inflammation. Clinical signs should resolve on exclusion of the offending dietary component and return with rechallenge with the original food. Objective criteria by which to judge such a response are lacking: monitoring changes in intestinal permeability or mesenteric arterial blood flow patterns by Doppler ultrasonography are not specific enough, and even repeat biopsy does not necessarily show resolution of any histologic changes, although this may be because they take longer than the improvement of clinical signs. A positive clinical response to an exclusion diet can reflect an allergy or intolerance, or occur by chance, and confirmation of the diagnosis of either allergy or intolerance requires rechallenge, but many clients refuse.

Serologic Tests[1465-1477]

Attempts have been made to devise tests for food allergy that avoid diet trials, but unfortunately, none in veterinary medicine is reliable. Food-specific serum IgE and/or IgG can be measured *in vitro*, but critical

appraisal suggests these tests are unhelpful because discrepancies between laboratories exist and results do not correlate with a patient's response to an exclusion diet trial. Intradermal skin testing and patch testing also have proven unreliable in the diagnosis of food-allergic GI disease. Gastroscopic food sensitivity testing (GFST), in which dietary antigens are instilled directly onto the gastric mucosa, theoretically should give results that are more specific in cases presenting with GI signs. However, correlation between GFST and clinical challenge trials is poor. Using the colonic mucosa as the testing surface (colonoscopic allergen provocation [COLAP] testing) could be more reproducible but has not been adopted widely.

Exclusion Diet Trial[1478-1482]

The principle of an exclusion (elimination) diet is to feed dietary components to which the animal has not previously, or at least recently, been exposed (see ch. 186). This diet should be the sole source of nutrition during the trial. Complete owner compliance is essential, and all treats and supplements must be withheld. Options for exclusion diets include home-prepared diets, single-source protein diets, and hydrolyzed protein diets. Home-cooked diets have been preferred to commercial diets because of reports of relapse when patients are switched to an equivalent commercial diet, and food analyses have shown undeclared proteins in some commercial diets. However, many clinicians recommend the use of a commercial diet initially because convenience improves compliance.

In single-source protein diets, the food contains only one protein source and one carbohydrate source. If a home-cooked diet is used, it is unlikely to be nutritionally balanced, but this is not generally important for the short duration of the trial. However, baby foods, although convenient, are not suitable for cats because they are relatively taurine deficient and often contain onion powder that can cause Heinz body anemia. Lamb or chicken with rice have been the standard choices, but given the increased diversity of pet foods, the patient might already have been exposed to these components and, therefore, they are not always appropriate. Thus, more esoteric food sources have become a requirement. An alternative to home-prepared diets is use of a commercial exclusion diet, and a wide range is now available, containing different sources of protein (e.g., chicken, soy, salmon, catfish, venison, or duck) and carbohydrate (e.g., rice, corn [maize], tapioca, or potato).

Hydrolyzed protein diets,[763,1483-1491] which usually are based on either chicken or soy protein, are an alternative exclusion diet and now are widely available. In principle, the hydrolytic process splits proteins into components of a molecular weight below that which would be expected to elicit an immune response. To completely abolish all antigenicity, peptides need to be less than 1 kD in size, but at that size they almost invariably have a bitter taste; only one anallergenic diet, based on feather protein and containing only peptides < 1 kD, is available. At the size achieved in the majority of hydrolyzed diets (7-10 kD), proteins still are potentially antigenic but are too small to be able to cross-link IgE molecules on mast cells, and type I reactions are abolished; however, type IV reactions still are possible. Hydrolyzed diets also are substantially more expensive to produce than are standard exclusion diets, and both palatability and owner compliance can be problematic. Nevertheless, such diets currently are the easiest way to guarantee the feeding of novel antigens, and this approach has become the preferred method for many clinicians. Studies have suggested a significant beneficial effect of such diets, and they appear to have an advantage over traditional single-source protein exclusion diets. However, lack of histologic resolution after a successful trial could indicate that the patient actually has idiopathic IBD, and the clinical improvement simply is due to feeding a more digestible diet.

A standardized protocol for diet trials has not been established, and the optimum duration for an exclusion diet trial is unknown.[1432] Three weeks has been chosen arbitrarily, but at least six weeks could be preferable, particularly if a partial response is seen by three weeks. Indeed, cases of food-allergic skin disease might require up to ten weeks to respond, probably because antigen translocated to the skin and stored in dendritic cells needs to be eliminated. Food-allergic GI disease often responds quicker such that it is, fortunately, rarely necessary to feed the exclusion diet for this length of time because it can become difficult to maintain patient and/or owner compliance. Challenge and provocation tests usually are conducted for up to 14 days but are concluded earlier if signs recur on two consecutive days.

1. Exclusion phase. The exclusion diet is fed as the sole source of food for a minimum of three weeks.
2. Challenge phase. Once remission is achieved, the animal should be challenged with the original diet to demonstrate relapse and confirm the diagnosis. Some animals might not relapse, perhaps because the mucosal barrier has been restored and further reactions are prevented. However, some clients refuse challenge, particularly if relapse is likely to bring recurrence of diarrhea.
3. Rescue and provocation phases. After relapse during the challenge phase, for clients who are willing, a series of provocation tests can be performed to identify the offending food(s). Remission is regained by "rescue" with the original exclusion diet, and single foodstuffs are then introduced sequentially. If there

is no relapse, the food is identified as "safe," and the next food is tested; if there is a relapse, rescue is repeated and the food is identified as "unsafe."

4. Maintenance phase. When all the offending foods have been identified, or at least sufficient safe ones have been recognized to permit the choice of a regular diet, the animal is maintained on a safe standard diet. Subsequent to the food trial, most animals can be maintained on one of the available antigen-limited diets.

Treatment[1492]

Treatment is simple once a diagnosis has been made: avoidance of the offending food prevents the occurrence of signs. Proprietary diets often are more suitable as maintenance diets and are preferred over home-prepared meals because they are nutritionally balanced. Continuing a hydrolyzed diet is an expensive alternative. Peptide immunotherapy is used in humans but is not yet available for animals.

Food Intolerance[1433,1434]

Gluttony, scavenging, and food poisoning are common and may be considered examples of food intolerance. However, they tend to be isolated, acute incidents. In contrast, true food intolerances are repeatable, but they can be predictable or unpredictable. Predictable intolerances occur in any animal after ingestion of a contaminated foodstuff or after consumption of a recognized toxin or excessive amounts of food. In contrast, unpredictable food intolerances, although repeatable in a susceptible individual, are idiosyncratic reactions. Reasons for idiosyncrasies include differences, genetically based or otherwise, in intestinal enzyme activities, intestinal permeability, postabsorption metabolism, mast cell stability, and in the microbiome.

Mechanisms

Most of the suggested mechanisms of food intolerance are extrapolated from humans and might or might not be valid for dogs and cats.

Food Poisoning

Food poisoning is most likely in dogs that scavenge and is caused by the presence of a toxin in food, or by its contamination with toxin-producing organisms, or infection by organisms that have multiplied in the food and subsequently cause acute GI signs, such as campylobacteriosis.

Pharmacologic Intolerances

Such intolerances result from the presence of pharmacologically active compounds (e.g., chocolate poisoning with methylxanthines). In humans, intolerances can result from naturally occurring compounds—vasoactive amines, cardiac glycosides, plant alkaloids, and fungal hallucinogens and tremorgens—or substances produced by intestinal bacterial metabolism.

Pseudo-Allergic Mechanisms[1493,1494]

These adverse reactions are histamine-mediated but arise from nonimmunologic mechanisms. A high histamine concentration can be present naturally in some foods, such as tuna, mackerel, and some commercial dog foods, or because of histamine-producing *Proteus* or *Klebsiella* organisms contaminating foods, such as cheese or canned fish. Some foods, such as shellfish, strawberries, and some food additives, such as tartrazine, can cause histamine release from mast cells without IgE mediation. This mechanism is well documented in humans, but not in small animals.

Metabolic Reactions[40,252,1495]

Such reactions are poorly documented in small animals. Carbohydrate malabsorption and intolerance can be features of a number of intestinal diseases, whereas specific intolerance to lactose can be associated with lactase deficiency. At weaning, activities of lactase decline, especially in cats, and animals can become lactose intolerant if fed excess milk. If an animal has underlying SI disease, dairy products should be avoided as marginal lactase activities will be reduced even further. However, allergy to bovine milk proteins or previously subclinical intestinal disease could also explain adverse reactions to milk.

Clinical Signs[1496]

The clinical signs of food intolerance include vomiting, diarrhea, and signs of abdominal discomfort.

However, pruritus and even anaphylaxis are possible if histamine release is involved. Behavioral problems (see ch. 9) can be diet-responsive through nonimmunologic mechanisms.

Diagnosis

The only reliable means of diagnosing food intolerance is by monitoring the response to a diet trial. Again, such trials do not define the exact pathogenetic mechanism involved. The results of serologic food allergy testing are irrelevant.

Gluten-Sensitive Enteropathy (GSE)[623,1497-1510]

Intestinal disease caused by dietary wheat gluten has been demonstrated in Irish Setters. Affected Setters typically are presented for veterinary attention due to poor weight gain and chronic intermittent diarrhea after weaning. However, the age of the dog when gluten is introduced and the dosage both affect expression of the disease, with some dogs becoming asymptomatic later in life.

The condition resembles gluten sensitivity (celiac disease) in humans, although clinical signs and mucosal atrophy are less marked. Celiac disease shows a clear genetic predisposition and, in Irish Setters, GSE is a familial condition with an autosomal recessive mode of inheritance. However, unlike human celiac disease, there is no relationship with major histocompatibility genes *DQA* and *DQB*, and the pathogenesis is different. GSE can affect other dog breeds but has not been reported in cats. Gluten sensitivity has been suggested in Soft-Coated Wheaten Terriers with PLE and protein-losing nephropathy.

Pathogenesis[430,1511-1524]

The pathogenesis of Irish Setter GSE remains incompletely characterized. Ingested wheat protein, gluten, either is directly toxic to the intestinal mucosa or induces an adverse immune reaction. In contrast to celiac disease, where there is cross-reactivity between gluten peptides and tissue transglutaminase, T-cell and immunoglobulin responses to gluten or mucosal antigens are not noted in Irish Setters. However, involvement of the immune system is suggested by the fact that increased lamina propria $CD4^+$ T-cell populations and decreased $CD8^+$ populations do occur. Clinical signs and histologic and biochemical changes resolve on a wheat-/gluten-free diet and relapse when gluten-containing diets are reintroduced. Abnormal mucosal permeability precedes the development of disease in affected Irish Setters, implying that an abnormality in the mucosal barrier could permit abnormal entry of gluten peptide.

Diagnosis[1498,1502,1525]

Histologic changes show partial villus atrophy and intraepithelial lymphocyte infiltration, with a variable lamina propria infiltrate. These changes and the clinical signs resolve when a gluten-free diet is fed, and relapse on wheat and gluten challenge.

Treatment

Successful treatment depends on the exclusion of gluten from the diet. Proprietary gluten-free food (i.e., lacking wheat, barley, or rye) is recommended.

Small Intestinal Bacterial Overgrowth (SIBO) and Idiopathic Antibiotic-Responsive Diarrhea (ARD)

Definitions[255,469,1526-1538]

True small intestinal bacterial overgrowth (SIBO) is defined by an increase in the absolute number of bacteria in the upper SI during the fasted state. The normal bacterial population of the SI is controlled by a number of mechanisms, and overgrowth is the uncontrolled proliferation of these bacteria rather than a specific infection. In human medicine, primary SIBO as a cause of diarrhea and irritable bowel syndrome remains controversial, but it is accepted that it does occur secondary to disorders that interfere with normal control mechanisms (Box 276-16). Historically, the term *idiopathic SIBO* was used to describe an antibiotic-responsive condition of large-breed dogs, especially German Shepherd Dogs, for which no underlying cause could be found, and where overgrowth was claimed. A positive response to a range of antibiotics usually is seen, but an enteropathy responsive only to tylosin has been reported. However, given concerns regarding whether a true increase in bacterial numbers exists in idiopathic canine cases, the alternative name of antibiotic-

responsive diarrhea (ARD) has been adopted, whereas SIBO is best considered a clinical sign or a secondary pathogenetic mechanism. Although cats might feasibly suffer from secondary SIBO, an idiopathic antibiotic-responsive condition similar to that seen in dogs has not been documented, except that the efficacy of metronidazole in mild IBD sometimes is noted.

Box 276-16

Causes of Secondary Small Intestinal Bacterial Overgrowth

Abnormal Anatomic Structure
- Blind loop (congenital or surgically induced)
- Surgical resection of ileocolic valve

Achlorhydria
- Acid blockers, especially proton pump inhibitors
- Spontaneous (atrophic gastritis)

Exocrine Pancreatic Insufficiency

Motility Disorder
- Functional
- Hypothyroidism
- Intestinal pseudo-obstruction

Mucosal Disease
- Chronic giardiasis
- Dietary sensitivity
- Inflammatory bowel disease (cause or effect?)
- Occult primary pathogens

Partial Intestinal Obstruction
- Chronic intussusception
- Stricture
- Tumor

The upper limit for normal duodenal bacterial numbers (reported as the number of colony-forming units cultured per milliliter [CFU/mL] of duodenal juice) in humans is $<10^5$ total or $<10^4$ anaerobic CFU/mL. That number was incorrectly extrapolated to dogs, and subsequent studies have demonstrated that a total count $\geq 10^5$ CFU/mL commonly is found in asymptomatic dogs. Therefore, although a true SIBO could exist secondary to conditions equivalent to those in humans, the premise of defining the idiopathic, antibiotic-responsive disease as SIBO, based on the original numeric cutoff, is flawed. In this chapter, cases with a documented underlying cause are defined as secondary SIBO, and the term *idiopathic ARD* is used for idiopathic antibiotic-responsive conditions.

Etiology and Pathogenesis[255,1539-1541]

Idiopathic ARD[255,760,1542-1562]

Several hypotheses as to the cause of idiopathic ARD exist. Originally, they were based on the belief that a true SIBO was present. Mechanisms allowing true SIBO, such as abnormal SI motility, are not proven in dogs or cats. Achlorhydria secondary to omeprazole treatment does qualitatively alter the microbiome in dogs, but this does not correlate with disease. More recent hypotheses focus on host-bacterial interactions.

Another hypothesized mechanism is secretory IgA (SIgA) deficiency. Studies that have documented low serum IgA concentrations are irrelevant, as mucosal SIgA secretion does not reflect serum concentrations. An absolute deficiency of fecal IgA in German Shepherd Dogs associated with EPEC infection has been demonstrated once but has not been reproduced by others. Yet a secondary SIgA deficiency in the German Shepherd Dog breed could exist, explaining decreased IgA production by intestinal biopsies cultured *in vitro,* despite increased numbers of mucosal IgA^+ plasma cells. The cause of this deficiency is not clear, but a complex defect is likely, involving abnormalities either in the production and release of IgA from the plasma

cell or in the pathway of translocation of IgA across the epithelium during secretion. Yet no abnormalities in J-chain or pIgR expression have been found. German Shepherd Dogs do possess a specific variant of the IgHA gene, and four mutations in the code for the hinge region of the IgA heavy chain could affect the efficacy of the molecule or its susceptibility to proteolysis. Yet all German Shepherd Dogs, irrespective of health status, are the same variant, C, and this finding is probably merely a breed-specific phenomenon.

Dogs with ARD have increased lamina propria $CD4^+$ T cells and increased expression of certain cytokines, suggesting immune dysregulation. Hypermethylation of genes controlling IgA switching has been shown in IBD and is associated with decreased mucosal IgA expression and perhaps a loss of tolerance toward endogenous bacteria. Alternatively, a polymorphism in TLR-5, the receptor for bacterial flagellin, is suspected in German Shepherd Dogs with perianal fistulae and ARD. Such a hypothesis is supported by the fact that antibacterials lead to resolution of clinical signs and decreased cytokine expression, but not to a decline in bacterial numbers. The fact that the most effective antibacterials also are those with immune-modulating properties (e.g., oxytetracycline, metronidazole, tylosin) could also support this hypothesis. Furthermore, there is anecdotal evidence that some German Shepherd Dogs affected by ARD in younger life go on to develop IBD later. An alternative hypothesis is that an unidentified pathogen is involved; candidates include intestinal *Helicobacter* spp. or enteropathogenic *E. coli.* The predisposition of German Shepherd Dogs to ARD could then be explained by infection in the perinatal period and/or genetic susceptibility to infection as a result of MHC II or TLR polymorphisms.

A true increase in bacterial numbers in the SI could cause malabsorption and diarrhea through several mechanisms: competition for nutrients; production of nutrients to create products that provoke diarrhea (e.g., deconjugated bile salts and hydroxylated fatty acids); and/or direct damage to the mucosal brush border. However, these mechanisms might not be relevant in idiopathic ARD because there is no increase in numbers, although reversible changes in brush border enzyme activity are seen in dogs responding to antibiotics.

Secondary SIBO[232,1563-1565]

True SIBO can occur secondary to (1) diseases that result in excess substrate in the intestinal lumen, (2) diseases that affect the clearance of bacteria, or (3) morphologic or functional derangement of the mucosa (see Box 276-16).

Clinical Presentation

Idiopathic Antibiotic-Responsive Diarrhea

Idiopathic ARD most commonly is recognized in young German Shepherd Dogs, although cases have been reported in other large dog breeds (but not in cats). The flora present is comprised predominantly of either aerobic or anaerobic bacteria, but it tends to be a mixed population with staphylococci, streptococci, coliforms, enterococci, and corynebacteria, and anaerobes such as bacteroids, fusobacteria, and clostridia. These bacteria generally are commensals found normally in the oropharynx, SI, and LI. Culture of fecal bacteria cannot be correlated with the SI bacterial flora and cannot be used for making a diagnosis of this condition.

Affected dogs most frequently show signs of chronic intermittent diarrhea accompanied by weight loss and/or stunted growth, and often associated with excessive intestinal gas production manifested as borborygmi and flatus. However, vomiting and signs of colitis are reported, and occasionally dogs are stunted in their growth yet do not have overt diarrhea. Appetite is variable; most affected dogs have polyphagia, pica, and/or coprophagia, but a few are anorectic, perhaps associated with acquired cobalamin deficiency. A positive response to antibiotics is expected, and the condition could deteriorate if corticosteroids are given. The major differential diagnoses are EPI and IBD, both of which are common in the breed.

Secondary SIBO

SIBO can occur secondary to numerous primary conditions (see Box 276-16), but clinical signs firstly relate to the underlying condition. When SIBO develops secondary to a partial obstruction or focal dysmotility, bacterial numbers can exceed 10^9 CFU/mL. However, signs of secondary SIBO also can be seen and are indistinguishable from those of idiopathic ARD, with diarrhea predominating. Clinical signs can be intermittent because recurrent diarrhea can temporarily flush out the overgrowth. Using the historical numeric cutoff of 10^5 CFU/mL total bacteria, secondary SIBO was considered common in chronic enteropathies. In reality, these numbers were normal, and true secondary SIBO is uncommon, with the

exception of SIBO secondary to EPI. An increase in SI bacterial numbers has been documented in experimentally induced EPI, and bacterial numbers decrease upon treatment of EPI with enzyme replacement. Therefore, in many cases, the SIBO itself is of no significance. However, a proportion of naturally occurring EPI cases responds suboptimally to pancreatic enzyme supplementation alone and might require concurrent antibiotic therapy. Given that the majority of dogs affected with EPI are German Shepherd Dogs, it is not clear whether this is the result of secondary SIBO or of concurrent idiopathic ARD.

Diagnosis[588,1528,1532,1566,1567]

The diagnosis of SIBO and ARD is controversial. In all cases, it is critical that a thorough investigation be conducted to eliminate causes of secondary SIBO before the patient is treated with antibacterials. Systemic disorders should be ruled out with a minimum database, EPI eliminated by serum TLI assay (see ch. 290), and diagnostic imaging performed to identify partial intestinal obstructions (see ch. 88). Fecal examination for parasitic and known bacterial pathogens is mandatory (see ch. 81).

Quantitative aerobic and anaerobic culture of duodenal juice was the gold standard for the diagnosis of SIBO but is no longer recommended for the reasons described above. This overdiagnosis of SIBO probably explains why it was reported in 50% of dogs with chronic intestinal disease. Culture of endoscopic biopsies has not been shown to be helpful.

Indirect Tests for SIBO/ARD

Indirect tests include serum biochemical markers and breath hydrogen analysis.

Serum Folate and Cobalamin Concentrations[405,469,1568-1570]

Bacteria can synthesize folate and prevent cobalamin absorption. Therefore, SIBO is predicted to be associated with an increased serum folate concentration or a decreased cobalamin concentration, or both, as seen in humans with secondary SIBO. Yet studies have demonstrated that these tests are of limited value in the diagnosis of idiopathic ARD. This poor performance could be related to dietary factors, the presence of concurrent disease, or the use of drugs that alter serum vitamin concentrations, or simply that bacterial numbers are not necessarily increased. Any alterations of serum folate and cobalamin noted in EPI could reflect pancreatic dysfunction rather than secondary SIBO. Although these tests often are the only tests available to practitioners, they generally are unhelpful in the diagnosis of idiopathic ARD and are not recommended.

Serum Unconjugated Bile Acids[469,470]

A preliminary study in dogs suggested that serum unconjugated bile acid (SUBA) concentrations increased in SIBO due to bacterial deconjugation of bile salts. However, later studies demonstrated that SUBA concentrations were neither sensitive nor specific for diagnosis of idiopathic ARD.

Other Biochemical Tests[473]

Measurement of increased amounts of a bacterial product made either naturally (e.g., urinary indican, p-nitrosonaphthol) or after oral administration of a test substance (e.g., sulfapyridine, PABA) could diagnose SIBO, but these tests have been unreliable.

Breath Hydrogen Excretion[1571]

Bacterial fermentation in the intestinal tract releases hydrogen, which, after systemic absorption, is exhaled and can be measured in breath samples. Theoretically, SIBO would result in a high resting breath hydrogen concentration and/or an early (or double) hydrogen excretion peak after ingestion of a test meal. However, increased breath hydrogen concentrations also can be seen with carbohydrate malabsorption or decreased orocecal transit time, and the lack of specificity means the test largely has been abandoned.

Intestinal Permeability[1572-1574]

Intestinal permeability can be abnormal in SIBO and can improve after antibiotic treatment. However, such findings are not pathognomonic for either secondary SIBO or idiopathic ARD and are not readily available in practice.

Lack of Histologic Changes on Intestinal Biopsy

Intestinal biopsies most often are histologically normal or demonstrate only subtle abnormalities in ARD. However, such findings cannot be diagnostic because other conditions yield similar results, and such findings have been described as "minimal change enteropathy."

Empiric Response to Antibiotics

Currently, the definitive diagnostic test for idiopathic ARD is, logically, the response to empirical therapy. However, a clinical response to antibacterials is not specific and indeed can be seen with IBD, infectious diarrhea, and even a range of nonenteric diseases such as portovascular anomalies. Furthermore, response to antibiotic therapy does not discriminate idiopathic ARD from secondary SIBO, and ARD is only a valid diagnosis after thorough diagnostic investigations have eliminated other possible causes.

Identification of Idiopathic ARD[469]

Both direct and indirect tests advocated for diagnosing idiopathic SIBO are of limited value. Therefore, the only available diagnostic test for ARD is response to an antibacterial trial. However, such a diagnostic process is appropriate only after thorough diagnostic investigations have eliminated all other causes of antibacterial responsiveness. In conclusion, four suggested criteria for a diagnosis of idiopathic ARD are (1) a positive clinical response to an antibiotic trial; (2) relapse of signs upon withdrawal of antibiotics; (3) remission on reintroduction of antibiotics; and (4) elimination of other causes based on the results of other diagnostic tests and histopathologic assessment.

Identification of Secondary SIBO

Although numerous tests are available to document true overgrowth, in practice it is more important to identify the underlying cause.

Treatment

Idiopathic ARD[75,102,107,1529-1531,1539,1545,1575-1579]

Antibacterials

No cure is available for idiopathic ARD, but signs can be controlled with antibiotics. A broad-spectrum antibacterial is indicated; suitable choices include oxytetracycline (10-20 mg/kg PO q 8 h), metronidazole (10-15 mg/kg PO q 12 h), and tylosin (20 mg/kg PO q 8-12 h). Oxytetracycline (OTC) is cheap but is not universally available. It can be given with food because systemic absorption is not required, but it cannot be used before permanent tooth eruption because it causes staining of tooth enamel. Some authors have criticized its use because it is associated with rapid development of plasmid-mediated antibiotic resistance. However, given that long-term efficacy is maintained in most cases, OTC might not be acting through its antibacterial properties, especially as it does not significantly reduce SI bacterial numbers. Rather, it could provide selective pressure on the intestinal flora, encouraging the establishment of less harmful bacteria, in the same way that tylosin has been shown to increase fecal lactobacilli and enterococci. Alternatively, OTC might exert immunomodulatory effects, which has been suggested for this antibiotic group and other antibacterials commonly used for treating ARD, namely metronidazole and tylosin. OTC has been shown to exert an effect on MVM enzyme activity, but it is not known whether this is through inhibition of microbial activity.

Whichever antibacterial is chosen, a 4- to 6-week course is given initially, although the antibiotic is changed after 2 weeks if the response has been suboptimal. In some cases premature cessation of treatment can lead to relapse, and prolonged therapy often is necessary. In some animals a delayed relapse occurs several months after cessation of antibiotics, and such cases require either repeated courses or indefinite therapy. Efficacy often is maintained despite a reduction in dosage or dosage frequency: once-daily antibacterials can maintain control of signs, and tylosin at 5 mg/kg has been shown to be as effective as the standard 20 mg/kg dosage. Dogs can also "outgrow" the problem with age, either as a result of a decrease in caloric intake or because of developing maturity of the mucosal immune system. In view of the public health concerns over prolonged use of antibiotics, it is appropriate to periodically stop treatment to determine whether it is still required.

Ancillary Treatments[79,103,591,773,775-777,1577,1580,1581]

Dietary manipulation can be a useful adjunctive treatment for both idiopathic ARD and secondary SIBO (see ch. 178). A highly digestible, low-fat diet is desired, to reduce the substrate available for bacterial use. Addition of FOS has been advocated to reduce SI bacterial numbers, although evidence of efficacy is

conflicting, with the greatest effect seen in the colonic flora. Probiotic use has not been assessed thoroughly in ARD. Finally, if low serum cobalamin concentrations occur, parenteral cobalamin therapy is warranted.

Secondary SIBO

Although antibacterial therapy improves clinical signs, appropriate treatment for the underlying condition is preferable. For EPI, pancreatic enzyme supplementation can reduce bacterial numbers because exogenous proteases have antibacterial properties (see ch. 290).

Inflammatory Bowel Disease

Definition[754,757,760,1544,1582-1592]

Inflammatory bowel disease (IBD) is a collective term that describes disorders of the GI tract characterized by persistent or recurrent GI signs and histologic evidence of intestinal inflammation. The disease bears little resemblance clinically or histologically to IBD (Crohn's disease and ulcerative colitis) of humans but might share the same etiology. However, the indiscriminate use of the term *IBD* is unhelpful, as several diseases are associated with chronic intestinal inflammation (Box 276-17), whereas, by definition, the cause of IBD is idiopathic. Variations in the histologic appearance of the inflammation suggest that idiopathic IBD is not a single disease entity (Figure 276-20), and the nomenclature merely reflects the anatomic distribution and the predominant cell type present. The inflammation can be confined to the SI or there can be diffuse gastroenterocolitis. Lymphocytic-plasmacytic enteritis (LPE) is the most common histologic form reported; eosinophilic enteritis (EE) and eosinophilic gastroenteritis (EGE) are less common; and granulomatous enteritis is rare. Underlying neutrophilic infiltration is a feature of early human IBD, and neutrophilic enteritis sometimes is seen in cats and rarely in dogs.

Box 276-17

Causes of Chronic Small Bowel Inflammation

Chronic Infection

- *Giardia* sp.
- *Histoplasma* sp.
- *Toxoplasma* sp.
- *Mycobacterium* sp.
- Protothecosis
- Pythiosis
- Pathogenic bacteria (*Campylobacter, Salmonella* spp., pathogenic *Escherichia coli*)

Food Allergy

Small Bowel Inflammation Associated with Other Primary Gastrointestinal Diseases

- Lymphoma
- Lymphangiectasia

Idiopathic Causes

- Lymphocytic-plasmacytic enteritis (LPE)
- Eosinophilic gastroenterocolitis (EGE)
- Granulomatous enteritis (same as regional enteritis?)
- Neutrophilic enteritis (possibly secondary to bacterial invasion)

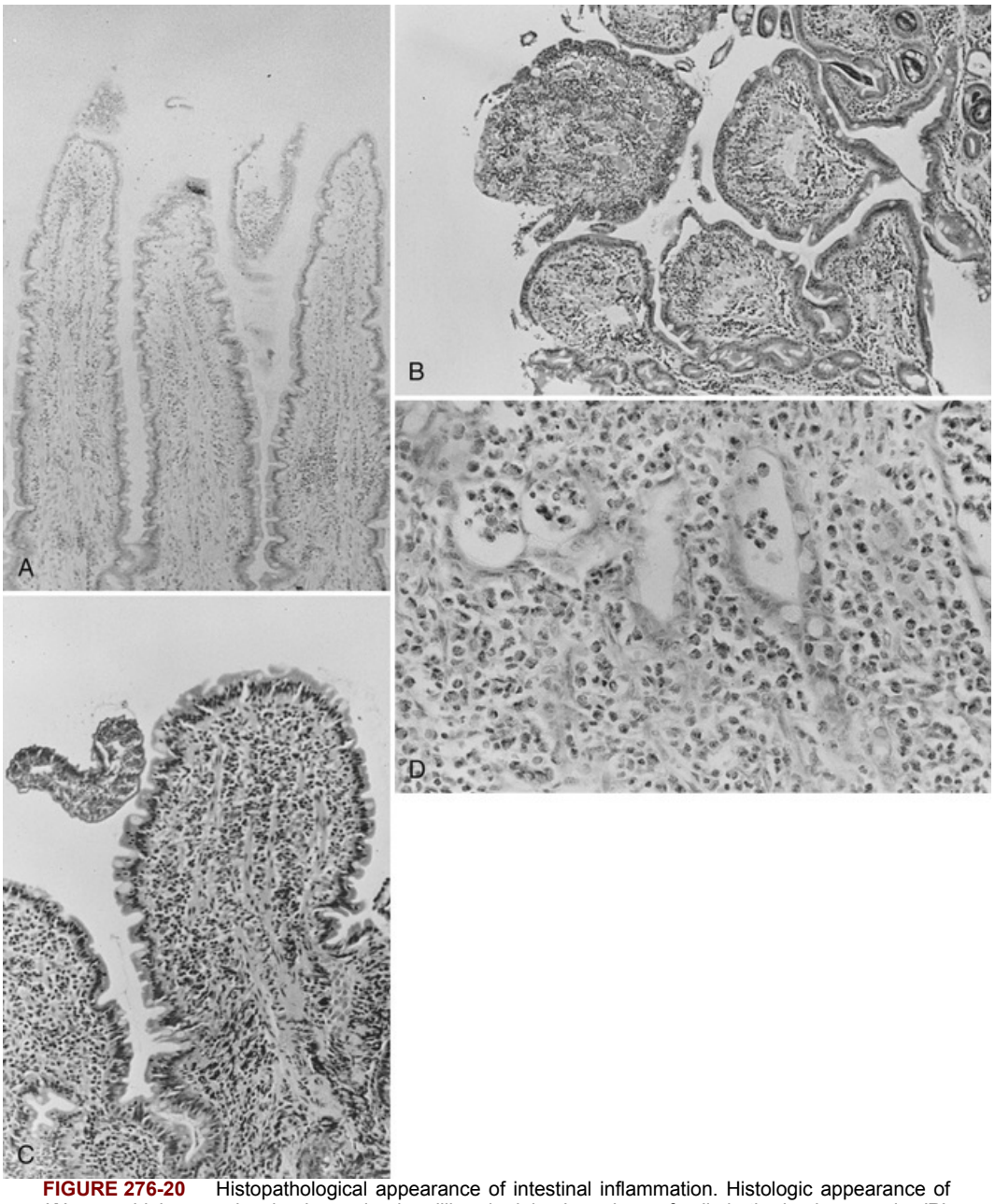


FIGURE 276-20 Histopathological appearance of intestinal inflammation. Histologic appearance of **(A)** normal jejunum, showing long, slender villi and minimal numbers of cells in the lamina propria; **(B)** idiopathic lymphoplasmacytic enteritis in a Dachshund, showing stunted villi and a lymphoplasmacytic infiltrate; **(C)** lymphoplasmacytic intestinal inflammation associated with *Strongyloides* infection (a worm is visible in the section on the mucosal surface); and **(D)** eosinophilic enteritis in a German Shepherd Dog, showing massive infiltration of the crypt area with eosinophils. (Courtesy G. R. Pearson.)

Clinical Presentation[780,1592-1602]

Idiopathic IBD is a common cause of chronic vomiting and diarrhea in dogs and cats, but its true incidence is unknown. In reality, it is probably overdiagnosed because of the relative ease of obtaining endoscopic biopsies and the difficulties in interpretation of such small histopathologic specimens, plus the failure to eliminate other causes of mucosal inflammation. No apparent gender predisposition occurs, but in both dogs and cats, IBD appears to develop most commonly in middle-aged animals, with intermittent signs sometimes seen at an earlier age. Although IBD potentially can occur in any animal, certain breed predispositions are recognized (see E-Table 276-5) and characteristic patterns of disease can be seen in specific breeds. In cats an association called *triaditis* exists between IBD, lymphocytic cholangitis, and chronic pancreatitis (see ch. 283).

Vomiting and diarrhea are the most common clinical signs in IBD, but an individual case can show some or all of the signs listed in Box 276-18. Sometimes an obvious precipitating event (e.g., stress, dietary change, acute gastroenteritis) is present in the history, but clinical signs can wax and wane spontaneously. The nature of signs crudely correlates with the region of the GI tract affected: vomiting is more common if gastric or upper SI inflammation is present; in cats, vomiting often is the predominant sign of SI IBD; weight loss is associated with SI disease; and LI-type diarrhea can be the result of primary colonic inflammation or can occur secondary to prolonged SI diarrhea (see ch. 277). The presence of blood in the vomit or diarrhea generally is associated with more severe disease and particularly EE/EGE. Severe IBD also is associated with weight loss and PLE, with consequent hypoproteinemia and ascites. Appetite is variable; polyphagia can be present in the face of significant weight loss, whereas anorexia typically occurs with severe inflammation. Eating grass can be increased in IBD but generally is considered a mechanism for inducing vomiting in a nauseated animal. Milder inflammation might not affect appetite, although signs of postprandial pain can be significant even without other signs.

Box 276-18

Clinical Signs Associated with Inflammatory Bowel Disease

- Vomiting
  - Bile
  - Food
  - With or without hair in cats
  - With or without grass in dogs
  - Blood (hematemesis)
- Small intestinal–type diarrhea
  - Large volume
  - Watery
  - Melena
- Thickened bowel loops
- Large intestinal–type diarrhea (see ch. 277)
  - Hematochezia
  - Mucoid stool
  - Frequency and tenesmus
- Abdominal discomfort/pain
- Excessive borborygmi and flatus
- Weight loss
- Altered appetite
  - Polyphagia
  - Decreased appetite/anorexia
  - Eating grass
- Hypoproteinemia
  - Ascites
  - Subcutaneous edema
  - Pleural effusion

Etiology and Pathogenesis[125,149-151,183-186,204-207,225,266,282-285,434,1545,1603-1658]

The underlying etiology of small animal IBD is unknown, but comparisons have been made with human IBD. In this regard, the breakdown of immunologic tolerance to luminal antigens (bacteria and dietary components) is thought to be critical, perhaps resulting from disruption of the mucosal barrier, dysregulation of the immune system, or disturbances in the microbiome, with upregulation of TLRs. Intestinal growth factors such as trefoil peptides from goblet cells and epidermal growth factor could be downregulated in IBD, inhibiting mucosal repair.

Antigens derived from the endogenous microflora are likely to be important in disease pathogenesis, and a potential role for diet-related factors is suggested by the clinical benefit of dietary therapy in some cases of IBD. Autoimmune enteropathy is a rare condition in humans that resembles LPE somewhat (i.e., villus blunting, mononuclear cell infiltrate, and crypt abscesses). However, there is no evidence for autoimmunity in small animal IBD.

Undiagnosed infection as a cause of SI inflammation remains an alternative possibility, considering the relatively recent identification of attaching and invading *E. coli* in granulomatous colitis of Boxers, a condition previously considered to be a manifestation of idiopathic IBD. Toxoplasmosis has been associated with SI inflammation (see ch. 221), and a PCR study identified *Mycobacterium avium* subspecies *paratuberculosis* in about 20% of presumed idiopathic IBD cases (see ch. 212). The presence of yeasts in the SI, the presence of anti-*Saccharomyces* antibodies in some cases of IBD, and anecdotal reports of improvement with oral nystatin suggest yeasts might sometimes be involved in IBD.

Genetic factors are likely to contribute to the pathogenesis of IBD, and in humans the strongest associations are with genes of the human MHC (human leukocyte antigen [HLA]). Furthermore, some human patients with Crohn's disease have a mutation in the *NOD2-CARD15* gene. This gene's product detects bacterial lipopolysaccharide and can activate the proinflammatory transcription factor NF-kappa-B. Such a link could explain the development of aberrant immune responses to bacteria in certain individuals. Genetic polymorphisms in either *NOD2* or TLRs have been shown in certain dog breeds. For example, single nucleotide polymorphisms (*snp*s) in exon 3 of the *NOD2* gene occur in German Shepherd Dogs with IBD, but not in other breeds and *snp*s also are recognized in genes encoding TLR4 and TLR5 in affected dogs of this breed. Upregulation of TLRs has been demonstrated in IBD. This could be an epiphenomenon associated with inflammation but could infer hyperresponsiveness of TLRs to luminal bacteria.

Diagnosis[609,1659-1661]

Intestinal biopsy is necessary for a diagnosis of intestinal inflammation, but the diagnosis of idiopathic IBD should be limited to cases in which histologic evidence of inflammation is found *without* an obvious underlying cause. All other etiologies, including infectious, diet-responsive, and antibacterial-responsive conditions, must be excluded. Therefore, before intestinal biopsy is undertaken, laboratory evaluation and diagnostic imaging are performed. Such tests cannot prove inflammation is idiopathic, but they can help eliminate known causes of intestinal inflammation and the possibility of anatomic intestinal disease (e.g., tumor, intussusception) or extraintestinal disease (e.g., pancreatitis). Furthermore, by determining whether focal or diffuse intestinal disease is present, the clinician can choose the most appropriate method of intestinal biopsy.

Complete Blood Count[1662]

Occasionally neutrophilia, with or without a left shift, is noted. Eosinophilia could suggest EE/EGE, but it is neither pathognomonic nor invariably present. Anemia can reflect chronic inflammation or chronic blood loss. Thrombocytopenia is seen in <3% of cases, but thrombocytosis often is noted with chronic GI bleeding.

Serum Biochemistry Profile[780]

No pathognomonic changes are seen in IBD, but diseases of other organ systems should be recognized and excluded. In addition, hypocholesterolemia suggesting malabsorption, hypocalcemia, and hypomagnesemia also can be found. Hypoalbuminemia and hypoglobulinemia are characteristic of PLE, and hypoalbuminemia correlates with a poorer prognosis. Intestinal inflammation in dogs can cause a "reactive hepatopathy," with mild elevations in serum activities of liver enzymes. In contrast, because of their shorter half-lives in cats, increases in serum activities of liver enzymes in this species are more likely to be the result of primary liver disease.

Fecal Examination[374,384,1660]

Fecal examination is important for eliminating other causes of mucosal inflammation, such as hookworms and whipworms, *Giardia,* and bacterial pathogens (see ch. 81). Given the potential for occult *Giardia* infection, empirical treatment is recommended in all cases (see above). Increased fecal alpha$_1$-PI concentrations would be expected in IBD as a marker of intestinal protein loss even before hypoproteinemia develops, and fecal calprotectin concentration should be increased if there is inflammation.

Serum Vitamin Concentrations[50,234,395,401,402,780,783,1663-1665]

Hypovitaminosis D can occur in IBD and can be associated with ionized hypocalcemia. Uptake of folate and cobalamin potentially are reduced by intestinal malabsorption, and therefore, SI inflammation can result in subnormal serum folate (proximal inflammation) or cobalamin (distal inflammation) concentrations, or both (diffuse inflammation). The degree of hypocobalaminemia in IBD correlates with the degree of histologic damage and a poorer prognosis. Although cobalamin deficiency is not pathognomonic for IBD, it does require therapeutic correction as it has systemic metabolic consequences (see ch. 292). Anecdotal evidence suggests that cobalamin-deficient cats with IBD require parenteral supplementation to respond optimally to immunosuppression.

Diagnostic Imaging[498,524-529,551,556,561,1666]

Information from imaging, together with specific clinical signs, allows the clinician to choose the most appropriate biopsy method. Plain radiographs can be useful for detecting anatomic SI disease but generally are unremarkable in IBD, and contrast studies rarely add further specific information. Ultrasonographic examination can document focal or diffuse disease and/or whether other organs are affected and is superior to radiography for identifying SI disease. It permits evaluation of intestinal wall thickness and can document mesenteric lymphadenopathy, while ultrasound-guided fine-needle aspiration (FNA) can provide samples for cytologic analysis (see ch. 89 and 93). However, increased intestinal wall thickness is not a feature of all cases of canine idiopathic IBD and is not pathognomonic. Mucosal heterogeneity is consistent with inflammation or crypt abscessation, while striations are indicative of lymphatic dilatation.

Intestinal Biopsy[144,565,570,571,577,581,603,604,609-616,1544,1590,1596,1667-1672]

Intestinal biopsy is necessary to document intestinal inflammation, which is essential for a diagnosis of IBD. Endoscopy is the safest method of biopsy (see E-Box 276-9), but it has limitations: samples are superficial and can be small and crushed, while histopathologic interpretation is prone to disparity both between pathologists, but also with the gross endoscopic appearance. An endoscopic scoring system has been published by the WSAVA GI Standardization Group to try to obtain reliability in the subjective assessment of mucosal erythema, irregularity, and friability,[609] similar to a standardized histologic grading system for SI and LI IBD in dogs and cats. These guidelines are not a numerical system for counting features and "scoring" intestinal inflammation, nor a weighted scale. Rather, the guidelines are a template that allow objective comparisons of individual findings to a reference point. They are intended to allow comparative, prospective studies to identify which changes are important in the histologic definition of IBD and thereby understand the correlation between clinical and histologic severity. A simplified model only assesses villus atrophy, epithelial injury, IELs, crypt changes, and LP infiltrate.

Endoscopic SI biopsies (see ch. 113) only can be collected from the proximal segment of the SI unless ileoscopy via colonic intubation is also performed (see E-Box 276-9). However, ileal biopsies appear to give a higher diagnostic yield. In some cases, full-thickness surgical biopsy is necessary, although the procedure is more invasive and dehiscence can be problematic, especially if severe hypoproteinemia is present. Laparotomy might be more suitable for cats, given the tendency for multiorgan involvement (i.e., triaditis). Histopathologic assessment of biopsy material remains the gold standard for the diagnosis of intestinal inflammation, and the pattern of histopathologic change dictates the name of the IBD type present. However, the limitations of histopathologic interpretation of intestinal biopsies are recognized: the quality of specimens can vary, agreement between pathologists is poor, and differentiation between normal specimens and mild LPE, and between severe LPE and lymphoma, can be difficult. Histologic grading schemes have been suggested, and standardized criteria have been produced and should be adopted. Importantly, mucosal inflammation on endoscopic biopsies is described broadly, emphasizing both architectural changes and the number of inflammatory cells in the LP (see E-Box 276-12). This approach considers that increased cellularity merely could be a reactive response, equivalent to enlargement of a draining lymph node, and that evidence

of mucosal damage also is necessary to confirm inflammation.

IBD Activity Indices[524,780,1673-1678]

Clinical activity indices aid quantification of the severity of IBD and show some correlation with ultrasound findings. They help researchers assess the response to treatment and compare studies, and allow practitioners to make a prognosis by comparison to published studies. The Canine IBD Activity Index (Table 276-11) correlates with histological severity and serum concentrations of acute phase proteins, such as C-reactive protein. Measuring trends in acute phase proteins also might be useful in monitoring response to treatment. The Canine Chronic Enteropathy Clinical Activity Index is a modification that includes serum albumin concentration and the presence of ascites and pruritus, but it remains to be independently evaluated.

TABLE 276-11

Indices for the Objective Assessment of Disease Severity in Inflammatory Bowel Disease

FEATURE	CIBDAI	SCORE	CCECAI	SCORE	FCEAI	SCORE
Attitude/activity	Normal	0	Normal	0	Normal	0
	Slight decrease	1	Slight decrease	1	Slight decrease	1
	Moderate decrease	2	Moderate decrease	2	Moderate decrease	2
	Severe decrease	3	Severe decrease	3	Severe decrease	3
Appetite	Normal	0	Normal	0	Normal	0
	Slight decrease	1	Slight decrease	1	Slight decrease	1
	Moderate decrease	2	Moderate decrease	2	Moderate decrease	2
	Severe decrease	3	Severe decrease	3	Severe decrease	3
Vomiting	None	0	None	0	None	0
	Mild (once/week)	1	Mild (once/week)	1	Mild (once/week)	1
	Moderate (2-3/week)	2	Moderate (2-3/week)	2	Moderate (2-3/week)	2
	Severe (>3/week	3	Severe (>3/week	3	Severe (>3/week)	3
Stool consistency	Normal	0	Normal	0	Normal	0
	Slightly soft, fecal blood, mucus or both	1	Slightly soft, fecal blood, mucus or both	1	Slightly soft, fecal blood, mucus or both	1
	Very soft feces	2	Very soft feces	2	Very soft feces	2
	Watery diarrhea	3	Watery diarrhea	3	Watery diarrhea	3
Stool frequency	Normal	0	Normal	0	Normal	0
	2-3/day	1	2-3/day	1	2-3/day	1
	4-5/day	2	4-5/day	2	4-5/day	2
	>5 per day	3	>5 per day	3	>5 per day	3
Weight loss (unintended)	Normal	0	Normal	0	Normal	0
	Mild (<5%)	1	Mild (<5%)	1	Mild (<5%)	1
	Moderate (5 to 10%)	2	Moderate (5 to 10%)	2	Moderate (5 to 10%)	2
	Severe (>10%)	3	Severe (>10%)	3	Severe	3
Serum albumin			>2 g/L	0		
			15-19.9 g/L	1		
			12-14.9 g/L	2		
			<12 g/L	3		
Ascites and/or peripheral edema			None	0		

			Mild	1		
			Moderate	2		
			Severe	3		
Pruritus			None	0		
			Occasional	1		
			Stops when sleeping	2		
			Wakes due to itching	3		
Endoscopic lesion					No	0
					Yes	1
Total protein					Normal	0
					Increased	1
ALT/ALP					Normal	0
					Increased	1
Phosphate					Normal	0
					Decreased	1
Final Score	Clinically insignificant	0-3	Clinically insignificant	0-3	Clinically insignificant	0-3
	Mild IBD	4-5	Mild IBD	4-5	Mild IBD	4-5
	Moderate IBD	6-8	Moderate IBD	6-8	Moderate IBD	6-8
	Severe IBD	≥9	Severe IBD	≥9	Severe IBD	≥9

ALT/ALP, Alanine aminotransferase/alkaline phosphatase; *CIBDAI*, Canine Inflammatory Bowel Disease Activity Index; *CCECAI*, Canine Chronic Enteropathy Clinical Activity Index; *FCEAI*, Feline Chronic Enteropathy Activity Index; *IBD*, inflammatory bowel disease.

To convert serum albumin concentration to mg/dL, divide the value in g/L by 10.

Other Diagnostic Investigations[108,384,420,434,618-627,633,1603,1679-1692]

Given the limitations of histopathology, other diagnostic modalities can be required. Cytologic examination is likely to be less sensitive or specific, but immunohistochemistry or flow cytometry can be used for analyzing immune cell subsets and RT-PCR to measure cytokine mRNA expression. However, such techniques are labor intensive, poorly standardized and unlikely to be generally available in the foreseeable future. The presence of perinuclear antineutrophilic cytoplasmic antibodies (pANCA), increased serum acute phase proteins, altered GI hormone concentrations, increased intestinal permeability, increased serum 3-BrY concentration, and fecal excretion of calprotectin can be useful markers of intestinal inflammation. Immunohistochemical evaluation of T- and B-cell markers and PCR for antigen receptor rearrangement (PARR) clonality testing to distinguish lymphoma from severe IBD also is of potential value, but clonal rearrangement also is seen in some patients with IBD.

Treatment[1631,1693-1696]

Whatever the histologic type of IBD, treatment usually involves a combination of dietary modification with antibacterial and/or immunosuppressive therapy. Objective information on efficacy is limited, and most recommendations are based on clinical experience. A staged approach to therapy is recommended whenever possible; sequential treatment trials of parasiticides, an exclusion diet, and antibacterials are tried to rule out known causes of inflammation before immunosuppressive medication is used. Mild cases frequently respond to a diet change and/or metronidazole, especially in cats. However, in some cases, clinical signs or mucosal inflammation are so severe that early intervention with immunosuppression is essential. If clinical signs are intermittent, the owners should keep a diary to track signs and activity, which can provide more objective comparisons.

Dietary Modification[658,1485,1697-1701]

An easily digestible diet that decreases intestinal antigenic load and reduces mucosal inflammation is indicated for patients with IBD (see ch. 178). Traditionally, antigen-limited diets based on a highly digestible,

single-source protein preparation have been recommended, eliminating the possibility of an adverse food reaction as the cause of GI inflammation. Such an exclusion diet trial is recommended in all cases where there is not a PLE and the patient is eating; most clients are happy to try this first, given concerns over the side effects of drug therapy.

Well-cooked rice is the preferred carbohydrate source because of its high digestibility, but potato, corn starch, and tapioca also are gluten-free. Fat restriction reduces clinical signs associated with fat malabsorption. Modification of the n3:n6 fatty acid ratio also can modulate the inflammatory response and could have some benefit both in treatment and in maintenance of remission. Supplementation with folate and cobalamin is indicated if serum concentrations are subnormal, although it is not yet clear whether cobalamin must be supplemented parenterally or whether oral supplementation produces a physiologic effect.

Exclusion diets also can help resolve any secondary sensitivities to dietary components that could have arisen following disruption of the mucosal barrier. Then, after the inflammation has resolved, the usual diet often can be reintroduced without the risk of an acquired sensitivity. More recently, hydrolyzed diets have been used in IBD with reportedly greater success, even in patients that have failed a trial with an antigen-limited exclusion diet. However, histologic improvement in mucosal cellularity has not been apparent, despite resolution of clinical signs. Downregulation of some proinflammatory cytokine mRNAs has been shown; therefore, the response to a hydrolyzed diet could indicate (1) simply that the hydrolyzed diet is so digestible that even a diseased SI can cope with it or (2) the IBD is in remission or even cured, but histologic improvement in cellularity takes longer than does the improvement in clinical signs. The latter explanation perhaps mirrors what happens to a draining lymph node after the primary infection is eliminated.

Antibacterial Therapy[691,1702-1708]

Treatment with antimicrobials can be justified in IBD, partly to treat any secondary SIBO and partly because of the importance of bacterial antigens in the pathogenesis of IBD. However, the only controlled study showed no benefit to giving metronidazole with prednisolone. Fluoroquinolones and metronidazole often are used in human IBD, and metronidazole is the preferred drug for small animals. The efficacy of metronidazole, especially in feline IBD, might not be related just to its antibacterial activity because it could exert immunomodulatory effects on cell-mediated immunity. Other antibacterials (e.g., oxytetracycline, tylosin) can also have immunomodulatory effects and some efficacy.

Immunosuppressive Drugs

The most important treatment modality in idiopathic IBD is immunosuppression, although this should be used only as a last resort (see ch. 165). In human IBD, glucocorticoids and thiopurines (e.g., azathioprine, 6-mercaptopurine) are used most widely.

Glucocorticoids[1702,1709-1711]

In dogs, glucocorticoids are used most frequently, and prednisone, prednisolone, and methylprednisolone are the drugs of choice. Dexamethasone should perhaps be avoided, because in rodents it, and not prednisolone, is deleterious to brush border enzyme expression. Budesonide is used on occasion; it is most popular for feline IBD.

Prednisolone/Prednisone

An initial dosage of 1-2 mg/kg PO q 12 h (i.e., 2-4 mg/kg/day) is indicated for 2-4 weeks; in severe IBD, it can be administered parenterally because oral absorption might be poor. The dosage then is tapered slowly over the subsequent weeks to months. Step-downs usually are performed every 3-4 weeks; the exact timings and amounts of dosage reductions are based on clinical response versus the tolerability of side effects, the convenience of tablet size, and reexamination availability. In dogs, signs of iatrogenic hyperadrenocorticism are common initially but most, except muscle atrophy, are transient and resolve as the dosage is reduced. Typically the first taper is from 1-2 mg/kg q 12 h to 1-2 mg/kg q 24 h; subsequent tapers usually are a halving of the dosage. In some cases, therapy can be completely withdrawn or at least reduced to a low dosage given every 48 hours.

Budesonide[1712-1717]

This is an enteric-coated, locally active corticosteroid, 90% of which is destroyed during its first pass through the liver. It is used for maintaining remission in human ileal Crohn's disease with minimal hypothalamic-pituitary-adrenal suppression. It is an attractive alternative in cats with IBD and diabetes mellitus secondary

to chronic pancreatitis and is relatively cheap in cats and small dogs. However, adrenal suppression has been documented in dogs and a steroid-hepatopathy can develop. A preliminary study showed apparent efficacy in dogs and cats, but a more recent study showed no benefit over prednisolone in canine IBD in terms of remission and side effect rates. Limited information is published on the use of this drug with very wide dosage ranges being suggested, but an initial daily oral dose of 1 mg per cat and 1/2/3 mg per small/medium/large dog is used most often.

Cytotoxic Drugs[1693,1718-1728]

If clinical signs of IBD recur consistently when the corticosteroid dosage is tapered, cytotoxic drugs can be added to provide a steroid-sparing effect. In dogs, azathioprine (2 mg/kg PO q 24 h) commonly is used in combination with predniso(lo)ne when the initial response to therapy is poor or when corticosteroid side effects are marked. However, azathioprine can have a delayed onset of activity (up to 3 weeks) and, given its myelosuppressive potential, regular monitoring of the CBC is necessary. Toxicosis can partly relate to a lack of thiopurine s-methyltransferase (TPMT) in individual dogs. The complete absence of TPMT in cats means that only low dosages of azathioprine are needed and it is not recommended unless reformulation is available. Chlorambucil (2 to 6 mg/m^2 PO q 24 h until remission, followed by tapering) with prednisolone probably is a better choice in cats. Similarly in dogs, a chlorambucil-prednisolone combination has been shown to be more effective than a prednisolone-azathioprine combination.

Other immunosuppressive drugs sometimes are used. Methotrexate is effective in the treatment of human Crohn's disease, but it is not widely used in dogs as it often causes diarrhea in this species. Cyclophosphamide has few advantages over azathioprine and is rarely used. The efficacy of mycophenolate mofetil in small animal IBD is unknown, but it is not very successful as a sole therapy in human IBD. However, cyclosporine has shown a predictably promising effect, given its T lymphocyte–specific activity and efficacy in canine perianal fistula treatment. Unfortunately, it is expensive, and studies in human IBD have shown variable efficacy and toxicity. Steroid resistance correlates with induction of P-glycoprotein expression; while this would be expected to confer resistance to cyclosporine also, response to cyclosporine in 11/14 dogs with steroid-resistant enteropathy has been reported.

Prebiotics and Probiotics[686,688,694,703,1650,1706,1729-1736]

Modulation of the enteric flora with probiotics or prebiotics could have benefits in targeting the pathogenesis of IBD; both can reduce intestinal inflammation in mouse models of IBD. Placebo-controlled probiotic trials in human IBD patients have shown promising results, and early trials in canine and feline IBD have shown modulation of the mucosal immune system and some clinical efficacy. Most effect has been seen with the Probiotic VSL#3 strains, but more targeted species-specific probiotics are needed.

Novel Therapies for IBD[8-13,690,1724,1737-1749]

Novel drug therapies increasingly are used in human IBD to target the underlying disease process more precisely. These therapies include new immunosuppressive drugs, monoclonal antibody therapy, cytokines, and transcription factors. Drugs that target TNF-alpha (e.g., thalidomide, oxpentifylline) are used in human IBD and could be suitable for the treatment of canine IBD because of the importance of this cytokine in the pathogenesis of this disease. Anti-TNF-alpha monoclonal antibody therapy is used in severe cases of human IBD. In the future, species-specific monoclonal antibodies might be used for treating canine and feline IBD, just as oclacitinib (Apoquel) is used in atopic dermatitis.

Fecal microbiota transplantation (FMT) was developed to treat humans with *Clostridium difficile* infection but is now being trialed for the treatment of Crohn's disease. Preliminary reports of success in treating canine IBD by FMT are appearing. Successful stem cell therapy in feline chronic enteropathy has been claimed, but objective assessment of success was lacking. Whole intestinal transplant has been performed in experimental pigs and in humans, but not dogs or cats.

Response to Treatment and Prognosis[317,780,1659,1677,1750-1758]

There is a perception that the treatment of canine idiopathic IBD with corticosteroids usually is successful and that full remission is the most likely outcome. This notion is not supported by critical evaluation of the literature; reported positive responses to parasiticides, dietary therapy, or antimicrobials alone suggest that some reported success were never truly idiopathic IBD. A negative outcome in dogs has been associated with more severe disease (as assessed clinically, endoscopically, or histologically), suspected concurrent pancreatic

disease indicated by high pancreatic lipase immunoreactivity, hypocobalaminemia, and hypoalbuminemia. P-glycoprotein expression and the differential expression of TLR-2 and TLR-4 also are predictive of response to treatment. It is not clear whether the correlation with hypoalbuminemia simply reflects disease severity or a greater likelihood of death from thromboembolic disease, since antithrombin (58 kDa) and albumin (70 kDa) are similar-size molecules.

The response to treatment in feline IBD appears better, and more often, remission is prolonged; metronidazole as a sole therapy in milder cases can be successful, and cats are more resistant to the metabolic effects of chronic corticosteroid usage. Prolonged survival also has been seen with simple prednisolone and chlorambucil therapy.

One surprising finding has been that clinical improvement is not necessarily accompanied by histologic improvement. This could reflect the difficulty in assessing intestinal inflammation histologically, but such discordance also is seen in human Crohn's disease, where histologic remission is slower than clinical remission. In some canine cases, an initially good response is followed by relapse that is refractory to further treatment, and a euthanasia rate of 10-20% often is reported. Failure to maintain remission could indicate development of corticosteroid resistance through P-glycoprotein expression, an initial misdiagnosis of alimentary lymphoma, or transformation of chronic inflammation into lymphoma.

Lymphocytic-Plasmacytic Enteritis[1759-1767]

Lymphocytic-plasmacytic enteritis (LPE) is the most common histologic manifestation of intestinal inflammation, characterized by a mucosal infiltrate of lymphocytes and plasma cells associated with mucosal architectural changes (see Figure 276-20). However, there are many other causes of lymphocytic-plasmacytic SI infiltration (see Box 276-18), including enteropathogens, bacteria, and *Toxoplasma.* All such underlying causes must be excluded before a diagnosis of idiopathic LPE is confirmed. LPE is prevalent in a number of pedigree dog and purebred cats, and in dogs it often causes a PLE. LPE typically affects older animals; it is rare (but not impossible) in individuals < 2 years of age.

Etiopathogenesis[629,1524,1656,1768]

Alterations in immune cell populations in canine LPE include increases in lamina propria T cells (especially $CD4^+$ cells), IgG^+ plasma cells, macrophages, and granulocytes, ranging in severity from mild to severe infiltration. Various nonspecific alterations in cytokine and chemokine gene expression between animals with IBD and normals have been shown both by gene array and mRNA expression. Increased concentrations of acute-phase proteins (e.g., C-reactive protein), which normalize after treatment, indicate an inflammatory response. Mucosal fibrosis can occur, especially in cats. There are changes in matrix metalloproteinase expression in LPE, and the fibrosis can be recognizable ultrasonographically.

Clinical Signs[1762]

Signs of LPE including chronic diarrhea and weight loss are not pathognomonic. Chronic vomiting can be the predominant sign, especially in cats.

Diagnosis

The approach to the diagnosis of LPE is the same as for any chronic enteropathy, although a definitive diagnosis ultimately depends on histolopathologic documentation of increased numbers of lymphocytes and plasma cells in association with architectural changes but no identifiable underlying cause (see ch. 113). Complete or partial villus atrophy can be present, with villus fusion and crypt abscessation in severe cases. The distinction between severe LPE and alimentary lymphoma can be difficult, and differences can exist between endoscopic biopsies and postmortem specimens from the same patient. Such discrepancies can occur because the two conditions may be present concurrently, because chronic intestinal inflammation ultimately can result in malignant transformation or because low-grade lymphoma could initially have been misdiagnosed.

Treatment and Prognosis

The treatment of and prognosis for LPE is that outlined above for idiopathic IBD.

Eosinophilic Enteritis[1172,1769-1772]

Eosinophilic enteritis (EE) is reported to be the second most common form of idiopathic IBD. Frequently, it also involves the stomach (eosinophilic gastroenteritis, EGE) and/or colon. Diffuse disease is most common, but segmental EE has been reported in dogs, and in cats, feline sclerosing eosinophilic fibroplasia could be a variant of EE. Histologically, variable mucosal architectural disturbances (e.g., villus atrophy) are present, with a mixed infiltrate of inflammatory cells in which eosinophils predominate. As with LPE, diagnostic criteria vary among pathologists; some define EE purely based on subjective increases in mucosal eosinophil numbers, whereas others apply stricter criteria (eosinophils must predominate in the lamina propria). Another criterion is the presence of eosinophils between epithelial cells of the villus and crypt, which suggests transepithelial migration. Nevertheless, the number of mucosal eosinophils can vary markedly in normal dogs, and therefore, this condition could be overdiagnosed. As with other forms of IBD, a diagnosis of idiopathic EE should be made only after other causes of eosinophilic inflammation, such as parasitism and food-responsive enteropathy, have been eliminated.

Clinical Signs[1772-1775]

EE can be seen in dogs and cats of any breed and age, although is most common in younger adult animals. Boxers and Dobermans might be predisposed, and an increased incidence in German Shepherd Dogs has been suggested. EE and EGE also can be associated with systemic eosinophilic disorders in both cats and dogs. The clinical signs reported, which depend on the area of GI tract involved, include vomiting, SI diarrhea, and LI diarrhea. Mucosal erosion/ulceration and hemorrhage may occur more frequently in EE than in other forms of IBD (see Figure 276-14, *F* and *G*); therefore, hematemesis, melena, or hematochezia can be seen. Severe EE has been associated with PLE and, rarely, spontaneous perforation of the GI tract.

Etiopathogenesis[1172,1222,1256,1776-1778]

An eosinophilic mucosal infiltrate can be related to dietary sensitivity, endoparasitism, visceral *larva migrans* or be idiopathic. Zoonotic infection with *A. caninum* has been associated with human EGE. The eosinophil infiltration is likely to be the result of local and systemic production of cytokines and chemokines, such as IL-5, and members of the eotaxin family. These mediators may be produced by the Th2 subset of $CD4^+$ T cells. Eosinophil infiltration also is seen as a paraneoplastic effect of mast cell tumors and, sometimes, lymphoma.

Diagnosis[1779]

The diagnosis of EE ultimately is made by histopathologic assessment of intestinal biopsies (see ch. 113) in conjunction with exclusion of parasites and food hypersensitivity. Eosinophilia is neither invariably present nor pathognomonic for EE because it also can occur with parasitism, hypoadrenocorticism, allergic cutaneous or respiratory disease, lymphoma, and mast cell neoplasia. Thickened bowel loops can be palpated in some affected cats, and thickening confirmed by ultrasound.

Treatment

Given that eosinophilic mucosal infiltrates can be related to endoparasitic diseases, empirical treatment with fenbendazole always is advisable. Subsequent to this, an exclusion diet trial should be instigated to eliminate the possibility of dietary sensitivity before immunosuppressive therapy is considered. The prognosis in idiopathic EE is guarded, even with a good initial response to treatment, because recurrence is common.

Feline Sclerosing Eosinophilic Fibroplasia[545,1161,1780-1785]

This histological variant of IBD probably represents an unusual manifestation of EE in cats. Fibrosis of the feline intestinal wall could be driven by chronic inflammation, as it is also reported in intestinal phycomycosis, and mast cell tumors. The idiopathic condition occurs most often in middle-aged cats and Ragdolls. Clinical signs of vomiting and diarrhea are common, and intestinal masses in the duodenum and ileum can be palpable. Histologically, an eosinophil infiltrate is interspersed with fibroblasts and bands of collagen. Bacteria are found within lesions in about half of cases, but reported cases tend to respond to prednisolone.

Neutrophilic Enteritis[634,1544,1786]

Although neutrophils are present in the normal intestinal mucosa, and they are the first cells to infiltrate the mucosa in human Crohn's patients when the disease comes out of remission, neutrophilic enteritis is rare in

dogs and only slightly more common in cats. Traditionally, when a predominance of neutrophils was found in the intestinal mucosa on biopsy, empirical treatment with antibiotics rather than immunosuppression was recommended first, as concerns existed about a potentially infectious cause. Recent studies using FISH justify this approach, as there appears to be an association between neutrophilic enteritis in cats and invasion by *Campylobacter coli,* and with *C. jejuni* and *Salmonella* in dogs.

Granulomatous Enteritis[1787-1792]

Granulomatous enteritis is a rare form of SI IBD characterized by mucosal infiltration with macrophages, resulting in the formation of granulomas. The distribution of inflammation can be patchy. This condition probably is the same as "regional enteritis," in which ileal granulomas have been reported. Granulomatous colitis is associated with an attaching and invading *E. coli* (see ch. 277). In cats, a pyogranulomatous transmural inflammation has been associated with FIPV infection (see ch. 224).

Proliferative Enteritis[1793-1796]

Proliferative enteritis is characterized by segmental mucosal hypertrophy of the intestine. Although many species can be affected, the condition is most common in pigs. The condition is rare in dogs. There have been suggestions of an underlying infectious etiology, and *Lawsonia intracellularis* has been implicated in some cases of canine IBD. Other infectious agents with a proposed link are *Campylobacter* spp. and *Chlamydia.*

Breed-Specific Forms of Inflammatory Bowel Disease[1797]

Idiopathic IBD is recognized in all pedigree breeds of dogs and mixed breeds, but certain pure breeds can be overrepresented. In some, such as the German Shepherd Dog, in which both LPE and EE are common, the assumption is still that they are affected by the same conditions as other dogs. Similarly, Siamese cats are predisposed to LPE. Yet while the same etiopathogenesis of intestinal inflammation could exist in all dogs, there might be underlying, breed-related genetic/immune dysfunctions that increase the risk of disease. In German Shepherd Dogs, *snp*s in the genes encoding TLRs show polymorphisms, suggesting a genetic basis. Rottweilers, Yorkshire Terriers, and Lundehunds are predisposed to intestinal inflammation, but it is usually associated with dilated lacteals and they generally are classified as having primary lymphangiectasia. Other breeds of dog, however, also are prone to idiopathic intestinal inflammation, but features of their condition suggest they do not have the universally recognized form of IBD.

Basenji Enteropathy[1666,1798-1805]

A severe, hereditary form of LPE is well characterized in Basenjis, although the mode of inheritance is unclear. It has been likened to immunoproliferative small intestinal disease (IPSID) in humans because both conditions involve intense intestinal inflammation. However, IPSID is associated with a gammopathy (alpha heavy chain disease) and a predisposition to lymphoma. Affected Basenjis often have hyperglobulinemia but not alpha heavy-chain disease, although they could be predisposed to lymphoma. The intestinal lesions are characterized by increases in $CD4^+$ and $CD8^+$ T cells.

Signs of chronic intractable diarrhea and emaciation are most common and usually progressive; spontaneous intestinal perforation can occur. Lymphocytic-plasmacytic gastritis, with hypergastrinemia and mucosal hyperplasia, can be seen in addition to the enteropathy. PLE with hypoalbuminemia often occurs, although ascites is less common. The approach to diagnosis is the same as for idiopathic IBD and ultimately depends on histopathologic examination of biopsy specimens (see ch. 113). Treatment generally is unsuccessful, with most dogs dying within months of diagnosis. However, early, intensive combination treatment with prednisolone, antibiotics, and dietary modification has achieved remission in some cases.

Familial Protein-Losing Enteropathy and Protein-Losing Nephropathy in Soft-Coated Wheaten Terriers[1504,1509,1679,1680,1754,1806-1810]

A clinical syndrome unique to Soft-Coated Wheaten Terriers has been characterized. Affected dogs present with signs of PLE, protein-losing nephropathy (PLN), or both (also see ch. 325). A genetic basis is likely, as pedigree analysis has demonstrated a common male ancestor, and mutations in the *NPHS1* and *KIRREL2* genes have been found in dogs with the PLN. The disease probably is immune-mediated, given the presence of inflammatory cell infiltration in the SI. A potential role for food hypersensitivity has been suggested because affected dogs have demonstrated adverse reactions during provocative food trials and alterations in

antigen-specific fecal IgE concentrations.

Signs of PLE tend to develop at a younger age than signs of PLN. Clinical signs of the PLE can include vomiting, diarrhea, weight loss, and pleural and peritoneal effusions. Occasionally, thromboembolic disease can occur. Preliminary laboratory investigations, as in most dogs with PLE, demonstrate panhypoproteinemia and hypocholesterolemia. In contrast, hypoalbuminemia (without hypoglobulinemia), hypercholesterolemia, proteinuria, and ultimately azotemia are seen if only PLN has developed. A positive pANCA test could be predictive of the disease. Intestinal biopsy reveals evidence of inflammation, villus blunting, and epithelial erosions. The treatment for PLE/PLN is similar to that described for idiopathic IBD, but the prognosis is usually poorer.

Lymphoplasmacytic Enteritis and Cobalamin Deficiency in Chinese Shar-Peis[400,1811-1815]

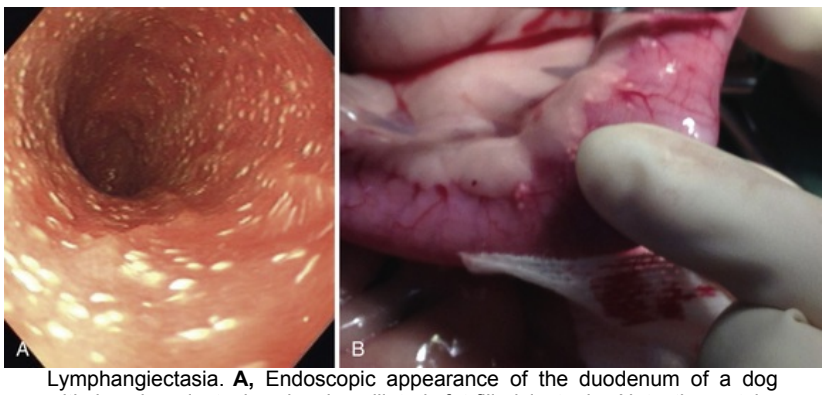
This breed is recognized as being predisposed to lymphoplasmacytic enteritis, and often, there is an associated, severe hypocobalaminemia. A genetic cause is suspected but unproven, and no link to Shar-Pei fever/amyloidosis has been shown; indeed this could just represent IBD.

Lymphangiectasia

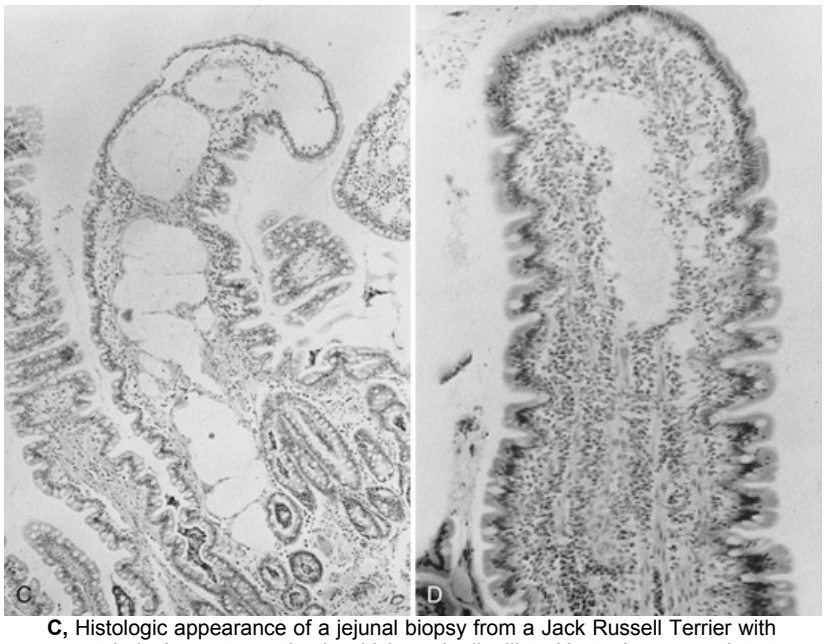
Definition and Cause[290,336-338,1816-1839]

Intestinal lymphangiectasia is characterized by marked dilation and dysfunction of intestinal lymphatics. Abnormal lacteals rupture, and protein-rich lymph leaks from villi into the intestinal lumen, a PLE that ultimately causes hypoproteinemia. Concurrent loss of lymphocytes can lead to immunodeficiency, and affected dogs then can be at risk of inflammatory or neoplastic disease; the Lundehund, which has an inherited form of the disease, is predisposed to gastritis and gastric carcinoma, for example. Lymphangiectasia can be a primary disorder or it can develop secondary to lymphatic obstruction. Primary lymphangiectasia usually is limited to the intestine, although it can be part of a more widespread lymphatic abnormality involving, for example, chylothorax. Lymphangiectasia often is considered congenital, although clinical signs are not usually present from birth. Lymphangiectasia has not been described in cats.

Mucosal inflammation and lipogranulomatous lymphangitis sometimes are reported in association with lymphangiectasia, and some authors consider this condition to be a variant of idiopathic IBD. However, the lymphatic abnormalities predominate and involve the full intestinal wall thickness, whereas in most cases of idiopathic IBD only mild lacteal dilatation is seen (Figure 276-21). It is not clear what the primary event is: leakage of lymph could cause inflammation and granuloma formation, or lymphangitis could cause lymphatic obstruction. The development of associated lipogranulomatous lymphangitis, superimposed on the congenital abnormalities, could be one reason for late onset and progression. The disease most commonly is seen in small terrier breeds (e.g., Yorkshire, Maltese), Rottweilers and the Norwegian Lundehund (E-Figure 276-22).



Lymphangiectasia. **A,** Endoscopic appearance of the duodenum of a dog with lymphangiectasia, showing dilated, fat-filled lacteals. Note the patchy nature of the changes. **B,** Appearance of lipogranulomatous lymphangitis in a dog with lymphangiectasia at celiotomy. Note the white spots on the mesenteric side of the jejunal serosa. (Courtesy Sophie Tyler.)



C, Histologic appearance of a jejunal biopsy from a Jack Russell Terrier with a protein-losing enteropathy, in which markedly dilated lacteals are consistent with a diagnosis of lymphangiectasia. **D,** Histologic appearance of a jejunal biopsy from a retriever with moderate lymphoplasmacytic enteritis and mild secondary dilation of the lacteals.

FIGURE 276-21

E-FIGURE 276-22 Lundehunds. Normal Lundehund (right) and one affected with lymphangiectasia (left), showing abdominal distension caused by ascites secondary to severe hypoalbuminemia. (Courtesy D. A. Williams.)

Secondary lymphangiectasia is caused by intestinal lymphatic obstruction. Underlying causes include (1) infiltration or obstruction of lymphatics by an inflammatory, fibrosing, or neoplastic process; (2) possibly obstruction of the thoracic duct; and (3) right heart failure due to congestive heart failure or cardiac tamponade.

History and Clinical Signs[1840-1847]

The clinical manifestations of lymphangiectasia largely are attributable to the effects of the enteric loss of lymph and consequent hypoproteinemia. Other intestinal functions remain intact, and hypoproteinemia even can be present without diarrhea. Diarrhea, steatorrhea, profound weight loss, and polyphagia are more typical, and vomiting, lethargy, and anorexia are seen occasionally. Signs can be insidious in onset and have an intermittent or fluctuating pattern. Ascites or subcutaneous edema can develop secondary to hypoalbuminemia; ascitic fluid usually is a pure transudate, but if right heart failure causes secondary lymphangiectasia, a modified transudate develops through portal hypertension. Chylous ascites can occur if the cisterna chyli is abnormal or abdominal lymphatics are obstructed by abdominal neoplasia such as a pheochromocytoma. Lymphangiectasia has been associated with granulomatous hepatopathy and, in Lundehunds, with chronic gastritis and gastric carcinoma.

Diagnosis[338,550,556,1845-1851]

Given that lymph is rich in lipoproteins and lymphocytes, laboratory analysis often shows panhypoproteinemia, hypocholesterolemia, and lymphopenia due to leakage of lymph. Hypomagnesemia and ionized hypocalcemia have been reported; the latter suggests vitamin D and calcium malabsorption, and intestinal loss of vitamin D binding protein could be involved. PLE can be documented by measuring fecal concentrations of $alpha_1$-PI. In affected Lundehunds, high fecal $alpha_1$-PI excretion occurs before changes in serum proteins.

Hyperechoic mucosal striations are recognized in this condition, but the specificity of this ultrasonographic change is not known. Gross findings at endoscopy include the presence of a milky white exudate and white lipid droplets or prominent mucosal blebs, which likely are the result of villus tip distension with chyle (see Figures 276-14, *H* and 276-20, *A*). Endoscopic biopsies can be supportive of the diagnosis, but full-thickness biopsies could be required to make a definitive diagnosis. Endoscopic biopsies can be too superficial, or the disease can be patchy and potentially missed. At exploratory laparotomy, most dogs show gross abnormalities, including thickened small intestine, dilated lymphatics (in the mesentery and intestinal serosa), and occasionally, adhesions. Mesenteric lymph nodes also can be enlarged, and yellow-white nodular masses (1 to 3 mm in diameter) often are observed in and around the mesenteric and serosal lymphatics (see Figure 276-21, *B*). These nodules are lipogranulomas, consisting of accumulations of lipid-laden macrophages; they seem to result from perilymphatic extravasation of chyle or are associated with a lymphangitis.

The definitive diagnosis of lymphangiectasia depends on intestinal biopsy, and some pathologists believe that full-thickness biopsies are necessary for a reliable diagnosis. However, there are risks involved with exploratory surgery in malnourished and hypoproteinemic dogs. Characteristic histopathologic changes include "ballooning dilatation" of lymphatics in both the mucosa and the submucosa. True lymphangiectasia must be distinguished both from normal postprandial dilation of lacteals and from the secondary lacteal dilatation occasionally noted with IBD (see Figure 276-21, *C* and *D*).

Treatment[1693,1852,1853]

Secondary lymphangiectasia is managed by specific treatment of underlying disease, such as pericardiocentesis or pericardectomy for cardiac tamponade (see ch. 102). The aim of treatment of primary lymphangiectasia is to decrease the enteric loss of protein and resolve associated inflammation to halt diarrhea, while controlling any edema or effusions. Dietary manipulation and glucocorticoids are the most important treatments.

Anti-inflammatory dosages of glucocorticoids (prednisolone 0.5-1 mg/kg PO q 12 h and then tapered) can be beneficial in some cases, especially if associated lymphangitis, lipogranulomas, and/or a lymphocytic-plasmacytic infiltrate is/are present in the lamina propria. Unfortunately, not all cases respond to such therapy. The use of antimicrobials (tylosin, metronidazole) has not shown any obvious benefit. Diuretics are indicated in the management of effusions, and combinations of diuretics are preferred (e.g., furosemide and spironolactone).

The ideal diet for cases of lymphangiectasia is fat-restricted, calorie-dense, and highly digestible, with claims it could be curative even if prednisolone is ineffective, as long as it is instituted before lipogranulomas develop. Weight-reduction diets, although low in fat, are inappropriate, because patients require a high energy-content diet; fat-restricted GI diets are preferred. Previously, administration of medium chain triglycerides (MCT) was recommended because these lipids were thought to be absorbed directly into the portal blood. However, this theory has been contradicted, and because MCT oil is not very palatable, its use is no longer recommended. Supplementation with fat-soluble vitamins is advised. Cyclosporine treatment could be effective, but there is confusion whether such cases are actually IBD with secondary lymphatic dilation or true lymphangiectasia.

The response to treatment is unpredictable, but cessation of clinical signs can occur spontaneously or be achieved temporarily with treatment, with remissions of months to several years. However, the overall long-term prognosis is poor, and patients almost invariably succumb ultimately to severe malnutrition, incapacitating effusions, and intractable diarrhea.

"Crypt Disease"[1854,1855]

The most common causes of PLE are lymphoma, IBD, and lymphangiectasia. However, there are reports of PLE associated with intestinal crypt lesions without evidence of neoplasia, lymphangiectasia, or substantial inflammation. A low frequency of crypt abscessation is seen in normal tissue, as several crypts form one crypt-villus unit, but increased numbers of crypt lesions have been associated with PLE. Superficial endoscopic biopsies could miss such cryptal lesions. Deeper biopsies show either abscessation (see Figure 276-14, *E*) or large numbers of dilated crypts filled with mucus, sloughed epithelial cells, and/or inflammatory cells. The underlying etiology of such lesions is not known. Response to therapy with antibacterials and immunosuppressive medication is variable; some dogs deteriorate suddenly and can die from thromboembolic disease.

Small Intestinal Neoplasia

Spectrum of Disease[1856-1865]

Lymphoma, adenocarcinomas, and mast cell tumors are the most common GI tumors in cats, with lymphoma predominating, whereas adenocarcinomas, smooth muscle, and other stromal cell tumors are more common in dogs. Intestinal fibrosarcoma (dogs), hemangiosarcoma (cats), schwannoma, neuroendocrine tumors, carcinoid, and plasma cell tumors are rare. Clinical signs usually include weight loss if the tumor is malignant, but a range of other signs can be seen including anorexia, diarrhea, melena, vomiting, abdominal discomfort, abdominal effusion, and anemia. Other rarer consequences of intestinal neoplasia include intussusception, intestinal perforation, and paraneoplastic effects. Ultrasonographic loss of wall layering is highly predictive, indicating a fifty-fold increase in the likelihood of neoplasia. Cytologic examinations of fine-needle aspirates only show ≈70% agreement with histologic evaluation. Diagnosis is based on finding a mass or thickened bowel loops on abdominal palpation and/or imaging, with definitive diagnosis ultimately requiring biopsy.

Intestinal Lymphoma[6,7,1866-1877]

Alimentary lymphoma (AL) is characterized by mucosal, submucosal, and/or epithelial infiltration by

neoplastic lymphocytes, invading the intestine in either a diffuse or a focal manner (Figure 276-23 and E-Figure 276-24). Focal infiltration can be nodular, plaquelike, or circumferential, but a diffuse distribution is most common. Focal forms can cause obstruction, while diffuse infiltration results in malabsorption and often a PLE in dogs. Microscopically, the neoplastic cells can infiltrate the epithelium (i.e., epitheliotropic) or lamina propria extending into the deeper, muscular layers and mesenteric lymph nodes. Most affected cats test negative for the feline leukemia virus (FeLV) at the time of diagnosis, and AL has become the most common form of lymphoma in cats following the decline of FeLV infection. AL can arise by mutation in promoter and/or suppressor genes or perhaps by progression from LPE. Chronic antigenic stimulation could lead to the selection of a malignant clone, and there is evidence of upregulation of IL-6 in both feline IBD and AL. Chronic antigenic stimulation in genetically predisposed patients might stimulate transformation to, and selection of, malignant T cells and progression to low-grade AL, as has been seen in humans with MALT gastric lymphomas associated with *Helicobacter* infection. AL often is associated with changes in the spatial distribution of the microbiome, although this is most likely an effect, not the cause, of AL. A broader discussion of lymphoma is presented in ch. 344.

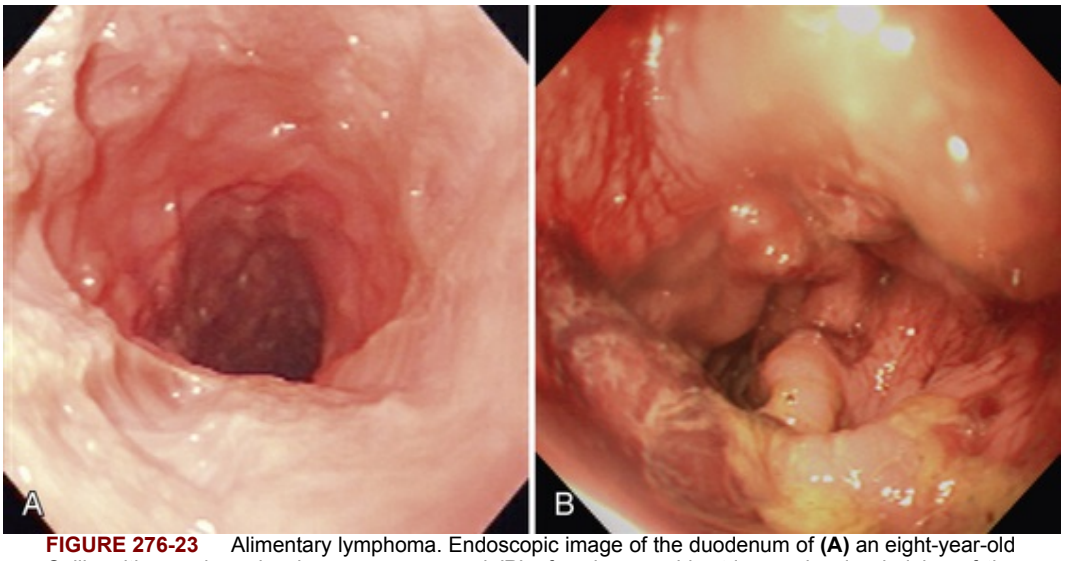
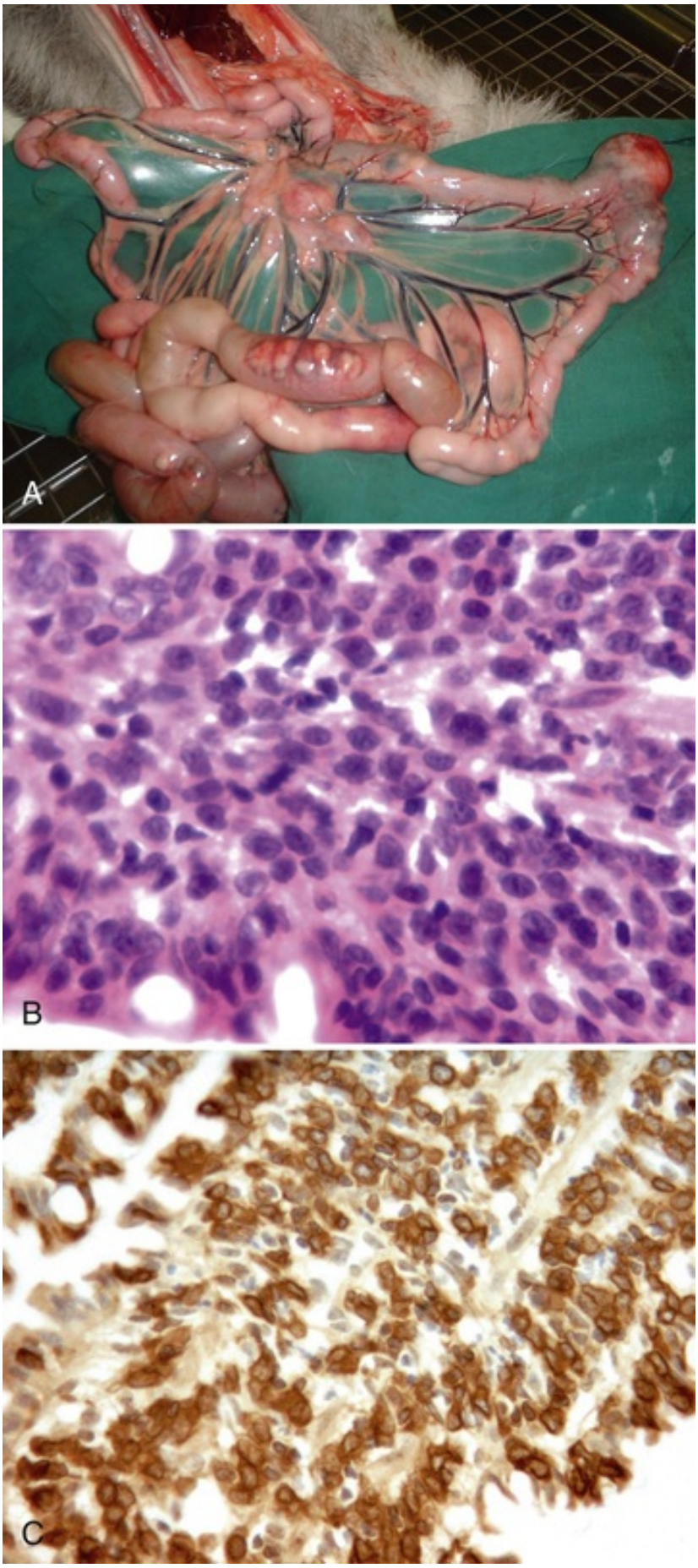


FIGURE 276-23 Alimentary lymphoma. Endoscopic image of the duodenum of **(A)** an eight-year-old Collie with very irregular, lumpy mucosa, and **(B)** of a six-year-old retriever, showing bulging of the mucosa caused by diffuse infiltration. Biopsy is required to confirm the cause of these changes as lymphoma. (**B** reprinted with permission from Lhermette P, Sobel D, editors: *BSAVA manual of canine and feline endoscopy and endosurgery*, Quedgely, Gloucester, England, 2008, BSAVA Publication.)


A
B
C

E-FIGURE 276-24 Alimentary lymphoma. **A,** Postmortem specimen showing both nodular and diffuse thickening of the intestine by lymphoma in a five-year-old Siberian husky. **B,** Histologic appearance of lymphoma, showing accumulation of malignant lymphocytes. **C,** Immunohistochemistry of biopsy using a marker for CD3 T cells (brown stain) identifying it as a T-cell tumor.

Clinical Findings[1877-1890]

Middle-aged or older dogs are most commonly affected by AL. Weight loss, chronic diarrhea, and progressive inappetence are common features; vomiting, hematemesis and melena also can be noted. Diffusely thickened intestines, intestinal mass lesions, mesenteric lymphadenopathy, and evidence of abdominal pain can be found on abdominal palpation. Concurrent hepatosplenomegaly and generalized lymphadenopathy are suggestive of multicentric lymphoma or an alimentary form involving the liver. Rarely, there is associated leukemia. Signs due to hypoproteinemia can develop if diffuse AL results in a PLE. Common clinical signs in cats with AL are vomiting (65%), diarrhea (52%), weight loss (46%) and palpable masses.

Complications[1025,1891,1892]

As well as the expected problems of malabsorption and PLE, AL can cause intestinal perforation with consequent peritonitis. Involvement of other sites (spleen, pancreas) can occur. Secondary infection by *Salmonella* and femoral arterial thrombosis have been reported.

Clinical Pathologic Findings[50,1665,1771,1778,1893-1898]

Anemia, characterized as either normocytic-normochromic nonregenerative or microcytic and hypochromic, usually is either anemia of chronic disease or chronic blood loss anemia, but a secondary Coombs'-positive anemia sometimes occurs. Neutrophilia can be evident, and occasionally paraneoplastic hypereosinophilia is found. Most affected cats are FeLV-negative. Routine biochemistry tests in dogs with AL can reveal panhypoproteinemia in animals with diffuse lymphoma causing a PLE, although B-cell AL occasionally can cause hyperglobulinemia via a monoclonal gammopathy. A PLE causing marked hypoproteinemia is unusual in feline AL. Reductions in serum folate or cobalamin concentrations can be the result of malabsorption, SIBO secondary to intestinal obstruction, or consumption of folic acid by tumor cells. Hypovitaminosis D can occur in AL.

Imaging[519,553,1880,1895,1899-1904]

Ultrasonography can demonstrate diffuse or focal intestinal wall thickening, loss of intestinal wall layering, and mesenteric lymphadenopathy (see ch. 88); it also facilitates fine-needle aspiration of mass lesions and gross thickening (see ch. 89). In cats, thickening of the muscularis mucosa is suggestive of AL: a muscularis to submucosa ratio >1 is indicative of an abnormal bowel segment but is not pathognomonic, as it also can be caused by foreign body obstruction and chronic enteropathies. Mesenteric lymphadenopathy also is not discriminatory. Endoscopically, abnormalities due to IBD or lymphoma cannot be reliably distinguished visually, and biopsies should always be taken for histopathologic analysis (Figures 276-12, *G* and 276-23).

Intestinal Biopsy[517,577,604,605,610,617,1905]

Full-thickness biopsy material is preferable to endoscopic pinch biopsies, which could miss the lesion or simply demonstrate adjacent LPE. This is, in part, related to the limited size and depth of endoscopic biopsies, but it also reflects the tendency of AL to occur predominantly more distally in the SI. Thus, endoscopic biopsies might be less sensitive than surgical biopsies unless ileoscopy is performed. Full-thickness biopsies give the most reliable diagnosis when neoplastic lymphocytes can be visualized infiltrating intestinal muscle layers. However, exploratory laparotomy is a risky procedure because many patients are severely debilitated and hypoproteinemic, and subjectively, healing of any intestinal incision is likely to be impaired by the neoplastic infiltration of normal connective tissue. Samples for cytologic evaluation can be collected at endoscopy by cytology brush or squash preparation, or by percutaneous fine-needle aspiration under ultrasound guidance, but in most cases intestinal biopsy is required. Percutaneous, ultrasound-guided biopsy of thickened SI and enlarged mesenteric lymph nodes sometimes is possible.

Histologic Findings

Routine Histopathology[1906-1911]

Although histopathologic assessment of biopsy material is the gold standard for diagnosis of AL, differentiation from severe LPE can be difficult, especially in endoscopic biopsies. Concurrent infiltration with eosinophils can occur and potentially cause misdiagnosis as a mast cell tumor. Further phenotyping can be required for a definitive diagnosis and could provide prognostic information.

Phenotyping[627,633,1682,1686,1906-1920]

Immunohistochemistry, flow cytometry, and assessment of T-cell clonality by PCR analysis of T- and B-cell receptor gene rearrangements improve the accuracy of diagnosis (see ch. 334). These molecular techniques allow a more accurate distinction of lymphoma from LPE and also classification of the lymphocyte lineage. Immunohistochemistry could aid in the diagnosis if all lymphocytes are found to be of a single lineage. B- and T-cell primary ALs have been reported in differing proportions, and clearly the original belief that all AL was always B cell in origin is incorrect.

Most recent research has been into feline AL, which seems to be increasing in incidence. Clinically, three main forms have been defined and all affect older cats (10-13 years) that are generally FeLV-negative. Intermediate- to high-grade AL often presents as a focal intestinal mass (sometimes with extraintestinal involvement). These are T- or B-cell tumors with a median survival time of 7-10 months following multiagent chemotherapy. Low-grade AL presents as diffuse intestinal thickening (sometimes with an intestinal mass and mesenteric lymph node involvement). These are mostly T-cell tumors with a median survival time of 19-29 months following chemotherapy with prednisolone and chlorambucil. Large granular lymphocyte lymphomas present as a focal intestinal mass (sometimes with extraintestinal involvement). These are mostly T-cell tumors (with immunohistochemical expression of granzyme B); median survival time is only 17 days after multiagent chemotherapy.

Pathologists have classified feline ALs using alternative terminology based on the human WHO classification as (1) mucosal T-cell lymphoma of small to intermediate cell type with involvement of the epithelium and lamina propria, (2) transmural T-cell lymphoma of large cell type that can show epitheliotropism and is most often a large granular lymphocyte lymphoma and (3) transmural B-cell lymphoma of large B-cell type.

Treatment and Prognosis[1884,1894,1903,1915,1921-1933]

Dogs with diffuse alimentary AL occasionally respond to multiagent chemotherapy (see ch. 344), but most respond poorly; and in those that do respond, there is a risk of intestinal perforation. The poor response is unlike canine multicentric lymphoma or lymphoma restricted to the canine rectum (see ch. 277). In contrast, the prognosis in cats is more favorable: some attain prolonged remission. Cell lineage appears to be important in determining the response to treatment and prognosis in cats: (1) mucosal T-cell lymphoma of small to intermediate cell type has long median survival time of 29 months, (2) transmural T-cell lymphoma of large cell type has a short median survival time of 1.5 months, and (3) transmural B-cell lymphoma has a median survival time of 3.5 months. Now, there is evidence that the first type (small cell) is increasing in incidence and fortunately has a much better prognosis than intermediate- and high-grade lymphomas. Good responses to combination chemotherapy have been reported, either with standard multidrug protocols or with an "oral-only" regimen (e.g., prednisolone and chlorambucil) for the small cell form. The latter treatment is well tolerated and could be particularly applicable to cases in which the differentiation between low-grade AL and LPE is uncertain, as the treatment is also applicable to severe IBD. Abdominal radiation therapy has been used as a rescue therapy.

Extramedullary Plasmacytoma[1934-1938]

These are rare tumors in the GI tract, and they occur mostly in the stomach or LI; they are sometimes found in the SI. They can be associated with a monoclonal gammopathy, but this has also been found in plasmacytic gastroenterocolitis.

Intestinal Adenoma and Adenocarcinoma[1857,1939-1954]

In dogs, both adenoma and adenocarcinoma are found more commonly in the LI than in the SI; the opposite is true in cats. In the canine SI, carcinoma has a predilection for the duodenum, whereas the jejunum and ileum are affected more commonly in cats (see E-Figure 276-11). Adenocarcinoma is most common in older dogs (mean age: 9 years) and cats (mean age: 11 years). Adenomas can be polypoid, whereas carcinomas are

more likely to grow as plaques or annular, stenotic lesions. Feline intestinal adenocarcinoma is more common than is adenoma, and Siamese cats might be over-represented, but adenomatous polyps are also seen in the feline SI. There is no known association with retrovirus infection in cats, and there is variable p53 expression in dogs.

Clinical Findings and Diagnosis[546,547,1862,1941,1950-1955]

Adenocarcinomata are locally infiltrative and can extend to the serosa and mesentery, and metastasize to local lymph nodes and/or the peritoneal cavity as well as hematogenously. Consequently, clinical signs relate to partial obstruction, or peritonitis when perforation has occurred, or intracelomic carcinomatosis. Abdominal palpation can reveal focal thickening of the intestine. Melena and anemia can be present if significant ulceration has occurred; the anemia usually is strongly regenerative but can become hypochromic and microcytic because of iron deficiency. Diagnostic imaging can delineate a mass lesion and ultrasound-guided FNAs can be helpful, although definitive diagnosis usually requires percutaneous (Tru-Cut) or surgical biopsy (see ch. 89).

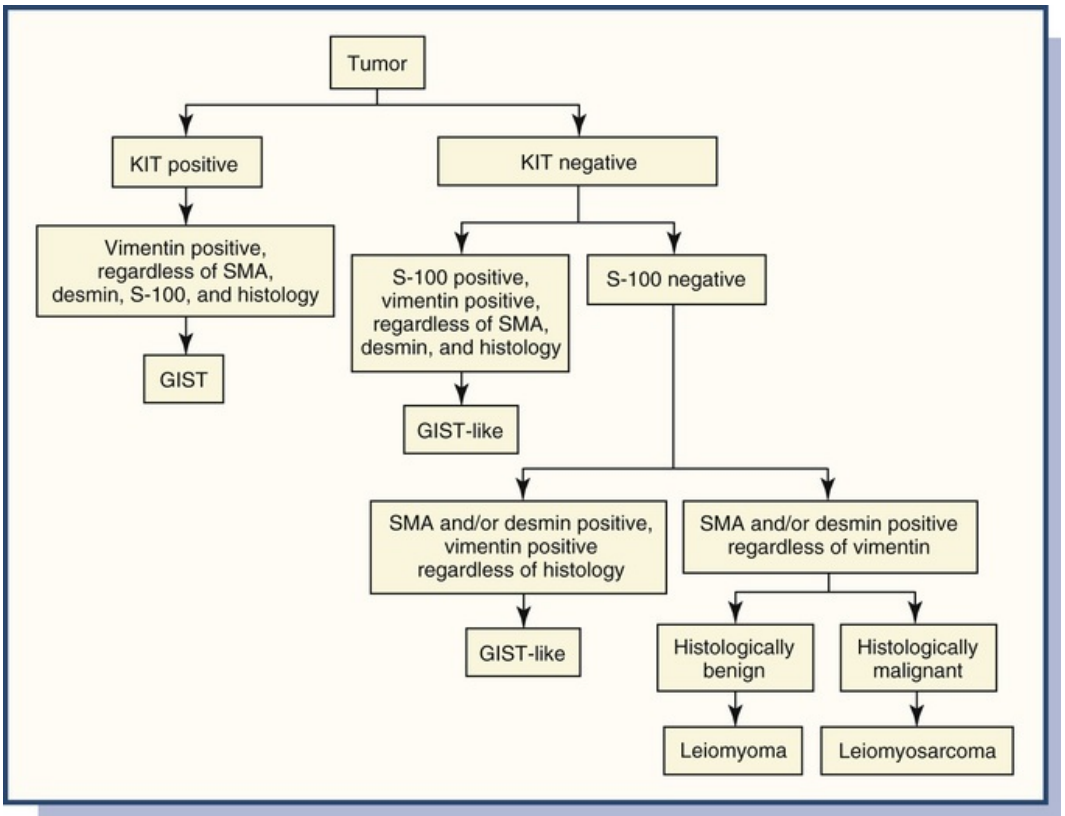
Treatment and Prognosis[1945,1956-1962]

Surgical resection is the treatment of choice. However, the prognosis usually is grave because tumors almost invariably have metastasized at the time of diagnosis. Remission times from surgery of up to 2 years have been reported, but survival time is often <6 months. For dogs, a median survival time of 10 months, with one- and two-year survival rates of 40.5% and 33.1%, respectively, are reported. Survival times are significantly shorter for dogs with histological evidence of metastasis at the time of surgery (median, 3.0 months) than for dogs with none (median, 15.0 months). Metastatic spread commonly involves local lymph nodes and the liver, as well as carcinomatosis, with metastasis to the testes, skin and other organs also reported. COX-2 expression has been documented in canine but not feline intestinal epithelial tumors and is a potential therapeutic target; standard adjunctive chemotherapy has not been demonstrated to be effective.

Smooth Muscle and Stromal Cell Tumors[1963-1981]

Smooth muscle tumors of the SI (leiomyoma and leiomyosarcoma) are an uncommon intestinal tumor of older dogs (average age: 10 years) and are rare in cats. The anatomical site in dogs typically is the jejunum or cecum, whereas in cats they are almost exclusively in the SI. The tumors often are nodular on the antimesenteric border. The histologic distinction between benign and malignant tumors is difficult, but metastatic spread of leiomyosarcoma to liver and local lymph nodes is uncommon anyway. The other tumor within this spectrum is the GI stromal tumor (GIST), which is histologically similar, but which arises from interstitial cells of Cajal.

The distinction of smooth muscle tumors from GISTs is by their differing expression of CD molecules such as CD34 and c-KIT (CD 117) and smooth muscle (vimentin, desmin, alpha-smooth muscle actin [SMA]) and neurogenic (S100, NSE, and synaptophysin) markers. Typically, smooth muscle tumors express SMA but are negative for the c-KIT (CD117) marker. Uncontrolled expression of c-KIT, a receptor tyrosine kinase, is an important marker of GISTs. Tumors otherwise resembling GISTs but showing no c-KIT expression are classified as GIST-like (E-Figure 276-25).



E-FIGURE 276-25 Classification of intestinal smooth muscle and stromal cell tumors. *GIST*, Gastrointestinal stromal tumor; *SMA*, alpha-smooth muscle actin. (Adapted from C. P. H. J. Maas: A new look in intestinal smooth muscle tumors: clinical histologic and immunohistochemical aspects for reclassification. Proceedings of the 18th Annual ECVIM Congress, Ghent, Belgium, 2008.)

Diagnosis[1982-1990]

Clinical Signs

Clinical presentation can vary and can include vomiting, diarrhea, anorexia, polyuria, polydipsia, melena, acute collapse, and weight loss. Many of these signs are the result of local tumor effects (i.e., obstruction, intussusception), acute bleeding, or iron-deficiency anemia. However, paraneoplastic effects are reported, especially hypoglycemia as a result of production of an insulin-like growth factor II–like peptide. Other paraneoplastic syndromes associated with leiomyosarcomas include erythrocytosis, due to the elaboration of an erythropoietin-like molecule, and nephrogenic diabetes insipidus (see ch. 352).

Laboratory Tests

Findings such as erythrocytosis or hypoglycemia reflect the consequences of direct or paraneoplastic effects, but test results can be unremarkable. Iron-deficiency anemia can develop without any overt GI signs due to chronic occult blood loss.

Diagnostic Imaging

Radiographs and especially ultrasound can aid the identification of a mass lesion (see ch. 88), and upper GI endoscopy can confirm the presence of a lesion if it is within reach and disrupting the mucosa (see ch. 113). However, pinch biopsies often are too superficial, and exploratory laparotomy is the technique of choice both for diagnosis and treatment.

Treatment and Prognosis[1991,1992]

The treatment of choice is surgical excision, and the prognosis is excellent for leiomyomas. Leiomyosarcomas are slow to grow and metastasize, and if surgical resection is complete the prognosis is good, with median survival times of 21 months. Prognosis is affected by gross, histologic, and immunohistochemical features such as tumor size, tumor location, mitotic index, AgNOR score, and Ki67 labeling. Even if metastasis is

evident at the time of surgery, the prognosis is reasonable, with prolonged survival reported in some cases. There appear to be no differences in prognosis for GISTs compared with smooth muscle tumors. In humans, the tyrosine kinase inhibitor imatinib prolongs survival in unresectable GISTs; clinical trials of masitinib and toceranib for canine GISTs are ongoing.

Amine Precursor Uptake and Decarboxylation Tumors[1993-1996]

Functional neuroendocrine, so-called amine precursor uptake and decarboxylation tumors (APUDomas)—vasoactive intestinal peptide tumors (VIPomas), pancreatic polypeptide tumors (PPomas)—have yet to be adequately described in dogs and cats. A functional carcinoid, with increased serum 5HT levels, has been described.

Other GI Neoplasms[1776,1781,1857-1861,1943,1952,1993,1994,1997-2012]

Rare tumors such as fibrosarcoma, osteosarcoma, schwannoma and nonfunctional carcinoid tend to be focally invasive and usually cause clinical signs similar to those of intestinal adenocarcinoma. Intestinal mast cell tumors tend to behave more like AL, but in cats they can be admixed with a marked fibrotic reaction and are described as feline sclerosing alimentary mast cell tumors (see above). Histiocytic sarcoma can infiltrate the SI and cause severe malabsorption. Hemangioma of the SI is very rare; hemangiosarcoma also rarely arises in the SI, but it does so more commonly in cats, wherein the signs often relate to hemorrhage and occasionally to mesenteric thrombosis. Intestinal melanoma is very rare. Hamartomatous polyps in dogs and adenomatous polyps affecting the SI in middle-aged cats can cause vomiting, hematemesis, or melena. However, chronic, occult blood loss can occur, and animals can present with iron-deficiency anemia. Ganglioneuromatosis is a very rare benign proliferation of ganglion and glial cells; in most species it occurs between muscle and submucosal layers, but a mucosal lesion that was successfully resected has been reported in a dog.

Other Small Intestinal Disorders

Adynamic Ileus and Intestinal Pseudo-Obstruction

Definition and Clinical Presentation[63,274-278,483,484,2013-2036]

Adynamic ileus is a common sequel to a variety of primary GI problems—abdominal surgery, parvoviral enteritis, pancreatitis, peritonitis, hypokalemia—and dysautonomia (see Boxes 276-5 and 276-10). Postoperative ileus can occur after any abdominal surgery. It is caused by a combination of local inflammation, increased inhibitory sympathetic tone, and often, the use of opioid analgesics. It is of clinical significance because it increases morbidity and prolongs hospitalization.

Dysautonomia often shows multiorgan involvement, affecting pupillary function, salivation, and bladder function, as well as gastroesophageal and intestinal motility. An epidemic in UK cats in the 1980s (so-called Key-Gaskell syndrome) waned, perhaps due to withdrawal of a potentially toxic but unidentified dietary component, but sporadic cases still are seen worldwide in both dogs and cats.

The term *intestinal pseudo-obstruction* describes a condition in which patients show clinical evidence consistent with an obstruction, but no mechanical cause can be found. The condition has been associated with both visceral neuropathies and myopathies in humans, and such causes can occur in small animals. There are many single case reports in the literature in dogs, but very few in cats. Most cases are associated with idiopathic leiomyositis and sclerosing enteropathy, with fibrosis and a mononuclear cell infiltrate of the tunica muscularis. Smooth muscle alpha-actin deficiency has been described in one Bengal cat, and feline intestinal pseudo-obstruction also can be secondary to intestinal lymphoma.

Management[490,2022,2037-2048]

After the possibility of mechanical obstruction has been eliminated, management of both adynamic ileus and intestinal pseudo-obstruction is aimed at identifying any underlying cause and providing specific treatment. Nonspecific therapy to stimulate intestinal motility also is indicated. Suitable prokinetic agents include the 5-HT_4 receptor agonists cisapride or mosapride, the D_2 dopaminergic antagonist metoclopramide, acetylcholinesterase inhibitors such as acotiamide, and motilin-like drugs such as erythromycin. In dogs and cats, cisapride appears to be the most effective agent, but it is no longer available in many countries because of human toxicosis. Antibacterials also can be appropriate, given the probability of secondary SIBO. Feeding is beneficial in humans, and nutritional support can be continued indefinitely, although vomiting and constipation or diarrhea usually continue. Unfortunately, most cases of idiopathic pseudo-obstruction reported in the veterinary literature have responded poorly to therapy, and the prognosis is grave; just one case responding to immunosuppressive dosages of corticosteroids combined with prokinetics has been reported.

Surgical Intestinal Disorders

Intestinal Obstruction[499,501,503,523,2049-2094]

Intestinal obstruction can be the result of extraluminal, intramural, or intraluminal lesions and can be classified as acute or chronic, partial or complete, and simple or strangulated. Most intraluminal obstructions are caused by a variety of foreign objects; radiolucent objects (socks, peach pits, corn cobs) can be the hardest to identify. Intramural causes of obstruction include intestinal neoplasia, parasites (rarely), hematomas (which are believed to occur spontaneously), granulomas (e.g., focal FIP, phycomycosis, embedded hair), and strictures (e.g., after foreign body impaction or surgery). Extraluminal causes include entrapment by hernias, mesenteric tears, congenital and acquired adhesions, and intussusceptions.

Most cases of SI obstruction can be identified on plain abdominal radiographs (see Figure 276-17). A dilated bowel >1.6× the height of the body of L5 at its narrowest point has been considered highly predictive of SI obstructions, but the value of such formulae is debated. Linear foreign bodies cause bunching of the SI and a characteristic pattern of comma-shaped gas bubbles. Ultrasonography is useful in detecting radiolucent foreign bodies, intussusceptions, and intramural obstructions, but intestinal gas accumulation can obscure the lesion.

The prognosis for surgical cure depends on the cause of the obstruction, the presence of perforation and peritonitis, the viability of the remaining intestine, and the severity of any associated metabolic abnormalities. Recovery is aided by a rapid return to enteral nutrition. The outcome is likely to be favorable with simple foreign bodies, but it is guarded for linear foreign bodies as it is likely that there are multiple perforations,

and it is grave for animals with volvulus or metastatic intestinal neoplasia. The patient is at risk of developing short bowel syndrome if an extensive length of SI must be resected (see below).

Intussusception[1858,1997,2095-2138]

The most common extraluminal cause of obstruction is intussusception, and ileo-colic intussusception is the most common anatomical variant. In severe cases the *intussusceptum* can migrate through the *intussuscipiens* and out through the anus, where it can be mistaken for a rectal prolapse. Retrograde, midjejunal and double intussusceptions are reported, whereas duodenogastric intussusceptions are rare and can cause vomiting and shock, although they could be reducible by endoscopy (Figure 276-26). Younger animals are more likely to develop intussusceptions, especially after a case of gastroenteritis or after intestinal surgery, and Maine Coon cats could be predisposed. Increased risk exists after experimental renal surgery, toxicoses affecting intestinal motility, congenital hypothyroidism, and postparturient queens. Neoplasia is the more frequent cause in middle-aged and older animals, with the mass acting as a nidus for the in-folding of the SI. Intussusceptions have also been associated with acute kidney injury due to leptospirosis.

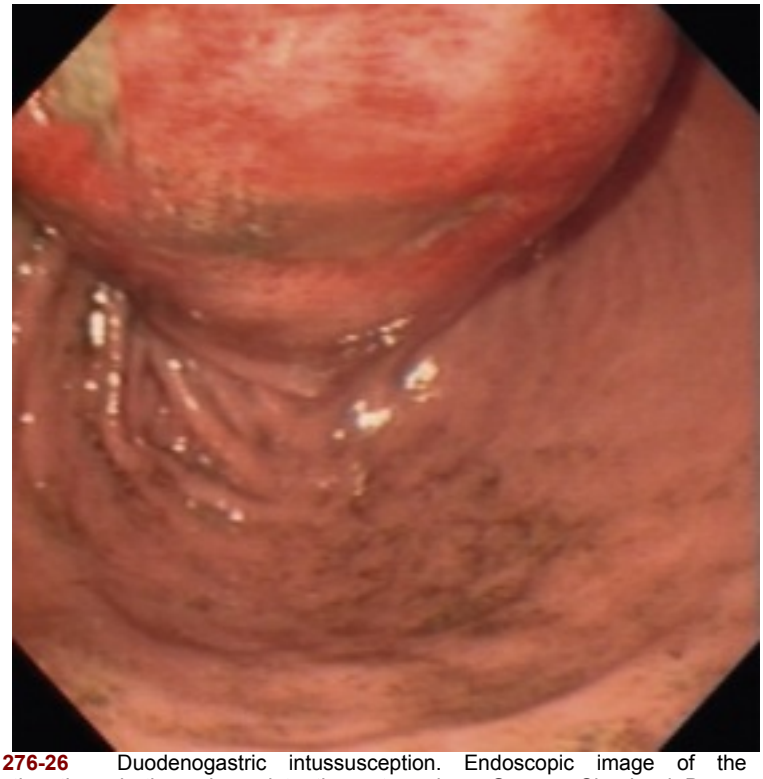


FIGURE 276-26 Duodenogastric intussusception. Endoscopic image of the duodenum intussuscepting through the pylorus into the antrum in a German Shepherd Dog presented for evaluation of vomiting.

The diagnosis of an intussusception is made via a combination of history, palpation of a "sausage-shaped" abdominal mass, radiographic evidence of a mass and SI obstruction, and ultrasonographic demonstration of a characteristic double-walled structure (Figure 276-12, *C*). Transient, clinically silent intussusceptions and spontaneous reductions after obstruction have been reported, but in most clinically affected cases, surgical correction is required. This can involve simple reduction or actual resection of the affected region with end-to-end anastomosis. Recurrence is a recognized risk and can in part be related to damage to the enteric nerves in the region. Rather than paralyze the SI postoperatively with antimuscarinic drugs, a rapid return to feeding and normalization of intestinal motility are recommended. Enteroplication can be performed to try to prevent recurrence, but it carries risks of perforation, entrapment, and stricture.

Intestinal Strangulation[558,2066,2139-2146]

Strangulation can occur if loops of bowel are incarcerated in umbilical or inguinal hernias; an internal hernia through a surgically-induced defect in the mesentery; omental, mesenteric or duodenocolic ligament tears; or

entrapment by adhesions following pubic bone fracture, or intraabdominal lipomas. As well as causing obstruction, intestinal ischemia is likely with the risk of reperfusion injury following surgical correction, or perforation if not corrected.

Intestinal Volvulus[2070,2110,2147-2156]

In this condition, the intestines rotate around the mesenteric axis, compromising the cranial mesenteric artery, and consequential complete vascular obstruction can lead to infarction. The typical radiographic finding is marked gas distension of much of the small intestine. Confirmation is made at surgery, and the possibility of euthanasia on the operating table should be discussed with the owner if laparotomy reveals diffuse intestinal ischemia and necrosis. Reports are sporadic and fortunately rare, as the prognosis is grave.

Intestinal Perforation[2068,2071,2157-2179]

SI perforation leading to septic peritonitis is caused most frequently by NSAID administration, ingestion of linear foreign bodies, and ingestion of sharp nondigestible objects (e.g., cocktail sticks, needles) or if the diagnosis of any SI foreign body has been delayed. Perforation by sharp bone fragments is reported rarely and might not be as much of a risk as the public has been led to believe; bones are softened by, and even dissolved in, gastric acid. Ingestion of multiple magnets has been associated with perforation, presumably because of necrosis of the bowel wall between two objects attracted magnetically. Traumatic avulsion of a mesenteric vessel will lead to ischemia and delayed perforation of the relevant intestinal segment. Tumors and fungal granulomas can perforate, and islands of heterotopic gastric mucosa in the SI also are prone to ulceration and even perforation.

Short Bowel Syndrome[2180-2191]

Short bowel syndrome (SBS) refers to the situation that occurs when large lengths of the SI (more than two thirds) are absent because of resection or, rarely, a congenital anomaly. Cases of SBS are mercifully rare in cats and dogs, as the option of euthanasia for severe cases exists and much information on management has been extrapolated from human GI surgery.

Clinical Signs

Clinical signs (e.g., diarrhea) are a result of insufficient functional mass of SI for assimilation of nutrients and electrolytes. In some cases, SBS can occur transiently after resection because adaptive hyperplasia in the remaining intestine can lead to subsequent clinical improvement. The degree of malabsorption depends on the length of intestine resected; in dogs, experimental studies suggest that removal of up to 85% of the intestine can be tolerated. The site of resection also is important: removal of the ileo-colic valve predisposes to ascending bacterial colonization. Massive resection also precipitates changes in GI hormones, leading to hypergastrinemia and increased acid secretion.

Diagnosis

The diagnosis of SBS usually is based on a history of intestinal resection with consequent diarrhea and weight loss. If a congenital lesion is suspected, contrast radiography can demonstrate the shortened SI length.

Treatment[2192-2195]

After massive resection, intensive parenteral fluid therapy (see ch. 129) and parenteral nutrition (see ch. 189) should be instigated. Oral feeding is restricted but not withheld completely because the presence of food, bile, and pancreatic secretions in the gut are important stimuli for intestinal adaptation. An isotonic, oligomeric, fat-restricted liquid diet can be fed initially, with a gradual transition first to a polymeric liquid diet and then to an easily assimilated, fat- and fiber-restricted diet. Malabsorption of fat- and water-soluble vitamins and minerals also can occur, and dietary or parenteral supplementation could be required. Parenteral cobalamin supplementation is essential if the ileum has been resected. H2-receptor antagonists or proton pump inhibitors can be used in the postoperative period to counteract possible hypergastrinemia. Antimicrobial agents can be necessary if the ileocecocolic junction has been resected or if secondary SIBO is suspected. If the response to diet and antibiotics is poor, antisecretory agents (loperamide, diphenoxylate, or octreotide) could be required. Bile salt binding resin (e.g., cholestyramine) might help reduce colonic secretion caused by bile salts malabsorbed after ileal resection; ursodeoxycholic acid has been shown to enhance intestinal adaptation in a feline surgical model.

Prognosis[1742]

The prognosis depends on the amount of SI left and response to therapy. Some animals undergo remarkable adaptive hyperplasia and can return to a normal diet, whereas others never respond adequately. Complications of human SBS include gallstones, oxalate uroliths, and D-lactic acidosis. In refractory cases, experimental surgical GI modifications to slow intestinal transit and increase absorptive area have been described; reconstruction, regeneration, or intestinal transplantation might be feasible in the future.

Irritable Bowel Syndrome

Definition and Diagnosis[2196-2198]

Irritable bowel syndrome (IBS) is characterized by recurrent, usually acute, episodes of abdominal pain, borborygmi, and diarrhea but which more commonly causes signs of LI dysfunction (see ch. 277). Disordered intestinal motility can be of primary importance (Box 276-19) because in the absence of morphologic changes, a functional disorder is considered the cause of this enigmatic problem.

Box 276-19

Potential Causes of Irritable Bowel Syndrome

- Primary motility disorders
- Psychosomatic disorders
- Undiagnosed food intolerance
- Undiagnosed inflammatory disease
- Visceral hyperalgesia

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CHAPTER 277

Diseases of the Large Intestine

Edward James Hall

Client Information Sheets:
Chronic Colitis
Granulomatous Colitis

Normal Structure and Function

Grossly, the canine and feline large intestine (LI) are simple tubular structures, comprising the colon, a small cecal diverticulum, and the rectum. However, they play a critical role in the control of fluid homeostasis, the host's interaction with the intestinal microbiome, and the storage and regulated evacuation of fecal material. Disorders of the LI are common in dogs and cats, and may cause either diarrhea or constipation and, if ulceration is present, the passage of fresh blood (*hematochezia*; see ch. 41). Importantly, most LI disorders, although usually not fatal, can have a significant effect on the patient's quality of life (QOL); children with chronic LI disease are recognized to have a very poor QOL,[1] and the distress caused to dogs, cats and their owners by LI disease is often evident in veterinary practice,[2] although QOL is not easily quantified.

Structure

Macroscopic Anatomy[3-8]

Anatomically, the tubular LI continues from the distal small intestine (SI), beginning at the ileocolic sphincter and ending at the anus, and is composed of three anatomically distinct sections: the cecum, the colon, and the rectum (Figure 277-1, *A*). The colonic section comprises three poorly delineated segments (right, transverse and left colon) demarcated by flexures which are not very pronounced, especially in cats where the transverse colon is also very short. The colon is supported on a loose mesentery, the mesocolon, so that its position on lateral radiographs may be in the dorsal or mid-abdomen.

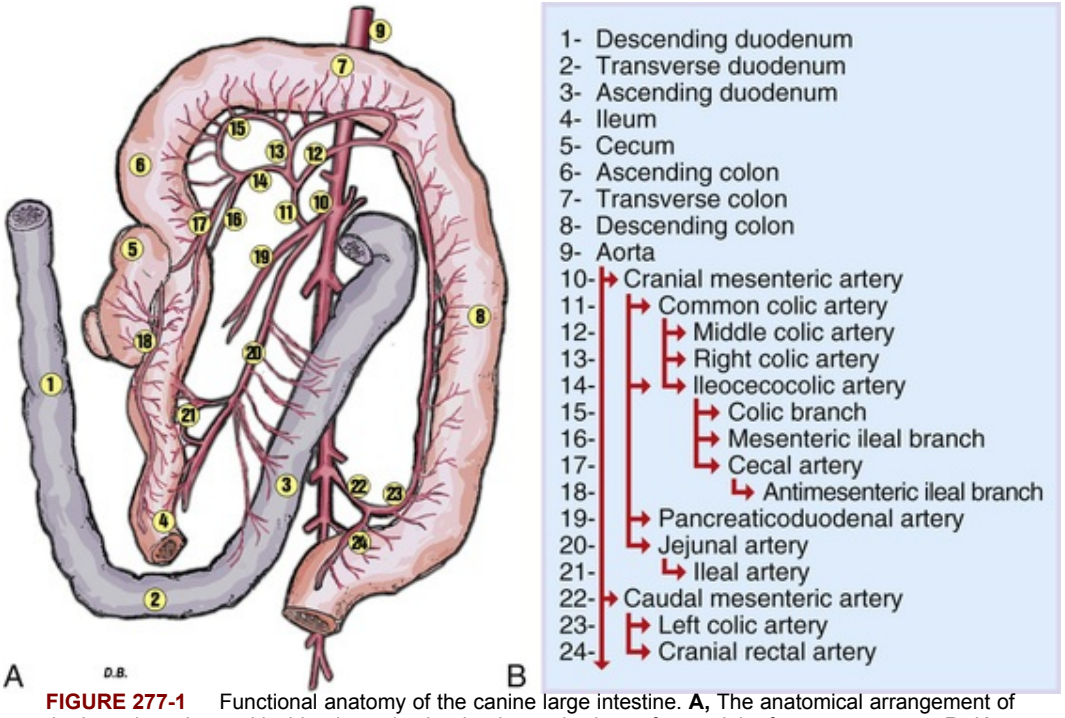


FIGURE 277-1 Functional anatomy of the canine large intestine. **A,** The anatomical arrangement of the large intestine and its blood supply; the duodenum is shown for spatial reference purposes. **B,** Key: Schematic representation of the sections of large intestine, and the divisions of its arterial blood supply. (Adapted and redrawn from Lecoindre P, Gaschen F, Monnet E, editors: *Canine and feline gastroenterology*, France, 2010, Wolters Kluwer.)

The gross structure of the colon is relatively simple with no longitudinal bands of muscle (taeniae), as seen in the human colon and, normally, no sacculations (haustra). The diameter of the colonic lumen is variable depending on the volume of gas and feces within, but it is generally twice the diameter of the SI. On average the LI is 60 to 75 cm long in dogs (range 25 to 90 cm), and ranges from 20 to 45 cm in cats. In both dogs and cats it contributes 20 to 25 per cent of the total (small and large) intestinal length.

Ileocolic Sphincter

The ileocolic papilla can be visualized during flexible colonoscopy: in dogs it appears endoscopically as a raised, mushroom-like protuberance (Figure 277-2, *A* and E-Figure 277-3), but in cats it is often quite flattened and slit-like. It is a sphincter through which liquid ileal contents periodically enter, and adjacent to it is the ceco-colic orifice, which leads into a blind-ending cecum.

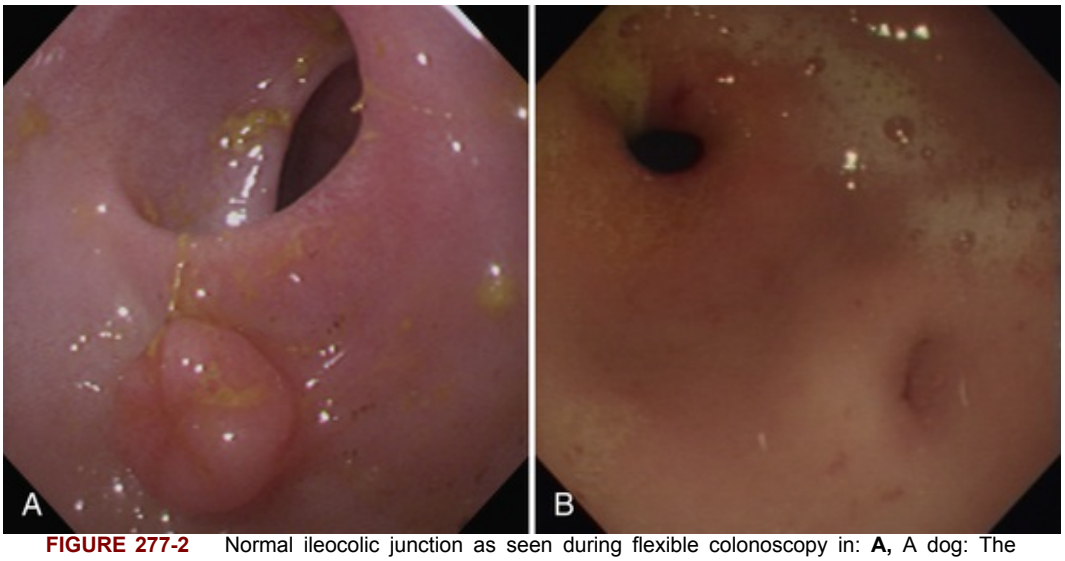
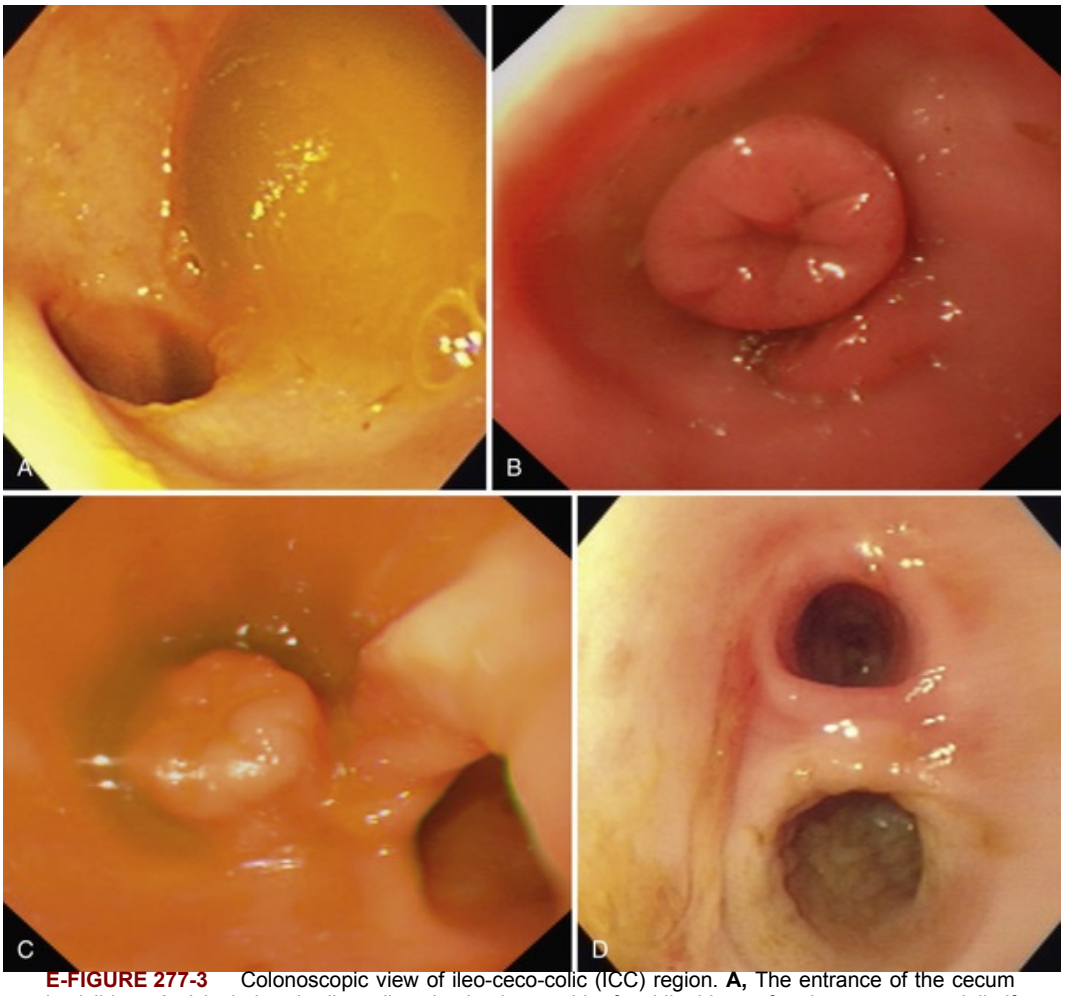


FIGURE 277-2 Normal ileocolic junction as seen during flexible colonoscopy in: **A,** A dog: The

mushroom-shaped ileocolic papilla is seen below the cecal orifice. **B,** A cat: The ileocolic papilla is much flatter and the cecum much smaller and shorter than in dogs.



E-FIGURE 277-3 Colonoscopic view of ileo-ceco-colic (ICC) region. **A,** The entrance of the cecum is visible at 8 o'clock, but the ileocolic valve is obscured by fecal liquid, as often happens, especially if cleansing has been inadequate. **B,** The ICC region is clear of material and the mushroom shaped IC papilla, with a central lumen, is visible. The cecal orifice is obscured by the flattened papilla. **C,** The ileocolic (IC) papilla is visible, with the adjacent cecum spiraling away from it. **D,** The ICC region in a dog after successful ileoscopy. Both the IC (uppermost) and cecal orifices are wide open, with thickening due to their respective sphincter muscles being visible.

Cecum

The cecum is a diverticulum arising from the proximal colon; the ceco-colic orifice is separate from the ileocolic papilla, and has its own sphincter muscle (see E-Figure 277-3, *D*). It lies approximately midway between the right flank and median plane, ventral to the duodenum at the level of the 3rd and 4th lumbar vertebrae, separated from it by the greater omentum. The canine cecum ranges from 8 to 30 cm in length and is sigmoid, spiraling towards its rounded, blind end. Ventrally it is attached to the antimesenteric border of the ileum. The cecum in cats is less twisted and is shorter (2 to 4 cm) and narrower, making endoscopic intubation difficult.

Proximal Colon

The colon runs cranially from the ileo-colic papilla as the *ascending* or *right* colon, which is the shortest colonic segment in dogs; the cecal appendage arises in the proximal right colon no more than 1 cm from the ileocolic papilla. The colon then turns at the *right colic* or *hepatic* flexure to pass across the body as the *transverse* colon, adjacent to the greater curvature of the stomach and left limb of the pancreas, and cranial to the root of the

mesentery. The right and transverse colon together are functionally considered the *proximal colon.*

Distal Colon

The transverse colon turns caudally in the cranial abdomen at the *left colic* or *splenic* flexure, becoming the *left* or *descending* colon, which is considered functionally to be the *distal colon.* The left colon is the longest colonic segment, and passes caudad past the ventromedial border of the left kidney and ventral to the sublumbar musculature and lymph nodes. At the level of the pelvic brim it becomes the rectum.

Rectum

The rectum is generally considered to be totally within the pelvic canal, starting where the cranial rectal artery enters and terminating at the anal canal. It is 4 to 6 cm long and 3 to 4 cm wide in average-sized dogs, and its middle portion is slightly wider, forming a rudimentary bulb. It normally lies midway between the sacrum and floor of the pelvis on lateral radiographs. Like the colon, it also has a smooth surface with no indentations. However, only the cranial half is covered in peritoneum; the distal half is retroperitoneal. The mucosa forms transverse folds which smooth out when the rectum is distended. The anatomy of the recto-anal region is described in ch. 278.

Blood Supply[9]

The cranial and caudal mesenteric arteries supply blood to the LI, and the pattern of distribution is important when planning any surgical resection (see Figure 277-1, *B*). The cranial mesenteric artery supplies the cecum and ascending colon via the ileo-ceco-colic and right colic branches respectively, and the transverse colon via the middle colic artery which anastomoses with the right and left colic arteries. The caudal mesenteric artery supplies the left colic artery which runs cranially along the left colon to anastomose with the middle colic artery, and caudally to anastomose with the cranial rectal artery. The rectum is supplied by the middle and caudal rectal arteries as well as the cranial rectal artery. Of these, the cranial rectal artery supplies the majority of the blood to both the terminal colon and rectum, and ideally should be preserved during any colonic/rectal resection. The veins of the colon all terminate in the portal vein, although veins from the retroperitoneal rectal segment can pass to the caudal vena cava.

Lymphatics[10,11]

Lymph from the colon drains to segmental (right, middle, and left) colic lymph nodes associated with the roots of the cranial and caudal mesenteric arteries. The number of nodes varies from one to nine, with an average of four. This is of importance in the surgical planning of any LI resection, although collateral drainage is established quite quickly.

Innervation[12-14]

The vagus nerve provides parasympathetic innervation to the proximal colon, whilst the pelvic nerves supply the distal colon. Sympathetic nerves arise from the paravertebral ganglia and follow the mesenteric arteries and lumbar splanchnic nerves to the LI. The intestines also contain an intramural nervous system, which is located between the longitudinal and circular muscle layers, and in the submucosa. Parasympathetic pre-ganglionic fibers and sympathetic post-ganglionic fibers synapse on cell bodies and dendrites of the intrinsic nervous system. Reflex pathways control colonic wall movement, water and electrolyte secretion, and local blood flow.

Microscopic Anatomy[7,8,15-37]

Histologically, the LI resembles the structure of the SI (see ch. 276), comprising four layers: mucosa, submucosa, muscularis, and serosa (Figure 277-4).

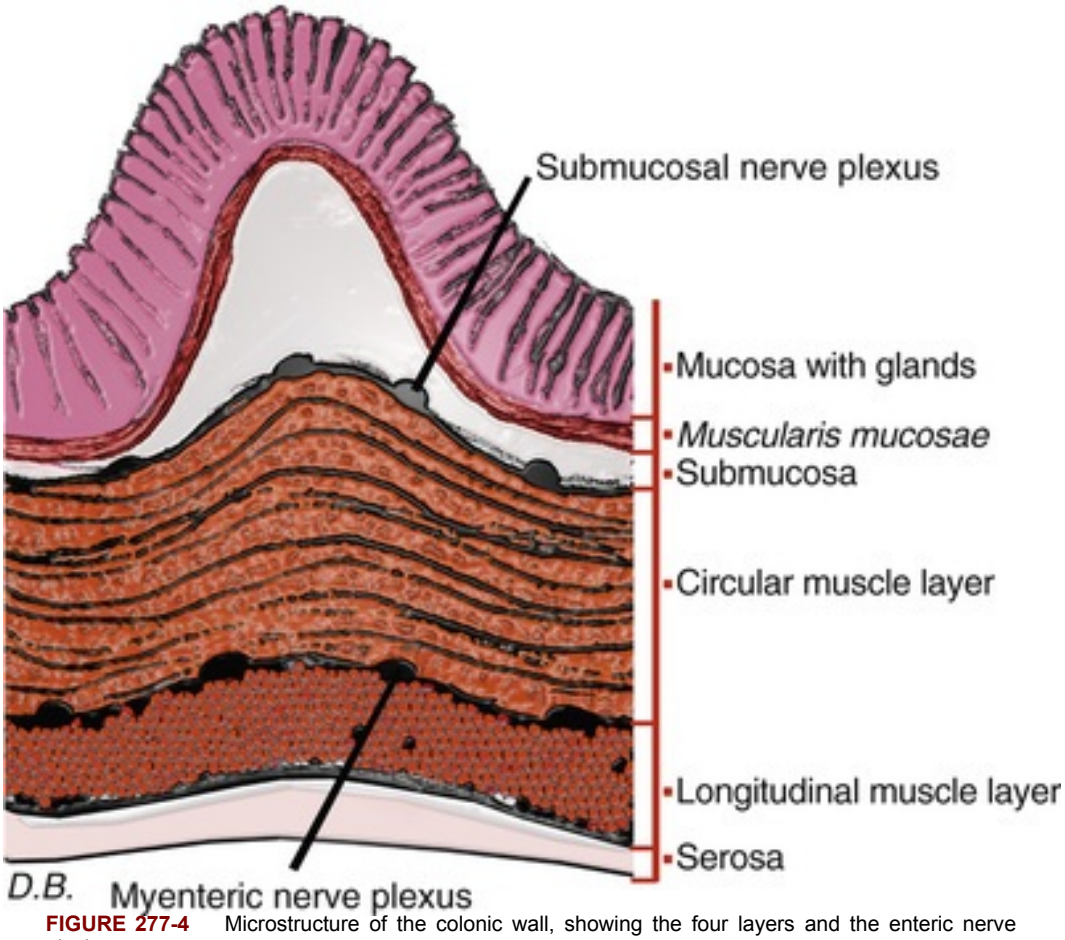


FIGURE 277-4 Microstructure of the colonic wall, showing the four layers and the enteric nerve plexi.

Mucosa

In comparison to the microscopic structure of the SI, the LI is a flat surface with no villi and the epithelial colonocytes expressing fewer microvilli, but there are many more mucus-secreting goblet cells (Figure 277-5).

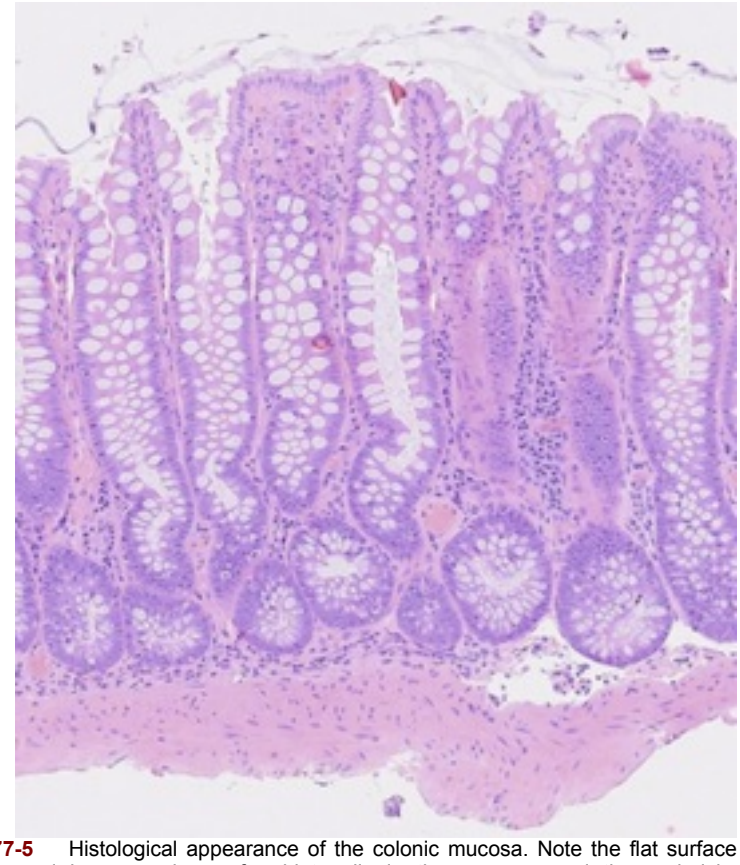


FIGURE 277-5 Histological appearance of the colonic mucosa. Note the flat surface with mucus, deep crypts and large numbers of goblet cells in the mucosa, and the underlying muscularis mucosae. (Image courtesy Michael Day, University of Bristol.)

Epithelium

Numerous straight, tubular crypts (≈500 microns long) are present in the colon, extending through almost the entire thickness of the mucosa. These crypts produce the epithelial, mucus-producing, and endocrine cells. Cells at the base of crypts continually divide and proliferate, migrating to the top of the epithelium as they mature: the cell turnover is slower than in the SI (four to seven compared to three days), but is affected by growth hormone (GH) with GH receptors up-regulated during colonic repair. As colonocytes migrate upwards, they differentiate and mature into epithelial cells, goblet cells, or endocrine cells. Ultimately these cells undergo apoptosis and slough into the lumen.

The flat absorptive surface is lined by a single layer of columnar cells lying on a basement membrane and interspersed with goblet cells (10 to 25 goblet cells per 100 epithelial cells). Goblet cells are important in the LI as they produce mucus that inhibits bacterial invasion as well as lubricating the passage of feces. The endocrine cells secrete somatostatin, polypeptide P, insulin-like growth factors, and glucagon-like peptides. Intraepithelial lymphocytes consist predominantly of the CD8+ T cell subtype.

Lamina Propria

The colonic intraepithelial lymphocytes migrate from the lamina propria (LP), which contains the various components of the mucosal immune system resembling those found in the LP of the SI (see ch. 276), namely mostly lymphocytes and plasma cells, with mast cells, macrophages, eosinophils and neutrophils present in lower numbers. Colonic LP lymphocytes are predominantly CD4+ T cells and IgA-secreting B cells and plasma cells. The overall structure of the mucosal immune system and the gut-associated lymphoid tissue (GALT) is described in more detail in ch. 274 and 276. The other cellular elements of the colonic LP include fibroblasts and enteric neurons which interact with both immune cells and the colonocytes.

Muscularis Mucosae

The innermost layer of the mucosa is separated from the submucosa by the thin layer of the *muscularis mucosae*.

Submucosa

The submucosa of the colon resembles that of the SI: it contains numerous blood and lymph vessels, and dense extracellular matrix sparsely infiltrated by fibroblasts and immune cells, with unmyelinated nerve fibers and ganglion cells forming the submucosal (Meissner's) plexus. The interstitial cells of Cajal are located on the submucosal surface of the circular smooth muscle, and play a dual role as smooth muscle pacemaker cells and as mediators of neuromuscular transmission in the colon. The submucosa is folded, and stretches and flattens when the colon is distended with gas or feces.

Muscularis

The colonic smooth muscle is composed of inner circular and outer longitudinal muscle layers, with the myenteric (Auerbach's) plexus interposed.

Serosa

This layer is composed of mesothelial cells covering the portions of the LI found within the peritoneal cavity. Its serous secretion lubricates and reduces friction caused by intestinal movements.

Function

The interaction of the microflora with colonic immune cells is an important part of the mucosal immune system (see ch. 274). However, the major functions of the colon are (1) the absorption of water and electrolytes from the proximal colon to produce feces of a suitable consistency, and (2) their storage in the distal colon and rectum to allow evacuation at an appropriate time through the coordinated process of defecation.

The LI is not primarily a digestive organ, but microbial fermentation of undigested material occurs within it, with usage by colonocytes of the short chain fatty acids (SCFAs) produced. Curiously, the canine colonic mucosa has also been shown to have the ability to transport amino acids and simple sugars but, except in neonates, it probably has no significant nutritional role compared with SI uptake.[38] However, it may form part of the adaptive mechanism seen in short bowel syndrome.

Absorption and Secretion of Water and Electrolytes[39-49]

The healthy LI has a large absorptive capacity and is able to absorb up to 90 per cent of the water entering the colon in order to produce feces of an acceptable consistency. Indeed it has some reserve capacity that can absorb increased amounts if some SI diarrhea enters the colon, but is overwhelmed if larger volumes of ileal content enter. In LI disease, the colon has a reduced capacity, which also leads to diarrhea.

Water is absorbed by passive osmosis following the active absorption of sodium, which largely occurs in the proximal colon. Absorption of sodium from, and secretion of potassium into the colonic lumen is also moderated by aldosterone and glucocorticoids, which stimulate the activity of the Na^+/K^+-ATPase pump. Sodium uptake is not linked to glucose absorption in the LI, and glucose-containing oral rehydration fluids are of no value in managing diarrhea of colonic origin.

Potassium is absorbed via a K^+/H^+ exchange transporter, but can be actively secreted in the distal colon. These mechanisms complement the control of potassium homeostasis by the kidneys. Chloride absorption follows the electrochemical gradient maintained by active sodium absorption, and by chloride-bicarbonate exchange. The colonic pH is more acidic than the SI, and is maintained by the exchange of sodium and potassium against bicarbonate and chloride: bicarbonate also neutralizes organic acids produced by luminal bacteria.

Mucus[50-55]

Colonic mucus is a mixture of high molecular weight glycoproteins or mucins produced by goblet cells and exfoliated epithelial cells. Mucin secretion is dependent on chloride secretion via the cystic fibrosis transmembrane regulator (CFTR), and exocytosis. Mucus is produced not only as a lubricant, thereby facilitating defecation, but also to protect the mucosa from damage. Pathogens and enterotoxins can be bound by mucus before they reach the epithelium as it acts as a physical barrier, but goblet cells also secrete antibacterial molecules and growth and repair factors, such as trefoil factors. Deficiencies in the mucus layer can predispose to or potentiate intestinal inflammation with increased amounts of mucus secreted in colitis or after parasympathetic stimulation.

Motility[13]

In order to perform its primary functions of water and electrolyte absorption in the proximal colon and the storage and control of defecation in the distal colon and rectum, LI motility and its coordination by the enteric nervous system are complex but crucial. A congenital lack of enteric ganglia in a section of the distal colon and rectum of children causes Hirschsprung disease.[86] The affected section requires surgical resection, but the condition has only ever been described in one cat and never in dogs.[87]

The inherent, spontaneous, contractile ability of normal colonic smooth muscle is influenced by the enteric nervous system and a range of transmitters including cholecystokinin, neurotensin, somatostatin, serotonin and substance P, as well as acetylcholine and epinephrine/norepinephrine from the autonomic nervous system.

There are regional differences in colonic motility patterns to facilitate the differing functions of the proximal and distal colon. In the proximal colon, smooth muscle tone together with electrical slow-wave activity, called rhythmic phasic contractions (RPCs), allow mixing of content and absorption of water. This function is enhanced by retrograde giant contractions (RGCs) initiated in the transverse colon and propagated towards the cecum, causing antiperistalsis. In the distal colon, migrating spike bursts and powerful giant migrating contractions (GMCs) propel the feces towards the rectum and help to expel them.

The sympathetic nervous system acts primarily to restrict progression of contents towards the rectum by inhibiting the activity of the enteric neurons that control motility and by relaxing the non-sphincter muscles and contracting the sphincters. Sympathetic activation also suppresses the secretion of water and electrolytes in the colonic lumen. Thus, sympathetic activity acts to reduce the need to defecate, which is appropriate during a "fight or flight" situation.

The control of defecation is discussed in detail in ch. 278. Briefly, it is a reflex that can be moderated by conscious processes so that in health it occurs at an appropriate time and place. The defecation reflex may be triggered by ingestion of a meal (gastrocolic reflex) as well as distension of the distal colon and rectum. Stimulation of the reflex causes contraction of colonic and rectal smooth muscle, usually commencing with GMCs, and relaxation of the anal sphincter at the same time as the patient adopts the required posture. Voluntary contraction of the anal sphincter can temporarily inhibit defecation, but ultimately the urge may overcome this control. In the diseased LI, the threshold for the urge to defecate is reduced, and so the animal typically defecates after only a small amount of fecal matter has accumulated in the rectum, and it continues to strain unproductively (fecal tenesmus) as it still has the urge although no rectal contents remain to be passed. Difficulty or pain on defecation (dyschezia) is a sign of recto-anal disease (see ch. 42 and 278).

Colonic Microbiome[43,88-106]

The colonic microbiome has essential functions interacting with the mucosal immune system, providing energy for utilization by colonocytes, and synthesizing amino acids and vitamins (see ch. 274). The colon harbors the highest concentration of bacteria in the gut, with up to 10^{12} organisms per gram of feces, representing ≈50% of fecal dry matter. In addition, fungal elements and some protozoa are normally present.

The bacterial species within an individual healthy animal's microbiome is relatively stable, but is influenced by age, breed, geographic locale, housing conditions, coprophagy and diet, and is altered in inflammatory conditions. Each individual animal has a unique bacterial flora, although each tends to have related organisms within each class that occupies a specific ecological niche within the LI. Historically, the composition of the colonic microflora, based on routine culture of feces, was believed to be mainly anaerobic bacteria, with species such as *Bifidobacterium, Bacteroides,* and *Clostridium* dominating, and with few aerobic bacteria, such as lactobacilli, enterobacteriaceae, and streptococci in dogs. Approximately equal numbers of aerobic and anaerobic bacteria were found in cat feces. However, most bacteria in the LI cannot be cultured *in vitro,* and up to 70% could represent unknown species. Using high throughput 16S rRNA gene sequencing, it is now possible to identify almost all bacterial DNA in the feces. Fusobacteriales are most abundant in the colon (≈33% of all identified clones), followed by Bacteroidales (≈30%) and Clostridiales of the cluster XIVa (≈26%). It has been shown that bacterial diversity in the gastrointestinal (GI) tract increases towards the colon in healthy dogs, and is depressed by the administration of antibiotics.

The colonic microflora metabolizes carbohydrates, proteins, and lipids into the SCFAs acetate, propionate, and butyrate, with byproducts of hydrogen, methane, sulfa compounds and carbon dioxide. Fermentable fiber which is not digested by the SI is a major substrate for the bacteria. The SCFAs produced by the bacteria are metabolized by colonocytes and provide an important energy supply to the LI epithelium. SCFAs also promote proliferation and differentiation of colonocytes, stimulate water and electrolyte absorption, and modify colonic motility. In addition, butyrate produced by commensal bacteria can induce anti-inflammatory cytokines such as interleukin (IL)-10.

The normal colonic bacterial microflora has an important function in mediating protection against pathogenic bacteria through a variety of mechanisms including competition for substrates and for mucin binding sites. Chronic intestinal inflammation is linked to alterations in composition of the bacterial population, and feeding of a fiber-free diet has been shown to induce colitis.

Immune Surveillance[7,23,107-112]

The healthy mucosal immune system in the gut evolves to be tolerant of food antigens and commensals, but remains able to respond rapidly to pathogenic microbes. The functional anatomy of the gut-associated lymphoid tissue (GALT) is described in detail in ch. 274 and 276. In the LI, it consists of inductive sites including lymphoid follicles in both the colon and rectum plus the colonic lymph nodes, and effector sites within the LP. So-called microfold (M) cells are particularly abundant in the epithelium overlying the lymphoid follicles in the LI which contain dendritic cells (DCs). The DCs in the LP have the important role of continuously sampling antigens from the lumen by extending dendrites between the epithelial cells, then activating various different immune cells of the adaptive immune system (T cells and B cells) as described in ch. 276. In addition, intestinal epithelial cells can act as non-professional antigen-presenting cells by continuously sampling antigens from the intestinal lumen and presenting them to LP cells through expression of major histocompatibility complex (MHC) II, as well as producing cytokines that will influence immune responses in the LP.

The innate immune system—comprised mainly of epithelial cells, macrophages, and DCs—appears to determine the ensuing immune response. Dysregulation of the balance between tolerance and inflammation can contribute to development of disease. Intestinal epithelial cells also constantly recognize commensals by their binding to toll-like receptors (TLRs). In the presence of commensals, and in normal intestinal homeostasis, a balance between effector and regulatory subpopulations of T cells is maintained through a tightly controlled cytokine network (see ch. 276).

Diagnostic Evaluation

The diagnostic investigation of colonic disease is guided by information obtained from the history and physical examination, absence of any signs of systemic illness, and whether the disease is acute or chronic or has occurred previously as this affects the differential diagnosis list (see Box 277-2). Logical diagnostic approaches to large bowel diarrhea, hematochezia and constipation are shown in Figure 277-6.

Box 277-2

Differential Diagnoses to Consider in Cats with Chronic Constipation[50]

Neuromuscular Dysfunction

Colonic smooth muscle: idiopathic megacolon, aging
Spinal cord disease: lumbosacral disease, cauda equina syndrome, sacral spinal cord deformities (Manx cat)
Hypogastric or pelvic nerve disorders: traumatic injury, malignancy, dysautonomia
Submucosal or myenteric plexus neuropathy: dysautonomia, aging

Mechanical Obstruction

Intraluminal: foreign material, neoplasia, rectal diverticula, perineal hernia, anorectal strictures
Intramural: neoplasia
Extraluminal: pelvic fractures, neoplasia

Inflammation

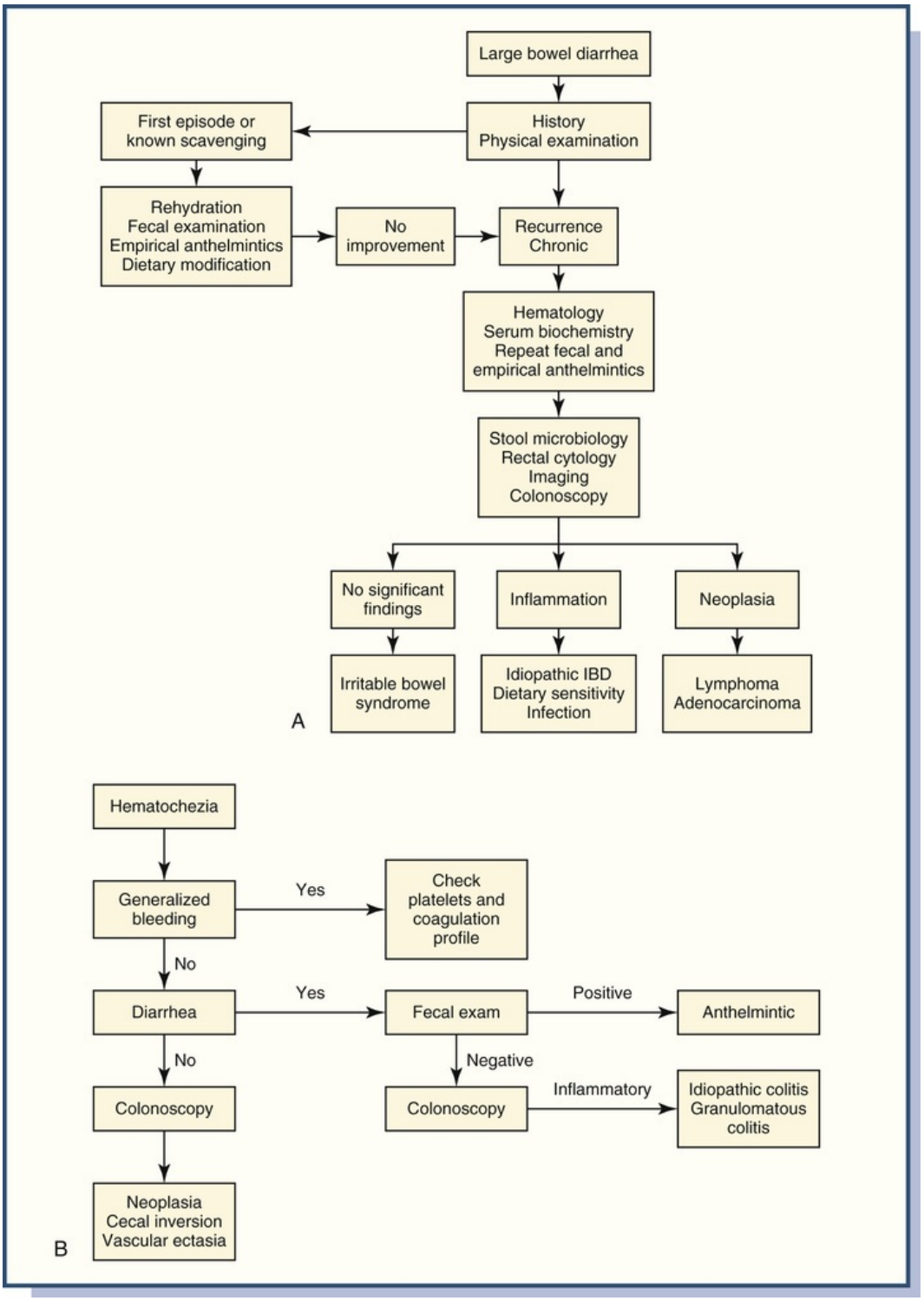
Perianal fistula, proctitis, anal sac abscess, anorectal foreign bodies, perianal bite wounds

Metabolic and Endocrine

Metabolic: dehydration, hypokalemia, hypercalcemia
Endocrine: hypothyroidism, obesity, nutritional secondary hyperparathyroidism

Environmental and Behavioral

Soiled litter box, inactivity, hospitalization, change in environment



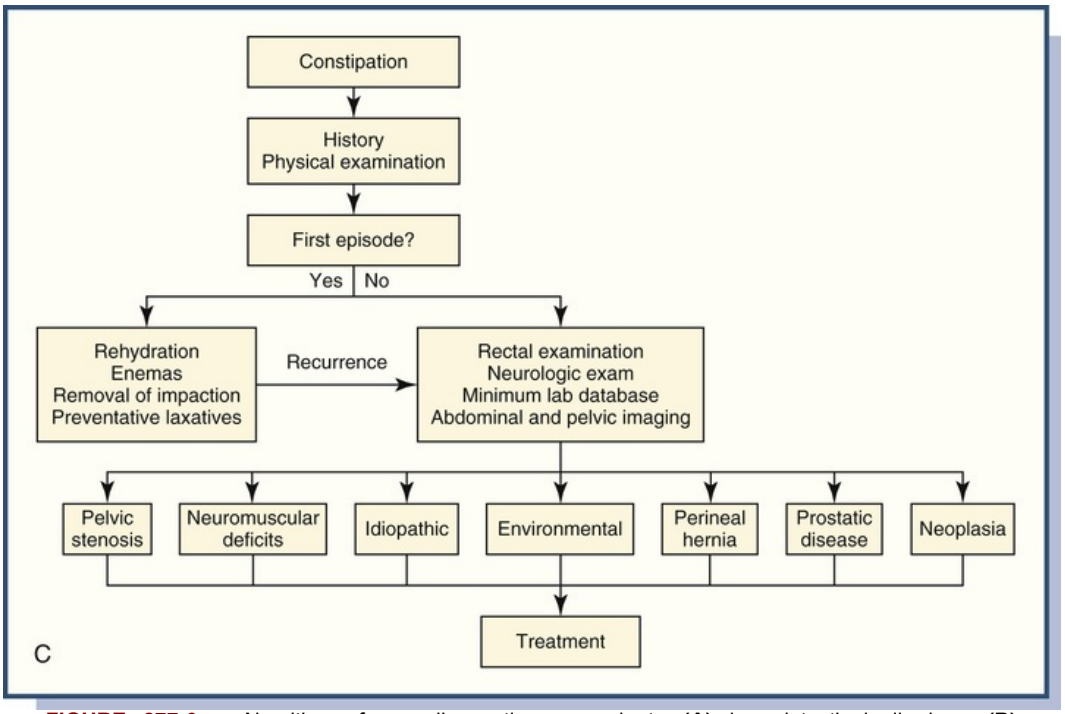


FIGURE 277-6 Algorithms for a diagnostic approach to **(A)** large-intestinal diarrhea, **(B)** hematochezia, and **(C)** constipation. *IBD*, Inflammatory bowel disease.

History

Dogs and cats with LI disease are usually presented for diarrhea, constipation, and/or hematochezia. Standard questions include those about the animal's diet, environment, travel history, vaccination, parasiticide treatments, concurrent medical diseases and any problems in in-contact animals. Weight loss is not a feature of LI disease except with advanced neoplastic conditions, or when the owner tries to control diarrhea by restricting food intake.

The owner should be specifically questioned about the pet's fecal consistency and character, and the frequency of defecation. Some historical findings, such as the presence of mucus in the feces (Figure 277-7), urgency, increased frequency, with or without hematochezia, and tenesmus after defecation are typical of LI diarrhea (Table 277-1). The presence of hematochezia indicates LI ulceration, and once a generalized bleeding problem has been ruled out, is suggestive of severe inflammation, *Ancylostoma* hookworm and *Trichuris* whipworm infection, intussusception or neoplasia.

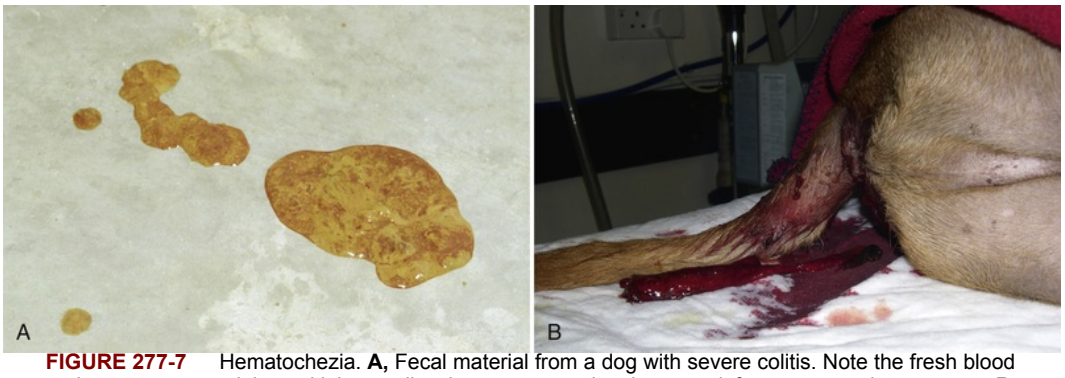


FIGURE 277-7 Hematochezia. **A,** Fecal material from a dog with severe colitis. Note the fresh blood and mucus, passed in multiple small volumes suggesting increased frequency and tenesmus. **B,** Hematochezia in a dog with severe colitis.

TABLE 277-1

Clinical Signs Associated with Large Bowel Diarrhea

SIGNS	FREQUENCY
Weight loss	Uncommon
Vomiting	Uncommon
Flatulence	Unusual
Defecation frequency	Marked increased in frequency
Fecal volume	Normal to mild decrease
Urgency	Usually present
Tenesmus	Usually present
Mucus in feces	Frequently present
Hematochezia	Often present
Abnormal stool color (e.g., green)	Rare
Melena	Absent
Steatorrhea	Absent

Constipation refers to reduced or absent defecation for several days to weeks. Sequelae include dehydration, weight loss, abdominal pain, and mild to moderate mesenteric lymphadenopathy. Tenesmus is also seen in constipation, but typically no feces are produced. However, occasionally the owner may report that the pet produces a few drops of fecal liquid that they may mistake for diarrhea, as secretions ooze past the impacted feces. Environmental factors (e.g., hospitalization, dirty cat litter) and dehydration which may predispose to constipation may be determined during history taking.

Clinical scoring schemes (the Canine and Feline Inflammatory Bowel Disease Activity Indices [CIBDAI, FIBDAI] and Canine Chronic Enteropathy Clinical Activity Index (CCECAI) and Feline Chronic Enteropathy Activity Index (FCEAI) have been published in an attempt to correlate clinical signs to disease outcomes.[113-115] Such scoring makes monitoring before and after treatment more objective and allows for comparisons of clinical severity between studies (see ch. 276). Young dogs with mild severity scores for colitis have been shown to respond well to elimination diets alone and have the best outcomes.

Physical Examination

Routine physical examination of dogs and cats with LI diarrhea may reveal no abnormalities. Attention should be given to findings such as pyrexia (cecal or colonic perforation, fungal infections) or uveitis (protothecosis, lymphoma, feline infectious peritonitis). Careful abdominal palpation is required to identify abdominal pain (colitis, colonic neoplasia, perforation), abdominal masses (colonic neoplasia, granulomatous colitis, ceco-colic or ileo-colic intussusception), SI thickening (concurrent SI inflammation or lymphoma), mesenteric lymphadenopathy (colitis, lymphoma, disseminated fungal diseases), and hepatosplenomegaly (lymphoma, disseminated fungal diseases).

Constipation is the second most common sign in patients presenting with underlying colonic disease, and is usually obvious on abdominal palpation or rectal examination. Although environmental factors may predispose to constipation, emphasis should be placed on finding underlying causes such as abdominal masses (neoplasia, prostatomegaly), abdominal pain (foreign bodies, colonic perforation), painful defecation (anal furunculosis/perianal fistulae, anal sac abscessation), autonomic neuropathy (dysautonomia), hindlimb paresis (spinal cord lesions), pelvic fractures, and perineal hernias.

In all cases of suspected LI disease, a digital rectal examination is mandatory, although this may require general anesthesia in cats and very small dogs. Recto-anal lesions such as anal sac abnormalities, perineal hernia, strictures, and rectal polyps and other rectal neoplasms should be palpable, and prostatic disease can be simultaneously evaluated as a cause of constipation (see ch. 111 and 337). Palpable irregularities of the colonic mucosa are suggestive of inflammatory or neoplastic infiltrations. At the end of the examination, rectal cytology can be performed by smearing the gloved finger on a microscope slide and staining with Diff-Quik or Wright's stain. A fecal sample can also be collected, and previously unrecognized diarrhea or hematochezia identified.

Laboratory Investigations[116,117]

Minimum Database

Routine laboratory analyses that include a complete blood count (CBC, serum biochemistry profile, and urinalysis are indicated in most cases of chronic colonic disease, but may be unnecessary in mild, acute disease. There are no pathognomonic hematologic or serum biochemical changes in patients with LI disease, but abnormal results can provide diagnostic clues. Abnormalities associated with colonic signs and their potential differential diagnoses are listed in Table 277-2.

TABLE 277-2

Abnormalities Associated with Colonic Disease and Their Potential Causes

FINDING	POTENTIAL CAUSE
Mild to moderate non-regenerative anemia	Chronic disease
Regenerative anemia (hypochromic, microcytic iron-deficiency if chronic bleeding)	Blood loss • Hookworms and whipworms • Intussusception and cecal inversion • Colitis • Neoplasia • Vascular ectasia
Leukocytosis	• Inflammation • Infection • Neoplasia
Eosinophilia	• Parasitism • Hypoadrenocorticism • Mast cell tumor • Hypereosinophilic syndrome • Paraneoplastic (lymphoma, anal sac adenocarcinoma, etc.)
Hypoalbuminemia	• Bleeding • Negative acute phase reaction • Concurrent protein-losing enteropathy
Hyperglobulinemia	• Feline infectious peritonitis • Intestinal inflammation • Neoplasia
Hypercalcemia	• Neoplasia • Fungal granulomas • *Heterobilharzia* infection
Hypoglycemia	• Leiomyosarcoma • GI stromal tumor (GIST) • Large abdominal tumor
Hyponatremia and concurrent hyperkalemia	• Hypoadrenocorticism • Salmonellosis • *Trichuris* infection

There are no pathognomonic laboratory changes in patients with colonic disease, but abnormal results can provide diagnostic clues.

Additional Laboratory Tests

Even in the absence of signs typical of SI disease, serum cobalamin and folate concentrations should be measured in animals with presumed colonic disease (see ch. 276). Low serum cobalamin concentrations indicate disease affecting the distal SI, even when the clinical presentation is more typical of colitis: indeed, persistent SI diarrhea could be the cause of colonic inflammation. Ileal biopsies, obtained via colonoscopy (see ch. 113), are indicated if serum cobalamin is abnormal.

Extension of pancreatic inflammation can also cause inflammation of the adjacent regions of the colon and signs of colitis. Thus, pancreatic lipase immunoreactivity (PLI) measurement may be indicated if there is any

suspicion of pancreatitis (see ch. 290 and 291). Similarly, depending on the index of suspicion, serologic tests for fungal disease could be indicated (see ch. 233 and 236).

In cats with chronic colitis or constipation, feline leukemia virus (FeLV; see ch. 223) and FIV (see ch. 222) testing should be performed, and serum thyroxine measured if there is diarrhea in an older cat (see ch. 301).

Fecal Examination[118-128]

Fecal parasitology (see ch. 81), including direct smears and zinc sulfate flotation, should be completed in all animals before colonoscopy, and empirical administration of broad-spectrum parasiticides may also be trialled first, especially in areas where *Trichuris* infection is endemic. Although primarily a SI parasite, *Giardia* organisms may also be involved in colitis and can be identified, not only by fecal flotation, but by an immunochromatographic test (Witness, SNAP) or by immunofluorescent staining (see ch. 221).

There are several methods for detecting *Tritrichomonas* infection in cats.[129,130] Infection may be identified in a fresh fecal sample: a drop of fresh diarrhea is mixed with a drop of warm saline on a slide, cover-slipped and examined under the ×40 microscope objective. Progressively motile trophozoites may be observed, but the test is quite insensitive. More sensitive are the InPouch culture system or polymerase chain reaction (PCR), for which a diarrheic sample is required, and for which a high colonic flush may be performed. Contamination of the sample with cat litter should be avoided as it may inhibit the PCR reaction.

Fecal bacterial culture is generally performed in dogs and cats with chronic colitis.[119,131-136] Colonic inflammation may be associated with infection by *Campylobacter* spp., *Clostridium perfringens* and *C. difficile*, *Salmonella* spp., and possibly *Yersinia* spp. However, these organisms can also be found in the stool of healthy animals, positive cultures must be interpreted in light of other clinical findings, and sometimes trial therapy will more effectively identify such infections. PCRs for a number of these organisms are now available and may be more sensitive as they do not require live organisms to be present, especially as *Campylobacter* spp. are quite fragile and soon die in *ex vivo* samples.

Quantitative culture of bacteria from the colon is not recommended, as the number of cultivable bacterial species in the colon is estimated to encompass only about 30% of the total microbiome. There is little information available on the specific microbiome abnormalities in the colon of dogs and cats with colitis, but it is likely that composition will be altered specifically for different diseases, as has been shown to be the case in humans with Crohn's disease or colonic cancer, and cats with inflammatory bowel disease (IBD).[137]

Cytology[138,139]

Cytology can be performed after digital rectal examination, by using a gloved finger or a cotton-tipped applicator to wipe the rectum, or by using cytology brushes endoscopically during colonoscopy (E-Figure 277-8). Typically, bacteria and debris predominate, but occasionally causative agents can be identified including fungal elements, neoplastic cells, or inflammatory cells such as lymphocytes, eosinophils, or neutrophils (Figure 277-9 and E-Figure 277-10).

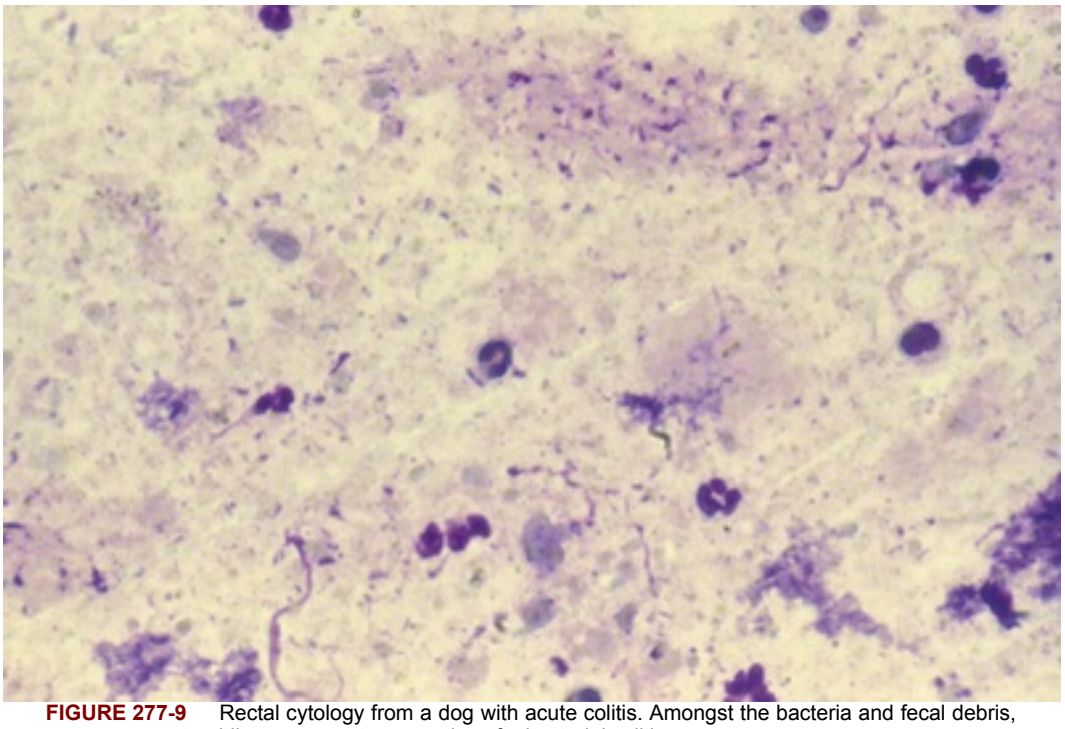
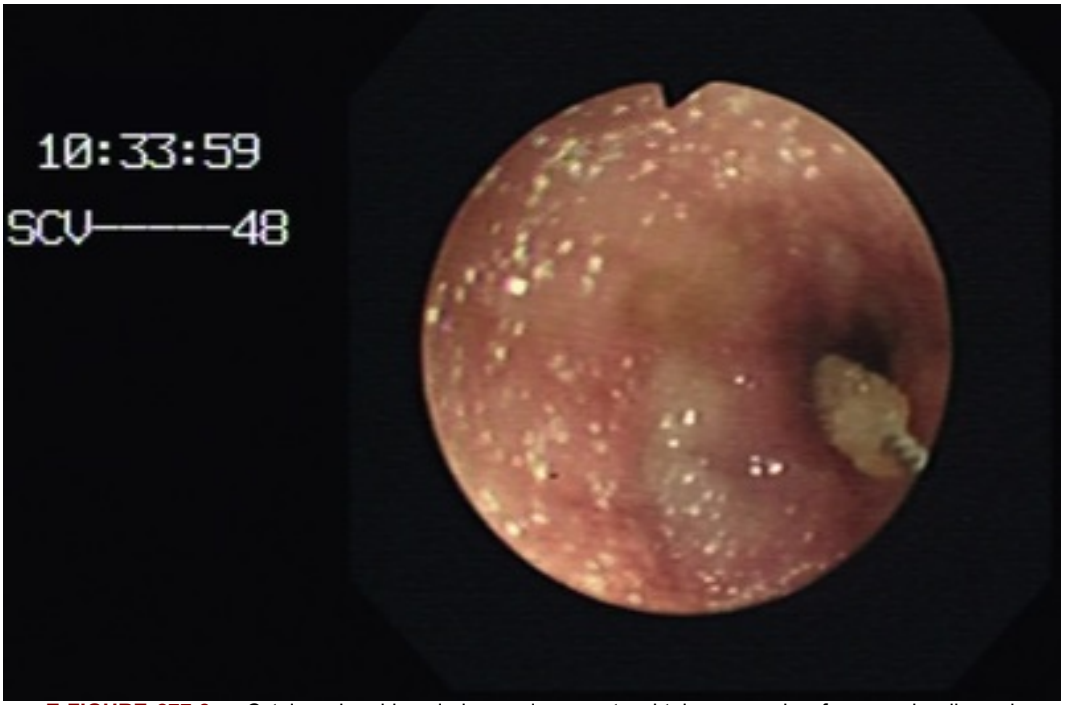
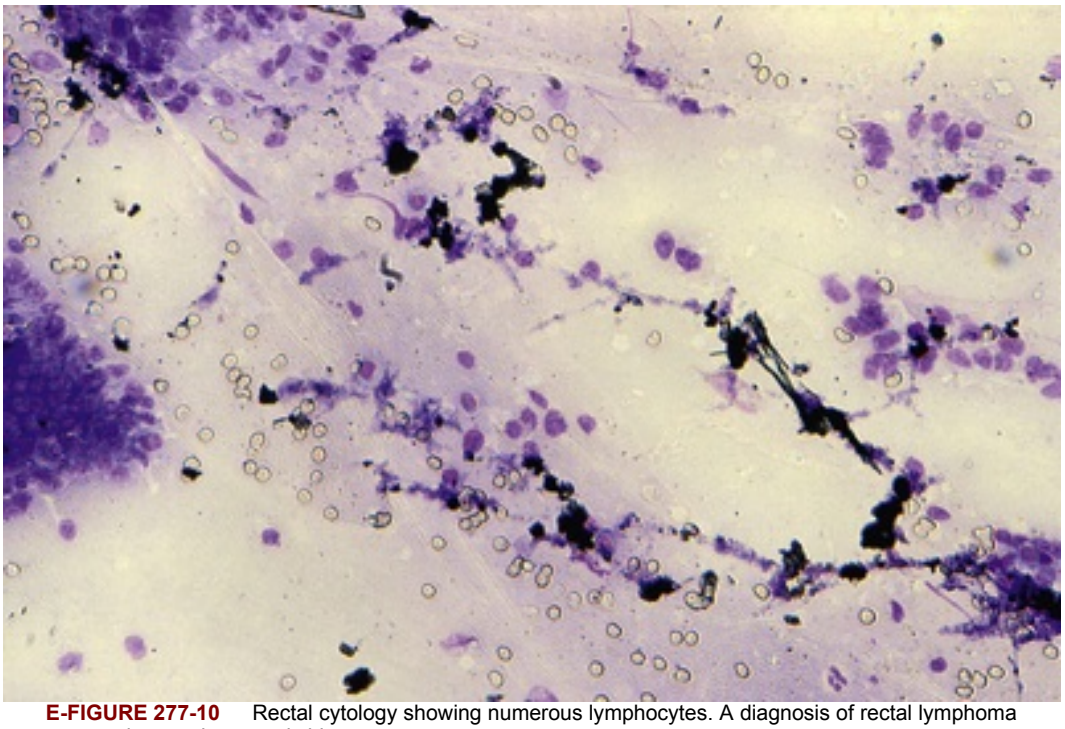


FIGURE 277-9 Rectal cytology from a dog with acute colitis. Amongst the bacteria and fecal debris, numerous neutrophils are present, suggestive of a bacterial colitis.



E-FIGURE 277-8 Cytology brushing during endoscopy to obtain a sample of mucosal cells and adherent bacteria.



E-FIGURE 277-10 Rectal cytology showing numerous lymphocytes. A diagnosis of rectal lymphoma was made on colonoscopic biopsy.

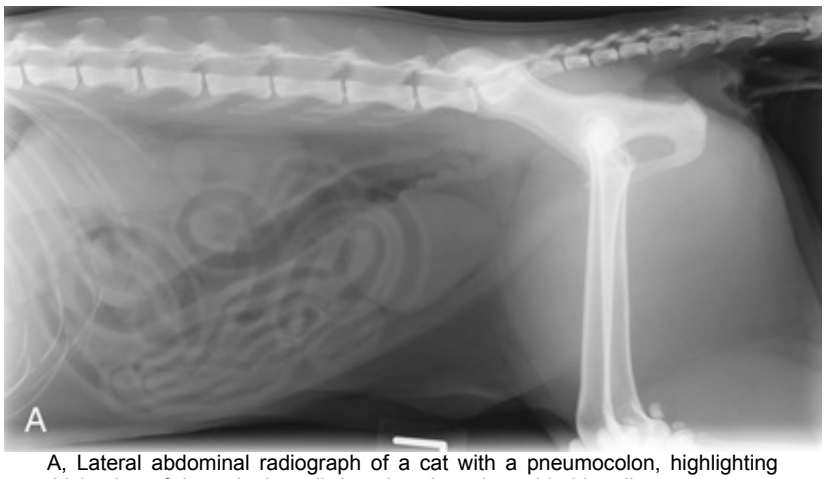
Imaging

Plain lateral and ventrodorsal radiographs of the abdomen and pelvic region can be useful in patients with hematochezia, dyschezia or suspected constipation, potentially identifying obstructions and megacolon, and confirming constipation; they are less likely to be helpful in patients with LI diarrhea, whereas ultrasonography may be more useful.

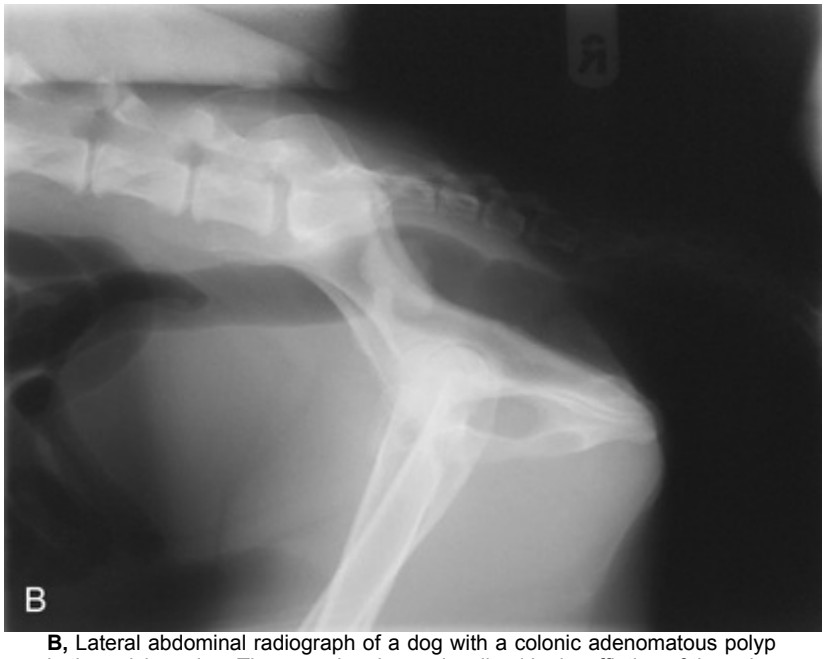
Radiography[140-144]

Survey radiographs may identify radiopaque foreign bodies, fecal impaction and extra-luminal causes of obstruction such as pelvic canal stenosis or prostatomegaly. Discrete masses in the colon are only likely to be detected if there is luminal gas to highlight them but sublumbar lymphadenopathy may give a clue to metastatic disease.

Sometimes it may be difficult to differentiate between gas-filled SI and colon and therefore to detect a SI obstruction. A negative contrast colonogram, insufflating with air when the colon is empty, may help in determining which structure on the radiograph is the colon, as well as potentially highlighting colonic wall thickening and masses (Figure 277-11). Thus a pneumocolonogram can be helpful, although it may preclude performing ultrasonography immediately afterwards because the gas interferes with the ultrasound. Colonic torsion is rare but may be identified radiographically by gaseous distension and displacement of the colon within the abdomen.[145-149]



A, Lateral abdominal radiograph of a cat with a pneumocolon, highlighting thickening of the colonic wall dorsal to the urinary bladder. (Image courtesy Virginie Barberet, University of Bristol.)



B, Lateral abdominal radiograph of a dog with a colonic adenomatous polyp in the pelvic region. The mass has been visualized by insufflation of the colon with air before taking the radiograph.

FIGURE 277-11

Pneumatosis coli, a form of *pneumatosis cystoides intestinalis,* is a very rare manifestation of colonic disease in live animals, although a recognized feature in post-mortem specimens following putrefaction. Free gas is visualized within the colonic wall below the submucosa or serosa. It can be associated with colitis or colonic neoplasia, or may be idiopathic and resolve spontaneously.[150-155]

Radiographs taken after a positive contrast follow-through study will eventually show barium in the colon and lesions may occasionally be identified (Figure 277-12). However, filling is often incomplete, and a barium enema is more likely to show problems such as intussusception, cecal inversion, and stricture. However, barium enemas, and especially double contrast studies,[144] are rarely performed nowadays unless

colonoscopy is unavailable. Positive contrast studies are unpleasant to perform, and prone to artifact as retained feces may mimic a filling defect caused by mass, also the normal narrowing of the colon at the pelvic brim is sometimes misinterpreted as a stricture.

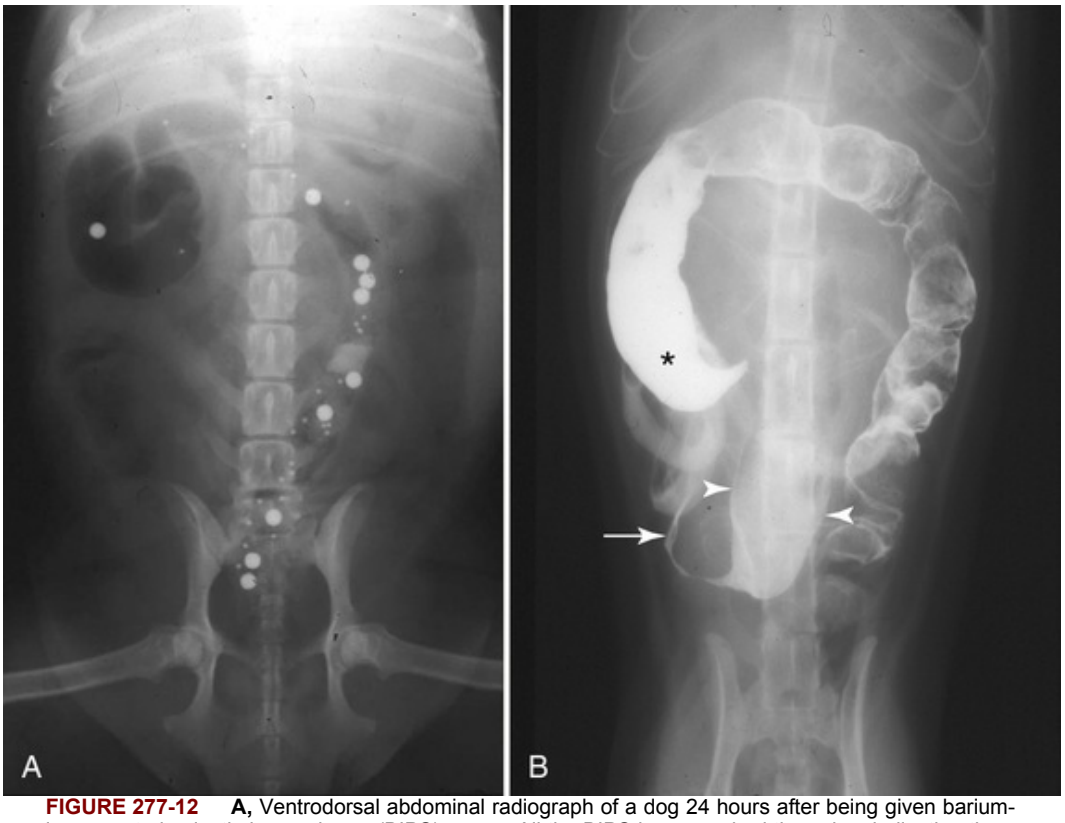


FIGURE 277-12 **A,** Ventrodorsal abdominal radiograph of a dog 24 hours after being given barium-impregnated polyethylene spheres (BIPS) *per os*. All the BIPS have reached the colon, indicating there are no partial obstructions preventing their passage. Gas fills the coiled cecum and proximal colon; fecal material is present in the distal colon. **B,** Ventrodorsal abdominal radiograph of a Siamese cat 24 hours after the oral administration of barium suspension. Barium fills the pointed cecum and the colon (asterisk), but a dilated small intestinal loop (arrowheads) is seen connected to the proximal colon by a thin streak of barium (arrow). This "apple core" sign is consistent with an ileal mass, and a carcinoma was confirmed at surgery.

Advanced imaging of the LI is possible,[156-159] and is especially useful for imaging the LI within the pelvic canal. "Virtual endoscopy" using helical CT has been developed in humans to identify colonic polyps and carcinomas, although it may not be as sensitive as colonoscopy.

Ultrasonography[143,160-169]

Using abdominal ultrasound, the ileum, ileocecal junction, cecum, and ascending, transverse, and descending colon can all potentially be identified (see ch. 88). A perineal approach is indicated if abnormalities are suspected in the intrapelvic LI.

If distended, a normal colon should have three layers and a thickness of ≤2 mm. An undistended colon may give an appearance of wall thickening, but the presence of air in the lumen can make it difficult to assess the whole organ. In colitis, there are often no radiographic or ultrasonographic findings or just diffuse thickening of the mucosa; focal infiltration and intramural masses are more suggestive of LI neoplasia.

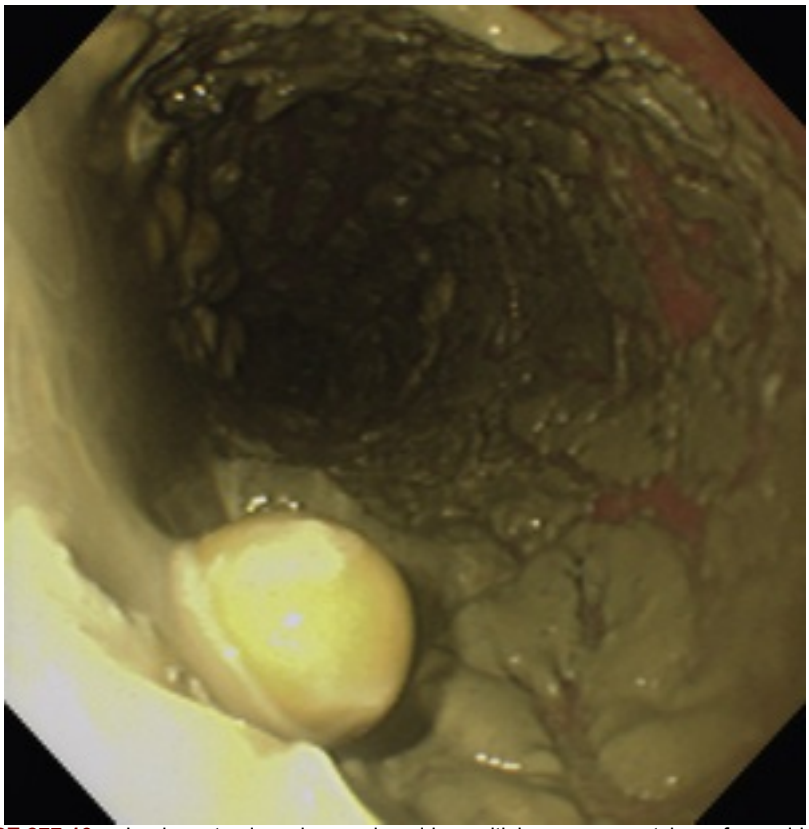
Colonoscopy[170]

Colonoscopy is indicated in patients with LI diarrhea and/or hematochezia, and occasionally in constipated patients after the LI has been emptied (see ch. 113). Hollow rigid endoscopes can be used to view the rectum and descending colon, but the view is limited, and the proximal colon cannot be examined. Flexible endoscopy is the method of choice for visualizing the entire colon and for obtaining mucosal biopsies. Concurrent ileoscopy is recommended unless a significant lesion that explains all of the clinical signs is found

in the LI. Surgery to obtain full-thickness colonic biopsies is not recommended because of the risks of wound dehiscence and septic peritonitis.

Preparation[171-175]

Successful colonoscopy depends on adequate cleansing of the colon (E-Figure 277-13). Dogs and cats should ideally be fasted for 36 to 48 hours before the procedure, and if multiple enemas are to be used, then large volume (each 30 mL/kg), high enemas are needed to provide adequate cleansing. Warm water alone is used for enemas and can be delivered using either an enema bucket or a Higginson pump (see ch. 114). Soap or laxatives, often used in managing constipated patients, should be avoided when preparing the patient for colonoscopy as they may induce histological changes in the colonic mucosa. Phosphate enemas may cause potentially fatal hyperphosphatemia in cats and small dogs.



E-FIGURE 277-13 Inadequate cleansing produced by multiple enemas; patches of mucoid diarrhea are stuck to the colonic surface, obscuring the view.

The most thorough cleansing is produced by the administration of an oral lavage solution which is a potent osmotic laxative. Polyethylene glycol (PEG) solutions, made isotonic with added electrolytes, are preferred (e.g., Colyte R, Golytely, and Klean-Prep). As these solutions have an unpleasant, soapy taste or have fruit flavoring added for human palatability, only a very few canine patients will drink them voluntarily. They, therefore, have to be administered by stomach tube in dogs or by naso-esophageal tube in cats the day before the procedure (see ch. 112). Instillation into the airways must be avoided as fatal inhalation pneumonia has been recorded. A large volume (25 to 30 mL/kg PO twice and preferably three times) has to be administered approximately 2 hours apart. Smaller volume, oral, osmotic laxatives, such as sodium phosphate, have been shown to produce poorer cleansing, and may induce abdominal cramping and vomiting. Warm water enemas are then administered the next day before the procedure, or whilst the animal is under anesthesia, until the LI is clean.

Examination

A complete colonoscopic examination includes visualization of the entire colon up to the ileocolic junction (Video 277-1 and ch. 113). Whenever possible, the cecum and ileum should be examined and biopsied as

well. The patient is positioned in left lateral recumbency, to allow insufflation of the proximal colon. After suctioning and washing out any remaining fecal material, the endoscope is advanced around the flexures until the ileocolic papilla is identified. In large dogs, the endoscope can also be retroflexed to allow better examination of the rectum (Figure 277-14, *A*) as it often fails to remain inflated during flexible endoscopy because air leaks through the anus even if an assistant tries to clamp it shut. Indeed, rigid endoscopy with a proctoscope is a better method for examining the rectal mucosa.

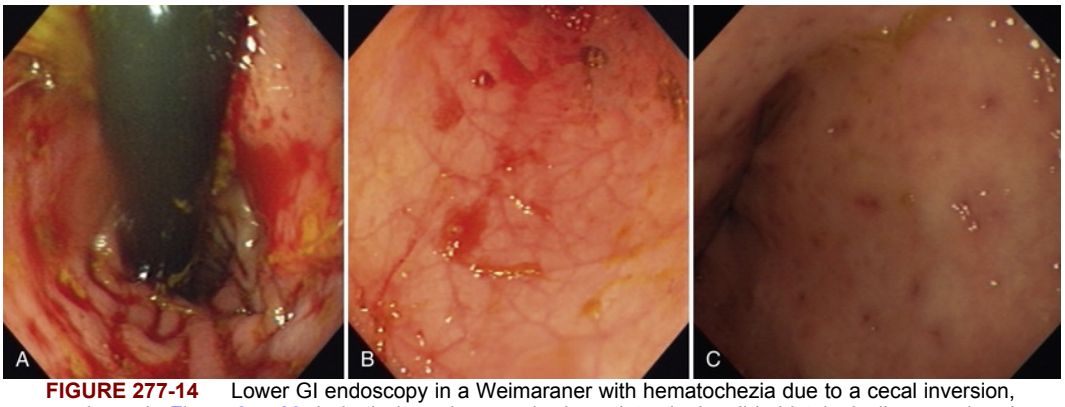


FIGURE 277-14 Lower GI endoscopy in a Weimaraner with hematochezia due to a cecal inversion, as shown in Figure 277-23. In both these images the large intestinal wall is histologically normal and the presence of luminal blood is due to bleeding from the more proximal cecal inversion. **A,** Retroflexed view of distal colon and rectum. **B,** Normal transverse colon, showing submucosal vessels. **C,** Multiple lymphoid follicles visible in the rectal mucosa of a German Shepherd.

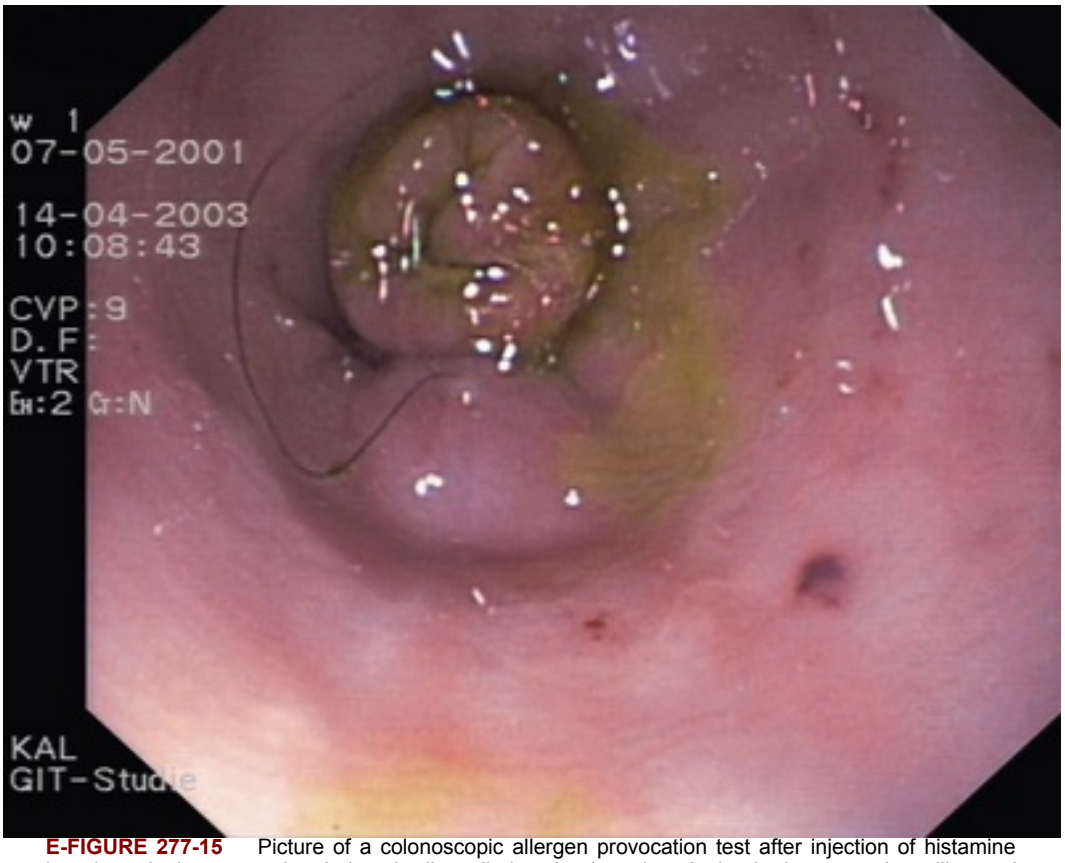
The normal colonic mucosa should appear pink, smooth, and glistening, and the submucosal vessels should be visible (Figure 277-14, *B*); loss of visualisation of the submucosal vessels suggests the mucosa is infiltrated and thickened, but biopsies are needed for confirmation. In the rectum, multiple small dark spots in the mucosa are lymphoid follicles (Figure 277-14, *C*).

Biopsies should be taken from diseased, normal appearing and transitional zone areas for histologic examination. If all the mucosa appears normal, six to eight biopsies from the descending, transverse, and ascending colon each should still be collected. The number and quality of biopsies taken during endoscopy are crucial to obtain an accurate histologic diagnosis. In addition, using the largest possible biopsy forceps (≥2.8 mm diameter) and using disposable biopsy forceps can help in obtaining the best quality endoscopic biopsies.

Other Endoscopic Techniques[176-178]

As well as being used to make a histologic diagnosis, colonoscopy can also be used both for advanced diagnostic testing and therapeutically (e.g., polypectomy, stricture dilatation), although these are rare indications in dogs and cats. If electrosurgery is performed to remove polyps, the colon should be insufflated with carbon dioxide to avoid a potentially explosive mixture of gases.

The colonoscopic allergen provocation (COLAP) test has been developed to identify antigens associated with food allergy or food intolerance, and has been used successfully in dogs but not cats.[179] Briefly, a sheathed sclerotherapy needle is advanced through the colonoscope, and antigen solutions, histamine (positive control) or saline (negative control) are injected into the colonic mucosa in a clock-face pattern around the ileocolic junction. A positive reaction is a demarcated swelling with edema, and hyperemia at the injection site 1 to 2 minutes after injection of the antigen (E-Figure 277-15). Thus, this reaction can be assessed directly on the colonic mucosa more easily than via gastroscopic food sensitivity testing.[180,181] However, false positives and negatives are possible, and COLAP does not appear to work in cats. Furthermore, the COLAP test is only helpful if the clinical signs in food-allergic dogs are caused by an immediate type I hypersensitivity reaction. Therefore, COLAP testing is very rarely used, even in tertiary referral centers.



E-FIGURE 277-15 Picture of a colonoscopic allergen provocation test after injection of histamine into the colonic mucosa just below the ileocolic junction in a dog. A clearly demarcated swelling and hyperemia can be seen.

Inflammatory Diseases

Inflammation of the LI is generally diffuse and simply termed *colitis*, but inflammation of specific regions is identified by the specific names of *typhlitis* (cecum), *colitis* (colon) and *proctitis* (rectum). Isolated typhlitis has been seen in association with impaction and fecolith formation.[182] Whipworm infection is much more common, although more often associated with generalized LI inflammation. Colitis is seen more frequently in dogs compared to cats, and may be acute or chronic.

Acute Colitis[183,184]

Acute colitis is, by definition, sudden in onset and is usually self-limiting. The condition is usually diagnosed on the basis of the characteristic clinical signs of mucoid diarrhea, hematochezia due to the inflammation and increased frequency and tenesmus due to altered colonic motility (see Figure 277-7). Often the cause is never identified, but there are many potential infectious causes (bacteria, protozoa, helminths), and known infectious causes of acute colitis are described later.

Acute colitis in dogs often follows dietary indiscretion although the exact cause is rarely identified. Carrageenan is a mucopolysaccharide extracted from seaweed added to some cat foods to form gels and is an ingredient of many processed human foodstuffs, and it has been suggested to be a cause of acute colitis in dogs stealing cat food. It may damage colonocytes and has been associated with colonic ulceration and neoplasia in rodent models. Traumatic colitis is caused by the inappropriate ingestion of bones, sand or sharp indigestible particles from so-called indestructible nylon bones and toys.

Management of acute colitis is largely supportive and nonspecific, as most cases are self-limiting. Withholding food temporarily and dietary modification (low fat, highly digestible diets) may be all that is required. Kaolin-based antidiarrheals may bind bacterial toxins and produce firmer stool. Diphenoxylate or loperamide can reduce the tenesmus that the patient and owner find most distressing. Antibiotics seem rarely indicated, but empirical treatment with metronidazole is often reported to be effective; a fashion for using trimethoprim-sulfa to treat colitis has thankfully passed. Yet reports of successful treatment with

metronidazole are rarely controlled studies, and it may be that the administration of probiotics or a placebo would be equally effective. Acute colitis that fails to respond becomes chronic colitis.

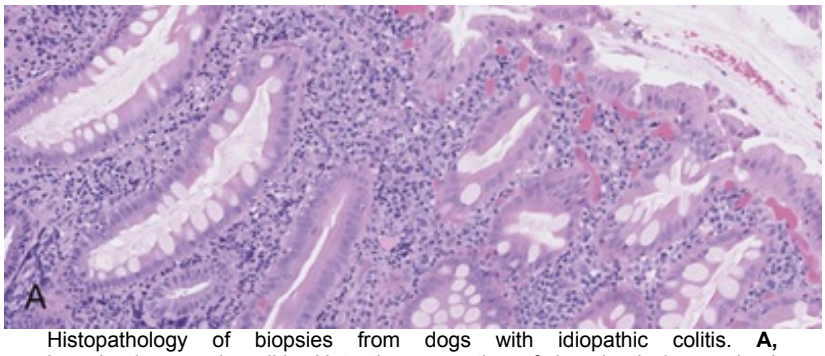
Idiopathic Chronic Colitis

Definition[185-191]

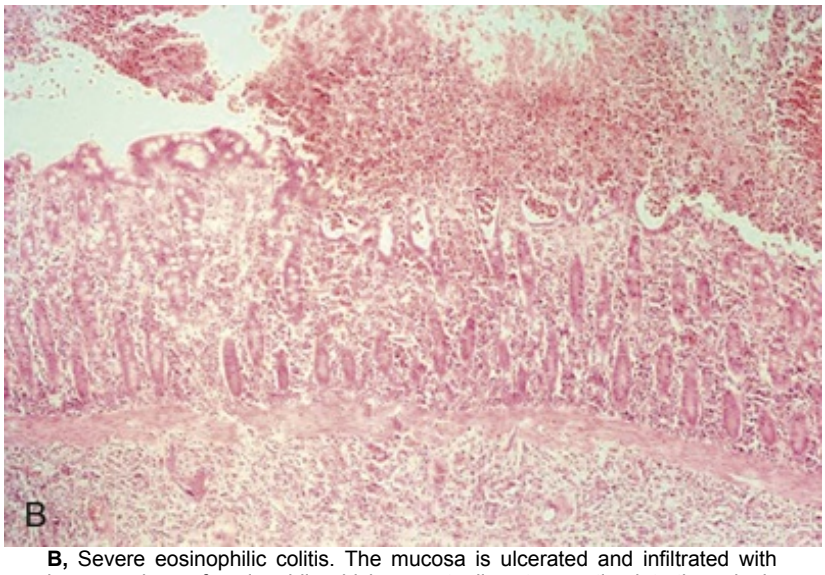
Idiopathic inflammatory bowel disease (IBD) is a disorder affecting the GI tract of dogs and cats where no cause for the inflammation can be identified. It can be classified on the basis of the region of the GI tract affected, and on clinical and histopathological criteria. Clinically, IBD is diagnosed in animals with chronic (>3 weeks in duration) GI signs including anorexia, vomiting, diarrhea and weight loss for which no other known cause can be identified.

If the colon is involved in IBD, the major sign is diarrhea, and typically with mucus, hematochezia, urgency, frequency and tenesmus. Affected animals fail to respond to symptomatic treatment with diet, parasiticides, or antibiotics.

In addition to this empirical elimination process, the histopathologic evaluation of the intestinal biopsies allows classification based on the type of inflammatory cell infiltrating the mucosa (Figure 277-16): such cells found in the colonic mucosa include lymphocytes and/or plasma cells (lymphocytic-plasmacytic colitis), eosinophils (eosinophilic colitis), neutrophils (neutrophilic or suppurative colitis), or macrophages (granulomatous colitis); or more often a combination thereof, but with one predominant cell type. Little is known as to why the predominant cell type differs in the lymphoplasmacytic and eosinophilic forms of colitis but it is often suggested, with little evidence, that eosinophilic disease is more likely a result of an immune reaction to food antigens. Differences in response of the histologic types to treatment are also poorly documented. Neutrophilic GI inflammation is often assumed to reflect a bacterial cause, and campylobacters are known to attract neutrophils, and so antibiotics are usually prescribed before immunosuppression.



Histopathology of biopsies from dogs with idiopathic colitis. **A,** Lymphoplasmacytic colitis. Note the separation of the glands by a mixed population of inflammatory cells, in which the predominant cells are lymphocytes and plasma cells. (Image courtesy Michael Day, University of Bristol.)



B, Severe eosinophilic colitis. The mucosa is ulcerated and infiltrated with large numbers of eosinophils which are actually extravasating into the colonic lumen. (Image courtesy Geoff Pearson, University of Bristol.)

FIGURE 277-16

The inflammatory process may affect the entire GI tract (gastro-entero-colitis), but can involve solely the colon (colitis), when the suggestion is that the prognosis is better. Idiopathic colitis is discussed here, but the whole spectrum of IBD is discussed in detail in ch. 276.

Pathophysiology and Mechanisms of Disease[192-203]

In people, IBD encompasses two main disorders: Crohn's disease is characterized by a transmural granulomatous or pyogranulomatous inflammation and can occur anywhere in the GI tract although is usually centered on the ileum; ulcerative colitis (UC) is restricted to the colon and is characterized by a more superficial, neutrophilic inflammation restricted to the mucosa. The exact pathogenesis of IBD in small animals has not been elucidated, but studies of human IBD and mouse models of colitis have led to the current hypothesis that there is a loss of immune tolerance to luminal bacteria and/or food antigens leading to an inflammatory response.

Recent studies performed in dogs and cats suggest a similar molecular pathogenetic process, potentially including a defective mucosal barrier, an abnormal immune system, and changes in the microbiome. Genetic predispositions to, and mechanisms involved in intestinal inflammation are discussed in detail in ch. 276, and are not repeated here as, at present, there is no evidence that there are significant differences between SI and LI IBD. Indeed, most IBD is either diffuse, involving both regions, or limited to the SI; in the author's experience isolated idiopathic colitis is unusual. Previous reports of colitis may not have recognized SI involvement because of the predominance of colitis-like signs and therefore failure to biopsy the SI. However, why there may be variations in the regional distribution of the inflammation, and whether the SI and LI forms have different etiologies, are unknown.

Immune Responses[204]

Several studies performed in dogs and cats have investigated the inflammatory process associated with colitis. Early studies focused on the description of the predominant inflammatory cell types found, and both T lymphocytes and B lymphocytes, as well as IgG-positive plasma cells, appear to be increased in the inflamed colonic mucosa of dogs with IBD. More recently, using quantitative reverse-transcriptase PCR (qRT-PCR), cytokine mRNA expression has been evaluated in colonic mucosal biopsies. In human IBD, Crohn's disease (Th1 and Th17) and UC (Th2) show distinct cytokine profiles, but results regarding the nature of the specific cytokine pattern seen in dogs with IBD are conflicting. In one study, the prevailing cytokine mRNA expression pattern in dogs was that of a Th1 immune response. However, the accuracy of these results has since been questioned: for example, the more reliable qRT-PCR showed a lack of difference in duodenal mucosal cytokine mRNA expression comparing healthy and diseased dogs. Colonic cytokine mRNA expression has not been re-investigated using qRT-PCR, and it is prudent not to overinterpret results from the

initial study. Cytokines of the IL-17 type may be important in canine and feline IBD, and were not investigated originally. No published data regarding cytokine expression in cats with colitis exist.

Effects of Inflammation on Colonic Function[205-207]

As described earlier, the main functions of the colon are the absorption of water and electrolytes (proximal colon) and storage of feces (distal colon). Colonic inflammation can disrupt these functions in many ways. Colitis may decrease the total absorptive capacity of the mucosa through loss of functional colonocytes, increased permeability, and disturbance of sodium and chloride transport. Additionally, colitis has direct effects on colonic motility, decreasing non-propulsive motility, explained by disturbances of the circular colonic smooth-muscle cells, and increasing giant migrating contractions (GMCs), resulting in frequent defecation and tenesmus. The inflammation may impair calcium mobilization, change the expression of key signaling molecules for excitation-contraction coupling, inhibit muscarinic signaling, and increase transcription of nuclear factor kappa B (NF-kappa B), a key step in causing inflammation. Finally, absorptive and motility disorders may change the composition of the luminal commensal microbiome that plays an important role in the maintenance of colonic function, thereby contributing to further deterioration.

Influence of Diet[208]

Food allergy has been associated with intestinal inflammation, but complete resolution would be expected in response to an appropriate exclusion diet (see ch. 178, 186, and 276). However, food antigens probably do not play a direct role in the pathogenesis of human IBD, but various dietary components can exert either deleterious or beneficial effects on the intestinal microbiome and the mucosa and thereby modify the mucosal inflammatory process. The effects of dietary antigens in IBD have not been studied in detail in dogs or cats, but dietary treatment is viewed as an integral component of therapy. A large proportion of dogs and cats with colitis responds clinically to dietary therapy alone (E-Table 277-3), although histological resolution usually does not occur.

E-TABLE 277-3

Efficacy of Various Dietary Treatments for Chronic Colitis in Dogs and Cats Based on Published Case Series

SOURCE	NUMBER OF ANIMALS	TREATMENT EVALUATED	SUCCESS RATE
Cats			
Nelson et al, 1984	6 cats	Homemade D (boiled lamb and rice) then switched to highly digestible commercial D. SS × 3 weeks in 1 cat with NR to commercial diet.	CR in 6 cats fed homemade D. Rec in 2 cats when switched to highly digestible diet. Both controlled with homemade diets, 1 required SS for 3 weeks.
Dennis et al, 1993	13 cats available for follow-up	F (high F diet or addition of F to diet) in 8 of 10 cats with CR or PR, highly digestible D in 2/7. CR cats received T and/or P initially that was then d/c. All cats with CR maintained on D alone. Cats with PR on P or SS as needed.	CR in 7 cats within 6-50 mo. PR in 3 cats. No change in one cat. Two cats with severe disease were euthanized without treatment.
Dogs			
Nelson et al, 1988	13 dogs	D, initially homemade (cottage cheese and rice), followed by commercial novel antigen or low residue diet. No medication.	CR to homemade diet in all dogs within 3 days to 6 weeks. Rec in 2/13 after switch to commercial novel antigen or low-residue diet. Rec in 9/11 after exposure to pretreatment diet.
Simpson et al, 1994	11 dogs	D (commercial restricted antigen), initially SS in 9 dogs, d/c after resp of clinical signs. No F supplementation.	SS could be d/c after 1 mo in 3/9, 2 mo in 8/9 but had to be resumed in 1 dog. Improvement in stool consistency, fecal mucus, and fecal blood but not in frequency of defecation in all dogs.

Leib, 2000	27 dogs available for follow-up	F (psyllium) added to various commercial or homemade (low-fat, low-residue, or novel protein) D.	Response excellent in 17, very good in 6, good in 3, and poor in 1 dog. Fiber could be d/c in 5/11 dogs, and special diet could be d/c in 5/7 dogs.
Allenspach et al, 2007	30 dogs	D (commercial novel antigen), P if NR to D after 10 days.	CR in 28, NR or PR in 2. No data about resp to P in these 2 dogs.

CR, Complete remission; *D*, diet; *d/c*, discontinued; *F*, fiber; *NR*, no response; *P*, prednisone; *PR*, partial remission; *rec*, recurrence; *resp*, response; *SS*, sulfasalazine; *T*, tylosin.

Hydrolyzed diets are now recognized as being efficacious in many cases of IBD that previously would have been treated by immunosuppression. However, follow-up biopsies often do not show histologic resolution despite the cessation of clinical signs. It is currently unknown whether this reflects the need to wait longer for histologic changes to resolve, or whether the highly digestible diet is merely masking the functional deficiencies of an inflamed gut.

Clinical Examination and History

Dogs with all forms of IBD tend to be middle-aged (median age of 6.5 years with a wide age range) whilst in cats with lymphocytic-plasmacytic colitis, the mean age of onset of clinical signs is similar (median 5.2 years, range 0.5 to 10 years). A predilection for certain dog breeds (e.g., German Shepherd, Shar Pei) is recognized and has been suggested for purebred cats, but with no sex predilection in either species reported.

Signs of chronic colitis are characterized by large-bowel diarrhea with frequent defecation of small volumes of soft to watery stool, often mixed with mucus and/or fresh blood. Urgency to defecate and tenesmus after defecation are often noticed, but vomiting is less frequent than in SI IBD. Abdominal pain, weight loss, anorexia, and lethargy may occur during episodes in severely affected animals, or in those with concurrent gastric and/or SI involvement.

A clinical scoring system to objectively grade the severity of disease in any pet with colitis is recommended in order to monitor treatment response as well as make comparative studies possible.[113-115] Young dogs with mild severity scores and colitis have been shown to respond well to elimination diets alone and have the best outcomes.

Physical Examination

Most dogs and cats with idiopathic colitis are in good general condition, except with severe disease, as their nutritional status is unchanged unless the owner imposes food restriction to try to control the diarrhea. If there is no SI involvement, abdominal palpation is often unrewarding, but it should be performed to rule out intussusception or neoplasia affecting the colon. Digital rectal examination may be painful due to anal and rectal inflammation associated with colitis. Anal furunculosis/perianal fistula (see ch. 278) is also seen in association with colitis in German Shepherd dogs.[209-212] The rectum may feel empty, or it may contain blood, mucus, and/or diarrheic stool. An abnormal, irregular surface of the rectal wall may be noticeable on rectal palpation.

Laboratory Investigation

Serum biochemistry, CBC, and urinalysis results are not usually significantly abnormal in dogs and cats with idiopathic colitis. This may be different in animals with generalized GI inflammation which includes the SI, where leukocytosis with neutrophilia and left shift, hypoproteinemia with hypoalbuminemia and hypoglobulinemia, and sometimes mildly to moderately increased liver enzyme activities can be present (see ch. 276). C-reactive protein (CRP) may be elevated but it is a non-specific marker that is increased in many diseases causing inflammation, and results in dogs and cats with severe IBD are inconsistent. The precise clinical relevance of serum markers of autoimmunity, such as perinuclear antineutrophil cytoplasmic antibodies (pANCA), still remains to be determined in dogs with IBD.[213-219]

A parasitological exam (see ch. 81) may identify parasite infection, such as *Trichuris*, causing colitis, but even in the absence of a positive identification, empirical treatment with fenbendazole (50 mg/kg PO daily for 3 days) is recommended to eliminate most GI helminths and protozoa. Cytological exam of rectal scrapings can reveal the presence of *Histoplasma capsulatum* (see ch. 233); neutrophils, a sign of inflammation (see Figure 277-9); or increased numbers of curved or gull-wing bacilli or gram-positive rods, perhaps indicative of *Campylobacter* infection or *Clostridium perfringens*, although identifying bacterial species on the basis of

morphology is inaccurate (see ch. 220). Usually, diagnostic imaging with radiographs and ultrasonography is not helpful in cats and dogs with colitis, unless there are masses or focal lesions visible, or if the disease extends to the SI. Thickening of the colonic wall may be found on abdominal ultrasound examination, but its absence is more useful for ruling out neoplasia.

Endoscopic Biopsy

When results indicate the possibility of LI IBD, a definitive diagnosis is best achieved with colonoscopy (Figure 277-17; see Video 277-1; see ch. 113). This should be preceded by gastroduodenoscopy in animals with suspected concurrent SI involvement. Flexible colonoscopy allows full visualization of the LI, and it is often possible to biopsy the ileum as well. Histopathologic examination allows neoplastic processes to be ruled out and differentiation between the various types of colonic inflammation.

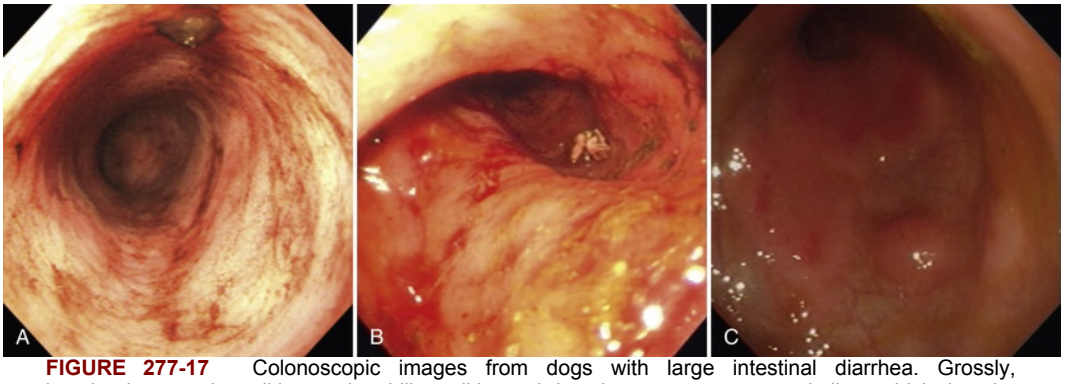


FIGURE 277-17 Colonoscopic images from dogs with large intestinal diarrhea. Grossly, lymphoplasmacytic colitis, eosinophilic colitis and lymphoma can appear similar, which is why endoscopic biopsies must be collected. **A,** Descending colon of a German Shepherd with moderate lymphoplasmacytic colitis. **B,** Descending colon and left colic flexure in a Black Labrador with moderate eosinophilic colitis. Submucosal vessels are obscured by the thickened, inflamed mucosa, which is irregular and ulcerated with spontaneous bleeding. **C,** Terminal colon of Siberian Husky with diffuse, nodular, alimentary lymphoma. Areas of grossly normal mucosa showing submucosal vessels are interspersed with thickened, almost nodular areas of tumor infiltration.

Lymphoplasmacytic colitis is the histologic form most frequently described with eosinophilic colitis being less common (see Figure 277-17). Pyogranulomatous colitis is uncommon and is associated with proliferative masses of several millimeters to centimeters in size visible during colonoscopy or palpable *per rectum:* affected dogs have severe clinical signs. Suppurative (neutrophilic) colitis has been reported as a probable variant of IBD in cats and often responds to the empiric treatment of colitis; there is emerging evidence that this may be due to a specific bacterial infection, as organisms are seen in the tissues using fluorescence *in situ* hybridization (FISH) techniques. Granulomatous colitis (GC) is described in detail in a separate section, as it is no longer considered to be part of idiopathic IBD.

Unfortunately, concordance among pathologists on the interpretation of intestinal biopsy samples submitted for histopathologic assessment is often lacking because, ultimately, it is a subjective assessment and complicated by artifacts caused by the quality of sampling, the processing and the staining techniques. A standardized histologic grading system for SI and LI IBD in dogs and cats, based on pictorial and written descriptions of pathological changes, has been published by the World Small Animal Veterinary Association (WSAVA) GI Standardization Group.[220] It took a broad approach to describing inflammatory changes in the mucosa of endoscopic biopsies, emphasizing both architectural changes and the number of inflammatory cells in the LP (Box 277-1). Controversially, it deliberately omitted evaluation of goblet cell numbers as an indicator of colitis because of a view that goblet cells that had already discharged their mucin content could be overlooked. This view has been challenged, and future schemes need to assess its value in accurately identifying colitis. However, there has been a general misunderstanding of what the WSAVA guidelines were supposed to achieve. It is not a numerical scoring system adding points for each feature, by which intestinal inflammation can then be graded. It is merely a template such that everyone can be confident that different pathologists all mean the same thing when describing a change as mild/moderate/severe. It is not a weighted scale and so a cumulative score may be irrelevant as we do not yet know which of the features examined are the most significant. The guidelines were published in order to allow comparative, prospective studies to analyze which changes are important in the histologic definition of IBD and thereby understand the

correlation between clinical and histologic severity.

Box 277-1

Histologic Scoring System for Objective Reporting of Colonic Inflammation in Dogs and Cats

Features to Assess and Score from Normal, Mild, Moderate, to Marked

Morphological Features

Surface epithelial injury
Crypt hyperplasia
Crypt dilation/distortion
Fibrosis/atrophy

Inflammation

Lamina propria lymphocytes and plasma cells
Lamina propria eosinophils
Lamina propria neutrophils
Lamina propria macrophages

Modified from Day MJ, Bilzer T, Mansell J, et al: Histopathological standards for the diagnosis of gastrointestinal inflammation in endoscopic biopsy samples from the dog and cat: a report from the World Small Animal Veterinary Association Gastrointestinal Standardization Group. *J Comp Pathol* 138(Suppl 1):S1-S43, 2008. Author note: Goblet cell numbers were excluded.

Treatment and Management

It is important to know whether a patient has idiopathic colitis or whether there is an underlying cause, and whether it is part of more generalized IBD, as the treatments differ. A patient presenting with signs of colitis but with abnormalities of serum folate and cobalamin concentrations almost inevitably has SI disease as well. Therefore, ideally, SI biopsies (obtained by upper GI endoscopy and ileoscopy) should also be collected rather than just performing colonoscopic biopsy when colitis is suspected.

Once known causes of colitis have been ruled out, a presumptive diagnosis of idiopathic colitis can be made and empirical treatment based on dietary modification and medications with minimal side effects started. Again, ideally, a precise diagnosis based on histological examination of colonic biopsies should be achieved before the use of glucocorticoids as they can have side effects and mask conditions if further diagnostic tests are then required. However, pragmatically, empirical glucocorticoid therapy may be attempted if other treatments fail. A histologic diagnosis is mandatory before the use of other immunosuppressive drugs, as they can have potentially permanent and even fatal side effects.

Dietary Management[43,221-223]

Diets recommended for pets with chronic colitis include exclusion diets based on highly digestible, low-residue diets or on a novel, single protein or hydrolyzed protein diet (see E-Table 277-3). If successful, most dogs and cats with colitis will have responded to such a diet change within two weeks.

Additional insoluble, dietary fiber may reduce nutrient digestibility but can have a beneficial, symptomatic effect in colitis partly through modification of colonic motility. Alternatively, psyllium is a soluble, indigestible fiber derived from the seed of *Plantago ovata* that is often recommended in the management of colitis. It has great water-holding capacity and forms gels with water, thereby contributing to improved fecal consistency. Psyllium has been shown to be efficacious in the treatment of chronic idiopathic colitis in dogs when added to a highly digestible diet. An initial daily dosage ranging from half a tablespoon for toy breeds to three tablespoons for large dogs is added to each meal, and the dosage is then adjusted to effect.

Fermentable fiber is soluble fiber that resists digestion in the SI and is then metabolized by colonic bacteria. The addition of such fiber has proven adjunctive benefit in clinical studies of canine and feline chronic colitis, and it is often added to commercial pet foods; examples include not only psyllium, but also beet pulp, fructo-oligosaccharides (FOSs), inulin, and mannanoligosaccharides (MOSs). Fermentable fibers are metabolized to SCFAs by the LI bacteria and provide a source of energy for colonocytes, and when this fiber is absent from the diet the structure of the intestinal epithelium becomes abnormal and diarrhea can occur. Acacia gum, and

alpha-glucan butyrogenic (a resistant starch synthesized from 1,4-alpha-D-glucans with polymer chain lengths of 10±35 glucose units) are good substrates for the production of SCFAs and are often found in combination products with probiotics, kaolin and other anti-diarrheals. As well as providing an energy source to colonocytes, the known beneficial effects of fermentable fiber include colonocyte proliferation through increased blood flow to the colonic mucosa and promotion of epithelial cell differentiation into fully functional colonocytes. Additionally, FOSs and MOSs are prebiotics and may influence the composition of the LI microbiome. In cats, they were reported to increase colonic fecal concentrations of *Bacteroides* and *Lactobacillus* spp. and to decrease those of *E. coli* and *C. perfringens.*

Probiotics[224-231]

Probiotics are live microorganisms that are beneficial to the host GI tract (see ch. 167). No clinical study has been able to document convincingly positive effects of probiotics in dogs and cats with chronic GI diseases, even though *in vitro* experiments and studies in canine and feline acute gastroenteritis and in human patients indicate potential benefits. The probiotic organism *Enterococcus faecium* (SF68) has been safely administered to the canine GI tract, and it has been shown to increase fecal IgA content and circulating mature B cells in young puppies. It has been suggested that this probiotic may be useful in the prevention or treatment of canine GI disease. Whilst there is emerging experimental evidence that probiotics do exert an effect on gut permeability and the mucosal immune response, until more studies prove clinical efficacy, veterinarians should probably view product claims with some skepticism.

Adjunctive Therapies

MPS Protect is a mucopolysaccharide also found in some combination anti-diarrheal products, and which theoretically enhances protective colonic mucus production. Herbal remedies have been shown to offer some protection to damage by nonsteroidals.[232,233] There is owner-derived data that homeopathy is effective in approximately two thirds of dogs with diarrhea, but no controlled studies prove any benefit.[234]

Fecal Microbial Transplant[235-240]

Transferring an inoculum of feces from a healthy patient to one with GI disease is becoming an accepted treatment of resistant *Clostridium difficile* infection in human patients, and is being applied in IBD. The concept has been extrapolated to the treatment of canine IBD with anecdotal reports of success so far. As the transplanted material is given in a retention enema, it is perhaps best suited to treating colitis. However, until more studies have been done, it cannot be recommended, particularly as how to screen for and choose healthy donors is debated.

Drug Therapy

Pharmacologic intervention (Table 277-4) is required if dietary and adjunctive therapy (probiotic, etc.) fails to control clinical signs or, in severe cases, may be initiated simultaneously with dietary modification.

TABLE 277-4

Pharmaceutical Therapy of Large-Bowel Inflammation

DRUG CATEGORY AND NAME	DOSAGE RECOMMENDATION	INDICATION
Antimicrobials		
Enrofloxacin	5 mg/kg PO q 24 h (D) for 4-8 weeks; culture and sensitivity for *Escherichia coli* recommended before starting treatment	GC
Metronidazole	10-15 mg/kg PO q 12 h (D, C) to q 8 h (D) For metronidazole benzoate, increase above dosage by approximately 50%	Acute and chronic colitis
Anti-Inflammatory Drugs		
Sulfasalazine	10-30 mg/kg PO q 8 h for 4-6 weeks, max 1 g total dose (D)	Colonic IBD refractory to diet

	5-12.5 mg/kg PO q 8 h for 2-4 weeks (C) Administer with food. Slowly decrease in 10- to 14-day steps to q 12 h, then half the dose q 12 h, then once daily. Regularly measure tear production.	and metronidazole
Olsalazine	5-15 mg/kg PO q 8 h for 4-6 weeks, max 1 g total dose (D) 2.5-7.5 mg/kg PO q 8 h for 2-4 weeks (C)	
Immunosuppressive Drugs		
Prednisone (prednisolone)	1-2 mg/kg PO q 12 h for 10-14 days, then slowly taper over several weeks	Colonic IBD refractory to diet and antibiotics
Azathioprine	Starting dosage: 2 mg/kg PO q 24 h (D) for 2 weeks, then 2 mg/kg every other day for 2-4 weeks, then 1 mg/kg PO every other day May take 2-4 weeks to have full effect	Steroid-refractory colonic IBD
Chlorambucil	Cats >4 kg: 2 mg per cat PO every other day for 2-4 weeks then tapered to the lowest effective dose (2 mg/kg per cat PO every 3-4 days) Cats <4 kg are started at 2 mg/kg per cat PO every third day	Refractory or severe feline IBD; combined with prednisolone
Cyclosporine	5 mg/kg PO q 24 h (D) for 10 weeks	Steroid-refractory chronic colonic IBD

C, Cat; *D*, dog; *GC*, granulomatous colitis; *IBD*, inflammatory bowel disease.

Metronidazole[241-245]

Among the antimicrobials, metronidazole is frequently used in dogs and cats with colitis. Besides its antimicrobial effects against obligate anaerobic bacteria, metronidazole is also effective against *Giardia,* although at standard antibacterial doses (i.e., 10 mg/kg) it only suppresses and does not eliminate infection. Furthermore, metronidazole has been shown to have immunomodulatory effects: it has been shown to be genotoxic to feline lymphocytes, and it affects various steps in innate and adaptive sequences of the immune response. It is used in dogs and cats with colitis to modify the intestinal flora, decreasing obligate anaerobes and inflammation. It is unpalatable, especially in cats, but other side effects are quite rare and include vomiting and diarrhea. Hepatotoxicosis and neurotoxicosis occur at higher dosages.

5-Amino Salicylic Acid

5-amino salicylic acid [5-ASA or mesalamine (mesalazine)] is a nonsteroidal anti-inflammatory drug molecule effective in the treatment of UC in human patients. The native molecule is potentially nephrotoxic if absorbed by the SI, so it is only available as an enteric-coated preparation that is dissolved by the acidic colonic pH, and as a foam enema. The safety of the enteric-coated preparation has not been established in dogs and cats and it is not recommended, whilst enema preparations are unlikely to be suitable. Therefore it is administered to dogs and cats as a pro-drug.

Sulfasalazine (Azulfidine, Salazopyrin) is a pro-drug consisting of 5-ASA linked by an azo bond to sulfapyridine.[223,246,247] It is administered orally, and the pro-drug reaches the distal SI and colon unchanged. There, the bacteria break the azo bond and liberate both molecules. 5-ASA exerts its anti-inflammatory effects directly on the colonic mucosa, inhibiting prostaglandin and leukotriene synthesis. The sulfapyridine is in essence a carrier molecule and is not thought to have therapeutic effect before being absorbed and eliminated by liver metabolism and urinary excretion. The main adverse effect of sulfasalazine is keratoconjunctivitis sicca (KCS); although the exact mechanism of action is unknown, sulfasalazine may damage the lacrimal glands. Early detection with immediate discontinuation of treatment is necessary to prevent the onset of irreversible KCS. Therefore, tear production must be measured at regular intervals in all dogs receiving sulfasalazine. Vomiting can occur and can be prevented if the drug is administered with food, but acute pancreatitis has been recorded as a side effect. Other pro-drugs with the same mechanism of action are available.

Olsalazine (Dipentum) consists of two molecules of 5-ASA linked by an azo bond. As two 5-ASA molecules are released for each olsalazine molecule administered, the dosage is 50% of the sulfasalazine drug. It was hoped that this would eliminate the risk of KCS, but it has still been reported, although more rarely.

Balsalazide is another pro-drug (4-aminobenzoyl-beta-alanine-mesalamine) with 5-ASA bound to an inert carrier, but its safety and efficacy in dogs and cats have not been demonstrated and it cannot be recommended.

Glucocorticoids

Glucocorticoids are used as a second line of treatment for dogs with colonic IBD that is refractory to dietary modification, metronidazole and sulfasalazine (see ch. 164 and 165). Due to the side effects, immunosuppressive dosages of prednisone are ideally reserved for patients that have histologically confirmed colitis and where underlying causes have been ruled out. As side effects tend to be fewer and less severe in cats, and because they may not tolerate three times daily medication with sulfasalazine, and are more susceptible to mesalamine toxicosis, glucocorticoids are a treatment option often considered earlier in cats than in dogs with colitis. Budesonide, which is 90 per cent metabolized via first-pass through the liver, is used in some cases of generalized IBD, but there are no reports of its success in isolated idiopathic colitis.

Cytotoxic Agents

Cytotoxic agents may be used as steroid-sparing agents to treat all forms of IBD, and are not specifically used for idiopathic colitis (see ch. 276). Due to potential side effects and financial considerations, they should be reserved for animals with documented colonic inflammatory disease that show no response to any other treatment. *Chlorambucil* has been used successfully in dogs and in cats with IBD. *Azathioprine* has been recommended for dogs with IBD refractory to immunosuppressive doses of corticosteroids. It is rarely effective as a single agent and should instead be used as adjunctive therapy as it has a significant steroid-sparing effect in canine IBD, although it may take several weeks for azathioprine to become maximally effective. Doses of 2 mg/kg orally every 24 hours in dogs and 0.3 mg/kg orally every 48 hours in cats have

been used with some success in IBD. It is cytotoxic and tablets must not be broken. Therefore, reformulation is needed to produce tablets of an appropriate size for cats and small dogs.

Cyclosporine

Cyclosporine (ciclosporin) reduces IL-2 production in T cells and therefore renders them more susceptible to apoptosis (see ch. 165). Its efficacy at a dosage of 5 mg/kg PO q 24 h for 10 weeks has been reported in 9 of 14 dogs with IBD that were steroid-resistant but none specifically had idiopathic colitis alone.[248-250]

Prognosis

The prognosis for colonic IBD depends on the response to treatment as well as on the initial disease severity. Young dogs that responded well to treatment with an elimination diet alone had a good prognosis, with most in remission within a year. Older dogs with severe disease and those which need steroids to control their clinical signs carry a much poorer prognosis.[113]

Granulomatous Colitis[251-292]

Definition

Formerly known as histiocytic ulcerative colitis (HUC), granulomatous colitis (GC) was for many years considered a form of idiopathic IBD, but is now recognized to be associated with an intracellular *E. coli* infection. It occurs most frequently in young Boxer dogs but is being seen with increasing frequency in French Bulldogs as the breed gains popularity. It has also been described occasionally in other breeds, such as Mastiffs, Alaskan Malamutes, and English Bulldogs, and in one cat. Since being described 50 years ago, the condition has been recognized worldwide, although currently it is most common in the United States and Australia, with rare sporadic reports in Europe. The disease is restricted almost exclusively to the colon, although cases with SI involvement have been noted, and it causes severe signs of colitis with mucoid diarrhea, hematochezia, urgency, and tenesmus. The condition is characterized histopathologically by the presence of macrophages full of Periodic-Acid-Schiff (PAS)-positive-staining material underlying an ulcerated colonic mucosa. Attempts to treat the condition with therapies used for idiopathic colitis (e.g., metronidazole, sulfasalazine, glucocorticoids) failed, and historically the severity of the disease almost inevitably led to the euthanasia of the patient.

Etiopathogenesis

The cause of canine GC has been debated for decades, although its occurrence in clusters and within certain kennels and presence of the PAS-positive material within macrophages suggested an infectious etiology. Early electron microscopic studies demonstrated so-called residual bodies resembling bacteria-like organisms in granules within PAS-positive macrophages. Specific infectious agents, such as mycobacteria, mycoplasmas, *Chlamydia,* and rickettsias have all been proposed to cause GC; attempts to reproduce the disease by infecting dogs with *Mycoplasma* spp. failed. In immunohistochemical studies, GC lesions are characterized by increased numbers of CD3-positive cells, IgG-positive plasma cells, and MHC class II–positive cells, which merely demonstrate an inflammatory response. Alternatively, the marked breed restriction of GC, with most of the affected dogs in the first report of HUC in 1965 being traced back to a single ancestor, suggests a genetic predisposition.

More recently, two independent studies reported simultaneously successful remission and likely cure following prolonged treatment with enrofloxacin.[256,263] A total of 12 cases were described and each showed a dramatic response to treatment with enrofloxacin (5 mg/kg PO q 24 h for 4 to 8 weeks) or a combination protocol with enrofloxacin, amoxicillin (20 mg/kg PO q 12 h), and metronidazole (10 to 15 mg/kg PO q 12 h). The reported response to enrofloxacin was dramatic, with all dogs responding within three to twelve days of initiating therapy, and several dogs being disease-free following a four- to six-week course of therapy. Some dogs apparently needed treatment for much longer than six weeks. Five dogs were re-biopsied when they were in clinical remission after completion of the antibiotic treatment. A dramatic improvement in the histologic lesions was evident in all, with disappearance of PAS-positive macrophages in three dogs and a marked reduction in the number of macrophages in the other two dogs.

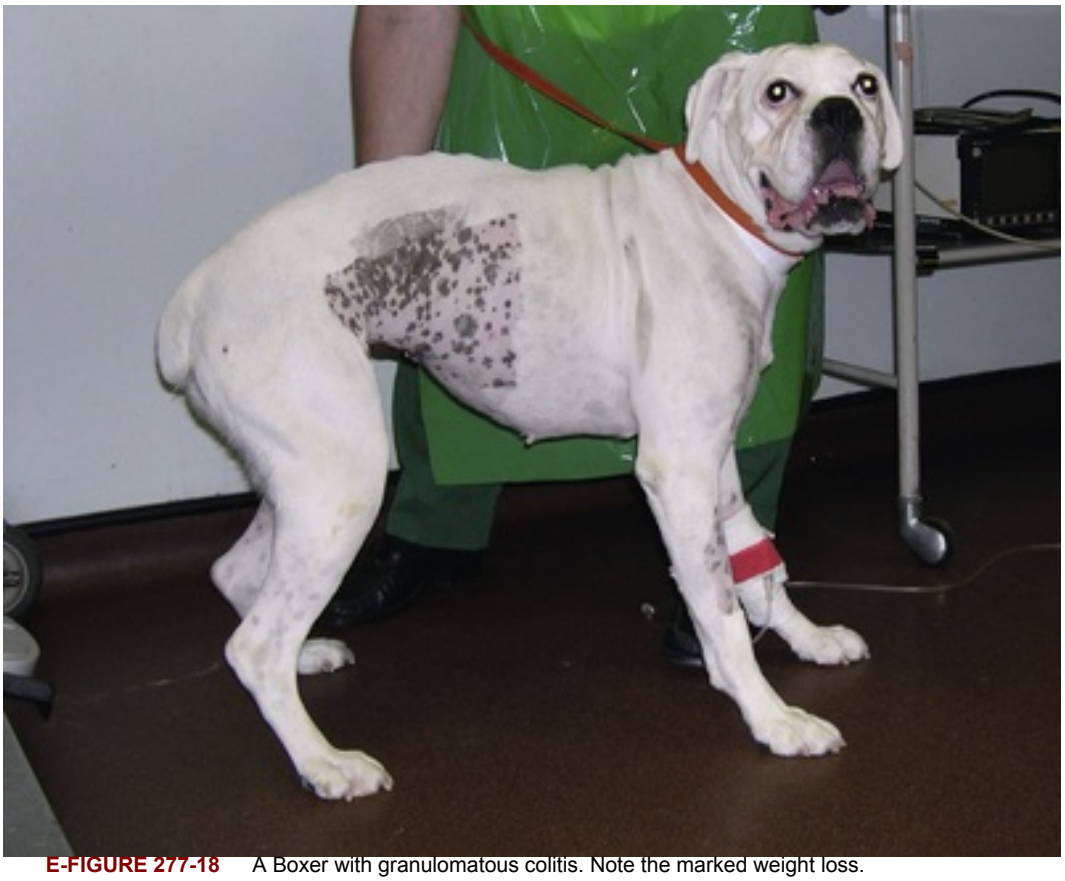
The success of enrofloxacin treatment in GC obviously resurrected the question of an infectious etiology. Using FISH, large numbers of coccobacilli were found in the colonic mucosa in Boxer dogs affected with GC

but not in histologically normal tissues or in the mucosa of dogs with other types of colitis.[275,276,282] Further studies identified the bacteria to be an *E. coli* localized in the intracellular compartment of the PAS-positive macrophages, which when co-cultured with epithelial cells and macrophages, revealed specific adherent and invasive properties. Indeed, the *E. coli* variant associated with GC has a phenotype that is similar to the adhesive and invasive behavior displayed by adherent and invading *E. coli* (AIEC) isolated from chronic urinary tract infections in women and bovine endometritis.[293] Similar *E. coli* have been associated with Crohn's disease in people, which has a similar granulomatous histologic appearance. AIECs replicate within the phagolysosomes of macrophages, provoking a granulomatous lesion rather than being cleared. These findings support the hypothesis that genetics play an underlying role in the infection that causes GC. People with Crohn's disease have polymorphisms in certain pattern recognition receptors (PRRs) of the innate immune system, such as NOD2 (nucleotide-binding oligomerisation domain receptor 2), linking a genetic defect in innate immunity with functional disease.[294] It was hypothesized that similar defects in PRRs could be present in GC as an underlying genetic predisposition, due to the preponderance of cases in young Boxer dogs. Confirmation and identification of mutations in PRRs, such as toll-like receptors (TLRs) or NODs, in Boxers with GC is still lacking. However, a defect in neutrophil killing activity has been identified, and this seems the most likely reason why the AIEC infection is not cleared.

Evaluation of the Patient

History and Physical Examination

The onset of disease is usually before 2 years of age. Clinical signs are those of severe, chronic, LI inflammation and include diarrhea, hematochezia, increased frequency of defecation, tenesmus, and presence of excessive mucus in the feces. Physical examination findings are normal in many dogs with GC, however weight loss and inappetence may be seen in severe cases (E-Figure 277-18). Fresh blood and mucus are found upon rectal examination.



E-FIGURE 277-18 A Boxer with granulomatous colitis. Note the marked weight loss.

Investigations

The diagnostic approach to dogs with GC is the same as described for idiopathic colitis. CBC, serum biochemistry, and urinalysis are necessary to exclude any extra-GI diseases. Parasitological examination of fecal samples and fecal culture should be performed (see ch. 81 and 221). An ultrasound exam of the abdomen (see ch. 88) may reveal a diffusely thickened colonic mucosa; however, in many dogs, no abnormalities are detected. Typically, colonoscopy reveals sites of severe colonic hemorrhage and ulceration interspersed with stretches of more normal-appearing mucosa (Figure 277-19). Biopsies should be taken from ulcerated and more normal mucosa, and from transition zones.

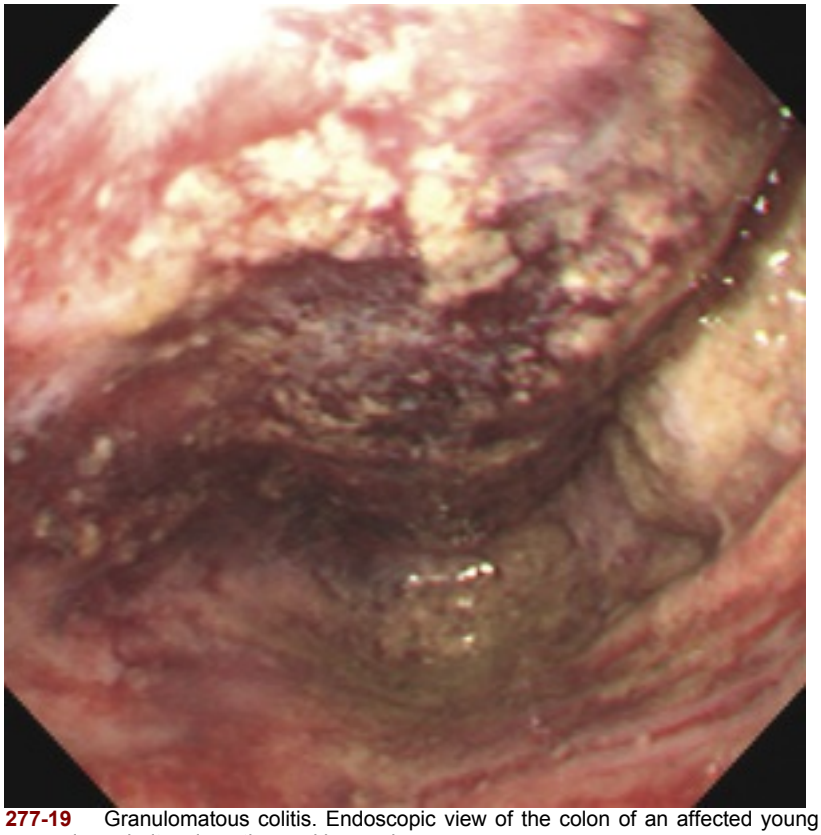


FIGURE 277-19 Granulomatous colitis. Endoscopic view of the colon of an affected young Boxer, showing severe irregularity, ulceration and hemorrhage.

Early lesions can consist of a mixed inflammatory infiltrate in the LP just below a degenerative epithelium. With increasing chronicity and severity, the ulceration worsens, with widespread loss of the epithelial surface and goblet cells. Below, there is severe infiltration of the LP and submucosa by neutrophils, macrophages, lymphocytes, plasma cells, and mast cells, representing a mixed inflammatory response, perhaps reflecting secondary invasion by luminal bacteria. Accumulation of large PAS-positive macrophages is virtually pathognomonic for GC. Fluorescence *in situ* hybridization (FISH) performed on biopsies demonstrates the presence of *E. coli* within the tissue. PAS-staining and FISH remain the best ways to confirm the diagnosis and distinguish GC from idiopathic lymphoplasmacytic colitis, which is seen more commonly even in Boxers.

Treatment and Management

The prognosis for HUC was considered to be grave when management consisted of various combinations of dietary management and anti-inflammatory or immunosuppressive treatment with sulfasalazine, prednisolone, and azathioprine (see above, section on chronic colitis). Inevitably these strategies were not successful, and most affected dogs were euthanized because they were refractory to treatment. The revelation of the success of enrofloxacin treatment has reversed the prognosis, and cure is possible. However, resistance to enrofloxacin has now developed, perhaps because of its inappropriate use in Boxers with colitis due to other causes, and some AIECs isolated from GC are now only sensitive to amikacin.[274]

Infection

GI infections can cause colonic inflammation and acute or chronic colitis. They are common in dogs and cats but most affect either the SI primarily or both the SI and LI together either sequentially or concurrently. Acute gastro-enterocolitis typically starts with inappetence, vomiting and SI-type diarrhea before signs of colitis (hematochezia, mucus, urgency tenesmus) occur, presumably reflecting the passage of the infectious agent down the GI tract. Infectious agents that primarily target the LI are described here.

There are no viral infections that solely affect the LI, although one uncommon manifestation of feline infectious peritonitis (FIP) is a pyogranulomatous mass at the ileo-ceco-colic area, causing either diarrhea or obstruction.[295-297] Information on parvovirus, enteric coronavirus and other viral diseases causing a generalized GI infection can be found in ch. 224, 225, 228, and 276. Similarly a number of causes of bacterial gastro-enterocolitis are discussed in more detail in the preceding chapter and ch. 220. Specific LI infections are mainly protozoa and metazoan parasites that presumably occupy an ecological niche which makes the LI their predilection site for infection.

Bacteria[298-300,320]

Enteropathogens such as *Campylobacter, Escherichia coli, Salmonella,* and *Yersinia* typically infect the SI, but may also cause colitis. Here again, the difficulty is that isolation does not prove causation, and these organisms can be found in the feces of clinically healthy animals. An attaching and invading *E.coli* is associated with granulomatous colitis in Boxer dogs (see above).

Anaerobiospirillum[301,302]

A small, Gram-negative, spiral bacterium, *Anaerobiospirillum* spp. can be isolated from the feces of dogs and cats. There are, however, reports of acute ulcerative or necrotizing ileocolitis in cats associated with this organism. It can be demonstrated within the crypts of biopsies stained with Giemsa or Steiner stains, or by PCR. There is no treatment published.

Brachyspira pilosicoli[303-309]

This organism is a spirochete and the cause of swine dysentery; it may be pathogenic in dogs. Massive infection with signs of acute colitis have been described in dogs kept in colonies with poor hygienic conditions.

Campylobacter spp[131,132,141,299,310-314]

Campylobacters are Gram-negative, motile, spiral-shaped bacteria that are often found in feces, even feces from healthy animals, and whether they are pathogenic in dogs and cats is debated (see ch. 220). They typically cause small intestinal disease, and are discussed in detail in ch. 276. However, there are reports of *Campylobacter* causing enterocolitis and isolated colitis.

Clostridium difficile[119,133,315-328]

A Gram-positive, anaerobic, spore-forming bacillus, *C. difficile* is a significant nosocomial pathogen in humans (see ch. 210 and 220). *C. difficile* produces two major toxins, A (an enterotoxin) and B (a cytotoxin), which can cause fatal pseudomembranous colitis in hospitalized human patients given antibiotics. In the human intestine, the toxins cause loss of epithelial integrity and cell death through glycosylation and inactivation of guanosine triphosphatases, resulting in F-actin depolymerization. They also cause inflammation by stimulating the production of prostaglandins and substance P, and mast cell degranulation. Their effect on canine intestinal epithelium is unknown, and pseudomembranous colitis after antibiotic therapy is not reliably documented in dogs. Indeed, isolation of the organism in diarrheic dogs is most commonly associated with both SI and LI signs.

The organism can be cultured from the feces of up to 40% of both healthy and diarrheic dogs, although its toxins are more frequently found in dogs with diarrhea. It is also reported to be present in the feces of over 90% of neonatal dogs with no clinical signs. Thus, it is difficult to prove a causal relationship between the presence of enterotoxin and disease in dogs, although the organism has been incriminated as a cause of nosocomial infection and diarrhea. Metronidazole (10 mg/kg PO q 8-12 h) is an effective treatment, as antibacterial resistance appears to be rare in canine isolates.

Clostridium perfringens[320,321,328-345]

This Gram-positive, anaerobic, spore-forming bacillus causes food poisoning in humans, and has been incriminated as a cause of canine acute colitis and hemorrhagic gastroenteritis (HGE). However, it is often present in the healthy canine LI, with recorded isolation rates of up to 80%. It can produce Type A toxins including major toxin A and an enterotoxin, also called *Clostridium perfringens enterotoxin (CPE). C. perfringens* organisms producing type A toxins have been associated with acute and often hemorrhagic enterocolitis in dogs, especially in kennels and under boarding conditions. The CPE can stimulate intestinal secretion and initiate apoptosis, but *C. perfringens* may also carry other virulence factors such as beta$_2$ toxin.

Historically, the secretion of CPE was associated with sporulation of the organism when environmental conditions were right, supposedly leading to diarrhea. This was often linked to the stress of hospitalization or kenneling, or a sudden dietary change, possibly causing a change in the colonic pH, with mucoid diarrhea typically occurring one to five days after admission, and typically responding to metronidazole or the addition of dietary fiber. Finding five sporulating organisms per high power field in a fecal smear was considered diagnostic. However, sporulation has now been shown not to correlate with CPE production, and since approximately 15% of healthy dogs can also harbor CPE-producing *C. perfringens,* its pathogenicity is not confirmed.

Isolation of *C. perfringens* by fecal culture is insufficient to prove it is the cause of colitis, but immunoassays are available to detect CPE in feces. PCR is also available for the detection of the *cpe* gene. Yet the clinical value of all of these tests is questionable, as CPE is detected with similar frequency in feces from healthy dogs.

C. perfringens is susceptible to metronidazole (8 to 15 mg/kg PO q 8-12 h) and also to amoxicillin, erythromycin and tylosin; resistance to tetracyclines is common. The prognosis is good, and supportive treatment alone, with the addition of dietary fiber or probiotics, is sometimes just as successful as antibiotic treatment, raising the question of whether antibiotics are indicated.[341] However, whether *C. perfringens* is actually a cause of colitis is debated, although emerging evidence indicates it does cause HGE. Recent studies demonstrate the presence of *C. perfringens* in the intestinal mucosa of dogs with HGE, but there is no association with CPE production.[330]

Escherichia coli[346-356]

E. coli is found in the GI tract of nearly all dogs and most cats, and is likely to be a commensal unless it carries specific plasmid genes that encode for pathogenic mechanisms. Some isolates typically cause SI disease primarily, e.g., enterotoxigenic *E. coli* (ETEC), which produces heat-stable and heat-labile toxins that stimulate excess secretion by the SI (see ch. 220 and 276). Others can damage both the SI and LI, e.g., enteropathic *E. coli* (EPEC), which causes attaching and effacing damage to intestinal epithelial microvilli through intimin expression by the *eae* gene. Fatal EPEC infection has been reported in a kitten and an adult cat in which attaching and effacing lesions were found in the ileum and colon. Death of puppies with EPEC infection is believed to be more common, but often there is a mixed infection with distemper, parvovirus and pathogenic protozoa contributing.

Some *E. coli* isolates, such as enterohemorrhagic *E. coli* (EHEC) have a tropism for the LI. Although non-invasive, EHECs produce Shiga-like toxins (verocytotoxin, cytotoxic necrotizing factors 1 and 2) that kill colonocytes by inhibition of protein synthesis, leading to edema, submucosal hemorrhage, arteritis and arteriolar thrombosis in the colon, and hence hemorrhagic diarrhea. Isolation rates range up to 15% of healthy dogs and 5% of healthy cats.

The EHEC of the serotype O157:H7, a commensal of cattle, also produces a toxin that causes potentially fatal, hemolytic uremic syndrome in humans. Although O157:H7 has been isolated from the feces of healthy dogs, there is no conclusive evidence of hemolytic uremic syndrome in the species, although it can be produced experimentally by IV injection of shiga-like toxin. The organism has also been associated with "Alabama rot," where ulcerative skin lesions and acute kidney injury occur.[357] Other serotypes are isolated more commonly at rates of up to 25% in Greyhounds, presumed to be because they are often fed raw meat. Verocytotoxin-producing *E. coli* are found more commonly in cats with diarrhea than healthy cats.

As the pathogenicity of any *E. coli* depends on which genes it carries, simple isolation by routine culture is meaningless, and PCR is needed to identify the gene or genes that encode for pathogenicity. Even then, identification does not necessarily equate with causation, as the organism may be present in healthy animals, and so attempts to vaccinate dogs against *E. coli* are speculative.

Enterohepatic *Helicobacter* spp.[358]

Gastric *Helicobacter* are well known, although their pathogenic potential in dogs and cats is still debated. However, enterohepatic helicobacters have also been identified and possibly incriminated in feline chlolangitis. Recently an association between the presence of *Helicobacter* organisms in colonic crypts and superficial mucus and histologic evidence of colitis in dogs and cats has been identified. However, a lack of proof of Koch's postulates so far, means we do not yet know their significance in the etiology of supposedly idiopathic colitis.

Salmonella spp.[356,359-388]

Salmonella organisms, most commonly *S. typhimurium* in dogs and cats, are a potential zoonotic risk. They attach to epithelial cells and M cells in the SI and LI, and can cause enterocolitis. Infection is fortunately generally quite uncommon (<2%), but fecal isolation rate is similar in healthy and diarrheic patients, ranging from one to 36% of all dogs, and one to 18% of healthy cats. The higher isolation rates reported are generally associated with feeding raw food, rawhide chews, and improperly cooked meat. Further information on the pathophysiology, clinical presentation, treatment and prognosis are discussed in ch. 220 and 276.

Yersinia enterocolitica[389-391]

Y. enterocolitica is a motile, Gram-negative coccobacillus, which can be isolated from the feces of clinically healthy dogs and cats. It has also, rarely, been associated with abdominal discomfort and/or bloody diarrhea, and in man, infection has been correlated with polymorphisms of CARD15/NOD2, a bacterial pattern recognition molecule in the innate immune system.[392]

Algae

Prototheca spp.[393-406]

Prototheca spp. are achlorophyllous algae which can cause protothecosis in dogs, cats and humans. *Prototheca zopfii* is typically associated with GI and disseminated disease in young dogs, and *Prototheca wickerhamii* with cutaneous infections in dogs and cats. The algae live in animal waste and sewage-contaminated food, soil, and water, and impaired host cellular immunity seems to play a role in infection and in disease dissemination. Primary colonic infection is followed by endosporulation and dissemination to other tissues.

Most dogs with disseminated disease have signs of intermittent or prolonged bloody diarrhea. Ocular and neurological signs often accompany the signs of colitis, and distemper should be included on the differential diagnosis list. Diagnosis is made by cytology of rectal or colonic scrapings and/or histology of affected tissues, showing the capsulated organisms. Culture from affected tissues is readily performed and allows species differentiation. Treatment of disseminated protothecosis with varying combinations of amphotericin B and itraconazole (see ch. 162) has been attempted but only slows progression; the ultimate outcome is invariably fatal.

Fungi

Systemic fungal infections, which may infect the GI tract, occur in certain geographic areas, and are described in detail elsewhere: *Histoplasma* (see ch. 233) typically affects the LI; *Aspergillus* (see ch. 234 and 235) can cause GI infection in immunosuppressed patients, and has been seen during cyclosporine therapy; and Oomycetes such as *Pythium insidiosum* and zygomycetes (see ch. 236) can infect the GI tract (phycomycosis).

Histoplasma capsulatum[407-409]

H. capsulatum is a dimorphic fungus whose free-living mycelial stage grows in warm, moist, nitrogen-rich soil contaminated with bat or bird droppings. In the United States, it mainly occurs along the Ohio, Mississippi, and Missouri rivers. Fungal spores are inhaled and then disseminated by macrophages to the GI tract and other organs; it is suspected that direct infection of the GI tract after ingestion, without pulmonary involvement, may also occur. Granulomatous inflammatory reactions with ulceration and blood loss occur in the GI tract and cause the typical clinical signs.

The organism causes chronic LI diarrhea in young dogs and cats: common signs include tenesmus, hematochezia, and mucus in the feces. Dogs may also show pyrexia, anorexia, vomiting, and weight loss. The SI can also be affected, with signs of weight loss and sometimes protein-losing enteropathy. Colonoscopy reveals severe granulomatous inflammation.

Histoplasma organisms are most reliably diagnosed within macrophages on cytologic smears from rectal

scrapings or cytology brush samples obtained during colonoscopy. Alternatively, lymph node aspirates, or histologic samples can be used for diagnosis. Fungal stains, such as PAS and Gomori's methenamine silver stains can help demonstrate the organisms in fixed tissues.

Supportive treatment with dietary modification, antibiotics, antidiarrheals and 5-aminosalicylates may provide some relief from signs, but definitive treatment is with itraconazole at 10 mg/kg PO q 24 h for 4 to 6 months. Treatment must be continued for at least 2 to 3 months beyond the resolution of clinical signs. The prognosis seems fair in dogs and cats.

Pythium insidiosum[410-412]

Pythium insidiosum, an aquatic organism belonging to the class Oomycetes, causes pythiosis. Large-breed male dogs, used as hunting dogs, are most commonly affected, as the organism lives in warm swamp water. Endemic areas are the Gulf Coast region of the United States, but the disease has been diagnosed as far north as Virginia and as far west as California.

The organism has a predilection for the skin and/or the GI tract, and if the GI tract is affected, upper GI obstruction is seen most commonly due to severe infiltration of the GI wall. Sometimes, the colon is affected as well, resulting in large-intestinal diarrhea. Further information on the diagnosis and treatment can be found in ch. 236 and 276.

Protozoa

The GI tract is host to a number of commensal protozoal organisms that form part of the normal microbiome, but some species are considered enteropathogens (see ch. 221). Most, such as coccidia [*Cryptosporidium, Cystoisospora* (formerly *Isospora*)] and *Giardia* are considered SI infections, but some *(Tritrichomonas)* are clearly LI pathogens. The significance of the presence of other protozoa, such *Balantidium* and *Pentatrichomonas,* is uncertain.

Balantidium coli[413-418]

The primary hosts of this ciliated parasite are pigs and non-human primates. Infection is reported rarely in dogs, and is typically associated with access to swine. *Balantidium coli* supposedly causes ulcerative colitis in dogs, with typical clinical signs of LI diarrhea, and extrapolating from human infection, treatment with tetracyclines or metronidazole should be effective. However, co-infection with *Trichuris vulpis* in reported cases confuses the significance of the organism's presence, especially as treatment of the helminth infection alone can resolve the signs.

Entamoeba histolytica[419,420]

Primarily an intestinal parasite in people and non-human primates, *Entamoeba histolytica* causes amoebic dysentery. Although amoebiasis is generally a mild disease in dogs and cats and the organism can also be found in healthy dogs and cats, one report describes severe colitis in a dog and a cat. The organism lives in the colon or attaches to the colonic wall, rarely disseminating to other organs. The rare cases described had signs of acute LI diarrhea, hematochezia, and tenesmus. The route of infection in pets is generally from humans, which raises important public health considerations if it is diagnosed in a pet. Diagnosis is best made by direct fecal smears. Eradication is achieved with metronidazole at 30 mg/kg PO q 12 h for 3 weeks; monitoring for neurotoxicosis is indicated.

Giardia intestinalis (lamblia)[421]

Giardia intestinalis infection of dogs and cats can cause clinical signs suggestive of colitis, but it is generally considered to be a SI infection. The highest concentration of organisms is found in the duodenum of dogs and the ileum of cats (see ch. 221 and 276).

Pentatrichomonas hominis[422-428]

This flagellate protozoan is generally considered a commensal in dogs, and is most important because it may be mistaken for *Giardia* in fresh fecal preparations. However, some suspicion exists that it can cause colitis, especially in kittens, although concurrent infections usually complicate the picture, and, at worst, it may only be an opportunistic pathogen.

Tritrichomonas foetus[129,130,423,425,426,429-451]

This protozoan is of emerging importance as a cause of persistent diarrhea in cats. It primarily colonizes the LI and causes chronic colitis; anal irritation and fecal incontinence can also be features of infection. Although primarily a feline enteropathogen, it was reported in breeding bitches in France, but was not found in a survey of 215 French puppies.[424] *Tritrichomonas foetus* is a flagellate protozoan similar in size and shape to *Giardia,* but it only exists in the trophozoite form. It is an important pathogen in cattle, causing infertility and abortion, but venereal transmission does not appear to be important in cats; transmission in cats occurs directly via the orofecal route.

Clinical Presentation

Cats of any age, breed or sex can be infected but infection most frequently occurs in young (<1 year old), pedigree cats in crowded catteries, rehoming centers, or multi-cat households. The prevalence in symptomatic cats in the UK has been estimated to be 20% healthy cats, but can be up to 31%. Persistent infection is most common and, although signs may spontaneously resolve, infection may remain latent and cats may suffer recrudescence when stressed. It is, therefore, most appropriate to look for the organism in kittens and younger cats with diarrhea, especially if from the right environment, and also older cats with recurrent colitis-like signs. Indeed, infection of any cat is possible and it should not be considered an infection restricted to pedigree cats. Furthermore, cats that are unresponsive to treatment for *Giardia* infection should be tested in case of misdiagnosis.

Waxing and waning large-bowel diarrhea, with mucus or fresh blood in foul-smelling feces are typical. Infected cats may have semi-formed feces, and exhibit fecal incontinence, and an edematous, painful anus. The cats may appear otherwise healthy. Clinical signs depend on the immune response of the host, the endogenous microflora, the pathogenicity of the parasite strain, and co-infections such as *Giardia.* Infected cats should also be tested for underlying FeLV and FIV infection.

Diagnosis

The organism may be identified on colonic biopsy, but it is preferable to make a diagnosis of a *T. foetus* infection by examination of feces (see ch. 81). There are several methods available, but none is 100% sensitive and antibiotic usage in the previous seven days may cause false negatives. Repeat testing should be considered where there is a high index of suspicion and yet a negative result; false negative results are more likely if formed feces are examined, and test sensitivities can be improved by only examining diarrheic samples. High colonic washings provide the best sample; the saline washings are centrifuged or allowed to settle and the sediment submitted for examination.

Methods of diagnosis include identification of motile organisms in a direct wet mount. Very fresh samples kept warm and then examined within minutes must be used, but even then the sensitivity is reported as only 14%. Specificity can also be low if the organism is misdiagnosed as *Giardia* spp. or *Pentatrichomonas. T. foetus* organisms have a characteristic forwardly progressive, jerky motion with an undulating membrane and three anterior flagellae (see ch. 207 and Video 207-1), whereas *Giardia* organisms have a slow tumbling motion.

The organism can be cultured using a commercially available culture system Feline In Pouch TF (Biomed Diagnostics), originally developed for the diagnosis of bovine venereal infection. Although more sensitive than direct smear examination, the method is laborious and the diagnosis potentially delayed as results can only be considered negative when there is no growth after 12 days.

PCR analysis of feces is relatively quick and is the most sensitive method of detecting *T. foetus:* as few as 10 organisms per gram of feces can be detected. The PCR is based on the conserved internal transcribed spacer region and the 5.8S rRNA gene. Ideally, fresh feces should be tested, but if there is a delay between collection and submission, the feces can be kept refrigerated for up to a week, although sensitivity declines with time. Quantitative PCR allows measurement of the number of organisms present, and can be used to monitor the response to treatment. Again sensitivity is improved by sampling diarrhea or colonic washings, and samples should not include cat litter, which can contain inhibitors of the PCR reaction.

Treatment

Only ronidazole (30 to 50 mg/kg PO q 12 h for 2 weeks) has been shown to be effective in treating cats with *T. foetus* infection. However, neurological side effects have been reported although they do disappear after discontinuing therapy, and clinical signs may resolve without treatment within 9 months of the onset of diarrhea. Relapses are common and can be provoked by diet change, medical treatment, travel, and stress. The disease has a fair long-term prognosis for spontaneous resolution.

Helminths

Heterobilharzia americana[452-460]

Schistosomiasis in dogs is caused by *Heterobilharzia americana,* a fluke parasite that produces acute or chronic LI diarrhea. Raccoons are the most important reservoir hosts, but others include mice, nutria, and rabbits. Canine infection is restricted to the southeastern and Gulf Coast areas of the United States. The *H. americana* life cycle involves at least one intermediate host, typically snails. The cercariae from the snail penetrate the dog's skin and migrate through the lung and the liver. The parasites mature in the liver and lay eggs in the terminal mesenteric venules. Ova then migrate through the bowel wall by releasing proteolytic enzymes and cause severe granulomatous inflammation at the site of penetration. Some ova do not reach the gut lumen and may be disseminated to the liver, pancreas and lungs, where they cause more granulomatous lesions that may result in liver failure.

Clinical signs include vomiting, LI diarrhea, and hematochezia. Serum biochemistry may reveal decreased serum albumin and increased globulin concentrations, and increased liver enzymes are often seen. In addition, granulomas may cause hypercalcemia. Diagnosis is confirmed by identifying eggs on direct fecal smears or saline flotation, or by tissue biopsy from the liver or intestines. An ELISA is available for occult infections. A combination protocol of fenbendazole with praziquantel is an effective therapy. The prognosis is good in acute cases but guarded to poor with longstanding disease involving the liver, where cirrhosis is often present.

Strongyloides tumefaciens[461,462]

Strongyloides spp. are uncommon parasites in dogs and typically infect the SI. *S. tumefaciens,* a feline threadworm, is a rare infection seen mainly in the Gulf Coast of the United States and in tropical areas. Infective larvae penetrate the skin or oral/esophageal mucosa and travel to the lungs. Larvae break into alveoli and are coughed up and swallowed. Adult parasites are exclusively parthogenetic females which burrow and persist in the colonic submucosa in epithelial-lined cavities with a luminal pore, and cause endoscopically visible nodules that may coalesce to form adenomatous masses. Embryonated ova or larvae are present in the feces. Infected cats may be asymptomatic, but the parasite may cause intractable diarrhea in young cats. Treatment with fenbendazole (50 mg/kg PO q 24 h for 5 days) is effective and the prognosis is good.

Trichuris spp.[463-470]

Whipworm infection is quite common in dogs in temperate and subtropical regions of the world and can cause acute or chronic signs of LI diarrhea. Infected dogs can be asymptomatic, or they may have mucoid feces, hematochezia, and tenesmus. *T. vulpis* is a common infection in dogs (and other canids) but is very rare in cats; *T. campanula* and *T. serrata* sporadically infect cats in Australia, the West Indies and Asia. *T. vulpis* has a direct life cycle; it is transmitted via the orofecal route, and eggs hatch in the host's SI where the larvae remain for 2-10 days after burrowing into the mucosa. The larvae then emerge and migrate to the colon, where they latch on to the mucosa; their predilection sites are the cecum and proximal colon, where their thin anterior portion burrows into the mucosa causing a localized granulomatous reaction, and occasionally may even stimulate a cecal inversion. The pre-patent period is 70-110 days, and adult worms live up to 18 months.

Clinical signs depend on the nature of the host's immune response, the nutritional status of the host, its environment, and the presence of other GI parasites. Signs and the degree of bleeding increase with the severity of the worm burden, and may include abdominal pain, vomiting, inappetence and weight loss in addition to the more common signs of diarrhea and hematochezia. On biochemistry profile, some dogs may show evidence of hyperkalemia and hyponatremia, mimicking hypoadrenocorticism, but they have a normal response to ACTH stimulation. Eosinophilia and anemia may be present, but the diagnosis is made by identifying the thick-walled, barrel-shaped eggs with two polar plugs on fecal flotation (see ch. 81). However, false negatives can occur as eggs are shed intermittently, and empirical treatment despite a negative fecal is recommended in endemic areas before colonoscopy is performed to investigate colitis, although the free posterior end of the whipworm will be seen if colonoscopy is performed. Commonly used parasiticides effective against *T. vulpis* include fenbendazole, pyrantel pamoate, febantel, moxidectin, and milbemycin oxime (see ch. 163). Due to a long pre-patent period (70 to 107 days), treatment should be repeated at three weeks and again at three months. Re-infection is likely in dogs living in contaminated environments as the ova are quite resistant, and heartworm prophylaxis with milbemycin oxime may help control infection.

Hematochezia

The presence of fresh blood in feces is indicative of LI bleeding. Hematochezia in association with mucoid diarrhea, urgency and tenesmus is most suggestive of colitis (see above), but the presence of blood without diarrhea and/or with dyschezia is more indicative of a focal, bleeding lesion, assuming a generalized bleeding problem has been ruled out. The diagnostic approach to hematochezia is outlined in Figure 277-6, *B*.

LI Neoplasia[471]

Tumors of the LI are associated with signs of mucosal ulceration and/or obstruction, such as hematochezia, tenesmus, and dyschezia. LI tumors are actually more common than tumors of the stomach and SI in dogs, and the mean age of dogs affected is usually 7 to 11 years; the mean age of cats affected with LI neoplasia is 12.5 years. Most canine colonic tumors are malignant, with adenocarcinoma followed by lymphoma being the most common. Most LI adenocarcinomas develop in the descending colon and rectum, with German Shepherds, Collies and West Highland White Terriers over-represented. Leiomyosarcomas of the LI are found more frequently in the cecum. Benign neoplasms such as adenomas and leiomyomas are much less common than malignant tumors in the canine LI although adenomatous polyps are relatively common. In the feline LI, surprisingly, the adenocarcinoma is more common (46%) than lymphoma (41%), whilst mast cell tumors (9%) are also seen (see ch. 349).

Colorectal Adenocarcinoma[472-481]

Canine intestinal adenocarcinomas are found most commonly in the distal colon and rectum, and can cause mechanical obstruction leading to dyschezia and ultimately constipation with unproductive straining. Observant owners may recognize that their dog is passing progressively deformed feces that are being squeezed past the tumor as it gradually narrows the lumen. Ulceration of the tumor surface leads to hematochezia, even if the fecal consistency is normal, and blood may be seen streaked on the surface. Diarrhea is less of a feature unless the obstruction and tumor invasion cause inflammation, fluid secretion, or malabsorption of water and salts. Local tumor invasion occurs at a relatively slow rate with canine colorectal adenocarcinoma, and metastasis to distant sites is uncommon. Devitalization and necrosis of the tumor can lead to spontaneous perforation and septic peritonitis; dogs may be moribund with fever, lethargy, anorexia, vomiting, abdominal pain, and collapse.

The most common sites of colonic adenocarcinoma in cats are the descending colon (39%) and the ileocolic region (28%), although exclusively ileal adenocarcinomas are more common, with a predisposition in older Siamese cats. Hematochezia, rather than obstruction and constipation, is the most likely sign in cats as the tumor tends to be proximal. Unlike in dogs, feline colonic tumors have a high rate (>60%) of local metastasis, which is associated with decreased survival time.

Diagnosis

Canine colorectal adenocarcinomas are palpable in about 70% of cases. Narrowing of the rectal lumen found on digital rectal examination is suggestive of neoplasia, as benign strictures are very rare. Proximal colonic and cecal lesions are not as readily apparent, although more than 50% of cats with colonic masses do have a palpable abdominal mass. Survey and contrast radiographic and ultrasonographic studies have been used with varying levels of success in the diagnosis of canine and feline colonic neoplasia. Annular stenotic lesions associated with adenocarcinoma of the colon may appear as proximal colonic dilation on survey radiographs. Radiographic contrast material more precisely outlines the narrowing of the lumen at the site of the tumor, but contrast studies have largely been superseded by ultrasonography, which is useful in evaluating mural lesions and lymphadenopathy; ultrasonography was reported to be useful in localizing about 84% of feline colonic neoplasia. CT has not been sufficiently evaluated for reasonable comparison to be made with ultrasonography but is likely to be more sensitive as luminal gas does not interfere.

Flexible colonoscopy with mucosal biopsy is the preferred method for the definitive diagnosis for colonic adenocarcinoma (Figure 277-20, Video 277-2; see ch. 113). Endoscopic abnormalities may include masses, spontaneous bleeding, increased friability, ulceration, and circumferential luminal narrowing. Multiple biopsy specimens should always be obtained from diseased tissue, adjacent healthy tissue, and the transition zone between these areas; the pathologist has a much better chance of diagnosing and staging the disease by evaluating non-necrotic tissue.

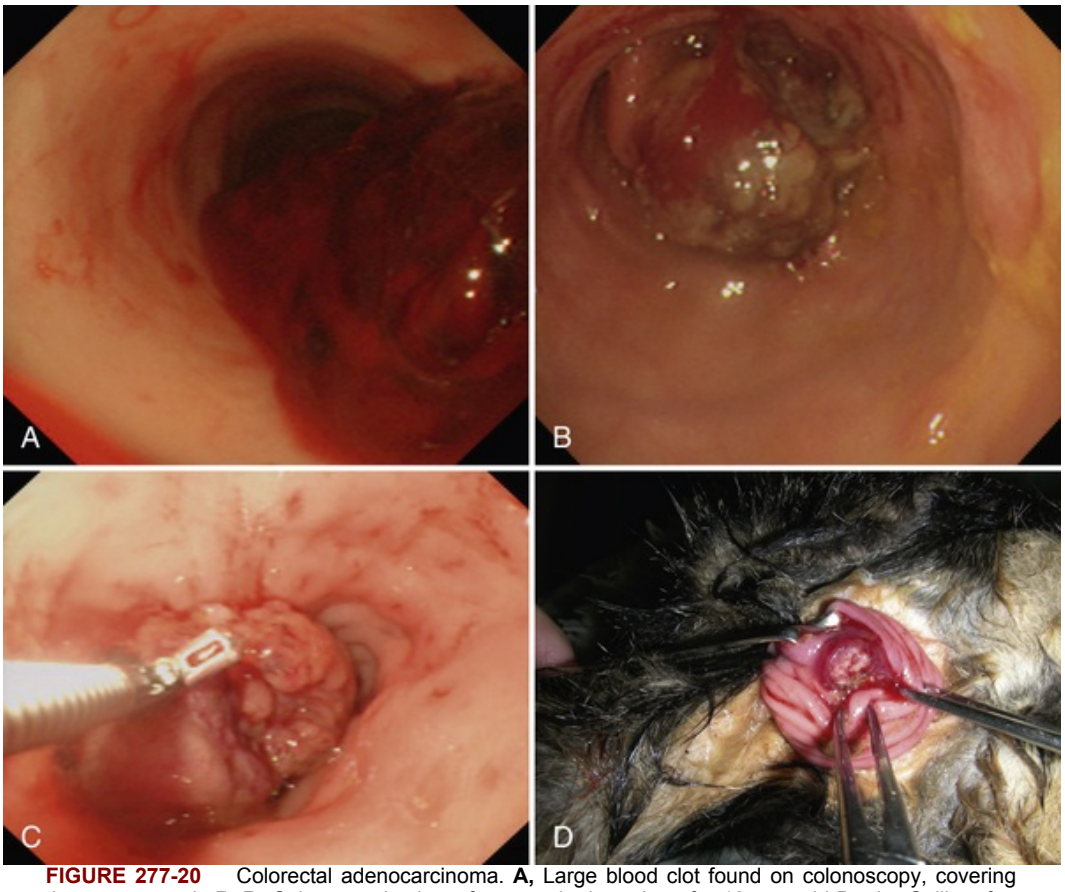


FIGURE 277-20 Colorectal adenocarcinoma. **A,** Large blood clot found on colonoscopy, covering the mass seen in **B. B,** Colonoscopic view of a mass in the colon of a 12-year-old Border Collie, after the blood clot has been removed. **C,** Endoscopic biopsy of a colonic adenocarcinoma in a 10-year-old West Highland White Terrier that had been exhibiting episodes of constipation. **D,** Adenocarcinoma in the rectum of a 12-year-old cat visualized by gradual progressive eversion of the rectum using tissue forceps.

Treatment

The most suitable treatment modality depends on anatomic location, and the presence and extent of metastases. Complete surgical excision is the recommended treatment for focal adenocarcinomas but access to intrapelvic masses may require splitting the pelvis, and may require an often aesthetically and functionally unsatisfactory endo-rectal pull-through procedure. Dogs with colorectal adenocarcinomas generally have a particularly poor prognosis with a median survival time (MST) of only 1.6 months, although in one study dogs having mass resection survived an average of 7 months longer than dogs that just had a biopsy. Radiation therapy has been used inconsistently to palliate recurrent adenocarcinomas, but post-radiation peritonitis and perforation have been reported. Cyclooxygenase 2 (COX-2) upregulation may contribute to the growth characteristics of some tumors, and selective COX-2 inhibitors (e.g., piroxicam, meloxicam) may therefore be useful although, ultimately, euthanasia is indicated.

Feline colonic adenocarcinoma is a locally invasive, highly metastatic tumor that is most often treated with wide surgical excision (subtotal colectomy) and systemic chemotherapy either with or without nonsteroidal anti-inflammatory medications. In one retrospective study, the outcome of subtotal colectomy and adjuvant carboplatin in 18 cats was assessed: the median disease-free interval was 251 days (range, 37-528 days) and the MST was 269 days (range, 40-533 days). Negative prognostic factors included nodal and distant metastasis (178 versus 328 days and 200 versus 340 days, respectively). Thus, subtotal colectomy and adjuvant carboplatin is a safe and potentially effective treatment for cats with colonic adenocarcinoma, with a longer survival time than those receiving mass resection only (MST of 138 days versus 68 days).

Adenomatous Colo-rectal Polyp[157,162,177,178,482-494]

Benign polyps sometimes occur in the terminal colon and rectum of mature dogs, and are recognized by the passage of fresh blood and clots on the surface of feces. Occasionally mistaken for colitis, the key feature is

that diarrhea is not present. Miniature Dachshunds are reported to be overrepresented, and in the author's experience, Cocker Spaniels and Shetland Sheepdogs appear predisposed. A familial adenomatous polyposis is recognized in humans. Malignant transformation of adenomatous polyps to carcinoma *in situ* and invasive adenocarcinoma is a real threat in human patients and has been demonstrated in dogs, although in most cases the polyp remains benign.

The diagnosis can usually be made on rectal palpation, where a mobile mass on a stalk can be felt. However, the tissue can be so soft that it is difficult to recognize the mass in a conscious dog, although copious bleeding occurs. Rectal examination should therefore be repeated once the animal is prepared and anesthetized for colonoscopy. It may be possible to exteriorize the polyp through the anal sphincter if it is in the terminal rectum, or view it with an anal speculum or proctoscope. Indeed, it may be missed by flexible endoscopy because the tip of the endoscope is inserted beyond the lesion before visualization is possible (Figure 277-21, Video 277-3).

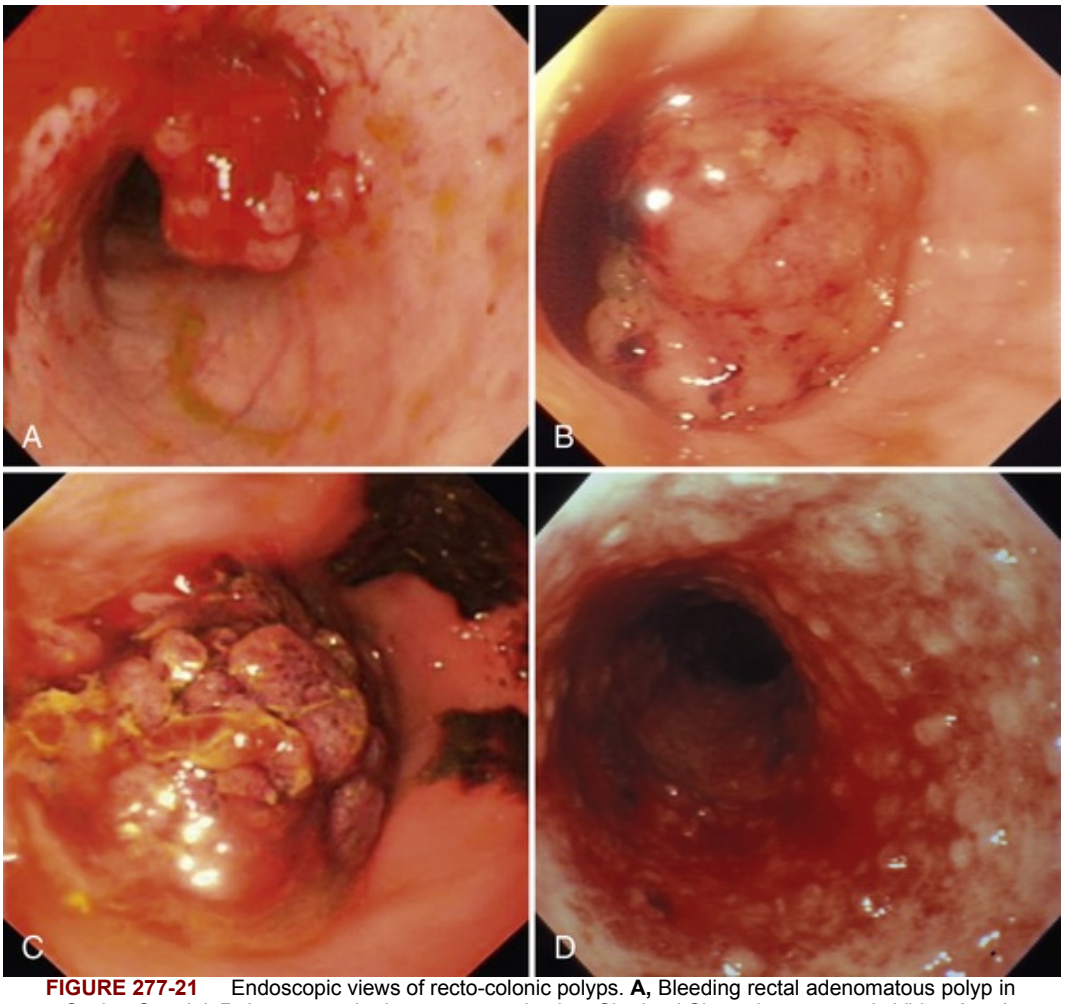
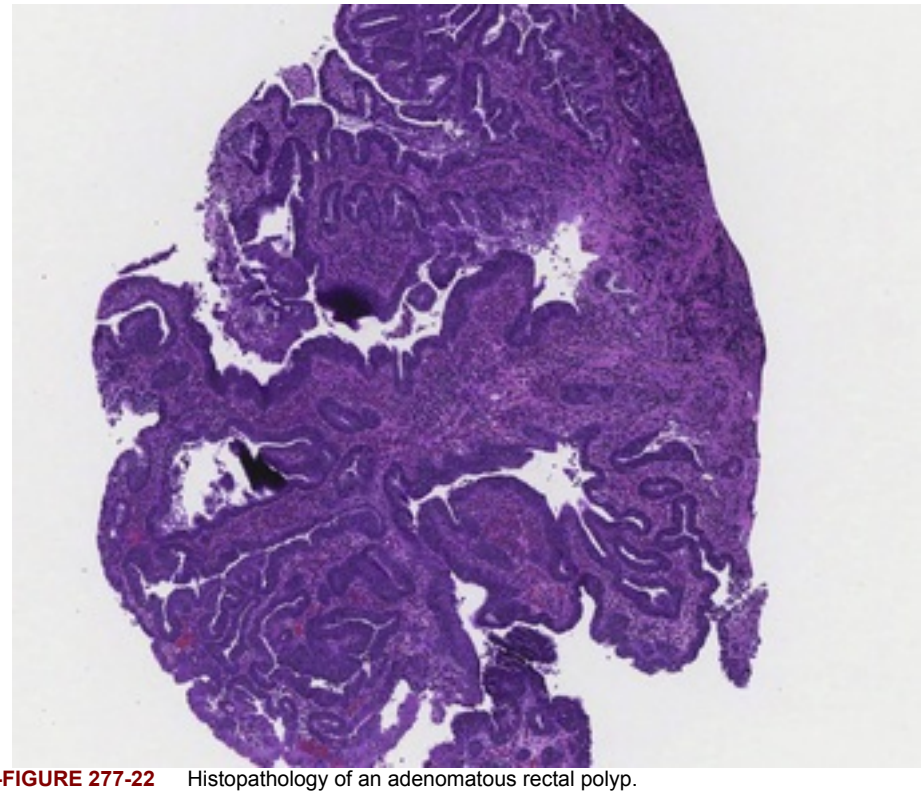


FIGURE 277-21 Endoscopic views of recto-colonic polyps. **A,** Bleeding rectal adenomatous polyp in a Cocker Spaniel. **B,** Large rectal adenomatous polyp in a Shetland Sheepdog as seen in Video 277-3. **C,** Colonic adenomatous polyp in a dog. **D,** Pseudo-polyposis in a Jack Russell Terrier.

Sometimes, digital rectal manipulation of the polyp results in the mass being accidentally removed, but the stalk remains and the polyp soon regrows and hematochezia recommences. Similarly, removal above a transfixation ligature in the stalk may allow recurrence. Gentle eversion of the rectal mucosa using Allis forceps and submucosal resection of the base of the polyp's stalk is curative. For polyps in the distal colon and proximal rectum, removal with a polypectomy snare and with a resectoscope has been reported. Alternatively, resection via laparotomy is possible for colonic polyps. Multiple polyps have been treated with polypectomy and argon plasma coagulation.

Histology may indicate a benign or inflammatory polyp (E-Figure 277-22), an adenoma or even a carcinoma *in situ*. Pseudopolyposis is a very rare condition wherein multiple nodules are found in the colon (see Figure

277-21, *D*). They are not true polyps as they do not have a stalk. They are treated with glucocorticoids.



E-FIGURE 277-22 Histopathology of an adenomatous rectal polyp.

Alimentary Lymphoma[481,495-501]

Alimentary lymphoma is generally a diffuse disease affecting the SI with or without involvement of the LI, and it can produce a variety of signs including anorexia, vomiting, diarrhea, melena, hematochezia and weight loss. It is emerging as the most common form of lymphoma in cats. In dogs, it is potentially a cause of a protein-losing enteropathy if it involves the SI but it is uncommon compared to multicentric disease in dogs. Rectal lymphoma in dogs is a subset of the condition, where the disease is restricted anatomically, and which responds well to combination chemotherapy. All other forms of canine alimentary lymphoma either respond very poorly to chemotherapy, or tumor lysis leads to intestinal perforation and septic peritonitis; remission is very rare.

Transabdominal fine needle aspiration (see ch. 89), peritoneal fluid cytology, and endoscopic exfoliative cytology may be useful in the diagnosis of lymphoma, but histology may be required for a definitive diagnosis.

Common clinical signs in cats with alimentary lymphoma are vomiting (65%), diarrhea (52%), weight loss (46%) and palpable masses. Most affected cats are FeLV-negative, and most colonic lymphomas in cats are B cell in origin. Combination chemotherapy (prednisone, vincristine, cyclophosphamide) has been used to treat colonic lymphoma.

Other Tumors[483,502-520]

Leiomyosarcoma have a predilection site for the canine cecum. GI stromal tumors (GISTs), which arise from the interstitial cells of Cajal, are very similar clinically and previously could not be distinguished. Indeed 42% of 50 tumors reported as leiomyosarcoma were shown to be GISTs by immunohistochemistry, detecting expression of desmin, smooth muscle actin and c-kit markers (see ch. 276). Smooth muscle tumors have been associated with hypoglycemia and the associated clinical signs of muscular weakness and seizure activity due to the release of an insulin-like factor, and erythrocytosis due to the release of erythropoietin. The prognosis for leiomyomas is generally favorable.

Extramedullary plasmacytomas are a rare tumor of the GI tract but can occur in the colon and rectum.

Functional plasmacytomas secrete a single class of immunoglobulin, and affected animals may go on to develop hyperviscosity syndrome (e.g., retinal bleeding, epistaxis). Plasmacytomas may be managed with adjuvant chemotherapy (e.g., prednisone, melphalan) after surgical excision.

A variety of other mesenchymal tumors can occur in the LI: neurofibrosarcoma, fibrosarcoma, ganglioneuroma, and hemangiosarcoma, with the last more common in the GI tract of cats than dogs.

Ceco-Colic Intussusception (Cecal Inversion)[521-524]

Invagination of the cecum into the colon is abnormal and initially may occur intermittently. However, ultimately, it will become trapped by the sphincter at the ceco-colic orifice. Impairment of venous drainage then leads to mucosal sloughing and intraluminal bleeding. Diarrhea is not a consistent finding, but fresh blood and clots may be seen partially mixed with feces. Dogs may show signs of abdominal discomfort, and the intussusception may be palpable. The lesion may be visible with radiography, with or without barium contrast or with ultrasonography, but a definitive diagnosis is made by flexible colonoscopy (Figure 277-23, *A*) when a bleeding protuberance is seen adjacent to the ileocolic papilla.

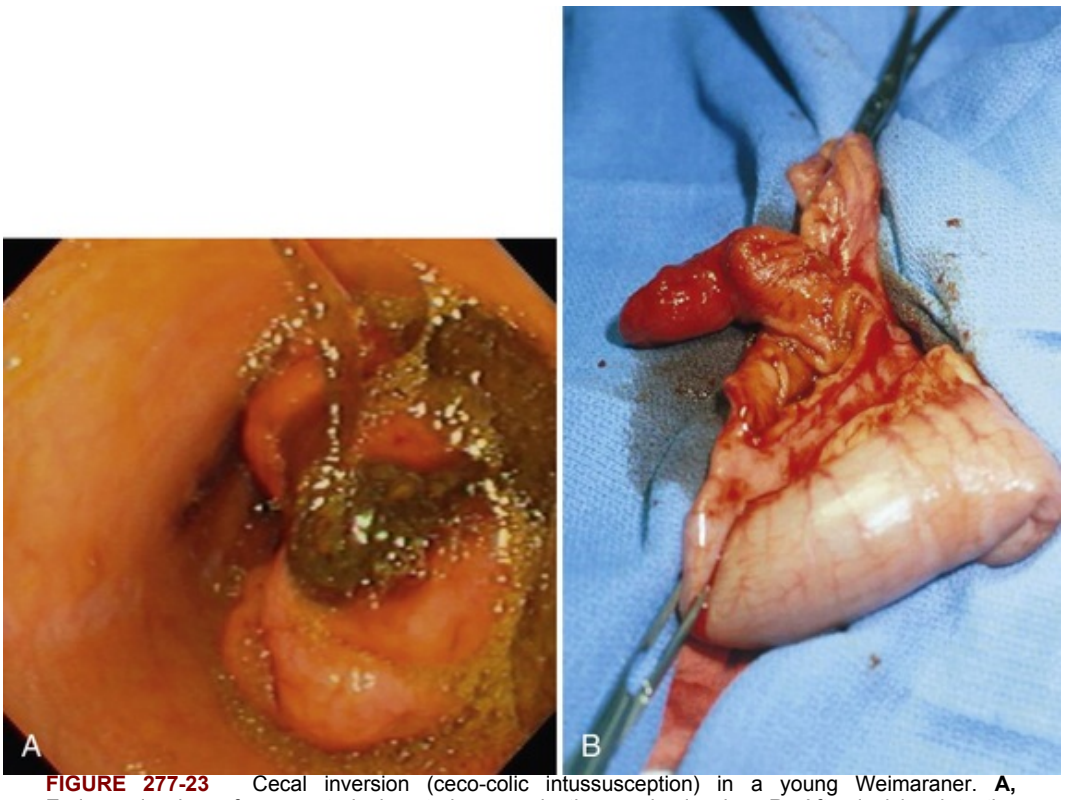


FIGURE 277-23 Cecal inversion (ceco-colic intussusception) in a young Weimaraner. **A,** Endoscopic view of an everted ulcerated cecum in the proximal colon. **B,** After incision into the proximal colon, the hemorrhagic everted cecum is exposed and can be removed by typhlectomy. (Images courtesy Alasdair Hotston-Moore.)

This unusual condition is reported exclusively in dogs, and is presumed to be rare in cats because they have a much shorter, less mobile cecum. *Trichuris* infection is claimed to predispose dogs to this condition, but it can be seen in dogs after diarrhea due to other causes. Treatment is by typhlectomy (Figure 277-23, *B*).

Colonic Vascular Ectasia (Angiodysplasia)[525-529]

There are a few case reports of angiodysplasia in the colon or rectum of young dogs. The vascular ectasia lesion(s) often bleed(s) profusely, leading to marked hematochezia, with patients sometimes needing blood transfusions. Diagnosis is made by colonoscopy when areas of coalescing, tortuous mucosal blood vessels are observed. It may be treated successfully by surgical excision of the affected region, but it can be challenging to detect the lesion at surgery from the serosal surface, and multiple surgeries may still be unsuccessful. Laser ablation and electrocoagulation may also be tried. However, in some cases the condition can affect much of

the colon and rather than perform subtotal colectomy, there are reports of successful management with estrogens.

Visceral Myopathy and Cecal Impaction[530]

A case of cecal impaction associated with visceral myopathy and intestinal pseudo-obstruction has been reported (see ch. 276).

Colonic Perforation[170,472,531-534]

Colono-rectal perforations are rare, but can be caused by trauma (e.g., pelvic fractures, over-vigorous colonic biopsy) and irradiation, or by insertion of a thermometer or other foreign objects. Perforation may also occur after neurogenic colonic ulceration.

Neurogenic Colonic Ulceration[535-537]

Very rarely, colonic ulcers develop in patients with acute intervertebral disc disease or after spinal surgery. They tend to occur in the proximal colon, especially at the left colic flexure. The mechanism is poorly understood, and is complicated by the fact that many of these patients are also treated with glucocorticoids. Localized ischemia and increased intraluminal pressure of neurogenic origin are thought to be involved, with glucocorticoids reducing mucin production and impairing healing. Initially, colonic ulceration will cause hematochezia, but eventually may lead to perforation and septic peritonitis. The prognosis is poor.

Diseases Causing Obstruction

Neoplasia of the LI is the most common cause of LI obstruction (see above). Other non-neoplastic, intramural processes such as intussusception, hematoma, and fibrosing stricture can potentially cause obstruction; FIP granuloma and phycomycosis (see above) should be included in the differential diagnosis list. Linear and nonlinear foreign bodies, and compression by an enlarged prostate, can also cause intraluminal and extraluminal obstruction respectively.

Intussusception[165,168,258,538-558]

An intussusception is an invagination of one segment of the GI tract *(intussusceptum)* into the lumen of the adjoining segment *(intussuscipiens).* Enterocolic intussusceptions account for the majority of cases reported and can be divided into three types: ceco-colic (or cecal inversion; see above), ileo-colic, and the very rare ileo-cecal. Of the three forms of entero-colic intussusception, the ileo-colic intussusception is the one most frequently encountered in practice and the one that most likely causes obstruction. Predisposing factors include intestinal parasitism, viral enteritis, foreign bodies, and masses, and can follow an episode of acute diarrhea. However, many ileo-colic intussusceptions are seen in young animals and appear idiopathic with a suggestion that there is underlying intestinal muscular incoordination because the enteric nervous system is not fully developed. Intussusceptions in older animals usually develop around a lesion such as a tumor or causes of focal peritonitis (e.g., perforation, wound dehiscence).

Pathophysiology

Invagination followed by intussusception of the ileum into the colon results in luminal obstruction and distension of the bowel segment proximal to the intussusception. Because the mesentery and blood supply are included in the invaginating segment, vascular compromise can occur, which initially leads to edema and intramural hemorrhage and eventually to ischemia and necrosis of the bowel.

Clinical Examination

Clinical signs of ileo-colic intussusception are intermittent vomiting, progressive loss of appetite, mucoid bloody diarrhea, and a palpable, cylinder-shaped mass in the cranial abdomen; abdominal pain is not a consistent finding. Most cases are acute, but chronic intussusception is possible when affected animals may eventually succumb to the effects of anorexia or blood loss rather than dehydration (Figure 227-24, *A* and *B*).

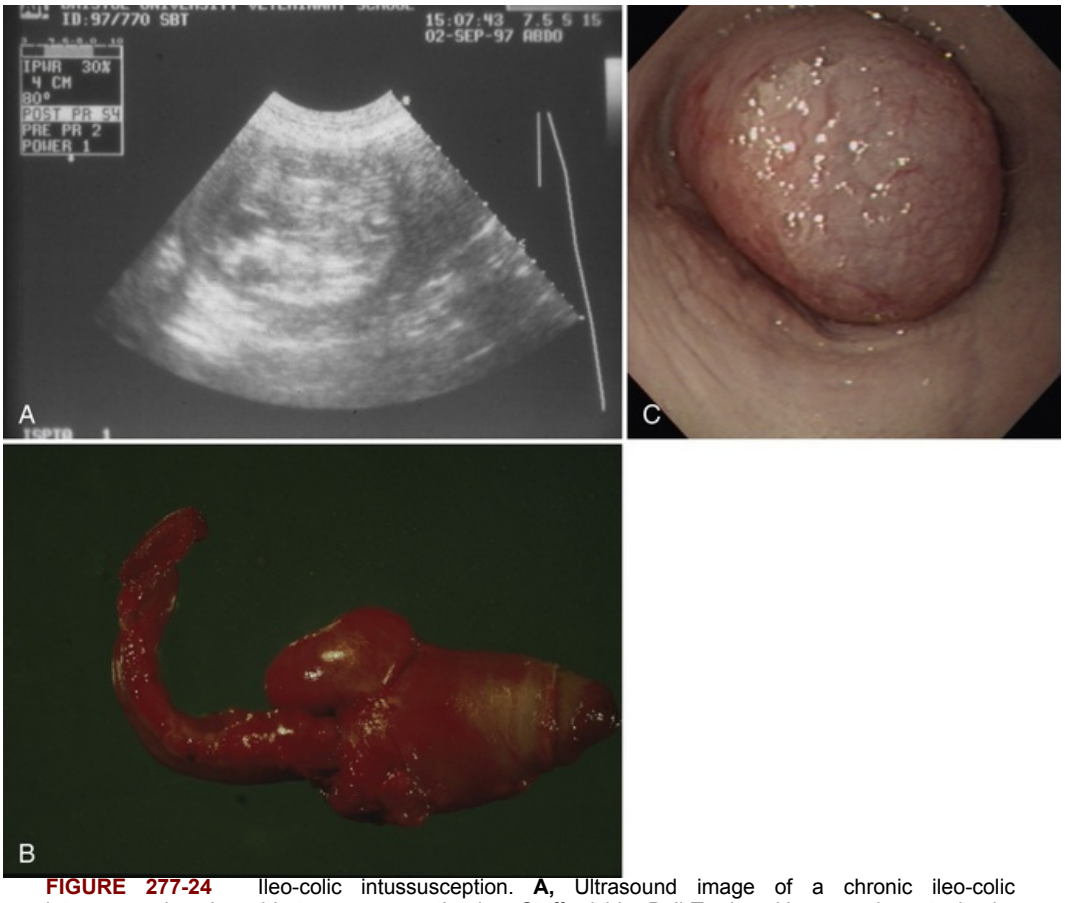


FIGURE 277-24 Ileo-colic intussusception. **A,** Ultrasound image of a chronic ileo-colic intussusception viewed in transverse section in a Staffordshire Bull Terrier with severe hematochezia. The normal double layering is not evident as the lesion has been present for 10 days and adhesions have developed between the intussusceptum and intussuscipiens. **B,** Ileocecocolic region resected from the dog in **A. C,** Endoscopic appearance of an early ileo-colic intussusception in a mix-breed dog.

Diagnosis

With some ileo-colic intussusceptions, the intussusceptum may eventually protrude through the anus, and must be differentiated from a rectal prolapse. A blunt probe passed between the protruding segment and the anal sphincter is indicative: if the probe can be passed cranial to the pubis without reaching a fornix, then the protruding bowel is the apex of an intussusception. Survey abdominal radiographic findings may be suspicious for intussusception, but abdominal ultrasonography is the preferred method of diagnosis. The appearance of a target-like mass consisting of two or more hyperechoic and hypoechoic concentric rings in transverse section, or multiple hyperechoic and hypoechoic parallel lines in longitudinal section, is virtually pathognomonic. Colonoscopy is rarely indicated, but if performed the intussusceptum may be visualized (Figure 277-24, *C*).

Treatment and Prognosis

Surgical management of ileo-colic intussusception involves either reduction or resection and anastomosis. If possible, the ileo-ceco-colic region is preserved to reduce reflux and fecal contamination of the ileum. Short bowel syndrome will occur if large lengths of the SI have to be resected (see ch. 276). The most common complications after surgery are recurrence, dehiscence and peritonitis, ileus, and intestinal obstruction. The recurrence rate in dogs is reported to be between 11% and 20%, and is most likely if there is any leakage at the anastomosis site causing a localized peritonitis. Historical attempts to prevent recurrence by administration of hyoscine to induce ileus may actually have an increased risk, and an early return to enteral nutrition and hopefully normal motility is now recommended. If recurrence occurs, surgical enteroplication of intestinal loops can be performed.

Stricture[176,472,477,559-562]

A benign LI stricture is rare in dogs and cats, and a suspicion of underlying neoplasia should always be considered, unless there is a history of previous LI surgery or foreign body impaction that could have caused a hematoma or ulceration with subsequent fibrosis. Inflammatory strictures have been reported in cats. Non-accidental injury must also be considered as potential cause. Constipation proximal to the stricture will occur, and treatment is by balloon dilatation or stenting.

Foreign Body

If an intestinal foreign body causes an obstruction, it is most likely to occur in the SI. Only occasionally do foreign bodies obstruct the colon as they first have to pass the much narrower SI and ileocolic sphincter.

Irritable Bowel Syndrome[1,563-568]

In human patients, irritable bowel syndrome (IBS) is a multifactorial, functional disorder of the GI tract, and is characterized by waxing and waning abdominal pain in association with diarrhea and/or constipation. Underlying psychological problems may predispose, and patients may have heightened awareness of GI motility, but IBS can also follow acute bacterial gastroenteritis, when the enteric nervous system remains disrupted for many months. The condition can be managed with central analgesics such as tricyclic antidepressants or selective serotonin reuptake inhibitors in addition to psychological interventions.

An idiopathic LI diarrheal syndrome has been characterized in dogs and has been likened to human IBS, yet whilst mucoid diarrhea and tenesmus predominate over constipation, hematochezia may occur. However, there are strict definitions (Rome III criteria) for diagnosing IBS in people, and hematochezia must not be present. Thus, it is not clear that dogs truly suffer IBS. Yet all investigations in dogs with this syndrome are negative for bacterial and other pathogens, histologic evidence of colitis, and colonic neoplasia, and the term chronic idiopathic large-bowel diarrhea has been used instead. Dogs affected with this syndrome may respond to the feeding of a highly digestible diet supplemented with soluble fiber. Anxiolytics (e.g., Librax [chlordiazepoxide with clidinium bromide, an antimuscarinic]) and antispasmodics (e.g., hyoscine, mebeverine, peppermint oil) are also reported to have some efficacy, although there is a suspicion of a strong placebo effect on the owner; this reduces the stress in the dog, which may actually be the cause or at least exacerbate the problem.

Constipation

Constipation and obstipation are manifestations of the same problem but of differing severity. Constipation is defined as infrequent or difficult evacuation of feces but does not necessarily imply a permanent loss of function; patients may suffer from one or two episodes of constipation without further progression. Intractable constipation that has become refractory to cure or control is referred to as obstipation and therefore implies a permanent loss of function. A patient is assumed to be obstipated only after several consecutive treatment failures. Dilated megacolon is the end stage of colonic dysfunction, whatever the cause (also see ch. 42).

Constipated animals typically show dyschezia: repeated unsuccessful attempts to defecate or pain on defecation, although sometimes liquid fecal material oozes out. With obstipation and megacolon, the patient may give up attempts to defecate, but eventually becomes unwell with vomiting, anorexia and dehydration. Megacolon develops through two pathologic mechanisms: dilation and hypertrophy. Hypertrophic megacolon develops as a consequence of obstructive lesions (e.g., malunion of pelvic fractures, tumors, foreign bodies). Hypertrophic megacolon due to pelvic constriction may be reversible with early pelvic osteotomy, or it may progress to irreversible dilated megacolon if appropriate therapy is not instituted. Dilated megacolon may occur secondary to electrolyte abnormalities, neuromuscular disorders or be idiopathic.

There are several factors that can predispose to constipation (see Figure 276-6, *C*; ch. 42) and hospitalized cats are particularly at risk because of lack of activity, unwillingness to defecate whilst kenneled, tendency to develop dehydration and hypokalemia when unwell, and the administration of opioid analgesics. Specific causes such as pelvic fracture and tail-pull neurological injuries are also more common in cats. Prostatomegaly in intact male dogs, and perineal hernia in bitches are more common reasons for constipation in dogs, which are also predisposed by eating bones.

A review of published cases suggests that 96 per cent of cases of obstipation in cats are accounted for by

idiopathic megacolon (62%), pelvic canal stenosis (23%), nerve injury (6%), or Manx sacral spinal cord deformity (5%). A smaller number of cases is accounted for by complications of colopexy (1%) and colonic neoplasia (1%); colonic hypoganglionosis or aganglionosis was suspected, but not proven, in another 2% of cases. Endocrine factors (e.g., obesity, hypothyroidism) were cited in several cases but were not necessarily implicated as part of the pathogenesis of megacolon. Thus the majority of cases are idiopathic, orthopedic or neurologic in origin.

Diagnosis

Constipation and obstipation are usually readily identified by abdominal palpation.

A complete neurologic examination should be performed with special emphasis on caudal spinal cord function, to identify spinal cord injury, pelvic nerve trauma, and Manx sacral spinal cord deformity (see ch. 259). Cats with constipation due to dysautonomia may have other signs of autonomic nervous system failure, such as urinary retention, regurgitation due to megaesophagus, mydriasis, decreased lacrimation, prolapse of the nictitating membrane, and bradycardia.

Digital rectal examination should be performed carefully, and always under sedation or anesthesia in cats. Pelvic fracture malunion may be detected and it may also identify foreign bodies, rectal diverticula, strictures, inflammation, or neoplasia.

Although patients are unlikely to have significant changes in laboratory data, a CBC and serum biochemistry profile should be performed in all patients with obstipation and megacolon where a physical cause cannot be found. Metabolic causes of constipation, such as dehydration, hypokalemia, and hypercalcemia may be detected. Basal serum thyroxine concentration and other thyroid function tests should also be considered in animals with recurrent constipation and other signs consistent with hypothyroidism.

Radiographs should be performed to characterize the severity of colonic impaction and to identify predisposing factors, such as intraluminal radiopaque foreign material (e.g., bone chips), intraluminal or extraluminal mass lesions, pelvic fractures, and spinal abnormalities (Figure 277-25). Extraluminal mass lesions may be further evaluated by abdominal ultrasonography and guided biopsy, whereas intraluminal mass lesions are best evaluated by endoscopy after the fecal material has been cleaned out (see ch. 114).

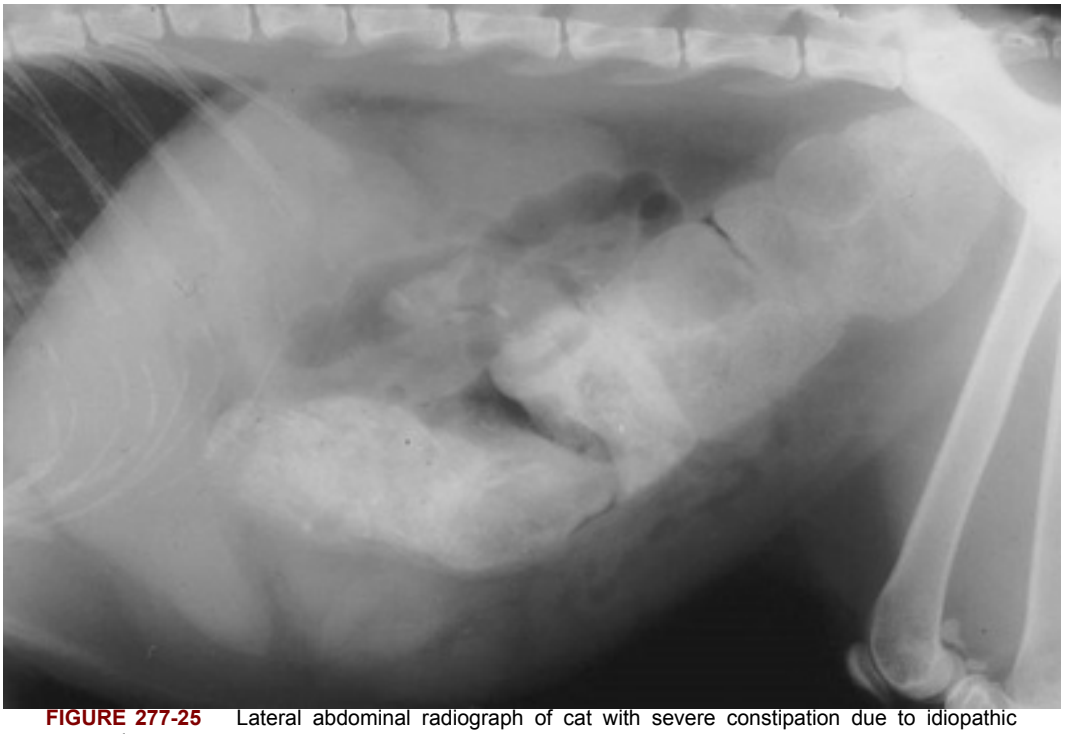


FIGURE 277-25 Lateral abdominal radiograph of cat with severe constipation due to idiopathic megacolon.

Treatment[45,171,175,569-577]

The specific therapeutic plan will depend upon the severity of constipation and the underlying cause. First episodes of constipation are often transient and resolve without therapy; hospitalized cats should be kept hydrated and fed a fiber-containing diet. Mild to moderate or recurrent episodes of constipation may be managed, often on an outpatient basis, with dietary modification, warm water enemas, oral or suppository laxatives, colonic prokinetic agents, or a combination of these therapies (see ch. 114). Severe cases of constipation usually require brief periods of hospitalization to correct dehydration and metabolic abnormalities and to evacuate impacted feces using water enemas, manual extraction of retained feces, or both. Follow-up therapy in such cats is directed at correcting predisposing factors and preventing recurrence. Subtotal colectomy will become necessary in cats suffering from obstipation or idiopathic dilated megacolon.

Removal of Impacted Feces

This may be accomplished through the use of suppositories, oral laxatives, enemas, rectal suppositories, or manual extraction.

Rectal Suppositories

Rectal suppositories may contain dioctyl sodium sulfosuccinate (DSS), an emollient laxative also called docusate; glycerol (syn. glycerin[e]), a lubricant laxative; or bisacodyl, a stimulant laxative. Their use requires a compliant pet and pet owner, but they can be used alone or in conjunction with oral laxative therapy as a first-line treatment, or as a way of preventing recurrence.

Laxatives

Laxatives promote evacuation of the bowel by stimulation of fluid and electrolyte transport and/or propulsive motility. Many products are available and most are bulk-forming laxatives containing dietary fiber supplements derived from cereal grains, wheat bran, or psyllium. Fiber supplemented diets are available commercially, or the pet owner may wish to add psyllium, wheat bran or pumpkin to canned food.

Emollient Laxatives

Emollient laxatives are anionic detergents that increase the miscibility of water and lipid in digesta, thereby enhancing lipid absorption and impairing water absorption. Docusate or DSS is available in oral and enema forms. Dioctyl calcium or potassium sulfosuccinate are alternatives in some countries.

Lubricant Laxatives

Lubricant laxatives include mineral oil ("liquid paraffin"), petrolatum (petroleum jelly) and a more palatable combination of white paraffin and beeswax (Katalax). The lubricating properties of these agents impede colonic water absorption and ease fecal passage. These effects are usually moderate and, in general, lubricants are only beneficial in mild constipation. Mineral oil use should probably be limited to rectal administration because of the risk of lipoid aspiration pneumonia with oral administration, especially in depressed or debilitated cats as it is tasteless and may be inhaled rather than swallowed. White paraffin products are more easily administered by cat owners, as they only need to be smeared on the cat on a site where it can be licked off.

Hyperosmotic Laxatives

Hyperosmotic laxatives consist of the poorly absorbed polysaccharides (lactose, lactulose, lactitol), magnesium salts (citrate, hydroxide, sulfate), and oral colonic cleansers such as hypertonic sodium phosphate and PEGs (see preparation for colonoscopy). Lactulose and PEGs are the most effective agents in this group. The organic acids produced from lactulose fermentation stimulate colonic fluid secretion and propulsive motility. Lactulose administered at an oral dosage of 0.5 mL/kg every 8 to 12 hours should consistently produce soft feces in cats. Many cats with recurrent or chronic constipation have been well managed with this regimen, but mild cases may be managed with just the addition of milk to the diet.

Stimulant Laxatives

Stimulant laxatives—bisacodyl, danthron (codanthramer), phenolphthalein, castor oil, cascara, and senna—are a diverse group of agents that stimulate propulsive colonic motility. Bisacodyl, for example, stimulates nitric oxide-mediated epithelial cell secretion and myenteric neuronal depolarization. Diarrhea results from the combined effect of increased mucosal secretion and colonic propulsion. Bisacodyl (at a dosage of 5 mg orally, every 24 hours) is the most effective stimulant laxative in the cat. Lubiprostane is a newer laxative

developed for people, which increases colonic secretion by stimulating chloride channels. Its use in animals has not been reported.

Enemas

Enemas may be required for moderate or severe episodes of constipation. Either warm tap water (5 to 10 mL/kg) or enema solutions including warm isotonic saline (5 to 10 mL/kg), DSS (5 to 10 mL/cat), mineral oil (5 to 10 mL/cat), or lactulose (5 to 10 mL/cat) can be used. They should all be administered slowly via a well-lubricated rubber catheter or feeding tube from an enema bucket or using a Higginson pump so that excessive pressure is not applied (see ch. 114). Enemas containing sodium phosphate are contraindicated in cats and small dogs because of their propensity for inducing fatal hypernatremia, hyperphosphatemia, and hypocalcemia.

Manual Extraction

Manual extraction of impacted feces is required for cases unresponsive to laxatives or enemas. Warm water or saline is infused into the colon, while the fecal mass is gently massaged by abdominal palpation. Digital extraction of feces from the rectum is then performed. It is often advisable to evacuate all of the fecal mass over a period of several days to reduce the risks of prolonged anesthesia and risk of perforation of a stretched and devitalized colonic wall. "Spoon" devices to evacuate the feces should only be used with great caution.

Preventative Therapy[477,578]

Once impacted feces have been cleared, it is important to institute measures to prevent recurrence. Any underlying cause should be corrected if possible (e.g., pelvic osteotomy, stricture dilatation or stenting [see ch. 123], castration to reduce prostatomegaly), and any predisposing factors such as dehydration, lack of exercise, over-feeding, etc., avoided. Feeding a diet with added fiber and/or milk are simple but often effective strategies, but in some cases, pharmacologic intervention is still required.

Colonic Prokinetic Agents[71-73,567,579-595]

In vitro studies have shown that cisapride stimulates feline colonic smooth muscle contraction. Although this has not yet been conclusively shown *in vivo,* a large body of anecdotal experience suggests that cisapride is effective in stimulating colonic propulsive motility in mild to moderate idiopathic feline constipation. Longstanding obstipation and megacolon cases are not likely to respond. Unfortunately, cisapride was withdrawn from many drug markets in 2000 after reports of cardiac side effects (prolonged QT) and sudden death in people. Ranitidine and nizatidine were suggested as alternatives, as they have prokinetic activity *in vitro* stimulating cholinergic activity, but experience indicates they are not very effective *in vivo.*

Tegaserod, a potent partial agonist at 5-HT_4 receptors and a weak agonist at 5-HT_{1D} receptors, was developed as it had definite prokinetic effects in the canine colon, but again it has been withdrawn because of prolongation of the QT interval. Prucalopride is related to cisapride with a similar prokinetic activity but no cardiac effects and is now available in Europe. It is a potent 5-HT4 receptor agonist that stimulates GMCs and defecation in dogs and cats. The related mosapride has no activity in the colon, and is as ineffective as metoclopramide in stimulating colonic motility.

Acotiamide facilitates muscarinic acetylcholine activity and has been shown to stimulate post-prandial gastroduodenal and colonic activity in dogs at a dosage of 30 mg/kg and has been approved (Acofide) for use in human patients in Asia. High dosages of mirtazapine have also been shown to accelerate gastric emptying and colonic transit, in addition to the better known appetite stimulant and anti-nausea effects. Finally intra-colonic installation of capsaicin, the ingredient of chilies, stimulates colonic motility and defecation, but when given orally slows SI transit.

Prognosis

Many animals can have one or two episodes of constipation without further recurrence, although others may progress to complete colonic failure. Cats with mild to moderate constipation generally respond to conservative medical management with dietary modification, emollient or hyperosmotic laxatives, and colonic prokinetic agents. Early use of colonic prokinetic agents, in addition to one or more laxative agents, is likely to prevent the progression of constipation to obstipation and megacolon in these cats, which otherwise eventually require colectomy.

Feline Idiopathic Megacolon[143,596-602]

Idiopathic megacolon is most commonly observed in middle-aged (mean: 5.8 years) male (70%) domestic shorthair (46%), domestic longhair (15%), or Siamese (12%) cats. Affected cats usually have reduced, absent, or painful defecation for a period of time ranging from days to weeks or months. Cats may be observed making multiple, unproductive attempts to defecate in the litter box, or just sitting in the litter box for prolonged periods of time. Colonic impaction is a consistent physical examination finding in affected cats. Other findings will depend upon the severity and chronicity of the obstipation and megacolon, and include dehydration, weight loss, debilitation, abdominal pain, and mild to moderate mesenteric lymphadenopathy.

The etiopathogenesis of idiopathic megacolon is incompletely understood but affected cats have permanent loss of colonic structure and function. Medical therapy (laxatives, prokinetics) may be effective initially, but most affected cats eventually require colectomy. The pathogenesis of idiopathic dilated megacolon appears to involve functional disturbances in colonic smooth muscle. The lesion may begin in the descending colon and progress to involve the ascending colon over time. *In vitro* studies show that colonic smooth muscle obtained from cats suffering from idiopathic dilated megacolon undergoing colectomy develops less isometric stress in response to neurotransmitters (acetylcholine, substance P, cholecystokinin), membrane depolarization (KCl), or electrical field stimulation when compared with healthy controls.

Subtotal colectomy should be considered in cats that are refractory to medical therapy.[603-611] Cats have a generally favorable prognosis for recovery after colectomy, especially if the ileocolic valve is preserved, although mild to moderate diarrhea may persist for weeks to months postoperatively in some cases.

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CHAPTER 278

Rectoanal Disease

Stefan Unterer

The distal portion of the digestive tract, including the anal canal and rectum, is a very sensitive part of the gastrointestinal (GI) tract and irritation of the rectal mucosa and perianal area frequently causes severe pain, tenesmus and dyschezia. Dysfunction of the anorectum can lead to fecal incontinence, which affects hygienic and social aspects of pet owners' lives and is associated with clinical distress of the patient. Immediate and intense symptomatic treatment and a thorough problem-oriented work-up usually are indicated in patients with rectoanal disease.

Anatomy

Rectoanal structures include the rectum, anal canal, internal and external anal sphincter, muscles of the pelvic diaphragm, as well as the anal sacs (paranal sinus) and circumanal glands (glandulae circumanales) (Figure 278-1). The rectum begins at the pelvic inlet. Before joining the short anal canal, it becomes dilated to form the rectal ampulla, which is absent in cats. The lumen of the anal canal is constricted at the rectoanal junction, where longitudinal folds of the mucosa (more prominent in dogs than in cats) press together to occlude the orifice. The mucosa of the anal canal is divided into three consecutive annular zones, the columnar, intermediate, and cutaneous zones. Endoscopically visible, small, solitary lymph nodules (1-3 mm) are a prominent feature of the rectal mucosa. Fecal continence depends primarily on two sphincters: the internal anal (thickened circular smooth muscle of the gut; continuous maximal contraction under involuntary control) and the external anal (striated muscle; contraction during phases of rectal distention under voluntary control) sphincters.

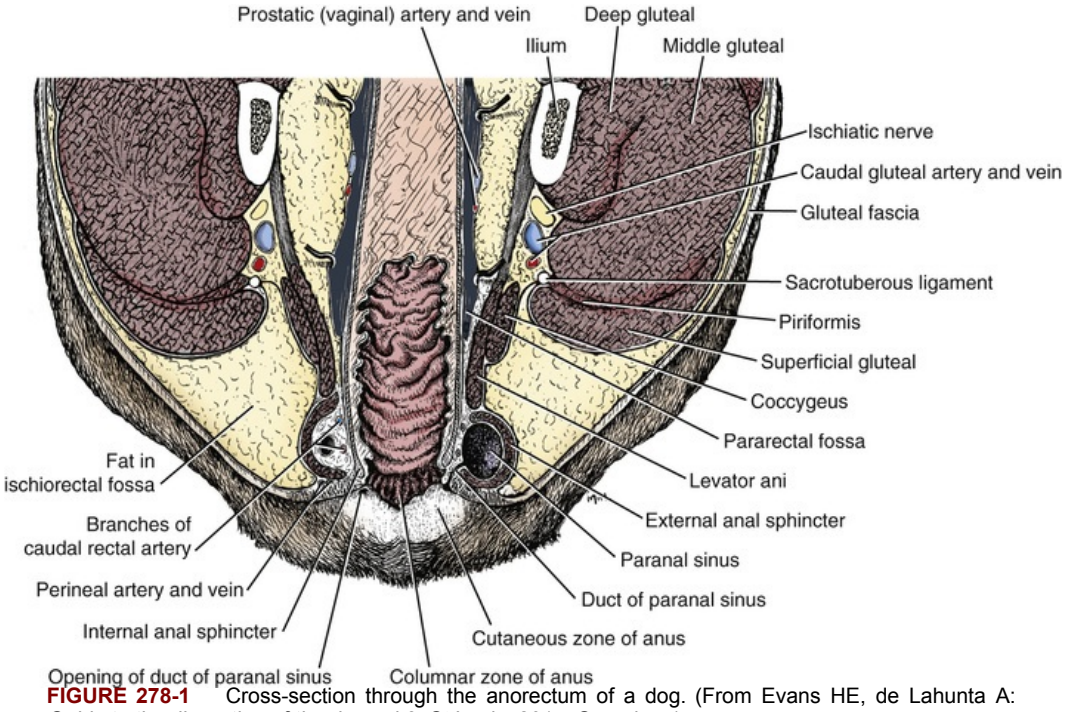


FIGURE 278-1 Cross-section through the anorectum of a dog. (From Evans HE, de Lahunta A: *Guide to the dissection of the dog*, ed 8, St Louis, 2017, Saunders.)

Three glandular areas are present in the rectoanal and perianal regions. The anal glands (glandulae anales) are tubuloalveolar glands that produce a fatty secretion and open to the outside in the columnar and intermediate zones. The paranal sinus glands (glandulae sinus paranalis) lie in the wall of, and open into, the paranal sinuses (anal sacs). Their foul-smelling, serous to pasty secretion is important for territorial marking. The anal sacs are located between the inner smooth and the outer striated muscle of the anus on each side of the anal canal and open ventrolateral to the anus through an aperture 1 to 2 mm wide. The apertures are visible, or can be exposed by pulling the skin on either side of the anus ventrolaterally.

The retroperitoneal part of the rectum and anal tract is supported by connective tissue and by the muscles of the pelvic diaphragm. The pelvic diaphragm is composed of two skeletal muscles (levator ani and coccygeus muscles) and two layers of fascia (external and internal fascia of the pelvic diaphragm). The paired rectococcygeal muscle detaches from the dorsolateral part of the longitudinal layer of the rectal smooth muscle and extends to the fifth and sixth tail vertebrae.[1] The coccygeus muscles cross the rectum laterally and tend to compress the tube, while the rectococcygeus aids the circular muscle layer in moving the fecal column to the outside.[2] Lymphatic drainage of the anal skin via the superficial inguinal lymph nodes and lymphatics from deeper tissues drain into the large medial iliac lymph node.

The descending colon, rectum, and internal smooth muscle sphincter of the anus are innervated by sympathetic fibers originating from L1-L4 or L5 spinal cord segments via the hypogastric nerves. The sympathetic innervation to the descending colon and rectum is inhibitory, whereas it is facilitory to the internal anal sphincter. Parasympathetic fibers originating in the sacral spinal cord innervate the descending colon and rectum via the pelvic nerve and stimulate colonic and rectal motility. Somatic fibers from the sacral cord innervate the striated muscle of the well-defined external anal sphincter via the pudendal nerve, leading to a conscious contraction of the sphincter. Afferent fibers from the rectal wall, sphincters, and perineum ascend in the dorsal and lateral funiculi to the brainstem centers for upper motor neuron regulation and to the cerebral cortex for conscious perception[3] (Figure 278-2).

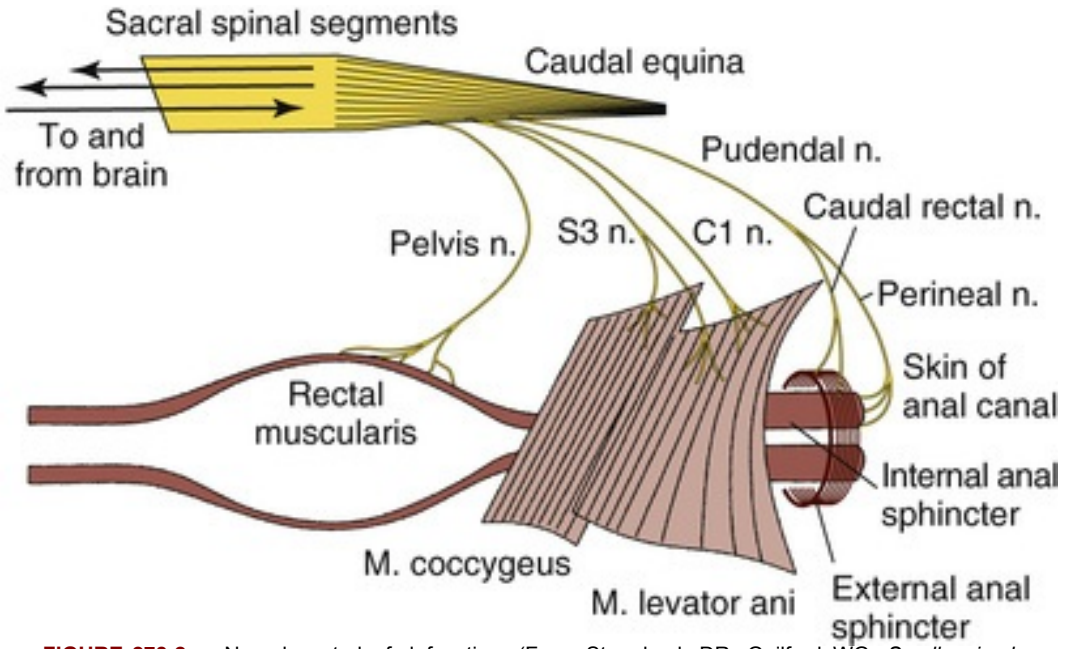


FIGURE 278-2 Neural control of defecation. (From Strombeck DR, Guilford WG: *Small animal gastroenterology*, ed 2, Davis, CA, 1990, Stonegate Publishing.)

Since innervation of the rectum is similar to that of the urinary bladder, dysuria also can be associated with neurologic disorders causing anorectal disease.

Physiology of Defecation

Food intake can stimulate defecation by inducing propagating pressure waves, which move intestinal content into the rectum (gastrocolic reflex).[4] Increased intrarectal pressure causes reflexive relaxation of the internal

anal sphincter (rectosphincteric inhibition reflex).[5,6] However, afferent fibers from the rectal wall ascend in the dorsal and lateral funiculi to the brainstem centers for upper motor neuron regulation and to the cerebral cortex for conscious perception. Prior to defecation, the rectosphincteric inhibition reflex is suppressed and the strength of the striated muscle in the external anal sphincter (mediated by somatic innervation from the sacral spinal cord) is increased until the conscious decision is made to initiate defecation.[7] If defecation is conscious, the suppressed intrarectal pressure declines through relaxation of the rectum (i.e., rectal accommodation). This allows a larger volume of stool to be maintained in the rectum at a lower intraluminal pressure (i.e., storage phase).[8] Progressively increasing fecal volumes stimulate progressively stronger urges to defecate. Defecation usually is preceded by colonic giant migrating contractions which produce the major propulsive power evacuating fecal materials from the rectum.[9,10] Ideally, dogs should be taken for a walk 20-30 minutes after eating to help produce a bowel movement. The actual impulse for defecation originates in the cerebral cortex and descends via motor tracts through the brainstem to the lower motor neurons. The parasympathetic innervation via the pelvic nerve stimulates colonic and rectal motility. Posturing and increasing intrapelvic pressure by contraction of the abdominal muscles and diaphragm facilitate defecation. Coordinated relaxation of the external anal sphincter, mediated by somatic fibers from the sacral plexus and the caudal rectal branch of the pudendal nerve, simulatenously occurring as intrarectal pressure increases, causes expulsion of stool.

History and Physical Examination in Patients With Suspected Rectoanal Disease

Patients with rectoanal disease can present with a variety of clinical manifestations. Common clinical signs include constipation, tenesmus, urgency to defecate, passage of mucus, and hematochezia/rectal bleeding (see ch. 42). Tenesmus ani (i.e., straining to defecate) frequently is observed in obstructive and inflammatory disorders of the anorectum. However, tenesmus also can be seen in patients with urogenital disorders and frequently owners are not able to differentiate between GI or urogenital signs. Asking about urinary habits, observing the patient's posture during straining, and palpation of the pelvic urethra and the prostate in male dogs will help the veterinarian localize the problem.

A good physical examination including a thorough abdominal palpation and digital rectal examination is the first step in differentiating between large bowel obstruction and inflammation once the problem is localized to the lower GI tract (see ch. 2). In obstructive disorders, the bowel typically is fecally impacted before the stenosis. Abdominal palpation often can detect an impacted colon; however, occasionally abdominal radiographs are required. A fecally impacted rectal ampulla can be identified with digital rectal examination. A substantial amount of feces in the rectum of a straining patient is indicative of constipation, and occasionally, rectal examination can identify a cause for obstruction (e.g., rectal stricture or mass, colonic deviation due to perineal hernia, pelvic canal stenosis). If no obstruction or deviation of the rectal wall can be detected, a motility disorder or ingestion of foreign material (e.g., bones, cat litter) is a frequent cause of impaction of the colon and rectal ampulla.

Proctitis—inflammation of the colorectal mucosa—is the most common cause of tenesmus in dogs and cats. It should be suspected with tenesmus, dyschezia, and/or hematochezia in the absence of constipation. The presence of concurrent large bowel diarrhea suggests more widespread inflammation of the colonic mucosa. The duration of clinical signs is of importance, because acute signs frequently are self-limiting and do not require an in-depth evaluation. In chronic disorders, owners should be asked if treatment trials have already been performed and whether a clinical improvement was observed with dietary changes, antimicrobial or anti-inflammatory/immunosuppressive treatment. Chronic tenesmus in a middle-aged to elderly, intact male dog in association with constipation and perianal swelling is typical for perineal hernia. Paradoxical large bowel diarrhea caused by fluid and mucus bypassing the retained fecal mass can be present. A digital rectal examination with unilateral or bilateral outpouching of the rectal wall should be diagnostic of perineal hernia; care must be taken not to perforate the distended rectal wall inadvertently. In dogs with a history of chronic tenesmus due to perineal hernia and an acute episode of severe straining or pain in the rectal area, an incarceration of the urinary bladder or intestine might be present. A retroflexed, filled urinary bladder should be suspected if the hernia is non-reducible by external digital pressure and a firm, fluid-filled structure is felt.

Rectal neoplasia can cause tenesmus/dyschezia due to obstruction (occluding or scirrhous tumors) or irritation of the rectal mucosa. Owners sometimes observe hematochezia and bright red blood coating the surface of formed stools. Rectal tumors are very easy to find when advanced; however, in the early stages, careful, methodical rectal examination and sometimes proctoscopy is necessary. Partial rectal strictures can

easily be missed in large dogs; in giant breeds, one may need to insert two or three fingers in order to see if the anus and rectum can expand to their normal diameters.

Perianal disorders can cause tenesmus/dyschezia due to anal stenosis (e.g., perianal/anal gland neoplasia, stricture formation secondary to chronic inflammation or perianal fistula), inflammation (e.g., perianal fistula associated with colitis, anal gland sacculitis), or constipation in patients avoiding defecation due to pain. Perianal licking and "scooting" are even more specific signs of perianal irritation. Diagnosis usually is straightforward by examination of the perianal area. Because of severe pain, sedation or general anesthesia sometimes is necessary to fully assess the severity of disease. In German Shepherds presenting with fistulous tracts in the perianal region, a diagnosis of perianal fistula usually can be made by physical examination alone. Other differentials for perianal ulceration and fistulation, such as neoplasia and rectal pythiosis, should be considered in any breed (see ch. 277). Anal sacculitis is a relatively common disease, but severe abscessation is infrequent. Careful palpation and expression of the anal sacs while one finger is inserted into the rectum are important to distinguish an impacted or abscessed anal sac from an anal sac tumor.

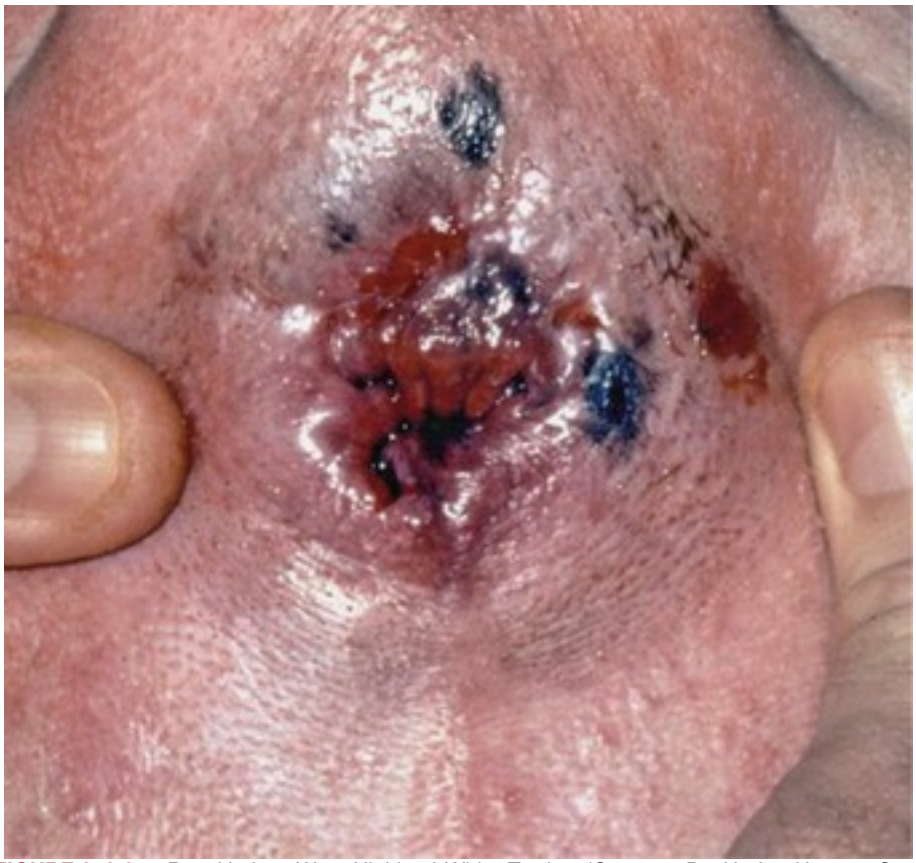
In animals with reservoir incontinence (i.e., altered rectal sensation due to inflammation), defecation usually is associated with tenesmus and urgency. In animals with sphincter incontinence (no conscious recognition of passage of feces) without obvious abnormalities of the anal sphincter, sacrococcygeal spinal cord dysfunction is very likely. A neurologic evaluation including observation of gait, evaluation of withdrawal reflexes and muscle tone of the pelvic limbs, evaluation of the perineal reflex and anal sphincter tone, and assessment of lumbosacral pain, is indicated in these cases.

Puppies and kittens with anorectal agenesis (imperforate anus) cannot defecate. During the first days postpartum, the abdomen progressively distends and the puppy or kitten becomes inappetent and lethargic. Patients with congenital anal stenosis and rectovaginal fistula can be asymptomatic for several weeks until constipation after weaning from the liquid diet occurs. Affected animals can be restless, start straining, and show an enlarged abdomen and bulging of the perineum.

Diseases of the Rectum

Proctitis

Proctitis—inflammation of the anus and rectum (E-Figure 278-3)—most commonly is associated with colitis (see ch. 277) or inflammatory perianal disorders such as perianal fistulas and sacculitis. Localized proctitis has been described in dogs following pelvic irradiation.[11] Additional causes include traumatic injury (e.g., foreign body) and mucosal reaction after rectal prolapse. Clinical signs of proctitis typically include tenesmus, dyschezia, and hematochezia. Urgency to defecate usually is a prominent sign and discharge of mucus, and less frequently of pus, can be observed. A thorough physical examination should be performed. A rectal examination can reveal evidence of neoplastic infiltration of the rectal wall or anus, a rectal stricture and/or a perineal hernia, all of which can cause clinical signs similar to those of proctitis. A fecal examination (see ch. 81) and rectal cytology are useful to detect parasites and an increased number of fecal leukocytes suggests infectious proctitis. The indication for proctoscopy (see ch. 113) and histologic evaluation of rectal mucosa, which is necessary for a definitive diagnosis, depends on the duration of clinical signs and success of treatment trials. Acute proctitis frequently is self-limiting or responds to empirical treatment with an easily digestible diet, anthelmintics (e.g., fenbendazole; see ch. 163), and short-term focal anti-inflammatory (e.g., budesonide rectal foam) and systemic analgesic (e.g., metamizole [dipyrone], buprenorphine; see ch. 126 and 166) medications. An increased number of leukocytes on fecal/rectal cytologic evaluation could be an indication for empirical antibiotic treatment (e.g., amoxicillin clavulanate, metronidazole; see ch. 220 and 277); routine fecal culture rarely is helpful.



E-FIGURE 278-3 Proctitis in a West Highland White Terrier. (Courtesy Dr. H. Jay Harvey, Cornell University.)

In chronic proctitis not responding to the above, proctoscopy and/or colonoscopy, with histologic evaluation of the colorectal mucosa, would be indicated (see ch. 113). The first biopsy, which should be taken with sterile forceps, should be submitted for culture and sensitivity testing for *E. coli* in order to identify an appropriate antibiotic in case granulomatous colitis/proctitis caused by invasive an *E. coli* strain is identified histologically.[12] Special stains (e.g., Gomori's methenamine silver, periodic acid-Schiff) might be necessary to detect invasive fungal infection.[13] In chronic idiopathic lymphocytic-plasmacytic or eosinophilic proctitis, systemic immunomodulatory drugs such as corticosteroids, aminosalicylates (not in cats), and/or cyclosporine should be used. Rectally administered topical agents could reduce the required dosage of systemic medication. Topical drugs currently used in human ulcerative proctitis include budesonide or hydrocortisone rectal foam, as well as 5-aminosalicylic acid and tacrolimus rectal preparations (see ch. 277).[14]

Perineal Hernia

The pelvic diaphragm of dogs is prone to herniation. Weak pelvic diaphragm muscles (coccygeal and levator ani muscles) fail to provide a strong support for the rectal wall. The muscles become thinner and stretched, resulting in focal, persistent rectal distention and potential fecal impaction. Perianal swelling or excessive laxity ventrolateral to the anus can be present. Due to rectal deviation, fecal material often becomes impacted in the rectum. General prevalence of perineal hernias (PH) in dogs is relatively low (≈0.1%-0.4%).[15] Canine PH occurs predominantly in middle-aged to elderly, intact male dogs and only occasionally in female dogs.[16] PH in cats is rare and generally secondary to underlying problems such as perineal urethrostomy, megacolon, perineal masses, or trauma.[17,18] Breed predispositions have been reported in the Boston Terrier, Boxer, Welsh Corgi, Pekingese, Collie, Poodle, Kelpie, Dachshund and Old English Sheepdog.[19,20]

Diagnosis

Perineal hernia typically can be diagnosed by history and clinical examination. Rectal examination will reveal a lack of support of the rectal wall with a deviation toward the side of the hernia for dogs with a unilateral

hernia and a dilation of the whole rectal ampulla for dogs with bilateral hernia. Most dogs with PH have chronic tenesmus and perianal swelling[21] (Figure 278-4) and typically are presented because of constipation or paradoxical large bowel diarrhea, as described above. Caudal displacement and herniation of the prostate, urinary bladder, and other abominal organs[21,22] can lead to dramatic clinical signs and occurs in 18% to 25% of affected dogs.[20,21,23,24] These structures can become strangulated, leading to an acute abdomen (see ch. 143). A retroflexed, full urinary bladder should be suspected if the hernia is non-reducible by external digital pressure and a firm, fluid-filled structure is felt; cystocentesis through the perineal wall can be confirmatory (see below). Abdominal radiographs can reveal fecal masses, soft tissue opacity due to herniated urinary bladder or prostate and air filled loops of small intestines in the perineal area (E-Figure 278-5 and Figure 278-6).[17] Positive (e.g., barium enema) or negative (e.g., insufflation of air) contrast studies of the rectum can confirm the diagnosis and assess severity and location (uni- versus bilateral) of the PH. Perianal ultrasound can evaluate contents within the hernia and identify urinary bladder retroflexion and herniation of the prostate (E-Figure 278-7). Imaging studies also are valuable for identifying some underlying diseases, such as colorectal obstruction (e.g., intra- and extraluminal masses), and prostatic (e.g., prostatitis, intra- and paraprostatic cysts) and lower urinary tract diseases (e.g., urolithiasis, neoplastic infiltration).

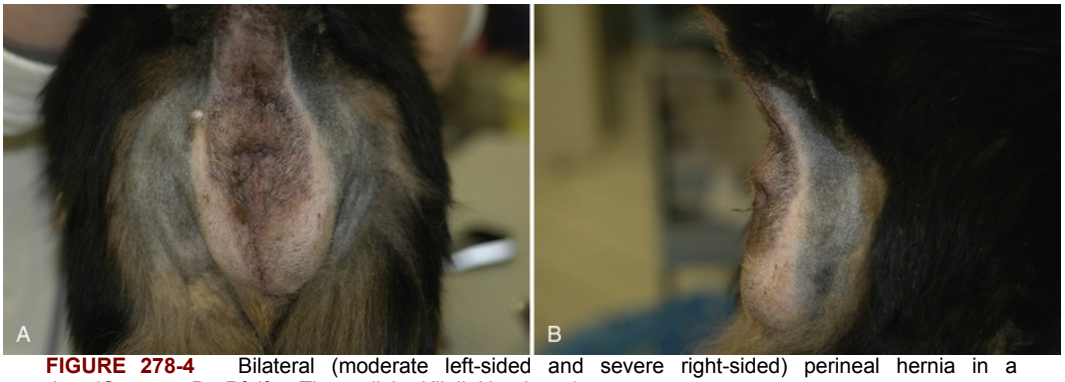


FIGURE 278-4 Bilateral (moderate left-sided and severe right-sided) perineal hernia in a dog. (Courtesy Dr. Pfeifer, Tierärztliche Klinik Nürnberg.)

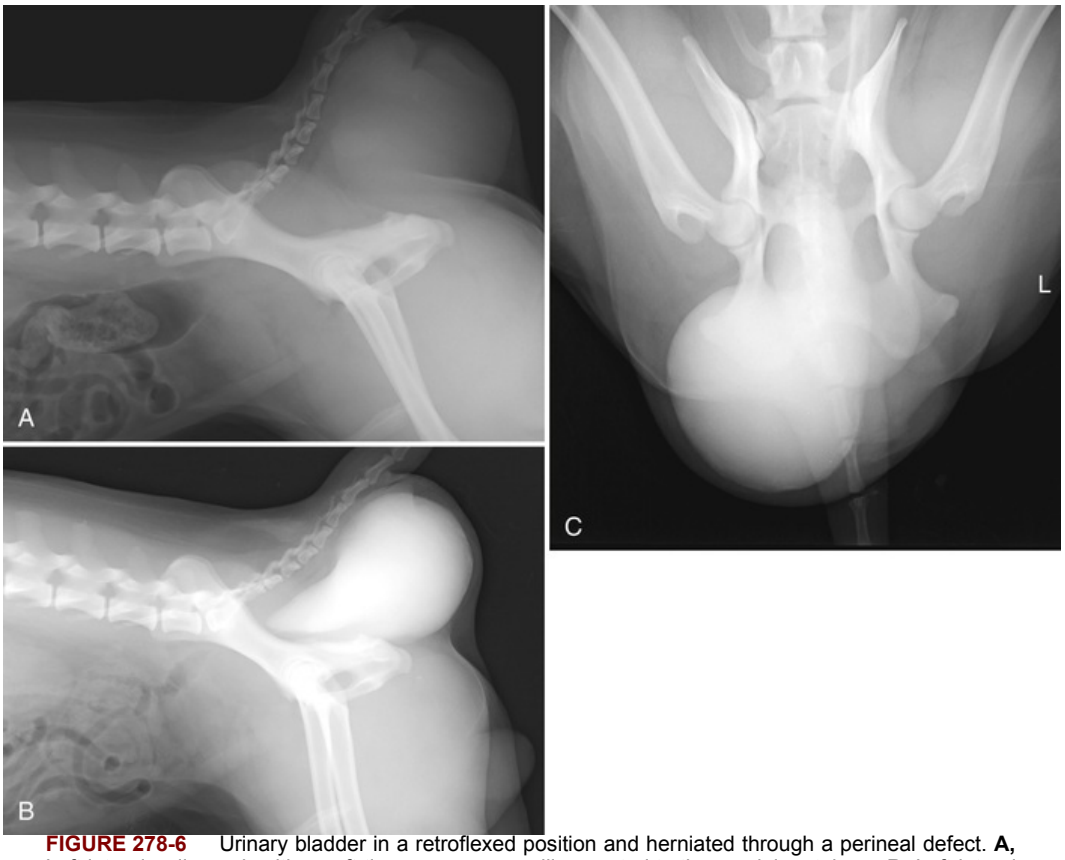
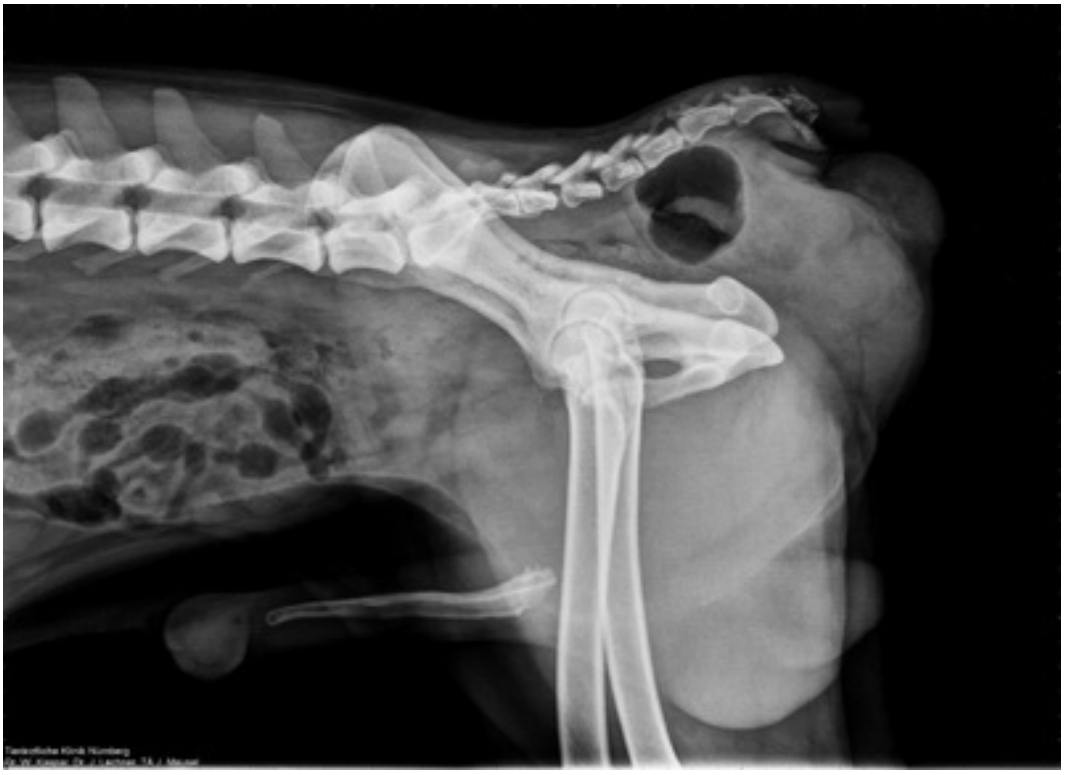
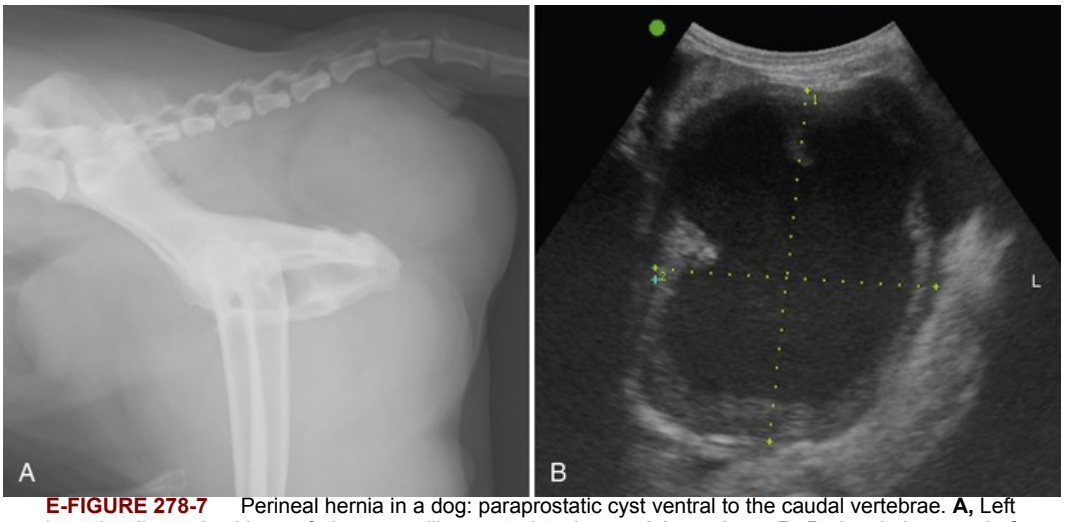


FIGURE 278-6 Urinary bladder in a retroflexed position and herniated through a perineal defect. **A,** Left lateral radiograph with a soft-tissue opaque swelling ventral to the caudal vertebrae. **B,** Left lateral and **(C)** ventrodorsal views of a positive contrast cystogram showing the retroflexed urinary bladder ventral to the caudal vertebrae. (Courtesy Dr. Ohlerth, Vetsuisse Faculty, University of Zurich, Switzerland.)



E-FIGURE 278-5 Intestinal loop within the perineal soft tissue opacity. (Courtesy Dr. Pfeifer, Tierärztliche Klinik Nürnberg, Germany.)



E-FIGURE 278-7 Perineal hernia in a dog: paraprostatic cyst ventral to the caudal vertebrae. **A,** Left lateral radiograph with a soft tissue swelling ventral to the caudal vertebrae. **B,** Perineal ultrasound of the herniated paraprostatic cyst, showing a large hypoechoic mass with hyperechoic rim. (Courtesy Dr. Ohlerth, Vetsuisse Faculty, University of Zurich, Switzerland.)

Bloodwork usually is normal but azotemia and hyperkalemia are possible with postrenal obstruction (e.g., retroflexed urinary bladder); an inflammatory leukogram can be noted with necrosis of incarcerated organs, prostatitis, or translocated bacteria through a damaged rectal wall. A minimum database can exclude concurrent disorders prior to anesthesia and surgical repair.

Pathogenesis

In dogs, breed- and sex-specific anatomical differences have been implicated in the development of PH.[25] Predisposition in brachycephalic dogs suggests an inherited weakness of the pelvic diaphragm in these breeds.[15] Finding PH almost exclusively in intact, male dogs suggests a hormonal basis,[15] although serum testosterone and estradiol 17-beta concentrations are not different between affected and non-affected dogs.[26] Increased incidence in male dogs compared to females has been linked to a weaker levator ani muscle, and a decrease in the number of androgen receptors in the levator ani and coccygeus muscle has been proposed.[27] Relaxin affects collagen metabolism, softening the connective tissue components (e.g., birth canal).[28] Relaxin in males mainly is synthesized in the prostate gland and it is secreted in seminal plasma.[29] A higher expression of relaxin receptors has been found in the muscles of the pelvic diaphragm of dogs with PH.[30,31] Growth factors (growth and differentiation) of skeletal muscle also could play a role, because increased expression of epidermal growth factor and active caspase-3, and decreased expression of transforming growth factor-alpha, have been identified in the levator ani from dogs with PH.[32]

Treatment

Patients with small PHs and minimal clinical signs often can be managed with stool softeners (e.g., dietary fiber, lactulose), periodic enemas (see ch. 114), and digital removal of feces. Underlying disorders causing chronically increased intra-abdominal pressure must be treated and/or ruled out. Owners have to be warned that progression of the disease is likely and incarceration of herniated organs is possible and signs could be acute when incarcerated organs are obstructed or ischemic, which represents an emergency situation (see ch. 150).

After assessing the patient's physical condition (signs of systemic illness, bradycardia due to hyperkalemia) and metabolic and hematologic situation (azotemia, hyperkalemia, hypoglycemia, anemia), immediate bladder decompression is indicated if the veterinarian believes the bladder is herniated. Ultrasound-guided cystocentesis from the perianal area using aseptic technique is a useful way to decompress the bladder: it is quick and easy to perform and anesthesia is usually not required. Higher potassium and creatinine

concentrations in aspirated fluid compared to blood also can confirm that the aspirated fluid is urine. The decompressed urinary bladder frequently can be repositioned by external digital compression but if this is not possible, catheterization can keep the urinary bladder empty until surgical repair of the hernia (see ch. 105 and 106).

Advanced PH (e.g., recurrent PH, major dilation of the hernial sac, prostatic disease requiring prostatic omentalization, retroflexed urinary bladder) is an indication for surgery. Defects in the pelvic diaphragm can be closed either with direct suturing or by using autogenous tissues or synthetic mesh. Reported postoperative complication rates of standard herniorrhaphy range from 28.6% to 61%, including a recurrence rate of 10-46%.[15] Currently, transposition of the internal obturator muscle is considered the most reliable technique and has long-term success rates > 90% in uncomplicated cases.[15,33] A 2-step surgical approach (pexy of the colon, urinary bladder, and ductus deferens; then internal obturator muscle flap) is recommended for advanced/complicated PH and has a 90% success rate.[24,34] However, a recent retrospective study reported that laparotomy was not indicated in dogs with PH and urinary bladder retroflexion because the bladder repositioning could be reliably performed during perineal surgery. Urinary bladder retroflexion did not significantly increase the incidence of postoperative complications and had no effect on the long-term outcome.[21]

Prosthetic material such as polypropylene mesh,[35] porcine[36] and canine[37] small intestinal submucosa, autologous fascia lata[38] and tunica vaginalis[16] usually is only needed in those recurrent PH patients with hernia dimensions that do not allow closure by conventional herniorrhaphy. Autologous tunica vaginalis can be harvested during castration.

Routine castration is recommended as a part of PH treatment because the risk of PH recurrence for castrated dogs is 2.7 times less than for non-castrated dogs.[19] Prostatic atrophy makes the pelvic entrance wider (making defecation easier) and relaxin levels are lower.

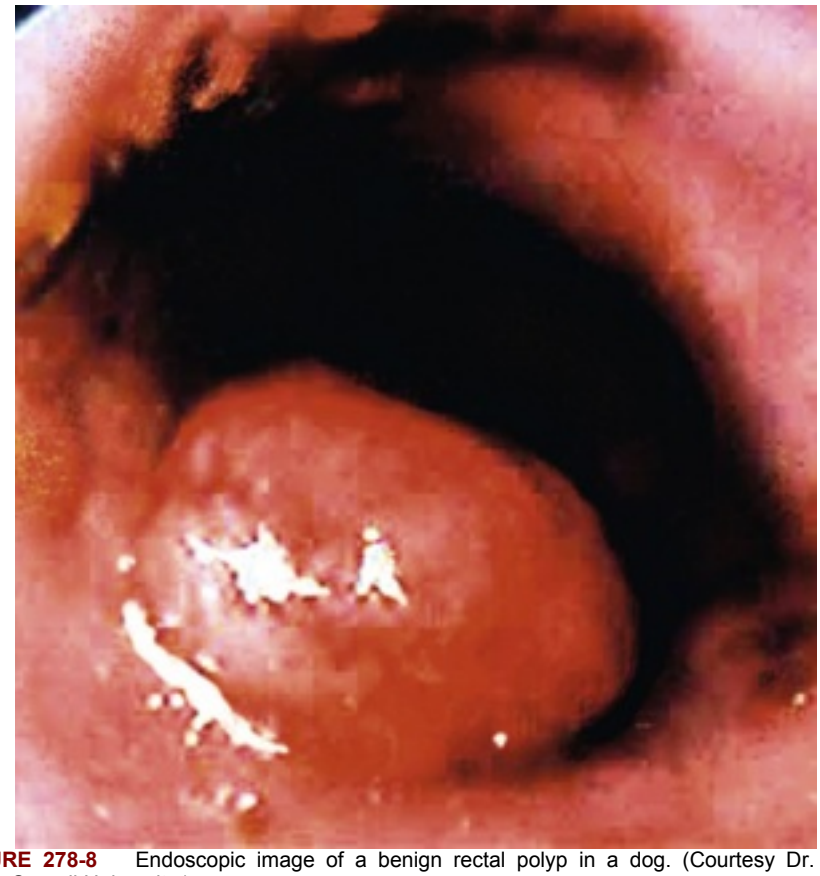
Pre- and postoperative medical management aims to treat and prevent infection due to bacterial translocation through the damaged rectal wall or to surgical wound infection; to keep the stool soft (e.g., psyllium-enriched diet, lactulose); to prevent tenesmus due to pain; and to address underlying disorders (e.g., chronic colitis, prostatitis, cystitis) predisposing to recurrence of PH (see ch. 277).

Prognosis

The high surgical success rate of >90% must be considered cautiously, because PH recurrence has been documented up to 4 years post-operatively.[2] The prognosis depends on successful treatment of underlying causes, severity and chronicity of disease, and skill of the surgeon in performing the most appropriate repair. In complicated cases with urinary bladder retroflexion, mortality rates of up to 30% have been reported.[20,25,39] Postoperative complications in 25-50% of patients include sciatic nerve injury, fecal incontinence, surgical site infection, prolapsed rectum with excessive straining, misplacement of sutures in the anal sac or rectal lumen, urinary bladder necrosis, urinary incontinence, and PH recurrence.[15]

Rectal Neoplasia

Rectal neoplasia is uncommon in dogs and cats. The most common clinical signs include hematochezia, tenesmus, dyschezia and/or flattened stools. In most cases, a mass can be palpated on digital rectal examination.[40-42] Benign polyps, adenocarcinoma, leiomyoma, leiomyosarcoma, lymphoma, fibrosarcoma, and plasma cell tumors have been reported (E-Figure 278-8).[40-43] Benign polyps can transform into adenocarcinoma *in situ*.[44] Lymphoma, the most common tumor in cats, primarily occurs in the small bowel or the ileocolic junction, but cats occasionally develop intestinal adenocarcinoma.[45,46] Siamese cats are overrepresented.[46,47] Collies and German Shepherds could be predisposed for intestinal tumors, especially adenocarcinomas, rectal carcinoma and polyps,[48,49] and miniature Dachshunds might be predisposed for inflammatory rectal polyps.[50]



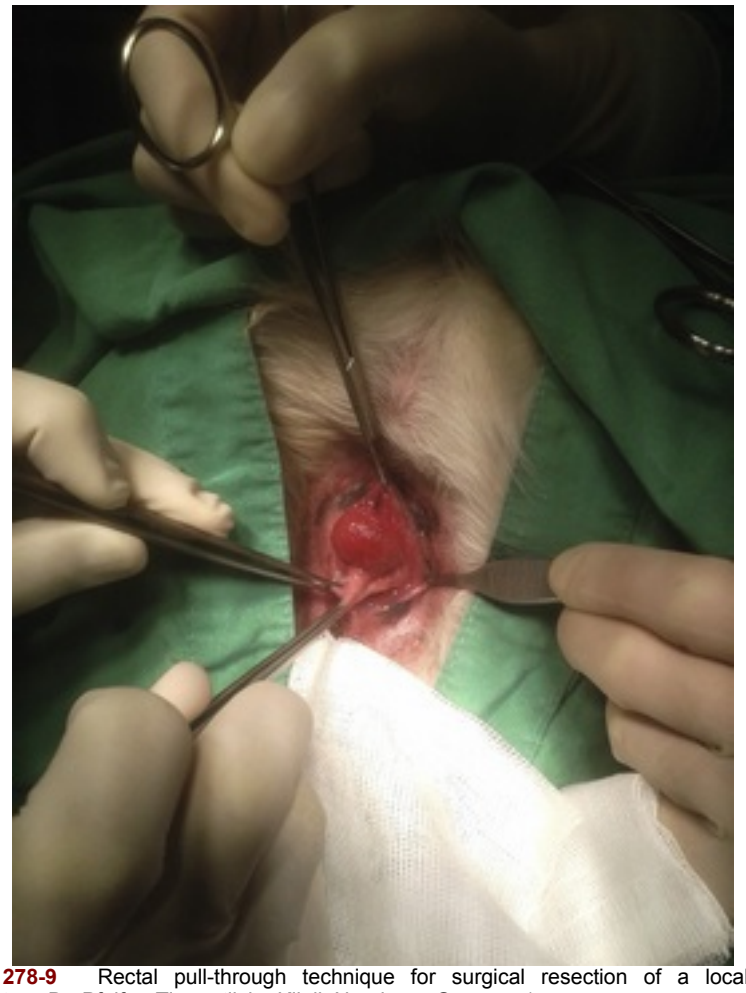
E-FIGURE 278-8 Endoscopic image of a benign rectal polyp in a dog. (Courtesy Dr. Melanie Craven, Cornell University.)

Diagnosis

The diagnosis requires cytologic and/or histopathologic analysis of samples obtained endoscopically or surgically (see ch. 113). It is critical to obtain substantial submucosal tissue to distinguish benign from malignant lesions. This can be done endoscopically, with training, using rigid biopsy forceps equipment; alternatively, full-thickness biopsy will be necessary. Full staging, including abdominal ultrasound, thoracic radiographs, a complete blood count, serum chemistry profile, and urinalysis, is recommended prior to therapy. This is because most affected dogs are middle-aged to older and can have co-morbidities. Furthermore, lymphoma by definition is a systemic disease, and metastasis from rectal adenocarcinoma has been reported.

Treatment

Surgical resection is the treatment of choice for malignant or benign localized rectal masses. A variety of surgical approaches has been described, including rectal pull-through (E-Figure 278-9), open abdominal or transpelvic approach for both benign and malignant masses, and transrectal endoscopic removal of benign tumors.[40,42,51-55] In addition to surgery, piroxicam, a nonsteroidal anti-inflammatory drug, may help alleviate and reduce clinical signs associated with rectal polyps in some dogs.[44]



E-FIGURE 278-9 Rectal pull-through technique for surgical resection of a localized rectal mass. (Courtesy Dr. Pfeifer, Tierärztliche Klinik Nürnberg, Germany.)

Prognosis

Survival times vary widely depending on tumor type, stage, and surgical technique used. Prolonged survival of many months to years after successful removal of the primary tumor[40,52] resection and/or chemotherapy of rectal lymphoma[43] has been reported.

Rectal Prolapse

Rectal prolapses are classified as complete external rectal prolapse (full thickness rectal prolapse; rectal wall externally visible, most common form), partial external rectal prolapse (mucosal prolapse; protruded mucosa externally visible, can sometimes be observed in patients during episodes of tenesmus or permanently in mild forms of rectal prolapse) (Figure 278-10), or internal rectal intussusception (invagination of rectal wall; not visible externally, not yet described in small animals).[56]

FIGURE 278-10 Mucosal rectal prolapse in a dog with colitis/proctitis. (Courtesy Dr. Tomsa, Ennetseeklinik für Kleintiere, Switzerland.)

Diagnosis

Rectal prolapse can be detected on physical examination; however, for accurate treatment selection, protruded rectal mucosa must be differentiated from an ileocolic intussuception that has prolapsed through the anus.[57] Careful insertion of a blunt, well-lubricated probe between the rectal wall and the prolapsed tissue will be possible if there is an intussusception but not if there is rectal prolapse.[58] The protruded rectal wall should be examined for neoplastic infiltrates. After repositioning, ultrasound, negative contrast radiographs, or endoscopy should be considered. For investigation of complex congenital abnormalities of the colonic wall (e.g., colonic duplication), negative contrast computed tomography or magnetic resonance imaging might be useful.[59] Abdominal imaging, endoscopic biopsies, and urinalysis could identify further causes of straining.

Pathogenesis

Rectal prolapse usually is due to an underlying urogenital or GI disorder producing severe or persistent straining. The most common causes of rectal prolapse are dyschezia from severe colitis or secondary proctitis due to parasites.[60] Other causes include:

- Intestinal conditions: intestinal neoplasia, foreign body, constipation, and congenital defects.[40,61-64]
- Anorectal abnormalities: perianal fistula, sacculitis, and surgical repair of perineal hernia without colopexy.[65]
- Anal sphincter incompetence, due to neurologic or muscular dysfunction.[66]
- Urogenital causes: lower urinary tract inflammation, urolithiasis, cystic or urethral neoplasia, and prostatic disorders.[62,67]
- A cystocele (protrusion of the urinary bladder into the vagina) has been reported.[68]
- Conformational abnormalities (recessed vulva, vestibulovaginal stenosis) causing stranguria.[69]

Treatment

Treatment should be prompt, to reduce further mucosal trauma and minimize discomfort. Conservative

management includes treating underlying causes of chronic straining and post-surgical tenesmus. Surgery usually is indicated, and three surgical techniques include perianal pursestring suture, colopexy, and rectal resection.[58,65] For mild rectal prolapse with minimal tissue damage, the protruded mucosa should be cleaned and rehydrated with a warm isotonic solution, lubricated with a water-based gel, and repositioned by gentle digital manipulation. A perianal pursestring suture is placed that leaves an opening large enough to allow passage of soft feces but not further prolapse; temporary placement of a tube through the anus during pursestring suturing, and removal of the tube immediately after the ligature is complete, can help prevent overtightening of the suture.[58] Medical management includes lactulose to keep the stool soft, topical corticosteroids (e.g., hydrocortisone foam), systemic corticosteroids (prednisolone 1 mg/kg PO q 24 h), metronidazole, and analgesic medications/opioids (e.g., buprenorphine). Defecation must be adequate to avoid constipation after pursestring suture placement.

Colopexy is useful where tissue is viable, if manual reduction of the prolapse is difficult or with recurrent prolapses.[34,70] It is usually performed by celiotomy and may be combined with other procedures (e.g., appositional herniorrhaphy with perineal hernias).[24,68,70,71] Minimally invasive laparoscopic technique is an alternative.[72] Rectal resection should be performed only when absolutely necessary and with the owner's full understanding of the risks, as serious complications may result.[58] Indications include necrotic mucosa and elimination of redundant rectal tissue. A silicone elastomer sling implantation technique has been described for patients with anal sphincter abnormalities. The resultant fibrous tissue can increase anal tone, preventing rectal prolapse during defecation.[66] Postoperative care is similar to rectal prolapse and, importantly, this includes addressing underlying causes.

Prognosis

The prognosis in mild forms with a treatable underlying cause usually is good. In patients with recurrent and severe forms of rectal prolapse requiring complex surgery procedures, the prognosis is guarded. Postoperative complications include stricture formation, incontinence, and dehiscence, which can be life-threatening.

Rectal and Anal Stricture

Rectal and anal strictures occur when the rectal lumen or anal opening is constricted by scar tissue from chronic inflammation, trauma or cancer.[73-75] Congenital stenosis also can narrow the rectoanal canal.[76] Rectal strictures in dogs are rare. Reported causes include: proctitis/colitis, anastomotic stricture post-neoplastic mass resection, chronic perianal inflammation, foreign bodies, histoplasmosis, and congenital malformation[75] and as a late complication of irradiation.[11] Rectal and anal strictures are uncommon in cats.

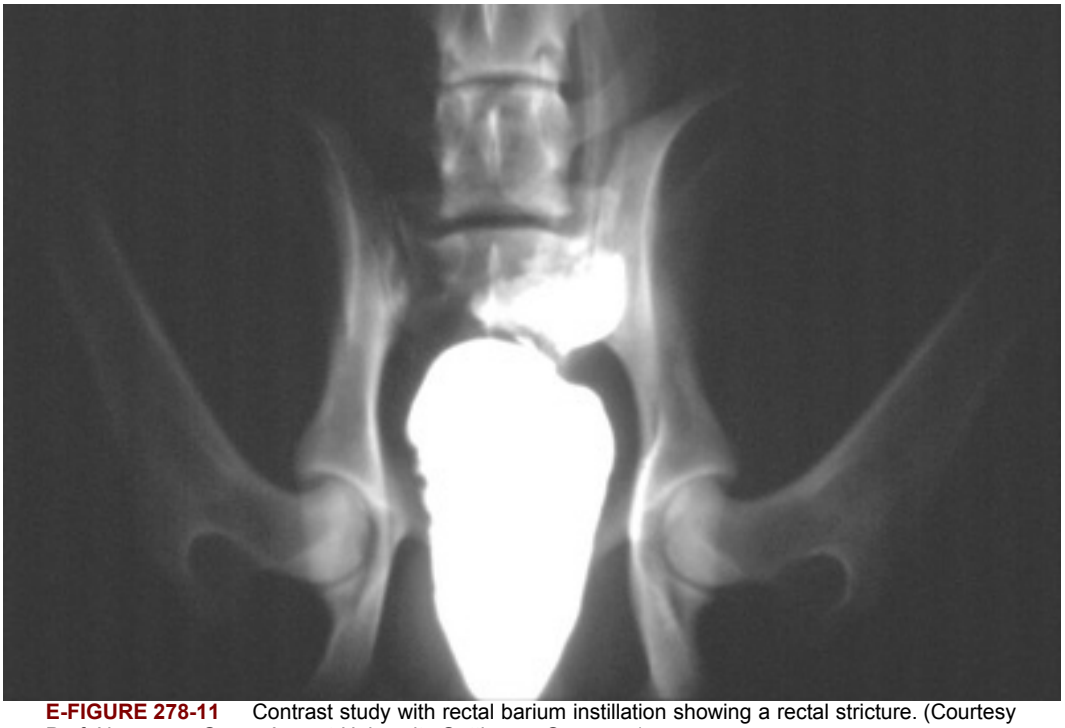
Since strictures can be congenital, inflammatory, or neoplastic, all ages can be affected. German Shepherd dogs are predisposed to perianal fistulas and inflammatory bowel disease, which can be associated with anorectal strictures.[77,78] Otherwise, no breed predilection is reported.[75] Strictures can be silent until the luminal caliber is small enough to cause obstruction. Most patients are presented because of tenesmus due to constipation.[75] Other clinical signs can include anorexia, abdominal pain, and vomiting.[79] Decreased intestinal motility and obstruction can lead to secondary intestinal bacterial overgrowth and excessive gas production manifested as abdominal bloating, borborygmus, and flatulence. Animals with partial obstruction can produce narrow ribbons of feces. Additional presenting complaints include hematochezia, diarrhea, and rectal bleeding.

Rectoanal strictures usually can be identified during digital rectal examination, which typically reveals a firm, circumferential fibrotic band that cannot be stretched.[75] In rectoanal stenosis due to infiltrative disorders, stenosis of the rectoanal canal can be present over a longer distance (several millimeters to centimeters), and sometimes an asymmetric mass can be felt. However, some colorectal carcinomas form strictures, which cannot be distinguished from benign fibrosing bowel constriction.[74] Sometimes, strictures with a very small luminal diameter (e.g., 1-2 mm) cannot be crossed by digital examination without causing tissue damage.

Diagnosis

Although strictures usually are detected by rectal examination, additional diagnostics characterize the lesion and identify underlying causes. Radiographic contrast studies (air and barium) (E-Figure 278-11) evaluate the

extent and location of rectal strictures.[73,75,76] Ultrasound can detect mural thickening of the rectal wall, abdominal lymph node enlargement, and metastatic lesions (intrapelvic location and colorectal gas might limit visualization). Proctocolonoscopy (see ch. 113) can allow visualization of the stricture but can be difficult to perform if the stricture is close to the anus.[80] When a distal stricture can be passed with a small diameter endoscope, a retroflexed view should be used for assessing the lesion (see ch. 277). Biopsies differentiate benign from malignant strictures.



E-FIGURE 278-11 Contrast study with rectal barium instillation showing a rectal stricture. (Courtesy Prof. Neumann, Georg-August-University Göttingen, Germany.)

Treatment

Optimal treatment depends on length, quality of tissue (fibrotic versus muscular) and underlying cause. Repeated balloon dilation under endoscopic or fluoroscopic control usually manages benign fibrotic rings,[73,75] exerting a radial force on the tissue and rupturing the fibrous, collagen-rich stricture. Multiple (1-3) procedures 4-6 days apart gradually increase stricture diameter without excessive tearing, thereby reducing likelihood of recurrent stricture formation. Treatment number depends on the degree of recurrent tissue contraction and clinical signs. Balloon size is based on the diameter of the stricture orifice, degree of tissue destruction, and size of the patient (e.g., cats and small breed dogs: 10-18 mm; medium and large breed dogs: balloon size in mm = weight in kg + 5). Concurrent intralesional triamcinolone injections could result in better success rates because corticosteroids inhibit scar tissue reformation.[73,81] Bougienage with a well-lubricated anal dilator might be easier and cheaper in medium- to large-breed dogs and can be continued, daily, by the owner at home to reduce the risk of restricturing. Self-expanding metallic stent placement for alleviation of colonic obstruction is a nonsurgical, palliative treatment for patients with metastatic or systemic disease in which surgical resection might not be possible or warranted (see ch. 123).[74,82] Surgical correction is reserved for strictures caused by rectoanal neoplasia, recurrent rectoanal strictures after unsuccessful dilation, and for long stenosis.[83,84] Transanal rectal pull-through amputation for *en bloc* resection can be associated with a high incidence of complications (e.g., fecal incontinence, rectal bleeding, dehiscence, infection).[55]

Additional treatments include a low-residue diet, stool softeners for several weeks, and pain management during the post-operative phase.

Prognosis

Many patients with benign strictures can be managed satisfactorily by dilation alone.[75] If surgery is necessary, postoperative complications confer a guarded prognosis. Malignant lesions are associated with a poor prognosis but palliative treatment can improve quality of life.[74]

Rectoanal Malformations

The most frequently reported rectoanal malformation in small animals is atresia ani, with a reported prevalence of ≈0.007% in dogs. As surgical correction is challenging and many affected dogs and cats are euthanized at the time of diagnosis, the true prevalence is difficult to determine. Females and some breeds (Finnish Spitz, Boston Terrier, Maltese, Chow Chow, German Shorthaired Pointer, Miniature Poodle, Toy Poodle, and Miniature Schnauzer) are predisposed.[85] Four types of atresia ani (Figure 278-12) include: Type I: congenital anal stenosis (fibrous ring at the anal opening); Type II: imperforate anus alone (just a thin membrane over the anus); Type III: imperforate anus combined with more cranial termination of the rectum as a blind pouch (in dogs ≥1 cm beneath the terminal rectal end and perineal skin); Type IV: discontinuity of the proximal rectum with normal anal and terminal rectal development. The embryonic cloaca represents a communication between GI, urinary, and reproductive tracts and rectoanal abnormalities occasionally are associated with urogenital malformations; rectovaginal fistula combined with type II atresia ani is the most common of these.[86-89] Rectoanal malformations also can be associated with other congenital anomalies (sacrocaudal dysgenesia and hydrocephalus).[86]

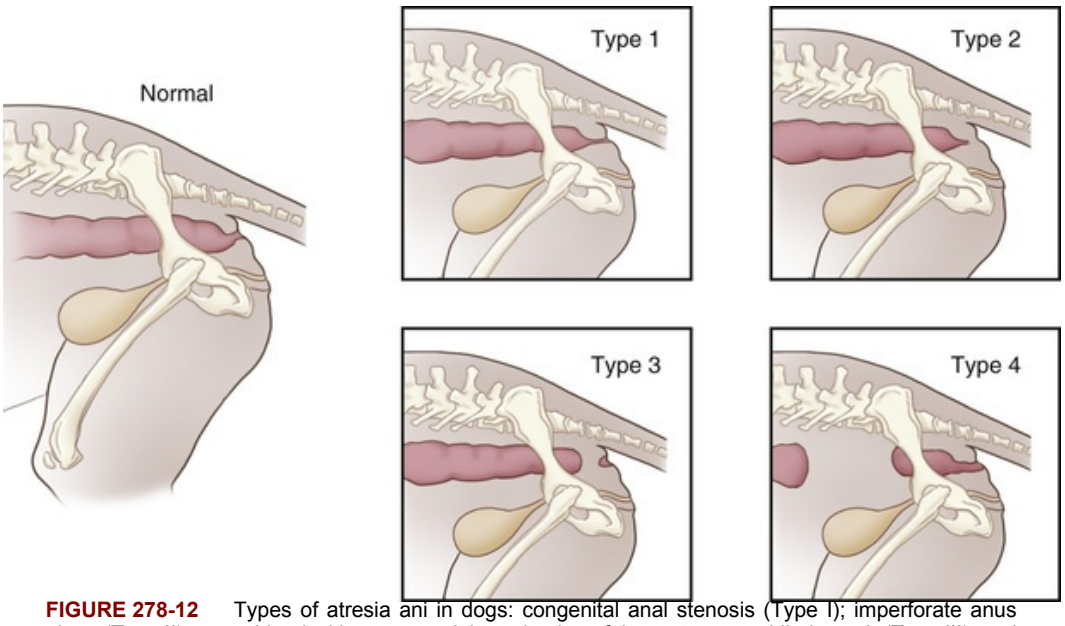


FIGURE 278-12 Types of atresia ani in dogs: congenital anal stenosis (Type I); imperforate anus alone (Type II) or combined with more cranial termination of the rectum as a blind pouch (Type III); and discontinuity of the proximal rectum with normal anal and terminal rectal development (Type IV). The red shaded areas identify the colon and rectum. (Redrawn from Vianna ML, Tobias KM: Atresia ani in the dog: a retrospective study. *J Am Anim Hosp Assoc* 41:317-322, 2005.)

Diagnosis

The diagnosis is based on history, clinical signs, and physical examination findings. Puppies and kittens with anorectal agenesis (imperforate anus) without fistula cannot defecate. Meconium and feces accumulate within the rectum postpartum, the abdomen progressively distends, and the puppy or kitten becomes inappetent and lethargic. Patients with congenital anal stenosis (atresia ani Type I) and with rectovaginal fistulas may be asymptomatic for several weeks until constipation after weaning from liquid diet occurs.[90] In female dogs or cats with passage of feces through the urogenital tract, vulvar irritation and cystitis will develop.[89,91] A ball-tipped probe can be used for gently exploring the anus and determining whether the tract ends blindly (i.e., Type I and IV).[87] Concurrent congenital abnormalities can include cleft palate, open fontanelle, hydrocephalus, skeletal deformation, abdomenal omphalocele, and congenital cardiac defects. Abdominal

radiographs can help determine the extent of rectal atresia, the degree of colonic dilation, and any sacrococcygeal deformities; iodinated contrast medium infused through the vagina or fistula can characterize the type of rectoanal malformation. Urinalysis with urine culture and sensitivity testing is indicated in every case with a communication between the GI and urinary tracts.

Treatment

Surgery is the treatment of choice for atresia ani, although anal stenosis has been corrected with bougienage and balloon dilation[90] (Figure 278-13 and ch. 123). All forms of imperforate anus (atresia ani type II-IV) require immediate surgical correction.[76,85,87] A fistula flap technique, described in the treatment of rectovaginal fistula and atresia ani, reduces the risk of iatrogenic damage to the external sphincter muscle and its innervation.[86] Postoperative analgesia and maintenance on a low-residue diet and stool softeners are recommended.

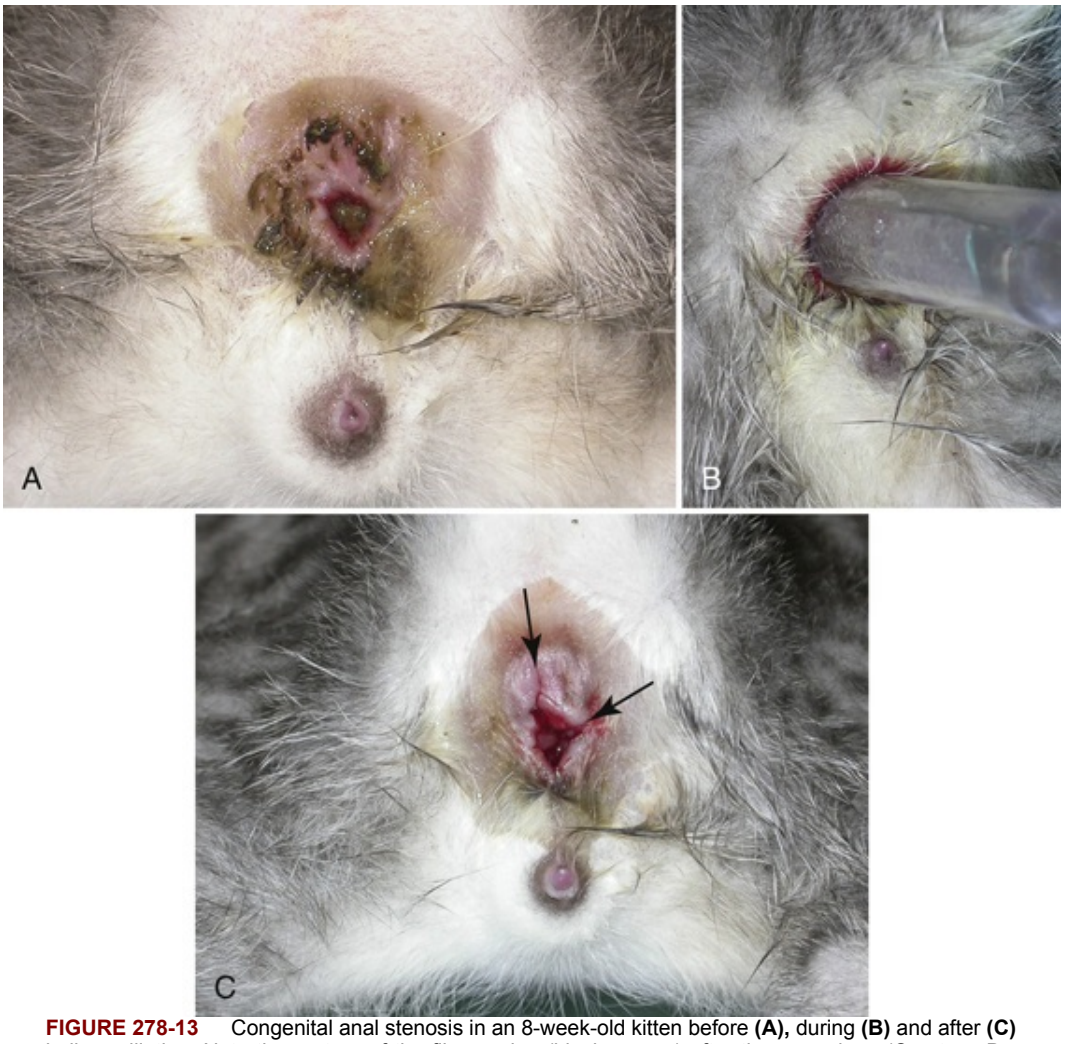


FIGURE 278-13 Congenital anal stenosis in an 8-week-old kitten before **(A),** during **(B)** and after **(C)** balloon dilation. Note the rupture of the fibrous ring (black arrows) after the procedure. (Courtesy Dr. Tomsa, Ennetseeklinik für Kleintiere, Switzerland, © GST | SVS.)

Prognosis

Surgical repair and balloon dilation of atresia ani type I and II result in fecal continence in most cases.[85,87,90] The prognosis for kittens and puppies with more complex anomalies (i.e., atresia ani type II and IV, rectovaginal fistula) is guarded. Postoperative wound dehiscence, stricture formation and incontinence are common complications.[76]

In contrast to older cats with megacolon, which is usually irreversible, colonic function and megacolon frequently improve after correction of atresia ani. Ascending urinary tract infection leading to chronic renal damage can affect the overall prognosis.[86]

Perianal Fistula

Perianal fistula (PAF, anal furunculosis) in dogs is a chronic inflammatory disease causing ulceration and fistulous tracts in the anal and perianal areas. As the disease progresses, perianal fistulization can become extensive (Figure 278-14). Anal stricture can develop. A multifactorial immune-mediated mechanism in genetically susceptible hosts is suspected.

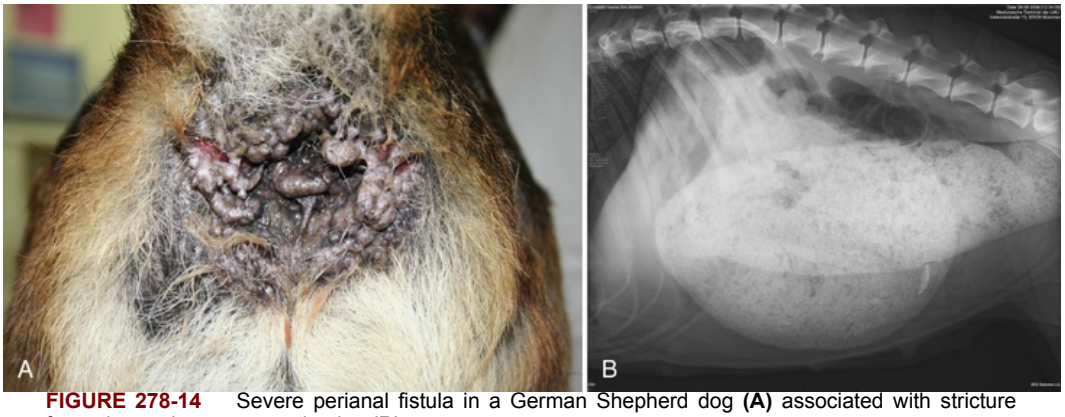


FIGURE 278-14 Severe perianal fistula in a German Shepherd dog **(A)** associated with stricture formation and severe constipation **(B).**

The German Shepherd breed is uniquely predisposed to PAF, representing >80% of cases.[92] Other breeds affected include the Irish Setter, Labrador Retriever, Old English Sheepdog, Collie, Border Collie, English Bulldog and Bouvier des Flandres.[92,93] A broad-based tail and a low tail carriage are hypothesized to predispose to bacterial overgrowth and inflammation. The disease usually affects middle-aged dogs, with a mean age of 4-7 years[94] and it is not reported in cats.

The presentation of PAF varies considerably. Initial clinical signs can include persistent perineal licking, then over time, dyschezia, hematochezia, tenesmus, purulent perianal discharge, self-mutilation, and fecal incontinence.[95,96] Dogs can present with obstruction due to scarring causing anal stenosis or, conversely, fecal incontinence due to damaged sphincter muscles and corresponding nerves. Weight loss and systemic illness can occur in severely affected patients.[77,97-101] Sedation and analgesia often are required for a thorough examination of the perianal area to accurately assess the severity (often after clipping and cleaning) and to perform a digital rectal examination with minimal discomfort. Examination—including evaluation of the anal sacs—aims to detect abscesses, determine the length and interconnection of fistulous tracts, assess any involvement of adjacent structures, and record the number and size of the fistula openings. Fistulous tracts should be flushed with sterile saline and probed with a sterile blunt instrument. The anal sphincter should be assessed for thickening and evidence of rectoanal stenosis. An associated perineal hernia gives a worse prognosis.

Diagnosis

Diagnosis is usually based on signalment (notably breed and age), history, and characteristic physical examination findings. Other causes of fistulization (e.g., chronic anal sac abscessation, perianal tumors, trauma from bites or foreign bodies) should be ruled out. Colonoscopy and colonic biopsies (see ch. 113) could be indicated, as 50% of dogs with PAF have concurrent colitis.[96] Histopathologic assessment of tissue can rule out neoplasia. Fistulograms can be helpful if surgical excision of draining tracts is considered; they also can document rare, true rectocutaneous fistulas. Abdominal radiographs are indicated to look for evidence of constipation, which can occur due to rectoanal stenosis or pain (see Figure 278-14).

Pathogenesis

Human Crohn's disease is associated with PAFs in 15-43% of patients.[102] By extrapolation, a similar, multifactorial, immune-mediated disease with a genetic predisposition is suspected in canine PAF. The responsiveness to immunosuppressive therapy, the histopathologic dense sheets of plasma cells and perivascular lymphoid nodules, and an increased expression of Th 1-cell-mediated cytokines (mRNA for IL-1-beta, IL-6, tumor necrosis factor alpha, IL-8, IL-10 and transforming growth factor beta) detected in biopsies from PAF tissues add support to this hypothesis.[103] The ulcerative nature of canine PAF could be due to an upregulation of macrophage-derived matrix metalloproteinase (MMP) enzymes, particularly MMP-9 and MMP-13, which are zinc-dependent endopeptidases capable of degrading components of the extracellular matrix.[104]

Canine PAF is thought to have a complex pathogenesis involving multiple genetic factors. A selective immunoglobulin A (IgA) deficiency demonstrated in the German Shepherd breed is a possible immunological factor leading to PAF.[105] A significant association with canine major histocompatibility complex (MHC) class II gene allele and PAFs has been described.[106] MHC class II molecules are responsible for antigen presentation and subsequent T-cell activation.

In humans, single nucleotide polymorphisms (SNPs) in the nucleotide oligomerization domain 2 *(NOD2)* play an important role in the etiology of Crohn's disease.[107] A recent mutational analysis study identified an association of four SNPs in exon 3 of *NOD2* with inflammatory bowel disease in the German Shepherd but no other canine breeds (genotype forms analyzed in an overdominant model).[108] Finally, a genome-wide association study to identify regions nominally associated with canine PAF in the German Shepherd revealed *ADAMTS16* and *CTNND2* gene regions on chromosome 34 were most significantly associated with disease.[109] Little is known about the function of *ADAMTS16*, but an inverse relationship between the expression of *ADAMTS16* and *MMP-13* was found in a previous study.[110] *MMP-13* is an endopeptidase that is overexpressed in canine PAF. It plays a potential role in the pathogenesis of human Crohn's disease.[104,111] The *CTNND2* gene encodes for delta-catenin, possibly responsible for dysregulation of angiogenesis.[109] Many other factors have been incriminated in the pathogenesis of PAF, including adverse food reaction,[112] anatomical factors such as higher density of apocrine glands in the perianal skin,[113] microenvironmental and hygienic factors due to tight tail carriage[95] and secondary bacterial infections.[92,114]

Treatment

Neither medical nor surgical therapy usually proves to be curative. The primary goal of therapy is to improve the patient's quality of life by inducing and maintaining remission. Medical management is the current treatment of choice. Surgery only is recommended for incompletely resolved fistulas after at least 6 weeks of medical treatment or for treatment of complications. Medical therapy includes immunosuppression, decreasing perianal area bacterial populations, helping the patient defecate, dietary therapy, and pain management.

The perianal area should be clipped of hair, kept dry, and cleansed daily with a mild disinfectant (e.g., diluted chlorhexidine solution, antimicrobial shampoo). Antibiotics effective against anaerobic bacteria (e.g., metronidazole) are administered for several weeks. Stool softeners (e.g., psyllium, lactulose) help to reduce pain during defecation, and analgesics that do not negatively affect GI motility (e.g., metamizole [dipyrone], gabapentin) are indicated. Attention to diet is recommended. An increased incidence of PAF in dogs with adverse food reactions[112] and a beneficial response to novel protein diets in combination with prednisolone have been reported (see ch. 178).[115] Cyclosporine (CsA), a calcineurin inhibitor, is the treatment of choice for PAF in German Shepherds.[116] It leads to inhibition of proliferation and activation of both T-helper and T-cytotoxic lymphocytes.[117] The microemulsion form of CsA (Atopica, Elanco) approved for atopic dermatitis is recommended. It offers greater bioavailability plus less variability in blood concentrations compared to other formulations.[118] 4 to 8 mg/kg PO is administered q 24 h for 2-4 months. Once clinical signs have improved substantially, the dosage can be reduced by approximately 25% every 4-8 weeks based on clinical response. Measurement of blood cyclosporine concentrations (see ch. 165) is only recommended with inadequate clinical improvement or suspicion of drug toxicosis (significant GI signs, serum liver enzyme concentrations > 3 times normal, acute renal azotemia). A strong correlation between cyclosporine blood concentrations and clinical efficacy has not been recognized.[118] Coadministration of ketoconazole (5-10 mg/kg PO q 24 h) usually halves the dose requirement of CsA via competitive inhibition of hepatic P450 microsomal enzymes, which can reduce costs when ketoconazole is less expensive than CsA. This combined therapy has produced a

remission rate of > 90% in 9-16 weeks in different studies.[99-101] An anti-inflammatory dosage of prednisolone (e.g., 1 mg/kg PO q 24 h, tapered as low as possible on improvement) can be a useful palliative treatment to increase appetite and well-being and reduce inflammation. Immunosuppressive dosages of prednisolone only improve one third of patients and unwanted adverse effects are common.[115] Azathioprine has been used as an adjunct to glucocorticoids but adverse effects can include GI signs, bone marrow suppression, hepatotoxicosis, and pancreatitis.[119]

Tacrolimus, another calcineurin inhibitor, is 10-100 times more potent than CsA. One study reported complete resolution of perianal lesions in 5/10 dogs, a partial response in 4/10 dogs and no improvement in 1 dog.[98] Tacrolimus (0.1%) is applied to the perianal region q 12 h (using gloves) in the induction phase, to reduce the dosage of concurrent systemic drugs. After complete resolution of clinical signs, application may be reduced to the lowest frequency that controls inflammation.

Due to the high complication rate of surgery (i.e., up to 70%)[120,121] and the high success rates with calcineurin inhibitors,[100,101] surgery should be restricted to resection of residual draining tracts and abscessed anal sacs after several weeks of intensive medical treatment.[97] Cryosurgery, laser excision, and chemical cauterization have been reported, with variable success rates.[122,123] Cautious anal dilation may be needed for treatment of anal stricture or stenosis.

Prognosis

With intensive medical treatment, including cyclosporine, metronidazole, local cleaning, and topical tacrolimus, many cases with mild to moderate disease will achieve complete remission. However, long-term immunosuppressive therapy usually will be necessary, and financial constraints can limit optimal treatment. Severe cases may require surgical therapy, which can result in complete resolution of PAF but risks complications.

Diseases of the Anal Sacs

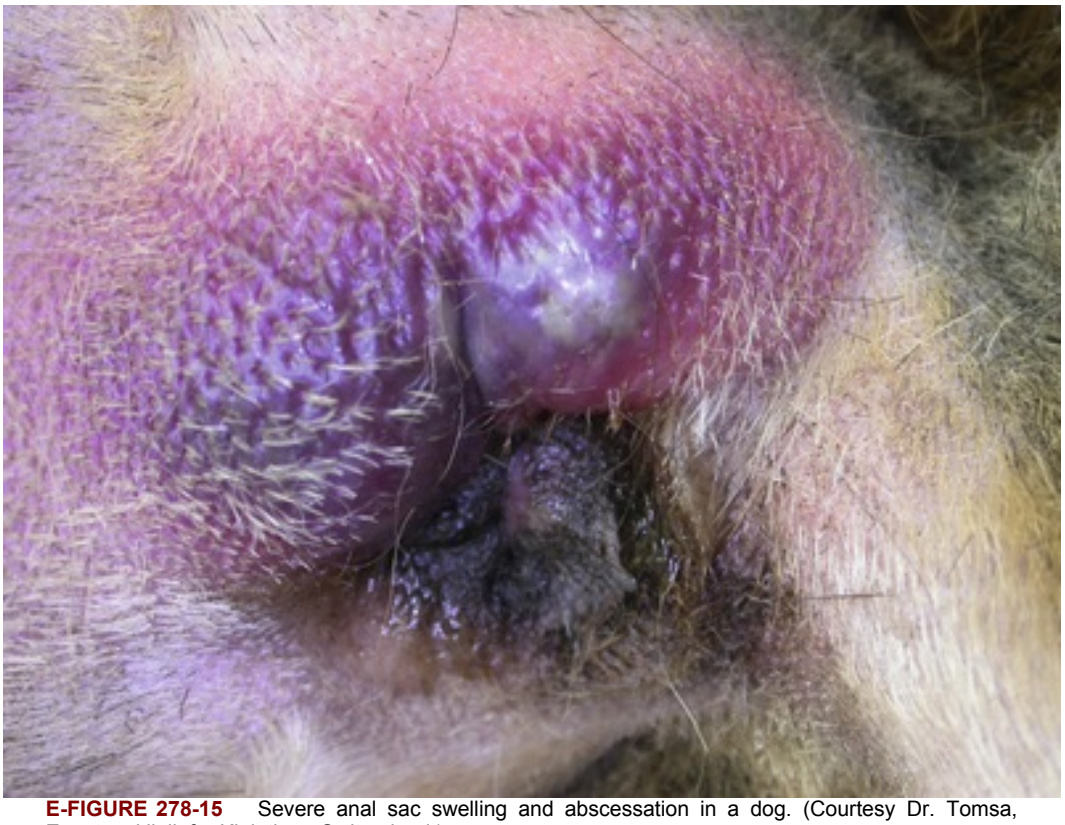
Anal Sac Impaction, Sacculitis and Abscess

Non-neoplastic anal sac disorders are relatively common in dogs, but infrequent in cats. Anal sac impaction was the third most prevalent health disorder recorded in dogs attending primary-care veterinary practices in England in one study.[124] Anal sacculitis and anal sac abscess can be difficult to manage. Sacculectomy is required in some cases with chronic and recurrent anal sac inflammation. Previous studies have reported perianal pruritus in >95% of dogs with anal sac disease,[125] while other causes include adverse food reactions and canine atopic dermatitis.[126]

Chihuahuas and Miniature Poodles have been reported as being predisposed to anal sacculitis and Cavalier King Charles Spaniels and Labrador Retrievers were significantly over-represented for anal sac disease in one study.[127]

Diagnosis

Diagnosis of canine anal sac disease is based on clinical signs, physical examination, and evaluation of anal sac secretions. Anal sac content varies in color and consistency in normal dogs, and is not a reliable basis for diagnosis of anal sac disease.[126,128] Anal sac impaction can be suspected if an anal sac is enlarged and difficult to express. Swollen and painful anal sacs suggest sacculitis (E-Figure 278-15). Microscopic examination of anal sac content is performed frequently. However, a recent prospective, blinded study of cytologic evaluation of anal sac secretions showed no significant difference in inflammatory cells and bacteria between asymptomatic dogs and dogs with a history typical of anal sac disease.[125] Differential diagnoses include anal sac or perianal neoplasia, fungal infection, perianal fistulae, and trauma.



E-FIGURE 278-15 Severe anal sac swelling and abscessation in a dog. (Courtesy Dr. Tomsa, Ennetseeklinik für Kleintiere, Switzerland.)

Pathogenesis

The specific cause of impaction and sacculitis is unknown[128]; foreign bodies are uncommon.[127] Antimicrobial substances, such as lysozyme, IgA, lactoferrin, and the peptide group of beta-defensins are products of the anal glands.[129] Changes in these secretory products could reduce the microbial defensive barrier, change the exudate consistency, or both. Soft feces and/or a small duct might predispose to anal sac obstruction and permit bacterial proliferation. *Escherichia coli, Streptococcus faecalis, Clostridium* spp. and *Proteus* are most commonly encountered in sacculitis.[130] Anal sac impaction, inflammation, and abscessation can develop in association with perianal fistulae.[77]

Treatment

Anal sac impaction is treated by manual expression of the anal sacs and possibly flushing with warm saline as needed. For sacculitis without abscessation, instillation of a topical antibiotic and corticosteroid ointment after flushing might suffice. Systemic antimicrobial treatment for 2-3 weeks (e.g., amoxicillin-clavulanate; cephalexin; or trimethoprim-sulfonamide) in combination with local therapy (e.g., cooling compresses, corticosteroid ointments) might be required in severe, resistant, or recurrent cases. Abscessed anal sacs (Figure 278-16) must be opened surgically and flushed under general anesthesia; warm packs applied prior to surgery can help bring the abscess to a point at which it can be opened.

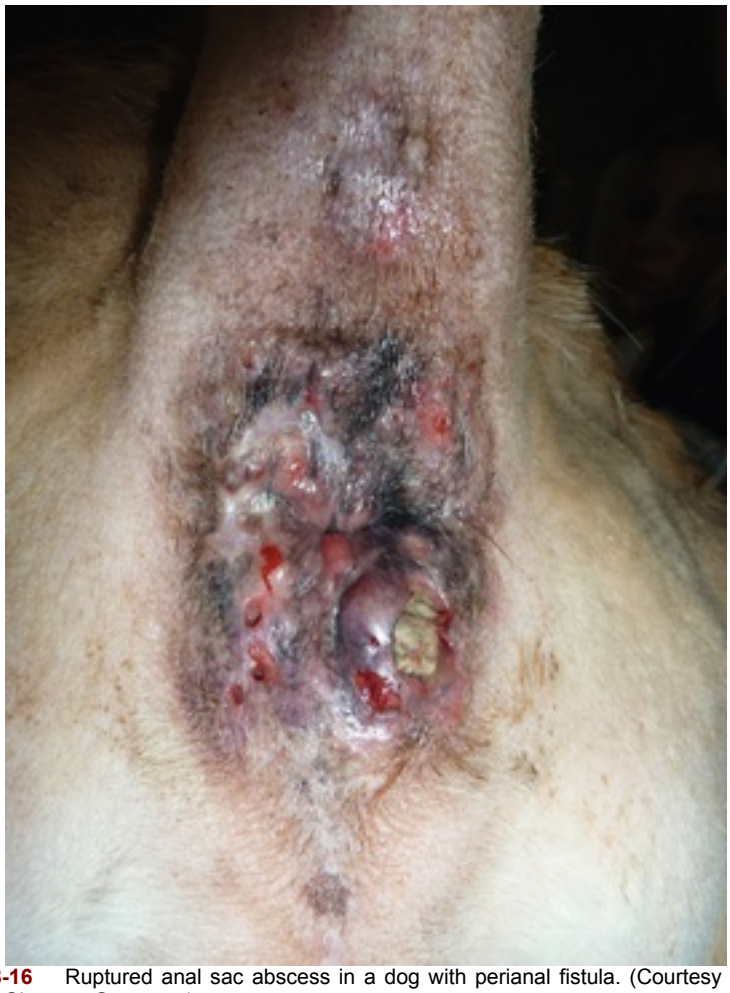


FIGURE 278-16 Ruptured anal sac abscess in a dog with perianal fistula. (Courtesy Dr. Schmitz, University of Giessen, Germany.)

Surgical anal sac removal should be considered in cases that do not respond satisfactorily to medical management. Closed techniques are reportedly associated with a lower complication rate compared to open techniques.[131] Pain management and preventing the dog from licking the perianal area is indicated in every case with substantial anal sac inflammation.

Prognosis

The prognosis with anal sac impaction and mild inflammation is generally good. Most patients with substantial inflammation respond to intensive medical treatment. Anal sacculectomy has an overall postoperative complication rate of 32%. Dogs weighing <15 kg had an increased risk of postoperative complications including perineal pruritus, incisional dehiscence, temporary fecal incontinence, constipation, and diarrhea in one study. The risk of permanent damage of the anal sphincter appears to be very low with careful surgical technique.[127]

Perianal Neoplasia

Perianal—or circumanal or hepatoid—glands (so named because cytologically and histologically, cells resemble hepatocytes) are considered nonsecretory, modified, sebaceous glands in the dog.[132,133] Cats do not have an analog to canine perianal glands and perianal adenoma and perianal adenocarcinoma are very rare.

Most cases of perianal adenoma have a history of non-painful, slow-growing mass or masses (E-Figure 278-17). Tumors can be single, multiple, or even diffuse. Typically found in the hairless perianal area, they can extend to haired regions, ulcerate, and become infected. They rarely adhere to deeper structures.[132] Perianal adenocarcinomas typically grow more rapidly, are larger and firmer, become ulcerated, and adhere to underlying tissues as compared to their benign counterpart.[134] Malignant disease should be suspected in

castrated males with a newly diagnosed or recurrent perianal tumor, because adenocarcinomas are not hormone-dependent.

E-FIGURE 278-17 Perianal adenoma in a dog. (Courtesy Dr. Pfeifer, Tierärztliche Klinik Nürnberg, Germany.)

Diagnosis

A routine geriatric work-up prior to anesthesia, potentially including thoracic radiographs and abdominal ultrasound, is desirable, even in an intact male dog with a perianal mass highly suspicious for benign perianal adenoma. Fine needle aspiration for cytologic evaluation might not differentiate benign from malignant perianal tumors, but it can rule out other forms of cancer or mass development. Histopathologic assessment of specimens is recommended. Metastasis in perianal adenocarcinoma is reported in 15% of cases.[134]

Pathogenesis

Perianal adenomas are the most common perianal neoplasm (59-96% of cases).[132,135] Tumor development and progression are androgen-driven and estrogen-suppressed. Older intact male dogs are at a high risk, with a mean age of 10 years.[136,137] Adenomas in female dogs are almost exclusively found in spayed females, where low estrogen levels do not suppress tumor formation; reports suggest testosterone secretion from adrenal glands in rare cases of hyperadrenocorticism.[138,139] Perianal gland adenocarcinomas are less common and represent 3-12% of perianal tumors.[134]

Treatment

Over 90% of intact male dogs will be cured with castration and mass removal and this is the treatment of choice for benign lesions.[132,136] Surgery is recommended in males with ulcerated or recurrent tumors and in female dogs. In addition to standard surgical techniques, cryosurgery and carbon dioxide laser for mass removal have been reported.[140,141] However, margin assessment for invasiveness, which is a hallmark feature of perianal adenocarcinomas, is not possible with these techniques.[142] For perianal adenocarcinomas, complete surgical removal with adequate margins is indicated.[136] As local recurrence is common with adenocarcinoma, incisional biopsy to plan for radical surgical resection is encouraged when this diagnosis is suspected. Postoperative radiotherapy might improve local control, but data are lacking.

Prognosis

Perianal adenomas have a good prognosis following surgery and castration, whereas for adenocarcinomas,

the prognosis is worse.[132,134,136] In one series of 41 dogs, tumors <5 cm in diameter (T2 stage) were associated with tumor control rates of >60% at two years. Metastasis at time of diagnosis was negatively related to survival. Median survival time for dogs with lymph node or distant metastasis was only 7 months in one study, but intensive treatment was not attempted in 5/6 dogs.[134]

Anal Sac Neoplasia

Apocrine gland adenocarcinomas arising from the anal sacs are rare, representing approximately 17% of all tumors in the perianal region and 2% of all skin and subcutaneous tumors.[133,142] This tumor is rare in cats, although the Siamese breed could be overrepresented.[143-148] The reported median age is 9-11 years in dogs and 12 years in cats.

There is no gender predilection.[135,149-151] For early identification and treatment, a thorough rectal and perianal examination should be routine for every adult dog presented in the clinic.[152-154]

Apocrine gland anal sac adenocarcinomas (AGASACA) usually affect one anal sac, but bilateral tumors have been reported.[152-155] These tumors can be very aggressive, and high metastatic rates at the time of diagnosis (average of 50%, range 46%-96%) have been reported. Metastasis is found most commonly in sublumbar/pelvic lymph nodes early or lungs and lumbar/pelvic bones later in the disease.[135,149-151,153-156] A study in English Cocker Spaniels, a high-risk breed, showed an association between tumor development and major histocompatibility complex haplotype (DLA-DQB1 allele), suggesting a genetic factor in tumor development.[157]

Clinical signs in dogs with AGASACA can be due to the physical presence of the primary mass, metastasis to regional lymph nodes, or paraneoplastic hypercalcemia (see ch. 352). Animals can show evidence of pain on defecation, hematochezia, and/or inflamed discharge from the anal sacs. In some cases, the problems caused by severely enlarged sublumbar lymph nodes, such as flattened stools or straining to defecate, dominate. Polyuria and polydipsia, anorexia, lethargy, or vomiting can be caused by paraneoplastic hypercalcemia, which is mediated by tumor secretion of parathyroid hormone-related peptide.[149,150] Approximately 27% of dogs with AGASACA have elevated serum calcium levels (see ch. 69). In up to 39% of dogs, the primary tumor has been an incidental finding on physical examination.[150] Like dogs, affected cats can be presented for tenesmus, constipation, scooting, presence of a mass, or hemorrhagic discharge.[143,146,147] Paraneoplastic hypercalcemia is not commonly reported in the cat.[143]

Diagnosis

A firm and discrete mass in the area of the anal sac, sublumbar lymphadenomegaly, and polyuria and polydipsia are highly suggestive. Tumors of the anal sacs can become secondarily inflamed and infected. Definitive diagnosis is made cytologically or histopathologically. Because AGASACAs have a very high rate of metastasis, staging should include thoracic radiographs and abdominal ultrasonography or abdominal radiographs. Ultrasonographic evaluation of lymph nodes is superior to plain radiographs and can identify other potential sites of abdominal metastasis.[158] Patients with lameness or bone pain should be evaluated radiographically or by nuclear scintigraphy for evidence of bony metastasis. A careful rectal examination and a complete blood count, serum chemistry panel, and urinalysis are recommended. Medical management of hypercalcemia or impaired kidney function could be necessary prior to surgery because hypercalcemia can result in kidney injury (see ch. 322 and 352). The same guidelines for staging anal sac tumors in dogs apply to feline patients with a suspected AGASACA.

Treatment and Prognosis

Comprehensive surgical removal of the primary tumor and enlarged metastatic sublumbar lymph nodes either alone or in combination with adjuvant chemotherapy and/or radiation therapy leads to median survival time of 16-18 months.[150,151] Even dogs with metastatic disease can have a good quality of life for months. Aggressive surgical resection of large tumors can risk causing fecal incontinence. Negative prognostic factors include large primary tumor size,[150,151] presence of lymph node metastasis,[151] presence of distant metastasis,[150,151] advanced clinical stage,[151] non-pursuit of surgery or chemotherapy alone,[150] and no therapy at all.[151] There are conflicting results regarding the prognostic significance of hypercalcemia in AGASACA.[149-151,153,154]

Radiation therapy can be palliative or definitive for nonresectable disease or treatment of metastatic lymph

nodes (see ch. 340).[159] Definitive radiation therapy is utilized for treatment of microscopic disease after surgical removal of the primary tumor to prevent local recurrence.[153] Side-effects can include intestinal irritation or rupture, diarrhea, and painful defecation in the short term and possibly rectal stricture long-term.[159]

The most commonly used chemotherapeutic agents are cisplatin, carboplatin, actinomycin D or mitoxantrone.[149,151,153] Toceranib phosphate, a tyrosine kinase inhibitor, has shown modest efficacy, with a median response duration of 19-23 weeks in 33 dogs refractory to prior therapies.[160] A significant relationship between a modified staging system and survival was found in a study of dogs treated prospectively according to a predefined management algorithm.[151] In cats, conflicting survival times and prognosis for this disease are reported. One study of 39 cats demonstrated a median survival time of 3 months (range 0-23 months) with 85% of cats succumbing to local or distant disease.[143]

Fecal Incontinence

Fecal incontinence is the involuntary passage of stool through the anus, in contrast to anal discharge of small amounts of mucus, pus, or blood. Continence depends on functional internal and external anal sphincters. Normal sensation of rectal distention and adequate reservoir capacity of the rectum are necessary to prevent fecal incontinence (reservoir incontinence). Anatomic derangements and neurologic diseases can be responsible for fecal incontinence. A detailed history is essential to differentiate reservoir from sphincter incontinence. Animals with sphincter incontinence are not aware of fecal passage and typically do not posture appropriately to defecate. With sphincter incontinence, unconscious anal dribbling can be worsened by increased intra-abdominal pressure (e.g., coughing, excitement). See also ch. 42.

In animals with reservoir incontinence, defecation is usually associated with tenesmus and urgency. Altered rectal sensation due to inflammation (e.g., proctitis) can produce incontinence. These animals typically have diarrhea, hematochezia, and fecal mucus.

Since neurogenic sphincter incontinence commonly is associated with cauda equina dysfunction,[161-163] evidence of lower motor neuron sacrococcygeal dysfunction should be sought (see ch. 266). The gait is assessed for ataxia; the pelvic limbs for decreased withdrawal reflexes and decreased muscle tone; and the tail for low carriage, reduced tone, and loss of sensation (see ch. 259).[164] The perineal reflex and anal sphincter tone can be reduced due to sacral nerve dysfunction. Loss of the detrusor reflex can produce urine dribbling due to overflow from a full bladder, in which case urine can be expressed easily. Fecal and urinary incontinence can occur with cauda equine syndrome, and the most common sign of this syndrome is pain elicited on palpation of the lumbosacral area or tail manipulation (see ch. 266). Severe lesions (e.g., those causing paraplegia) cranial to the sacral spinal cord (i.e., upper motor neuron dysfunction), can cause loss of voluntary control over defecation.

Diagnosis

A complete neurologic examination usually will reveal deficits that suggest neurogenic and anatomic reasons for incontinence. The rectum and perianal area should be carefully evaluated for non-neurogenic causes of incontinence. With disease localized to the sacrococcygeal spinal cord, survey radiographs often identify discospondylitis, fractures, or neoplasia, although computed tomography and magnetic resonance imaging are more sensitive,[165,166] especially for compressive spinal cord lesions missed by myelography. Inflammatory spinal cord disease can be identified with cerebrospinal fluid examination (see ch. 115), and myoneural abnormalities can be detected by electrodiagnostics (see ch. 117). The diagnostic approach for reservoir incontinence includes fecal examination for parasites (see ch. 81) and proctoscopy/biopsy for diagnosis of proctitis or neoplastic infiltration (see ch. 113).

Pathogenesis

Defecation involves coordinated activity in the autonomic (both parasympathetic and sympathetic) and somatic nervous systems. Dysfunction in the sacral components of this innervation causes neurogenic sphincter incontinence. In young animals, congenital abnormalities of the anorectum can be associated with anal sphincter incompetence (e.g., atresia ani type I, rectovaginal fistula). In adult dogs and cats, severe inflammation (e.g., perianal fistula), neoplastic infiltration, trauma, and perianal surgical procedures can damage the anal sphincter or its innervation.

Treatment and Prognosis

Decompressive laminectomy is effective for degenerative lumbosacral stenosis causing cauda equine syndrome in dogs, and fecal incontinence can improve postoperatively. A retrospective study of 69 dogs showed that fecal incontinence was present prior to surgery in 6% of these cases. In general, dogs with urinary or fecal incontinence have a worse prognosis than do dogs that are continent before surgery.[167] When due to compressive thoracolumbar disc disease, a 6.8% prevalence of permanent fecal incontinence has been reported. Dogs with paraplegia before surgery had a higher frequency of fecal incontinence compared to dogs that were ambulatory.[168] Fecal incontinence caused by postoperative and/or traumatic rectoanal injury can improve with time. Fecal incontinence was the most common (42 of 74 dogs) complication after rectal pull-through surgery in dogs with rectal masses and was transient in 19, and permanent in 23, dogs.[55] Postoperative defecation complications have occurred in 9/62 dogs following anal sacculectomy.[127] Fecal incontinence occurred in 2/51 dogs after surgical management of perianal fistula.[169] Novel surgical techniques and experimental studies for patients with loss of anal sphincter function have been described, including spiral rectal diaphragm technique,[170] implantation of a silicone elastomer sling,[66] transposition of a semitendinosus muscle flap[171] and reinnervation of the anal sphincter with a femoral motor nerve to pudendal nerve transfer.[172] Inflammatory colorectal disease can cause incontinence and should be treated (see above and ch. 277). Treatments include anthelmintics, hypoallergenic diets, antibiotics (e.g., tylosin), and/or anti-inflammatories (e.g., corticosteroids, sulfasalazine). Some patients with inflammatory bowel disease can respond to a high-fiber diet. Others benefit from highly digestible, low-residue diets, which reduce fecal volume and frequency of defecation. Administration of small-volume enemas (see ch. 114) to periodically stimulate defecation can keep the colon and rectum empty and improve continence in some cases. Loperamide (0.1-0.2 mg/kg PO q 8 h), an opioid that slows colonic transit and increases internal anal sphincter tone, might help manage fecal incontinence in diarrheic patients. Loperamide should not be used in dogs with MDR1 defect.

Fecal incontinence can be difficult to manage. Although it does not represent a life-limiting problem, some patients will be euthanized due to inconvenience and hygiene aspects.

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CHAPTER 279

Peritonitis

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Anatomy and Physiology of the Peritoneum

The peritoneal cavity extends from diaphragm to pelvis and is bordered by the lumbar vertebrae, sublumbar musculature, and oblique, transversus, and rectus abdominis muscles. The diaphragm has three natural openings (esophageal, caval, and aortic hiatuses), as well as paired slit-like openings dorsally that can allow movement of fluid or air between the pleural and peritoneal cavity.[1,2] The peritoneum, a serosal membrane of embryonic mesodermal origin, is composed of a single layer of mesothelial cells anchored on a basal membrane with a deeper connective tissue layer of adipose cells, macrophages, lymphocytes, fibroblasts, and elastic collagen fibers.[1,3-6] The parietal peritoneum lines the abdominal cavity and reflects into the visceral peritoneum to cover the abdominal organs; the peritoneal reflections form the mesenteries, omentum, and abdominal ligaments. The peritoneal cavity is a potential space between the parietal and visceral peritoneum.[1,2] The peritoneum is highly permeable to water and low-molecular weight solutes, allowing bidirectional exchange between the peritoneal cavity and plasma; a fenestrated basement membrane allows some particulate matter to pass easily into lymphatics.[5,7] Healthy animals have peritoneal fluid that consists of <1 mL/kg of clear, straw-colored plasma dialysate characterized as a transudate, with <3000 nucleated cells (monocytes, lymphocytes and mesothelial cells)/mcL and <2.5 g/dL (<25 g/L) of protein (albumin).[5,8] Mesothelial cells make small amounts of surfactant to lubricate organs and prevent friction.[6] The peritoneum is capable of both absorption and exudation and in the normal patient there is a balance between them.[7] Changes in intraabdominal pressure during respiration promote circulation of peritoneal fluid cranially along the ventral abdomen, then dorsally along the diaphragmatic surface of the liver.[9] Peritoneal fluid drains via diaphragmatic lymphatics and the thoracic duct to the sternal and mediastinal lymph nodes.[1] Thus, sternal lymphadenopathy identified on thoracic radiographs likely reflects intraabdominal disease. Innate peritoneal defenses consist of complement, neutrophils, basophils, mast cells, lymphocytes, macrophages, natural killer cells, lymphatic drainage, peritoneal-associated lymphoid tissue, absorption and localization capacity, and omentum, which has immunogenic activity.[10] Peritoneal compartmentalization of disease results in greater concentrations of inflammatory cytokines and biomarkers in peritoneal fluid than in peripheral blood; the peritoneum can act as a barrier to decrease the absorption of substrates to create this gradient.[11]

Definitions, Classification, and Pathophysiology

Peritonitis, inflammation of the peritoneum, can be caused by non-infectious or infectious etiologies (Table 279-1). Peritoneal injury elicits an intense inflammatory reaction, resulting in accumulation of inflammatory cytokines in the peritoneal cavity, complement activation, immunoglobulin production, release of vasoactive substances, and an imbalance of pro-inflammatory and anti-inflammatory mediators. Inflammation results in vasodilation, increased vascular permeability, occlusion of peritoneal stomata by fibrin, and adhesion formation. Peritonitis can lead to systemic inflammatory response syndrome (SIRS) and attendant clinical features (see ch. 132).[1,3]

TABLE 279-1

Etiology of Peritonitis (Primary[12,13] versus Secondary[14-37])

PRIMARY CAUSES	EXAMPLES

Viral	Feline infectious peritonitis (FIP)
Bacterial *most common isolates	*E. coli**, *Enterococcus* spp.*, *Clostridium* spp.*, *Salmonella typhimurium, Chlamydia felis, Propionibacterium, Bacillus, Staphylococcus, Bacteroides, Fusobacterium, Actinomyces, Morganella morganii, Peptostreptococcus* spp.
Parasitic	*Mesocestoides, Sparganum proliferum*
Fungal	*Blastomyces, Histoplasma,* and *Candida* spp.
SECONDARY CAUSES	**EXAMPLES**
Chemical	Gastric acid, bile, pancreatic enzymes, urine, barium
Mechanical, foreign body	Suture, hair, surgical swabs ("gossypiboma") Cotton, silk, linen, migrating grass awn
Starch, granulomatous	Surgical glove powder (talc, corn starch)
Parasitic	Cestodes
Protozoal	*Neospora, Toxoplasma*
Septic causes	
Gastrointestinal origin	Leakage/rupture (secondary to ulceration, foreign body obstruction, neoplasia, trauma, torsion with ischemic damage or dehiscence of a previous surgical incision)
Hepatobiliary origin	Liver abscess, liver lobe torsion/ischemia with bacterial colonization, ruptured biliary tract (caused by necrotizing septic cholecystitis, iatrogenic or blunt trauma), septic necrotizing pancreatitis or pancreatic abscess
Urogenital origin	Septic uroperitoneum, renal abscess, pyometra, uterine rupture, uterine torsion/ischemia with bacterial colonization, traumatic breeding, prostatic abscess
Hemolymphatic origin	Splenic abscess, splenic torsion/ischemia with bacterial colonization, mesenteric lymph node abscess
Penetrating wounds	Bite wounds, gunshot wounds, vehicular trauma
Iatrogenic surgical	Surgical peritoneal contamination
Peritoneal dialysis or abdominal drainage (closed suction, open abdomen)	If ascending bacteria/fungal infection

Peritonitis can be classified by etiology (primary vs. secondary vs. tertiary), distribution (focal or diffuse), and duration (acute or chronic).[1] Primary peritonitis is caused by an extra-abdominal source, such as hematogenous dissemination, and likely some component of immunocompromise. Other proposed routes are via translocation from the gastrointestinal (GI) tract, across the natural openings of the diaphragm from the pleural space, and from the ovarian bursae.[5,12] The best example of primary peritonitis in veterinary medicine is the effusive form of feline infectious peritonitis (FIP) caused by hematogenous spread of mutated feline enteric coronavirus (see ch. 224). Other reported causes of primary peritonitis in veterinary medicine include infection with bacteria, fungi, and parasites (see Table 279-1).[12,13]

Secondary peritonitis is caused by septic or aseptic intra-abdominal disease and is the most common type in dogs and cats (see ch. 143). Secondary septic peritonitis from GI leakage or rupture caused by ulceration (selective cyclooxygenase-2 inhibitor administration),[14,15] infiltrative disease, foreign body obstruction, leakage of feeding tube sites, neoplasia, penetrating trauma, ischemic damage, torsion, volvulus, or dehiscence of a previous surgical incision is common.[16-29] The most frequent origin of GI leakage reported in dogs is surgical wound dehiscence,[18,29] although perforating intestinal foreign body has also been reported as the most common cause.[20,25] In one study, GI leakage in cats primarily was associated with neoplasia,[24] while another study identified trauma as the predominant cause.[26] Septic peritonitis is often polymicrobial, but the most frequently isolated microbe regardless of underlying cause is *E. coli.*[20,21] Bile peritonitis develops as a consequence of biliary tract trauma, necrotizing cholecystitis, and post-operative complications of biliary tract surgery (e.g., dehiscence of a cholecystotomy incision)[30-33]; bile from normal dogs is sterile, and septic biliary peritonitis is associated with a higher mortality rate. Proposed sources of bacteria include open or penetrating wounds, rupture of an infected gallbladder, ascension from the GI tract, translocation of enteric bacteria, or

systemic and portal endotoxemia and bacteremia.[31,33] Blunt abdominal trauma with subsequent rupture of the urinary bladder is the most common cause of uroperitoneum in dogs and cats (see ch. 143). Other causes of uroperitoneum include rupture secondary to urethral obstruction, neoplasia, and iatrogenic (urethral catheterization, manual bladder expression, cystocentesis, inadvertent penetration during abdominal surgery).[34-37]

Tertiary peritonitis is recurrent intra-abdominal infection after initial surgical and antimicrobial therapy of secondary bacterial peritonitis.[3] This category predominantly is recognized in human medicine.

Historical Findings, Clinical Signs, and Physical Examination

Signalment can help prioritize the likely causes of peritonitis. Young animals are more likely to have foreign body obstruction or infectious disease, while neoplasms are more likely in geriatric patients. In sexually intact patients, prostatitis and pyometra are differentials. Large- and giant-breed dogs are predisposed to intestinal and gastric volvulus. Pertinent historical information to gather in all cases includes: toxin exposure, dietary indiscretion, possible foreign body ingestion, other animals in the household affected, preexisting medical conditions (e.g., mast cell tumor), current medications (nonsteroidal anti-inflammatory drugs [NSAIDs], glucocorticoids), history of trauma or recent GI surgery, exposure to other animals, progression and duration of clinical signs (acute versus chronic), and review of systems.

Clinical signs can be variable and non-specific depending on inciting cause. Signs can include anorexia, lethargy, depression, weakness, collapse, vomiting, diarrhea, polyuria/polydipsia, dysuria, anuria, hematuria, and vulvar or preputial discharge. In a recent study, only 48% of cats with peritonitis had a history of vomiting; depression/lethargy and anorexia were the most common findings.[26] Physical examination abnormalities can include evidence of peritoneal effusion (distended abdomen, fluid wave on ballottement [see ch. 17]); signs consistent with systemic inflammatory response syndrome (SIRS), such as tachycardia/bradycardia, tachypnea, pyrexia/hypothermia, and leukocytosis/leukopenia; and clinical signs consistent with progressive states of shock. Other findings could include penetrating wounds, hernias, icterus, and abdominal pain. Dogs are more likely than cats to exhibit signs of abdominal pain.[5] In two recent studies, only about half of cats with peritonitis exhibited signs of abdominal pain.[24,26]

Diagnostics

History and physical examination often guide initial diagnostics, but peritoneal fluid analysis is likely the most beneficial diagnostic test. Abdominocentesis can be done blindly if large volumes of fluid are present, or with ultrasound guidance for smaller volumes. Ultrasound-guidance, four-quadrant sampling, or diagnostic peritoneal lavage (see ch. 90) increase success rate and yield. Peritoneal fluid analysis includes evaluation of the gross appearance (color, character), protein concentration, specific gravity, and cytologic examination (see ch. 74). Biochemical analysis (glucose, bilirubin, creatinine, potassium) of the effusion can help differentiate underlying causes in some patients.

In most patients with peritonitis, fluid will be an exudate (protein >3.5 g/dL [>35 g/L]; nucleated cell count >5000/mcL). Fluid from a septic abdomen is an exudate with predominantly degenerate neutrophils and infectious organisms such as intracellular bacteria. The accuracy of cytologic examination of fluid for the diagnosis of septic peritonitis has ranged from 57-100%[5,21,38,39]; previous antibiotic therapy or location of sample collection could result in false negatives. Peritoneal fluid nucleated cell count is considered one of the most reliable variables for diagnosis of septic effusion in dogs and cats.[38] In one study, a peritoneal fluid nucleated cell (predominantly neutrophils) count > 13,000 cells/mcL was 86% sensitive and 100% specific in dogs, and 100% sensitive and 100% specific in cats, for the diagnosis of septic effusion.[38] A difference of >20 mg/dL (>1.1 mmol/L) between paired blood and peritoneal fluid glucose was 100% sensitive and 100% specific for the diagnosis of septic peritonitis in dogs, and 86% sensitive and 100% specific in cats. A lactate difference <2 mmol/L between blood and peritoneal fluid was predictive of septic peritonitis in dogs (63% sensitivity, 100% specificity); this same association has not been demonstrated in cats.[38] Levin et al found all dogs with septic effusions had a peritoneal fluid lactate >2.5 mmol/L.[39] Blood-to-peritoneal fluid glucose and lactate difference might not be as dependable for the diagnosis of septic peritonitis postoperatively when evaluating abdominal fluid collected from closed suction drains.[40] Dogs with neoplasia have had significantly lower glucose concentrations and higher lactate levels in their abdominal fluid than dogs without neoplasia.[41] Peritoneal fluid protein concentrations do not reliably distinguish septic and non-septic effusion in either

dogs or cats. Bacterial aerobic and anaerobic culture and sensitivity of abdominal effusion obtained at the time of preliminary diagnosis and prior to initiation of antibiotic therapy is recommended in cases of suspected septic peritonitis. Uroperitoneum is diagnosed if peritoneal fluid creatinine concentration exceeds the serum creatinine concentration greater than two-fold, or if peritoneal fluid potassium concentration exceeds the serum potassium concentration by more than a factor of 1.4 (dogs) or 1.9 (cats).[34-37] Bile peritonitis is diagnosed if peritoneal fluid bilirubin concentration exceeds serum bilirubin concentration by greater than a factor of 2; cytological examination can reveal bile pigment or crystals.[31]

A complete blood count (CBC), serum biochemistry profile, arterial blood gas analysis (see ch. 128), and coagulation panels (see ch. 196) are recommended to guide treatment. These tests contribute prognostic information, but results can be non-specific and vary with etiology. CBC abnormalities can include marked neutrophilia with a left shift, toxic changes, and anemia, especially in cats. In a study of cats with septic peritonitis, band neutrophilia was identified in 64%, toxic leukocytes in 36%, and anemia in 35%.[24] Leukopenia and marked neutrophilia have been associated with increased mortality in cats.[42] The severity of a degenerative left shift is significantly associated with outcome (risk of death or euthanasia) in dogs and cats with septic peritonitis.[43,44]

Common abnormalities on serum biochemistry profiles and blood gas analyses include metabolic acidosis with hyperlactatemia; hypocalcemia; hyperkalemia (uroperitoneum); hyperglycemia followed by hypoglycemia (cats>dogs>people); hypoalbuminemia; elevated liver enzyme activities and hyperbilirubinemia; and azotemia of prerenal, renal (acute kidney injury) or post-renal (uroperitoneum) origin. High plasma lactate concentration on admission, poor lactate clearance, and persistent postoperative hyperlactatemia are associated with increased mortality and morbidity in dogs with septic peritonitis (see ch. 70).[45] Hypocalcemia is common in critically ill patients, including those with septic peritonitis, but the pathophysiologic mechanism has not yet been clearly established. Persistent hypocalcemia during hospitalization could be a negative prognostic indicator in both dogs and cats with septic peritonitis.[46,47] Uroperitoneum patients develop hyperkalemia because urine, which is high in potassium, accumulates in the abdominal cavity and potassium is reabsorbed into the systemic circulation through the peritoneum; life-threatening cardiac arrhythmias can result (see ch. 248).[35,37] Peritoneal effusions have been associated with a decreased sodium : potassium (Na : K) ratio.[48,49] Proposed mechanisms include decreased effective circulating volume due to loss of sodium-rich fluid and subsequent activation of the renin-angiotensin-aldosterone system (RAAS), and antidiuretic hormone (ADH) release. Decreased sodium delivery to the distal renal tubules and decreased kaliuresis can decrease Na : K ratio.[50] Abnormalities in blood glucose concentration can be a feature of peritonitis. In a study of cats with septic peritonitis, hypoglycemia was identified in 10, and hyperglycemia in 6, of 46 patients.[24] Hypoalbuminemia is common with septic and non-septic peritonitis and has been reported as a complication of open peritoneal drainage in dogs and cats.[24] Increased activities of alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) are associated with increased mortality in dogs with diffuse peritonitis treated with open peritoneal drainage.[20] Hyperbilirubinemia can be seen in dogs and cats with various causes of peritonitis, especially bile peritonitis or pancreatitis.

The presence of bacteriuria and pyuria in a urine sample should prompt urine culture and sensitivity, as bacteria in urine could be similar to those found in peritoneal fluid if septic. With severe sepsis, there can be prolongation of clotting times (PT, PTT), thrombocytopenia, decreased fibrinogen, elevation in fibrin degradation products and D-dimers, and/or decreased antithrombin (AT) levels, consistent with disseminated intravascular coagulation (see ch. 197). Deficiencies of protein C and AT, and hypercoagulability, appear to be consistent features of naturally occurring canine sepsis and could be useful prognostic indicators in canine septic peritonitis.[51] Ancillary tests, such as pancreatic-specific lipase immunoassays (PLI), can be helpful in evaluation of pancreatitis (see ch. 289, 290, and 291) as a possible cause of peritonitis.

Abdominal imaging can help in the diagnosis of peritonitis. Survey radiographs can show local or generalized loss of detail, evidence of volvulus or torsion, a GI foreign body or evidence of mechanical obstruction, mass effect, prostatomegaly, pyometra, or pneumoperitoneum. GI rupture secondary to gastric dilation-volvulus, neoplasia, NSAIDs, or glucocorticoids accounted for the majority of cases of spontaneous pneumoperitoneum in one study.[52] Horizontal beam radiography is more sensitive for detection of small volumes of gas and can help differentiate gas bubbles superimposed over the GI tract.[52] Idiopathic pneumoperitoneum is a diagnosis of exclusion when intraabdominal disease is absent and it is considered a nonsurgical disorder.[53-56] Abdominal ultrasonography can show localized peritoneal effusion, define an underlying etiology of peritonitis, and help guide abdominal fluid sampling (see ch. 88 and 89). Contrast

radiography can evaluate the upper GI tract and assess gastrostomy or jejunostomy tube site integrity; excretory urography or cystourethrography can confirm uroperitoneum. Contrast-enhanced multi-detector computed tomography (CE-MDCT), where available, can be performed safely and successfully in awake or lightly sedated patients with acute abdominal conditions[57] and can accurately differentiate surgical from non-surgical acute abdominal conditions in dogs (also see ch. 143).[58]

Treatment

Medical Stabilization

The goals of medical treatment are to restore effective circulating volume, correct acid-base disturbances, maintain electrolyte balance, and minimize ongoing contamination. Patients can present in varying degrees of hypovolemic shock (see ch. 127) and require fluid resuscitation with crystalloids and/or colloids (see ch. 129), and blood products (see ch. 130). The goals during the first 6 hours of resuscitation using the approach of early goal-directed fluid therapy are: mean arterial pressure (MAP) ≥65 mm Hg (see ch. 99), central venous pressure (CVP) 8-12 mm Hg (see ch. 76), urine output ≥0.5 mL/kg/h (see ch. 106), central venous oxygen saturation ≥70% (see ch. 98), and lactate <2 mmol/dL (see ch. 70).[59-62] Fluid resuscitation is initiated using small boluses (10-20 mL/kg over 5-15 minutes) of isotonic crystalloids, barring clinically significant primary heart disease. Similarly, synthetic colloids can be administered in dosages of 5 mL/kg over 5-10 minutes and/or hypertonic saline (7-7.5% sodium chloride) given at 4-6 mL/kg.[63,64] Vasopressors, such as norepinephrine, epinephrine, vasopressin, and dopamine, are advocated for shock that does not respond to fluid resuscitation; norepinephrine is the first-line vasopressor for septic shock.[65] Electrolytes (potassium, phosphate, magnesium) and dextrose can be supplemented if indicated. Albumin administration may be needed in hypoalbuminemic patients with decreased colloid osmotic pressure (see ch. 130). The need to give large volumes of plasma to increase circulating albumin concentrations makes concentrated albumin sources preferred unless unavailable. Human serum albumin (5% and 25% solutions) has been transfused safely in critically ill patients, including those with peritonitis, to increase albumin concentrations and systemic blood pressure.[66,67] Lyophilized (5%) canine albumin has been given to hypoalbuminemic dogs following surgical treatment for septic peritonitis.[68]

Intensive monitoring may be needed for hemodynamically unstable patients. Arterial catheters (see ch. 75) allow measurement of blood gas values and continuous direct blood pressure monitoring. Jugular central venous catheters, or peripherally inserted central catheters (see ch. 76), allow measurement of central venous pressure and aid in deciphering whether a patient has received an adequate fluid volume or is fluid overloaded. Central venous pressure measurement can help determine when vasopressors are required beyond fluid resuscitation. Urinary catheters (see ch. 106) allow assessment of urine production and monitoring of fluid needs, and may be used for urine diversion in patients with uroperitoneum. Fresh whole blood, packed red blood cells and plasma administration may be indicated in patients with anemia or coagulopathies (see ch. 130).

Early initiation and appropriate selection of broad-spectrum antibiotic therapy are important in septic peritonitis. Antimicrobials likely to be effective against the bacterial organisms causing septic shock (predominantly *E.coli, Clostridium* spp. and *Enterococcus* spp.[21]), and that have good penetration into presumed infected tissues should be given intravenously within the first hour after severe sepsis or septic shock has been recognized (see ch. 161). Source control should be attempted within 6 hours.[65] After initial broad-spectrum antibiotic therapy, the antibiotic regimen should be reviewed based on the patient's condition and results of culture and sensitivity to reduce therapy to the fewest drugs and lowest dosages necessary (antibiotic de-escalation).[65] For community-acquired infection with no evidence of renal insufficiency, a combination of amikacin (15 mg/kg IV q 24 h) and clindamycin (12 mg/kg IV q 12 h) is recommended. If there is evidence of renal insufficiency, then a third-generation cephalosporin, such as cefotaxime (22 mg/kg IV q 8 h), is recommended in place of amikacin. If *Enterococcus* infection is suspected, then either of the previous regimens in conjunction with ampicillin (22 mg/kg IV q 8 h) is advised.[69]

Treatment: Surgical Stabilization

The need for surgical treatment depends on the underlying cause of peritonitis. Immediate surgical intervention might not be necessary for primary bacterial peritonitis, idiopathic pneumoperitoneum, and uroperitoneum.[12,13,37,53-56] Surgical goals for septic peritonitis are abdominal exploration, elimination of the

source of contamination, debridement of necrotic material, repair, lavage, and drainage. Feeding tube placement should be considered during initial surgical exploration (see ch. 82). The omentum should be preserved for its beneficial functions including fluid drainage, adhesion, angiogenesis, and immune activity.[1] There is no reported difference in outcome between open, closed, or closed-suction drain management of septic peritonitis.[20-23,29,70,71] Primary closure without drainage is recommended if the source of contamination can be controlled with repair, debridement and lavage.[22] Open abdominal drainage and closed-suction drains are recommended if debridement and lavage cannot remove the infectious and foreign material load, or if the source of contamination cannot be repaired. Closure of an open abdomen can typically be performed 3-5 days following the initial surgery. Disadvantages of open peritoneal drainage are loss of copious amounts of fluid and plasma proteins from the peritoneal cavity, evisceration of abdominal organs, nosocomial infections, the need for intensive nursing care, adhesion of viscera to bandage material, and continued peritonitis and sepsis.[20,23] Vacuum-assisted closure has been used successfully in veterinary medicine for the management of septic peritonitis (Video 279-1).[70,71]

Postoperative Care

Comprehensive postoperative management and intensive monitoring in critically ill patients with peritonitis may be necessary. Placement of an arterial catheter, central venous catheter, and urinary catheter will allow more sophisticated monitoring. A urinary catheter can be used for measuring intraabdominal pressure, using the intravesicular technique, to prevent the abdominal compartment syndrome.[72] Cardiac telemetry monitoring provides information on heart rate and cardiac dysrhythmias that could necessitate treatment (see ch. 248). Abdominal drain management consists of keeping exit sites clean, monitoring and recording drainage volume and character, and serial cytologic examinations of the fluid. The clinician should monitor fluid "ins" received and "outs" lost in urine, bandages, and drainage, and adjust fluid therapy accordingly. Analgesia predominantly is provided by constant rate infusion of opioids, but multimodal analgesia with ketamine, lidocaine, local anesthetics, dexmedetomidine, and epidural continuous infusion might be necessary to control severe pain (see ch. 126). Early enteral nutrition via nasoesophageal, nasogastric, esophagostomy, or gastrostomy feeding tubes is advocated in critically ill patients (see ch. 82). Possible complications of enteral feeding include vomiting/regurgitation, diarrhea, electrolyte/acid-base disturbances, and feeding tube malfunction (obstruction, dislodgement, exit site infection). Parenteral nutrition (see ch. 189) can be delivered through a central vein (total parenteral nutrition) or a peripheral vein (peripheral or partial parenteral nutrition). Parenteral nutrition is associated with more metabolic complications and intensive nursing care is needed for aseptic admininstration.[73] A study in dogs that survived septic peritonitis found that early nutrition (within 24 hours of hospitalization for both parenteral and enteral routes) was associated with significantly shorter hospitalization length (by 1.6 days).[74] Other specific postoperative care can be directed towards treatment of secondary complications including anemia (see ch. 198), systemic inflammatory response syndrome (see ch. 132), disseminated intravascular coagulopathy (see ch. 197), aspiration pneumonia (see ch. 242), pancreatitis (see ch. 290 and 291), vasculitis, and multiple organ dysfunction (acute kidney injury, hepatic dysfunction and cholestasis, acute respiratory distress syndrome).

Prognosis

The prognosis associated with peritonitis varies with underlying etiology, species, patient population, comorbidities, and medical or surgical management of cases. The overall survival rates for animals with septic peritonitis are reported as being between 47-85% in dogs[12,16,18,20-23,25,29,68-70] and 44-71% in cats.[12,13,16,21,23,24,28] Poor prognostic indicators in septic peritonitis include high serum liver enzyme activities (GGT, ALT),[20] refractory hypotension, cardiovascular collapse, disseminated intravascular coagulopathy, pulmonary dysfunction, and multiple organ dysfunction.[15,75] The overall survival rate for dogs with septic bile peritonitis is 27-45% and 87-100% for non-septic bile peritonitis.[30,31] The reported survival rate of cats with uroperitoneum without concurrent traumatic injuries was approximately 62% in one study; there are no corresponding studies for dogs.[34] A favorable outcome for patients with peritonitis depends on early recognition, intensive medical stabilization, source control using surgical management when needed, and comprehensive post-operative care.

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SECTION XIX

Hepatobiliary Disease

OUTLINE

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CHAPTER 280

Diagnostic Evaluation of the Liver

Sarah Cocker, Keith Richter

Introduction

The liver plays a critical role in many biologic processes essential to life. Major functions of the liver include: immunoregulation; storage of vitamins, trace minerals, glycogen, blood, and triglycerides; detoxification and excretion of toxins and other substances; digestive functions; and metabolism of carbohydrates, lipid, protein, vitamins, and endocrine hormones.[1] The liver has a remarkable regeneration capacity after significant loss. The liver can restore itself to its original size with removal of up to 70% within only 5-7 days in rats.[2] However, liver diseases associated with fibrosis, inflammation or viral infections impair this regenerative process and liver function deteriorates.[2] Because the liver has such an incredible ability to regenerate, more specific signs of liver disease such as icterus, ascites, bleeding tendencies, hypoglycemia, and hepatic encephalopathy (HE) typically do not develop until the end stages of a disease process. Early clinical signs of liver disease such as vomiting, diarrhea, lethargy, polyuria (PU), polydipsia (PD), and inappetence are extremely nonspecific. Thus, diagnosing primary hepatobiliary disease can be challenging. A logical approach encompassing patient signalment, history, physical exam findings, biochemical and hematologic abnormalities, diagnostic imaging, and liver sampling should be used to obtain a diagnosis.

Signalment and History

Breed Predispositions

For some liver diseases there are strong breed predispositions that can help raise the suspicion of hepatobiliary disease even in light of nonspecific early signs, as well as suspicion for specific hepatopathies. In other instances, the history is often very suggestive of a specific hepatopathy. For example, middle-aged, overconditioned cats with a recent history of weight loss and anorexia should raise suspicion for feline hepatic lipidosis (FHL).[3] Accumulation of copper within hepatocytes can occur secondary to increased intake, primary defects in hepatic copper metabolism, or from altered biliary excretion of copper.[4] Histopathologic findings in patients with inherited copper storage disorders will demonstrate copper accumulation located centrilobularly, whereas in patients with copper accumulation secondary to cholestasis, copper is found in the periportal parenchyma.[4,5] While there are many breeds predisposed to copper storage disease, such as the Labrador Retriever, Doberman Pinscher, Dalmatian, Skye Terrier, and the West Highland White Terrier, the specific gene mutation (COMMD1) has only been found in the Bedlington Terrier.[4] Accumulation of copper in hepatocytes may start in patients when they are less than a year old, but they typically do not present with clinical signs until they are at least a few years of age.[4] Dobermans and Labradors seem to have a female predilection.[4] Copper storage disease has also been diagnosed in cats, with possible predispositions for Siamese and European Shorthair breeds.[4] Idiopathic chronic hepatitis has been described to be breed-related in Labrador Retrievers, Standard Poodles, Doberman Pinschers, American and English Cocker Spaniels, and English Springer Spaniels (in the United Kingdom).[4,6,7] Chronic hepatitis is often seen along with copper storage accumulation in Labradors and Doberman Pinschers. Hepatic amyloidosis has been documented in Abyssinian, Oriental, and Siamese cats, as well as in Chinese Shar-Pei dogs.[8,9]

Portosystemic Shunts

Portosystemic shunts (PSS) can be congenital or acquired (see ch. 284). Congenital PSS are typically a single intra- or extrahepatic shunting vessel. Dogs with congenital extrahepatic PSS are typically pure-breed small-

and toy-breeds. The most common breeds affected include Yorkshire Terriers, Havanese, Maltese, Dandie Dinmont Terriers, Pugs, and Miniature Schnauzers.[10] Most congenital intrahepatic PSS are found in larger breed dogs, with an increased prevalence in Irish Wolfhounds, Labrador and Golden Retrievers, Australian Cattle Dogs, and Australian Shepherds.[10] In cats, PSSs tend to be extrahepatic, and overrepresented breeds include the Domestic Short Hair, Persian, Siamese, Himalayan, and Burmese.[10] The majority of pets with congenital PSS on presentation are less than 1-2 years of age, but may not present until they are much older. The median age of animals with multiple acquired extrahepatic PSS has been reported as 3 years of age at the time of presentation. These pets are typically small in stature, with a history of being dull or lethargic at times. They may have a history of anesthetic intolerance, weight loss, ataxia, and bizarre behavior (intermittent blindness, head-pressing, staring into walls or corners, pacing, random barking, or aggression).[10] Association between meal ingestion and onset of signs has been reported in 30-50% of patients.[11] A history of gastrointestinal signs, PU/PD and lower urinary tract signs is also fairly common. In cats, copper-colored irises inappropriate for the breed has been documented (Figure 280-1).[12]

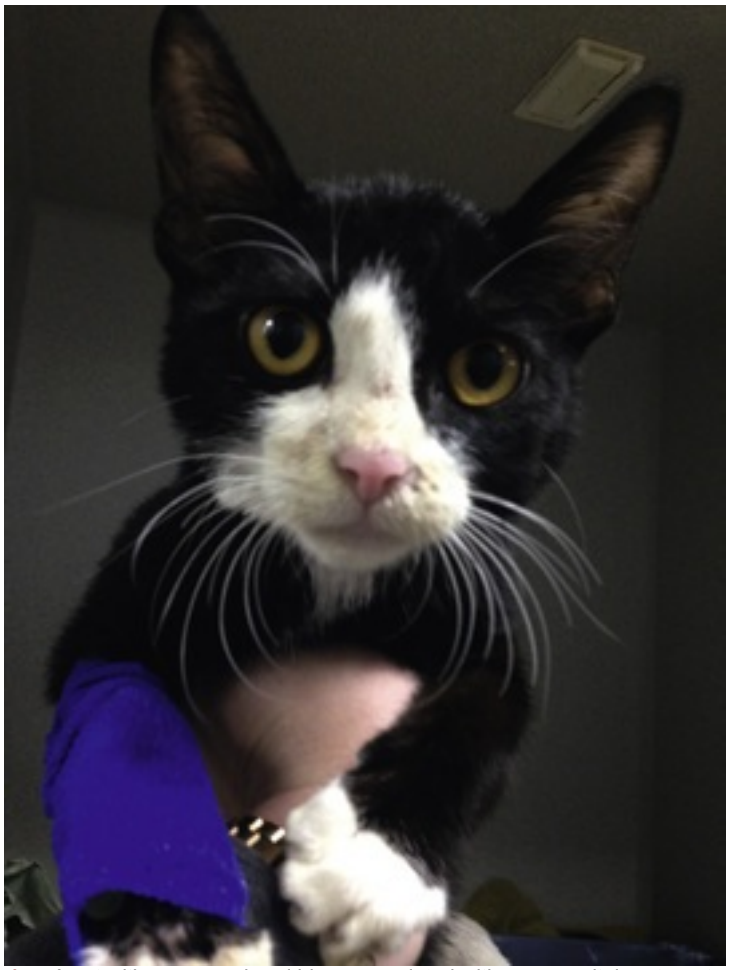

FIGURE 280-1 A cat with copper colored irises associated with a congenital portosystemic shunt.

Other Hepatopathies

Patients with congenital portal vein hypoplasia (PVH) without a macroscopic shunt (also known as microvascular dysplasia or MVD) present later in life, rarely develop clinical signs, and have an excellent long-term prognosis (see ch. 284). Maltese dogs, and Cairn and Yorkshire Terriers are overrepresented in patient populations with MVD.[13-15] The median age of these patients at the time of presentation is 3.25 years, but may range up to 10 years of age.[13] Progressive vacuolar hepatopathy is recognized as a breed-related

disorder in Scottish Terriers.[15,16] A recent study showed that vacuolar hepatopathy in this breed may be linked to adrenal steroidogenesis and a predisposition to hepatocellular carcinoma.[16]

General Information to Obtain

Pertinent historical information includes current medications as well as exposure to drugs, toxins, nutraceuticals, and supplements that may be kept in the home; the environment of the patient including time and supervision outdoors; exposure to environmental toxins and infectious agents; travel history; and vaccination status. See Box 280-1 for a list of common liver toxins. Box 280-2 lists common infectious agents affecting the liver. Middle aged, overconditioned cats with a recent history of weight loss and anorexia should raise suspicion for feline hepatic lipidosis (FHL).[3]

Box 280-1

Common Liver Toxins

Environmental Agents

Cycad palms
Amanita mushrooms
Aflatoxin
Blue-green algae

Food Additives

Xylitol

Chemicals

Heavy metals
Arsenic

Drugs

Acetaminophen
Amiodarone
Azathioprine
Carprofen
Corticosteriods
Diazepam (oral; cats)
Diethylcarbamazine—oxibendazole
Doxycycline
Griseofulvin (cats)
Halothane
Ketoconazole
Lomustine
Mebendazole
Methimazole (cats)
Methotrexate
Mitotane
Nitrofurantoin
Phenazopyridine
Phenobarbital
Stanozolol (cats)
Sulfonamides
Tetracycline
Thiacetarsamide
Zonisamide

Box 280-2

Common Infectious Agents Affecting the Liver

- Bacterial
  - Leptospirosis
  - *Mycobacterium tuberculosis*
  - *Escherichia coli*
  - *Clostridium perfringens*
- Viral
  - Canine adenovirus-1
- Fungal
  - *Blastomyces dermatitidis*
  - *Cryptococcus neoformans*
  - *Histoplasma capsulatum*
  - *Coccidioides immitis*
- Parasitic
  - *Platynosomum fastosum*
  - Toxoplasmosis
  - Schistosomiasis
  - Migrating larvae

Physical Examination

Icterus

One of the most common manifestations of hepatobiliary disease is icterus. The most sensitive places to look for icterus on physical examination are the sclera, third eyelid, soft palate, and below the tongue (Figure 280-2). Usually, icterus cannot be detected until the serum bilirubin concentration is greater than 3.0 mg/dL (and often up to 5.0 mg/dL). On the other hand, visibly icteric plasma (seen on microhematocrit tubes) or serum can be seen when the bilirubin concentration is over 0.5-1.0 mg/dL. A discussion of bilirubin is found below later in this chapter.

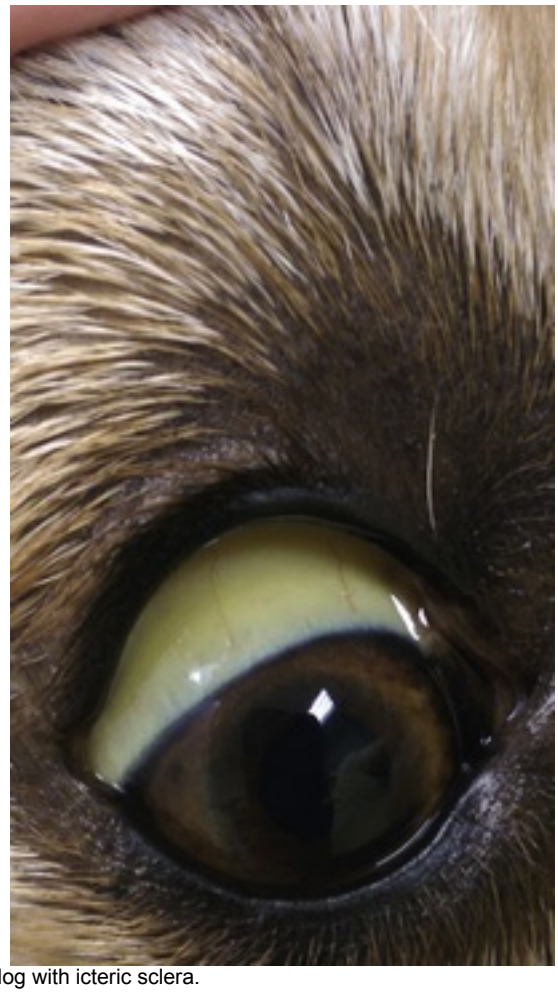

FIGURE 280-2 A dog with icteric sclera.

Dermatologic Signs

Hepatocutaneous syndrome is a form of superficial necrolytic dermatitis and has been reported in some dogs and cats with liver disease (see ch. 285). It typically manifests in dogs as hyperkeratosis with subsequent crusting and fissuring of the paw pads. Erythema, erosions or ulcerations, serous to purulent discharge, crusts, and hyperkeratotic plaques may be seen at other sites including perioral, perianal, perivulvar, preputial, and scrotal skin.[17] Lesions in cats may not appear on the footpads as they do in dogs. Ulceration and crusting of oral mucocutaneous junctions and ulceration of the pinnae, periocular areas, interdigital areas, ventral abdomen, and inguinal areas with or without crust formation is seen in cats.[17]

Ascites

Ascites is the accumulation of free fluid within the abdominal cavity (see ch. 17). Dogs and cats with severe ascites may present with a distended abdomen (Figure 280-3) and have a ballottable fluid wave on abdominal palpation (see ch. 17). Ascites in liver disease is typically due to portal hypertension (PH), though decreased vascular oncotic pressure from hypoalbuminemia may also play a role. Ascites can also be seen secondary to gallbladder rupture or effusion from hepatic neoplasms (including hemoabdomen). Ascites solely secondary to decreased oncotic pressure typically doesn't occur until serum albumin concentrations are <1.5 g/dL.[18] Portal hypertension occurs secondary to increased resistance, increased blood flow or both in the portal circulation.[19] Causes of PH are classified based on anatomical location as prehepatic, intrahepatic, or posthepatic.[19-24] Prehepatic causes occur because of increased resistance in the extrahepatic portal vein and are associated with mural or intraluminal obstruction (e.g., congenital atresia or fibrosis, thrombosis, neoplasia) or extraluminal compression.[5,20,25-31] Hepatic arteriovenous fistulas also cause prehepatic PH (see

ch. 284).[5,32-34] Patients with prehepatic PH are typically young, and have ascites and signs of hepatic encephalopathy.[19] Intrahepatic PH occurs because of increased resistance in the microscopic portal vein tributaries, sinusoids, or small hepatic veins.[19] Intrahepatic PH is further divided into presinusoidal, sinusoidal, and postsinusoidal.[19] Chronic hepatitis with fibrosis or cirrhosis is the most common cause of intrahepatic PH. Posthepatic PH occurs secondary to obstruction of larger hepatic veins such as the posthepatic caudal vena cava or the right atrium.[19] Examples of posthepatic PH include right heart failure, pericardial disease, pulmonary hypertension, and Budd-Chiari syndrome.[35-38] Ascitic fluid secondary to prehepatic and presinusoidal PH and possibly sinusoidal intrahepatic PH has a low protein concentration (<2.5 g/dL), whereas ascitic fluid secondary to posthepatic, postsinusoidal, and sinusoidal intrahepatic PH has a high protein concentration (>2.5 g/dL).[19] Portal hypertension can also lead to the development of multiple acquired portosystemic shunts (MAPSS) and hepatic encephalopathy.[19]

FIGURE 280-3 A dog with a distended abdomen due to ascites.

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a dysfunction of the brain secondary to liver dysfunction (see ch. 281 and 284).[39] This syndrome occurs less commonly in cats than in dogs.[18] The pathogenesis for HE is multifactorial, and is associated with toxins derived in the gastrointestinal tract that bypass hepatic metabolism.[19] Ammonia is one of the most important of these toxins. Other toxins implicated in the pathogenesis of HE include aromatic amino acids, bile acids, endogenous benzodiazepines, gamma aminobutyric acid, glutamine, phenol, short-chain fatty acids, tryptophan, decreased alpha-ketoglutarate, and false neurotransmitters.[10] There are two forms of HE: an acute type and a chronic type. The acute form is caused by fulminant hepatic failure. These animals typically die within a few days and the encephalopathy is severe.[18] The chronic form is much more common than the acute and carries a better prognosis as long as the underlying liver disease is reversible.[39,40] The chronic form is typically secondary to a lesion in portosystemic collateral circulation (multiple acquired PSS or congenital PSS).[18] Chronic HE can also be seen in cats with hepatic lipidosis because cats cannot synthesize arginine in the liver and depletion of arginine occurs with prolonged fasting.

Arginine is necessary for completion of the urea cycle and without it ammonia detoxification is impaired.[18] Rare causes of chronic HE are congenital disorders of metabolism in which one of the enzymes involved in ammonia metabolism is abnormal.[18] Early clinical signs of HE are subtle and include apathy, listlessness, and decreased mental alertness. In advanced, more severe disease, signs include ataxia, circling, head pressing against stationary objects, salivation, stupor, and coma. Seizures are uncommon, but may be seen in conjunction with other signs of HE.[18] Ammonia tolerance testing can be used to try and help confirm the diagnosis of HE if an ammonia level is not conclusive and HE is still suspected. The performance of this test is discussed in the ammonia section of this chapter. This test is not useful in patients with elevations in basal ammonia values, because HE is already proven.[41]

Laboratory Evaluation of Hepatobiliary Disease

Liver Enzymes (also see ch. 65)

Overview

Elevated serum liver enzyme activities are often the first finding that prompts suspicion of the presence of hepatobiliary disease. Liver enzymes evaluated on typical biochemical panels include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT). These enzymes reflect hepatocyte membrane integrity (ALT and AST), hepatocyte or biliary epithelial necrosis (ALT and AST), cholestasis (ALP and GGT), or an induction phenomenon (ALP and GGT).[42] The pattern of liver enzyme elevations can be helpful in prioritizing a differential list. Liver enzymes are classified into hepatocellular leakage enzymes (ALT, AST) indicating hepatocellular injury, and inducible enzymes (ALP, GGT) associated with increased synthesis. The magnitude of liver enzyme elevation is considered mild if <5 times the upper reference range; moderate if 5-10 times the upper reference range; and markedly elevated if >10 times the upper reference range.[42] It is important to remember that abnormal liver enzyme activity is more common than the presence of primary liver disease as there are several other clinical conditions that increase liver enzyme activities (Box 280-3). Elevated liver enzyme activities in the absence of hepatobiliary damage can be a consequence of exogenous administration of corticosteroids or phenobarbital, endogenous increases in corticosteroids, damage in non-liver tissues which also contain these enzymes (e.g., bone isoenzyme of ALP), and secondary injury from damage to organs that have portal venous drainage, especially the gastrointestinal tract and pancreas. The latter process is known as a reactive hepatopathy. There are also significant diseases of the liver that can have normal or only mildly elevated liver enzyme activities. These include vascular disorders (PSS and MVD), metastatic hepatic neoplasia (up to half of these cases can have normal liver enzyme activities), and end-stage cirrhosis (in which there is enzyme depletion).

Box 280-3

Causes of Elevated Liver Enzymes in the Absence of Primary Hepatobiliary Disease

Medication

Glucocorticoid therapy
Phenobarbital therapy

Inflammation/Infection

Pancreatitis
Gastrointestinal disorders
Sepsis
Systemic infections
Muscle injury

Endocrine Disease

Hyperadrenocorticism
Diabetes mellitus
Hyperthyroidism
Hypothyroidism

Hypoxia

Congestive heart failure
Status epilepticus
Severe hypotension
Shock

Other

Osteosarcoma or other bone tumors
Acute severe hemolysis
Postcaval syndrome
Mammary tumors
Young growing animal
Laboratory error

While elevations in serum hepatobiliary enzyme activities are very sensitive for the detection of hepatobiliary disease and the magnitude of elevation can correlate with the degree of damage, they are not indicative of the anabolic or catabolic functional capacity of the liver. Other biochemical parameters and liver function tests need to be assessed to determine the functional capacity of the liver.

ALT and AST

Elevations in activities of ALT and AST occur secondary to leakage from the hepatocyte after damage to the hepatocyte membrane; thus they are termed hepatocellular leakage enzymes. The half-life ($T_{1/2}$) of ALT is 48-60 hours in the dog and presumed to be around 6 hours in the cat.[43,44] The plasma $T_{1/2}$ of AST is approximately 22 hours in the dog and an estimated 77 minutes in the cat.[45,46] Typically, ALT activity is elevated to a greater magnitude than AST activity, partly due to its longer half-life. Hepatocellular leakage enzymes are present in high concentrations in the liver, but are also found in other tissues. AST is found in high concentrations in the liver, muscle, and red blood cells.[42] ALT, however, is primarily located in the liver with concentrations many times higher than in muscle.[42] Because the vast majority of ALT is found in the liver compared to the other hepatocellular enzymes, it is the most specific of the hepatocellular enzymes for liver injury. Evaluation of serum creatinine kinase (CK) activity is often helpful in differentiating ALT and AST elevations due to muscle injury versus liver injury.[47] The activity of CK increases rapidly after muscle injury, with peak levels occurring approximately 6 to 12 hours post-injury, and decreases within 24 to 48 hours due to a short half-life.[48] Elevations in AST activity typically parallel those of ALT but to a smaller magnitude.[44] Increased AST activity with a normal ALT indicates an extrahepatic enzyme source (muscle or red blood cell). Thus, if serum AST activity is greater than serum ALT activity, elevated serum CK activity supports a muscle origin of AST. If serum CK activity is normal with the pattern of serum AST greater than serum ALT, red blood cell origin of AST is another explanation (as would occur with *in vitro* or *in vivo* hemolysis).

Most ALT and AST resides within the soluble fraction of the cytosol and about 20% of AST is found within mitochondria.[42] The presence of a portion of AST in the mitochondria is one reason elevation of its serum activity is less sensitive than ALT for detecting liver injury (along with its shorter half-life). Additionally, because AST is found in high concentration in other organs, it is less specific than ALT for hepatocellular injury. The largest increases in ALT occur secondary to hepatocellular necrosis and inflammation, while moderate to severe elevations can occur with hepatic neoplasia, biliary tract disease (obstructive or nonobstructive), and cirrhosis.[42,49] Following severe hepatocellular injury, ALT activity typically increases markedly within 24-48 hours to values of 10- to 100-fold greater than normal, peaking the first 5 days post-injury.[50-56] In acute liver disease, a decrease of 50% or more over a few days (the half-life of serum ALT) is considered a good prognostic sign.[42] It is important to note, however, that declining liver enzyme activities may represent a decline in viable hepatocytes in chronic liver disease, severe toxicosis, or toxin-suppressed transaminase synthesis (e.g., microcystin, aflatoxin).[42] Chronic hepatitis is associated with fluctuations in liver enzymes. As the injury resolves, ALT declines, but serum ALP may increase due to the regenerative

proliferative process.[42] Following severe acute hepatocellular necrosis, AST drastically increases in the first 3 days to values 10- to 30-fold above the reference range in dogs and up to 50-fold above the reference range in cats.[50,52,57] Administration of glucocorticoids to dogs may cause a mild increase in serum AST that will resolve several weeks after discontinuing glucocorticoid therapy.[58]

ALP

In contrast to the liver leakage enzymes, ALP is attached to cell membranes by glucosyl phosphatidylinositol linkages.[42] The release of ALP from its cell membrane linkage is facilitated by the presence of bile acids, which exert a detergent-like effect on the membrane anchor.[59,60] Increases in serum ALP occur secondary to *de novo* hepatic synthesis or elution of the enzyme from the cellular membrane. Elevated ALP is the most common abnormality on canine biochemical panels, and of the liver enzymes, has the lowest specificity for hepatobiliary disease.[42] In dogs, the sensitivity and specificity of elevated ALP for hepatobiliary disease is 80% and 51%, respectively.[44] Alkaline phosphatase in the dog is present in the highest quantities, in descending order, in the intestinal mucosa, renal cortex, placenta, liver, and bone.[42] In the cat it is debatable which tissues contain the highest concentrations of ALP.[61-63] There are three major ALP isoenzymes in canine serum: bone-induced (B-ALP), liver-induced (L-ALP), and corticosteroid-induced (C-ALP).[64-67] The intestinal, renal, and placental isoenzymes contribute little, if any, to elevations in serum ALP due to their extremely short half-lives.[42] In adult dogs, it is primarily L-ALP and C-ALP that are responsible for elevated serum ALP on the biochemistry panel, whereas in adult cats it is primarily L-ALP.[42] The plasma $T_{½}$ of L-ALP and C-ALP is 70 hours in the dog, whereas the plasma $T_{½}$ of the liver isoenzyme is only 6 hours in the cat.[61,68,69] Total serum ALP activity can be induced in dogs, but not in cats, by exogenous or endogenous steroids and certain drugs.[42] Measuring the specific C-ALP fraction is not clinically useful in differentiating between primary hepatobiliary disease or the effects of endogenous or exogenous glucocorticoids because C-ALP activity is elevated in many primary hepatopathies. In cats, ALP is less sensitive (50%) but more specific (93%) for hepatobiliary disease due to its short half-life, the fact that cats lack C-ALP, and because feline hepatocytes contain less ALP.[44] Elevations in serum B-ALP are seen due to its release secondary to bony growth and remodeling in juvenile dogs and cats, or with pathologic conditions such as osteomyelitis, osteosarcoma or other bone tumors, or renal secondary hyperparathyroidism.[42,61,64,69,70] The B-ALP may also contribute significantly to the elevations in serum ALP noted in some cats with hyperthyroidism.[63,70-72] The largest elevations in serum ALP activity (up to 100 times normal or greater) in dogs are seen with cholestatic disorders, massive hepatocellular carcinoma, bile duct carcinoma, and with administration of glucocorticoids.[42]

GGT

Like ALP, GGT is bound to the cell membrane of hepatocytes. GGT in dogs and cats is found in highest concentrations in the kidney and pancreas, with lesser amounts in the liver, gallbladder, intestine, spleen, heart, lungs, skeletal muscle, and erythrocytes.[73-75] Serum GGT activity is largely derived from the liver, and increased serum GGT reflects enhanced liver synthesis and elution from cellular membrane surfaces.[42] Similar to their influence on ALP, glucocorticoids and other microsomal enzyme inducers may stimulate GGT production in dogs.[42] In dogs, the sensitivity and specificity of GGT for detection of hepatobiliary disease is 50% and 87%, respectively.[44] Concurrent elevations in ALP increase the specificity for hepatobiliary disease to 94%.[44] Serum GGT is more sensitive (86%) but less specific (67%) than ALP in cats with inflammatory liver disease.[44,76] In cats with hepatic lipidosis, where the underlying cause is not associated with necroinflammatory hepatobiliary disease, the magnitude of increased serum ALP activity (relative to the upper limit of normal) will almost always be greater than the magnitude of increased serum GGT activity. In contrast, cats with necroinflammatory hepatobiliary disorders, with or without secondary hepatic lipidosis, will usually have increases in GGT activity of a greater magnitude than elevations in serum ALP activity.[42] Neonatal dogs can have elevations in GGT activity secondary to colostrum ingestion; this is not the case for the cat.[77-79]

Liver Function Parameters and Liver Function Testing

Glucose

Hypoglycemia only occurs after approximately 75% of hepatic function is lost and is the result of reduction in hepatic glycogen stores, gluconeogenesis, and clearance of insulin (see ch. 61).[44,47] Hypoglycemia can also be seen periodically in patients with PSS. It is important to remember that there are many other differentials for hypoglycemia other than synthetic liver failure, such as hypoadrenocorticism, sepsis, decreased intake in young growing animals, toxins (xylitol) with or without hepatic involvement, insulinomas, and other neoplasms causing a paraneoplastic syndrome (see ch. 352).

Blood Urea Nitrogen (BUN)

With a significant decrease in liver function or shunting of blood past the liver, the conversion of ammonia to urea decreases and a low BUN may be noted on biochemical profiles.[44] The abnormal shunting of blood around the liver in patients with PSS results in decreased delivery of ammonia to the liver for entry into the urea cycle, which results in hyperammonemia and decreased BUN.[47] Patients on strict low-protein diets and anorexic patients may also exhibit low BUN (see ch. 62).

Albumin/Globulin

The liver is responsible for the synthesis of albumin. Hypoalbuminemia can occur with chronic liver disease once approximately 70% of liver function has been lost.[44] Generally, when the serum albumin concentration is low due to advanced liver disease, the serum concentration of globulins will be normal to increased. Hyperalbuminemia has rarely been reported in patients with hepatocellular carcinoma.[80] The liver is responsible for the synthesis of alpha and beta globulins and these can be decreased with hepatobiliary disease, but gamma-globulin production is primarily dependent on B lymphocytes and plasma cells.[47] Hypoglobulinemia is mainly seen with gastrointestinal protein loss, not with liver dysfunction. Hyperglobulinemia can be seen in patients with shunts or decreased hepatic mass (fewer Kupffer cells) secondary to decreased filtration and clearance of toxins and microbial agents from the portal circulation (see ch. 60).[47]

Cholesterol

Serum cholesterol concentrations can be variable with hepatobiliary disease (see ch. 63). Cholestatic disease is typically associated with hypercholesterolemia, whereas hypocholesterolemia may be seen in end-stage liver disease.[44]

Bilirubin

Bilirubin is the pigment that gives bile its yellow-brown color.[18] Elevated bilirubin in the systemic circulation can lead to accumulation in tissues and clinical icterus (see Figure 280-2). Causes of hyperbilirubinemia are divided into three main categories: increased production (hemolysis), also termed prehepatic; hepatic disease causing inadequate uptake, conjugation and/or excretion of bilirubin; and posthepatic causes (abnormal biliary excretion of bilirubin) (Figure 280-4).[18,44] Hyperbilirubinemia can also be caused by cholestasis of sepsis, where cytokines inhibit the expression of hepatocyte transporters necessary for bilirubin transport, and can occur without the presence of hepatobiliary disease.[44] Mild elevation of serum bilirubin can also occur with the artifacts of hemolysis or lipemia. The measurement of direct (conjugated) or indirect (unconjugated) bilirubin is of no value in distinguishing causes of increased serum bilirubin. Patterns in liver enzyme elevations are also of little help to the clinician in determining if the bilirubin elevation is secondary to hepatic or posthepatic causes. Rather, imaging (most commonly ultrasound examination) is required to distinguish hepatic or posthepatic causes of elevated serum bilirubin concentration.

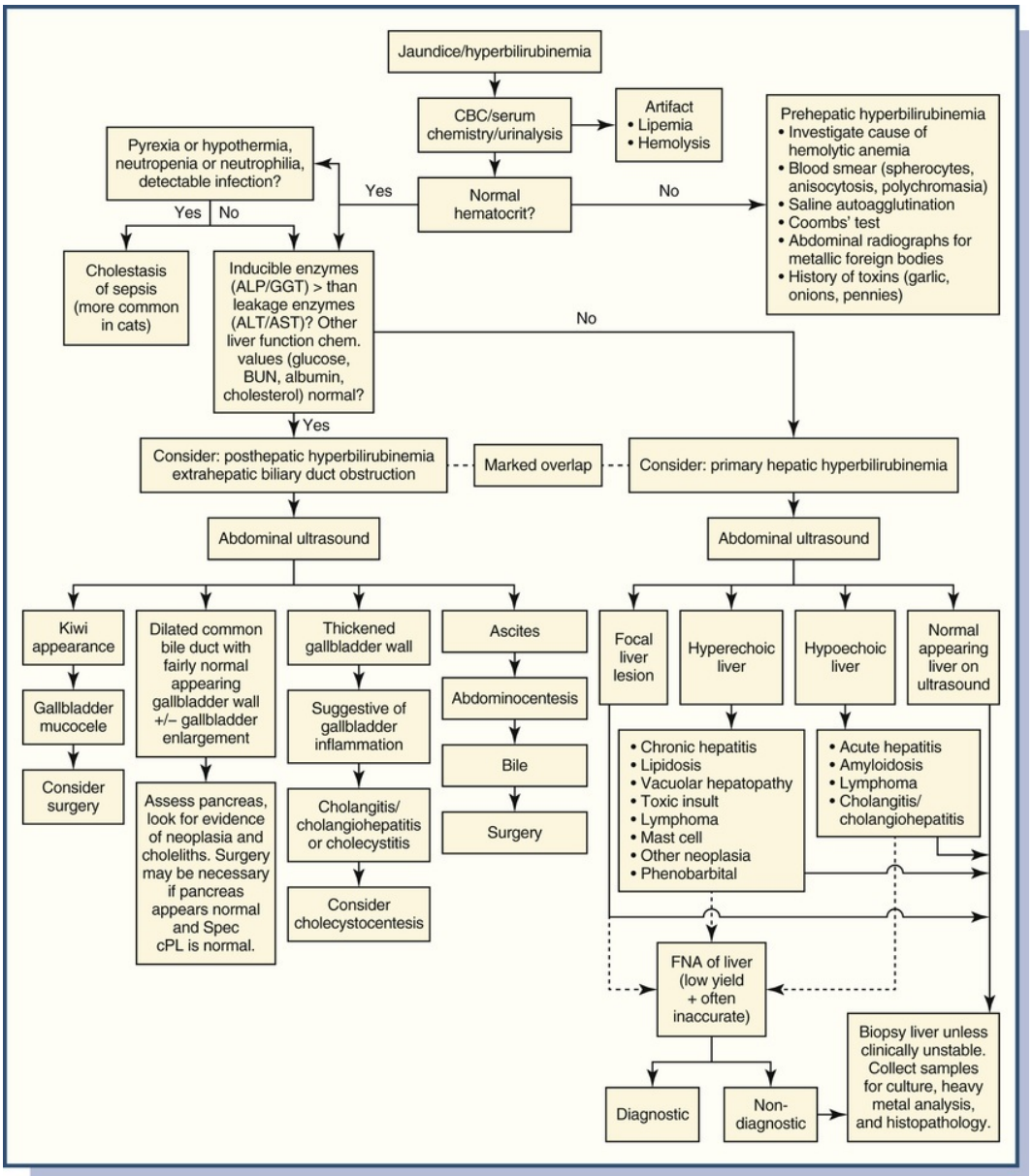

FIGURE 280-4 Diagnostic algorithm for hyperbilirubinemia. *ALP,* Alkaline phosphatase; *ALT,* alanine aminotransferase; *AST,* aspartate aminotransferase; *BUN,* blood urea nitrogen; *CBC,* complete blood count; *GGT,* gamma glutamyltransferase; *Spec cPL,* canine pancreas-specific lipase.

Usually prehepatic causes (hemolysis) are detected when the hematocrit is significantly decreased, and/or other hallmarks of hemolytic anemia are present (such as spherocytosis and/or a positive Coombs' test). Approximately 10% of all patients with liver disease have clinical jaundice.[18] In cats with hepatic lipidosis, greater than 95% present with hyperbilirubinemia.[3] Complete extrahepatic biliary duct obstruction (EHBDO) may cause acholic feces due to absence of stercobilin in stools.[18] With bile duct obstruction, conjugated bilirubin in plasma binds irreversibly covalently with albumin (called delta bilirubin), whose half-life is about 2 weeks. Therefore, a patient may remain visibly icteric for several weeks despite resolution of a bile duct obstruction.[18] Bilirubin concentration is not affected by abnormal liver perfusion; therefore, animals with congenital PSS will not be icteric.[18]

Bile Acids

Bile acids are synthesized by the liver exclusively from cholesterol, which is the major route of cholesterol excretion.[18] Bile acids are then excreted into the biliary tract and stored in the gallbladder. Cholecystokinin is secreted by the duodenal mucosa in response to fat or protein in ingesta and acts as the major stimulus for

contraction of the gallbladder.[81-84] The gallbladder contraction occurs slowly, over 1-2 hours.[18] Once the gallbladder contracts, bile acids are excreted into the duodenum to help solubilize dietary lipids.[85] They are then reabsorbed in the ileum and transported back to the liver via the portal vein, where >95% of the bile acids are removed and the process starts all over again.[85] This pathway is called the enterohepatic circulation, and its disruption due to liver dysfunction or portosystemic shunting leads to elevations in serum bile acids concentration. Increases in serum bile acid concentration can be seen with portosystemic shunts, parenchymal hepatic disease, and cholestasis.[86]

An estimation of the efficacy of enterohepatic circulation can be done by evaluation of serum bile acids. A blood sample is typically taken after a 12-hour fast (preprandial) and then two hours after a small meal (postprandial).[44] Typical cutoff values for pre- and postprandial bile acids are 15 mcmol/L and 25 mcmol/L, respectively. Pre- and postprandial bile acids elevations have been reported to be 99% sensitive and 95-100% specific for the diagnosis of a PSS in dogs and cats.[10,44] A study investigating the sensitivity and specificity of fasting bile acids in diagnosing PSS found them to be 93% and 67% in dogs, and 100% and 71% in cats, respectively. When increasing the cutoff value to 58 mcmol/L in dogs and 34 mcmol/L in cats the sensitivity was unchanged in dogs (91%) and was decreased in cats (83%), but the specificity increased in both species (84% in dogs, 86% in cats).[85]

While bile acids are quite useful for the diagnosis of PSS in dogs and cats and cirrhosis in dogs (sensitivity of essentially 100%), their value is limited for the screening of most other hepatobiliary diseases (sensitivity 54-74%).[44] Higher pre- than postprandial values may occur secondary to interdigestive gallbladder contraction or due to variations in gastric emptying, intestinal transit, or response to cholecystokinin release. This has no clinical significance, and whichever value is highest is used for interpretation. Falsely elevated postprandial values can occur with lipemia. Falsely decreased postprandial values may result from failure of cholecystokinin release to result in gallbladder contraction if the meal is inadequate in fat or protein content or an insufficient amount is consumed.[44] Severe ileal disease or previous resection of the ileum can decrease bile acid reabsorption, thus decreasing postprandial bile acids.[44] When used as a test of hepatobiliary function, the magnitude of elevation in serum bile acids does not allow differentiation of the category of disease, with the exception that patients with vacuolar hepatopathy rarely have marked elevations (greater than 75-100 mcmol/L).

Ammonia

Ammonia is derived primarily from the action of colonic bacteria on the breakdown products of ingested protein.[19] Intestinal ammonia is absorbed and enters the portal vein. In healthy states, ammonia is nearly completely removed from portal circulation during one passage through the liver via conversion to urea in the urea cycle.[18,85] The liver has a huge reserve capacity for detoxifying ammonia; therefore, HE typically only occurs when ammonia-rich blood bypasses the liver due to portosystemic shunting.[18] Hyperammonemia can also occur secondary to errors of metabolism in the urea cycle. This can be seen in anorexic cats with liver disease due to a lack of arginine, which is essential as a substrate for the detoxification of ammonia in the urea cycle.[85] Hepatic failure must cause an approximately 70% reduction in urea cycle function in order for hyperammonemia to develop.[12] Normal plasma ammonia levels in healthy animals are low (<45 mcmol/L).[18] The sensitivity and specificity of utilizing elevations in fasting ammonia for the diagnosis of PSS in dogs is reported to be 98% and 89%, respectively.[87]

Sample handling is extremely important for accurate measurement of ammonia. Ammonia should be measured in a fasted patient from non-hemolyzed fresh blood samples collected in lithium heparin tubes. Samples should be spun down in a refrigerated centrifuge within 30 minutes of collection and transferred on ice.[18,85] If kept at room temperature, ammonia is spontaneously liberated from nitrogenic sources.[18] The unreliability of enzymatically determined ammonia measurements and the lability of ammonia compromise the use of this test for diagnosing HE.[3] If bile acids and baseline ammonia are equivocal, the ammonia tolerance test can be performed to better assess the presence of HE. The ammonia tolerance test is performed by administering 2 mL/kg of a 5% NH_4Cl solution deep (10-20 cm) rectally via a soft catheter. A pre NH_4Cl sample as well as samples at 20 and 40 minutes post administration are collected. Patients without HE will have basal values within the normal range and will show a minimal increase in ammonia with this test. This test is not safe to perform in patients with basal ammonia values >150 mcmol/L.[41]

Coagulation Proteins

The liver can affect hemostasis in many ways. First, the liver produces all of the clotting factors except for the von Willebrand subtype of Factor VIII.[18,88] Second, cholestasis can cause malabsorption of fat-soluble vitamins such as vitamin K.[47] Vitamin K dependent clotting factors are II, VII, IX, X, protein C, and protein S.[89] Malabsorption of vitamin K and decreased activation of vitamin K dependent factors may lead to a prolonged prothrombin time (PT), but does not usually lead to a clinical coagulopathy.[90,91] This is the most common coagulation abnormality in cats with hepatobiliary disease.[92] Third, many clotting inhibitory proteins, including antithrombin III, protein C, and protein S, are synthesized in the liver. Fourth, splanchnic pooling of blood can lead to prolonged capturing of platelets at their degradation site in the spleen, which can induce thrombocytopenia. This is termed hypersplenism and occurs secondary to portal hypertension. Hypersplenism has been documented in humans, but to date has not been reported in veterinary patients with portal hypertension.[18,89] Fifth, some clotting factors, such as fibrinogen, act as acute phase reactants and are produced in excess by hepatocytes in cases of inflammatory or neoplastic disease, which leads to an increased consumption of fibrinogen.[18] This typically occurs in diffuse liver diseases associated with significant hepatocyte necrosis such as active forms of hepatitis and hepatic lymphoma.[88] Finally, some hepatobiliary disease can lead to disseminated intravascular coagulation (DIC). This is represented biochemically as low fibrinogen concentration, thrombocytopenia, prolonged PT and activated partial thromboplastin times (aPTT), and elevated fibrinogen degradation products and D-dimers (see ch. 197). While coagulation test abnormalities are common in dogs and cats with hepatobiliary disease, spontaneous bleeding is very rare. However, the presence of marked coagulation abnormalities in patients with liver disease is prognostic and seems to parallel the extent of functional hepatic failure.[93]

Plasma protein C is a disulfide-linked glycoprotein with a molecular weight similar to that of albumin. As stated earlier, it is synthesized in the liver and circulates as a plasma zymogen with a $T_{½}$ of approximately 6 hours. Once activated, protein C binds protein S and together they exert their anticoagulant effects by degrading factors Va and VIIIa.[94] In a study assessing the utility of plasma protein C for the detection of hepatobiliary disease and PSS in dogs, it was found that a protein C activity of less than 70% was common in patients with PSS (88%), but rare in patients with MVD (5%).[94]

Hematologic Findings

The most consistent abnormalities found on a complete blood cell count (CBC) include microcytosis (associated with impaired iron transport in patients with vascular abnormalities), target cells, poikilocytosis and Heinz body formation (cats).[44] Anemia may occur secondary to hemorrhage from gastrointestinal ulceration seen with advanced liver disease, a bleeding disorder, or anemia of chronic disease.[44] Some patients may also have a mild thrombocytopenia.[44] Poikilocytosis is found in 63% and anemia is noted in 22% of cats on presentation with hepatic lipidosis.[3]

Urinalysis

There are a few abnormalities one may note on analysis of the urine that may be consistent with the presence of liver disease (see ch. 72). The majority of these are nonspecific. The one specific finding for liver disease on a urinalysis is that of bilirubinuria in cats. Bilirubin in feline urine is always abnormal and indicates hepatobiliary or hemolytic disease.[18] In dogs, however, particularly in male dogs, there is a low threshold for bilirubin excretion. Additionally, their kidneys have the enzymes necessary to produce bilirubin from heme and to conjugate it. Thus, the urine of healthy dogs, especially males, may contain bilirubin.[18] Cats with hepatic lipidosis may have refractile fat globules in the urine (lipiduria) on urine sediment examination.[3] About half of dogs with portosystemic shunts will have ammonium biurate crystals found on urine sediment examination.[18] These crystals can also be found in the urine sediment of cats with portosystemic shunts.[95] This occurs because of the reduced hepatic conversion of uric acid to allantoin and of ammonia to urea.[96] Ammonia and uric acid aggregate in acidic urine to form crystals.[18] These crystals are infrequently associated with hepatic insufficiency due to other causes.[97] It is important to remember, however, that there are certain breed predispositions for the development of ammonium biurate crystals in the absence of hepatobiliary

disease, such as the Dalmatian, English Bulldog, and possibly Siamese cats.[98-101] The urine specific gravity in patients with hepatobiliary disease may be low. This is thought to be secondary to a loss of renal medullary hypertonicity (due to low BUN concentrations), impaired hormone metabolism (decreasing cortisol metabolism and creating a "Cushing's-like" syndrome), and psychogenic polydipsia may also play a role.[102] A Fanconi-like syndrome (presence of glucosuria despite euglycemia ± proteinuria; see ch. 326) has recently been recognized in some patients with copper storage hepatopathies secondary to accumulation of copper in the renal tubules.[103]

Imaging of the Liver

Radiography

In comparison with scintigraphic and ultrasonographic imaging, measurements made from right lateral abdominal radiographs have been found to have the highest correlation with actual liver weight in dogs.[104,105] The liver size can be determined on radiographs by measurement of the length of the liver and based on gastric axis position.[106-109] The normal gastric axis is described as perpendicular to the spine to parallel with the last rib.[110] Radiographically, hepatomegaly appears as round or blunted caudoventral liver margins, extension of liver margins beyond the costal arch, and displacement of the gastric axis.[106] Microhepatica appears as cranial displacement of the gastric axis and decreased distance between the diaphragm and gastric lumen on radiographs.[107] The position of the gastric axis can be affected by factors other than the size of the liver; therefore, measurement of the liver length may be more reliable for assessing liver size.[108,109] This can be done by measuring the length of the liver in cm as the length of the axis from the ventral border of the caudal vena cava to the apex of the hepatic caudal border and comparing it to the length of T11 (measured at the level of the midpoint parallel to the long axis of the vertebral body).[110] The normal length of the liver has been stated to be 5.5 ± 0.8 times the length of T11.[109] A recent study evaluating normal liver length in Pekingese dogs found it to be less than the previously stated normal range at 4.64 times the length of T11.[110] Loss of serosal detail is suggestive of the presence of ascites.[19] Free gas in the region of the liver is concerning for a ruptured hepatic abscess or emphysematous cholecystitis (see ch. 288).

Ultrasonography (see ch. 88)

The typical hepatic features evaluated during abdominal ultrasound examination include parenchymal echogenicity, parenchymal uniformity, vascular structures, biliary structures and an estimate of liver size.[111-115] These features are evaluated to determine: (1) the presence of focal lesions; (2) the liver architecture and structure; (3) the diameter of the lumen and the thickness of the wall of the extrahepatic and intrahepatic bile ducts and the gallbladder; (4) vascular changes, especially of the portal vein but also the presence of arteriovenous fistulas; (5) the presence of free abdominal fluid; and (6) echo Doppler evaluation of the portal blood flow velocity and direction.[88] It is important to remember that the liver may appear sonographically unremarkable even in the presence of severe disease.[116] While an unremarkable ultrasound exam was statistically significantly associated with the absence of histopathologic liver disease, 63% of these cases had abnormalities on histopathology in a study comparing hepatic ultrasound findings with histopathology.[117] The majority of dogs in this study with hepatobiliary disease and unremarkable ultrasound exams were diagnosed with inflammatory hepatopathies or degenerative lesions. Hepatic ultrasound changes are also not predictive of the presence, absence, or degree of hepatic fibrosis.[117] Hyperechoic hepatic parenchyma can be seen with chronic hepatitis, lipidosis, steroid hepatopathy, other vacuolar hepatopathies, toxic insult, lymphoma, mast cell disease, histiocytic sarcoma, and phenobarbital administration.[118] To determine if the liver is hyperechoic, its echogenicity should be compared to that of the falciform fat or spleen, both of which should normally be more hyperechoic (brighter) than the liver. Hypoechoic hepatic parenchyma may be noted with acute hepatitis, amyloidosis, lymphoma, or cholangitis/cholangiohepatitis.[118]

Ultrasound examination is quite useful for the assessment of EHBDO (see ch. 288). Neoplasia, pancreatitis, choleliths, sludge balls, inflammation, or gallbladder mucoceles can cause EHBDO.[118] The common bile duct can measure up to 3 mm in diameter in normal dogs and up to 4 mm in diameter in normal cats.[119,120] Color Doppler can be used to differentiate biliary from vascular structures. The gallbladder may be normal in size or enlarged with EHBDO. Therefore, the presence of a normally sized gallbladder should not be used to rule

out an EHBDO.[118] Portal markings may appear prominent, the gallbladder and bile duct walls may be thickened, and there may be increased amounts of sludge in the gallbladder with cholangiohepatitis.[118] Cholecystitis is indistinguishable from cholangiohepatitis on ultrasound exam.[118] A thickened gallbladder wall can also be seen with hepatitis, free peritoneal fluid, and hypoproteinemia.[121] In a previously mentioned study, sonographic identification of a thickened gallbladder wall was significantly associated with inflammation on histopathology.[117] Choleliths are more common in dogs than cats and appear as hyperechoic structures within the gallbladder or bile duct that produce acoustic shadowing.[118] Emphysematous cholecystitis can be seen as gas within the biliary tract and may be due to infections with *Escherichia coli* or *Clostridium perfringens* bacteria and has also been associated with diabetes mellitus.[118]

Ultrasonographic features of gallbladder mucoceles include immobile bile sludge that does not change according to gravity, and/or echogenic bile in a stellate or finely striated pattern, also called the "kiwi fruit-like" pattern (see ch. 288).[122] No association has been found between the ultrasonographic bile pattern and the likelihood of cholecystic rupture in a study of 14 dogs with gallbladder mucoceles.[123] However, another study showed that an incomplete stellate pattern was statistically more common in dogs that ruptured their gallbladder, although this was not pathognomonic for gallbladder rupture and gallbladder rupture was still unable to be predicted based on the ultrasonographic bile patterns.[122] Most of the dogs in this study did not develop thickened gallbladder walls or extrahepatic bile duct dilation. When gallbladder rupture does occur, it is typically diagnosed by observing a discontinuation of the gallbladder wall directly and indirectly based on evidence of pericholecystic changes such as hyperechoic fat and fluid accumulation.[122] The sensitivity for diagnosing gallbladder rupture via ultrasonography is reported as 85%.[124] It is important to remember that biliary dilation is not always associated with active biliary disease, because the canine biliary tract may remain dilated after resolution of disease.[125]

Ultrasonography can be helpful in the diagnosis of PSS (see ch. 284). The reported sensitivity for ultrasonographic identification of MAPSS is 67% compared with that of congenital PSS (90-100%),[126] though the detection of shunts is very operator- and machine-dependent. One study found the liver to be small in 96% of dogs with primary vascular disease, and in 100% of dogs with MVD.[117] Portal vein : aorta and portal vein : caudal vena cava ratios of greater or equal to 0.8 and 0.75, respectively, consistently ruled out an extrahepatic PSS in one study.[126] Portal vein : aorta ratios less than or equal to 0.65 were consistently found in extrahepatic shunts.[126] Uroliths and renomegaly are common findings in dogs and cats with PSS.[127-129] Extrahepatic shunting vessels generally originate from the portal, splenic, right or left gastric, or gastroepiploic vein.[126,130] Portocaval shunts terminate in the caudal vena cava and their entrance is characterized by turbulent flow with color and spectral Doppler.[118] Ascites can be seen with portal hypertension and MAPSS, but is uncommon with CPSS.[30,131-133] Typically, MAPSS are visualized in the left dorsal perirenal area as a plexus of small, tortuous splenic to renal vessels.[5,126,134,135] Other findings suggestive of portal hypertension include reduced portal blood flow velocity (<10 cm/s), hepatofugal flow, enlarged portal vein, and a dilated left gonadal vein.[19] Arteriovenous fistulas create connections between the portal vein and hepatic arteries.[121]

The presence of a hepatic mass on abdominal ultrasound examination should raise concern for neoplasia (see ch. 287). A study by Murakami et al reported that dogs with large liver masses and peritoneal effusion were most likely to have malignant hepatic neoplasia.[136] However, the diagnosis must be confirmed with histopathology as there are several benign conditions that may appear mass-like on ultrasound such as degeneration, inflammation, or nodular hyperplasia.[117] Hepatic abscess can have a variable mass-like appearance on ultrasound and may be associated with the presence of free gas (reverberation artifacts).[118] Cystic lesions appear as anechoic cavitary structures that generally have sharply defined borders; they can be round or irregular in shape, and may contain hyperechoic septae.[118] Other anechoic lesions in the liver include necrosis and some cavitary neoplasms. Granulomas can be secondary to a multitude of infectious organisms or foreign material and appear sonographically as multifocal hyperechoic and well-marginated parenchymal lesions.[118,121] Liver lobe torsion is rare in dogs. The affected lobe appears hypoechoic, and color Doppler shows reduced or absent blood flow within the lobe.[118]

Contrast-enhanced ultrasound allows assessment of the perfusion patterns of organs in a noninvasive manner. It is typically used to try and distinguish malignant from benign lesions and is divided into the early phase and the late phase. The early phase is composed of an arterial phase (wash-in) and a portal venous

phase (wash-out).[118] During portal and late phases all benign lesions, except cysts and thrombosed hemangiomas, exhibit isoenhancement or slight enhancement compared to surrounding liver tissue. Malignant liver lesions show hypoenhancement or do not perfuse at all.[137] The sensitivity and specificity for diagnosing benign versus malignant liver nodules is 100% and 94.1%, respectively.[118]

Other Imaging Modalities

Computed Tomography (CT)

CT can be useful for determining liver size, and for the diagnosis of hepatic mass lesions and PSS. Contrast enhancement of masses may help in differentiation benign versus malignant lesions.[118] CT angiography has a sensitivity of 96% and specificity of 89% for the diagnosis of congenital PSS in dogs and is 5.5 times more likely to correctly determine the presence or absence of a congenital PSS than abdominal ultrasound.[138] CT has many advantages: it is noninvasive, is able to accurately depict the origin of the anomalous vessel, has the potential for three-dimensional reconstructions, and is less operator-dependent than ultrasonography.[118,139,140] The disadvantages are that general anesthesia is required in most cases and the possibility of motion artifact exists, which can require repeat scanning.[118] CT is quickly becoming one of the more commonly used methods of diagnosing extrahepatic PSS.

Magnetic Resonance Imaging (MRI)

Similar to CT, MRI has been shown to be helpful for the diagnosis of hepatic mass lesions and PSS. One study investigating the utility of contrast-enhanced MRI for distinguishing benign versus malignant mass lesions found MRI to be accurate in 33 of 35 lesions for a sensitivity and specificity of 100% and 90%, respectively.[141] The reported sensitivity and specificity of magnetic resonance angiography for the diagnosis of single congenital PSS are reported to be 79% and 100%, respectively.[142] MRI is rarely used for the diagnosis of PSS because CT angiography is able to provide similar detail more rapidly and at a lower cost compared to MRI.[143]

Portal Scintigraphy Using ^{99M}Tc-Sulfur Colloid

^{99M}Tc-sulfur colloid are small colloidal particles that localize within the reticuloendothelial system. In normal dogs, most of the ^{99M}Tc-sulfur colloid will localize in the liver, whereas in patients with PSS a significant portion will localize within the lung.[144] This technique is not specific for PSS in dogs because uptake in the lungs occurs with other causes of hepatic insufficiency and cannot be used in cats for the diagnosis of PSS because lung uptake is seen in normal cats.[144,145]

Per-Rectal Portal Scintigraphy (PRPS)

This technique involves administration of a radionuclide (typically sodium pertechnetate) into the colon. In normal patients, pertechnetate will first be visualized in the liver and then the heart. In patients with PSS, the portal blood containing the pertechnetate bypasses the liver and will be seen in the heart first.[146] Lower magnitude shunts may have simultaneous arrival of the pertechnetate to the liver and heart.[146] Quantitative analysis of the PRPS can be performed with an imaging computer that calculates a shunt fraction (SF), which is an estimation of the percentage of portal blood that bypasses the liver.[145,147] Normal dogs should have a SF of <5%. Most patients with congenital PSS will have SFs >60% and typically between 80-95%.[146] The main disadvantage of PRPS is that there is poor anatomic detail, so the exact location and type (congenital or acquired) of the shunt is usually unable to be identified and the studies can occasionally be nondiagnostic (typically due to poor absorption from the colon).[146] Patients with MVD will appear normal with PRPS.[146]

Trans-Splenic Portal Scintigraphy (TSPS)

Trans-splenic portal scintigraphy is performed using ultrasound guidance for injection of the radiopharmaceutical (sodium pertechnetate) into a central region of splenic parenchyma.[146] The resulting images are of higher quality than those obtained using PRPS.[148,149] Normally, the radiopharmaceutical is rapidly absorbed from the spleen into the splenic vein, flowing into the left gastric vein and then into the main portal vein to be delivered to the liver. The radiopharmaceutical will then pass through hepatic

sinusoids, to the hepatic vein, caudal vena cava, and then to the heart.[146] The normal SF for dogs is approximately 2.64%.[146] Visualization of shunting vessels occurs in 90% of cases.[148,149] Trans-splenic portal scintigraphy can distinguish between portoazygous and portocaval/splenocaval shunts, and sometimes between congenital versus acquired shunts.[146] Portosystemic shunts located caudal to the entrance of the splenic vein into the portal vein may be missed with this technique.[146] Similar to PRPS, lower-magnitude shunts may have simultaneous arrival of the pertechnetate to the liver and heart.[146] ^{99m}TC-mebrofenin can be used as an alternative to sodium pertechnetate and may allow the location of the shunt to be more easily identified.[146] As with PRPS, TSPS is not useful for the diagnosis of MVD.[146]

Sampling of the Liver

Fine-Needle Aspiration of the Liver

Fine-needle aspiration (FNA) of the liver is much less invasive, has fewer risks, yields faster results, and is less expensive than obtaining hepatic biopsy samples (see ch. 89 and 93). This procedure typically can be performed without the use of sedation, analgesia, or anesthesia unless the patient is aggressive or struggling in response to restraint. Local anesthetics are also typically not used. Fine-needle aspiration of the liver is generally considered safe, but owners should be warned of the risk of hemorrhage, though this is rare. Fine-needle aspiration of the liver should be performed with ultrasound guidance and typically using a 22G to 25G needle. Often less blood contamination is obtained with rapid agitation of the needle without a syringe ("sewing machine technique") compared with aspiration using a syringe. Several aspirates from different sites should be collected in patients with diffuse disease. The collected sample should be sprayed onto glass slides and thin smears should be made. The authors advise staining 1-2 slides with a Diff-Quik stain in hospital and evaluating those slides under light microscopy to look for the presence of hepatocytes. This ensures an adequate sample has been collected prior to submission for cytology review. Specific stains can be applied to the slides to look for intrahepatic copper granules (rubeanic acid or rhodanine stain), lipids (Sudan stain) and glycogen (periodic acid-Schiff stain).[88]

The main disadvantages of cytologic diagnosis from FNAs of the liver are the high frequency of inaccurate results due to low cellularity and artifacts, and the absence of tissue architecture for assessing lesions.[150] The overall agreement of cytologic and histologic diagnosis is reported to range between 30-61%.[151,152] A recent retrospective study evaluating the accuracy of ultrasound-guided FNA of focal liver lesions found the highest sensitivity for vacuolar change (57.9%), followed by neoplasia (52%).[153] This study also showed that round cell tumors (positive predictive value [PPV] 75%) and non-hepatocellular origin carcinomas (PPV 85.7%) were the most readily diagnosed neoplasms with cytology. The PPV for hepatocellular carcinoma was 100%. The study also found that only approximately 50% of patients with a histopathologic diagnosis of neoplasia had neoplastic cells detected on cytology. These findings suggest that while a diagnosis of neoplasia on cytology is most likely correct, cytology alone cannot be used to exclude the diagnosis of neoplasia.

Cytology of FNAs of the liver can be helpful in confirming the diagnosis of feline hepatic lipidosis (see ch. 284). Diffuse hepatocellular triglyceride vacuolation is characteristic of this syndrome.[3] However, if the underlying cause of hepatic lipidosis is a primary liver disease, a definitive diagnosis could be missed with cytology alone, as cytologic diagnosis of other hepatobiliary disorders can be remarkably discordant with biopsy specimens.[3]

Hepatic Biopsy

The diagnosis of most hepatobiliary diseases requires histopathologic examination of liver tissue. Diffuse liver disease may be sampled randomly, but focal lesions require more selective sampling (see ch. 89 and 95). For large focal lesions, samples should be collected at the periphery of the lesion as large masses may have a necrotic center. Risks of hepatic biopsy include anesthetic complications especially in patients with advanced liver disease due to an inability to metabolize anesthetic agents, hemorrhage, air embolism (laparoscopy) and vagotonic shock.[3,88,154] Vagotonic shock is typically associated with needle biopsy and the risk is increased in patients with dilated bile ducts and when a rapid-firing automatic biopsy needle is used. There is little objective evidence that coagulation status assessed via PT, aPTT, fibrinogen concentration, platelet count, or buccal mucosal bleeding time (BMBT; see ch. 80) correlates with the risk of bleeding following liver biopsy.[155,156] Vitamin K_1 and/or fresh frozen plasma can be administered prior to pursuing a liver biopsy if

the clinician is concerned about an increased bleeding risk.

The three most common hepatic biopsy techniques are core needle biopsy, laparoscopic biopsy, and surgical biopsy. General anesthesia is required for surgery and laparoscopy, and may be necessary for some patients undergoing core needle biopsies. Needle biopsies have limitations due to their small sample size. One good core needle biopsy represents 1/50,000 of the entire liver.[157] A 14G needle diameter is recommended for medium to large dogs and 16G for small dogs and cats.[88] Needle biopsies can be obtained percutaneously with ultrasound guidance or under visual control during laparoscopy or surgery. The Tru-Cut-type needle technique is the most widely used and typically can be performed with ultrasound guidance.[88] There are 3 types of Tru-Cut-type needles: manual, semi-automatic, and automatic. Manual devices are difficult to handle and are only advised with direct visual control during surgery.[88,155] Semi-automatic and automatic types are more commonly used. The main disadvantages of ultrasound-guided liver biopsy include the need for sedation or anesthesia in some patients, difficulty of imaging small livers, difficulty of obtaining liver tissue in patients with fibrosis, and samples that carry a questionable representation of the underlying hepatic disease process. This questionable accuracy is in most part due to potential for sampling error. This method still results in a relatively small sample size, possible fragmentation of fibrous tissue, and may not enable sampling of abnormalities located in other lobes (the left medial or lateral lobes are generally sampled due to their ease of imaging). In one study, the diagnostic accuracy of the Tru-Cut needle biopsy was compared to the gold standard of surgical wedge biopsy of the liver in 124 patients.[158] The overall discordance between the two methods was 53% in dogs and 50% of cats, with >60% discrepancy occurring with chronic hepatitis or cirrhosis, cholangitis/cholangiohepatitis, portosystemic vascular anomalies, microvascular dysplasia, fibrosis, and miscellaneous disorders. These disorders are the most commonly seen among dogs and cats with hepatobiliary disease. The greatest accuracy was with neoplasia (80% concordance). Use of a 14G needle versus 18G may reduce this discordance as it increases the number of portal triads sampled. A recent study investigating transjugular liver biopsy in canine cadavers found it to be a feasible technique. However, further studies are needed before this technique can be recommended in the clinical setting.[159]

Laparoscopy involves distention of the abdominal cavity with gas followed by placement of a rigid telescope though a portal (cannula) in the abdominal wall to examine the contents of the peritoneal cavity (see ch. 91).[155] Biopsy forceps and other instruments are then passed into the abdomen via adjacent portals to allow more thorough inspection of abdominal organs and collection of biopsy samples.[88,155] This technique enables gross evaluation of the entire liver, extrahepatic biliary system, and surrounding structures while obtaining multiple large specimens of liver (see ch. 283). The ability to obtain multiple samples decreases the risk for sampling artifact in cases of regional diversity within the liver. Additionally, by directly visualizing the hepatic parenchyma, the clinician can correlate the histopathologic findings and clinical data with the gross appearance of the liver to render the most accurate diagnosis. This method also enables the visualization of smaller masses and irregularities that may not be evident with ultrasonographic imaging. There is generally minimal bleeding during this procedure, even in patients with *in vitro* coagulopathies. Using a "spoon" or oval cup forceps typically results in a marked decrease in the amount of hemorrhage when compared to needle biopsies. Any hemorrhage can be directly visualized for adequate clot formation. If hemorrhage persists, direct pressure using a blunt probe for five minutes can be used. If the site continues to bleed, electrocautery can be applied to the biopsy site or a topical hemostatic agent (Gel Foam) can be placed directly on the biopsy site using laparoscopic forceps. The main disadvantages of laparoscopy are the need for general anesthesia, increased cost, and the need for technical expertise and equipment. In an unpublished review, the complication rate of diagnostic laparoscopy was less than 2%.[88] Laparoscopy can also be used to obtain biopsies of other organs besides the liver such as the pancreas, kidney, spleen, lymph node, and intestine, as well as for cholecystocentesis (aspiration of the gallbladder).[88] Biopsy samples obtained via laparoscopy are significantly larger (approximately 5 × 10 mm) than those obtained by needle biopsy, but are still smaller than samples obtained surgically (1-2 cm).[88]

Liver biopsy alone is rarely an indication for surgery if laparoscopy is available. Laparotomy is indicated over laparoscopy when there is concern for a biliary duct obstruction or vascular anomaly that may require surgical correction in addition to obtaining a liver biopsy, or when the patient is undergoing surgery for an issue unrelated to its hepatobiliary disease. The advantage of surgery is the exposure, ability to manipulate the tissues, ability to obtain a larger sample, and ability to monitor the biopsy site for bleeding.[88] The major disadvantages to surgery are the increased pain and postoperative recovery time.

The World Small Animal Veterinary Association (WSAVA) has set standards for unification of diagnostic

criteria and nomenclature of liver diseases.[5] The authors obtain at least 4-5 biopsies from different liver lobes for histopathology, 1 biopsy for aerobic and anaerobic culture, and 1 for quantitation of copper and other heavy metals.[88] It may be necessary to obtain additional samples for histopathology when using needle biopsy techniques to improve the likelihood of obtaining a diagnosis.

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CHAPTER 281

General Principles in the Treatment of Liver Disease

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Client Information Sheet: Treatment of Liver Disease in Dogs and Cats

Veterinarians are frequently required to devise therapeutic plans for dogs and cats with hepatic disease. This can prove to be challenging for a number of reasons. First, the efficacy of many of the drugs and nutraceuticals that are used to treat hepatic disease in these species has not been rigorously established.[1] Therefore, the decision to use these agents is often made based on there being a supporting pathophysiologic rationale, evidence inferred from studies in humans, a lack of perceived adverse effects, or a combination of these reasons. This lack of evidence is concerning and as a profession we should strive to confirm the efficacy and safety of the drugs that we use by performing randomized placebo controlled clinical trials. Additionally, the underlying etiology of many canine and feline liver diseases has not been well established. For example, in many cases the underlying cause of canine chronic hepatitis cannot be identified.[2] This means that we are often limited to the provision of supportive rather than definitive treatment. Finally, because of the limitations of the current non-invasive tests for hepatic disease, assessing a patient's response to therapy can be challenging.

Drugs Commonly Used to Treat Hepatic Disease

Cytoprotective Agents (Table 281-1)

Because of its functional location between the splanchnic and systemic circulations, its central role in the metabolism of drugs and toxins, as well as its large resident population of macrophages (Kupffer cells), the liver is susceptible to oxidative damage.[3] Glutathione, a tripeptide synthesized from L-glutamate, L-cysteine, and glycine, is an essential antioxidant that is mainly stored in hepatocytes.[4] Reduced hepatic concentrations of glutathione have been found in cats with extrahepatic bile duct obstruction, cats with hepatic lipidosis, and dogs and cats with necroinflammatory liver disease, supporting the importance of oxidative injury in a wide range of canine and feline hepatobiliary diseases.[5]

TABLE 281-1

Hepatic Cytoprotective Agents

AGENT	CLASS/MECHANISM OF ACTION	SUGGESTED INDICATIONS	DOSAGE	POTENTIAL SIDE EFFECTS	COMMENTS
S-adenosyl methionine	Antioxidant, anti-inflammatory, modulates apoptosis, anticarcinogenic	Acute liver injury, canine chronic hepatitis, feline hepatic lipidosis	20 mg/kg PO q 24 h	Occasional vomiting and decreased appetite	Give at least 1 hour before feeding, u proven bioavailal product
N-acetylcysteine	Antioxidant	Acute liver injury, feline hepatic lipidosis	140 mg/kg IV initially followed by dosages of 70 mg/kg q 8-12 h	Often leads to vomiting if administered PO; well	Use instead of S-adenosyl methionine in patients who can

				tolerated when given IV	tolerate oral medications, administer a 10% solution diluted 1 over 20 minutes through a 0.25 micron non-pyrogenic in-line filter
Silymarin	Antioxidant, immunomodulator, antifibrotic, choleretic	Acute liver injury, canine chronic hepatitis, feline hepatic lipidosis	5-10 mg/kg PO q 24 h (combined with phosphatidylcholine) in dogs and 10 mg/kg PO q 24 h in cats (combined with phosphatidylcholine)	Generally well tolerated	Phosphatidylcholine increases the absorption of silymarin; use a proven bioavailal product
Vitamin E	Antioxidant	Acute liver injury, canine chronic hepatitis, feline hepatic lipidosis	Alpha-tocopherol acetate 10-15 IU/kg PO q 24 h	Generally well tolerated	Ideally give with foo efficacy has not been proven
Ursodeoxycholic acid	Choleretic, displaces hydrophobic bile acids, antiapoptotic	Feline cholangitis, chronic hepatitis, non-surgical gall-bladder mucoceles	10-15 mg/kg PO q 24 h	Occasional diarrhea	Does not appear to have an importar effect on serum b acid testing

S-adenosyl Methionine (SAMe)

S-adenosyl methionine (SAMe) plays a central role in the synthesis of glutathione via the transsulfuration pathway.[4] Therefore, the main rationale for treating dogs and cats with SAMe is that it may help to prevent oxidative damage by preventing the depletion of hepatic glutathione. It has also been claimed that SAMe may have anti-inflammatory properties, modulate apoptosis, and be anticarcinogenic.[4] At the recommended dosage of 20 mg/kg PO q 24 h on an empty stomach, SAMe has rarely been reported to have side effects in dogs or cats other than causing occasional vomiting and a decreased appetite.[6] There is limited evidence that SAMe is efficacious in dogs and cats. First, it has been shown that a combination of SAMe and silymarin inhibits the production of proinflammatory cytokines and the development of oxidative stress in canine hepatocyte cell cultures.[7] Second, oral administration of SAMe was shown to improve hepatic and erythrocyte redox status in healthy cats.[8] Additionally, a study of 12 healthy dogs showed that administration of SAMe diminished the oxidative stress associated with the administration of an immunosuppressive dosage of prednisone although it failed to prevent the development of histological changes consistent with vacuolar hepatopathy.[9] Lastly, in a study of dogs being treated with the chemotherapeutic agent lomustine, dogs supplemented with a product containing silymarin, SAMe, and phosphatidylcholine (Denamarin) were shown to have smaller increases in serum alanine aminotransferase and alkaline phosphatase activities and serum bilirubin concentration than those that were not, suggesting a hepatoprotective effect.[10] However, further clinical trials are needed to fully assess the efficacy of SAMe in treating dogs and cats with hepatic disease. From a practical perspective, because of the important role of oxidative injury in experimental models of hepatic disease and humans with hepatic disease, the author uses SAMe as an adjunctive treatment in a wide variety of hepatic diseases in dogs and cats. These include acute liver injury due to drugs or intoxications in dogs and cats, chronic hepatitis in dogs, copper associated chronic hepatitis in dogs, and feline hepatic lipidosis.

N-acetylcysteine (NAC)

N-acetylcysteine (NAC) is a formulation of L-cysteine that helps replenish hepatic intracellular cysteine and

glutathione concentrations, thereby providing protection against oxidative injury.[3] Oral administration of NAC is frequently associated with vomiting in dogs and cats.[6] Therefore, this medication is usually given intravenously when it is used to treat hepatic disease in these species. In a study of dogs undergoing bile duct ligation, NAC improved markers of hepatic circulation and redox status.[11] Additionally, a recent study demonstrated that supplementation with NAC during the first 48 hours of hospitalization stabilized erythrocyte glutathione concentrations in ill dogs.[12] However, investigators were unable to show a beneficial effect of NAC in experimental canine models of ischemic liver injury and reperfusion.[13] Intravenous NAC has been shown to be beneficial in treating acetaminophen intoxication in humans and is an accepted albeit not critically evaluated therapy for acetaminophen intoxication in dogs and cats. NAC is usually given as a 10% solution diluted 1 to 2 with saline as an IV bolus over 20 minutes through a 0.25 micron non-pyrogenic in-line filter at a dosage of 140 mg/kg initially followed by dosages of 70 mg/kg q 8-12 h.[6,14] Concern has been raised that administration over longer periods of time might lead to the impairment of ammonia metabolism via the urea cycle.[14] The author considers using this drug as part of the initial treatment of dogs and cats with acute liver injury due to other drugs or intoxications and of cats with hepatic lipidosis. Once these patients can tolerate oral SAMe, the NAC is discontinued.

Silymarin

Silymarin is a mixture of at least 7 flavanolignans and 1 flavonoid extracted from the milk thistle plant.[15] Silibinin is the most abundant and biologically active component of silymarin.[16] Silymarin is believed to have antioxidant effects by scavenging free radicals and reducing lipid peroxidation.[17] Experimental evidence and studies in human patients suggest several other potential benefits. First, silymarin is believed to have several anti-inflammatory effects, including suppression of tumor necrosis factor-alpha, interleukin-1 beta, and nuclear factor kappa-beta and may also inhibit hepatic fibrosis by reducing hepatic stellate cell DNA synthesis, proliferation and migration, as well as reducing hepatic collagen expression.[18-20] Additionally, silymarin has been shown to act as a choleretic agent in rats.[21] At commonly used doses silymarin does not appear to cause any side effects.[18] Despite decreasing the activity of cytochrome P-450 enzymes, UDP-glucuronosyltransferase enzyme, and reducing P-glycoprotein transport in humans silymarin has a limited effect on the pharmacokinetics of several drugs *in vivo.* However, care is still advised when co-administering silymarin and pharmaceuticals to human patients.[22] The bioavailability of silymarin is improved when it is combined with phosphatidylcholine, which acts as a solubilizing agent.[23] For this form of the drug a dose of 5-10 mg/kg PO q 24 h has been proposed. It has been recommended to give less bioavailable forms of silymarin at a dose of 20-50 mg/kg/day PO divided q 6-8 h.[6] However, currently there is limited evidence supporting the efficacy of this nutraceutical in the veterinary literature. It has been shown that a combination of SAMe and silymarin inhibits canine hepatocyte inflammation and oxidative stress *in vitro.*[7] In one study of Beagles administered *Amanita phalloides* toxin, all 11 dogs treated with intravenous silibinin survived whereas four of twelve control dogs died.[24] Therefore, it is prudent to administer silymarin to dogs and cats with *Amanita* mushroom intoxication. Another study did not find strong evidence that silymarin has a protective effect after carbon tetrachloride ingestion in dogs.[25] When used in combination with SAMe and phosphatidylcholine, silymarin was shown to have a hepatoprotective effect when dogs were administered the chemotherapy agent lomustine.[10] Although more clinical trials are needed to prove its efficacy, the author uses silymarin in dogs and cats with acute liver injury due to drugs/toxins, dogs with chronic hepatitis, dogs with copper associated chronic hepatitis, and cats with hepatic lipidosis (see ch. 282-286).

Vitamin E

Vitamin E is actually a family of eight lipid soluble vitamins, alpha-tocopherol being the most biologically active.[1] The main role of vitamin E is that of an antioxidant, protecting phospholipids from oxidative injury by scavenging free radicals.[26] Generally vitamin E is well tolerated in dogs and cats and side effects are rarely observed.[6] Alpha-tocopherol is usually given at a dosage of 10-15 IU/kg PO q 24 h to dogs and cats. Some clinicians consider using this supplement as part of the treatment regimen for dogs and cats with liver diseases that can lead to oxidative damage, such as acute liver injury due to drugs or intoxications, feline hepatic lipidosis, chronic hepatitis, and copper associated chronic hepatitis.[6] There is currently no clinical evidence supporting the efficacy of vitamin E in dogs or cats with hepatic disease. However, recent studies have shown a beneficial effect (improved clinical signs, markers of oxidative stress, or inflammatory markers)

in dogs with atopic dermatitis[27] or degenerative joint disease[28] suggesting that vitamin E can be an effective antioxidant in this species.

Ursodeoxycholic Acid (UDCA)

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid that is believed to have several beneficial properties: UDCA may displace more toxic hydrophobic bile acids from the circulating pool,[29] it has a choleretic effect[30] which increases the excretion of endogenous toxins in the bile, it has a cytoprotective effect by inhibiting hepatocyte apoptosis,[31] and immunomodulatory effects, such as the suppression of interleukin-2 expression.[32] It is the only Federal Drug Administration approved treatment for primary biliary cirrhosis in humans.[33] When used at a dosage of 10-15 mg/kg PO q 24 h in dogs and cats, this drug has few side effects other than occasionally causing diarrhea.[6] Because of its choleretic effect and the displacement of more toxic hydrophobic bile acids, there is a rationale behind using this drug in dogs and cats with intrahepatic and extrahepatic cholestasis, such as cholangitis in cats. In a recent retrospective study of cats with lymphocytic cholangitis, those treated with prednisolone survived longer than those treated with UDCA.[34] However, this study does not prove that UDCA lacks efficacy for treating feline lymphocytic cholangitis as for ethical reasons treatment was not compared to a placebo. The use of UDCA in dogs and cats with complete bile duct obstruction is controversial as some clinicians are concerned about the possibility of it increasing the probability of gallbladder rupture.[6] Other clinicians feel comfortable using UDCA in this situation and studies in rats where bile duct ligation was performed actually indicate that it has a beneficial effect on markers of oxidative stress and apoptosis.[35] However, it is important to note that surgical intervention is indicated in most dogs or cats with complete bile duct obstruction. Where the patient has no or mild clinical signs, UDCA is sometimes used as part of the medical management of non-obstructed, canine gallbladder mucoceles.[36] Furthermore, due to its purported immunomodulatory and antiapoptotic effects there is a theoretical reason to use UDCA in dogs with chronic hepatitis although its efficacy in this condition has not been critically evaluated.

Anti-Inflammatory/Immunosuppressive Drugs

Corticosteroids

Corticosteroids are used to treat alcoholic liver disease[37] and autoimmune hepatitis[38] but at higher doses they may increase viral load in human patients with hepatitis C infection.[39] As inactive prednisone is converted to active prednisolone by the liver theoretically it makes more sense to treat dogs with advanced liver disease with the latter.[40] However, it is not known if this choice makes any difference in their clinical outcome. Cats should be given prednisolone in preference to prednisone. While hepatic copper accumulation is an important cause of chronic hepatitis, for a large proportion of dogs with chronic hepatitis an underlying etiology cannot be identitifed.[2] Frequently these dogs have hepatic inflammation and necrosis often in the periportal zones. There is an association between chronic hepatitis and dog leukocyte antigen class II alleles and haplotypes in Doberman Pinschers[41] and English Springer Spaniels[42] supporting the role of autoimmunity in causing chronic hepatitis in these breeds. However, further studies are needed to determine whether or not autoimmunity is a cause of chronic hepatitis in these and other breeds. There is some clinical evidence to suggest that prednisolone is an effective treatment for chronic hepatitis in dogs. A retrospective study of 151 dogs with chronic hepatitis of various causes found that those treated with corticosteroids survived longer than those that were not.[43] However, these results should be interpreted with caution as the retrospective design of this study meant that it was susceptible to bias as the clinicians may have decided to start corticosteroids in dogs that were more likely to have a favorable response. The results of a more recent retrospective uncontrolled study of 36 dogs with idiopathic chronic hepatitis found that hepatic inflammation decreased and coagulation parameters returned to normal after 6 weeks prednisolone treatment and in some dogs the stage of hepatic fibrosis remained the same or improved. However, the majority of these dogs had a recurrence of clinical signs or residual disease at the end of treatment.[44] It should also be noted that glucocorticoids often cause adverse effects including polyuria/polydipsia, polyphagia, panting, dermatological changes, and importantly can have a detrimental effect on the liver causing vacuolar hepatopathy and possibly oxidative stress.[8] Prospective placebo controlled clinical trials assessing the efficacy of prednisolone in treating canine idiopathic chronic hepatitis are needed before definitive recommendations can be made. The author considers performing a therapeutic trial with prednisolone in dogs with chronic

hepatitis that do not have chronic copper associated hepatitis (based on copper staining and quantification) and have a negative hepatic and/or bile bacterial culture, especially if there is moderate to severe hepatic inflammation on histological examination of a liver biopsy specimen. Prednisolone/prednisone are usually given at a dosage of 1-2 mg/kg PO q 24 h with a subsequent gradual taper.[45] As glucocorticoid administration makes it difficult to assess the patient's response to treatment by serial measurement of serum liver enzyme activities, some clinicians advise that liver biopsy is repeated 6 weeks after starting treatment.[46] Prednisolone is often used to treat cats with lymphocytic cholangitis and chronic neutrophilic cholangitis after a negative bile bacterial culture and failure to respond to trial therapy with antimicrobials. Cats with lymphocytic cholangitis that were treated with prednisolone were shown to survive longer than those treated with UDCA.[34]

Azathioprine

Azathioprine is a purine analog that is occasionally used as an immunosuppressive agent in dogs with idiopathic chronic hepatitis, usually with the aim of allowing a lower dosage of prednisolone/prednisone to be used.[46] A dosage of 2 mg/kg PO q 24 h for 2 weeks then reduced to q 48 h has been advised for this purpose. However, the efficacy of azathioprine for treating canine idiopathic chronic hepatitis has not been evaluated and in a recent study 5 out of 34 dogs (15%) treated with this drug were suspected to have developed hepatotoxicosis.[47] Azathioprine should not be used in cats.

Cyclosporine

Cyclosporine is a T-cell inhibitor than has been use to induce remission of autoimmune hepatitis in children.[48] A few dogs with idiopathic chronic hepatitis have been reported to respond well to cyclosporine (5 mg/kg PO q 12-24 h) without concurrent corticosteroid use (David Twedt and Allison Bradley, unpublished communication). However, critical evaluation of the efficacy and safety of using cyclosporine in this setting is needed before it can be recommended.

Medications Used to Treat Hepatic Copper Accumulation

D-penicillamine

D-penicillamine is a chelating agent that combines with copper (and certain other heavy metals), allowing it to be mobilized from the liver and excreted in the urine. Penicillamine may also have an antifibrotic effect as it prevents the formation of crosslinks between collagen molecules[49] and may have immunomodulatory properties.[50] This drug is indicated for the treatment of copper associated chronic hepatitis in dogs.[51] D-penicillamine is effective at reducing hepatic copper concentrations in Bedlington Terriers, but lifelong treatment and a copper restricted diet seem to be required.[52] D-penicillamine treatment has also been shown to be effective at treating chronic copper associated hepatitis in Labrador Retrievers[53] and Doberman Pinschers.[54] This drug is given at a dosage of 10-15 mg/kg PO q 12 h and pharmacokinetic studies indicate that it is better absorbed when given on an empty stomach.[55] Gastrointestinal side effects are common in dogs receiving D-penicillamine. When these occur, dose reduction, administration with a small amount of food, or discontinuation may be necessary.[51] Prolonged chelation can lead to copper deficiency, manifested by microcytic hypochromic anemia, anorexia, vomiting, and weight loss.[52,56] In humans penicillamine has been associated with a variety of side effects including fever, cutaneous eruptions, lupus like syndromes, lymphadenopathy, proteinuria, cytopenias, and it has also been shown to be teratogenic.[57] In humans D-penicillamine can also cause depletion of vitamin B_6[58] and although this has never been reported to occur in dogs, some clinicians supplement this vitamin during treatment. Recently copper chelation using D-penicillamine was reported in 5 cats with presumed primary or secondary hepatic copper accumulation. Notably, one of these cats developed hemolytic anemia that resolved upon discontinuation of D-penillamine.[59]

Trientine (2,2,2-Tetramine)

Trientine (2,2,2-tetramine) is another chelating agent that can be used in dogs with copper associated chronic hepatitis. This drug is usually a second choice treatment in dogs that have not tolerated D-penicillamine due to its gastrointestinal side effects. Trientine has been shown to be effective at causing increased urinary

excretion of copper in dogs[60] and is used in human patients with Wilson's disease.[61] Trientine may remove more copper from the circulating pool and less from the tissue pool compared to D-penicillamine[61] and therefore might be a good choice in a dogs with hemolysis caused by high serum copper. This drug is given at a dosage of 10-15 mg/kg PO q 12 h and should be given on an empty stomach.[51] This drug is thought to be associated with fewer side effects than D-penicillamine, although vomiting and anorexia can still occur and there is currently little clinical data to support its use in dogs.

Zinc

Zinc decreases the absorption of copper from the gastrointestinal tract. Its mechanism of action is that it induces increased synthesis of metallothionein by enterocytes. Metallothionein binds copper with a higher affinity than zinc, thus preventing the copper from entering the circulation. When the intestinal cells die and are sloughed, the copper inside them is passed in the feces.[61,62] Oral zinc acetate supplementation was shown to decrease hepatic copper concentrations in dogs with primary hepatic copper accumulation over several years without apparent side effects.[63] In a recent study of Labradors with copper associated chronic hepatitis, adjunctive treatment with zinc did not appear to increase the copper-lowering effects of dietary management.[62] Once chelation therapy has reduced the hepatic copper concentration to a level that is close to normal, zinc is commonly used in conjunction with dietary copper restriction as a maintenance treatment.[51] It is interesting to note that because of its efficacy and a reduced rate of adverse effects, zinc has been recommended as sole treatment for humans with asymptomatic Wilson's disease in place of chelating agents.[61] Zinc is usually given to dogs at a dosage of 5-10 mg/kg elemental zinc PO q 12 h, ideally between meals. However, it is sometimes necessary to give it with a small amount of food as zinc can cause vomiting and nausea.[51] Zinc acetate is better tolerated than other forms of zinc. Plasma zinc concentrations should be monitored during therapy. Normal plasma zinc concentrations for dogs are 70-200 mcg/dL. Concentrations around 200 mcg/dL seem to effectively reduce copper absorption[63] but concentrations exceeding 800-1,000 mcg/dL may cause hemolysis.[64] Commercial diets formulated for dogs and cats with hepatic disease are often supplemented with zinc.

General Treatment Recommendations

Acute Liver Injury/Acute Liver Failure

Acute liver injury can lead to acute liver failure, which in humans is characterized by increased serum bilirubin concentrations, hepatic encephalopathy, and coagulation disorders.[65] When treating dogs and cats with acute liver injury, it is important to attempt to address the underlying cause. Examples are discontinuing a hepatotoxic drug, inducing emesis in a patient that has recently ingested a hepatotoxic substance, or treating leptospirosis with doxycycline. However, etiology specific treatment is not always possible, and as liver transplantation is not an option in dogs and cats, supportive care is crucial. As oxidative injury is often a primary or secondary component of acute liver injury, treatment with antioxidants including SAMe, vitamin E, and silymarin is justifiable.[6] In patients that cannot tolerate oral medications, NAC can be given intravenously in place of SAMe. As multiple organ dysfunction syndrome, acute kidney injury, and acquired respiratory distress syndrome are complications of acute liver failure, the function of other organ systems should be closely monitored. Fluid therapy is often required and care should be taken to address dehydration, acid-base abnormalities, and electrolyte abnormalities as these can precipitate hepatic encephalopathy (HE). Vomiting patients benefit from treatment with antiemetic drugs such as ondansetron (0.2 mg/kg IV q 8-12 h for dogs and q 12 h for cats) and metoclopramide (1-2 mg/kg/day IV as a constant rate infusion). Maropitant is metabolized by hepatic cytochrome P-450 enzymes so it may be prudent to decrease the dose and/or the frequency of administration when using this drug in patients with hepatic failure. Gastroduodenal ulceration is also a potential complication of acute liver injury and when suspected, treatment with omeprazole (0.5-1 mg/kg PO q 12-24 h) or pantoprazole (0.5-1 mg/kg q 12-24 h) and sucralfate (0.5-1 g/dog or 0.5 g/cat PO q 8 h) is indicated. Cerebral edema is a recognized complication of acute liver failure in humans[65] and HE is also associated with low-grade cerebral edema.[66] If signs suggesting cerebral edema, such as worsening forebrain deficits, and increased systemic blood pressure possibly with reflex bradycardia, are noted, mannitol (0.5-1 g/kg IV) should be administered.[67] Slight elevation of the patient's head may facilitate venous drainage and help reduce intracranial pressure. Human patients with acute liver failure by definition have coagulopathies, but these infrequently lead to spontaneous bleeding. Therefore, in

human patients it has been recommended that plasma and other blood products should be reserved for those with spontaneous bleeding or in preparation for an invasive procedure.[65] Further research is needed to determine whether or not this recommendation is also appropriate for dogs and cats with acute liver failure. Care should be exercised when administering stored red blood cells to dogs and cats with acute liver injury as ammonia concentrations can increase substantially during storage.[68] As patients with acute liver injury are sometimes vitamin K deficient due to cholestasis, treatment with vitamin K (0.5-1.5 mg/kg SC q 12 h for 3 doses) is recommended. Sepsis is a potential complication of human patients with acute liver failure.[69] Prophylactic antimicrobial use decreases the incidence of infection but has not been shown to confer a survival benefit and may promote the development of antimicrobial resistant infections.[70] Therefore, it is recommended that dogs and cats with acute liver failure be actively screened for infection and that broad-spectrum antimicrobials are only started if bacterial infection is suspected.

Chronic Hepatitis

Chronic hepatitis is more common in dogs than cats, the latter more frequently developing cholangitis. Although the hepatoprotectant agents described above are often used and may be beneficial in treating dogs with chronic hepatitis, they are not a substitute for treating the underlying causes of liver disease. Hepatic biopsy is required to diagnose chronic hepatitis and also to attempt to identify an underlying etiology.[46]

Copper accumulation is an important cause of chronic hepatitis in dogs, so sections of liver should routinely be stained for copper and an unfixed liver biopsy specimen should be sent for quantitative copper analysis. Even then, deciding in which cases to initiate copper chelation is not always straightforward (Figure 281-1). For most laboratories the reference interval for the hepatic copper concentration of healthy dogs is <400 mcg/g dry weight. However, 9 healthy research dogs fed a standard commercial diet were shown to have hepatic copper concentrations ranging from 199 to 997 mcg/g while feral dogs presumed to eat a diet of foraged food had concentrations ranging from 69 to 372 mcg/g.[71] This might be because commercial dog food contains more copper than the foraged food. Hepatic copper accumulation can occur due to inherited defects in copper excretion or secondary to cholestasis. In dogs with primary copper hepatopathy, the copper tends to accumulate in the centrilobular zone of the liver and be present in high concentrations, typically >1,000 mcg/g dry weight. When copper accumulation occurs secondary to cholestasis it tends to be located in the periportal zones of the liver, is associated with lower copper concentrations, typically <750 mcg/g dry weight, and usually does not require chelation.[18,72] Based on work in Bedlington Terriers most laboratories report that concentrations >1,500 mcg/g dry weight are toxic to the liver.[73] However, these values may represent too high a threshold for the initiation of chelation in other breeds. Further research is needed to define exactly when it is appropriate to start chelation therapy. From a practical perspective, even if it is not the primary insult, hepatic copper accumulation has the potential to cause oxidative damage and subsequent necroinflammatory activity. Therefore, the author institutes chelation therapy in dogs with hepatic copper concentrations >1,500 mcg/g dry weight regardless of the distribution and considers doing so when hepatic copper concentrations are >750 mcg/g dry weight if there is centrilobular copper accumulation, especially in breeds known to develop primary copper hepatopathy. These dogs should be fed a copper restricted diet. In a recent study, Labrador Retrievers with hepatic copper concentrations >1,500 mcg/g dry weight needed treatment for at least 10 months to reach a hepatic copper concentration of 400 mcg/g dry weight, and those with initial hepatic copper concentrations between 1,500 mcg/g and 1,000 mcg/g dry weight needed treatment for approximately 6 months.[53] Successful treatment is ideally confirmed 6 months after starting chelation by measuring the copper concentration of a liver biopsy specimen. For breeds other than Bedlington Terriers, it is often possible to stop chelation therapy and start maintenance treatment with zinc while continuing to feed a copper restricted diet.

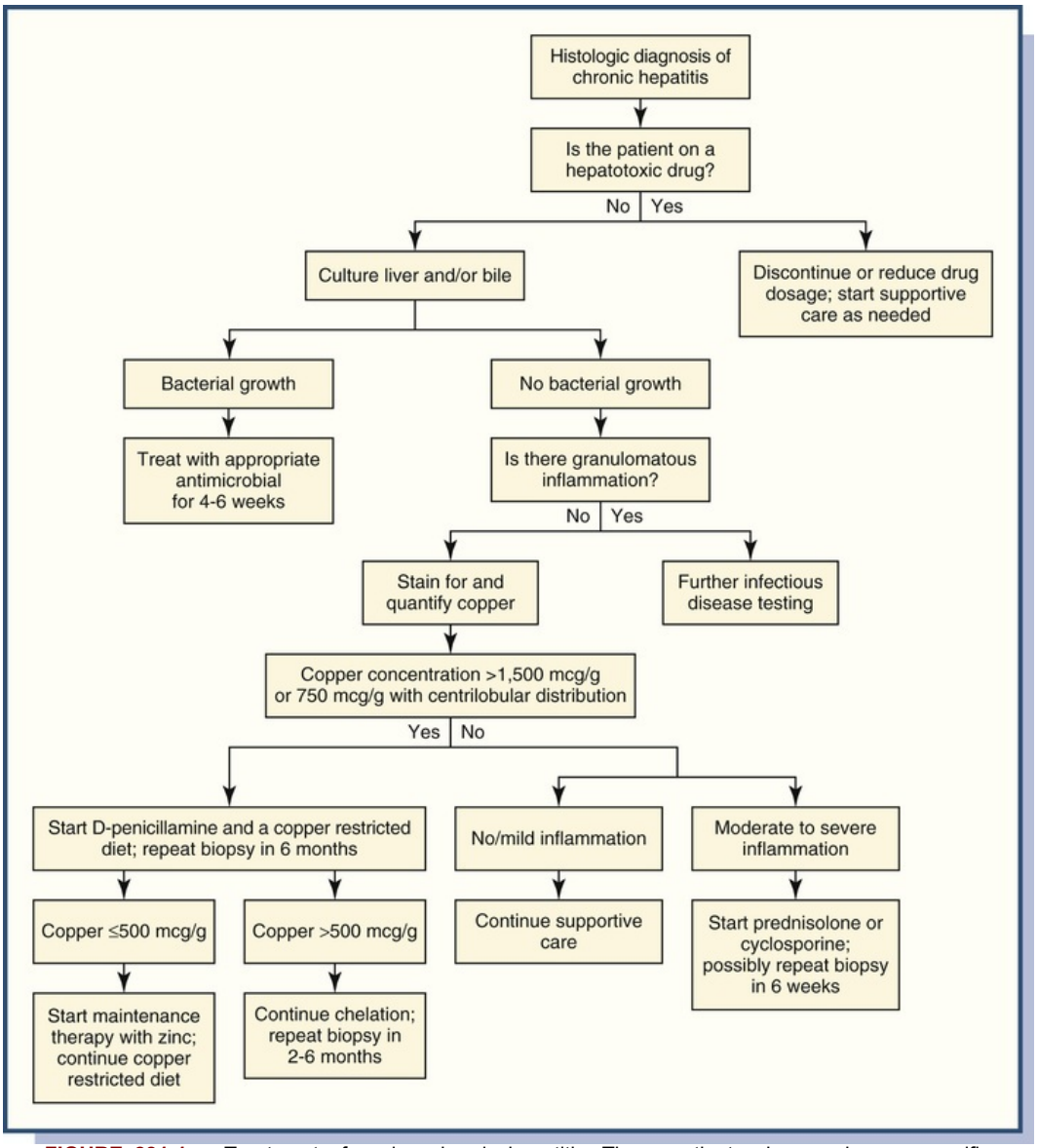

FIGURE 281-1 Treatment of canine chronic hepatitis. These patients also require non-specific supportive treatment including cytoprotective agents (see Table 281-1), and when necessary treatment of the gastrointestinal complications of hepatic disease, hepatic encephalopathy, or ascites. When granulomatous hepatitis is diagnosed, further testing for infectious causes is indicated, including histological staining for bacterial and fungal organisms, PCR testing for *Bartonella* spp., testing for canine schistosomiasis if geographically relevant, and possibly culture for mycobacteria.

Aerobic and anaerobic bacterial infections should also be ruled out by culturing bile and liver tissue. When granulomatous hepatitis is diagnosed further testing for infectious causes is indicated, including histological staining for bacterial and fungal organisms, polymerase chain reaction (PCR) testing for *Bartonella* spp., testing for canine schistosomiasis if geographically relevant, and possibly culture for mycobacteria. Even if these organisms are not identified it may be prudent to perform therapeutic trials with medications that should be effective against them before immunosuppressive medications are started. If the chronic hepatitis is suspected to be caused by chronic exposure to a drug, such as phenobarbital, the drug is discontinued if possible. If there is a convincing component of inflammation, especially if it is lymphoplasmacytic in nature, in the absence of a treatable underlying cause, trial treatment with prednisolone should be considered.[43] Once prednisolone has been started, the serial assessment of serum liver enzyme activities should be performed but has limited value for monitoring the response to treatment. Therefore, repeated hepatic biopsy 6 weeks after the initiation of treatment to determine whether or not there has been a beneficial effect has been recommended.[44,46] As discussed above, there is a pathophysiological basis for treating these dogs with SAMe, silymarin, UDCA, and vitamin E.[6] General supportive care is also important for dogs with chronic hepatitis.

Dogs with hepatic disease, especially those with portal hypertension, are at increased risk of gastroduodenal ulceration.[74] Consequently, if gastroduodenal ulceration is confirmed or suspected, omeprazole and sucralfate should be started. Antiemetic drugs may also be indicated. The provision of adequate high quality nutrition is important and dogs without HE do not need to be fed a protein restricted diet.[75]

Hepatic Fibrosis

There are no proven treatments for hepatic fibrosis of dogs or cats so the following recommendations are made based on pathophysiological principles and data generated from other species. Chronic hepatic inflammation can lead to activation of myofibroblasts including hepatic stellate cells and portal fibroblasts, which can in turn cause hepatic fibrosis.[76] Where possible, addressing the underlying cause of hepatic inflammation is essential. Treatment with anti-inflammatory/immunosuppressive agents is also rational when it is not possible to successfully identify/treat the underlying cause of the chronic inflammation. In a previously mentioned study of dogs with idiopathic chronic hepatitis, after treatment with prednisolone, hepatic fibrosis resolved in 14% of dogs and improved in a further 11%.[44] Oxidative injury may also lead to hepatic stellate cell activation[77] so antioxidants such as SAMe and silymarin may also be indicated. Colchicine binds to tubulin thereby inhibiting microtubule polymerization during mitosis therefore impeding several cellular processes including inflammation and fibrosis. However, there is insufficient evidence in the human literature to determine the efficacy of colchicine for treating hepatic fibrosis in patients with alcoholic liver disease and its use is associated with high rate of adverse effects.[78] Other than a few case reports,[79-81] from which it is difficult to establish a positive effect, the efficacy of colchicine has not been evaluated in dogs. Because of this and the high incidence of gastrointestinal side effects associated with colchicine, the author does not advocate its use. The therapeutic use of this drug has not been reported in cats and this species seems to be particularly susceptible to the toxic effects of colchicine, which can be fatal.[82] In rats the angiotensin II receptor antagonist losartan has been shown to have an antifibrotic effect on the liver. However, these results have not been consistently reproduced in human patients[83,84] and there are no studies evaluating the efficacy of this drug for treating hepatic fibrosis in dogs or cats.

Hepatic Encephalopathy

It is important to identify and manage factors that potentially precipitate HE such as gastrointestinal bleeding, infection, dehydration, electrolyte abnormalities, and alkalosis, as well as to provide supportive care.[85] As in humans[86] severe protein restriction is no longer recommended for dogs with HE as this can lead to protein malnutrition.[75] Non-meat protein-based diets are often recommended for dogs with HE. In a study of dogs with congenital portosystemic shunts fed two types of low-protein diets, one with meat and the other with soy, both diets decreased the severity of HE. However, improvements in ammonia concentrations and coagulation parameters were significantly greater in dogs fed the soy-based diet.[87] Once the signs of HE are controlled with a commercial hepatic support diet, it has been recommended to add non-meat protein to the patient's diet to help prevent protein malnutrition.[88] Cats have higher dietary protein requirements than dogs as they cannot downregulate protein catabolism even when food is withheld.[89] Therefore, severe protein restriction is inappropriate for this species. The osmotic laxative lactulose is commonly used to treat HE in dogs and cats. Lactulose can be given orally to patients with chronic HE at a dosage of 1-3 mL per 10 kg body weight q 6-8 h for dogs and cats. This is then adjusted until the patient passes three to four soft stools per day. Lactulose can be given *per rectum* after a cleansing warm water enema in patients that are stuporous or comatosed.[67] Neomycin is a poorly absorbed aminoglycoside antibiotic that is sometimes used to treat HE in dogs and cats (20 mg/kg PO q 8 h). The gastrointestinal absorption of neomycin is usually very low but substantial systemic absorption can cause ototoxicity and nephrotoxicity. In humans, neomycin is no longer used in the treatment of HE for these reasons.[90] Metronidazole is sometimes used for the treatment of HE in dogs and cats (7.5 mg/kg PO q 8-12 h). Metronidazole is metabolized by the liver and can have neurological side effects that mimic those of HE. However, these are more likely to occur at the higher dosages used for other purposes.

Ascites

Furosemide can lead to dehydration/hypovolemia, hypokalemia, and metabolic hypochloremic alkalosis, all

of which can precipitate HE in humans.[66] For this reason, the aldosterone receptor antagonist spironolactone, initially started at a dose of 2 mg/kg PO q 24 h, is preferred for the treatment of ascites that is caused by hepatic disease in dogs and cats. This dosage can gradually be increased to 4 mg/kg PO q 24 h. It is prudent to check the patient's body weight, hydration/circulatory status, hematocrit, serum creatinine concentration, and serum electrolyte concentrations during diuresis. If treatment with spironolactone is ineffective, furosemide can be started at a low dosage (1-2 mg/kg PO q 12 h).[91] Once the ascites resolves it may be possible to taper the dose of diuretics. Mild dietary sodium restriction is also advisable and commercial diets for dogs and cats with liver disease meet this specification. Therapeutic abdominocentesis can lead to worsening of hypoalbuminemia and therefore should be reserved for animals that are refractory to medical management and/or have respiratory compromise due to a large volume of ascites. In humans, abdominocentesis has been reported to lead to hypovolemia.[92] Therefore, simultaneous volume expansion with a synthetic colloidal solution or plasma should be considered in dogs and cats undergoing this procedure.[91]

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CHAPTER 282

Canine Inflammatory/Infectious Hepatic Disease

Craig B. Webb

Hepatic disease in humans most often is caused by a viral infection (hepatitis A-E) or alcoholism.[1] Chronic alcohol consumption is not an issue in veterinary patients, and with the advent of canine adenovirus-2 (CAV-2) vaccines, infectious canine hepatitis is now a rare cause of acute liver disease in dogs.[2] Two less common hepatic diseases in humans, non-alcoholic fatty liver disease and autoimmune hepatitis, may have relevance to the veterinary population because of potential similarities in pathophysiology or treatment strategies (see ch. 280).[3] Even within our small animal patients, the primary location of hepatic lesions appears distinctly different between cats and dogs, with the biliary system being predominantly affected in cats and the parenchyma being the primary target of disease in dogs.

The World Small Animal Veterinary Association Liver Standardization Group standardized the classification and nomenclature for canine and feline liver diseases.[4] Cholangitis (inflammation of the bile duct) is divided into four groups: neutrophilic cholangitis, lymphocytic cholangitis, destructive cholangitis, and chronic cholangitis associated with liver fluke infestation. Neutrophilic and lymphocytic cholangitis are found almost exclusively in cats, fluke infestation is found predominantly in cats, while destructive cholangitis is a rare condition of dogs.[4] Portal inflammation, fibrosis, and bile duct proliferation are consistent histopathologic findings in cases of cholangitis, but ultrasound of the biliary system and cytologic examination and culture of the bile are required for the most clinically useful diagnosis. Feline hepatic disease is covered in ch. 283.

Hepatitis (inflammation of the hepatic parenchyma), seen predominantly in dogs, is most often classified into acute and chronic forms.[5] The chronic form is further characterized histopathologically according to the pattern, location, cellular infiltrate, severity and extent of inflammation, hepatocyte apoptosis and necrosis, fibrosis, cirrhosis, and loss of architecture.[6] Infectious causes of canine hepatic disease exist within each of these categories, although an acute infectious hepatitis can start progressive changes that result in chronic hepatitis after the original infectious agent is gone. Granulomatous, eosinophilic, and lobular dissecting hepatitis are three additional but rare histopathologic classifications. The majority of cases of primary canine hepatitis, as opposed to secondary or reactive hepatitis, are idiopathic. Specific causes of acute hepatitis in dogs are shown in Box 282-1. For chronic hepatitis, most cases also are idiopathic, although differentials to consider include infection, toxins, drugs, metabolic causes, and an immune-mediated process.[7]

Box 282-1

Causes of Acute Canine Hepatitis

Infectious

CAV-1 (adenovirus)
Leptospirosis
Clostridium spp.
Canine monocytic ehrlichiosis *(E. canis)*

Toxins (see ch. 152)

Mycotoxins, aflatoxicosis
Cyanobacteria—microcystin toxicosis ("blue green algae" or algal bloom)
Amanita mushrooms
Xylitol (sugar substitute)

Manganese overdose (joint supplement)
Alpha lipoic acid
Organic solvents (CCl_4)

Drugs

Carprofen, acetaminophen
Trimethoprim-sulfonamide antibiotic
Azathioprine
Amiodarone
Mitotane

Idiopathic

Acute Hepatitis

Similar to acute pancreatitis, acute hepatitis in dogs can be rapidly fatal, completely reversible, or progress to a condition of chronic hepatitis over time. Early recognition and intensive intervention, starting with specific treatment of the inciting cause, if known, are keys to a successful outcome in these cases. The clinical presentation is sudden in onset and can include any number of nonspecific signs, such as lethargy, anorexia, vomiting or diarrhea, fever, abdominal pain, polyuria and polydipsia, and dehydration. Some dogs can be jaundiced, while few if any would be expected to present with ascites. These dogs often have marked elevations of serum alanine aminotransferase (ALT) or alkaline phosphatase (ALP) liver enzyme activity, with variable elevations in serum gamma glutamyltransferase (GGT) and aspartate aminotransferase (AST) activity. Dogs may or may not present with hyperbilirubinemia and decreased serum blood glucose, cholesterol, or blood urea nitrogen (BUN), depending in part on the time frame and severity of the inciting cause. Hypoalbuminemia rarely is present in acute cases, and clotting abnormalities are unlikely, although hemostasis should be monitored. A complete blood count (CBC) could indicate stress or inflammation while urinalysis may be unremarkable. A histopathologic diagnosis is rarely sought in cases of acute hepatitis where the inciting cause is more likely to be identified through history of exposure to drugs and toxins, or with various blood tests and serology looking for infectious agents.

Dogs with infectious canine hepatitis caused by CAV-1 present acutely with fever, lethargy, anorexia, cranial abdominal pain, melena, vomiting, diarrhea, and biochemical abnormalities indicative of liver and kidney involvement. Dogs can develop bronchopneumonia, conjunctivitis, photophobia, and a corneal opacity or "blue eye," the result of anterior uveitis and corneal edema (see ch. 11). With the advent of effective vaccination protocols that include CAV-2 to induce cross-protection without pathogenicity, the prevalence of this disease has been significantly reduced, although not eliminated.[2,8,9]

Leptospirosis currently is the most commonly recognized infectious cause of acute hepatitis in dogs, although historically the infection most frequently has been associated with acute kidney injury and more minor liver involvement (see ch. 217).[10,11] Leptospirosis, caused by serovars of *Leptospira interrogans* or *kirschneri* in dogs, also is an important zoonotic disease, and appropriate isolation and barrier precautions should be used in suspect cases. The most prevalent serovars and risk factors seen with affected dogs shift with the advent of different vaccine protocols and products, as well as exposure and environmental factors.[12-15] Common clinical signs include vomiting, lethargy, icterus, diarrhea, polyuria/polydipsia, and anorexia. Conjunctivitis and uveitis can be seen, as well as signs of pulmonary disease and respiratory compromise, coagulopathies, and vasculitis. Dogs often are febrile, azotemic, with elevated serum liver enzyme activities, hyperbilirubinemia, electrolyte abnormalities, leukocytosis, thrombocytopenia, and possibly prolonged clotting times. The urinalysis can reveal hyposthenuria, glucosuria, and proteinuria, with bilirubin, red blood cells, and white blood cells present.[16] Diagnostic evaluation and treatment recommendations[16] are presented in ch. 217 and Table 282-1.

TABLE 282-1

Treatment Considerations for Canine Acute and Chronic Hepatitis

CONDITION	TREATMENT	DOSE AND DOSAGE CONSIDERATIONS*

Leptospirosis	Doxycycline Ampicillin	5 mg/kg PO or IV q 12 h for 2 weeks 20 mg/kg IV q 6 h in hospital
Enterobacteriaceae: *E. coli* *Enterococcus, Bacteroides, Streptococcus, Clostridium*	Ciprofloxacin Aminoglycosides Others: enrofloxacin, clindamycin, cephalexin, etc.	
Acute hepatitis	Plasmalyte, Normosol: balanced isotonic crystalloid Fresh frozen plasma: colloid, clotting factors 2.5% dextrose + 0.45% NaCl: fluid supplementation, hypoglycemia	Variable, based on multiple parameters Variable, based on multiple parameters Variable %, based on serum blood glucose
	Vitamin K_1: vitamin K-dependent clotting factors	2.5 mg/kg SC q 12 h, 1.6 mg/kg PO q 24 h
	N-acetylcysteine: antioxidant, methyl donor, ↑[Glu]	140 mg/kg IV once, 70 mg/kg IV/PO q 6 h
Hepatic encephalopathy	Lactulose; ↓colonic pH, trap ammonia, osmotic agent	Variable, based on signs and consistency of stool, 5-30 mL PO or enema
	Metronidazole: antibiotic, anaerobes	7.5 mg/kg PO q 12 h
	Neomycin: antibiotic, poorly absorbed	22 mg/kg PO q 8 h
	S-adenosylmethionine: (SAMe) antioxidant, methyl donor, transsulfuration	20 mg/kg PO q 24 h
	Silymarin: *Amanita* mushroom intoxication, antioxidant, anti-inflammatory, anti-fibrotic, hepato-protective	20-50 mg/kg PO q 24 h
	Vitamin E: lipid peroxidation antioxidant, anti-fibrotic	400-600 IU PO q 24 h
	Vitamin B complex	1-4 mL/dog SC, IM, IV q 24 h
Enteric cyanotoxins	Cholestyramine: bile acid sequestrant	172 mg/kg PO q 24 h
Chronic hepatitis	Diet: low Cu content, Zn & antioxidants added	Protein: ↓quantity ↑quality; ↑fermentable CHO; ↓Na
	Prednisolone: contraindicated in acute hepatitis	1-2 mg/kg PO q 24 h, taper per response
	Azathioprine: purine antagonist immunosuppressive	2 mg/kg PO q 24 h, then taper
	Cyclosporine: cellular immunosuppressive	5 mg/kg PO q 12 h
	Mycophenolate mofetil: purine synthesis inhibition	10 mg/kg PO q 12 h
	Ursodeoxycholic acid: hydrophilic bile acid, choleresis, immune modulation, ↑ [Glu] production, cytoprotective	7.5 mg/kg q 24 h or 10-15 mg/kg PO q 24 h
Copper accumulation	D-Penicillamine: chelates Cu in circulation	5-15 mg/kg PO q 12 h, 2 h before food 6 months minimum
	Zinc acetate: (35% elemental Zn), prevents Cu absorption	15 mg/kg q 12 h with food
	2,2,2-tetramine tetrahydrochloride (Trientine): Cu chelator	5-15 mg/kg PO q 12 h, 2 h before food
	Ammonium tetrathiomolybdate	20 mg PO q 8 h
Fibrosis	Colchicine	0.025-0.03 mg/kg PO q 24 h
	Polyunsaturated phosphatidylcholines	50-100 mg/kg PO q 24 h
Portal hypertension	Spironolactone: aldosterone antagonist diuretic Furosemide: loop diuretic	1-2 mg/kg PO q 12-24 h 2-4 mg/kg PO or IV q 8-12 h

*Disclaimer: Clinicians should always check dose/dosage recommendations with the most currently available information.

Glu, Glutathione.

Clostridium spp. cholangiohepatitis was diagnosed by ultrasound-guided cholecystocentesis and culture of bile in a Yorkshire Terrier presenting for acute onset of vomiting and diarrhea. Biochemical abnormalities were consistent with cholestasis and histopathologic evaluation showed hepatic inflammation and necrosis. The dog was treated successfully with clindamycin, amoxicillin-clavulanate, and ursodeoxycholic acid.[17]

Clostridium piliforme was identified in one puppy with multifocal necrotizing hepatitis.[18] *Clostridium* spp. are one of the most common isolates from biliary cultures in dogs and cats with hepatobiliary disease.[19]

There is one report of an adult German Shepherd presenting with clinical signs and biochemical abnormalities consistent with acute hepatitis where the eventual diagnosis was *Ehrlichia canis* infection; following identification of *E. canis* using cytologic, immunohistochemical, and polymerase chain reaction (PCR) testing, the dog was treated successfully with supportive care and doxycycline.[20]

Acute hepatitis secondary to aflatoxicosis has been seen in dogs following ingestion of contaminated commercial dog food. Presenting signs are consistent with an acute toxic hepatopathy and historical identification of a probable source of exposure should prompt discontinuation and testing of the product. Treatment is nonspecific and supportive.[21,22]

Acute hepatitis caused by cyanobacterial microcystin toxicosis following exposure to an algal bloom usually is fatal, but several dogs have been treated successfully with some combination of 0.9% NaCl fluid supplemented with KCl and dextrose, fresh frozen plasma and whole blood, S-adenosylmethionine (SAMe) and silibinin, vitamin B complex, vitamin K, famotidine, procaine penicillin G, and the oral bile acid sequestrant cholestyramine.[23-25]

Amanita spp. mushroom ingestion causes acute hepatic inflammation, necrosis, and failure in dogs. The diagnosis is often presumptive based on exposure and clinical signs, although alpha-amanitin can be detected in liver tissue by liquid chromatography-mass spectrometry.[26] There are rare reports of successful treatment of *Amanita* mushroom intoxication, but the condition most often is fatal despite the use of N-acetylcysteine and silibinin.[27]

Hepatocellular necrosis has been reported secondary to carprofen administration in a number of dogs. Clinical signs include anorexia, vomiting, and icterus. Biochemical abnormalities include hyperbilirubinemia and elevated liver enzyme activity. Urinalysis is consistent with renal tubular disease. Supportive care results in successful resolution in many, but not all, cases, and the toxicosis is thought to be an idiosyncratic drug reaction (see ch. 169).[28,29]

Hepatic necrosis and failure have been reported in 4 dogs within a month of starting trimethoprim-sulfonamide (TMS) antibiotic administration. All of these patients died or were euthanized despite intensive supportive care, and it was determined that TMS hepatotoxicosis most likely is an idiosyncratic drug reaction.[30]

Although copper accumulation is presented as a form of chronic hepatitis, there is a report of acute hepatic failure in a young Dalmatian associated with excess hepatic copper accumulation.[31] This could be an indication that copper toxicosis has a genetic component in this breed.

Chronic Hepatitis

The majority of cases of canine chronic hepatitis are idiopathic.[5,32] The etiology most commonly identified as a cause or contributor to chronic hepatitis is excess hepatic copper accumulation. In at least one breed, copper accumulation is the direct result of a metabolic defect, while in other breeds it may be an epiphenomenon, albeit a treatable one. In cases of acute hepatitis, there could be a morphological and clinical progression to chronic hepatitis despite the elimination of the original inciting cause, and in this sense, many of the differentials for acute hepatitis (see Box 282-1) can be included as potential causes of chronic hepatitis. Some form of immune-mediated process is also postulated as an etiology for chronic hepatitis in dogs, and although this condition remains poorly defined, it is frequently the target of chronic hepatitis treatment.

The clinical presentation of canine chronic hepatitis varies from little more than persistently elevated liver enzyme activity, to a gradual decrease in the dog's activity, appetite, and weight that may be attributed to "old age," to the seemingly acute onset of jaundice, anorexia, ascites, and abnormal mentation indicative of hepatic encephalopathy. Biochemical abnormalities can indicate a significant reduction in hepatic metabolism, including hypoglycemia, hypocholesterolemia, hypoalbuminemia, a low BUN, and hyperbilirubinemia, along with an elevation in liver enzyme activity. Eventually, the liver enzyme activities can appear normal, or even below the reference range, because of a severe loss of hepatic parenchyma (see Box 280-3). A decrease in the clotting factors normally produced by the liver can be clinically apparent as prolonged bleeding from a venipuncture site, or as prolonged clotting times (see ch. 196). If serum total bilirubin is not yet elevated in cases of suspected chronic hepatitis, a pre- and post-prandial serum bile acids test is an excellent measure of hepatic function (see ch. 280). Although non-hepatic differentials for hyperbilirubinemia must be considered, bile acids testing will be abnormal in dogs if total bilirubin is

significantly elevated because of liver disease, and bile acids are therefore a redundant test in this situation. These dogs often are polyuric, polydipsic and can be hyposthenuric. Other urinalysis abnormalities include hyperbilirubinuria (0 to 1+ being considered normal in a dog) and ammonium biurate crystalluria. A CBC likely will show a stress or inflammatory leukogram and could reveal the anemia of chronic disease. Alternatively, the CBC could show a microcytic, hypochromic anemia consistent with a chronic gastrointestinal (GI) bleed secondary to portal hypertension and intestinal edema. Imaging can reveal a small, bright, irregular liver with evidence of portal hypertension or acquired shunts and ascites. The gold standard for the diagnosis and characterization of chronic hepatitis is liver biopsy. Unfortunately, these dogs often are presented when the disease process makes them poor anesthetic or surgical candidates. Even attempting laparoscopic liver biopsy in dogs with end-stage chronic liver disease could result in further decompensation of the clinical condition. However, laparoscopic liver biopsy (see ch. 91) with histopathologic evaluation, metal analysis (copper, iron, and zinc), and culture of tissue or bile, is an excellent diagnostic opportunity in those dogs that are relatively stable, presumably earlier in the disease process, and possibly suffering from a treatable condition or at least treatable component, such as copper accumulation. The presence of bridging fibrosis or cirrhosis distorting the hepatic parenchyma, along with hepatocellular necrosis and mixed inflammation is both diagnostic, and unfortunately, likely prognostic, in cases of chronic hepatitis.

Acute hepatitis caused by toxins (e.g., aflatoxicosis) or drugs (e.g., TMS, nonsteroidal anti-inflammatory drugs) can progress to chronic hepatitis over time if the dog survives the initial insult. The drugs most commonly associated with chronic hepatitis following chronic administration are anticonvulsants.[33,34] Although primidone is rarely used, there are reports of phenytoin hepatotoxicosis, and phenobarbital remains a common choice for treating seizures in dogs.[35-37] Although phenobarbital is thought to induce the production of canine ALP liver enzyme activity much like glucocorticoids, histopathologic examination suggests that the elevation of ALT activity with phenobarbital therapy could be due to hepatic damage.[38-40]

As with toxins, infectious causes of acute hepatitis can set the foundation for morphologic changes that eventually manifest as chronic hepatitis. With early recognition and treatment, many dogs with acute leptospirosis-associated hepatitis recover, do well, and possibly clear the organism. Some percentage of these dogs could go on to develop chronic hepatitis much later in life, whether due to a persistent low-grade infection, an immune-mediated reaction to the original infection, or a continuation of the inflammatory response. Identifying infectious causes of chronic hepatitis has otherwise been challenging.[41,42] In dogs and cats with hepatic inflammation, the most common organisms cultured from bile were *E. coli, Enterococcus* spp., *Bacteroides* spp., *Streptococcus* spp., and *Clostridium* spp.[19] *Helicobacter canis* was isolated from the liver of one dog with multifocal necrotizing hepatitis, while *Yersinia pseudotuberculosis, Salmonella* spp., *Clostridium piliforme, Campylobacter jejuni,* and rickettsial organisms also are potential causes of infectious chronic hepatitis.[43] Granulomatous hepatitis is a form of chronic hepatitis where the etiology often is infectious, including mycobacteria (see ch. 212), fungal organisms, migrating nematode larvae, *Leishmania* (see ch. 221), and possibly *Bartonella* spp. (see ch. 215).[44,45] Chronic hepatitis with a large eosinophilic component also can be caused by parasitic infections and migrating larvae. Histopathologic assessment and microbial culture would be essential components of a correct diagnosis and an effective treatment plan. Young female English Springer Spaniels appear predisposed to a form of chronic hepatitis where the histopathologic findings are similar to those of viral hepatitis in humans, but to date, no causal virus has been identified.[46] Serologic testing, PCR testing, and fluorescence *in situ* hybridization (FISH) are advanced technologies currently being employed as diagnostic tools in the search for infectious causes of hepatic inflammation. As this latter technology becomes more readily available, it is very likely to clarify the role of bacteria in canine hepatitis, and in doing so, help target specific antibiotic therapy to those cases where it is most appropriate.

Anti-inflammatory and immunosuppressive therapy often are used in the treatment of canine chronic hepatitis, frequently to good effect according to anecdotal reports. This would suggest that some number of these cases have an immune-mediated component to either the etiology or the progression of the disease. Ideally, a diagnosis of an immune-mediated condition would include the direct demonstration of that arm of the immune system that is responsible for the disease, whether it be antibody- or cell-mediated. Unfortunately, that level of specificity rarely exists in veterinary medicine (e.g., immunohistochemistry and electron microscopy in cases of glomerulonephritis). Most often the evidence is circumstantial, as with the infiltration of lymphocytes and plasma cells in cases of inflammatory bowel disease, red blood cell agglutination in immune-mediated hemolytic anemia, or the marked response to immunosuppressive drugs in cases of immune-mediated polyarthritis. Circumstantial evidence also exists for an immune-mediated component to canine chronic hepatitis, but response-to-treatment remains the most compelling clinical argument for the continued use of immune-modulatory drugs in cases of canine chronic hepatitis.[47-51]

Hepatic copper accumulation is the most commonly diagnosed treatable component of canine chronic hepatitis. Copper (Cu) exists in a number of forms, of which the cupric oxidation state (Cu^{2+}) likely is responsible for most of copper's hepatotoxicity. Copper is a key component in the redox cycling that generates oxidative radicals that deplete hepatic antioxidant defenses and damage multiple cellular components.[52] A tremendous amount of ongoing research is aimed at identifying a genetic defect or marker in a number of breeds, the specific metabolic defect involved, the role of dietary copper, and the most effective treatment protocol for this aspect of the disease process.

The copper hepatopathy seen in Bedlington Terriers is the result of a primary defect in hepatic copper metabolism resulting in marked lysosomal copper accumulation.[53,54] At least one genetic defect has been identified in affected Bedlington Terriers, a deletion in exon 2 of the *COMMD 1* (copper metabolism gene MURR1-containing domain 1) gene and the pattern of inheritance appears to be autosomal recessive.[55-58] The metabolic consequence of this mutation is a defect in the ability to excrete copper from hepatocytes into bile canaliculi.[7,59,60] The role of dietary copper and oxidative damage is further discussed in ch. 285. The diagnosis of copper toxicosis in the Bedlington is based on histopathologic features and hepatic copper concentration and location.[61,62] Hepatic copper accumulation, clinical signs, decreased hepatic function, and morphological damage are progressive in this breed. The condition can present as an acute hepatopathy or the more common chronic form, both of which are clinically similar to other forms of acute and chronic hepatitis. Young Bedlington Terriers can be pre-clinical and asymptomatic except for an elevation in hepatic enzyme activity. An acute hemolytic crisis is a rare presentation, following massive release of copper from the liver into the circulation, which can happen in any dog with excessive hepatic copper storage. Normal hepatic copper content is <400 ppm dry weight, while levels >2000 ppm result in functional, morphological, and clinical disease. Bedlington Terriers present with the highest levels of copper accumulation, up to 50 times normal, while other breeds most often present with 10-20 times normal levels. In Bedlington Terriers homozygous for the genetic defect, hepatic copper accumulation can begin as early as 8 to 12 weeks of age, or might not be evident until a year of age, and is progressive. In heterozygotes, there can be an increase in accumulation around 6 months of age, but hepatic copper levels normalize by 15 months of age. Clinicians cannot rely on serum liver enzyme elevations as a sole marker of copper storage disease in this breed, because these can be normal in some cases. This pattern makes genetic testing an important diagnostic tool when attempting to determine which individuals are affected at a young age. The "CT deletion test" and "CT Marker Test" are available from Veterinary Genetic Services and can help guide breeders facing husbandry decisions.[63]

So far, the Bedlington Terrier is the only breed where a genetic cause for copper storage hepatopathy has been identified. The possible heritability of the condition in Doberman Pinschers has been studied extensively, although, as with many breeds, it is not yet established whether Cu accumulation is a primary problem or a secondary consequence.[64-66] In West Highland White Terriers, Skye Terriers, Dalmatians, and Labrador Retrievers, it could be a familial condition.[67-71] A growing number of other breeds present with excess hepatic copper storage as either a cause or a consequence of their condition. The increasing prevalence of copper toxicosis in both purebred and mongrel dogs highlights the likely importance of environmental factors, particularly dietary, that undoubtedly contribute to this condition.[72]

The histologic distribution of hepatic copper could assist in differentiating primary from secondary causes. If copper is found both in hepatocytes adjacent to necrotic, inflammatory tissue and in hepatocytes distant from these lesions, it suggests that copper accumulation is the primary cause of the hepatopathy. In these cases, copper accumulates in zone 3 (centrilobular) as well as in regenerative nodules, and the degree of accumulation in Kupffer cells and hepatocytes correlates with the histopathologic severity (see ch. 285). If copper accumulation is secondary to some other disease process, it usually is found in zone 1 (periportal), restricted to those areas of tissue directly adjacent to cellular injury, and not correlated with the severity of the disease. One reason histopathologic evaluation of a tissue specimen is preferred over cytologic evaluation of liver aspirates is because of the importance of these zonal patterns of distribution. Even the histopathologic findings can be variable and range from no cellular changes other than copper accumulation in zone 3, to lipogranulomas and mixed inflammatory infiltrate with cytosolic copper, to fibrosis, cirrhosis, and loss of normal hepatic architecture. Rubeanic acid and rhodamine are copper-specific stains, but a quantitative measure of copper (atomic absorption spectroscopy) is ideal. A copper level >400 ppm dry weight is abnormal, with many cases of hepatitis reaching levels >800 ppm, and severe cases measuring >1,500 ppm. Zinc and iron are the two other metals most often quantified from hepatic biopsies. Both metals have complex roles in liver disease, and both are potentially therapeutic targets, with zinc supplementation and iron

chelation, although neither is as direct a concern as copper accumulation.[73]

Treatment (see Table 282-1)

To date, there is surprisingly little evidence on which to base treatment decisions in cases of acute or chronic hepatic inflammation. The first target—treating the cause—is rarely an option because in the majority of cases the inciting cause is never identified and the label "idiopathic" has to be applied. In the absence of a specific target, the focus of therapy becomes the pathophysiologic processes at work, and the clinical consequences of those processes. These processes include the extent and severity of inflammation and the predominant cell type involved; biliary stasis; copper accumulation; the amount and extent of fibrosis, the loss of normal architecture, the progression to cirrhosis with portal hypertension; and the loss of liver function.

In cases of acute hepatitis secondary to toxin or drug ingestion, the offending agent, if known, is discontinued immediately. Because of the liver's central role in metabolism, hepatotoxicosis is one of the most frequently listed side effects for a wide variety of medications, and a common target of toxins and toxic metabolic byproducts. A careful and complete history, including all prescription and non-prescription drugs, nutraceuticals, supplements, and treats, is a critical part of the assessment. Inadvertent or malicious intoxication also can occur through diet or environmental exposure, so both of these must be queried. Leptospirosis is a particularly important differential for acute hepatitis because of the imminent zoonotic risk, the time and effort required to reach a definitive diagnosis, and the minimal and safe treatment requirements (see ch. 217). Even in an area with a low prevalence and questionable exposure, appropriate barrier precautions and antibiotic treatment frequently are implemented as soon as the patient is hospitalized, until such time as leptospirosis can be confidently removed from the list of possible etiologies. Further information on the handling and treatment of dogs with leptospirosis can be found in the 2010 ACVIM consensus statement.[16]

The foundation of treatment for cases of acute hepatic inflammation is otherwise supportive care, dictated in large part by the condition of the patient. Fluid therapy is a key component in correcting dehydration (see ch. 129); addressing acid-base status and electrolyte balance (see ch. 128); supporting volume, blood pressure, and tissue and organ perfusion (see ch. 99 and 127); and supplementing glucose. Antibiotics and ursodeoxycholic acid were the most frequently employed treatments in one survey of idiopathic acute hepatitis, while prednisone, D-penicillamine, and zinc gluconate were most commonly administered in cases of copper-associated acute hepatitis.[5] N-acetylcysteine acts as a free radical scavenger and a methyl donor, and is used in cases of acute, severe hepatitis to increase hepatic concentrations of the antioxidant glutathione. Several other antioxidants and glutathione precursors can be given in cases of acute hepatitis, such as SAMe, silymarin (silibinin), and vitamin E, although the administration of oral medications is often problematic in acute hepatitis.[74] Colloid support is controversial, although plasma is still used in cases of documented coagulopathy. Antiemetics, gastric acid reducers, gastric ulceration medications, appetite stimulants, and analgesics are all non-specific treatment considerations in these cases. Glucocorticoids are contraindicated in the majority of cases of acute hepatitis.

Treatment of chronic hepatitis also is dictated by the condition of the patient, and ideally, by WSAVA Standardized histopathologic findings, copper quantification, culture results, and sequential monitoring of clinical and biochemical parameters. If a cause is identified, it is targeted specifically, but the majority of cases are, again, idiopathic.[75]

The use of antibiotics clearly can be called for in cases of suspected leptospirosis; following a positive bacterial culture result; in a febrile dog with CBC changes that include a left shift or toxic neutrophils; with a suppurative inflammatory hepatic infiltrate; or in those cases where advanced diagnostics such as FISH identify a target organism in association with the inflamed tissue. In these cases, the choice of antibiotic usually is based on the desire to cover a broad spectrum of possible organisms, or is targeted toward those organisms most frequently identified in culture-positive samples: *Escherichia coli*, *Enterococcus* spp., *Bacteroides* spp., *Streptococcus* spp., and *Clostridium* spp.[19] Antibiotic susceptibility is becoming a key component of effective therapy in veterinary medicine. The majority of Enterobacteriaceae isolated from gallbladder aspiration were susceptible to ciprofloxacin or aminoglycosides in one report, with first-generation aminopenicillins and cephalosporins being much less effective.[19] Doxycycline, enrofloxacin, clindamycin, cephalexin, amoxicillin-clavulanic acid, and marbofloxacin all have been used in cases of suspected bacterial hepatitis.

Antibiotics also are indicated in cases of hepatic encephalopathy. Here, the goal is to impact the GI microbiome in such a way as to decrease the production, and therefore the potential absorption, of ammonia.

Hence, antibiotics are chosen based on their targeting of specific components of that microbiome, such as metronidazole, or based on their predominant site of action being the GI tract, such as neomycin. Lactulose is another standard therapy for patients with signs of hepatic encephalopathy, the goal being a reduction in the absorption of ammonia by changing the pH of the GI contents.[76,77]

The targeted treatment of hepatic copper accumulation is most strongly justified in patients for whom the actual hepatic copper content has been quantified at >1,500-2,000 ppm. Outside of the Bedlington Terrier and perhaps several other breeds, the role of copper accumulation as a primary defect is less clear and the indiscriminate use of copper chelating therapy is more problematic. However, in cases where hepatic copper accumulation is demonstrated, studies show that the long-term use of D-penicillamine is beneficial.[78,79] A low-copper diet and zinc supplementation also are used commonly to reduce copper exposure and remove accumulated copper; therapy is required for months and ideally, follow-up includes a repeated liver biopsy and copper quantification.[80-82] If used concurrently, D-penicillamine actually can chelate zinc from the blood, reducing its effectiveness. D-penicillamine can cause substantial GI side effects. Trientine HCl is one alternative Cu chelator with anecdotal evidence of efficacy in a number of dogs, and ammonium tetrathiomolybdate, historically used for copper poisoning in sheep, is being investigated for use in dogs.[83,84]

Therapy aimed at reducing ongoing oxidative damage and addressing depleted antioxidant defenses most commonly includes the nutraceuticals SAMe, silymarin (silibinin), and vitamin E. Although the depletion of antioxidant defenses has been shown in dogs with hepatic disease, effective antioxidant supplementation strategies are still based predominantly on theoretical considerations.[85]

Ursodiol (ursodeoxycholic acid), a synthetic hydrophilic bile acid, can have a number of properties that would be beneficial in cases of hepatic inflammation. Ursodiol is a choleretic that is used frequently to combat cholestasis and displace toxic, hydrophobic bile acids, and it can help flush out excess iron or copper. Ursodiol could have immunomodulatory and cytoprotective properties, as well as an ability to replenish antioxidant defenses.[74]

Portal hypertension is common in cases of chronic hepatic inflammation where fibrosis has progressed to cirrhosis. Portal hypertension, often occurring in dogs that are also hypoalbuminemic, results in ascites, edema, and ulceration of the GI tract, and signs of hepatic encephalopathy. Treatment of the GI signs is nonspecific and supportive, and includes the use of sucralfate, H2 blockers, and proton pump inhibitors. Plasma, colloids, or human albumin can be used for trying to maintain vascular oncotic pressure, but these treatments carry with them substantial side effects. Spironolactone in combination with furosemide is a medical approach to ascites, if time and clinical signs permit; otherwise, therapeutic abdominocentesis is used in cases where the ascites is causing cardiorespiratory compromise (see ch. 90). Signs of hepatic encephalopathy (HE) call for dietary intervention with a high quality but decreased quantity of protein, preferably plant-based, with fermentable fiber and limited fat content. Lactulose, given orally or as an enema, is a standard HE treatment used to acidify the colonic pH and reduce ammonia production and absorption.

Large amounts of inflammation without evidence of infection, lymphocytic-plasmacytic infiltration consistent with an immune-mediated process, or the need to address significant fibrosis, are all arguments for the use of corticosteroids in cases of chronic hepatitis.[86] Ongoing corticosteroid treatment is contraindicated in cases of infectious hepatitis, but because of the diagnostic uncertainty, corticosteroids often are co-administered with antibiotics early in the course of treatment. This strategy has a number of potential pitfalls and it highlights the importance of a thorough diagnostic work-up and rigorous follow-up to help direct therapy. Colchicine and zinc also are used for trying to slow the progression of fibrosis, while additional immunomodulatory drugs being used with some frequency include azathioprine, cyclosporine, and mycophenolate mofetil.

Summary

Important advances are being made in our understanding of inflammatory and infectious liver disease in dogs. The standardization of histopathologic interpretation and nomenclature has unified the classification scheme for liver disease in dogs. Continued advancements in molecular techniques and diagnostic technologies such as PCR and FISH will continue to help identify and unravel the underlying etiology in canine liver disease. Finally, new frontiers in treatment, particularly of canine chronic hepatitis, include exciting possibilities such as tissue transplantation and stem cell therapy.[87,88]

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CHAPTER 283

Feline Inflammatory/Infectious Hepatic Disease

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Client Information Sheet: Feline Inflammatory/Infectious Liver Disease

Introduction

Feline inflammatory and infectious hepatobiliary diseases are common causes of morbidity and less frequent mortality in cats.[1] Inflammatory hepatobiliary diseases are one of the most common feline hepatic conditions in the United States, United Kingdom and Europe.[2] In one study, 45 of 175 feline liver biopsies (26%) revealed inflammatory disease.[3] Two common feline inflammatory hepatopathies include cholangiohepatitis (acute [suppurative] and chronic [non-suppurative or mixed]) and lymphocytic portal hepatitis.[3,4] More recently, the World Small Animal Veterinary Association (WSAVA) standardization committee recommended a distinct classification system for histologic features of lymphocytic portal hepatitis and chronic lymphocytic cholangitis[5] and an internationally accepted group of diagnostic terminologies for hepatopathies.[6] This scheme differentiated inflammation of the bile ducts (cholangitis) into 4 categories: neutrophilic cholangitis, lymphocytic cholangitis, destructive cholangitis, and chronic cholangitis associated with liver fluke infestation.[6]

Infectious hepatobiliary diseases, diagnosed less often, remain an important differential diagnosis when formulating treatment plans. Overlap in defining infectious from inflammatory hepatobiliary diseases exists, especially with neutrophilic cholangitis. Multiple primary hepatic infectious diseases have been documented which result in secondary inflammation. Feline hepatic lipidosis, the most common hepatic disease in cats, is covered in ch. 285. Hepatic neoplastic conditions and copper storage diseases are possible and will be briefly discussed (also see ch. 285). Signalment clinical signs, minimum database, and imaging can help differentiate inflammatory, infectious, and neoplastic conditions, as well as hepatic lipidosis. However, cytology or histology is essential to reach a definitive diagnosis.

Neutrophilic Cholangitis/Cholangiohepatitis

Definitions

Neutrophilic cholangitis (NC) is more common in cats than in dogs[6] and is subclassified into acute neutrophilic cholangitis (ANC) and chronic neutrophilic cholangitis (CNC).[1] The proposed pathogenesis is an ascending intestinal bacterial infection.[1,7] Histologically, neutrophils are noted within the bile duct lumen, closely associated with the bile duct or between the biliary epithelial cells. If the inflammation extends beyond the limiting plate and into the hepatic parenchyma, the diagnosis is cholangiohepatitis (CH). Progressive disease can result in bile duct rupture with bile leakage, necrosis or abscesses.[6]

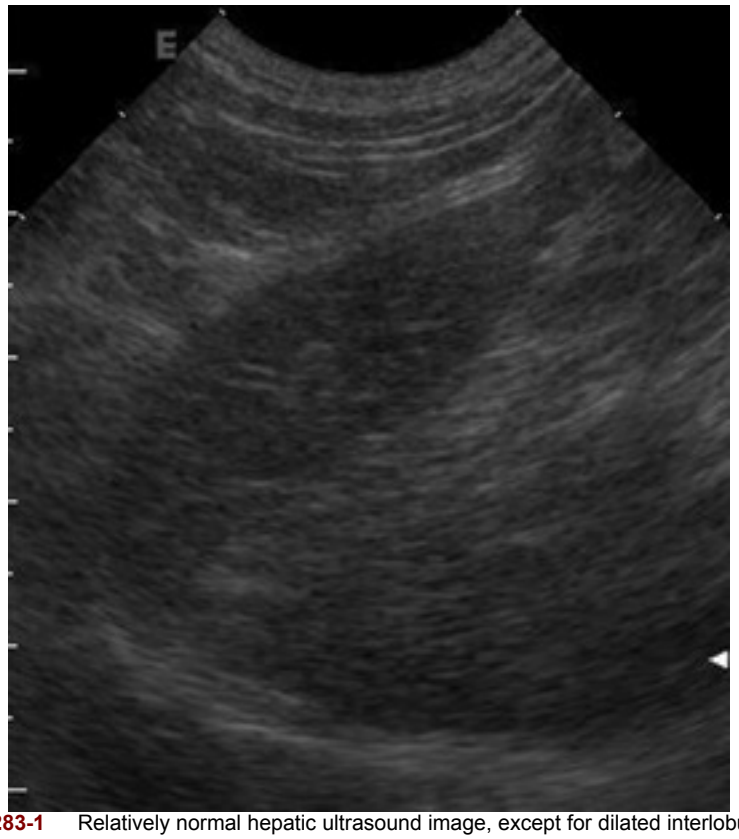
Clinical and Routine Laboratory Features

Early reports suggested cats with acute neutrophilic disease were younger and more likely to have fever, weight loss, and a neutrophilic left shift.[3,5,8] More recently, overlap in clinical and laboratory findings were noted in cats with acute or chronic disease.[1] Common clinical signs included lethargy, vomiting, weight loss and decreased appetite. Physical examination abnormalities are not common, but include fever (22%), icterus (34%) and hepatomegaly (21%). Abnormalities on complete blood counts (CBCs) are detected in less than half of cats with NC and, when present, include leukocytosis (39%), band neutrophils (33%), and anemia (34%).

Cats with moderate to severe cholangitis can have normal serum liver enzyme activities but increases in aspartate transaminase activity (AST) have been noted in 98% of cats. Variable increases in alanine transaminase (ALT) in 50-57%, alkaline phosphatase activities (ALP) in 14-48% and gamma-glutamyl transferase (GGT) have been noted. Many cats with cholangitis have liver enzyme values (ALT, ALP, GGT) within laboratory reference intervals, but about 2/3 are hyperbilirubinemic.[3] Hepatic function parameters were infrequently abnormal (hypoglycemia 7%, decreased blood urea nitrogen 0%, hypoalbuminemia 13%, and hypocholesterolemia 6%).[1,3] Fasting and post-prandial serum bile acid concentrations, using cutoffs of 15 micromol/L and 20 micromol/L, respectively, had higher specificity than did enzymatic testing and should be considered if hepatic disease is suspected in cats with normal enzyme activities and bilirubin concentration.[9] For coagulation testing, the most common abnormalities cited have varied and are most likely influenced by the studied population and testing methodology.[10] Abnormalities included prolongation of prothrombin time (PT: 4-77% of cases), prolonged partial thromboplastin time (PTT: 25-55%), reduced activities of factors VII (68%) and XIII (31-78%, 75% for cats with inflammatory liver disease) and increased PIVKA (75%), D-dimer concentrations (83%) and alpha-2-plasmin inhibitor activity (67%) (see ch. 196).[10-12]

Ultrasonography (US) and US-Guided Fine-Needle Aspiration (FNA)

Hepatobiliary abnormalities are frequently detected during abdominal US examination in cats with NC, including hyperechoic parenchyma with or without hepatomegaly, bile duct or gallbladder distension and increased gallbladder sediment (see ch. 88 and E-Figure 283-1). Other abnormalities commonly noted in cats with NC are pancreatic enlargement, hypoechoic parenchyma and hyperechoic peri-pancreatic parenchyma. Gastrointestinal (GI) tract abnormalities include thickened walls and fluid distension.[1] One retrospective study of several hepatobiliary US assessments (liver parenchymal echogenicity and echotexture, portal venous clarity, gallbladder wall thickness, bile duct diameter, and character of gallbladder content) failed to differentiate healthy cats from those with diffuse infiltrative hepatic disease (inflammation, cancer, or lipidosis).[13] Another study failed to detect any features to discriminate lymphocytic from neutrophilic forms of cholangitis.[14] Diagnosis of diffuse liver disease based solely on US ± routine clinical biochemical or hematologic data should be made with caution, even by skilled ultrasonographers.[13]



E-FIGURE 283-1 Relatively normal hepatic ultrasound image, except for dilated interlobular ducts in

an l4-year-old female spayed Domestic shorthair cat with *E. coli* growth from a hepatic biopsy sample and marked neutrophilic portal hepatitis with bile duct hyperplasia.

US does permit guided percutaneous collection of samples for cytologic or histologic examination (see ch. 89). FNA with cytologic examination has distinct advantages and limitations in evaluating cats with hepatic disorders. It is cost-effective, expedient, relatively straight-forward to perform, provides quick diagnostic information as compared with liver histopathology, complications are uncommon, needed pre-procedure testing is limited (coagulation is not typically required) and can usually be performed without anesthesia or sedation.[15] With US-guidance, FNA can be helpful diagnostically in cats with diffuse or focal disease. The important limitation with liver cytology is the small sample size (cells), which does not reflect morphology of the parenchymal architecture and limits the ability to correctly identify the primary hepatic disorder.[15] In one study, only 51% of cats had overall agreement in both the cytologic and histopathologic diagnosis. Inflammatory disease was correctly diagnosed in 27% of the cases.[16] Vacuolar hepatopathies had the highest agreement rate, correctly diagnosed in 83% of the cases.[16] However, 4 cats with lymphoma were incorrectly diagnosed as having hepatic lipidosis on FNA cytology.[17] The concern raised in this report was that FNA cytology may not detect infiltrative lesions, particularly if nodular, multifocal, or periportal.[17] While FNA cytology is a useful diagnostic procedure with advantages, a logical step-by-step diagnostic approach is preferred, especially in cats with nonvacuolar disease, equivocal diagnoses, or a cytologic diagnosis of hepatic lipidosis without improvement with treatment.[15,17]

Biopsy and Culture

Overview

Histopathology results from cats with hepatic disorders are classified as focal, multifocal, zonal, locally extensive, or diffuse panlobular.[18] Cholangitis, initially described as a diffuse process, is now either classified as diffuse or limited in distribution (focal, multifocal).[6,8,19] Severity of liver histopathology varies between liver lobes,[1] supporting the recommendation to obtain liver biopsies from multiple liver lobes.[1]

US-Guided Percutaneous Techniques and Complications

Automated spring-triggered biopsy needles are most commonly used for percutaneous sampling, but manual biopsy needles are used and recommended (see ch. 89).[20] Needle biopsies provide a rapid, cost-effective, minimally invasive method to obtain liver tissue; however, compared to wedge biopsies, this technique has been shown to result in a 1/3 reduction in the median surface area of the biopsy specimen (Figure 283-2), which can result in sampling errors, missed pathologic lesions, and severity being misjudged.[18] Fragmentation of needle biopsy specimens, common with needle biopsies, does not cause significant interference in reaching a diagnosis.[18] While 18G needle biopsies are generally too small, 16G needle devices provide good samples in cats.[15] Needle biopsy sampling was believed to have a low incidence of complications.[18] A more recent report included fatal complications that might have occurred secondary to intense vagotonia and shock when using an automatic biopsy instrument (Pro-Mag Ultra). This complication was not observed with use of a semiautomatic device (VET-core biopsy needle).[20] The most common adverse reaction, hemorrhage, has been shown to be independent of prior coagulation testing results, aside from being more likely to occur if a cat has thrombocytopenia (≤80 × 10^3/mcL platelets) or elevated activated PTT (aPTT). Other less frequent complications include sampling unintended tissues (e.g., large blood vessels, biliary structures, body wall, digestive tract, pancreas, diaphragm or lung), and pain.[18,20-22] Major complications are usually noted within 30 minutes to an hour, but can be recognized as long as 10 hours after the procedure.[15,22]

FIGURE 283-2 This photograph shows 3 hepatic biopsies obtained with a 16G ultrasound-guided percutaneous needle biopsy device.

Laparoscopic-Assisted Biopsy or Surgical Wedge Biopsy

The major advantage of laparoscopic-assisted biopsies or wedge biopsies obtained via a laparotomy is the larger sample size, allowing opportunity for more accurate diagnosis (see ch. 91).[18] Laparoscopic biopsy forceps typically provide samples about 5 mm in diameter (45 mg of liver tissue; Figure 283-3). Surgically obtained samples are, ideally, 2 cm deep.[15] Disadvantages of laparoscopy may include cost, facilities required, need for advanced operator training, longer procedural times (compared to percutaneous needle biopsy but usually shorter than laparotomy), and requirement of general anesthesia. Advantages of laparoscopy in cats include the ability to obtain a large biopsy sample size, improved accuracy in obtaining liver, an ability to visualize the liver and target abnormal areas for sampling, a limited degree of invasiveness, an opportunity to obtain non-hepatic biopsies (pancreas, kidney, spleen, lymph node, and intestine) or perform gallbladder aspiration (cholecystocentesis).[15] Magnification available with laparoscopy allows location of small (<0.5 cm) lesions, not easily observed otherwise.[15] Other advantages of laparoscopy include rapid recovery, shorter hospital stays, and low rates of postoperative morbidity, infection, or pain (Figure 283-4).[15] While laparoscopic-assisted cholecystectomy or cholecystostomy tube placement have been performed in cats, they are not common.[23] Most feline hepatopathies (NC/CH) are nonsurgical. Conventional surgical laparotomy with wedge biopsy is indicated if a cat has a primary hepatic or concurrent abdominal, surgical condition, or if laparoscopic-assisted biopsy is not an option.

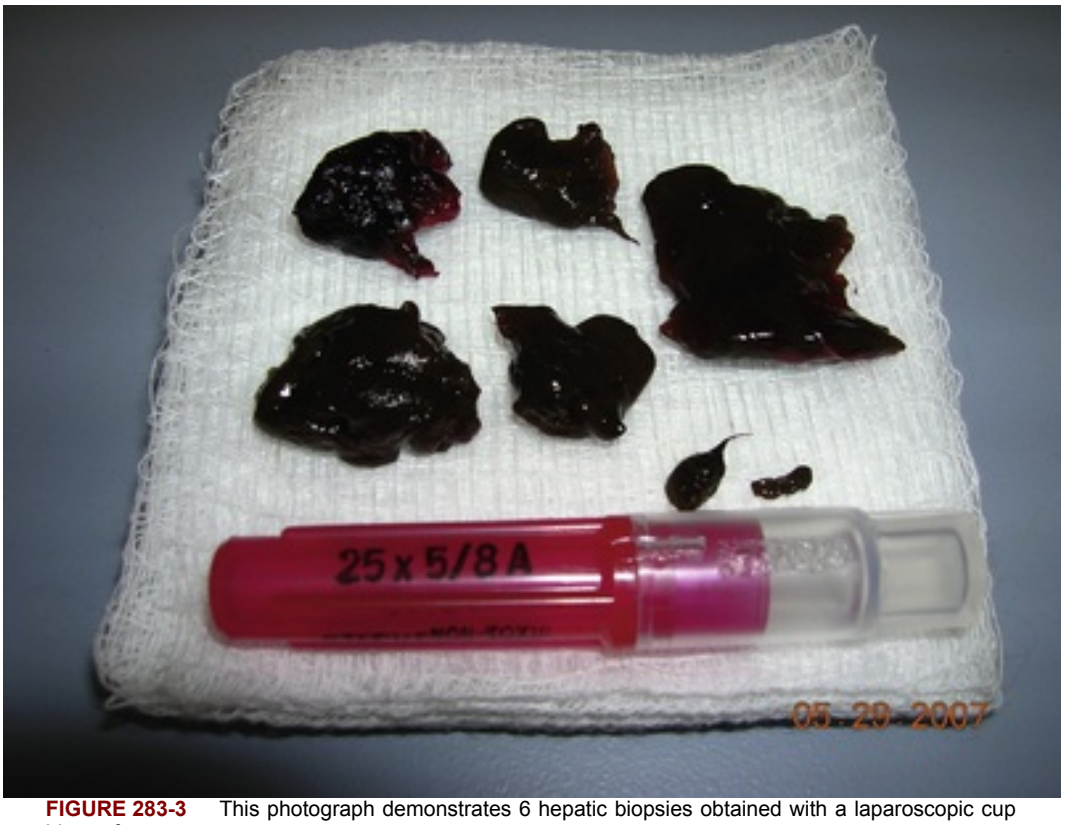


FIGURE 283-3 This photograph demonstrates 6 hepatic biopsies obtained with a laparoscopic cup biopsy forceps.

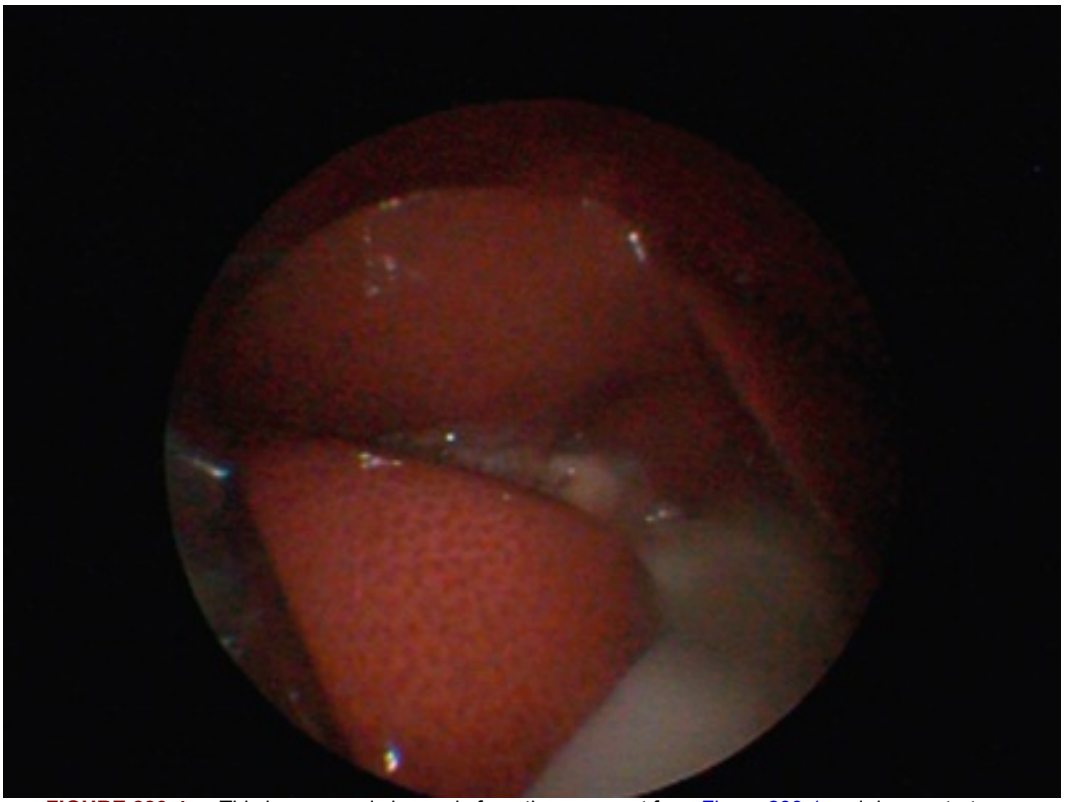


FIGURE 283-4 This laparoscopic image is from the same cat from Figure 283-1 and demonstrates a relatively normal hepatic appearance except for rounding of the liver margins.

Culture

Aerobic and anaerobic bacterial cultures can be quite valuable in evaluating cats with hepatobiliary disease. In one study, 36% of bile samples and 14% of liver tissue samples had positive bacterial growth, with 83% of cats having a single bacterial species.[24] Bile samples can be obtained by percutaneous US-guided cholecystocentesis, laparoscopic-assisted cholecystocentesis, or at surgery (see ch. 88 and 89).[25] Uncommon complications include gallbladder rupture and bile peritonitis.[5,25] Cats with NC may have evidence of neutrophilic inflammation in their bile. *E. coli*, alone or in combination with obligate or facultative anaerobes, is the most common organism in bile cultures, but other organisms include Enterobacteriaceae (*Salmonella enterica, Klebsiella, Enterobacter), Streptococcus, Enterococcus, Actinomyces, Acinetobacter, Pasteurella, Clostridium* and *Bacteroides* species.[5] Bacteria have been isolated via aerobic or anaerobic culture in a minority of cats with NC/CH.[4] Use of newer tests, such as fluorescent *in situ* hybridization (FISH), may be more sensitive for detecting bacterial infection.[7] Ascending infection with enteric bacteria is the most likely source of these infections; however, hematogenous seeding is possible.[5,7] The unique dual entry of the common bile and pancreatic ducts at the major duodenal papilla in the duodenum increases risk of enteric content and/or pancreatic secretion reflux.[5] The association of pancreatitis and cholangitis may be associated with this anatomic condition.[1]

Treatment and Prognosis

Antibiotics

Antibiotics are the primary therapy for NC/CH (Table 283-1).[26] Ideally, antibiotics are chosen based on results of bacterial culture and sensitivity testing. Often, however, antibiotics are started empirically until the culture results are available. Antibiotics should be active against aerobic and anaerobic enteric bacteria and excreted while active into bile. Commonly utilized antibiotics include ampicillin, amoxicillin and clavulanate potassium (Clavamox), ampicillin-sulbactam (Unasyn), ticarcillin disodium and clavulanate potassium (Timentin) and metronidazole. Less frequently used antibiotics include chloramphenicol, tetracycline, and erythromycin. Therapy for 2 months has been suggested, but the optimal duration is not known.[4]

TABLE 283-1

Medical Therapies for Feline Hepatopathies

TREATMENT	DOSE
Fluid Therapy (see ch. 129)	
Isotonic crystalloids: i.e., 0.9% NaCl	Shock 45-55 mL/kg/h IV; correct dehydration; Maintenance 40-45 mL/kg/day IV
Synthetic colloids: Hetastarch, dextran 70	2-5 mL/kg IV once; if needed, 10 mL/kg/day IV CRI
Fresh frozen plasma transfusion	10-40 mL/kg IV over 24 h
Antihypotensive Agents	
Dopamine HCl	5-15 mcg/kg/min IV CRI
Dobutamine HCl	0.2-2 mcg/kg/min IV CRI
Epinephrine	0.5-2 mcg/kg/min IV CRI
Norepinephrine	0.5-2 mcg/kg/min IV CRI
Vasopressin	0.01-0.04 U/min IV (in patients with vasodilatory shock unresponsive to fluid resuscitation and catecholamine)
Antibiotics	
Ampicillin	20-40 mg/kg IV q 6-8 h

Amoxicillin	10-20 mg/kg PO, IV, SC q 12 h
Amoxicillin + clavulanic acid (Clavamox)	10-20 mg/kg PO q 8 h
Ampicillin + sulbactam (Unasyn)	20-40 mg/kg IV q 8-12 h
Ticarcillin disodium and clavulanate potassium (Timentin)	40-60 mg/kg IV q 6-8 h
Metronidazole (Flagyl)	15 mg/kg PO, IV q 12 h
Chloramphenicol	10-20 mg/kg PO, IV, IM, SC q 12 h
Tetracycline	7 mg/kg IV, IM q 12 h
Erythromycin	10-20 mg/kg PO, IV q 8 h
Appetite Stimulants	
Mirtazapine (Remeron)	3.75 mg (1/4 of a 15-mg tablet) PO q 24-72 h
Cyproheptadine (Periactin)	2-4 mg/cat PO q 12-24 h
Diazepam (Valium)	1-4 mg/cat PO q 12-24 h
Nausea/Vomiting Therapy	
Ranitidine	0.5-2 mg/kg PO, IV q 12 h
Famotidine	0.5-1 mg/kg PO, IV, SC, IM q 12-24 h
Metoclopramide	0.2-0.4 mg/kg PO, SC, IM q 8 h* 1-2 mg/kg/day IV CRI
Chlorpromazine	0.5 mg/kg IV, IM, SC q 6-8 h
Dolasetron mesylate	0.6-1 mg/kg PO, IV, SC q 12 h
Ondansetron	0.1-1 mg/kg IV (slowly), SC, IM or PO q 6-12 h
Maropitant citrate	1 mg/kg SC, PO q 24 h
Pain Management	
Buprenorphine	0.005-0.01 mg/kg IV, IM q 4-8 h
Butorphanol	0.2-0.4 mg/kg IM q 2-4 h
Assorted Medications	
Cobalamin (Vitamin B_{12})	250 mcg/cat SC weekly
Prednisolone	2.2-4.4 mg/kg PO q 24 h 1-2 mg/kg PO q 12 h
Ursodeoxycholic acid (Actigall)	10-15 mg/kg PO q 24 h
Vitamin K_1	5 mg/cat IM q 24-48 h
Lactulose	0.5-1 mL/kg PO q 8 h
Neomycin	20 mg/kg PO q 8-12 h
Azathioprine	0.3 mg/kg PO q 48-72 h
Methotrexate	0.4 mg per cat total dose given on one day in three divided doses. Repeat every 7-10 days. Use in conjunction with ursodeoxycholic acid (15 mg/kg PO q 24 h) and folate (0.25 mg/kg PO q 24 h).
Cyclosporine	3-4 mg/kg PO q 12 h
Praziquantel	20 mg/kg SC or IM, q 24 h, 3-5 consecutive days

*Consider alternative therapy; less efficacious in cats.

CRI, Constant rate infusion; *IM*, intramuscular; *IV*, intravenous; *PO*, by mouth; *SC*, subcutaneous.

Nonspecific Therapies

Some cats with NC/CH are critically ill and require therapy for dehydration (see ch. 129), serum electrolyte abnormalities (see ch. 67-69), coagulopathies (see ch. 197), and/or hypotension (see ch. 159). Other cats may benefit from use of appetite stimulants (mirtazapine, cyproheptadine; see Table 283-1) if they have low-grade inappetence. Persistent inappetence can be managed with placement of an enteral feeding tube (esophagostomy or gastric tube; see ch. 82). Protein restriction is only required in cats with hepatic encephalopathy; otherwise, a highly digestible, moderate fat level diet is often chosen (see ch. 180).[27] Hepatic encephalopathy is less common in cats with acquired liver disease. If present, it can be managed with lactulose and/or antibiotics (see ch. 281 and 284). Other nonspecific treatments include controlling nausea and/or vomiting, lowering gastric acid production, and reducing pain (more commonly detected with pancreatitis). Surgery is likely necessary for cats with complete biliary obstruction and for some cats with choleoliths (Figure 283-5). While biliary-to-intestinal diversion (i.e., cholecystoduodenostomy or cholecystojejunostomy) have been performed for obstructive disease, post-surgical morbidity has been high.[28] Alternative techniques have been proposed that include choledochal stenting (E-Figure 283-6; see ch. 120 and 123).[29] It appears, however, that cats have greater morbidity with choledochal stenting than do dogs.[29] Therefore, ursodeoxycholic acid (Actigall) often is given for its anti-inflammatory, immunomodulatory, and antifibrotic properties. Ursodeoxycholic acid increases the liquid nature of biliary secretions, but benefits of its use should be weighed against risk for a biliary obstruction or choleliths. The prognosis in cats with acute cholangitis is good, with median survival times >1 year.[3,5] Poor outcomes are most likely related to concurrent conditions, such as pancreatitis, inflammatory bowel disease, and to a lesser degree, nephritis.[3,30,31]

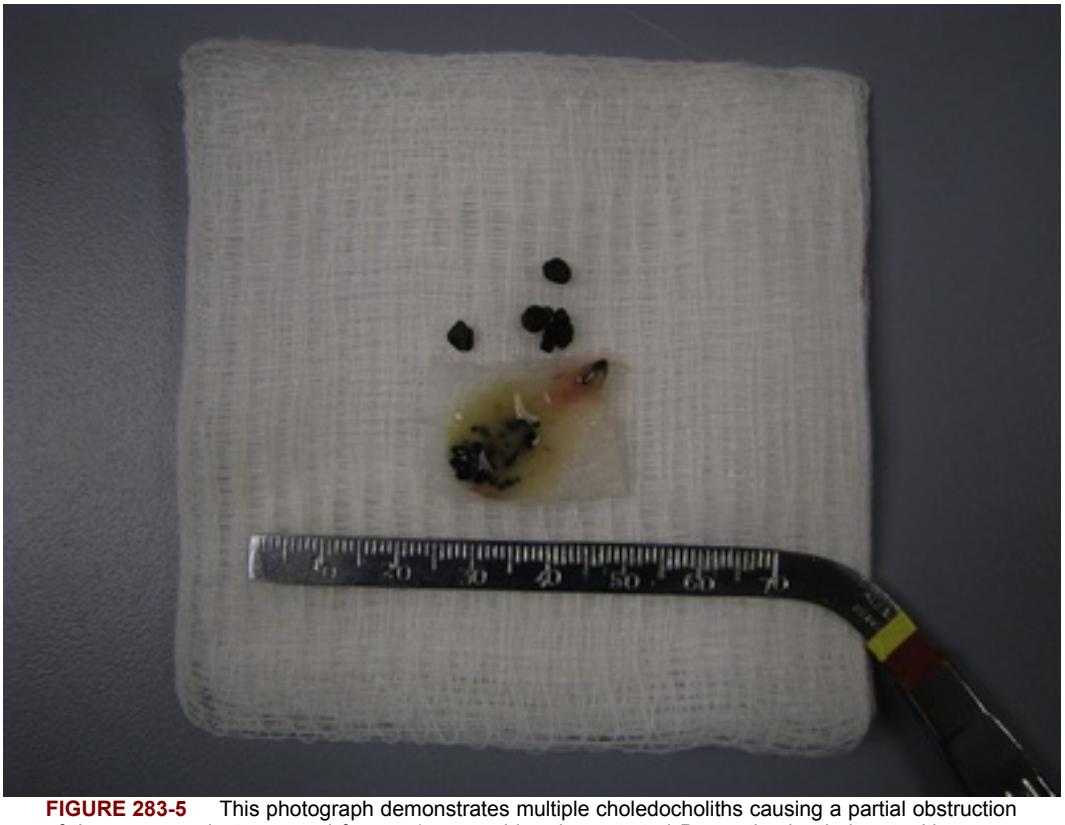
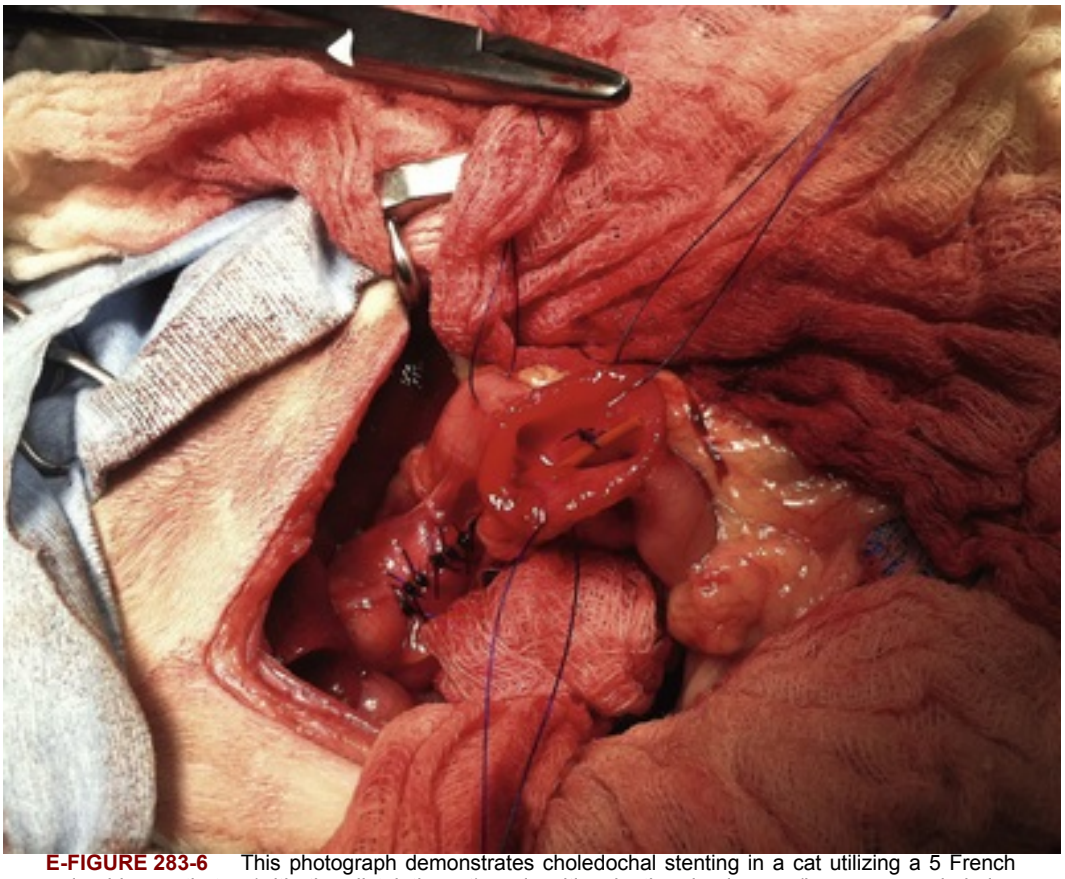


FIGURE 283-5 This photograph demonstrates multiple choledocholiths causing a partial obstruction of the common duct removed from a 14-year-old male castrated Domestic shorthair cat with severe lymphoplastic and neutrophilic cholecystitis.



E-FIGURE 283-6 This photograph demonstrates choledochal stenting in a cat utilizing a 5 French red rubber catheter (with the distal tip cut) and exiting in the duodenum (lumen opened during placement).

Lymphocytic Cholangitis

Overview

The signalment, clinical signs and diagnostic evaluation for lymphocytic cholangitis (LC) is reviewed in the "Neutrophilic Cholangitis/Cholangiohepatitis" section with a few exceptions. In addition to nausea, vomiting, lethargy (listlessness) and inappetence, cats with LC often develop gradual weight loss and jaundice (E-Figure 283-7 and Figure 283-8).[32] In contrast to NC/CH, the most consistent biochemical abnormality in cats with LC is hypergammaglobulinemia; however, increases in hepatic enzyme activities and total bilirubin are detected in some cats.[32]

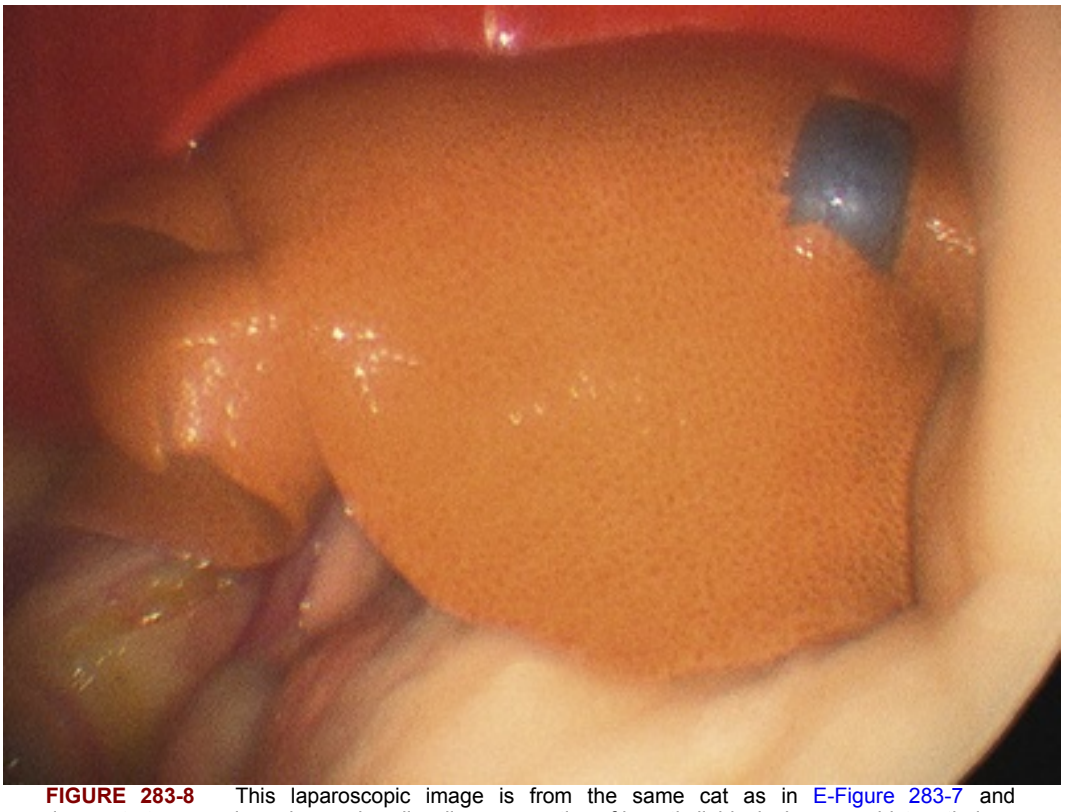
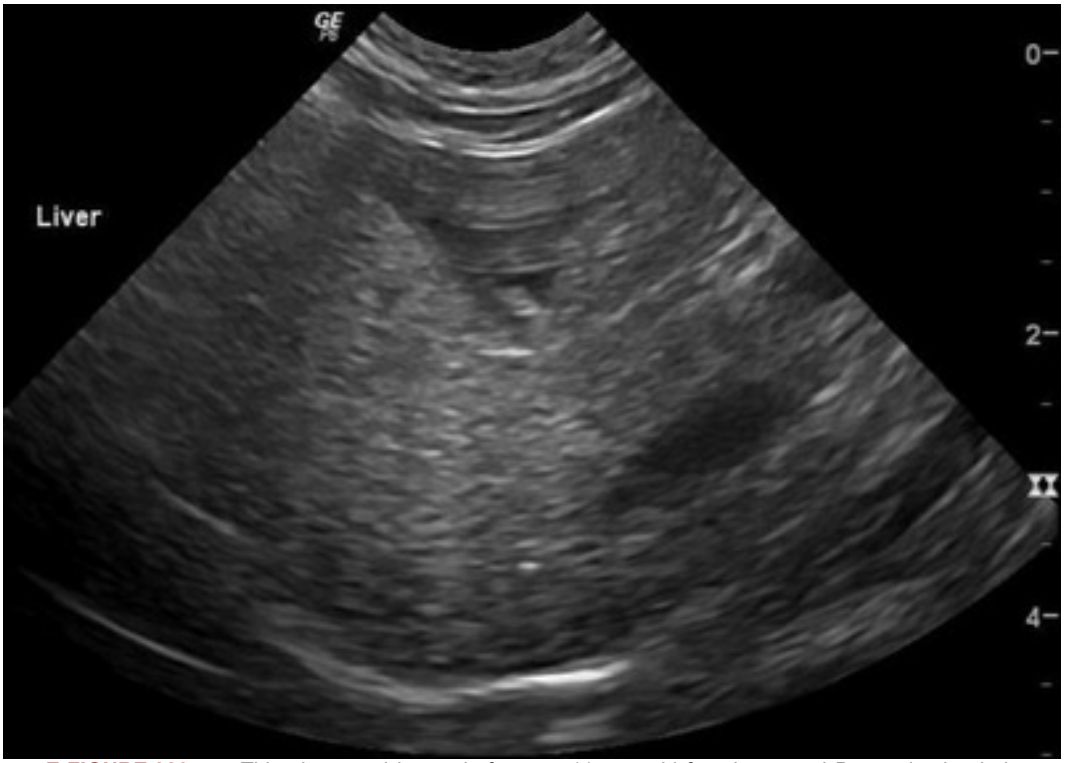


FIGURE 283-8 This laparoscopic image is from the same cat as in E-Figure 283-7 and demonstrates an enlarged, grossly yellow liver suggestive of hepatic lipidosis; however, histopathology revealed moderate chronic lymphocytic and neutrophilic cholangitis and moderate diffuse hepatic lipidosis.



E-FIGURE 283-7 This ultrasound image is from an 11-year-old female spayed Domestic shorthair cat with moderate chronic lymphocytic and neutrophilic cholangitis and moderate diffuse hepatic lipidosis; however, the ultrasound image revealed hyperechoic hepatomegaly suggestive of hepatic

lipidosis.

Pathogenesis

The pathogenesis of LC was thought to be the consequence of chronic bacterial infection in cats with NC.[8] Recent studies using FISH found little evidence to support bacterial colonization as a component of the etiopathogenesis. Rather, immune-mediated mechanisms have been proposed.[7,33] However, a provocative polymerase chain reaction (PCR) study in cats demonstrated *Helicobacter* spp. DNA in 26% of cats with LC (controls 16%) and suggested an etiological role of *H. pylori* in feline LC.[34] In an experimental setting, LC has been induced by inoculating specific pathogen–free cats with *Bartonella henselae*– and/or *Bartonella clarridgeiae*–infected cat blood.[35]

Histologically, LC is characterized by dense aggregates of lymphocytes surrounding bile ducts but not invading the biliary epithelium. Lymphocytes may be detected in the bile lumen (in contrast to NC).[6] The major differential diagnosis is hepatic lymphoma. In addition to histopathologic features, immunophenotyping (B-cell and T-cell) and PCR for T-cell receptor (TCR) gene rearrangement have been shown to assist in discriminating LC from hepatic lymphoma. Bile duct targeting, ductopenia, peribiliary fibrosis, portal B-cell aggregates, portal lipogranulomas and polyclonal TCR are features of LC.[6,33]

Treatment and Prognosis

Specific and nonspecific therapies for LC and NC/CH are similar (see Table 283-1).[4] Many cats are treated with antibiotics while awaiting histopathology and culture results. When infectious causes have been ruled out and/or cats fail to respond to antibiotics, immune suppressive therapy is recommended, assuming that the liver injury is immune-mediated.[4] Prednisolone, the first choice in immunosuppressive therapy, results in longer survival times when compared with cats given ursodeoxycholic acid.[32] In addition to its immunosuppressive properties, prednisolone may limit hepatocellular injury and enhance the appetite. Based on treatment response (resolution of clinical signs) and serial biochemical values, prednisolone can be slowly tapered, but many cats require long-term therapy.[4] The optimal duration of treatment has not been determined. Persistent or progressive increase in ALT and/or ALP activities and serum total bilirubin concentration suggest that treatment has been inadequate.[4] In cats who fail therapy, it is important to ensure the cat does not have occult lymphoma. In cats with confirmed, prednisone-resistant LC/CH, alternative therapies include azathioprine, methotrexate, and cyclosporine.[4] The prognosis in cats with LC is good and likely better than for cats with NC/CH. In one study, median survival time was 795 days with survival rates for 1, 2, and 3 years being 74%, 56%, and 35%, respectively.[32] Purebreds with LC may be more likely to have shorter survival times than Domestic shorthairs.[32]

Infectious Hepatobiliary Diseases

Bacterial Infection

Compared to inflammatory hepatobiliary diseases, primary feline infectious hepatobiliary diseases are reported less frequently. Infection is seen in about 15% of cats with hepatobiliary disease.[1,36] Bacterial infections are more common in NC/CH. Even though cats are the natural reservoir for *Bartonella henselae*, peliosis hepatis secondary to *B. henselae* is not seen in cats.[37] The proposed pathogenesis is a secondary infection due to ascending intestinal bacteria. Both micro- and macrohepatic abscesses have been reported in cats. Other pathogenesis concepts include trauma, alterations in blood flow, liver lobe torsions, extrahepatic infection, sepsis, clinically immunocompromised states and neoplasia.[38] Ultrasound permits detection and diagnosis, via FNA cytology and culture, of hepatic abscesses (see ch. 88 and 89). Aerobic and anaerobic bacterial culture results in cats with hepatic abscesses are similar to those of cats with NC/CH with clinically rare isolates being *Klebsiella, Listeria, Salmonella, Brucella, Yersinia pseudotuberculosis, Actinomyces, Nocardia* and *Pasteurella.*[38] Polymicrobial growth is detected in >50% of cats with solitary abscesses.[38,39] Due to the frequency of polymicrobial growth, broad spectrum antimicrobial treatment that is directed at both aerobes and anaerobes, independent of anaerobic culture results, should be given for at least 6 weeks.[38] Focal abscesses may require surgical drainage or partial hepatectomy. US-guided percutaneous drainage of hepatic

abscesses has been reported in dogs[40] and has been used successfully in cats. In a single study of 14 cats with hepatic abscesses, the overall mortality rate was 79%. Survivors had partial hepatectomies followed by medical management.[39] *Mycobacterium* spp. rarely cause hepatic bacterial infections in cats (see ch. 212). Histopathology may reveal extensive granulomatous disease.[38]

Platynosomum Infections

Chronic cholangitis has been associated with liver fluke infestation from the Platynosomum group (*P. fastosum, P. concinnum* and *P. illiciens;* and may be synonymous to *P. planicipitus, Dicrocelium concinnum, D. lanceolatum* var. *symmetricum* and *Concinnum concinnum*) and *Amphimerus pseudofelineus.*[41,42] *Platynosomum fastosum,* which is prevalent in tropical and sub-tropical regions of North, South and Central America, the Caribbean, and parts of Africa and Asia, is a small hepatic trematode detected in cats' biliary ducts and gallbladder.[42] Lizards, terrestrial snails, and isopods are implicated as intermediate/paratenic hosts.[42] Platynosomiasis or "lizard poisoning" is the name given to this fluke-induced condition. Affected cats likely acquire the parasite by eating infected lizards. Clinical signs can range from none to severe. Signs are secondary to biliary tract obstruction and hepatic failure.[42] Other clinical signs and the diagnostic evaluation for *P. fastosum* are reviewed in the "Neutrophilic Cholangitis/Cholangiohepatitis" section. CBC may reveal eosinophilia in heavily infected cats. Embryonated eggs (golden brown [unstained] oval, 34-50 × 23-35 micron, thick-shelled) are shed in the stool of infected cats; an exception is cats with complete bile duct obstruction.[42] Adult flukes (lanceolate, covered by a thin cuticle, 2.9 to 8 mm long × 0.9 to 2.5 mm wide, sub-terminal oral sucker and a ventral sucker) can be detected in the bile or liver, gallbladder and/or bile ducts. The most effective treatment is praziquantel.[42] In cats with bile duct obstruction, aggressive supportive care and biliary-to-intestinal diversion (i.e., cholecystoduodenostomy or cholecystojejunostomy) or choledochal stenting is indicated (see ch. 123).

Viral Infections

Feline Leukemia Virus (FeLV)

Cats persistently infected with the FeLV often develop leukemia/lymphoma complex or fibrosarcoma. They also develop a wide spectrum of non-neoplastic diseases.[43] In one post-mortem study, 77% of FeLV cats had non-neoplastic FeLV-associated disease and 23% had cancer.[43] In this study, 25% of the icteric cats were FeLV-positive and 8% of FeLV-infected cats were icteric. Histopathology in FeLV-infected cats revealed liver degeneration, described as cell dissociation, fatty liver and focal necrosis. Fatty liver disease and focal liver necrosis were significantly more common in the FeLV-infected cats. The pathogenesis of the liver injury associated with FeLV infection is unknown but may in part be secondary to anemia.[43] See ch. 223.

Feline Calicivirus (FCV)

Virulent mutants of FCV rarely cause hepatic infection in cats, with high morbidity and mortality.[44] FCV is highly infectious and typically causes acute oral and upper respiratory tract disease, but a mutant virus has been identified. Many cats infected with the mutant FCV have died with clinical signs characterized by jaundice, edema, upper respiratory tract disease, ulcerative dermatitis, fevers, lameness, voice loss and inappetence.[44] Hepatic histopathology has revealed disseminated hepatocellular necrosis with mild inflammatory infiltration on light microscopy. FCV antigen in parenchymal and Kupffer cells may be identified by immunohistochemistry. Calicivirus-like particles within hepatocytes can be seen with electron microscopy.[44] Treatment involves aggressive supportive care and strict quarantine to avoid infecting healthy cats, even if vaccinated.[44] See ch. 229.

Feline Infectious Peritonitis (FIP)

FIP, a mutant coronavirus infection, causes clinical disease with high mortality once clinical signs appear. Rarely, infected cats survive for weeks, months or years.[45] FIP is most prevalent among cats <3 years of age (especially those 4-16 months old).[45] Hyperbilirubinemia and hyperbilirubinuria are common in cats with FIP, due to increased red blood cell destruction, slow breakdown and delayed recycling of bilirubin and biliverdin. They usually do not have increased liver enzyme activities. Primary hepatic FIP is not common.[45] The diagnostic evaluation of FIP is reviewed in ch. 224. Ultrasound-guided percutaneous liver biopsy and

FNA liver cytology in 16 of 25 cats were consistent with FIP based on intra-parenchymal pyogranulomatous lesions and/or fibrinous perihepatitis. Feline coronavirus antigen was detected in 6 cats. Of 22 cats, cytologic findings were consistent with FIP in 14 (64%) based on highly cellular pyogranulomatous inflammation. Their livers frequently had histologic FIP lesions, even in the absence of macroscopic changes.[46]

Feline Immunodeficiency Virus (FIV)

FIV, a lentivirus, has been identified in cats throughout the world (see ch. 222). FIV is associated with cytopenias and cancers.[47,48] In the absence of concurrent conditions, FIV rarely causes hepatic disease. In an experimental population of 20 specific pathogen–free cats infected with FIV, only 1 developed primary hepatic disease.[48] This cat had cholangitis, biliary duct hyperplasia, peribiliary fibrosis, and microabscessation. A second cat developed hepatic-renal lymphoma. It was also reported that some FIV cats had generalized hepatic degeneration.[48] Experimental cats infected with FIV and later challenged with *Toxoplasma gondii* developed acute generalized toxoplasmosis, including multifocal to coalescing hepatic necrosis.[48] *T. gondii* tachyzoites were occasionally detected.[48] In a post-mortem study of cats with histologically verified toxoplasmosis, 70% of 90 liver samples examined revealed *Toxoplasma gondii* organisms.[49]

Fungal Infection

The fungal organisms *Histoplasma capsulatum* (see ch. 233), *Coccidioides immitis* (see ch. 232), *Blastomyces dermatitidis* (see ch. 233), *Aspergillosis* sp. (see ch. 235), *Cryptococcus* sp. (see ch. 231), and *Sporothrix schenckii* (see ch. 236) can, rarely, cause primary or disseminated infectious hepatobiliary disease.[38] *Histoplasma capsulatum* is the second most common systemic fungal disease in cats and likely the most common hepatic fungal infection. The liver is involved in cats with disseminated disease along with the spleen, gastrointestinal tract, bone and bone marrow, integument, and eyes.[50] Definitive diagnosis is obtained by demonstration of organisms via cytopathology or culture. The treatment of choice is itraconazole 5-10 mg/kg PO q 12 h for a minimum of 4 to 6 months.[50] In certain regions, epidemics of *Sporothrix schenckii* infections have been noted in cats, dogs and humans. In one small study, all studied cats (n = 10) with sporotrichosis had *S. schenckii* detected by histopathology or culture from the liver. All of these cats were treated with itraconazole; however, 60% had progression of their disease.[40]

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CHAPTER 284

Hepatic Vascular Anomalies

Chick Weisse, Allyson C. Berent

Portosystemic shunts (PSSs) are vascular anomalies that connect the portal vein to the systemic circulation, bypassing the hepatic sinusoids and liver parenchyma.[1-6] They are considered the most common hepatobiliary congenital abnormality. Normally, venous blood draining the spleen, pancreas, stomach, and intestine enters the portal vein, perfuses the liver through the sinusoidal network, and drains through the hepatic veins into the caudal vena cava (CVC).[3] Portal blood carries many substances to the liver, including trophic hormones (intestinal and pancreatic), nutrients, bacterial products, and intestinal-derived toxins.[1,2,6] The fetal liver has limited function to process these products, and a large shunting vessel, the ductus venosus, bypasses the hepatic circulation as a protective mechanism.[3,6] This fetal vessel, located on the left side of the liver, normally closes by 3-10 days of age.[3,4,7] Closure is initiated by blood pressure changes after umbilical venous flow ceases; thromboxane or various adrenergic compounds can stimulate contraction of the musculature of the ductus venosus and might aid in the vessel's closure.[3,5,6-8] If the ductus venosus remains patent, or other congenital communications exist, a PSS results. When blood bypasses the liver, trophic factors (particularly insulin and glucagon) are not available to encourage hepatic growth, resulting in poor hepatic development, deficient protein production, reticuloendothelial dysfunction, altered fat and protein metabolism, hepatic atrophy, and eventually liver failure.

Clinical signs are associated with the volume and origin of blood bypassing the liver, resulting in impaired hepatic function, hepatic encephalopathy (HE), chronic gastrointestinal (GI) signs, lower urinary tract signs, coagulopathies, and delayed growth.[2,3,5,6,9] These problems are the result of the body accumulating both exogenous and endogenous toxins that are normally metabolized or eliminated by the liver (E-Table 284-1), as well as the failure of normal hepatic function (e.g., gluconeogenesis, urea cycle, uric acid cycle, glycogenolysis).[2,6,9-12]

E-TABLE 284-1

Toxins Implicated in Hepatic Encephalopathy[10-12,31-33]

TOXINS	MECHANISMS SUGGESTED IN THE LITERATURE
Ammonia	Increased brain tryptophan and glutamine; decreased ATP availability; increased excitability; increased glycolysis; brain edema; decreased microsomal Na-K-ATPase in brain
Decreased alpha-ketoglutaramate	Diversion from Krebs cycle for ammonia detoxification; decreased ATP availability
Glutamine	Alters blood-brain barrier amino acid transport
Aromatic amino acids	Decreased DOPA neurotransmitter synthesis; altered neuroreceptors; increased production of false neurotransmitters
Short-chain fatty acids	Decreased microsomal Na+, K+-ATPase in brain; uncouples oxidative phosphorylation, impairs oxygen utilization, displaces tryptophan from albumin, increasing free tryptophan
False neurotransmitters Tyrosine → octopamine Phenylalanine → phenylethylamine	Impair norepinephrine action Impairs norepinephrine action Synergistic with ammonia and SCFA Decreases ammonia detoxification in brain urea cycle; GIT-derived (fetor hepaticus—breath odor in HE); decreased microsomal Na^+, K^+-ATPase

Methionine → mercaptans	
Tryptophan	Directly neurotoxic; increases serotonin: neuroinhibition
Phenol (from phenylalanine and tyrosine)	Synergistic with other toxins; decreases cellular enzymes; neurotoxic and hepatotoxic
Bile acids	Membranocytolytic effects alter cell/membrane permeability; blood-brain barrier more permeable to other HE toxins; impaired cellular metabolism due to cytotoxicity
Gamma-aminobutyric acid (GABA)	Neural inhibition: hyperpolarize neuronal membrane; increase blood-brain barrier permeability to GABA
Endogenous benzodiazepines	Neural inhibition: hyperpolarize neuronal membrane

ATP, Adenosine triphosphate; *DOPA*, dihydroxyphenylalanine; *GIT*, gastrointestinal tract; *HE*, hepatic encephalopathy; *SCFA*, short-chain fatty acids.

Embryology

The veins in the abdomen are derived embryologically from the umbilical, vitelline, and caudal cardinal veins (Figure 284-1). The paired vitelline veins originate at the yolk sac and form the left hepatic vein, the hepatic sinusoids, the hepatic portion of the CVC, the prehepatic portal vein, and its tributaries.[7] The vitelline and umbilical systems combine to form the ductus venosus and the left branch of the portal vein. The nonportal abdominal, renal, and gonadal veins are derived from the cardinal venous system. The caudal cardinal veins form the CVC caudal to the liver, and the azygos vein.[3,7] In normal animals, the prehepatic and intrahepatic segments of the CVC join at the communication between the cardinal and the vitelline systems. Numerous nonfunctional portocaval and portoazygos communications are present in the fetus but are not patent in the adult unless portal hypertension occurs, forming multiple acquired extrahepatic shunts. When developmental errors create abnormal communications between these two systems, congenital extrahepatic portosystemic shunts (EHPSSs) result.[7] Abnormal vessel patency, or other abnormal development in the vitelline venous system, results in congenital intrahepatic PSS (IHPSS). The majority of IHPSSs are not necessarily subsequent to a patent ductus venosus, and the cause of other left, right, and central divisional IHPSSs or EHPSSs is currently unknown.

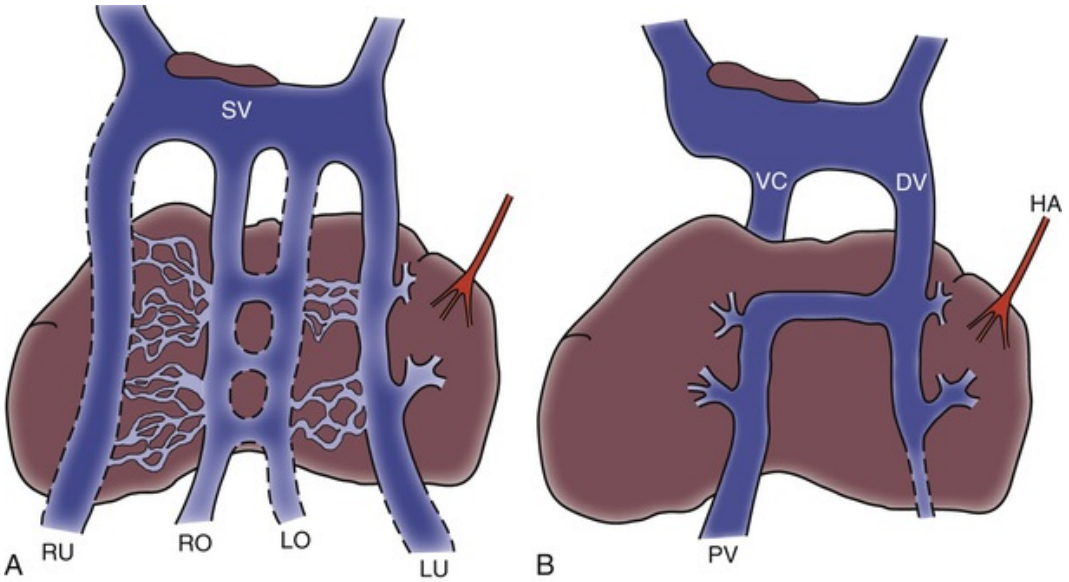


FIGURE 284-1 **A,** Vascular anatomy of the fetal liver. **B,** Developmental changes in the vasculature of the fetal liver. The omphalomesenteric (vitelline) veins form the prehepatic portal vein. Portions of the left umbilical vein and vitelline veins form the ductus venosus (DV). *HA,* Hepatic artery; *LO,* left omphalomesenteric (vitelline) vein; *LU,* left umbilical vein; *PV,* portal vein; *RO,* right omphalomesenteric (vitelline) vein; *RU,* right umbilical vein; *SV,* sinus venosus; *VC,* vena

cava. (Courtesy Dr. Pamela Whiting.)

Anatomy/Classification

The portal vein is formed by the confluence of the cranial and caudal mesenteric veins, providing up to 80% of the blood and 50% of the oxygen content to the liver, with the remainder being supplied by the hepatic arterial blood.[3,5,6,13] Blood from the GI tract, spleen, and pancreas is drained by their respective veins, which join the portal vein. In the dog, the portal vein enters the liver, branching into left and right vessels that supply the various liver lobes. The main right branch supplies the right lateral and caudate process of the caudate lobe, and the main left branch supplies all other lobes, giving off a central branch that supplies the right medial lobe.[3,13] In the cat, the portal vein separates directly into left, central, and right branches.[3,5,13] The portal vein branches into smaller venules where the blood enters the parenchyma via the portal triads. That blood travels through the hepatic sinusoids, is cleansed by the reticuloendothelial system, then drains into central veins that form larger hepatic venules and ultimately hepatic veins that empty into the CVC. When the path is interrupted by an anomalous vessel, blood is diverted away from the liver and along the path of least resistance, reaching the systemic circulation without having traversed the hepatic circulation.

The most recent classification of hepatic vascular anomalies suggests three categories (Box 284-1): (1) congenital IHPSSs and EHPSSs; (2) disorders associated with abnormal hepatic blood flow or portal hypertension, currently termed *primary hypoplasia of the portal vein* (PVH); and (3) disturbances in outflow. The second category, PVH, remains confusing and includes processes that might or might not result in portal hypertension. These are *PVH with portal hypertension* (noncirrhotic portal hypertension [NCPH]/hepatoportal fibrosis[14]/idiopathic hepatic fibrosis[15]/veno-occlusive disease[16]/idiopathic chronic liver disease/nonfibrosing liver disease[17]) and *PVH without portal hypertension* (formerly termed *microvascular dysplasia* [MVD]).[18,19]

Box 284-1

Types of Hepatic Vascular Disease

Congenital (CPSSs)

- Macrovascular portosystemic shunts
  - Intrahepatic (IHPSSs)
  - Extrahepatic (EHPSSs)
- Primary portal vein hypoplasia (PVH)
  - PVH with portal hypertension (e.g., noncirrhotic portal hypertension [NCPH])
  - PVH without portal hypertension (formerly microvascular dysplasia [MVD])
- Disturbances in outflow

Acquired (APSSs)

- Multiple, extrahepatic shunts
  - Secondary to hepatic fibrosis (cirrhosis)
  - Secondary to hepatic arteriovenous malformations (HAVMs)

PSSs can either be congenital or acquired. Congenital shunting is reported in 0.18% of all dogs and 0.05% of mixed-breed dogs.[20] Congenital PSS most commonly occurs as a single vessel that provides direct vascular communication between the portal venous supply and the systemic venous circulation (CVC or azygos veins). This commonly occurs as a single intrahepatic or extrahepatic communication (80%). Rarely, some animals have two or more congenital communications.[21] There are several types of congenital PSS found in both dogs and cats, including intrahepatic portocaval shunts, extrahepatic portocaval shunts, extrahepatic portoazygos shunts, portal vein atresia with resultant multiple portocaval anastomoses, hepatic arteriovenous malformations (HAVMs) causing portal hypertension-induced patency of portosystemic anastomoses, and microintrahepatic PSS (PVH without portal hypertension, formerly MVD).[2,5,22-26] Approximately 25-33% of congenital PSSs are intrahepatic (IHPSSs) in both dogs and cats. Single EHPSSs, with a major solitary portocaval shunt being the most common, constitute 66-75% of congenital single PSSs in both species.[1-4,26]

Most IHPSSs occur in larger-breed dogs, whereas most EHPSSs occur in smaller breeds.[26] Some EHPSSs, like splenocaval shunts, may be associated with less severe clinical signs because splenic blood is not of GI origin and less portal blood is shunted away from the liver. Dogs with IHPSSs generally have the largest volume of diverted portal blood, causing clinical signs earlier, or signs that are more severe.[1,2,27,28]

Acquired shunts (20%) most commonly occur secondary to chronic portal hypertension in which increased portal pressures lead to the opening of fetal, vestigial blood vessels. These have also been seen as congenital abnormalities. These vessels provide an outlet for hypertensive portal blood. Acquired shunts usually are multiple, tortuous, extrahepatic, and located near the kidneys.[22-24] The most common causes of acquired extrahepatic shunts are hepatic fibrosis (cirrhosis), PVH with portal hypertension (congenital NCPH),[23] or HAVMs.[24]

PVH with portal hypertension, or NCPH, has been described in various dog breeds.[23,29] This condition is diagnosed when there is intraabdominal portal hypertension with a patent portal vein and a noncirrhotic liver. The underlying cause is unknown; speculations include severe, diffuse intrahepatic vascular malformations without cirrhosis, resulting in portal hypertension and multiple EHPSSs.

PVH without portal hypertension, formerly MVD, is a microscopic malformation of the hepatic vasculature.[25,28] It is characterized by small intrahepatic portal vessels, portal endothelial hyperplasia, portal vein dilation, random juvenile intralobular blood vessels, and central venous hypertrophy and fibrosis. These lesions can allow for abnormal communications between the portal and systemic circulation at a microvascular level. This can occur as an isolated disease, or in combination with macroscopic PSS. Fifty-eight percent of dogs and 87% of cats with PVH have concurrent congenital macroscopic PSS.[18] Clinical signs in dogs with PVH can be similar to those of PSS; however, when PVH exists without a macroscopic shunt, signs are often less severe, occur later in life, and result in a better long-term prognosis with medical management alone.

HAVM is a rare condition of multiple high-pressure arterial and low-pressure venous communications. This condition, previously termed *hepatic arteriovenous fistula,* is more appropriately named a malformation because most are composed of numerous communications (malformation) rather than a single communication (fistula). They are usually congenital and have been described in both dogs and cats.[24,30] Usually, a branch of the hepatic artery communicates directly with the portal vein via multiple (dozens to hundreds of) aberrant shunting vessels. The high pressure causes hepatofugal blood flow and arterialization of the portal vein; the resulting portal hypertension, which opens multiple extrahepatic shunts to decompress this system, often is associated with ascites. The long-term prognosis for HAVM has been inferior to the more common PSS or PVH.[2,3,24]

Hepatic Encephalopathy

Most of the clinical signs associated with PSSs are due to hepatic encephalopathy, a neuropsychiatric syndrome involving a number of neurologic abnormalities that occurs when more than 70% of liver function is lost.[10-12,31-37] HE is discussed further in ch. 280-283 and 285.

Diagnostic Evaluation

Signalment

Congenital EHPSSs are seen most commonly in small/toy-breed dogs: in a large case series, the Yorkshire Terrier, Havanese, Maltese, Dandie Dinmont Terrier, Pug, and Miniature Schnauzer breeds all had an odds ratio for being affected that was >19.[5,20,26] PSS is suspected to be hereditary in Yorkshire Terriers, where an odds ratio for PSS is 35.9 times greater than that for all other breeds combined.[20,38] In the Maltese, a recessive, partially-penetrant mode of inheritance is suspected for both macroscopic PSS and PVH.[39] In cats, EHPSSs are more commonly identified,[3,38] though IHPSSs are reported.[40-41] Domestic shorthair, Persian, Siamese, Himalayan, and Burmese breeds are overrepresented.[4,41-44] Intrahepatic shunts are overrepresented in larger breed dogs, including the Irish Wolfhound, Retrievers (Labrador, Golden), Australian Cattle Dogs, and Australian Shepherds.[3,4,45-47] Left divisional IHPSSs have been considered heritable in the Irish Wolfhound,[48,49] and right divisional IHPSSs have been overrepresented in the Australian Cattle Dog and male dogs in Australia.[47,50] The Cairn Terrier has been documented to have hereditary PVH that is suspected to be an autosomal inherited trait, and the Yorkshire Terrier was also overrepresented with MVD/PVH in one

report.[25,28] In a recent report[51] of dogs with congenital (CPSS) or acquired portosystemic shunts (APSS), dogs with APSS were older, heavier, in poorer body condition, and were more likely to have ascites, but less likely to have central nervous system (CNS) signs than those with CPSS.

History

Most dogs and cats with PSSs have signs of chronic or acute illness before 1-2 years of age, though some have been older than 10 years of age.[26,52] PSS is far more common in dogs than cats. Multiple acquired EHPSSs in dogs are diagnosed at a median age of 3 years (range: 7 months–7 years),[22] and the median age of dogs diagnosed with PVH is 3.25 years (range: up to 10 years).[2,25] There is no clear gender predisposition in dogs, but males could be overrepresented in cats.[1,26] The history typically suggests the pet has "failed to thrive" since birth, is small in stature (or the runt of the litter), has weight loss (11% of cases) or failure to gain weight, has anesthetic intolerance, is dull or lethargic at times, and displays "bizarre behavior" (41% to 90% stargazing, head pressing, staring into walls or corners, random barking, intermittent blindness, pacing or aggression).[1,2,5,26,53] Some pets have a history of dysuria.[2,54] Polyuria and polydipsia (PU/PD) is common in dogs, possibly due to a poor medullary concentration gradient from a low blood urea nitrogen (BUN), to increased renal blood flow, to increased adrenocorticotropic hormone (ACTH) secretion and associated hypercortisolism, and to psychogenic polydipsia from HE.[3,5,6,55] Ascites occurs in 75% of dogs with HAVMs[24] and can be seen with venous-venous PSSs if hypoalbuminemia is severe. This complication is seen with concurrent protein-losing enteropathy, often associated with GI ulceration/bleeding or inflammatory bowel disease ± lymphangiectasia.

Clinical Signs/Physical Examination

The three most commonly affected body systems are the CNS, GI, and urinary systems.[2,3,5,26] Signs of HE can be obvious or quite subtle and typically are associated with aberrant behavior (see also ch. 9). More obvious CNS signs include ataxia, unresponsiveness, pacing, circling, blindness, seizures, random barking, and coma.[3,7,22,53] Onset of signs correlating with meal ingestion has been reported in only 30%-50% of pets.[5] GI signs (vomiting, diarrhea, anorexia, pica, and/or GI bleeding/melena/hematemesis) occur in ≈30% of dogs but are less frequent in cats.[5,22,26,41] Ptyalism, thought to be a manifestation of HE or GI upset, is very common in cats (75%).[5,6,41,53,56] GI hemorrhage occurs more often in large-breed dogs with IHPSS prior to repair (≈30%) than in dogs with EHPSS.[57] Some animals (20-50%) have signs of lower urinary tract disease: hematuria, stranguria, pollakiuria, or urethral obstruction.[2] Due to decreased urea production, increased ammonia excretion, and decreased uric acid metabolism, formation of ammonium urate calculi is common (30-35.8% of pets with PSSs reported, including in cats[58]) and can be associated with bacterial urinary tract infections.[26,54,58] Cats with PSS and urate urolithiasis tend to be younger (2 versus 7 years) than those with urate urolithiasis without known PSS.[58]

Shunt morphology can be associated with clinical signs. In one case series, preoperative clinical signs occurred in 88% of dogs with portocaval CPSSs, compared to 58% of dogs with portoazygos CPSSs.[59] Clinical signs also were more common if the shunt inserted caudal to the liver (91%) than if it inserted between the liver and diaphragm (67%).[59] CNS signs were most frequent with splenocaval CPSSs, and urinary signs were more common with right gastric vein than gastrosplenic vein origin.[59] With EHPSS, older dogs have been found to have splenophrenic and splenoazygos shunts more commonly than right gastrocaval or splenocaval shunts.[60]

Concurrent congenital defects are common in animals with PSSs. These include cryptorchidism (30% of male cats in one study[61] and 50% of male dogs in another[62]), heart murmurs that could be incidental flow murmurs in young pets or could indicate congenital cardiac defects,[3,5,53,61] and copper-colored irises that are inappropriate for the breed, particularly in cats.[63]

Animals with PVH without macrovascular shunts have a similar signalment and clinical signs to those described earlier. These dogs and cats typically are older and the signs frequently are mild or nonexistent.[5,25] PVH with portal hypertension is diagnosed when there is intraabdominal portal hypertension with a patent but small portal vein and a noncirrhotic liver. Purebred dogs are overrepresented, particularly Doberman Pinschers (27% of cases). Most dogs are <4 years of age and weigh >10 kg.[23] Signs are similar to PSSs or to

hepatic cirrhosis with concurrent portal hypertension, resulting in ascites (60% of cases), PU/PD, GI upset, HE, and weight loss, in association with multiple EHPSSs (Figure 284-2).

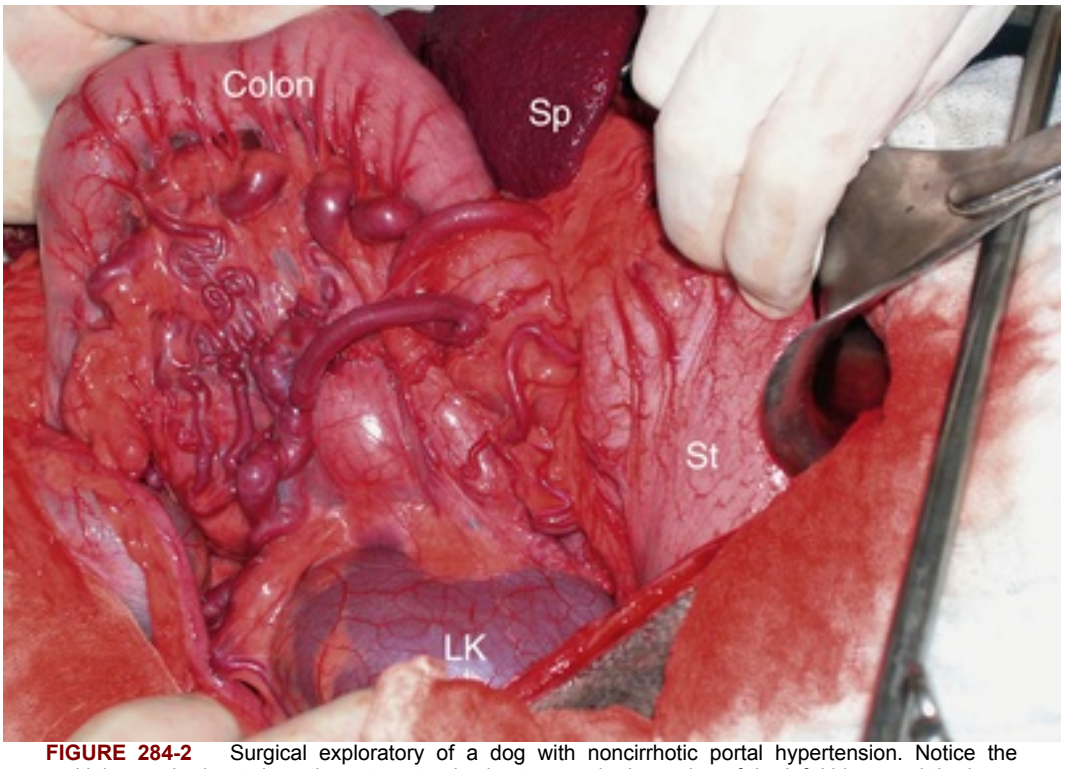


FIGURE 284-2 Surgical exploratory of a dog with noncirrhotic portal hypertension. Notice the multiple acquired extrahepatic portosystemic shunts seen in the region of the left kidney and the large dilated/tortuous veins throughout the abdomen secondary to portal hypertension. *LK,* Left kidney; *Sp,* spleen; *St,* stomach.

Clinical signs associated with HAVMs can be acute or chronic. Most affected pets are diagnosed in the first year of life and signs are associated with multiple EHPSSs from the portal hypertension, or with ascites. All sizes of dogs and a small number of cats have been reported.[5,24] GI signs are common, and many dogs have stunted growth and lethargy.[24] Ascites has been documented in ≈75% of dogs, less than previously suspected, presumably due to decompression of the portal system by the acquired shunts in the remaining 25% (Figure 284-3). Heart murmurs were documented in 20% of dogs with HAVMs in one study.[24] Signs of HE are reported less frequently with HAVMs. In some animals, the sound of turbulent blood flow (bruit) can be ausculted over the liver.

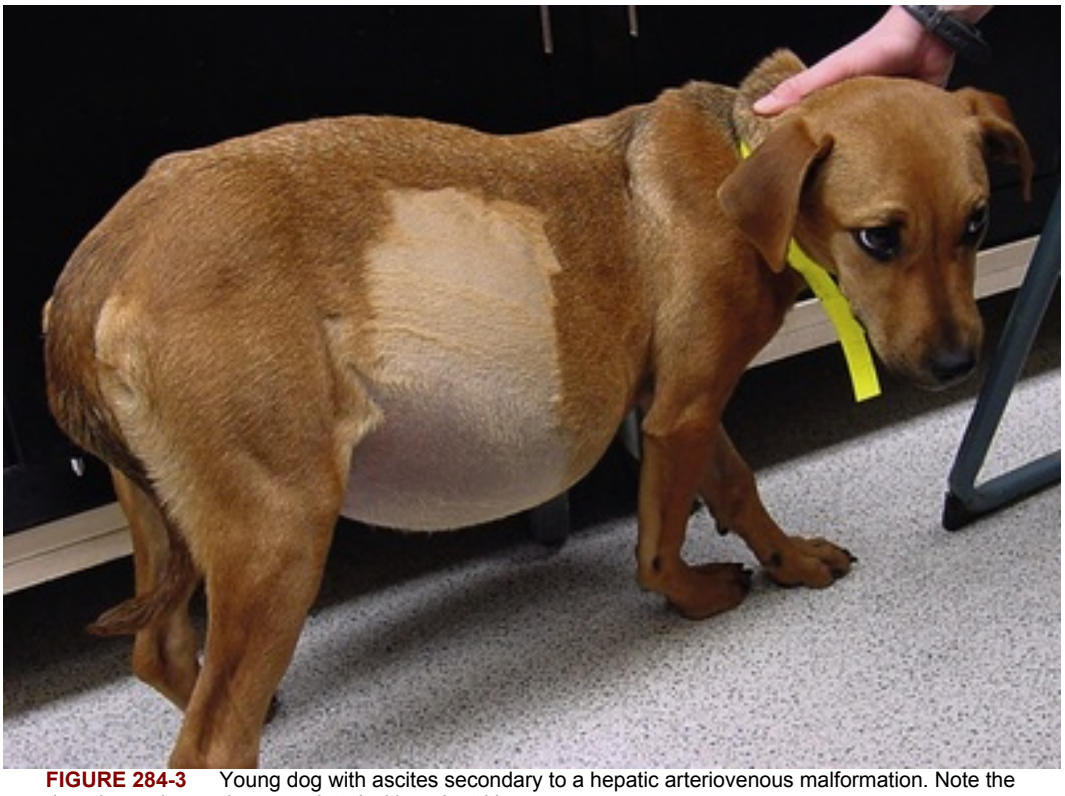


FIGURE 284-3 Young dog with ascites secondary to a hepatic arteriovenous malformation. Note the dorsal muscle wasting associated with malnutrition.

Clinicopathologic Findings

Hematologic changes often include a mild to moderate, microcytic, normochromic, nonregenerative anemia. Erythrocyte target cells in dogs, and poikilocytes in cats, are common on morphologic evaluation.[64] The cause of the microcytic anemia is not fully understood, although studies suggest a defective iron-transport mechanism, decreased serum iron concentrations, decreased total iron-binding capacity, and increased hepatic iron stores in Kupffer cells. This could suggest iron sequestration.[65,66] Microcytosis has been reported with or without anemia in 60-72% of dogs, but only in ≈30% of cats.[3,65,66] Microcytosis usually resolves after shunt correction and is not seen routinely in dogs with PVH/MVD.[5,25] Leukocytosis, due to inadequate hepatic endotoxin and bacteria clearance from the portal circulation, has been associated with a poor prognosis.[1,2,26,45,67] Monocytosis and elevated C-reactive protein concentrations are more commonly associated with HE.[36]

Serum biochemical abnormalities are extremely common in animals with PSSs. Most are due to decreased hepatic synthesis: low albumin (50%), low BUN (70%), hypocholesterolemia, and hypoglycemia. In cats, hypoalbuminemia is uncommon but low BUN and creatinine are common.[42,56] High serum liver enzyme activities are also common. These are usually mild to moderate increases (twofold to threefold) in alkaline phosphatase (ALP) and alanine aminotransferase (ALT).[64] These abnormalities are typical of any hepatic vascular anomaly. Interestingly, the serum ALP concentration typically is higher than the ALT concentration in dogs with PSSs, likely due to the contribution of bone isoenzyme in growing animals, or hepatic organelle injury and increased release or decreased elimination of canalicular ALP.[5,64] In one study, dogs with APSS were more likely to have a lower hematocrit, higher mean corpuscular volume, and higher ALT than dogs with CPSS.[51] In 81% of dogs with CPSS, renal volume and glomerular filtration rate are abnormally high prior to shunt attenuation, and decrease significantly after ligation.[55] This could explain, in part, the low BUN and creatinine concentrations seen biochemically.[55] High hyaluronic acid levels in dogs with CPSS, suspected to be caused by reduced hepatic clearance, improve with shunt attenuation.[68] This suggests that hyaluronic acid levels could be a good test of liver function, including for evaluating the success of shunt attenuation in dogs with CPSS.

Urinalysis abnormalities with CPSS include a low urine specific gravity (>50% are hyposthenuric or isosthenuric) and ammonium biurate crystalluria.[3,5,8,53] The low specific gravity likely results from polydipsia, as well as the poor medullary concentration gradient that occurs with low BUN subsequent to a deficient urea cycle. Hyperammonuria, also resulting from the deficient hepatic urea cycle, combined with hyperuricacidemia due to a deficiency in hepatic purine and pyrimidine metabolism (uric acid cycle), result in excessive renal ammonia and urate excretion. These compounds can precipitate into crystals or stones in the kidney or bladder (stones seen in 30-36% of cases).[8,12,26,54] Ammonium biurate crystalluria is common and can be seen in 26-57% of affected dogs and 16-42% of affected cats.[54,58,62,69,70] Male gender, older age, history of medical management prior to evaluation, but not shunt morphology, appear to be associated with urolithiasis in dogs with congenital EHPSS.[54] Proteinuria is common in dogs with PSSs, suspected to be secondary to glomerulopathy (e.g., glomerular sclerosis, glomerulofibrosis, membranoproliferative glomerulonephritis; see ch. 325).[71] This link between severe liver disease and glomerulonephritis, which has been seen in people, is speculated to follow accumulation of antigens reaching the kidneys that the liver would have otherwise cleared with a normal portal circulation and resulting in immune-mediated glomerulonephritis.[72]

Liver Function Testing

Measurement of fasting (12-hour) and 2-hour postprandial serum bile acid (SBA) is the test of choice for evaluating liver function in animals suspected of having PSSs. Bile acids are synthesized in the liver from cholesterol and, following conjugation, are secreted into the bile canaliculi and stored in the gallbladder until released into the duodenum. They aid lipid absorption via intestinal fat emulsification and metabolism, are reabsorbed from the ileum, transported into the portal system, and extracted by hepatocytes for recirculation.[73-76] Production, excretion, and enterohepatic recirculation are all evaluated when measuring bile acid concentrations. These measurements can be affected by the timing of gallbladder contraction, the rate of intestinal transport, the degree of bile acid deconjugation in the small intestine, the rate and efficiency of bile acid absorption in the ileum, portal blood flow, and the function of the hepatocyte uptake and canalicular transport. Increases in postprandial bile acids have been found to be 100% sensitive for detecting PSSs in dogs and cats in some studies.[73-76] Others suggest paired samples are 100% sensitive, but not individual measurements. A small subset of affected animals have normal postprandial bile acids, with elevated fasting samples, and an even larger number have normal fasting and elevated postprandial bile acids.[26,74] Normal Maltese dogs can have elevated SBAs without evidence of hepatocellular dysfunction.[50] Other "false"-positive results unrelated to PSSs are due to inappropriate sample timing, other hepatobiliary diseases/cholestasis, glucocorticoid or anticonvulsant therapy, tracheal collapse, seizures, and GI disease.[6,64,75,77] Falsely low results can occur with delayed intestinal absorption from prolonged transport time, lack of gallbladder contraction, inadequate food intake/delayed gastric emptying, and malabsorption or maldigestion. Gallbladder contraction can occur between meals, resulting in higher preprandial than postprandial bile acid levels. The persistent bile acid concentration elevations identified in animals with PSSs are due to the shunting of reabsorbed SBA to the systemic circulation.[6,64,75]

When false-negative test results are suspected, an ammonia tolerance test can be performed. Two samples are evaluated: prior to, and 30 minutes following, ammonium chloride administration (100 mg/kg; maximum, 3 g) via nasogastric tube, oral capsule, or a high colonic infusion enema. This test has been documented to have a sensitivity of 95-100% for hepatic insufficiency.[8,78,79] The test should be considered carefully and is contraindicated in animals with HE.[79] The primary source of blood ammonia is from GI tract absorption, with >75% being generated by colonic bacterial metabolism.[6,12,53] Portal blood delivers ammonia to hepatocytes, where it is converted to urea via the urea cycle. In animals with PSSs, or other liver deficiencies, this conversion does not occur efficiently, resulting in increased concentrations of ammonia. Plasma separation and laboratory analysis need to be done within 20 minutes of sample collection, making this test problematic. In cats with hyperammonemia and HE, an inborn error in ammonia metabolism due to an enzyme deficiency (ornithine transcarbamylase) in the urea cycle has been reported.[80] Other causes of hyperammonemia in young animals include methylmalonic acidemia, other urea cycle enzyme deficiencies, and urethral obstruction–induced hyperammonemia.[5,80] These conditions are not associated with PSSs.

Ammonia concentrations are not as sensitive (62-88% of PSS animals are abnormal) as the SBA test, especially after prolonged fasting or with effective medical management of HE.[6,26,50,62] Both false-positive

(Irish Wolfhound puppies), and false-negative, baseline ammonia levels have been documented, making a high ammonia level supportive of, but not diagnostic for, PSSs.[26,79,81] Measurement of 6-hour postprandial blood ammonia concentrations increased detection sensitivity from 62% to 91% in dogs with PSSs.[82] Elevations in any of these function tests are suggestive of hepatic insufficiency, but are not diagnostic for PSSs.

Coagulation Profiles

Prolonged coagulation times (see ch. 196) are recognized in most dogs with PSSs, though spontaneous bleeding is rare and does not usually occur until surgical intervention is attempted.[83,84] In one study, postoperative mortality increased in those dogs that had a dramatic worsening of coagulopathy after surgery.[85] Because liver parenchymal cells synthesize most clotting factors (I, II, V, IX, X, XI, XIII [and VIII via the liver vascular endothelium]), animals in liver failure, as seen in PSSs, would be expected to have some deficiencies and resultant coagulopathies. Prolonged prothrombin time (PT) and/or activated partial thromboplastin time (PTT) occur after ≈65-80% of factor loss occurs.[6,12,83] The liver also regulates coagulation via clearance of activated factors, so that regeneration of inactivated factors and fibrinolytic factors can occur.[84,86,87] Animals with chronic liver disease, as with PSSs, typically have prolongation only of PTT, whereas animals with acute liver disease can have prolongations of both PT and PTT.[86] The prolonged PTT in PSSs is suspected to be due to impaired hepatic synthesis, qualitative abnormalities, and clearance of coagulation factors.[83-85] Interestingly, deficient factors include those involved in the common (II, V, and X) and extrinsic (VII) pathways, leading one to expect the PT to be prolonged as well. One possible explanation is a factor XII deficiency that can cause prolongation in PTT alone without overt bleeding.

Dogs with PSSs have abnormally low platelet counts preoperatively, which is worse postoperatively (mean: 161,000/mcL).[83] No reported decrease in platelet count has been low enough to cause clinical bleeding. This may be supportive of a postoperative consumptive coagulopathy. Overall, coagulation status (PT, PTT, and platelet count) returned to normal in one study by 6 weeks after PSS surgical correction, but not in animals that had persistent shunting.[83]

In some dogs with CPSS, coagulation parameters and thromboelastography have revealed hemostatic abnormalities consistent with markers for coagulopathy and a concurrent hypercoagulable state.[88] In this study, the presence of a hypercoagulable state was found to be 40 times more likely to be associated with clinical HE.[88]

Abdominal Effusion

Ascites is rarely seen in dogs with single congenital PSSs, unless there is severe hypoproteinemia, severe GI bleeding, or portal hypertension associated with HAVM, NCPH, or acquired multiple EHPSS (chronic liver disease/cirrhosis). Typically, the fluid for any of these conditions is a pure transudate that is clear and relatively acellular with total protein <2.5 g/dL, specific gravity <1.017, and <1000 nucleated cells/mcL.[64]

Histopathology

Most dogs with CPSSs have microscopic bile duct proliferation, hypoplasia of intrahepatic portal tributaries, hepatocellular atrophy (lobular), arteriolar proliferation or duplication, lipidosis and cytoplasmic vacuolar changes (lipogranulomas), smooth muscle hypertrophy, increased lymphatics around central veins, and Ito cell and Kupffer cell hypertrophy.[6,89-92] Some animals have evidence of mild fibrosis around the central veins and a few have signs of necrosis or inflammation.[6,89] In an evaluation of histopathologic data versus prognosis in dogs with CPSS, there was no statistically significant association between histologic features and survival times.[89] Historically, histologic features associated with a poor prognosis included fibrosis, biliary hyperplasia, and necrosis.[5,6,90] Some dogs with PSSs have focal lesions consisting of Kupffer cells and/or macrophages with cytoplasmic brown pigments (ceroid and hemosiderin) and lipid vacuoles called *lipogranulomas*.[92] These changes have inconsistently been associated with prognosis.[89,92,93]

Another study assessed hepatic histopathologic lesions in relation to clinical findings and ability to completely attenuate the shunt in dogs with CPSS.[94] The lack of identifiable portal veins (36% of dogs) was associated with increased hepatic arteriolar proliferation, decreased tolerance to complete surgical

attenuation, and decreased opacification of intrahepatic portal vessels on portovenography. Surgical CPSS attenuation resulted in significant clinical, serum biochemical and portovenographic changes indicative of improved liver function, but only subtle changes on hepatic histologic re-examination.[94]

In a study of dogs with congenital EHPSS, larger liver volumes were associated with fewer lipid droplets per tissue point histopathologically.[93] The number of lipogranulomas was positively associated with age, but the presence of hepatic lipidosis and lipogranulomas had no demonstrable effect on development of acquired shunts or the magnitude of increased liver volume after shunt attenuation.[93] In a study of 40 cats with CPSS evaluated before and after surgical attenution histopathologic analysis showed portal vein hypoplasia and arteriolar hyperplasia in all samples.[95] Hepatocyte swelling with microvesicular vacuolar change (50%), fibrosis (42.5%), hepatocyte swelling with macrovesicular vacuolar change (30%), biliary hyperplasia (20%), and hemosiderin within Kupffer cells (5%) were seen in variable amounts. Cats with macrovesicular vacuolar changes were significantly older (median age 18.5 months versus 8.5 months). On follow-up biopsy samples after partial attenuation, there were no significant differences in histopathological features, though intrahepatic vasculature was improved on portovenography.[95]

Dogs with PVH without (MVD) or with (NCPH) portal hypertension share hepatic histopathologic changes seen in dogs with macroscopic CPSS. These syndromes can, therefore, be confused histologically if correct history and signalment are not provided.[23,25,29] Dogs with NCPH often have more significant fibrosis that extends into the parenchyma, particularly along the portal tracts or even bridging to other portal areas or central veins.[23]

Dogs with HAVMs that have had biopsies taken from liver lobes not involved in the arteriovenous communication often have similar histopathologic findings to those with venous-venous shunting. The liver tissue in close proximity to the malformation often has largely dilated portal venules, marked arteriolar hyperplasia, muscular proliferation, and sinusoidal capillarization. Some portal veins have evidence of thrombus formation and recanalization.[5,24]

Dogs with HE can have histopathologic changes in the CNS that include polymicrocavitation of brainstem, cerebellar nuclei, or cerebral cortex, and hypertrophy and hyperplasia of cerebral cortical protoplasmic astrocytes.[3,8]

Diagnostic Imaging

Various imaging modalities can be used for diagnosing PSSs. Survey abdominal radiographs often demonstrate microhepatica (60-100% of dogs, 50% of cats) and bilateral renomegaly.[3,5] In dogs with PVH, liver and kidney size can be normal radiographically.[5,25] Marginally radiopaque calculi can be seen in the bladder, urethra, ureters, and/or kidneys. These are usually ammonium biurate stones with associated calcium salt or struvite shells; these stones also can be radiolucent. To definitively diagnose a macroscopic shunt using contemporary imaging modalities, abdominal ultrasonography, scintigraphy, angiography (portal or arterial), computed tomographic angiography (CTA), or magnetic resonance angiography (MRA) may be necessary.

Abdominal Ultrasonography

Ultrasonography (US) is the most widely used diagnostic tool for PSSs. It is noninvasive, does not require general anesthesia (though sedation makes finding EHPSSs more reliable in many circumstances), and does not require special licensing/handling (versus scintigraphy). Decreased numbers of hepatic and portal veins, a subjectively small liver, and an anomalous vessel are most often seen in congenital PSSs (Figure 284-4). EHPSSs have been documented to be more difficult to diagnose with US due to small patient size, small vessel size, variable location, and the presence of gas in the bowel and lungs. Multiple EHPSSs often are harder to find and typically are located near the left kidney. Sensitivity for detection of shunts has ranged from 74% to 95% and specificity from 67% to 100%.[96-98] Correct distinction of IHPSS from EHPSS was possible in 92% of cases in one study. Sensitivity is higher for IHPSS (95-100%) than EHPSS due to the presence of liver parenchyma surrounding the shunting vessel, and the typically large diameter of the intrahepatic shunting vessel and associated portal vein.[96] Results are operator- and experience-dependent. Color-flow and pulsed-wave Doppler imaging are useful for identifying changes in flow direction because HAVMs classically have hepatofugal flow and venous-venous shunts have hepatopetal flow through the portal vein (Figure 284-5). Portal flow velocity was increased or variable in 53% of dogs with EHPSS and in 92% of dogs with IHPSS.[5] Dogs and cats with EHPSS have been documented to have reduced portal vein-to-

aorta size ratios. US also is useful for detecting uroliths in dogs and cats with hepatic vascular anomalies because these stones often are radiolucent.[96,99,100]

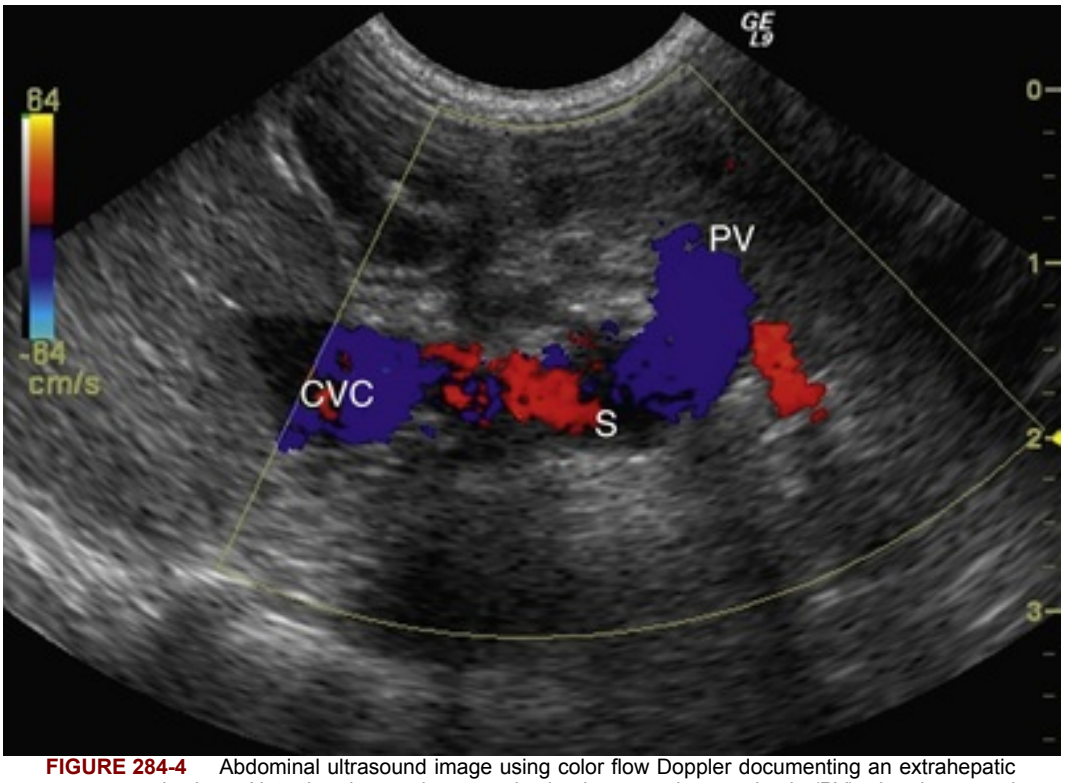


FIGURE 284-4 Abdominal ultrasound image using color flow Doppler documenting an extrahepatic portosystemic shunt. Note the abnormal communication between the portal vein (PV), shunting vessel (S), and caudal vena cava (CVC).

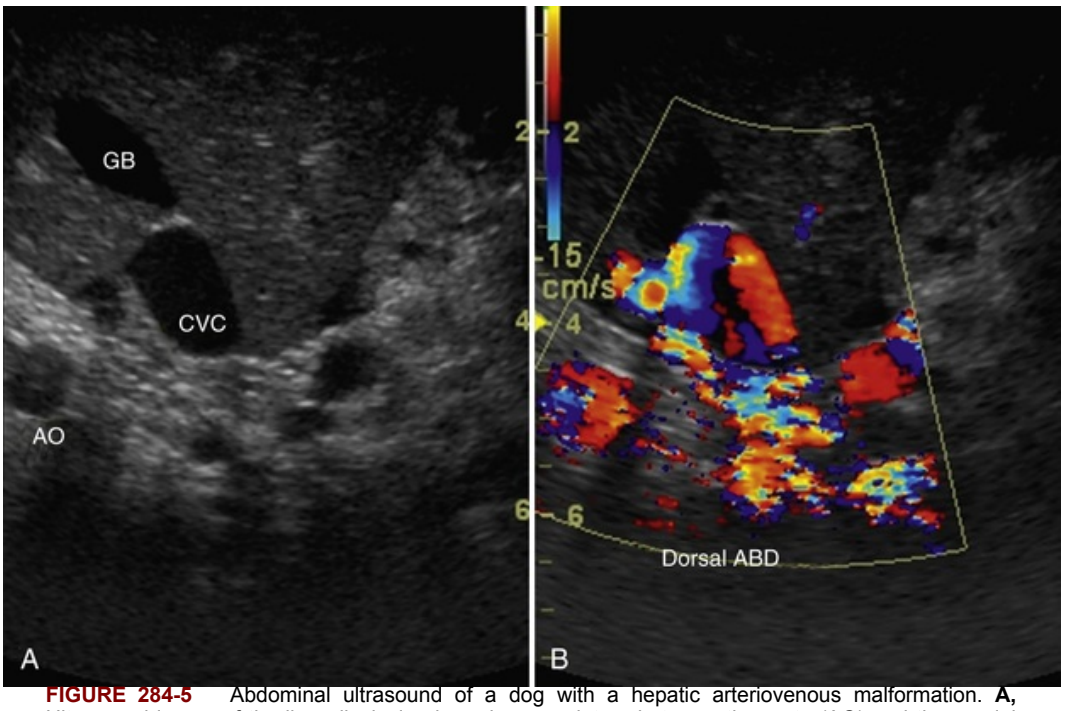


FIGURE 284-5 Abdominal ultrasound of a dog with a hepatic arteriovenous malformation. **A,** Ultrasound image of the liver displaying irregular vasculature between the aorta (AO) and the caudal vena cava (CVC). **B,** Color flow Doppler of the turbulent flow of blood in the portal vein and acquired

shunts. *ABD*, Abdomen; *GB*, gallbladder.

Ultrasound contrast venography has involved US-guided percutaneous injection of a mixture of agitated saline and 1 mL autologous heparinized blood into the spleen.[101] When visualizing the vena cava, portal vein, and right atrium in dogs with CPSS, it is possible to differentiate between intrahepatic and extrahepatic shunts depending on the entry point of microbubbles into the CVC. Portoazygos and portocaval shunts also can be differentiated this way.[101]

Scintigraphy

Transcolonic scintigraphy utilizing the radioisotope technetium (^{99m}Tc) pertechnetate is a useful, noninvasive method for detecting a PSS.[100] A bolus is infused into the colon, per rectum, and the pet is imaged with a gamma camera. The isotope normally, in order, is absorbed and drained through colonic veins and then the caudal mesenteric vein, portal vein, liver, and heart. In a PSS, the isotope reaches the heart, bypassing the liver, and then returns to the liver through the arterial circulation (Figure 284-6).[100] If a shunt is present, a shunt fraction can be calculated, giving an estimate of the percentage of portal blood bypassing the liver. A fraction <15% is considered normal, whereas most dogs with PSS have fractions >60% to 80%. Some cats (52% in one study) have lower fractions than dogs.[102] There is considerable variation (variable colonic absorption, operator variability, fecal matter in the colon), so comparisons at different time points are difficult and should not be used for assessing postoperative success.[103] If the isotope is administered "too high" into the rectum, absorption directly into the CVC can occur, resulting in falsely elevated shunt fractions. The half-life of technetium pertechnetate is 6 hours, so animals must be isolated for at least 24 hours after the procedure. Scintigraphy does not provide morphologic information regarding shunt type or location, cannot distinguish IHPSS from EHPSS, and cannot differentiate single from multiple shunts. Scintigraphy can be normal or abnormal in dogs with MVD/PVH. Shunt fractions can be lower in dogs with MVD than macroscopic PSSs. Shunt fraction estimation is inexact and prone to interoperator and intraoperator variability. Use of transsplenic portal scintigraphy for diagnosis of a PSS, using $^{99M}TCO_4^-$, has helped distinguish single from multiple shunts but not IHPSS from EHPSS, and is not used routinely.[104]

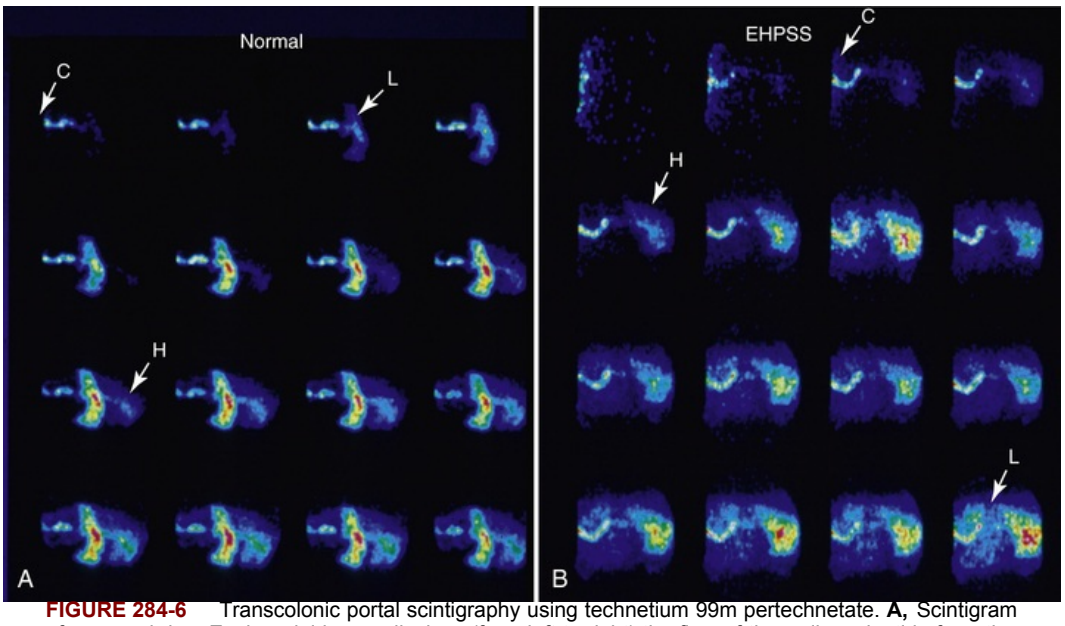


FIGURE 284-6 Transcolonic portal scintigraphy using technetium 99m pertechnetate. **A,** Scintigram of a normal dog. Each serial image displays (from left to right) the flow of the radionucleotide from the colon (C), where it is initially rapidly absorbed, to the portal vein, perfusing the liver (L), later reaching the heart (H). When this is compared with **B,** a dog with an extrahepatic portosystemic shunt (EHPSS), the nucleotide is seen to reach the heart (H) prior to the liver (L), indicating a portosystemic shunt. (Courtesy Dr. Lillian Aronson.)

A recent study correlated liver volume, portal vascular anatomy on CTA, hepatic perfusion, and

scintigraphy in dogs with CPSS before and after attenuation with an ameroid constrictor.[105] Decreased hepatic arterial perfusion and portal shunt fraction, based on scintigraphy, correlated with liver volume, and were both indicators for successful shunt attenuation. Additionally, dogs that did not have visible portal vasculature on CTA preoperatively had visible vasculature postoperatively.[105]

Computed Tomographic Angiography (CTA)

CTA is the gold standard for evaluating the portal venous system in people.[106] It is noninvasive, fast, and it images all portal tributaries and branches from a single peripheral venous contrast injection. It can be used in any species and any size of animal with accuracy, allowing for further image manipulation after completing a study. Dual-phase CTA provides a complete evaluation of portal and hepatic vasculature and is considered superior to single-phase CT.[107] This study is most valuable in animals with suspected IHPSS, HAVM, or for which US is not diagnostic and more invasive imaging such as portography is not desired (Figure 284-7). CTA is helpful in preprocedural planning for both surgical and interventional radiologic (IR) approaches to IHPSS or HAVM by reducing excessive liver dissection or manipulation during surgery and minimizing contrast load during IR procedures.

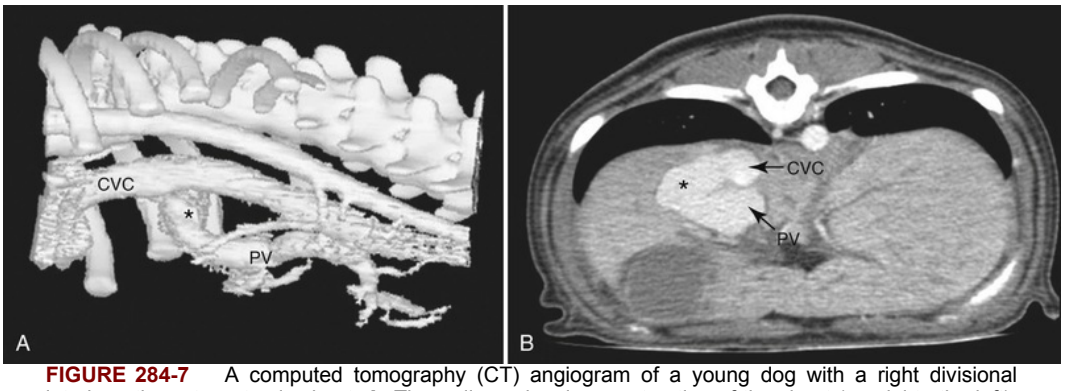


FIGURE 284-7 A computed tomography (CT) angiogram of a young dog with a right divisional intrahepatic portosystemic shunt. **A,** Three-dimensional reconstruction of the shunt (cranial to the left). The portal vein (PV) can be seen terminating in the shunt (*), which enters the caudal vena cava (CVC). **B,** Axial CT dual-phase angiographic image; the right side of the dog is on the left of the image. Note the contrast material enhancing the communication between the PV and CVC through the shunt.

A recent study of canine EHPSS using CTA found that CTA provided an excellent overview of shunt anatomy, and provided information about various tributary vessels that could be overlooked during surgical exploration.[108]

Magnetic Resonance Angiography (MRA)

MRA also can provide three-dimensional, preoperative shunt images, aiding in preprocedural planning (Figure 284-8). Images from dual-phase CTA are relatively easy to interpret, provide superior detail (particularly with newer multisliced CT scanners), and are less costly than MRA. Magnetic resonance imaging without gadolinium-enhanced angiography is less promising, with sensitivities ranging from 63% to 79%, though specificity as high as 97% has been described.[5] Contrast enhanced MRA (CE-MRA) can identify both EHPSS and IHPSS,[109] and was diagnostic of a portal vascular anomaly in 16/17 dogs, including IHPSS (n = 13), EHPSS (n = 2), HAVM (n = 1), and no shunt (n = 1) in one study.[110]

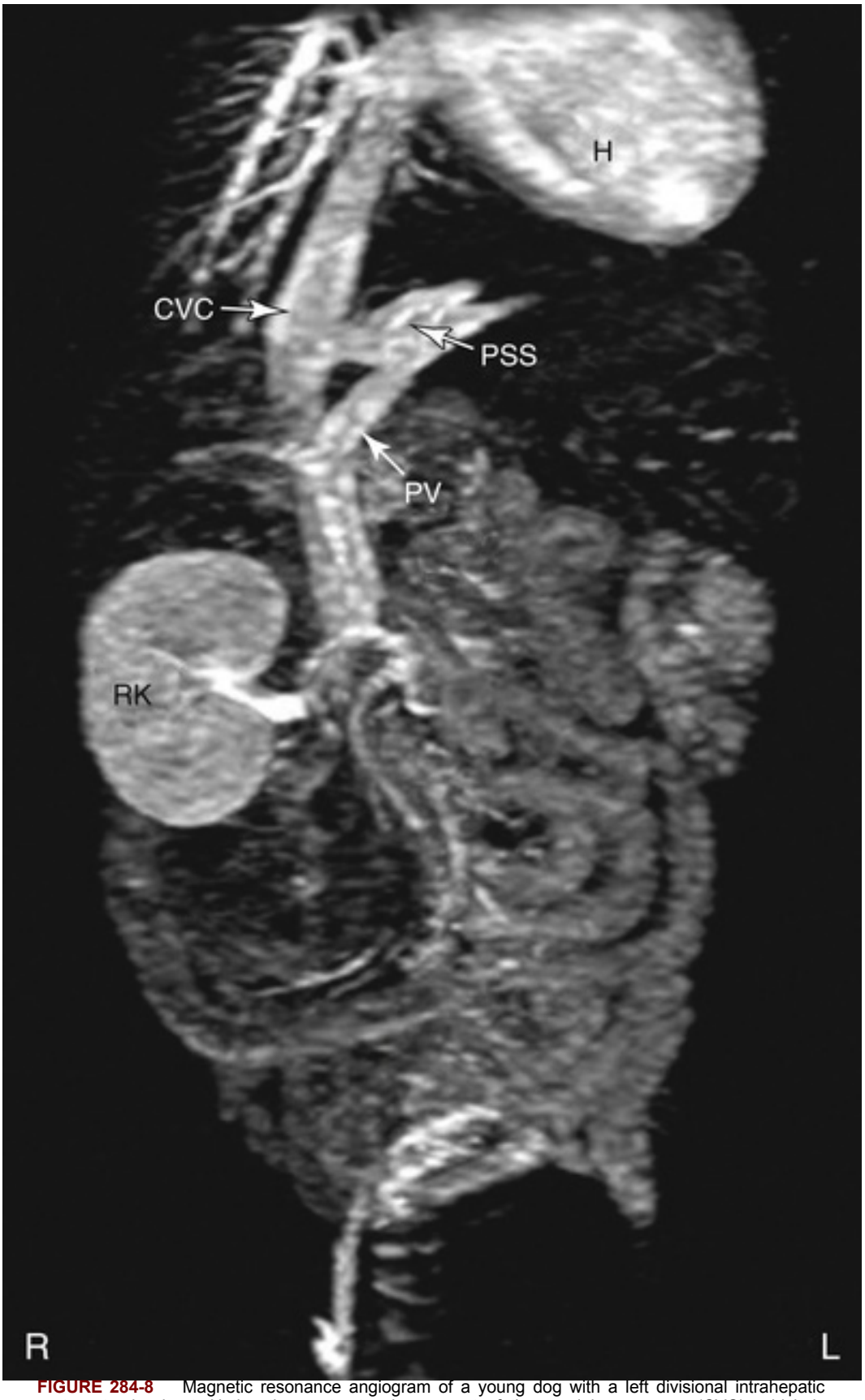


FIGURE 284-8 Magnetic resonance angiogram of a young dog with a left divisional intrahepatic portosystemic shunt. Notice the contrast enhancement of the caudal vena cava (CVC), which is communicating with the portal vein (PV) through the abnormal portosystemic shunting (PSS) vessel. *H,* Heart; *RK,* right kidney.

Portovenography

Portography/portovenography is not commonly performed due to availability of other less invasive imaging modalities (US, scintigraphy, CTA/MRA). Surgical mesenteric portography is the most commonly performed angiographic test for documenting PSSs in dogs and cats. It allows visualization of a shunting vessel but requires a laparotomy, fluoroscopy, and intravenous (IV) contrast material (Figure 284-9). The sensitivity of intraoperative portography is 85-100% and is dependent on patient positioning and the presence of digital subtraction of the fluoroscopic image.[3-5] Classically, differentiation of IHPSS from EHPSS on portography is based on the point where the shunt diverges from the portal vein. If this point is cranial to the thirteenth thoracic vertebra, the shunt is typically intrahepatic, and caudal to the thirteenth thoracic vertebra is usually extrahepatic.

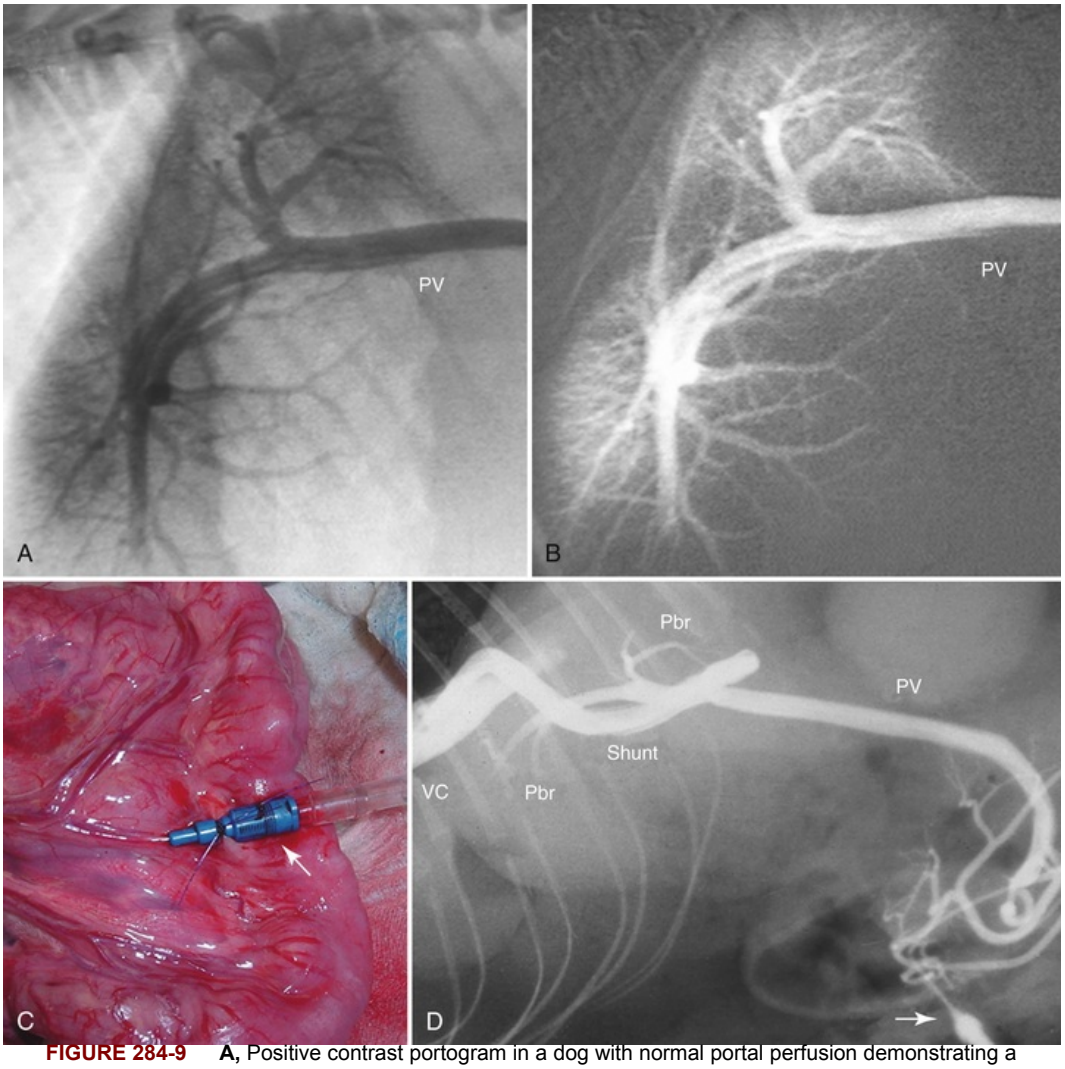


FIGURE 284-9 **A,** Positive contrast portogram in a dog with normal portal perfusion demonstrating a well-developed portal vein (PV) and portal branching. **B,** Digital subtraction portogram of the same dog demonstrating improved visualization of vascular anatomy. **C,** Jejunum with 22-gauge catheter secured in a jejunal vein for performing portography and portal pressure measurements. **D,** Mesenteric portogram performed through jejunal catheter (arrow) demonstrating PV and hypoplastic portal branches (Pbr), as well as portosystemic shunt (Shunt) entering the caudal vena cava (VC).

An alternative to surgical portal venography is percutaneous, ultrasound-guided splenic venography. Under US guidance, a bolus of ≈2-4 mL/kg of iohexol (240-360 mg/mL) is injected into a splenic vein. Fluoroscopy or radiography is used for imaging splenic venous drainage through the portal vein, and hepatic or systemic venous flow is identified (Figure 284-10). Caudally-located EHPSSs can be missed with this technique, however, if the portal branch communicates with the CVC in a more caudal location than the splenic vein.[111]

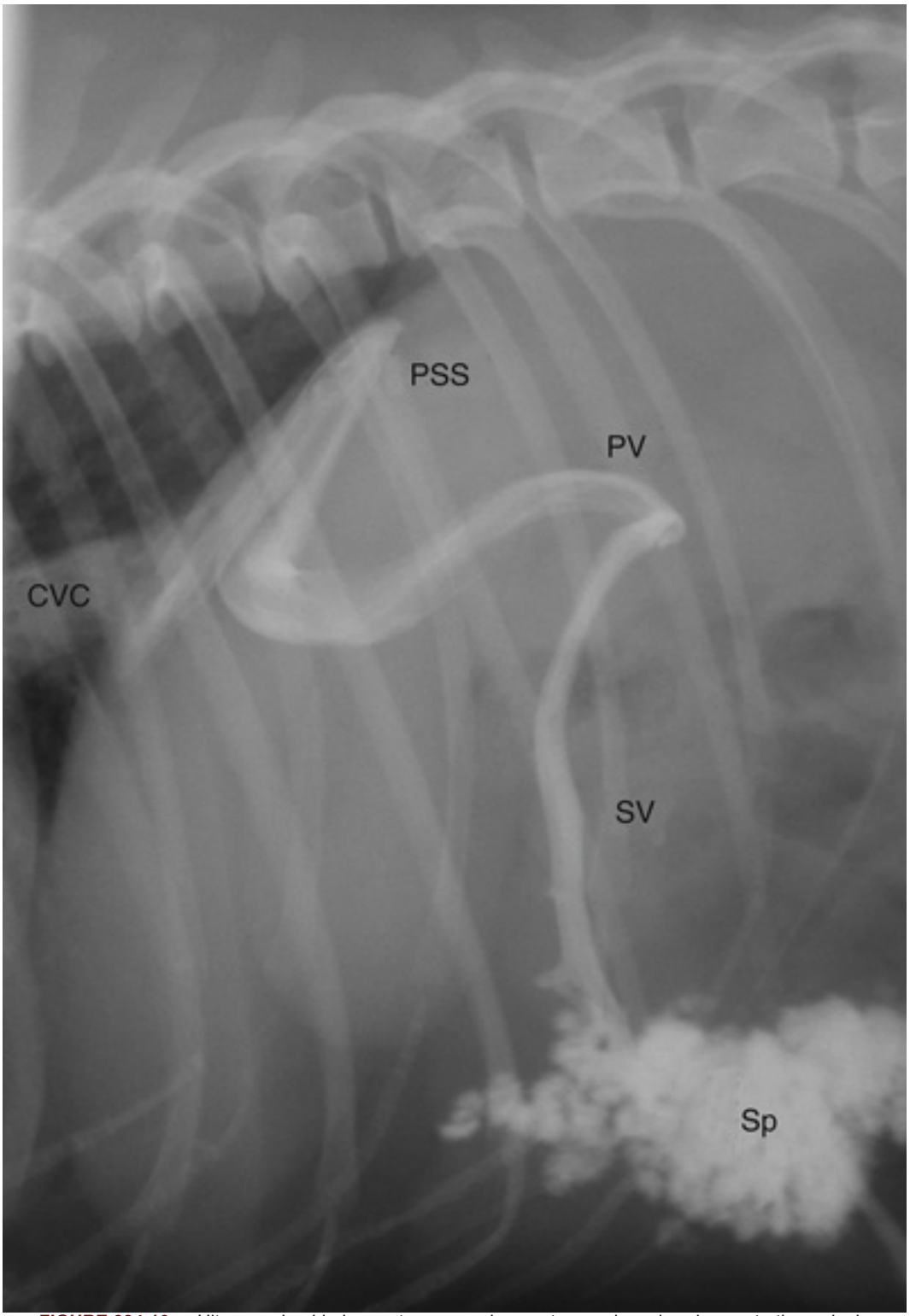


FIGURE 284-10 Ultrasound-guided percutaneous splenoportogram in a dog demonstrating splenic contrast uptake (Sp), splenic vein (SV), portal vein (PV), and portosystemic shunt (PSS) entering the caudal vena cava (CVC). Notice the obvious lack of portal perfusion present in this liver. (Courtesy Dr. Skye Stanley.)

Injection of contrast material into the mesenteric artery, known as a *cranial mesenteric arteriogram* via access through the femoral artery, is not commonly utilized due to many less invasive alternatives.

Differential Diagnosis

In any animal suspected of having a congenital PSS, conditions causing similar clinical signs (e.g., GI parasitism, hypoadrenocorticism, protein-losing enteropathy, other primary hepatopathies, MVD/PVH, NCPH, and HAVM) should be ruled out. If bile acid concentrations are suggestive of PSSs, differentiating MVD, NCPH, HAVM, and PSS is necessary, notably with the diagnostic imaging modalities mentioned above. Plasma protein C activity has been documented to help differentiate MVD from PSS (protein C levels were >70% in 88% of dogs with MVD and low in dogs with PSS).[112] If a macroscopic PSS still is not identified but remains highly suspected, then liver biopsy with or without measurement of portal pressures should be obtained to diagnose various forms of PVH. If an HAVM is not found in a young dog with ascites and clinicopathologic evidence of hepatic dysfunction, then NCPH is possible and histologic examination of liver tissue is necessary to rule out other severe hepatopathies and to guide treatment. Other liver diseases (chronic hepatitis, cirrhosis, or leptospirosis) can produce similar signs but are more common in older dogs and they often have hyperbilirubinemia. If hyperammonemia and HE are detected in an animal without evidence of PSS, a urine metabolic screen should be evaluated for evidence of ornithine transcarbamylase deficiency, methylmalonic acidemia, or other urea cycle metabolic abnormalities.[80]

Treatment

Medical Management

Medical management (Table 284-2) of animals with portovascular anomalies should be required prior to surgical or IR correction of PSS, in cases of MVD or NCPH, or for macrovascular shunts where surgery is not possible or is declined. Medical management is aimed at controlling clinical signs associated with shunting but does not treat the underlying diminished hepatic perfusion. When a dog or cat with signs of HE is examined, rapid stabilization is required and intensive efforts should be implemented to decrease ammonia levels to near normal. Nothing should be given orally until the pet is alert and aware. IV fluid therapy to replace and maintain hydration can be necessary, especially if an animal is unable to drink or is dehydrated. Lactated Ringer's solution often is avoided due to the need for hepatic conversion of lactate to bicarbonate. Potassium supplementation often is necessary due to potassium depletion from chronic diarrhea or decreased intake, and hypokalemia can also contribute to HE.[10,53]

TABLE 284-2

Recommended Medical Management for Portosystemic Shunts

DISORDER	THERAPY
Bacterial translocation/decreasing bacterial byproduct absorption (ammonia)	Cleansing enemas with warm water or 30% lactulose solution at 5-10 mL/kg (see ch. 114) Oral lactulose: 0.5-1 mL/kg PO q 6-8 h to effect of 2-3 soft stools per day Antibiotics Metronidazole 7.5 mg/kg IV or PO q 12 h Ampicillin 22 mg/kg IV q 6 h Neomycin 22 mg/kg PO q 8 h (avoid if any evidence of intestinal bleeding, ulcerations or kidney disease)
Coagulopathy (symptomatic; postoperative)	Fresh frozen plasma 10-15 mL/kg over 2-3 h (see ch. 130) Vitamin K_1 1.5-2 mg/kg SC or IM q 12 h for 3 doses, then q 24 h (see ch. 197)
Gastrointestinal ulceration (very common with IHPSS—begin treatment before intervention) (very common with HAVM due to portal hypertension)	Gastric acid suppressant Famotidine 0.5-1 mg/kg IV or PO q 12 h Omeprazole 0.5-1 mg/kg PO q 12-24 h Esomeprazole 0.5 mg/kg IV q 12-24 h Misoprostol 2-3 mcg/kg PO q 12 h Protectant Sucralfate: 1 g/25 kg PO q 8 h Correct coagulopathy
Seizure control	Avoid benzodiazepines* Phenobarbital (4 mg/kg IV q 3-6 h for 4 doses)

	KBr: should be avoided in cats due to bronchospasm Loading: 400-600 mg/kg/day divided over 1-5 days PO with food; can be given per rectum if needed Maintenance: 20-30 mg/kg PO q 24 h Sodium bromide can be used if an IV form is necessary Propofol 1-3.5 mg/kg IV bolus, followed by CRI of 0.01-0.25 mg/kg/min* Keppra 20 mg/kg (up to 60 mg/kg) PO or IV q 8 h (*there is no evidence-based medicine to support this)
Decrease cerebral edema	Mannitol: 0.5-1 g/kg bolus over 20-30 min
Nutritional support	Moderate protein restriction 18%-22% for dogs and 30%-35% for cats (on dry matter basis); dairy or vegetable proteins preferred Vitamin B complex supplementation (1 mL/L IV fluid therapy) Multivitamin supplementation
Hepatoprotective therapy (for chronic conditions that are unable to be fixated-MVD, NCPH, MEHPSSs, etc.)	S-adenosyl-L-methionine: 17-22 mg/kg/day PO Ursodeoxycholic acid: 10-15 mg/kg/day PO Vitamin E: 15 IU/kg/day PO Milk thistle (silymarin): 8-20 mg/kg PO divided q 8 h L-carnitine: 250-500 mg/day PO (cats)

*Controversial.

CRI, Constant rate infusion; *HAVM*, hepatic arteriovenous malformation; *IHPSS*, intrahepatic portosystemic shunt; *MVD*, microvascular dysplasia; *NCPH*, noncirrhotic portal hypertension; *MEHPSSs*, multiple extrahepatic portosystemic shunts.

Metabolic acidosis (see ch. 128) can contribute to HE and should be corrected slowly with fluid therapy and, rarely, sodium bicarbonate. It is important to verify that concurrent respiratory acidosis does not exist prior to sodium bicarbonate therapy. Glucose should be supplemented in IV fluids, particularly in young puppies with PSS, where glycogen stores and gluconeogenesis are minimal. Therapy for acute, severe HE includes feeding nothing by mouth (PO), administering cleansing enemas with warm water and/or lactulose (see ch. 114), oral lactulose therapy, antibiotic therapy (metronidazole, ampicillin, or neomycin), and anticonvulsant therapy if necessary (see Table 284-2). Gamma-aminobutyric acid (GABA) and its receptors have been implicated in the pathogenesis of HE.[10] Using a benzodiazepine antagonist like flumazenil (0.02 mg/kg IV to effect) has been shown to be of benefit in humans with HE-induced comas. Mannitol should be considered in pets with severe HE or after seizure activity (see ch. 148).[10] In people, there is an association between HE and cerebral edema.[2,10]

Seizure control often is initiated with low-dose midazolam (a benzodiazepine that is preferred to diazepam due to the lack of propylene glycol as a carrying agent, which requires liver metabolism). Once seizures are controlled, loading with either phenobarbital, potassium bromide, sodium bromide, or levetiracetam (Keppra) can be considered (see Table 284-2 and ch. 35 and 260). A study found that significantly fewer (0/42) dogs pretreated with levetiracetam (20 mg/kg PO q 8 h for a minimum of 24 h preoperatively) experienced postoperative seizures after attenuation of CPSS, whereas 4/84 (5%) of dogs not pretreated with levetiracetam experienced seizures.[113] In 3 dogs with status epilepticus after PSS attenuation, a propofol bolus and constant rate infusion, combined with phenobarbital, led to recovery and discharge in all dogs over 7-9 days, without recurrent CNS signs.[114]

Lactulose, a disaccharide that is metabolized by colonic bacteria to organic acids, can be administered either by enema or PO. It promotes the acidification of colonic contents, trapping ammonia in the form of ammonium, while decreasing bacterial numbers and eliminating ammonium and bacteria in the feces. The osmotic effect results in catharsis, reducing fecal transit time and exposure to bacteria for proliferation and ammonia production. Antibiotics, such as metronidazole, neomycin, or ampicillin, decrease GI bacterial numbers, allowing for a further reduction in ammonia production. Metronidazole and ampicillin also decrease the risk of bacterial translocation and systemic infections. In pets with signs of bleeding or anemia, transfusion of packed red blood cells, whole blood, or fresh frozen plasma may be of benefit (see ch. 130). If there is evidence of HE, fresh whole blood is preferred, as stored blood contains a decreased number of clotting factors and elevated ammonia levels, potentially worsening HE.

Nutritional management is important, particularly in young animals with poor body condition. Diets should be readily digestible, contain a protein of high biologic value (enough to meet the animal's needs, but not to encourage HE), supply enough essential fatty acids, maintain palatability, and meet the minimum requirements for vitamins and minerals. Milk and vegetable proteins are lower in aromatic amino acids

(tyrosine and phenylalanine) and higher in branched-chain amino acids, such as valine, leucine, and isoleucine. These sources are less likely to precipitate HE.[2,10] Protein content of 18-22% for dogs and 30-35% for cats (dry matter basis) should be the goal, with dairy or vegetable proteins preferred.

Gastric bleeding/ulceration should be treated with acid receptor blockade (famotidine), proton pump inhibitor (omeprazole) +/- with sucralfate. Animals with IHPSS have a predisposition to develop GI ulcerations (Figure 284-11).[57,115] Use of lifelong gastric acid suppressant therapy in dogs with IHPSS decreases morbidity associated with GI bleeding. Nonsteroidal antiinflammatory drugs (NSAIDs) should be avoided in any dog with liver disease, but particularly those with IHPSS, as this could perpetuate GI ulceration.

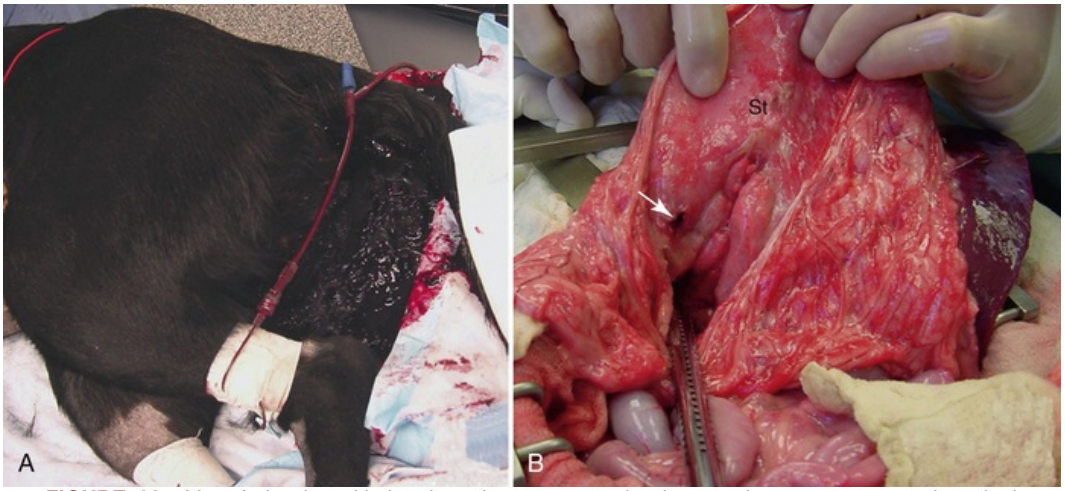


FIGURE 284-11 Labrador with intrahepatic portosystemic shunt and concurrent gastrointestinal ulceration. **A,** Severe hematochezia and melena requiring packed red blood cell transfusion. **B,** Exploratory laparotomy in the same dog demonstrating perforated ulcer (arrow) in the pyloric antral portion of the stomach (St).

Ascites and fibrosis can occur in pets with HAVM and NCPH, but rarely with PSSs unless there is severe hypoalbuminemia. If ascites is due to poor oncotic pressure, colloidal therapy should be considered. If ascites is due to portal hypertension, diuretic therapy and low sodium diets should be considered (see ch. 183). Additional sodium sources (particularly treats) can exacerbate ascites and should be avoided. Spironolactone is the initial diuretic of choice for its potassium-sparing effects. Furosemide also can be necessary but should be used with caution because it potentiates further hypokalemia. In some instances, therapeutic abdominocentesis is necessary to make the pet more comfortable and make ventilation easier (see ch. 90). A number of drugs theoretically could decrease connective tissue formation and hepatic fibrosis: prednisone (1 mg/kg PO q 24 h), D-penicillamine (10-15 mg/kg PO q 12 h), and colchicine (0.03 mg/kg PO q 24 h).

Supportive nutraceutical therapy has been recommended for a variety of liver diseases but is not necessary in portovascular anomalies that can be repaired surgically or interventionally. For those animals that do not have a corrective alternative (MVD, NCPH, multiple EHPSS) or when shunts remain patent (e.g., HAVMs, many IHPSSs), some nutraceuticals may be useful, including S-adenosyl-L-methionine (SAMe), ursodeoxycholic acid, vitamin E, and milk thistle/silymarin (see Table 284-2). SAMe has hepatoprotective, antioxidant, and antiinflammatory properties. It is important in membrane structure, fluidity, and function. It also aids in the metabolism of glutathione (GSH), which participates in many metabolic processes and plays a critical role in detoxification mechanisms of the cell. Depletion of hepatic GSH can indirectly cause toxic effects in these cells by increasing oxidative stress, particularly in cats. Vitamin E is another antioxidant and it should be considered to prevent and minimize lipid peroxidation within hepatocytes. Ursodeoxycholic acid is recommended for most inflammatory, oxidative, and cholestatic liver diseases and often is used in NCPH. It has antiinflammatory, immunomodulatory, and antifibrotic properties, as well as increasing fluidity of biliary secretions, promoting choleresis and decreasing the toxic effects of hydrophobic bile acids on hepatocytes. Silymarin is the active extract in milk thistle. There is an abundance of data in both *in vivo* and *in vitro* experimental animal models showing the antioxidant and free radical scavenging properties of silymarin.[10] Specifically, it has been shown to inhibit lipid peroxidation of hepatocyte and microsomal membranes and protect against gene damage by suppression of hydrogen peroxide, superoxide, and lipoxygenase. Silymarin

also increases hepatic GSH content, appears to retard hepatic collagen formation, and has hepatoprotective effects through inhibition of Kupffer cell function. Milk thistle has low toxicity and few side effects.

Outcomes with Medical Management Alone

In humans with congenital PSSs, the long-term prognosis without surgery is reported to be excellent. In veterinary medicine, one report describes 27 dogs with CPSSs that were evaluated after long-term medical management alone; 14/27 (51.8%) were euthanized, with a median survival time (MST) of 9.9 months (median age at the time of euthanasia: 20 months); 4/27 (14.8%) were lost to follow-up; and 9/27 (33%) survived long term with an MST of 56.9 months (4.7 years; range 5 months to >7 years) with many of those still alive at the time of evaluation.[45] Of 27 dogs, 9 had EHPSS, 17 had IHPSS, and 1 was complex. This distribution likely is due to the fact that more veterinarians are hesitant to treat IHPSS surgically than EHPSS due to reported complications and technical difficulty. Dogs with IHPSS treated only medically had CNS signs as or more often, GI signs less often, and urinary tract signs as often as they had prior to treatment. In contrast, dogs with EHPSS had clinical signs occur with similar or lower frequency once medicated.[45] Dogs treated medically had a significant decline in total protein, ALP, and ALT levels. Bile acids, BUN, albumin, and mean corpuscular volume did not show significant changes long term. Eleven of 17 (64.7%) dogs with IHPSS were euthanized, usually due to uncontrolled signs of HE, and 3/9 (33%) dogs with EHPSS were euthanized.

Prognostic indicators for medical management of dogs with CPSS include age at onset of clinical signs (longer survival in older dogs) and BUN level (higher level associated with longer survival); there were no correlations among bile acid levels, serum protein levels, albumin, ALP, ALT, MCV, and survival time. Overall, >50% of dogs treated medically could be expected to be euthanized within 10 months of diagnosis and ≈33% can survive long term with medical management alone, though clinical signs do not necessarily resolve. Euthanasia is most often due to persistent signs of HE, and in some cases, progressive hepatic fibrosis and subsequent portal hypertension.[63] A second study of dogs with CPSS found that 24/27 dogs (88%) treated only medically died or were euthanized, compared to 21/97 dogs (21.6%) treated surgically.[116] Survival in this study was not affected by age or shunt morphology. Considering these statistics, surgical or interventional attenuation, when possible, is the treatment of choice for congenital PSS.[116,117]

Surgical Management

Presurgical Patient Management

Many pets are debilitated, in poor body condition, and not neurologically stable prior to anesthesia and surgery. Intensive medical management as described earlier is recommended routinely, even in animals without clinical signs. Following diagnosis, the pet may be discharged to return for surgery weeks to months later. No time for performing surgery has been identified as ideal, but most surgeons prefer to have the pet treated medically first, in order to improve clinical signs, control encephalopathy, and gain weight prior to intervention. In addition to the potentially reduced risk of postoperative seizures, smaller debilitated pets are at risk for perioperative hypothermia, hypoglycemia, and complications associated with intraoperative hemorrhage. The use of preoperative anticonvulsant therapy remains a debated topic, and is often employed for patients that present with HE. Preliminary evidence shows that pretreatment with levetiracetam can decrease the risk of postoperative seizures and improve survival (see above).[113,118] It is not clear whether anticonvulsants should routinely be employed preoperatively while the patient is receiving appropriate medical therapy.

General anesthesia for animals with liver disease has been described elsewhere.[119] Briefly, anesthetic agents that are highly protein-bound or dependent on liver metabolism are avoided. In addition, glucose support is often initiated with anesthesia because these animals often are thin, debilitated, and have been fasted prior to surgery. Colloidal support often is used (particularly in IHPSS cases) with anesthesia induction (see ch. 130). Although plasma can be utilized without excessive expense in small pets, the authors prefer synthetic colloids (1-2 mL/kg/h IV) when possible to reduce the risk of blood transfusion reactions and perioperative thrombosis of the manipulated PSS that could theoretically result from excessive plasma administration. Additionally, since these patients are not routinely clinically hypocoagulable, and more data would support a hypercoagulable state, the use of plasma for colloidal support should not be recommended routinely. Perioperative antibiotics are recommended for these patients, who are young and immunologically incompetent, as well as the fact that an implant is being used. Many already receive antibiotics as part of the preoperative medical management regimen. Blood type and coagulation screens are obtained routinely, particularly in IHPSS, regardless of risk of bleeding.

Clipping of fur should be wide and should include the thorax (particularly for IHPSSs being treated surgically or when the anatomy of the shunt is unknown preoperatively) in order to prepare for a caudal sternotomy. Clipping of the ventral neck can be helpful if jugular catheterization is used because intraoperative central venous pressures are occasionally desired. Hypothermia should be anticipated and forced warm air or fluid blankets with or without warm water bottles should be used. Water bottles cool quickly, so they should be changed regularly. For interventional procedures both jugular veins (IHPSS) or the femoral artery (HAVM) should be clipped of fur for venous access.

Surgery

The goal of surgery for PSSs is to attenuate the abnormal vessel in order to reestablish blood flow through the hepatic parenchyma. Complete shunt attenuation remains the goal of surgery because partial shunt occlusion has a worse prognosis.[91,120] Unfortunately, the majority of affected pets have insufficient portal development to permit complete acute shunt ligation at surgery, and ≈32-52% of dogs with EHPSS and <15% of dogs with IHPSS have tolerated complete shunt attenuation (Figure 284-12).[91,120-122] Therefore, a delicate balance remains: shunt attenuation in order to increase portal blood pressure sufficiently to encourage development of portal perfusion without causing excessive portal hypertension. If portal hypertension occurs acutely, the patient could develop ascites, intestinal congestion, diarrhea, hypoxemia, and possibly bowel death. If portal hypertension occurs more chronically, when the portal vasculature fails to develop, multiple acquired PSSs may develop. The introduction of progressive occlusion devices can reduce the risk of acute portal hypertension, but it remains unclear if these devices reduce the development of chronic portal hypertension and subsequent multiple acquired shunts. Reportedly, 40-50% of dogs redevelop clinical signs following partial ligation of EHPSS, months to years after surgery (not including gradual occlusion devices).[26,120,123] It is not clear if these dogs had a worse prognosis because of the partial attenuation or the reduced portal vascular development present at the time of surgery that prevented complete acute attenuation. Further, it is often unclear whether these dogs had persistent shunting or developed acquired PSSs.[91]

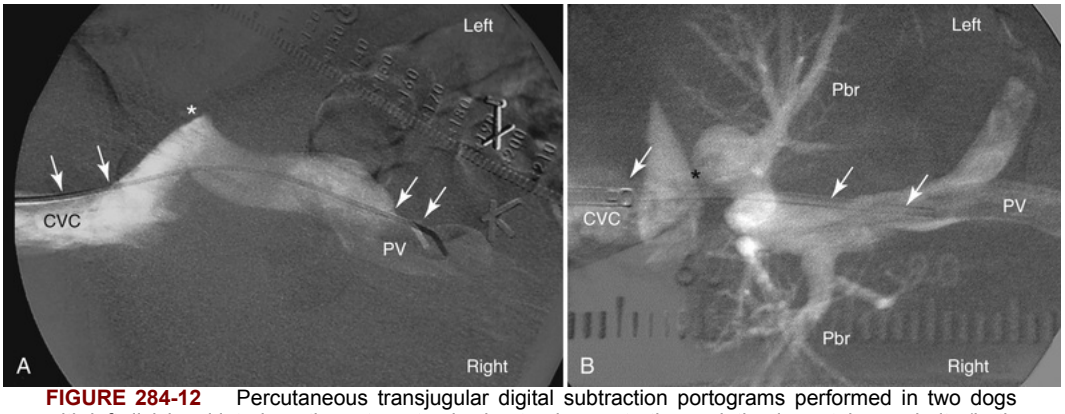


FIGURE 284-12 Percutaneous transjugular digital subtraction portograms performed in two dogs with left divisional intrahepatic portosystemic shunts, demonstrating variation in portal vascularity (both dogs in ventrodorsal position with head to the left). **A,** Portogram with catheter (arrows) through the shunt (*) and in the portal vein (PV) demonstrating the shunt entering the caudal vena cava (CVC) and no portal perfusion evident. **B,** Portogram with catheter (arrows) through the shunt (*) and in the PV demonstrating good portal perfusion via developed portal branches (Pbr) throughout the liver.

Following identification and careful dissection, the shunt is isolated and an encircling suture is placed as close to the systemic circulation (shunt termination) side as possible. Shunt attenuation in this location ensures that all portal vessels joining the shunt will be attenuated as well. Placement of the shunt occlusion on the portal vein side of the shunt (shunt origin) may permit continued shunting around the liver if any contributing branches are missed. The surgical procedure has been described in detail elsewhere.[123-131] It is important to note that following temporary shunt attenuation, intraoperative portal pressures >9-10 cm water above resting (preligation) pressures or absolute pressures >17-24 cm water have been associated with greater postoperative complications.[91,132,133] Clinical signs also have been used for determining if complete acute shunt occlusion can be tolerated. In one study, 11 of 12 nonencephalopathic dogs with clinical signs attributable only to ammonium biurate urolithiasis tolerated complete occlusion safely.[134] Animals with portal aplasia apparently are surviving due to hepatic arterial perfusion, often indicated by liver biopsies

describing hepatic arteriolar proliferation.[89,90] It is more likely that there is a wide spectrum of shunt size and portal vascular development in these pets, which would explain why a portion with PSSs have minimal clinical signs and can live long lives with or without medical therapy.

When performing surgery, complete abdominal exploration is indicated because animals with one congenital abnormality often have others. The urinary bladder should be carefully palpated to identify the presence of calculi that should be removed. Spay or castration is recommended. Liver biopsies have been recommended, though one study reported no ability to predict prognosis based upon preligation biopsy results alone.[89] The authors do not perform liver biopsies routinely; however, liver biopsy may be indicated when a macroscopic shunt cannot be identified with surgery or portography.

Extrahepatic Portosystemic Shunts

Following identification of the EHPSS, the surgeon may decide if complete attenuation is possible using portal pressure measurements, portal venography, and/or visual inspection. If complete acute shunt attenuation is possible, it is recommended; however, complete attenuation may increase the risk of the procedure.[91,120]

Gradual-occlusion devices, such as ameroid constrictors (ACs) and cellophane bands (CBs) have changed the way the majority of EHPSSs are managed. Historically, it was believed that the hygroscopic casein in ACs gradually absorbs peritoneal fluid, resulting in expansion that is concentric, not eccentric, due to a surrounding stainless steel ring (Figure 284-13). This produced complete shunt attenuation in 6/12 dogs at 1 month and an additional 3/12 dogs by 7 months of surgery.[128] However, different results, including partial occlusion and thrombosis, have been noted with ACs placed on dogs' iliac veins.[135] Furthermore, if shunt occlusion is too rapid (or if occlusion is affected by the amount of dissection needed for AC placement, the weight of the AC on the thin-walled PSS vessel, repeated resterilization of an AC,[136] or the size of the AC or extent of tissue reaction surrounding the AC[137]), multiple acquired PSSs could result, as has been reported in 17% of dogs following AC placement.[127,128] Reported complication rates are 7-20% and mortality rates are 0-17% following AC placement for EHPSS, with good to excellent outcomes in 94% of dogs and estimated median survival times of 152 months.[26,127,128,138,139] Dogs with incomplete shunt attenuation can still have a good prognosis: continued flow through the shunt after AC placement was identified in 21% in one study with good to excellent outcomes.[138] Compared with suture ligation, ACs have been demonstrated to reduce surgery times, as well as intraoperative complication rates.[138,140] With AC placement for EHPSS in dogs, CTA and perfusion scans have demonstrated smaller preoperative liver volumes to have the largest subsequent increases in volume, and hepatic arterial perfusion and portal scintigraphy both have correlated with successful shunt attenuation.[105]

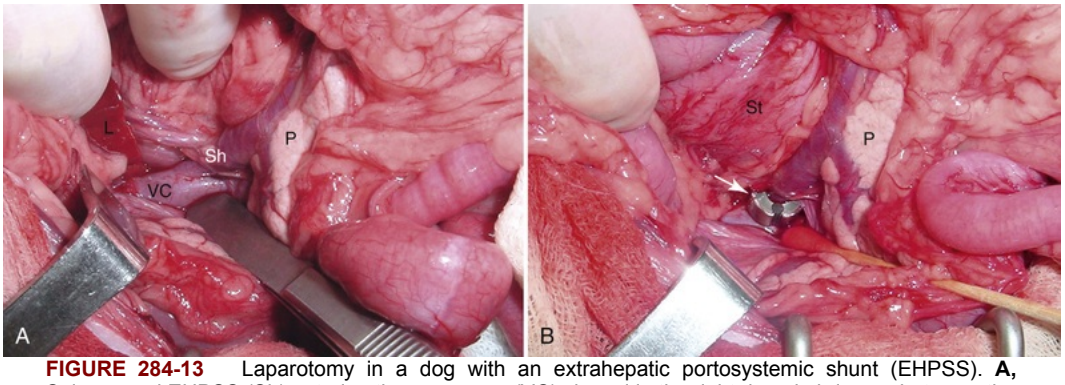


FIGURE 284-13 Laparotomy in a dog with an extrahepatic portosystemic shunt (EHPSS). **A,** Splenocaval EHPSS (Sh) entering the vena cava (VC) viewed in the right dorsal abdomen between the liver (L) and pancreas (P). **B,** The same dog following placement of an ameroid constrictor (arrow) at the shunt termination onto the VC. *St,* Stomach.

The alternative implant evaluated for gradual occlusion of EHPSS has been CBs. This inexpensive material is derived from plant cellulose and often is obtained from cigarette or giftwrap packaging. This material is inflammatory and causes progressive fibrosis around vessels. The material is easily sterilized and stored, lightweight (will not kink the PSS), and requires less dissection around the shunt. Recent evidence suggests

that most commercially available "cellophane materials" are not actually consistent with cellophane, the latter being distinguished from the others by visible striations (and confirmed using infrared spectroscopy).[141] The more progressive attenuation achieved with a CB in experimental studies[126] is hypothesized to reduce the incidence of acquired PSS.

Following shunt dissection and isolation, a three-layer folded piece of cellophane ≈3-4 mm in diameter is placed around the shunt and secured with hemoclips (Figure 284-14). Complete shunt occlusion appears to be possible without initial shunt attenuation during placement, and in fact partial attenuation at the time of CB placement could be associated with development of APSSs.[142]

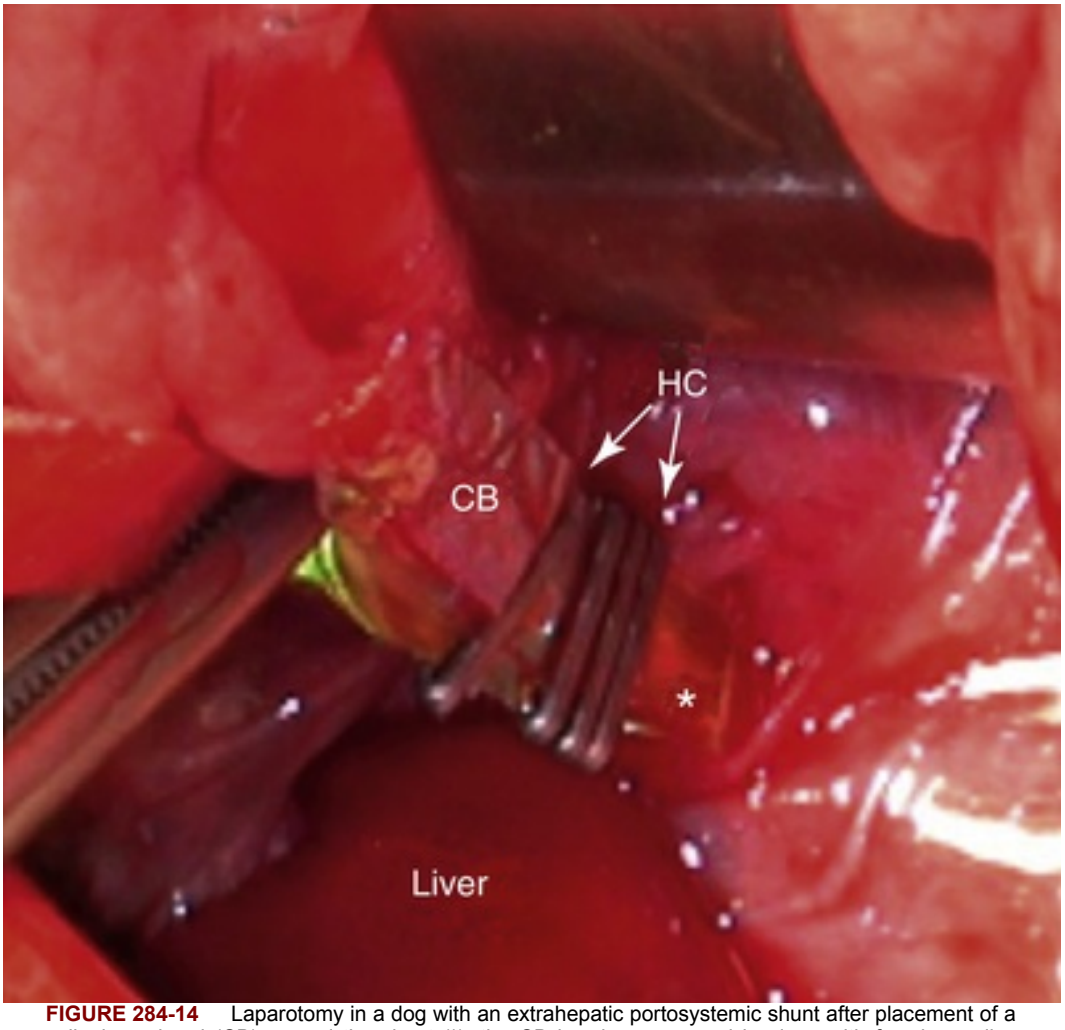


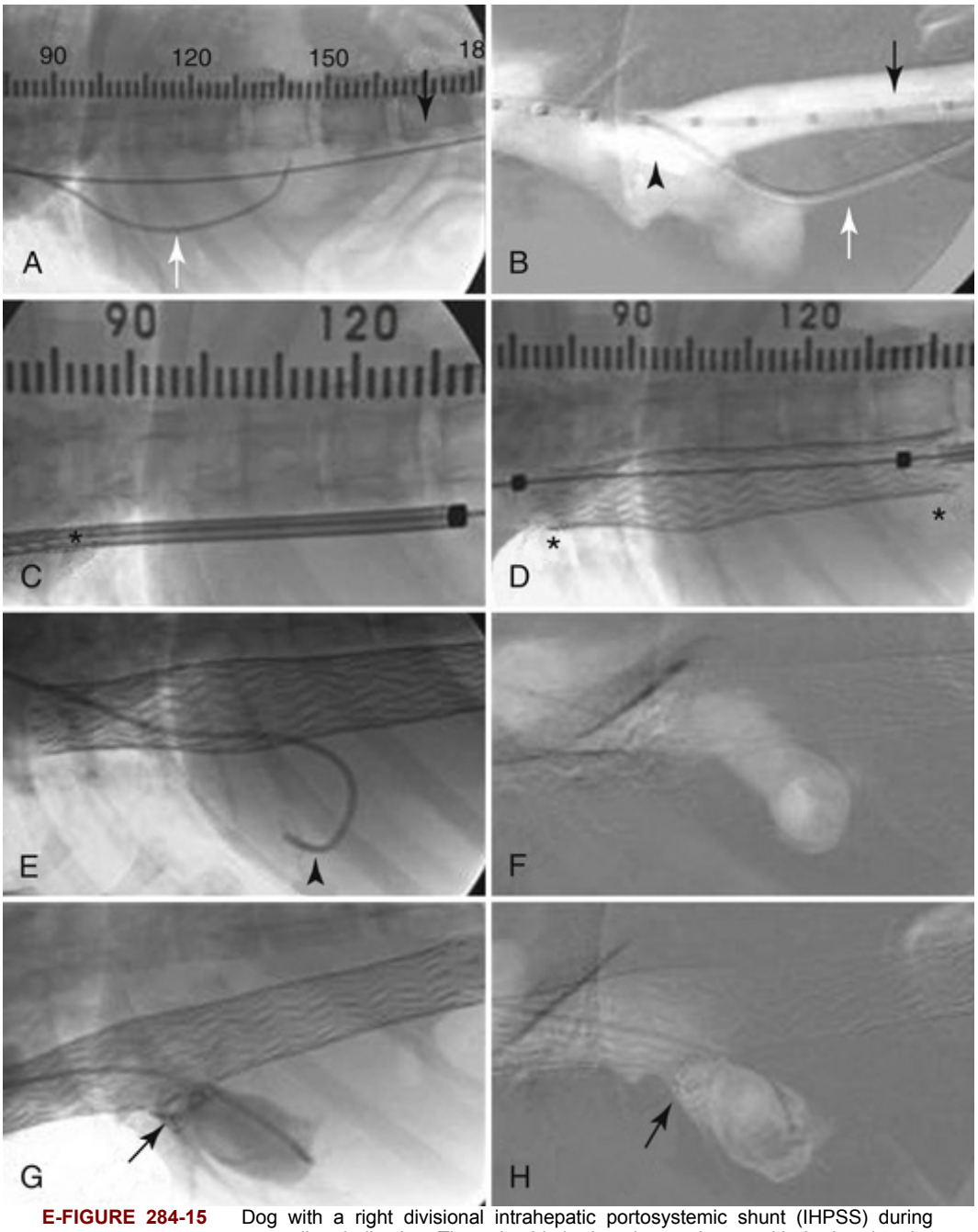
FIGURE 284-14 Laparotomy in a dog with an extrahepatic portosystemic shunt after placement of a cellophane band (CB) around the shunt (*); the CB has been secured in place with four hemoclips (HC). (Courtesy Dr. Eric Monnet.)

Complication rates are ≈10-13% and mortality rates 3-9% following CB of EHPSS, with good to excellent outcomes in ≈84% of dogs.[142,143] However, multiple APSSs were demonstrated in 3/16 dogs (19%) with elevated shunt fractions 6 weeks following CB placement.[144] In general, on review of the literature, it would seem that many dogs with PSSs can experience resolution of clinical signs with persistent shunting.[121,138,139,144]

Intrahepatic Portosystemic Shunts

Dogs and cats with IHPSSs represent a much more complex situation. These shunts typically are much larger, located within the hepatic parenchyma, and often are not readily apparent. Soft spots can occasionally be felt within the affected lobe where the often large IHPSS resides, but this may not help identify the ideal location for dissection. When treated surgically, left divisional shunts are commonly approached posthepatically

(cranial to the liver) because these often enter the left hepatic vein that enters the CVC at the level of the diaphragm. For right and central divisional shunts that often enter the CVC intrahepatically, the surgical approach is often performed prehepatically (caudal to the liver) in order to dissect the contributing portal vein branch (which typically is much larger than the left portal branch). Various preoperative (CTA, MRA) and intraoperative (portovenography) methods can help identify shunt anatomy. Surgical options include surgical dissection and attenuation with suture, AC, CB, or hydraulic occluder (HO), complete IHPSS occlusion with jugular venograft creation of an EHPSS, temporary hepatic inflow occlusion with intravascular dissection, and percutaneous transvenous coil embolization (PTCE) via the jugular vein (the latter described in detail in ch. 123) (E-Figure 284-15).[2,57,132,143,145-151]



E-FIGURE 284-15 Dog with a right divisional intrahepatic portosystemic shunt (IHPSS) during percutaneous transvenous coil embolization. The animal is in dorsal recumbency with the head to the left in each image. **A,** A guidewire (black arrow) is placed from the jugular vein, through the cranial and caudal vena cava (CVC) and extending down the CVC. A second catheter is extending from the jugular vein, through the cranial and CVC, the right hepatic vein, the portosystemic shunt, and into the portal vein (white arrow). **B,** An angiogram being performed under digital subtraction angiography fluoroscopy. Contrast material is in both the CVC and portosystemic shunting vessel. The mouth of the

shunt is apparent (arrowhead). Using a marker catheter (black arrow), the CVC measurements can be extrapolated for appropriate stent size selection. **C,** The constrained stent and delivery system (asterisk) are advanced over the wire and across the mouth of the shunt. **D,** The stent is then deployed in the selected location with each end confirmed to extend beyond the shunt (asterisks). **E,** The mouth of the shunt is again selected with a catheter (arrowhead). **F,** Repeat digital subtraction angiography confirms that the stent is covering the entire mouth of the shunt. **G,** Thrombogenic coils are placed through the catheter and into the shunting vessel (arrow) until portal pressures have increased sufficiently. **H,** Repeat digital subtraction angiogram is performed, and final portal pressures are recorded.

Surgical complication rates are substantially higher in IHPSS (29-77%) compared with EHPSS.[123,152] Mortality rates are 6-23% following ligation or 0-9% following placement of an AC, with good to excellent outcomes in ≈75-100% of dogs following ligation and ≈70-90% following AC placement.[147,153,154] Good to excellent outcomes were reported in only 50% of dogs that underwent CB with a 55% perioperative complication rate and a 27% perioperative mortality rate.[143]

Persistent shunting and unreliability of progressive occlusion devices led to investigating HOs, an adjustable silicone cuff placed around the IHPSS and attached to actuator tubing, and a vascular access port placed SC at the time of surgery (Figure 284-16). This device can be manually inflated with saline using a Huber needle placed transcutaneously into the port in the awake dog weeks to months after placement, as needed, to slowly inflate the cuff and progressively occlude the shunt.[155] Immediate survival was 100% for 10 dogs undergoing HO attenuation of intrahepatic shunts with a 20% intraoperative complication rate, and surgical revisions were needed in 3 of 10 dogs before device modifications were made. Resolution of clinical signs, and long-term survival, were documented in eight dogs,[155] but persistent shunting, APSSs, and/or hepatic dysfunction was suspected based on persistently elevated bile acids (4/8) and positive scintigraphy scans (5/8) 2 weeks following complete HO closure.[21,147,155,156]

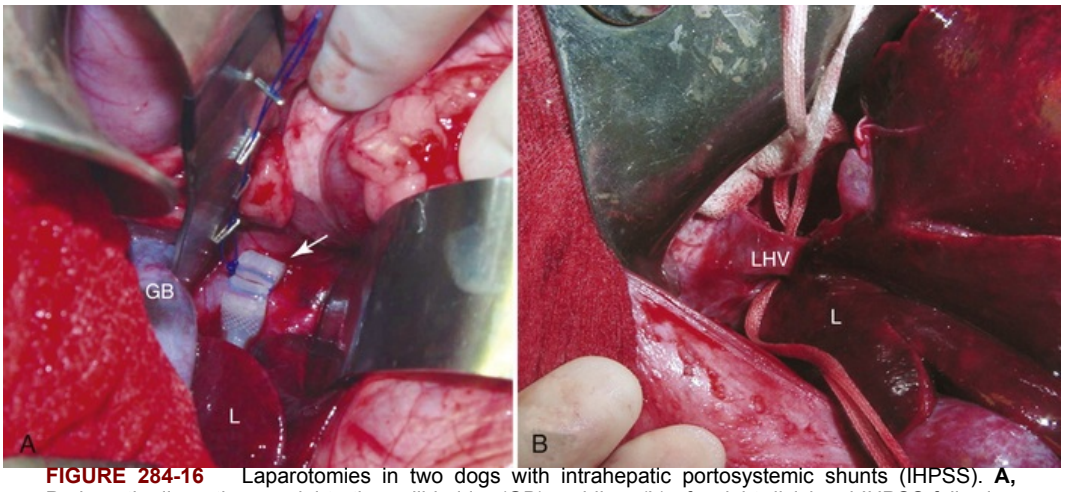


FIGURE 284-16 Laparotomies in two dogs with intrahepatic portosystemic shunts (IHPSS). **A,** Prehepatic dissection caudal to the gallbladder (GB) and liver (L) of a right divisional IHPSS following placement of a hydraulic occluder (arrow) secured in place with polypropylene suture. **B,** Posthepatic dissection of the left hepatic vein (LHV) between the liver (L) and diaphragm for a left divisional IHPSS before placement of a suture. (**A,** Courtesy Dr. Chris Adin.)

Complications Following PSS Attenuation

Intraoperative complications typically are associated with anesthetic complications or hemorrhage during shunt dissection. Postoperative complications associated with PSS usually include neurologic abnormalities, acute portal hypertension, and persistent shunting (either through the original shunt or via the development of APSSs). Postoperative seizures not associated with HE or hypoglycemia have been reported in up to 12% of dogs.[118] Preoperative phenobarbitone appeared to reduce the severity but not the incidence of neurologic sequelae following shunt surgery in one study.[118] In another study, levetiracetam 20 mg/kg PO q 8 h for ≥24 h preoperatively significantly reduced the incidence of postoperative seizures in dogs with EHPSS.[113] Postoperative seizures occur in dogs and cats, are independent of the type of attenuation performed, can occur days later, and do not appear to be caused by the original HE. Reports are conflicting as to whether

older animals are at increased risk.[118,157,158] Possible explanations include the acute removal of endogenous benzodiazepines or changes in brain amino acid concentrations or ratios.[10,11,159] All patients having undergone surgery for PSS should be monitored closely for neurologic sequelae. There is no agreed-upon algorithm for treating these signs; however, intensive management should be instituted immediately with anticonvulsant therapy and/or propofol boluses (1-3.5 mg/kg IV) followed by propofol IV constant rate infusions (CRIs) (0.1-0.2 mg/kg/min or higher).[160] Phenobarbital loading is preferred because therapeutic plasma levels can be achieved rapidly and levels can be readily monitored. The concern over using a potentially hepatotoxic medication in a patient with a PSS is of less concern when the expectation is for short-term use. Recumbent, sedated, and possibly comatose pets are difficult to load with potassium bromide, and levetiracetam (Keppra) levels are not yet well understood or measurable in dogs.

Ventilation may be necessary in some pets and others can take weeks or longer to recover. Acepromazine has been reported to help decrease seizure activity in dogs without PSS, contrary to the previous concern of acepromazine decreasing the seizure threshold.[161] It has been used at low dosages (0.005-0.01 mg/kg IV) for postprocedural seizures. In general, the prognosis is considered poor; however, many can recover with time and aggressive supportive care. Recovery might not be complete and some could still display some degree of neurologic dysfunction in the long term. Reports have described 6 of 10 dogs and 9/11 dogs recovering completely following postligation neurologic dysfunction, albeit some incompletely.[118,143]

Some degree of portal hypertension can occur following acute partial or complete shunt attenuation as characterized by mild ascites with or without incisional drainage. Life-threatening forms, however, are fairly uncommon, particularly with the introduction of progressive attenuation devices. Worrisome postoperative signs include vomiting, abdominal distension, progressive ascites, abdominal pain, and hypotension. These can lead to shock and disseminated intravascular coagulation. Immediate removal of the attenuating device is recommended in those dogs and cats that do not respond to initial intensive supportive care; however, once clinical signs have been recognized, patient recovery is uncommon. The use of anticoagulants and/or thrombolytics postoperatively to prevent or manage these situations has not been sufficiently evaluated. Portal hypertension has not been a problem with the IHPSS PTCE technique in general.[21] This is likely due to the fact that shunt attenuation occurs post-sinusoidally at the shunt orifice on the CVC. Increased pressures generated at this location seem to be relieved through intrahepatic venous collaterals before (at lower pressures) pre-sinusoidal portal hypertension is experienced. This has the dual effect of reducing the risk of portal hypertension complications and reducing the likelihood of restoring complete hepatic portal flow without some degree of shunting; this may be a reasonable trade-off between risk and benefit and likely occurs with any type of IHPSS attenuation performed at this location. This phenomenon also likely explains the persistence of abnormal clinical, biochemical, and scintigraphic evaluations following what was perceived to have been a complete shunt occlusion at the time of the procedure using a variety of shunt attenuation techniques.[21]

Postoperative hypoglycemia (see ch. 61) and hypothermia (see ch. 49) usually can be prevented with appropriate patient care. Recently, hypoglycemia was reported in 44% of dogs following EHPSS surgery and approximately one third did not respond to dextrose supplementation. Some of these animals can respond to supraphysiologic glucocorticoid administration (dexamethasone 0.1-0.2 mg/kg IV once) as well as hastened anesthesia recovery. A relative glucocorticoid insufficiency (see ch. 133) has not been documented in these animals.[162]

Recurrence or persistence of clinical signs is the most common long-term complication seen after treatment of PSS. Many reports do not have sufficient long-term follow-up to know the true incidence of these problems. Recurrence of clinical signs suggests that the original shunt remains patent, another shunt was present originally, an incorrect vessel was attenuated, multiple acquired shunts have developed, concurrent hepatic parenchymal disease is present, or concurrent neurologic disease is present. Serum biochemistry and liver function tests can confirm this suspicion but additional imaging is needed to identify the cause. If imaging confirms shunt occlusion without APSSs, a presumptive diagnosis of PVH/MVD can be made.

Dogs with IHPSS have a separate but important additional potential complication: severe GI ulceration and bleeding, the most common cause of long-term morbidity and mortality in one case series.[21] Following the introduction of lifelong gastric acid-suppressing therapy in IHPSS dogs, mortality from GI ulceration in our cases decreased from 25% to 3.2%. There are many theories as to why GI ulceration occurs so commonly in dogs with IHPSS (e.g., hypergastrinemia, abnormal GI blood flow, hypoprostoglandinemia, poor mucosal integrity, abnormal mucus production, abnormal cell turnover). Hypergastrinemia does not seem to be the cause.

Surgical Management of Feline Portosystemic Shunts

Perioperative management of cats is similar to dogs; however, a higher frequency of neurologic signs both preoperatively and postoperatively, despite appropriate medical treatment, has resulted in use of anticonvulsant therapy preoperatively in cats. Levetiracetam or phenobarbital can be used, due to potential respiratory complications associated with the use of potassium bromide. Surgical management of PSSs in cats is technically similar to dogs in terms of shunt identification and methods of attenuation. Although some surgeons use suture ligation, most use AC or CB in cats even though there are some concerns regarding the feline inflammatory response to such devices being sufficient to consistently result in progressive fibrosis and occlusion of a shunt.

Like in dogs, the perioperative mortality rate for feline EHPSS is low.[56,163,164] Two critical differences between PSS management in cats (compared with dogs) are the high perioperative complication rates and the worse long-term outcomes, particularly due to continued neurologic sequelae. Complication rates have been approximately 37-60% (neurologic sequelae) following suture ligation, 8-77% following AC placement, and in 1/5 cats and 3/9 cats following use of CB.[56,143,163-166] Neurologic signs include seizures in 8-33% of cats and central blindness (usually transient) in up to 44%.[52,143,163-165] Lower intraoperative mesenteric portography scores (reduced portal perfusion) recently have been shown to be associated with a higher incidence of post-attenuation neurological complications.[166] A more recent, separate classification of splenosystemic shunts in cats has been described, predominantly identified in older spayed female cats often with concurrent hepatopathies that may have been associated with portal hypertension; this is a different population of PSS patients and therefore, treatments will vary accordingly.[167]

Outcomes must be interpreted with caution due to different follow-up durations; however, fair to excellent outcomes have been reported in 75% of cats following suture ligation, 25-75% following AC placement, and 66% and 100% (5/5) following CB placement.[52,143,163-165] Many cats have a good clinical outcome despite persistent biochemical signs of liver dysfunction: about 33-66% of cats have had abnormal liver function testing and 57% have had persistent shunting postoperatively.[143,163,164] The contrary is also true because some cats with persistent CNS dysfunction show normalized liver function test results.[56] In that same report, approximately one third of cats were euthanized within 1 year due to persistent CNS dysfunction following AC placement, despite most having normalized liver function test results.[56] IHPSSs are rare in cats, making predictions on outcome difficult. Feline IHPSS can be treated similarly with suture, AC, CB, or transvenous coil embolization.[56,143,145,163,164]

Surgical and Interventional Treatment of Hepatic Arteriovenous Malformations

HAVMs are rare vascular anomalies involving multiple arterial communications to the portal vein (Figure 284-17). Because they usually involve multiple, rather than single, communications with a central nidus, or "nest," the term *malformation* rather than *fistula* is appropriate. These communications are usually from the hepatic artery but also have involved the gastroduodenal artery, left gastric artery, and phrenic arteries. Angiography, CTA, or MRA helps identify the origin and course of these numerous vessels (Figure 284-18). Due to the high-pressure arterial blood shunting to the portal vein, there is severe, chronic portal hypertension (often with subsequent massive ascites) that results in multiple APSSs to decompress the portal vein, as discussed in detail earlier. Multiple APSSs have been observed in every dog with HAVM.

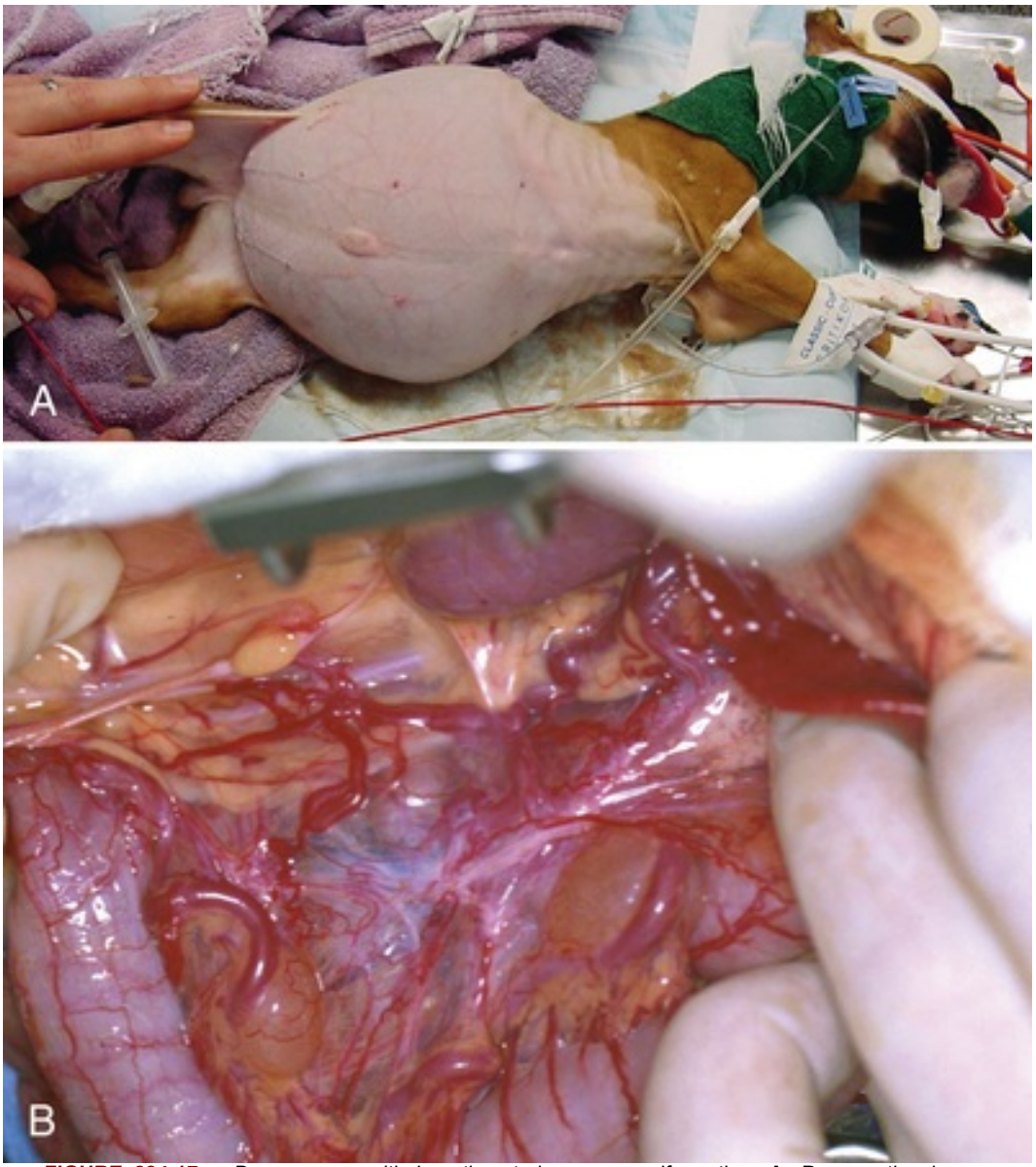


FIGURE 284-17 Boxer puppy with hepatic arteriovenous malformation. **A,** Preoperative image demonstrating severe abdominal distension due to ascites, and marked muscle wasting. **B,** Intraoperative image following abdominal fluid removal, showing multiple acquired extrahepatic portosystemic shunts resulting from severe portal hypertension.

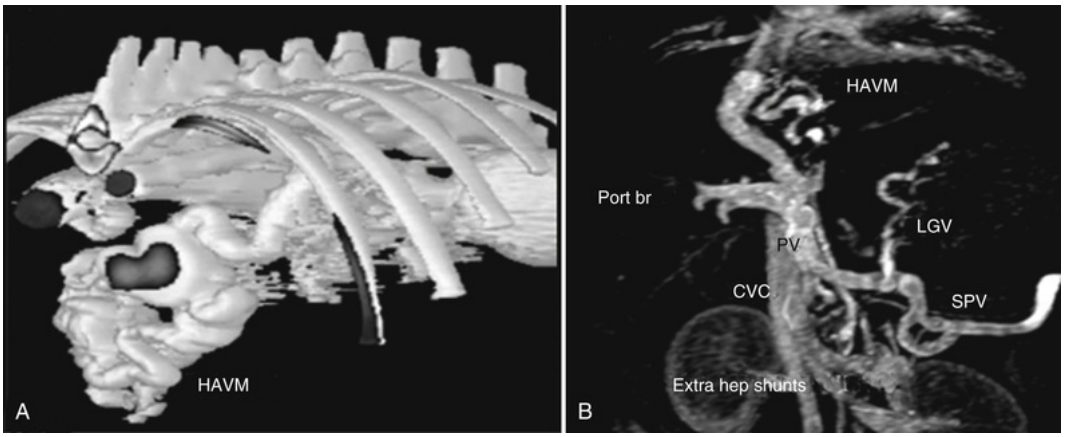


FIGURE 284-18 **A,** Three-dimensional reconstructed computed tomography angiogram of a dog with a hepatic arteriovenous malformation (HAVM). **B,** Magnetic resonance angiogram of a different dog with an HAVM demonstrating the left gastric vein (LGV), splenic vein (SPV), portal vein (PV), portal branches (Port br), caudal vena cava (CVC), and acquired multiple extrahepatic portosystemic shunts (Extra hep shunts).

Treatments for HAVM have included liver lobectomy, ligation of the nutrient artery, or fluoroscopically-guided glue embolization of abnormal arterial vessels.[24,168] Most HAVMs are located in the right or central liver lobes, and 25% have involved two lobes. Lobectomy can be challenging because of vascularity and proximity to the gallbladder and CVC (Figure 284-19). Temporary occlusion of the portal vein and celiac artery (and often the cranial mesenteric artery) is recommended during partial lobectomy to reduce intraoperative hemorrhage.[168] In addition, lobectomy may be contraindicated if the HAVM involves the majority of the liver parenchyma, because the remaining liver mass after arteriovenous malformation (AVM) resection might not provide sufficient hepatic function. For glue embolization of HAVM (E-Figure 284-20), the procedure is described in ch. 123. More recently the authors have been investigating venous occlusion of HAVM, as these vascular anomalies resemble the large pelvic AVMs in humans that can benefit from a venous (rather than arterial) embolization. The concept is that a single, proximal draining vein immediately distal to the AVM nidus will provide occlusion and such occlusion could be safer and more effective than attempting to embolize the innumerable small arterial feeding branches just proximal to the nidus. Although this approach is promising, only a single case has been treated to date.[169]

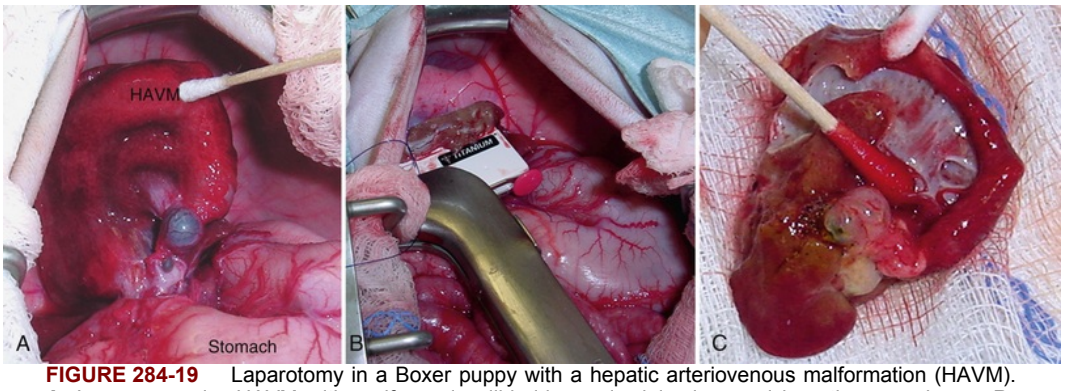
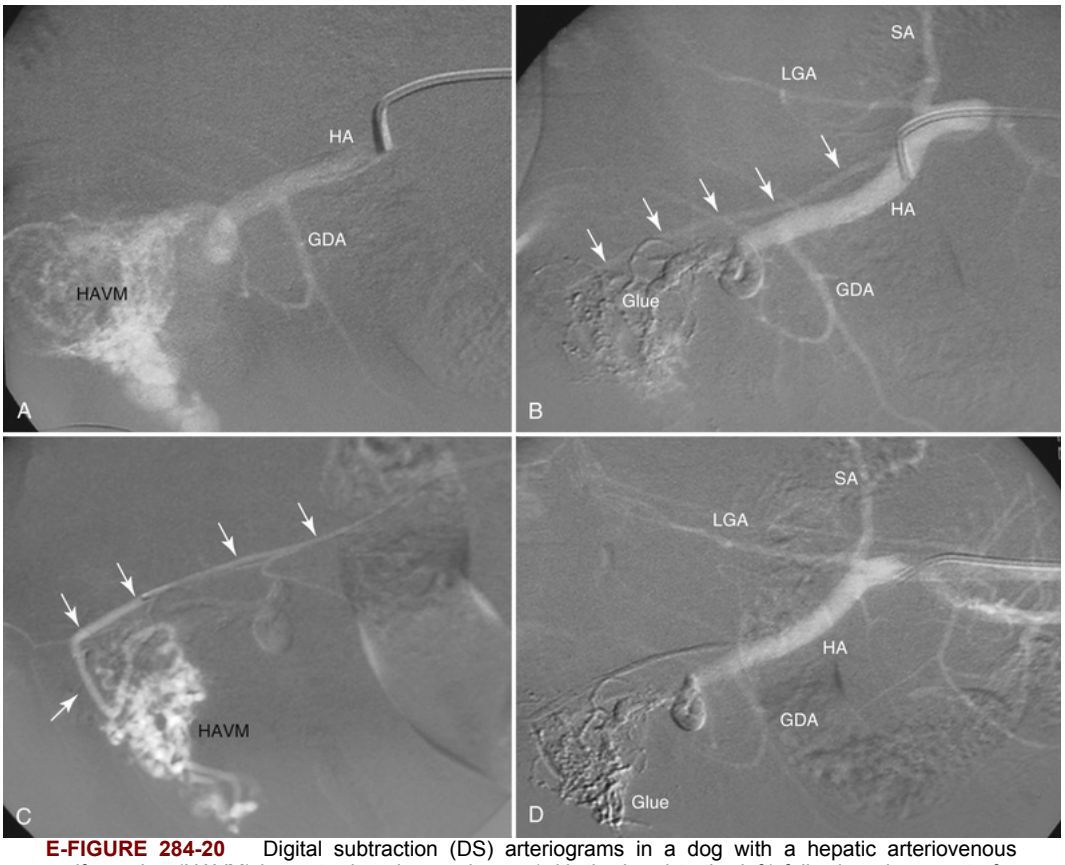


FIGURE 284-19 Laparotomy in a Boxer puppy with a hepatic arteriovenous malformation (HAVM). **A,** Large, vascular HAVM with malformed gallbladder and minimal normal hepatic parenchyma. **B,** Thoracoabdominal stapler across the base of the HAVM after stapling and excision of the involved lobe. **C,** Sectioned HAVM following excision demonstrating vascular dilations within the parenchyma.



E-FIGURE 284-20 Digital subtraction (DS) arteriograms in a dog with a hepatic arteriovenous malformation (HAVM) in ventrodorsal recumbency (with the head to the left) following placement of a 4-Fr catheter in the hepatic artery. **A,** DS hepatic arteriogram demonstrating enlarged hepatic artery (HA) and normal gastroduodenal artery (GDA) with large, vascular HAVM and little perfusion to the hepatic parenchyma. **B,** Repeat DS hepatic arteriogram following glue embolization of the HAVM demonstrating improved perfusion of the splenic (SA) and left gastric arteries (LGA) with reduced HAVM perfusion and appearance of a previously unidentified contributing vessel (arrows). **C,** DS arteriogram of contributing branch (arrows) demonstrating substantial HAVM filling. **D,** Repeat DS hepatic arteriogram following glue embolization of contributing branch confirming complete HAVM embolization.

Complications of surgery include hemorrhage, portal hypertension, systemic hypotension, bradycardia, and portal or mesenteric vein thrombus formation.[24] Perioperative survival was 100% in dogs undergoing glue embolization, with or without partial hepatectomy, and 75% to 91% of dogs undergoing surgery alone.[24] Long-term outcome was fair or good for 38% to 57% of dogs treated with surgery alone and 100% for a small number of dogs treated with glue embolization. Overall, 75% of dogs continue to require dietary or medical management of clinical signs due to patent acquired EHPSS.[24] Recurrence of arteriovenous communications can occur and recurrence of clinical signs has been seen requiring additional embolization procedures. Long-term survival is considered fair to good with this interventional technique, but too few cases have been performed to be certain.

Postoperative Care

After surgery or IR treatment, patients are maintained on IV fluids until they are eating and drinking. Dextrose is added to the fluids when blood glucose is <80 mg/dL. Patients are monitored for hypoglycemia (see ch. 61), hypothermia (see ch. 49), delayed anesthetic recovery, hemorrhage (see ch. 135), seizures (see ch. 35), and signs of portal hypertension. Animals usually require opioid analgesics such as buprenorphine for 1 to 3 days after surgery, although no analgesics have been necessary following PSS coil embolization. Sedation with a low dosage (0.005-0.02 mg/kg IV) of acepromazine might be necessary if dogs are vocalizing or showing abdominal splinting, as these activities will increase portal pressure. Acepromazine does not seem to precipitate seizures in dogs with shunts (and may even prevent them); however, it should not be used in hypotensive animals.[161]

A protein-restricted diet, antibiotics, and lactulose are continued after surgery until liver function improves.

Weaning protocols vary among surgeons and no ideal protocol has been demonstrated. Weaning may be further delayed for gradual occlusion devices, particularly the CB that has the slowest attenuation rate. Biochemical panels are evaluated 1 month after surgery. If liver functional parameters are normal, medical management is then weaned over 2-4 weeks. At 3 months, SBAs are evaluated in EHPSS dogs and cats. This is not routinely done in IHPSS dogs, or dogs with HAVMs, particularly if the patients are doing clinically well and are able to be weaned off of medical management because persistent shunting is common; instead, in these patients, preprocedural and postprocedural protein C levels have been monitored instead along with routine complete blood count and biochemistry values.[112] If bile acid concentrations are moderately increased, animals are rechecked 5 to 7 months after surgery. Some clinicians recommend supplementation with silymarin (milk thistle) or S-adenosyl-L-methionine because of their hepatoprotective and antioxidative effects (see Table 284-2); clinical studies of efficacy in animals with congenital PSSs or PVH are lacking.[171]

Patients are weaned off medical therapy typically 1 month after IR treatment, and this weaning process takes approximately 1-2 months starting with the metronidazole, then the lactulose, then transitioning to an adult maintenance food (see ch. 180). If this is all well tolerated, blood count and serum protein C and biochemical parameters improve (mean corpuscular volume; albumin, BUN, cholesterol, glucose), and no return of clinical signs occur, then the outcome is considered good, regardless of bile acids test results. It has been shown repeatedly that return of bile acids to normal after PSS attenuation is not necessarily correlated with long-term outcome.[26,83,120,152]

Prognosis

Prognostic indicators, outcomes, and survival are described in Table 284-3.[170]

TABLE 284-3

Reported Prognosis for Hepatic Vascular Anomalies

HEPATIC VASCULAR ANOMALY	PROGNOSIS
Medical management[45]	The **prognosis** for medical management alone is *guarded to poor* due to progressive hepatic atrophy and progressive clinical signs. **Prognostic indicators** for animals with medical management alone: age at onset of clinical signs (older → longer survival), BUN (higher level → longer survival). No correlation between survival time and bile acid levels, serum protein levels, albumin, ALP, ALT, or MCV.
EHPSS[26,52,67,83,121,125,138,142,143]	**Mortality rates:** 2-32% (ligation), 7% (ameroid constrictor placement), 6-9% (cellophane banding). **Age** has been shown *not* to be associated with long-term outcome: older dogs (>4 years) have done as well as younger dogs at the time of surgery. The most common **cause of death** after PSS attenuation is severe persistent neurologic signs. Other causes include intraoperative hemorrhage, postoperative coagulopathy, portal hypertension, and hemorrhagic gastroenteritis. In dogs undergoing **ameroid constrictor placement,** preoperative hypoalbuminemia has been associated with persistent postoperative shunting. **Other factors:** Preoperative hypoalbuminemia or leukocytosis, occurrence of seizures after surgery, and persistent shunting at 6-10 weeks after surgery are reported to be predictive of poor long-term outcome.
IHPSS[21,46,67,120,123,132,133,143,152,153,172-174]	Reported **median survival times** range between 1 and 3 years. **Better short-term outcome and lower risk of complications** have been noted in association with body weight (>10 kg), and total protein (>4 g/dL), serum albumin (>2.6 g/dL), and BUN (>7.4 g/dL) levels. **Better long-term survival** has been associated with higher PCV and total protein (>4 g/dL). **Poorer long-term outcome** has been associated with preoperative hypoalbuminemia or leukocytosis, occurrence of seizures after surgery, and persistent shunting at 6-10 weeks after surgery. **Postoperative complications** have been reported to be as high as 77% with

	surgery, with short-term mortality ranging from 11-28%. **Overall mortality rates** range from 23-63.6%. In dogs with IHPSS, postoperative serum bile acid levels returning to normal have *not* been associated with short- or long-term survival (have remained elevated in dogs with improved clinical signs, irrespective of complete or partial ligation). **Perioperative mortality during the PTCE procedure** has declined to <5%, with long-term mortality <30% (<15% since initiating lifelong gastric acid suppressant therapy). **Gastrointestinal (GI) ulceration and bleeding** is the most common cause of long-term morbidity and mortality in these patients. With lifelong gastric acid suppression therapy, mortality from GI ulceration has decreased from 25% to 3.2%.
HAVM24,169	**Survival:** Dogs with HAVM have had a periprocedural survival rate of 100% with glue embolization, with or without hepatectomy, and 75%-91% with surgery alone. **Long-term outcome** has been fair or good for 38-57% of dogs (surgery) alone and closer to 70% (glue embolization). Serial embolization procedures may be necessary as arterial tributaries open up. Overall, 75% of dogs continue to require dietary or medical management of clinical signs regardless of approach. It is possible that these patients could benefit from caval banding if the portal system is well-developed.
MVD/PVH25	**Survival:** 22/24 (92%) have had good long-term survival or have died of reasons unrelated to MVD.
NCPH23	**Survival:** 13/33 have survived long term (40%), but many were euthanized due to findings at surgery without attempting medical management. The overall prognosis should be considered favorable.
Feline PSS5,41,42,56,145,163,164,175,176	**Perioperative mortality rates:** 0-23% after attenuation. **Postoperative complications** are reported in up to 75% of cats. The most common are neurologic dysfunction, including generalized seizures and central blindness, which can resolve a few months after surgery. **Outcome.** Of surviving cats available for follow-up, good or excellent long-term outcome has been reported in 66-80% undergoing various attenuation techniques. Excellent outcome has been reported in 25% of cats with persistent shunting; conversely, continued or recurrent neurologic abnormalities have been reported in 57% of cats with normal scintigraphy or hepatic function tests. Persistent shunting is common in cats after the procedure, likely due to the development of multiple EHPSS. Despite the higher rate of complications in cats, the mortality rate is low, comparing favorably to dogs.
Acquired PSS3,5,22,23,173	**Ligation of the individual shunts** is *not* considered appropriate or effective since they are typically relieving portal hypertension. **Caval banding** (surgical constriction of the caudal vena cava cranial to the EHPSS) to redirect blood flow to the portal vein has been attempted. Complications that can occur include ascites, hindlimb edema, development of other portoazygos shunts, and persistent poor portal perfusion. Survival times in these cases, compared to those treated medically, are similar. **Multiple EHPSSs have been reported to occur after ameroid placement** in both dogs and cats for single congenital EHPSS in nearly 10%-20% of cases. Treatment should be aimed at controlling the clinical signs of HE and slowing the progression of the liver disease (typically hepatic fibrosis).

ALP, Alkaline phosphatase; *ALT*, alanine aminotransferase; *BUN*, blood urea nitrogen; *EHPSS*, extrahepatic portosystemic shunt; *HAVM*, hepatic arteriovenous malformation; *HE*, hepatic encephalopathy; *IHPSS*, intrahepatic portosystemic shunt; *MCV*, mean corpuscular volume; *MVD*, microvascular dysplasia; *NCPH*, noncirrhotic portal hypertension; *PCV*, packed cell volume; *PSS*, portosystemic shunt; *PTCE*, percutaneous transvenous coil embolization; *PVH*, portal vein hypoplasia; *SBA*, serum bile acid.

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CHAPTER 285

Metabolic Diseases of the Liver

Penny J. Watson

Introduction

The liver is centrally involved in many metabolic pathways in dogs and cats (see ch. 280 and 281). It is therefore not surprising that the liver is affected by many metabolic diseases. There are notable species differences in many of the liver's metabolic pathways, which are particularly marked between cats and dogs. This could partly explain why the metabolic diseases seen in dogs and cats often are very different.

A metabolic hepatopathy could be defined as any insult to the liver due to accumulation of products of normal or abnormal metabolic pathways. This encompasses primary and secondary conditions and there is an overlap between these two. For example, a secondary, clinically insignificant accumulation of fat (steatosis) due to primary familial hyperlipidemia in a dog may be associated with development of gallbladder mucocele and clinically significant biliary stasis. Copper accumulation also can result in primary liver disease in true copper storage disease, or can be secondary to dietary overload and biliary stasis, but in both cases copper accumulation can lead to hepatocyte necrosis, particularly if accompanied by another insult such as nonsteroidal anti-inflammatory drug toxicosis.

Vacuolar Hepatopathies, Steatosis, Hyperlipidemia and Feline Hepatic Lipidosis

Introduction

The most common predominantly secondary metabolic hepatopathies in small animals are the vacuolar hepatopathies, where hepatocytes become loaded with fat (steatosis) or glycogen or water (hepatocellular swelling, or cloudy swelling).[1] There are histological features that help differentiate the types of vacuolation (Figure 285-1), but this can be challenging and special stains are necessary to be certain (periodic acid–Schiff [PAS] for glycogen and oil red O for fat). Several lysosomal storage diseases in dogs and cats also lead to hepatocyte vacuolation. Cloudy swelling occurs when hepatocytes are injured and less able to maintain fluid homeostasis. If hepatocyte swelling is severe and chronic, it can cause hepatocyte death, fibrosis, and even cirrhosis.

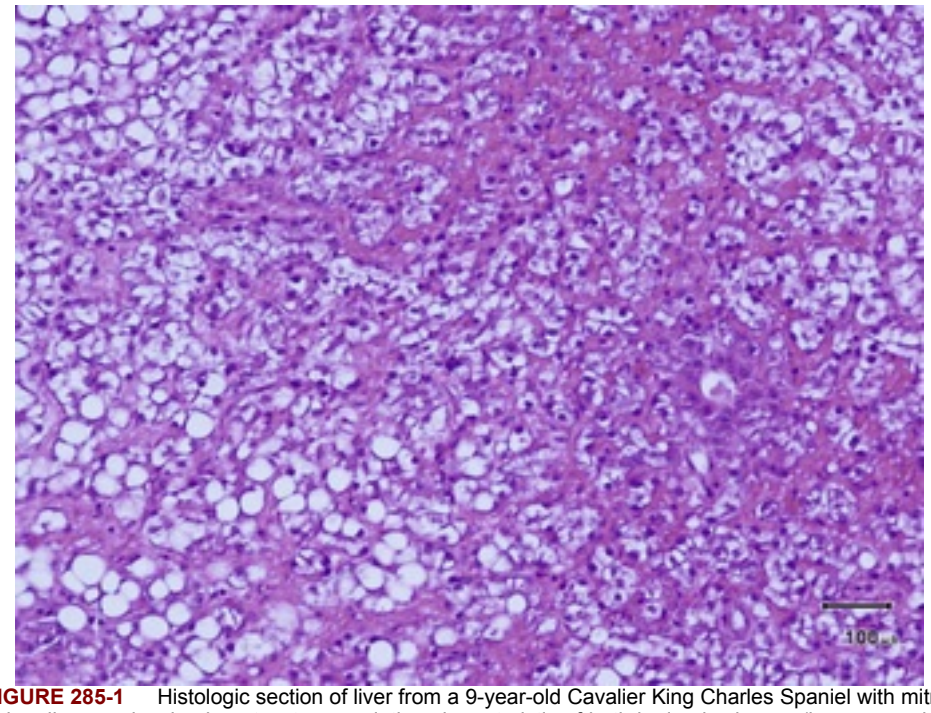

FIGURE 285-1 Histologic section of liver from a 9-year-old Cavalier King Charles Spaniel with mitral valve disease showing hepatocyte vacuolation characteristic of both hydropic change (lacey vacuoles; right-hand side of picture) and steatosis (cells with clear cytoplasm; left-hand side of picture). Special stains would be necessary to confirm this. The dog was on a number of medications for heart disease and a high-fat diet but the cause of the vacuolation was unclear. Hematoxylin and eosin stain ×100. (Image courtesy the Pathology Department; Department of Veterinary Medicine; University of Cambridge, UK.)

Many insults can cause vacuolar hepatopathy, such as hepatic hypoxia associated with right-sided congestive heart failure or intoxication (Box 285-1). Severe congenital cobalamin deficiency also has been reported to cause foamy vacuolation of hepatocytes, lipogranulomas, single cell necrosis, and mild fibrosis in dogs, possibly due to secondary hyperhomocysteinemia.[2] Therefore, "vacuolar hepatopathy" is not a diagnosis and is not always due to glucocorticoid excess; rather, this histologic finding should trigger a search for an underlying disease or intoxication (see ch. 286). The process is not always benign and reversible; in dogs, progression to overt hepatic dysfunction and death has been recorded,[3] and predisposition to hepatocellular carcinoma is possible in humans[4] and Scottish Terriers.[5]

Box 285-1

Causes of Primary and Secondary Vacuolar Hepatopathies in Dogs and Cats

Steroid Hepatopathy and Cloudy Change

- Steroid hepatopathy—secondary to high concentrations of circulating corticosteroids (exogenous or endogenous)
- Vacuolar hepatopathy of Scottish Terriers (overlap with steroid hepatopathy?)
- Deficiency or toxicosis, e.g., severe cobalamin deficiency in dogs
- Secondary to hepatic insult from another disease process, e.g., congestive heart failure, neoplasia, other hepatobiliary disease, gastrointestinal disease, renal disease, infectious disease

Steatosis

- Feline hepatic lipidosis—primary or secondary
- Toxicoses—for example, aflatoxin (dogs); vitamin A intoxication (cats)
- Secondary to canine familial hyperlipidemia
- Secondary to endocrine disease: hypothyroidism and diabetes mellitus (dogs); occasionally

hyperthyroidism (cats)

Steroid Hepatopathy

The distinctive hepatopathy seen in dogs receiving exogenous glucocorticoids or with hyperadrenocorticism was first reported in 1977.[6] Typically, hepatocytes become vacuolated with marked cytoplasmic, or even nuclear, increases in glycogen.[1] Vacuolation starts in the centrilobular region (zone 3) and becomes generalized when chronic.[7] The associated marked increase in serum alkaline phosphatase (ALP) is unique to dogs and it could be a result of delayed clearance of the intestinal isoenzyme due to hyperglycosylation in the liver under the influence of glucocorticoids, although it is unknown why this occurs in dogs and no other species.[8]

Steroid hepatopathy traditionally has been considered benign in dogs. However, the reported association between glycogen-like hepatopathy and hepatic remodeling and carcinoma in Scottish Terrier dogs, and between hyperadrenocorticism and gallbladder mucocele, suggests that all canine vacuolar hepatopathies should be taken more seriously, particularly when they are chronic and severe.

The most effective treatment for steroid hepatopathy is to remove the source of exogenous or endogenous glucocorticoids. Where this is not possible, antioxidants are indicated (see ch. 281). S-adenosylmethionine given to dogs with steroid-induced hepatopathy has increased total hepatic glutathione and had a beneficial effect on the oxidized : total glutathione ratio in hepatocytes, but had no effect on the histological appearance of vacuoles.[9]

Glycogen-Like Vacuolar Hepatopathy of the Scottish Terrier

A particular form of idiopathic vacuolar hepatopathy has been reported in Scottish Terriers in the USA and France. It is characterized by a marked increase in serum ALP and an apparently increased risk of hepatocellular carcinoma.[5,10,11] The syndrome is most common in middle-aged dogs (median age, 8 years [range 1-14 years]; mean age, 8.3 years), although dogs with hepatocellular carcinoma are older. There is no gender predominance. There is usually a moderate to marked elevation in serum ALP and a milder increase in alanine aminotransferase (ALT) and nearly half of affected dogs show clinical signs suggestive of hyperadrenocorticism (hepatomegaly; pot-bellied appearance; polydipsia and polyuria). However, the results of adrenal function testing are variable: there is an inconsistent cortisol response to adrenocorticotropic hormone (ACTH) stimulation testing and low-dose dexamethasone suppression testing, and 5/7 dogs showed normal results of urine cortisol : creatinine ratio testing in one study (also see ch. 306).[5] The most consistent endocrine abnormalities in affected dogs are increases in progesterone and androstenedione post-ACTH stimulation. Adrenal glands were enlarged on ultrasound in 26% of cases. Gallbladder mucocele was reported in 16% of cases.[5] Ultrasonographically, the liver most often has a mottled or coarse appearance. The development of hypoechoic nodules appears to mirror hepatocyte death and collapse histologically.[5] Affected dogs appear to respond poorly to traditional treatments for hyperadrenocorticism, with severe side-effects reported with mitotane or ketoconazole and lack of efficacy of trilostane. Current treatment recommendations are therefore unclear, apart from regular monitoring with ultrasound for development of hepatocellular masses or mucocele and surgery as necessary. It would make sense also to give affected dogs antioxidant supplements, particularly S-adenosylmethionine, given the reduction in oxidized glutathione reported with S-adenosylmethionine supplementation in other vacuolar hepatopathies in dogs.[9,12]

Hepatic Steatosis

Accumulation of fat within hepatocytes is termed *steatosis* (or lipidosis or fatty change by veterinary pathologists). Steatosis is the preferred term as it is used in human medical and toxicology textbooks and avoids confusion with the clinical syndrome of hepatic lipidosis in cats.[1] In routine, formalin-fixed sections, fat appears as clear vacuoles in the cytoplasm because lipid is lost in processing. Demonstrating fat with special stains therefore requires frozen sections. Microvesicular steatosis describes multiple vacuoles that are smaller than the cell nucleus and it is typical of diabetes mellitus in dogs (see Figure 285-1). Macrovesicular steatosis describes larger vacuoles, which often displace the nucleus to the periphery of the cell. Feline hepatic lipidosis usually is associated with a mixture of micro- and macrovesicular steatosis[1] (Figure 285-2).

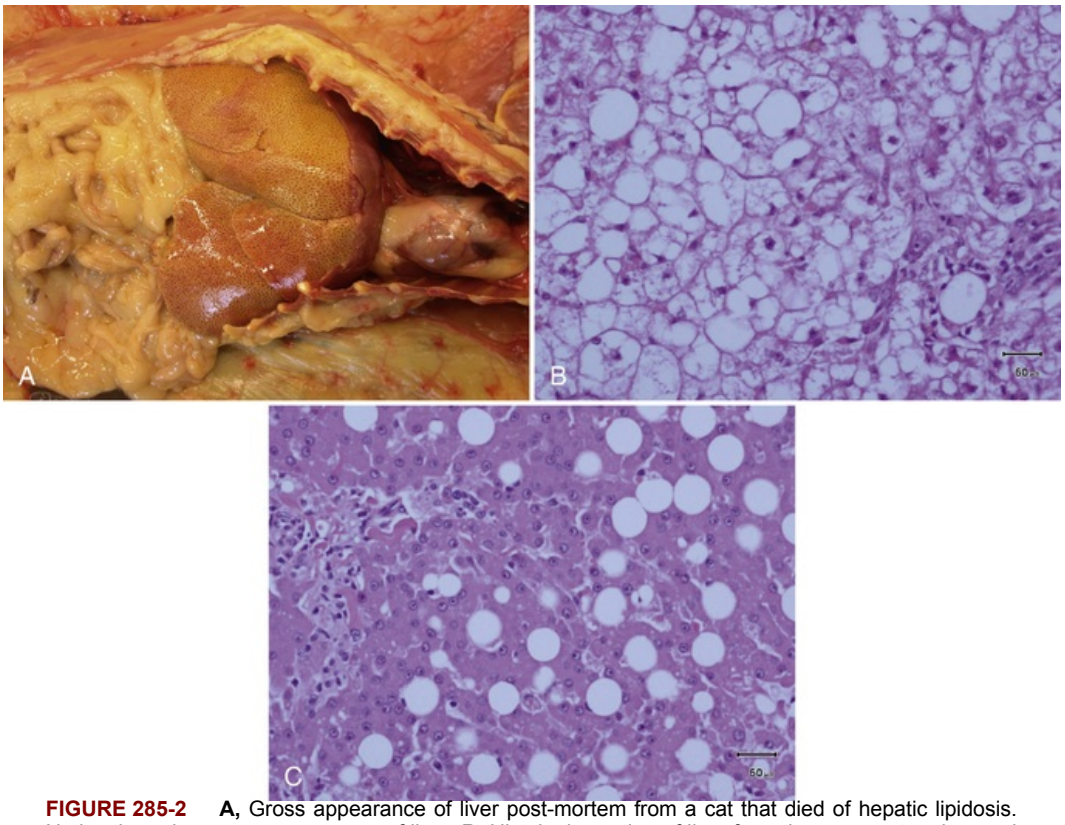

FIGURE 285-2 **A,** Gross appearance of liver post-mortem from a cat that died of hepatic lipidosis. Notice the pale orange appearance of liver. **B,** Histologic section of liver from the same cat as in panel A, showing marked steatosis of hepatocytes. Hematoxylin and eosin stain ×200. **C,** Histologic section from a different cat showing prominent Ito (stellate) cells. Note the large cells with pale cytoplasm and peripherally placed nucleus. Surrounding hepatocytes appear normal. This is a common response to hepatic insult or increased vitamin A in the diet and should not be confused with hepatic lipidosis. (Images courtesy Fernando Constantino-Casas, the Pathology Department; Department of Veterinary Medicine; University of Cambridge, UK.)

Steatosis can occur as a result of hepatocyte injury (fatty degeneration), as with aflatoxicosis in dogs.[13] Chronic vitamin A intoxication in cats results in hypertrophy of lipid-laden hepatic stellate cells with or without hepatocellular steatosis and fibrosis.[1,14] Steatosis also has been reported in dogs with congenital portosystemic shunts, although it is apparently of no prognostic significance post-ligation.[15,16] Hepatocyte steatosis also occurs secondary to a number of primary or secondary disorders of fat metabolism in dogs and cats (see ch. 182). In cats with hepatic lipidosis, this fat accumulation is severe enough to cause inhibition of hepatocyte function and an acute, reversible liver failure (see Feline Hepatic Lipidosis, below). However, in dogs, although hepatic steatosis can become very marked in such diseases as diabetes mellitus, it is not believed to result in inflammatory liver disease and liver failure. This is in contrast to humans where non-alcoholic liver disease and steatohepatitis is an increasingly important cause of progressive liver disease, cirrhosis, and liver failure. Fat metabolism differs in important ways between dogs and humans (see ch. 182) —notably, dogs are very resistant to atherosclerosis and do not develop the triad of hyperlipidemia, hypertension, and type 2 diabetes known in humans as the metabolic syndrome.[17] This might partly explain why dogs are so resistant to progressive hepatic failure with steatosis.

Feline Hepatic Lipidosis

Introduction

Feline hepatic lipidosis (FHL) was first reported in 1977 in two cats in the USA.[18] Many reports followed in the USA but it remained uncommonly reported in Europe. However, more recently, the recognition of FHL has been increasing in Europe, where the secondary disease appears to be more common than the primary idiopathic disease. The reasons for the changing epidemiology are unclear. FHL has been defined as "a diffuse involvement of >50% of hepatocytes with cytoplasmic vacuoles consistent in appearance with lipid."[19] Cats have a propensity to develop mild to moderate hepatic steatosis when anorexic for any reason and also

in response to toxic hepatic insults. It is important to differentiate this mild steatosis from true hepatic lipidosis. It is also important to differentiate lipidosis of hepatocytes from Ito cell proliferation (Figure 285-2).

Pathophysiology

Although the pathophysiology is still poorly understood, obesity, anorexia, and stress are important predisposing factors. FHL is reported in two forms: primary idiopathic and secondary. The primary form occurs in overweight cats that have been fasted for a prolonged period of time but have no identified underlying disease. The period of fasting and degree of obesity required to produce the disease seem to be variable. In one study, cats developed hepatic lipidosis after more than 25% weight loss.[19] In another study, six obese laboratory cats developed FHL after 6-7 weeks of anorexia and a 30-40% loss of body weight.[20] Secondary FHL is recognized in association with another disease, particularly cholangitis, pancreatitis, inflammatory bowel disease, neoplasia, diabetes mellitus, or hyperthyroidism.[19,21,22] In both primary and secondary disease, it is proposed that fasting combined with stress increases peripheral lipolysis and that there is a bottleneck effect in the liver, such that the mobilized lipids become trapped, with reduced export. Cats with FHL have elevated circulating triglycerides and non-esterified fatty acids, consistent with lipolysis of peripheral fat and reduced function of hormone sensitive lipase.[23] The triglyceride content of a normal cat's liver is 1% whereas it increases to 43% in a cat with FHL[24] (see Figure 285-2). They also have higher serum beta-hydroxybutyrate levels than do normal cats, indicating hepatic ketogenesis.[25] The cat is still able to mobilize triglycerides from the liver to some degree, as demonstrated by studies showing significant increases in very low-density lipoproteins in the serum of cats with FHL.[25] It is proposed that they cannot remove triglycerides fast enough to compensate for the marked increase in mobilization. The reason for this imbalance remains unclear, as does the reason why some cats appear to be more susceptible than others. It has been suggested that concurrent protein deficiency and negative nitrogen balance associated with fasting reduce the ability to produce apoproteins to export fat from the liver and that taurine and carnitine deficiencies contribute to the pathogenesis, although the experimental evidence for these effects is limited.

Circulating insulin concentrations of cats with FHL are normal or reduced, suggesting affected cats are not insulin-resistant[23,26] which also contrasts with the situation in human non-alcoholic fatty liver disease (NAFLD). When obesity is induced experimentally in cats, they do develop insulin resistance and high insulin concentrations, but this is then replaced by low insulin levels during anorexia and the development of FHL. It is also notable that it takes many months to induce obesity in cats with dietary manipulation, but only a few weeks of fasting an obese cat to cause FHL.[27] A recent study showed that affected cats have high adiponectin and leptin concentrations.[26] This, too, contrasts with humans with NAFLD, where adiponectin is reduced. High leptin concentrations should result in reduction of the lipid content of non-adipose tissues like liver, so affected cats must be leptin-resistant.

The resultant marked steatosis of hepatocytes interferes with the metabolic activity of the cells and produces a secondary cholestasis due to compression of small intrahepatic cholangioles. Thus, the result is a form of acute (potentially reversible) liver failure, with severe clinical signs and effects on hepatic function. This acute clinical syndrome associated with hepatic lipidosis in cats is in marked contrast to humans and dogs where hepatic steatosis occurs but does not result in liver failure. Clinical signs in humans only occur late in the disease process when the disease becomes inflammatory (steatohepatitis).

Signalment and Clinical Findings

Clinical studies report an increased prevalence of FHL in younger to middle-aged female cats. Most, although not all, affected cats are reported to be obese prior to the onset of a period of anorexia and then the disease. Idiopathic cases tend to be younger than secondary cases.[19,23] Clinical signs are typical of acute-onset hepatic insufficiency with vomiting, anorexia, weakness, and weight loss. Hypersalivation and depression occur, likely as manifestations of hepatic encephalopathy, whereas other manifestations of encephalopathy are uncommon. On physical examination, affected cats usually have palpable hepatomegaly and jaundice. Dehydration is common and evidence of recent weight loss usually is apparent, with loss of body mass over the spine but retention of inguinal and abdominal fat typical of weight loss in cats. The falciform fat pad typically is retained and can be seen on abdominal radiographs.

Diagnosis

The diagnosis relies on results of hepatic biopsy, but the history and typical clinicopathologic and imaging

findings increase the index of suspicion of FHL. Serum biochemistry results typically reveal moderate to marked elevations in bilirubin, ALP, and ALT, while in primary cases, gamma-glutamyl transferase (GGT) typically is normal. Finding a marked elevation in ALP with normal or only mildly elevated GGT in a cat increases the index of suspicion for FHL rather than biliary tract disease.[19] However, a cat with severe secondary FHL also can have a very elevated GGT if it has concurrent disease with biliary stasis (e.g., pancreatitis, cholangitis). Hypokalemia is a common finding, due to prolonged anorexia and vomiting, and has been reported as a poor prognostic indicator.[19] Hyperglycemia is common (40-50% of cats) but usually is transient.[19,23] However, since diabetes mellitus is a reported predisposing factor for secondary FHL, this must be carefully differentiated, such as with measurement of serum fructosamine and serial monitoring of blood glucose during treatment. Moreover, if the cat has ketosis it is likely to have diabetes mellitus. Coagulation times are prolonged in about half of affected cats but clinically significant bleeding is rarely reported.[19]

Abdominal ultrasound examination usually shows a diffusely hyperechoic liver that is more hyperechoic than the adjacent falciform fat. Visualization of hepatic blood vessels may be reduced. Ultrasound also allows assessment of other organs for concurrent disease, particularly the pancreas. In one study assessing diagnostic accuracy of ultrasound for liver diseases in dogs and cats, FHL had the highest accuracy with a correct diagnosis in 50-71% of cases, depending on the ultrasonographer.[28] Obese cats without lipidosis can have a hyperechoic liver[29] so the sonographic appearance should be interpreted along with clinical and clinicopathological findings.

Definitive diagnosis requires histologic assessment of a tissue biopsy. Ideally, an ultrasound-guided core biopsy (see ch. 89) or a wedge biopsy (see ch. 91) should be taken to rule out significant underlying disease. Fine-needle aspiration (FNA) with cytologic evaluation of smears has been unreliable in some cases and can even lead to a false diagnosis of FHL in a cat with hepatic lymphoma or cholangitis.[30,31] In these cases, it is probable that FHL is present but as a secondary change to an underlying severe liver disease. However, taking a biopsy requires normalization of coagulation times and general anesthesia, which carries an increased risk in the acutely sick cat. An FNA of the liver can be taken quickly and safely, either with ultrasound guidance or blindly under digital guidance if there is palpable hepatomegaly. Blind aspiration should be performed on the left side to avoid puncturing the gallbladder. If cytologic features of smears are strongly suggestive of FHL, the cat can be treated appropriately including intensive feeding. If the cat fails to respond as expected to treatment, then a biopsy should be taken when the cat is stable. The clinician and owner should be aware of the increased risk of liver biopsies in cats with FHL: coagulation times should be normalized first, and if an ultrasound-guided biopsy is undertaken, the use of semi-automated biopsy guns should be avoided because fatalities have been reported in cats when these are used.[32] Laparoscopy or laparotomy for wedge biopsies are the preferred techniques, not least because the liver can be monitored for hemorrhage and the pancreas and other organs can also be inspected for abnormalities. The liver is friable with hepatic lipidosis and in one study of 195 dogs and 51 cats undergoing various biopsies of abdominal organs in one institution, only 3 animals had major post-biopsy complications: two were cats and both had FHL.[33]

Treatment

The single most important factor affecting prognosis in cats with FHL is early intensive feeding, which usually requires some form of tube feeding (see ch. 82). Without assisted feeding, the mortality rate in affected cats has been up to 90%, whereas with the institution of intensive dietary management, mortality has fallen to 40% or lower.[19] Appetite stimulants are not indicated in cats with FHL because they are not effective enough and cats with FHL will not reliably resume voluntary feeding. Rapid institution of tube feeding in one study resulted in a survival rate of 6/7 cats (86%).[20] Another study identified that mortality was slightly higher in cats with secondary FHL compared with primary FHL, which could reflect a delay in instituting tube feeding.[19] It is equally important to institute early, intensive nutritional management in cats with secondary disease as with primary disease. However, it is also important to identify and treat any underlying disease in these cats as well.

Tube feeding can be commenced within 12 hours as soon as fluid and electrolyte imbalances have been addressed (see ch. 82 and 180). Nasoesophageal tube feeding is useful in the short term because it has the advantage of not requiring general anesthesia for placement. However, a more permanent tube such as an esophagostomy or gastrostomy tube will need to be placed once the cat has stabilized since spontaneous return to voluntary food intake takes at least 12-16 days and often longer.[20] Feeding should be introduced slowly using as high a protein-content diet as possible. High-protein diets are the most effective at reducing

hepatic lipid in experimentally induced FHL.[34] There is a significant reduction in stomach volume in cats after prolonged fasting.[35]

In the acute stage, cats almost invariably will need intravenous fluid therapy (see ch. 129) to reverse dehydration and correct electrolyte abnormalities, particularly hypokalemia (see ch. 68). Addition of potassium chloride to the tube feed is also wise and potassium or sodium phosphate may need to be added if the serum concentrations fall on re-feeding. The re-feeding syndrome has been reported in a tube-fed cat with FHL, with a precipitous drop in serum potassium and phosphate resulting in hemolysis, so these parameters should be monitored carefully in affected cats.[36] Some authors also recommend adding other nutrients to the tube feed, such as B vitamins, carnitine, and taurine, but there is no evidence that routine addition of extra nutrients to feline critical care diets is necessary. However, it is wise to measure serum cobalamin in affected cats because it may be low, particularly in cats with concurrent gastrointestinal disease. Parenteral supplementation of cobalamin is recommended if it is deficient. There is strong evidence that affected cats have systemic and hepatic oxidant injury; therefore, supplementation with antioxidants such as S-adenosylmethionine (20 mg/kg PO q 24 h on an empty stomach, or 100-400 mg/cat/day) and vitamin E (ideal dosage unclear, but 100 IU PO daily is convenient) is wise.[12] Affected cats often have prolonged coagulation times and these normalize with parenteral vitamin K treatment. Supportive therapy may also be necessary: antiemetics if the cat is vomiting, with maropitant being an ideal choice because it also has an anti-nausea effect. Prokinetics might be necessary if there is delayed gastric emptying after tube feeding. Ranitidine is a good initial choice because of its prokinetic cholinergic action and it can be given intravenously.

A small number of cats can develop clinically significant hepatic encephalopathy (HE), which needs to be managed. This aspect of treatment is discussed in ch. 281, 283, and 284. Current advice for treatment of cats with FHL and HE is not to feed a reduced-protein diet, but to reduce the amount fed; feed in smaller, more frequent meals; and institute therapies for any concurrent inflammatory disease.

Canine Hyperlipidemia

Hyperlipidemia is defined as an increase in either triglycerides or cholesterol in the serum or both.[37-55] Lipid disorders are described in ch. 182.

Gallbladder Mucocele

A gallbladder mucocele describes cystic mucinous hyperplasia of the gallbladder wall with accumulation of thick mucus.[41,56-64] First reported in dogs in 1995,[56] they are uncommon but appear to be increasing in frequency and show an association with vacuolar hepatopathies.[57] This disorder is covered in ch. 288.

Superficial Necrolytic Dermatitis

Introduction and Pathophysiology

Superficial necrolytic dermatitis (hepatocutaneous syndrome, metabolic epidermal necrosis, necrolytic migratory erythema) is an uncommon but very characteristic hepatopathy that is assumed to be secondary to an underlying metabolic disorder. The resulting hepatic and cutaneous changes are characteristic and much more severe and serious than those associated with the common secondary vacuolar hepatopathies reported with many endocrinopathies. In humans, most cases have a glucagon-secreting tumor and concurrent diabetes mellitus (DM). A few dogs have been reported with glucagonomas, which are usually metastatic,[65-67] and one case has been reported in a dog with an insulinoma.[68] However, in most canine cases, there is no identifiable mass, serum glucagon concentration is normal, and the cause remains obscure. Superficial necrolytic dermatitis also has been reported in 11 dogs being treated with phenobarbital,[69] although the contribution of the antiepileptic to the disease was unclear in this retrospective study and the response to stopping treatment was not known.

The characteristic features are typical histologic findings on skin biopsies and the characteristic appearance of the liver on ultrasound. The underlying pathogenesis of the skin lesions appears to involve amino acid deficiencies. Low serum amino acid concentrations have been found in all affected dogs in which they have been measured.[66,67,70] Zinc and fatty acid deficiencies also are implicated and, in humans, multiple deficiencies have been identified, including B vitamins. Deficiencies are proposed to be due to upregulated hepatic metabolic activity under the stimulus of increased glucagon activity, or to an unidentified stimulus in

dogs with normal glucagon concentrations.[71]

Clinical Presentation

Superficial necrolytic dermatitis most commonly affects older, small-breed dogs, although it has been reported in a variety of breeds including Golden Retrievers and Border Collies. In one study, 75% of affected animals were male with both mean and median age of 10 years and a range of 5 to 15 years.[70] Affected dogs usually present because of the skin lesions: typical lesions are hyperkeratotic, erythematous, crusting lesions particularly on the extremities (paw pads, nose, periorbital and perianal regions), around the genitals, and often on pressure points. Lesions often develop fissures and become secondarily infected with bacteria and are painful. Dogs may also show signs of diabetes mellitus (DM) which affects between 25 and 40% of cases, although DM often develops later in the disease. In humans, it is proposed that DM develops due to the marked insulin resistance caused by high circulating glucagon concentration. In dogs with normal glucagon concentrations, the cause of DM is unclear. Presentation because of clinical signs of liver disease is uncommon. In cases with glucagonoma, dogs may also present with clinical signs of metastatic neoplasia.

Dogs with superficial necrolytic dermatitis associated with phenobarbital treatment also have been older, with a median age of 10 years. In one study, dogs had been receiving phenobarbital for a median duration of 6 years before developing lesions.[69]

Diagnosis

The diagnosis is made on the basis of skin biopsy results, ruling out other causes, and the typical appearance of the liver on imaging and histology. Skin biopsies show typical parakeratotic hyperkeratosis with inter- and intracellular edema, which results in a classic "red, white, and blue" appearance on hematoxylin and eosin–stained sections of skin. The only differential diagnosis for this is zinc responsive dermatosis, which can be ruled out on the basis of breed and diet history (see ch. 10 and 186).

On the serum biochemistry profile, elevations of ALP and ALT are common and about half of reported cases have hypoalbuminemia, suggestive of negative nitrogen balance. Hyperglycemia and glucosuria are recognized in those cases with concurrent diabetes mellitus.

Ultrasound of the liver demonstrates a very characteristic Swiss cheese–like appearance, with variably sized, hypoechoic nodules surrounded by hyperechoic borders.[72] This corresponds histologically to nodular areas of normal hepatocytes surrounded by zones of collapsed parenchyma with vacuolated hepatocytes. With glucagonoma or other pancreatic tumor, the primary mass and metastases may be visible on ultrasound, but histologic evaluation with immunohistochemical stains are necessary to identify the tumor type.

Treatment

Superficial necrolytic dermatitis carries a poor prognosis in most dogs, with death or euthanasia often reported within 6 months of diagnosis. Cure is very unusual: there is a report of resolution of skin lesions after complete removal of a pancreatic tumor. Another case with metastatic glucagonoma was controlled for 6 weeks with subcutaneous octreotide injections, although the dog was then euthanized because of signs related to the tumor.[65] It is unknown whether cessation of phenobarbital therapy and replacement with an alternative anticonvulsant would resolve superficial necrolytic dermatitis in those cases associated with phenobarbital therapy.

In most cases, where no underlying cause is identified, treatment is supportive. The most important consideration is an ample supply of amino acids, because the disease is associated with amino acid deficiency. Proprietary hepatic diets therefore are not indicated, as they are protein-restricted. Ideally, a high-quality, digestible, high-protein diet should be fed, such as a food designed for gastrointestinal disease or convalescence. Supplementation with extra zinc and essential fatty acids is also often recommended. Some authors report administering weekly parenteral amino acid treatment although there are too few cases treated to give evidence for the efficacy of this approach. Feeding egg yolks has been reported to be beneficial in humans and in one dog that was fed a daily egg yolk together with hepatic support diet, essential fatty acids, and colchicine. The skin lesions resolved and the dog was well 22 months after presentation.[73]

Supportive treatment of skin lesions should include appropriate antibiotics for secondary infections, topical shampoos, and analgesia. The use of corticosteroids should be avoided if at all possible because of the risk of precipitating diabetes mellitus.

Superficial Necrolytic Dermatitis in Cats

Superficial necrolytic dermatitis is much less commonly reported in cats than in dogs. Of five reported cases, 3 had pancreatic tumors, suggesting a pathophysiologic mechanism similar to that of humans.[74,75] Presentation and diagnosis are similar to dogs.

Hepatopathies Caused by Excessive Normal or Abnormal Storage of A Metal or Metabolite

Copper and the Liver

Excessive accumulation of copper within the liver is an important cause of chronic hepatitis in dogs[76-79] and to a lesser degree in cats.[80,81] This process is described in ch. 281 and 282.

Iron Overload: Hemochromatosis

Iron overload in the liver, or hemochromatosis, also can occur as either a primary or a secondary condition. Iron is not excreted in bile, so secondary disease will occur if there is increased absorption in the intestine, abnormal excretion, or increased hepatic storage secondary to red cell hemolysis.

Primary hemochromatosis is relatively common in humans and is inherited in an autosomal recessive manner. More than 90% of cases in Northern Europe are due to one mutation, which can be traced back to Celtic ancestry. Iron accumulates periportally, leading to fibrosis and hepatic lesions. This contrasts with reports in dogs and cats, where increases in iron are very commonly reported in the liver, but are always secondary and do not appear to result in lesions unless the iron build-up is marked or accompanied by other metals. In one study, increases in iron in the livers of dogs only resulted in lesions when combined with increases in copper.[78] It is possible to give dogs clinically significant hemochromatosis experimentally with marked dietary iron overload[82] and liver lesions also have been reported in dogs with severely increased liver iron concentrations associated with hemolytic anemia due to pyruvate kinase deficiency[83] and repeated therapeutic blood transfusions.[84] In all these cases, the liver lesions have been similar to those of humans with hemochromatosis, with loading of macrophages and Kupffer cells with hemosiderin, hepatocellular degeneration, and periportal fibrosis progressing to bridging fibrosis and cirrhosis. There is no doubt, therefore, that excessive iron is damaging to the liver. However, this is rare in dogs and cats. Anecdotal reports of hemochromatosis in litters of Yorkshire Terriers in the UK and USA have not been confirmed with publications.

Alpha-1 Anti-Trypsin Deficiency

Alpha-1 anti-trypsin deficiency was suggested as a cause of liver disease in dogs in Sweden, particularly Cocker Spaniels, in 1994.[85] However, there have been no further reports in the veterinary literature since 1982 and the original studies described a syndrome that was rather different from alpha-1 anti-trypsin deficiency in humans, so the potential contribution of alpha-1 anti-trypsin deficiency to liver disease in dogs remains unconfirmed.

Alpha-1 anti-trypsin is a neutrophil elastase manufactured in the liver. Alpha-1 anti-trypsin deficiency is a common disease in humans, resulting in hepatopathies in some affected patients. The predominant clinical sign of alpha-1 anti-trypsin deficiency in humans is emphysema as a result of unregulated neutrophil elastase activity in alveolar walls, and only a small proportion of individuals suffer from liver disease. Affected humans typically present in infancy, in a similar way to a lysosomal storage disease, with giant cell hepatitis and PAS-positive diastase-resistant granules in hepatocytes.

In dogs, three forms of alpha-1 anti-trypsin have been identified by isoelectric focusing, termed fast, intermediate, and slow.[85] The intermediate form was most common in Cocker Spaniels with chronic hepatitis, although it was not identified in all the Cocker Spaniels with chronic hepatitis in one study.[85] Some dogs also had globular inclusions in their endoplasmic reticulum. However, the serum concentrations of alpha-1 anti-trypsin in most dogs were normal or increased. It is possible to measure canine alpha-1 anti-trypsin concentrations in both serum and feces,[86] but serum deficiency is extremely rare in dogs. The fecal test is much more frequently used as a test of protein-losing enteropathy.

Measurement of alpha-1 anti-trypsin has been validated in cats and fecal alpha-1 anti-trypsin appears to be

increased in protein-losing enteropathy in this species.[87] There are no reports of serum deficiency or liver disease associated with alpha-1 anti-trypsin deficiency in cats.

Amyloidosis

Amyloid is a complex protein which can exist in two forms: either the "normal" soluble form or an "abnormal" auto-aggregated fibrillar form of beta-pleated sheets. It is the accumulation of the aggregated form that causes disease. Amyloidosis can be systemic or local, and familial or acquired (sporadic). There are many different amyloid proteins associated with different diseases. Some are found in single organs, such as the form reported in human and feline pancreatic islets, whereas others are more generalized. The most common generalized form reported in small animals is serum amyloid A (SAA), which is usually secondary to inflammatory disease. SAA is an acute phase protein that is made by hepatocytes and its transcription is regulated by cytokines. Together with C-reactive protein, it is the acute phase protein that is produced in the largest amount in the face of inflammation. An increase in SAA is necessary to develop consequent amyloidosis, but not all individuals with increased SAA develop disease: the reason why some animals develop amyloidosis and others do not is poorly understood but likely involves an interaction of genetic predisposition and environmental triggers.

Amyloidosis due to amyloid AL, which is monoclonal IgG light chain, is rarely reported in small animals although it has been described in association with tracheal disease in dogs and extramedullary plasmacytoma in both dogs and cats. Liver involvement does not appear to be important with amyloid AL.

Feline Hepatic Amyloidosis

Introduction and Signalment

The tissue tropism of SAA varies between dogs and cats and between individual animals and breeds. Hepatic amyloidosis, where the liver is the primary site of clinical importance, is described most commonly in cats. Amyloidosis in cats is most commonly familial and systemic (associated with SAA), although it can be sporadic. In Abyssinian cats, the disease usually presents as chronic kidney disease, with the renal medulla involved more than the glomeruli (see ch. 324). The liver often is involved in Abyssinians, but usually is not the reason for clinical presentation or death. However, Siamese cats with amyloidosis often present with hepatic involvement and the majority of cases of predominantly hepatic amyloidosis in the veterinary literature are in Siamese cats. Hepatic amyloidosis also has been reported in domestic shorthairs (DSHs), oriental shorthairs and a Devon Rex.[88-91] Cases are usually young adults. Studies of the structure and genes coding for feline SAA have shown that both Siamese and Abyssinian cats produce a very limited range of SAA types compared with DSH cats. Distinctive Abyssinian and Siamese SAA molecules have been identified but it is unknown if these differences account for the different tissue tropisms in different breeds.[90,92]

Clinical Presentation

Cats with hepatic amyloidosis most commonly present because of acute intraabdominal bleeding from the fracture of a very friable liver, causing anemia and hypotension that can be fatal. Non-fatal cases autotransfuse and slowly recover, but can suffer repeated episodes.[91] Cats also can present with jaundice and hepatomegaly as primary findings. On physical examination, hepatomegaly is common. The physical exam also should aim to identify any concurrent inflammatory disease, such as chronic gingivitis or upper respiratory tract disease that could predispose to production of SAA.

Diagnosis

The definitive diagnosis relies on histologic findings from a liver biopsy, to be performed only after careful assessment of coagulation times. Amyloidosis is not reliably diagnosed with FNA and cytology, although this has been reported to be diagnostic in a canine case.[93] Clinicopathological and ultrasonographic findings are supportive but not diagnostic. Cats with predominantly hepatic amyloidosis often have elevations of liver enzyme activities and bilirubin, and anemia. There are mild to marked increases in ALT activity and globulins but biliary enzymes are rarely increased. Azotemia is found in some but not all cats.[91] Cats may have concurrent inflammatory diseases, which complicates the blood picture: one cat with hepatic amyloidosis also had feline infectious peritonitis (FIP) as a co-morbidity.[91] Ultrasonography shows hepatomegaly with a normal biliary tract and a diffuse increase in hepatic echogenicity. FIP, lymphoma and

hepatic lipidosis are important rule-outs.

Treatment

To date, there is no effective treatment for feline hepatic amyloidosis. Supportive care and control of concurrent systemic inflammatory disease is the current standard of care in affected cats. Colchicine is used in Shar Pei dogs and humans with familial Mediterranean fever but there are no reports of its use in cats and its toxicity is likely to be limiting in this species. Treatments blocking interleukin 1-beta are being trialed in humans but have not yet been reported in small animals.

Amyloidosis in Dogs

Dogs, like cats, suffer most from the renal effects of serum amyloid A. They most commonly present with protein-losing nephropathy as a result of predominantly glomerular disease (see ch. 325). There are two main groups of canine amyloidosis: the form seen in a variety of dog breeds, which is relatively common, affects predominantly older animals, and rarely affects organs other than the kidneys; and the multi-organ disease recognized in Chinese Shar Pei dogs, which can affect the liver.[94]

The disease in Chinese Shar Peis causes recurrent episodes of fever and joint swelling, which is similar to Mediterranean fever in humans (see ch. 203). Primary hepatic involvement is not common, but has been reported in four dogs where it was the predominant cause of clinical signs.[93,95,96] Three dogs were spayed females and one was a neutered male; they presented with anorexia and lethargy and serum biochemical abnormalities suggestive of cholestatic disease. One suffered spontaneous hepatic rupture. All cases were diagnosed on liver biopsy, although diagnosis of hepatic amyloidosis with FNA and cytology also has been reported in one Shar Pei.[93] Affected dogs are treated with colchicine (see ch. 281).

Lysosomal Storage Diseases and the Liver

A large number of lysosomal storage diseases reported in dogs[1] (and humans) result in vacuoles in hepatocytes and sometimes hepatomegaly. However, the predominant clinical signs usually are not hepatic but rather neurological and skeletal (see ch. 260). The exception is lipid storage disease (cholesterol ester storage disease), which has been reported in one small family group of Fox Terriers in Germany and in which the predominant clinical sign is hepatosplenomegaly due to accumulation of lipid and cholesterol crystals in the liver and spleen.[97] The prognosis for affected dogs is unclear but this is considered a benign disease in humans.

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CHAPTER 286

Toxic Hepatic Diseases

Lauren A. Trepanier

Introduction

The liver is a common target of xenobiotic toxicity. It is the site of first-pass biotransformation of many orally absorbed compounds, some which can generate reactive metabolites. Two major categories of drug-induced hepatotoxicosis are recognized.

The first is cytotoxic, due to hepatocyte toxicosis from the parent compound or a locally generated metabolite; this mechanism typically leads to a hepatocellular pattern of liver injury due to hepatocyte necrosis. The second mechanism is cholestasis, which can occur when compounds inhibit or downregulate transporter pumps in the sinusoidal or canalicular membranes, thus interfering with bile salt efflux and hepatocyte function. A cholestatic pattern can also result from mitochondrial injury leading to steatosis, as seen in alcoholic liver disease in humans.[1] In humans, these patterns are defined using an "R" value based on serum alanine aminotransferase (ALT) and serum alkaline phosphatase (SAP) activities, where R = (ALT/upper limit of normal)/(SAP/ upper limit of normal). An R value > 5 indicates hepatocellular injury, an R < 2 indicates cholestatic injury, and an R of 2 to 5 represents a mixed pattern.[2]

Hepatotoxicosis can also be characterized as dosage-dependent or idiosyncratic, although there can be some overlap between the two. For dosage-dependent, or intrinsic, hepatotoxicosis, there is increasing toxicity with increasing dosage in one or more species, and virtually all members of a population or species will be affected at high enough dosages. Dosage-dependent hepatotoxicosis can be caused by the parent compound, or by a metabolite that is reliably generated in the treated species (Figure 286-1). These reactions are relatively predictable, and therapeutic drug monitoring may be helpful in prevention. They require a dosage reduction, but usually not permanent drug discontinuation (Box 286-1).

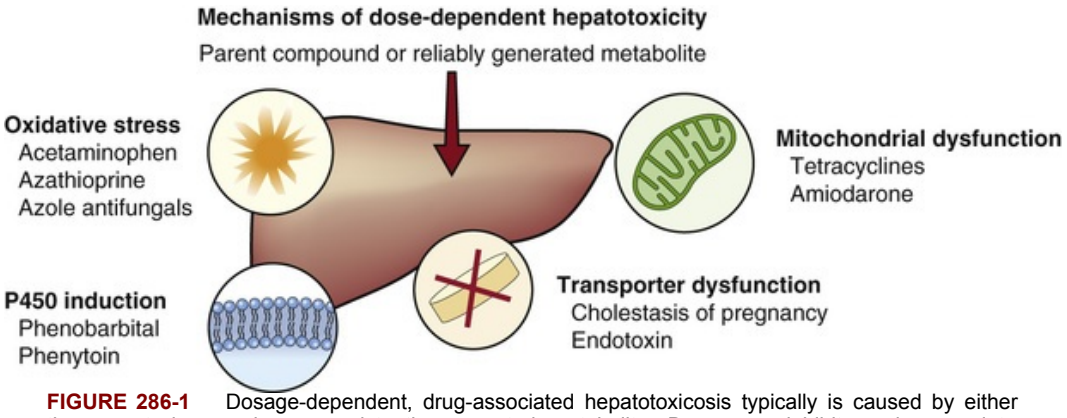

FIGURE 286-1 Dosage-dependent, drug-associated hepatotoxicosis typically is caused by either the parent drug or by a consistently generated metabolite. Drugs can inhibit or downregulate transporter pumps and lead to a functional cholestasis, as can occur with endogenous hormone metabolites during pregnancy. Many drugs yield reactive metabolites that cause oxidative stress; examples include acetaminophen, azathioprine, and azole antifungals. For these compounds, antioxidant supplementation may be effective for treatment or prevention of liver toxicosis. Drugs that interfere with mitochondrial function can lead to steatosis from inhibition of fatty acid beta-oxidation, or can lead to more severe hepatocellular damage due to impaired cellular respiration. Finally, drugs that act as P450 inducers, such as phenobarbital, may mediate hepatotoxicosis by chronic bioactivation of environmental toxins.

Box 286-1

Drugs and Chemicals Commonly Associated with Dosage-Dependent Hepatotoxicosis in Dogs (D) or Cats (C)

Acetaminophen (D, C)
Aflatoxin (D, C)
Amanita mushrooms (D, C)
Amiodarone (D)
Azathioprine (D)
Azole antifungals (D, C)
CCNU (D)
Cycads (Sago palm) (D)[92]
Glipizide (C)[93]
Phenazopyridine (rhabdomyolysis predominates)[94]
Phenobarbital (D)
Phenytoin (D)[95]
Primidone (D)[95]
Xylitol (D)

Idiosyncratic hepatotoxicosis is more difficult to predict, since these reactions develop in only a small proportion of patients that are exposed (Box 286-2). Toxicity does not increase with dosage in the general population (therefore they are not considered "dosage-dependent"), but toxicity can increase with dosage in susceptible individuals. Idiosyncratic toxicity is often caused by reactive metabolites that are variably generated among individuals. These reactive metabolites may cause oxidative stress, mitochondrial damage, or lead to haptens that trigger a humoral or T cell–mediated immunologic response (Figure 286-2). Although idiosyncratic hepatotoxic reactions are sometimes called drug hypersensitivities, they may or may not involve an adaptive immune response. Idiosyncratic hepatotoxicosis usually requires discontinuation of the suspect drug, and structurally related drugs can cause a similar reaction. Also see ch. 169.

Box 286-2

Drugs Most Associated with Idiosyncratic Hepatotoxicosis in Dogs (D) or Cats (C)

Carprofen (D)
Diazepam (C)
Mitotane (D)[96]
Methimazole (C)
Potentiated sulfonamides (D)
Zonisamide (D)[97,98]

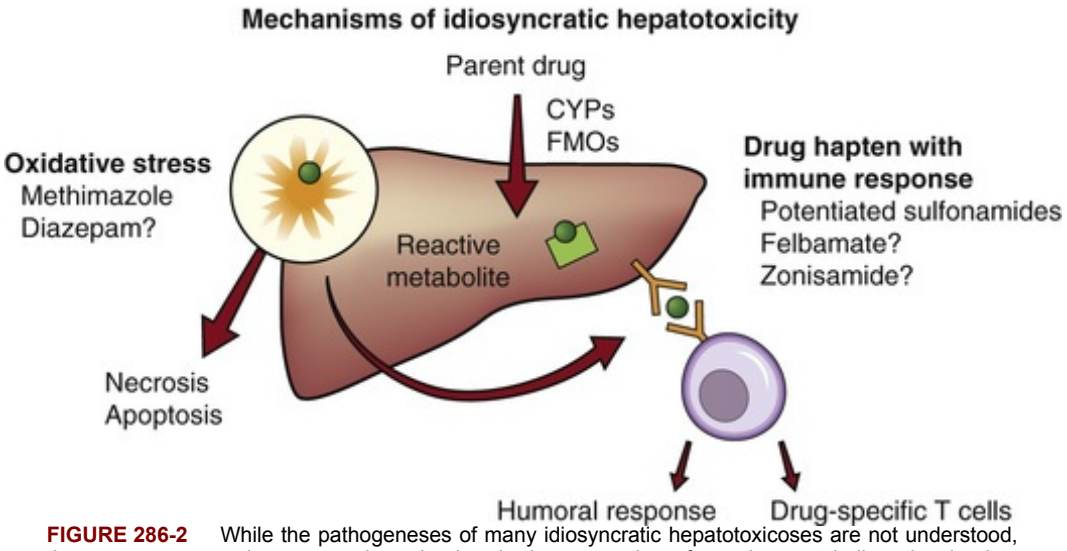

FIGURE 286-2 While the pathogeneses of many idiosyncratic hepatotoxicoses are not understood, the most common, demonstrated mechanism is the generation of reactive metabolites that lead to oxidative stress and/or hapten formation. Reactive metabolites are typically generated locally in the liver by cytochrome P450s (CYPs), flavin mono-oxygenases (FMOs), or other pathways. These metabolites may bind to critical proteins and impair hepatocyte function, or generate reactive oxygen species that damage hepatocyte membranes. Drug-protein adducts also can be processed and presented to the immune system in association with MHC molecules. In the presence of a "danger" signal such as oxidative stress, presentation of drug-bound peptides can lead to clonal expansion of drug-specific T cells, and/or the generation of drug-specific antibodies that target hepatocyte proteins.

Dosage-Dependent, Drug-Induced Hepatotoxicoses

Acetaminophen

Acetaminophen is a classical dosage-dependent hepatotoxin in many species. This drug can be safely used as an antipyretic and analgesic in dogs at dosages of 10-15 mg/kg PO q 8 h, without the gastrointestinal (GI) toxicity of standard nonsteroidal anti-inflammatory drugs (NSAIDs). However, dosages >150-250 mg/kg lead to acute centrilobular hepatic necrosis.[3] In cats, hematologic toxicosis, characterized by methemoglobinemia and cyanosis, appears to predominate over direct liver toxicosis.[4] Cats are much more susceptible to acetaminophen toxicity due to absent expression of UGT1A6, the enzyme that glucuronidates acetaminophen[5] and possibly also due to decreased expression of the ABCG2 transporter, which exports acetaminophen sulfate in humans.[6]

Acetaminophen is bioactivated to the reactive metabolite, NAPQI (N-acetyl-p-benzoquinone imine), which is detoxified by glutathione conjugation. This provides the rationale for treatment of overdoses with the standard regimen of the glutathione precursor N-acetylcysteine (140 mg/kg loading IV, then 70 mg/kg q 6 h for 7 treatments). Although N-acetylcysteine is most effective in humans when given within 8 hours of acetaminophen ingestion, this antidote still has beneficial effects on survival when given much later in the course of intoxication.[3]

S-adenosylmethionine (SAM-e) also can be used for intoxication in dogs that can tolerate oral medications; the protocol that has been used successfully is a 40 mg/kg PO loading dose, followed by 20 mg/kg PO q 24 h for 7 days.[7] Cimetidine has been recommended to inhibit oxidation of acetaminophen to NAPQI; however, this drug has no effect on NAPQI generation *in vitro*,[8] and is not effective in humans with acetaminophen overdose. Cimetidine is therefore not recommended.[3] For dogs and cats with accompanying methemoglobinemia from acetaminophen intoxication, ascorbate (vitamin C; 30 mg/kg SC or IV q 6-8 h) may be effective to restore functional hemoglobin.[9] However, the efficacy of ascorbate for acetaminophen intoxication in dogs and cats has never been evaluated.

Phenobarbital

Hepatotoxicosis from phenobarbital appears to be dependent on cumulative dose, with possible individual modulating factors. Signs typically develop after a year or more of phenobarbital treatment, and the duration

of administration is associated with the degree of histologic injury in epileptic dogs.[10] Presentation can range from subclinical increases in serum bile acids to fulminant liver failure.[11] Typical histologic findings in dogs with clinical signs are bridging portal fibrosis, bile duct hyperplasia, and nodular regeneration. Higher phenobarbital dosages or serum drug concentrations have not been correlated with the development of abnormal serum bile acids across epileptic dogs; however, individual dogs with phenobarbital hepatotoxicosis can improve clinically following phenobarbital dosage reduction.[11]

One hypothesized mechanism of phenobarbital hepatotoxicity is induction of cytochrome P450 enzymes, with secondary bioactivation and hepatotoxicity of other drugs, dietary components, or environmental toxins.[10] For example, phenobarbital increases the hepatotoxicity of carbon tetrachloride in dogs,[12] of chloroform in mice,[13] and of acetaminophen in human hepatocytes.[14] Phenobarbital hepatotoxicity could therefore be modulated by environmental exposures in individual dogs. It is interesting to note that phenobarbital does not lead to either enzyme induction[15] or hepatotoxicosis in cats.

For dogs with hepatotoxicosis during chronic phenobarbital treatment, phenobarbital should be discontinued, or the dosage minimized, by adding another anticonvulsant (see ch. 35 and 260). For example, potassium bromide (KBr) can be substituted at a maintenance dosage of 40-60 mg/kg PO q 24 h, and phenobarbital can then be discontinued with a rapid taper over 1-3 weeks. Clinically significant hepatotoxicosis can be preempted in most dogs by serial monitoring of serum bile acids, phenobarbital concentrations, and a liver panel, ideally every 6 months. Serum phenobarbital concentrations >40 mcg/mL should be avoided, as this can be a risk factor for hepatotoxicosis.[11] In addition, the presence of hyperbilirubinemia, new hypoalbuminemia, or discordant increases in serum ALT > SAP is clinically significant. Newly noted sedation on a stable dosage of phenobarbital might also indicate impaired hepatic clearance of the drug, and is an indication for bile acids testing.

Azole Antifungals

Ketoconazole, itraconazole, and fluconazole all can lead to increases in serum ALT in dogs, although clinical signs such as jaundice are uncommon.[16,17] Mild, clinically insignificant increases in ALT also have been reported in cats treated with itraconazole and fluconazole.[18,19] In dogs with blastomycosis, higher dosages of itraconazole (10 mg/kg/day PO) have been associated with a greater risk of ALT abnormalities than 5 mg/kg/day PO, with no difference in efficacy.[20] Further, increases in both ALT and SAP have been correlated with itraconazole plasma concentrations, which supports a dosage-dependent mechanism.

In animal models, ketoconazole hepatotoxicity has been attributed to an oxidative metabolite, N-deacetyl ketoconazole, which leads to covalent binding to liver proteins and glutathione depletion.[21,22] Fluconazole appears to be less hepatotoxic overall than either ketoconazole or itraconazole in both humans and animal models.[23-25] In dogs with blastomycosis, we observed increases in serum ALT in 26% of dogs treated with itraconazole (median increase: 2.7-fold), and in 17% of dogs on fluconazole (median increase: 1.5-fold).[17] While these were not statistically different, we have anecdotally observed increases in serum ALT during treatment with itraconazole that have resolved following a switch to fluconazole during treatment for blastomycosis in dogs.

Subclinical hepatopathies during azole antifungal treatment are common enough to warrant routine monitoring.[17,20] If new increases in liver enzymes are noted (particularly ALT), an antifungal dosage reduction is indicated, preceded by a rest period depending on severity. When the drug is initiated at a lower dosage, repeat clinical and biochemical monitoring should be performed in one week and at subsequent rechecks. For dogs that develop hepatotoxicosis with itraconazole, a switch to fluconazole may be considered, with careful follow-up monitoring. Given the data in rodent models of hepatotoxicosis, co-treatment with glutathione precursors such as SAM-e can also be considered in dogs that develop increased liver enzyme activities on azole antifungals.

Azathioprine

Azathioprine can lead to increases in ALT and/or SAP activities in about 20% of dogs[26]; these abnormalities usually are subclinical, but have been associated with jaundice and clinical signs in some dogs.[27] Liver enzyme abnormalities are observed a median of 14 days (range, 9-52 days) after starting azathioprine, which is significantly sooner than when cytopenias typically develop (median of 53 days).[26]

In animal models, azathioprine liver injury is associated with the generation of oxidative metabolites and

depletion of hepatic antioxidants,[28,29] and can be prevented by pre-treatment with N-acetylcysteine experimentally.[30] Oxidative metabolites of azathioprine are generated by xanthine oxidase; in fact, the xanthine oxidase inhibitor allopurinol has been used for preventing azathioprine hepatotoxicosis in human patients.[28] However, this intervention requires careful monitoring of azathioprine metabolites to avoid exacerbation of myelosuppression, and is not recommended in dogs.

Dogs treated with azathioprine should be routinely monitored for increases in liver enzyme activities, especially in the first 2-8 weeks of treatment.[26] If glucocorticoids are also being administered, liver enzyme interpretation can become clouded; however, discordant increases in ALT relative to SAP, or even subtle increases in serum bilirubin, are cause for concern. Risk factors for azathioprine hepatotoxicosis in dogs are not clear, but German Shepherds appear to be at higher risk for these enzymopathies.[26] Liver enzyme activities can stabilize or normalize with azathioprine dosage reduction. Supplementation with glutathione precursors might be effective in preventing or reversing azathioprine hepatotoxicosis in dogs, but this has yet to be evaluated.

Amiodarone

Amiodarone leads to clinically significant hepatotoxicosis in about 45% of dogs treated for refractory atrial fibrillation and ventricular arrhythmias, a median of 16 weeks after starting maintenance therapy.[31,32] Predominant increases in ALT are typically observed, with or without hyperbilirubinemia. Hepatopathy can be accompanied by neutropenia in some dogs.[31] These abnormalities slowly resolve over 1-3 months after drug discontinuation.

Toxicity in animal models has been attributed to two oxidative metabolites, mono-N-desethylamiodarone (MDEA) and di-N-desethylamiodarone (DDEA), which generate reactive oxygen species that uncouple oxidative phosphorylation and lead to mitochondrial damage.[33] These metabolites are generated by CYP3A4 in humans, and their generation can be inhibited by ketoconazole *in vitro*.[33]

Because of the prevalence of hepatotoxicosis and neutropenia, a baseline complete blood count (CBC) and serum biochemical panel are recommended in all dogs prior to amiodarone initiation, with a recheck of liver enzymes after a loading period and monthly during treatment.[32] The development of substantial increases in serum ALT is an indication for dosage reduction or drug discontinuation.

Lomustine (CCNU)

CCNU is an alkylating agent used for single agent chemotherapy in dogs with mast cell tumors, lymphoma, histiocytic sarcomas, and other tumors. However, CCNU is associated with substantial increases in serum ALT (>5 fold baseline) in about 29% of dogs.[34,35] Enzyme elevations can occur suddenly, and are most common after 1 to 3 doses of CCNU when given at 3- to 4-week intervals. Dogs also can develop modest hyperbilirubinemia. The risk of ALT elevations is greatest in the Boxer breed and in younger dogs (≤5 years old).[34]

Clinical signs of hepatotoxicosis occur in an estimated 6% of CCNU-treated dogs, are most commonly noted after a median of 4 doses, and are associated with a higher cumulative dosage (median, 350 mg/m^2).[36] Histopathologic evaluation of the liver shows portal aggregates of hemosiderin-laden Kupffer cells, enlargement of hepatocyte nuclei, and hepatocyte vacuolization.[34,36]

The mechanism(s) for CCNU hepatotoxicity is/are not known. Hepatotoxicosis is not a common side effect of CCNU in human patients, and while rats dosed with CCNU show liver toxicosis, the cholestatic pattern and bile canalicular lesions that develop appear to be distinctly different from those seen in dogs.[37]

Dosage reduction or drug discontinuation (for severe enzyme elevations) is associated with improvement in ALT activities in most dogs. However, discontinuation of CCNU chemotherapy is not ideal in tumor-bearing dogs. Some dogs that first presented with advanced liver disease (ascites and acquired shunts) have been euthanized; therefore, liver enzyme monitoring is warranted in all dogs treated with CCNU. In a randomized, placebo-controlled trial, SAM-e in combination with silybin (Denamarin, Nutramax Laboratories, Lancaster, SC) was effective in decreasing the incidence and severity of CCNU hepatopathy in client-owned dogs with various tumors.[38] Therefore, this supplement should be considered for adjunctive therapy in all dogs treated with CCNU.

Tetracyclines

Historically, high dosages of intravenous tetracycline have been associated with microvesicular steatosis in human patients, particularly in pregnant women.[39] The mechanism appears to be inhibition of beta-oxidation of fatty acids in hepatic mitochondria, as well as inhibition of hepatic lipoprotein secretion.[39,40] Although tetracycline inhibits fatty acid beta-oxidation in canine hepatocytes *in vitro*,[41] there is no histologic evidence for steatosis from either tetracycline or doxycycline use in dogs.

In a recent retrospective study of 386 dogs treated with doxycycline (median dosage, 16 mg/kg/day), 36-39% of dogs showed an increase in ALT or SAP into the abnormal range during treatment. Increases were up to 23-fold for ALT and up to 16-fold for SAP.[42] However, no control group was followed, and liver enzymes were checked at clinician discretion, so other causes of enzyme increases could not be ruled out. Given the widespread use of doxycycline and the lack of reports of hepatopathy with clinical signs, these findings are surprising and need further evaluation.

Idiosyncratic, Drug-Induced Hepatotoxicoses

Potentiated Sulfonamides

Potentiated sulfonamides are the most common antimicrobials associated with idiosyncratic hepatotoxicosis in the dog. Trimethoprim-sulfadiazine (Tribrissen, Coopers Animal Health), ormetoprim-sulfadimethoxine (Primor, Zoetis Animal Health), and generic trimethoprim-sulfamethoxazole have all been implicated. Clinical signs are usually seen 5-30 days after starting sulfonamides, with a mean of 12 days.[43] A hepatocellular pattern can progress over several days to cholestatic in some dogs. Hepatic necrosis is the predominant histologic lesion. Signs also can include fever (55% of cases), transient neutropenia, thrombocytopenia, hemolytic anemia, polyarthropathy, proteinuria, keratoconjunctivitis sicca, skin lesions, or uveitis.[43] Dobermans are overrepresented among dogs with idiosyncratic sulfonamide toxicosis, although arthropathy and glomerulonephropathy, not hepatotoxicosis, are typically reported in this breed.[44,45]

Sulfonamide antimicrobials are oxidized to form nitroso metabolites that covalently bind to proteins and act as haptens. Idiosyncratic sulfonamide toxicosis is convincingly immune-mediated in humans, with anti-drug antibodies and drug- and metabolite-specific T cells documented. If potentiated sulfonamides need to be prescribed, the client should be educated to look for any subtle signs of illness. Failure to discontinue sulfonamide antibiotics at the time of initial development of adverse signs can lead to fatal outcomes.

Although specific antidotes for sulfonamide hypersensitivity have not been evaluated, this author recommends supplementation with a glutathione precursor (SAMe or N-acetylcysteine, using the same protocols as for acetaminophen toxicosis, above) and ascorbate (30 mg/kg IV q 8 h [empirical dosage]), based on our finding that both glutathione and ascorbate can reverse haptenization of the nitroso metabolite to canine liver microsomes *in vitro* (Lavergne & Trepanier, unpublished observations). Glucocorticoids are not recommended during the acute hepatic necrosis stage because of the potential risk of exacerbating hepatic encephalopathy or bacterial translocation, but based on our experience, glucocorticoids may be considered in the subacute setting, particularly if a cholestatic pattern persists after drug discontinuation and support.

Carprofen

Potential hepatotoxicosis from carprofen is well-recognized among veterinary clinicians, with an estimated incidence from the manufacturer of 1.4 cases per 10,000 dogs treated (0.05%). Clinical signs of acute hepatic failure are noted 5 to 30 days after drug initiation, with a median of 19 days.[46,47] Clinical signs have even been seen in an untreated dog that ingested feces from another carprofen-treated dog in the household.[48]

A predominant hepatocellular or mixed pattern is found in all reported dogs.[46-48] Importantly, no dogs have been reported with increased SAP activities in the absence of clinically significant concurrent increases in ALT activities. Bridging hepatic necrosis is the predominant histopathologic finding. Although Labrador Retrievers were overrepresented in the initial report,[46] this most likely reflects the high ownership of this breed and its risk for osteoarthritis, since the syndrome could not be reproduced in Labradors under controlled conditions (Personal communication, Pfizer Animal Health).

Given the low incidence and abrupt onset of idiosyncratic hepatotoxicosis from carprofen in dogs, routine monitoring of liver enzymes is not an efficient approach to preventing clinical toxicosis. It is more important to educate dog owners to watch for subtle signs of illness during NSAID administration, to include

inappetence, vomiting, diarrhea, lethargy, or dark urine. Dogs should be promptly evaluated if clinical signs are seen. A normal ALT in the face of clinical illness essentially rules out carprofen hepatotoxicosis. If carprofen hepatotoxicosis is diagnosed, inflammatory pain control should be addressed with a structurally different NSAID, but only after recovery is complete.

Methimazole

About 1-2% of hyperthyroid cats that are given the antithyroid drug methimazole develop clinical evidence of hepatopathy with jaundice,[49] typically in the first month of treatment. These changes are distinct from "innocent" increases in ALT and SAP seen with untreated hyperthyroidism. Hepatopathies can present with a predominantly hepatocellular or cholestatic pattern, with or without hyperbilirubinemia. These reactions usually are reversible with drug discontinuation, but can be fatal if not detected promptly.

Methimazole hepatotoxicosis in animal models presents as increases in serum ALT and dosage-dependent centrilobular hepatic necrosis, which are manifested in the presence of glutathione depletion.[50] Hepatotoxicity has been attributed to an oxidative metabolite, N-methylthiourea, which is directly generated by flavin mono-oxygenases.[51] This pathway has yet to be evaluated in cats.

Cats treated with methimazole should be screened for increases in ALT and SAP if clinical signs of lethargy or anorexia are noted. If cats develop adverse clinical signs, idiosyncratic toxicosis (hepatopathy, blood dyscrasias, or facial excoriation) should be ruled out with a physical exam, CBC, and biochemical panel. The presence of these idiosyncratic adverse events warrants discontinuation of methimazole, given the risk of progression to more severe manifestations.[49] The transdermal route does not appear to be beneficial in preventing idiosyncratic methimazole toxicosis, including hepatotoxicosis.[52] Given the role of glutathione depletion in methimazole hepatotoxicosis in experimental models, the efficacy of glutathione precursors needs to be evaluated in the management of this adverse drug reaction.

Diazepam

Diazepam represents a classic idiosyncratic in cats, first recognized and reported in the mid-1990s.[53-55] Cats developed clinical signs of anorexia and overt sedation 5 or more days after drug initiation, with progression to jaundice and overt hepatic failure. Blood work showed dramatic increases in ALT activities in all cats. Marked centrilobular hepatic necrosis, with mild to marked biliary hyperplasia, was seen on liver biopsies.[53] Relative hypoglycemia was common. Affected cats typically were healthy prior to oral diazepam administration for behavioral problems. The syndrome of diazepam hepatotoxicosis in cats has been reported with both generic and brand-name diazepam,[53] but has not been observed with parenteral diazepam administration as a pre-medicant.

Unfortunately, the mechanism for this potentially fatal adverse drug reaction has not been explored. Comparable chronic daily dosages of diazepam in rats lead to necrotic changes, but without the fulminant presentation seen in cats.[56] A similar clinical syndrome has not been reported in humans.

Subsequent reports of diazepam hepatotoxicosis have since appeared on online veterinary message boards (Veterinary Information Network) in cats given oral diazepam for seizures or urethral spasm. Although toxicosis appears to be relatively rare, there are safer alternative drugs for behavioral problems, seizures, and urethral spasm in cats. This makes chronic oral diazepam administration a poor first choice in this species, particularly without an adequate discussion of risks and alternatives with the client.

Household and Environmental Hepatotoxins

Aflatoxin

Aflatoxins are produced by *Aspergillus* spp. and can be found in moldy corn, peanuts, or soy; contaminated pet food, and wild bird seed.[57] Aflatoxin B1 is a dosage-dependent hepatotoxin in many mammals, including dogs and cats.[58] Aflatoxin B1 is bioactivated by cytochrome P450 enzymes to electrophilic epoxide metabolites that lead to protein and DNA adducts and glutathione depletion.[59] Several large outbreaks of aflatoxin hepatotoxicosis from commercial dog foods have been reported recently, involving more than one hundred fatalities in pet dogs.[57,60]

Clinical signs of aflatoxin hepatotoxicosis are typical for acute liver failure, and can include peracute death.[60,61] Decreases in serum protein C, antithrombin, and cholesterol appear to be more sensitive than

increases in liver enzyme activities or bilirubin early in the course of disease.[60] As expected, hyperbilirubinemia, hypoalbuminemia, and hypocholesterolemia are poor prognostic indicators. The most prominent histopathologic finding is diffuse hepatocyte lipid vacuolation, along with fibrosis and biliary hyperplasia; cirrhosis also can be seen with chronic exposure.[60,62] It is important to note that massive hepatic necrosis is not a feature of aflatoxicosis in dogs.

If a patient is suspected of aflatoxin hepatotoxicosis, a careful dietary history over the previous 8 weeks should be obtained, because some dogs are affected only after subchronic exposure.[61] Owners might report an initial reluctance to eat a new brand or bag of dog food when first introduced.[63,64] Samples of food (several unopened cans or 1 kg of dry food) should be reserved for analysis of aflatoxin B1,[63] and vomitus, serum, and urine should be saved for analysis of the M1 metabolite of aflatoxin B1.[62] In addition, the pet food label and lot number should be documented, and both the manufacturer and the Food and Drug Administration should be contacted. The prognosis is guarded, and only about one third of affected dogs survive with intensive treatment for hepatic failure.[60,61]

Xylitol

The artificial sweetener xylitol is found in sugarless chewing gums, hard candies, baked goods, toothpastes, nasal sprays and even some drug suspensions and total parenteral nutrition formulas. When ingested by dogs at dosages of 0.15 g/kg or higher, xylitol leads to acute intoxication characterized by insulin release and clinical signs of hypoglycemia within 30 to 60 minutes (see also ch. 152).[65] In some dogs, this can be followed by acute hepatic necrosis 6 to 72 hours after exposure, sometimes leading to a consumptive coagulopathy and fulminant liver failure.[65,66] However, not all dogs that develop hepatopathy have evidence of preceding hypoglycemia.

The mechanism of xylitol hepatopathy is not known, but could be due to interference with intermediary metabolism or accompanying redox stress.[65] Oral ingestion does not lead to hepatopathy in other species, but high-dosage intravenous administration leads to hepatic depletion of ATP in humans,[67] and has been associated with hyperbilirubinemia (apparently without increases in transaminases) in human subjects.[68]

Vomiting should be induced in dogs that are observed to ingest xylitol (see ch. 151), but is contraindicated once signs of hypoglycemia are observed. Activated charcoal is not contraindicated but might not effectively adsorb xylitol.[69] Dogs should be further monitored for signs of hepatocellular damage for up to 72 hours after ingestion, and early treatment with a glutathione precursor (SAM-e or N-acetylcysteine) is probably indicated.[65,66]

Amanita Mushroom

The death cap mushroom *(Amanita phalloides)* is found throughout North America, and in the U.S., it is concentrated in forests on the West coast from Los Angeles to Vancouver, and the East coast from Maryland to Maine.[70] These fungi contain amatoxins, notably alpha-amanitin, which are highly toxic to humans and other mammals. Amatoxins inhibit RNA polymerases,[71,72] which leads to decreased mRNA generation, arrested protein synthesis, and necrosis of metabolically active cells, including intestinal crypt cells, hepatocytes, and renal tubular cells.[73,74]

Dogs can be exposed to *Amanita* spp. while foraging in the woods. Clinical signs of vomiting, bloody diarrhea, and abdominal pain occur within 6 to 24 hours of ingestion, followed by severe hypoglycemia at 24 to 48 hours, caused by insulin release stimulated by alpha-amanitin.[75] Finally, massive hepatic necrosis and renal tubular necrosis develop after 36 to 84 hours.[73] As little as one or two mushrooms can be fatal to an adult dog.

Silybin, found in milk thistle, inhibits amatoxin uptake by hepatocytes *in vitro,* which is mediated by the OATP1B3 transporter.[76,77] Notably, silybin (50 mg/kg PO) prevented fatalities when given at 5 and 24 hours after experimental *Amanita* intoxication in dogs.[78] Other inhibitors of OATP1B3 include, in order of decreasing potency, cyclosporine A, rifampicin, montelukast, penicillin G, and prednisolone phosphate[77]; in fact, penicillin G has also been shown to be protective against alpha-amanitin toxicosis in rodent models.[79]

A definitive diagnosis of aflatoxicosis can be made by measuring alpha-amanitin in urine, serum or plasma, kidney, or liver, although mushroom fragments also can be found in vomitus or gastric contents.[73] If a sample

of the suspect mushrooms can be obtained, the website of the North American Mycological Association can provide the names of volunteers nationwide who can assist with mushroom identification (http://www.namyco.org/toxicology/index.html). Any wild mushroom ingestion in a dog should be considered serious, and admitting clinicians should contact a veterinary poison control hotline for advice specific to their region.[80]

Blue-Green Algae

Blue-green algae, which are not actually algae but are photosynthetic cyanobacteria, proliferate in warm, stagnant, nutrient-rich waters. Genera that produce hepatotoxins include *Microcystis aeruginosa* (found in freshwater lakes, ponds, and reservoirs) and *Nodularia spumigena* (found in brackish and ocean waters). The cyanotoxins microcystin and nodularin inhibit serine/threonine protein phosphatases in the liver,[81] with subsequent hyperphosphorylation and disruption of cytoskeletal proteins. This leads to hepatocyte dissociation, hepatic necrosis, and glutathione depletion.[82,83]

Dogs can be exposed while drinking or swimming in warm, stagnant waters with visible blue-green "pond scum" or "algal bloom," or by eating mats of scum washed onshore.[84] Dogs can develop signs of acute illness and hepatic failure within hours of ingestion. Exposure to nodularin can also lead to proximal renal tubular necrosis and anuric kidney injury,[85,86] and can resemble acute leptospirosis at clinical presentation.

A diagnosis can be supported by cytologic exam of vomitus,[84] and toxicologic analysis of water, vomitus, feces, or samples of liver for nodularin or microcystin.[86-88] Although hepatotoxicosis can be rapidly fatal, dogs have been reported to survive with intensive supportive therapy, including glutathione precursors (see above).[89] In addition, cholestyramine can avidly bind cyanotoxins in the gut, and was associated with clinical response and survival in a single case report (cholestyramine 170 mg/kg PO q 24 h) of a dog with confirmed microcystin intoxication.[90]

Cycad Palms

The Sago palms (or fern palms; *Cycas revoluta, Cycas circinalis,* and *Zamia floridana*) are cycad plants found in subtropical regions. Intoxications in the U.S. are seen predominantly in the southern states, where seeds fall to the ground in early spring.[91] Seeds are most toxic, but ingestion of roots and leaves also can lead to clinical signs.[92] The toxic principle, cycasin, is bioactivated to methylazoxymethanol by gut bacteria; this metabolite leads to gastrointestinal and hepatic toxicosis.

Gastrointestinal signs can develop within minutes to hours of ingestion, while biochemical signs of hyperbilirubinemia and increases in hepatocellular and cholestatic enzyme activities may not develop for 24 to 48 hours.[92] Neurologic signs such as ataxia, proprioceptive deficits, or seizures are seen in 20-50% of dogs with cycad toxicosis.[91,92] Histopathologic liver lesions include centrilobular hemorrhage and necrosis, with stromal collapse seen in more severely affected dogs.[91]

Mortality rates can approach 50%,[91,92] and intensive monitoring and support are indicated. Administration of activated charcoal is associated with improved survival.[91]

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CHAPTER 287

Neoplasms of the Liver

Nick Bexfield

Client Information Sheet: Tumors of the Liver

Introduction

Prevalence

Tumors of the liver and the biliary tree in dogs and cats may be primary or metastatic. Primary tumors are relatively uncommon, representing 0.6-1.5% of all tumors in dogs.[1-3] Primary liver tumors represent about 1-3% of all tumors in cats, but up to about 7% of all nonhematopoietic tumors.[4,5] Metastatic tumors are approximately three times more frequent than primary liver tumors in dogs and most commonly originate from spleen, gastrointestinal (GI) tract and pancreas.[3,6] Primary tumors are more common than metastatic tumors in cats.[4] Benign tumors are more common in cats, but in dogs they are usually malignant.[1,3,5,7,8] Although peak incidence of primary hepatobiliary cancer occurs at 10-12 years of age in both species, cats develop malignant hepatic tumors at a younger age than benign tumors.[3,6,8-11]

Primary Tumor Tissues of Origin and Morphology

There are four general tissue types from which primary hepatic tumors are derived: hepatocellular, bile duct, neuroendocrine and mesenchymal. The morphologic types of primary hepatic tumor are massive, nodular and diffuse.[1] "Massive" is defined as a large solitary mass confined to one liver lobe; "nodular" tumors are multifocal and may involve multiple lobes; and "diffuse" disease includes multifocal or coalescing nodules affecting all lobes or diffuse effacement of the hepatic parenchyma.[4,12] The liver can also be involved in other neoplastic processes, including lymphoma (see ch. 344), systemic mastocytosis (see ch. 349) and malignant histiocytosis (see ch. 350).[5,12]

Dogs

The most common primary hepatic tumors in dogs are the hepatocellular adenoma and carcinoma. Bile duct adenoma and carcinoma are observed less frequently.[1] Fibromas, fibrosarcomas, hemangiomas and hemangiosarcomas are relatively uncommon primary hepatic neoplasms in dogs. In one study, 106 canine primary hepatic neoplasms were separated into well-defined groups based on histopathology and immunohistochemical stains for markers representative of hepatocytic and cholangiocytic (bile duct) lineages.[13] Results demonstrated 77% hepatocellular, 9% bile duct, and 3% hepatic neuroendocrine tumors.[13]

Cats

Bile duct adenomas are the most common (>50%) primary feline hepatobiliary tumor.[8,10,14-16] In a report of 61 feline primary liver tumors, classified into well-defined groups based on histopathologic and immunohistochemical examination, there were 41% bile duct, 34% hepatocellular, and 13% hepatic neuroendocrine tumors.[17] In this latter study, all the bile duct tumors were carcinomas, and no bile duct adenomas were identified. Further studies using immunohistochemistry may lead to an improved understanding of canine and feline primary hepatic tumors.

Nodular Hyperplasia: An Important Differential Diagnosis for Any Liver Mass

Hepatic nodular hyperplasia is relatively common and is identified in 15-60% of older dogs.[5] Nodular hyperplasia also occurs in older cats and can result in single or multiple nodules, often as an incidental finding during laparotomy or at post-mortem examination.[17,18] Nodular hyperplasia is often diffuse with a "classic appearance" of liver cancer. Thus, histology must be performed before condemning a dog or cat.

Pathology

Hepatocellular Tumors

Hepatocellular Carcinoma (HCC)

HCC is the most common primary hepatic tumor in dogs, accounting for >50% in some studies. It is the second most common tumor in cats.[1,4,5,8,10,12-14] The average age of affected dogs is 12 years; >80% of dogs are >10 years of age.[1,2,19] Although most studies failed to identify a breed or sex predisposition, 16% of affected dogs in one report were Miniature Schnauzers.[1,2,13,19] Morphologically, 53-83% of HCCs are massive, 16-25% are nodular and up to 19% are diffuse.[1,12] The left lateral and medial lobes and the caudate lobe are involved in over two thirds of dogs with massive HCC.[1,2,19,20] Metastasis is more common in dogs with nodular or diffuse HCC; common sites include the regional lymph nodes, peritoneum and lungs.[1,12,14] The metastatic rate varies from 0-37% for dogs with massive HCCs and 93-100% for dogs with nodular or diffuse HCCs.[1,2,8,10,12,14,19,20]

Hepatocellular Adenomas (Hepatomas)

Hepatomas are often an incidental finding at necropsy in dogs and only rarely cause clinical signs unless they rupture and hemorrhage.[12] In cats hepatocellular adenoma occurs more frequently than HCC.[14] In dogs and cats, adenomas can be encountered as palpably obvious abdominal masses that are sometimes pedunculated. Care must be taken to distinguish benign from metastatic disease. Solitary adenomas can become quite large and encroach onto other organs. Hepatoblastoma is rare and only reported in one dog.[21]

Tumor Lineages

On the basis of histopathology and immunohistochemical stains for markers representative of hepatocytic and cholangiocytic lineages, hepatocellular tumors in dogs could be divided into three subgroups, each with specific morphologic and immunohistochemical characteristics.[13] By far the largest subgroup were hepatocellular tumors with 0-5% positivity for keratin 19 (K19), likely derived from mature hepatocytes, which were well differentiated and had no evidence of metastasis.[13] A second group contained tumors with >5% positivity for K19, which were poorly differentiated and had intrahepatic and/or distant metastasis. These exhibited characteristics of hepatic progenitor cells (HPCs) without further differentiation towards cholangiocytic or hepatocellular lineages and may be derived from HPCs or through dedifferentiation of mature hepatocytes. A final small group had an intermediate position with regard to K19 staining and malignancy. In a similar study in cats, histopathology and immunohistochemistry classified 21 of 61 primary hepatic tumors as being of hepatocellular origin, and these were subdivided into adenomas (n = 18) and carcinomas (n = 3).[17] All of the hepatocellular carcinomas had evidence of intrahepatic and/or distant metastases.[17]

Bile Duct Tumors

There are two bile duct tumor types in dogs and cats: bile duct carcinoma and adenoma. Previous studies report that bile duct carcinoma, or cholangiocarcinoma, is the most common malignant non-hematopoietic hepatic tumor in cats, and second most common in dogs (Figure 287-1).[1,8,10,12,14] In a recent study where feline primary hepatic tumors were classified based on histopathology and immunohistochemical stains for markers representative of hepatocytic and cholangiocytic lineages, bile duct tumors (100% of which were malignant) were most common.[17] Previous reports suggested bile duct carcinomas account for 22-41% of all malignant liver tumors in dogs.[1,6] In one study, however, there was a relatively low frequency (9%) of bile

duct tumors in dogs.[13] In this study, all canine bile duct carcinomas were positive for immunohistochemical markers suggestive of derivation from differentiated mucin-producing cholangiocytes normally present in larger bile ducts.[13]

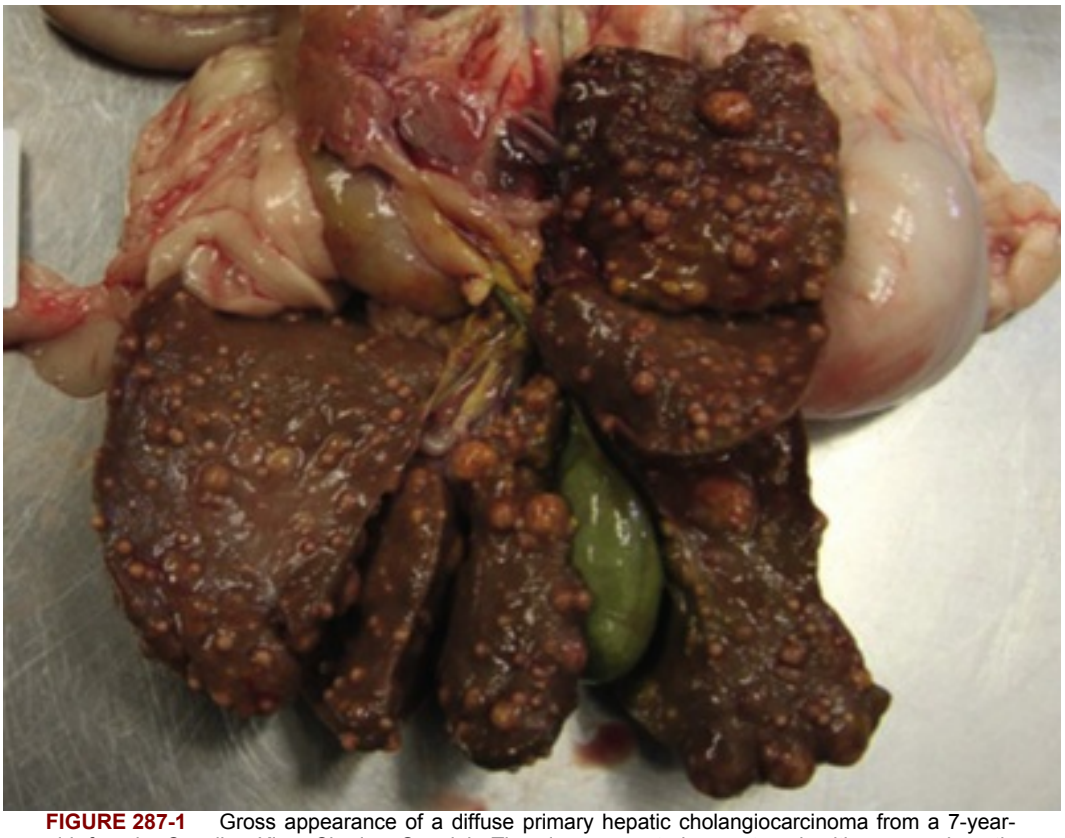

FIGURE 287-1 Gross appearance of a diffuse primary hepatic cholangiocarcinoma from a 7-year-old female Cavalier King Charles Spaniel. The dog presented comatosed with severe hepatic encephalopathy.

A breed predilection for Labrador Retrievers[22] and a sex predisposition for females have been suggested for canine bile duct tumors.[1,23,24] There are no apparent breed or sex predispositions for bile duct carcinomas in cats, in whom 37-46% are massive, up to 54% are nodular and 17-54% diffuse.[1,12,22,24] Bile duct carcinomas can be intrahepatic, extrahepatic or within the gallbladder. Intrahepatic locations are more common in dogs, whereas an equal distribution of intrahepatic to extrahepatic tumors has been reported in cats.[1,14] Bile duct carcinoma of the gallbladder is rare in dogs and cats and is an aggressive cancer with metastatic rates as high as 88% in dogs and 78% in cats. Metastasis occurs most often to the regional lymph nodes and lungs.[1,8,10,14,22,24] In one study, all feline bile duct tumors had infiltrative growth or vascular invasion together with intrahepatic and/or distant metastases. Three tumors were associated with adult-type congenital hepatic cystic disease.[17] In cats, 67-80% had diffuse intraperitoneal metastasis and carcinomatosis.[8,10]

Benign adenomas of the bile duct, due to their cystic appearance, are also called biliary or hepatobiliary cystadenomas. They can be single or multiple and usually do not cause clinical signs until large and compressing adjacent organs.[15,16,25] They have accounted for more than 50% of all feline primary hepatobiliary tumors.[5,8,10,14,15,25] However, in a recent study using histopathology and immunohistochemical stains for markers representative of hepatocytic and cholangiocytic lineages, none of 61 primary feline hepatic tumors was an adenoma.[17] In other reports, male cats appear to be predisposed, although no clear breed predispositions have been reported.[15,16] In a similar study using histopathology and immunohistochemistry, no biliary adenomas were noted among 106 dogs with primary hepatic tumors.[13]

Neuroendocrine Tumors

Neuroendocrine tumors, also known as hepatic carcinoids, arise from neuroectodermal cells and are infrequently reported in dogs and cats.[1,10,12-14,26,27] In one study, the frequency of neuroendocrine carcinomas in dogs (3%) and cats (13%) was relatively low.[13,17] Immunohistochemical stains used in the identification of human neuroendocrine tumors are useful in determining cell origin.[13,17,26,27] They are usually intrahepatic, although neuroendocrine tumors of the gallbladder have also been reported.[26,28-30] They tend to occur at a younger age than other hepatobiliary tumors, with a mean age of 7 years.[1,29] Primary hepatic neuroendocrine tumors are biologically aggressive and not usually surgically resectable due to their diffuse nature.[1,26,29] Frequent sites of metastasis include the regional lymph nodes, peritoneum, and lungs, with other reported sites including the heart, spleen, kidney, adrenal glands and pancreas.[29]

Mesenchymal and Other Tumors

Primary tumors of mesenchymal origin are rare in cats and dogs.[1,8,10,12,14,31] In two recent studies of 106 primary hepatic tumors in dogs and 61 in cats, no mesenchymal tumors were identified.[13,17] Hemangiosarcoma, leiomyosarcoma and fibrosarcoma are more frequently identified. Other reported sarcomas include rhabdomyosarcoma, liposarcoma, osteosarcoma, chondrosarcoma and malignant mesenchymoma.[1,8,10,12,14,31-36] Hemangiosarcoma is the most frequently reported primary hepatic mesenchymal tumor in cats and leiomyosarcoma the most common in dogs. Massive and nodular morphology have been reported in 33% and 67% of cases respectively.[1,31] Males appear predisposed to mesenchymal tumors with no known breed associations.[1] Hepatic mesenchymal tumors are biologically aggressive, with pulmonary and splenic metastasis reported in 86-100% of dogs.[1,31] Dogs with disseminated histiocytic sarcoma often have hepatic involvement.[37-39] Myelolipomas are a benign hepatobiliary tumor of cats and can be single or multifocal.[4,5,40,41] Histologically they are composed of adipose tissue intermixed with normal hematopoietic elements. They are usually benign in behavior.

Clinical Signs and Physical Examination Findings

Clinical signs of hepatic neoplasia are usually vague, nonspecific, and they include lethargy, inappetence, weight loss, vomiting, polyuria/polydipsia, pyrexia and ascites.[5] Uncommonly, neurologic signs may develop due to paraneoplastic hypoglycemia, hepatic encephalopathy or central nervous system metastasis.[1,26,27,42,43] Weakness due to myasthenia gravis associated with a HCC has been described in one dog.[44] Icterus is more common in dogs with bile duct carcinomas and diffuse neuroendocrine tumors.[1,12,24] Clinical signs are of relatively little value in differentiating primary or metastatic liver tumors from nonneoplastic hepatic disease. Approximately 50% of cats and 25% of dogs with hepatobiliary tumors show no clinical signs. Many are diagnosed with a liver tumor only during investigation of increased liver enzyme activities.[5] Physical examination is often unrewarding, aside from palpating a cranial abdominal mass or hepatomegaly in up to 75% of dogs and cats with a liver tumor. Paraneoplastic alopecia has been reported in one cat with an advanced HCC.[45]

Diagnosis

Clinical Pathology

Hematology and Coagulation Testing

Clinicopathologic features are usually nonspecific. Hematology may reveal a mild nonregenerative anemia due to chronic disease, red blood cell (RBC) sequestration, RBC destruction or iron deficiency.[5,46] Neutrophilic leukocytosis may be seen with neoplasia-associated inflammation or necrosis.[1,2,19,20] Thrombocytosis is seen in approximately 50% of dogs with massive HCC.[20] Primary or metastatic hepatic hemangiosarcomas may result in a regenerative anemia and thrombocytopenia.[5] Prolonged coagulation times are a potential consequence of any liver disease, although they are rarely clinically significant unless liver failure has occurred as a consequence of diffuse disease. About 20% of dogs with extensive or advanced HCC have prolonged coagulation times (see ch. 196 and 197).[19,20] Animals with hepatic hemangiosarcoma are at

risk of developing disseminated intravascular coagulation (DIC).[47]

Serum Biochemistries

Liver enzyme activities are commonly increased in dogs and cats with hepatobiliary tumors, indicative of hepatocellular or biliary epithelial damage or biliary stasis.[5,48] However, increased hepatic enzyme activity is not specific for hepatic neoplasia and does not reflect degree of hepatic neoplastic involvement. Compared with metastatic hepatic tumors, primary hepatic tumors are more likely to result in hypoproteinemia, hypoglycemia and increases in serum alkaline phosphatase and alanine transaminase activities. They are less likely to cause hyperbilirubinemia.[3,48] In dogs, an aspartate aminotransferase to alanine aminotransferase (AST : ALT) ratio of <1 was consistent with a HCC or bile duct carcinoma in one study, whereas a higher ratio was more likely with neuroendocrine or mesenchymal tumors.[1]

Hepatic Testing

Elevated serum bile acid concentrations, a nonspecific abnormality, have been reported in 50-75% of dogs and 33% of cats with liver tumors. While biliary neoplasia is more common in cats, only 33% have icterus. Other biochemical changes may include hypercalcemia, hyperglobulinemia, and hypoglycemia.[1] Hypoglycemia may be seen as a paraneoplastic effect due to a large tumor mass consuming glucose or reflect production of an insulin-like substance (see ch. 352).[42,43] Hypoalbuminemia, more common in dogs than cats, may reflect a negative acute phase response, catabolism and poor nutritional intake, or hepatic insufficiency. Increased serum pancreatic lipase (PL) activity was reported in six dogs with either pancreatic or hepatic neoplasia.[49] Alpha-fetoprotein (AFP), a glycoprotein produced by fetal, neoplastic, and regenerating hepatocytes, is increased in about 75% of dogs with HCC and 55% with bile duct carcinomas.[50,51] Serum AFP levels decrease in dogs after surgical removal of HCC.[52] However, AFP has multiple potential sources in dogs, both neoplastic and non-neoplastic, limiting its utility as a diagnostic or therapeutic marker.[50,51] No studies have been performed to assess AFP in cats with liver tumors.

Imaging

Radiology

Imaging is valuable for the diagnosis, staging and surgical planning of animals with hepatobiliary tumors. Abdominal radiography may identify a cranial abdominal mass with caudal and lateral displacement of the stomach. Ascites may interfere with visualizing a mass.[5,19,23] Occasionally, dystrophic mineralization of a mass or the biliary tree is identified.[4] Assessment of thoracic radiographs is considered critically important to exclude metastatic disease.

Abdominal Ultrasound (US)

Abdominal US (see ch. 88) offers several advantages over abdominal radiographs in animals with hepatic disease. It can be used for determining presence of a hepatic mass and for identifying any mass as massive, nodular or diffuse.[5,53-55] In focal disease, US can be used to determine mass size, location, and its relationship to surrounding structures. For the detection of mass lesions, however, sensitivity varies widely and is dependent on operator skill, equipment, and tumor type.[55,56] Diffuse tumors are usually seen as having hypoechoic, heterogeneous, or multifocal parenchymal nodules or masses. Less commonly, mass lesions appear diffusely hyperechoic or, occasionally, normal.[57] A cystic component may be seen in biliary cystadenomas or hepatic hemangiosarcomas. However, one must be cautious with hepatic masses seen on US since a recent study demonstrated marked variability in US appearance for all types of liver disease in dogs. No associations between US appearance and histologic diagnosis could be made.[57] The most prevalent US features were multifocal hepatic lesions in 63% of dogs with hemangiosarcoma and 43% with HCC. Target lesions associated with malignancy were identified in 67%.[57] Doppler (color flow) assessment of mass lesions may demonstrate vascularization patterns helping to distinguish tumors from other benign processes.[5,58] The Doppler perfusion index can be of value in assessing lymph nodes and liver for metastases.[59] Contrast-enhanced US can help differentiate benign from malignant lesions.[60-62]

Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) Scans

Advanced imaging techniques can be useful for diagnosis and staging of liver tumors. MRI of focal hepatic or splenic lesions in dogs was reported to have high sensitivity (100%) and specificity (90%) in differentiating malignant from benign masses. MRI results correctly identified HCC.[63] In humans, CT and MRI are excellent for detecting small hepatic lesions and determining the relationship of liver masses to surrounding structures.[32] MRI provides superior soft-tissue contrast and is likely to provide better lesion detection, quantification and localization when compared to CT.

Fine Needle Aspiration (FNA) and Biopsy

Results of diagnostic imaging and clinical pathology do not typically provide definitive diagnoses in patients with liver masses. Obtaining samples for cytology and/or histology can be vital in providing additional information and, in many cases, a definitive diagnosis. Exceptions may be made for solitary and massive hepatic masses, when surgical resection is performed without a preoperative histologic diagnosis because surgery can provide both diagnosis and treatment. Samples can be collected by FNA or biopsy via US-guided needle core biopsy (see ch. 89), laparoscopy (see ch. 91), or laparotomy. Coagulation profiles are advised prior to any biopsy (see ch. 196). Mild to moderate hemorrhage is a relatively frequent complication (about 5%).[53,55,56,64] General anesthesia or heavy sedation should be used to avoid patient movement during needle biopsy.

The main disadvantage of FNA cytology is its limited diagnostic accuracy. In one study, agreement between cytology and histopathology was about 30% in dogs and 50% in cats.[65] With focal lesions, FNA can prove useful and may negate need for biopsy. In dogs with focal hepatic lesions, sensitivity of US-guided FNA cytology versus histopathology for the identification of neoplasia was 52%. Cytology had the highest positive predictive value when the lesion was neoplastic (87%).[66] FNA for diagnosis of diffuse hepatic neoplasia is generally more reliable.[67] More invasive techniques, such as laparoscopy and laparotomy can also be used to obtain tissue for definitive diagnosis or staging. Follow-up US several hours after biopsy should also be performed to assess the biopsy site for bleeding. Careful postoperative monitoring, ideally for 24 hours, is also advised.

Treatment

Solitary Hepatocellular Carcinoma

Surgical resection, usually lobectomy, is recommended for most solitary primary hepatic tumors that have not metastasized, especially in dogs with a massive HCC.[20] Surgery is rarely an option for most nodular or diffuse hepatobiliary tumors, as complete resection is impossible. However, localized resection of primary or metastatic nodules is sometimes considered if likely to provide palliation of clinical signs, such as reducing potential for life-threatening hemorrhage. Biliary tree diversion (biliary enteric anastomoses) should be considered for obstructive lesions involving the extrahepatic biliary structures because long-term palliation is possible and chronic biliary tree occlusion results in cirrhosis. Advanced imaging prior to surgical resection of liver tumors can accurately assess tumor location and extent. Preoperative preparation of patients for liver lobectomy includes correction of volume deficiency, electrolyte abnormalities, anemia and clotting factor deficiencies. In 42 dogs with massive HCC treated by liver lobectomy, intraoperative mortality rate was about 5% and the complication rate almost 30%.[20] Complications of surgical resection include hemorrhage, vascular compromise, reduced hepatic function and hypoglycemia.[4,20,69]

Nodular or Diffuse Hepatocellular Carcinoma

Radiation therapy has little place in managing hepatic tumors. The liver is exquisitely sensitive to even low amounts of radiation and there is difficulty in limiting tissue exposure.[5] HCC is considered "chemo-resistant" in humans, with response rates <20%.[32] Adjunctive, postoperative chemotherapy generally does not provide significant benefit in dogs or cats with primary liver tumors. However, single-agent gemcitabine therapy has been used in dogs with HCC (4 massive, 10 nodular and 4 diffuse). Their median survival time was 983 days.[70] In one study, 1/4 dogs with massive HCC treated with mitoxantrone had complete resolution.[71] No comparable information is available on the use of gemcitabine or mitoxantrone in cats.

Although liver transplantation, directed delivery of chemotherapeutic agents (intraarterial chemotherapy), transarterial chemoembolization, and immunotherapeutic regimens using tumor-specific antigen have been

used in humans with HCC, these have not been explored extensively in animals.[72,73] Blind embolization and chemoembolization have been reported with moderate success in treating a limited number of dogs with non-resectable HCC (see ch. 125).[74,75] Liver lobectomy is recommended for cats with a single bile duct adenoma or multiple lesions confined to one or two lobes.[8,10,15,16,25] Lobectomy is also recommended for cats and dogs with a massive bile duct carcinoma.

Nodular or Diffuse Bile Duct Carcinomas

There is no known effective management option for animals with these cancers. Surgical resection is not possible and these tumors are not sensitive to radiation or chemotherapy.[5] As most neuroendocrine tumors are nodular or diffuse, and behave aggressively, they are generally not amenable to surgical resection. There are no reports of the use of radiation therapy or chemotherapy for this tumor type in dogs or cats.

Solitary Massive Mesenchymal and Other Tumors

Lobectomy is recommended for solitary and massive mesenchymal tumors, although many have metastasized at the time of diagnosis.[1,31] Radiation therapy is usually of limited efficacy in primary hepatic mesenchymal tumors. There are few reports of chemotherapy for the management of these hepatic cancers. Based on the response to chemotherapy for mesenchymal tumors at other sites, it is likely that primary mesenchymal hepatic tumors will respond poorly. However, adjunctive chemotherapy may be considered for visceral hemangiosarcomas.[76-78] There are few reports on management options for unusual primary hepatic tumors, although liver lobectomy is recommended for cats with a single primary hepatic myelolipoma.[5] Hepatic lymphoma (see ch. 344), systemic mastocytosis (see ch. 349) and malignant histiocytosis (see ch. 350) may all be managed by systemic chemotherapy.[5]

Prognosis

Dogs

Prognostic factors for dogs with massive HCC include tumor location, serum ALT and AST activity, and ratios of alkaline phosphatase (ALP) to AST and ALT to AST.[20] Histopathologic subtype of HCC and anaplastic characteristics may also influence prediction of metastasis and prognosis. Median survival time of 42 dogs with massive HCC managed by liver lobectomy was not reached after more than 1460 days of follow-up.[20] In comparison, the median survival time was only 270 days for dogs managed conservatively, and these were about 15 times more likely to die of tumor-related causes than dogs treated surgically.[20] While location of a massive HCC may increase surgical risk, location has no impact on outcome for dogs that survive surgery. The prognosis for dogs with massive HCC is good, with local tumor recurrence reported in 0-13% following lobectomy.[19,20] However, metastatic disease to other parts of the liver or other organs has been reported to be as high as 37%.[19,20] In contrast, as surgical resection is not usually possible, the prognosis for dogs with nodular and diffuse HCC is poor.

Cats

The prognosis for cats with surgically resectable bile duct adenomas is excellent, with no reports of local recurrence or malignant transformation.[8,15,25] However, survival times for cats and dogs with massive bile duct carcinoma managed by surgical resection are poor, with the majority dying within six months due to local recurrence or metastatic disease.[5,8] The prognosis for primary hepatic neuroendocrine tumors is poor as they are rarely resectable, and metastasis to regional lymph nodes, peritoneum and lungs has usually occurred by the time of diagnosis.[1,29] Despite surgical resection being an option for some primary hepatic mesenchymal tumors, as metastatic disease is often present at the time of diagnosis, the prognosis is again poor.[1,31] However, this strategy may provide palliation of space-occupying effects of the tumor, or prevent life-threatening hemorrhage from occurring. The prognosis for cats with primary hepatic myelolipoma is excellent, with prolonged survival times and no reports of local recurrence.[4,41]

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CHAPTER 288

Diseases of the Gallbladder and Extrahepatic Biliary System

Ale Aguirre

Client Information Sheet: Diseases of the Gallbladder

Anatomy and Physiology

The gallbladder is a teardrop-shaped organ situated in the cranioventral abdomen between the right medial and quadrate liver lobes. The gallbladder is a reservoir where bile is stored, modified, and eventually expelled. Bile is formed in the hepatocytes and is actively secreted into the bile canaliculi. From the canaliculi, bile flows to the intralobular ducts and ultimately to the lobar ducts. The lobar ducts give rise to the left and right hepatic ducts. The cystic duct is an offshoot of the hepatic ducts and travels toward the gallbladder. The cystic duct is an important landmark distinguishing the otherwise continuous hepatic ducts from the common bile duct (Figure 288-1). There is substantial variation in the number of hepatic ducts and their anastomoses with the common hepatic and cystic ducts.[1-3] Bilobed and duplex gallbladders have been observed in some cats.[4]

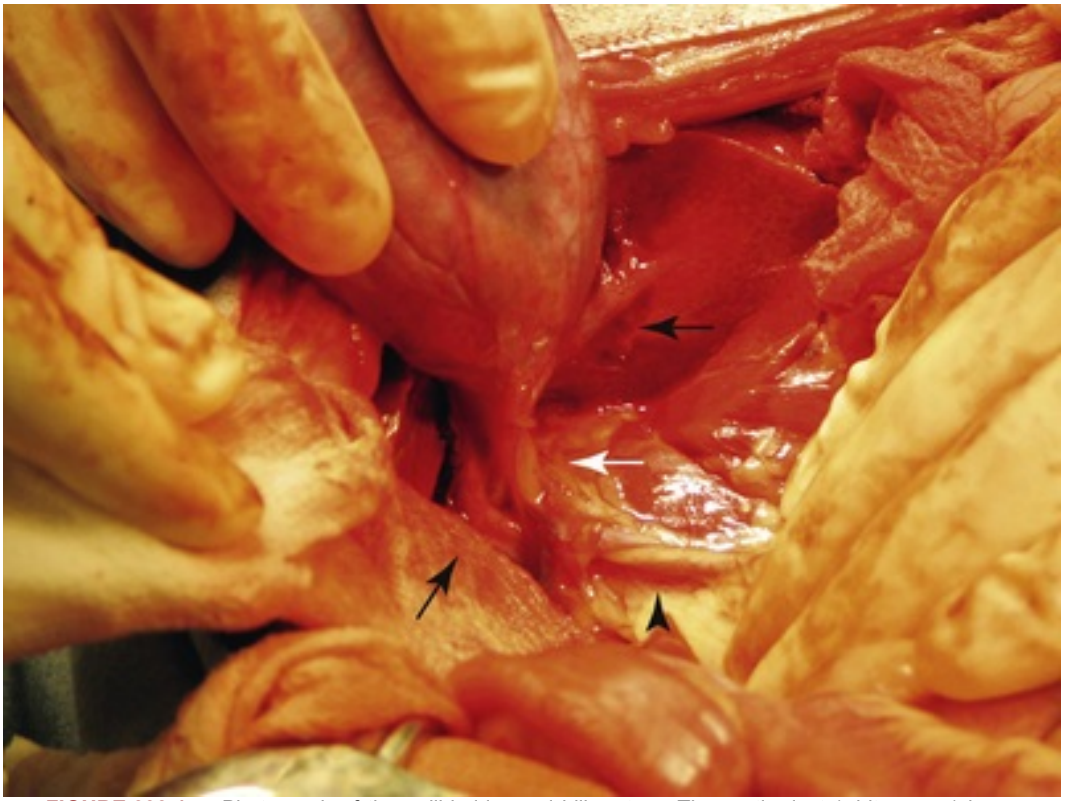

FIGURE 288-1 Photograph of the gallbladder and biliary tree. The cystic duct (white arrow) is an important landmark because it joins the gallbladder to the biliary tree and separates the more proximal hepatic ducts (black arrows) from the more distal common bile duct (black arrowhead).

Bile is composed of cholesterol, lecithin, phospholipids, and bile salts. Bile emulsifies fat and neutralizes acid in partially digested food. Gallbladder contraction releases bile into the common bile duct where it enters the duodenum through the sphincter of Oddi. In the dog, the common bile duct joins the minor pancreatic duct and both exit separately at the major duodenal papilla.[5] In the cat, the common bile duct fuses with the major pancreatic duct before entering the duodenum.[1]

See algorithm for diseases of the gallbladder and extrahepatic biliary system (Figure 288-2).

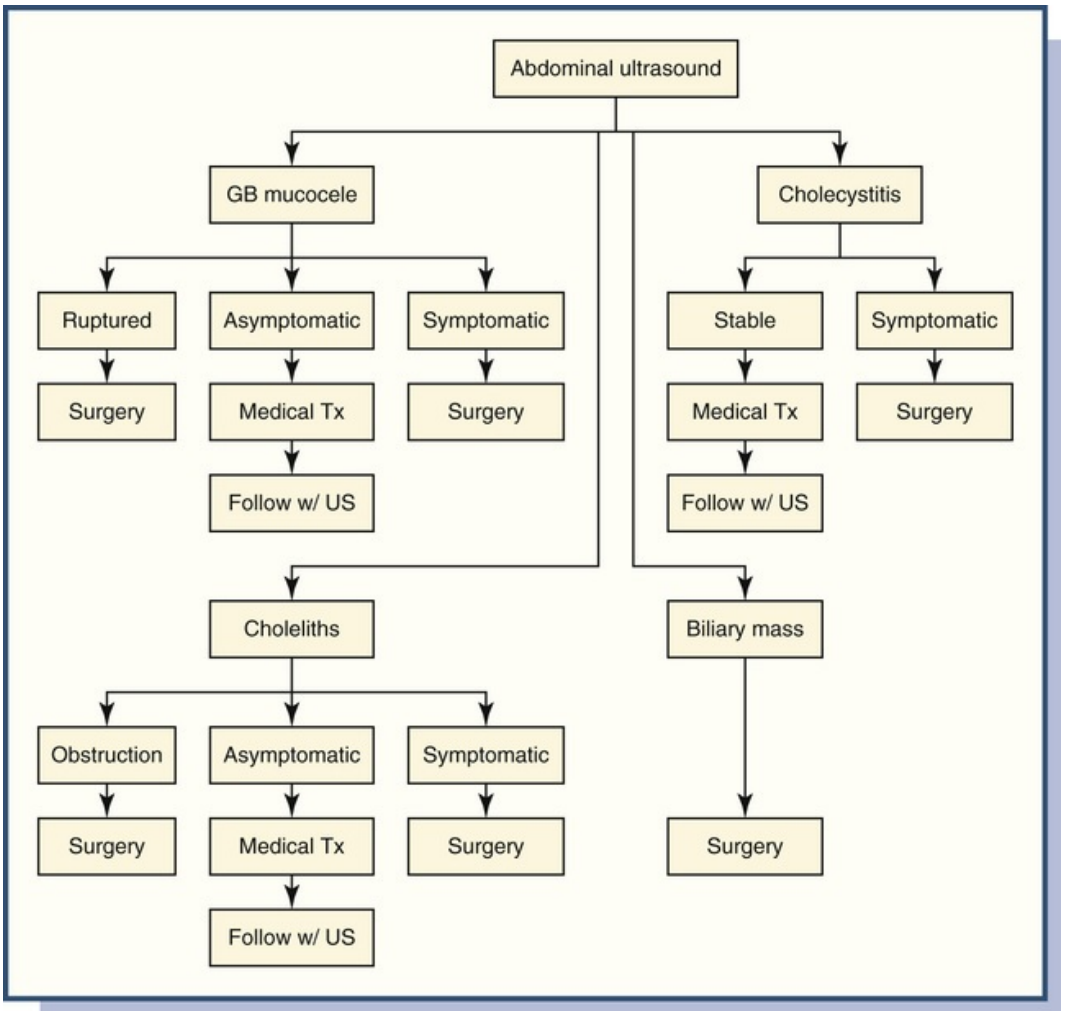

FIGURE 288-2 Algorithm for diseases of the gallbladder and extrahepatic biliary system.

Cholelithiasis and Choledocholithiasis

Etiology

Choleliths, or gallstones, are one of the more commonly recognized abnormalities of the gallbladder.[6,7] Older female dogs are predisposed and breeds most commonly affected include Miniature Schnauzers and Miniature Poodles. In the dog, cholesterol, bilirubin, and mixed choleliths have been reported.[6] Calcium-based stones are rare due to the ability of the canine gallbladder to absorb free calcium in bile.[2,8] Feline choleliths contain cholesterol, bilirubin derivatives, and calcium salts.[9]

The origin of choleliths is only partly understood and species variation is evident. Cholesterol is strongly hydrophobic, necessitating transport in micelles to remain suspended in solution. When an imbalance occurs between bile salts and cholesterol, bile becomes more viscous leading to the formation of gallstones. Various abnormalities may promote cholelithiasis. These include gallbladder dyskinesia, hypercholesterolemia,

hypertriglyceridemia, hyperbilirubinemia, endocrine disease, and cholesterol absorption and transport defects in the gallbladder. Breed and species predisposition also play a role.[10]

Choledocholiths, stones in the common bile duct, may be primary or secondary. Primary stones develop directly in the common bile duct. Secondary stones are more common and form in the gallbladder, later passing into the common bile duct.

Clinical Signs

A variety of clinical presentations are possible with choleliths. Many small animal patients are asymptomatic. In more serious cases, the gallbladder or bile duct may rupture, leading to bile peritonitis.[11] Of those presenting for medical care, abdominal pain, vomiting, anorexia, and icterus are the most consistent clinical signs. Caution must be taken in interpreting clinical signs as many abdominal disorders such as pancreatitis, gastroenteritis, gastrointestinal foreign bodies, and abdominal neoplasia manifest in similar manners.[2,6,7]

Diagnosis

Laboratory findings vary widely with cholelithiasis. A stress leukogram is the most common finding. However, a neutrophilic leukocytosis with a left shift is typical in patients with biliary rupture. Mild to moderate nonregenerative anemias occur in patients with chronic disease. The total bilirubin, alkaline phosphatase (ALP), and gamma-glutamyltransferase (GGT) are frequently elevated. Bilirubinuria is often evident and generally precedes clinical jaundice. Due to the short half-life of ALP in the cat (6 hours compared with 72 hours in dogs), even mild increases are significant.[2,12] Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations, when present, are less dramatic than rises in ALP and GGT. Mild hypercholesterolemia occurs with cholestasis and severe elevations are observed with biliary obstruction. Hypoalbuminemia and hypoglycemia may occur if sepsis or endotoxemia are present.[2,6,7]

Abdominal radiographs are often of limited diagnostic value as most stones contain insufficient calcium to be seen. If visualized, they appear as single or multiple radiopaque structures in the cranioventral abdomen on lateral radiographs and in the right cranial abdomen on ventrodorsal radiographs.[6]

Ultrasonography is the diagnostic modality of choice. An experienced ultrasonographer may identify gallstones, thickened gallbladder wall, biliary tree dilation, or pericholecystic fluid.[6,13-15] Extrahepatic ductular dilation may be evident within 24 to 48 hours of complete obstruction, whereas intrahepatic duct dilation takes 5 to 7 days to develop.[13] In cats, a common bile duct greater than 5 mm is indicative of extrahepatic biliary obstruction.[14] Ultrasonographic gallbladder contraction studies using Lipofundin and erythromycin have been studied and may aid in the determination of a biliary obstruction.[16-20]

Treatment

Medical dissolution therapy for acute obstructing choleliths is rarely successful. Treatment is aimed at supportive care until the stone or stones pass. Intravenous fluids, antibiotics, and analgesics aid patients with mild to moderate biliary obstruction. In patients with severe obstructive disease, reestablishing patency of the biliary tract is paramount and best accomplished with surgery. Multiple surgical procedures have been described. Choleliths lodged in the bile ducts may often be removed after a cholecystectomy, but occasionally require a choledochotomy. Cholecystectomies and choledochotomies have lower morbidity and mortality rates and are therefore the treatments of choice.[21] In contrast, other procedures may be necessary depending on several factors including viability of the bile ducts, presence of strictures, and location of the biliary obstruction, but these generally carry higher mortality rates.[5,22,23] Minimally invasive biliary diversions techniques exist and include ultrasound-guided transhepatic or transabdominal percutaneous drainage or laparoscopic assisted transperitoneal percutaneous catheter placements.[24,25]

Biliary Stenting

Surgically and endoscopically placed choledochal stents are revolutionizing the treatment of extrahepatic biliary disorders in both dogs and cats (see ch. 123).[26-29] Two general types of biliary stents exist. Plastic (polyurethane) stents are used to facilitate drainage and to maintain patency of the biliary tree. Plastic stents often dislodge after weeks to months on their own or they may be removed endoscopically if desired (

Video 288-1). Self-expanding metallic stents are considered more permanent and are generally reserved for recurrent disease or malignancies of the bile duct (Figure 288-3). Both types of stents have been successfully placed for quite some time through open surgical approaches.[26,27,29]

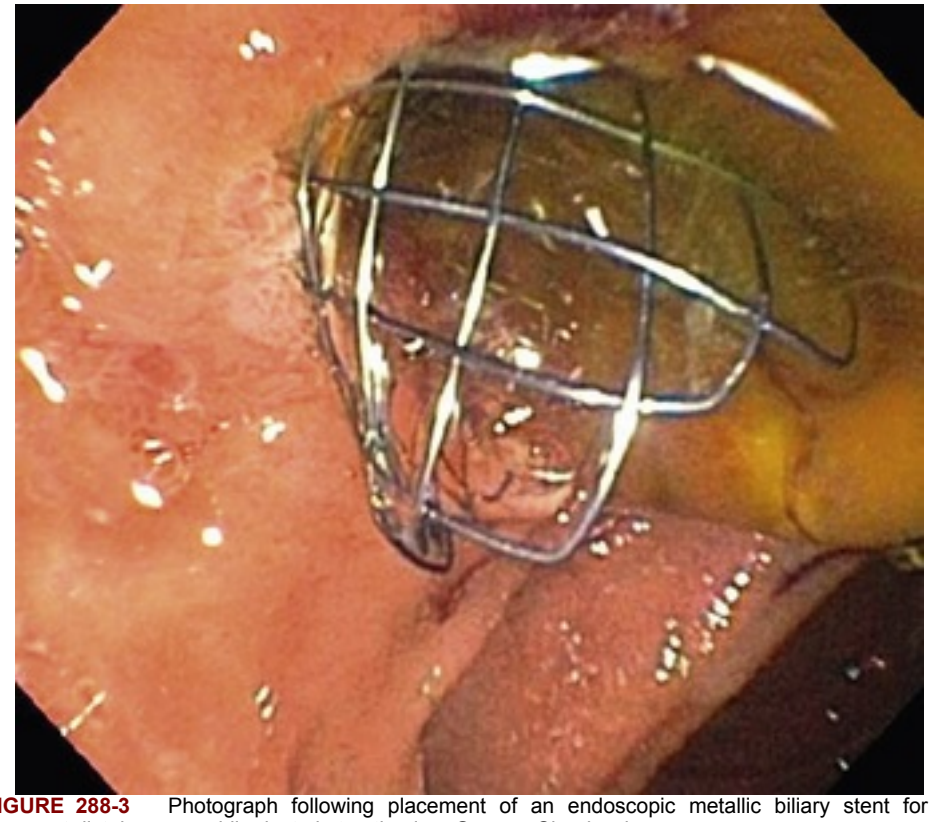

FIGURE 288-3 Photograph following placement of an endoscopic metallic biliary stent for a recurrent distal common bile duct obstruction in a German Shepherd.

Endoscopic retrograde cholangiopancreatography (ERCP) uses a combination of endoscopy and fluoroscopy to evaluate the biliary tree in a less invasive manner (see ch. 123). New reports have demonstrated its use in clinical patients.[28-32] A side-view endoscope is advanced in the proximal duodenum allowing for direct visualization of the major duodenal papilla. A sphicterotome catheter and guidewire are inserted through the endoscope into the major duodenal papilla. Fluoroscopy is used to monitor the advancement of the guidewire. Once access to the common bile duct has been obtained, contrast is injected and monitored fluoroscopically during the ERPC portion of the procedure. Strictures, stones, and malignancies are visualized with experience. A sphincterotomy is performed to open the sphincter of Oddi and to facilitate the advancement of other instrumentation. Stones or sediment, if present, may be removed by sweeping the bile duct with balloons. In addition, dilation of strictures and tumors may be performed to restore the flow of bile. To maintain patency of the biliary tree, a stent can be placed in the common bile duct via the endoscope (see Video 288-1). Complications are infrequent, but may include pancreatitis, duodenal or biliary perforation, bacterial cholangitis/cholangiohepatitis, and stent-induced strictures.[28,29,33]

Cholecystitis

Etiology

Cholecystitis has been used to define both inflammatory conditions of the gallbladder, as well as gallbladder-related symptoms in the absence of gallstones.[34] The term encompasses a wide variety of acute and chronic diseases, with or without bacterial or parasitic infections. The origin of cholecystitis in companion animals is poorly understood. Predisposing factors include bile stasis, gallbladder mucoceles, ascending bacterial or parasitic diseases, and biliary neoplasia.[34] Infarction and hematogenous spread of bacteria may also be involved. In cats, bacterial infections are thought to be secondary to inflammation rather than the inciting

factor.[35] Concurrent choleliths are identified in some patients, but the causal relationship is unknown.[2,6,36]

Some patients with cholecystitis develop necrotizing cholecystitis. Necrotizing cholecystitis is often referred to as a separate disease entity because of its severe manifestation, increased risk of complications, and higher mortality rate.

Clinical Signs

Cholecystitis may be either acute or chronic in nature. Mild cases are often asymptomatic. With moderate to severe acute cholecystitis, anorexia, vomiting, abdominal pain, and fever predominate. The presence of icterus is variable. Chronic cholecystitis is much more difficult to diagnose. Clinical signs may include intermittent anorexia, vomiting, and progressive weight loss. Abdominal pain may be present, but can be difficult to detect on examination. Abdominal effusions occur with cholecystitis due to gallbladder rupture and bile peritonitis.

Diagnosis

Similar to cholelithiasis, laboratory findings vary widely with cholecystitis. Most clinicopathologic changes are consistent with cholestasis or posthepatic biliary disease.[2,36] In cats with cholecystitis, elevations in ALT, ALP, and total bilirubin correlate well with ultrasonographic changes and potentially indicate more clinical significance.[37]

Aspirates of effusion typically yield a yellow green fluid suggestive of bile.[38,39] Analysis of bilious effusion is characterized by suppurative inflammation with or without bile pigment. Intracellular and extracellular bacteria are common. Total protein measurements range from 2.9 to 5.6 g/dL. If the bilirubin in the effusion is greater than twice that of circulating blood, then a biliary rupture is present.[38,39]

Radiographic features vary and may include decreased serosal detail consistent with an abdominal effusion, choleliths, or emphysema of the gallbladder.[39] Diagnosis through ultrasonography is the current gold standard in companion animals.[13] Ultrasound reliably reveals suspended sediment, choleliths, thickened gallbladder wall, extrahepatic biliary obstruction, and emphysema of the gallbladder (Figure 288-4). Hyperechoic sludge in the gallbladder or extrahepatic biliary tree is particularly concerning in cats and is often indicative of cholecystitis.[14,37,40] In contrast, biliary sludge is common in older dogs and is often insignificant.[41] In cats, a gallbladder wall thickness of greater than 1.0 mm accurately predicts gallbladder disease.[42] Pericholecystic fluid and omental adhesions, if detected, are suggestive of perforation.[15] Abdominal effusions are readily observed and may contain particulate material.

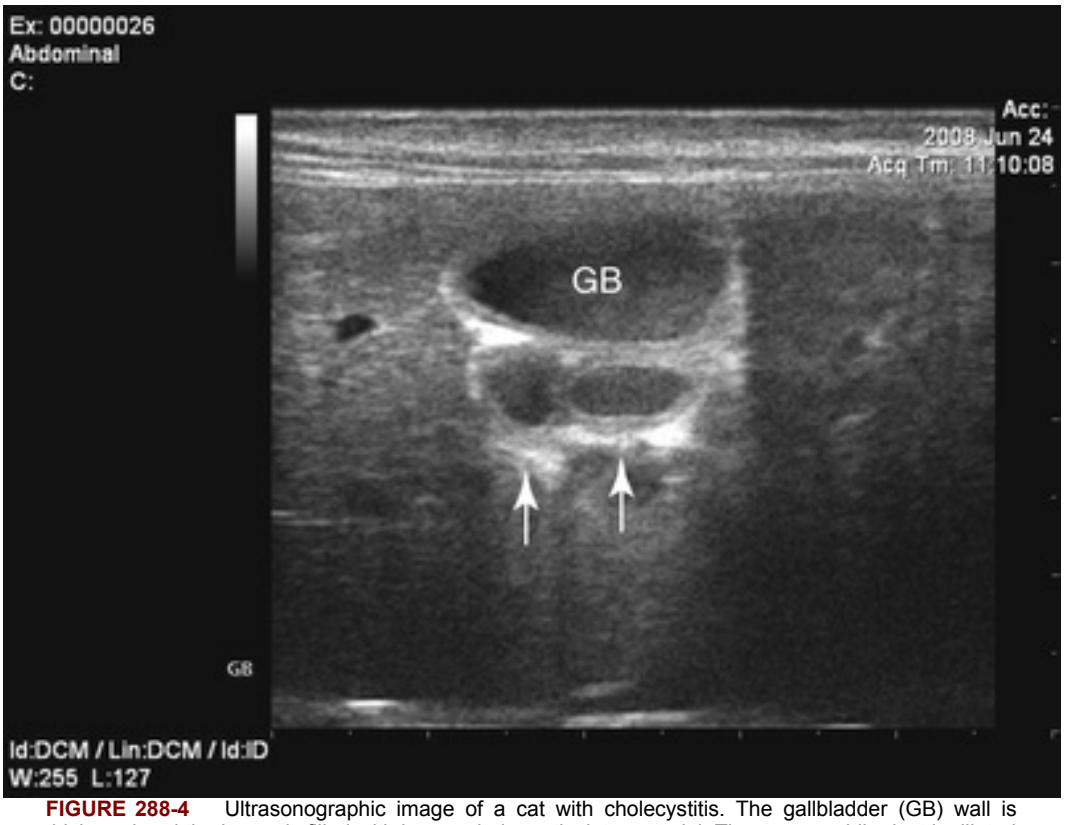

FIGURE 288-4 Ultrasonographic image of a cat with cholecystitis. The gallbladder (GB) wall is thickened and the lumen is filled with hyperechoic particulate material. The common bile duct is dilated and tortuous (arrows).

Treatment

Both medical and surgical management are available for patients with cholecystitis.[2,6,36,43] Medical management routinely includes antimicrobials, IV fluids, and analgesics. Cholecystocentesis is useful both as a diagnostic tool and method of therapy.[44] The transhepatic approach is preferable as the liver provides internal compression at the drainage site. The procedure has minimal risk when the gallbladder is drained completely, limiting the possibility of leakage. Bile peritonitis and vasovagal collapse are known complications. Positive bacterial cultures have been found in 62% of patients with cholecystitis. *Escherichia coli, Enterococcus* spp., *Bacteroides* spp., *Streptococcus* spp., *Clostridium* spp., and *Helicobacter* spp. are the most common isolates.[35,45] Culture results revealed 80% of the organisms were sensitive to ciprofloxacin and aminoglycosides. First-generation penicillin and cephalosporin efficacy is less reliable.[45] Antibiotic selection should be based on specific culture results when possible and treatment continued for a minimum of 1 month and potentially longer to ensure adequate resolution. In severe cases of cholecystitis or patients with bile peritonitis, cholecystectomy is the preferred treatment as it immediately removes the major source of infection.[36,39] Ultrasonographic gallbladder contraction studies may aid in the decision whether to pursue medical versus surgical treatment.[16-20]

Emphysematous Cholecystitis

Emphysematous cholecystitis is a rare manifestation of acute cholecystitis complicated by gas-producing organisms.[11,46-50] Gas may accumulate in the lumen, wall, or pericholecystic tissues. It is a rare disease entity in the dog and extremely rare in cats. An association with diabetes mellitus has been documented in the dog.[48]

Clinical signs and clinicopathologic data are similar to cholecystitis. Radiographically, the disease is characterized by a spherical to ovoid gas opacity superimposed over the hepatic silhouette.[46-48] On ultrasound, a gas interface is seen in the area of the gallbladder with variable distal shadowing. The

gallbladder wall, echogenic sediment, and fluid may be obscured depending on the amount of reverberation.[46-48] Adhesions, localized pericholecystic fluid, or generalized echogenic effusions often correlate with biliary rupture.[15] Computed tomography (CT scan) is ideal for the diagnosis as it allows for direct visualization of gas in the gallbladder lumen, wall, and biliary ducts.[34] Surgical intervention is most appropriate due to the high risk of gallbladder rupture and septic peritonitis.[36,39,46-48] Anaerobes are most commonly isolated and include *E. coli* and *Clostridium perfringens.*[48] Fluoroquinolones, metronidazole, and chloramphenicol are commonly used as they achieve high concentrations in bile and have strong anaerobic activity. Necrotizing cholecystitis and small bacterial abscesses in the gallbladder wall are often seen on histopathology.[36,48] A favorable prognosis is possible if the patient survives the perioperative period. Death is often due to sepsis, shock, or peritonitis.

Biliary Neoplasia

Primary tumors of the gallbladder and biliary tree are exceedingly rare, yet the number of reported cases is increasing in both dogs and cats.[2,51-57] Biliary cystadenomas and biliary adenocarcinomas (cholangiocarcinoma) are well-established tumors of the biliary tree.[58] Recently large cell lymphoma in dogs as well as small cell lymphoma and neuroendocrine carcinomas in cats have been recognized due to improved diagnostic capabilities.[54-57]

Biliary Cystadenomas

Biliary cystadenomas occur with some frequency in elderly cats and are rare in dogs. They arise most commonly from the intrahepatic bile ducts and less frequently from the extrahepatic bile ducts.[53] They comprise greater than 50% of all feline hepatobiliary tumors.[51] A male predisposition has been observed in the cat.[53] They can be single or multifocal and involve one or more hepatic lobes. Malignant transformation has been observed in some cats.[51]

Biliary cystadenomas are often incidental findings in older cats.[51-53] Hematologic changes are generally absent. Mild elevations in hepatic transaminases on routine health screens may be the only indication. Few clinical signs are noted and if present are associated with space-occupying disease. Ultrasound-guided aspirates of cystadenomas typically reveal a yellow to clear fluid with variable cellularity. A definitive diagnosis is best achieved with a tissue core, laparoscopic wedge, or open surgical biopsies.

Small multifocal cystadenomas should be followed with ultrasound and surgical resection is rarely necessary. Large cystadenomas may require surgery and carry a favorable prognosis even when partial resection is achieved.[51,53]

Biliary Carcinomas (Cholangiocarcinoma)

Biliary carcinomas are the most common feline hepatobiliary tumor and the second most common hepatobiliary tumor in dogs.[51] Biliary carcinomas are likely to arise from intrahepatic ducts in dogs; however, cats may have both intrahepatic and extrahepatic tumors. Labrador Retrievers and female dogs are thought to be at increased risk.[51] Biliary carcinomas of the gallbladder itself are exceedingly rare in both species.

Most biliary carcinomas are slow-growing neoplasms that are initially locally aggressive. Tumors are often advanced at the time of diagnosis, as clinical signs are rarely present prior to the onset of biliary obstruction. Patients with advanced biliary adenocarcinomas often present with lethargy, vomiting, weight loss, and icterus.[59] Metastatic disease is common at the time of diagnosis. In cats, chronic parasitic cholangitis may lead to biliary adenocarcinomas.[60]

Surgical resection is the treatment of choice for biliary adenocarcinomas when the tumor or tumors are confined to a single lobe and there is no evidence of metastatic disease.[51,59] Diffuse biliary adenocarcinomas carry a grave prognosis. Biliary diversion techniques using various stents have been investigated for nonmalignant diseases and are currently being evaluated for nonresectable tumors.[26,27] Percutaneous arterial embolization and chemoembolization of hepatic tumors have been performed in a small number of patients and their use is steadily growing.[61]

Parasitic Disease of the Biliary System

Etiology

Some species of flukes readily infect the biliary tree and liver of cats (*Platynosomum fastosum, Platynosomum concinnum,* and *Amphimerus pseudofelineus*).[2,60,62-65] Ova of the flukes are passed in the feces of the cat. A land snail must ingest the ova. An amphibian or reptile such as a toad, gecko, or lizard subsequently eats the snail. Cats ingest the second intermediate hosts to maintain the cycle. Outdoor predatory cats are at increased risk, particularly if they live in the Southeast United States, Caribbean, or Hawaii.[2] There is no known breed or sex predilection. Bacterial cholangitis, cholangiohepatitis, ductal fibrosis, extrahepatic biliary obstruction, hepatic failure, and death are known sequelae of parasitic cholangitis.[2,60,62,63,65] A recent investigation revealed chronic biliary parasitism may lead to the development of cholangiocarcinomas.[60]

Clinical Signs

The clinical signs of parasitic biliary disease depend on the degree of liver injury and biliary obstruction. Many cats are asymptomatic carriers. Weight loss, anorexia, and vomiting are the most common complaints in symptomatic cats. Jaundice and abdominal distention may be identified on physical examination in endemic parts of the country.[2,62,63]

Diagnosis

Complete blood counts are often nonspecific but may include a stress leukogram or mature neutrophilia. An eosinophilia is suggestive of parasitic infection if present. Clinical chemistries are variable but may include elevated liver values and total bilirubin, particularly if the patient is clinically ill. Fecal sedimentation (ch. 81) is the most reliable method of confirming a diagnosis.[2] Abdominal radiographs are usually unremarkable or may reveal hepatomegaly. Ductal dilation, hepatic cysts, and biliary obstruction are well documented and are readily seen on abdominal ultrasound. Aspiration and cytology of bile are useful for identifying fluke eggs if fecal testing is negative.[63,65] Hepatic biopsies may reveal flukes and/or ova.[62,63]

Treatment

Anthelminthics are the treatment of choice. Praziquantel at 20 mg/kg as a single dosage or once daily for 3 consecutive days is effective in eliminating the parasite.[2] Dosages as high as 40 mg/kg once daily for 3 days may be necessary, particularly with *A. pseudofelineus*.[64] Ursodiol may be helpful as a choleretic and an anti-inflammatory, but controlled studies demonstrating a definitive benefit are lacking. The acute death of numerous flukes may incite a severe inflammatory response. Steroids and antihistamines, started prior to treatment, may help limit the inflammatory cascade.[63] Patients presenting with biliary obstruction frequently require surgery. Antibiotics are indicated in patients with neutrophilic cholangitis on histopathology. Patients requiring surgery and those with extensive hepatic involvement have a guarded prognosis.[2,62,63]

Gallbladder Mucoceles

Etiology

A gallbladder mucocele is defined as the presence of bile-laden semisolid to immobile mucoid material within the gallbladder.[66-70] The mucocele has become one of the preeminent biliary diseases of the dog. Expansion of the mucocele within the gallbladder lumen is thought to stretch the gallbladder wall and disrupt blood flow, resulting in pressure necrosis of the wall and subsequent bile peritonitis.[66,68,69] Predisposing factors include dyslipidemias, dysmotility of the gallbladder, endocrine disease, and exogenous steroid administration.[68] Breed predispositions include Shetland Sheepdogs, Cocker Spaniels, and Miniature Schnauzers.[66,68,70] Mucoceles occur most commonly in older canine patients. The median age is 10 years with a range of 3 to 17 years.[66,68-70] Potential complications of mucoceles include extrahepatic bile duct obstruction, cholecystitis, necrotizing cholecystitis, bile peritonitis, and pancreatitis.

Recent advancements have proposed etiologies for mucoceles. Hyperadrenocorticism is known to dramatically increase the risk of a mucocele.[71] New investigations have found that high-dosage exogenous

steroids result in significantly higher levels of unconjugated bile acids within the extrahepatic biliary tree.[72] Unconjugated bile acids are more hydrophobic and when in disproportionate levels, lead to injury of the biliary epithelium. Mucin secretion increases as a result of the injury and ultimately leads to mucinous hyperplasia, one of the defining histologic features of a mucocele.[73-75] Hypothyroidism has also been speculated as a mechanism by which mucoceles form. It has been established that bile flow is reduced in humans with hypothyroidism. With reduced levels of thyroxine, sphincter of Oddi relaxation is impaired, liver cholesterol metabolism is altered and bile secretion diminishes.[76,77] Mucin is thought to organize and solidify under these conditions. Interestingly, xenobiotics have recently been linked with the development of mucoceles. Shetland Sheepdogs treated with flea products containing imidacloprid were more likely to develop a mucocele than members of the breed that were not treated with the drug. Other breeds did not display the same sensitivity making the findings specific to Shetland Sheepdogs.[78]

The identification of gallbladder mucoceles in cats is increasing.[79-81] Biliary stasis is suspected to be the predominant mechanism as endocrinopathies are less common. An estimated 12% of cats have congenital biliary abnormalities, which may suggest an underlying structural or drainage issue predisposing to the development of mucoceles and other biliary diseases in this species.[82]

Clinical Signs

Gallbladder mucoceles are thought to develop slowly, and therefore clinical presentation varies widely. Increased awareness of the disease has facilitated the detection of incidental mucoceles on abdominal ultrasonography. Alternatively, patients may present with signs of an acute abdomen associated with extrahepatic bile duct obstruction, pancreatitis, or bile peritonitis. Symptomatic patients are frequently evaluated for vomiting, anorexia, lethargy, and abdominal pain. Fever is commonly associated with bacterial cholecystitis or bile peritonitis. Icterus is apparent in approximately 40% of patients.[66,69,70]

Diagnosis

Routine clinicopathologic abnormalities are often indistinguishable from other hepatobiliary diseases. ALP is the predominant enzyme elevation.[66-70] ALT, GGT, and total bilirubin are frequently elevated, particularly in symptomatic patients. Cholesterol is markedly elevated in patients with bile duct obstruction. Neutrophilic leukocytoses and left shifts occur most commonly with bile peritonitis, bacterial cholecystitis, or bacterial cholangiohepatitis.

Abdominal radiographs are useful to exclude other hepatobiliary diseases, but are inadequate to definitively diagnose patients with mucoceles. Ultrasound remains the gold standard for gallbladder mucocele detection.[66-70] Ultrasonographic changes are often marked by stark contrasting layers within the gallbladder (Figure 288-5 and Video 288-2). In the immature mucocele, hyperechoic biliary sludge may be suspended or gravity dependent. Anechoic fluid, or liquid bile, is present in varying amounts. A hypoechoic to anechoic rim (mucin layer) separates the biliary sludge from the gallbladder wall. Fracture lines are often visible in the mucin layer and typically form either a stellate or striated appearance.[66] It is the striated or stellate appearance that is often referred to as a kiwi fruit. In the mature gallbladder mucocele, a hypoechoic to anechoic rim is the predominant finding and the biliary sludge is often centrally located and immobile. Mucin fragments and choleliths may be seen suspended in the gallbladder, lodged in the cystic or common bile ducts, and in rare cases, free in the abdominal cavity. The gallbladder wall may be normal or diffusely thickened. Fluid and hyperechoic fat may be visualized near the gallbladder and are suggestive of gallbladder rupture or localized peritonitis.[15] It is important to note that the appearance of mucoceles can vary widely and the ultrasonographic pattern does not always correlate with the severity of disease.[82]

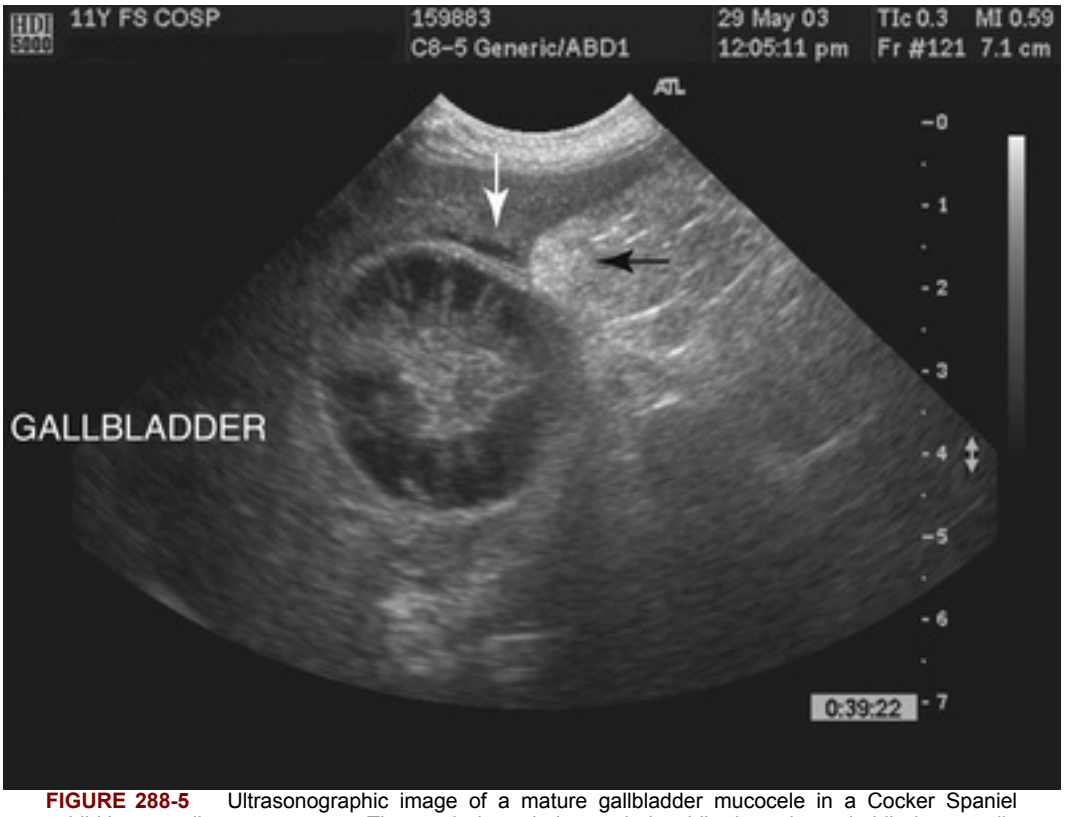

FIGURE 288-5 Ultrasonographic image of a mature gallbladder mucocele in a Cocker Spaniel exhibiting a stellate appearance. The mucin layer is hypoechoic while the echogenic bile is centrally located. There is a small volume effusion (white arrow) and the adjacent fat is hyperechoic (black arrow). Both features are suggestive of gallbladder rupture. Note the resemblance to a cut kiwi fruit.

Histologically, mucoceles are characterized by cystic mucinous hyperplasia of the gallbladder mucosa with thick gelatinous mucin adhered to the luminal surface.[66,68-70] Lymphoplasmacytic or neutrophilic cholecystitis, or a combination of both, may be present.

Treatment

Surgical correction is indicated in many patients and is essential when bile peritonitis is present.[66,68-70] A cholecystectomy is the most common curative procedure and in uncomplicated mucoceles may be performed laparoscopically.[83] Aerobic and anaerobic cultures are essential at surgery as 9% to 66% of patients have concurrent bacterial infections.[66,70] Bacterial organisms may include *Enterococcus* spp., *Enterobacter* spp., *E. coli, Staphylococcus* spp., and *Streptococcus* spp.[66,68,69]

Medical therapy for gallbladder mucoceles has been successful in some patients, particularly those with hypothyroidism.[66-68] A combination therapy of cholerectics and antibiotics is most frequently attempted. Cholerectics, such as ursodiol and S-adenosylmethionine (SAMe), alter the microenvironment of the gallbladder and increase bile flow. Ursodiol is a hydrophilic bile acid that decreases the secretion of mucin from the biliary epithelium and reduces the formation of cholesterol crystals.[84] Care should be taken in patients with biliary obstruction as cholerectics may induce rupture of the gallbladder or biliary tree. Antibiotic selection based on culture results of bile is ideal. However, empiric therapy against anaerobic bacteria is a logical choice. Therapy should be continued for a minimum of 4 to 8 weeks.[42-44] In addition, low-fat diets are likely beneficial.[67,68]

The long-term prognosis for patients with gallbladder mucoceles is highly variable. Patients with septic and bile peritonitis carry the highest mortality rate. Stable patients with nonruptured mucoceles have the most favorable prognosis. Perioperative mortality for patients varies from 22% to 40%.[66,70] The prognosis is excellent for patients surviving the perioperative period.[66,68-70] Evaluation and treatment of concurrent endocrine diseases is always advised.

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SECTION XX

Pancreatic Disease

OUTLINE

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CHAPTER 289

Pancreatitis

Etiology and Pathophysiology

Thomas Spillmann

Acute pancreatitis (AP) in dogs and cats is defined as a fully reversible inflammation of the pancreas with the histologic presence of edema, neutrophilic infiltrate, and necrosis. The disease can be local or can lead to the systemic inflammatory response syndrome (SIRS; see ch. 132) with possibly fatal multiple organ failure.[1-6] Chronic pancreatitis (CP) is characterized by continuing inflammation (lymphocytic/lymphoplasmacytic) with irreversible changes such as fibrosis. The clinical course of CP can be subclinical or recurrent with episodes of more or less severe illness, as in acute-on-chronic pancreatitis. In some cases, the loss of pancreatic tissue leads to decreased exocrine and/or endocrine function.[1-6] Canine and feline pancreatitis present with a wide variety of clinical signs overlapping not only with non-pancreatic diseases but also between AP and CP (see ch. 290 and 291).[4,5] Also, clinical signs and results of laboratory tests and abdominal ultrasound can be conflicting.[3-8] The morphologic differentiation of pancreatic inflammation is, however, rarely performed, despite the proven safety and validity of ultrasound-guided fine-needle aspiration (see ch. 89) and surgical or laparoscopic pancreatic biopsy (see ch. 91).[9-14] The diagnostic value of the procedures is, however, influenced by an uneven distribution of pancreatic inflammation.[1,2]

The etiology of acute and chronic pancreatitis remains idiopathic. Several risk factors have been proposed for both dogs and cats, most based on experimental studies, analogies from human medicine, or case reports.

Breed predisposition has been documented in retrospective and case-control studies. Miniature Schnauzers, as well as Yorkshire and other Terriers, appear to be predisposed to AP.[15-19] The majority of cats with acute necrotic and suppurative pancreatitis is of the domestic shorthaired breed.[20,21] CP appears to more often affect Cavalier King Charles and English Cocker Spaniels, Boxers, and Collies.[22-24]

Genetic associations with cationic trypsinogen *(PRSS1)*, cystic fibrosis transmembrane conductance regulator *(CFTR)*, and serine protease inhibitor Kazal-type 1 *(SPINK1)* genes are documented in humans. In dogs, no association of pancreatitis with *PRSS1* or *CFTR* gene mutations has been found. The role of *SPINK1* gene variants in Miniature Schnauzers remains controversial.[16,17,25,26] There have so far been no such studies in cats.

Gender association appears possible for dogs with AP. Retrospective, partly case-controlled studies have proposed being neutered (male/female) or male as risk factors.[18,19,27] Post-mortem examinations in dogs with CP revealed that being female did not increase the relative risk for the disease, despite a higher number of affected females.[22]

Hypertriglyceridemia and obesity have been considered important risk factors for canine pancreatitis.[27] Prospective case-control studies in Miniature Schnauzers revealed that dogs with a history of pancreatitis were five times more likely to have hypertriglyceridemia. In dogs with serum triglyceride levels ≥862 mg/dL (≥9.7 mmol/L), a 4.5-fold higher likelihood of having serum canine pancreatic lipase immunoreactivity (PLI) values consistent with pancreatitis was observed.[15,28] A prospective cross-sectional study in overweight and obese dogs demonstrated an association of hypertriglyceridemia with a markedly increased serum cPLI concentration, but no development of clinical pancreatitis.[29]

Dietary indiscretion, including access to trash and table scraps, was regarded a risk factor for AP in dogs in a retrospective case-control study and one case report.[27,30] Although fat-rich diets have been proposed as a risk factor, this association has never been reliably documented.

Infections have been reported in connection with canine and feline AP. In dogs with babesiosis, AP was

documented in several retrospective studies and appears to be of prognostic value for patient survival.[31-34] Canine monocytic ehrlichiosis does not cause AP in experimentally infected Beagles, but spontaneously diseased dogs can have increased serum cPLI concentrations without clinically apparent pancreatitis.[35] AP in connection with granulocytic ehrlichiosis and leishmaniasis was documented in two case reports, suggesting an individual complication rather than a regular sequela of these infections.[36,37] Bacterial or septic pancreatitis has not been reported so far. However, bacterial translocation to the pancreas can be induced experimentally in both dogs and cats.[38-40] Recently, bacterial colonization was documented in the pancreas of cats with spontaneous pancreatitis, with fluorescence *in situ* hybridization indicating more frequent colonization in moderate to severe than in mild pancreatitis.[41,42] Bile duct obstruction might exacerbate pancreatitis and impair the ability to clear bacteria in cats with pancreatic fibrosis and disorders of the major papilla due to the joint termination of the common bile duct and pancreatic duct in this species.[6,42,43] Successful culture of bacteria *(Enterococcus hirae)* has, however, been reported in only one cat with ascending cholangitis and pancreatitis.[44] Concurrent inflammation of the pancreas, liver, and intestine is considered a frequent sequela in cats, but the cause-effect relationship is still open.[42] A highly virulent feline calicivirus infection with severe AP was reported in two independent case series.[45,46] Pancreatic and hepatic flukes rarely have been involved in feline pancreatitis, being documented only in occasional case reports.[47-50] *Toxoplasma gondii* and *Bartonella* spp. do not appear to cause feline pancreatitis. A recent study found no significant association between feline PLI serum concentrations and the presence of antibodies against both pathogens.[51]

Drug reactions appear to be idiosyncratic rather than true risk factors, as proposed for potentiated sulfonamides (see ch. 286).[52,53] Widely used drugs with occasional case reports of AP include azathioprine, L-asparaginase, meglumine antimonate, N-methyl-glucamine, and clomipramine.[54-62] Prospective studies have revealed no evidence for pancreatitis in dogs receiving L-asparaginase for lymphoma or meglumine antimonite for leishmaniasis.[58,59] Phenobarbital/potassium bromide treatment was suspected to cause pancreatitis in up to 10% of treated dogs included in one retrospective study.[63] This has been supported by findings of elevated serum cPLI concentrations and hypertriglyceridemia in dogs treated with these antiepileptic drugs.[64,65] In cats, experimental acute hypercalcemia induced AP after local arterial but not after peripheral venous calcium gluconate infusion.[66-68] There have been no reports of spontaneous hypercalcemia with AP in cats. Cholecystokinin-8 and cerulein injections can induce AP in dogs.[69-71]

Intoxications appear to be rare causes of AP, with zinc intoxication being documented in several case reports.[72-75] Snake bites can be of regional importance, as reported for fatal *Vipera xanthina palestinae* envenomation with acute necrotic pancreatitis (see ch. 156).[76] Organophosphate intoxication was investigated in experimental trials showing that the canine but not the feline pancreas is sensitive (see ch. 152). In contrast to dogs, cats do not appear to have abundant pancreatic tissue-fixed butyrylcholinesterase.[77,78] Easter lily poisoning in cats is rather nephrotoxic, and the pancreotoxic effect is limited to the degeneration of acinar cells without inflammation (see ch. 155).[79]

Endocrine disorders linked to canine AP include hyperadrenocorticism (see ch. 306), hypothyroidism (see ch. 299), and diabetes mellitus (see ch. 304) including diabetic ketoacidosis.[19,80-82] CP is considered a cause rather than a consequence of diabetes mellitus in both species.[4,83,84]

Trauma and surgical or minimally invasive interventions also are possible risk factors. Traumatic pancreatitis can result from high-rise syndrome in cats.[85] Previous surgery other than neutering has been associated with an increased odds ratio (OR = 21.1) for pancreatitis in dogs.[27] Endoscopic retrograde cholangiopancreatography (ERCP) has the potential to induce AP (see ch. 123). Dogs and cats can have transiently elevated serum pancreatic enzyme activities and concentrations after ERCP without clinical signs of pancreatitis.[46,86-90] This phenomenon might be caused by subclinical inflammation.[91]

The pathophysiology of acute pancreatitis has been the focus of recent, thorough, topical reviews.[3,5,6,42,92-94] Experimental animal models are the main basis for current knowledge on subcellular events leading to acinar cell destruction, as well as factors promoting complex local and systemic inflammatory responses.[92-94] Acute pancreatitis (AP) and acute pancreatic necrosis are suggested to be responses to the same stimuli with a different progression and outcome. Mild AP, therefore, is a localized process with uncomplicated full recovery. In contrast, severe AP with necrosis can be localized but also cause SIRS, resulting in multiple organ dysfunction syndrome (MODS) and death.[3,5,92-94]

The key factor initiating pancreatic inflammation appears to be the activation of trypsin within the acinar cells, being caused by three basic scenarios: (1) blockage of the acinar cell apex in the pancreatic duct, leading to the co-localization and fusion of zymogen and lysosomal granules; (2) oxidative stress; or (3) hypotension. The self-defense mechanism against activated trypsin is its neutralization by an intracellular pancreatic secretory trypsin inhibitor, which is overwhelmed when more than 10% of intracellular trypsin is activated.[3,93] Trypsin, in turn, activates other inactive pro-enzymes that normally are stored in zymogen granules. The release of activated digestive enzymes into the pancreatic tissue initially causes local inflammation with migration of neutrophils to the pancreas. This is followed by the subsequent production of reactive oxygen species and nitric oxide, which contributes to the inflammation.[3,93] The shift from apoptosis to necrosis is thought to be caused by neutrophils along with endothelin-1 and phospholipase A3.[3,93] Disturbed pancreatic microcirculation and increased vascular permeability contribute to pancreatic edema and necrosis, with necrotizing pancreatitis resulting in a progressive reduction in capillaries not responsive to fluid resuscitation.[93] Further local inflammation and SIRS is caused by a combination of different inflammatory pathways involving a large variety of mediators such as tumor necrosis factor-alpha, interleukin (IL)-1beta, IL-6, IL 10, platelet activating factor, intercellular adhesion molecule-1, CD40L, complement component C5a, chemokines, substance P, and hydrogen sulfide, as well as the kinin-kallikrein and the renin-angiotensin-aldosterone systems.[93,94] Of possible clinical value are the discoveries that pancreatic substance P and neurokinin (NK)-1 receptors are highly upregulated in mice with induced AP, and that knockout mice deficient in NK1 receptors are protected against AP and the associated lung injury.[95,96] NK1-receptors also appear to play a role in mediating pancreatic pain in rats, and their blockage protects septic mice against lung injury.[97,98] The usefulness of NK1-receptor antagonists for treating dogs and cats with AP remains to be studied.[93]

The development of systemic complications can be summarized as the following chain of events: AP leads to SIRS, which results in MODS. Features of MODS requiring special attention in humans and being partly documented in dogs and cats with AP include acute lung injury (see ch. 242), acute kidney injury and uremia (see ch. 322), disseminated intravascular coagulation (see ch. 197), and cardiac arrhythmias (see ch. 248).[93,98-101] Local complications after AP include pancreatic fluid accumulation, pseudocysts, and necrotic pockets that are prone to infections in humans. Case reports in dogs and cats have, however, only described sterile processes.[93,102-104]

Chronic pancreatitis is thought to be either a late complication of AP or a consequence of chronic immune-mediated inflammation, as proposed for the duct-destructive CP of English Cocker Spaniels.[4,5,24,93] In cats, CP is considered to be more common than AP.[6] Canine and feline CP is characterized by pancreatic tissue loss due to fibrosis, which can, in its end stage, lead to exocrine pancreatic insufficiency (EPI) and/or diabetes mellitus.[4,5,6,23,42,105,106] In dogs, EPI is, however, more often caused by pancreatic acinar atrophy following another pathophysiologic mechanism (see ch. 292).[107] The clinical course of CP extends from subclinical to recurrent episodes of acute-on-chronic pancreatitis. The pathophysiology of this phenomenon still needs to be elucidated. It is thought that increased pancreatic duct pressure might be a contributing factor to acute-on-chronic pancreatitis. Pancreatic duct abnormalities are a feature of CP in humans and also have been documented with magnetic resonance cholangiopancreatography in cats with induced or spontaneous CP.[108-110]

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CHAPTER 290

Canine Pancreatitis

Diagnosis and Treatment

Jörg M. Steiner

Client Information Sheet: Pancreatitis in Dogs

Introduction

Canine pancreatitis is now recognized to be a common disease in dogs. In one study of more than 200 dogs that had died or had been euthanized for a wide variety of reasons and that were evaluated at necropsy, more than 8% showed macroscopic evidence of pancreatitis.[1] Furthermore, approximately 50% of these dogs had microscopic lesions suggestive of chronic pancreatitis and approximately 30% had lesions suggestive of acute pancreatitis.[2] This work has raised the awareness of clinicians for pancreatitis dramatically, but many cases, especially those that are subclinical, remain undiagnosed. The consequences of failing to diagnose subclinical pancreatitis are unknown. However, known consequences of mild chronic pancreatitis are acute exacerbations, diabetes mellitus, and exocrine pancreatic insufficiency. Thus, diagnosis of pancreatitis, even in cases of mild chronic disease would therefore be beneficial to the DVM, the pet and the owner.

Diagnosis

Clinical Presentation

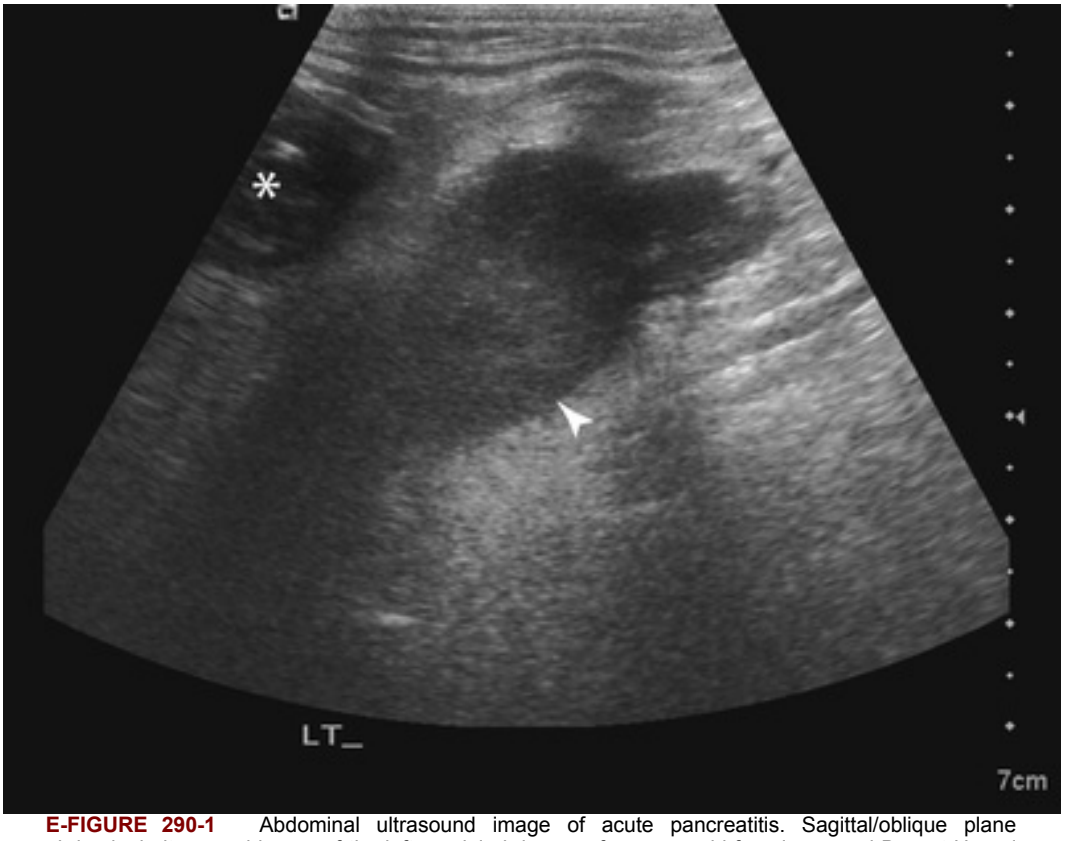
The clinical presentation of dogs with pancreatitis can range widely. Many dogs, especially those with chronic disease, are subclinical, while others have mild nonspecific clinical signs, and yet others show clinical signs of severe disease and systemic complications. The classical clinical signs associated with severe acute pancreatitis in dogs include vomiting, abdominal pain, lethargy, and dehydration.[3] Some patients may also have diarrhea and others may have fever.[3] Systemic complications of canine pancreatitis are associated with clinical signs of that specific complication. For example, kidney injury may be associated with oliguria, anuria, or even polyuria; pulmonary failure is associated with an increased respiratory rate and effort; pancreatic encephalopathy can be associated with neurologic signs, and disseminated intravascular coagulation can be associated with bleeding diatheses. In contrast, patients with chronic mild disease may only show nonspecific clinical signs, such as hyporexia or anorexia, lethargy, or behavioral changes.[4]

Diagnostic Imaging

Pancreatitis can be associated with radiographic changes, such as decreased contrast in the cranial abdomen and displacement of abdominal organs.[3] However, these changes are subjective and abdominal radiography is insensitive and nonspecific for canine pancreatitis. Nonetheless, abdominal radiography is important in dogs with suspected pancreatitis to rule out other differential diagnoses, such as a gastrointestinal foreign body in a patient with acute vomiting and abdominal pain.

Abdominal ultrasound can be very useful for the diagnosis of canine pancreatitis, but does have important limitations. The sensitivity of abdominal ultrasonography is dependent on several factors, including equipment resolution, operator skills, level of suspicion of the ultrasonographer, but most importantly the severity of disease. In dogs with severe acute pancreatitis, pancreatic necrosis is evidenced by hypoechoic areas within the pancreas (E-Figure 290-1).[3] Other ultrasonographic findings in dogs with pancreatitis include

pancreatic enlargement, peritoneal effusion, hyperechoic peripancreatic fat or mesentery, an enlarged duodenal papilla, or a dilated pancreatic duct.[3] Some patients with chronic pancreatitis may show a hyperechoic pancreas due to pancreatic fibrosis.[5] The specificity of abdominal ultrasound is limited by other lesions that lead to the same or similar ultrasonographic changes as those seen in patients with pancreatitis (Videos 290-1 and 290-2). For example, any disease process leading to abdominal effusion could potentially be misinterpreted as pancreatitis.[5] Pancreatic enlargement can also occur due to portal hypertension.[6] Finally, pancreatic nodular hyperplasia, a condition that is recognized to be extremely common in older dogs and is not believed to be associated with current or previous pancreatitis, can lead to echogenicity changes that may be misinterpreted as pancreatitis.[7] Thus, diagnostic success is dependent on judicial utilization of this modality by an experienced ultrasonographer.



E-FIGURE 290-1 Abdominal ultrasound image of acute pancreatitis. Sagittal/oblique plane abdominal ultrasound image of the left cranial abdomen of a 7-year-old female spayed Basset Hound with pancreatitis. The left lobe of the pancreas (arrowhead) is enlarged, rounded, and hypoechoic. The surrounding fat is hyperechoic and hyperattenuating. The stomach (*) shows mild diffuse wall thickening, which is consistent with gastritis and/or gastric wall edema. (Image courtesy Dr. Jay Griffin, Texas A&M University.)

Abdominal computed tomography and magnetic resonance imaging are routine procedures in humans suspected of having pancreatitis, but historically both were considered to be insensitive for the diagnosis of pancreatitis in the dog.[8] However, newer studies would suggest that the diagnostic accuracy of these diagnostic modalities can be improved.[9,10]

General Clinical Pathology

A wide variety of hematological and serum biochemical changes has been reported in dogs with acute severe pancreatitis.[3] However, these changes should be viewed as manifestations of the systemic condition of the patient and as an indication of potential systemic complications, rather than as a direct indication of pancreatic inflammation. Also, findings on a complete blood count (CBC) and serum chemistry profile may help to direct the clinician towards alternative differential diagnoses and should thus be considered crucial for the work-up of any dog suspected as having pancreatitis.

Serum Amylase Activity

Amylases are enzymes that catalyze the hydrolysis of complex carbohydrates and are synthesized and secreted by several different cell types in the body, including pancreatic acinar cells. While some dogs with spontaneous pancreatitis do show increases in serum amylase activity, many others do not. Also, because amylases are synthesized and secreted by other tissues, increases in serum amylase activity can also be seen with various other conditions.[11] Thus, measurement of serum amylase activity is of little value in the diagnosis of canine pancreatitis.

Total Serum Lipase Activity

Lipases hydrolyze lipids, such as triglycerides, which are apolar lipids that are very important for long-term energy storage in the body. As a result, triglycerides need to be moved in and out of cells on a routine basis and because triglycerides are completely apolar, they first must be hydrolyzed into more polar lipolysis products, such as glycerol, monoglycerides, diglycerides, and fatty acids. This is why there are many different lipases in the body, including gastric lipase, pancreatic lipase, hepatic lipase, and hormone-sensitive lipase. The exact number of lipases in the body is unknown, but there are many, and while some of them show structural similarities, many of them just share function (i.e., lipolytic activity). Total serum lipase activity can be measured by many different methodologies, all using a different substrate. Many assays utilize 1,2-diacylglycerol as a substrate. These assays have been shown to have a limited specificity (approximately 50%) for the exocrine pancreas and a limited sensitivity (also approximately 50%) for canine pancreatitis.[11] Over the last 20 years a synthetic substrate, resorufin (DGGR), has been used as an alternative substrate in both human and veterinary medicine. While some studies would suggest a higher specificity for the exocrine pancreas than 1,2-diacylglycerol-based assays, other studies did not confirm these findings.[12,13] While the overall clinical utility of DGGR-based assays is probably better than those based on 1,2-diacylglycerol, more studies are needed to confirm these results, and this substrate is by no means specific for the exocrine pancreas in dogs. Also, a point of care assay has been described that uses triolein as a substrate.[14] However, thus far the only study available shows this assay to correlate with the measurement of serum pancreatic lipase immunoreactivity when exclusively evaluated in serum samples that are not lipemic, icteric, or hemolyzed, changes that are rather common in dogs with pancreatitis.[14] Also, this assay is not specific for the exocrine pancreas.

Trypsin-Like Immunoreactivity

Trypsin-like immunoreactivity (TLI) is specific for exocrine pancreatic function. However, the sensitivity of serum TLI concentration for pancreatitis in dogs is much lower than that of serum cPLI concentration or abdominal ultrasound.[15] This is probably due to the fact that trypsinogen, which is the form of trypsin present in tiny quantities in the serum under physiologic conditions, is very small and thus is quickly removed from the vascular space through renal excretion. During pancreatitis, trypsinogen is prematurely activated to trypsin, but trypsin is quickly scavenged from the serum by proteinase inhibitors. However, it must be noted that serum cTLI concentration remains the diagnostic test of choice for the diagnosis of exocrine pancreatic insufficiency (EPI; see ch. 292).

Pancreatic Lipase Immunoreactivity (PLI)

A specific assay for the measurement of pancreatic lipase immunoreactivity in dogs (cPLI, now measured by Spec cPL, IDEXX Laboratories, Westbrook, Maine) is available.[16] This assay is based on the detection of pancreatic lipase by use of a specific antibody. Thus, this is the only assay that can measure pancreatic lipase exclusively. This was confirmed by immunohistochemistry, which showed that of all tissues evaluated, only pancreatic acinar cells stained positive for pancreatic lipase.[17] Also, serum cPLI was measured in a group of dogs with EPI, showing undetectable or severely decreased serum cPLI concentrations in all dogs.[18] In another study serum cPLI was evaluated in healthy dogs that had been euthanized at an animal shelter showing a specificity of serum cPLI concentration (as measured by Spec cPL) of 97.5%.[19] Serum cPLI concentration was significantly increased in dogs with experimentally induced chronic kidney disease, but most dogs had serum cPLI concentrations within the reference interval and none of the dogs had serum cPLI concentrations that were above the recommended cut-off value for pancreatitis.[20] Also, long-term oral

administration of prednisone did not have any effect on serum cPLI concentrations.[21]

Several clinical studies have evaluated the sensitivity of serum cPLI concentration in dogs with pancreatitis. In general, the sensitivity is dependent on the severity of disease, but in most studies, sensitivities above 80% have been described for dogs with acute clinical pancreatitis and sensitivities above 60% for dogs with mild pancreatitis.[15,22-24] These data show that serum cPLI concentration is the most sensitive diagnostic tool for the diagnosis of canine pancreatitis currently available, though, as for most diagnostic tests in veterinary or human medicine, sensitivities are less than 100% and careful integration of history, other clinical data, and measurement of serum cPLI concentration are required to arrive at the correct diagnosis.

Also, a patient-side test for the semi-quantitative assessment of cPLI is available (SNAP cPL, IDEXX Laboratories, Westbrook, Maine).[24] This test is useful to rule out pancreatitis in dogs with suggestive clinical signs when the test is negative. Also, a positive test result suggests pancreatitis. However, a serum sample should also be sent to the laboratory for measurement of cPLI (by Spec cPL) to confirm the diagnosis and to achieve a baseline value that can then be used to monitor progression of the disease.

Special mention should be made of dogs that either have no clinical signs or only have clinical signs that are not commonly associated with pancreatitis, but show a serum cPLI concentration that is diagnostic of pancreatitis (Figure 290-2). The first response should be to have a thorough discussion with the owner to ensure that no subtle clinical signs are present (e.g., behavioral changes, finicky eating behavior, or other). If such signs are absent, the cPLI should be re-evaluated after 10 to 14 days. If cPLI has decreased by this time no further work-up is required. If, however, cPLI continues to be increased, the patient should be evaluated for any risk factors of chronic pancreatitis by assessing serum triglyceride and calcium concentrations and discussing the drug history with the owner. If a risk factor is identified, the patient should be managed accordingly. However, even if no such risk factors can be identified, further diagnostics and management are prudent to prevent long-term complications from chronic mild pancreatitis.

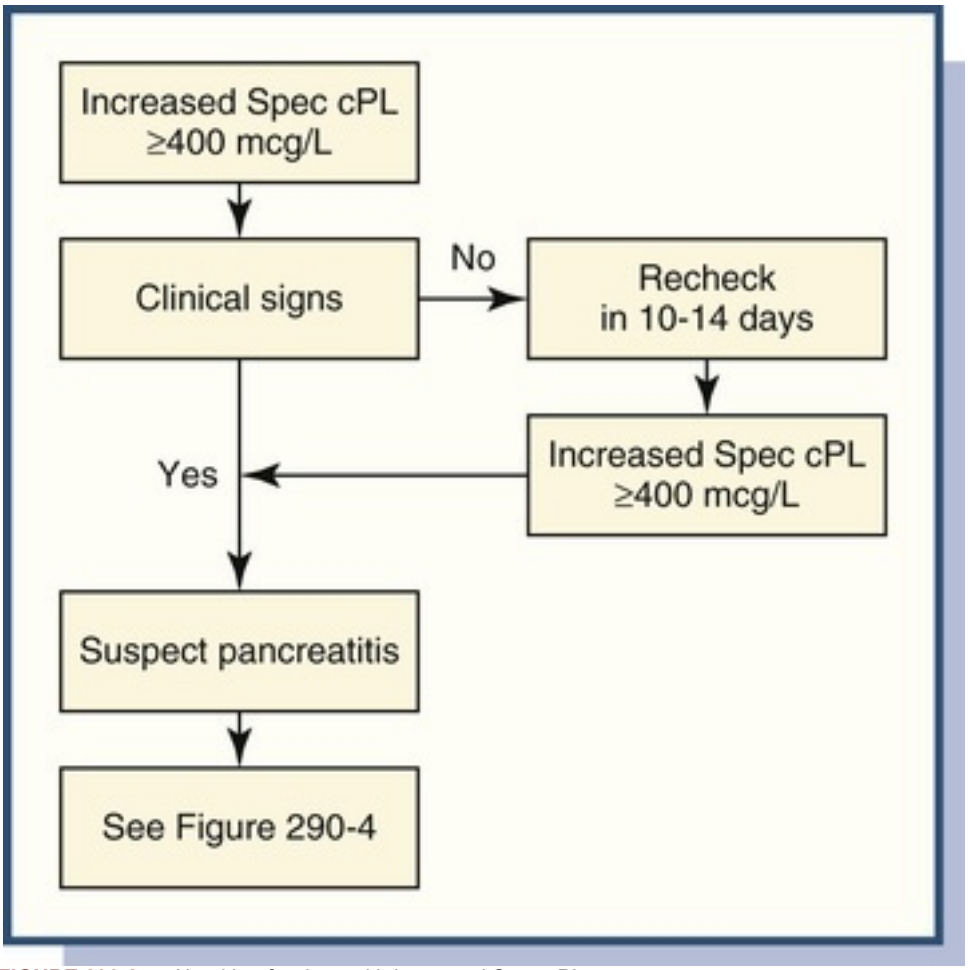
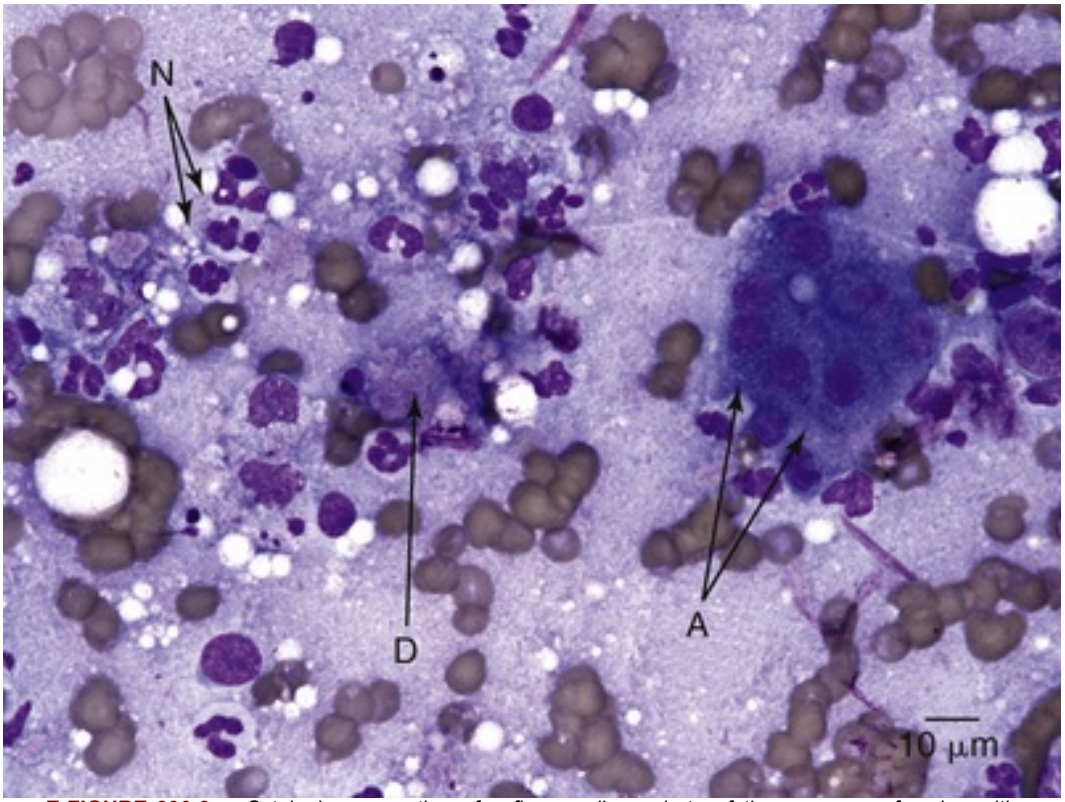


FIGURE 290-2 Algorithm for dogs with increased Spec cPL.

Cytology and Histopathology

Cytologic evaluation of a fine-needle aspirate of the pancreas (see ch. 89) is a great diagnostic modality to confirm a diagnosis of pancreatitis. Various studies have shown that there is little risk of a fine-needle aspirate of the pancreas.[25] The presence of pancreatic acinar cells confirms the successful aspiration of the pancreas and a presence of inflammatory cells in the same aspirate confirms the presence of pancreatic inflammation (E-Figure 290-3).[26] However, in patients with severe pancreatic necrosis, only cellular debris may be aspirated and the cytological evaluation may be inconclusive. Also, lack of inflammatory cells in the infiltrate does not rule out pancreatitis as inflammatory lesions may be highly localized.[1]



E-FIGURE 290-3 Cytologic preparation of a fine-needle aspirate of the pancreas of a dog with suspected pancreatitis. Note the neutrophilic infiltration (N). Some intact acinar cells (A) can also be seen. The image also shows debris (D), suggesting pancreatic necrosis. (Image courtesy Dr. Mark Johnson, Texas A&M University.)

Traditionally, histopathologic evaluation of a pancreatic biopsy has been viewed as the most definitive diagnostic tool for pancreatitis. Pancreatic biopsies can be collected during abdominal exploratory or by laparoscopy (see ch. 91).[27,28] The presence of pancreatitis can easily be suggested by gross appearance of the pancreas in some cases and histopathologic evaluation can definitively confirm pancreatitis.[22,28] However, the absence of pancreatitis cannot be proven by histopathology even if multiple biopsies are taken. With mild chronic pancreatitis, lesions can be highly localized.[1] It should also be noted that while a pancreatic biopsy in itself is not associated with many complications, many patients with severe pancreatitis pose a high anesthetic risk and the potential of hypotension; anesthesia is considered a risk factor for worsening pancreatitis.[28]

Treatment of Acute Severe Pancreatitis

Ultimately, acute and chronic pancreatitis can only be conclusively differentiated based on histopathology (i.e., chronic pancreatitis is characterized by irreversible changes such as pancreatic atrophy and pancreatic fibrosis). However, many if not most cases of mild acute pancreatitis are probably not presented to a veterinarian and most cases of chronic pancreatitis are mild.

Treatment of Cause

Whenever possible the cause of the disease should be removed or treated. However, this may prove difficult to accomplish as most cases of canine pancreatitis are considered idiopathic. Several causes and risk factors for canine pancreatitis have been identified. Dietary indiscretion is considered to be an important risk factor for pancreatitis in dogs.[29] Also, severe hypertriglyceridemia is considered a risk factor for the disease and in one study serum triglyceride concentrations > 850 mg/dL (approximately 9.6 mmol/L) were associated with a significant increase in the risk for pancreatitis in Miniature Schnauzers.[30,31] Pancreatitis is especially common in the Miniature Schnauzer and recently, 3 different mutations in the SPINK-1 gene have been identified in affected dogs.[32] While mutations of this gene have also been associated with hereditary pancreatitis in humans, SPINK-1 mutations are not a common cause of hereditary pancreatitis in humans. Blunt external trauma (e.g., due to road traffic accidents) can also cause pancreatitis in dogs. Surgical trauma can cause pancreatitis, but human patients that undergo surgery of organs distant from the pancreas have also been shown to be at an increased risk for pancreatitis, suggesting that hypoperfusion of the pancreas during anesthesia may be of bigger concern than surgical handling of the organ itself.[33] In rare instances, infectious organisms have been suspected to cause pancreatitis, including *Babesia canis* and *Leishmania infantis*.[34,35] Many pharmaceutical compounds have been implicated in causing pancreatitis in humans, most of them causing pancreatitis as an idiosyncratic reaction that is not predictable or dose-dependent.[36] In dogs there is some evidence that potassium bromide, phenobarbital, calcium, and L-asparaginase can cause pancreatitis, but many drugs may be responsible for isolated cases.[37-39] A careful history will be useful to identify many of the risk factors mentioned, including a history of trauma or dietary indiscretion. Also, a careful drug history may identify drugs that have been described as potential risk factors for pancreatitis. If the patient has been on any medication, it should be carefully evaluated whether the patient needs this specific medication or whether the drug can be discontinued or replaced with a different drug. A complete blood count and a serum chemistry profile, including triglycerides and calcium, may provide further clues as to a possible etiology.

Supportive Care

Aggressive fluid therapy is the mainstay of supportive care for dogs with severe forms of pancreatitis (see ch. 129). Fluid, electrolyte, and acid-base imbalances need to be assessed and corrected as early as possible. This is especially important since systemic complications are associated with a worse outcome and many of the systemic complications, once established, are difficult if not impossible to treat. Recent studies in humans have shown that minimal differences in blood urea nitrogen (BUN) concentrations at time of admission to the hospital and also minimal changes of BUN during the first 24 to 48 hours after admission to the hospital can have a dramatic impact on the outcome in patients with acute pancreatitis.[40]

Traditionally, food was withheld from dogs with pancreatitis, but over the last 10 years this practice has been questioned based on experiences in humans.[41] There is good evidence in humans with severe forms of pancreatitis that alimentation is crucial to counterbalance the catabolic effects of the disease.[42] Also, it has been shown in several studies that enteral nutrition is superior to parenteral nutrition.[43] A recent study has made similar observations in dogs.[44] While there was no difference in mortality between dogs fed by esophagostomy tube or total parenteral nutrition, dogs fed by esophagostomy tube improved significantly faster than did dogs fed parenterally.[44] Also, studies in humans have shown that alimentation entering the digestive tract before the duodenal papilla is not associated with a worse outcome when compared to patients fed by a jejunostomy tube.[45] Thus, in general, dogs with pancreatitis should be fed whenever possible.[45] An ultra-low-fat diet should be chosen. If patients are not interested in eating, feeding by gastrostomy, esophagostomy, or nasogastric tube should be attempted (see ch. 82).[45] If the patient vomits relentlessly (i.e., consistent vomiting even with aggressive antiemetic therapy), a jejunostomy tube should be placed or the patient should be fed by partial or total parenteral nutrition.[45]

Analgesia

Abdominal pain is the key clinical sign in human patients with both acute and chronic pancreatitis and is described in excess of 90% of all human patients (see ch. 143).[46] Abdominal pain is not always appreciated in dogs with pancreatitis. In one report only 58% of dogs with severe pancreatitis were considered to have abdominal pain.[3] However, it would appear unlikely that abdominal pain occurs less frequently in dogs than

in humans and it appears more plausible that pain remains unidentified in many canine patients. Thus, the presence of abdominal pain should be assumed and analgesic drugs utilized in all dogs with pancreatitis (see ch. 126). Meperidine, butorphanol tartrate, buprenorphine, morphine, fentanyl, methadone, or combinations of multiple analgesic drugs all at standard dosages can all be used in hospitalized patients.

Antiemetics

Antiemetic therapy (see ch. 39) is important for the treatment of patients with severe pancreatitis not only because nausea and vomiting are incapacitating, but also because nausea and vomiting may prevent proper nutritional support. Maropitant, an NK_1 antagonist, is the drug of choice as an antiemetic agent for dogs with severe pancreatitis.[47] It acts centrally by inhibiting substance P in the central nervous system and thus blocks both peripheral and central stimuli for vomiting. Maropitant is given subcutaneously at a dosage of 1 mg/kg q 24 h. Once the patient no longer vomits, the drug can also be given orally at 2 mg/kg q 24 h. While vomiting in many patients can be successfully managed with maropitant alone, addition of a 5-HT_3-antagonist such as ondansetron can have additive effects. Similarly to maropitant, 5-HT_3-antagonists act on both peripheral and central receptors, and they also block both peripheral and central stimuli for vomiting. Ondansetron is used at a dosage of 0.1-0.2 mg/kg slowly IV q 6-12 h. Once vomiting has stopped, the drug may also be administered orally. Other 5-HT_3 antagonists are also available. Metoclopramide is not a strong antiemetic and is usually insufficient in dogs with severe pancreatitis.

Proteinase Inhibitors

Based on the understanding of the pathophysiology of acute pancreatitis, proteinase inhibitors have long been at the center of new strategies for the management of pancreatitis. Unfortunately, no studies have been able to show strong evidence that such proteinase inhibitors are efficacious in dogs with spontaneous pancreatitis. This is in contrast to experimental pancreatitis in dogs where the proteinase inhibitor Trasylol had been shown to prevent death when administered at the same time as pancreatitis is being induced.[48] This is likely due to the fact that, while premature activation of trypsinogen to trypsin plays a role in the initial pathogenesis of pancreatitis, it does not appear to play an important role in the progression and development of systemic complications.

Fresh Frozen Plasma

Fresh frozen plasma and fresh whole blood contain alpha$_2$-macroglobulin, albumin, and both anticoagulant and coagulation factors (see ch. 130). In clinical trials in human patients with acute pancreatitis, there was no benefit of plasma administration.[49] There has been a recent study in dogs that would even suggest that the administration of fresh frozen plasma is associated with a worse outcome.[50] However, the study design was retrospective and it is possible that patients with more severe disease and more complications more likely received plasma.[50] Anecdotally, fresh frozen plasma is believed to be useful in dogs with severe forms of pancreatitis. Further studies are needed to answer this question definitively.

Antibiotics

In contrast to humans, dogs with pancreatitis rarely have bacterial infectious complications. Also, even though such complications do frequently occur in human pancreatitis patients and are estimated to be responsible for approximately 25-50% of all deaths associated with acute pancreatitis, a clear advantage of routine antibiotic use has not been demonstrated to date.[51,52] Therefore, the use of antibiotic agents should be limited to those dogs that have a demonstrated bacterial infectious complication (e.g., aspiration pneumonia, infected necrosis) or where such an infectious complication is strongly suspected.

Anti-inflammatory Agents

Glucocorticoids have not been shown to have any benefit in human patients with severe pancreatitis that do not have autoimmune pancreatitis and their use should be limited to canine pancreatitis patients with cardiovascular shock. Nonsteroidal anti-inflammatory agents all have been implicated in potentially causing pancreatitis and also did not show any benefit in human studies.

Other Therapeutic Strategies

Many other therapeutic strategies have been evaluated either in experimental models of pancreatitis or in clinical trials. However, no consistent beneficial effect could be demonstrated for any of these treatment strategies. Many studies have evaluated the benefit of various antioxidants in patients with severe acute pancreatitis, but none of the controlled studies was able to show any benefit.[53] One study evaluated the use of a probiotic in patients with severe acute pancreatitis, but outcome was worse in treated patients than those not treated with the probiotic.[54] Also, antacids and antisecretory agents (i.e., anticholinergics, calcitonin, glucagon, somatostatin) have not shown any promise. Treatment with platelet activating factor inhibitors (PAFANTs) initially showed promising results, but a large international multi-center trial failed to demonstrate any benefits.[55,56] Dopamine has been shown to be useful in preventing progression of pancreatitis in cats with experimentally induced pancreatitis when administered within 12 hours of initiating the disease.[57] While this time-limit would preclude dopamine to be effective in routine therapy of pancreatitis, patients that have to undergo anesthesia may benefit from treatment with dopamine during anesthesia.

Surgical Intervention

In human pancreatitis, management of patients with severe acute pancreatitis has become more and more conservative over the last 30 years.[58] While historically necrosectomy or abdominal lavage were considered useful, these interventions are now believed to be detrimental to the patient. The only scenarios where surgical intervention would appear indicated in canine patients with severe pancreatitis would be those with an infected necrotic or other type of infected fluid accumulation (some of which have previously been termed pancreatic abscess, but this term is no longer used in human pancreatology). Most patients with secondary biliary obstruction do not have a complete obstruction and rupture of the bile duct is rare. Thus, surgical intervention is rarely needed and may prove detrimental to an already debilitated patient.[59]

Treatment of Mild Chronic Pancreatitis (Figure 290-4)

Many dogs with pancreatitis have mild forms of chronic pancreatitis.

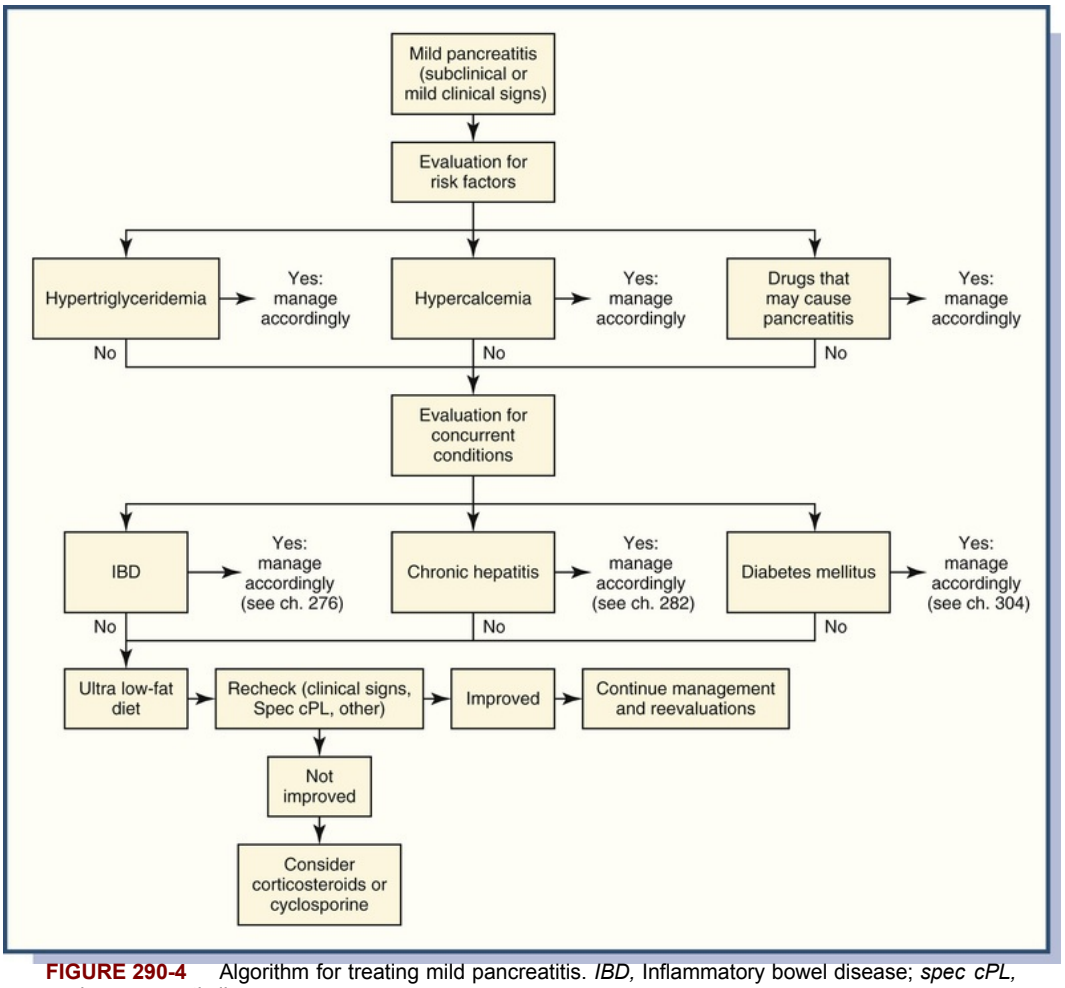


FIGURE 290-4 Algorithm for treating mild pancreatitis. *IBD*, Inflammatory bowel disease; *spec cPL*, canine pancreatic lipase.

Treatment of Cause

As for acute pancreatitis, treatment of the cause of mild chronic pancreatitis is also of prime concern. For this purpose, several risk factors should be evaluated, including evaluation of the patient for hypertriglyceridemia and hypercalcemia, and obtaining a detailed drug history. Also, the patient should be evaluated for any possible concurrent conditions that may have an impact on management, such as idiopathic inflammatory bowel disease, chronic hepatitis, and diabetes mellitus. While definitive diagnosis of such concurrent conditions may be challenging, the clinician should look at reasonable evidence for such complicating conditions, including serum glucose concentration, serum cobalamin and folate concentrations, and serum hepatic enzyme activities. Further diagnostics may be warranted if any abnormalities are identified and the overall management of the patient may need to be adjusted. Also, the patient should be carefully evaluated to determine whether antiemetic and/or analgesic therapy is needed. If the patient has no clinical signs at all, pain medication may not be warranted. If the patient does not have any signs of abdominal discomfort, but is otherwise unwell, mild analgesics such as oral butorphanol or tramadol may be administered (see ch. 356). Overt abdominal discomfort may require the use of fentanyl patches (see ch. 126). Any sign of vomiting or nausea (i.e., hyporexia, anorexia, salivation, gagging) may require the use of an effective antiemetic, such as maropitant and/or a 5-HT_3-antagonist (see ch. 39). Standard dosages are used orally for about 5 days, which hopefully is long enough for pancreatitis to improve and associated clinical signs to ameliorate. Dogs with chronic mild pancreatitis should be switched to an ultra-low-fat diet, which is a diet with less than 20 g of fat/1,000 kcal (see ch. 179). Also, it is crucial to discuss dietary fat intake with the owners and remind them that treats may also contain significant amounts of fat. Thus, it is important to switch the patient to low-fat treats, such as vegetables, fruits, low-fat treats that follow the same guidelines as mentioned above, or home-made treats (for example, made from ultra low-fat diets). Some patients may have concurrent conditions that

may also require special dietary considerations, such as concurrent food hypersensitivity (see ch. 178 and 186) or chronic kidney disease (see ch. 184). In most of these patients, the dietary requirements for pancreatitis trump those of the concurrent condition, as pancreatitis may lead to an acute exacerbation more quickly than does the concurrent condition. Another alternative is to consult with a veterinary nutrition service to have a home-prepared diet formulated that fulfills the dietary requirements for both pancreatitis and the concurrent condition. Initially, the patient should be rechecked every 2-3 weeks to evaluate the clinical signs and measure a serum Spec cPL concentration. As the condition improves or reaches a plateau, the frequency of rechecks can be decreased based on the individual patient.

Over the last two decades, a new form of pancreatitis, autoimmune pancreatitis, has been described in humans; it is characterized by a lymphocytic-plasmacytic infiltration of the pancreas.[60] Humans with autoimmune pancreatitis respond favorably to the administration of corticosteroids. Recently, there have been a few publications describing English Cocker Spaniels with chronic pancreatitis that share some of the features of human autoimmune pancreatitis.[61,62] Also, several clinicians have started to cautiously treat canine patients with chronic pancreatitis using corticosteroids when such patients do not respond to other treatments, and have found this treatment strategy to be beneficial in a portion of cases. The author utilizes a treatment protocol of measuring a baseline Spec cPL concentration, then treating the dog with prednisone for 5 days at 2 mg/kg PO q 12 h, followed by 1 mg/kg PO q 12 h for another 5-7 days, and a recheck of clinical signs and another Spec cPL concentration. If there is any improvement of clinical signs or the Spec cPL is significantly decreased, prednisone therapy is continued at a slowly decreasing dosage. Also, successful treatment of a canine patient with chronic pancreatitis with cyclosporine has been reported in one case and a clinical trial is under way.[63] The author measures a baseline serum Spec cPL concentration and then uses 5 mg/kg of Atopica PO q 24 h for 3 weeks, after which another recheck is performed to evaluate the patient clinically and measure another Spec cPL concentration. Treatment continues long-term based on above mentioned criteria. However, further studies are needed before these treatment strategies can be recommended for more routine use in dogs.

Prognosis

The prognosis for dogs with pancreatitis is directly related to disease severity, extent of pancreatic necrosis, occurrence of systemic and pancreatic complications, duration of the condition, and the presence of concurrent disease. Several prognostic systems have been developed to predict the outcome in human pancreatitis patients early after admission to the hospital.[64-66] All of these systems are aimed at identifying high-risk patients early on and to be able to aggressively treat these patients. Several of these systems have been adapted for and evaluated in dogs.[67,68] Unfortunately, none of these prognostic systems has proven useful in a routine clinical setting.

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CHAPTER 291

Feline Pancreatitis

Diagnosis and Treatment

Craig G. Ruaux

Client Information Sheets:
Managing Acute Pancreatitis in the Cat
Managing Chronic Pancreatitis in the Cat

Our understanding and recognition of inflammatory diseases of the feline pancreas has undergone a remarkable change within a relatively short period of time. As recently as the late 1990s, acute pancreatitis in cats was felt to be a relatively uncommon disorder and chronic pancreatitis was thought to have "limited clinical importance."[1] We now know that pancreatitis is the most common disorder of the exocrine pancreas in cats[2] and chronic pancreatitis is common as a primary disease and a comorbidity with many other diseases of the cat.[3-5] In no small part this explosion in our understanding of the disease is due to marked improvements in diagnostic imaging modalities, minimally invasive clinical chemistry testing methods, and the simple recognition that the clinical manifestations of pancreatic disease in the cat are markedly different from those seen in the dog.

Histological Characterization of Pancreatitis in Cats

As pancreatitis is, by definition, an inflammatory disease, objective documentation of the presence of inflammation in the pancreatic parenchyma via histopathological examination is still held to be the gold standard for diagnosis of this disorder.[6-8] Histological scoring systems for assessing the type and degree of severity of pancreatitis in the cat have been described.[6] Most authors make a distinction between acute pancreatitis (typified by interstitial edema, neutrophilic infiltration and possible mesenteric fat necrosis) and chronic pancreatitis (typified by lymphocytic infiltration, fibrosis and cystic acinar degeneration) when describing inflammatory disease in the pancreas of the cat.[1,6] However, it is common for histological sections of the pancreas to show a mixed pattern of infiltration, and the distribution of lesions within the feline pancreas may be patchy, as has been described in dogs.[9]

Some reports suggest that chronic pancreatic inflammation (particularly lymphocytic infiltrates and/or fibrosis) is quite common in the domestic cat. In one study describing 115 cats presented for necropsy, regardless of cause, evidence of pancreatitis was found in 67% of sick cats and 45% of clinically normal cats (i.e., cats with no history of disease, typically dying because of trauma).[6] Chronic pancreatitis was the most common finding, being observed in 60% of all samples; just over 50% of the samples had only chronic pancreatitis. In the same group of cats, acute pancreatitis was documented in 18 cases (15.7%), with 7 cases showing only acute pancreatitis and 11 cases showing a mix of acute and chronic changes. In a recent study assessing indications for and complications from pancreatic biopsy, chronic or "acute on chronic" pancreatitis was identified in 10/19 cats, while "pancreatitis" without specification of acute vs. chronic was identified in another two cases, giving a total of 12/19 (63%) of cases where pancreatic inflammation was identified in cats with a clinical suspicion of pancreatic disease.[10] It is interesting to note that in this study, dogs were less frequently diagnosed with pancreatic lesions than cats were.

Clinical Signs of Pancreatitis in the Cat

One of the great challenges in managing the cat with pancreatitis is the vague nature of clinical signs typically manifested in these cats. Based on the aggregation of data from three studies, involving a variety of underlying histological diagnoses and apparent disease severities, the most common clinical signs of pancreatitis in the cat are reduced appetite, lethargy, dehydration and vomiting (Table 291-1). Abdominal pain, a very common clinical sign of pancreatitis in the dog, is much less frequently recognized in the cat. Accurate assessment of abdominal pain in the cat (see ch. 126) can be quite difficult, and thus the true frequency of this problem in cats with pancreatitis may be underestimated[11]; however the central observation that abdominal pain is rarely appreciated by clinicians assessing cats with pancreatitis remains true. Given the vague nature of clinical signs of pancreatitis in the cat, this disease should be considered in the differential diagnosis of any cat with vomiting, anorexia/hyporexia or lethargy where another, more proximate cause has not been identified.

TABLE 291-1

Common Historical and Clinical Signs of Pancreatitis in Cats Aggregated from Three Separate Studies[1,12,28]

CLINICAL SIGN	STUDY				TOTAL	OVERALL PREVALENCE
	STOCKHAUS ET AL[28]	FERRERI ET AL[12] (ANP)	FERRERI ET AL[12] (CP)	HILL & WINKLE[1]		
Number of cats	33	30	33	40	136	
Inappetence	32 (97%)	19 (63%)	23 (70%)	39 (98%)	113	83%
Lethargy	33 (100%)	15 (50%)	17 (52%)	40 (100%)	105	77%
Dehydration	24 (73%)	10 (33%)	17 (51%)	37 (93%)	88	65%
Vomiting	18 (55%)	13 (43%)	13 (39%)	14 (35%)	58	43%
Icterus	6 (18%)	5 (16%)	8 (24%)	21 (53%)	40	29%
Weight loss	3 (9%)	12 (40%)	7 (21%)	NS	22	16%
Abdominal pain	17 (52%)	NS	NS	10 (25%)		

Cats from one study (Ferreri et al.[12]) are subdivided into acute necrotizing (ANP, n = 30) and chronic nonsuppurative (CP, n = 33) presentations. NS = Not specified. Overall prevalence is rounded to the nearest whole percentage value.

It is not possible to distinguish acute from chronic pancreatitis in cats based on clinical presentation, duration of clinical signs or apparent severity of the disease.[2,12,13] While chronic pancreatic disease is commonly thought to be less severe than acute pancreatitis in the cat,[13] either disease can present with complications or comorbidities that are potentially life-threatening, and attempting to draw a distinction between these two conditions is not particularly clinically helpful.

The Diagnostic Approach to the Cat with Suspected Pancreatitis

Routine Biochemistry and Complete Blood Count

Clinical biochemistry and hematological abnormalities are common in cats with pancreatitis, but there are no individual abnormalities or patterns of findings that are specific for pancreatitis in the cat. Abnormalities that are commonly encountered include leukocytosis, left shift neutrophilia, elevated ALT and ALP activities, elevated bilirubin, azotemia, hypercholesterolemia, hypoalbuminemia, hypokalemia, hypocalcemia and hyperglycemia.[11-14] The presence of hypocalcemia is often associated with more severe, necrotizing presentations and warrants more aggressive therapy (see below).[11,14,15]

While no specific pattern of results in routine biochemistry panels suggests pancreatitis in the cat, routine clinical pathology testing remains a valuable part of the diagnostic and therapeutic plan. Recognition of serum biochemical abnormalities, particularly elevated liver enzyme activities, elevated bilirubin, and electrolyte abnormalities is an important part of treatment planning and is critically important in the early

recognition of common comorbidities such as hepatic lipidosis (see ch. 285) and diabetes mellitus (see ch. 305) that require additional interventions.

Pancreas-Specific Diagnostic Tests

The lack of specific biochemical findings, vague nature of clinical signs, and variable presence of abdominal pain in the cat with pancreatitis all combine to make the search for sensitive, specific and minimally invasive diagnostic tests for pancreatic disease in the cat one of great recent interest and activity. It is still common for many reference laboratories and in-house chemistry systems to provide estimates of serum amylase and lipase catalytic activities on routine chemistry panels in both dogs and cats (see ch. 64). These enzyme activities are widely considered to have poor to no diagnostic utility for the assessment of pancreatic disease in the cat.[2,11-13,16,17] Additionally, very high degrees of inter-instrument and between-instrument variability have been reported for these (and many other) clinical pathology analytes in the cat[18,19]; thus, the use of traditional amylase and lipase activities, regardless of laboratory type, has questionable utility in the assessment of the feline patient.

The pancreas is a source of several proteins and peptides that are solely synthesized in this organ. Several of these proteins (see ch. 271) have received at least some attention as diagnostic tests for pancreatitis in the cat, including feline trypsinogen (fTLI),[20] the trypsin-activation peptide (TAP),[21] and pancreas-specific lipase (fPLI & Spec fPL) (see ch. 289).[22] The underlying assumption with these tests is that only very small amounts of these proteins are normally present in the circulation (often at concentrations at or below the detection limit of the assay), but in the presence of acinar cellular dysfunction, these proteins leak into the interstitium and circulation, where they may be detected. The detection of increased concentrations of these proteins is thus considered to be evidence of acinar cellular abnormalities, and felt to be consistent with a diagnosis of pancreatitis.[8,13]

The actual sensitivity and clinical utility of both fTLI and fPLI/Spec fPL have been assessed in numerous studies. Using a serum fTLI concentration >100 mcg/L as a threshold value for diagnosing pancreatitis, sensitivities ranging from approximately 28 to 64% have been reported by various authors for the detection of either acute or chronic pancreatitis in cats.[20,21,23] These studies are quite variable in terms of patient numbers, study designs, and additional diagnostic methods used, and thus, direct comparison of the reported sensitivities is questionable. Regardless, the highest reported sensitivity, approximately 64%, is suboptimal at best given that it was obtained in a relatively small group (n = 10) of cats with strong evidence of significant pancreatic disease (either characteristic ultrasonographic changes or histologically confirmed on pancreatic biopsy). A normal serum fTLI concentration does not reliably rule out the presence of pancreatic disease in the cat.[24] The specificity of elevated fTLI concentrations has also been thrown into doubt by some authors, who identified elevated fTLI concentrations in cats with no strong evidence of pancreatic disease and in the presence of other, significant diseases such as idiopathic inflammatory bowel disease, gastrointestinal lymphoma, and azotemia.[23,25] An alternative interpretation of these data, supported by the observation that pancreatic disease in the cat often has vague or "silent" clinical signs and is a common comorbidity of many conditions, would be that comorbid pancreatic disease was quite likely in many of these cases.

Detection of elevated serum concentrations of specific pancreatic lipase (fPLI or Spec fPL) has a higher reported sensitivity and specificity than fTLI. In one study, where fTLI achieved overall sensitivity and specificity of 28% and 82%, respectively, fPLI achieved overall sensitivity and specificity of 67% and 67%, respectively.[26] In the same study, sensitivity of fPLI for the diagnosis of "moderate to severe" pancreatitis was 100%. A larger study (n = 182 cats) of the Spec fPL assay reported an overall sensitivity for this test of 79%, with a specificity of 82% for detection of pancreatitis in this group.[27] Overall, the Spec fPL has the highest currently reported sensitivity and specificity of any diagnostic modality for the detection of pancreatitis in the cat.[24] The use of Spec fPL measurement as a prognostic marker and monitoring parameter for recovery has received limited attention at this time.[28] Elevation of Spec fPL to >20 mcg/L was found to be associated with a poorer prognosis in cats hospitalized with pancreatitis. No data in the literature indicate that greater elevations in Spec fPL are associated with poorer response to therapy in cats with chronic pancreatitis, assuming adequate management of comorbidities.

The low sensitivity and specificity of traditional amylase and lipase activities for the diagnosis of pancreatitis, in all species, may be partly explained by low substrate specificity for most of the catalytic assays. The substrates used in these assays vary in terms of selectivity for pancreatic lipase, with some substrates showing much higher selectivity for pancreatic-origin lipases in the circulation. 1-2-o-Dilauryl-*rac*-

glycero-3-glutaric acid-(6'-methylresorufin) ester (DGGR) is a lipase substrate with relatively high substrate specificity for pancreatic lipases.[29] This assay has been validated and assessed in the domestic cat.[30] The overall agreement between DGGR-lipase and Spec fPL was high, with Cohen's kappa coefficients between 0.60 (moderate agreement) and 0.75 (substantial agreement) at varying cutoffs applied for either DGGR-lipase activity and Spec fPL values for diagnosing pancreatitis.[30] In this same study of 251 client-owned cats with a clinical suspicion of pancreatitis, DGGR-lipase activity >26 U/L showed a sensitivity of 48% with a specificity of 63%, while Spec fPL >5.3 mcg/L showed a sensitivity of 57% and specificity of 63%.[30] This study suggests that DGGR-lipase activity may have some clinical utility in the assessment of cats; however, this would be reliant on the use of this specific substrate in whichever analytical system is being used. Information regarding the actual substrates used by the various reference laboratories and in-house chemistry systems commonly found in veterinary practice is not readily available at this time.

Diagnostic Imaging

Plain radiographic changes accompanying acute pancreatitis in the cat are similar to those described in dogs, and include reduced abdominal contrast, dilation of bowel loops and pleural effusion. These signs are subtle, non-specific, and show low sensitivities (28-50% for reduced abdominal contrast, 24-42% for bowel dilation, 20-29% for pleural effusion).[1,12,20,31,32] Plain radiographic signs of chronic pancreatitis in the cat are not well characterized.

The increasing availability of high-resolution abdominal ultrasonography in companion animal practice (see ch. 88) has dramatically improved the use of diagnostic imaging to characterize pancreatic disease in the cat. The ultrasonographic appearance of the normal feline pancreas, and changes consistent with pancreatic disease, have been described (Figure 291-1, *A* and *B*).[12,32-34] Pancreatic enlargement, hyperechoic mesentery and abdominal fat, altered parenchymal echogenicity (most commonly hypoechogenicity or a mixed pattern), abdominal effusions, pancreatic cysts or pseudocysts, corrugation of the duodenum and dilation of the pancreatic duct are all considered consistent with pancreatitis in cats with compatible clinical signs.[12,23,32,35] While these findings are reasonably specific indicators of the presence of pancreatic disease, their sensitivity for accurate diagnosis of histologically confirmed pancreatitis is quite variable, with reported sensitivities ranging from ≈11 to 80%.[12,23,26] Sensitivity of abdominal ultrasound for the detection of feline pancreatic disease appears to be highly operator-dependent.[32] Several recent publications have investigated the degree of agreement between abdominal ultrasonography findings and pancreas-specific, minimally invasive tests (Spec-fPL and DGGR lipase activity).[35,36] Given the variable and often low sensitivity of abdominal ultrasound examination for the diagnosis of pancreatitis in cats, this modality cannot be reliably used as a "rule-out" test for this disease. However, significant additional information useful for management of these cases is often obtained, particularly when screening for comorbid conditions such as cholangitis/cholangiohepatitis or the presence of extra-pancreatic disease that could explain the clinical signs. Thus, abdominal ultrasonography, carried out by a well trained and experienced operator, is recommended in all cats where there is a clinical suspicion of pancreatitis.

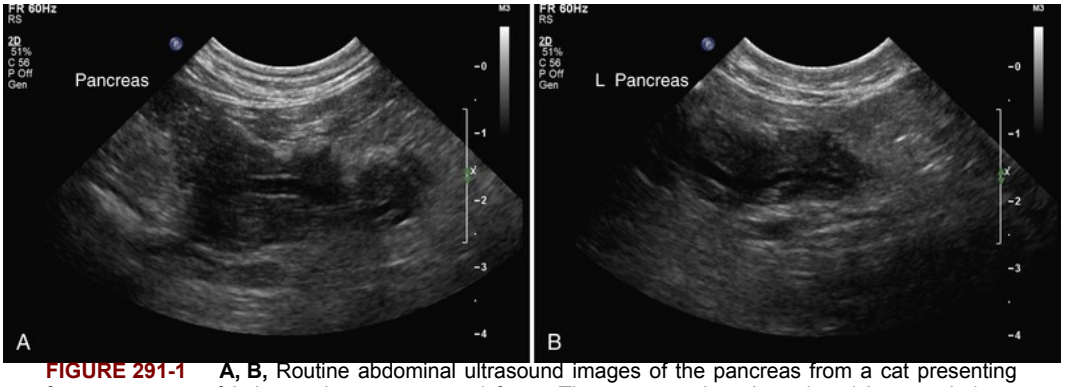

FIGURE 291-1 **A, B,** Routine abdominal ultrasound images of the pancreas from a cat presenting for acute onset of lethargy, inappetence and fever. The pancreas is enlarged and heteroechoic to hypoechoic, while surrounding mesenteric fat is hyperechoic. The pancreatic duct is prominent and increased in diameter (approximately 4 mm). These findings are consistent with the presence of acute pancreatitis in this patient.

A recent report described the use of endoscopic ultrasonography in the cat, including both healthy controls and cats with a diagnosis of pancreatitis.[37] While this study showed that the technique is feasible in the cat, and visualization of the entire pancreas appeared better with the endoscopic technique, endoscopic ultrasonography did not alter the diagnosis in these cats.

Higher-level imaging modalities, such as computed tomography, have received some attention in cats with pancreatitis.[20,26,38] In these studies, sensitivity was low, or changes in pancreatic appearance were not appreciated between normal and symptomatic groups. Combined with the cost of computed tomography examination and need for either heavy sedation or anesthesia for this procedure, these findings argue strongly against the use of computed tomography in the assessment and diagnosis of pancreatitis in the cat.

Pancreatic Biopsy and Histopathology

As stated earlier, most sources consider the histological demonstration of pancreatic inflammation as the gold standard diagnostic test for pancreatitis, regardless of species.[10,24] Pancreatic biopsy in the cat has not been a common procedure in routine veterinary practice, likely due to both the invasiveness of celiotomy/laparotomy approaches and ongoing concern that surgical manipulation of the pancreas may result in post-surgical pancreatitis.[7] A recent retrospective study has shown that pancreatic biopsy often yields diagnostically useful information, with biopsies from 14/19 cats with a clinical suspicion of pancreatitis showing at least some degree of histological abnormality.[10] In this study, chronic pancreatitis was the most commonly detected abnormality in the feline patients.

Laparoscopic techniques for visualization and biopsy of abdominal organs, including the pancreas, have a lower level of invasiveness than exploratory laparotomy, and have been shown to be safe in clinically healthy cats (see ch. 91).[39,40] An earlier retrospective study reported that only 9/13 cats undergoing laparoscopy for assessment of signs consistent with pancreatitis actually had a pancreatic biopsy taken, yet in the same report there were no postoperative complications noted (n = 31 cases).[7] In a more recent report,[10] postoperative complications were seen in 10/43 dogs and cats following surgical biopsy of the pancreas, with 5/10 cases showing signs suggestive of post-surgical pancreatitis. In the feline patients, 3/19 showed some evidence of post-surgical signs that could be considered suggestive of pancreatitis.

While surgical biopsy of the feline pancreas is underutilized, and the relatively low rate of minor complications reported in the literature to date argues that this modality should be considered more frequently, some shortcomings of pancreatic biopsy need to be recognized. In the dog, pancreatic lesions often show a patchy distribution, and assessment of multiple biopsies is necessary to obtain the greatest utility from this technique.[9] While similar studies have not been published in cats, it is reasonable to assume that pancreatic lesion distribution may be similarly patchy in this species, and assessment of a single biopsy (common with laparoscopic biopsies) may result in false negative findings. Even using laparoscopic techniques, surgical biopsy of the pancreas is invasive and expensive, requiring specialized equipment and skills. Surgical biopsy requires anesthesia, which may be high-risk in hemodynamically unstable patients with more severe presentations; therefore, the greatest use of this procedure is likely to be in cats with chronic pancreatitis.[7,24,40]

Therapeutic Approach to the Cat with Suspected Pancreatitis

A rational approach to the initial assessment, therapeutic planning and management of a cat with suspected pancreatitis is given in Figure 291-2. As necrotizing "acute" pancreatitis and non-necrotizing, "chronic" pancreatitis in the cat cannot be distinguished on the basis of clinical findings, abdominal imaging, clinical chemistries or results of specialized pancreatic tests, and pancreatic biopsy is still a relatively uncommon procedure, the initial diagnostic step necessary in these cases is to assess the overall state of health of the patient and apparent severity of the disease. Cats with suspected pancreatitis presenting with marked abdominal pain, tachypnea, tachycardia, significant fever, collapse or other evidence of systemic inflammatory syndrome or circulatory shock are considered to have severe disease, and require immediate and aggressive, hospital-based care. The existence of multiple abnormalities in screening clinical chemistries, particularly hypoalbuminemia and hypocalcemia, is a strong indicator of severe and potentially life threatening disease.[11] Cats presenting with weight loss, poor appetite, occasional vomiting and lethargy but without immediate evidence of significant hemodynamic compromise are considered to have less severe, likely chronic, disease and are treated on an outpatient basis.

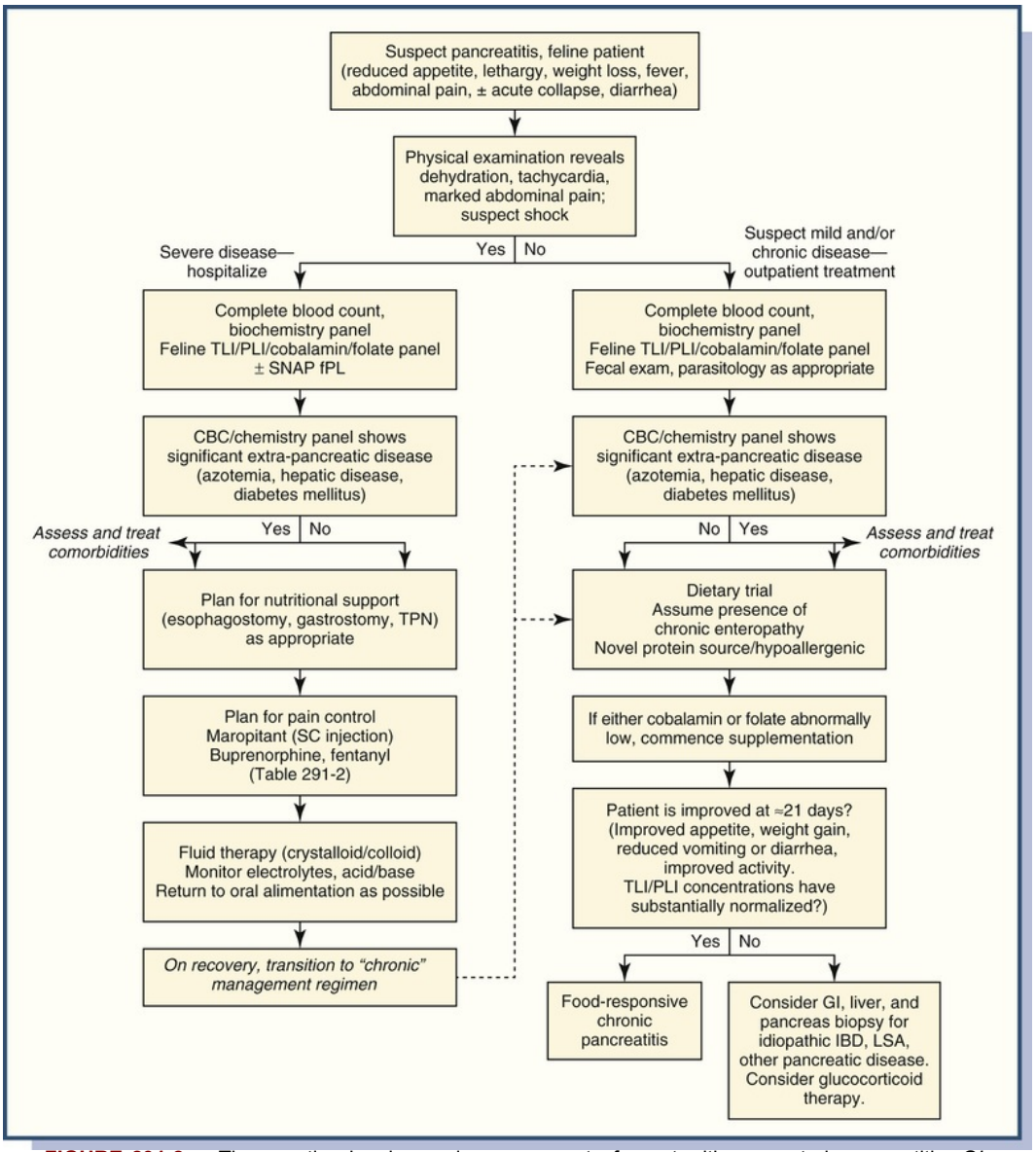

FIGURE 291-2 Therapeutic planning and management of a cat with suspected pancreatitis. *GI,* Gastrointestinal; *IBD,* inflammatory bowel disease; *LSA,* lymphoma; *PLI,* pancreas-specific lipase; *SC,* subcutaneous; *TLI,* trypsin-like immunoreactivity; *TPN,* total parenteral nutrition.

Cats presenting with severe disease require aggressive therapy, including fluid therapy (see ch. 129), effective analgesia (see ch. 126), and early planning for nutritional support (see ch. 82 and 189) given the risk of hepatic lipidosis as a comorbidity. The aims of therapy are to replace circulating fluid volume, restore and maintain end organ perfusion (particularly of the pancreas, as pancreatic ischemia is a significant contributor to the development of necrotizing pancreatitis[13]), and restore and maintain plasma colloid oncotic pressure. Colloid fluids, such as synthetic hydroxyethyl starches, are often highly beneficial in the initial resuscitation of these cases. Fresh-frozen feline plasma can also be considered, and likely provides oncotic support while replenishing coagulation cascade proteins (see ch. 130); however, there is little information in the veterinary literature regarding use of plasma in severe feline pancreatitis cases. We typically use a combination of synthetic colloid and crystalloid fluids for initial resuscitation and volume maintenance in these cats in our clinic. Substantial electrolyte abnormalities, particularly hypokalemia and hypocalcemia, should be anticipated in these cats.[2,11] Supplemental potassium is administered in combination with crystalloid fluids following routine guidelines for concentrations based on serial determination of serum potassium (see ch. 68 and 129).

Effective analgesia and control of vomiting are important aspects of management of severe pancreatitis in all species, including the cat. A selection of medications that are often useful in the management of

pancreatitis in the cat is summarized in Table 291-2. Narcotic pain control is typically indicated in cats with sufficiently severe pancreatitis to warrant hospitalization. Transdermal fentanyl patches (25 mcg/h) can be very effective for longer term (up to 72 h) analgesia without the need for frequent handling and injection in these patients, but initial therapy with an injectable or sublingual agent (commonly buprenorphine) is necessary as it can take up to 12 hours for therapeutic fentanyl concentrations to be reached.[2] Maropitant, a neurokinase-1 receptor antagonist, is both an effective antiemetic and has antinociceptive effects in the viscera.[41] The combination of maropitant with a 5-HT_3-receptor antagonist, such as ondansetron or dolasetron (see Table 291-2), provides an effective control for vomiting and nausea in these patients with minimal need for repeated handling during the day.

TABLE 291-2

Common Medications Used in the Management of Cats with Pancreatitis

CLASS	DRUG	MECHANISM	MAIN INDICATION	DOSAGE AND ROUTE	ADMINISTRATION NOTES
Analgesic	Buprenorphine	Opioid	Acute, severe	0.01-0.02 mg/kg SC, IM, IV, TM	Mixed agonist/antagonist.
	Fentanyl	Opioid	Acute, severe	25 mcg/h transdermal patch 5 mcg/kg IV bolus, CRI 2-4 mcg/kg/h	Titrate CRI to effect; start with low dosage in critical patients.
	Butorphanol	Opioid	Acute, severe	0.1-0.5 mg/kg SC, IM, IV	
Antiemetic Antinausea	Maropitant	Neurokinin-1 receptor antagonist	Acute, severe Chronic	1 mg/kg SC q 24 h 1 mg/kg PO q 24 h	Also provides some pain control. May be useful in outpatient management for acute-on-chronic disease.
	Dolasetron, ondansetron	5-HT_3 receptor antagonist	Acute, severe	0.8-1 mg/kg IV q 24 h	Can use in combination with maropitant, metoclopramide.
	Metoclopramide	Dopamine D_2 receptor antagonist	Acute, severe	0.2-0.5 mg/kg PO, SC, IM q 6-8 h 1-2 mg/kg/24 h CRI	Recommend use as CRI in critical patients.
Gastric acid suppressant	Omeprazole	Proton pump inhibitor	Acute, severe	1-1.3 mg/kg PO q 12 h	q 12 h dosing is necessary for effective gastric pH control in cats.[48,49]
	Pantoprazole	Proton pump inhibitor	Acute, severe	0.7-1 mg/kg IV q 12 h	Useful in patients where vomiting is not yet controlled.
	Ranitidine	Histamine H_2 receptor antagonist	Acute, severe	3.5 mg/kg PO q 12 h	Used mainly for prokinetic effect, NOT an effective acid suppressant in cats.
Anti-inflammatory	Prednisolone, prednisone	Glucocorticoid	Chronic	2-4 mg/kg PO daily, tapering at 0.5 mg/kg increments every 14 days	Taper and titrate doses to minimum effective dosage. Insulin resistance may limit utility in diabetic/prediabetic cats. Many cats show poor response to prednisone (ineffective).
	Cyclosporin A	Calcineurin inhibition	Chronic	5 mg/kg PO q 12-24 h	Consider in poorly regulated patients, or those with history of diabetes mellitus.

	Chlorambucil	Alkylating agent	Chronic	0.1-0.2 mg/kg/day PO or 0.15-0.3 mg/kg PO q 72 h	Consider in poorly regulated patients, or those with history of diabetes mellitus. Monitor for myelosuppression. Taper dosage to minimum effective over several months.
Appetite stimulant	Mirtazapine	Tricyclic antidepressant	Acute, severe Chronic	3.75 mg/cat PO q 72 h	Dose represents ¼ of a 15 mg tablet.
	Cyproheptadine	Histamine H_1 and 5HT receptor antagonist	Chronic	1-4 mg/cat/day PO	Questionable efficacy.

CRI, Constant-rate IV infusion; *TM*, transmucosal.

Extra-pancreatic comorbidities, particularly hepatic disease and diabetes mellitus, should be screened for and treated appropriately, including early reintroduction of feeding as appropriate. While there are limited data available regarding cats and early enteral nutrition with severe pancreatitis, our clinical experience is that this is generally well tolerated and advantageous. In both humans and dogs, there is accumulating evidence that early return to enteral nutrition is associated with improved outcomes, shorter hospital stays and a low frequency of side-effects.[42-44]

Cats with a clinical suspicion of chronic pancreatitis are treated in essentially the same manner as cats with chronic enteropathies or diagnoses of idiopathic inflammatory bowel disease (see ch. 276). There is no meaningful way to distinguish between chronic pancreatitis as a solitary disease entity and the presence of multi-organ inflammatory disease (so-called feline inflammatory disease or "triaditis").[5,45] Initially, dietary modification, typically by use of a novel protein source or hypoallergenic diet, is suggested. In contrast to dogs, where fat restriction is a cornerstone of management for most cases of chronic pancreatitis, fat restriction is not recommended in cats due to their high constitutive requirement for arachidonic acid.[46,47] Many cats will respond to dietary manipulation; in those who fail to respond to dietary manipulation, it is rational to consider anti-inflammatory or immune-modulatory therapies, assuming that there are no other comorbidities present that would contraindicate the use of these medications.

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CHAPTER 292

Exocrine Pancreatic Insufficiency

Jörg M. Steiner

Client Information Sheet: Exocrine Pancreatic Insufficiency

Introduction and Definition

Exocrine pancreatic insufficiency (EPI) describes a syndrome that is characterized by the insufficient synthesis and secretion of digestive enzymes from the exocrine pancreas. The most common cause of EPI is an absolute lack of pancreatic acinar cells that is due to destruction of acinar cells due to chronic pancreatitis (both dogs and cats) or depletion of acinar cells due to pancreatic acinar atrophy (dogs). In either, all pancreatic digestive enzymes are lacking. In rare cases a single enzyme may be lacking, but lack of a single enzyme, even if complete, most often does not lead to clinical signs. However, isolated pancreatic lipase deficiency has been reported as a cause of clinical signs of EPI in humans and in one dog.[1,2] Another infrequent cause of EPI is an obstruction of the pancreatic duct by either a tumor or surgical damage, which can lead to lack of digestive enzymes in the small intestinal lumen, despite normal acinar production. Pancreatic aplasia or hypoplasia could also lead to clinical signs of EPI. This may be suspected when patients are being diagnosed with EPI at a very early age (Figures 292-1 and 292-2), but to date no case has been conclusively demonstrated in a puppy or kitten.

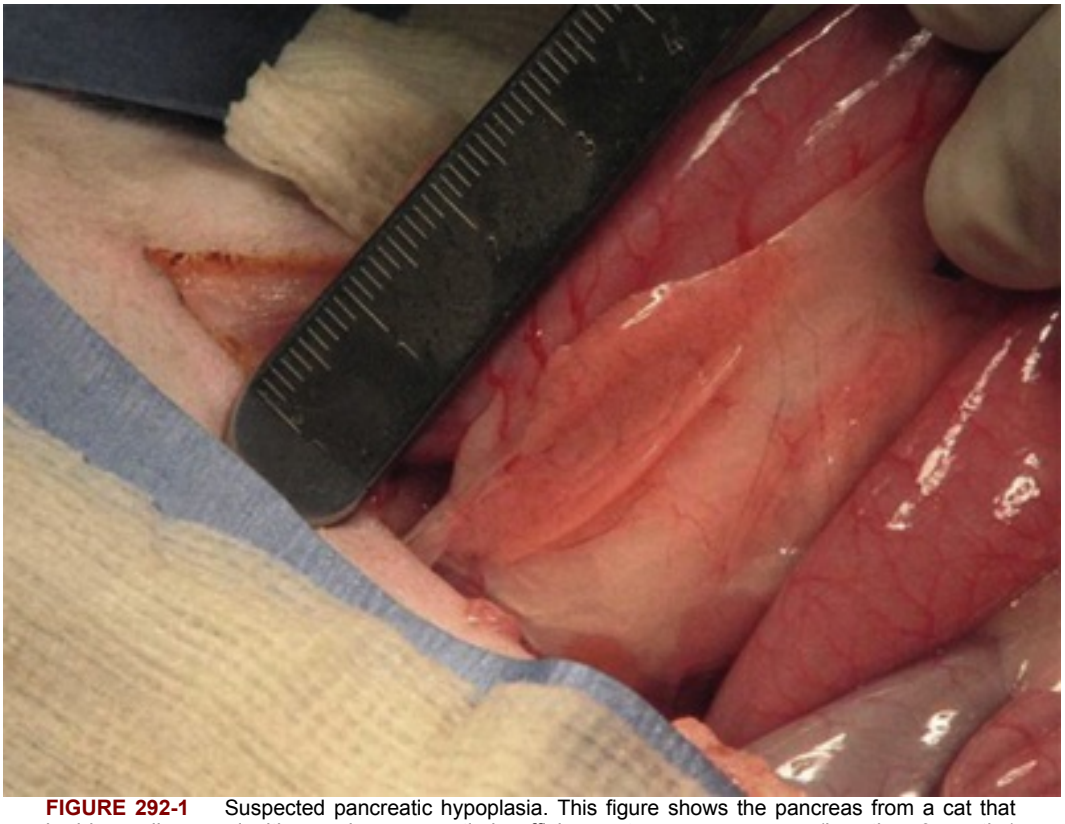

FIGURE 292-1 Suspected pancreatic hypoplasia. This figure shows the pancreas from a cat that had been diagnosed with exocrine pancreatic insufficiency at a very young age (less than 3 months)

during a routine spay. Note that the pancreas appears extremely small in size, suggesting pancreatic atrophy or pancreatic hypoplasia.

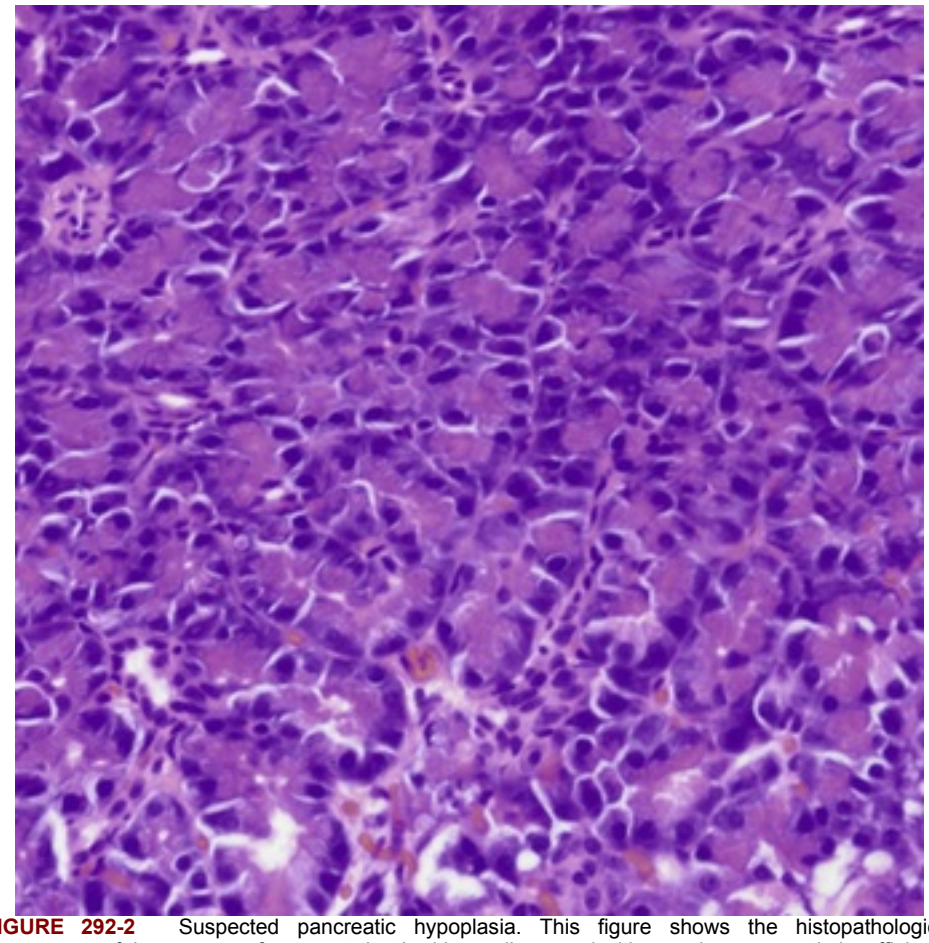

FIGURE 292-2 Suspected pancreatic hypoplasia. This figure shows the histopathological appearance of the pancreas from a cat that had been diagnosed with exocrine pancreatic insufficiency at a very young age. Note that the acinar structure appears to be normal and there is no evidence of either inflammation or fibrosis, suggesting pancreatic hypoplasia.

Etiology

The most common cause of EPI in both dogs and cats is chronic pancreatitis, which is suspected to be the cause of EPI in nearly 100% of cats and in approximately 50% of dogs with EPI. In dogs, the other approximately 50% of EPI cases are caused by pancreatic acinar atrophy (PAA), which is almost exclusively seen in German Shepherd dogs, Rough-coated Collies, and Eurasians.[3,4] Several studies have suggested that PAA is inherited as an autosomal recessive trait in the German shepherd dog and also the Eurasian.[5-7] However, the search for a genetic marker for this disease has been largely unsuccessful, despite the entire canine genome having been scanned using a set of microsatellite markers and SNPs, having revealed several regions that appear to be associated with the condition.[8] Interestingly, a breeding study of an affected male and an affected female German Shepherd only resulted in 2 of 6 affected offspring, strongly suggesting against inheritance as a simple autosomal recessive trait.[9] Thus, this condition is likely polygenic.[10]

Pathogenesis

Digestive enzymes or inactive preforms of digestive enzymes (i.e., zymogens) for the digestion of all major food components are secreted by pancreatic acinar cells. When pancreatic acinar cells are lacking, regardless of the cause, maldigestion ensues. It is, however, important to note that the gastrointestinal (GI) tract is highly

redundant and that there is usually more than one digestive enzyme that fulfills the same digestive function. For example, pancreatic lipase is crucial for fat digestion, but the stomach also synthesizes and secretes gastric lipase, which is responsible for a significant portion of normal fat digestion in the dog.[11] Also, physiologically, the exocrine pancreas has a large reserve capacity, and it has been estimated that clinical signs of EPI only ensue when more than 90% of exocrine pancreatic function has been lost.

Maldigestion leads to undigested food components in the intestinal lumen, which can lead to diarrhea, proliferation of the small intestinal microbiota, and weight loss. However, it has been suspected that clinical signs are not only due to maldigestion, but that EPI also leads to malabsorption. This has been theorized to be due to a lack of trophic factors normally secreted by the exocrine pancreas that help maintain a normal GI mucosa.

The exocrine pancreas also is the major source of intrinsic factor in both dogs and cats.[3] In sharp contrast to humans, where intrinsic factor is mainly secreted by the gastric mucosa, intrinsic factor in dogs and cats is mainly of exocrine pancreatic origin (see ch. 271).[12] In one study, 82% of dogs with EPI were shown to have a decreased serum cobalamin concentration with 36% having marked hypocobalaminemia.[13] All cats with EPI described in the literature where cobalamin has been assessed were found to have hypocobalaminemia.[14-16]

Clinical Presentation

EPI can be subclinical and two large case series of German Shepherd dogs identified several dogs with severely decreased serum trypsin-like immunoreactivity (TLI) concentrations that did not have any clinical signs.[7,17] Some of the dogs underwent exploratory laparotomy and the pancreatic mass was found to be severely decreased.[17] The most common clinical sign reported in both dogs and cats with EPI is weight loss (Figures 292-3 and 292-4).[15,18] Loose stools are also commonly observed (Figure 292-5), but watery diarrhea is rather uncommon.[15,18] Often times, patients have a poor hair coat and dogs with EPI are commonly reported to have borborygmus and increased flatulence.[18] Many dogs and cats with EPI will show an increased appetite, while dogs may even show coprophagia or pica.[18] In cats, a greasy soiling of the hair coat in the perineal region can be observed, but this is not a common finding.[15]

FIGURE 292-3 Cat with EPI. This photograph shows Theo, a 4-year-old male castrated cat with exocrine pancreatic insufficiency (EPI). Note the thin appearance of the cat. (Photograph courtesy Dr.

Kenneth Jones, Jones Animal Hospital, Santa Monica, CA; Reprinted from Steiner JM: Exocrine pancreatic insufficiency. In August JR, editor: *Consultations in feline internal medicine*, St Louis, 2010, Saunders Elsevier, pp 225-231.)

FIGURE 292-4 Cat with exocrine pancreatic insufficiency, treated. This picture shows Theo, the cat shown in Figure 292-3, two months after starting enzyme replacement therapy. Theo had gained almost 3 pounds during this time and was reported to be more active. (Photograph courtesy Dr. Kenneth Jones, Jones Animal Hospital, Santa Monica, CA; Reprinted from Steiner JM: Exocrine pancreatic insufficiency. In August JR, editor: *Consultations in feline internal medicine*, St Louis, 2010, Saunders Elsevier, pp 225-231.)

FIGURE 292-5 EPI stools. This large stool sample is from a cat with exocrine pancreatic insufficiency (EPI) (cat shown in Figure 292-3). Note the typical loose consistency and the light brown color. Also, the stool sample appears to contain a lot of undigested food particles. (Photograph courtesy Dr. Kenneth Jones, Jones Animal Hospital, Santa Monica, CA; Reprinted from Steiner JM: Exocrine pancreatic insufficiency. In August JR, editor: *Consultations in feline internal medicine*, St Louis, 2010, Saunders Elsevier, pp 225-231.)

Diagnosis

Measurement of serum TLI is the diagnostic test of choice for both dogs and cats suspected of having EPI. Serum concentration is measured by a species-specific assay for TLI. The TLI assay measures the concentration of cationic trypsinogen, cationic trypsin, and some cationic trypsin molecules bound to proteinase inhibitor molecules. Under physiologic conditions, only a small amount of the trypsinogen synthesized by pancreatic acinar cells is released into the vascular space. Trypsinogen and trypsin are rather small molecules and thus are quickly excreted by the kidney. Therefore, only if the pancreas is functioning normally can a small amount of trypsinogen be detected in the serum (Video 292-1). In contrast, in patients with EPI, regardless of the cause, the amount of trypsinogen released into the blood stream is severely decreased (current cut-off values for a diagnosis of EPI: 2.5 mcg/L in dogs and 8.0 mcg/L in cats) to undetectable (see Video 292-1). In general, serum TLI is highly sensitive and specific for the diagnosis of EPI in both dogs and cats. There are two special scenarios, however, where serum TLI can be normal despite the patient having EPI. The first scenario is isolated pancreatic lipase deficiency, which has been described in one dog.[2] The second scenario where serum TLI concentration could be normal in a patient with EPI is a patient with an obstructed pancreatic duct. Such cases have not yet been described in the literature but a single dog with this condition has been identified (Hill S, personal communication, 2007).

There are other tests that have been recommended for the assessment of exocrine pancreatic function, including the plasma turbidity test, the para-amino benzoic acid test, and fecal proteolytic activity; however, none of them is considered useful for a diagnosis of EPI in dogs or cats.[19,20] Also, a fecal assay for the measurement of pancreatic elastase is now marketed in Europe. Initial studies showed acceptable sensitivity and specificity of the assay, but the estimated positive predictive value was less than 60%.[21,22] In another study, fecal elastase concentration was shown to be associated with a high number of false positive test results (23%).[23] Thus, a diagnosis of EPI based on a severely decreased fecal elastase concentration must be

verified by measurement of serum TLI concentration to prevent a misdiagnosis of EPI.

Therapy

Digestive enzyme replacement is the mainstay of therapy for EPI.[24,25] Pancreatic enzymes can be replaced by a variety of different options and a wide variety of products and options is listed at epi4dogs.com.[26] Dried pancreatic extract from pork pancreas is by far the most common and effective means of pancreatic enzyme replacement. Therapy is started with 1 teaspoon of dried extract per 10 kg body weight and meal. After the patient completely responds to therapy, the dosage can be slowly decreased until a minimally effective dose has been reached. It is important to note that the content of enzyme activity in the product may vary from container to container and thus the minimally effective dose may vary slightly over time. Pancreatic enzymes are also available as tablets and capsules but studies in humans and dogs have shown that powder is preferable to other formulations.[25,27] Complications of enzyme supplementation are rare, but one study reported 3 of 25 dogs being treated with pancreatic enzyme supplements developing oral bleeding.[28] When this occurs, a coagulation profile should be evaluated to exclude a vitamin K responsive coagulopathy, which has been reported in two cats with EPI.[29] In case of a normal coagulation profile, the dosage of pancreatic enzymes should be lowered. Two dogs in the study cited above continued to do well on the lower dosage, but in one of the dogs clinical signs did return.[28] If a patient does refuse to consume the pancreatic powder mixed into the food or in the rare case of a food allergy to the porcine pancreatic powder, fresh raw pancreas from various species can also be used.[25] Beef, pork, sheep, and game pancreas have all been used. One to 3 ounces (approximately 30 to 90 g) of raw pancreas replace 1 teaspoon of dried pancreatic extract. The pancreas should be finely chopped, divided into portions for one meal each, and immediately frozen. The frozen pancreatic tissue maintains its enzymatic activity for long periods of time. Concerns have been raised about the potential threat of infectious contamination of such raw frozen pancreas. Theoretically, raw bovine and ovine pancreas carries the risk of bovine spongioform encephalopathy transmission and raw porcine pancreas carries the risk of transmission of pseudorabies (Aujeszky's disease). However, this risk is more or less academic, as dried pancreatic powder would carry exactly the same risk. Game and ovine pancreas can be infested with *Echinococcus* spp. and infestation with this parasite could potentially cause significant disease and even death. This risk should thus be discussed with the owner before initiating therapy with raw pancreas from these sources. Preincubation of the food with the pancreatic extract does not appear to be necessary to achieve a therapeutic response.

Some authors have recommended feeding of a low fat diet. However, experimental studies have shown that in dogs treated with pancreatic supplements, fat digestibility does not return to normal, suggesting that fat restriction would only increase the risk of deficiencies of fat-soluble vitamins and essential fatty acids.[30] One study did not show any benefit of feeding fat-restricted diets in dogs with EPI.[13] Also, two other studies did not reveal a significant effect of diet on treatment success in dogs with EPI.[31,32] Therefore, the author believes that a high-quality maintenance diet would best be used. However, diets with high fiber content should be avoided as dietary fiber may interfere with fat absorption.

As mentioned above, many patients with EPI are cobalamin deficient and thus every dog and cat with EPI should be evaluated for possible cobalamin deficiency. While the measurement of serum cobalamin concentration cannot provide an estimate of cobalamin status on a cellular level, measurement of methylmalonic acid (MMA) in serum is more expensive and only available on a limited basis, and thus measurement of serum cobalamin is considered the routine tool for assessment of cobalamin status in both dogs and cats. Based on the measurement of both cobalamin and MMA in large numbers of dogs and cats, it is currently recommended to supplement any patient with EPI if the patient has a serum cobalamin concentration less than 400 ng/L. Traditionally, cobalamin is supplemented by weekly subcutaneous injections of cyanocobalamin (250 mcg in cats and 250-1,500 mcg in dogs, roughly based on body weight). Rarely, hydroxocobalamin is used. Doses are given weekly for 6 weeks, then one more dose after a month, and a recheck of serum cobalamin concentration a month later. There are some preliminary data that would suggest that daily oral supplementation is equally effective, but this needs to be confirmed by a prospective trial before using this treatment modality routinely.[33] Many EPI patients that have been treated appropriately will have a normal or even supranormal serum cobalamin concentration at the time of re-evaluation and cobalamin supplementation can be discontinued, but many others need to be supplemented life-long. Serum concentrations of most fat-soluble vitamins have been shown to be decreased in dogs with EPI and can also be assumed to be decreased in cats.[31] However, systematic vitamin supplementation of fat-soluble vitamins

has not been investigated in these patients and over-supplementation with fat-soluble vitamins may cause side effects. Anecdotal reports of vitamin E supplementation (400-500 IU PO q 24 h for 1 month) are available but the beneficial effect of such therapy has not been evaluated.

Many patients with EPI will respond well to enzyme replacement therapy and cobalamin supplementation, if indicated. However, some patients may not respond adequately to standard therapy. Potential causes of treatment failure should be evaluated. The type, formulation, and dosage of the enzyme supplement should be reviewed and if there is any suspicion that enzyme replacement may be insufficient, the protocol should be adjusted accordingly. Also, patients should be evaluated for concurrent conditions, such as inflammatory bowel disease (see ch. 276), diabetes mellitus (see ch. 304 and 305), or small intestinal dysbiosis (see ch. 276). If there is no evidence of any concurrent disease, a therapeutic trial with an antimicrobial agent can be attempted. The treatment of choice is tylosin (Tylan powder at 25 mg/kg PO q 12 h for 6-8 weeks), but other antibiotic agents, such as metronidazole, may also be used.

If patients still do not respond to treatment, antacid therapy can be attempted. A large portion of pancreatic lipase supplemented orally is irreversibly destroyed by the low pH in the stomach.[34] By increasing the pH in the stomach this portion may be decreased and the therapeutic response may improve. However, it must be noted that while an increase in gastric pH will decrease the amount of pancreatic lipase being destroyed during passage through the stomach, it also will increase the amount of gastric lipase being destroyed and the final result may not lead to a significant change in fat digestibility. However, a trial with omeprazole at 0.7-1 mg/kg PO q 12 h can be attempted and may be associated with significant improvement.

If none of these measures leads to control of the clinical signs, a decrease in the dietary fat content may be effective. However, as mentioned above, feeding a low-fat diet may be associated with complications and should only be viewed as a last resort.

Prognosis

EPI has traditionally been considered a life-long condition as pancreatic acinar cells were generally considered to not be able to regenerate. However, there are experimental data that would suggest some regenerative capacity of pancreatic acinar cells.[35] Also, there are anecdotal reports of isolated patients with EPI who improve and no longer require enzyme supplementation. One study has evaluated prognostic factors for dogs with EPI.[13] The only factor associated with a poor outcome in this study was the presence of marked hypocobalaminemia, which was associated with a median survival time of 1346 days compared to dogs without such marked hypocobalaminemia of 2709 days ($p = 0.012$).[13] In general, most dogs and cats with EPI can be successfully managed and will have a normal quality of life and a normal life expectancy.

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CHAPTER 293

Exocrine Pancreatic Neoplasia

Peter Bennett

Client Information Sheet: Cancer of the Pancreas

Incidence and Origin

Exocrine pancreatic tumors, usually identified in older dogs, may have an increased incidence in Airedale Terriers and females.[1-5] The prevalence of pancreatic carcinoma has been variably described, usually as uncommon to rare.[1,3,6-10] Estimated rates of about 18 and 12 per 100,000 patient years at risk have been reported for dogs and cats, respectively.[5] Benign hyperplasia and adenomas are uncommon, of little clinical relevance, and most frequently described as an incidental finding at post mortem in cats.[4,8,11-13]

Pancreatic carcinoma is one of the more common causes of cancer-related death in people and has shown little improvement in outcome in the last 40 years.[14] Malignant exocrine pancreatic tumors arise from either pancreatic ducts or acinar structures. In dogs, malignant exocrine pancreatic tumors are typically of acinar origin, whereas in man (and possibly cats) they are more often ductal.[4,10,12,15,16] Some tumors have characteristics of both acinar and ductal tissue.[17] Studies have demonstrated that pancreatic carcinoma cells display such marked plasticity that origin cannot be readily determined using routine histology.[18,19] Pancreatic neoplasia cells with mixed exocrine and endocrine characteristics have been reported in dogs and cats.[20,21] Carcinosarcoma has been diagnosed in a cat.[22]

Etiology and Pathophysiology

An etiological cause for pancreatic neoplasia has not been identified in dogs or cats, but injecting the carcinogen N-ethyl-N′-nitro-N-nitrosoguinidine into pancreatic ducts of normal dogs led to development of pancreatic exocrine carcinoma.[23] In people, there have been links with high fat diets, cigarette smoking, chronic alcohol abuse, chronic pancreatitis, and exposure to industrial carcinogens or alkylating chemotherapy agents.[24,25] Cases with concurrent neoplastic and inflammatory disease are reported.[25] One young Bengal cat with pancreatic pseudocysts developed exocrine pancreatic carcinoma within 6 months.[26] Early onset exocrine pancreatic carcinoma was reported in two gray Collie dogs with cyclic hematopoiesis but the relationship between the two conditions is unknown.[27] K-ras mutations have been identified in people and dogs with exocrine pancreatic cancer.[28-30]

While biologic behavior of pancreatic carcinomas can vary, they are typically aggressive with local invasion and metastases present at time of diagnosis.[1,2,10,12,31] The duodenum, regional lymph nodes, liver and lungs are the most common metastatic sites.[8] Abdominal carcinomatosis likely arises from direct seeding of cancer cells into the peritoneal cavity.[32] Most case reports describe rapid progression from the time of diagnosis, but there are exceptions.[33] A series of dogs with a hyalinizing variant of pancreatic carcinoma had better outcomes than are usually reported; 1 dog with metastatic disease at diagnosis lived 15 months without treatment.[34] Aggressiveness of exocrine pancreatic carcinoma and its resistance to therapy appears associated with, in part, the limited vascular network that contributes to hypoxia and poor nutrient supply. A complex reprogramming of metabolic pathways enables cancer cell survival. Targeting such dysregulated pathways may provide a means of improving outcome (see ch. 338).[14]

Clinical Signs and Physical Examination

Patients with exocrine pancreatic neoplasia have a wide range of signs.[13,35] Vague and nonspecific signs include reduced appetite, weight loss, diarrhea and abdominal discomfort. Some pets have signs consistent with acute pancreatitis: nausea, vomiting, anorexia and abdominal pain (see ch. 290 and 291).[9,12,36-40] Abdominal effusions can be seen.[40] Pain, common in people, is not prominent in dogs or cats.[16] The duration of signs can range from days to months.[13,35]

Cats can have extensive alopecia, most prominent on the ventral abdomen but sometimes involving the limbs and paws; such paraneoplastic alopecia has been observed with other internal malignancies (see ch. 352).[41-45] Bone metastases are uncommon, but could cause pain or lameness.[38] Multifocal necrotizing steatitis has been reported in a few dogs and one cat leading to multiple SC masses, fever and draining tracts.[46,47] Polyuria and polydipsia have been reported secondary to paraneoplastic hypercalcemia and 1 dog had a metastatic lesion in the pituitary leading to central diabetes insipidus.[48,49] Two dogs, one with an adenoma the other with a carcinoma, had a combination of panniculitis, polyarthritis and osteomyelitis.[50]

Often, pets with a pancreatic adenoma have no clinical signs unless the tumor has caused ascites, if it is causing obstruction or, in cats, where it can be large enough to be palpated.[51] Pancreatic carcinomas may also be palpable.[52] Pain is variable and not observed as often as in people.[53] Palpation of the mass can induce nausea. Compression of the extrahepatic bile duct can lead to icterus (Figure 293-1). About 10% of cases of extrahepatic biliary obstruction are due to pancreatic exocrine carcinoma.[54] Evidence of weight loss will be seen in some patients. In cats with alopecia, the skin can appear glossy and thin.

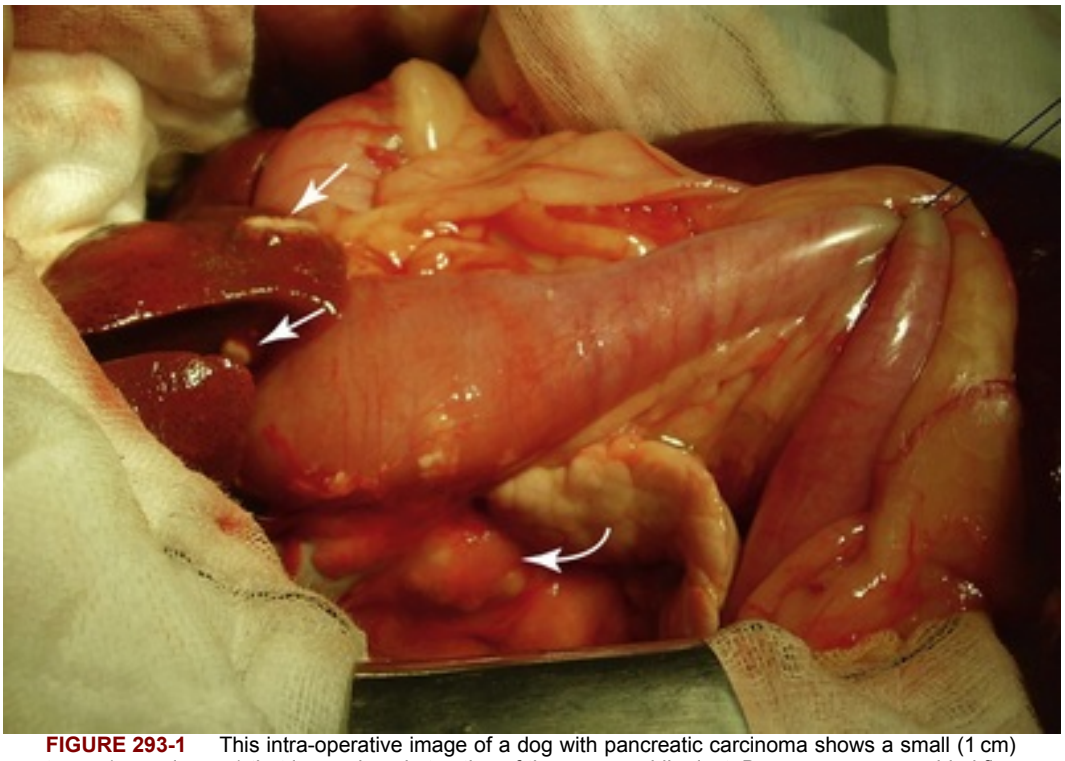

FIGURE 293-1 This intra-operative image of a dog with pancreatic carcinoma shows a small (1 cm) tumor (curved arrow) that is causing obstruction of the common bile duct. Bypass surgery provided five months of good quality life. Metastatic lesions are visible in the liver (straight arrows).

Diagnosis

Routine Hematology, Serum Biochemistry and Urinalysis Results

Routine hematology results are often nonspecific.[8] Mild to moderate nonregenerative anemia can be seen, as with any chronic disease. White cell parameters can be normal or, if there is significant peri-tumoral inflammation, exhibit a neutrophilic left shift.[12,55] Unless there is significant bleeding, platelet counts are

usually normal. Thrombocytopenia has been reported with bone marrow metastases.[55]

Serum biochemical results may include increased amylase and lipase values. Lipase may be markedly elevated.[2,50,56] Marked lipase increases in conjunction with minimal changes to amylase should lead to suspicion of pancreatic or hepatic neoplasia.[56] Bilirubin and liver enzyme activities can be increased secondary to obstruction of the common bile duct or with liver metastases (see ch. 53 and 65).[2] The changes in liver parameters can be more prominent than markers of pancreatic disease.[1] Hypercalcemia has been reported in some affected dogs.[48] Urinalysis is usually unremarkable unless positive for glucose. Neither diabetes mellitus (DM) nor exocrine pancreatic insufficiency is associated with pancreatic tumors in dogs or cats.[1,8,57] However, the conditions may occur concurrently. Two cats were reported to have concurrent DM and exocrine pancreatic carcinoma, but each had hyperadrenocorticism.[58] In a recent review of exocrine carcinoma in cats, 5/34 had DM.[40]

Imaging

Radiographic abdominal changes are often minimal, but mass effect with displacement of the duodenum and/or loss of serosal detail due to ascites can be seen.[1,38,59] A mass effect can be seen in cats with nodular hyperplasia or adenoma.[51] Nodular lung disease can be seen with lung metastases. Ultrasound (US) is useful for diagnosis of pancreatic carcinoma and is more sensitive than radiography (see ch. 88).[60] Even with US, differentiating early carcinoma from chronic pancreatitis or nodular hyperplasia can be difficult.[61] The pancreas usually appears larger than usual and can be hypoechoic or have a mixed appearance. Cystic lesions are uncommon in dogs and cats. Surrounding fat can be normal, or have the hyperechogenicity typical of pancreatitis. Enlargement of the regional lymph nodes is common.[51] The liver should be examined carefully for nodular lesions that can be hypoechoic, hyperechoic or mixed, including target lesions. If ascites is the result of carcinomatosis, the peritoneal lesions are usually not visualized.[32] Mass lesions including pseudocysts and abscesses, sometimes seen following acute pancreatitis, can be large enough to palpate in dogs and must be differentiated from neoplastic lesions.[62,63] Use of US contrast agents may help in differentiating chronic pancreatitis from pancreatic carcinoma. Contrast may also improve identification of hepatic metastases.[64] Contrast US, in dogs, may improve discrimination of pancreatic exocrine from endocrine tumors.[65] Endoscopic US improves the visualization of the pancreas in people.[66] There are no studies on the sensitivity of computerized tomography (CT) versus US in dogs and cats, but CT is considered superior in people.[25] CT is also more sensitive for identifying metastases. There does not appear to be an advantage in using magnetic resonance imaging (MRI) for pancreatic neoplasia in people.[67]

Fine Needle Aspiration (FNA), Cytology and Biopsy

Cytology (see ch. 93) has a fairly good positive predictive value but moderate to poor negative predictive value.[9,35,68,69] Risk of complications following FNA in people is low.[68] Atypical cells can be identified in ascitic fluid.[2,35] Cystic lesions, not often noted in dogs or cats, may be somewhat common in people. FNA of such cystic fluid had fewer false negatives than either surgical or needle biopsy-obtained samples.[70] Cytology can be helpful in diagnosing metastases from distant cancers to the pancreas, such as lymphoma.[17]

Biopsy and histopathology is the gold standard for diagnosis of pancreatic neoplasia.[36] Samples can be obtained using core biopsy needles under US-guidance or during surgical exploration (see ch. 89 and 91).[35] As with cytology, if biopsies are taken from metastatic sites, it is usually not possible to definitively identify the tissue of origin as pancreas. Biopsy results may be described as consistent with pancreatic carcinoma. Use of immunohistochemical stains for amylase and carboxypeptidase may help in determining that metastatic lesions were of pancreatic origin.[71] In cats with alopecia, the lesions are characterized by follicles in late telogen with moderate epidermal hyperplasia, hyperkeratosis and superficial, perivascular dermatitis.[44] These lesions are similar to those seen in hyperadrenocorticism, but skin fragility is not a feature.[44]

Treatment

When resection is possible, surgery has had the best long-term outcome in afflicted people. Results may be similar in dogs and cats, but surgery is not likely curative given the high metastatic rate prior to diagnosis.[1,8,9]

Cure is possible but requires a lesion that is completely removable and in people is more likely if the regional lymph nodes are negative.[72] Total and subtotal pancreatectomy has been described in normal dogs with acceptable morbidity and long-term management with insulin and pancreatic enzyme supplementation (see ch. 293, 304, and 305).[73] There are few reports of surgery of the pancreas in cats.[74] Surgery can be palliative in many pets by relieving obstruction.[36] Various techniques are being evaluated in people due to continued poor surgical outcomes.[66,75] Common bile duct stenting may relieve obstructions (see ch. 123), while duodenal obstructions can be relieved with Billroth type II procedures. Both are considered palliative, having been used in people in combination with other therapies.[66]

Pancreatic carcinoma has shown a poor response to chemotherapy in people as well as dogs and cats. Gemcitabine is the chemotherapy drug of choice for afflicted people. It has been used alone or in combination with carboplatin in cats and dogs with carcinoma of the exocrine pancreas.[40,76,77] Preclinical work with targeted drugs, especially tyrosine kinase inhibitors, had promise which has not translated to clinical utility. Small improvements in survival have been found when the tyrosine kinase inhibitor erlotinib, that has activity against the epidermal growth factor receptor, was given in addition to gemcitabine chemotherapy.[76] Radiation has been used, including intraoperative therapy, in people. Normal dogs treated during surgery in conjunction with a Billroth procedure suffered high rates of morbidity and mortality.[78] Use of nonsteroidal anti-inflammatory drugs in patients with exocrine pancreatic carcinoma might be of limited value. In a study looking at COX-2 expression in carcinomas from cats, positive staining was seen only in 25%.[79]

Prognosis

Overall, the outlook for patients with carcinoma of the exocrine pancreas is very poor. In cats, the overall median survival was 97 days.[40] There was improvement in survival to a median of 165 days in cats managed with either surgery or chemotherapy, compared to cats that had palliative treatment or had abdominal effusions. Median survivals were 26 and 30 days, respectively.[40] In 8 cats reported, most died or were euthanized within a week of diagnosis.[13]

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SECTION XXI

Endocrine Disease

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CHAPTER 294

Feline Growth Hormone Disorders

Stijn J.M. Niessen

Client Information Sheet: Feline Hypersomatotropism/Acromegaly

Feline Hyposomatotropism

Prevalence

Growth hormone (GH) is critically important in terms of its direct and indirect anabolic effects. Lack of GH during growth, the most important anabolic phase of an animal's life, causes dramatic pathological consequences. Congenital feline hyposomatotropism (CHS; "pituitary dwarfism") seems rare, since only a few such cats have been described.[1,2] Documented acquired feline hyposomatotropism (AHS) is also rare, with the exception of the assumed asymptomatic documented decreases after hypophysectomy to remove a pituitary tumor.

Causes

CHS is thoroughly described in dogs, in whom the condition may represent primary failure of complete differentiation of the craniopharyngeal ectoderm of Rathke's pouch into a healthy functioning anterior pituitary; mutations in the *LHX3*-gene encoding transcription factors essential to pituitary development have been implicated (see ch. 20 and 295).[3] The cause(s) in cats is unknown, although similar deficiencies may be relevant. An association with congenital hydrocephalus was implied in one cat.[2] AHS could be a consequence of a process impairing normal anterior pituitary lobe production and secretion of GH, including any inflammatory, infectious, immune-mediated, traumatic (including iatrogenic via hypophysectomy) or neoplastic process.[1]

Clinical Presentation

Congenital Feline Hyposomatotropism

Veterinary consultation of a GH-deficient kitten is usually sought when stunted growth is observed at 1 to 2 months of age. This is most obvious when a littermate is available for comparison (Figure 294-1). The initial postnatal growth period of 1 to 2 months is mostly genetically determined and, therefore, appears normal. Concerns develop when the second GH-driven growth phase does not materialize.[1] If isolated GH deficiency is present (all other pituitary hormones normal) the short stature will be proportional (proportionate dwarfism). Should a kitten be deficient in other anterior pituitary hormones, particularly TSH, proportions may well be distorted. Physical features of congenital hypothyroidism in kittens may include a square, chunky contour, as seen with isolated congenital hypothyroidism (see ch. 299 and 300).[1] CHS may also cause prolonged retention of deciduous teeth. The hair coats of affected cats are often dry and dull with potential for retention of secondary hairs and concurrent lack of primary or guard hairs.[1,2] Bilateral corneal edema, due to reduction in corneal endothelial cell density and corneal epithelial cell layers, was reported in one cat who may have had hypothyroidism.[2] Other observations include generalized weakness and lethargy. Hypoglycemia could be associated with enhanced insulin sensitivity caused by the absence of the anti-insulin effects of GH or low glucose may merely be related to the fragile nature of a small unthrifty kitten with limited gluconeogenic capacity.

FIGURE 294-1 Two sibling Domestic Short Hair cats of 5 months of age; the cat on the right was presented for stunted growth, displayed proportionate small stature and was subsequently diagnosed with congenital hyposomatotropism, through documentation of an undetectable serum IGF-1 and exclusion of more common causes for stunted growth. (Photo credit: Dr Ruth Gostelow, Royal Veterinary College.)

Feline Acquired Hyposomatotropism

AHS has not been reported in cats.[1] After completion of the growth phase, the clinical ramifications of GH deficiency would likely be subtle, possibly too subtle for owners or veterinarians to notice. People with adult-onset acquired GH deficiency have increased morbidity and mortality together with decreased quality of life.[4-6] As experience with hypophysectomy to treat feline hypersomatotropism and other pituitary tumors increases, AHS could become a matter of concern. However, clearly deleterious clinical consequences have not been our experience in cats with subnormal serum insulin-like growth factor-1 (IGF-1) concentrations following hypophysectomy.

Diagnosis

CHS should be based on a suggestive clinical picture and exclusion of more common causes of proportionate dwarfism that include hepatic disease (particularly portosystemic shunt), malnutrition, gastrointestinal disease, renal or cardiovascular disease, or inappropriate growth expectations. Diagnosis can be confirmed with randomly obtained, below-reference-range serum GH concentrations. However, reliable feline GH assays are rarely commercially available. When available, results from healthy cats and those with CHS might overlap, in part because GH, like all anterior pituitary hormones, is secreted in a pulsatile manner.[7] Stimulation (provocative) tests that are gold standards for diagnosing a GH deficient state in humans and dogs have not been validated in cats.

An alternative to GH-based testing is to document low or undetectable serum IGF-1 concentrations. Hepatic IGF-1 production is primarily induced by GH, its secretion is non-pulsatile, and results reflect GH concentrations over the preceding 24 hours. Clinicians should bear in mind that certain diseases and medications can influence both GH and IGF-1 testing, falsely implying deficiencies. For example, IGF-1, primarily synthesized by the liver, might be decreased with liver dysfunction. Moderate but not severe

decreases in IGF-1 have been reported in cats with lymphoma, newly diagnosed diabetes mellitus (DM), and renal disease.[7,8] Serum IGF-1 concentrations also correlate with body size, which could be relevant in small-stature kittens. A 7-month-old male kitten with congenital hypothyroidism and retarded disproportionate growth had moderately decreased serum IGF-1 concentrations that normalized after 6 weeks of thyroid replacement therapy.[9]

Treatment and Prognosis

GH replacement therapy has not yet been described for the cat, though it likely is similar to that for dogs (see ch. 295). Since there are no commercial feline GH products, there is concern over antibody formation when using GH from another species (porcine, human). Concurrent pituitary hormone deficiencies, if present, should be treated. If GH replacement is too expensive or undesirable (a major potential adverse effect is development of DM), treatment of concurrent pituitary hormone deficiencies (if present) could be the sole management strategy. Progestins have been employed to induce mammary gland secretion of GH in dogs (see ch. 295) but failed to increase GH or IGF-1 concentrations in cats, despite the expression of feline GH genes in mammary tissue undergoing progestin-induced fibroadenomatous changes.[10,11]

Replacement GH therapy for AHS, post-hypophysectomy, has not been pursued given the perceived lack of significant clinical consequence. An adjustment in the daily caloric intake seems appropriate in cats with documented decreases in IGF-1 or GH, because GH deficient people have increases in their fat mass (especially abdominal).[4] In our experience, there is risk of obesity in cats undergoing successful hypophysectomy.

Few GH-deficient cats have undergone treatment and been reported. This precludes full assessment of treatment alternatives or prognosis of feline CHS. Left untreated, the condition seems to carry a poor prognosis with a shorter lifespan and development of infectious, degenerative or neurological complications.[1,2]

Feline Hypersomatotropism

Overview

While GH deficiency appears to be a clinical concern only in kittens and young cats with growth issues, feline hypersomatotropism (FeHS; acromegaly) should be considered in any middle-aged to older cat with DM. Excess GH causes insulin resistance and subsequent DM by reducing insulin receptors, interfering with a range of post-insulin-receptor processes, and other mechanisms.[12]

Prevalence

FeHS is a relatively common underlying cause for feline DM. Prevalence rates have ranged from 18-32%, with potential for geographic variances and/or differences in recruitment or screening methods.[12-15] In the largest screening study to date, conducted on 1221 cats in the United Kingdom, recruitment was initiated by offering free fructosamine determinations for cats with DM. Spare serum was assayed for IGF-1 and, if extremely increased, confirmative tests (including contrast-enhanced pituitary computed tomography [CT]) were offered. From the 1221 samples assayed for IGF-1 (IGF-1 >1000 ng/mL was the arbitrary cutoff), 319 cats (26%) were suspected and 95% of those cats were confirmed to have FeHS.[15] Based on these prevalence data and the precedent of screening for less common conditions (e.g., urinary tract infections in feline DM; prevalence estimate 12%), it is recommended that cats with recently diagnosed DM be screened for FeHS (Figure 294-2).[16] Screening all newly diagnosed diabetics is wise when the dramatic implications of concurrent FeHS are considered. Treatment, potential for diabetic remission, and prognosis are changed.

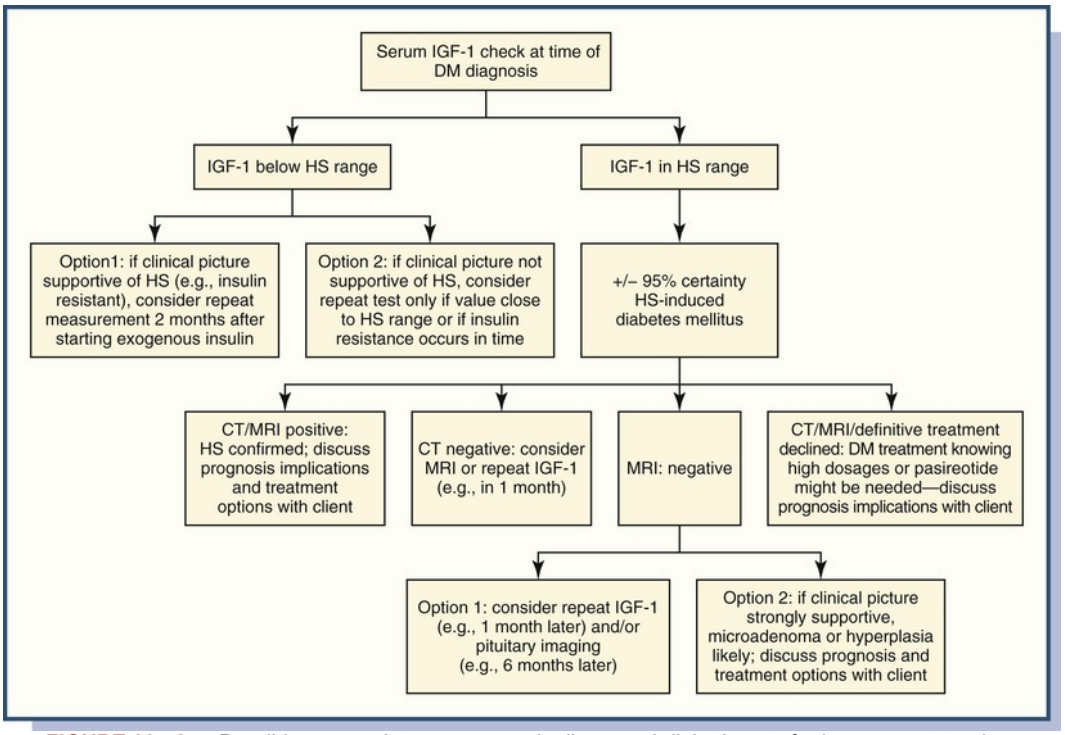

FIGURE 294-2 Possible approach to screen newly diagnosed diabetic cats for hypersomatotropism (HS). *IGF-1,* Insulin-like growth factor-1; *DM,* diabetes mellitus.

Causes

Overview

FeHS is caused by a neoplastic transformation of acidophils (somatotrophs) in the anterior pituitary, leading to increased frequency and amplitude of the pulsatile secretion patterns of GH. Most such tumors are adenomas, but a small number of pituitary carcinomas and some non-neoplastic hyperplasias have been described.[12,17] The cause for tumor development is not understood, with environmental and genetic factors proposed.

Environmental Causes

Organohalogenated contaminants (OHCs) have been implicated in endocrine oncogenesis conditions in various species, including humans and cats.[18-24] OHCs are persistent and bio-accumulative chemicals found in organochlorine pesticides, industrial chemicals (such as polychlorinated biphenyls [PCBs]), and brominated flame retardants (BFRs) added to materials to reduce flammability (such as polybrominated diphenyl ethers [PBDEs]). Cats and humans are continuously exposed to such chemicals, at least in part via food and indoor (dust) contamination. Dust may be especially relevant in cats with their intense grooming behavior. In one report, significantly higher levels of all studied contaminants were identified in cats with FeHS as compared to cats with primary DM and those without an endocrinopathy.[18] Data also suggested that FeHS may reduce a cat's capacity to metabolize persistent chemicals like PCBs. Similar contaminants have been implicated in the emergence of feline hyperthyroidism (see ch. 301).[19-22]

Genetic Causes

Human pituitary adenomas were considered monoclonal in origin, suggesting they form as a consequence of an acquired single cell somatic mutation.[25] It was then demonstrated that an additional mechanism for development of GH-secreting pituitary adenoma involved germline mutations that inactivate tumor suppressor genes.[26-30] Mutations of the aryl-hydrocarbon-receptor interacting protein (AIP) gene, a tumor suppressor protein, have been demonstrated in as many as 40% of people with isolated familial or spontaneous GH secreting adenomas. AIP has a range of effects that include activation of xenobiotic metabolizing enzymes, making the previously discussed link with exposure and accumulation of

environmental OHCs even more interesting.[27-30] In a study of genomic DNA, 2 of 10 cats with FeHS (and no control) had a single non-conservative single nucleotide polymorphism in exon 1 of the AIP gene (AIP:c.9G>T), suggesting some cats may be genetically predisposed to developing FeHS.[31]

Clinical Presentations

Early Signs of FeHS

Initial clinical signs in cats with FeHS are determined, in part, by the timing of owner concern. Most cats ultimately diagnosed as having FeHS are first seen by a veterinarian after an owner becomes concerned about polyuria and polydipsia (PU/PD) secondary to DM and the osmotic effects of glucosuria. Insulin treatment is usually initiated and can lead to successful amelioration of clinical signs in some cats (temporary diabetic remission can even occur). In most, however, it is difficult to attain reasonable glycemic control. Only rarely have cats with FeHS not had concurrent DM. These cats may have phenotypic acromegalic changes, described in this section, and/or extreme polyphagia. In a study of 319 cats suspected as having FeHS, their mean age was 11.3 years (range 4-19) and 70% were neutered males. While many breeds were included, 87% were Domestic Short Hair cats.[15] These observations are similar to those for cats with primary DM and not useful in gaining an index of suspicion of FeHS. Body weight and fructosamine were significantly higher in cats with IGF-1 in the hypersomatotropism range (compared to those with IGF-1 < 1000 ng/mL), despite significantly higher daily insulin dosages (mean 15 IU/day versus 6 IU/day).[15] Nevertheless, cats with FeHS ranged in body weight from large to small and in insulin requirements (from modest to high). Data suggest that FeHS should be suspected when weight gain is noted in a cat with suboptimal diabetic control or whenever unexplained insulin resistance is encountered. Characteristic phenotypical changes eventually develop as a consequence of the anabolic effects of both GH and IGF-1 and are only obvious when a cat has had longer-standing disease. Only 24% of clinicians indicated a strong suspicion of FeHS before their patient was identified as having the condition.[15]

Signs Associated with Chronic FeHS

When the condition becomes chronic, cats with FeHS may have "classic" clinical signs (Box 294-1). The relatively high incidence (53%) of upper respiratory stridor in cats with FeHS is due to tissue swelling. The narrowed nasopharynx often causes an owner to notice their cat "snoring."[17,32] Increased width of the head and broad facial features (Figure 294-3) might be the most obvious feature on physical examination. However, these changes can be subtle and difficult to appreciate because of facial hair, breed-related conformational variation and the tendency for owners not to notice changes that have developed quite gradually. In summary, presence of so-called typical physical changes might help the clinician, though their absence should not decrease the suspicion of FeHS, especially in cats with DM. Further, it seems more appropriate to use the term "hypersomatotropism" and not acromegaly because the latter term incorrectly implies that affected cats should have characteristic phenotypical changes.

Box 294-1

Possible Clinical Signs Encountered in Cats with Hypersomatotropism

1. Diabetes mellitus-related signs (polyuria, polydipsia, polyphagia)
2. Weight gain despite suboptimal diabetic control (although weight loss is also possible)
3. Polyphagia independent of diabetic control (possibly extreme)
4. Inspiratory stridor (snoring)*
5. Broad facial features* (see Figure 294-3)
6. Prognathia inferior (protrusion of lower jaw)* (see Figure 294-3)
7. "Clubbed" paws (enlarged distal limbs/ paws)*
8. Abdominal enlargement with organomegaly*
9. Mobility problems due to arthropathy* and/or diabetic neuropathy
10. Insulin resistance (exogenous insulin requirement exceeding 1.5 IU/kg/injection)
11. Heart murmur and congestive heart failure*
12. Central nervous system signs (e.g., circling, blindness, seizures, depression)*

*Indicates presence is usually only associated with longstanding disease; clinical signs are not consistently present.

FIGURE 294-3 An 11-year-old Domestic Short Hair cat suffering from hypersomatotropism-induced diabetes mellitus. Broad facial features can be seen, though they had not been noted by the cat's owner. These facial changes tend only to be present when hypersomatotropism has been present for a longer period of time.

Diagnosis

Serum or Plasma GH and IGF-1

For most veterinarians, serum total IGF-1 assessment represents the most feasible and accessible means of screening for FeHS.[17] Fortunately, the positive predictive value of an IGF-1 > 1000 ng/mL was shown to be a respectable 95% with one particular radioimmunoassay.[15,17] However, readers are warned to only use independent and specific laboratory-generated reference ranges. An IGF-1 ELISA assay has been validated.[33]

The weakness of randomly obtained blood samples for IGF-1 concentrations as a screening test for FeHS is that hepatic IGF-1 synthesis is dependent on adequate concentrations of portal insulin. Such insulin can be deficient in cats newly diagnosed with DM, resulting in false-negative IGF-1 results in about 9% of untreated cats. Additionally, increased IGF-1 concentrations have been reported in non-FeHS diabetic cats.[17] Further, differences in IGF-1 assays exist.[34] All these factors should be kept in mind when screening cats with DM for FeHS (see Figure 294-2). Serum IGF-1 concentrations are useful as a marker for treatment success post-

hypophysectomy, but not adequately sensitive to document the less pronounced GH decreases that might occur following radiotherapy.[17] Commercially available GH assays remain elusive, despite all tested cats with FeHS having shown an elevation above the reference interval.[7] GH suppression tests (often using oral glucose) considered gold standard for the diagnosis of human hypersomatotropism have thus far not been found useful in the cat.[7,17]

Alternative Blood Tests

Since FeHS is associated with tissue growth, serum type III procollagen propeptide (PIIIP), a peripheral indicator of collagen turnover, has been evaluated.[35] Median serum PIIIP was five times higher in cats with FeHS-induced DM as compared to cats with primary DM. Serum ghrelin, a GH secretagogue, was shown to be lower in FeHS as compared to healthy control cats, but results were similar to those from cats with primary DM.[36] Serum ghrelin monitoring might prove useful in assessing treatment. Significant increases were documented after successful radiotherapy for FeHS while changes in IGF-1 were not significant.[36]

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) Scans

Advanced imaging confirmation of FeHS is recommended and often helpful by demonstrating pituitary enlargement using either contrast-enhanced CT (Figure 294-4) or MRI. Absence of a mass or of enlargement should not, however, be interpreted as excluding the possibility of FeHS. Microadenomas and acidophil hyperplasia can occur and might be more common than is currently appreciated. As cats are diagnosed earlier in the course of disease, the number of visible masses on advanced imaging is expected to decline. In longer-standing cases, CT may demonstrate FeHS-related prognathia inferior (about 25% of affected cats), temporomandibular-joint malformations, and increased thickness of the skin, subcutaneous tissues and calvarium bone.[32]

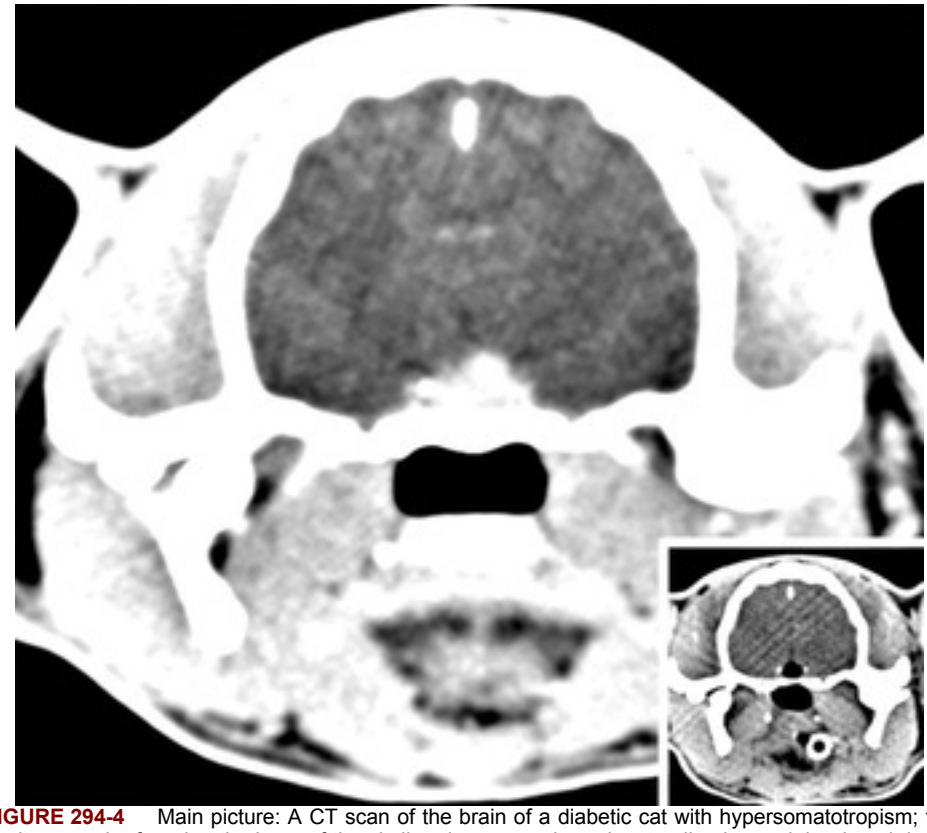

FIGURE 294-4 Main picture: A CT scan of the brain of a diabetic cat with hypersomatotropism; the pituitary can be found at the base of the skull and proves enlarged, extending beyond the dorsal rim of the sella turcica and showing heterogeneous contrast uptake. Inset: CT scan of the same cat after successful hypophysectomy. The pituitary is approached through the nasopharynx, after incision of the soft palate. The cat entered diabetic remission 2 weeks after the procedure.

Treatment and Prognosis

Hypophysectomy

As veterinary experience with hypophysectomy continues, it is recognized as the definitive, "gold standard" treatment for FeHS, provided there are no contraindications.[37,38] Contraindications, still being evaluated, include a particularly large tumor size, significant comorbidities that prevent a safe anesthetic and postoperative recovery (particularly significant renal or cardiovascular disease), or an owner who opposes surgery. The financial commitment for surgery can be an obstacle, although it is important for the owner to be educated about the cost of ineffective insulin treatment or radiotherapy.

In our experience, pituitary tumors are approached from the skull base, with the neurosurgeon operating through the cat's mouth and nasopharynx (transsphenoidal approach; soft palate is incised). Approximately 85% of cats enter diabetic remission within 2 months of surgery and the remainder attain good glycemic control with more traditional insulin dosages. These responses demonstrate the enormous resilience of the cats' pancreatic beta-cells, which seem to recover after months or even years of severe insulin resistance. The peri- and postoperative mortality rate, in our experience, is about 10%. This is an acceptable risk for most cat owners, especially given the paucity of effective treatment alternatives. After surgery, cats are treated with low hydrocortisone and levothyroxine dosages (both lifelong) and desmopressin acetate (DDAVP, which can be discontinued in most cats). GH replacement therapy is not deemed necessary (see previous discussion on AHS).

Medical Management

Somatostatin (SST) analogues and dopamine agonists have not been effective.[17] Fortunately, pasireotide (Signifor, Novartis, Basel, Switzerland), a novel multi-receptor ligand SST analogue with high binding affinity for SST receptor subtypes 1, 2, 3 and 5, has recently been shown to effectively suppress the somatotropinoma in cats with concurrent FeHS and DM.[39,40] Treated cats had significant decreases in serum IGF-1, average 12-hour blood glucose, fructosamine and insulin requirements. A short-acting q 12 h injectable form and a once-monthly long-acting injectable form have been tested. About 25% of cats treated with the once monthly form entered diabetic remission. Disadvantages include mild gastrointestinal side-effects (loose stools/diarrhea) and cost.

Radiotherapy

Although radiotherapy was initially suggested to be optimal, even use of stereotactic or gamma-knife technology fails to rival results of hypophysectomy.[17,41-45] The effect of radiotherapy has proven particularly unpredictable in terms of whether response will occur; when a response should be expected; to what extent radiotherapy will change insulin requirements; and how long effects of radiotherapy will persist. Lack of response in terms of IGF-1 normalization puts further doubt over its true efficacy, even in cats who required less insulin.[36] Indeed, FeHS changes have been shown to progress, even if diabetic improvement or resolution is achieved.[45] Radiotherapy can still serve as a valuable method for shrinking a tumor and can be considered for cats with a large pituitary mass that increases risk of surgery, or when hypophysectomy or pasireotide treatments are declined.

Diabetes Mellitus Treatment Only

If definitive treatment options are declined by owners, the only remaining therapeutic option (barring euthanasia) is to solely treat the secondary DM. Treatment approach is that recommended for primary DM (see ch. 305), apart from the fact that high insulin dosages will often be needed to achieve an acceptable quality of life. Some suggest insulin dosages should not exceed a certain level, but our experience indicates that use of extremely high doses is sometimes the only way to achieve an acceptable quality of life. Use of high-dose insulin therapy does mean owners need to be prepared for, and indeed need to accept, the possibility of iatrogenic hypoglycemia, but it seems to be rare. The pituitary tumor does retain its pulsatile GH secretory patterns, which explain the episodes of low GH and increased insulin sensitivity.

Appropriate insulin dosages should be determined by gradually increasing the amount as required, usually increasing by no more than 1 IU/injection/cat/week. Ideally, periodic blood glucose curves are obtained along with careful assessment of the clinical condition. If insulin doses increase too quickly, there is increased risk of encountering Somogyi phenomena. Negative sequelae of the progressive acromegalic changes may require attention: including treatment for arthropathies (see ch. 203 and 353), congestive heart failure (see ch. 247), or

chronic kidney disease (see ch. 324). Central nervous system signs (e.g., seizures, blindness, depression) due to an expanding pituitary mass are rare, given their slow-growing nature. However, signs can occur and could warrant additional palliative treatment strategies (see ch. 260). Regular quality of life assessments should be planned and euthanasia considered if treatment response proves unsatisfactory (see ch. 7).[46] This is especially important in those cats whose DM cannot be controlled or those suffering from GH-induced extreme polyphagia. Fluoxetine has been used to decrease polyphagia with mixed success.

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CHAPTER 295

Canine Growth Hormone Disorders

Hans S. Kooistra

Client Information Sheets:
Pituitary Dwarfism in Dogs
Acromegaly (Growth Hormone Excess) in Dogs

Growth Hormone

Sources

Growth hormone (GH) is a rather large single-chain polypeptide containing 190 amino acids. The amino acid sequence of GH varies considerably between species, but GH in dogs and pigs is identical.[1] Anterior pituitary hormones, including GH, are secreted in rhythmic pulses separated by intervening troughs. Pituitary GH secretion is regulated mainly by the opposing actions of the stimulatory hypothalamic peptide GH-releasing hormone (GHRH) and the inhibitory hypothalamic peptide somatostatin (Figure 295-1). The GH pulses predominantly reflect the pulsatile delivery of GHRH, whereas the concentrations between pulses are primarily controlled by somatostatin. GH synthesis and secretion can also be stimulated by non-GHRH secretagogues, which exert their effect via non-GHRH receptors. The endogenous ligand for these receptors is ghrelin, synthesized and secreted from the stomach.[2] In young dogs, ghrelin is more potent than GHRH in stimulating synthesis and secretion of GH.[3] Ghrelin also stimulates food intake as well as gastric and intestinal emptying. Fasting and food intake are associated with higher and lower circulating ghrelin concentrations, respectively.[4]

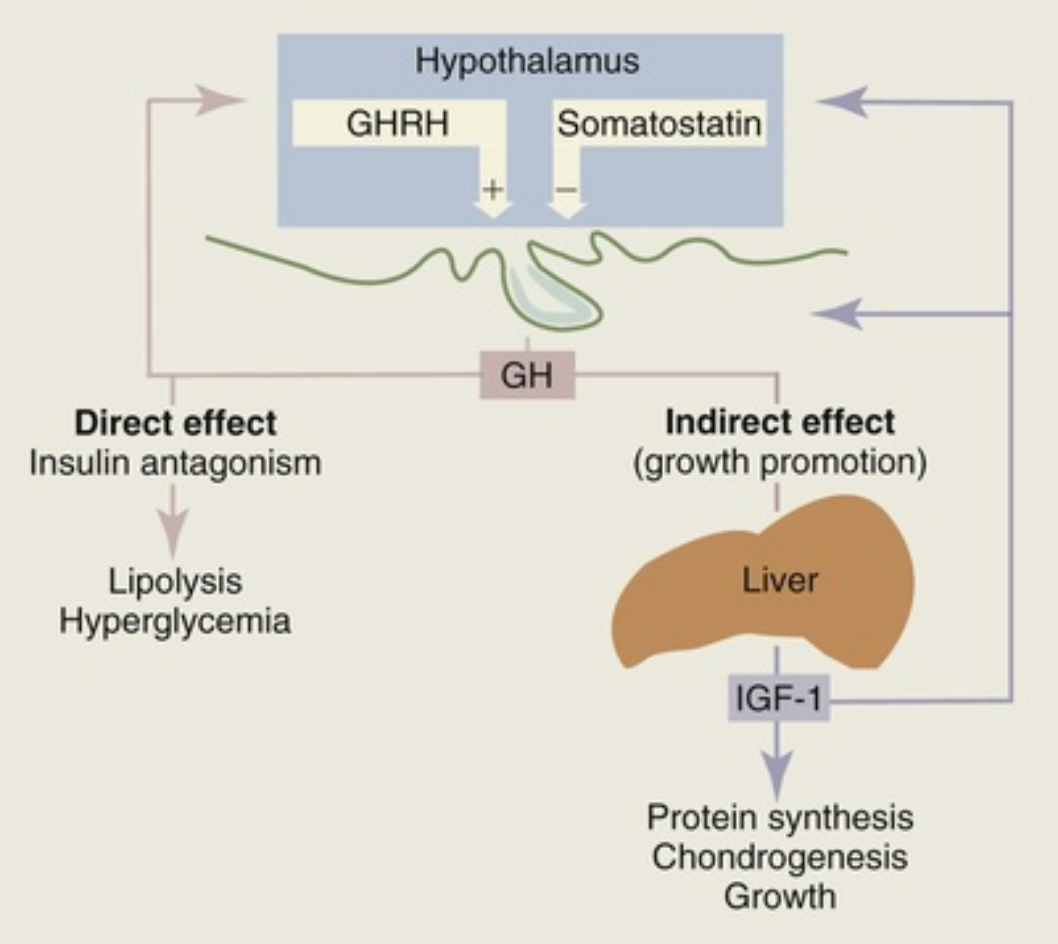

FIGURE 295-1 The pituitary secretion of growth hormone (GH) is under inhibitory (somatostatin) and stimulatory (GH-releasing hormone [GHRH]) hypothalamic control and is also modulated by negative feedback control of insulin-like growth factor-1 (IGF-1) and GH itself. The direct catabolic (diabetogenic) actions of GH are shown on the left side of the figure, and the indirect anabolic actions are shown on the right. (Redrawn from Rijnberk A, Kooistra HS, editors: *Clinical endocrinology of dogs and cats*, ed 2, Hannover, Germany, 2010, Schlütersche.)

In dogs, GH is synthesized in both pituitary and mammary tissues. Administration of progestins can increase plasma GH concentrations in dogs but this secretion is not pulsatile, not sensitive to GHRH, and not inhibited by somatostatin. Moreover, progestin-induced plasma GH concentrations do not decrease after hypophysectomy, indicating that this GH originates from an extra-pituitary site. Rather, this GH is synthesized in foci of hyperplastic mammary ductular epithelium.[5] Mammary GH is biochemically identical to pituitary GH and the gene encoding mammary GH is identical to that in the pituitary gland.[6]

The typical pulsatile secretion pattern of GH changes during the luteal phase (diestrus) of healthy bitches, with higher basal concentrations and fewer pulses. Progesterone-induced mammary GH may partially suppress pituitary GH secretion. Thus, mammary GH synthesis is normal during diestrus in healthy bitches, likely promoting proliferation of mammary tissue in preparation for lactation via local autocrine and paracrine effects.[7] Significant GH concentrations have been identified in canine mammary gland secretions and, particularly, in colostrum.[8] Colostrum GH may promote neonatal gastrointestinal development. The progestin-induced mammary GH production may also play a role in mammary gland tumor development or tumor progression.

Physiologic Effects

The effects of circulating GH can be divided into two main categories: rapid catabolic actions and slow (long-lasting) anabolic actions (see Figure 295-1). The rapid effects are mainly due to insulin antagonism, resulting in enhanced lipolysis, gluconeogenesis, restricted glucose transport across cell membranes and hyperglycemia. Slow anabolic effects are mediated by insulin-like growth factors (IGFs) produced in a variety

of tissues (primarily the liver) that have about 50% sequence similarity with insulin. These IGFs have local paracrine or autocrine growth-promoting effects. In contrast to insulin, IGFs are bound to binding proteins (IGFBPs), which prolongs half-life and is consistent with long-term growth-promoting actions. IGFs are important determinants in the regulation of body size, by stimulating protein synthesis, chondrogenesis, and growth.

Distinction of the opposing biologic effects of GH is neither strict nor absolute. There is evidence that GH exerts its growth-promoting effect not only via IGFs but also directly on target cells. GH may be the major determinant of body size. It appears that young large breed dogs go through longer periods of high GH release (i.e., juvenile hypersomatotropism) than do young small breed dogs.[9] On the other hand, there is strong linear correlation between plasma IGF-1 concentrations and body size. Furthermore, an IGF-1 single-nucleotide polymorphism haplotype has been reported as a major factor in the final body size of dogs.[10] IGF-1 exerts an inhibitory effect on GH release, directly inhibiting secretion and indirectly inhibiting secretion via stimulating release of somatostatin. GH also suppresses GHRH synthesis and secretion at the hypothalamic level (see Figure 295-1).

Acromegaly

Pathogenesis

Acromegaly is a syndrome of bony and soft tissue overgrowth and insulin resistance due to chronic and excessive GH secretion. In middle-aged and elderly dogs, either endogenous progesterone (luteal phase of the estrous cycle) or exogenous progestins may cause excess GH due to mammary GH secretion. Acromegaly has also been reported in a dog with a GH-producing mammary tumor.[11] Hypothyroidism, in dogs, is associated with increased plasma concentrations of GH and IGF-1.[12,13] Rarely, a pituitary somatotroph adenoma may cause acromegaly in dogs, in contrast to the much greater frequency of this condition in cats (see ch. 296).[14]

Clinical Manifestations

Signs of GH hypersecretion tend to develop slowly and often include soft tissue swelling of the head, neck and abdomen. In some acromegalic dogs, severe hypertrophy of oral and pharyngeal soft tissues can cause snoring and even dyspnea (Figure 295-2). Articular cartilage proliferation, periarticular periosteal reaction and spondylosis deformans may result in stiffness, difficulty in rising, and neck rigidity. Affected dogs often have polyuria and sometimes polyphagia. The polyuria is usually without glucosuria, but diabetes mellitus (DM) can develop due to insulin resistance. Physical examination may reveal thick skin folds, especially in the neck; prognathism; and wide interdental spaces (see Figure 295-2). Chronic GH excess may also lead to generalized increase in organ size and subsequent abdominal enlargement. Laboratory investigation often reveals hyperglycemia. Increased serum alkaline phosphatase activity may be the result of the intrinsic glucocorticoid activity of progestins. German Shepherd Dogs appear predisposed to acromegaly.[15] Acromegaly secondary to hypothyroidism tends to be far more subtle than in other types. Large compressive somatotroph adenomas may cause central nervous system signs.

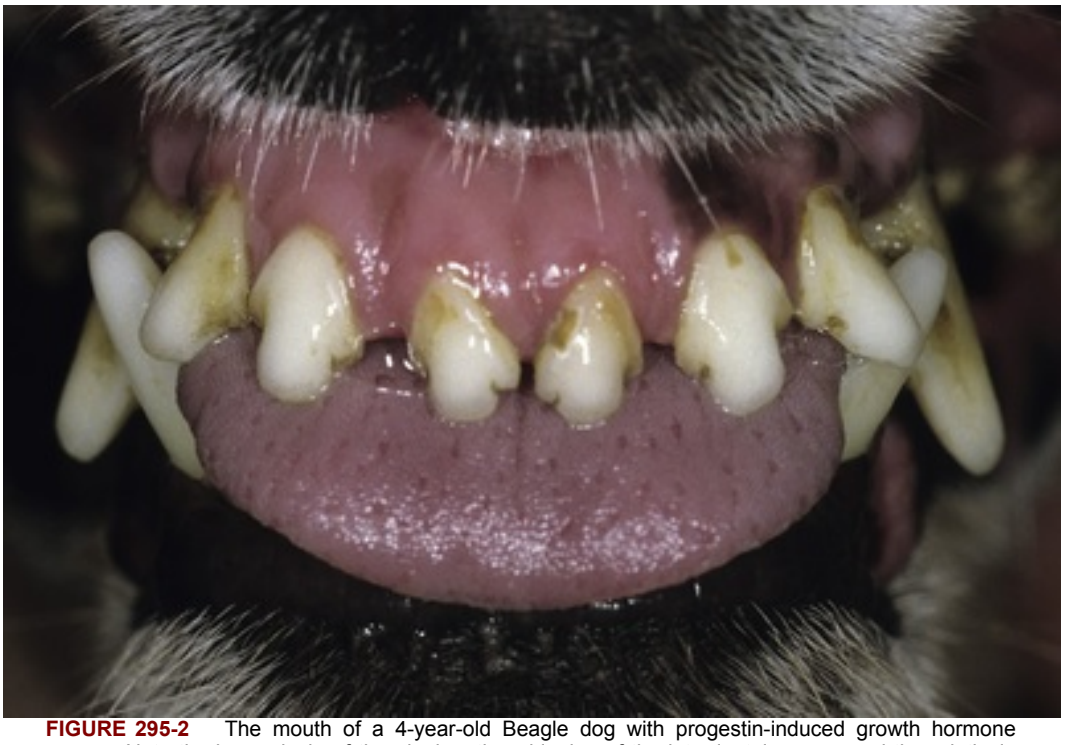

FIGURE 295-2 The mouth of a 4-year-old Beagle dog with progestin-induced growth hormone excess. Note the hyperplasia of the gingiva, the widening of the interdental spaces and the relatively large tongue.

Diagnosis

Basal plasma GH concentrations in acromegalic dogs often exceed the reference range, but may not be abnormal if the condition is mild or early in its course. Increased GH concentrations, alone, may result from sampling soon after a GH pulse secretion from a normal pituitary. Diagnosis of acromegaly is supported if GHRH (1 mcg/kg IV) fails to stimulate GH secretion or if somatostatin (10 mcg/kg IV) fails to suppress GH. Because the amino acid sequence of GH varies among species, GH should be determined by a species-specific, homologous assay. Commercial GH assays are not widely available.

Since plasma IGF-1 is bound to plasma proteins, its concentration does not fluctuate as widely as does GH. In addition, the amino acid sequence of IGF-1 is less species-specific and concentrations can be determined with heterologous (human) assays. Because of the strong linear correlation between the plasma IGF-1 concentration and body size, breed-specific reference ranges are required.[16] If GH excess is noted in a dog not given progesterone or progestins, one should test for hypothyroidism. Advanced diagnostic imaging of the pituitary area may reveal a somatotroph adenoma.

Treatment

Progesterone-induced acromegaly in dogs can be treated effectively by ovariectomy. If GH excess did not lead to complete exhaustion of the pancreatic beta cells, ovariectomy may prevent or reverse DM. Dogs with progestin-induced GH excess should have those drugs discontinued. Administration of progesterone receptor blockers, such as aglépristone, significantly decreases plasma concentrations of GH and IGF-1 in dogs with progestin-induced acromegaly.[17] Treatment of dogs with primary hypothyroidism with levothyroxine results in normalization of plasma concentrations of GH and IGF-1.[12]

In dogs with acromegaly due to a somatotroph adenoma, treatment should be directed at the pituitary mass. Therapeutic options include medical management, radiation treatment, and hypophysectomy. Medical treatment with (expensive) long-acting somatostatin analogues, such as octreotide and lanreotide, decreases symptoms, normalizes plasma IGF-1 concentrations, and reduces tumor size in about 50% of acromegalic people. GH-receptor antagonists developed for human use, such as pegvisomant, also may be effective in dogs. Radiation may shrink a pituitary tumor. Disadvantages of radiation therapy include persistent excess GH secretion despite shrinkage, limited availability, extended hospitalization, frequent anesthesias, expense,

and the possibility of relapse should an initial response be seen. Transsphenoidal hypophysectomy has been performed successfully in dogs with hypercortisolism due to a corticotroph adenoma and in cats with acromegaly due to a somatotroph adenoma.[18] Experience in dogs with acromegaly is limited.

Pituitary Dwarfism

Pathogenesis

Any defect in pituitary gland organogenesis may cause isolated or combined pituitary hormone deficiencies. Congenital GH deficiency or pituitary dwarfism is the most striking example of pituitary hormone deficiency. Congenital GH deficiency has been described in several dog breeds. The condition is encountered most often as a simple, autosomal recessive inherited abnormality in the German Shepherd Dog. Genealogical investigations indicate that the origin of the recessive gene is a mutation that occurred around 1940, with several champion carrier dogs identified.[19,20] German Shepherd Dog dwarfs typically have combined GH, thyroid stimulating hormone (TSH), and prolactin deficiencies, impaired release of gonadotropins, and normal adrenocorticotropic hormone (ACTH) secretion (Figure 295-3).[21] Congenital GH deficiency was thought to result from pressure atrophy of the anterior pituitary due to cyst formation in Rathke's pouch. Indeed, pituitary cysts are present in most German Shepherd Dog dwarfs.[21] However, young German Shepherd Dog dwarfs may have no or only a small cyst and little evidence for pressure atrophy.[21] Further, preservation of ACTH secretion argues against cyst formation in Rathke's pouch as the primary cause of pituitary dwarfism.

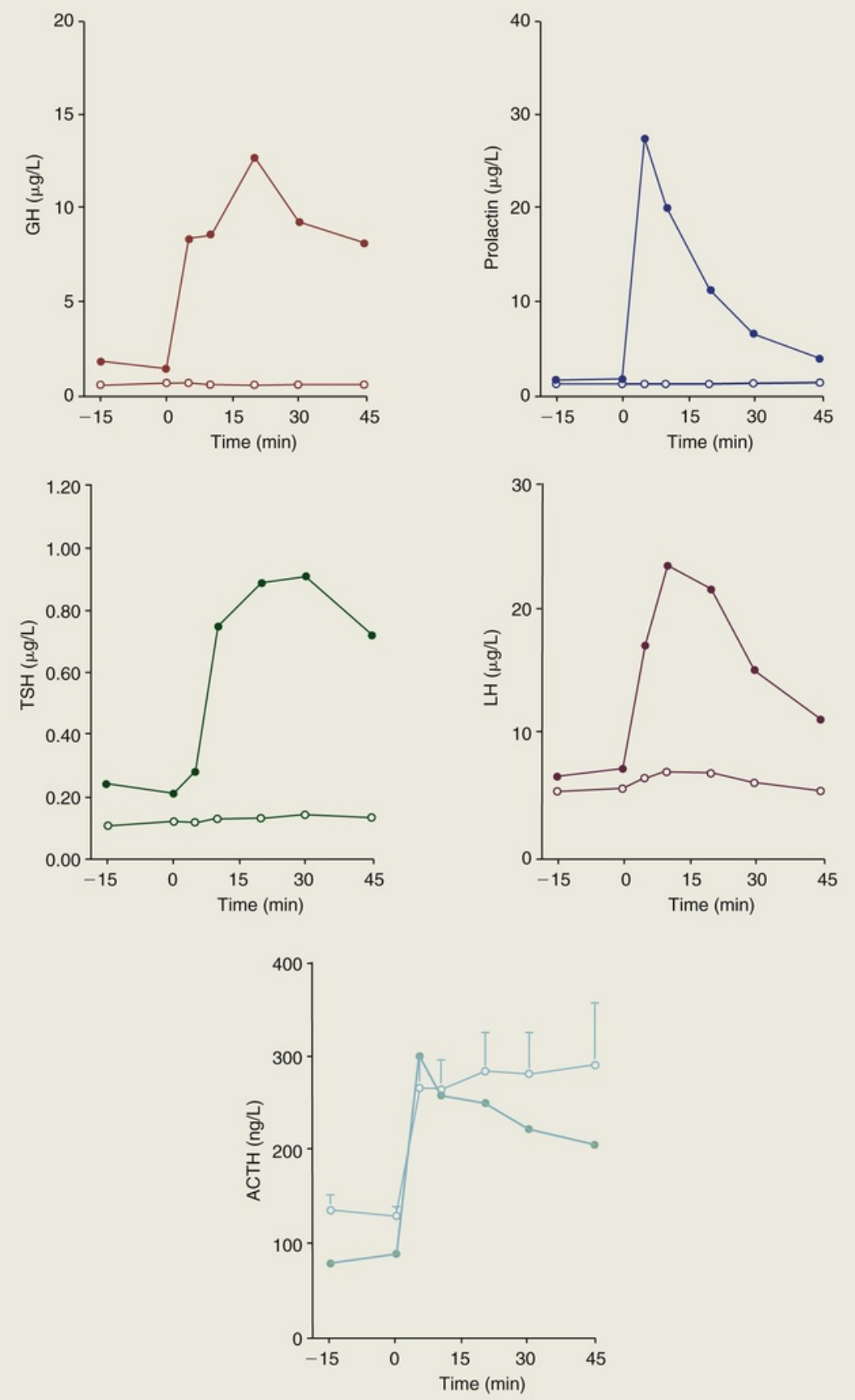

FIGURE 295-3 Results of a combined pituitary anterior lobe function test (mean and SEM) in eight German Shepherd Dogs with dwarfism (○) and in eight healthy Beagle dogs (●). *ACTH,* Adrenocorticotropic hormone; *GH,* growth hormone; *LH,* luteinizing hormone; *TSH,* thyroid-stimulating

hormone. (From Kooistra HS, Voorhout G, Mol JA, et al: Combined pituitary hormone deficiency in German Shepherd Dogs with dwarfism. *Domest Anim Endocrinol* 19:177, 2000. With kind permission of Domestic Animal Endocrinology.)

Genetic studies have demonstrated that pituitary dwarfism is due to a mutation in *LHX3*.[22] LHX3 is a member of the LIM homeodomain protein family of DNA-binding transcription factors. Molecular defects in the *LHX3* gene in humans and mice result in deficits of all anterior pituitary hormones, sparing ACTH. These findings are identical to the endocrine phenotype of German Shepherd Dog dwarfs. Analysis of intron 5 of *LHX3* revealed that dwarfs have a deletion of one of six 7 base pair (bp) repeats, reducing the intron size to only 68 bp, resulting in defective *LHX3* splicing.[22] This genetic defect is also the cause of pituitary dwarfism in Saarloos Wolfdogs and Czechoslovakian Wolfdogs; both are German Shepherd dog-wolf cross-breeds.[23] Screening a number of clinically healthy Saarloos and Czechoslovakian Wolfdogs demonstrated that 31% and 21%, respectively, are carriers. These results indicate that pituitary dwarfism is a relevant disorder and the need for screening is emphasized. Pituitary dwarfism and its associated DNA defects are often incompatible with life, explaining why the condition is uncommon.

Clinical Manifestations

Pituitary dwarfism can lead to a wide range of clinical manifestations.[24] Pituitary dwarfs are usually brought to a veterinarian between 2 and 5 months of age because of proportionate growth retardation, retention of lanugo or secondary hairs, and lack of primary or guard hairs (Figure 295-4). The lanugo hairs are easily epilated and there may be gradual development of truncal alopecia, beginning at the points of wear, sparing the head and the extremities. The skin becomes progressively hyperpigmented and scaly. Secondary bacterial infections are common. The dwarfs usually have a pointed muzzle, resembling a fox. Due to impaired gonadotropin release, male dwarfs often have unilateral or bilateral cryptorchidism and females commonly fail to ovulate due to absence of a luteinizing hormone surge. The *LHX3* mutation is also associated with malformations of the atlanto-axial joint, which can lead to instability and dynamic compression of the cervical spinal cord.[25] Pituitary dwarfs are usually active and alert, but inappetence and decreased activity usually develops by about 2-3 years of age due to secondary hypothyroidism and impaired renal function.

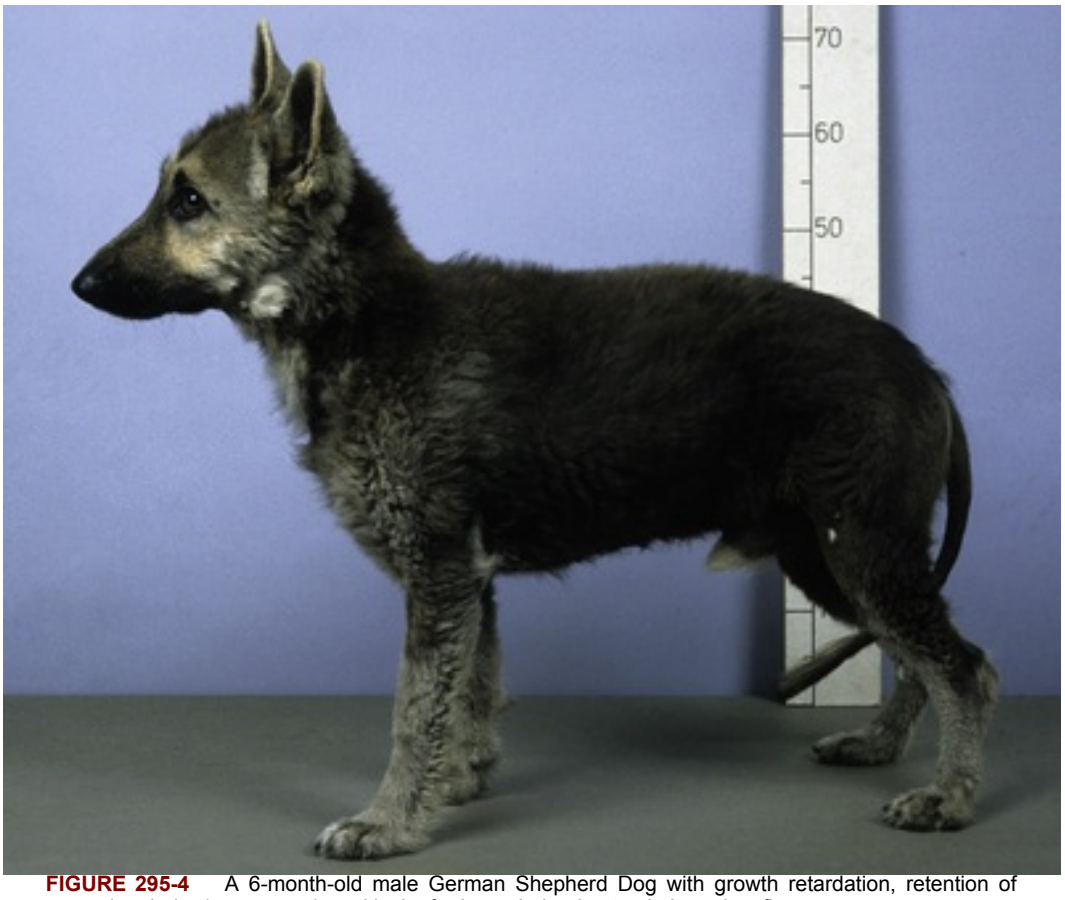

FIGURE 295-4 A 6-month-old male German Shepherd Dog with growth retardation, retention of secondary hairs (puppy coat), and lack of primary hairs due to pituitary dwarfism.

Diagnosis

Although the clinical signs of pituitary dwarfism may be obvious, other endocrine and non-endocrine causes of growth retardation and/or alopecia must be excluded. No abnormalities, aside from increases in serum creatinine, are noted on routine laboratory examination of dogs with naturally occurring pituitary dwarfism.[21] GH deficiency (± thyroid hormone deficiency) causes abnormal glomerular development and impaired renal function. Low plasma IGF-1, TSH, and serum T_4 concentrations are common. However, low IGF-1 concentrations do not provide a definitive diagnosis of pituitary dwarfism.

Because basal plasma GH values may also be low in healthy animals, the definitive diagnosis of GH deficiency should be based on results of stimulation testing. For this purpose GHRH (1 mcg/kg) or alpha-adrenergic drugs, such as clonidine (10 mcg/kg) or xylazine (100 mcg/kg) can be used. The plasma GH concentration should be determined immediately before and 20 to 30 minutes after IV administration of the stimulant. In healthy dogs, plasma GH concentrations should increase at least twofold to fourfold after stimulation. In dogs with pituitary dwarfism there is no significant rise in circulating GH levels (see Figure 295-3). Supra-pituitary stimulation with corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), or gonadotropin-releasing hormone (GnRH) may reveal the presence of other pituitary hormone deficiencies.[21] A plasma GH concentration more than 5 mcg/L, 20 minutes after IV administration of 2 mcg/kg ghrelin, excludes pituitary dwarfism.[26]

Diagnostic imaging of the pituitary area (computed tomography or magnetic resonance imaging) often reveals the presence of pituitary cysts in dogs with congenital GH deficiency.[21] Despite the presence of cysts, the majority of young dogs with pituitary dwarfism have an extremely small pituitary, compatible with pituitary hypoplasia (i.e., a lack of endocrine cells in the pituitary anterior lobe). Cyst size gradually enlarges during life.[27] When cysts are large, pituitary size may also increase. Because healthy dogs may have pituitary cysts, definitive diagnosis of pituitary dwarfism cannot be based solely upon the presence of pituitary cysts.

A DNA test has been developed to aid in identifying the *LHX3* mutation.[22,23] The availability of this test

not only allows a proper diagnosis of dogs with congenital GH deficiency, but also enables breeders to prevent dwarfs from being born by testing the carrier status of potential breeding animals and applying a correct breeding program.

Treatment

Canine GH is not available. Attempts have been made to treat dogs with congenital GH deficiency using heterologous GH. Antibody formation precludes the use of recombinant human GH.[28] Administration of porcine GH does not result in antibody formation, because the amino acid sequence of porcine GH is identical to that of canine GH.[1] The recommended SC dosage for porcine GH, 0.1 to 0.3 IU/kg three times per week, may result in GH excess and side-effects, such as DM. Therefore, monitoring of plasma GH and glucose concentrations is recommended 3 times during each week of treatment. Long-term dosages should be determined based on measurements of the plasma IGF-1 concentration. Whether administration of porcine GH will lead to linear growth is dependent on the status of the growth plates when treatment is initiated. A beneficial response in the skin and lanugo hair growth usually occurs within 6 to 8 weeks of starting therapy, but growth of guard hairs is variable.

Demonstration of progestins' ability to induce expression of the GH gene in the canine mammary gland, with subsequent secretion of GH into the systemic circulation, has raised the possibility of treating congenital GH deficiency with progestins. Treatment of young German Shepherd dwarfs with SC injections of medroxyprogesterone acetate using dosages of 2.5 to 5 mg/kg, initially at 3-week intervals and subsequently at 6-week intervals, resulted in some increase in body size and development of an adult hair coat. Parallel with the physical improvements, plasma IGF-1 concentrations rose sharply while increases in plasma GH concentrations were seen but did not exceed the reference range upper limit.[27] Treatment of pituitary dwarfs with proligestone has been reported to result in the development of an adult hair coat, increased body weight, and elevated plasma IGF-1 concentrations.[29] However, administration of progestins may cause recurrent periods of pruritic pyoderma, skeletal maldevelopment, development of mammary tumors, acromegaly, DM and cystic endometrial hyperplasia. As with the treatment using porcine GH, monitoring plasma concentrations of GH, IGF-1 and glucose is important. Bitches should be ovariohysterectomized before starting progestin treatment. Treatment with levothyroxine should be started as soon as there is evidence of secondary hypothyroidism.

Prognosis

The long-term prognosis of German Shepherd Dog dwarfs is usually poor without treatment. By 3 to 5 years of age, these dogs usually become dull, thin, and bald. These changes may be due to progressive loss of pituitary functions, continuing expansion of pituitary cysts, and progressive renal failure. At this stage, owners usually request euthanasia. Although the prognosis improves considerably when dwarfs are properly treated with levothyroxine and either porcine GH or progestins, their prognosis still remains guarded.

Acquired GH Deficiency (AGHD)

In addition to dogs and cats who develop AGHD following elective hypophysectomy to remove a tumor and those who develop AGHD following traumatic brain injury, there are reports of mature dogs developing naturally occurring GH deficiency.[30] It has been proposed that GH deficiency may explain some forms of alopecia in the Pomeranian, Miniature Poodle, Chow Chow, Keeshond, and others. The alopecia has been described in dogs of either gender, neutered or sexually intact, and of any age. However, the condition is most commonly recognized in dogs 1 to 3 years of age. Their alopecia usually involves the trunk, caudal thighs, perineum, and neck and their skin often becomes darkly pigmented. This alopecia does not appear to be attributable to any of the endocrine diseases known to result in skin atrophy and hair loss (i.e., hypothyroidism, hypercortisolism, or hyperestrogenism due to testicular tumor). Although treatment with heterologous GH[31] or medroxyprogesterone acetate[32] has had poor to moderate results, the condition has been given names such as “adult-onset GH deficiency” and “GH-responsive dermatosis.”

Uncertainty about the role of GH in this condition is further illustrated by other names it has received, such as “castration-responsive alopecia,” “biopsy-responsive alopecia,” and “alopecia X.”[31,32] The entity is not well defined because one-third of dogs have a normal GH response to stimulation. Yet in some with a normal response to stimulation, treatment with GH was reported to be effective. In others, seemingly unrelated

measures such as castration or administration of testosterone were followed by the appearance of a new hair coat.[33] When GH stimulation tests were performed on Pomeranians with alopecia and a control group without alopecia, mean circulating GH concentrations failed to increase significantly in either group.[34] Thus, the association between some forms of this adult-onset alopecia and decreased GH secretion is poorly supported. True GH deficiency is not likely since plasma IGF-1 concentrations have invariably been within reference ranges.[31]

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CHAPTER 296

Diabetes Insipidus

Robert E. Shiel

Client Information Sheet: Diabetes Insipidus

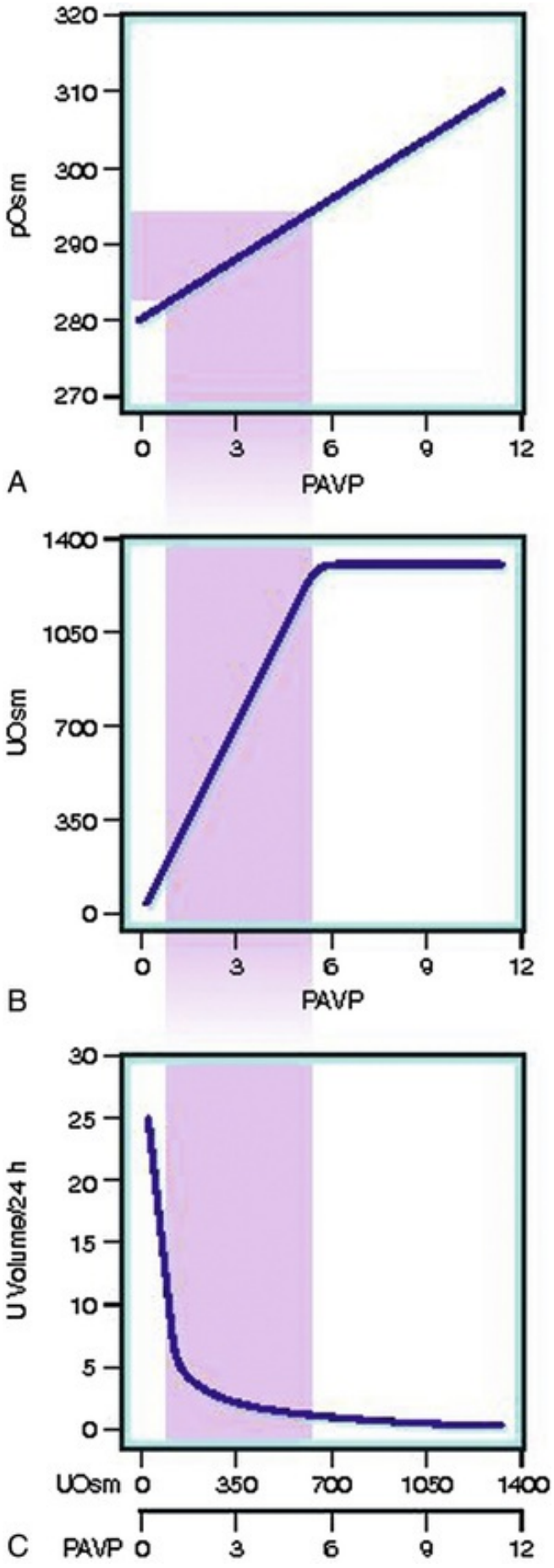
Physiology

Source and Structure of Vasopressin

Arginine vasopressin (AVP), the principal hormone responsible for water homeostasis, is a small peptide derived from a larger precursor within magnocellular neurons of the hypothalamic paraventricular and supraoptic nuclei.[1,2] Pre-pro-vasopressin is comprised of the signal peptide and the polypeptides that later form AVP, neurophysin-2 and the glycoprotein copeptin. Following cleavage of the signal peptide, pro-vasopressin is transported into the endoplasmic reticulum. Neurophysin 2 is necessary for correct processing, transport, cleavage and may have a role in protecting AVP from enzymatic degradation. The function of copeptin is unknown. The prohormone is packaged in neurosecretory granules before axonal transport through the hypothalamic-neurohypophyseal tract and storage in the posterior pituitary. Enzymatic cleavage into the constituent molecules occurs during transport and storage.

Secretion Stimuli

In response to a stimulus for AVP release, an action potential is generated in the hypothalamic cell body and is propagated along the axon to the posterior pituitary with resultant calcium-dependent exocytosis of granule contents and release of all three products. As the posterior pituitary gland lacks a blood-brain barrier and contains fenestrated capillary vessels, entry into the systemic circulation is rapid.[3] The main stimulus for AVP release is an increase in plasma osmolality (OSM) (E-Figure 296-1). Various circumventricular organs, including the subfornical organ and the organum vasculosum of the lamina terminalis, act as osmoreceptors with the capacity to alter AVP secretion and thirst.[4] In addition, magnocellular neurons can be directly stimulated via alterations in plasma sodium (Na^+) concentration.[5] A 1% increase in plasma OSM is sufficient to stimulate AVP release. As the half-life of AVP is estimated to be <6 minutes in dogs, a decrease in plasma OSM is quickly followed by decreases in AVP secretion.[6] Blood volume is primarily controlled by the renin-angiotensin-aldosterone system. However, high-pressure arterial baroreceptors in the carotid sinus and aortic arch and low-pressure volume receptors in the atria and pulmonary venous system can inhibit AVP secretion via the glossopharyngeal and vagal nerves.[2] A 10-15% decrease in blood volume or pressure can decrease this inhibitory input, resulting in AVP secretion. Other factors affecting AVP secretion include stress, nausea, pain, structural brain disease, drug therapy, hypoglycemia and exercise. Drinking, associated with decreases in AVP secretion prior to changes in plasma OSM, may be mediated by pharyngeal volume- or osmo-receptors.[7,8]


320
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300
290
280
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pOsm
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3
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PAVP
A
1400
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UOsm
0
3
6
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12
PAVP
B
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15
10
5
0
U Volume/24 h
UOsm 0
350
700
1050
1400
C
PAVP 0
3
6
9
12

E-FIGURE 296-1 Effect of change in plasma osmolality (pOsm, in mOsm/kg of H_2O) on plasma arginine vasopressin (PAVP, in pg/mL) and consequent effects on urine osmolality (UOsm, in mOsm/kg of H_2O) and urine volume (L/day). The shaded area represents the normal range. **A,** Small changes in pOsm induce changes in PAVP, typically between less than 0.5 and 5 to 6 pg/mL. **B,** Changes in PVAP induce changes in UOsm through the full range, from maximally dilute to maximally concentrated urine. Although PAVP can rise to higher levels than 6 pg/mL, this does not translate into increased UOsm, which has a maximum determined by the osmolality of an inner medulla of the kidney. **C,** The relationship of urine volume to UOsm is logarithmic, assuming a constant osmolar load and the urine volume that would excrete that osmolar load at the UOsm indicated. As a result, urine volume changes relatively little with small changes in the other parameters until there is almost complete absence of PAVP, after which the urine volume increases dramatically. (Calculated from a formula presented in Robertson G, Shelton R, Athar S: The osmoregulation of vasopressin. *Kidney Int* 10:25-37, 1976. Figure by A.G. Robinson, University of California at Los Angeles, used with permission of Macmillan Publishers, Ltd.)

Interaction of Regulatory Mechanisms and Various AVP Sites of Action

Regulatory mechanisms are highly interactive. For example, increased concentrations of angiotensin II can stimulate both AVP secretion and thirst via the subfornical organ while baroreceptors can stimulate both renin and AVP release.[4] Similarly, natriuretic peptides contribute to regulation of Na^+ and water balance. Brain (B-type) natriuretic peptide has an inhibitory effect on renin, aldosterone and AVP release. AVP and angiotensin II have stimulatory effects on atrial natriuretic peptide (ANP) release.[9,10]

The actions of AVP are mediated through a variety of G-protein associated receptors. In the absence of AVP, principal renal luminal collecting duct cell surfaces have minimal permeability to water. AVP binding to basolateral V2 receptors increases cyclic AMP and activates protein-kinase A, a phosphorylative pathway that causes fusion of aquaporin 2-containing intracytoplasmic vesicles (known as aggregophores) with apical cell membranes. The resultant increased expression of aquaporin 2 enhances permeability and water reabsorption via passive movement of molecules from the hypotonic tubular lumen to the isotonic cortex and/or hypertonic medullary interstitium. Once receptor stimulation has ceased, the aquaporins are re-internalized and stored into aggregophores through a clathrin-mediated process. Stimulation of magnocellular neurons also leads to increased synthesis of AVP; however, there is a lag effect of several hours before newly formed AVP is ready for release. For that reason, relatively large quantities of AVP are stored within the posterior pituitary. Release of AVP is not restricted to the nerve terminals and axonal swellings within the posterior pituitary; release can occur from various sites within the neuron, including the hypothalamic soma and dendrites, and undilated axons.

The actions of AVP extend far beyond the control of water balance. Binding to V2 receptors can lead to the release of von Willebrand factor, tissue plasminogen activator and atrial natriuretic peptide. AVP also stimulates synthesis of nitric oxide and increases circulating concentrations of coagulation factor VIII. Activation of V1a receptors causes vascular smooth muscle contraction, glycogenolysis and platelet activation. Binding to V1b receptors within the anterior pituitary acts synergistically with corticotropin releasing hormone to stimulate ACTH release. Stimulation of V1b receptors in other endocrine tissues can increase catecholamine and insulin secretion. AVP has also been identified as an important neurotransmitter and chemical mediator within the brain, with central roles in various areas including memory retrieval, learning, circadian timekeeping and social behavior.

Pathophysiology of Diabetes Insipidus (DI)

Overview

DI is associated with decreased production or action of AVP. Although rare in dogs and cats, the condition is well described and is an important differential for polyuria and polydipsia (PU/PD), particularly when severe.

Central Diabetes Insipidus (CDI)

CDI is characterized by complete or partial deficiencies in AVP. In people, traumatic pituitary stalk transection or pituitary surgery may lead to a pattern known as triphasic DI.[2,27,28] The first stage is acute CDI due to axon shock and an inability to release AVP. The second, antidiuretic phase, is due to unregulated AVP release from large posterior pituitary reservoirs. Phase 3 begins after these AVP stores are depleted and CDI

recurs. This third phase may be permanent, but partial recovery and subclinical deficiencies can occur due to the capacity for AVP release from the remaining neuron components.

CDI can also be caused by mutations within the AVP gene of people, usually affecting the signal peptide or neurophysin.[2] It is likely that mutant precursors are retained in the endoplasmic reticulum, explaining decreases in AVP and the cellular toxicity observed in some cases. Such genetic causes have not been investigated in dogs or cats, but congenital CDI has been described in Afghan Hound littermates.[15] Individual young dogs and cats have been described with either partial or complete CDI.[11,20,25]

In dogs and cats, CDI has been described most commonly due to structural defects within the hypothalamus, posterior pituitary or both. Pituitary neoplasia is most often implicated in dogs and trauma in cats; however, several other causes are described (Box 296-1).[11-26] The triphasic pattern described in some people has not been observed in dogs or cats, but hypophysectomy in dogs with pituitary-dependent hyperadrenocorticism leads to prolonged CDI (greater than 2 weeks post-surgery) in 53% of dogs. Approximately 42% of those dogs require permanent therapy.[29] Changes during the initial post-operative period are not well characterized due to the frequent supplementation of dogs with synthetic AVP following surgery, but CDI was more likely in dogs with pituitary enlargement. CDI may be less common following hypophysectomy in cats.[30] Idiopathic CDI has been reported in both dogs and cats. Advanced imaging was not performed in many of those pets and the possibility of underlying disease not excluded.

Box 296-1

Causes of Central and Nephrogenic Diabetes Insipidus in Dogs and Cats

Idiopathic
Trauma
Neoplasia
  Craniopharyngioma
  Meningioma
  Chromophobe adenoma or carcinoma
  Lymphoma
  Metastatic neoplasia
Surgery
Congenital defects
Infection
Inflammation
Cysts

Nephrogenic Diabetes Insipidus (NDI)

NDI is characterized by decreased action of AVP within the kidneys. Secondary NDI is a feature of several conditions (see ch. 45) including hyperadrenocorticism (see ch. 306), pyometra (see ch. 316), hypercalcemia (see ch. 69 and 297), hyponatremia (see ch. 67 and 309), pyelonephritis (see ch. 327), and liver disease (see ch. 284). Primary (familial) NDI is a rare genetic disorder, associated with qualitative or quantitative alterations in aquaporin-2 expression. In people with familial NDI, specific mutations have been identified which affect the V2 receptor and aquaporin-2 genes, with >90% of patients having an X-chromosomal mutation (sex-linked) of the V2 receptor gene.[31] About 10% of these people are believed to develop *de novo* mutations. Autosomal aquaporin-2 mutations are less common.

Primary NDI was suspected in a litter of Siberian Huskies in which 3 of 4 males had normal V2 receptor numbers within the inner medulla but a ten-fold lower binding affinity for AVP.[32] Since clinical signs were confined to males, involvement of the V2-receptor gene, also located on the X-chromosome in dogs, was implicated. Isolated cases of primary NDI have been reported.[33-35] Primary NDI has not been reported in cats.

Clinical Features

Signalment

DI can occur at any age and in any breed. Signalment depends largely upon the underlying cause. Neoplastic causes are more likely in older animals and congenital disease in the young. Clinical signs may develop acutely or gradually progress over weeks to months.

Clinical Signs

DI is classically associated with severe polyuria and polydipsia (PU/PD), with water intake commonly estimated by owners as 5-20 times normal. Animals may display continuous thirst and select water over food, which can lead to weight loss. Ingestion of large volumes can lead to vomiting. The severe PU often causes nocturia and urinary overflow incontinence. Neurological abnormalities are common in dogs with hypothalamic or pituitary neoplasia (see ch. 259). In one series, 7 of 17 dogs with CDI developed neurological signs 2 weeks to 12 months after initial diagnosis.[11] Signs included seizure, obtundation, behavioral changes and tremor. Neurological abnormalities can also develop if water is withheld or if the animal fails to drink. The resultant hypertonic dehydration can lead to cellular dehydration and the development of anorexia, weakness, ataxia, seizures and death. Hypertonic dehydration may also cause development of osmotic demyelination. Likewise, neurological signs may develop in animals given free access to water following a period of water restriction. This can cause rapid decrease in plasma OSM and cerebral edema.

Clinical signs associated with endocrine abnormalities may also be observed. For example, dogs with a functional pituitary chromophobe tumor and secondary cortisol excess may only have signs of hyperadrenocorticism. Likewise, hypothalamic and pituitary structural defects or hypophysectomy can lead to clinical signs associated with central hypothyroidism, or less commonly, secondary hypoadrenocorticism.[36] Deficiencies of growth hormone and gonadotropin may occur, but do not cause signs. Persistent endocrine deficiencies are common in people following head trauma.[37] Such deficiencies may be subclinical and underrecognized in dogs and cats.[12,24,38]

Routine Testing

Routine clinicopathologic testing may reveal no abnormalities in animals with CDI, provided water has not been restricted and other disorders are not present. Decreased urea concentration may be due to renal medullary washout and decreased AVP-dependent reabsorption. If water has been restricted, changes indicative of dehydration may develop, including increases in hematocrit, protein, Na^+, or chloride, as well as pre-renal azotemia. Serum OSM may be normal or increased in affected dogs. Hyposthenuria is the only consistent clinicopathological finding in animals with complete CDI or NDI. In partial CDI, isosthenuria or minimally concentrated urine may be observed. In one series, bacterial cystitis was detected in 4 of 17 dogs.[11] Bacterial culture should be performed in all cases to exclude pyelonephritis as a cause of secondary NDI.

Confirmatory Testing

Central and Nephrogenic DI versus Primary Polydipsia (PP)

There is no single test with excellent sensitivity and specificity for diagnosing DI. Due to the effects of multiple conditions on AVP release and action, it is essential to exclude other causes of PU/PD before pursuing a diagnosis of DI. Several methods are available to distinguish between CDI, primary NDI and PP. Primary NDI can usually be excluded based on signalment. However, distinguishing CDI from PP can be challenging and test interpretation complicated by not fully understanding the pathophysiological processes in these conditions. For example, AVP secretion is not normal in most people with PP, with altered rates and set-points for AVP release.[39,40] It is unclear if these changes represent downregulation of AVP release in response to chronic overhydration or if primary abnormalities in the control of AVP exist, while osmoreceptor disorders may concurrently affect both thirst regulation and AVP secretion. Similarly, the AVP response and urine concentrating ability in dogs with PP have been characterized as exaggerated, subnormal or nonlinear.[41,42] This is further complicated by the pulsatile and variable nature of AVP secretion in dogs and the potential effects of chronic over- or underhydration on AVP secretion and action.[43]

The Modified Water Deprivation Test (MWDT)

Indications and Phase 1

The MWDT is the most commonly recommended aid for discriminating CDI, NDI and PP (Figure 296-2). The test is time-consuming and can be associated with risk, even if appropriately performed. Phase 1 of the test is a 3- to 5-day period of progressive water restriction. In theory, this allows re-establishment of some renal medullary concentration gradient, likely to be decreased in animals with chronic PU/PD. Dry food should be fed and a calculated total volume of water divided and given in as many small portions as possible, to avoid prolonged periods of complete water deprivation. Although often performed at home, it is possible that hypertonic dehydration and associated signs could develop during this water restriction phase. Therefore, owners must be educated regarding potential adverse effects of restricting water and they should monitor their pet's body weight and demeanor. Hypertonic dehydration is more likely to occur in animals with severe PU. Therefore, it may be prudent to hospitalize such pets for observation.

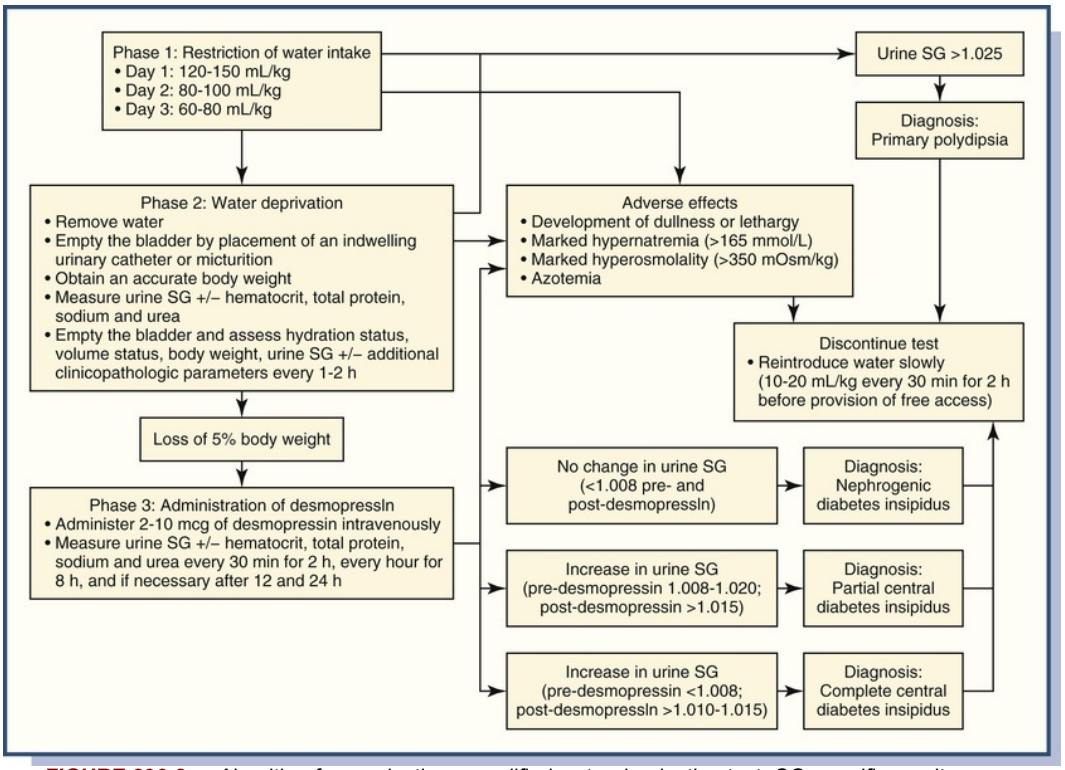

FIGURE 296-2 Algorithm for conducting a modified water deprivation test. *SG*, specific gravity.

Phase 2

Water is completely withdrawn to begin Phase 2. Adequate monitoring is essential because life-threatening hypertonic dehydration can develop quickly. The test is begun early in the morning to enable close observation of the patient throughout the day. An accurate scale is essential as the pet should be weighed at least every 60 minutes with the beginning of Phase 2. Also essential is the ability to monitor serum electrolyte concentrations, blood urea nitrogen, hematocrit and total solids at least every 60 minutes. The MWDT should be discontinued if the pet becomes dull, lethargic, azotemic, or if the serum Na^+ concentration increases excessively. Urine specific gravity and OSM, emptying the bladder each time, should be monitored every 30-60 minutes. Water deprivation is continued until 3-5% of body weight has been lost or until urine specific gravity exceeds 1.025. In most animals with complete CDI or primary NDI, this endpoint is achieved within 3-10 hours. However, in animals with partial CDI or PP, it may take considerably longer. If urine specific gravity increases to >1.025, a diagnosis of PP can be made and the test discontinued.

Phase 3

This phase begins once the pet has lost 3-5% of body weight and has been given desmopressin (1-deamino, 9-D-arginine vasopressin [DDAVP]), a synthetic analogue of AVP (2-10 mcg, IV). Maintenance volumes of fluid can be given IV during this stage to decrease likelihood of progressive dehydration. Urine specific gravity is

monitored every 30 minutes for 2 hours, then every hour for 8 hours, and if necessary after 12 and 24 hours. Maximal urine concentration is typically observed after 4-8 hours; however, the test can be discontinued sooner if the urine specific gravity increases to greater than 1.015. Following completion of the test, water should be reintroduced slowly, about 10-20 mL/kg every 30 minutes for at least 2 hours before providing free access to water. If the pet begins drinking ravenously, free access should be discontinued immediately to avoid vomiting and risk of severe dehydration.

Test Interpretation

Interpretation of results can be challenging. PP is characterized by an increase in urine specific gravity in response to water restriction alone. However, failure to restore the renal medullary concentration gradient may result in an incomplete response. Increased urine specific gravity after administering DDAVP is consistent with CDI, while a lack of response suggests NDI. Partial CDI may be associated with limited concentration in response to water restriction, and a further increase in urine specific gravity after DDAVP is administered (Figure 296-3). However, in some partial CDI cases, the presence of severe dehydration could induce maximal secretion of AVP and a failure to respond to DDAVP.

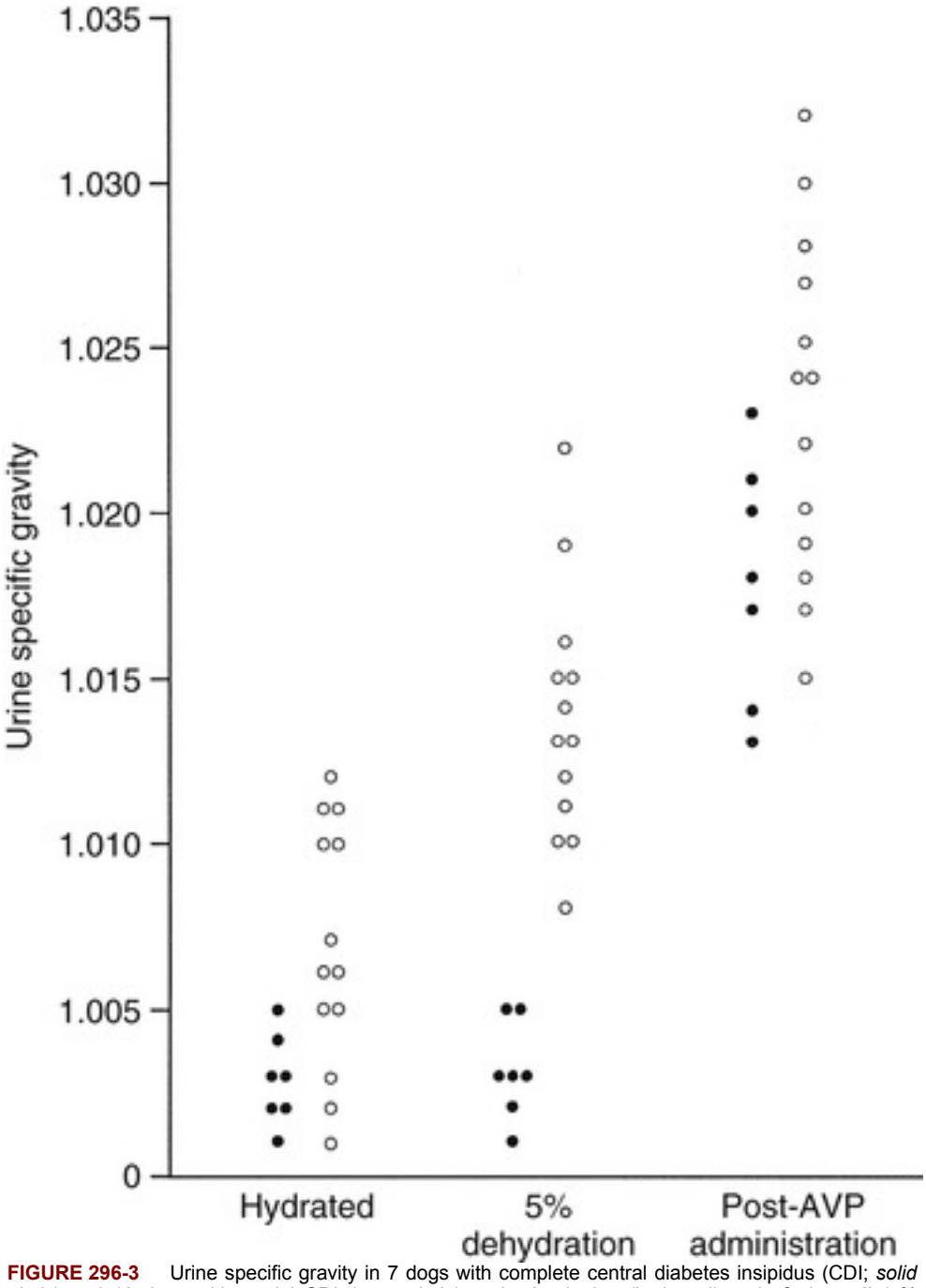

FIGURE 296-3 Urine specific gravity in 7 dogs with complete central diabetes insipidus (CDI; *solid circle*) and 13 dogs with partial CDI *(open circle)* at the beginning (hydrated) end of phase II (5% dehydration) and end of phase III (post-arginine vasopressin [AVP] administration) of the modified water deprivation test. Note the similarity of response between urine specific gravity and urine osmolality. (From Feldman EC, Nelson RW, Reusch CE, et al: *Canine & feline endocrinology,* ed 4, St Louis, 2015, Elsevier, Inc.)

Trial Desmopressin (DDAVP) Therapy

A simple alternative to the MWDT is DDAVP trial therapy. Average daily water intake is determined by the owner prior to commencement. Therapy is administered over 5-7 days and response assessed by noting changes in water intake. Urine specific gravity measurements can be made to confirm subjective opinions. In dogs with CDI, a dramatic decrease in water intake and increase in urine specific gravity is typically observed. Dogs with primary NDI and those with PP fail to respond. Exclusion of other causes of PU/PD is essential before commencing DDAVP. Partial responses may be observed in animals with secondary NDI or

PP. Advantages of trial therapy include a lower risk of life-threatening dehydration, decreased need for intensive monitoring and the ability to conduct the trial without hospitalization. Although adverse effects associated with DDAVP are rare, giving this drug to an animal with persistent increased water intake due to PP could, theoretically, result in water intoxication and hyponatremia.

Other Tests

Measurement of AVP alone provides little diagnostic value due to the pulsatile and variable nature of AVP secretion. Samples require meticulous handling and validated assays are not widely available. The hypertonic saline infusion test was once considered the gold standard method for differentiating between CDI, NDI and PP. The test is based upon the AVP response to a 20% sodium chloride infusion. A decreased AVP response is considered consistent with CDI. A normal or exaggerated AVP response without a corresponding increase in urine specific gravity is supportive of NDI, while a normal AVP response with appropriate rise in urine specific gravity suggests PP. However, the test does not reliably differentiate between CDI and PP.

Urinary aquaporin-2 expression has been shown to closely reflect changes in AVP exposure in healthy dogs, but has not been used clinically. Similarly, the concentration of plasma copeptin, the c-terminal of the AVP precursor, has been shown to correlate with AVP secretion in humans and to be of value in evaluating DI suspects, but this marker has not been evaluated in dogs or cats.[44] Magnetic resonance imaging (MRI) and computed tomography may be useful to document structural pituitary and hypothalamic lesions such as those associated with neoplasia or trauma.[45,46] In people, hyperintense MRI signals within the sella turcica are believed to represent phospholipid or secretory granules within the neurohypophysis and are absent in most CDI patients. In dogs, neurohypophysis intensity on T1 weighted MR images has been shown to be proportional to AVP content. However, changes have not been investigated in a clinical setting.

Treatment

Central Diabetes Insipidus

Treatment of CDI may not be necessary in all cases, provided access to water is continuously available and the PU/PD is not distressing to animal or owner. The synthetic AVP analogue desmopressin (DDAVP) can be used in cases of complete and partial CDI. Although it is a potent V2 receptor agonist, excessive volume expansion and hyponatremia have not been reported with currently recommended treatment protocols in dogs with CDI. DDAVP has minimal effects on V1a receptors and hypertension has not been reported as an adverse effect. The administration of DDAVP is successful in controlling clinical signs in most pets. The optimal dosage and dosing frequency is largely anecdotal, and regimens have been appropriately based on individual response. DDAVP, available as an intranasal solution for people, is commonly administered at empirical doses in dogs. Dosages have ranged from 1-4 drops (about 1.5-5 mcg/drop) into the conjunctival sac or nose, q 24 h to q 8 h. Alternatively, injectable preparations can be administered at a dosage of 2-5 mcg q 24 h or q 12 h. The tablet form can be given at dosages of 100 mcg q 24 h or q 12 h. Although experimental studies have demonstrated a dose-dependent increase in plasma concentrations of desmopressin following oral administration of the drug, the therapeutic response is variable. In cats, oral (25-50 mcg q 12 h or q 8 h), SC (4 mcg q 24 h) and conjunctival (1 drop q 12 h) routes of administration have been described. In both dogs and cats, dosage and dosing interval should be adjusted to achieve adequate control in each individual. Response to treatment is rapid and PU returns rapidly if treatment is discontinued. Some owners may elect to treat only at night to decrease the likelihood of nocturia.

Nephrogenic Diabetes Insipidus

Primary NDI is extremely rare in dogs and cats. Most treatment recommendations have been extrapolated from people, in whom a minority experience partial antidiuretic effects to high dosages of DDAVP.

Thiazide diuretics decrease Na^+ absorption from distal tubules, resulting in decreased blood volume and subsequent decreased glomerular filtration rate with increases in Na^+ and water reabsorption from proximal tubules. As a result, there is decreased water delivery to the distal tubule and decreased water loss. Additional effects may include a tubuloglomerular feedback response-mediated reduction in glomerular filtration rate and up-regulatory effects on aquaporin-2 and distal Na^+ transporter expression.[47-49] To further decrease the urinary solute load, a diet low in Na^+ and protein is recommended. Nonsteroidal anti-inflammatory drugs (NSAIDs) may have a synergistic effect; however, adverse effects are common.[50]

Potassium-sparing diuretics may also be used to help avoid iatrogenic hypokalemia. Chlorpropamide has been used, although usually for treating partial CDI. Its mode of action is not known, although evidence suggests it may exert its effect through upregulation of AVP receptors and unmasking constitutive receptor signalling.[51] Thiazide diuretics have been given to dogs with primary NDI. Effect has been variable, with urine volume reduced by as much as 50% in a minority.[33-35] The recommended dosage of hydrochlorothiazide is 2.5-5 mg/kg PO q 12 h in both dogs and cats.

Prognosis

The prognosis for dogs with CDI is variable depending upon the cause. Idiopathic and traumatic cases can be successfully managed for several years while those with progressive hypothalamic or pituitary neoplasia have a poorer prognosis. In one case series, seven of 17 dogs were alive 18-72 months after diagnosis.[11] The remaining ten dogs died or were euthanized 1 week to 2 years after diagnosis, most commonly because of the development of neurological signs.

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CHAPTER 297

Primary Hyperparathyroidism

Barbara J. Skelly

Client Information Sheet: Primary Hyperparathyroidism

Calcium Homeostasis in Dogs and Cats

Calcium—Function

Calcium (Ca), the most abundant element in the body due to its presence in skeletal bone, is necessary for diverse processes, such as transmitting many signals received on cell surfaces to intracellular locations, nerve conduction, neuromuscular transmission, muscle contraction, blood coagulation, hormone secretion and hepatic glycogen metabolism. Adverse effects on organ systems are noted when Ca homeostasis is disrupted. The skeleton acts as a reservoir of Ca for correcting decreases in serum concentrations. Ca can be excreted or absorbed in the kidneys and the small intestine. The Ca sensing receptor (CaSR), responsible for ensuring that circulating Ca concentrations are maintained within a limited range, is a G-protein present in parathyroid glands, kidneys, cartilage and bone.[1] Interactions between the CaSR and parathyroid hormone (PTH), synthesized and secreted by the parathyroid glands, can lead directly or indirectly to effects on skeletal bone, gastrointestinal (GI) tract, and kidneys to maintain circulating Ca concentrations within a narrow reference range.[2]

Calcium Measurement and Its Serum Regulation

Calcium, in common with other important electrolytes, is regulated closely to maintain narrow reference intervals. Total serum Ca concentrations (TCa) are usually about 2.3-2.8 mmol/L (9.2-11.2 mg/dL) in dogs and 2.1-2.5 mmol/L (8.4-10.0 mg/dL) in cats. Reference intervals vary between laboratories. Whenever there are concerns about this electrolyte, it is recommended that both TCa and ionized Ca concentrations (iCa), the biologically active form of the electrolyte, be assessed. About 50% of the TCa concentration is iCa, about 40% is protein-bound (albumin plus a small amount of globulin) and <10% is complexed with anions, such as bicarbonate or citrate. Spectrophotometric methods are used to measure TCa in serum or heparinized plasma. The anticoagulants citrate, ethylenediamenetetraacetic acid (EDTA), and oxalate are not suitable as they chelate calcium. Hemolysis and lipemia can falsely increase measured TCa concentrations. Hypoproteinemia lowers measured TCa concentrations but does not affect measured iCa concentrations. Clinically, the most important serum Ca concentration is the iCa, measured with an ion-specific electrode. However, the proportion of iCa in a sample can be altered by sample handling. When samples are stored, red cell metabolism increases lactic acid concentrations, pH decreases, and the iCa fraction increases. Conversely, when samples are exposed to air, CO_2 is lost, the pH rises, and the iCa fraction decreases.

Control of Serum Calcium Concentration

Circulating Ca concentrations are under control of four main factors: parathyroid hormone (parathormone, PTH), parathyroid hormone–related protein (PTHrP), vitamin D (vitamin D_3, calcitriol, 1,25-$[OH]_2$-cholecalciferol), and calcitonin. The CaSR senses extracellular Ca concentrations. Hypercalcemia activates the CaSR, reducing PTH synthesis and secretion. Hypocalcemia inactivates CaSR, increases PTH secretion, enhances *PTH* gene expression, and promotes parathyroid gland cellular proliferation. Ca homeostasis is disrupted when CaSR activity is abnormal or when pathological processes interfere.

Parathyroid Hormone

Description and Function

PTH is a small polypeptide hormone (84 amino acids) synthesized and secreted by the parathyroid glands. Dogs and cats have four parathyroid glands (two pairs). One pair is either embedded within or closely associated with each thyroid lobe (Figure 297-1). Cranial, "external," glands are usually situated outside the thyroid capsule and caudal, "internal," glands are usually located within thyroid tissue. Parathyroid glands consist of cords or nests of cells around capillaries (Figure 297-2). Parathyroid chief cells synthesize PTH, which increases serum Ca concentrations (both TCa and iCa) and decreases serum phosphate concentrations either directly or indirectly via activity in 3 major target organs: bone, kidney, or GI tract (Figure 297-3). PTH is continuously synthesized by chief cells and metabolized quickly. Secretory granules within chief cells contain intact active hormone, including the 34-amino-acid, biologically active N-terminus and the carboxy-terminus portions required for PTH activity.[2-4] When the serum Ca concentrations are low, the secretory granule rate of degradation is reduced. Conversely, when serum Ca concentrations are increased, the degradation rate is enhanced. Vitamin D influences the dynamics of PTH synthesis and secretion: high concentrations of vitamin D slow PTH gene transcription and reduce the rate of synthesis of the hormone. High phosphate concentrations reduce intact PTH breakdown and increase hormone secretion.

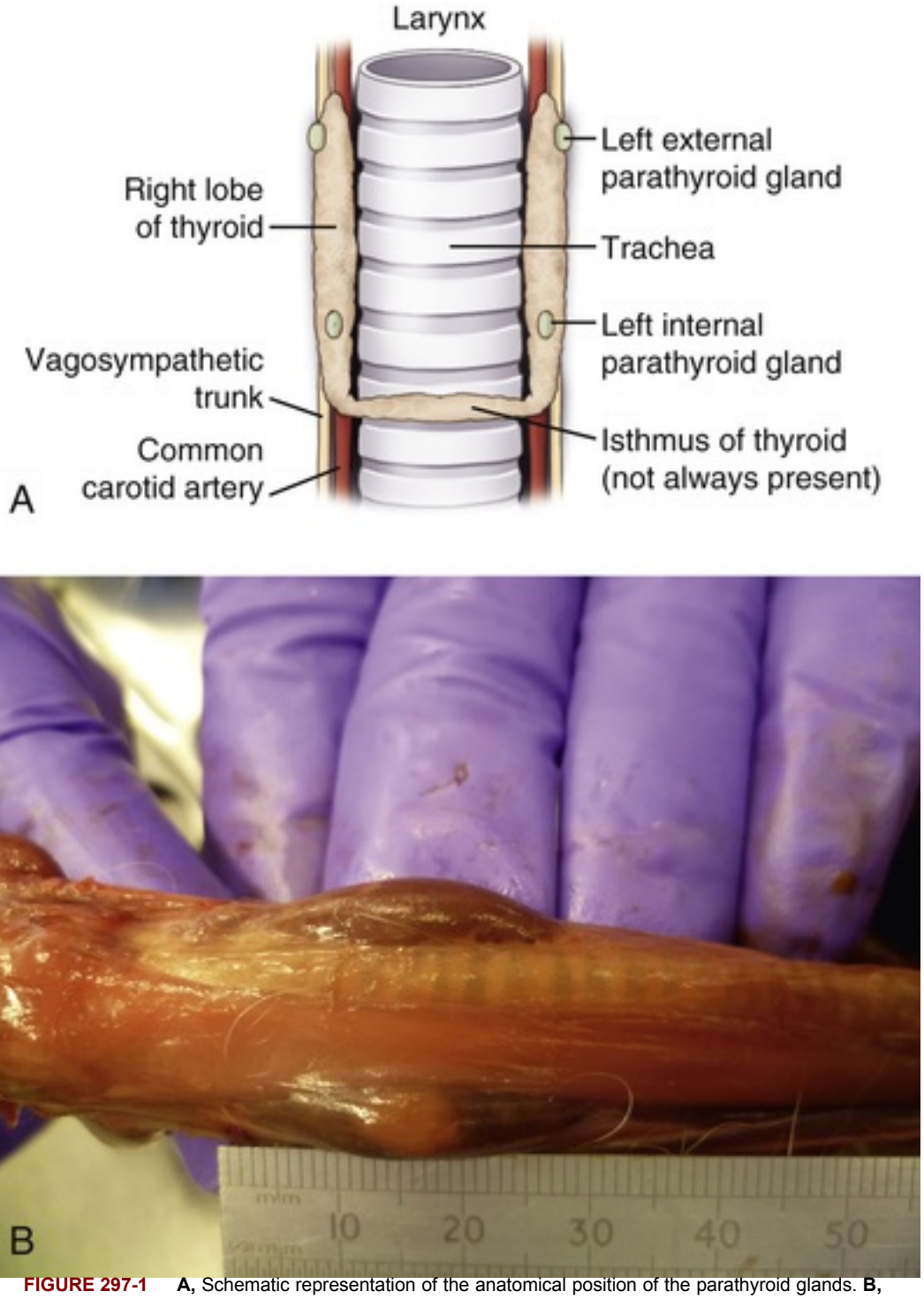


FIGURE 297-1 **A,** Schematic representation of the anatomical position of the parathyroid glands. **B,** Gross pathological specimen showing dissection of the ventral cervical region from a cat with an enlarged parathyroid gland. (Photo courtesy Fernando Constantino-Casas.)

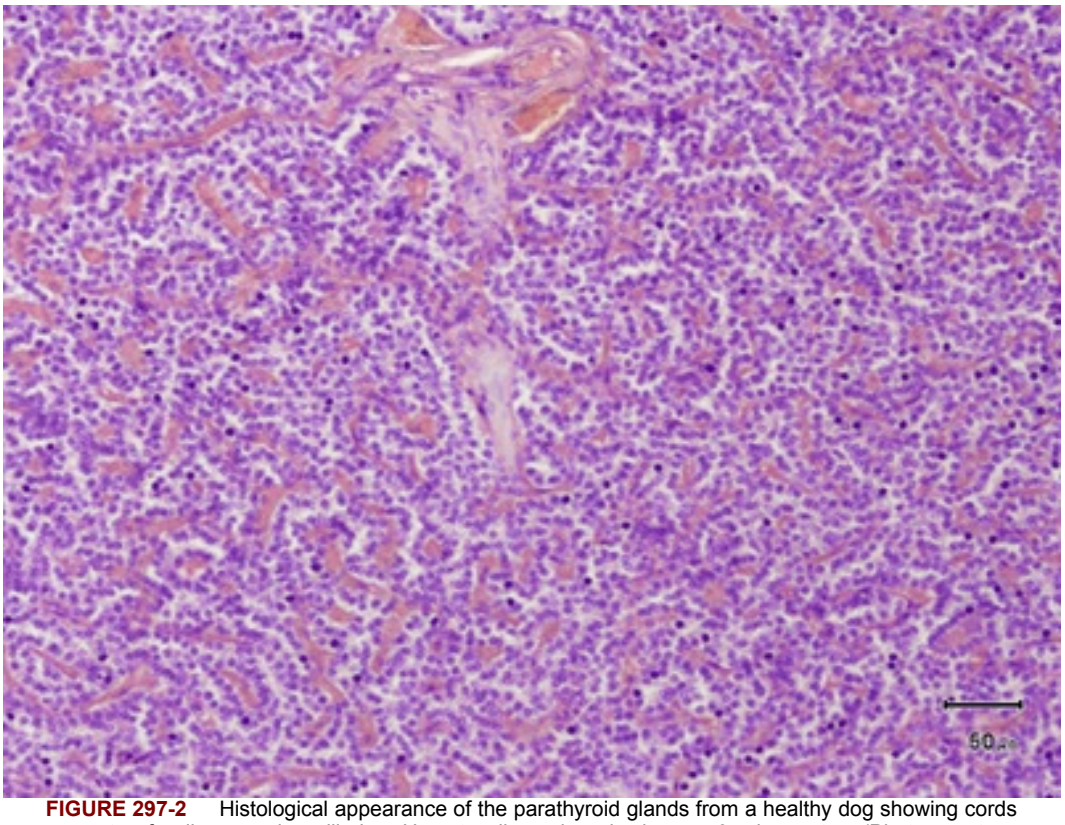


FIGURE 297-2 Histological appearance of the parathyroid glands from a healthy dog showing cords or nests of cells around capillaries. Hematoxylin and eosin, bar = 50 micrometer. (Photo courtesy Fernando Constantino-Casas.)

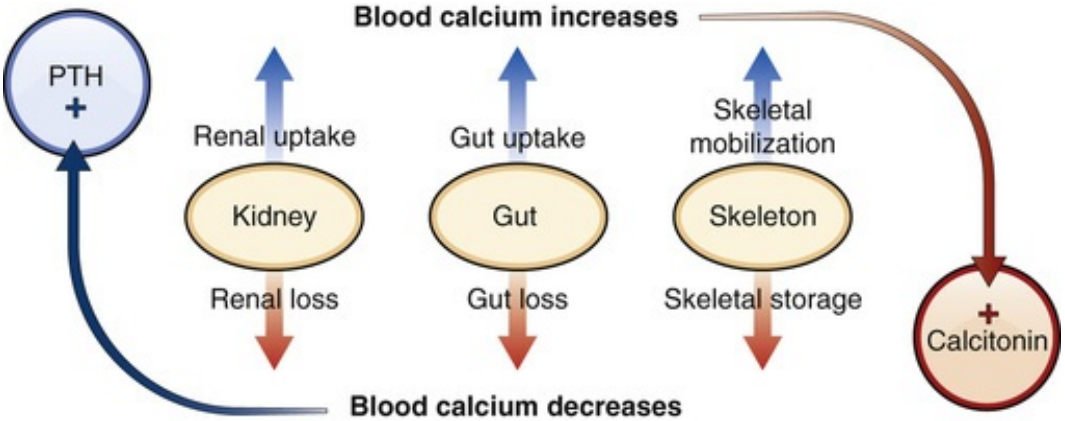


FIGURE 297-3 Calcium homeostasis. The release of PTH causes increased uptake of calcium in the kidney and gut and mobilization from the skeleton.

Parathyroid Hormone Assays

PTH and its fragments cleaved from the intact molecule circulate. Biologically active intact PTH (amino acids 1-84) must be measured for reliable assessment of parathyroid function.[5,6] Assays developed for PTH are sensitive and specific. Older PTH assays used antibodies directed at both the C-terminal (amino acids 39-84) and N-terminal (amino acids 12-24, or 26-32). However, such assay results included concentrations of some fragments cleaved between amino acids 1-12. Current (usually ELISA) assays use antibody combinations that only measure intact hormone.[7] A canine-specific ELISA, which has also been validated for cats, is available. Some laboratories have validated human-specific PTH testing kits for use in the dog and cat.[8,9] Since assay availability changes, new methods should be validated for the species being tested. EDTA plasma samples are

preferred for assaying PTH. Since PTH is labile, samples should be immediately separated and frozen until assayed. The laboratory should provide handling information, and many also provide freezer packs for sample submission. The reference interval for PTH is approximately 20-65 pg/mL in the dog and <25 pg/mL in the cat but may differ depending on the laboratory and assay system used.

Parathyroid Hormone–Related Protein

Description and Function

PTHrP is integral to calcium homeostasis in the fetus. Following birth, PTHrP becomes virtually undetectable in healthy animals. Increased concentrations of PTHrP have been proven to cause humoral hypercalcemia of malignancy (HHM).[10] PTHrP has the same physiological effects as PTH, increasing concentrations of TCa and iCa, while decreasing serum phosphate concentrations. Measuring PTHrP is an important and valuable aid in evaluating hypercalcemic dogs and cats, particularly when neoplasia is possible. Normal or low PTHrP concentrations do not definitively exclude the possibility of a neoplastic process, whereas increases are usually associated with a malignant cancer (see ch. 352).

Assaying PTHrP

PTHrP can be reliably measured using two-site immunoradiometric (IRMA) or N-terminal radioimmunoassays (RIAs). Several circulating forms of PTHrP, in addition to the intact 1-141 amino acid hormone, have biological activity. These include an N-terminal 1-36 amino acid fragment and a 1-86 amino acid N-terminal-and-midregion fragment. Roles of these different forms are not completely understood. Like PTH, PTHrP is not stable, is measured preferentially in EDTA plasma, and samples should be handled as described for PTH. The reference interval for PTHrP is generally <0.5 pmol/L in both dogs and cats.

Vitamin D (Vitamin D_3, Calcitriol, 1,25-$[OH]_2$-Cholecalciferol)

Synthesis of cholecalciferol, hydroxylated once by the liver to produce 25-OH-cholecalciferol (25-OH vitamin D, calcidiol) and not closely regulated, produces a reservoir pool of inactive vitamin D ready for activation to 1,25-$(OH)_2$-vitamin D, calcitriol. This step *is* regulated, takes place in the kidney, and its synthesis is stimulated by PTH via alpha-1-hydroxylase and suppressed by increased concentrations of phosphate. 25-OH-cholecalciferol can also be catabolized by 24-hydroxylation, then excreted. Vitamin D (25 and 1,25-$[OH]_2$ D) can be measured in cats and dogs by veterinary specialist laboratories.

Calcitonin

Calcitonin, a peptide synthesized by thyroid gland C cells, reduces serum Ca concentrations and has a role in limiting postprandial hypercalcemia. Though calcitonin can counteract the effects of PTH, its role is relatively minor. Following total thyroid and parathyroidectomy, the clinical consequence is hypocalcemia due to hypoparathyroidism, not hypercalcemia due to calcitonin deficiency. Similarly, when there is neoplasia of the C cells (medullary thyroid carcinoma) and excessive production of calcitonin, calcium homeostasis is not disrupted. In people, release of calcitonin by Ca-stimulated CaSR activity is unlikely to substantially contribute to Ca homeostasis. Calcitonin is not usually assessed in patients with Ca disorders, and no assays are commercially available.

How Do These Hormones Act Together to Maintain Calcium Homeostasis?

PTH is the primary regulator of Ca homeostasis. PTH increases serum Ca concentrations by enhancing resorption via increasing the number of osteoclasts on bone surfaces, by increasing renal tubular Ca absorption from distal convoluted tubules and thick ascending loops of Henle, and by increasing the hydroxylation of 25,OH vitamin D to 1,25-$(OH)_2$ vitamin D, which increases Ca absorption from the small intestine.[2,3]

The Differential Diagnosis of Hypercalcemia in Dogs

Hypercalcemia can be caused by access to exogenous agents that alter Ca concentrations or it can be the result

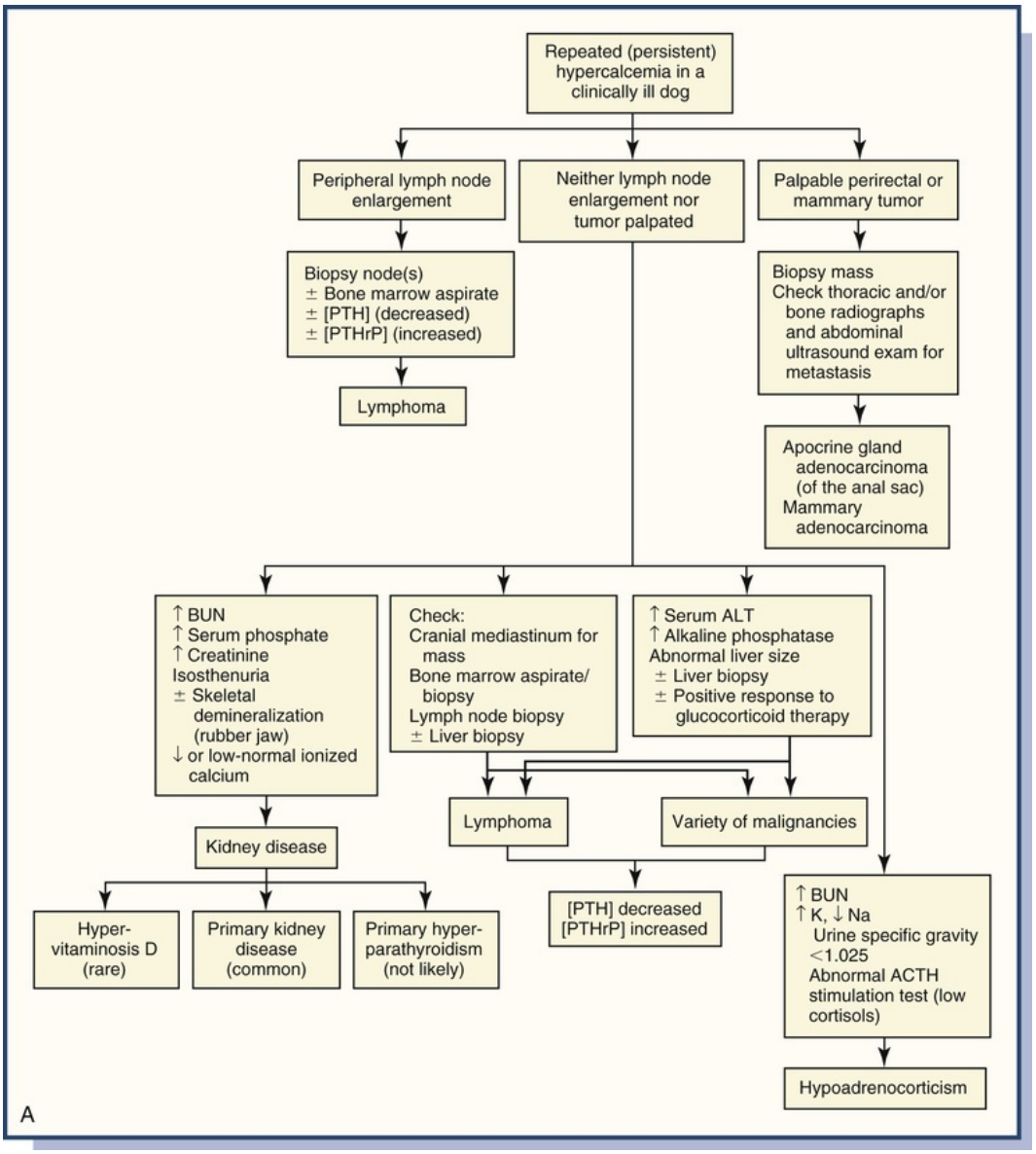
of abnormalities in one of the endogenous homeostatic mechanisms (Table 297-1; see ch. 69). The approaches used in the systematic workup of clinically stable or ill hypercalcemic dogs are reviewed in Figure 297-4, *A* and *B*.

TABLE 297-1

Classification, Cause and Characteristics of Various Hypercalcemic Conditions

CLASSIFICATION	CAUSE	CHARACTERISTICS
Parathyroid dependent	Primary hyperparathyroidism (parathyroid adenoma, hyperplasia, or adenocarcinoma)	PTH within reference range or increased tCa and iCa both elevated PO_4 low or low normal
	Chronic kidney disease	PTH elevated tCa mildly elevated iCa usually normal PO_4 elevated
Parathyroid independent	Malignancy (lymphoma, anal sac adenocarcinoma, other carcinomas, thymoma, multiple myeloma, metastatic or primary bone neoplasia)	PTH normal or low PTHrP may be elevated; not all tumors associated with hypercalcemia produce PTHrP Osteolytic bone lesions
Vitamin D dependent	Iatrogenic (cod liver oil supplementation, etc.) Plants (calcitriol glycosides found in "nightshade" fruits and vegetables, jasmine/jessamine plants and flowers, and other plants) Rodenticide intoxication (cholecalciferol) Antipsoriasis creams (calcipotriol and calcipotriene)	PTH suppressed tCa and iCa elevated PO_4 elevated Vitamin D may be measurably elevated depending on which form has been ingested
Granulomatous disease—dependent on local vitamin D production	Panniculitis Blastomycosis Other granulomatous disease	Can be difficult to characterize due to unknown etiology of hypercalcemia. Sometimes elevated vitamin D is implicated.54-56 Elevated PTHrP also reported.57
Mechanism unknown	Hypoadrenocorticism (Addison's disease) Feline idiopathic hypercalcemia (FIH)	Associated with no measurable changes in key molecules

iCa, Ionized calcium; *PTH*, parathyroid hormone; *PTHrP*, parathyroid hormone-related peptide; *tCa*, total calcium.


Repeated (persistent) hypercalcemia in a clinically ill dog
Peripheral lymph node enlargement
Neither lymph node enlargement nor tumor palpated
Palpable perirectal or mammary tumor
Biopsy node(s)
± Bone marrow aspirate
± [PTH] (decreased)
± [PTHrP] (increased)
Lymphoma
Biopsy mass
Check thoracic and/or bone radiographs and abdominal ultrasound exam for metastasis
Apocrine gland adenocarcinoma (of the anal sac)
Mammary adenocarcinoma
↑ BUN
↑ Serum phosphate
↑ Creatinine
Isosthenuria
± Skeletal demineralization (rubber jaw)
↓ or low-normal ionized calcium
Check:
Cranial mediastinum for mass
Bone marrow aspirate/ biopsy
Lymph node biopsy
± Liver biopsy
↑ Serum ALT
↑ Alkaline phosphatase
Abnormal liver size
± Liver biopsy
± Positive response to glucocorticoid therapy
Kidney disease
Lymphoma
Variety of malignancies
Hyper-vitaminosis D (rare)
Primary kidney disease (common)
Primary hyper-parathyroidism (not likely)
[PTH] decreased
[PTHrP] increased
↑ BUN
↑ K, ↓ Na
Urine specific gravity <1.025
Abnormal ACTH stimulation test (low cortisols)
Hypoadrenocorticism
A

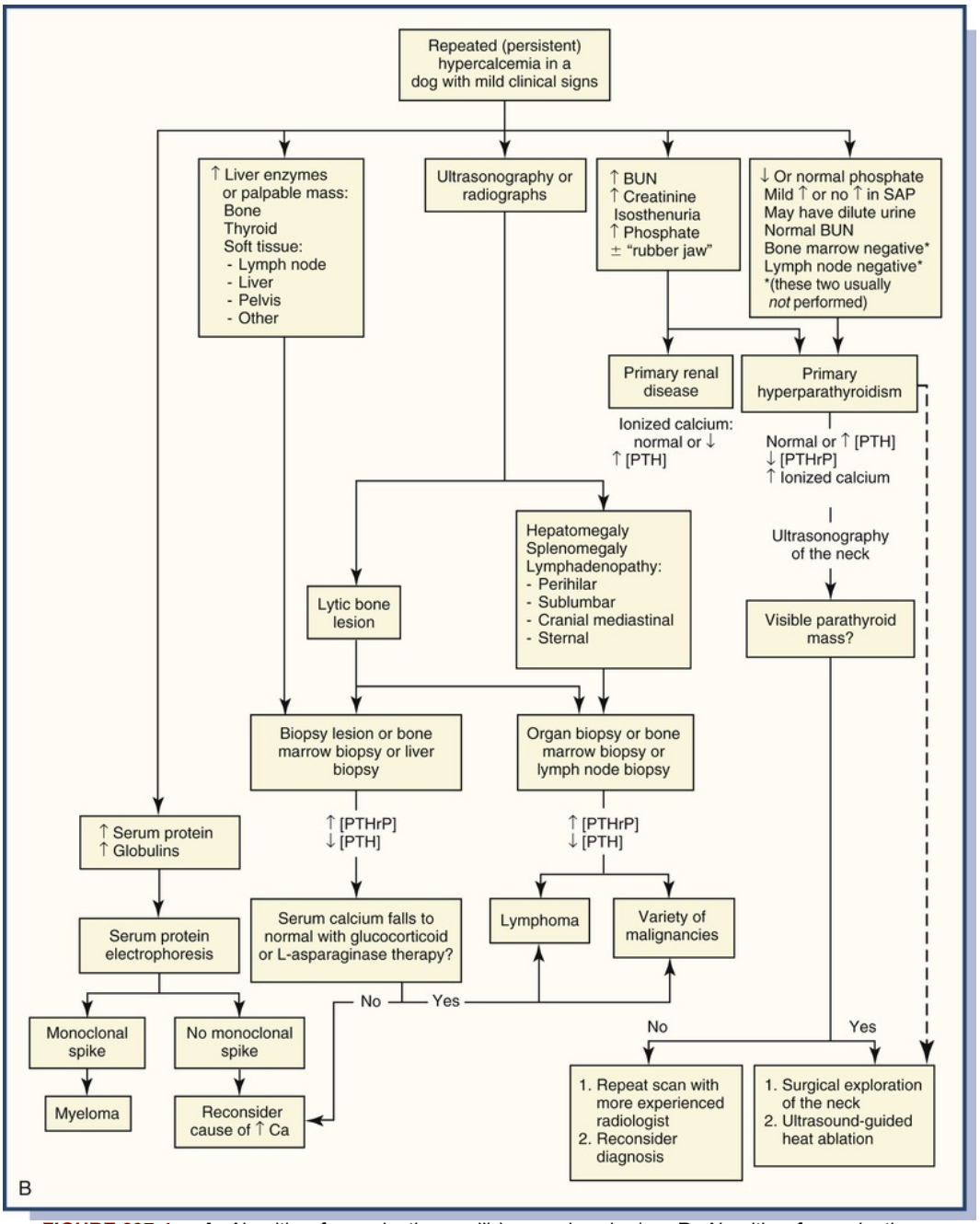


FIGURE 297-4 **A,** Algorithm for evaluating an ill hypercalcemic dog. **B,** Algorithm for evaluating a dog with hypercalcemia but without serious or worrisome clinical signs. *ACTH,* Adrenocorticotropic hormone; *ALT,* alanine aminotransferase; *BUN,* blood urea nitrogen; *PTH,* parathyroid hormone; *PTHrP,* parathyroid hormone–related protein; *SAP,* serum alkaline phosphatase. (From Feldman EC, Nelson RW, Reusch CE, et al: *Canine and feline endocrinology,* ed 4, St Louis, 2015, Elsevier.)

Primary Hyperparathyroidism (PHPT) in Dogs

Definition

PHPT, an uncommon condition in dogs and rare in cats, should be considered among the possible causes of hypercalcemia, particularly in older relatively asymptomatic dogs.[12-14] PHPT is defined by hypercalcemia and inappropriately high concentrations of PTH (either within or above the reference interval), with no other identifiable underlying cause (Figure 297-5).

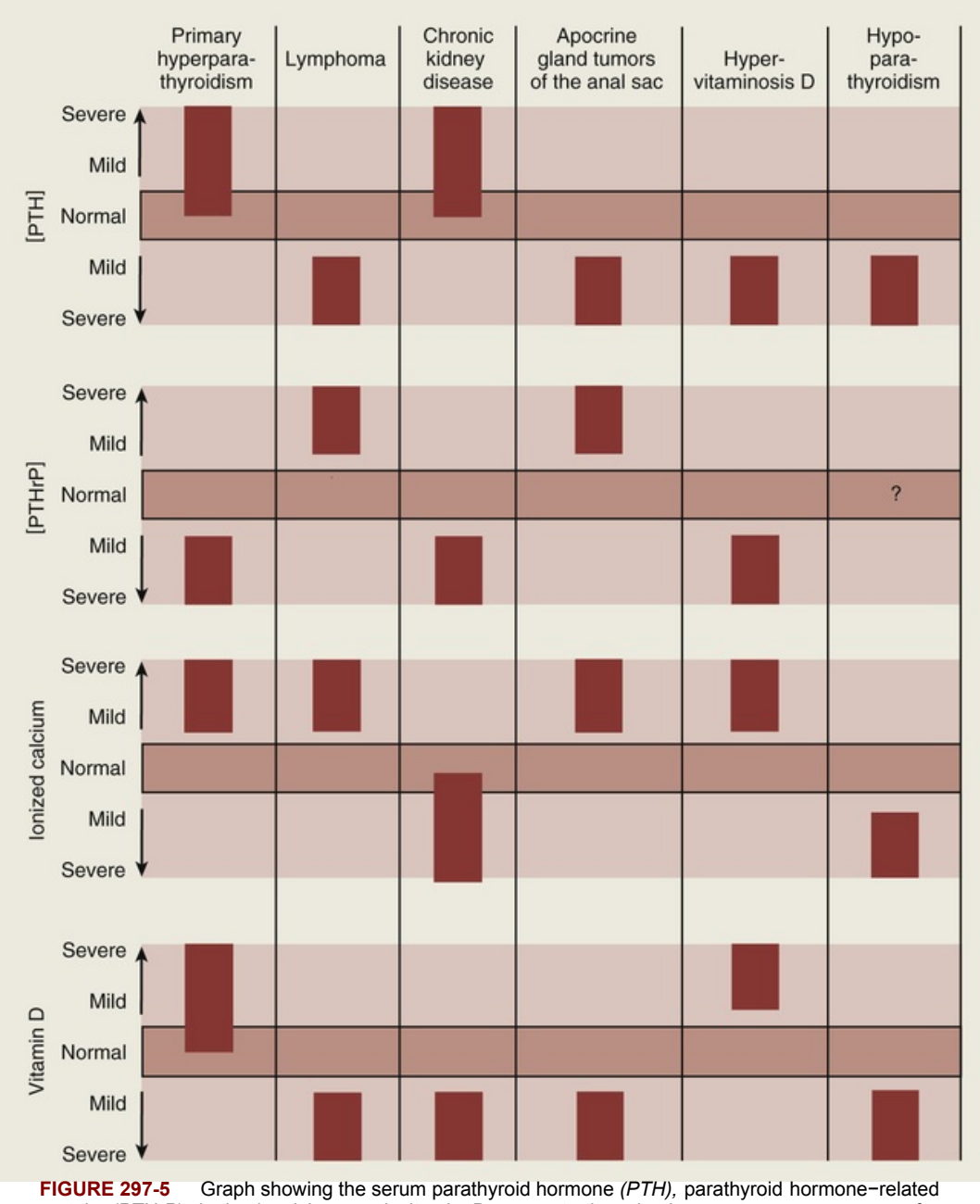


FIGURE 297-5 Graph showing the serum parathyroid hormone *(PTH),* parathyroid hormone−related protein *(PTHrP),* ionized calcium, and vitamin D concentrations in the most common causes for hypercalcemia of dogs. (From Feldman EC, Nelson RW, Reusch CE, et al: *Canine and feline endocrinology,* ed 4, St Louis, 2015, Saunders.)

Cause

PHPT develops after one or more parathyroid glands begins to function autonomously. Secondary hyperparathyroidism develops after nonendocrine disruption of Ca homeostasis associated with chronic kidney disease (CKD) or chronic deficiency in dietary Ca. PHPT is usually caused by a solitary adenoma, carcinoma or adenomatous hyperplasia of one parathyroid gland. More than one gland involved is noted in <10% of dogs with PHPT. In a case series of dogs that went to surgery, 87% had a solitary adenoma, 8% had hyperplasia and 5% had carcinoma.[15] Functional metastatic parathyroid tissue has been reported in only 1 of hundreds of dogs with PHPT in the veterinary literature.[16]

As a consequence of the pathological change in one or more parathyroid glands, persistent excess secretion of PTH, independent of serum Ca concentration, takes place. When hyperparathyroidism is primary, usually one affected gland is the source of autonomous PTH secretion. In the secondary condition,

hyperparathyroidism is usually due to hyperplasia of more than one parathyroid gland in response to more generalized stimuli to produce PTH. In reality, discriminating primary from secondary hyperparathyroidism can be difficult. Histologic evaluation of extirpated parathyroid glands seldom shows clear-cut and definitive evidence of being benign or malignant. Hyperplasia may not affect each gland uniformly and, though most frequently associated with secondary disease, has been described as a cause of PHPT in cats and dogs.[14,17,18]

Comparisons with Human PHPT

In humans, PHPT can occur sporadically or be associated with a syndrome including other endocrine or neoplastic diseases. Sporadic PHPT has been found to be initiated by somatic *MEN1* mutations (the gene mutated in cases of multiple endocrine neoplasia) in approximately 35% of cases. Other mutations occur at low frequencies[19,20] Nonsporadic forms of the disease include familial isolated hyperparathyroidism, the only nonsyndromic manifestation (FIH, OMIM:145000), familial hypocalciuric hypercalcemia (FHH, OMIM:145980), multiple endocrine neoplasia type 1 (MEN1, OMIM:131100) and type 2A (MEN2A, OMIM:171400) and hyperparathyroidism-jaw tumor syndrome (HPT-JT, OMIM:145001). Separate genes have been associated with FHH (calcium-sensing receptor *[CaSR],* adaptor protein-2 *[AP2S1],* G-protein subunit alpha11 [GNA11]), MEN1 (*MEN1,* encoding a tumor suppressor), MEN2 *(RET)* and HPT-JT (*HRPT2,* encoding parafibromin, another tumor suppressor).[21-24] Mutations in these genes do not account for all clinical cases, suggesting that other loci may be involved. FIH has been associated with mutations in three genes, *MEN1, CaSR* and *HRPT2*.[25,26] A diagnosis of FIH is reached if the diagnostic criteria for any of the other phenotypes are not met when using standard, nonmolecular genetic tests. In human FIH patients, the *MEN1* and *CaSR* genes are assessed initially, since *HRPT2* is a less common cause of disease.[26,27] The Keeshond is the only dog breed identified to have a familial predisposition to PHPT. Keeshonden have been studied using a candidate gene approach.[28,29] *MEN1, CaSR* and *HRPT2* mutations were ruled out as causative mutations leading to PHPT in the Keeshond. Despite using genome-wide association analysis in the Keeshond, the causative mutation has yet to be defined.

Signalment

PHPT is a disease of older dogs (mean age 11.2 years; range 6-17 years) with no apparent gender predisposition.[15] In one review, Keeshonden were found to have the highest breed-associated odds ratio, at 50.7.[28,30,31] Cats are infrequently affected, and no information about breed predisposition is available. Neonatal PHPT has been reported in a litter of German Shepherd puppies, but this seems to have been an isolated event.[17]

History and Clinical Signs

Overview

PHPT is not a dramatic disease. Rather, PHPT is slowly progressive, insidious, and subtle (Box 297-1). Since affected dogs tend to be older, many clinical signs are attributed to simple aging by owners who may not seek veterinary advice until later in the course of the disease. Hypercalcemia is usually a serendipitous finding when blood samples are taken for other reasons. Of 210 dogs with PHPT, 42% were identified as having hypercalcemia when presented for other reasons, such as a routine geriatric check, or when preanesthetic blood testing was performed for procedures such as dental treatment.[30] An association between owners concerned about their dog having jaw pain or difficulty eating hard foodstuffs and PHPT may exist, particularly in the Keeshond. The most common reason for seeking veterinary advice were clinical signs related to urolithiasis (pollakiuria, stranguria and hematuria) or urinary tract infection (50% of the 210 cases).[30] Urolithiasis can cause acute urinary outflow obstruction in dogs with PHPT (see ch. 107 and 331).

Box 297-1

Clinical Signs of Hypercalcemia/Primary Hyperparathyroidism

Renal and Urinary Tract Signs

Polyuria

Polydipsia
Urinary incontinence
Stranguria
Pollakuria
Urolithiasis

Gastrointestinal Signs

Vomiting*
Inappetence
Constipation

Neuromuscular Signs

Depression
Exercise intolerance
Shivering*
Muscle twitching*
Seizures*

Other

Dental pain
Difficulty eating
Stiff gait*
Lameness*

*Uncommon to rare.

Polyuria and Polydipsia (PU/PD) and Other Signs *(see Box 297-1)*

PU/PD were noticed by <10% of owners of dogs with PHPT; this is a surprisingly small number, given that Ca antagonizes effects of vasopressin (antidiuretic hormone, ADH) in the collecting ducts of the kidney and hypercalcemia inhibits tubular uptake of sodium and chloride, further inhibiting urine concentrating mechanisms. Affected dogs are PU with secondary compensatory PD. This clinical sign may be overlooked by dog owners because it progresses gradually and, perhaps, nocturia and incontinence in these older animals is simply tolerated. Dogs with PHPT often have reduced activity levels, appear listless and may seem depressed. Again, these signs may be attributed to aging and sometimes are not mentioned until after successful treatment, when dogs are often described as having been "rejuvenated."

In people, the signs of PHPT are remembered using the mnemonic "stones, bones, abdominal groans, thrones and psychiatric moans." Some people with PHPT are depressed and/or debilitated by bone pain. The "thrones" in the mnemonic refers to the constipation commonly noted in people with PHPT. However, recent literature suggests this classic view is changing, as more patients are diagnosed despite having few or no symptoms and the disease usually progresses in a benign manner, even without treatment.[32,33] Whether this is also true in dogs and cats is unclear, as there are no large-scale animal studies. In contrast to the canine experience, people with PHPT are at risk of an uncommon and potentially life-threatening hypercalcemic crisis. This syndrome is associated with rapid multiorgan functional deterioration and is associated with a 100% mortality rate, if untreated.[34] There are no veterinary reports of this syndrome, but there is a spectrum of disease severity and progression among dogs diagnosed as having PHPT. Each dog must be assessed individually and requirement for intervention evaluated. GI signs include inappetence, vomiting and constipation. These signs can be secondary to Ca-induced gut smooth muscle hypoexcitability and dysmotility.

Kidneys and Urinary Tract Stone Formation

In addition to causing PU and compensatory PD, hypercalcemia due to PHPT may increase risk of developing kidney failure. Kidney failure affects some dogs with PHPT, but not others. Phosphate concentrations should be at the low end or below reference intervals in dogs with PHPT. If this were not the case, renal insufficiency might already be developing, albeit before overt azotemia is recognized. In these cases, closer monitoring and a more guarded prognosis should be given. It has been suggested that

calculating the Ca × phosphate product may help predict the likelihood of renal failure; dogs with PHPT with low phosphate concentrations and a relatively low Ca × phosphate product are thought to be at lower risk. In the large case series of 210 dogs, the risk of renal failure was deemed to be low, while in a smaller case series (29 dogs), approximately 25% developed chronic kidney disease (CKD). In that study, the Ca × phosphate product was a poor predictor of renal impairment.[35] The genetically homogeneous Keeshond population allows investigation of CKD in those carrying the mutation linked to PHPT. If untreated, some PHPT dogs continue to have normal renal function despite having prolonged, and in some cases severe, hypercalcemia (>4.0 mmol/L). Other PHPT dogs succumb to renal failure with much more modest Ca elevations. Some dogs develop nephroliths and urolithiasis. One dog with PHPT died with a large nephrolith and renal failure after disease management had seemingly been successful (Figure 297-6). It is therefore clear that predicting long-term outcome with or without treatment is fraught with problems. Erring on the side of caution when managing hypercalcemia is recommended and delays to treatment should be avoided to protect renal function.

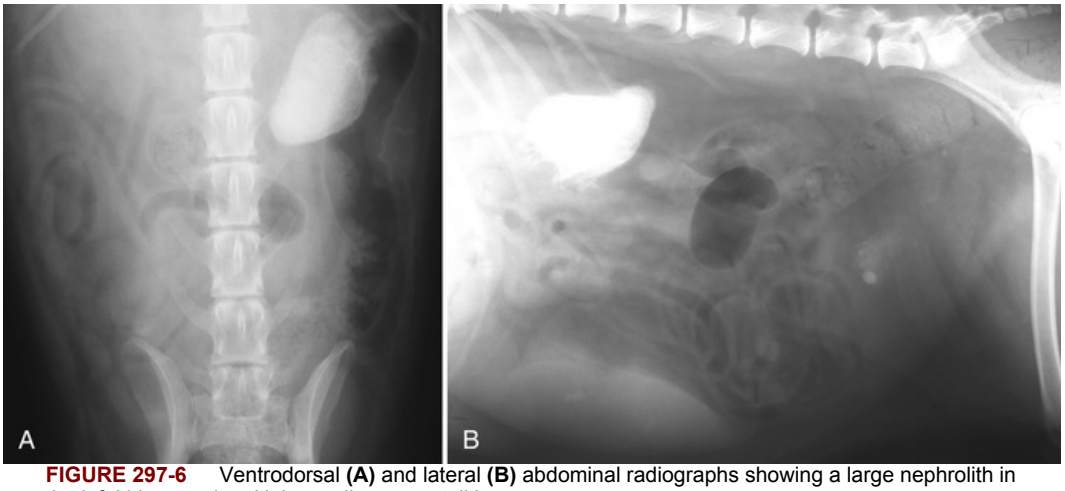


FIGURE 297-6 Ventrodorsal **(A)** and lateral **(B)** abdominal radiographs showing a large nephrolith in the left kidney and multiple smaller urocystoliths.

Urolith formation is common in dogs with PHPT due to the increased concentrations of Ca filtered by the kidney and lost in urine (see ch. 331). Although PTH increases Ca uptake from renal tubules, in PHPT there is also overt hypercalciuria, presumably as reuptake is unable to match the amount of Ca filtered. Dogs with PHPT also have increased phosphate excretion, and their urine is, therefore, supersaturated with both Ca and phosphate. This enhances precipitation and stone formation. Dietary oxalate uptake from the gut is reduced when there is abundant intraluminal Ca, because Ca oxalate is not absorbable from the intestine. If intestinal Ca absorption increases, oxalate absorption also increases. In this scenario, the kidney filters more Ca and oxalate, again leading to urine supersaturation. In hypercalcemic people, evaluation of the quantity of Ca lost into urine is commonly assessed by measuring the calcium-to-creatinine ratio in urine. Such studies have not been widely used in animals (see ch. 73).

Physical Examination (PE)

Relevant findings on PE are few and nonspecific (see Box 297-1). They may include stiffness and gait abnormalities, dull mentation, weakness, and muscle wastage. Little information is gathered from palpation of the ventral neck area as parathyroid masses are usually too small to be palpated.

Total Calcium (TCa), Ionized Calcium (iCa), Phosphate, PTH, PTHrP

TCa and iCa

When hypercalcemia is identified, one should also assess iCa, phosphate, PTH and PTHrP. The hallmark of PHPT is an increase in both TCa and iCa while PTH concentrations are within or above reference intervals. In the series of 210 dogs with PHPT, mean TCa concentration was 3.6 mmol/L (14.5 mg/dL).[30] There was a range in severity of hypercalcemia: mild increases in 52% of dogs (>3.0-≤ 3.5 mmol/L, >12-≤14.0 mg/dL), moderate

increases in 30% (>3.5 to < 4.0 mmol/L, >14.0 to <16.0 mg/dL), serious increases in 12% (>4.0-≤4.5 mmol/L, >16.0 to <18.0 mg/dL), and severe hypercalcemia (>4.5 mmol/L, >18 mg/dL) in 6%. iCa concentrations paralleled TCa concentrations in the 210 dogs. The mean plasma iCa concentration was 1.71 mmol/L (range 1.22-2.41 mmol/L, reference range 1.12-1.41 mmol/L).

Severity of hypercalcemia is likely dependent on disease duration. Keeshonden from families with PHPT generally start to show mild hypercalcemia (up to 3.5 mmol/L, 14 mg/dL) when they are 6-8 years of age, and this gradually worsens over subsequent years. Some untreated dogs continue to experience increased Ca concentrations until serious hypercalcemia is reached (>4.0 to <4.5 mmol/l, >16 to < 18.5 mg/dL). After this point some stabilization occurs and concentrations do not continue to rise inexorably, similar to the condition in people. Keeshonden who are untreated have had serious hypercalcemia until their deaths due to other diseases at ages ranging between 13 and 15 years. As the genetic basis for PHPT in other breeds is not known, it is not clear how reproducible this pattern is between breeds, but in all breeds the disease appears slow and insidious. Affected dogs are not considered to be ill by their owners.

Phosphate

PHPT, hypercalcemia and normal renal function causes hypophosphatemia, an unusual finding in dogs (Box 297-2). PTH inhibits renal phosphate resorption, and serum concentrations are low-normal or below reference ranges. In the series of 210 dogs with PHPT, the mean serum phosphate concentration was 2.8 mg/dL (0.9 mmol/L; range 1.3 to 6.1 mg/dL, 0.4 to 1.9 mmol/L; reference range 3.0-6.2 mg/dL, 0.9-2.0 mmol/L).

Box 297-2

Causes for Hypophosphatemia

Decreased Intestinal Absorption

Decreased dietary intake
Malabsorption/steatorrhea
Vomiting/diarrhea
Phosphate-binding antacids
Vitamin D deficiency

Increased Urinary Excretion

Primary hyperparathyroidism
Diabetes mellitus ± ketoacidosis
Hyperadrenocorticism (naturally occurring/iatrogenic)
Fanconi syndrome (renal tubular defects)
Diuretic or bicarbonate administration
Hypothermia recovery
Hyperaldosteronism
Aggressive parenteral fluid administration
Hypercalcemia of malignancy (early stages)

Transcellular Shifts

Insulin administration
Parenteral glucose administration
Hyperalimentation
Respiratory alkalosis

Parathyroid Hormone

Circulating PTH concentrations should be assessed in hypercalcemic dogs, after increases in TCa and iCa have been confirmed and more obvious causes ruled out (lymphoma). If a hypercalcemic dog has a PTH concentration within the upper half or above the reference range (i.e., in the upper half of the reference interval >35 pg/mL for dogs, reference range 20-65 pg/mL), it is abnormal and consistent with PHPT. In most cases of hypercalcemia not caused by PHPT, TCa and iCa concentrations are increased but PTH concentrations are low or undetectable.

Parathyroid Hormone–Related Peptide

PTH is usually measured in conjunction with PTHrP. If PHPT is not the cause of hypercalcemia, PTHrP results may aid in narrowing the differential list to include malignancies that may not have been identified. The reference interval for PTHrP is generally <0.5 pmol/L in both dogs and cats.

Other Biochemistries, Complete Blood Count (CBC), Urinalysis

Serum biochemistries, other than Ca and phosphate, are usually unremarkable in dogs with PHPT. Since hypercalcemic dogs may be at risk for renal damage, blood urea nitrogen, creatinine and phosphate should be assessed and may be increased due to pre-existing renal damage or prerenal factors. This may complicate diagnosis, since changes associated with PHPT with secondary renal failure can mimic those of primary renal disease with secondary PTH elevation and hypercalcemia (Table 297-2). CBC parameters show no consistent changes, although anemia of chronic disease may be identified if the hypercalcemia is chronic. Since hypercalcemia causes secondary nephrogenic diabetes insipidus, urine specific gravity is expected to be <1.020 and some are hyposthenuric. Hematuria, proteinuria, bacteriuria, pyuria and crystalluria are common.

TABLE 297-2

A Comparison of the Clinicopathological Features of PHPT and Renal Secondary Hyperparathyroidism

	PRIMARY HYPERPARATHYROIDISM	SECONDARY RENAL HYPERPARATHYROIDISM
Total calcium	↑	↓ or normal or ↑
Ionized calcium	↑	↓ or normal
Phosphate	↓	↑
PTH	↑ or high normal	↑ or high normal
PTHrP	Normal	Normal

Imaging

Ultrasonography (US) of the ventral neck is the most useful imaging modality when investigating a dog suspected of having PHPT, with 90-95% having a parathyroid nodule identified by experienced radiologists.[30] A high-frequency transducer of 7.5-10 MHz is required for adequate resolution. In healthy dogs and cats, the parathyroid glands are usually <3 mm in greatest diameter, seen only with excellent facilities and expertise. When they are either hyperplastic or enlarged and adenomatous, or when there is a parathyroid carcinoma, the parathyroid glands are identified as 2-20 mm diameter, round to oval, hypoechoic nodules within or near thyroid tissue (Figure 297-7).[36] Incidentally identified thyroid nodules were identified on cervical US in 14 of 91 (15%) dogs being evaluated for hypercalcemia.[37] The finding of a thyroid nodule may complicate diagnosis because it may not represent the origin of hypercalcemia but may indicate multiple concerns. Scintigraphy using technetium-99m sestamibi has been tried in dogs as an aid to parathyroid identification, but unlike in humans, it lacks sensitivity and specificity and is not recommended.[38] Plain abdominal radiographs or US is recommended to search for any abnormalities, including calcium-containing renal or cystic calculi. Rarely, extensive renal calcification is noted (see Figure 297-6).

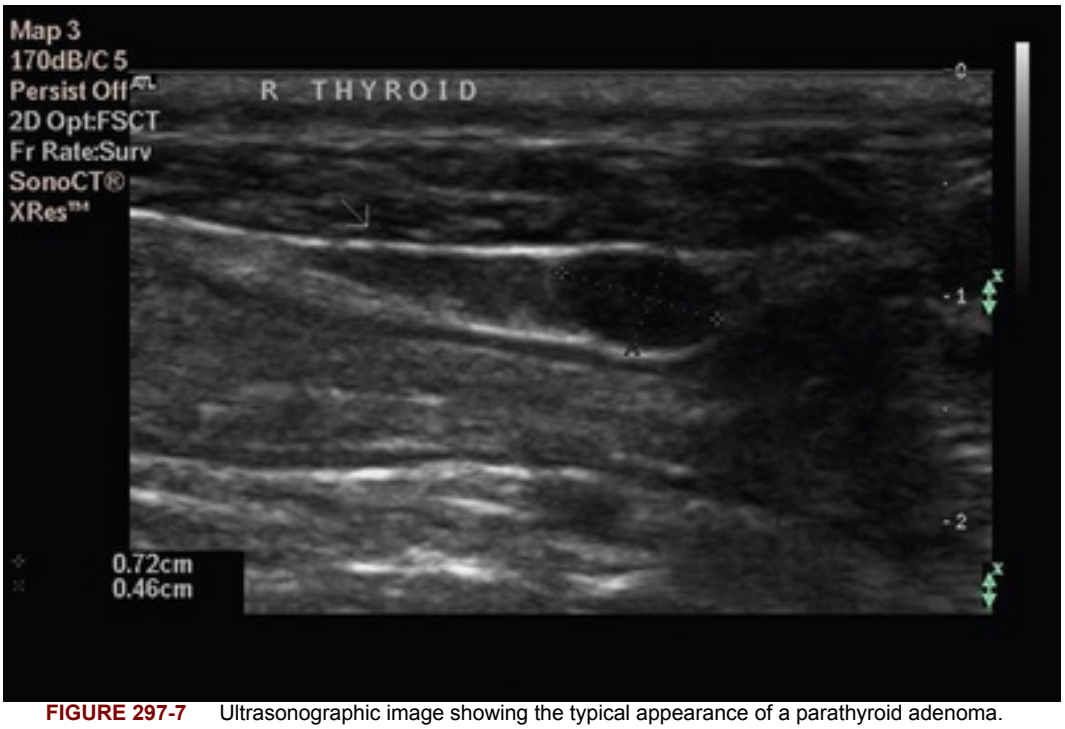


FIGURE 297-7 Ultrasonographic image showing the typical appearance of a parathyroid adenoma.

Genetic Testing for PHPT in the Keeshond

A genetic test for familial PHPT in the Keeshond is available, which aims to identify Keeshonden that carry the mutated allele responsible for the autosomal dominant disease. The test is available through the Animal Health Diagnostic Center at Cornell University, and details are available at: https://ahdc.vet.cornell.edu/Sects/Molec/PHPTtesting.cfm. Since the molecular basis for this test has not been peer-reviewed, sensitivity and specificity are not known. It is recommended that Keeshond breeders be aware of the genotype of their breeding lines and that they test the progeny of untested dogs. Keeshonden at risk should be monitored periodically to identify hypercalcemia, usually noted by 6-8 years of age. However, PHPT can develop earlier or later, or indeed may never manifest in the dog's lifetime.

Pretreatment Management of Hypercalcemia

Fluid Therapy

Emergency therapy for hypercalcemia is rarely required in dogs with PHPT unless the Ca concentration is in the "serious" to "severe" range. Some believe that virtually no dog with PHPT requires therapy of any kind prior to specific treatment of the PHPT, regardless of the degree of hypercalcemia. Others suggest that serious to severe hypercalcemia be treated in an attempt to lower serum Ca concentrations while awaiting test results. Since PTH and PTHrP assays are usually performed by specialist laboratories, there may be a delay between making a presumptive diagnosis of PHPT and having that diagnosis confirmed. Renal damage caused by persistent hypercalcemia due to PHPT is quite uncommon but impossible to predict (see ch. 324). All affected animals must be considered at risk if significantly hypercalcemic.

Fluid therapy (see ch. 129) focuses on enhancing renal Ca excretion and minimizing bone resorption. It is the cornerstone of managing hypercalcemia. Diuresis using 0.9% sodium chloride at rates of 5-10 mL/kg/h should increase renal Ca excretion and lower serum concentrations. Fluid therapy should aim to correct any dehydration or volume deficit and expand the extracellular fluid volume to increase glomerular filtration rates. Sodium chloride is the fluid of choice because sodium ions compete with Caions and reduce tubular reuptake. When an animal is considered optimally hydrated, furosemide (2 mg/kg PO q 12 h/q 8 h) can further enhance renal Ca excretion. When using sodium chloride at high rates, particularly coupled with furosemide, one must avoid inducing hypokalemia. If fluid therapy fails to lower serum Ca concentrations, glucocorticoids, bisphosphonates, calcitonin, or plicamycin can be considered.

Glucocorticoids

Glucocorticoids do not have much effect on serum Ca concentrations in dogs with PHPT and rarely lower measured values. The use of glucocorticoids (in the dosage range of approximately 1 mg/kg prednisolone or equivalent) to decrease the serum Ca should be restricted to those dogs clearly diagnosed but in whom there will be a delay in treatment and are most effective when given to pets with hypercalcemia of malignancy. Glucocorticoids cause rapid tumor lysis and reduce synthesis and secretion of PTHrP. Glucocorticoids increase renal Ca loss, decrease intestinal calcium uptake and decrease bone resorption. When used in undiagnosed patients, there is risk of masking and complicating the diagnosis of neoplasia.

Bisphosphonates

Bisphosphonates decrease bone resorption by inhibiting osteoclastic activity and inducing osteoclast apoptosis. Several different bisphosphonates have been employed. Those used most include oral drugs (clodronate, etidronate, alendronate) and IV pamidronate. Although oral preparations are convenient for owners, this route is not very effective, with <1% of a dose being absorbed.[39] An IV infusion of pamidronate is more reliable (1.3-2 mg/kg in 150 mL of 0.9% saline, given over 2 hours). Pamidronate, approximately 100 times more potent than etidronate, has effects that can last up to 3 weeks. Dosing can be repeated as required. This drug is generally well tolerated[40] but can cause GI side effects and hypocalcemia, particularly if overdosed. Pamidronate has been used frequently to treat people with hypercalcemia of malignancy, but a more potent bisphosphonate, zoledronate, is now superseding pamidronate as the drug of choice. Zoledronate is more than 100-850 times more active than pamidronate, can be infused more rapidly, but has not been used much in dogs.[41]

Calcitonin

Salmon calcitonin is commercially available and, like bisphosphonates, inhibits osteoclastic activity. It also inhibits renal reabsorption of Ca. It is useful as an emergency treatment to decrease Ca concentrations but carries the disadvantage in that after the initial IV infusion (4 IU/kg), treatment must continue daily (4-8 IU/kg, SC, q 12-24 h).[42] Calcitonin can cause anorexia and vomiting, is expensive, and is rarely used. Animals may become resistant to the effects of calcitonin after a few days of treatment.

Plicamycin (Mithramycin)

There are few reports of this drug being used in dogs. A dosage of 25 mcg/kg, IV, in 5% dextrose over 2-4 hours every 2 to 4 weeks has been suggested.[43]

Cinacalcet

This drug is a calcimimetic that interacts with the Ca sensing receptor directly and can control Ca, phosphate and PTH concentrations in human dialysis patients. It has been suggested that this drug may be useful in dogs and cats with hypercalcemia, particularly cats with idiopathic hypercalcemia but there are no data to support its use.

Definitive Treatment Options

Surgical Parathyroidectomy

Surgery is the treatment of choice at many referral institutions, especially if the parathyroid nodule is large (>10 mm in greatest diameter).[44] Good visualization of each thyroid lobe is essential during surgical exploration of the neck, achieved using a ventral midline approach. Parathyroid adenomas, carcinomas or hyperplastic glands are usually easily discriminated from normal parathyroid glands, often looking darker and larger (Figure 297-8). When the internal parathyroid glands are affected, they can be identified by palpation and may be visible through the ventral or dorsal aspect of the thyroid gland. Identification of the solitary, autonomously functioning, abnormal parathyroid tissue can be aided greatly if its location has been previously identified with US.

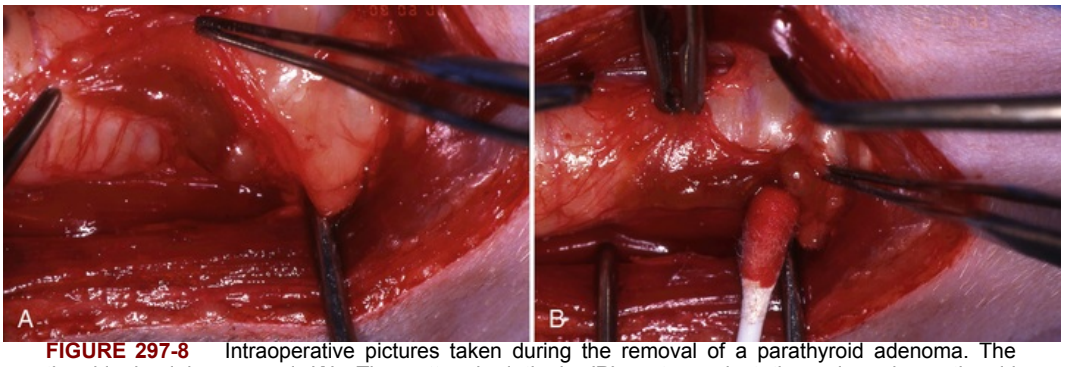


FIGURE 297-8 Intraoperative pictures taken during the removal of a parathyroid adenoma. The thyroid gland is exposed **(A).** The cotton bud tip in **(B)** rests against the enlarged parathyroid gland. (Photos courtesy Ed Friend.)

Parathyroid adenomas can be removed either by dissection of the enlarged gland from the adjacent thyroid tissue or by partial thyroidectomy, where the parathyroid nodule and part of the thyroid gland are removed *en bloc.* In dogs with PHPT, usually only one gland is affected. If more than one gland is enlarged, then up to three glands may be removed at one time. At least one parathyroid gland should be left *in situ* so that Ca homeostasis can be maintained. When multiple glands are enlarged, it is more likely that they are hyperplastic rather than adenomatous, and therefore secondary rather than primary hyperparathyroidism should be suspected.

Techniques to determine if functional abnormal parathyroid tissue has successfully been removed intraoperatively have been described.[45] In one study, samples were taken pre-, intra-, and postoperatively (20 minutes after adenoma removal) to evaluate how PTH concentrations varied and to try to confirm that functional tissue had been removed. All dogs in this study showed a significant decrease in PTH concentration from pre- to postoperative samples with an increase in PTH at times when parathyroid gland manipulation was taking place. This may help with surgical identification of parathyroid tissue but only retrospectively as analysis of samples in most veterinary centers is not done on site and inevitably involves a delay of several days.

Percutaneous, Ultrasound-Guided Ethanol Ablation

In order for parathyroid nodules to be effectively treated using ethanol injection, they must be identified by US examination and be >3 mm in greatest diameter so that a 27-gauge needle can be inserted into the nodule accurately. Animals must be under general anesthesia. Ethanol causes coagulation necrosis and thrombosis in the parathyroid nodule.[46] Success is operator-dependent, in that skill is needed for accurate needle placement and injection so that the closely associated carotid artery and vagosympathetic trunk are not compromised. When three techniques for treating PHPT were compared, ethanol ablation was the least successful, with a positive outcome achieved in 13/18 procedures (72%), compared with 45/48 (94%) for surgery and 44/49 (90%) for heat ablation.[44] However, only a small number of cases were treated by ethanol ablation and in a more recent report, a success rate of >90% in 30 dogs was reported.[47]

Percutaneous, Ultrasound-Guided Heat Ablation

This technique is the least frequently used of the three because few institutions have the necessary equipment. The technique involves inserting an insulated needle attached to a radiofrequency unit into the parathyroid nodule. The radiofrequency unit is turned on and wattage adjusted to achieve visible thermal necrosis at the needle tip.[48] The dog is anesthetized, positioned on an electrocautery ground pad, and a 20-gauge over-the-needle catheter is inserted into the affected parathyroid nodule. Usually, the initial radiofrequency is applied at 10 watts and slowly increased as needed until the entire gland becomes hyperechoic (Video 297-1).

Pre- and Post-Treatment Considerations

Vitamin D

When PHPT is treated successfully, serum PTH and, therefore, Ca concentrations should decrease rapidly and, in some circumstances, a hypocalcemic crisis may be encountered. This usually happens if the

pretreatment Ca has been seriously or severely elevated for some time prior to treatment. Predicting the dogs at greatest risk for a hypocalcemic crisis is difficult.[49-50] Generally, hypocalcemia is more likely to be encountered if the pretreatment TCa is >3.5 mmol/L (14 mg/dL) or the iCa >1.80 mmol/L for more than a few months, although this is variable. Also pivotal to the development of clinical signs may be the rate at which the iCa concentration decreases. Occasionally (rarely), clinical signs of hypocalcemia (muscle fasciculations, vocalization, panting and tetany; see ch. 298) can be seen in animals whose Ca is dropping sharply but is not yet within or below the reference range.

Presence of an autonomously functioning parathyroid adenoma causes the previously normal parathyroid glands to atrophy, making them unable to immediately support normal Ca homeostasis once abnormal tissue is removed. This effect may be more pronounced if more than one parathyroid gland is removed. Such a crisis can be averted by administering vitamin D ± oral Ca in the immediate post-treatment period or, when the Ca concentration is moderately to severely elevated, by starting calcium and vitamin D supplementation 12-24 hours before treatment. Vitamin D is available in several different preparations. It is important to use a preparation that will have a relatively rapid onset of action or the time of initiation of treatment has to be earlier. The two preparations most frequently recommended are calcitriol and alfacalcidol. Calcitriol (1,25-dihydroxycholecalciferol) is active vitamin D and does not require metabolism to become active. It has a rapid onset of action (1-4 days) and a short half-life. Toxic effects would be expected to resolve in 2-7 days. This drug comes in capsules of 0.25 or 0.5 mcg. The dosage used is 20-30 ng/kg PO q 12 h.[51] Alfacalcidol is a formulation also commonly used. The hepatic 25-hydroxylation required before this drug becomes active occurs rapidly in a relatively unregulated fashion. There is no significant difference in the time required to reach maximal effect, as compared with calcitriol. The drug is available as 0.25, 0.5 and 1 mcg capsules and as a liquid (2 mcg/mL) at a dosage of 0.01-0.03 mcg/kg q 24 h. However, these *dosages have flexibility and must be titrated* up or down as needed by the individual animal.

Calcium

Vitamin D may be given with or without oral Ca supplementation. Three Ca options include Ca gluconate, Ca lactate, or Ca carbonate. These doses are calculated on the basis of **elemental** calcium in each preparation (25-50 mg/kg/day divided q 12 h or q 8 h), **not** on the mg tablet content. Thus, the dosages are the same once the elemental Ca content has been taken into account (e.g., 1 mg elemental Ca = 11.2 mg Ca gluconate, 7.7 mg Ca lactate, or 2.5 mg Ca carbonate). Often, (particularly when postoperative hypocalcemia has been severe and symptomatic), Ca supplementation is used for short-term patient stabilization. In the longer term, it is rarely necessary to use Ca supplementation because most pet foods contain more than adequate amounts of Ca. Vitamin D dosage is quite important, as it allows dietary Ca to be absorbed.

Emergency, Short-Term Treatment of Hypocalcemia

IV Ca supplementation may be required for dogs that become seriously hypocalcemic after treatment, either symptomatically or asymptomatically. The clinical signs of hypocalcemia are listed in Box 297-3 and are described in ch. 298. Dogs hospitalized and not being exercised or unduly stressed may be stable with Ca concentrations below the reference interval, but they are best supplemented and carefully monitored in an attempt to avoid a hypocalcemic crisis. When a hypocalcemic crisis is encountered, IV 10% Ca gluconate is the treatment of choice. Symptomatic (tetanic) dogs can be given 0.5-1.5 mL/kg, IV, slowly over 20-30 minutes until clinical signs have subsided and the dog is considered stable. Ideally, an ECG is used to monitor cardiac activity during infusion. Less sensitive pulse monitoring can be used if necessary. The IV Ca infusion should be stopped if ST segment elevation, QT shortening or arrhythmias develop.

Box 297-3

Signs of Hypocalcemia

Signs Associated with Neuromuscular Excitability

Muscle fasciculations or tremors
Face rubbing, biting the paws
Hypersensitivity to external stimuli
Stiff, stilted gait

Tetanic seizures
Respiratory arrest

Behavioral Changes

Agitation
Anxiety
Vocalization
Aggression

Other

Panting
Hyperthermia

Thereafter, a CRI of 10-15 mg/kg/h (10-15 mL/kg over 24 h) should be employed until oral therapy can be safely started. IV Ca can be a caustic vascular irritant leading to thrombophlebitis if the concentration of infused Ca is maintained at a high level for a protracted period (more than 1-2 days). IV catheters should be repeatedly inspected for patency and efficacy in an attempt to avoid extravasation of Ca-containing fluids outside the vein. This also can result in extensive tissue damage (Figure 297-9).

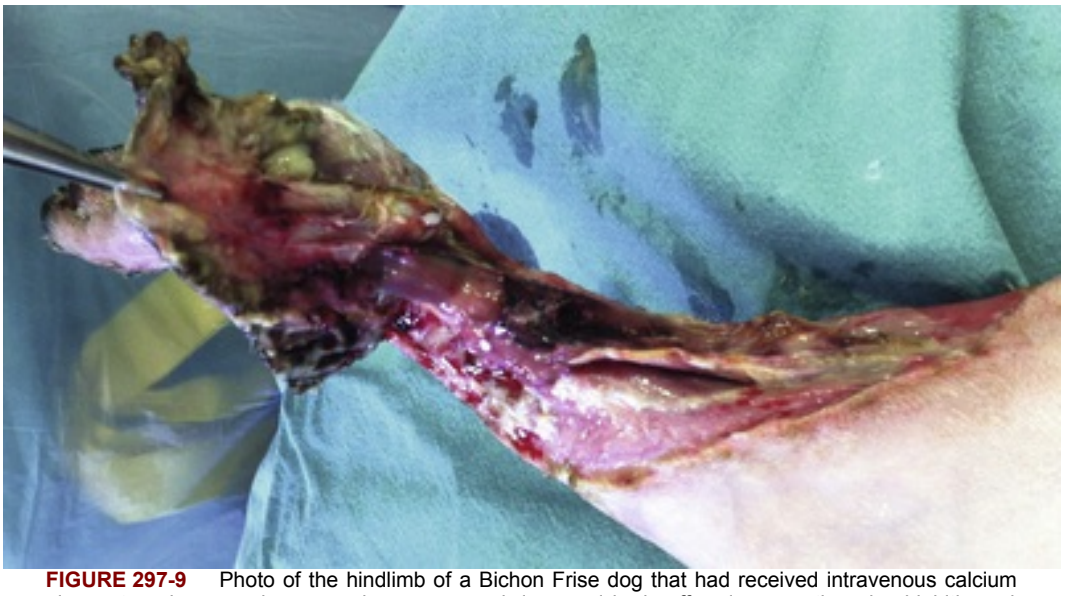


FIGURE 297-9 Photo of the hindlimb of a Bichon Frise dog that had received intravenous calcium gluconate using a saphenous vein over several days and had suffered severe thrombophlebitis and tissue sloughing as a consequence of the irritant effects of calcium. (Photo courtesy Christina Strand Thomsen and James Warland.)

There are varying opinions regarding use of SC Ca supplementation. Sterile abscess formation and skin sloughing have been reported in some dogs after Ca salts were administered SC.[13] However, some authors recommend Ca gluconate be so-administered, as it is much less likely to cause a problem. Although it is true that Ca gluconate may be given SC with no adverse effects, it can cause dramatic skin sloughing. For this reason, only IV and oral routes of administration are recommended (Table 297-3). When the pretreatment TCa concentration is >3.5 mmol/L (14 mg/dL) or the iCa >1.8 mmol/L and particularly when the increase in TCa or iCa is severe (>4.0 mmol/L, 16 mg/dL; >2.0 mmol/L), it is advisable to begin vitamin D supplementation 24-36 hours before treatment in order to slow the decrease in Ca after treatment and avoid severe hypocalcemia. This treatment is always something of a balancing act, as it is not advisable to exacerbate the pre-existing hypercalcemia. However, given the known delay in onset of activity of the vitamin D preparations, pretreatment for one day is not expected to be detrimental.

TABLE 297-3

Calcium and Vitamin D Drugs Available for Treating Hypocalcemia

	DRUG	DOSAGE	PRECAUTIONS
Acute	10% Calcium gluconate	0.5-1.5 mL/kg over 20-30 minutes	Monitor heart by auscultation, pulse palpation or ECG for bradycardia, shortened QT interval and ST segment elevation
	10% Calcium borogluconate	0.5-1 mL/kg over 20-30 minutes	
	10% Calcium chloride	0.16-0.5 mL/kg over 20-30 minutes	
Subacute	10% Calcium gluconate	10-15 mL/kg over 24 hours in 0.9% NaCl	Do not give subcutaneously
	10% Calcium borogluconate	6-9 mL/kg over 24 hours in 0.9% NaCl	
	10% Calcium chloride	3-5 mL/kg over 24 hours in 0.9% NaCl	
Chronic	Calcium carbonate Calcium gluconate Calcium lactate	25-50 mg/kg of *elemental* calcium*	Can be stopped once vitamin D dosage is appropriate
	Calcitriol	20-30 ng/kg/day PO divided twice a day	Time to maximum effect < 4 days
	Alfacalcidol	0.01-0.03 mcg/kg daily	Time to maximum effect < 4 days
	Dihydrotachysterol	0.02-0.03 mg/kg daily reducing to 0.01-0.02 mg/kg every 24-48 hours as required	Time to maximum effect < 7 days

*1 mg calcium = 11.2 mg calcium gluconate = 7.7 mg calcium lactate = 2.5 mg calcium carbonate.

ECG, Electrocardiogram.

Prognosis

The short- to mid-term (<2 years) prognosis for PHPT is excellent in all breeds. In all breeds except the Keeshond, the long-term prognosis also appears to be good. In Keeshonden, as in many human forms of PHPT, recurrence is a distinct possibility. This is not surprising in people, given the mechanisms of pathogenesis of the disease and the role of tumor suppressor genes in the evolution of hyperparathyroidism. When PHPT is managed surgically in humans, a subtotal parathyroidectomy is carried out, where only a small amount of parathyroid tissue remains *in situ* for ongoing calcium homeostasis. Keeshonden have a genetic drive to develop parathyroid adenomas, and after one has been removed more may follow if the dog lives long enough. Keeshonden that have had PHPT should be monitored throughout life for disease recurrence, particularly if first surgery was performed at a relatively young age (<9 years). An alternative approach would be to remove all but one parathyroid gland at the time of the first surgery in Keeshonden with inherited PHPT. In this author's experience, this can result in severe postoperative hypocalcaemia, which in some cases requires lifelong supplementary therapy to control. One Keeshond, first successfully treated at the age of 10 years, became hypercalcemic again at 11 and a half and had a second surgery. Although two parathyroid glands remained, this dog was never able to maintain a normal serum calcium concentration and received vitamin D until he died of other causes several years later. This variability in response to surgery and requirement for supplementary calcium makes successful perioperative disease management complex with the Keeshond, especially presenting many longer-term difficulties.

Primary Hyperparathyroidism in Cats

PHPT has been reported in a few middle-aged to older cats. Clinical signs described have included vomiting, PU/PD, weight loss and palpable cervical mass.[52] Although the abnormal parathyroid gland may not be palpable, similar to dogs, parathyroid disease is often associated with cystic structures that make the mass effect more noticeable. Since hyperthyroidism is a much more common cause for palpating a cervical mass in cats, this condition must be ruled out first. PU/PD may be more subtle in cats and urine specific gravity may

not be significantly altered unless the cat is suffering from concurrent renal insufficiency.[14] Cats, like dogs, may also suffer from calcium-containing urolithiasis.[53] The treatment of choice for PHPT in cats is removal of abnormal parathyroid tissue.[12] As in dogs, treatment success is greatly enhanced when US is used before surgery to identify the parathyroid mass or masses. Long-term prognosis is good postsurgery. Other treatment techniques have not been reported in cats. Treatment with Ca and vitamin D analogues may be necessary in cats due to the development of hypocalcemia after parathyroid gland removal. There is less information available in cats about when to prescribe calcium and vitamin D to pre-empt a postoperative hypocalcemic crisis, but the same principles apply that have been outlined for dogs. Again, it is difficult to predict which patients will need supplementation and for how long.

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CHAPTER 298

Hypoparathyroidism

Patty Lathan

Client Information Sheet: Hypoparathyroidism

Background

The parathyroid glands were first discovered in the Indian rhinoceros by Richard Owen in 1850. Ivar Sandstrom was the first to name and describe them in 1880 while Giuilo Vassale and Francesco Generali in 1900 reported that complete parathyroidectomy resulted in tetany.[1] Naturally occurring hypoparathyroidism was first described in dogs in 1966 and cats in 1990.[2,3] Idiopathic primary hypoparathyroidism remains an extremely uncommon disease in both dogs and cats.

Pathophysiology

Normal parathyroid physiology is presented in ch. 297. Loss of parathyroid hormone (PTH) or its activity results in hypocalcemia and hyperphosphatemia through a combination of mechanisms: decreased resorption of calcium (Ca; see ch. 69) from bone causing decreased release of Ca and phosphorus (PO_4) into the circulation, decreased absorption of Ca and PO_4 from the small intestine, and decreased reabsorption of Ca and decreased excretion of PO_4 via the renal tubules. Renal effects of PTH have the greatest impact on serum PO_4 concentration. Lack of PTH leads to hyperPO_4. In health, Ca stabilizes neuronal membranes by limiting sodium (Na) permeability and membrane depolarization. In hypoCa, however, both peripheral and central nervous system neurons become hyperexcitable, leading to the common signs of seizures, muscle tremors/fasciculations, and stiff gait (due to muscle pain and/or muscle tetany).

Etiology

Most severely hypoCa dogs and cats without a history of neck surgery or trauma are classified as having idiopathic primary hypoparathyroidism. However, an immune-mediated etiology is suspected in some since the parathyroid glands can be quite small on necropsy and their histology often reveals markedly decreased numbers of parenchymal cells, infiltration with lymphocytes and, to a lesser degree, plasma cells and neutrophils.[4-6] Resolution of hypoparathyroidism in one dog given immunosuppressive therapy supports an immune-mediated process as cause in some.[7]

Clinical Features in Dogs

Signalment

Dogs with primary hypoparathyroidism, at the time of diagnosis, have ranged in age from 6 weeks to 13 years (mean: about 6 years). Females, Miniature Schnauzers, Poodles, German Shepherd Dogs and Terriers are predisposed.[4,5,8,9] St. Bernards are overrepresented in Australia and New Zealand.[8,10]

Clinical Signs

Most clinical signs associated with hypoparathyroidism are related to neuromuscular "tetany" or "hyperexcitability." Seizures, muscle tremors, muscle fasciculations, and a stiff gait are reported in most dogs, and jaw "champing" is seen in about half of the dogs with fasciculations (Video 298-1).[4,8] Panting, facial

rubbing, biting at paws, and behavior changes (such as restlessness, anxiety, and aggression) are often identified on careful owner questioning. These signs may be explained either by muscle cramping and pain or a tingling sensation in the muscles.[4,8] On occasion, ataxia or circling is noted. Nonspecific signs include inappetence, vomiting, "weakness," lethargy, and diarrhea. The duration of clinical signs preceding diagnosis ranges from a few hours to a year or more (median: about 2 weeks).[4,8] Neuromuscular signs typically become more severe with time, are episodic, and are exacerbated by exercise or excitement. Virtually every clinical sign associated with hypoparathyroidism resolves with therapy.

Physical Examination

On physical examination dogs with primary hypoparathyroidism are often hyperthermic, tense, anxious, nervous, stiff-gaited and may growl or snap at being touched or palpated. For example, a tense abdomen may be due to pain in the abdominal muscles, pain elsewhere, or the dog may be anticipating pain because petting may have caused muscle cramping and pain in the past. Dogs may sometimes be aggressive or resist petting, particularly on the head. Thoracic auscultation reveals tachyarrhythmias in some dogs. Lenticular cataracts, appearing as small punctate to linear opacities in the anterior and posterior cortical subcapsular region, may be noted at initial presentation or following initiation of therapy (see ch. 11). The mechanism of cataract formation is unclear, but they do not appear to impair vision.[4,8,11]

Clinical Features in Cats

In contrast to dogs, male cats are overrepresented in those with primary hypoparathyroidism. The clinical signs in cats are similar to those in dogs, but cats are inappetent and lethargic more often. Lenticular cataracts and/or prolapse of the third eyelids are seen in some cats.[3,11-13] A cat with myocardial failure and echocardiographic findings consistent with dilated cardiomyopathy had resolution of cardiac changes after treatment for hypoparathyroidism.[14]

Diagnostic Evaluation in Dogs and Cats (Figure 298-1)

Serum Biochemistry, Complete Blood Count (CBC), Urinalysis (UA), Electrocardiogram (ECG)

At diagnosis, hypoCa is present in all pets with hypoparathyroidism and almost all are hyperPO_4. Repeating the serum total Ca (tCa) is recommended in pets with severe hypoCa, simply because the condition is uncommon but especially if clinical signs are not consistent. Using blood from an EDTA ("purple top") tube or even contaminating the needle with EDTA prior to injecting blood into another tube can artificially decrease Ca due to its binding by EDTA. Since ionized Ca (iCa) is biologically active, its measurement may provide a more accurate representation of the severity of hypoCa. In hypopara, the decreases in tCa and iCa tend to be similar in severity. In the absence of hypoalbuminemia, if measurement of iCa is not possible, repeatedly demonstrating low tCa concentrations in a patient with compatible clinical signs is generally adequate to confirm hypocalcemia. Clinical signs of hypoCa are not usually observed until the tCa concentration is <7 mg/dL or the iCa concentration <0.8 mmol/L. Signs may occur at higher values in acute hypoCa. Patients with hypoparathyroidism may have profoundly decreased tCa concentrations (as low as 2.7 mg/dL).[4,8] Since some dogs and cats do not exhibit clinical signs, it is assumed that their disease has progressed so chronically that there has been some physiologic adaptation.[11]

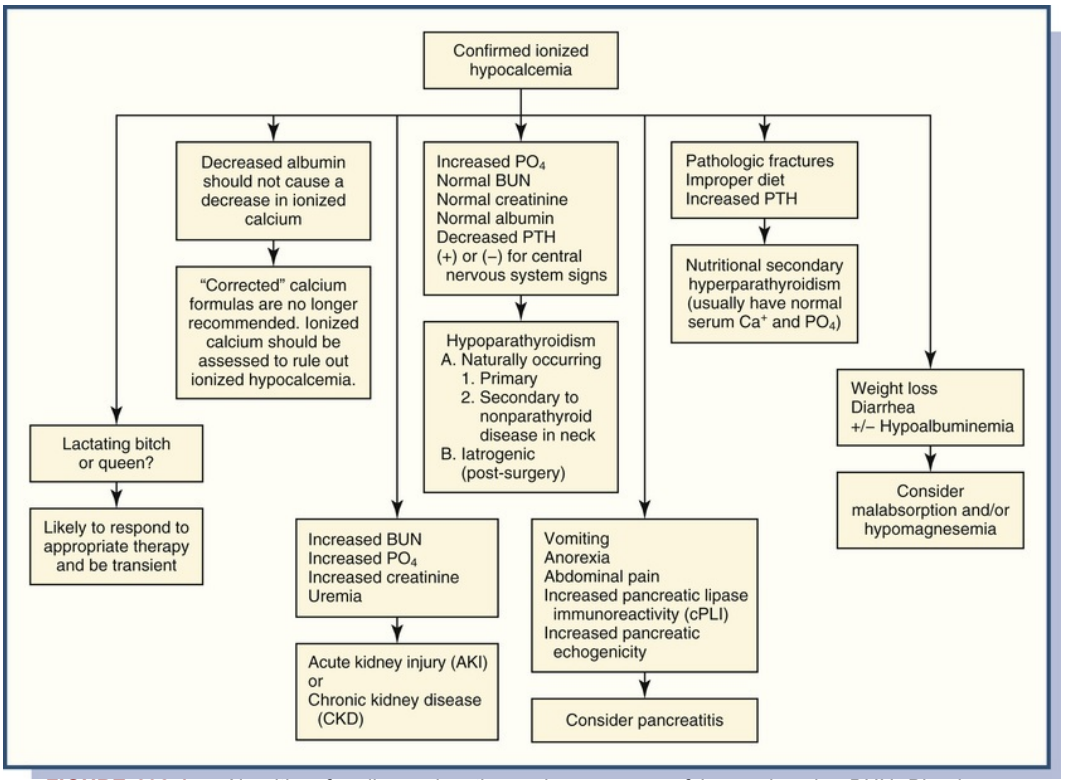

FIGURE 298-1 Algorithm for diagnosing the various causes of hypocalcemia. *BUN,* Blood urea nitrogen; *PTH,* parathyroid hormone. (From Feldman EC, Nelson RW, Reusch CE, et al: *Canine and feline endocrinology,* ed 4, St Louis, 2015, Saunders.)

Hypomagnesemia (Mg; see ch. 68) has been documented in Yorkshire Terriers with concurrent hypoCa and protein-losing enteropathy. The low Mg concentrations may contribute to decreased PTH secretion.[15] However, Mg concentrations are normal in most dogs with primary hypoparathyroidism and only mildly to moderately decreased in a few. Since these dogs recover without Mg supplementation, the significance of this finding is unknown.[4,11] The balance of serum biochemistries, CBC, and UA is unremarkable in pets with primary hypoparathyroidism. Increased creatine kinase activity has been reported in a cat and dog and would be expected in any animal with excess muscle activity.[14,16] HypoCa causes prolonged duration of ECG cardiac action potentials, resulting in S-T segment, and subsequent QT-interval, prolongation (see ch. 248).[8]

Parathyroid Hormone

Diagnosis of primary hypoparathyroidism requires the documentation of low Ca concentrations with inappropriately low PTH concentrations. Due to tight Ca regulation, PTH concentrations should be increased above the reference range in healthy animals with hypoCa. Thus, serum PTH concentrations in dogs and cats with primary hypoparathyroidism may be low or in the low end of the reference range.

Differential Diagnoses

The differential diagnosis of hypoCa includes a few common conditions and a variety of uncommon causes. The parathyroid-related conditions include primary gland concerns, such as immune-mediated destruction, idiopathic destruction, surgical removal, and rare conditions in people not yet reported in dogs or cats (see ch. 69). Conditions uncommonly associated with hypoCa are hypomagnesemia, acute kidney injury (AKI), chronic kidney disease (CKD), pancreatitis, diabetes mellitus, eclampsia, malabsorption syndromes, urinary tract obstruction, and use of phosphate-containing enemas. Hypoalbuminemia causes nonworrisome decreases in tCa but not iCa because of albumin binding. Other miscellaneous causes have been seen (see ch. 69).

Therapy

Acute Treatment

Intense IV

Dogs with severe hypoCa should be treated initially with an IV bolus of Ca gluconate and maintained using a constant rate infusion (CRI) of Ca gluconate (usually in the IV fluids) (see ch. 146). Oral Ca supplementation is also provided until calcitriol (1,25-dihydroxycholecalciferol; 1-25-dihydroxyvitamin D_3; active vitamin D_3) takes effect for long-term management. Initially, a tetanic dog or cat should be given the IV 10% Ca gluconate, 0.5-1.5 mL/kg (5-15 mg/kg) slowly, over 10-15 minutes. Note that 10% Ca gluconate contains 9.3 mg Ca/mL. The ECG should be monitored during infusion and the infusion discontinued if bradycardia, premature ventricular contractions, or shortening of the Q-T intervals are seen. Once the ECG normalizes, infusion can begin again, but at a slower rate. Ca chloride should not be used in dogs and cats since it is extremely caustic and can cause tissue sloughing if extravasated (see next section on SC calcium administration). Following initial Ca gluconate bolus, the serum tCa or iCa concentration should be rechecked. Clinical signs in most pets improve significantly, well before the Ca concentrations normalize.

After stabilization, Ca gluconate should be added to any maintenance IV fluids and given at 2.5-3.5 mg/kg/h (0.3-0.4 mL/kg/h), remembering that there is 9.3 mg/mL of Ca/mL.[17] Repeated boluses are only recommended for acute signs of tetany. Ca concentrations should be checked once to twice daily for the first few days and infusion rates adjusted accordingly. Following oral supplementation of Ca and vitamin D (calcitriol) and stabilization of serum Ca concentrations, the pet can be weaned off calcium.

Subcutaneous (SC) Conservative Therapy

SC Ca gluconate therapy has been used as an alternative to CRI. While uncommon, SC Ca can cause significant morbidity due to tissue damage (resulting in death in one dog) and is no longer recommended. If for any reason a CRI is not possible, the owners should be counseled on the potential complications of SC Ca administration. Calcinosis cutis has been reported in two dogs and a cat after each received SC Ca gluconate.[8,16,18] One protocol for SC therapy involves giving the same dose SC as was given in the initial IV bolus, diluted 1 part Ca gluconate to 1 part crystalloid, q 6-8 h. Frequency and dosage are decreased as oral Ca and calcitriol begin to take effect.[17]

Chronic Treatment

Background

In primary hypoparathyroidism, Ca cannot be obtained from the skeleton or diet without PTH or vitamin D, nor is it reabsorbed by the kidneys. Since PTH is not commercially available, oral vitamin D analogues are cornerstones in the long-term treatment of hypoparathyroidism. Supplementation with oral Ca may be used early in therapy and can usually be discontinued after a few weeks if the dog or cat is eating well, because dietary Ca should be sufficient for daily needs. Currently available options for vitamin D supplementation include calcitriol and ergocalciferol (vitamin D_2). Dihydrotachysterol, a synthetic vitamin D analogue, is no longer commercially available.

Calcitriol

Calcitriol is the active form of vitamin D_3 with a much shorter time to maximal effect (1-4 days) and less time required to resolve toxicosis (1-7 days) than ergocalciferol (5-21 days and 1-18 weeks, respectively). Thus, calcitriol is preferred over ergocalciferol, unless financial limitations preclude its use (see ch. 297 for alternatives to calcitriol).[11] Initial dose of calcitriol (20-40 ng/kg/day; 0.02-0.04 mcg/kg/day) is usually given for 2 to 4 days and then decreased to 10-20 ng/kg/day (0.01-0.02 mcg/kg/day). Dosing calcitriol using commercially available formulations can be challenging since gel capsules only come in limited sizes (0.25 microgram and 0.5 microgram, Rocaltrol), which are not convenient for use in dogs and cats. Based on clinical observation, compounded formulations have not provided consistent products. Thus, for each patient, the product should be purchased from the same experienced compounding pharmacy each time and should not be used past the marked expiration date.

Ergocalciferol

The initial dosage of ergocalciferol is 4000-6000 U/kg/day. Once serum Ca concentrations stabilize between 8 and 9.5 mg/dL, the dose can usually be decreased to every other day. From that point, the patient should

determine frequency need via monitoring. Ca concentrations should then be monitored weekly and the dose adjusted as necessary.[11]

Oral Calcium

Oral Ca supplementation should also be provided initially but can usually be tapered and discontinued within a week of starting calcitriol. The starting dosage in cats is 0.5-1 g/day, divided. In dogs, 1-4 g/day is given, divided. Ca gluconate and lactate can be used, but Ca carbonate is most frequently chosen due to its availability. It is important to dose based on the amount of elemental Ca. Ca carbonate, gluconate, and lactate are 40%, 9%, and 13% elemental Ca, respectively (1 g of Ca carbonate contains 400 mg elemental Ca).[19]

Treatment Goals

The goal is to maintain serum Ca concentrations just below the low end of the reference range (about 8-9.5 mg/dL). This is high enough to prevent clinical signs of hypocalcemia, decreases degree of calciuresis due to the lack of PTH, and is low enough to prevent vitamin D toxicosis: hyperCa, hyperPO_4, and AKI. As soon as serum Ca concentrations increase to 7.5-8 mg/dL on oral vitamin D and Ca and the patient is eating and drinking well, they are returned to the owner. Rechecks initially should be every 2 to 3 days. As serum Ca concentrations stabilize, recheck intervals can be progressively prolonged, up to once every 2 to 3 months. Owners should be instructed to return if any signs of hypoCa or hyperCa occur. HyperCa should be treated by discontinuing vitamin D administration until it normalizes; additional therapy, including IV fluids and furosemide, is infrequently necessary.

Prognosis

Hypoparathyroid dogs and cats with dedicated and capable owners have an excellent prognosis. Owners must be reminded that this disease requires life-long therapy and frequent monitoring to help prevent hypocalcemia or hypercalcemia. Most dogs and cats die of causes unrelated to hypoparathyroidism if appropriate therapy is pursued.[4,8,11]

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CHAPTER 299

Canine Hypothyroidism

Carmel T. Mooney

Client Information Sheet: Canine Hypothyroidism

Introduction

Hypothyroidism is the most common thyroid disease and one of the most common endocrine disorders in dogs. Its prevalence has been estimated between 0.2 and 0.8%.[1-3] A survey of insured dogs from Sweden, however, suggested a lower prevalence of 0.07%.[4] This may be a more accurate reflection as it is not biased towards a referral population and includes a large number of pedigree animals more likely to suffer from hypothyroidism.[5]

Physiology

The thyroid gland of dogs consists of two separate lobes, one on either side of the trachea. Each lobe is composed of microscopic follicles lined by a single layer of thyroid epithelium. The lumen of each follicle contains colloid, a storage substance for thyroglobulin secreted by follicular cells. Thyroglobulin is a large glycoprotein containing iodotyrosines, components of thyroid hormones. Most of the steps involved in thyroid hormone synthesis are catalyzed by the enzyme thyroid peroxidase (TPO).

The primary function of the thyroid gland is to produce the active thyroid hormones, 3,5,3′,5′-L-tetraiodothyronine (thyroxine, T_4) and 3,5,3′-L-triiodothyronine (triiodothyronine, T_3; Figure 299-1). Almost all these hormones are protein-bound in the circulation. Approximately 60% of T_4 is bound to thyroxine binding globulin, 17% to transthyretin, 12% to albumin and 11% to various lipoprotein fractions.[6] T_3 binding is similar. Binding affinities for thyroid hormones are lower in dogs than humans and, consequently, canine total concentrations are lower, free fractions higher (estimated at approximately 0.1-0.3% for T_4 and 1% for T_3), and serum half-lives shorter (10-16 h for T_4 and 5-6 h for T_3). Only the free fraction is metabolically active with the protein bound moiety serving as a passive reservoir to buffer hormone delivery to tissues. T_3 is approximately three to five times more potent than T_4. Up to 60% of T_3 is produced not by the thyroid gland but by peripheral outer ring monodeiodination of T_4, a step that may be autoregulated. Inner ring deiodination results in formation of metabolically inactive reverse T_3 (rT_3).

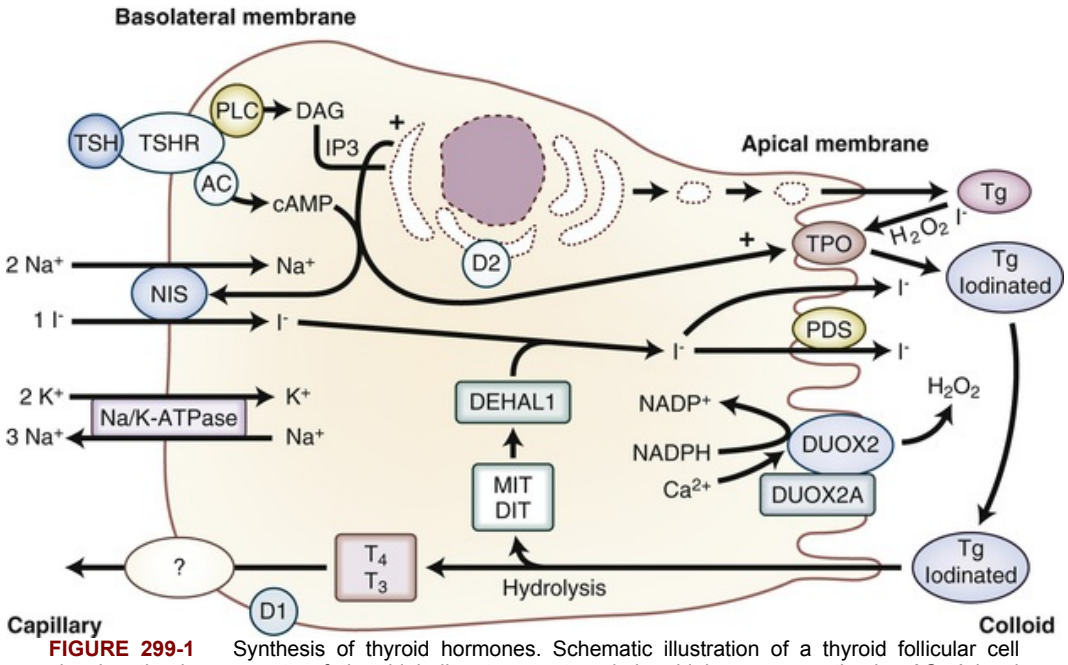

FIGURE 299-1 Synthesis of thyroid hormones. Schematic illustration of a thyroid follicular cell showing the key aspects of thyroid iodine transport and thyroid hormone synthesis. *AC,* Adenyl cyclase; *ATPase,* adenosine triphosphatase; *cAMP,* cyclic adenosine monophosphate; *D1,* thyroidal deiodinase type 1; *D2,* thyroidal deiodinase type 2; *DAG,* diacylglycerol; *DEHAL1,* iodotyrosine dehalogenase 1 (1YD); *DIT,* diiodotyrosine; *DUOX,* dual oxidase; *IP3,* inositol triphosphate; *MIT,* monoiodotyrosine; *NADP,* oxidized form of nicotinamide adenosine dinucleotide phosphate; *NADPH,* reduced nicotinamide adenosine dinucleotide phosphate; *NIS,* sodium-iodide symporter; *PDS,* pendrin (SLC26A4); *PLC,* phospholipase C; T_3, triiodothyronine; T_4, thyroxine; *Tg,* thyroglobulin; *TPO,* thyroid peroxidase; *TSHR,* thyrotropin receptor. (From Salvatore D, Davies TF, Schlumberger MJ, et al: Thyroid physiology and diagnostic evaluation of patients with thyroid disorders. In Melmed S, Polonsky KS, Larsen PR, et al, editors: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Elsevier, pp 327-361.)

Thyroid hormones affect most body tissues largely by interaction with specific nuclear receptors to modify the expression of a diverse array of genes. Thyroid hormones therefore influence multiple metabolic processes from regulation of mitochondrial oxygen demand to control of protein synthesis. Some effects can be demonstrated within minutes to hours but others may require weeks to months. Thyroid hormone production is controlled principally by negative feedback (Figure 299-2). The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates specific anterior pituitary cells to promote synthesis and secretion of thyrotropin (thyroid-stimulating hormone; TSH). TSH promotes iodide trapping by the thyroid, as well as the synthesis and release of thyroid hormones.

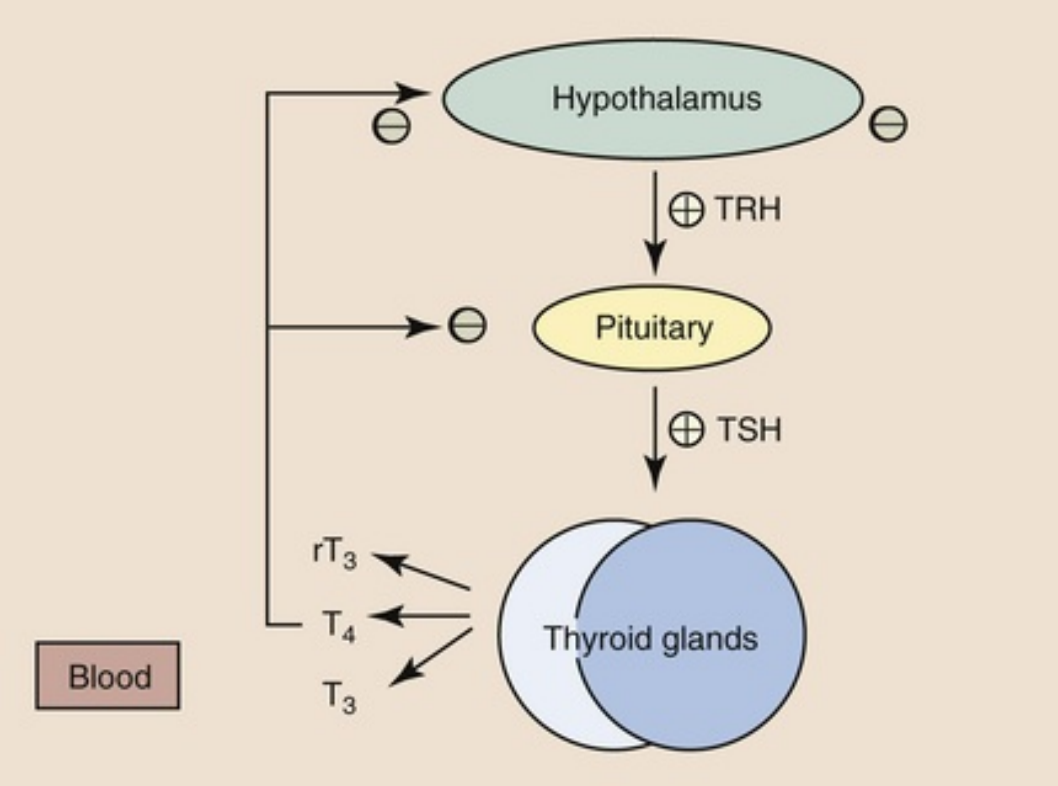

FIGURE 299-2 Regulation of thyroid hormone concentrations. Thyroid hormone concentrations are controlled by the hypothalamic-pituitary-thyroid axis, which operates as a negative feedback loop. Thyrotropin (TSH) causes synthesis and release of T_4 and lesser amounts of T_3 from the thyroid gland. Intracellular T_3, derived from deiodination of T_4 within the pituitary gland, causes decreased TSH synthesis and secretion and is the main determinant of TSH concentration. Thyrotropin-releasing hormone (TRH), secreted by the hypothalamus, modulates TSH release from the pituitary gland. Increased thyroid hormone concentrations are also believed to decrease TRH synthesis and secretion. Hormones that inhibit TSH secretion include dopamine, somatostatin, serotonin, and glucocorticoids. TRH, prostaglandins, and alpha-adrenergic agonists increase TSH secretion. (From Scott-Moncrieff CR: Hypothyroidism. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine,* ed 7, St Louis, 2010, Elsevier, pp 1751-1761.)

The presence of excess circulating free T_4 (FT_4) and T_3 produces negative feedback to the hypothalamus and anterior pituitary, decreasing TRH and TSH synthesis and release and, subsequently, thyroid hormone production. Thyroid hormones have a major influence on metabolic rate, growth, central nervous system (CNS) development, and tissue turnover. Thyroid hormones have positive inotropic and chronotropic effects on the heart, are necessary for cholesterol synthesis and metabolism, and are capable of stimulating erythropoiesis. When deficient, the spectrum of possible abnormalities is extensive.

Pathogenesis of Hypothyroidism

Overview

Hypothyroidism results from decreased production of T_4 and T_3. It can arise because of an abnormality in any step of the hypothalamic-pituitary-thyroid axis. It is referred to as primary or central (including secondary and tertiary) depending on whether the underlying lesion lies within the thyroid gland (primary), pituitary gland (secondary) or hypothalamus (tertiary). It is also described as congenital or acquired depending on the age at which it develops.

Congenital Hypothyroidism

Congenital hypothyroidism is significantly less common than acquired. It results from thyroid hypoplasia or aplasia, dysgenesis or dyshormonogenesis. Congenital hypothyroidism may be more prevalent than currently appreciated because some are undiagnosed and others die at birth or shortly thereafter. Central hypothyroidism (resulting from TSH or TRH deficiency) has been reported sporadically and in one family of

Giant Schnauzers.[7-11] TSH deficiency is common in pituitary dwarfism, and dogs with thyroid dysgenesis have been noted.[12-14] Congenital hypothyroidism with goiter, as a result of dyshormonogenesis and TPO deficiency, has been reported sporadically and as a fully penetrant autosomal recessive disorder in Toy Fox and Rat Terriers for whom genetic tests are available.[15-17] Different mutations with a similar phenotype have been reported in Tenterfield Terriers, Spanish Water Dogs and Papillons.[18-20] Congenital hypothyroidism may develop in pups born to dams fed an iodine-deficient diet, dams given various drugs, or pups exposed to iodine deficiency or excesses when young.[21-23]

Acquired Hypothyroidism

Central

Central disease (TRH or TSH deficiency) is rare, accounting for <5% of hypothyroid dogs. Pituitary neoplasia and surgical hypophysectomy account for the vast majority of reported cases, with posttraumatic deficiencies less common.[24-26] One dog with tertiary hypothyroidism related to neoplasia has been reported, but this is so uncommon that clinical indications for differentiating secondary from tertiary disease appear limited.[27] Secondary hypothyroidism is a potential, uncommon and reversible condition due to glucocorticoid excess.[28,29] Central hypothyroidism results in thyroid atrophic degeneration, characterized by follicles distended with colloid and flattened surrounding epithelium, changes quite different from those associated with primary thyroid disease.[11]

Primary

Acquired primary thyroid disease accounts for the overwhelming majority of dogs with hypothyroidism. Histologically, lymphocytic thyroiditis and thyroid atrophy are equally common. Lymphocytic thyroiditis is a destructive autoimmune process characterized by multifocal or diffuse infiltration of the thyroid gland by lymphocytes, macrophages and plasma cells and progressive replacement by fibrous connective tissue.[30,31] It is associated with systemic inflammation and a dominant cellular immune response.[32] By contrast, idiopathic atrophy is described as a degenerative process with minimal inflammatory change and gradual replacement of thyroid tissue by adipose and connective tissue.[30] Some believe that idiopathic atrophy is the end stage of lymphocytic thyroiditis and associated with similar markers of inflammation.[32] Regardless, the inciting cause for these conditions is unclear.

Thyroid biopsy is required for definitive diagnosis of lymphocytic thyroiditis, but its existence can be inferred by demonstration of circulating autoantibodies to thyroid antigens such as thyroglobulin, T_4, T_3 and thyroid peroxidase. Thyroglobulin autoantibodies (TgAAs) are most common, while the others rarely occur in isolation.[33-35] TgAA assays, widely available, have excellent diagnostic sensitivity and specificity.[36-38] Approximately 50% of hypothyroid dogs have circulating TgAAs, corresponding to the frequency of lymphocytic thyroiditis.[35,39-44] Lymphocytic thyroiditis is slowly progressive, causing signs of hypothyroidism after about 75% of the gland has been destroyed. Its progression can be divided into four stages (Table 299-1). The rate of progression through these stages is variable, and not all dogs develop functional hypothyroidism. Approximately 20% of TgAA-positive euthyroid dogs develop hormonal evidence of thyroid dysfunction within a year of testing, but only 5% become clinically hypothyroid.[45] Most dogs remain TgAA positive and asymptomatic, while a small number later test negative without evidence of thyroid dysfunction. Some TgAA-positive hypothyroid dogs later become TgAA negative, supporting the concept that thyroid atrophy represents an end stage of lymphocytic thyroiditis. Theoretically, the complete destruction of all thyroid tissue leads to a reduction in immune stimulation, absence of histologic thyroiditis, and conversion to autoantibody negativity. Histopathologic progression from lymphocytic thyroiditis to follicular atrophy has been described.[46] Moreover, TgAA-positive euthyroid dogs (silent/subclinical thyroiditis) are younger than both TgAA-positive dogs with hypothyroidism and TgAA-negative hypothyroid dogs.[42] The proportion of hypothyroid dogs that are TgAA-positive or -negative varies from breed to breed, reflecting different rates of disease progression or different susceptibilities.

TABLE 299-1

The Progressive Stages of Lymphocytic Thyroiditis

	THYROID TISSUE HISTOPATHOLOGY	TgAA STATUS	THYROID HORMONE CONCENTRATIONS	
			TSH	T_4/T_3
Silent	Majority normal, mild infiltration	Positive	Normal	Normal
Subclinical	More marked infiltration	Positive	Increased	Normal
Clinical	>75% replaced	Positive	Increased	Decreased
	Minimal thyroid tissue, limited inflammation	Negative	Increased or decreased	Decreased

TgAA, Thyroglobulin autoantibody; *TSH*, thyroid stimulating hormone (thyrotropin); T_4, thyroxine; T_3, triiodothyronine.

This classification system is largely based on studies indirectly assessing lymphocytic thyroiditis by measurement of circulating thyroglobulin autoantibody status.

From Mooney CT: Canine hypothyroidism. A review of the aetiology and diagnosis. *N Z Vet J* 59:105-114, 2011.

Reported breed predispositions, together with the familial nature of hypothyroidism in purebred dogs, are consistent with a strong hereditary component to the condition.[47] Some breeds have a high prevalence of TgAA positivity and a significantly increased risk for developing hypothyroidism. These breeds include but are not confined to the English Setter, Golden Retriever, Rhodesian Ridgeback, Cocker Spaniel and Boxer.[42] Familial hypothyroidism is also recognized in Great Danes, Beagles and Borzoi colonies, and, in Sweden, Hovawarts and Giant Schnauzers.[40,46,48,49] Several genetic and environmental risk factors have been recognized for development of autoimmune thyroid disease in people, but similar observations are less clear in dogs. In dogs, specific major histocompatibility (MHC) dog leukocyte antigen (DLA) haplotypes and alleles confer an increased susceptibility for hypothyroidism in a number of breeds: Doberman Pinscher, Rhodesian Ridgeback, English Setter and Giant Schnauzer.[50-53] Anecdotally, a link between intensive vaccination protocols and development of autoimmune disease in general and thyroiditis in particular has been suggested but not supported in studies of thyroiditis in Beagles.[54] Season of the year (summer versus fall) and geography (different states within the USA) may influence prevalence via unknown mechanisms.[42]

Clinical Observations

Signalment

Hypothyroidism can occur in dogs of any breed but typically affects the purebred animals listed. The mean age at diagnosis is approximately 7 years and ranges from 0.5 to 15 years. It is an uncommon diagnosis in dogs less than 2 years of age. Breeds predisposed to lymphocytic thyroiditis tend to develop hypothyroidism at an earlier age. Intact males and neutered females may be at increased risk for becoming hypothyroid.[1-3]

Clinical Signs

General Features

Hypothyroidism causes a variety of clinical signs (Table 299-2). The onset of hypothyroidism is insidious, and since there are no pathognomonic features, hypothyroidism is included as a differential for both common and uncommon problems. The most common clinical signs relate to metabolic and dermatological abnormalities that occur concurrently in about 70% of affected dogs. Often the dermatological features are most prominent and worrisome for owners. Less commonly, cardiovascular, neuromuscular, reproductive, ophthalmic, and/or gastrointestinal signs are described.

TABLE 299-2

Clinical Abnormalities Associated with Hypothyroidism

Metabolic signs	Lethargy
	Obesity or weight gain
	Exercise intolerance
	Cold intolerance

Dermatological abnormalities	Alopecia
	Dry/poor-quality coat
	Skin hyperpigmentation
	Pyoderma
	Seborrhea
Others	Various neuropathies, central vestibular disease, myxedema coma, subclinical myopathy, lipid corneal dystrophy, bradycardia, disproportionate dwarfism, decreased fertility, parturient problems, decreased tear production

Metabolic Features

A decline in metabolic rate is typical.[55] Associated clinical signs, noted in about 80% of dogs, include lethargy, weight gain, exercise intolerance, mental dullness, cold intolerance, generalized weakness and shivering.[1,2] Although 40 to 50% of affected dogs are overweight or obese, hypothyroidism is the cause in only a minority of obese dogs.

Dermatological Features

Thyroid hormones play an important role in the maintenance of hair growth, and in humoral, and cellular immune responses. Dermatological abnormalities occur in up to 80% of hypothyroid dogs and can be extensive.[1,2,56] Changes include hair thinning, dry coarse hair coat, alopecia that usually involves the flanks and thighs, and failure to regrow hair after clipping. Hypothyroidism is classically associated with an "endocrine alopecia" that is non-pruritic, bilaterally symmetrical, and a tendency to spare the head and extremities. Alopecia is often noted in areas of friction. These include the neck in dogs that wear collars, the lateral extremities in large dogs, and the tail, resulting in the so-called "rat-tail" of hypothyroidism. Focal, multifocal and asymmetric alopecia can occur. While alopecia involving the nasal planum is thought to be highly associated with hypothyroidism, it is nonspecific. In a few dogs, retention of the coat occurs and it becomes dull and often lighter in color because of environmental bleaching. Other signs of hypothyroidism include dry scaly skin, seborrhea, otitis, hyperpigmentation, and secondary bacterial infections (although pyoderma is reported in <10% of affected dogs). *Malassezia* has also been reported. Pruritus may be present if infection or pyoderma occurs. Hypothyroidism may be suspected particularly after standard treatment is ineffective.

In people, hypothyroidism is associated with accumulation of hyaluronic acid in the dermis (myxedema) resulting in a non-pitting puffy appearance to the skin that is pale and cool to the touch. Myxedema also occurs in dogs, is most noticeable over the head, and gives rise to the "tragic facial expression" caused by thickened lips, thickened skin over the forehead, and drooping of the eyelids. Rarely, mucinous vesiculation may develop.[57] Common histologic changes associated with hypothyroidism are also observed in other endocrine disorders, including a predominance of hairs in telogen and hairless telogen follicles (kenogen follicles).[58,59] While hyperpigmentation, atrophic and dystrophic follicles are also described, they are less common as compared with other endocrine disorders. A thickened dermis and vacuolated erector pili muscles are considered more specific for hypothyroidism.[59] Dermatitis with secondary infection may obscure these findings.

Cardiovascular Features

Thyroid hormones have a direct positive inotropic effect, which stimulates myocardial function and increases responsiveness to adrenergic stimulation. Theoretically, hypothyroidism could significantly impair cardiac function but does so rarely. In reports on large numbers of hypothyroid dogs, cardiac abnormalities are rarely recorded apart from dogs (about 15%) with asymptomatic bradycardia.[1,2] On the electrocardiogram, hypothyroidism is associated with low-voltage R waves, inverted T waves, sinus bradycardia and occasionally first- or more rarely second-degree atrioventricular block.[60,61] Hypothyroidism is a possible cause for bradydysrhythmias, particularly if other consistent clinical signs are present.

Echocardiographically, hypothyroidism is associated with a reversible decrease in fractional shortening and a mild increase in left ventricular end systolic diameter, suggestive of reduced myocardial function. There are a few case reports of congestive heart failure and myocardial dysfunction with atrial fibrillation partially or fully responsive to appropriate cardiac and/or thyroid hormone supplementation.[62-64] However, it is unclear

whether hypothyroidism was causative, coincidental or capable of exacerbating an underlying subclinical cardiomyopathy. Larger studies have focused on breed-specific dilated cardiomyopathies. The prevalence of hypothyroidism is no higher in Dobermans with dilated cardiomyopathy (with or without congestive heart failure) compared with those with non-cardiac disease.[65] A causal relationship between hypothyroidism and dilated cardiomyopathy may exist, as not all dogs in the non-cardiac group underwent echocardiography. Some may have had subclinical disease. Another study failed to demonstrate an association between hypothyroidism and dilated cardiomyopathy in Dobermans, but there is increased risk of hypothyroidism in Dobermans with dilated cardiomyopathy.[66] These results may reflect independent predispositions for the conditions or a common pathway in their pathogenesis.

In humans, atherosclerosis is a known complication of the hypercholesterolemia and lipid abnormalities induced by hypothyroidism. Atherosclerosis is rare in dogs, presumably because of differences in their lipoprotein composition and metabolism (see ch. 182). Of the limited number of postmortem cases reported, hypothyroidism, like diabetes mellitus, appears to be common.[67,68] Cholesterol concentrations are consistently highest in dogs that develop atherosclerosis, but specific patterns of hyperlipidemia have not yet been elucidated. The clinical consequences of atherosclerosis are unclear but may affect the cardiovascular and neurological systems. There are a few reports of aortic thromboembolism and severe atherosclerosis associated with hypothyroidism.[62,69] A cholesterol-based pericardial effusion has been described in a hypothyroid dog.[70]

Neuromuscular Features

Various neurological disorders have been associated with hypothyroidism, from dysfunction of single or multiple cranial nerves, to generalized peripheral neuropathies, and CNS disease. Although hypothyroidism can interfere with neurologic function through accumulation of mucopolysaccharides, impaired axonal transport, or atherosclerosis, there is limited evidence of a direct causal effect. Reports of Horner's syndrome, facial nerve paralysis and laryngeal paralysis caused by hypothyroidism are unreliable due to questions concerning diagnosis.[71-73] Facial nerve paralysis, laryngeal paralysis, megaesophagus, peripheral vestibular disease and lower motor neuron dysfunction (generalized weakness, proprioceptive deficits, diminished segmental reflexes with potential progression to paraparesis or tetraparesis) have all been described in hypothyroid dogs.[1,2,74,75] Thyroid hormone-responsive cricopharyngeal achalasia has been described.[76]

Although experimental induction of hypothyroidism does not accurately reflect the insidious course of the naturally occurring disease, neurological dysfunction is rare after radioactive iodine thyroid ablation.[77] In hypothyroid dogs, a concurrent disorder may be responsible for the neurological signs. In others, response to thyroid hormone supplementation is difficult to assess either because other treatments may have been employed or because spontaneous resolution of the neurologic condition may have occurred. While a reasonable response to thyroid hormone supplementation is expected in hypothyroid-induced neurological dysfunction, only a minority of dogs with megaesophagus exhibits discernible clinical or radiographic response.[74,78] Indeed, hypothyroidism is not a significant risk factor for developing megaesophagus.[79] Similarly, myasthenia gravis has been associated with hypothyroidism but may represent a concurrent immune-mediated disease.[2,80,81]

Reports of CNS disease in hypothyroidism are less common but perhaps less tenuous. Central vestibular dysfunction is a rare but reversible complication, even if other signs of hypothyroidism are absent.[82,83] Potential mechanisms include atherosclerotic vascular disease causing brain infarction and/or metabolic derangements directly due to thyroid hormone deficiency. CNS atherosclerosis has been described in one dog and suspected in Labrador Retrievers with neurological disease and severe hyperlipidemia.[84,85] Hypothyroidism has also been associated with myxedema coma, a life-threatening sequela characterized by profound mental dullness, stupor, weakness, hypothermia (often without shivering), hypoventilation, bradycardia and hypotension.[86-88] In many, there is evidence of precipitating factors: surgery, cardiac failure, drug therapies or overwhelming sepsis. Seizures have been described in a hypothyroid dog with atherosclerosis, but hypothyroidism has only been diagnosed in about 3% of dogs with metabolic or toxin-associated seizures.[89,90]

Perhaps the most controversial association between hypothyroidism and the nervous system relates to behavior (see ch. 9). There is little evidence to support the suggestion that hypothyroidism causes aggressive behavior. The few case reports of dominance- and fear-related aggression in hypothyroid dogs were usually longstanding behaviors that did not entirely resolve with thyroid hormone supplementation.[91-93] The

prevalence of hypothyroidism in dogs with behavior problems is low and no greater than in dogs without such problems.[94,95]

It can be difficult to distinguish clinical signs due to neuropathies (see ch. 268) from those due to myopathies (see ch. 354). Myopathies due to hypothyroidism may cause gait abnormalities, weakness and exercise intolerance (see ch. 31). Experimentally, hypothyroidism could cause exercise-induced hyperkalemia that may contribute to decreased performance and endurance.[96] In situations in which experimental hypothyroidism did not cause neuropathy, it did result in subclinical, biochemical, electrophysiologic and morphologic evidence of myopathy.[97] Histologically, myopathies are usually characterized by nemaline rod inclusions, an increase in type I myofibers, a decrease in type II fibers, abnormal mitochondria and myofiber degeneration with substantial depletion of skeletal muscle free carnitine.[97] Nemaline rod myopathy has been associated with clinical signs, including cardiac involvement in two dogs.[98,99]

Ophthalmic Features (see ch. 11)

Hypothyroidism, via hyperlipidemia, can result in arcus lipoides. Although not common, it has been well described, particularly in German Shepherd Dogs.[100] Association between keratoconjunctivitis sicca and hypothyroidism is speculative. In experimental hypothyroidism, the Schirmer tear test, intraocular pressure measurements and ophthalmoscopy remained unchanged for as many as 17 weeks. No histologic abnormalities were noted after necropsy.[101] Reduced tear production has been reported in hypothyroid dogs that could exacerbate other underlying ocular pathology.[102]

Reproductive Features

Various reproductive abnormalities have been ascribed to hypothyroidism. Short-term (median 19 weeks) experimental induction of hypothyroidism in bitches resulted in prolonged parturition and reduced pup survival without affecting the interestrus interval, fertility, litter size or gestation length.[103] More chronic hypothyroidism (at least 40 weeks) resulted in decreased fertility, increased periparturient mortality and lower birth weights, without effect on interestrus interval, gestation duration or breeding behavior.[104] Experimentally induced hypothyroidism is not associated with any effect on male reproductive indices (sperm count, scrotal width, sperm motility/morphology, libido) over a 2-year period.[105] A survey of five breeds (Great Dane, Dogue de Bordeaux, English Mastiff, Leonberger and Golden Retriever) identified no association between infertility and hypothyroidism, but the prevalence of hypothyroidism was too low for firm conclusions.[106] One dog with hypothyroidism, hyperprolactinemia and galactorrhea was described.[107] Pituitary function tests in hypothyroid dogs suggest that hyperprolactinemia is only likely in intact bitches.[108]

Other Features

Anecdotally, constipation, vomiting and diarrhea have been associated with hypothyroidism, but evidence is lacking.[1,2] Hypothyroid people are often constipated due to decreased gastrointestinal (GI) peristaltic activity.[109] Diarrhea associated with small intestinal bacterial overgrowth, possibly due to reduced intestinal motility, has been suspected.[110] An association between gallbladder mucocele and hypothyroidism has been proposed but not confirmed.[111,112] Hypothyroidism is not associated with either acute or chronic kidney disease or polyuria/polydipsia except in rare cases of thyroiditis-associated-glomerulonephritis.[113] Decreases in glomerular filtration rate have been demonstrated in hypothyroidism, but its significance is not known.[114,115] It has been suggested but not demonstrated that hypothyroid dogs require less anesthetic agents for a given effect and are more difficult to manage during anesthesia. Experimentally, the cardiovascular effects and minimum alveolar concentrations of isoflurane were not different in hypothyroid versus healthy dogs.[116,117]

Congenital Hypothyroidism

Dogs affected early in life can develop any of the signs noted in hypothyroid adults. However, dogs with congenital hypothyroidism have striking disproportionate dwarfism. Affected pups appear normal at birth, but signs usually become evident by about 8 weeks of age. Affected animals have disproportionately wide skulls, macroglossia, delayed dental eruption, a square trunk and short limbs.[20] These features help differentiate this condition from the proportionate features of pituitary dwarfism. Constipation may be noted, and mental impairment is usually obvious. Goiter may or may not be evident depending on the underlying

cause. When present, goiter can mechanically cause dysphagia/dyspnea. Radiographically, delayed skeletal maturation and epiphyseal dysgenesis are common and may eventually cause degenerative joint disease or other orthopedic disorders.[13,118]

Immunoendocrinopathy Syndromes

Most autoimmune endocrine disorders in people occur in isolation, but there are instances when two or more such disorders occur concurrently or sequentially. Autoimmune polyendocrine syndrome type 1 (APS-1) is a rare autosomal recessive disorder characterized by the triad of mucocutaneous candidiasis, autoimmune thyroid disease and Addison's disease. These people have increased susceptibility to other autoimmune diseases.[119] Autoimmune polyendocrine disease type II (APS-II) is more common, less well defined, and is associated with familial aggregation and susceptibilities determined by multiple genetic factors.[119] Previously known as polyglandular autoimmune disease or Schmidt's syndrome, it is usually defined by the development of two or more of the following: Addison's disease, Graves' disease, autoimmune thyroiditis, type 1A diabetes mellitus, primary hypogonadism, myasthenia gravis and celiac disease. Addison's disease together with type 1 diabetes mellitus (52% of patients) or with hypothyroidism (69% of patients) is most common.[120,121]

Such disorders are less well defined in dogs. Single case reports and case series have described combinations that mimic the human condition, including hypothyroidism and diabetes mellitus,[1-3,122-124] hypothyroidism and hypoadrenocorticism,[3,125-133] together with adenohypophysitis,[134] hypothyroidism, hypoadrenocorticism, diabetes mellitus and hypoparathyroidism,[128] hypothyroidism and myasthenia gravis,[2,80,81] and occasionally with other autoimmune diseases.[135] The prevalence of diabetes mellitus in hypothyroid dogs has been estimated as between 1.2% and 10% while the prevalence of hypothyroidism in diabetic dogs is estimated at 4%.[1,3,124] The prevalence of hypoadrenocorticism in hypothyroid dogs ranges from 1% to 3% while the prevalence of hypothyroidism in dogs with hypoadrenocorticism is about 4%.[2,3,128] Hypothyroidism should be suspected in dogs with hypoadrenocorticism, particularly if there is a poor response to mineralocorticoid therapy, persistent hyponatremia or bradycardia, inappropriate hypercholesterolemia or other supportive clinical signs.[129] In a study of 35 dogs with two or more concurrent endocrine disorders, the combination of hypothyroidism and diabetes mellitus (29%) was more common than hypothyroidism and hypoadrenocorticism (23%).[136]

Undoubtedly, there are difficulties in reliably confirming hypothyroidism in dogs suffering from other illnesses. The combinations are all potentially immune-mediated and may be genetically related, but other explanations are possible. Clinically, hypothyroidism has been recognized as an uncommon cause of insulin resistance in diabetic dogs.[122] Hypothyroidism is known to induce insulin resistance in experimental dog models. Their glucose tolerance is maintained via compensatory increase in insulin secretion.[137,138] While obesity may play a partial role in resistance, other factors associated with thyroid hormone deficiency may also be important.[137] Naturally occurring and experimental hypothyroidism has been associated with growth hormone (or IGF-1) excess, perhaps due to transdifferentiation of somatotropic pituitary cells to thyrosomatotropes.[108,137,139-141] Growth hormone excess is highly diabetogenic.[142] One dog with hypothyroidism, acromegaly, and diabetes mellitus reversed with thyroid hormone supplementation.[143] Additional genetic and clinical studies are required to fully investigate the existence of autoimmune polyendocrine disorders in dogs.

Routine Clinicopathology

Overview

Various hematological and biochemical changes are described as “common” in hypothyroid dogs, but none is specific. Their presence provides supportive evidence of hypothyroidism but, more importantly, they may aid in including or excluding non-thyroidal illnesses. Non-thyroidal illness may account for a patient's clinical signs or may affect interpretation of thyroid function tests. The most frequent abnormalities in hypothyroidism include anemia, hypercholesterolemia, hypertriglyceridemia, increased creatine kinase (CK) activity and decreased fructosamine concentrations.

Complete Blood Count (CBC)

The anemia in hypothyroidism is typically mild, normochromic and normocytic. It occurs in 32 to 44% of cases.[1,2,144] Hematocrit values are rarely below 25%, an anemia not often detected on physical examination. Often termed a "physiological" anemia, it is likely the result of decreased erythropoietin production and the lack of stimulatory effect of thyroid hormones on bone marrow.[145] Non-anemic hypothyroid dogs usually have red cell counts in the lower quartile of the reference interval. An increased white cell count is extremely unusual in hypothyroid dogs.

Hypothyroidism has been associated with increased platelet counts and small platelet size, a result of an inverse relationship between thrombopoiesis and erythropoiesis.[148] Easy bruisability has anecdotally been associated with hypothyroidism, perhaps the result of decreases in plasma von Willebrand factor antigen (vWf:Ag).[149] However, hypothyroidism is not associated with prolonged buccal mucosal bleeding times or significant changes in vWf:Ag concentrations, which decrease with thyroid hormone supplementation.[150,151] Links between hypothyroidism and von Willebrand's disease likely reflect breed predispositions to both conditions. Thyroid supplementation of euthyroid Dobermans with von Willebrand's disease does not affect the concentration or activity of vWf:Ag in plasma.[152]

Serum Biochemistry Results

Hypercholesterolemia occurs in about 75% of hypothyroid dogs and is often accompanied by hypertriglyceridemia.[1,2,144] The higher the cholesterol concentration, the more likely a dog is to have hypothyroidism. Thyroid hormones stimulate lipid synthesis, mobilization and degradation. Degradation is more severely affected in hypothyroidism, resulting in lipid accumulation. Plasma lipoprotein analyses of hypothyroid dogs demonstrate increased concentrations of low density lipoprotein, very low density lipoprotein, and high density lipoprotein.[146] Increased CK activity occurs in 18 to 35% of hypothyroid dogs but does not usually exceed twice the upper limit of the reference interval.[1,2] Often considered to result from decreased metabolism or excretion, hypothyroid-induced myopathy may also be responsible for changes in CK.[97] Fructosamine concentrations are high in 36-82% of cases, presumably due to reduced protein turnover rather than significant prolonged hyperglycemia.[1,147] Such increases may impact treatment monitoring in diabetic dogs with hypothyroidism. Mild increases in liver enzyme activities, particularly alkaline phosphatase and gamma-glutamyltransferase, occur in as many as 30% of hypothyroid dogs, perhaps due to mild hepatic lipid deposition.[1,2] If enzyme activities are markedly increased, another underlying disorder should be considered.

Thyroid Testing

Overview

The ability to accurately diagnose hypothyroidism, while greatly improved in recent years, can be challenging. Several tests are available and recommendations for their use and interpretation vary. Commonly used assays include total T_4 (TT_4), total T_3 (TT_3), free T_4 (FT_4), canine TSH (cTSH), the presence of TgAA, T_4AA, and T_3AA. Assays for free T_3 and reverse T_3 (rT_3) are available but not used in diagnosis. Dynamic function tests include TRH and TSH stimulation tests. The thyroid gland may be assessed by ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), or by qualitative and quantitative thyroid scintigraphy. Not all tests directly assess thyroid function but may provide indirect evidence of thyroid abnormalities. Of the tests available, no single test has 100% diagnostic sensitivity. Importantly, there is a myriad of non-thyroidal factors that may influence results of thyroid testing, adversely affecting diagnostic specificity.

Non-Thyroidal Factors Affecting Thyroid Hormone Concentrations

Breed, gender, age, neuter status, body condition and physical activity are known to significantly affect thyroid hormone concentrations. Importantly, non-thyroidal illness and previous and ongoing drug therapies can alter results. Assay methodology may influence accuracy and credibility of the results obtained.

Assay Methodologies

Total Thyroid Hormone Assays

Total thyroid hormone assays measure circulating protein-bound and free concentrations. Radioimmunoassay (RIA) remains the standard reference technique for measurement of TT_4 and TT_3. Assays have evolved to include non-isotopic methods and the more research-utilized liquid chromatography-tandem mass spectrometry (HPLCMS). RIAs are less expensive and use smaller sample volumes but are subject to radiation restrictions and cannot be fully automated. Non-isotopic methods can be fully automated (preferred by commercial laboratories) or developed for in-house use. These methods use enzymes, chemiluminescence or fluorescence, rather than radioisotopes as signals. They can be quantitative (preferred) or semi-quantitative.

There is reasonable agreement across the different assay methodologies for TT_4 even when human RIAs are used, if modified to allow measurement of the lower concentrations found in dogs.[153-155] Different concentrations do occur with different assay types, emphasizing the need for method- and laboratory-specific reference intervals. Anecdotally, erroneous values are more likely with enzyme or fluorescence methods. Enzyme methods are considered least accurate.[156] TT_3 concentrations are similar in humans and dogs, such that assays designed for human use do not require modification.

Both TT_4 and TT_3 results can be affected by autoantibodies, which can falsely increase or decrease results, depending on the assay and separation systems used. Autoantibodies increase measured values with assay systems that use the antibody-bound hormone for estimating hormone concentrations, as with most of the commonly used TT_4 assay systems. When T_4AAs are present, the measured value may be within or above the reference interval. If the estimation of hormone concentration is based on the unbound hormone fraction, autoantibodies falsely decrease results. Some TT_3 assays are thus affected, with concentrations becoming undetectable.

There are few studies objectively assessing the effect of autoantibodies on test results. One study identified no difference in TT_4 concentrations estimated by chemiluminescence and HPLC (theoretically free from interference with autoantibodies) in dogs that were T_4AA positive with reference interval TT_4 concentrations.[157] However, only two such samples were evaluated and the thyroid status of each patient was unclear. Others suggest that TT_4 concentrations are below, within or above the reference interval in approximately 54%, 34% and 12% of T_4AA-positive hypothyroid dogs, respectively (PA Graham, personal communication). Increased and reference interval TT_4 results have been reported in several TgAA-positive, confirmed hypothyroid dogs.[158]

Free (Unbound) Hormone

Circulating FT_4 concentrations are similar in humans and dogs. As such, assays used for people can be employed without modification. Equilibrium dialysis and ultrafiltration-based methods are generally considered to be gold standards for measuring FT_4 concentration. Such methods involve separating the FT_4 fraction followed by its estimation using a highly sensitive RIA. These assays, used by large commercial laboratories, are laborious and expensive. However, accurate measurement of FT_4 concentration by other methods is controversial. The most frequently used assays use hormone analogs with molecular structures similar to T_4 and claim to be non-reactive with binding proteins, thus being able to compete with FT_4 within the sample. In humans, they are thought to merely estimate FT_4 concentrations, offering little advantage over TT_4 assays. Use of these assays is considered most problematic in accurately measuring FT_4 concentrations in patients with disorders associated with abnormal thyroid hormone binding proteins, non-thyroidal illness, high free fatty acid concentrations and thyroid hormone autoantibodies.[159]

In comparison to techniques using equilibrium dialysis, FT_4 concentrations in dogs are significantly lower using different direct FT_4 analog RIAs, particularly in patients with non-thyroidal illness.[160] The accuracy and agreement between direct chemiluminescent and equilibrium dialysis FT_4 assays have been reported as adequate or limiting.[161,162] However, combined measurement of TT_4 and FT_4 by analog methods adds little diagnostic information to assaying either alone, suggesting that the assays may not be measuring FT_4 concentrations.[163] These assays, like TT_4, are influenced by the presence of T_4AAs.[158]

Thyroid Stimulating Hormone (TSH) Assays

The assessment of TSH requires a species-specific assay. Canine-specific TSH (cTSH) chemiluminescent and

immunoradiometric assays are available and reasonably correlated.[164] These assays fail to detect low concentrations, which is less important in dogs with primary hypothyroidism as they should have increased cTSH results. However, this limitation can have implications when attempting to diagnose central hypothyroidism or when assessing overdose in thyroid hormone–treated dogs.

Thyroglobulin Autoantibody (TgAA) Assays

Species-specific assay methods for canine TgAA are commercially available. The assay has been modified to decrease nonspecific IgG binding, thereby reducing the rate of false-positive and equivocal results previously reported. The presence of T_3AAs and T_4AAs may be inferred if discordant total hormone results are detected in TgAA-positive dogs. They can also be specifically measured by some specialized laboratories.

Storage and Interferences

Most thyroid hormones and cTSH are relatively stable in storage. However, concentrations of FT_4 significantly increase if stored at room temperature for prolonged periods. Sample separation, refrigerated transport and expedient measurement are indicated. RIAs are generally resistant to the effects of hemolysis, lipemia and hyperbilirubinemia, but the same cannot be guaranteed with non-isotopic methods.[165] Severe lipemia may falsely increase FT_4 concentrations when measured by equilibrium dialysis.[166]

Physiologic Factors

Sample Timing, Age, Gender

Sample timing is not important, as a circadian rhythm for thyroid hormone secretion has not been identified in dogs. Episodic fluctuations occur that may cause spurious subnormal results.[167-169] TT_4 concentrations decline with age and may be below reference intervals in older dogs.[170] Conversely, dogs <3 months of age have values two to five times higher than adults. Gender and stage of estrus have been variably reported to affect thyroid hormone concentrations but are not clinically significant.

Breed and Exercise

Initial investigations suggested that thyroid hormone concentrations were lower in larger dogs, but these observations were likely breed-, not size-, related.[171] Sighthounds, for example, are known to have relatively low circulating thyroid hormone concentrations. Magnitude and hormones affected vary among breeds. TT_4 values below standard reference intervals are noted in about 90% of Greyhounds, 75% of Basenjis, 65% of Sloughis, 55% of Salukis, 25% of Whippets, but only 5% of Scottish Deerhounds.[172-177] In many, concentrations are so low (at or below limit of detection of assay) that a breed-specific reference interval cannot be calculated. Low TT_3 results are found in Salukis and Irish Wolfhounds, but not Greyhounds.[172,175,178] FT_4 concentrations can measure low in Greyhounds, Irish Wolfhounds, and Salukis, but not Whippets.[172,175,176,178] TT_4 concentrations are also low in the Dogue de Bordeaux and Giant Schnauzer.[171,179] TSH concentrations appear to be largely unaffected by breed. Intense training and exercise are associated with decreases in thyroid hormone concentrations, but brief exercise has little effect.[176,180-183]

Non-Thyroidal Illness

Illness can induce profound changes in thyroid hormone concentrations in people (Table 299-3). Previously dubbed "euthyroid sick syndrome," "low T_3 syndrome" and the "low T_4 state of medical illness," the term "non-thyroidal illness syndrome" is now used to describe changes in thyroid hormone concentrations secondary to acute and chronic illnesses. There are numerous potential mechanisms for this condition, including reduced peripheral conversion of T_4 to T_3, reduction in binding affinity of the thyroid hormone binding proteins, altered thyroid hormone metabolism, changes in thyroid hormone receptor expression or function, or altered hypothalamic/pituitary function. The most common abnormality associated with non-thyroidal illness syndrome in people is suppression of circulating TT_3 concentrations with TT_4 values remaining within reference intervals.[184] As diseases progress in severity, suppression of both T_3 and total T_4 occurs, and this is associated with a poorer outcome. FT_4 and TSH concentrations are less affected, but in severe illness suppression of both may be observed. Occasionally, transient increases in FT_4 are observed.

Circulating TSH values may increase during the recovery phase of illness.

TABLE 299-3

The Effect of Non-Thyroidal Illness on Serum Concentrations of Thyroid Hormones and Thyrotropin

SEVERITY OF ILLNESS	HORMONE			
	TOTAL T_3	TOTAL T_4	FREE T_4	TSH
Mild	↓	↔	↔	↔
Moderate	↓↓	↓	↔↓↑	↔↓
Severe	↓↓↓	↓↓	↔↓	↓↓
Recovery	↓↔	↓↔	↔↓	↑↔

T_3, Triiodothyronine; *T_4*, thyroxine; *TSH*, thyroid stimulating hormone (thyrotropin); ↓, concentrations decrease; ↔, concentrations remain the same; ↑, concentrations increase.

These effects are largely known for T_3 and T_4. In the case of TSH, data are extrapolated from humans. Most research concerning dogs has not implicated any effect of illness on TSH, but this is complicated because of the inability of the currently used assay to detect low and suppressed concentrations.

The number of arrows indicates increasing severity.

From Mooney CT: Canine hypothyroidism. A review of the aetiology and diagnosis. *N Z Vet J* 59:105-114, 2011.

Decreased thyroid hormone concentrations have been reported in a wide variety of illnesses affecting numerous body systems.[185-197] Mechanisms have not yet been elucidated, but a preliminary study demonstrated decreases in transthyretin concentration, although likely to be of minor importance.[198] Recombinant interleukin-2 infusions have been shown to induce changes similar to those in non-thyroidal illness in experimental dogs.[199] In one comprehensive study of non-thyroidal illness in dogs, concurrent reductions in TT_3 and TT_4 followed sole reductions in TT_3. Isolated suppression of TT_4 was uncommon.[188] Greater decreases in TT_4 and TT_3 were associated with more severe illness and poorer prognosis.[186-188,200-202] FT_4 concentrations (by equilibrium dialysis) are typically maintained within reference intervals in all but the most severe illnesses[187,188] and in hyperadrenocorticism.[28,187,188] Occasionally, increases in FT_4 are noted, although poorly defined.[203,204] Understanding the influence of illness on cTSH concentrations is hampered by the poor sensitivity of current assays, as normal values cannot be distinguished from low values. Increases are known to occur in the recovery phase of illnesses.[203,204] Altered thyroid hormone concentrations should not be expected in minor illness and, if present, another explanation should be sought. Thyroid hormone concentrations are unaffected by osteoarthritis, recurrent seasonal flank alopecia, atopic dermatitis, or pyoderma.[205-208]

Drug Therapy

Several drugs are known to alter thyroid hormone concentrations, ranging from TT_4 alone to a state mimicking primary hypothyroidism (Table 299-4). Offending drugs include but are not confined to glucocorticoids, phenobarbital, aspirin, ketoprofen, carprofen, clomipramine and sulfonamide-containing antibiotics.[209-213] For many, dosage and duration of therapy dictate magnitude of effect. Sulfonamides require special mention, as they may induce hypothyroidism and even myxedema coma because of their ability to reversibly inhibit TPO.[214-218] About an additional 15% decrease in TT_4 concentration is expected in ill dogs being treated with thyroid-suppressive medications.[188] The effect of numerous other drugs has not been specifically evaluated in dogs, but they can be considered as affecting hormone concentrations until proven otherwise. Thyroid hormone concentrations normalize once drug therapy is withdrawn. For many drugs, including thyroxine, at least a 6-week withdrawal period is recommended before thyroid function testing, perhaps longer after sulfonamide treatment.[209,218,219]

TABLE 299-4

The Effect of Drug Therapy on Serum Concentrations of Thyroid Hormones and Thyrotropin

DRUG	HORMONE		
	TOTAL T_4	FREE T_4	TSH
Prednisone/prednisolone	↓↔	↓↔	↔↓
Phenobarbital	↓↔	↓↔	↔↑ (↓)*
Potassium bromide	↔	↔	↔
Sulfonamides	↓	↓	↑
Propranolol	↔	↔	↔
Clomipramine	↓	↓	↔
Aspirin	↓	↓↔	↔
Ketoprofen	↓	↔	↔
Carprofen	↓↔	↓↔	↔↓
Deracoxib	↔	↔	↔

*Phenobarbital has been associated with a significant increase in TSH concentrations. However, values rarely exceed the upper limit of the reference interval. The increase in TSH is unexpectedly low for the decrease in thyroid hormone concentrations and this may indicate a suppressive effect of this drug on TSH.

Data compiled from references 209-218.

T_4, Thyroxine; *TSH,* thyroid stimulating hormone (thyrotropin).

From Mooney CT: Canine hypothyroidism. A review of the aetiology and diagnosis. *N Z Vet J* 59:105-114, 2011.

Diagnosis of Hypothyroidism: Basal Hormone Tests

Overview

The various diagnostic tests used in the investigation of hypothyroidism are summarized in Table 299-5.[36-38,189,194,220,221]

TABLE 299-5

The Diagnostic Performance of Thyroid Hormone Concentrations, Thyrotropin and Thyroglobulin Autoantibodies for Diagnosing Hypothyroidism

	TOTAL T_4	FREE T_4	TSH	TGAA
Sensitivity	89-100%	80-98%	58-87%	91-100%
Specificity	73-82%	78-94%	82-100%	94-100%

T_4, Thyroxine; *TgAA,* thyroglobulin autoantibodies; *TSH,* thyroid-stimulating hormone (thyrotropin).

Data compiled from references 36-38, 189, 192, 194, 220, 221.

TT_3 Concentrations

Measurement of TT_3 is of limited value for diagnosing hypothyroidism due to its low sensitivity. TT_3 values are maintained within or above reference intervals in up to 90% of hypothyroid dogs.[192] These findings may be related to enhanced secretion of T_3 from the thyroid gland or peripheral conversion from T_4 as thyroid function declines. This is of potential short-term benefit to the individual, as T_3 is the more potent of the active thyroid hormones. Depending on the assay system used, the presence of T_3AAs may also play a role by falsely increasing measured concentrations. T_3AAs are present in >5% of samples from dogs suspected of having hypothyroidism.[34] While this seems small, T_3AAs are present in >40% of TgAA-positive hypothyroid

dogs.[42] Specificity of TT_3 for diagnosing hypothyroidism is also poor. Low values are common in certain breeds, in association with non-thyroidal illness, and with administration of various drugs. The only value of measuring TT_3 is in breeds such as the Greyhound, known to have low TT_4 but to maintain TT_3 concentrations within reference intervals.[172]

TT_4 Concentrations

Circulating TT_4 concentrations are decreased in most hypothyroid dogs. Its diagnostic sensitivity is excellent and it is frequently recommended as a screening test. Results within reference intervals are often used for ruling out hypothyroidism, but T_4AAs can falsely increase results. T_4AAs are present in <2% of samples from dogs suspected of having hypothyroidism, but the number of dogs with T_4AAs increases to 14% among TgAA-positive hypothyroid dogs.[34,42] This decreases diagnostic sensitivity and means hypothyroidism cannot be ruled out by either a reference interval or increased TT_4 result. An even greater concern of relying solely on TT_4 is its poor specificity due to the myriad non-thyroidal factors that result in decreased concentrations in euthyroid animals. These include breed, age, non-thyroidal illness and drug therapies. TT_4 should never be used as the sole diagnostic test for hypothyroidism in dogs.[175]

FT_4 Concentrations

FT_4 values are below reference intervals in most hypothyroid dogs. It is unclear why a small proportion of hypothyroid dogs has results in the low end of the reference range, but this decreases diagnostic sensitivity. However, FT_4 concentrations (by equilibrium dialysis) are less affected than TT_4 by extrathyroidal factors. Thus, its diagnostic specificity for hypothyroidism is high. Measurement of FT_4 is, therefore, considered the single most accurate test for diagnosing hypothyroidism.[220]

cTSH Concentrations

cTSH concentrations are expected to be increased in dogs with primary hypothyroidism due to a lack of thyroid hormone negative feedback. However, the cTSH assay has only moderate sensitivity as a diagnostic test because results from a significant proportion of hypothyroid dogs are within reference intervals. Perhaps a proportion of hypothyroid dogs have central rather than thyroid-mediated disease, but this is unlikely given that values are often within reference intervals rather than decreased or at the limit of detection of the assay. Random fluctuation of cTSH within reference intervals has been demonstrated to occur in hypothyroid dogs but is an unlikely explanation for all of the low values encountered.[222,223]

There is evidence from experimental studies that pituitary secretion of TSH decreases with chronic hypothyroidism, presumably as a result of TRH-receptor desensitization. Such a phenomenon could occur in the naturally occurring disease.[108,139-141] While this may be a plausible explanation for reference interval cTSH values in some hypothyroid dogs, it could be argued that few have disease spanning the time period necessary to induce such changes. It is possible that high cTSH values are suppressed in hypothyroidism because of concurrent non-thyroidal illness or drug therapies.[220] It has also been suggested that current assays do not measure all possible isomers of cTSH. Although diagnostic sensitivity of this test is poor, measurement of cTSH concentration offers relatively good diagnostic specificity. High results are less commonly encountered in euthyroid dogs, as cTSH is largely unaffected by non-thyroidal illness or drugs, with the exception of sulfonamides. High values are, however, a feature of silent and subclinical hypothyroidism.[42]

Thyroglobulin Autoantibodies (TgAA)

Positive TgAA results are associated with lymphocytic thyroiditis but may be present in the circulation long before a dog becomes clinically hypothyroid.[42] As such, TgAAs provide no information on thyroid function. TgAA positivity, uncommon in dogs with non-thyroidal illness, is suggestive of underlying pathology.[38,43,224] A positive TgAA does, indirectly, support a diagnosis of hypothyroidism.

Basal Hormone Tests in the Context of Clinical Information

As discussed, less than ideal sensitivity and specificity of the tests available create difficulties in reliably confirming a diagnosis of hypothyroidism, and this diagnosis should never rely solely on test results. Rather,

testing should be carried out on dogs likely to have the disease: those of appropriate signalment with supportive clinical and clinicopathological features having significant non-thyroidal illness excluded and with no history of recent thyroid suppressive medication (Figure 299-3). Then, a combination of tests with high sensitivity/low specificity and high specificity/low sensitivity should be selected, which reduces their weaknesses. Use of TT_4 with cTSH offers the most cost-effective and widely available combination. FT_4 can be reserved for dogs whose TT_4 is likely to be affected by concurrent illnesses or drug therapies. Measurement of TgAA serves as a screen for the potential influence of T_4AA and also provides information on pathogenesis.

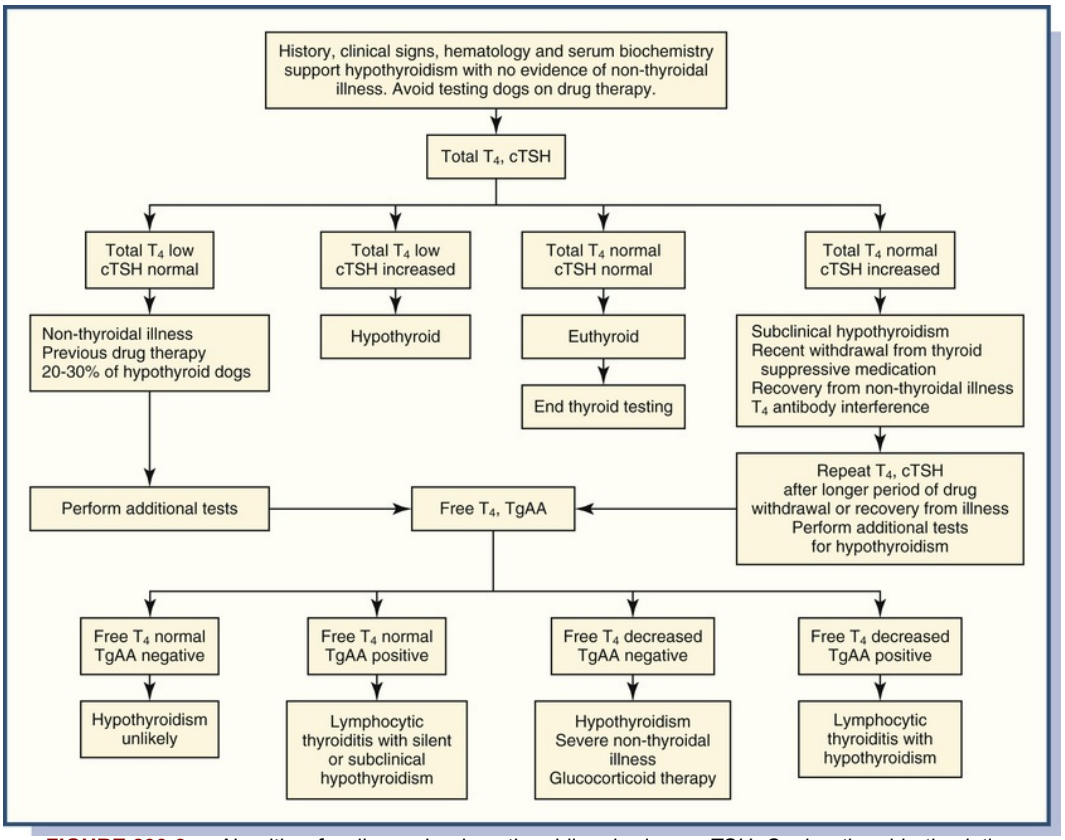

FIGURE 299-3 Algorithm for diagnosing hypothyroidism in dogs. *cTSH,* Canine thyroid stimulating hormone; *T4,* thyroxine; *TgAA,* thyroglobulin autoantibody. (From Mooney CT: Canine hypothyroidism. A review of the aetiology and diagnosis. *N Z Vet J* 59:105-114, 2011.)

Diagnosis of Hypothyroidism: Use of Stimulation (Provocative) Tests

Indications

The TSH and TRH stimulation tests previously were routinely recommended as aids for confirming a diagnosis of hypothyroidism. Provocative testing should now be reserved for dogs whose diagnosis cannot be confirmed using clinical signs and basal tests. Stimulation tests may also be used for evaluating test performance when a reliable and independent method of differentiating hypo- from euthyroidism is required.

TSH Stimulation

The TSH stimulation test was considered the "gold standard" for diagnosing canine hypothyroidism. In early studies, bovine TSH, no longer available, was used. Comparable results are obtained using human recombinant (rh) TSH.[225] Recommended IV dosages include 50 to 75 mcg per dog or 100 mcg for dogs >20 kg, with samples taken before and 6 hours after administration.[226-228] A 150-mcg per-dog dose has been suggested to more accurately distinguish hypothyroidism from non-thyroidal illness.[229] Unlike bovine TSH, adverse reactions have not been reported, even with repeated administrations. Reconstituted rhTSH can be

stored at 4°C for 4 weeks or −20°C for up to 12 weeks without loss of biological value, allowing multiuse from one vial, and reducing cost.[227,230] Criteria for interpretation vary.[231] Generally, euthyroid dogs increase their TT_4 concentration >1.5 times the basal level with an absolute value >30 nmol/L. Hypothyroid dogs show minimal stimulation, with a post-TSH TT_4 <20 mmol/L. Some dogs have results that do not fall into either category and are difficult to interpret.

TRH Stimulation

The TRH response test, whereby TT_4 concentration is measured before and after TRH administration, was once recommended as a useful alternative to TSH stimulation. Unfortunately, the TRH response test is considerably less reliable than most of the other currently available baseline tests. At best, a good response to TRH can confidently exclude hypothyroidism. However, the lack of T_4 response to TRH is not confirmatory of hypothyroidism, being a common finding in a wide variety of non-thyroidal illnesses, in dogs receiving certain medications, and in health.[232]

The cTSH response to TRH can be assessed.[140] Low dosages (10 mcg/kg) of TRH cause peak pituitary stimulation about 20 minutes after IV administration, while minimizing side-effects. Humans with primary hypothyroidism exhibit an exaggerated and prolonged TSH response to TRH. However, while there is limited TSH response to TRH in hypothyroid dogs, the test adds little to information gained from basal thyroid hormone analyses.[233] TRH stimulation is largely confined to research studies.

Diagnostic Imaging

Overview

Thyroid imaging is a well-established tool for investigating cats with hyperthyroidism and dogs with thyroid neoplasia.[234,235] Theoretically less affected by non-thyroidal illness or drugs, interpretation of certain imaging techniques is similar to that of TgAA. Thus, imaging can provide information on gross appearance rather than thyroid function.

Ultrasonography (US)

Each thyroid lobe is usually described as fusiform in longitudinal section, triangular in cross section, having a smooth capsule, and an echogenicity that is homogeneous and isoechoic or hyperechoic compared to the adjacent sternothyroid muscle in healthy dogs and dogs with non-thyroidal illness. Thyroid lobes of hypothyroid dogs display significantly less echogenicity, are not homogeneous but irregular in outline, are small, and more rounded.[185,236,237] Any of these changes may be present in hypothyroid dogs, and appearance of the lobes may differ. However, there may be differences in thyroid US results depending on breed.[238] In addition, results of thyroid US is dependent on operator skill, experience and opinion.

Advanced Imaging

CT and MRI of thyroid lobes in healthy dogs have been described.[239,240] Comparisons with hypothyroid dogs are not yet published. Given their expense and need for anesthesia, advanced imaging has limited usefulness.

Technetium-99M Scans

Use of technetium-99M (as pertechnetate ($^{99M}TcO_4^-$) for quantitative calculation of thyroid gland uptake (TCTU) has been suggested as the most accurate technique for distinguishing dogs with primary hypothyroidism from those with non-thyroidal illness.[241] Uptake values in hypothyroid dogs range from 0.03-0.26% and in euthyroid animals with low total T_4 concentrations from 0.39-1.86%. However, these marked differences are not uniformly accepted, as glucocorticoids in particular appear capable of decreasing TCTU, producing equivocal results.[242] In people, altered radioisotope uptake has been described in association with several non-thyroidal illnesses and medications. The scintigraphic appearance of inflammatory thyroid disease is variable. However, evaluation of TCTU has shown promise in confirming euthyroidism in Greyhounds, in investigating central hypothyroidism and in differentiating dysgenesis from dyshormonogenesis in congenital hypothyroidism.[235,243]

Treatment

Background

Hypothyroid dogs require thyroid hormone replacement therapy (THRT) for life. "Natural" or desiccated thyroid extracts are crude and unreliable compared to synthetic products, which are more predictable and have a longer shelf life. Synthetic T_4 is the treatment of choice as it is the principal secretory product of the thyroid gland and is the physiologic prohormone for the more metabolically active T_3. Administration of T_3 circumvents this normal physiological process, increasing the risk of thyrotoxicosis. Since T_3 has a shorter half-life, it must be given several times a day and may cause T_4 deficiency in the brain and pituitary gland, although the consequences of this are unclear. Products containing a combination of T_4 and T_3 used in humans are not recommended for dogs as the ratio is inappropriate, resulting in excess T_3. T_4 is widely available as generic and licensed proprietary forms and both tablet and liquid formulations for oral administration.

T_4 Supplementation

Dosage

The total daily secretion of T_4 in dogs has been estimated to be about 2.5 mcg/kg.[244] However, when this amount of T_4 is given IV or SC to thyroparathyroidectomized dogs, circulating concentrations remain severely low.[245] An IV dosage four times greater is needed to normalize T_4 concentrations, and even higher oral dosages are required. The oral requirement can be explained because GI absorption of T_4 is estimated to be only 10 to 50% of that given orally. But the reasons for a high IV dosage requirement are unknown.[244] Poor GI absorption is presumably related to intraluminal contents, dietary factors and intestinal bacteria that bind T_4 and reduce its availability. The bioavailability of T_4 is almost halved when administered with food.[246] This does not imply that all dogs should be fasted prior to T_4 administration; instead, the temporal association between feeding and oral dosing must be standardized in each animal, particularly on the day of monitoring. Varying dietary components could have an effect on T_4 absorption. Therefore, providing a consistent diet is recommended.[247] Bioavailability will also vary depending on the T_4 product used. Greater variation in bioavailability occurs with generic products but can also occur with proprietary products.[248] The bioavailability of an oral liquid formulation was approximately twice that of a tablet in one study but was comparable using different products in another, indicating that not all products can be used interchangeably.[246,249]

Frequency

The pharmacokinetics of T_4 are similar in hypothyroid and healthy dogs.[250] When administered orally (either once or twice daily), T_4 is rapidly absorbed, peak concentrations are achieved at about 3 to 5 hours, and the serum half-life is usually 9 to 15 hours.[246,250,251] Higher dosages are associated with shorter half-lives, suggesting a degree of dose-dependent kinetics.[251] In a large number of hypothyroid dogs, peak T_4 concentrations were noted about 4 to 6 hours after administration.[248] Steady-state concentrations are quickly established, allowing early evaluation of efficacy (e.g., within two weeks) after initiating therapy.[246]

The optimum dosage and frequency of administration of T_4 for hypothyroid dogs remain somewhat controversial. Total daily doses ranging from 0.02 to 0.04 mg/kg BW and given once, twice or three times daily have been recommended. Most published studies have evaluated the use of 0.02 mg/kg administered once daily, on the premise that the serum half-life of T_4 does not necessarily reflect its biological effect.[55,252,253] This regimen has been successful, although an increase in dosage is required by about 35% of dogs.[253] This percentage can be lowered depending on the T_4 preparation used and by ensuring consistency with feeding times.[252] The number of dogs requiring a dosage reduction with this protocol is about 6-10%. Twice-daily dosing is associated with lower peak concentrations and less fluctuation in circulating TT_4.[248] Twice-daily dosing of 20 mcg/kg has also been used successfully but may not be superior to once daily. There are no reports evaluating the number of dogs in which dosage adjustments are required using twice-daily dosing. It

is important to note that the effect of a given dose of T_4 varies with each individual. Thus, clinical, clinicopathological and hormonal monitoring is critically important in determining each dog's T_4 dosage and frequency. This may require several adjustments. A practical advantage of once-daily dosing could be related to greater owner compliance, as therapy is lifelong.

Clinical Response

Adequately treated hypothyroid dogs should have no clinical signs of disease, remembering that improvement can take weeks to months to become apparent. Generally, metabolic changes such as dullness and lethargy are first to improve within days of commencing therapy and an expected 10% loss of weight occurs within the first few months. Dermatological improvements are expected within a month of commencing treatment but can take 2-3 months to normalize, often with a phase of increased hair loss preceding hair regrowth. Improvement in neurological signs may take as long as 6 months.[254]

Clinicopathologic Response

Normalization of the clinicopathologic abnormalities associated with hypothyroidism occur broadly in parallel with the clinical response.[253] Serum cholesterol and triglyceride values often decrease dramatically, while red blood cell values increase progressively during the first 3 months of THRT. Fructosamine concentration decreases significantly, as protein turnover increases.[147,253] THRT rapidly reverses hypothyroid-induced changes in adiponectin, leptin and glomerular filtration rate.[115,255]

Monitoring

Therapeutic monitoring is aimed primarily at understanding owner satisfaction with response to treatment, together with identifying the peak circulating TT_4 concentration. Successful response in dogs treated once daily is associated with a median peak TT_4 concentration (6 hours after administration) of approximately 4 mcg/dL (50 nmol/L).[55,253] Values below 2.7 mcg/dL (35 nmol/L) are usually associated with an inadequate clinical response, and an increase in dosage is indicated. Markedly increased peak TT_4 concentrations >7 mcg/dL (>90 nmol/L) occasionally occur. Although dogs are usually resistant to severe clinical thyrotoxicosis, such values should prompt a decreased dosage. Using twice-daily dosing, TT_4 values should be at the high end or just above the reference interval 4-6 hours after administration and remain within the reference interval prior to the next dose. In general terms, doubling the T_4 dose administered increases peak circulating TT_4 concentrations by about 50 to 60% because of bioavailability issues and dose-dependent pharmacokinetics.[248,251] While this can be used to select the exact magnitude of a dosage alteration, it is more usually dictated by the next available tablet size when tablets are used. More accurate dosage adjustment may be possible using the liquid formulation.

Measurement of cTSH provides a longer-term assessment of the adequacy of treatment, unlike TT_4, which only provides information concerning treatment on that particular day.[253] Measurement of cTSH assists in identification of poor owner compliance where a particular effort to administer the medication is made on days corresponding to the monitoring visit. Unfortunately, in the hypothyroid dogs that did not have increased pretreatment cTSH values, measurement during THRT is of no value. Additionally, circulating cTSH can be highly sensitive to the effects of THRT, such that suppression of cTSH may be achieved without achieving optional clinical control. The limitations of the current cTSH assay do not allow identification of oversupplementation.

Overdose

Dogs appear to be particularly resistant to the thyrotoxic effects of excessive T_4 supplementation.[252,253] Some dogs require up to 20 times the standard dosage of T_4 to induce clinical thyrotoxicosis. Clinical signs of thyrotoxicosis include polydipsia, polyuria, polyphagia, panting, weight loss, hyperactivity, tachycardia and hyperthermia. Most signs should resolve within a few days of withdrawing therapy. Corresponding TT_4 concentrations are usually >7 mcg/dL (>90 nmol/L). The development of thyrotoxicosis has been reported in one dog because of the consumption of feces from a supplemented housemate.[256]

Gradual Introduction of T_4 Supplementation

Gradual introduction of supplementation (25-50% of starting dose) has been recommended in dogs with concurrent illnesses such as cardiac disease, hypoadrenocorticism and diabetes mellitus. However, using a once-daily dose of 20 mcg/kg was not associated with adverse effects in dogs with such disorders, conferring another advantage to this regimen.[253]

Failure to Respond

A failure to respond to therapy usually arises because of a failure to achieve appropriate circulating thyroid hormone concentrations and usually responds to dosage adjustment. However, the use of T_3 may be required in dogs with concurrent GI disease and impaired T_4 absorption. Failure to achieve the expected clinical response when thyroid hormone concentrations are adequate should prompt investigation of another underlying disease process. Daily but not every-other-day antiinflammatory doses of prednisolone in treated hypothyroid dogs decrease TT_4 concentrations; however, dosage adjustments are not required as FT_4 concentrations remain unaffected.[257]

Myxedema

Myxedema coma is associated with a significant reduction in metabolic rate and, potentially, hypovolemia/dehydration. Neither oral nor SC/IM routes of administration are adequate, at least initially. In these dogs, T_4 should be administered IV at a dosage of 5 mcg/kg q 12 h. Once stabilized, oral administration can be substituted. Resolution of abnormal mentation, ambulation and systolic hypotension should be expected within 30 hours.[86,88]

Anecdotal Treatments

T_4, potentially, has numerous pharmacological effects unrelated to its physiological effects when supplemented in thyroid-deficient states. As a consequence there are anecdotal but rarely proven accounts of the use of T_4 in various clinical situations including the use of T_4 to improve coat condition.[58] THRT has been used in dogs with owner-directed aggression and borderline low thyroid hormone concentrations without any significant effect.[258] In humans, T_4 treatment of patients with non-thyroidal illness syndrome is controversial and there is limited persuasive evidence that it improves outcome with the possible exception of patients with cardiac disease.[184] In dogs, the addition of T_4 to standard therapy for congestive heart failure due to myocardial failure does not improve survival compared to placebo (see ch. 133).[259] Equally, T_4 supplementation does not alter the development of cardiac complications of chronic doxorubicin treatment in dogs.[260]

Prognosis

Overall the prognosis for hypothyroid dogs is excellent.

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CHAPTER 300

Feline Hypothyroidism

Sylvie Daminet

Client Information Sheet: Feline Hypothyroidism

Etiology

Overview

Iatrogenic, congenital and spontaneous naturally occurring adult-onset hypothyroidism have been described in cats. Practitioners are most likely to be confronted with *iatrogenic* hypothyroidism. The potential impact of iatrogenic hypothyroidism on renal function merits particular attention. Although a few well-documented cases of *congenital* feline hypothyroidism have been reported, *spontaneous* adult-onset feline hypothyroidism has been only rarely recognized.

Iatrogenic Hypothyroidism

Iatrogenic hypothyroidism is a well-recognized consequence of treating cats for hyperthyroidism (see ch. 301). It can result from an overdose of anti-thyroid drug administration, bilateral thyroidectomy or radioactive iodine (^{131}I) therapy. Unilateral thyroidectomy may result in transient hypothyroidism. Anti-thyroid drug administration commonly leads to serum total thyroxine (TT_4) concentrations below the reference range, often without clinical signs, perhaps because total tri-iodothyronine (TT_3) concentrations (the active hormone) are usually normal.

Hyperthyroidism, usually caused by autonomously functioning abnormal thyroid tissue, chronically suppresses endogenous thyroid stimulating hormone (TSH) release from the pituitary, ultimately leading to atrophy of normal thyroid tissue. After treating hyperthyroidism with ^{131}I (see ch. 301), the combination of destroying cells that were previously over-active together with the slow recovery of hormone production from atrophied "normal" thyroid tissue can lead to a period of transient hypothyroidism. This simple explanation for the pathogenesis of iatrogenic hypothyroidism is similar to the transient hypothyroidism that follows surgery or even medical treatment. Once the TT_4 decreases in a cat that was hyperthyroid, TSH concentrations should increase. TSH, in turn, stimulates atrophied thyroid cells to function. Following ^{131}I treatment or after thyroidectomy, a transient period of iatrogenic hypothyroidism is common.[2] Hyperthyroid cats with normal renal function and transient hypothyroidism after treatment do not usually have clinical signs of hypothyroidism and do not need hormone supplementation. Administration of thyroid medication will actually delay the recovery of atrophied cells. The incidence of post-radioactive iodine hypothyroidism likely depends, at least in part, on dosage of ^{131}I administered, length of follow-up and the criteria used to define low thyroid function. Thus, the reported incidence varies from as uncommon as 5% to as common as 83%.[2,3] Cats with scintigraphic uptake by both lobes on a pertechnetate scan appear predisposed to development of hypothyroidism after treatment with ^{131}I.[3]

Congenital Hypothyroidism

In general, congenital primary hypothyroidism can be divided into two main categories: *thyroid dyshormonogenesis* (a defect in the biosynthesis of thyroid hormones) and *thyroid dysmorphogenesis* (a defect in anatomic thyroid development, usually described as hypoplasia or aplasia). Both forms in people are likely due to an inherited, autosomal recessive, genetic defect. Dyshormonogenesis is a condition of decreased

synthesis of thyroid hormone, decreased negative feedback to the pituitary (and hypothalamus), increased TSH secretion, thyroid gland hyperplasia, and thyroid gland enlargement (goiter). Dyshormonogenesis associated with defective thyroid peroxidase activity and impaired iodine organification has been described in related domestic shorthair and Abyssinian cats.[4,5] Dysmorphogenesis does not cause thyroid enlargement and has been documented in related cats, whose condition is consistent with an autosomal recessive mode of inheritance.[6] Hypothyroidism secondary to TSH resistance has been suggested in a family of Japanese cats.[7] Hypothalamic or pituitary deficiencies, with secondary congenital hypothyroidism (central hypothyroidism), have not yet been reported in cats.

Adult-Onset Hypothyroidism

Only a few well-documented cats with *spontaneous* (naturally occurring) acquired primary hypothyroidism have been described.[8-10] Histopathologic features of their thyroid glands have been diverse. They include marked lymphocytic infiltration, idiopathic atrophy, and diffuse hyperplastic goiter. Secondary hypothyroidism due to head trauma has been reported.[11]

Clinical Manifestations

Overview

The most common clinical manifestations of iatrogenic, congenital and adult acquired forms of feline hypothyroidism are outlined in Table 300-1 and illustrated in Figure 300-1, *A* and *B* and Video 300-1. Although many signs of hypothyroidism in cats are similar to those considered typical in hypothyroid dogs (see ch. 299), there are differences. For example, few hypothyroid cats, regardless of etiology, develop severe bilaterally symmetrical, non-pruritic alopecia. Inappetence and profound mental dullness are frequently seen. Kittens with congenital hypothyroidism can develop severe constipation.

TABLE 300-1

The Most Important Clinical Features Observed with Iatrogenic, Congenital and Naturally Occurring Adult-Onset Hypothyroidism in Cats

	IATROGENIC HYPOTHYROIDISM	CONGENITAL HYPOTHYROIDISM	NATURALLY OCCURRING ADULT-ONSET
Lethargy	+	+ (May include mental dullness)	+ (May include mental dullness)
Weight gain or obesity	+	+	+
Inappetence	+	+	+*
Constipation	+	+* (May include megacolon)	+
Goiter	− or +	Possible	−
Disproportionate dwarfism	−	+*	−
Delayed closure of growth plates (radiographically)	−	+*	−
Dermatological signs (especially seborrhea and easy to epilate)	+	+	+*

*Indicates this is a key feature.

Clinical features can be mild or severe.

+, Usually present; −, absent.

From Mooney CT, Peterson ME, editors: *Manual of canine and feline endocrinology*, ed 3, Gloucestershire, England, 2011, British Small Animal Veterinary Association, pp 111-115.

FIGURE 300-1 **A,** This 5-year-old male neutered Devon Rex had a history of lethargy, mental dullness and inappetence. The cat also had diabetes mellitus. This cat had low TT_4 serum values, as well as an increased cTSH, confirming primary hypothyroidism. This cat also had a seborrheic hair coat that was easily epilated. Note the bilateral ceruminous otitis. **B,** Same patient as in **A,** one year before onset of clinical signs of hypothyroidism. (Photograph from E. Mercier and S. Daminet.)

Adult-Onset Hypothyroidism (Iatrogenic and Spontaneous)

Lethargy, inappetence and skin changes are common clinical signs and may be severe. Dermatologic signs are characterized by a dull, dry, unkempt haircoat (with possible matting) and seborrhea sicca. Alopecia of the pinnae can develop in some cats. The hair coat is easily epilated and poor regrowth after clipping is possible. Hypothermia and bradycardia are occasionally noted on physical examination. In naturally occurring adult hypothyroidism, signs are often pronounced, perhaps as a result of the profession's low index of suspicion. Thus, the condition is not recognized until it is severe. A puffy face, presumably resulting from myxedema, was reported in one cat.[8]

Congenital Hypothyroidism

Many of the signs observed in adult-onset hypothyroidism can also be seen in affected kittens. Since thyroid hormone is essential for normal post-natal skeletal and nervous system development, kittens with congenital hypothyroidism have striking disproportionate dwarfism and neurologic abnormalities. Affected kittens usually appear normal at birth. Their delayed growth, as compared with littermates, usually becomes evident by 2 month of age and their disproportionate dwarfism develops over the following months. Signs include a large broad head, small ears, a round body, short neck and short limbs. Affected kittens seem mentally dull. They may suffer from severe recurrent episodes of constipation. Sometimes, dullness and retarded growth may go unrecognized by the owners, who present their cat because of recurrent constipation. Seizures were reported as a major problem in two littermates with congenital hypothyroidism.[6] Affected cats have hair coats covering their entire body, but their hair is mainly undercoat with few guard hairs. The teeth are underdeveloped and delays in tooth eruption and replacement of deciduous teeth are common. On physical examination, hypothermia, bradycardia and sometimes palpable goiter (with organification defects) may be detected.

Survival of untreated affected kittens depends largely on the etiology of the congenital hypothyroidism. It is likely that many affected kittens die undiagnosed as part of the "fading kitten syndrome." Affected kittens can die within a few months, while those with partial defects in peroxidase activity can live to adulthood without ever displaying obvious clinical signs of the disease.

Diagnosis

Overview

Diagnosis of feline hypothyroidism can be challenging, regardless of underlying cause. As in dogs, a presumptive diagnosis can be made based on a combination of compatible clinical features and abnormalities noted on routine laboratory test results (anemia and hypercholesterolemia). Confirming a diagnosis of hypothyroidism requires hormone testing or thyroid scintigraphy. Even cats with *iatrogenic hypothyroidism* present a few diagnostic pitfalls despite their recent history of being treated for hyperthyroidism. As geriatric individuals, concomitant conditions are common (e.g., chronic kidney disease), potentially causing the so-

called "euthyroid sick syndrome" (see ch. 299). Also misleading to an owner or veterinarian can be reduced activity and/or weight gain post-therapy. On one hand, these changes are expected as hyperthyroidism resolves. But, on the other hand, they may represent illness or hypothyroidism. Thus, the clinical signs of iatrogenic hypothyroidism and those expected with return to a euthyroid status can somewhat overlap.

Therapy for Hyperadrenocorticism Causing Hypothyroidism or Azotemia

After therapy with ^{131}I, many cats develop a marked but transient decrease in TT_4 to below normal followed by a return to euthyroidism within 3 to 6 months. In most treated hyperthyroid cats with normal renal function, their transient hypothyroidism is not clinically significant and does not need to be treated. It is advisable to wait 3 to 6 months after therapy with ^{131}I before making a diagnosis of *permanent* iatrogenic hypothyroidism, especially if clinical signs of hypothyroidism are not convincing and the cat remains non-azotemic.

There is potential for serious negative impact of hypothyroidism on renal function (see ch. 301), especially in cats with a pre-existing renal condition.[1,12,13] Cats with iatrogenic hypothyroidism (following ^{131}I or thyroidectomy) and azotemia should be treated with L-thyroxine supplementation without delay, because it should enhance glomerular filtration rate, improve renal function, and reduce the severity of azotemia. If a hyperthyroid cat becomes azotemic while receiving anti-thyroid medication, its dosage should be tapered or discontinued. Iatrogenic hypothyroidism has been shown to worsen azotemia and shorten life expectancy in cats with pre-existing chronic kidney disease (CKD).[1] Administration of L-thyroxine immediately following hospitalization after ^{131}I treatment is recommended.[14] Preliminary results in hyperthyroid cats with CKD IRIS stage 2 or 3 suggest the benefit of treating iatrogenic hypothyroidism to avoid worsening azotemia.[14] Also, a protocol using ultra-low dosages of ^{131}I (1-2 mCi) was effective in restoring euthyroidism without inducing iatrogenic hypothyroidism (3%) in mildly hyperthyroid cats with small thyroid nodules.[15]

Spontaneous (Congenital and Adult-Onset) Hypothyroidism

Spontaneous (congenital and adult-onset) hypothyroidism is probably underdiagnosed, but remains rare. Kittens often appear normal at birth and the onset of typical features such as disproportionate dwarfism is often delayed. Some kittens die early or could be misdiagnosed as having idiopathic megacolon or some other congenital condition.

Routine Clinicopathological Features

The incidence of mild normochromic normocytic anemia and/or hypercholesterolemia in hypothyroid cats is not known, but they are observed most frequently in cats with the iatrogenic condition. In congenital hypothyroidism, these changes are inconsistent.[6]

Hormone Concentrations (Figure 300-2)

Total Thyroxine (TT_4)

Low circulating TT_4 concentrations are expected in any hypothyroid cat. A TT_4 result within reference intervals strongly supports euthyroidism and strongly refutes hypothyroidism as a concern. As in dogs, however, TT_4 can be suppressed by non-thyroidal illnesses and the more severe the condition, the lower the TT_4 concentration. Therefore, a decrease in TT_4 concentration is sensitive but nonspecific and should not be considered diagnostic of hypothyroidism. In addition, a variety of drugs has been shown to significantly suppress TT_4 concentrations in dogs.[17] This has not yet been investigated in cats. Because the diagnosis of primary spontaneous hypothyroidism should not be based solely on basal TT_4 results, serum canine TSH (cTSH) measurement, recombinant human TSH (rhTSH) response test or thyroid scintigraphy is indicated to confirm the disease.

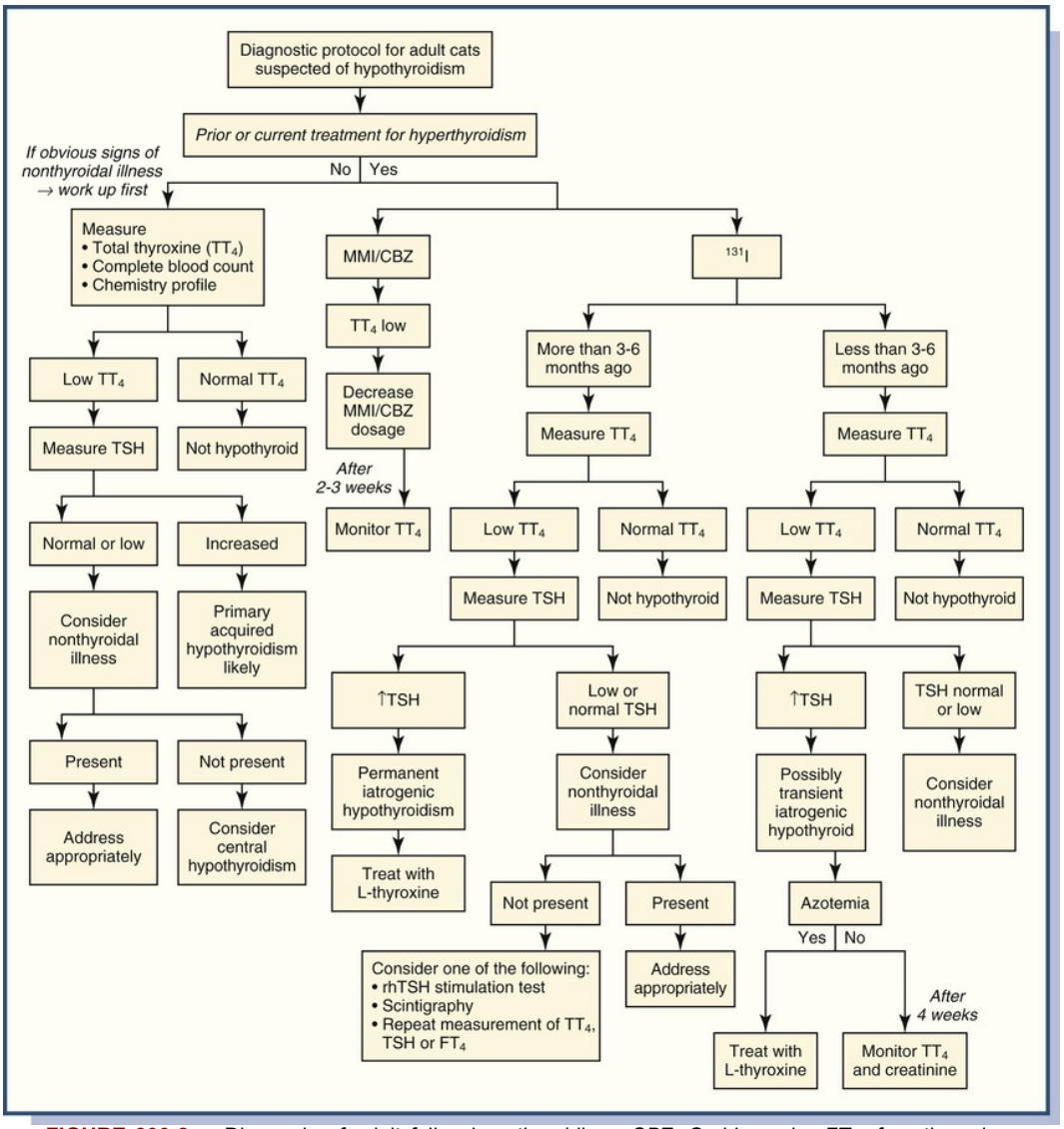

FIGURE 300-2 Diagnosis of adult feline hypothyroidism. *CBZ,* Carbimazole; *FT_4,* free thyroxine; *MMI,* methimazole; *rhTSH,* recombinant human thyroid stimulating hormone; *T_4,* thyroxine; *TSH,* thyroid stimulating hormone.

Free Thyroxine (FT_4)

In contrast to dogs, the benefit of measuring FT_4 as compared with that of TT_4 as diagnostic aids for cats is unclear. Decreased values for FT_4 (after equilibrium dialysis) are expected in hypothyroid cats, but also in the presence of non-thyroidal illness. In one report, however, increased FT_4 concentrations were noted in euthyroid cats with non-thyroidal illness.[16,18]

Endogenous Thyrotropin (TSH)

In dogs with hypothyroidism, an increased serum TSH concentration may confirm primary (located within the thyroid gland) hypothyroidism. A specific assay for feline TSH measurement is not yet available. However, the use of the canine immunoradiometric assay has been described in cats.[19] An increased cTSH concentration was observed in two cats with primary adult-onset hypothyroidism.[9,10] Cats with iatrogenic hypothyroidism should also have increased serum cTSH concentrations.[1,20,21] Use of cTSH (and hopefully feline TSH in the near future) should be helpful in discriminating congenital primary from secondary hypothyroidism (TSH deficiency).

Dynamic Thyroid Function Testing

The rhTSH response test has been described in cats to distinguish non-thyroidal illness from iatrogenic hypothyroidism following ^{131}I therapy.[22] Although evaluated in a limited number of cats, it appears to be a valuable alternative to bovine TSH for stimulation testing. To perform the rhTSH stimulation test in cats, a blood sample is collected for basal TT_4 measurement. Then, 25 mcg rhTSH is administered IV and finally a second blood sample is taken 6 hours later. rhTSH is available as Thyrogen (Genzyme Corporation, The Netherlands) and vials can be aliquoted and stored frozen as previously described to make this test more affordable.[22,23]

Diagnostic Imaging

Radiography

As in dogs (see ch. 299), radiography can be particularly useful in recognizing congenital hypothyroidism. Many of the changes observed are virtually pathognomonic. Radiographs demonstrate retarded skeletal development particularly epiphyseal dysgenesis of vertebral bodies and long bones.

Thyroid Scintigraphy

Uptake of technetium as pertechnetate (99m $TcO4^-$) by thyroid lobes is both sensitive and specific for the diagnosis of canine hypothyroidism or feline hyperthyroidism (see ch. 301) and holds promise for becoming an important tool for diagnosing feline hypothyroidism. It might be especially useful in cats in whom the diagnosis is in doubt, such as in cats with concomitant disease (euthyroid sick syndrome). The expected finding in adult-onset hypothyroidism is a reduction or absence of uptake of 99m $TcO4^-$ by the thyroid glands (Figure 300-3, *A* and *B*). Thyroid scintigraphy was used as a non-invasive technique to confirm the diagnosis of spontaneous hypothyroidism in one cat.[9]

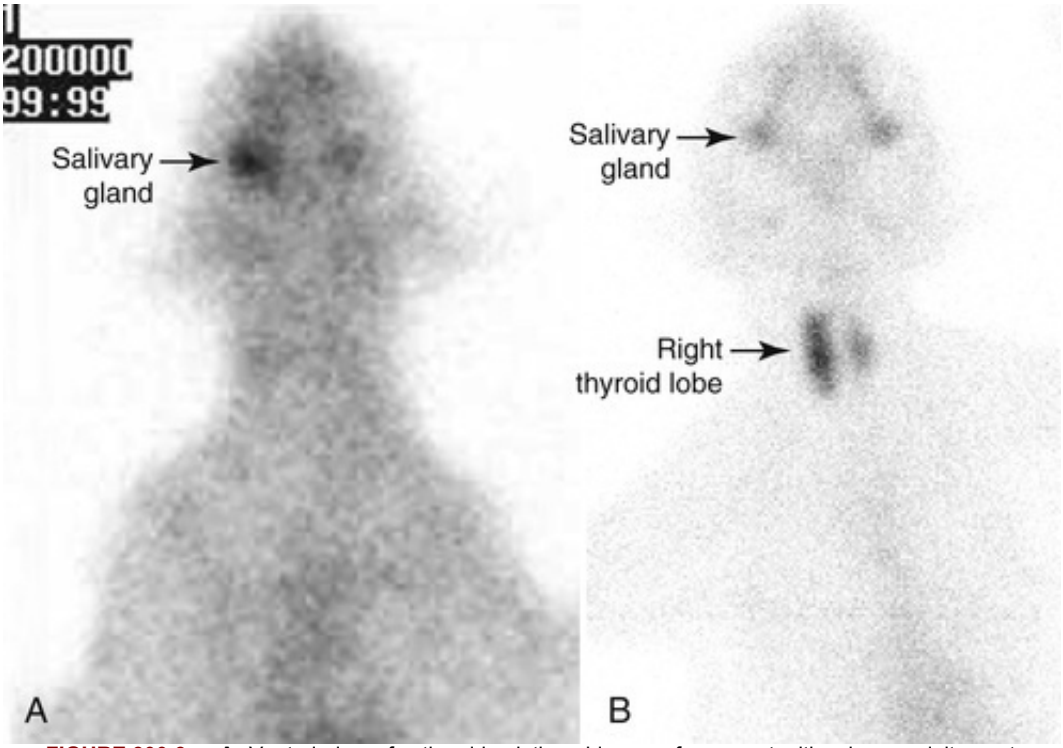

FIGURE 300-3 **A,** Ventral view of a thyroid scintigraphic scan from a cat with primary adult onset hypothyroidism. Note the uptake of pertechnetate in the salivary glands (arrow), and the absence of uptake in the cervical (thyroid) region. **B,** For illustration purposes, this figure shows the increased uptake of pertechnetate visible in the thyroid glands of a hyperthyroid cat. (Images from K. Peremans.)

Further, scintigraphy with ^{123}I can be a helpful diagnostic tool to clarify the underlying mechanism in

congenital hypothyroidism. In cases of dysmorphogenesis, an absence of uptake of ^{123}I is expected. Uptake of ^{123}I may be normal in cases with a thyroid peroxidase deficiency. However, organification (incorporation of iodine) is deficient and abnormal discharge of ^{123}I is observed after administration of perchlorate (perchlorate discharge test).

Practitioners have often used trial therapy with levothyroxine as a diagnostic tool for hypothyroidism. Unfortunately, positive response to treatment does not mean the cat is truly hypothyroid. Combining TT_4 and cTSH measurements is likely to be the most efficient and economic method for diagnosing primary hypothyroidism. When results are equivocal, further diagnostic tests such as rhTSH stimulation test or scintigraphy should be considered before initiating trial therapy with levothyroxine.

Treatment

Although pharmacokinetic data are only available in healthy cats, recommended oral dosages for thyroxine supplementation vary between 100 mcg per cat q 24 h and 10 to 20 mcg/kg q 24 h. Recent preliminary data suggest that twice daily treatment (0.075 mg q 12 h) on an empty stomach might be most efficacious.[24] As in dogs, affected cats should be re-evaluated after 4 to 8 weeks. Further adjustment of therapy should be based on clinical response and post-pill total T_4 therapeutic monitoring. With appropriate therapy, the prognosis is excellent in acquired hypothyroidism. For congenital hypothyroidism, the prognosis is guarded and will largely depend on the underlying etiology of the hypothyroidism and age at diagnosis.

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CHAPTER 301

Feline Hyperthyroidism

Thomas K. Graves

Client Information Sheet: Feline Hyperthyroidism

Since its first description in the veterinary literature only 35 years ago, hyperthyroidism has become the most common endocrine disease of domestic cats and one of the most important diseases in feline practice. There are various prevalence estimates of the disease in North America and Europe indicating that the incidence of the condition appears to be increasing.[1-3] The overall prevalence of feline hyperthyroidism (FHT) is 2% to 4% and at least 6% in cats >9 years of age. By some estimates nearly 10% of geriatric cats will develop FHT.

Pathophysiology

Human Hyperthyroid Conditions (Graves' Disease and Toxic Nodular Goiter)

Thyroid hormones control the body's metabolic rate (thyroid physiology is reviewed in ch. 299). Increase in systemic thyroid hormone concentrations leads to a hypermetabolic state responsible for the abnormalities seen in hyperthyroidism. In people with Graves' disease, the most common form of hyperthyroidism, the condition is the result of autoantibodies activating thyrotropin (TSH) receptors which, in turn, leads to excess synthesis and secretion of thyroid hormone. Evidence of an immune-mediated cause has not been identified in cats, whose thyroid condition is often considered analogous to human toxic nodular goiter (Plummer's disease).[4,5] Toxic nodular goiter and FHT share some histopathologic features. Both are caused by adenomatous hyperplasia of thyroid tissue leading to nodules that secrete thyroid hormone autonomously, escaping control by the hypothalamus and pituitary gland. These nodules rarely demonstrate characteristics of malignancy and are considered benign endocrine tumors. Although there is some controversy in the literature, Plummer's disease is thought to be caused by activated mutations in the TSH receptor or its downstream signaling molecules, leading to high constitutive secretion of thyroid hormone.[6]

Feline Hyperthyroidism

There are conflicting results in the literature, but TSH receptor mutations have been identified in some hyperthyroid cats, as have mutations in the cAMP-activating G protein alpha subunit.[7,8] Decreases in expression of inhibitory G proteins have also been demonstrated in feline goiters, which could decrease the ability to inhibit cAMP production resulting in sustained secretion of excess thyroid hormone.[9] This is likely one of many factors that may contribute to development of FHT. There have been several studies implicating goitrogens in food. Certain types of canned cat food have been implicated in a few epidemiologic studies of FHT and this association continues to be studied.[10,11] It has been suggested that widely disparate concentrations of iodine in commercial cat foods could be responsible for varying levels of TSH stimulation and development of thyroid nodules in cats.[11]

The presence of polybrominated diphenyl ethers (PBDEs) in canned food and in the cat's indoor environment have also been suggested to play a role in the etiopathogenesis of FHT.[12,13] PBDEs are used as flame retardants in any number of household products and can be highly concentrated in house dust ingested by cats during self-grooming. Thyroid disruption caused by PBDEs is postulated to lead to chronic and excessive TSH secretion, which could have a hypertrophic effect on the thyroid gland and eventually result in adenomatous hyperplasia or neoplasia. An association between PBDEs and FHT has not been proven, in part

due to lack of a reliable feline TSH assay and difficulties of studying effects of endocrine disruptors over the lifespans of cats.

Unilateral and Bilateral Thyroid Disease and Histology

Hyperfunctioning thyroid nodules in cats most commonly affect both thyroid gland lobes. Unilateral disease is found in less than a third of cases.[14] Bilateral asymmetric disease occurs in >50% of cats with FHT. Ectopic disease is relatively uncommon, occurring in about 4% of cats. A small percentage of cats with FHT has been diagnosed as having a functional thyroid adenocarcinoma.[14-16] Incidence of thyroid carcinoma has been estimated to be 1-2%, but this is questionable because histology is not often available in afflicted cats.

Clinical Features

Signalment

The largest surveys of clinical findings in cats with FHT were published decades ago.[17-19] Veterinarians have progressively become more aware and better at diagnosing the disease. Thus, some previously published clinical descriptions are no longer commonly encountered.[17-19] FHT is a disease of middle-aged and older cats with no clear breed or sex predilection. In our review of 160 cats with FHT seen at the University of Illinois, the mean age at diagnosis (12.5 years) agrees with earlier reports suggesting 12 to 13 years with a range from 4 to 20 years of age.[17-19]

History (Clinical Signs)

Common

The clinical signs of FHT are variable, reflecting the generalized and multi-systemic nature of the disease. Because of its high prevalence, routine screening with basal serum thyroid hormone testing in middle-aged and older cats is common. FHT diagnosis is often made in cats with subtle (or absent) clinical signs. Common clinical signs (Table 301-1) include weight loss, increased appetite, hyperactivity, vomiting, diarrhea, polyuria/polydipsia, poor grooming, and behavioral changes. Any combination of clinical signs and varying degrees of severity are common. Weight loss is the most common sign of FHT. Afflicted cats are often in poor body condition and have a generally unkempt appearance. Despite their age, cats with FHT may appear hyperactive, aggressive, or exhibit signs of anxiety. Impaired stress tolerance and panting are common.

TABLE 301-1

Percentage of Each Clinical Finding Among Hyperthyroid Cats

HISTORICAL FINDINGS		PHYSICAL EXAM FINDINGS	
Weight loss	88%	Goiter	83%
Polyphagia	49%	Thin	65%
Vomiting	44%	Heart murmur	54%
PU/PD	36%	Tachycardia	42%
Hyperactivity	31%	Gallop	15%
Decreased appetite	16%	Aggression	15%
Diarrhea	15%	Unkempt	9%
Lethargy	12%	Increased nails	6%
Weakness	12%	Alopecia	3%
Dyspnea	10%	CHF	2%
Panting	9%	Neck ventroflexion	1%
Large fecal volume	8%		
Anorexia	7%		

CHF, Congestive heart failure; *PU/PD,* polyuria/polydipsia.

From Broussard JD, Peterson ME, Fox PR: Changes in clinical and laboratory findings in cats with hyperthyroidism from 1983 to 1993. *J Am Vet Med Assoc* 206:302, 1995.

Uncommon

While hyperactivity and increased appetites are common, a small percentage of FHT cats are lethargic, obtunded and have poor appetites. This uncommon condition is referred to as "apathetic" hyperthyroidism. In people, apathetic hyperthyroidism, also termed asymptomatic hyperthyroidism, occurs mainly in the elderly in association with concurrent diseases and/or therapies that cause the lethargy and decreased appetite.[20,21] However, this condition has been described in younger patients.[22] The mechanism of apathetic FHT has not been established. An association between underlying disease states and apathetic FHT has not been published.

Thyroid Palpation

One or more thyroid nodules are usually palpable in FHT. Differing techniques for palpating the feline thyroid gland have been described. The most common and successful technique is performed by placing the cat in a sitting position and extending the head to expose the ventral neck (Figure 301-1, Video 301-1). While holding the cat's head and neck in extension with one hand, the thumb and forefinger of the other hand are slid with moderate pressure from the larynx caudally to the thoracic inlet several times in a slow sweeping motion. Enlargement of the thyroid gland will be felt as a slip of nodular tissue passing under the fingertip. Nodules may be felt on one or both sides of the trachea. This method of palpation is well-tolerated by most cats. Ventral cervical nodules are also palpable in many non-hyperthyroid cats.[23,24] In one study, palpable ventral cervical nodules were present in nearly 70% of euthyroid cats suspected of having FHT.[25] The clinical significance, if any, of these nodules is unknown. In some cats, they may represent non-functional benign adenomas of thyroid or parathyroid origin.[23] Such nodules may or may not progress to endocrine disease. While cats with FHT tend to have larger palpable goiters than those without the disease, no clear relationship between thyroid palpation and functional activity of the feline thyroid gland has been established.

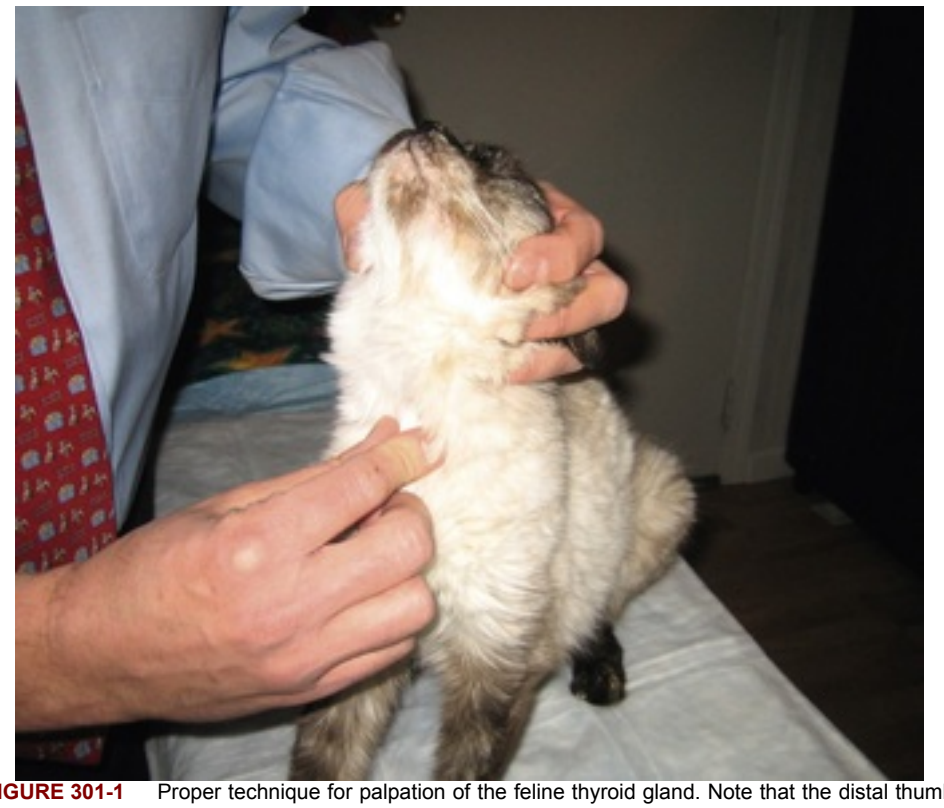

FIGURE 301-1 Proper technique for palpation of the feline thyroid gland. Note that the distal thumb

and forefinger should be extended to provide as much contact with the surface of the cat's ventral neck as possible.

General Examination

Many of the signs described by owners are also obvious on physical examination. Some cats with FHT are periodically or persistently resistant to restraint. Use of an open basket may relax some cats with FHT, allowing a more thorough examination (see ch. 2). Strong or firm restraint of any cat is not recommended, but can result in severe signs in cats with FHT. Weight loss, the most common clinical sign, can be associated with decreased skin elasticity. These cats are not usually dehydrated but can be easily over-loaded if mistakenly thought to be in need of fluid therapy.

Cardiovascular System

The Heart

Systolic heart murmurs, tachycardia, and gallop rhythm are common in cats with FHT, occurring in 54%, 42% and 15%, respectively. Overt congestive heart failure is diagnosed in about 2% of cats with FHT. Thyroid hormone, mainly tri-iodothyronine (T3), has a wide range of cardiac effects.[26] Thyroid hormone has a positive chronotropic effect, causes shorter atrioventricular conduction times, and upregulates myocardial beta-adrenergic receptors. The positive inotropic effects of thyroid hormone (both T3 and thyroxine [T4]) are due to alterations in ion channel activities and enhanced activities of cardiac myosin isoenzymes. Myocardial hypertrophy is common in cats with FHT and is due to increased expression of myocardial proteins and, perhaps, to concurrent hypertensive myocardial hypertrophy.

Blood Pressure

The association between FHT and hypertension is somewhat tenuous. Recognizing hypertension in cats with FHT is not straightforward. Blood pressure measurements are fairly reliable in healthy cats using either oscillometry or Doppler ultrasonography (see ch. 99). Both correlate well with intra-arterial measurements.[27,28] The "white coat effect" is not always recognized in cats, but it may be more pronounced in the stress-intolerant cat with FHT. Initially, prevalence of hypertension in cat with FHT was thought to be high. One publication identified a prevalence of 87%, but their definition of "hypertension" may have been unrealistically low.[29] While the study was well-controlled, with FHT cats being compared to normal cats and to cats with chronic kidney disease (CKD), later reports identified prevalence rates of 5% and 20%.[30,31] Significant "white coat effect" in cats with FHT has been demonstrated, with no decrease in blood pressure after treatment.[30] Interestingly, an increased occurrence of hypertension in cats was seen after being treated for FHT.[31]

Hypertension occurs rarely in hyperthyroid people, and when associated with thyrotoxicosis, the hypertension is usually systolic only. Thyroid hormone causes pronounced decrease in peripheral vascular resistance. Hemodynamic effects of thyrotoxicosis include increased heart rate and increased stroke volume. It has been proposed that increased heart rates cause summation of pressures in peripheral arteries resulting in overall systolic hypertension.[32] Whether or not this also occurs in cats with FHT is not known. Cats with FHT have been reported to have diastolic hypertension, possibly related to underlying CKD. Furthermore, beta-adrenergic blockers are effective in treating hyperthyroid people with systolic hypertension, but the effect of atenolol on hypertension in FHT cats is inconsistent.[33] It is difficult to know if FHT causes hypertension. There is an association between the two, but cause and effect has not been established and hypertension may not be common. In one study, only 5 of 30 cats with hypertension had FHT.[34] In a study of cats with hypertensive retinopathy, only 5 of 69 cats were hyperthyroid.[35]

Urinary System

Polyuria and polydipsia (PU/PD) are seen in more than a third of FHT cats and several mechanisms may explain this effect. Hyperthyroid people have exaggerated thirst responses to small changes in plasma osmolarity as compared with euthyroid subjects. This led investigators to propose primary polydipsia as a cause of polyuria in hyperthyroidism.[36] Thyroid hormone–associated down-regulation of aquaporin water channels in the renal tubules and increased tubular solute excretion have also been implicated as possible

causes of primary polyuria in hyperthyroidism.[37] Neither mechanism has been examined in cats with FHT, but either or both could have roles.

Thyroid hormones affect a wide range of physiologic processes taking place in the kidneys.[38-40] Because thyroid hormone affects cardiac output and peripheral vascular tone, thyroid hormone impacts renal blood flow and glomerular function. The concept of increased renal blood flow in FHT is supported by thyroid hormone–induced decrease in systemic vascular resistance causing relaxation of smooth muscle within capillaries. Also, relaxation of smooth muscle follows action of local vasodilators, increased responsiveness to acetylcholine, and decreased response to endothelin.

In the renal cortex, thyroid hormone excess is accompanied by increased nitric oxide synthase activity (causing increased vasodilation), increased numbers of beta-adrenergic receptors, and decreased vascular resistance. These may lead to activation of the renin-angiotensin-aldosterone system. Decreased afferent arteriolar resistance and increased hydrostatic pressure lead to increases in glomerular filtration rate. There are also multiple effects of thyroid hormone on renal tubular function, including upregulation of chloride channels and enhanced reabsorption of chloride ion in proximal tubules and the loop of Henle. This, in turn, decreases the chloride load sensed in the macula densa of the distal tubule, increases tubuloglomerular feedback, and increases glomerular filtration. Excess thyroid hormone increases sodium-potassium ATPase activity and sodium-hydrogen exchange, leading to enhanced Na+/Ca++ exchange and tubular re-absorption of calcium ion. An association between hyperthyroidism and mild hypercalcemia, while not documented in cats, has been recognized for many decades in thyrotoxic people. The opposite, hypocalcemia, has been reported in FHT cats.[41,42] Thyroid hormone decreases serum creatinine concentrations by increasing its tubular secretion, increasing GFR, and decreasing skeletal muscle mass. Serum creatinine, derived from the breakdown of creatinine and phosphocreatine in muscle, is inversely proportional to muscle mass. Despite mechanisms that could lower serum creatinine concentrations in FHT cats, roughly 25% are azotemic at the time of diagnosis. While increased serum urea nitrogen was noted in 26% and creatinine in 23% of cats with FHT, these findings likely reflect the reality of both conditions being common in cats.[18]

Gastrointestinal System

Vomiting and diarrhea are common in cats with FHT (see Table 301-1). Vomiting in non-pregnant thyrotoxic people is uncommon and thought to be caused by thyroid hormone stimulating the chemoreceptor trigger zone or related to gastric stasis.[43,44] The mechanism of hyperemesis in FHT is not clear. Thyrotoxicosis changes small intestinal muscular contractions, increases intestinal motility, and markedly decreases mouth-to-cecum transit times, contributing to the diarrhea common in hyperthyroidism.[45,46]

Routine Diagnostic Evaluation

Urinalysis

There are no urinalysis findings that are specific for FHT. However, FHT cats are often isosthenuric, as previously discussed. Because FHT cats may have concurrent CKD, diabetes mellitus, or a myriad of other conditions, urinalysis is essential (see ch. 72).

Complete Blood Count

Mild erythrocytosis is noted in about half the cats with FHT. Because "anemia of chronic disease" is expected in older sick cats, a high-normal or slightly increased hematocrit should alert the clinician to consider FHT even if serum thyroid hormone concentrations are normal. Increased cellular oxygen demand is an established mechanism of thyroid hormone-erythropoietin-induced erythropoiesis in hyperthyroidism.[47,48] Thyroid hormone may also act directly on the bone marrow. Eosinopenia and lymphopenia are additional complete blood count (CBC) abnormalities in FHT cats, occurring in 34% and 40%, respectively.[18]

Serum Biochemistry

Increased liver enzyme activity is common in hyperthyroid cats.[17-19] More than 80% of cats with FHT have increased alanine aminotransferase activities and more than half have increased alkaline phosphatase activities. The causes for these changes are multifactorial and are likely related to metabolic hepatic stress, passive congestion, direct toxicity of thyroid hormone, and other factors. About one fourth of hyperthyroid

cats are azotemic at the time of diagnosis. Some of this can be pre-renal, but concurrent renal disease is common.

Confirming the Diagnosis

Total and Free Thyroxine (tT4, fT4), T3, and Thyroid Stimulating Hormone (TSH) Assays (Figures 301-2 and 301-3)

Blood Tests Available and Use of Total T4 as a Screening Test

Thyroid hormone assays, including assays for total thyroxine (tT4), total tri-iodothyronine (tT3), and, to a lesser extent, free T4 (fT4), are widely available. Serum thyrotropin (TSH) measurement is not widely used cats, but may be of value. Measurement of basal serum concentrations of tT3 is not of diagnostic value because of the large degree of overlap between normal cats, FHT cats, and cats with non-thyroidal illness.[49,50] The most commonly used screening test is measuring the serum tT4 concentration. A result above reference intervals confirms the diagnosis in more than 91% of FHT cats.[50]

FIGURE 301-2 Daily fluctuation of serum total T4 concentrations in a cat with hyperthyroidism over a period of 15 days. Fluctuation into the normal range (shaded area) may explain the phenomenon of occult hyperthyroidism in some cats. (Data from Peterson ME, Graves TK, Cavanagh I: Serum thyroid hormone concentrations fluctuate in cats with hyperthyroidism. *J Vet Intern Med* 1:142, 1987.)

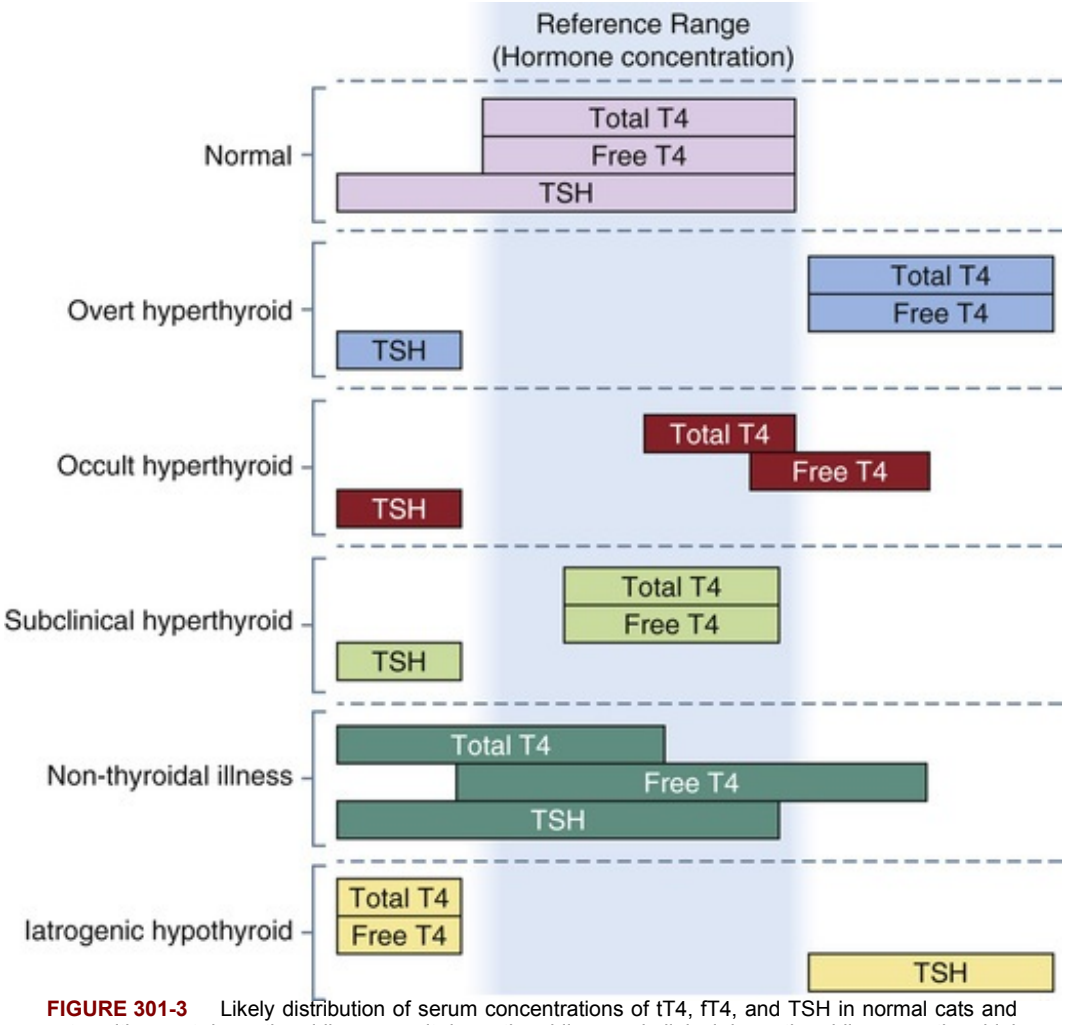

FIGURE 301-3 Likely distribution of serum concentrations of tT4, fT4, and TSH in normal cats and cats with overt hyperthyroidism, occult hyperthyroidism, subclinical hyperthyroidism, nonthyroidal illness, and iatrogenic hypothyroidism. The normal reference ranges for all three hormones are represented by the shaded area. (Based on data published in references 3, 50, 51, 52, 53, 54, 55, and 57.)

tT4 within Reference Limits?

Finding a normal serum tT4 concentration does not exclude the diagnosis of FHT. A relatively high number of hyperthyroid cats have normal or high-normal serum basal tT4 results, a phenomenon referred to as "occult hyperthyroidism" with several possible explanations. First, thyroid hormones fluctuate from day to day in FHT.[51] Even cats with severe FHT have tT4 concentrations that occasionally decrease into reference ranges for a few days at a time (Figure 301-2). Therefore, the simplest approach to a cat strongly suspected to have FHT but in which the tT4 concentration is normal is to simply recheck the tT4 on another day. Another possible explanation for the finding of normal serum tT4 concentration in a cat with FHT is presence of non-thyroidal illness (Table 301-2). Almost any concurrent disease can lower serum tT4 concentrations, causing false negative test results in FHT.

TABLE 301-2

Mean Serum Total Thyroxine (tT4) Concentrations in Normal Cats and Cats with Various Nonthyroidal Illnesses

DISEASE	MEAN TOTAL T4
Diabetes mellitus	4 nmol/L

Hepatic disease	8 nmol/L
Chronic kidney disease (CKD)	10 nmol/L
Systemic neoplasia	12 nmol/L
Congestive heart failure	11 nmol/L
Inflammatory bowel disease	18 nmol/L
Inflammatory airway disease	14 nmol/L
Focal neoplasia	16 nmol/L
Normal cats	**24 nmol/L**

From Peterson ME, Gamble DE: Effect of nonthyroidal illness on serum thyroxine concentrations in cats: 494 cases (1988). *J Am Vet Med Assoc* 197:1203, 1990.

Free T4 (fT4)

fT4 represents the small fraction of tT4 not bound to serum proteins. fT4, therefore, is available for conversion to T3 (the active hormone). Diagnosis of FHT can be confirmed by measuring serum concentrations of fT4, provided that the assay is validated for cats. fT4 has a high sensitivity for FHT, being positive in more than 98% of cats with FHT.[50] Possibly more important is the finding that serum fT4 concentrations are increased in 95% of cats with occult hyperthyroidism.[50] Even though the sensitivity of fT4 appears to be higher than that of tT4, it is not recommended as a first-line diagnostic screening test for FHT because of its poor specificity and its poor positive predictive value. As many as 12% of cats with non-thyroidal disease have increased serum concentrations of fT4, indicating that a given fT4 measurement only be interpreted in context of the clinical signs and results of the urinalysis, CBC, serum chemistry profile and tT4.[49,52]

In addition to its lower specificity, fT4 assays tend to be expensive and assay methodologies can be controversial. There are various types of assays for fT4 and correct assay methods should be used. Basically, there are two general types of fT4 assays. In the one-step assay, fT4 is measured in plasma or serum in the presence of protein-bound T4. In two-step assays, techniques such as dialysis or ultracentrifugation are used to separate the fT4 from the sample in the first step, and then a highly sensitive fT4 assay is used. While the equilibrium dialysis method of assaying fT4 is valid, published studies to support the recommendation that only this type of assay be used are lacking.

Combined Use of Total and Free T4

Although one study indicated that combining serum tT4 and fT4 did not improve diagnostic accuracy of either test used alone,[53] the combination may still be of use in individuals. Cats with non-thyroidal illness and an increased fT4 are expected to have a low serum tT4 concentration and cats with occult FHT are expected to have an increased fT4 and a normal or high-normal tT4. However, tT4 concentrations below the mid-point of reference ranges have been reported in cats with occult FHT.[51]

Serum TSH

In one series of cats with both FHT and CKD, serum TSH concentrations were low in all cats.[54] TSH values have been used to describe "subclinical hyperthyroidism" in cats as well.[3,55] In subclinical FHT, basal serum thyroid hormone concentrations, including fT4, are normal, while serum TSH is low. Cats with this constellation of hormone results have an increased likelihood for histologic evidence of nodular hyperplasia and/or adenoma of the thyroid gland.[55] These cats are more likely to develop FHT within a shorter time-frame than cats with normal serum TSH concentrations.[3] However, reliable assays for feline TSH measurement are not widely available. Canine TSH assays have been used, but when using recombinant feline TSH, the canine assay detects ≤40% of feline TSH, making low concentrations difficult to interpret.[56] Finding an increased serum TSH result may be more useful because it can indicate iatrogenic hypothyroidism following treatment of hyperthyroidism.[57]

T3 Suppression Testing

Indications

In cats with clinical signs of FHT but with equivocal basal thyroid hormone results, T3 suppression testing can be used.[58,59] FHT cats have autonomously functioning thyroid nodules that secrete thyroid hormone independent of pituitary control. As such, pituitary TSH secretion is expected to be chronically suppressed. In normal cats, administration of exogenous T3 suppresses pituitary TSH secretion and subsequently causes a drop in the serum concentration of tT4. In cats with FHT, however, administration of exogenous T3 has little or no effect on serum tT4 concentrations. The T3 suppression test reliably differentiates cats with occult hyperthyroidism from cats with normal thyroid function. The test takes 2 days and 2 hospital visits for blood collection and may be inconvenient.

Protocol and Interpretation

Blood is collected, serum separated, and stored frozen or refrigerated before giving 7 doses of T3 (liothyronine sodium, Cytomel, Pfizer, New York, NY). Beginning the day after initial blood sampling, T3 is administered (25 mcg/cat PO q 8 h for 2 days). On the morning of day 3, the cat is given its seventh dose of T3 and then returned to the clinic for post-T3 blood sampling. Both the pre- and post-T3 samples are assayed for tT4 and tT3 on the same assays to mitigate intra-assay variation. If owners were successful in administering T3, the serum concentration of tT3 is higher in the second sample (the only reason tT3 is measured). In healthy cats, serum concentrations of tT4 are suppressed by exogenous T3, whereas in FHT cats, decreases in serum tT4 are either blunted or absent. There is little or no overlap between post-T3 serum tT4 concentrations comparing euthyroid and hyperthyroid cats. The T3 suppression test can be valuable for diagnosing FHT in cats with normal basal thyroid hormone test results.

Thyrotropin-Releasing Hormone Stimulation Testing

When administered IV to healthy cats, TRH causes consistent increases in serum tT4 concentrations, usually about twofold. In FHT cats, the post-TRH rise is either blunted or absent, potentially making the test a useful tool for diagnosis of occult FHT.[60] This test is performed by measuring serum tT4 concentrations before and 4 hours after IV TRH (0.1 mg/kg); normal cats exhibit >60% increase in tT4. tT4 increases in cats with FHT are <50%.[60] While this test may be of use in diagnosing FHT in cats with normal resting serum tT4 concentrations, it has significant drawbacks. While available in some countries, commercial TRH was removed from the U.S. market in 2002 and laboratory-grade TRH cannot be recommended for clinical patients.[61] One report suggested limited diagnostic accuracy of the TRH stimulation test in cats with concurrent illness, a group that may include cats with the occult form of FHT.[62] Administration of TRH often causes severe cholinergic and central nervous system–mediated reactions.[63-66] Within seconds of being given TRH, cats often exhibit transient but severe salivation, tachypnea, micturition, nausea, vomiting and diarrhea.

Thyroid Scintigraphy

Thyroid gland uptake of pertechnetate or radioactive iodine is extremely sensitive for diagnosing FHT.[67] Either thyroid pertechnetate uptake or thyroid-to-salivary ratio can be calculated. Both correlate strongly with hyperthyroxinemia. The use of these tests is limited by their availability. In a recent large-scale study of thyroid scintigraphy results in FHT, nearly 99% had a thyroid-to-salivary ratio of >1.5 versus healthy cats' ratio of <1 (Figure 301-4). Thyroid-to-background ratio is less sensitive than the thyroid-to-salivary ratio. Because these tests require sophisticated facilities, sedation, and injection of a radioactive agent, thyroid scintigraphy is not commonly used to confirm a diagnosis of FHT. Its greatest value may be in the pre-surgical evaluation of cats undergoing thyroidectomy because it can be used to identify unilateral versus bilateral disease, ectopic disease, intrathoracic disease, and can raise the index of suspicion for thyroid carcinoma.

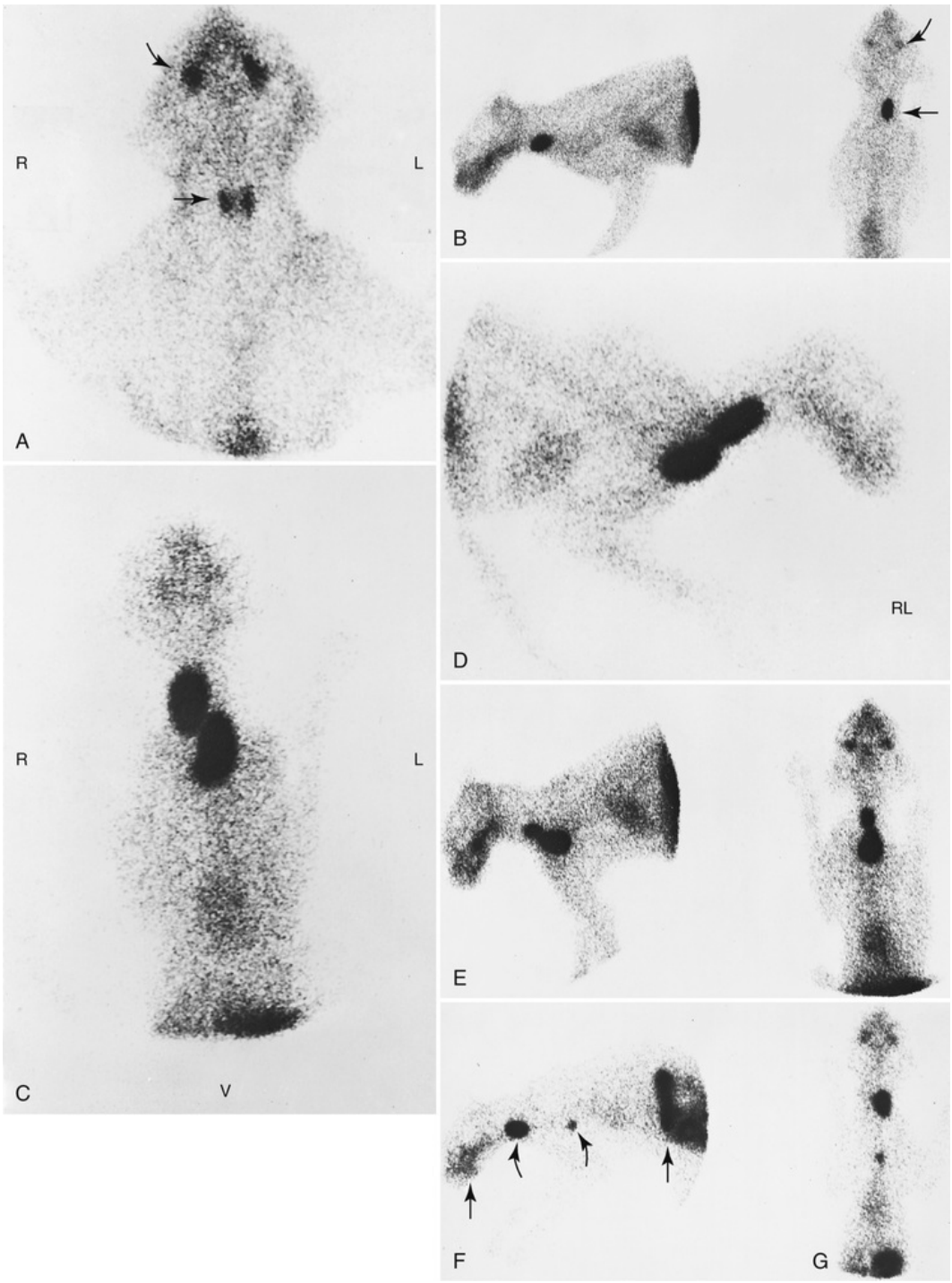

FIGURE 301-4 **A,** Thyroid scan (radioactive technetium-99m [99mTc]) of a normal cat. Note the similar size and density of the thyroid lobes (straight arrow) and the salivary glands (curved arrow). **B,** Thyroid 99mTc scan from a thyrotoxic cat with a unilateral thyroid tumor. Note the density of the thyroid (straight arrow) compared with that of the salivary glands (curved arrow). **C** and **D,** Thyroid 99mTc scan from a thyrotoxic cat with bilaterally symmetric adenomatous hyperfunctional thyroids. **E,** Thyroid 99mTc scan from a thyrotoxic cat with bilaterally asymmetric adenomatous hyperfunctional thyroids. **F** and **G,** Lateral and dorsoventral views of a thyroid 99mTc scan from a thyrotoxic cat with bilaterally asymmetric adenomatous hyperfunctional thyroids. Note that this scan shows the larger thyroid above the smaller rather than the more common larger mass descending further and usually located below the smaller mass **(C-E). F** and **G,** Note the large thyroid in the neck (large curved arrow on lateral view); the small, adenomatous thyroid tissue in the anterior mediastinum (small curved arrow); the salivary glands and the saliva, which concentrates pertechnetate (small straight arrow); and the gastric mucosa, which concentrates pertechnetate (large straight arrow). (From Feldman EC, Nelson RW, Reusch CE, et al: *Canine and feline endocrinology and reproduction,* ed 4, St Louis, 2015, Saunders.)

Treatment

Overview and Prognosis

If hyperthyroidism is untreated, the condition usually progresses to severe metabolic compromise, heart disease, and death. Although survival times in untreated FHT have not been reported, median survival times for cats treated with radioiodine have ranged from 2 to over 5 years (Table 301-3).[68-70] Although female cats apparently survive longer than do males after FHT treatment, both can live long lives. FHT can be treated with anti-thyroid drugs (thioureylenes), radioiodine, surgical thyroidectomy, or via dietary elimination of iodine (Table 301-4). Side-effects are associated with all treatments for FHT. Adverse effects after resolving FHT include renal insufficiency and hypothyroidism.

TABLE 301-3

Effect of Age and Gender at Diagnosis on 5-Year Survival Rates in Cats with Hyperthyroidism

AGE AT DIAGNOSIS	GENDER	5-YEAR SURVIVAL
10 years	F M	42% 28%
13 years	F M	25% 13%
16 years	F M	11% 4%

Data from Slater MR, Geller S, Rogers K: Long-term health and predictors of survival for hyperthyroid cats treated with iodine 131. *J Vet Intern Med* 15:47, 2001.

TABLE 301-4

Comparison of Treatment Considerations for Feline Hyperthyroidism

	THIOUREYLENE DRUGS	RADIOIODINE	THYROIDECTOMY
Initial cost	Low	High	High
Long-term cost	Moderate	Low	Low
Anesthesia	Never	Sometimes	Always
Ease of use	Easy	Moderate	Difficult
Recurrence	Common	Rare	Moderate
Time to euthyroid	2-4 weeks	Immediate	2-4 weeks
Hospitalization	None	3-10 days	1-3 days
Blood dyscrasias	Rare	Never	Never
Hypocalcemia	Never	Never	Common
GI side-effects	Common	Never	Never

Thioureylene Anti-Thyroid Drugs

Action

Methimazole is the most commonly used drug to treat FHT. Methimazole is available and approved for use in cats in the United States, while both methimazole and carbimazole, a "pro-drug" of methimazole, are approved for use in Europe. A third anti-thyroid drug, propylthiouracil, is available but rarely used due to early reports of its causing hemolytic anemia and thrombocytopenia.[71,72] Thioureylenes inhibit thyroid follicular cell thyroperoxidases, inhibiting iodination of tyrosyl residues in thyroglobulin, and inhibiting

coupling of tyrosyl residues into T4 and T3. These drugs decrease production of thyroid hormone, deplete follicular cellular stores of pre-made hormone, decrease circulating concentrations of thyroid hormone and reverse thyrotoxicosis.

Oral Administration

Because the degree of thyrotoxicosis varies from patient to patient, anti-thyroid drugs must be titrated to individual needs.[73] The recommended methimazole starting dose is about 2.5 mg/cat PO q 12 h. Carbimazole, available in a sustained-release formulation, is started at 10 or 15 mg, PO, once daily. Dosage adjustments should be based on response to treatment. Euthyroidism should return within 2 to 3 weeks if the dose of anti-thyroid drug is adequate. Most cats are controlled on the 2.5 mg PO q 12 h dose of methimazole, and reported successful doses have ranged from 2.5 to 20 mg/day for methimazole and 10 to 20 mg/day for sustained-release carbimazole. In general, doses should be adjusted to achieve a basal serum tT4 concentration that is at or below the middle of the reference range for tT4. Methimazole-treated cats with high-normal serum tT4 concentrations do not consistently exhibit resolution of clinical signs.[74] While some have suggested larger once-daily doses of methimazole can be substituted for the recommended q 12 h protocol, once-daily methimazole is not as effective.[75]

Transdermal

Although oral anti-thyroid drugs are typically well-tolerated by cats and the owners who are required to administer the pills, some cats cannot be so-treated.[76] Some cats exhibit adverse gastrointestinal (GI) effects and some owners are unable to administer the medication. In such cases, transdermal methimazole can be used.[77,78] Transdermal formulations are typically produced by compounding pharmacies and care must be taken to ensure their quality and consistency (see ch. 168). Effective dosages of transdermal methimazole do not differ significantly from oral requirements, but some considerations must be kept in mind. First, there is evidence to suggest that it takes longer to achieve euthyroidism (4 weeks) with transdermal methimazole.[78] It is reasonable, therefore, to begin monitoring tT4 later. Also, owners must be warned to use gloves when administering transdermal methimazole to avoid all dermal contact. Methimazole is much more potent in people than cats and transdermal methimazole is highly effective in treating hyperthyroid people, so even small amounts could have an effect on an owner.[79] Response to transdermal methimazole has been less consistent than with the oral drug in achieving reference range serum tT4 concentrations.[80]

Severe Adverse Side-Effects

Unwanted side-effects are common when treating cats with antithyroid drugs. Because some adverse reactions can be life-threatening (Table 301-5), it is important to initially monitor cats closely. Adverse reactions usually occur within the first 3 months of starting treatment and this is the recommended time period to closely monitor cats.[74] Life-threatening adverse reactions include agranulocytosis, thrombocytopenia, severe hepatopathy, and non-thrombocytopenia-associated bleeding. If any of these reactions occurs, the anti-thyroid drug used must be stopped immediately. The mortality rate with these adverse drug reactions is high. These severe adverse reactions seen with methimazole therapy are not reported with carbimazole, but they can still happen. It makes little sense that adverse reaction profiles would be very different between the two drugs because carbimazole is metabolized to methimazole in order to exert its therapeutic effect. It is also important to note that while GI side-effects are less common in cats treated via the transdermal route, the risk of life-threatening adverse reactions is certainly not mitigated by switching from oral to transdermal therapy, and may even be worse. No cohesive study comparing the adverse effects of randomly assigned anti-thyroid drugs used to treat FHT has been completed, so drug comparisons are difficult.

TABLE 301-5

Frequency of Suspected Life-Threatening Adverse Reactions to Methimazole

	ORAL METHIMAZOLE	TRANSDERMAL METHIMAZOLE
Hepatopathy	2.6%	4%

Bleeding diathesis	2.5%	Not reported
Thrombocytopenia	2.8%	8%
Agranulocytosis	2.7%	6.1%

Other reported suspect adverse reactions include case reports of myasthenia gravis and aplastic anemia.

Adapted from Daminet S, Kooistra HS, Fracassi F, et al: Best practice for the pharmacological management of hyperthyroid cats with antithyroid drugs. *J Small Anim Pract* 55:4, 2014.

Common and Mild Adverse Effects

The more common adverse reactions seen with anti-thyroid drugs are not life-threatening but can be reasons for treatment failure (Table 301-6). GI signs, including nausea, vomiting, lethargy, and diarrhea, are common. Carbimazole apparently carries a greater risk of GI side-effects.[73] Leukopenia, eosinophilia, and lymphocytosis have been noted. These changes should be monitored, as they usually resolve despite continuing treatment. The mild leukopenia seen with thioureylene use can be unsettling because of the fear of agranulocytosis, but stopping treatment is not usually necessary. Facial excoriation, a severe but not life-threatening reaction, is seen in some cats treated with anti-thyroid drugs. It is thought that cats probably experience pruritus in their facial skin as a drug reaction, since they scratch themselves excessively, causing bleeding wounds of the face, head, and neck. This adverse drug reaction requires cessation of anti-thyroid drug therapy. When side-effects that are not life-threatening necessitate cessation of an anti-thyroid drug, reactions to later re-challenge with the drug are not predictable.

TABLE 301-6

Frequency of Suspected Non-Life-Threatening Adverse Reactions to Methimazole and Carbimazole

	ORAL METHIMAZOLE	TRANSDERMAL METHIMAZOLE	ORAL CARBIMAZOLE
Gastrointestinal signs (vomiting, anorexia)	22%	3.7%	33%
Mild hematological abnormalities (leukopenia, eosinophilia, lymphocytosis)	16.4%	Not reported	34.9%
Facial excoriations	4%	8%	11.6%

Adapted from Daminet S, Kooistra HS, Fracassi F, et al: Best practice for the pharmacological management of hyperthyroid cats with antithyroid drugs. *J Small Anim Pract* 55:4, 2014.

Owner Compliance

One of the major drawbacks of using methimazole or carbimazole for the long-term management of FHT is the need for prolonged owner compliance. Because anti-thyroid drugs do not "cure" the clinical condition, they must be given for the life of the cat and this can be difficult for some owners. In addition, the disease tends to advance despite treatment with anti-thyroid drugs, and this commonly necessitates increases in the drug dosage over time in order to maintain euthyroidism. Although reasons are not clear, one study indicated that cats treated with methimazole alone have less than half the median survival of cats treated with radioiodine or those cats initially treated with methimazole and eventually treated with radioiodine.[69] This may have nothing to do with the treatment, but rather on the condition of the cats and the financial means of the owners when selecting treatment.

Radioiodine Therapy

Overview

Use of ^{131}I may be the treatment of choice for FHT.[70,81] Thyroid hormones and thyroglobulin are the only iodinated organic molecules in the body, so any ingested or injected iodine is taken up by the sodium-iodide symporter of thyroid follicular epithelial cells. Thus, radioactive isotopes of iodine are concentrated in the thyroid gland where their beta-particles exert significant local tissue damage, destroying hyperactive thyroid tissue. Adjacent normal tissue can certainly be affected as well, but radioiodine is administered at dosages

aimed to achieve euthyroidism.

Dosage, Protocol and Adverse Effects

Several methods are used for calculating dose of radioiodine needed to treat FHT. Use of radioiodine tracer kinetic studies is the most cumbersome method for dose determination. Some clinicians use a fixed dose of ^{131}I for all cats, typically 4 to 5 mCi. A third method of radioiodine dose determination uses a scoring rubric that employs thyroid gland size, clinical signs, and the serum tT4.[70] No method has a clear advantage. Different methods of administering radioiodine include IV, SC, and PO.[81] It is common for FHT cats to be treated with anti-thyroid drug therapy prior to choosing radioiodine therapy. Radiation therapists often recommend that methimazole use be discontinued for a specified period of time prior to radioiodine administration, but this practice is questionable. In a report of response predictors for radioiodine therapy, there was no difference in treatment outcomes in comparing cats whose methimazole was withheld more or less than 5 days prior to treatment.[82] Other than post-treatment renal insufficiency and, sometimes, hypothyroidism, adverse reactions to radioiodine therapy are rare. Transient dysphagia, likely due to radiation-induced inflammation in the thyroid gland, has been reported rarely.[70]

Patient selection is important when considering radioiodine therapy. Most cats tolerate radioiodine therapy without problems. Because cats will be housed in an isolated environment for radiation safety purposes, cats with concurrent medical conditions that require frequent observation or treatments are poor candidates, as are cats suffering from extreme anxiety due to separation from their families. Hospitalization times for cats undergoing radioiodine therapy typically range from 3 to 10 days depending on the individual facility's radiation licensing requirements.

Surgical Thyroidectomy

When performed by a skilled and experienced surgeon, results of surgical thyroidectomy are usually satisfactory for permanently resolving FHT with few complications (Figure 301-5).[16] Surgical complications included transient hypocalcemia (due to removal of or damage to the parathyroid glands or their blood supply) in 6% of cats and death within 3 days of surgery in 3%. Development of hypocalcemia is the most important reason to monitor cats for 2 to 3 days post-surgically in-hospital. If hypocalcemia develops, it is treated with calcium and vitamin D supplementation (see ch. 298). Hypocalcemia is nearly always transient. An argument against surgical thyroidectomy as a treatment for FHT is anesthetic risk. Therefore, it is often recommended that cats be treated to achieve euthyroidism with anti-thyroid drugs prior to surgical thyroidectomy. While logical, there are no reports supporting this recommendation.

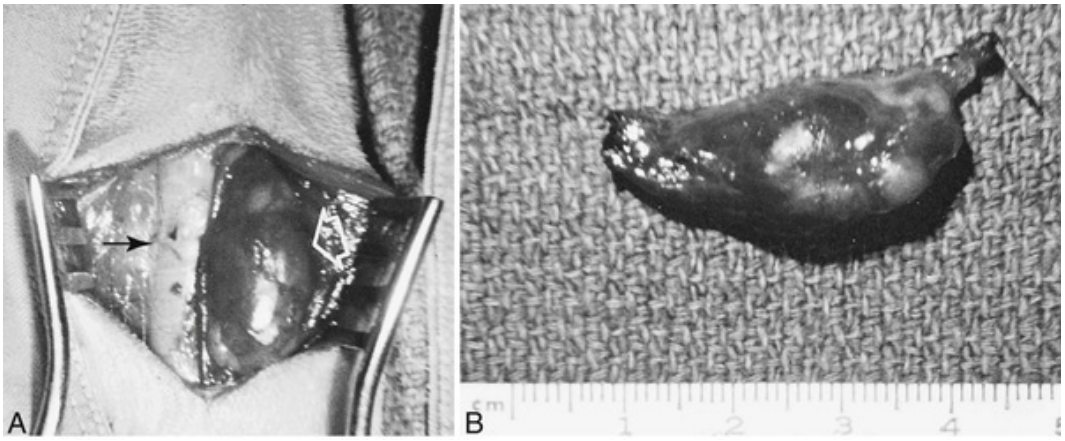

FIGURE 301-5 **A,** Photograph of the thyroid (open arrow) at surgery in a cat with unilateral hyperthyroidism. Note the trachea (closed arrow). **B,** The solitary adenoma after complete excision. (From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction*, ed 3, St Louis, 2004, Saunders.)

Dietary Management

Background

An iodine-restricted diet for treating FHT (Hill's y/d) is commercially available. Iodine is necessary for the production of thyroid hormone. Strict restriction of dietary iodine can be expected to reduce thyroid hormone concentrations. Early data on the efficacy of this diet were only available in abstract form, authored by the manufacturer. This raised concern regarding the effectiveness of diet in controlling hyperthyroxinemia and its clinical signs. There were also concerns about possible adverse effects of iodine deficiency in cats. A prospective non-controlled study, funded by the diet manufacturer, provides answers to some of these concerns.[83]

Efficacy

A large number of FHT cats, some previously treated with a different modality and some newly diagnosed, were fed the iodine-restricted diet for 8 weeks in a recent study. Clinical signs of FHT, as reported by owners or primary care clinicians, improved significantly by week 4 of dietary management. No adverse effects observed. Serum tT4 concentrations decreased to the reference range in 68% of cats at week 4 and in 75% of cats at week 8. Serum tT4 concentrations, however, remained in the upper reference range. Ratios of upper limit of normal tT4 concentration to measured value were 0.91 and 0.69 at 4 and 8 weeks, respectively. Some could consider it questionable that clinical hyperthyroidism would resolve when tT4 concentrations remain at the upper end of the normal range. Cats exhibit reversal of signs more consistently, for example, when post-methimazole serum tT4 concentrations are in the lower half of the normal range.[74] A compelling result from the study of van der Kooij et al is that there was no decrease in serum creatinine or urea nitrogen concentrations in the cats fed the iodine-restricted diet. This could have important implications for cats that develop renal failure following treatment of hyperthyroidism; conversely, it could be viewed as further evidence that dietary treatment was not effective.

Recommendation

If an iodine-restricted diet is chosen to treat FHT, the following points should be taken into consideration. First, because little iodine is required for thyroid function, only the iodine-restricted diet can be fed. All other food, treats, or captured prey would likely have enough iodine content to counteract the effects of the diet. Second, FHT cats in multi-cat households must either be fed separately or all cats in the household must be fed the iodine-restricted diet. The possible deleterious effects of long-term iodine restriction on cats, normal or hyperthyroid, have not been reported.

Other Treatments

Various other treatments for feline hyperthyroidism have been described. Non-surgical treatment of thyroid nodules using ultrasound-guided percutaneous radiofrequency heat ablation or intrathyroidal ethanol injection has been studied.[84-86] These techniques are of questionable efficacy and safety, and are not recommended. Iopanoic acid, an orally administered contrast agent used in cholecystography, has been evaluated to a limited extent for use in the treatment of FHT. While it can lower serum thyroid hormone concentrations, long-term use is not recommended because of the transient effect of the drug.[87]

Post-Treatment Renal Insufficiency

Overview

Most cats treated for hyperthyroidism eventually develop chronic kidney disease (CKD; see ch. 324) and die of renal failure.[68,69] Treatment of FHT can have deleterious effects on renal function in cats, likely because FHT may mask pre-existing underlying CKD.[88-93] Treatment of FHT, regardless of modality, causes a consistent, and sometimes disastrous, drop in glomerular filtration rate (GFR) and development of overt CKD. Estimates of CKD prevalence following treatment of FHT vary, 15% over an 8-month period in one study and 60% over a 6-month period in another.[93,94]

Predicting Post-Treatment Renal Failure

Pre-treatment clinical parameters that could help predict development of post-treatment renal failure in FHT have not been convincing.[93,95] There is a commonly held belief that cats with well-concentrated urine (specific

gravity > 1.035) have adequate renal function and less risk of post-treatment renal insufficiency.[96,97] This is not supported by evidence. In one report, 20 cats with FHT that developed overt renal insufficiency within 6 months of radioiodine treatment were compared to 19 post-treatment cats in which overt renal failure did not develop.[95] Ten of the 20 cats that developed azotemia (50%) had urine specific gravity measurements before treatment that were greater than 1.035. Three of those cats had urine specific gravity measurements above 1.050. Therefore, urine specific gravity should not be used as a predictor of post-treatment renal status in hyperthyroid cats.

It may be unwise to treat hyperthyroidism in a cat with questionable renal function. This has led to the recommendation that cats with impaired renal function be treated with methimazole initially, because its effects may be reversible. One study showed consistent decreases in GFR with methimazole treatment of FHT. Reversal of this effect was noted when methimazole therapy was stopped in one cat.[89] While it seems logical to choose a reversible treatment for FHT and to assess the renal response to treatment prior to treatment with radioiodine or surgery, there are no studies to confirm the benefits of this strategy. When renal insufficiency is diagnosed in a cat previously treated for FHT, clinicians must attempt to balance treatments for FHT and renal failure.

Managing Post-Treatment Renal Insufficiency

Clinicians managing cats in overt renal failure after being treated for FHT may consider thyroid hormone supplementation as a means of restoring renal blood flow and increasing GFR. There is evidence to suggest that iatrogenic hypothyroidism contributes to the development of renal failure after treating FHT.[93] In that study, development of azotemia did not affect the survival times of cats that were euthyroid following treatment of FHT. However, cats that were both hypothyroid and azotemic following treatment for FHT survived for a shorter period of time, suggesting that iatrogenic hypothyroidism may contribute to the development of azotemia in cats treated for FHT.

Because iatrogenic hypothyroidism has been associated with decreased survival and azotemia in cats with FHT, the renal effects of reducing dosages of carbimazole or methimazole to achieve euthyroidism were studied.[94] Restoring euthyroidism was accompanied by a decrease in serum concentrations, but this was accompanied by decreases in body weight and increases in heart rate, hematocrit, and serum alkaline phosphatase activities. Thus, decrease in muscle mass may have contributed to the decline in serum creatinine concentrations. The other changes are consistent with uncontrolled FHT. In an unpublished study, we followed cats treated with thyroxine following post-treatment renal failure and found discouraging results. Treatment with thyroxine resulted in an increase in the concentration of tT4 in the serum, as expected, but there was no significant decrease in blood urea nitrogen or creatinine. Body weight and body condition remained unchanged in our small group of cats.

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CHAPTER 302

Canine Hyperthyroidism

Cynthia R. Ward

Unlike in cats, hyperthyroidism is an uncommon clinical condition in dogs that almost always arises from a functional, malignant, thyroid tumor that secretes excessive thyroid hormone. Thyroid tumors are usually easily palpable cervical masses. Uncommonly, feeding uncooked diets containing thyroid gland tissue may cause clinical hyperthyroidism.

Pathogenesis

Naturally Occurring Thyroid Cancer

Thyroid cancer has a prevalence of 1% to 4% of all reported neoplasms in dogs and is their most common neuroendocrine tumor. Canine thyroid tumors are usually malignant. Ten to 30% of canine thyroid tumors are benign adenomas.[1,2] Adenomas, typically small and nonfunctional, are usually not diagnosed until noted as an incidental necropsy finding. With increased use of cervical ultrasonography (US), however, incidentally discovered thyroid masses have been noted.[41] Size is not a predictor of malignancy.[1] Most clinically significant thyroid tumors are carcinomas, either follicular cell or medullary cell in origin; the latter also are termed *parafollicular cell* or *C-cell carcinomas.* Follicular cell carcinomas, about 70% of canine thyroid tumors, arise from thyroid follicular cells that stain for thyroglobulin on immunohistochemistry. Medullary thyroid carcinomas, about 30% of tumors, arise from parafollicular cells that produce calcitonin and stain for calcitonin antibodies on immunohistochemistry.[3-5]

Iatrogenic Hyperthyroidism

Clinical signs of hyperthyroidism can be seen in dogs without primary thyroid gland disease. Iatrogenic hyperthyroidism may result when a dog is oversupplemented with L-thyroxine for hypothyroidism or by accidental ingestion. In general, dogs seem resistant to exhibiting signs of hyperthyroidism if there are small excesses of exogenous thyroid hormone. Recent reports have implicated food sources, including raw food or dried uncooked diets that contain thyroid tissue, as a cause of thyrotoxicosis in dogs.[6,7] The dogs described in these studies had clinical signs of hyperthyroidism that resolved when the suspect diets were removed.

The Role of Thyroid Stimulating Hormone (TSH) in Tumor Development

The etiology of canine thyroid carcinoma is unknown. In people, risk factors include exposure to radiation and lack of dietary iodine intake.[8] Individuals who lack dietary iodine or who consume iodine-blocking foods have decreased pituitary negative feedback and excess thyroid stimulating hormone (TSH) secretion (see ch. 299). TSH directly stimulates thyroid cell mitogenesis, hormone synthesis, and has been postulated to be involved in thyroid neoplastic transformation (Figure 302-1). Other evidence of excess of TSH activity causing development of thyroid neoplasia is the mutations in the TSH receptor that have been shown to cause benign toxic nodular goiter in humans.[9] Furthermore, increased TSH concentrations have been shown to induce angiogenesis in thyroid cancer cell lines, which may be relevant to thyroid tumor development in dogs.[10] About 50% of Beagles with induced untreated lymphocytic thyroiditis and increased TSH concentrations developed thyroid tumors. Carcinomas were more common than adenomas.[11] Thus, chronic exposure to excess TSH can cause unregulated cell growth and function in dogs. A familial relationship in the development of thyroid carcinoma was also demonstrated in the colony of Beagles by sibling pair analysis.

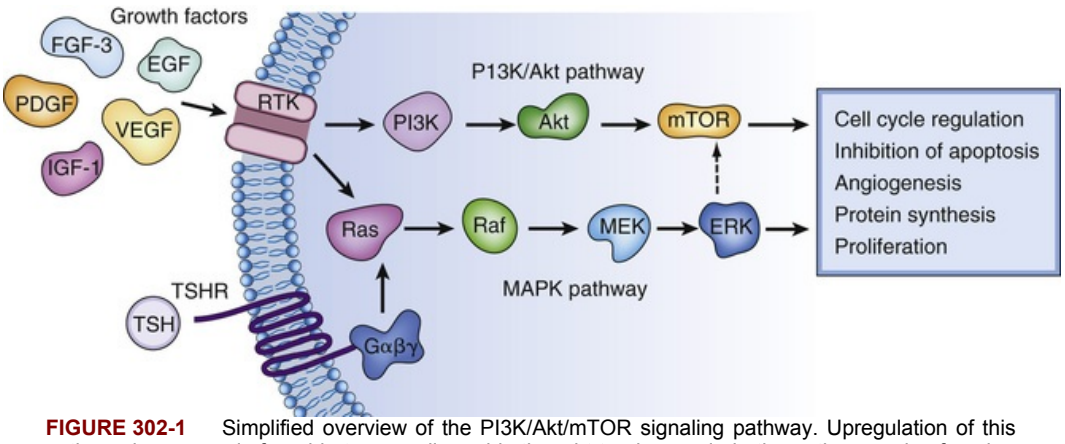

FIGURE 302-1 Simplified overview of the PI3K/Akt/mTOR signaling pathway. Upregulation of this pathway is commonly found in tumor cells and is thought to play a role in the pathogenesis of canine thyroid carcinoma. *EGF,* Epidermal growth factor; *ERK,* extracellular-signal-regulated kinase; *FGF-3,* fibroblast growth factor-3; *IGF-1,* insulin-like growth factor-1; *MAPK,* mitogen-activated protein kinase; *MEK,* MAPK/ERK kinase; *mTOR,* mechanistic (or mammalian) target of rapamycin; *PDGF,* platelet-derived growth factor; *PI3K,* phosphoinositide 3-kinase; *RTK,* receptor tyrosine kinase; *VEGF,* vascular endothelial growth factor; *TSH,* thyroid-stimulating hormone; *TSHR,* TSH receptor. (Illustration by Katie Yost, MS. ©2015 The University of Georgia Research Foundation, Inc.)

Genetic Etiology of Tumor Development

Several genetic abnormalities in cell signal transduction proteins have been described as causative agents for human thyroid carcinoma. These include point mutations in the ras gene and abnormalities in the PI3K/Akt pathway (see Figure 302-1). These signal transduction pathways are coupled to cell surface receptor tyrosine kinases and G protein–coupled receptors such as the TSH receptor. In human follicular cell carcinoma, abnormalities in the PI3K/Akt pathway have been implicated.[12] Important genes in this pathway are the vascular endothelial growth factors *VEGFR-1* and *VEGFR-2*. VEGF is a target for TSH activation of angiogenesis in thyroid cancer cell lines.[13] In 74 dogs with thyroid neoplasia, immunohistochemical staining revealed VEGF in follicular cell and medullary carcinomas, supporting a role as an angiogenic factor in development of thyroid carcinoma.[14] As canine thyroid carcinoma cells bind TSH in a normal fashion, this may explain the effect of chronic excess TSH exposure contributing to the neoplastic transformation seen in the Beagle colony dogs.[11,15]

Studies of genetic signaling molecule abnormalities in canine cancer cells have been limited. Point mutations of p53, a tumor suppressor gene, were found in only 1 of 23 dogs with canine thyroid carcinoma.[13] In 59 dogs with canine thyroid carcinoma, mRNA expression of several genes in the PI3K/Akt pathway were greater than those in normal canine thyroid tissue.[16] In addition, missense mutations of K-RAS that would cause unregulated activation were documented. Microarray analysis comparing thyroid tumor versus normal thyroid gene expression in dogs identified differential expressions of osteopontin, a protein overexpressed in human follicular cell carcinomas and implicated in activation of the PI3K/Akt pathway. This was found in all five dogs with thyroid tumors, but also in four euthyroid dogs.[17] Molecular abnormalities in mitogenic pathways are a likely component of canine thyroid carcinoma pathogenesis.

Signalment

The mean age of dogs with thyroid carcinoma is 9 to 11 years.[3,18-22] One study suggested that the median age may be somewhat older at 10 to 15 years.[2] There is no sex predilection. Breeds that may be predisposed to thyroid carcinoma include Golden Retrievers, Beagles, Boxers, and Siberian Huskies.[2,3] Medullary thyroid carcinoma in a family of mixed breed dogs with Alaskan Malamute influence on the pedigree has been reported.[23]

History

The initial presenting complaint for most dogs with thyroid carcinoma is the owner's discovery of a cervical

mass. Most animals are diagnosed within 1 to 2 months after discovery of the mass; however, there may be delays of 1 to 2 years.[37] On palpation, thyroid masses are usually firm, nonpainful, freely movable or fixed. Mass "movability" is an important factor in tumor staging and for predicting surgical success (see Table 302-1). Both right and left thyroid lobes may be involved equally in tumor development, and tumors may be bilateral.[19,21] Sedation may improve one's ability to fully palpate the area, but usually is not needed. Regional peripheral lymph nodes should also be palpated carefully for increased size or pain. Ectopic thyroid carcinomas may be suspected if a non-painful swelling is noted in any location from the tongue to the thoracic inlet.[39]

Most thyroid carcinomas are not functional. Clinical signs, therefore, are usually associated with space-occupying issues caused by the mass and these can include difficulty swallowing, dysphonia, coughing, dyspnea or recognizable head or forelimb edema.[3,18,24] Dyspnea may also occur because of metastatic tumor spread to the lungs. Thyroid carcinomas have been reported to invade major blood vessels causing local or thoracic bleeding.[25] Ectopic thyroid carcinomas have been reported in the mediastinum, heart base and sublingually; therefore, clinical signs may relate to tumor size in these areas or invasion into these tissues.[26-33] Thyroid hormone status can vary in dogs with thyroid carcinoma; approximately 10% are hyperthyroid.[22,34-36] Hyperthyroid dogs often show classic signs of vomiting, diarrhea, weight loss, hyperactivity, panting, polyuria/polydipsia, and systemic hypertension (Figure 302-2; see ch. 301).

FIGURE 302-2 A 10-year-old female, spayed mixed breed dog was diagnosed with a functional thyroid carcinoma. Her clinical signs included weight loss, polyuria, polydipsia, panting, and hyperactivity. Her serum T_4 was elevated. A well-encapsulated thyroid carcinoma was removed surgically. Her thyrotoxicosis resolved after surgery.

Diagnosis

Differential Diagnosis

Most dogs with thyroid carcinoma are brought to a veterinarian after an owner notes the presence of a cervical mass. However, signs of hyperthyroidism may be the first concern seen by some owners. In those dogs, a palpable cervical mass is usually noted on physical examination. Differential diagnoses of a cervical mass include an enlarged lymph node, salivary gland, granuloma, abscess, or foreign body. Thus, a complete diagnostic work up should be pursued and further examination of the cervical mass attempted.

Laboratory Testing

If a thyroid tumor is present, blood work may reveal paraneoplastic hypercalcemia (see ch. 352).[38] Urine specific gravity is often <1.020 if a dog is hypercalcemic and/or hyperthyroid. To determine tumor function, serum total T_4 (TT_4), freeT_4 (fT_4) by equilibrium dialysis, and canine TSH (cTSH) concentrations should be evaluated. Anti-T_4 antibodies should also be assessed. If a functional thyroid tumor is present, usually both

TT_4 and fT_4 are increased. The cTSH should be decreased due to negative feedback caused by the excess thyroid hormone (see ch. 299). T_4 autoantibodies that may interfere with certain assay procedures should not be measurable.

Imaging

Plain radiographs often confirm the presence of a soft-tissue mass deviating or compressing the trachea, larynx, and/or esophagus. Ultrasound (US), a rapid, noninvasive, and reliable screening modality for defining thyroid tumors, can provide additional detail regarding vascularity and/or invasion of other structures (Figure 302-3).[40] Clinicians should interpret US findings cautiously, however, as clinically insignificant thyroid masses can be identified. Fourteen of 91 hypercalcemic dogs (15%) without a palpable cervical mass had a total of 15 thyroid masses identified on US examination; 2 were thyroid adenocarcinomas and 13 masses were likely insignificant cysts or benign nodules.[41] Computed tomography (CT) can provide further information regarding the nature of thyroid masses, especially invasion of surrounding tissues (Figure 302-4).[39,42] In a study of 23 dogs with suspected thyroid carcinoma, CT had the highest specificity (100%) and magnetic resonance imaging (MRI) had the highest sensitivity (93%) in diagnosing thyroid carcinoma.[40] CT also allows assessment of the lungs for possible metastases. It is recommended that CT or MRI be performed for tumor staging and prior to potential surgery.

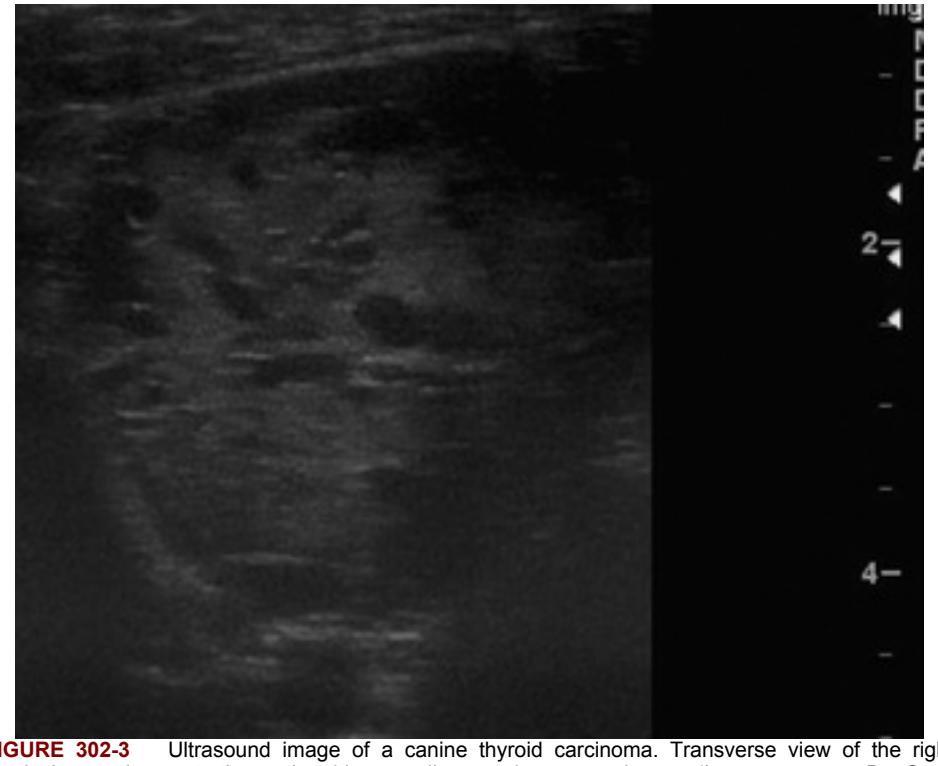

FIGURE 302-3 Ultrasound image of a canine thyroid carcinoma. Transverse view of the right cervical area demonstrating a thyroid mass diagnosed as a carcinoma. (Image courtesy Dr. Scott Secrest.)

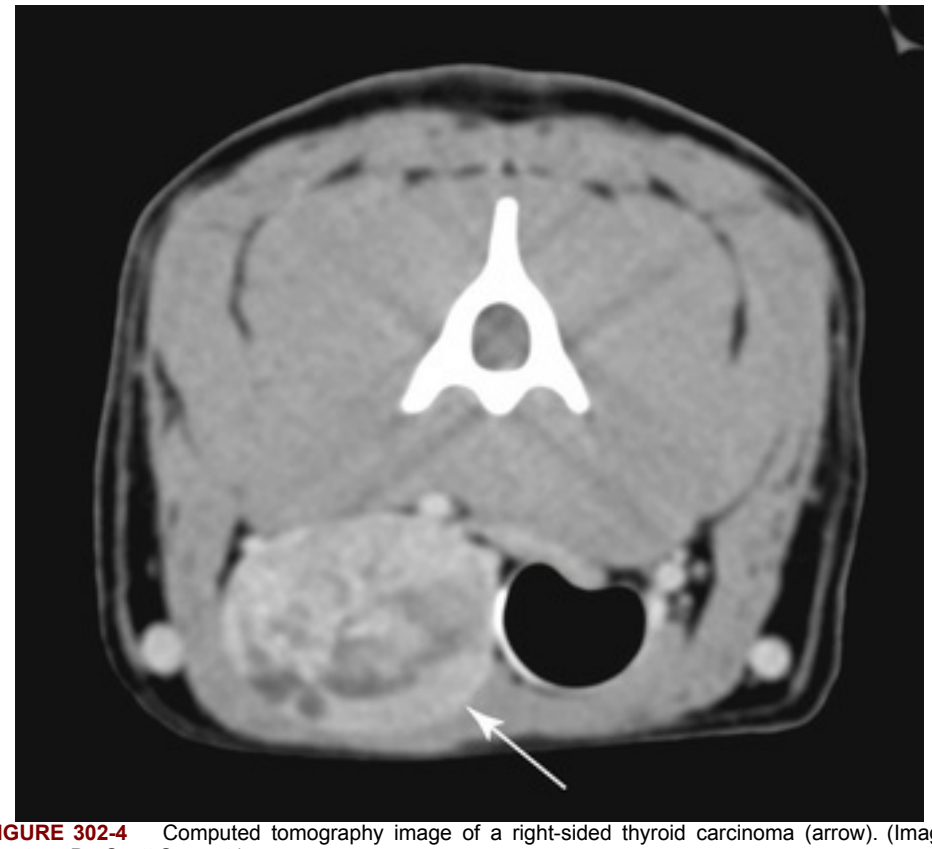

FIGURE 302-4 Computed tomography image of a right-sided thyroid carcinoma (arrow). (Image courtesy Dr. Scott Secrest.)

Scintigraphy is an effective imaging modality to aid in the diagnosis and staging of thyroid carcinoma. ^{99m}Tc-pertechnetate ($^{99m}TcO_4$) uses the relatively specific sodium-iodide transporter present in thyroid and salivary glands. Since the transporter protein is upregulated as thyroid gland activity increases, levels of radionuclide uptake can be correlated with thyroid function. Therefore, scintigraphy is sensitive for identifying some thyroid carcinomas and, potentially, ectopic and/or metastatic tissue (Figures 302-5 and 302-6).[32] The pattern of radionuclide uptake cannot be correlated with tumor histology, but it can predict the degree of capsular disruption and local tissue invasion.[19,43] This information can be helpful in predicting surgical resectability and long-term prognosis, as invasive thyroid carcinomas carry a poorer prognosis.[44] Scintigraphy is not sensitive in identifying pulmonary metastases and is inferior to plain thoracic radiographs and CT for staging.[3,19,43] ^{123}I may be superior to $^{99m}TcO_4$ for scintigraphy since the target-to-background ratio favors specific uptake by thyroid tissue. However, lower radioactivity of the compound requires longer image acquisition times, so it may not be practical.[43]

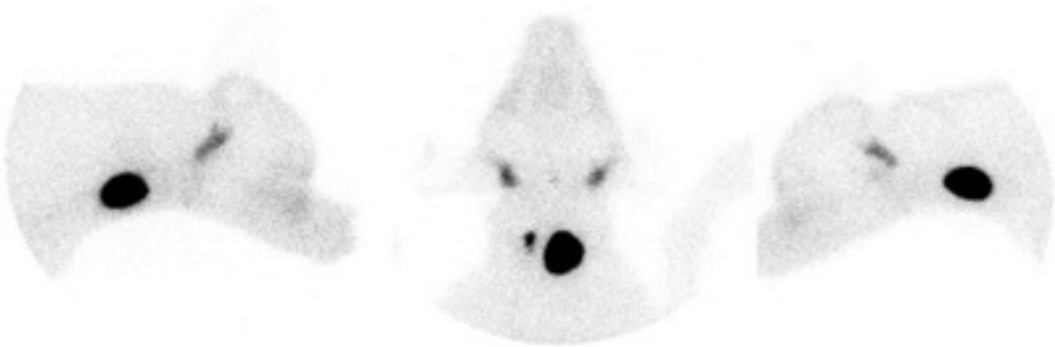

FIGURE 302-5 Scintigraphic images of a dog with a functional thyroid carcinoma. Note the increased uptake in the left lobe of the thyroid gland with minimal uptake in the right. This indicates decreased right thyroid activity in response to thyroid stimulating hormone suppression caused by the

unregulated excess secretion of the tumor. (Image courtesy Dr. Gregory Daniel.)

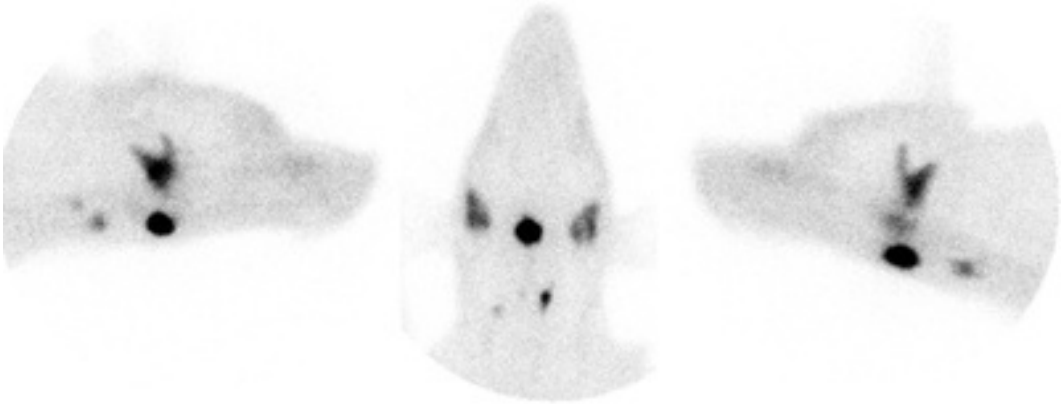

FIGURE 302-6 Scintigraphic images of a dog with ectopic, sublingual thyroid carcinoma. Note the increased uptake in the sublingual area with minimal uptake in the thyroid glands. (Image courtesy Dr. Gregory Daniel.)

Histology

Definitive diagnosis of thyroid carcinoma requires identification of malignant cells in a cytologic or, preferably, a histologic sample. Cytology via fine needle aspirate (FNA) is often used for definitive diagnosis of thyroid carcinoma in humans,[8] but its use for canine thyroid carcinoma is less reliable (see ch. 93). Since thyroid carcinomas are highly vascular, samples obtained by FNA often contain few cells but large amounts of blood.[22] However, depending on owner or patient restrictions, FNA cytology can provide an inexpensive and noninvasive means of diagnosis.[45] US guidance is recommended for FNA to avoid highly vascular areas.

Histology is the gold standard by which thyroid carcinomas are diagnosed. For small and noninvasive tumors, excisional biopsy may provide diagnosis and be curative. Usually, canine thyroid tumors are moderately to well differentiated.[1,3,20] Malignancy is defined by the presence of capsular or vascular invasion. Unlike people, histologic subtype does not appear to carry prognostic significance in dogs with well-differentiated thyroid tumors.[3,20,22] Therefore, it is crucial to determine invasive qualities of the tumor for prognosis. Since thyroid tumors are highly vascular, a hypothesis has been promoted that identifying microvessels is prognostic. However, microvessel density was not shown to help predict metastasis or survival.[21] Immunohistochemistry is essential for determining origin of thyroid carcinomas.

Staging

Canine thyroid tumors are staged based on the size of the primary tumor and whether spread to regional lymph nodes or distant metastases is identified (Table 302-1). Full staging of dogs with thyroid carcinoma is recommended so appropriate treatment options and prognoses may be presented to the owners.

TABLE 302-1

Clinical Staging of Canine Thyroid Tumors

STAGE	PRIMARY TUMOR DIAMETER	REGIONAL LYMPH NODE INVOLVEMENT	DISTANT METASTASIS
I	<2 cm; a or b	No	No
II	No evidence of tumor (microscopic disease)	Ipsilateral	No
	<2 cm; a or b	Ipsilateral	No
	2-5 cm; a or b	None or ipsilateral; a	No
III	>5 cm	Any	No

	Any size	Ipsilateral or bilateral; b	No
IV	Any size	Any	Yes

Substage a = tumor or lymph node freely movable. Substage b = tumor or lymph node fixed to surrounding structures.

Adapted from Owen LN, editor: *TNM classification of tumours in domestic animals,* Geneva, IL, 1980, World Health Organization, pp 51-52.

Treatment

Surgery

For the solitary, well-encapsulated, freely movable thyroid carcinoma, surgical excision is recommended (see Figure 302-2).[20,24] Mass removal not only reduces tumor burden but also may relieve compression of surrounding tissues. Invasive tumors are less amenable to surgical excision. Adjacent structures invaded by thyroid tumors include the recurrent laryngeal nerves, carotid artery, jugular vein, larynx, trachea, or esophagus. These structures could be further damaged if surgical excision is attempted. Additionally, thyroid carcinomas are highly vascular and extensive hemorrhage may result from a poorly planned surgery or by coexisting bleeding disorders.[22] Advanced imaging should be employed prior to surgery to determine extent of invasion. Other potential complications of surgery include hypocalcemia from removal of parathyroid glands or disruption of their blood supply. This would be quite rare if a unilateral thyroidectomy is performed. Bilateral thyroidectomy may be attempted in those unusual cases in which discrete, movable carcinomas are present in both thyroids. In these cases, parathyroid glands must be preserved by the surgeon or removed parathyroid tissue should be minced and re-implanted in a location other than the neck.[46,47] Most dogs undergoing bilateral thyroidectomy require life-long thyroid hormone replacement to manage the iatrogenic hypothyroidism (Table 302-2). If no parathyroid tissue is preserved, dogs can be successfully treated with long-term calcitriol therapy to correct hypoparathyroidism (see Table 302-2; see also chs. 297 and 298). However, long-term treatment of hypoparathyroidism is difficult and should be avoided if possible. Median survival time for dogs after unilateral thyroidectomy is approximately 3 years and for bilateral thyroidectomy, it is a similar 30 to 39 months.[46,47] Removal of ectopic thyroid carcinoma is also recommended if possible. A surgical technique has been described involving partial resection of the hyoid apparatus during surgical excision of ectopic cervical thyroid carcinomas in five dogs, four of whom survived at least 20 months after surgery.[33]

TABLE 302-2

Medications Used for Supportive Treatment for Canine Hyperthyroidism

DRUG	CLASS	INDICATION	DOSAGE	MONITORING
Methimazole	Anti-thyroid	Thyrotoxicosis	2.5-5 mg PO q 12-24 h Titrate dosage according to serum T_4 concentrations	Serum T_4 1-2 weeks following initiation of medication
Atenolol	Beta-adrenergic blocker	Prevention of thyroid storm	0.25-1 mg/kg PO q 12 h	Blood pressure
Propranolol	Beta-adrenergic blocker	Prevention of thyroid storm	0.1-0.2 mg/kg PO q 8 h	Blood pressure
Enalapril or Benazepril	Angiotensin-converting enzyme (ACE) inhibitor	Thyrotoxic hypertension	0.25-0.5 mg/kg PO q 12-24 h	Blood pressure
Amlodipine	Calcium channel blocker	Thyrotoxic hypertension	0.1-0.5 mg/kg PO q 24 h	Blood pressure
Pamidronate	Bisphosphonate	Paraneoplastic hypercalcemia	1-2 mg/kg IV diluted in 250 mL 9% NaCl and given over 2 hours q 3-4 weeks	Renal function parameters and serum calcium
Alendronate	Bisphosphonate	Paraneoplastic	0.5-1 mg/kg PO q 24 h	Esophageal erosions and

		hypercalcemia		serum calcium
Calcitriol	Vitamin D analog	Post-surgical hypocalcemia	0.03-0.06 mcg/kg/day	Maximal effect in 2-4 days. Monitor serum calcium
Levothyroxine	Thyroid supplementation	Post-surgical hypothyroidism	0.022 mg/kg q 12-24 h	Monitor serum T_4

External Beam Radiation

In dogs with a thyroid tumor that is fixed due to extensive local invasion, surgery is not usually a reasonable option. Radiation therapy should be considered as either a primary therapy for local control or as a means for reducing tumor size so that surgery may be a future option. External beam radiation is most commonly used in dogs with thyroid carcinoma.[21,48,49] In 25 dogs with non-resectable thyroid carcinoma and no visible metastases, the mean progression-free interval was 45 months after radiation therapy.[21] The 1- and 3-year progression-free survival rates were 80% and 72%, respectively. The time to maximal tumor reduction was a highly variable 8 to 22 months. In a study of eight dogs, the median survival time was 24.5 months after radiation therapy; none had primary tumor regrowth, but four died from metastatic disease.[48] Acute side-effects of radiation therapy include inflammation of the esophagus, trachea, or larynx resulting in dysphagia; cough or hoarseness; and alopecia and erythema at the radiation site. These occurred in approximately half of the dogs treated; however, they resolved in most dogs within 2 to 3 weeks. Late side-effects including permanent alopecia, chronic dry cough, and skin fibrosis may occur.[21]

In dogs with metastatic disease, external beam radiation therapy may provide palliation of the primary tumor. This takes advantage of the generally slow-growing nature of thyroid carcinomas so that any procedure to reduce tumor burden is beneficial. In 13 dogs with metastatic disease receiving weekly fractionated radiation, tumor growth was halted in all dogs and 10 of the tumors decreased in size by at least 50%.[49] Median survival time was approximately 8 months, including the dogs with previously identified pulmonary metastases.

Radionuclide Therapy

Radioiodine (^{131}I) therapy is commonly used postoperatively in humans with thyroid carcinoma.[8] It is effective at delivering high dosages of beta-emitting radioactivity to the thyroid gland and is used to destroy microscopic carcinomas anywhere in the body. Uptake of ^{131}I is enhanced by treatment with TSH, usually given immediately prior to ^{131}I. ^{131}I has been shown to be taken up by thyroid carcinoma cells, although at lower levels than by normal thyroid cells.[50] ^{131}I has been effective in treating dogs with stage II to IV thyroid carcinoma.[44,51,52] Direct comparison of studies is difficult due to differing ^{131}I dosing protocols, the absence or presence of concurrent treatment with TSH, a variety of adjunctive therapies, and differing pre-treatment hormone evaluations. However, in 100 dogs, median survival times ranged from 12 to 34 months and were longest in dogs given ^{131}I as an adjunct to surgery.[44,52] Effectiveness of ^{131}I treatment was not correlated to thyroid status in these studies. A serious side-effect of ^{131}I therapy includes irreversible bone marrow suppression, seen in dogs given doses ≥0.2 GBq/kg or 5.5 mCi/kg.[51,52]

Although ^{131}I shows some promise in the treatment of thyroid carcinomas, especially as an adjunct to surgery, handling large amounts of radioactivity and providing appropriate isolation areas to house radioactive dogs remains problematic. In humans, TSH is routinely given with ^{131}I in order to decrease the iodine dosage. The use of recombinant human TSH on the uptake of radioactive iodine in nine dogs with thyroid tumors was reported using the isotope ^{123}I, with a shorter half life than ^{131}I. TSH administration had no effect on ^{123}I uptake in the thyroid glands of these nine dogs.[53]

Chemotherapy

There are few studies examining the role of chemotherapeutic agents in treating canine thyroid carcinoma, probably because initial results have been disappointing. Doxorubicin, cisplatin, and mitoxantrone have been used in small numbers of dogs with thyroid malignancy.[54-57] Of these, cisplatin was demonstrated to have the greatest effect, with a median survival of 11 months. The greatest effect of these drugs is likely against

microscopic metastatic disease, and further studies are required to demonstrate possible effectiveness as adjunctive therapy.

Supportive Medical Therapy

Approximately 10% of canine thyroid carcinomas are functional and secrete excess thyroid hormone systemically.[22,34-36] Affected dogs may have classic signs of hyperthyroidism including polyuria, polydipsia, hyperactivity, weight loss, hypertension, polyphagia, and tachycardia. Thyrotoxicosis should be treated before a dog undergoes anesthesia for advanced imaging or surgical techniques. Furthermore, the hyperthyroidism in dogs with nonresectable functional thyroid tumors should be treated to enhance longevity and quality of life. Hyperthyroidism can be managed with methimazole, similar to its use in cats (dosage = 2.5 to 5 mg/dog PO q 24 h or q 12 h). Serum T_4 levels should be monitored 1 to 2 weeks after initiation of therapy and suitable adjustments initiated. Treatment effectively controls clinical signs with negligible side-effects. In hyperthyroid dogs undergoing anesthesia or surgery, a beta-adrenergic blocker, such as atenolol, should be considered the night before and the day of the procedure to prevent tachycardias related to potential thyroid storm (see Table 302-2; see also ch. 301).[58]

Hyperthyroid dogs may also have significant systemic hypertension (see ch. 99).[36] Although removal of the functional thyroid tumor may return blood pressure to normal, systemic hypertension should be managed in dogs with non-resectable tumors or in those with functional metastatic thyroid carcinoma (see ch. 158). Antihypertensives such as an ACE inhibitor and/or amlodipine may be used for such patients. Paraneoplastic hypercalcemia may also occur in rare cases of thyroid carcinoma (see ch. 352).[38] Calcium-lowering drugs such as pamidronate or alendronate may be used to manage such cases if the tumor burden cannot be lowered (see Table 302-2; see ch. 297 and 298).

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CHAPTER 303

Insulin-Secreting Tumors

Johan P. Schoeman

Client Information Sheet: Insulin-Secreting Tumors

Insulinoma is an insulin-secreting tumor of pancreatic beta cells. Excess insulin secretion causes clinical signs of hypoglycemia. It is an uncommon condition in dogs and rare in cats. This chapter will focus on canine insulinoma, first described in a dog in 1935.[1]

Pathology

Insulin-secreting pancreatic beta cells comprise approximately 70% of cells in the islets of Langerhans and, consequently, beta cell tumors are the most common canine islet-cell neoplasm. Most canine insulinomas are malignant; in one report utilizing immunocytochemistry, 17 of 18 were carcinoma, and 1 was an adenoma.[2] About 80% of insulinomas are solitary, located in one pancreatic limb rather than in the body of the pancreas (Figure 303-1).[3-5] Occasionally, no discrete nodule is seen during gross pancreatic examination and histology is required to identify the tumor.

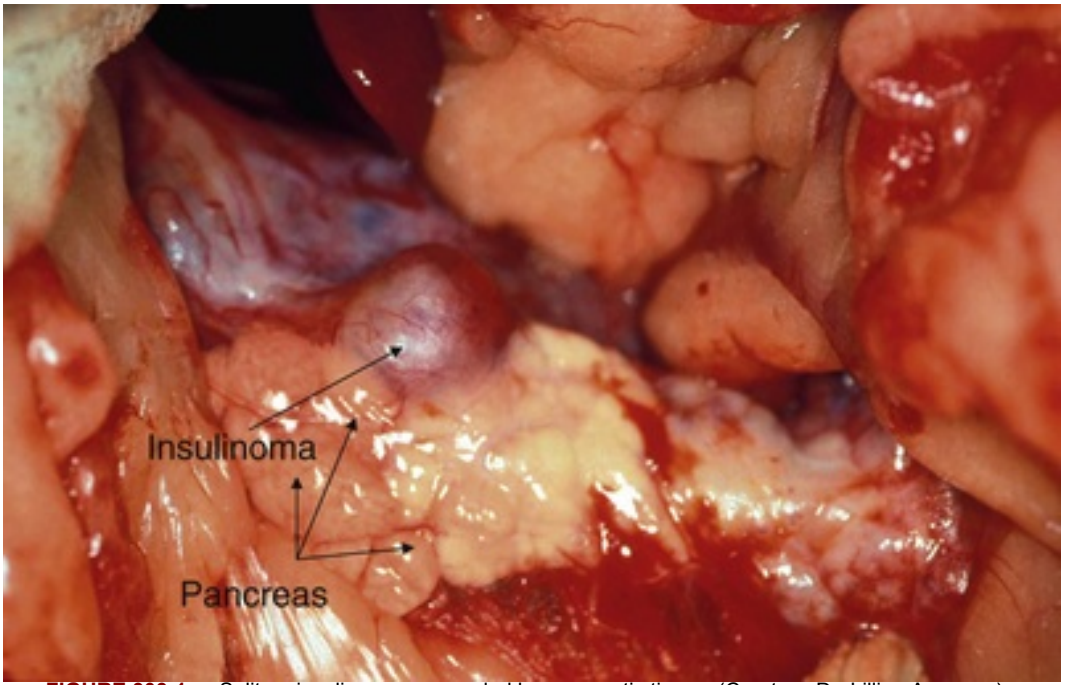

FIGURE 303-1 Solitary insulinoma surrounded by pancreatic tissue. (Courtesy Dr. Lillian Aronson.)

The rate of detected metastatic lesions in 179 dogs from different studies ranges from 45% to 64%. It is higher in studies based on necropsy versus studies using samples obtained surgically.[3,6,7] Clinical staging of pancreatic tumors according to the World Health Organization defines stage I as $T_1N_0M_0$ (presence of a primary Tumor and absence of regional lymph Node or distant Metastases), stage II as $T_1N_1M_0$, and stage III

as $T_1N_1M_1$ or $T_1N_0M_1$. The majority of dogs with insulinoma have stage II or III disease and the most common sites of metastases are regional lymph nodes and liver. Metastatic disease has an unlimited distribution.[8] Although the etiology of insulinoma is not known, local growth hormone (GH) production not associated with increased plasma GH concentrations has been documented in primary and metastatic canine insulinoma, possibly promoting islet cell proliferation via paracrine or autocrine mechanisms.[9]

Pathophysiology

Neoplastic proliferation of pancreatic beta cells causes autonomous excess secretion of insulin and resultant hypoglycemia. The most important compensatory mechanisms for hypoglycemia are inhibition of insulin secretion and stimulation of counter-regulatory hormone secretion. Glucose, the primary regulator of insulin secretion, enters pancreatic beta cells, is metabolized to ATP and closes ATP-sensitive K^+ channels. Closure results in decreased K^+ efflux, depolarization of beta cells, opening of voltage-sensitive Ca^{+2} channels and insulin exocytosis. In healthy animals, insulin secretion is completely inhibited when blood glucose is <80 mg/dL. However, insulin secretion from neoplastic beta cells, independent of blood glucose concentration, persists despite low blood glucose concentrations and represents one of the biochemical hallmarks of insulinoma: high or normal blood insulin concentrations despite low blood glucose concentrations. The four counter-regulatory hormones secreted in response to hypoglycemia are glucagon, catecholamines, GH, and glucocorticoids. Of these, glucagon and catecholamines are most important in short-term responses to low blood glucose concentrations.

Clinical Features

Signalment

The mean age of dogs with insulinoma is 9 years, with a range of 3 to 15 years. Although any breed of dog can develop insulinoma, it has been reported most commonly in medium- to large-breed dogs. Controlled studies of breed risk for insulinoma have not been published and there is no apparent sex predilection for the disease.

Clinical Signs

Clinical signs are usually due to the effect of hypoglycemia on the central nervous system (neuroglycopenia), or to hypoglycemia-induced release of catecholamines. Glucose is the single most important source of energy for the brain. Because both carbohydrate storage and the brain's ability to utilize other fuels are limited, function is dependent on a continuous glucose supply. Clinical signs attributable to neuroglycopenia include seizures, collapse, weakness, ataxia, disorientation, mental dullness, and visual disturbances. Clinical signs related to excess catecholamine release and stimulation of the sympathetic nervous system include tremors, hunger, and nervousness.

Severity of clinical signs is partly correlated to the blood glucose nadir. Severe hypoglycemia can ultimately result in coma and death. However, clinical signs may also be related to the duration and rate at which hypoglycemia develops because gradual decreases in blood glucose concentration are less likely to stimulate catecholamine secretion. Occasionally, clinical signs are episodic, because secretion of counter-regulatory hormones increases blood glucose concentration, transiently resolving neuroglycopenic signs. Feeding can alleviate clinical signs if it restores blood glucose concentration to normal. However, feeding may also counter-intuitively exacerbate clinical signs by stimulating further insulin secretion. Moreover, fasting, exercise, or excitement can worsen clinical signs by decreasing blood glucose concentration or increasing sympathetic stimulation. Clinical signs reported in 198 dogs from several studies are listed in Table 303-1. Although most dogs have more than one of these clinical signs, some dogs have none. Reported duration of clinical signs prior to diagnosis varies from 1 day to 3 years.

TABLE 303-1

Clinical Signs Due to Insulinoma Reported in 198 Dogs from Several Studies[3-5,7,8,10]

CLINICAL SIGN	NUMBER (%) OF 198 DOGS

Seizure	95 (48)
Collapse	79 (40)
Generalized weakness	74 (37)
Shaking/trembling/muscle twitching	40 (20)
Ataxia	40 (20)
Exercise intolerance	30 (15)
Hind limb weakness	28 (14)
Disorientation/bizarre behavior/hysteria	19 (10)
Polyphagia	16 (8)
Polyuria and polydipsia	16 (8)
Stupor/lethargy	12 (6)
Focal facial seizures	6 (3)
Obesity or weight gain	6 (3)
Blindness	5 (2.5)
Anorexia	5 (2.5)
Diarrhea	4 (2)
Head tilt	2 (1)
Nervousness	2 (1)

Physical Examination

Physical examination is unremarkable in most dogs with insulinoma.[4,6,10] Dogs may be overweight due to the anabolic effects of insulin. Postictal changes may be apparent if a seizure occurred quite recently. A peripheral polyneuropathy characterized by posterior paresis or tetraparesis and decreased or absent appendicular reflexes has been described in 13 dogs with insulinoma.[8,11,12] The etiology of this insulinoma-associated peripheral neuropathy is not known, but may develop as a paraneoplastic immune-mediated disorder unrelated to the metabolic changes of insulinoma.[12]

Differential Diagnoses

Differential diagnoses for hypoglycemia may be separated into those associated with excess secretion of insulin or insulin-like factors, those caused by decreased glucose production, others due to excess glucose consumption, the occasional drug-associated scenario, or the hypoglycemia could be spurious. Disorders in which the most important mechanism for hypoglycemia is excess secretion of insulin or insulin-like factors include insulinoma, extrapancreatic tumor (i.e., hepatic tumors), or beta cell hyperplasia. Conditions associated with decreased glucose production include hypoadrenocorticism (see ch. 309), hypopituitarism (see ch. 295), GH deficiency (see ch. 295), liver insufficiency (see ch. 280 and 285), and glycogen storage diseases (see ch. 260). Neonates and toy breeds may have impaired glucose production. Fasting, malnutrition, or pregnancy may also result in hypoglycemia. Excess glucose consumption may develop in sepsis or extreme exercise (especially in hunting dogs). Some of the many drugs reported to induce hypoglycemia in people include insulin, oral hypoglycemics (e.g., sulfonylurea), salicylates (e.g., aspirin), acetaminophen, beta-blockers (e.g., propranolol), beta-2 agonists, ethanol, monoamine oxidase inhibitors, tricyclic antidepressants (e.g., amitriptyline), angiotensin-converting enzyme inhibitors (e.g., captopril), antibiotics (e.g., tetracycline), lidocaine overdose, and lithium. Fictitious hypoglycemia may occur when blood cells are not promptly separated from serum or in animals with severe polycythemia or leukocytosis.

Diagnostic Evaluation

Serum Glucose and Insulin Concentrations

An algorithmic approach to hypoglycemia is depicted in Figure 303-2. Clinical suspicion of insulinoma begins

with documentation of appropriate clinical signs, hypoglycemia (blood glucose concentration less than 60 mg/dL), and concurrent hyperinsulinemia (serum insulin concentrations within or above reference intervals).[13] Identification of a pancreatic mass with imaging studies may strengthen this suspicion. The diagnosis of insulinoma is confirmed with histologic examination and immunohistochemical staining of a pancreatic mass.

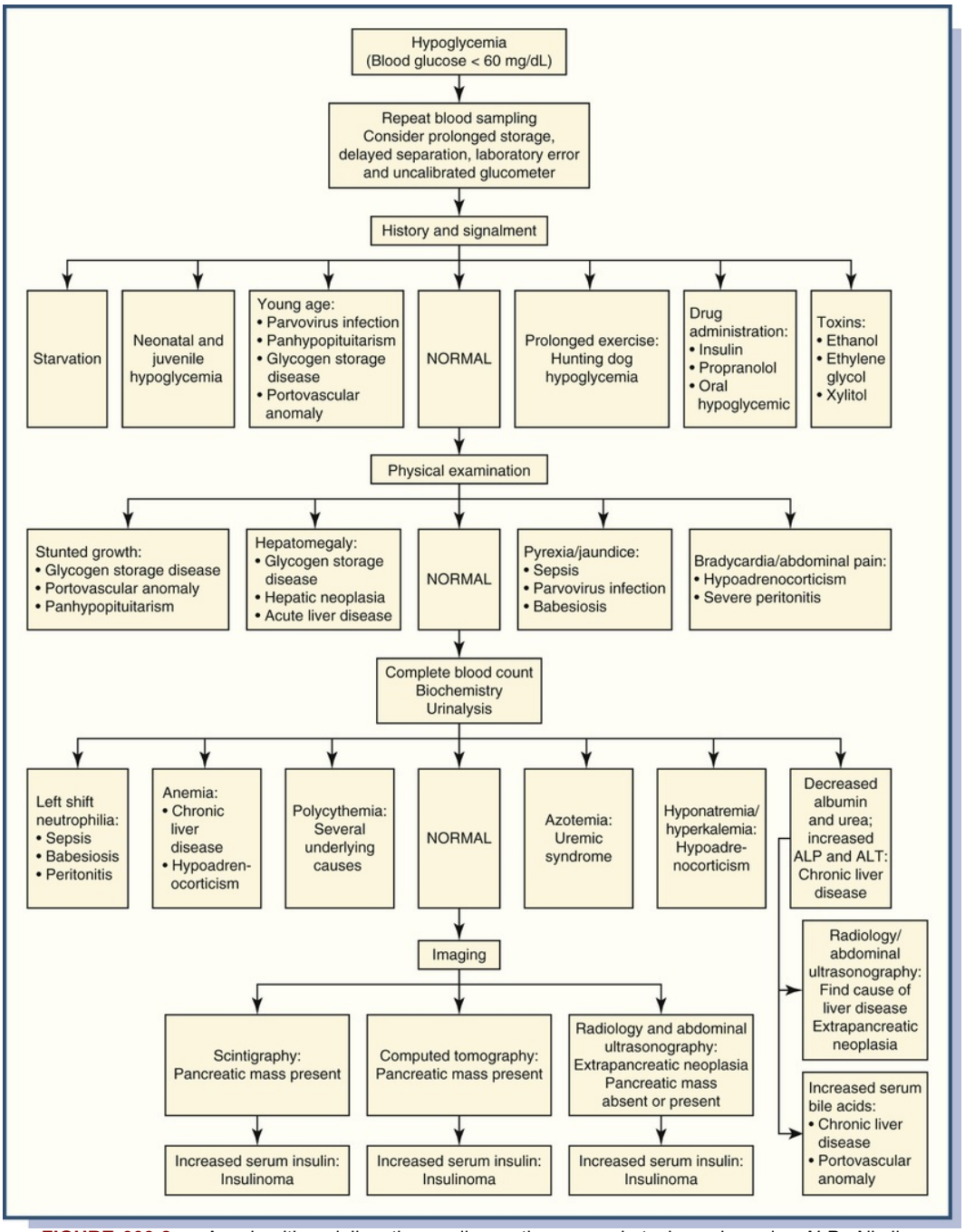

FIGURE 303-2 An algorithm delineating a diagnostic approach to hypoglycemia. *ALP,* Alkaline phosphatase; *ALT,* alanine aminotransferase.

Aside from the often serendipitous hypoglycemia, complete blood count, chemistry screen, and urinalysis are usually unremarkable.[4,7] Although hypoglycemia is observed on randomly obtained blood from most dogs with insulinoma, especially if repeated, it is important to note that some are euglycemic.[7,14] Mild hypokalemia and increased alkaline phosphatase and/or alanine aminotransferase (ALT) activities have been

documented.[5,7] When a dog suspected of insulinoma is euglycemic, it should be closely monitored for hypoglycemia when fasted. Blood glucose concentration should be measured every 30 to 60 minutes. In most dogs with insulinoma, hypoglycemia (blood glucose <60 mg/dL) develops within 12 hours of the previous meal.

Serum for measurement of insulin concentration should be submitted from the same sample in which hypoglycemia is documented. An extremely limited number of dogs with insulinoma do not exhibit hypoglycemia, even with repeated measurements or after a prolonged fast of 48 to 72 hours.[7] Low fructosamine has been used to strengthen the clinical suspicion of insulinoma in several dogs with euglycemia.[14] Glycosylated hemoglobin A1c concentration has been low in some, but not all, dogs with insulinoma.[15] Repetition of serum insulin measurements may also aid in the diagnosis. One study of canine insulinoma found that 76% of dogs had increased serum insulin concentration when measured once and 91% when measured twice.[7]

Ratios and Other Tests

Other tests have been described for the diagnosis of insulinoma in euglycemic dogs with normal serum insulin concentrations. Insulin-to-glucose and glucose-to-insulin ratios are not recommended because of their low sensitivity, and the amended insulin-to-glucose ratio is not recommended because of its low specificity. Additional tolerance and stimulation tests have been described, but are not advocated because of questionable usefulness and/or potentially fatal side effects due to hypoglycemia.

Imaging

Radiographs and Ultrasonography

Most dogs with insulinoma have unremarkable abdominal and thoracic radiographs.[4,6,8,16] When combining results of studies in which abdominal ultrasonography (US) was performed, 49 of 87 (56%) dogs had a pancreatic mass identified. Abdominal metastases were noted in 17 (19%).[3,5,8,16] Although abdominal US may be helpful in supporting a clinical suspicion of a pancreatic mass and metastases, both false-positive and false-negative results have been described (Figure 303-3). Recently, contrast-enhanced US was successfully employed in discriminating insulinoma from pancreatic carcinoma.[17,18]

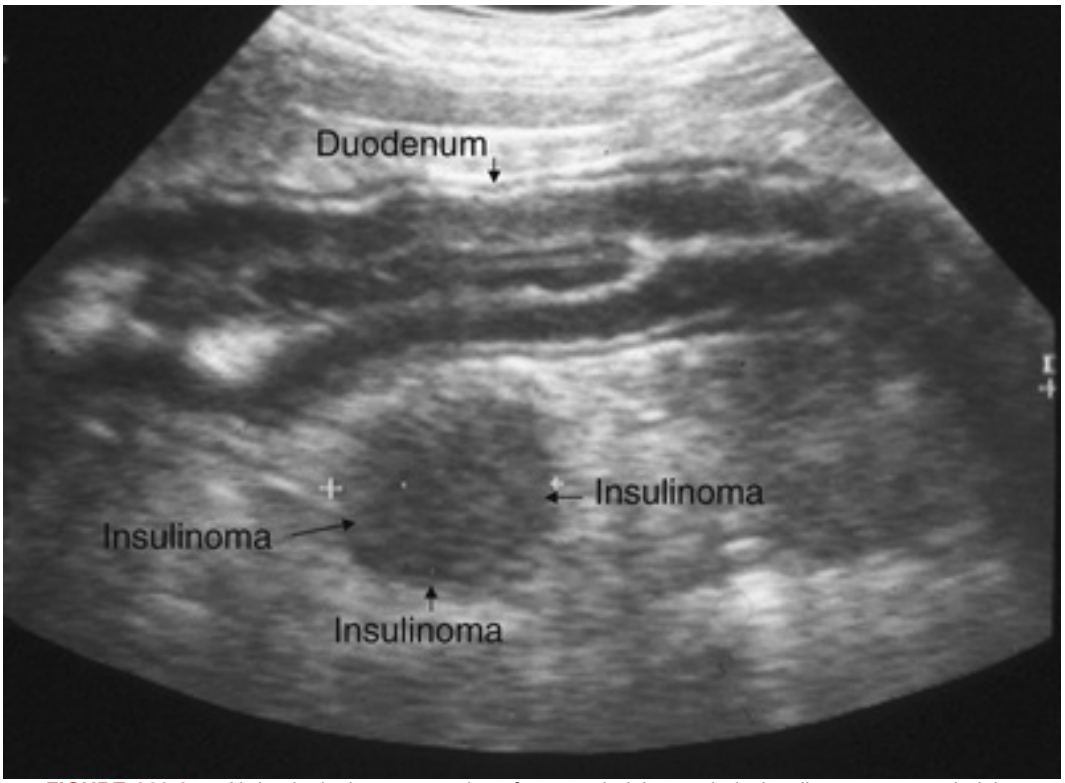

FIGURE 303-3 Abdominal ultrasonography of a rounded hypoechoic insulinoma surrounded by pancreatic tissue. Above the pancreas, the duodenum is visualized. (Courtesy Dr. Wilfried Mai.)

Advanced Imaging

An optimal imaging technique for identifying insulinoma in people has yet to be identified.[19] However, high-quality, dual-phase, thin-section multidetector computed tomography (CT) of the pancreas is effective in identifying a pancreatic mass in most.[19] In people, intraoperative, intra-duct US (not widely available) is more sensitive than CT in detecting small (1- to 3-mm diameter) insulinomas.[19] Use of CT has been reported in a small number of dogs with insulinoma, but its sensitivity has yet to be determined.[20-22] In one study, 14 insulinomas were imaged by US, CT, and single-photon emission CT. CT scans correctly identified the highest number of tumors (10/14, 71%).[22]

In another study, each of three dogs with insulinoma had a mass detected with dual-phase CT angiography (CTA), two of which did not have a pancreatic mass detected on US.[20] Two of these dogs had strong enhancement of their insulinoma only noted during the arterial phase of the study, underscoring the value of dual-phase (Figures 303-4, 303-5, and 303-6).[20] Intravenous (IV) administration of radioactively labeled synthetic somatostatin followed by whole body scintigraphy is of limited value in visualizing insulinomas in people, likely because the number of somatostatin receptors expressed in human insulinomas is low.[19] Somatostatin-receptor-scintigraphy has been reported in a small number of dogs with insulinoma.[23,24] Abnormal foci of activity were observed 1 to 24 hours after administration of the radioligand, but accurate localization of the tumor was achieved in only 1 of 5 dogs.[24]

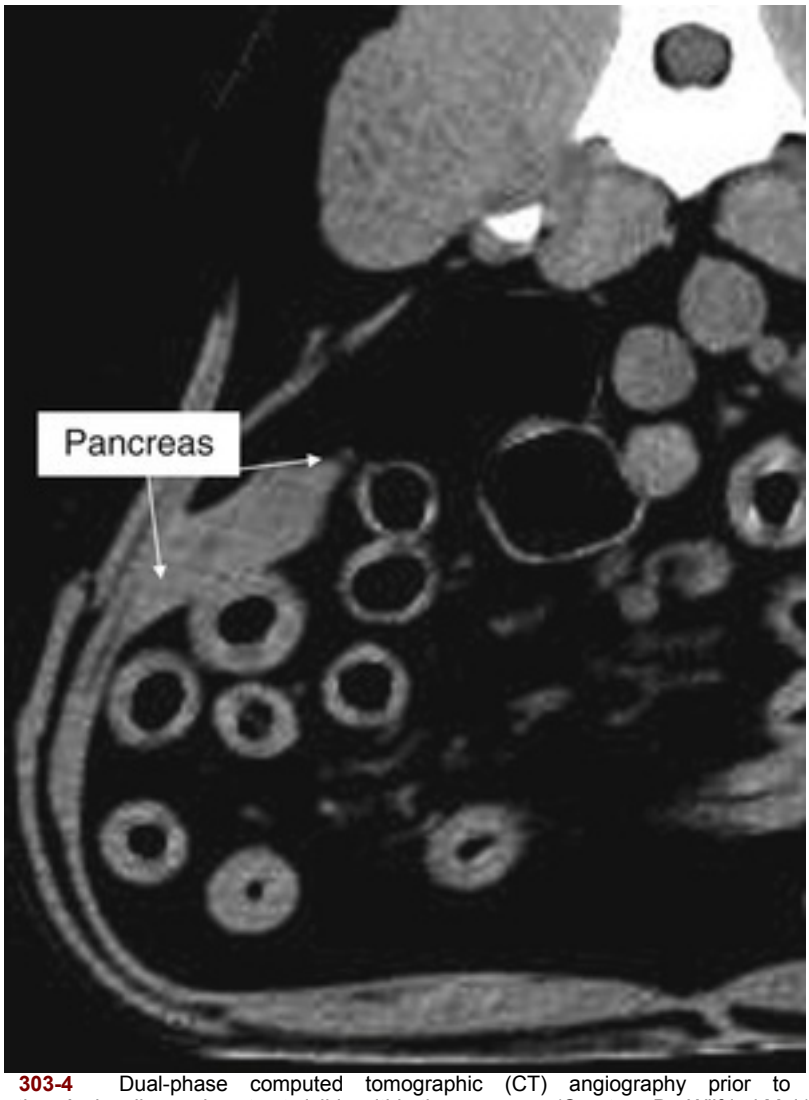

FIGURE 303-4 Dual-phase computed tomographic (CT) angiography prior to contrast administration. An insulinoma is not yet visible within the pancreas. (Courtesy Dr. Wilfried Mai.)

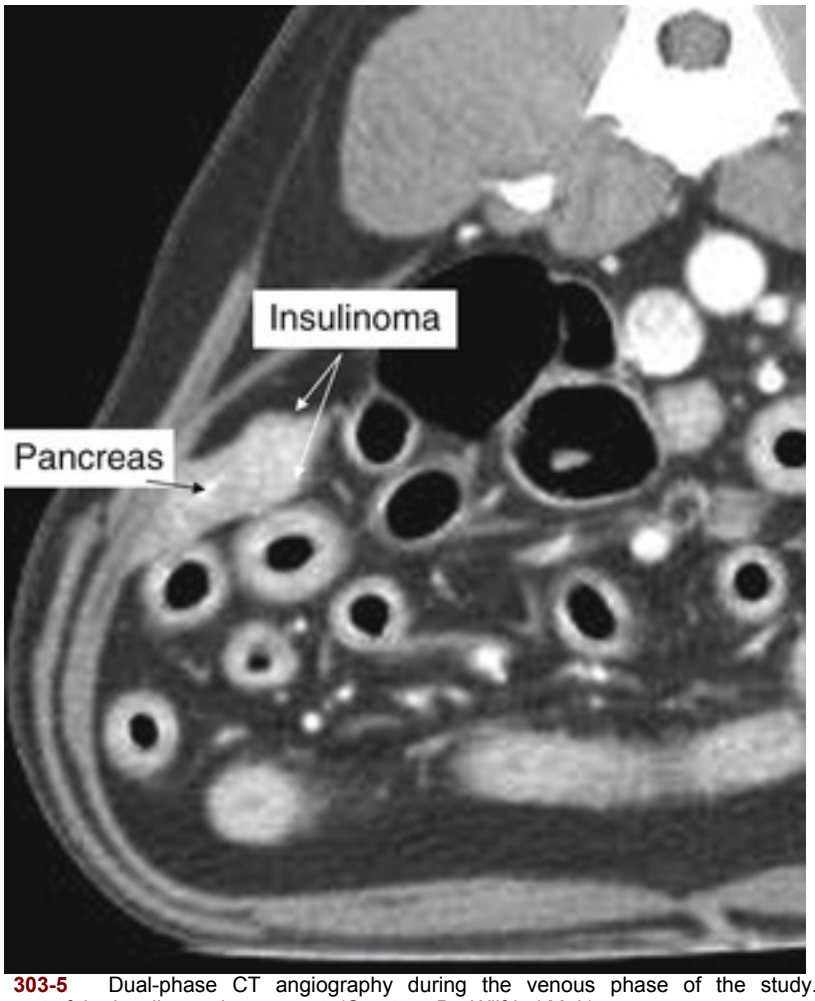

FIGURE 303-5 Dual-phase CT angiography during the venous phase of the study. Some enhancement of the insulinoma is apparent. (Courtesy Dr. Wilfried Mai.)

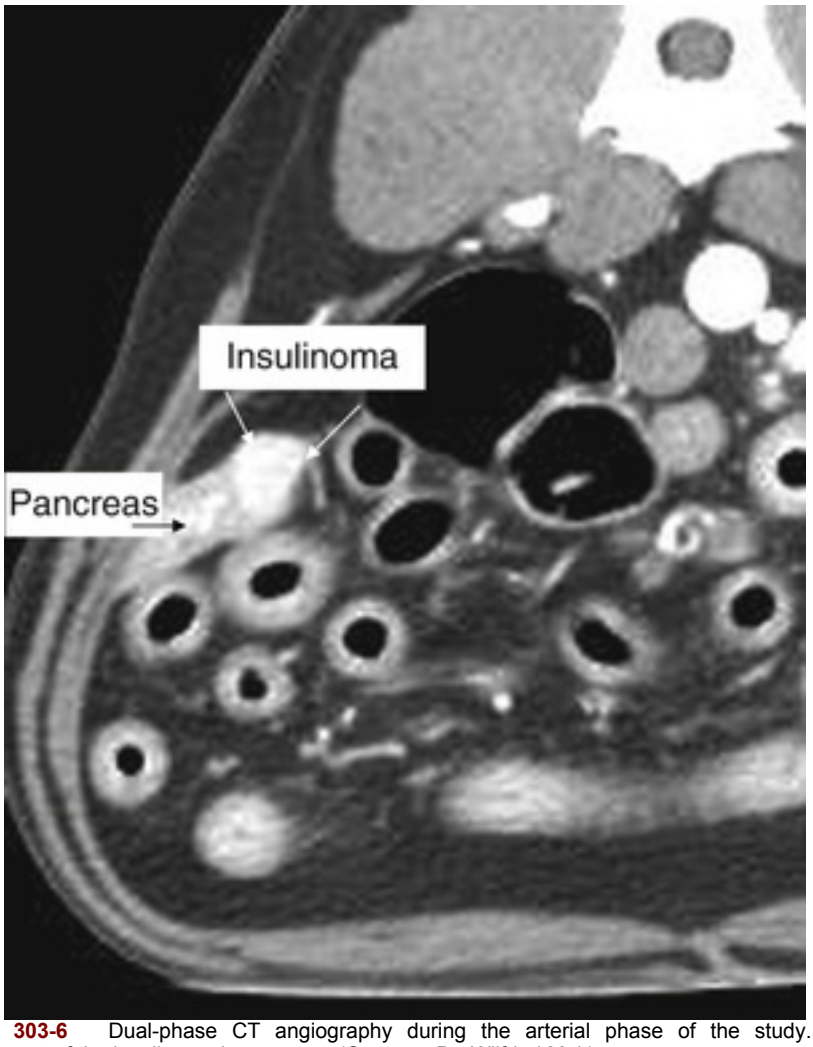

FIGURE 303-6 Dual-phase CT angiography during the arterial phase of the study. Strong enhancement of the insulinoma is apparent. (Courtesy Dr. Wilfried Mai.)

Treatment

Acute Hypoglycemia

During an acute hypoglycemic crisis, 50% dextrose should be given as a slow bolus (0.5 g/kg IV, diluted at a ratio of 1 : 3 in 0.9% sodium chloride). The bolus should be followed with an IV continuous rate infusion (CRI) of 2.5% to 5% dextrose. The lowest amount of glucose deemed necessary must be administered with caution because glucose stimulates insulin secretion. This can cause rebound hypoglycemia and a vicious circle that may be difficult to break. Dextrose administration should be discontinued when clinical signs resolve, even if mild hypoglycemia persists. In most dogs, neuroglycopenia will resolve with administration of dextrose. However, if the animal fails to respond to dextrose administration alone, dexamethasone (0.1 mg/kg IV q 12 h) and/or a somatostatin analogue (10 to 50 mcg SC q 8-12 h) may be administered. In severe cases, the animal may benefit from sedation with diazepam or pentobarbital for several hours to resolve seizure activity. Cerebral hypoxia may lead to cerebral edema and, if suspected, can be treated with mannitol (1 g/kg IV given as a 20% solution at 2 mL/kg/h) and furosemide (1 to 2 mg/kg IV q 4 h) (see ch. 148).[25]

An IV CRI of glucagon (5 to 13 ng/kg/min with or without concurrent 10% dextrose) has been reported in one dog with insulinoma-associated hypoglycemia. Clinical signs attributed to hypoglycemia resolved within 20 minutes and hypoglycemia resolved within an hour. Glucagon increases blood glucose concentration by promoting glycogenolysis and gluconeogenesis. However, glucagon also increases insulin secretion and animals so-treated also require close monitoring for worsening or rebound hypoglycemia.[26]

Long-Term Care

Surgery

The long-term treatment of choice for insulinoma is surgical resection of both the tumor and any obvious metastases.[5] Two dogs have reportedly undergone successful resection of tumor thrombi that had extended into their pancreaticoduodenal veins.[27] One dog had a prolonged disease-free interval after primary tumor resection, despite presence of metastatic lesions.[28] Surgical exploration and biopsy of a pancreatic mass can confirm a diagnosis and may help in estimating survival time.[10] When postoperative hyperglycemia develops, it is usually transient and resolves once normal beta cells, suppressed by autonomous insulin secretion from neoplastic cells, regain function. About 10% of dogs with an insulinoma develop diabetes mellitus after tumor removal and require exogenous insulin for a completely unpredictable length of time (1 to 37 months).[6,7,10] Other postoperative complications include pancreatitis, diabetic ketoacidosis, delayed wound healing, cardiac arrhythmias or arrest, hemorrhage, sepsis, and leukopenia.[3,5,7]

Medical Therapies

Overview

This review of medical therapy is limited to agents whose use has been reported in dogs with naturally occurring insulinoma. The use of additional medications is discussed elsewhere.[25] Medical treatment may be indicated prior to surgery, postoperatively if needed, and in dogs in which surgery is not performed. Medical therapy can be divided into cytotoxic treatment directed at destroying insulin-secreting beta cells versus treatment aimed at relieving hypoglycemia.

Streptozocin

Streptozocin, a nitrosourea antibiotic, selectively destroys beta cells in pancreatic or metastatic locations. The drug is nephrotoxic in dogs. Diuresis with saline decreases drug contact time with renal tubular epithelial cells and may reduce risk of nephrotoxicosis. In one study, 17 dogs, most of which had surgery with incomplete resection of gross lesions, were treated with 0.9% sodium chloride (18 mL/kg/h IV) for 3 hours prior to, 2 hours during, and 2 hours following streptozocin infusion. Streptozocin (500 mg/m^2) was given every 3 weeks for 5 treatments. Butorphanol (0.4 mg/kg IM) was administered immediately following streptozocin therapy as an antiemetic, but vomiting was still observed in about one-third of treatments. Other side effects included diabetes mellitus; transient hypoglycemia and seizures; transient hyperglycemia; transient increase in ALT activity; azotemia; mild thrombocytopenia; or mild neutropenia. Median duration of normoglycemia in streptozocin-treated dogs was 163 days, not significantly different than that of dogs treated surgically or medically.[8] In a study of 19 dogs, the same dosage and saline protocol was used, but at an intensified 2-week interval. Unfortunately, 8/19 developed diabetes mellitus and 2/19 had nephrotoxicity, while the median progression free interval was similar (196 days).[29] Further studies are necessary before recommending streptozocin therapy.

Common Therapies

The main modes of relieving hypoglycemia include dietary modification and treatment with prednisone, diazoxide, or synthetic somatostatin. Small, frequent meals (every 4 to 6 hours) of a diet high in proteins, fats, and complex carbohydrates are recommended (see ch. 181). Simple sugars (present in soft moist dog foods and IV solutions) should be avoided. Prednisone, the least expensive and most commonly used drug, increases blood glucose concentration by increasing gluconeogenesis and glucose 6-phosphatase activity while decreasing blood glucose uptake into tissues and stimulating glucagon secretion. Glucocorticoids can be administered IV during an acute hypoglycemic crisis as dexamethasone. Prednisone is usually used when a dog is stable, given at an initial oral dosage of about 0.5 mg/kg/day. Doses can be gradually increased as needed usually until the drug no longer is perceived as decreasing seizure episodes or intolerable signs of iatrogenic hyperadrenocorticism (polyuria/polydipsia) develop.[10,25]

Diazoxide

Diazoxide is a benzothiadiazine derivative whose main action is to inhibit closure of pancreatic beta cell ATP-dependent K^+ channels, preventing depolarization and inhibiting opening of voltage-dependent Ca^{2+} channels. Decreased Ca^{2+} influx results in decreased exocytosis of insulin-containing secretory vesicles.

Diazoxide also increases blood glucose concentration by increasing glycogenolysis and gluconeogenesis and inhibiting tissue uptake of glucose.[30] About 70% of dogs exhibit a response to diazoxide doses of 10 to 40 mg/kg/day PO divided q 12 h or q 8 h. Again, it is important to begin with the lowest dosage and gradually increase as needed.[7] Side effects in dogs are uncommon and include ptyalism, vomiting, and anorexia. Additional limitations of diazoxide therapy are its limited availability and considerable expense.

Octreotide

Octreotide is a long-acting synthetic somatostatin analogue whose primary mode of action is inhibition of insulin secretion through its binding affinity to any of five somatostatin receptor subtypes present in insulin-secreting tumors. Dogs show a variable response to octreotide, likely because octreotide variably inhibits glucagon and GH secretion.[31] If suppression of glucagon and GH secretion is of greater magnitude and duration compared with suppression of insulin secretion, octreotide may actually worsen hypoglycemia. While some canine insulinomas may lack somatostatin receptors, 12 dogs with insulinoma treated with a single octreotide dose of 50 mcg/dog SC (median weight 23 kg) had decreases in plasma insulin concentration but concentrations of glucagon, GH, and ACTH were not changed.[32] These findings warrant studies using long-acting octreotide in dogs with insulinoma. No adverse side effects were reported. Side effects in people include mild pain at the injection site (lessened if warmed before administration), nausea, vomiting, abdominal pain, constipation, or steatorrhea.

Prognosis

Median survival time of 142 dogs that underwent partial pancreatectomy, reported in different studies, was 12 to 14 months with a range of zero days to 5 years.[3-5,7,10] Dogs with clinical stage I disease have a significantly longer disease free interval; about 50% are expected to be normoglycemic 14 months postoperatively, compared to only 20% of dogs in clinical stage II or III.[6] Additionally, young dogs and those with persistent post-operative hypoglycemia have a poorer prognosis.[6] In contrast, dogs with postoperative hyperglycemia or normoglycemia have a significantly better prognosis.[3]

One study reported a median survival time of 785 days in 19 dogs with insulinoma that underwent partial pancreatectomy, which improved to 1316 days in the subgroup of dogs that also received prednisone.[33] These survival times are most likely attributable to earlier detection, more radical tumor resection protocols and continued medical therapy following relapse. It was also demonstrated that tumor size and mitotic rate, as depicted by the Ki67 index (a proliferation marker), act as significant prognostic markers in canine insulinoma.[34] This was followed up with a tissue microarray immunohistochemistry study, which corroborated the above findings in 32 insulinoma samples. Multivariate analysis showed that tumor size and Ki67 index retained predictive power for survival time, as did tumor size for disease free interval.[35] Conversely, age, sex, body weight, clinical signs and their duration, US detection of pancreatic mass, tumor location, gross presence of metastatic disease, and blood glucose or insulin concentration have not been significantly associated with prognosis.

Insulin-Secreting Islet Cell Neoplasia in the Cat

Feline insulinoma is rare and has been reported in seven cats ranging in age from 12 to 17 years. Three of these cats were Siamese and five were neutered males.[25,36-38] History and clinical signs are similar to those reported in dogs with insulinoma. Diagnosis is based on documentation of increased serum insulin concentration at the time of hypoglycemia and is aided by abdominal US and histology.[38] Immunohistochemistry of feline insulinoma revealed insulin, chromogranin A and somatostatin expression, with no glucagon or pancreatic polypeptide expression.[39] Care must be taken to use an insulin assay validated for cats. Therapy consists of surgical resection of the pancreatic mass and metastases followed by prednisone treatment and frequent small meals. Use of neither diazoxide nor octreotide has been reported in cats.

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CHAPTER 304

Canine Diabetes Mellitus

Federico Fracassi

Client Information Sheet: Canine Diabetes Mellitus

Introduction

Diabetes mellitus (DM) is a common endocrine disorder characterized by chronic hyperglycemia resulting from a deficit in insulin production, action, or both. The prevalence of DM in dogs has been estimated from about 1% of dogs in referral institutions to about 0.3% in first opinion practices.[1-4] The reported incidence of DM in a population of 182,087 insured dogs in Sweden was about 13 cases per 10,000 (0.13%) dog-years at risk.[5]

Classification and Etiology

"Types" of Diabetes Mellitus

There are two predominant forms of DM in people, once referred to as "juvenile-onset" and "adult-onset" DM. These terms were updated to "insulin-dependent" (IDDM) and "non-insulin-dependent" (NIDDM). Currently, the terms type 1 and type 2 DM are employed, with type 1 explaining the condition for about 10% of diabetic people and type 2 DM, almost identical to the previous "NIDDM," used to define the condition in about 90% of people with DM worldwide.[6] The most common form of DM in dogs resembles the human type 1 condition, characterized by permanent hypoinsulinemia, no increase in endogenous serum insulin or C-peptide concentrations following administration of an insulin secretagogue (e.g., glucose, glucagon, amino acids), and an absolute need for exogenous insulin to control glycemia, avoid ketoacidosis, and survive.[7] With rare exceptions, all diabetic dogs require exogenous insulin therapy to manage their hyperglycemia.[8]

Histology and Possible Primary Causes

Common histologic observations in pancreatic tissue from dogs with DM include a reduction in the number and size of pancreatic islets, a decreased number of beta cells within islets, and beta cell vacuolization, enlargement and degeneration.[9,10] The underlying cause of pancreatic beta cell dysfunction/destruction in dogs is not established. In humans and dogs, DM is undoubtedly a multifactorial disease involving both genetic and environmental factors (Box 304-1).[8,11-15] The concept of genetic predisposition has been based on familial associations, pedigree analyses of Keeshonden and several other breeds, and genomic studies to identify susceptibility and protective major histocompatibility complex haplotypes.[1,5,16] A number of genes linked with susceptibility to DM in people are also associated with increased risk in dogs.[17] Canine DM has been associated with major histocompatibility complex (MHC) class II genes (dog leukocyte antigen; DLA). Similar haplotypes and genotypes have been identified in the most susceptible breeds. A region containing a variable number of tandem repeats (VNTR) as well as several polymorphisms has been identified in the canine insulin gene, with some alleles associated with susceptibility or resistance to DM in a breed-specific manner.[17]

Box 304-1

Potential Factors Involved in the Etiopathogenesis of Canine Diabetes Mellitus

Insulin Deficiency

Insulin deficiency in dogs is characterized by a loss of beta cells. The etiology of beta cell deficiency/destruction in diabetic dogs is currently unknown but a number of disease processes are thought to be involved:

- Congenital beta cell hypoplasia/abiotrophy
- Immune-mediated beta cell destruction
- Beta cell loss associated with pancreatitis
- Beta cell exhaustion/glucose toxicity as a consequence of prolonged insulin resistance

Insulin Resistance

Insulin resistance usually results from antagonism of insulin function by other hormones and can also be exacerbated by the presence of infection or inflammation:

- Diestrus/pregnancy
- Concurrent hormonal disease
  - Cushing's syndrome
  - Hypothyroidism
  - Acromegaly
- Iatrogenic
  - Glucocorticoids
  - Progestagens
- Carbohydrate intolerance associated with obesity
- Infection
- Concurrent illness
- Renal insufficiency
- Cardiac disease
- Hyperlipidemia
- Insulin receptor deficits such as those seen in humans might exist in canine diabetic patients, although these have not so far been reported

Modified from Davison LJ: Canine diabetes mellitus. In Mooney CT, Peterson ME: *BSAVA manual of canine and feline endocrinology*, ed 4, Gloucester, England, 2012, British Small Animal Veterinary Association, p 117.

The American Diabetes Association has recommended sub-categorizing human type 1 DM (T1DM) into types 1A (immune-mediated) and 1B (idiopathic severe insulin deficiency).[18] Type 1A DM is characterized by lymphocytic infiltration of the islets, known as "insulitis," and by the presence of serum autoantibodies to pancreatic components (insulin, intracellular glutamic acid decarboxylase 65 [GAD65] or insulinoma antigen 2 [IA-2]) prior to development of hyperglycemia (Figure 304-1).[19] An immune-mediated component has been implicated in development of canine DM. Lymphocytic infiltration of pancreatic islets has been reported and antibodies directed against islet cells, insulin, proinsulin, GAD65 and IA-2 have been identified in dogs with DM.[20-24] Despite these studies, the role of autoimmunity in the pathogenesis of canine DM remains unsettled. A recent study did not find evidence for an islet autoimmune etiology.[9] Unlike human T1DM, which occurs primarily in adolescence and early adulthood, dogs are usually diagnosed when middle-aged or older.[25] It has been proposed that canine DM most closely resembles people with "latent autoimmune diabetes of adults" (LADA).[11,26]

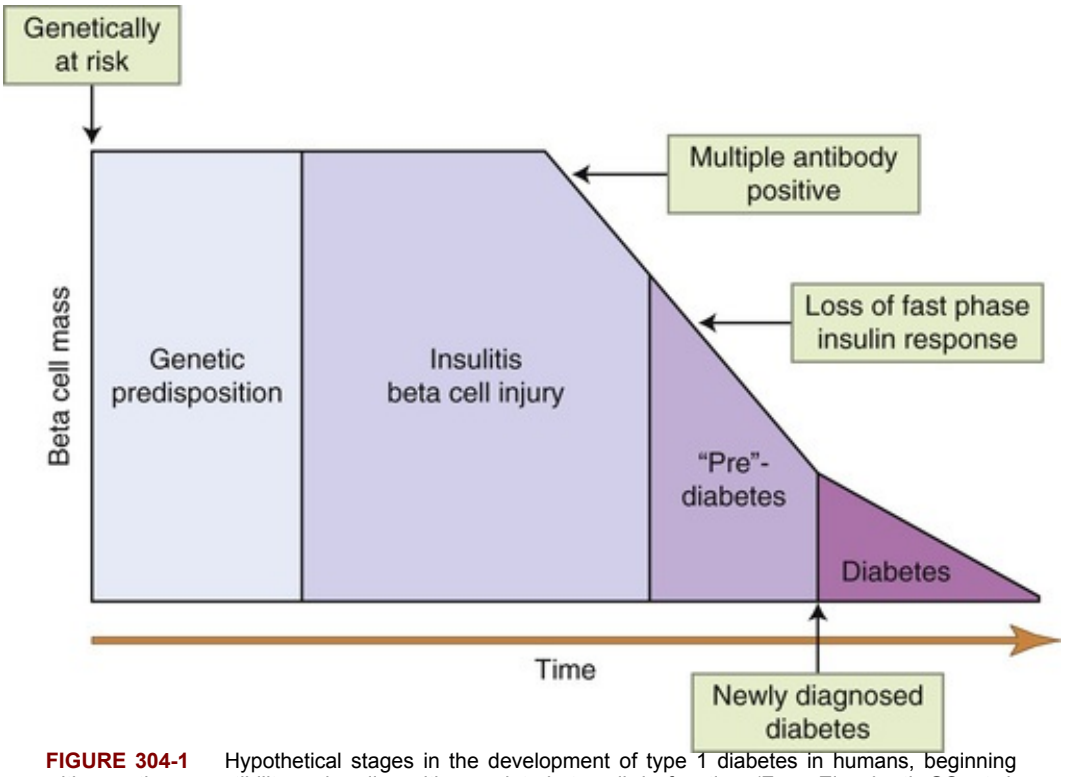

FIGURE 304-1 Hypothetical stages in the development of type 1 diabetes in humans, beginning with genetic susceptibility and ending with complete beta cell dysfunction. (From Eisenbarth GS, et al: Type 1 diabetes mellitus. In Kronenberg HM, Melmed S, Polonsky KS, et al, editors: *Williams textbook of endocrinology*, ed 11, Philadelphia, 2008, Saunders Elsevier, p 1398.)

Secondary Causes

DM may occur secondary to disorders of the exocrine pancreas or any process that diffusely injures the pancreas, most notably pancreatitis.[27] The incidence of histologically identifiable, often severe, pancreatitis in diabetic dogs ranges from 30% to 40% and is believed to be a contributor to development of DM and diabetic ketoacidosis (DKA).[28-30] Loss of beta cell function is irreversible in dogs with DM and lifelong insulin therapy is necessary for survival. Transient or reversible DM is extremely uncommon in dogs, usually recognized in subclinical diabetics with a concurrent insulin-antagonistic condition (i.e., diestrus, pregnancy) or who were given an insulin antagonistic drug (i.e., glucocorticoids). Following estrus, all normal bitches (pregnant or not) enter the luteal, progesterone-dominated phase (diestrus) of their ovarian cycle. Diestrus lasts 60 to 90 days, every 6 to 12 months. Progesterone (Pg) stimulates growth hormone (GH) secretion from mammary tissue. Both Pg and GH antagonize the effects of insulin.[31] Older females are frequently diagnosed with DM while in diestrus (whether or not pregnant), when serum Pg and GH concentrations are increased.[32-34] Treatment with ovariohysterectomy removes the source of Pg and, in turn, the stimulus for GH secretion. If an adequate population of functional beta cells is still present in the pancreas, hyperglycemia may resolve without insulin treatment. Failure to quickly correct insulin resistance often results in progressive loss of beta cells and a greater likelihood of permanent insulin dependency.[33]

"Honeymoon Period"

A "honeymoon period" occurs in some dogs with newly diagnosed DM, characterized by excellent glycemic control in response to small doses of insulin (<0.2 U/kg/injection), presumably due to residual beta cell function. Typically, glycemic control in these dogs becomes more difficult and insulin doses need to be increased within months of beginning treatment, as those residual functioning beta cells die and fail to be replaced. Endogenous insulin secretion declines.[35] Type 2 or NIDDM is rare in dogs and usually associated with a concurrent insulin antagonistic condition or treatment. Obesity-induced insulin resistance has been documented in dogs although progression to type 2 DM has not yet been demonstrated.[36]

Pathophysiology

Diabetes mellitus is the result of a relative or absolute deficiency of insulin secretion by pancreatic beta cells. Insulin deficiency, in turn, causes decreased tissue utilization of glucose, amino acids, and fatty acids, accelerated hepatic glycogenolysis and gluconeogenesis, and accumulation of glucose in the circulation, causing hyperglycemia.[37] Neither intestinal glucose absorption nor glucose entry into erythrocytes, kidney or brain is affected. As renal tubular capacity for glucose reabsorption is exceeded, usually when blood glucose concentrations are >180 to 220 mg/dL, glycosuria occurs. The resulting glucose-induced osmotic diuresis causes polyuria (PU), water loss, and activation of the thirst mechanism (polydipsia; PD). The negative calorie balance resulting from an inability to utilize glucose, some loss of calories via glycosuria, and tissue catabolism leads to polyphagia (PP).

The physiology of the consequences of DM is virtually identical to that of starvation. Protein metabolism shifts toward decreases in synthesis and increases in proteolysis. These available amino acids increase hepatic gluconeogenesis, a good response to starvation, but in DM it further contributes to hyperglycemia at a price of negative nitrogen balance, loss of muscle mass and possible cachexia.[38] The continuing lack of insulin and intracellular glucose then accelerate lipid catabolism with mobilization of triglycerides that leads to increased levels of plasma free fatty acids (FFAs). FFAs are transported to the liver where they undergo beta-oxidation to acetyl CoA, the amount of which may exceed the need for ATP production via oxidation in the Krebs cycle. Acetyl CoA is, therefore, metabolized into its alternative product: ketone bodies. Again, in response to starvation, ketones are an acceptable short term source for energy. In prolonged starvation or in DM, production of excess ketone bodies can lead to ketosis and, in diabetics, ketoacidosis. Increased hepatic concentration of fatty acids also increases hepatic synthesis of both triglycerides and very low density lipoproteins (VLDL), causing hyperlipidemia and hepatic lipidosis (see ch. 285).

Signalment

DM is most commonly diagnosed in middle-aged and older dogs, 5 to 12 years of age.[1,3,5] Rarely, DM in juvenile dogs has been reported.[3,39] Peak prevalence is 7 to 10 years and most, but not all, studies suggest females are at a greater risk.[1,3-5,40] Regional differences in breed popularity or variation in neutering practices may influence sex predispositions within a population, although associations identified between neutering and diagnosis of DM also vary. Genetic predisposition for or against the development of DM in dogs has been suggested (Table 304-1). For example, Boxer dogs are seldom reported in epidemiologic studies on DM and may have one of the lowest incidences. Genetic differences within the same breed due to different blood-lines also impact predispositions. For example, Swedish and Norwegian Elkhounds, Australian Terriers and Samoyeds have the highest incidence of DM in Sweden while Irish Setter and English Setter dogs are overrepresented in Italy.[2,5]

TABLE 304-1

Breed Risks for Developing Diabetes Mellitus

BREEDS AT HIGH RISK	ODDS RATIO	BREEDS AT LOW RISK	ODDS RATIO
Australian Terrier	9.39	German Shepherd Dog	0.18
Standard Schnauzer	5.85	Collie	0.21
Miniature Schnauzer	5.10	Shetland Sheepdog	0.21
Bichon Frise	3.03	Golden Retriever	0.28
Spitz	2.90	Cocker Spaniel	0.35
Fox Terrier	2.68	Australian Shepherd	0.44
Miniature Poodle	2.49	Labrador Retriever	0.45
Samoyed	2.42	Doberman Pinscher	0.49
Cairn Terrier	2.26	Boston Terrier	0.51
Keeshond	2.23	Rottweiler	0.51

Maltese	1.79	Basset Hound	0.56
Toy Poodle	1.76	English Setter	0.60
Lhasa Apso	1.54	Beagle	0.64
Yorkshire Terrier	1.44	Irish Setter	0.67

Derived from analysis of the Veterinary Medical Database (VMDB) from 1970 to 1993. The VMDB comprises medical records of 24 veterinary schools in the United States and Canada. VMDB case records analyzed included those from first hospital visits of 6078 dogs with a diagnosis of diabetes mellitus and 5922 randomly selected dogs with first hospital visits for any diagnosis other than diabetes mellitus seen at the same veterinary schools in the same year. Only breeds with more than 25 cases of diabetes mellitus are included.

From Guptill L, et al: Is canine diabetes on the increase? In *Recent advances in clinical management of diabetes mellitus,* Dayton, Ohio, 1999, Iams Company, p 24.

Anamnesis

The typical history of a dog with DM includes the classical clinical signs of PU/PD/PP and weight loss. PU/PD are constant in diabetic dogs. PP may be diminished by a concurrent condition that decreases appetite (e.g., pancreatitis, ketosis, DKA). Weight loss may not be noticed in dogs that have only recently become diabetic. The most common reasons for dogs with undiagnosed DM to be brought to their veterinarian are their need to urinate at night or that they urinate in the home. In the event that a dog has free access to urinate out-of-doors, the owner may consult the veterinarian due to concerns over weight loss, ravenous appetite, sudden blindness caused by cataract formation (Figure 304-2), or signs associated with DKA (e.g., lethargy, anorexia, vomiting, weakness). Time from onset of clinical signs to development of DKA is unpredictable, ranging from days to months, and may be dependent on type and severity of concurrent disorders causing insulin resistance and/or stimulating ketone production.

FIGURE 304-2 Bilateral complete cataracts secondary to diabetes mellitus causing blindness in a dog.

Physical Examination

In dogs with newly diagnosed DM, abnormalities detected on physical examination (PE) depend on the duration of DM, presence of concomitant disorders, and whether DKA has developed. A thorough PE is critically important, especially to detect issues due to a concomitant disease. Dogs with uncomplicated DM are usually in good condition and their PE may be unremarkable. Diabetic dogs can be of normal weight, underweight or obese. Lethargy may be evident. The haircoat in newly diagnosed or poorly controlled DM may be dull. Hepatomegaly due to diabetes-induced hepatic lipidosis is commonly palpable. Cataracts are also common. Anterior uveitis and keratoconjunctivitis sicca may be present. The neurologic signs commonly observed in diabetic cats (e.g., weakness in the hind limbs, ataxia, plantigrade stance) are uncommon in dogs.

Diagnosis

The diagnosis of diabetes mellitus is made on the basis of appropriate clinical signs, persistent fasting hyperglycemia (>200 mg/dL), and concomitant glycosuria. Persistent hyperglycemia and glycosuria are both of paramount importance in the diagnosis of DM. Hyperglycemia distinguishes DM from primary renal glycosuria and glycosuria separates DM from other causes of hyperglycemia (Box 304-2). Mild hyperglycemia, concentrations below renal threshold (>100 and <180 mg/dL), is asymptomatic and often viewed as an incidental finding. DM is quite unlikely if a dog has mild hyperglycemia without glycosuria. Stress-induced hyperglycemia is common in cats, but rare in dogs. A diagnostic evaluation for disorders causing insulin resistance is indicated if mild hyperglycemia persists in a fasted, unstressed dog, but insulin therapy is not indicated because clinical DM is not present. Concurrent evidence of ketonuria establishes a diagnosis of diabetic ketosis (DK), whereas ketonuria and metabolic acidosis with increased anion gap establishes a diagnosis of DKA. Blood ketone concentrations can be assessed with one drop of blood, using a hand-held electrochemical sensor for 3-beta-hydroxybutyrate (3-HB). Low to moderate 3-BH blood concentrations are usually indicative of DK, whereas higher values (>3.8 mmol/L) are suggestive of DKA (see ch. 142).[41]

Box 304-2

Causes of Hyperglycemia and Glycosuria in Dogs

Hyperglycemia Causes

Diabetes mellitus
Stress, aggression, excitement, nervousness, fright (quite uncommon)
Pancreatitis
Postprandial (diets containing monosaccharides, disaccharides, and propylene glycol)
Hormonal antagonism:
- Cushing's syndrome
- Diestrus
- Pheochromocytoma
- Acromegaly

Iatrogenic:
- Glucocorticoids
- Progestagens
- Thiazide diuretics
- Alpha 2-agonist sedatives
- Dextrose-containing fluids
- Parenteral nutrition solution

Head trauma

Glycosuria Causes

Diabetes mellitus
Renal tubular dysfunction:
- Fanconi syndrome
- Primary renal glycosuria
- Acute kidney injury (e.g., leptospirosis)

- Nephrotoxins

Iatrogenic:

- Dextrose-containing fluids

Causes of false positive glycosuria:

- Glucose in the owner's collecting jar for urine (e.g., jam jar)
- Vitamin C or pigment in urine can affect dipstick results

Once DM is diagnosed, it is extremely important to thoroughly evaluate the overall health of a dog. One should identify any clue to a condition that may have contributed to DM development (e.g., Cushing's syndrome [see ch. 306], hypothyroidism [see ch. 299], pancreatitis [see ch. 290]) or which could represent a consequence of DM (e.g., weight loss, weakness, urinary tract infection). The minimum laboratory evaluation in a dog newly diagnosed with DM should include a complete blood count (CBC), a serum biochemical profile that includes a serum fructosamine concentration, and urinalysis with bacterial culture. Serum Pg concentrations should be assayed in any intact diabetic female. Abdominal ultrasound (US; see ch. 88) is indicated to evaluate patients for evidence of pancreatitis, adrenal enlargement, masses, pyometra, ovarian cysts, and other concerns. Because of the relatively high prevalence of pancreatitis, pancreatic lipase immunoreactivity (cPLI) should be considered, especially if US is unavailable. Other tests, including thoracic radiographs, may be indicated (Box 304-3).

Box 304-3

Clinicopathologic Abnormalities Commonly Found in Dogs with Uncomplicated Diabetes Mellitus

Complete Blood Count

1. Typically normal
2. Neutrophilic leukocytosis or toxic neutrophils may be observed if pancreatitis or infection is present

Biochemistry Panel

1. Hyperglycemia
2. Hypercholesterolemia
3. Hypertriglyceridemia (lipemia)
4. Increased alanine aminotransferase activity (typically <500 IU/L)
5. Increased alkaline phosphatase activity (typically <500 IU/L)

Urinalysis

1. Urine specific gravity typically >1.025
2. Glycosuria
3. Variable ketonuria
4. Proteinuria
5. Bacteriuria

Ancillary Tests

1. Hyperlipasemia if pancreatitis is present
2. Serum trypsin-like immunoreactivity usually normal
   a. Low with pancreatic exocrine insufficiency
3. Pancreatic lipase immunoreactivity usually normal
   a. High with acute pancreatitis
   b. Normal to high with chronic pancreatitis
4. Variable serum baseline insulin concentration
   a. Insulin-dependent diabetes mellitus: low, normal
   b. Insulin-resistance-induced: low, normal, increased

Management Issues

Plan and Therapeutic Goals

Successful treatment of DM in a dog requires excellent owner compliance and excellent owner/veterinary team interaction. The "owner" may be one person or several while the veterinary team involved in the long-term care of these dogs should include veterinarians, technicians, and non-technical personnel. The owner should be thoroughly educated regarding DM, how it is managed differently in dogs when compared with people, and the goals of therapy. Establishing and agreeing on the definition of "successful management" is extremely important. For most veterinarians, their primary goal in the long-term management of DM should be to have the owner pleased with the status of their dog. This is usually achieved if PU can be eliminated or significantly reduced, body weight is stable and acceptable, PP is tolerable, and the dog interacts normally with others in the home. Owners who are informed and involved in the management of their dog seem to have more success and satisfaction in providing care. A highly motivated owner who works with their veterinarian is key. Dogs with DM typically require two daily injections of insulin and a relatively fixed routine. Owners must be willing to administer insulin, and have sufficient finances for insulin, consumables, testing necessary to manage the DM over time, as well as possible intermittent periods of hospitalization.[42] It is important to give the owners detailed information on all the technical aspects of DM and to provide ready access to care, if needed. Furthermore, treatment should follow a precise and understandable protocol (Box 304-4).

Box 304-4

Protocol for the Management of Diabetic Dogs

- Diagnosis of diabetes mellitus (history, physical examination, hyperglycemia, glycosuria, increased fructosamine)
- Routine laboratory evaluation (complete blood count, serum biochemistry, urine analysis, urine culture)
- Abdominal ultrasonography, canine pancreatic lipase immunoreactivity if indicated
- Cessation of diabetogenic drugs
- Administration of intermediate-/long-acting insulin (Caninsulin/Vetsulin, NPH, Lantus): 0.25 U/kg SC q 12 h
- Institution of treatment for concurrent problems (e.g., urinary tract infection)
- Prescribe a commercial "diabetic" diet. Feed the dog with 2 meals of equal size just before each insulin injection. If overweight, aim to achieve 1% to 2% weight loss per week. High-fiber, low-calorie diets should not be fed to thin or emaciated diabetic dogs until glucose control is established and a normal body weight is attained using a calorie-dense, lower-fiber diet designed for maintenance. Dietary recommendations for concurrent disorders (e.g., chronic kidney disease, food allergy, pancreatitis) have priority over a specific diabetic diet.
- Owner instructions (requires at least 1 hour)
  - With intact bitches, make an appointment with the owner for spaying. This procedure should be done soon as possible.
  - Provide written instructions

Reevaluation 1 Week after Diagnosis

- History, physical examination, body weight
  - Administration of food and insulin at the clinic. For dogs that are unwilling to eat at the clinic, food and insulin are given at home and the blood glucose curve (BGC) started upon arrival at the clinic (as soon as possible).
- Glucose measurement every 1-2 hours for the remainder of the day
- Fructosamine
- Adjustment of insulin dosage if required: 10% to 25%

Reevaluation 2 to 3 Weeks after Diagnosis

- Repeat all the procedures performed at the first reevaluation (history, physical examination, body weight, BGC, fructosamine, dosage adjustment)
- Introduction to home monitoring (HM) and instruction on all relevant technical aspects (requires at

least ½ hour)
- Owner should measure fasting blood glucose twice weekly and generate a BGC twice a month

Reevaluation 6 to 8 Weeks after Diagnosis
- Repeat all procedures performed in first reevaluation (history, physical examination, body weight, BGC, fructosamine, dosage adjustment). BGC may not be required if the dog appears clinically well, if blood glucose measured close to the time of insulin administration is 180 to 250 mg/dL, and fructosamine is 350 to 450 micromol/L.
- Owner administration technique should be evaluated for those doing HM

Reevaluation 10 to 12 Weeks after Diagnosis
- Repeat all procedures done 6 to 8 weeks after diagnosis

Further Reevaluations Every 4 Months
- Repeat all procedures done 6 to 8 weeks after diagnosis

Goals of Therapy
- Clinical signs: resolution of polyuria/polydipsia and polyphagia, normal body weight
- Blood glucose concentration: ideally between 250 mg/dL (before insulin administration) and 90 mg/dL (nadir)
- Fructosamine concentration: ideally between 350 and 450 micromol/L. (please note: fructosamine concentration is the least important variable for evaluation of metabolic control)

Initiating Insulin Therapy

Once diagnosed, treatment for DM should begin. Dogs in good condition and with an excellent appetite can be managed as "uncomplicated diabetics," even in the presence of ketonuria. The goals of therapy are to reduce or resolve clinical signs, prevent short-term complications (e.g., hypoglycemia, DKA), achieve the previously discussed areas of clinical improvement, and have a good quality of life. In DM dogs, this can be accomplished with exogenous insulin therapy, an appropriate diet, exercise, prevention or control of concurrent inflammatory, infectious, neoplastic or hormonal disorders, and avoidance of insulin-antagonistic drugs (see ch. 358). Aiming for normal or near-normal blood glucose concentrations is not recommended, as it increases risk of hypoglycemia, a common, serious and potentially life-threatening complication. Hypoglycemia is usually the result of overzealous insulin therapy. Most diabetic dogs are described as being well if their blood glucoses are maintained between 90 to 250 mg/dL.

Owner Education (see ch. 79)

Educating owners is of paramount importance to achieve success in managing a dog with DM. Owners should be familiar with the clinical signs of DM. They should be aware of changes in water intake, urine output, appetite and body weight. Poor appetite, vomiting, diarrhea or unusual lethargy is always worrisome and worth veterinary consultation. Insulin should, initially, be given after the dog eats to avoid the conundrum of having given insulin to a dog who refuses to eat. It should be emphasized that consistency in timing of injections, meals, type and amount of food, and exercise will make control of DM easier. Owners must learn the signs of hypoglycemia and DKA. Unfortunately, many dogs with DM become blind from cataract formation (see Figure 304-2). This may occur despite an owner's best efforts for excellent control.

While owners are the key to good DM control, decisions regarding insulin, dose and frequency of administration must always be made by the owner/veterinary team. Insulin should be stored in a refrigerator in an upright position. Insulin must be mixed correctly. Vetsulin/Caninsulin should be shaken, some insulins do not require mixing, and some insulin products should be gently rolled. Owners must use appropriate syringes (40 U/mL for veterinary insulin products and 100 U/mL for human insulin products), learn to eliminate air bubbles, and administer the insulin SC over the lateral wall of the chest. The use of nonmatching syringes based on conversion tables for U40 and U100/mL, or the owner's own calculation, should be avoided as it can be confusing. Often U40 insulin syringes have scales in both mL and Units; the owner must be instructed to use the Units scale. The injection technique should be demonstrated until the owner is comfortable (practice at home with an over-ripe banana can be beneficial). If an insulin pen device is to be

used for insulin administration, owners must be specifically trained with this tool. Written instructions are useful. Owners of DM dogs should be encouraged to keep detailed records of their dogs' blood glucose, urine glucose, urine ketones, and any change in other parameters.

Dietary Recommendations (see ch. 181)

Food given to DM dogs must be palatable to ensure regular consumption. Diets must be nutritionally complete and have day-to-day consistency with regard to composition, ingredients and calories. These factors improve the chance for consistent insulin requirements and consistent response. Ideally, near optimal body condition is achieved and maintained. A dog with DM may be overweight or underweight. In either, near ideal weight is a reasonable goal. Insulin is an anabolic hormone and insulin-treated diabetics gain weight easily. Since insulin is anabolic, having an obese dog with DM lose weight is far more difficult. However, obesity-induced insulin resistance has been documented in dogs and weight loss improves glucose tolerance.[43] Weight loss diets should be considered for obese DM dogs as they are typically rich in insoluble fiber, low in fat, and have decreased caloric density. Such diets should not be fed to underweight DM dogs. Once glucose control is established and a near-normal body weight attained, giving a consistent calorie-dense and lower-fiber diet designed for maintenance should be considered.[37]

Several commercial prescription diets are available for DM dogs. To minimize postprandial hyperglycemia, no diet should contain significant amounts of simple sugar. Calories should be provided mainly by complex carbohydrates and proteins. The amount of fat in the diet should be minimized to avoid increasing circulating cholesterol, triglycerides, free glycerol, and free fatty acids.[44] Dietary fat may directly contribute to insulin resistance, promote hepatic glucose production and, in healthy dogs, suppress beta cell function.[45,46] Dietary fat should be particularly restricted in any dog with a history of pancreatitis or persistent hyperlipidemia.

Several, but not all, studies evaluating the role of high-fiber diets in the management of DM dogs demonstrated higher dietary fiber content improves glycemic control.[47-49] One study failed to demonstrate benefit from feeding normal weight DM dogs a high-fiber diet.[44] Most diets for DM contain a blend of soluble and insoluble fibers. Common complications of feeding high-fiber diets include increased frequency of defecation (insoluble fiber); constipation and obstipation (insoluble fiber); soft to watery stools (soluble fiber); and excessive flatulence (soluble fiber).[37] Problems with palatability, which are usually the result of switching diets too quickly, can be avoided in many by gradually transitioning from one diet to another. With time, dogs may become less interested in fiber-rich diets and palatability can be improved by adding minced boiled meat. Diet should also take concurrent conditions into consideration (i.e., inflammatory bowel disease, chronic kidney disease, food allergy/intolerance), which may have priority over a specific DM diet.

To simplify management, most DM dogs should be fed two equal-sized meals daily, about every 12 hours, immediately prior to giving insulin, thus avoiding the situation of a dog refusing to eat after receiving insulin. In dogs with a consistently good appetite, food can be given immediately after the insulin injection, helping the dog associate the unpleasant injection with the more pleasurable meal. Ad libitum feeding can be of benefit in some diabetic cats but is not recommended in dogs. Dogs who are finicky eaters should be fed at the time of insulin administration and have any uneaten food available throughout the day.

Exercise

Consistent exercise can make management of canine DM easier and should be encouraged (see ch. 355 and 359). Physical activity decreases glucose concentrations by increasing the absorption of insulin from its injection site, increasing blood flow and insulin delivery to exercising muscles, stimulating translocation (i.e., upregulation) of glucose transporters (primarily GLUT-4) in muscle cells, and increasing glucose disposal despite basal insulin concentrations.[50,51] Timing and amount of exercise each day should be as consistent as timing of meals and insulin. For example, it is not appropriate for a diabetic dog to have little or no exercise during the week and then work hard on weekends. Strenuous and sporadic exercise can induce hypoglycemia and should be avoided. On the day that a DM dog is expected to be involved in intense or unusual exercise (i.e., hunting), it is important to reduce that morning dose of insulin. The percent reduction necessary to prevent hypoglycemia is not predictable; thus, an initial reduction of 50% is reasonable. Further adjustments should be based on experience with issues like symptomatic hypoglycemia or PU during or after exercise. Owners of DM dogs should always have a glucose source readily available, in case signs of hypoglycemia are observed while doing physical activity.

Insulin

Overview

Various types of insulin are used to treat DM long-term. Based on duration of action and potency, they include intermediate-acting (lente, Neutral Protamine Hagedorn [NPH]) and long-acting insulins (protamine zinc insulin [PZI], insulin glargine, insulin detemir) (Table 304-2). Lente (Vetsulin, Caninsulin) is a porcine–origin zinc 40 U/mL insulin consisting of 30% short-acting amorphous insulin and 70% long-acting, microcrystalline insulin. NPH (100 U/mL; Humulin N, Novolin N) is recombinant human insulin, usually administered q 12 h. Postprandial hyperglycemia can occur in some well-regulated dogs.[58] A long-acting PZI 40 U/mL insulin made with recombinant human insulin is approved for use in cats (ProZinc). This insulin may be useful for some dogs in whom duration of intermediate-acting insulins is too short.[54] The insulins glargine and detemir are synthetic long-acting insulin analogues designed to maintain basal insulin concentrations in diabetic people. Their use in dogs is increasing.

TABLE 304-2

Commonly Used Insulin Preparations for Treating Uncomplicated Diabetes Mellitus in Dogs

INSULIN	PRODUCT	ORIGIN	CONCENTRATION (U/mL)	DURATION OF EFFECT (hours)	FREQUENCY OF ADMINISTRATION	STARTING DOSAGE (U/kg/injectio
Lente	Vetsulin/Caninsulin	Porcine	40	8-14	q 12 h	0.25
NPH	Humulin N, Novolin N	Recombinant human	100	4-10	q 12 h	0.25
PZI	ProZinc	Recombinant human	40	10-16	q 12 h	0.25-0.5
Glargine	Lantus	Recombinant human	100	8-16	q 12 h (q 24 h)	0.3
Detemir	Levemir	Recombinant human	100	8-16	q 12 h (q 24 h)	0.1

*Dogs weighing <15 kg.

†Dogs weighing >15 kg.

NPH, Neutral protamine Hagedorn; *PZI*, protamine zinc insulin.

Insulin Analogues

Insulin analogues are modified from human insulin peptides, have similar physiologic effects, and are commonly used in treating diabetic cats and dogs.[59] The amino acid asparagine in human insulin is replaced with glycine at position A21 and two positively charged arginine molecules are added to the C-terminus of the B chain to create insulin glargine (Lantus).[60] This structure results in low aqueous solubility at neutral pH but complete solubility at a pH of 4. The acidic glargine solution injected into the pH-neutral milieu of the SC forms insulin-analogue-microprecipitates that slow absorption and delays onset of action. The result is a

relatively constant, peakless, basal supply of insulin.[60] Due to the importance of pH, glargine should never be diluted or mixed with any solution that could alter pH. In dogs, insulin glargine has been shown to be safe and efficacious for good to moderate glycemic control.[55,56]

The amino acid threonine, at position 30 of the B chain, has been removed and a 14 carbon fatty acid (myristic acid) has been bound to the amino acid lysine at B chain position 29 to create insulin detemir (Levemir). These modifications permit this insulin to reversibly bind to albumin, slowing absorption and prolonging its consistent metabolic effect for as long as 24 hours in people.[61] In dogs, insulin detemir is about four times more potent as compared with other insulin preparations. Insulin detemir, given SC, q 12 h, is a potential treatment for dogs with DM. Due to the higher potency of this insulin in dogs, lower dosages are required to control glycemia. A starting dose of 0.1 U/kg, q 12 h is recommended. Detemir should be used with caution, especially in small dogs.[57] Use of diluent specifically designed for this insulin allows safer delivery of small doses.

Storing, Mixing and Diluting Insulin

Freezing or heating inactivates insulin. While storing insulin at room temperature is acceptable, owners should be instructed to store insulin inside the refrigerator door to maintain a stable and consistent environment, bottle to bottle, patient to patient. Some veterinarians recommend replacing insulin every month to avoid inactivation or contamination. However, the "shelf-life" of commercially produced insulin, stored and handled appropriately, is much longer than the manufacturer's recommendations. Problems with loss of insulin potency or sterility are extremely rare. Routine monthly replacement is not recommended. While shaking rather than gentle mixing was thought to inactivate insulin, recent studies again demonstrate that insulin is resistant to being destroyed in this manner. For consistency, however, gentle rolling is suggested for most insulin products. Vetsulin/Caninsulin, should be "shaken thoroughly" until a homogeneous, uniformly milky, suspension is seen. Diluting insulin can be quite useful in small dogs, particularly when using detemir that is four times more potent than other insulins. Only diluent solutions provided by the manufacturer should be used. It is important to emphasize that insulin glargine is pH-dependent and should not be diluted.

Insulin Pen Devices

Dosing pens, designed for use by diabetic people, should make measurement and administration of insulin easier, less painful, and more accurate. Insulin dosing pens have been shown to decrease anxiety, discomfort, and social embarrassment associated with insulin administration.[62] Limited information is available on using these devices in dogs. Lente porcine insulin is the only veterinary insulin product marketed with a pen. They are available in two sizes, a maximum 8 U/dose VetPen (0.5 to 8 U) with 0.5 U dose increments and a maximum 16 U/dose VetPen (1 to 16 U) with 1 U increments. Owners choosing to use this apparatus must be trained in its assemblage (Video 304-1) and use (Video 304-2).

Initial Insulin Recommendations

Treatment of canine DM requires exogenous insulin to maintain glycemic control. In newly diagnosed DM dogs, the first insulins usually recommended are from the intermediate-acting group, such as lente (Vetsulin, Caninsulin) or recombinant human NPH. With either, one should begin with about 0.25 U/kg SC q 12 h. This conservative approach should be sufficient to prevent symptomatic hypoglycemia or the Somogyi response. Dogs may be hospitalized for 1 or 2 days to complete the diagnostic evaluation and begin therapy. Blood glucose concentrations should be checked two to three times daily to identify hypoglycemia, if present. If the blood glucose decreases <80 mg/dL, the insulin dosage should be reduced. It is not recommended to increase the dosage if glucoses remain high, however, because insulin action may improve after a few days (so-called equilibrium).[38] Insulin therapy can be started on an outpatient basis, which is less expensive and considered more efficacious by some.

Females in Diestrus

Intact bitches diagnosed with DM should undergo ovariohysterectomy as soon as feasible, ideally 1 to 3 days after starting insulin.[38] Ovariohysterectomy is most important if the bitch is in diestrus and under the

influence of Pg, because surgery will reduce insulin resistance by eliminating Pg and, in a few dogs, remission of DM may occur after a few days or weeks.[63] All intact bitches with DM should be spayed, even if no obvious relationship is established between diestrus and onset of DM. After spaying, glycemic control should be closely monitored with appropriate adjustments in insulin dosage. Although spaying does not lead to remission of DM in most dogs, it does prevent Pg-induced secretion of mammary-derived GH in subsequent cycles, insulin resistance, and worrisome decompensation. If spaying is not possible, administration of the Pg receptor antagonist aglepristone may reduce insulin resistance.[64]

Concurrent Conditions

Concurrent inflammatory, infectious, neoplastic and metabolic conditions are common in dogs newly diagnosed with DM, can interfere with tissue responsiveness to insulin, and can produce a negative impact on DM management. Similarly, glucocorticoids and Pgs reduce sensitivity to insulin (ch. 358). Concurrent disorders and diabetogenic drugs may cause insulin resistance by altering insulin metabolism (pre-receptor issues), decreasing concentration or binding affinity of cell membrane insulin receptors (receptor issues), interfering with the insulin receptor signaling cascade (post-receptor issues), or any of these in combination.[37] Insulin resistance can be mild (e.g., obesity) to severe (e.g., Cushing's syndrome) or may fluctuate (e.g., chronic pancreatitis) (Table 304-3).

TABLE 304-3

Recognized Causes of Apparent Insulin Ineffectiveness or Insulin Resistance in Diabetic Dogs

CAUSED BY INSULIN THERAPY	DISORDERS TYPICALLY CAUSING SEVERE INSULIN RESISTANCE	DISORDERS TYPICALLY CAUSING MILD OR FLUCTUATING INSULIN RESISTANCE
Inactive insulin	Cushing's syndrome	Obesity
Diluted insulin	Diestrus in intact female	Infection
Improper administration technique	Progesterone secreting adrenocortical tumor	Hypothyroidism
Inadequate dose	Diabetogenic drugs	Chronic inflammation
Somogyi response	GlucocorticoidsProgestagens	Chronic pancreatitis
Inadequate frequency of insulin administration		Inflammatory bowel disease
Impaired insulin absorption		Disease of the oral cavity
Insulin-binding antibodies		Chronic kidney disease
		Hepatobiliary disease
		Cardiac disease
		Hyperthyroidism
		Pancreatic exocrine insufficiency
		Hyperlipidemia
		Neoplasia
		Glucagonoma
		Pheochromocytoma

From Feldman EC, Nelson RW, Reusch C: *Canine and feline endocrinology*, ed 4, St Louis, 2015, Saunders.

Thorough evaluation (history, PE and in-hospital testing) of dogs newly diagnosed with DM is extremely important. Identification and treatment of concurrent diseases are integral to successful management of DM. Some conditions (e.g., chronic pancreatitis) are, like DM, never permanently resolved and require long-term management. Owners should be informed that treating DM alone can be challenging. Concurrent conditions can make successful therapy even more difficult. Frequent monitoring and dosage adjustments are almost always required. Administration of glucocorticoids or Pgs should be discontinued and alternative medications used if possible (see ch. 358). If glucocorticoids are absolutely required, dosage and frequency should be kept as low as possible. Consistency in dosage and frequency will make control easier to achieve.

Monitoring Diabetes Mellitus

Overview

Long-term care of diabetics and adjustments in their medications should be based, primarily, on owner observations supplemented by periodic in-hospital examinations. The in-hospital assessments should include

body weight, PE, and serum glucose and fructosamine concentrations. Glucose levels and glucose curves should initially be carried out in-clinic. Subsequently, if appropriately trained, most owners are able to perform home monitoring by measuring capillary blood glucose with a portable blood glucose meter (PBGM).

Frequency of In-Hospital Evaluations (see Box 304-4)

Veterinary team members and owners should appreciate that 1 to 3 months are typically required before reasonable and stable glycemic control is achieved. In some, the process is straightforward and takes little time. In others, adjustments in insulin and other factors never cease. Periodic monitoring is used to help ensure safe and effective treatment. Initially, reevaluations are recommended at 1, 2 to 3, 6 to 8, and 10 to 12 weeks after diagnosis. Dogs are then usually examined about every 4 months, or as needed.

History and Physical Examination

The most relevant parameters for assessment of glycemic control are owner opinions regarding their pet, specifically, status of PU/PD/PP, body weight, and general health. Body weight is emphasized since insulin-underdosed diabetics tend to lose weight and insulin-overdosed diabetics tend to gain weight. Well-controlled diabetics have stable, near ideal, body weight. Objective findings on PE are used in concert with owner thoughts. If the owner is satisfied, body weight stable, and PE consistent with good glycemic control, further testing is only directed at avoiding overdose. Owners should specifically report any possible hypoglycemic episodes (e.g., weakness, ataxia, "acting intoxicated"). Persistence or recurrence of clinical signs or unwanted change in weight are suggestive of poor glycemic control or presence of a concurrent disease. Serum fructosamine concentration and blood glucose curves (BGCs) may help characterize the issue, guide changes in treatment, and may indicate need for additional testing.

Serum Fructosamine

Fructosamines are glycated proteins produced via irreversible non-enzymatic reactions between glucose and plasma proteins present in the circulation.[65] It is estimated that fructosamine concentrations in dogs are determined by the average blood glucose concentration over the previous 2-3 weeks. Serum fructosamine is not affected by acute changes in blood glucose. Higher average glucose levels result in greater amounts of blood fructosamines. Excellent glycemic control, defined as blood glucose concentrations near normal most of the time, results in fructosamine concentrations within or only slightly above reference ranges. Lower fructosamine, independent of blood glucose, has been observed with hypoproteinemia, azotemia, hypoalbuminemia, hyperlipidemia, and hemolysis.[66,67] Increased serum fructosamines have been observed in hypothyroidism and in 2 dogs with hyperglobulinemia caused by multiple myeloma.[68,69] Each laboratory should generate a reference range, but most are from about 200 to 360 micromol/L.

In most newly diagnosed diabetic dogs, fructosamine levels are >400 micromol/L. Some may reach 1500 micromol/L. It is important to remember that neither normoglycemia nor normal fructosamine concentrations should be the therapeutic target when treating dogs with DM. Blood glucose concentrations, in well-controlled DM dogs, fluctuate between normal and slightly above renal threshold. Well-controlled dogs usually have some glycosuria and are moderately hyperglycemic throughout the day. Thus, serum fructosamines within reference intervals (especially in the lower half) are more suggestive of prolonged episodes of hypoglycemia due to insulin overdose. Serum fructosamine concentrations of 360 to 450 micromol/L suggest good glycemic control, 450 to 550 micromol/L suggest moderate control, and concentrations >550 micromol/L suggest poor DM control.

Increased fructosamine concentrations, even if >550 micromol/L, do not help identify a cause for poor control. All possible causes must be considered. These include insulin underdose, short duration of insulin effect, errors in preparation or administration of insulin, improper diet, any disease known to cause insulin resistance, and the Somogyi response (see Table 304-3). Serum fructosamine concentration should never be used as the sole indicator of glycemic control and should always be interpreted in conjunction with owner opinion, clinical signs, body weight and blood glucose concentrations. Discrepancy between a fructosamine concentration and the clinical picture/blood glucose concentration profile are sometimes observed. For example, a high fructosamine concentration suggests poor control. But, if the dog is clinically well with glucoses within a desired range, one should maintain current therapy and reassess. The discrepancy between fructosamine concentrations and the clinical picture may remain ambiguous and there may be individual

differences with regard to protein glycation.[70] In some, fructosamine is not helpful.

Urine Glucose Monitoring

Daily owner monitoring of urine for sugar and ketones can be useful. Most diabetics have varying amounts of glucose present in virtually every urine sample, with an occasional negative. Persistent absence of sugar may be indicative of insulin overdosage or excellent control. Ketonuria suggests inadequate control and decompensation. Upon seeing ketones in the urine of a pet who rarely has them, the owner should contact the veterinarian. Decisions are usually based on the dog's condition. Owners should not adjust insulin dosage on the basis of morning urine glucose because this commonly leads to overdose and increases likelihood of insulin-induced hypo- followed by hyperglycemia (Somogyi response). Excess glucose in the urine can be caused by numerous issues.

Single Blood Glucose

A single blood glucose measurement is rarely useful in monitoring DM with the exception of finding a low result, always indicative of an overdose. Single glucose measurements may be sufficient when an owner believes the dog is virtually asymptomatic, the PE is unremarkable and serum fructosamine levels are between 360 to 450 mcmol/L. In such cases, glucose concentrations between 180 and 250 mg/dL around the time of the insulin injection are consistent with good glycemic control and additional blood glucose measurements are not usually necessary.

Portable Blood Glucose Meters

During the initial adjustment phase and in subsequent long-term management phases of therapy, if signs of DM persist, signs recur, or fructosamine levels are high, single glucose measurements should be avoided and a BGC obtained instead. Serial BGCs can provide guidelines for making rational adjustments in insulin therapy. Blood glucose concentrations are typically determined by a hand-held portable blood glucose meter (PBGM). To avoid multiple venipunctures, one may collect capillary blood from the ear (Videos 304-3 and 304-4; see also ch. 79).[71] Several portable glucose meters are available. The accuracy of PBGM devices designed for people varies considerably when used in dogs.[71-75] Some PBGM devices designed for humans are sufficiently accurate and precise to monitor canine blood glucose concentrations. However, most give lower results than laboratory reference methods. This bias may result in an incorrect diagnosis of hypoglycemia or the misconception that the animal's glycemic control is better than it actually is. The AlphaTRAK blood glucose meter (Abbott Animal Health) is specifically designed for use in dogs and cats and is more accurate and precise than the PBGMs designed for humans.[73] Additional advantages of the AlphaTRAK are the small volumes of blood needed (0.3 mcL) and the extended measurement range (20 to 750 mg/dL). Conversely, AlphaTRAK tends to overestimate blood glucose values, potentially missing hypoglycemia. The meter is less accurate in dogs with a hematocrit <30%.[76] If there is any doubt regarding accuracy, measurements can be compared with laboratory results.

Blood Glucose Curves and Insulin Dose Adjustments

When conducting a BGC, the dog should be seen early in the morning and blood glucoses sampled every 1 to 2 hours throughout the day. One should begin just prior to the first insulin dose and continue until the next dose is due. A recent study failed to find relevant differences in glucose concentrations during the day versus night. Most dogs respond well to the same dose of insulin morning and evening.[77] If different blood glucose concentrations are suspected during day versus night (e.g., good BGC and control of clinical signs during the day but presence of PU/PD during the night), a 24-hour BGC or use of a continuous blood glucose monitoring device should be considered.[37]

When performing a BGC, the insulin and feeding schedules followed by the owner should be maintained. Poor appetite can strongly affect the results of a BGC. Food and insulin can be administered at the clinic after the first blood glucose measurement. If a dog refuses to eat in the clinic, the BGC should be abandoned. Subsequently, the owner should feed the dog at home, administer insulin, and then bring the dog to the clinic as soon as possible to begin the BGC. The evaluation of the BGC allows the clinician to determine if the insulin administered is effective and identify the glucose nadir, time of peak insulin effect, duration of insulin

effect, and degree of fluctuation in blood glucose concentrations. In well-controlled DM, glucose concentrations should stay between 90 and 250-300 mg/dL (Figure 304-3). Insulin efficacy is evaluated, in part, by determining the difference between highest and lowest glucose concentrations. A small difference (e.g., 50 mg/dL) is acceptable if the highest blood glucose level recorded is <220 mg/dL but not acceptable if it is >300 mg/dL.[38] The most important parameters are the glucose nadir and the duration of the insulin effect.

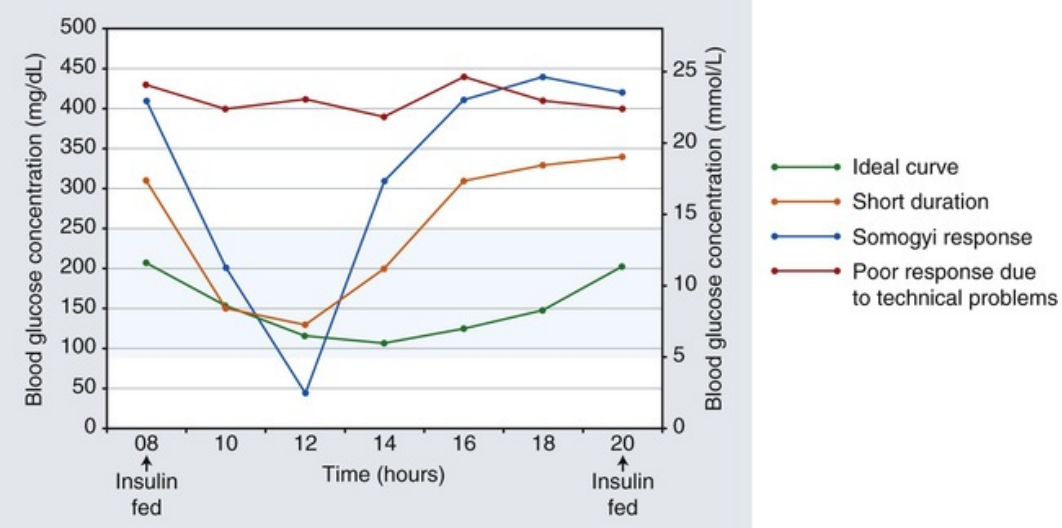

FIGURE 304-3 Representative blood glucose curves in dogs treated with an intermediate-acting insulin q 12 h. The blue area is the preferred range of blood glucose concentration in treated diabetic dogs (90 to 250 mg/dL). Green line: ideal curve. Orange line: short duration of insulin effect. Blue line: Somogyi response with counterregulation after rapid decrease in blood glucose concentration. Red line: poor response due to technical problems, the counterregulatory phase of the Somogyi response, insulin resistance, poor insulin absorption, or insulin antibodies. (Modified from Reusch CE, Robben JH, Kooistra HS: Endocrine pancreas. In Rijnberk A, Kooistra HS, editors: *Clinical endocrinology of dogs and cats*, ed 2, Hannover, Germany, 2010, Schlütersche, p 165.)

The glucose nadir should, ideally, be between 90 and 150 mg/dL. A lower nadir can be caused by insulin overdose, excessive overlap of the insulin action (common if long-acting insulin analogues are used), prolonged periods without food (the dog refused to eat in-hospital), or strenuous exercise. A glucose nadir >160 mg/dL can be caused by an insufficient insulin dose, insulin resistance, counterregulatory phase of the Somogyi response, stress, and technical problems attributable to the owners. In a dog already treated with high dosages (e.g., >1.5 U/kg per injection), owner error, insulin resistance and the Somogyi response are the main differential diagnoses.

Duration of insulin action can be determined if the glucose nadir falls within the desired range. Duration is defined as the time from injection through the glucose nadir until the glucose concentration exceeds 250 mg/dL. When duration is too brief (e.g., <8 hours), signs of DM are usually exhibited. When duration is too long (e.g., >14 hours), risk of hypoglycemia or Somogyi response is higher. Duration of action may be altered with changes in diet. One may change to an insulin product with a different action profile. Performing BGCs on consecutive days is not recommended because it promotes stress-induced hyperglycemia.

BGCs should never be assumed to be reproducible. Day-to-day variables and the diabetic condition itself are rarely static. Variables include the amount of insulin drawn into the syringe each time, the amount of insulin absorbed after each injection, and the interactions between insulin, diet, exercise, stress, excitement, presence of concurrent disorders, and secretion of the counterregulatory hormones (e.g., glucagon, epinephrine, cortisol, growth hormone). All these factors change with time and alter chances of reproducible BGCs. Lack of consistency in BGC results can create frustration unless expected. Lack of consistency is common and reflects any variable that could alter glucose concentrations. When dose change appears appropriate, it should not exceed 10% to 25%. However, in documented or suspected hypoglycemia, the dose should be decreased by at least 50%. Insulin doses should not be modified more frequently than every 5 to 7 days, except in hypoglycemia.

Home Monitoring

Owners should be encouraged to assess their dog's DM on a daily basis (see earlier section). Initially, body weight should be measured and recorded every week. Glucose measurement with PBGM using capillary blood is feasible at home and should be recommended. Capillary blood can be obtained using lancing devices on various sites: the inner aspect of the pinna is a good site for capillary sampling (see Video 304-4; see also ch. 79); good alternatives are the buccal mucosa (Video 304-5) or the paw pad (Video 304-6).[78] Owners must be thoroughly familiar with their PBGM, but access to veterinary support should be available. A good time for introducing the concept of home monitoring is after 3 to 4 weeks of treatment. By that time, the client will be somewhat familiar with DM and will understand the time needed for its care. Once familiar with the procedure, the owner can perform a BGC by measuring the morning blood glucose concentration before giving insulin and food, and then every 2 hours until the next injection is due. Interpretation of home BGCs should be the same as those performed in-hospital. One problem that can be anticipated are the overzealous owners who monitor blood glucose concentrations too frequently and begin to interpret the results and adjust the insulin dosage without consulting the veterinarian, a practice that frequently leads to confusion, poorer control of DM and increased risk of overdose.

Continuous Glucose Monitoring

Continuous glucose monitoring systems (CGMSs) are routinely used for people with DM and are beginning to be used in DM dogs.[79] These systems allow glucose concentrations to be monitored without need for repeated blood sampling. The CGMS measures interstitial glucose rather than blood glucose concentrations. Interstitial fluid is easily accessible and results are virtually the same as with blood glucose.[79-81] The CGMS most frequently used (Guardian REAL-time) measures interstitial glucose with a small, flexible sensor inserted through the skin into the SC space and secured to the skin with tape. The sensor, connected to a transmitter and also fixed with tape, sends wireless data over a maximal distance of 3 meters to a pager-sized monitor. Data are collected every 10 seconds and a mean glucose value computed every 5 minutes. Data can be downloaded to a computer for analysis.

CGMS devices have some limitations. They need to be calibrated two to three times daily, which requires blood sampling. Sensors are quite expensive and can be used only for days. The monitor displays glucose concentrations from 40 to 400 mg/dL; concentrations outside this range are correctly recorded but need to be downloaded to be seen. A new CGMS (FreeStyleLibre by Abbott) produced for humans has extremely small sensors, does not require calibration, is rather inexpensive and the sensor can be used for as long as 14 days (Figure 304-4). One recent study has shown that this CBGM is accurate in hyperglycemia and euglycemia, but less accurate if blood glucose concentrations are <100 mg/dL.[81a] CGMS can provide insight into glucose levels throughout the day and help identify fluctuations, episodes of hypoglycemia and trends that may otherwise go unnoticed.[70]

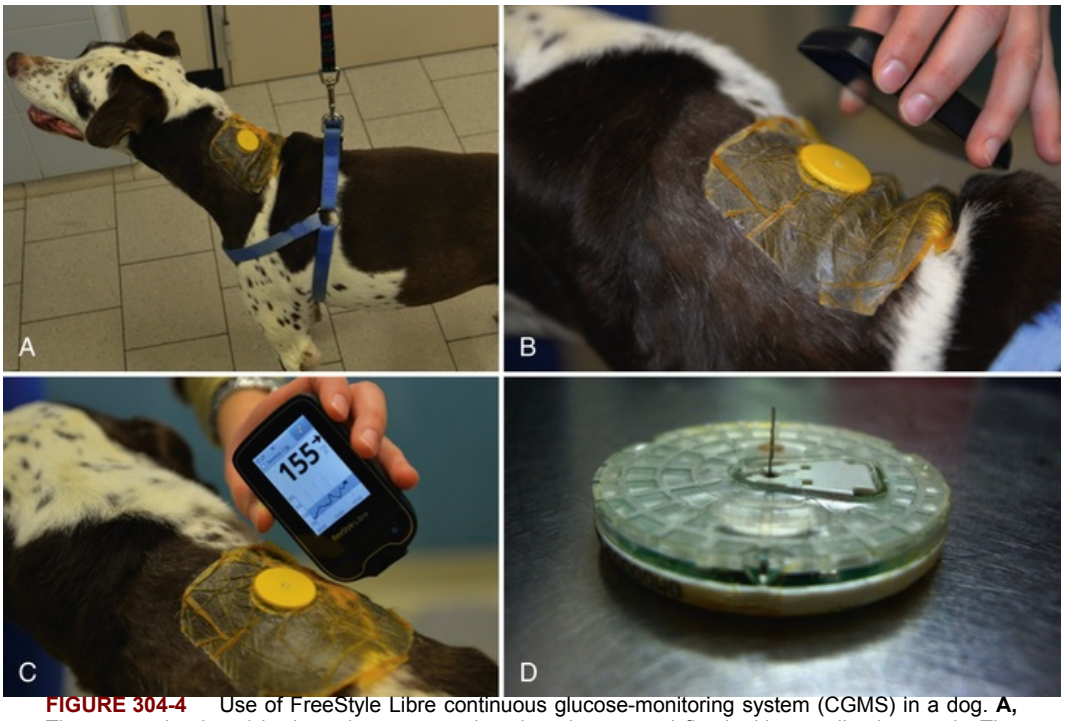

FIGURE 304-4 Use of FreeStyle Libre continuous glucose-monitoring system (CGMS) in a dog. **A,** The sensor is placed in the subcutaneous dorsal neck area and fixed with an adhesive patch. The sensor in this picture has been in place for 12 days (the regrowth of the hair below the patch is evident). **B,** The sensor patch must be "scanned" with the reader to obtain real time glucose values. This can be done holding the reader within 4 cm of the sensor. The sensor patch stores up to 8 hours of glucose data at that time (values are taken every minute). **C,** Glucose levels are displayed in real time. Here the glucose is 155 mg/dL. **D,** Sensor removed 14 days after placement.

Conditions Causing Persistence or Recurrence of Clinical Signs

Overview

Persistence or recurrence of clinical signs is a frequent problem in any dog with DM. Recurrence of signs can be noted at any time. Common causes include technical issues in administering insulin, use of the incorrect (for this patient) insulin type, and less than ideal dosage or frequency of administration. Other common problems are insulin responsiveness caused by concomitant inflammatory, infectious, neoplastic or hormonal disorders (Figure 304-5).

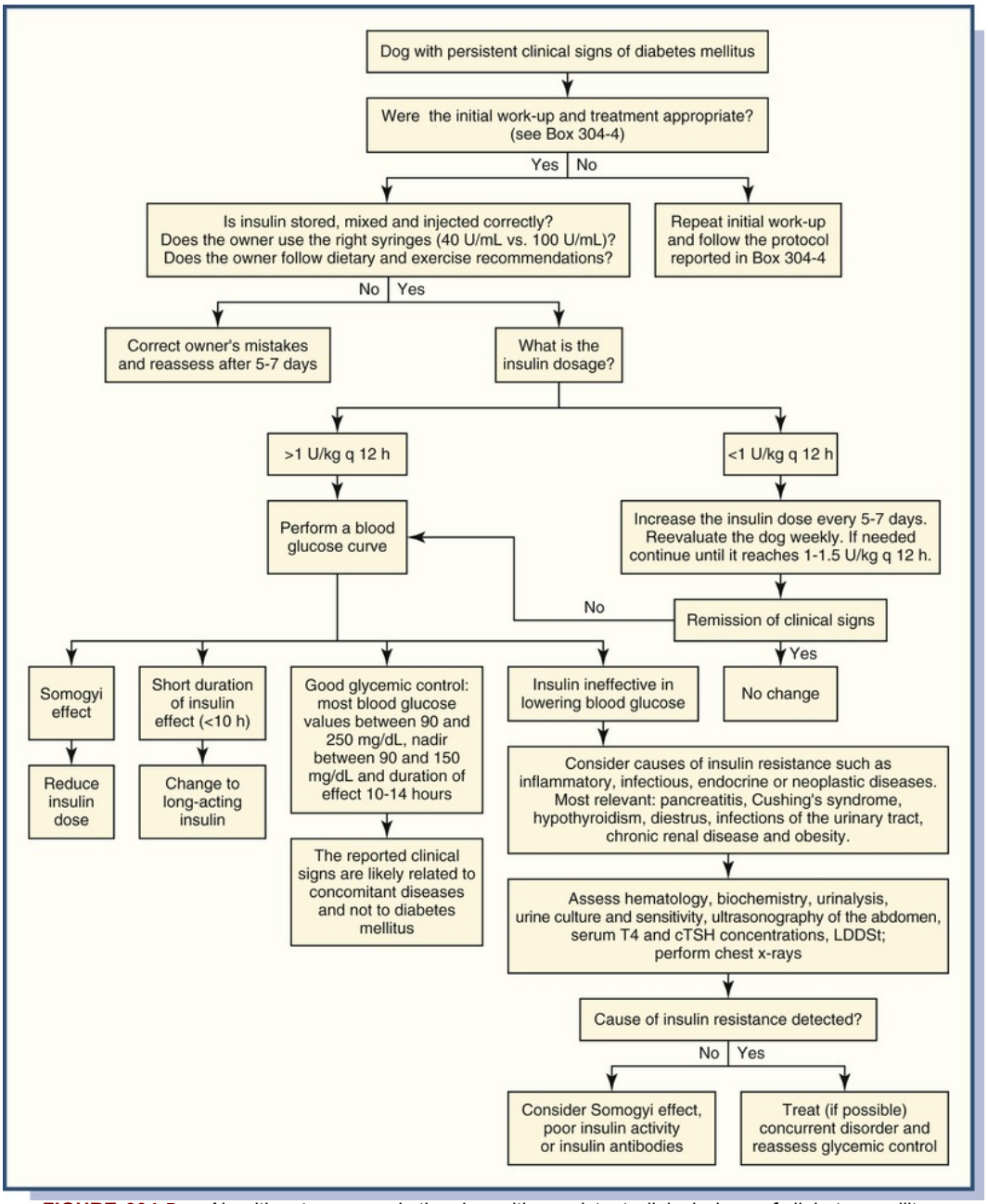

FIGURE 304-5 Algorithm to approach the dog with persistent clinical signs of diabetes mellitus. *cTSH,* Canine thyroid-stimulating hormone; *LDDSt,* low-dose dexamethasone suppression test; *T4,* thyroxine.

Technical Issues

Common reasons for poor glycemic control are errors in handling or injecting insulin. Specifically, failure to mix the preparation correctly; use of an improper diluent; use of insulin that has been frozen, heated, or is out of date; incorrect injection technique using a syringe or insulin dosing pen, or inappropriate insulin dose or syringe size (U-40/mL vs. U-100/mL is a frequent error). These problems can be identified by carefully evaluating the history and asking the owner to bring their insulin and syringes or pen device to appointments. If concerns arise, the veterinarian or technician can observe the entire procedure, providing assistance until the owner is able to master the technique.

Insulin Underdose

Most dogs are well controlled with insulin doses ≤1 U injection/kg SC q 12 h. If the insulin dosage is considerably less than 1 U injection/kg and the dog is receiving insulin q 12 h, underdosing can explain poor glycemic control. In this scenario, the dose should be gradually increased by 10% to 25% per week.

Insulin Overdose and Glucose Counterregulation (Somogyi Response)

The Somogyi response is defined as rebound hyperglycemia caused by the physiologic response to hypoglycemia, which induces secretion of counterregulatory hormones. In the acute response, glucagon and epinephrine are secreted. They, in turn, stimulate the longer acting response via secretion of cortisol and GH. This "counterregulation" occurs when the blood glucose is <65 mg/dL, although it may also occur when blood glucose concentrations drop rapidly (in 2 to 3 hours) regardless of the nadir.[82] Clinical signs due to hypoglycemia are not seen in every case, whereas signs of the hyperglycemic response (PU/PD) are obvious. Thus, a cyclic history of days of good control followed by several days of poor control should raise the suspicion of a Somogyi response.

Diagnosis requires evidence of hypoglycemia or rapid drop of glucose followed within hours by hyperglycemia (>300 mg/dL). Serum fructosamine concentrations are unpredictable but are usually increased (>500 micromol/L). Rebound hyperglycemia and insulin resistance can persist for 24 to 72 hours. Diagnosis may be difficult and may require several BGCs, best conducted in the home using a PBGM or a CBGMS. Sometimes it is not easy to differentiate Somogyi response from a short duration of insulin effect. If Somogyi is documented or assumed to have occurred, the insulin dose should be arbitrarily reduced gradually (1 to 5 U depending on the size of the dog and dosage of insulin) and the owner should monitor the dog's clinical signs over the following 2 to 5 days. If no change is seen, further dose reductions may be attempted. If clinical signs worsen, a different cause for insulin ineffectiveness should be considered (i.e., short duration of insulin effect; see Table 304-3).

Short Duration of Insulin Action

In some diabetic dogs, the effect of NPH and lente insulins may last less than 8 hours (see Figure 304-3). As a result, significant hyperglycemia (above the renal threshold of about 200 mg/dL) may continue for hours each day. Owners of dogs whose insulin is not lasting long enough usually report PU/PD. The issue may be demonstrated on a BGC. Treatment involves switching to a long-acting insulin q 12 h (i.e., PZI, glargine or detemir; see Table 304-2).

Prolonged Duration of Insulin Effect

Problems with prolonged duration of action may occur if insulin lasts longer than 12 hours; in these cases q 12 h-administered insulin overlaps and increases risk of hypoglycemia. Hypoglycemia, in turn, could lead to the Somogyi response and to clinical signs caused by hypoglycemia, hyperglycemia, or both. Prolonged duration of insulin action is usually observed when the glucose nadir occurs 10 or more hours after injection. Treatment options include decreasing the frequency of administration from q 12 h to q 24 h when using detemir or glargine. One may also consider changing insulin to one with a shorter duration of action.

Anti-Insulin Antibodies

Canine, porcine and human insulin are similar. Development of significant insulin antibodies is uncommon in DM dogs treated with porcine or recombinant human insulin.[22] Canine and beef insulins, however, differ significantly. Antibodies to insulin have been identified in 40% to 65% of dogs treated with beef/pork or 100% beef source insulin.[83,84] The presence of anti-insulin antibodies may alter exogenous insulin pharmacokinetics and/or pharmacodynamics. The result is usually an erratic response to insulin, poor control of glycemia, inability to control DM for extended periods of time, need for frequent adjustments of the insulin dose and, occasionally, development of insulin resistance.[37] Bovine insulin, widely used in the past to treat canine DM, is no longer used, decreasing the incidence of anti-insulin antibodies. Although uncommon, insulin antibodies may develop in dogs treated with recombinant human insulin and should be considered as a possible cause of poor glycemic control if no other explanation is identified.[37] Documentation of serum anti-insulin antibodies should utilize assays validated for dogs. Switching to a 100% porcine-source insulin should be considered if anti-insulin antibodies are identified in a poorly controlled DM dog.

Concurrent Disorders Causing Insulin Resistance

Most DM dogs can be regulated with insulin doses ≤1 U/kg q 12 h. In dogs with higher insulin requirements, concurrent disorders should be suspected after "technical problems," Somogyi response or short duration of insulin action have been ruled out. No insulin dosage clearly defines insulin resistance. It has been proposed that insulin resistance should be suspected when glycemic control is poor despite insulin doses >1.5 U/kg q 12 h, when high doses (>1.5 U/kg) are required to maintain blood glucose <300 mg/dL, or when glycemic control is erratic and the insulin dose must be continuously adjusted.[37] Any inflammatory, infectious, neoplastic or endocrine disorder can cause insulin resistance, as do obesity and many drugs, especially glucocorticoids and progestagens.

Insulin resistance is most commonly caused by glucocorticoid administration, diestrus, hypothyroidism, chronic pancreatitis, chronic kidney disease, infection, neoplasia, hyperlipidemia, severe obesity, and Cushing's syndrome. The most common sites of infection are oral (dental) and urinary tract. Other less common causes of insulin resistance are pancreatic exocrine insufficiency, cardiac disease, liver insufficiency, glucagonoma and pheochromocytoma (see Table 304-3).

Anamnesis and physical examination are the most important first "tests" in trying to identify concurrent disorders. In most instances, a complete diagnostic work-up, including CBC, serum biochemical profile, urinalysis with bacterial culture, abdominal US and thoracic radiographs should be considered as initial "screens" for concurrent illness. When indicated, one may consider a low-dose dexamethasone suppression test, serum progesterone concentration (in intact females), thyroid function tests, serum pancreatic lipase immunoreactivity (cPLI), serum trypsinlike immunoreactivity (TLI) and computed tomography or magnetic resonance imaging (pituitary mass).

Long-Term Complications of Diabetes Mellitus

Hypoglycemia

Hypoglycemia is an extremely common complication of insulin treatment. It is, rarely, fatal.[85] Hypoglycemia may be due to large increases in insulin dosage, sudden increase in insulin sensitivity due to treatment or improvement of concurrent disorders (e.g., treatment of hypothyroidism), inadvertent insulin overdose, overly stringent glycemic control, excessive overlap of the insulin action in dogs receiving insulin q 12 h, excessive exercise, and inappetence resulting in relative insulin overdose. Signs of hypoglycemia include lethargy, weakness, ataxia and increased appetite. Most owners describe hypoglycemia as their dog appearing intoxicated. If the dog is not fed and the hypoglycemia allowed to progress, seizures, coma and death can occur.

Symptomatic hypoglycemia should be treated with glucose administered as sugar-rich food. If the dog is unable to eat, glucose can be applied to the dog's oral mucous membranes in the form of glucose gel or glucose solution (Karo syrup), where it can be directly absorbed. Once recovered, the dog should be fed.[42] Collapsed dogs should be given IV dextrose immediately as an initial IV bolus of 1 mL/kg of 33% dextrose followed by a 5% dextrose infusion. Rates can be changed if necessary. After symptomatic hypoglycemia, owners should be instructed to stop insulin until glycosuria recurs and then give 25% to 50% less. Subsequently, the insulin dose should be adjusted as needed to improve clinical response and blood glucose measurements.[37] Treatment of asymptomatic hypoglycemia also requires insulin dosage reductions of about 10% to 20%, or that insulin should be replaced with one that has a shorter duration of effect.

Ocular Complications

Cataract formation is the most common long-term complication in diabetic dogs (see Figure 304-2). A retrospective-cohort study on 132 DM dogs referred to a university referral hospital found cataract formation in 14% of DM dogs at the time of diagnosis. In that study, the time interval for 25%, 50%, 75%, and 80% of the study population to develop cataracts was only 60, 170, 370, and 470 days, respectively.[86] Cataracts are thought to occur as a result of altered osmotic relationship in the lens induced by intra-cellular accumulation of sorbitol and galactitol, produced following the metabolism of glucose and galactose by enzymes within the lens. The accumulation of sorbitol and galactitol in lens cells increases intracellular osmolality, causes an influx of fluid with subsequent swelling and rupture of lens fibers, and causes the development of cataracts.[87] Once cataract formation begins, it is irreversible and can evolve quite rapidly. Blindness may be avoided by removing the abnormal lens. Vision is restored in 80% to 90% of DM dogs that undergo cataract removal.[88,89]

Other ocular complications of diabetes can include uveitis, keratoconjunctivitis sicca, bacterial conjunctivitis and diabetic retinopathy.

Diabetic Neuropathy

Diabetic neuropathy has been described in dogs, although its prevalence is unknown.[90-93] Subclinical neuropathy seems to be most common. Clinical signs of diabetic neuropathy (weakness, muscle atrophy, hyporeflexia, hypotonia) are most commonly recognized in dogs that have been diabetic for 5 years or longer.[37,93] Diabetic neuropathy in dogs is primarily a distal polyneuropathy, characterized by segmental demyelination and axonal degeneration.

Diabetic Nephropathy

Diabetic nephropathy has occasionally been reported in diabetic dogs but its clinical relevance remains unknown. Microscopic changes can include membranous glomerulonephropathy with fusion of the foot processes, glomerular and tubular basement membrane thickening, increase in the mesangial matrix material, presence of subendothelial deposits, glomerular fibrosis, and glomerulosclerosis.[94,95] Microalbuminuria is used as an early marker for the development of diabetic nephropathy in humans. In one study, increased urine albumin was found in 11 (55%) of 20 DM dogs, with over half having concurrent increases in urinary protein-to-creatinine ratio.[96] Similar results were observed in a study where proteinuria, blood pressure and diabetic retinopathy were monitored over a 2-year follow-up period. No significant effect of time since diagnosis or glycemic control was detected for any of the measures examined.[97] The predictive value and the clinical relevance of microalbuminuria in diabetic dogs remains to be clarified. In most DM dogs, chronic kidney disease is thought to develop as an independent condition.[37]

Prognosis

The prognosis for dogs diagnosed with DM depends, in part, on the owner's commitment to treating the disorder, ease of glycemic regulation, presence and reversibility of concurrent disorders, and avoidance of chronic complications associated with the diabetic state. In a large study involving insured dogs in Sweden, 347 dogs survived at least 30 days after the first DM claim. The proportion of those surviving 1, 2, and 3 years was 40%, 36% and 33%, respectively.[5] A relatively high mortality rate exists during the first 6 months of treatment due to concurrent diseases such as ketoacidosis, pancreatitis or infections. It is a common opinion that well-controlled diabetic dogs that survive the first 6 months of treatment have a life expectancy similar to that of non-diabetic dogs of the same age, gender and breed.

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CHAPTER 305

Feline Diabetes Mellitus

Jacquie Rand, Susan A. Gottlieb

Client Information Sheet: Feline Diabetes Mellitus

Pathogenesis

Types of Diabetes Mellitus

Diabetes mellitus (DM) is characterized by persistent hyperglycemia caused by insufficient insulin secretion from pancreatic beta-cells. The mechanisms involved in the failure of pancreatic beta-cells form the basis for classification of types of DM. Current classifications used in human DM, and generally accepted in veterinary medicine, involve four types: 1, 2, gestational and other specific types.[1] Type 1 DM in people follows immune-mediated destruction of beta-cells with genetic predispositions and environmental triggers, leading to an absolute insulin deficiency.[1] Type 1 DM is rare in cats based on histological studies and absence of circulating beta-cell autoantibodies.[2,3] However, clinical signs, histologic findings, and islet cell antibodies consistent with type 1 DM were reported in a 5-month-old kitten.[4] Type 2 DM is characterized by insulin resistance with concomitant failure of beta-cells to mount an adequate compensatory response to maintain euglycemia.[1] Type 2 is the most common form of DM in cats, based on risk factors (old age and obesity), clinical and endocrine characteristics (insulin resistance, variable insulin secretion and remission) and islet histology (islet vacuolation and amyloid deposition).[5-7] Type 2 DM appears to account for about 80% to 90% of cats examined at primary care veterinary practices in Western countries based on remission rates and other clinical and phenotypic characteristics.[8,9] Gestational DM is first diagnosed during pregnancy, but has not been reported in cats, but is reported in dogs.[1,10,11]

Other specific types of DM, in cats, include loss of pancreatic islets due to pancreatitis or neoplasia. Insulin resistance and DM can occur secondary to hypersomatotropism (acromegaly; see ch. 294) or hyperadrenocorticism (Cushing syndrome; see ch. 307) in cats.[2,12-15] These "other" types of feline DM probably represent less than 20% of cases seen at primary care practices, but may be overrepresented in referral practices. Acromegaly typically begins clinically as poorly controlled DM, despite use of insulin doses considered adequate.[15,16] Pancreatic adenocarcinoma is reported in 8-19% of feline DM euthanized in tertiary referral institutions.[2,12] Pancreatitis (see ch. 291) is present at the time of DM diagnosis in as many as 60% of cats based on biochemical and imaging findings, although clinical signs are infrequent.[17-19] Histologically, most lesions are consistent with chronic pancreatitis, while acute or subacute necrotizing pancreatitis is a cause of mortality.[2,20] In most cats, pancreatitis does not appear to be sufficiently severe to cause DM, but may contribute to beta-cell loss and reduce probability of DM remission.[19,20]

Prevalence and Risk Factors

Estimates regarding the prevalence of feline DM vary from about 0.25-1%.[21-25] Several studies from Australia and the UK place the prevalence at about 1 in 200 cats (0.5%).[23,24,26] In the U.S., the reported prevalence in veterinary teaching hospitals increased from 1 in 1250 (0.08%) in 1970 to 1 in 81 (1.2%) in 1999.[25] It is not known whether this apparent increased prevalence is due to factors such as obesity.[25] Breeds with increased susceptibility to DM include the Burmese in Australia, New Zealand, and the UK; Maine Coon, Russian Blue and Siamese in the United States.[23,24,27-29] The Burmese has a DM frequency about 4 times the rate in other cats, and about 10% ≥8 years of age have DM. The gene or genes involved in this process appear to be

autosomal rather than sex-linked, with few signs of fully penetrant dominant gene action.[22-24,27,30]

Type 2 Diabetes

Human versus Cats

Human type 2 DM has a complex etiology, is caused by genetic factors and environmental interactions, and risk increases with age.[1] Similarly, risk factors for feline DM include old age, male gender (male : female ratio 1.5 : 1), obesity, physical inactivity, indoor confinement, breed, and repeated or long-acting steroid or megestrol acetate administration.[21,24,25,31] Most of these factors decrease insulin sensitivity and increase demand on beta-cells to produce insulin.[32-34] Type 2 DM in humans is a polygenic disease with complex inheritance, although genetic variants account for <10% of overall risk, highlighting the importance of environmental factors.[35] Over 60 genetic loci are associated with type 2 DM and most are involved with beta-cell biology, reflecting the significance of beta-cell failure in pathogenesis.[36,37] In domestic cats, polymorphism in the melanocortin 4 receptor gene *(Mc4R)* is associated with DM in overweight cats, similar to humans.[38] Mutations of this gene in people increase appetite and obesity. In cats, the mutation also appears associated with progression to DM.[38] This polymorphism was 3.7 times more likely in overweight DM cats vs. overweight non-DM, but no difference was noted between obese and lean non-DM cats.

In humans, some genetic loci associated with increased risk for the metabolic syndrome are located within genes known to be associated with lipid metabolism.[39] Burmese cats appear to have a propensity for dysregulation in lipid metabolism, and lean Burmese cats demonstrate similar gene expression patterns to obese domestic cats.[40] Clinical features of DM in cats are similar to an atypical DM seen in African-Americans and Asians: classical signs of polyuria, polydipsia (PU/PD) and weight loss, and relatively high blood glucose concentrations. They are susceptible to ketosis but many go into remission within a few weeks of starting insulin therapy. Patients have a type 2 phenotype and a family history of DM.[41,42,42a] Atypical DM is associated with a number of genetic loci.[43-45]

Insulin Resistance

Type 2 DM is a multifaceted disease characterized by beta-cell failure and insulin resistance.[35] Insulin sensitivity, defined as the ability of a given concentration of insulin to decrease blood glucose, is genetically determined in people. Insulin sensitivity decreases with obesity, physical inactivity and is a side effect to glucocorticoids and progestins.[32,46-50] Reduced insulin sensitivity (resistance) is the key feature of type 2 DM. Cats with DM are about six times less sensitive to insulin than normal, causing increased hepatic glucose production and reduced glucose utilization in peripheral tissues.[7,51] Each kg increase in body weight above ideal in cats causes about a 30% decrease in insulin sensitivity and a gain of 44% reduces insulin sensitivity and glucose effectiveness (capacity of glucose to enhance its own cellular uptake and to suppress endogenous production) by 50%.[32,47,52] Although it is unclear if insulin sensitivity is genetically determined, lean cats with underlying low insulin sensitivity are at increased risk for developing glucose intolerance with obesity.[32]

Reduced Insulin Secretion

Reduced insulin secretion secondary to beta-cell failure is the second key feature of type 2 DM. In health, beta-cells respond to changing requirements and undergo hypertrophy and hyperplasia to meet increased needs, such as with obesity.[53] However, in a minority of obese patients, beta-cells fail. Processes associated with obesity (disturbed glucose, fatty acid, and amino acid metabolism) damage beta-cells, reducing their secretory capacity.[35] Obesity and type 2 DM are associated with chronic inflammation that increases cytokine and immune-cell infiltration into tissues involved in energy homeostasis (fat, liver, muscle, pancreatic islets).[35] Such infiltrates have been reported in DM and obese cats.[19,54-57] The inflammatory cytokine interleukin-1beta and its expression was increased in a hyperglycemic/obese cat model.[58]

Beta-cell failure is not fully understood, especially in early stages. Several mechanisms adversely affect beta-cells and impair insulin secretion via decreased insulin gene expression and reduced beta-cell capacity to proliferate in response to increased demand. These factors contribute to beta-cell death (E-Box 305-1).[35,59] Toxicity of misfolded and polymerized intracellular fibrils (oligomers) of islet amyloid polypeptide (IAPP) and glucolipotoxicity are involved in triggering some of these mechanisms. Both islet amyloid deposition of misfolded IAPP oligomers (Figures 305-1 and 305-2) and glucotoxicity are documented to decrease beta-cell

numbers and their function in cats.[6,60-63] Although not an initial cause of beta-cell failure, chronic hyperglycemia has a central role in beta-cell dysfunction and the progressive inability to secrete insulin.[62-64] In cats, glucose toxicity is dose dependant. At persistent glucose concentrations of 540 mg/dL (30 mmol/L), insulin concentrations are reduced to basal values within 3-7 days. Ketonemia occurs within 10 to 30 days of marked insulin deficiency (E-Figure 305-3).[62,63] Increased free fatty acids also reduce beta-cell function, predominantly observed in the presence of high glucose (glucolipotoxicity).[62,64]

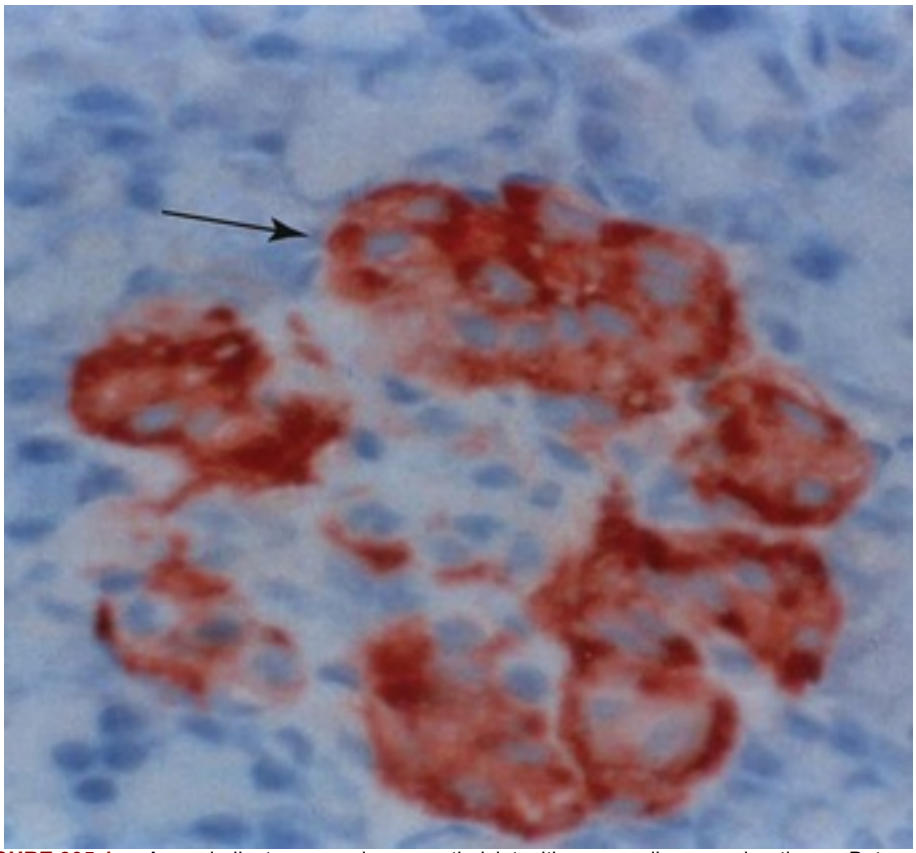


FIGURE 305-1 Arrow indicates normal pancreatic islet with surrounding exocrine tissue. Beta-cells are stained in the islet to show the hormone amylin (islet amyloid polypeptide or IAPP). (Courtesy T. Lutz, Dr. Med. Vet., PhD, University of Zurich, Switzerland. In Rand JS, Martin GJ: Management of feline diabetes mellitus. *Vet Clin North Am Small Anim Pract* 31[5]:881-913, 2001.)

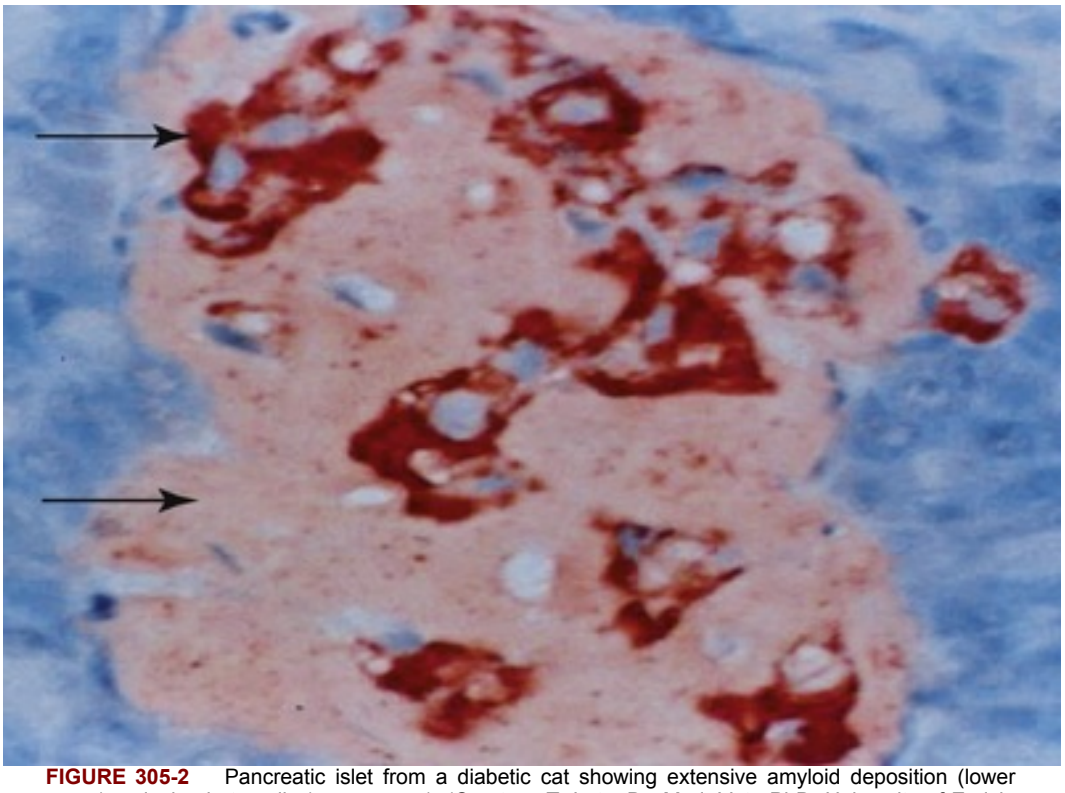


FIGURE 305-2 Pancreatic islet from a diabetic cat showing extensive amyloid deposition (lower arrow) replacing beta-cells (upper arrow). (Courtesy T. Lutz, Dr. Med. Vet., PhD, University of Zurich, Switzerland. In Rand JS, Martin GJ: Management of feline diabetes mellitus. *Vet Clin North Am Small Anim Pract* 31[5]:881-913, 2001.)

E-Box 305-1

Mechanisms Contributing to Beta-Cell Failure by Impairing Insulin Secretion, Reducing Beta-Cell Capacity to Proliferate and Increasing Beta-Cell Dedifferentiation and Beta-Cell Death[35,59,67,71,72,244-251]

Mechanisms

Accumulation of misfolded IAPP oligomers as aggregates and fibrils in beta-cells, and as amyloid within islets, leads to beta-cell death. Intracellular aggregation is particularly toxic and triggers apoptosis. It also contributes to islet inflammation by recruiting and activating macrophages and beta-cell production of chemokines and cytokines.

Generation of reactive oxygen species (ROS) secondary to nutrient overload. Chronic hyperglycemia increases glucose metabolism through oxidative phosphorylation, which induces mitochondrial dysfunction and production of ROS. ROS are also increased in chronic hyperlipidemia. Oxidative stress results in down-regulation of insulin and amylin production, and up-regulation of pro-inflammatory and apoptotic pathways.

Beta-cell endoplasmic reticulum (ER) stress occurs secondary to conditions that require prolonged high insulin production such as insulin resistance and high glucose concentrations, and with lipotoxicity and inflammatory conditions. ER stress results in reduced protein folding capacity of the ER, and accumulation and aggregation of unfolded proteins, including insulin. If the accumulation of unfolded protein is in excess of what can be managed by the unfolded protein response (UPR), it reduces insulin secretion and triggers apoptosis.

Increased glucose flux through the hexosamine biosynthetic pathway results in alteration in protein function, changes in gene expression, and decreased insulin secretion.

Exposure of beta-cells to overabundant supply of nutrients—glucose, free fatty acids and branched chain amino acids—associated with insulin resistance and obesity leads to beta-cell dysfunction and

death.

Chronically increased glucose leads to **glucotoxicity,** which has a central role in beta-cell failure by decreasing both beta-cell function and mass.

Increased long chain free fatty acids (FFAs) and lipid intermediates associated with obesity lead to **lipotoxicity.**

Enhanced toxicity occurs when both glucose and free fatty acids are increased (glucolipotoxicity).

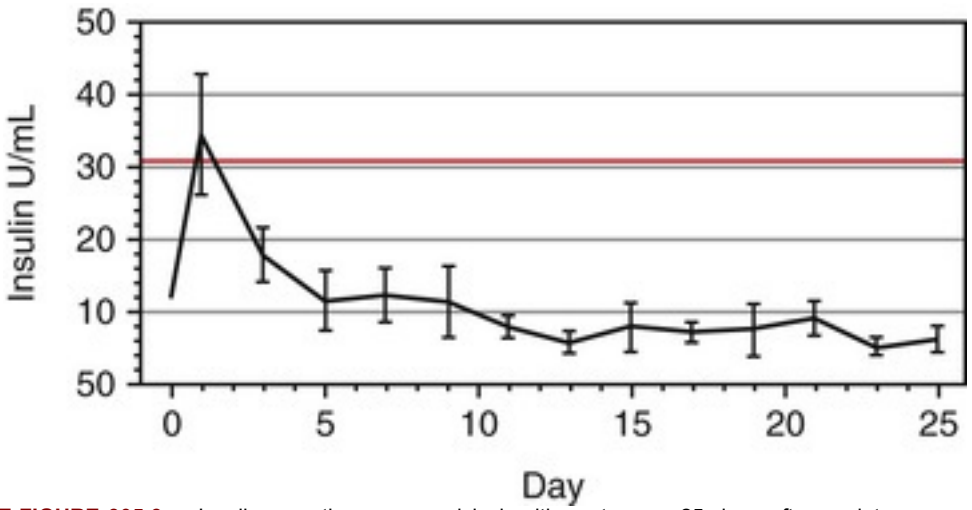
Increased branched-chain amino acids may have a role in beta-cell failure—for example, increased leucine results in decreased beta-cell function and insulin resistance.

Advanced glycation end products (AGEs) form secondary to increased glucose concentrations and result in damage to tissues including beta-cells.

Inflammation is initiated when there is over-nutrition and obesity resulting in high concentrations of glucose, free fatty acid and branched chain amino acids, but the mechanism is not fully characterized. Beta-cell induction of proinflammatory cytokines and chemokines results in immune cell infiltration into islets, including macrophages. Islets respond to glucolipotoxicity by generating inflammatory factors such as IL-1 and IL-6. IL-1 release is stimulated by hyperglycemia and IL-1 blockade improves beta-cell function.

Beta-cell dedifferentiation: Beta-cells progressively lose beta-cell characteristics, which to a certain degree is reversible. Dedifferentiation is triggered by glucolipotoxic conditions, ER and oxidative stress, and inflammation, but the relative contribution to beta-cell dysfunction and loss in type 2 diabetes is unknown.

Beta-cell death through apoptosis, necrosis and autophagy (programmed cell death) is triggered by many of the mechanisms above.



E-FIGURE 305-3 Insulin secretion measured in healthy cats over 25 days after an intravenous glucose infusion was begun at day 0. Persistently high blood glucose concentrations in the range typically seen in newly diagnosed diabetic cats (e.g., 540 mg/dL; 30 mmol/L) cause rapid suppression of insulin secretion from beta-cells even in healthy cats, to levels seen in newly diagnosed diabetic cats. Ketonemia occurs 10-30 days after insulin suppression. Eventually glucotoxicity leads to loss of beta-cells.

Amylin and Islet Amyloid Polypeptide (IAPP)

Deposition of misfolded amylin or IAPP is typical of type 2 DM in humans and cats.[6,58,60,61,65] Amylin or IAPP is a hormone which modulates insulin action, is co-secreted with insulin, and larger quantities are secreted by individuals with insulin resistance.[61] Amylin, in humans and cats, may fold into beta-pleated sheets and form polymerized and misfolded amylin oligomers which act as toxic intracellular aggregates and fibrils. They contribute to islet inflammation and beta-cell death.[60,61,65] Islet amyloid deposition is enhanced in feline models of hyperinsulinemia due to insulin resistance and is associated with overt DM.[66] Islet amyloid deposition and toxic intracellular IAPP oligomers or fibrils, as contributors to beta-cell failure, may explain why humans and cats are uniquely susceptible to type 2 DM, whereas obese dogs and other species

do not develop type 2 DM.

Oxidative Damage

Oxidative stress and modifications likely play a central role in beta-cell dysfunction. Beta-cells have limited antioxidant capacity and are susceptible to oxidative stresses.[67] Glucotoxicity and lipotoxicity are associated with oxidative modifications to beta-cells via excessive production of reactive oxygen species secondary to increased cellular respiration.[68,69] Induction of uncoupling protein-2 (UCP-2) is initially used by beta-cells as a mechanism to protect against excessive mitochondrial respiration. However, activation of UCP-2 causes increased oxygen free-radical generation and oxidative stress.[70] Oxidative stress down-regulates insulin and amylin production while up-regulating pro-inflammatory or apoptotic pathways such as NF-κB and c-JUN N-terminal kinase (JNK).[67,71,72]

Diagnosis

Blood Glucose, Glucose Tolerance and the Diagnosis of Overt Diabetes Mellitus

Once blood glucose concentration exceeds proximal tubular capacity for reabsorption from the glomerular filtrate (approximately 250-290 mg/dL or 14-16 mmol/L), glycosuria occurs.[73,74] Glucose loss in urine contributes to weight loss and stimulates appetite, but not nearly as significantly as cellular inability to gain access to glucose for normal function. Water losses caused by the glucose-osmotic diuresis stimulate polydipsia to maintain fluid balance. Thus, the classic clinical signs of DM result: polyuria, polydipsia, polyphagia, and weight loss. The upper limit for blood glucose concentration in cats is about 113-117 mg/dL (6.3-6.5 mmol/L) using a portable glucose meter and after overnight hospitalization and an 18-24 hour fast.[75,76] Concentrations persistently above this should be considered pre-DM unless overt DM is confirmed. Values ≥180-288 mg/dL (≥10-16 mmol/L) have been reported to be diagnostic for overt DM.[77,78]

The statistically established glucose value in senior cats (≥8 years) is <176 mg/dL (<9.8 mmol/L) 2 hours after 0.5 g/kg glucose, or <117 mg/dL (<6.5 mmol/L) 3 hours after 1 g/kg glucose, as measured in a simplified glucose tolerance test.[75,76] Using these criteria, 20% of obese cats ≥8 years of age are glucose intolerant.[75] It is recommended that the measured 2 hour glucose concentration be adjusted downward by 1.8 mg/dL (0.1 mmol/L) for each body condition score unit above 5 out of 9, to account for relative glucose overdosing in obese cats.[79] Abnormal glucose tolerance is best confirmed by a repeat test.

Impaired Glucose Tolerance and Pre-Diabetes Mellitus (Pre-DM)

Humans with blood glucose concentrations above normal but below DM when fasted or at the 2-hour point in a glucose tolerance test are classified as having impaired fasting glucose or impaired glucose tolerance, respectively.[1,80] They are considered pre-DM and at high risk of developing type 2 DM (5-10% progress to overt DM/year).[1,80-83] Over 50% of DM people are undiagnosed and 3 to 4 times more have undiagnosed pre-DM.[1,80,84] The undiagnosed number of cats with DM may be as large. If identified before progression to overt DM, people often have reasonable glycemic control with weight loss, dietary management, and exercise.[80] Twelve percent to 26% of people in the USA, Europe and Australia have impaired fasting glucose, a percent that increases to 39% by age 65.

Impaired fasting glucose is rarely diagnosed in cats. Mild hyperglycemia is often attributed to stress caused by travel to the clinic, the "white coat effect," restraint, or illness.[81,84-86] As in people, identification and treatment of pre-DM or subclinical DM in cats may delay or prevent progression to overt DM. Most cats in DM remission continue to have disturbed glucose metabolism consistent with pre-DM and have high risk of relapse.[76] Cats in DM remission with normal fasting glucose concentrations and normal glucose tolerance did not develop DM within 12 months. However, DM reoccurred within 9 months of testing in 67% of cats with moderately impaired glucose tolerance (>252 mg/dL; >14 mmol/L at 3 hours during a 1 g/kg IV glucose tolerance test) and in 100% of cats with moderately impaired fasting glucose (≥135-162 mg/dL; ≥7.5-9 mmol/L).[76] Blood glucose concentrations below the renal threshold (250-290 mg/dL; 14-16 mmol/L) but above the point for DM (180 mg/dL; 10 mmol/L) are unlikely to cause clinical signs and should be classified as subclinical DM.[73] Asymptomatic cats with persistent blood glucose concentrations above 117 mg/dL

(6.5 mmol/L) may avoid overt DM or would likely benefit from a low carbohydrate diet, weight loss, and, perhaps, insulin sensitizers such as darglitazone.[87]

Screening Blood Glucose Results (see ch. 61)

When blood is obtained soon after arrival to a clinic, a normal screening blood glucose should be <166 mg/dL (9.2 mmol/L). This high upper value for normal is due to the confounding effect of stress on blood glucose concentrations in cats, capable of markedly increased glucose concentrations within minutes of a stressor.[88] Peak glucose concentrations occur 10 minutes after acute stress and do not return to baseline, in some cats, for >3 hours.[85] Struggling alone increases glucose concentration a mean of 74 mg/dL (4.1 mmol/L) and as much as 195 mg/dL (10.8 mmol/L) within 10 minutes in some cats. This increase parallels lactate and norepinephrine concentrations.[85] Due to the effects of stress, screening blood glucose may not be a useful predictor of DM relapse in cats that had been in remission because of the confounding effects of the stress of travel and handling, and in some cats, the effects of eating (Figure 305-4).[76] Senior cats with glucose concentrations >117 mg/dL (>6.5 mmol/L) should be hospitalized, retested 4 and 24 hours later and managed appropriately based on test results (Figure 305-5).

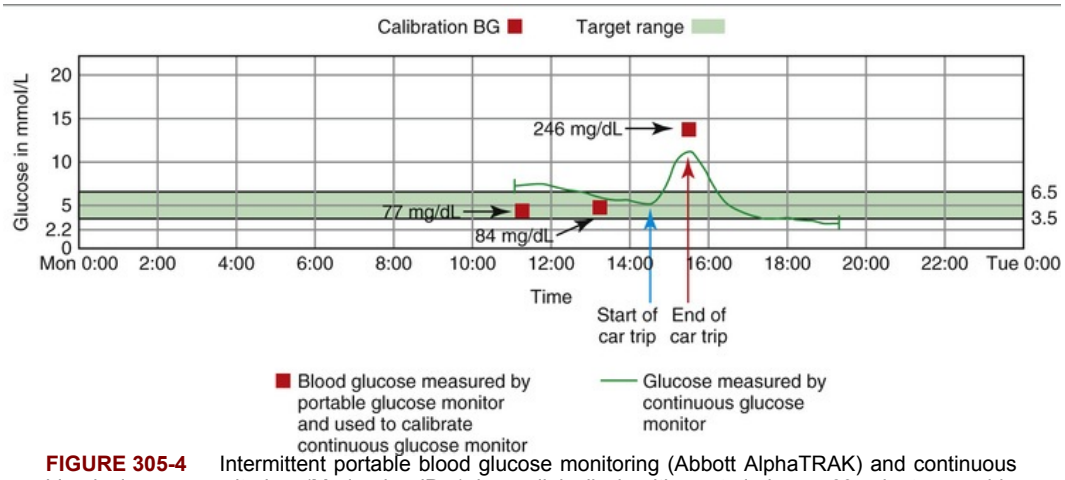


FIGURE 305-4 Intermittent portable blood glucose monitoring (Abbott AlphaTRAK) and continuous blood glucose monitoring (Medronics iPro) in a clinically healthy cat during a 60 minute car ride between the clinic and home. Blood glucose concentrations steadily increased from 84 mg/dL (4.7 mmol/L) to 245 mg/dL (13.6 mmol/L), and decreased to normal over a similar time.

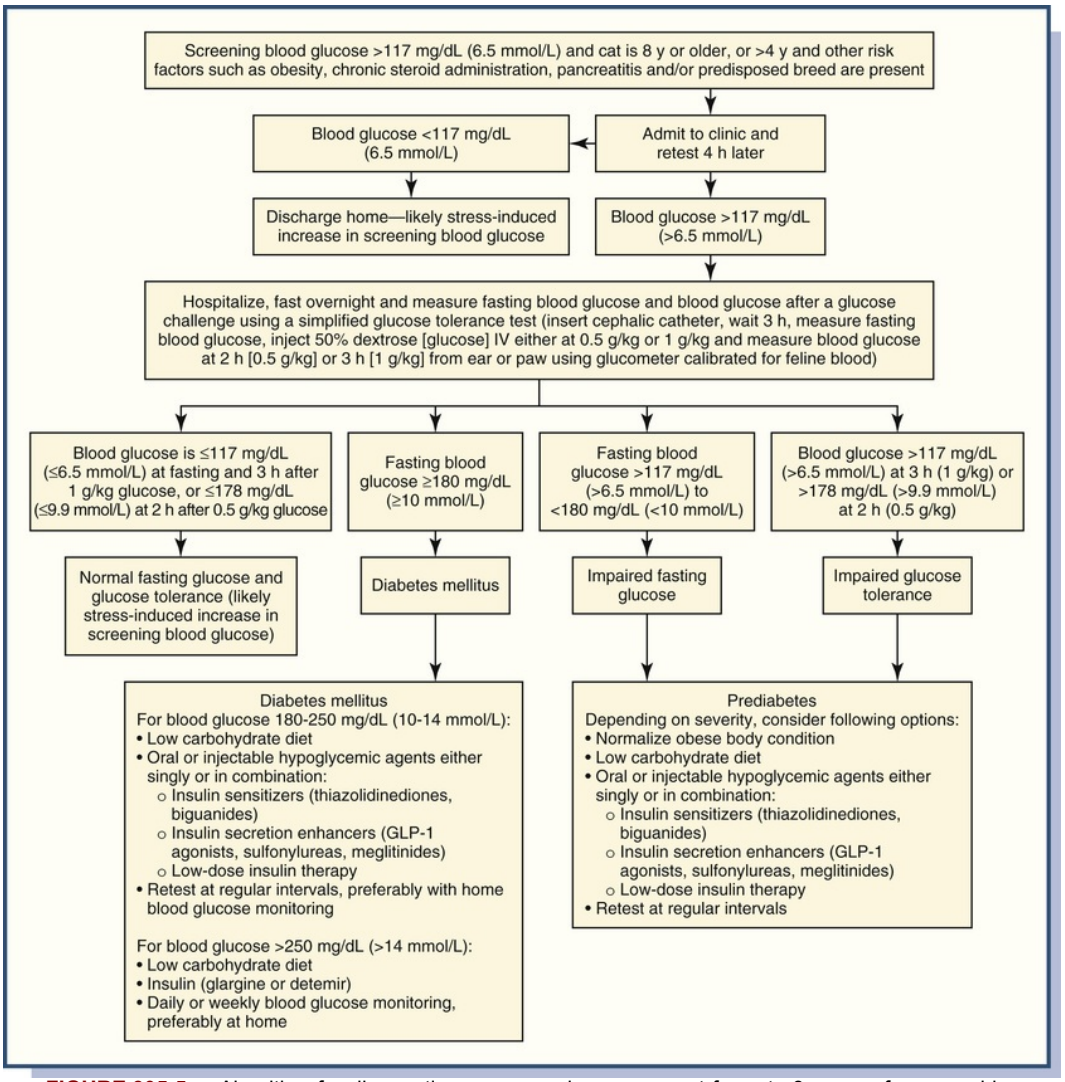


FIGURE 305-5 Algorithm for diagnostic process and management for cats 8 years of age or older with screening blood glucose (not fasted and on entry to the clinic) >117 mg/dL (6.5 mmol/L). *GLP-1*, Glucagon-like peptide 1.

Diabetic Ketosis (DK) and Diabetic Ketoacidosis (DKA) (see ch. 142)

At the time of DM diagnosis, 12-37% of cats have DKA and some are ketotic but not acidotic (DK).[2,77] DKA can be triggered by concomitant disease (especially infection) and signs include depression, vomiting and anorexia.[89] Ketosis can occur over a period of 10 to 30 days once a cat becomes markedly insulinopenic, and does not necessarily require concomitant disease.[63] Once ketotic and without insulin treatment, DKA progresses rapidly. Small doses of insulin can prevent acidosis, even if hyperglycemia persists.[63] Sixteen days after healthy cats had experimentally induced hyperglycemia (540 mg/dL; 30 mmol/L), beta-hydroxybutyrate ketonemia (>0.5 mmol/L) was evident. Ketonemia did not occur at glucose concentrations of 306 mg/dL (17 mmol/L), reflecting the protective effect of insulin.[63] Beta-hydroxybutyrate ketonuria occurred after marked hyperglycemia persisted for a mean of 23 days, although individual times varied widely, as did the renal threshold (19.6 mg/dL, range 3.1-40.6 mg/dL; 1.88 mmol/L, range 0.3-3.9 mmol/L). Ketonuria was detected after 5 days with urine test strips that measured acetoacetate and acetone. By day 27, most cats had acetone-smelling breath and gross lipemia. Based on this study, when blood glucose concentrations are <360 mg/dL (<20 mmol/L), plasma betahydroxybutyrate is unlikely to be increased (>10 mg/dL; >1 mmol/L) and should not be relied on to differentiate stress hyperglycemia from diabetes.

Fructosamine

Fructosamine is produced by a non-enzymatic reaction between glucose and amino groups of plasma proteins, and is a useful measure of glycemic control for cats where home or in-hospital blood glucose monitoring is not possible. It may also aid in diagnosing DM.[90] When hyperglycemia (306 or 540 mg/dL; 17 or 30 mmol/L) was experimentally induced in cats, fructosamine concentrations increased above the reference range (331 mcmol/L) within 3 to 5 days. However, mean fructosamine level did not increase above 350 mcmol/L when blood glucose was maintained at 306 mg/dL (17 mmol/L) for 6 weeks.[91] In cats, fructosamine concentration probably reflects the mean blood glucose concentration for the preceding week. Only changes >33 mcmol/L in an individual are likely to have significance.[91] Fructosamine should not be used to differentiate stress-hyperglycemia from DM when the blood glucose concentration is ≤360 mg/dL (20 mmol/L). Differentiation should be based on serial blood glucose concentrations, and if present, glycosuria and clinical signs. For a given blood glucose concentration, plasma fructosamines vary widely between individual cats. False-positive results (normal cats with high fructosamine levels) and false-negative results (DM cats with normal fructosamine levels) occur, including in DM cats with hyperthyroidism.[90,92,92a]

Goals of Therapy and Diabetic Remission

Newly Diagnosed Diabetics

Tight Glycemic Control

In newly diagnosed DM, the aim of therapy is normal or near-normal blood glucose concentrations (72 to <180 mg/dL; 4 to < 10 mmol/L) while avoiding clinical hypoglycemia. Excellent glycemic control to resolve glucotoxicity, achieved early in newly diagnosed DM cats, increases the probability of DM "remission," defined as persistent euglycemia for at least 2 to 4 weeks without need for exogenous insulin or oral hypoglycemic therapy.[8,76,93] For example, 84% of newly diagnosed DM cats started on a protocol aimed at rigorous glycemic control achieved remission within 6 months, as compared with only 35% ($p < 0.001$) when tight glycemic control was not instituted for at least 6 months.[94]

Remission

Factors reported associated with DM remission include a low carbohydrate diet (12% versus 26% of energy), long-acting insulin (glargine versus PZI or lente), higher age, lower maximum dose of insulin (mean maximum dose of glargine of 0.4 U/kg versus 0.7 U/kg or <3 U/cat versus >3 U/cat), early institution of tight glycemic control (<6 months versus ≥6 months), recent corticosteroid administration, absence of neuropathy, lower mean blood glucose concentrations after treatment with insulin, and lower cholesterol concentrations.[8,93-96] Older cats developing DM have higher remission rates, possibly suggesting a slower disease progression.[93] Mean blood glucose <288 mg/dL (<16 mmol/L) after 17 days of glargine treatment was significantly associated with remission.[8]

Although remission is reported with a variety of oral hypoglycemic drugs, insulin therapies, insulin dosing protocols and diets, the highest remission rates (>80%) are reported in newly diagnosed diabetic cats managed with a protocol aimed at achieving normal or near-normal blood glucose concentrations using a long-acting insulin (glargine or detemir), a low carbohydrate diet (≤6% of energy from carbohydrate), frequent in-hospital or home blood glucose monitoring and appropriate insulin dosage adjustments using a dosing protocol aimed at tight glycemic control.[8,94,97] However, the contributions of small case numbers, lack of blinding, or reliance on owner interpretation are not known.[98]

Corticosteroid Administration

Corticosteroid administration in the 6 months before diagnosis of DM is associated with the highest remission rates.[94] In humans, drug-induced DM is considered an "other specific type" distinct from type 2. It may be easier to reverse this underlying pathophysiologic process or steroid administration may unmask beta-cell defects associated with another disease such as type 2 DM or pancreatitis, resulting in the owner seeking treatment more promptly (see ch. 358).[1]

Peripheral Neuropathy (PN)

PN at the time of DM diagnosis is associated with decreased probability of remission (Figure 305-6 and Videos 12-2, 305-1, and 305-2) and was present in 79% of cats that did not achieve remission despite

implementation of a protocol aimed at intensive glycemic control.[94] Because neuropathy appears later in the course of the disease, it is likely that these cats had DM chronically, with greater beta-cell damage.[94]

FIGURE 305-6 A plantigrade stance and/or muscle weakness is observed in a significant proportion of newly diagnosed diabetic cats and is negatively associated with the probability of diabetic remission. (Photo with permission from R. Marshall.)

Long-Term Diabetes Mellitus without Remission

Cats managed for more than 6 months without achieving DM remission have slightly different treatment goals: to control clinical signs while avoiding clinical hypoglycemia. Remission may be noted in a small number of cats, even after 2 years or more of insulin treatment, if rigorous glycemic control is implemented.

Relapse

Most cats in DM remission do not have normal beta-cell function or sufficient insulin to maintain normal tolerance when challenged with glucose and they should continue to be considered pre-DM. Approximately 76% have impaired glucose tolerance evident after a glucose challenge and 19% have impaired fasting glucose concentrations (mild persistent hyperglycemia >117 mg/dL to <180 mg/dL; >6.5 to <10 mmol).[76] A reduced number of pancreatic islet cells is evident histologically, despite DM remission, including decreased beta-cell density when compared to control cats (1.4% compared to 2.6%).[96] Approximately 25-30% of cats in DM remission relapse, once again requiring exogenous insulin, and <25% of those cats achieve a second remission.[76,93,94] Home blood glucose monitoring and glucose tolerance tests can be used to identify cats at risk of relapsing. Fasting blood glucose of ≥135 mg/dL (≥7.5 mmol/L) and moderate impaired glucose tolerance with either ≥5 hour return to ≤117 mg/dL (≤6.5 mmol/L) or blood glucose concentration >252 mg/dL (>14 mmol/L) at 3 hours during a glucose tolerance test (1 g/kg dextrose IV) were each associated with relapse within 9 months of achieving remission.[76]

Remission was longer in cats with higher body weight at the time of diagnosis, possibly indicating that cats with lower body weight had longer duration of DM and fewer functional beta-cells.[93] As in pre-DM people, drugs which improve insulin sensitivity (thiazolidinediones, biguanides), improve insulin secretion

(glucagon-like peptide 1 [GLP-1] agonists, sulfonylureas, meglitinides) or low-dose insulin therapy may have a role in managing cats with impaired glucose tolerance or increased fasting blood glucose to reduce probability of DM relapse.[80]

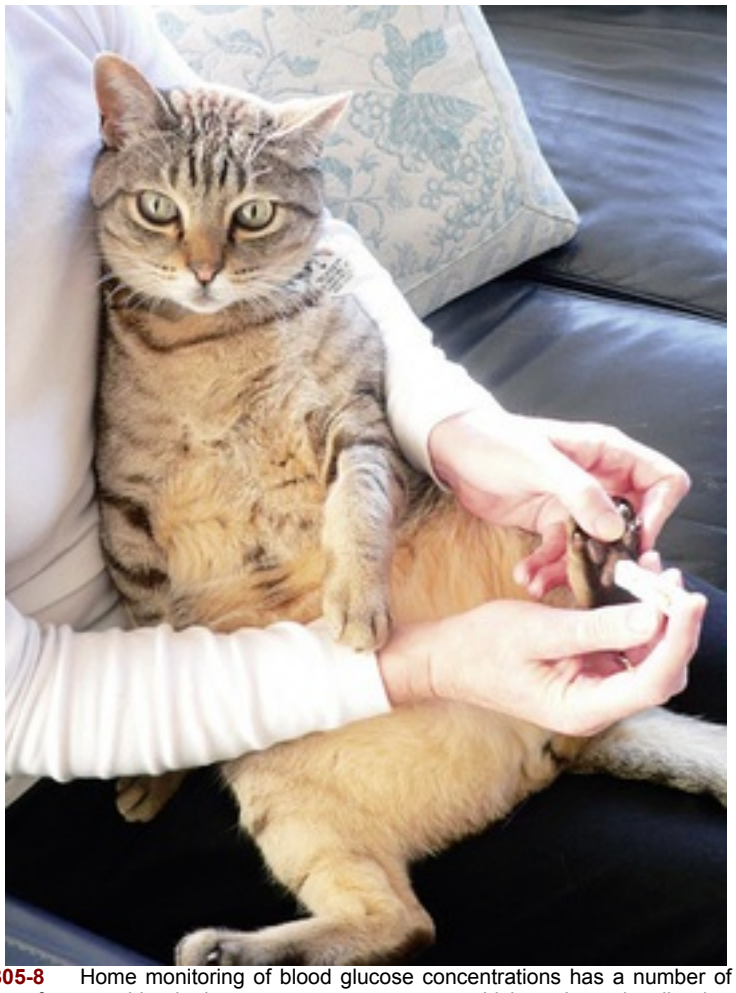
Monitoring Response to Treatment

Blood Glucose, Fructosamine

The aim of therapy is to achieve consistently normal or near-normal blood glucose concentrations (3-10 mmol/L) to maximize chances of remission, minimize clinical signs of hyperglycemia, and avoid hypoglycemia. Monitoring clinical signs (water intake, body weight, appetite) is useful but a relatively insensitive indicator of glycemic control, particularly when glucose concentrations are below renal threshold (252-288 mg/dL; 14-16 mmol/L). Fructosamine is a useful indicator of glycemic control over the previous week, but different assays vary in methodology and reference ranges (321-400 mcmol/L), so within-cat comparisons over time are most useful.[76,91,99,100] Measuring home water consumption correlates more closely with mean blood glucose concentration in a 24 hour period than does fructosamine concentration.[101]

To maximize the probability of DM remission, blood glucose concentration is the most useful variable for adjusting insulin dosage, especially when near normal. Blood glucose concentration is best measured with a portable glucose meter calibrated for cats and measured from the ear or pad (Figure 305-7 and E-Figure 305-8; see ch. 79). Because stress hyperglycemia can be unpredictable and confusing, home blood glucose monitoring is recommended. It is most valuable prior to insulin injection, to prevent inadvertent over-dosing when blood glucose concentration is around the normal range.

FIGURE 305-7 Ear sampling of blood for home blood glucose monitoring. (Photo from Mia Reeve-Johnson.)



E-FIGURE 305-8 Home monitoring of blood glucose concentrations has a number of advantages including more frequent blood glucose measurements on which to base insulin dose increases. Glucose concentration is less likely to be affected by stress or inappetence. Reduced cost and greater convenience for the owner are also factors. Foot pad is warmed for 20 seconds using a warmed, moist cotton wool ball, or massaged to facilitate blood flow. (Photo from W. Milledge with permission.)

Continuous Blood Glucose Monitoring Systems (CBGMS)

CBGMS facilitate identification of hyperglycemia and hypoglycemia and are primarily used for monitoring blood glucose in hospitalized cats. With more compact units becoming available which provide 6 to 7 days of data, they will increasingly be used for home monitoring.[102-104] CBGMS reduce the number of blood samples required during intensive monitoring, guide insulin dosing for tight regulation, are useful for difficult-to-stabilize DM cats fluctuating between hyperglycemia and hypoglycemia, and assist with identification of short-duration of insulin action and rebound hyperglycemia (Somogyi).[102] Units provide real-time or retrospective data. Compact units are suited to home monitoring. Real-time units are most used in-hospital, where they provide immediate information for adjusting each insulin dose.

Disadvantages of current CBGMS are considerable: they are expensive, they require calibration 2 to 3 times a day with blood glucose measurements obtained by other methods, the glucose concentration range measured is less than most portable glucose meters, transmitting range of wireless units is restricted, and life of the sensor is finite (needing replacement within 3 to 7 days) (E-Table 305-1). Sensors can be placed in the flank, lateral thorax, inter-scapular space, lateral stifle fold or dorsal neck. The neck site provides the best continuity of data (Figure 305-9, Video 305-3).[102,104,105] Depending on the expected activity of the cat, the monitor may need to be secured in place with tissue glue, taping or bandaging.[102]

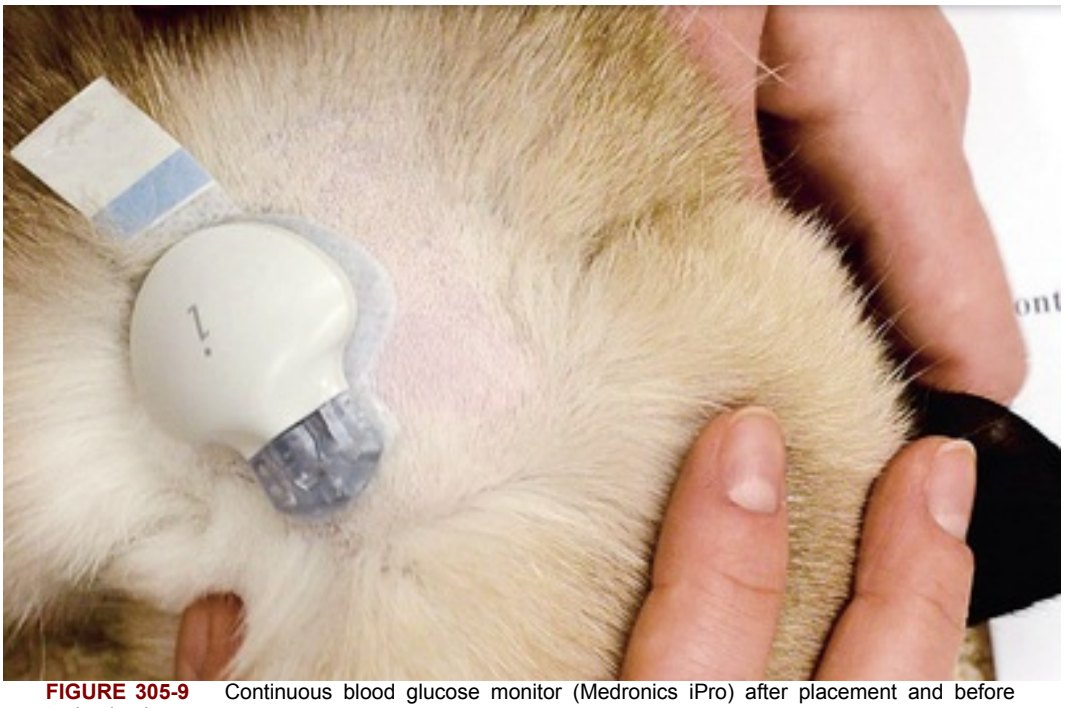


FIGURE 305-9 Continuous blood glucose monitor (Medronics iPro) after placement and before taping in place.

E-TABLE 305-1

Specifications of Continuous Glucose Monitors[102]

	GUARDIAN REAL-TIME	I-PRO	GLUCODAY	FREESTYLE NAVIGATOR
Company	Medtronic	Medtronic	Menarini Diagnostics	Abbott
Vet evaluation	Yes	No	Yes	No
Recording range	40-400 mg/dL (2.2-22.2 mmol/L)	40-400 mg/dL (2.2-22.2 mmol/L)	20-600 mg/dL (1.1-33.3 mmol/L)	40-400 mg/dL (2.2-22.2 mmol/L)
Real-time display	Yes	No	Yes	Yes
Retrospective analysis	Yes	Yes	Yes	Yes
Wireless transmitter (range)	Yes (4 ft, 1.2 m)	No N/A	Yes N/A	Yes (10 ft, 3 m)
Calibration frequency	2 h after insertion, within the next 6 h, then every 12 h	1 and 3 h after insertion, then minimum every 12 h	Minimum of 1 time point per 48 h, 2 if used in real time	10 h after insertion, within the next 2-4 h, then every 12 h
Recording frequency	Data every 10 s, mean value every 5 min	Data every 10 s, mean value every 5 min	Data every 1 s, mean value every 3 min	Data every 10 s, mean value every 5 min
Sensor weight (including recorder if on patient)	2.8 oz (80 g)	2.8 oz (80 g)	N/A	0.48 oz (13.61 g)
Sensor size (L × W × H)	1.64 × 1.4 × 0.37 in (4.2 × 3.6 × 0.9 cm)	1.64 × 1.4 × 0.37 in (4.2 × 3.6 × 0.9 cm)	N/A	2.5 × 1.23 × 0.43 in (5.2 × 3.1 × 1.1 cm)
Needle insertion size	27G (Enlite sensor)	24 G	18 G	21G
Sensor life	144 h (Enlite sensor)	144 h (Enlite sensor)	48 h	120 h
Initialization period	2 h	1 h	1 h	2 h

Monitor (recorder) weight	4 oz (114 g)	N/A	8.6 oz (245 g)	3.5 oz (100 g)
Monitor size (L × W × H)	3.2 × 0.8 × 52 in (8.1 × 2 × 5.1 cm)	N/A	4.3 × 1 × 3 in (11 × 2.5 × 7.5 cm)	2.5 × 3.2 × 0.9 in (8.1 × 2.0 × 5.1 cm)

Insulin Therapy

Exogenous insulin is the most effective and reliable treatment for attaining excellent glycemic control.[8,106] There are several types of insulin available for therapy.

Lente Insulin (Caninsulin/Vetsulin, Merck Animal Health)

Lente (Vetsulin Caninsulin) is an intermediate-acting, porcine derived, 40 U/mL insulin that consists of 30% amorphous semilente (short-acting) and 70% crystalline ultralente (long-acting).[107] The 40 U/mL concentration differs from the 100 U/mL insulins registered for human-use and some veterinary-registered insulins. To avoid dosing errors, it is important that the appropriate 40 U/mL syringes are not inadvertently changed for 100 U/mL syringes. Starting dosages for lente insulin are 0.25 to 0.5 U/kg body weight SC q 12 h and should not exceed 3 U/cat (E-Table 305-2).[108] In a 12-month study of 25 cats (15 newly diagnosed), 84% were considered to have a good or excellent response to treatment, based on owner satisfaction and resolution of clinical signs and 28% achieved DM remission within 16 weeks of starting treatment.[109] Median starting dosage was 0.5 U/kg SC q 12 h and did not change significantly over the course of the study. In another study of 46 DM cats (39 newly diagnosed), good to excellent control was achieved in 72%, based on resolution of clinical signs, and 15% achieved remission within 20 weeks.[110] Clinical signs of hypoglycemia were evident in 20% of the cats, and mostly occurred at dosages greater than 0.5 U/kg or 3 U/cat.[110]

E-TABLE 305-2

Parameters for Insulin Dosage and Frequency Based on Blood Glucose Measurements Using Lente (Caninsulin/Vetsulin; Merck Sharp and Dohme) or NPH in Diabetic Cats*

BLOOD GLUCOSE VARIABLE	RECOMMENDATION
Use an initial dosage 0.5 U/kg of lean body weight SC q 12 h if blood glucose is >360 mg/dL (>20 mmol/L) and 0.25 U/kg q 12 h if glucose <360 mg/dL (<20 mmol/L); do not increase in first week, but decrease if necessary	
If pre-insulin blood glucose concentration is ≤180 mg/dL (≤10 mmol/L)	Provided cat has been treated for a minimum of 2 weeks with insulin, withhold insulin and monitor blood glucose carefully over next 24-48 hours to determine if cat is in diabetic remission; if treated for less than 2 weeks, reduce dose by 1 U/cat and recheck in 1 week
If pre-insulin blood glucose concentration is 198-270 mg/dL (11-15 mmol/L)	Total dose should be no more than 1 U/cat q 12 h
If nadir blood glucose concentration is <72 mg/dL (<4 mmol/L)	Dosage should be reduced by 50%
If nadir blood glucose concentration is 72-90 mg/dL (4-5 mmol/L)	Dosage should be reduced by 1 U if poor control of clinical signs of diabetes, to determine if dose was excessive and leading to reduced duration of insulin action or a Somogyi effect. If clinical signs do not substantially improve within 7 days, switch to long-acting (glargine or detemir). Dosage should remain the same if exemplary control of clinical signs.
If nadir blood glucose concentration is 91-180 mg/dL (6-9 mmol/L)	Dosage should remain the same
If nadir blood glucose concentration is	Dosage should be increased by 1 U

>180 mg/dL (>10 mmol/L)	
If nadir blood glucose concentration occurs within 3 hours of insulin administration, or blood glucose returns to baseline within 8 hours	Change to longer acting insulin (i.e., glargine, detemir or PZI) or increase frequency of administration
If the nadir blood glucose concentration occurs at 8 hours or later	Once daily administration may be used, although twice daily administration at a reduced dose is preferred

*Based on monitoring blood glucose concentration in hospital or at home every 1 to 2 weeks with serial measurements every 2 hours over 12 hours using a portable glucose meter calibrated for feline blood measuring whole blood glucose concentration

Normal reference range for cats (54-117 mg/dL; 3-6.5 mmol/L) as target glucose concentrations.[113]

After giving lente to DM cats, the blood glucose nadir typically occurs in about 3 to 6 hours (mean 4 hours), and blood glucose concentration returns to pre-injection values between 8 to 10 hours (termed return to baseline or duration of action).[110,111] Because of this relatively short duration of action, even with q 12 h dosing, hyperglycemia typically occurs for several hours twice daily (prior to each injection).[111,112] As a result, even though appropriate nadirs may be achieved, blood glucose concentration is often high (≥360 mg/dL; ≥20 mmol/L) prior to each insulin injection, making this our fourth choice insulin in cats. Twice daily marked hyperglycemia likely contributes to lower remission rates in cats treated with lente insulin compared to long-acting insulin. Insulin dosage should be adjusted based on nadir glucose concentrations to achieve concentrations in the normal range. Do not base the dosage on blood glucose concentration at the time of insulin injection, unless the concentration is <360 mg/dL (<20 mmol/L). This indicates that insulin action is longer than 12 hours, or more often, return of endogenous insulin secretion and pending remission (see E-Table 305-2).[113]

Protamine Zinc Insulin (PZI)

PZI has protamine and zinc added to prolong its duration of action.[114] While not available for human use since the 1990s, it is still available for use in cats in the USA and the United Kingdom. Originally animal-origin, it is now human-recombinant PZI (ProZinc, Boehringer Ingelheim).[115,116] ProZinc has a concentration of 40 U/mL, and therefore, use of appropriate insulin syringes must be discussed with the owner to avoid inadvertently using 100 U/mL syringes and incorrect dosing. Some compounding pharmacies in the USA provide bovine origin PZI for veterinary use, but in one study only 1 of 12 pharmacies consistently made PZI that met required specifications of the United States Pharmacopeia.[117] Recommended initial dosage is either 1-3 U/cat or 0.25-0.5 units/kg ideal body weight, with the actual dosage chosen based on severity of clinical signs and hyperglycemia (Table 305-3).[8,118]

TABLE 305-3

Glargine, Detemir or PZI Dosing Protocol, Monitoring Glucose Every 1-2 Weeks Using a Glucometer Calibrated for Cats (e.g., AlphaTRAK, Abbott Animal Health)

PARAMETER USED FOR DOSAGE ADJUSTMENT	CHANGE IN DOSAGE
Begin with 0.5 U/kg SC q 12 h if blood glucose >360 mg/dL (>20 mmol/L) or 0.25/kg SC q 12 h of ideal weight if blood glucose is lower Do not increase in first week unless minimal response to insulin occurs, but decrease if necessary. Monitor response to therapy for first 3 days. If no monitoring is occurring in first week, begin with 1 U/cat SC q 12 h	
If pre-insulin blood glucose concentration >216 mg/dL (>12 mmol/L) provided nadir is not in hypoglycemic range **OR** If nadir blood glucose concentration >180 mg/dL (>10 mmol/L)	Increase by 0.25-1 U depending on total insulin dose (greater or less than 3 U/cat) and degree of hyperglycemia (how close blood glucose is to 180 mg/dL [10 mmol/L])

If pre-insulin blood glucose concentration ≥180-≤216 mg/dL (≥10-≤12 mmol/L) **OR** Nadir blood glucose concentration is 90-160 mg/dL (5-9 mmol/L)	Same dosage
If nadir glucose concentration is 63-<72 mg/dL (3.5-<5 mmol/L)	Use nadir glucose, water drunk, urine glucose and next preinsulin glucose concentration to determine if insulin dosage is decreased or maintained
If pre-insulin blood glucose concentration <180 mg/dL (<10 mmol/L) **OR** If nadir blood glucose concentration <63 mg/dL (<3.5 mmol/L)	Reduce by 0.25-1 U depending on total insulin dose (greater or less than 3 U/cat) and degree of hyperglycemia (how close blood glucose is to 180 mg/dL [10 mmol/L]) If total dose is 0.5-1 U q 12 h, change to q 24 h If total dose is 0.5-1 U q 24 h, stop insulin and check for diabetic remission
If clinical signs of hypoglycemia are observed	Reduce by 50%

If using a plasma-equivalent meter calibrated for human blood, decrease target blood glucose concentration by 9 mg/dL; 0.5 mmol/L.[8,94,97]

Of 133 DM cats treated with PZI (120 newly diagnosed and 13 previously treated with other insulin), 85% obtained good control within 45 days based on improved clinical signs, stabilization of body weight and reduction in the mean blood glucose concentration 9 hours after PZI administration and/or reduced serum fructosamine concentration.[116] Biochemical hypoglycemia was identified in 64% of the cats, although only 2 had clinical signs. In a study of newly diagnosed DM cats, 3/8 achieved remission within 112 days, not significantly different from the remission rate of 2/8 achieved in cats treated with lente insulin.[8] In healthy cats, PZI results in a biphasic blood glucose concentration curve. The first nadir occurs at about 4 hours (range 1.5 to 8 hours), and a second nadir at 14 hours (range 6 to 24 hours). Mean duration of action is 21 hours (range 9 to >24 hours).[119] In DM cats, the first nadir blood glucose concentration occurred at 5 to 7 hours.[116] This is our third choice for DM in cats.

Glargine (Lantus, Sanofi-Aventis, Patent Protection Expired Feb 2015)

Glargine (100 U/mL) is a long-acting human insulin analogue. Asparagine at position A21 is replaced by glycine, and two arginines added to the B chain at positions 31 and 32, hence the name.[120] These alterations result in insulin that is soluble in acidic solutions but which microprecipitates in the neutral pH of SC tissues, prolonging its release.[120,121] In humans, glargine provides basal insulin concentrations for 24 hours, and is typically used together with short-acting insulin administered at the time of eating to mimic normal patterns of endogenous insulin secretion.[120] Using the euglycemic clamp method in healthy cats, glargine had a duration of action of 10 hours (6.6-13 hours).[122] However, using an insulin response test in healthy cats, their glucose nadir was reached at 14 hours (10-24 hours), after glargine administration, and duration of action was 22 hours (12->24 hours).[119] In healthy cats, duration of action is significantly longer than lente insulin (10 hours, range 5-24+), although similar to PZI (21 hours, range 9-24+).[119] In healthy cats, no significant difference in duration of action was noted in comparing doses of 0.5 U/kg SC q 24 h and 0.25 U/kg SC q 12 h.[123]

It is recommended that glargine (q 12 h) be used as a sole insulin for cats with DM, together with a low carbohydrate diet to minimize postprandial increases in blood glucose.[119] Dosing q 12 h facilitates overlap of insulin action from one injection to the next, resulting in consistent glucose lowering effects over 24 hours, increasing chances of DM remission.[119,122,123] Importantly, glycemic control was not significantly different between glargine administered once daily and lente administered twice daily.[124] Recommended starting dosages for glargine are 0.25 U/kg of ideal body weight SC, if blood glucose concentration is <360 mg/dL (<20 mmol/L), or 0.5 U/kg (maximum 3U/cat) SC if blood glucose is higher (see Tables 305-3 and 305-4).[8,94,118] If no blood glucose monitoring is intended in the first week of therapy, a starting dose of 1 U/cat is recommended, although this approach may delay resolution of clinical signs. When transitioning from another insulin to glargine, if the dose is <3 U, one should use the same dose. For doses ≥3 U, conservative dosing is recommended: for example, starting with 50-66% of the dose, but increasing within 48-72 hours if control is not adequate.[125]

TABLE 305-4

Glargine or Detemir Dosing Protocol and Intensive Home Blood Glucose Monitoring (Minimum 3 Measurements Per Day with Average of 5) during Stabilization Period (6-12 Weeks) Using a Plasma-Equivalent Meter Calibrated for Cats (e.g., AlphaTRAK from Abbott Animal Health)[94]

PARAMETER USED FOR DOSAGE ADJUSTMENT	CHANGE IN DOSAGE
Phase 1: Initial dosage and first 3 days on glargine.	
Begin with 0.25 U/kg of ideal weight SC q 12 h **OR** If the cat received another insulin previously, increase or reduce the starting dose, taking this information into account. Glargine has a lower potency than lente insulin or PZI in most cats.	
Cats with a history of developing ketones and blood glucose remains >300 mg/dL (>17 mmol/L) after 24-48 hours of beginning insulin	Increase by 0.5 U
If nadir blood glucose is <72 mg/dL (<4 mmol/L) and no clinical signs of hypoglycemia.	Reduce dose by 0.25-0.5 U depending on whether cat is on low or high dose of insulin (greater or less than 3 U/cat) and severity of hypoglycemia
Phase 2: Increasing the dosage.	
If nadir blood glucose concentration >300 mg/dL (>16.6 mmol/L)	Increase every 3 days by 0.5 U
If nadir blood glucose concentration 200-300 mg/dL (11.1-16.6 mmol/L)	Increase every 3 days by 0.25-0.5 U depending on whether cat is on low or high dose of insulin and severity of hyperglycemia
If nadir blood glucose concentration 117-<200 mg/dL (6.5-<11 mmol/L) and peak is >200 mg/dL (>11 mmol/L)	Increase every 5-7 days by 0.25-0.5 U depending on whether cat is on low or high dose of insulin, and severity of hyperglycemia
If nadir blood glucose is <63 or <72 mg/dL (<3.5 or <4 mmol/L)	Actual concentration used to decrease dose depends on frequency of monitoring and previous response to insulin dose changes when blood glucose is around the lower limit of the normal range. Reduce dose by 0.25-0.5 U depending on whether cat is on low or high dose of insulin. If clinical signs of hypoglycemia occur, reduce dose by 0.5 to >1 U depending on severity
If blood glucose at the time of the next insulin injection 72-117 mg/dL (4-6.5 mmol/L)	Initially test which of the alternate methods is best suited to the individual cat: a. Feed cat and reduce the dose by 0.25-0.5 U depending on whether cat is on low or high dose of insulin b. Feed the cat, wait 1-2 hours and when the glucose concentration increases to >117 mg/dL (>6.5 mmol/L) give the normal dose. If the glucose concentration does not increase within 1-2 hours, reduce the dose by 0.25 U or 0.5 U (as above). c. Split the dose: feed cat, and give most of dose immediately and then give the remainder 1 to 2 hours later, when the glucose concentration has increased to >117 mg/dL (>6.5 mmol/L) If all these methods lead to increased blood glucose concentrations, give the full dose if pre-insulin blood glucose concentration is 72-117 mg/dL (4-6.5 mmol/L) and observe closely for signs of hypoglycemia. In general for most cats, the best results in phase 2 occur when insulin is dosed as consistently as possible, giving the full normal dose at the regular injection time.
Phase 3: Holding the dosage. Aim to keep blood glucose concentration within 72-200 mg/dL (4-11 mmol/L) throughout the day.	
If nadir blood glucose is <63 or 70 mg/dL (<3.5 or 4 mmol/L)	Reduce dose by 0.25-0.5 U depending on whether the cat is on low or high dose of insulin
If nadir or peak blood glucose	Increase dose by 0.25-0.5 U depending on whether the cat is on low or high dose of

concentration >200 mg/dL (>11.0 mmol/L)	insulin and the degree of hyperglycemia
Phase 4: Reducing the dosage. Phase out insulin slowly by 0.25-0.5 U depending on dosage.	
When the cat regularly (every day for at least one week) has its lowest blood glucose concentration 63-117 mg/dL (4-6.5 mmol/L), and stays under 117 mg/dL (6.5 mmol/L) overall	Reduce dose by 0.25-0.5 U depending on whether the cat is on low or high dose of insulin
If the nadir glucose concentration is 55-<63 mg/dL) (3-<4 mmol/L) at least three times on separate days	Reduce dose by 0.25-0.5 U depending on whether the cat is on low or high dose of insulin
If nadir is <55 mg/dL (<3 mmol/L) once	Reduce dose immediately by 0.25-0.5 U depending on whether the cat is on low or high dose of insulin
If peak blood glucose concentration >200 mg/dL (>11 mmol/L)	Immediately increase insulin dose to last effective dosage
Phase 5: Remission. Euglycemia for a minimum of 14 days without insulin. Monitor blood glucose at least 2 to 3 times daily for 14 days to ensure it remains ≤117 mg/dL (≤6.5 mmol/L), then 1 to 2 times weekly thereafter. If blood glucose increases to 117-<180 mg/dL (6.5-<10 mmol/L), institute other therapy such as insulin sensitizers or GLP-1 agonists to maintain blood glucose ≤117 mg/dL (≤6.5 mmol/L); if ≥180 mg/dL (≥10 mmol/L), reinstitute insulin once or twice a day depending on severity of hyperglycemia.	

Significantly lower mean blood glucose concentrations at day 17, and significantly higher remission rates were achieved by 16 weeks of treatment with glargine (8/8 cats), compared to lente insulin (2/8) and PZI (3/8) in newly diagnosed DM, fed a low carbohydrate diet (6% of energy from carbohydrate) and given insulin q 12 h.[8] Eighty-four percent of 55 DM cats achieved remission within 6 months of diagnosis after being treated with glargine and using a protocol aimed at achieving euglycemia.[94]

In humans with type 1 and type 2 DM, fewer hypoglycemic episodes are reported with glargine compared to shorter-acting insulins.[126,127] While biochemical hypoglycemia (<54 mg/dL or <3 mmol/L) occurred in newly diagnosed DM cats treated with glargine, none of 8 cats developed clinical signs, compared to 2 cats treated with lente and 1 cat treated with PZI.[8] In a larger study of 55 cats treated with glargine and a protocol aimed at achieving euglycemia, biochemical hypoglycemia (<50 mg/dL or <2.8 mmol/L) was frequent when measured with a glucose meter calibrated for whole human blood, although only one cat developed mild signs of clinical hypoglycemia (restlessness).[94] Glargine is our first choice of insulin in cats and can also be used for treatment of DKA (see ch. 142).[128]

Detemir (Levemir, NovoNordisk)

Detemir (see ch. 304) is a long-acting human insulin analogue (100 U/mL). The B30 amino acid threonine is removed and a 14-carbon, myristoyl fatty acid is covalently bound to lysine at position B29.[121] The protracted action of detemir is a result of slow absorption into blood after injection because it self-associates into hexamers and dihexamers that also reversibly bind to albumin, prolonging residence time at the injection site. Some further retention occurs in the circulation associated with albumin binding.[121,129,130] In type 2 DM humans, detemir and glargine are similar in action, but detemir has less variability in effect.[130] While q 24 h dosing is adequate in humans to provide basal insulin concentrations, duration of action in healthy cats using the euglycemic clamp method is shorter and q 12 h is recommended.[122] Detemir has a slightly later onset of action compared to glargine (1.8 hours, range 1.1–2.5 vs. 1.3 hours, range 0.9-1.6) in healthy cats using the euglycemic clamp method. Duration of action (11.7 hours, range 9.1-14 compared to 10 hours, range 6.6-13) and end of action (13.5 hours, range 11-16 compared to 11.3 hours, range 8-14.5) were not significantly different from glargine, but there was less variability between cats than with glargine.[122]

Initial dosages and protocol for dosage increases are the same as for glargine (see Tables 305-3, 305-4, and E-Table 305-5).[97,118] Most cats initially require about 25-30% less detemir than glargine (1.75 U compared to 2.5 U), although final dosages may be similar.[94,97] Cats can exhibit an initial increased sensitivity to detemir, which is transient and typically lasts for 24-48 hours. Therefore, if changing from glargine or other insulin, start with about half the current insulin dosage and increase within 48 hours if insufficient glucose lowering is

occurring. Increase the dosage every 3-7 days until blood glucose is controlled. Similar to findings in glargine-treated cats, remission occurred in 81% of cats treated with detemir within 6 months of diagnosis and a protocol aimed at euglycemia, whereas this was only 42% if tight glycemic control was delayed for 6 months or longer.[97] Detemir is our second choice insulin due to less experience, but cats on glargine with poor control, especially with short duration of action, should be tried on detemir while looking for concomitant disease.

E-TABLE 305-5

Simplified Home Blood Glucose Monitoring Protocol for Clients Dosing Glargine and Using Only Pre-Insulin Blood Glucose Concentration to Adjust Dosage (Glucose Cutpoints Are for a Human Plasma-Equivalent Glucometer)

Pre-Insulin Blood Glucose	
Newly Diagnosed Diabetics (<2 Months Insulin Therapy)	
Blood glucose concentration >215 mg/dL (>12 mmol/L)	Increase the dose by 0.5 U
Blood glucose concentration 108-215 mg/dL (6-12 mmol/L)	Keep the dose the same
Blood glucose concentration 54-<108 mg/dL (3-<6 mmol/L)	Decrease the dose by 0.5 U
Blood glucose concentration <54 mg/dL (<3 mmol/L)	Do not give insulin and call the clinic to discuss. If signs of hypoglycemia, measure blood glucose and call clinic immediately.
Longer-Term Diabetics (>2 Months Insulin Therapy)	
Blood glucose concentration >450 mg/dL (>25 mmol/L)	Increase the dose by 1 U
Blood glucose concentration 252-450 mg/dL (14-25 mmol/L)	Increase the dose by 0.5 U
Blood glucose concentration 108-<252 mg/dL (6-<14 mmol/L)	Keep the dose the same
Blood glucose concentration 72-<108 mg/dL (4-<6 mmol/L)	Decrease the dose by 0.5 U
Blood glucose concentration <72 mg/dL (<4 mmol/L)	Do not give insulin and call clinic to discuss. Check for diabetic remission depending on insulin dose.

If using a meter calibrated for feline blood, increase glucose cutpoints by 9 mg/dL or 0.5 mmol/L). Protocol used in a feline-only practice for 8 years in >80 diabetic cats (unpublished data Marshall and Gottlieb).

Insulin Storage

The manufacturer's recommended shelf-life at room temperature after opening glargine is 28 days and 6 weeks for detemir. However, they are relatively stable in solution, and many owners of DM cats effectively use refrigerated glargine or detemir for 6 months or longer. The short expiration periods on multiple-use injectable medication vials, even if a preservative is present, is due to the FDA's assessment of bacterial contamination risk, which is extremely low. Glargine and detemir preparations contain the antimicrobial preservative meta-cresol, which is bacteriostatic and most effective at room temperature. Owners should be instructed to immediately dispose of insulin appearing cloudy or discolored.

Administering Small Doses of Glargine and Detemir

Administering small doses using 100 U/mL insulin (detemir or glargine) can be problematic and limits their use when doses of less than 1 U are required. Dosing pens are recommended for doses less than 2 U, providing better accuracy, stability, and minimizing risk of bacterial contamination compared to diluting insulin.[131-133] Insulin dosing pens such as the HumaPen Luxura HD (Eli Lilly) and the NovoPen Junior

(USA)/Demi (other countries) (NovoNordisk) deliver accurate and precise insulin doses in 0.5 U increments (see ch. 304). However, in some cats, particularly those going into remission and regaining some beta-cell function, dosage adjustments may be required in increments less than 0.5 U.

Detemir can be diluted using a special diluting medium available from NovoNordisk, but in some countries the company will not supply this to veterinarians. Detemir can also be diluted with sterile water or saline, but this also dilutes the antimicrobial additive (meta-cresol).[134] Minimize bacterial contamination risk by diluting just prior to each administration. If diluted in a bottle and kept refrigerated, discard insulin after 30 days. Potency may be adversely affected using this method. Neither dilution nor mixing with other insulins is recommended for glargine. However, humans with DM have successfully mixed glargine with other insulins, despite a cloudy precipitate forming in the syringe.[135] Dilution of both detemir (1 : 10) and glargine (1 : 100) with saline is reported for management of transient human neonatal DM to facilitate administration of very small doses, although the effect of dilution on efficacy or stability has not been reported for humans or cats.[134]

Choosing an Insulin

Prior to the availability of long-acting insulin, the aims of treating DM cats were to resolve clinical signs and improve quality and length of life. Given the high rates of DM remission when using long-acting insulin, low carbohydrate diets, and protocols aimed at achieving normal or near-normal blood glucose concentrations, insulin should be chosen to maximize this opportunity. DM remission has welfare advantages for the cat, cost advantages for owners, and quality of life advantages for both. Glargine and detemir are associated with the highest rates of remission in cats with newly diagnosed DM. These should be the first choice insulins for a newly diagnosed DM cat. However, neither glargine nor detemir is registered for use in cats. In some countries, laws require use of veterinary-approved products first, and only allow off-label use of glargine or detemir if there is failure of treatment. If use of veterinary-registered insulin is legally mandated, PZI is recommended, but it is only available in a limited number of countries.

Diet

Background

The role of diet in the management and prevention of DM is unquestioned (see ch. 181). Commercial feline dry food diets derive up to 60% of energy from carbohydrates (mean 41%).[25,136,137] Cats are obligate carnivores and, based on meta-analysis of data from 27 studies of natural prey of feral cats, their mean daily energy intake is about 2% carbohydrate (nitrogen free extract), 52% crude protein, and 46% crude fat.[138] Cats are relatively glucose intolerant as compared with dogs and humans.[1,139-141] There is evidence that cats limit intake when carbohydrate content is >40% ME (E-Table 305-6).[139,142-145]

E-TABLE 305-6

Characteristics of Glucose Metabolism in Cats, Some of Which Contribute to the Higher and Longer Postprandial Increase in Blood Glucose Concentrations and Relative Glucose Intolerance Following a High Carbohydrate Load in Cats Compared to Dogs

Markedly reduced or absent hepatic glucokinase concentrations[252,253]	• Cats rely on low-capacity hexokinase to clear a glucose load
Delayed gastric empyting[143]	• When fed mean energy requirement (MER) once a day and food is consumed shortly after feeding, food is slowly released from the stomach over 24-26 hours. When fed 50% MER, food is released over 12-14 hours.
Reduced and delayed insulin secretion[139]	After high protein, low carbohydrate meal with added glucose (2 g/kg) in dogs and cats • Peak insulin secretion was half that of dogs and occurred three times later (210 min versus 90 min) • Peak glucose concentration was higher in cats (10.0 mmol/L; 180 mg/dL versus 6.3 mmol/L; 114 mg/dL) • Peak glucose concentration occurred later in cats (120 min versus 60 min)

	• Return to baseline for glucose concentration was longer in cats (270 min versus 90 min), indicating relative glucose intolerance compared to dogs
Reduced small intestinal disaccharidase activity139,254	• Prolongs glucose absorption from the gastrointestinal tract, and reduces peak postprandial concentrations
Reduced downregulation of gluconeogenic pathways255	• Hepatic glucose production continues after eating even after a high carbohydrate meal

Role of Diet in Preventing Diabetes

Overweight cats have 4.6 times greater risk of DM than cats in ideal body condition and obesity is the most important acquired risk factor (see ch. 176).[24,77] Approximately 25 to 63% of cats are overweight or obese and 20% of obese cats >8 years of age are pre-DM with impaired glucose tolerance or impaired fasting glucose.[75,146-150] In cats, humans and dogs, carbohydrate is the principal macronutrient determining the magnitude of the postprandial increase in plasma glucose and insulin.[151-153] In either meal or *ad libitum* fed lean cats, carbohydrate results in significantly higher postprandial blood glucose concentrations than equivalent amounts (% ME) of protein or fat. Peak glucose concentration was 151 mg/dL (8 mmol/L) or 31% higher for a high carbohydrate diet (carbohydrate 47% ME, 12.9 g/100 kcal) than for a high protein diet (protein 46% ME, carbohydrate 27% ME, 7.1 g/100 kcal) with a peak of 115 mg/dL (6 mmol/L) ($P < 0.001$). Postprandial insulin concentrations had a similar trend.[153] There also was a consistent trend for glucose and insulin concentrations to be lowest for the high protein diet compared to the high fat diet (both with 27% ME from carbohydrate).

Importantly, the magnitude and duration of postprandial hyperglycemia is exacerbated by weight gain.[32,154] In overweight cats fed a high carbohydrate commercial diet (51% ME; 14.5 g/100 g/kcal), mean postprandial glucose concentrations over 24 hours were 119 ± s.d. 18 mg/dL (6.6 ± 1 mmol/L) and peak glucose concentrations were as high as 241 mg/dL (13.4 mmol/L) and in the DM range for cats.[77,154] Feeding high fat diets in excess of maintenance energy requirements is associated with obesity, and therefore increases the risk of DM.[150,155,156] One study comparing wet and dry foods found that cats fed only wet diets (higher in fat, lower in carbohydrate) had 3 times higher risk of DM, while feeding only dry diets (higher carbohydrate, lower fat) was associated with 2 times higher risk, suggesting that the adverse effect of obesity from a higher fat diet is a greater risk for DM, although a higher carbohydrate intake also increases risk, presumably from increased postprandial glycemia.[24] While high carbohydrate diets (≥50% ME) may have insufficient protein for cats, moderate carbohydrate diets (20-30% ME) are unlikely to be detrimental to young adult, lean cats with normal beta-cell function. However, diets with ≤12% of energy from carbohydrate are indicated for cats at increased risk of DM. Since age is a risk factor for DM, older cats with other risk factors (breed, corticosteroid use, obesity) would likely benefit from a low carbohydrate diet to minimize the insulin secretion required to maintain euglycemia.[157]

Role of Diet in Managing Diabetes (see ch. 181)

The primary goal in managing feline DM is to achieve remission. Minimizing dietary carbohydrate (CHO) reduces demand on pancreatic beta-cells to produce insulin. Data from a number of studies in DM cats indicate that low-carbohydrate diets (≤13% ME; <4 g/100 kcal ME) may improve glycemic control, reduce fructosamine concentration and increase the probability of diabetic remission.[8,94,95,97,158,159] When fed over 16 weeks to 63 diabetic cats (11 newly diagnosed and 52 previously diagnosed), a low carbohydrate–low fiber diet (12% ME; 3.5 g CHO/100 kcal) resulted in significantly higher remission rates (68% versus 41%) and better glycemic control based on resolution of clinical signs and serum fructosamine concentrations <400 mcmol/L (81% versus 56%) compared with a moderate carbohydrate–high fiber diet (7.6 g CHO/100 kcal, 26% ME).[95] There are no reported studies comparing diets of ≤6% ME with 12% ME.[98] However, the highest reported remission rates (>80%) are associated with using a carbohydrate restricted diet (<6% ME) combined with insulin protocols aimed at achieving normal or near-normal blood glucose concentrations.[8,94,97] In long-term obese DM cats who have not lost weight or achieved remission with appropriate management, DM remission is unlikely. Priority should then be given to achieving an ideal body condition to reduce the risk of other comorbidities associated with obesity in cats.

Normalizing body condition and muscle mass are dietary goals and controlled weight loss via energy restriction is important.[157] Although remission may occur prior to significant weight loss, achieving ideal body condition is likely important for maintaining remission and improving insulin sensitivity.[47,93,94] A suitable weight loss diet for a DM cat is fat <4 g/100 kcal, carbohydrates <3 g/100 kcal and protein >10 g/kcal, however, energy intake must also be controlled.[157] Canned food helps decrease energy intake and body weight because moisture increases food volume and hydration.[160]

Chronic kidney disease (CKD) is reported in 26-62% of DM cats (see ch. 324).[94,97] Controlled amounts of protein and restricted phosphorus improve survival time in cats with CKD and, therefore, high-protein and low-carbohydrate diabetes diets are likely contraindicated, especially in cats with IRIS 2 or 3 CKD (see ch. 184).[161] If a cat has a good appetite, administering acarbose with a moderate-carbohydrate prescription renal diet may assist in reducing postprandial glucose concentrations.[162] Grocery-line ultra-low carbohydrate diets (≤2% ME), mostly fish or meat-based, are often considerably higher in phosphorus than available veterinary prescription diets designed for feline DM and should be avoided in CKD.

Oral Hypoglycemics

Background

Oral hypoglycemic medications may be used as the sole therapy in diabetics with sufficient endogenous insulin to maintain euglycemia or combined with insulin therapy. The oral drugs act by stimulating insulin secretion from pancreatic beta-cells, increasing insulin sensitivity in tissues, or slowing intestinal absorption of glucose.[163] In general, unless the client would otherwise elect euthanasia, oral hypoglycemic drugs are not recommended as sole agents in newly diagnosed DM cats with overt signs because their glycemic control is far better with insulin.[8,106,173] However, oral hypoglycemics could be effective in managing subclinical or pre-DM in cats, and in some cats, when combined with insulin therapy.

Sulfonylureas

Sulfonylureas stimulate insulin secretion from pancreatic beta-cells by binding to ATPases, which sequentially close potassium (K) and open calcium (Ca) channels in cell membranes. The resulting influx increases intracellular Ca concentrations, triggering release of stored insulin.[164,165] Glipizide is the most often used sulfonylurea in cats. It improved signs in 30% of DM cats, with 15% having good to excellent control based on near-normal blood glucose concentrations, resolution of clinical signs and no glycosuria.[106,166] However, 56% had worsening of glucose concentrations and required insulin.[106] DM remission has been reported in only 12% of newly diagnosed cats treated with glipizide.[106] Cats most likely to respond are non-ketotic, have mild signs of DM, acceptable body condition and good health.[167] Recommended starting dose is 2.5 mg PO q 12 h with food, which can be increased to 5 mg PO q 12 h if no improvement in glycemic control is noted.[166,167] In 5-10% of cats, glycemic control becomes inadequate within weeks to years, necessitating insulin therapy.[166,168]

Meglitinides

These drugs also stimulate insulin secretion by binding to ATPases on pancreatic beta-cells at different sites than the sulfonylureas, and trigger the same cascade of reactions. Synergistic effects occur when the 2 are combined.[164,169] The effect of the meglitinide nateglinide on blood glucose and insulin secretion were compared with the sulfonylurea glimepiride in healthy cats using a 0.5 g/kg IV glucose tolerance test. Nateglinide had a faster onset of action (20 minutes vs. 60) but shorter duration of action (60 minutes vs. 180).[170]

Biguanides

Biguanides have an insulin sensitizing effect that requires functional beta-cells since they increase hepatic and peripheral tissue response to insulin thereby decreasing glucose production and increasing glucose uptake.[169-171] Although the exact mechanism of action is unknown, they interrupt mitochondrial oxidative processes in the liver and correct imbalances in intracellular Ca metabolism in peripheral tissues.[172]

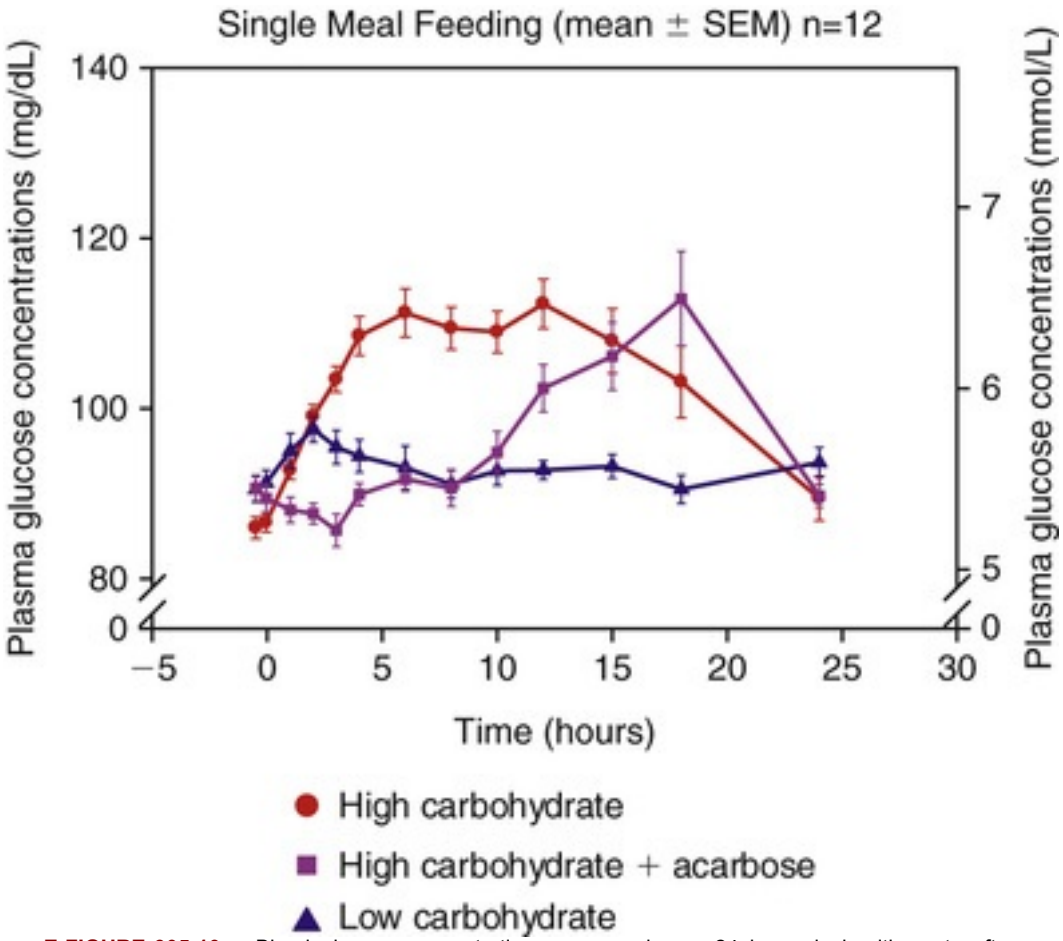
Metformin, the only commercially available biguanide, was given to 5 newly diagnosed DM cats (mean blood glucose concentrations 487 mg/dL or 27 mmol/L); 1 of the 5 had measurable serum insulin concentrations pre-treatment and this was the only cat that achieved good glycemic control (mean blood glucose concentration 167 mg/dL or 9.3 mmol/L). That cat required a dose of 50 mg PO q 12 h for >8 weeks.[173]

Thiazolidinedione

Thiazolidinediones (TZDs) bind to the peroxisome proliferator-activated receptor-gamma in the nucleus and alter gene expression, leading to improved insulin sensitivity in adipose tissue, muscle and liver.[174,175] This decreases hepatic gluconeogenesis and increases glucose metabolism in muscle, resulting in decreased fasting blood glucose concentrations.[174] Darglitazone increased insulin concentrations in obese cats during an IV glucose tolerance test, but did not normalize their insulin secretion pattern.[87]

Alpha-Glucosidase Inhibitors

Drugs such as acarbose reduce postprandial blood glucose concentrations by inhibiting action of membrane-bound brush-border disaccharidases (glucoamylase, sucrose, isomaltase, maltase) in the small intestine. By delaying breakdown of complex carbohydrates, they slow intestinal glucose absorption and reduce peak postprandial glucose concentrations.[166,169] In healthy cats, acarbose administered at 25 mg/cat PO q 24 h with a high carbohydrate meal (50% energy from carbohydrate) significantly reduced mean glucose concentrations in the first 12 hours compared to cats fed the meal alone (91 mg/dL or 5.1 mmol/L vs. 106 mg/dL or 5.9 mmol/L) (E-Figure 305-10).[162] However, blood glucose concentrations were not significantly lower (93 mg/dL or 5.2 mmol/L) than cats fed a low carbohydrate meal (6% energy from carbohydrate) and there was no difference in mean blood glucose concentrations when the low carbohydrate diet was fed with or without acarbose.[162] The glucose lowering effect was only evident in the first 12 hours after acarbose administration and was minimally effective in cats eating multiple small meals. In cats with CKD, where a restricted-protein, moderate-carbohydrate diet is indicated, acarbose can be used to reduce glucose absorption from the gastrointestinal tract. However, because acarbose is most effective when cats consume all their food within a short time after administration, it is likely to be minimally effective in cats with IRIS stage 3 or 4 CKD that have reduced appetite and consume small amounts of food multiple times daily. Acarbose administered at 12.5 mg/cat PO q 12 h, with a low carbohydrate diet were not associated with greater reductions in median insulin requirements or glycemic control than cats fed the low carbohydrate diet alone (insulin dosage reduction from 5 U/cat SC q 12 h to 1 U/cat SC q 12 h).[159]



E-FIGURE 305-10 Blood glucose concentrations measured over 24 hours in healthy cats after eating a meal of a high carbohydrate (50% ME) or low carbohydrate (6% ME) diet. Note that blood glucose concentrations after eating a high carbohydrate diet remain elevated for 20 hours after eating, and are significantly higher than after eating a low carbohydrate diet. Some cats fed the high carbohydrate diet were given acarbose 25 mg/kg orally at the time of feeding. Acarbose decreases blood glucose concentrations for 8 hours after eating. Feeding a low carbohydrate diet is as effective as acarbose. (From Singh R, Rand J, Coradini M, et al: Effect of acarbose on postprandial blood glucose concentrations in healthy cats fed low and high carbohydrate diets. *J Feline Med Surg* 17[10]:848-857, 2015.)

Trace Elements

Chromium, vanadium and tungsten may improve insulin sensitivity. Chromium is a cofactor for insulin function that increases glucose transport to the liver, adipose tissue and muscle.[169] Oral supplementation at doses of greater than 300 ppb resulted in improved glucose tolerance, with doses of 600 ppb leading to a significant decrease in blood glucose concentration (139 mg/dL or 7.7 mmol/L compared to 150 mg/dL or 8.3 mmol/L) in healthy normal weight cats.[176] Lower doses of 100 mcg in obese cats had no effect on glucose tolerance.[177] Vandium at 0.2 mg/kg/day reduced blood glucose and serum fructosamine concentrations and improved clinical signs (polyuria and polydipsia) in cats with early DM.[178] In DM cats treated with PZI, vanadium supplementation at 45 mg/cat/day improved glycemic control, with a mean insulin requirement of 3 U in vanadium-supplemented cats compared to 5 U in cats treated with PZI alone.[179]

New and Emerging Therapies

Incretin-Based Therapies

Incretins are gastrointestinal hormones (see ch. 310) rapidly released in response to food intake that stimulate synthesis and release of insulin while suppressing glucagon secretion.[180] They include glucagon-like peptide

1 (GLP-1), secreted by L cells in the distal portion of the intestinal tract that bind to G-protein-coupled receptors in pancreatic alpha and beta-cells.[180-182] GLP-1 also enhances beta-cell survival, delays gastric emptying, and suppresses appetite.[181,182] GLP-1 has a short half-life and is degraded by dipeptidylpeptidase-4 (DPP-4), found in various tissues and the plasma. Within the intestine it degrades GLP-1 by cleaving the molecule and decreasing receptor affinity.[181,183] GLP-1 concentrations are reduced in obese cats and humans after glucose challenge. The insulinotropic effect of GLP-1 is reduced in human type 2 DM.[184-187]

Additional drugs include GLP-1 agonists that are resistant to DPP-4 degradation, and DDP-4 inhibitors.[185,188] As GLP-1's actions are glucose dependent, hypoglycemia is rare.[186] Exenatide (twice-daily) and extenatide extended-release (once weekly) are injectable GLP-1 agonist preparations used as adjunctive or sole therapy in human type 2 DM.[186] In healthy cats, exenatide (1 mcg/kg) increased insulin by 2.4 fold within 15 minutes during a hyperglycemic isoglycemic clamp.[189] During a meal response test in healthy cats, 2 mcg/kg (exenatide) and 200 mcg/kg (extended release) were the optimum dosages, increasing insulin concentrations by 330% and 178%, respectively.[190] In healthy cats, insulin response after a meal was similar comparing exenatide, exenatide extended-release, and the DPP-4 inhibitor sitagliptin.[191] Transient mild gastrointestinal effects (vomiting and diarrhea) were seen with all 3 drugs. In newly diagnosed DM cats treated with glargine and a low-carbohydrate diet, cats also treated with exenatide extended-release tended to improved glycemic control, lower insulin dose, and higher remission rates (44% vs. 25%) compared with placebo-treated cats.[192] Mild and transient adverse-effects included reduced appetite, nausea, and vomiting.

Amylin

Amylin, co-secreted with insulin from pancreatic beta-cells, suppresses glucagon secretion, delays gastric emptying and promotes satiety.[193,194] In DM, decreases in amylin production are associated with pancreatic beta-cell dysfunction and loss.[193,195] In human type 1 and type 2 DM patients using insulin, the synthetic amylin analogue pramlintide injected at meal times decreased postprandial glucose concentrations and insulin dose, decreased energy intake, improved postprandial satiety and induced weight loss.[194,196,197] In healthy cats, amylin given 5 minutes before beginning an IV arginine stimulation test (0.2 g/kg), IV glucose tolerance test (0.5 g/kg) or meal response test caused a decrease in plasma glucagon and insulin concentrations in the IV arginine and glucose tolerance tests.[198]

Smart Insulin

One synthetic insulin product designed to be long-lasting and responsive to glucose concentrations displayed activities similar to that of healthy mouse pancreas. Addition of an aliphatic domain to the insulin facilitates hydrophobic interactions and provides longer residence time in blood. An attached phenylboronic acid (PBA) molecule reversibly binds glucose, resulting in activation of insulin only when glucose concentrations are high.[199] Clinical trials are pending.

Poorly Controlled Diabetic Cats

Differential Diagnosis

While good glycemic control or remission is achieved in most DM cats once appropriate insulin therapy and monitoring are instituted, some cats are difficult to control, often requiring high doses of insulin. Failure to achieve clinical and glycemic control of DM may be due to poor owner compliance or administration technique, inappropriate insulin or dosing (dosage and/or frequency), or underlying diseases contributing to insulin resistance.

Storage, Mixing, Syringes

Inappropriate storage of insulin leading to loss of potency, incorrect administration (e.g., poor injection technique, drawing up some air bubbles) or irregular dosing can each contribute to poor glycemic control.[74] Inadequate mixing of lente insulin suspension can result in erratic dosing because insulin concentrations vary with each dose. These should be ruled out by discussion with clients before further investigation. These factors may be easily rectified with proper education. Insulin dosing errors can occur when one type of syringe is changed for another and the owner continues to dose insulin based on number of gradations on the

syringe barrel. For example, if a cat receiving porcine lente insulin (40 U/mL, Vetsulin/Caninsulin, Intervet) and normally dosed with 40 U/mL syringes (1 gradation = 0.025 mL) has the type of syringe inadvertently changed to 0.3 mL, 100 U/mL syringes (1 gradation = 0.01 mL), it will result in only 40% of the dose being administered. Similar errors occur when 0.3 mL syringes are accidently dispensed to a client using 1 mL insulin syringes (1 gradation = 0.02 mL). However, if the substitution is in reverse, it may appear there is increased sensitivity to insulin leading to hypoglycemia.

Short Duration of Insulin Action

In cats treated with intermediate-acting insulin such as lente, duration of action may be too short to maintain prolonged decreases in blood glucose concentration even when given q 12 h.[111,119] Nadir blood glucose concentration is reached 3 to 5 hours after porcine lente injection in DM cats, and blood glucose concentrations typically return to baseline within 9-10 hours.[110,111] Therefore, most cats treated q 12 h with porcine lente insulin have no appreciable glucose lowering effect from exogenous insulin for 2 to 3 hours prior to each insulin injection. Continued presence of basal insulin concentrations is important in suppressing hepatic gluconeogenesis.[200] The short duration of action likely accounts for the marked hyperglycemia (≥360 mg/dL; 20 mmol/L) prior to each insulin injection in many lente-treated cats, even when there is good glucose lowering following insulin administration, and appropriate nadir concentrations are achieved. Serial blood glucose measurements, especially if measured at home, can help identify this problem. In these cats, a change to longer-acting insulin such as glargine or detemir typically resolves the poor control.

Underlying Disease

Background

Underlying diseases can contribute to insulin resistance and poor control despite good client compliance and appropriate insulin selection and dosing. Further testing should be offered if insulin doses exceed 1.0-1.5 U/kg q 12 h, and blood glucose control remains poor (mean blood glucose >270 mg/dL or >15 mmol/L).

Acromegaly

Acromegaly, or hypersomatrotropism, results from increased production of growth hormone (GH), typically due to a pituitary adenoma (see ch. 294). Increased GH causes post-receptor defects in insulin action at target tissues. This insulin resistance may be extreme.[14] Despite substantial beta-cell hyperplasia, insulin resistance may exceed the insulin secretory capacity to maintain euglycemia resulting in concurrent DM.[14] Secretion of insulin-like growth factor 1 (IGF-1) also increases, mediating the associated anabolic changes.[201] Common clinical signs of acromegaly in cats include polyuria and polydypsia, polyphagia and weight gain. Enlarged abdominal organs, a systolic heart murmur, broadening of the facial features, prognathia inferior, clubbed paws and respiratory stridor may also occur as the disease progresses. Initially, many cats with acromegaly appear normal.[16] Acromegaly, with its anabolic effects, should be considered in the differential diagnosis of any poorly controlled DM cat with stable or increasing body weight.[14,202] Acromegaly is the most common underlying disease in poorly controlled DM cats, perhaps accounting for 25-30%.[15,201,203] A small minority of DM acromegalic cats initially respond to insulin and occasionally even achieve remission. However, acromegalic cats typically require more than twice the insulin of non-acromegalic DM, with median doses of 7 U q 12 h (range 1-35 U), and some doses are so extreme (20 to >70 U) they would induce fatal hypoglycemia in most cats with DM.[16,201]

IGF-1 testing is the most commonly used diagnostic test for acromegaly, with concentrations typically increased >1000 mg/mL in afflicted cats.[201] Because production of IGF-1 is dependent on stimulation of hepatic GH receptors by insulin, the insulinopenia present at the time of DM diagnosis may falsely lower results. It is recommended that IGF-1 testing be delayed until 6 to 8 weeks after insulin therapy is started.[16] In practical terms, it is rare to identify insulin resistance before 6 weeks after initiation of therapy because insulin dose is slowly increased and some weeks are often required before resistance would be recognized. Intracranial imaging with magnetic resonance imaging or computed tomography is also useful to confirm diagnosis, particularly if curative treatment is being considered. Treatment options include palliation with insulin, surgery, radiation and medical management. Surgical hypophysectomy has high success rates and the majority of cats achieve diabetic remission.[204,205] Radiation therapy may reduce tumor size and hormone secretion, but does not normalize GH and IGF-1 concentrations.[16,202,206] Both surgical and radiation treatment

are limited in their geographical availability. Although medical options have previously been unsuccessful, in a recent report, a novel somatostatin analogue (Pasireotide, Novartis) reduced insulin requirements of acromegalic cats, but is prohibitively expensive.[16] Palliation with high insulin doses is a conservative approach and is likely the most common method used. In some cats, it can be moderately successful in controlling clinical signs of DM for a period of time. Home blood glucose monitoring is recommended if increasing insulin doses are being used to control blood glucose concentrations, because of fluctuation in GH secretion, and therefore, of blood glucose concentrations.

Hyperadrenocorticism (HAC), Glucagonoma

HAC is characterized by excess endogenous glucocorticoids caused by either a functional pituitary tumor increasing secretion of adrenocorticotropic hormone (ACTH) and subsequently adrenal cortisol, or a functional tumor of the adrenal cortex increasing secretion glucocorticoids (see ch. 307).[16] Glucocorticoids induce DM by impairing insulin sensitivity, decreasing glucose uptake in peripheral tissues, increasing hepatic gluconeogenesis, and may inhibit insulin secretion from pancreatic beta-cells.[16] Excess cortisol concentrations commonly lead to abdominal fat accumulation, which also is a predisposing factor for insulin resistance and DM.[207-209] About 80% of cats with HAC have DM at the time of diagnosis.[202] HAC is a less common cause of insulin resistance than acromegaly, and rarely results in insulin doses as high.[16] There is concern that poorly controlled DM may increase activity of cats' hypothalamus-pituitary-adrenal gland axis that may cause abnormal test results. However, a low-dose dexamethasone suppression test performed in 22 diabetic cats 6 weeks after insulin therapy showed complete suppression at 4 and 8 hours in 20 cats regardless of glycemic control, concluding that this is a suitable test for diabetic cats. The remaining two cats had HAC.[210]

Glucagon is an insulin antagonist. Tumors producing glucagon would be expected to induce or worsen DM.

Pancreatitis

Pancreatitis can destroy pancreatic beta-cells, cause loss of function, and decrease tissue sensitivity to insulin (see ch. 289 and 291).[18,202] It may worsen glycemic control, decrease probability of DM remission, or be associated with DM relapse.[19,76] Pancreatitis can be difficult to diagnose, relying on interpretation of clinical signs, ultrasonography (US) and feline serum pancreatic lipase immunoreactivity (fPLI) assay results. While few DM cats have clinical signs of pancreatitis, about 60% have biochemical and imaging findings consistent with pancreatitis at diagnosis.[2,19] However, histologic evidence of pancreatitis is also common in non-DM cats (14-67%). The number of neutrophils, macrophages, T and B lymphocytes and pancreatitis scores were not different in DM and non-DM cats, making the clinical relevance of the findings debatable.[17,19,55,211]

Pancreatitis was only diagnosed in 14% of DM cats investigated for poor glycemic control.[2] DM cats with post-mortem histologic evidence of chronic pancreatitis had higher mean blood glucose concentrations than cats without histologic lesions, but this was not significant, nor was there a difference in mean survival time between the two groups.[2] The percentage of DM cats (83%) with increased fPLI >11 mmol/L was greater than for non-diabetic cats (66%), but there was no significant association between fPLI concentrations in DM cats and their glycemic control.[212] In 17% of DM cats, fPLI was markedly (>50 mcg/L) increased, whereas only moderate (20-50 mcg/L) or mild (12-20 mcg/L) increases were present in non-DM cats.[212] DM cats with chronic pancreatitis may benefit from budesonide, cyclosporine (5 mg/kg PO q 12 to 24 h), or chlorambucil (2 mg/cat PO q 48 to 72 h) if pancreatitis recurs frequently and is associated with poor glycemic and insulin resistance.[18,213] Cats diagnosed with acute pancreatitis around the time of DM onset can achieve remission and some may return to normal glucose tolerance with resolution of their disease.[18,76] However, acute necrotizing pancreatitis can be a cause of mortality in DM cats.[2]

Hyperthyroidism, Urinary Tract Infections (UTI), Other Conditions

Impaired glucose tolerance has been reported in hyperthyroid cats, but in DM cats, insulin resistance is not usually clinically appreciable (see ch. 301).[214] Infections of the urinary tract, oral cavity, skin or other organs may contribute to insulin resistance.[202] Decreased glucose tolerance, insulin resistance and hyperinsulinemia occur as side-effects of bacterial infections in humans.[215,216] About 12-13% of DM cats have a UTI (most often *E. coli*), perhaps due to decreased urine concentration and glucosuria (see ch. 330).[217,218] People with DM

have increased risk of fungal UTI *(Candida albicans* or *C. glabrata)* which have been reported in cats.[219,220]

Chronic Kidney Disease

Diabetic nephropathy, characterized primarily by glomerular disease, is diagnosed in 20-40% of DM people.[196] Hyperglycemia alters microvascular anatomy and causes glomerular damage by changing blood flow, vascular permeability, cell loss and decreased production of trophic factors.[221] Although CKD is common in older cats, DM nephropathy is an uncommon histological finding (see ch. 324). However, 50% of DM cats had glomerular changes compatible with those seen in DM people and 33% had tubule-interstitial changes.[222] In non-DM cats with CKD, glomerular lesions were identified in 15% and tubulointerstitial disease in 70%.[223] In people, DM nephropathy begins with microalbuminemia and progresses to overt proteinuria.[196] Microalbuminemia and urine protein/creatinine ratio were demonstrated to be significantly higher in DM cats (70% and 70%, respectively) compared with healthy controls (18% and 9%, respectively).[224,225] Research is needed to study the importance of proteinuria in cats with DM. Urea and glucose were significantly higher in cats in DM remission compared to control cats, even after exclusion of cats with IRIS stage ≥2 CKD. The increase in urea may be because it is a by-product of the glucose-alanine cycle. Pyruvate in muscle is converted to alanine and transported to the liver where it is converted to pyruvate, releasing urea. Pyruvate is a substrate for gluconeogenesis, a likely contributor to the mild hyperglycemia in these cats.[226]

Hypoglycemia

Diagnosis and Management

Physiology and Signs

Hypoglycemia is a potential complication of insulin treatment in any diabetic (see ch. 61 and 303). In cats, low glucose can be a mainly biochemical, asymptomatic issue or it can be symptomatic. Signs of hypoglycemia variably appear at blood glucose concentrations <60 mg/dL (<3.5 mmol/L) and severe hypoglycemia (≤18 mg/dL or 1 mmol/L) is life-threatening.[227,228] The brain is unable to synthesize or store glucose. It requires a continual supply from the blood and the cells do not require insulin for use.[227-230] Clinical signs of hypoglycemia in cats include lethargy, trembling, depression, ataxia, or in severe cases, seizures and coma. In people, repeated episodes of hypoglycemia can impair compensatory responses and result in hypoglycemic unawareness. Early clinical warning signs such as trembling, normally triggered in response to epinephrine release, are absent. In these individuals, sudden onset of seizures or coma are associated with neuronal glycopenia.[231] A similar condition has been reported in dogs and may occur in cats.[89,232] In humans, cut-offs for biochemical hypoglycemia have been determined based on the threshold for glucagon and epinephrine activation (<70 mg/dL or <3.9 mmol/L).[231] In cats, blood glucose concentrations <50 or 54 mg/dL (<2.8 or 3 mmol/L) have been used as indicators of biochemical hypoglycemia when measured with a meter calibrated for whole human blood.[8,94] When measured with a meter calibrated for feline blood, the lower limit was 50 mg/dL (2.8 mmol/L) in cats fasted and hospitalized overnight.[76]

Iatrogenic hypoglycemia in DM occurs due to insulin overdose. This may occur in cats recovering the ability to synthesize and secrete endogenous insulin, i.e., pending remission.[8] In this scenario, there is risk of administering too much insulin when blood glucose concentrations are no longer high. Other common causes of overdose leading to hypoglycemia include errors in drawing insulin into a syringe or when an incorrect syringe is used. Such errors can be life-threatening and not detected until serious hypoglycemia occurs. The hypothalamus contains glucose sensing neurons that detect and respond to hypo- or hyperglycemia.[227] Rapid compensation for hypoglycemia occurs by inhibiting insulin production while stimulating pancreatic glucagon and adrenal epinephrine.[228] Decreasing pancreatic insulin cannot occur in DM, since the insulin was administered exogenously.[231] Glucagon increases hepatic glycolysis and gluconeogenesis. Epinephrine acts on both the liver and kidney to increase glucose production.[200,228] However, glucagon's production by pancreatic alpha-cells in response to hypoglycemia can be absent or diminished in DM, secondary to lack of signaling from pancreatic beta-cells.[229]

Management

If possible, hypoglycemic cats are fed a high carbohydrate meal (>35% of energy from carbohydrate) and insulin therapy discontinued until hyperglycemia recurs (recommendations vary from >117 to >216 mg/dL; >6.5 mmol/L to >12 mmol/L). Subsequent insulin doses should be reduced by 25-50%.[89,233] If more severe signs occur, such as ataxia, a glucose containing syrup designed for human or veterinary DM patients can be administered orally or mixed in food (give 0.5-1 g and repeat 15-20 min later if required). Honey or maple syrup can be used in home emergencies, but Karo syrup (corn syrup with 15-20% glucose) is preferred. In an emergency, prior to or during transport to the hospital, one can rub glucose solutions onto the gums or give them via enema.[227,234] In-hospital treatment typically consists of an initial IV dextrose bolus (0.5 g/kg) followed by continuous infusion (CRI) of 2.5% dextrose until normal or increased blood glucose concentrations are maintained.[227,234]

In people with DM and severe hypoglycemia, glucagon injection can be used to stimulate hepatic gluconeogenesis and glycolysis.[228] Glucagon has successfully been used in dogs with refractory hypoglycemia or seizures associated with insulin overdose, insulinoma, and paraneoplastic hypoglycemia (see ch. 303).[235,236] In a cat, glucagon markedly improved neurologic signs which had persisted after euglycemia had been restored by dextrose infusion.[235] No adverse effects of the infusion were noted. Glucagon for injection (1 mg vial) is readily available, is reconstituted with the manufacturer's diluent, and their instructions for use should be followed. It can be added to 1000 mL of 0.9% NaCl (not to any dextrose infusion), and administered IV as an initial bolus of 50 ng/kg, then as a CRI at 10 to 15 ng/kg/min. The dosage may need to be adjusted as high as to 40 ng/kg/min.[235]

Somogyi (Insulin-Induced Hypoglycemia with Rebound Hyperglycemia)

Hypoglycemia due to insulin overdose may trigger a counter-regulatory response leading to a rebound hyperglycemia, known as the Somogyi effect.[89,237] A recent study of 10,767 blood glucose curves from 55 cats treated with an intensive glargine protocol found that while biochemical hypoglycemia occurred frequently (93%), only 0.42% of blood glucose curves were consistent with rebound hyperglycemia (<50 mg/dL or <2.8 mmol/L followed by >300 mg/dL or >16.7 mmol/L within 4-10 hours).[238] Numerous studies in people with DM have concluded that rebound hyperglycemia is rare and is not associated with higher levels of GH, cortisol, or glucagon, but is inversely correlated with insulin concentrations.[239-243] Therefore, most cases of apparent rebound hyperglycemia result from relative insulin deficiency rather than a response to antagonist hormones.

While the dose of any insulin should be reduced if a cat develops asymptomatic hypoglycemia, it should not be reduced on the assumption of a Somogyi event when blood glucose concentrations are high and poorly responsive to insulin. In the initial weeks of insulin treatment, blood glucose concentrations commonly fluctuate. This usually resolves with time and consistent dosing but could be incorrectly attributed to rebound hyperglycemia.

Summary

In summary, in general veterinary practice, DM affects approximately 1 in 200 cats, most of whom have type 2 disease. Other types of DM occur and acromegaly appears common in poorly controlled cats. Goals of therapy involve early implementation of rigorous glycemic control to maximize the probability of remission while avoiding clinical hypoglycemia. The highest remission rates reported involve use of long-acting insulin (glargine or detemir), a low carbohydrate diet (≤6% of energy from carbohydrate), frequent glucose monitoring, preferably at home, and appropriate adjustment of insulin dosage aimed at achieving normal or near-normal glucose concentrations. Most cats in DM remission have abnormal glucose homeostasis and should be considered pre-DM. Diabetic relapse occurs in 25-30% of cats within 1-2 years and is more likely in cats with moderately impaired fasting glucose concentrations (≥135-162 mg/dL; 7.5-9 mmol/L). Continued home blood glucose monitoring is recommended for cats in remission to detect early deterioration in blood glucose homeostasis and facilitate early implementation of appropriate therapy.

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CHAPTER 306

Hyperadrenocorticism in Dogs

Dolores Pérez-Alenza, Carlos Melián

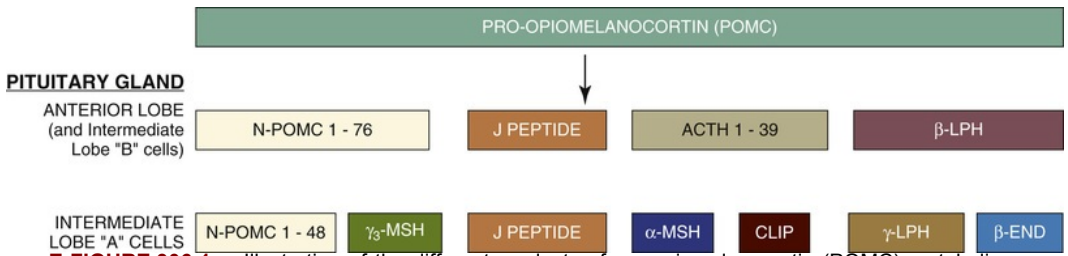
Client Information Sheet: Hyperadrenocorticism in Dogs: Initial and Long-Term Management

In 1932, Dr. Harvey Cushing described clinical signs in people with pituitary basophil adenomas. The tumors likely produced excessive adrenocorticotropic hormone (corticotrophin, ACTH) causing chronic excessive stimulation of the adrenal cortices, secondary bilateral adrenocortical hyperplasia and chronic excesses in serum cortisol concentration, a "hallmark" of hyperadrenocorticism (HAC). The most common cause of naturally occurring canine HAC is pituitary dependent hyperadrenocorticism (PDH), in which a functioning pituitary adenoma (rarely, a carcinoma) autonomously and excessively secretes ACTH and causes the same changes as outlined. A hypothalamic disorder causing pituitary hyperplasia has not been documented in dogs. Ectopic (non-pituitary) excess ACTH production has been described in dogs, but is extremely rare. The second most common cause of canine HAC is a functional adrenocortical tumor (FAT; adenoma or carcinoma) that autonomously produces excessive cortisol. Readers are reminded that the most common cause of "Cushing's syndrome" in dogs is iatrogenic, as use of glucocorticoids is common in managing a variety of neoplastic, inflammatory or immune-mediated conditions (see ch. 164 and 165).

Physiology of the Hypothalamus–Pituitary–Adrenal Axis

Hypothalamus

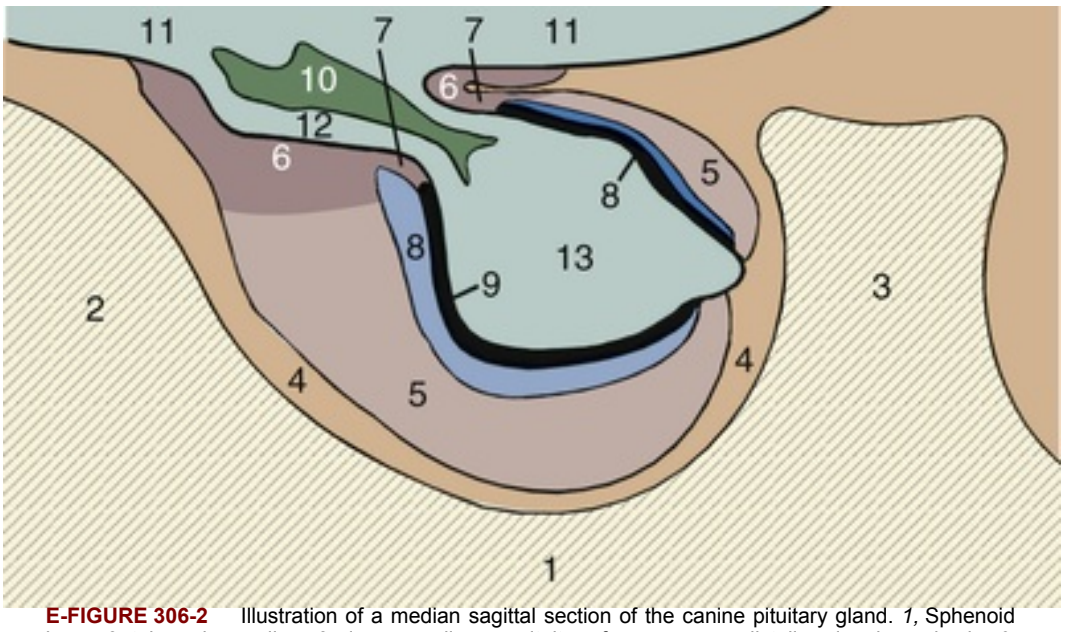
The hypothalamus has primary control of pituitary gland function. The pituitary regulates adrenocortical function and cortisol secretion. Corticotropin-releasing hormone (CRH), a 41 amino acid polypeptide, has a plasma half-life of about an hour. The hypothalamus-hypophyseal portal system delivers CRH to the anterior pituitary, where it stimulates corticotropes to secrete ACTH. Stimulation of hypothalamic CRH secretion is mediated by cytokines (interleukins [IL] 1 and 6, TNF-alpha), leptin, dopamine, arginine-vasopressin (AVP) and angiotensin II.[1] Inhibition of CRH is mediated by glucocorticoids and somatostatin. Glucocorticoids are the dominant negative-feedback regulators of CRH. ACTH (molecular weight: 4500 daltons), a single-chain 39-amino acid peptide hormone, is cleaved from the precursor molecule pro-opiomelanocortin (POMC). Canine and human ACTH differ by the amino acid residue at position 37. The 1 to 18 amino terminal end of the ACTH molecule is responsible for its biologic activity. Other POMC fragments are biologically active (E-Figure 306-1): beta-lipoprotein (beta-LPH), beta-endorphin, alpha and gamma-melanocyte–stimulating hormone (MSH), joining peptide (J peptide) and N-terminal fragment.[2,3]



E-FIGURE 306-1 Illustration of the different products of pro-opiomelanocortin (POMC) metabolism in the anterior lobe of the pituitary as compared with the products formed in the intermediate lobe of the pituitary. *ACTH,* Adrenocorticotropic hormone; *CLIP,* corticotropin-like intermediate lobe peptide; *END,* endorphin; *J peptide,* joining peptide; *LPH,* lipoprotein; *MSH,* melanocyte-stimulating hormone.

Pituitary

There are three functional units in the canine pituitary gland: the anterior pituitary (formed by the pars infundibularis and pars distalis); the intermediate lobe (pars intermedia) and the posterior pituitary (neurohypophysis; E-Figure 306-2). One pars distalis product, ACTH (less importantly, beta-LPH), is stimulated primarily by CRH and suppressed primarily by glucocorticoids (cortisol). The pars intermedia contains "A" cells that produce alpha-MSH and corticotropin-like intermediate lobe peptide (CLIP) and "B" cells that synthesize POMC cleaved to ACTH and beta-LPH. "B" cells are regulated, in part, by tonic dopaminergic inhibition.[4-6] Secretion of beta-LPH and beta-endorphin is similar to that of ACTH; stress and hypoglycemia increase their secretion while glucocorticoids suppress it. Beta-endorphins may act as "endogenous opiates," suggesting a role in pain alleviation; the physiology of beta-LPH is unknown. MSH is involved in secretion of melanin (melanogenesis) by melanocytes in skin and hair. Hypoglycemia increases plasma levels of N-terminal fragments, but their role is unknown. In humans, both CRH and ACTH are secreted in a pulsatile manner with a diurnal rhythm that results in a peak before waking in the morning. In dogs, ACTH is also secreted in a pulsatile manner, with 6 to 12 daily peaks. A diurnal rhythm has not been identified. Secretion of ACTH is regulated by CRH, response to stress, feedback inhibition by cortisol, and immunologic factors. Physical, emotional, and chemical stressors such as pain, trauma, hypoxemia, acute hypoglycemia, cold exposure, surgery, and pyrogens stimulate ACTH and cortisol secretion.



E-FIGURE 306-2 Illustration of a median sagittal section of the canine pituitary gland. *1,* Sphenoid bone; *2,* tuberculum sellae; *3,* dorsum sellae; *4,* pituitary fossa; *5,* pars distalis adenohypophysis; *6,* pars infundibularis adenohypophysis; *7,* transitional zone; *8,* hypophyseal cleft or cavity; *9,* pars intermedia adenohypophysis; *10,* third ventricle; *11,* hypothalamus (median eminence); *12,* pars proximalis neurohypophysis; *13,* pars distalis neurohypophysis. (From Meij B: Hypophysectomy as a treatment for canine and feline Cushing's disease. *Vet Clin North Am Small Anim Pract* 31:1015-1041, 2001.)

The Adrenal Cortices

The adrenal cortices have three distinct layers (zones): the outer zona glomerulosa, the middle zona fasciculata, and the inner zona reticularis. Synthesis of most adrenal steroids is mediated by cytochrome P450 oxygenase enzymes. Due to differences in these enzymes, the adrenal cortex functions as distinct units. The outer zona glomerulosa, the only source of mineralocorticoids (primarily aldosterone), is deficient in 17-alpha-hydroxylase activity and unable to synthetize cortisol or androgens. Aldosterone synthesis is regulated primarily by the renin–angiotensin system and serum potassium concentrations. ACTH has a minor role.

The fasciculata and reticularis zones of the cortices function similarly with regard to cortisol and androgen production. Only cells in these zones have 17-alpha-hydroxylase activity and can synthesize 17-alpha-

hydroxypregnenolone and 17-alpha-hydroxyprogesterone, precursors of cortisol and adrenal androgens. These two zones are regulated primarily by ACTH, which stimulates rapid synthesis and secretion of cortisol (and androgens). Chronic ACTH stimulation leads to adrenocortical hyperplasia. Chronic ACTH deficiency results in decreased steroidogenesis and adrenocortical atrophy (see ch. 309).

Pathogenesis

Pituitary-Dependent Hyperadrenocorticism

About 80 to 85% of dogs with naturally occurring HAC have PDH: excessive secretion of pituitary ACTH (>90% have a detectable pituitary tumor), bilateral adrenocortical hyperplasia, and chronic excessive secretion of glucocorticoids (Figure 306-3).[7] Pituitary tumors may arise from the pars distalis (about 70%) or from the pars intermedia (about 30%).[7] While ACTH secretion in the relatively avascular pars intermedia is regulated in part by CRH, pars intermedia activity is mainly controlled by dopaminergic and serotoninergic fibers from higher centers. The predominant cells of the pars intermedia (A cells) immunostain intensely for alpha-MSH and weakly for ACTH whereas pars intermedia B cells stain strongly for ACTH and weakly for alpha-MSH. The intense ACTH staining of pars intermedia B cells is similar to the staining characteristics of ACTH-producing pars distalis cells.[7,8]

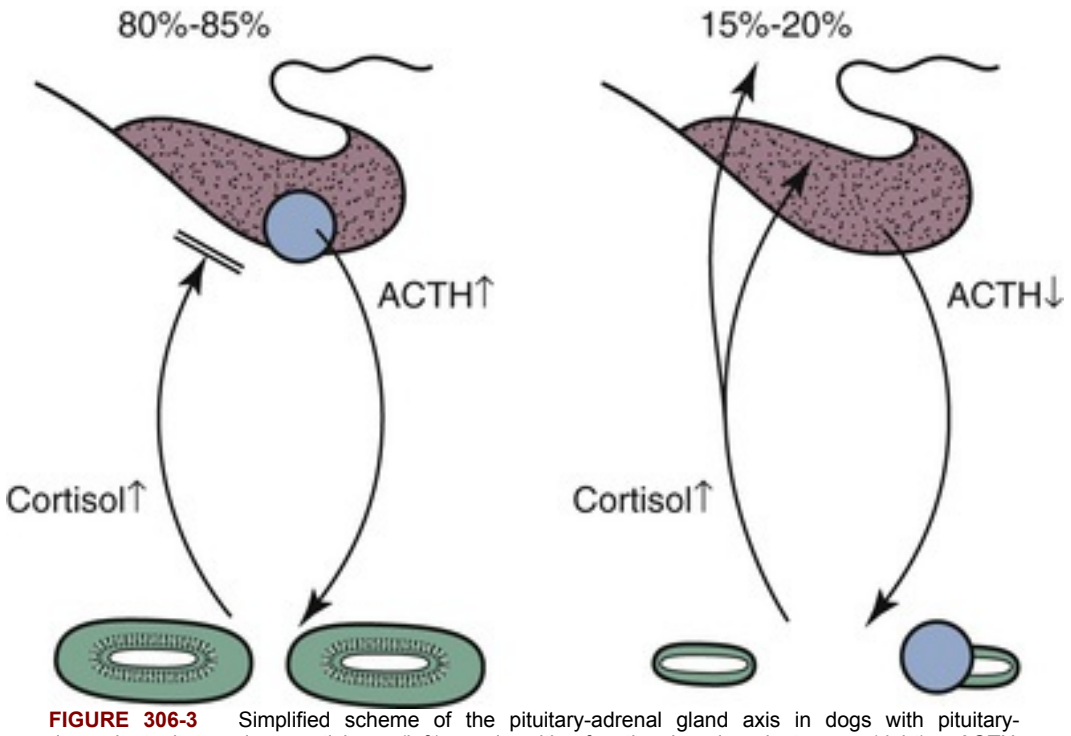


FIGURE 306-3 Simplified scheme of the pituitary-adrenal gland axis in dogs with pituitary-dependent hyperadrenocorticism (left) and with functional adrenal tumor (right). *ACTH*, Adrenocorticotropic hormone.

Pituitary tumors are usually classified histologically as adenoma (well delineated from adjacent parenchyma), invasive adenoma (exhibiting local invasion of brain parenchyma or adjacent structures) or carcinoma (with distant intra- or extracranial mestastasis).[9] Twenty of 33 dogs with pituitary tumors had an adenoma in one study, and 80% had HAC; 11/33 had an invasive adenoma, and 45% had HAC; and 2/33 had HAC and a carcinoma.[9] Since large pituitary tumors tend to be resistant to dexamethasone negative feedback, pituitary tumor size may be related to that tumor's degree of insensitivity to glucocorticoid feedback. Tumors originating in the pars intermedia may grow larger than those in the pars distalis, but pituitary tumors do not always maintain their characteristics of origin. Tumors from dogs with PDH cannot easily be distinguished as originating from the pars distalis or pars intermedia, even with plasma alpha-MSH levels or dexamethasone resistance.[10-12] Pituitary hyperplasia has also been mentioned as a cause of PDH in dogs; however, proof of such a condition is lacking.

The two mechanisms proposed regarding the pathogenesis of pituitary tumors include (1) a hypothalamic theory and (2) a monoclonal (pituitary) theory.[13] The hypothalamic theory, not widely accepted, is that chronic stimulation of pituitary corticotrophs by hypothalamic CRH and vasopressin, together with acquired glucocorticoid receptor defects, lead to a lower inhibitory action of cortisol. Also, dopaminergic neurodegeneration in aged animals or lower expression of dopamine receptors contribute to decreased feedback actions of cortisol. This reduced inhibition could lead to excessive secretion of ACTH, pituitary hyperplasia, and eventually neoplastic transformation of some corticotrophs, due to a somatic mutation.

The pituitary theory is that a tumor is the primary cause of HAC and it developed after somatic mutation of a corticotroph, creating a tumor clone.[13] This theory is widely accepted and is supported, in part, by low CRH concentrations reported in dogs with PDH together with studies demonstrating that nearly all corticotroph adenomas are monoclonal.[14,15] The occurrence of PDH in a family of seven Dandie Dinmont Terriers is also supportive.[16] Canine corticotroph adenomas likely contain stem cells that drive tumor growth and are the result of a multistage process of tumorgenesis, the first being the somatic mutation preceding clonal expansion of the tumor.[17]

Functional Adrenocortical Tumors

About 15 to 20% of dogs with naturally occurring HAC have an adrenocortical tumor that autonomously secretes excessive amounts of cortisol. Hypothalamic CRH and circulating plasma ACTH concentrations are suppressed by cortisol from the tumor, causing atrophy of the opposite uninvolved adrenal and of non-neoplastic cells in the tumor-containing adrenal. No clinical or biochemical feature allows dogs with FAT due to adenoma to be discriminated from those with carcinoma.[18] Adrenal masses >2 cm in diameter and those invading regional vasculature are more likely to be carcinomas. Malignancy is confirmed if distant metastases appear similar histologically. Cytology is not reliable in discriminating benign from malignant tumors and even histologic differentiation can be difficult. Malignancy is more likely with masses that have broken through the capsule or invaded the vasculature.[19] FATs are usually unilateral with no obvious tendency regarding side. Bilateral adrenocortical tumors have been described. A few dogs have had a cortisol-secreting adrenal tumor in one gland and a pheochromocytoma (see ch. 311) in the other.

Cortisol secretion by FATs is episodic, random, independent of ACTH control and suppresses ACTH synthesis and secretion. The role of ACTH receptors (ACTHR) in cortisol secretion by FAT may be limited. Some dogs with a FAT exhibit no cortisol response to exogenously administered ACTH, some dogs have a normal response and still others have exaggerated responses. Up-regulation of steroidogenic enzymes does not appear to be involved in FAT pathogenesis but down-regulation of ACTHR may be related to malignancy.[20] Ectopic expression of gastric inhibitory polypeptide (GIP) and vasopressin 2 (V2) receptor proteins obeserved in the zona fasciculata of FATs may have a role in tumor pathogenesis.[21] Steroidogenic factor 1 (SF1), associated with the pathogenesis of adrenal tumors in humans, is expressed in canine FAT and may have use as a prognostic marker or a therapeutic target.[22]

Concurrent PDH and FAT, Nodular Hyperplasia, Ectopic ACTH Secretion

The coexistence of pituitary and adrenal tumors has been described in 17 dogs. Each had an adrenocortical tumor and contralateral adrenal hyperplasia; 10 dogs had a unilateral adrenocortical adenoma; 4 had bilateral adrenal cortical adenomas; and 3 had an adrenal carcinoma.[23] Pituitary lesions included a chromophobe microadenoma in 12, pituitary macroadenoma in 4, and pituitary carcinoma in 1 dog. It is possible that such adrenal tumors have transitioned from initial hyperplasia. Dogs with PDH usually develop symmetrical bilateral adrenocortical hyperplasia. However, some may develop adrenocortical *nodular* hyperplasia, in which one or both glands can have one or many varying sized nodules. With time, such nodules may be difficult to distinguish from adrenocortical tumors.

Ectopic ACTH secretion, derived from any of a variety of tumor types, is responsible for about 15% of people with HAC.[24] The ectopic HAC condition can be clinically more severe than PDH. Small cell lung carcinoma is the most common cause of ectopic ACTH secretion in humans, but it has been associated with carcinoid tumors (i.e., of the lung, bronchus, gut, liver, pancreas, and ovary), thymoma, pancreatic islet cell tumors, olfactory neuroblastoma, medullary carcinoma of the thyroid, and pheochromocytoma.

The ectopic ACTH syndrome is exceedingly rare cause of HAC in dogs. An 8-year-old German Shepherd Dog with ectopic ACTH secretion, thought initially to have PDH, was treated with transsphenoidal

hypophysectomy but had recurrence of clinical signs, plasma ACTH concentrations and abnormal urine corticoid to creatinine ratios. A pancreatic mass with liver involvement was then detected. Histologic examination revealed a neuroendocrine tumor, considered the source of ectopic ACTH secretion. The dog was treated and responded well to trilostane.[25]

Epidemiology

Hyperadrenocorticism is relatively common in older dogs. In one study during a 15-year period at a veterinary teaching hospital, HAC was diagnosed in more than 1 per 100 dogs, exceeding previous estimates of 1-2/1000.[26,27] This apparent rising disease prevalence can be due to an increase in the life expectancy of dogs, increased awareness of the disease, and the reality that the study was completed at a referral center.

Signalment

Naturally occurring HAC is most commonly diagnosed in middle-aged to older dogs. The age at diagnosis ranges from 6 months to 20 years with a mean age of 11 years. Almost all dogs with HAC are older than 6 years at diagnosis.[28,29] More than 75% of dogs with PDH and 90% of dogs with FAT are >9 years of age at the time of diagnosis. HAC is a disorder without significant breed predisposition.[27] PDH tends to occur in smaller dogs: Poodles, Dachshunds, Terrier breeds. About 75% of dogs with PDH weigh less than 20 kg whereas almost 50% with FAT weigh more than 20 kg. Sex predilection in dogs with HAC is possible, with 60 to 65% being female.[29]

Clinical Manifestations

Overview

Most clinical and laboratory abnormalities in dogs with HAC are caused by chronic cortisol excess. In a few dogs, signs may be caused by pituitary or adrenal tumor growth and/or invasion, metastases, diabetes mellitus (DM), systemic hypertension, or thromboembolism. Clinical signs are a consequence of the combined gluconeogenic, immune-suppressive, anti-inflammatory, protein catabolic, and lipolytic effects of glucocorticoids. PDH cannot be distinguished from FAT on signs nor their duration.[30] Signs vary from being subtle to quite severe. Some dogs have HAC confirmed after following their progress with time. Because of the heightened awareness of HAC by veterinarians, dogs are being evaluated at earlier stages of the disease, when clinical manifestations may be mild.[30]

History

Duration

HAC is typically a chronic and progressive disease. Clinical signs might be present for months since these dogs are usually in good condition with an excellent appetite. Owners might attribute early signs to normal aging and seek veterinary help only when signs become intolerable: polyuria (urinating in the house) or polyphagia (stealing food, eating garbage, begging continuously, and occasionally aggressively attacking or protecting food).

Questions to Consider

The first step in gaining a suspicion that a dog may have HAC is always based on the history. Owner-noted clinical signs must be carefully obtained. One must avoid “leading the owner.” Rather than asking whether their pet is drinking and urinating excessively, it is preferred to ask vaguely about water intake and urine output. Also, it is important to be aware of signs not consistent with HAC (e.g., vomiting, diarrhea, anorexia, or pain), to avoid performing tests for HAC on dogs with non-adrenal illnesses.[30] Medication history can be extremly important, including topical drugs, since the clinical signs of iatrogenic and naturally occurring Cushing's syndrome are identical. Several medications (e.g., anticonvulsants, diuretics, etc.) have side effects that mimic HAC. Some of the most important questions when HAC is suspected include: (1) Has your dog currently or recently been given any medication?; (2) What is your dog's drinking, urinating and appetite like now as compared with 12 months ago?; (3) Can your dog jump off furniture or out of a car and, if “yes,” can the dog jump into the car or onto furniture? If “no,” how long?; (4) What is the dog's breathing like (dog

panting while at rest)?; and (5) Is the dog sleeping more? Dogs with HAC may have just one or several clinical signs, each of which may vary in intensity. Either polydipsia-polyuria (PU/PD; the most common clinical sign) or alopecia suggestive of an endocrine disease can be the only clinical sign in some dogs with HAC.

Common Signs

Classic owner observations include PU/PD, polyphagia (PP), apparent weight gain (pot belly), muscle weakness, panting, and hair loss (Table 306-1). PU/PD is observed in about 90% of dogs with HAC. PU is likely due to increased glomerular filtration rates and inhibition of antidiuretic hormone (ADH) action at the renal tubular level, leading to a decrease in renal tubular water reabsorption. Exogenous ADH causes dramatic reduction in PU/PD, suggesting that cortisol interference with ADH release is responsible.[29] Urinary tract infections (UTI) are common in dogs with HAC and are likely due to: immunosuppressive effects of cortisol excess, decreased bactericidal properties of dilute urine, and urine retention that occurs, especially in indoor dogs. Many PU dogs develop a degree of decreased bladder tone, which can lead to overflow incontinence. However, signs of pollakiuria, hematuria, and stranguria are not common, perhaps due to the anti-inflammatory actions of cortisol.

TABLE 306-1

Clinical Manifestations of Canine HAC at the Time of Initial Presentation

COMMON	LESS COMMON	UNCOMMON
Polydipsia	Lethargy	Thromboembolism
Polyuria	Hyperpigmentation	Ligament rupture
Polyphagia	Comedones	Facial nerve palsy
Panting	Thin skin	Pseudomyotonia
Abdominal distention	Poor hair regrowth	Insulin-resistant diabetes mellitus
Endocrine alopecia	Urine leakage	
Hepatomegaly	Testicular atrophy	
Muscle weakness	Persistent anestrus	
Systemic hypertension		

HAC, Hyperadrenocorticism.

Modified from Behrend EN, Kooistra HS, Nelson R, et al: Diagnosis of spontaneous canine hyperadrenocorticism: 2012 ACVIM consensus statement (small animal). *J Vet Intern Med* 27:1292, 2013.

Appetite, Appearance, Muscle Strength, Respiration

Most dogs with HAC are described as having an excellent appetite or PP, a direct and unique canine response to glucocorticoids. Even though some dogs with HAC gain weight, most have a pot-bellied appearance (Figure 306-4) that mimics weight gain. Five to 10% of dogs with HAC develop diabetes mellitus (DM, see in this chapter "Serum Biochemistry Profile: Blood Glucose" and ch. 304) and these dogs may exhibit weight loss (Figure 306-5). The pendulous abdomen is secondary to weakness of the abdominal musculature coupled with increased weight of abdominal content due to hepatomegaly, a chronically distended bladder, and re-distribution of peripheral fat to the mesentery. Leptin concentrations are significantly higher in obese HAC dogs than in healthy obese dogs and may be a factor.[31] Muscle weakness is quite common, resulting from muscle wasting secondary to the catabolic effects of glucocorticoids. Infrequently, muscle weakness is so profound that dogs may not be capable of rising and may have difficulty standing. Excessive panting is common and attributed to decreased pulmonary compliance, respiratory muscle weakness, pulmonary hypertension, or the direct effects of cortisol on the respiratory center. Signs may be exaggerated by excitement or exercise. Pulmonary thromboembolic disease, a rare complication of HAC, can also cause moderate to severe respiratory distress (see ch. 243). Radiographic evidence of pulmonary mineralization is common in dogs with HAC and might contribute to hypoxemia in some.[32]

FIGURE 306-4 Distended abdomen and dermatological signs in a French Bulldog with pituitary hyperadrenocorticism.

FIGURE 306-5 Muscle wasting and distended abdomen in a mixed-breed dog with hyperadrenocorticism and diabetes mellitus.

Central Nervous System (CNS)

CNS signs develop in 10-25% of dogs with PDH due to the "pituitary macrotumor syndrome," a tumor invading and compressing tissues dorsal to the sella turcica. Moderate to severe lethargy is the most common disturbance, but other signs include inappetence or even anorexia, stupor, circling, aimless wandering (Video 306-1), ataxia, behavioral changes and seizures.

Uncommon Signs/Myotonia

Less common clinical signs in dogs with HAC are ligament laxity that may lead to tearing and lameness (Figure 306-6), unilateral or bilateral facial nerve paralysis, anestrus, testicular atrophy, or thromboembolism due to hypercoagulability.[30] Adrenal tumors can invade the phrenicoabdominal vein, caudal vena cava, or both, causing thrombus formation. Quite uncommonly, tumors can cause abdominal or retroperitoneal hemorrhage or pelvic limb edema. Rarely, dogs with HAC develop a myopathy characterized by persistent, active muscle contraction after cessation of voluntary effort, known as Cushing's pseudomyotonia. It usually affects the pelvic limbs causing a stiff gait (Video 306-2) or, in more advanced cases, an inability to ambulate (Figure 306-7). Diagnosis may be confirmed by electromyography (see ch. 117), on which myotonic, bizarre and high frequency discharges are noted. Muscle histology reveals a noninflammatory degenerative myopathy.

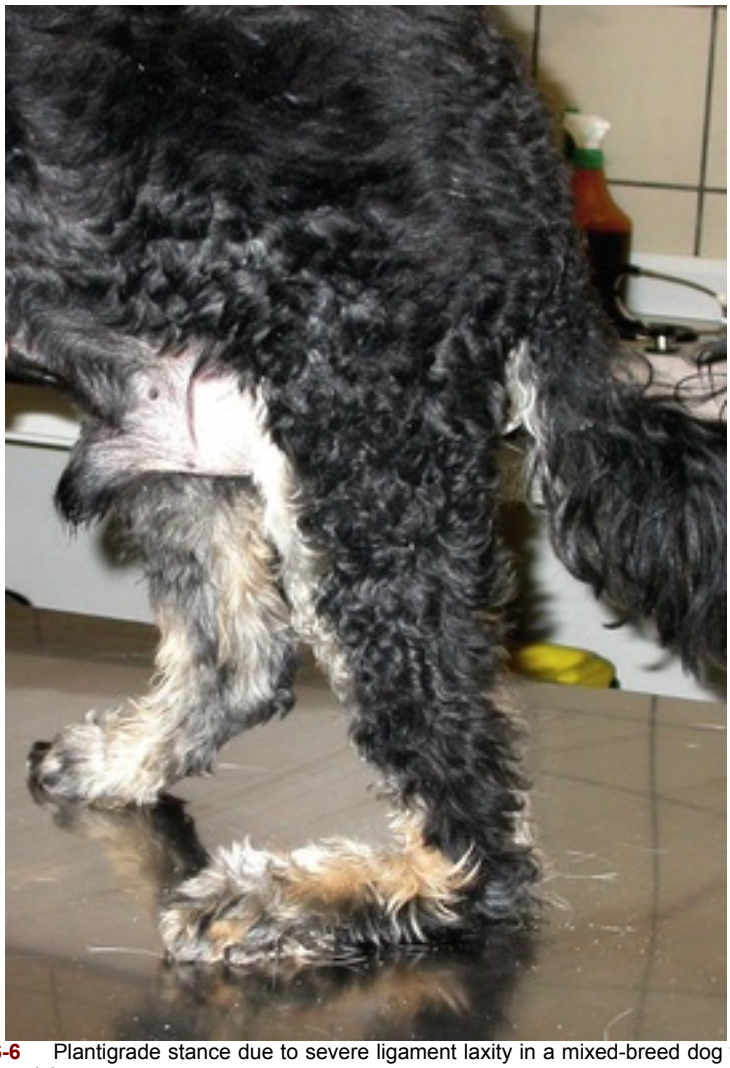


FIGURE 306-6 Plantigrade stance due to severe ligament laxity in a mixed-breed dog with pituitary hyperadrenocorticism.

FIGURE 306-7 Mixed-breed dog with hyperadrenocorticism causing advanced clinical signs including pseudomyotonia.

Physical Examination

Common Features

Abdominal distension is the most common feature on physical examination of dogs with HAC. Truncal, bilaterally symmetrical, endocrine alopecia is common. Initially, the hair coat becomes dull and dry. With time, the skin becomes hypotonic and signs such as failure to regrow shaved hair, comedones, increased susceptibility to bruising, hyperpigmentation, and seborrheic changes may occur. Some dogs have severe alopecia, with only the head and distal extremities retaining a coat. The thin skin and the suppressed immune system predispose dogs with HAC to pyoderma, present in about 50% of dogs with HAC.

Calcinosis Cutis

This is an uncommon but characteristic dermatologic condition in dogs with either naturally occurring or iatrogenic Cushing's syndrome (see ch. 10 and Figure 306-8). It is characterized by irregular plaques in or under the skin caused by dystrophic calcium deposition and located on the temporal areas of the head, dorsal midline, neck, ventral abdomen, or inguinal areas. The gluconeogenic and protein catabolic activities of cortisol are involved in the pathogenesis of calcinosis cutis, in which rearrangement of molecular protein structures leads to formation of an organic matrix that attracts and binds calcium, forming apatite crystals.[33]

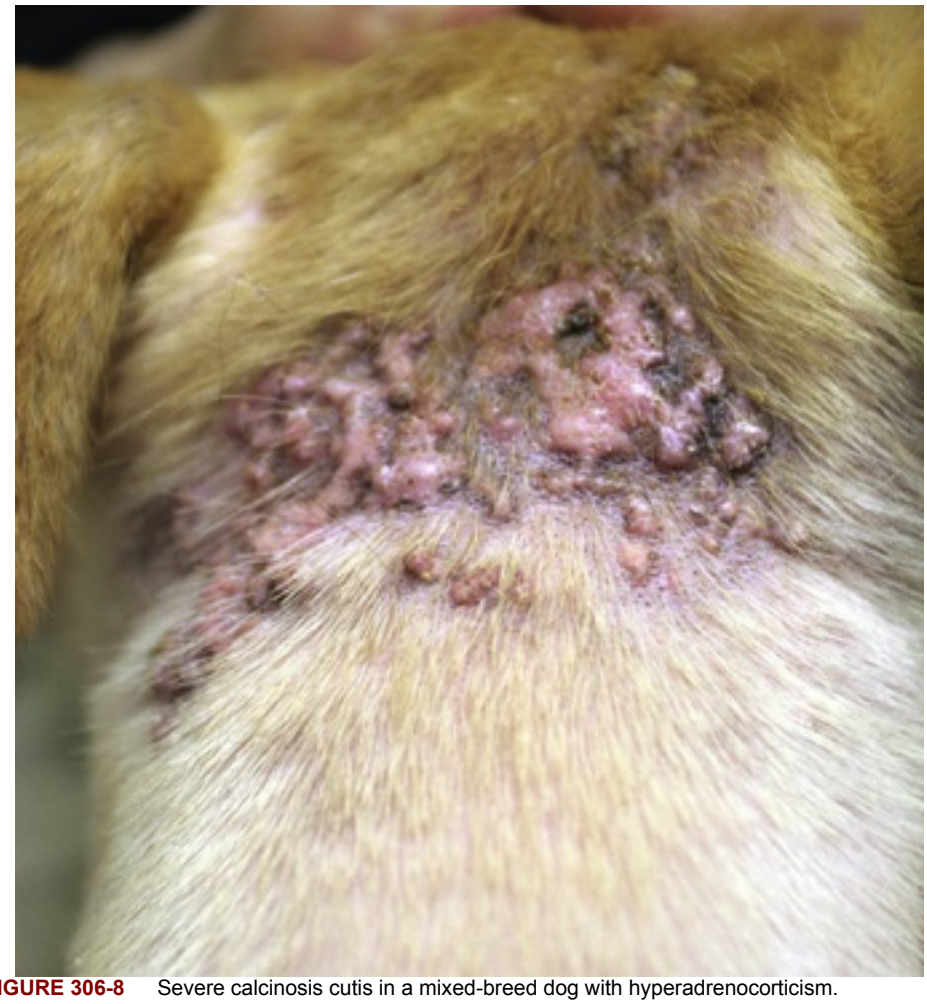


FIGURE 306-8 Severe calcinosis cutis in a mixed-breed dog with hyperadrenocorticism.

Sexually Intact Dogs

Testicular atrophy and anestrus in females are less common sequelae to HAC. Cortisol's negative feedback to the pituitary gland decreases synthesis and secretion of FSH and LH. Males usually have bilaterally small, soft, spongy testicles and females are in anestrus, the duration of which may be indicative of the duration of HAC.

Acute Illness

Occasionally, dogs with HAC may develop acute signs of severe lethargy, weakness, pale mucous membranes and pain. This rare complication may occur as a consequence of an adrenal tumor rupture leading to acute intra-abdominal or retroperitoneal hemorrhage and is one of the few scenarios (along with pulmonary thromboembolism, which is also rare) in which a dog with HAC may have an acute, life-threatening condition.[34]

Sudden Acquired Retinal Degeneration Syndrome

An association between sudden acquired retinal degeneration syndrome (SARDS), an idiopathic retinal disorder that produces sudden and permanent blindness in adult dogs (see ch. 11), and HAC has been suggested, but evidence is lacking.[35] Loss of vision in dogs with PDH, while quite uncommon, has been related to increased serum triglyceride concentrations or changes in retinal vascular flow.[36] Blindness, associated with increased IL-6 and decreased nitric oxide concentrations adversely affects blood flow and increases risk of vision loss.[37]

Clinicopathologic Findings (Table 306-2)

Overview

Diagnosis of HAC should always be initially suspected from owner observations, with or without physical alterations. Endocrine tests should only be performed when clinical signs are consistent with HAC.[30] With a clinical suspicion of HAC, results of complete blood count (CBC), serum chemistry profile, urinalysis with culture, and abdominal ultrasound (US) should be reviewed before considering hormone testing. Various alterations are common, but none is pathognomonic for HAC. Absence of abnormalities does not rule out HAC.

TABLE 306-2

Common Laboratory Abnormalities in Dogs with HAC

CBC	SERUM BIOCHEMISTRY PANEL	URINALYSIS
Neutrophilic leukocytosis	Increased alkaline phosphatase	Specific gravity ≤1.018-1.020
Lymphopenia	Increased alanine aminotransferase	Proteinuria
Eosinopenia	Hypercholesterolemia	Urinary tract infection (often without evidence of inflammation)
Thrombocytosis	Hypertriglyceridemia	
Mild erythrocytosis	Hyperglycemia (mild and not associated with diabetes mellitus)	

CBC, Complete blood count; *HAC*, hyperadrenocorticism.

Modified from Behrend EN, Kooistra HS, Nelson R, et al: Diagnosis of spontaneous canine hyperadrenocorticism: 2012 ACVIM consensus statement (small animal). *J Vet Intern Med* 27:1292, 2013.

Complete Blood Count (CBC)

Lymphopenia due to steroid lympholysis, eosinopenia caused by bone marrow sequestration, neutrophilia, and monocytosis due to steroid-enhanced capillary demargination are common in dogs with HAC. Together, these white blood cell changes are referred to as "stress leukogram" but are not specific. Other CBC changes associated with HAC include increased platelet counts and a mild erythrocytosis (direct bone marrow stimulation or ventilatory issues).

Serum Biochemistry Profile

Serum Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Cholesterol, Triglyceride

Increases in ALP activity are the most consistent laboratory abnormality, observed in 85-95% of dogs with HAC. In many, the increases are marked (>10 times the reference interval) but results are not specific (observed in numerous conditions). ALP should never be considered a sceening test for HAC. There is no correlation between ALP activity and HAC severity, response to therapy, or prognosis.[38] Almost all ALP in dogs with HAC is a steroid-induced hepatic isoenzyme (SALP), an isoenzyme response unique to dogs. Normal SALP can help rule out HAC.[39,40] Alanine aminotransferase (ALT) activities are often increased in dogs with HAC, but are usually mild to moderate. These increases may be due to damage caused by swollen hepatocytes, glycogen accumulation, interference with hepatic blood flow, or hepatocellular necrosis. Mild to moderate increases in cholesterol and triglyceride concentrations are observed in >50% of dogs with HAC.

Blood Glucose

Mild fasting hyperglycemia (below the threshold necessary for glucose to appear in the urine) is common in dogs with HAC. Overt DM (glucose >250 mg/dL and glucosuria) is not common, occurring in about 5% of dogs with HAC. Glucocorticoids increase hepatic gluconeogenesis and decrease peripheral utilization of

glucose by interfering with insulin action at the cellular level (receptor and post-receptor defects). Gene expression of insulin signal molecules (post-receptor) is suppressed in dogs with HAC.[41] Hypercortisolism-induced hyperinsulinemia to maintain carbohydrate tolerance is usually not adequate to completely normalize glycemia in all dogs.[42] Hyperinsulinemia and insulin resistance are probably related to abdominal fat and adipokines, as obese dogs with HAC have higher leptin and insulin concentrations when compared with healthy obese dogs. Concentrations of leptin and insulin decline with trilostane therapy.[31] Other adipokines and related factors (adiponectin, TNF-alpha, IL-6) are not different.[31] Dogs with HAC and DM usually are insulin-resistant. Adrenocortical testing may be considered in dogs with DM and persistently poor response to high dosages of insulin. However, the reader is encouraged to appreciate the numerous potential explanations for a diabetic dog appearing to be insulin-resistant (see ch. 304). In this context, HAC is an uncommon explanation.[30]

Blood Urea Nitrogen (BUN), Phosphate (PO_4), Calcium (Ca), Bile Acids, Pancreas

Approximately 30 to 50% of dogs with HAC have a BUN below reference intervals due to diuresis. Azotemia is uncommon in dogs with HAC and, if present, is an indication not to treat HAC, for some authors. Hypophosphatemia might occur in dogs with HAC due to increased urinary excretion. Urinary Ca is also increased and may result in secondary hyperparathyroidism and hyperphosphatemia in >40%.[38,43,44] Bile acid test results may be mildly increased in as many as 30% of dogs with HAC.[45] HAC dogs without clinical pancreatitis have higher levels of canine pancreatic lipase immunoreactivity (cPLI) than do healthy dogs, but specificity is low (45-65% depending on technique). Increased cPLI in dogs with HAC must be interpreted with caution (see ch. 290).[46]

Coagulation Parameters

Pulmonary thromboembolism (see ch. 243) is a recognized complication in dogs with HAC, perhaps due to an underlying hypercoagulable state (see ch. 196). While not completely understood, increases in procoagulant factors (factors II, V, VII, IX, X, XII, and fibrinogen) and decreases in antithrombin were described in one study. In another study, no difference in coagulation parameters, using whole blood viscoelastic assays, were identified.[47,48] Decreased antithrombin levels and increased platelet aggregation were observed in dogs treated with prednisone.[49] Furthermore, a hypercoagulable tendency, defined as finding at least one abnormality in a coagulation panel utilizing thromboelastography and coagulation profiles, has been observed in >80% of dogs with HAC.[50,51] The most common abnormalities include shorter prothrombin times (PT), higher fibrinogen concentrations, and increased thrombin-antithrombin complexes. Among the thromboelastography parameters, higher maximum angle (MA) thrombin, increased alpha-angles and shorter k values were documented.[50-52] Most of these abnormalities persist despite trilostane treatment.[52] Co-morbidities (hypertension, hypercholesterolemia, DM) might be associated with hypercoagulability. Correlation between blood pressure, cholesterol concentration, or triglyceride concentration was not observed with any coagulation testing result.[50]

Urinalysis (see ch. 72)

Most dogs with HAC have PU and urine specific gravities <1.020 (commonly <1.012). Glucose is usually negative. Proteinuria is common, with urine protein to creatinine ratios (UP : C) not usually higher than 1 to 6. The UP : C was >1.0 in about 45% and >0.5 in about 70% of dogs with untreated HAC.[53-56] Proteinuria persists in about 20-40% of dogs with controlled HAC.[53-55] Pretreatment glomerular filtration rates are increased in about 60% of dogs with HAC, which decreases with treatment.[55] Thus, UP : C should be initially measured in dogs with HAC and monitored during treatment in proteinuric dogs. Dogs with HAC are predisposed to UTI due to immunosuppression and urine retention. Approximately 40% to 50% of dogs with Cushing's syndrome have a UTI at the time of initial examination.[57] However, due to the anti-inflammatory effects of chronic hypercortisolism, many of these dogs do not have clinical signs nor alterations in urinalysis suggestive of UTI and, therefore, urine culture using a sample obtained by cystocentesis is recommended.

Thyroid Function Tests

Dogs with HAC and those with hypothyroidism have some overlap in clinical and laboratory results, including alopecia, weight gain, lethargy and hypercholesterolemia. Dogs with HAC have polyphagia whereas hypothyroid dogs have poor appetites. Serum total thyroxine (TT_4) and free T_4 (fT_4) concentrations are commonly decreased in dogs with HAC.[58-60] fT_4 concentrations are increased in some.[58-60] Alterations in serum thyroid hormone binding or in peripheral hormone metabolism may contribute. Dogs with HAC who have decreased thyroid hormone concentrations tend to have normal to decreased circulating thyroid-stimulating hormone (cTSH) concentrations whereas hypothyroid dogs have normal to increased results. The hypothalamic-pituitary-thyroid axis is suppressed by cortisol excess and, after successful treatment, cTSH concentrations increase.[59]

Diagnostic Imaging

Thoracic Radiographs

Dogs suspected or known to have HAC should be evaluated with thoracic radiographs to search for metastatic lesions and to evaluate the patient for any unsuspected concern. Common nonspecific findings in dogs with HAC are an interstitial lung pattern in many and mineralized bronchi or tracheal rings in a smaller number.[20]

Dogs with HAC and pulmonary thromboembolism (PTE), rare despite their "hypercoagulable state," may have hypovascular lung fields (areas of increased radiolucency due to decreased perfusion distal to a thrombus) or alveolar pulmonary infiltrates. Alveolar infiltrates correspond to areas of atelectasis, hemorrhage, or infarction. Enlargement of the main pulmonary artery, right-sided cardiomegaly, and pleural effusion have been reported in dogs with PTE.

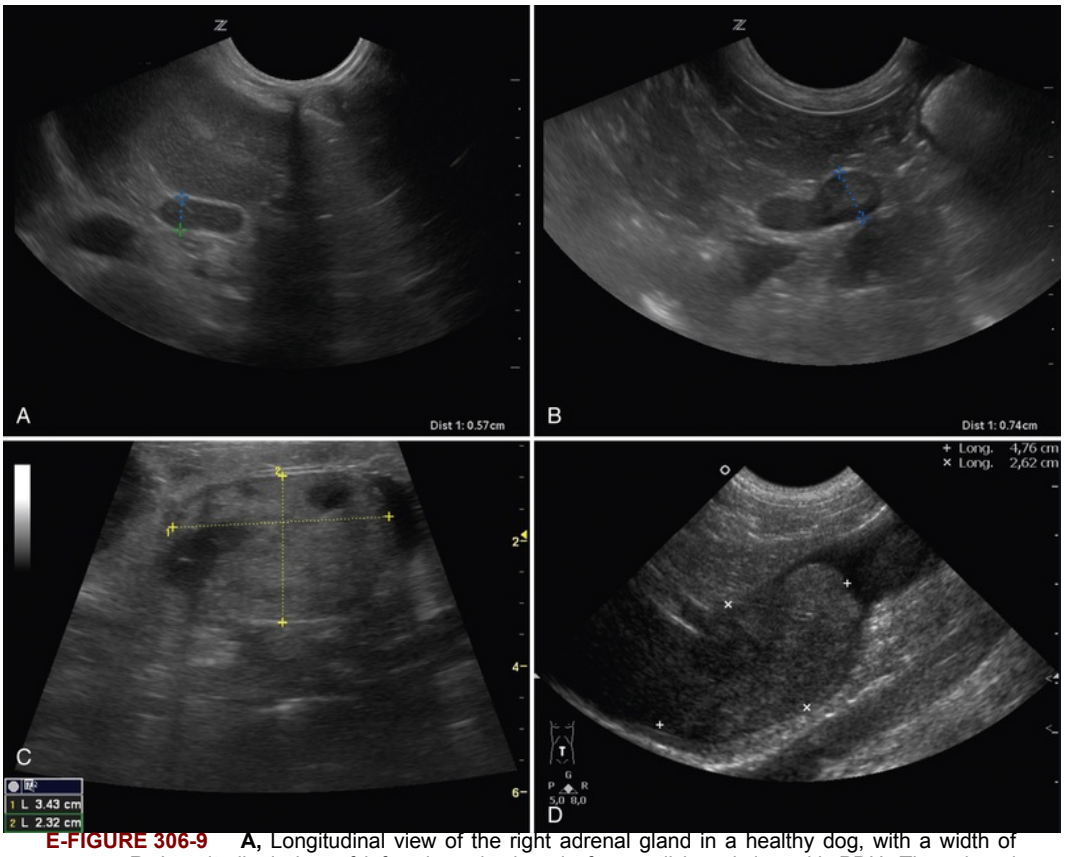
Abdominal Radiographs

Abdominal distension, excellent radiographic contrast due to abdominal fat deposition, hepatomegaly and bladder distension are commonly observed in dogs with HAC. Calcium-containing uroliths are occasionally identified.[61] About half of adrenal adenomas and carcinomas calcify, allowing their visualization, but not indicating their malignant potential.[62] Dystrophic calcification in skin, renal pelvis, liver, gastric mucosa, or branches of the abdominal aorta has been reported in dogs with HAC. Osteopenia is mild and not of clinical importance. Radiographic assessment of bone density is not sensitive.[63]

Ultrasonography (US)

Pituitary-Dependent Hyperadrenocorticism (PDH)

Complete abdominal US, including visualizing both adrenal glands, is a valuable diagnostic aid in evaluating dogs with suspected HAC (see ch. 88). US may be useful for differentiating PDH from FAT. If an adrenal mass is visualized, US should be used to evaluate size, invasive nature, and possible metastasis. US can help assess squelae to HAC (urinary calculi, gallbladder mucocele, etc.) and to rule out nonadrenal conditions (Video 306-3). The adrenal glands are normally hypoechoic, flattened, bilobed organs located craniomedial to the kidneys (E-Figure 306-9, *A*). Adrenal gland width is considered the most reliable indicator of enlargement and a limit of 7.4 mm, regardless of the dog's size or breed, was used as the upper limit of normal.[64,65] However, recent studies have shown the reference range threshold does vary by breed and body size. The upper limit of height at the caudal adrenal pole in a longitudinal plane is 5.4 mm (left) and 6.7 mm (right) in Yorkshire Terriers and 7.9 mm (left) and 9.5 mm (right) for Labrador Retrievers.[66] Adrenal glands of older dogs tend to be larger than those of younger dogs.[67] A majority of PDH dogs have bilaterally symmetrical adrenomegaly (see E-Figure 306-9, *B*), although at least 25% have normal-sized glands.[68] In some PDH dogs, adrenal enlargement can be asymmetrical due to nodular hyperplasia and is more difficult to interpret (Video 306-4). Adrenal gland size should not be used to diagnose HAC, due to the overlap between normal dogs, ill dogs, and those with HAC.[64,65]



E-FIGURE 306-9 **A,** Longitudinal view of the right adrenal gland in a healthy dog, with a width of 5.7 mm. **B,** Longitudinal view of left enlarged adrenal of a small breed dog with PDH. The adrenal gland has an increased thickness (7.4 mm) while maintaining its characteristic peanut shape. **C,** Longitudinal view of a rounded, left adrenocortical tumor (23.2 mm) in a dog with adrenal hyperadrenocorticism. **D,** Caudal vena cava thrombus in a dog with a right adrenal tumor and hyperadrenocorticism.

Functional Adrenocortical Tumor (FAT)

US can be valuable in visualizing a FAT and vascular or local tissue invasion (see E-Figure 306-9, *C* and *D*). An adrenal tumor should be suspected if the gland is enlarged, irregular (losing its normal peanut shape), or invading or compressing adjacent structures. Echogenicity of a FAT ranges from solid to mixed-cystic appearances. The finding of moderate asymmetry, contralateral adrenocortical atrophy (adrenal width <4-5 mm), destruction of normal tissue architecture, or some combination of these is consistent with a FAT. US does have limitations: it is difficult to differentiate bilateral nodular hyperplasia from bilateral adrenal tumors, benign masses cannot be distinguished from malignant, and a FAT cannot be distingished from pheochromocytoma, aldosteronoma, a metastatic mass, or a non-functional adrenal tumor.

Contrast-Enhanced Ultrasonography (CEUS)

CEUS is a noninvasive method for quantifying adrenal gland vascular patterns in dogs.[69,70] Adrenal blood flow and volume increases in PDH dogs. Their perfusion patterns were not similar to those in control dogs, but more studies are needed.

Computed Tomography (CT), Magnetic Resonance Imaging (MRI) Scans and the "Macrotumor Syndrome"

Pituitary tumors >1 cm in diameter (macroadenomas or macroadenocarcinomas) are relatively easy to visualize with either CT or MRI. Smaller masses approaching 1 cm in greatest diameter may be identified via CT scan but MRI is more sensitive for visualizing pituitary microadenomas. Fifty-six percent of dogs with PDH have a normal-appearing pituitary gland using CT.[71] CT or MRI should be performed in dogs with PDH with central nervous system (CNS) signs. Signs associated with a large pituitary mass can be vague or severe.

Vague subtle signs include lethargy, inappetence and mental dullness. Among many more worrisome signs are severe obtundation, aimless wandering (see Video 306-1), complete anorexia, circling, and changes in behavior. Sixty-six percent of PDH dogs with neurological signs had a detectable pituitary tumor. However, >70% of dogs without neurological abnormalities had a detectable pituitary mass and 20% had a macrotumor (i.e., a tumor ≥10 mm in height).[72]

Abdominal CT or MRI Scanning and the Incidentally Identified Adrenal Mass

CT and MRI are considered accurate and reliable modalities for visualizing adrenal glands. With CT or MRI, adrenal tumor location, presence of vascular or tissue invasion and distant metastasis can be identified. CT may help differentiate PDH from FAT.[71] An unexpectedly visualized adrenal mass (*adrenal incidentaloma,* see ch. 308) is detected in a small percentage of people or dogs undergoing abdominal imaging.[73-75] Most incidentally discovered masses are benign and non-functional.

Endocrine Tests

Overview of Screening and Discrimination Testing

Endocrine testing is essential in diagnosing HAC, but test results should only be used to confirm a strong clinical suspicion. Indications for pursuing a diagnosis of HAC include a history suggestive of HAC, visualizing a pituitary macrotumor or an adrenal mass, a diabetic dog with insulin resistance not attributed to another cause, or persistent hypertension.[30] Many diseases affect the results of HAC tests. Thus, testing for HAC should be avoided in dogs with moderate to severe non-adrenal illness. Further, it is extremely rare to recommend therapy for HAC in any dog ill from a non-HAC condition. Once HAC is confirmed, clinicians then can attempt to discriminate PDH from FAT.

Screening tests most commonly used for distinguishing dogs with from dogs without HAC include the urine corticoid to creatinine ratio (UCCR), the ACTH stimulation test (ACTHST), and the low-dose dexamethasone suppression test (LDDST). No test is 100% accurate and each has advantages and disadvantages. Since these tests were introduced to veterinary medicine years ago, reference ranges and cut-off values should be periodically re-established by each laboratory.[30] Tests used to discriminate PDH from FAT include the LDDST, high-dose dexamethasone suppression test (HDDST), HDDST using the UCCR, measurement of ACTH concentrations, and adrenal US, CT and MRI scans.

Distinguishing Dogs with HAC from Dogs without HAC (Screening Tests)

Urine Corticoid to Creatinine Ratio

Urinary corticoid excretion, determined from a morning sample, is a reflection of adrenal glucocorticoid secretion over a period of several hours, negating concerns regarding fluctuating blood concentrations. Several studies have demonstrated UCCR as a sensitive screening test (nearly 100%) but with low specificity (20-77%).[76-79] Due to its sensitivity, UCCR is a good test for ruling out HAC, since a normal result makes the diagnosis extremely unlikely. Since the UCCR is non-specific and increased in dogs with various conditions, further testing is warranted if the UCCR is increased in a dog suspected of HAC. Urine is best obtained at home, at least 2 days after visiting a veterinarian, to avoid the effect of stress.[80] Dogs with PDH tend to have higher UCCR values than those with FAT and if >100 (reference range, <10), the probability of PDH is 90%.[81] UCCR requires little time, and is not invasive. Determination of basal UCCR can be performed in tandem with a HDDST, allowing evaluation of cortisol production and sensitivity of the pituitary gland to exogenous glucocorticoid administration.[30]

Hair Cortisol

It has been reported that hair cortisol concentrations are higher in dogs with HAC compared to control dogs.[82,83] This noninvasive technique might be considered as a screening test for HAC in dogs, but further studies are needed.

ACTH Stimulation Test

The ACTHST evaluates adrenocortical response to maximal ACTH stimulation, is a test of adrenal gland reserve and is the test of choice for identifying iatrogenic HAC (Figure 306-10). Dogs with naturally occurring HAC may have a normal or exaggerated response to exogenous ACTH and those with iatrogenic Cushing's syndrome have a sub-normal response. The sensitivity of ACTH stimulation test is 85% for the diagnosis of PDH and 60% for the diagnosis of FAT, and specificity is 85% to 90%.[84]

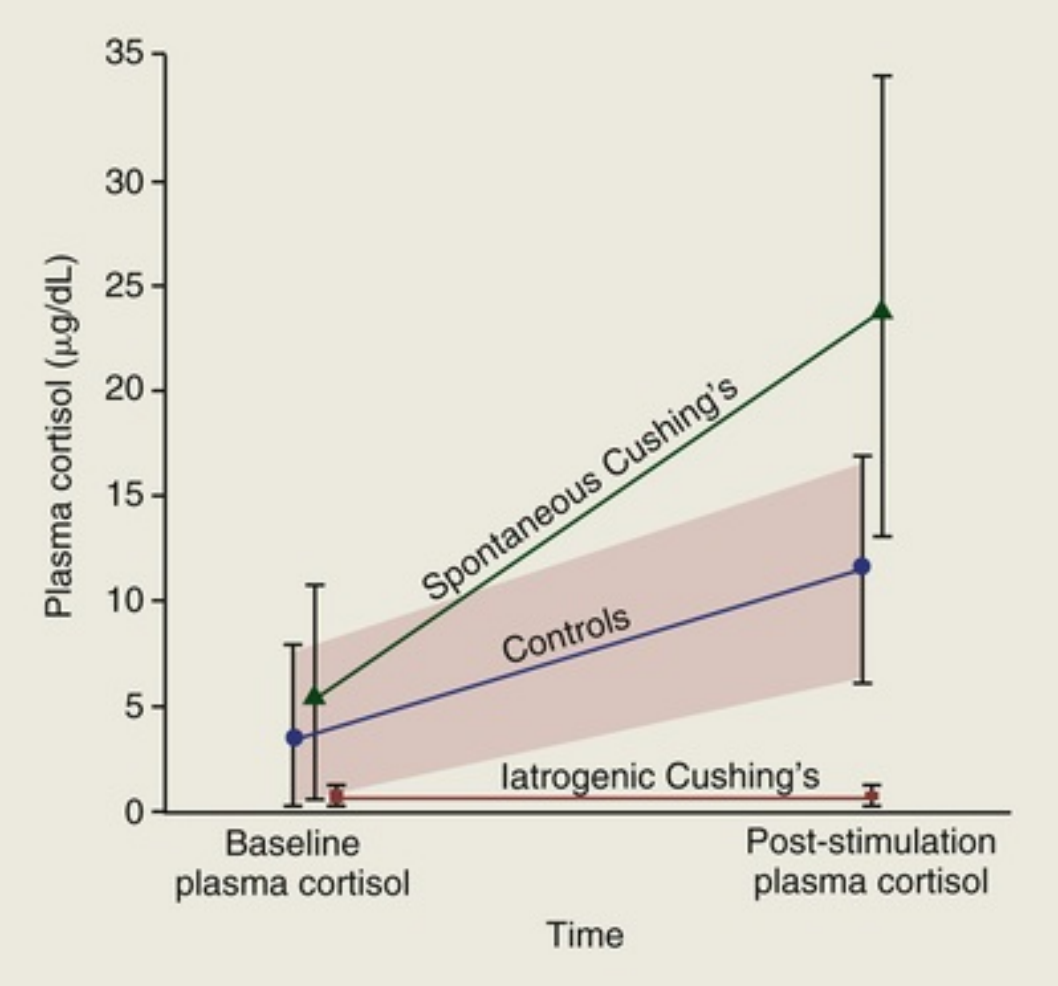


FIGURE 306-10 ACTH stimulation test. Mean radioimmunoassay plasma cortisol concentrations (±2 SD) determined before and 1 hour after administration of synthetic adrenocorticotropic hormone in control dogs, dogs with spontaneous hyperadrenocorticism, and dogs with iatrogenic hyperadrenocorticism.

Several test protocols have been described using either a synthetic peptide containing the first 24 amino acids of ACTH (Cortrosyn, Synacthen, Nuvacthen) or aqueous porcine ACTH gel (Acthar Gel, Questcor Pharmaceuticals, Inc., Union City, CA, USA; not available in certain countries). Most recommend obtaining blood before and 1 hour after giving 250 mcg/dog or 5 mcg/kg of ACTH IM or IV.[85,86] Reconstituted ACTH can be stored in plastic syringes at −20° C for 6 months.[87] Depot tetracosactide (250 mcg/kg IM) and cosyntropin (5 mcg/kg IV) produced similar responses after 60 minutes in healthy dogs.[88] When using ACTH gel, plasma or serum samples for cortisol are obtained before and 1 to 2 hours after IM injection of 2.2 IU/kg. The relatively low sensitivity of ACTHST results together with the limited availability and rising cost of synthethic ACTH have reduced its use. ACTHST results cannot differentiate PDH from FAT. Despite its relatively low sensitivity, it is less affected by non-adrenal illness, is not time-consuming and is the only test for differentiating iatrogenic from naturally occurring HAC.

"Atypical" HAC and ACTHST

Another potential use for the ACTHST is for dogs suspected of having *"atypical"* HAC. *"Atypical" or "occult"*

HAC refers to a dog with clinical signs, physical examination and clinicopathologic findings compatible with HAC but with results of LDDST, UCCR, and ACTHST within reference ranges. It has been hypothesized that these dogs have a derangement of the steroid synthesis pathway which leads to abnormally increased precursor concentrations but normal concentrations of cortisol. Measurement of 17-hydroxyprogesterone (17-OH-P), a cortisol precursor, before and after ACTHST might help diagnose this rare form of HAC by documenting an exaggerated 17-OH-P response to ACTH.[89,90] However, results of ACTHST should be interpreted carefully since false positive results have been documented in dogs with nonadrenal illness and no evidence of HAC.[91] The diagnosis of "atypical" HAC has been questioned. Dogs with mild or early HAC "normal" on tests using current cutoff values may be diagnosed using revised reference ranges. Also, variable cortisol sensitivity might exist and some dogs with high sensitivity may show clinical signs of HAC at lower cortisol concentrations than others.[30,92]

The Low-Dose Dexamethasone Screening Test

The LDDST is considered the "test of choice" for confirming a diagnosis of naturally occurring HAC in dogs.[30,93] The normal pituitary-adrenocortical axis response to the negative feedback associated with exogenous dexamethasone (a glucocorticoid) is ACTH suppression causing decreases in cortisol secretion. Dogs with HAC are abnormally resistant to dexamethasone suppression. LDDST sensitivity is excellent. Results are consistent with HAC in about 90-95% of PDH dogs and virtually 100% of dogs with a FAT. While LDDST sensitivity is excellent, specificity can be as low as 40 to 50%, especially when assessed in a population of dogs with non-adrenal illness.[79] Thus, diagnosis of HAC should never be based solely on LDDST results. Testing should be delayed in any ill dog. The test is not helpful in the detection of iatrogenic HAC, is affected by more variables than the ACTHST, requires 8 hours (or 3 days if using the UCCR protocol; see below), and does not provide information useful in monitoring treatment.

Serum or plasma samples are collected for cortisol concentration before, 4, and 8 hours after dexamethasone administration. Dexamethasone in polyethylene glycol (0.015 mg/kg, IV or IM) or dexamethasone sodium phosphate (0.01 mg/kg, IV) can be administered with equivalent results (Figure 306-11).[29] Reliable results may not be obtained from dogs under stress or being treated with phenobarbital. In a dog with clinical signs of HAC, lack of adequate cortisol suppression is consistent with the diagnosis. Basal and 8-hour post-dexamethasone cortisol results are used for the "screening" portion of interpretation. Results from the sample taken after 4 hours may be helpful for discriminating PDH from FAT. Approximately 30% of dogs with PDH exhibit serum cortisol suppression at 4 hours (< 1.4 mcg/dL or <40 nmol/L), with a higher cortisol concentration at 8 hours. This escape or "V" pattern is consistent with PDH and further discriminatory tests are not necessary.[84] Dogs with a serum cortisol concentration at 4 or 8 hours that has decreased to less than 50% of the baseline serum cortisol concentration (pre-dexamethasone) are also most likely to have PDH. Approximately 65% of dogs with PDH demonstrate suppression using one of these 3 criteria.[93] Failure to suppress (cortisol at both 4 and 8 hours >1.4 mcg/dL and >50% of basal cortisol concentration) is consistent with a diagnosis of HAC, but is not helpful in discriminating PDH from FAT. LDDST interpretation should be based on updated reference ranges and cut-off values established by each laboratory.

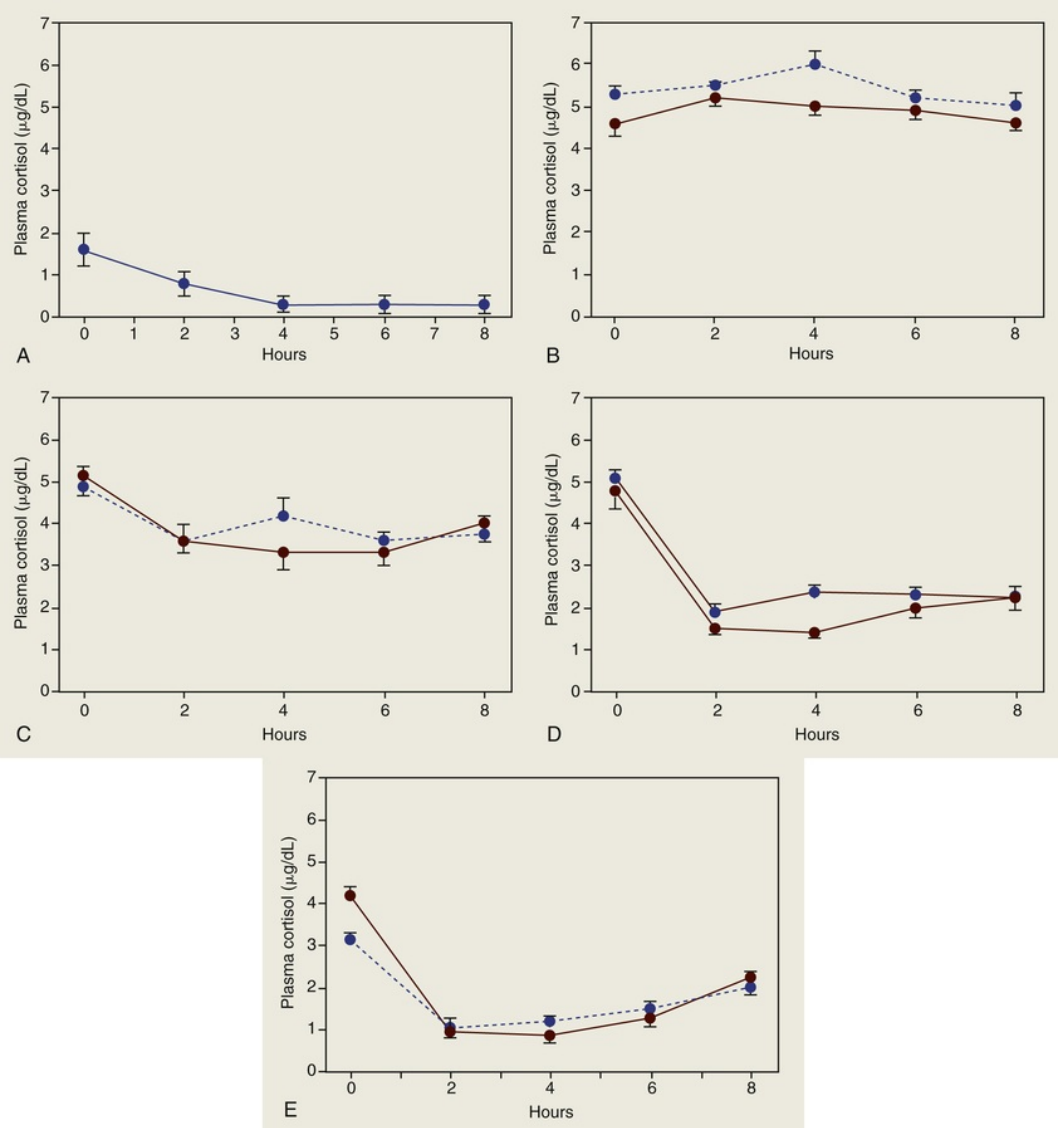


FIGURE 306-11 Mean plasma cortisol concentrations before and after administration of a low dose of dexamethasone in 27 normal dogs **(A);** 48 dogs with adrenocortical tumors **(B);** 130 dogs with pituitary-dependent hyperadrenocorticism (PDH) **(C);** the dogs among the 178 with Cushing's syndrome that had at least one plasma cortisol concentration less than 1.4 mcg/dL after dexamethasone administration (total, 54; each had PDH) **(D);** and the dogs among the 178 with Cushing's syndrome that, after dexamethasone administration, had at least one plasma cortisol concentration decreased to less than 50% of the baseline concentration (total, 95; each had PDH) **(E).** Note the two curves for graphs **B, C, D,** and **E.** These represent the use of dexamethasone sodium phosphate (dashed line) and dexamethasone in polyethylene glycol (solid line). No significant difference in results is seen with these dexamethasone products. (From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction,* ed 2, Philadelphia, 1996, Saunders, p 227.)

UCCR/LDDST Combined

The LDDST can be carried out by obtaining urine for UCCR rather than using serum or plasma cortisol.[94] With this protocol, the owner collects urine samples on 2 consecutive mornings at about 8 a.m. for baseline UCCRs. After collecting the second sample, the owner gives 0.01 mg/kg dexamethasone PO. The dog's bladder should be emptied voluntarily or via catheterization at 2 p.m. A third and final urine sample is collected at 4 p.m., 8 hours after giving dexamethasone. Results suggest that >50% suppression in mean UCCR and a decrease in ratio to <10 would be expected in healthy dogs.[94] Dogs with HAC would not be expected to demonstrate suppression.

Discrimination Tests in Dogs with HAC (PDH versus FAT)

LDDST

The LDDST can aid in discriminating PDH from FAT. Results are consistent with PDH if 1 of 3 criteria is met: (1) a 4-hour cortisol concentration <1.4 mcg/dL; (2) a 4-hour cortisol concentration <50% of basal; (3) an 8-hour cortisol concentration <50% of basal but ≥1 mcg/dL). About 65% of dogs with naturally occurring PDH meet at least one of these criteria.[93] However, updated cut-off values are also needed. Dexamethasone resistance, in which none of these criteria is met, is seen in about 35% of dogs with PDH and virtually all dogs with a FAT. In these dogs, another discrimination test is indicated.

High-Dose Dexamethasone Suppression Test

Most dogs with PDH exhibit some resistance to suppression during the LDDST, but higher doses of dexamethasone can overcome this resistance. In contrast, due to chronic suppression of pituitary ACTH in dogs with a cortisol-secreting FAT, administration of dexamethasone, regardless of dose, fails to suppress cortisol concentrations.[93] The recommended protocol for HDDST is to collect blood before and 4 or 8 hours after giving 0.1-1 mg/kg dexamethasone (IV or IM). Dexamethasone in polyethylene glycol or dexamethasone sodium phosphate can be used with equivalent results.

Demonstrating a decrease in cortisol concentration <1.4 mcg/dL (40 nmol/L) is generally considered diagnostic for PDH and excludes a FAT. Interpretation of results should also be based on the laboratory's reference ranges for both dose and dexamethasone used. Lack of suppression is not diagnostic for a FAT, as about 35% of dogs with PDH fail to demonstrate cortisol suppression. Evidence suggests that dogs with large pituitary tumors are less likely to demonstrate response, regardless of dosage.[95] In dogs with confirmed HAC that do not demonstrate suppression via HDDST, there remains a greater chance of PDH than FAT.

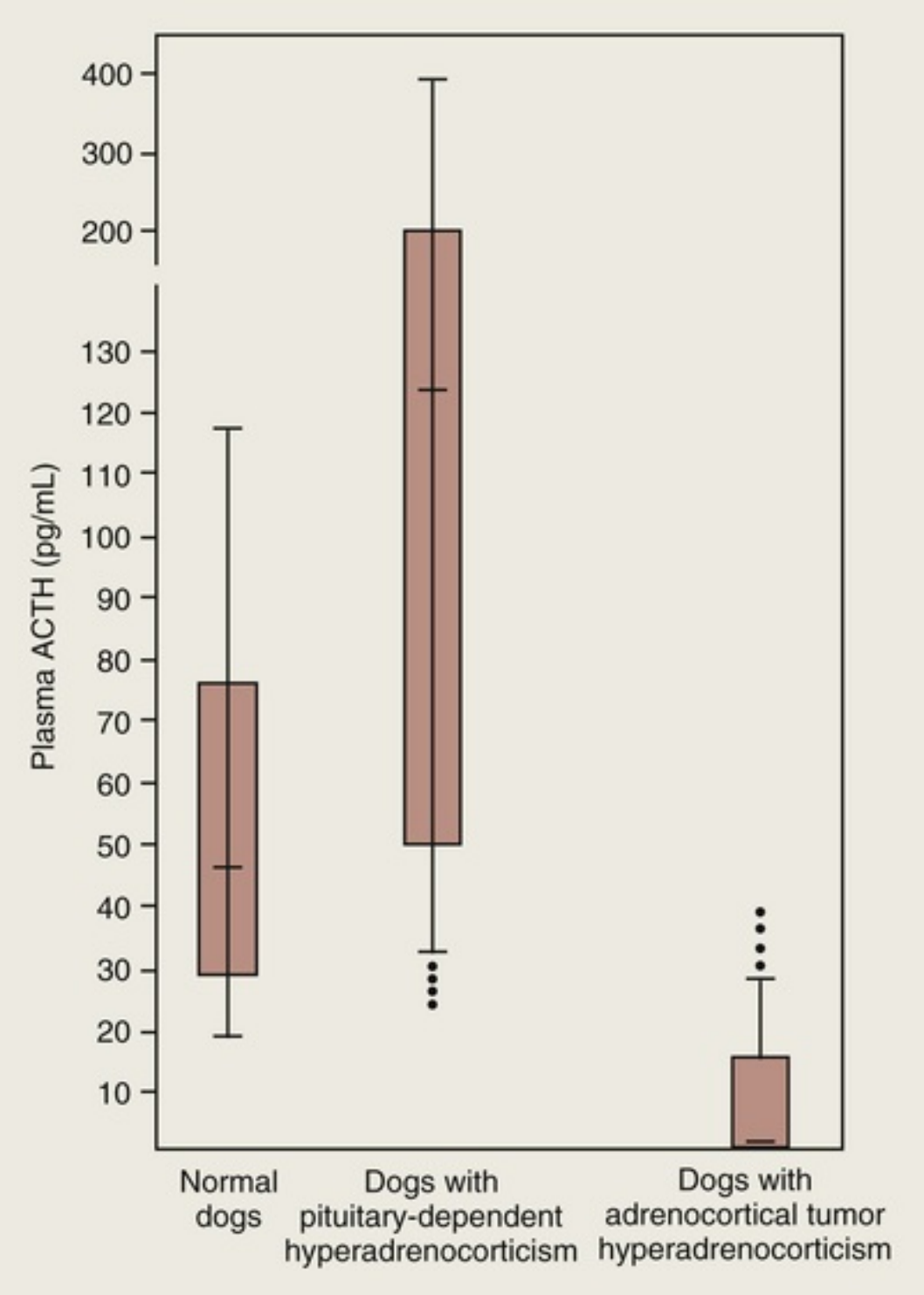
Most of the dogs with PDH that show suppression of cortisol on HDDST also show cortisol suppression on the LDDST. The HDDST results provided additional information in only about 10% that failed to suppress on LDDST.[93] Therefore, it is useful to perform a LDDST routinely in dogs suspected of having HAC. However, when dexamethasone resistance is demonstrated on the LDDST, it would be more efficient to perform another differentiating test, such as adrenal imaging or measurement of endogenous ACTH.

UCCR/HDDST Combined

This combination can be used as the initial endocrine test in evaluating a dog for HAC. A urine sample is collected on 3 consecutive mornings, at home, for UCCR. After the second sample is collected, the owner gives 0.1 mg/kg dexamethasone, orally, to the dog 3 times at 8-hour intervals. The mean baseline UCCR is calculated from the first two results. If the baseline UCCR is increased, consistent with HAC, PDH is likely if the third UCCR result is <50% of baseline.[81]

Endogenous ACTH (eACTH)

Measurement of basal eACTH concentration is of little value as a screening test for HAC, but it can be valuable to discriminate PDH from FAT after HAC has been confirmed. There is little overlap in eACTH concentrations in results from dogs with PDH versus those with FAT.[96] eACTH concentrations are normal to increased in dogs with PDH (e.g., >40 pg/mL or >8.8 pmol/L) and usually low or undetectable (e.g., <20 pg/mL or <4.4 pmol/L) in dogs with FAT or iatrogenic HAC (E-Figure 306-12). Approximately 20% of dogs with HAC have randomly obtained eACTH results in a nondiagnostic range (20-40 pg/mL) and, in such dogs, the test can be repeated or an imaging study may be indicated.



E-FIGURE 306-12 Endogenous plasma adrenocorticotropic hormone (ACTH) concentrations from clinically normal dogs, dogs with pituitary-dependent hyperadrenocorticism, and dogs with functioning adrenocortical carcinomas or adenomas. Each box represents the interquartile range from the 25th to the 75th percentile (the middle half of the data). The horizontal bar through the box is the median. The "whiskers" represent the main body of data, which in most cases is equal to the range. Outlying data points are represented by the circles. (From Feldman EC, Nelson RW, Reusch CE, et al: *Canine and feline endocrinology and reproduction,* ed 4, St Louis, 2015, Saunders.)

Sampling, handling, and assaying samples for reliable eACTH results can be difficult and costly. Samples must be collected in heparin or EDTA tubes and centrifuged immediately. Plasma is then placed into plastic or polypropylene tubes (ACTH will adhere to glass) and immediately frozen until assayed. Plasma samples should be sent on dry ice by overnight delivery service. If such conditions are not feasible, aprotinin, a

protease inhibitor, can be added to the EDTA tube as a preservative for ACTH; in such cases, the sample can be shipped cold via refrigeration packs and freezing is not necessary.[97]

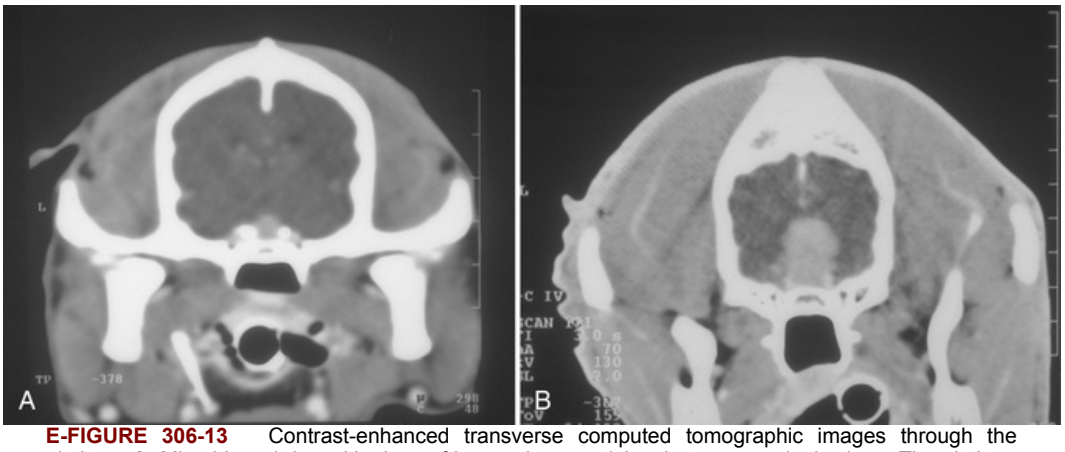
Ultrasonographic Examination of the Abdomen and Adrenal Glands

Bilateral symmetrical enlargement is expected in dogs with PDH. A solitary adrenal mass and atrophy of the contralateral gland is expected in dogs with FAT. However, some dogs with PDH have normal-appearing adrenal glands while others have asymmetrical nodular hyperplasia that can be mistaken for an adrenal mass. Some dogs with adrenal masses have a normal-appearing contralateral gland. Maximal thickness of the smaller gland is helpful to differentiate adrenal tumors (<5 mm) versus asymmetrical hyperplasia (>5 mm).

Computed Tomography and Magnetic Resonance Imaging Scans

US is usually acceptable for assessing adrenals for a mass while CT and MRI are the only modalities available for visualizing a pituitary mass. CT and MRI scan results cannot be used to replace endocrine function testing. About 50% of pituitary tumors are not visible with either modality and neither can determine function.[45] Invasive adenomas, seen with CT or MRI have a mean height (1.8 ± 0.7 cm) significantly greater than non-invasive adenomas.[9] Pituitary tumors in dogs usually expand dorsally due to the minimal resistance encountered at the incomplete diaphragma sella. Growth may result in invagination into the third ventricle and may compress and/or invade the hypothalamus. The optic chiasm, rostral to the pituitary, is rarely impacted by an expanding pituitary mass, sparing vision.

Pituitary gland size depends on breed and individual variation. Pituitary gland CT measurements in healthy dogs revealed sizes of 3.2-5.1 mm (height), 4.2-6.9 mm (width), and 3.6-7.2 mm (length).[98] The first sign of pituitary enlargement is an increase in height (dorsal extension into the suprasellar region). When the dorsal contour of the gland protrudes above the suprasellar extension of the intercrural cisterns, easily recognized on CT scans, enlargement is likely (E-Figure 306-13).[95] Alternatively, ratio of pituitary height to brain area as measured on an image through the center of the pituitary (P : B ratio) can be used to discriminate between an enlarged (P : B >0.31) or normal (P : B ≤0.31) pituitary gland size.[98]

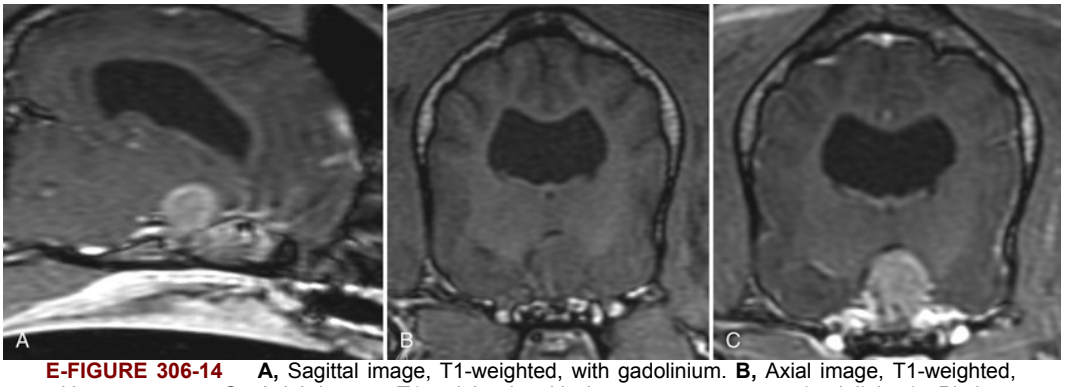


E-FIGURE 306-13 Contrast-enhanced transverse computed tomographic images through the pituitary. **A,** Mixed-breed dog with signs of hyperadrenocorticism but no neurologic signs. The pituitary is enlarged (0.6 cm in height). **B,** Bergamasker with hyperadrenocorticism that had been treated with mitotane for 2 years, after which neurologic signs developed (i.e., disorientation, ataxia, aggressive behavior). The pituitary is grossly enlarged (2.1 cm in height).

Large tumors are usually easily detected on contrast-enhanced CT images because of their size and altered shape. In 50% to 60% of dogs with PDH, a pituitary mass can be detected by CT. Forty percent to 50% of PDH dogs have a smaller tumor (<3-4 mm), not visible despite contrast enhancement. CT modalities using a series of transverse scans through the center of the pituitary during and after rapid IV injection of contrast medium ("dynamic" CT) can often help distinguish the posterior from anterior pituitary, due to differences in vascularity. In normal dogs, an early, strong enhancement of the central posterior pituitary ("pituitary flush") is seen, as well as a slightly delayed, weaker enhancement of the peripheral anterior gland. Displacement or distortion of the posterior flush may reveal the existence of small tumors.[99]

Although CT and MRI are both effective at identifying large pituitary tumors, MRI is superior at defining

the full tumor extent and its effect on surrounding structures. It appears more accurate in identifying small masses (E-Figure 306-14). Size, signal, and contrast enhancement MRI characteristics of the normal canine pituitary gland have been described. One study found that about 50% of PDH dogs with no neurologic signs have a pituitary tumor that can be visualized on MRI scans, ranging from 4 to 12 mm in size.[100,101]



E-FIGURE 306-14 **A,** Sagittal image, T1-weighted, with gadolinium. **B,** Axial image, T1-weighted, without contrast. **C,** Axial image, T1-weighted, with intravenous contrast (gadolinium). Pituitary enlargement (13.3 mm antero-posterior, 11.1 mm latero-lateral, and 12.9 mm dorso-ventral diameters, respectively) with suprasellar extension and hydrocephalus in a female Boxer dog with PDH causing neurologic signs (stupor, head-pressing, and anorexia). The dog was treated with trilostane. (Images obtained in a General Electric 3 Tesla in the Ruber Internacional Hospital. Courtesy Dr. Ana Vicente, Montaña.)

Treatment

Treatment Considerations

The choice of treatment for a dog with HAC depends on several factors: PDH vs FAT, severity of the condition, presence of HAC complications or concurrent diseases, the available treatments, treatment efficacy, side effects, and clinician and client preferences. Cost and need for frequent follow-up evaluations may be essential considerations. It is important to remember, however, that not all dogs with HAC, especially dogs with PDH, need immediate treatment. Since none of the screening or differentiating tests for HAC is perfect, a dog that has no signs or only minimal clinical signs despite abnormal biochemical and/or endocrine tests consistent with HAC should not be treated.[30] Treatment of HAC is never benign and should not be initiated unless the dog shows unambiguous clinical signs of the condition. These factors are further emphasized with the goals of therapy being, primarily, owner-perceived clinical improvement.

Overview of Treating Pituitary-Dependent Hyperadrenocorticism

PDH can be treated medically or surgically. Hypophysectomy is the treatment of choice in humans with PDH and has been well described in dogs. Hypophysectomy is not widely used due to the limited number of surgeons with expertise, its related side effects, and the success achieved with medical therapies. Most dogs with PDH are treated medically with drugs that inhibit synthesis of adrenocortical hormones (i.e., trilostane or ketoconazole) or that cause partial or complete necrosis of the adrenal cortices (i.e., mitotane). A drug claimed to decrease ACTH secretion (selegiline) is not efficacious.

While trilostane has become the treatment of choice for dogs with HAC, mitotane also has successfully been used to resolve the clinical and biochemical abnormalities of HAC. Both trilostane and mitotane have caused serious adverse side effects. Both drugs decrease plasma cortisol and increase ACTH secretion, which may enhance pituitary tumor growth.[102-104] Dogs with pituitary macroadenomas can benefit from radiation therapy, which can decrease tumor size and reduce neurological signs. On one hand, treating PDH is costly and requires periodic monitoring; on the other, most dogs have a good or excellent response to treatment.

Trilostane Therapy

History and Pharmacology

Use of trilostane for treatment of canine PDH was first reported in 1998 and several studies have confirmed its clinical efficacy for treating dogs with HAC.[102,103,105-117] Trilostane is a synthetic steroid analogue that acts as a competitive inhibitor of the enzyme 3-beta-hydroxysteroid dehydrogenase (3-beta-HSD), which catalyzes adrenocortical conversion of pregnenolone to progesterone. Inhibiting this enzyme's action blocks synthesis of cortisol and, to a lesser extent, aldosterone (Figure 306-15).[106] Trilostane reaches peak concentrations <2 hours after administration and is completely metabolized within 10-18 hours. Trilostane's inhibition of 3-beta-HSD is confirmed by decreases in plasma cortisol concentrations with concurrent increases in 17-alpha-OH-pregnenolone. 17-alpha-OH-progesterone concentrations do not change, suggesting that trilostane may also inhibit 11-beta-hydroxylase, influencing the interconversion of active cortisol to inactive cortisone by 11-beta-hydroxysteroid dehydrogenase (11-beta-HSD).[102] Adrenal gland mRNA and protein expression of 11-beta-HSD type 1 are increased while mRNA and protein expression of 11-beta-HSD type 2 are decreased.[118]

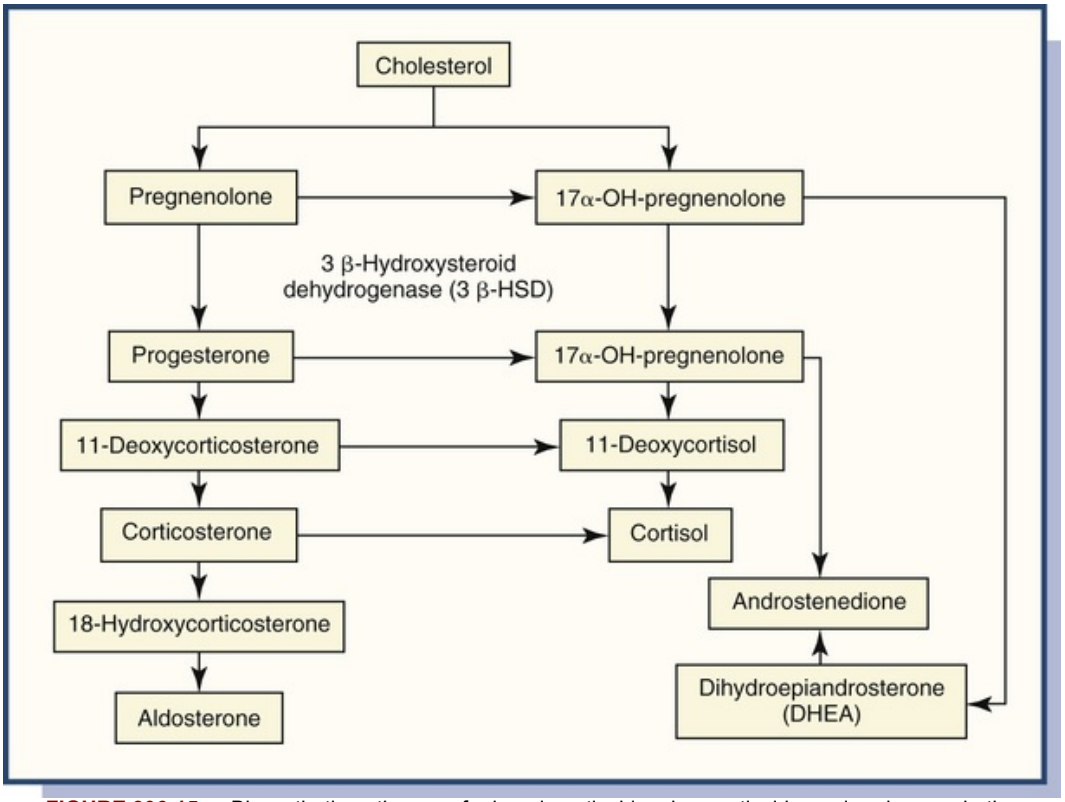


FIGURE 306-15 Biosynthetic pathways of mineralocorticoids, glucocorticoids, and androgens in the adrenal cortex. **3-Beta-hydroxysteroid dehydrogenase,** which converts pregnenolone to progesterone and dehydroepiandrosterone to androstenedione, is blocked by trilostane.

Initial Dosage and Frequency of Administration

Dosage, frequency of administration and monitoring protocols for trilostane continue to be evaluated. Dosages used in early studies (as much as 50 mg/kg/day) were higher than current recommendations. Manufacturer-recommended starting dosages range from 3-6.7 mg/kg PO q 24 h, depending on body weight. However, several studies have shown that doses as low as 0.2-1 mg/kg PO q 12 h are effective and may cause fewer adverse side effects.[113,114,116,117] As body weight increases, required trilostane dosage decreases.[113,114] The initial dosage of trilostane should be based on body weight and planned frequency of administration. In dogs with HAC, the duration of cortisol suppression caused by trilostane varies. In most, cortisol concentrations were suppressed for <12 hours, explaining why q 24 h protocols are not effective in all dogs.[105,108] The proportion of dogs demonstrating good control of their HAC improves with q 12 h administration.[108,109,113,115-117] Also with q 12 h protocols, the total daily dose needed for good control is generally lower.[108,109,113-117] One study evaluating survival time of q 12 h-trilostane-treated PDH dogs, found higher median survival times (900 days) than reported in a study evaluating PDH dogs treated q 24 h (662

days).[110,111] Even though most dogs with HAC are well controlled with q 24 h or q 12 h administration, some respond best to trilostane given q 8 h.[108,113]

An initial dose of 0.5-1 mg/kg PO twice a day is recommended. Once-daily protocols (1-2 mg/kg) should be reserved for owners who refuse the q 12 h alternative. Although low initial dosages may prolong the time needed to control clinical signs, more often these dosages have been adequate while reducing risk of overdose.[108] Some dogs fail to exhibit a good clinical response on q 24 h treatment despite test results indicating adequate cortisol suppression at trilostane peak effect. In these dogs, consideration should be given to q 12 h (see use of urine specific gravity). Regardless of the selected initial dosage and frequency of administration, treatment must be individualized to the needs of the patient and the owner.

Judging Trilostane Response and Dosage Adjustments

It is expected that trilostane-treated dogs will require dosage adjustments, based on clinical response and/or test results. Within 7-10 days of starting trilostane, owners should notice increased activity and decreased PU/PD/PP. PP, of the 3, may decline more slowly, over several weeks. Dermatological problems may take months to completely resolve. The hair coat in some dogs initially appears to worsen, as dead hair and dead dry skin is shed, creating worsening alopecia and severe flaking.

Treatment adjustments should be based on clinical signs (PU), CBC, serum biochemical profile, and ACTHST results (Figure 306-16). ACTHST results reflect adrenocortical reserve and this is the most objective, specific, and sensitive test for assessing therapeutic response.[102,119-121] ACTHS testing in relation to time of trilostane administration is extremely important. Recommendations include starting the test to coincide with either the peak (2-3 hours post-pill) or trough (just before giving the next dose) in trilostane action. In a study comparing results of ACTHST performed 2 versus 4 hours after trilostane administration, maximal effect in most dogs (lowest cortisol concentration) was detected when starting the test 2 hours post-pill.[121] Results of this study also emphasize the importance of consistency in timing ACTHST. The ACTHST can be started 8-12 hours post-pill in dogs treated q 12 h to evaluate trough effects and duration of action.[108,109] Starting the ACTHST 24 hours post-pill can similarly document trilostane's duration of action, if it is being given once daily.

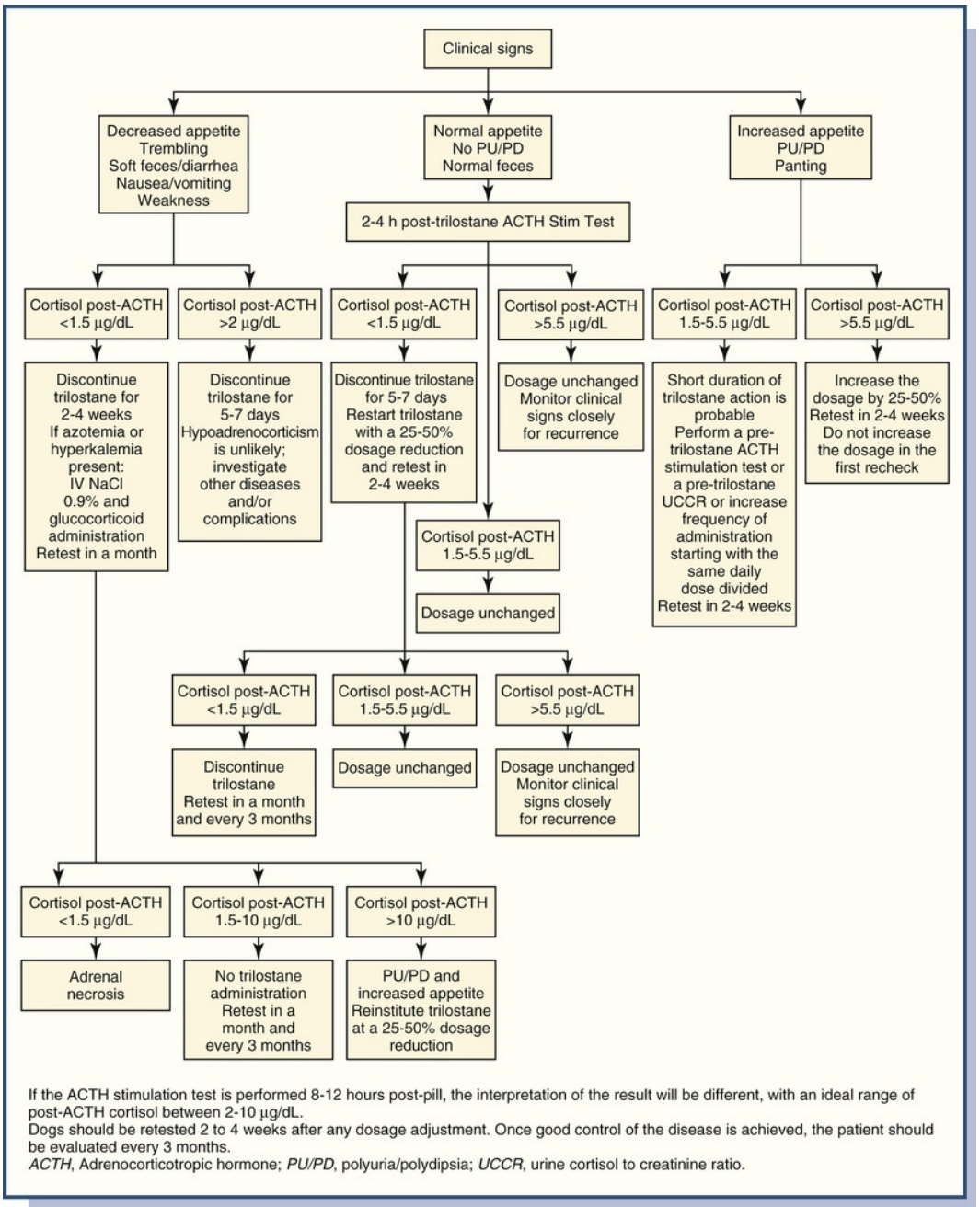


FIGURE 306-16 Algorithm for monitoring dogs with hyperadrenocorticism treated with trilostane.

Judging Trilostane Response and Dosage Adjustments without Access to ACTH Stimulation Testing

See E-Box 306-1.

E-Box 306-1

Monitoring Trilostane Treatment of Canine Hyperadrenocorticism without Access to ACTH Stimulation Testing

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Glasgow, United Kingdom

ACTH is not consistently available or it may be prohibitively expensive. There is need, therefore, to identify alternative methods for monitoring trilostane treatment in order to obtain safe and reasonable control of clinical signs without risk of iatrogenic hypoadrenocorticism. Owner opinion regarding response to trilostane administration is the most important information for any veterinarian to consider when treating a dog for hyperadrenocorticism. Daily owner records, similar to those kept by owners of diabetic pets, may help the veterinarian appreciate any trend or concern. However, if owner opinion and records are used as the sole criteria for assessing control and for dose adjustments, there is a risk of trilostane overdosing if subtle early warning signs are missed by an owner. Secondly, clinicians less familiar with trilostane and/or hyperadrenocorticism may not feel as confident in assessing information provided by owners. Some owners may themselves be unreliable in their assessments and recording. Finally, a clinical history provided by even the best of owners does not provide parameters for safely determining how much change in trilostane dose might be indicated to improve response.

A proposed method for monitoring dogs being treated with trilostane without the use of ACTH stimulation test results includes the use of the serum cortisol concentration measured just before giving the morning dose of trilostane.[1,2] The "pre-pill cortisol" has been found to be in better agreement with an owner-based scoring scheme than the post-ACTH cortisol in one study based on 70 measurements made on 53 dogs, most treated once daily but some being treated twice daily, when monitored after 1 month on a consistent dose of trilostane.[3,4]

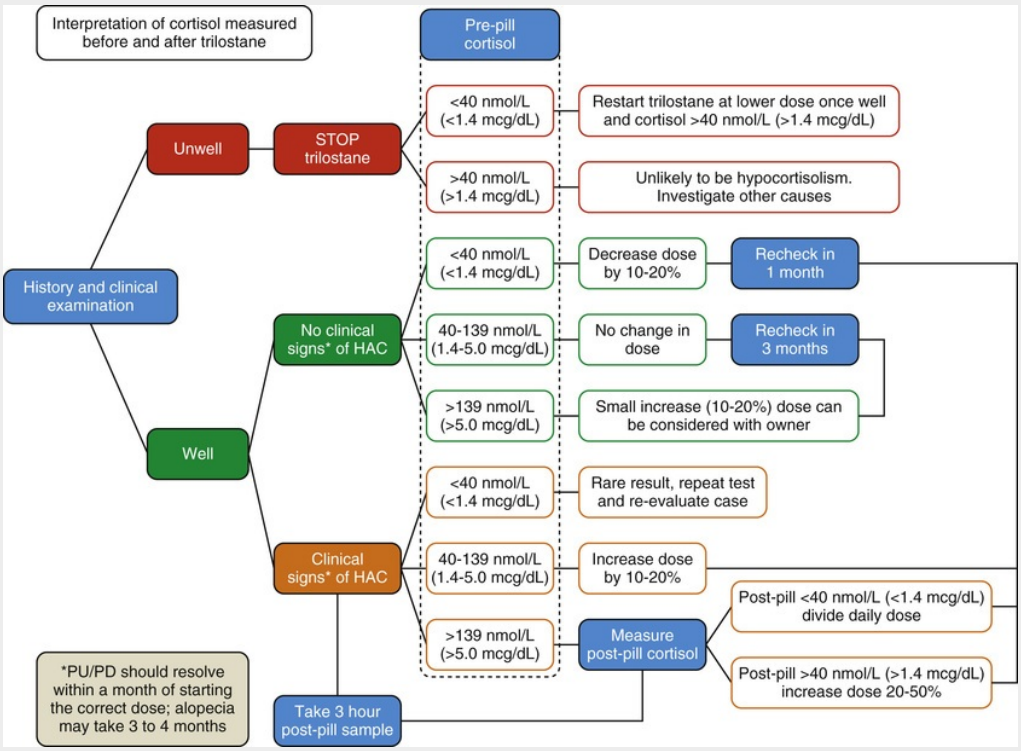
Good clinical control tends to be associated with pre-pill cortisol concentrations in the range of 40-139 nmol/L (1.4-5.0 mcg/dL) and can be regarded as the approximate target range. As with ACTHST results, it is imperative that the results of pre-pill cortisol measurements be interpreted in the context of owner observations and physical examination. If, for example, the clinical signs of polyuria, polydipsia and polyphagia have resolved but the pre-pill cortisol concentration is higher than ideal, it may be sensible to continue the same dose and monitor closely or employ a small (10-20%) dose increase. Decisions regarding changing dose and/or frequency of administration are best made by the veterinarian-owner team, rather than by either alone.

If the clinical signs have resolved but the pre-pill cortisol concentration is less than 40 nmol/L (1.4 mcg/dL) then a dose reduction of 10 to 20% is warranted, even if the dog is clinically well.

If the dog is not well controlled and the pre-pill cortisol concentration is in the target range, the implication is that trilostane's duration of action is long enough but that degree of suppression is insufficient for that particular dog and a small (10-20%) increase in dose should be discussed with the owner.

Some dogs that are not well controlled may have a pre-pill cortisol above the target range. Another serum sample obtained at the nadir for post-pill cortisol concentrations may assist in dose change decisions. This nadir is about 3 hours after giving trilostane.[5] If the post-pill concentration is >40 nmol/L then about a 20-50% increase in dose may be required. If the post-pill concentration is <40 nmol/L then an increase in frequency, while keeping the total daily dose the same, may be useful.[6]

A summary flowchart of these interpretations is provided below. Regardless of monitoring method selected, it is important that the cortisol assay employed be properly validated and the appropriate reference ranges used. The figures provided (cortisol values) are valid for one type of chemiluminescent assay (Immulite series; Siemens).



5 Case Scenarios Are Provided Below

CLINICAL HISTORY	PRE-PILL	POST-PILL	ACTIONS
Vomiting, diarrhea and off food	168 nmol/L (2.1 mcg/dL)	ND	Stopped trilostane. Diagnosed with gastric mural mass, pancreatitis. Euthanized at owner's request.
Generally well but slightly lethargic	34 nmol/L (0.7 mcg/dL)	23 nmol/L (0.8 mcg/dL)	Stopped trilostane. Dog reported to be much livelier within 24 hours. Diagnosed hypocortisolism. Treatment restarted at 50% of original dose once dog well.
Polyuria, polydipsia after 2 months of treatment	169 nmol/L (6.1 mc	154 nmol/L (5.6 mc	Increased dose by 50%. One month later pre-pill cortisol reduced to 148 nmol/L and post-pill cortisol to 75 nmol/L and dog was clinically better.

	g/dL)	g/dL)	
Not PU/PD but still alopecic after 2 months of treatment	89 nmol/L (3.2 mcg/dL)	17 nmol/L (0.6 mcg/dL)	No change in treatment. Re-examined 2 months later, coat regrown and dog still doing very well.
Very well, would not know dog had HAC	53 nmol/L (1.9 mcg/dL)	20 nmol/L (0.7 mcg/dL)	No change in dose. Rechecked every 3 months for a year. Consistently similar results.

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Adverse Side Effects to Trilostane

Trilostane is well-tolerated in most dogs. Side effects, if present, are usually mild and caused by low cortisol and/or low aldosterone concentrations. Some dogs may develop lethargy and decreased appetite within a few days of initiating therapy. Severe adverse effects may occur. These include depression, anorexia, vomiting, diarrhea, shaking, weight loss, obtundation and death. If a trilostane-treated dog has worrisome signs, trilostane should be immediately discontinued while serum electrolytes, renal parameters, blood glucose, and blood pressure are assessed.[107,109,110] An ACTHST can be completed, although results may not be as helpful in managing an acute severe illness or crisis.

Trilostane-Induced Adrenocortical Necrosis

Once overdosed with trilostane, adrenal function in dogs may remain suppressed for days, months or longer.[109] Prolonged hypoadrenocorticism is not anticipated after giving a drug known to inhibit the adrenocortical enzymes for <12 hours, but variable degrees of adrenocortical necrosis and hemorrhage caused

by trilostane, especially within the zona fasciculata, have been documented.[122] Prolonged hypocortisolism can occur with or without mineralocorticoid deficiency. Worrisome adverse effects have been documented to begin days, months or years after beginning treatment in as many as 25% of trilostane-treated dogs.[109,123] A study in rats given increasing trilostane dosages demonstrated that secondary increasing eACTH concentrations may be responsible for the adrenal necrosis.[124] Therefore, avoiding hypocortisolism may prevent signs and decrease chances of adrenal necrosis. Considering these potentially serious complications, it is extremely important to carefully monitor dogs receiving trilostane and perform the recommended evaluations, even if a dog is doing well clinically.

Long-Term Trilostane Dosage and Frequency Adjustments

Dogs given trilostane should be evaluated after 10 to 15 days of treatment and again after 1 month, 3 months and every 3-6 months thereafter. At each recheck, a complete history and physical examination should be obtained. CBC and serum biochemical panel with electrolytes may be indicated. In addition, one should perform an ACTHST at each visit. The test should be started 2 to 4 hours after trilostane administration and that time interval should be maintained on all subsequent rechecks. Dosage adjustments should be based on clinical response and results of routine and endocrine testing (see Figure 306-16). A post-ACTH cortisol concentration of 1.5-5.5 mg/dL (41-152 nmol/L) is considered adequate when the ACTHST has been performed at 2-4 hours post-pill.[125,126] The primary goal of the first re-evaluation is to avoid an overdose. Trilostane dosage should not be increased on the first assessment, even if clinical signs have not improved and post-ACTH cortisol concentration is above 5.5 mcg/dL. After the first recheck, if clinical signs of HAC persist and the post-ACTHST cortisol is >5.5 mcg/dL, the dosage of trilostane should be increased. If a dog on q 24 h or q 12 h trilostane is doing clinically well but the post-ACTHST cortisol concentration is <1.5 mcg/dL, trilostane must be discontinued for 5-7 days and then restarted at a 25-50% lower dosage. If, after another 2 to 4 weeks, the serum cortisol values remain low, trilostane should be discontinued indefinitely and ACTHST scheduled every few months or whenever an owner observes recurrence of signs. Trilostane should only be re-started if clinical signs of HAC recur and post-ACTHST cortisols are once again increased.

Long-Term Trilostane Dosage and Frequency Adjustments Using Urine

One can use urine obtained prior to trilostane administration to aid in long-term adjustments. In this scenario, ACTHST results are used to determine trilostane **dosage** and urine specific gravity used to determine **frequency.** For example, if a dog continues to exhibit PU/PD, has a pre-pill urine specific gravity <1.020 (glucose negative), and post-ACTHST serum cortisol concentration >1.5 and <5.5 mcg/dL, frequency of administration should be increased.[104,108,113]

Hypocortisolism

If clinical signs consistent with hypocortisolism are seen, trilostane should be stopped while an ACTHST and serum biochemistry profile are obtained and assessed. If hypocortisolism is confirmed but serum electrolytes are normal, one should stop trilostane, administer glucocorticoids as needed, and repeat the ACTHST 2-4 weeks later. Based upon these results, trilostane may need to be reinstituted if the dog begins showing clinical signs of HAC and the post-ACTHST cortisol concentration is >10 mcg/dL. If hypoadrenocorticism persists, adrenal necrosis is likely. If hypoadrenocorticism is confirmed together with hyperkalemia and/or hyponatremia, one should discontinue trilostane for at least a month and treat as an Addisonian crisis (see ch. 309). ACTHSTs should be repeated after a month and then every 3 to 6 months to determine when treatment for Addison's can be stopped and whether trilostane therapy should be restarted.

Use of Trough Cortisols and/or US

Assessing the basal cortisol at peak trilostane action (usually 2 to 4 hours post-pill) has been evaluated as a monitoring tool in dogs with HAC and to detect hypocortisolism (cortisol <1.5 mcg/dL). A 2- to 4-hour post-trilostane basal cortisol concentration 1.5-4.4 mcg/dL has been considered indicative of adequate control. This approach is not widely accepted, in part because of considerable overlap between excessive, adequate and inadequate control. ACTHSTs are considered far more informative than basal cortisol assessment.[119,120]

The US appearance of adrenal glands changes with trilostane treatment, usually enlarging due to increases in ACTH secretion secondary to reduced cortisol negative feedback.[118,127,128] A marked increase in echogenicity of the outer zone has also been described. Small and heteroechoic adrenal cortices may be indicative of necrosis.[123]

Alternative Therapies

Discussion of mitotane, retinoic acid, cabergoline, ketoconazole and other drugs for treatment of HAC is reviewed in E-Boxes 306-2 and 3. A recombinant ACTH vaccine resulted in production of antibodies against ACTH in healthy dogs; however, effect on the pituitary adrenal axis is subtle and transient.[145] Epidermal growth factor receptor (EGFR) has been proposed as a therapeutic target for canine ACTH secreting tumors.[146].

E-Box 306-2

Mitotane and Other Therapies

Mitotane

Mitotane is an adrenocorticolytic agent with a direct cytotoxic effect on the adrenal cortex, resulting in selective, progressive adrenocortical necrosis and atrophy.[29,32,34,35,39,40,42,45,47,53,54,57-65,74-81,84-87,89-91,93-112,122,123,125-134] Mitotane causes selective necrosis of the zona fasciculata and zona reticularis of the adrenal cortex (sites of glucocorticoid production). The zona glomerulosa (site of mineralocorticoid production) is less sensitive to this drug; however, at high dosages, mitotane can cause complete necrosis of the adrenal cortex. Mitotane is fat-soluble and should always be administered with a meal. This drug can be used in an attempt to cause partial destruction of the adrenal cortex, preserving the zona glomerulosa (standard protocol) or complete necrosis of the entire adrenal cortex (nonselective protocol).

Standard Protocol: Initial Induction or Loading Dosage

The induction dosage of mitotane is 30 to 50 mg/kg/day, administered orally for 10 days or until adverse effects suggestive of hypoadrenocorticism develop.[135] An induction dosage of greater than 50 mg/kg/day is rarely required and will cause a higher incidence of hypoadrenocorticism. In moderate- to large-sized dogs, dividing the daily dosage into two equal doses may be better; however, because mitotane is available only as a scored, 500-mg tablet, it may be impossible to divide the daily dosage in small and toy breeds of dog.

Concurrent oral glucocorticoid supplementation with prednisone or prednisolone (0.15 to 0.25 mg/kg/day, up to a maximal daily dose of 5 mg/day/dog) can be used to mitigate the adverse effects associated with serum cortisol concentrations falling rapidly into the normal or subnormal range during this initial treatment period. The major disadvantage of providing a low-maintenance dosage of glucocorticoid during the induction period is that it may not be possible to know if and when an adequate total induction dose of mitotane has been administered, or even if overdosage has occurred, because clinical signs of glucocorticoid deficiency may not develop. If the veterinarian elects not to provide glucocorticoid supplementation during the induction period, it is imperative that owners be supplied with prednisone or prednisolone in case signs of life-threatening hypoadrenocorticism develop and immediate veterinary care is not available.

Clinical signs that the owners should monitor both before and during the administration of mitotane to their dog include the dog's attitude, appetite, and water intake. Awareness of these signs will help determine if the drug should be stopped before completion of the 10-day induction period and when monitoring by the ACTH stimulation test is necessary. Inasmuch as the ACTH stimulation test is the best means to determine the ability of the adrenal cortex to secrete cortisol (and therefore judge the thinning of the cortex), this is the test of choice for monitoring the effects of mitotane.

At home, the most reliable means that the owner has of monitoring the effects of mitotane induction is careful monitoring of the dog's appetite. A common, early adverse sign is decrease in appetite, which almost always occurs before development of any of the other adverse clinical signs (such as vomiting, weakness, and complete anorexia). Therefore, the dog's appetite should be observed by the owner before administration of the daily dosage. If the dog rapidly consumes the meal, the owner should administer the dose of mitotane immediately after the dog finishes the food. If the dog's appetite diminishes (the food is consumed either slowly or not at all), the owners should not administer any more mitotane, at least until they consult with their veterinarian. In addition to providing an important monitoring tool, administrating mitotane at the time of feeding enhances its gastrointestinal absorption because it is a fat-soluble drug.

After completion of mitotane induction, the veterinarian should again see the dog and complete a

thorough history and physical examination. Whether the dog has responded clinically or not, the efficacy of induction should always be determined by performing an ACTH stimulation test. If glucocorticoid was administered during mitotane induction, it should not be given on the morning of ACTH stimulation testing, because most glucocorticoids (e.g., prednisone and prednisolone) can cross-react in the cortisol assay to falsely elevate the serum cortisol concentration. Once the ACTH stimulation test has been completed, that day's glucocorticoid dose can be given, if needed.

The goal of treatment with mitotane is to achieve an ACTH stimulation test result that suggests relative, but not complete, hypoadrenocorticism. In other words, the basal (resting) cortisol should be lowered into the reference range (1 to 4 mcg/dL; or 25 to 125 nmol/L), with little to no rise in cortisol concentration after ACTH stimulation (i.e., post-ACTH cortisol concentration should also be lowered into the reference range for basal cortisol, i.e., <4 mcg/dL or <125 nmol/L). In most dogs with PDH, initial daily mitotane treatment succeeds in decreasing both basal and post-ACTH serum cortisol concentrations into the desired range. In some dogs, however, the ACTH-stimulated serum cortisol concentration will be subnormal (<1 mcg/dL or <25 nmol/L) after the initial treatment period, indicating near-total adrenocortical destruction. In this situation, mitotane should be stopped and glucocorticoid provided until the serum cortisol concentration rises to within the reference range for basal cortisol (1 to 4 mcg/dL; or 25 to 125 nmol/L). After overtreatment with mitotane, the low serum cortisol concentration typically increases naturally into the normal resting range within 2 to 6 weeks; however, in a few dogs, cortisol remains low for up to 18 months without further mitotane. Conversely, about 10% to 15% of dogs still respond to exogenous ACTH with the serum cortisol concentration rising to above the desired range (>4 mcg/dL; or >125 nmol/L) after initial daily mitotane treatment. In these dogs, daily mitotane administration should be continued and the ACTH stimulation test repeated at weekly intervals until adverse clinical signs develop or the circulating cortisol concentration falls into the desired range. Dogs have individual sensitivity to mitotane during the induction period and the length of daily treatment needed to adequately reduce adrenal reserve can range from 5 days to 2 months. No reliable method has been determined for predicting either the duration of treatment necessary or the amount of mitotane necessary to destroy enough adrenal tissue for a detectable response.

Standard Protocol: Maintenance Dosage

Once adrenal reserve has been appropriately reduced, as determined by ACTH stimulation test results, orally-administered mitotane should be continued at a maintenance dosage of approximately 50 mg/kg/week, divided into two to four equal doses. In small or toy breeds of dogs, it may not be practical to attempt to divide the weekly dosage. Daily glucocorticoid supplementation is rarely necessary during maintenance mitotane treatment. During periods of stress or illness, however, glucocorticoid support may be necessary. Despite initial control of HAC with mitotane, relapse commonly occurs during long-term treatment.

About half of dogs treated with initial loading and maintenance dosages of mitotane relapse within 12 months of treatment, as evidenced by recurrence of clinical signs and higher than desired basal and ACTH-stimulated cortisol concentrations. To ensure continued control and prevent serious relapse during mitotane treatment, ACTH stimulation testing should be repeated after 3 and 6 months of maintenance treatment and every 6 months thereafter. If basal and post-ACTH cortisol concentrations rise above desired ranges (>4 mcg/dL; or >125 nmol/L), the dog should be reloaded (i.e., the mitotane dosage should be increased to 30 to 50 mg/kg PO daily for 5 to 7 days, or longer if needed). Once circulating cortisol concentrations have been again lowered into the desired range, the weekly maintenance dosage should be increased by approximately 50% to help prevent further relapse. Because of multiple relapses, some dogs eventually require extremely high mitotane dosages to control HAC.

Side effects are relatively common and should be anticipated during mitotane administration, especially during induction with mitotane. The adverse effects most commonly observed include lethargy, weakness, anorexia, vomiting, diarrhea, and ataxia. Up to a quarter of dogs can develop one or more of these problems during the initial daily mitotane administration, but they are relatively mild in most dogs. These effects develop as the serum cortisol concentration falls rapidly to normal or subnormal (glucocorticoid withdrawal) and typically resolve rapidly when mitotane is discontinued and glucocorticoid supplementation increased.

When side effects develop during the induction period, mitotane should be discontinued and a glucocorticoid administered (e.g., prednisone, 0.2 to 0.5 mg/kg PO q 24 h) until the dog can be examined, and ACTH stimulation testing performed to evaluate adrenal reserve. Most dogs show a clinical response to the glucocorticoid dosage within 2 to 3 hours; persistence of problems for longer than a few

hours after administering or increasing the glucocorticoid dosage usually signifies another medical problem.

Likewise, adverse reactions may occur in dogs during maintenance mitotane therapy, most commonly shortly after beginning maintenance therapy or during relapses when daily therapy is reinstituted. Again, the development of side effects is associated with a subnormal circulating cortisol concentration in most dogs. If side effects occur during the maintenance period, mitotane should be discontinued and glucocorticoid supplementation provided. Should adverse signs persist for longer than a few hours after administration of a glucocorticoid, the dog should be evaluated as soon as possible to exclude other disorders including mineralocorticoid insufficiency. In most dogs, it will be necessary to resume maintenance mitotane in 2 to 8 weeks as determined by ACTH stimulation test results and clinical signs.

In a few dogs treated with mitotane, adverse reactions may result from direct drug intolerance rather than absolute or relative hypoadrenocorticism. In such dogs, the serum cortisol concentration is not low and no improvement in adverse clinical signs occurs with glucocorticoid supplementation. First, one must be certain that the drug is given immediately after the dog has eaten. Giving this drug on a full stomach enhances absorption and reduces adverse effects. In addition, dividing the daily or weekly dose of mitotane into smaller doses may lessen or eliminate the adverse reactions in these dogs.

The most serious adverse effect associated with mitotane administration is the development of total or near-total adrenocortical destruction, with concomitant glucocorticoid and mineralocorticoid deficiency and hyperkalemia and hyponatremia (Addison's disease). Iatrogenic Addison's disease secondary to mitotane is relatively rare with this protocol, developing in fewer than 5% of dogs. The complication may develop any time during maintenance treatment but is most likely to develop during the first year. Unfortunately, predicting which dogs will develop Addison's disease does not seem possible. In one study, no difference was found in the maintenance dosages of mitotane between those dogs that developed complete adrenocortical insufficiency and those that did not.

In general, Addison's disease should be suspected if a dog develops side effects during mitotane administration and does not promptly respond to glucocorticoid supplementation. Iatrogenic Addison's disease is confirmed in these dogs by ACTH stimulation testing (i.e., undetectable serum cortisol concentration) and serum electrolyte determination (i.e., hyperkalemia and hyponatremia). If Addison's disease does develop, mitotane should be discontinued and appropriate glucocorticoid and mineralocorticoid replacement therapy instituted immediately. Of the dogs that develop complete, iatrogenic adrenal insufficiency, all can be expected to require mineralocorticoid and glucocorticoid replacement therapy for the remainder of their lives. Therefore, further mitotane administration is usually not necessary.

Nonselective Protocol

This protocol consists of a longer period of daily treatment with mitotane to produce a complete destruction of the three layers of the adrenal cortex with resultant iatrogenic hypoadrenocorticism.[136,137] In this protocol, mitotane is administered orally at a dosage of 50 to 75 mg/kg/day (divided into two or three smaller doses given with food) for 25 days. Life-long administration of mineralocorticoids (fludrocortisone, 0.01 mg/kg PO q 12 h) and glucocorticoids (prednisone, 0.2 mg/kg; or hydrocortisone, 1 to 2 mg/kg/day) is started on the third day of mitotane administration. The dose of fludrocortisone is adjusted based on the clinical response and results of biochemical evaluation including BUN and serum electrolytes. The dose of glucocorticoids will be adjusted to the lowest dose needed to achieve a good clinical control of hypoadrenocorticism (usually hydrocortisone 0.5 to 1 mg/kg/day). Dogs treated with the nonselective protocol are less likely to have a relapse of HAC (30% to 40%) compared with dogs treated with the standard protocol (50% to 60%). In a large number of dogs, however, daily mitotane administration must be stopped for a short period because of adverse side effects, such as anorexia, vomiting, diarrhea, weakness, and neurologic symptoms.

Ketoconazole

Ketoconazole is an imidazole antifungal drug that also inhibits the synthesis of glucocorticoids and androgens.[138,139] It effectively lowers circulating cortisol concentrations but has minimal effect on mineralocorticoid production. Ketoconazole controls HAC in some dogs, but unfortunately, the drug is not efficacious in many dogs with the disease. In our experience, one third to one half of dogs fail to adequately respond.

Ketoconazole is started at a dosage of 5 mg/kg PO q 12 h for 1 week. If the drug is well tolerated (i.e., no decrease in appetite or icterus is seen), the dosage is increased to 10 mg/kg PO q 12 h for 2 weeks. The

efficacy of the initial 14-day course of treatment is determined by an ACTH stimulation test. To ensure adequate control of HAC, both the basal and post-ACTH serum cortisol concentrations must be lowered into the basal reference range. If the serum cortisol concentrations remain above this range, the dosage is increased to 15 mg/kg PO q 12 h, and an ACTH response test repeated in 14 days. Most dogs require an oral daily dose of 30 mg/kg for a long period to achieve good clinical control. The disadvantages of ketoconazole are the expense, the requirement for twice-daily administration for life, side effects, and the drug's lack of efficacy in some cases. Less than 2% of veterinary specialists (internal medicine and dermatology) use ketoconazole as the treatment of choice for HAC.[133]

Selegiline Hydrochloride

Cushing's disease in dogs can be caused by adenoma or hyperplasia of cells in either the pars distalis or pars intermedia.[10] Approximately 70% of dogs with Cushing's disease have a pituitary adenoma that arises from the pars distalis, whereas 30% have a tumor that arises from the pars intermedia. In dogs, the neurotransmitter dopamine appears to primarily inhibit the secretion of ACTH peptides from the pars intermedia and a central disturbance of dopamine may play a role in the pathogenesis of canine Cushing's disease. L-deprenyl (selegiline hydrochloride) is a selective and irreversible inhibitor of monoamine oxidase type B, which helps restore the central dopamine concentration and facilitates dopaminergic transmission by several mechanisms. L-deprenyl may down-regulate ACTH secretion by enhancing the dopamine concentration, thereby controlling PDH. The use of L-deprenyl for the treatment of HAC in dogs is controversial. Selegiline has been described as a safe and effective treatment after a partial to complete clinical improvement was observed in more than 80% of treated dogs with PDH.[140] However, later studies that included an adrenal function test to evaluate the efficacy of the drug have shown that this drug is ineffective.[141,142] Several of the owners reported an increase in the level of activity of the dog during treatment. L-deprenyl is metabolized into substances with amphetamine-like structures, which may explain the increased activity.

Other Drugs

A variety of other drugs (bromocriptine, cyproheptadine, metyrapone, aminoglutethimide) have been investigated for the treatment of HAC without favorable results. Two medical therapies (cabergoline and retinoic acid) for canine Cushing's syndrome have also been described.[143,144] These treatments might be helpful in decreasing ACTH secretion, urine cortisol to creatinine ratio, and the size of the pituitary tumor. However, additional studies are warranted before recommending this treatment to general practitioners (see E-Box 306-3).

E-Box 306-3

Treatment of Pituitary-Dependent Hyperadrenocorticism (PDH) without Access to Trilostane or Mitotane

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Overview of Need for Alternative Therapies

PDH is diagnosed in dogs by veterinarians worldwide. While success has been achieved in treating afflicted dogs with trilostane or mitotane (o,p'-DDD), there are countries in which these medications are not available and alternatives are used.

Ketoconazole (also see E-Box 306-2)

Background

When given at dosages higher than those used for combatting fungal disease, ketoconazole reversibly suppresses steroid synthesis, including cortisol, mineralocorticoids, estrogen, testosterone and progesterone. Ketoconazole may also directly suppress adrenocorticotropic hormone (ACTH)-secreting pituitary tumors, perhaps explaining the lack of increased ACTH concentrations despite suppression of cortisol synthesis.

Protocol

Ketoconazole is recognized to cause adverse side effects in dogs, especially at dosages required to control PDH. Side effects include anorexia, vomiting, diarrhea and an idiosyncratic hepatopathy. Side effects can be minimized or completely avoided by initiating ketoconazole at sub-therapeutic doses and slowly increasing to effective amounts. While the initial low dosages have little effect on PDH, dogs usually develop a tolerance to the drug over a period of 1 to 4 weeks. Initially, 5 mg/kg PO q 24 h should be administered following a meal. Every 2 or 3 days, the oral dose should be increased by 2.5 mg/kg until reaching 20 mg/kg/day. Serum biochemical profiles should be evaluated every 2 to 3 weeks to identify hepatotoxicosis reflected as increases in alanine aminotransferase (ALT).

Cabergoline

Overview

Corticotropic cells express D2 dopaminergic receptors. Function of both the pituitary pars intermedia and pars distalis can be suppressed by dopamine, inhibiting the synthesis of ACTH and melanocyte stimulating hormone (alpha-MSH). In dogs, ACTH-secreting tumors can originate in either or both areas of the pituitary. Cabergoline is a D2 dopaminegic receptor agonist. It has high affinity for the pituitary, with anti-proliferative and pro-apoptotic effects in dogs. Together with its action on the dopaminergic system, cabergoline may normalize enzymatic pro-convertases (cleavage of ACTH to yield alpha-MSH). Inhibitory effects on the thyroid axis and hypotension have also been described.

Protocol, Side Effects, Response

Initially, cabergoline should be administered at a dosage of 0.022 mg/kg PO q 48 h. The first few doses often cause vomiting, but subsequent doses are usually better tolerated. Less worrisome side effects (8-12 % of dogs) include dry hair coat, lack of hair growth, and change in coat color. Approximately 40% to 60% of cabergoline-treated dogs begin to demonstrate resolution of clinical signs after about a month of treatment. Along with clinical improvement, there is decrease in urinary cortisol, ACTH, and alpha-MSH concentrations. Pituitary tumor size may also decrease. In animals responding favorably, survival is longer than in dogs treated only with ketoconazole. Therapy with cabergoline is most effective in dogs with pars intermedia pituitary tumors <5 mm in greatest diameter. Following early response for several months, some dogs appear to become resistant to cabergoline.

Retinoic Acid

Background

Retinoic acid can inhibit cell proliferation and induce apoptosis. It affects receptors at the genomic level that regulate gene expression of transcription factors required for synthesis of pro-opiomelanocortin (POMC), the precursor of ACTH. Retinoic acid not only suppresses tumor synthesis of POMC and ACTH, but it also suppresses tumor growth by inhibiting mitosis and inducing apoptosis.

Protocol

Retinoic acid is administered as the isoform isotretinoin 9-Cis (enteric capsule; 2 mg/kg PO q 24 h given in the evening). About 80% of dogs treated with retinoic acid have demonstrated clinical improvement after approximately a month, in association with decreases in urinary cortisol, ACTH, and alpha-MSH concentrations. Pituitary tumor size has also decreased in some dogs. Side effects include mild diarrhea, skin dryness and hyperkeratosis. While hepatotoxicosis has been described, this author has administered retinoic acid to dogs for as long as 6 months, safely. Frequent liver function test assessments are recommended and the drug should be discontinued if increases occur. No other side effects have been observed. (Editor's note: The proven risk of severe human teratogenicity and fetotoxicity must be discussed with the owner, who must accept full responsibility for appropriate and safe handling, use, and storage of the drug, prior to prescription and/or refill.)

Combination Protocols

Cabergoline and Retinoic Acid

These drugs have different mechanisms of action and together they have a particularly strong synergistic effect, especially in dogs with mixed tumors (pars distalis and intermedia). Dosages for each drug are the same as described for single drug therapy: cabergoline 0.022 mg/kg PO q 48 h plus isotretinoin (2 mg/kg/day PO). This mixed protocol can be used safely for 6 months. After this period, the dog should be examined to determine if medication can be completely stopped since treatment often has a residual effect. Alternatively, some dogs either continue with this or another protocol according to the response. (Editor's note: Owner informed consent is mandatory, as indicated above.)

Cabergoline and Ketoconazole

This combination provides rapid resolution of clinical signs due to ketoconazole effect and at the same

time, it allows an upregulation of the D2 receptors (dopaminergic) as the ACTH-secreting pituitary adenoma becomes more sensitive to the effect of cabergoline.

Pasireotide (SOM 230)

SOM 230 (pasireotide) is an analogue of somatostatin with the ability to affect the receptors (SSTR) of the subtypes 1, 2, 3 and especially 5 in pituitary ACTH-secreting adenomas. SOM 230 has antiproliferative and anti-secretory actions. Dogs treated with pasireotide have demonstrated clinical improvement, usually without side effects. The side effect to consider is that it can generate hyperglycemia, as the analogues of the somatostatin inhibit insulin secretion at the pancreatic level, and diminish glucagon-like peptide 1 release, even though insulin sensitivity is not affected. Treated dogs have also shown significant decreases in urinary cortisol concentrations, serum ACTH concentrations, and in pituitary tumor size. Pasireotide can be considered a therapeutic alternative for dogs that do not respond to conventional treatments.

Suggested Readings

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Surgical Treatment of PDH (Hypophysectomy)

Transsphenoidal surgical removal of the pituitary tumor causing PDH is the treatment of choice for humans, while complete surgical hypophysectomy has been used for dogs with PDH.[7,147,148] After hypophysectomy in PDH dogs, the 1-year estimated relapse-free fraction was 90%. The 1, 2, 3, and 4-year estimated survival rates (86, 83, 80, 79%, respectively) compare favorably to results seen in dogs treated with either mitotane or trilostane.[148]

Complications associated with hypophysectomy include permanent or prolonged diabetes insipidus, secondary hypothyroidism, transient reduction or cessation of tear production, transient mild postoperative hypernatremia, and recurrence of PDH months later. Treatment failures included procedure-related mortalities and incomplete hypophysectomies. Central diabetes insipidus occurred more frequently in dogs with enlarged pituitaries than in dogs with nonenlarged pituitaries. Factors related with an increased risk of death are old age, large pituitary size, and increased preoperative plasma eACTH concentrations. Factors associated with disease recurrence were large pituitary size, thick sphenoid bone, high urinary cortisol/creatinine ratio, and increased plasma alpha-MSH concentrations before surgery.[148] A modification of the transsphenoidal approach using CT localization of the sella turcica with a high definition video telescope system has recently been used in dogs with HAC. Their reported 1-year survival rate was >80%.[149]

Radiation Therapy for PDH

Reducing Mass Size

Cobalt 60 radiotherapy has potential for dramatically reducing size of a visible pituitary tumor in dogs with PDH without neurologic signs.[150] In one study, 6 dogs received radiation doses of 44 Gy divided into 11 equal fractions using a telecobalt 60 unit. Plasma eACTH concentrations transiently decreased in all dogs; however, clinical signs of HAC resolved in only 3/6 dogs and recurred in 2 of those 3. One year after radiotherapy, no tumor could be visualized in 4 dogs and tumor size decreased by 25% in 2. No dog developed neurologic abnormalities. Experience with radiation therapy for dogs with large pituitary masses has varied.[45,151,152] In 24 dogs with pituitary macrotumors and neurologic signs treated with megavoltage irradiation (48 Gy during 4 weeks on an alternate-day schedule of 4 Gy/fraction), a significant correlation was found between relative

tumor size (i.e., size of tumor relative to calvarium size), severity of neurologic signs, and remission of those signs after radiation.[151] As severity of neurologic signs worsened, prognosis worsened. This was the most reliable prognostic factor. Since radiation therapy is more effective in dogs with relatively small tumors, early treatment should improve prognosis and longevity. It has been recommended that dogs with pituitary masses equal to or greater than 8 mm at greatest vertical height undergo radiation as the initial mode of therapy.[45] Since radiation effectively shrinks tumors but is far less successful at resolving clinical HAC, use of medical management should be anticipated. There are few complications. Disadvantages of radiation include cost and availability.

Clinical Response

Pituitary tumors are relatively sensitive to radiation. Dramatic and relatively rapid improvement may be seen in some dogs despite initial severe neurologic signs. Generally, prognosis and severity of clinical signs are inversely related: dogs with severe neurologic signs and a tumor >20 mm at greatest diameter have a much poorer prognosis than dogs with more mild signs and a mass <20 mm. While some dogs improve during radiation therapy, others require weeks or months. Therefore, owners should be encouraged to allow their dogs several months to respond.

Endocrine Response

In most dogs with PDH, radiation has little effect, no effect, or only a transient influence on the tumor's secretory nature. Therefore, medical treatment is usually required to control HAC, despite mass shrinkage. Recurrence of neurologic signs weeks to years later is possible but rare. In such dogs, deterioration may be rapid. CT or MRI could be recommended for each dog diagnosed as having PDH, but especially dogs exhibiting dexamethasone resistance on LDDST or HDDST. Radiaton therapy is advisable for dogs with tumors >7 mm, regardless of presence or absence of neurologic signs.[150]

Stereotactic Radiosurgery (SRS)

SRS delivers a single large radiation dose to a well-defined target and has been used for dogs with pituitary tumors.[153] SRS treatment requires only a single anesthetic procedure, has fewer acute adverse effects, and survival times in early studies appear comparable to conventional radiation therapy.

Treatment: Functional Adrenocortical Tumors

Overview

Ideal treatment for dogs with FAT causing HAC is surgical removal of the tumor. Surgery can be curative, permanent, and requires no long-term therapy. However, some dogs with FAT are treated medically. Reasons for medical therapy include: to improve a patient's clinical condition prior to surgery, an inoperable tumor, metastases at the time of diagnosis, poor surgical candidate, or owner decision. The adrenocorticolytic drug mitotane (o,p'-DDD) can be used in an attempt to destroy the tumor, but this is rarely achieved.[154] Trilostane is efficacious for controlling signs of HAC, improving quality of life, and survival times are similar to those achieved with surgery or mitotane.[155,156] In dogs diagnosed with FAT, pre-surgical trilostane (0.2-1 mg/kg PO q 12 h) is recommended to resolve clinical signs and laboratory abnormalities (which might take 1 to 2 months). Surgery is then done on a healthier individual.

Adrenalectomy

Surgical adrenalectomy is considered the treatment of choice for adrenal tumors. Adrenalectomy, via celiotomy or laparoscopy, is technically challenging and should be performed by a skilled surgeon. Postoperative complications, including pancreatitis, pneumonia, pulmonary thromboembolism, acute kidney injury/oliguria/anuria, sepsis, disseminated intravascular coagulation and hypoadrenocorticism, are worrisome but less common after appropriate pre-treatment.[45] Intraoperative and postoperative complications have been reported in a highly variable percentage of dogs with FAT.[157-162] As surgical skill and patient management improves, morbidity and mortality rates are decreasing. Perioperative mortality (13.5-30%) is decreasing and use of minimally invasive technology (laparoscopy) are anticipated to decrease mortality and morbidity further.[157-162]

Prognostic Factors

In one review of dogs with FAT treated with adrenalectomy, tumor size (≥5 cm), distant metastases and vein thrombosis (vena cava) were associated with poorer prognosis.[161] In another study, invasion of the caudal vena cava was associated with a higher surgical mortality rate but did not affect long term prognosis.[162] The median survival time of dogs with FAT undergoing adrenalectomy is about 2 to 4 years.[160-162] It is important to remember that the average age at diagnosis is about 11 years.

Pre-Surgery

Prior to adrenalectomy, HAC should be treated and controlled with trilostane. Immediately prior to surgery, results of a CBC, serum chemistry profile, and thoracic radiographs should be assessed. Repeat US is helpful not only for visualizing the mass, but to search for evidence of metastasis or venous tumor thrombosis (Video 306-5). US has a reported sensitivity of 100% and specificity of 96% in correctly identifying abdominal metastases.[163] Autonomous cortisol secretion from the tumor results in atrophy of the contralateral gland and thus, intraoperatively and postoperatively glucocorticoid supplementation is necessary. IV fluids should be administered at a maintenance rate at the start of anesthesia, during surgery and in the postoperative period (see ch. 129). When the surgeon recognizes the adrenal tumor, dexamethasone should be placed in the IV infusion bottle at a dosage of 0.05 to 0.1 mg/kg and given over a 6 hour period. Dexamethasone should be given 2 or 3 times daily until oral medication can be tolerated.[29] Hydrocortisone, with both glucocorticoid and mineralocorticoid activity, can replace dexamethasone. During surgery, hydrocortisone can be given IV (4 to 5 mg/kg) and thereafter 1 mg/kg, IV, every 6 hours until oral medication is tolerated. An ACTHST, completed the morning after surgery and about 8 hours after the last dose of dexamethasone, helps to determine whether the tumor was completely excised (low serum cortisol concentrations before and after ACTH) and to determine need for continuing glucocorticoid supplementation.

Post-Surgery

Intensive postoperative monitoring is essential for preventing or responding to complications. Hyperkalemia and/or hyponatremia should be treated with mineralocorticoid (see ch. 309): oral fludrocortisone (0.01 to 0.02 mg/kg q 12 h) or IM desoxycorticosterone pivalate (DOCP; 2.2 mg/kg SC every 21-25 days). Electrolyte abnormalities may reflect mineralocorticoid deficiencies and are usually, but not always, transient, only lasting a few days. Antibiotics, analgesia, and heparin (75 units/kg SC q 8 h) are recommended.[162] Pre-surgical trilostane treatment for a month or 2 may negate the need for heparin. Oral prednisone should be considered for all dogs whose post-surgical ACTHST results were below normal. An initial dosage of 0.5 mg/kg PO q 12 h for 3 days is then tapered to 0.2 mg/kg/day over 2-4 weeks. Results of an ACTHST performed then, and months later, should be used to determine need for continuing glucocorticoid supplementation.

Medical Management of Adrenocortical Tumors: Mitotane

When the patient is not a good candidate for adrenal surgery, mitotane is an alternative option to attempt complete or partial destruction of the adrenal tumor. Dogs with FAT can be treated with the standard mitotane protocol previously described for dogs with PDH (see mitotane treatment for PDH), but at a daily dosage of 50-75 mg/kg PO. An ACTH stimulation test is performed every 10 to 14 days to evaluate adrenal reserve. An oral glucocorticoid (e.g., prednisone or prednisolone, 0.2 mg/kg/day) is administered throughout the period of mitotane administration to try to avoid clinical signs of hypoadrenocorticism. Daily mitotane (loading dose) is continued at this dosage or increased until desired cortisol levels are reached or drug intolerance develops. In dogs with FAT, this loading period is usually longer compared to dogs with PDH, with a cumulative mitotane induction dose up to 10 times higher than dogs with PDH. Once adequate post-ACTH cortisol concentrations are achieved, maintenance mitotane is started at 75 to 100 mg/kg PO, weekly, in divided doses together with daily glucocorticoid supplementation. In dogs with adrenal tumors, a maintenance dose of mitotane is also commonly greater than 100 mg/kg, and relapses during treatment are common (more than 60% of dogs).[164] Trilostane is preferred to mitotane because it is more efficacious in the control of clinical signs. Mitotane-related side effects, seen in as many as 60% of treated dogs, include anorexia, weakness, vomiting, diarrhea, and lethargy. Adverse effects may be due to development of hypoadrenocorticism, but in approximately 50% of dogs, they are due to direct drug toxicity.[164] If adverse reactions do occur, the drug should be stopped and the dog evaluated as soon as possible since complete glucocorticoid and mineralocorticoid deficiency (Addison's disease) may occur. If toxicosis is suspected,

mitotane must be discontinued. It can be re-started again 5-7 days later at a 25% to 50% lower dosage. Reinstitution of the higher maintenance dosage can be attempted later but usually results in recurrence of adverse effects. In this situation, a different treatment (trilostane) might be chosen.

Medical Treatment of FAT: Trilostane

The efficacy of trilostane in controlling clinical signs of hypercortisolism in dogs with FAT has been demonstrated.[155,156,165,166] Furthermore, the survival time of dogs with FAT treated with trilostane (median 11.5 to 14 months) is similar to that observed in dogs treated with mitotane (median 3 to 15.6 months).[155,156] Thus, trilostane is the best medical treatment for dogs with FAT.

Complications and Concurrent Conditions Associated With HAC

Large Pituitary Tumors

Definitions

Approximately 50% of dogs with PDH have a tumor visible on CT or MRI scan at the time of diagnosis. Neurologic signs caused by expansion of a pituitary tumor are seen in about 15% to 20% of dogs with PDH, including a small number of dogs with signs when first diagnosed as having HAC. Most are diagnosed sometime after treatment is started.[100] Improved long-term medical management of dogs with PDH may simply provide enough time for smaller masses, which represent the majority at the time of PDH diagnosis, to expand sufficiently to cause clinical signs. Most PDH dogs with signs caused by a large tumor have been medically treated for more than 6 months, some more than several years. Pituitary tumors are often categorized according to size as macrotumors (≥10 mm in greatest diameter) or microtumors (<10 mm). These arbitrary designations, however, have little use clinically.[72] Clinical manifestations of an enlarging pituitary tumor do not correspond only to size, but may be related to growth rate, size of the skull cavity, or the presence of peri-tumoral inflammation, edema or hemorrhage. It seems more appropriate to use the term "macrotumor" to describe tumors visible by means of CT or MRI and the term "microtumor" for masses that only be visualized microscopically.[45]

Signs, Diagnosis, Treatment

The onset of neurologic signs may precede, coincide with, or follow (most commonly) diagnosis and long-term medical management of HAC. The initial clinical signs associated with an expanding pituitary mass are usually subtle decreases in appetite and changes in behavior noted only by someone extremely familiar with the dog. Other signs that begin slowly and progress are dullness, listlessness, restlessness, loss of interest in normal activities, episodes of apparent disorientation, severe loss of appetite, and weight loss. Later in the course of the disease, signs may include ataxia, aimless pacing, circling, stupor, and seizures. Antemortem confirmation of a pituitary tumor requires advanced imaging, such as CT or MRI. Radiation or hypophysectomy are available therapeutic options, discussed previously (see Surgical Treatment of PDH).

Hypertension

Systemic hypertension, defined as systolic blood pressure greater than 160 mm Hg (see ch. 99), is present in 38% to 86% of dogs with untreated HAC (see ch. 157).[55,167] Systemic hypertension may lead to proteinuria, also frequently noted in dogs with HAC (44 to 68%). Both may improve or resolve with treatment, but neither resolves in all treated dogs.[55] Glomerular filtration rates are increased before treatment and decrease with treatment for PDH. Persistence of proteinuria or hypertension after successful HAC treatment should warrant attention.[55] Plasma aldosterone concentrations may contribute to hypertension in dogs with untreated HAC. However, several studies have found that aldosterone levels are often below normal in dogs with PDH but high in dogs with FAT.[167,168] Further studies are needed to elucidate the mechanism of hypertension in dogs with HAC. Proteinuria and systemic hypertension (present in up to 80% of dogs with untreated HAC) are major factors in the development and progression of chronic kidney disease, and should be monitored in dogs with HAC with persistent hypertension despite a good control of HAC.

Diabetes Mellitus (see ch. 304)

The diagnosis of HAC in dogs already diagnosed as having diabetes mellitus (DM) should not be

complicated, assuming that classic signs of HAC are observed. For example PU (with a urine specific gravity <1.008), bilaterally symmetrical alopecia, pot belly, thin skin, panting, calcinosis cutis and low BUN are typical of HAC but not DM. Since the most common signs of DM are the same as those in HAC (PU/PD/PP), diagnosis in poorly controlled diabetics with only these signs must be questioned. Appropriate use of screening tests enhances their sensitivity and specificity, but they should never be used as the sole indicator of HAC. US diagnosis of adrenalmegaly is non-specific. No diagnostic aid is as sensitive and specific as history and physical examination.

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CHAPTER 307

Feline Hyperadrenocorticism

Ian K. Ramsey, Michael E. Herrtage

Client Information Sheet: Feline Hyperadrenocorticism (Cushing's Disease)

Introduction

Feline hyperadrenocorticism (HAC; Cushing's syndrome; hypercortisolism) is less common but more serious and more challenging to diagnose or treat than canine hyperadrenocorticism. Feline HAC has a worse prognosis than the condition in dogs. Unlike dogs, feline HAC is strongly associated with diabetes mellitus (DM) and/or a skin hyperfragility syndrome, either of which may complicate management. Basic pathophysiology and other aspects of feline HAC are similar to the canine (see ch. 306). This chapter focuses on the clinical condition resulting from the chronic excessive production of cortisol or other hormones with a cortisol-like action. Cats with progesterone-secreting adrenocortical tumors may have clinical signs consistent with feline HAC (see ch. 308).[1,2] Some adrenocortical tumors can cause primary hyperaldosteronism (see ch. 308).

Pathophysiology

Feline HAC is a multisystemic disorder resulting from excessive production of cortisol by the adrenal cortices. There are single case reports describing cats with HAC and several case series that, together, total more than 100.[3-24] Both pituitary-dependent HAC (PDH), caused by excessive pituitary secretion of adrenocorticotropic hormone (ACTH), and adrenal-dependent HAC (ADH), caused by a functional adrenocortical tumor, have been reported in cats.[4] About 85% of cats with naturally occurring HAC have PDH and the remaining 15% have ADH (E-Table 307-1). ADH may be caused by either a benign or a malignant adrenocortical tumor. A small number of cats with multihormonal pituitary tumors, including ACTH-secreting tumors causing PDH, has been reported.[18,25-28] Iatrogenic HAC has been described in cats associated with glucocorticoid or progestogen administration.[29-31] The progestogen megestrol acetate, a particularly potent steroid in cats, may cause prolonged adrenocortical suppression after being discontinued.[32]

E-TABLE 307-1

Feline Hyperadrenocorticism Case Series

	NELSON AND OTHERS 1988[3]	IMMINK AND OTHERS 1992[4]	DUESBERG AND OTHERS 1995[5]	WATSON AND HERRTAGE 1998[6]	MEIJ AND OTHERS 2001[7]	NEIGER AND OTHERS 2004[8]	MELLETT KEITH AN OTHERS 2013[9]
General							
Number (total)	7	4	10†	6	7	5	15
PDH + ADH	5 + 2	2 + 2	8 + 2*	5 + 1	7 + 0*	5 + 0*	14 + 1*
Median age (range)	10 (8-15)	9.5 (6-12)	9.5 (4-14)	9.25 (4.5-13.5)	10.5 (6-13)	11 (8-15)	12.3 (2.8-16)
Sex (M + F)	3 + 4	0 + 4	6 + 4	3 + 3	1 + 6	2 + 3	7 + 8

Clinical Signs							
Thin skin	3	0	7	2		2	12
Spontaneous tears of the skin	2	0	5	1		1	8
Dry/seborrhea		3		3		3	
Alopecia	5	1	6	2		0	4
Polyuria/polydipsia	7	3	9	5		2	14
Polyphagia	5	4	9	3		3	5
Abdominal distension	5		9			3	8
Lethargy	3	3		3		1	
Weight gain/obesity			5	6		1	
Weight loss/muscle atrophy	3		7	1		1	
Others	Dyspnea/panting (2) Hyperpigment (1)		Abnormal gait (3)				
Concurrent Conditions							
Diabetes	7	3	10	3	4	3	9
Others	Recurrent bacterial infections (2)	CKD (1)	Recurrent bacterial infections (5)				Pancreatitis (
Diagnostic Tests							
Biochemistry							
Increased ALP	1 of 7	0 of 4		4 (mild)		2	6
Increased ALT	2 of 7	3 of 4		3		2	6
Increased cholesterol	7 of 7						9
Urine							
USG < 1.030	2 of 8 specimens	1 of 1					
Proteinuria?	7 of 8	1 of 1					5 of 10
Hematology							
Neutrophilia?		3		2			
Lymphopenia?	5 of 7	2		4			
Eosinopenia	4 of 7	3					
Endocrine							
ACTH stim positive	3 of 4		6 of 9	5 of 5	N|D	5 of 5	
Low-dose dex screen positive	4 of 4	4 of 4	7 of 7		5 of 6		
Dex suppression positive	3 of 4	1 of 1	>4 of 6			2 of 2	10 of 13
Endog ACTH	3 of 3				2 of 6	2 of 2	

useful?							
Imaging							
Abdominal US useful				3 of 4		4 of 4	13 of 15
MRI/CT useful					2 of 7 enlarged		
Treatment‡							
Died, no definitive treatment	4	4	5 of 22 (died within 2 months)	2 (died within 1 month)			
Bilateral adrenalectomy	1		8 (3 died in 2 weeks)	3 (1 died in 2 weeks)			
Unilateral adrenalectomy	2 (on same cat at different times)		2	1 (died in 2 weeks)			
Pituitary surgery	0	0	0	0	7 (1 died after 1 day, 1 died after 2 weeks)		
Mitotane	1 (failed)		4 of 22 (all failed)				
Trilostane						5 (3 improved)	15 (13 improved
Metyrapone			2 of 22 (both failed)				
Ketoconazole			2 of 22 (both failed)				
Radiotherapy	1 (cobalt)						

*As these papers were selected on therapy used, so case selection may influence balance of PDH and ADH.

†At least one of these cases, which underwent unilateral adrenalectomy twice, was likely to have been included in an earlier reference (Nelson et al, 1988).

‡Definitions: *failed,* died within 2 months without improvement; *improved,* some resolution of clinical signs and clinicopathological changes (e.g., reduced cortisol).

Where no data are shown, then data were not recorded or the test was not done.

ACTH, Adrenocorticotropic hormone; *ADH,* adrenal tumor-dependent hyperadrenocorticism; *ALP,* alkaline phosphatase; *ALT,* alanine aminotransferase; *CT,* computed tomography; *dex,* dexamethasone; endog, endogenous; *MRI,* magnetic resonance imaging; *NID,* not in database; *PDH,* pituitary-dependent hyperadrenocorticism; *US,* ultrasound; *USG,* urine specific gravity.

Clinical Signs

Overview

Many of the earliest reported cats with HAC had dramatic and obvious clinical signs. Clinical signs had often been present for many months before diagnosis. Now, feline HAC is becoming better recognized, with variations in clinical presentation and associated biochemical disorders better appreciated (see E-Table 307-1).[6] Earlier diagnosis may avoid severe clinical signs particularly in the diabetic cat population (Table 307-2 and Figure 307-1).

TABLE 307-2

Approximate Frequency of Clinical Findings in Feline Hyperadrenocorticism

FINDING	FREQUENCY
Concurrent diabetes mellitus	79%
Polyuria/polydipsia	79%
Polyphagia	60%
Abdominal distension	54%
Alopecia/failure to regrow hair	43%
Skin hyperfragility/spontaneous tearing	40%
Weight loss/muscle atrophy	31%
Weakness/lethargy	29%
Weight gain/obesity	23%
Poor coat (dry, seborrhea, etc.)	15%

From data provided in seven published series of cases with a combined total of 77 cases.[3-6,8-10] Note that three of these series (a total of 30 cases) were selected by treatment modality; however, there was no apparent difference in the presenting signs. See E-Table 307-1 for further information.

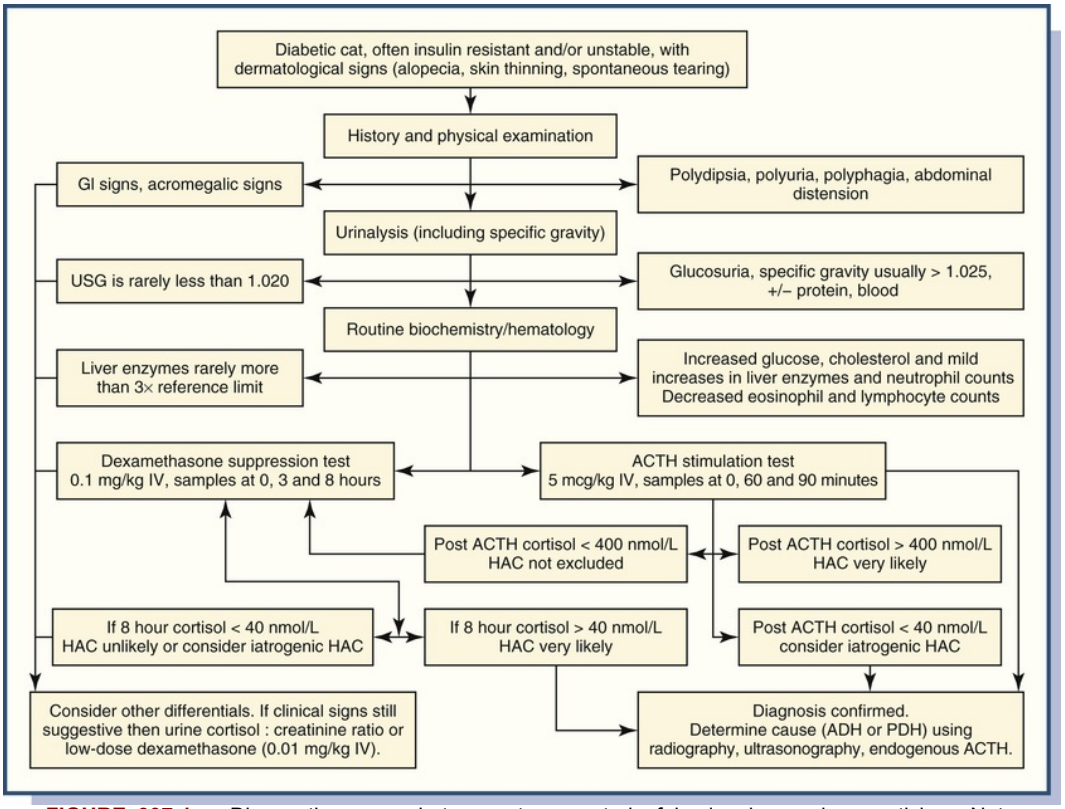


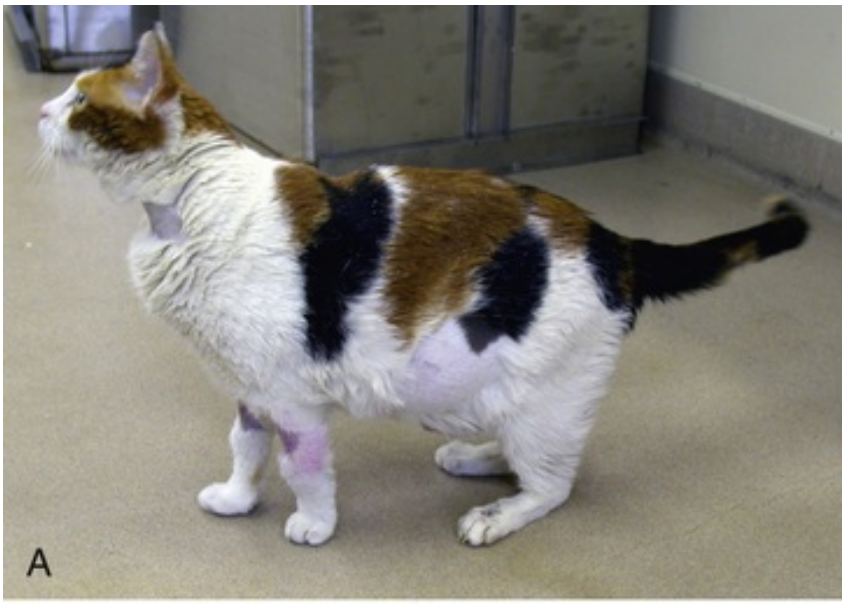
FIGURE 307-1 Diagnostic approach to a cat suspected of having hyperadrenocorticism. Note 400 nmol/L = 14.5 mcg/dL and 40 nmol/L = 1.4 mcg/dL. *ACTH,* Adrenocorticotropic hormone; *ADH,* adrenal tumor-dependent hyperadrenocorticism; *GI,* gastrointestinal; *HAC,* hyperadrenocorticism; *PDH,* pituitary-dependent hyperadrenocorticism; *USG,* urine specific gravity.

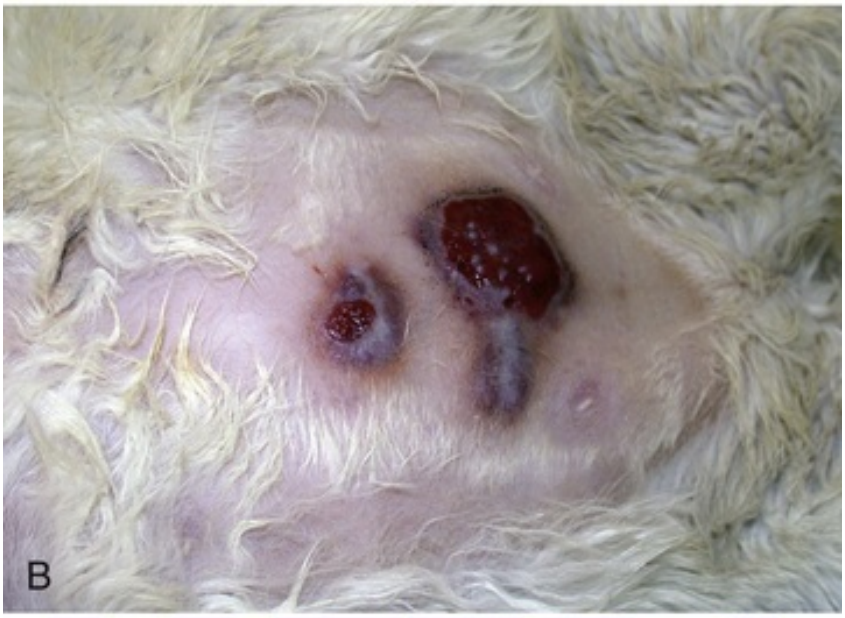
Age, Breed and Sex

Feline HAC is most common in middle-aged to older cats (median age in the various studies was 9.5 to 13 years; range from 3 to 15 years). There appears to be no sex or breed predilection.

Skin Changes

Cutaneous manifestations of feline HAC include truncal and abdominal alopecia, but far less frequently than in dogs. An unkempt hair coat and seborrhea are common. Their thin skin is prone to traumatically induced tears, bruising and secondary bacterial or fungal infection (Figures 307-2 and 307-3). The hyperfragile skin is particularly distressing to owners and unwary clinicians. Cats with HAC should always be treated gently (Figures 307-4 and 307-5). Calcinosis cutis has not been reported in naturally occurring nor iatrogenic HAC.


A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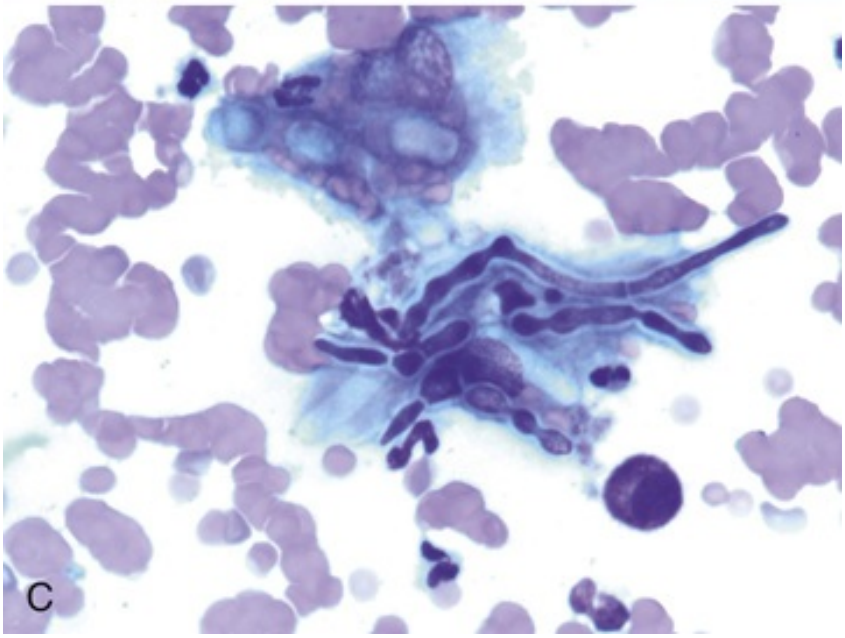
C

FIGURE 307-2 **A,** An 11-year-old neutered female domestic shorthair cat with pituitary-dependent hyperadrenocorticism and diabetes mellitus. **B,** There were two non-healing granulomatous skin lesions on the ventral abdomen. **C,** Cytology and culture revealed *Alternaria* spp. as an opportunistic infection.

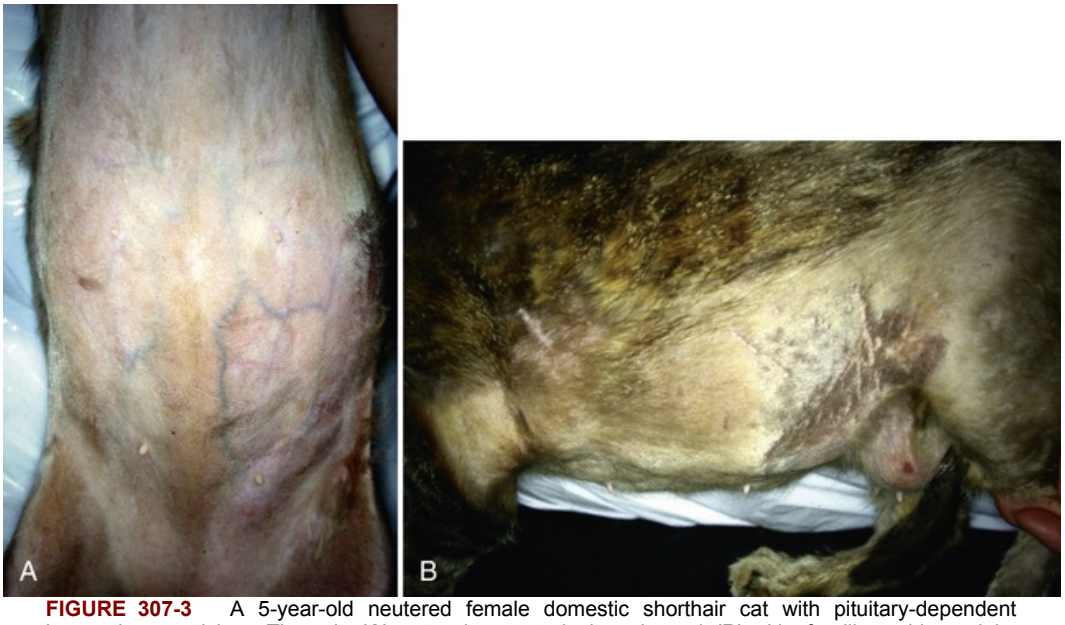

FIGURE 307-3 A 5-year-old neutered female domestic shorthair cat with pituitary-dependent hyperadrenocorticism. There is **(A)** extensive ventral alopecia and **(B)** skin fragility evidenced by scarring from previous surgical repair of skin tears.

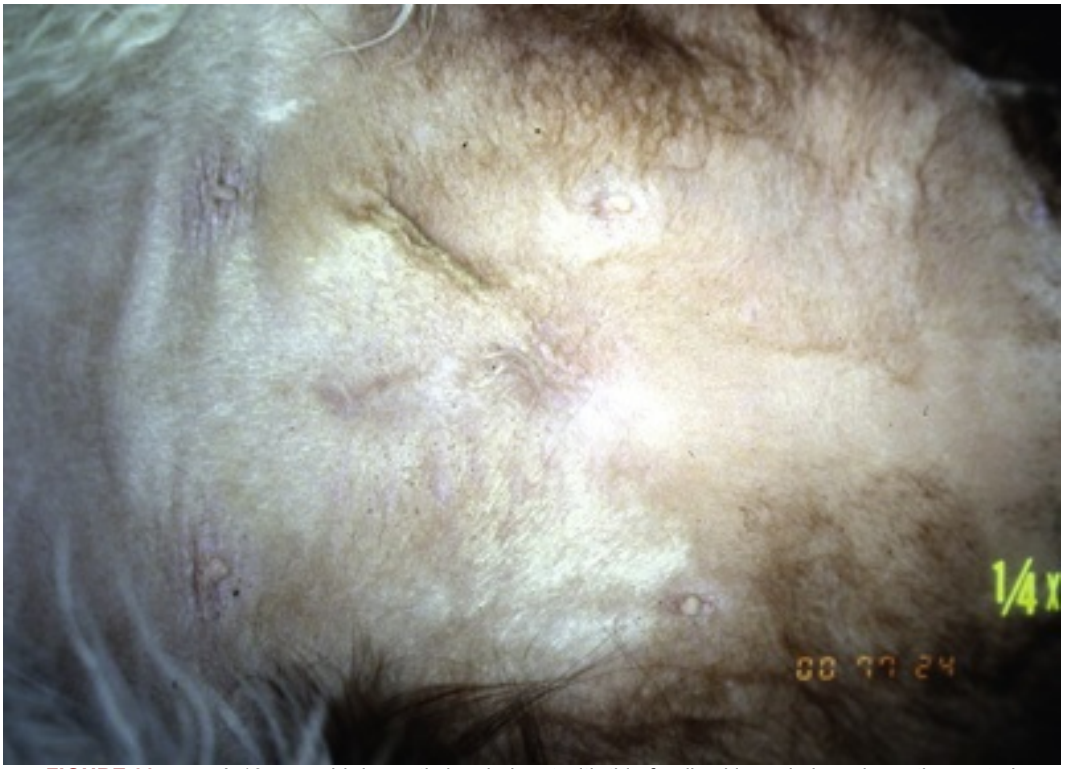

FIGURE 307-4 A 10-year-old domestic longhair cat with thin fragile skin and alopecia on the ventral abdomen.

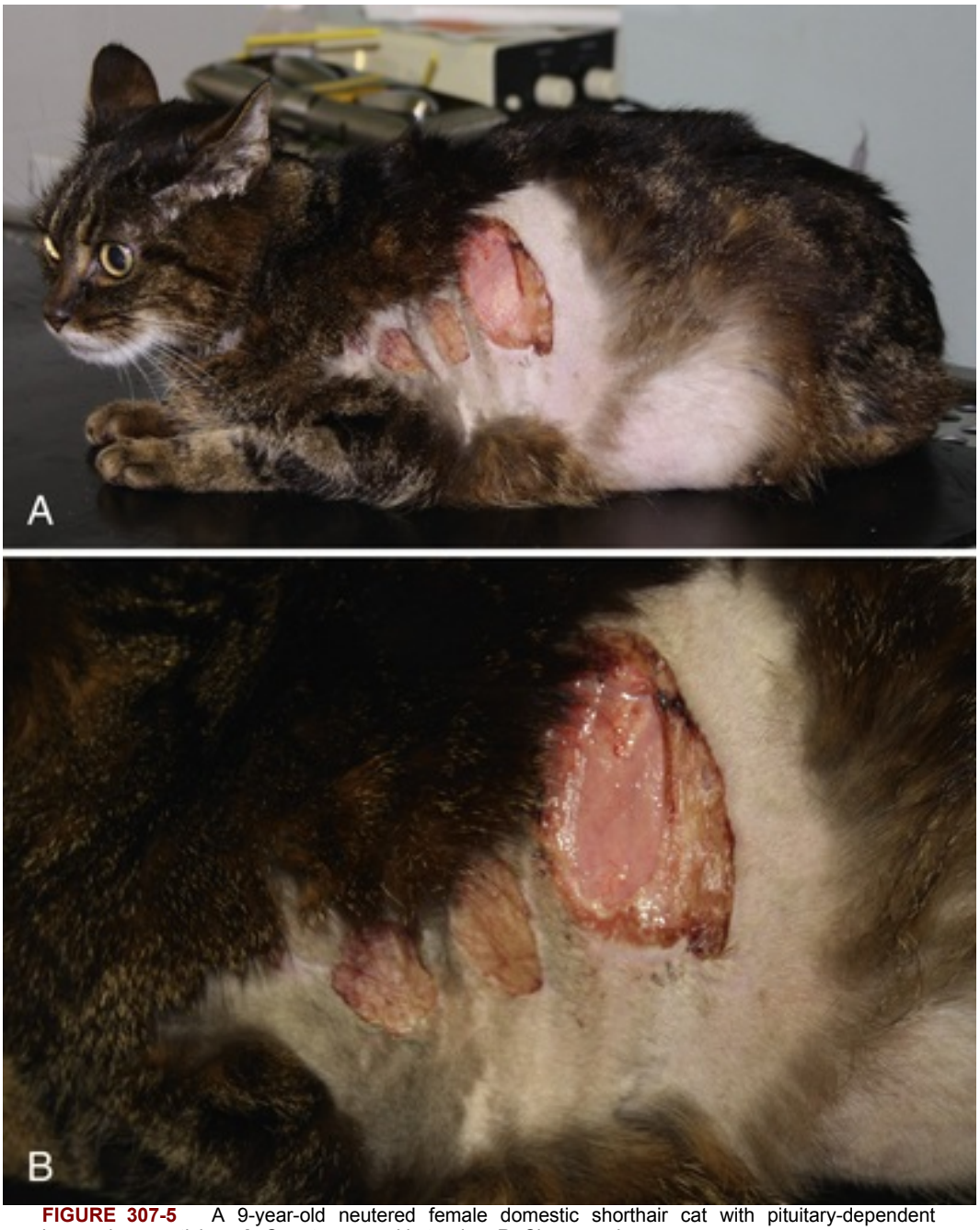

FIGURE 307-5 A 9-year-old neutered female domestic shorthair cat with pituitary-dependent hyperadrenocorticism. **A,** Spontaneous skin tearing. **B,** Close-up view.

Metabolic Alterations

Polyuria, polydipsia (PU/PD) and polyphagia (PP) are the most commonly reported metabolic signs of HAC in cats. PU/PD and PP are usually associated with glucocorticoid-induced DM with its consequent glycosuria and osmotic diuresis. PU/PD in feline HAC can also be associated with chronic kidney disease (CKD), a rare concomitant condition in dogs with HAC. Weight loss may be observed in feline HAC, but some cats exhibit weight gain despite their poorly controlled DM (Figures 307-6 and 307-7). PU/PD does not appear to be a feature of the disease in the absence of DM or CKD. Thus, PU/PD cannot be used to recognize the early stages of disease.

FIGURE 307-6 A 10-year-old domestic longhair cat with hyperadrenocorticism and diabetes which had lost a significant amount of weight. The coat is in poor condition.

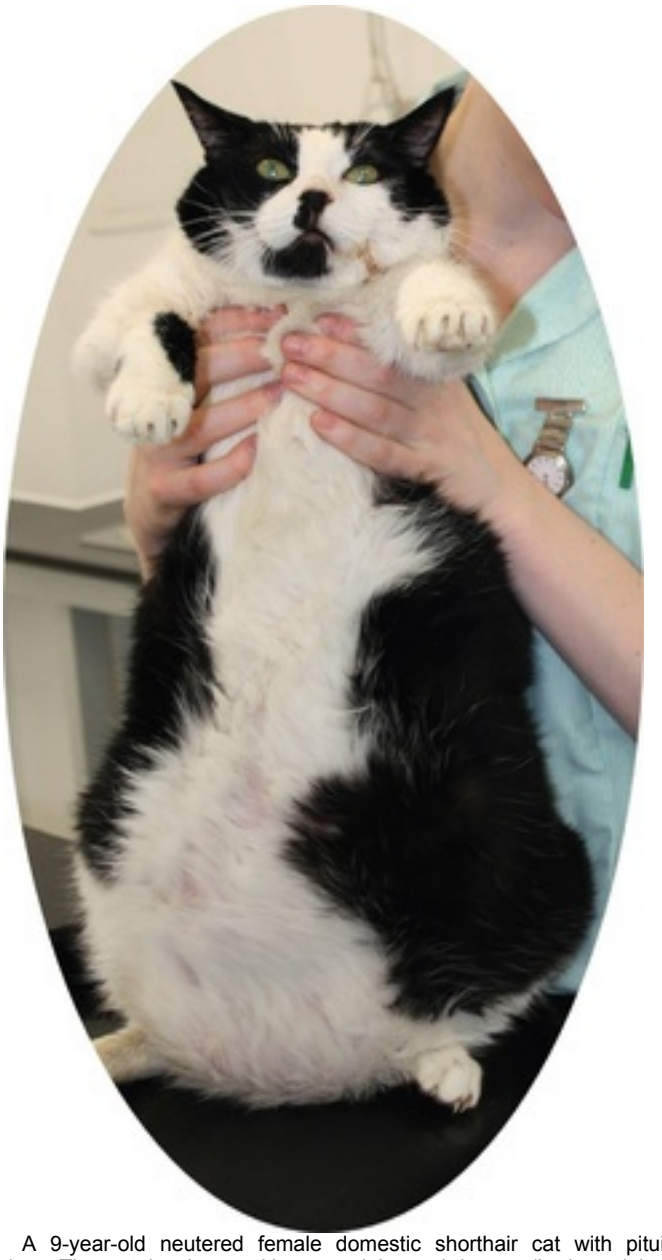

FIGURE 307-7 A 9-year-old neutered female domestic shorthair cat with pituitary-dependent hyperadrenocorticism. The cat is obese with a pendulous abdomen (body weight 10 kg) despite diabetic ketoacidosis and pancreatitis.

Physical Changes

A pendulous abdomen, generalized muscle wasting, hepatomegaly and weight gain are common. A minority of afflicted cats lose weight and some have softer tongue barbs. Occasionally, ulcers along the periphery of the tongue are noted (Figure 307-8), although not reported in any case series.

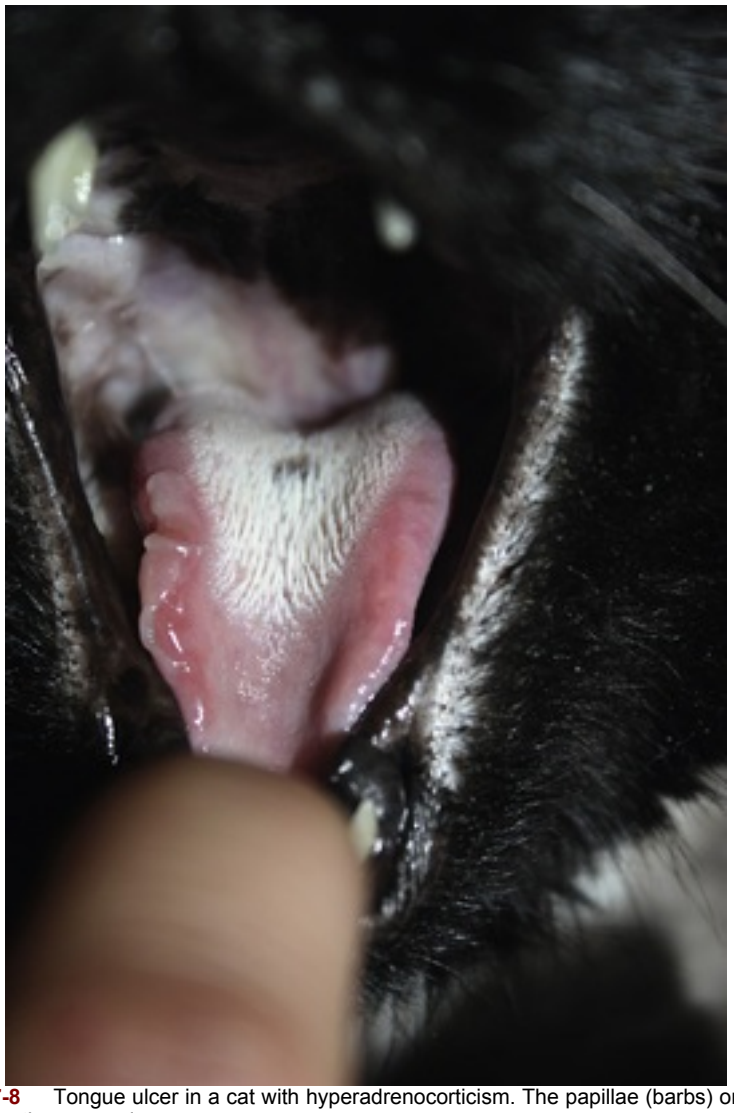

FIGURE 307-8 Tongue ulcer in a cat with hyperadrenocorticism. The papillae (barbs) on the tongue were far softer than normal.

Concurrent Diseases

Most cats diagnosed with HAC also have DM; in one case series, 27 of 30.[10] Several other series have indicated that a majority, but not all, cats with HAC have concurrent DM.[6,9] Cats with concurrent DM and HAC are often insulin resistant, requiring large daily doses of insulin (≈2 units/kg) to control their hyperglycemia and glycosuria.[3,6]

Many cats with HAC develop infections, sometimes unusual, but almost always difficult to resolve.[3,8,10,16] This apparent predisposition to infection suggests that cats with HAC are more immunosuppressed than dogs with HAC or that their fragile skin, DM, and other concurrent conditions increase infection severity.

Cats with HAC may have concurrent CKD (also see ch. 324). There is no evidence of a direct correlation between the two nor that presence of one makes the other more difficult to manage.[10] The incidence of cats with both conditions is far greater than with HAC dogs. Most HAC cats with urine specific gravity <1.020 have also had CKD. Cats with HAC may also develop pancreatitis (also see ch. 291), but the effect of increased cortisol concentrations on feline pancreatic lipase immunoreactivity (fPLI) has not been investigated. By extrapolation from the dog, fPLI may not be a reliable indicator of pancreatitis in cats with HAC.[10,33] About 20% of cats with HAC are hypertensive (see ch. 99), less common than in canine HAC.[10,34] Acute blindness due to bilateral retinal detachment was reported in a hypertensive cat with HAC (see ch. 157).[22]

General Laboratory Testing and Diagnostic Imaging

Serum Biochemistry, Complete Blood Count, Urinalysis

Hyperglycemia, seen in about 80% of cats with HAC, is the most common laboratory abnormality. A majority of these cats also have overt DM, but hyperglycemia is often present even in those who do not have overt DM (Table 307-3). Hypercholesterolemia has been reported in about 50% of cats with HAC, probably related to poorly controlled DM and increased lipolysis. In one review, >50% of cats with HAC also had increases in blood urea nitrogen (BUN) and >25% had increases in both BUN and creatinine concentrations.[35] In contrast to dogs, cats lack a steroid-induced isoenzyme of alkaline phosphatase (ALP) and the half-life of feline ALP is shorter. Mild increases in ALP activity are present in about 30% of cats with HAC. Increases in ALP and the hepatocellular enzyme alanine aminotransferase (ALT) are probably related to DM. The distribution of white blood cells expected with hypercortisolemia, lymphopenia, eosinopenia and neutrophilia occurs inconsistently in cats with HAC. Despite a glucose-induced diuresis in cats with both HAC and DM, non-diabetic cats with HAC seem able to maintain urine specific gravities >1.020. In comparison to dogs with HAC, cats tend to have more dramatic physical changes and less dramatic clinicopathological changes.

TABLE 307-3

Approximate Frequency of Clinicopathologic Findings in Feline HAC

FINDING	FREQUENCY
Biochemical	
Hyperglycemia	>43 of 47 (>91%)
Hypercholesterolemia	>16 of 31 (>51%)
Increased ALT	16 of 45 (35%)
Increased ALP	11 of 46 (24%)
Urinalysis	
Glucosuria	>41 of 47 (>87%)
USG < 1.030	10 of 28 (36%)
Proteinuria	23 of 29 (79%)
Hematological	
Anemia	16 of 44 (36%)
Neutrophilia	21 of 39 (54%)
Lymphopenia	26 of 45 (58%)
Undetectable eosinophils	7 of 11 (63%)

ALP, Alkaline phosphatase; *ALT*, alanine aminotransferase; *USG*, urine specific gravity.

From data provided in four published series of unselected cases with a combined total of 47 cases.[3,4,6,10]

Diagnostic Imaging

Overview

Advances in diagnostic imaging have improved the ability of veterinarians to identify a pituitary mass or bilateral adrenal enlargement in cats with PDH and adrenal masses in cats with ADH, as well as vessel or organ invasion usually by a malignant adrenal tumor. This information can be used to tailor treatment for each individual. However, identifying a pituitary or adrenal mass does not necessarily indicate function. Therefore, diagnostic imaging should always be interpreted within the context of clinical signs and endocrine test results.

Radiography

Radiographic examination of the thorax and abdomen is advisable in all cats suspected or proven to have

HAC. Although "diagnostic" information is only obtained in the small number of cats in which adrenal enlargement can be detected (Figure 307-9), survey radiographs of the thorax and abdomen may allow identification of concurrent abnormalities, which may alter treatment plan and/or prognosis. Abdominal contrast is usually enhanced by the marked increase in intra-abdominal fat. Neither steroid-induced osteopenia nor calcium containing uroliths have been reported in cats with HAC. Parathyroid hormone activity in cats with HAC has not been reported.[36] In dogs, adrenal mineralization is usually associated with benign or malignant adrenal neoplasia. However, adrenal calcification may be a benign and incidental finding in older cats (Figure 307-10).

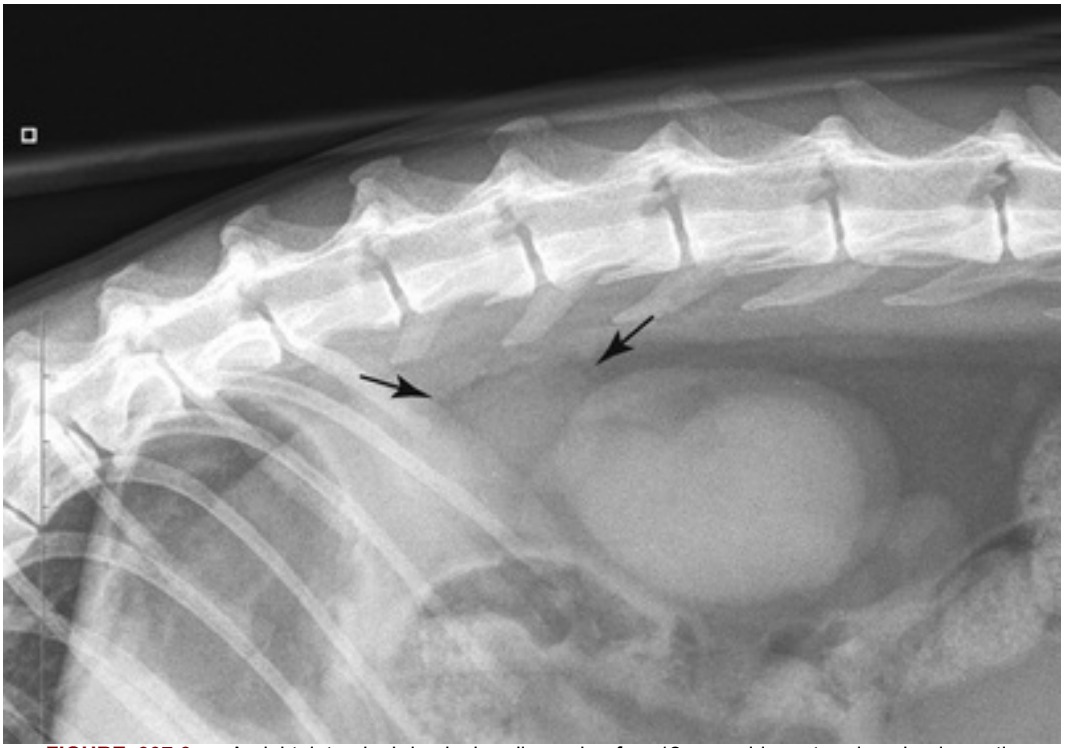

FIGURE 307-9 A right lateral abdominal radiograph of a 12-year-old neutered male domestic shorthair with hyperadrenocorticism due to an adrenal mass (arrows).

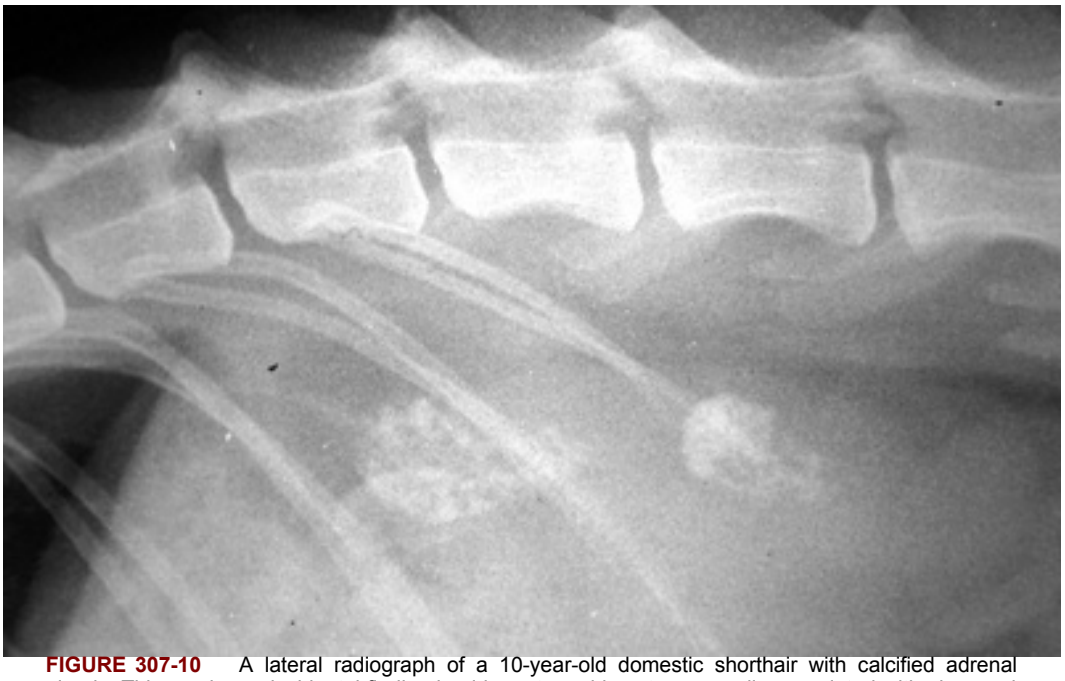

FIGURE 307-10 A lateral radiograph of a 10-year-old domestic shorthair with calcified adrenal glands. This can be an incidental finding in older cats and is not necessarily associated with abnormal adrenal function.

Abdominal Ultrasonography (US)

Using high-resolution US equipment, an experienced ultrasonographer can usually identify both adrenal glands in most healthy cats (see ch. 88). The best adrenal images are obtained by scanning from the right and left lateral intercostal and abdominal approaches. The right adrenal gland is more difficult to identify because of its deeper cranial location under the ribs. Normal feline adrenal glands are oval to bi-lobed and hypoechoic compared with the surrounding tissues. The healthy adrenal medulla can be slightly hyperechoic compared to the cortex, but is not always clearly visible. Healthy feline adrenal glands are about 4.5-13.7 mm in length and 2.9-5.3 mm in width.[37]

The challenge for the ultrasonographer is to distinguish normal from hyperplastic or neoplastic glands. Although the adrenal glands of cats with PDH have been characterized as being symmetrically enlarged and of normal conformation, diagnosis of adrenal hyperplasia can be subjective. Hyperplastic adrenals tend to be larger and easier to identify than healthy glands, but should still have a normal homogeneous hypoechoic pattern (Figure 307-11). US can increase suspicion for presence of an adrenal tumor (Figure 307-12). Bilateral adrenal tumors have been reported, but are rare.[2,3] Malignant adrenal tumors have a propensity to invade nearby blood vessels and surrounding tissues. Thus, thorough US examination of adjacent vessels and tissues should be performed. If an adrenal mass is identified, the liver, spleen and kidneys should also be carefully examined for evidence of metastases.

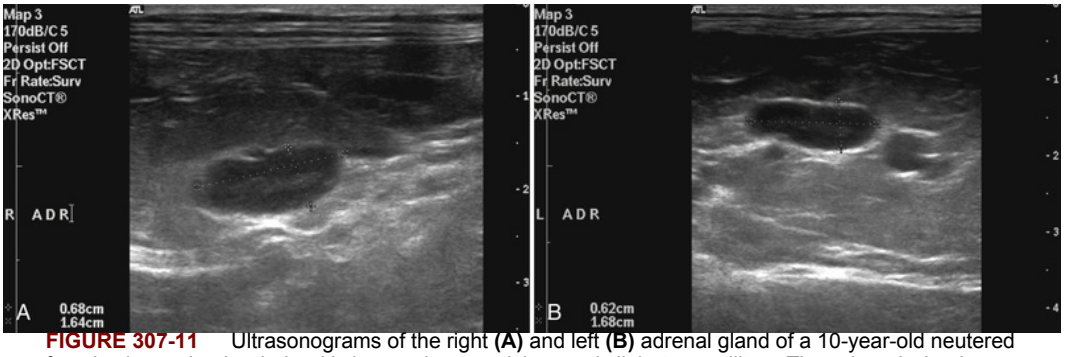

FIGURE 307-11 Ultrasonograms of the right **(A)** and left **(B)** adrenal gland of a 10-year-old neutered female domestic shorthair with hyperadrenocorticism and diabetes mellitus. The adrenal glands are both enlarged, with the width greater than 0.53 cm (>5.3 mm). The adrenals are of normal shape and

similar size, indicating that the cause is pituitary dependent.

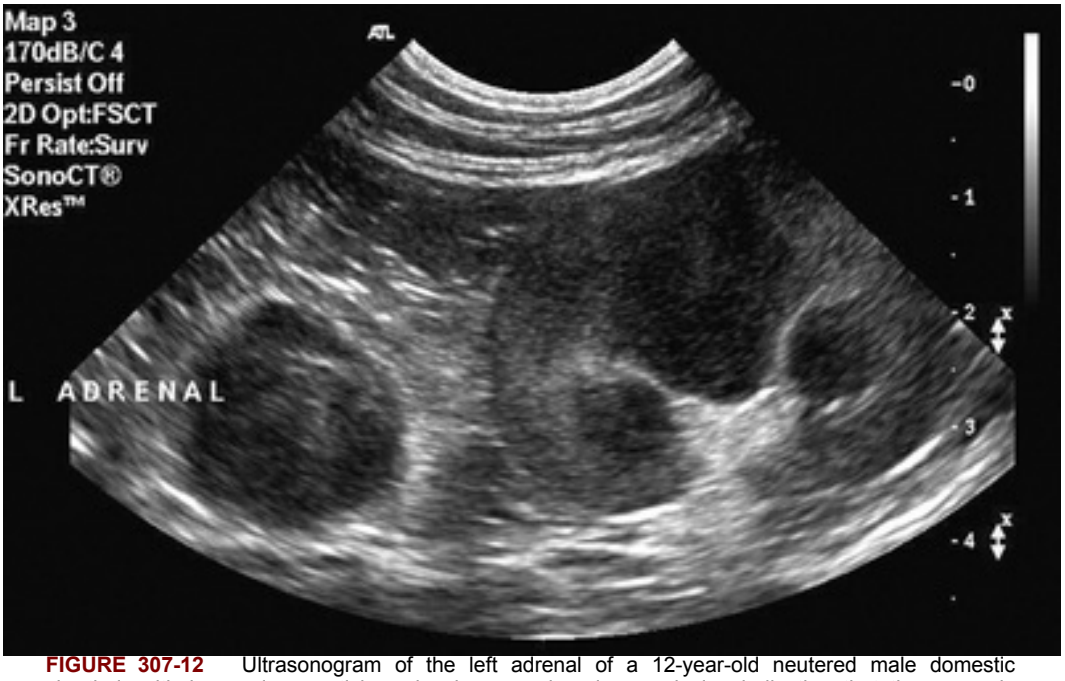

FIGURE 307-12 Ultrasonogram of the left adrenal of a 12-year-old neutered male domestic shorthair with hyperadrenocorticism showing an adrenal mass lesion indicating that the cause is adrenal dependent.

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) Scans

CT and MRI scanning have proved useful in the diagnosis of adrenal tumors, adrenal hyperplasia and pituitary tumors. Contrast abdominal CT may also help identify tumor invasion of the caudal vena cava, invasion of other blood vessels, or adhesions in the area of the mass. These considerations comprise some of the presurgical planning in cats for whom adrenalectomy is an option.

Correlation between pituitary tumor size and presence or development of neurological signs is not clear. In those cats with neurological signs, MRI or CT examination of the brain is essential if pituitary surgery or irradiation is being considered.

Endocrine Testing

Overview (see E-Table 307-1 and Figure 307-1)

The "best test" for confirming a diagnosis of feline HAC has not been established. Basal cortisol concentrations are of little use in the assessment of adrenal function in cats and therefore dynamic testing is essential (Table 307-4). Measurement of cortisol in feline plasma has not been subjected to as much scrutiny as for dogs. Even assuming similar methodologies, reference ranges generated in different laboratories using different machines cannot be used interchangeably.[38,39] Clinicians should, wherever possible, use the specific reference range from their laboratory and should consult with their laboratory personnel before using values from other laboratories or the literature in test interpretation.

TABLE 307-4

Approximate Frequency of Endocrine Findings in Feline HAC

TEST	CRITERIA FOR DIAGNOSIS OF HAC	FREQUENCY
ACTH stimulation test	60 or 90 minute post ACTH cortisol greater than	28 of 39

	400 nmol/L (14.5 mcg/dL)	(71%)
Low-dose (0.01 mg/kg IV) dexamethasone screening test positive (greater than 27 nmol/L [1 mcg/dL])	8 hour post dexamethasone greater than 27 nmol/L (1 mcg/dL)	25 of 26 (96%)
Dexamethasone suppression test (0.1 mg/kg IV)	8 hour post dexamethasone greater than 27 nmol/L (1 mcg/dL)	38 of 45 (84%)
Endogenous ACTH	Greater than 20 pg/mL (=4.4 pmol/L) to diagnose PDH	14 of 19 (73%)
Adrenal ultrasound	Bilateral adrenomegaly or symmetrical adrenal glands (PDH) Adrenal mass (ADH)	49 of 53 (92%)

From data provided in eight published series of cases with a combined total of 84 cases.[3-10] Note that four of these series (a total of 37 cases) were selected by treatment modality.

ACTH Stimulation Test (ACTHST)

The ACTHST can be useful for the diagnosis of feline HAC. However, the peak response in cats is variable in both timing and magnitude. Samples should be obtained at 60 and 90 minutes after administering tetracosactrin, 5 mcg/kg or 0.125 mg/cat IV.[40,41] Reported test sensitivity varies from 56 to 80%.[3,6,8,10] Normal cats and cats with chronic disease rarely have a post-ACTH cortisol >400 nmol/L (>14.5 mcg/dL).[42] However, some conditions (e.g., hyperthyroidism) can result in post-ACTH cortisol concentrations as high as 600 nmol/L (21.7 mcg/dL). As in the dog, cortisol values >600 nmol/L (>21.7 mcg/dL) are quite suggestive, and values between 400 and 600 nmol/L (14.5 and 21.7 mcg/dL) are supportive of HAC in the context of appropriate clinical signs. However, cats with HAC tend to have lower cortisol concentrations than dogs with HAC and they rarely have post-ACTH cortisol concentrations >800 nmol/L (>29 mcg/dL). An ACTHST result within that laboratory's reference interval does not rule out a diagnosis of feline HAC.

Dexamethasone Suppression Tests (DST)

Both the degree and duration of adrenocortical suppression produced by dexamethasone varies among healthy cats. Generally, the "low-dose" DST uses a higher dosage (0.1 mg/kg IV) in cats than for dogs. Serum cortisol concentrations in healthy cats are reliably suppressed with this dose and the test is excellent if used as a screening test to distinguish cats with HAC from those who do not have the condition. However, the test has also been used as an aid in discriminating ADH from PDH without evidence that this is an appropriate use.[3,5,42] Importantly, cortisol concentrations after giving 0.1 mg/kg dexamethasone are suppressed in cats with DM but not those with HAC and DM, independent of glycemic control.[43] The 0.1 mg/kg DST has good specificity. However, while cortisol fails to suppress at either 3-4 or 8 hours in cats with ADH, some cats with PDH suppress at 8 hours, reducing sensitivity. It has been recommended that the low-dose DST, using the standard "canine dose" (0.01 mg/kg IV; with blood samples obtained before and 8 hours after injection), be used to "screen" cats for HAC.[3] However 20% of healthy cats do not suppress after being given 0.01 mg/kg.[44] Thus, increased sensitivity is offset by a lack of specificity. This "low-dose DST" may be useful in certain circumstances since "normal suppression" would make the diagnosis of HAC quite unlikely. Equally, if a cat showing clinical signs of HAC has a "normal response" on the 0.1 mg/kg DST, then the 0.01 mg/kg test may be indicated. Four cats in one study had both dexamethasone tests performed, but their results did not alter diagnosis in any cat.[10]

Urine Corticoid : Creatinine Ratio (UCCR)

Urine should always be collected at home (not in the hospital environment) as any stressful situation may increase the ratio. Almost all cats with HAC will be positive (good sensitivity), but false-positive test results may be seen in cats with non-adrenal illness (poor specificity).[45] Importantly, hyperthyroid cats often have increased UCCR results.[42,46] Thus, the UCCR must be regarded as lacking specificity in a group of cats that might be suspected of having HAC. It is known that there are considerable differences between tests for urinary corticoids in the dog. Since the same may be true regarding assay validity for cats, results may vary according to the assay; thus, an individual reference range should be generated for a specific test rather than

using published reference ranges.[47,48]

Other Tests

A combined DST/ACTHST protocol was suggested for cats; however, it has not been sufficiently validated to be recommended. Thyroid hormone concentrations are usually normal in cats with HAC, which is important since hyperthyroidism may be considered in any cat with PU/PD and weight loss. In one study, 4 of 25 cats with HAC had a low thyroxine level.[10] It has been suggested that endogenous ACTH precursors (pro-opiomelanocortin [POMC] and pro-ACTH) may be useful in identifying cats with PDH.[49] However, such assays are not yet widely available.

Tests to Distinguish Between PDH and ADH (see E-Table 307-1)

The reliability of any test for distinguishing cats with PDH from those with ADH has not been assessed. Endogenous plasma ACTH concentrations should be normal or increased in cats with PDH and low or non-detectable in cats with an adrenal tumor. This test appears to be useful for distinguishing PDH from ADH, once the diagnosis of feline HAC has been confirmed. However, it is essential that any assay be validated for cats.[9,10] Radiography, US, CT, and MRI can be extremely helpful in distinguishing PDH from ADH.[3,6,7,49]

Treatment

Cats with HAC, whenever possible, should be treated. Diabetic control will likely improve if treatment is successful and the risk of serious adverse consequences of chronic HAC likely reduced, e.g., skin hyperfragility and unusual or difficult-to-treat infections.

Surgery

ADH

Whenever possible, adrenal tumors should be surgically removed. Accurate diagnostic imaging with abdominal US or contrast-enhanced CT should be employed, if available, to assess for invasion of major vessels or kidneys. Post-operative hypoadrenocorticism is common and requires management with fludrocortisone or desoxycortone pivalate (though this has not been reported). Prednisolone, needed initially, can usually be tapered over time. Diabetic cats may go into remission in the months following surgery. Those that remain diabetic often require much lower insulin doses.[5] Successful laparoscopic adrenalectomy has been reported and should be considered for the treatment of unilateral functional adrenal neoplasia in cats when diagnostic imaging has ruled out intravascular invasion and metastatic disease.[50]

PDH

Surgical options for PDH include trans-sphenoidal hypophysectomy and bilateral adrenalectomy.[5,7] Cats successfully treated with either modality require medical therapy afterwards. Trans-sphenoidal hypophysectomy is the only definitive treatment for PDH. The first report of 7 cats with PDH undergoing trans-sphenoidal hypophysectomy included 2 cats dying within weeks. However, in the surviving 5 cats the treatment was successful. With greater experience in managing concurrent illnesses and careful closure of the soft palate, success rates will improve.[7,51] Post-operative treatment for central diabetes insipidus (see ch. 296) is needed. Mineralocorticoid and glucocorticoid replacement are usually required for several weeks. Despite high initial remission rates in dogs with PDH following hypophysectomy, recurrence in about 25% is a concern.[52] Similar rates of recurrence may be seen in cats, though there are no published studies. Morbidity and mortality appear less for cats undergoing bilateral adrenalectomy than dogs; however, complications are frequent.[5,6] Resolution or improvement of the diabetic state may be seen in the months following surgery, but long-term prednisolone and fludrocortisone are required. As such, surgery is not a reasonable option for cats difficult to medicate orally. It should be noted that skin wounds caused by spontaneous tearing should be closed. One of the authors has found tissue glue to be effective, thereby avoiding the need for anesthesia and further risk of tearing. Suturing is also possible.

Medical Treatment

Trilostane

Trilostane, a competitive inhibitor of 3beta-hydroxysteroid dehydrogenase, has been successfully used to treat cats with HAC.[8,9] Of 20 cats in two series, 17 survived for more than 3 months and many survived more than 1 year. This is much better than with any other medical treatment. There have been no pharmacokinetic studies of trilostane or its metabolites in cats; however, on the basis of one case in which cortisol was measured sequentially, it would appear that the effect on cortisol production is rapid and its duration of action is <12 hours.[8] Manufacturers do not recommend trilostane be used if concurrent hepatic or renal disease is present.

Trilostane should be given at a starting dosage of 1-2 mg/kg PO q 24 h. However, it would seem logical to give trilostane at the same frequency as insulin. If insulin and trilostane are being used twice daily, the trilostane dose should also be divided, given at a dosage of 0.5-1 mg/kg PO q 12 h. Reformulation is often necessary. Trilostane seems to be well-tolerated and improvement is often noted within weeks.[9] In a series of 9 cats with HAC and DM treated with trilostane, insulin dosage requirements decreased by 36% on average in 6 cats. One cat had an insulin dosage requirement increase. DM remission did not occur.[9] Important possible complications of trilostane include anorexia, lethargy, hyponatremia and/or hyperkalemia.

There are no published criteria critically evaluating any method to monitor treatment response. Although the ACTHST is often used, target cortisol concentrations and test timing have been extrapolated from dogs. However, cats have been successfully treated with trilostane using these extrapolated values.[8,9] In general, the target is a post-ACTHST cortisol concentration, 4 hours after trilostane dosing, >40 nmol/L (>1.4 mcg/dL) and below about 140 nmol/L (5 mcg/dL). However, ACTHST results have now been shown to be unreliable predictors of clinical status in dogs with HAC being treated with trilostane. Therefore, it is recommended to closely monitor history and physical examination as critical parameters during treatment.

Other Medical Options

Mitotane (o,p'-DDD, Lysodren) appears to be well tolerated by cats despite their sensitivity to chlorinated hydrocarbons.[11] However, mitotane is frequently ineffective in controlling clinical signs of feline HAC in cats.[3] One reported case given 50 mg/kg/day PO for 1 week then 50 mg/kg/wk PO was well controlled for 40 weeks before developing signs compatible with hypoadrenocorticism.[12]

If trilostane and mitotane are unavailable or ineffective, other steroid synthesis inhibitors may be used. Metyrapone, an inhibitor of the 11beta-hydroxylase enzyme that converts 11-deoxycortisol to cortisol, proved effective at least transiently in controlling clinical signs and suppressing cortisol production in one cat (65 mg/kg PO q 12 h).[14] Whether long-term therapy with metyrapone can control feline HAC or whether rising ACTH concentrations eventually break the blockade has not been determined. It would, however, appear to be potentially useful for presurgical stabilization.[13]

Ketoconazole, an antifungal imidazole, is an inhibitor of steroidogenesis in humans and dogs, but is ineffective in cats. Its safety has been questioned because anorexia, weight loss, vomiting, and diarrhea have been commonly reported. Hepatotoxicosis and thrombocytopenia have also been noted.[53,54] Ketoconazole is no longer available in some parts of the world, having been replaced by itraconazole. There are no reports of the use of itraconazole for feline HAC.

Pituitary Irradiation

For cats with neurologic signs associated with a large pituitary tumor, pituitary radiation therapy can prove beneficial. In one report, neurologic signs and endocrine signs improved following radiation therapy in 7 cats with either HAC or acromegaly caused by large pituitary tumors.[55] Median survival was 17.4 months, but detailed evaluation of changes in endocrine status was not reported. Pituitary irradiation has been associated with improved diabetic control in acromegalic cats, but similar improvement in diabetic control in cats with HAC has not been reported.[56]

Prognosis

Untreated or unresponsive feline HAC is a progressive disorder with a poor prognosis. These cats usually die from severe infection, uncontrolled DM or are euthanized. With appropriate therapy, cats with adrenal adenomas or PDH appear to have a good to excellent prognosis. Many of the diabetic cats with feline HAC require less insulin to manage their diabetes. Complete remission of DM may occur in those cats undergoing

successful definitive treatment for HAC.

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CHAPTER 308

Non-Cortisol-Secreting Adrenocortical Tumors and Incidentalomas

Ellen N. Behrend

Client Information Sheet: Non-Cortisol-Secreting Adrenocortical Tumors and Incidentalomas

Introduction

Non-cortisol-secreting adrenal tumors are being recognized more often due to the common use of abdominal ultrasonography (US). An adrenal mass is not necessarily a primary adrenal tumor (AT) and not all ATs are cortisol-secreting. Non-tumor possibilities include nodular hyperplasia, cyst, abscess, hematoma, and granuloma. In one study, 27% of canine and 60% of feline ATs were metastatic lesions.[1] Pulmonary, mammary, prostatic, gastric, and pancreatic carcinomas and melanoma had the highest rates of adrenal gland metastasis in dogs. A primary AT can be benign or malignant and may or may not be functional (i.e., secreting a hormone); myelolipomas or lipomas can occur in the adrenal cortex. Functional masses secrete steroids from the cortex or adrenergic hormones from the medulla, i.e., a pheochromocytoma (see ch. 311). Of primary ATs, approximately 75% are adrenocortical and 25% are of neuroendocrine origin.[2]

Incidentaloma

Clinical Presentation

Ultrasonography is employed routinely for evaluation of abdominal soft tissue structures (see ch. 88). Occasionally, a seemingly incidental adrenal gland mass (IAGM), i.e., an "incidentaloma," is seen. These are defined as "a focal enlargement of the adrenal gland in patients without prior evidence of adrenal gland disease." An AT should be suspected when there is loss of the typical shape of an adrenal gland regardless of size, when asymmetry in shape and size between the adrenal glands is present, or the mass appears to have infiltrated the phrenicoabdominal vein, vena cava, or surrounding soft tissues (see Figures 306-9 and 307-9 to 307-12). The incidence of IAGM is estimated at 4% overall in dogs, but in one study dogs with an IAGM were significantly older and heavier than a control group.[3] Only 17% of dogs with IAGM were <9 years of age, and the median weight of dogs with an IAGM was 21 kg as compared to 14 kg in the control group. Incidence of adrenal incidentalomas in cats is unknown. As the first step, abdominal US should be repeated to ensure that a mass is consistently seen (Figure 308-1). Once an IAGM is confirmed, a number of differentials, as discussed, need to be considered. Many factors influence the aggressiveness of the diagnostic and therapeutic approach. These include the severity of concurrent problems, the original reason for performing abdominal US, age, the likelihood the mass is hormonally active and/or malignant, the size and invasiveness of the mass, and the client's desires.

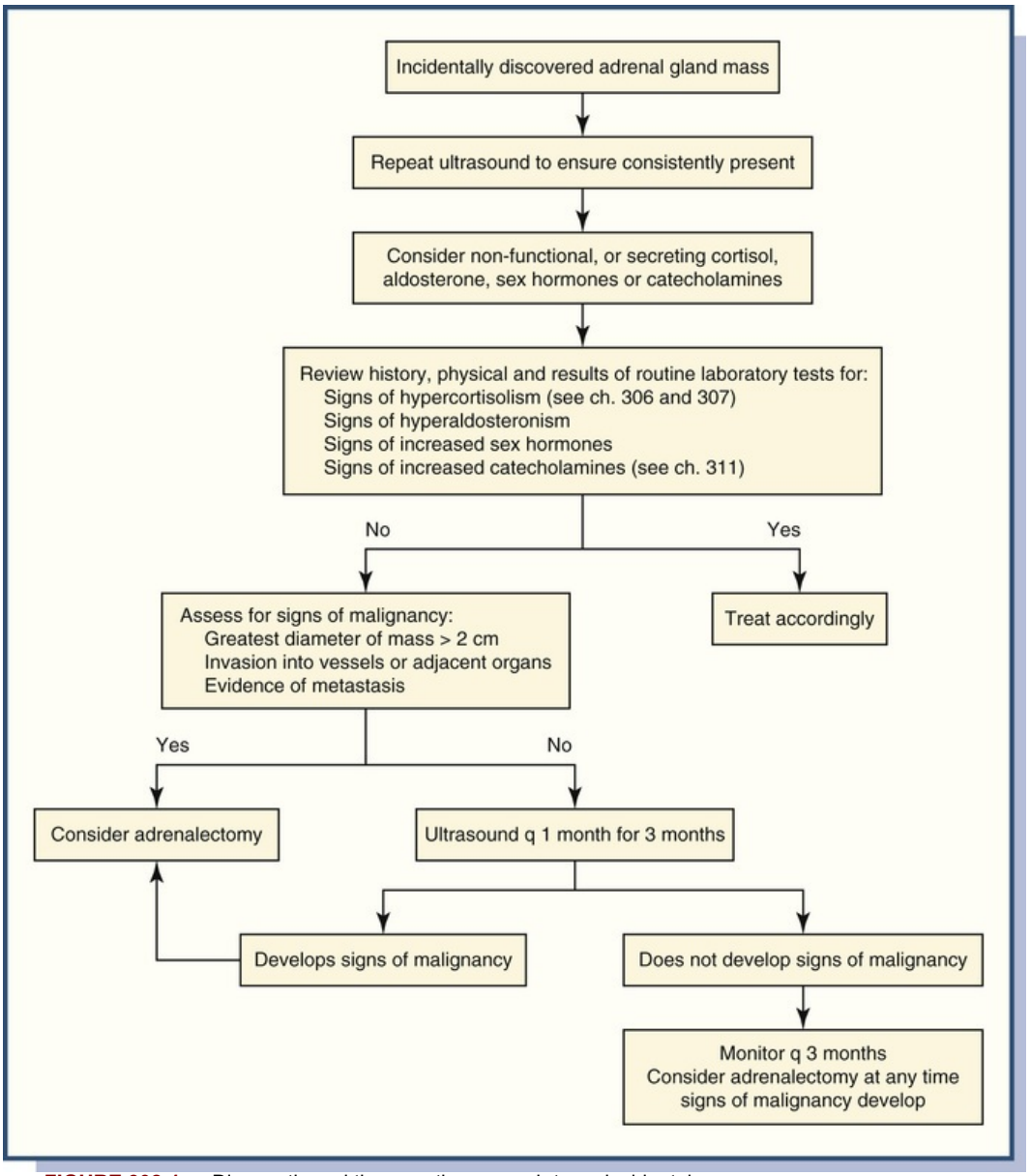

FIGURE 308-1 Diagnostic and therapeutic approach to an incidentaloma.

Diagnostic Approach

Initial Database

Results of the history, physical examination, and routine blood and urine tests should be assessed for evidence of hypercortisolism (see ch. 306 and 307), hyperaldosteronism, pheochromocytoma (see ch. 311), or sex hormone excess. Appropriate testing should be performed as indicated. Aldosterone- and sex hormone–secreting tumors are discussed in this chapter.

Malignancy Assessment with US

While 14 to 30% of IAGMs are malignant, it is difficult to determine whether one particular IAGM is neoplastic and/or malignant.[3] These diagnoses require histologic evaluation. Although cytology has 90-100% accuracy for differentiating cortical from medullary origin, it is not reliable for distinguishing benign from malignant.[4] Imaging may be helpful but must be interpreted carefully. Characteristics that do not help differentiate adrenal adenoma and carcinoma are mineralization or US echogenicity. Both adenomas and carcinomas can contain mineral densities or appear as a mass cranial to the kidney (see Figures 307-9 and 307-

10). While diffuse, ill-defined mineralization usually is associated with adrenal neoplasia, discrete, well-marginated mineralization develops in clinically normal animals and may be a dystrophic change.[5] On US, both benign and malignant ATs may be hypo-, iso- or hyper-echoic compared to the renal cortex or have mixed echogenicity.

Thoracic Radiographs and US-Guided Sampling

Evidence of metastases may be identified on thoracic radiographs. Suspected metastases to abdominal organs, especially the liver, can be visualized and confirmed by US-guided biopsy (see ch. 89). If the greatest diameter of the AT is >2 cm, chances of malignancy and growth are increased.[3,6] Evidence of invasion into surrounding tissues and/or the vena cava is suggestive of a carcinoma. Invasive nature of masses, however, may not be observed.[7] Of 34 dogs with 36 ATs, US was 100% sensitive and 96% specific for identifying the presence of a tumor thrombus within the caudal vena cava. However, when all forms of vascular invasion were evaluated, including vascular wall invasion without a concurrent thrombus, sensitivity and specificity were 76% and 96%, respectively.[8] The presence of tortuous vessels and heterogeneity of contrast enhancement as judged by contrast-enhanced US may also be markers of malignancy.[9]

Computed Tomography (CT)

On abdominal CT, poor glandular demarcation, irregular contrast enhancement and a non-homogenous texture are evidence of malignancy.[10] Vascular invasion can be detected using CT with high, but not perfect, accuracy.[11-13] In one study, vascular invasion was identified correctly using contrast-enhanced CT in 11 of 12 dogs. The sensitivity and specificity of contrast-enhanced CT for vascular invasion, compared with surgery or necropsy, were 92% and 100%, respectively. In one dog, invasion of the phrenicoabdominal vein was not identified on CT.[11] Conversely, enlarged adrenal glands may adhere to or compress the vena cava suggesting invasion when not present.[10]

Management and Follow-Up

If the IAGM is suspected to be malignant, adrenalectomy is recommended. If clinical signs, physical examination, or results of routine blood and urine tests are not consistent with a functional AT, there is no evidence of tissue or vascular invasion or of malignancy, and the tumor is <2 cm in greatest diameter, a conservative non-surgical approach is suggested. Initially, monthly US monitoring is recommended to determine if the mass is growing or changing in appearance. Growth of IAGM is unpredictable. In a study on 7 dogs with an IAGM, 3 of the suspected masses were not identified >4 months later on repeat US and no growth was detected after >6 months in 2 dogs. In 1 dog, the IAGM grew from 1.6 to 2.5-cm in greatest diameter and had invaded the vena cava within 10 months. In 1 dog, the IAGM grew from 2.5 to 3.1 cm in greatest diameter within 8 months.[3] In 9 dogs with non-cortisol-secreting AT followed for 12 months, no change was seen in 7. The two tumors that did grow were originally 2.0 and 2.5 cm in length.[6]

If an IAGM has not increased in size after 3 months, the time interval between US evaluations can be increased. However, if the IAGM is enlarging, changing in appearance, compressing or infiltrating surrounding blood vessels or soft tissues, or if clinical signs affiliated with excess hormone secretion develop, adrenalectomy may be warranted. For non-cortisol-secreting ATs, median survival without surgery in 14 dogs was 29.8 ± 8.9 months (range 1-96 months). Larger tumor size was associated with shorter survival.[6]

Aldosterone-Secreting Adrenal Tumors

Aldosterone is the principal mineralocorticoid synthesized and secreted by the zona glomerulosa, the outermost zone of the adrenal cortices. Its primary functions are regulation of serum sodium (Na) and potassium (K) concentrations and intravascular fluid volume homeostasis. Increases in serum K directly stimulate aldosterone secretion. Decreases in blood pressure, primarily sensed within the kidneys, stimulate synthesis and release of renin which, through angiotensin II, stimulates aldosterone secretion, i.e., the renin-angiotensin-aldosterone system (RAAS; see ch. 246). Aldosterone acts on distal nephrons to promote Na reabsorption and K and hydrogen excretion. In conserving Na, aldosterone indirectly conserves water, raising blood volume and, in turn, blood pressure; it also directly increases blood pressure via enhancement of total peripheral resistance (see ch. 157). Aldosterone is synthesized in heart, brain and vasculature tissues as well, where it may have paracrine or autocrine actions.[14]

Hyperaldosteronism can be primary or secondary. Primary hyperaldosteronism (PHA) is defined as autonomous aldosterone secretion by adrenocortical cells. It is characterized by circulating aldosterone excess and, through negative feedback, renin suppression. Secondary hyperaldosteronism is the result of a condition, e.g., heart failure or chronic kidney disease (CKD), which stimulates the RAAS. Thus, it is associated with enhanced renin concentrations.

Feline Aldosterone-Secreting Tumors

Definitions of Primary Tumor-Related PHA and Non-Tumor-Related PHA

Feline PHA was first reported in 1983,[15] and has been diagnosed increasingly in the last 20 years. Cats with an AT causing PHA, i.e., aldosteronoma, usually have a unilateral cortical adenoma or carcinoma, but bilateral adrenal adenomas have been reported.[16] The incidence of malignant tumors exceeds that of benign.[17] Non-tumor-related PHA (see ch. 324) has been described.[18-20] Affected cats have bilateral adrenocortical hyperplasia and most have evidence of CKD. Some cats have nodular hyperplasia of the zona glomerulosa, renal arteriolar sclerosis, glomerular sclerosis, tubular atrophy and interstitial fibrosis.

Signalment and History in Tumor-Related PHA

No breed predisposition for feline aldosteronoma is apparent. Median age at diagnosis is approximately 13 years and the majority are >10 years of age. Both genders have been represented and most affected cats have been neutered.[21] Clinical signs relate mainly to hypokalemia or systemic hypertension. The most common clinical signs are persistent and progressive weakness, i.e., "hypokalemic polymyopathy,"[17] typically observed when serum K concentration is <3 mmol/L. Cervical ventroflexion, hindlimb weakness (sometimes plantigrade stance), difficulty jumping, listlessness, and ataxia are common owner concerns. A few cats have had limb rigidity, dysphagia, or collapse. Episodic signs and acute onset have been reported.[18] Respiratory failure secondary to respiratory muscle weakness is rare.[22,23] Owners may note acute blindness and/or see a sudden change in eye color, typically due to intraocular hemorrhage or retinal detachment (see ch. 11) secondary to hypertension (see ch. 157). On occasion, hypertension may cause seizures, ataxia or behavior changes as a result of central nervous system edema, hemorrhage or ischemia.[21] Polyuria and polydipsia (PU/PD) occurs in <20% of cats with PHA.[21] Some cats with PHA have had concurrent progestogen excess, which may cause PU/PD.[24,25] Hypokalemia can cause reversible nephrogenic diabetes insipidus and PU/PD. Appetite is variable and can be increased, normal or decreased. Polyphagia may be a sign of concurrent excess of another hormone, e.g., progesterone.

Physical Examination

Physical examination findings are usually related to hypokalemia (see ch. 68) or hypertension (see ch. 157). Weakness is usually apparent. Evidence of hypertension includes tortuous retinal vessels and retinal detachment, hemorrhage, and/or edema (see ch. 11). Clinical signs consistent with glucocorticoid or progestogen excess include fragile skin, alopecia and a pot belly (see ch. 307). Heart murmurs, gallop rhythms or arrhythmias may be auscultated secondary to left ventricular hypertrophy, a sequela of hypertension (see ch. 55).

Diagnosis

Routine Laboratory Testing

The single abnormality typical for PHA on routine laboratory testing is hypokalemia (see ch. 68). Most cats with an aldosteronoma have had moderate to severe hypokalemia, possibly because PHA is not considered until persistent hypokalemia, especially despite K supplementation, is documented.[17] An increased urinary fractional K excretion can confirm the etiology of hypokalemia to be renal (see ch. 73). Due to an "aldosterone escape" phenomenon, hypernatremia is uncommon in PHA. Hypertension and volume expansion can overcome the Na-sparing effects of aldosterone and cause natriuresis (see ch. 73). Creatine kinase (CK; see ch. 66) is usually increased due to hypokalemic myopathy, but its severity is variable. Metabolic alkalosis is common, likely due to aldosterone-mediated hydrogen ion excretion.[17] Aldosteronoma should be considered

in any cat with unexplained hypertension, especially if refractive to therapy. About 85% of affected cats are persistently hypertensive.[14]

Imaging

Radiology is not often helpful, but a large tumor may be visible on abdominal imaging (see Figure 307-9). Adrenal calcification is present in approximately 33% of older, healthy cats, and should not be over-interpreted (see Figure 307-10). Pulmonary metastases are uncommon. Conversely, US is highly useful. All reported cats with aldosteronoma have had an AT detected with US (see Figures 307-11 and 307-12). A few cats have had bilateral AT and only one of two tumors visualized.[16,26] The contralateral adrenal gland should be evaluated since a decrease in size suggests the AT is functional and secreting glucocorticoids or progestogens.[25] Bilateral masses are uncommon, but do occur.[16] Evidence of malignancy should be sought. Lack of apparent invasion into surrounding tissues or vasculature should be viewed with caution, as US has failed to identify existing vascular invasion in some cats with aldosteronoma.[26,27] Abdominal CT and magnetic resonance imaging (MRI) can be used, but reports are limited.[16,27] Adrenal mass cytology can be helpful in determining origin, but not function or its malignant versus benign nature.[28]

Serum Aldosterone

While presence of an AT in a cat with persistent hypokalemia and/or hypertension is highly indicative of aldosteronoma, confirmation relies on demonstration of increased basal aldosterone concentrations. Assays are usually available and no special sample handling is required. To date, aldosterone concentrations have been increased in all cats reported to have an aldosteronoma. The highest aldosterone concentrations occur with AT. However, aldosterone concentrations reported for primary and secondary hyperaldosteronism overlap. Concentrations >1000 pmol/L have been reported with secondary PHA, especially in cats with CKD. In addition, as suspicion for PHA is becoming more common, testing will likely occur earlier in the course of disease. In early disease it is anticipated that aldosterone concentrations in some cats with PHA will be within the upper end of reference ranges.

Plasma Renin Activity (PRA)

Since increased aldosterone concentrations are not 100% specific for a diagnosis of aldosteronoma, diseases that cause secondary hyperaldosteronism must be ruled out. Hypertensive cats can have elevated aldosterone concentrations.[29] It is difficult to distinguish PHA from CKD, and they often coexist. CKD can cause hyperaldosteronism and vice versa. Ideally, PRA and aldosterone concentrations would be assessed on one sample. In cats with PHA, PRA has been below or within the reference range because the hyperaldosteronism and hypertension exert negative feedback to decrease PRA. In secondary hyperaldosteronism, such as CKD, PRA is increased. Unfortunately, a feline PRA assay is not currently commercially available in the United States; in addition, they require a large volume of plasma, and separated plasma must be instantly frozen.

Other Endocrine Tests

Other confirmatory tests for PHA, besides PRA, have been investigated. Measurement of a urinary aldosterone to creatinine ratio (UACR) theoretically provides a reflection of aldosterone concentrations over time, whereas blood provides the concentration at a single moment in time. However, in 9 cats with PHA, only 3 had increased UACR.[19] A test requiring administration of fludrocortisone, a synthetic corticosteroid with mineralocorticoid activity, has also been investigated, as oral mineralocorticoid administration (0.05 mg/kg PO q 12 h × 96 h) significantly suppresses aldosterone secretion (median 78% from baseline) in healthy cats.[19,30] One cat with confirmed metastatic aldosteronoma had an increased UACR following fludrocortisone administration.[30] The diagnosis of PHA in hypertensive cats, with or without hypokalemia, can be excluded if the UACR on day 4 suppresses >50%, from baseline.[19]

Thus, fludrocortisone suppression has merit as a diagnostic test for feline PHA. However, urine is not the route of excretion of major aldosterone metabolites in cats and urinary aldosterone concentration may not accurately reflect blood concentrations.[31] Indeed, in one study, basal plasma aldosterone concentrations more clearly separated cats with and without PHA than did the UACR.[19] Additionally, urine collection from cats in a hospital setting typically requires cystocentesis, which can be difficult with insufficient bladder size or a fractious cat. Urine collection at home can be cumbersome or impossible and twice-daily oral administration of fludrocortisone for 4 days can be challenging. Further, the fludrocortisone can suppress serum K

concentrations below reference ranges and cause muscle weakness.[19] In healthy cats, administration of only 3 doses of fludrocortisone (0.05 mg/kg PO q 12 h) significantly suppressed serum aldosterone concentration, but further study in cats with PHA is needed to determine test utility.[32] Due to the glucocorticoid activity of fludrocortisone, as few as 3 doses significantly suppress cortisol concentrations; thus, signs of glucocorticoid deficiency could occur after a suppression test is complete.[32]

In conclusion, suspicion of aldosteronoma arises with identification of hypokalemia and hypertension (Figure 308-2). Elevated plasma aldosterone concentration and identification of a discrete tumor within an adrenal gland are required for diagnosis. Histopathologic confirmation of tumor origin, resolution of clinical signs, and normalization of aldosterone concentrations postoperatively further confirm the diagnosis.

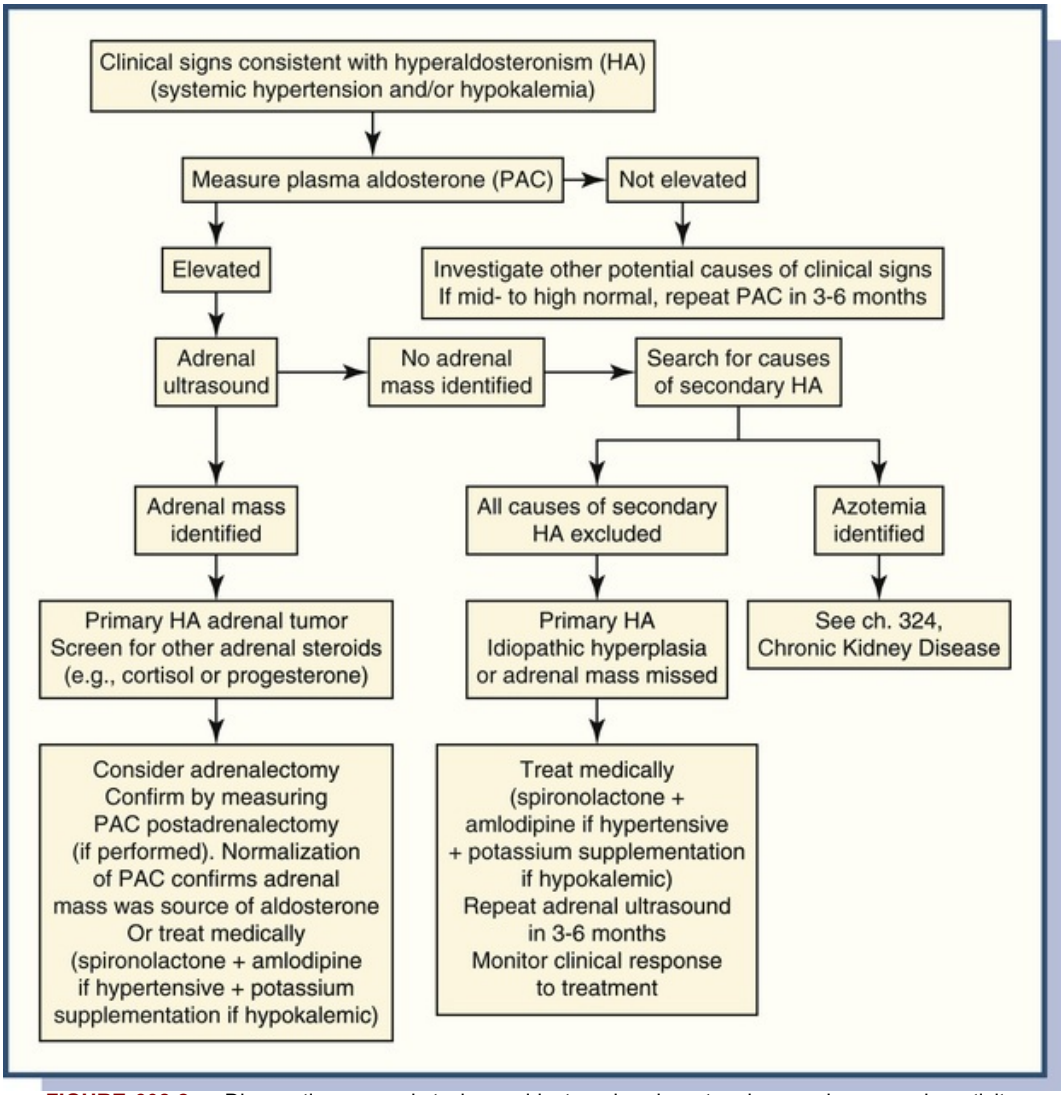

FIGURE 308-2 Diagnostic approach to hyperaldosteronism in cats when a plasma renin activity (PRA) assay is not available. (Reprinted with adaptation from Refsal KR, Harvey AM: Primary hyperaldosteronism. In August JR, editor: *Consultations in feline internal medicine,* vol 6, St Louis, 2010, Saunders, Figure 24-9, *B*, p 262. With permission.)

Treatment and Prognosis

Adrenalectomy via celiotomy or laparoscopy is the treatment of choice for feline aldosteronoma.[27,33] Unilateral adrenalectomy is potentially curative; however, it is a high risk, challenging procedure and should be undertaken only by experienced surgeons in a hospital with a well-equipped intensive care unit (ICU) and 24-hour observation and care. Preoperatively, hypokalemia should be corrected with oral and/or parenteral

K. Assessment for tumor thrombi and metastases is imperative. The presence of tumor thrombi may increase the possibility of complications. Metastases may decrease chances of survival, and surgery will not be curative. In addition, the possibility of the tumor secreting a hormone other than aldosterone should be considered and tested for as indicated. If a glucocorticoid or progestogen is secreted, adrenalectomy can cause transient cortisol deficiency (see ch. 307).

In theory, autonomous aldosterone secretion from an AT should suppress normal zona glomerulosa cells within the contralateral adrenal gland and hypoaldosteronism could occur postoperatively. Serum electrolyte concentrations must be monitored frequently and IV fluid therapy adjusted accordingly to maintain serum K and Na concentrations within or near reference intervals. Administration of a synthetic mineralocorticoid post-surgically to manage hypoaldosteronism is not usually necessary.

In earlier reports, perioperative complications occurred in 8 of 17 cases, including lethargy, anorexia, vomiting, dysphagia, hyperthermia, upper respiratory infection, intra- or post- operative intra-abdominal hemorrhage, acute kidney injury, sepsis and suspected thromboembolism. In 6 of these 8 cats, the outcome was fatal.[14,27] In a more recent report, only 2 of 10 cats with aldosteronoma had a fatal outcome.[27] The mean perioperative hospital stay for all cats was 5 days. Two cats were euthanized 2 and 10 days postoperatively due to surgical complications (1 also had a pancreatic mass). Hemorrhage was not predicted by tumor type, location, size, or vascular invasion. Of the 8 cats discharged from the hospital, blood pressure and serum K concentrations normalized and long-term therapy was unnecessary. Long anesthesia time was significantly associated with decreased survival. Median survival was 1,297 days (range 2-1,582 days) and there was no significant difference in length of survival comparing cats with adenoma (median, 1,329 days) and those with adenocarcinoma (248 days; P = 0.2), but the number of cats was small. Blindness due to retinal detachment may resolve with time (see ch. 11). No deaths after discharge were known to be due to the AT. However, 2 cats were euthanized due to CKD, which would have been exacerbated by the PHA.[27]

Cats that do not undergo surgery can be treated medically to control the hypokalemia and/or systemic hypertension. Potassium supplementation (2-6 mEq PO q 12 h) has been effective. Amlodipine besylate (0.625-1.25 mg/cat PO q 24 h) is the treatment of choice to lower blood pressure (see ch. 158). Up to 2.5 mg can be used if the blood pressure is not controlled; however, hypertension may become refractory to the medication. Spironolactone, a competitive aldosterone receptor antagonist, can be used (2-4 mg/kg PO q 24 h) to both decrease blood pressure and increase K. Doses in excess of 4 mg/kg may cause anorexia, vomiting and diarrhea. Medical management has yielded survival times of 7 months to 984 days in 4 cats, but another survived only 50 days due to owner non-compliance.[17]

Canine Aldosterone-Secreting Tumors

Background and Clinical Signs

In dogs, PHA is typically caused by a unilateral solitary adenoma or carcinoma. Rarely, bilateral idiopathic adrenocortical hyperplasia is diagnosed.[34-37] Primary hyperaldosteronism is a disease of middle-aged to older dogs and common owner concerns include lethargy, anorexia, weakness and PU/PD. Also, like cats with an aldosteronoma, tumors secreting both mineralocorticoids and glucocorticoids occur uncommonly,[35-37] so clinical signs and laboratory changes consistent with glucocorticoid excess may be present.

Diagnosis

The presence of hypokalemia and a serum Na concentration at the upper end of or mildly above the reference range together with finding an AT on US should raise suspicion for PHA. Some aldosterone-secreting tumors are quite small and not seen on US. Alternatively, idiopathic adrenocortical hyperplasia may be present. Other findings consistent with a diagnosis of PHA include systemic hypertension and the presence of a metabolic alkalosis. Confirmation of an aldosteronoma requires documentation of an increased baseline plasma aldosterone concentration and suppressed PRA in conjunction with exclusion of other causes of hypokalemia. In dogs with aldosteronoma, aldosterone concentrations have been >3000 pmol/L. Unfortunately, a canine PRA assay is not currently available. Urine tests, such as the UACR, may have limited to no diagnostic value in dogs. The major aldosterone forms that are present in human urine are free aldosterone, aldosterone-18-glucuronide and tetrahydroaldosterone.[38] Kits available for aldosterone measurement detect free aldosterone and aldosterone-18-glucuronide (after acid hydrolysis of the glucuronide). Canine urine contains less aldosterone-18-glucuronide than does human urine and, unlike cats or people, contains no detectable free aldosterone.[31]

Treatment

Unilateral adrenalectomy is the treatment of choice for a solitary adrenal mass, especially if no evidence of distant metastasis, vascular invasion, or infiltration into the kidney or body wall is found. Oral K, mineralocorticoid receptor blockers (spironolactone), and anti-hypertensive drugs (amlodipine) should be administered until surgery can be performed. Medical therapy is indicated for the long-term management of PHA when adrenalectomy is not performed and for dogs with suspected idiopathic adrenocortical hyperplasia.

Serum electrolyte concentrations must be monitored frequently postoperatively and IV fluid therapy adjusted to maintain serum K and Na concentrations within or near reference intervals. If hypokalemia persists, oral K supplementation can be initiated. Serum ionized magnesium concentrations should be monitored and hypomagnesemia treated, especially if hypokalemia is refractory to IV fluid therapy (see ch. 68). Mineralocorticoids (oral fludrocortisone acetate or injectable desoxycorticosterone pivalate [DOCP]) should be administered if hyperkalemia and hyponatremia persist for longer than 72 hours, but this is rarely needed. Only one injection of DOCP is usually needed and if daily fludrocortisone acetate is employed, it can usually be tapered and discontinued within a week. Systemic hypertension usually improves or resolves within 48 to 72 hours of adrenalectomy. Anti-hypertensive medication should be initiated if hypertension persists. Attempts to wean off anti-hypertensive medications should be initiated during the ensuing month. Glucocorticoid replacement therapy is usually not indicated postoperatively, unless the tumor was secreting a glucocorticoid. An ACTH stimulation test can be performed 6 to 8 hours after adrenalectomy to assess the function of the remaining adrenal gland (see ch. 306).

Prognosis

Surgical removal of an adenoma carries an excellent prognosis. The prognosis is guarded for dogs with a carcinoma. If metastatic sites exist, hyperaldosteronism, hypokalemia and the associated clinical signs usually persist or recur. However, these tumors can be slow-growing and recurrence may not occur for more than a year. Management of recurrence with metastasectomy can be successful.[37] The prognosis for idiopathic adrenocortical hyperplasia is unknown and depends on the effectiveness of medical therapy. Bilateral adrenalectomy in theory, may offer a cure, but glucocorticoids and mineralocorticoids would be needed for life.

Non-Aldosterone, Mineralocorticoid-Secreting Tumors

Tumors secreting mineralocorticoids other than aldosterone, e.g., desoxycorticosterone, are rare.[39-41] Clinical findings are the same as with PHA but aldosterone concentrations are low. As no desoxycorticosterone assay is commercially available, diagnosis would be presumptive based on the constellation of diagnostic test results.

Sex Hormone–Secreting Adrenal Tumors

Overview

Adrenocortical tumors have the potential for synthesizing and secreting a variety of steroids other than cortisol and aldosterone. Excess secretion of sex hormones by tumors may be associated with aberrant biosynthetic pathways and/or enzyme deficiencies. Progestins may bind glucocorticoid receptors or displace cortisol from its binding protein, increasing serum free cortisol concentrations.[42,43] In dogs, progestins suppress endogenous ACTH secretion and cause adrenal atrophy, actions consistent with glucocorticoid activity.[44]

Feline Sex Hormone–Secreting Adrenocortical Tumors

Clinical Information

A small number of cats with sex hormone–secreting AT has been described.[24,25,45-48] Six cats ranged in age from 7-15 years; 2 were spayed females and 4 were neutered males. Breeds included domestic longhair and shorthair and Himalayan. A 14-year-old, female spayed domestic shorthair cat with bilateral adrenal enlargement and excessive estradiol and testosterone production has been reported.[49] Excess production of a

progestin (e.g., progesterone or 17-hydroxyprogesterone) may cause signs of cortisol excess, such as a poor haircoat, dermal atrophy and skin fragility. Three of 4 cats with a progesterone-secreting tumor had diabetes mellitus, described as poorly regulated in 2.[24,25,45,46] Excess androgen production can cause a change in the urine odor, urine spraying behavior, aggression and development of penile spines.[47,49] Hyperestrogenemia may cause cyclic estrous behavior and vulvar enlargement.[48,49] Tumor type was known in 5 cats: 1 adenoma, 4 carcinoma.[24,25,45-48]

Diagnosis

Suspicion of a sex hormone–secreting tumor begins with clinical signs. No result of a routine test, e.g., CBC or serum biochemistry profile, will aid in diagnosis. Finding an AT on US should increase suspicion. As with aldosteronomas, sex hormone–secreting tumors are typically seen with US. In one cat, however, the tumor had replaced the normal tissue and only mild enlargement and a round shape were noted on US.[48] Signs of malignancy should be sought and thoracic radiographs obtained.

Definitive diagnosis of tumor functionality and type of hormone secreted has been made, for the most part, using ACTH stimulation testing (125 mcg cosyntropin IV per cat) with blood drawn before and 1 hour after injection.[24,25,45-48] Cortisol and sex hormones are measured pre- and post-ACTH. If a progestin is secreted, cortisol concentrations will be at the lower end or below the reference range. Thus, if a cat appears to have hypercortisolism but does not have the expected abnormalities on tests for hyperadrenocorticism, consideration of a sex hormone disorder is reasonable. Estradiol does not increase with ACTH injection. In a cat with an estrogen-secreting tumor, the basal estradiol concentration was increased but the post-ACTH value was not.[48]

Treatment and Prognosis

Surgical or laparoscopic removal of an AT is the treatment of choice. Prognosis may depend on presence of metastasis, successful tumor removal, and patient stability preoperatively. If cortisol secretion has been suppressed by the tumor, glucocorticoid replacement must be given postoperatively. Hyperprogesteronism can cause issues such as thin skin that make a cat a poor surgical candidate.[46] Four cats with sex hormone–secreting AT have undergone adrenalectomy. One cat died due to unknown causes 3 days postoperatively.[24] One cat was euthanized 10 months postoperatively with CKD, and 2 cats were lost to follow-up at 8 weeks and 12 months post-surgery.[45,47,48] Aminoglutethimide is the only medical treatment that has been tried to control sex hormone secretion from an AT, and response was transient.[46] Trilostane was used to control secretion of sex hormones in a cat with bilateral adrenal hyperplasia. After approximately 6 months, clinical signs returned, and no further assessment or treatment were sought.[49]

Canine Sex Hormone–Secreting Adrenocortical Tumors

Clinical Information

A small number of dogs with sex hormone–secreting AT has been reported but none with clinical signs of hyperestrogenemia or hyperandrogenemia.[50-53] Two dogs with AT, an 11-year-old spayed female Labrador Retriever and a 9-year-old castrated male miniature Poodle, had clinical signs of hyperadrenocorticism despite markedly suppressed ACTH-stimulated serum cortisol concentrations.[52] Thus, the clinical signs were likely due to hyperprogesteronemia. Both dogs had PU/PD and polyphagia. One also had changes in coat color, weight gain, increased panting and abdominal enlargement. Signalment and clinical signs in other dogs with sex hormone–secreting tumors were not delineated but presenting complaints were stated to be consistent with hypercortisolism.[50,51,53]

Diagnosis

Suspicion for a sex hormone–secreting AT will arise with clinical signs. The primary indication for sex hormone measurement is the finding of cortisol concentrations below reference intervals in a dog tested for hyperadrenocorticism using ACTH stimulation or low-dose dexamethasone suppression testing (see ch. 306).[52,53] If exogenous glucocorticoids in any form or medications that alter cortisol synthesis (e.g., ketoconazole) are ruled out, a sex hormone–secreting AT may be present. Ultrasound finding of an AT further supports the diagnosis, but lack of a detected adrenal mass does not rule out the diagnosis.

To document sex hormone elevations, an ACTH stimulation test should be performed (see ch. 306). Sex

hormones are measured in samples drawn before and 1 hour after administration of ACTH. However, sex hormone concentrations should be interpreted cautiously. For estradiol, a wide range of variability exists within and between dogs; random, basal estradiol concentrations in individual dogs often exceed the reference range.[54] Many dogs without hyperadrenocorticism can have sex hormone concentrations as much as 40-50% above reference intervals.[55-57] In 6 dogs with pheochromocytoma or non-functional AT, androstenedione, progesterone, 17-hydroxyprogesterone, testosterone and/or estradiol concentrations were increased.[58]

Treatment and Prognosis

Adrenalectomy, in theory, is the treatment of choice. However, detailed information is available for only two dogs with sex hormone–secreting AT. One dog underwent adrenalectomy and did well for at least 13 months after surgery. A second was treated medically with mitotane for approximately 20 days at a dosage of 47 mg/kg daily with no response, and the owners declined further therapy. Given the resistance of AT in general to mitotane, lack of response is not surprising given the dose and short duration of treatment.

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CHAPTER 309

Hypoadrenocorticism

Rebecka S. Hess

Client Information Sheet: Hypoadrenocorticism (Addison's Disease)

Introduction

Dr. Thomas Addison first described disease of the "supra-renal capsule" (adrenal cortex) in an 1855 case series describing 11 people with what is now known as hypoadrenocorticism (HA) or Addison's disease.[1] The adrenal cortex is divided into three layers: the outermost zona glomerulosa, the widest middle zona fasciculata, and the innermost zona reticularis. The adrenal cortex secretes glucocorticoids and mineralocorticoids, essential for survival. Therefore, hypofunction or dysfunction of the adrenal cortex, such as that seen in HA, can be life-threatening. Glucocorticoids are secreted from all three cortical layers whereas aldosterone, the most important mineralocorticoid, is secreted from the zona glomerulosa, the only zone containing aldosterone synthase. Basic adrenal physiology is discussed in ch. 306. Hypoadrenocorticism is common in dogs and rare in cats. Therefore, the discussion that follows pertains to dogs and is followed by a brief discussion of HA in cats.

Pathophysiology

In humans, HA is a rare autoimmune disorder. Most patients have antibodies against the steroidogenic enzyme 21-hydroxylase, present in all three adrenal cortical layers.[2] These antibodies are believed to lead to destruction of the adrenal cortices.[3] Presence of 21-hydroxylase antibodies or other adrenal autoantibodies in dogs with naturally-occurring HA has not been documented in sufficient numbers to support antibodies being the cause.[4] However, lymphoplasmacytic adrenalitis and adrenocortical atrophy have been documented in some dogs with HA, in support of this being an immune-mediated disease.[5] Dogs that develop both HA and hypothyroidism support the concept of a systemic immune-mediated process.[6] Adrenal lymphocytic inflammation and formation of autoantibodies precedes atrophy of other endocrine glands (such as the thyroid gland). Finally, some of the genetic characteristics of the disease involve immune function.

The concept of a genetic component being involved in the etiology of canine HA is supported by the fact that certain breeds are known to be at increased risk. Familial HA has been reported in some breeds (Leonbergers and Pomeranians) and Great Danes have greater risk as compared with other dogs.[7-9] A study of the heritability of the disease in Bearded Collies revealed that the mode of inheritance was not autosomal dominant and that more than one major gene was involved in the pathophysiology of the disease.[10] However, in Standard Poodles and Portuguese Water Dogs, the inheritance does appear to be influenced by a single locus with a major effect, and the mode of inheritance in these breeds may be autosomal recessive.[11-13] In Portuguese Water Dogs and Springer Spaniels two immune function genes, the major histocompatibility complex coding for dog leukocyte antigens and the cytotoxic T-lymphocyte-associated protein 4, are reportedly associated with HA.[10,14] A third immune function gene, *PTPN22*, is over-expressed in Cocker Spaniels with HA.[15]

The major histocompatibility complex has been reported to have a role in the etiology of HA in the Nova Scotia Duck Tolling Retriever, Cocker Spaniel, Labrador Retriever, West Highland White Terrier, Bearded Collie, and standard Poodle.[14,16,17] However, methodologies employed in some of these studies have come under question and further studies are needed.[18] It is possible that the genetic etiology of the disease is different among breeds. Importantly, it is not yet clear whether any of these genetic differences are

responsible for formation of anti-adrenal autoantibodies and atrophy of the adrenal cortices.

Classification

Primary Hypoadrenocorticism

Primary HA is the most common form of the disease. It involves direct failure of the adrenal cortices. Classic HA involves a decrease in both glucocorticoid and mineralocorticoid secretion from the adrenal glands. *Atypical primary HA* is a term used to describe direct failure of the adrenal cortex in which cortisol secretion is absent but sodium (Na) and potassium (K) concentrations are still normal.[19] Some dogs are initially diagnosed with only a glucocorticoid deficiency based on normal Na and K concentrations but develop hyponatremia and hyperkalemia with time.[7,19,20] In these dogs, the "atypical" HA is transient. However, other dogs diagnosed as having atypical HA maintain normal Na and K concentrations for years.[19,20] Interestingly, some dogs with documented HA with normal Na and K concentrations have low aldosterone concentrations suggesting that maintenance of electrolyte concentration in these dogs is not completely dependent on aldosterone.[20] If HA in dogs is indeed an immune-mediated condition developing due to anti 21-hydroxylase antibodies, it is possible that the destruction of the zona glomerulosa, the aldosterone producing zone, lags behind destruction of the other two zones because its concentrations of 21-hydroxylase are lowest of the three zones.

Primary HA, whether typical or atypical, develops as a result of adrenal cortex atrophy (Figure 309-1). Rarely, HA develops secondary to an infiltrative process which destroys the adrenal cortex. Neoplasia is the most common cause of this rare condition, while tuberculosis, fungal disease, other granulomatous or infectious diseases, and infarcts are possible.[21-23] A rare case of HA in which aldosterone depletion preceded glucocorticoid depletion has been reported.[24] Primary transient or permanent iatrogenic HA can be caused by the drugs used to treat hyperadrenocorticism (Lysodren or trilostane; see ch. 306). Isolated hypoaldosteronism (without glucocorticoid deficiency) has been reported but is extremely rare.

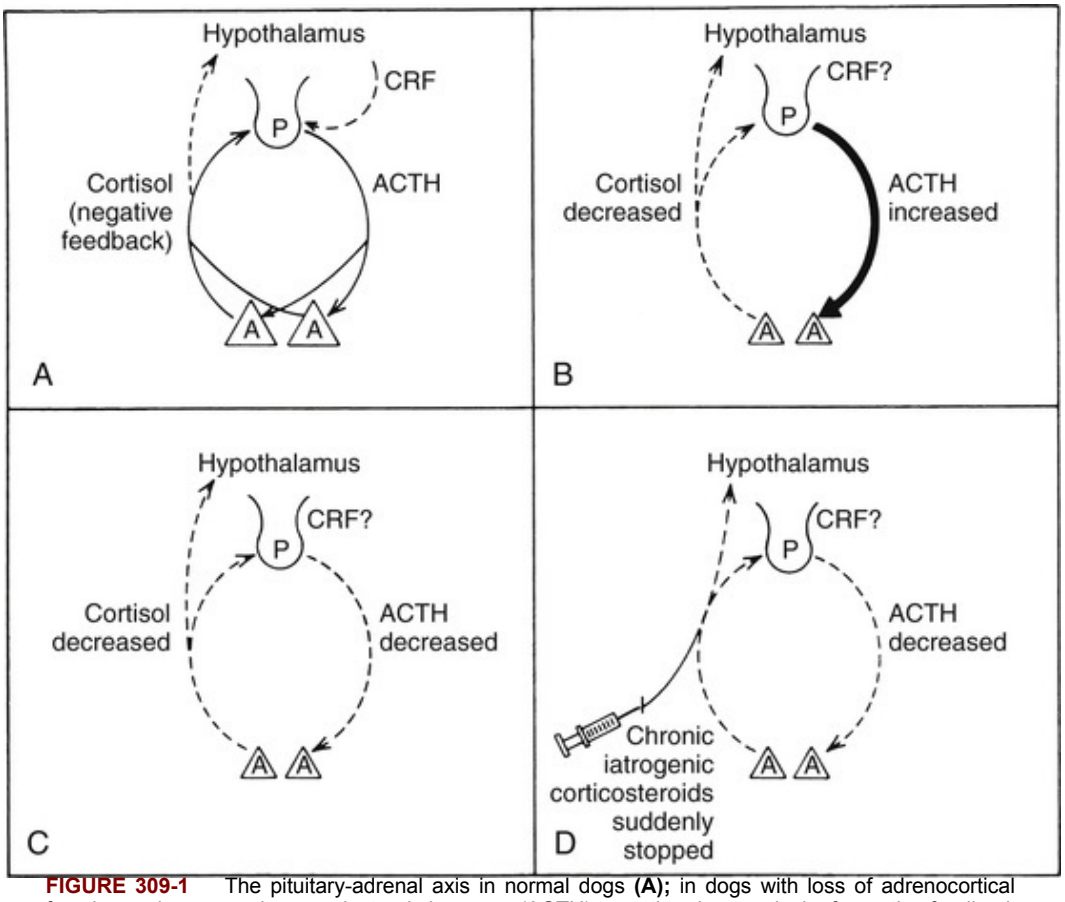

FIGURE 309-1 The pituitary-adrenal axis in normal dogs **(A);** in dogs with loss of adrenocortical function and excess adrenocorticotropic hormone (ACTH) secretion due to a lack of negative feedback

(the most common form of hypoadrenocorticism) **(B);** in dogs with failure to secrete ACTH and secondary atrophy of the adrenal cortex, specifically the zona fasciculata and zona reticularis **(C);** and in dogs that are chronically overtreated with exogenous glucocorticoids, causing insufficiency in pituitary ACTH secretion and secondary atrophy of the adrenal cortex **(D).** *A,* Adrenal; *CRF,* corticotropin-releasing factor (hormone); *P,* pituitary. (From Feldman EC, Nelson RW, Reusch CE, Scott-Moncrieff JCR: *Canine and feline endocrinology and reproduction,* ed 4, St Louis, 2015, Saunders.)

Secondary Hypoadrenocorticism

Secondary HA is rare. It is due to failure within the hypothalamus or pituitary due to neoplasia, inflammation, infection, infarct, or trauma, causing impaired adrenocorticotropic hormone (ACTH) secretion from the pituitary or decreased corticotropin-releasing hormone (CRH) secretion from the hypothalamus.[25-28] As with most diseases of the central nervous system (CNS), neurologic signs and other hormonal deficits would be expected, but enigmatic idiopathic secondary HA has been reported in dogs with no neurologic signs and long-term survival with glucocorticoid therapy alone. Since aldosterone secretion is regulated largely by the renin-angiotensin-aldosterone system (RAAS), and not by ACTH or CRH, this condition involves only glucocorticoid deficiency, with Na and K concentrations normal. Unlike atypical primary HA in which Na and K are also normal, in secondary HA, ACTH concentrations are low (see Figure 309-1). Iatrogenic secondary HA can develop with long-term hypophysectomy or steroid administration (see Figure 309-1).[29] Exogenous steroids suppress ACTH secretion, and time is required for those cells to regain function after steroid administration is stopped. This is the reason that glucocorticoid administration should always be decreased gradually, allowing ACTH secreting cells and then adrenocortical cells to return to normal function.

Signalment, History, Signs, Physical Examination

Age

HA is a disease of young to middle aged dogs, with an approximate median age at diagnosis of 3-4 years. However, the age range at diagnosis is wide: 2 months to 12 years (Table 309-1). Females may be at increased risk for the disease.[7,30] Hypoadrenocorticism can develop in any breed but a specific genetic disposition in certain breeds was discussed. Golden Retrievers, Yorkshire Terriers, Pit Bulls, Chihuahuas, and Lhasa Apsos have decreased risk.[31]

TABLE 309-1

Comparison of Clinical Characteristics and Complete Blood Count Findings in Sick Dogs with and without Hypoadrenocorticism

VARIABLE	53 DOGS WITH HYPOADRENOCORTICISM	110 DOGS IN WHICH HYPOADRENOCORTICISM WAS SUSPECTED AND EXCLUDED	P
Age (years)	4.8 (0.6-11.8)	6.8 (0.4-16.0)	0.07
Vomiting with or without diarrhea	43 (81%)	88 (80%)	0.87
Hematemesis or melena with or without hematochezia	6 (11%)	28 (26%)	0.04
Depression, weakness, or lethargy	51 (96%)	85 (77%)	0.002
Abdominal pain	14 (26%)	45 (41%)	0.07
Systolic blood pressure (mm Hg)	90 (40-150)	140 (50-210)	<0.001
Length of hospitalization (hours)	49 (16-240)	66 (3-312)	0.02
Survived to hospital discharge	52 (98%)	100 (91%)	0.11
Hematocrit (RR: 40.3-60.3%)	46.1 (20.1-68.8)	42.2 (14.1-61.5)	0.006

WBC count (RR: 5.3-19.8 cells × 103/mcL)	11.7 (5.6-31.2)	12.6 (0.9-64.2)	0.87
Neutrophils (RR: 3.1-14.6 cells × 103/mcL)	7.75 (2.77-25.90)	9.87 (0.68-53.93)	0.007
Lymphocytes (RR: 0.9-5.5 cells × 103/mcL)	2.38 (0.80-8.20)	1.07 (0-6.00)	<0.001
Eosinophils (RR: 0-1.6 cells × 103/mcL)	0.57 (0-4.00)	0.12 (0-7.00)	<0.001
Neutrophil : lymphocyte ratio	3.00 (0.76-14.59)	9.51 (1.23-95.15)	<0.001

Data are expressed as median (range) or number (frequency). Hypoadrenocorticism was diagnosed if serum cortisol concentration was ≤1.0 mcg/dL 1 hour after adrenocorticotropic hormone (ACTH) administration. The diagnosis of hypoadrenocorticism was excluded if basal serum cortisol concentration was >2.0 mcg/dL, or if serum cortisol concentration after exogenous ACTH administration was >5.0 mcg/dL.[30]

History and Clinical Signs

History in General

Dogs with HA may exhibit one or more of the following clinical signs with various degrees of severity: anorexia, weight loss, vomiting, diarrhea, lethargy, weakness, polyuria (PU), polydipsia (PD), shaking, and in extreme cases, collapse (see Table 309-1). Most clinical signs are attributed to lack of cortisol. Clinical signs can be mild, vague and wax and wane over a period of time until an astute owner seeks veterinary care or the dog undergoes rapid deterioration requiring emergency intervention. Sometimes stressful circumstances, such as surgery or boarding at a kennel, can push a borderline compensated "occult HA" dog with little adrenocortical reserve and limited capacity to devolve into a crisis.

Role of Glucocorticoids and Mineralocorticoids

Glucocorticoids are important for maintaining the mucosal gastric barrier, which protects the gastrointestinal (GI) mucosa from its acidic contents. Glucocorticoids also help maintain blood pressure, body temperature, and glucose concentrations.[32] If the GI mucosal barrier is ineffective due to HA, anorexia, vomiting, diarrhea, and ensuing weight loss are common, but bloody vomiting and diarrhea are not (see Table 309-1). In a study of dogs admitted for intensive care in need of IV fluid resuscitation, hematemesis, melena, and hematochezia were significantly less common in dogs with HA when compared with non-HA dogs. In that same study, weakness and lethargy were significantly more common in HA dogs.[30] Lethargy, weakness, shaking, and collapse can develop due to hypoglycemia if glucose is inadequately synthesized due to lack of glucocorticoids. Glucocorticoids mediate catabolism of glycogen and synthesis of glucose by gluconeogenesis in fasting or stressful conditions. PU is attributed to lack of mineralocorticoids. Aldosterone deficiency causes Na loss via the urine. That urine Na acts as an osmotic agent, leading to osmotic diuresis. PD is compensatory for the PU in an attempt to maintain hydration.

Physical Examination

Physical examination abnormalities vary from mild to severe and can include: weak pulses, dehydration, hypotension, bradycardia, muscle weakness, thin body condition, abdominal pain, and in extreme cases, hypovolemic or hypotensive shock or seizures (see ch. 2). Dehydration in dogs with HA is due to urine Na losses, the ensuing osmotic diuresis, and then illness, which interferes with water intake. Among dogs requiring IV fluid resuscitation, dogs with HA have lower systolic blood pressure compared to dogs in which a diagnosis of HA was excluded. Median systolic blood pressure (see ch. 99) in 53 dogs with HA was 90 mm Hg (range 40-150 mm Hg; see Table 309-1). Hypotension is attributed to the lack of glucocorticoids and their important role in maintaining normal blood pressure (see ch. 159).[33] Bradycardia is attributed to hyperK. When K concentration in cardiac extracellular fluid is abnormally high, the concentration gradient between the intracellular and extracellular compartments decreases and K is retained in the cells. The outward K current needed for phase 3 final rapid repolarization of the cardiac action potential diminishes, leading to bradycardia (see ch. 248). Abdominal pain is thought to develop due to lack of the gastroprotective effects of glucocorticoids.

Diagnosis

Overview

Suspicion of HA begins with the history, clinical signs, and physical examination findings. Careful interpretation of complete blood count (CBC) and chemistry screen should be helpful in deciding when to pursue adrenal axis testing. The diagnosis of HA can be confirmed with results of an ACTH stimulation test (ACTHst). Adrenal axis testing requires only 1 to 2 hours for completion. A urinalysis and urine culture should be considered when evaluating any dog with PU/PD. Fecal analysis for parasites, fecal bacterial culture for *Salmonella* and *Campylobacter,* and abdominal radiographs may be warranted for evaluation of anorexia, vomiting, or diarrhea. If acute pancreatitis is suspected, abdominal ultrasound (US) and measurement of pancreatic lipase concentration might be warranted. When arrhythmias are noted, an electrocardiogram and chest radiographs can be of value.

Complete Blood Count

A study of 53 dogs with HA who were compared with 110 sick control dogs highlighted some useful differences between CBC findings in dogs with and without HA.[30] While median blood cell counts in dogs with HA were within reference limits, dogs with HA had lower neutrophil counts and higher lymphocyte and eosinophil counts than did ill dogs without HA (see Table 309-1). An absolute lymphocyte count >2000 cells/mcL was about 58% sensitive and 85% specific as a screening tool for HA.[30]

Routine Serum Biochemistry Profile

Overview

The chemistry screen can reveal no or many abnormalities, which can be mild or severe. Most of the abnormalities noted on initial laboratory tests in dogs with HA resolve within hours to days of starting treatment. Severe biochemical abnormalities are rarely irreversible. This is important when discussing possible outcomes with an owner before intensive care or a definitive diagnosis has been established. Unlike other diseases, severe azotemia, increased liver enzyme activities, and other altered parameters are almost always completely reversible with treatment.

Electrolyte, Kidney and Acid-Base Values

Numerous electrolyte abnormalities including hyponatremia, hyperkalemia, hypochloremia, hypercalcemia (hyperCa), and mild acidosis are common in dogs with HA. Hyponatremia and hyperkalemia have been documented in >80% of dogs with HA due to aldosterone deficiency.[7,31] Using the Na : K ratio allows the clinician to use both measurements when deciding whether to pursue testing for HA. When cutoffs of >27 or 28 are used as the reference value for Na : K, about 95% of dogs are identified correctly as either having or not having HA.[7] When the Na : K ratio is <24, it is quite likely that an ACTHst result will confirm HA.[7] Use of both the lymphocyte count and the Na : K ratio as screening tools maximizes the likelihood of making the correct decision in regard to performing an ACTHst. Lymphocyte counts are affected by glucocorticoids and the Na : K ratio is influenced by mineralocorticoids.

Pre-renal azotemia is common in dogs with HA secondary to hypovolemia and dehydration. Severe dehydration can lead to acute kidney injury (AKI), but in most HA dogs, renal parameters quickly and completely return to reference values with therapy. There is no evidence suggesting that any permanent kidney damage follows a life-threatening hypovolemic crisis due to HA. Since aldosterone facilitates urine hydrogen ion excretion, mineralocorticoid deficiency leads to acidemia in about 60% of HA dogs.[7,34] Hypochloremia is observed in 40-60% of dogs with HA, probably because Na and chloride (Cl) are co-transported from blood to urine.[7,31,35] Hypercalcemia has been reported as an increase in total Ca (tCa) and less commonly an increase in ionized Ca (iCa). The pathophysiology of hypercalcemia in dogs with HA is incompletely understood, but does not appear related to altered parathyroid hormone, parathyroid hormone–related protein, or serum 1,25 dihydroxyvitamin D concentrations.[36,37] Glucocorticoids facilitate calciuresis and their deficiency can lead to Ca retention and hypercalcemia. It is also possible that acidemia contributes to an increase in iCa concentration as an excess of positively charged hydrogen ions compete for albumin binding and displace positively charged Ca ions.

Glucose, Cholesterol, Albumin, Liver Enzymes, and Urinalysis

Hypoglycemia develops in <20% of dogs with HA and tends to be mild when present. Quite uncommonly, hypoglycemia can be life-threatening and cause seizures.[38] Hypoglycemia is likely the result of cortisol deficiency decreasing both glycogen breakdown and gluconeogenesis. Increased insulin secretion does not appear to be a cause of hypoglycemia.[39] Leakage of cytosolic enzymes is attributed to poor perfusion and ischemic damage to hepatocytes. Hypoalbuminemia and hypocholesterolemia are not common, but are likely due to acute GI tract ischemia rather than liver dysfunction.[7,31] Urinalysis commonly reveals isosthenuria due to Na loss and resultant PU.

Other Tests

The extent and focus of other testing depends on individual clinical signs. Dogs with mild waxing and waning lethargy, inappetence, and weight loss will be assessed differently than dogs critically ill with acute severe vomiting and dehydration. Additional testing is performed to identify a variety of possible conditions in either scenario. In dogs with HA, urine culture, fecal parasite exam, and fecal cultures are typically negative. Abdominal radiographs are usually normal, although some dogs with HA have been described as having a small liver. In dogs with bradycardia, an electrocardiogram might reveal complete lack of P waves, wide QRS and tall T waves, and possibly some degree of heart block, consistent with hyperK (Figure 309-2). Thoracic radiographs may reveal microcardia due to severe hypovolemia (Figure 309-3). Megaesophagus, reported anecdotally in humans with HA, has not been established as occurring secondary to HA in dogs. If acute pancreatitis is suspected, abdominal US and pancreatic lipase quantification might be warranted. US should not be used to assess adrenal function, but thickness of adrenal glands in dogs with HA is usually <3 mm.[40]

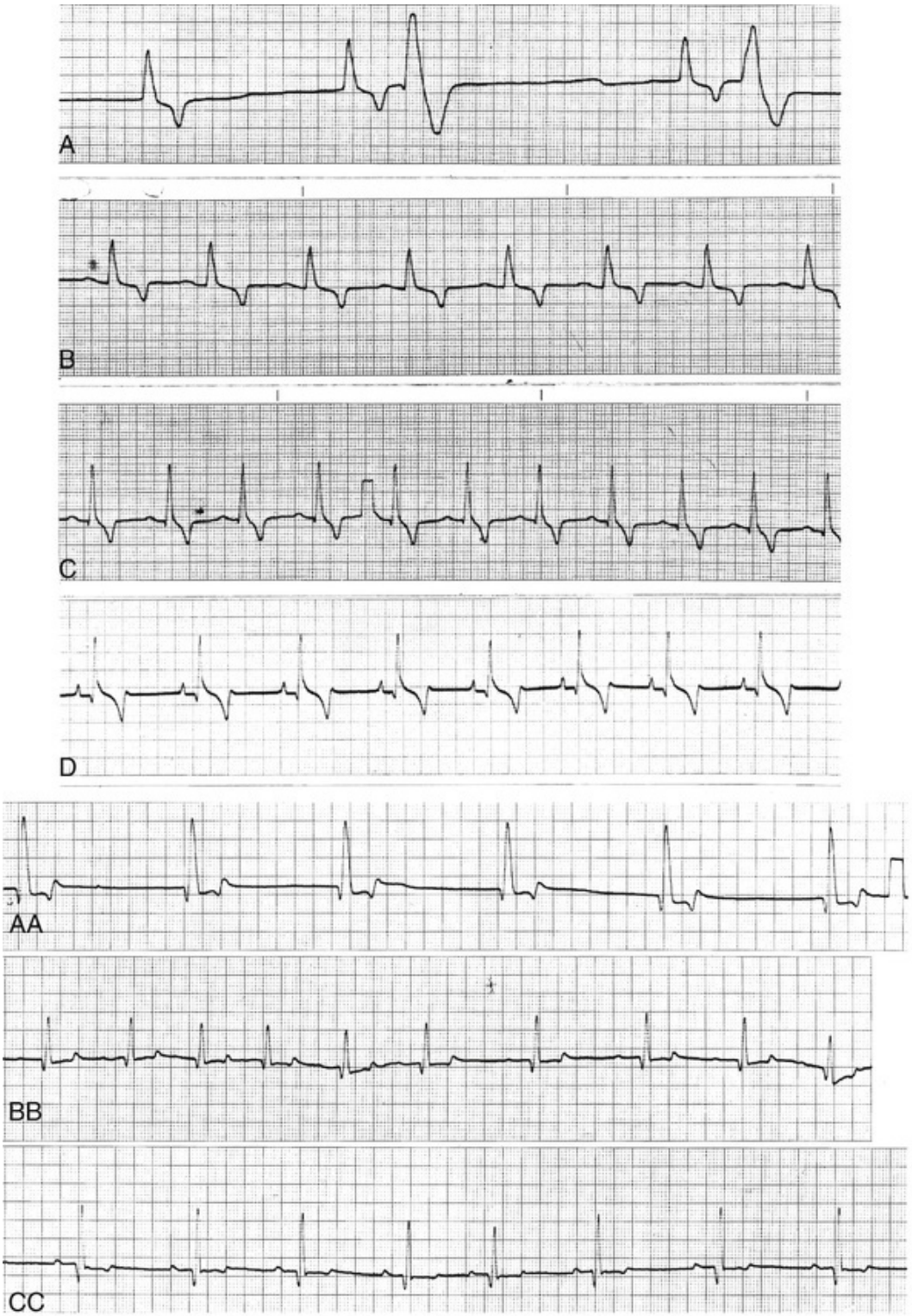

FIGURE 309-2 Serial electrocardiogram (ECG) segments obtained from two dogs with hypoadrenocorticism and hyperkalemia. **A** and **AA** both illustrate the effect of severe hyperkalemia, with the dog in **A** having a serum potassium concentration of 8.6 mEq/L and the dog in **AA** a measurement of 9.4 mEq/L. Note the lack of visible P waves, the short and wide QRS complexes, and the T waves, which are not of excessive amplitude. The ECG in **A** also reveals two instances of a bizarre-looking QRS complex following a more normal-appearing QRS complex at a shorter R-R interval (i.e., 2 wider, more bizarre-looking premature beats). These represent premature ventricular complexes that could be the result of acidemia, myocardial hypoxia, or other metabolic imbalances. **B** and **BB** are ECGs from the same dogs as in **A** and **AA,** respectively. They were each obtained approximately 1 hour after institution of intravenous normal saline as the only treatment. The serum potassium concentrations had decreased to 7.6 mEq/L and 7.9 mEq/L, respectively. Two important factors to note: (1) improvement is seen in each case with the return of P waves, a more rapid heart

rate, and disappearance of ventricular escape beats; and (2) abnormalities are still present, most obviously the prolonged P-R intervals (first-degree heart block), which alone suggest hyperkalemia, especially when associated with a widened QRS complex and a short Q-T interval. There are numerous other causes of P-R interval prolongation. In **C** and **CC,** the serum potassium concentrations are considerably lower, 6.2 mEq/L and 5.9 mEq/L, respectively. The P-R interval and P, QRS, and T waves are of shorter duration, and the R waves are taller. **D,** ECG from the dog in **A;** the serum potassium concentration is 5.6 mEq/L and a more spiked T wave is seen. (From Feldman EC, Nelson RW, Reusch CE, et al: *Canine and feline endocrinology and reproduction,* ed 4, St Louis, 2015, Saunders.)

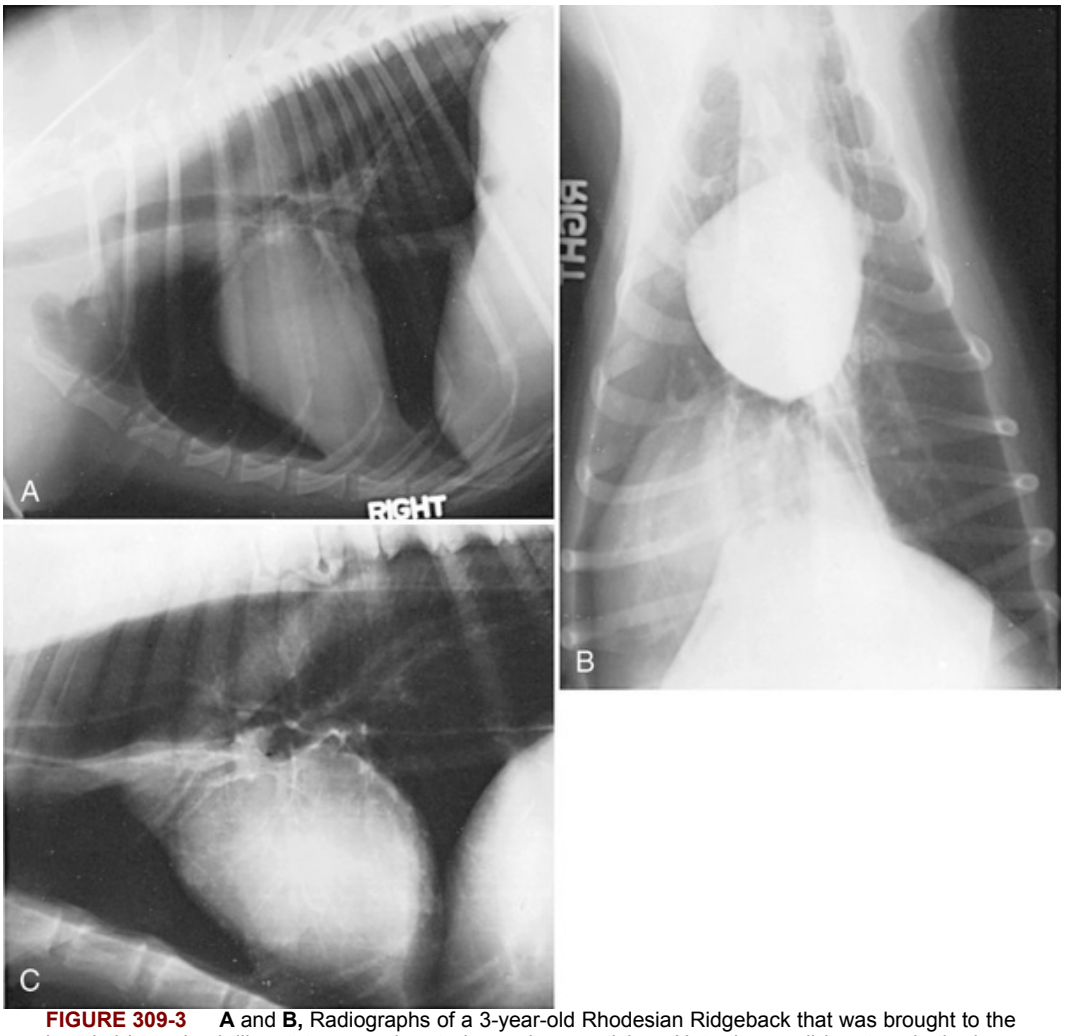

FIGURE 309-3 **A** and **B,** Radiographs of a 3-year-old Rhodesian Ridgeback that was brought to the hospital in a shock-like state secondary to hypoadrenocorticism. Note the small heart on both views and the small pulmonary vasculature due to poor cardiac output. **C,** Lateral thoracic view radiograph of a 5-year-old hypoadrenal dog with microcardia, a flattened caudal vena cava, and a dilated, air-filled esophagus. The esophageal dilation, which may be associated with hypoadrenocorticism resolved with appropriate hormonal therapy for the primary disease. (From Feldman EC, Nelson RW, Reusch CE, et al: *Canine and feline endocrinology and reproduction,* ed 4, St Louis, 2015, Saunders.)

Adrenal Axis Testing

ACTH Stimulation Testing (ACTHst)

Confirming a diagnosis of HA requires testing adrenal gland function. Glucocorticoid and mineralocorticoid functions are investigated independently and the ACTHst is the test of choice for the diagnosis of HA. The ACTHst is performed by measuring serum cortisol concentrations before and 1 hour after giving 5 mcg/kg synthetic ACTH, IV.[41] Since the volume of ACTH is small, care must be taken to ensure IV administration. If accidentally given SC, ACTH will not stimulate the adrenal glands and could lead to erroneous test results.

Because synthetic ACTH is expensive, some clinics save any excess to reduce client cost. After reconstitution with 0.9% saline, the ACTH can be refrigerated or frozen. Refrigeration (4-8° C) for up to 60 days has been reported for use in humans. Our experience suggests using refrigerated synthetic ACTH within 14 days or using previously frozen ACTH (at −20° C in plastic syringes) within 6 months.[42,43]

In a dog with normal adrenal function, injection of ACTH should result in a surge of cortisol secretion from the adrenal glands. Therefore, serum cortisol concentration before ACTH administration is expected to be between 0.5-6 mcg/dL and after ACTHst it is expected to be >2 mcg/dL. In a dog with HA, the adrenals have been destroyed and are unable to mount an appropriate response to ACTH. In most dogs with HA, serum cortisol concentrations before and after ACTHst are <1 mcg/dL (undetectable; Figure 309-4). A small number of dogs with HA can have serum cortisol concentrations between 1-2 mcg/dL after ACTHst; however, diagnosis of HA with serum cortisol concentration >1 mcg/dL post-ACTH should be made with caution and only when all other differential diagnoses have been excluded.

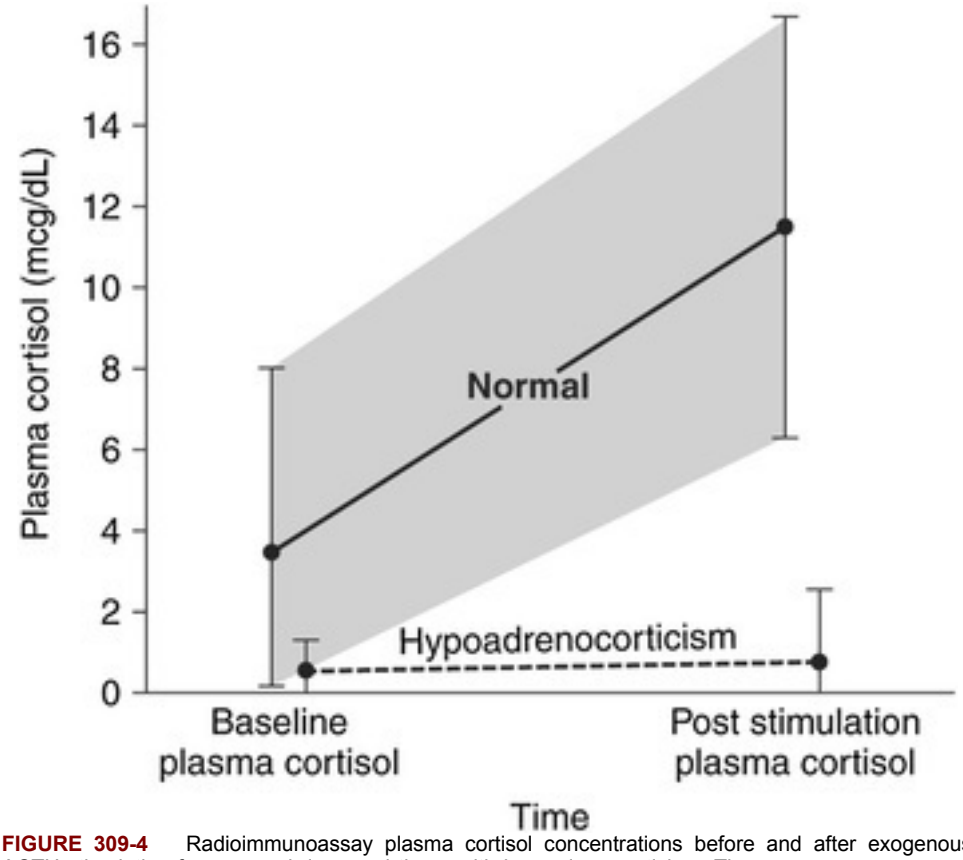

FIGURE 309-4 Radioimmunoassay plasma cortisol concentrations before and after exogenous ACTH stimulation from normal dogs and those with hypoadrenocorticism. The ranges are means ± 2 SD. (From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction*, ed 3, St Louis, 2004, Saunders.)

Cortisol: Endogenous ACTH ratio (C : eACTH)

The cost of synthetic ACTH and its lack of availability in some countries have led to studies investigating other options for HA diagnosis. While most dogs with HA have resting (basal) serum cortisol concentrations <1 mcg/dL, this may also be true of a few dogs who do not have HA. Thus, resting cortisol alone cannot be used to diagnose HA.[44,45] C : eACTH holds promise as a diagnostic aid for diagnosis of HA, requiring only one blood sample. The C : eACTH has been shown to be significantly lower in HA dogs when compared to healthy dogs, with no overlap in ratio results.[46] In a study of C : eACTH in 15 dogs with HA compared to 5 dogs with non-adrenal disease in which HA was suspected and excluded, there was again no overlap between the ratio results from the two groups.[47] Five of the 15 dogs with HA, however, had their eACTH measured after exogenous ACTH had been administered.[47] A larger number of dogs must be studied before

this test can be recommended for the definitive diagnosis of HA.

Mineralocorticoid Testing

Assessing serum Na and K concentrations is an indirect but good reflection of aldosterone function. The ratio of plasma aldosterone concentration to plasma renin activity in dogs with HA has been investigated and shown to be significantly lower than in healthy dogs, with no overlap.[46] However, overlap was noted between individual plasma aldosterone concentrations and plasma renin activities, indicating that the individual test results are less specific than their ratio.[46] It remains to be seen whether the ratio can be used to confirm a diagnosis of HA.

Basal Cortisol Concentrations

While not useful for diagnosing HA, basal cortisol concentrations are quite useful as a simple screening test to exclude HA from any list of differential diagnoses. Dogs with basal cortisol concentrations >2 mcg/dL are unlikely to have HA.[44] This test is particularly useful in dogs with normal Na : K ratios suspected of having glucocorticoid deficiency only.

Secondary Hypoadrenocorticism and Isolated Hypoaldosteronism

Rarely, dogs have "secondary" HA caused by a deficiency of pituitary ACTH. The eACTH concentrations from these dogs are low while serum Na and K concentrations should be within reference intervals. Regulation of Na and K is controlled primarily by renin and angiotensin, not by the pituitary or hypothalamus. In the singular instance of isolated hypoaldosteronism, cortisol concentrations before and after ACTHst are normal. These dogs can be identified by the combination of hyperkalemia, hyponatremia, low plasma renin activity, and low aldosterone concentrations before and after ACTHst.[48]

Critical Illness

A review of the hypothalamic-pituitary-adrenal axis response to critical illness and the condition's effect on testing is provided in ch. 133.

Differential Diagnoses

The term *"pseudo-Addison's disease"* is used to describe conditions that resemble Addison's disease in their clinical and/or clinicopathologic results. This is especially true of concurrent hyperkalemia and hyponatremia. Some severe GI diseases (especially trichuriasis and salmonellosis), periparturient illnesses, and chylothorax are among the conditions that may mimic HA.[49-52] ACTHst results should discriminate HA from other conditions. The differential diagnoses for PU/PD (see ch. 45), azotemia (see ch. 62), isosthenuria (see ch. 72), eosinophilia (see ch. 58), hyperkalemia (see ch. 68), hyponatremia (see ch. 67), hypercalcemia (see ch. 69), hypoglycemia (see ch. 61), increased liver enzymes (see ch. 65), hypocholesterolemia (see ch. 63), hypoalbuminemia (see ch. 60), and acidemia (see ch. 128) are covered in their respective chapters.

Treatment

Acute Hypoadrenal Crisis

Overview and Fluid Therapy

Fluid therapy is the single most important and vital component of therapy (see ch. 129). Although no studies yet guide specific fluid choices, 0.9% NaCl (saline) is recommended because it contains more Na and Cl and less K than other crystalloid fluids. Concerns can be raised regarding the relatively low pH of saline, but the clinical significance of hyponatremia and hyperkalemia far outweighs risk of iatrogenic acidosis. Any acidosis associated with HA is usually mild and corrects within 12-24 hours of IV saline administration. Glucose and insulin are occasionally employed. Dexamethasone is rarely administered in the peracute stages of therapy, in order to begin and complete ACTHst. Bicarbonate treatment is not indicated.

Sodium (Na) and Potassium (K)

Acute and profound hyponatremia can cause brain edema. Rapid correction of hyponatremia can also result

in potentially fatal osmotic shifts. It is recommended that hyponatremic people have their serum Na concentration increase about 1-2 mEq/L in the first 2-3 hours of treatment and about 8-12 mEq/L during the first 24 hours.[53] During the first few hours of treatment, Na and K concentrations should be measured every 2-6 hours, depending on severity of the electrolyte abnormalities and the dogs' clinical status. Hyperkalemia usually dramatically improves and sometimes resolves with intensive IV saline alone.

Glucose, Insulin, DOCP, Bicarbonate

If severe hyperkalemia persists following 6-8 hours of fluid therapy or if bradycardia is profound, IV dextrose can be administered. Glucose stimulates insulin secretion, which moves K from the extracellular fluid into cells, quickly decreasing circulating K concentrations. If dextrose administration alone fails to decrease the K, IV insulin can be safely administered if the blood glucose concentration is above 200 mg/dL. When insulin is administered, glucose must be monitored closely to ensure that hypoglycemia can be quickly identified and treated, if needed. Severe hypoglycemia (blood glucose <60 mg/dL) at admission or after insulin administration should be addressed with adequate glucose added to the IV saline to create a 5% dextrose solution. Alternatively, a dextrose bolus (0.25-0.5 g/kg, diluted 1 : 3) can be given IV. It is important to remember that glucose administration may cause transient hyperglycemia. Hyperglycemia, in turn, causes serum Na concentrations to measure low because the increasing glucose concentration results in fluid shifting to the extracellular space, diluting Na. In humans it has been suggested that there is usually about a 1 mEq/L decrease in measured serum sodium concentration for every 62 mg/dL increase in glucose concentration above normal. Finally, once the dog is rehydrated, if hyperkalemia and hyponatremia persist, the ACTHst is completed, and other major differential diagnoses excluded, dogs should be treated with IM or SC DOCP (2.2 mg/kg) to provide long-term, effective, mineralocorticoid replacement. In the very unlikely event that acidosis is severe (pH < 7.1) and does not correct with fluid therapy, bicarbonate can be administered at increments of 1/4 (0.3 × base deficit × body weight in kg) every 20 minutes while monitoring venous pH.

Glucocorticoid Therapy

Usually it is not necessary to administer glucocorticoids in the acute stage of treatment and it is possible to wait at least the 1 hour needed to complete the ACTHst. Since ACTHst results may dictate lifelong treatment, it is best to avoid concerns of glucocorticoid treatment initiated before or during ACTHst. Once beginning glucocorticoid treatment, it must be withdrawn gradually. Dogs must not receive oral prednisone for at least 48 hours before an ACTHst. If glucocorticoids are deemed vital before an ACTHst is performed, dexamethasone is preferred and given IV. It has a rapid onset of action and does not interfere with cortisol assays if an ACTHst is subsequently performed. While dexamethasone does not cross-react with cortisol assays, it does suppress pituitary secretion of ACTH and CRH from the hypothalamus. This could impact ACTHst results.

Long-Term Therapy

Overview

Long-term treatment begins after an HA dog is hydrated, fluid therapy has been discontinued, serum electrolyte concentrations have normalized, and the dog no longer has vomiting, diarrhea, or anorexia. This stage of treatment generally begins 24-48 hours after admission for a crisis, or on an outpatient basis, if the diagnosis is established. Long-term treatment consists of mineralocorticoid and glucocorticoid supplementation. In dogs with normal serum Na and K concentrations, only glucocorticoids are needed.

Glucocorticoids

Glucocorticoids can be supplemented with prednisone, the most commonly used glucocorticoid, or fludrocortisone acetate. Immediately following an acute crisis, prednisone can be administered at a relatively high dosage of 0.5 mg/kg PO q 12 h for 2-3 days. Following these first few days, the prednisone dosage can be quickly decreased to physiologic needs (0.1-0.2 mg/kg PO q 12-24 h). Many dogs require much lower dosages for health. Low dosages should avoid the polyphagia, weight gain, PU/PD, and other adverse side effects typically caused by glucocorticoids in dogs. Finding the “best” dosage is based on trial and error. If lethargy, anorexia, vomiting, and diarrhea recur, the dosage of prednisone can be increased. Owners should have extra prednisone available for a crisis or in anticipation of stressful situations (travel, kennel, house guests). In these situations, owners are instructed to give higher dosages of prednisone (0.5 mg/kg). Fludrocortisone acetate contains both glucocorticoids and mineralocorticoids. However, it is difficult to supplement both hormones

properly with this drug. Some dogs develop typical glucocorticoid-induced side-effects when given enough fludrocortisone to correct electrolyte abnormalities. Others require prednisone in addition to the fludrocortisone to prevent GI clinical signs consistent with HA.

Mineralocorticoids

Mineralocorticoids can be supplemented with DOCP or fludrocortisone acetate. DOCP is administered SC approximately every 25 days.* The recommended dosage is 2.2 mg/kg q 25 days, but clinical experience and reports suggest that DOCP can successfully maintain normal serum Na and K concentrations at lower dosages and/or when given less often.[54] One should begin treatment at the labeled dosage of 2.2 mg/kg SC, measuring serum Na and K 14 and 25 days later. If the Na : K ratio is above 32 at day 14, the next dose of DOCP can be decreased by about 10% (2 mg/kg). If the Na : K ratio is above 32 on day 25, the DOCP injection can be postponed for at least 5 days, at which time the process is repeated. Once the serum Na begins to decrease or the serum K increases, the DOCP should be given. The new time between injections can be maintained. If the interval between injections is increased, the Na : K ratio should be measured in the middle and end of this new interval, with a goal of 29-32. The dose is increased or interval decreased if <28 and the opposite if >32. This process should be repeated several times during the first few months (Figure 309-5).

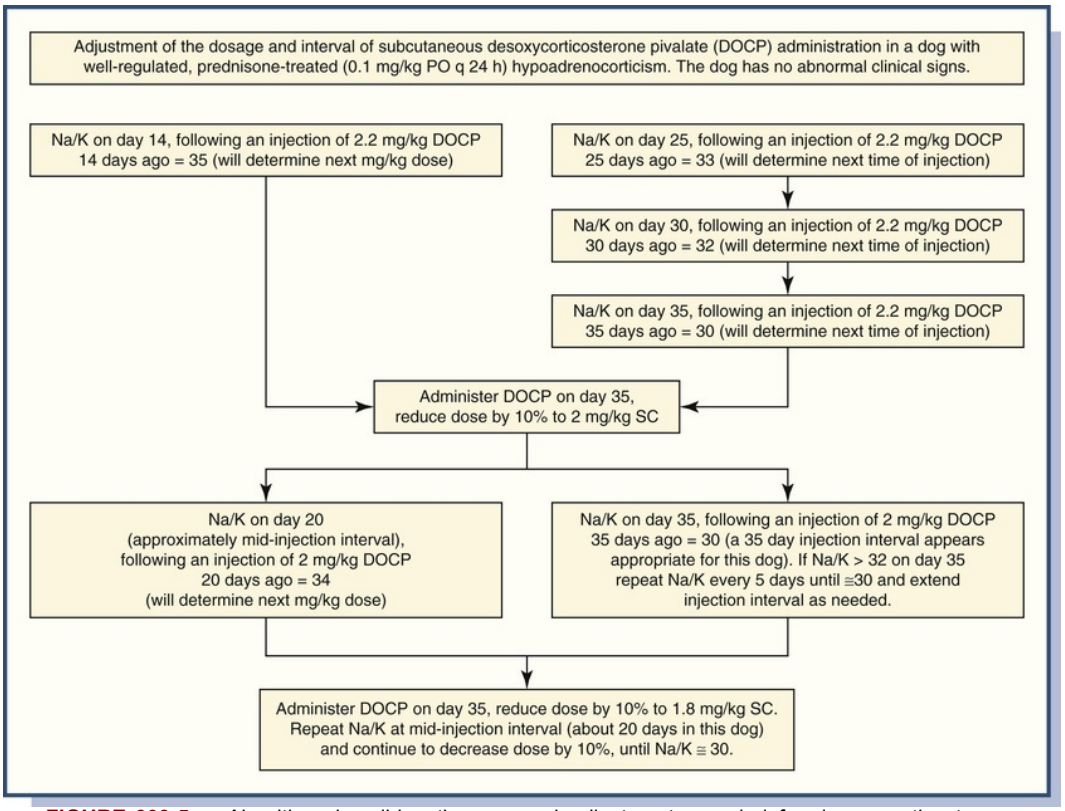

FIGURE 309-5 Algorithm describing the use and adjustments needed for desoxycorticosterone pivalate (DOCP) treatment of dogs with hypoadrenocorticism.

Fludrocortisone is given orally, in tablet form twice daily (0.01 mg/kg PO q 12 h).[55] The dosage should be adjusted by assessing serum Na and K concentration every 5 days and it should be increased until the Na : K ratio is above 28. Treatment of dogs with DOCP and prednisone allows for successful supplementation of glucocorticoids and mineralocorticoids, separately. A recent study also reported that DOCP was more effective than fludrocortisone in decreasing plasma renin activity, increasing Na, and decreasing K in dogs with HA.[56]

Monitoring

The recommended treatment protocol of monitoring and adjusting the dosage of DOCP requires frequent

veterinary visits. Although there is expense, the costs of treating a second HA crisis or of the drugs used in treatment are also significant. Ultimately it is less expensive to determine needed doses. If one can give a smaller dose, less frequently, it will be best for the dog and less expensive for the owner. Owners must keep in mind that a "perfect dose" can change for any of a myriad of reasons. Rechecking Na and K concentrations is warranted every few months, even in well-regulated dogs.

Glucocorticoid doses should be tapered as needed for the dog to appear stable and healthy. One wants to avoid signs and biochemical alterations of hypo- or hyperadrenocorticism. Monitoring mineralocorticoid treatment is performed by measuring the Na : K ratio, as described. Plasma renin activity can also be used to monitor mineralocorticoid treatment; however, the assay is not widely available.[56] Owners should monitor their dog carefully and report any worrisome clinical signs, especially those suggestive of too much or too little glucocorticoid. PU/PD can develop in dogs treated for HA for several reasons and identifying the specific cause can be challenging. DOCP can cause PU/PD without causing any increase in serum Na. Specific glucocorticoids or fludrocortisone can cause PU/PD. Thus, PU/PD are signs of HA and of hyperadrenocorticism. Further, any dog can develop another of the many conditions that cause PU/PD. Therefore, this relatively common issue must be evaluated carefully.

It is important to remember that dogs diagnosed with atypical HA may well progress to a state in which they are mineralocorticoid-deficient. Therefore, periodic assessment of their Na and K concentrations should be considered critically important.

Prognosis

The prognosis for HA is excellent, provided that the acute crisis is treated successfully and a diagnosis is established. Most dogs with HA that require IV fluid therapy are discharged from the hospital about 48 hours after admission (see Table 309-1).

Feline Hypoadrenocorticism

Hypoadrenocorticism is extremely rare in cats, but from the few cases published, cats appear to have similar clinical signs, physical examination findings, and clinicopathologic abnormalities as seen in dogs with HA.[57] Spontaneous typical and atypical HA, iatrogenic HA associated with withdrawal of steroids, and neoplastic invasion of adrenals have been reported.[57-60] Pseudohypoadrenocorticism with hypoNa and hyperK has also been documented in 4 cats with peritoneal effusion.[61] Feline HA should be suspected after more common disorders have been excluded, and clinicopathologic findings are supportive of the diagnosis. The protocol for an ACTHst in cats is different than the protocol in dogs (see ch. 306). Treatment is based on glucocorticoid and mineralocorticoid supplementation, after treating the acute crisis. The prognosis for cats with HA does not appear to be as good as it is for dogs.[57]

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*Editor's comment: Recently, the DOCP commercially available in Europe (and perhaps elsewhere) seems far more potent and much longer lasting than any previous report would indicate. Veterinarians are encouraged to consult with specialists in their area to understand if the dose and/or frequency of administering DOCP has changed since publishing this textbook.

CHAPTER 310

Gastrointestinal Endocrinology

Thomas Schermerhorn

Client Information Sheet: Gastrointestinal Neuroendocrine Tumor (NET)

Introduction

By some measures, the gastrointestinal (GI) tract is the largest endocrine organ in the body. Endocrine functions of the pancreas and GI tract are diverse and involve more than 30 hormones responsible for integrating and coordinating physiologic processes that regulate appetite, digestion, and energy metabolism.[1] These are true hormones, entering the bloodstream to act at target tissues distant from their site of origin. Some products have paracrine or neurotransmitter functions. Some hormones have multiple isoforms and others produce different actions depending on the tissue target. The biochemical diversity of the hormones produced by the GI tract and pancreas is as broad as the functions they regulate, resulting in a complex clinical endocrinology. Within some hormone families, such as gastrin and glucagon, further diversity is conveyed by the production of alternatively spliced mRNAs and the production of preprohormones by specific genes that then undergo various post-translational modifications to produce a variety of structurally-related but functionally-distinct protein products. Thorough exploration of the genetic, biochemical, and physiologic mechanisms that regulate these complex hormones is beyond the scope of this chapter, but a brief review allows discussion of clinical syndromes associated with abnormalities of gut hormone production. Many GI and pancreatic hormones share biochemical and structural similarities that permit classification into various hormone families (Table 310-1). From a clinical perspective, the secretin, insulin, and gastrin families are among the most relevant. Other hormones, such as serotonin that cause defined syndromes in humans, have less defined roles in animals. Some, such as ghrelin and glucagon-like peptide-1 (GLP-1), may have emerging roles in the treatment of endocrine disorders (see ch. 304 and 305).

TABLE 310-1

Overview of Important Gastrointestinal Hormones

SUBSTANCE	PHYSIOLOGIC STIMULUS	TARGET TISSUE	PHYSIOLOGIC EFFECTS
Gastrin	Gastric distention Intraluminal peptides	Gastric parietal and chief cells Pancreatic acinar cells Gastric, intestinal, pancreatic tissue	Acid and pepsinogen secretion Pancreatic enzyme secretion Trophic effect: growth
Cholecystokinin	Nutrients in duodenum (fatty acids, amino acids) Hydrogen ion (H^+)	Gallbladder Sphincter of Oddi Pancreatic acinar cells Stomach	Contraction Relaxation Enzyme secretion Trophic effect: pancreatic growth Inhibits gastric emptying
Secretin	Intraduodenal fatty acids Hydrogen ion (H^+)	Ductal cells (pancreas) Biliary tree Duodenum	Stimulates secretion of bicarbonate and water
Glucagon-like peptide-1 (GLP-1)	Intraluminal fatty acids (duodenum and ileum)	Pancreatic islets of Langerhans (beta cells) Stomach	Incretin effect: stimulates insulin secretion in presence of glucose Inhibits gastric emptying

Gastric inhibitory peptide (GIP)	Nutrients in duodenum (fatty acids, glucose, amino acids)	Gastrointestinal tract (stomach, duodenum, jejunum, ileum)	
Somatostatin	Nutrients (lipid and protein) Bile	Stomach Gallbladder Pancreas Intestine	Inhibits acid and pepsinogen secretion Inhibition of gallbladder contraction Inhibition of insulin and exocrine secretion Inhibition of intestinal motility; decrease nutrient absorption
Motilin	Nutrients (lipid) Hydrogen ion (H^+)	Intestine	Coordinates migrating motility complex (MMC) Coordinates gastric, pancreatic, and biliary secretions
Ghrelin	Nutrients (protein)	Pituitary	Modulates growth hormone

Pancreatic and Gut Hormones

This family of hormones includes various products of GI or pancreatic islet origin. Clinically important members of the secretin family include secretin, glucagon, glucagon-like peptide (GLP), and gastric inhibitory peptide (GIP). Other important hormones in this group include gastrin, cholecystokinin (CCK), somatostatin, motilin, ghrelin, and serotonin.

Secretin

Secretin, a peptide hormone produced by S cells located principally in the duodenum, is released in response to hydrogen ions (H^+) contained in gastric secretions.[2] Like some other gut hormones (e.g., CCK), secretin circulates in one of several sized molecular forms (27-, 28-, 30-, and 71- amino acid polypeptides have been described). Each polypeptide may serve a slightly different function. The major endocrine actions of secretin are stimulation of bicarbonate-containing fluid and bile, respectively, from pancreatic ductal cells and biliary epithelium. Other effects include inhibition of gastrin secretion, gastric acid production, and GI motility. Expression of secretin or its receptor has been reported in central nervous system (CNS) neurons, heart and lung, but further study is needed to define its role(s) in these non-enteric sites.

Glucagon, Glucagon-Like Peptide, and Gastric Inhibitory Peptide

Glucagon from pancreatic islet alpha cells and enteroglucagons from GI L cells are products of the same gene. Diversity within this peptide family arises from tissue specific processing of primary gene transcripts. In islet alpha cells, primary mRNAs encode glucagon while in L cells, mRNAs derived from the same gene encode GLP, GIP, enteroglucagon and glicentin.[3] Glucagon, a vital hormone in energy homeostasis and nutrient metabolism, has actions that generally counter the anabolic actions of insulin. Glucagon is the principal hormone stimulus for hepatic glycogenolysis and gluconeogenesis, actions opposite those of insulin. GLP (GLP-1 and GLP-2) and GIP are enteroglucagons known as incretins because their actions enhance nutrient-induced insulin secretion. Of the incretins, GLP-1 is the most potent insulin secretagogue. It has been studied extensively as a potential therapeutic aide for diabetes mellitus (DM). GLP-1 and GLP-2 are released from L cells in response to intraluminal nutrients and they also modulate intestinal glucose absorption via inhibition of gastric motility and GLP-2 mediated upregulation of glucose transporters.[4,5]

Gastrin

Gastrin, synthesized and secreted by neuroendocrine G cells located in the stomach antrum and duodenum, is stimulated by ingested protein and gastric distention and inhibited by low intraluminal pH (<3). Gastrin circulates in several different molecular forms that vary in molecular weight (e.g., gastrin-34, -17, and -14), which bind on target tissue surfaces.[6] Gastrin-34 is the major circulating gastrin, but the less abundant gastin-17 has more potent biological effects on gastric acid secretion, the primary biologic action of this hormone. Gastrin acts in concert with acetylcholine from autonomic parasympathetic nerve endings and histamine to regulate H^+ secretion from gastric parietal cells. Gastrin has trophic effects on gastric epithelium and stimulates mucosal blood flow, pepsinogen release, and antral motility. Gastrin also influences pancreatic

enzyme production and has trophic effects on pancreatic and duodenal tissue.

Cholecystokinin (CCK)

CCK, synthesized by I cells located in the duodenum and jejunum, is released in response to a variety of substances entering the duodenum, especially H^+, fatty acids, and amino acids.[7] During synthesis, the CCK transcript undergoes processing that results in a multitude of circulating isoforms. Of the seven CCK isoforms identified, CCK-33, CCK-39, and CCK-58 are responsible for the principal GI effects. CCK-8, expressed in neurons, serves as a peptide neurotransmitter in the enteric nervous system. Other isoforms, such as CCK-5, CCK-12, and CCK-63, have functions of lesser GI importance. Major CCK actions include stimulating gallbladder contraction and pancreatic enzyme secretion, both mediated via presynaptic cholinergic neurons. CCK also serves to coordinate overall digestive function including stimulation of pancreatic fluid secretion (in the presence of stimulatory levels of secretin), inhibition of gastric emptying, sphincter of Oddi relaxation, and stimulation of pancreatic growth.

Somatostatin

The peptide somatostatin is synthesized in the hypothalamus, pancreatic islet delta cells, GI D cells, and subsets of neurons in the CNS and enteric nervous system. Intestinal D cells release somatostatin in response to nutrients (fats and protein) and bile in the gut lumen. The endocrine, paracrine, and neurotransmitter effects of somatostatin principally inhibit: gastric acid, pepsinogen, gallbladder contraction, insulin secretion, pancreatic exocrine function, GI motility, and nutrient (amino acids and glucose) absorption.[8]

Motilin

Motilin, a peptide hormone synthesized in GI cells, is structurally related to ghrelin. Secretion is cyclic, dependent on being in a fasted or fed state, but its main endocrine actions occur during fasting. Between meals, motilin initiates and coordinates migrating motility complexes (MMCs), which serve to clear the intestines in interdigestive states. After eating, motilin is released in response to stomach acid (H^+) or lipid entering the small intestines. In the fed state, motilin serves to coordinate gastric, pancreatic, and biliary secretions.[9]

Ghrelin

The hormone ghrelin, structurally related to motilin, was recently identified as an important mediator of appetite and energy metabolism.[10] Ghrelin, synthesized and secreted in the stomach, stimulates appetite, adipocyte growth, and pituitary growth hormone (GH) synthesis and secretion. Ghrelin provides a link between dietary nutrients, caloric energy, and the pituitary-GH axis vital for growth regulation.

Serotonin

Serotonin (5-hydroxytryptamine [5-HT]) is a neuropeptide and hormone located within enteric neurons and enterochromaffin cells distributed throughout the GI tract. 5-HT of enterochromaffin origin acts as an endocrine and paracrine agent to stimulate GI smooth muscle contraction and intestinal secretion.[11]

Insulinoma

Neuroendocrine tumors, uncommonly diagnosed in dogs and cats, are most often located in the pancreas, where they arise from islet cells (islet cell tumors; see ch. 303). Metastatic lesions are common in the mesentery, intestine, and liver. Insulinoma is uncommon, but is the most common neuroendocrine tumor reported in dogs, and is rare in cats (see ch. 303).[12-15] The pancreas is the most frequent location for insulinoma formation but these tumors may also be found in mesenteric, splenic, and hepatic locations. It is not clear whether non-pancreatic insulinomas represent primary or metastatic tumors. Insulinomas cause fluctuating increases in circulating insulin concentrations that are not under physiologic control. As a result, pets with an insulinoma have episodic hypoglycemia. The balance of this chapter is focused on gastrinoma, glucagonoma, and other less common conditions.

Gastrinoma

Overview

Gastrinoma is an uncommon tumor of dogs and cats[16-20] and no large-scale studies of canine or feline gastrinoma have been published. Gastrin overproduction by gastrinomas may lead to the Zollinger-Ellison syndrome, clinically associated with gastric antral hypertrophy, hyperacidity and ulceration.[21] Treatment is surgical removal. Supportive treatment is directed at suppressing gastric acid production.

Signalment and Clinical Signs

The veterinary literature cites fewer than 50 cases of gastrinoma in dogs and cats, most in dogs. Mean age at diagnosis in dogs is about 8 years and cats have been slightly older. Frequent owner observations include vomiting, diarrhea, and weight loss. Less frequent concerns include apparent abdominal pain, GI bleeding, polydipsia, and constipation. Gastrin-induced hyperacidity can lead to reflux esophagitis with resultant regurgitation, and esophageal colic (see ch. 273). Gastropathy, characterized by mucosal hypertrophy, mucosal ulceration, and, in severe cases, outflow obstruction, leads to vomiting and weight loss. Diarrhea may develop due to the inhibitory effects of gastrin on intestinal water absorption. Gastrinomas, usually quite small, are not typically detected during abdominal palpation. Physical examination findings depend on the stage of disease. Signs, if any, are not specific. Early in the disease, the physical examination is often unremarkable. Animals with esophagitis, gastric ulceration or gastric perforation exhibit pain on esophageal or abdominal palpation, evidence of dehydration, fever, and signs of shock.

Laboratory Findings

Gastrinoma is not associated with specific changes on complete blood count (CBC) or serum biochemistry panels. Non-specific findings of leukocytosis, neutrophilia with left shift, anemia, and pan-hypoproteinemia caused by inflammation and blood loss may be seen secondary to gastric ulcerations. Other reported biochemical abnormalities include hypoalbuminuria, hypokalemia, hypochloremia, hyponatremia, metabolic alkalosis, hyperbilirubinemia, and increased liver enzyme activities. Biochemical changes may not be caused by gastrinoma per se, but may develop secondary to consequences of hypergastrinemia, such as chronic vomiting, diarrhea, or hepatic metastasis. Some dogs with gastrinoma had concurrent disorders (myelofibrosis, bile duct obstruction) that contributed to clinicopathologic disturbances. Some gastrinomas may produce and secrete hormones in addition to gastrin; concurrent secretion of insulin and adrenocorticotropic hormone (ACTH) have been reported.

Routine Diagnostic Imaging

Ultrasonography (US; see ch. 88) is generally more useful than radiography in the diagnostic work-up for gastrinoma. Abdominal US, more efficient in detecting a pancreatic mass than radiographs, may reveal gastric changes consistent with ulceration, mucosal and rugal fold hypertrophy, and thickened gastric walls. US may allow detection of metastases to extra-pancreatic sites, such as liver or lymph nodes. Plain radiography is generally not helpful or reveals only nonspecific changes. The use of contrast radiography, described in several case reports, identified gastric rugal fold hypertrophy, narrowing of the antrum due to hypertrophy, and mucosal defects caused by ulceration. Endoscopy, of limited value in obtaining a definitive diagnosis, may provide useful information regarding esophageal inflammation and ulceration, prominent gastric folds, antral hypertrophy, gastric and duodenal ulceration, and hypersecretion of gastric fluid (see ch. 113). Endoscopic biopsy may permit histologic characterization of GI changes but is not likely to provide definitive diagnosis of gastrinoma.

Diagnosis

Overview

An array of testing options is available, including measuring serum gastrin concentrations, basal acid production, secretin- and calcium-stimulation of gastrin secretion and tumor imaging using a labeled somatostatin for scintigraphic localization. In dogs and cats, these studies are not common.

Basal Measurements: Serum Gastrin Concentrations and Gastric pH

Serum gastrin concentrations are usually increased in people and dogs with gastrinoma. In people, serum gastrin levels > 1000 ng/L together with gastric pH < 2.5 is considered diagnostic for gastrinoma. This pairing of gastrin and gastric acid measurements has not been used extensively in veterinary medicine. Serum gastrin concentrations in dogs with histologically confirmed gastrinoma have ranged several fold above the upper limit of reference ranges, but no specific cutoff for normal has been established. Blood gastrin concentrations in dogs and cats may be increased in kidney disease, gastropathies, hepatopathies, and with use of drugs that inhibit gastric acid production. Measurements of pH and/or gastric acid secretion, reported in a few dogs with gastrinoma, have noted low gastric pH. Measurement of serum gastrin concentrations cannot be used as a sole test to confirm gastrinoma, even if high. Such results are most helpful when clinical suspicion for gastrinoma is high and other disorders that might cause hypergastrinemia have been ruled out.

Provocative Testing

Provocative tests measure gastrin release in response to secretin or calcium (Ca). Neither secretin nor Ca injection leads to an increase in gastrin in normal individuals but both cause gastrin release from gastrinomas. The secretin stimulation test is the most frequently employed provocative test in people, but experience with this test in animals is quite limited. The test principle relies on the enhanced responsiveness of gastrinoma tissue to secretin. One protocol used in dogs was to obtain serum samples before and 2, 5, 10 and 20 minutes after IV injection of secretin (2 to 4 U/kg).[22] An alternative protocol is to obtain samples before and 2, 5, 10, 30 and 60 minutes after IV injection of 2 U/kg secretin.[23] Samples from the 2- and 5-minute periods are most useful for gastrinoma diagnosis, since tumor response to injected secretin is typically rapid and short-lived. Humans with gastrinoma have about a two-fold increase in gastrin following secretin injection. While reports of secretin stimulation tests in dogs are scarce, results have been similar to those reported in humans. However, not all dogs with gastrinoma showed an increase in gastrin more than two-fold above baseline.[22]

The Ca stimulation test, an alternative to secretin stimulation, may be preferred because it is inexpensive and widely available. Adverse cardiac effects during infusion are a potential disadvantage, requiring appropriate precautions (see ch. 298). The protocol described includes serum samples collected before and 15, 30, 60 and 90 minutes after IV infusion of Ca (2 mg/kg IV, given over 1 minute).[24] Maximum gastrin secretion was detected at 60 minutes. Humans with gastrinoma typically have a two-fold increase in serum gastrin concentrations after stimulation, as did the few dogs with confirmed gastrinoma.

Pathology

Gastrinomas are usually solitary neoplastic nodules located in the pancreas, but multiple masses have been reported. In the dog, the tumor is more often located in the right limb or body of the pancreas and metastases are common at the time of diagnosis. Metastatic lesions may be identified in non-pancreatic sites (lymph nodes, mesentery, peritoneal surfaces, spleen and liver) in as many as 85% of cases. Microscopically, gastrinomas are carcinomas of endocrine cell origin and stain using immunohistochemistry. On ultrastructural studies, identification of specific intracellular granules may permit definitive diagnosis of gastrinoma. Although rarely performed, hormone measurements on extracts of tumor tissue may also be used to confirm gastrin production. GI ulceration secondary to hypergastrinemia is common, may affect esophagus, stomach, and intestine, and may result in perforation and peritonitis. Hypertrophy of the gastric wall has been reported. Additional endocrine disorders noted in some dogs include thyroid carcinoma and adrenal hyperplasia.

Glucagonoma

Overview

Glucagonoma is a rare endocrine tumor that has been reported in a several dogs[25-27] and a single cat.[28] It arises from neuroendocrine alpha cells in pancreatic islets. Excess circulating glucagon concentrations are due to autonomous secretion that induces hepatic gluconeogenesis and glycogenolysis, which in turn produce insulin resistance, glucose intolerance and, in some cases, overt DM. Definitive treatment is accomplished by surgical removal of the glucagonoma. Necrolytic migratory erythema (NME), a dermatologic condition characterized by crusting and a rash, is considered pathognomonic for glucagonoma in people.[29] In dogs, this condition has been seen in glucagonoma, but is most commonly associated with liver disease (see ch. 10 and 285).[30]

Signalment and Clinical Signs

At diagnosis, the few dogs described to have glucagonoma were middle-aged or older and the cat was 6 years old. Along with nonspecific signs, such as lethargy and decreased appetite, a few dog owners were concerned about non-healing skin erosions and ulcers. The distribution of lesions and involvement of mucocutaneous sites are also consistent with auto-immune skin diseases. Lesions have been reported to involve lips, nose, ears, muzzle, paws, the ventrum, inguinal region, and extremities (Figure 310-1). Dogs with uncontrolled DM at the time of diagnosis exhibit polydipsia, polyuria, and weight loss. Insulin therapy may be relatively ineffective in controlling the hyperglycemia, requiring high doses.

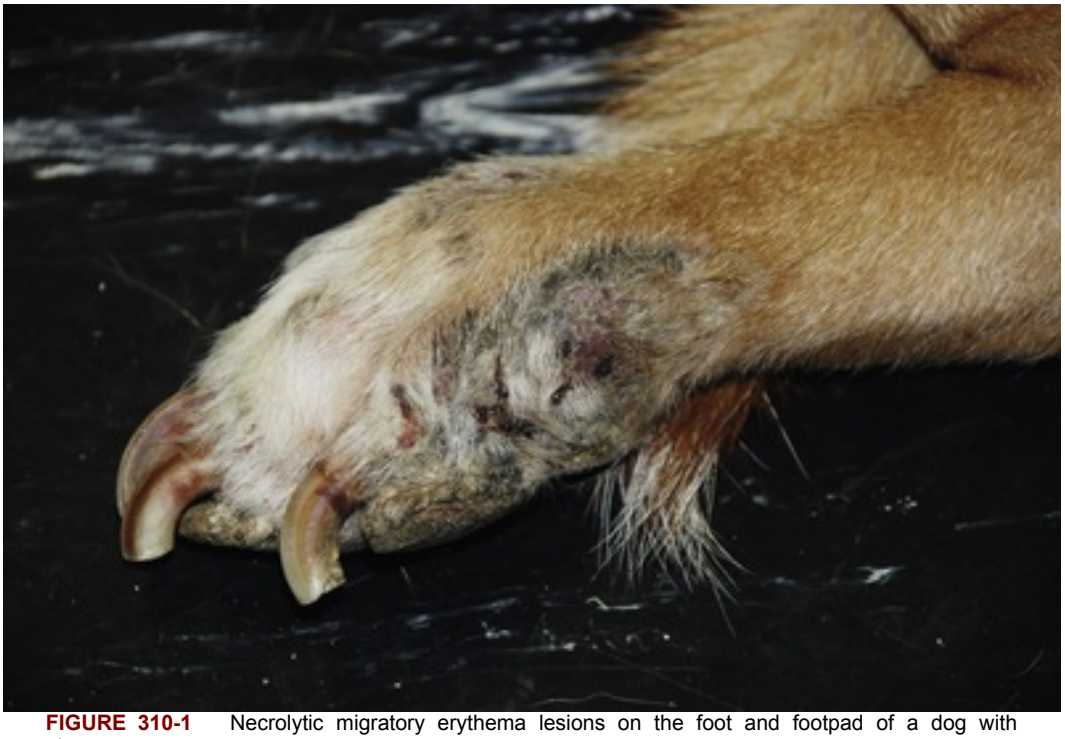

FIGURE 310-1 Necrolytic migratory erythema lesions on the foot and footpad of a dog with glucagonoma.

Laboratory Findings

Numerous nonspecific laboratory abnormalities have been reported in dogs with glucagonoma, but none is specific. Increased serum activities of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) together with decreases in albumin, blood urea nitrogen (BUN) and cholesterol have been identified in some dogs with NME and glucagonoma. When considering a diagnosis of glucagonoma, it is worth remembering that abnormal liver parameters in dogs with glucagonoma mimic primary liver disease, a more common cause of NME in dogs. Liver function tests, such as bile acids and blood ammonia levels, have been normal in dogs with glucagonoma but may be important when investigating the possibility of liver disease.

Diagnostic Imaging

Abdominal US (see ch. 88) is more sensitive than radiography for detecting a pancreatic mass but masses have not been detected in most dogs with glucagonoma reported. Computed tomography (CT) examination identified a pancreatic mass in one dog. Abnormalities in the US appearance of the liver were frequently observed in dogs with glucagonoma but no consistent pattern was noted. In dogs with NME, it is important to remember that liver disease is a more common cause than glucagonoma. Hepatic abnormalities on US should be assessed in the context of whether or not a pet has primary liver disease or glucagonoma.

Diagnosis

Definitive diagnosis of glucagonoma relies on demonstration of hyperglucagonemia, noted in most dogs with glucagonoma previously reported. The hyperglucagonemia in affected dogs showed variability, with elevations ranging from approximately 1.5 to 15 times the upper limit of reference range. No serum concentration is diagnostic of glucagonoma but serum concentrations of >1000 ng/L are considered diagnostic for glucagonoma in humans. Since serum glucagon may increase in disorders other than glucagonoma, diagnosis is appropriately made only when hyperglucagonemia occurs in association with clinical signs of hormone excess. Diagnostic efforts may be complicated by lack of commercially available serum assays for canine and feline glucagon. Measurement of plasma amino acids may provide support for a diagnosis of glucagonoma. Hyperglucagonemia stimulates hepatic gluconeogenesis, accelerates amino acid turnover and lowers plasma amino acid concentrations. Concentrations of arginine, histidine, and lysine were reduced in all of the dogs with glucagonoma in which measurements were performed.

Pathology

Pancreatic glucagonoma is usually a solitary neoplasm that can arise from any region of the pancreas (limbs, body) and reports suggest that metastasis is common in dogs. The liver was the primary site of metastasis in most, although lymphatic metastasis has been seen. Metastatic nodules may be functional (liver metastasis was the only site where glucagon production was documented in one dog with glucagonoma), suggesting incomplete surgical removal of metastases could result in persistent signs. By convention, these tumors have positive staining for glucagon when examined using immunohistochemistry. Expression of other islet hormones and neuroendocrine markers may be detected. Most dogs with glucagonoma have exhibited positive cellular staining against multiple hormones although it is not clear whether these tumors secrete hormones other than glucagon.

Other Neuroendocrine Tumors

Carcinoid

Neuroendocrine tumors that secrete vasoactive substances such as 5-HT (also known as serotonin) or kinins are referred to as carcinoid tumors. These tumors may arise from neuroendocrine cells located in the epithelium of the bronchial tree, lung, biliary system, GI tract, and other sites. In people, the "carcinoid syndrome" is characterized by watery diarrhea, abdominal discomfort, abdominal cramps, bronchoconstriction and hyperemia of the cheeks and forehead ("facial flushing"). Carcinoid tumors are rare in dogs and cats. Most information about these tumors has come from single case descriptions.[31] In dogs, carcinoids have been found in the stomach, duodenum, jejunum, ileocolic region, colon, and rectum.[32-36] Based on just a few reports featuring cats, locations included the liver, pancreas and GI tract.[37,38] Metastasis to lymph nodes and other sites, including lung, was common.

The majority of carcinoids reported in dogs and cats cause signs related to the physical presence of the tumor and do not appear to be functional. The carcinoid syndrome has not been reported in cats. The one dog reported to have carcinoid syndrome did not have elevated concentrations of vasoactive substances 5-HT or kinins.[39] Diagnosis of carcinoid is often made postmortem but when identified antemortem, surgical removal of the carcinoid is recommended. Tumor removal may improve signs that result from its physical presence (intestinal obstruction, for example) although the high frequency of metastasis makes complete tumor removal unlikely. In the sole case report of suspected carcinoid syndrome in a dog, tumor removal resulted in improvement or resolution of the dog's clinical signs.[39] Serum concentrations of 5-HT and other vasoactive substances may be measured to confirm suspected carcinoid in people but these tests have not been performed in animals. Histologic examination of tumor tissue is required to confirm the diagnosis.

Pancreatic Polypeptidoma

Pancreatic polypeptidoma is a poorly understood neuroendocrine tumor that occurs as part of the multiple endocrine neoplasia (MEN) syndrome in people but also develops sporadically in humans and has been reported in the dog.[24] Many functional neuroendocrine tumors of pancreatic islet origin stain positively for several peptide hormones, including pancreatic polypeptide (PP). When the principal protein hormone expressed is PP, the tumor is designated a pancreatic polypeptidoma. The clinical signs associated with excess PP secretion are minimal and most pancreatic polypeptidomas are considered non-functional.[40] A minority of human pancreatic polypeptidomas has been suspected of producing clinical signs related to tumor release of

PP. Signs reported with PP excess include abdominal pain and diarrhea. Some have had pancreatitis. In a dog, increased plasma PP concentrations were associated with chronic vomiting, duodenal ulcers, and evidence of hypertrophic gastritis. The dog also had a pancreatic adenocarcinoma, which stained positively for PP and insulin but not other peptides typically produced by canine pancreatic neuroendocrine tumors (gastrin, glucagon, or somatostatin).[24]

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CHAPTER 311

Pheochromocytoma

Sara Galac

Client Information Sheet: Pheochromocytoma

Background and Definition

Pheochromocytoma is a catecholamine-producing neuroendocrine tumor arising from chromaffin cells of the adrenal medulla.[1] It is considered to be malignant. The manifestations are diverse and can mimic those of various conditions, which often results in erroneous and delayed diagnosis. Not surprisingly, pheochromocytoma has therefore earned the title "great mimic." The clinician's awareness of pheochromocytoma represents a crucial initial step in making a diagnosis, but for confirmation, biochemical evidence of excessive catecholamine production and diagnostic imaging are needed.[2,3] Most pheochromocytomas are unilateral, but occasionally both adrenals are affected. Pheochromocytoma may coexist with other endocrine neoplasms, such as cortisol-secreting adrenocortical tumor, adrenocorticotropic hormone (ACTH)-secreting pituitary tumor, thyroid tumor, insulinoma, or parathyroid tumor or hyperplasia.[4-8] The etiology of pheochromocytoma in dogs is largely unknown. Recently, mutation analysis demonstrated a missense mutation of succinate dehydrogenase subunit D (*SDHD*).[9] In humans, germline mutation of *SDHD* is commonly present in familial forms of pheochromocytoma, in addition to *SDHD, NF1, RET1,* and *VHL* mutations.[10,11] There is a high sequence homology between canine and human *SDHD* and theoretically this mutation could be responsible for the development of pheochromocytoma in dogs.[9]

Physiology

The adrenal medulla originates from the sympathetic nervous system, but without the axons and dendrites of neurons. The medullary cells, called pheochromocytes or chromaffin cells, release epinephrine and norepinephrine into the bloodstream. The medulla is highly vascularized and directly connected to the abdominal aortic system. There is a close vascular relationship between the medulla and the cortex. Blood flowing from the zona reticularis leaves the gland via vessels in the medulla. The unique innervation and vascularization of the adrenal medulla underlies the "fight or flight" response.[12]

Catecholamines (epinephrine and norepinephrine) are synthesized from the amino acid tyrosine via a series of modifications (Figure 311-1). When tyrosine enters chromaffin cells, it is converted to L-dihydroxyphenylalanine by the enzyme tyrosine hydroxylase. This first step in the pathway is the committed rate-limiting step and is feedback-inhibited by norepinephrine. Intracellular catecholamine depletion rapidly increases enzyme activity, whereas increased catecholamine levels lead to its downregulation.[13] In most sympathetic postganglionic neurons, norepinephrine is the final product. However, the adrenal medulla expresses an additional enzyme not present in adrenergic neurons, phenylethanolamine-N-methyltransferase (PNMT).[12] Because only the adrenal medulla is exposed to high levels of cortisol (due to the centripetal blood flow from the cortex), induction of *PNMT* gene expression is allowed. This physiological mechanism needs to be taken into account in diagnostic procedures for pheochromocytoma.[14] Within the adrenal medulla, norepinephrine is released from the chromaffin vesicles to the cytoplasm and is converted to epinephrine. The amount of stored epinephrine and norepinephrine varies from species to species. In dogs, catecholamines usually include more epinephrine (70%) and less norepinephrine (30%). The percentages are 60 and 40% in cats, 80 and 20% in humans.[15]

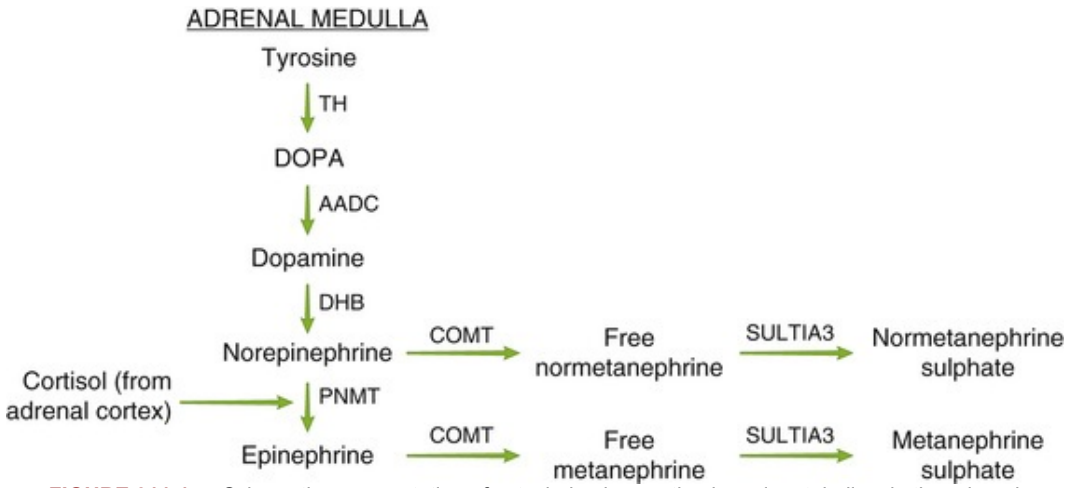

FIGURE 311-1 Schematic representation of catecholamine synthesis and metabolism in the adrenal gland. Tyrosine is converted to L-dihydroxyphenylalanine (DOPA) by the enzyme tyrosine hydroxylase (TH), and subsequent metabolism to dopamine is orchestrated by the enzyme aromatic L-amino acid decarboxylase (AADC). Dopamine is converted by the enzyme dopamine beta-hydroxylase (DHB) to norepinephrine, which is finally converted to epinephrine by the enzyme PNMT, stimulated by cortisol from the adrenal cortex. The catecholamines are metabolized by the enzyme catechol-O-methyltransferase (COMT) and can be measured as free normetanephrine and normetanephrines in plasma. The conjugation of normetanephrine and metanephrine by the enzyme sulfotransferase (SULTIA3) occurs in the gastrointestinal tract, kidneys, and liver, and sulfate-conjugated metanephrines can be measured in urine.

Catecholamines are released by exocytosis upon stimulation of the chromaffin cell by acetylcholine from the sympathetic nervous system. The release signal is triggered by stressors, such as anxiety, fear, pain, trauma, hemorrhage or other fluid loss, changes in blood pH, hypoglycemia, or exposure to excessive heat or cold. The plasma half-life of circulating catecholamines is short and their inactivation begins within a few minutes.[16,17] They are metabolized in the liver and kidney but can also be inactivated by deconjugation in the gastrointestinal (GI) tract. In addition to this extra-adrenal metabolism of circulating catecholamines, there is continual metabolism of norepinephrine and epinephrine within the adrenal medulla due to leakage of norepinephrine and epinephrine from their storage granules. This leads to the substantial intracellular production of O-methylated metabolites, metanephrine (MN) and normetanephrine (NMN) (see Figure 311-1). These metabolic processes within the medulla are independent of exocytotic release of catecholamines, and represent the primary source of circulating MN and NMN. In humans, about 93% of circulating MN and 25 to 40% of circulating NMN are derived from catecholamine metabolism within adrenal chromaffin cells. There is a misconception that vesicular stores of catecholamines exist in a static state until a stimulus evokes release into the extracellular space.[13] Rather, vesicular stores are in a highly dynamic equilibrium with catecholamines in the surrounding cytoplasm. Rapid active transport from the cytoplasm to vesicles counterbalances passive outward leakage from vesicles. Although only a small fraction of the catecholamines in the cytoplasm escapes vesicular sequestration, it remains a major source of catecholamine metabolites.[18] Catecholamines activate adrenergic G-protein-coupled receptors, which are divided into alpha and beta types and their subtypes. An overview of the location of the receptors and their physiological relevance is given in Table 311-1.

TABLE 311-1

Catecholamine Types and Subtypes, Tissue Location, and Effects

ORGAN/TISSUE	RECEPTOR TYPE	EFFECT
Cardiovascular system	Beta-1	Increase in heart rate and contractility
	Alpha-2	Vasoconstriction
	Beta-2	Vasodilatation of skeletal muscle arterioles, coronary arteries, and all veins
Bronchial muscles	Beta-2	Relaxation

Gastrointestinal tract	Beta-2	Decrease in motility
Pancreatic islets	Alpha-2	Decrease in insulin and glucagon secretion
	Beta-2	Increase in insulin and glucagon secretion
Liver	Beta-2	Increase in glycogenolysis and gluconeogenesis
Adipose tissue	Beta-2	Increase in lipolysis
Urinary bladder	Alpha-2	Increase in sphincter tone
	Beta-2	Relaxation of detrusor muscle
Eye	Alpha-1	Mydriasis

Modified from Galac S, Reusch C, Kooistra H, et al: Adrenals. In Rijnberk A, Kooistra HS, editors: *Clinical endocrinology of dogs and cats*, ed 2, Hannover, 2010, Schlütersche, p 140.

Clinical Manifestations

Signalment

Pheochromocytoma is diagnosed most often in older dogs (average: 11 years).[5,7,19] There is no apparent gender or breed predilection. The frequent description of pheochromocytoma in some breeds (Rhodesian Ridgeback, Labrador Retriever, Boxer, Golden Retriever, Terrier breeds) reflects their popularity more than their relative risk of disease.[15,20] In cats, pheochromocytoma is considered extremely rare; only three cases have been reported in the veterinary literature.[21-23]

Clinical Signs

Clinical signs associated with pheochromocytoma are related to the direct actions of secreted catecholamines and/or the space-occupying or invasive nature of the adrenal mass. Hormone secretion from the tumor is sporadic and unpredictable. Clinical manifestations due to excess circulating catecholamines vary considerably. Dogs with pheochromocytoma most often have intermittent episodes of collapse, weakness, and/or panting.[5,7,19] The episodes are paroxysmal and may occur several times per day or per week, or only at intervals of weeks to months. They can be mild or life-threatening and may progress with time. Clinical manifestations related to catecholamine excess can be categorized as follows[15]:

- Cardiorespiratory system and/or systemic hypertension: tachypnea, panting, tachycardia, arrhythmias, collapse, pale mucous membranes, nasal-, gingival-, or ocular hemorrhage, acute blindness
- Neuromuscular system: weakness, anxiety, pacing, muscle tremors, seizures
- Nonspecific: anorexia, weight loss, lethargy
- Miscellaneous: polyuria/polydipsia, vomiting, diarrhea, abdominal pain

Large pheochromocytomas may become invasive. Their heterogeneous structure makes them predisposed to episodes of bleeding and necrosis. Clinical manifestations of a space-occupying adrenal pheochromocytoma may be related to:

- Invasion by the tumor of the vena cava: ascites, hind limb edema, distension of the caudal epigastric veins
- Invasion by the tumor of the aorta (aortic thromboembolism): painful and weak hind limbs, paraparesis, absence of the femoral pulse, cold distal extremities[5,24]
- Spontaneous tumor rupture: retroperitoneal hemorrhage (lethargy, tachypnea, tachycardia, weakness, pale mucous membranes, abdominal pain)[25]

In dogs, pheochromocytomas may metastasize to the liver, kidneys, spleen, regional lymph nodes, lungs, heart, bone, and the central nervous system (CNS). Metastatic disease can cause organ-specific clinical signs. In dogs, paresis due to metastasis within the vertebral canal and lameness, swelling, and pain due to metastasis to bones have been reported several times.[26-28]

Physical examination is most often unremarkable. When signs are present, panting and tachypnea are most common, followed by weakness, tachycardia, and cardiac arrhythmias.[7,29,30] However, physical findings greatly depend on the presence or absence of secretory activity by the tumor. This kaleidoscope of clinical manifestations and the infrequent diagnosis of pheochromocytoma require a high level of clinical awareness

for diagnosis; otherwise, this condition can be easily overlooked.

Diagnostic Evaluation

Overview

Pheochromocytoma is a diagnostic challenge (Figure 311-2). Initial suspicion could follow the fortuitous finding of an adrenal mass during diagnostic imaging, commonly referred to as an "incidentaloma" (see ch. 308). Confirmation of this diagnosis, however, requires biochemical evidence of excessive catecholamine production.[31] Veterinary diagnosis of pheochromocytoma improved dramatically with introduction of assays for plasma and urinary catecholamine metabolites, NMN and MN.[15] There are not, as yet, generally accepted guidelines for a "test of choice" or for algorithms used in confirming, locating or excluding the diagnosis of pheochromocytoma.

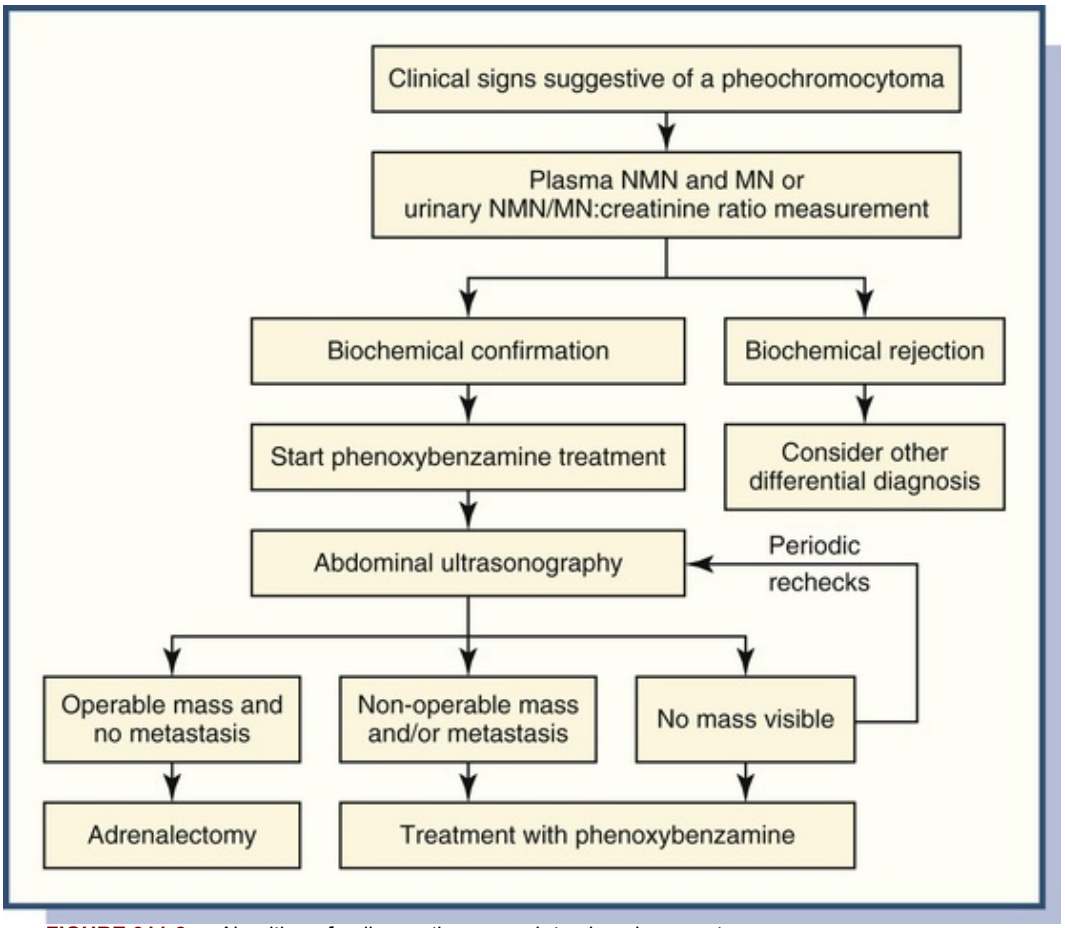

FIGURE 311-2 Algorithm of a diagnostic approach to pheochromocytoma.

Clinical Pathology

No specific abnormality in complete blood count (CBC), serum biochemical panel, or urinalysis would raise suspicion of pheochromocytoma.[15] Many abnormalities identified in results of routine blood and urine tests are caused by concurrent disorders that are commonly present in dogs with pheochromocytoma. Increases in serum liver enzyme activities have been reported in 10 to 25% of dogs with pheochromocytoma,[7] but abnormal values may be secondary to systemic hypertension and changes in hepatic perfusion, or may be caused by any number of potential concurrent diseases. The CBC is usually unremarkable. Hyperglycemia has been reported in approximately 20% of dogs with pheochromocytoma. Proteinuria, a result of hypertensive glomerulopathy or concurrent illness, is also observed in approximately 20%.[5,7]

Hyposthenuria/isosthenuria may be due to the inhibitory effect of circulating catecholamines, especially norepinephrine, on antidiuretic hormone (ADH) secretion and activity.[15]

Systemic Blood Pressure

Although arterial hypertension is one of the hallmarks of the disease, it is detected in only about 50% of dogs with a pheochromocytoma at the time of examination.[15] Various patterns of hypertension have been described in humans with pheochromocytoma.[2,16] They can have persistent and stable hypertension or hypertension/normotension with paroxysmal peaks of extreme hypertension; about 10% are normotensive. It has been suggested that such variable blood pressure patterns exist in dogs as well, but this awaits confirmation in a large group of patients.[32] Measurement, preferably repeated, of systemic arterial blood pressure (see ch. 99) is indicated in any dog with suspected pheochromocytoma, because hypertension requires prompt treatment (see ch. 158). On the other hand, a failure to document systemic hypertension does not rule out pheochromocytoma.

Diagnostic Imaging

Overview

Diagnostic imaging provides important information about adrenal size and structure, unilateral or bilateral involvement, and contact with or invasion of neighboring organs and blood vessels.[1,30] Based on selective criteria, imaging can provide an estimate of potential malignancy and can be extremely helpful in selecting the best therapeutic approach, but it cannot predict the histological type of the adrenal mass.

Radiology

Abdominal radiographs are of little value in visualizing pheochromocytoma, because in contrast to cortical tumors, they are usually not mineralized.[30] Thoracic radiography, prior to adrenalectomy, was recommended to screen for metastasis, but has been largely replaced by computed tomography (CT) scanning.[30,33,34] Abnormalities on thoracic radiographs may include generalized cardiomegaly, right or left ventricular enlargement, pulmonary congestion, and pulmonary edema, presumably resulting from systemic hypertension.

Abdominal Ultrasonography (US)

Pheochromocytomas may be visualized as nodules a few millimeters in diameter or as heterogeneous masses with a diameter >10 cm. Their echogenicity may be hypoechoic or heterogeneous, and large masses may have a multilobular and/or multicystic architecture with anechoic foci of necrosis and hemorrhage. There is no US observation considered pathognomonic for pheochromocytoma.[30,35] Most pheochromocytomas are unilateral, enlarged, adrenal gland masses with a contralateral adrenal gland that is normal in size and shape. However, bilateral pheochromocytomas do occur and are challenging to differentiate from adrenocortical hyperplasia. An attempt to differentiate between adrenal tumor types has been made using contrast-enhanced US.[36] In pheochromocytomas, there is no contrast enhancement in necrotic or hemorrhagic areas or cysts, but the same is true of adrenocortical carcinomas. The most important differential diagnosis is between cortical and medullary neoplasia and these cannot be discriminated via US. Pheochromocytomas are reported to invade the surrounding structures and blood vessels more often than do other types of adrenal tumor. Invasion of the caudal vena cava occurs in 15 to 55% of pheochromocytomas. Right-sided adrenal tumors are more likely to invade the caudal vena cava.[29,37,38] Invasive behavior does not necessarily indicate malignancy; rather, it can represent mass expansion into areas presenting the least resistance.[2]

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) Scans

CT imaging scans are considered more accurate than abdominal US for detecting vascular luminal invasion by adrenal masses.[30,33,39] Presence and extent of vascular invasion influences choice of therapy and are, therefore, important. Pheochromocytomas have variable appearances in CT images, having multiple foci of low attenuation interspersed with hyperattenuating, highly vascularized areas, especially in large tumors.[30,39] These features, typical of hemorrhage and necrosis, are not specific for pheochromocytoma and are more likely when adrenal tumors attain a certain size. One additional benefit of CT scanning is that abdominal

imaging can be combined with thoracic screening for metastases. The use of an IV contrast medium is controversial in patients suspected of having a pheochromocytoma. In people, an ionic contrast medium may stimulate release of catecholamines and induce a hypertensive crisis.[40,41] Although no such complications with ionic contrast media have been reported in dogs with pheochromocytoma, non-ionic contrast media are preferred because they do not exert such an effect on catecholamines. Alternatively, MRI scanning can be performed without any IV contrast agents. The sensitivity and specificity of CT and MRI scanning of pheochromocytomas are comparable in humans,[42] but there have as yet been no reports of MRI scanning results of pheochromocytomas in dogs.

Nuclear Imaging

The primary indication for nuclear imaging in people is to detect any extension of pheochromocytoma not identified by anatomic imaging (CT or MRI scan), such as bilateral or multiple tumors or metastatases.[31] The procedure of choice is scintigraphy using ^{123}I-MIBG (metaiodobenzylguanidine), a radiopharmaceutical which competes with norepinephrine for uptake and storage in neurosecretory granules of catecholamine cells, thereby revealing functional medullary tissue. Its use in dogs has been reported.[43] Positron emission tomography (PET) with ^{18}F-MIBG (fluorobenzylguanidine) is reserved for rapidly growing, dedifferentiated tumors in which ^{123}I-MIBG uptake is negative. There is little experience with functional imaging of pheochromocytoma in dogs.[44]

Percutaneous Fine-Needle Aspiration Biopsy

Use of cytology is straightforward in discriminating primary cortical adrenal masses from those of medullary origin.[45] While large case studies would be needed to confirm the reliability of this approach, the question remains whether the benefits of this procedure outweigh its risks. Adrenal biopsy can, potentially, have fatal complications associated with catecholamine release; hence, fine-needle aspiration biopsy is suggested in people only after pheochromocytoma has been ruled out.[46,47] Although published reports in the veterinary literature have described no complications, their numbers are small. Concerns about the risks associated with this procedure remain. Given that the cytological findings usually do not change management strategies and cannot discriminate between benign and malignant primary adrenal tumors, this approach remains controversial.

The Incidentally Discovered Adrenal Mass

The prevalence of a pheochromocytoma in dogs who have had an adrenal mass identified serendipitously on an imaging study is unknown (see ch. 306, 308, and 310). Since dogs with a pheochromocytoma can have any of a plethora of clinical signs and can be easily missed, testing for a pheochromocytoma is recommended for a dog with an incidentally discovered adrenal mass. This is emphasized when the imaging phenotype of heterogeneity, calcification, irregular borders, local invasion, and/or areas of necrosis are suspected. If a diagnosis of pheochromocytoma cannot be made, but there is strong suspicion of malignancy on imaging, endocrine testing for cortisol and aldosterone excess should be performed before adrenalectomy. Here, the purpose of testing is to anticipate proper postoperative hormonal supplementation. Confirming malignancy is difficult even on histopathology. Therefore, imaging can only provide a suspicion. In clinical situations, when there is lack of structural changes in the adrenal mass, monitoring mass size, at 3- to 6-month intervals, is recommended. Although no size cut-off has been identified that can confirm or exclude malignancy, an increase in size of adrenal masses, if corroborated by other imaging and/or clinical features, is an indication for adrenalectomy.

Biochemical Testing

Overview

Biochemical demonstration of excessive production of catecholamines is essential for the diagnosis of pheochromocytoma.[31,48] Biochemical evaluations typically include measurement of plasma and urinary catecholamines and their metabolites, MN and NMN, the so-called metanephrines.[3] The principle of measuring metanephrines is based on the intramedullary metabolism of catecholamines. The production of metanephrines in tumor cells is autonomous and continuous. Metanephrine concentrations more accurately reflect tumor mass than catecholamine concentrations, which are secreted episodically.[13] In humans,

measurement of urinary-fractionated metanephrines or plasma-free metanephrines provides better diagnostic sensitivity than do urinary or plasma measurements of catecholamines (epinephrine and norepinephrine) and other catecholamine metabolites.[3,48]

Urinary Catecholamines

Measurement of urinary catecholamines in dogs should be performed on a single voided sample, with concentrations expressed as a ratio to the creatinine concentration in that same sample.[32,49] The urinary NMN-to-creatinine ratio has a higher sensitivity than the MN-, epinephrine-, or norepinephrine-to-creatinine ratios.[49] While urinary epinephrine- and norepinephrine-to-creatinine ratios overlapped to some degree between healthy dogs and those with pheochromocytoma, urinary NMN was consistently higher in those with pheochromocytoma. This might indicate that most pheochromocytomas produce norepinephrine, which is metabolized to NMN and continuously released into the circulation, while norepinephrine is secreted only paroxysmally.[31,50] Corresponding to urinary measurements of NMN, measurement of plasma free NMN was superior to measurement of free MN in the diagnosis of pheochromocytoma.[51,52] There is no consensus on plasma versus urine testing; however, according to the latest studies, the urinary NMN-to-creatinine ratio has been most reliable.[52] In addition to assay accessibility and personal experience, the availability of reference ranges may influence whether one uses plasma or urine for these tests. For example, plasma-free NMN and MN are much higher in healthy dogs than in humans, and the importance of species-specific reference ranges should not be underestimated.

Interfering Drugs and Conditions

An important aspect of the biochemical diagnosis of pheochromocytoma is the interference by some drugs with measurements of catecholamine and their metabolites.[17] Phenoxybenzamines increase norepinephrine and NMN concentrations in people. Testing in dogs with suspected pheochromocytoma should be completed before any treatment. Endogenous and exogenous glucocorticoids have physiological interactions with catecholamines and increase their production.[13] In addition, there are similarities in the clinical features of pheochromocytoma and hyperadrenocorticism, making their differentiation even more challenging. The discrimination between the two groups was again superior for NMN, but there was some overlapping of NMN values in both plasma and urine between the groups. In people, a cut-off value 4 times the upper limit of normal is recommended to distinguish true-positive from false-positive results in patients with hypercortisolism, and a similar rule has been proposed for dogs.[49] This merits further study.

Serum Inhibin

Measuring serum inhibin concentrations can be helpful. Inhibin should be undetectable in dogs with pheochromocytoma, but not in those with hyperadrenocorticism.[53] This assay is not applicable in sexually intact dogs because serum gonadal and adrenocortical inhibin cannot be distinguished.

Treatment

Background

Adrenalectomy is the optimal treatment for a dog with pheochromocytoma.[15,54] Removal of the adrenal tumor will reverse the clinical signs and symptoms associated with catecholamine release and avoid the complications of uncontrolled growth of the tumor. Complications occurring during and after surgery are catecholamine-induced effects, which are serious and potentially life-threatening. Prerequisites for success are preoperative medical treatment, an experienced anesthetist, and intensive postoperative care.[1] If the tumor is inoperable or surgery is prevented by concurrent disorders or for other reasons, medical treatment is indicated to block alpha-adrenergic response to circulating catecholamines.[29] Medical treatment does not appear to alter secretion or growth of pheochromocytomas.

Preoperative Management

The aim of medical treatment is to prevent catecholamine-induced complications: hypertensive crisis, cardiac arrhythmias, pulmonary edema, and cardiac ischemia. Phenoxybenzamine is an alpha-adrenergic receptor antagonist that irreversibly binds to $alpha_1$- and $alpha_2$-adrenergic receptors and blocks the alpha-adrenergic

response to circulating epinephrine and norepinephrine.[55] Since phenoxybenzamine has a long duration of action, surges of circulating catecholamines cannot override inhibition. In dogs pretreated with phenoxybenzamine, the mortality rate after adrenalectomy was significantly lower than in untreated dogs.[29] The current recommendation is to start with a dosage of 0.25 mg/kg PO q 12 h and to increase it stepwise every few days until the final dosage of 1 mg/kg is reached. During this period, the dog should be monitored for clinical signs of hypotension (lethargy, weakness, or syncope) or other adverse effects (vomiting, tachycardia) and the dosage adjusted, if needed.[15] Pretreatment with phenoxybenzamine should be initiated at least 2 weeks prior to adrenalectomy. However, the optimal dosage and duration of treatment have not yet been established.

In patients with tachyarrhythmia, blocking of beta-adrenoreceptors should be added to alpha-blockade (e.g., atenolol, 0.2 to 1 mg/kg PO q 12-24 h). This addition, however, should never be initiated before the blockade of alpha-adrenoreceptors, since loss of beta-adrenoreceptors-mediated vasodilatation leaves alpha-adrenoreceptor stimulation unopposed, which could result in hypertensive crises.

Surgery

Adrenalectomy should only be undertaken by an experienced surgeon in adequate facilities. Close communication between the surgeon and the anesthetist is essential, because manipulation of the tumor can cause a surge in catecholamine release, leading to hypertension, tachycardia, and arrhythmias. The anesthetist should be able to anticipate these critical stages by deepening the anesthesia in advance. If this is not sufficient, a short-acting alpha-adrenergic antagonist can be administered to combat hypertension. An ultra-short-acting $beta_1$ antagonist may be added if tachycardia persists.[15] Laparoscopic adrenalectomy has gained popularity. Observational studies have shown more rapid recovery, shorter hospitalization, fewer wound complications, and shorter surgical time compared to laparotomy.[56,57] The size of the adrenal tumor and the extent of vascular invasion are the most important criteria in choosing between laparoscopy and open laparotomy. Masses up to 5 cm in diameter and without invasion of the caudal vena cava are amenable to laparoscopy, while open adrenalectomy is indicated if there is invasion of the vena cava. Removal of tumor thrombi and thrombectomy are possible and not associated with higher morbidity and mortality with an appropriate team approach.[34,58-60] However, an extensive tumor thrombus is associated with higher postoperative mortality.[29]

Postoperatively, patients should be kept under close surveillance for at least 48 hours. Complications include cardiac arrhythmias (see ch. 141 and 248), respiratory distress (see ch. 139), hemorrhage (see ch. 135 and 197), and hypertension (see ch. 157 and 158). Hypotension (see ch. 159) is also possible, due to the abrupt fall in circulating catecholamines after tumor removal in the continuing presence of alpha-adrenoreceptor blockade (by phenoxybenzamine).

Medical Therapy

In dogs with an unresectable pheochromocytoma, metastasis, serious concurrent disease, and/or owner constraints, medical treatment with phenoxybenzamine is used.[15] The preoperative management protocol is applied and if there are tachyarrhythmias, a selective $beta_1$ antagonist can be added after an alpha-adrenergic blocker has been administered for at least a few days. There are as yet insufficient data for an appraisal of the survival of dogs receiving medical treatment alone.

Histopathology

The definitive diagnosis of pheochromocytoma rests upon histological examination. Pheochromocytomas consist of neoplastic cells arranged in lobules supported by a fine fibrovascular stroma. The neoplastic cells are round to polyhedral with eosinophilic to basophilic cytoplasm and hyperchromatic nuclei with variable mitotic activity.[7,30] There may be compression of the adrenal cortical zonal architecture, as well as necrosis and hemorrhage, especially in large tumors. Differentiation between cortical and medullary adrenal tumor is made by immunohistochemistry. Neuroendocrine markers are stained, chromogranin A being the most commonly used.[61] It is normally present in chromatin granules in cells of the medulla but not in adrenal cortical cells, which renders it an ideal marker. Differentiation between benign and malignant pheochromocytoma based on histopathology is unreliable. The presence of metastasis is the only reliable

indicator of malignancy,[62] while the significance of capsular and vascular invasion with tumor thrombi remains controversial.[62,63]

Prognosis

The size of the tumor, its endocrine activity, vascular invasion, and the presence of metastasis may affect the prognosis. With regard to surgical removal, both pretreatment with the alpha$_2$-adrenergic blocker phenoxybenzamine and the extent of vascular invasion play a role. Additional prognostic factors are age, general well-being, and the presence of concurrent disease.

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SECTION XXII

Reproductive Diseases

OUTLINE

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Chapter 313 Effect of Spay or Castration on Long-Term Health of Dogs and Cats
Chapter 314 Clinical Feline Reproduction
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CHAPTER 312

Reproductive Endocrinology and Breeding Husbandry of the Bitch

Stefano Romagnoli, Cheryl Lopate

Client Information Sheets:
Manipulation of the Estrous Cycle
Estrous Cycle and Estrous Cycle Abnormalities
How to Manage an Accidental Breeding

The Reproductive Cycle

The canine reproductive cycle has historically been divided into 4 stages: proestrus (attractive to males but unwilling to breed), estrus (receptive to mating), diestrus (luteal/progestational phase that follows breeding) and anestrus (reproductive quiescence). Such classification was proposed by Heape in 1900 and is based on reproductive behavior and related clinical changes of external genitalia of the bitch without taking into account the fine interplay of reproductive hormones.[1] Despite the abundance of diagnostic tools now available, Heape's classification remains valid and continues to be used in scientific as well as clinical settings. The term *estrus* may be understood by some, but breeders and dog owners commonly employ the term *heat* in reference to the entire follicular phase (proestrus + estrus). The term *standing heat* is used to denote the period of breeding (estrus). The term *diestrus* does not fully encompass the canine luteal phase, which begins early in estrus due to pre-ovulatory luteinization. However, diestrus is regarded as an appropriate term to indicate the period during which the canine corpora lutea (CLs) are actively secreting progesterone (P4) and the bitch is no longer willing to breed. The term *metestrus* in food animals refers to the entire time a female is under the influence of CLs and includes the early period of developing (but immature) CLs with little if any serum P4 production.

Seasonality of Estrous Cycles and Interestrous Intervals

The canine is generally regarded as a mono-estrus species (only one estrus is completed during each reproductive cycle) and non-seasonal (the occurrence of estrus is not influenced by season of the year). Family pets housed indoors tend to come in season in any month of the year[2] although cycling activity estimates based on litter registration data of the American Kennel Club show peaks in late winter and spring.[3] Such spring peaks of cycling activity have been observed in Beagle bitches housed outdoors in Northern Europe[2] and are anecdotally reported elsewhere in dogs living in temperate climates. Seasonality of canine reproduction has been an object of debate based on the seasonality (one cycle yearly) of wolves, dingoes and Basenjis.[4,5] Although most domestic dog breeds appear to have lost their photo-responsiveness, an influence of photoperiod on the hypothalamic-pituitary function of the bitch is demonstrated by an annual rhythm to prolactin (PRL) secretion in mixed-breed dogs housed constantly outdoors.[6] Genetic selection for performance and external appearance may have diluted effect of season which may remain in individual females or in some bloodlines within specific breeds. From a practical standpoint, spring should always be considered as a time of the year in which the probability of any bitch coming in season may be highest.

The interval between the beginning of consecutive canine estrous cycles (interestrous period) varies a great deal within and among breeds. The vast majority of pure- and mixed-bred dogs cycle every 5½ to 6½ months. There are a few notable exceptions: the Basenji and Tibetan Mastiff cycle once yearly and some Collie bitches cycle every 9 to 11 months. Some lines of German Shepherd, Doberman, Rottweiler, Labrador

Retriever, Basset Hound and Cocker Spaniel cycle 3 times yearly.[7-14] Variations in interestrous intervals are likely due to genetic differences in anestrus duration.[7] In general, there seems to be a negative correlation between body size and cycle frequency. Large-size bitches have fewer estrous cycles yearly when compared to the smaller breeds. Dogs >6 years of age tend to have progressively lengthening interestrous intervals. Whether or not gestation, followed by whelping and lactation, increases duration of interestrus is debatable and onset of proestrus in individuals is unpredictable.[2,9-11]

Proestrus

Definition, Estrogen-Induced Changes and Signs *(Table 312-1)*

The term *proestrus* describes the transition phase between reproductive quiescence and the onset of breeding behavior. The onset of proestrus is usually signaled by the appearance of a bloody vaginal discharge, lasting an average of 9 days, but duration can vary from a few days to almost 4 weeks.[11,12] Proestrus begins with development of ovarian follicles and secretion of their primary product: 17-beta-estradiol (E2), which increases progressively throughout proestrus to peak at concentrations of 50-120 pg/mL.[13,14] The increasing serum E2 concentrations increase blood flow to the reproductive system, affecting the endometrium (by causing growth and branching of endometrial glands with consequent increased thickness of the entire endometrium), the cervix (by causing cervical relaxation and secretion of mucus), the vagina (by causing growth of mucosal folds, increased elasticity and mucus secretion) and the vulva (by causing increased thickness of the mucosa, swelling and turgidity), but does not appear to involve mammary tissue.[14,15] Proestrual changes in blood flow and hormonal status cause vaginal and anal sac secretions to release potent pheromones to attract males.[16,17] Breeding is not allowed by the bitch in proestrus. She may join activities normally preceding mating but often powerfully refuses any further approach by turning on or growling at male dogs if she is during early or mid-proestrus. By late proestrus, the bitch may reject breeding by simply sitting or lying down.

TABLE 312-1

Relationship between Cytologic (1st Day of Cytologic Diestrus), Behavioral (End of Male Acceptance) and Endocrine Parameters vs. the Surge in Luteinizing Hormone (LH), Ovulation, Cervical Closure and Onset of Diestrus in the Bitch

	1ST DAY OF CYTOLOGIC DIESTRUS (DAYS)	END OF MALE ACCEPTANCE (DAYS)	SERUM PROGESTERONE CONCENTRATION (ng/mL)
LH surge	−7 to −10	+6 to +19	2.0
Ovulation	−5 to −8	+3 to +10	4.0-10.0
Cervical closure	−2 to 0	−1 to +3	≈25.0 or higher
1st day of cytologic diestrus		−2 to + 2	≧19.0-25.0

Serum progesterone (P4) is the more reliable way of staging the cycle, but the information from a single sample may not allow precise staging in specific cases unless vaginal cytology and/or behavior are assessed jointly. Vaginal cytology alone is more reliable than behavior alone, but behavioral assessment may become important when evaluating serum P4 data if a vaginal smear could not be collected.

Vaginal Discharge and Endoscopy

The bloody vaginal discharge observed in proestrus is the result of mostly red but also white blood cell diapedesis through intact endometrial capillaries into the uterine lumen, then flowing through the cervix due to myometrial contractions, and finally mixing with cervico-vaginal fluids. Pulsatility of canine E2 secretion makes serum assays less useful than vaginal cytology. Vaginal cytology is an excellent reflection of 24-hour E2 secretion by maturing follicles (see ch. 44 and 119). Vaginal smears from bitches in early proestrus contain predominantly red blood cells, a few white blood cells, and mostly non-keratinized (parabasal, small and large intermediate) vaginal epithelial cells. In most bitches, the number of red blood cells decreases during the progression from proestrus to estrus (making the vulvar discharge progressively less bloody in appearance)

while the ratio between keratinized and non-keratinized cells progressively increases, reaching values of 30-50% in late proestrus. E2 causes the vaginal mucosa to become deep pink and edematous which, on vaginoscopy, during proestrus and early estrus, appears as round and swollen vaginal folds with some blood-tinged fluid between (see ch. 119).[18] The canine cervix also is swollen and palpable abdominally from late proestrus onward. As the cervix is not normally palpable during anestrus, its palpation can be an indirect sign that the bitch is in heat. Also the uterus becomes enlarged and more easily identifiable on abdominal palpation.

Hormone Profile *(see Table 312-1)*

Following the initial estrogen increase responsible for clinical signs of proestrus, serum E2 concentrations continue to rise, peaking in late proestrus. This peak and the following decrease marks the end of proestrus and likely contributes to stimulating the LH surge, onset of estrus and ovulation. Although E2 is the most important hormone of canine proestrus for all its clinically relevant effects on behavior and the reproductive system, increasing concentrations of other reproductive hormones also play roles. Serum progesterone (P4) increases >0.5 ng/mL, to about 1.0 ng/mL, during the final 24-48 hours of proestrus. This indicates that development of luteal tissue within the wall of maturing canine follicles has begun. This early rise of serum P4, called *pre-ovulatory luteinization,* is a peculiarity of the canine and is also of value in staging ovulation.[19,20]

In late anestrus, serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) concentrations increase above basal values to values of about 1-6 and 150-300 ng/mL, respectively (Figures 312-1 and 312-2). E2 production from cohorts of growing tertiary follicles stimulates the pituitary without causing enough LH-FSH release to cause pre-ovulatory luteinization. LH and FSH values then decrease as proestrus progresses, due to E2 and inhibin negative feedback, and remain low until the end of proestrus. The continuing follicular growth despite decreases in LH-FSH values in early proestrus likely indicates that follicular development in dogs is autonomous.[21] Androgen concentrations (testosterone and androstenedione) increase in late proestrus, reaching levels at the time of the LH peak comparable (10-25 ng/mL) to those of adult intact males.[22] No correlation has been made between such androgen values (which may reflect intermediate conversion steps between progesterone and estrogen) and expression of estrous behavior in the bitch, despite the occasional observation of male-like or mounting behavior in some bitches.

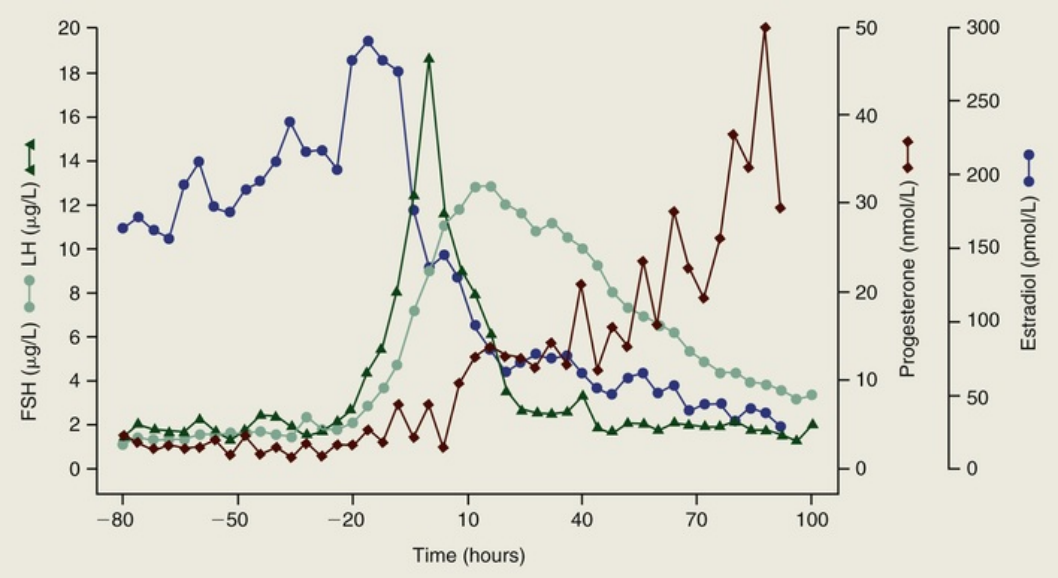

FIGURE 312-1 Diagram of the hormonal profile typical of a dog progressing from late proestrus into estrus. (Modified from Schaefers-Okkens AC: The ovaries. In Rijnberk A, editor: *Clinical endocrinology of dogs and cats,* Dordrecht, Netherlands, 1996, Kluwer Academic.)

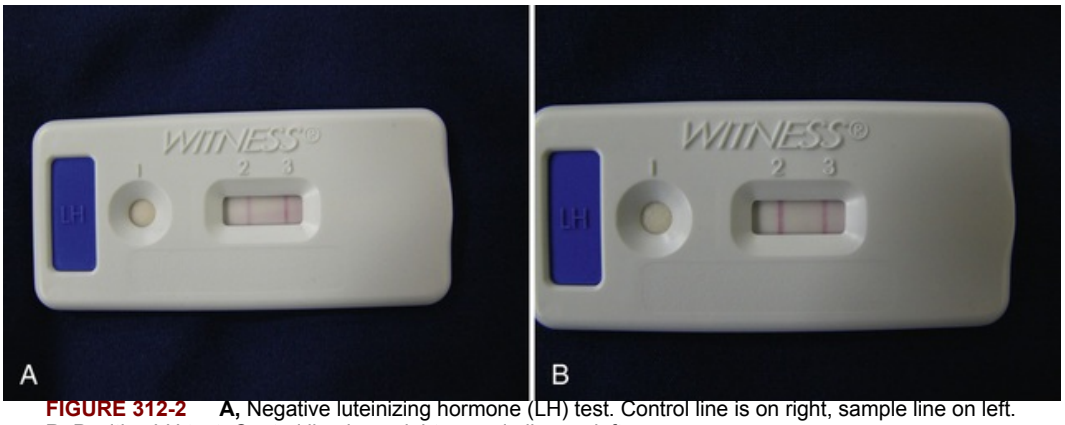

FIGURE 312-2 **A,** Negative luteinizing hormone (LH) test. Control line is on right, sample line on left. **B,** Positive LH test. Control line is on right, sample line on left.

Estrus

Definition and Signs

Estrus is the stage in which both breeding and ovulation occur (Figure 312-3). Clinical signs of proestrus remain evident during estrus although they tend to change slightly: the vulva is still larger than normal but becomes softer while the vulvar discharge becomes progressively less bloody and more straw-colored. Both the cervix and uterus are palpable abdominally. Behavioral signs of receptivity increase in intensity during estrus, as bitches in estrus accept the male's interest, are amenable to play and to be mounted. The most obvious and consistent signs of the follicular phase (proestrus + estrus) are "winking" (upward tipping of the vulva when the dorsal aspect of the vulvar skin is touched), stiffening of the hind limbs (when the skin on either side of the vulva is touched), and "flagging" (vertical or contralateral deviation of the tail when the vulvar skin is touched on either side). These signs are almost always fully displayed during estrus and may be observed near the end of proestrus in some. The onset of "flagging" signals the beginning of estrus, willingness to breed, and is coincidental with the LH peak on the first day of estrus. Occasionally, bitches may remain unreceptive to mating throughout the entire estrus despite no other abnormal finding. In Beagle bitches, cervical closure occurred 5 +/− 1 days after ovulation or as early as 1 day prior to the end of estrus, with serum P4 concentrations averaging 25 +/− 4 ng/mL.[23]

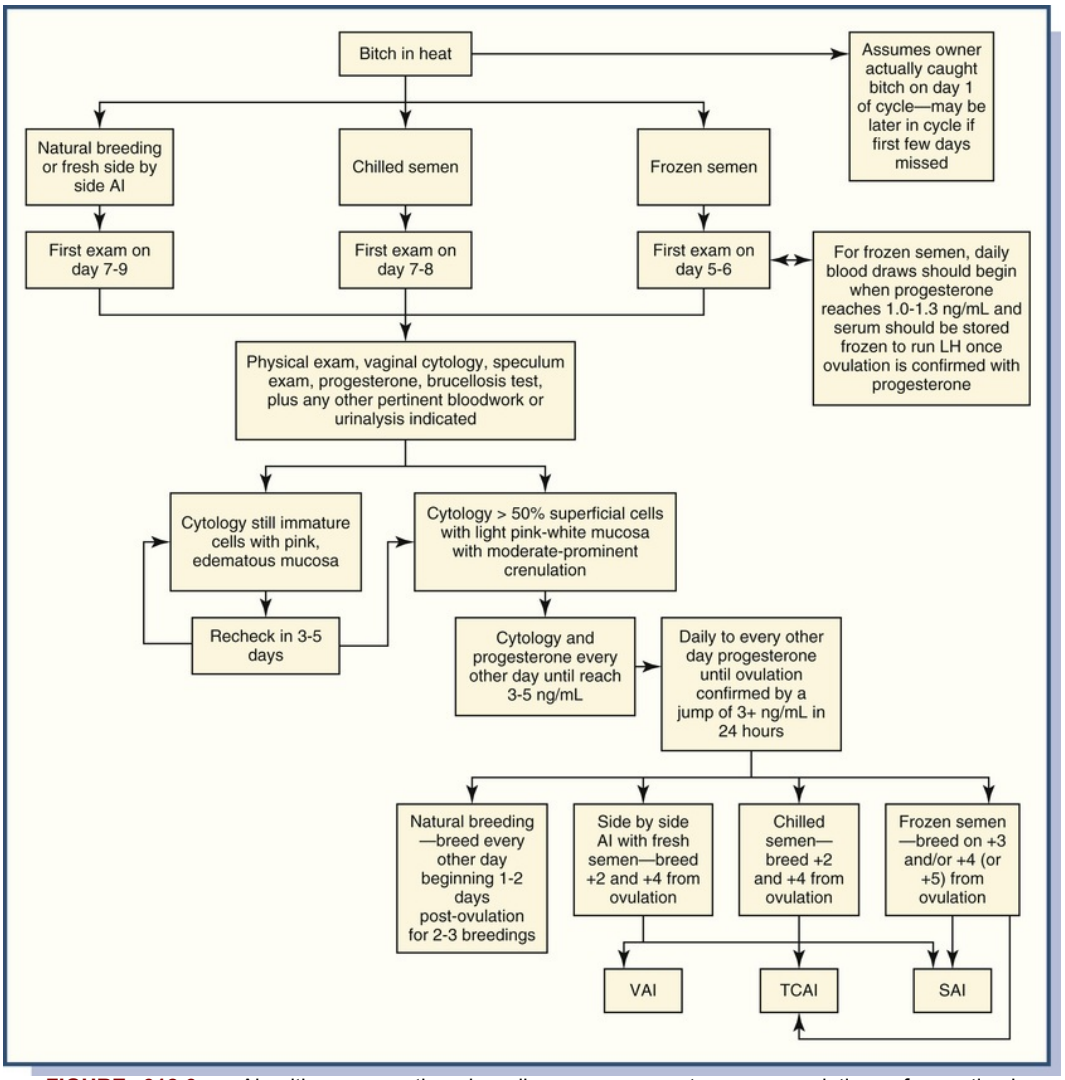

FIGURE 312-3 Algorithm presenting breeding management recommendations for optimal conception rates in healthy bitches. *AI,* Artificial insemination; *SAI,* surgical artificial insemination; *TCAI,* trans-cervical artificial insemination; *VAI,* vaginal artificial insemination.

The average duration (9 days) and range (4-24 days) of canine estrus are based on the number of days that bitches are willing to breed per cycle.[9,24] There is remarkable variation in breeding behavioral patterns in dogs. Although rare, an estrous bitch may refuse to be bred by a specific male because she is dominant or because of apparent dislike which may lead the owner to think that a bitch is not yet or no longer in estrus. Thus, the duration of estrus as judged by clinical observation may not be entirely correct and can explain discrepancies between vaginal cytology and behavior. Individual bitches may begin breeding from 2-3 days before to as long as 4-5 days after reaching >50% keratinization of their vaginal smear.[25,26]

Vaginal Cytology and Endoscopy *(see Table 312-1)*

A pattern of >50% vaginal epithelial cell keratinization (nucleated and anuclear superficial cells) reflects onset of sexual receptivity in most bitches. This percent of superficial cells present on vaginal cytology is not sensitive nor specific, as it may appear for the first time as early as 6 days before to as late as 4 days after a bitch is willing to breed.[27] "Full estrus" is diagnosed when >70% of vaginal epithelial cells appear keratinized (see ch. 44 and 119).[28] The effect of decreasing E2 concentrations can be observed in the quick resorption of edema from the vaginal mucosa. On endoscopy, vaginal mucosal folds appear dry, white, and wrinkled. Such a pattern is described as "crenulation" and is indirect proof of decreasing E2.[18]

Hormonal Profile *(see Table 312-1)*

The three key hormonal patterns of estrus are the LH peak, decreasing concentrations of E2 (from the peak reached at the end of proestrus) and rising concentrations of P4. Coincidental with or within a few hours following E2 reaching its peak proestrus concentrations, pituitary LH secretion increases rapidly from basal concentrations to values of 10-22 ng/mL and maintained at that serum level for about 24 hours. Duration of the LH surge can be as brief as 18 to as long as 96 hours.[20,26,29-32] Ovulation occurs about 2 days after the onset of the LH surge and continues within a narrow standard deviation of this date.[12] The fine balance and synergism of E2, P4 and LH play major roles in breeding behavior. E2 secreted during proestrus "primes the system" and P4 secreted at ovulation "activates the system." Full receptivity appears to be triggered by the coincidental decrease of E2 and increase in P4.[33,34] The decrease in E2 probably plays the major role as this is what actually causes the LH surge, while the P4 increase seems to enhance and synchronize the bitch's estrous behavior.[35]

Serum P4 concentrations rise from values <1.0 ng/mL at the end of proestrus to around 2.0 ng/mL on the day of the LH peak, subsequently reaching values of 4-10 ng/mL 2 days later when ovulation is taking place and primary oocytes are being released into the oviducts where they undergo their final maturation. The initial rise of serum P4 >2.0 ng/mL is generally coincident with the LH surge, although the surge may occur up to 20 hours after in a few bitches.[32] During the ovulatory process, serum P4 concentrations rise quickly with daily increases of 3-10 ng/mL or more. The magnitude of increase is due to the number of follicles ovulated, follicular size, the amount of developing luteal tissue, and how much P4 each CL produces. Increases <3 ng/mL/day should be a reason for concern as they may suggest ovulation failure and additional samples should be obtained over the next 1-2 days. Following completion of the ovulatory process and final CL maturation, serum P4 concentrations continue to increase during the first 2 weeks following estrus to values in the range of 15-60 or more ng/mL.

Use of Serum P4 Assay Results for Ovulation Timing *(Table 312-2; see Figure 312-3)*

Serum P4 assay results can help discriminate bitches in early estrus (who might not achieve the best conception rate, or might even not conceive if bred by a male of low fertility) from those who are ovulating and most fertile. Assay results can confirm ovulation and stage the estrous cycle reliably from 2 days before to 2 days after ovulation, a time when P4 concentrations rise from 1-2 ng/mL to >10-12 ng/mL. However, assaying a single serum P4 sample collected at or after onset of the LH surge is less informative regarding the number of days that have elapsed since the beginning of ovulation due to individual, breed, or age-related variabilities. Serum P4 results are comparable, regardless of radioimmunoassay (RIA), chemiluminescent immunoassay (CLIA) or enzyme-linked fluorescent assay (ELFA).[26,36,37] If a human assay is used, care should be taken to calibrate it for canine serum. Species-specific differences in degree of hormonal binding to carrier proteins in serum may alter results as much as 20%. Assays should be validated on an annual/biannual basis or every 1000-3000 samples run by commercial veterinary laboratories using hormonal kits marketed for human use. A conversion factor is generally necessary when using a human ELFA system.[37]

TABLE 312-2

Progesterone Concentrations and Associated Follicular Events

ENDOCRINE/FOLLICULAR ACTIVITY	PROGESTERONE CONCENTRATION (RANGE ng/mL)
Baseline	<0.5
Early follicular development	0.5-1.3
LH surge	1.3-1.9
Ovulation begins	4-8 average (range 4-10)
Post-ovulation	>10 ng/mL

Combining Behavior Observation, Vaginal Cytology and Serum Hormone Analysis

Assay of serum E2 is not used because of its pulsatility. However, vaginal cytology remains an excellent biologic assay for E2. Vaginal cytology data coupled with serum P4 concentrations and behavioral assessment are instrumental in staging the estrous cycle and identifying ovulation. However, each of these tools, alone, is

far less reliable. Estrous behavior, vaginal cytology and serum P4 assay remain the 3 fundamental pillars for breeding management (see Management of Breeding section) as well as for determining length of estrus and ruling in/out ovarian conditions (ovarian cysts/neoplasia). Additional diagnostic tests (such as LH assay, ovarian ultrasonography, vaginoscopy) can be helpful in improving the accuracy of estrus and ovulation staging if one uses them consistently, developing specific expertise. Impedometry and arborization of cervical mucus are not accurate in ovulation timing (see Table 312-1).

Diestrus

Definition and Signs

Diestrus is defined as the luteal or progestational phase of the cycle. Diestrus normally follows ovulation and lasts precisely 8 weeks in pregnant vs. 6-10 weeks in non-pregnant bitches. The vulva, which becomes less edematous and swollen during the last few days of estrus, continues to shrink through the first week or so of diestrus. Little to no bloody vulvar discharge is present and male dogs are not attracted. The vaginal mucosa appears flat, thin, dry and blotchy pink to red, with capillaries easily visible on vaginoscopy (see ch. 119). The cervix is palpable for the first few days of diestrus, while the uterus remains palpable and may increase in size under the influence of P4.

Vaginal Cytology, Behavior

Clinically, the first day of diestrus (D1) is defined as the first day a bitch refuses to breed or as the day on which a sudden change in vaginal cytology is seen: keratinized vaginal epithelial cells decrease from 70-100% to <30% on cytology, replaced by large and small intermediate and parabasal epithelial cells. White blood cells, absent from cytology smears after the first few days of proestrus and throughout estrus, reappear (see ch. 119). These changes usually occur within 24 hours of the onset of diestrus although either can first be observed within a range of 4 days; willingness to breed may stop 1-2 days prior to or persist 1-2 days after onset of "cytologic diestrus." Changes in vaginal cytology may occur 5-8 days following ovulation and 7-10 days after the LH surge (see Table 312-1).

Observing D1 on a vaginal smear indicates that estrus has ended and that it probably is too late to achieve optimal conception rates (normal litter size) using natural breeding. However, fertility rates of 5 to 40% have been reported in Beagles when natural breeding occurred between D1 and D3. Although litter size is likely to be small with natural breeding in early diestrus, normal litter size can still be achieved using intrauterine semen deposition during this same time frame.[23] Clinically, D1 can be considered the end of the first week of pregnancy: therefore, in pregnant bitches the interval between D1 and parturition is approximately 57+2 days.[38]

Reproductive behavior is not as reliable as vaginal cytology in determining D1. P4 concentration should not be of use, as P4 progressively increases throughout estrus and this trend continues for the first few weeks of diestrus. Nevertheless, behavioral assessment should never be disregarded and particularly so when discussing progression from estrus into diestrus. Breeders should always be encouraged to identify the first day a bitch refused to breed, as this information is used in determining duration of estrus and may help in timing ovulation. However, it is wise to ask if someone observed the refusal to breed or was this assumed based on other criteria. Breeders should be instructed and encouraged to establish dates of onset and cessation of male acceptance by watching the behavior of their bitches when brought to an intact male on a daily basis.

Hormonal Profile

Serum P4 concentrations continue to increase, reaching peak values of 15-90 ng/mL about 2 to 4 weeks into the luteal phase. Subsequently, serum P4 starts a gradual decline in both pregnant and non-pregnant bitches. The decrease in P4 usually does not drop to <5.0 ng/mL until the last week in pregnant bitches and it never drops below 2.0 ng/mL until 24-36 hours pre-partum. Luteotrophic support for canine CLs appears to originate from the pituitary, with PRL being regarded as the most important factor supporting canine ovarian P4 production. LH has a stimulatory rather than permissive role.[39-41] Canine PRL starts to be secreted during the 4th week of the luteal phase as soon as serum P4 concentration begins to decline.[42] The actions of canine PRL include supports of ovarian P4 synthesis and mammary tissue development regardless of pregnancy, but of greater magnitude in pregnant bitches. Serum PRL concentrations are significantly higher in pregnant vs. non-pregnant bitches after about day 35 post-LH peak. Administration of PRL to bitches during the luteal phase causes an increase in P4 secretion.[43-45] The CLs of pregnant bitches produce more P4 than those of the

non-pregnant. Since P4 metabolism is higher in pregnant bitches, differences between the pregnant and non-pregnant are not always obvious.[14,20,29,46] The increase in ovarian P4 production observed in pregnant females following implantation may be mediated by pregnancy-specific relaxin secreted from the ovaries during diestrus. Canine placental syncytiotrophoblasts, during pregnancy, contribute to the onset of PRL secretion.[47,48] Relaxin acts by inhibiting myometrial contractility and promotes modification of the cervix at the end of pregnancy in preparation for parturition.[49] The roles of estradiol, testosterone and androstenedione produced during the luteal phase by CLs[22,50-52] are not clear. Their concentrations are likely the result of intermediate steps in the synthesis of P4, and their measurement is currently considered of little, if any clinical use.

Progesterone and Pregnancy Monitoring *(see Tables 312-1 and 312-2)*

The magnitude of P4 concentration reached during the first 3 weeks following D1 may depend on breed, age, health, degree of environmental and social stress, and perhaps level of inbreeding. There is a lack of homogenous data on canine serum P4 concentration for different breeds and age classes throughout pregnancy, preventing provision of reliable guidelines on "normal" values of serum P4 during the canine luteal phase or "minimum thresholds" of serum P4 concentrations below which intervention (e.g., supporting a pregnancy with exogenous P4) may be justified. Anecdotally, the minimum P4 concentration for maintaining pregnancy during weeks 3 through 7 is likely >15 ng/mL. P4 concentrations <15 ng/mL in a high-risk pregnancy or in a bitch with a history of recurrent pregnancy failure may indicate need for exogenous P4.[53]

At the end of the luteal phase, cessation of ovarian P4 production occurs abruptly (within 24-36 hours) in pregnant and gradually (over 1-2 weeks) in non-pregnant bitches.[11,39,42] The luteolytic effect of endogenous prostaglandin F2-alpha (PGF2-alpha) plays a major role in terminating luteal activity in pregnant bitches. There is no increase in PGF2-alpha secretion in non-pregnant bitches so CLs function longer and are terminated by an immune-mediated process driven by leukocyte-derived cytokines (interleukin [IL]-8, IL-10, IL-12, tumor necrosis factor alpha and transforming growth factor-beta-1) which are increasingly present within the canine luteal tissue throughout diestrus.[50,54] In pregnant bitches, the abrupt decline in serum P4 occurring at the end of the luteal phase triggers a decrease in body temperature and an increase in serum PRL. A decrease of about 1.0-2.0 °C in rectal temperature, after the decline in serum P4, is often observed in whelping bitches or following a PGF2-alpha or aglepristone treatment, while it is not reported in non-pregnant bitches at the end of the luteal phase due to their gradual fall of serum P4.[55]

Prolactin, Progesterone and Whelping

The increase in serum PRL concentration is immediate and strong prior to whelping as a consequence of the sudden pre-partum luteolysis while the increase is more subtle in non-pregnant females, again due to the slower demise of their CLs.[56] Regardless of pregnancy, PRL secretion at the end of the luteal phase has little effect on CLs but does stimulate onset of lactation and maternal behavior. The strict interdependence between P4 and PRL in dogs has several practical implications: the use of antiprolactinic drugs (dopamine agonists or serotonin antagonists) at any time from mid-pregnancy onwards (when P4 concentrations are still high) will cause luteolysis and abortion,[57] while any time P4 concentration drops (i.e., following a luteolytic or a progesterone receptor blocker treatment, ovariectomy in diestrus, withdrawal of a progestin treatment, etc.) there will be a rise in serum PRL followed by milk secretion and display of maternal behavior. Monitoring serum PRL concentrations is not commonly used, despite potential clinical applications in monitoring pregnancy or pseudopregnancy. Monitoring serum P4 concentrations, however, is a fundamental tool in canine reproduction to stage ovulation and for managing bitches with luteal insufficiency, prolonged gestation, dystocia or elective C-section.

Effects of Progesterone and Growth Hormone (GH)

A further clinically relevant implication of ovarian P4 production during diestrus is secretion of GH from the mammary glands,[58] a normal physiologic process. Under the influence of P4, mammary duct epithelial cells secrete GH increasing basal serum GH levels, and then negatively feeding back to suppress normal and pulsatile pituitary GH secretion.[59] Mammary GH promotes the normal proliferation of mammary glands through local autocrine/paracrine effects, prepares the endometrium for implantation by promoting (together with ovarian P4) hyperplasia of the uterine epithelium, and causes insulin resistance. This latter effect may

have evolved to avoid hypoglycemia when pregnant, since predators often have extended intervals between meals. Clearly, these GH effects in the bitch carry a potential risk for causing or exacerbating clinical conditions such as mammary and uterine disease as well as diabetes. Therefore, as appropriate, some bitches might benefit from careful monitoring during diestrus: clinical, hormonal, uterine ultrasonography, and particularly serum biochemistry in case of suspected diabetes mellitus.[60,61] There is also evidence that mammary GH concentrates in colostrum, thus stimulating gastric and intestinal development of suckling newborns.[62]

Pseudopregnancy

The most common effect of the concerted actions of P4 and GH is mammary development during the second half of the luteal phase followed by the onset of lactation (as soon as P4 drops and PRL peaks) occurring in both pregnant and non-pregnant bitches, albeit with much less intensity in the latter group. The occurrence of mammary development, lactation and display of maternal behavior in non-pregnant bitches is referred to as pseudopregnancy or pseudocyesis, a paraphysiologic condition. In wolves, pseudopregnancy in some is of benefit if a female dies or is otherwise unable to nurse her litter after parturition to allow another pack member to assume that role. Since PRL secretion normally occurs in non-pregnant as well as pregnant bitches, pseudopregnancy is considered a normal phenomenon. The condition undergoes spontaneous remission, but becomes obvious when hormone secretion is high causing persistent lactation and strong maternal behavior, two conditions which prompt the bitch to become nervous, adopt inanimate objects and be anorectic. When necessary, this condition can be treated with antiprolactinic drugs such as cabergoline (5 mcg/kg PO q 24 h), metergoline (0.5 mg/kg PO q 12 h) or bromocriptine (20-50 mcg/kg PO q 12 h).

Anestrus

Definitions, Signs

In bitches, diestrous and anestrous behaviors do not differ, with the exception of the first few days of cytologic diestrus, during which some bitches may still attract males and occasionally breed. Past those few days, the clinical, metabolic and behavioral transition from diestrus to anestrus is smooth and devoid of any relevant clinical signs. As in diestrus, the vulva is small, no vulvar discharge is present and male dogs are not attracted. On vaginoscopy, the vaginal mucosa is dry and thin, appears flat and pinkish-red to dark red and blotchy, with capillaries readily visible. As a consequence, anestrus cannot be differentiated from diestrus based on reproductive behavior. Anestrus varies from as short as 2 to as long as >9 months. Variations in the duration of anestrus account for the difference in interestrous intervals between individuals. While the P4 of diestrus is a potential source of clinical problems in bitches at risk for pyometra, mammary neoplasia or diabetes, anestrus is not characterized by such issues, as the ovaries do not secrete significant quantities of E2 or P4. Educating caregivers regarding these differences is important, since they should be aware of diestrus-associated diseases.

Hormone Profile

Anestrus is defined as the period beginning with serum P4 concentrations <1.0 ng/mL. A precise serum P4 concentration defined as basal is still a matter of study. Functioning luteal tissue is considered absent when P4 is <1.0 ng/mL. Bitches in anestrus have serum P4 concentrations <0.7 ng/mL, usually <0.3 to 0.5 ng/mL. Concentrations <0.3 ng/mL could be a requirement for stimulating onset of proestrus.[11] This low (and perhaps progressively decreasing) serum P4 concentration persists for 1 to 6 months in most healthy bitches, only to increase after pre-ovulatory luteinization occurs in late proestrus of the following cycle. During early to mid-anestrus, E2 concentrations are also low at 5-10 ng/mL.[30] Because of this low ovarian steroid secretion pattern, the first 1-2 months after the end of diestrus may be referred to as early or "deep" anestrus due to the poor sensitivity of canine ovaries to GnRH.

As anestrus progresses, there is an increase in the number and amplitude of hypothalamic GnRH pulses, paralleled by increased pituitary responsiveness and an increase in ovarian sensitivity to gonadotropins through development of FSH and LH receptors.[63] This is followed by episodes of E2 secretion which enhances hypothalamic estrogen receptors and establishes a positive feedback loop.[64,65] This interplay of hypothalamic-pituitary-ovarian events in late anestrus confirms earlier observations of occasional elevations of E2 levels to 25-50 ng/mL during the 2 months preceding the onset of proestrus.[25,30,66] Late anestrus increases in E2 concentrations are associated with a slight vaginal keratinization but not vulvar swelling or

serosanguineous vulvar discharge.[30] GnRH secretion followed by higher serum concentrations of FSH and LH are two key factors in the onset of proestrus, as supported with GnRH being given in pulses or via subcutaneous (SC) implant, or LH- or FSH-based products that can induce proestrus.[67]

Dopamine and Estrus Induction

Studies on the role of dopaminergic pathways on resumption of cyclicity in the bitch have involved 3 major brain circuits: the mesolimbic, mesocortical and nigrostriatal pathways which innervate the limbic system (memory, behavior), frontal cortex (cognitive control, emotional response) and striate nucleus (motor control), respectively. A 4th dopaminergic pathway is the tuberoinfundibular pathway, connecting hypothalamus with the pituitary, where it influences the secretion of hormones such as PRL. The observations that dopamine agonists lower serum PRL concentrations and shorten anestrus led to the conclusion that the two events were related: that lowering PRL was important for estrus induction in the bitch.[68] However, non-dopamine-agonist PRL-lowering drugs do not shorten anestrus when used at pharmacologic dosages and anestrus can be shortened using dopamine agonists at dosages too low to suppress PRL concentrations.[69,70] Activating the tuberoinfundibular neural pathway in the bitch by giving a dopamine agonist is followed by a resumption of basal serum FSH and LH concentrations which mimic the physiologic milieu occurring in late anestrus, followed by the onset of proestrus. Dopamine agonists such as bromocriptine (20 mcg/kg PO q 12 h) and cabergoline (5 mcg/kg/day PO or as low as 0.6 mcg/kg/day) shorten the duration of anestrus (thereby inducing estrus) in the bitch, with their effectiveness increasing as the bitch advances further into her mid or late anestrus.[70-72]

Uterus in Anestrus

Uterine involution requires desquamation of the endometrial lining followed by its complete regeneration. This is a fundamental prerequisite for maximizing chances of fertility on the following cycle. When parturition and fetal membrane detachment occur normally after parturition, endometrial repair starts immediately, but requires an estimated 143 to 155 days after the onset of estrus to be completed. In the non-parous bitch, this process is complete approximately 2 weeks earlier.[73]

Irregular Patterns of Ovarian Cyclicity

Importance of a Thorough History

Bitches may show irregular patterns in any cycle stage. Some owner concerns may be due to a lack of understanding what is considered "normal." Therefore, clinicians should always carefully review as much historical data as possible with the caregiver. One should verify date/s of onset of proestrus and male acceptance/refusal as well as timing and pattern of vulvar discharge. Any previous serum P4 profile can be quite valuable. Occurrence of behavioral or mammary signs of false pregnancy (indicating the ovulation took place 1-2 months previously) should be noted.

Prolonged Proestrus or Estrus

Failure to Ovulate

The duration of the canine follicular phase exhibits great variation. Both proestrus and estrus can last from a few to as many as 24 days.[9,11,12,24] Rarely, follicular phases lasting as long as 40 days have been reported and care should be taken to differentiate normal but unusual cycles from true abnormalities such as split heat or slow P4 rise. Normal ovulation is the result of a complex process that requires sufficient follicular estrogen to stimulate hypothalamic release of GnRH which causes the pituitary to release adequate LH to cause normal luteinization of pre-ovulatory follicles. Disruption at any step due to environmental, management, social or health stress may cause ovulation to fail. Diagnosis of anovulation is based on serum LH and P4 concentrations failing to exceed 2.0 and 10 ng/mL respectively, using a quantitative assay (CLIA, RIA or ELFA) on serum samples collected daily, or less ideally, every other day during proestrus and estrus. Quantitative LH assays are not widely available. Use of qualitative testing is less ideal since the LH surge may be <24 hours in length and even daily testing may not be frequent enough. Since serum LH concentrations in anovulatory bitches has never been reported, the extent and amount of LH secretion in these bitches is unknown. Therefore, the value of quantitative assaying LH to diagnose failure to ovulate is questionable, although serum LH may not reach the typical ovulatory concentration of 4-10 ng/mL. Thus,

failure to ovulate is typically documented by progesterone never exceeding 10 ng/mL.

Bitches experiencing an anovulatory cycle typically have normal patterns of vaginal keratinization, attract males and often stand to be mounted. However, serum P4 fails to increase >10 ng/mL.[74,75] Failure to ovulate is rare, estimated to occur in about 1% of bitches seen for breeding management.[74] The authors have anecdotally observed failure to ovulate more frequently in medium-large size bitches (e.g., German Shepherds, Bernese Mountain Dogs, Labrador Retrievers, Bullmastiffs). Anovulation, in theory, could be treated using GnRH, hCG or deslorelin, but there is a lack of scientific studies using these drugs for this purpose. The potential for disrupting normal ovarian function should not be underestimated. Because of its rare incidence, anovulation could be regarded as a physiologic derangement. Once potential stressors are identified and removed, it would probably be wiser to wait for (or perhaps induce) the next heat, rather than treat an anovulatory bitch with hormones.

Slow P4 Rise

Pre-ovulatory luteinization of mature ovarian follicles causes serum P4 concentrations to increase marginally (1-2 ng/mL) prior to and during the LH peak. The LH surge then causes a steady progression of follicular wall luteinization after ovulation with serum P4 concentrations reaching 4-10 ng/mL within 48 hours. Lack of increasing concentrations, with serum P4 concentrations remaining at values compatible with the LH peak stage, indicates an abnormality in the ovulatory process defined as slow P4 rise.[75] When serum P4 rises slowly, its concentration will remain at values corresponding to the LH peak (2.0 ng/mL) from a few to 7 days but eventually this plateau is followed by a rise to values compatible with ovulation.

There is little information on incidence and etiology of this condition. Causes for slow P4 rise include too little estrogen to stimulate the hypothalamic release of GnRH, too little LH from the pituitary or delayed response of follicles to LH, or simply more pre-luteinization of pre-ovulatory follicles prior to the LH surge. The duration of the LH peak in normal bitches has been reported to be as long as 96 hours.[20,26,29-32] Therefore, it is possible that bitches experiencing a 3-4 day plateau in serum P4 may have had a longer, slower rise in LH with the peak occurring around a P4 concentration of 3-4 ng/mL instead of the usual 1.3-2 ng/mL. Ovulation has been shown to begin soon after the LH is >1 ng/mL and is considered the first day of ovulation. Retrospectively, counting back from parturition, the estimated day of the LH peak may be found to be either at the beginning or at the end of the P4 plateau.[75]

Although bitches with a slow P4 rise will eventually ovulate and therefore can be bred, breeding management of these animals is more complicated, as it may require repeatedly monitoring serum P4 concentrations and, possibly, LH as well. Therefore, when a slow P4 rise is suspected or confirmed, the use of frozen or chilled semen or traveling long distances to reach an important stud should be avoided, and the bitch bred to a local male. Also, establishing the due date based on serum P4 concentration can be more challenging and should be confirmed with ultrasonography between 25 and 35 days from the first breeding.[76]

Split Heat

Split heat is defined as a short follicular phase, often with signs typical of proestrus or even by short-lived male acceptance, but serum P4 concentrations fail to increase above basal. Such brief anovulatory cycles are followed by an ovulatory cycle, in about 50% of bitches, within 3 months. Normal cycles may follow a normal interestrous interval (for that breed) in the others.[74] Split heat may recur as suggested by the bitches presented with split heat who may have a history of short interestrous intervals (<3 months). Although short interestrous intervals may be caused by an insufficient luteal phase, whenever a bitch has a history of short interestrous intervals, breeding management should be carefully reviewed, taking into account the possibility of a split heat. Causes of split heat are thought to be the same as those of failure to ovulate and slow P4 rise: low estrogen secretion, low hypothalamic GnRH release, low pituitary LH release, failure of follicles to respond to LH. Deciding whether or not to treat a bitch with split heat to induce ovulation should be carefully considered as there is no information on effectiveness of any suggested treatments. In bitches with a history of short interestrous intervals who present with a split heat, the use of mibolerone at the dosage suggested for estrus suppression has been advocated to prolong the interestrous interval to 6 months.[75,77] Pregnancy can be achieved in these dogs if the post-mibolerone progesterone profile is normal.[75]

Hypoluteoidism

Also termed luteal insufficiency, premature luteolysis, or insufficient luteal phase, *hypoluteoidism* is defined as

a failure of luteal P4 to be maintained at necessary concentrations for an appropriate length of time, normally 63 days from ovulation to maintain pregnancy. Serum P4 concentrations may decrease to <2.0 ng/mL shortly after ovulation (in late estrus) or at any time during diestrus. Although rare, luteal insufficiency has been reported in pregnant, but not non-pregnant bitches.[78-82] Causes of canine luteal insufficiency have not been reported. In first-trimester women, luteal insufficiency may be due to polycystic ovarian disease. Thyroid and prolactin-related disorders have been demonstrated. It may follow use of GnRH analogs in assisted reproduction. Premature luteolysis had been reported in bitches treated with deslorelin to induce estrus but there is a lack of information on other potential endocrine or stress-related causes of this condition.[83-85] Diagnosis of luteal insufficiency in mated bitches requires elaborate diagnostics as other potential causes of low P4 concentration must be ruled out: e.g., fetal distress or fetal death may result in decreased P4 concentration as a normal physiologic response; therefore fetal viability and viral or bacterial conditions affecting fetal or maternal health must be ruled out.[86] In mated bitches where hypoluteoidism is a concern, serum P4 should always be assayed after pregnancy is confirmed on routine ultrasonography. Assaying serum P4 concentrations when a bitch is found not pregnant on routine ultrasound will help rule in/out luteal insufficiency.

Birth of normal healthy litters has been achieved in hypoluteoid pregnant bitches using parenteral progesterone in oil (2 mg/kg IM every 3 days [range 2-4]),[75,78] oral megestrol acetate (2.2 mg/kg q 48 h from day 25 onward),[80] ally-trenbolone (0.088 mg/kg PO daily),[82] and medroxyprogesterone acetate (0.1 mg/kg PO daily).[53,81] The authors have successfully used oral micronized progesterone capsules (Prometrium Merck; 100 mg/dog or 5 mg/kg q 12 h). During therapy, serum P4 concentrations should be assayed every 2-3 days. It is estimated that additional medication is needed if serum P4 concentrations drop <15.0 ng/mL during weeks 3-7 of pregnancy or <5.0 ng/mL in weeks 8 and 9. When supplementing with a progesterone that can be monitored via blood testing, trying to maintain a normal progesterone profile during the second half of pregnancy is ideal, with peak values of 15-20 ng/mL around mid-pregnancy followed by a slow decline to 5 ng/mL during the last week of pregnancy. All supplements should be discontinued 2-3 days prior to the bitch's due date to allow normal whelping. During the first month of gestation, the use of natural progesterone compounds is preferred to reduce risk of congenital fetal malformations. Use of synthetic compounds is regarded as safe in the second half of pregnancy.[87] Synthetic compounds have the advantage of patient serum P4 concentrations reflecting endogenous production.

Persistent Estrus

Persistent manifestations of estrous behavior can be iatrogenic (i.e., due to treatment with GnRH agonists or estrogens) or may occur naturally during estrus.[88,89] The latter is usually due to an abnormality of ovarian function, characterized by estrous behavior, a fully keratinized vaginal smear and low (pre-ovulatory) serum P4 concentrations that persist for >21 days. Causes of persistent estrus can be ovulation failure, the “slow rise in P4” syndrome, or conditions such as ovarian follicular cysts or granulosa cell tumors. Diagnosis of persistent estrus can be challenging when due to anovulation or slow P4 rise, requiring careful assessment of history as these conditions may go unnoticed prior to presentation, while ovarian abnormalities (follicular cysts or ovarian neoplasia) are easily diagnosed by ultrasound.

Other than the suggestion that persistent estrus may resolve naturally, treatment has not been described. Hormonal preparations stimulating follicular growth (e.g., pregnant mare serum gonadotropin) should not be used as they may further increase estradiol secretion, increasing risk of bone marrow arrest and/or pyometra. Use of human chorionic gonadotropin (hCG; 22 IU/kg IM once daily for 3 days) has been anecdotally reported as effective in terminating estrus by triggering onset of diestrus or anestrus.[90] We have used a combination of hCG (500-1000 IU IM, 2 doses, 48 h apart) and GnRH (1.5 mcg/kg IM q 24 h × 4 days; or placement of a 2.1-mg deslorelin implant until luteinization is documented: progesterone >5 ng/mL). Rarely, ovulation occurs. More commonly, luteinization of follicles or a follicular cyst allows the bitch to exit estrus. Fertile ovulation is unlikely because oocytes have degenerated by the time diagnosis is made and therapy started. Breeding or insemination should not be done.

Prognosis for fertility following a persistent estrus is anecdotally reported as poor. It still may be worth attempting natural breeding on the next estrus, if preceded by a normal interestrous interval. Pyometra has been reported in a bitch with persistent estrus following successful hCG treatment. Ovariohysterectomy is always an option for successful resolution.

Short Interestrous Intervals

Interestrous intervals vary with breed and within breeds. Intervals of 4 months between consecutive heats are considered normal in some bloodlines of German Shepherd, Rottweiler, Akita, Labrador Retriever, Cocker Spaniel, and Basset Hound, despite their more common interestrous intervals of about 6 months. Short interestrous intervals in these and other individual bitches are an occasionally described.[53,91] Bitches with short interestrous intervals have a tendency of brief luteal function.[91] Incidence of this condition is unknown, but may occur in as many as 5-10% of healthy dogs. Causes of short interestrous intervals are unknown but the role of ovarian progesterone production is likely to be relevant. It has been suggested that "a progesterone rise of sufficient amplitude and duration is necessary to be recognized as a cycle by the hypothalamus and institute an anestrus of sufficient duration (>3 months) for a normal interestrous interval."[75] A subsequent study concluded that bitches with short interestrous intervals have a tendency towards deficient luteal function.[91] Therefore, a direct relationship between length of diestrus and length of anestrus is likely.

Anestrus plays an important role in uterine involution and resumption of cyclicity. In the non-parous bitch, endometrial repair is complete about 135 days after the onset of estrus. The number and amplitude of hypothalamic GnRH pulses and pituitary and ovarian responsiveness increases as anestrus progresses.[32,73] A short anestrus will shorten the duration of the interestrous interval, thereby negatively affecting fertility of the subsequent cycle by preventing normal endometrial repair to be completed and/or a normal response of the hypothalamic-pituitary-ovarian axis. Fertility following a short interestrous interval may be decreased. Diagnostically, karyotyping should be considered as chromosomal abnormalities may cause short interestrous intervals and infertility.[92,93] Successful management has been reported by giving mibolerone at least 30 days prior to the next anticipated cycle, daily, as needed.

Breeding Management

Pre-breeding

Age of First Breeding

The age recommended for a first mating depends on breed, use, health and owner preferences. It is recommended that small and toy breeds be >18 months of age and medium-giant breeds >24 months. These recommendations should allow full maturation and growth of the bitch prior to becoming pregnant. While puberty may occur long before these ages in most breeds, physical and psychologic development is not complete and the negative effects of pregnancy are permanent.

Genetic Testing

Necessary tests vary with breed and may include radiographic screening (e.g., OFA and PennHIP), specialist evaluation (e.g., cardiology, ophthalmology), and genetic screening of blood, hair or cheek swabs (e.g., OptiGen, PennGen, VetGen) (see ch. 3 and 4).[94] If concerns are raised by genetic test results, the breeder must consider these concerns. There is no perfect dog, so there are times when breeding an animal with a genetic disorder may be acceptable to introduce specific preferred traits into the bloodline or breed. Careful consideration of the mate for these individuals can reduce the risk of passing on the disorder to the offspring (i.e., breeding an affected animal to one free of disease).

General Health and *Brucella* Testing

Complete blood counts (CBC), serum chemistries and urinalysis are recommended, particularly when breeding bitches >4 years of age. Specifically, bitches should be screened for renal disease since the renal and ovarian arteries arise from the same vessels and pregnancy may divert blood away from the kidneys in favor of the gravid uterus. Urinalysis, urine microalbuminuria, and/or urine protein : creatinine ratios are recommended in older bitches. Other specific tests may depend on the area where the bitch resides (i.e., tick titers, heartworm testing). Thyroid testing is generally not necessary unless there are clinical signs, since it has been documented that hypothyroidism has little impact on fertility (may impact the length of stage 2 and 3 labor).[95-103] Since autoimmune thyroiditis may have a genetic basis, bitches with thyroid disease should be evaluated. Those with clinical hypothyroidism due to idiopathic thyroid atrophy may be bred following treatment with thyroid replacement hormone and confirmation of an acceptable response. They should then have thyroid concentrations monitored monthly during pregnancy, since pregnancy affects metabolism and may increase the demand for thyroid supplementation. Both bitch and male should be tested for brucellosis

within 8 weeks of breeding (see ch. 213).[104-106] Brucellosis may be spread by aerosol contact or breeding. Screening tests include the rapid slide agglutination test (RSAT), enzyme-linked immunosorbent assay (ELISA), and tube agglutination test (TAT). If positive, confirmatory testing can be performed (agar gel immunodiffusion test [AGID], blood cultures, polymerase chain reaction [PCR]).

Physical Examination

A complete physical examination of the bitch and dog should be performed prior to breeding to ensure both are adequately healthy for breeding and that the bitch is able to carry pregnancy to term (see ch. 2). Special attention should be paid to body condition. Obese bitches have reduced ovulation rates, decreased stamina, may have more difficulty breathing in late pregnancy when the gravid uterus compresses the diaphragm. Overweight bitches (see ch. 176) have a higher incidence of uterine inertia and obstructive dystocias due to increased pelvic fat. Obese males may not have the stamina or capability to accomplish a natural breeding. Scrotal insulation with fat may affect semen quality. The mammary glands should be palpated for masses or other abnormalities and a digital vaginal exam should be performed to rule out the presence of vestibulo-vaginal strictures, septa, hymenal remnants, vulvar strictures, vaginal masses or cysts or other impediments to copulation or whelping.

Ovulation Timing and Semen Management

Ovulation timing is recommended for all breedings to minimize the matings needed, conserve sperm, maximize use of males, reduce the number of sperm inseminated into bitches predisposed to mating-induced endometritis, improve rates of conception, maximize litter size, allow determination of a whelping date window (see Tables 312-1 and 312-2; see also Figures 312-1, 312-2, and 312-3). Knowing the whelping date is valuable for elective or emergency C-sections, management of high-risk pregnancy, and provision of care during whelping by the caregivers and the veterinary team. For breedings using fresh semen, ovulation timing does not need to be as closely monitored as for chilled or frozen semen because sperm survive for extended periods in fresh semen as opposed to chilled or frozen semen. Also, unlimited access to the male should maximize conception rates. In situations where the male is being bred to multiple females at the same time, closer monitoring is indicated to maximize sperm quantity for each breeding. Frozen semen breedings require the most accurate ovulation timing because sperm survival is brief, usually only 8 to 12 hours, making it imperative that all oocytes have been ovulated and are mature enough for fertilization prior to insemination.

Behavior and Physical Changes

Best conception rates are achieved by combining behavior assessment with physical changes, perineal anatomy, vaginal cytology, vaginal speculum examination, P4 concentrations and LH testing (see ch. 119). These complimentary techniques offer the best opportunity to accurately determine the fertile period by timing from the onset of ovulation. While there is a typical pattern that the majority of bitches follow, exceptions in healthy normal bitches do occur. In early proestrus (and sometimes for up to a month before) males are attracted to the female perineal area and areas where she urinates. Urine marking behaviors increase as the bitch approaches and enters proestrus. The vulvar lips will begin to swell and vulvar discharge will begin. Initially, the bloody discharge is dark red/dark brown. Its source is the uterus due to increased capillary fragility as a result of increasing estrogen concentrations. As the bitch progresses from proestrus to estrus, bleeding decreases and the discharge becomes more straw colored. Some bitches stop bleeding during the fertile period while others will bleed through the fertile period into diestrus. As the bitch gets closer to the fertile period, the vulvar edema subsides resulting in softening of the vulvar lips, allowing intromission. Bitches with a hooded or infantile vulva may have improved conformation during estrus or the vulvar opening may continue to make natural breeding difficult.

Breeding behavior by the bitch and the highest male interest coincides with changes in the estrogen (E2):progesterone (P4) ratio. E2 concentrations begin to decrease prior to the rapid rise in P4, causing receptive behavior. Bitches with atypical cycles (short or long proestrus or estrus) may not appropriately correlate receptive behavior with their fertile period. This can be mistaken by breeders who believe the male can determine when the bitch ovulates. However, due to survival of sperm in the bitch's reproductive tract as long as 11 days, breeding up to 7-10 days before ovulation may still result in pregnancy.[107-109] If the breeder believes that the bitch was bred at ovulation when she was actually she was bred much earlier, calculated due dates (based on breeding dates) will be significantly early. For these reasons, veterinarians must use extreme

caution determining due dates from breeding dates. As a general rule, the bitch's due date can be anywhere from 54-72 ± 2 days from any given breeding date.

Use of Vaginal Cytology (see ch. 119)

Slides for vaginal cytology should be obtained beginning 5-8 days after the bitch starts having bloody discharge or earlier in bitches with a history of early ovulation. Some bitches may not bleed much, some may pool blood in the cranial vagina, some lick meticulously and remain free of blood in the perineal region, and sometimes the first few days of the cycle are missed by inattentive or inexperienced owners. If there is swelling and male interest for several days, performing an early cytology (and speculum exam) will ensure that the early stages of the cycle were not missed. Cytology should be done every 2-4 days until there are at least 50% superficial cells, at which point P4 testing should be added. Use of vaginal cytology should be continued at least every 2-4 days to ensure that the cycle is progressing normally. Cycle abnormalities will typically be noted on cytology long before endocrine results indicate any concern (e.g., split heat or anovulatory cycles). Vaginal cytology can also be used to document day 1 of diestrus, which is as useful as progesterone in determining a bitch's due date, especially if the day of ovulation is missed (see progesterone section).

Use of the Vaginal Speculum Examination

Speculum examination can be performed simply using an otoscope and clean otoscope cone and should be performed each time a cytology is obtained (see ch. 44 and 119). Progression from a pink edematous mucosa in early proestrus to a white and prominently crenulated mucosa is another indicator that the cycle is progressing normally. The rate at which the changes occur are an indicator of the development and maturation cycle of the follicles. These changes, coupled with cytology, P4 concentrations, and behavioral changes help the practitioner determine when to see the bitch for the next ovulation timing appointment. Once ovulation is confirmed, continuing to do cytology and speculum examinations can help determine diestrus day 1, as the mucosa begins to flatten and becomes a blotchy pink on this transitional day.

Progesterone (P4) Monitoring

Early in proestrus, P4 concentrations are basal; typically <1 ng/mL (when reported in nmol/L divide by 3.14). As follicles become mature, small pulses of LH begin to cause pre-luteinization of the follicular wall, resulting in a slow but gradual rise in P4. Once the follicles are mature, the pre-ovulatory LH surge is stimulated. Generally, when the P4 doubles from basal, the LH surge is likely (see Tables 312-1 and 312-2). Once ovulation occurs, P4 concentrations increase rapidly for 2-3 weeks. The rise in P4 between the LH surge and ovulation is more gradual than the rise after ovulation. Some bitches have a plateau in P4 between 2 and 8 ng/mL for one or more days, making it critical that P4 be monitored until ovulation is confirmed by a rise of 3 or more ng/mL in a 24-hour period. It is important to remember that ovulation does not occur at any specific P4 value, but rather is confirmed by a rapid and progressive rise, typically of 3 or more ng/mL in a 24-hour period once it reaches about 4-10 ng/mL. After the initial post-ovulation increase, daily changes may be faster or slower. Occasionally, the P4 may only rise by 2-2.5 ng/mL on the day(s) post-ovulation. Addition of LH testing on these bitches may be helpful. P4 testing can be done less frequently in early-mid-proestrus (every 3-5 days). Once cytology indicates the majority of cells are superficial it should be performed more frequently. Once progesterone reaches the ovulation range (3-5 ng/mL), daily to every other day testing is recommended.

Luteinizing Hormone (LH) Monitoring

LH is initially released in small pulses during mid-proestrus, followed by a large pre-ovulatory surge in late proestrus-early estrus, lasting 12 to 96 hours. The LH surge is usually followed 2 days later by ovulation. Because of the variability in LH surge duration, daily blood draws are necessary for documentation and its beginning is considered the inciting event for ovulation, so even if a surge is 2-3 days long, using the first day as “day 0” is correct when ovulation timing. LH testing is typically performed using a membrane flow assay (Witness LH, Zoetis Corp; see Figure 312-2). The in-house test kit is useful because it allows for interpretation of the intensity of the color change compared to the control, as well as reducing turnaround time, which can be quite limiting. In some, the LH surge must be identified by extrapolating from P4 data. Remember that a LH surge does not ensure ovulation. So, it is critical to always confirm ovulation by assessing P4 concentrations. Waiting until ovulation is documented helps reduce the number of LH tests to be run.

Artificial Insemination

See ch. 118 and E-Box 312-1.

E-Box 312-1

Artificial Insemination (AI)

Advantages of AI include prevention of injury or transmission of disease between the bitch and dog; it allows the semen to be evaluated prior to insemination to ensure that fertility is adequate and that the AI technique being performed is appropriate for the semen quality; it allows for semen to be shipped to the bitch rather than shipping the bitch to the dog or vice versa, thereby reducing shipping stress and transportation costs; it increases the number of bitches that may be bred at the same time by a single male.[206] Disadvantages of AI include increased time and labor for collection, evaluation, preparation and insemination; increased costs of equipment and staff; requisite training for programs to be successful.

Artificial insemination may be performed using one of 3 techniques: vaginal AI (VAI), transcervical AI (TCAI), or surgical AI (SAI).[207-215] Either TCAI or SAI may be used to bypass the cervix and inseminate directly into the uterus. This is advantageous when the cervix may be closed towards the end of the fertile period but while oocytes are still viable for fertilization.[23,216,217] Vaginal AI is typically used for males with normal semen quality and sperm numbers being bred to bitches with normal fertility.[213,214] The larger the bitch, the more vaginal folds and vaginal capacity, thus the greater the number of sperm needed for successful AI. With VAI, an insemination pipette is passed over the urethral orifice using the guidance of a finger in the vaginal canal, into the mid-vagina and the sperm is deposited. Care must be taken to not mistakenly pass the pipette into the urethra. After insemination, the bitch's hindquarters are often elevated for 10-20 minutes to facilitate the ejaculate volume "bathing" the cervix with fluid; however, this practice may not be necessary for success.[218] After insemination, feathering (stroking the dorsal wall of the vaginal canal) is performed to elicit uterine contractions that will facilitate sperm transport to the oviductal reservoirs. Vaginal AI may be used for fresh or fresh-chilled semen, but is not recommended for frozen semen because sperm numbers in each breeding dose are so low that it requires multiple breeding doses (at least 3-5) for each breeding and also because motility of frozen semen is thought to be lower than motility of fresh semen which may delay or make it very difficult for frozen/thawed sperm to cross the cervix.

Transcervical insemination involves either the use of an endoscope to visualize the cervix or the Norwegian catheter, where the cervix is cannulated blindly using a rigid catheter system.[207,209-211] Both techniques require significant training. Endoscopic equipment is expensive but with the newer endoscopes (ureteroscope), bitches of any size or weight can be inseminated while with the older style (cystourethroscope), it may be impossible to inseminate bitches under 25 pounds and some of the largest giant breeds. Occasionally, the position of the cervix may preclude catheterization but with practice, almost 100% of bitches can be catheterized with the newer scopes. TCI is beneficial for poor quality semen; fresh, fresh-chilled, or frozen semen of any quality; and with subfertile bitches (to ensure intrauterine insemination [IUI]). Insemination volumes have traditionally been small, but use of larger volumes has recently been recommended to more closely approximate what occurs with natural breeding. Slow, steady insemination techniques allow the use of much larger volumes of inseminate. Most bitches stand quite readily for the procedure, although rarely, very nervous bitches may require very light sedation. Location of insemination (intrauterine) is exactly the same for TCAI and SAI.

Surgical insemination requires the use of general anesthesia and a midline laparotomy.[208,210,212,215] This allows for direct visualization and palpation of the uterine horns to assess for pathology and possibly address any problems that are found. Because the ovaries are surrounded by the ovarian bursa, their direct visualization is not possible. The inseminate volume used is much lower because uterine tone is very high and the lumen does not distend well. Semen may be deposited equally into both horns, into the uterine body or into one horn. Care should be taken to not extravasate any sperm into the abdominal cavity as this can cause a sperm peritonitis.[219] SAI can be used with any type of semen but is more commonly used with poor quality semen, very low sperm numbers and with frozen semen.

Insemination Frequency

Natural breeding or use of fresh or fresh, chilled semen should be performed once or twice, beginning 2 days post-ovulation (4 days post-LH) and again 2 days later. Planned single inseminations (including surgical insemination) are usually done in the middle to end of the fertile period. Frozen semen breedings should be performed only after complete maturation of all oocytes; day 3 or 4 post-ovulation (days 5 or 6 post-LH surge).

Strategies for Misalliance (Figures 312-4 and 312-5)

Confirm Pregnancy

If an accidental breeding occurs, it is ideal to examine the dog as soon as possible for vaginal cytology and a serum P4 concentration. This allows staging of her cycle and helps determine likelihood of pregnancy being established. Sperm are often seen on vaginal cytology if the bitch was bred recently. If she is in early in proestrus or diestrus, pregnancy is unlikely. If she is in estrus, pregnancy is quite likely if she was actually bred. Before initiating pregnancy termination, pregnancy must be confirmed (see ch. 315). Only about 60% of bitches seen for pregnancy termination are pregnant after an unwanted mating, likely because they were suspected as having mated, but did not. Palpation, even by experienced clinicians, is not perfect. Thus, pregnancy should be confirmed via ultrasound (US; as early as 19 days post-LH), relaxin test (100% accurate >30 days of gestation) or radiographs (after day 43 post-LH).[110-115]

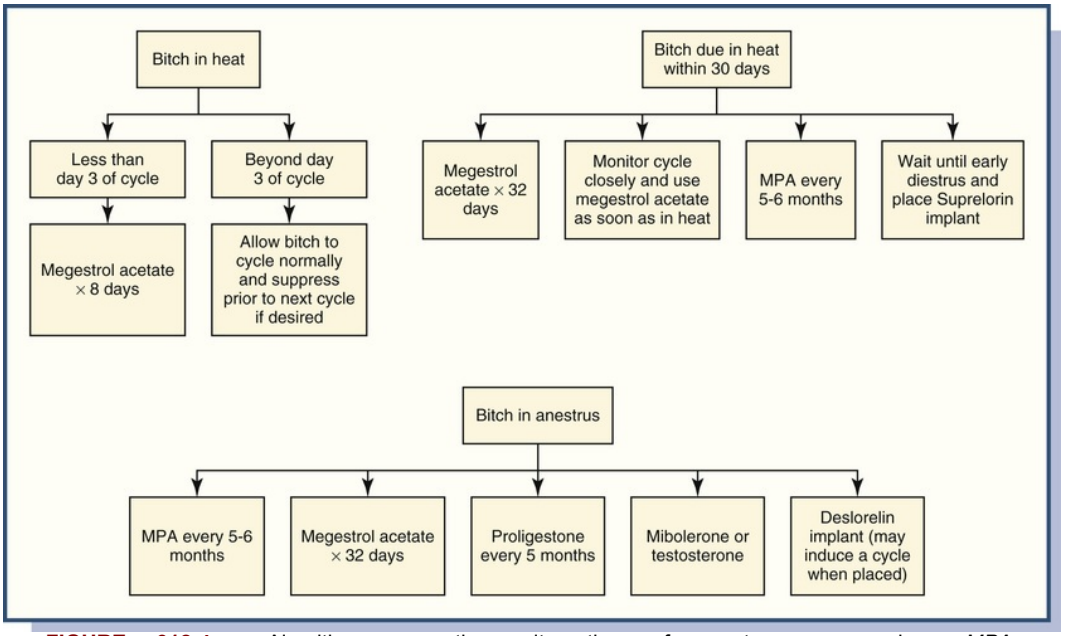

FIGURE 312-4 Algorithm presenting alternatives for estrus suppression. *MPA,* Medroxyprogesterone acetate.

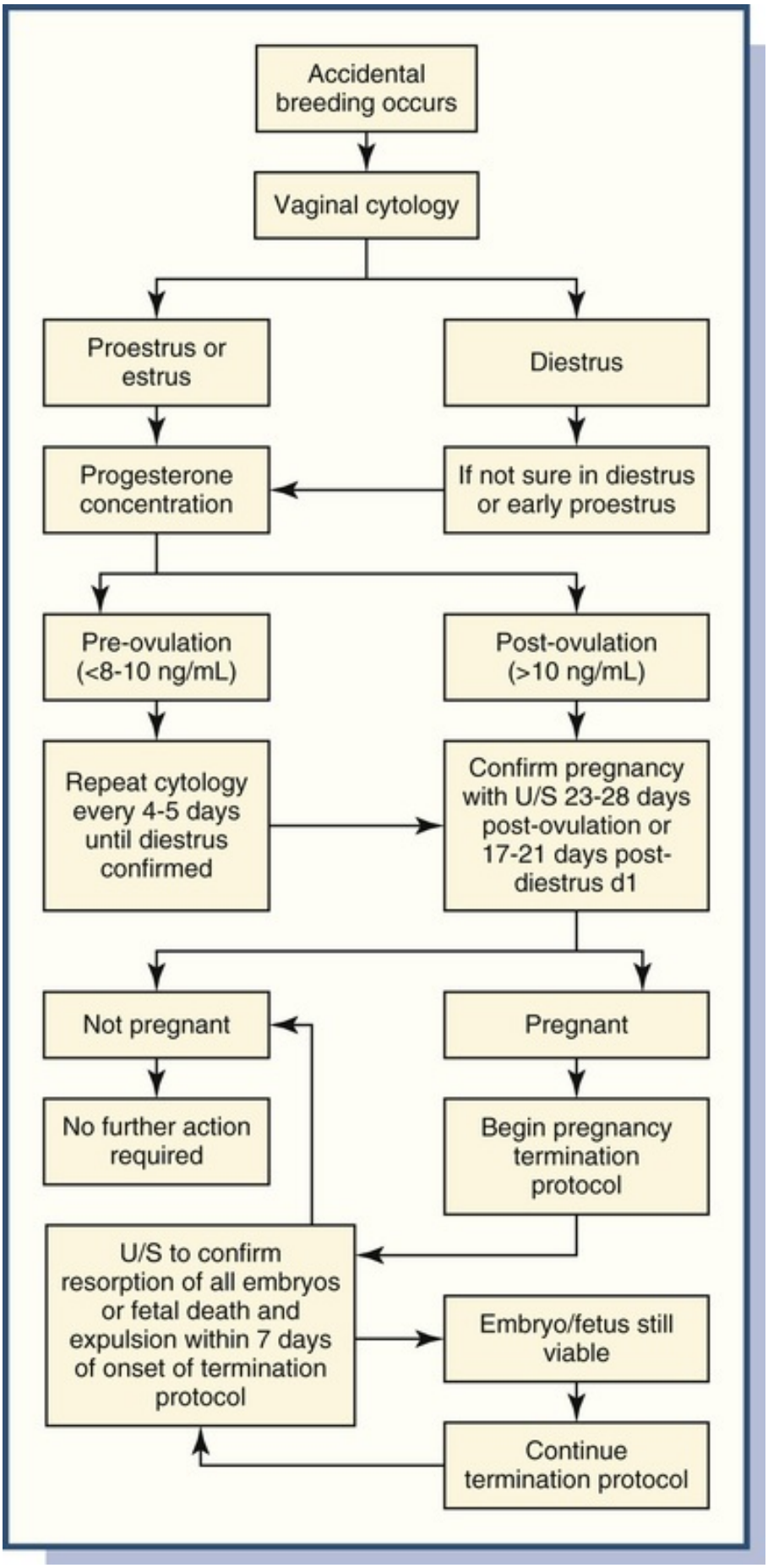
Accidental breeding occurs
Vaginal cytology
Proestrus or estrus
Diestrus
Progesterone concentration
If not sure in diestrus or early proestrus
Pre-ovulation (<8-10 ng/mL)
Post-ovulation (>10 ng/mL)
Repeat cytology every 4-5 days until diestrus confirmed
Confirm pregnancy with U/S 23-28 days post-ovulation or 17-21 days post-diestrus d1
Not pregnant
Pregnant
No further action required
Begin pregnancy termination protocol
U/S to confirm resorption of all embryos or fetal death and expulsion within 7 days of onset of termination protocol
Embryo/fetus still viable
Continue termination protocol

FIGURE 312-5 Algorithm presenting recommendations for pregnancy termination in bitches following misalliance.

Surgical Management

Bitches not intended for breeding should be ovariohysterectomized (OHE; spayed) any time after an accidental breeding, regardless of whether she is pregnant.[110-118] Surgical risk is low and ovariectomy can be considered for very young dogs in estrus or early diestrus, but any bitch with possible uterine pathology or who has had an estrous cycle should undergo OHE, as leaving the uterus may result in stump granuloma or pyometra. Bitches that are spayed in mid-late diestrus may develop pseudocyesis due to the abrupt decline in P4. If lactation is excessive, use of antiprolactin agents may be considered.

Reasons for Pregnancy Termination, Background

Owners may wish to terminate pregnancy in their dog for numerous reasons: disease in the bitch threatening her life if pregnancy continues; accidental unwanted breeding; or unintentional breeding of related animals or juveniles. With most pregnancy termination protocols, the interestrous interval may be shortened because diestrus has been effectively shortened. Numerous protocols have been recommended for pregnancy termination, depending on stage of pregnancy.[110-117,119-134] P4, synthesized and secreted from CLs is required to maintain pregnancy in the dog.[135-137] The CLs are supported by LH and PRL.[41,118] Most protocols involve suppressing production of one or both, or prevent P4 from binding to uterine receptors. Bitches in the last 10 days of pregnancy will abort live fetuses, requiring owner or veterinarian to monitor, support, or humanely euthanize premature fetuses. If stage of pregnancy is unknown, serial US examinations at 1-week intervals beginning 3 weeks after the bitch was bred, is appropriate until pregnancy can be confirmed or confidently refuted. The number of exams will depend on operator experience, facilities, patient size and preparation (clipping, lubricating gel, positioning, respiratory rate).

Prostaglandins (PGF2-alpha)

These compounds may be used alone or in combination for pregnancy termination without affecting future fertility.[110-118] PGF2-alpha initiates luteolysis and causes uterine evacuation.[110-118,138-148] It can be used as early as diestrus day 8-10, but pregnancy cannot yet be confirmed. "High likelihood" of pregnancy can be assumed if the mating was seen and vaginal cytology is consistent with estrus.[142,147] PGF2-alpha may be given q 12 h or q 48 h, depending on protocol and on use of the natural or synthetic product (Table 312-3). It has been shown that low dosages are as effective as the previously-used dosages but cause far fewer side effects.[147-149] When started in early diestrus, PGF2-alpha therapy should be continued until luteolysis is complete, while in later pregnancy the end point of treatment is complete uterine evacuation. Canine CLs are notably resilient; they may resume function after luteolysis appears complete.[110-118,149] Thus, P4 concentration should be <1.5 ng/mL at the conclusion of therapy and 48 to 72 hours later, to ensure that pregnancy is not maintained. Luteolysis usually requires at least 7 days during the first 30 days of gestation while as few as 4 days after day 30. Adding PGE1 (misoprostol) daily to the cervix beginning at the time of PGF2-alpha and continuing until vaginal discharge is noted, can reduce the number of days necessary for uterine evacuation by facilitating cervical relaxation. PGE1, however, does not have luteolytic properties.[150]

TABLE 312-3

Drug Protocols for Termination of Pregnancy

DRUG 1	DOSAGE	DURATION	DRUG 2	DOSAGE	DURATION
Natural PGF2-alpha	10-50 mcg/kg SC q 8-12 h	4-7+ days			
Natural PGF2-alpha	10-50 mcg/kg SC q 12 h	4-7+ days	Cabergoline	5 mcg/kg PO q 24 h	7-10 days
Natural PGF2-alpha	10-50 mcg/kg SC q 12 h	4-7+ days	Bromocriptine	10-20 mcg/kg PO q 12 h	10 days
Natural PGF2-	10-50 mcg/kg SC q	4-7+ days	Aglepristone	10 mg/kg SC—2	If pregnancy still viable in

alpha	12 h			doses 24 hours apart	7-10 days, repeat 3rd dose
Cloprostenol	1 mcg/kg SC q 48 h	3-4 doses (6-8 days)			
Cloprostenol	1 mcg/kg SC q 48 h	1-3 doses	Cabergoline	5 mcg/kg PO q 24 h	7-10 days
Cloprostenol	1 mcg/kg SC q 48 h	2-3 doses	Bromocriptine	10-20 mcg/kg PO q 12 h	10 days
Cloprostenol	1 mcg/kg SC q 48 h	2-3 doses	Aglepristone	10 mg/kg SC—2 doses 24 hours apart	If pregnancy still viable in 7-10 days, repeat 3rd dose
Aglepristone	10 mg/kg SC—2 doses 24 hours apart	If pregnancy still viable in 7-10 days, repeat 3rd dose			
Dexamethasone	200 mcg/kg PO q 12 h	10-12 days: continue until abortion is completed			

Side effects caused by PGF2-alpha are varied and their severity depends on dosage.[110-115,118,139-141,143,151] Bitches gain a tolerance to PGF2-alpha when it is repeatedly given. PGF2-alpha affects smooth muscle and common side effects include tachypnea, bronchoconstriction, hypersalivation, nausea, vomiting, defecation, and bradycardia. High dosages may cause mild motor incoordination and central nervous system depression. The effects of PGF2-alpha analogues, which have a higher affinity to bind to PGF2-alpha receptors, are more pronounced than natural PGF2-alpha; thus dosing is less frequent.[110,114,144,145,148] Extreme caution should be used in brachycephalic dogs, as bronchoconstriction and tachypnea may be life-threatening. Administration of atropine, prifinium bromide or metopimazine 15 minutes prior to PGF2-alpha injection minimizes effects on smooth muscle and the negative side effects in more than 50% of dogs.[151]

Dopamine Receptor Agonists (DRA)

Bromocriptine and cabergoline, ergot alkaloid derivatives with dopamine receptor agonist activity, inhibit synthesis of luteotrophic PRL.[68,110-118,152-155] PRL secretion begins in mid-pregnancy. Thus, the DRAs are useful after 30-35 days of gestation. Either medication can cause pregnancy termination but duration of treatment is much shorter with concurrent PGF2-alpha (see Table 312-3). The added benefit of DRA therapy is that mammary gland development is also suppressed. Lactation is unlikely if pregnancy is terminated with combination PGF2-alpha and DRA.[153,154] Bromocriptine causes more vomiting and anorexia. Fertility on subsequent cycles is not affected by this treatment.

Dexamethasone

Dexamethasone (regardless of route of administration) induces abortion when given for 10 days or more to pregnant bitches (see Table 312-3).[156-158] Fetal death begins 5-9 days after therapy is initiated but some fetuses may remain viable up to 12 days. This drug should not be used in late pregnancy because it may induce delivery of live fetuses. If treatment is started before day 40, fetal resorption occurs, while after day 40, abortion will result. It is critical that therapy be continued until all fetuses are confirmed dead; otherwise pregnancy may continue to term and fetuses may be affected by palatoschisis or cheiloschisis (cleft palate or hare lip). Side effects include polydipsia, polyuria, and anorexia lasting for the entire treatment. Fertility on subsequent cycles is anecdotally unaffected by these medications.

Progesterone Receptor Antagonists

Mifepristone (RU486) and aglepristone (RU534) have been used successfully for pregnancy termination (see Table 312-3). These drugs have 3 times the affinity for uterine receptors as compared with P4.[159-162] They have slight anti-glucocorticoid activity and do not lower serum P4 concentrations. Aglepristone is available for SC (<5 mL/injection) administration commercially in Europe, South America, Canada, Australia and Asia but not in the U.S., without special permit. Since the drug is in an oil base, injection sites should be massaged to facilitate absorption and reduce local irritation. These drugs can be administered from day 1 of diestrus until day 45 of pregnancy. If administered after day 45, live and possibly premature fetuses may be delivered. In early pregnancy, before day 30, fetuses are usually resorbed. Between days 30 and 45, bloody vaginal

discharge or expulsion of dead fetuses may be observed. These medications should not be used in patients with hypoadrenocorticism, diabetes mellitus, chronic obstructive pulmonary disease, endocarditis or hepatic disease. Side effects may include local irritation at the injection sites, anorexia, vomiting, diarrhea, excitation or depression. Pseudocyesis may occur following pregnancy termination.

Megestrol Acetate

Bitches bred on the first 2-3 days of estrus can have the cycle suppressed by 8 days of 2.2 mg/kg megestrol acetate.[114] There is some risk of pyometra or endometritis when adult or older bitches are treated with this medication while healthy, young adult bitches are unlikely to develop any uterine condition (see ch. 315 and 316). It is important to confirm the cycle has been interrupted (no ovulation occurs) because if the cycle progresses, the bitch may become pregnant and the client may not recognize this until later in pregnancy when termination protocols may not be possible or may result in delivery of live fetuses.

Estrogens

Historically, estrogens have been used for pregnancy termination.[163-169] Their use is now contraindicated because there are other effective options with less severe and significant side effects. Estrogens, administered early in pregnancy, can affect oocyte or embryo movement through the oviduct and into the uterus, alter the oviductal environment causing oocyte degeneration, be directly embryotoxic or interfere with embryo implantation. Estrogens increase uterine contractility and relax the cervix. Side effects include bone marrow suppression, cystic endometrial hyperplasia, pyometra, and suppression of future fertility via long-term effects on gonadotropin secretion. Estrogens are no longer considered safe for pregnancy termination.

Tamoxifen Citrate

Tamoxifen citrate likely terminates pregnancy via its estrogenic activity by altering embryo transit time through the oviducts or interfering with implantation.[170] This medication may be effective when given in proestrus through day 15 of diestrus, but not after. Negative side effects include ovarian cysts, endometritis or pyometra.

Manipulating the Canine Reproductive Cycle

Estrus Suppression

Manipulating a reproductive cycle includes performing estrus suppression, defined as stopping or reducing an activity which is in progress. Thus, *estrus suppression* is used for treating bitches in proestrus/estrus (to stop their heat). The terms *estrus postponement* or *prevention* for bitches in anestrus involves complete avoidance of proestrus/estrus. The indications for these distinct conditions separate owner concerns and drugs needed. Estrus suppression is requested most often for show, racing or hunting dogs as a sudden, almost emergency-type concern. As such, once the sport or show event during which proestrus occurs is over the bitch may be allowed to cycle again, which makes suppression a short-term treatment. Therefore, short-acting progestins are preferred.

The only short-acting progestin currently available on the veterinary market is megestrol acetate (MA). It is sold as an oral drug in most European countries, Australia, South America, and elsewhere. MA has a half-life of a few hours and an affinity for P4 receptors 15-25 times higher than the activity of endogenous P4 but also remarkable affinities for the androgen (75%) and glucocorticoid (37%) receptors, respectively.[171,172] MA likely acts on the ovaries and the hypothalamic-pituitary axis. It suppresses pituitary function, thereby suppressing ovarian activity and causing cycle activity to cease. When given for 8 consecutive days (2.2 mg/kg/day) in early (within the first 3 days of) proestrus, MA is effective in suppressing heat in 92-97% of treated bitches, within in 3-8 days.[173-175] Effectiveness may not be as good in bitches with quite short or long proestrus periods.[173-175] The interval from treatment to return to estrus averages 4-6 (range 1-9) months and post-treatment fertility is usually normal.[174,175] Treating bitches for three or more consecutive cycles or at the puberal estrus should be avoided. Proligestone, a long-acting progestin, is marketed for estrus suppression using a single administration of 10-33 mg/kg SC (varying the dosage inversely with body weight).[176] While proligestone is effective for estrus postponement, little information is available on its use for estrus suppression in the bitch.

The use of MA at the above dosage in bitches which are young and healthy may stimulate appetite and decrease activity (thereby causing weight gain). Some dogs exhibit mild mammary and endometrial

enlargement, but this is not worrisome.[175,177] Evidence of pyometra was reported in 0.8% of 389 MA-treated bitches and the incidence of mammary neoplasia was not increased in another survey of 700.[173,175] MA is diabetogenic and it may cause adrenocortical suppression, but only after using dosages higher than and/or treatment length longer than 2.2 mg/kg/day PO for 8 days.[178-180] When used at low dosages (see later section), MA can be administered daily for up as long as a year without side effects.[172] Because of its endocrine actions, MA is contraindicated in diabetic bitches or bitches with a history of mammary, uterine or liver disease.

Estrus Postponement with Megestrol Acetate (MA)

Overview

Postponement of estrus is used when trying to avoid a bitch coming into proestrus/estrus or becoming pregnant, usually for a period of 6 to 18 months. Progestin administration causes the bitch to be in an artificial luteal phase that blocks cyclicity via negative feedback suppression of LH and FSH release. Progestin administration reduces target tissue estrogen receptors, promotes endometrial growth and secretion, causes cervical closure, alters gamete transport, decreases motility within the reproductive tract and suppresses ovulation.[21] The antiovulatory effect of progestins on the LH surge depends on timing of administration: if given at or shortly after the E2 peak, ovulation can be stimulated while the same treatment several days or longer before the E2 peak suppresses it.[176] Medroxyprogesterone acetate (MPA) alters canine ovarian E2, inhibin, and activin secretion, inhibiting the pituitary pre-ovulatory FSH-LH peak.[181,182] Progestin-induced postponement is less effective as anestrus advances. Therefore, progestin treatment in early-mid-anestrus is more effective and causes a later return to cycle activity versus treatment in late anestrus, often characterized by a shorter effect.

Protocols

MA (0.55 mg/kg/day PO for 32 days) effectively suppressed estrus in 199 late anestrous bitches, 98% failed to show cycle activity throughout treatment.[173] This estrus suppression dosage has become quite popular. However, much lower daily doses (0.01-0.05 mg/kg PO for 32 days) are effective in preventing cycle activity for as long as a year.[172] The effect of beginning MA at varying times within anestrus was not clear.[172] Return to heat following MA administration in 5 bitches was 218 days (range 116-311) with the 0.05 mg/kg/day dosage 94 days in 5 dogs (range 22-243) with the 0.01 mg/kg/day dosage and 120-180 days in 199 bitches (range 30-210) with the 0.55 mg/kg/day/32-day protocol.[172,173]

Side Effects

The side effects associated with estrus postponement with MA are similar to those reported for estrus suppression, although the dosage of MA for estrus postponement is much lower and risk for side effects less. No information regarding side effects to MA treatment was provided in the low-dose study.[172] In cats treated with low MA dosages (2.5 mg/week PO for 30 weeks), the most common side effects were increased appetite and body weight, temperament change and mammary enlargement.[183] Short-term, reversible, adrenocortical suppression and/or diabetes mellitus may follow use of intermediate dosages (2.5 mg/day for a few weeks), while long-lasting, potentially non-reversible mammary gland, uterine and endocrine conditions may follow use of high dosages (2.5 mg/day for months or 2.5 mg/week for years).[183] Although reports of MA-induced side effects in dogs are not as worrisome, there are indications that similar concerns do develop in some.

Estrus Postponement with Medroxyprogesterone Acetate (MPA)

Protocols

MPA has been used in dogs for many years and a great deal of scientific information is available regarding efficacy and side effects. MPA's receptor affinity is less than MA: it is only 5 times as potent as P4 and its affinity for androgen and glucocorticoid receptors is 100 and 1000 times less than that of MA. However, MPA has a longer half-life: 12 to 17 hours after oral administration or 40-50 days when given parenterally. Since injections are required only twice a year to dogs in anestrus, MPA has been used for prolonged postponement at dosages of 2 mg/kg/3 months, 3 mg/kg/4 months, or 2.5 mg/kg/5 months SC.[176,177,184] However, lower dosages are probably effective. Giving MPA (1.5 mg/kg) every 13 weeks inhibited ovulation in Beagle

bitches.[185] Also, 5 adult Beagle bitches treated daily with oral MPA (0.05 mg/kg) did not show estrus for the entire 365-day treatment period.[172]

Side Effects

Relationship between MPA dosage and side effects is likely in dogs, with lower dosages only controlling cyclicity and behavior while higher dosages can cause long-lasting uterine, mammary and endocrine effects. Epidemiologic studies have demonstrated greater risk of malignant mammary tumors in bitches treated chronically with MPA.[186] Unfortunately, reports on side effects caused by MPA have been vague and independent of treatment dosage or duration. Results from chronic MPA toxicity studies in dogs may overemphasize some side effects.[177,185,187-189] MPA acts on the same target tissues as MA, i.e., uterus, mammary gland, endocrine system, basal metabolism and appetite. Parenteral treatment with dosages <2 mg/kg every 5-6 months can likely be used safely in young to young-adult healthy bitches for more than one year (i.e., up to 3 consecutive administrations). Shorter treatment periods are recommended for middle-aged or older bitches with age-related changes within their uterus and mammary glands. Lower dosages may be associated with an earlier return to estrus; however, this would be counterbalanced by a lower health risk for treated bitches. Doses >2.5 mg/kg or those given more often than every 5 months are too high and should not be used. Such higher dosages increase risk of (benign and/or malignant) mammary nodules, cystic endometrial hyperplasia, insulin resistance, and mammary secretion of GH leading to acromegaly.[182,190,191]

Estrus Postponement with Proligestone (PGS)

Overview

PGS is an injectable progestin marketed for use in small animals in Europe with an indication for estrus postponement. PGS should be administered at the dosage of 10 (for large size bitches) to 33 (for small size bitches) mg/kg at 0, 3 and 7 months, and then every 5 months. Efficacy of this protocol is reported to be >95%.[177,192] Breakthrough heats may occur during chronic administration, although little is known on the incidence. Although initially thought to be characterized by a milder progestational and hypothalamic-pituitary-gonadal axis action when compared to MA and MPA, later studies demonstrated that the same side effects of MA and MPA can be achieved with proligestone.[177] Endometrial stimulation leading to cystic endometrial hyperplasia and pyometra as well as mammary hypertrophy accompanied by secretion of GH leading to acromegaly have been reported in dogs during chronic PGS administration, although admittedly at a higher than normal dosage, 5-10 mg/kg SC every 3 weeks. Incidence of pyometra and/or mammary tumors when using the normal protocol is reported as low or irrelevant.[193] The interval from treatment to cycle activity following treatment with PGS can be from 3 to 9 months.[177]

Estrus Postponement with Androgens

Testosterone and its derivatives are widely available. Stanozolol and nandrolone decanoate–based drugs have been available for veterinary use in Europe, North America and elsewhere. Their non-reproductive indications have been described but their action on the canine reproductive cycle has not been accurately investigated. Prolonged high levels of androgens given to males cause negative feedback to the hypothalamic-pituitary axis, reducing pituitary LH and FSH secretion and also binding to androgen receptors. Similar actions may occur in bitches given androgens, with pituitary suppression and consequent decreases in response to E2 since they also bind androgen receptors on E2 target tissues.[176] Parenteral formulations of testosterone propionate (100 mg/dog/week) or mixed testosterone esters (25 mg/kg every 4-6 weeks) or oral formulations of methyl-testosterone (0.25-0.5 mg/kg/day or 25 mg/dog/week) are commonly used to postpone estrus in racing Greyhounds. A depot formulation of testosterone cypionate (2 mg/kg IM) has been effective in postponing estrus for 239 days in 4/5 treated bitches.[194] Treatment should be started at least one month prior to the onset of proestrus to enhance efficacy.[195] Return to estrus following treatment withdrawal may vary from a month to years.

Mibolerone, a synthetic androgen marketed in North America, is an oral, once daily formulation for bitches to postpone cycle activity for as long as 3 years. However, treatment for longer than 2 years is not recommended. Dosage depends on breed and body weight. German Shepherds and German Shepherd mixes should be given the maximum dose (180 mcg/day), while Bedlington Terriers should not be treated at all due to their history of liver dysfunction. Other dog breeds can be treated based on body weight with bitches of

<12, 12-23, 23-45 and over 45 kg receiving 30, 60, 120 and 180 mcg/day, respectively. The interval from treatment to the following estrus is about 2 months (7 to 200 days).

Any androgen can cause increased muscle mass, clitoral hypertrophy (potentially irreversible after prolonged therapy), deepening of the bark, change of temperament (aggressiveness), and mounting behavior. Anestrus should always be confirmed and pregnancy ruled out (to avoid risk of potential masculinization of female fetuses) before administering an androgen.[196]

GnRH Agonists and Antagonists

See E-Box 312-2.

E-Box 312-2

GnRH Agonists and Antagonists

GnRH agonists have been available for experimental use in small animals since the turn of the century, and for the last decade or so a GnRH agonist-based product has been marketed for use in male dogs to suppress fertility. These compounds suppress the reproductive system by downregulating the pituitary reducing its LH and FSH secretion, thereby causing a blockade of follicular growth. In bitches, the use of GnRH agonists such as deslorelin or nafarelin has proven effective but not practical as a flare-up reaction induces a fertile estrus within days when females are treated in anestrus.[201,220,221] A concomitant administration of short-acting progestins has proven only partially effective to avoid this problem.[222] Treatment in diestrus avoids this estrus induction effect[211] but estrus induction has been occasionally reported in bitches treated in diestrus.[202,204] A serum P4 concentration of 5 ng/mL at the time of implantation is reported as a potential threshold above which estrus is not induced.[223] Also, middle-aged or elderly bitches may have some degree of cystic endometrial hyperplasia which may cause pyometra to develop coincidentally with a GnRH agonist treatment performed in diestrus. For these reasons, the use of GnRH agonists for prolonged estrus suppression is acceptable only in healthy, young adult bitches. The authors currently do not recommend using GnRH agonists for estrus suppression in the bitch.

GnRH antagonists are human drugs which temporarily suppress fertility by inhibiting GnRH receptor gene expression leading to a rapid pituitary suppression without an initial flare-up stimulation of the pituitary-gonadal axis which is typical of GnRH agonists. Their experimental use in bitches prevents ovulation and interrupts pregnancy, but not enough information is available for their use in field trials to be advised.[224]

Immunocontraception

See E-Box 312-3.

E-Box 312-3

Immunocontraception

The use of vaccines against GnRH, LH or zona pellucida antigens has been an active area of research over the last decade with several products tried in bitches with varying degree of success.[225] An LH vaccine has provided a (fully reversible) 11-month estrus suppression in adult bitches.[226] Zona pellucida vaccines have produced inconsistent results on antibody production and have not been effective at preventing fertility in bitches, although recent studies show promising results.[227] A GnRH vaccine developed for use in wild female ungulates (deer, horses, burros) and currently marketed for use in boars in Europe has been successfully used as part of population and rabies control efforts in Mexican free-roaming dog populations.[228] However, dogs are prone to developing adverse reactions at the injection site when using this product. Experimental use of these vaccines in dogs is ongoing and the GnRH vaccine looks the most promising one. However, there is currently no anti-fertility vaccine which can be considered safe or appropriate for field testing in dogs.

Estrus Induction

Overview

Estrus induction may be requested when trying to shorten a normal or longer than normal interestrous interval, and can be achieved with gonadotrophins, dopamine agonists or GnRH agonists. While suppression or postponement of estrus is relatively easy, inducing estrus is a challenge because of the lack of consistency of response to different treatments. A variety of treatments have been tried in the bitch with variable and often unsatisfactory (when considering pregnancy rate and litter size) results, including LH and FSH alone or in combination, pregnant mare serum gonadotropin (PMSG) as well as estrogens and naloxone.[67] The use of GnRH agonists and dopamine agonist antiprolactinic drugs is characterized by satisfactory results and should be preferred in clinical practice.

Dopamine Agonists

When administered at their normal antigalactogenic dosage daily starting in anestrus, dopamine agonists such as cabergoline (5 mcg/kg PO q 24 h) and bromocriptine (20-50 mcg/kg PO q 12 h) can shorten the duration of anestrus, thereby advancing the onset of proestrus.[71,197,198] A low dosage of cabergoline (0.6 mcg/kg) has been used with success.[70] Serotonin antagonists can also be successfully used to induce heat but only at higher than normal dosages (metergoline, 0.56-1.2 mg/kg IM q 72 h until proestrus); a high metergoline dosage will exert dopamine agonist effects as opposed to the normal antigalactogenic dosage of 0.5 mg/kg which cannot shorten anestrus.[69,199,200] A dopamine-agonist treatment length of 2-4 weeks is normally sufficient to induce onset of proestrus, although occasionally bitches may not respond until 35 or 40+ days of therapy. There are not enough data on the percentage of bitches responding and what is the maximum duration of administration beyond which the treatment should be stopped. Success rates of 50-80% and potential breed differences in the effectiveness of dopamine agonists for termination of anestrus have been reported. Treatment should be continued until mid-proestrus. Fertility of a cycle induced using a dopamine agonist is regarded as normal. The use of hCG once estrus becomes manifest does not seem to provide any significant help.[70]

GnRH Agonists

When used in anestrous bitches, GnRH agonists such as deslorelin (at the dosage of 1.05 mg, 2.1 mg or 4.7 mg) will induce resumption of cyclicity within 2-9 days.[83,85,201,202] The interval from proestrus onset to ovulation may be shorter in deslorelin-induced bitches than in spontaneously cycling bitches; however, all other fertility parameters appear to be normal.[83,85,202] Because of the well-known suppressive effect of a deslorelin implant on progesterone secretion around mid-pregnancy,[83-85,201] implants administered to induce estrus should be removed between proestrus onset and ovulation in order to avoid pregnancy loss due to premature luteolysis.[83,85,203] Placing an implant in an easily accessible location such as the periumbilical area, the vestibular mucosa or the medial side of the limb helps with locating it and removing it quickly at the proper time. Deslorelin tends to be more effective when administered in late, as compared to early anestrus, and in general is regarded as a very safe and effective drug to induce fertile estrus in the canine. Bitches treated in late anestrus show heat within 4.2 +/− 1.4 days in 97% of cases, ovulation occurs in 83% of cases and quite constantly 12 +/− 3 days after treatment, and pregnancy rate is approximately 70%.[85] However, the need to act invasively to achieve early removal in order to avoid premature luteal failure remains an issue. Also, prolonged heats and anovulatory cycles have been reported.[84,85,201,204,205] In order to avoid unnecessary ovarian stimulation, implants should be removed no later than 15 days post-treatment even if the bitch has not ovulated yet.[85]

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CHAPTER 313

Effect of Spay or Castration on Long-Term Health of Dogs and Cats

Hilde de Rooster, Nathalie Porters

Client Information Sheet: Recommendations Concerning Neutering in Cats and Dogs

Background

Surgical gonadectomy (i.e., the removal of the ovaries from females or testes from males) remains the most reliable and only permanent, rapid onset, neutering method for reproduction control in companion animals.[1] Neutering is by far the most common surgical procedure in small animal practices.[2] Elective gonadectomy, however, is still prohibited in a few countries, but in most it is well accepted, and generally viewed as harmless or beneficial for the animal's health.

Veterinarians have the important role of informing pet owners about the benefits and risks of gonadectomy, but the optimal age for gonadectomy is not known. In this debate, distinction should be made between unowned animals (population) and those privately-owned (individuals). Traditionally, elective gonadectomy in dogs and cats is performed at 6 to 9 months of age despite a lack of evidence for this recommendation.[3,4] Since many cats enter puberty before 6 months of age, females may become pregnant prior to gonadectomy. In dogs, timing of their first heat cycle is size- and breed-dependent. First heat would seem a better decision point than actual age. Prepubertal gonadectomy (PPG), defined as gonadectomy performed before 4 months of age or sexual maturity, has been promoted for shelter animals, first in the US, then in the UK, and more recently in other countries.[5-16] The literature has few studies that evaluate short- and long-term effects of neutering at various ages. Rather, information usually compares neuter status at the time of disease, rather than pediatric versus traditional-aged gonadectomy. In studies where age at the time of surgery was taken into account, interpretation of data is complicated by the varying definitions used to group dogs as having been neutered "early" or "late" in life. A comparison of pre- and postpubertal neutering would reveal the most relevant data about risks and benefits.

Anesthesia and Surgery

Elective gonadectomy should only be performed on animals that can safely undergo the procedure, reducing risk of complications.[7,17,18] Particularly in shelter animals, infectious diseases are the main cause of health issues and mortality shortly after PPG.[4,19] Kittens and pups are more vulnerable to infectious diseases than immunized adults and their response to vaccination is often unknown due to presence of maternally-derived antibodies (see ch. 208).[20] It is suggested that gonadectomy be delayed until privately owned pets are fully vaccinated.[15,18,21]

Different anesthetic protocols have proved to be safe and effective for gonadectomy in kittens and puppies.[9,15,17,22-26] Compared to adults, puppies and kittens have immature organ systems, placing them at greater risk for hypoglycemia, hypothermia, bradycardia, hypotension and hypoxemia.[12,17,27-29] These physiological differences are important in anesthetic and surgical planning. While protocols for gonadectomy in pediatric animals are similar to those for adults, their immature tissues are more fragile and even minimal blood loss can quickly become worrisome.[4,9,15,17]

Long-Term Health

Despite the high prevalence of (early age) gonadectomy in veterinary practice, there are few studies of adequate quality and size regarding effect of gonadectomy, as well as age at time of gonadectomy, on health and disease in dogs and cats. Evidence regarding risks of various disease entities following neutering is generally poor, given the practical difficulties in controlling for confounding variables. Most data are obtained through database searches and thus report the difference in simple counts. The neuter status of diseased animals is often not adequately compared to the status of the general hospital population. Furthermore, confounding variables are not taken into account. Owners of neutered pets may present their animal more regularly to a veterinarian, increasing likelihood of diagnosing a disease. Similarly, neutered animals have longer lives and have more time to develop age-related conditions. It is quite conceivable that (early-age) gonadectomy not only influences the genital tract, but other organ systems as well. The majority of health advantages related to neutering outweigh potential disadvantages (see ch. 319).

Benefits

Societal

A societal benefit of elective gonadectomy is the animal's contribution to population control and animal welfare.[3] Unwanted puppies and kittens contribute to the increasing number of animals entering animal shelters, joining feral populations, or being killed.[30-32] Neutered animals are less likely to be relinquished to a shelter.[32-35]

Health

Gonadectomy in dogs and cats is accompanied by an array of health benefits, first by decreasing risk of many genital tract diseases later in life. Removal of both gonads completely eliminates pregnancy- and parturition-related diseases as well as ovarian disease (cysts, neoplasia) in female dogs and cats. Similarly, testicular diseases are eliminated in castrated males. Elective ovariohysterectomy (spay) eliminates any possibility of cystic endometrial hyperplasia, pyometra, or uterine neoplasia. Elective spay also decreases the incidence of vaginitis, vaginal prolapse, false pregnancy and feline mammary hypertrophy. Castrated males are less likely to have benign prostatic hyperplasia or prostatitis. Timely removal of the ovaries is also associated with a smaller risk of mammary cancer.[3,36] Risk of feline mammary carcinoma is drastically reduced in cats spayed before 1 year of age.[37] Early studies on canine mammary gland tumors reported a significantly reduced risk of malignant transformation by PPG, but more recent systematic review only found some evidence to suggest such protective effect.[38,39] Other studies in dogs with mammary gland cancer showed a positive effect on survival by spaying at the time of mastectomy.[40] Other substantial health advantages of gonadectomy include reduced incidence of injuries associated with roaming and a decreased transmission risk of infectious diseases because of reduced copulation and inter-male fighting.[41] Any advantage associated with neutering should be further studied with regard to additional sparing effects gained by prepubertal versus postpubertal gonadectomy.

Potential Detriments

Non-Neoplastic Urogenital Disorders

External Genitalia

Gonadal hormones are responsible for the normal development of the external genitalia in cats and dogs.[42-44] Female cats neutered at 7 weeks or 7 months had a smaller vulva compared to sexually intact cats at 12 months of age.[43] Similar observations have been made in female dogs.[44] Complete penile extrusion was impossible in PPG male cats and possible in only 60% of cats gonadectomized at 7 months.[42] Likewise in male dogs, early neutering resulted in smaller prepuces.[44] There is no evidence of clinical significance of these anatomic differences.

Urethral Diameter

There is concern that (prepubertal) gonadectomy may result in smaller diameter urethras in male cats and dogs, increasing risk of urethral obstruction (see ch. 335).[44,45] Studies have failed to demonstrate urethral narrowing in intact male cats versus those neutered at different ages.[42,46] In long-term cohort studies, no

correlation has been found between age at gonadectomy and incidence of feline lower urinary tract disease (FLUTD) in either gender.[11,19,47] Nevertheless, gonadectomy at any age in cats has been described repeatedly as one of the potential risk factors for FLUTD.[48-51] There is no reported clinical sequela of castration on the male urethra in dogs whereas conflicting data have been reported on the risk of cystitis in female dogs. More gonadectomized than intact bitches had persistent or recurrent cystitis in one study.[52] Several studies showed that bladder stones were more often observed in neutered versus intact dogs (see ch. 331).[53] Two studies had differing conclusions regarding PPG influencing likelihood of developing cystitis later in life when compared to traditional-aged gonadectomized dogs.[47,54]

Incontinence

Fewer than 1% of sexually intact bitches develop acquired urinary incontinence (AUI) at some point in life (see ch. 335).[55,56] However, AUI in neutered bitches varies from 2 to 20%.[57] When female dogs spayed between 12 weeks and 6 months of age were compared to postpubertally neutered bitches, breed and body size rather than the timing of the gonadectomy were associated with observed rates of incontinence.[58] In a case-control study, prepubertally neutered bitches were less likely to develop urinary incontinence than dogs spayed later in life.[59] The lower incidence was also observed by others, although more distinct clinical signs of urinary incontinence were noted in affected prepubertally spayed dogs.[60]

Skeletal Growth

There is ample evidence that most physes close postpubertally.[44,61,62] Lack of gonadal hormones negatively affects closure of selected physes.[43,44,63-67] Some have concluded that this delay, especially observed following PPG, may result in longer bones.[65,66] In parallel, it was hypothesized that affected growth plates may be more susceptible to injury and fracture.[43,44,66,68] The clinical relevance of delayed physeal closures following PPG compared to traditional-age gonadectomy, is largely questioned.[11,19,47] Most cats with femoral capital physeal fractures were obese neutered males.[66,69] Because gonadectomy increases incidence of obesity, gonadectomy might be an independent risk factor.

In dogs, hip dysplasia (HD) and cranial cruciate ligament disease (CCLD) have been associated with neutering (see ch. 353).[70-72] It is hypothesized that asymmetric closure of growth plates could cause deformity and laxity of hip and stifle joints.[44,73] Castrated male dogs are considered more likely to have HD and early neutered dogs seem at higher risk.[47,70,74] Both neutered males and females have a greater likelihood of CCLD.[70,74] There does not seem to be evidence of a difference in the risk to develop CCLD between pre- and postpubertal gonadectomy dogs.[47,54] Both these orthopedic conditions, however, are multifactorial in development. Genetic background, breed predisposition, and obesity are among the factors that may influence risk of developing these orthopedic disorders.[75]

Overweight and Obesity

Overweight companion animals are common. Gonadectomy is one of many risk factors for becoming overweight (see ch. 176).[76-84] Some dog breeds appear more prone to weight gain after neutering.[85] Risk of being overweight was not different according to age at gonadectomy.[86] Surprisingly, some suggest that dogs neutered prepubertally would be less likely than dogs neutered at a later age to gain excessive weight.[47] More objective novel insights in cats challenge the previous suggestion.[87] Given the potential contribution of obesity to most other conditions, the role of the veterinarian to tactfully instruct pet owners to avoid excessive weight gain following (early age) gonadectomy by means of energy restriction as they reach maturity is crucial.[77,86,88,89]

Neoplastic Disorders (also see ch. 344-351)

In dogs, the increased prevalence of a variety of neoplastic diseases attributed to gonadectomy implies that gonadal hormones may have protective qualities against neoplastic proliferation in selected tissues.[90-92] Yet, the role of sex hormone removal in the pathophysiology of such neoplastic diseases remains largely unknown. The fact that individual dog breeds may vary in predisposition further complicates interpretation

of data. For cats, only isolated equivalent data of risk analysis for neoplastic conditions have been produced. Prostatic carcinoma is relatively uncommon in both neutered and intact male dogs (see ch. 337). However, a significantly higher incidence of prostatic cancer is described in castrated dogs.[92-94] In contrast, one report suggested that prepubertal castration of male dogs reduced the risk of neoplastic prostatic disease.[95] An increased prevalence of canine bladder cancers has been noted in neutered male and female dogs.[93] Neither of these studies separated dogs by pre- versus postpubertal gonadectomy.

It has been hypothesized that development of canine lymphoma is suppressed by endogenous gonadal hormones in intact female dogs. Intact males and especially neutered animals of both genders are at greater risk.[91] In Golden Retrievers, a study focusing on health implications of neutering demonstrated that males castrated before 1 year of age were nearly 3 times more likely to develop lymphoma as compared with intact males (see ch. 344). No dog castrated when older developed lymphoma.[74] Neutered cats have increased risk of intestinal lymphoma, but it might have been a direct reflection of age rather than neuter status itself.[96]

Gonadectomy in dogs of either gender was found to be correlated with a two-fold increased risk of osteosarcoma (see ch. 348).[97] A cohort study of Rottweilers, a predisposed breed, further indicated that gonadectomy performed before 1 year of age resulted in the highest risk.[90] Although this might suggest a protective effect of gonadal hormones, nothing is known about a possible mechanism.

Compared with sexually intact female dogs, gonadectomized bitches were at significantly increased risk to have cardiac and/or splenic hemangiosarcoma (see ch. 347), but equivalent differences were less obvious in males.[98,99] In Golden Retrievers, no differences in disease rate were apparent between early spayed and intact females, but female dogs spayed later than 1 year of age had a significantly increased risk.[74] In studies on canine cutaneous mast cell tumors (see ch. 349), neutering was identified as a risk factor in females.[74,100]

Other Diseases (Endocrine, Reproductive, Immune-Mediated)

Vaccination Reactions, Asthma, and Skin

In studies in dogs and cats, hypersensitivity reactions following vaccination were more common in neutered animals.[101,102] It was hypothesized that a lack of negative feedback by the gonadal hormones increases pituitary hormone secretion, influencing the immune response to vaccination. It has been suggested that neutering before 5.5 months was associated with a reduced incidence of feline asthma and gingivitis compared to cats undergoing gonadectomy between 5.5 and 12 months of age.[47] Another cohort study, however, did not observe a significant increase in incidence of disorders of the integumentary system (including minor skin allergies) between animals neutered before versus after 24 weeks of age.[11] Also, based on recent findings, age of gonadectomy is unlikely to be associated with feline hypersensitivity skin disorders.[19]

Diabetes Mellitus

Neutering is associated with an increased risk of diabetes in dogs and cats of either gender, though weight was not considered (see ch. 304 and 305). Spaying female dogs prevents progesterone-induced diabetes mellitus (quite rare) but increases the risk of diabetes mellitus due to obesity.[103,104] In neutered cats, greater risk of diabetes may reflect obesity as a risk factor rather than neutering.[105] Obesity and neutering are associated with decreased sensitivity to insulin.[106]

Other Conditions

Conflicting data on the incidence and prevalence of many other disease conditions and longevity after neutering have been reported. Neutered dogs may be at higher risk for hypothyroidism.[107,108] Similarly, acute pancreatitis was diagnosed more often in neutered animals than in intact animals.[109,110] Although exceptional longevity was claimed in female intact Rottweilers, most studies suggest that neutered animals live longer.[111-114] A major methodological issue regarding potential effects of neuter status on lifespan is that the animals are roughly categorized as neutered or intact based upon gonadal status at time of death, with no indication of age at neutering.[115]

Summary

Decisions regarding elective (prepubertal) gonadectomy in an individual animal depend on several factors. In cats, from a population control perspective, it is vital for neutering to occur before they can reproduce. This implies that shelter kittens and cats be gonadectomized before adoption. Client-owned cats, not intended for breeding, should be neutered around 4 months of age, once adequately vaccinated. Harmful outcomes associated with neutering in cats are extremely rare.

The decision-making in dogs is less clear-cut. For a privately owned dog, numerous and interacting variables factor into determining the best age for neutering. Sexually intact female dogs are at risk for common and serious diseases (mammary gland tumors, pyometra) that can be successfully reduced or prevented by timely elective spaying. Ideally, they should be neutered before or just after their first heat cycle. In male dogs, the health benefits of elective castration are far less obvious and may not outweigh the potential detriments of neutering. Breed-specific disease vulnerabilities should be thoughtfully considered in the decision about neutering.

Whereas it should be easy for veterinarians to promote client education regarding societal concerns, such as pet population, owner education on individual animal concerns, and altered incidence of disease, remains far more complex. More prospective research is needed, not only to quantify incidences of clinically relevant diseases, but also to identify confounding variables that might influence the observed risks.

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CHAPTER 314

Clinical Feline Reproduction

Eva Agneta Axnér

Client Information Sheet: Clinical Feline Reproduction

Seasonality

The domestic cat is a "long-day breeder" because increases in day-length stimulate cyclicity.[1,2] The duration of the reproductive season will differ with geographic location, with no seasonality near the equator.[1] Individual cats kept under identical photoperiods, however, show wide variations in length of reproductive season and number of estrous cycles.[3] There are also breed differences in the tendency for seasonal reproduction. For example, Persian cats have a more pronounced seasonality than do Burmese cats. Husbandry conditions may also affect cycles, as artificial light may interfere with seasonality. To stimulate estrus, cats can be kept in a controlled light environment with at least 12-14 hours of light each day.[2] Estrous activity will cease when day-length is set to less than 8 hours of light.[2] The effect of season or day-length on male reproduction is less pronounced, but there are seasonal fluctuations in testicular activity and sperm quality. Males usually sire kittens throughout the year, although sperm quality may be lower in the non-reproductive season.[4,5]

Puberty

The first estrus usually occurs between 4 and 21 months of age in female cats. Pregnancy has, however, occasionally been observed in kittens younger than 4 months of age.[6-8] Because cycles are seasonal, age at puberty is affected by the month of birth. Females may enter their first estrus the first breeding season after being born or in their second year.[3] Puberty is less obvious in males. Testes are descended at birth or within a few days.[9] Spermatogenesis is usually established by 6-8 months and puberty is associated with an increase in testicular weight and in serum testosterone concentrations.[10,11] Age of first mating, however, may be affected by various factors.[12] Secondary androgen-dependent characteristics develop in males in association with increased androgen production. Mature males have well developed penile spines (Figure 314-1). These spines will regress after castration when testosterone drops to basal levels. In kittens, the prepuce is tightly adhered to the penis and partially detaches around 5 months of age. The penis and the prepuce are separated under the influence of androgens.[12] If the male is castrated before puberty, this adherence may therefore remain (see ch. 313).[13] Other physical characteristics of mature intact male cats include thick skin, well developed cheeks, and territory marked by urine. Urine of intact males has an androgen-dependent, strong odor. The tendency and age of urine spraying varies. At puberty, roaming behavior and a tendency to fight with other intact males also increases.[14]

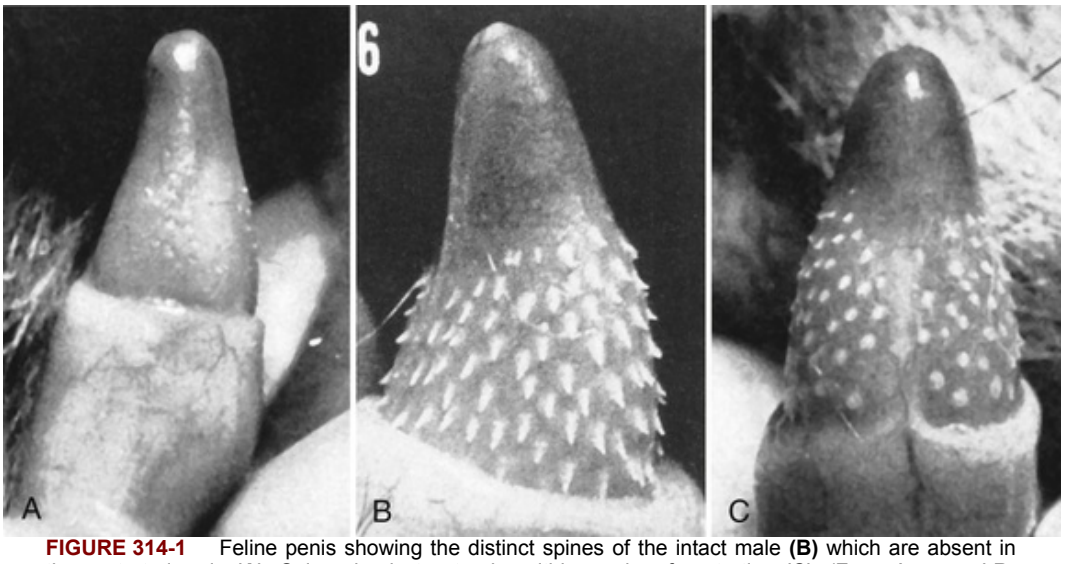

FIGURE 314-1 Feline penis showing the distinct spines of the intact male **(B)** which are absent in the castrated male **(A).** Spines begin to atrophy within weeks of castration **(C).** (From Aronson LR, Cooper ML: Penile spines of the domestic cat: their endocrine behavior relations. *Anat Rec* 157:71-78, 1967; used with permission.)

Estrous Cycle

Queens are seasonally polyestrous. Although the cat is considered to be an induced ovulator, spontaneous ovulation may occasionally occur. The cycle can be divided according to ovarian activity.

The Follicular Phase (Proestrus and Estrus)

The follicular phase is characterized as the stage in the estrous cycle when there are active follicles in the ovaries and serum estradiol concentrations increase (Figures 314-2 and 314-3). Onset of the follicular phase is abrupt and can be subdivided into proestrus and estrus. Proestrus is usually less than a day in length, is not longer than 2 days, and may not be seen at all. Proestrus begins with development of ovarian follicles and the queen displaying estrous behavior but not mating. Increased concentrations of serum estradiol induce estrous behavior, defined as the period when the queen allows mating. Ovarian follicles have usually reached a size of 2-3 mm in diameter at the beginning of estrus.[15] Typical estrous behavior includes vocalization, lordosis with lowering of the chest, elevation of the pelvis and lateral deflection of the tail, rubbing and rolling. When the female displays lordosis, she will often tread with her hindlegs. A scant amount of clear vaginal discharge may be observed. The specific day of estrous behavior in relation to follicular maturation varies.[16] The duration of estrus is usually 5 to 8 days but can be as short as 2 to as long as 19 days.[16,17]

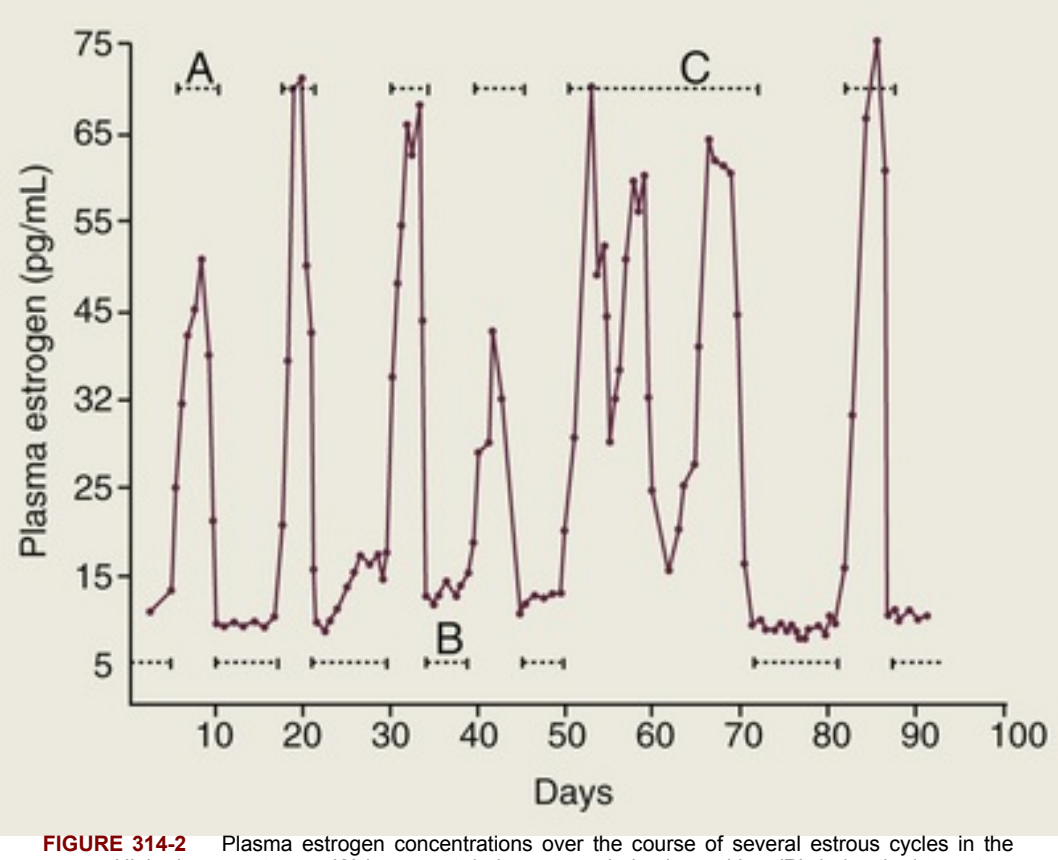

FIGURE 314-2 Plasma estrogen concentrations over the course of several estrous cycles in the queen. High plasma estrogen **(A)** is present during estrous behavior and low **(B)** during the interestrus interval. Plasma estrogen may not return to baseline between cycles and could cause an apparent prolongation in estrous behavior **(C).** (From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction, ed 3,* St Louis, 2004, Elsevier; used with permission.)

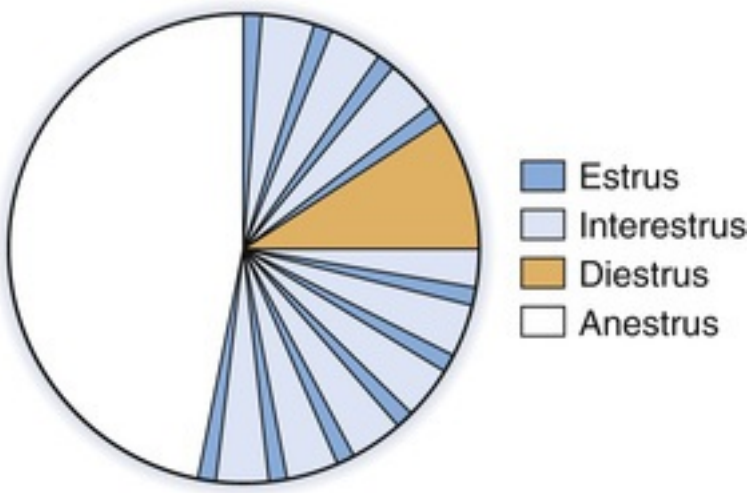

FIGURE 314-3 The reproductive pattern in the non-pregnant domestic cat in a 12-month period. In the average queen, the reproductive season is during the photoperiod with long days. In the absence of ovulation, there will be follicular atresia and no increase in serum progesterone. After a spontaneous ovulation or a sterile mating, serum progesterone is increased and the queen will be in diestrus. A period of diestrus will typically prolong the cycle. Individual variability is, however, very large with some queens cycling more or less throughout the year while other queens may only be in estrus once or twice in a year.

Vaginal cytology can be used to diagnose the follicular phase (Video 314-1). Elevated serum estradiol

concentrations cause thickening and cornification of the vaginal epithelium. In order to take a vaginal smear, the queen is grabbed firmly by the scruff of the neck and a cotton swab moistened with saline is inserted into the vulvar opening, advanced into the vestibule of the vagina, rolled and withdrawn. A smear with >80% cornified cells indicates that serum estradiol is above basal concentrations (Figure 314-4). The initial rise in serum estradiol often precedes estrous behavior and vaginal cornification by a day.[16]

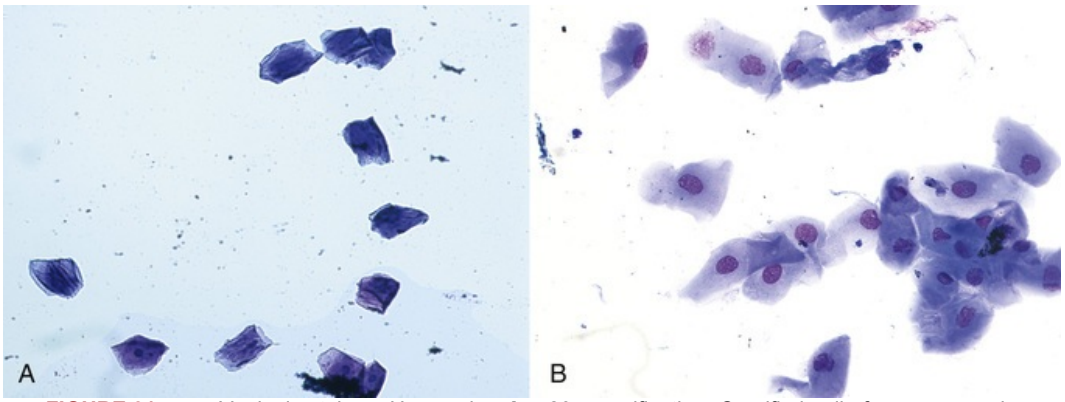

FIGURE 314-4 Vaginal cytology. Hemacolor. **A,** ×20 magnification. Cornified cells from a queen in estrus. **B,** ×40 magnification. Intermediate cells from a queen that is not in estrus. Note the granulated nuclei compared with the cornified cells in **A.**

Interestrus

Interestrus is defined as an inactive period between two estrus periods during the active season. If the queen does not ovulate, ovarian follicles will regress and serum estradiol will return to basal concentrations. Estrous behavior will cease and the ovaries are in an inactive stage. The duration of interestrus can be as short as 2 days but is typically around 1 to 2 weeks (see Figures 314-2 and 314-3).

Diestrus without Pregnancy (Pseudopregnancy)

Diestrus, the luteal phase, is the stage in which active corpora lutea in the ovaries are synthesizing and secreting progesterone. This phase can occur after a sterile mating or a spontaneous ovulation. Serum progesterone increases above basal concentrations (>3 nmol/L). The duration of the non-pregnant luteal phase (pseudopregnancy) varies from about 4 to 8 weeks, with a mean of 38 days (see Figure 314-3).[18]

Anestrus

Anestrus is a longer period without cycle activity. Ovaries are inactive and serum estradiol and progesterone concentrations are basal (see Figure 314-3). There is no definition that characterizes the difference in length between interestrus and anestrus phases. Anestrus typically begins as day-length begins to shorten, but there is significant individual variation in the length and timing of anestrus. Many cats remain in anestrus during warm-to-hot summers.

Estrous Cycle Duration

The length of the complete estrous cycle (i.e., from day 1 of estrus to day 1 of the next estrus) varies between and within individuals. In part, variation depends on whether or not the queen has ovulated. Typically, a queen will come into estrus every second or third week during the reproductive season (see Figures 314-2 and 314-3). The interestrous interval may, however, be as short as 2 days in a normal queen. If the queen ovulates, the cycle is usually 6 to 10 weeks in duration because of pseudopregnancy and the suppressive effect of progesterone on follicular activity.[18] A period of anestrus will also prolong the time between estrus periods. Some queens will cycle more or less throughout the year while other queens may cycle only once or twice a year.

Mating and Ovulation

Considering that cats are territorial, it is advised that mating take place in the male's "territory."[19] However, sometimes the chance of success is better if the male is moved to the female's territory, especially if the female appears frightened. The male initiates mating by grasping the female by the scruff of the neck, often inducing a more pronounced lordosis. Intromission is rapid and ends when the queen emits a characteristic shriek. Unless the male quickly retreats, the female may strike at him. She then begins the typical post-coital reaction: rolling intensely on the floor and licking the genital area. Mating will be repeated when the queen allows. Mating usually stimulates release of gonadotropin-releasing hormone (GnRH) from the hypothalamus which, in turn, induces release of pituitary luteinizing hormone (LH). Several matings may be required to reach the LH threshold to induce ovulation.[20] Follicles are not always mature the first days of estrous behavior. Thus, it is advised to not separate cats before day 3 or 4 of estrus to ensure that ovulation will occur. Once the threshold for LH secretion has been reached, all mature follicles ovulate. Ovulation is completed 25 to 32 hours after mating.[21] Oocytes can be fertilized up to 49 hours after induction of ovulation.[22]

Pregnancy and Parturition (see ch. 315)

Permanent and Temporary Control of Reproduction

Neutering

Cats not intended for planned breeding should be spayed or neutered. This avoids unplanned litters and behaviors related to gonadal hormones (see ch. 313). In breeding catteries, there is often the need to temporarily control reproduction. Frequent estrous cycles are associated with weight loss and it becomes difficult to keep a queen in good condition. Further, repeated cycles likely increase the risk of cystic endometrial hyperplasia (CEH) and pyometra (see ch. 316). The most natural method to suppress estrus would be to decrease the amount of daily light, but this is often complicated in a home environment. There may be a desire to temporarily reduce androgen-related behaviors in males. Male cat behavior, particularly urine spraying, often makes it difficult to keep an intact male cat free in a home as a pet.

Ovulation Induction

Ovulation increases the interestrous interval (see Figures 314-2 and 314-3) and can be induced by vaginal stimulation with a cotton swab. Some cats can be induced to ovulate when petted. Some castrated males continue to mate and some breeders keep them with estrous females to prolong the interestrus intervals. The risk of pyometra must be considered when a luteal phase is induced.

Progestagens

Progestagens used in cats include medroxyprogesterone acetate (MPA), proligestone, and megestrol acetate (MA). Their availability for veterinary use varies. Other progestagens have been used off-label in cats, but detailed studies on their effects and side effects are lacking. Depending on the active ingredient and dosage, effects and the risk of side effects vary.[23] Proligestone is only available for IM deposition while MPA and MA are available as tablets for oral use and in a depot formulation for IM administration.[23] For breeding females, the short-acting tablets are preferable as the duration of the treatment effect is easier to control. Progestagens have also been used to suppress male behavior via their anti-androgenic actions. Although sperm quality may decrease as a result of progestagen treatment, males can usually still sire litters.

Potential side effects include development of CEH, pyometra, mammary hypertrophy, acromegaly, diabetes mellitus, and mammary tumors. Skin alterations at injection sites, including discoloration, alopecia, skin atrophy, and calcinosis circumscripta, have been reported.[23-27] It is recommended that progestogen administration begin during interestrus or anestrus phases at dosages high enough to completely suppress estrus but as low as possible to avoid side effects. Also, it is best to avoid treating for extended periods, as side effects are likely to be total-dose dependent. Pregnancy should be ruled out before initiating treatment because progestagens can masculinize fetuses and inhibit parturition. Although progestagen administration can induce unwanted side effects, regular and frequent estrous activity may not be a better alternative.

GnRH-Agonists

Although not licensed for use in cats, slow-release GnRH-agonist implants have been studied and commonly

used for reversible suppression of fertility in cats.[27] After initial stimulation, the implant down-regulates secretion of FSH and LH which, in turn, suppresses testosterone and estradiol production from the testes and ovaries. Deslorelin is available as 4.7 mg and longer-acting 9.4 mg implants. Initial stimulation may induce estrus or, if implanted during estrus, ovulation. If the queen is mated in the induced estrus, she may become pregnant and carry the litter to term or she may abort. Maternal care and lactation may be absent even if the queen goes to term.[27] Duration of effect has been reported to vary between 16 months and more than 37 months with the 4.7 mg implant.

Males, after an initial stimulation, exhibit downregulation of spermatogenesis, decreased testicular volume, and basal serum testosterone concentrations. Penile spines regress and treated males behave like neutered tom cats. The duration of the 4.7 mg implant varies between 430 and 705 days, but may be >3 years.[27] Because of significant variability in response and reversibility of infertility, owners must be informed that pregnancies can occur despite treatment. In order to be able to shorten the duration of the treatment effect, implants are usually placed SC in the umbilical area for easy removal.

Melatonin

Although not licensed for use in cats, an 18 mg implant licensed for sheep (Melovine, CEVA Sante Animal, Libourne, France) has been used for short term (2 to 4 months) reversible suppression of estrus in queens. Duration of effect is longer when the implant is placed during interestrus.[28] No side effects were reported.[28,29]

Termination of Pregnancy

Medical termination of pregnancy should always be followed up with ultrasound 7 to 10 days after treatment to confirm treatment effect.

Ovariohysterectomy (Spay)

The most common method of terminating pregnancy in cats is by spay, preferably as early in pregnancy as possible.

Medical Abortion

Progesterone Receptor Blockade

Queens intended for breeding may be medically induced to abort. There are, however, no drugs licensed for this purpose in cats. Aglepristone (Alizine, Virbac S.A. France) is licensed in several countries for induction of abortion in bitches and is effective in queens by blocking progesterone receptors. Two injections of 10-15 mg/kg, SC, are given 24 hours apart.[30,31] Efficacy approaches 100% in early pregnancy but is lower (≈88%), in mid-pregnancy.[30,31] Side effects are more common and more pronounced in mid- or late pregnancy compared to treatment in early pregnancy and may include anorexia, partial abortion, no effect, retention of dead fetuses, retention of placental membranes, vaginal discharge, uterine infection, and reversible swelling at injection sites. Treatment can be initiated from the day of mating and should begin as early as possible, preferably before implantation. Treatment initiated on day 45 of pregnancy induced abortion in 4/6 cats (67%) but treatment is not recommended after day 45.[32] Late treatment in the queen decreases efficacy and increases risk of delivering live premature kittens.

Cabergoline

Cabergoline, a dopamine agonist, can be used to block prolactin. It is licensed in some countries to block milk production in the bitch and queen and to treat psuedopregnancy in the bitch. Prolactin is a necessary luteotroph in the second half of pregnancy in the queen and the administration of a dopamine agonist after this time causes a drop in serum progesterone concentrations and subsequent termination of pregnancy. Treatment can be initiated after day 30 of pregnancy. Combining cabergoline with cloprostenol is more efficient than cabergoline alone. Daily treatment can be started on day 25 (5 mcg/kg cabergoline PO q 24 h) for 7 to 10 days until pregnancy termination, combined with cloprostenol 2.5 mcg/kg, SC, on days 1, 3 and 5. Starting treatment after day 48 is not recommended, as it may result in birth of premature live kittens that will starve because lactation will have been suppressed.[33] Other dopamine agonists are associated with more side

effects than cabergoline.

Prostaglandins

$PGF2_{alpha}$, used to terminate pregnancy in cats, is luteolytic and induces uterine contractions. Its weak luteolytic effect, not as effective in cats as in many other species, explains why relatively high dosages are required for termination of pregnancy. A dose of natural $PGF2_{alpha}$ (2 mg/cat IM q 24 h for 5 days) starting about day 33 after mating induced abortion in 4/4 cats.[34] Side effects included nausea, vomiting and diarrhea. Because of these side effects, combination with cabergoline as described is recommended to enable use of lower dosages with fewer side effects.

Estrogens and Glucocorticoids

Neither estrogens nor glucocorticoids are recommended for pregnancy termination because of the paucity of documentation, potential risk of side effects and the availability of better alternatives.

Estrous Cycle Abnormalities

Prolonged Estrus

Estrous behavior lasting longer than 16 to 19 days is likely to indicate an abnormality within the ovaries. However, sometimes queens display estrus-like behavior in the absence of increased serum estradiol concentrations.[16] Vaginal cytology can be used to distinguish true estrus from estrus-like behavior in the absence of elevated estradiol. Prolonged estradiol secretion caused by ovarian disorders must be differentiated from a normal cycle with a short interestrus interval before initiating treatment. Follicular cysts or functioning ovarian tumors can secrete estrogen and cause chronic increases (see ch. 351).

Ultrasound (US) cannot be used to diagnose hormone-producing cysts as there may be other types of cysts within or near an ovary without clinical significance (e.g., rete ovarii cysts and remnants of the mesonephric duct). Hormone production can be confirmed with vaginal cytology (see Figure 314-4). Ovariohysterectomy is the treatment of choice for ovarian cysts. However, medical treatment may be attempted for valuable breeding queens. Induction of ovulation with human chorionic gonadotropin (hCG; 250 IU, IM q 24 h for 2 days) may cause cyst luteinization.[35] Treatment with short acting progestagens (medroxyprogesterone acetate) is an alternative that usually causes cyst atrophy. However, risk of inducing uterine disease must be considered before medical treatment is initiated. Surgical removal of the cysts may be an alternative for a valuable breeding queen.[36]

Primary Anestrus

Puberty can occur as late as 21 months of age. If a queen has not exhibited estrus before 2 years of age, primary anestrus is suspected. Developmental disorders are uncommon in cats but can cause primary anestrus. Hermaphroditism, X-chromosome monosomy, pseudohermaphroditism, and defective androgen receptors have been reported. Karyotyping and laparotomy to evaluate the inner reproductive organs and histology of the gonads may be required for a definitive diagnosis. Sometimes, ambiguous external genitalia may raise a suspicion of a developmental disorder.[37]

Secondary Anestrus

Some healthy cats have only one or two estrous cycles per year. The most common reason for prolonged anestrus is insufficient amount of light. Endocrine disorders as a cause of prolonged anestrus have not been described. Iatrogenic anestrus can be caused by administration of or exposure to progestagens or long-acting GnRH-agonists.

Previous Ovariectomy

If the history of the female is unknown, spay status can be evaluated with estradiol evaluation after buserelin stimulation, measuring serum LH concentrations, or evaluation of antimüllerian hormone (AMH).[38-40] Measuring LH is easy to perform in-house, has high sensitivity and specificity, but is not as reliable as the other two tests. Intact females have low serum LH concentrations while spayed females have increased

concentrations, due to absence of negative feedback. Measuring LH is best performed together with vaginal cytology to rule out estrus, which may cause increased LH concentrations in intact females. Both false positives and false negatives may occur. Basal serum estradiol is not useful as serum concentrations in intact and spayed females overlap. However, 120 minutes after an injection of 0.4 mcg/kg IM buserelin, intact females have increased concentrations of serum estradiol that do not overlap with concentrations from spayed females.[38] In females, antimüllerian hormone is only produced by granulosa cells and is therefore basal in spayed females and above basal in intact females.[40] Evaluation of AMH is thus a reliable test for the presence of ovaries.

Induction of Estrus

The best and most natural method to induce estrus is to increase the amount of daylight in a controlled light environment. This may require covering the windows during the dark photoperiod, otherwise the stimuli from outdoor daylight changes may be stronger than indoor artificial light. Contact with cycling females or male cat odor may also have a stimulatory effect. Medical induction can be accomplished with eCG (100-150 IU, IM). Higher doses may cause ovarian hyperstimulation.[41] Repeated injections with FSH will also induce estrus but may be less practical than eCG. Medical estrus induction should not be attempted in prepubertal queens. Diestrus should be ruled out before treatment by confirming basal serum progesterone concentrations.

Silent Estrus

Estrous behavior is usually quite obvious but can sometimes be vague or absent, even in a female with normal follicular waves (see Figure 314-2).[16] Silent estrus can be diagnosed with repeated samples for vaginal cytology. However, it may be necessary to take samples as often as two to three times per week in order to detect a silent estrus.

Uterine Disorders and Vaginal Tumors

See ch. 316 and 351.

Problems Related to the Mammary Glands

Mammary Gland Tumors

See ch. 351.

Mastitis

See ch. 315.

Mammary Hyperplasia

Abnormal mammary enlargement, known as feline mammary hypertrophy, mammary hyperplasia or mammary fibroadenomatous hyperplasia is a non-neoplastic condition. It is progesterone-dependent, with most affected animals being young intact females that have ovulated or cats that have been treated with progestagens.[42] A few cats have been described who did not have known previous exposure to progesterone or exogenous progestagens.[43,44] Although the condition is usually benign, it may become fatal due to necrosis and overwhelming infection. While spontaneous remission is possible, treatment may be necessary. Ovariohysterectomy in intact females that have ovulated removes the source of progesterone and results in regression of the mammary tissue. It may, however, take as long as 5-6 months before the condition regresses completely. Removal of affected mammary glands has been recommended but surgery may be difficult in advanced cases. Although not licensed for cats, treatment with the progesterone blocker aglepristone (Alizine, Virbac S.A. France; 10-20 mg/kg SC once weekly) will cause remission.[44] Marked response can be expected within 1-2 weeks with complete remission after 4 weeks.[44] It is important to remember that treatment with aglepristone will terminate any pregnancy.

Mating Problems

Most mating problems are related to management and temperament rather than pathological conditions. Partner preference, insecurity, and a female being in proestrus or in the interestrus phase rather than estrus are potential causes for failure to breed. If more than one tom is kept in the same area, the dominant male may suppress mating by subordinate toms.[19] A persistent frenulum can make it impossible for the male to breed and is easily corrected. It is not known if the condition is heritable.[45] Penile hair rings may cause mating problems in long-haired males and are easy to remove once identified. Cats with mating problems because of poor libido should be removed from the breeding pool to avoid the same problems in future generations.

Conception Failure With Apparently Normal Estrus and Mating

Anovulation

If a queen returns to estrus 2-3 weeks after mating, it is most likely that she failed to ovulate. Mating too early in estrus or too few matings may result in anovulation. It is not always obvious if cats actually mate. Failure to mate is the most likely reason for apparent anovulation. Failure to ovulate can be confirmed with a progesterone sample 1-3 weeks after mating (Figure 314-5).

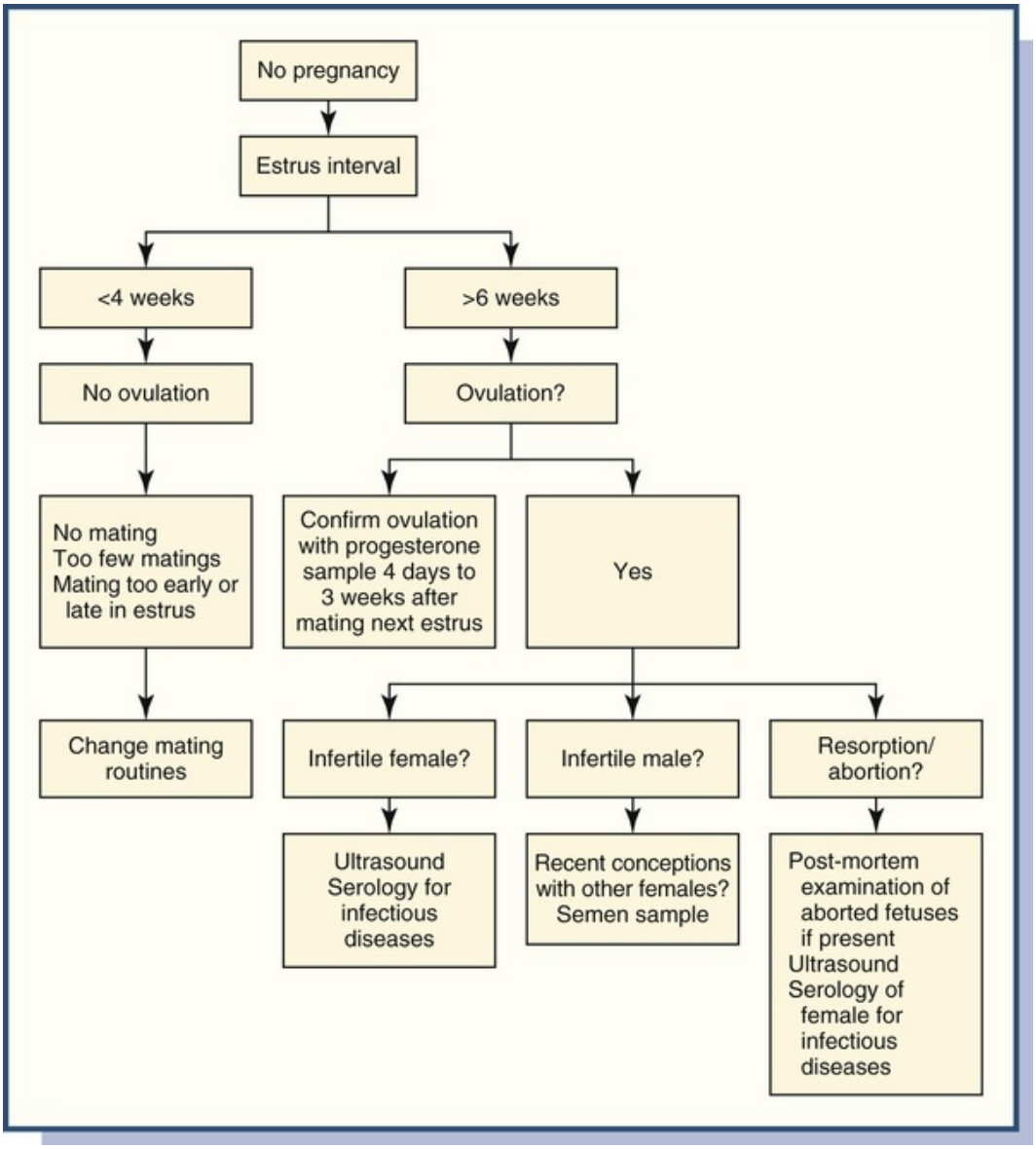

FIGURE 314-5 Algorithm for evaluation of infertility in cats.

Developmental Abnormalities

Abnormal development of the Müllerian duct can cause aplasia of the cranial vagina and absence of the cervical os, resulting in failure of sperm transport.[46,47]

Nutrition

Insufficient dietary taurine, arachidonate or copper are associated with lowered conception rates.[48-50] With increasing use of homemade diets, including raw food diets, there is a risk of nutritional imbalances as well as ingestion of food-borne pathogens (see ch. 192).

Chromosome Aberrations

Fetal chromosome aberrations have been identified as a cause of pregnancy failure but are extremely difficult to diagnose under clinical conditions.[51]

Stress

Stress may enhance synthesis and secretion of stress hormones, including catecholamines, glucocorticoids, and progesterone. Although stress is not a proven cause of fertility problems in cats, abnormal hormonal profiles associated with stress are known to interfere with early pregnancy in other species.

Infectious Causes for Infertility and Subfertility

See ch. 317.

Infertility in the Male Cat

Poor Semen Quality

Poor semen quality can be due to congenital issues in males with testicular hypoplasia or acquired in males with testicular degeneration. In the male with poor semen quality caused by testicular degeneration, the condition may improve while the prognosis for testicular hypoplasia is hopeless.[4,45] The two conditions can not always be distinguished clinically or even histologically. A male that previously has produced kittens is, however, likely to have a better prognosis than a male without previous proven fertility. Small testes and complete azoospermia are unfavorable signs. Chromosomal disorders in male cats have mostly been described in tortoiseshell males. Both red and non-red coat colors are linked to extra X-chromosomes needed for the tortoiseshell coat pattern. Although the tortoiseshell pattern is a marker for a chromosomal disorder, extra X-chromosomes occur also in males with other coat colors.[45]

Disorders of the Penis

Hypospadias is a rare congenital condition with abnormal localization of the urethral opening and has been described in the cat.[52] Priapism, persistent painful erection, is unusual and will usually require penile amputation due to ischemic damage.[53]

Cryptorchidism

Cryptorchidism is the result of failure of one or both testes to descend into the scrotum. Although testes are normally descended at birth in cats, they may move freely up and down the inguinal canal prior to puberty. Definitive diagnosis should not be made before a cat is at least 6 months old. Incidence has been reported to be 1.3-1.9 % of all male cats, with an over-representation of Persians.[54-56] Unilateral is more common (83-90% of cases) than bilateral and the inguinal location is most common.[54,55] Bilateral castration is recommended as these males should be removed from breeding programs and to avoid male cat behavior. It is not known if cryptorchidism increases the risk of testicular neoplasia in cats as there are few cases of testicular neoplasia

reported. Ultrasound can be used to locate undescended testes.[57] When the history of the cat is unknown, inspection of the penis for the presence of penile spines or evaluation of serum AMH will distinguish bilaterally cryptorchid males from previously neutered males.[40] Polyorchidism (extra testes) and monorchidism (absence of a testis) are extremely rare.[55,58]

Semen Collection

Most but not all toms in a cat colony can be trained for semen collection. Semen is collected with a custom made artificial vagina and the tom is allowed to mount an estrous female.[22] In a clinical situation, semen collection with an artificial vagina is unlikely to be successful. Electroejaculation under anesthesia or urethral catheterization under deep sedation with an alpha-2-agonist are alternatives that don't require prior training or the need to keep the male in his own territory.[59,60] For the urethral catheterization method, an open-end urinary catheter is inserted approximately 9 cm into the urethra in a male that is deeply sedated with an alpha-2-agonist, and then the catheter is withdrawn. Seminal fluid will accumulate in the catheter and can be flushed into a small test tube.[59]

Semen volume and sperm numbers are low when compared with dogs. Normal semen volume usually varies from 10 to 200 mcL and is affected by collection method. Larger mean volumes are collected with electroejaculation than with other methods. Sperm numbers vary from 3 million to 150 million, with higher values when collected with an artificial vagina. Sperm morphology is highly variable among individual males, with a large proportion of males producing high proportions of abnormal spermatozoa. Sperm morphology may also vary within individuals. It seems that toms can produce high proportions of abnormal spermatozoa without being infertile, depending on the type of sperm abnormalities. However, males with poor fertility often have high numbers of sperm abnormalities originating from the testes or may be completely azoospermic.[4]

Artificial Insemination

Artificial insemination is not a routine procedure in the cat. However, demand from cat owners is increasing and methods for semen preservation and intrauterine insemination are improving. In the absence of mating stimuli, ovulation can be induced with hCG (75-100 IU, IM). Determining the optimal time for ovulation induction is complicated by individual variations among healthy queens, but most queens will respond on day 3 or 4 of estrus. Ultrasound can be used to follow oocyte maturation for more exact timing, with induction of ovulation when at least one ovarian follicle has reached 3 mm in diameter.[15] Fresh semen can be deposited in the cranial vagina using a thin open-ended tom cat catheter. Frozen semen should be deposited in the uterus for better results.[61] Vaginal insemination can be performed without sedation or anesthesia, depending on the temperament of the cat, while intrauterine insemination requires anesthesia. Surgical intrauterine deposition has been used but transcervical deposition methods have been developed and should be considered as the first choice alternative.[61]

Pre-Breeding Examination

Cat registries often require that breeding cats be documented to be free from umbilical hernia and that stud cats have normally developed testes. These criteria for breeding animals should be applied, whether or not required by a cat registry. There are also breed-specific recommendations for heritable disease testing.[62] Breeding cats should be tested routinely for feline leukemia virus (FeLV) and feline immunodeficiency and only cats tested negative allowed in contact with cats in the cattery. FeLV vaccines are not 100% effective and will not prevent infection (see ch. 223). Therefore, routine testing is preferable to vaccination for breeding catteries.[63] Routine testing for other infectious diseases may also be warranted in some circumstances but the strategy for handling a positive test for agents that are widespread in the population should be considered first. For some breeds, such as the Rex breeds, British Shorthair and Sacred Birman, blood group testing before breeding is recommended to avoid feline neonatal isoerythrolysis.

It is beneficial to boost core vaccines for breeding catteries before each breeding to increase the amount of maternal antibodies that will be transferred to the kittens with colostrum and to protect fetuses from infections (see ch. 208). Vaccination during pregnancy is, however, not recommended.

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CHAPTER 315

Pregnancy, Parturition and Periparturient Problems in Dogs and Cats

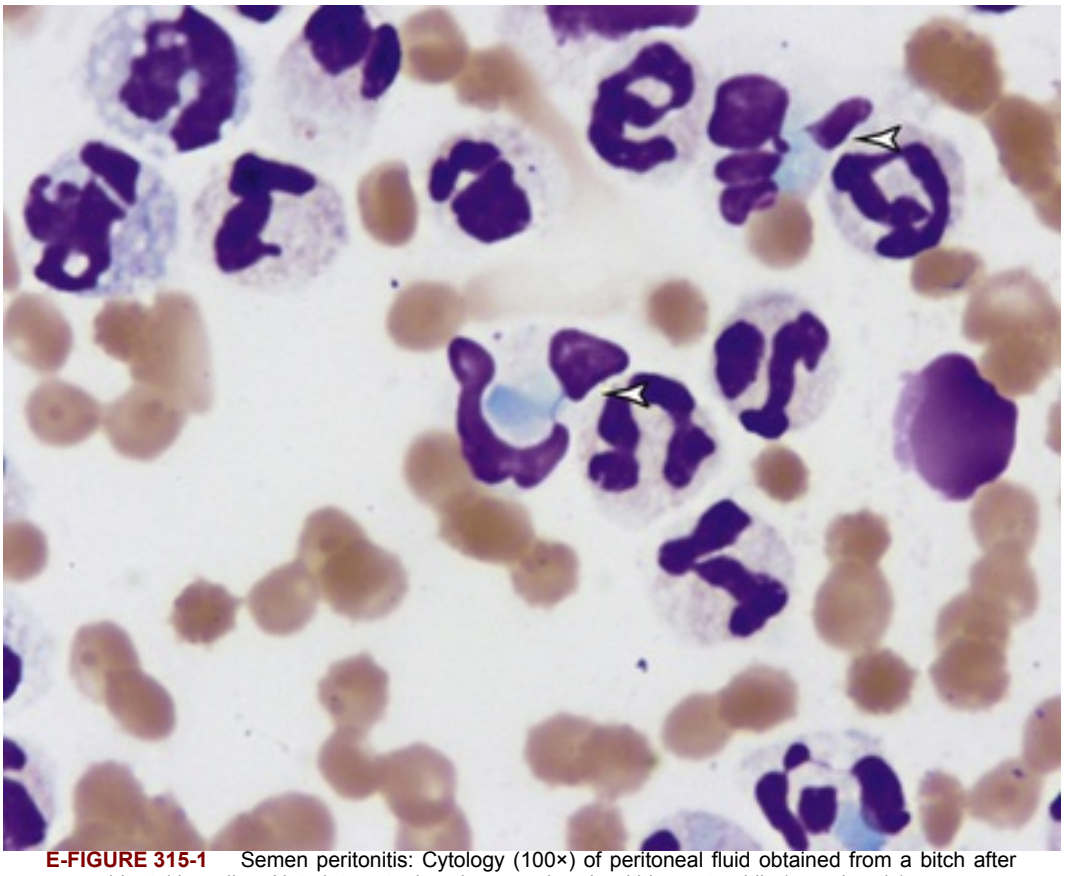
Autumn P. Davidson

Client Information Sheets:
Brucellosis in Dogs
Use of Cabergoline in Dogs and Cats
Canine Dystocia
Herpesvirus Infection in Dogs
Normal Whelping in the Bitch
Nutrition for Pregnant and Nursing Bitches
Post-Cesarean Section Neonatal Puppy Care
Canine Pseudopregnancy
Vaginal Hyperplasia in the Dam
When to Schedule an Elective Cesarean Section (C-section) in Your Bitch

The periparturient period begins about 9 weeks before parturition (pre-partum) and continues for about 30-45 days postpartum until weaning. Diagnosis of periparturient problems first requires differentiation from normal events. Effective treatment then depends on both a timely diagnosis and therapeutic intervention. The periparturient period can be associated with high morbidity and even mortality for the dam and neonates.

Semen Peritonitis

The common differential diagnoses for a sexually intact bitch with acute onset signs of abdominal pain should include pyometra, uterine rupture and uterine torsion. Acute peritonitis secondary to the deposition of semen into the abdominal cavity, an extremely unusual condition, should be considered among the possible conditions that could cause those signs in the estrual bitch. Usually such dogs have recently had exposure to an intact male dog or artificial insemination. Semen is forced into the uterus during the copulatory lock due to the large amount of prostatic fluid in the final fraction of the canine ejaculate. Normally, semen does not enter the peritoneal cavity of bitches after mating. However, if mating involves a much larger male or a diseased uterus, semen could be forced into the peritoneal cavity through trauma or via the fallopian tubes. Intraperitoneal deposition of semen may cause suppurative peritonitis and a systemic inflammatory response because prostatic fluid contains a large amount of foreign antigen (E-Figure 315-1). Stabilization followed by exploratory laparotomy and lavage of the abdomen are indicated. Inspection of the vagina and uterus for perforation should be carefully performed. This syndrome has high morbidity and mortality.



E-FIGURE 315-1 Semen peritonitis: Cytology (100×) of peritoneal fluid obtained from a bitch after an accidental breeding. Note intracytoplasmic sperm heads within neutrophils (arrowheads).

Hyperemesis Gravidarum

Bitches can experience a transient loss of appetite and, sometimes, vomiting during the second and third weeks of gestation. While this usually resolves spontaneously, marked anorexia can hinder adequate nutrition during gestation. Metoclopramide (0.1-0.2 mg/kg PO or SC q 12 h) can help. Alternative antiemetics may not be safe or recommended in pregnant dogs. Clinicians must evaluate risk vs benefit. In uncommon cases, force feeding must be undertaken.

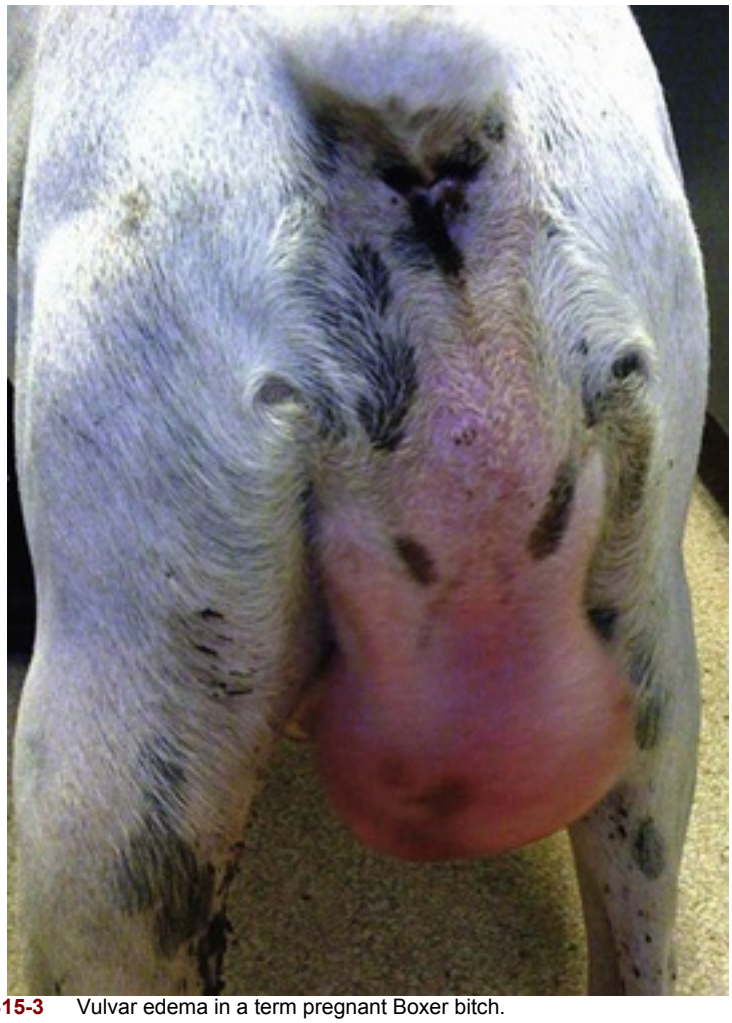
Vasculitides: Pregnancy Thrombosis

Pregnancy results in a hypercoagulable state, which becomes problematic in people with genetic prothrombosis. Hypercoagulability has been documented in pregnant dogs. Affected bitches are at risk for either arterial or venous thrombosis, as evidenced by elevated D-dimer levels (see ch. 196). Ultrasound (US) can be used to document thrombosis, most commonly involving the caudal vena cava and causing pelvic limb venous congestion (E-Figure 315-2 and Video 315-1). Antithrombotic therapy with low molecular weight heparin is used in women but has not been evaluated in the pregnant bitch. Abortion due to placental or fetal hemorrhage is a risk. Warfarin is contraindicated in pregnancy as it crosses the placenta. Aspirin causes congenital defects (cleft palates). The condition is believed to be inherited in women; affected bitches should probably be removed from the breeding pool.

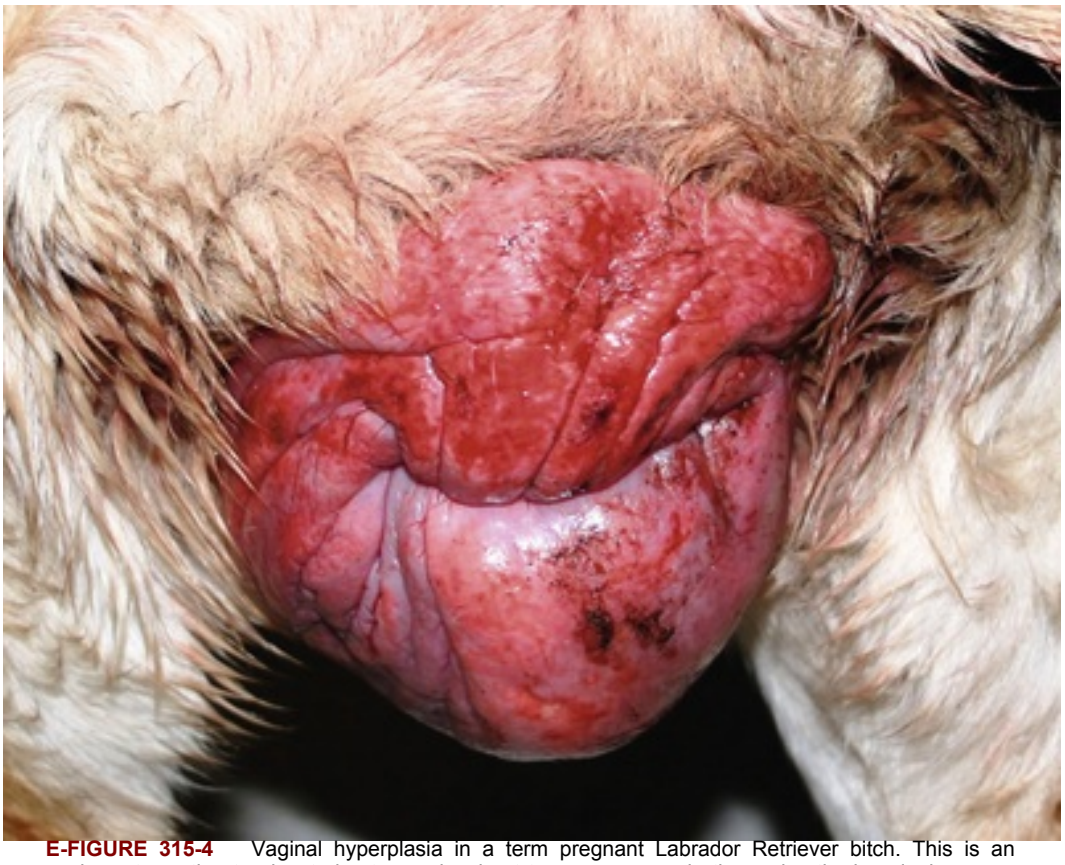
E-FIGURE 315-2 Venous congestion in a term pregnant Labrador Retriever bitch with venal caval thrombosis.

Pregnancy Edema

Marked edema of the distal pelvic limbs, caudal mammary glands, and perineum is occasionally observed in large breed bitches with large litters and normal serum albumin concentrations (E-Figure 315-3). Venous thrombosis should be ruled out with Doppler US. Vaginal hyperplasia can occur at term and be mistaken for pregnancy edema (E-Figure 315-4; see ch. 146). Mild normal estradiol increases near gestation term can induce reformation of vaginal hyperplasia (more commonly seen during estrus), and compromise the birth canal, which is an indication for elective cesarean section. Vaginal hyperplasia can be confirmed by digital examination of the vagina and finding a mass originating cranial to the urethral papilla. If pregnancy edema is confirmed, mild exercise (walking or swimming) can be helpful. The use of diuretics is not advised because complications have been noted (fetal polyuria, dehydration) and teratogenicity suspected. Severe edema of the perineum can cause dystocia.



E-FIGURE 315-3 Vulvar edema in a term pregnant Boxer bitch.



E-FIGURE 315-4 Vaginal hyperplasia in a term pregnant Labrador Retriever bitch. This is an exuberant reaction to elevated estrogen levels at term pregnancy in the periurethral vaginal mucosa resulting in extrusion of vaginal tissues through the vulva.

Pregnancy Loss

Overview

Abortion of all or some of a litter can result from traumatic, infectious, metabolic or degenerative conditions. Early embryonic loss is not usually recognized because resorption occurs. Mid-gestational fetal loss, from 21-30 days gestation, can be recognized with US (Figure 315-5). Late gestational loss (>40 days) usually causes recognizable abortion. Infectious causes of resorption in the bitch include *Brucella canis, Toxoplasma gondii, Neospora caninum,* canine herpesvirus-1, canine minute virus, also known as canine parvovirus type 1, *Cryptosporidium canis* or any ascending opportunistic bacteria.[1,2] Infectious causes of resorption/abortion in the queen are usually viral: leukemia virus, panleukopenia virus, herpesvirus and immunodeficiency virus. Resorption/abortion can also be due to protozoal *Toxoplasma gondii* or several bacteria: *Streptococcus* spp., *Escherichia coli, Campylobacter* spp. and *Salmonella* spp.[2,3]

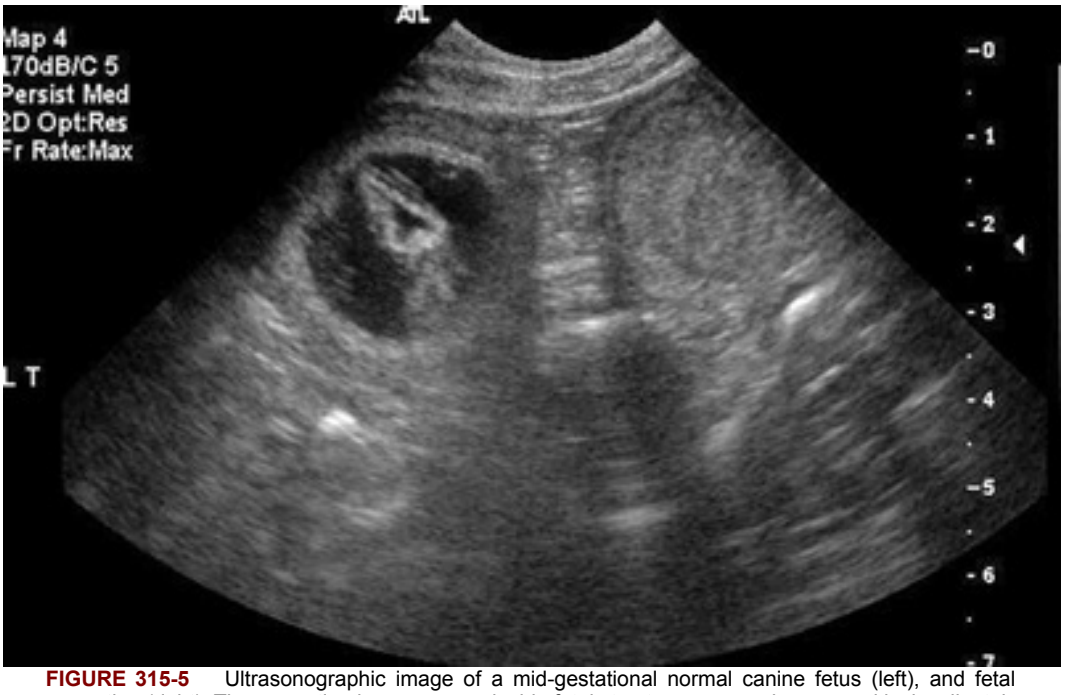


FIGURE 315-5 Ultrasonographic image of a mid-gestational normal canine fetus (left), and fetal resorption (right). The resorption has no recognizable fetal structures or membranes and lacks allantoic fluid.

Brucellosis (see ch. 213)

Canine brucellosis uncommonly causes abortion/resorption, which can occur early (before day 20) in gestation resulting in fetal resorption or more commonly (75%) later in gestation (generally 45-59 days) resulting in abortion. Any bitch with unexplained pregnancy loss should be screened for *Brucella.* Serology, blood or tissue culture, histology and polymerase chain reaction (PCR) techniques are appropriate for the diagnosis. A positive serologic evaluation is detectable in most infected dogs within 8-12 weeks. Since incubation ranges from 2-12 weeks, there is a window of time in which an infected individual can elude diagnosis serologically. The correct interpretation of serologic results is critical to making an accurate diagnosis. Screening serology is sensitive but not specific: a high rate of false positives occurs because surface antigens of *B. canis* cross-react strongly with antibodies to several non-pathogenic bacterial species. There can be as many as 50-60% false positives because of crossreacting *Bordetella* spp., *Pseudomonas* spp., *Moraxella* spp., and *B. ovis* antibodies. False negatives are rare unless testing is performed early in the infection. Confirmatory testing is needed because of the high incidence of false positives. For this reason, testing is recommended at least 1 month prior to a planned breeding, enabling more accurate testing if the initial screening test is positive. A false negative can occur if a recently infected dog or bitch is less than 8 weeks post infective exposure and the titer has actually not yet become positive. Otherwise, a negative test is usually indicative of a truly negative dog. Infected dogs and bitches should be removed from breeding programs and quarantined. Eradication of the disease in kennel situations has not been successful without removal (culling) of all infected (current or historically) dogs.

Canine Herpesvirus (see ch. 228)

Clinical signs of canine herpesvirus 1 infection in adult dogs are mild and suspicion of a kennel infection often begins with neonatal deaths and/or illness in pups. Problems are dependent on stage of pregnancy when infection occurs. Infection in early stages causes fetal death and mummification; in mid-pregnancy it may result in abortion; and in later stages, premature birth. In naturally occurring disease, pups are usually born apparently healthy but become ill and die during the first several weeks postpartum. Normally, immunity in the bitch develops and even those who have lost a litter because of herpesvirus infection can later give birth to normal litters.[4,5] Until recently, treatment of canine herpesvirus infection in neonates has been unrewarding and recovery may be associated with cardiac or neurologic damage. Treatment with immune serum from affected dams is ineffective in infected puppies. Acyclovir is an antiviral agent with

activity against a variety of viruses including herpes simplex. Its use in veterinary medicine is not well established and it should be used only in situations where indicated and with caution. Safety and effectiveness in humans less than two weeks of age is not established. The dosage (20 mg/kg PO q 6 h × 7 days) is extrapolated from human use. Canine herpesvirus vaccination may be available but indications and efficacy remain unsubstantiated.

Infections in Cats

Appropriate viral screening in catteries should reduce the incidence of viral associated pregnancy loss. Abortion in herpesvirus infected queens is related to systemic disease rather than a direct impact on the reproductive tract. Feline panleukopenia infection during early pregnancy causes subfertility and resorption; infection in mid-pregnancy is typically associated with abortion or fetal mummification. The classic feline panleukopenia-associated neonatal cerebellar hypoplasia (see ch. 225) manifests clinically as tremors and incoordination in neonates and is associated with late pregnancy infection. Feline leukemia and/or immunodeficiency virus-infected queens exhibit subfertility, arrested fetal development, abortion, stillbirths and/or low birth weight kittens. *Toxoplasma gondii*-infected queens, especially if immunocompromised, can produce stillbirths or low birth weight kittens.

Late Term Gestational Loss

Late term gestational loss can occur as a result of pre-term or premature labor. Both hypoluteoidism and inappropriate uterine activity accompanied by cervical changes have been implicated in the pathophysiology of preterm birth in dogs and cats. Premature labor is defined as uterine activity and cervical changes leading to the loss of pregnancy via resorption or abortion before term, for which no metabolic, infectious, congenital, traumatic or toxic cause is identified. Premature labor is associated with progesterone levels <2 ng/mL and is often a retrospective diagnosis after thorough evaluation of the dam and fetuses has been performed because of pregnancy loss. This evaluation should include metabolic screening of the dam for systemic and infectious diseases. Histopathology and culture of expelled fetuses and placentae should be done. Kennel/cattery nutrition, medications and environmental factors should be assessed. Dams experiencing premature myometrial activity in one pregnancy may or may not have issues in subsequent pregnancies.

Pre-Term Birth

Overview of the Human Experience

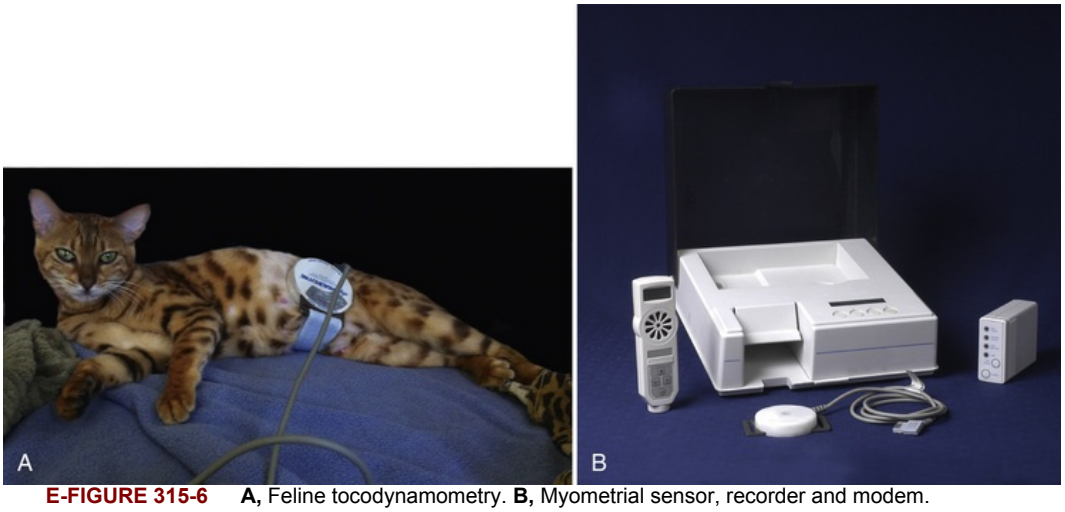
In women, preterm birth occurs in 10-12% of human pregnancies, but it accounts for 80% of fetal morbidity and mortality. The diagnosis of preterm labor requires evaluation of uterine contractility by tocodynamometry, fetal fibronectin, and measuring transvaginal cervical length with US. Together, these parameters have high negative predictive value. Women having preterm delivery are at risk for this same issue with subsequent pregnancies. Antibiotics, hydration, and rest do not have benefit. If intervention is indicated, tocolytic agents have been advocated. Contraindications to tocolytics include severe preeclampsia, placental abruption, intrauterine infection, lethal congenital or chromosomal abnormalities, advanced cervical dilation, and evidence of fetal compromise or placental insufficiency. Tocolytic agents inhibit myometrial contractions and include beta mimetics (terbutaline, ritodrine), magnesium sulfate, calcium channel blockers and prostaglandin synthetase inhibitors (indomethacin, ketorolac, sulindac).

Clinical trials in people given prophylactic progestational compounds have not consistently helped. Based on meta-analysis, prevention of preterm delivery or the prevention of recurrent miscarriage appears to be based on use of the natural metabolite of progesterone, 17 alpha-hydroxyprogesterone caproate (17P). Maintenance of canine or feline pregnancy requires serum progesterone levels >1-2 ng/mL and during normal pregnancy they are 15 to 90 ng/mL, declining gradually during the latter half of gestation, and then abruptly decreasing to basal concentrations at term (usually the day before or the day of parturition). Progesterone promotes the development of endometrial glandular tissue, inhibits myometrial contractility (causes relaxation of myometrial smooth muscle), blocks the action of oxytocin, inhibits formation of gap junctions and inhibits leukocyte function *in utero*. In several species, changes in progesterone or in progesterone : estrogen ratios in placenta, decidua or fetal membranes are important for initiating labor. Progesterone antagonists administered at term can result in an increased rate of spontaneous abortion.

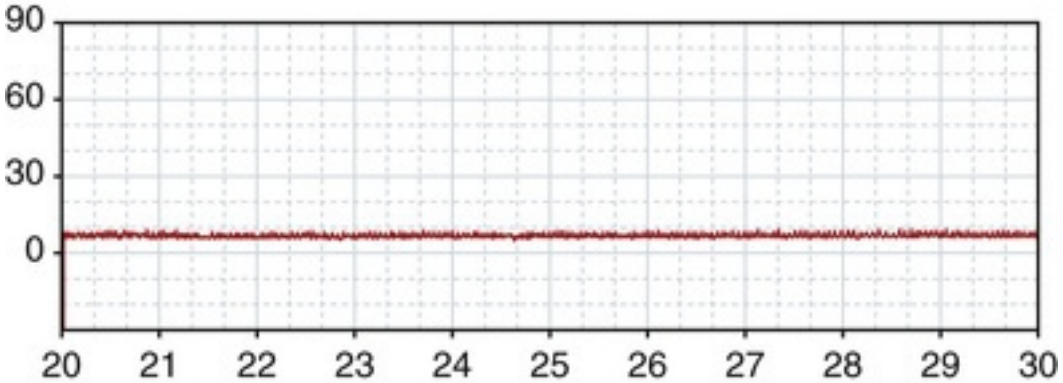
Hypoluteoidism in Dogs and Cats

In the bitch, ovarian corpora lutea are the sole source of progesterone. In queens, placental progesterone production occurs in the latter half of gestation. Canine luteal function is autonomous early in pregnancy but supported by luteotrophic hormones (LH and prolactin) after the second week of gestation. Hypoluteoidism, primary luteal failure occurring before term gestation, has not been a documented cause of late term abortion in bitches, but induction of abortion requires reducing plasma progesterone levels <2 ng/mL. The diagnosis of gestational loss caused by premature luteolysis is difficult, requiring documentation of inadequate plasma progesterone levels prior to abortion for which no other cause is found. Measurement of precise progesterone levels, especially in the critical 1-3 ng/mL range, is not accurate using currently available rapid in-house ELISA kits. For low concentrations, use of commercial laboratories is needed. A few laboratories provide rapid (<8 h) turnaround, facilitating the diagnosis.

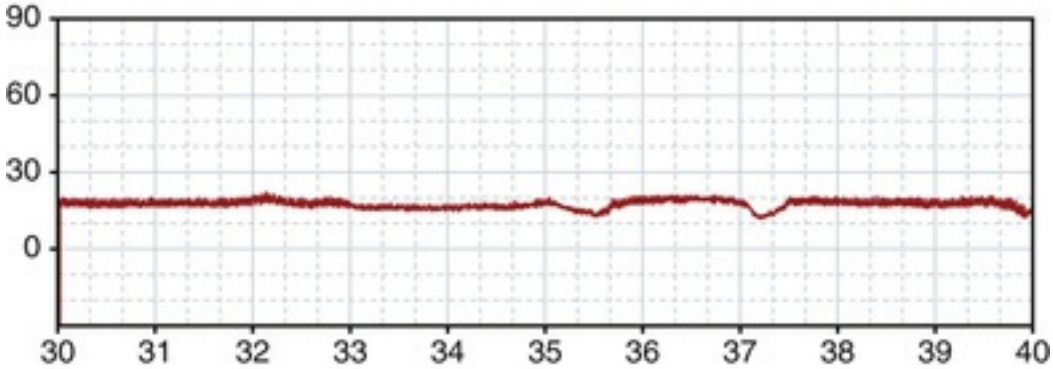
Progesterone levels diminish in response to fetal death; thus, documentation of a low progesterone level after an abortion does not establish a diagnosis of hypoluteiodism. Giving progesterone to maintain pregnancy in dams with primary fetal abnormalities, placentitis, or intrauterine infection can cause continued fetal growth with the possibility of dystocia and sepsis. Administration of too much progesterone to maintain pregnancy in a dam not actually requiring therapy can delay parturition, impact lactation, endanger the lives of bitch and fetuses, and can masculinize female fetuses. Dams with documented low progesterone levels and historical late term loss of pregnancy with no apparent pathology can also be evaluated for premature myometrial activity midgestation, using tocodynamometry (E-Figures 315-6, 315-7, and 315-8). Elaboration of prostaglandins from the endometrium and placenta in association with premature myometrial activity can result secondarily in luteolysis.



E-FIGURE 315-6 **A,** Feline tocodynamometry. **B,** Myometrial sensor, recorder and modem.

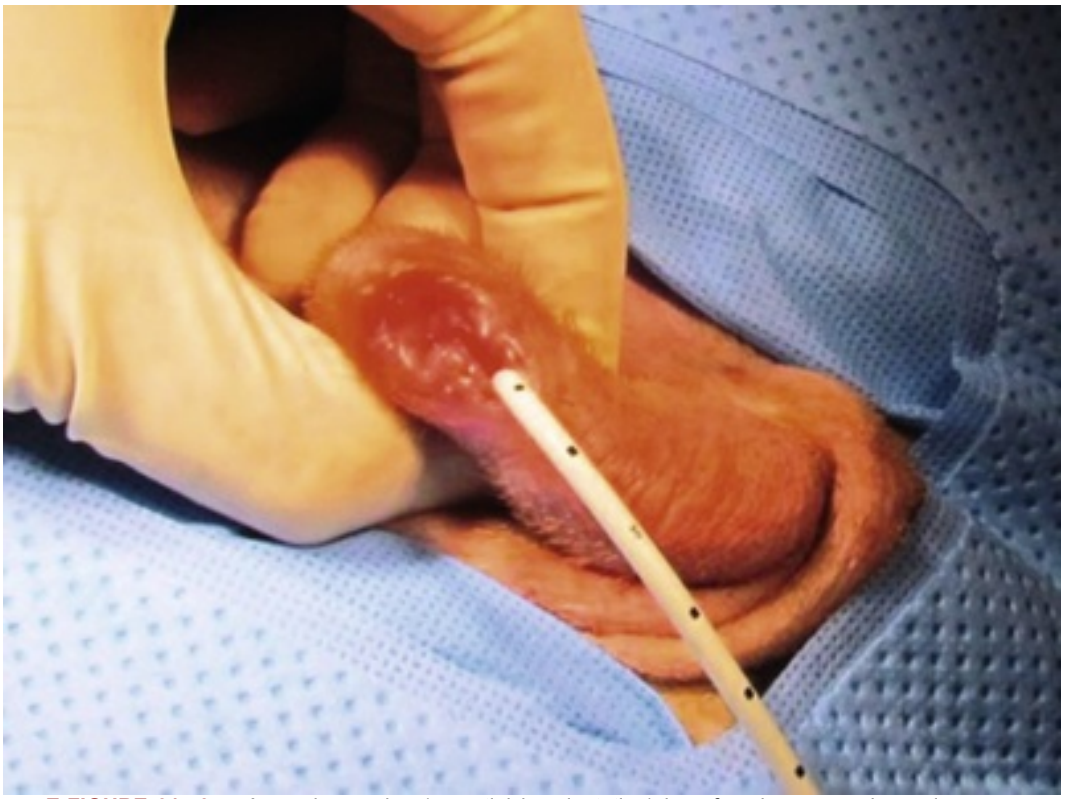


E-FIGURE 315-7 Tocodynamometry: normal quiescent uterus. X axis: time in minutes. Y axis: strength of contraction in mm Hg.



E-FIGURE 315-8 Tocodynamometry: uterine irritability mid-gestation. X axis: time in minutes. Y axis: strength of contraction in mm Hg.

Premature uterine activity endangering fetal survival has been identified before complete luteolysis occurs and intervention is indicated if the pregnancy is normal otherwise.[6] Tocolytic agents, alone or in combination with progesterone, decrease myometrial activity. Terbutaline (Brethine, Ciba Geigy; 0.03 mg/kg PO q 8 h) has been used to suppress uterine contractility in bitches and queens with historical preterm loss of otherwise normal pregnancies. Ideally, the dosage is titrated to effect using tocodynamometry and is discontinued 24 hours before term. Progesterone supplementation is only advised late in gestation if progesterone is <2-3 ng/mL to avoid teratogenic consequences (E-Figure 315-9). Serum progesterone can be monitored only when supplemented with the natural product (progesterone in oil, 2 mg/kg IM q 72 h). Altrenogest (Regumate, Merck Animal Health), a synthetic progestagen used in mares, is dosed orally at 0.09 mg/kg q 24 h. Both forms of supplementation must be discontinued in a timely fashion to avoid interfering with normal parturition. Usually, oral synthetic products are stopped within 24 hours of the due date and the injectable depot form 72 hours before. This protocol requires accurate prior ovulation timing (parturition expected to occur 64-66 days from the LH surge or initial rise in progesterone, or 56-58 days from the first day of cytologic diestrus). Less accurate identification of gestational length can be attempted with breeding dates (58-72 days from the first breeding), radiography, or US. Bitches and queens successfully managed for uterine irritability or preterm labor frequently have uterine inertia and require cesarean section.



E-FIGURE 315-9 Anomalous vulva (preputial in orientation) in a female puppy whose dam was treated mid-gestation with Altrenogest.

Metabolic Conditions

General Observations

Blood volume increases by 40% during pregnancy, providing adequate reserve to restore blood and fluid lost at parturition. Increases in plasma volume cause hemodilution, and the expected hematocrit is usually 30% to 35% at term. Increased cardiac output is caused by enhanced heart rate and stroke volume. Lung functional residual capacity is decreased by cranial displacement of the diaphragm by the gravid uterus. Oxygen consumption during pregnancy increases by 20%. Pregnant dogs may have delayed gastric emptying, displacement of the stomach, and increased risk of gastroesophageal reflux. Acromegalic signs can occur in the bitch secondary to progesterone-induced excesses in growth hormone (GH) secretion.[7] Gestational diabetes mellitus is rare in the bitch or queen and when present, is attributed to the anti-insulin effects of progesterone (mediated by increased levels of growth hormone; see ch. 304 and 305). Large fetuses that predispose to dystocia can result because of their enhanced insulin in response to maternal hyperglycemia. However, it is not common for diabetic dogs to carry a litter to term.

Pregnancy Toxemia

Pregnancy toxemia in the bitch occurs as a result of altered carbohydrate metabolism in late gestation resulting in ketonuria without glycosuria or hyperglycemia. This is most commonly due to poor nutrition (lack of nutrition or decreased appetite due to another issue) during the last half of gestation. Hepatic lipidosis can occur (see ch. 285). An improved plane of nutrition can resolve the condition, but termination of the pregnancy may be indicated in severe cases.

Eclampsia and Hypocalcemia (see ch. 146)

Definition

Puerperal tetany or eclampsia, life-threatening hypocalcemia, occurs most commonly in dogs during the first 4 weeks postpartum, but can occur in the last few weeks of gestation and is seen in queens. The condition is

caused by depletion of ionized calcium (iCa) in the extracellular compartment due to improper perinatal nutrition, inappropriate Ca supplementation, or serious losses into milk.[8,9] Small dams with large litters are at increased risk. Excessive prenatal Ca supplementation increases risk of eclampsia by suppressing parathyroid hormone release, interfering with normal mechanisms to mobilize Ca and utilize dietary Ca.

Prophylaxis

A balanced growth commercial (puppy/kitten) diet without additional vitamin or mineral supplementation should be given during the second half of gestation and throughout lactation. Cottage cheese and similar products should be avoided. They disrupt normal dietary Ca-phosphorus-magnesium balance. Metabolic conditions which favor protein binding of serum Ca and promote or exacerbate hypocalcemia include alkalosis from prolonged hyperpnea during labor. Hypoglycemia and hyperthermia may also occur.

Signs and Treatment

Signs preceding the development of tonic-clonic muscle contractions (not actually seizures) include behavioral changes, salivation, facial or distal extremity pruritus, stiff gait, limb pain, ataxia, hyperthermia, and tachycardia. Therapeutic intervention, initiated immediately upon recognizing signs of tetany without waiting for biochemical confirmation, include immediate slow IV infusion of 10% Ca gluconate (1-20 mL [0.5 mL/kg]) given to effect (see ch. 298). Cardiac monitoring for bradycardia and arrhythmias should accompany administration, and if seen, warrants temporary discontinuation of treatment and a slower subsequent rate. Mannitol may be indicated for cerebral inflammation and swelling. Corticosteroids are undesirable because they promote calciuria, decrease intestinal Ca absorption and impair mobilization from bone. Hypoglycemia should be corrected if present. Resolving the hypocalcemia usually resolves hyperthermia as well. Once acute neurologic signs are controlled, the volume of Ca gluconate given IV should be given SC, diluted 50% with saline. This can be repeated q 6-8 h until the dam is stable and able to take oral supplementation. Efforts to diminish lactation losses from the dam and improve her plane of nutrition are indicated. If response to therapy has been prompt, nursing can be gradually reinstituted until the neonates can be safely weaned, usually at a slightly early age (3 weeks). Concurrent supplementation with commercial bitch/queen milk replacement is encouraged. Administration of Ca throughout lactation, but not gestation, may be attempted in dams with a history of recurrent eclampsia (Ca carbonate 500-4000 mg/dam/day PO, divided).

Dystocia

Goals in Diagnosis and Management

Veterinary involvement in canine and feline obstetrics has several goals: to increase live births (minimizing stillbirths resulting from the difficulties in the birth process), to minimize morbidity and mortality in the dam, and to promote increased survival of neonates during the first week of life. Neonatal survival is directly related to the quality of labor. Dystocia (see ch. 146) is defined as difficulty in the normal vaginal delivery of a neonate from the uterus and various criteria are applied to identify this condition (Box 315-1 and Figure 315-10). Dystocia must be diagnosed in a timely fashion for medical or surgical intervention to improve outcome. Cause of dystocia must be identified to guide therapeutic decisions.

Box 315-1

Clues to Recognize Dystocia

Failure to initiate stage I labor at term (prolonged gestation)
- >72 days from first breeding
- >64-66 days from date of LH surge or initial rise in progesterone (1.5-2.5 ng/mL)
- >56-58 days from day 1 diestrus (first day vaginal cytology is <50% superficial cells; bitch usually non-receptive to male on that date)

Failure to enter stage I >24 h after temperature drop <99° F (<37.2° C) or when progesterone <2.0 ng/mL

Failure to proceed to stage II after 24 h in stage I

Failure to deliver all in timely manner (6-8 h); strong abdominal contractions for >1h without delivery (cannot evaluate uterine contractions without tocodynamometry); weak abdominal contractions >4-6 h

Fetal or maternal distress (stillbirths, difficult to resuscitate neonates, exhausted/weak, painful or shocky

bitch)
Copious vaginal hemorrhage
Uteroverdin without immediate delivery, indicating placental separation
Irreversible history of dystocia (chondrodystrophic breeds, pelvic abnormalities, vaginal strictures, masses or hyperplasia)
Radiographic abnormalities: obstruction, malposition, intrauterine/fetal gas suggesting fetal death, oversized fetus(es)
Persistent fetal bradycardia (HR <170-200 bpm)

From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction*, ed 3, St Louis, 2003, Saunders.

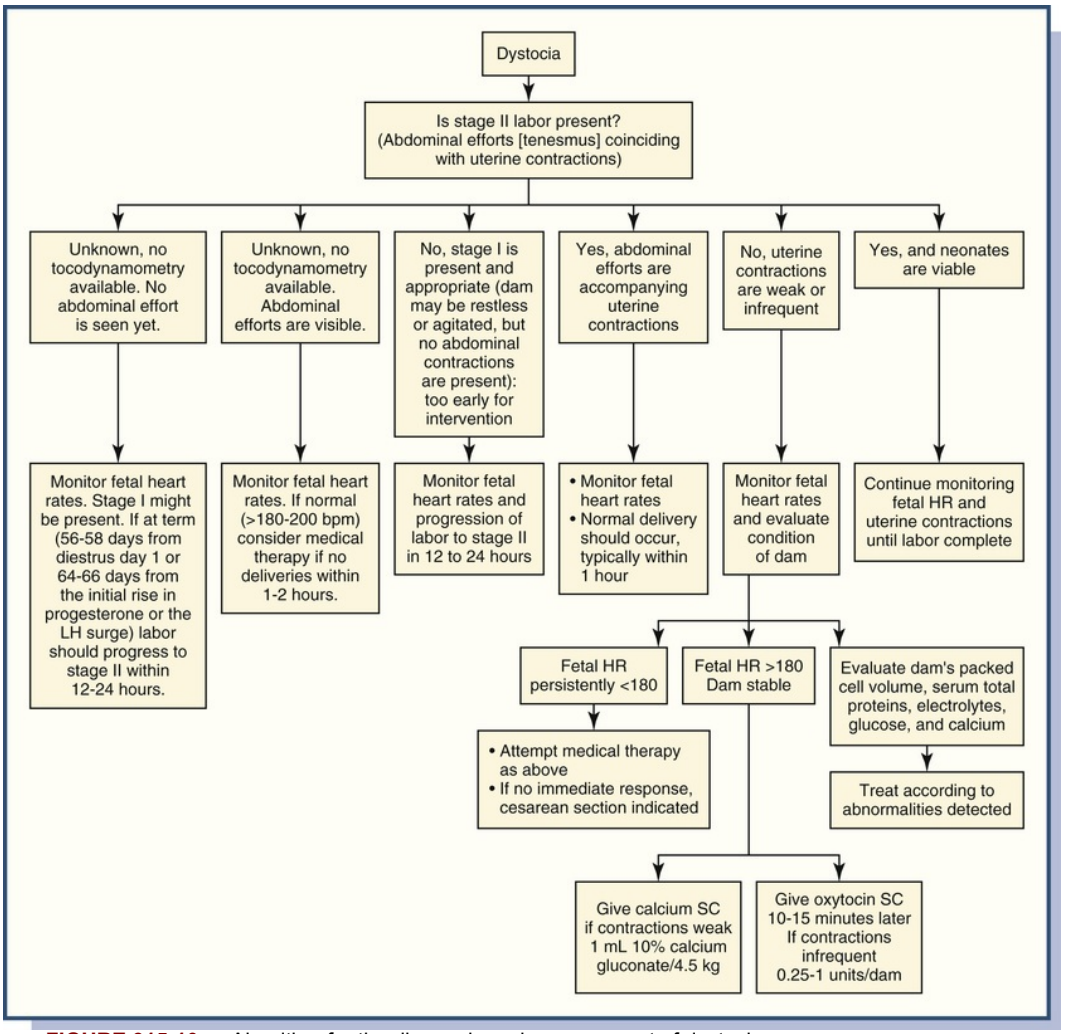


FIGURE 315-10 Algorithm for the diagnosis and management of dystocia.

Normal Parturition

Gestation

Clinicians are commonly asked if a bitch or queen is at term of pregnancy and if she is ready to deliver a litter, and then to intervene if labor has not begun. Accurate determination of gestational length is difficult if numerous copulations occurred and ovulation timing was not performed. Prolonged gestation is a form of dystocia. Gestation in the bitch is more challenging to calculate than in cats, because bitches are spontaneous ovulators. Normal gestation in the bitch is 56 to 58 days from the first day of diestrus (detected by serial vaginal cytologies, defined as the first day that cytology returns to ≤50% cornified/superficial cells; see ch.

119), 64 to 66 days from the initial rise in progesterone from baseline (generally >2 ng/mL), or 58 to 72 days from first breeding. Predicting gestational length without prior ovulation timing is difficult because of the potential disparity between estrual behavior and the actual time of conception in bitches, and the length of time semen remains viable within the reproductive tract of the bitch (>7 days).

Breeding dates do not correlate closely with whelping dates. Additionally, clinical signs of term pregnancy are not specific: radiographic appearance of fetal skeletal mineralization varies at term, fetal size varies with breed and litter size, and the characteristic drop in body temperature (typically <99° F [<37.2° C]) varies and may not be detected in all bitches. Breed, parity and litter size can also influence gestational length.[10] Because the queen is an induced ovulator (ovulation follows coitus by 24-36 hours), gestational length can be predicted more accurately from breeding dates, assuming that mating took place over a limited number days. Gestation duration in queens ranges from 52-74 days (mean 65-66 days), as measured from the first to last day of breeding. Because of poor outcomes with delivery of premature puppies and kittens, intervention is best delayed until stage I labor has begun, or prolonged gestation confirmed (see Figure 315-10).

Labor and Delivery

Bitches typically enter stage I labor within 24 hours of a decline in serum progesterone <2-5 ng/mL due to prostaglandin release and is commonly associated with a transient drop in body temperature (<99° F; <37.2° C). Queens typically enter stage I labor 24 hours after serum progesterone levels fall to <2 ng/mL. Monitoring serial progesterone levels for impending labor is problematic because in-house kits for quick results are inherently less accurate between 2-5 ng/mL and because a rapid decline in progesterone levels can occur over a period of a few hours. Commercial laboratories offering quantitative progesterone by chemiluminescence typically have a 12 to 24 hour turnaround time, not rapid enough to enable decisions about immediate need for obstetrical intervention.

Stage I labor in the bitch normally lasts from 12 to 24 hours, during which time the uterus has myometrial contractions of increasing frequency and strength, causing cervical dilation. Abdominal effort (visible external contractions) is not usually evident during stage I labor, but bitches may exhibit changes in disposition and behavior, becoming reclusive, restless, nesting intermittently, often refusing to eat and sometimes vomiting. Panting and trembling may occur. Vaginal discharge should be clear and watery. Normal stage II labor in the bitch begins when external abdominal efforts can be seen. Myometrial contractions culminate in the delivery of a neonate. Presentation of the fetus at the cervix triggers the Ferguson reflex, promoting the release of endogenous oxytocin from the hypothalamus. Typically, labor does not last longer than 1-2 hours between puppies, although great variation exists. The entire delivery can take between 1 to >24 hours, but usually less. Vaginal discharge can be clear, serous to hemorrhagic, or green (uteroverdin). Typically bitches continue to nest between deliveries, and may nurse and groom neonates intermittently. Anorexia, panting and trembling are common. Stage III labor is defined as the delivery of the placenta. Bitches typically vacillate between stages II and III of labor until all pups are delivered. Stages of labor in the queen are similarly defined. Stage I labor in the queen is reported to last 4-24 hours and stages II and III from 2 to 72 hours, although complete delivery of neonates within 24 hours is expected with normal queening.

Causes of Dystocia

Maternal Factors

Uterine inertia is the most common cause of dystocia. Primary uterine inertia results in the failure of delivery of any neonates at term and its causes are multifactorial, including genetic components and metabolic defects at the cellular level.[11] An intrinsic failure to establish a functional, progressive level of myometrial contractility occurs. Secondary uterine inertia is the cessation of labor after one or more neonates have been delivered, but not the entire litter. It can result from metabolic, anatomic (obstructive), or genetic causes. Birth canal abnormalities such as vaginal strictures, stenosis from previous pelvic trauma, stenosis in particular breeds, and intravaginal or intrauterine masses can cause obstructive dystocia. In most cases, canal abnormalities can be detected in the prebreeding examination and resolved or avoided by elective cesarean section (C-section). Causes of compromise rendering the dam unable to complete delivery include hypocalcemia (see ch. 69), hypoglycemia (see ch. 61), systemic inflammatory reaction (see ch. 132), sepsis (see ch. 132), and hypotension (due to hemorrhage or shock; see ch. 159).

Fetal Factors

Fetal factors contributing to dystocia most commonly involve mismatch of fetal and maternal size, fetal

anomalies and fetal malposition and/or malposture. Prolonged gestation with small litter size can cause dystocia due to an oversized fetus(es). Fetal anomalies such as hydrocephalus and anasarca similarly can cause dystocia. Fetal malposition (ventrum of fetus proximal to the dam's dorsum) and fetal malposture (flexed neck and scapulohumeral joints most commonly) promote dystocia as the fetus cannot transverse the birth canal smoothly.

Diagnosis (see Figure 315-10 and Box 315-1)

Overview

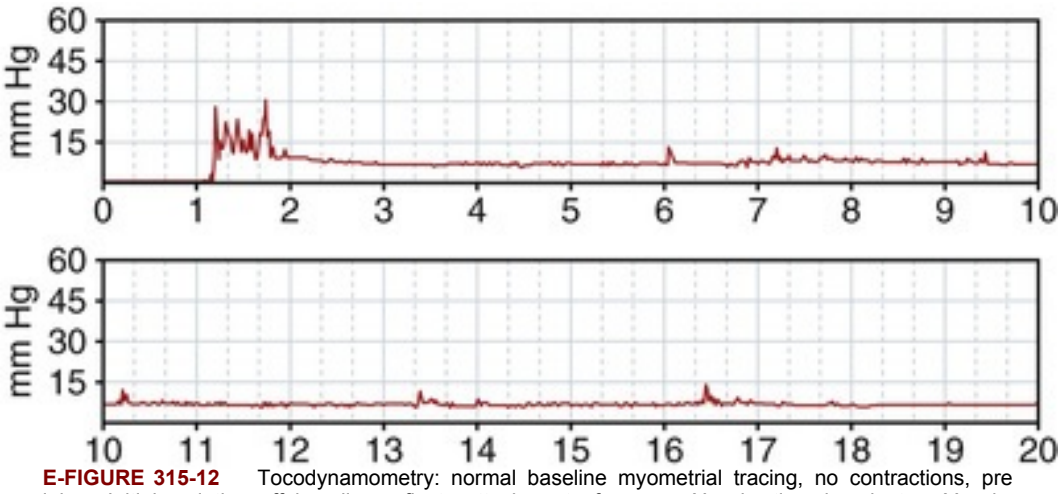
The clinician must quickly obtain a careful reproductive history detailing breeding dates, any ovulation timing performed, historical and recent labor, as well as a general medical history. Physical examination should address the general status of the patient, as well as include a digital and/or vaginoscopic pelvic exam for patency of the birth canal, evaluation of litter and fetal size (radiography most useful), assessment of fetal viability (Doppler or real time ultrasound ideally) and uterine activity (tocodynamometry most useful).

Fetal and Uterine Monitoring

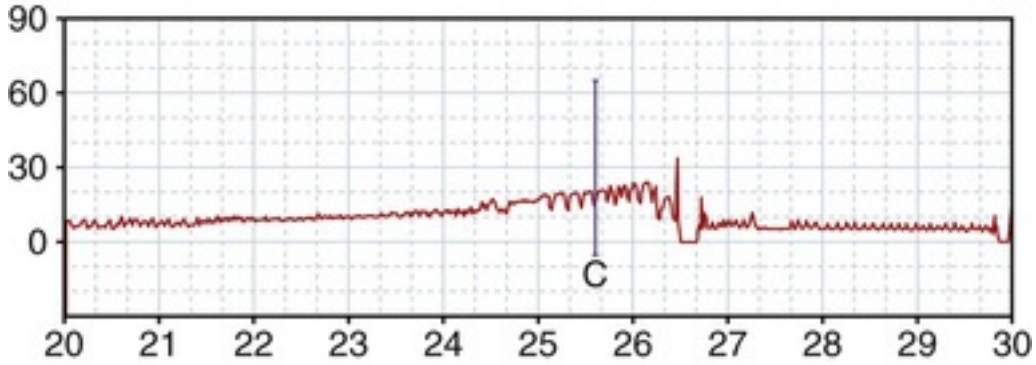
Current approaches to veterinary obstetrical monitoring involve the use of external monitoring devices using tocodynamometry (Healthdyne Inc., Marietta, GA, USA) and a hand-held Doppler (Sonicaid, Oxford Instruments, England) to detect and record uterine activity and fetal heart rates. These devices can be used either in the home or at the veterinary clinic. Their use requires that the hair coat be lightly clipped caudal to the ribcage and over the gravid area of the lateral flanks to allow proper contact of the uterine sensor and fetal Doppler. The uterine sensor detects changes in intrauterine and intra-amniotic pressures. The sensor, strapped over the clipped area of the bitch's/queen's caudolateral abdomen using an elasticized strap, is usually well tolerated. The sensor's recorder is worn in a small backpack placed over the caudal shoulder area. Bitches/queens should be at rest in the whelping/queening box or in a crate or cage during the monitoring sessions (E-Figures 315-6 and 315-11). Fetal Doppler monitoring is performed bilaterally with a hand-held unit with bitches/queens in lateral recumbency, using acoustic coupling gel. Directing the Doppler perpendicularly over a fetus results in a characteristic amplification of the fetal heart sounds, distinct from maternal arterial or cardiac sounds, which enables determination of fetal heart rates. Interpretation of the contractile pattern in strips produced by the uterine monitor requires training and experience. Data are transferred by modem to trained obstetrical personnel who subsequently consult with the attending veterinary clinician and client. Recordings are made twice daily, each an hour long when home monitoring is performed, then intermittently on bitches or queens at home as indicated during active labor, or on site in the veterinary clinic for shorter periods of time (minimally 20 minutes) when patients are being evaluated for suspected dystocia.

E-FIGURE 315-11 Chihuahua bitch undergoing tocodynamometry during evaluation for dystocia.

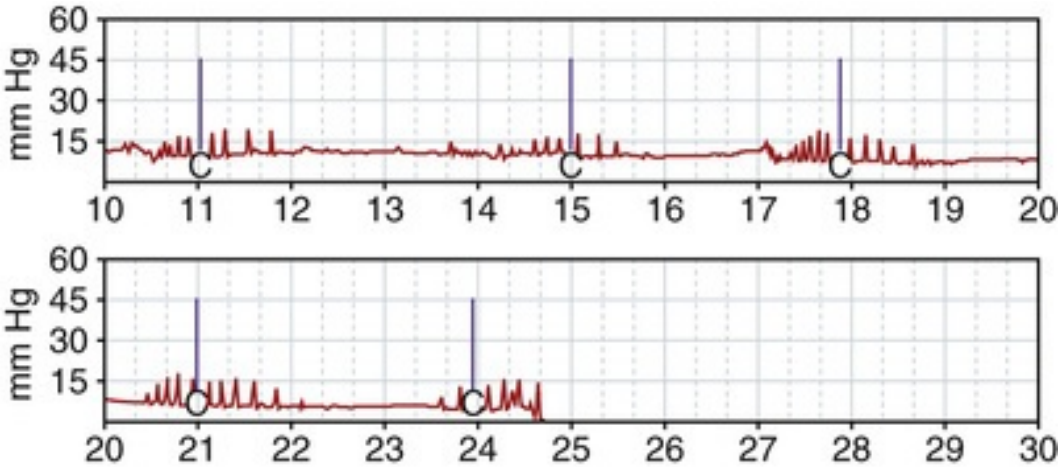
The canine and feline uterus each has a characteristic pattern of contractility, varying in frequency and strength before and during the different stages of labor. Late in gestation, the uterus may contract once or twice an hour before actual stage I labor is initiated. Thus, normal sessions can show no activity (E-Figure 315-12). During stage I and II labor, uterine contractions vary in frequency from 0 to 12 per hour, and in strength from 15 to 40 mm Hg, with spikes up to 60 mm Hg (E-Figure 315-13). Contractions during active labor can last 2 to 5 minutes in duration. Recognizable patterns exist during pre-labor and active (stages I-III) labor. Aberrations in uterine contractility can be detected during monitoring. Uterine inertia can be determined even when external, abdominal efforts are seen (E-Figure 315-14). Abnormal, dysfunctional labor patterns can be weak or prolonged, and often are associated with fetal distress (E-Figure 315-15). Completion of labor can be evaluated via tocodynamometry.



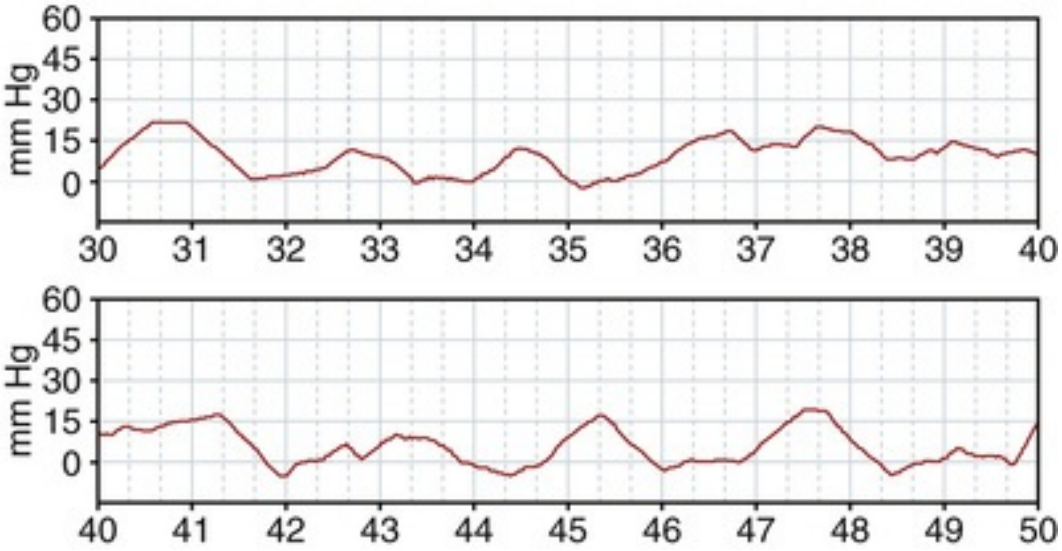
E-FIGURE 315-12 Tocodynamometry: normal baseline myometrial tracing, no contractions, pre labor. Initial variation off baseline reflects attachment of sensor. X axis: time in minutes. Y axis: strength of contraction in mm Hg.



E-FIGURE 315-13 Tocodynamometry: Early active labor, stage II, uterine contractions and abdominal pushing. X axis: time in minutes. Y axis: strength of contraction in mm Hg. *C,* Contraction.



E-FIGURE 315-14 Tocodynamometry: abdominal pushing with uterine inertia. X axis: time in minutes. Y axis: strength of contraction in mm Hg. Vertical spikes (c) indicate abdominal efforts.



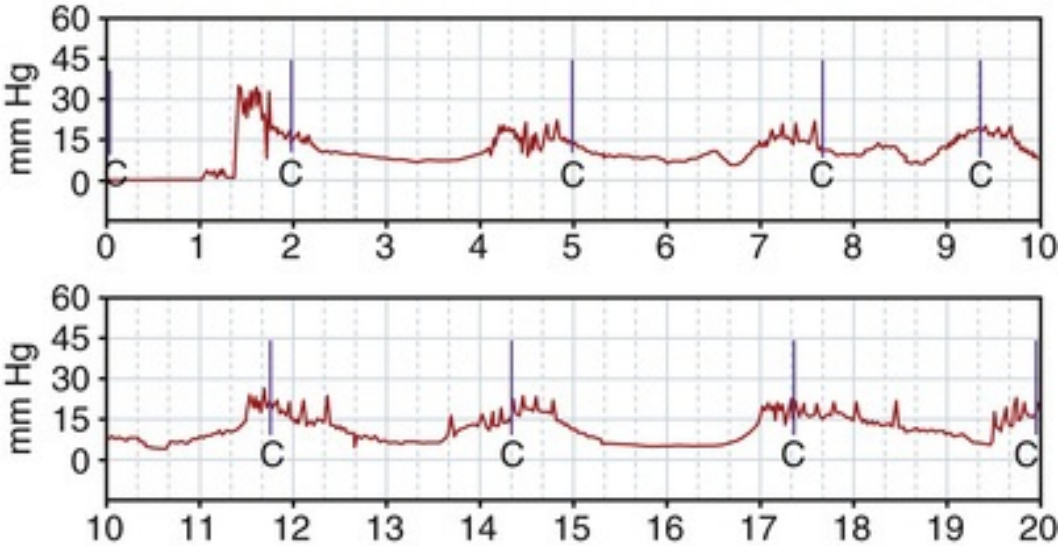
E-FIGURE 315-15 Tocodynamometry: Obstructive pattern. X axis: time in minutes. Y axis: strength of contraction in mm Hg.

Fetal Distress via Monitors

The presence of fetal distress is detected by sustained heart rate deceleration. Normal canine and feline fetal heart rates at term are from 170 to 230 beats per minute (bpm) or at least 4× the maternal heart rate. In the periparturient period, fetal cardiac output is mainly dependent on rate as the right ventricle is relatively stiff (low compliance) and the autonomic nervous system is immature (minimal inotropic response to catecholamines). Decelerations associated with uterine contractions suggest mismatch in size between the fetus and dam or fetal malposition. Transient normal accelerations occur with fetal movement. Fetal heart rates ≤150 to 160 bpm indicate stress, rates ≤130 bpm are associated with poor survival if not delivered within 30-60 minutes. Fetal heart rates ≤100 bpm indicate need for immediate delivery of neonates (medical or surgical). The use of uterine and fetal monitors allows the veterinary clinician to detect and monitor labor, as well as manage labor medically or surgically with insight. At one dog breeding facility, stillbirth rate declined from 9.2% to 2.5% with use of uterine and fetal monitoring.

Medical Therapy for Dystocia

Medical therapy for dystocia, administration of Ca gluconate and oxytocin, can be directed and tailored based on the results of monitoring (see ch. 146). Generally, giving Ca increases strength of myometrial contractions, while oxytocin increases their frequency (E-Figure 315-16). Ca is given before oxytocin in most cases, improving contraction strength before increasing frequency. Ca gluconate (10% solution with 0.465 mEq Ca/mL; 1 mL/5.5 kg SC [Fujisawa Inc., USA]) is given as indicated, noting the strength of uterine contractions, usually every 4-6 hours. Oxytocin (10 USP units/mL; American Pharmaceutical Partners Inc., Los Angeles, California, USA) is effective starting with 0.25 units SC or IM to a maximum of 2 units per bitch or queen. High dosages of oxytocin, or IV boluses, can cause tetanic, ineffective uterine contractions that can further compromise fetal oxygen supply by placental compression. The frequency of oxytocin administration is dictated by the labor pattern and it is generally given about q 30-60 minutes. Additionally, the action of oxytocin appears to be improved when given 15 minutes after Ca. Most bitches/queens are eucalcemic, suggesting that the benefit of Ca is at a cellular or subcellular level.



E-FIGURE 315-16 Same bitch as in E-Figure 315-13, treated with 6 mL 10% calcium gluconate SC and 0.5 USP unit oxytocin IM. Abdominal pushing evident in conjunction with uterine contractions. Neonate was delivered in 26 minutes.

Surgical Therapy (Cesarean Section [C-Section])

Indications

Surgery is indicated if a bitch or queen fails to respond to medical management or if fetal distress is evidenced despite adequate to increased uterine contractility (suggesting mismatch of maternal birth canal to fetal size, fetal malposition or malposture incompatible with vaginal delivery), or if aberrant contractile patterns are noted by uterine monitoring. Well-orchestrated C-sections are the result of established and coordinated anesthetic and neonatal resuscitative protocols together with optimal preoperative preparation of the dam. It should always be remembered that the dam may be debilitated and require careful anesthetic management, there may be little time for routine pre-anesthetic preparation, and she may have been fed recently. Minimally, the hematocrit, total solids, serum Ca and glucose levels should be evaluated preoperatively. IV fluid support is indicated (5-10 mL/kg/h; see ch. 129).

Pre-Anesthesic and Anesthetic Agents

Spinal blocking protocols are described in ch. 146. Atropine is not advised for premedication because it crosses the placenta, blocks the adaptive bradycardic fetal response to hypoxemia, and relaxes the lower esophageal sphincter, making maternal aspiration more likely. However, the use of an anticholinergic is indicated for the dam because of the anticipated vagal stimulation during uterine manipulation. Glycopyrrolate (0.01-0.02 mg/kg SC) does not cross the placenta and is preferred. Most dams do not need preanesthetic tranquilization, which has a depressant effect on fetuses. Phenothiazine tranquilizers are transported rapidly across the placenta. Alpha 2-adrenoreceptor agonists (dexmedetomidine, xylazine) and opiates are contraindicated because of their severe cardiorespiratory depressant effects. If tranquilization is necessary with an intractable dam, narcotic sedatives are preferable as their effects can be reversed (naloxone 1-10 mcg/kg IV or IM) during neonatal resuscitation (see Video 146-1). Metoclopramide (0.1-0.2 mg/kg) can be administered SC or IM prior to induction of anesthesia, reducing risk of vomiting. Pre-oxygenation by mask (5-10 minutes) is always indicated (see ch. 131). Initial preparation of the abdomen can be started during this time. For induction of anesthesia, dissociative agents such as ketamine and the barbiturates are best avoided because they can profoundly depress fetuses. Propofol (6 mg/kg IV to effect) appears to be most useful; its rapid redistribution limits fetal issues after delivery. Alfaxalone (Alfaxan, Jurox) 1.5-4.5 mg/kg IV (canine) and 2.2-9.7 mg/kg IV (feline) has been used as an induction agent for C-sections, but fetal and neonatal depression occur and studies in pregnant or lactating dams are needed. Mask induction causes more maternal and fetal hypoxemia than propofol.

For maintenance of anesthesia, volatile agents are preferable, especially those with low partition coefficients (isoflurane and sevoflurane). These agents show rapid uptake, quick elimination, and may have better cardiovascular margins of safety than more soluble agents (halothane). Nitrous oxide may be used to reduce

the dose of other anesthetic agents, it is transferred rapidly across the placenta and, although it has minimal effects upon the fetus *in utero*, it may result in significant diffusion hypoxia after delivery. Using a local anesthetic (bupivacaine 2 mg/kg) line block in the skin and SC tissues prior to incising permits a more rapid entry to the abdomen while the dam is making the transition from propofol induction to inhalant maintenance, and helps with postoperative discomfort.

Surgery/Ovariohysterectomy (OVH)

OVH at the time of C-section is an option for surgeon and owner, but results in longer anesthetic time, delays neonatal nursing, and increases the chance of maternal blood loss. OVH should be postponed if reasonable. There is some belief that estrogen acts in a permissive fashion for prolactin receptors in the mammary glands, making ovary removal undesirable. If uterine viability is questionable, OVH should be performed. In the normal dam, the uterus will begin to involute shortly after removal of the fetuses, but if this is not the case oxytocin may be administered (0.25-1.0 units per dam) to facilitate involution, help slow any bleeding, and promote milk letdown. Elective C-sections are common in people (>50% of deliveries in the USA). Breeders may request elective C-section when apprehensive about the whelping process. There are pros and cons to consider when counseling clients about elective C-sections. Indications for elective C-section include singleton litter, oversized fetuses, brachycephalic or hydrocephalic breed, or historical inability to whelp vaginally (E-Boxes 315-2 and 315-3). 60% of bitches undergoing C-section can whelp vaginally on subsequent pregnancies.

E-Box 315-2

Positive Considerations for an Elective Cesarean Section

- More predictable outcome in *most* cases
- Scheduled, not emergency time frame
- Single method of delivery
- Sometimes more cost-effective
- Proactive pre-operative management
- Proactive pain management
- Increased veterinary involvement in delivery
- Promotes ovulation timing for gestational aging to select date of cesarean
- Avoids complications of unrecognized dystocia
- Immediate veterinary evaluation of neonates
- Avoids visit to emergency clinic unfamiliar with client and bitch
- Staff enthusiasm

E-Box 315-3

Negative Considerations for an Elective Cesarean Section

- Anesthetic risks
- Surgical risks
- Invasiveness
- Drug delivery to neonates
- Expense
- Bypasses exposure to normal protective vaginal flora (increase in neonatal pathogens)
- Exposure to infectious disease in veterinary clinic
- Loss of selection for natural whelping
- Maternal stress
- Maternal surgical pain
- Maternal drug delivery
- Delayed or abnormal maternal behavior

- Requires neonatal resuscitation

Post-Surgery

Discomfort should be anticipated in the dam, and once the fetuses are removed, narcotic analgesia should be administered to her. Postoperatively, nonsteroidal anti-inflammatories are not advisable due to their uncertain metabolism by the nursing neonates with immature renal and hepatic metabolism. Narcotic analgesia is preferable. Oral narcotics such as tramadol, 10 mg/kg/day PO in divided doses, provide excellent analgesia for nursing bitches with minimal neonatal sedation. In all cases, clients should be advised to closely monitor bitches postoperatively until normal maternal behavior emerges. Post C-section, bitches can be clumsy, inattentive, and even aggressive to their puppies. The normal mechanisms of maternal bonding have been bypassed by surgery and neonatal care is usually fine with time.

Immediate Postpartum Period

Normally, dams remain close to their offspring during the first 2 weeks postpartum, leaving the whelping/queening box briefly, if at all, to eat and eliminate. They should be alert and content to remain with their offspring. Some protective dams may show aggression to housemate animals or people initially. Such behavior tends to dissipate after 1-2 weeks of lactation. Lactation is likely the greatest nutritional and caloric demand of the female's life. Weight loss and dehydration should be avoided because of danger to the dam and because lactation will be negatively impacted. Food and water must be made readily available. Sometimes both food and water need to be placed in the nest box of a nervous dam. Partial anorexia can be exhibited during the last weeks of gestation and in the immediate postpartum period, but appetite should return and increase as lactation progresses. Poor appetite during the last weeks of gestation can be due to displacement or compression of organs (stomach) by the gravid uterus. Early postpartum partial anorexia has been noted after consumption of placentae, causing digestive upset. Diarrhea can be secondary to the bitch being given more food and/or richer food than usual. Also, bacterial overgrowth secondary to carbohydrate malassimilation may occur. Marked postpartum effluvium is normal in bitches, usually occurring 4-6 weeks after whelping and sparing only the head. This is usually more marked than that which occurs in conjunction with the typical estrous cycle. Owners should be assured that is not problematic, despite being noted to happen in conjunction with the weight loss typically associated with lactation.

The body temperature of the dam may be mildly elevated (<103.0° F [<39.4° C]) in the immediate postpartum period, reflecting normal inflammation associated with parturition. It should return to normal levels within 24-48 hours. If a C-section took place, differentiating normal post-surgical inflammation from fever associated with illness may be difficult. Physical examination and a complete blood count may help. Normal postpartum lochia is brick-red in color, non-odorous, and diminishes over several days to weeks (uterine involution and repair progress for up to 16 weeks in bitches). The mammary glands should not be painful, hot, erythematous, or hard. They should be symmetric and moderately firm. Normal milk is gray to white in color and of watery consistency.

Inappropriate Maternal Behavior

Appropriate maternal behavior is critical to neonatal survival and includes attentiveness, protection, facilitation of nursing, herding neonates, and grooming. Although maternal behavior is instinctual, it can be negatively influenced by anesthetic drugs, pain, stress, and human interference. Maternal bonding is pheromone-mediated and initiated at parturition. Whelping and queening should take place in quiet, familiar surroundings with minimal human interference, yet adequate supervision. Dams with good maternal instincts exhibit caution when entering or moving about the nest box so as not to traumatize neonates by stepping or lying on them. A guardrail along the inside of the whelping box can help prevent inadvertent smothering of puppies.

The neuroendocrine reflex regulating mammary gland myoepithelial cell contraction and subsequent milk ejection is mediated by oxytocin and activated by neonatal suckling. During stress, epinephrine induces vasoconstriction, blocking the entry of oxytocin into the mammary gland and preventing milk letdown. A nervous, agitated dam will likely have poor milk availability. Dopamine antagonist tranquilizers, with minimal prolactin interference (acepromazine 0.01-0.02 mg/kg PO q 6-24 h) can be given at the lowest effective dosage to minimize neonatal sedation. This may improve maternal behavior and milk availability in nervous dams. Piling of littermates near their dam facilitates the maintenance of appropriate body

temperature (neonates cannot thermoregulate/shiver until up to 4 weeks of age) and makes nursing readily available. Normal maternal behavior includes gentle retrieval of neonates who become dispersed and isolated across the nest box. Grooming of the neonates immediately following parturition stimulates their cardiovascular and pulmonary functions and removes amniotic fluids. Dams demonstrating little interest in resuscitating neonates can have poor maternal behavior throughout the postnatal period. Later, maternal grooming stimulates reflex neonatal urination and defecation as well as keeping neonatal coats clean and dry. Occasionally, excessive protective behavior or fear-induced maternal aggression can occur. Mild tranquilization of the dam can help, but neonatal drug administration via the milk can be problematic. Benzodiazepines, GABA synergists, are superior to phenothiazines for fear-induced aggression (diazepam 0.55-2.2 mg/kg PO q 8-12 h).

Uterine Disorders

Uterine Prolapse and Rupture

Complete or partial prolapse of the uterus is uncommon in the bitch and rare in queens (Figure 315-17). Diagnosis is based on palpation of a firm tubular mass protruding from the vulva postpartum and an inability to identify the uterus with abdominal US. Vaginal hyperplasia and prolapse should be ruled out by physical examination, vaginoscopy, or contrast radiography (see ch. 146). Prolapsed tissues can be macerated and/or infected from exposure and contamination. The size of most bitches and queens precludes manual replacement; laparotomy and OVH are usually indicated.

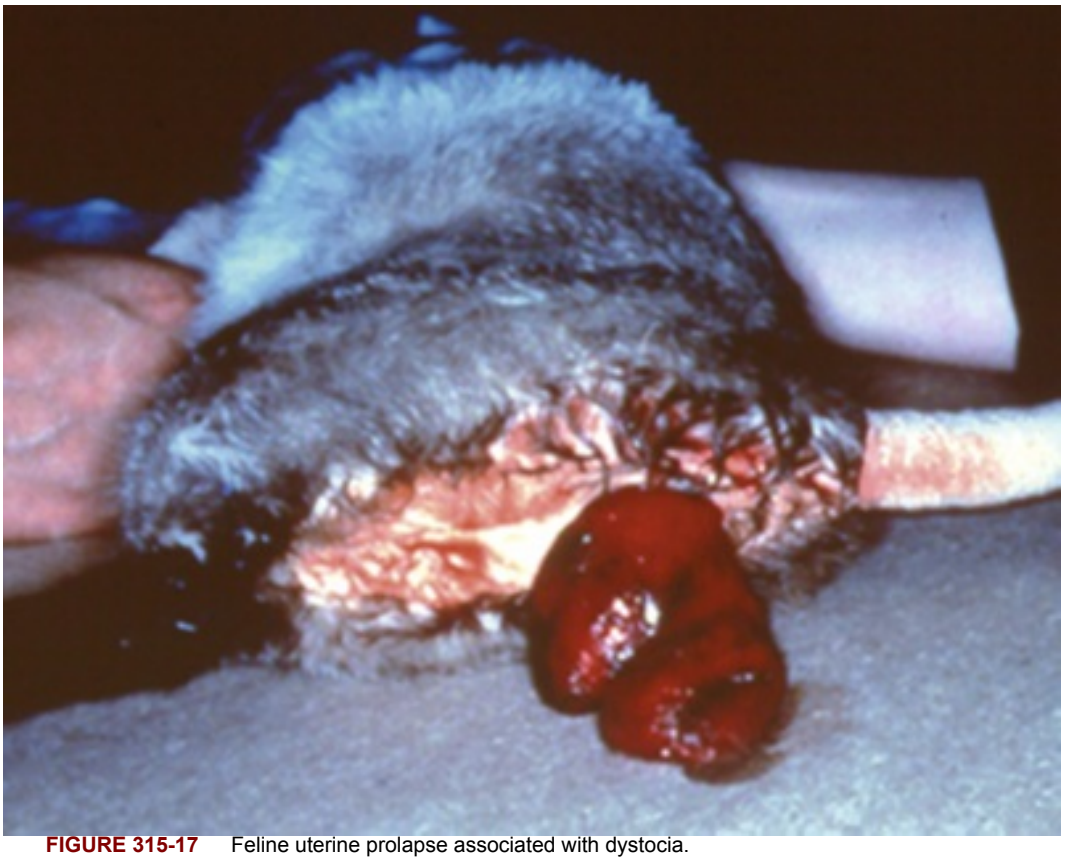


FIGURE 315-17 Feline uterine prolapse associated with dystocia.

Rupture of the uterus occurs most commonly in dogs with quite large litters that can cause stretching and thinning of the uterine wall, especially in multiparous dams with dystocia. Rupture can also occur with inappropriate use of ecbolic agents (Figure 315-18). Immediate laparotomy is indicated to retrieve fetuses, repair or remove the uterus, and culture/lavage the abdominal cavity. The uterus should be carefully examined at any C-section for rupture or fragile areas. Peritonitis (see ch. 279) can result with even small uterine tears. Unilateral hysterectomy can be considered if the damaged area is limited and the dam valuable

to a breeding program.

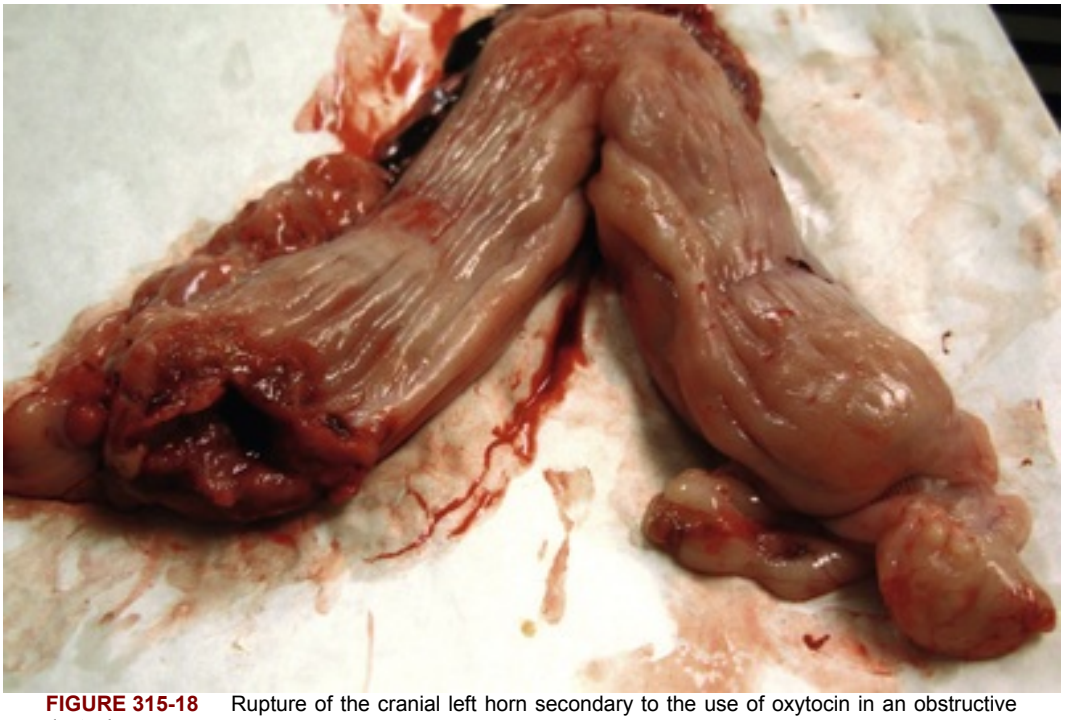


FIGURE 315-18 Rupture of the cranial left horn secondary to the use of oxytocin in an obstructive dystocia.

Subinvolution of the Placental Sites (SIPS)

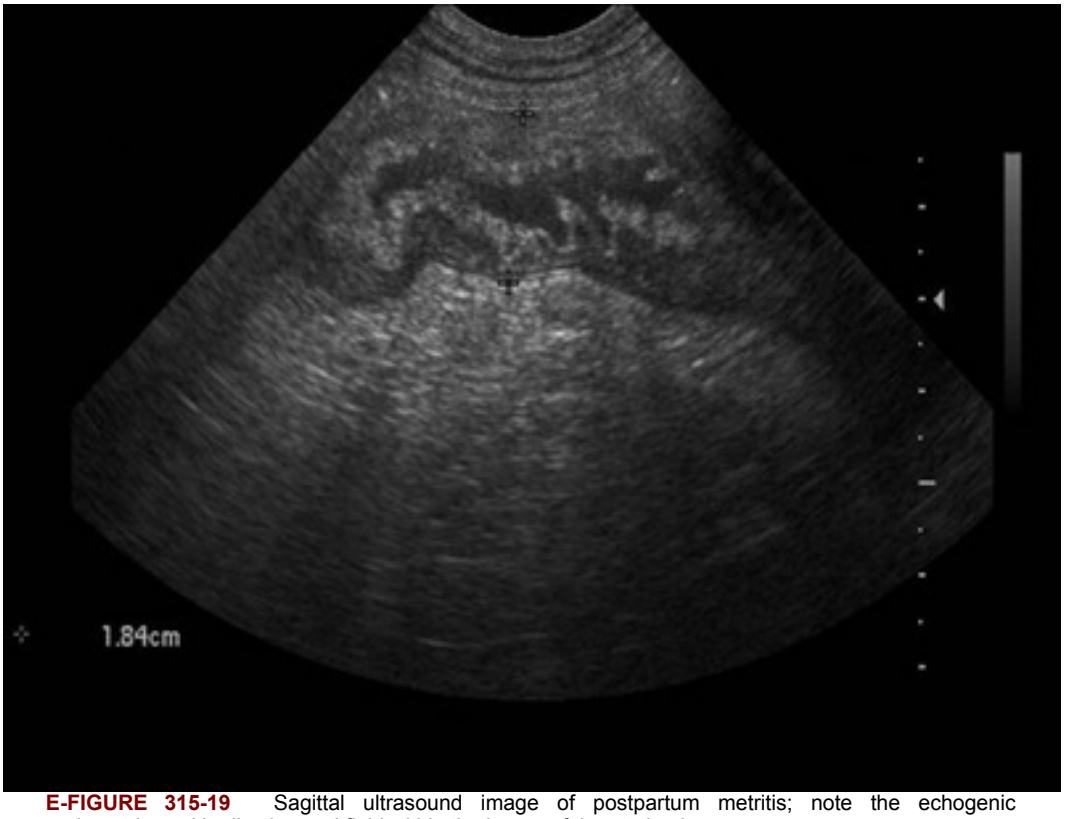
The persistence of serosanguineous to hemorrhagic vaginal discharge beyond 16 weeks postpartum can indicate SIPS, a condition in which fetal trophoblastic cells persist in the myometrium (they should degenerate), endometrial vessel thrombosis is lacking, normal uterine involution is prevented, and normal interplacental regions exist. Eosinophilic masses of collagen and dilated endometrial glands protrude into the uterine lumen and seep blood. Cause is unknown, blood loss is usually minimal, intrauterine infection is usually not present, and fertility is unaffected. Treatment is generally not necessary, as recovery is spontaneous and symptoms mild.

If vaginal bleeding from SIPS is copious and causing anemia, bleeding disorders (likely defects in the intrinsic pathway or thrombocytopenia/thrombocytopathies), trauma, neoplasia of the genitourinary tract, metritis and proestrus should be ruled out. Vaginal cytology, vaginoscopy, coagulation testing and abdominal US should be considered. The benefit of prostaglandins, oxytocin or other ecbolics is questionable and not proven. The preventative value of mini-dose oxytocin given in the immediate postpartum period is also unproven but probably not harmful. Laparotomy and OVH are curative if blood loss is significant or problematic to an owner. Histologic examination of the uterus is indicated to confirm the diagnosis.

Metritis

Metritis, a serious acute infection of the postpartum endometrium, should be suspected if lethargy, anorexia, decreased lactation, fever, malodorous vaginal discharge, and/or poor mothering are observed. Metritis may be preceded by dystocia, contaminated obstetrical manipulations, retained fetuses, and/or retained placentae. Hematologic and biochemical changes often suggest septicemia, systemic inflammation and endotoxemia. Vaginal cytology shows a hemorrhagic to purulent septic discharge. Abdominal US is excellent for evaluation of the uterine wall and the intrauterine contents for fetal or placental material. Metritis is characterized by an echogenic plicated endometrium with fluid within the uterine lumen (E-Figure 315-19). A guarded cranial vaginal culture will likely be representative of intrauterine flora and should be submitted for both aerobic and anaerobic culture/sensitivity, permitting retrospective assessment of empirically selected antibiotic therapy. Bacterial ascension from the lower genitourinary tract is more common than hematogenous spread.

Escherichia coli is the most common causative organism in bitches and queens.



E-FIGURE 315-19 Sagittal ultrasound image of postpartum metritis; note the echogenic endometrium with plication and fluid within the lumen of the uterine horn.

Therapy consists of IV fluid and electrolyte support, appropriate antibiotics, and uterine evacuation using prostaglandin F_{2alpha} (0.1-0.2 mg/kg SC q 12-24 h) or cloprostenol (1-3 mcg/kg SC q 12-24 h) for 3-5 days or until evacuation of the uterus is complete and the bitch or queen is stable. Cephalexin (10-20 mg/kg PO q 8-12 h) or amoxicillin-clavulanate (14 mg/kg PO q 12 h) are safe for neonates and used pending culture and sensitivities. Many affected dams can be managed on an outpatient basis, permitting neonatal nursing to continue at home. OVH may be indicated if peritonitis occurs and response to medical management is poor. Oxytocin is unlikely to promote effective uterine evacuation when administered >24-48 hours postpartum. Nurslings should be hand reared if the dam is seriously sick. Metritis can become chronic and cause infertility. Retained placentas are usually not problematic and are passed 1-2 days postpartum without complication.

Mammary Disorders: Agalactia, Galactostasis, Mastitis

Agalactia

Agalactia is defined as a failure to provide milk to neonates. Primary agalactia, a lack of mammary development during gestation, results in a failure of milk production, is uncommon, and a defect in the pituitary-ovarian-mammary-gland axis is suspected. Use of progesterone compounds late in gestation can interfere with lactation. Secondary agalactia, a lack of milk availability due to a failure of ejection or letdown, is more common. Mammary development is marked, but milk cannot be readily expressed through the teat sphincter. Production of colostrum in the immediate postpartum period should not be confused with agalactia. Agalactia can occur secondary to premature parturition, stress, malnutrition, debility, pain, metritis, or mastitis. Treatment includes milk supplementation for the neonates, encouraging neonatal suckling, providing optimal nutrition and water to the dam, and resolution of any underlying disease. If detected early, milk letdown can often be induced pharmacologically with mini-dose oxytocin (0.25-1 units, SC q 2 h). Neonates are removed for 10-30 minutes before injection, then encouraged to suckle. The owner can gently "strip" the glands. Metoclopramide (0.1-0.2 mg/kg SC q 12 h) may promote prolactin release. Milk letdown is

usually noted within 24 hours.

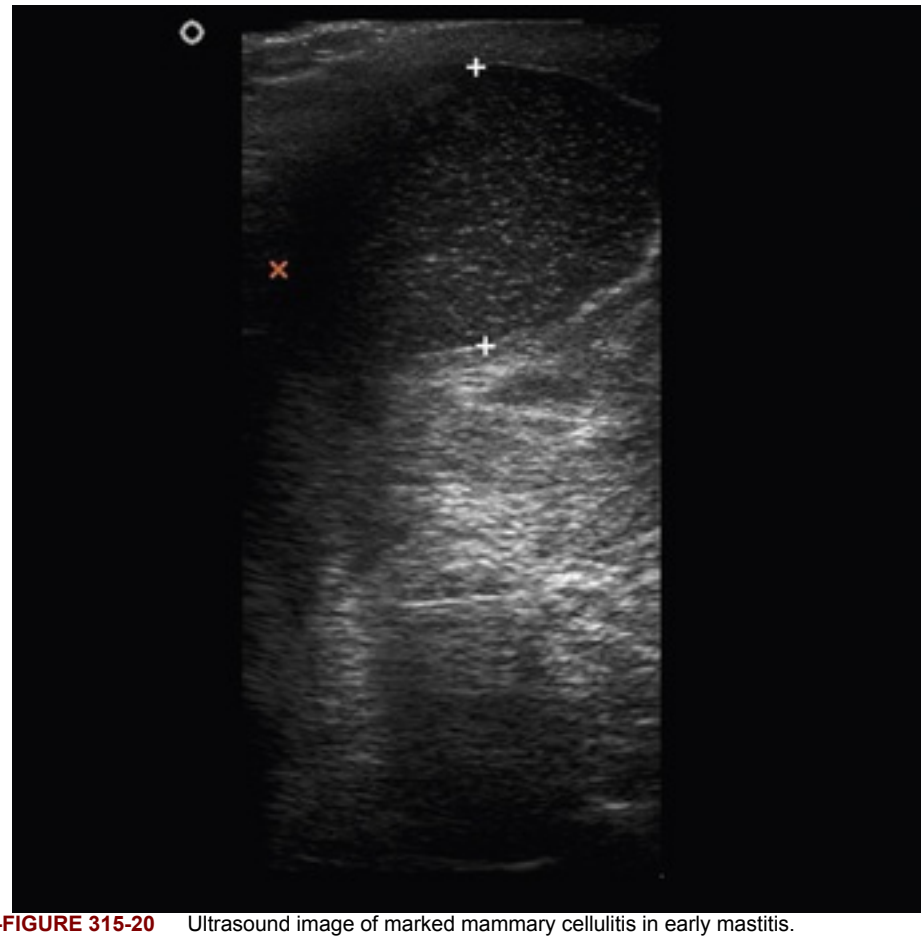
Galactostasis

Galactostasis results in engorgement and edema of the mammary glands with discomfort that interferes with further nursing and can be self-perpetuating. It may occur secondary to inverted or imperforate teats, failure to rotate nurslings, litter loss, an unusually small litter, or rarely in pseudocyesis. Encouraging suckling or gently manually evacuating affected glands is advised. If galactostasis occurs during weaning, the use of cabergoline 2.5-5 mcg/kg/day PO for 4-6 days may be helpful.

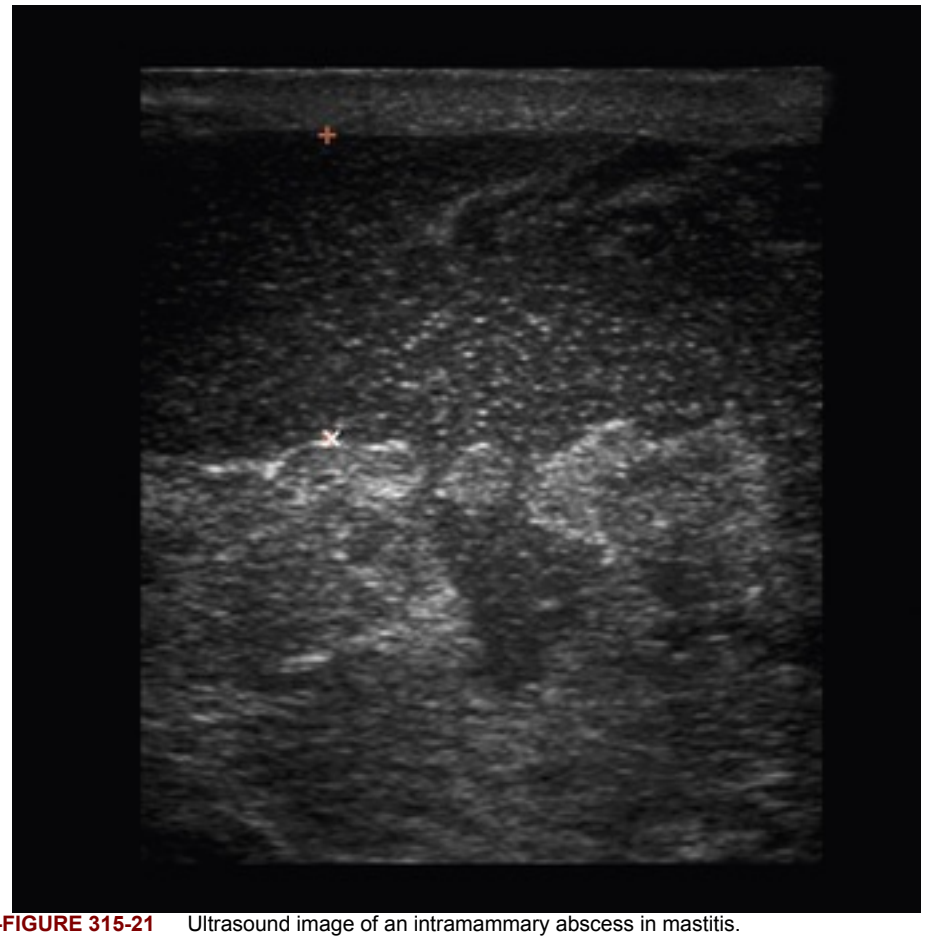
Mastitis

Mastitis is septic inflammation of one or multiple mammary glands. It can be acute and severe or chronic and low grade. Coliforms, staphylococci, and streptococci are most commonly isolated from both bitches and queens. The source of bacteria is cutaneous, exogenous or hematogenous. Mastitis can be associated with metritis. Mild mammary discomfort and heat, galactostasis, cutaneous inflammation, and a palpable intramammary mass are the earliest signs. The milk may be red or brown due to red blood cells and white blood cells. Some dogs exhibit pain, reluctance to nurse or lie down, anorexia and lethargy. Fever can be marked and may precede other clinical signs. Advanced cases can progress to septic shock with abscessed or necrotic glands. Diagnosis is based on physical examination. Milk cell counts in bitches are not predictive of mastitis. Culture and sensitivity of milk collected aseptically from affected glands allows retrospective evaluation of antibiotic selection.

Therapy should include antibiotics and gentle physical therapy. Analgesics may be indicated; neonates tolerate opioid analgesia in the dam. Cephalexin (10-20 mg/kg PO q 8-12 h) and amoxicillin-clavulanate (14 mg/kg PO q 12 h) are advised and safe for the neonates. Antibiotic therapy may be warranted until weaning and can preclude further nursing if the condition forces use of a drug potentially toxic to neonates. Warm compresses or whirlpool therapy of the affected gland with gentle stripping of milk may help avert abscessation and/or rupture. Severe necrosis warrants mastectomy when the dam is stabilized, and aggressive wound management. Ultrasound can guide management of a developing abscess (E-Figures 315-20 and 315-21). Antiprolactin therapy (cabergoline 1.5-5 mcg/kg/day PO divided q 12 h) may be indicated if severe, to reduce lactation if weaning is timely. Early weaning is not advised as it promotes galactostasis. There is no evidence that nursing from affected glands is problematic for neonates, but they tend to avoid glands if milk is not readily produced. The affected gland should be protected from nestbox-edge trauma or trauma from neonatal claws. Mastitis can recur in subsequent lactations regardless of preventative measures taken; prophylactic antibiotics are not advised; instead, good hygiene and avoidance of galactostasis are indicated.



E-FIGURE 315-20 Ultrasound image of marked mammary cellulitis in early mastitis.



E-FIGURE 315-21 Ultrasound image of an intramammary abscess in mastitis.

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CHAPTER 316

Pyometra and Cystic Endometrial Hyperplasia

Annika Bergström

Client Information Sheet: Pyometra

Definition

Cystic endometrial hyperplasia (CEH) and pyometra are the most frequent disorders of the uterus in middle-aged and older intact dogs. CEH includes development of pathological cysts and thickening of the endometrium. This is an abnormal response of the canine and feline uterus to repeated long periods of high serum-progesterone concentrations during the luteal phases of their estrous cycle, even though anestrous bitches can be diagnosed with pyometra.[1] Pyometra is a disease characterized by purulent material within the uterus. Bilaterally ovariectomized dogs do not develop pyometra, since ovarian steroids are required. Pyometra is life-threatening, especially in cases where the cervix is closed.

Epidemiology

Due to long periods of high serum progesterone concentration, CEH and pyometra are common in intact bitches. Cats are also affected, but not as frequently as bitches. Pyometra is more frequently diagnosed in certain breeds, such as Rough Collies, Rottweilers, Cavalier King Charles Spaniels, Golden Retrievers and Bernese Mountain Dogs.[2,3] About 15% of all Beagle bitches develop pyometra.[4] In some breeds, the incidence of pyometra by the age of 10 years is as high as 50%. On average, about 25% of all intact bitches develop pyometra by ten years of age.[2] The incidence of CEH is higher in colony-reared than feral cats. The feral cats have a greater number of ovarian interstitial cells but their significance is not known. In cats >5 years of age, the frequency of CEH was about 90% and about 30% of 2-4 year old cats had histologic evidence of CEH.[5] Pyometra is more common in queens >7 years of age. In insured cats, the incidence rate was 17 cats per 10,000 cat years at risk (CYAT) and Sphinx cats ran the highest risk (433/10,000 CYAT). The mortality in this study was about 6%.[6]

Pathophysiology

Hormones Associated with CEH and Pyometra

During the canine estrous cycle, the uterus is under the influence of estrogen relatively briefly, but is under the influence of progesterone for 9-12 weeks following ovulation regardless of pregnancy, resulting in increased endometrial growth, glandular secretions, and inhibition of drainage by stimulating closure of the cervix (see ch. 312). Progesterone also decreases myometrial contractions and inhibits leukocyte activity in the endometrium, increasing risk for bacterial growth.[7] The diestrual period creates an excellent uterine environment for bacteria to thrive.[8] CEH, in which the endometrium becomes thickened due to an increased number of cystic glands, develops after repeated luteal phases and increasing age in all bitches.[1] There are no significant differences in serum hormone concentrations in bitches developing pyometra compared to healthy bitches (see ch. 312). It has therefore been suggested that uterine hormonal receptors may have a role in the pathogenesis of pyometra.[9-11] Studies of uterine estrogen and progesterone receptors in bitches with CEH have provided inconsistent results.[12-14]

Classically, CEH has been considered the predecessor to pyometra. An alternative hypothesis is that a low-grade bacterial infection within the uterus causes endometrial proliferation and CEH. All bitches with CEH

do not develop pyometra and bitches may develop pyometra not preceded by CEH.[15] Clinically healthy bitches can have uterine changes, e.g., those with CEH may accumulate sterile mucoid, serous or hemorrhagic fluid without signs of illness.[16] Pyometra usually develops during diestrus, when the serum progesterone concentration is increased and the ovaries usually have visible *corpora lutea* (Figure 316-1). While less common, pyometra in cats also develops secondary to uterine progesterone sensitization. CEH is not commonly diagnosed in queens. Based on histopathology and hormone analysis, 40-57% of female cats with pyometra or endometritis were in the luteal phase and 43% of female cats with pyometra were in the follicular phase.[17]

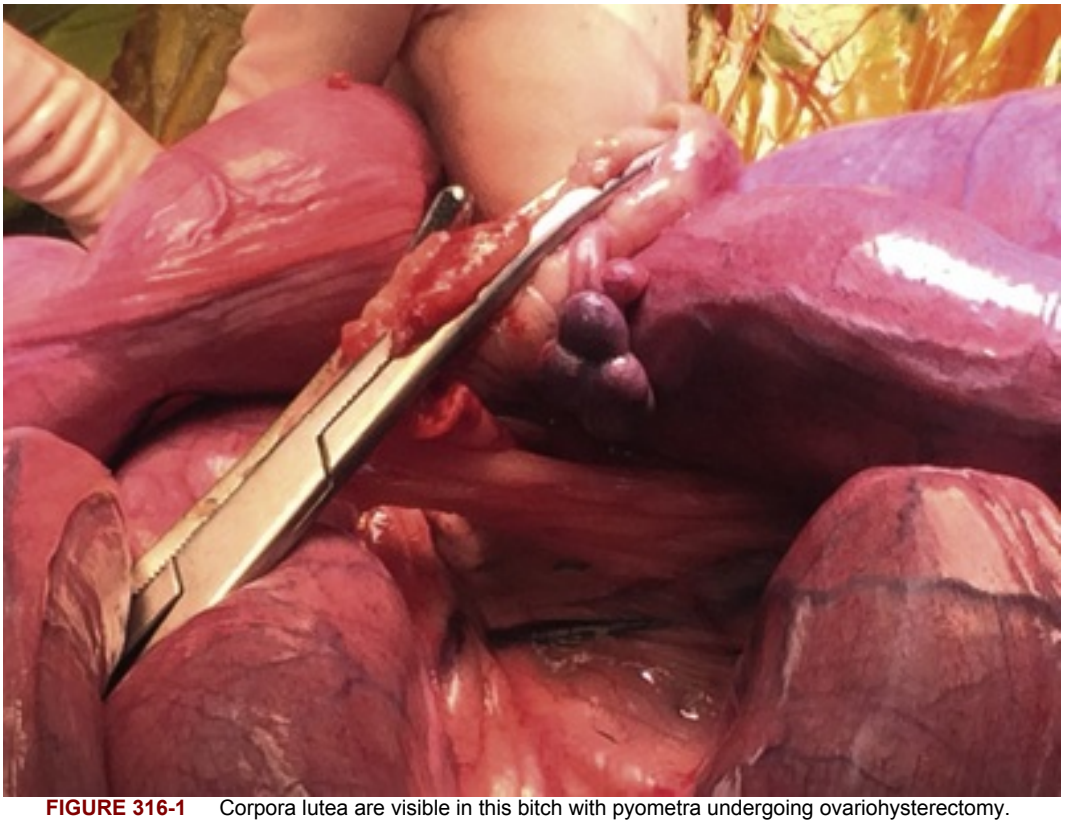

FIGURE 316-1 Corpora lutea are visible in this bitch with pyometra undergoing ovariohysterectomy.

Less commonly, pseudoplacentational endometrial hyperplasia (deciduoma), a form of CEH, has been described.[18,19] Pseudoplacentational endometrial hyperplasia represents luteal phase placentation, similar to the normal histology of the endometrium at placentation sites in normal pregnancy.[19]

Bacteria Associated with Pyometra

During estrus, bacteria from the normal vaginal flora may ascend into the uterus through the open cervix, including *Escherichia coli* (most common), *Streptococcus* spp., *Enterobacter* spp., *Proteus* spp., *Klebsiella* spp. and *Pseudomonas* spp. *E. coli* may adhere to specific receptors in the endometrium and myometrium.[8] Bacterial endotoxins may cause damage to several organs. This is especially true for lipopolysaccharide endotoxin (LPS) from *E. coli*. The polydipsia seen in bitches with pyometra is a compensatory mechanism to replace water lost through the kidneys (see ch. 45). Bacterial endotoxins impair the ability of the loop of Henle to reabsorb sodium and chloride. *E. coli* endotoxins also have the ability to cause tubular insensitivity to antidiuretic hormone (ADH), which causes further loss of urinary concentration ability (see ch. 296).[8]

Cystic Endometrial Hyperplasia (CEH)

The only clinical sign associated with CEH is infertility—there are no other clinical signs. If the CEH progresses into a fluid-filled uterus, the principal sign may be similar to that of a bitch or queen with

pyometra: vaginal discharge. Polyuria, polydipsia and decreased general health may be noted. No medical treatment for CEH has been recognized.

Pyometra

Risk factors for the development of pyometra in dogs and cats include use of progestogens for estrus suppression, or estrogen for estrus induction or pregnancy termination.[3,9,14,20] Estrogen upregulates endometrial progesterone and estrogen receptors.

Clinical Signs and Diagnosis

Timing and Signs

Pyometra in bitches usually develops 4 weeks to 4 months after estrus, during diestrus, when the dominance of progesterone is required to maintain pregnancy.[21] Dogs with pyometra are usually middle-aged or older, but bitches of any age have been diagnosed. In queens, the median age for development of pyometra in one study was 32 months and within 8 weeks after estrus.[22] Pyometra is common and should always be included as a possible diagnosis if an intact female dog or cat is ill. The uterus may be slightly increased in size or severely dilated (Figure 316-2). Differential diagnoses with similar appearance on ultrasound (US) examination are the non-life-threatening hydrometra, mucometra and hemometra.[16]

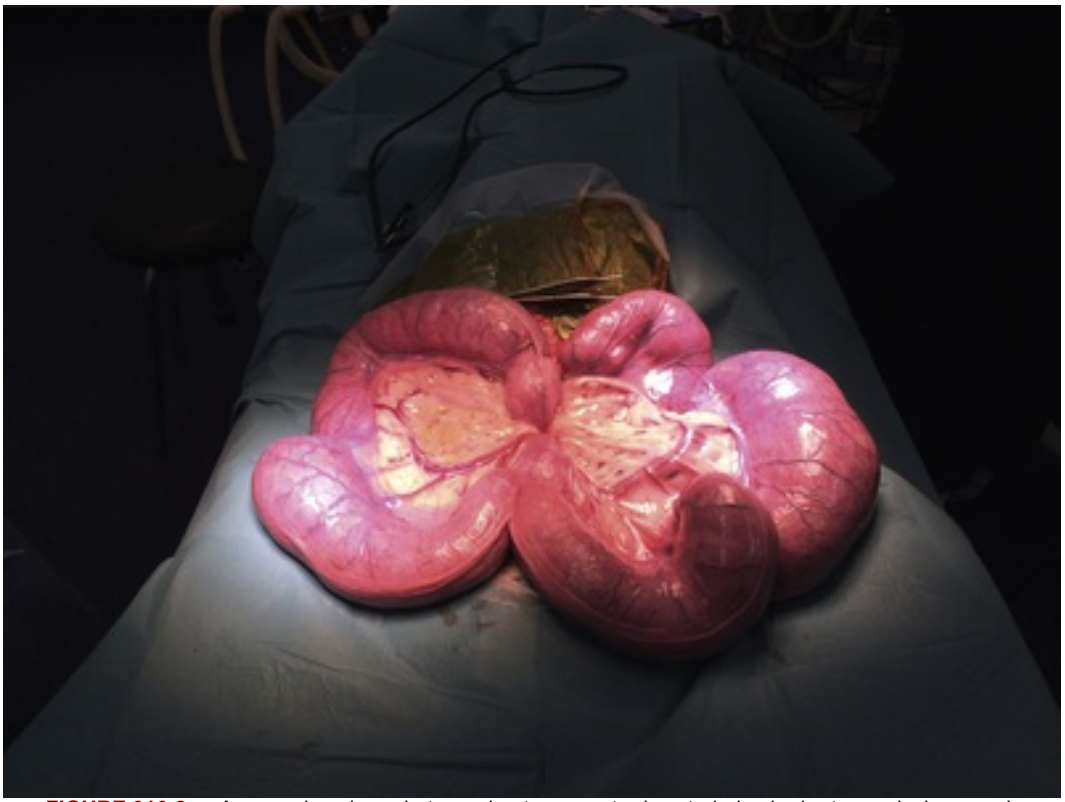

FIGURE 316-2 A severely enlarged uterus due to pyometra is exteriorized prior to surgical removal. The risk for rupture and septic peritonitis is impendent.

Pyometra usually results in vaginal discharge if the cervix is open, allowing drainage of hemorrhagic, serosanguineous or mucopurulent fluid from the uterus. If the cervix remains closed, there is no vaginal discharge and the uterine contents may increase in volume, resulting in risk for uterine rupture and peritonitis if not recognized and treated in a timely manner. Dogs and cats with closed cervix pyometra are often inappetent, obtunded, lethargic, polyuric, polydipsic, and may have abdominal distention.[21] Fever may be present. Septicemia, toxemia, systemic inflammatory response syndrome (SIRS), DIC, shock and death may occur (see ch. 132, 146, 207, and 279). Potential clinical signs include tachycardia, prolonged capillary

refill time and weak femoral pulses.[16] The rate of SIRS correlates positively with duration of clinical signs, indicating that a delay in treatment leads to rapid progression of clinical illness.[23]

In some pets, uveitis (see ch. 11), joint pain (see ch. 203) and swollen joints may develop secondary to the systemic inflammatory response. Abdominal palpation may reveal an enlarged uterus, but the uterus can be difficult to palpate. Careful palpation is strongly recommended to prevent uterine rupture. Due to severity of inflammation and endotoxemia, some bitches are severely ill despite having a relatively small or slightly distended uterus. Vaginal examination in dogs is recommended to exclude vaginal disease, e.g., neoplasia, as the cause of vaginal discharge. In queens, the most common clinical signs are vaginal discharge, anorexia and lethargy.[24]

Laboratory Testing and Imaging Recommendations

Complete Blood Count (CBC)

Some bitches may have normal blood parameters, depending on severity of disease. Most bitches with pyometra have marked CBC changes that correlate with severe infection and/or chronic inflammation. Normocytic normochromic anemia has been noted in about 70% of dogs with pyometra, likely caused by decreased erythropoiesis.[25] Decreased iron concentrations secondary to chronic inflammation may decrease erythropoiesis. Toxic effects on the bone marrow due to sepsis can further suppress erythropoiesis. A marked increase in total white blood cell count (WBC) is common in pyometra, but significantly less so in bitches with CEH.[26,27] Leukocytosis with severe neutrophilia, left shift, and monocytosis are frequently seen. Bitches with closed cervix pyometra have the highest WBC.[8] In severe illness, endotoxemia may progress to suppress the bone marrow and lead to neutropenia, especially as neutrophils continue to flood the uterus. Predictors of peritonitis in bitches with pyometra are leukopenia, fever and hypothermia. In bitches with leukopenia, the risk for peritonitis is 18 times higher and the hospitalization time is 3.5 times increased.[31]

Serum Biochemistries and Biomarkers

Serum alkaline phosphatase (ALP) activity, globulin and total protein commonly increase in bitches with pyometra. C-reactive protein (CRP) and serum-amyloid A (SAA) may be markers to help distinguish pyometra from CEH.[26] Increases in ALP, bilirubin and cholesterol may be due to intrahepatic cholestasis.[28] Pre-renal azotemia occurs secondary to dehydration and renal azotemia can be due to reversible tubular damage. Serum concentrations of insulin growth factor 1 (IGF-1) and iron are decreased in bitches with pyometra, secondary to the inflammatory response. C-reactive protein and SAA are increased in dogs with pyometra and SAA is likely increased in pyometra cats as well. These biomarkers may be used to identify sepsis in dogs with pyometra, as they are significantly lower in healthy and CEH bitches.[26,29,30]

CRP may also be a useful marker for assessment during the postoperative period as a trend marker for postoperative complications.[29,32,33] Preoperative serum lactate concentration was neither related to systemic inflammatory response syndrome nor to prolonged hospitalization.[34] Repeated measurement of serum lactate may be recommended in severely ill bitches with pyometra to ensure that cellular energy consumption is regained (see ch. 70). Plasma PGF_{2alpha} is increased both in bitches and queens with pyometra, compared to healthy animals.[35,36] The increase in plasma prostaglandins probably originates from endometrial synthesis due to stimulation from bacterial endotoxins.

Imaging

The most commonly used modalities for confirming a diagnosis of pyometra are abdominal ultrasound (US; see ch. 88) or radiology. US is the most sensitive and specific test that may also aid in differentiating pyometra from mucometra. In pyometra, the uterine wall is thickened, the lumen distended with serous to viscous heteroechogenic fluid. In mucometra the uterine fluid is more uniformly hypoechoic. Other diagnostic modalities such as computed tomography and magnetic resonance imaging may be used, but are not usually necessary.

Bacterial Culture

The most common bacteria sampled from a pyometra uterus in dogs and cats are *Escherichia coli*. Bacterial sensitivity to antimicrobials is usually high based on a study where only 10% of *E. coli* from uterine pyometra samples were resistant to amoxicillin.[37] Sampling the cranial vagina with a guarded swab may be useful for

open cervix pyometra treated medically, but vaginal bacteria may differ from those in the uterus. The clinical importance of sampling bacteria from the ovarian bursa is unclear. Samples may be positive in healthy bitches and in bitches with mucometra. Also, only about half of the bacterial samples from the ovarian bursa in bitches with pyometra were the same as those recovered from the uterine pus.[38]

Urinalysis

Urinary tract infection (UTI) may occur simultaneously with pyometra, with identical bacterial isolates (see ch. 330).[39,40] After surgical treatment of pyometra, UTI usually resolves spontaneously. Cystocentesis is not recommended in bitches with pyometra due to the risk of perforating the purulent uterus, but may be performed intra-operatively in a controlled manner. Due to immune complex deposition in the glomeruli, proteinuria may be seen in some bitches, which usually resolves with resolution of the condition.[8] Urine specific gravity may be normal, decreased or increased depending on endotoxemia, hydration status, the effects of *E. coli* interfering with ADH action at the renal tubular level, and presence of UTI.

Treatment

Initial Stabilization

The bitch or queen with pyometra may require life-saving treatment before surgical or medial management, including fluid therapy (see ch. 129) and treatment of acidosis (see ch. 128), electrolyte disturbances (see ch. 67, 68, and 69) and hypoglycemia (see ch. 62). Endotoxemia is approached with aggressive fluid therapy (see ch. 146). Antimicrobial therapy should be directed against *E. coli,* and amoxicillin is effective in 90% of cases (also see ch. 161).[37] If resistance to amoxicillin is noted on sensitivity testing, a different appropriate antibiotic should be chosen. Antimicrobials are not recommended for stable bitches and queens, since the source of the infection is surgically removed (OHE). Since 15% of bitches with pyometra had a positive blood culture, all bitches with clinical signs of septicemia and fever should be treated with antimicrobials perioperatively.[41] In cases with septic peritonitis due to leakage of pus into the abdomen (see ch. 279), antimicrobials are continued for ten days. In others, antimicrobials are not given, or are discontinued after surgery.

Severity of disease correlates with the level of bacterial toxins that cause clinical signs and an essential component of treatment is adequate fluid therapy. If dogs have ventricular tachyarrhythmias, concurrent, inciting abnormalities should be managed and antiarrhythmic treatment may be considered (see ch. 248). In medically treated bitches, antimicrobials are given until the uterus appears normal on US, usually after about 3 weeks. Antimicrobial therapy may aggravate the endotoxemia as LPSs are released when the bacteria die.[42] Close monitoring and sufficient fluid therapy is therefore important.

Medical Management

Background and Case Selection

Surgery is the preferred treatment for pyometra. Medical treatment for pyometra is recommended only in stable brood bitches without signs of sepsis, endotoxemia, hypothermia or fever (Figure 316-3). Also, only dogs without liver or kidney dysfunction should be treated medically. It is extremely important to closely monitor these pets during treatment, as peritonitis or endotoxemia may develop. Bitches with a closed cervix should be treated surgically, despite some recommendations to the contrary.[43,44] Before recommending medical management, one should consider the increased risk for pyometra in the offspring of the bitch being treated. Genetic factors for development of pyometra are likely, as some breeds are known to be more prone to the disease (see above).

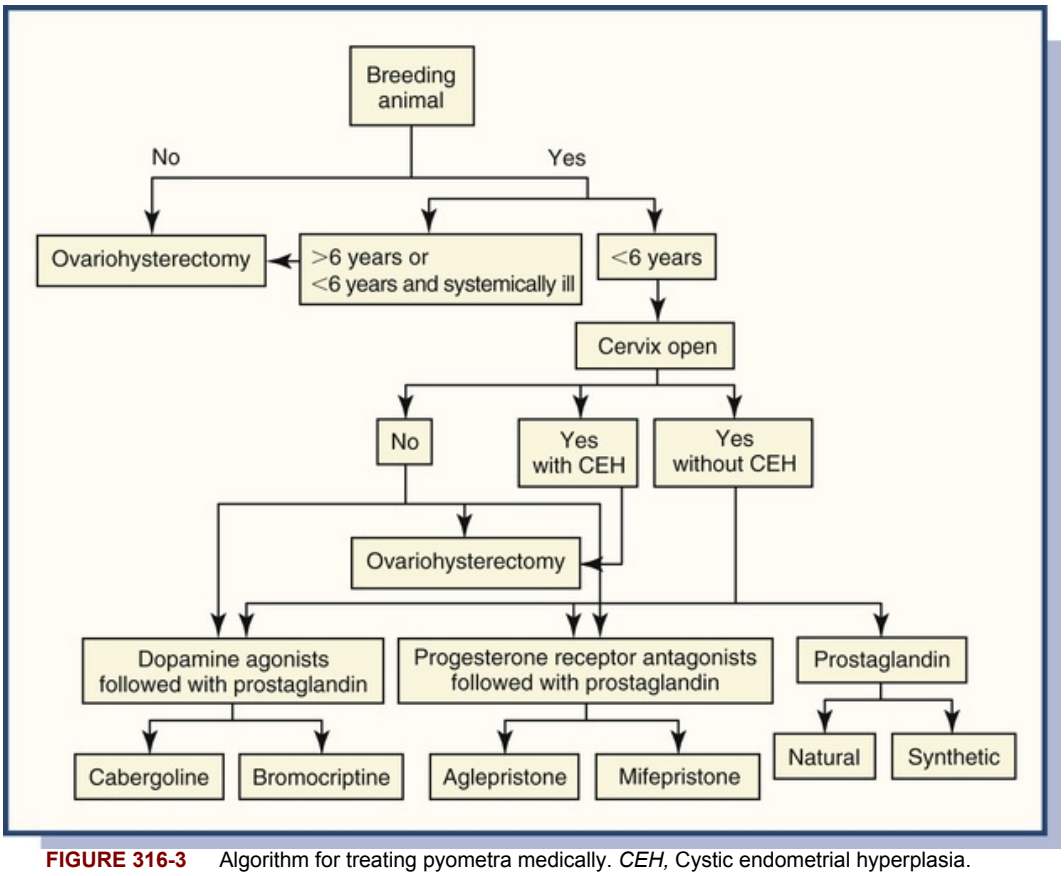

FIGURE 316-3 Algorithm for treating pyometra medically. *CEH,* Cystic endometrial hyperplasia.

Prognosis after medical treatment depends on the presence and severity of metritis, if the cervix was closed or open, and occurrence of cervical or endometrial cysts. Female dogs are more likely to become pregnant after treatment if they are five years old or younger.[44,45] It is important to mate bitches in the first or second estrus after finishing medical treatment. Antimicrobial therapy is given simultaneously and should be based on vaginal culture taken with a guarded swab. US is used to evaluate the effects of medical treatment on a weekly basis (Table 316-1).

TABLE 316-1

Medical Treatment Protocols in Bitches and Queens Diagnosed with Pyometra

MEDICAL TREATMENT	DOSAGE (SC INJECTIONS)	EFFECT	REFERENCE
Natural PGF_{2alpha} (dinoprost)	Day 1: 0.1 mg/kg q 24 h Day 2: 0.2 mg/kg q 24 h Day 3-7: 0.25 mg/kg q 24 h Cat: Day 1-3(5): 0.1 or 0.25 mg/kg q 12 or 24 h	64-100% success, depending on length of treatment Cat: 95% success	8, 22
Synthetic PGF_{2alpha} (cloprostenol)	DAY 1-7: 1-2.5 mcg/kg × 1 Cat: Day 1-3: 5 mcg/kg q 24 h	75-90% success, depending on length of treatment 5/5 cats healthy	63, 64
Progesterone-receptor blocker (aglepristone)	Day 1, 2 & 7/8: 10 mg/kg q 24 h Day 1 & 2, 7 & 8: 10 mg/kg q 24 h Cat: Day 1, 2, 7, 14: 10 mg/kg q 24 h	93% success 10% recurrence 75% success 48% recurrence 9/10 cats healthy	49-51
Combination:	A: Day 1, 2 & 8: 10 mg/kg q 24 h	85% success	43, 52

Aglepristone (A) and cloprostenol (C)	C: Day 3-7: 1 mcg/kg q 24 h C: Days 3, 5, 8, 10, 12: 1 mcg/kg q 24 h Open and closed cervix pyometra	13-20% recurrence at one year	

All injections are given subcutaneously.

Prostaglandins

Prostaglandins stimulate cervical dilatation and increase myometrial activity, which leads to expulsion of uterine content. After giving prostaglandins several times, lysis of corpora lutea follows. Corpora lutea are the sole source of progesterone and as they lyse, progesterone concentrations decline to basal (anestrous) levels (see ch. 312). Synthetic prostaglandins cause fewer side effects but may be less effective than natural prostaglandins.[44] To decrease the side effects of natural prostaglandins, lower dosages may be used and the dosage is increased gradually (see Table 316-1).[46] As many as 5 injections daily may be recommended, depending on the protocol.[1]

Side effects from prostaglandins may be moderate to severe, and include panting, nausea, vomiting, diarrhea and salivation. To reduce the risk of anorexia and nausea, prostaglandins should be given before feeding. There is always a risk for uterine rupture, especially with a closed-cervix pyometra. The medically treated female dog or cat should be kept in the clinic at least 4 hours after treatment, but can stay at home overnight between injections.[8] Recurrence after treatment is common; in one study, 4 of 10 treated dogs developed pyometra after a subsequent estrus.[47] In cats, prostaglandins have been successfully used for treating pyometra and are considered an alternative to surgery. Eighty-one percent of treated cats delivered a litter after successful treatment.[22] Anecdotally, prostaglandin E (misoprostol) administered intra-vaginally has been used for treatment of pyometra in dogs. Prostaglandin E induces cervical relaxation.[48]

Progesterone Receptor-Blocker (Aglepristone)

Aglepristone may open a closed cervix and is used for treatment of unwanted pregnancy in bitches and queens as well as for pyometra in dogs and cats.[49-51] This product is not commercially available in the United States or Canada, but is used in Europe. The side effects are less severe than with prostaglandins and include restlessness, loss of appetite, diarrhea and abdominal cramps. The success rate in dogs is about 75% for long-term recovery and regained fertility; success has been reported in cats as well.[43,49,51] The risk for recurrence of pyometra is higher in bitches with cystic ovaries and/or cystic endometrium.[50] Bitches and queens are usually kept at home between injections.

Combination of Prostaglandins and Progesterone Receptor-Blockers

Combining these drugs decreases side effects and improves results, with 84% of the bitches clinically healthy after treatment using a protocol that included both agents.[52] The prostaglandin is a more effective uterotonic agent, resulting in a faster decrease in luminal diameter and decrease of progesterone compared to if aglepristone is used alone. When cloprostenol is administered together with aglepristone, a low dosage with few or no side effects is used (1 mcg/kg).[44]

Dopamine Agonists (Prostaglandin, Cabergoline)

These agents reduce plasma progesterone concentration quickly due to rapid luteolysis.[53,54] This medically induced luteolysis can be used to induce parturition and to treat pyometra. Effect is expected within 48 hours of initiating treatment that includes prostaglandins, prostaglandins and progesterone receptor-blocker or prostaglandins and dopamine agonists. If the effect of medical treatment is unsuccessful, OHE should be recommended.

Transcervical Drainage

Drainage of a diseased uterus has been performed using catheters placed in the uterine lumen through cervix to vagina.[55] Use of transcervical endoscopic catheterization for diagnosis, artificial insemination, or uterine drainage has been suggested for dogs and cats, but use in pyometra is infrequent.[56-58]

Surgical Management: Ovariohysterectomy (OHE)

Overview

Ovariohysterectomy (OHE) is the recommended treatment for pyometra. After preoperative stabilization, the surgery is performed as soon as the animal is stable. In cases of septicemia due to the infected uterus, surgery must be performed quickly and, therefore, aggressive fluid therapy is required (see ch. 129 and 146). If the uterus is ruptured, the abdomen is lavaged with 200-300 mL/kg of fluid and closed suction drainage is recommended (see ch. 279). Survival after open peritoneal lavage and closed suction drainage is 70% in septic peritonitis in cats and dogs.[59,60] Closed suction drainage is easy to use and does not require repeated anesthesia as is the case with open peritoneal lavage.

Surgical/Anesthetic Complications

Postoperative complications include hemorrhage, peritonitis, wound infections, fistulous tracts and anesthesia-related concerns. In bitches with SIRS and sepsis, ventricular arrhythmias may develop and ECG should be closely monitored in the postoperative period. Postoperative sepsis may develop, and both CRP and IGF-1 may be useful markers to assess in the postoperative period.[29,32]

Ovarian Remnant Syndrome

Ovarian remnant syndrome may occur after OHE and is a result of unsuccessful surgical removal of all ovarian tissue (see ch. 319). If the pet starts to show estrus behavior in spite of OHE, abdominal ultrasound should be performed in search of ovarian tissue. Hormonal assays for estradiol, progesterone, and luteinizing hormone are also recommended, together with vaginal smears to verify presence of cornified cells and thereby confirm remnants of ovarian tissue. The ovarian remnant syndrome may be more common in bitches, as the ovarian tissue is deeper located and more difficult to reach during the surgical procedure in comparison to queens. Ovarian remnant tissue in dogs and cats may be surgically treated by open or laparoscopic surgery.[61]

Uterine Stump Pyometra

Uterine stump pyometra in dogs and cats has a similar clinical appearance as pyometra, except that OHE has been previously performed. Remnant ovarian tissue is commonly seen in the abdomen after surgery in cases of stump pyometra. Ultrasonography may be used for diagnosis, and will reveal fluid filled areas in the cervical region. The treatment is surgical, and includes treatment of the cervical abscess as well as removal of any ovarian tissue remnants.[62]

Prognosis

Dogs and cats with CEH or low-grade pyometra without SIRS or sepsis have good prognosis after OHE. In severely ill animals the diagnosis is more guarded, but with aggressive preoperative fluid therapy and fast surgical intervention, most animals survive. After medical treatment in stable animals without signs of sepsis, endotoxemia, hypothermia or fever, prognosis is good, and chances of regained fertility are considered to be good—especially in younger animals.[1] The risk of recurrence is high after medical treatment, though.

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CHAPTER 317

Other Infectious Causes of Infertility and Subfertility in Dogs and Cats

Sophie Alexandra Grundy

Client Information Sheets:
Be Prepared: Reproductive Tract Sample Collection at Home
Pre-Breeding Vaginal Cultures

Introduction

Infectious diseases can usually be identified with culture, polymerase chain reaction (PCR), or histology (see ch. 207). Obstacles to obtaining a definitive diagnosis of reproductive organ infectious disease in clinical practice include lack of sample, cost, and challenging interpretations. Thus, the true impact of infectious disease on canine and feline reproductive performance is difficult to establish. PCR techniques increase availability of cost effective multi-pathogen diagnostic screening, but sample collection, sample site selection, and laboratory quality control each have potential to impact positive and negative predictive values. Results may be confusing since reproductive pathogens may also be considered "normal flora" in healthy pets. Diagnostic panels that combine culture, PCR, and histopathology provide an opportunity to understand the true relationship between infectious disease and reproductive performance in cats and dogs. Client education regarding available testing options and sample requirements is an essential component of the diagnostic process as typically it is clients that have greater access to tissue types such as the placenta, or an aborted fetus.

Sample Collection, Type and Site

There are 4 main categories of infectious reproductive pathogens: bacterial, viral, protozoal, and fungal. Any of these can cause similar "storms" of reproductive failure within a breeding population. All cases of reproductive loss benefit from the collection of samples appropriate for culture, histology, and PCR.[1] PCR, of great diagnostic value for identifying infectious disease, enables rapid identification of pathogens and is highly sensitive. As a result, it is important to consider sample collection protocols. Many reproductive pathogens are environmentally ubiquitous and normally found in oral, genital, urinary, or gastrointestinal flora. Interpretation must be made in the context of environment, sample type, location, and method of collection. All samples for PCR and culture should be collected in as sterile a manner as possible to avoid contamination. Plastic stemmed cotton tipped applicators, gloves, sterile instruments and a clean surface are advised when collecting samples. Samples should be refrigerated until submitted.[2]

Placental tissue can be extremely useful for understanding reproductive concerns in gravid bitches and queens. The placenta may be considered the immune guardian of the developing fetus. When sampling the placenta, a touch slide preparation should be made for prompt *Brucella canis* and *Campylobacter jejuni* screening. Two tissue samples should be collected: one for formalin fixation and one for PCR. If available, samples of fetal kidney, liver, spleen, and lung should also be collected in duplicate: one for formalin fixation and one for PCR. A sample of fetal liver or a swab of the abdomen is ideal for bacterial culture. EDTA whole blood and serum should be collected from the dam, in addition to a vaginal swab for PCR. PCR samples should be kept refrigerated.

When evaluating the male for infectious reproductive pathogens, semen should be cultured and, ideally, the colony count compared to a urethral culture (see ch. 318). Samples of ejaculate may also be submitted for infectious disease screening by PCR. Various combinations of culture, PCR, and histology are available

through private and university laboratories. These panel, or combination test packages offer a cost effective option for multi-pathogen screening.

Pre-Breeding Vaginal Cultures

Normal Flora

It is common to be asked to perform a bacterial culture of the vaginal vault as a pre-breeding screen. There is an incorrect tendency to presume that a positive vaginal culture is abnormal and indicative of an infected and abnormal uterus.[3-11] Some breeders incorrectly believe the normal vaginal canal to be sterile and require a negative pre-breeding culture prior to permitting live cover. However, the normal vaginal canal has aerobic and anaerobic bacterial populations and 60-100% of healthy bitches have positive vaginal cultures.[3-10] Considering anatomical exposure to oral and gastrointestinal bacteria, the common vaginal isolates from bitches include *Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pasteurella multocida* and bacteria associated with the skin (*Streptococcus* spp. and *Staphylococci* spp.) (Table 317-1).[3-10] Although bacterial cultures are typically limited to aerobes, anaerobes are also included among normal vaginal flora (*Bacteroides* spp., *Peptostreptococcus* spp., *Clostridium* spp.).[9] Whilst there are slightly different relative frequencies for each isolate, the "normal organisms" are consistent across studies.[3-10] The types of bacteria isolated per healthy bitch are relatively stable during the reproductive cycle, but count and number of isolates tend to increase during proestrus and estrus.[4,5] During proestrus and estrus, it has been shown that the uterine bacterial population reflects the vaginal bacterial population, presumably due to relaxation of the cervix and hormonal changes that decrease uterine immune responses.[4] During diestrus and anestrus, uterine bacterial populations typically clear, making it rare to isolate bacteria during this time.[4,8]

TABLE 317-1

Frequency of Vaginal Bacterial Isolates in Healthy Bitches across Selected Studies, 1978-2012

BACTERIAL ORGANISM	PERCENT POSTIVE BACTERIAL ISOLATES (HEALTHY BITCHES) PER STUDY						
	LING, 1978[10]	ODSBALDISTON, 1972[11]	HIRSCH, 1977[3]	OLSON, 1978[6]	BABA, 1983[9]	BJURSTROM, 1992[8]	GROPETTI, 2012[5]
Arcanobacterium pyogenes							2.9
Bacillus spp.				3.7			
Bacteroidaceae spp.		10			55		
Corynebacterium spp.	35		6	2.5		40.7	
Enterococci		10				44.1	
Enterococcus faecalis			4				23.5
Escherichia coli	25	50	22	18.5	23	84.7	2.9
Haemophilus		10					
Klebsiella pneumoniae							2.9
Moraxella spp.	10						
Mycoplasma spp.	30				43	59.3	
Pasteurella spp. *Pasteurella multocida*	5			9.9	34	67.8 98.3	8.8
Peptococcaceae (*Clostridium* spp.)					27		
Proteus spp.	5*		6*	4.9	9	25.4*	2.9*
Pseudomonas aeruginosa	5	10	2				
Staphylococci spp.	70	10	13	6.2	20		2.9

coagulase-positive							
Staphylococci spp. coagulase-negative	5		6	6.2	4	22.0	
Streptococcus spp.		10			52		2.9
Beta-hemolytic	35		9	14.8	89.8		20.6
Streptococci "viridans"	20		14	13.6		55.9	26.4

**Proteus mirabilis.*

Bacteria in shaded rows indicate that they are more frequently isolated across all studies.

Vaginal Cultures During Proestrus and Estrus

Specific concerns are often raised with respect to positive cultures of *E. coli* or *Streptococcus* spp. as they are commonly associated with pyometra, mastitis, and neonatal septicemia. However, a large majority of vaginal cultures from healthy bitches are positive for *E. coli*.[4,6,8,12] One study associated a positive proestrus *Streptococcus* spp. vaginal culture with a *decreased risk* of uterine infection during diestrus.[5]

With years of literature support, there is no evidence to support routine culture or antibiotic treatment of an asymptomatic bitch with a positive pre-breeding vaginal culture. Future studies quantifying microbial levels of the normal vaginal microbiome may be used to define pathogenic vaginal bacterial populations. Since vaginal cytology is frequently evaluated during proestrus of bitches (see ch. 119 and 312) and often reveals large numbers of bacteria or phagocytized bacteria, caregivers may request treatment of these bacteria. However, no correlations have been made between vaginal bacteria (phagocytized or not), vaginal neutrophils, and fertility in an asymptomatic bitch.[5] Bacteria in the vaginal canal are normal and cytologically observed bacteria are not valid reasons for antimicrobial treatment during proestrus. Caregivers should be informed that most bitches undergoing pre-breeding vaginal cultures are in proestrus or estrus, times when results are *expected* to be positive. While there may be pressure from owners of the bitch or stud dog to treat a bitch with a positive vaginal culture with antibiotics prior to breeding, one should also note the increasing evidence that indiscriminate use of antimicrobials in breeding bitches is correlated with induction of multi-resistant bacteria which can alter vaginal flora and promote growth of pathogenic bacterial populations. This places kennels and neonates at greater risk and does not improve reproductive performance.[13-15] When should a bitch with a positive pre-breeding culture be treated? As a general rule, treatment during proestrus should be considered for a bitch that is exhibiting a clearly abnormal vaginal discharge *and* with significant growth of either a single pure normal bacterial species, or atypical bacterial isolate (see provided Client Information Sheet online).

Vaginal Discharge and Culture

Bacterial cultures of vaginal discharge generally differ from normal flora only with respect to the number of bacteria isolated.[3] In symptomatic dogs or cats, treatment is advised for a single bacterial isolate present in high numbers, typically a 3+ to 4+ on a four-point scale.[3,16] Antimicrobial choice should be made with consideration to sensitivity and minimum inhibitory concentration (MIC).

Mycoplasma and *Ureaplasma*

Positive *Mycoplasma* vaginal cultures are common in bitches and not of clinical significance with respect to fertility. In stud dogs, however, positive *Mycoplasma* culture *may* be associated with infertility if the quantitated culture count of the semen is 2 $\log_{10}$ times greater than that of the urethra.[22*] Many studies evaluating canine vaginal cultures do not comment on *Mycoplasma*. *Mycoplasma* spp. do not grow easily under standard aerobic culture conditions.[4-6,17] When specifically evaluated, positive *Mycoplasma* and *Ureaplasma* vaginal culture rates in the healthy bitch are reported to be as high as 88% and 50%, respectively; *Ureasplasma*, when present, is typically in association with *Mycoplasma*.[18-20] In one study, positive *Ureaplasma* vaginal culture rates were higher in bitches with a vaginal discharge (75%), but there was no significant relationship between *Mycoplasma*, *Ureaplasma*, and fertility.[19] Seventy-two percent to 84% of semen samples from healthy

stud dogs culture positive for *Mycoplasma*.[19] Whilst implicated in some cases of canine orchitis, *Mycoplasma* is not isolated more frequently in infertile dogs.[17,19,21] *Ureaplasma* are generally not present in the prepuce or semen of fertile males, but are found in around 70% of infertile males, typically isolated in association with *Mycoplasma*.[19] For both bitch and stud, *Mycoplasma canis* is the most frequent isolate. In males, *Mycoplasma cynos* is also noted.[19] Females often have multiple species identified.[18-20] Concurrent semen evaluation is advised.

Campylobacter Jejuni

Campylobacter jejuni has been reported in association with abortion in the bitch.[23-25] In all cases, the classic feature is late term abortion or intrauterine fetal death about one week prior to the anticipated whelping date. Bitches may also have a hemorrhagic vaginal discharge.[23-25] Entire litters may be aborted dead, but partial live litter delivery is also reported. As the fetuses are not yet at term, they may be born live, but not viable at less than 61 (females) or 62 (males) days gestation with day 0 defined by the luteinizing hormone surge.[26] An important differential for this clinical presentation is *Brucella canis* (see ch. 213), the major cause of bacterial abortion in the dog. Personal protective equipment should be used when evaluating these cases due to the zoonotic potential of both organisms. Diagnosis is based on either positive bacterial culture, or positive PCR, of the placenta, *and* fetal liver, or lung.[23-25] Successful treatment is rare.

Leptospirosis

Leptospiral organisms induce marked uterine inflammation and abortion is the most common reproductive sign of leptospiral infection in the bitch.[27,28] There is return to fertility after successful treatment. In stud dogs, leptospirosis-induced vasculitis may cause breakdown of the blood testes barrier and any stud dog diagnosed with leptospirosis should have a semen evaluation performed initially at 65 days post recovery to evaluate reproductive potential (see ch. 217).

Other Bacteria

Salmonella and *Listeria* are both reported as a cause of reproductive tract disease in the bitch and queen. *Salmonella* is an uncommon cause of reproductive loss and most often associated with systemic disease.[29] *Listeria* has been reported as a cause of abortion in the literature but is considered an uncommon pathogen.[30] *Bartonella* spp. have been associated with reproductive losses under experimental conditions but this is challenging to prove in clinical cases due to the difficulties isolating the organism (see ch. 215 and 216).[31]

Viral Pathogens

Viral pathogens are an important consideration when evaluating reproductive losses in the bitch and queen as they may cross the placenta, infecting embryo or fetus, in addition to debilitating the dam.[32] Many viral infections can be confirmed by PCR on tissue samples in combination with histology. For an in-depth discussion of the major viral pathogens, the reader is referred to the individual discussions in the infectious disease section (see ch. 222-225 and 229).

Although herpesvirus (see ch. 227 and 228) is reviewed, it is worth highlighting that the reproductive impact of canine herpesvirus (CHV) is extremely difficult to define as a result of its latency, poor immunogenicity, short-lived antibody production, and transient viral excretion.[33] Reproductive hormone fluctuations appear to alter viral reactivation, but it is not clear how this impacts the course of clinical disease.[33,34] Indeed, given that there is no difference in antibody titers between healthy bitches and those with reproductive abnormalities, in addition to zero recovery rates from vaginal PCR in kennels with endemic disease, reproductive loss due to CHV is extremely difficult to document unless associated with neonatal loss.[33-35] Vaccination when available is advised 10 days after mating and again 6 weeks later as it is thought that higher antibody titers in diestrus may protect against reproductive failure.[33,36] Successful medical management of neonatal CHV using acyclovir is described (see ch. 162).[37]

Protozoal Pathogens

Toxoplasma may be associated with reproductive loss in the queen mainly due to systemic effects of disease in the dam.[12] Transplacental transmission of *Neospora* is known to occur in the bitch but the impact of this organism on reproductive performance is unclear.[12] A single case report of *Leishmania*-associated abortion is reported in the literature.[38] The reader is referred to ch. 221 for an in-depth discussion of protozoal disease.

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*2 $\log_{10}$ refers to a 100 fold difference between the quantified microbe count, or a 99% difference in bacterial population.

CHAPTER 318

Breeding Soundness Examination and Disorders of Reproduction in Male Dogs

Gary C.W. England, Lúcia Daniel Machado da Silva

Client Information Sheet: Semen Collection and Evaluation in the Dog

Breeding Soundness Examination

Overview

Breeding soundness examination (BSE) is commonly performed to assess fertility in young dogs prior to breeding, monitor fertility during breeding careers, ensure fertility in an aging animal, investigate possible infertility, monitor recovery after reproductive disease, and as part of a semen preservation and artificial insemination program. Performing a BSE may also be important prior to purchase.

Behavior and Health

Veterinarians commonly focus upon the reproductive tract when undertaking a BSE. Further assessment of general health and temperament should be included. One may recommend genetic or other screening tests. This requires knowledge of many relevant behavioral problems and conditions which can be reviewed elsewhere in this textbook or through helpful websites, such as the Canine Health Information Center (www.caninehealthinfo.org), a centralized canine health database sponsored by the Orthopedic Foundation for Animals.

Examination of the External and Internal Genitalia

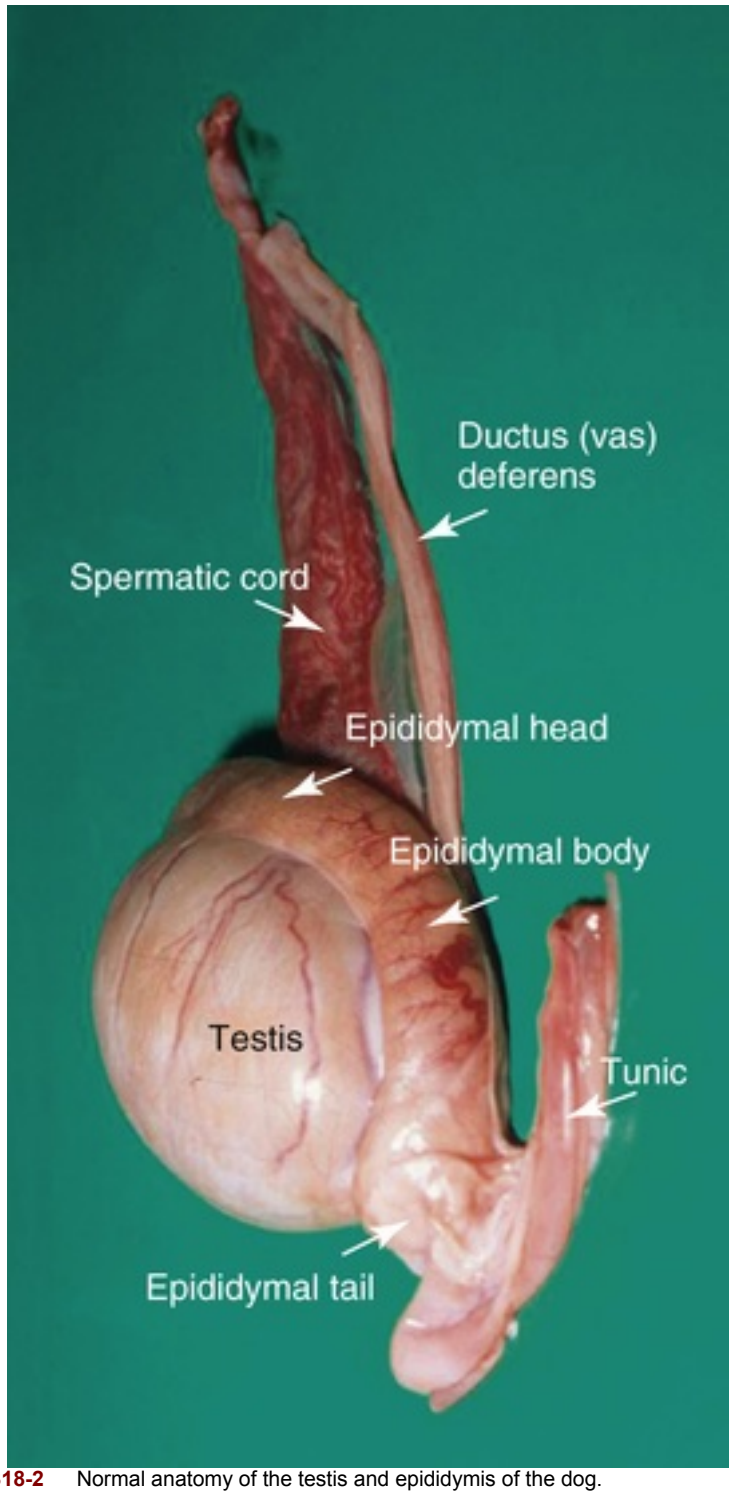
The Penis

The penis and prepuce should be examined to ensure suitability for normal breeding and absence of disease. Examination is best performed prior to the introduction of the teaser bitch. Small volumes of mucopurulent preputial discharge is common and normal (E-Figure 318-1). The prepuce should cover the length of the penis and the penis should be relatively easy to protrude from the prepuce; in experienced dogs this may initiate ejaculation and should be anticipated so that semen can be collected if this occurs. The penile skin should be smooth, with an absence of vesicular or papular lesions. However, raised lymphoid nodules at the base of the penis are common and normal, especially when there is preputial discharge. The *os penis* can be palpated through the prepuce and should be smooth and not painful. The urethra can be palpated caudally along the perineum to the anus.

E-FIGURE 318-1 A small volume of mucoid to mucopurulent preputial discharge is common and normal in dogs.

The Scrotum and Testes

Scrotal skin should have no lesions. Thickened skin or evidence of scarring may indicate a previous scrotal (testicular) insult. The neck of the scrotum should be palpated to allow identification of the vas deferens and to confirm absence of inguinal hernia. The testes are positioned almost horizontally, and one may be positioned slightly cranial. They should be freely mobile within the scrotum, similar in size, and firm but not hard. Testis size is related to body mass; for example, each testis in a 15 kg healthy dog is about 3.0 × 2.0 × 1.5 cm. The body of the epididymis runs along the dorsal surface of the testis and the tail of the epididymis is at the caudal pole (E-Figure 318-2).



E-FIGURE 318-2 Normal anatomy of the testis and epididymis of the dog.

The Prostate

The prostate gland is the sole accessory gland. If normal, it can be readily palpated per rectum as symmetrical and divided into 2 lobes (each about 2 cm in diameter) by a central longitudinal groove. The prostate should be firm in texture, non-painful and freely moveable within the pelvis.

Assessment of Libido

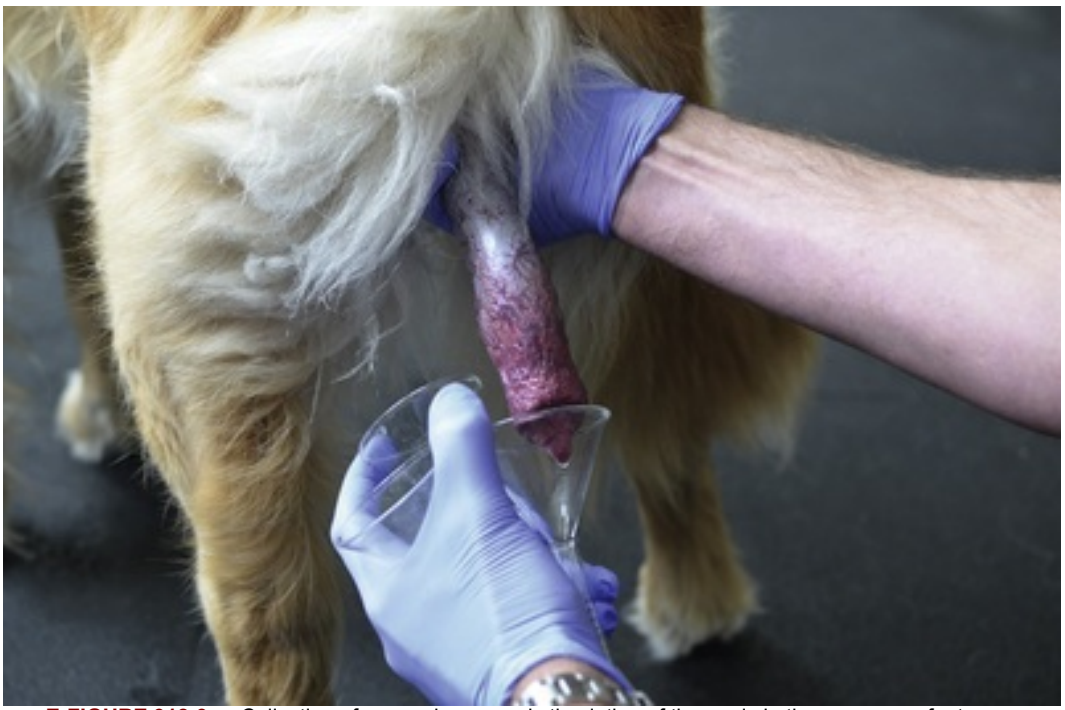
Male behavior when introduced to a female in estrus and breeding is frequently overlooked in a BSE. This can

provide useful information regarding "infertility" caused by behavior issues, negative previous experiences, or pain at coitus. Healthy dogs and bitches exhibit play behavior when first introduced, occasionally including mounting of the female. At this time the dog may ejaculate a small volume of clear fluid. This is the first fraction of the ejaculate and does not contain sperm. The dog will continue to mount, thrust, and dismount until his position allows the penile tip to enter the vagina. After intromission, the dog will achieve a full erection, continue thrusting movements and the second (sperm rich) fraction of the ejaculate is produced. Once thrusting has subsided the dog will turn through 180° and dismount while the penis does not change position, remaining within the vagina. The dog and bitch now stand tail-to-tail (this is called the copulatory tie) while the third (prostatic) fraction is ejaculated. Ties last an average of 20 minutes but vary considerably between dogs and can be as short as 5 minutes or more than 60 minutes.

Semen Collection and Evaluation

Collecting the Ejaculate

Semen collection is straightforward; samples can be collected by manual stimulation of the penis with or without an estrous teaser bitch (Video 318-1). The dog will first achieve a partial erection and then show thrusting movements during which time the first and second fractions of the ejaculate are produced. As thrusting ceases the second (sperm rich) fraction of the ejaculate continues to be produced briefly. Then the dog will lift one hind-leg (as in the copulatory tie) and it is necessary to turn the penis so that the tip faces in a caudal direction between the hind limbs while the third (prostatic) fraction is produced. The three fractions can be collected separately using clear plastic funnels directed into separate tubes (E-Figure 318-3). Since many materials are toxic to canine sperm, all tubes, syringes and pipettes should be carefully tested prior to routine use. Collection equipment should be clean and dry. After collecting semen, samples should be kept warm since cooling can reduce motility and give a false impression of poor semen quality. There are a number of aspects to semen evaluation as detailed below.



E-FIGURE 318-3 Collection of semen by manual stimulation of the penis in the presence of a teaser bitch. The three fractions of the ejaculate are collected into separate test tubes by non-toxic glass funnels.

Ejaculate Volume, Color, Concentration and Total Sperm Count

Volume is measured using a graduated test tube or by pipetting. It is important to have an accurate measurement of second fraction volume to enable calculation of the total sperm output. In a medium-sized

dog the fractional volumes are approximately 0.5-2 mL (first fraction; usually clear and transparent), 0.5-1.5 mL (second fraction; usually white or creamy in color), and 15-20 mL (third fraction; usually clear and transparent), although commonly the entire third fraction is not collected (Figure 318-4). Cytological examination of centrifuged and stained smears may help establish the nature of any contamination.

FIGURE 318-4 The fractions of the canine ejaculate. The first fraction (left) originates from the prostate gland and contains no sperm, the second fraction (middle) is sperm rich, and the third fraction (right) is again prostatic in origin and sperm free.

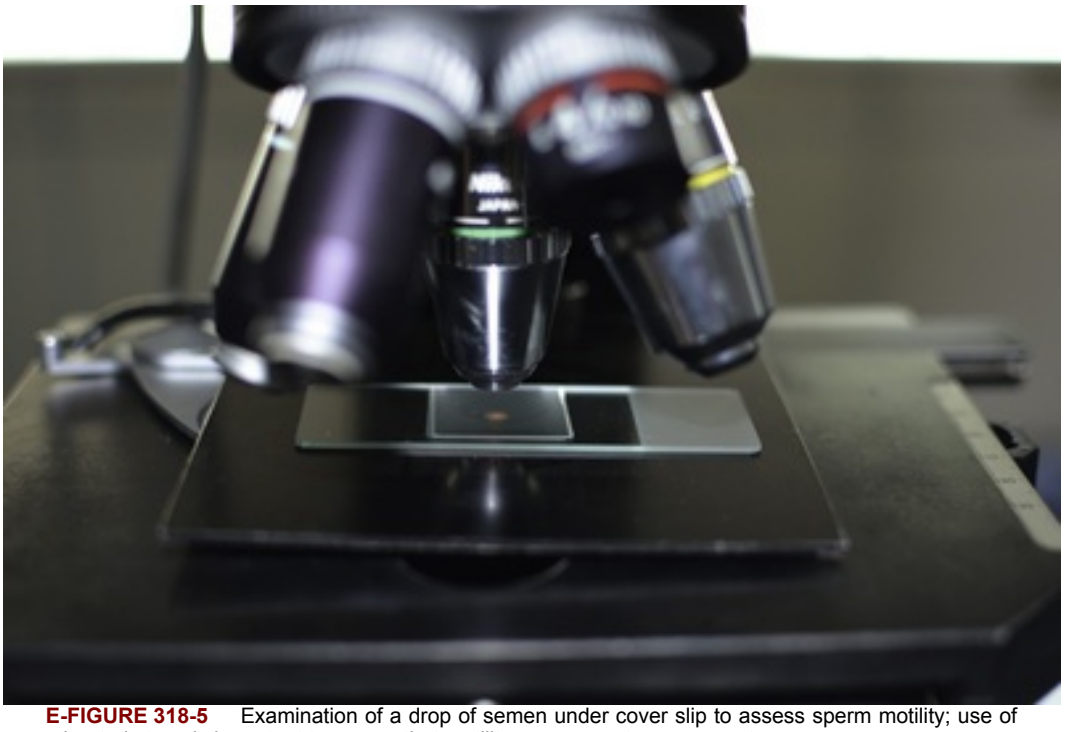
It is common to measure semen concentration using a hemocytometer. A small volume of the second fraction is diluted at a standard rate to enable sperm counting. Distilled water with detergent is often used as a diluent to kill sperm and prevent clumping. Diluted sperm are placed into the chamber and the number of sperm counted; the dilution factor is then used to calculate the initial sperm concentration. However, the total spermatozoal output is a more useful measure than concentration. Total sperm output (TSO) is the total number of sperm within the ejaculate and is calculated by multiplying the second fraction volume by the sperm concentration. TSO is more meaningful than concentration or volume. Normal dogs produce 300-1000 $\times 10^6$ spermatozoa within each ejaculate. Since there is a pool of sperm stored within the epididymides, some of which are removed at each ejaculation, the number of sperm found within a given ejaculate is determined by the number of sperm stored and the frequency of ejaculations (frequent ejaculation will deplete the epididymal reservoir). If collected daily for 4 to 5 days, the number of sperm present in ejaculates is indicative of the daily sperm production. In normal dogs a good correlation exists between daily sperm production and both the volume of the testes and the width of the scrotum.

Sperm Motility

Sperm motility is commonly evaluated subjectively, although in referral centers there is increasing use of computer image analysis. For subjective examination, a drop of semen is placed onto a warmed microscope slide, covered with a cover slip and maintained at 30-35° C (E-Figure 318-5). Evaluation at low temperatures may give erroneous results. Motility decreases over time when the slide is left on the microscope stage (probably due to the effect of light and cooling). Samples should therefore be assessed quickly. Subjectively, the percentage of sperm within each of the following five categories are noted:

- Category O: non-motile spermatozoa
- Category I: spermatozoa which are motile but are not progressive
- Category II: spermatozoa which are motile but poorly progressive

- Category III: spermatozoa which are motile but moderately progressive
- Category IV: spermatozoa which are motile, rapidly progressive and swimming in a forward direction

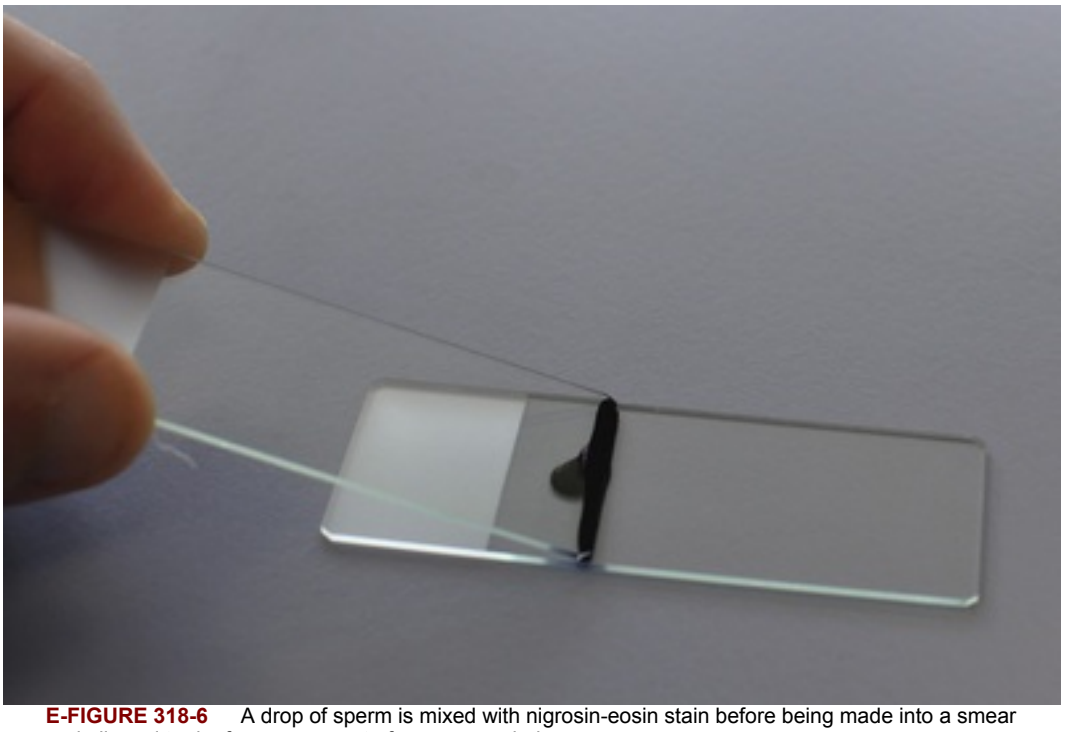


E-FIGURE 318-5 Examination of a drop of semen under cover slip to assess sperm motility; use of a heated stage is important to ensure that motility assessments are accurate.

Using these criteria normal dogs have more than 70% spermatozoa with Category IV motility and 90% total motility (sum of Category I-IV).

Sperm Morphology

A simple method for assessing sperm morphology and membrane integrity is use of eosin combined with the background stain, nigrosin. Semen is mixed 1:5 on a volume basis with the nigrosin/eosin stain and then a drop is transferred to a slide, a smear is made and allowed to dry (E-Figure 318-6). Spermatozoa are silhouetted against the purple-blue nigrosin; white sperm are classified as live (these sperm have intact membranes which prevent the eosin from penetrating into the sperm) and pink sperm are classified as dead. Smears should be examined at ×100 magnification under oil immersion and at least 100 sperm classified according to their staining characteristics and morphology. Most fertile dogs will have more than 60% live and morphologically normal sperm.



E-FIGURE 318-6 A drop of sperm is mixed with nigrosin-eosin stain before being made into a smear and allowed to dry for assessment of sperm morphology.

Normal sperm have a typical appearance (Figure 318-7) and there are a variety of methods used for classification of abnormal sperm. It has been common to classify according to whether abnormalities occurred during (a) spermatogenesis (primary abnormalities), (b) the epididymal phase of development (secondary abnormalities), or (c) collection and processing (tertiary abnormalities). However, a recently proposed system describes sperm as being compensable (abnormalities which render the sperm unable to reach the egg) or non-compensable. The term compensable indicates that the abnormality does not prevent normal sperm from fertilizing an egg; as long as there are sufficient normal sperm, the abnormal sperm can be compensated for. Compensable abnormalities include substantially misshapen heads, tail defects, immature and immobile sperm. Other sperm abnormalities are described as non-compensable since these sperm can reach the oocyte and trigger oocyte depolarization, but then there is either failure of fertilization or later failure of the embryo. In this manner these sperm effectively block other normal sperm from achieving normal fertilization. Large numbers of normal sperm cannot compensate for the abnormal sperm present. Sperm with subtly misshapen heads or nuclear vacuoles are typical of non-compensable abnormalities. Other classification systems use terminology that describes the overall changes in semen quality; for example, oligozoospermia is the term used to describe an ejaculate that contains low numbers of morphologically normal sperm. This type of system may then be subdivided with descriptions of the predominant abnormality (such as acrosome, neck, mid-piece, tail) with a consideration of their significance. This method may not be applicable when there are multiple abnormal forms rather than one or two predominant types.

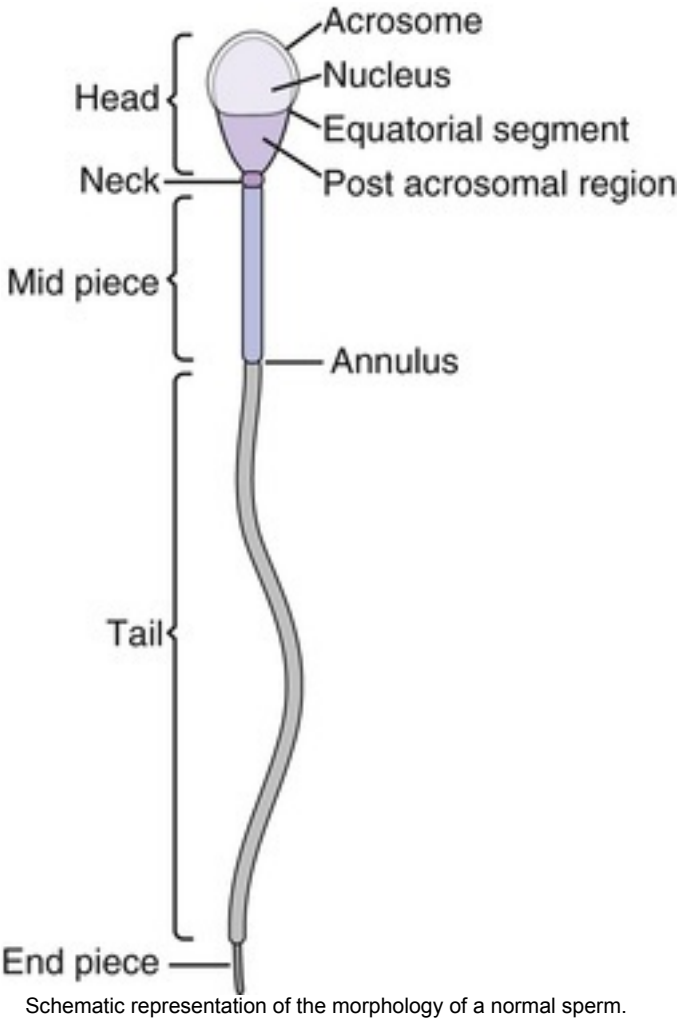


FIGURE 318-7 Schematic representation of the morphology of a normal sperm.

Other Cells in Ejaculates

Ejaculates should be checked for non-sperm cells. Common hematology stains can be used either on air-dried smears or samples concentrated by centrifugation, aiding in detection of prostatic conditions. This may also help confirm azoospermia when spermatogenic cells may be found. Medium neutrophil numbers are common, usually originating from the prepuce (Figure 318-8).

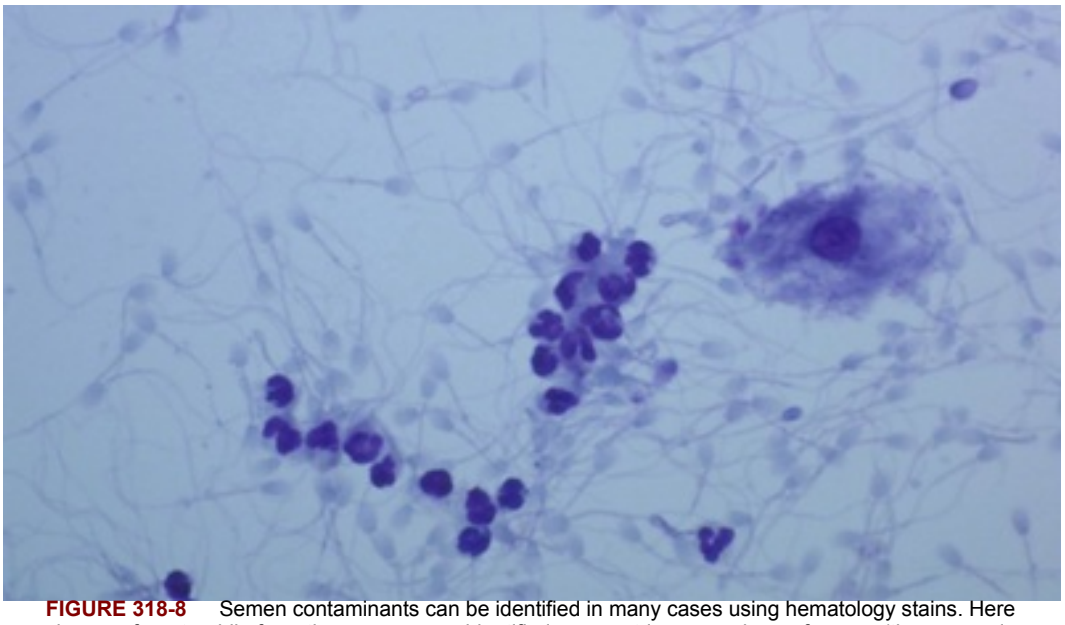


FIGURE 318-8 Semen contaminants can be identified in many cases using hematology stains. Here clumps of neutrophils from the prepuce are identified amongst large numbers of sperm (the sperm do not stain well using the hematology stain).

The Hypo-Osmotic Swelling Test

The hypo-osmotic swelling test is considered by some to be a test of functional sperm membrane integrity. Normal sperm, exposed to a hypo-osmotic medium, absorb water and develop coiled/bent tails. In this manner, simply counting the percentage of sperm with bent tails when exposed to hypo-osmotic medium can be considered to be a marker of membrane function. Most normal samples have more than 70% of sperm with bent tails using this method.

Sperm-Oocyte Binding or Penetration Assay

These tests assess binding or penetration of oocytes by sperm. A pre-determined number of sperm are incubated with homologous oocytes or hamster oocytes (which allow most sperm to penetrate), and the numbers of oocytes bound or penetrated after a specific time are counted. This provides assessment of sperm ability to acrosome react, change their motility characteristics (become hyperactivated) and bind to/penetrate oocytes.

Sample Archive

After semen samples are evaluated, it is prudent to archive a portion for comparison with future evaluations. Samples can be preserved by 1:1 dilution with buffered formal saline followed by storage in a sealed vial. This enables samples to be stored at room temperature for many years without substantial changes in sperm morphology or staining characteristics.

Predicting Fertility

Overview

It is difficult to precisely predict fertility because of the wide range in seminal characteristics seen in fertile animals. Broad normal ranges have been defined (Table 318-1) and semen within these limits are considered likely to be fertile, as long as libido and copulatory ability are normal. In many dogs, one or more assessments may be borderline. If an ill-at-ease dog produces a poor sample, repeat examination is indicated since there may have been incomplete ejaculation. If samples are just outside the normal range the dog may still have normal fertility if the mating regime is adjusted (e.g., mating more frequently in the window shortly after ovulation). When a sample contains no sperm (is azoospermic), a second sample should be collected or an attempt made to establish whether ejaculation did indeed occur by measurement of alkaline phosphatase concentration.

TABLE 318-1

Seminal Characteristics from Fertile Dogs

	PROGRESSIVE, CATEGORY IV, MOTILITY (%)	SPERM-RICH SECOND FRACTION VOLUME (mL)	SECOND FRACTION SPERM CONCENTRATION ($\times 10^6$/mL)	TOTAL SPERM OUTPUT ($\times 10^6$)	LIVE NORMAL SPERM (%)
Mean	82	1.2	330	410	74
Range	40-95	0.3-3.3	50-820	36-1980	50-92

Semen Alkaline Phosphatase Concentration

Large quantities of alkaline phosphatase (AP), produced by the epididymis, are present in normal ejaculates (>5,000 IU/L). Azoospermic samples with increased AP concentrations (5,000-20,000 IU/L) are truly azoospermic, whereas those with low AP concentrations (<5,000 IU/L) either had incomplete ejaculation, retrograde ejaculation, or have an epididymal or vas deferens obstruction. If no sperm are seen on repeated collection, the urine should be assessed for sperm and, if positive, a diagnosis of retroejaculation considered.

Ultrasound (US) Examination of the Reproductive Tract

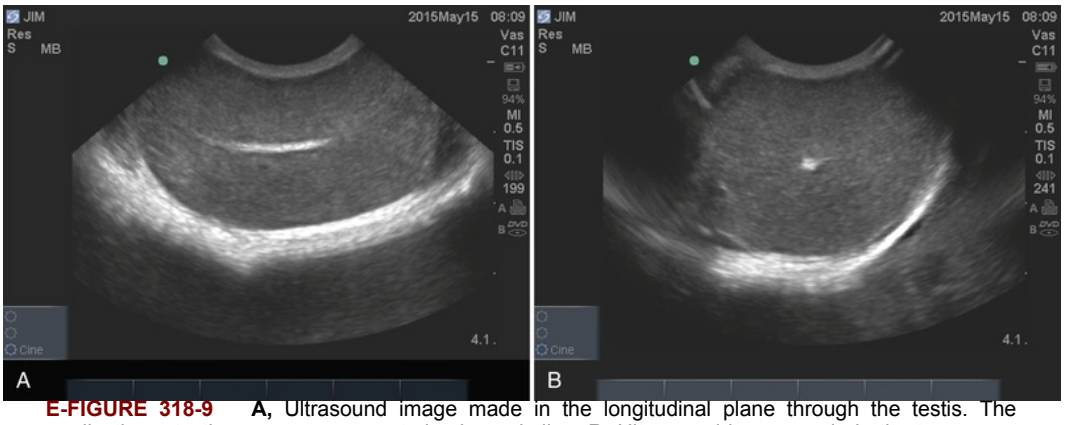
Overview

US examination of the reproductive tract should be a routine component of the BSE. Use of color Doppler and pulsed Doppler US can be used to assess testicular and prostatic blood flow. A small number of studies have described contrast-enhanced US for detection of reproductive tract disorders.

Scrotal Ultrasound

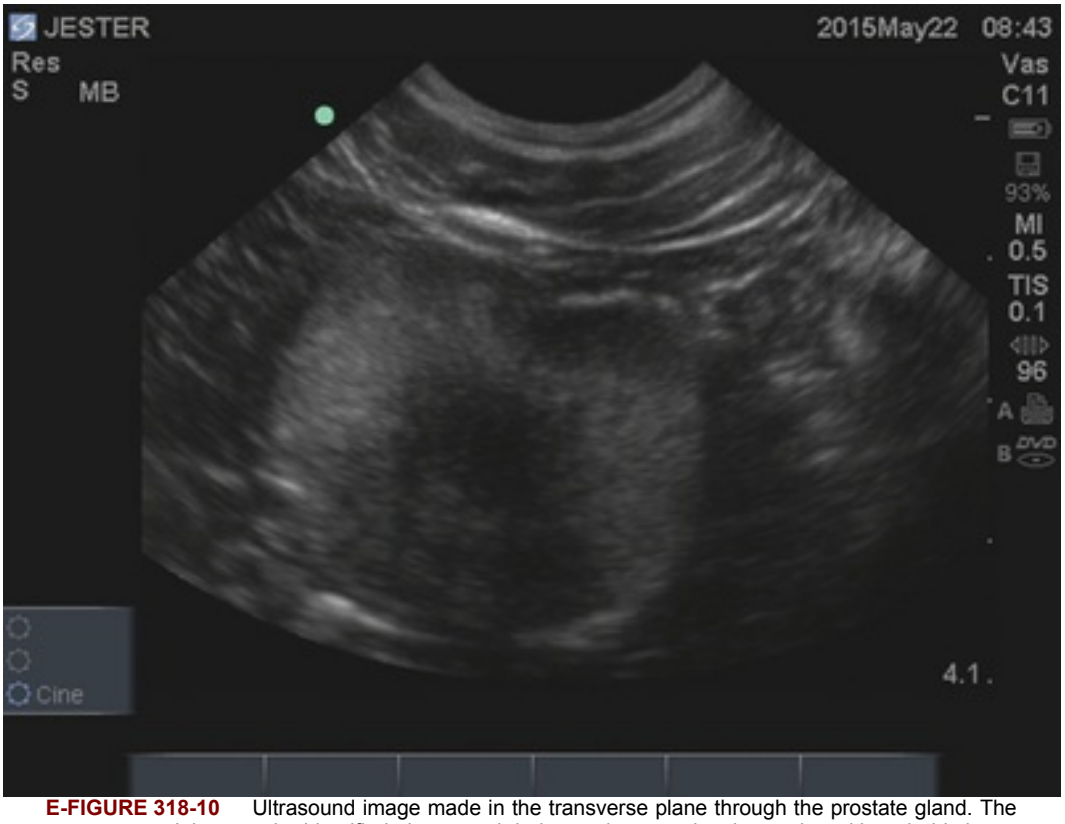
Examination of the scrotum can be undertaken with high frequency linear or sector transducers after application of copious amounts of US gel. It is prudent not to clip the scrotal hair as this often results in irritation and secondary self-trauma following incessant licking. Examination of the neck of the scrotum may be undertaken to rule out scrotal hernia. The testes and epididymides are usually examined in sagittal, transverse and frontal (dorsal) planes. The epididymides are most easily identified using the longitudinal plane with the transducer placed on the ventral surface of the testes; in this manner, the tubular longitudinal section of the epididymal body and triangular appearance of the epididymal tail can easily be identified on the far (dorsal) surface of the testis.

Normal testicular parenchyma is relatively hypoechoic with regular diffuse echogenic stippling, which represents an extension of the fibrous mediastinum responsible for supporting the parenchyma. The mediastinum itself appears as a linear echo extending from the cranial to the caudal pole when imaged in the longitudinal plane and an approximate 2 mm circular echo when imaged in the transverse plane (E-Figure 318-9, *A* and *B*). Acoustic shadowing is common distal to the mediastinum testis. The testis is bordered by the combined testicular and vaginal tunics which appear as a single echogenic line, unless there is a hydrocele and fluid which creates 2 lines. The epididymis is hypoechoic and stippled when compared with testicular parenchyma. Testes which appear more heterogeneous are often associated with poor semen quality, as are those which appear overall to be more hypoechoic or hyperechoic. US can be used to accurately measure testicular size and to calculate testicular volume. There is usually good relationship between testicular volume and body size and a general relationship between testicular size and semen quality. Pulsed Doppler US has been used to measure testicular artery blood flow. Differences have been identified comparing pre-pubertal and pubertal dogs as well as fertile and infertile dogs. Color Doppler may also aid in identifying increased perfusion associated with pathological conditions. Similarly, contrast-enhanced US (a technique where microbubbles are injected into a vessel) may be used to accurately document vascular perfusion and to highlight lesions.



E-FIGURE 318-9 **A,** Ultrasound image made in the longitudinal plane through the testis. The mediastinum testis appears as a central echogenic line. **B,** Ultrasound image made in the transverse plane through the testis. The mediastinum testis appears as a central echogenic spot.

The Prostate (E-Figure 318-10; See Ch. 337)



E-FIGURE 318-10 Ultrasound image made in the transverse plane through the prostate gland. The two separate lobes can be identified; the central darker region contains the urethra although this is not clearly demarcated in this image.

Endocrine Assessment

Assessing circulating reproductive hormones are of limited value. Administration of exogenous gonadotropin-releasing hormone stimulates increases in luteinizing hormone (LH) within 30 minutes and increases in testosterone within 60 minutes. Administration of exogenous human chorionic gonadotropic (hCG; LH-like activity) results in testosterone increases. Such tests have been employed to detect presence of testicular tissue and are not used for subtle changes in pituitary or testicular function. Basal hormone

concentrations in dogs vary considerably throughout the day. Plasma testosterone concentrations in healthy intact dogs are usually >4.0 ng/mL (14.0 nmol/L) and castrated dogs have testosterone concentrations <2.0 ng/mL (7.0 nmol/L). Dogs with impaired spermatogenesis usually have normal results, as do dogs that are bilaterally cryptorchid. Both LH and follicle stimulating hormone (FSH) concentrations vary markedly throughout the day and there is limited information on normal values and how they change in various conditions. LH and FSH concentrations may be increased in dogs with impaired spermatogenesis, but results do fluctuate.

Bacterial Infection Screening

Owners and breeders may have concerns regarding routine screening of both sires and dams for bacterial venereal pathogens. In countries where *Brucella canis* is endemic, screening for this organism is crucial prior to breeding (see ch. 213). It is particularly important that females be screened, since they may harbor the organism with few clinical signs. The history may reveal previous acute infection that caused orchitis or epididymitis that cause systemic signs of illness, pain, discharge and loss of libido. Chronic infection may lead to testicular degeneration, although in some dogs fertility is restored after the acute phase of infection. Multiple sperm abnormalities and sperm agglutination may be detected. *Brucella canis* may be isolated from semen of infected dogs.

Apart from *Brucella canis* there is no evidence that other bacteria are venereal pathogens in dogs. All dogs have a resident commensal microflora and these bacteria may change. Commonly isolated bacteria include hemolytic streptococci, other streptococci, staphylococci, *Escherichia coli*, and others. Most dogs have a mixed flora with 2-5 different species present. Routine screening is unnecessary and use of antibiotics for commensal bacteria does not meet current best practice guidelines.

Virus Screening

Stud dogs may become infected with canine herpesvirus and, with reactivation, small red raised, sometimes ulcerated, lesions on the penis and inner surface of the prepuce may be noted. Virus may be detected by PCR offered by many commercial laboratories. Canine herpesvirus vaccine does not appear to protect dogs from infection or to reduce viral recrudescence (see ch. 228).

Karyotype

Gross abnormalities of underdevelopment of genitalia may be indicative of genetic issues that can be identified with chromosome studies on EDTA blood that can be cultured and examined. Normal dogs have 78 chromosomes: 38 pairs of acrocentric autosomes and 2 metacentric sex chromosomes.

Testicular Fine Needle Aspiration (FNA) and Biopsy

Testicular FNA may be useful if there are gross testicular abnormalities or if a focal lesion has been seen with US (see ch. 87 and 93). US guidance is particularly useful for precise sampling. The dog should be sedated before placing a 20G needle, attached to a syringe, into the region of interest. Biopsy allows evaluation of spermatogenesis and detection of inflammatory or neoplastic cells. However, biopsy is invasive and can itself cause severe testicular changes. It is not recommended.

Additional Prostatic Evaluations

Additional methods for examination of the prostate include cytology of prostatic fluid, FNA, and biopsy (see ch. 111). The first and third fractions of canine ejaculate are primarily prostatic and can be collected by manual stimulation. Each phase of the ejaculate can be collected separately, cultured and evaluated cytologically. If an ejaculate cannot be obtained, prostatic fluid can be obtained by massaging the prostate transrectally while simultaneously flushing the prostatic urethra with 5-10 mL of saline. One can simply place a urethral catheter to the level of the prostate gland and apply suction to retrieve cells for cytologic examination. FNA of the prostate can be done via a transabdominal approach, especially if the gland is large. If the prostate remains within the pelvic canal, a perineal approach is required (see ch. 337). Either technique can be assisted by the use of US guidance. Canine prostate-specific esterase (CPSE) is a serine protease found in normal prostate epithelial cells, prostatic fluid, and in serum or plasma. CPSE concentrations are higher in older dogs and may be a marker of benign prostatic hyperplasia (BPH). BPH is a normal aging change in the

dog and frequently is associated with no clinical signs.

Puberty, Fertility, and Clinical Disorders

Overview

Plasma testosterone concentrations reach adult concentrations with maturation of Leydig cells after about 5 months of age. Large breeds typically demonstrate secondary sexual characteristics later than small breeds. Medium-sized males reach puberty at 10 to 12 months and can ejaculate normal sperm. Total sperm numbers in the ejaculate increase and plateau at about 2 years of age. About 80-90% of breedings of normal fertile males and females result in pregnancy. Veterinary opinion may be sought for males failing to sire litters with two or more healthy bitches. If a dog is used infrequently, there may be long periods before recognizing a possible problem. It is wise to consider routine BSE every 12 months.

Poor Libido, Failure to Achieve an Erection or Intromission

Poor libido is an uncommon cause of infertility in dogs seen most commonly in older males or those with hypogonadism. Poor libido is not associated with low testosterone in the absence of obvious testicular disease. Exogenous testosterone supplementation is not recommended to improve libido in dogs, since this can suppress pituitary function and decrease semen quality. Common causes of apparent poor libido include male inexperience, poor breeding management, or having the female brought to the male at an inappropriate time. Some dogs may have been previously reprimanded when they have shown interest in bitches and this has resulted in a psychological barrier to the normal expression of male sexual behavior. Some dogs benefit from being allowed to mate an experienced and quiet bitch.

Rarely, dogs have failure of erection separate from poor libido or disinterest in females and are reluctant to mate. In these dogs even manual stimulation of the penis fails to stimulate an erection. Previous trauma (fracture of the *os penis*) can cause failure of the corpus cavernosum to fill with blood, resulting in partial or complete erectile failure. Abnormalities may be detected by observing the penis when attempting to collect semen. Off-license treatment with sildenafil has not been useful. Sometimes it is best to collect semen for artificial insemination of the bitch. Failure to achieve normal intromission may be the result of abnormalities of the penis or sheath, the result of disease that causes pain and thus prevents intromission, or abnormality of the caudal female reproductive tract that prevents intromission.

Penile, Preputial and Related Abnormalities

Persistent Penile Frenulum

Failure of rupture of the penile frenulum at puberty may result in a ventral deviation of the penis during erection and failure to breed. In some dogs, traction on the frenulum causes pain or tearing and bleeding of the penile skin. Persistent frenulum can be detected by inspection of the penis. The frenulum (which is normally avascular) can be incised to enable an effective cure. Since this may be an inherited trait, it should be considered before breeding such males.

Fractured *Os Penis*

Traumatic fracture of the *os penis* usually causes acute swelling, urethral hemorrhage and dysuria. Following healing there may be residual pain, deviation of the penis, or abnormalities of erection. Each can result in inability to achieve normal intromission. Some of these males never achieve normal coitus and breeding has to be assisted by the use of semen collection and artificial insemination.

Lymphoid Hyperplasia

Small, 1 to 2 mm diameter raised lymphoid nodules are commonly present on the caudal glans in the region of the preputial reflection at the base of the penis and are especially common in dogs with a muco-purulent preputial discharge. This discharge is usually normal and associated with commensal bacterial growth within the prepuce. Occasionally these lymph nodules can be numerous or particularly protuberant and traumatized when the prepuce is retracted at the time of mating or semen collection. Extensive lymphoid hyperplasia may cause pain and bleeding at coitus but usually they do not prevent breeding.

Penile Neoplasms

Tumors of the penis are rare. Squamous cell carcinomas are most common; they spread locally and metastasize to the inguinal lymph nodes. Hemorrhage from an ulcerated neoplasm may be the first clinical sign, although usually there is frequent penile licking. When lesions are large they may prevent normal intromission. Radical surgical resection is warranted in the absence of metastases. Transmissible venereal tumor (TVT; see ch. 351) is a consideration, but a mass is not always present. Diagnosis of TVT is important as transmission of cells from the infected individual seeds the genital mucosa of the recipient. In the early stage, small tumors do not prevent breeding. Animals should not be used for breeding if any active tumor tissue is present. Spread to the oral or nasal cavity is common due to licking. Most dogs are cured with chemotherapy.

Phimosis

An abnormally small preputial orifice may occur either congenitally or result from trauma or inflammation. A narrow stream of urine during micturition and urine pooling within the prepuce can result and cause balanoposthitis. Affected dogs are not able to copulate and show signs of pain during erection and intromission. Surgical enlargement of the orifice is usually curative.

Musculoskeletal Pain Preventing Intromission

Some dogs may be unable to breed due to musculoskeletal pain due to spine or orthopedic issues (see ch. 353). In non-hereditary disease, males may breed after being given anti-inflammatory agents, but others may require semen collection and artificial insemination.

Female Causes of Failure of Intromission

Various abnormalities within the bitch's caudal reproductive tract may prevent intromission. Careful examination of the bitch for the presence of vulvar hypoplasia, vaginal strictures or vaginal hyperplasia should be routinely assessed prior to mating. Detection of these problems is important since if attempted mating causes either the dog or the bitch to suffer pain, this can result in psychological problems that inhibit future breeding.

Failure to Produce an Ejaculate

Retrograde Ejaculation

Retrograde ejaculation, rare in dogs, is usually a neurological condition causing deposition of sperm into the bladder rather than the emission of semen. In most afflicted dogs, no ejaculate is seen although some produce small volumes of the second ejaculate fraction. Lavage of the bladder with physiological saline after mating may be diagnostic. Some dogs with retrograde ejaculation can be managed by preventing urination prior to mating or semen collection and others respond to sympathomimetic agents (phenylpropanolamine). In unresponsive dogs, the bladder can be emptied of urine, partially filled with saline before being stimulated, and the bladder lavaged afterward. Sperm collected in this manner can be used for artificial insemination.

Tubular Obstruction

Obstruction of the tubular genital tract can result in absence of sperm from the ejaculate, although in most cases the condition is unilateral and results in low numbers of ejaculated sperm rather than a complete absence. If bilateral, there is usually an obvious lesion of the scrotum, testes or epididymides, and it is rare for a dog to present solely with obstructive azoospermia. Potential causes include acute inflammation, sperm granuloma, neoplasia, previous vasectomy and segmental aplasia. With bilateral lesions, ejaculates are azoospermic, urine contains no sperm, and concentrations of alkaline phosphatase are low.

Failure to Ejaculate

Failure to ejaculate can be the result of psychological issues similar to those reported in poor libido and most common in young dogs, inexperienced dogs, or dogs who experienced pain during previous matings. These dogs often fail to thrust forward during intromission, exhibit lack of excitement, and they may fail to develop a complete erection (the copulatory tie is usually absent). Patience and use of an experienced bitch may overcome these issues. Teasing the dog for a time before mating may increase excitement and help overcome the problem.

Poor Semen Quality

Overview

One of the most important aspects of investigating male infertility is the performance of a detailed semen evaluation, since certain characteristics of semen quality are predictive of fertilizing ability. As discussed, it is possible to classify semen abnormalities according to their origin, whether they are compensable or not, or using terminology that describes the overall changes in semen quality.

Hemospermia

Blood or red-coloration to ejaculates is relatively common in dogs. Usually, blood is noted in the prostatic fractions (first or third) of the ejaculate. Occasionally, red blood cells are identified microscopically when not seen grossly. Since the prostate is the sole male dog accessory gland, bleeding or discoloration is nearly always associated with prostatic disease, commonly BPH. Presence of blood warrants further prostatic evaluation (see ch. 337). If contamination of the second fraction is significant and semen is to be used for artificial insemination, one may centrifuge the semen, remove the fluid containing erythrocytes and re-suspend the sperm in a semen extender.

Urospermia

The first fraction of the ejaculate flushes the urethra of urine, cellular debris, and is voided before intromission. It is common, therefore, to find urine in the first fraction and, if allowed to mix with the second fraction, may have a toxic effect. Contamination of the second fraction with first fraction should be avoided and if it occurs, semen should be diluted with an extender, centrifuged, supernatant removed, and the sperm re-suspended in fresh extender.

Azoospermia

Overview

Apparently normal ejaculate containing no sperm is azoospermia. There are various explanations. Diagnosis often requires biochemical and cytological examination of the ejaculate, US examinations and testicular fine needle aspiration (Figure 318-11). Common causes include acquired gonadal dysfunction, incomplete ejaculation, lack of emission (see above), and congenital gonadal dysfunction.

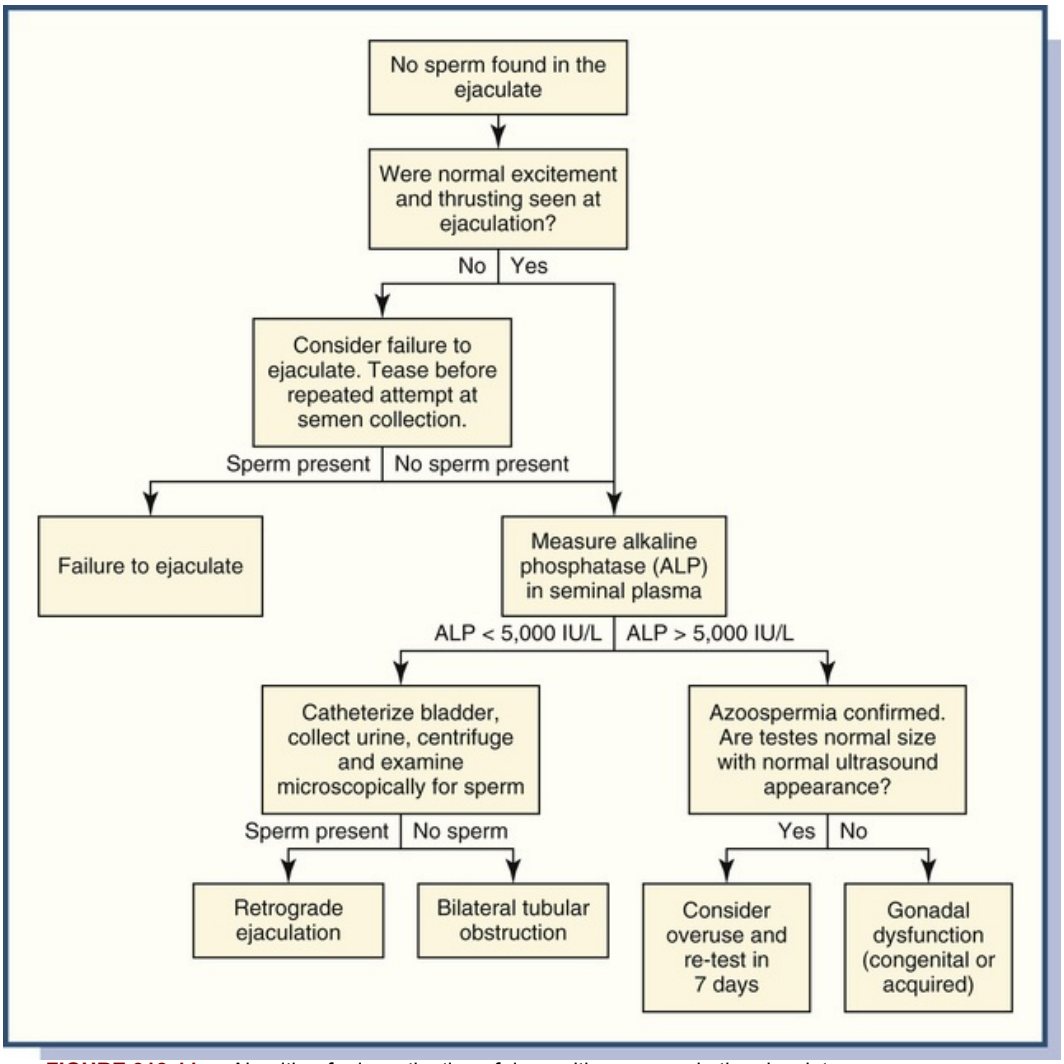


FIGURE 318-11 Algorithm for investigation of dogs with no sperm in the ejaculate.

Acquired Gonadal Dysfunction

Acquired gonadal dysfunction accounts for >55% of "infertile" males. The condition may be called spermatogenic arrest or testicular degeneration. Many of these dogs were previously fertile, but developed decreased fertility (both the percentage of bitches pregnant and a decrease in litter size) before developing azoospermia. In some breeds (Labrador Retriever, Welsh Springer Spaniel) the problem occurs within specific genetic lines and may have an immune-mediated etiology. In the Beagle, a relationship between focal degenerative orchitis and thyroiditis has been established. In many, unrecognized exposure to toxins or use of drugs that cause azoospermia will lead to testicular degeneration. Most azoospermic dogs have normal ejaculate alkaline phosphatase concentrations, confirming ejaculation in the absence of sperm. There are often changes in testicular size, calcification or fibrosis noted on US of testicular parenchyma. FNA and cytology may be useful. In the majority the prognosis for fertility is hopeless. However, azoospermia is reversible following sexual rest in a minority of dogs. The etiology is not understood, although these dogs do not have small testes or US evidence of disease. It is plausible that incomplete ejaculation has occurred. These dogs should be re-examined after a period of sexual rest before diagnosing irreversible azoospermia.

Incomplete Ejaculation

Nervous inexperienced males commonly have an incomplete ejaculation or failure of ejaculation. Diagnosis depends on age, breeding history, observation of a mating, collection of a semen sample and detection of low concentrations of alkaline phosphatase concentration. Examination of urine after centrifugation can be useful for distinguishing these two conditions, since dogs without obstruction may have sperm present within the

bladder, but not the pathological condition of retrograde ejaculation. This is a common observation in normal dogs. Incomplete ejaculation can be treated by changing breeding practices to increase the dog's experience and by teasing the dog for an extended time prior to breeding. Allowing the dog to breed an experienced bitch may improve performance.

Congenital Gonadal Dysfunction

Congenital gonadal dysfunction is usually seen in dogs that are phenotypically male but with chromosomal abnormalities (XXY or XX-male syndromes). Such dogs usually have an absence of spermatogenesis and, as such, are relatively easy to diagnose since there is usually testicular hypoplasia on examination. Testes are palpably small and soft. They are usually hyperechoic on US.

Lack of Emission

Both retrograde ejaculation and tubular obstruction (if bilateral) can result in azoospermia as discussed.

Oligozoospermia

Definition

Oligozoospermia is the term used to describe ejaculates containing low numbers of morphologically normal sperm. It is uncommon in dogs and may occur as a result of incomplete ejaculation, overuse, or retrograde ejaculation.

Incomplete Ejaculation

Incomplete ejaculation caused by inexperience or a previously painful mating is probably the most common cause of oligozoospermia. In these cases there may be a low number of normal sperm within the ejaculate. The condition can be diagnosed and managed as described above.

Overuse

Often, older dogs may have oligozoospermia if frequently used in breeding. It is likely that daily sperm production is low and that frequent ejaculation depletes the extragonadal sperm reserve. Sexual rest may allow the reserves to increase to appropriate numbers. Semen quality of dogs begins to decline at about 7 years of age. Careful management of the time of mating is required in older dogs to ensure that appropriate numbers of sperm are available for fertilization.

Retrograde Ejaculation

In retrograde ejaculation, a small volume of the second ejaculate fraction may be collected and found to contain low numbers of normal sperm. This is uncommon and in most cases there is a complete absence of sperm and the condition can be diagnosed and treated as previously discussed.

Teratozoospermia

Teratozoospermia is the presence of sperm with abnormal morphology. In many cases, such morphological abnormalities result in impaired motility such that teratozoospermia and asthenozoospermia occur concurrently. There is little information about specific sperm abnormalities and fertility in dogs. Large numbers of sperm with abnormal midpieces, head-base/midpiece abnormalities and midpiece swellings have been related to infertility in dogs. Sperm with midpiece defects and deformed acrosomes are also associated with experimental *Brucella canis* infection. There is no direct link explaining why these sperm abnormalities cause infertility. In dogs, this is not especially important as long as the abnormalities associated with infertility are recognized. In some dogs, several abnormalities may be seen. In general, when >40% of sperm are morphologically abnormal there is a decline in fertility. Cause of teratozoospermia is not often determined. Many dogs are in early stages of testicular degeneration after an insult and later are azoospermic. Repeated semen evaluation after about 2 months should allow the progression of the disease process to be established. In some cases, teratozoospermia is seen in older dogs as a result of senile degenerative changes within the testes.

Asthenozoospermia

Asthenozoospermia refers to normal sperm morphology but reduced motility. As previously described, careful assessment of motility is necessary to ensure detection. Cooled semen samples often have sperm with reduced motility. Other recognized causes include immune-mediated disease and contamination of the ejaculate. The latter is not an infertility condition.

Agglutination of Sperm

Antisperm antibodies can cause agglutination and poor motility. Although the cause of such antibody production is usually not known, it has been demonstrated in experimental infection with *Brucella canis*. In most dogs the prognosis for fertility is guarded.

Contamination of the Ejaculate

Contamination of ejaculate with toxic compounds (water, urine, certain plastics, some lubricants, residue from sterilizing agents, and latex artificial vagina liners) can all reduce motility or produce immotile sperm without obvious morphological changes. Careful evaluation of semen collection methods and handling should be undertaken.

Normospermia

There are many dogs who appear infertile despite having normal semen quality. In many, there are anatomical, physical or psychological problems that prevent normal courtship, intromission and ejaculation. Some suggest that a positive semen culture and/or changes in pH, biochemistry or cellularity of the prostatic fluid or seminal plasma can influence fertility. In general, however, when there are such changes in the ejaculate, there are also secondary changes in sperm morphology that influence fertility.

Suggested Readings

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CHAPTER 319

Reproductive Disorders in the Neutered Male or Female Dog

Autumn P. Davidson

Client Information Sheets:
Stump Pyometra
Canine Pseudopregnancy
Puppy Vaginitis
Stopping Signs of Heat
Septate Vaginal Strictures
Priapism
Ovarian Remnant Syndrome

Introduction

Medical disorders of the reproductive tract are not limited to "intact" male and female dogs. Genitourinary disorders occur in neutered dogs of both genders and several medical conditions can be traced to the presence of gonadal remnants after an incomplete neutering procedure. The benefits of neutering pet dogs are well documented. Identification and proper management of neutering-related disorders is important in veterinary medicine.

Urinary Incontinence in the Ovariectomized Bitch

Urinary incontinence is a common and predictable complication of ovariectomy in the bitch (see ch. 333). Urinary incontinence in older neutered dogs is less common and usually related to a myelopathy rather than hypogonadism. Urethral sphincter incompetence resulting in urinary incontinence occurs most commonly in larger (>20 kg) ovariectomized bitches over 8 years of age; the time of ovariectomy is not implicated unless the dog was <12 weeks.[1] Important rule-outs include overflow incontinence due to isosthenuria or hyposthenuria (see ch. 45), urinary tract infection (see ch. 330), undiagnosed ectopia, behavioral or submissive urination, and genitourinary tract inflammatory or neoplastic disorders (see ch. 351). Quantitative urethral pressure profiling is a "gold standard" for diagnosing urethral disorders, but is not commonly available (see ch. 335). Urinary incontinence is problematic for house dogs and it increases the incidence of urinary tract infection (UTI) caused by ascending bacteria.

Once diagnosed, usually by a process of elimination, therapy for urethral sphincter incompetence-associated urinary incontinence involves either estrogen replacement (estrogens sensitize the urethral sphincter alpha1-adrenoreceptors to norepinephrine), phenylpropanolamine (a sympathomimetic which improves urethral tone via the alpha1-adrenoreceptors), or combining the two, since their effects are synergistic (see ch. 333).[1] For dogs failing medical management, endoscopic periurethral collagen implantation can improve the condition for weeks to months but availability is limited. Surgical options include colposuspension, urethral infolding, trans-obturator vaginal taping and urethral hydraulic occluder placement (see ch. 124); all have shown benefit in small numbers of cases (see ch. 335).

Chronic Vestibulovaginitis

History

Bitches with chronic vestibulovaginitis may have a purulent or mucoid-to-hemorrhagic vulvar discharge (see

ch. 44) and, usually, signs of discomfort (licking, scooting, and pollakiuria). Perivulvar and vulvar dermatitis is frequently present and can be severe. The condition is seen in ovariectomized bitches of any age, months to years post-neutering. The history usually includes multiple therapeutic efforts without resolution, although transient improvements can occur. The duration is usually from weeks to months, but sometimes lasts years.

Etiology

The etiology of chronic vestibulovaginitis is multifactorial. The primary cause may be masked and/or exacerbated by common therapies: long-term antimicrobial use, self-mutilation, and douching. Vaginal mucosal biopsy frequently shows nonspecific lymphoplasmacytic inflammation, but sometimes the inflammation is suppurative (neutrophilic) or eosinophilic. Vaginal cultures can show overgrowth of an atypical, often resistant bacterial species (pure Gram-negative cultures, *Pseudomonas* spp.), especially if antibiotics have been used extensively. Occasionally, a yeast overgrowth is identified. Primary bacterial vestibulovaginitis is rare. Vaginal strictures are commonly identified but rarely contributory, and usually represent misinterpretation of the normal narrowing at the vestibulovaginal junction in a maiden bitch. True circumferential vaginal strictures are cranial to the urethral papilla and thus do not contribute to urine pooling. Septate dorsoventral vaginal anomalies are also usually positioned cranial to the urethral papilla. Both can interfere with copulation or whelping, but are unlikely to contribute to vestibulovaginitis in the ovariectomized bitch. Neither previous juvenile ("puppy") vaginitis nor ovariectomy prior to the first estrous cycle predisposes an adult to chronic vestibulovaginitis.[2] Many are classified as idiopathic (E-Box 319-1).

E-Box 319-1

Common Etiologies of Chronic Vestibulovaginitis

1. Extensive perivulvar dermatitis associated with redundant dorsal and lateral vulvar folds
2. Granulomatous uterine stump (rule out stump pyometra/ovarian remnant)
3. Vaginal foreign bodies (foxtails, bone fragments)
4. Chronic urinary tract infection with urethritis/vestibulitis/vulvitis
5. Urinary bladder, urethral, vaginal or vestibular neoplasia
6. Os clitoris, clitoral hyperplasia
7. Significant vaginal stricture occluding the vault
8. Vaginal hemorrhage associated with vascular anomalies or bleeding disorders

Clinical Evaluation

Physical Examination (PE), Laboratory Testing, Imaging

PE of the vulvovaginal area without sedation/analgesia may be precluded due to pain or fear. A minimum data base including a complete blood count (CBC), serum chemistries, urinalysis (UA, preferably acquired by cystocentesis) and urine culture are advised. Radiography (vaginogram/urethrogram/cystogram/IVP) and/or ultrasound (US) of the entire genitourinary tract can be helpful in identifying abnormalities and for eliminating differentials (see ch. 88). US is preferred as it does not require anesthesia and evaluation of the entire abdomen can be performed with particular focus on the genitourinary tract, including the former ovarian sites and the uterine stump (Figure 319-1).[3]

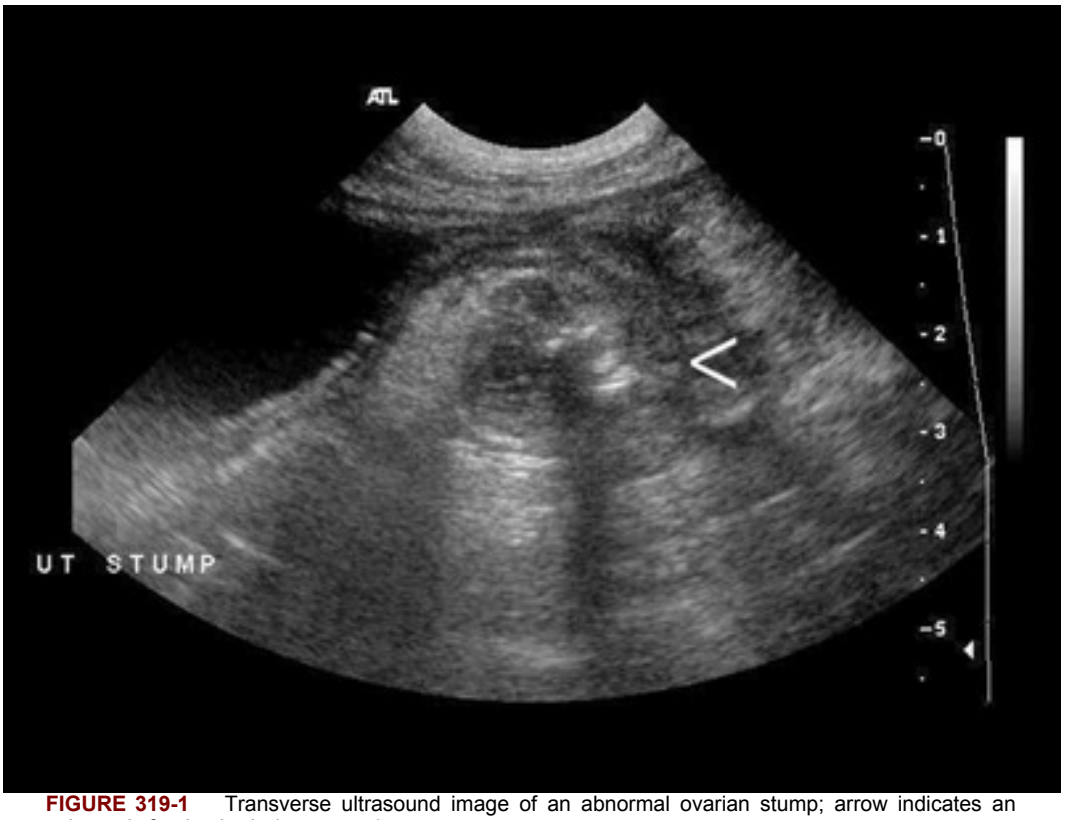

FIGURE 319-1 Transverse ultrasound image of an abnormal ovarian stump; arrow indicates an echogenic foreign body (grass awn).

Endoscopic Examination

When abnormalities are not identified with US (i.e., uterine stump granuloma, chronic cystitis, urolithiasis, trigonal lesions), thorough vaginal examination under adequate (heavy) sedation or anesthesia should be considered (see ch. 44 and 119). Endoscopic equipment allowing evaluation of the entire vaginal vault should be used. A rigid cystourethroscope with saline infusion is optimal. Otoscopes and vaginal speculums do not permit adequate evaluation of the entire vaginal vault. Pediatric proctoscopes lack the sensitive optics of cystourethroscopes. Vaginoscopic evaluation should include visualization of the external vulva, clitoral fossa, vestibule, urethral papilla ± urethra/urinary bladder, vestibulovaginal junction, vagina and caudal cervix (see ch. 108 and 119).[4] Appearance and health of the mucosa throughout the tract, presence of masses, foreign bodies, and source of any discharge should be determined. If a vaginal stricture or marked narrowing of the vestibulovaginal junction is identified, it is important to note if vaginal inflammation secondary to retention of secretions is present cranial to the stricture. If the cranial vagina is normal, the stricture or narrowing is likely not contributory to vestibular-vaginitis (Figures 319-2 to 319-4).

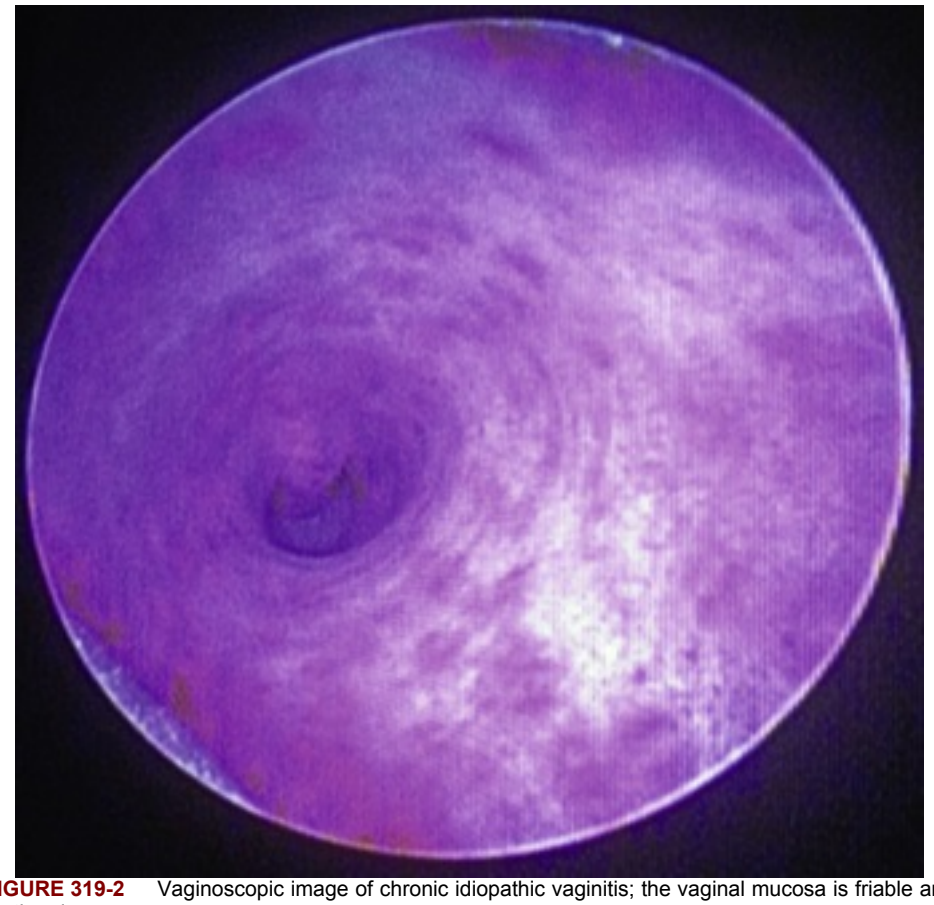

FIGURE 319-2 Vaginoscopic image of chronic idiopathic vaginitis; the vaginal mucosa is friable and erythemic.

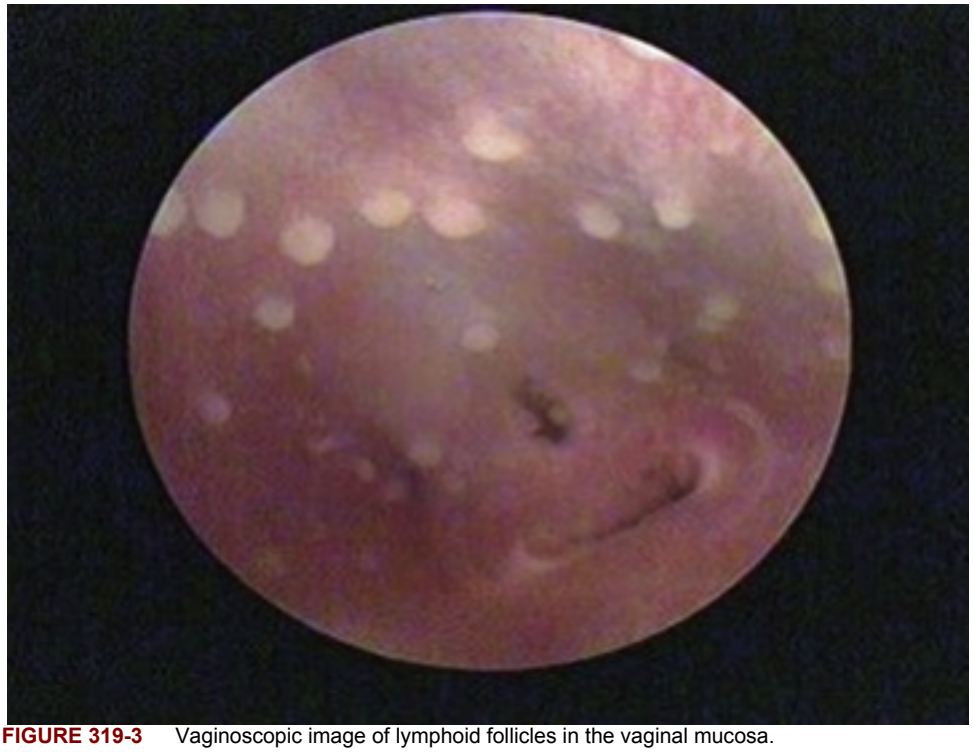

FIGURE 319-3 Vaginoscopic image of lymphoid follicles in the vaginal mucosa.

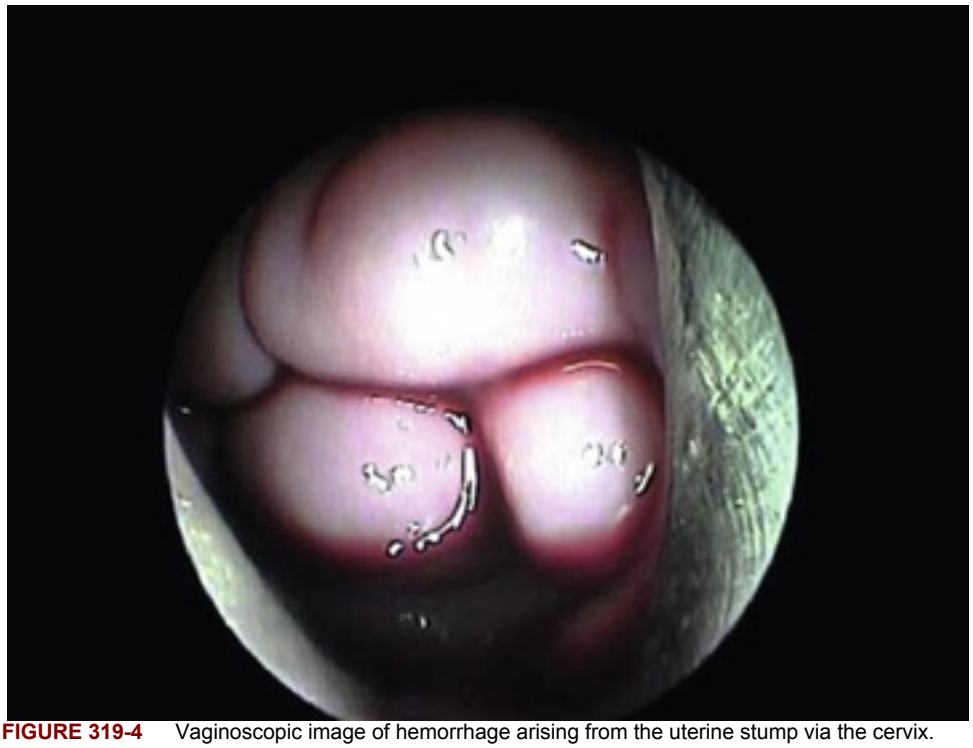

FIGURE 319-4 Vaginoscopic image of hemorrhage arising from the uterine stump via the cervix.

Cytology, Biopsy, Culture

Cytology of vulvar discharge, vaginal mucosal cytology, aerobic guarded vaginal cultures and pinch biopsy of affected vaginal mucosa may be helpful in better understanding this condition (see ch. 119). Interpretation of vaginal cultures should take into consideration previous antimicrobial therapies that could impact normal vaginal flora (mixed gram negative and positive bacteria including *Mycoplasma* spp.). Identification of any contributory anatomic abnormality is important (significant strictures, mass lesions, redundant dorsal or lateral vulvar folds, anomalous ureteral anatomy). It is helpful to have evaluated the bitch in a normal standing position to accurately assess external anatomy (vulvar folds?), after urination, and again after recumbency (urine pooling and scalding?). This complete examination often can only take place after a bitch is sedated or anesthetized (Figures 319-5 and 319-6). The presence of urine pooling in the vaginal vault during anesthesia can be misleading. Presence of redundant vulvar folds can be difficult to visualize if the bitch is positioned sternally or dorsally.

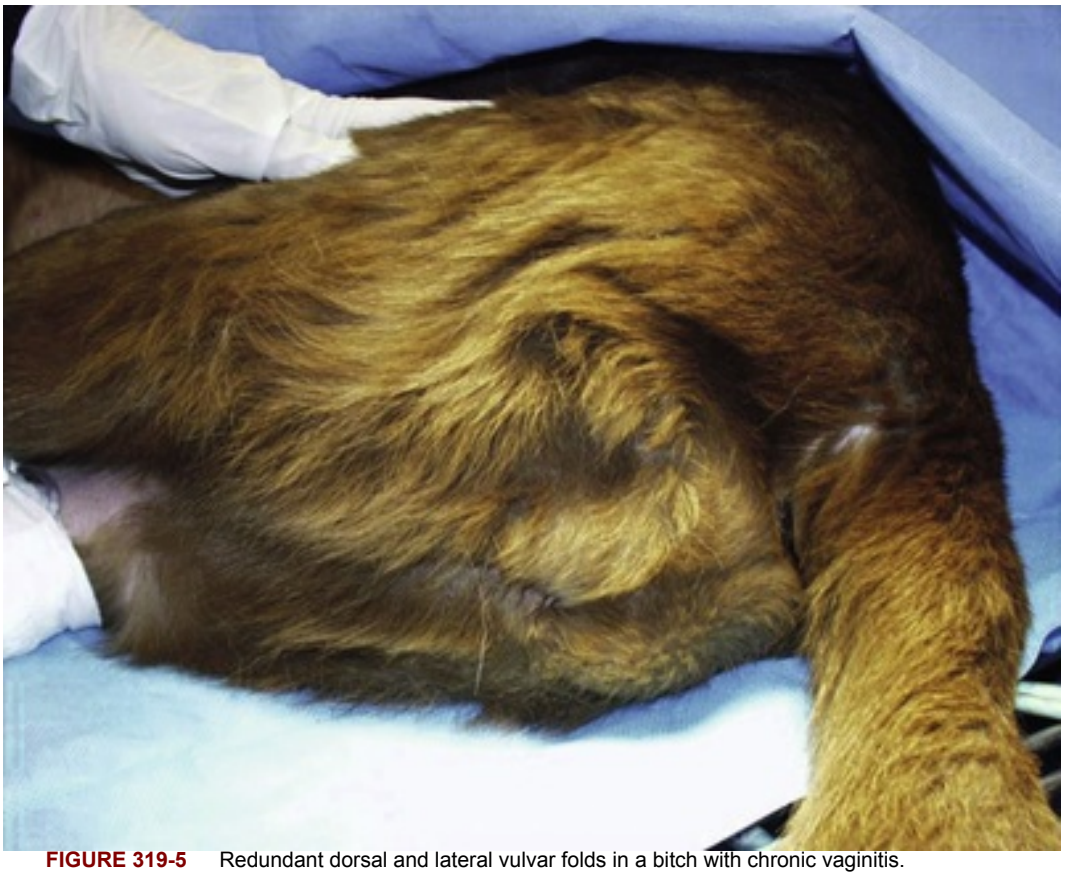

FIGURE 319-5 Redundant dorsal and lateral vulvar folds in a bitch with chronic vaginitis.

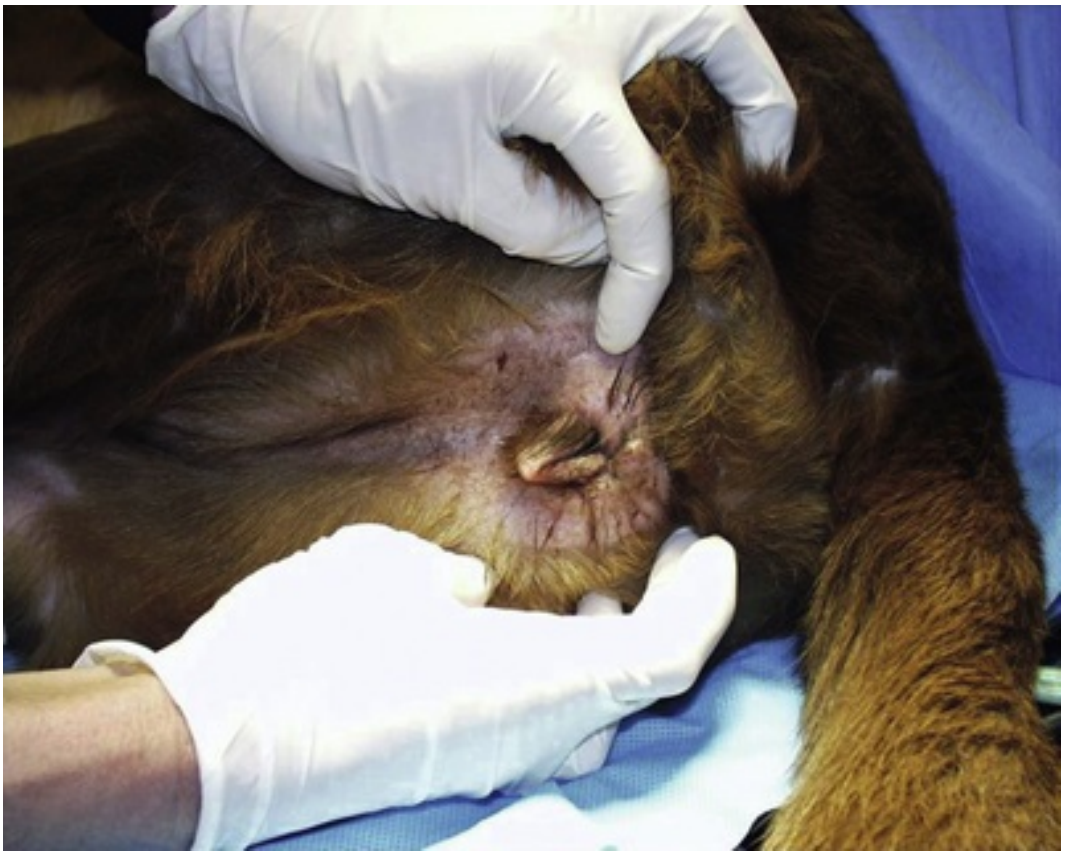

FIGURE 319-6 Marked perivulvar dermatitis made visible by retraction of the redundant folds in the same dog as seen in Figure 319-5.

Treatment

General Guidelines

Most dogs are managed by discontinuing any topical irrigations/douching, prevention of self-mutilation with Elizabethan collars and initiation of antimicrobial therapy only when indicated by proper interpretation of culture and sensitivity testing. Antimicrobial therapy should be limited to dogs with pathogens that have displaced normal flora (e.g., *Pseudomonas* spp.). Analgesia and anti-inflammatory therapy are indicated in most cases. NSAIDS are superior to corticosteroids because the latter increases risk of UTI. Narcotics such as tramadol (2-5 mg/kg PO q 8 h) and gabapentin (10-60 mg/kg divided PO q 8-12 h) can be beneficial for adequate analgesia.

Specific Conditions

If a specific cause of chronic vaginitis is identified, resolution can be straightforward. The identification and removal of foreign bodies should be curative (Figure 319-7). Surgical correction with careful post-operative prevention of self-mutilation is indicated if anatomic abnormalities (redundant dorsal or lateral vulvar folds, significant vaginal stricture, granulomatous uterine stump) have contributed to or caused the condition (Figure 319-8).[5-7] Appropriate management of chronic urinary tract infection, if identified, should resolve associated vaginitis. Surgery and/or chemotherapy may be indicated for urogenital masses or neoplasia (Figure 319-9).

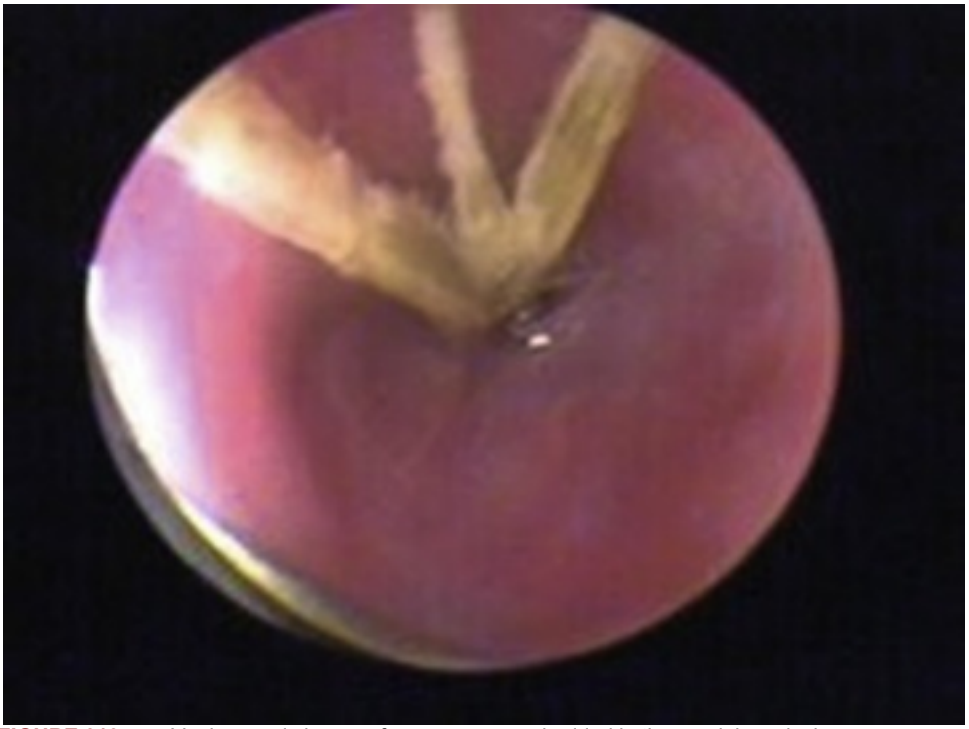

FIGURE 319-7 Vaginoscopic image of a grass awn embedded in the caudal cervical os.

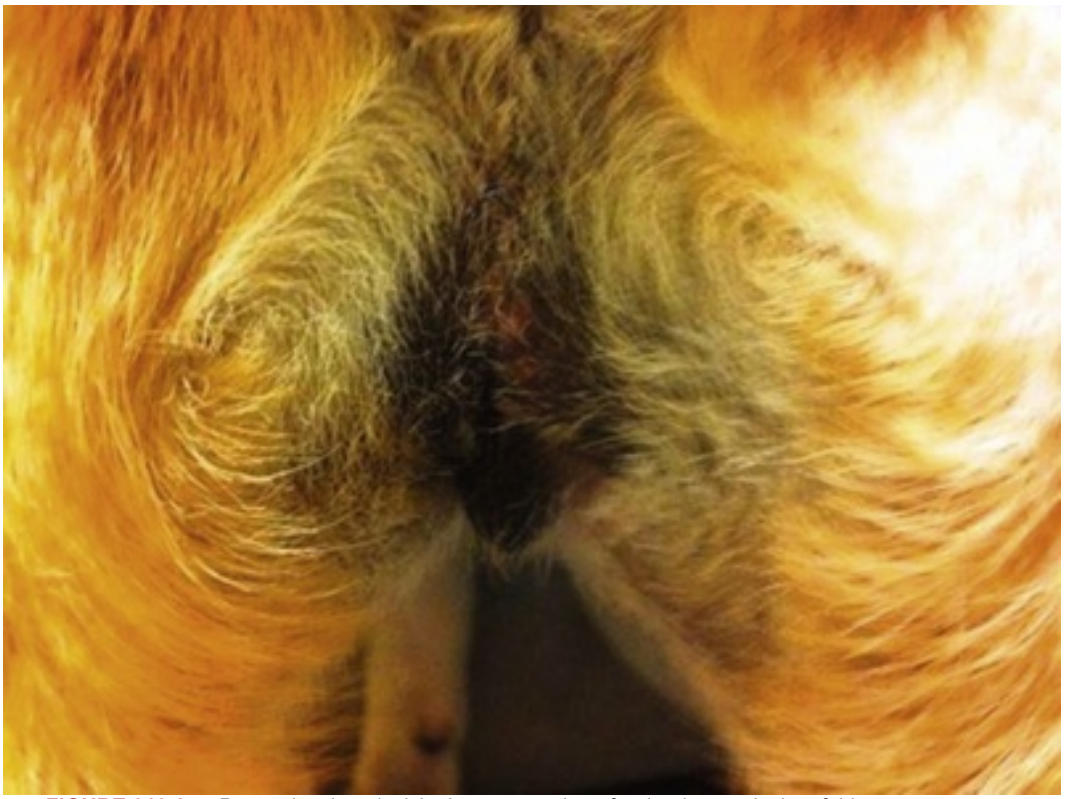

FIGURE 319-8 Post-vulvaplasty/episioplasty correction of redundant perivulvar folds.

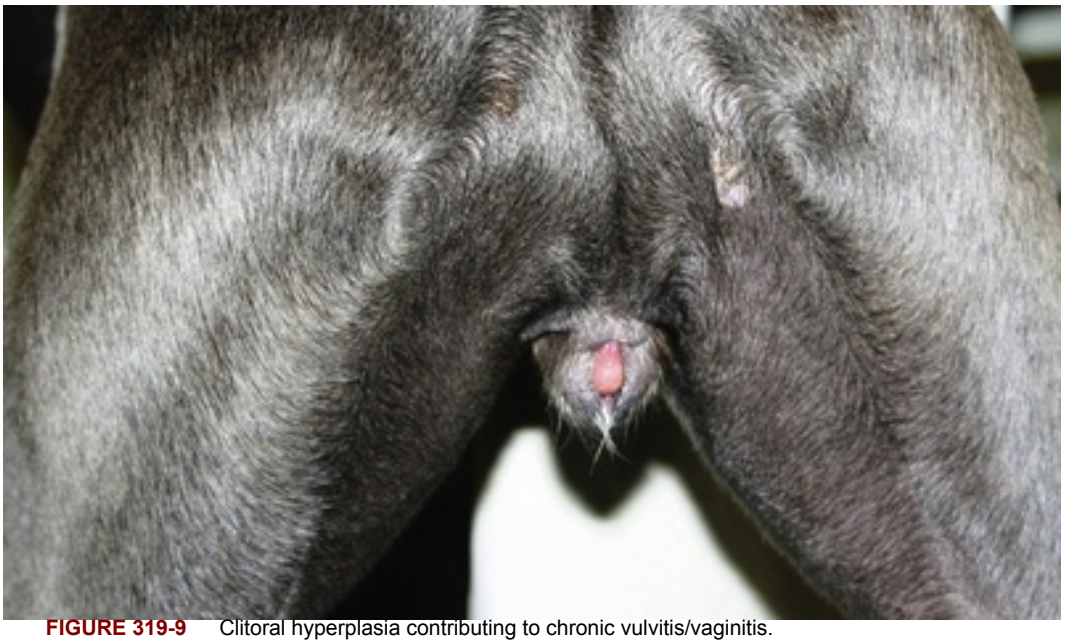

FIGURE 319-9 Clitoral hyperplasia contributing to chronic vulvitis/vaginitis.

Idiopathic

The condition is idiopathic if no anatomic, foreign body, infectious, granulomatous or neoplastic cause can be discerned. Oral estrogen replacement therapy is often helpful in establishing normal mucosal integrity and eventual normalization of the vaginal vault. Idiopathic vaginitis in ovariectomized bitches is similar to post-menopausal estrogen-deplete vaginitis in women. Women improve with intravaginal estrogen application,

which is difficult in the dog.[8] Oral estrogen (Estriol, Incurin, Merck or compounded diethylstilbestrol, DES) is advised; the dose is empiric and usually the same as used for urinary incontinence due to urethral sphincter incompetence (Estriol 0.5-2 mg/bitch PO q 24-48+ h; DES 0.20-1 mg/bitch PO q 48-72 h). Several weeks of therapy are required before improvement is recognized. Side effects are uncommon: overdosage results in signs of proestrus/estrus (attracting male dogs, vulvar swelling); myelosuppression is highly unlikely if the recommended dosage is followed. Analgesics and anti-inflammatories should be continued until an estrogen effect with relief is established. Vaginal cytology or vaginoscopy (see ch. 119) can confirm estrogen effect (Figure 319-10 and Video 319-1).

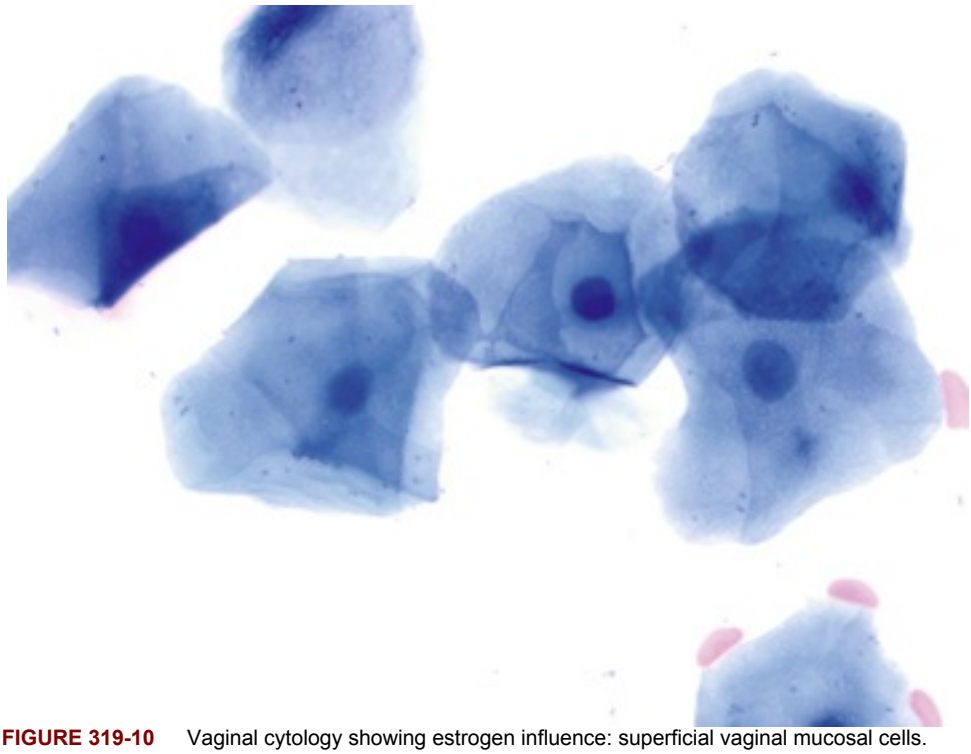

FIGURE 319-10 Vaginal cytology showing estrogen influence: superficial vaginal mucosal cells.

Estrogen Toxicosis in the Ovariectomized Bitch

Signs and Sources of Estrogen

Hyperestrogenism causes behavioral and/or physical signs of estrus in a bitch. Sources of estrogen in a spayed bitch are limited. Endogenous estrogen sources include functional residual ovarian tissue (ovarian remnant syndrome) or adrenal gland disease. Exogenous estrogen most commonly results from consumption of human hormone replacement transdermal products, but it can also occur with overdosage of veterinary prescribed estrogen for urinary incontinence. Excess estrogen in a neutered bitch causes attraction of male dogs, swelling of the vulva, mucoid to sanguineous vulvar discharge, passive interaction with male dogs, flagging, and sometimes copulation. Sanguineous discharge associated with estrogen is of uterine origin, indicating presence of a uterus or uterine stump. Chronic excess estrogen can cause symmetric alopecia, gynecomastia, and/or lactation.

Ovarian Remnant Syndrome (ORS)

Etiology

ORS is reported to be responsible for about 17% of complications post-ovariectomy/-ovariohysterectomy because both ovaries were not completely removed. There is no correlation with age at surgery, difficulty of surgery, obesity of the dog, or experience of the surgeon. The presence of anatomically abnormal ovarian tissue (fragmentation into the broad ligament) is possible but quite uncommon. A “supernumerary ovary” is

extremely rare. Experimentally, functionality can return to ovarian tissue removed from its vascular supply and replaced into or onto the lateral abdominal wall. No breed predisposition or geographic distribution has been reported for this condition.[9]

Signs

The signs of an estrous cycle usually occur months to years after ovariectomy/ovariohysterectomy, but can begin within days. Signs of proestrus last an average of 9 days. Signs of estrus last an average of 9 days; if ovulation occurs, diestrus (progesterone influence) follows and lasts 45-60 days. The average interval between signs of estrous cycles is 7 months (see ch. 312). Of note, the signs are usually cyclical or periodic (about every 5-8 months) rather than constant if a functional ovarian remnant is present. Stump pyometra causing a purulent vulvar discharge can develop when a bitch is under progesterone influence (see ch. 142 and 316). Constant signs of estrogen effect suggest an exogenous source, usually a transdermal human hormone product. Remnant ovarian disease (follicular cyst, functional neoplasia), or rarely, adrenal gland disease, are other possibilities.[10] The clinician must consider multiple differentials (E-Box 319-2).

E-Box 319-2

Differential Diagnoses for Hyperestrogenism

1. Ovarian remnant syndrome
2. Inadvertent exposure to human transdermal hormone replacement product
3. Excessive estrogen administration (for urinary incontinence or idiopathic vaginitis)
4. Ovarian remnant follicular cyst formation or malignant transformation
5. Excessive phytoestrogen ingestion (e.g., flaxseed)
6. Adrenal gland disease

Testing and Diagnosis *(Figure 319-11)*

A minimum database including a CBC, biochemistry panel and UA with culture should be performed, but are usually unremarkable. Evidence of chronic blood loss anemia may be noted if vaginal hemorrhage is profound, but is uncommon. Chronic blood loss has been seen in dogs with ovarian neoplasia, follicular cysts, bleeding disorder, or other systemic disease. Pancytopenia is possible from estrogen toxicosis (see ch. 52 and 54). Vaginal cytology will identify estrogen effect: vaginal mucosal cornification is a bioassay for elevated plasma estradiol concentrations (see Figure 319-10; see ch. 119). A serum progesterone concentration >2 ng/mL (measured 1-3 weeks after behavioral estrus) is consistent with functional luteal tissue and consistent with ORS. GnRH (50 mcg IM), hCG (400 IU IV) or hCG (1,000 IU: 1/2 IV, 1/2 IM) can be used to induce ovulation or luteinization for diagnostic purposes, but this is rarely informative due to the refractory nature of ovarian remnants. The test with either drug involves assessing serum progesterone concentration 2-3 weeks after dosing. A positive anti-mullerian hormone (AMH) result, now commercially available (MOFA), in a bitch > 6 months of age (post-pubertal) supports presence of ovarian tissue.[11] It is the screening test of choice. Exogenous estrogen exposure will not affect AMH results, permitting differentiation of ovarian remnant from exogenous estrogen toxicity. Luteinizing hormone assay (Witness LH, Zoetis) results are increased (>1 ng/mL) in ovariectomized bitches due to lack of negative pituitary feedback. However, when a positive result is obtained, a repeat test is advised in 24 hours to rule out detection of the 12-24 hour LH surge in an intact, estrual bitch (she should have representative vaginal cytology; see ch. 119 and 312). If results are positive several days apart, complete gonadectomy is supported. A negative test (<1 ng/L) is found with intact bitches unless performed at the moment of the LH surge during proestrus.[12] Exogenous estrogen exposure in a gonadectomized dog can cause the LH to become negative misleadingly.

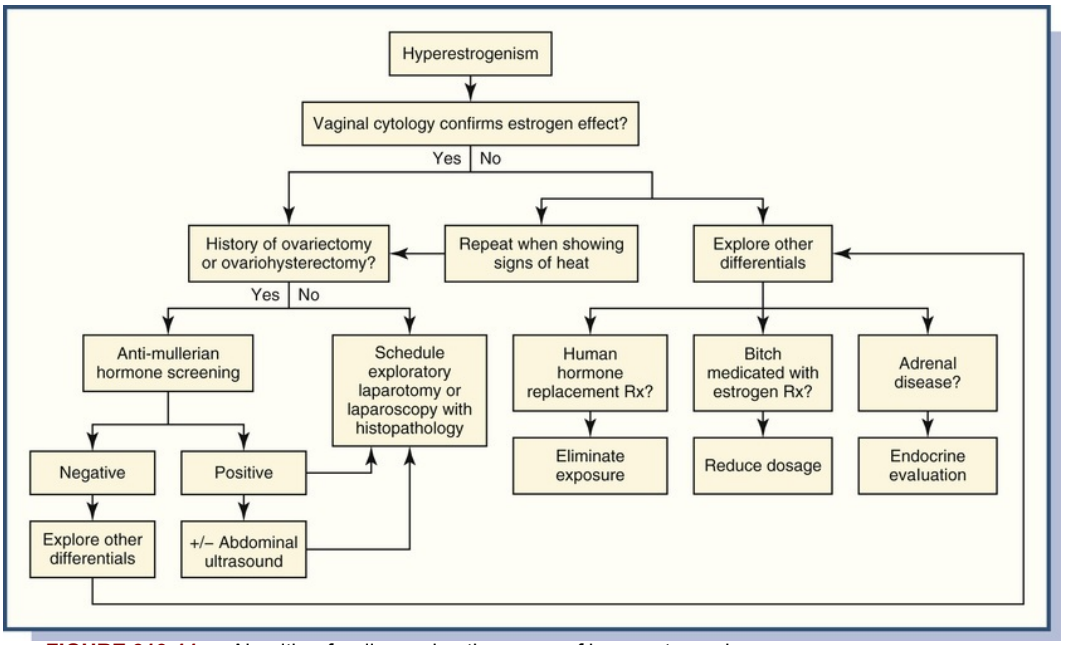

FIGURE 319-11 Algorithm for diagnosing the cause of hyperestrogenism.

US can be used to support a diagnosis of ovarian remnant syndrome initially suspected on history, clinical signs, vaginal cytology and a positive AMH (see ch. 88). Imaging should begin in a sagittal plane slightly caudolateral to the kidneys (where remnant ovarian tissue is expected). Remnant ovarian tissue may be visible only during the follicular phase (anechoic, cystic structures) or luteal phase (hypoechoic or isoechoic cystic structures) (Figure 319-12, Videos 319-2 and 319-3). Ectopic ovarian tissue can be difficult to locate and image with US and requires expertise. When positive, one can have added confidence in proposing laparotomy. The adrenal glands should be evaluated at the same time for size and shape (see ch. 308).[3]

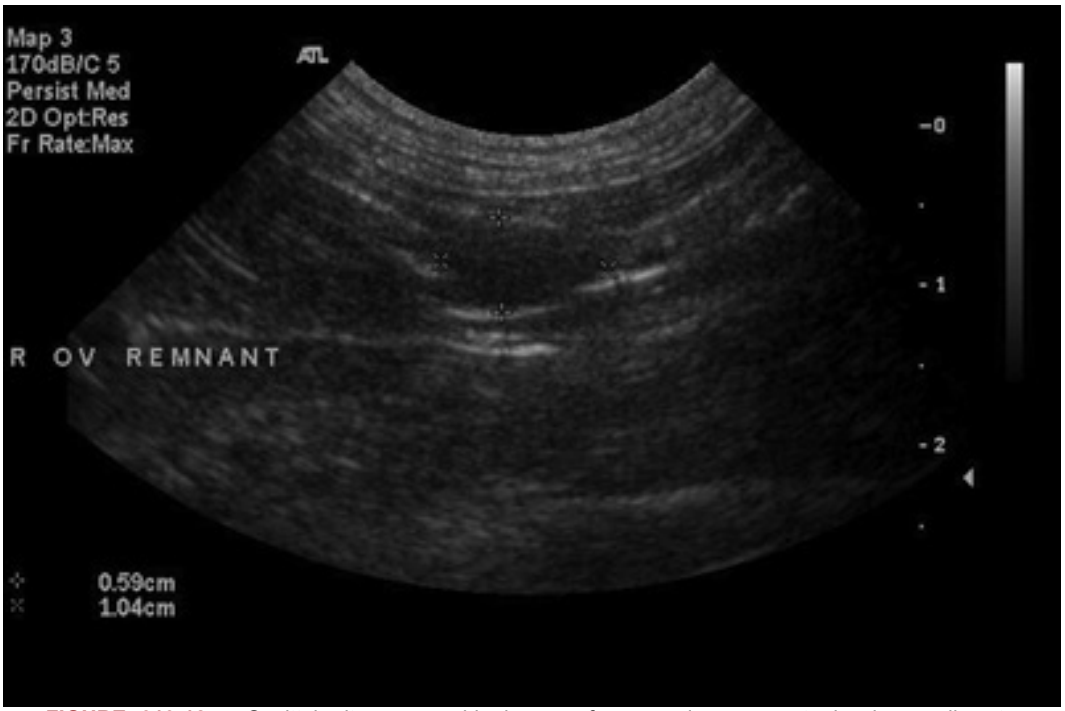

FIGURE 319-12 Sagittal ultrasonographic image of an ovarian remnant showing a discrete hypoechoic follicular structure (cursors).

Surgical Treatment

Exploratory laparotomy with the goal of removing residual ovarian tissue confirms and resolves the problem. Identification of residual ovarian tissue is facilitated by the presence of active follicles or resultant corpora lutea; the clinician should schedule the surgical procedure when clinical signs are present. Because the uterus has been removed in part or whole, the usual concerns about performing surgery in an estrual bitch are lessened. All visible ovarian tissue should be removed and evaluated histologically. If no visible ovarian tissue is identified, all residual tissue at the ovarian pedicles should be resected and submitted for histology. Histopathology is important if neoplastic transformation has occurred. A stump granuloma or pyometra should be removed. Removal of functional luteal tissue may induce transient signs of pseudopregnancy in bitches post-operatively due to resultant increases in prolactin (see ch. 315). If profound, anti-prolactin therapy (cabergoline; Galastop 2.5 mcg/kg PO q 24 h for 4-6 days) can be given. Successful removal of remnant ovarian tissue should result in cessation of clinical signs of estrus, even if ovarian disease is present.

Medical Treatment

Medical therapy is often requested by clients not eager to pursue a second surgical procedure. Progestational or androgenic compounds used to suppress follicular ovarian activity are not recommended because of undesirable side effects (mammary neoplasia, diabetes mellitus, undesirable behavior). Immunocontraception or GnRH agonist administration will offer a viable alternative to laparotomy when perfected and commercially available in the United States. In dogs being given or consuming estrogen, successfully avoiding all estrogen exposure should lead to resolution of clinical signs in 2-4 weeks (Figure 319-13).[13] Owners are commonly unaware that medication in transdermal products is active after consumption by pets.

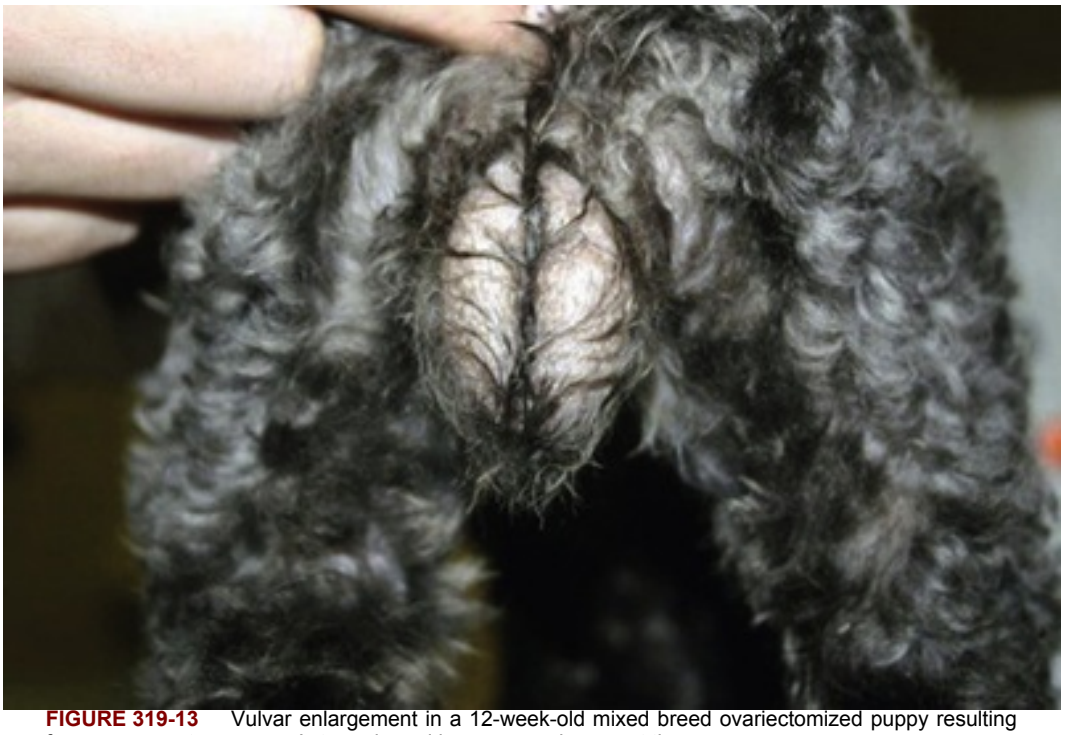

FIGURE 319-13 Vulvar enlargement in a 12-week-old mixed breed ovariectomized puppy resulting from exposure to an owner's transdermal hormone replacement therapy.

Prostatic Adenocarcinoma

Overview

Prostatic adenocarcinoma is a disease of male dogs usually neutered and older than 10 years of age (see ch. 337 and 351). It carries a poor prognosis. Prostatic adenocarcinoma originates from the glandular portion of the prostate; other prostatic tumor types include fibrosarcoma, leiomyosarcoma, transitional cell carcinoma (TCC) and squamous cell carcinoma. TCC and prostatic adenocarcinoma (ACA) are the most common

primary prostatic malignancies. TCC originates from the transitional epithelium extending from the bladder into the prostate or from the uroepithelium of the prostatic urethra. Most prostatic adenocarcinomas do not express androgen receptors and do not appear influenced by androgens. In contrast, castration (especially <1 year of age) appears to be a risk factor for its development. Previous benign prostatic hyperplasia is not a risk factor for prostatic neoplasia.[14,15]

Clinical Findings and Testing

Stranguria, dysuria, tenesmus, small stools, lumbar pain and gait abnormalities are common clinical signs. Tumors are often detected after metastatic spread as clinical signs occur late and early screening is unavailable. On rectal examination, a large (especially since the dog is neutered), asymmetrical, irregular painful prostate can be identified. Commonly, affected dogs have abdominal pain, lumbosacral pain, and/or sublumbar lymphadenopathy. Anorexia and associated weight loss reduce body condition. CBC and chemistry panel findings reflect chronic disease and inflammation. Post-renal azotemia can occur if the mass is obstructive, causing hydroureter and hydronephrosis. An elevation of alkaline phosphatase occurs in ≈50% of dogs, perhaps associated with axial bone metastasis. Hematuria, pyuria, bacteruria and atypical transitional cells may be noted on urinalysis (see ch. 72). UTI is a common comorbidity (see ch. 330). Malignant transitional cells appear similar to reactive transitional cells making biopsy important. Thoracic radiographs are indicated to screen for pulmonary metastasis. Lumbar spinal radiographs can show vertebral metastasis. Mineralization in the enlarged prostate and/or sublumbar lymphadenomegaly is suggestive of malignant disease.

Abdominal US is a valuable diagnostic tool, permitting evaluation of the prostatic parenchyma, regional lymphatics, extension into the urinary bladder, urethral or trigonal obstruction and presence of hydroureter and hydronephrosis. Focal or multifocal hyperechoic prostatic parenchyma with asymmetry, irregular capsule outline, and mineralization are common. Cavitary regions due to necrosis and hemorrhage may be present and sublumbar lymphadenomegaly can be marked (Figure 319-14).[16] US and US-guided fine needle aspirate (FNA) or biopsy (see ch. 89 and 93) are useful, but risk of tumor seeding makes open biopsy preferable. Histopathology (rather than cytology) is usually required to differentiate tumor type.

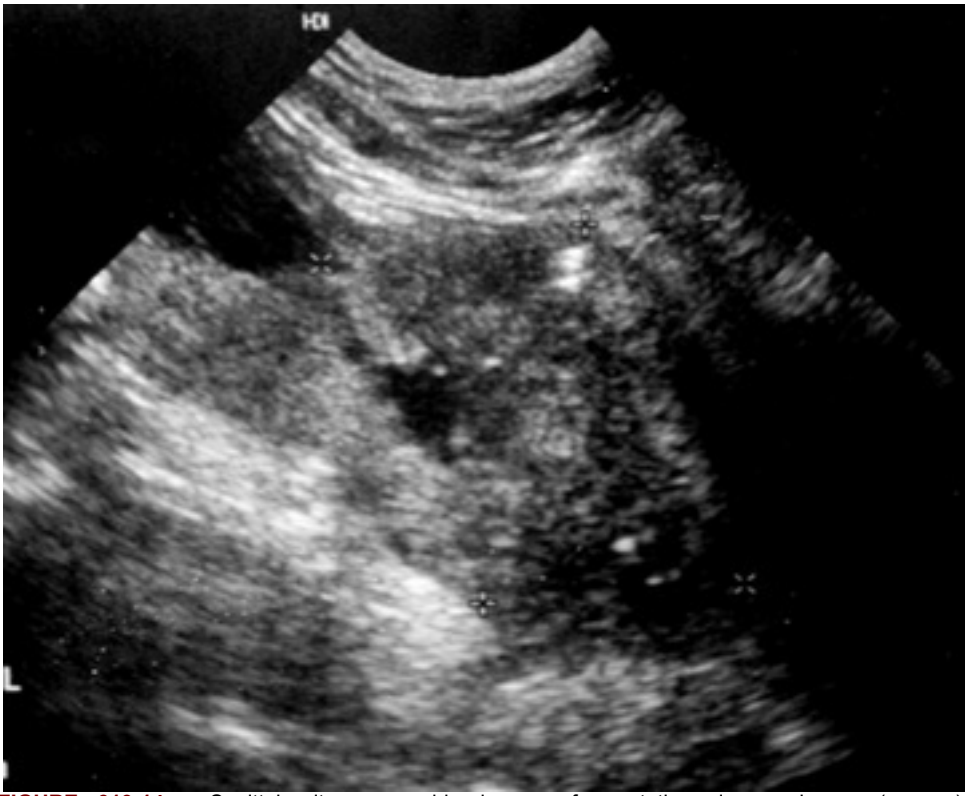

FIGURE 319-14 Sagittal ultrasonographic image of prostatic adenocarcinoma (cursors); mineralization is evident.

Treatment (see ch. 337 and 351)

Therapy with NSAIDs often in combination with oral analgesics can prolong life. Chemotherapy (carboplatin, cisplatin, doxorubicin, gemcitabine) can improve signs, but cure is unlikely. Prostatectomy can prolong life if the cancer is confined within the prostatic capsule, but there is a high complication rate (incontinence, urethral stenosis). Palliative radiation and/or urethral stenting offer short-term relief. Stool softeners are indicated with tenesmus. IV bisphosphonates such as pamidronate (0.65-2 mg/kg IV, slow infusion with 0.9% NaCl over 2 h) can help with pain relief from skeletal metastases.

Squamous Prostatic Metaplasia

Squamous prostatic metaplasia occurs as a consequence of hyperestrogenism, either of endogenous (functional Sertoli cell tumor, adrenal gland dysfunction) or exogenous (therapy for benign prostatic hyperplasia inadvertent consumption of owner transdermal hormone medication) origin. Prostatic epithelial squamous metaplasia is accompanied by secretory stasis and the potential for intraprostatic cysts. The prostate gland is usually large for a neutered dog and firm on palpation. Compression of the urethra and colon can cause dysuria and tenesmus. Other physical findings typical of hyperestrogenism can be present: attractiveness to males, gynecomastia, symmetric alopecia, hyperpigmentation, and a pendulous prepuce. Presence of an abdominal (cryptorchid) testis should be ruled out with US if both testes are not palpable. Estrogen toxicosis to the bone marrow can cause pale mucous membranes (anemia; see ch. 52), petechiation or hemorrhage (thrombocytopenia; see ch. 54), and fever (secondary to neutropenia). A careful history should be taken concerning possible exposure to human transdermal hormone medications or past purposeful therapy with estrogen for prostatomegaly.

A CBC, serum chemistry panel and UA/culture should be assessed for myelotoxicosis and general health. Changes are variable, depending on exposure duration, dose, and time between insult and testing. In the initial 2-3 weeks, either thrombocytopenia or thrombocytosis may be noted with progressive anemia and leukocytosis (WBC count may exceed 100,000/mcL). After 3 weeks, pancytopenia and aplastic anemia may be noted. Hematuria may occur due to thrombocytopenia or prostatic bleeding. Squamous epithelial cells exhibiting estrogen influence can be seen in the urine or recognized in samples from the preputial mucosa.

In a neutered dog with no scrotal testes, abdominal US should be performed to screen for a malignant-transformed cryptorchid testis or an unusually enlarged, hyperechoic, cavitary prostate. Assessing serum luteinizing hormone (LH, Zoetis) concentrations may indicate presence of testicular tissue, if low. If an abdominal testis with a parenchymal mass or an enlarged prostate is discovered with US, FNA or biopsy samples may provide cytologic evidence of functional testicular neoplasia or prostatic epithelial squamous metaplasia (see ch. 89 and 93). Therapy is dictated by the clinical findings, but discontinuing exogenous estrogen exposure or therapy is important. Castration should be recommended if cryptorchid. Concurrent prostatic infection or abscessation can be present and should be treated appropriately (see ch. 337).

Priapism

Definition and Etiology

Priapism is a persistent penile erection without sexual stimulation categorized as either nonischemic (arterial, high flow) or ischemic (veno-occlusive, low flow) and occurs most commonly in neutered dogs (Figure 319-15). Ischemic priapism is quite painful and considered an emergency, as rapid necrosis can result. Either form can result in significant trauma to the penile tissues (see ch. 146).[17] Castration of a dog with priapism is not helpful as the condition is not mediated by testosterone. Priapism should be differentiated from paraphimosis, which occurs more commonly in intact male dogs after semen collection or masturbation and results from constriction of the erect penis by the preputial opening (Figure 319-16). Priapism should also be differentiated from other causes of penile swelling, such as a hematoma, trauma or mass lesions (Figures 319-17 and 319-18). Penile hematomas usually form as a result of trauma or bleeding disorders. Simple visual inspection and palpation of the penis are usually sufficient to differentiate the conditions, but US and/or color-flow Doppler examination may further help differentiate these disorders from priapism (Figure 319-19). US of the perineum and the entire penile shaft may aid in identifying neoplasia, os penis fracture, hematoma, or thromboemboli (Videos 319-4 and 319-5).

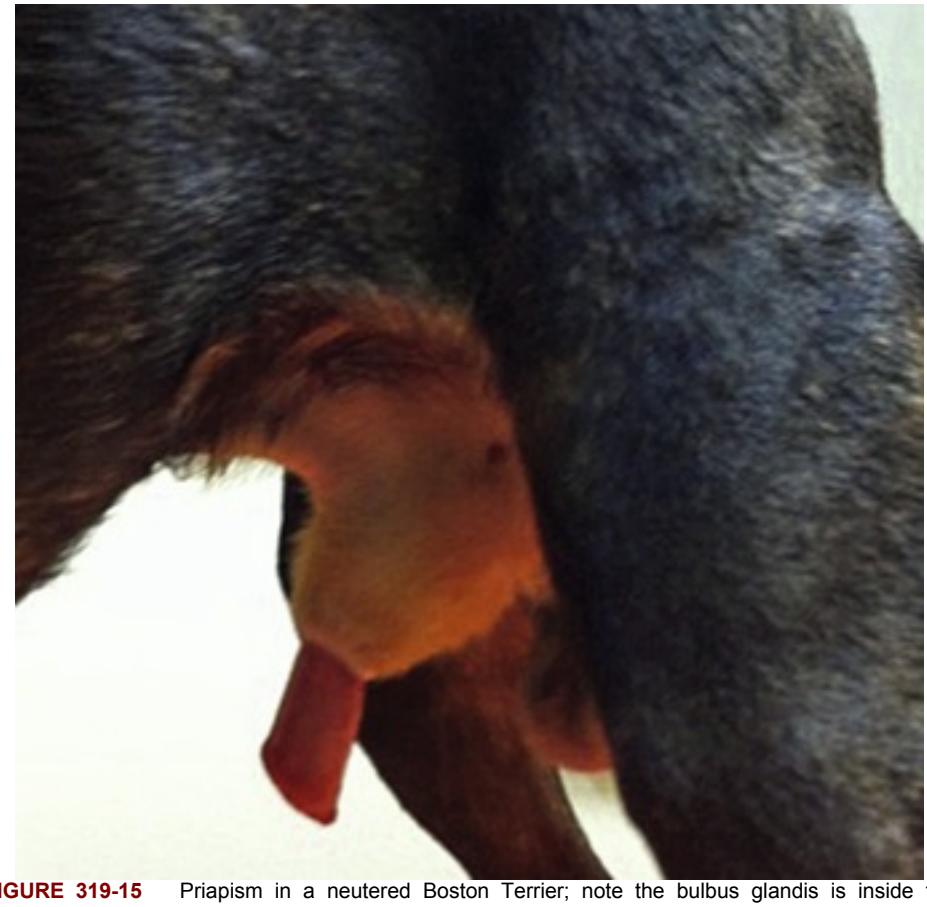

FIGURE 319-15 Priapism in a neutered Boston Terrier; note the bulbus glandis is inside the prepuce.

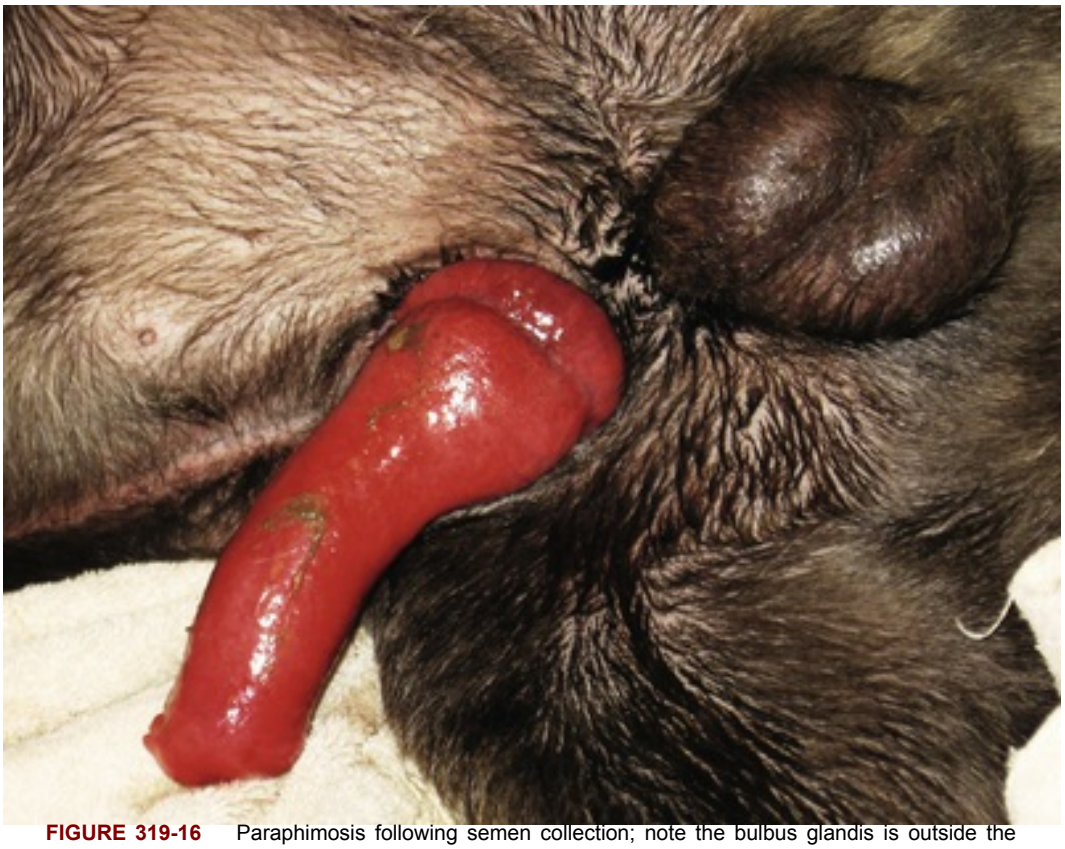

FIGURE 319-16 Paraphimosis following semen collection; note the bulbus glandis is outside the prepuce.

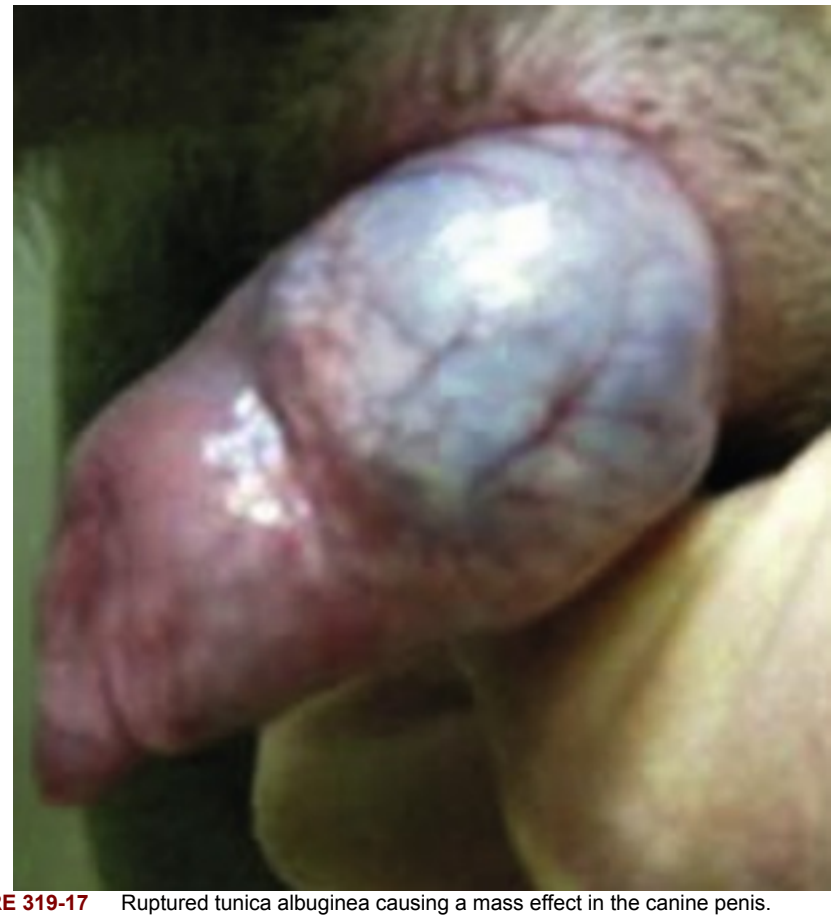

FIGURE 319-17 Ruptured tunica albuginea causing a mass effect in the canine penis.

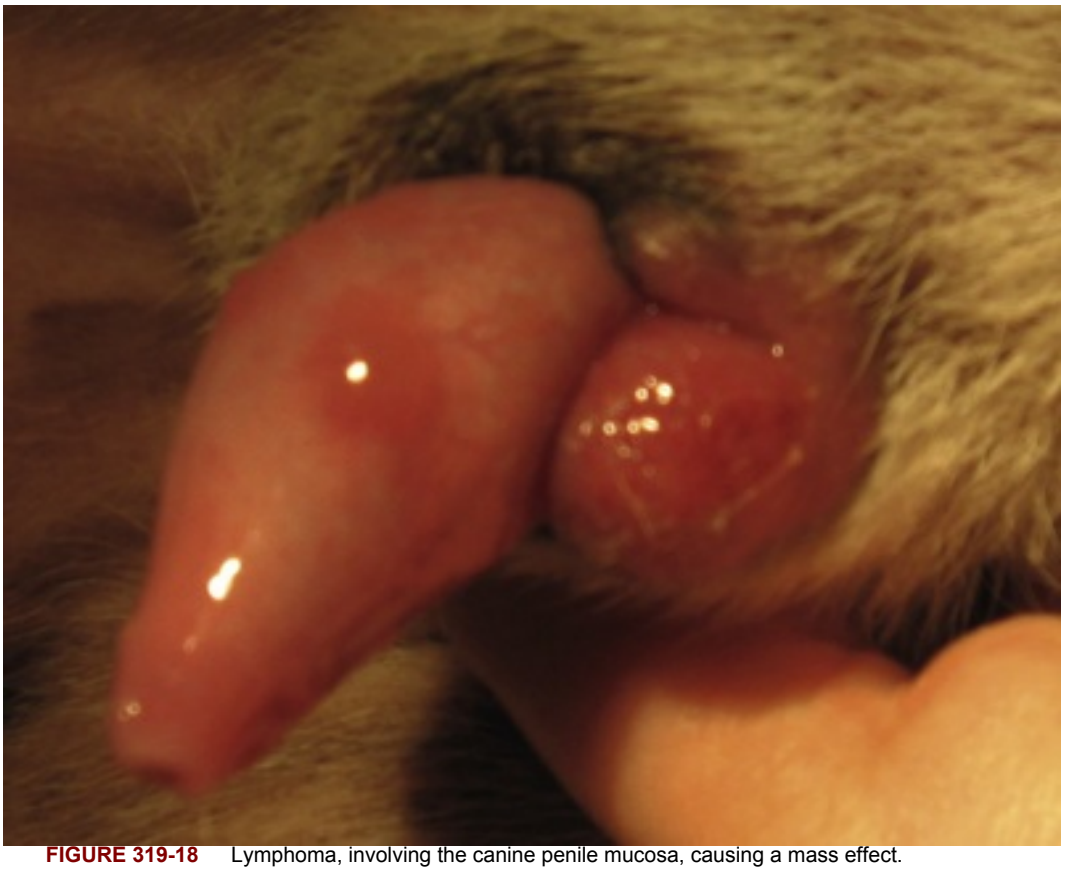

FIGURE 319-18 Lymphoma, involving the canine penile mucosa, causing a mass effect.

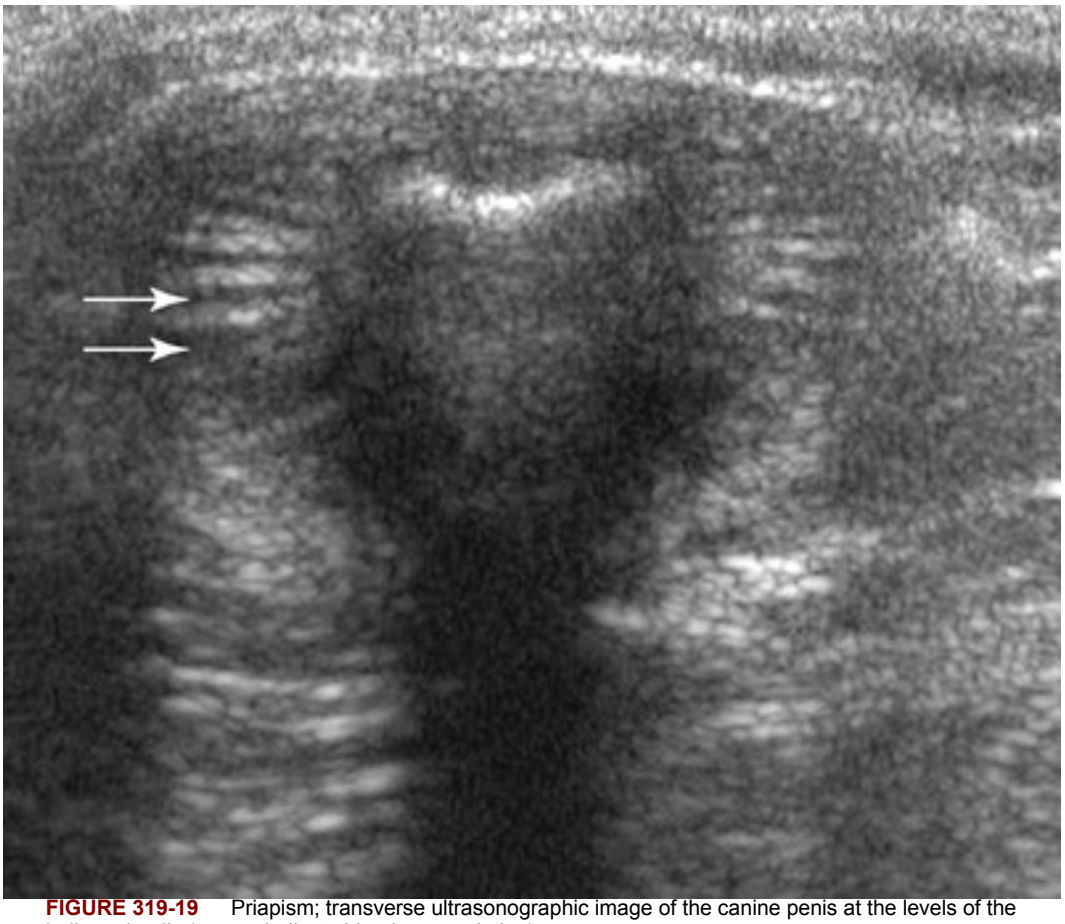

FIGURE 319-19 Priapism; transverse ultrasonographic image of the canine penis at the levels of the bulbus glandis (arrows indicate blood accumulation).

The canine erection is mediated through the pelvic nerve, which arises primarily from the first and second sacral nerves (S1-S2) and is composed of parasympathetic nerve fibers. Pelvic nerve stimulation causes erection by increasing penile blood pressure, partially inhibiting venous drainage, and dilating penile arteries. The pudendal nerve, which arises from the sacral nerves S1-S3, is involved as well, by stimulating contraction of the extrinsic penile muscles. The hypogastric nerve, a sympathetic nerve originating from the lumbar L1-L4 spinal cord segments, may also have a regulatory role. The hypogastric nerve is responsible for prostatic fluid secretion and ejaculation. Sympathetic chain fiber stimulation increases arterial resistance, decreases corpus cavernosal pressure, decreases venous resistance and inhibits erections. The sympathetic inhibition of the erectile process is mediated by the alpha-1 adrenergic system.[18] True priapism (either form) can be associated with vascular disorders (efferent or afferent), neuropathy, or a myelopathy (lumbosacral). One hypothesis on the pathophysiology of priapism suggests dyssynergic neurostimulation of inflow and outflow penile blood vessels causing vasospasms or smooth muscle spasms. This dysregulation may occur at the level of the penis, the CNS (spinal cord), or in the peripheral nervous system.

Diagnosis and Treatment

Distinguishing ischemic (proceeds to gangrene) from non-ischemic priapism is important, as is identifying and treating the underlying cause. If determined to be ischemic, prompt aspiration of the corpora cavernosa under sedation or anesthesia with or without irrigation should be done (see ch. 146). Intracavernosal injections of phenylephrine should be considered, but they carry some risk as appropriate dosages in dogs and cats have not been determined. Therefore, starting with low dosages (1-3 mcg/kg) and cardiovascular monitoring is important. Providing lubrication is important to limit tissue damage secondary to exposure and excoriation. An Elizabethan collar is indicated. If intracavernosal drainage and injections are not successful or significant tissue damage has occurred, penile amputation and perineal urethrostomy may be necessary.

Nonischemic priapism can resolve spontaneously, but can take hours to days. Thus conservative therapy using analgesia, protecting penile integrity with lubrication, and use of an Elizabethan collar are

recommended. Sedation with a phenothiazine drug can be helpful. Several systemic medications are of potential benefit, although little controlled data exist regarding efficacy. Gabapentin (10-60 mg/kg PO daily, divided q 8-12 h), terbutaline (1.25-5 mg/dog PO q 8-12 h) or ephedrine (1-2.5 mg/kg PO q 12 h) should be tried. Incrementally increasing dosage is advised. If detumescence is not achieved after several days of treatment with one drug then switching to another may be successful.

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CHAPTER 320

Pediatric Care during the Postpartum Period

Margret L. Casal

Definitions

The "postpartum period" in women is defined as the first 6 to 8 weeks that follow giving birth. During this time, the uterus returns to its normal non-pregnant size. This is also the time period during which most neonatal deaths occur.[1,2] In veterinary medicine, the postpartum period has been described as about 2 (discharge of lochia) to 8 weeks (the time it takes the uterus to return to its normal size macroscopically).[3-6] The focus of this chapter is the most critical time period for neonates: the first 2 to 3 weeks of life.

Pre-Partum

Raising healthy neonates begins before they are born. Physical examination of dam and sire should be performed and is an opportunity to identify possible infectious or genetic issues (see ch. 2). Genetic screening can be considered in purebreds (see ch. 3 and 4). Bitch and stud should be screened for *Brucella* (see ch. 213) and queen and tom for feline leukemia virus (see ch. 223) and feline immunodeficiency (see ch. 222). Fecal examinations should be performed (see ch. 81) and both sire and dam should be current on parasite control (see ch. 163) and vaccines (see ch. 208). The dam's diet should be adjusted to meet demands of pregnancy and her body weight monitored since mortality rates are higher in litters from under- or overweight queens and bitches (ch. 315). Raw foods during pregnancy are not recommended because of possible exposure to bacteria (e.g., *Salmonella* spp.) or parasites (e.g., *Toxoplasma gondii*) (see ch. 192).[7,8] Most commercial diets are adequate and can be supplemented with puppy or kitten food during the last trimester. Adding vitamins or other supplements is not necessary and may be detrimental. Excessive vitamin A, for example, can cause midline defects in fetuses. Modified live vaccines administered during pregnancy may also cause fetal defects or cause active disease. Fenbendazole is safe for deworming bitches during pregnancy to reduce transplacental transmission of *Toxocara canis* and pyrantel pamoate for queens to decrease shedding of *Toxascaris leonina*.

The Immediate Post-Partum Period

Stress should be minimized by providing a whelping/queening room with a clean dry box and by reducing human and animal traffic to avoid introduction of infectious diseases. The queening or whelping box should be made of a material that can easily be sanitized, such as stainless steel or plastic. Bedding should be washable (blankets, towels) or disposable (newspapers, diapers). Other materials that might be needed include species-appropriate milk replacer, feeding tubes, a gram scale, digital thermometers that can measure as low as 32°C (89.5°F), warm water bottles/gloves or heating blankets, stethoscope, fluid bags (Ringer's or 0.9% NaCl), a fluid line, needles, syringes, shoe covers, and hand sanitizer (see ch. 171). Heating devices should be used cautiously, as neonates may not be able to escape if the temperature is too high. Shoe covers and hand sanitizers are used to minimize chance of disease transmission in kennels or catteries.

The ambient temperature for neonates should be relatively high (29.5-32.2°C; 85-90°F), as neonates cannot regulate their body temperature. During the first week of life, the temperature should be adjusted to 24-26.7°C (75-80°F) for haired breeds of dogs and cats. Hairless breeds (e.g., Mexican Hairless dogs, Sphinx cats) may require slightly higher ambient temperatures. Low body temperature interferes with cellular immune function. Maintaining proper ambient temperatures decreases morbidity. To prevent dry skin, the humidity levels should be about kept at 55-65%; higher humidity is conducive to infectious diseases. Cattery and kennel staff should care for the youngest animals first to decrease transmission of infectious disease to this most vulnerable subpopulation.

Assessment and Care of Neonates

Overview

Each neonate should be examined once the entire litter has been delivered, including testing of basic reflexes (righting, rooting, suckling, lumbar reflex), checking for cleft palate, umbilical hernia, open fontanelle, atresia ani, symmetry, muscle tone, and for any other gross congenital defects. The neonates should be identified individually, and all findings recorded in their respective charts. Body weights should be recorded daily for the first three weeks of life, as decreased weight gain, lack of weight gain or weight loss can be the first sign of illness. Daily observation and quick physical examinations are important for recognizing emerging signs of illness, such as sepsis, infection behind closed eyelids, diarrhea, change in mentation, dehydration, and hypothermia. Other than injury resulting from trauma, it is often difficult to determine cause of illness in neonates. Most exhibit weight loss, hypothermia, hypoglycemia, and/or dehydration. Injuries may result from accidentally being crushed by the dam, overzealous grooming by the dam or human, or being bitten by the dam or another animal. Wounds are treated accordingly and antibiotics that are safe for the age group (penicillins, cephalosporins) are administered.[9]

Hydration

Body water content is increased in neonates (≈80%) and they are unable to concentrate urine. Dehydration is always a concern to avoid. Autoregulation of renal blood flow, not yet developed, results in decreased glomerular filtration rate. Compensatory mechanisms such as increasing the heart rate and cardiac contractility in response to dehydration are limited in neonates. Their high metabolic rates and insensible losses (evaporation and respiration) contribute to fluid needs and dehydration can develop rapidly. Even mild dehydration can compromise health and needs to be treated immediately. Checking moisture of the oral mucous membranes allows for better assessment of hydration than skin tenting, which occurs later in neonates than in adults. Clinical signs include tacky to dry mucous membranes (5-7% dehydration), very dry mucous membranes plus a noticeable decrease in skin elasticity (10% dehydration) and circulatory collapse (upwards of 12% dehydration). Diarrhea, vomiting, inappetence, starvation, and neglect are the most common causes for dehydration.

In mild cases, fluids can be administered SC, where absorption is slow and less likely to overload the system. Ideally, fluids are administered IV via the jugular or cephalic vein (see ch. 129). In the absence of IV access, intraosseous (IO) catheters can be placed in the femur or humerus using an 18 to 22G needle or a 20G × 3.75 cm spinal needle (see ch. 77). At the site of placement, a small amount (less than 0.5 mL) of lidocaine is injected infiltrating the cutaneous, subcutaneous, and periosteal tissues. The area should be aseptically prepared. Access to the marrow space is gained through the trochanteric fossa for the femur or through the greater tubercle for the humerus. Maintenance fluid requirements are high at 80-100 mL/kg/day (3-4 mL/kg/h), yet total volumes administered are small, and volume overload occurs quickly due to the neonate's inability to process fluids quickly.

In moderate to severe dehydration or shock, 30-40 mL/kg of isotonic crystalloids can be given as a bolus over 5-10 minutes. Before administration, fluids should be warm, but not higher than 1°C (2.2°F) above body temperature. Fluid lines can be run through a warm water bath or under a heating blanket to keep them from cooling. Once stabilized, neonates can be maintained at 6 mL/kg/h with 50% of the deficit added over 6 hours (deficit = BW × % dehydrated) for rehydration. The lungs should be ausculted often to ensure that volume overload does not occur.

Hypothermia

Neonates are not able to regulate body temperature. Hypothermia can be serious and caused by maternal neglect or decreased metabolism for a variety of reasons.[10] Whatever the cause, it needs to be addressed immediately after obtaining samples for diagnostics. Hypothermia results in decreased gut motility, which can ultimately lead to ileus. Tube feeding or force-feeding neonates can cause aspiration followed by pneumonia or bloat resulting in increased intrathoracic pressure and labored breathing. Neonates in pain or who have difficulty breathing often swallow air and worsen bloat. This vicious circle can result in circulatory distress and death. Also, cellular immune function is inhibited by hypothermia, increasing susceptibility to infection.

Hypothermia in a neonatal puppy or kitten is defined as body temperatures dropping below 34.4°C (94°F) at birth, below 35.6°C (96°F) at 1-3 days of age, or below 37.2°C (99°F) at one week of age. Chilled neonates

with body temperatures above 31.1°C (88°F) may show restlessness, continuous crying, red mucous membranes, and skin that is cool to the touch. Muscle tone may be acceptable but respiratory rates will be above 40/minute and the heart rates above 200/minute. At body temperatures in the range of 29.4°C (85°F), neonates appear lethargic and uncoordinated but will respond to stimuli. Moisture and small bubbles of saliva are seen at the lip commissures. Heart rates drop to less than 50/minute and respiratory rates will be between 20 and 25/minute. Abdominal sounds will be absent and metabolism will be greatly decreased, resulting in hypoglycemia. Neonates with a body temperature under 21°C (70°F) may be comatose but treatment should be attempted if extreme methods of arousal produce a response.

Affected neonates should be kept dry, hydrated, and slowly warmed as described by not increasing temperature more 1°C (2.2°F) per hour. If the neonate is premature (and/or of low birth weight), humidity and temperature may be briefly raised to 85-90% and 29.5-32.2°C (85-90°F), respectively. The higher temperature and humidity will help to maintain neonatal core body temperature, hydration, and metabolism. Overheating should be avoided and the neonate's body position changed frequently to reduce vomiting and thus aspiration. Oxygen cages and human neonatal incubators provide oxygen and warm air to safely and quickly rewarm neonates.

In severe hypothermia, warm fluids can be administered IV or by intraosseous catheter. If warmed too quickly, neonates can suffer heat prostration. Clinical signs include increased respiratory rate and effort, cyanosis, diarrhea, and ultimately seizures. Life-threatening conditions often result if the body temperature is raised at more than 2°C (4.5°F) per hour. Overheating can be corrected with cool air and lukewarm water baths. However, delayed organ failure and death still may occur despite initial positive response. Skin burns can occur if neonates cannot escape a heat source. Treatment consists of local application of petroleum jelly to prevent drying, IV crystalloids, and systemic or oral antibiotics. Burn wounds require a large amount of energy for healing and thus, caloric supplementation at 2-4 times maintenance should be provided.

Hypoglycemia

Defined as a serum glucose <30 mg/dL (some suggest <75 mg/dL), hypoglycemia is the most common cause of neonatal seizures. Other clinical signs include tremors, crying, irritability, dullness, lethargy, coma, and stupor. Common causes for hypoglycemia in neonates are starvation, neglect, inborn errors of metabolism such as glycogen storage disease, portosystemic shunts, and hypopituitarism. Therapy consists of administering dextrose IV at 0.5-1 g/kg as a 2.5-5% dextrose solution in lactated Ringer's or normal saline. The osmolality of higher dextrose solutions (>5%) can be caustic and cause phlebitis. If needed, dextrose can be applied directly to oral mucous membranes. Regulatory mechanisms are not fully developed in neonates; thus, blood glucose levels should be closely monitored during therapy to avoid hypo- or hyperglycemia. However, no more than 5% of an ill neonate's blood volume should be removed each week, i.e., no more than 0.5 mL blood/100g body weight. Blood taken must be carefully limited.

Feeding

If a neonate is not gaining or maintaining body weight, supplementation may be required (see ch. 171).[10] Neonatal puppies and kittens should be able to ingest daily requirements for both calories and fluid in four to five feedings. Puppies are expected to gain approximately 2.2 grams per kilogram of the anticipated adult weight per week. Kittens are usually born at 80-120 grams and should gain 70-100 grams per week. However, it is common for neonates to lose or maintain weight during the first day or two of life. As long as they are vigorous and nursing, no treatment is required. Only species-appropriate milk replacement should be used. The most common problems with supplementation are over- or underfeeding. Overfeeding milk replacers almost always results in diarrhea and underfeeding may result in dehydration and insufficient weight gain. Homemade formulas and many commercial milk replacers that contain cow's milk may be deficient in growth factors, amino acids and other essential nutrients. The caloric density of the formula is often high but the fluid content low. Therefore, the fluid needs may not be fulfilled despite energy requirements being met. Diluting the formula to meet caloric and fluid requirements can resolve the issue if multiple feedings per day are possible. If necessary, the milk can be of high caloric density and SC fluids can be given. Neonates should be encouraged to urinate and defecate after each feeding by stimulating the anogenital area with a moist cotton ball. At this time, lack of anal patency or diarrhea might be noted. Highly concentrated urine may be indicative of dehydration. Also, constipation may be noted, suggesting inappropriately prepared milk replacer or hypothyroidism in kittens.

During their first three weeks of life, neonates should be weighed daily to be certain of weight gain.

Neonates should never be supplemented if their body temperature is below 35.6°C (96°F), as the intestinal tract slows and aspiration may occur. Feeding can be initiated if intestinal sounds are present. Supplemental feeding can be provided by tube feeding or placing a neonate with a surrogate mother. In the latter case, the neonate may need to be rubbed against the other neonates in the litter (or even their feces) to entice a surrogate mother to adopt and care for an orphan.

Some neonates can be bottle-fed to meet their needs (see ch. 171). For this, the neonate is held upright, allowing placement of the front paws on the bottle or the person's hand. Enough time is allotted for the neonate to swallow and breathe in between sips, otherwise they tend to swallow air or aspirate. Tube feeding is a convenient way to supplement the neonate with nutritional needs, especially if malformations are present or the neonate is weak.[10] Exact amounts can be fed and it is less time consuming when multiple neonates need to be supplemented. Depending on neonatal size, a 5 or 8 F plastic feeding tube can be used for tube feeding. To determine length of tubing needed and to have the tip of the tube rest just past the lower esophageal sphincter, the feeding tube is placed along the side of the neonate from the tip of the nose to the last rib. A mark is made at three quarters of the measured length from the tip of the feeding tube and this will indicate the portion of the feeding tube to be placed. Correct placement of the tube is indicated by negative pressure when pulling back on the plunger of the syringe, vocalization by the neonate, and the fact that the neonate swallowed the tube. Feeding should occur at the dosage and rate indicated on the milk replacer packaging. Sometimes it may need to be diluted. Caloric and fluid content of canine, feline, bovine and caprine milk are indicated in Table 320-1.

TABLE 320-1

Nutrient Content of Milk from Different Species

	BITCH'S MILK	QUEEN'S MILK	COW'S MILK	GOAT'S MILK
Fluid content (%)	77.3	79.0	87.7	87.0
Fat (%)	9.5	8.5	3.6	4.1
Protein (%)	7.5	7.5	3.3	3.6
Lactose (%)	3.3	4.0	4.7	4.0
ME kcal/100 mL milk	146	121	64	69

Note the differences in metabolizable energy (ME) between the different species. When mixing cow or goat's milk as a milk replacer for neonates, it is important to be aware that in order to cover the energy requirements, the lactose concentrations will be far too high and cause diarrhea. Commercial milk replacers are a better choice.

Adapted from Casal ML: Management of orphan puppies and kittens. In Lopate C, editor: *Management of pregnant and neonatal dogs, cats, and exotic pets*, Ames, IA, 2012, Wiley Blackwell, pp 207-216.

Fading Puppy Syndrome

The fading puppy or kitten syndrome is not a diagnosis but rather a clinical condition characterized by anorexia, lethargy, emaciation, birth defects, and death.[11] Neonates may be too weak at birth to nurse, resulting in dehydration, hypothermia, hypoglycemia, and death within hours to days.[12] Diagnosing the underlying cause begins with a thorough history (see ch. 1), including information on the queen or bitch, the environment, ingestion of colostrum, milk replacers and any medications given.[13] After thorough physical examination (see ch. 2), decisions regarding need for blood and urine testing can be made. Patients may require stabilization before complete physical examination and diagnostics are pursued. Results from blood work, urinalyses, and/or radiographs should be compared with age-matched normal controls if possible. In neonates suspected of having congenital or genetic disease, careful review of the pedigree and a detailed history on previous litters can prove helpful.[14] It may be necessary to euthanize the sickest neonate in the litter and submit it necropsy to better understand the cause of illness, if multiple neonates are affected in a litter.[15]

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SECTION XXIII

Renal Diseases

OUTLINE

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CHAPTER 321

Clinical Approach and Laboratory Evaluation of Renal Disease

Harriet M. Syme, Rosanne Jepson

Introduction

The function of the kidneys is to regulate the volume and composition of extracellular fluid by the formation of urine. This is achieved by formation of an ultrafiltrate of plasma by the passage of solutes, small proteins and other non-cellular constituents of the blood across the glomerular filtration barrier. The volume of ultrafiltrate formed is primarily determined by the number of functioning nephrons but is also affected by the hydrostatic pressure within the glomerular capillary tuft. Following filtration, the composition of this fluid is altered according to the physiological needs of the animal by the secretion and reabsorption of solutes and water as it passes along the nephron. In a healthy animal, under normal physiological conditions, less than 1% of the fluid that is filtered by the glomerulus will eventually be excreted as urine.

Kidney disease can influence these processes in a number of different ways. Most frequently kidney disease is diagnosed when glomerular filtration rate (GFR) is decreased (usually recognized as azotemia), in a patient with either chronic kidney disease (CKD) or acute kidney injury (AKI). These syndromes are discussed in detail in ch. 324 and 322, respectively. Kidney disease may also be recognized when a patient develops proteinuria due to damage to the glomerular filtration barrier (see ch. 325). Renal tubular defects may result in altered urine (and as a consequence plasma) composition (see ch. 326), or urolithiasis (see ch. 331 and 332). In addition, the kidney has a number of endocrine functions and is integral in the maintenance of blood pressure (see ch. 157).

Clinical Approach

Investigation of a patient for renal disease may be initiated by the presenting clinical problems (polyuria/polydipsia, signs relating to uremia, abnormal renal palpation, edema or ascites) or after performing routine blood work and urinalysis in a patient with nonspecific presenting signs (depression and anorexia, for example) or in which "wellness" screening tests are performed.

History

Owners of patients with CKD will usually report that their animal is drinking and/or urinating more than normal. Polydipsia has been defined as an intake of >100 mL/kg/day in dogs (and perhaps half this amount in cats) but even if this threshold is not exceeded, an increase in reported thirst may still be significant. The volume of urine that is produced is rarely quantified but owners may notice that this is increased, or that the urine is more dilute than normal. It is important to differentiate polyuria from pollakiuria (with small volume), dysuria, and urinary incontinence, which are generally referable to problems of the lower urinary tract rather than the kidneys. However, it is quite common for disease to co-exist in the lower and upper urinary tract (for example polyuria will exacerbate urinary incontinence, pyelonephritis usually results from ascending urinary tract infections and obstructive lesions may result in post-renal azotemia) so these problems may also be of relevance. There are a great number of potential causes of polyuria and polydipsia (see ch. 45) of which renal disease is just one, and a careful complete medical history should be obtained as much to try to exclude some of these differential diagnoses as to try to confirm that renal disease is present. Reduction in appetite or weight loss may be reported in patients with renal disease but also occurs with many other diseases. Signs referable to systemic hypertension (hyphema, mydriasis, blindness) may be reported by the owners of cats with CKD, but are much less common presenting signs in dogs.[1-3]

The history in patients with AKI may be very nonspecific (lethargy, inappetence) but is typically of short

duration. In some instances, patients will have a long history relating to a medical condition that predisposed them to the development of AKI, and this chronicity can cause confusion in differentiating acute from chronic disease. Occasionally patients with AKI will have a history of known toxin ingestion or of prescribed, potentially nephrotoxic, medications.

Physical Examination

A complete physical examination should be performed in all patients with kidney disease (see ch. 2). The kidneys should be assessed for their size and contour and whether palpation of them elicits signs of discomfort. The kidneys of cats are easily palpated but in dogs they are often difficult to identify conclusively. The size of the bladder may be important; a large bladder in a patient that urinated recently suggests polyuria, bladder turgidity may indicate obstruction, and an empty bladder in a patient that hasn't urinated recently may indicate oliguria.

Hydration status may be abnormal in patients with renal disease with dehydration and/or hypovolemia sometimes occurring as a consequence of polyuria or contributing to the development of AKI. Edema and/or ascites are features of nephrotic syndrome but also can develop as a consequence of overhydration in patients that are oligo-anuric. Cats are particularly vulnerable to the development of pleural effusion with overhydration and may become dyspneic.

Patients with chronic disease may be in poor body condition. When CKD occurs in young, growing animals, deformity of the maxilla and mandible ("rubber jaw" due to fibrous osteodystrophy) may be present although this presentation is uncommon. Older animals occasionally suffer pathological fractures due to CKD-mineral and bone disorder (MBD). Mucous membranes may be pale in patients with CKD due to anemia. Uremic ulceration of the oral mucosa (Figure 321-1) and tongue tip necrosis can be present if azotemia is severe but does not differentiate between acute and chronic renal disease.

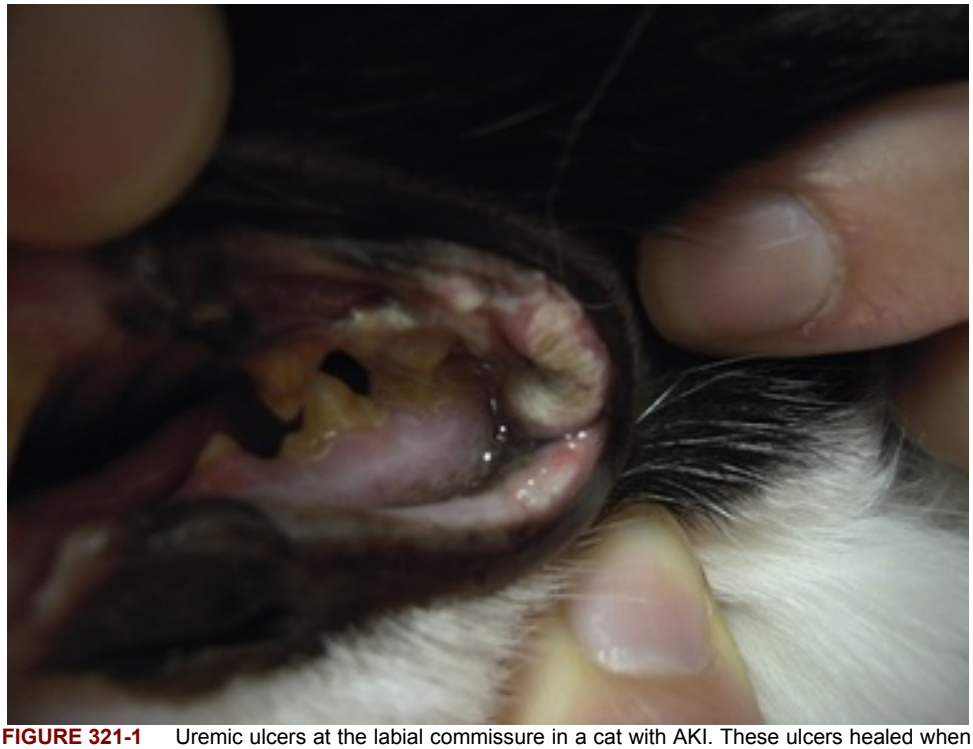


FIGURE 321-1 Uremic ulcers at the labial commissure in a cat with AKI. These ulcers healed when the cat's azotemia, which occurred as a result of lily ingestion, improved. (Picture courtesy Helen Wilson.)

Blood pressure measurement should be performed in all patients with renal disease (see ch. 99). Fundic examination should ideally be performed in all patients but particularly in any dog or cat with systolic pressure greater than 160 mm Hg (see ch. 11).

Differentiation of Acute and Chronic Disease

Chronic kidney disease (CKD) is usually defined as a problem that has been present for a prescribed period of time (typically 2-3 months or longer); however, conceptually it may be more useful to consider CKD as a condition characterized by a permanent loss of functioning nephrons. The condition is irreversible without any possibility of true recovery although the remaining nephrons may hypertrophy and hyperfiltrate. It is therefore vital to differentiate patients with CKD from those with AKI, in which recovery is possible (see ch. 322), since the management of these two groups of patients is very different.

Differentiation of acute and chronic disease is often easily done based on the patient's history and physical examination findings. A longstanding history of polyuria and polydipsia is usually present in dogs and cats with CKD although occasionally their owners do not recognize this. Weight loss due to a poor appetite may be a feature of the patient's history, or poor body or coat condition evident on physical examination, if the disease has been chronic. These features are not, however, invariably present and may sometimes have alternative causes if the patient has more than one disease.

Renal size and shape may provide valuable clues to whether the azotemia is acute (normal or enlarged size, normal shape, occasionally abnormally turgid feeling) or chronic (small and/or irregular in shape). Renal palpation is usually much more informative in cats than it is in dogs. Diagnostic imaging can be used to provide further information. This allows a more objective assessment of renal size and contour, together with evaluation for mineralization and loss of internal architecture, changes consistent with chronicity.

Non-regenerative anemia may be present in patients with CKD (see ch. 199). The causes are multifactorial but relative erythropoietin deficiency is thought to be the most important. Anemia may also occur in patients with AKI for a number of reasons; for example, patients with overhydration, leptospirosis or hypoadrenocorticism may be anemic. Additionally, hemorrhage or hemolysis resulting in hypoxia/hypotension may serve as an inciting cause for AKI. Documentation of anemia should not, therefore, be considered to indicate invariably that azotemia is chronic in nature, and particularly if the anemia is regenerative (see ch. 198) then alternative causes for anemia and possible AKI should be sought.

Hyperkalemia is most often associated with AKI and particularly with post-renal causes of azotemia. Hyperkalemia may, however, occasionally develop in dogs with CKD that are eating renal diets especially if they are concurrently treated with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers.[4] Complete urinalysis is mandatory in the investigation of azotemia and may provide valuable clues to its underlying cause (see ch. 72); for example, pyuria, bacteriuria and white cell casts would be consistent with pyelonephritis, calcium oxalate monohydrate crystals suggest ethylene glycol poisoning, and glucosuria indicates proximal tubular dysfunction. However, pyelonephritis and proximal tubular dysfunction can be either acute or chronic in nature. Large numbers of granular casts, and renal epithelial tubular cell casts, are indicative of acute tubular necrosis.

In a small proportion of cases with newly documented azotemia, it remains unclear after careful review of the history and physical examination, ultrasonographic examination of the kidneys, and routine hematology, biochemistry and urinalysis whether the problem is acute or chronic in nature. This scenario may occur when a patient displays no evidence of chronic disease but its azotemia does not improve substantially with appropriate supportive management for presumed AKI. Additional tests that may be useful in differentiation of acute and chronic disease in these select cases include radiographing the mandible/maxilla to look for loss of the lamina dura around the teeth[5,6]; ultrasound examination of the parathyroid glands to detect hypertrophy consistent with chronic stimulation[7]; and, in theory at least, measurement of carbamylated hemoglobin (which is reflective of the prevailing urea concentration), although tests for this are not currently commercially available.[8,9] Renal biopsy (discussed below) is also occasionally used to differentiate acute and chronic disease.

Differentiation of Pre-Renal, Renal, and Post-Renal Azotemia

The distinction between pre-renal and renal causes of azotemia is most often made on the basis of measurement of urine specific gravity (USG). If the USG is greater than 1.030 in a dog, or 1.035 in a cat, then the azotemia is considered to be pre-renal in origin. However, certain caveats to these rules should be noted. Cats with chronic kidney disease (CKD) will sometimes retain significant urine concentrating ability (>1.035 or even 1.040) even once azotemic. Concentrated urine has been documented in cats following 7/8ths nephrectomy.[10] Dogs and cats with primary glomerular disease also sometimes retain concentrating ability even once they have developed azotemia. Conversely, it is important to consider that the patient will only be able to concentrate urine in the face of pre-renal azotemia if tubular/collecting duct mechanisms for doing so

are intact. If there is a lack of medullary hypertonicity (for example in a patient with hypoadrenocorticism, or eating a very protein-restricted diet) or interference with tubular (patients receiving diuretics) or collecting duct (patients with primary or secondary causes of diabetes insipidus) function then creation of concentrated urine will not be possible, even when azotemia is pre-renal. In these patients, the pre-renal nature of the azotemia is confirmed by administering intravenous fluids (or reducing the dose of diuretics) and documenting its resolution.

Post-renal azotemia is usually suspected on the basis of the patient's history and physical examination, with signs referable to lower urinary tract obstruction or rupture (see ch. 150 and 335). Diagnostic imaging may also be informative, particularly in patients with partial obstruction, or unilateral ureteral obstruction where clinical signs are less obviously indicative of the problem. If fluid is present in either the retroperitoneal or peritoneal cavity, then a sample should be collected for analysis; creatinine concentration in the fluid greater than twice that in the blood is consistent with urinary tract rupture. Urine is a chemical irritant so non-septic, neutrophilic inflammation is common but the amount of associated hemorrhage and inflammation is variable.[11]

Assessing Disease Severity

The International Renal Interest Society (IRIS) has developed a staging scheme for CKD, which was subsequently endorsed by the Society for Nephrology and Urology in 2006, and is now in widespread use (see ch. 324). More recently a grading system for AKI has been developed (see Table 322-1).

Laboratory Diagnostics

Evaluation of Renal Function

Glomerular Filtration Rate

Direct assessment of glomerular filtration rate (GFR) is the gold standard for assessing the filtration and excretion function of the kidney.[12-14]

Global GFR is the sum total of single nephron GFRs from both kidneys. Key factors determining GFR include oncotic and hydrostatic pressure of plasma and ultrafiltrate within the Bowman's space in addition to the capillary surface area for filtration and capillary permeability, which is given the term ultrafiltration coefficient. GFR can therefore be defined as $Kf[(P_{GC}-P_b)-(pi_{GC}-pi_b)]$ (Kf, ultrafiltration coefficient; P_{GC}, hydrostatic glomerular capillary hydrostatic pressure; P_b, hydrostatic pressure in Bowman's space; pi_{GC}, oncotic pressure in glomerular capillaries; pi_b, oncotic pressure in Bowman's space).

Evaluation of GFR may be of benefit in a number of key situations including evaluation of renal function in patients suspected to have non-azotemic kidney disease (e.g., non-azotemic patient presenting with polyuria and polydipsia or persistently low urine specific gravity), where the clinician wishes to exclude renal disease as an underlying cause for the presenting signs. GFR may be useful as a screening tool for patients where incipient renal disease is anticipated (e.g., breeds with known juvenile or adult onset nephropathies) or in patients undergoing administration of potentially nephrotoxic medications where detection of reducing renal function might lead to altered therapeutic approach. GFR measurement may also have utility in patients with renal disease where an estimation of renal function reduction is needed in order to adjust dosing of medications undergoing renal excretion. There is currently no evidence to support the routine use of GFR assessment in patients with azotemic CKD, where creatinine is an appropriate surrogate marker of renal function.

Several methodologies have been evaluated and validated in both dogs and cats for direct assessment of GFR including assessment of urinary and plasma clearance. Markers of GFR must have a number of key characteristics: They must be freely filtered at the glomerulus, not circulate bound to plasma proteins, not undergo reabsorption or be secreted by the tubules, and must not themselves alter GFR or be toxic to the kidneys.

GFR measurements, irrespective of methodology, require standardization prior to interpretation particularly considering the potential effects of body weight, breed, sex and age. The most commonly used standardization is for GFR to be expressed in terms of body weight, although this assumes that the relationship between body weight and GFR is linear. Although exact values will vary depending on the methodology used, and direct comparisons should only be made between identical methods, GFR is typically 3.5-4.5 mL/min/kg for dogs and 2.5-3.5 mL/min/kg for cats. However, due to metabolic scaling, body weight may not be an appropriate standard, particularly in dogs <10 kg or >50 kg. Whilst alternative parameters for

standardization such as body surface area (BSA) and extracellular fluid volume (ECFV)[15,16] may seem appealing, the optimal formula for calculation of body surface area is yet to be determined.[17] Studies in dogs suggest that standardization to BSA may be preferable to body weight.[18-23] GFR, as assessed by endogenous creatinine clearance, has previously been documented to be higher in both puppies and kittens.[24-26] In male dogs creatinine is actively secreted in small amounts by the renal tubule, potentially overestimating GFR when assessed by creatinine clearance.[27]

Renal or Urinary Clearance

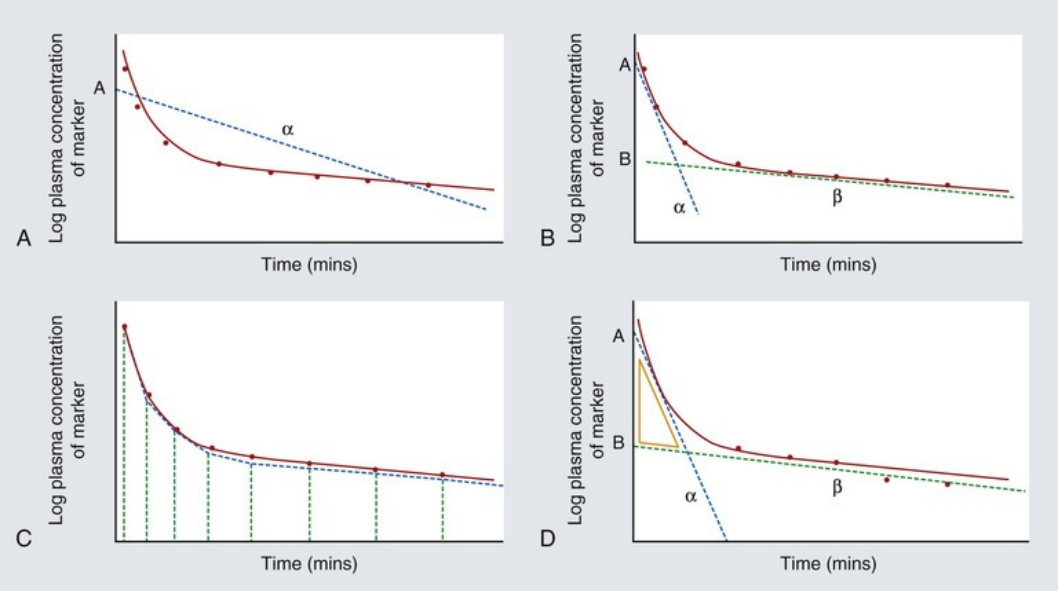
Renal or urinary clearance relates to the rate at which a filtered substance is cleared from a given volume of plasma by the kidneys into the urine, providing information about the amount of marker appearing in the urine per unit of time. Assessment of urinary clearance requires that the amount of substance, either exogenous or endogenous, is assayed both in the plasma and in the urine (see ch. 73) over a given time period. Urinary clearance is calculated using the following formula: C = (Uv × Uc)/Pc where C = clearance (mL/minute), Uv is urine flow rate (mL/minute), Uc is concentration of the solute in urine and Pc is the concentration of the solute in plasma. Urinary clearance necessitates placement of a urinary catheter (see ch. 105), and repeated and complete bladder emptying typically over a 12-24 hour urine collection period, although shorter sampling/collection protocols have been described.[28-30] All urine must be collected over the timed period of the study as failure to do so will lead to an underestimation of GFR. Urinary clearance of inulin has been considered the gold-standard method of estimating GFR but limited availability of inulin and of laboratories performing inulin quantification, and the relative difficulty of performing complete urine collection mean this method is rarely used clinically.[28,30-37] Alternative methodologies utilize either endogenous or exogenous creatinine or iohexol renal clearance.[29,38]

Endogenous urinary creatinine clearance assesses GFR by quantifying creatinine concentrations in blood and urine.[31-33,39] Methodologies utilizing creatinine quantification measured by the Jaffe method are subject to issues relating to non-creatinine chromogens whereby these give falsely increased results.[40] The effect of this is greatest when the non-creatinine chromogens make up a greater proportion of the result (i.e., when patient creatinine concentration is within reference interval). This effect is not identified when enzymatic methodologies are used for creatinine quantification. In order to minimize the effect of non-creatinine chromogens, exogenous renal creatinine clearance methodologies were developed with a goal of increasing creatinine concentrations to the point that non-creatinine chromogens reflect only a small proportion of the total creatinine measured in a patient.[32-34,38,41-44]

Plasma Clearance

Plasma clearance is a more frequently used methodology in clinical practice as it avoids the requirement for urine collection. Timed samples must be obtained accurately to avoid errors in calculation of the AUC. Markers of plasma clearance which have been used include inulin, exogenous creatinine, iohexol and radiolabeled markers such as [^{125}I] sodium iodohippurate, ^{51}Cr-ethylenediaminetetraacetic acid (EDTA), and ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA). Although urinary clearance of inulin is considered to be the gold standard, plasma clearance of inulin is not recommended since up to 40% of inulin is excreted via non-renal routes in the dog.[32] Extra-renal clearance of inulin has not been studied in the cat.

GFR determined by plasma clearance is calculated using the equation C_{plasma} = D/AUC where D = dose of the substance administered and AUC is the area under the plasma concentration versus time curve (also see ch. 160). The AUC is determined by obtaining the plasma concentration of the substance at multiple timed intervals over a pre-determined period of time. A number of different pharmacokinetic models can be used to determine the AUC depending on the analyte and sampling frequency. One-compartment, two-compartment, multi-compartment and non-compartmental pharmacokinetic models have previously been used for estimation of the AUC in veterinary GFR studies (E-Figure 321-2). The number of compartments or the model used impact the calculation of the AUC and therefore the resulting GFR calculated.[45] Multiple sampling protocols may be less than ideal, particularly in small or anemic patients. Therefore, numerous studies have recently focused on the validation of limited sampling or single sample protocols, which provide an easier approach to assessment of GFR by plasma clearance in the clinic.



E-FIGURE 321-2 Models used for calculation of GFR from plasma clearance. **A, One-compartment models** consider the patient as a single compartment and assume immediate distribution of the substance used as the marker of GFR throughout the body and that the marker is excreted from that compartment only. The plasma concentration of the chosen marker (dots) is plotted against time. A linear slope is constructed (dashed line) and area under the slope is calculated by dividing the zero time intercept (A) by the slope of the exponential (alpha). Clearance of the marker is determined by dividing the dose of marker by the area under the curve. Using this model, the plasma concentration of the marker immediately after injection exceeds that estimated by the one-compartment model which may lead to overestimation of GFR. **B,** The **two-compartment model** assumes that the marker is initially distributed from the vasculature (central compartment) to the extracellular fluid volume (ECFV; peripheral component). A subsequent second elimination phase from the body allows slow redistribution of the marker back to the plasma from the interstitial fluid as the marker undergoes renal clearance. The log plasma concentration of the chosen marker (dots) is plotted against time. The area under the curve is calculated from two straight lines (dashed lines) representing an initial steep redistribution (alpha) from plasma to ECFV and the second terminal elimination (renal clearance) phase (beta). The area under the curve is calculated using the following equation: [A/ alpha + B/ beta], where A and B represent the zero time intercepts of the first (distribution) and second (elimination) phase, respectively, and alpha and beta represent the slope of their respective exponentials. **Multi-compartmental models** are similar to the two-compartment model except that each component is resolved to a series of straight lines providing a theoretically more accurate representation of the area under the curve but with the limitation that a more frequent sampling protocol would be required. **C,** In a **non-compartmental model** the area under the curve is calculated by adding the area of trapezoids defined by the curve. Unlike compartmental models, a non-compartmental model is free from assumptions regarding the redistribution and elimination phases. Errors in GFR calculation from this approach may arise because the terminal phase of elimination from the last sample to the time of theoretical zero must be estimated and also when early ending of plasma sampling means that a greater proportion of the curve must be estimated. **D, Slope-intercept technique for estimation of GFR.** The slope-intercept technique can be used for estimation of GFR using a limited number of samples (red dots) from only the elimination phase. Exclusion of the distribution phase will lead to an overestimation of GFR (orange triangle) as the area under the curve will be under-estimated. This overestimation will be proportionally larger for patients with near normal GFR compared to patients with low GFR as the distribution phase in such patients contributes to a greater extent of the overall area under the curve. A correction formula is applied to adjust for this.

Single sample methods for GFR estimation have also been evaluated both in dogs[22,23,74] and cats[22,23,72] using linear regression or non-linear regression approaches to determine the best single sample timing from multi-sample methods.[79] True assessment of GFR using a single sample method requires that the volume of distribution is known and that the sample is collected at a time point when there is complete mixing of the marker through the volume of distribution.[79-82] Such an approach has recently been evaluated in the cat and suggests that optimal sampling time is 180 minutes after iohexol marker administration.[83] Although this will be applicable for the majority of cats where GFR measurement is clinically required (i.e., cats with near normal GFR), timing of sampling would need to be delayed for any cat anticipated to have low GFR.[83]

Plasma Exogenous Creatinine Clearance

Creatinine is produced from breakdown of creatinine phosphate within muscle tissue with minimal impact

from protein intake.[39] It is freely filtered at the glomerulus and does not undergo reabsorption. In male dogs there may be a small amount of tubular secretion, which can lead to overestimation of GFR.[46] Exogenous creatinine has been used as a plasma marker of filtration although lack of availability of a medical grade creatinine product can limit utility outside a research setting. Exogenous creatinine plasma clearance has been used in both dogs[32,41,47,48] and cats[49-54] for assessment of GFR. Creatinine has a larger volume of distribution than other markers and this therefore leads to a longer test time being required.[32,55] This can also result in a larger extrapolated region in the AUC calculation than for other markers and particularly for patients with reduced renal function this may lead to inaccuracies in GFR estimation. In dogs, extra-renal clearance of creatinine has also been identified which may falsely increase GFR assessment, although this association has not been explored in the cat.[56]

Radiocontrast Agents

Both iohexol and gadolinium have been evaluated as markers of filtration although iohexol is the most frequently used marker.[57,58] Iohexol is a non-ionic iodinated, water soluble, low osmolar contrast agent, which can be used as a marker for plasma clearance. Contrast agents such as iohexol have been associated with AKI in human patients but such an association has not been reported in veterinary medicine and use of iohexol is therefore widely considered safe in veterinary patients. Iohexol remains within the extracellular space, does not undergo significant metabolism and protein binding is negligible. It is a stable molecule such that samples can be readily transported to the laboratory without concern regarding degradation. Several methods have been used for quantification of iohexol but most recent studies use high performance liquid chromatography (HPLC) or high performance capillary electrophoresis (HPCE) technologies.[42,59-61] Iohexol exists as two isomers, endo- and exo-iohexol, that can be quantified separately if HPLC methodologies are used.[62] The predominant isomer quantitatively is known to be exo-iohexol. In cats, several studies have suggested differential excretion of endo- and exo-iohexol, suggesting that there may be inaccuracies if only total-iohexol plasma clearance of GFR is evaluated.[50,63] However, a recent study by Finch and colleagues did not demonstrate a difference in clearance of the two isomers and similar findings have been demonstrated in dogs.[45,64,65] There was also no significant conversion of one isomer to the other after administration.[45] Evaluation of total iohexol for plasma iohexol clearance is therefore preferred.

Plasma iohexol clearance has been widely used in both the dog[23,42,60,61,65-68] and the cat.[19,23,43,49-52,54,69-71] Studies evaluating plasma iohexol clearance have mainly been compared to exogenous or endogenous clearance of creatinine rather than inulin. Although some differences exist depending on the model used for calculation of AUC, plasma clearance of iohexol performs well in comparison to renal clearance of exogenous creatinine.[42,60] Plasma iohexol clearance is currently the most frequently used methodology for assessment of GFR in clinical practice.

Radioisotopes

Radiolabeled markers such as [^{131}I] sodium iodohippurate [^{125}I] sodium iothalamate, ^{51}Cr-ethylenediaminetetraacetic acid (EDTA), and ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) are freely filtered at the glomerulus and do not undergo reabsorption or secretion in the tubules and have therefore been used for assessment of GFR via both plasma and renal clearance.[44,50,72-75] Use of older radiolabeled markers such as [^{131}I] sodium iodohippurate [^{125}I] sodium iothalamate has largely been superseded by those with a shorter half-life such as ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA; 6 hours) meaning that patients are cleared of radioactivity within a 24-48 hour period. Limitations of using radiolabelled markers for plasma or renal clearance include the availability of laboratories for measuring such markers, difficulties associated with transportation of samples and appropriate facilities in which to conduct nuclear medicine and to hospitalize the patient post-procedure.

Limited Sampling Protocols

In an attempt to simplify the assessment of GFR for clinical patients where repeated sampling is not feasible, limited sampling protocols have been developed. Using a two-compartmental model (see E-Figure 321-2), a minimum of four samples is required to generate the biexponential curve. However, in order to minimize the number of samples required, an estimation of GFR may be made by using only the elimination phase and excluding the distribution phase that is assumed to be independent of renal clearance. The methodology used to estimate GFR from a limited number of samples using only the elimination phase is the **slope-intercept**

technique (see E-Figure 321-2).[23,54,66] A correction formula is subsequently applied to obtain the corrected slope-intercept clearance. Several formulae have been used in humans[76-78] and dogs[18] and more recently a feline specific formula has been evaluated.[14,45]

Alternative Methodologies for GFR Assessment

- **Radioisotope markers:** One of the primary advantages to evaluating a radiolabeled marker is the potential to perform renal scintigraphy using a gamma camera. This allows assessment of both global and individual kidney GFR by measuring the percentage dose update of the marker by each kidney separately. However, difficulties associated with renal scintigraphy include the experience of personnel in defining the area of interest, requirement for sedation/general anesthesia, adjusting for kidney depth, availability of appropriate facilities for scintigraphy and hospitalization facilities post-procedure. Several studies have evaluated nuclear scintigraphic determination of GFR in dogs and cats using ^{51}Cr-EDTA and ^{99m}Tc-DTPA.[31,35,75]
- **Computed tomography:** Computed tomography has been used in conjunction with iohexol administration to provide both global and individual kidney estimation of renal uptake in a similar manner to scintigraphy.[84-91] Due to the ease of performing such studies and the relatively wide availability of computed tomography, further studies evaluating this approach are warranted.
- **Fluorescent-labeled markers:** Sinistrin is a polyfructran, which has been evaluated as a potential marker for plasma clearance.[92] A preliminary study has evaluated fluorescence-labeled sinistrin as a transcutaneous marker of GFR that holds promise for the future as a non-invasive methodology.[93] A further study has evaluated fiberoptic radiometric fluorescence as a method for GFR.[94]
- **Estimated GFR:** In human medicine GFR is routinely estimated from plasma creatinine concentration or cystatin C (estimated GFR; eGFR) using equations which take into consideration other factors such as age, gender, race, and measurements of body size that reflect muscle mass.[95-97] Such equations appear to offer advantages in terms of assessment of renal function when compared to plasma creatinine or cystatin C concentrations alone. To date only one study has attempted to formulate such an equation for cats but the eGFR did not offer substantial benefit over the use of plasma creatinine as an estimate of GFR.[98]

Surrogate Plasma/Serum Markers of Glomerular Filtration Rate

For most clinical patients initial assessment of renal function will be made using a surrogate marker of GFR, most commonly urea and creatinine quantification.

Urea

Urea is produced from ammonia derived from amino acids as part of the ornithine cycle within the liver. Amino acids used in the production of urea can originate either from endogenous or exogenous protein sources. Urea is filtered at the glomerulus but undergoes passive reabsorption within the tubules. The degree of reabsorption increases with slower tubular flow rates, which are typically identified in patients that are either hypovolemic or dehydrated. Plasma/serum urea concentration is commonly reported as blood urea nitrogen (BUN) in the United States and urea elsewhere in the world, which has great potential for confusion since two conversion steps are required, first from BUN to urea, and then from traditional (mg/dL) to SI (mmol/L) units.

One of the main limitations of urea as a marker of renal function is that production and excretion are not constant and can be influenced by a number of factors. It is widely recommended that both dogs and cats have food withheld for a minimum of 8-12 hours before assessment of urea concentrations to avoid the effects of dietary protein ingestion on urea concentrations. Conditions associated with increased protein catabolism (e.g., fever, burns, infection, starvation, hyperthyroidism) increase urea.[99] In particular, upper gastrointestinal hemorrhage is an important cause of elevated urea concentrations and urea : creatinine ratio in dogs and cats.[100] Conversely, reduced hepatic function, portosystemic shunting, and low protein diets may contribute to reduced urea concentrations. In-house reagent test strips are available for rapid and inexpensive assessment of urea and have demonstrated good sensitivity and specificity in dogs and cats.[101]

Creatinine

Creatinine is the most widely used surrogate marker of GFR in clinical practice.[102] It is produced from dehydration of creatine and dephosphorylation of phosphocreatine in muscle. Provided muscle mass remains stable, creatinine is produced at a constant daily rate. However, creatinine concentrations are affected by lean

body mass and as such, young animals and those with poor muscle mass will have proportionally lower plasma/serum creatinine concentrations than mature or well-muscled individuals.[103] Studies suggest that plasma creatinine concentrations increase gradually over the first year of life in dogs but then remain stable or increase moderately up until 8-10 years of age[102] whilst in kittens creatinine concentrations are relatively high at birth but are similar or lower than in adults by 8 weeks of age.[104] Greyhounds have been documented to have higher creatinine concentrations than other breeds, likely as a consequence of their muscling.[105] In cats, breed-related differences have been reported and in particular the Birman has been reported to have high plasma creatinine concentrations.[106-108] There is no apparent effect of sex on plasma creatinine in either the cat or the dog. Creatinine is freely filtered at the glomerulus. It is very weakly secreted in renal tubules in dogs, especially males, but this is of negligible clinical significance even in a patient with reduced renal function.[32,41,46,109]

Serum concentrations of creatinine are reported to be 5-10 micromol/L (0.05-0.1 mg/dL) higher than in plasma. Creatinine is less influenced by recent protein ingestion than urea. However, studies evaluating the effect of feeding on creatinine concentrations have been variable, with those reporting feeding of raw or cooked meat indicating increases for up to 12 hours post-prandially, whilst other studies indicate a decrease or no change after feeding of commercial foods.[110-112] It is nevertheless preferred to evaluate creatinine in a patient that has been fasted for 8-12 hours.

Creatinine concentrations in the laboratory are usually measured either by the nonspecific Jaffe method (based on the formation of a yellow-orange chromogen when creatinine is mixed with picrate ion in alkaline conditions) or by specific enzymatic techniques. Non-creatinine chromogens may interfere with measurement of creatinine when using the Jaffe reaction.[113,114] However, the relative degree of interference decreases in patients with kidney disease as true creatinine concentration increases. Enzymatic methods are not affected by non-creatinine chromogens but may be influenced by hyperbilirubinemia.[113] The laboratory reference intervals reported can vary widely and it is therefore important to always compare results with the relevant reference interval and ideally for comparative samples from the same patient to be analyzed either at the same laboratory or using the same in-house analyzer.[115]

Creatinine has an exponential relationship with GFR (Figure 321-3).[116] This means that in patients with a near normal GFR, creatinine is an insensitive marker of renal function, as change in GFR results in only a relatively small increase in plasma creatinine concentration. The relationship between creatinine and GFR is only valid in patients where renal function is in a steady state. The magnitude of alteration in creatinine and urea concentrations cannot be used to determine whether azotemia is pre-renal, renal or post-renal in origin nor the potential for reversibility of the azotemia.

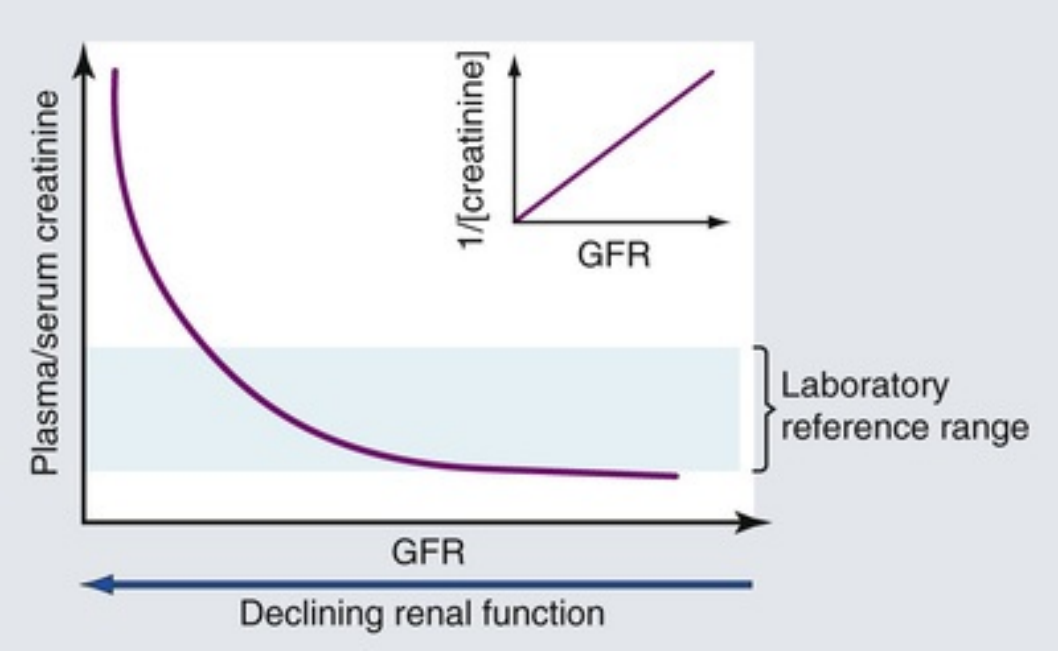


FIGURE 321-3 Creatinine demonstrates an exponential relationship with GFR (purple line) when

plotted directly, while the relationship between the reciprocal of creatinine plotted against GFR approximates a straight line (inset).

Symmetric Dimethylarginine

Symmetric dimethylarginine (SDMA) is a dimethylated derivative of arginine produced from intranuclear methylation of L-arginine residues by protein-arginine methyltransferase along with its stereoisomer asymmetric dimethylarginine (ADMA). SDMA is primarily excreted via renal filtration, indicating that it has characteristics required for an endogenous marker of renal function.[117] Plasma SDMA has been demonstrated to correlate well with plasma creatinine concentration.[118,119] In azotemic and non-azotemic cats, a linear relationship has been demonstrated between the reciprocal of SDMA (1/SDMA) and GFR assessed by plasma iohexol clearance performing in a similar manner to the reciprocal of creatinine (1/creatinine).[120] Studies suggest that SDMA concentrations are less influenced by body muscle mass than plasma creatinine.[103,119,121] Preliminary studies suggest that SDMA may be a more sensitive marker of early decline in renal function in cats.[122] Assessment of SDMA does not appear to be affected by feeding a renal diet supplemented with both fish oil or L-carnitine in the dog.[121] However, further work is still required to determine the effect of concurrent disease on this novel marker. Historically, assessment of SDMA has been limited by requirement for quantification by liquid chromatography mass spectrometry. However, development of a commercially available immunoassay has recently made this marker widely available as a clinical diagnostic test (see also ch. 324).[123]

Cystatin C

Cystatin C is a low molecular weight (13 kilodalton [kDa]) protein which acts as a proteinase inhibitor and which is produced at a constant rate because it is encoded by an intracellular housekeeping gene.[124,125] Cystatin C is not bound to plasma proteins and is freely filtered at the glomerulus.[126] However, cystatin C, unlike other markers, is reabsorbed by megalin-mediated endocytosis within the proximal tubules and is catabolized.[126-128] No tubular secretion of cystatin C occurs and in human medicine, it has been proposed as a more sensitive marker of GFR than plasma creatinine concentration.[129] In addition, as urinary cystatin C is typically very low, the presence of an increased concentration of urinary cystatin C may indicate tubular dysfunction.[130] Numerous studies have evaluated the potential use of cystatin C in dogs and cats. However, to date these studies have not demonstrated consistent superiority over creatinine and confounding factors may limit the utility of this marker in practice.[124] Indeed two recent studies indicate that serum cystatin C is not a useful marker for identification of reduced renal function in the cat.[124a,124b]

Fully automated particle-enhanced turbidimetric immunoassay (PETIA) has been used for quantification of cystatin C in both urine and serum/plasma from dogs[131-134] whilst a particle-enhanced nephelometric immunoassay (PENIA) has been validated in cats.[135,136] Both methodologies are dependent on cross-reactivity between serum cystatin C and polyclonal rabbit anti-human cystatin C antibodies. However, direct comparison of the PETIA and PENIA methodologies with simultaneous GFR assessment remains to be performed to determine which methodology is superior.[137] One study has identified an effect of age and body weight on serum cystatin C in dogs,[138] although other studies have not confirmed this finding.[134] Of concern, plasma cystatin C decreased significantly 1 hour post-prandially.[138] This decrease persisted for up to 9 hours before returning to baseline and based on this data a minimum period of 12 hours fasting would be advocated prior to assessing cystatin C in dogs. Whether this change in cystatin C reflects alteration in GFR after feeding remains to be determined. The most recent validation study in cats by Ghys and colleagues suggested that there was no influence of age, sex or breed.[136] Recently, feline specific recombinant cystatin C monoclonal antibodies have been developed which may lead to the development of a feline specific assay in the future.[139]

In human medicine, a number of concurrent conditions may influence serum cystatin C concentrations including thyroid function, neoplastic disease, asthma and inflammation.[140] Serum cystatin C concentrations may be increased and decreased in hyper- and hypothyroidism, respectively, relating to the stimulatory effect of thyroid hormones and also TGF-beta on cystatin C production.[141] Decreased regulation by cystatins is responsible for increased activity of cysteine protease in neoplastic cells and individuals with carcinomas and leukemia have been shown to have significantly higher cystatin C concentrations pre- versus post-treatment,

although not all studies have shown this association with malignancy.[142,143]

Studies have indicated that serum cystatin C concentrations are significantly higher in dogs with CKD than control dogs.[138,144] However, overlap existed between groups in the studies. A study using a renal mass reduction model identified that the correlation between the reciprocal of cystatin C was superior to the reciprocal of creatinine when compared with GFR initially when GFR was very low (0.5 ± 0.15 mL/min/kg) but that after 10 weeks when GFR increased (1.00 ± 0.27 mL/kg/min) there was no apparent difference between the two parameters.[133] Studies have indicated that cystatin C may have a higher sensitivity (76%) when compared to creatinine (65%) for the detection of a decreased GFR as measured by exogenous creatinine clearance, although specificity for both markers was similar (cystatin C 87% and creatinine 91%).[134] In cats, serum cystatin C has been shown to be significantly higher with CKD than in control cats, although there was overlap between groups.[135] Few studies have evaluated urinary cystatin C but those performed in both dogs[131] and cats indicate that urine cystatin C concentrations are higher in patients with CKD than controls.[135]

To date, few studies have evaluated the potential confounding factors relating to cystatin C quantification in veterinary patients. The study by Almy and colleagues revealed that cystatin C was not a good marker of pre-renal azotemia in an experimental study where dogs were administered furosemide.[133] Studies support that cystatin C may be elevated in patients with leishmaniasis when creatinine concentrations were not correspondingly elevated.[145] In dogs, preliminary studies suggest that cystatin C may decrease with weight loss.[146] In cats, the effect of diabetes mellitus has been evaluated and appears to have no impact on cystatin C measurement, but a preliminary study evaluating hyperthyroidism suggested that this may impact on measurement as in human studies.[147,148] Two recent studies have demonstrated that serum cystatin C is not a reliable indicator of renal function in cats and that this marker fails to identify azotaemic cats with CKD.[124a,124b] Further study is warranted to fully determine the effect of concurrent disease before the utility of cystatin C can be determined for dogs.

Evaluation of Proteinuria

Proteinuria is the term used to describe the presence of increased amounts of protein within the urine. Providing pre-renal (e.g., Bence Jones proteins) and post-renal (lower urinary tract inflammation) causes of proteinuria can be excluded, the proteinuria can be considered to be renal in origin. The glomerular filtration barrier composed of the glomerular capillary endothelium, basement membrane and epithelial podocytes limits the passage of medium and high molecular weight proteins from the blood to the glomerular filtrate with albumin (69 kDa) and larger proteins typically being retained. Proteins that do undergo filtration, in health, are effectively reabsorbed via megalin- and cubulin-mediated endocytosis within the proximal tubular cells such that the magnitude of proteinuria is typically low. Proteinuria can originate either from change in structure or function of the glomerular filtration barrier, glomerular proteinuria, or can be due to reduced capacity of the proximal tubular cells to reabsorb proteins—tubular proteinuria. Proteinuria should be evaluated in all patients with CKD as part of the IRIS staging scheme (see ch. 324). In other patients, proteinuria may be investigated when a positive result is obtained on a urine dipstick or protein-losing nephropathy is a clinical differential in a patient presenting with cavitary effusion or peripheral edema suggestive of nephrotic syndrome or hypoalbuminemia, especially when globulin concentration is normal. Numerous methodologies are available for the assessment of proteinuria.

Colorimetric Biochemical Reagent Urine Dipstick

Urine dipsticks are the most frequently used screening test for the detection of proteinuria. They typically have a higher sensitivity for albuminuria than other urinary proteins with a lower limit of detection of 30 mg/dL. In general, these dipsticks have reasonable sensitivity (>80%), but very poor specificity, particularly in cats.[149,150] False negative results may occur with Bence Jones proteinuria, dilute or acidic urine. False positive results are reported more commonly in cats and may be the consequence of alkaline or highly concentrated urine, pyuria/hematuria or not reading at the correct time interval.[149,151,152] Given the limitations of this test, in any patient for which there is concern regarding the presence of proteinuria, further assessment with a urine protein to creatinine ratio (UPC) is warranted.

Sulfosalicylic Acid Test

The sulfosalicylic acid (SSA) test is performed in some diagnostic laboratories as a confirmatory test with a reported limit of detection of 5 mg/dL.[151,153] Unlike urine dipsticks, the SSA test can detect globulins and Bence Jones proteins within urine.

False positive results may occur in patients that have received radiocontrast agents, cephalosporins, and penicillins, and protein content may be overestimated if urine samples are turbid and not centrifuged prior to evaluation.[153] Sensitivity and specificity to detect microalbuminuria (1 mg/dL) compared to a species-specific ELISA are only moderate (cat sensitivity 58%, specificity 25%; dog sensitivity 73.3%, specificity 63.9%).[149] In a study evaluating 237 cats with CKD the SSA test (positive results >5 mg/dL) had a 63% sensitivity and 96% specificity for the detection of microalbuminuria.[150]

Microalbuminuria

Microalbuminuria is defined as a concentration of albumin that is >1 mg/dL but below that typically detectable by urine dipsticks, <30 mg/dL.[151] Microalbuminuria can be measured either by species-specific point-of-care semi-quantitative tests or by species-specific ELISA techniques. Similar to urine protein concentrations, urine albumin when quantified should be standardized either to urine creatinine concentration to give a urine albumin to creatinine ratio or to a urine specific gravity of 1.010. Screening for microalbuminuria can be considered in patients where there is concern for a false negative result on a routine urine dipstick, where low level proteinuria may be predictive of the onset of hereditary glomerular disease, in geriatric patients where a more sensitive screening test is desired, or for monitoring of known microalbuminuria. The interpretation of microalbuminuria is important as the presence of microalbuminuria may be affected by post-renal causes. However, the effect of hematuria and pyuria on microalbuminuria is variable. Studies suggest that microalbuminuria concentrations are unlikely to exceed 1 mg/dL until urine is grossly hematuric (>250 red blood cells/hpf) and that in a group of 70 urine samples with pyuria (>5 white blood cells/hpf) 67% had negligible urine albumin concentrations.[154] Any positive result should be repeated after 7-14 days to ensure that this is a true and persistent finding. Discordant results suggest that the first was likely to be a transient phenomenon but if both are positive then this is support for continued monitoring or assessment of UPC.

Urine Protein to Creatinine Ratio

Urine protein to creatinine ratios are the most commonly used method for quantifying proteinuria. A UPC >0.4 in the cat and >0.5 in the dog corresponds to urine albumin concentrations >30 mg/dL and is considered abnormal if this is a persistent finding (≥3 occasions ≥2 weeks apart).[155] UPC >2.0 are strongly suggestive of underlying glomerular disease although other etiologies cannot be excluded without renal biopsy.[155-157] Studies have demonstrated that spot UPC correlates well with 24-hour urine protein quantification, negating the requirement for 24-hour urine collection in clinical patients.[158-160] UPC ≥0.2 in both the dog and the cat has a good level of specificity for detection of microalbuminuria (>1 mg/dL) being 98.6% and 90.8%, respectively. However, the sensitivity for UPC to detect low level microalbuminuria is not as good, being 47.9% in the dog and 32.7% in the cat.[149] However, a further feline study suggested that UPC performed well with sensitivity 84.6% and specificity 81.8% when compared to a positive result on a semi-quantitative microalbuminuria dipstick.[150]

Recent studies support that there is little difference in UPC result obtained from a free catch urine sample, mid-stream compression sample versus cystocentesis.[161,162] However, one study has shown that in dogs, UPC values obtained in a hospitalized environment may be higher than at home.[163] Studies suggest that UPC is unlikely to be influenced by hematuria unless gross hematuria (>250 red blood cells/hpf) is identified and that the effect of pyuria is likely to be minimal in most patients.[154] There appeared to be little inter-laboratory variability when assessing UPC with three different methodologies and reagents.[164] However, considerable day-to-day individual variability was reported in a study that evaluated dogs with X-linked hereditary nephropathy. This study supported that UPC must change by 35% for patients with UPC ≈12 and by 80% for patients with UPC ≈0.5 for this to reflect a true change in UPC rather than day-to-day variability.[165] Furthermore, whilst one sample may be sufficient for evaluation of UPC in dogs with UPC <4.0, for patients that are more markedly proteinuric (UPC >4.0) then >2 samples should be evaluated and averaged to give a true representation of that patient's magnitude of proteinuria.[165] Pooling an equivolume of urine from three samples is a more cost effective and comparable way to evaluate proteinuria in patients with UPC >4.0.[166]

Renal Biopsy

Renal biopsy is most often performed in patients where there is a high index of suspicion for primary glomerular disease. Current International Renal Interest Society guidelines suggest that renal biopsy is considered for patients with persistent substantial proteinuria (UPC >3.5), in patients where proteinuria is unresponsive to anti-proteinuric therapy, or the patient is demonstrating a progressive increase in proteinuria or decline in renal function despite instituting standard therapy for proteinuria (see ch. 325). Renal biopsy may also be considered if the clinician is contemplating the use of immunosuppressive therapy in a patient with suspected primary glomerular disease in order to determine the presence of immune complex glomerulonephritis. In certain circumstances renal biopsy may be considered in patients with AKI, particularly if there is concern regarding an acute glomerulonephritis or where a client may be considering the merit of continuing with long-term dialysis and would benefit from knowledge regarding whether there is evidence of a regenerative response within the remaining renal parenchyma. However, in most situations, renal biopsy would not lead to definitive identification of the etiology of AKI.

A comprehensive diagnostic investigation should always be performed prior to performing renal biopsy in order to evaluate for any underlying disease process contributing to the patient's proteinuria (e.g., neoplastic or infectious disease etiology), to document that the proteinuria is a persistent finding, and to ensure that it cannot be attributed to either pre- or post-renal origins (see ch. 325).[157] Key considerations for patients undergoing renal biopsy should include control of systemic hypertension when present (see ch. 99 and 157), discontinuation of anti-thrombotic therapy a minimum of 72 hours prior to renal biopsy procedure and assessment of hemostasis (platelet count, activated partial thromboplastin time, prothrombin time, thromboelastography, buccal mucosal bleeding time [see ch. 80], blood typing). Contraindications for renal biopsy include IRIS stage 4 CKD where the degree of severity of underlying renal disease is unlikely to be reversible irrespective of renal biopsy findings, patients with primary tubulointerstitial disease where there is no index of suspicion for glomerular disease that could be responsive to immunosuppressive therapy, evidence of hydronephrosis, pyelonephritis, hemostatic disorders and renal abscessation. There is also little purpose in performing a renal biopsy in a patient where there is a high index of suspicion for either amyloidosis or a hereditary nephropathy given that, to date, there is no evidence that such patients will respond to immunosuppressive agents.

Several methods are available for renal biopsy including ultrasound-guided Tru-Cut (see ch. 89), laparoscopic biopsy (see ch. 91), keyhole surgical and full exploratory laparotomy with either Tru-Cut or surgical wedge biopsy.[167-169] Irrespective of the technique used, it is important to ensure that the biopsy is obtained from cortical tissue only (Figure 321-4). This ensures not only that the area of interest is available for examination (i.e., glomeruli that are located within the cortex), but also reduces the risk of substantial hemorrhage, which may occur if the corticomedullary junction is crossed due to the location of the arcuate arteries within this region. In particular, caution should be exercised when using a Tru-Cut biopsy device in conjunction with either a keyhole or full exploratory surgical approach to ensure that the device remains within the cortical tissue. The number of glomeruli obtained has been documented to be significantly higher when a 14-gauge Tru-Cut device is used compared to 18-gauge whether performed laparoscopically or with ultrasound guidance with increased crush artifact evident on 18-gauge biopsy samples.[170] However, in most patients an 18-gauge Tru-Cut biopsy device will obtain a satisfactory sample although in large patients use of a 16-gauge device may be preferable.[168] A minimum of two 10-mm length cores of cortical tissue should be obtained. In the event that the core of renal tissue is shorter than 10 mm or there is concern for substantial crush artifact, then a third sample should be obtained.[168] Irrespective of the methodology, providing the operator is experienced, satisfactory renal biopsies can be obtained in both cats (86.2%) and dogs (87.6%).[171] Samples are more likely to be of satisfactory quality when performed under general anesthesia, which in particular allows control of respiration for patients undergoing ultrasound-guided Tru-Cut renal biopsy, although this procedure is also reportedly performed with success under deep sedation.[168]

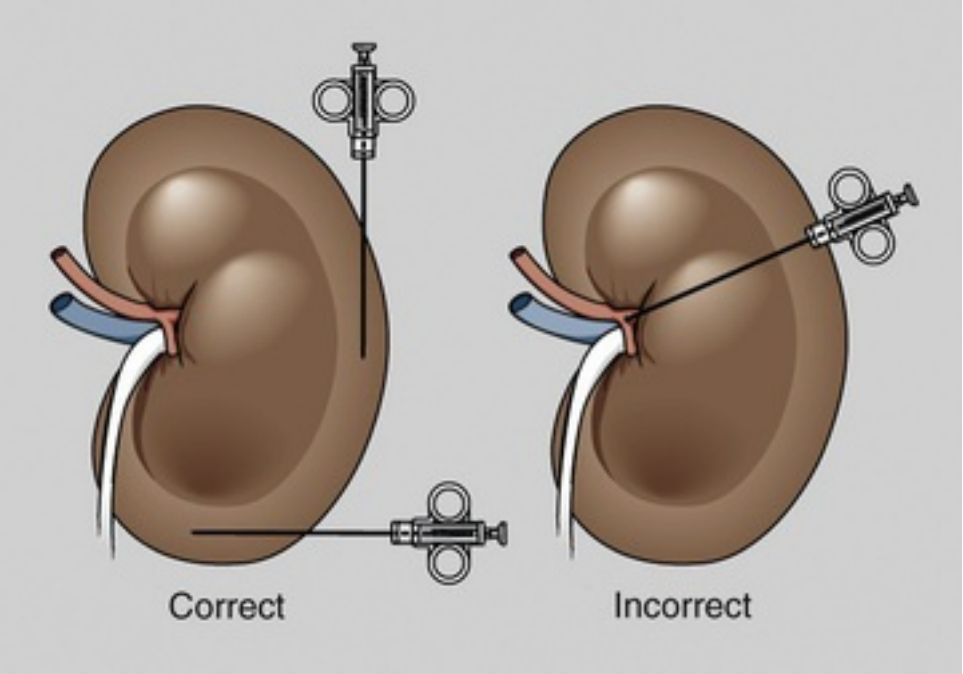


FIGURE 321-4 Demonstration of renal biopsy technique showing correct and incorrect placement of the biopsy instrument in the kidney. (Courtesy Dr. Shelly Vaden, North Carolina University, Raleigh, N.C.)

After procurement, the renal biopsy sample should be handled carefully to avoid crush or handling artifact, ideally maintaining the samples in physiological saline. Confirmation of glomeruli present within the samples can be performed by examination under 10×-40× magnification.[168] The samples should be carefully divided for evaluation by light microscopy (formalin fixed), transmission electron microscopy (TEM, glutaraldehyde) and immunofluorescence (Michel's medium).[168] Due to the specialist nature of renal biopsy interpretation, samples should be reviewed by a specialist veterinary nephron-pathologist where possible (Box 321-1). Light microscopy should not be restricted to hematoxylin and eosin (H&E) but should also incorporate evaluation with Masson's trichrome (MT) to identify collagen and connective tissue. Periodic acid Schiff hematoxylin (PASH) highlights the junction between tissue compartments (e.g., tubular, Bowman's capsule and capillary basement membrane); Jones methenamine silver (JMS) stains the fine structures of the glomerular basement membrane, which is useful for identifying immune complex deposits; and Congo red (CR) identifies amyloid.[172,173] A recent study indicated that in approximately 27.4% of cases, TEM was required either to confirm or make the diagnosis of immune-complex-mediated glomerulonephritis, which would otherwise have been inappropriately classified on the basis of light microscopy alone.[156] When immune-complex deposits are identified, immunofluorescence can subsequently be used to determine their origin with antibodies directed against IgG, IgA, IgM, C1q, C3, lambda and kappa light chains.[168,172,173]

Box 321-1

WSAVA Renal Biopsy Service Providers

International Veterinary Renal Pathology Services
Dr. Rachel Cianciolo (phone: 614-292-9717, email: rachel.cianciolo@cvm.osu.edu)
The Ohio State University
301 Goss Laboratory
1925 Coffey Road
Columbus, OH 43210
N.B. This has replaced the service that was previously provided at Texas A & M by Dr. George Lees.
Dr. Luca Aresu (email: luca.aresu@unipd.it)
European Veterinary Renal Pathology Service
Department of Comparative Biomedicine and Food Science

University of Padova
Viale dell'Università 16
Legnaro (PD)
35020, Italy
N.B. This has replaced the service that was previously provided at Utrecht.

Studies evaluating the effect of repeated renal biopsy on renal function in healthy dogs and cats have not documented a significant impact on GFR.[174,175] However, complications have been reported to occur in 13.4% of dogs and 18.9% of cats.[171] Factors that have been associated with an increased risk at the time of renal biopsy include patients of small size (<5 kg), severe azotemia (serum creatinine >5 mg/dL) and evidence of disorders of hemostasis.[171] Hemorrhage is reported in 9.9% of dogs and 16.9% of cats and should be treated aggressively when identified. Other complications reported include gross hematuria (4.2% of dogs, 3.1% of cats) although microscopic hematuria may be more common, hydronephrosis (0.4% dogs, 3.1% cats) and death (2.5% dogs and 3.1% cats).[171,176] Linear infarcts are commonly observed after renal biopsy in both dogs and cats.[171]

Renal fine needle aspirates are rarely rewarding in patients where there is a high index of suspicion for primary glomerular disease. However, for underlying inflammatory, primary or metastatic neoplastic disease (e.g., lymphoma), this may be a low-risk alternative to renal biopsy and is reported to provide a cytological diagnosis in 78% of canine renal lymphoma cases.[177]

Assessment of Hypercoagulability in Glomerular Disease

Hypoalbuminemia may be identified in patients with moderate to marked proteinuria and is a component of nephrotic syndrome along with hypercholesterolemia, proteinuria and either cavitary effusion or peripheral edema (see ch. 60). Traditionally the development of a hypercoagulable state in patients with glomerular disease has been attributed to the loss of **antithrombin,** which has a comparable molecular weight to albumin and can therefore be lost via the urine. However, the association between proteinuria and antithrombin concentrations is weak. **Thromboelastography** (TEG) provides a global assessment of coagulation status. Numerous review articles cover the principles of this diagnostic test.[178-180] Dogs with glomerular disease, including those with nephrotic syndrome, have been identified to be hypercoagulable on the basis of thromboelastography.[181,182] An early study suggested that dogs with glomerular disease and protein losing nephropathy had significantly lower antithrombin and significantly higher protein C than dogs with other systemic disease.[181] However, a more recent study evaluating 28 dogs with protein-losing nephropathy (UPC >2.0) showed that although dogs were hypercoagulable according to their TEG parameters, there was no association between TEG, UPC, antithrombin or serum albumin concentrations.[182] This study indicates that neither the magnitude of hypoalbuminemia, antithrombin concentrations nor magnitude of proteinuria can be used as a predictor of risk for thrombotic complications in dogs with glomerular disease or to guide anti-thrombotic therapy. In such patients, a comprehensive assessment of the coagulation system may be required.[182] For information on management of hypercoagulability in glomerular disease, see ch. 196, 197, and 325.[183]

Genetic Testing in Renal Disease

A number of breeds of dogs and cats are known to have genetic mutations that are causative for underlying renal disease (see ch. 328). For some of these conditions, genetic tests are available from commercial laboratories. To date, no hereditary glomerular conditions have been identified which benefit from immunosuppressive therapy and therefore performing an appropriate breed related genetic test might assist in precluding the requirement for renal biopsy. A genetic origin for several tubular disorders (e.g., cystinuria, hyperoxaluria, hyperuricosuria) has been identified and can now be tested for.[184-187] As the field of canine and feline genetics expands and new technologies become more widely available, our understanding of underlying genetic mutations as causes for renal conditions in both dogs and cats is likely to expand.[188]

Urinalysis

Urinalysis (see ch. 72) is an important component of assessing renal function, particularly in terms of urine

concentrating ability, glomerular and tubular function, and the presence of urinary tract infections, which in certain situations may ascend to affect the renal parenchyma and result in pyelonephritis. Biochemical evaluation of renal function should always be performed in conjunction with concurrent urinalysis.

Urine Concentrating Ability

Urine concentrating ability is to some extent species-specific, with, for example, the cat capable of achieving greater urine concentration than the dog. The majority of water is reabsorbed within the proximal tubules, loop of Henle, and early distal convoluted tubule (≈85%). The remainder is reabsorbed in the late distal tubule and collecting ducts under the control of antidiuretic hormone (ADH), otherwise referred to as arginine vasopressin (AVP) and which facilitates the insertion of aquaporin 2 water channels. Release of ADH is controlled both by plasma osmolarity and also by blood volume, giving the capacity to both actively concentrate and dilute urine. ADH driven water reabsorption is dependent on the medullary-concentrating gradient maintained by the countercurrent multiplier system.

Normal urine contains predominantly low molecular weight molecules (e.g., electrolytes and urea). **Urine osmolality** is the concentration of osmotically active molecules dissolved in urine being dependent only on the number of molecules and not related to their molecular size or weight and is reported as osmoles per kg (Osm/kg) (see ch. 73). Urine osmolality (U_{Osm}) is measured in laboratories using freezing depression point osmometers based on the principle that each mole of dissolved solute will depress freezing by 1.86 °C. The relationship between osmolality and specific gravity is considered linear[189] and therefore urine specific gravity measured by hand-held refractometer is more frequently used as an approximation to urine osmolality in clinical practice. The term **isosthenuria** is used to define USG between 1.008-1.015 (urine osmolality 300 mOsm/kg) and indicates that the urine has the same solute concentration as the glomerular filtrate and plasma. The term **hyposthenuria** is used to define USG <1.008 (U_{Osm} <300 mOsm/kg) indicating active tubular dilution whereas **hypersthenuria,** which is an infrequently used term, would imply USG >1.015 (U_{Osm} >300 mOsm/kg). Urine dipsticks are not a reliable methodology for assessment of USG.[190]

Urine specific gravity (USG) is typically evaluated by use of a hand-held refractometer and is defined as the ratio of the weight of a volume of liquid to the weight of an equal volume of distilled water. It is dependent on the number, size and weight of the particles in the urine.[191] Early studies suggest that feline urine has a higher refractive index than human or canine urine and that use of refractometers designed for human use would lead to factitiously high results.[191] This has led to the development of feline specific refractometers or, alternatively, the use of a **feline conversion factor** (0.846 × medical refractometer specific gravity) + 0.154.[191] However, more recent studies call into question this difference between species.[192-194] Studies evaluating both digital and optical analogue refractometers suggest that results are likely to be comparable both in dogs and cats.[194,195]

Other endogenous factors which may influence USG include severe proteinuria or glucosuria, which will result in slight overestimation of USG with every gram of protein per deciliter increasing USG by 0.003-0.005 and every gram of glucose per deciliter increasing USG by 0.004-0.005.[196] Exogenously administered substances that increase USG measurements include colloids, mannitol and iohexol.[197]

In patients with normal renal function, urine concentration is very variable. A patient with normal renal function that is dehydrated or has pre-renal azotemia is anticipated to have maximal urine concentration in order to preserve fluid volume and therefore a USG >1.030 in the dog and >1.035 in the cat.

A recent study showed that when USG was evaluated in 976 healthy cats of variable age from a first-opinion setting, 91% had USG >1.030 and 88% >1.035 on spot assessment.[198] Age has been reported to have an effect on USG with cats >9 years having an increased probability of USG <1.035 and an increased chance of identifying an underlying condition relating to reduced urine concentrating ability.[198,199] Kittens reportedly have urine concentrating ability comparable to adults from 8 weeks of age and puppies do from 4 weeks of age. Dietary moisture intake may affect urine concentrating ability.[200] Studies evaluating the effect of dietary moisture content on USG in cats have been variable with some supporting that feeding a wet diet may contribute to a lower USG[198] whilst others have shown no effect when comparing dry versus moist urinary diets.[201,202]

Water deprivation testing (WDT) is used as a test of tubular response to AVP in patients with polyuria and polydipsia where all differentials have been excluded apart from nephrogenic or central diabetes insipidus and psychogenic polydipsia (see ch. 296).[203] Any patient that is azotemic or has developed a pre-renal

azotemia in the face of inappropriately dilute urine (USG <1.030) has already in effect failed a WDT and should not have further water restriction.

Markers of Tubular Dysfunction/Damage

A number of markers can give information about apparent change or loss of tubular function and may be important in the evaluation of certain acute and chronic kidney diseases.

Glucosuria

Filtered glucose is almost completely reabsorbed within the proximal tubular cells via the SGLT2 (and to a lesser extent SGLT1) transporters and in health should not be identified in the urine of dogs or cats. Glucosuria is identified if the renal threshold and tubular maximum for glucose absorption (180 mg/dL; 10 mmol/L in the dog and 300 mg/dL; 16.6 mmol/L in the cat) is exceeded. Glucosuria is most commonly identified in patients demonstrating concurrent hyperglycemia (see ch. 61); however, primary renal glucosuria in the face of euglycemia indicates alteration in renal tubular function. Renal glucosuria has been identified either as a single or complex renal tubular disorder. In the latter, increased excretion of other molecules (e.g., amino acids, phosphate, bicarbonate and electrolytes) may occur and can be either inherited (e.g., Fanconi syndrome [see ch. 328]) or acquired (see ch. 322 and 326). Glucosuria can be identified using a colorimetric dipstick test based on a glucose oxidase enzymatic reaction. Certain antibiotics such as ciprofloxacin[204,205] when using the glucose oxidase reaction and penicillin and cephalosporins[205,206] when using a copper sulfate based reagent may give false positive results on a urine glucose dipstick test due to sugar reducing properties.

Fractional excretion (FE) of electrolytes is the fraction of the amount of a measured electrolyte that is filtered which is excreted into the urine (see ch. 73). Determination of FE usually requires collection of urine over a protracted period of time (≈24 hours) with the patient ideally placed in a metabolic cage or catheterized to ensure complete urine collection. However, this is largely impractical in the clinical setting and spot assessment FE of electrolytes is therefore more commonly used. Spot evaluation of FE can be calculated using the following formula:

$$\begin{aligned}\%\,\mathrm{FE} = &((\text{Urine concentration of E})\\ &\times(\text{Plasma concentration of creatinine})/\\ &(\text{urine concentration of creatinine})\\ &\times(\text{Plasma concentration of E}))\times 100\end{aligned}$$

Non-protein bound electrolytes are freely filtered at the glomerulus and are then reabsorbed within the tubules. For conserved solutes (e.g., amino acids and glucose) reabsorption within the proximal tubule is virtually complete (>99%) such that fractional excretion in health is <1%. However, for solutes such as sodium and potassium, approximately 2/3 of reabsorption occurs irrespective of body requirements (proximal and distal tubule and loop of Henle) with the remainder being either excreted or reabsorbed depending on homeostatic hormonal regulation (e.g., aldosterone). Similarly, calcium reabsorption (proximal and distal tubules) is tightly regulated by parathyroid hormone and phosphorus reabsorption (proximal and distal tubules) is controlled by the combination of parathyroid hormone and fibroblast growth factor 23/alpha-Klotho complex.[207]

Numerous exogenous and endogenous factors influence the FE of electrolytes, such as age, breed, food intake, dietary composition, exercise, ultrafiltration rate, the individual's solute and volume status, renal function and drug administration.[12, 208] Calculation of FE of electrolytes from a spot sample is at best a crude assessment of 24 hour urinary excretion of electrolytes in dogs and cats as a consequence of the inaccuracies of using creatinine as a marker of GFR, fluctuations in urine electrolyte concentrations due to dietary change, and circadian rhythms.[208-211] No clearly defined reference intervals exist for FE of electrolytes although values considered normal are reported.[208] FE of electrolytes is rarely used clinically in veterinary medicine

due to marked inter- and intra-patient variability (see ch. 73).

For patients where quantification of FE of electrolytes is being considered, it has been suggested that a standardized diet be fed for a minimum of a 1-week period to prevent the effect of dietary fluctuations and that the patient has been normally hydrated for several days.[12] FE of most electrolytes increases as GFR decreases, which limits the value of this test in clinical patients with renal dysfunction.[12,208] This may be the consequence of the compensatory response and hypertrophy of remaining nephrons allowing for enhanced reabsorption despite substantial functional renal mass reduction. Recently however, serial evaluation of FE of sodium has been reported as a potentially prognostic indicator of AKI outcome.[212]

Aminoaciduria occurs when amino acids, which are normally effectively and completely reabsorbed by the proximal tubule cells (>99%), are identified within the urine. This may occur due to excess circulating concentrations of a given amino acid leading to filtrate concentrations that exceed the tubular maximum for reabsorption, through an intrinsic defect in the tubular reabsorptive mechanism, or due to failure of intracellular processing or transport mechanisms on the basolateral surface of the proximal tubular cell. Aminoaciduria may be an isolated finding due to a defect in an individual transport protein, e.g., cystinuria, although other amino acids may be involved (lysine, glycine, ornithine and arginine) and hyperuricosuria, or may be part of a complex renal tubular disorder such as Fanconi's syndrome, which may be inherited (e.g., Basenji) or acquired (e.g., AKI) (see ch. 326). Urine amino acid profiling which may indicate a primary or secondary renal tubular disorder is currently available at the University of Pennsylvania (PennGen).

Acid-Base Evaluation and Urine pH

The kidney is intrinsically involved in acid-base homeostasis with the proximal tubule being responsible for absorption of both hydrogen ions and bicarbonate but the distal tubule being the important location for homeostatic regulation of hydrogen ion secretion and adjustment of urine pH.[207] Evaluation of acid-base status via blood gas analysis (see ch. 128) can be important in the management of patients with both CKD (see ch. 324) and AKI (see ch. 322) where metabolic acidosis may be identified. In addition, renal tubular acidosis is a rare group of disorders that lead to metabolic acidosis where evaluation of both acid-base status and urinary pH are fundamental to achieving a diagnosis (see ch. 326).

Urine pH in both dogs and cats is variable and can be influenced by a number of external and internal factors including diet, medication or underlying acid-base disorders. Urine pH can be assessed either by biochemical reagent dipstick testing or using a calibrated hand-held pH meter. Biochemical reagent dipsticks are routinely used for urine pH assessment in clinical practice although studies have shown that they are accurate to within only ±0.5 pH and therefore where accurate assessment of urine pH is required calibrated pH meters should be used.[213-215]

Markers of Tubular Injury

In recent years there has been considerable interest in the development of novel biomarkers of tubular injury that could be used for the early detection of AKI and/or CKD prior to the onset of overt azotemia. Such biomarkers would offer the opportunity to intervene clinically at an earlier time point and might also show prognostic potential. To date, the majority of these markers is used on an experimental or research basis and are not widely commercially available. Early studies evaluating nephrotoxins (e.g., gentamicin) focused on the role of **urinary enzymes** (e.g., N-acetyl-beta-d-glucosaminidase, gamma-glutamyl-transferase, lactate dehydrogenase, alkaline phosphatase, alanine aminopeptidase and the feline specific enzyme cauxin) which, when released into the urine from their brush border location, indicate regional tubular damage. More recently, studies have explored the use of **low molecular weight proteins** (LMW <35 kDa; e.g., retinol binding protein, $beta_2$-microglobulin, $alpha_1$-microglobulin). These are freely filtered at the glomerulus and reabsorbed via megalin and cubulin mediated endocytosis. Tubular damage reduces the capacity for this reabsorption and hence increased concentrations of LMW proteins are expected in the urine with primary tubular disease. Alternative markers include **tubular proteins** (e.g., neutrophil gelatinase-associated lipocalin [NGAL], kidney injury 1 [KIM1] and clusterin) or **inflammatory markers** (IL-8), which again inform regarding direct tubular damage or the inflammatory processes taking place during renal injury.[216,217] Of these, NGAL has received the most attention as a potential marker of AKI (see ch. 322). More recent studies evaluating CKD in cats have begun to explore urine excretion of **profibrotic markers** such as transforming growth factor-beta[218] and potential **markers of hypoxia** (e.g., vascular endothelial growth factor). For all urinary markers, it is important that the measured concentrations or enzymatic activities are reported in

association with urine creatinine concentrations or standardized urine specific gravity to account for urine volume.

Urinary enzymes are located both on the brush border and in intracellular locations within tubular cells. Being medium to high molecular weight proteins, typically >150 kDa, it is anticipated that enzyme activity identified in the urine is likely to be of renal origin. Knowledge of the location of urinary enzymes within the nephron and alteration in either urine enzyme concentration or activity could therefore be used to indicate either damage or an alteration in activity of cells from that region of the tubule. To date the urine enzymes that have received the most attention are gamma-glutamyl-transferase (GGT), N-acetyl-beta-d-glucosaminidase (NAG) and the feline specific enzyme cauxin, although other tubular enzymes have also been evaluated (e.g., lactate dehydrogenase, alkaline phosphatase and alanine aminopeptidase).[216,217]

Gamma-glutamyl-transferase is a proximal tubular enzyme located on the brush border. It has predominantly been investigated as a marker of acute tubular injury with studies demonstrating increase in urine GGT : creatinine index in experimental gentamicin toxicity studies prior to the onset of azotemia.[219,220] A more recent study has evaluated GGT in healthy, CKD, and AKI dogs and although GGT : creatinine index was significantly higher in dogs with AKI there was significant overlap between groups. Studies suggest that urine pH and also gender in dogs may influence GGT activity and due to inter-individual variability the GGT : creatinine index may be most useful where there is a known risk of inducing AKI (e.g., administration of nephrotoxic drug) and longitudinal monitoring with a rapid turn-around time is available.[221]

N-acetyl-beta-d-glucosaminidase is predominantly a proximal tubular enzyme but for which two isoenzymes exist; NAG-A which is located on the brush border and NAG-B which is an intracellular enzyme. In veterinary studies performed to date, total NAG activity has been assessed in relation to urine creatinine concentrations to give a total NAG index. However, it has been suggested that elevation in individual NAG isoenzyme may differentiate tubular cell damage from altered tubular cell activity (i.e., due to proteinuria) and protein processing by the proximal tubular cells. NAG index has been more extensively studied than other urinary enzymes due to superior stability in urine with storage and has been evaluated in both acute and chronic kidney disease.[221,222] Studies have indicated that NAG index may be significantly higher in dogs with X-linked hereditary nephritis prior to the onset of azotemia although not prior to the onset of proteinuria.[223] However, after the development of azotemia, urine NAG index plateaued, suggesting that subsequent alteration in renal function was not indicated by change in NAG index. Although NAG index was predictive of the development of azotemia in healthy geriatric cats (>9 years), it did not perform as well as other more traditional markers such as UPC.[224] Substantial overlap between healthy and CKD patients has been identified both in dogs and cats, and similar to GGT this inter-individual variability in spot assessment may limit the utility of NAG index as a marker of tubular injury in chronic disease.[222,225]

Cauxin is a feline specific carboxylesterase enzyme which has been localized to the proximal tubular cells involved in the production of the pheromone felinine.[226,227] Early studies suggested via immunohistochemistry that cauxin expression was reduced in cats with advancing CKD.[228] However, a study evaluating the relative concentration of urine cauxin to creatinine ratio in cats with variable renal function suggested no association with creatinine concentration as a marker of azotemia and only a mild association with proteinuria.[229]

Low molecular weight (LMW) proteins (<35 kDa) are freely filtered at the glomerulus and in health should be readily reabsorbed via megalin and cubulin mediated endocytosis within the proximal tubular cells. Tubular injury may result in reduced reabsorption such that increased concentrations of LMW proteins are identified within the urine. Several such proteins have been investigated including retinol binding protein (RBP), $beta_2$-microglobulin and $alpha_1$-microglobulin. Similar to urinary enzymes, it is important that urinary low molecular weight proteins are standardized to urine creatinine concentration in order to compensate for urine volume.

Retinol binding protein is a 21 kDa protein which in the unbound form is freely filtered at the glomerulus and, in health, efficiently and almost completely reabsorbed and catabolized by proximal tubular cells. RBP has been identified in the urine of both dogs and cats.[230,231] In dogs urinary RBP : creatinine ratios have been shown to be elevated with CKD with strong correlation with urea and creatinine.[225] Similar findings have been identified in dogs with X-linked hereditary nephritis where urinary RBP : creatinine ratio showed progressive increase prior to the onset of azotemia and also a continued significant increase with declining renal function.[223] In cats, urine RBP : creatinine ratio has been evaluated in CKD and also as a predictor of azotemia after treatment of hyperthyroidism.[232,233] However, high interindividual variability appears to limit its utility in this species, which may reflect poor specificity of the assay.

Beta$_2$-microglobulin (11.8 kDa) is a LMW protein expressed on all nucleated cells, freely filtered at the glomerulus and reabsorbed within the proximal tubular cells. Beta$_2$-microglobulin has been explored in dogs with X-linked hereditary nephritis. Urine beta$_2$-microglobulin : creatinine ratio was found to be an independent predictor of GFR, increasing prior to the onset of azotemia although not preceding the onset of proteinuria in these dogs. It was also noted to reach a plateau during the later stages of disease, suggesting it may be less useful in chronic disease and after the onset of azotemia in predicting change in renal function.[223] However, the utility of beta$_2$-microglobulin is limited due to poor thermostability and instability at acid pH values.

Proteins of renal origin, which may be released or upregulated and released into urine after tubular or glomerular damage, have also been investigated including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury 1 (KIM1) and clusterin.

Clusterin is a glycoprotein which is upregulated during renal damage although the location of injury leading to increased urine clusterin : creatinine ratio is nonspecific. To date one study has validated an ELISA for quantification of clusterin in canine urine and demonstrated that in dogs with leishmaniasis, urine clusterin : creatinine ratios increased with declining renal function,[234] and a further study has suggested potential in the detection of AKI.[235] To date no published studies have evaluated clusterin in cats.

Kidney injury molecule-1 is a type-1 cell membrane glycoprotein, which is expressed at low levels in the normal kidney. It is considered to be specific for the detection of proximal tubular cell damage in AKI. Expression of KIM1 is upregulated with ischemic or toxic renal injury with the ectodomain being shed into urine and demonstrating stability for subsequent identification and quantification.[236,237] To date, KIM1 has only been evaluated in cats where three expressed gene transcripts have been identified and immunohistochemistry localized expression to the proximal tubular cells. An immunoassay has been validated for urinary quantification of KIM1 and KIM1 was detectable in urine from cats with AKI but not those with CKD.[236] To date, no published studies have evaluated KIM1 in the dog.

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa protein expressed not only by neutrophils but also by epithelial cells and specifically the proximal tubular cells within the kidney. In human medicine, NGAL may exist as a monomer, dimer or complexed to matrix-metalloproteinase-9 (MMP-9). A recent study has identified these different forms of NGAL in canine urine.[238] A canine specific NGAL ELISA has been developed and validated.[223] Studies have demonstrated that urinary NGAL : creatinine ratio is increased in dogs with both naturally occurring and experimentally induced AKI.[239-241] Furthermore, two studies evaluating urinary NGAL : creatinine have demonstrated that the ratio is significantly higher in dogs with AKI than in CKD or control dogs, although there is overlap between these groups.[241,242] In dogs with X-linked hereditary nephritis, similar to previous biomarkers, urine NGAL : creatinine ratio was significantly increased prior to the onset of azotemia in affected dogs.[223] However, given the expression of NGAL by neutrophils, concern has been raised about the potential impact of urinary tract inflammation and infection on urine NGAL concentrations. Studies have documented that urinary NGAL : creatinine ratio in dogs with urinary tract infections is significantly higher than control dogs and dogs where there was suspicion for a urinary tract infection but culture proved negative. However, urinary NGAL:creatinine ratios in dogs with UTI were significantly lower than in dogs with either CKD or AKI.[238,241,243] There has also been recent interest in evaluation of serum/plasma NGAL concentrations. Studies have shown that serum/plasma NGAL concentration is higher in dogs with CKD than controls, increases with advancing stage of CKD and may be significantly higher in patients with AKI than CKD.[242,244] Further work is needed to determine the effect of concurrent disease on both urine and plasma/serum NGAL and whether differentiation of monomer, dimer or complexed NGAL offers any advantage over total NGAL assessment. To date, poor cross-reactivity between currently available human and canine antibodies with feline NGAL has precluded assessment of this biomarker in cats.

Inflammatory markers may also provide information about both acute and chronic kidney injury with the potential to provide information about the pro-inflammatory state of the kidney (e.g., IL-18), renal hypoxia (e.g., vascular endothelial growth factor [VEGF]) and a pro-fibrotic environment (e.g., transforming growth factor-beta [TGF-beta] and transglutaminase).[245-248] However, to date, only preliminary research orientated studies are available evaluating these molecules in either the dog or cat and further validation is required before any clinical utility can be considered.

Indicators of Renal Disease on Urinalysis

Routine urinalysis consists of evaluation of specific gravity for assessment of urine concentrating ability (see above), biochemical reagent dipstick evaluation (see above for discussion regarding pH, glucosuria and protein evaluation), microscopic sediment examination and urine culture. Collection of urine for analysis is considered in ch. 105. In relation to renal disease specifically, urinalysis is beneficial for detection of reduced urine concentrating ability (see USG above), urinary tract infections and secondary pyelonephritis (see ch. 327), identification of hematuria, which may be renal in origin, indicators of AKI (e.g., cast formation or calcium oxalate monohydrate crystals in patients with ethylene glycol toxicosis) and may give an indication regarding tubular dysfunction either through alteration in pH, presence of glucosuria and proteinuria or through the presence of certain types of crystals on sediment examination (e.g., cystinuria). Urinalysis should ideally always be performed on a fresh sample evaluated at room temperature. Consideration should be given to the methodology used for urine collection when interpreting laboratory findings. The urine should initially be assessed in terms of gross appearance (see ch. 77) including color, odor and turbidity. Readers are directed to numerous comprehensive reviews on performing complete urinalysis and pre-/post-analytical factors that may influence results.[249-251]

Hematuria

Excessive numbers of red blood cells (RBC) in the urine is referred to as hematuria and can be either microscopic (detectable only on dipstick or microscopic examination) or macroscopic (grossly visible). There are numerous potential causes for hematuria originating from the kidney, although lower urinary tract (e.g., urinary tract infection) and systemic causes (e.g., coagulopathy) are more commonly identified and all must be differentiated from hematuria occurring as a consequence of disease occurring in the genital tract (see ch. 47). Low levels of RBC can be identified in normal urine from the dog and cat, with values typically being <5 RBC/hpf on free catch. However, increased numbers may be identified in patients where urine is collected either by catheterization or cystocentesis (<20 RBC/hpf). Occasionally, erythrocyte casts may form and be identified in the urine. When identified, this implies a renal origin of hemorrhage (e.g., idiopathic renal hematuria).

Pyuria

Pyuria refers to the presence of increased white blood cells (WBC) in urine (Figure 321-5) and is most likely to be identified in patients with urinary tract inflammation and infection (see ch. 350) or bacterial infection that has ascended to the kidney resulting in pyelonephritis (see ch. 327). However, the presence of pyuria alone cannot be used to differentiate whether the infection is localized to the lower or upper urinary tract unless cellular casts composed of white blood cells can be identified (Figure 321-6) indicating renal involvement, or the sample has been obtained directly from the renal pelvis by performing pyelocentesis.

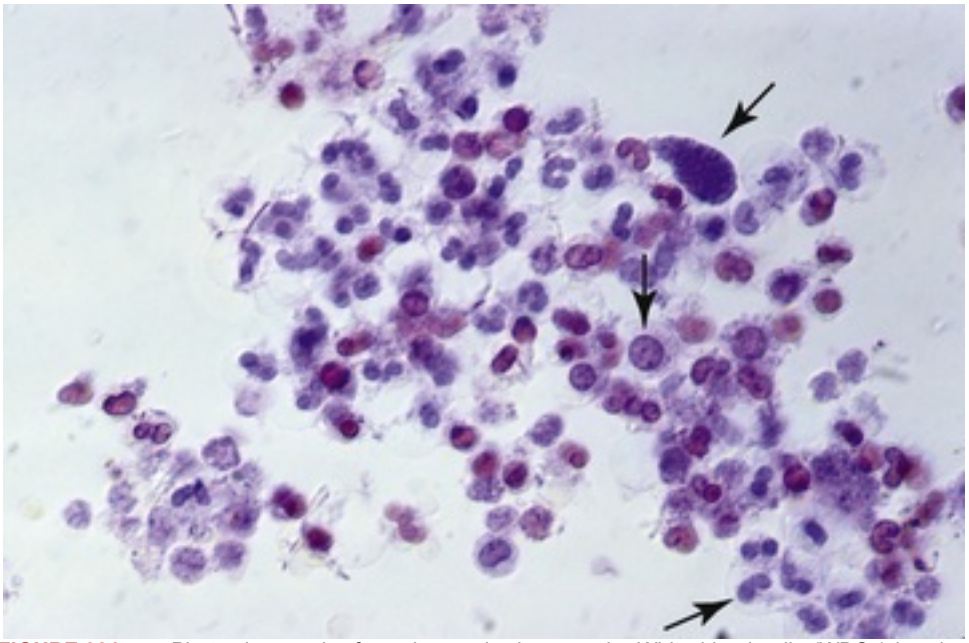


FIGURE 321-5 Photomicrograph of an abnormal urine sample. White blood cells (WBCs) in urine

are subject to degenerative changes that may complicate their identification. They may shrink in concentrated urine or swell in dilute urine. Clumps of WBCs are often associated with infection. Occasional transitional epithelial cells are present in this field (top two arrows) and a neutrophil with a polymorphonuclear nucleus and swollen cytoplasm is also seen (bottom arrow).

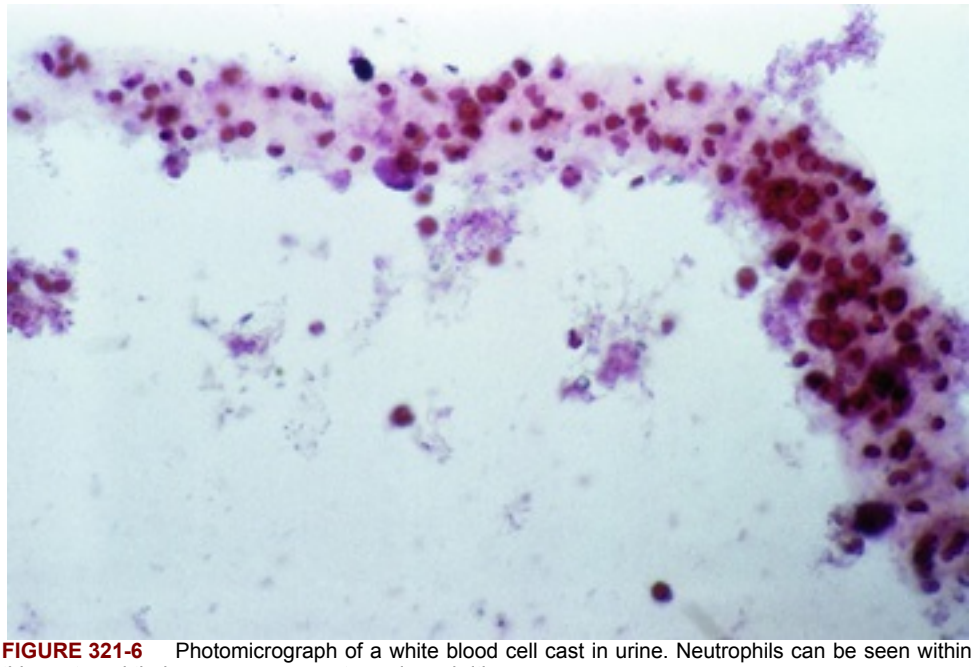


FIGURE 321-6 Photomicrograph of a white blood cell cast in urine. Neutrophils can be seen within this cast, and their presence suggests pyelonephritis.

The leukocyte esterase pad contains indoxyl which is released by esterases from either intact or lysed leukocytes and reacts with diazonium salt to give a blue color after oxidization. This reaction has been shown to be specific for pyuria in canine urine but has a low sensitivity.[252] In the cat, the leukocyte esterase pad is modestly sensitive but nonspecific, likely as a consequence of urinary esterase enzymes.[253] On microscopic sediment examination, the total number of white cells identified is usually low (<3 WBC/hpf cystocentesis, <5 WBC/hpf catheterized, <8 WBC/hpf free catch). Increased WBC count within urine may also be present due to hematuria and the degree of blood contamination and peripheral white cell count may therefore need to be taken into consideration, particularly if gross hematuria is present. The potential for contamination from the genital tract must also be considered depending on the method used for urine collection.

Epithelial Cells

Both squamous and transitional epithelial cells may be identified in urine sediment and low numbers of such cells can be considered normal. Squamous epithelial cells (Figure 321-7) may be noted in higher numbers in both voided and catheterized samples and are of limited clinical significance in relation to renal disease as they are likely to reflect contamination from the urethra or vagina. Transitional epithelial cells are derived from urothelium and may originate from the renal pelvis to the urethra and therefore could reflect damage at the level of the kidney (Figure 321-8). They are variable-sized cells but are typically smaller with tapered ends (caudate cells) when originating from the renal pelvis (Figure 321-9). However, a definitive renal origin can only be determined if epithelial cells form epithelial cellular casts (Figure 321-10) confirming a tubular origin.

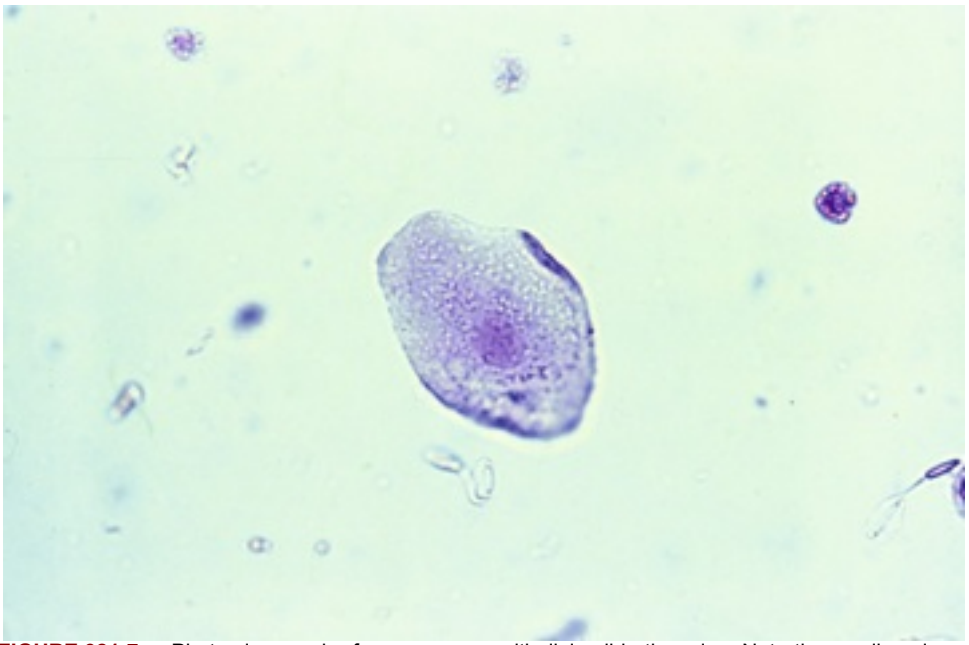


FIGURE 321-7 Photomicrograph of a squamous epithelial cell in the urine. Note the small nucleus, irregular cell shape, and folding of the cytoplasmic margin in some areas.

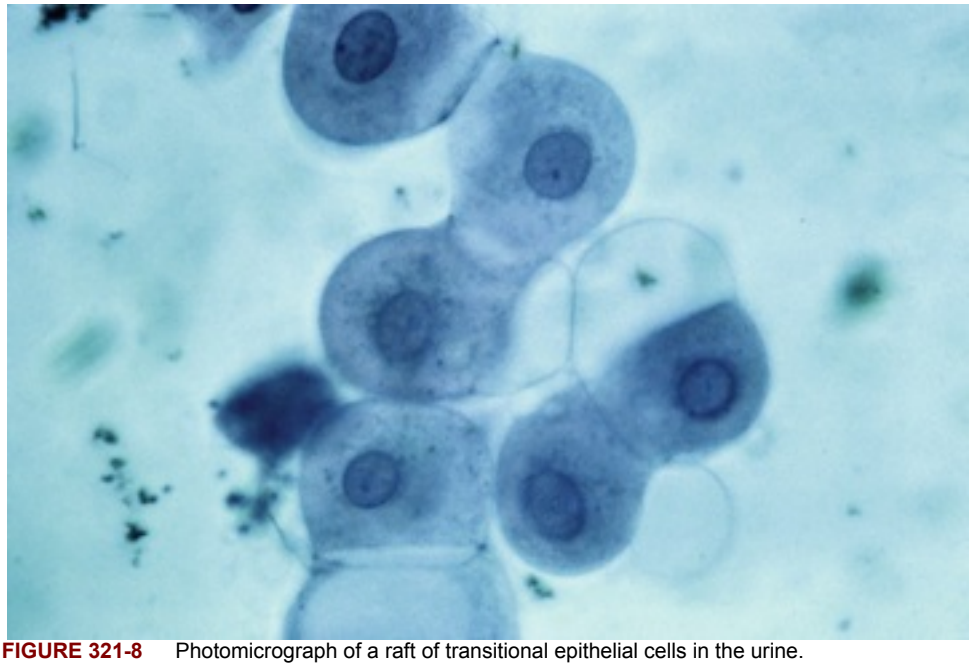


FIGURE 321-8 Photomicrograph of a raft of transitional epithelial cells in the urine.

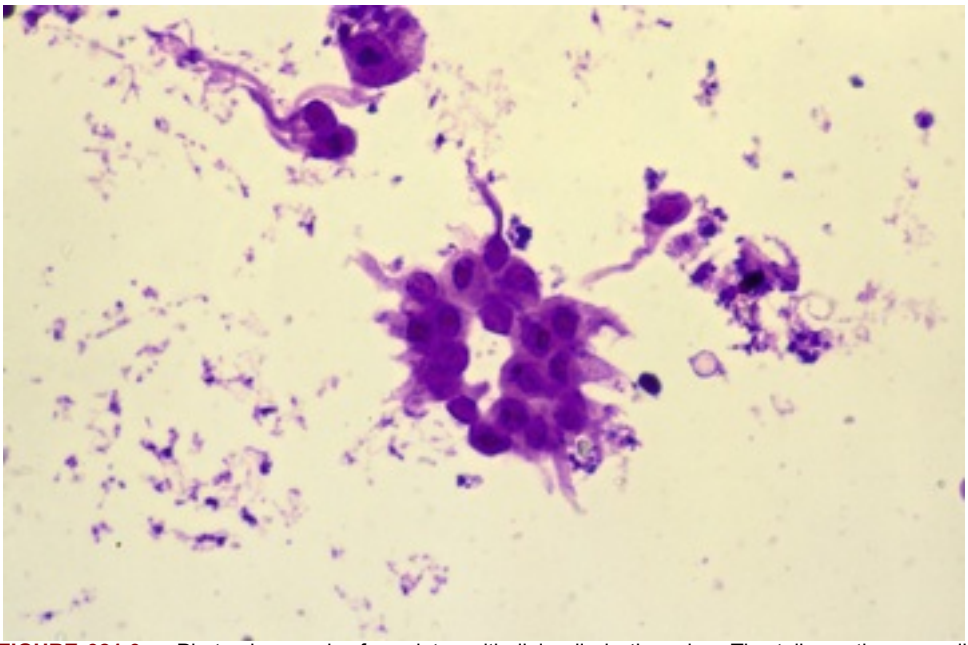


FIGURE 321-9 Photomicrograph of caudate epithelial cells in the urine. The tails on these small epithelial cells suggest that they originated in the renal pelvis.

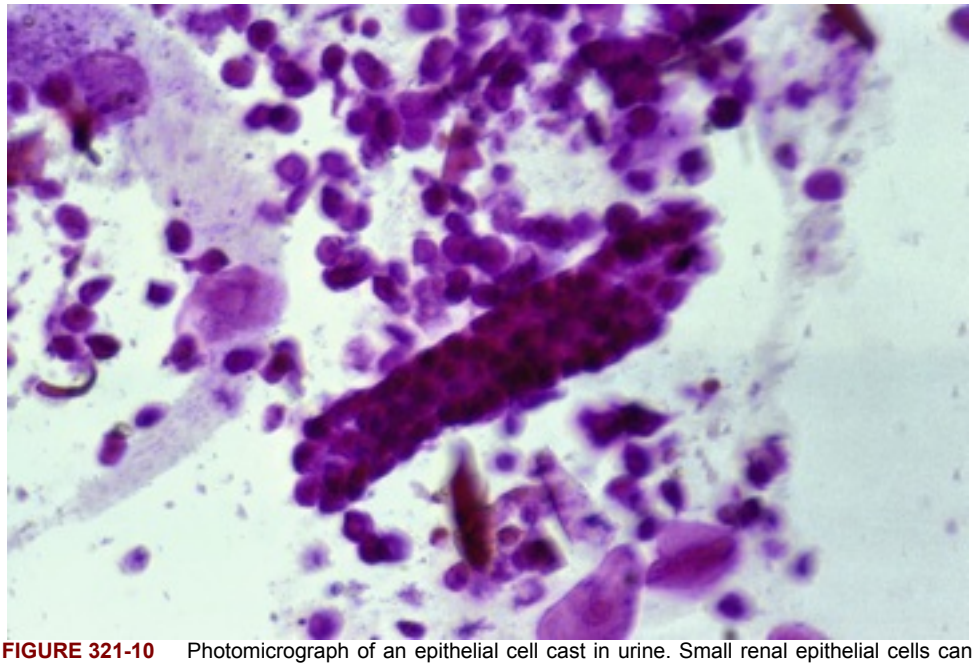


FIGURE 321-10 Photomicrograph of an epithelial cell cast in urine. Small renal epithelial cells can be identified in this cast.

Bacteriuria

Traditionally it has been considered that urine within the bladder is a sterile environment whilst the distal urethra and genital tract may harbor bacteria. However, this is not necessarily the case and subclinical bacteriuria, may occur. Subclinical bacteriuria refers to the identification of bacteria in urine by positive bacterial culture from a cystocentesis sample in the absence of either clinical evidence of a urinary tract infection.[254,255] The prevalence of subclinical bacteriuria in dogs and cats is low in healthy individuals (2-9%)[256-259] but may be higher (up to 30%) in patients with concurrent disease (e.g., hyperthyroidism, diabetes

mellitus and chronic kidney disease).[260-262] Clinicians should therefore consider carefully the method used for sample collection (i.e., cystocentesis, catheterization, voided), concurrent urinalysis findings (e.g., presence of an active sediment), quantitative culture results (expressed in colony forming units/mL urine), as well as a patient's clinical signs before diagnosing a urinary tract infection and administering antimicrobial therapy.[255] Further information regarding the diagnosis and management of lower urinary tract infections and pyelonephritis is provided in ch. 330 and 327, respectively.[263-268]

Crystalluria

In the context of renal disease, crystalluria may provide information about alteration in tubular function. The presence of crystalluria in canine and feline urine is dependent on urine pH, temperature, and length of time between collection and examination and the concentration of solutes that may form crystals. Crystalluria may be identified in the absence of urolithiasis and certain types of crystalluria (struvite, amorphous phosphate, calcium oxalate) may be a normal phenomenon in both dogs and cats. *In vitro* crystalluria formation has been shown to occur in approximately 30% of samples and is more likely to occur with prolonged storage (24 hr >6 h), with refrigeration increasing both the number and size of crystals identified.[269] Equally, urolithiasis may be detected without any evident crystalluria (see ch. 331, 332 and 334).[250]

Cylindruria (Cast Formation)

Casts can be identified in urine sediment examinations as elongated cylindrical structures and the presence of casts immediately implies a renal origin of damage as they are typically formed within the ascending limb of the loop of Henle and the collecting duct where tubular flow rates are slowest. The presence of casts within urine is referred to as cylindruria. Rare hyaline or granular casts may be normal in dogs and cats but the presence of higher numbers or cellular casts is always abnormal and implies tubular renal damage. Casts can be classified as hyaline, granular, waxy, fatty, cellular (epithelial, white blood cell, red blood cell), may contain crystals and/or microorganisms or can be mixed in origin.

Hyaline casts are composed entirely of proteinaceous material (mucoprotein, Tamm-Horsfall protein/uromodulin, albumin) and have a colorless cylindrical appearance (Figure 321-11). Low numbers may be identified in individuals after extreme exercise or with fever but they may be identified more commonly in the urine of patients with marked proteinuria. However, they can be missed if there is a delay in sediment examination being performed or in alkaline or dilute urine due to dissolution. If epithelial cells become entrapped within the mucoprotein then these are referred to as ***epithelial casts*** (see Figure 321-10) where cells are clearly visible and imply the presence of direct tubular cellular damage (e.g., with gentamicin toxicosis). **Granular casts** (Figures 321-12 and 321-13) are identified where there has been partial degradation of the cellular components of a cast and are typically indicative of either an ischemic or nephrotoxic renal tubular insult. **Waxy casts** (Figure 321-14) refer to the situation where complete cellular degradation has occurred leaving a cast that has a smooth, waxy texture. Waxy casts form during protracted periods of tubular stasis, are relatively stable and are described often as convoluted with blunt ends. **Fatty casts** are rarely identified but when present can imply a disorder in lipid metabolism (e.g., diabetes mellitus or nephrotic syndrome). **Erythrocyte casts** indicate marked renal hemorrhage (e.g., post-renal biopsy or idiopathic renal hematuria), whereas **white blood cell casts** (see Figure 321-6) can be identified with marked renal inflammation (e.g., pyelonephritis) or with acute tubular necrosis.

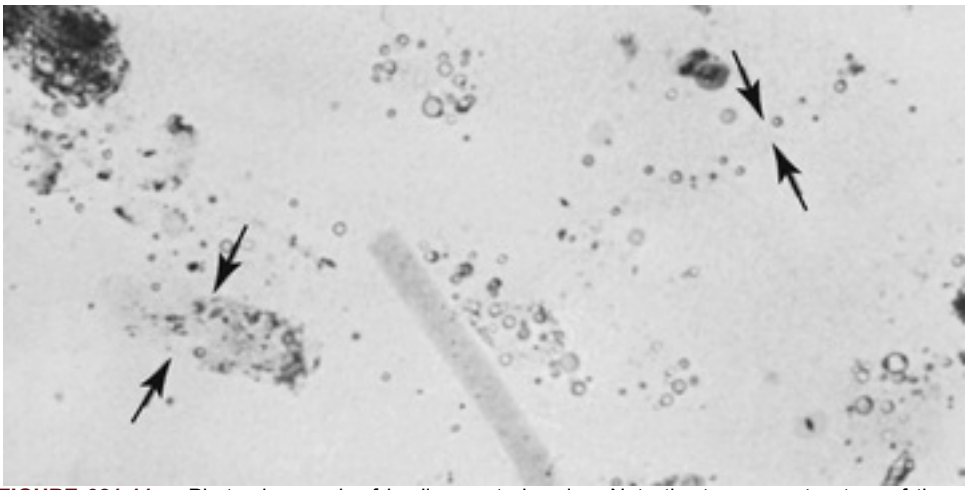


FIGURE 321-11 Photomicrograph of hyaline casts in urine. Note the transparent nature of these casts (between arrows). The casts are easily missed because their optical density is very low, necessitating low illumination for optical visualization. The darker cast in the center of the field is a waxy cast. Many lipid droplets are present in the background.

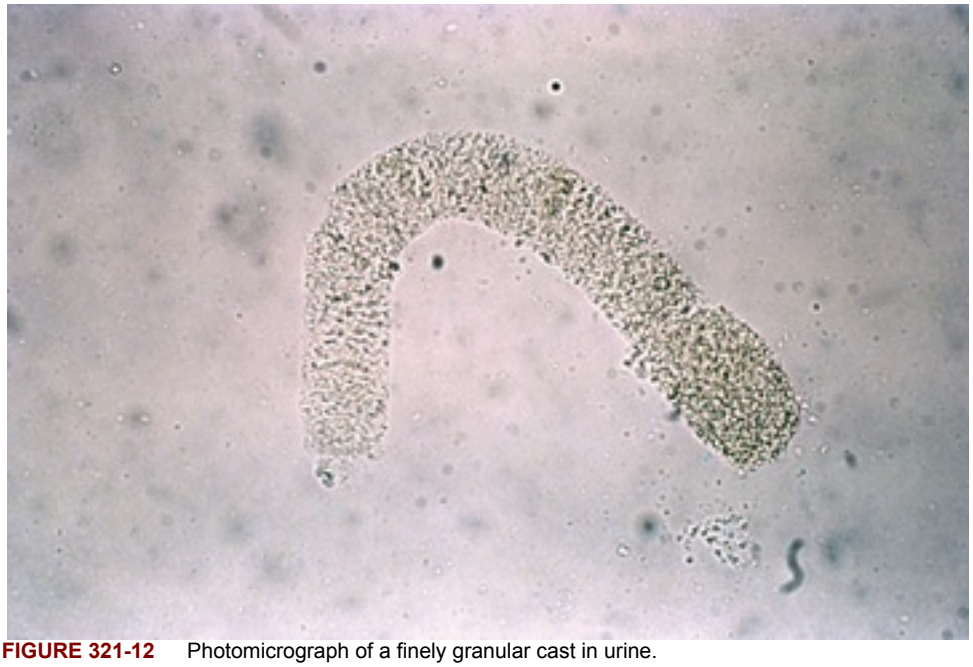


FIGURE 321-12 Photomicrograph of a finely granular cast in urine.

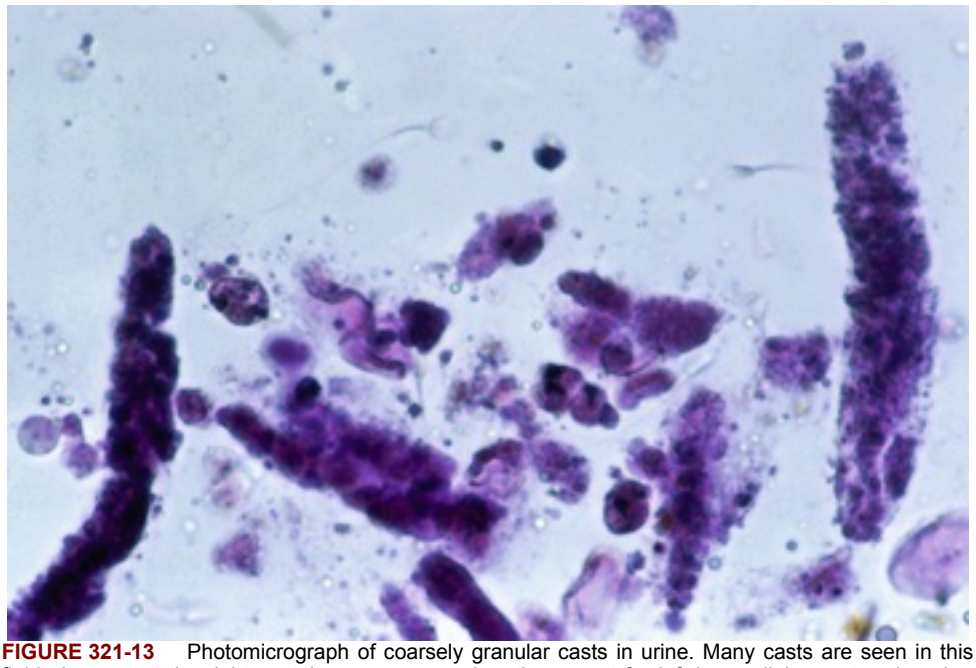


FIGURE 321-13 Photomicrograph of coarsely granular casts in urine. Many casts are seen in this field; the cast at the right contains coarse granules, the one at far left is a cellular cast undergoing degeneration.

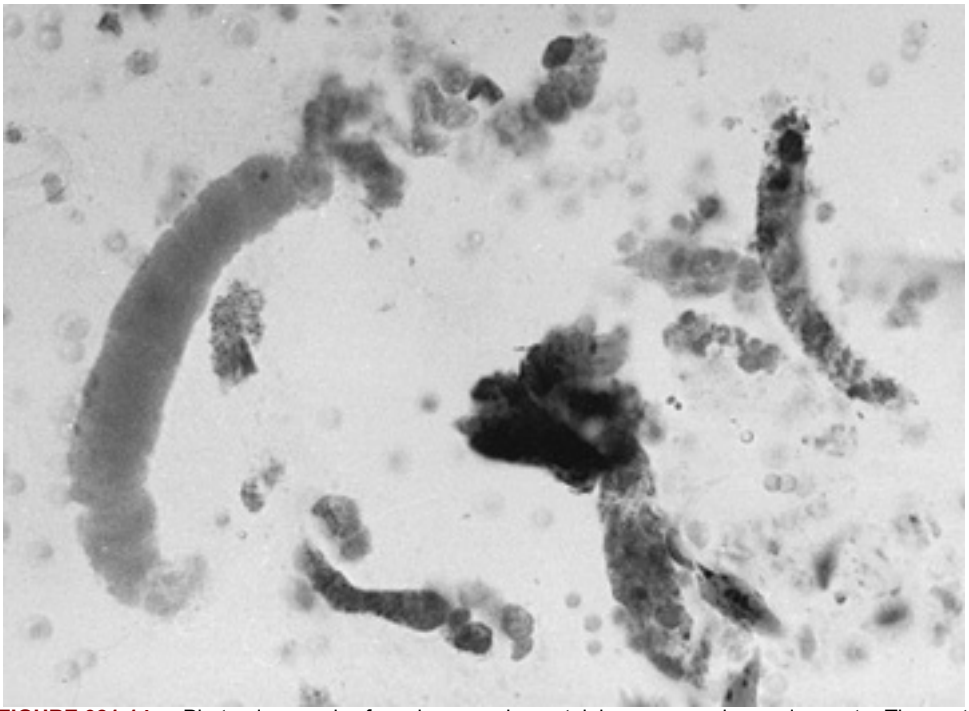


FIGURE 321-14 Photomicrograph of a urine sample containing waxy and granular casts. The cast at the left is waxy, whereas the others are granular. Note that the waxy cast is translucent, whereas hyaline casts are transparent. Waxy casts are brittle and often have cracks or sharply broken ends.

Bilirubinuria

See ch. 53.

Ketonuria

See ch. 142.

Parasites

Rarely, parasitic ova from *Stephanurus dentatus*, *Capillaria plica* (Figure 321-15), *Capillaria felis*, and *Dioctophyma renale* may be identified in urine. Microfilariae of *Dirofilaria immitis* may rarely be observed in canine urine sediment.[250]

FIGURE 321-15 Egg from *Capillaria plica* identified in the urine of a dog presenting with clinical signs of pollakiuria. (Reproduced by kind permission of Alice Hughes.)

Diagnostic Imaging

Diagnostic imaging often forms an integral part of the diagnostic workup of the dog or cat with renal disease. Multiple imaging modalities are available, each with inherent advantages and limitations, which should be considered when devising a diagnostic plan for an individual patient. Details of technique and normal imaging findings are not described in depth; readers are referred to diagnostic imaging texts and appropriate reviews for further information.[270-275]

Radiology and Computed Tomography (CT)

Plain radiographs can be used to provide information about renal size. To account for variation according to body weight, the length of the kidney is typically evaluated as a ratio to the length of the second lumbar vertebrae on a ventrodorsal view; the reference values for the ratio that are most often quoted are 2.5-3.5 for the dog,[276] and 2.4-3.0 for the cat,[277] however, numerous studies have found that the renal size in normal animals may extend beyond these limits so these measurements should be interpreted cautiously.[278,279] Renal volume can be accurately estimated from CT scans using the voxel count method.[280]

Radiographs also provide some information about renal contour. However, ultrasonography and advanced imaging techniques are now usually used in preference to radiography for this assessment, due to the additional information these techniques provide regarding the internal renal architecture. Renal and ureteric calculi are often radiopaque and consequently these may be visible on abdominal radiographs. However, even uroliths of mineral composition that are typically radiopaque (calcium oxalate, struvite and calcium phosphate) may not be visible if the stones are very small, a particular problem with feline ureteral stones (see

ch. 329). Dystrophic mineralization and nephrocalcinosis are sometimes visible radiographically if the changes are extensive but are more often detected with ultrasound.

Excretory urography (intravenous urography) may be performed to provide additional information about the renal collecting system (renal pelvis, ureters, ureterovesicular junction), such as in the work-up of a patient with suspected urinary tract obstruction, rupture or urinary incontinence (see ch. 329). Although excretory urography may also provide information regarding renal number, size, contour and internal architecture, its use has largely been superseded by ultrasonography and other imaging modalities and is rarely used for this primary purpose.

CT imaging of the kidneys may be selected in preference to other imaging modalities when the focus of interest is the renal pelvis and ureter (usually due to concern for ureteral obstruction or ectopia)[281,282] or when a mass is present in, or close to, the kidney.[283-287] The triphasic patterns of contrast uptake and excretion in dogs undergoing CT imaging have been described,[288] as have techniques for CT-angiography for the characterization of vascular anatomy prior to renal donation for transplant.[289,290]

Ultrasonography

Ultrasonography is a useful diagnostic imaging modality in the investigation of kidney disease as it can provide important anatomical information concerning the renal size, shape and internal architecture. It should also be recognized, however, that the appearance of the kidneys can be completely normal, even when significant renal disease is present.

Renal dimensions in the dog are correlated with body weight, although it is actually renal volume that is linearly related to body weight and the relation with renal length (which is what is most often determined clinically) departs from linearity in patients weighing less than 10 kg.[291] Methods for indexing renal length to the aortic diameter,[292] or to the length of the body of L5,[293] have been proposed as alternative methods for evaluating renal size but are not in widespread use. Subjective assessment of renal size is common, but given that the overall variability in renal size is enormous, the validity of this approach seems doubtful. Normal renal size in cats is typically considered to be between 3.0 and 4.5 cm,[294] although it may be greater in male intact cats,[295] and recent studies suggest that renal lengths of up to 5.0 cm are common, even in neutered animals.[296-298] Diffuse renal enlargement with relatively normal internal renal architecture may occur due to compensatory hypertrophy, AKI of various causes, amyloidosis, lymphoma, portosystemic shunts, and acromegaly.[271,299-302] Small kidneys are found with congenital renal hypoplasia or dysplasia, chronic end-stage renal disease of many etiologies, and as a sequela of chronic ureteral obstruction.[271,303-307]

Kidneys are usually less echogenic than the liver and spleen, but their echogenicity may vary with the frequency of the transducer being used.[308] In addition, fat vacuoles in the renal tubular epithelium are thought to affect the echogenicity of feline kidneys, with the result that renal cortical tissue in healthy cats may be isoechoic or hyperechoic to the adjacent hepatic parenchyma.[309] Diffuse increase in cortical echogenicity is a very nonspecific indicator of renal disease, which has been reported in association with glomerulonephritis, pyelonephritis, leptospirosis, acute tubular necrosis, end-stage renal disease, feline infectious peritonitis, nephrocalcinosis, renal lymphoma and other tumors, and ethylene glycol toxicosis.[300,303,310-316] In ethylene glycol toxicosis, the increase in echogenicity is often dramatic, and may suggest the diagnosis, but for the other disorders, the increase in echogenicity is usually non-discriminatory.[275] Changes in echogenicity have been found to be only weakly correlated with histological findings.[317] Increased renal echogenicity is often observed in association with a lack of corticomedullary definition, which is another very nonspecific finding commonly associated with CKD, whatever the underlying etiology. In a study of young dogs with renal dysplasia, loss of corticomedullary definition and increased echogenicity were found to mirror the severity of the renal histopathologic changes, even in the absence of azotemia.[318]

Focal lesions are the easiest to identify with renal ultrasonography. Cystic lesions have round to oval contour, echo-free contents, thin walls and show strong distal acoustic enhancement. Single, simple cysts are usually incidental findings. Multiple small cyst-like lesions may be seen with end-stage kidney disease; if these are due to glomerulocystic lesions they may be confined to the renal cortex,[319] and certain familial diseases may result in cystic lesions at the corticomedullary junction specifically,[320,321] but otherwise cysts may be present in both cortex and medulla. Autosomal dominant polycystic kidney disease (PKD) is commonly found in Persian and related breeds,[322-324] and occasionally in dogs[325-327] resulting in multiple,

variably sized cysts throughout the cortex and medulla (see ch. 328). If cystic lesions have thick or irregular walls, internal septations, or if the contents are not completely anechoic, then other disorders, such as hematomas, abscesses and tumors should be considered in the differential diagnosis.[271,275,286,328-331]

Solid renal masses are commonly neoplastic and may be hypoechoic, isoechoic or hyperechoic to the surrounding renal parenchyma, or may have a mixed pattern.[273,274,300,330,332] The appearance of these lesions is not characteristic of the tumor type and so aspirate or biopsy is required for differentiation. Granulomas, or calcified hematomas or abscesses, are potential differential diagnoses for this type of lesion, but are much less common than tumors. An acute renal infarct may initially appear isoechoic or hypoechoic and could be confused with a mass lesion, but more typically these are diagnosed once they are chronic, resulting in hyperechoic, wedge-shaped lesions that are widest toward the outer surface of the kidney.[273-275]

Fluid surrounding the kidney can be subcapsular or peri-renal and this may be difficult to differentiate. Small volumes of fluid may be accumulations of urine, blood, transudate or exudate and may be seen with urine leakage, AKI, ureteral obstruction, renal abscessation, hemorrhage or neoplasia.[274,275,313,333,334] Presence of a large volume of anechoic fluid is likely to represent a perinephric pseudocyst; these are more common in cats than dogs, usually found in association with CKD, and may be unilateral or bilateral.[335,336] Hypoechoic subcapsular thickening mimicking fluid accumulation is a relatively common appearance of renal lymphoma in cats.[337] Demonstrating blood flow within the subcapsular region using Doppler shows this is cellular accumulation, not fluid.

Sometimes a distinct hyperechoic line is present parallel to the corticomedullary junction: the so-called medullary rim sign. This finding is considered to be a normal variant in cats.[309] Although when first reported this finding was associated with renal disease in dogs,[338-340] it is also considered by many to be a normal variant, particularly when found in the absence of other signs of disease.[341] More recently it has been suggested that the outer medulla may often be relatively hyperechoic in dogs, particularly those of small breeds, and this may be confused with a true medullary rim sign (which is not located directly adjacent to the renal cortex but slightly distanced from it, within the medulla).[342] In addition, a diffuse band of hyperechoic tissue within the inner medulla has been reported in some dogs with acute leptospirosis[313] (Figure 321-16).

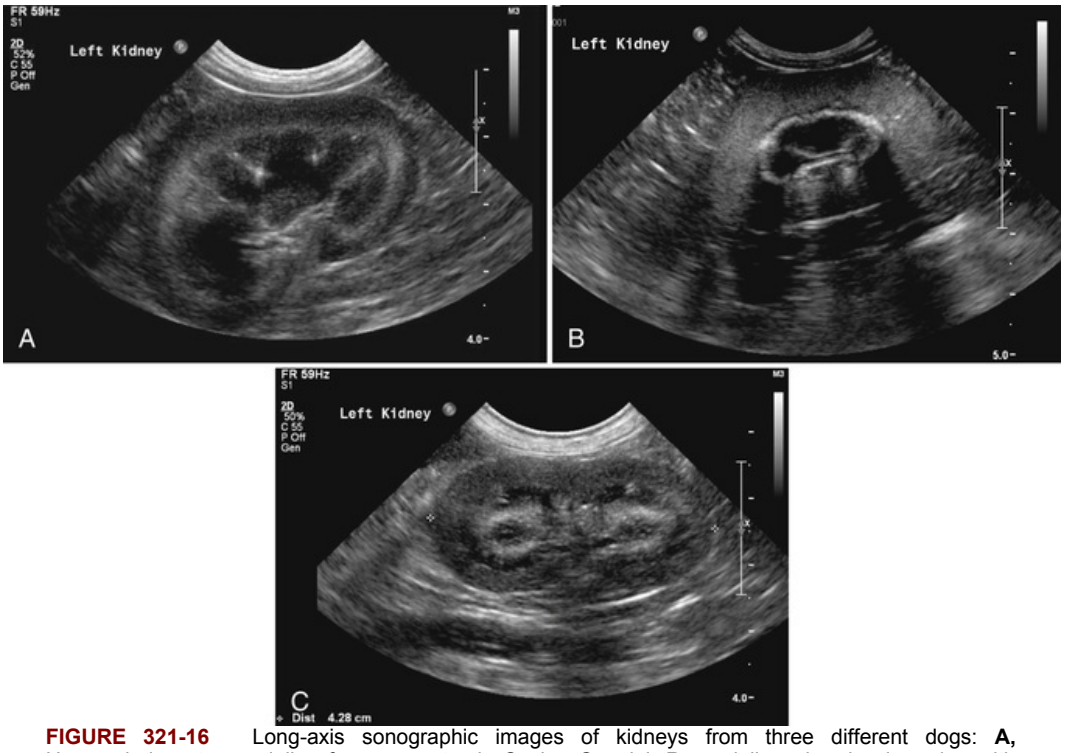


FIGURE 321-16 Long-axis sonographic images of kidneys from three different dogs: **A,** Hyperechoic outer medulla of a non-azotemic Cocker Spaniel; **B,** medullary rim sign in a dog with ethylene glycol poisoning; and **C,** medullary band sign in the inner medulla of a dog with AKI due to leptospirosis. (All images are reproduced from Hart DV, Winter MD, Conway J, et al: Ultrasound appearance of the outer medulla in dogs without renal dysfunction. *Vet Radiol Ultrasound* 54:652-658, 2013.)

In normal dogs and cats, urine cannot be visualized within the renal pelvis; however, current high-resolution ultrasound equipment allows detection of mild pyelectasia during diuresis.[343,344] This may be asymmetric. The differential diagnosis for renal pelvic dilation therefore includes all polyuric renal diseases, as well as obstructive lesions and pyelonephritis.[312,344,345] Sonographic changes are not always present in patients with pyelonephritis; however, changes that have been reported, in addition to pyelectasia, include increased echogenicity of the medulla and/or renal cortex, and hyperechogenicity of the mucosal lining of the renal pelvis.[271,275,312] When the reason for pelvic dilatation is uncertain, ultrasound-guided percutaneous antegrade renal pyelography may be used to definitively identify and characterize ureteral obstruction (see ch. 329).[346,347]

Doppler Assessment of Renal Blood Flow Indices

Pulsed-wave Doppler examination of blood flow in the interlobar or arcuate arteries can be performed as an aid to the detection of increased vascular resistance that may occur due to renal disease or ureteral obstruction. A unitless variable, the resistive index (RI), is most commonly used to quantify this. This is calculated by subtracting the end diastolic velocity from the peak systolic velocity and dividing the result by the peak systolic velocity. Increases in vascular resistance cause an increase in RI because the effect on blood flow in diastole is greater than the effect on blood flow during systole.

In general a value of greater than 0.70 (or sometimes 0.71 in cats, 0.73 in dogs) has been considered to be abnormal in clinical studies.[275,296,348-353] Intrarenal RI is increased in some, but not all, dogs and cats with renal disease. In humans, glomerular disease is thought to be less likely to result in increases in RI, and this seems to also be true in dogs and cats.[354,355] In AKI swelling of the interstitial tissues may increase resistance to renal blood flow. Increased RI has been documented in some dogs and cats with azotemic-AKI, and may decrease with recovery of the patient.[354,356,357] Sensitivity of RI for detection of AKI may depend on the nature of the injury.[349] RI may also increase in some dogs and cats with CKD.[354,355,357,358]

RI has been proposed as an aid in differentiating obstructive from non-obstructive renal disease.[354,359] Obstruction typically causes an increase in RI in the affected kidney but varies with the completeness and chronicity of the obstruction. Sensitivity of the test can be increased by not only considering the absolute value for RI but also comparing measurements from obstructive and non-obstructive kidneys.[360,361] Inducing diuresis may accentuate this difference, improving the sensitivity of RI for detection of obstruction, but results with this technique have been inconsistent.[360-362] RI has been proposed as a means to detect acute allograft rejection[356]; however, it has not been found to be clinically useful in cats following renal transplant.[363]

In clinical practice, there are many limitations to the interpretation of Doppler blood flow indices. Sedation and anesthesia have been found to have variable effect on RI,[348,350,364,365] and it is also increased by a variety of non-renal disorders including hepatic disease,[366] hyperadrenocorticism, diabetes mellitus,[367] anemia,[368] mitral valve disease[369] and babesiosis.[370]

Contrast-Enhanced Ultrasound

The assessment of renal perfusion potentially can be enhanced by use of ultrasound contrast agents; these are inert microbubbles, administered as intravenous boluses, that are small enough to pass through the microcirculation and transiently enhance the echogenicity of blood. Enhancement of echogenicity of the cortex is more marked, and occurs sooner, than enhancement of the medulla.[371] The risk of renal injury with use of these contrast agents is minimal.[372] Perfusion patterns in the kidneys of normal dogs[373-375] and cats[371,376] have been described.

In humans, contrast-enhanced ultrasound has been used to detect a wide range of renal conditions. It has particular indications for detection of parenchymal lesions in acute pyelonephritis,[377] evaluation of renal allografts[378] and in the differentiation of tumors from benign anatomical variants and cystic lesions.[379,380] In veterinary patients, the use of contrast-enhanced ultrasound to image focal renal lesions[330] and to diagnose renal hemorrhage in a case of renal rupture[381] has been described. It has also been employed in experimental canine studies demonstrating its potential as a noninvasive tool for the detection of conditions where renal perfusion may be altered, either focally or globally.[382,383]

Renal Scintigraphy

The radioisotope most frequently employed in dogs and cats is ^{99m}Tc-DTPA, which can be used in the estimation of GFR as described above. Injection of furosemide immediately after the initial scan can provide additional information regarding the patency of the ureters because ^{99m}Tc-DTPA is rapidly cleared from the kidneys by the diuretic if no obstruction is present.[384,385] Other scintigraphic techniques that have been occasionally described in dogs and cats include ^{99m}Tc-mercaptoacetyltriglycine (MAG-3) and ^{99m}Tc-dimercaptosuccinic acid (DMSA) scintigraphy.[386-389] Concentration of ^{99m}Tc-MAG-3 and ^{99m}Tc-DMSA within renal tissue predominantly occurs due to proximal tubular uptake of these isotopes, not glomerular filtration. ^{99m}Tc-MAG-3 scans are performed dynamically and provide an assessment of renal blood (plasma) flow and ^{99m}Tc-DMSA scans are static and provide superior images for the assessment of differential renal function. In one study in dogs these techniques were found to be more sensitive for detection of gentamicin-induced nephrotoxicosis than measurement of GFR.[387] In humans these techniques are used to detect areas of decreased isotope uptake due to conditions such as acute pyelonephritis, infarction and renal scarring.[390,391]

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CHAPTER 322

Acute Kidney Injury

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Client Information Sheet: Acute Kidney Injury

Introduction

The kidneys are at high risk for ischemic and nephrotoxic insult due to a variety of factors, including the kidney's high proportion of cardiac output (20%) in comparison to total body weight (0.5%), high metabolic demand, and potential for nephrotoxin concentration in tubular epithelial cells.[1,2] Acute kidney injury (AKI) accounts for 1% to 4% of hospital admissions, complicates an estimated 7% to 36% of inpatient episodes in people, and complicates sepsis at an even higher rate (47%).[3-9] The incidence of naturally acquired AKI in pets is unknown, but its effects can be devastating. AKI developed in 15% to 22% of hospitalized dogs and cats, specifically 12% of dogs with abdominal sepsis in one study, and even minor renal injury increases mortality in people and animals.[10-14] In several studies of nonrenal disease, increased blood urea nitrogen (BUN) or serum creatinine concentrations were inconsistently associated with mortality.[15-20]

Definition and Grading Aki

Classic versus More Sensitive

AKI has classically been defined as an increase in serum creatinine above the upper limit of the reference range, in the absence of chronicity.[21-23] This definition is sensitive but not specific. AKI is not only a rapid decline in renal function, but is often associated with retention of uremic wastes, deranged fluid status, electrolyte imbalances and acid-base disorders. An increase of >0.3 mg/dL or >25% increase from baseline creatinine are two of many AKI definitions used in people to detect subtle renal injury.[24,25] Because creatinine is poorly correlated with glomerular filtration rate (GFR) at low levels of dysfunction, such changes in creatinine may represent a dramatic decrease in renal function but still remain within the reference range (see ch. 62). Such increases may not fit the classic definition, but they do represent AKI, in which even mild changes have prognostic implications.[13]

Grading AKI

Various grading schemes have been applied to AKI in people and animals. In a retrospective study of dogs in intensive care, developing even a low level of AKI (increase in creatinine of ≥0.3 mg/dL or 1.5-2 times baseline creatinine) was associated with higher mortality than no AKI (58% vs. 16%).[10] In another study of hospitalized and out-patient dogs and cats, dogs but not cats who remained nonazotemic with an increase in creatinine of ≥0.3 mg/dL had three times higher 90-day mortality compared to those in which the creatinine did not change.[11] In both dogs and cats that developed azotemic AKI, mortality was 3 times higher at 30 and 90 days, compared to no AKI.[11] Because of inconsistencies in defining AKI, a grading scheme was adopted by the International Renal Interest Society (IRIS) in which separate criteria are based on changes in creatinine, preexisting renal disease and urine output (Table 322-1).[26]

TABLE 322-1

IRIS Classification Scheme for Acute Kidney Injury[200]

AKI GRADE	BLOOD CREATININE (MG/DL)	CLINICAL DESCRIPTION
Grade I	<1.6	Nonazotemic AKI: a. Documented AKI: (Historical, clinical, laboratory, or imaging evidence of AKI, clinical oliguria/anuria, volume responsiveness*) … and/or b. Progressive nonazotemic increase in blood creatinine; ≥0.3 mg/dL (≥26.4 mcmol/L) within 48 h c. Measured oliguria (<1 mL/kg/h) or anuria over 6 h
Grade II	1.7-2.5	Mild AKI: a. Documented AKI and static or progressive azotemia b. Progressive azotemic increase in blood creatinine; ≥0.3 mg/dL (≥26.4 mcmol/L) within 48 h, or volume responsiveness* c. Measured oliguria (<1 mL/kg/h) or anuria over 6 h
Grade III	2.6-5.0	Moderate to severe AKI: a. Documented AKI and increasing severities of azotemia and functional renal failure
Grade IV	5.1-10.0	
Grade V	>10.0	

*Volume responsive is an increase in urine production to >1 mL/kg/h over 6 hours and/or decrease in serum creatinine to baseline over 48 hours.

AKI, Acute kidney injury; *IRIS*, International Renal Interest Society.

Etiology

Categories

The causes of AKI have, classically, been subdivided into: hemodynamic (prerenal), intrinsic renal, and postrenal causes (Figure 322-1). Conceptually, each category is distinct, but may overlap in an individual, which complicates distinguishing the role of each. Persistent extrinsic renal damage can lead to intrinsic renal damage, because they are different points on a continuum. The term *acute uremia* encompasses biochemical changes induced by all categories. In people, it is estimated that 20% to 80% of acute uremias have hemodynamic causes, 5% to15% have postrenal causes, and 10% to 45% are the result of intrinsic renal failure. The most common intrinsic causes are ischemic and nephrotoxins, with lower incidences of large vessel, microvasculature, glomerular, or acute tubulointerstitium disease.[27-29] In people, acute uremia on hospital admission is due to hemodynamic causes in 70% of cases, is the result of a single condition without other organ involvement, and generally carries a good prognosis. Acute uremia that develops in hospital is generally caused by multiple insults, has multiple organ system involvement, is associated with hemodynamic causes in 40% of cases, and generally has a worse prognosis.[6,30,31]

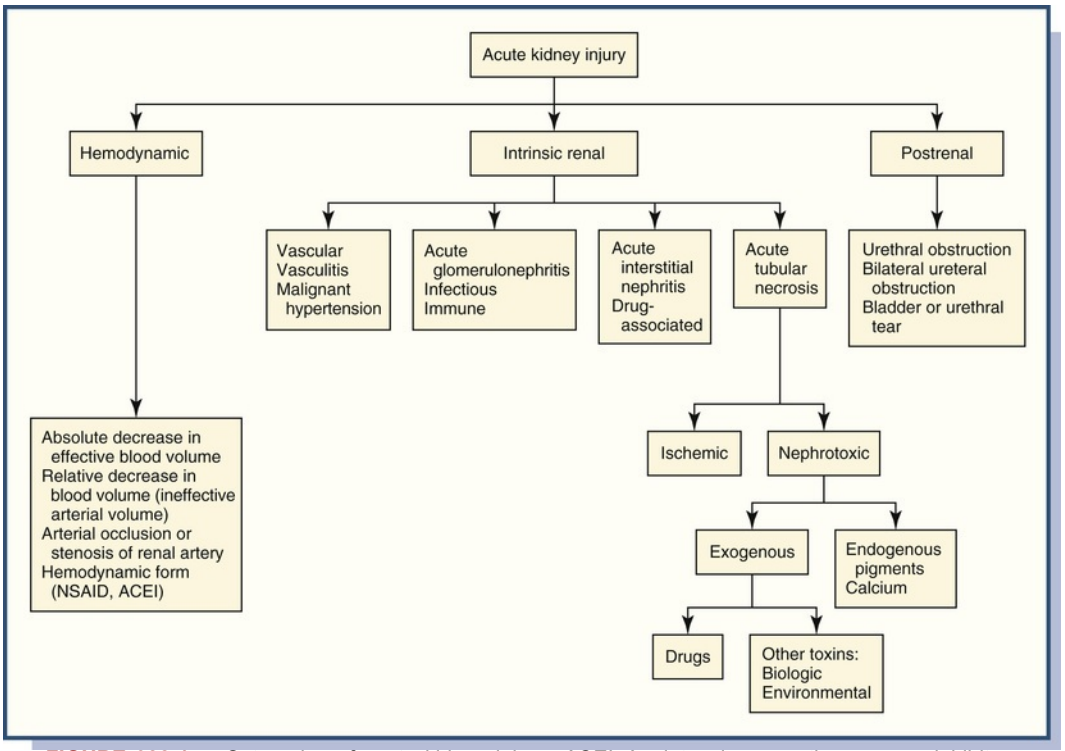


FIGURE 322-1 Categories of acute kidney injury. *ACEI*, Angiotensin-converting enzyme inhibitor; *NSAID*, nonsteroidal anti-inflammatory drug.

Volume-Responsive Azotemia (Hemodynamic Azotemia)

Insufficient delivery of blood to functional kidneys may impair clearance of solutes and uremic toxins. While this condition is typically called prerenal azotemia, different terminologies have been suggested to help clarify the cause of this phenomenon, including hemodynamic azotemia, transient azotemia, and volume-responsive azotemia.[32-36] Any process that decreases renal blood flow, including dehydration, hypovolemia, hypotension, decreased effective circulating volume (i.e., cardiac failure, hepatic cirrhosis, nephrotic syndrome), anesthesia, hypoadrenocorticism, trauma, surgery, shock (hypovolemic, hemorrhagic, hypotensive, septic), heatstroke, hypoalbuminemia, or renal hypoperfusion (i.e., secondary to nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme [ACE] inhibitors) can contribute to this functional disturbance.

Hemodynamic azotemia is characterized by increased BUN and creatinine concentrations in conjunction with a concentrated urine specific gravity. The fractional excretion of sodium (Na) in the urine is usually low, except in Na-avid states such as congestive heart failure, liver failure, and nephrotic syndrome (see ch. 73).[37] Hemodynamic azotemia is characterized by rapid reversal when the underlying condition is corrected (i.e., replacing fluid deficits and maintaining mean arterial blood pressure above 80 mm Hg).[36,38,39] If these hemodynamic factors are not addressed rapidly, the patient may progress to a volume-nonresponsive state. In one study on people, transient azotemia that resolved within one day doubled the odds ratio of mortality compared to no azotemia. Perhaps hemodynamic azotemia should be renamed transient AKI.[33-35] While many pets with poor renal perfusion (e.g., dehydration, hypotension) respond to IV fluids, some do not (e.g., congestive heart failure, sepsis).[36] Although reduced renal blood flow and ischemia have been considered major contributors to the pathogenesis of AKI, renal hypoperfusion alone (80% reduction of renal blood flow for 2 hours) did not induce sustained AKI.[40] Local and systemic inflammatory responses, changes in intrarenal blood flow distribution, microcirculatory dysfunction, and glomerular hemodynamics contribute to renal dysfunction.[41] These factors are not corrected with fluid therapy.

Intrinsic Renal Failure

Contributors

Intrinsic renal failure may follow damage to any section of the kidney: glomeruli, tubules, interstitium, or vessels. Most commonly, intrinsic renal failure follows ischemic or toxic tubular damage (Table 322-2). Ischemia, usually due to hypoperfusion, is the most common cause of intrinsic renal failure in people.[30,42] Together, hemodynamic and intrinsic renal causes account for 70% to 75% of AKI.[6,43] Prolonged obstruction (>1 week) can also lead to intrinsic renal failure.[39] Multiple factors may be present and it may be difficult to determine the relative contribution of each. Specific contributors to intrinsic renal failure from ischemia include progression of hemodynamic azotemia, hypotension, hypovolemia, circulatory collapse, excessive renal vasoconstriction, or renal vascular disease (thrombosis, disseminated intravascular coagulation, or stenosis), extensive cutaneous burns, and transfusion reactions. A variety of infectious diseases can lead to AKI. Bacterial pyelonephritis is usually caused by ascending infection from the lower urinary tract, but infection may be hematogenous in origin (see ch. 327). Most urinary tract infections (UTIs; 74%) are caused by Gram-negative organisms.[44,45] *Escherichia coli* is most common and accounts for 37% to 45% of UTIs while Gram-positive organisms account for 25% to 30%.[44,45] Predisposing conditions for the development of pyelonephritis include bacterial endocarditis, discospondylitis, and pyometra.[44]

TABLE 322-2

Causes of Intrinsic Acute Renal Failure

ISCHEMIC EVENTS	PRIMARY RENAL DISEASES	SECONDARY DISEASES WITH RENAL MANIFESTATION	NEPHROTOXINS
Shock (hypovolemic, hemorrhagic, hypotensive, septic) Decreased cardiac output (congestive heart failure, arrhythmias, cardiac arrest, cardiac tamponade) Deep anesthesia/extensive surgery Trauma Hyperthermia/hypothermia Extensive cutaneous burns Transfusion reaction Renal vessel thrombosis/DIC Hyperviscosity/polycythemia NSAIDs	Infectious (pyelonephritis, leptospirosis, borreliosis) Immune-mediated (acute glomerulonephritis, SLE, renal transplant rejection, vasculitis) Neoplasia (lymphoma)	Infectious (feline infectious peritonitis, babesiosis, leishmaniasis, bacterial endocarditis) Systemic inflammatory response syndrome, sepsis, multiple organ failure, disseminated intravascular coagulopathy Pancreatitis Hepatorenal syndrome Malignant hypertension	Exogenous toxins Drugs Endogenous toxins

DIC, Disseminated intravascular coagulation; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *SLE*, systemic lupus erythematosus.

Leptospirosis

Leptospirosis (see ch. 217) is caused by multiple serovars of *Leptospira interrogans* or by *Leptospira kirschneri* serovar grippotyphosa. It is a filamentous, motile bacterium. Each serovar is maintained by one or more natural hosts. Clinically important serovars and their normal hosts in North America include canicola (dog), icterohaemorrhagiae (rat), grippotyphosa (vole, raccoon, skunk, opossum), pomona (cow, pig, skunk, opossum), hardjo (cow), and bratislava (rat, pig, potentially horse). Host-adapted species do not usually develop disease from the serovar they carry, but infection in an incidental host can cause severe disease. The primary method of transmission is via water contaminated with urine, although urine-contaminated soil, bedding, and food are also routes of exposure. Organisms can penetrate mucous membranes, wet or macerated skin, or intact skin. Exposure to urine, blood, or saliva can also transmit disease. The organism prefers a warm, moist, alkaline environment, and is more likely to be present in stagnant or slow-moving water. An increase in incidence is common following periods of flooding. Peak incidence in dogs is from July to November.[46-50] Adult large-breed male dogs with access to outdoors are more likely to contract leptospirosis, although one recent study found that smaller dogs (<7 kg) had the highest prevalence, perhaps because this group was less often vaccinated.[46-48,51-53] Small intestinal intussusception has been noted in puppies and adult dogs with leptospirosis-induced AKI.[54] Although cats have traditionally been thought to be resistant to leptospirosis, cats with kidney disease were more likely to be seropositive than cats without

kidney disease.[55] A rapidly progressive AKI with nephrotic syndrome has been recognized in dogs with positive serology for *Borrelia burgdorferi.* Despite aggressive therapy, many patients fail to respond.

Nephrotoxins

There is a wide range of nephrotoxic causes of AKI (Table 322-3; see ch. 152-156). The most common causes of nephrotoxicosis in dogs are ethylene glycol, nonsteroidal anti-inflammatory drugs (NSAIDs), cholecalciferol, and aminoglycosides.[56] The most common causes in cats are ethylene glycol, cholecalciferol, and lilies.[56] Increased use of NSAIDs for perioperative pain management may increase the incidence of AKI. Primary acute renal diseases include immune, neoplastic, or degenerative conditions. Systemic diseases may cause AKI by affecting renal hemodynamics or creating a systemic inflammatory response. Systemic diseases associated with AKI include feline infectious peritonitis, pancreatitis, sepsis, systemic inflammatory response syndrome, multiple organ failure, disseminated intravascular coagulation, hemolytic anemia, hyperthermia, heart failure, and hyperviscosity.

TABLE 322-3

Nephrotoxins[56,201]

CLASS OF AGENT	EXAMPLES
Antibacterials	Aminoglycosides, cephalosporins (cephaloridine, cefazolin, cephalothin), penicillins, sulfonamides, fluoroquinolones, tetracyclines, vancomycin, carbapenems, aztreonam, rifampin, nafcillin, polymyxin
Antiprotozoals	Trimethoprim-sulfamethoxazole, sulfadiazine, thiacetarsamide, pentamidine, dapsone
Antifungals	Amphotericin B
Antivirals	Acyclovir, foscarnet
Chemotherapeutics	Cis- or carboplatin, doxorubicin, azathioprine, methotrexate
Immunosuppressives	Cyclosporine, interleukin-2
Nonsteroidal anti-inflammatories	All
Angiotensin-converting enzyme inhibitors	All
Diuretics	All
Radiocontrast agents	
Misc. therapeutics	Allopurinol, cimetidine, apomorphine, Dextran 40, penicillamine, EDTA, streptokinase, methoxyflurane, tricyclic antidepressants, lipid-lowering agents, calcium antagonists, vitamin D_3 analogs (psoriasis medications), lithium, phosphorus-containing urinary acidifiers
Heavy metals	Mercury, uranium, lead, bismuth salts, chromium, arsenic, gold, cadmium, thallium, copper, silver, nickel, antimony
Organic compounds	Ethylene glycol, chloroform, pesticides, herbicides, solvents, carbon tetrachloride and other chlorinated hydrocarbons
Miscellaneous toxins	Gallium nitrate, bisphosphonates, mushrooms, grapes, raisins, snake venom, bee venom, lilies, vitamin D_3–containing rodenticides, sodium fluoride, superphosphate fertilizer
Endogenous toxins	Hemoglobin, myoglobin

Postrenal AKI

Postrenal azotemia is caused by urine leakage within tissue or urinary obstruction. Obstructions may occur in the urethra, both ureters, or one ureter with a solitary functional kidney (see ch. 329-332 and 335). Urinary obstruction decreases renal clearance by a combination of neurohumoral events and increased back-pressure in the kidney. An increase in pressure in the collecting system after obstruction disrupts the balance of

hydrostatic and oncotic pressures and decreases GFR. Azotemia is rapidly reversed by relieving obstruction, although long-standing obstruction may lead to intrinsic renal failure. Ureterolithiasis in cats is increasing in frequency, commonly seen as acute severe uremia in what was an apparently healthy cat.[57] Azotemia secondary to leakage is rapidly reversed by providing drainage of urine out of the body, either a peritoneal catheter for uroabdomen or urinary diversion (i.e., urethral catheter or stent extending above and below a rupture site). Urine is caustic and inflammatory. It can lead to sterile peritonitis (see ch. 143). Urine leakage into the abdomen in a pet with a UTI can lead to a septic peritonitis, a surgical emergency (see ch. 279).

The Four Phases of AKI

AKI begins without clinical signs as an ischemic or nephrotoxic insult and continues until there is a definable change in renal function (increase in BUN or creatinine; decreased urine output). The length of time necessary to see changes is variable, depending on the insult's nature and severity.[58] During this stage, early intervention may prevent progression. The second stage is an extension of the first, with continuing hypoxia and inflammatory responses propagating kidney damage.[59] Cortical structures (proximal tubule and loop of Henle) are predisposed to toxic and ischemic damage because they receive 90% of renal blood flow and are highly metabolic. Hypoxia leads to a decrease in ATP which, in turn, impairs the Na^+K^+ pump with subsequent cellular swelling and death.[60] After tubular cell injury, there is loss of the brush border of apical and basal cell surfaces, likely caused by increase in cytosolic calcium (Ca).[61] The sublethal injury may progress to cell death. Intervention may not be successful in this phase.

Phase 3 is the maintenance phase, generally lasting 1 to 3 weeks.[58] Urine output may be increased or decreased and it resembles the ultrafiltrate, with little modification by tubular processes. In this stage, a critical amount of irreversible damage has occurred. The fourth, recovery phase, is heralded by an increase in urine output that may or may not be accompanied by a decrease in urine Na because the proximal tubules and ascending limbs of the loops of Henle have reductions in the number of Na transporters and aquaporin-2 proteins.[58,62] During this period, extreme Na losses lead to volume depletion that can delay or interrupt renal recovery. Regeneration and repair of the renal tissue may take weeks to months.

Cellular Mechanisms of the Pathophysiology of AKI

See E-Box 322-1.

E-Box 322-1

Cellular Mechanisms of the Pathophysiology of AKI

Although acute intrinsic renal failure is commonly called acute tubular necrosis, histologically, necrosis is not prominent. Acute tubular injury is a better description.[61] The two major mechanisms for a reduction in glomerular filtration rate (GFR) associated with ischemic injury are intrarenal vasoconstriction and tubule dysfunction. Although the kidneys receive a large proportion of cardiac output, most blood is delivered to the cortex. The outer medulla exists in a state of chronic oxygen deprivation normally, despite the high metabolic activity of the S3 segment of the proximal tubule and medullary ascending thick loop of Henle because of the activity of the basolateral Na^+K^+-ATPase pump.[43] Intrarenal vasoconstriction may be because of an imbalance in endothelin and decreased nitric oxide production caused by sublethal endothelial injury. The tubular dysfunction is characterized by tubular obstruction from detached tubule epithelial cells and debris, and by back-leakage of the tubules.[28]

A variety of factors contribute to the cellular mechanisms of damage. Under conditions of oxygen depletion, adenosine triphosphate (ATP) is converted to adenosine monophosphate (AMP), leading to an energy deficit. Prolonged ischemia causes mitochondrial damage and impairs the ability to regenerate ATP. ATP depletion reduces activity of the Na^+K^+-ATPase pump, with resultant disruption of Na^+ and K^+ concentration gradient. This allows cell swelling, which causes tubule obstruction and vascular congestion. Mannitol may alleviate these problems, probably by hemodynamic alterations, osmotic diuresis, and scavenging of hydroxyl ions. The role of increased intracellular free calcium is still uncertain. When the intracellular calcium concentration is abnormally high, which occurs in energy-

depleted states because of lack of activity of intracellular calcium pumps, the mitochondria uptake calcium, leading to mitochondrial swelling and uncoupling of oxidative phosphorylation. Calcium channel blockers, especially diltiazem and verapamil, ameliorate acute kidney injury (AKI) if given to human kidney transplant donor and recipient. The effect is not clearly a result of reducing cytosolic calcium. These drugs improved renal hemodynamics and stabilized cell membranes. Other factors that contribute to renal ischemic damage on a cellular basis are reperfusion injury, oxidant injury, intracellular acidosis, phospholipase activation, and protease activation.[28]

The actin cytoskeleton plays important role in renal cell function and energy depletion causes cytoskeletal injury.[28,61] The normal reabsorption and unidirectional transport of sodium depends on cell polarity. With ATP depletion, disruption of actin cytoskeleton impairs the fence function of junctional complexes which prevent migration of certain cell membrane structures. This allows epithelial cells to lose polarity in proximal tubules, although it is a reversible change. Sodium/potassium pumps remain functional but are redistributed from basolateral to apical membrane. Disruption of the actin core bundle damages the structural integrity of microvilli, causing them to slough and leads to tubular obstruction with fragments of brush border in more distal segments. Normally, the actin cytoskeleton is important in limiting paracellular reabsorption at junction complex. Ischemia increases permeability of tight junctions. The resultant back-leakage of glomerular filtrate decreases GFR (despite only subtle histologic changes).

Disrupted cell-substrate attachment from damage to the cytoskeleton and integrin (molecules that mediate cell-cell adhesion) leads to denudement of cells from basement membrane. This allows back-leakage of glomerular filtrate, loss of tight junction complex function, and frank cell necrosis. Adhesion of detached renal epithelial cells to sublethally injured cells still attached to basement membrane causes aggregation of detached cells within lumen, leading to cast formation and tubule obstruction.

Renal recovery depends on recovery of sublethally injured cells with realignment of polarity, migration of viable cells, removal of necrotic cells and intratubular casts, and regeneration of renal cells. Normally quiescent renal tubule cells enter a growth cycle and proliferate to complete the recovery process.[28,61]

Diagnosis

Clinical Presentation

Animals with AKI usually have <1 week of anorexia, lethargy, nausea or vomiting, diarrhea, polyuria/polydipsia (PU/PD) or oliguria/anuria, and weakness. Animals with exposure to a nephrotoxin may have no other significant historical findings. Lily ingestion by cats may be associated with vomiting of leaves or other plant parts. Acute central nervous system (CNS) signs may be present early in the course of ethylene glycol toxicosis (see ch. 152) in dogs and cats. Physical examination may reveal variable degrees of hydration, generally good body condition, uremic halitosis or oral ulceration with severe uremia, renal pain (specific or nonspecific abdominal pain), renal enlargement, tachycardia, or bradycardia.

Laboratory Evaluation

Initial clinical evaluation generally includes hematology (complete blood count [CBC]), urinalysis, and serum biochemistries. Abnormalities may include azotemia (elevated BUN, creatinine), increased phosphate, metabolic acidosis, hypocalcemia, and/or hypo- or hyperkalemia. Anemia can follow blood loss, if gastrointestinal (GI) bleeding occurs. Urinalysis may reveal isosthenuria or minimally concentrated urine specific gravity (<1.035), proteinuria, and glucosuria. Casts in the urine sediment (see ch. 72) indicate ongoing renal damage, but are fragile and may disintegrate if evaluation is delayed (as with shipping samples to a laboratory). Red blood cells (RBCs), white blood cells, or bacteria may be present. Calcium oxalate crystals may indicate ethylene glycol toxicosis (see ch. 152). Urine culture may reveal a bacterial (rarely fungal) pyelonephritis as the cause of AKI.

Imaging

Radiographs may demonstrate normal to enlarged kidneys and/or nephroliths/ureteroliths. Abdominal ultrasound may show normal or enlarged kidneys (see ch. 88). With ethylene glycol toxicosis, the kidneys may appear hyperechoic (E-Figure 322-2). Perirenal fluid accumulation can be seen with leptospirosis in dogs, lymphoma in cats, and other conditions. Hydronephrosis may indicate obstruction or pyelonephritis (E-

Figure 322-3). Mild renal pelvic dilation may follow aggressive fluid therapy. Mild ureteral dilation extending only minimally past the renal pelvis supports inflammation associated with pyelonephritis. A dilated ureter may be traced to an obstructing stone (frequently difficult to visualize). Intravenous (IV) or antegrade pyelography or computed tomography (CT) may better demarcate a ureteral obstruction (Figure 322-4).

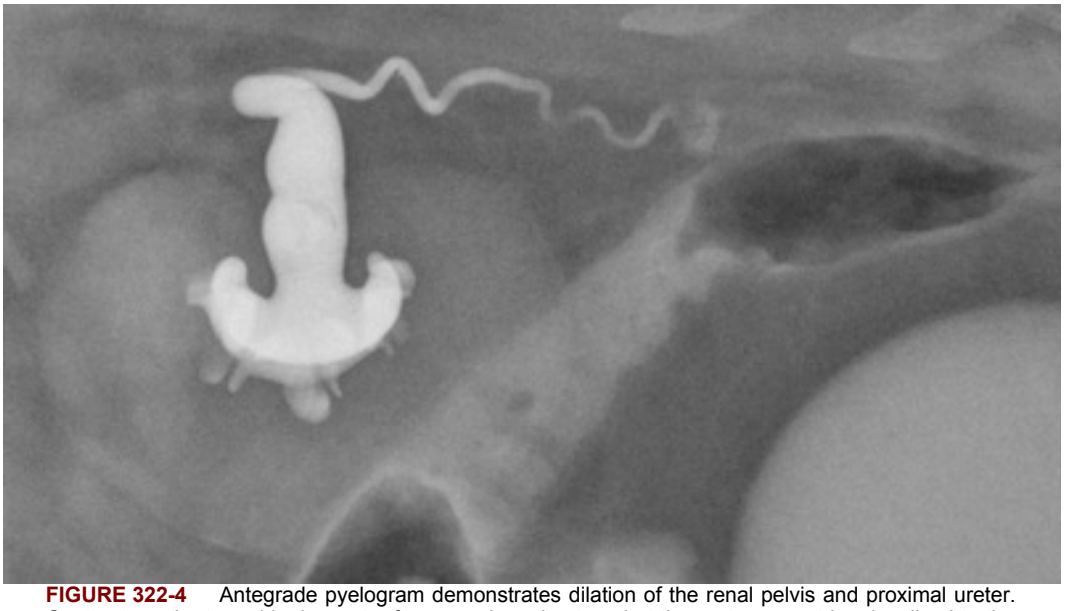
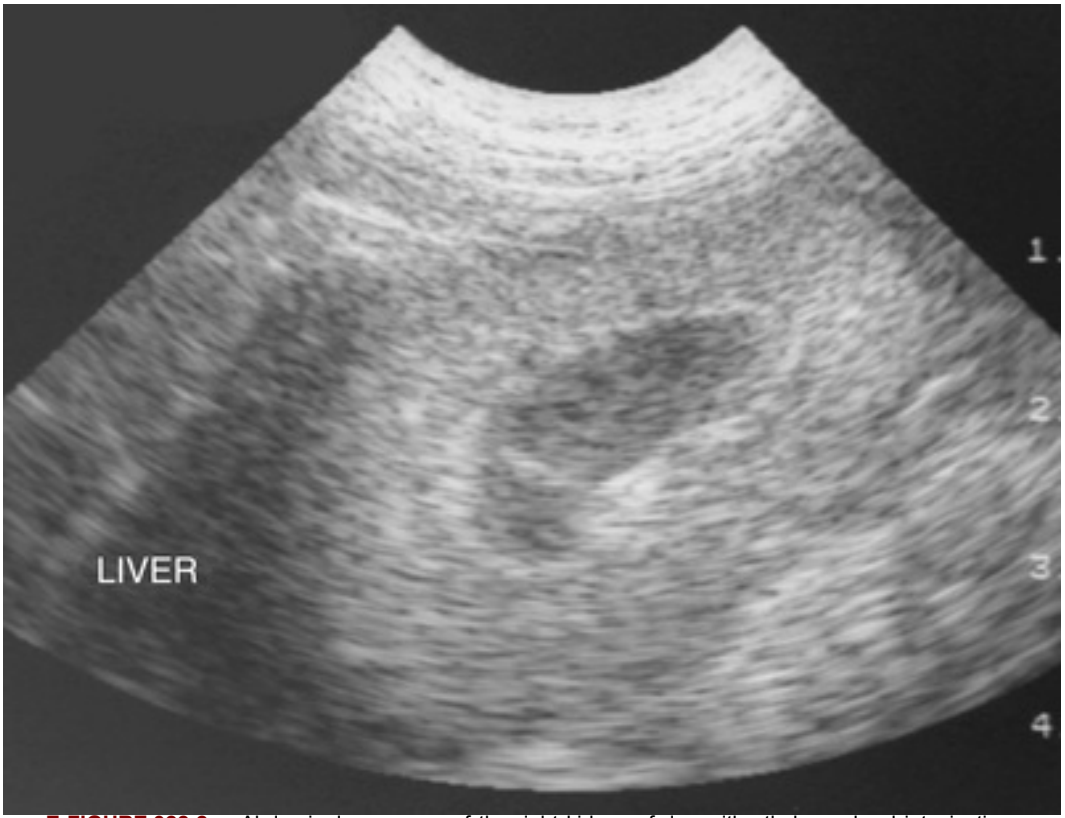
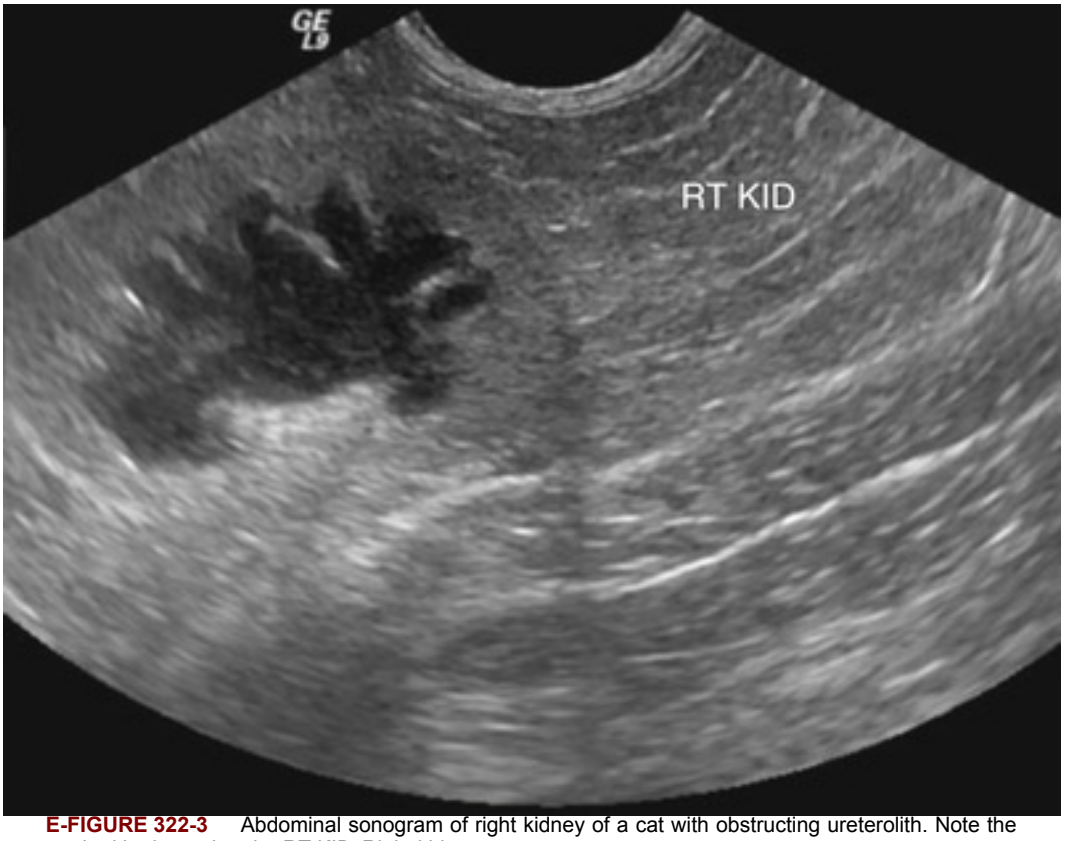


FIGURE 322-4 Antegrade pyelogram demonstrates dilation of the renal pelvis and proximal ureter. Contrast can be traced in the ureter for several centimeters, but the ureter cannot be visualized to the bladder. The bladder contains contrast from the contralateral kidney.



E-FIGURE 322-2 Abdominal sonogram of the right kidney of dog with ethylene glycol intoxication. The renal cortex is hyperechoic in comparison to the liver and the corticomedullary junction is

prominent.



E-FIGURE 322-3 Abdominal sonogram of right kidney of a cat with obstructing ureterolith. Note the marked hydronephrosis. *RT KID*, Right kidney.

Renal Fine Needle Aspirate (FNA) and Biopsy

Fine-Needle Aspirate (FNA)

Renal FNA (see ch. 89 and 93) may be helpful in establishing a diagnosis of renal lymphoma. FNA, using a 22- or 25-gauge needle, with or without ultrasound guidance, can be performed with heavy sedation. Risk of bleeding is low. Renal lymphoma can be confirmed with cytology, but failure to confirm still leaves it as a possibility. FNA cytology cannot definitively diagnose most other conditions.

Biopsy

Percutaneous ultrasound-guided needle biopsy can be performed after the pet is given a quick-acting injectable anesthetic (see ch. 89). The biopsy needle is directed across the greater curvature of the kidney into the cortex, or through the cortex and medulla into the renal pole. The renal pelvis and major vessels must be avoided. Advantages of this procedure include avoidance of a surgical wound and general anesthesia, but disadvantages include small sample size and inability to control bleeding. Laparoscopic needle biopsy (see ch. 91) or a surgical wedge biopsy through a keyhole incision in the flank usually provides sufficient sample for accurate diagnosis. Renal biopsy may identify a specific diagnosis (i.e., ethylene glycol toxicosis, renal lymphoma, leptospirosis), or it may show acute tubular necrosis—a specific pathologic finding but one caused by many conditions. Risk of bleeding when uremia is severe is high because of the thrombocytopathy (see ch. 197).

Specific Tests of Renal Function

Serum Creatinine and GFR

Serum creatinine is probably one of the most commonly used measures of renal function in clinical medicine but is an insensitive marker for mild renal dysfunction (see ch. 62, 321, and 324). Only small changes in serum creatinine occur despite large decreases in GFR when renal function is close to the normal, whereas small changes in GFR lead to large changes in serum creatinine when function is severely compromised (Figure 322-5). In people, equations factoring in different variables (i.e., age, gender, ethnicity) have been developed to estimate GFR from serum creatinine, to avoid the encumbrance of measuring GFR, but similar equations have not been considered useful in veterinary medicine. Normal values for GFR in dogs vary by size and breed.[63,64] There are useful methods of measuring GFR, including plasma clearance (iohexol, exogenous creatinine), urine clearance (endogenous or exogenous creatinine), or renal scintigraphy. GFR is rarely measured in pets with AKI because of risk, cost, or promptness of getting results, or because the GFR is not in a steady state in patients with AKI.

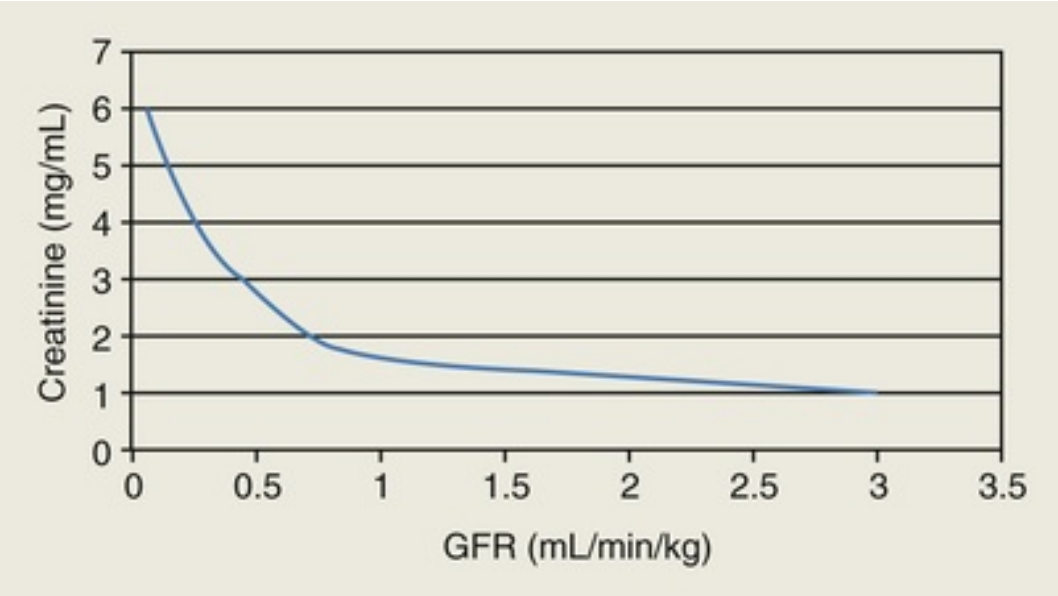


FIGURE 322-5 Glomerular filtration rate (GFR) and serum creatinine concentration.

Fractional Excretion of Sodium (FE_{Na})

FE_{Na} (see ch. 73) can be used to help differentiate hemodynamic from intrinsic renal azotemia and is calculated from the equation:

$$FE_{Na} = [(\text{Urine Na} \times \text{plasma creatinine}) / (\text{plasma Na} \times \text{urine creatinine})] \times 100$$

With hemodynamic azotemia and volume depletion, the kidneys conserve Na effectively, resulting in a fractional excretion <1%. With intrinsic renal damage, the FE_{Na} will be higher. Results are difficult to evaluate with concurrent diseases that may impair urine concentrating ability, or diuretic use. Fractional reabsorption of urea has been evaluated to help distinguish hemodynamic from intrinsic renal azotemia but lacks specificity.[65,66]

Biomarkers

Biomarkers of renal function more sensitive than creatinine are being sought.[67] Ideally, a panel of biomarkers would be able to detect kidney dysfunction much earlier (when interventions are more likely to be effective), distinguish acute from chronic disease, give some indication of the duration and severity, and be prognostic.

Cystatin C correlates to GFR better than serum creatinine in dogs, and will probably rise before creatinine in early renal disease.[68] However, cystatin C has not yet been evaluated in dogs with AKI. Gamma-glutamyl transpeptidase (GGT) and N-acetyl-beta-D-glucosaminidase (NAG) are urine biomarkers of tubular (or interstitial) damage and are elevated in early kidney disease (see ch. 321).[69] Neutrophil gelatinase-associated lipocalin increases before creatinine in AKI and seems useful in differentiating acute from chronic kidney disease (CKD).[70-73] Fibroblast growth factor 23 and symmetric dimethylarginine (SDMA) are also being evaluated as early markers of renal disease (see ch. 324).

Tests for Specific Diseases

Specific diagnostic tests are available for certain causes of AKI. Rapid ethylene glycol testing may be performed with a commercially available in-house test kit (EGT Test Kit, PRN Pharmacal, Pensacola, FL; see ch. 152). False-positive results are possible if drugs containing propylene glycol (e.g., etomidate, diazepam, activated charcoal) have been administered. False-negative results are possible with cats because of the lower limit of detection of test kit (50 mg/dL). Determination of blood concentrations of certain drugs is available to determine if a toxic concentration is present and to monitor response to therapy. Leptospirosis (see ch. 217), Lyme disease (see ch. 211), Rocky Mountain spotted fever (*Rickettsia rickettsii* infection; see ch. 218) can cause oliguric renal failure. Signs of vasculitis, polyarthritis, meningitis, and mild thrombocytopenia are likely as AKI develops. *Ehrlichia canis* can produce a similar spectrum of clinical signs, although renal lesions are more likely to be glomerular damage with proteinuria rather than AKI.

Risk Factors for AKI

Hospital Acquired

AKI developing prior to veterinary examination is generally owing to a single cause (i.e., ingestion of nephrotoxin by previously healthy pet). Multiple risk factors increase risk of AKI. In pets with preexisting risk factors, careful attention to avoiding or minimizing other risks is prudent (Box 322-2). In a retrospective study of 29 dogs with hospital-acquired AKI, 72% were exposed to a nephrotoxin, 69% were >7 years of age, 41% had chronic heart disease (see ch. 357), 35% had preexisting renal disease, 31% had neoplasia, 28% had fever, and 14% had undergone anesthesia.[22] This study did not include data on hydration status, so the contribution of hemodynamic effects cannot be determined. Volume depletion is a significant predisposing factor for developing hospital-acquired AKI.[1,37] Volume depletion exacerbates renal hypoperfusion and increases risk of postoperative AKI.[74] Because the three major physiologic determinants of renal blood flow are cardiac output, intravascular volume, and renal perfusion pressure, attention to all are necessary, although AKI can develop even if all of these parameters are normal.[75,76] If hypotension is present and the pet is euvolemic, pressor agents may be needed, but there is risk of their causing intrarenal vasoconstriction.[1,77]

Box 322-2

Risk Factors for Hospital-Acquired AKI[1,22,60,199]

Clinical Conditions

- Hypoperfusion
  - Volume depletion
  - Hypoalbuminemia or decreased COP
  - Decreased cardiac output
  - Systemic hypotension
  - Increased blood viscosity
- Electrolyte abnormalities
- Acidosis
- Systemic hypertension
- Fever
- Sepsis
- Anesthesia

Surgery
Shock
Multiple organ failure
Gastric torsion
Nephrotoxic drugs, especially:
Radiocontrast media (potentiated by hyponatremia)
NSAIDs (potentiated by anesthesia, sodium or volume depletion, sepsis, CHF, nephrotic syndrome, hepatic disease)
Nephrotoxic drug combinations (aminoglycosides + furosemide, ACEI + diuretic)

Preexisting Diseases

Renal insufficiency
Pancreatitis
Hepatic insufficiency
Diabetes mellitus
Cardiovascular disease
Multiple myeloma
Trauma
Extensive burns
Increasing age
Vasculitis
Fever
Neoplasia

ACEI, Angiotensin-converting enzyme inhibitor; *CHF,* congestive heart failure; *COP,* colloid osmotic pressure; *NSAIDs,* nonsteroidal anti-inflammatory drugs.

Sepsis (see ch. 132)

In people with sepsis, norepinephrine was shown to be more efficacious at improving blood pressure, causing diuresis, and lowering mortality when compared with high-dose dopamine.[77,78] Arginine vasopressin, a potent pressor agent, is recommended for patients who are hypotensive despite norepinephrine.[77] Vasopressin causes more efferent arteriolar constriction whereas norepinephrine has more effect on the afferent arteriole. Vasopressin was more effective in reducing progression of AKI when compared with norepinephrine in patients with septic shock.[79] Maintenance of adequate cardiac output and prevention of peripheral vasoconstriction has been shown to decrease risk of AKI.[80] In high-risk patients, avoid use of any potentially nephrotoxic drugs. Anesthesia protocols should focus on avoiding hypotension and maintaining normal blood volume and pressure. Electrolyte disorders have been shown to increase risk of AKI. Low Na potentiates radiocontrast-media–induced AKI in dogs. Hypokalemia, metabolic acidosis, hypocalcemia, and hypomagnesemia enhance gentamicin's nephrotoxicity.[1] Strict control of hyperglycemia with insulin therapy decreases AKI in critically ill nondiabetic people.[75,81]

Aminoglycosides

Aminoglycosides are commonly associated with nephrotoxicosis in dogs and cats because they are not metabolized, are a low molecular weight, and are water soluble (see ch. 161). These factors lead to their almost exclusive excretion in urine.[82] They easily ionize to cationic complexes that bind to anionic sites on epithelial cells of the proximal tubule, are then internalized by pinocytosis, which leads to renal cortical concentrations 10 times that of the plasma and can cause renal tubular damage.[82] Factors that increase the risk of toxicosis include prolonged use (>5 days), elevated trough levels (>2 mcg/mL for gentamicin and tobramycin, >5 mcg/mL for amikacin), preexisting renal disease, dehydration, hypokalemia, hypocalcemia, hypomagnesemia, metabolic acidosis, age, concurrent nephrotoxic drug administration, diuretic administration, and antiprostaglandin therapy.[1,83]

Aminoglycoside toxicosis can be reduced by less frequent dosing.[1] Efficacy of aminoglycosides is determined by peak concentration (6 to 10 mcg/mL for gentamicin, 25 to 30 mcg/mL for amikacin), but toxicosis is closely correlated to trough concentrations.[83] Dosing once daily instead of three times daily can

achieve therapeutic blood levels, result in lower but still effective trough levels, and decrease the incidence of AKI from 24% to 5%.[74,83-85] Daily monitoring of fresh urine sediments for protein or casts can give an indication of renal damage prior to the onset of azotemia (see ch. 72). If a pet is azotemic before therapy, an alternative drug regime should be chosen or the dosing interval prolonged by a factor related to the serum creatinine (i.e., if serum creatinine is 4 mg/dL, increase interval from 8 hours ×4 to 32 hours), if the drug must be used.[82]

Other Antibiotics

Giving expired tetracyclines can cause a Fanconi-like syndrome (glucosuria, aminoaciduria, hyperphosphatemia) due to accumulation of metabolites in mitochondria that interfere with proximal tubular oxidative enzymes.[2] Penicillins are not directly nephrotoxic, but they may induce a hypersensitivity reaction because the penicillin derivative may act as a hapten.[83] Sulfonamides act by causing intratubular crystals, exacerbated by renal damage, lower urine output, and higher urine acidity.[83]

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs inhibit the cyclooxygenase (COX) enzyme, which acts on arachidonic acid to form prostaglandins (see ch. 164). NSAIDs have a low potential for nephrotoxicosis in healthy postoperative patients.[84,86] Renal function is more dependent on prostaglandin synthesis in situations when blood flow may be decreased, such as during anesthesia, surgery, Na or volume depletion, hypotension, sepsis, congestive heart failure, nephrotic syndrome, hepatic disease, preexisting renal disease, old age, or concomitant drug therapy (especially other NSAIDs). This is because the predominant prostaglandin in the kidneys causes afferent arteriolar dilation, which maintains renal blood flow and counteracts the effects of systemic vasoconstriction.[87] By blocking prostaglandin production, NSAIDs carry a higher risk for toxicosis in these settings.[1,87]

The two isoforms of cyclooxygenase are COX-1 and COX-2. COX-1 isoforms are constitutively expressed throughout the body and are responsible for generating prostaglandins involved in routine physiologic functions. COX-2 enzymes are rapidly induced at sites of inflammation. Selective COX-2 inhibitors should have good clinical effect with fewer adverse GI effects than nonselective COX inhibitors. However, COX-2 can be constitutively expressed in kidneys, and expression can be upregulated by a number of situations that lead to decreased actual or effective circulating volume.[88] COX-2 selective NSAIDs appear to be no safer for kidneys than nonselective NSAIDs.[86,88] Perioperative NSAID use in cats has been associated with AKI even when doses were within the recommended range.[89] The prognosis for NSAID toxicosis is favorable if recognized early.[56,87]

Nephrotoxic substances should be avoided if possible in patients with risk factors for AKI.[80] Diuretics should be avoided if hemodynamic azotemia is present.[80] Less nephrotoxic drugs should be used preferentially, such as lipid emulsified or liposomal amphotericin B instead of regular amphotericin B, or carboplatin instead of cisplatin.[84,90-96] If the nephrotoxic drug must be given, modest volume expansion may decrease nephrotoxicosis in select cases, including the use of radiocontrast agents, amphotericin, cisplatin, and drugs that induce crystalluria.[84,97-99] Volume expansion and natriuresis help prevent AKI in some cases.[1]

Monitoring

Overview and Hydration

Any critically ill pet is at risk for developing AKI and appropriate parameters should be monitored. Those with additional specific risk factors may require specific monitoring. Monitoring may allow for optimization of hemodynamic parameters, surveillance for common uremic complications, and evaluating response to therapy.[100] Frequency of monitoring depends on severity of disease.

Monitoring hydration status is a key ongoing process to appropriate fluid therapy plans (see ch. 129). Readily available accurate tools to assess blood volume are not yet feasible in veterinary practice, but blood volume can be measured using indicator dilution techniques, radioactive tracers, bioimpedance spectroscopy, or other methods. Despite a lack of precise objective data, there are many ways to estimate hydration. Diminished skin turgor may indicate dehydration (5% of body weight or greater), recent weight loss, or loss

of elasticity because of aging. Dry mucous membranes or sunken eyes also suggest dehydration, although uremic pets may have xerostomia. Overhydration may cause moist mucous membranes, increased skin elasticity (heavy or gelatinous), shivering, nausea, vomiting, restlessness, serous nasal discharge, chemosis, tachypnea, cough, dyspnea, pulmonary crackles and edema, pleural effusion, ascites, diarrhea, or subcutaneous (SC) edema (especially intermandibular space and hock joints).[39,101] However, pets with low colloid osmotic pressure (i.e., hypoalbuminemia) or alterations in vascular permeability may appear overhydrated based on skin turgor assessment, yet have intravascular volume depletion. Body weight should be measured three to four times a day on the same scale to monitor fluid balance. Changes in body weight during hospitalization primarily reflect changes in body water. A sick animal may lose up to 0.5% to 1% body weight per day because of anorexia; changes in excess of this amount are caused by changes in fluid status.[102]

Blood Pressure, Packed Cell Volume, Total Solids, Central Venous Pressure

Since either hypertension or hypotension can be detrimental to renal function, blood pressure monitoring may be critical (see ch. 157-159). Oscillometric methods or Doppler technology are commonly used indirect measures (see ch. 99). Direct measurement is most accurate for assessing blood pressure, but not often used because it involves arterial cannulation. Blood pressure <80 mm Hg is insufficient for adequate renal perfusion and should be immediately addressed to avoid further renal damage.[39] An increase in blood pressure may indicate a gain of fluid; conversely, a decrease in blood pressure may indicate a net fluid loss. Because of the high percentage of patients with hypertension (80% of dogs with severe AKI, 20% to 30% of dogs and cats with CKD), trends in pressures rather than absolute values are of more utility in assessing changes in hydration status.[39,103-105] Similarly, trends in packed cell volume and total solids may reflect changes in volume in the absence of bleeding or blood transfusion. Since each parameter is impacted by aspects beyond hydration status, these factors must be viewed in aggregate. Central venous pressure measurement via a central IV catheter (see ch. 76) has been advocated to help determine volume status, but does not predict volume-responsiveness since there are myriad factors that impact it.[106,107]

Cardiac Monitoring, Acid-Base, Urine Output

Cardiac output monitoring requires a pulmonary artery catheter, special equipment, and is rarely used.[108] Electrocardiogram (ECG) is the only tool which allows recognition of arrhythmias that can be life threatening due to decreasing cardiac output (see ch. 103). ECG can be used to aid in recognizing conduction disturbances caused by hyperkalemia (see ch. 248). Echocardiography may be used to assess myocardial performance and can provide information about volume status by evaluating chamber volume (see ch. 104). Venous blood gas analysis is useful for determining acid-base status (see ch. 75 and 128). Electrolyte abnormalities are both a risk factor for and an effect of AKI. Therefore, regular electrolyte monitoring is advised. BUN and creatinine concentrations are easily measured, but are insensitive markers of early renal dysfunction, because the GFR must be less than 75% of normal for these values to be elevated.

The importance of monitoring urine output and composition cannot be overemphasized. Urine production in a healthy animal is about 1 to 2 mL/kg/h and a decrease may be an appropriate renal response to hypovolemia or a pathologic change in renal function. AKI may also cause polyuria (>2 mL/kg/h). Methods for determining urine volume include placing an indwelling urinary catheter with a closed collection system, collection of naturally voided urine, metabolic cage, or weighing cage bedding/litter pans (1 mL of urine = 1 g; see ch. 105 and 106). An indwelling catheter is most precise, although technical issues such as urine leakage around the catheter or inadvertent disconnection may cause incorrect measurements. Risk of an iatrogenic UTI can be decreased by careful attention to catheter hygiene, including cleaning the external portions of the catheter with antiseptic multiple times daily and changing the collection bag and tubing daily.[109] Complete collection of voided urine is difficult because of lack of pet cooperation or incontinence. An accurate scale is necessary to measure small volumes of urine in cats and small dogs, but weighing cage bedding or litter pans before and after use may provide an adequate assessment. Fluid losses from vomiting and diarrhea are usually estimated. Other losses (draining ascites or pleural effusion) or nasogastric tube suctioning should be measured. When renal damage has occurred, urine casts may appear before the urea or creatinine levels increase. Therefore, urine sediment should be evaluated daily in animals receiving aminoglycosides or other potential nephrotoxic medications (see ch. 72).

Prevention

Prevention of AKI involves avoiding or ameliorating risk factors while using renoprotective drugs. Radiocontrast agents cause vasoconstriction of the renal circulation.[80] The incidence of contrast-induced nephrotoxicosis is difficult to estimate, but can be as high as 30% in people with preexisting risk factors but less than 10% in people with no risk factors.[110,111] Reports of contrast-induced AKI in dogs are rare.[112] Studies evaluating the incidence of adverse effects of iodinated radiographic contrast agents in dogs and cats did not find postcontrast renal failure, but the small number of pets evaluated and delay between contrast administration and postcontrast evaluation of BUN and creatinine (mean 38 to 60 days for dogs, 3 to 105 days for cats) impair accurate assessment.[113,114] Of 3 cats evaluated within 3 days of receiving an iodinated contrast agent (nonionic), 2 had postcontrast increases in BUN and creatinine, but both were being evaluated for ureteral obstruction and were azotemic prior to contrast administration.[114] Saline diuresis prior to administration decreases toxicity.[80] Recommendations for preventing radiocontrast-induced AKI in acutely ill patients include aggressive, rapid volume expansion prior to performing the radiographic study, avoid mannitol, avoid furosemide, use a low dose of contrast or a nonionic agent.[74,84] Although use of acetylcysteine has not been proven effective, because of its low cost and few side effects, its use could be considered.[74,115]

There is no evidence that prophylactic treatment with furosemide protects against hospital-acquired AKI.[116] Studies have shown deleterious effects of prophylactic loop diuretic administration in patients predisposed to AKI, despite theoretical reasons to use furosemide to prevent AKI.[77,117] Calcium channel blockers have been used to prevent AKI in people receiving transplants, but they do not prevent AKI in the nontransplant setting.[116,118] Fenoldopam, a selective dopaminergic 1 (DA-1) receptor agonist, may dilate renal arteries, inhibit Na^+/K^+-ATPase activity, inhibit angiotensin II, and inhibit antidiuretic hormone.[119] It does not have DA-2, alpha, or beta-adrenergic activity, so it does not cause vasoconstriction, tachycardia, or arrhythmias sometimes seen with dopamine.[58,116] Fenoldopam maintained renal blood flow in an experimental model of hypovolemia in dogs, suggesting that it may have a renoprotective effect in acute ischemic injury.[120,121] In a study of healthy cats, diuretic effect and transiently increased GFR were noted 4 to 6 hours after a 2-hour infusion of fenoldopam. One of 6 cats had a decrease in GFR 2 hours after the infusion.[119] Various other therapeutic agents have been investigated for potential use in AKI, including atrial natriuretic peptide, theophylline, insulin-like growth factors, antibodies to adhesion molecules, scavengers of oxygen free radicals, amino acid infusion, and prostaglandins. None has been proved to be safe or effective for people.[43] In an experimental model of ischemic AKI in rats, a single dose of erythropoietin or darbepoetin administered 6 hours after the ischemic insult significantly inhibited subsequent apoptotic cell death, enhanced tubular epithelial regeneration, minimized the severity of renal dysfunction, and promoted more rapid renal functional recovery, but results of clinical trials are not available.[122]

Treatment

Goals

Treatment goals for the patient with AKI are aimed at limiting further renal damage and enhancing cellular recovery. Strategies for improving renal oxygen delivery, reducing metabolic demand, and maintaining urine output used for preventing AKI are equally important in treatment. Limiting cytotoxic and inflammatory responses and promoting regeneration of tubular cells is desirable.[116] Treatment is most successful during the induction and extension phases, and success diminishes once the maintenance and later phases have been reached. Therefore, prompt recognition of the disease process and institution of specific therapy are important.

Fluid Treatment Strategies

Source of Losses

The most effective therapy of AKI is careful management of fluid balance, which involves thoughtful assessment of hydration, a fluid treatment plan personalized for the specific patient, and repeated and frequent reassessment of fluid and electrolyte balance, with appropriate changes in the treatment plan in response to changes in patient status (see ch. 129). Normal fluid losses consist of insensible and sensible

losses. Insensible losses are not consciously perceived, such as water lost via respiration, stool, or sweating. Sweating is negligible in dogs and cats. There is variation in respiratory fluid loss in dogs (normal: ≈22 mL/kg/day) since they may lose considerable amounts via panting. The major source of sensible fluid loss is urine; others include vomiting, diarrhea, body cavity drainage, burns, etc. In healthy animals, losses are replaced by consumption of water and food, but the ill do not typically consume adequate amounts. With renal disease, urine volume is frequently high, low, or inappropriate.

Traditional Fluid Therapy

Traditionally, one administers IV fluids to correct dehydration and then uses aggressive rates of fluid administration to force diuresis. If azotemia does not resolve, one then increases the fluid rate. However, evidence now implies that this approach may actually worsen kidney function and impair their ability to recover. In a study of dogs undergoing anesthesia and surgery for cranial cruciate repair being given 10 mL/kg/h lactated Ringer's solution (LRS), GFR and urine output did not increase, but body weight increased from a mean of 32.6 kg to a mean of 33.7 kg. These dogs were systemically normal and although some received carprofen, it did not have an effect on renal and fluid parameters.[123] After administration of crystalloid fluid, 80% moves into the interstitium, causing interstitial edema, which leads to impaired oxygen and metabolite diffusion, and may worsen renal and overall outcome.[124,125] The kidneys are physiologically adapted to conserve Na and fluid rather than excrete excesses.[125] In healthy patients, it may take days for that fluid to be excreted.[124,126]

Revised Fluid Therapy Approach

Fluid therapy may be best considered as a three-step process: (1) acute resuscitation to restore effective intravascular volume, organ perfusion and tissue oxygenation, causing a positive fluid balance; (2) maintenance of intravascular volume homeostasis without fluid accumulation; and (3) fluid removal during convalescence to remove hemodynamically unnecessary volume.[127]

Hypovolemic Shock

Some pets with AKI present in hypovolemic shock (see ch. 127), with signs of dull mentation, hypotension (systolic blood pressure <80 mm Hg; see ch. 99 and 159), poor perfusion (cold extremities, pale/grey mucous membranes with slow capillary refill time), hypothermia, or tachycardia.[128] Immediate therapy is necessary to prevent further organ damage with crystalloids given at about 60 to 90 mL/kg for dogs and 45 to 60 mL/kg for cats (see ch. 129). About 25% of that volume is given over 5 to 15 minutes.[129] If hemodynamic parameters do not improve sufficiently with this first dose, a second and equal dose should be given. Aggressive fluid efforts are continued until the patient is hemodynamically sound and has adequate tissue perfusion. In dogs with shock resuscitated to traditional endpoints (heart rate, mean arterial pressure, urine output), 38% had persistent decreased central venous oxygen saturation, suggesting they had occult shock, despite seemingly normal perfusion parameters.[130]

Adequate resuscitation as assessed by achievement of identifiable goals decreases renal morbidity as compared with using standard resuscitation doses in people.[100] Perfusion parameters are targeted to be corrected within 6 hours of goal-directed therapy. With early and aggressive therapy to measurable physiologic endpoints, the volume of fluid administered during this resuscitation phase may be high, but less is given subsequently, such that the total volume administered during hospitalization is the same with goal-directed therapy compared to conventional therapy, but mortality and incidence of AKI are less with goal-directed therapy.[131]

Rehydration

The volume to fluids that need to be administered to correct dehydration is calculated from a formula: body weight (in kg) × estimated % dehydration* = fluid deficit in L. Because dehydration <5% cannot be detected clinically, pets who appear hydrated (but not overhydrated) should receive about 5% of their body weight in fluids over 2 to 4 hours to rapidly reverse any ongoing renal damage from poor perfusion and to quickly assess urine output. Fluids can be administered over a longer time frame if cardiovascular compromise prohibits rapid fluid administration. If a fluid bolus was used for initial resuscitation, that volume is subtracted from the dehydration deficit. Maintaining adequate renal perfusion, by correcting dehydration/volume depletion and restoring blood pressure and cardiac output, are essential.

"Maintenance" Fluid Therapy

Overview

Commonly estimated to be about 66 mL/kg/day, "maintenance" fluid dose presumes "normal" urine output without excessive losses (i.e., vomiting, diarrhea). Urine output in a pet with AKI may or may not be "normal." Even if the urine output is normal (0.5 to 2 mL/kg/h), damaged kidneys may not be able to alter the volume to excrete a fluid load. These patients have relative oliguria. Giving IV fluids in excess of "maintenance" needs has long been advocated as a method of forced diuresis, to promote toxin removal and flush out tubular casts. While of value in certain situations (e.g., radiocontrast nephropathy), this approach is now considered suboptimal.[125] Not only is aggressive fluid therapy not helpful, volume overload has repeatedly been shown to worsen outcome because it does not increase renal oxygen delivery despite improved cardiac output and renal blood flow.[41,132,133] Maintaining optimal hydration while assiduously avoiding overhydration or underhydration is one of the most important and most difficult challenges in treating AKI.

Ins and Outs

The "Ins-and-Outs" method of fluid administration helps maintain an appropriate fluid balance by matching the volume administered to the volume excreted. It is useful for all AKI settings, including anuria/oliguria, relative oliguria, and PU AKI. This method of determining fluid rate does not account for dehydration and should only be used after rehydration is complete. The three components of volume calculation are insensible losses (fluid lost via respiration and normal stool; 22 mL/kg/day), urine losses (calculated by actual measurement), and ongoing losses (i.e., estimated from vomiting, diarrhea, body cavity drainage). If a fluid pump is not available, fluid dosage can be determined by calculating daily insensible fluid needs and dividing by administration interval (i.e., if adjusting fluid rate 4 times a day, dividing daily fluid need by 4); to this volume, the amount of urine produced in the previous 6 hours (or appropriate interval), and a volume estimate of other losses should be added. If a fluid pump is available, daily insensible fluid needs can be calculated and divided by 24 to calculate an hourly rate. To this, the hourly volume of urine output over the previous monitoring interval should be added, plus an estimate of ongoing losses (Box 322-3). Other administered fluids that should be included in calculations include medications, transfusions, and nutrition. Anuric patients should receive fluids to replace insensible losses only. If the patient is overhydrated, the insensible loss should be withheld. Overhydration in an anuric patient or inability to induce diuresis in an oliguric or anuric patient is an indication for dialysis, which is the only other effective therapeutic option (see below and ch. 110).

Box 322-3

Sample Calculations for Ins-and-Outs Fluid Therapy

Sample Calculations without Fluid Pump

4.5 kg cat × 22 mL/kg/day = 100 mL/day
100 mL/day ÷ 4 = 25 mL per 6 hours
30 mL urine output over previous 6 hours
Vomiting about 3 times a day (≈8 mL each time) = 6 mL over 6 hours
25 + 30 + 6 mL = 61 mL to administer over next 6 hours

Sample Calculations with Fluid Pump

4.5 kg × 22 mL/kg/day = 100 mL/day
100 mL/day ÷ 24 = 4 mL/h
30 mL urine output over previous 6 hours ÷ 6 = 5 mL/h
Vomiting about 3 times a day (≈8 mL each time) = 1 mL/h
4 + 5 + 1 = 10 mL/h

When the patient has stabilized and is entering a recovery phase, any accumulated fluid should gradually be removed by decreasing the volume administered to a volume less than that being excreted. If excessive fluid has accumulated, diuretics may hasten fluid removal. Diuretics are ineffective in preventing or treating AKI, and although one study found lower mortality in patients with AKI receiving higher furosemide doses,

this effect was not significant when controlling for fluid balance.[116,117,134-137] In other words, the benefit of furosemide was in controlling the fluid overload associated with worse outcomes.[137] In some pets, profound PU develops during recovery that can lead to dehydration and worsening renal perfusion if the volume of fluids given is inadequate. In those situations, IV fluid therapy is continued until the patient can maintain adequate hydration with enteral (via voluntary intake or feeding tube; see ch. 82) and SC fluids. It can take weeks to regain sufficient urine concentrating ability to wean off IV fluids in more extreme cases.

Fluid Type

Choices

Of the various types of fluid available, a balanced polyionic solution (i.e., LRS, Plasmalyte, Normosol) is appropriate in most situations (see ch. 129). Fluids with chloride concentrations approximating plasma (i.e., LRS, Plasmalyte, at 98-111 mEq/L) are associated with lower incidence of AKI compared to higher chloride concentration fluids (i.e., 0.9% saline, 150 mEq/L), although there was no effect on mortality.[138-140] As a higher concentration of chloride is presented to the distal tubule, the macula densa will induce renal afferent arteriolar vasoconstriction.[141] Physiologic saline (0.9% NaCl) is indicated if hyponatremia is present, but fluids lower in Na are more appropriate if high Na is present (i.e., 0.45% NaCl with 2.5% dextrose, 1/2-strength LRS with 2.5% dextrose). Dextrose 5% in water (D5W) is rarely appropriate as the sole fluid choice, but may be combined with LRS or 0.9% saline to make 1/2- or 3/4-strength Na solutions (25 mL LRS + 25 mL D5W = 50 mL 1/2-strength LRS + 2.5% dextrose).

Colloidal solutions (i.e., hydroxyethyl starch) have been recommended with persistent hypotension or if hypoalbuminemia is present (e.g., protein-losing nephropathy, diseases associated with vasculitis, or severe GI losses or bleeding), at a dosage of 20 mL/kg/day. Despite early reports that colloids could expand the vascular volume with lower doses than crystalloids, recent reports refute this finding. In a large study in human intensive care settings, the hetastarch group received less fluid than the saline group, and had a lower positive fluid balance (921 ± 1069 mL vs. 982 ± 1161 mL, p = 0.03), but the fluid sparing effect was less than predicted.[142,143] Colloids rapidly escape the vascular compartment, as do crystalloids.[132,144] Hetastarch is associated with a higher risk of AKI and mortality in critically ill patients; licensing has been restricted in Europe and the U.S. Food and Drug Administration (FDA) has approved a boxed warning about use in septic patients.[145-149] An alternative to synthetic colloids is human albumin, but this product carries risk of anaphylaxis (see ch. 130).[150,151]

Oliguria and Anuria

Definitions

A decrease in urine production may be due to hemodynamic, intrinsic renal, or postrenal causes. An appropriate renal response to inadequate renal perfusion from hypovolemia or hypotension includes fluid retention with a concomitant decrease in urine volume. Renal perfusion should be optimized before determining whether oliguria is pathologic or physiologic. A volume of fluid equal to 3% to 5% of body weight should be administered to patients that appear normally hydrated because dehydration of less than 5% cannot be detected clinically. In pets that are clearly volume overloaded, this fluid administration is not necessary. Healthy kidneys can autoregulate renal blood flow at perfusion pressures between 80 to 180 mm Hg, but perfusion may be more linear in damaged kidneys.[38,102] The mean arterial pressure should be maintained above 60 to 80 mm Hg, or the systolic pressure above 80 to 100 mm Hg when measured by Doppler technology (see ch. 99). Apparent anuria can be caused by obstruction of the urinary tract or leakage into the peritoneal, retroperitoneal, or SC tissues and must be excluded before determining that a lack of urine is a result of intrinsic renal damage. Anuria is defined as essentially no urine production.[39] Various values have been used to define oliguria, including <0.25 mL/kg/h, <0.5 mL/kg/h, and <1 to 2 mL/kg/h.[39] In a hydrated, well-perfused pet, <1.0 mL/kg/h can be considered absolute oliguria and urine volumes of 1 to 2 mL/kg/h in a pet on aggressive fluid therapy is considered relative oliguria.[39,102] Urine volume above 2 mL/kg/h is considered PU.

Assessing Diuretic Action

There is no evidence that diuretics improve the outcome of AKI. The ability to respond to diuretics may be a marker of less severe renal injury and a better prognosis. In people, increased urine output with diuretic use

delays referral for dialysis, perhaps inappropriately.[135] However, in veterinary medicine, where dialysis is not as readily available to control fluid status, an increase in urine output from diuretic use may allow an increase in the volume of other medications or nutrition, and may be justified even without improvement in renal function. Volume overload has been associated with worse outcome.[152-157]

Mannitol/Glucose

Mannitol is an osmotic diuretic that causes extracellular volume expansion and inhibits renal Na reabsorption by inhibiting renin. Mannitol also increases tubular flow, which may relieve intratubular obstructions from casts and debris. Mannitol decreases vascular resistance and cellular swelling; increases renal blood flow, GFR, and solute excretion; protects from vascular congestion and RBC aggregation; scavenges free radicals; induces intrarenal prostaglandin production and vasodilation; and induces atrial natriuretic peptide release.[39,58,102,158] Mannitol may blunt the influx of Ca into mitochondria of sublethally injured renal cells, thus decreasing the risk of injury progressing to lethal damage. Despite the theoretical advantages, no randomized studies have shown a better clinical response with the use of mannitol and volume expansion than with volume expansion alone in people or healthy cats.[58,159] Mannitol should be administered as a slow IV bolus of 0.25 to 1 g/kg. If urine production increases, it may be administered as a constant rate infusion (CRI) of 1 to 2 mg/kg/min IV or 0.25 to 0.5 g/kg q 4-6 h (see ch. 78).[39] Doses in excess of 2 to 4 g/kg/day may cause AKI. Mannitol should not be given to patients that are dehydrated, because it will further exacerbate intracellular dehydration. Conversely, it is also contraindicated if overhydration is present, and may worsen pulmonary edema. Hypertonic dextrose can be used as an osmotic diuretic, if mannitol is not available. The total daily dose of 22 to 66 mL kg of a 20% dextrose solution should cause hyperglycemia and glucosuria.[160]

Loop Diuretics

Loop diuretics (furosemide) can increase urine flow without increasing GFR.[58,77,84,159,161] Despite the increase in urine output, loop diuretics do not improve outcome, suggesting that those who respond have less severe renal failure, resulting in a better outcome for recovery independent of drug therapy.[58,77,84,161,162] For example, people who could be converted from oliguric to nonoliguric renal failure had better APACHE scores and higher creatinine clearance prior to treatment, suggesting that they had less severe renal injury.[162] Because of the perception that there is a low complication rate associated with the loop diuretics, they are often used despite lack of proven benefit. Loop diuretics inhibit the $Na^{+2}Cl^{-}K^{+}$ pump in the luminal cell membrane of the loop of Henle, decreasing transcellular Na transport. Basal Na^{+}/K^{+}-ATPase activity becomes unnecessary and medullary oxygen consumption decreases, which may protect the kidney from further injury.[162,163] The amount of structural damage to the thick ascending limb of the loop of Henle decreases after furosemide administration when evaluated in isolated perfused kidneys.[163] Loop diuretics also have renal vasodilatory effects.[116]

Despite these theoretical reasons to use loop diuretics, one retrospective study in people showed an increased risk of death or failure of renal recovery in a furosemide treatment group. Potential explanations included detrimental drug effects, delay in recognizing severity of renal failure with subsequent delay in starting dialysis, or preferential use of loop diuretics in patients with a more severe course of disease.[77,135] Loop diuretics may make fluid management easier in people, without changing the outcome.[162] Established indications for use of furosemide in veterinary medicine include treatment of overhydration or hyperkalemia.[39] Furosemide should not be given patients with aminoglycoside-induced AKI.[102]

An increase in urine output should be apparent 20 to 60 minutes after an IV furosemide dose of 2 to 6 mg/kg. Ototoxicosis has been reported at high doses in people, and doses of 10 to 50 mg/kg may cause adverse effects in animals (apathy and anorexia in cats; hypotension, apathy, ataxia in dogs).[102] If there is no response to high doses, therapy should be discontinued. If a response does occur, this dose can be administered every 6 to 8 hours or until volume overload has been corrected. CRI provides more sustained diuresis with a lower cumulative furosemide doses versus repeated bolus infusions.[77] In people, the time to maximal effect with a loading dose and CRI is 1 hour, and without a loading dose is 3 hours. The dosage in people is about 0.01 to 0.15 mg/kg/h with some reports using dosages as high as 0.75 mg/kg/h.[164] In normal dogs, 0.66 mg/kg/h resulted in diuresis, and dosages of 0.25 to 1 mg/kg/h have been used in dogs and cats with naturally occurring renal failure.[39,165,166] Because electrolyte and fluid balance disorders can develop rapidly if diuresis ensues, frequent monitoring is necessary.

Dopamine/Fenoldopam

Dopamine has been shown to make some human oliguric patients nonoliguric, but it does not increase GFR or improve outcome.[58,84,167,168] Because of lack of efficacy and side effects associated with dopamine, it is no longer recommended for treatment of oliguric renal failure, except for pressor control.[39,169] Fenoldopam, a selective DA-1 receptor agonist, increases urine output.[58,116] Its effects on GFR and renal outcome are not known.

Calcium Channel Antagonists

Calcium channel antagonists presumptively reverse renal vasoconstriction by causing predominantly preglomerular vasodilation, inhibit vasoconstriction induced by tubuloglomerular feedback mechanisms, cause natriuresis independent of GFR, and decrease renal damage after transplantation.[170] Although results of one study using diltiazem in addition to standard care in dogs with AKI from leptospirosis were not statistically significant, there was a trend toward increased urine output and more complete resolution of azotemia.[170]

Renal Replacement Therapy

Indications

Renal replacement therapy is used for patients that fail to respond to medical management (Figure 322-6; see ch. 110). The appropriate time to institute dialytic therapy is not clearly established, although intractable hyperkalemia, life-threatening volume overload, or persistent uremic symptoms are uncontroversial (Boxes 322-4 and 322-5). Early institution of dialysis in people may improve outcome compared with starting later in the course of the disease. Starting dialysis at a lower level of overhydration improves outcome in pediatric patients.[103] Renal transplantation is not an emergency procedure (see ch. 323). If a cat with AKI is stabilized but does not recover renal function, transplantation can be considered.

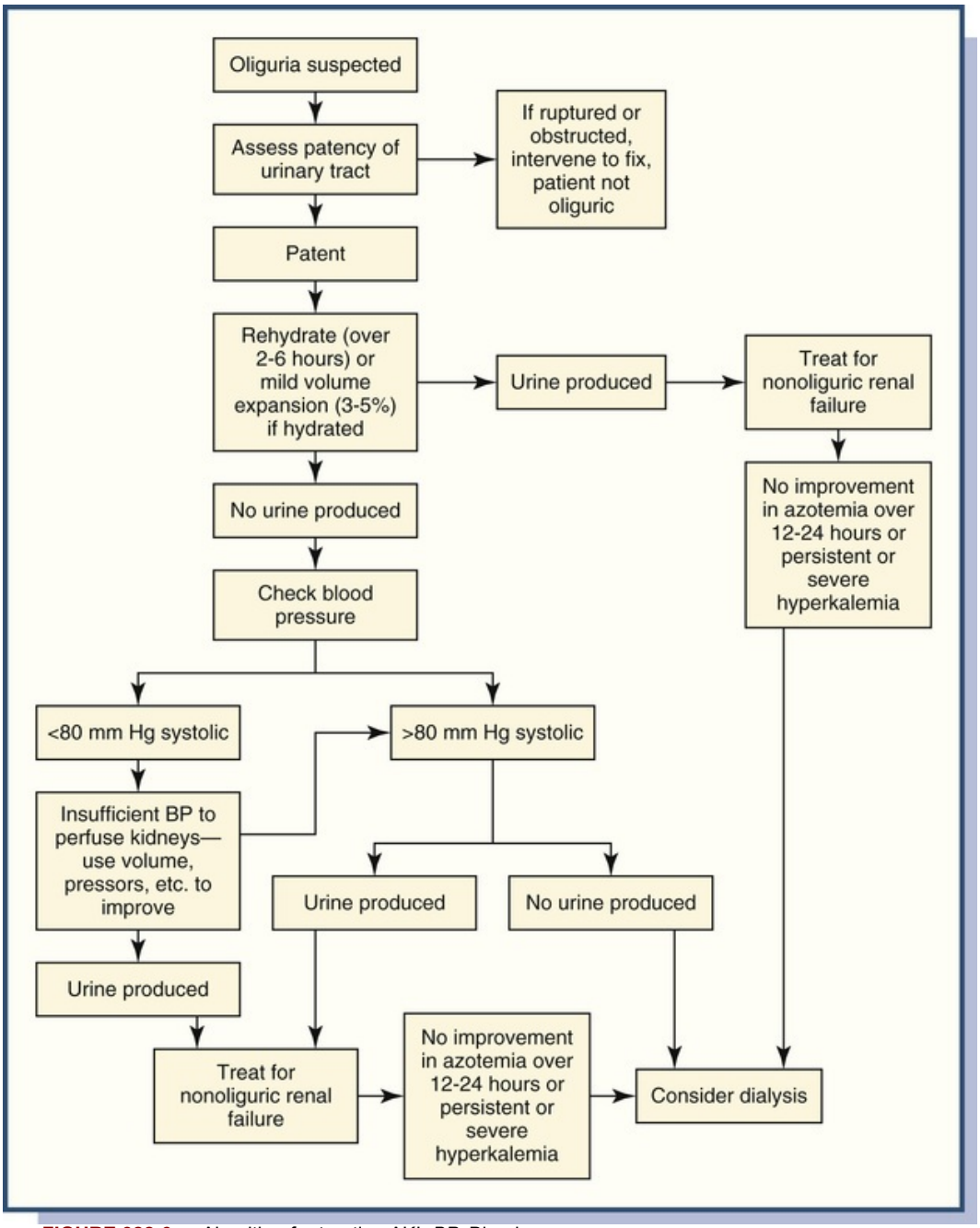


FIGURE 322-6 Algorithm for treating AKI. *BP,* Blood pressure.

Box 322-4

Indications for Renal Replacement Therapy

Inadequate urine production
Life-threatening pulmonary edema or fluid overload
Hyperkalemia or other life-threatening electrolyte or acid-base disturbance
Progressive/unremitting azotemia
Diuretic resistant congestive heart failure or severe overhydration in absence of renal disease
Acute poisoning/drug overdose with substance that can be removed by dialysis

Box 322-5

Patient Characteristics for Renal Replacement Therapy

≥2.5 kg
Systolic blood pressure ≥ 80 mm Hg
Tractable

Peritoneal Dialysis

Peritoneal dialysis is rarely used for AKI in critically ill people, but is more readily available for animals than hemodialysis or hemofiltration.[171] Peritoneal dialysis removes uremic toxins by diffusion from the peritoneal membrane into abdominal infused dialysate and then drained. Necessary supplies are readily available, but the procedure is time-consuming (see ch. 109). Common complications include catheter occlusion and peritonitis. Outcomes similar to hemodialysis have been documented in cats treated with peritoneal dialysis, with 10 out of 22 cats surviving to hospital discharge, but historical outcomes with peritoneal dialysis in dogs are less favorable (26% survival).[172-174]

Extracorporeal Renal Replacement Therapy (ERRT; see ch. 110) (Video 322-1)

ERRT includes intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT). ERRT removes uremic toxins from the bloodstream by diffusion and/or convection. During treatment, patient blood is continuously carried to the dialyzer through disposable tubing (extracorporeal circuit) and then returned. The dialyzer, or artificial kidney, contains a porous membrane whose size and charge determine which particles are filtered. Small- to middle-sized molecules in high concentration, such as urea and creatinine, diffuse through the pores into a dialysate solution on the opposite side of the membrane. Large molecules, such as albumin and cells, are too large to pass through the pores. Electrolytes, such as Na, can easily pass through the membrane. Thus, dialysate solutions have physiologic electrolyte concentrations to prevent significant loss. Ultrafiltration removes fluid from the patient by creating a hydrostatic pressure gradient between the blood compartment and the dialysate compartment. Solutes dissolved in the fluid are also removed via convective clearance. If a large volume of fluid is removed to achieve adequate solute clearance by convection, fluid is infused into the extracorporeal circuit to avoid dehydration. There are several models and manufacturers of dialysis machines but each must be able to circulate blood in the extracorporeal circuit, to circulate dialysate or replacement fluid, and to precisely control ultrafiltration.

IHD involves rapid blood flow and rapid dialysate flow for efficient removal of uremic toxins and fluid, allowing treatments to occur at intervals. One regimen might include several hours per treatment, three to four times a week. Machines designed for IHD are capable of supplying the large volume of dialysate necessary by mixing purified water with concentrated electrolyte solutions. Na and bicarbonate concentrations can be independently adjusted and tailored to the patient's needs. Because of the complexity of equipment and the possibility of acute changes in patient status during treatment, IHD is usually performed by specially trained dialysis personnel. CRRT can be performed until renal recovery occurs or until the pet is stable and can be transitioned to IHD. Prepackaged sterile dialysate is used with these machines, and solutions with various concentrations of solutes (i.e., Na, K, bicarbonate) are available. Dialysate flow rates are much slower with CRRT (up to 8 L/h) compared with IHD (20 to 50 L/h), but duration of treatment is longer. Choice of modality, whether IHD or CRRT, has not been proven to affect outcome.[84,171] Both IHD and CRRT require vascular access. For short-term treatment, double lumen catheters, placed percutaneously with a guidewire (Seldinger technique; see ch. 76) or via minor surgical exposure of the vessel, are used. These catheters can be placed with a local anesthetic and mild sedation.

Anticoagulants

Some form of anticoagulation is needed during dialysis to prevent thrombosis in the extracorporeal circuit. Unfractionated heparin is commonly used and is monitored by activated clotting time. With regional citrate anticoagulation, citrate administered as a CRI into the extracorporeal circuit binds Ca and prevents coagulation in the circuit. Because the anticoagulation occurs outside the patient, bleeding complications associated with anticoagulation are minimal. Calcium chloride is administered through a centrally placed IV catheter, or via the extracorporeal circuit just at the point where the blood is reentering the body, to prevent hypocalcemia in the patient.

Complications

Complications encountered during dialytic management may be a result of the dialysis procedure or of the underlying renal failure. Dialysis disequilibrium syndrome is a condition characterized by a rapid decline in blood osmolality caused by rapid removal of osmoles (especially urea) by dialysis, and it leads to CNS signs (e.g., seizures, mentation changes). In small animals, removal of the blood volume necessary to fill the dialysis circuit can result in hypotension. Hemorrhage related to heparin anticoagulation is most likely during the first few dialysis treatments, while the individual response to heparin is being determined, and with prolonged sessions (>6 hours). Thrombosis at the tip of the dialysis catheter in the right atrium is common with catheters in place for over 3 weeks, and impairs adequate blood flow.

Treatment of Ureteral Obstruction

Ureteral obstruction is a relatively frequent cause of AKI in cats (see ch. 329). Some ureteral stones pass into the bladder within hours to days, but if not, relief of the obstruction is necessary to regain renal function. Obstructions that persist for 7 days are expected to permanently reduce renal function by a third and, after 40 days, no return of function is expected. Relief can be provided by surgical ureterotomy, placement of a ureteral stent, or placement of a ureteral bypass device, which involves connecting a nephrostomy tube placed in the kidney with a cystostomy tube placed in the bladder (see ch. 124). Cats too ill for anesthesia may benefit from dialysis (peritoneal or extracorporeal). An alternative to dialysis is placing a percutaneous nephropyelostomy tube, which should resolve azotemia within a few days if it was postrenal, but a definitive procedure to remove or bypass the obstruction will eventually be required.[175,176]

Treatment of Specific Diseases

Antimicrobials

Penicillin derivatives and doxycycline are an excellent initial choice for dogs with leptospirosis (see ch. 217), although penicillins do not eliminate the carrier state. Doxycycline and erythromycin are effective against the carrier state. Treatment should be continued for at least 4 weeks. *Borrelia burgdorferi* can be treated with doxycycline (see ch. 211). Pyelonephritis is usually caused by Gram-negative bacteria, against which fluoroquinolones have good spectrum and good renal tissue penetration. Ampicillin, amoxicillin, amoxicillin-clavulanic acid, or cephalosporins may be effective. Trimethoprim-sulfa drugs are effective against *E. coli* and Gram-positive bacteria. Sulfonamides do not reach effective intrarenal concentrations; only the trimethoprim component is effective. Aminoglycosides should be avoided due to potential nephrotoxicosis. Pyelonephritis treatment should continue for at least 4 to 6 weeks. Urine should be cultured 3 to 7 days after completing antibiotic therapy and repeated in 1 month if negative. If the culture is positive, treatment is indicated for an additional 4 weeks with appropriate antibiotic.

Other Medications

Use of 4-methylpyrazole or ethanol for ethylene glycol intoxication should be started within 8 hours of ingestion (see ch. 152). In addition to improving renal perfusion with fluid therapy, NSAID intoxication can be treated with misoprostol, a prostaglandin E analogue (1-3 mcg/kg PO q 6-8 h). When treating aminoglycoside toxicosis, ticarcillin and carbenicillin will complex aminoglycosides, thus preventing renal uptake and may be an early treatment after excessive dosing.[83] Urinary alkalinization is recommended for sulfonamide toxicosis and pigment nephropathy.[80,83] Maintenance of high urine flow rates with mannitol and high-volume fluid therapy may also be beneficial.

Treatment of Uremic Complications

Hyperkalemia

Acute Therapies

Renal excretion is the major mechanism for removing K from the body (see ch. 68). Chronic hyperkalemia is unlikely with normal renal function. Hyperkalemia, possibly life-threatening, is more likely to develop in oliguric or anuric AKI as compared with PU.[102] Increased extracellular K changes the electrical potential of excitable cells. Typical ECG changes include bradycardia, tall, spiked T waves, shortened QT interval, wide

QRS complex, and a small, wide or absent P wave. Severe hyperkalemia can lead to a sinoventricular rhythm, ventricular fibrillation, or standstill. Muscle weakness may be present with a serum K concentration >8 mEq/L.[177] A pet with suspicious ECG changes may require emergency therapy before results of the serum K are available. Ca gluconate 10% (0.5 to 1 mL/kg IV to effect, given slowly) can be used in critical situations to restore cardiac membrane excitability, but does not decrease K concentrations. During infusion the ECG must be monitored and the rate slowed or stopped if arrhythmias worsen. The cardiac effects should be apparent within minutes, but duration of effect is less than an hour.[178] Giving Ca increases risk of soft tissue mineralization if hyperphosphatemia is present.

Insulin, Glucose, Bicarbonate

Several methods can be used to move K from the extracellular space intracellularly. Regular insulin (0.5 units/kg IV) has an effect within 20 to 30 minutes. Dextrose (1 to 2 g per unit insulin as an IV bolus, then 1 to 2 g per unit insulin in IV fluids given over the following 4 to 6 hours) is necessary to prevent hypoglycemia when insulin is used. Dextrose induces endogenous insulin release in nondiabetic patients and can be used without concurrent insulin administration to control mild to moderate hyperkalemia, at a dosage of 0.25 to 0.5 g/kg IV.

Metabolic acidosis from mineral acids (e.g., NH_4Cl, HCl) but not organic acids (e.g., lactic acid, ketoacids) causes K to shift from cells to the extracellular space and circulation as hydrogen ions enter cells. Correction of metabolic mineral acidosis with bicarbonate causes K to return to cells as H^+ is combined with HCO_3^- and removed. The dose of Na bicarbonate used to treat hyperkalemia is based on calculation of the base deficit (ideally), or a fixed dosage of 1 to 2 mEq/kg IV over 10 to 20 minutes. Na bicarbonate is contraindicated if the partial pressure of carbon dioxide (PCO_2) is increased or if metabolic alkalosis is present as it may cause hypernatremia or paradoxical CNS acidosis. If the ionized Ca concentration is low, dextrose is preferred to bicarbonate because alkalemia exacerbates hypocalcemia (see ch. 69).[102]

Albuterol, Exchange Resins and Drugs to Avoid

The beta-agonist albuterol has been used to treat hyperkalemia in people because it moves K into cells.[102] The cation exchange resin sodium polystyrene sulfonate (Kayexalate, Kionex) can be administered orally or by enema (dosage: 2 g/kg q 6-8 h as a suspension in 20% sorbitol).[39] This binds K in the GI tract, releases Na, takes several hours to act, and includes side effects such as hypernatremia and constipation. The K-lowering effects of these drugs, with the exception of polystyrene sulfonate, are temporary. Serum K concentrations gradually rise within several hours of administration unless urine production is induced. Once even minimal urine production resumes, serum K concentrations usually decrease. Peritoneal or hemodialysis may be necessary to ultimately control K if oliguria or anuria persist. Drugs that contribute to hyperkalemia should be avoided, including nonspecific beta-blockers, digoxin, ACE inhibitors, angiotensin receptor antagonists, nonsteroidal anti-inflammatory drugs, K-sparing diuretics (spironolactone, amiloride, triamterene), high doses of trimethoprim, cyclosporine, and total parenteral nutrition (TPN).[69]

Hypokalemia

Low K can occur with AKI because of excessive urinary losses due to PU, diuretic use, or losses due to vomiting or diarrhea. The amount of K chloride added to IV fluids should be based on the serum concentration (see ch. 68). Oral K supplementation (1 to 3 mEq/kg/day) may be used for pets that are eating or have a feeding tube. The serum K concentration should be monitored frequently to avoid hyperkalemia or hypokalemia.

Sodium (Na)

Serum Na concentrations may be normal, increased, or decreased in AKI (see ch. 67). Hypernatremia prior to fluid therapy indicates excessive free water loss. Administration of Na bicarbonate or hypertonic saline may cause hypernatremia. Hyponatremia may indicate losses due to excessive urinary excretion, vomiting, diarrhea, or transient dilutional hyponatremia after giving mannitol, hypertonic dextrose, or colloid solutions. Solutions low in Na (5% dextrose, TPN, enteral formulations) may cause hyponatremia. In many situations, initial dehydration follows isonatremic fluid losses and a normal Na concentration.[39,102] Clinical signs are unlikely unless rapid changes occur in serum Na concentrations and are generally related to neurologic

dysfunction. The rate of Na change should not be more than 12 mEq/L per day.[179] Chloride changes tend to parallel Na changes.

Metabolic Acidosis

Metabolic acidosis is common in AKI. Daily H^+ load is excreted with NH_3 as NH_4^+ or with phosphate as $H_2PO_4^-$ (see ch. 128). Failing kidneys are unable to excrete H^+ or reabsorb HCO_3^-. Acidosis can be worsened by lactic acidosis from dehydration and poor perfusion. Intravenous Na bicarbonate therapy can be considered if acidosis persists after correcting dehydration and is usually reserved for animals with a pH less than 7.2 or HCO_3 < 12 mEq/L. Treatment with Na bicarbonate is geared toward causing acid (H^+) to combine with bicarbonate (HCO_3^-) to form H_2CO_3, which dissociates to H_2O and CO_2. If the lungs are unable to eliminate the CO_2, the reaction does not proceed. Bicarbonate administration, however, can increase the PCO_2 and lead to paradoxical CNS acidosis. Since CO_2 is highly diffusible, moving quickly from the circulation into the CNS, it is converted back to acid (H^+) in that environment. Na bicarbonate treatment is also contraindicated with hypernatremia. Bicarbonate doses are calculated from the formula: 0.3 × body weight (kg) × base deficit, where the base deficit = 24 − patient HCO_3. Give ¼ to ½ directly, IV, and an additional ¼ to ½ dose in the IV fluids over the next 2 to 6 hours. Adjust any subsequent doses based on serial evaluation of blood gas determinations. Oral alkalinizing agents can be used once oral intake is possible. K citrate (40 to 75 mg/kg PO q 12 h) addresses metabolic acidosis and hypokalemia. Oral Na bicarbonate (8 to 12 mg/kg PO q 12 h) is more palatable in tablet form compared with powder. Doses should be adjusted based on need.

Calcium (Ca) and Magnesium (Mg)

Hypocalcemia

One of many causes for Ca disorders in pets with AKI includes an acute decrease in glomerular filtration leading to an abrupt increase in phosphorus, which causes acute hypocalcemia due to the law of mass action (see ch. 69). Decreases in Ca stimulate parathyroid hormone synthesis and secretion, which increases Ca back to normal. Metabolic acidosis increases the ionized Ca (iCa) fraction. Symptomatic hypocalcemia (tetany) occurs infrequently in AKI. Hypocalcemia may be more severe with antifreeze-induced AKI (see ch. 152), because antifreeze phosphate can cause acute severe hyperphosphatemia while ethylene glycol is converted to oxalate which complexes Ca. Treatment with Ca increases risk of soft tissue mineralization in hyperphosphatemic pets. The minimal dosage of Ca gluconate that controls clinical signs should be used when needed. 10% Ca gluconate can be used (dosage: 0.5 to 1.5 mL/kg IV over 20 to 30 minutes). As when treating hyperkalemia, it is important to monitor the ECG during infusion.

Hypercalcemia

Hypercalcemia, based on total serum Ca concentrations, is usually mild and associated with normal iCa with no treatment necessary. If the iCa is increased, it may resolve with fluid therapy. Ca-containing fluids (such as LRS) should be avoided. Saline (0.9% NaCl) is an ideal fluid because the Na content increases calciuresis. Furosemide also promotes urinary Ca excretion. Na bicarbonate therapy decreases iCa as more Ca binds to serum proteins. Hypercalcemia from renal failure is not glucocorticoid-responsive.[180] Calcitonin or bisphosphonates could be considered if the hypercalcemia is severe, although bisphosphonates can induce renal failure.[180]

Magnesium (Mg)

Since the kidneys are the primary route of excretion, Mg concentrations may be increased in AKI, but specific therapy is generally not necessary (see ch. 68). Mg, such as that found in some phosphate binders, should be avoided. Hypomagnesemia may occur with PU and renal failure. Hypokalemia may be refractory to therapy if concurrent hypomagnesemia is present. Mg sulfate or Mg chloride can be given IV. Various forms are available for oral supplementation.[181]

Phosphorus (PO_4)

Dietary PO_4 is readily absorbed from the GI tract and excreted by the kidneys (see ch. 69). Decreased excretion commonly leads to hyperphosphatemia in both AKI and CKD. Intravenous fluid therapy may partially control PO_4 concentrations by addressing the hemodynamic component and improving renal blood flow. There are no specific treatments to decrease serum PO_4 in AKI other than renal replacement therapy. PO_4 binders prevent absorption from food. Oral PO_4 binders can be added when enteral feeding is started. Aluminum hydroxide or aluminum carbonate is administered at 30 to 90 mg/kg/day divided with meals. Ca acetate (60 to 90 mg/kg/day) and Ca carbonate may cause hypercalcemia and should be avoided in hypercalcemia. Ca carbonate combined with chitosan is a veterinary product for binding PO_4.

Hypertension

Hypertension is a common complication of AKI, affecting 37% of dogs at admission and increasing to over 80% during hospitalization (see ch. 157 and 158).[105] Progressive volume loading as a result of IV fluid therapy may contribute to the incidence and severity of hypertension. Acute hypertension can cause ocular damage (detached retina, hyphema, retinal edema; see ch. 11), CNS signs from hemorrhage (see ch. 260), cardiac abnormalities (see ch. 253), or progression of renal damage. Treatment is indicated if the systolic blood pressure is >180 mm Hg. Pets with both AKI and volume excess may also have hypertension that responds to decreasing volume overload. If antihypertensive medications are required, the goal is to decrease systolic pressure to <180 mm Hg, but to avoid precipitous decreases. Amlodipine (0.18 to 0.3 mg/kg PO q 24 h for cats, 0.2 to 0.4 mg/kg PO q 24 h for dogs) may provide a response within 24 to 48 hours. If the blood pressure does not improve within a few hours, additional doses can be administered in dogs, up to a maximum of 1 mg/kg/day.[105] ACE inhibitors are generally avoided in AKI because they may decrease renal perfusion by causing afferent arteriolar constriction. If immediate control of hypertension is necessary, the onset of action of hydralazine (2.5 mg/cat PO or SC once, 0.5 to 3 mg/kg PO q 12 h for dogs) is 15 minutes (SC) to 1 hour (PO). Blood pressure must be monitored closely after administration (see ch. 99).

Hematologic Disorders

Anemia may occur with AKI because of GI bleeding, repeated blood sampling, or dilution associated with volume overload. If clinical signs of anemia are present (i.e., tachycardia, heart murmur, weakness, dull mentation, anorexia), blood transfusion is indicated (see ch. 130). Packed RBC transfusion is preferred to whole blood if the pet is volume overloaded and/or oliguric. There is no absolute degree of anemia to dictate transfusion. More liberal criteria are generally used if the anemia develops acutely. Recombinant erythropoietin products (e.g., Epogen, Darbepoetin) can increase RBC production over a week. They have been used when anemia is anticipated, to decrease eventual transfusion requirements, although there are risks of immunologic reactions. Uremia induces platelet function defects. The buccal mucosal bleeding time (see ch. 80) will be prolonged despite a normal coagulation profile. Desmopressin (1-deamino-8-arginine vasopressin [DDAVP]; see ch. 201 and 296) is used in uremic people with active bleeding, but this treatment has not been evaluated in animals. Duration of activity in people is short (less than 24 hours), and would be considered immediately prior to invasive procedures.[182]

Gastrointestinal (GI) Disorders and Pancreatitis

GI complications (anorexia, nausea, vomiting, ileus) occur commonly in AKI, with bleeding in 10% to 30% of affected people.[80] Histamine blockers or proton pump antagonists are commonly used in AKI to inhibit gastric acid secretion. Because some of these drugs are excreted via the kidneys, dosage and frequency should be adjusted. Antiemetics are frequently needed (see ch. 39). Motility modifiers are indicated if ileus is present. If there is evidence of GI ulceration (e.g., hematemesis, melena, increased BUN : creatinine ratio, panhypoproteinemia with acute anemia), a gastric protectant (Sucralfate) should be administered (Table 322-4). Pancreatitis is common in AKI (see ch. 290 and 291). Antiemetics, pain management, and early nutritional support (parenteral [see ch. 189] if vomiting is not controlled, by feeding tube [see ch. 82] if patient is anorexic but not vomiting) are recommended.

TABLE 322-4

Common Drugs Used to Treat Gastrointestinal Signs in Uremia*

DRUG	INDICATION	DOSAGE—DOGS	DOSAGE—CATS	ADJUSTMENT FOR RENAL FAILURE AND COMMENTS
Famotidine	Decrease acid	0.5-1 mg/kg PO, IM, IV q 12-24 h	0.25-0.5 mg/kg PO, SC q 24 h	Prolong interval or decrease dosage
Ranitidine	Decrease acid, motility modifier	0.5-2 mg/kg PO, IV q 8-12 h	0.5-2.5 mg/kg PO, SC, IM, IV q 12 h	Prolong interval or decrease dosage
Cimetidine	Decrease acid	5-10 mg/kg PO, IM, IV q 4-6 h	5-10 mg/kg PO, IM, IV (slow) q 6-8 h	Prolong interval or decrease dosage
Omeprazole	Decrease acid	0.5-1 mg/kg PO q 24 h	0.7 mg/kg PO q 24 h	Do not open capsules
Pantoprazole	Decrease acid	0.5-1 mg/kg IV (over 15 min) q 24 h	0.5-1 mg/kg IV (over 15 min) q 24 h	
Metoclopramide	Antiemetic, motility modifier	0.1-0.5 mg/kg PO, SC, IM q 6-8 h, 0.01-0.02 mg/kg/h CRI	0.2-0.4 mg/kg SC q 6-8 h or 0.01-0.02 mg/kg/h CRI	Decrease dosage
Ondansetron	Antiemetic	0.1 mg/kg PO q 12-24 h	0.1 mg/kg PO q 6-8 h, 0.1-0.3 g/kg IV q 6-8 h	
Dolasetron	Antiemetic	0.5 mg/kg PO SC, IV q 24 h	0.5 mg/kg PO, SC, IV q 24 h	
Maropitant	Antiemetic	2 mg/kg PO q 24 h or 1 mg/kg SC q 24 h for 5 days	1 mg/kg PO, SC daily for 5 days	
Mirtazapine	Antiemetic, appetite stimulant	1.1-1.3 mg/kg PO q 24 h	1.88 mg per cat PO q 48 h	
Chlorpromazine	Antiemetic	0.2-0.5 mg/kg IM, SC q 6-8 h	0.2-0.5 mg/kg IM, SC q 8 h	
Prochlorperazine	Antiemetic	0.1-0.5 mg/kg IM, SC q 8-12 h		
Sucralfate	Gastric protectant	0.5-1 g PO q 6-8 h	0.25 g/cat PO q 8 h	
Misoprostol	Cytoprotective PGE analogue	1-3 mcg/kg PO q 6-12 h		
Cisapride	Motility modifier	0.1-0.5 mg/kg PO q 8-12 h	2.5-5 mg/cat PO q 8-12 h	

*Most of these drugs have not been approved for use in the dog or cat.

CRI, Continuous rate infusion; *PGE*, prostaglandin.

Nutritional Support

AKI is a highly catabolic condition. Although difficult to clearly identify the contribution of nutritional management to outcome, poor nutritional status is a major factor in increasing morbidity and mortality.[183] Early enteral feeding can help preserve GI mucosal integrity.[184] Although renal diets (reduced PO_4 and high-quality protein) are indicated for treating CKD, the ideal diet for AKI is not known (see ch. 184).[185,186] In the absence of information, enteral diets for critically ill animals or people have been used.[102] Anorexia is common in the hospitalized renal failure patient (see ch. 23). If the appetite does not return within a few days of therapy, feeding tube placement (see ch. 82) may allow administration of an appropriate quantity of the desired diet, easy administration of oral medications, and is strongly recommended in animals not voluntarily consuming adequate calories. If vomiting prohibits enteral feeding, partial parenteral nutrition or TPN may be used (see ch. 189).

Whether supplementation is enteral or parenteral, the volume that can be administered may be limited in anuric or oliguric patients. Most liquid diets suitable for use in a nasoesophageal or nasogastric tube have a caloric density around 1 kcal/mL.[187] Provision of 100% of the basal energy requirements generally will require

a volume of about twice insensible fluid requirements. Common formulas for calculation of total parenteral nutrition also use almost twice the insensible fluid requirements.[188] Need for nutritional support is an indication for fluid removal via dialysis in the oliguric patient. Glutamine supplementation may improve survival in human AKI patients, but further research is needed.[189]

Infections

Infections occur in 30% to 70% of people with AKI because of impaired defenses secondary to the uremia combined with use of antibiotic therapy.[80] Primary sites of infection include the urinary tract, sites where breaks occur in normal barriers (e.g., IV catheters), and the respiratory tract.[80] The infection rate in veterinary patients with AKI is unknown, but the rate of infections in dogs and cats receiving hemodialysis (predominantly for AKI) is at least 25%.

Prognosis

The mortality of both hospital-acquired and community-acquired AKI is high. In dogs with a mild increase in creatinine (<50% increase from baseline or ≥0.3 mg/dL increase but nonazotemic), mortality was 55% to 58%. In dogs and cats developing more severe AKI in the hospital, mortality was 41% to 66% in dogs and 58% to 73% in cats.[10,11,22] The mortality rate in dogs with community-acquired AKI was 56%.[21] Mortality rates in cats with community-acquired AKI, were 47% to 64%.[23,190] The mortality rate in people is about 50%.[191] Decreased urine production is a poor prognostic factor in dogs and cats with AKI.[22,23] The severity of azotemia was not predictive of outcome in most studies of cats or dogs with AKI, whereas an initial severe increase in serum creatinine was associated with failure to recover from AKI in one study in dogs.[21-23,192,193] In one case series of cats with AKI, for each unit increase in serum potassium, in mEq/L, there was a 57% decrease in chance of survival.[23] In another study, lower body temperature, serum albumin, and lactate dehydrogenase were predictive of mortality.[190] Of cats that survive the AKI episode, about half were discharged with a normal serum creatinine concentration. The other half of the survivors had persistent azotemia.[23] In dogs with AKI, 24 of 99 developed CKD (24 of 43 survivors).[21] Disease etiology is a prognostic factor with AKI (Table 322-5). In one study, 50% of cats with a nephrotoxic or other cause survived, whereas 75% of cats with ischemia survived.[23] In dogs with hospital-acquired AKI, 43% of dogs with nephrotoxicant exposure survived, although no association between type of renal insult and outcome was found in that study.[22]

TABLE 322-5

Survival Rates for Various Etiologies of AKI[2,23,52,202]

CATEGORY	NONDIALYTIC MANAGEMENT	HEMODIALYSIS
Obstructive (cats)	91%	70%-75%
Infectious	82%	58%-86%
Metabolic/hemodynamic	66%	56%-72%
Other	50%	29%-56%
Toxic	43%-69%	18%-35%

Overall, 40% to 60% of patients with AKI treated with hemodialysis survive, a notable achievement given that the patient population is comprised of animals unresponsive to conventional medical management.[194,195] The survival rate for AKI from infectious causes was about 58% to 100%.[192,193,196,197] Hemodynamic and metabolic causes had a 40% to 72% survival rate.[193,198] Only 20% to 40% of patients with AKI from toxic causes survive.[192,193] Of the patients receiving hemodialysis that do not survive, about half of those die or are euthanatized because of extrarenal conditions (e.g., pancreatitis, respiratory complications). About a third of nonsurvivors are euthanized because of failure of recovery of renal function. Ongoing uremic signs, dialysis complications, and unknown causes account for the remaining patient deaths. As with patients treated

medically, approximately half regain normal renal function (defined by normal serum creatinine concentration) and half have persistent CKD.

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*As a decimal (e.g., for 7%, use 0.07).

CHAPTER 323

Renal Transplantation

Chad W. Schmiedt

Client Information Sheet: Renal Transplantation

Renal Transplantation in Cats

Candidate Selection

The ideal renal allograft recipient is a cat with significant, compensated, chronic kidney disease (CKD) that is otherwise healthy. The optimal timing of transplantation relative to stage of kidney disease is unknown. Delaying transplantation until a cat is in end-stage uremia is not desirable, as the degree of azotemia is a known risk factor for poor outcomes.[1,2] Conversely, kidney transplantation in cats with asymptomatic, early-stage CKD also is not optimal given the long survival times that exist with medical management and the perioperative risk associated with transplantation. Several centers use a minimum serum creatinine of 4.0 mg/dL as a benchmark to maximize beneficial opportunities of medical management and mitigate perioperative risk for minimally affected cats.

Older cats have been identified as living shorter durations after transplantation compared to younger cats.[1,2] However, older cats without other significant comorbidities may still experience substantial improvement in quality of life following transplantation. Therefore, older animals may qualify for transplantation and should be considered in light of their complete clinical picture.

Prior to transplantation, a thorough systemic evaluation is performed to maximize the opportunity for a successful outcome and to ensure the donor's kidney is not wasted. While criteria vary slightly between transplantation centers, and these should be confirmed with each site, generally required testing is listed in Box 323-1. Conditions which definitively rule a cat out for transplantation include feline immunodeficiency virus (FIV) or feline leukemia virus (FeLV) infection, moderate to severe heart disease, neoplasia, pyelonephritis, other significant comorbidities, or an inability for owners to medicate or obtain veterinary care for their cat. Conditions that preclude transplantation until they are addressed include systemic hypertension, hyperthyroidism, active infection, and periodontal disease.

Box 323-1

General Testing Required Prior to Renal Transplantation

- Complete blood count and serum biochemical profile
- Urinalysis and culture
- Urine protein to creatinine ratio
- Blood pressure measurement
- Serum thyroid hormone concentration (T_4)
- Infectious disease testing
  - Feline immunodeficiency virus
  - Feline leukemia virus
  - *Toxoplasma* IgG and IgM
  - ±Coronavirus titers
  - ±*Mycoplasma* titers
  - ±*Bartonella* Western blot

- Echocardiogram
- Abdominal and thoracic radiographs
- Abdominal ultrasound
- Blood type
- Dental examination

Cats for which veterinarians have a clinical suspicion of a latent infection may undergo a cyclosporine trial for 1-3 months prior to transplantation. The goal of a cyclosporine trial is to achieve therapeutic blood concentrations of cyclosporine (300-500 ng/mL) and monitor for infection prior to the definitive procedure. Animals with CKD secondary to or concomitant with calcium oxalate urolithiasis may still undergo renal transplantation with good outcomes, although calcium oxalate nephrolithiasis in the allograft is possible.[3]

Donor Selection

Kidney donors should be young cats (≈1-2 years) that are free of disease. Transplant programs require the recipient's owners to adopt donor cats. The source of donor cats may be the recipient's household, a shelter or humane society, an intramural colony at the transplantation center, or a USDA-licensed, Class A vendor. The latter is most common as the use of purpose-bred cats minimizes potential risks of disease transmission. Donor candidates should be thoroughly screened for disease. Transmission of disease through the donated kidney is possible.[4,5] To optimize surgical planning, cross-sectional imaging can be used for investigating the donor cat's renal vasculature prior to surgery.[6]

Especially in Europe, there are ethical concerns about feline kidney transplantation, and particularly about using healthy cats as kidney donors.[7] Maintaining rigorous recipient criteria, positively impacting recipient quality of life, and rehoming shelter or purpose-bred research cats with devoted owners may mitigate concerns of removing a kidney from a donor cat. One study that followed 16 renal donors 2 to 5 years after uninephrectomy found renal and erythropoietic function to be preserved in 14 cats, while 2 cats developed dilute urine and proteinuria.[8]

Surgery

Details of surgical technique vary by surgeon; however, long-term surgical outcomes have been relatively consistent, suggesting long-term consequences of surgical preference are minimal.[1,2] Unless there is an indication, the two native kidneys are not removed. Renal allografts are implanted in a heterotopic location caudal to the native kidneys. The renal artery is anastomosed end-to-side with the aorta, and the renal vein is anastomosed end-to-side with the caudal vena cava.

There are two strategies for anesthetic and surgical timing of the kidney donor and recipient. With the simultaneous transplantation strategy, the renal donor and recipient are anesthetized at the same time.[9] Two surgical teams work side-by-side and coordinate donor harvest and recipient implantation. In this strategy, the overall ischemia time is reduced, as is the surgical stress endured by a single surgeon performing both the harvest and implantation. In contrast, in the sequential transplantation strategy, the kidney is harvested from the donor, flushed and stored in cold sucrose-phosphate solution, and implanted into the donor usually a few hours after harvest.[2] The longest reported cold ischemic storage time in cats using sucrose-phosphate is 7 hours.[10]

The advantages of the sequential strategy include requiring only one anesthetic and surgical team and utilizing the protective effects of cold ischemia to reduce cell injury.[11] Despite the longer ischemic time, cooling of the allograft reduces cellular damage associated with the injurious warm ischemic period. The sucrose phosphate solution significantly reduces cold ischemic injury compared to flushing with saline.[12] Regardless of the transplantation strategy employed, the goal is to limit warm ischemia time (i.e., the vascular anastomosis time) to 60 minutes or less. In the simultaneous technique, warm ischemia time begins at harvest, and in the sequential technique, warm ischemia time begins when the allograft is removed from the organ storage solution. Warm ischemia ends when blood flow is restored to the allograft.

Following release of the vascular clamps and restoration of blood flow to the allograft, the ureter is implanted into the host bladder. There are two major techniques currently employed for neoureterocystostomy. In the mucosal apposition technique, the ureter is transected near the donor

ureterovesical junction during the harvest procedure. The ureter is shortened and the distal end of the transected ureter is spatulated. The ureteral mucosa is sutured to the recipient's bladder mucosa by intra- or extravesical techniques.[13] The second technique is the ureteral papillae technique, wherein the donor's ureteral papillae is harvested along with the ureter and extravesically sutured to the recipient's bladder and serosa.[14]

Immunosuppression

Following renal transplantation, microemulsified cyclosporine and prednisolone are most commonly used for immunosuppression (see ch. 165). Cats are generally started with a cyclosporine dosage of 4 mg/kg PO q 12 h and the dosage is then adjusted based on whole blood concentration. Target blood concentration in the 3-6 months following transplantation is ≈500 ng/mL and reduced to ≈300 ng/mL over time. Importantly, microemulsified or modified cyclosporine (Neoral, Atopica) should be prescribed as it is more bioavailable and efficacious compared to non-emulsified cyclosporine.[15] Ketoconazole has been used for inhibiting cyclosporine metabolism and enable once daily dosing, which may be important for some owners (also see ch. 165).[16] Gastrointestinal cyclosporine absorption varies significantly between cats; therefore, the cyclosporine dosage should be based on an individual's blood concentration. Cyclosporine blood concentrations are monitored frequently (weekly) immediately after transplantation until the appropriate oral dosage is identified. Frequency of monitoring is extended over time with a maximum interval of every 3 months. In cats with poor absorption of microemulsified cyclosporine, treatment with vitamin B may increase absorption.[17]

Low-dosage prednisolone (0.25-0.5 mg/kg PO q 12 h) also is used frequently. Prednisolone can be continued chronically if well tolerated and required, or reduced or discontinued if complications develop. Other immunosuppressive regimens have been described experimentally in cats following renal transplantation[18] or suggested as options based on *in vitro* experiments.[19]

Complications

Several acute complications are predictable given the required surgical manipulations and they include hemorrhage, thromboembolism, and uroabdomen. Doppler ultrasound studies or ultrasound with contrast are performed routinely postoperatively to evaluate blood flow within the allograft (Video 323-1). Perioperatively, recipient cats can become hypotensive if hypovolemic secondary to anastomotic hemorrhage. Anemia also can be present and related to preexisting CKD or secondary to intraoperative hemorrhage. Perioperative blood transfusions should be administered if the animal has moderate to severe and/or symptomatic anemia (see ch. 130). Chronically, the return to normal of erythropoietin concentration and the concomitant resolution of anemia are extremely variable.[20] Most cats will return to a hematocrit above 28% around 1 month after transplantation.[20] In the absence of active postoperative hemorrhage, low-dosage heparin (125 U/kg SC q 8 h) is used for approximately 5 days after transplantation to minimize the risk of thromboembolism.

Severe systemic hypertension has been reported acutely after renal transplantation and is associated with neurologic clinical signs (see ch. 157).[21] In one study, 21/34 cats became severely hypertensive (systolic blood pressure ≥ 170 mm Hg) and treatment with hydralazine reduced occurrence of neurologic complications compared to a historical cohort (see ch. 158).[21,22] In feline kidney transplant recipients, the typical initial dosage of hydralazine for treatment of severe hypertension is 1 mg/cat SC. The cat's blood pressure is then monitored for reduction over 15-20 minutes (see ch. 99). If no improvement is observed, additional 1- to 2.5-mg increments are administered every 15 minutes to a maximum total dose of 5 mg.

Delayed graft function is a term used for describing lack of function in an allograft with otherwise normal blood flow and no evidence of post-renal urinary obstruction. It has been defined in the veterinary literature as the presence of a serum creatinine concentration ≥3 mg/dL occurring 3 days after transplantation and has been reported in 5 of 60 cats undergoing renal transplantation.[2] Delayed graft function is a consequence of pre-, peri-, or intraoperative graft injury. For example, in humans, allografts taken from older donors, diabetic or hypertensive donors, non-heart-beating cadavers, transplantation surgeries with long ischemic times, or allografts with postoperative ureteral obstruction are at greater risk of delayed graft function.[23] Allografts with delayed function often will eventually develop normal function, but have an increased risk of early and late allograft loss.[23] Concerns about marginal quality of donor kidneys are not an issue in veterinary

transplantation because of our ability to select healthy donors; thus, relevant risk factors in veterinary transplantation for delayed graft function relate to intraoperative ischemic injury or postoperative complications (e.g., ureteral stricture, thrombosis, etc.).

An acute rejection reaction is characterized by palpable enlargement of the allograft, hyperthermia or hypothermia, malaise, loss of appetite, weight loss, and loss of allograft function. Affected cats can be asymptomatic.[24] If cats undergo renal transplantation and do not receive immunosuppressive treatment, the median survival time is 23 days.[24] On an ultrasound examination, an allograft experiencing acute rejection has an enlarged cross-sectional area and loss of the definition of the corticomedullary junction because of increased echogenicity of the medulla (Figure 323-1).[25] There also can be perirenal or peritoneal fluid. The resistive index frequently is measured in renal allografts, but it has not been shown to be a sensitive indicator of allograft rejection.[25,26] Changes in ultrasonographic measurement of renal allograft size (length, width, cross-sectional area) have been associated with allograft dysfunction.[26] An allograft biopsy rarely is necessary and a delay in treatment for biopsy confirmation could be disastrous. A low cyclosporine blood concentration, azotemia, leukocytosis, characteristic ultrasound changes, absence of active infection, and an ill feeling patient, all support the working diagnosis of allograft rejection.

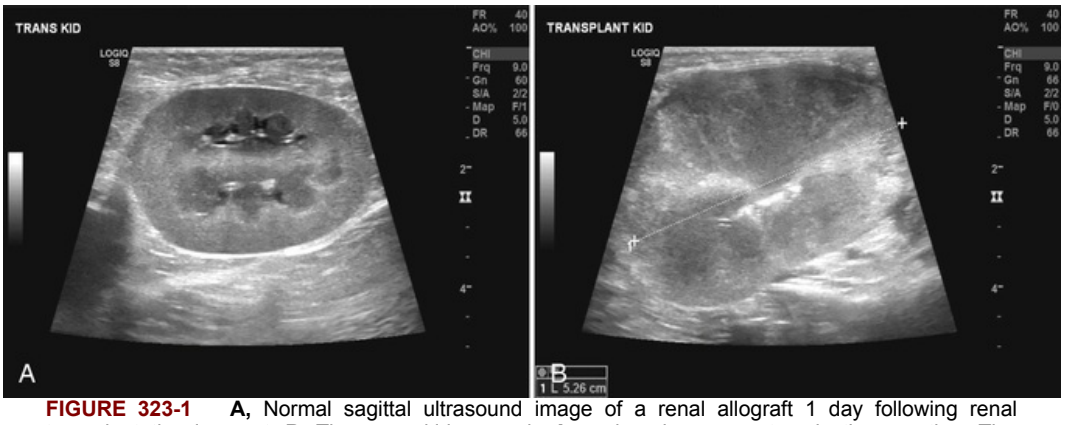

FIGURE 323-1 **A,** Normal sagittal ultrasound image of a renal allograft 1 day following renal transplantation in a cat. **B,** The same kidney as in **A,** undergoing an acute rejection reaction. The allograft is increased in size and has a heterogenous echotexture with loss of distinction of the corticomedullary junction.

Often, an acute rejection reaction can be controlled and reversed with intravenous administration of immunosuppressive dosages of corticosteroids, cyclosporine, and fluid therapy. Therapy should continue until the serum creatinine concentration plateaus, which often takes several days. The allograft may regain baseline function, depending on how rapidly the rejection reaction is diagnosed and appropriately treated. Often, even with successful treatment, there is some loss of function, increased antigenicity of the allograft, and an increased risk of future rejection reactions.[27]

Chronic complications are common following renal transplantation, necessitating dedicated postoperative management. A delayed acute rejection reaction can occur at any time after surgery if the immunosuppressive regimen is discontinued, if medication is administered incorrectly, or if there is altered drug absorption secondary to gastrointestinal disease or diet change. Frequent evaluation of cyclosporine blood concentrations is indicated to minimize the risk of a delayed acute allograft rejection.

Chronic, gradual loss of allograft function is a major problem in renal transplantation, especially in people. Historically, this condition was called *chronic rejection,* but has since been termed *chronic allograft nephropathy, chronic allograft dysfunction,* and, more recently, *interstitial fibrosis* and *tubular atrophy,* to describe the condition relative to hallmark histopathological lesions.[27] Changes characteristic of human chronic allograft nephropathy as they relate to feline renal allografts have been described.[28] Approximately 70% of evaluated feline allografts had histologic evidence of chronic allograft nephropathy.[28]

Because of the requirement for chronic immunosuppression, transplant recipients are at greater risk of infection. Infection can be *de novo*, a recrudescence of a latent infection, or transmitted to the recipient through the allograft. Infections following renal transplantation have been reported in 25-36% of patients.[2,29] Most infections are bacterial, but viral, fungal, protozoal, and mycobacterial infections also have been reported.[2,29]

The presence of uroabdomen and diabetes mellitus have been identified as risk factors for post-transplantation infection in cats.[2,29] Transmission of toxoplasmosis through the allograft and recrudescence of toxoplasmosis in feline transplant recipients has been reported. Treatment of active toxoplasmosis in immunosuppressed cats is routinely unsuccessful, underscoring the requirement for thorough screening for this disease prior to surgery.[4,5]

Following renal transplantation, cats have a ≈6-fold increased risk of developing cancer compared to age-matched control cats.[30-33] This problem is well recognized in people after solid organ transplantation and relates to the chronic antigenic stimulation of the allograft as well as the immunosuppressive and oncogenic influence of many immunosuppressive regimens.[34,35] Cyclosporine can promote oncogenesis by several mechanisms, including promoting tumor angiogenesis, inhibition of DNA repair, inhibition of apoptosis, and synthesis of transforming growth factor-beta (TGF-beta).[36,37] In cats, as in people, lymphoma is the most common malignant neoplasm to develop after renal transplantation and is commonly a mid- to high-grade, diffuse, large–B-cell lymphoma (see ch. 344).[30,32,33] Survival following diagnosis frequently is poor, with reported median survival times between 2 and 15 days.[30-32]

Peritoneal fibrosis has been reported in cats following renal transplantation.[38,39] Retroperitoneal fibrosis was reported in 21% of cats after transplantation,[38] but is not reported frequently in other case series.[1,2] Clinically, the condition is characterized by nonspecific signs including lethargy, anorexia, and a recurrence of azotemia. The allograft and associated ureter become encased in a fibrotic capsule, which results in ureteral obstruction, post-renal azotemia, hydroureter, and hydronephrosis.[39] The condition is reported to occur a median of 62 days after transplantation, and risk factors are unknown.[39] Treatment is surgical débridement of the scar tissue and ureterolysis, or surgically freeing the ureter from the retroperitoneal scar. Recurrence occurred in 6 of 25 cats that underwent surgery and those were treated by repeat ureterolysis.[39] Intraoperative prophylactic treatment with carboxymethylcellulose has been suggested as a means to minimize adhesion formation.[39]

Following renal transplantation, nutrition should be adjusted to the needs of the individual patient. If urinary stones were present prior to transplantation, an appropriate diet should be selected to prevent occurrence of these stones in the allograft (see ch. 324). Maintenance of cats on a renal diet after transplantation could increase the likelihood of obesity because of the increased carbohydrate content of these diets. Selecting a diet lower in carbohydrates, like a senior diet, and frequently monitoring weight may help to minimize weight gain. Diabetes mellitus is common in feline transplantation recipients and obesity will further predispose patients to developing diabetes. Transplant recipients have a 5.4-fold greater likelihood of becoming diabetic compared to control cats with CKD, and the occurrence of diabetes results in a 2.4-fold increase in mortality.[40] Risk factors for development of diabetes in the feline transplantation population are unknown.

Outcomes

Following transplantation, the 6-month survival is approximately 60-65% and the 3-year survival is around 40%.[1,2] When these statistics are considered for cats discharged from the hospital, the 6-month survival increases substantially to 84% and the 3-year survival increases slightly to 45%.[2]

Although it seems obvious, increasing age has been associated with shorter survival times.[1,2] Other factors reportedly associated with overall survival include preoperative azotemia, body weight, postoperative creatinine concentration, percentage of creatinine decline from preoperative levels, Doppler-derived arterial blood pressure, and the presence of preoperative infectious disease.[2] Further work is required to validate these risk factors in other patient populations.

Renal Transplantation in Dogs

Several clinical case series have been published regarding renal transplantation in dogs.[41-43] Uniformly, clinical outcomes have not been as positive as renal transplantation in humans or cats. These poor outcomes exist even after decades of experimental research evaluating a variety of immunosuppression regimens.[44] In the most recent clinical study, 26 dogs undergoing renal transplantation and receiving variations of a cyclosporine-based immunosuppressive regimen were reviewed; the median survival time was 24 days.[41] Dogs in that study had significant morbidity and mortality associated with thromboembolism and infection.

Another cohort of 15 dogs was reported previously and received a regimen of rabbit antidog antithymocyte serum, cyclosporine, azathioprine, and prednisone. These dogs achieved a median survival time of 8 months, with technical failures (venous avulsion, graft torsion), graft rejection, and infection accounting for most of the mortality.[42]

Technically, renal transplantation in dogs is easier to perform because of the typically larger size of the renal vasculature and ureter; however, other factors contribute to the poor outcomes described above. Optimal donor-recipient matching may be more difficult in dogs given the greater number of erythrocyte antigen types in dogs. The clinical studies described above used dog erythrocyte antigen matching alone or in combination with mixed lymphocyte response testing to pair donors and recipients. Suppression of rejection reactions in dogs is particularly challenging with current immunosuppressive protocols, and, frequently, if sufficient immunosuppression is achieved, dogs succumb to opportunistic infection. Additionally and especially in larger dogs, the cost of the immunosuppressive medications can be dramatic. Finally, the preponderance of dogs has a significant glomerular component to their renal disease, which may predispose them to thromboembolic events.[41] How proteinuria changes following transplantation is unknown. Currently, to help minimize some of these issues, renal transplantation is recommended only if related donors are available and it may be more economically feasible in smaller dogs.

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CHAPTER 324

Chronic Kidney Disease

David James Polzin

Client Information Sheet: Chronic Kidney Disease

Overview of Chronic Kidney Disease

Definitions

Chronic kidney disease (CKD) is the most commonly recognized form of kidney disease in dogs and cats. It is defined as structural and/or functional abnormalities of one or both kidneys that have been continuously present for 3 months or longer. The archaic descriptors *kidney insufficiency* and *kidney failure* have not been uniformly and adequately defined; therefore, they have been replaced by a CKD staging system developed by the International Renal Interest Society (IRIS; www.iris-kidney.com). The IRIS CKD staging system provides specificity regarding the extent of kidney dysfunction and recognition of the full breadth of structural and functional CKD. The kidneys of dogs and cats with CKD have permanent reductions in their number of functioning nephrons. Although renal structure and function are not consistently parallel, primary kidney diseases usually display evidence of both structural and functional derangements. The clinical presentation of patients with CKD typically reflects the extent of reduction in renal function rather than the impact of structural lesions.

In most instances, CKD is irreversible and progressive, even with treatment. However, it is common for prerenal or postrenal azotemia or active kidney diseases (called acute-on-chronic kidney disease) to exist with CKD. In contrast to CKD, these complications may be reversible (e.g., pyelonephritis, ureteral obstruction, dehydration, etc.). After correcting reversible primary diseases and/or prerenal or postrenal conditions, further improvement in kidney function should not be expected because compensatory and adaptive mechanisms designed to sustain kidney function have largely already occurred, changes which promote progressive loss of remaining nephrons and kidney function. This characteristic of CKD (called "spontaneous progression of CKD") has been explained by the "trade-off hypothesis" which states that the consequence of the renal adaptive processes maximizing residual kidney function to sustain homeostasis results in a trade-off of ongoing damage to surviving nephrons. Thus, it is not necessary for the initial disease process to persist for the progressive decline in kidney function to continue.

CKD typically causes a slow but inexorably progressive decline in function. In some patients, this pattern follows an almost linear decline, while in others the pattern is characterized by periods of relative stability followed by episodes of precipitous decline in renal function. Some patients may have multiple periods of stable renal function and a series of precipitous declines before succumbing to CKD. However, exceptions to this progressive pattern are recognized, particularly among a substantial subset of cats who have stable renal function for years. In one recent study, only 101 of 213 (47%) cats with CKD showed evidence of progressive increase in serum creatinine values.[1] This pattern of stability may also be observed in some young dogs with renal dysplasia. Unless additional kidney injury occurs or CKD is advanced, rapid deterioration of remaining kidney function is atypical. Rather, kidney function often remains stable or declines over months to years.[2,3] Thus, regardless of initiating cause, CKD is an irreversible and slowly progressive disease. While no treatment can correct existing irreversible kidney lesions of CKD, the clinical and biochemical consequences of reduced kidney function can often be ameliorated by supportive therapy, and the natural progressive course of CKD may be slowed by therapeutic intervention.

Prevalence and Affected Populations

Overall Prevalence

The prevalence of kidney disease has been estimated to range between 0.5% and 7% in dogs and between 1.6% and 20% in cats.[4] However, it has been suggested that a reasonable estimate of the overall prevalence of CKD in general small animal practice in the United States would be 1% to 3% of cats and 0.5% to 1.5% of dogs.[5] One study estimated the prevalence of CKD in United Kingdom dogs to be 0.02% to 1.44%.[6] Of the dogs studied in this report, 95/136 (63.6%) were IRIS CKD stages III or IV, whereas 37/136 (26.6%) had blood urea nitrogen (BUN) concentrations at or above 112.0 mg/dL.

Cats

Although frequently considered a disease of older animals, CKD occurs with varying frequency in dogs and cats of all ages. In a retrospective study of cats with CKD, 53% of affected cats were >7 years old, but the age range was 9 months to 22 years.[7] In a study on age distribution of kidney disease in cats from data submitted to the Veterinary Medical Data Base at Purdue University between 1980 and 1990, 37% of cats with a diagnosis of "renal failure" were less than 10 years old, 31% of cats were between the ages of 10 and 15, and 32% of cats were older than 15 years of age.[8] Similarly, in a study of cats with CKD reported in 1988, their mean age was 12.6 years with a range of 1 to 26 years.[3,9] Mean age among 45 control cats in this study was 10.0 years. During the year 1990, the prevalence of kidney disease among cats of all ages was reportedly 16 cases for every 1000 cats examined. During the same year, the prevalence of kidney disease among cats 10 years of age or older was 77 per 1000 cats examined, and among cats older than 15 years, 153 per 1000.[7] In a study of cats >9 years of age, 30.5% of cats developed azotemia within 12 months.[10] Maine Coon, Abyssinian, Siamese, Russian Blue, and Burmese cats were disproportionately reported as affected.

Dogs

Dogs from the United Kingdom ≥12 years of age had 5.5 times the chance and dogs aged 4 to 7 years had 0.22 times the odds of CKD compared with dogs aged 7 to 12 years.[6] In the same study, Cocker Spaniels and Cavalier King Charles Spaniels had increased odds of CKD compared with crossbreds. However, purebred dogs did not show increased odds of CKD, either overall or for those younger than 5 years of age. An association between CKD and smaller body size has previously been reported in dogs, but no such association was found in the UK study.[6,11] Although CKD apparently occurs less commonly in dogs than in cats, the incidence increases with age in both. Based on data submitted from 1983 to 1992 to the Veterinary Medical Data Base at Purdue University, 18% of dogs with a diagnosis of "renal failure" were <4 years of age, 17% were 4 to 7 years, 20% were 7 to 19 years, and 45% were >10 years of age. The prevalence of a diagnosis of "renal failure" among dogs of all ages was 9 cases for every 1000 dogs examined. The prevalence of "renal failure" among dogs 7 to 10 years of age was 12.5 per 1000 dogs examined, for dogs 10 to 15 years it was 24 per 1000, and among dogs >15 years it was 57 per 1000. More recently, prevalence of CKD in dogs seen in general practice was estimated to be as high as 1.5%.[5] The observation of increasing odds of CKD with increasing age is consistent with the theory of CKD progression from early subclinical kidney damage to clinical disease.

Causes of CKD

Initial Suspicion

Most dogs and cats are initially suspected of having CKD after being noted to have an increase in serum creatinine concentration. Serum creatinine values above reference ranges imply that glomerular filtration rate (GFR) has decreased by 75% or more and that at least 75% of the nephrons in both kidneys have been injured or lost. Thus, diagnosis of CKD in dogs and cats is recognized relatively late in the course of disease. Typically, the kidneys are small because lost nephrons are replaced by scar tissue and chronic inflammation that fails to provide much guidance as to the etiologic origin of injury (Figure 324-1). Further, surviving nephrons reflect adaptive and compensatory modifications that may interfere with establishing the etiologic origin of CKD. Thus, the etiologic basis of kidney disease is not usually determined. Perhaps earlier detection of CKD (e.g., IRIS CKD stage I) might provide an opportunity to establish the initiating disease(s) responsible for CKD.

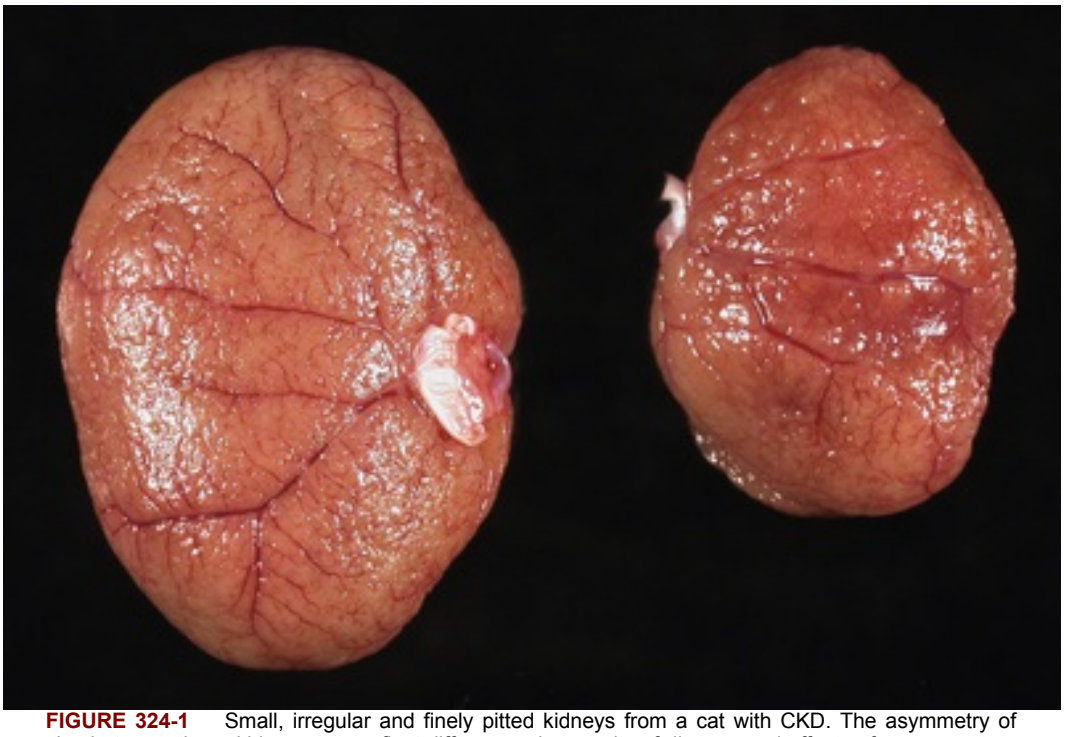

FIGURE 324-1 Small, irregular and finely pitted kidneys from a cat with CKD. The asymmetry of size between these kidneys may reflect differences in severity of disease and effects of compensatory hypertrophy.

Dogs

CKD may begin with a variety of different familial, congenital, or acquired conditions. Biopsy findings in 37 dogs with primary renal azotemia revealed that 58% had chronic tubulointerstitial nephritis, 28% had a glomerulonephropathy, and amyloidosis was observed in 6%, although earlier estimates suggested glomerular disease may account for over 50% of the CKD in dogs.[12,13] Over the past decade, the occurrence of glomerular disease appears to have increased substantially in selected geographic areas due to increased prominence of certain infectious diseases such as borreliosis in the United States (see ch. 211) and leishmaniasis in Europe (see ch. 221).[14] Many of these dogs have or develop CKD; however, an accurate measure of the prevalence of glomerular disease in dogs has not been established. The proportion of CKDs due to glomerular disease is confounded by affected dogs having several concurrent renal syndromes, including CKD, acute kidney injury (AKI), nephrotic syndrome, or isolated proteinuria (initially IRIS CKD stage I).

Cats

In cats with CKD, 70% had tubulointerstitial nephritis, glomerulonephropathy was seen in 15%, lymphoma in 11%, and amyloidosis in 2%. As with dogs, the initiating cause(s) of CKD often cannot be determined. The etiologic basis of diseases in the tubulointerstitium has been especially elusive. Glomerulonephropathies have been linked to a variety of neoplastic, metabolic, and infectious and noninfectious inflammatory processes.[15] Several infectious agents are proposed as possible factors promoting the remarkably high prevalence of feline CKD. Feline immunodeficiency virus (FIV) has been linked to renal disease in cats, although few with CKD are FIV positive.[16,17] A feline morbillivirus has been associated with tubulointerstitial lesions in cats.[18] Feline herpesvirus 1, calicivirus, and panleukopenia virus vaccines grown in feline tissue culture and given to kittens subcutaneously induce anti-feline-renal-tissue antibodies in serum, prompting concerns that vaccinations may play a role in development of CKD.[19-21] While these causes have been proposed as possible causes for feline CKD, they remain largely unsubstantiated.

It has been hypothesized that at least in some cats, renal disease may be an adaptive mechanism associated with normal aging.[22] Early onset renal tubulointerstitial changes occur in younger adult cats and this has been proposed as a defensive adaptation. Further, while older cats succumbed to overt renal disease with increased frequency, cats with renal tubulointerstitial changes have longer life spans regardless of cause of

death. More telomere shortening was noted in cats with CKD in their proximal and distal tubular epithelial cells than in healthy young or geriatric cats.[23] Telomere shortening was not detected in skin or liver samples from any of the cats, suggesting that it is specific to the kidneys. It was concluded that feline CKD is associated with shortened telomeres and increased cellular senescence in affected kidneys, which may present future targets for interventional therapy.

Specific Therapies

Despite the irreversibility of generalized renal lesions associated with CKD, it is important to formulate diagnostic plans to try to identify the underlying cause and to determine if it is still active. Although specific therapy directed at eliminating or controlling the primary cause will usually not substantially alter existing renal lesions, it is important in the context of minimizing further nephron damage. Renal diseases potentially amenable to specific therapy include bacterial pyelonephritis, obstructive uropathy, nephrolithiasis, renal lymphoma (particularly in cats), hypercalcemic nephropathy, perinephric pseudocysts, and some glomerulopathies.

Prognosis of CKD

Influencing Factors

Many factors influence the prognosis of CKD, both favorably and unfavorably, including the quality of medical care provided and level of owner commitment. Prognosis often influences an owner's choice of treatment and compliance in following recommendations. Therefore, it is important to provide the most accurate prognosis possible, best established after reviewing results of a comprehensive evaluation. Factors to be considered in establishing a prognosis for a pets with CKD include: (1) the nature of the primary renal disease, (2) severity and duration of clinical signs and complications of uremia, (3) probability of improving renal function (reversibility, primarily of prerenal, postrenal, and newly acquired primary renal conditions), (4) severity of intrinsic renal functional impairment, (5) rate of progression of renal dysfunction with or without therapy, and (6) patient age. While severity of uremic signs may be a reasonable predictor of short-term prognosis in some individuals, prerenal, postrenal, and active renal complications may be the instigators of signs and may be reversible. In order to most accurately establish the prognosis relating to the underlying CKD, prerenal, postrenal, and active complications (e.g., pyelonephritis) should first be treated. The IRIS CKD staging system is a useful guide for providing a preliminary prognosis. Cats with CKD survive longer than dogs.

Prognosing Cats with CKD

In a retrospective study, median survival time for 211 cats with CKD and serum creatinine concentrations 2.3 to 2.8 mg/dL was 771 days.[24] However, survival varied significantly with IRIS CKD stage. Cats with IRIS CKD stage II had a median survival time of 1,151 days with a 95% confidence interval (CI) of 1,014 to 1,565 days. Because these data only include a subset of IRIS CKD stage II cats, survival durations might have been longer had all stage II cats been included (1.6-2.3 mg/dL). Median life expectancy for cats with IRIS CKD stage III was 679 days (95% CI: 445-910 days) and it was 35 days for cats in IRIS CKD stage IV (95% CI: 21-99 days). In this study, serum phosphorus (PO_4) and IRIS stages were the only baseline parameters that significantly affect survival time. However, severity of proteinuria also influences survival.[25-27] Hypertension does not appear to be a primary determinant of survival in cats with CKD but does affect severity of proteinuria. Both concerns may be masked by the effect of antihypertensive therapy.[25,26]

Unlike people and dogs, amlodipine therapy of hypertension in cats is associated with a reduction in proteinuria which does influence survival stratified by IRIS staging.[27] Anemia has been found to be a prognostic indicator in some, but not all studies. Dehydration and therapy may confound use of packed cell volume as a prognostic indicator. In one study, weight loss was the most reliable indicator of clinical deterioration in cats with CKD and nephrolithiasis was identified as a common comorbid factor in cats with CKD.[1] In a case-control study of 14 cats with stages II and III CKD, nephrolithiasis unassociated with urinary obstruction was not associated with increased mortality rates or in rate of disease progression.[29]

Prognosing Dogs with CKD

In 228 dogs diagnosed at a first-opinion practice as having CKD, their median survival time from diagnosis

was 226 days (95% CI: 112-326 days).[6] During the study, 118/228 (52%) dogs died, 99/118 had been euthanized. IRIS CKD stage and BUN concentration were found to significantly influence their survival. Compared to IRIS CKD stages I and II, dogs with IRIS CKD stage III had 2.6 times and IRIS CKD stage IV had 4.7 times the mortality. Dogs with BUN concentrations ≥112 mg/dL at initial diagnosis had 7.8 (95% CI: 2.6-22.7) times the mortality rate due to CKD than dogs with BUN values <44.8 mg/dL.

Treatment of CKD in dogs appears to affect prognosis. In a clinical trial of 38 dogs with spontaneous CKD, mean serum creatinine concentration did not appear to influence survival when dogs were fed a renal diet and median survival for 21 dogs with a mean serum creatinine concentration of 3.3 mg/dL was 615 days. Median survival for the dogs in this group with serum creatinine values between 2.0 and 3.1 mg/dL was also 615 days.[2] However, in 17 dogs who had a mean serum creatinine of 3.7 mg/dL and were fed a maintenance diet, median survival was 252 days, and in those with serum creatinine values 2.0 to 3.1 mg/dL, it was 461 days. Less information has been reported on prognosis and risk factors for dogs versus cats with CKD. Proteinuria has been identified as a risk factor for development of clinical signs of uremia and for death in dogs with CKD.[30] In one study, proteinuria had a progressively adverse effect on outcome: risk of death due to CKD increased by 60% for each unit of urine protein-to-creatinine ratio (UPCR) >1.0.

Arterial hypertension (see ch. 157) has been identified as a risk factor for mortality in dogs with CKD, but as in cats, adverse effects of hypertension in dogs may be mediated, at least in part, by proteinuria.[31] Dogs with CKD and the highest baseline systolic blood pressures have a greater decline in renal function over time, have increased risk of uremic crises and death. While this does not prove a cause-and-effect relationship between hypertension and progressive renal disease, it does suggest that initial blood pressure values should be considered in formulating a prognosis for dogs with CKD. Higher body condition score (see ch. 170) is associated with a better prognosis (longer survival time) in dogs with CKD.[32] Similarly, obesity is associated with longer survival in humans with CKD, consistent with starvation having a significant role in the outcome (see ch. 176 and 177).

Congenital/Familial Diseases

Compared to the rate of progression of CKD in middle-aged to older dogs with acquired renal disease, CKD may progress more slowly in many dogs with congenital or familial nephropathies not characterized by proteinuria (renal dysplasia; see ch. 328). A comparably slower rate of progression has also been observed in young dogs with acquired CKD (e.g., following nephrotoxin exposure). Many such dogs appear remarkably resistant to developing clinical signs of uremia despite substantial elevations in serum creatinine and urea nitrogen concentrations.

Clinical Consequences of Chronic Kidney Disease

Uremia

Definition

Uremia is the clinical syndrome that results from loss of kidney functions. Impaired renal glomerular, tubular and endocrine functions lead to retention of toxic metabolites, changes in the volume and composition of body fluids, and excesses or deficiencies of some hormones. Clinical signs of uremia reflect the sum effect of these derangements throughout the body. An alternative definition of uremia is "the ill effects of renal failure that we cannot yet explain."[33,34] The pathogenesis of some abnormalities previously regarded as part of the uremic syndrome are now understood (e.g., hypertension due to volume overload, anemia due to erythropoietin [EPO] deficiency), so they would no longer be considered to be part of the uremic syndrome using this newer and more restrictive definition.

Clinical Signs

The clinical signs most likely to prompt veterinary consultation are polyuria and polydipsia (PU/PD). The most prominent clinical signs of uremia are related to the gastrointestinal (GI) tract: anorexia, nausea, vomiting, oral ulcerations, stomatitis, necrosis of the margins of the tongue, halitosis (uremic breath), diarrhea, melena, and hematochezia. Other clinical findings in dogs and cats with CKD may include: weight loss, muscle wasting, hypothermia, lethargy, weakness, muscle tremors, uremic pericarditis and pneumonitis, hypertension, altered behavior (uremic or hypertensive encephalopathy), renal osteodystrophy, and hemorrhagic diatheses. In one study, the most common signs of CKD were vomiting (50%), PU/PD (44%), impaired appetite (40%), diarrhea/melena (37%), weight loss/cachexia (29%), lethargy/depression (22%),

urinary incontinence (20%), halitosis (12%), and anemia (4%).[6]

Pathogenesis

The pathogenesis of specific signs of uremia is variably understood. In general, three major mechanisms are involved: (1) disturbed excretion of electrolytes and water, (2) reduced excretion of organic solutes (i.e., uremic toxins), and (3) impaired renal hormone synthesis. These alterations affect virtually every organ system, thereby producing the uremic syndrome. More than 70 clinical signs have been identified in uremic people.

Disturbed Excretion of Electrolytes and Water

A primary function of the kidneys is to maintain water and electrolyte balance. Excretion of water and electrolytes must accommodate changes in intake. As glomerular filtration rate (GFR) declines with kidney disease, the need for excretion of water and electrolytes remains the same unless intake is modified. As GFR declines, the excretory load of electrolytes and water per surviving nephron substantially increases but excretion of many substances can be maintained through parallel reductions in degree of tubular reabsorption. If GFR declines by three-fourths, the remaining nephrons must each excrete four times more sodium (Na). Thus, maintaining fluid and electrolyte balance requires that more water and electrolytes be excreted per surviving nephron. For Na, potassium (K) and water, a steady state can be maintained even though GFR may be reduced by more than 80%.[35] Although the kidneys have remarkable ability to maintain water and electrolyte balance well into advanced stages of disease, compensatory mechanisms are limited and ultimately fail in end-stage disease. The compensatory mechanisms for some electrolytes are more effective in maintaining balance. For example, adaptive excretion of PO_4 is less effective than adapted excretion of Na. If PO_4 intake continues unchanged and GFR declines, the requirement for PO_4 excretion may exceed adaptive maximum daily rates of PO_4 excretion, and PO_4 begins to accumulate, leading to progressive hyperphosphatemia (hyperPO_4). Clinical manifestations of disturbed water and electrolyte excretion may include edema, hypertension, hypoNa, hyperK, metabolic acidosis and hyperPO_4.

Reduced Excretion of Organic Solutes

Although urea and creatinine are the best known, the kidneys excrete a wide variety of organic solutes (see ch. 62). Many of these solutes are handled primarily by glomerular filtration, but renal tubular secretion and reabsorption may affect net renal excretion. An important difference between renal handling of organic solutes and renal handling of electrolytes and water is that excretion of organic solutes is generally not actively regulated and blood concentrations begin to rise with the initial decline in GFR and continue to progressively increase as renal function continues to decline.[33,34] When GFR declines below about 10% of normal, clinical signs may begin to appear, usually attributed to increased concentrations of organic solutes. However, presence of an increased concentration of a substance does not prove it is a uremic toxin. Nonetheless, that uremic solutes may in fact be contributory to the uremic syndrome is supported by the observation that some uremic abnormalities are transferable with uremic serum or plasma. Abnormalities that have been thus demonstrated include: inhibition of Na-K adenosine triphosphatase (ATPase), inhibition of platelet function, leukocyte dysfunction, loss of erythrocyte membrane lipid asymmetry, and insulin resistance.

In excess of 100 potential uremic solutes have been listed by the European Uremic Toxin Work group (EUTox).[33,34] However, it has been difficult to confirm substances as true uremic toxins. It has been suggested that most retained uremic solutes are probably not toxic, and those that are toxic may only exert their effects when present in combination with other uremic solutes. Urea and creatinine, by themselves, are not uremic toxins. However, plasma urea concentration is believed to be a good reflection of the systemic concentrations of many uremic solutes. Thus, demonstrating that a treatment lowers urea concentrations in and of itself is not conclusive evidence of reduced uremic toxicity (see ch. 62).

In addition to impaired excretion, many middle-sized molecules and various cytokines and growth factors accumulate in CKD because the kidney's capacity for catabolizing many substances is also impaired. Further, plasma levels of many polypeptide hormones, including parathyroid hormone (PTH), insulin, glucagon, luteinizing hormone, and prolactin, increase in patients with CKD because of impaired renal catabolism as well as enhanced glandular secretion.

Impaired Renal Hormone Synthesis

The kidneys normally produce a number of essential hormones, including calcitriol (vitamin D; 1,25-dihydroxycholecalciferol), EPO, prostaglandins, kinins and renin. In particular, calcitriol and EPO have well-established roles in the pathogenesis of clinically important consequences of severe CKD. Calcitriol, the most metabolically active form of vitamin D, is essential for Ca and skeletal metabolism. Vitamin D deficiencies can result in renal secondary hyperparathyroidism and renal osteodystrophy. PTH has been identified as a uremic toxin, although the consequences of hyperparathyroidism beyond its role in renal osteodystrophy in CKD are poorly established. In addition, most cells have receptors for calcitriol and inadequate activation of these receptors may contribute to clinical signs of uremia. It appears that restoration of adequate levels of calcitriol in dogs and humans with CKD may slow progression of kidney disease and prolong survival.[36] EPO deficiency is associated with nonregenerative anemia that may promote weakness, lethargy, and hyporexia.

Gastrointestinal Consequences

Anorexia, Vomiting

GI complications are the most common and obvious clinical signs of uremia. Clinical signs may include nausea, vomiting (see ch. 39), reduced appetite (see ch. 23), stomatitis, GI ulceration, diarrhea and colitis (see ch. 40). Decreased appetite and weight loss are nonspecific findings that may precede other signs of uremia in dogs and cats. Appetite may be selective for certain foods and may wax and wane. Factors promoting weight loss and malnutrition include anorexia, nausea, vomiting and the subsequent reduction in nutrient intake, hormonal and metabolic derangements, and catabolic factors related to uremia, particularly acidosis. Anorexia appears to be multifactorial in origin. Studies using rodent models suggests that a middle molecule "anorectic factor," perhaps a peptide, in the plasma can suppress appetite.[37] Elevated serum leptin concentrations have also been implicated as a factor contributing to anorexia.[38] Vomiting is frequent but inconsistent in uremia and may result from the effects of unidentified uremic toxins on the medullary emetic chemoreceptor trigger zone and from uremic gastroenteritis. Severity of vomiting correlates variably with the magnitude of azotemia. Because uremic gastritis may be ulcerative, hematemesis may occur. Although vomiting has been thought to be more frequent in uremic dogs, it occurs in about 25% to 33% of uremic cats.[3] Vomiting may impair compensatory PD, enhancing the risk of dehydration, and exacerbating prerenal azotemia and clinical signs of uremia.

Uremic Gastropathy

Definition

Uremic gastropathy and its associated clinical signs appear to be more common in dogs than cats.[39] In dogs it is characterized microscopically by mineralization of mucosal and submucosal blood vessels, edema, and glandular atrophy.[39] Mineralization appears to be related to the Ca × PO_4 product. Increased gastrin levels due to reduced renal clearance may have a role in development of uremic gastropathy.[40] Cats with CKD also have elevated levels of gastrin that worsen with severity of CKD.[40] Gastrin induces gastric acid secretion directly by stimulating receptors located on gastric parietal cells as well as by increasing histamine release from mast cells in the gastric mucosa. Enhanced histamine release may also promote GI ulceration and ischemic necrosis of the mucosa through a vascular mechanism characterized by small venule and capillary dilatation, increased endothelial permeability, and intravascular thrombosis.[41] However, gastric hyperacidity has not been documented in uremic dogs or cats, and mucosal necrosis and ulceration appear to be uncommon findings in uremic gastropathy in dogs.[39]

In a recent study of 37 cats with CKD, gastric ulceration, edema, vascular mineralization and hemorrhage were not observed; however, 16/37 (43%) cats had gastric fibrosis of varying severity and 14/37 (38%) cats had mineralized gastric walls.[42] Gastric mineralization was restricted to cats in IRIS CKD stages III and IV. Increased Ca-PO_4 products correlated with disease severity. Serum gastrin levels were significantly higher in CKD cats compared to nonazotemic cats, but increased gastrin concentrations were not associated with gastric ulceration. While inappetence occurred in 84% (26/31) and vomiting occurred in 45% (14/31) of the cats with CKD, significant relationship was not apparent between these clinical signs and gastric lesions and there was no significant relationship between clinical signs and gastrin concentrations. Cats with gastric

mineralization had poor appetites, suggesting that clinical signs of nausea and vomiting in cats with CKD are more likely to be due to the effects of uremic toxins on the chemoreceptor trigger zone than pathologic lesions of the gastric wall.

Dysphagia

In a study of 80 cats with spontaneous CKD, dysphagia and oral discomfort occurred in about 8% of uremic cats and 38% of cats with end-stage CKD.[3] Periodontal disease was observed in 31% of uremic and 35% of end-stage CKD cats. Halitosis was reported in about 8% of cats in both groups. Moderate to severe CKD may result in uremic stomatitis characterized by dry mucous membranes (xerostomia) oral ulcerations (particularly located on the buccal mucosa and tongue), brownish discoloration of the dorsal surface of the tongue, necrosis and sloughing of the anterior portion of the tongue (associated with fibrinoid necrosis and arteritis), and urine-smelling breath. Degradation of urea to ammonia by bacterial urease may contribute to these signs. Poor oral hygiene and dental disease may exacerbate onset and severity of uremic stomatitis.

Uremic Enterocolitis

Enterocolitis causes diarrhea and occurs in dogs and cats with severe uremia. It is typically less dramatic and less common than uremic gastritis. In one study, diarrhea was not reported by owners of 80 cats with spontaneous CKD.[3] When present, uremic enterocolitis is often hemorrhagic, although this GI hemorrhage may initially escape clinical detection. It may also be complicated by intussusception. Uremic enterocolitis may, at least in part, result from the irritant effect of increased ammonium production in the colon associated with high concentrations of urea. In contrast to diarrhea, constipation is relatively common in cats with CKD. However, it appears to be primarily a manifestation of dehydration rather than GI dysfunction. It may also occur as a complication of intestinal PO_4 binding agents.

Impaired Urine Concentrating Ability, Polyuria, Polydipsia and Nocturia

Among the earliest and most common clinical manifestations of CKD are PU/PD, nocturia and urinary incontinence due to reduced urine concentrating ability (see ch. 45 and 296). PD was the most common clinical sign reported in a study of 80 cats with CKD. Cat owners recognized PD more often than PU. Although urine specific gravity values of cats in CKD stages II through IV are usually below 1.035, some cats appear to retain adequate urine concentrating ability (i.e., specific gravity >1.035) especially early in the course of their CKD. Decreased urine concentrating ability results from several factors including: increased solute load per surviving nephron (solute diuresis), impaired genesis of the hypertonic gradient of the renal medulla due to disruption of the renal medullary architecture and counter-current multiplier system by disease, and impairment in renal responsiveness to antidiuretic hormone (ADH). Impaired responsiveness to ADH may result, at least in part, from an increase in distal renal tubular flow rate, which limits equilibration of tubular fluid with the hypertonic medullary interstitium. Additionally, ADH-stimulated adenyl cyclase activity and water permeability in the distal nephron may be impaired in uremia.[43] As urine concentrating ability is lost, urine volume is determined by the daily urine solute load. The solute load is predominantly composed of salt and urea, both of which can be modified by altering the dietary salt and protein content, respectively. Other important factors that can influence urine volume are thirst (water consumption) and therapeutic administration of fluids. PD is a compensatory response to PU. If fluid intake fails to keep pace with urinary fluid losses, dehydration will ensue because of the inability to conserve water by concentrating urine. Dehydration subsequent to inadequate fluid intake is a common problem in cats with CKD. Some dogs and cats with advanced CKD have limited ability to excrete ingested water, causing mild hyponatremia.

Arterial Hypertension and Cardiovascular Consequences

The major mechanisms thought to contribute to hypertension in CKD include fluid retention, activation of the renin-angiotensin-aldosterone system (RAAS), and increased activity of the sympathetic nervous system (see ch. 157).[35,44] Hypertension in humans with CKD is predominantly attributed to volume expansion. Removing fluid with diuretics or dialysis either eliminates hypertension or makes it more responsive to medications.[35] Similarly, hemodialysis that includes removal of excess fluids (ultrafiltration) have often been observed to reduce or normalize blood pressure in dogs and cats that were hypertensive prior to treatment. Where volume expansion is not the cause for hypertension in humans with CKD, increased RAAS activity appears to be an important determinate of hypertension. Enhanced renin release is presumed secondary to vascular

disease or focal areas of ischemia within the diseased kidneys. However, a study in cats reported that hypertensive cats often have significantly increased plasma aldosterone concentrations with decreased plasma renin activities, and that plasma renin activity declines with antihypertensive therapy, suggesting that retention of salt and water may be the major cause for hypertension. This may also explain, at least in part, why angiotensin-converting enzyme (ACE) inhibitors may be ineffective antihypertensive drugs in cats with CKD.

Hypertension may be primary (idiopathic) or secondary to diseases such as CKD. In dogs and cats, CKD is the most common cause for secondary hypertension while primary hypertension appears to be uncommon (see ch. 157). Hypertension may adversely affect long-term prognosis in dogs and cats with CKD, at least in part by promoting proteinuria.[31] Arterial hypertension has been purported to be among the more common complications of CKD; however, the true prevalence of arterial hypertension among dogs and cats with CKD is not known. Some studies have suggested that hypertension may be unusual in dogs with CKD, while other studies have reported that as many as 66% of cats and 50% to 93% of dogs with CKD have hypertension.[6,31,46,47] However, other studies in dogs suggest that a prevalence of 20% to 30% may be more accurate.[25,48] Dogs with glomerular diseases may be at higher risk for elevated blood pressure.[49] One study estimated the prevalence of systolic hypertension in cats with CKD to be approximately 13% to 28%.[46] The true prevalence and clinical impact of hypertension remains to be more clearly established in dogs and cats, but there appears to be a consensus among veterinary nephrologists that elevated blood pressures may lead to end-organ injury in dogs and cats with CKD and therefore warrants detection and treatment.[50] Organ systems most commonly affected by elevated blood pressure include the eyes, kidneys, nervous system and cardiovascular system.

Hypertension is present when there is persistent elevation of systolic and/or diastolic blood pressure, or when a patient previously diagnosed as hypertensive is receiving antihypertensive medication (regardless of the current blood pressure level). It is generally accepted that systolic blood pressure measurements in awake, nonanxious cats and dogs should not exceed about 160 to 170 mm Hg, and these figures probably represent a reasonable estimate of treatment threshold. In order to make blood pressure terminology more familiar to veterinarians and pet owners, the IRIS has changed its terminology to be similar to that used by the American Heart Association (Box 324-1). Categories from "normotensive" through "severe hypertension" imply sequentially minimal, low, moderate or high risk of hypertension-associated organ injury.[50]

Box 324-1

IRIS CKD Staging in Dogs and Cats

Data from http://iris-kidney.com/pdf/staging-of-ckd.pdf.

A IRIS CKD Stage

STAGE	SERUM CREATININE VALUES (mg/dL / mcmol/L)	
	DOGS	CATS
Stage I	<1.4 / <125	<1.6 / <140
Stage II	1.4-2.0 / 125-179	1.6-2.8 / 140-249
Stage III	2.1-5.0 / 180-439	2.9-5.0 / 250-439
Stage IV	>5.0 / >440	>5.0 / >440

B IRIS CKD Subclassification by Proteinuria (Urine Protein-to-Creatinine Ratio)

CLASSIFICATION	URINE PROTEIN-TO-CREATININE RATIO	
	DOGS	CATS
Proteinuric (P)	>0.5	>0.4
Borderline proteinuric (BP)	0.2-0.5	0.2-0.4

Nonproteinuric (NP)	<0.2	<0.2

C IRIS CKD Subclassification by Blood Pressure Stages for Dogs and Cats

ARTERIAL PRESSURE		
CATEGORY	**SYSTOLIC BLOOD PRESSURE (mm Hg)**	**DIASTOLIC BLOOD PRESSURE (mm Hg)**
Normotension (N)	<150	<95
Borderline hypertension (BH)	150 to 159	95 to 99
Hypertension (H)	160 to 179	100 to 119
Severe hypertension (SH)	≥180	≥120

Anemia

Anemia is a common in dogs and cats with CKD, although its magnitude is usually mild until the advanced stages of CKD. In humans, the packed cell volume begins to decline when GFR has reduced to about 40% of normal, and thereafter the severity of anemia is typically proportional to the loss of kidney function.[35] The anemia of CKD typically is characterized as normochromic, normocytic, and nonregenerative (see ch. 50 and 199). Bone marrow biopsy (see ch. 92) is typically characterized by hypoplasia of the erythroid precursors with little or no interference with normal leukopoiesis and megakaryocytopoiesis. On blood smears, spiculated and deformed red cells (burr cells or echinocytes) may be noted. Clinical signs of anemia include pallor of the mucous membranes, fatigue, listlessness, lethargy, weakness, and anorexia.

The primary cause for anemia of CKD is inadequate secretion of EPO by the kidneys. EPO is a glycoprotein hormone produced in the kidneys in response to decreased oxygen delivery. EPO binds to a receptor on erythroid progenitors causing these cells to differentiate into normoblasts and then mature erythrocytes. Inadequate EPO production results from the decline in renal functional mass. While the precise intrarenal site of EPO production has been elusive, peritubular capillary endothelial cells may be the most likely location.[35] The renal oxygen sensor is probably a heme protein that undergoes a transformational change in response to decreased oxygen delivery which increases EPO mRNA.[35] Hypoxia-inducible factors (HIF), and in particular HIF-2, have emerged as the transcription factor that regulates EPO synthesis in the kidney and plays a critical role in the regulation of intestinal iron uptake.[51]

Anemic CKD patients have a relative rather than absolute EPO deficiency in that plasma levels typically exceed the normal range, but are low relative to the severity of anemia.[52] Anemic CKD cats have been reported to have plasma EPO concentrations similar to normal cats.[53] Thus, the primary causes for anemia of CKD are insufficient renal EPO production, shortened red cell life span, nutritional abnormalities (notably iron, B_{12} and folate deficiencies), EPO inhibitor factors in uremic plasma, blood loss, and myelofibrosis.

Renal Secondary Hyperparathyroidism

Prevalence and Pathophysiology

Multiple factors promote development of renal secondary hyperparathyroidism (RSHP; see ch. 69 and 297). PO_4 retention, a consequence of declining GFR, even in early renal failure is closely associated with development of RSHP.[58,59] Increases in fibroblast growth factor-23 (FGF-23), in response to RSHP, also develops early in CKD. As a phosphaturic hormone, the action of FGF-23 is to mitigate PO_4 retention early in the course of CKD, but it also inhibits renal 1-alpha-hydroxylase activity, thus leading to decreased calcitriol levels.[59] The decline in calcitriol levels is among the earliest changes that promotes development of RSHP. RSHP is present in an estimated 47% of asymptomatic cats with only biochemical evidence of CKD. It develops prior to azotemia in some cats, even when serum PO_4 and Ca are within reference ranges.[54-56] The overall prevalence of RSHP in cats with CKD was about 84% in one study and all with "end-stage" CKD have RSHP. In general, plasma PTH levels increase as serum creatinine concentration increases.[57]

A relative deficiency of calcitriol has been described in dogs with CKD, although absolute concentrations

were within reference ranges.[60] Relative or absolute deficiency of calcitriol has been hypothesized to play a pivotal role in development of RSHP.[61] PTH promotes renal 1-alpha-hydroxylase activity and formation of calcitriol. In turn, calcitriol limits PTH synthesis by feedback inhibition. Absent this normal feedback inhibition, PTH levels increase. Initially, RSHP increases 1-alpha-hydroxylase activity despite continued PO_4 retention, thereby restoring calcitriol production toward normal. However, normalization of calcitriol production occurs at the expense of persistently increased plasma PTH activity: a classic example of the "trade-off hypothesis." As CKD continues to progress, loss of viable renal tubular cells ultimately limits renal calcitriol synthesis and concentrations remain low. Deficiency of calcitriol leads to skeletal resistance to the action of PTH and elevates the set-point for Ca-induced suppression of PTH secretion. Skeletal resistance to PTH limits skeletal release of Ca, while elevating the set-point for PTH secretion allowing RSHP to persist even when plasma ionized Ca concentrations are normal or elevated.[57,61]

PO_4 retention likely promotes RSHP directly. PO_4 restriction in dogs and people with CKD has been shown to decrease PTH secretion without influencing calcitriol levels.[62-64] In untreated people with mild to moderate CKD (serum creatinine concentration ≤3.0 mg/dL), serum PO_4 concentrations correlated directly with PTH, independent of serum Ca or calcitriol concentrations.[65] This correlation was present despite most patients having serum PO_4 concentrations within the reference range. Importantly overt hyperphosphatemia may not be a prerequisite for phosphorus to have an effect on PTH secretion. Reduced calcitriol levels may have a permissive effect and/or an additional direct effect on PTH secretion in this setting.[65]

In more advanced CKD, the presence of uremic toxins appears to prevent the inhibition of parathyroid cell proliferation induced by calcitriol.[66] At this point, only serum Ca concentration correlates with serum PTH activity.[65] Impaired GI absorption of Ca due to low serum calcitriol levels likely plays an important role in RSHP. Blood ionized Ca (iCa) concentrations are often reduced in cats with CKD. While iCa concentrations have been reported to range from low to high in dogs with CKD in one study, >50% of cats with advanced end-stage CKD were hypocalcemic.[54,67]

Clinical Consequences

Although RSHP and renal osteodystrophy are well-documented sequelae of CKD, renal osteodystrophy is uncommon in dogs and cats. In dogs, it most often occurs in the immature, presumably because metabolically active growing bone is more susceptible to the adverse effects of RSHP. For unexplained reasons, bones of the skull and mandible are usually the most severely affected and may become so demineralized that the teeth become moveable and fibrous changes are obvious, particularly in the maxilla (Figure 324-2). Marked proliferation of connective tissue associated with the maxilla may cause distortion of the face. Jaw fractures are uncommon. Other possible but uncommon clinical manifestations of severe renal osteodystrophy include cystic bone lesions, bone pain, and growth retardation. Potential nonskeletal consequences of RSHP include mental dullness and lethargy, weakness, anorexia, and an increased incidence of infections due to immunodeficiency.[57] Excess PTH levels may also promote nephrocalcinosis and consequent progressive loss of renal function.

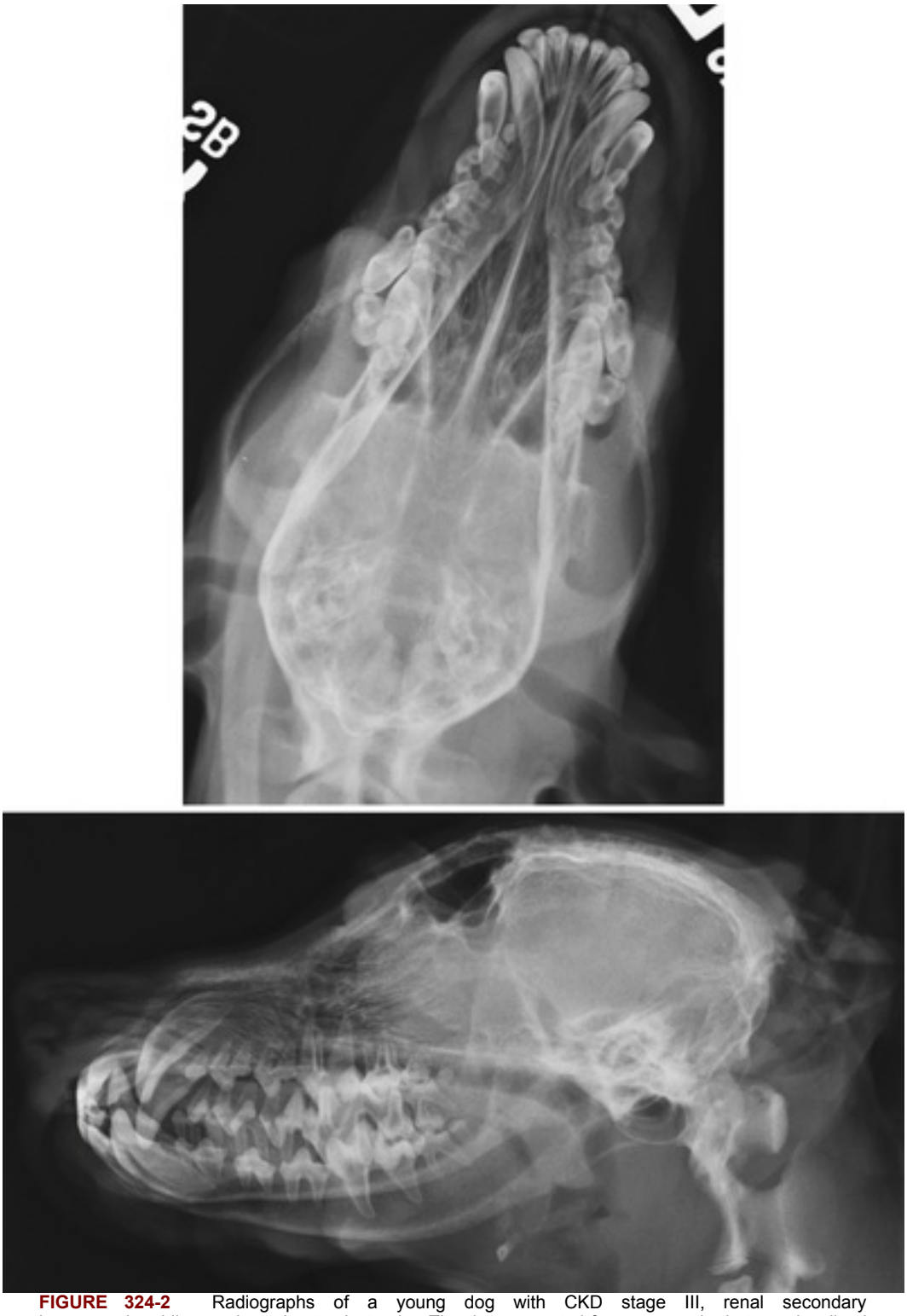

FIGURE 324-2 Radiographs of a young dog with CKD stage III, renal secondary hyperparathyroidism and renal osteodystrophy. The dog presented for severe pain that was localized to the skull and particularly the maxilla and mandible. Pathologic examination of the bone structure revealed fibrous-cystic osteodystrophy.

RSHP may be associated with substantial enlargement of the parathyroid glands (see ch. 298). This is of clinical importance in cats because hyperthyroidism is also common and palpation of a cervical mass logically may raise suspicion of thyroid rather than parathyroid disease. However, in one report, hyperplastic parathyroid glands were palpable as paratracheal masses in 11 of 80 cats with CKD.[3] Care should be taken to confirm either condition prior to starting treatment.

Laboratory Findings

Metabolic Acidosis

Metabolic acidosis is relatively common in CKD, but severe acidosis is primarily noted in those with advanced CKD (see ch. 128).[28,68] A study on 59 cats with CKD revealed that blood pH <7.27 was found in 10 of 19 cats with severe azotemia, 3 of 20 cats with moderate azotemia and none of 20 cats with mild azotemia. Metabolic acidosis was not found to be a prognostic factor in cats or dogs with CKD.[24,26] However, metabolic acidosis is now recognized to promote CKD progression in humans, although this has not been confirmed in dogs or cats.[68-70]

A combination of tubular reabsorption of filtered bicarbonate and excretion of hydrogen ions with ammonia and urinary buffers, primarily PO_4, maintain normal acid-base balance. As renal function declines, hydrogen ion excretion is maintained largely by increasing the quantity of ammonium excreted by surviving nephrons. While the quantity of ammonium excreted increases per surviving nephron, total renal ammonium excretion typically does not increase above normal. At some level of CKD, the capacity to enhance renal ammonia production is lost and metabolic acidosis ensues. Decreased medullary recycling of ammonia due to structural renal damage may also contribute to impaired ammonium excretion.[28] Decreased filtration of titratable acids as PO_4 and sulfate compounds plus impaired renal tubular proton secretion may also contribute.[71] Impaired renal tubular reabsorption of filtered bicarbonate is not typical of dogs and cats with CKD, but may occur in selected tubular disorders such as Fanconi syndrome (see ch. 326). Retention of PO_4 and organic acid (uric acid, hippuric acid, lactic acid, etc.) in CKD promotes an increased anion gap. However, hyperchloremic acidosis (normal anion gap), high anion gap or mixed hyperchloremic-high anion gap acidoses may all occur in CKD. Hyperchloremic acidosis is more likely in less severely azotemic patients.

Chronic metabolic acidosis may promote anorexia, nausea, vomiting, lethargy, weakness, muscle wasting, weight loss, and malnutrition. Dietary acidification of dogs and cats can cause negative Ca balance, bone demineralization or negative potassium balance which may in turn promote hypokalemia, renal dysfunction, and taurine depletion.[72] Chronic acidosis may promote protein malnutrition despite adequate dietary intake.[68] Protein catabolism increases in patients with acidosis, providing a source of nitrogen for hepatic glutamine synthesis, the substrate for renal ammonia synthesis.[73] The combined effects of reduced protein synthesis due to uremia and accelerated proteolysis due to acidosis promote elevations in BUN, increased nitrogen excretion, and negative nitrogen balance typical of uremic acidosis. Alkalization therapy effectively reverses acidosis-associated protein breakdown and reverses many signs.

Dietary protein requirements appear to be similar for normal and those with CKD unless uremic acidosis is present (see ch. 184). When acid-base status is normal, adaptive reductions in skeletal muscle protein degradation protects those consuming low-protein diets from losses in lean body mass. Metabolic acidosis blocks the metabolic responses to dietary protein restriction in two ways: (1) it stimulates irreversible degradation of the essential, branched chain amino acids, and (2) it stimulates degradation of protein in muscle.[73] Thus, acidosis may limit the ability of patients to adapt to dietary protein restriction. Metabolic acidosis also suppresses albumin synthesis in humans and may reduce the concentration of serum albumin.

Azotemia, Blood Urea Nitrogen, Creatinine

Azotemia is defined as excess urea or other nonprotein nitrogenous compounds in the blood (see ch. 62). Loss of renal function leads to accumulation of a wide variety of nonprotein nitrogen-containing compounds, including urea and creatinine. Many waste products of protein catabolism are excreted via glomerular filtration. Thus, those with primary CKD have impaired ability to excrete proteinaceous catabolites largely because of marked reduction in GFR. Since these compounds are derived almost entirely from protein degradation, their production increases when dietary protein increases. Urea is synthesized using nitrogen derived from amino acid catabolism and it may be excreted by the kidneys, retained in body water, or metabolized to ammonia and amino acids plus carbon dioxide by bacteria in the GI tract. Regardless of whether urea *per se* is toxic, BUN concentrations are typically related to dietary protein content. Further, BUN concentrations tend to correlate reasonably well with clinical signs of uremia. For practical purposes, BUN may thus be viewed as a surrogate marker of retained "uremic toxins."

In addition to increasing protein intake and declining renal function, BUN concentrations may also be increased by GI hemorrhage, enhanced protein catabolism, decreasing urine volumes (due to prerenal factors such as dehydration), and certain drugs (e.g., glucocorticoids). BUN concentrations may decline with portosystemic shunts, hepatic failure, low protein diets, and starvation. In some settings, a reduced BUN may

indicate protein calorie malnutrition due to inadequate intake as a consequence of improperly formulated diets or inappetence. Because many extrarenal factors influence BUN, creatinine is a more reliable measure of GFR in CKD. BUN and serum creatinine concentrations should be used together in evaluating patients, particularly patients consuming reduced protein diets. The ratio of BUN to serum creatinine concentration should decline when dietary protein intake is reduced. In patients consuming reduced protein diets, an increase in the ratio of BUN to serum creatinine concentrations may suggest poor dietary compliance, enhanced protein catabolism, GI hemorrhage, dehydration, anorexia or declining muscle mass.

Hyperphosphatemia

The kidneys are responsible for PO_4 excretion, with amount in urine representing that in glomerular filtrate less that absorbed via tubules (see ch. 73). If dietary PO_4 intake remains constant, a decline in GFR leads to retention and ultimately hyperphosphatemia. However, during early stages of CKD, serum PO_4 typically remains within reference limits because of compensatory decreases in reabsorption by surviving nephrons. This renal tubular adaptation is a consequence of the phosphaturic effects of FGF-23 and PTH. When GFR declines below about 20% of normal, this adaptive effect reaches its limit and hyperphosphatemia ensues.

The primary consequence of PO_4 retention and hyperphosphatemia is progression of CKD. Serum PO_4 concentrations have been shown to be directly linked to mortality in humans, cats and dogs with CKD.[24,26,74,75] A recent study in people with CKD noted that every 1 mg/dL increase in serum PO_4 was associated independently with increased risk of kidney failure and mortality.[76] Higher plasma PO_4 concentration has been shown to predict progression in cats with IRIS CKD stage III.[1] The Ca × PO_4 product also has a mortality risk trend. Products >72 have an increased relative mortality.[74] Mortality risk associated with hyperphosphatemia appeared to be independent of elevated PTH levels, which alone appeared to have only a weak association with mortality. Analysis of Ca revealed no correlation with relative risk of death.

Hypercalcemia, Hypocalcemia, and Hypermagnesemia

Concentrations of total, ionized, complexed protein-bound Ca vary widely in CKD patients (see ch. 67-69).[67] Increases in iCa were detected in 6% and decreases in 26% of 80 cats with CKD.[67] The mean blood iCa concentration was significantly lower in CKD cats than in healthy controls; >50% of cats with advanced (stage IV) CKD were hypocalcemic. However, when these same 80 cats were evaluated using total serum Ca (tCa) concentrations, hypercalcemia was found in 21% and hypocalcemia in 8%. Clearly, serum tCa concentrations do not reliably reflect iCa concentrations in cats with CKD. Similar discrepancies have been observed in dogs.[67,77] Metabolic acidosis of CKD does not appear to explain the discrepancies between iCa and tCa concentrations in dogs.[78] Mechanism of increased serum tCa despite normal to reduced iCa concentrations is likely explained by the increased concentrations of Ca complexed to retained organic and inorganic anions such as citrate, PO_4, or sulfate.[67] Because of this effect, formulas developed to "correct" for variations in serum albumin are not useful in dogs and cats with CKD.

Hypermagnesemia is common in CKD because the kidneys are primarily responsible for magnesium (Mg) excretion.[54] Typically in CKD, protein binding of Mg is normal, complexed Mg is increased, and ionized Mg (iMg) may be increased, normal or decreased. Although the homeostatic mechanisms involved in the control of Mg are not well documented, they appear to rely on bone, gut and kidney, as found with Ca and PO_4 control.

Hypokalemia and Primary CKD

An association between CKD and hypokalemia has been described in cats but is uncommon in dogs.[78,79] Dietary Na restriction in cats with CKD may be associated with inappropriate kaliuresis that may promote hypokalemia.[48] Kaliuresis may result from dietary Na restriction activating the RAAS. Other factors that may promote hypokalemia are reduced food intake and persistent low-grade dehydration, both of which are common in cats with CKD (see ch. 68).

While hypokalemia continues to be detected in many cats with CKD, muscle weakness is uncommon. Likely this improvement is the result of increasing the K content of therapeutic diets. Although generalized muscle weakness has been described as the cardinal sign of hypokalemia, decreased renal function and anorexia are probably more likely explanations. In many cats with CKD and hypokalemia, renal function improves with K supplementation and restoration of normal K concentrations, suggesting that hypokalemia

may induce a reversible, functional decline in GFR. Interestingly, renal function was shown to be adversely affected in normal cats when an acidified, K-restricted diet was fed, the two possibly being additive.[82] On the basis of these results, it was hypothesized that CKD cats have a self-perpetuating cycle of excessive urinary K loss and whole body K depletion, likely to further decrease renal function.

Hypokalemia as a Cause of CKD

There is limited evidence that in addition to being a consequence of CKD, hypokalemia may be a cause of or promoter of progressive CKD in cats. In an uncontrolled study of the long-term effects of feeding a K-restricted and acidifying diet, evidence of renal dysfunction developed in 3 of 9 cats while lymphoplasmacytic interstitial nephritis and interstitial fibrosis were observed in 5 of 9.[79] However, it is not clear whether K depletion or hypokalemia precede the onset of CKD. In another study, 4 of 7 cats with induced CKD fed a diet containing 0.3% K developed hypokalemia while 4 cats with normal renal function fed the same diet did not.[80] Interestingly, muscle K content decreased in normokalemic cats with spontaneous CKD, suggesting that total-body K deficits may develop well before the onset of hypokalemia.[81]

Primary Hyperaldosteronism in Cats as a Cause of CKD

Primary hyperaldosteronism (PHA) has been described in a few geriatric cats.[100,101] These cats have been described as having hypokalemia that is often severe and associated with hypokalemic polymyopathy, and hypertension that may be marked, refractory and commonly associated with retinal lesions and blindness (see ch. 308). In addition, cats with PHA often appear to have concurrent evidence of kidney disease. Because cats with CKD may also have concurrent hypokalemia and hypertension, discriminating cats with PHA from cats with CKD is important.

It has been recommended that the diagnosis of PHA in cats be based on plasma aldosterone concentrations (PAC), plasma renin activity (PRA), and the calculation of the aldosterone-to-renin ratio (ARR).[101] It is suggested that low PRA and increases in both PAC and PAC : PRA ratio be considered consistent with diagnosis of PHA.[100,101] However, a recent study of 196 cats over 9 years of age and without a diagnosis of PHA reported that PAC is significantly increased in azotemic hypertensive cats compared with normotensive cats matched for renal function.[45] Further, PRA was significantly lower in hypertensive cats compared to nonhypertensive, nonazotemic cats, and ARR was significantly higher in azotemic, hypertensive cats. These data suggest that many cats with CKD and hypertension have low renin, high PRA values. The authors of this report suggested that since the increase in PAC was not driven by PRA, the increased PAC could be primary adrenal tumor-dependent. In another study, bilateral adrenocortical hyperplasia may be an "almost ubiquitous" finding in cats over 9 years of age (97%) and histopathologic scoring of adrenal lesion severity failed to discriminate normotensive from hypertensive cats.[102] These findings fail to confirm that an adrenal disorder is driving the elevation in PAC in hypertensive cats.

Because PAC, PRA and ARR testing trend similarly in cats with CKD and cats with PHA, confirming the diagnosis of PHA should be approached cautiously. In general, cats with PHA are likely to have higher PAC and ARR levels compared to those found in cats with CKD, but clear cutoff values have not been validated. Since adrenal adenomas and carcinomas are responsible for most reported cases of feline PHA, adrenal imaging should be included in the diagnostic workup.[100] Ultrasound findings in cats with PHA are reported to include adrenal masses, adrenal calcification or changes in adrenal echogenicity. Computed tomography (CT) and magnetic resonance imaging (MRI) may also be used to image the adrenals. However, presence of lesions in the adrenals is not proof of PHA because adrenal masses in cats are often incidental findings (see ch. 308). Surgical removal of the adrenal mass, when possible, may be curative.[100]

Diagnostic Evaluation

Overview

Appropriate diagnostic testing facilitates optimum treatment and accurate prognosis. The evaluation has six goals: (1) confirm the presence of kidney disease, (2) differentiate acute from chronic disease, (3) stage CKD, (4) identify all biochemical and hematological complications, (5) determine the type and/or cause of kidney disease if possible, and (6) identify the presence of any comorbid conditions (Table 324-1; see ch. 62, 321, and 357).

TABLE 324-1

Complications and Comorbid Conditions in CKD

COMPLICATIONS OF CKD	COMORBID CONDITIONS
Anemia	Cardiac disease
Arterial hypertension	Degenerative joint disease
Dehydration	Dental and oral diseases
Hyperparathyroidism	Hyperthyroidism (cats)
Hyperphosphatemia	Nephroliths and ureteroliths
Hypocalcemia and hypercalcemia	Urinary tract infections
Hypokalemia	
Malnutrition	
Metabolic acidosis	
Uremic signs	

Confirming the Diagnosis of CKD

Definition

Kidney disease is defined as either a functional or structural abnormality in one or both kidneys. Functional renal diseases are most commonly recognized by azotemia or other test abnormalities, whereas structural renal disease may be palpated or seen on imaging studies or renal biopsy. Abnormalities are considered "markers" of kidney disease and should prompt further investigation to determine whether they result from kidney disease (Box 324-2).

Box 324-2

Markers of Kidney Damage

Blood Markers*

Azotemia
Hyperphosphatemia
Hypoalbuminemia
Hyperkalemia
Hypokalemia
Metabolic acidosis
Hypocalcemia
Hypercalcemia
Hypoproliferative anemia
Hypoalbuminemia
SDMA

Urine Markers

Impaired urine concentration
Impaired urine dilution
Proteinuria
Cylindruria
Hematuria
Pyuria
Inappropriate urine pH
Inappropriate urine glucose
Cystinuria
Bacteriuria

Imaging Markers—Abnormalities in Kidney

Increased or decreased kidney size
Renal mineralization, nephroliths or ureteroliths
Abnormal renal shape
Absence of a kidney
Abnormal renal echo texture by ultrasonography

Arterial Hypertension

Measured blood pressure
Retinal lesions consistent with hypertension

SDMA, Symmetric dimethylarginine.

*Markers must be confirmed to be of renal origin to be evidence of kidney damage.

Serum Creatinine Concentration

Serum creatinine concentration, a surrogate for GFR, is the primary laboratory test used to identify impaired kidney function. However, it is relatively insensitive in estimating GFR until a substantial reduction in kidney function has occurred. A 75% reduction in GFR is needed before serum creatinine values consistently exceed reference ranges. The insensitivity of serum creatinine results from at least two important factors: the innate relationship between GFR and serum creatinine and understanding that conditions other than intrinsic renal disease can cause the serum creatinine concentration to increase.

The relationship between serum creatinine and GFR is such that every time the GFR declines by half, the serum creatinine concentration doubles. For example, if a dog has a baseline creatinine of 0.5 mg/dL and its GFR declines by 50%, the serum creatinine only increases to 1.0 mg/dL, still well within reference intervals. If a further reduction of 50% in GFR occurs (now 25% of the original GFR), the creatinine will rise to about 2.0 mg/dL, slightly abnormal and often recognized. A further decline of 50% in GFR (to 12.5% of normal) is reflected in a serum creatinine of about 4.0 mg/dL. Thus, the slope of the rise in serum creatinine concentration becomes much steeper after a substantial loss of GFR has occurred, but it is flat over most of the range of GFR. It follows that the wider the normal range for serum creatinine concentration, the less sensitive it is for detecting intrinsic kidney disease. However, if the range becomes too narrow, serum creatinine will lose specificity because other factors may influence the value: body muscle mass, breed, etc. This conundrum is intrinsic to the nature of serum creatinine and limits its utility in diagnosis of early CKD.

Blood Urea Nitrogen Concentration

Although BUN has traditionally been viewed as an additional surrogate for estimating changes in GFR, it is influenced by several important factors that do not relate to GFR, including renal perfusion, protein ingestion, upper GI bleeding, time interval between food intake and blood sampling, drugs (e.g., corticosteroids), urine flow rate, and liver function. In addition, urea excretion is the sum effect of glomerular filtration and renal tubular reabsorption. Thus, BUN values may diverge substantially from serum creatinine concentrations due to factors unrelated to GFR.

BUN may be better than creatinine as a measure of uremic toxins and thus tends to correlate better than serum creatinine concentration with clinical signs and prognosis.[6] However, interpretation of BUN values can be complex and even misleading. One goal of dietary protein restriction is to lower levels of uremic toxins and such a diet typically lowers BUN, seemingly a favorable change. However, lower BUN levels may are seen when little or no food is eaten. The low BUN in this instance can be misinterpreted as a favorable response to therapy when it is actually the result of starvation. Simultaneous measurement of serum creatinine and BUN has been shown to be of limited benefit compared to measuring serum creatinine alone.[83]

Azotemia versus Uremia

The terms *azotemia* and *uremia* are not interchangeable. Azotemia is defined as abnormal concentrations of urea, creatinine, and other nonprotein nitrogenous substances in blood, plasma, or serum. It is a laboratory finding that can have several fundamentally different causes. It does not imply presence or absence of clinical signs. Because azotemia may be caused by factors that are not directly related to the urinary system and by abnormalities of the lower urinary tract not directly related to the kidney, *azotemia* should not be used as a synonym for kidney disease or uremia. Azotemia may result from prerenal, renal or postrenal causes. Since

nonprotein nitrogenous compounds (including urea and creatinine) are endogenous substances, abnormal increases in serum may be caused by an increased rate of production (by the liver for urea; by muscles for creatinine), or by a decreased rate of loss (primarily by the kidneys). Prerenal azotemia may result from impaired renal perfusion (e.g., dehydration, cardiac failure, shock, etc.) or increased production of nonprotein nitrogenous compounds. Prerenal azotemia is not evidence of kidney disease and can be corrected by eliminating the cause for impaired renal perfusion or increased production of nonprotein nitrogenous compounds.

Uremia is defined as the polysystemic clinical syndrome that results from extensive loss of kidney functions. Kidney disease may be present without azotemia or uremia. Azotemia may occur absent uremia or kidney disease (e.g., prerenal azotemia). Uremia does not occur absent azotemia, but uremia can occur absent kidney disease (e.g., leakage of urine from the ureters or bladder into tissues may lead to azotemia and uremic signs).

Renal azotemia confirms a diagnosis of kidney disease and is the result of reduced GFR consequent to primary kidney disease or injury. It may or may not be reversible over time, but does not resolve in response to fluid therapy. Urine concentrating ability is impaired in dogs and cats with renal azotemia. Urine specific gravity values less than 1.030 in dogs and less than 1.035 in cats are considered to be evidence of "inadequate urine concentration" in azotemic or dehydrated patients. Finding azotemia concurrent with urine specific gravity values less than 1.030 in dogs and less than 1.035 in cats is highly suggestive of renal azotemia. Note that nonazotemic dogs and cats with adequate renal perfusion (normal hydration and renal blood flow) may normally have urine specific values below 1.030 or 1.035, respectively. Renal azotemia and prerenal azotemia may occur together. This combination should be considered when pets have azotemia and inadequate urine concentrating ability (renal azotemia), yet fluid therapy partially reduces the magnitude of azotemia (the prerenal component of the overall azotemia).

Postrenal azotemia is the result of obstructed urine flow or urine leakage into a body cavity or tissues (e.g., urinary bladder rupture). Urine specific gravity is of no use in identifying postrenal azotemia. Distension of the urinary collection system (ureter[s] and/or bladder) is suggestive of postrenal azotemia, as is urine in the peritoneal cavity or tissues around the urinary system. Contrast imaging studies of the urinary collection system may be used to confirm urinary obstruction or leakage. Correction of the urinary obstruction or defect usually resolves the azotemia. However, prolonged urinary obstruction (mostly with partial obstruction) may lead to renal injury and renal azotemia. Postrenal azotemia may occur concurrently with primary azotemia and/or prerenal azotemia.

Urine Specific Gravity

Obtaining a urine specific gravity (USG) at the same time as a serum creatinine concentration is pivotal for correct interpretation (see ch. 62, 72, and 321). As stated, USG is essential for immediate differentiation between prerenal and primary renal azotemia. Urine samples obtained after giving fluids or some drugs are likely to be altered, thus eliminating the value of USG. In general, serum creatinine concentration is interpreted as consistent with primary azotemia when USG is <1.030 in dogs and <1.035 in cats. Most dogs and many cats with CKD have USG values between 1.006 and 1.020, and, when in advanced stages of CKD, isosthenuria (USG = 1.008 to 1.012) is common. Finding isosthenuria indicates the kidneys are not modifying the concentration of urine from the concentration of plasma. A USG <1.006 is not consistent with renal azotemia because concentrations below isosthenuria requires adequate kidney function. Some cats with CKD may retain substantial urine concentrating ability (i.e., 1.020 to 1.035 and occasionally >1.035). An alternative means of differentiating primary from prerenal azotemia is to repeat the serum creatinine concentration after an appropriate IV fluid challenge that eliminates the prerenal condition. If azotemia resolves 24 to 48 hours after giving fluids, the pet is considered "fluid responsive" and, therefore, azotemia was due to prerenal causes.

SDMA in CKD

The process of protein degradation includes arginine being methylated and forming numerous molecules, including asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA).[84] ADMA is an endogenous inhibitor of nitric oxide synthase and is associated with endothelial dysfunction, vasoconstriction, and increases blood pressure. It is cleared by the liver and kidneys. In contrast, SDMA has little physiologic activity and ≥90% is eliminated by the kidneys. Renal clearance is through filtration, without tubular reabsorption.[85] Serum SDMA concentrations correlate well with GFR in cats and dogs. In dogs with X-linked hereditary nephropathy, serum SDMA correlated with both creatinine and GFR estimated by

iohexol.[86] In a canine model of CKD, SDMA correlated better with GFR than did creatinine.[87] In 69 client-owned cats with CKD, SDMA concentrations were increased and correlated with creatinine; SDMA also correlated well with a range of GFRs in aged cats.[88,89]

SDMA has been shown to be a marker for early kidney disease in dogs, cats and humans.[86,90,91] Dogs with X-linked hereditary nephropathy rapidly progress from normal at birth to end-stage renal disease. In a cohort of male X-linked hereditary nephropathy dogs the measurements of serum SDMA, creatinine and GFR estimated by iohexol clearance were followed over the course of their disease. SDMA increased earlier than creatinine. The SDMA value increased with 30% declines in GFR, whereas serum creatinine did not increase until 50% to 60% loss of kidney function. Creatinine was evaluated both as a single serum cutoff value and as trending over time and in both instances SDMA proved to be an earlier indicator of loss of kidney function.[86] Trending serum creatinine increases its sensitivity in detecting reduced kidney function and is better than a single measurement. However, SDMA outperformed creatinine trending and proved to be a better indicator of early kidney disease. Retrospective longitudinal studies in dogs and cats that developed CKD have provided further evidence that serum SDMA increases earlier than creatinine. Two retrospective studies on both dogs and cats conducted over several years as they developed naturally occurring CKD showed SDMA increasing before creatinine by a mean of 17 months in cats (range 1.5-48 months) and 10.2 months in dogs (range 0.5-32 months). SDMA increased after about a 40% decrease in GFR (25% in one case).[92]

SDMA is useful for identifying and monitoring kidney disease in sarcopenic patients (see ch. 177). A major issue with creatinine is its relationship to muscle mass. Increased muscle mass promotes higher creatinine values while reduced muscle mass is associated with lower values. For example, aged cats with CKD often develop severe sarcopenia. Because of their muscle mass loss, serum creatinine concentrations are low relative to GFR and underestimate severity of renal dysfunction. In contrast, SDMA is minimally impacted by muscle mass in dogs and cats.[86,91-95] In a study in dogs comparing lean body mass, age, serum creatinine and SDMA showed that lean body and age were significant variables for creatinine but not SDMA concentrations.[96] SDMA is best utilized to complement existing kidney tests. Serum SDMA concentrations >14 mcg/dL are abnormal in dogs and cats. Increases in SDMA and serum creatinine concentrations with concurrent inappropriately concentrated urine are consistent with kidney disease. Increased SDMA and a serum creatinine concentration within reference limits suggests early kidney disease. However, persistent increases in SDMA over months is stronger evidence of kidney disease. Persistent SDMA increases for >3 months in dogs with serum creatinine <1.4 mg/dL or cats with serum creatinine <1.6 mg/dL are consistent with a diagnosis of IRIS CKD stage I. Unlike creatinine, SDMA is not influenced by lean body mass and will therefore be a better marker of kidney disease in animals with low body condition scores. The IRIS board provides guidelines for using SDMA to adjust treatment recommendations in patients with low body condition scores (see CKD staging system).

Acute versus Chronic Kidney Disease

Diagnosis of CKD requires confirmation of kidney disease and evidence of chronicity. In CKD, *chronic* means an irreversible and usually progressive loss of kidney function and/or structure. In this scenario, capacity for kidney compensation has reached a maximum, which typically reflects duration of approximately 3 months or longer. In contrast, AKI (see ch. 322) is potentially reversible, either by resolving at least part of the kidney injury, development of adaptive compensatory enhancements in kidney function, or both. Thus, short- and long-term consequences of AKI and CKD are potentially quite different.

Chronicity of CKD may be estimated from the medical history, physical examination, historical changes in laboratory findings, or renal structural changes observed by imaging studies or renal pathology. The occurrence of weight loss, PU, PD, decreased appetite and other signs for about 3 months or longer provides substantial evidence of chronicity. Likewise, declining nutritional status and hair coat quality are more typical of CKD than AKI. Documented increases in serum creatinine over a period of ≥3 months add conclusive support for diagnosing CKD. The criterion of at least 3 months of reduced renal function is based on the observation that renal compensatory hypertrophy may continue for that long after AKI. Proteinuria persisting for ≥3 months also supports diagnosis of CKD. While nonregenerative anemias (see ch. 199) are typical, they are not diagnostic because unrelated conditions may cause anemia. Palpably small kidneys or small size noted on imaging strongly supports diagnosis of CKD; loss of nephrons is usually associated with fibrosis. In some instances, especially in cats, one kidney may become enlarged in association with compensatory changes after the other kidney shrinks due to fibrosis (see Figure 324-1). While uncommon, skeletal changes consistent with renal osteodystrophy (see Figure 324-2) may confirm presence of CKD because of the time

required for its development.

Staging CKD

Overview

The International Renal Interest Society (IRIS) has proposed a four-tier system for staging CKD in dogs and cats based on renal function, proteinuria and blood pressure (see Box 324-1). Such staging facilitates application of appropriate guidelines for diagnosis, prognosis and treatment. Although the specific values used to categorize patients with CKD into these stages are based largely on observational data, staging is nonetheless useful for establishing prognosis and managing patients with CKD.[6,24]

Assigning IRIS CKD Stage and Its Treatment

Staging CKD is based on the patient's serum creatinine concentration. As described, serum creatinine remains the most commonly used estimate of GFR in dogs, cats and humans. However, its limited specificity and sensitivity can lead to misclassification. Staging, therefore, should be based on a minimum of two serum creatinine values obtained when the patient is fasted, well hydrated, and determined over a period of several weeks. If stable, it is characteristic of CKD. The overall clinical status should be considered when interpreting serum creatinine concentrations and other laboratory tests and when planning patient management.

Interlaboratory variations, patient-specific characteristics (e.g., breed, age, gender, body condition and lean body mass) and transient prerenal and postrenal events may influence serum creatinine values. Reduced muscle mass is a common manifestation of advanced CKD and may result in a substantial reduction in serum creatinine concentration relative to true GFR, particularly in cats. The IRIS suggests that SDMA values may be used to modify IRIS CKD staging in dogs and cats where body muscle mass is markedly reduced (see www.iris-kidney.com). In IRIS CKD stage II pets with low body condition scores and an SDMA concentration ≥25 mcg/dL, extent of renal dysfunction is likely to be underestimated and treatment recommendations listed under IRIS CKD stage III should be considered. In IRIS CKD stage III pets with low body condition scores and an SDMA concentration ≥45 mcg/dL, the extent of renal dysfunction is likely underestimated and treatment recommendations listed under IRIS CKD stage IV should be considered.

The diagnosis of CKD should be based on the serum creatinine range established for your laboratory, rather than the IRIS CKD stage II cutoff value. Since published reference ranges for serum creatinine are often broad, however, some pets classified as having mild renal azotemia (stage II) may have serum creatinine values within published reference ranges. To avoid misdiagnosis, it is important that evidence of CKD beyond the serum creatinine value be sought. In addition, larger body size may be associated with a higher upper limit of serum creatinine in dogs. Preliminary studies suggest that these limitations of serum creatinine concentration may be clarified by concurrently measuring serum SDMA concentration.

Clinical Descriptions of IRIS CKD

Stages

Stage I includes nonazotemic dogs and cats with CKD. Stage II CKD includes dogs and cats that are mildly azotemic. Other than PU/PD, pets in one of these stages usually do not have clinical signs of kidney dysfunction. Occasionally cats and dogs in stage II have weight loss or selective appetites. However, many pets have clinical signs resulting from their kidney lesions (e.g., acute pyelonephritis, nephrolithiasis). Those with marked proteinuria or systemic hypertension due to CKD may have clinical signs related to these issues. Renal function is often stable or slowly progressive for an extended period in nonproteinuric, nonhypertensive dogs and cats with stages I and II CKD. However, when progression does occur, it is important to determine whether the primary etiopathologic process underlying their CKD may be contributing to progression.[4] Patients with stages I and II CKD should be evaluated with the goal of identifying and providing specific treatment for their primary renal disease where possible. In addition, renal function should be monitored for possible progression of their CKD.

Pets with moderate azotemia are classified as stage III CKD and they may have clinical signs referable to their loss of kidney function; however, with appropriate treatment, they typically do not have clinical signs of overt uremia. Since stage III CKD is typically progressive, in addition to identifying and treating primary CKD, therapy designed to modify factors promoting progression of CKD may be of benefit. Stage IV CKD includes dogs and cats with severe azotemia (serum creatinine values >5.0 mg/dL) and, usually, clinical signs

of uremia. Diagnostic and therapeutic initiatives in this stage include those appropriate for stage III patients as well as therapy designed to prevent or ameliorate signs of uremia.

Substaging IRIS CKD Stages

Because it may be useful therapeutically and prognostically, the IRIS staging system further subclassifies pets according to the magnitude of their proteinuria and/or arterial blood pressure. Before performing a UPCR, urinalysis and urine culture should be performed to rule out infection, hemorrhage, or inflammation as a cause for increased UPCR. The urine sediment should be determined to be inactive before performing the UPCR. Unless markedly elevated or <0.2, it is recommended that the UPCR be rechecked 2 to 3 times over at least 2 weeks. The average of these determinations should be used to classify the patient as nonproteinuric, borderline proteinuric or proteinuric (see Box 324-1). Urine collected at home has lower UPCR values than samples collected in-hospital.[97] Pets with borderline proteinuria should be reevaluated after 2 months. In some pets, classification of proteinuria may change due to the course of their disease or in response to therapy.

Systemic arterial pressure should also be determined several times over several weeks (see Box 324-1). Blood pressure measurement should be performed before physical examination or collecting blood or urine. This aids in minimizing "white-coat" hypertension. Ideally the pet is taken into a quiet exam room soon after clinic arrival. Owner and pet should not be disturbed for about 5 to 10 minutes to minimize anxiety. Then a veterinary technician trained to perform blood pressure measurements should quietly enter the room and obtain 5 to 10 measurements with as little pet restraint as possible. The values should be documented along with the heart rate and comments on the perceived anxiety level of the patient.

Identifying Clinical, Biochemical, or Hematological Complications of CKD

History and Physical Examination

When obtaining the history (see ch. 1), one should seek clinical signs that may date the onset of kidney disease (e.g., PU, PD, weight loss, decreased appetite), information on possible congenital or hereditary diseases, evidence of current or past infections, neoplasia, metabolic diseases, lower urinary tract signs or problems, drug history (current and past), toxin exposures, diet, appetite, and evidence of previous kidney problems. Physical examination (see ch. 2) should emphasize dental and oral conditions, retinal examination for hypertensive lesions, hydration, edema, body condition score, assessment of lean body mass, accurate body weight, hair coat quality, pulse rate and quality, palpation of the urinary tract, bone pain, body temperature (uremia may be associated with low body temperature), and rectal examination. In cats, the cervical area should be carefully examined for evidence of thyroid enlargement.

Recommended Testing

Since most body systems are affected by CKD and uremia, the recommended initial diagnostic database is broad. The minimum should include the medical history, physical examination, arterial blood pressure (see ch. 99), complete blood count (CBC), a complete serum chemistry panel including serum electrolytes, acid-base status (serum bicarbonate or total CO_2 concentration or blood gas analysis), complete urinalysis (see ch. 72), urine culture, UPCR, and survey abdominal radiographs and/or abdominal ultrasound (ideally both). In cats, T_4 testing should be performed to rule out concurrent hyperthyroidism (see ch. 301).

Renal Biopsy

Biopsy and histologic assessment of tissue obtained may be useful in identifying the cause of kidney disease (see ch. 89). However, dogs and cats in IRIS CKD stages III and IV typically have small fibrotic kidneys. Also, regardless of CKD stage, hypertension and small kidneys are relative contraindications to biopsy because of risks of hemorrhage and loss of renal mass. Recent reports on the histopathologic findings in cats with CKD have described renal lesions and linked some renal lesions to clinicopathologic characteristics; however, these studies have not revealed the etiopathological origins of the CKD.[98,99] The primary indication for biopsy is proteinuria (see ch. 325) where the biopsy findings may influence treatment.

Treatment of CKD

Overview and Goals

Conservative medical management is standard and the only realistic option for most dogs and cats with CKD. It consists of supportive and symptomatic therapy designed to ameliorate clinical signs, correct fluid deficits or excesses as well as electrolyte, acid-base, endocrine, and nutritional balance. Therapy should minimize clinical and physiologic consequences of reduced renal function and should be designed to slow progressive loss of kidney function. Specific therapy for active kidney disease and management of comorbid conditions may also be indicated. In order to best meet these goals, treatment recommendations must be individualized and based on their unique clinical and laboratory status. Because CKD is progressive and dynamic, serial clinical and laboratory assessment of the pet, and modification of the therapy in response to changes, is integral to conservative medical management. The treatment plan should take into account considering each pet's IRIS CKD stage, clinical signs, risk factors for progression, existing complications and comorbid conditions. Therapy being given for active renal disease must be identified. Despite the renal lesions of CKD being irreversible, progression may be slowed or stopped with therapy designed to eliminate active renal diseases. Thus a thorough diagnostic evaluation should include a search for active disease that may be complicating CKD.

Managing patients with CKD requires ongoing engagement with the pet owner. Thus, successful CKD management is optimized by developing a long-term plan that includes: (1) introductory owner education regarding their pet's disease and its management, (2) a specific plan for monitoring progress and response to treatment, and (3) ongoing facilitation of the pet owner's engagement in the treatment plan.[103] Failure to include owners on the decision-making team often results in a suboptimum therapeutic response. A well-developed early plan for facilitating initial success in implementing the treatment plan has the potential to greatly enhance the long-term clinical outcome through enhanced compliance (Box 324-3).

Box 324-3

Checklist for Managing Chronic Kidney Disease

1. Confirm that the patient has kidney disease.
   a. Renal function tests (serum creatinine, BUN, SDMA)
   b. Urinalysis, urine protein-to-creatinine ratio, and/or urine culture
   c. Imaging studies
2. Confirm that the kidney disease is chronic.
   a. Medical history
   b. Physical examination
   c. Renal imaging studies
3. Establish the IRIS CKD stage of the patient (see Box 324-1).
   a. Two fasting serum creatinine values in a well-hydrated patient
   b. Urine protein-to-creatinine ratio (2-3 values)
   c. Arterial blood pressure (2-3 values)
4. Develop a treatment plan for the patient's CKD.
   a. Determine the treatment options appropriate for the patient.
   b. Prioritize and select which treatment options to recommend based on medical priority and pet owner's preferences (which may include cost, demands on the pet owner, and owner's preferences).
5. Review treatment plan with pet owner and confirm willingness to engage in the selected treatments.
6. Schedule follow-up appointment(s) to assess patient response to therapy.
7. Arrange for regular telephone updates to evaluate response to therapy and confirm owner compliance and commitment to the treatment plan.
   a. Assess owner's understanding of the treatment plan.
   b. Determine if the owner is having compliance issues.
   c. Assess patient's response to therapy and determine whether the patient needs to be seen before next scheduled appointment.
      i. Activity
      ii. Behavior
      iii. Appetite and quantify food intake (and body weight if available)
      iv. Water consumption
      v. Owner's perception of the pet's well-being

Factors likely to influence the success of a therapeutic plan include: (1) pet owner attitude toward and acceptance of the therapeutic plan, (2) patience and sometimes creativity in promoting owner and pet acceptance of the recommended treatments, and (3) maintaining continuing owner commitment to the treatment plan and connection to the veterinary team for the duration of the pet's life. The first step in developing a long-term management plan for dogs and cats with CKD is to develop a treatment plan that works for the pet owner as well as the pet. If a treatment plan is too involved, time consuming, expensive, or if it is perceived as disrupting the human-animal bond, it is unlikely to be successful.

The final key to optimizing the long-term outcome of pets with CKD is a plan for active follow-up initiated by the veterinarian. In addition to scheduling follow-up clinic visits, it is highly useful for a veterinary technician familiar with the pet, owner, and treatment plan to maintain contact with caregivers at least weekly until the owner is comfortable that the treatment plan is going well and all questions have been satisfactorily answered. Reasons for maintaining communication are to encourage and coach the caregiver regarding the treatment plan, to assess response to therapy, determine whether there are problems with compliance, and to decide if any warning signs have developed indicating need for a recheck examination or phone discussion with the veterinarian.

Dietary Therapy *(see ch. 184)*

Overview

Of all therapies used to treat dogs and cats with CKD, renal diets have the greatest benefit and the most evidence to support their effectiveness.[103] Although commonly called "low-protein" diets, renal diets should not actually be low in protein. Renal diets should have other modifications, including reduced PO_4 and Na, added B vitamins, increased caloric density, added soluble fiber, a neutral effect on acid-base balance, and supplementation of omega-3 polyunsaturated fatty acids and antioxidants. In addition, feline renal diets typically contain supplemented K.

Dietary Phosphorus

Most maintenance diets contain substantial quantities of PO_4. Hyperphosphatemia and hyperparathyroidism develop when maintenance diets are consumed by dogs and cats with CKD. Protein typically contributes a substantial amount of the PO_4 in pet foods, but they are not the sole source. Studies in cats and dogs with CKD have linked hyperphosphatemia to decreased survival and renal lesions.[24,26,58,75] Limiting dietary PO_4 is indicated for dogs and cats in IRIS CKD stages II through IV.[104] Benefits of reducing PO_4 intake include reduced retention, lower serum PO_4, decreased RSHP, slowing progression of CKD and reduced mortality.[58]

Omega-3 Polyunsaturated Fatty Acids and Antioxidants

Oxidative stress appears to have adverse consequences in chronic kidney disease.[105] Dietary supplementation with omega-3 polyunsaturated fatty acids (PUFAs) has been shown to be beneficial in dogs with induced CKD.[106] Compared to dogs fed diets high in saturated fats or omega-6 PUFAs, CKD dogs given omega-3 PUFAs had lower mortality, better renal function, fewer renal lesions, less proteinuria, and lower cholesterol levels.[106] These benefits may be the result of favorable effects on lipid metabolism and renal hemodynamics, suppression of inflammation and coagulation, reduced blood pressure, and antioxidant actions.[107] One study evaluated the effects of giving omega-3 PUFAs (omega-6 to omega-3 ratio of 5 : 1) and dietary antioxidants (vitamin E, carotenoids, lutein) on progressive decline in GFR of dogs with induced CKD. Results indicated that both omega-3 PUFA supplementation and the antioxidants were beneficial.[108] However, combining the two may have had synergistic benefits. Thus, dietary supplementation with omega-3 PUFAs and antioxidants is recommended for dogs and cats with CKD. The optimum quantities and ratio of omega-3 to omega-6 PUFAs have not been established. Although omega-3 PUFA and antioxidant therapy in cats with CKD are unavailable, vitamin E, C and beta-carotene supplementation reduces oxidative stress in cats.[109]

Protein

Waste products of protein catabolism are thought to contribute to clinical signs of uremia. While the ideal quantity of protein to feed dogs and cats with CKD has not been established, the general consensus is that limiting dietary protein intake ameliorates clinical signs of uremia in CKD and is therefore indicated for CKD stages III and IV. While not regarded as an important uremic toxin, BUN is a surrogate marker for retained

nonprotein nitrogenous waste products and typically correlates better with clinical signs than serum creatinine concentration. However, reducing dietary protein intake in CKD pets that do not have clinical signs of uremia has been questioned. Limiting their protein intake has been justified by its potential to slow progression of CKD.[110] However, some have argued that high dietary protein intake has not been unequivocally shown to promote progression of CKD and may be needed to maintain adequate nutrition. Nonetheless, when consumption of a renal diet is adequate and protein restriction is not excessive, renal diets do not cause malnutrition. An additional reasonable argument for recommending renal diets in IRIS CKD stage II and early III is that it may be easier to initiate conversion to renal diets well before the onset of clinical signs of uremia.[104]

Diet Therapy—Evidence from Clinical Trials

Dogs

The effectiveness of diet therapy in minimizing uremic episodes and reducing mortality in dogs and cats with naturally occurring CKD has been established.[2,111,113] Studies compared a renal diet with omega-3 PUFAs to a prototypical maintenance diet. Renal diets had limited protein, PO_4, and Na compared to an adult maintenance diet. In dogs, the risk of developing a uremic crisis was reduced by about 75% when fed the renal diet.[2] The median symptom-free interval in dogs fed a renal diet was 615 days compared to 252 days for dogs fed an adult maintenance diet. Risk of death, regardless of cause, was reduced by 66% and the risk of death due to renal causes was reduced by 69% for dogs consuming a renal diet. Median survival time for dogs consuming a renal diet was 594 days compared to 188 days for dogs consuming a maintenance diet. In addition, owners who fed a renal diet reported significantly higher quality of life scores for their dogs than owners who fed a maintenance diet.

Cats

Forty-five cats with serum creatinine values of 2.0 mg/dL to 4.5 mg/dL (IRIS CKD stages II and III) were separated into two groups: 22 were fed a commercial renal diet and 23 were given a maintenance diet.[113] Risks of uremic crises and renal deaths were reduced when a renal diet was fed. Among the 22 cats fed a renal diet, there were no uremic crises, no renal deaths, and 3 deaths due to nonrenal causes over 2 years. Of the 23 cats consuming a maintenance diet, 6 developed uremic crises and 5 died of renal causes. Two additional studies, a nonrandomized trial and a retrospective study, support the effectiveness of renal diets in cats with CKD.[9,112] The nonrandomized clinical trial compared a manufactured renal diet to no diet change.[10] While neither randomized nor blinded, results yielded strong evidence supporting the efficacy of feline renal diets. Cats fed a renal diet (mean survival of 633 days) lived substantially longer than cats consuming their regular diet (mean survival of 264 days). In addition, cats fed a renal diet had lower BUN, serum PO_4, and PTH concentrations. A study performed in 31 first-opinion veterinary practices in The Netherlands compared survival times for cats fed one of seven commercial feline renal diets to cats fed a maintenance diet.[113] Median survival time for the cats fed a renal diet was 16 months compared to 7 for cats fed their usual diet. Further, feeding renal diets lowers plasma PO_4 and FGF-23 levels compared to cats with CKD consuming their usual diet.[113] Increases in PO_4 and FGF-23 concentrations have been implicated in promoting progression of CKD.

Summary

The clinical studies described here clearly support the use of renal diets for dogs in CKD stages III and IV and cats with CKD stages II through IV. The value of renal diets in dogs with CKD stage II has not been critically evaluated but they are beneficial in reducing the magnitude of proteinuria.[114] Thus, renal diets are recommended for all dogs with proteinuric kidney disease.[115,116] These studies did not selectively determine the benefits of modifying individual dietary components, but rather report the results of a "diet effect."

Phosphorus Retention, Hyperphosphatemia and Renal Secondary Hyperparathyroidism (RSHP)

Overview

Because the capacity to excrete PO_4 declines as CKD progresses, intake must be reduced in parallel with the decline in kidney function (see ch. 69 and 321). If not, PO_4 retention, hyperphosphatemia and RSHP will

develop, enhancing progressive decline in kidney function and mortality.[35,58,117] Minimizing retention and hyperphosphatemia is an important therapeutic goal in dogs and cats with CKD because it appears to slow progression of CKD and prolong survival.[58,75,118] Because impaired renal perfusion increases serum PO_4 concentrations, the first step toward correcting hyperphosphatemia is to assure that the pet is well hydrated. Then, minimizing PO_4 retention and hyperphosphatemia is furthered by limiting dietary content and/or using oral agents that bind PO_4 within the intestines.[119] The usual approach is to start with renal diet therapy. Binding agents are used when a renal diet, alone, fails to bring the serum PO_4 concentration into the target range (Box 324-4). Renal diets, alone, usually normalize serum PO_4 concentrations in most CKD stage II and many CKD stage III pets. Pets in advanced IRIS CKD stage III and stage IRIS CKD IV typically benefit from being given an intestinal PO_4 binder to achieve goals.[57,118] Current evidence suggests that the critical target is serum PO_4, rather than PTH.

Box 324-4

Recommended Treatment Goals for Serum Phosphorus Concentrations

IRIS STAGE	TARGET SERUM PHOSPHORUS CONCENTRATION	
STAGE	(mg/dL)	(mmol/dL)
I	2.5-4.5	0.81-1.45
II	2.5-4.5	0.81-1.45
III	2.5-5.0	0.81-1.61
IV	2.5-6.0	0.81-1.94

Dietary PO_4 Restriction

Treatment target goals are linked to the IRIS CKD stage (see Box 324-4). Reference or "normal" ranges for serum PO_4 concentration *are not the therapeutic goal* in pets with CKD. When the serum PO_4 concentration is greater than the goal, it should be considered increased and reducing its concentration is usually indicated for dogs and cats with CKD stages II through IV. Serum PO_4 concentration should always be assessed after a 12-hour fast to avoid postprandial effects and such diets require several weeks for results. In cats with CKD, full dietary effect was apparent after 28 to 49 days.[118] Serum PO_4 concentrations should be rechecked 4 to 6 weeks after initiating the renal diet. If in the target range, the diet should be continued and the serum PO_4 reassessed every 3 to 4 months (every 4-6 months may be adequate for IRIS CKD stage II dogs and cats if two sequential results are within the goal range). If a renal diet alone fails to achieve the serum PO_4 target after 4 to 6 weeks, adding an intestinal binding agent is reasonable.

Intestinal Binding Agents

Medications that trap PO_4 in the intestine prevent its absorption. The PO_4 binder must be present in the intestine at the same time as the food with its PO_4. Binders are most effective when given in conjunction with PO_4 restricted diets because less needs to be bound. High dietary PO_4 content may greatly limit the effectiveness of binding agents or substantially increase the dosage required to achieve the desired therapeutic effect. Administration of 1500 to 2500 mg of aluminum carbonate to dogs with moderate CKD failed to consistently correct hyperphosphatemia when dogs were fed diets containing greater than 1% PO_4 on a dry matter basis.[119] Because many dog and cat maintenance diets contain high levels of PO_4, it is unlikely that treatment targets can be achieved solely by adding binding agents. Minimizing the quantity of PO_4 needed to be bound is important because giving too much may decrease appetite or cause nausea, vomiting, diarrhea and constipation.[120]

Intestinal binding agents containing aluminum as hydroxide, oxide or carbonate salts have been the first choice in dogs and cats because they are effective and inexpensive (Table 324-2).[121] Although aluminum-containing binding agents are usually well tolerated and safe in dogs and cats, aluminum toxicosis has been reported in dogs with advanced CKD treated with high doses.[122] Toxicosis was noted as cranial, peripheral, and junctional neuropathies. Clinical signs included weakness, ataxia, absence of patellar reflexes, decreased pelvic limb withdrawal, decreased menace response, obtundation, tetraparesis, and lateral recumbency. Microcytosis was also noted and may be useful in the early detection of aluminum toxicosis. Chelation therapy was necessary to correct the toxicosis. Aluminum-based PO_4 binders may decrease palatability and cause constipation.

TABLE 324-2

Intestinal Phosphate Binding Agents

INTESTINAL PHOSPHATE BINDER	DOSAGE RECOMMENDATIONS
Aluminum hydroxide (Alternagel; 600 mg/5 mL)*	30 to 90 mg/kg/day† PO
Lanthanum carbonate (Fosrenol; 500 mg/chewable tablet)	12.5 to 25 mg/kg/day† PO
Lanthanum carbonate octahydrate (Renalzin; 200 mg/mL)	2 mL PO in food 1-2 times daily†
Calcium carbonate (Tums; 500 mg/tablet)	30 mg/kg† PO
Chitosan and calcium carbonate (Epakitin; powder)	4.4 g/10 kg† PO
Sevelamer hydrochloride (Renagel; 400 mg/tablet)	33-54 mg/kg† PO

*Aluminum hydroxide USP is also available as a powder.

†Daily dosage should be divided among daily meals (usually 2-3 feedings/day). Product should be either mixed into the food or administered immediately before or after each meal.

Calcium-based PO_4 binding agents are effective but they may cause hypercalcemia, especially when also giving calcitriol. That combination should be avoided. People given non–Ca PO_4 binders had reduced all-cause mortality as compared with people given Ca-based binders.[123] iCa concentrations should be monitored when Ca-based binders are used. Lanthanum carbonate and other salts of lanthanum appear to be quite effective in binding PO_4. These have few side effects because lanthanum is not absorbed, reducing risk of toxicosis when compared to aluminum salts. Lanthanum is well accepted and tolerated by cats and lanthanum carbonate has been reported to inhibit intestinal oxalate absorption, preventing nephrocalcinosis in a rat model.[124,125] Sevelamer, an anion-exchange resin, is not commonly used in dogs and cats. Unlike most PO_4 binders, sevelamer does not release a cation, but it can cause metabolic acidosis and hypercalcemia. Lanthanum salts and sevelamer hydrochloride are generally far more expensive than Ca or aluminum salts.

When to Administer Binding Agents

PO_4 binding agents must be given at or around meal time with a goal of binding dietary PO_4. Administering binders other than with meals markedly reduces their effectiveness. Ca-based binding agents that are given between meals function as a Ca supplement rather than as a PO_4 binder. The agents should be administered "to effect," meaning doses should be adjusted from the starting dosage to achieve the targeted serum PO_4 concentration without excessive doses. Therapy is usually begun using the lowest recommended dosage and increased as needed every 2 to 4 weeks. If dosage substantially exceeds those recommended, it is best to add a different binding agent rather than risk overdosage. Different binding agents may be combined to minimize the risk of overdosing one drug.

Dehydration and Fluid Therapy

Overview

Preventing and correcting dehydration is extremely beneficial for dogs and cats with CKD (see ch. 129). Fluid

balance in pets with PU should be maintained by compensatory PD and dehydration results if adequate quantities fail to be consumed. Cats with CKD appear to be particularly susceptible to chronic dehydration, perhaps because their compensatory PD is inadequate. Lack of access to good drinking water, some environmental conditions, and concurrent illness that limits fluid intake or promotes fluid losses (e.g., pyrexia, vomiting or diarrhea) may lead to dehydration. Dry oral membranes and decreased skin elasticity are common in dehydration, but these findings can be misleading. Xerostomia (dry oral membranes) may result from uremia. Loss of skin elasticity is common in dogs and cats that have lost weight, are older, or in poor nutritional health. Chronic dehydration can decrease appetite and/or cause lethargy, weakness, constipation, prerenal azotemia, and predisposition to AKI. AKI in pets with preexisting CKD is a common cause of disease progression (also see ch. 322). Owners of pets with CKD should be educated regarding episodic fluid losses due to vomiting or diarrhea that might have been minor when their pet was healthy but could lead to serious deterioration of kidney function or precipitate uremic crisis when their pet is afflicted with CKD.

Indications

One should consider giving subcutaneous (SC) fluids to CKD pets with signs of chronic or recurrent dehydration. The benefits of SC fluid therapy include improved appetite, increased activity, and less constipation. Recommendations regarding SC fluids should be made on a case-by-case basis. Not every pet with CKD requires or will benefit from such therapy. While many cats with CKD appear to benefit from SC fluid therapy, fewer dogs require it. Also, home administration of SC fluids is not appropriate for all owners. While inexpensive, SC fluid administration requires time and may be stressful on the owner-pet relationship. It also has the potential to promote hypernatremia, hypokalemia, hypertension and fluid overload.

Fluid Choice, Volume, Frequency

Usually, a balanced electrolyte solution (e.g., lactated Ringer's solution) is given SC every 1 to 3 days, as needed. The volume administered depends upon pet weight. Most cats are given about 75 to 125 mL per dose. If the clinical response is suboptimal, the dose can cautiously be increased, but fluid overload must be avoided. In addition, Na-containing fluids given SC do not provide the electrolyte-free water that healthy individuals consume. Therefore, it is physiologically more appropriate to provide water via a feeding tube, which may be easier than SC for some clients (see ch. 82). Since excess Na intake may harm the kidneys, recommendations for long-term Na administration in any form should be carefully considered.[126] Response to long-term SC fluid therapy should be assessed by frequently checking hydration status, clinical signs, blood pressure, kidney function and, possibly, electrolyte values. If a detectable improvement in clinical signs and/or renal function does not accompany fluid therapy, the need for long-term therapy should be reassessed.

Managing Gastrointestinal Signs of Uremia

Antiemetic Therapy

Poor appetite, nausea and vomiting are among the most common signs of CKD and uremia. Over time, the most important complication of CKD is inadequate food intake, making starvation the most common factor leading to death in dogs and cats with CKD. Gastric complications of uremia differ in dogs versus cats. While uremic gastritis with ulceration may develop in dogs, cats are more likely to have gastric fibrosis and mineralization.[42] The lesions in dogs are thought to be the result of increases in serum gastrin concentrations, which stimulates gastric hyperacidity. Use of H2-blockers (e.g., famotidine, ranitidine), proton pump inhibitors (omeprazole, pantoprazole, esomeprazole) and sucralfate is recommended for dogs with inappetence, nausea and vomiting. These therapies would be seemingly inappropriate in cats with CKD. Use of proton pump inhibitors has been linked with AKI in older people.[127]

In dogs and cats, activation of the chemoreceptor trigger zone by uremic toxins promotes anorexia, nausea and vomiting. Uremia likely also has direct GI effects. Antiemetic therapy is useful in managing uremic nausea and vomiting. Use of antiemetic drugs does not directly improve appetite, but they may minimize loss of food and fluids via emesis. Maropitant and ondansetron act on the chemoreceptor trigger zone as well as in the gut. Oral maropitant (4 mg/cat/day for 2 weeks) has been an effective antiemetic for cats with IRIS CKD stages II and III.[128] Maropitant can be used in dogs and cats with CKD at a dose of 1-2 mg/kg/day PO or 1 mg/kg/day SC or IV. Maropitant is not limited to 5-day treatment periods. While ondansetron has been documented to be effective in uremic humans, pharmacokinetic studies have indicated poor bioavailability when it is given orally with a short half-life in cats and dogs.[129] Ondansetron (0.1-1 mg/kg SC) has better

bioavailability and a longer half-life in cats.

Appetite Stimulation Therapy

Mirtazapine (1.87 mg/cat PO q 48 h; 3.75-30 mg/dog PO q 24 h) significantly increased appetite, activity, and body weight in cats with CKD while decreasing vomiting.[130] Overdose may cause hyperexcitability, tremors and vocalization. Cyproheptadine cannot be used concurrently with mirtazapine. A study in 6 Beagles indicated that dogs may have a different pharmacokinetic profile compared to cats and humans.[131]

Esophagostomy Feeding (see ch. 82)

Failure to stabilize a pet at an acceptable body condition score is likely to adversely affect long-term outcome. Esophagostomy tube feeding can be quite beneficial for dogs and cats with progressively declining body weight despite all efforts to achieve adequate nutrition. Esophagostomy tubes are painless, effective and convenient for delivering food, water and medications to dogs and cats with CKD. It is a useful means of stabilizing or improving nutrition, clinical signs, longevity and owner satisfaction. In general, tube placement is less likely to be effective when the decision to proceed is delayed until advanced uremia and malnutrition have developed.

Metabolic Acidosis

Diagnosis

Acidosis of CKD can promote malnutrition, clinical signs of uremia, and renal osteodystrophy (see ch. 128).[75] Studies in humans and rodents suggest that metabolic acidosis may also promote progression of CKD; however, it is unclear whether this is linked to low serum bicarbonate, high dietary acid load or both.[132,133] While data are not available for dogs, metabolic acidosis is reported to affect about 15% of cats with IRIS CKD stage III and about 53% with IRIS CKD stage IV.[28] These observations suggest that only a minority of cats with clinically stable IRIS CKD stages II and III are likely to benefit from routine alkalization therapy. Thus, the decision to intervene with alkalization therapy should be based on a laboratory assessment of acid-base status. Low serum or plasma total CO_2 values obtained by autoanalyzer techniques should be confirmed by blood gas analysis (see ch. 128).[134] When considering therapy for acidosis of CKD, acid-base status should be assessed by blood gas analysis when the pet is well hydrated. Oral therapy for acidosis should be considered when blood gas analysis confirms plasma bicarbonate values remain below 15 mmol/L. However, parenteral intervention should be considered for cats with metabolic acidosis and a blood pH <7.10 to increase the value over 7.20.[135]

Treatment

Treatment options for alkalization therapy include renal diets, K citrate, and Na bicarbonate. Most renal diets are neutral to slightly alkalinizing. If diet therapy alone fails to ameliorate metabolic acidosis, alkalization therapy should be considered. K-citrate solution provides both K and alkalization and is usually more palatable than Na bicarbonate. Dosage is "to-effect," with starting dosages of 40 to 60 mg/kg q 8-12 h and a goal of maintaining reference range blood bicarbonate concentrations. Na bicarbonate (initial dose: 8 to 12 mg/kg q 8-12 h) is generally unpalatable except when given by tablets. These medications should be given as small doses frequently to minimize blood pH fluctuations. Response to therapy should be assessed after 10 to 14 days, before the drug is given, and dosage adjusted accordingly.

Potassium Disorders (Hypokalemia and Hyperkalemia)

Hypokalemia (see ch. 68 and 321)

Potassium (K) depletion and hypokalemia (hypoK) are relatively common in cats with CKD stages II and III, estimated to occur in 20% to 30%. It is less common in stage IV cats.[3,7,8] Hypertensive cats have also been reported to have significantly decreased plasma K concentrations.[46] Total body K depletion is likely more common than hypoK.[81] By contrast, hypoK is uncommon in dogs with CKD. The mechanisms underlying development of hypoK in cats with CKD remain unclear, but inadequate intake, increased urinary loss, and enhanced activation of the RAAS due to chronic dehydration and/or dietary salt restriction may play roles.[48] While increasing K content of renal diets has reduced both incidence and severity of overt clinical signs of

hypoK, it remains a common laboratory finding in CKD cats. Of note, the antihypertensive agent amlodipine may promote hypoK in cats with CKD.[136]

HypoK and K depletion may adversely affect kidneys and muscle of cats with CKD. Diets low in K and high in acid have been implicated in impairing renal function and promoting development of lymphoplasmacytic tubulointerstitial lesions in cats.[82-85] K depletion may lead to reduced renal blood flow and GFR as a consequence of angiotensin II and thromboxane-mediated renal vasoconstriction. In addition, hypoK may promote PU by impairing renal responsiveness to ADH (see ch. 45 and 296) and by stimulating the brain thirst centers via angiotensin II. Hypokalemic polymyopathy, characterized by generalized muscle weakness and cervical ventroflexion, is a well-recognized complication of CKD in cats, although now less commonly observed perhaps due to K supplementation of feline renal diets.

While there is a consensus that cats with hypoK should receive supplementation to correct or prevent renal and muscular consequences of K depletion and hypoK, the value of "prophylactic" supplementation to normokalemic cats has not been established. Oral replacement is the safest and preferred route. Parenteral therapy is generally reserved for cats requiring emergency reversal of hypoK or for cats that cannot or will not accept oral therapy. As much as 30 mEq/L of K chloride may be added to fluids intended for SC administration. Oral K may be supplemented as gluconate or citrate salts; K chloride is not recommended because it is not palatable and is acidifying. The gluconate form (2 to 6 mEq/cat/day) is available as tablets, flavored gel, or a palatable powder (Tumil-K). Acidosis is a major risk factor for development of hypoK and therefore should also be treated. The citrate solution (40 to 60 mg/kg/day q 6-8 h; Polycitra-K Syrup, Baker Norton) is an excellent alternative with the advantage of providing simultaneous alkalinization therapy. Muscle weakness usually resolves within 1 to 5 days of starting K supplementation. Dosage, thereafter, is adjusted based on clinical response and serum K concentrations, which should initially be monitored every 7 to 14 days. In cats with hypokalemic polymyopathy, it may be necessary to monitor serum concentrations every 24 to 48 hours initially. It is unclear whether all cats require long-term K supplementation.

Intensive fluid therapy during uremic crises, particularly with K-deficient fluids, may promote hypoK in cats or dogs not previously hypoK. Therefore, serum K concentrations should be monitored during fluid therapy and maintenance fluids should be supplemented with K chloride to prevent iatrogenic hypokalemia (concentrations of 13 to 20 mEq/L are appropriate for maintenance fluids). IV K should not be given at rates exceeding 0.5 mEq/kg/h.

Hyperkalemia

Hyperkalemia (hyperK) is uncommon in CKD; however, it may develop in advanced IRIS CKD stage IV (see ch. 68 and 321). It tends to occur when food consumption approaches adequate calorie intake, most commonly with feeding by tube, and/or with use of ACE inhibitors or angiotensin receptor blockers (ARBs). HyperK can be managed by reducing dietary K or by preventing intestinal uptake.[137] Polymer resins (e.g., Na polystyrene sulfonate) have been found less than adequate. In humans with CKD, Na zirconium cyclosilicate, a highly selective cation exchanger that traps K within the intestine, has been shown to be effective in mitigating hyperK.[138]

Arterial Hypertension

Rationale for Therapy

CKD is the most commonly recognized cause for hypertension in dogs and cats. It has been linked with renal, ocular, neurological and cardiac complications (see ch. 157). Retinopathy occurs in about 60% of hypertension cats and is its most common clinical manifestation.[139] Clinical signs seen with hypertension in cats include lethargy, blindness, retinal hemorrhage, retinal detachment, cerebral hemorrhage, seizures, stupor, and ventricular hypertrophy.[140-142] In one study, retinopathy and hypertensive encephalopathy were reported in 3 of 14 dogs with blood pressure values >180 mm Hg.[46] Preexisting CKD reportedly increases the vulnerability of the kidneys to hypertension injury.[143] Hypertension may be an independent risk factor for progression of CKD in dogs, although proteinuria was not included in one statistical model used to confirm this association.[31] However, in CKD cats, hypertension is associated with increased proteinuria in dogs and cats, and, since proteinuria appears to promote progressive renal injury in both species, lowering blood pressure to limit proteinuria is an appropriate goal.[35,144] Clinical evidence from humans, dogs and cats indicates that pharmacological reduction in blood pressure (BP) is likely to reduce the risk of hypertensive organ injury. SC hydralazine has been reported to reduce the prevalence of seizures developing as a

consequence of hypertension after renal transplantation (see ch. 323).[141] Further, in an induced model of hypertensive kidney disease, only 2 of 10 cats receiving the amlodipine developed evidence of retinal lesions compared to 7 of 10 cats given placebo.[140]

Indications for Treatment

The indication for antihypertensive therapy is to treat and/or prevent development of end-organ injury including the kidneys, eyes, brain and heart (see ch. 158). However, the BP above which progressive renal injury may be induced is unknown. The IRIS recommendations for treating hypertension are based on risk estimates of end-organ injury developing in specific BP ranges in dogs or cats with CKD. Dogs and cats with mild hypertension (systolic pressures 160 mm Hg to 179 mm Hg) should have their hypertension confirmed with at least three determinations over a 1- to 2-month period. Treatment should be withheld until measurements establish that hypertension is persistent. In dogs and cats with more severe hypertension (systolic pressures >180 mm Hg), the waiting period should be reduced and the two rechecks completed in 1 to 2 weeks. However, when there is evidence for hypertension-related organ injury or if the systolic blood pressure is at emergency levels (>200 mm Hg), antihypertensive therapy should be started immediately. Reasonable efforts should be made to minimize risk that measured elevations in blood pressure represent a transient "white coat" effect, rather than a sustained elevation.[145] It is deemed unlikely that systolic pressures>200 mm Hg reflect any anxiety response. Note that some dog breeds, notably healthy sight hounds, may have BP ranges up to 40 mm Hg higher than those provided in these guidelines, and decisions on diagnosis and treatment should be adjusted accordingly. Evidence suggests that dogs and cats with CKD may be at increased risk for additional renal injury or developing complications associated with elevated BP.[31,51,140-142] Pets with IRIS CKD stages I through IV and confirmed hypertension or severe hypertension should be treated.

Goals and Guidelines for Treating Hypertension in CKD

The optimum endpoint for antihypertension therapy has not been established for dogs and cats with CKD (see ch. 158). In the absence of such information, treating arterial hypertension should be initiated cautiously with the goal of reducing BP to *at least* <160/100 mm Hg. Except in pets with acute, severe ocular or neurological lesions, rapid reduction in BP is not indicated. Dogs with hypertension may require several dosage and drug adjustments, taking weeks to months to achieve satisfactory control. In contrast, cats often respond much quicker. Reducing BP is a long-term process where gradual and sustained reduction should be the goals. Sudden or severe decreases in BP are never indicated, because it is important to avoid clinical hypotension. Treatment should be carried out in a step-wise fashion and adjustments made until the therapeutic endpoint is achieved (i.e., systolic pressure <160 mm Hg). While it is unclear whether Na restriction is effective in lowering BP in dogs or cats with hypertension, a gradual change to a lower Na diet is recommended at the time that pharmacologic intervention is begun. Generally, avoid initiating antihypertensive therapy until hydration is cautiously restored to avoid abrupt decreases in BP and/or renal perfusion. ACE inhibitors such as enalapril and benazepril, and the Ca channel blocker amlodipine, are the mainstays of antihypertensive therapy in dogs and cats. These drugs may have unique renoprotective benefits and are therefore appropriate initial options for managing hypertension in CKD.

Drugs, Dosages, Combinations

Treatment should begin with an ACE inhibitor given at a standard dosage (Table 324-3). The dosage may need to be progressively increased, with doubling the maximum recommended. If the target has not been achieved despite dosage adjustments, a Ca channel blocker (amlodipine) should be implemented. Again, the dosage may be increased to a double maximum, as needed. The ARB and/or hydralazine may be added if the other drugs have failed to achieve the target. People being treated for proteinuria with both an ACE inhibitor and an ARB, rather than just one, may be at risk of developing hyperkalemia, hypotension and/or renal failure.[146] The clinician should consider terminating the ACE inhibitor before adding the ARB or should monitor for hyperkalemia, hypotension and/or progressive azotemia. Treatment should begin with the Ca channel blocker amlodipine. If the initial dosage fails to normalize BP, the dosage may be gradually increased to a maximum of 1.25 mg/kg/day PO. If additional antihypertensive drug support is needed, the clinician should consider adding an ACE inhibitor to the Ca channel blocker. Treatment for arterial hypertension is usually lifelong. Once treatment has achieved the stated target BP, monitoring is essential for continued control. Dogs and cats on BP therapy should be monitored no less often than every 3 months (see ch. 158).

Examination for retinal lesions secondary to hypertension (see ch. 11 and 157) should be performed at the time as BP monitoring (see ch. 99). Using the step-wise medical scheme described, dosage adjustments are made as needed to keep BPs <160/100 mm Hg.

TABLE 324-3

Drugs Used to Manage Proteinuria and Hypertension in Dogs and Cats

DRUG (MECHANISM)	INITIAL DOSAGE	ESCALATING DOSAGE SCHEME
Benazepril (ACE inhibitor)	0.5 mg/kg PO q 24 h	Increase by 0.5 mg/kg/d to a maximum of 2 mg/kg/d
Enalapril (ACE inhibitor)	0.5 mg/kg PO q 24 h	Increase by 0.5 mg/kg/d to a maximum of 2 mg/kg/d
Telmisartan (ARB)	1 mg/kg PO q 24 h	Increase by 0.5 mg/kg/d to a maximum of 2 mg/kg/d
Losartan (ARB)	0.125 mg/kg/d PO	0.25 mg/kg/d in azotemic dogs 0.5-1.0 mg/kg/d PO in nonazotemic dogs
Amlodipine (CCB) Cats	< 5 kg: 0.625 mg PO q 24 h / cats ≥ 5 kg: 1.25 mg PO starting dose	Double dosage if blood pressure remains elevated (dose is per cat)
Amlodipine (CCB) Dogs	0.1-0.3 mg/kg PO q 24 h	Can increase dosage incrementally up to 0.75 mg/kg PO q 24 h until blood pressure reduced to target pressure (systolic BP < 160 mm Hg)

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *CCB*, calcium channel blocker.

Increases in serum creatinine concentration, low BP and clinical signs of hypotension should prompt reassessment of the antihypertensive drugs and dosages. Small increases in serum creatinine that are not progressive may safely occur with antihypertensive therapy. However, large or progressive increases of creatinine concentration may reflect drug or dosage problems. If systolic BP persistently declines below 120 mm Hg or signs of hypotension such as weakness or tachycardia develop, antihypertensive drugs and dosages should be adjusted to increase BP and ameliorate the clinical signs.

Treatment of Anemia of CKD

Causes

Anemia of CKD can have a profound effect on quality of life. As many as 65% of cats develop anemia as CKD progresses.[147] Anemia in pets with CKD is often multifactorial in origin. The primary cause for anemia is inadequate production of EPO. Iatrogenic and spontaneous blood loss, poor nutrition (including protein, iron, folate and perhaps others), chronic inflammation/infection, and reduced red blood cell (RBC) life spans may complicate and contribute to anemia. Excessive blood sampling is worrisome and should be avoided. Failure to identify and correct these complications can impair the effects of hormone replacement.

Chronic low-grade GI blood loss can promote moderate to severe anemia in pets with CKD that would otherwise have sufficient endogenous EPO production to maintain their RBC counts and packed cell volumes (PCVs) in the subclinical range. These pets may or may not have overt GI signs or melena. Iron deficiency and BUN-to-creatinine ratios above what is expected in context of the diet may provide indirect evidence of occult GI blood loss. Thrombocytosis and hypochromic RBCs are consistent with iron deficiency and GI bleeding. Because of difficulty in confirming GI hemorrhage, a therapeutic course with histamine H2 receptor antagonists or H2 blockers and sucralfate should be considered. Improvements in PCV and/or appetite support a role for GI hemorrhage in the genesis of anemia. While gastric ulcerations are common in dogs with CKD, they are not common in cats, whose uremic gastropathy appears to differ.[42]

Erythrocyte-Stimulating Agents

The most effective means of correcting anemia of CKD is use of erythrocyte-stimulating agents (ESAs) to correct the EPO deficiency common in CKD. Absent factors that impair their effectiveness, administration of ESAs induces a dose-dependent increase in PCV. In dogs and cats, increasing the PCV to the low end of the normal range takes about 2 to 8 weeks, depending on initial PCV and dose administered. As the anemia is

corrected, most pets show increases in appetite, body weight, energy level and sociability.[148] The ESAs currently available include epoetin alfa (R-HuEPO: Epogen, Amgen; Procrit, Centocor Ortho Biotech Products; Eprex, Janssen), epoetin beta (Neo-Recormon, Roche), darbepoetin alfa (Aranesp, Amgen) and continuous EPO receptor activators (Mircera, Roche).[147] The principal differences among these products is their degree of glycosylation. This affects their renal clearance and therefore influences their duration of action. Clinical efficacy among these products is reported to be similar in humans. Available ESAs are based on human EPO. Canine and feline EPOs share 81.3% and 83.3% homology, respectively, with human EPO.[147] These levels of homology allow these drugs to be effective in stimulating substantial PCV increases in both dogs and cats. However, over the course of therapy, there is risk of developing anti-EPO antibodies, recognized in both dogs and cats, primarily with epoetin alfa.

ESA-Induced Antibodies

Approximately 25% to 30% of cats and up to 50% of dogs receiving epoetin develop neutralizing anti-EPO antibodies; however, not all cases with anti-EPO antibodies develop anemia.[148] These antibodies cross-react with all ESAs including the pet's endogenous EPO. Development of anti-EPO antibodies can markedly suppresses erythropoiesis and result in a pure red cell aplasia (PRCA; see ch. 199). Many pets with PRCA become transfusion dependent, although if they live long enough, response to endogenous EPO may return. Although controlled studies on development of antibodies directed at the ESA darbepoetin are not available, it appears that this product is much less immunogenic as compared to R-HuEPO.[149,150] It is suggested that the longer half-life of darbepoetin may reduce the antigen load administered compared to R-HuEPO, thereby reducing the risk of antibody formation.[147]

Other EPO-Related Adverse Effects

While development of anti-EPO antibodies is the most important adverse reaction linked to ESAs, other effects reported in dogs and cats have included systemic hypertension, seizures, reactions at injection sites, vomiting and fever.[148,149] Hypertension may develop or increase in severity due to increased peripheral vascular resistance secondary to improved oxygen delivery and reversal of the vasodilation induced by chronic hypoxia. Increased blood viscosity due to the increased PCV is thought to be minor. Seizures, reported in dogs and cats being treated with rHuEPO, are not directly caused by ESAs, but rather related to compensatory adaptations to increases in RBC mass.[148] Allergic reactions including cutaneous or mucocutaneous reactions or cellulitis sometimes with fever and arthralgia occasionally occur in both dogs and cats early in the course of EPO therapy.[148] Lesions generally resolve within a few days and most do not recur when therapy is reinstated.

rHuEPO versus Darbepoetin

ESAs are indicated in dogs and cats with: (1) advanced CKD (IRIS CKD stages III and IV), (2) PCV values below 22%, and (3) those with clinical signs attributable to anemia: tachypnea, tachycardia, weakness, and anorexia. While rHuEPO and darbepoetin are both available, darbepoetin is preferred for dogs and cats. The advantages of darbepoetin over epoetin include seemingly lower risks of anti-EPO antibodies and weekly administration. One study reported 56% (14/25) of cats given darbepoetin achieved the target PCV (25%). The cats reaching the target survived significantly longer than cats that did not respond (mean of 238 days for responders; 83 days for nonsurvivors).[149] In another study, 7 of 7 cats with CKD reached the target PCV (30%), and none had evidence of anti-EPO antibodies.[150]

Darbepoetin Protocol

Darbepoetin is initially given SC (1 mcg/kg, weekly) and continued until the pet's PCV reaches the low end of the target range (cats: 25%-35%; dogs: 37%-42%). Once achieved, either the dose of darbepoetin is reduced by 20% to 25% or the frequency of dosing is decreased to once every 2 weeks. The maintenance dose can then be adjusted monthly, as needed, to keep the PCV within the target range. Since excessive ESA doses have been linked to adverse outcomes in humans, it is recommended that abnormally high PCVs be avoided.[151] Initially, physical examinations and BP assessments (see ch. 99) should be performed weekly until the target PCV is achieved and then continued monthly. Usually, the PCV increases about 1% to 3% weekly; more rapid rates of increase should be avoided because of an association with hypertension. Once stable, recheck examinations should be conducted every 1 to 3 months. It is essential that regular follow-up examinations continue as long

as darbepoetin therapy continues.

Iron Deficiency

Many dogs and cats with advanced CKD are iron (Fe) deficient. Increasing the number of RBCs requires Fe iron, which should be given early with ESA therapy. While Fe can be supplemented orally, it is difficult to provide adequate amounts without causing GI complications. Therefore, Fe dextran (50 mg/cat; 50-300 mg/dog) should be given by injection. Although rare, Fe dextran can cause an anaphylactic reaction, so it is prudent to inform owners of this possibility and to observe the pet for a period of time after administration. If needed, Fe dosing can be repeated monthly.

Several causes of blunted response or failure to resolve anemia with ESA therapy have been identified: Fe deficiency, ongoing GI losses, hemolysis, concurrent inflammatory or malignant disease, and aluminum overload. Owner error related to drug storage, handling, or administration may account for poor response. If the anemia corrects with ESA therapy, but then PCV values again decline, development of anti-EPO antibodies should also be considered. The diagnostic approach to ESA treatment failure should consider history of drug administration, physical examination, CBC, serum chemistry profile, serum cobalamin, an Fe panel (serum Fe, ferritin, and transferrin saturation), bone marrow biopsy, and imaging (evidence of infectious or neoplastic disease). When these tests fail to identify a cause for treatment failure in dogs and cats that have initially responded to ESA therapy, anti-EPO antibodies should be suspected and ESA therapy stopped.[104] Absent an anti-EPO antibody assay, bone marrow myeloid-to-erythroid ratios may provide the best method to ascertain if resistance is due to antibody formation. When EPO is stopped early, antibody titers may decline and suppressed erythropoiesis may reverse.

Calcitriol Therapy

Rationale

Calcitriol (1,25-dihydroxyvitamin D), the most active metabolite of vitamin D, results from renal hydroxylation of 25-hydroxyvitamin D. It enhances GI Ca and PO_4 uptake, inhibits PTH synthesis and secretion, suppresses parathyroid gland growth, and activates cellular receptors. Possible causes of reduced calcitriol levels in CKD include PO_4 retention, increased levels of FGF-23, and reduced renal mass. PO_4 retention and hyperphosphatemia reduce calcitriol production by inhibiting renal 1-alpha-hydroxylase activity which converts 25-hydroxy-cholecalciferol to calcitriol.[59] As CKD progresses, reduced renal mass further limits the number of cells available to hydroxylate 25-hydroxyvitamin D. Calcitriol therapy has been shown to reduce PTH levels in dogs and cats with CKD.[57,36] Although PTH has been claimed to be a uremic toxin responsible for many constitutional signs or uremia, clinical benefits of reducing PTH have not been conclusively documented.[52,152] Results of one clinical trial indicated that calcitriol reduced mortality in dogs with CKD stages III and IV by slowing the progression of CKD.[36] People with CKD have had similar survival benefit after being treated with calcitriol.[153] However, a similar clinical trial in cats revealed equivocal benefits for calcitriol in altering the course of CKD. Neither study could confirm or refute a proposed drug-related improvement in clinical signs.

Treatment Guidelines

Calcitriol therapy (2-3 ng/kg PO q 24 h) is indicated for dogs with CKD stages III and IV and possibly those in CKD stage II to slow progressive deterioration in renal function, but its use in cats remains speculative. Prior to giving calcitriol, neither serum PO_4 nor iCa should be increased since calcitriol increases GI absorption of both. Both must be monitored during therapy to avoid hyperphosphatemia and ionized hypercalcemia. It is unclear whether renoliths containing Ca constitute a relative contraindication to calcitriol therapy. Life-long treatment is necessary to achieve the desired effect of reduced renal mortality. Because it enhances GI absorption of Ca and PO_4, calcitriol should not be given with meals. Giving calcitriol in the evening on an empty stomach reduces risk of inducing hypercalcemia. A compounding pharmacy is needed to prepare formulations that can be used in dogs and cats because the human formulation is too strong.

Overdose

Overdosage of calcitriol is dangerous and should be avoided due to the induction of hypercalcemia with possible renal injury (hypercalcemic nephropathy). Early detection of hypercalcemia, should it occur, is indicated to limit the extent of renal injury. However, hypercalcemia after giving vitamin D is unpredictable

(i.e., it may occur after days to months of treatment). Therefore, continued monitoring of serum Ca, PO_4, and creatinine concentrations after 2, 5, and 8 weeks is necessary to detect hyperCa, hyperPO_4, or deteriorating renal function before irreversible renal damage ensues. Hypercalcemia is more likely to occur when calcitriol therapy is combined with Ca-containing PO_4 binding agents, particularly Ca carbonate. If serum PO_4 and iCa concentrations remain well controlled after 8 weeks of calcitriol therapy, monitoring should continue every 1 to 2 months. The product of serum tCa × PO_4 concentrations should not exceed 60; the goal is values between 42 and 52.[69]

Calcitriol's rapid onset (about 1 day) and short duration of action (half-life less than 1 day) permits rapid control of unwanted hypercalcemia by stopping it completely. Therapy may be reinstituted at a reduced dose or altered dosing strategy after the serum Ca and PO_4 concentrations return to target levels. When calcitriol therapy is associated with hypercalcemia, the daily dose may be doubled and given every other day. This approach may be safer because the effect of calcitriol on the GI tract is related to duration of cell exposure to the calcitriol. When plasma PTH concentration is markedly elevated or when standard therapy with calcitriol fails to normalize plasma PTH levels, pulse calcitriol therapy has been recommended.[52] In this approach, pets receive 20 ng/kg of calcitriol PO twice weekly in the evening on an empty stomach. Pulse therapy is usually used no longer than 1 to 2 months to suppress resistant RSHP. If successful, calcitriol is then given at the standard daily dose. While calcitriol is effective in lowering PTH, the importance of measuring PTH concentrations during calcitriol therapy is unclear and the clinical benefits of suppressing RSHP remain unproven. In the canine study that confirmed survival benefits after therapy with calcitriol, doses were increased as high as 5 ng/kg/day (mean: 1.9 ng/kg/day) to lower PTH values into the normal range, unless hypercalcemia ensued. If hypercalcemia developed, the dosage of calcitriol was reduced.

Minimizing Progression of CKD

All pets with CKD are at risk for disease progression as a consequence of the primary renal disease, in association with a variety of secondary factors that may promote progressive renal disease, or both. An important therapeutic goal for managing patients with CKD is to minimize or prevent progressive loss of renal function. Treatment designed to limit progression of kidney disease may involve a variety of interventions including diet therapy, minimizing proteinuria, controlling hypertension, and calcitriol therapy. A recent hypothesis proposes that blood pressure, proteinuria and phosphate may in fact be linked in their effects on progression of CKD through, in part, the FGF-23/klotho system and calcitriol deficiency.[154] Effectiveness of diet therapy in prolonging survival of dogs and cats with CKD has been described. Renal diets are clearly indicated for dogs with CKD stages III and IV and in cats with CKD stages II through IV. Proteinuria and hypertension are well-established risk factors for progression of renal disease in humans.[55,156] Clinical studies have confirmed that proteinuria is a risk factor for increased mortality in dogs and cats.[25,31] In dogs, the risk of an adverse event (uremic crisis or death) was found to increase by 1.5-fold for every 1-unit increase increment in UPC above 1.0.[31] Elevated BP has been reported to be a risk factor for increased mortality in dogs, but not in cats.[31,144]

Treatments designed to limit proteinuria and hypertension have been proven to be of value in slowing progression of CKD in humans. The evidence in dogs and cats is similar, although somewhat less compelling. In dogs with glomerulopathies, treatment with the ACE inhibitor enalapril significantly reduced proteinuria, but the duration of the study was too brief to adequately assess the renoprotective value of the therapy.[157] However, in a study examining the effects of enalapril in Samoyed Dogs with hereditary nephritis, treated dogs survived 1.36-fold longer than untreated dogs. In cats with UPC values >1.0, treatment with benazepril appeared to be associated with longer survival times, although the effect did not achieve statistical significance. In cats with UPC values <1.0, the data were equivocal.[26] This later finding is consistent with observations in humans suggesting that the magnitude of benefit accruing from ACE inhibitors is proportional to the magnitude of reduction in proteinuria.

The ACVIM Proteinuria Consensus Group has advocated initiating efforts toward reducing glomerular proteinuria in dogs and cats with CKD stages I through IV.[50] Therapeutic intervention is indicated when the UPCR is >2.0 in dogs and cats with CKD stage I, and when it exceeds 0.5 in dogs and 0.4 in cats with CKD stages II through IV. It is now well established in people that therapeutically reducing proteinuria by suppressing the RAAS ameliorates the adverse effects of proteinuria on the kidneys. Experimental and clinical evidence has confirmed the beneficial effect of BP control on slowing progression of diabetic and nondiabetic nephropathies in humans.[155,158] In one large clinical trial, the renoprotective effect of

antihypertensive therapy was further enhanced by maintaining BP below the usual target value.[159] As a consequence, the "ideal" BP to attain using antihypertensive therapy in people with CKD depends on clinical characteristics of the patient. Factors such as presence or absence of proteinuria may influence the goals of therapy. Antihypertensive therapy was most effective in limiting progression of kidney disease in patients with proteinuria. Greater reduction in BP appears to be necessary for equivalent renoprotection with greater levels of proteinuria.[155,159] Studies performed in dogs with induced CKD indicate that administration of the ACE inhibitor enalapril limited glomerular and systemic hypertension, proteinuria and glomerular and tubulointerstitial lesions.[160] Interestingly, enalapril was renoprotective in this study despite the fact that the dogs had only mild hypertension and relatively modest proteinuria.

The renoprotective effects of ACE inhibitors cannot be explained entirely by their effects on blood pressure alone. It is likely that renoprotection results in part from suppressing renal levels of angiotensin II. Because of the role of angiotensin II in progression of CKD, angiotensin receptor blockers have also been considered for humans with CKD.[161] Angiotensin receptor blockers and ACE inhibitors differ in the mechanism by which they inhibit angiotensin II. The ACE inhibitors block conversion of angiotensin I to angiotensin II. However, angiotensin II formation is not completely inhibited because it can also be generated by a non-ACE-dependent pathway such as by the enzyme chymase. Also, because bradykinin is normally degraded by ACE, ACE inhibitor therapy is associated with elevated bradykinin levels. Bradykinin is a vasodilator that may have renoprotective effects by stimulating nitric oxide production. Angiotensin receptor antagonists block the type 1 receptor, but leave type 2 receptor effects unopposed, which appears to be important in vasodilation. In rats with nephropathy, angiotensin II antagonism has been reported to normalize proteinuria, eliminate inflammatory cell infiltration, and ameliorate glomerular and tubular structural changes.[162] A combination of an angiotensin receptor antagonist and an ACE inhibitor has been suggested as a way to maximize blockade of the renin-angiotensin system by affecting both the bioavailability of angiotensin II and also by affecting its activity at the receptor level.[163]

Each type of drug has been shown to be effective in reducing proteinuria and slowing progression of renal disease. However, in experimental and clinical models in humans, combination therapy has proven more effective than either drug alone.[161] In humans, there does not appear to be an increase in toxicoses or adverse events with combination therapy.[158] Whether combination therapy is safe, effective, and provides a therapeutic advantage needs to be determined for dogs and cats with CKD. However, the angiotensin II receptor blocker losartan may not achieve effective blood levels, possibly due to inadequate conversion to the active metabolite.[164] It is not known whether the same is true of irbesartan, but recommended dosages of irbesartan are much higher than those recommended for humans, suggesting a potential problem with conversion of this drug as well. Blockade of the renin-angiotensin system limits both angiotensin II and aldosterone while retarding progression of renal disease. Recent studies have implicated aldosterone as an important pathogenic factor in this process.[165,166] Selective blockade of aldosterone, independent of renin-angiotensin blockade, reduces proteinuria and glomerular lesions in rats with experimental kidney disease. Where blockade of the RAAS ameliorates proteinuria and glomerular injury, selective reinfusion of aldosterone restores proteinuria and glomerular lesions despite continued blockade. This observation suggests an independent pathogenic role for aldosterone as a mediator of progressive renal disease. Aldosterone appears to promote progressive renal injury through both hemodynamic effects and direct cellular actions.[165] It appears to have fibrogenic properties in the kidneys, perhaps in part by promoting production of the profibrotic cytokine transforming growth factor-beta (TGF-beta).[166] Experimental studies have shown that the aldosterone-receptor antagonist eplerenone may attenuate proteinuria and renal damage, independent of its effect on blood pressure. While ACE inhibitors initially cause an acute reduction in aldosterone concentration, this effect is not sustained. It has been proposed that use of aldosterone-receptor antagonists in addition to ACE inhibitors will have additional benefits toward protecting the kidneys.[165] However, the role of this form of therapy has yet to be established in dogs and cats. As described above, calcitriol appears to have renoprotective effects in dogs. It has also been reported to be renoprotective in humans with CKD. The mechanisms of renoprotection have not been fully elucidated, but may include activation of vitamin D receptors on various tissues in the body, improvement in podocyte viability, suppression of RSHP, and suppression of the RAAS.[117,153,167,168]

Patient Monitoring

Response to treatment should be monitored at appropriate intervals so that treatment can be individualized

to the specific, and often changing, needs of the patient. The database obtained before initiating therapy or after correcting an overt uremic crisis should be used as a baseline for comparison of the patient's progress. This evaluation should be repeated at appropriate intervals. In general, evaluations every 2 to 4 weeks are suggested until the initial response to therapy can be established. However, the frequency of evaluation may vary depending on severity of renal dysfunction, complications present in the patient, treatments applied, and response to treatment. Patients receiving therapy with EPO or calcitriol require frequent monitoring life-long. After the initial response to therapy, if any, has been established, dogs and cats in stage I CKD may require evaluation as infrequently as every 6 to 12 months, depending on the nature of their disease. For example, stage I dogs with substantial proteinuria may require monitoring much more frequently depending on the course of their disease. Cats in stage II CKD typically should be monitored about every 3 to 6 months. Dogs in stage II CKD and dogs and cats in stage III CKD should be reevaluated about every 2 to 4 months, depending on the stability of their renal function. Specific recommendations for monitoring are described in the various treatment sections.

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CHAPTER 325

Glomerular Diseases

Shelly L. Vaden

Client Information Sheet: Glomerular Diseases

Glomerular diseases are a leading cause of renal disease in dogs.[1] In randomly selected dogs, the prevalence of glomerular lesions is as high as 43% to 90%,[2] and the prevalence appears to increase with age.[3] Glomerular diseases also occur in cats, although they are less common. Immune complex glomerulonephritis (ICGN), amyloidosis and glomerulosclerosis are considered to be the most common glomerular diseases of dogs, comprising nearly 84% of the lesions described in a recent report of 501 dogs with glomerular disease (Box 325-1).[4] Progress has been made in trying to develop a deeper understanding of the differing clinical presentations of the varied glomerular diseases that occur in dogs; fewer studies have been done in cats. Consensus recommendations have been published regarding the approach to the diagnosis, standard therapy and immunosuppressive treatment for dogs with suspect glomerular disease.[5-9]

Box 325-1

Glomerular Diseases Described in Dogs and Cats

- Immune-complex glomerulonephritis (ICGN)
  - Membranous*
  - Membranoproliferative
  - Lupus nephritis
  - Proliferative (rare)
  - Crescentic type (rare)
  - IgA nephropathy (rare)
- Glomerulosclerosis
  - Focal segmental glomerulosclerosis
  - Global glomerulosclerosis
- Amyloidosis
- Hereditary nephritis
- Minimal change glomerulopathy (rare)

*Membranous glomerulopathy is the most common glomerular disease in cats; other glomerular diseases appear to be uncommon.

Normal Glomerular Structure and Function

The glomerulus is a modified capillary bed that functions as a filter, across which an ultrafiltrate of the plasma is formed.[10,11] The filtration barrier is composed of three layers: the fenestrated endothelium, glomerular basement membrane (GBM), and visceral epithelial cells, or podocytes (Figure 325-1). Slit diaphragms are specialized cell junctions present between the podocytes that bridge the filtration slits. The filtrate passes through the endothelial fenestrae, permeates the GBM, and then passes through the filtration slits of the epithelial cells and into the urinary space.[12] This complex structure is freely permeable to water and small dissolved solutes, but retains cells and most macromolecules, such as proteins. The major

determinant of passage into the filtrate is molecular size; ionic charge may be of lesser importance. The epithelial slits likely provide resistance to liquid flow, whereas the GBM is probably the primary determinant of the size-selective barrier by acting as a modified gel through which macromolecules pass.[13] Small molecules, such as inulin (5000 Daltons), pass freely through the filter. Substances are retained with increasing efficiency as they increase in size to approximately 60,000 to 70,000 Daltons; only small amounts of substances larger than this are filtered. Albumin, a negatively charged protein with a molecular weight of 69,000 Daltons, is normally largely excluded from the filtrate. In the end, albumin is prevented from passing into the filtrate. It has long been believed that ionic charge also influences filtration, and that negatively charged proteins are retained to a greater extent than would be predicted by size alone.[14] The podocyte foot processes and the slit diaphragms between them, as well as the basement membrane and the endothelium, are rich in negatively charged glycoproteins, creating this charge barrier. These polyanions are believed to play an important role in the maintenance of normal glomerular permeability and visceral epithelial cell shape. Despite this complex filtration system, small amounts of albumin and other proteins are normally found in the filtrate. Substantial degradation of these proteins occurs, resulting in excretion only of peptide fragments, which are not detected by routine total protein assays. Proteins and peptide fragments may also undergo resorption in the nephron distal to the glomerulus.[14]

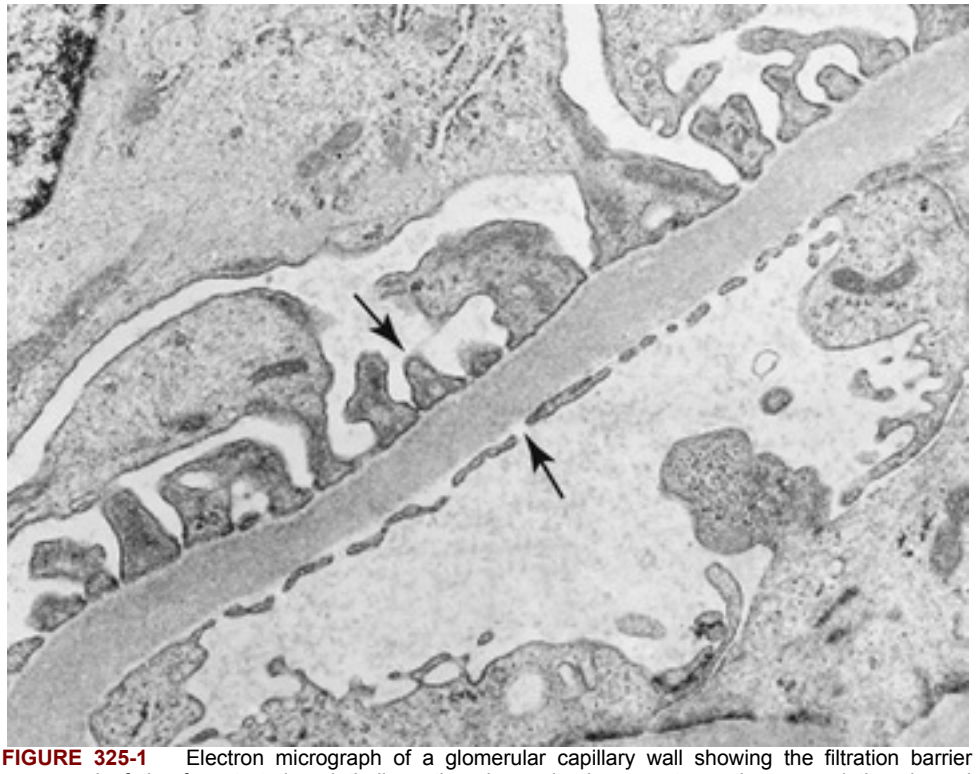


FIGURE 325-1 Electron micrograph of a glomerular capillary wall showing the filtration barrier composed of the fenestrated endothelium, the glomerular basement membrane, and the visceral epithelial cell (podocyte). (Courtesy J.C. Jennette, School of Medicine, University of North Carolina, Chapel Hill, NC.)

Clinical Findings

Signalment

Glomerular disease can develop at any age, but appears to be most common in middle-aged to older dogs. The prevalence of microalbuminuria, a marker of increased glomerular permeability, increases as dogs age, with more marked increases seen beyond 6 years of age.[15] The average age of 375 dogs with a variety of glomerular diseases reported in five studies was 8.3 years.[1,16-19] Dogs with nephrotic syndrome (NS) may present at a younger age (mean 6.2 years).[20] Male and female dogs were equally represented. However, the average age and gender predilection seen with specific glomerular diseases varies somewhat from the overall

averages. Glomerular diseases often occur secondary to another disease process. Infectious and noninfectious inflammatory diseases may be more likely in young and middle-aged animals, whereas neoplasms are more common as dogs become older. Familial glomerular diseases often are manifested at an early age. Several breeds of dogs are known to have familial glomerular diseases (Table 325-1); many of these are discussed in detail in ch. 328. Labrador Retrievers and Golden Retrievers may have a higher incidence of glomerular disease; however, the possibility that this increased representation reflects the popularity of these breeds requires further evaluation.[16,21]

TABLE 325-1

Select List of Breeds of Dogs and Cats with Familial Glomerulopathies

BREED	GLOMERULAR DISEASE
Abyssinian Cat	Focal proliferative glomerulopathy
Beagle	Amyloidosis
Bernese Mountain Dog	Mesangiocapillary glomerulonephritis
Bullmastiff	Glomerulopathy
Bull Terrier	Hereditary nephritis
Cocker Spaniel (especially English)	Hereditary nephritis
Dalmatian	Hereditary nephritis
Doberman Pinscher	Glomerulosclerosis, cystic glomerular atrophy
English Foxhound	Amyloidosis
French Mastiff	Progressive juvenile glomerulopathy
Greyhound	Glomerular vasculopathy and necrosis
Newfoundland	Glomerulosclerosis
Pembroke Welsh Corgi	Glomerulosclerosis, cystic glomerular atrophy
Rottweiler	Atrophic glomerulopathy
Samoyed (rare)	Hereditary nephritis
Shar-Pei	Amyloidosis
Soft Coated Wheaten Terrier	Podocytopathy

History

The clinical signs associated with glomerular disease vary considerably, depending on the severity of proteinuria and the presence or absence of renal azotemia.[16,17,22] Many animals with glomerular disease are asymptomatic, and proteinuria is detected during routine health screening. Alternatively, animals may manifest specific signs related to an underlying inflammatory, infectious, or neoplastic condition (E-Boxes 325-2 and 325-3). Signs of glomerular disease may be nonspecific (e.g., weight loss, lethargy) or consistent with chronic kidney disease or uremia (polyuria, polydipsia, anorexia, vomiting, and malodorous breath). Acute kidney injury is not a common presentation in animals with glomerular disease but does occur on occasion. When urinary protein losses are severe, signs of fluid retention (e.g., abdominal enlargement consistent with ascites, peripheral edema) or thromboembolism (e.g., dyspnea, loss of limb function) may be present. Hypertensive damage to the central nervous system (see ch. 260), eyes (see ch. 11), or heart may induce a variety of clinical signs (see ch. 157).

E-Box 325-2

Diseases Reported in Association with Glomerular Disease in Dogs

Systemic Disease

Infectious

Bacterial
- Anaplasmosis
- Borreliosis (MPGN)
- Bartonellosis (G)
- Brucellosis (G)
- Endocarditis (G)
- Pyelonephritis (A)
- Pyometra (A, G)
- Pyoderma (A, G)
- Other chronic bacterial infections (A, G)

Protozoal
- Babesiosis (MPGN)
- Hepatozoonosis (G)
- Leishmaniasis (A, MPGN, MN, P-E and M)
- Trypanosomiasis (G)

Rickettsial
- Ehrlichiosis (G)

Viral
- Canine adenovirus type 1 (P-M)

Parasitic
- Dirofilariasis (A, MPGN, MN)
- *Heterobilharzia americana* (MPGN)

Fungal
- Blastomycosis (A)
- Coccidioidomycosis (A, G)

Inflammatory

Chronic dermatitis (A, G)
Inflammatory bowel disease (G)
Pancreatitis (A, G)
Periodontal disease (A, G)
Polyarthritis (A, G)
Systemic lupus erythematosus (A, MPGN, MN, P-E and M)
Other immune-mediated diseases (G)

Neoplastic

Leukemia (G)
Lymphoma (A, G)
Mastocytosis (G)
Primary erythrocytosis (MCD?)
Systemic histiocytosis (G)
Other neoplasms (A, G, MN)

Miscellaneous

Corticosteroid excess (G)
Trimethoprim-sulfa therapy (G)
Masitinib (MCD)
Hyperlipidemia (?)
Chronic insulin infusion (A)
Congenital C3 deficiency (MPGN)
Cyclic hematopoiesis in gray Collies (A)

Familial (see Table 325-1)

Idiopathic (A, G, MPGN, MN, MCD, P-E or M)

A, Amyloidosis; *G,* glomerulonephritis, uncharacterized; *MCD,* minimal change disease; *MN,* membranous nephropathy; *MPGN,* membranoproliferative (mesangiocapillary) glomerulonephritis; *P,*

proliferative (*E*, endocapillary or *M*, mesangial).

E-Box 325-3

Diseases Reported in Association with Glomerular Disease in Cats

Systemic Disease

Infectious

Bacterial
- Chronic bacterial infections (G)
- Mycoplasmal polyarthritis (G)

Viral
- Feline immunodeficiency virus (G)
- Feline infectious peritonitis (MN)
- Feline leukemia virus (G, MN)

Inflammatory
- Pancreatitis (G)
- Cholangiohepatitis (G)
- Chronic progressive polyarthritis (G)
- Systemic lupus erythematosus (MN)
- Other immune-mediated diseases (G)

Neoplastic
- Leukemia (MN)
- Lymphoma (MN)
- Mastocytosis (G)
- Other neoplasms (G)

Miscellaneous
- Acromegaly (?)
- Mercury toxicosis (MN)

Familial (MN)

G, Glomerulonephritis, uncharacterized; *MN*, membranous nephropathy.
Idiopathic (MN)

Physical Exam Findings

The physical examination (see ch. 2) is often unremarkable in dogs with glomerular disease.[16,17,22] Nonspecific evidence of systemic disease may be present (e.g., poor body condition or poor haircoat). Dogs with advanced kidney disease may have oral ulcerations, pale mucous membranes, or dehydration. Subcutaneous edema or ascites or both are sometimes noted (see ch. 18). Occasionally dogs have physical evidence of thromboembolic disease, such as dyspnea or a decreased or absent peripheral pulse (see ch. 256). Evidence of a predisposing inflammatory, infectious, or neoplastic process may be detected during the physical examination. The kidneys of affected animals are variable in size. Animals with chronic kidney disease often have small, firm, irregularly shaped kidneys (see ch. 324), whereas those with disease of shorter duration often have normal-sized or, occasionally, enlarged kidneys (see ch. 322).

Clinicopathologic and Imaging Findings

Proteinuria is the hallmark of glomerular disease and is discussed in ch. 72. Thorough assessment of proteinuria includes locating the source and evaluating for persistence and magnitude.[5] A urine protein–to-creatinine ratio (UPC) >0.5 or 0.4 in a dog or cat, respectively, is abnormal in a urine sample free of inflammation or discoloration from hematuria (or >150 RBC/hpf). There is no magic number or range of numbers for the UPC that is diagnostic for any one renal disease; the overlap in expected ranges is too broad to be clinically reliable.[23] However, the greater the magnitude of proteinuria, as assessed by the UPC, the

greater the likelihood that the animal has glomerular disease. In three studies of urine albumin in canine models of glomerular disease, microalbuminuria was detected before increases in the UPC, and the magnitude of microalbuminuria increased over time in dogs that eventually developed an increased UPC.[24-26] A dog with persistent microalbuminuria of increasing magnitude should be assessed as having an injurious process to the glomerular filtration barrier and may eventually develop overt proteinuria. Glomerular lesions also have been identified in dogs without proteinuria.[27-29]

Isosthenuria is a variable finding in dogs and cats with glomerular disease. The presence of renal azotemia and an intact concentrating ability is indicative of glomerular disease. In one study, 37% of dogs with glomerulonephritis (GN) had urine specific gravities in excess of 1.035, and isosthenuria was detected in only 29%.[17] However, in dogs with amyloidosis, dilute urine (i.e., a urine specific gravity less than 1.016) was more common, occurring in 63% compared with only 5.1% showing evidence of being able to concentrate above 1.035.[22] Cylindruria is common in dogs with glomerular disease; casts are most often hyaline but can be granular, waxy, or fatty (see ch. 72). Proteinuria promotes the precipitation of Tamm-Horsfall mucoprotein, which in turn envelops the protein in the tubular lumen into a hyaline cast, thereby protecting the renal tubular epithelium from the protein's damaging effects. Granular and waxy casts form in the progressive degeneration of cellular casts, which are the result of damaged tubular epithelial cells. Renal hematuria develops with glomerular injury in humans and is more common in specific diseases (e.g., IgA nephropathy, mesangial proliferative glomerulonephritis), but it appears to be less common in dogs with glomerulopathies.[11] Erythrocytes that have passed through the abnormal glomerular capillary bed are often misshapen; the morphology of urine erythrocytes can be used to differentiate hematuria of glomerular origin from that resulting from other causes.

Hypoproteinemia caused by hypoalbuminemia develops in many dogs and cats with glomerular disease and is more likely in animals with heavy proteinuria. Hypoalbuminemia occurred in 60% and 70% of dogs with GN or amyloidosis, respectively.[17,22] Azotemia, hyperphosphatemia, and metabolic acidosis, consistent with renal failure, may be present in dogs with severe disease. Of dogs with GN or amyloidosis, 53% and 26%, respectively, were not azotemic at the time of diagnosis.[17,22] Nonregenerative anemia that develops secondary to chronic kidney disease or a systemic disease is observed in many affected animals. Other hematologic abnormalities also may reflect concurrent and possibly underlying systemic diseases. Thrombocytosis and hyperfibrinogenemia are common findings in dogs with glomerular disease.

The nephrotic syndrome (NS) of hypoalbuminemia, proteinuria, hypercholesterolemia, and edema, although pathognomonic for glomerular disease, was present in only 15% of dogs with GN in one study.[17] Incomplete NS (i.e., without edema or ascites) was more common, occurring in 49% of dogs.[17] NS is expected to occur more commonly in dogs diseases associated with marked proteinuria but was not associated with any specific histologic diagnosis in one study.[20]

The *nephritic syndrome* is a term that has primarily been used in people to describe a set of signs that develop secondary to renal inflammation, generally acute, that extends into the glomeruli. In people this syndrome is characterized by hematuria and RBC casts with one or more of the following: subnephrotic proteinuria, edema, hypertension, azotemia, and oliguria. Although the nephritic syndrome has not been fully characterized in dogs, perhaps because of the probable low prevalence of acute glomerulonephritides in dogs, it is possible that dogs with acute Lyme nephritis may have a "nephritic-like" syndrome (see ch. 211).

Radiographically, the kidneys may appear normal or small and irregular; some animals may have enlarged kidneys. Similar changes in shape and size can be seen with ultrasonographic scans; increased echogenicity of the cortex and loss of corticomedullary distinction may also be noted. The renal pelvis may be mildly dilated if polyuria is present or fluids are being administered.

Consensus recommendations state that the diagnostic evaluation should be more extensive for a dog with UPC above 3.5 and/or more clinical abnormalities as a result of glomerular injury than for a dog with only mild proteinuria.[5] An extensive evaluation would include tests that would facilitate the detection of underlying infectious, inflammatory, or neoplastic diseases (see E-Boxes 325-2 and 325-3). A thorough physical examination should be performed; diseases of the oral cavity or skin should not be overlooked as potential underlying disorders (see ch. 10 and 272). Aspiration cytology should be performed on all cutaneous and subcutaneous masses (see ch. 86). Serologic testing for regional infectious diseases should be performed. Evaluation might include tests for autoantibodies (e.g., antinuclear antibody, ANA) in animals with extrarenal abnormalities (e.g., thrombocytopenia, polyarthritis; see ch. 205). During radiographic or ultrasonographic evaluation of the abdomen, attention should be given to other organs to detect extrarenal disease processes (see ch. 88). Thoracic radiographs, particularly in middle-aged to older dogs, should be

evaluated for any evidence of neoplastic disease.

Renal Biopsy and Histologic Diagnoses

Renal biopsy provides a definitive diagnosis of glomerular disease, but may not be needed if treatment of a potential underlying disease leads to resolution of the proteinuria or end-stage renal disease is already present. When evaluated appropriately, renal biopsy specimens can provide important clinical information about the type and severity of lesions in dogs and cats with glomerular disease. In fact, obtaining an accurate histologic diagnosis may be one of the more important factors in successful management of the dog or cat with glomerular disease. Clinical decisions regarding the diagnosis, treatment, and prognosis can be made from the information obtained through renal biopsy.

Procurement and Processing of the Renal Biopsy Specimen

The procedure used to obtain a renal biopsy specimen is discussed in ch. 89 and 321. The renal biopsy procedure requires expertise and should be performed only by experienced personnel.[30] Hypertension (see ch. 157) and coagulation disorders (see ch. 196) should be controlled prior to biopsy. When a specimen is to be used for evaluation of glomerular disease, only cortical tissue should be obtained; biopsy of the medulla is not needed and is associated with a greater risk of hemorrhage, infarction, and fibrosis. The use of general anesthesia is associated with an ability to obtain better-quality specimens. An adequate sample of cortex has a minimum of five glomeruli when examined by light microscopy, although one glomerulus may be all that is needed to make a definitive diagnosis in animals in which the disease is diffuse (i.e., one in which most glomeruli are involved) and easily recognizable (i.e., amyloidosis).

If a percutaneous method is used to obtain a renal biopsy specimen from a patient with glomerular disease, at least two quality samples of renal cortex (i.e., each >10 mm long) should be obtained, using either a 16- or 18-gauge needle. A dissecting microscope can be used to verify that adequate biopsy samples have been obtained. One sample should be placed in formalin, and the other should be divided into two smaller pieces containing glomeruli. One piece is put into a fixative suitable for transmission electron microscopy (TEM) (e.g., 4% formalin plus 1% glutaraldehyde in sodium phosphate buffer), and the other piece is frozen for immunofluorescent microscopy (IFM). An alternative to freezing is to immerse the tissue in ammonium sulfate-N-ethylmaleimide (i.e., Michel's solution), which preserves tissue-fixed immunoglobulins. Wedge biopsies should be divided in a similar fashion; tissue for TEM should be minced appropriately. Tissue for TEM should be put into the fixative within 5 minutes of biopsy.

Thin sections (2 to 4 mm) of paraffin-embedded tissue should be used for light microscopy because standard sections of 5 to 6 mm are too thick for adequate assessment of glomerular cellularity and capillary loop thickness.[10,23] Hematoxylin and eosin staining can be used for initial assessment; however, periodic acid–Schiff (PAS), which stains glycoproteins, is the preferred stain of many nephropathologists and is particularly useful for demonstration of interstitial and glomerular scarring and assessment of the GBM. Methenamine silver specifically stains the basement membrane of the tubules, glomeruli, and Bowman's capsule. Trichrome is useful for evaluation of the mesangium and is also the best light microscopic stain for visualization of immunoglobulins. Congo red can be used to demonstrate the presence of amyloid. IFM or immunohistochemistry should include at a minimum stains for immunoglobulin M (IgM), IgG, IgA, and C3.

Evaluation of the Renal Biopsy Specimen

Only pathologists who have expertise in renal pathology should evaluate renal biopsy specimens. The inclusion of TEM and IFM are not only feasible, but required for determining the presence or absence of immune-complexes and making an accurate and clinically useful morphologic diagnosis.[23] Limiting the evaluation to light microscopy alone often allows for only a subjective interpretation of the glomerular lesion. A standard classification system for the characterization of glomerular lesions in dogs has been proposed.[23]

The normal glomerulus contains four to eight lobules, each composed of capillaries supported on a centrilobular core of mesangial matrix (Figure 325-2).[10,11] The GBM is thin, delicate, PAS-positive, and argyrophilic. The glomerular capillary lumen is normally widely patent and lined with eosinophilic endothelial cell cytoplasm (Figure 325-3). There should be only one or two nuclei per mesangial cell region. Parietal epithelial cells, visceral epithelial cells, endothelial cells, and mesangial cells comprise the normal glomerulus and can easily be identified by TEM (see Figure 325-1). The flattened parietal epithelial cells line the inner surface of Bowman's capsule. The visceral epithelial cells (podocytes) line the outer surface of the capillary loops and rest on the GBM. The podocytes, which are characterized by their foot processes, form the

outermost layer of the capillary wall. The endothelial cells line the inner surface of the capillary loops, with the nuclei disposed centrilobularly toward the mesangium. The fenestrations of the endothelial cell cytoplasm can be visualized easily. The normal GBM should be approximately the same thickness as the base of a foot process turned 90 degrees.

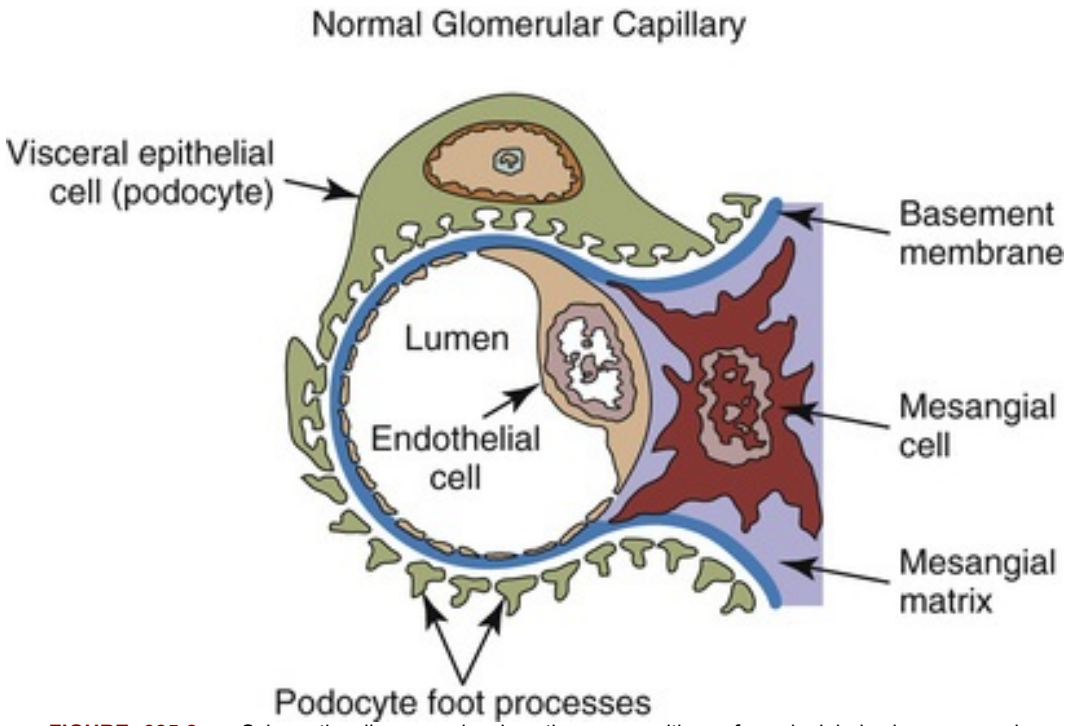


FIGURE 325-2 Schematic diagram showing the composition of each lobule in a normal capillary. (Courtesy J.C. Jennette, School of Medicine, University of North Carolina, Chapel Hill, NC.)

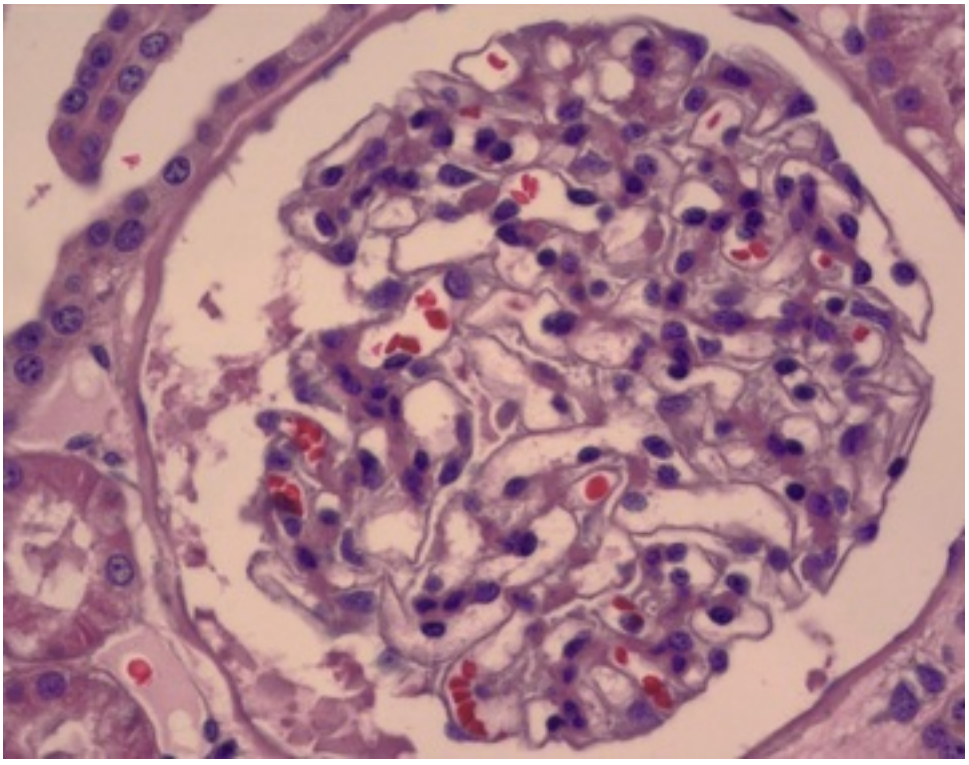


FIGURE 325-3 Normal glomerulus from a dog. Note that the capillary lumens are widely patent and the capillary loops are thin, often appearing discontinuous. Hypercellularity is not present.

Glomerular Diseases

Many glomerular diseases affect dogs; fewer appear to affect cats (see Box 325-1). The historical approach of lumping these under the umbrella of "GN" has limited advancement of our understanding and management of these disorders. A better approach is to treat these disorders as separate disorders to the best of our ability. This section outlines what is known about the individual diseases in dogs and cats, with additional information garnered from the wealth of knowledge on these diseases in humans. Acquired glomerular injury is the result of damage sustained after immune complex formation or deposition (e.g., membranous nephropathy, MN; membranoproliferative glomerulonephritis, MPGN) or damage caused by systemic factors that affect the glomerulus (e.g., amyloidosis). In a large study of 501 dogs, 48.1% had ICGN.[4] Immune complexes that are deposited in the glomerulus or that form *in situ* initiate glomerular damage.[31] Cell-mediated immune mechanisms also take part in the pathogenesis of glomerular inflammation. Once glomerular damage has been initiated, other processes contribute to glomerular injury, including activation of complement and the coagulation cascade and resident cells; influx of neutrophils, monocytes, and platelets; release of proteolytic enzymes; synthesis of cytokines or other growth factors; generation of proinflammatory lipid mediators; and alteration of hemodynamic factors. The mechanisms that determine whether progressive renal damage or resolution of the process occurs are unclear.

Membranoproliferative Glomerulonephritis

MPGN is one of the most common glomerular diseases in dogs. Although reported in up to 60% of dogs in various studies, in a recent report where renal biopsies underwent extensive pathologic evaluation, MPGN was identified in 26% of the 89 biopsies.[1,23,32] Glomerular lesions are most likely to be called MPGN when evaluation has not included the use of IFM and EM; the incidence of MPGN is most certainly overestimated in previous studies.

Clinical Features

The mean age of dogs with MPGN in one study was 10.5 years.[19] Males and females appear to be equally affected. Even though the disease is common, no thorough study of MPGN as a distinct glomerular disease has been done in dogs. In humans, the disease is characterized by a slowly progressive course, and about 50% of those affected develop NS. In a study of NS in dogs, 36% of dogs with MPGN had NS.[20] In one study of dogs, MPGN was associated with the most severe constellation of clinical abnormalities; the cluster of dogs with MPGN had among the highest median UPC ratio, the highest median serum creatinine concentrations, the lowest serum albumin concentrations, and higher frequency of hypertension than any other cluster.[23]

MPGN has been identified as a familial disease in Bernese Mountain Dogs. A unique, rapidly progressive form of MPGN that is accompanied by tubular necrosis and interstitial inflammation and is uniformly fatal has been reported in association with *Borrelia burgdorferi* infection in dogs.[21] The average age of affected dogs was only 5.6 years. Labrador Retrievers and Golden Retrievers were significantly predisposed to developing this lesion.

Pathogenesis

The form of MPGN identified in dogs more closely aligns with type I MPGN in people, which is also called *mesangiocapillary glomerulonephritis,* is often induced by infectious diseases and is characterized by immune complex accumulation on the subendothelial side of the GBM.[10,11] MPGN has been associated with a variety of infectious diseases in dogs (see E-Boxes 325-2 and 325-3). The accumulation of immune complexes leads to cytokine-mediated complement activation, expansion of the mesangium and an inflow of leukocytes.

In humans with MPGN, hypocomplementemia is so common that this disease is sometimes called *hypocomplementemic glomerulonephritis.* Hypocomplementemia appears to develop either from increased consumption secondary to immune complex activation of the classic pathway or from the presence of anticomplement autoantibodies known as nephritic factors. Interestingly, type I MPGN also occurs in Brittany Spaniels and humans with congenital C3 deficiency.[27] The pathogenic role of hypocomplementemia is not understood.

Histopathologic Characterization

MPGN is diagnosed when both thickened capillary loops and mesangial hypercellularity (more than three nuclei per mesangial region) are present (Figure 325-4 and E-Figure 325-5).[10,11,19,23] The glomerulus may become enlarged and segmented or lobular in appearance. The activated mesangium expands the capillary walls and extends into the subendothelial space, causing the double contour, or "railroad," appearance of the GBM that can be seen with light microscopy. With IFM, immune complex deposition can be identified in MPGN as granular deposits of C3 in combination with IgG, IgM, or IgA, or combinations thereof, in the GBM or mesangium or both. TEM can also be used to identify the immune deposits in MPGN.

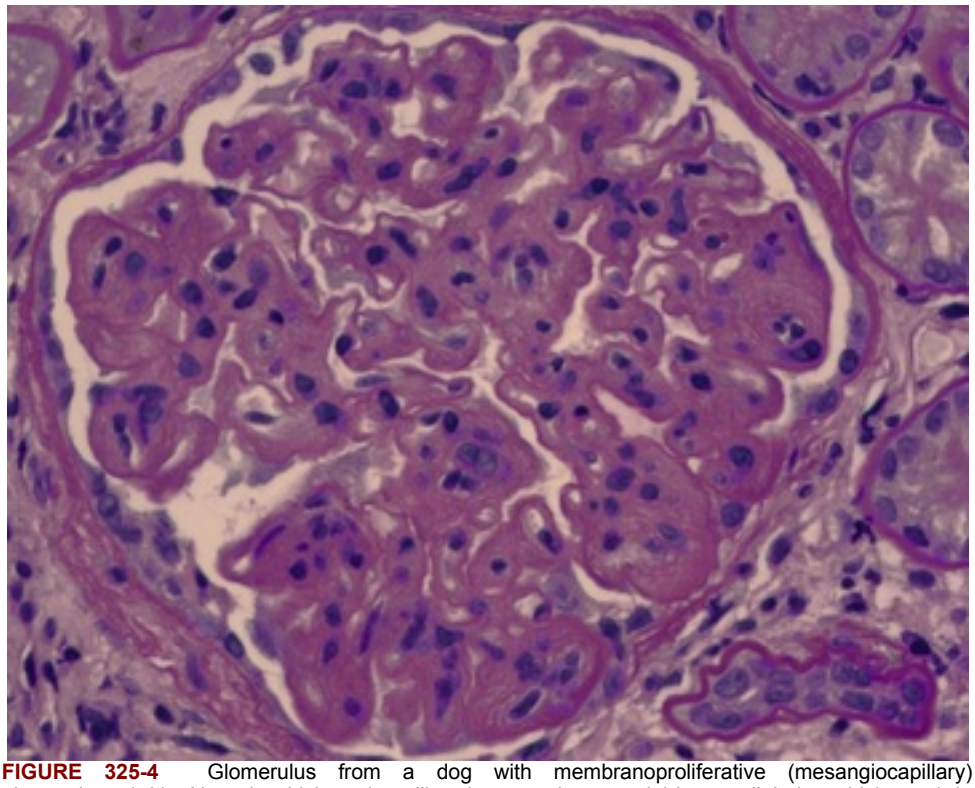
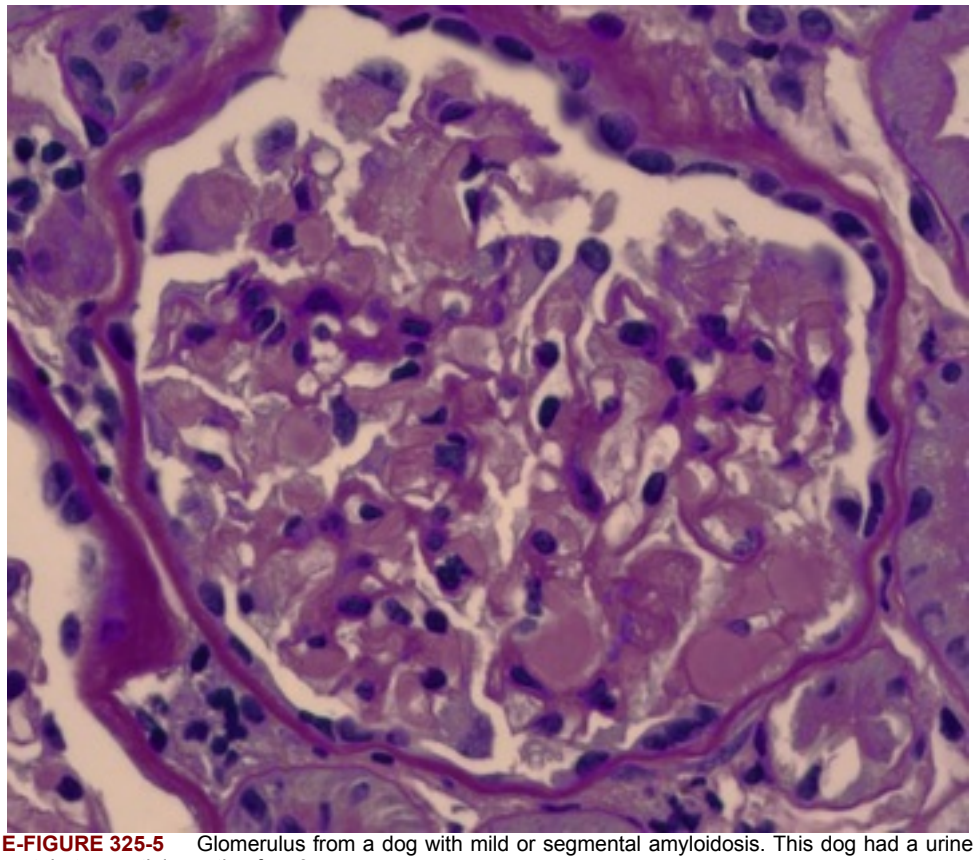


FIGURE 325-4 Glomerulus from a dog with membranoproliferative (mesangiocapillary) glomerulonephritis. Note the thickened capillary loops and mesangial hypercellularity, which result in the segmented and lobular appearance.



E-FIGURE 325-5 Glomerulus from a dog with mild or segmental amyloidosis. This dog had a urine protein-to-creatinine ratio of 4.73.

Specific Treatment

Effective treatment of the underlying infectious, inflammatory, or neoplastic disease is the cornerstone of management of patients with MPGN (see below). Immunosuppressive therapy should be considered in dogs that have severe, persistent or progressive disease. Because activation of platelets appears to be involved in the pathogenesis of this disease, antiplatelet drugs also should be given.[11]

Prognosis

Specific data regarding the prognosis of MPGN in dogs are lacking. In people, azotemia, severe proteinuria, systemic hypertension, and marked tubulointerstitial lesions at presentation are the most significant predictors of an unfavorable outcome.[11]

Membranous Nephropathy

MN is another common glomerular disease in dogs. While reported in up to 45% of dogs in various studies, it was identified in 26% of the thoroughly evaluated biopsies in a recent study.[2,19,23,33-35] It is the most common glomerular disease in cats, in which other forms of glomerular disease are uncommon.[36,37] The disease is sometimes called a *glomerulopathy* or *nephropathy*, rather than GN, because there is rarely evidence of an inflammatory response in the glomeruli or interstitium.

Clinical Features

MN appears to be more common in male dogs and cats (approximate male to female ratios, 1.75 : 1 in dogs and 6 : 1 in cats). The mean age of affected dogs from four studies was 8 years, but there was considerable range (1 to 14 years). The disease is more common in younger cats, with an approximate mean age of only 3.6 years (range, 1 to 7 years).[36] There does not appear to be any breed predilection, although a preponderance of Doberman Pinschers was seen in one report. Interestingly, four of five of these Dobermans were 3 years of age or younger, which may suggest a familial pattern.[34]

Proteinuria in animals with MN may be massive.[29] In a study of NS in dogs, 38% of dogs with MN had NS.[20] Microhematuria is reported in 30% to 40% of humans with MN, but has not been systematically studied in dogs and cats.[11] Cats and dogs with MN may present with signs of advanced kidney disease. Many cats have normal to enlarged kidneys at presentation.

MN has four ultrastructural stages that correlate with the temporal evolution of the disease and the clinical presentation in dogs, cats, and humans.[10,11,34,36] Although not universally accepted, there is some suggestion that these stages correlate with therapeutic outcomes in humans with MN, in that people may be more likely to respond to appropriate management if they are in one of the first two stages. More advanced stages in cats and dogs have been shown to correlate with more severe azotemia, whereas animals with milder disease were more likely to have NS.[34,36] In some cases, different stages were found within a single biopsy specimen.

Pathogenesis

In humans, MN is considered to be either primary (i.e., idiopathic) or secondary to another disease process; primary disease is most common.[11] The finding of antibodies on the subepithelial side is unique to MN and suggests that binding occurs on the urinary side of the GBM. The subsequent activation of complement and cytokine responses may be reduced, because the site of reaction is distant to the circulation, which contributes to the lack of inflammation associated with MN.

Although the exact pathogenesis of this disorder is unknown, primary MN is considered to be an ICGN. In humans with primary MN, the weight of evidence supports that immune complexes form *in situ*, when unbound antibody reacts with fixed antigens of the podocyte. In this regard, primary disease may be a true autoimmune disorder.

Circulating immune complexes most likely play a larger role in patients with secondary disease. Proteinuria probably develops through a complement-dependent mechanism, independent of inflammatory cells. The terminal complement complex (C5b-9 membrane attack complex) has been implicated in the pathogenesis of this disease. Increased urinary concentrations of the membrane attack complex have been demonstrated in some, although not all, individuals with MN. Demonstration of this complex may be more likely early in the disease process, when active immune deposit formation occurs. Myriad immune system irregularities have been reported in association with MN in humans (e.g., altered CD4+ to CD8+ ratio, Fc receptor dysfunction, and impaired lymphocyte and suppressor cell function), which supports a pathogenic role for an underlying immunologic defect. These irregularities are perhaps based on a genetic susceptibility, a theory supported by familial clustering of MN in humans.[10,11]

Histopathologic Characterization

The normally lacy-appearing GBM becomes uniformly thickened and more rigid as a result of the deposition of immune complexes in the subepithelial spaces in MN (Figure 325-6).[10,19,23] New basement membrane material accumulates around the immune deposits. Because the deposits do not become impregnated with silver, "spikes" may be identified on the outside of the GBM when an appropriate silver stain is used (E-Figure 325-7). Advanced cases may show irregular thickening and distortion of the capillary walls with occasional widening of the mesangium. IFM is useful in determining the site of immune complex deposition. Staining of the immune complexes produces a beaded appearance along the GBM and can be so heavy that it may be difficult to differentiate from a linear pattern. In secondary cases the mesangial spaces are also positive.

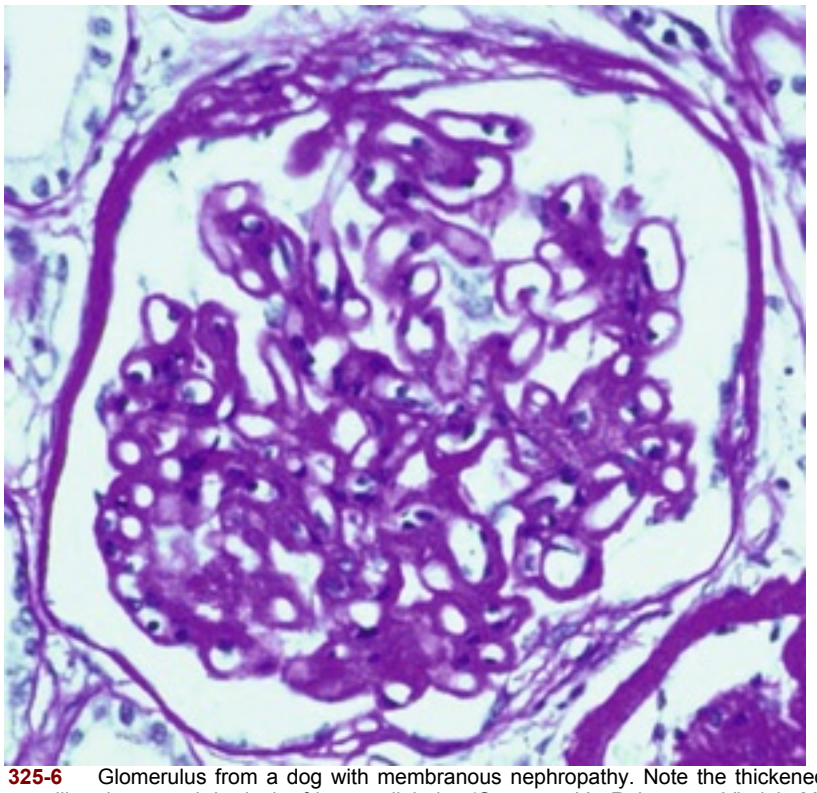
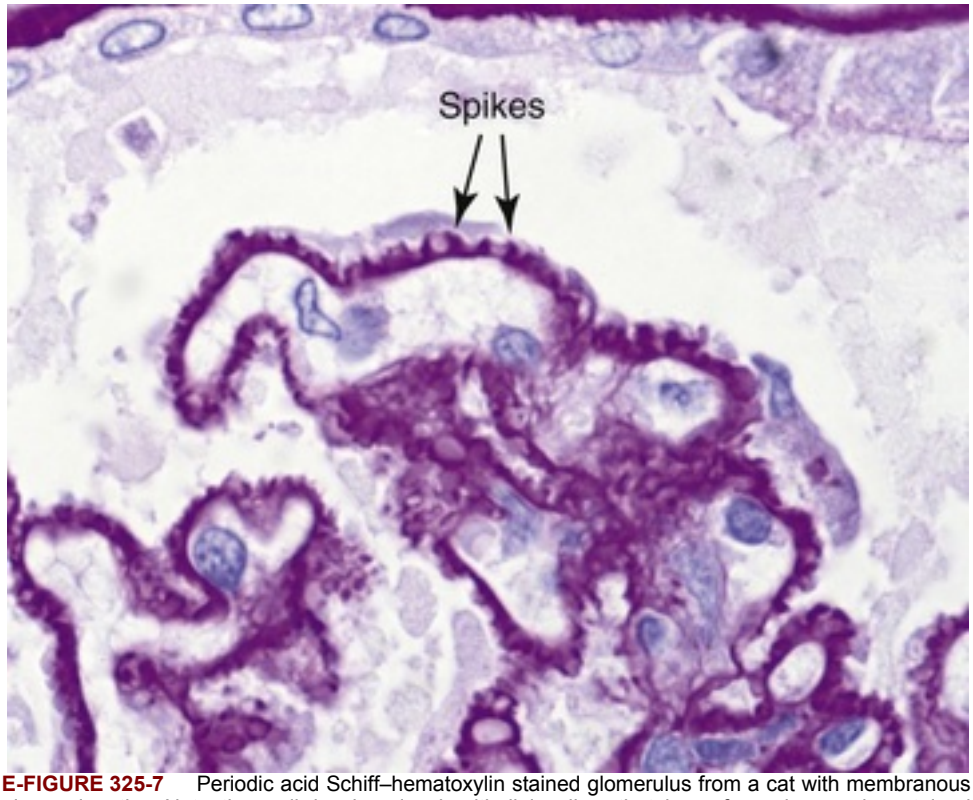


FIGURE 325-6 Glomerulus from a dog with membranous nephropathy. Note the thickened, rigid-appearing capillary loops and the lack of hypercellularity. (Courtesy J.L. Robertson, Virginia Maryland Regional College of Veterinary Medicine, Blacksburg, VA.)



E-FIGURE 325-7 Periodic acid Schiff–hematoxylin stained glomerulus from a cat with membranous glomerulopathy. Note the well-developed subepithelial spikes that have formed around unstained immune deposits.

TEM should be used to confirm the location of the immune deposits and characterize the stage of disease progression (Figure 325-8).[11,23,34,36] Deposition of immune complexes, progressive engulfment of the complexes by the surrounding GBM, and eventual resolution of the deposits characterize the stages. Stage I has subepithelial dense immune deposits without adjacent projections of basement membrane material and only minimal thickening of the GBM. Projections of adjacent GBM material, or spikes, are identified in stage II. These projections eventually surround the immune deposits (stage III). In stage IV the GBM is markedly thickened, and electron-lucent zones have replaced some or all of the electron-dense deposits. In advanced stage IV disease, sometimes referred to as stage V, there is variable thickening of the GBM and apparent resolution of the electron-dense deposits. Sometimes staging is difficult because several stages of disease may be present simultaneously.

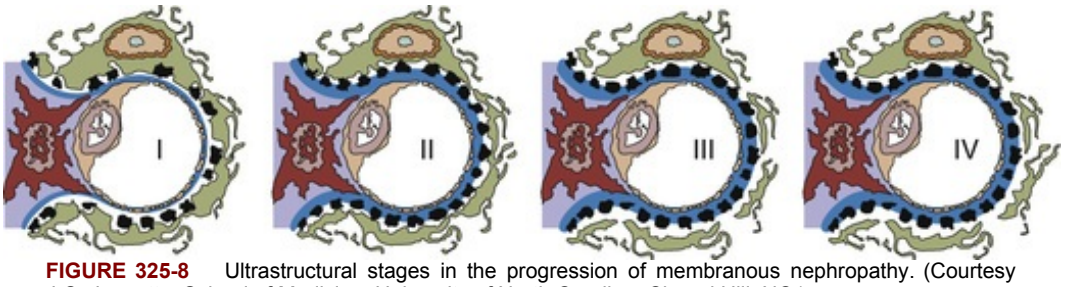


FIGURE 325-8 Ultrastructural stages in the progression of membranous nephropathy. (Courtesy J.C. Jennette, School of Medicine, University of North Carolina, Chapel Hill, NC.)

Specific Treatment

In addition to identification of potentially inciting disease processes and nonspecific management of proteinuria, immunosuppressive therapy may be warranted in dogs or cats with severe, persistent or progressive disease. Affected humans with similar clinical pictures may respond to immunosuppressive therapy.[11] Even when treatment is effective, relapses may occur. The use of immunosuppressive therapy in dogs and cats with MN needs to be studied.

Prognosis

Although MN appears to be progressive in some dogs and cats, the progression may be slow enough that many animals can lead relatively normal lives. In a study of 24 cats with MN, 4 (17%) survived 4 to 10 months, and 8 (33%) had long-term survival of 2.5 to 6 years; clinical remission occurred in 7 (29%) of the cats. Corticosteroids were administered to three of the eight long-term survivors. However, 11 cats (46%) died or were euthanized because of NS or advanced renal disease shortly after diagnosis.[37] Long-term survivors had only IgG deposition, C3 deposition, or both; cats that also had deposition of IgM or IgA had a shorter survival period. Stage III and IV MN, defined by the presence of intramembranous deposits, was associated with a poorer prognosis.[37]

Survival data for dogs appear to be similar to what has been reported in cats, with reported survival ranging from 4 days to greater than 3 years.[34] Spontaneous remissions have been reported. Spontaneous remission occurs in 20% to 30% of humans with MN, whereas 20% to 40% of cases progress to chronic kidney disease.[11] The risk of progression in humans appears to correlate with the magnitude of proteinuria and renal function impairment; patients with the highest degree of proteinuria and azotemia are more likely to have more rapid progression compared with other patients.

Proliferative Glomerulonephritis

Proliferative GN, caused by endocapillary or mesangial proliferation, accounted for 2% to 16% of glomerular lesions in dogs in two studies but none were identified in a recent pathologic study, most likely because uncommon diagnoses were excluded.[19,23,32] In humans, a pathologic diagnosis requires both a morphologic description (e.g., mesangial proliferative GN), and a specific disease designation (e.g., IgA nephropathy, lupus GN).[10,11] With the exception of IgA nephropathy, proliferative GN in dogs has not included the specific disease designation.[38,39]

Clinical Features

Dogs with proliferative GN reported in two studies were on average between 7 and 9 years of age.[18,19] Proteinuria and renal azotemia were the most common presenting signs. Azotemia may be mild or moderate and acute or chronic. Although hematuria is associated with this disorder in people, its presence in dogs is unknown.[11]

Pathogenesis

Proliferative GN is an ICGN. Anti-GBM disease causes proliferative GN in humans but has not been described in the dog or cat. Post-infectious GN of humans is a form of proliferative GN that most commonly occurs after resolution of a streptococcal infection. Persistent infections are more likely to cause MPGN or MN.[10]

Histopathologic Characterization

Mesangial proliferative GN is characterized by mesangial cell hyperplasia (≥4 cells per mesangial area) that is often accompanied by increased mesangial matrix (Figure 325-9).[10,19] Endocapillary proliferative GN has a proliferation of endothelial cells with or without increased mesangial cellularity that is partially due to an influx of mononuclear cells. Evaluation by IFM reveals fine granular deposits of IgG or IgM or both in the GBM and mesangium. TEM further localizes the immune complexes. Because proliferative GN often develops secondary to systemic diseases, immune complexes are frequently identified in the mesangium, although some complexes may be found in the capillary walls.

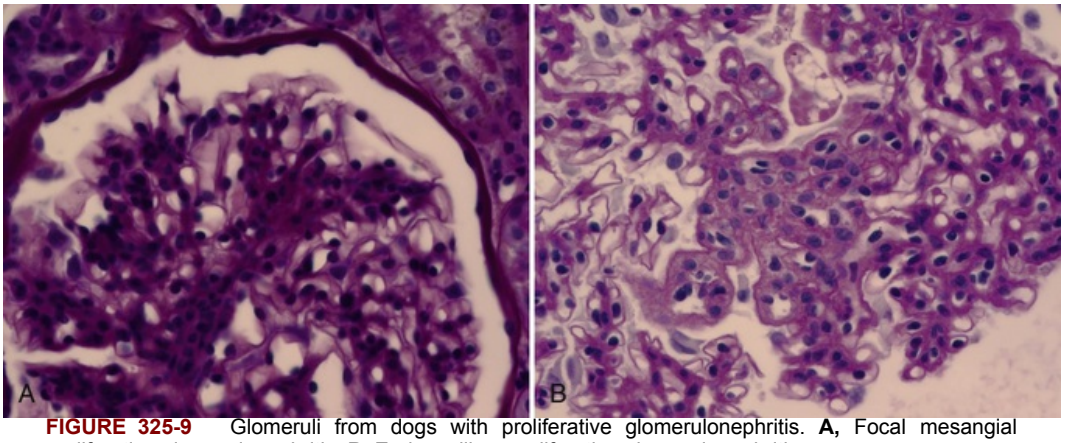


FIGURE 325-9 Glomeruli from dogs with proliferative glomerulonephritis. **A,** Focal mesangial proliferative glomerulonephritis. **B,** Endocapillary proliferative glomerulonephritis.

Specific Treatment

The potential source of immune complexes should be removed, and nonspecific management of glomerular diseases should be followed. Immunosuppressive therapy may be warranted in animals with severe, persistent or progressive disease.

Prognosis

While the prognosis has not been fully evaluated in dogs, the presence of advanced azotemia or the formation of crescents is likely associated with a poorer prognosis.

Immunoglobulin A Nephropathy

In several studies of canine glomerular disease, IFM has demonstrated mild to moderate frequency of IgA positivity, suggestive of IgA nephropathy.[38,39] IgA is predominantly polymeric in dogs and it may be nonspecifically trapped in the mesangium, more so than monomeric IgA, the predominant form in humans. The diagnosis of IgA nephropathy requires a predominance of IgA positivity on IFM evaluation; co-deposits of IgG, IgM, or C3 may be present but should be less intense than IgA. Mesangial proliferative GN is the

expected light microscopic lesion; some humans do not have any apparent glomerular lesions. In one study of clinically normal dogs with glomerular lesions, 85% had IgA deposits.[28] In another study of 100 dogs with and without renal disease, 47 had IgA deposition; in 6 dogs, IgA was the only immunoglobulin detected.[39] Increased deposition of IgA was associated with increased cellular proliferation. Dogs with enteric or hepatic diseases had the highest prevalence of IgA deposition. Excessive IgA immune complex formation caused by enteric disease or decreased clearance of IgA complexes in association with liver disease have been proposed in the pathogenesis of secondary IgA nephropathy in humans.[11]

IgA nephropathy was described in three young to middle aged (4 to 7 years) male dogs, demographics that are consistent with those of affected people.[11,38] The dogs had proteinuria, varying degrees of azotemia, and episodes of hematuria. Dogs were housed together but predisposing environmental factors were not identified. The most severely affected dog had uncontrolled hypertension and co-deposits of IgG or IgM, both of which are negative prognostic indicators in humans.

Treatment of patients with secondary IgA nephropathy should be directed at treatment of the associated systemic disease and control of hypertension. Fish oil rich in omega-3 fatty acids administered to affected humans resulted in slowed progression of renal disease but did not lead to a reduction in proteinuria.[11]

Amyloidosis

Amyloidosis accounts for approximately 15% of the glomerular lesions in dogs.[4] The term *amyloidosis* refers to a diverse group of diseases that have in common the extracellular deposition of fibrils formed by polymerization of proteins with a beta-pleated sheet conformation.[40] Reactive amyloidosis is the most common form of amyloidosis in dogs and cats, with the dog being the domestic animal most commonly affected by amyloidosis. With the exception of the Chinese Shar-Pei, amyloid is deposited primarily in the glomeruli of affected dogs.[22,41] Amyloidosis is relatively uncommon in the cat, with the exception of Abyssinians and Siamese (especially the Oriental shorthair color variant).[42] In Abyssinians, amyloid is deposited primarily in the renal medulla, although glomerular involvement has been described.

Clinical Features

Renal amyloidosis is more common in older dogs. The mean age of affected dogs was 9.2 years in one study, in which 85% of affected dogs were 7 years of age or older.[22] Females appear to be affected more often than males (the male to female ratio is 1 : 1.7). Collies and Walker Hounds may be at increased risk for amyloidosis; the disorder is familial in the Chinese Shar-Pei and may be familial in Beagles and English Foxhounds.[22,43]

Because proteinuria associated with amyloidosis may be massive, many animals brought to the veterinarian are in NS. In a study of NS in dogs, 56% of dogs with amyloidosis had NS.[20] However, contrary to popular belief, dogs with amyloidosis did not have higher UPC ratios or serum creatinine concentrations or lower serum albumin concentrations than dogs in other disease clusters.[23] In another study, six of seven dogs with amyloidosis had nonselective proteinuria, suggesting a marked loss of the size-selective properties of the glomerular capillary wall.[29] Although amyloid may be deposited in other organ systems (liver [see ch. 285], spleen, adrenal glands, gastrointestinal tract), clinical signs associated with deposition in these organs are rare in dogs. Chronic infectious and noninfectious inflammatory diseases and neoplasia have been reported in association with reactive amyloidosis in 32% to 53% of affected dogs; however, many dogs and cats with reactive amyloidosis do not have an identifiable inflammatory process at the time of presentation.[16,22]

Renal amyloidosis in the Shar-Pei develops at an earlier age (mean age 4.1 years) than in other dogs with amyloidosis, but like other breeds, the disease is more common in females (male to female ratio of 1 : 2.5).[41] In Shar-Peis, amyloid is most commonly deposited in the renal medulla; only 64% of Shar-Peis had glomerular involvement.[41] As a result, as few as 25% to 43% of affected Shar-Peis have proteinuria. Affected dogs may have signs of involvement of other organs, particularly the liver (see ch. 285). Many Shar-Peis have a history of recurrent fever and swelling of the tibiotarsal joints (commonly called *Shar-Pei fever* or *Shar-Pei swollen hock syndrome*; see ch. 203) before the development of renal amyloidosis, suggesting that this may be an animal model of familial Mediterranean fever.

Pathogenesis

The primary protein involved in the formation of amyloid deposits in dogs and cats is amyloid A protein

(AA), which is formed by the polymerization of the amino terminal portion of serum amyloid A protein (SAA), an acute-phase reactant.[40] SAA is synthesized and released by hepatocytes after they have been stimulated by macrophage-derived cytokines (e.g., interleukin-1 [IL-1], IL-6, tumor necrosis factor). Because of the association of amyloid A with inflammatory diseases, this form of amyloidosis has been termed *reactive*, or *secondary*, amyloidosis.

Concentrations of SAA increase 100- to 1000-fold after tissue injury. Although concentrations decrease to baseline by 36 to 48 hours after removal of the inflammatory stimulus, they remain increased if inflammation persists.[40] Chronic inflammation and persistent or prolonged increases in SAA concentrations are required for the development of reactive amyloidosis. Humans with familial Mediterranean fever, a disease similar to that reported in Shar-Peis, have defective formation of pyrin, a protein involved in the down-regulation of mediators of inflammation.[44] Because only a small percentage of animals with chronic inflammation develop amyloidosis, other factors must be involved in the pathogenesis.[40] There are multiple polymorphs of SAA, and certain polymorphs perhaps are more amyloidogenic. There may be inherited and acquired variations in the ability to degrade SAA, a two-step process that involves cell surface–associated proteases contained in monocytes. A defect in the second step of this process may predispose some individuals to the development of amyloidosis. It has been demonstrated that the AA-degrading property of normal serum is decreased in humans with reactive amyloidosis. This activity correlated with serum albumin concentrations; hypoalbuminemia associated with the inflammatory process or amyloidosis may contribute to decreased AA-degrading activity. Increased concentrations of other acute-phase reactants that are protease inhibitors (e.g., antitrypsin and antichymotrypsin) also may contribute to the pathogenesis of amyloidosis.

SAA concentrations are increased during the predeposition phase, before the appearance of tissue amyloid deposits, but may persist during the deposition phase. Abyssinians with renal amyloidosis have increased SAA concentrations.[40] Chinese Shar-Peis with renal amyloidosis have increased serum concentrations of IL-6, a cytokine that stimulates SAA synthesis and release.[45] The deposition phase, during which amyloid deposits appear in the tissue, is subdivided into two phases. The rapid phase is characterized by rapid increases in the amount of amyloid, whereas the plateau phase is a time when little net change occurs in tissue deposition.

Histopathologic Characterization

The beta-pleated conformation is responsible for the characteristic staining properties of the amyloid deposits.[10] When the kidney is evaluated by conventional light microscopy, amyloid deposits in the glomeruli appear as acellular material that expands the mesangium and GBMs and stains homogeneously eosinophilic with hematoxylin-eosin (Figure 325-10 and E-Figure 325-11). Glomerular deposits are most often diffuse and global but occasionally are focal and segmental. Deposits sometimes can be found in the walls of small blood vessels, tubular basement membranes, and interstitial tissues. When stained with Congo red and evaluated by conventional light microscopy, amyloid deposits take on various shades of red, depending on the amount of amyloid and the thickness of the section. Deposits stained with Congo red and evaluated by polarizing microscopy are birefringent and have an apple green color (Figure 325-12). Reactive amyloidosis can be confirmed by decolorization of the Congo red–stained amyloid deposits by potassium permanganate oxidation. TEM is not needed to confirm a diagnosis of amyloidosis.

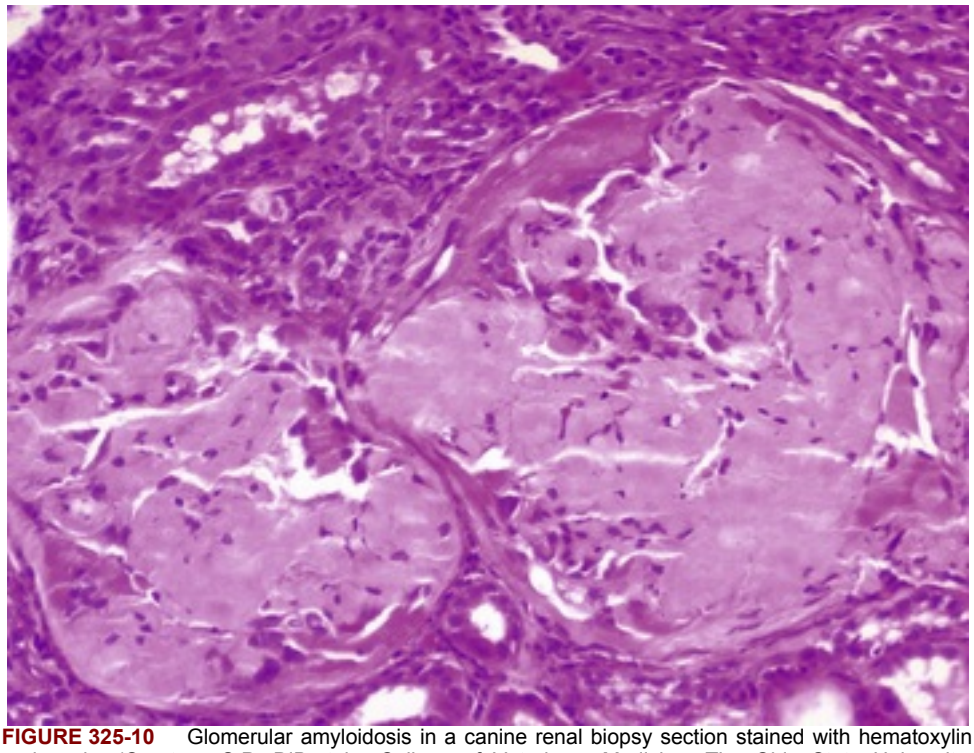


FIGURE 325-10 Glomerular amyloidosis in a canine renal biopsy section stained with hematoxylin and eosin. (Courtesy S.P. DiBartola, College of Veterinary Medicine, The Ohio State University, Columbus, OH.)

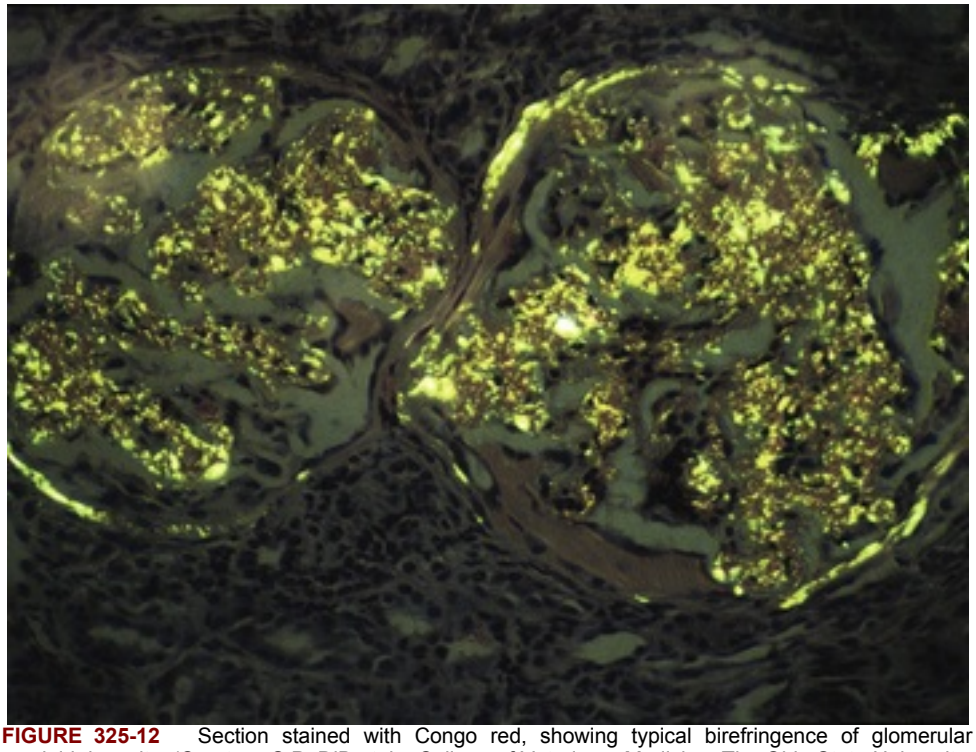
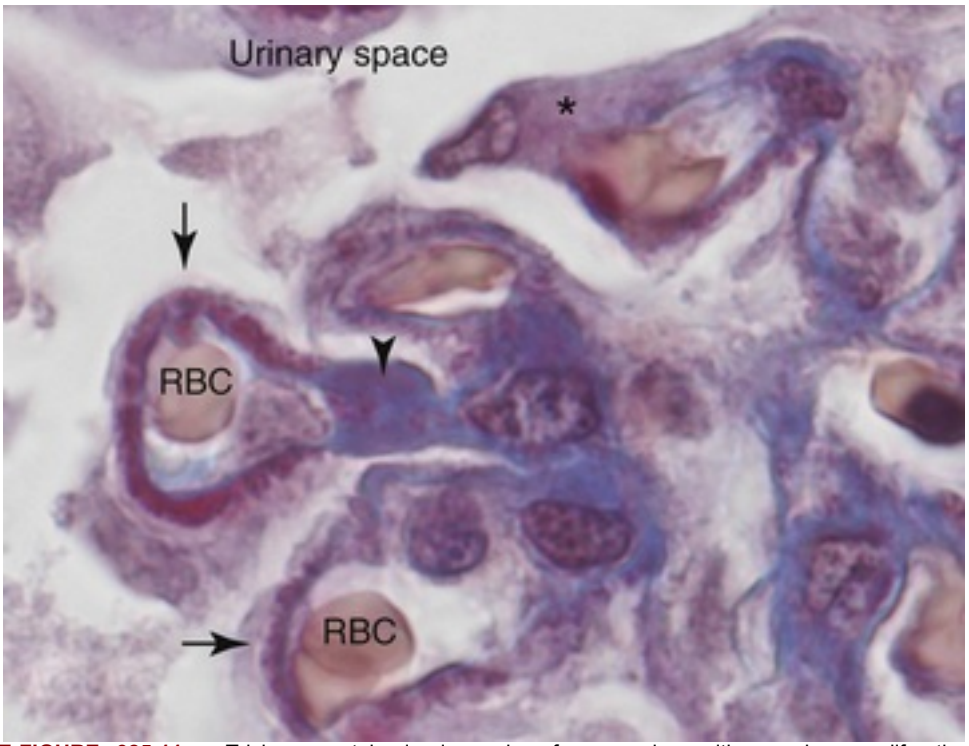


FIGURE 325-12 Section stained with Congo red, showing typical birefringence of glomerular amyloid deposits. (Courtesy S.P. DiBartola, College of Veterinary Medicine, The Ohio State University, Columbus, OH.)



E-FIGURE 325-11 Trichrome stained glomerulus from a dog with membranoproliferative glomerulonephritis. Note the large magenta deposits within the capillary wall (arrows), with fine deposits also present in the mesangial areas (arrowhead). Podocyte hypertrophy (*) is also present. Erythrocytes are present in the capillary lumen. Mesangial matrix and basement membrane stained blue with this stain. *RBC*, Red blood cell.

Specific Treatment

The beta-pleated sheet configuration of amyloid fibrils leads to their insolubility and resistance to proteolysis, making specific treatment relatively ineffectual. In humans with familial Mediterranean fever, colchicine prevented the development of renal amyloidosis even in patients who continued to have recurrent febrile episodes.[44,46] This led to the recommendation that colchicine be used in the management of Shar-Peis with renal amyloidosis. Ideally this drug is administered during the predeposition phase, which in Shar-Peis is presumably characterized by recurrent fevers and swollen hocks. However, colchicine administration may lead to remission of proteinuria even after the appearance of amyloid deposits. No evidence supports the effectiveness of colchicine once amyloidosis has resulted in persistent azotemia or hypoalbuminemia. Although the effects of the drug in the treatment of amyloidosis are not fully known, colchicine does impair the release of SAA from hepatocytes by binding to microtubules and preventing secretion. In addition, colchicine may prevent the production of amyloid-enhancing factor. The dosage of colchicine used is 0.01 to 0.03 mg/kg given orally every 24 hours. Gastrointestinal upset is the primary side effect. Colchicine use has been recommended on occasion for people with renal amyloidosis from causes other than familial Mediterranean fever and warrants further evaluation in dogs.

Dimethylsulfoxide (DMSO) has been shown to be beneficial in a limited number of dogs with renal amyloidosis, although the exact benefit remains controversial.[46] If given during the rapid deposition phase, DMSO leads to a decrease in SAA concentrations and resolution of tissue deposits. However, the amount of amyloid deposited in the kidneys of humans was unchanged after DMSO administration, which lends support to the current belief that DMSO does not solubilize amyloid fibrils. The anti-inflammatory effects of DMSO may account for some of the beneficial effects. Reduction of interstitial fibrosis and inflammation may lead to improved renal function and reduced proteinuria. DMSO has an unpleasant smell that may cause poor owner compliance. Furthermore this drug may contribute to signs of nausea and anorexia seen in some dogs. The recommended dosage is 90 mg/kg given orally or subcutaneously three times weekly. DMSO should be diluted 1 : 4 with sterile water before injection to limit the pain associated with injection.

Prognosis

The prognosis for dogs and cats with renal amyloidosis is generally poor. In one study of dogs with amyloidosis, 58% died or were euthanized at the time of diagnosis. In the remaining dogs, survival ranged from 2 to 20 months; survival of a year or longer was reported in only 8.5%.[40] The longest survival was observed in a dog treated with DMSO.

Hereditary Nephritis

The term *hereditary nephritis* (HN) refers to a diverse group of inherited glomerular diseases that are the result of a defect in basement membrane collagen (type IV).[47] These diseases are discussed in ch. 328. A brief discussion of hereditary nephritis is included in this chapter because it should be considered as a differential diagnosis for any dog presenting with proteinuric renal disease, particularly if the dog is young.

Clinical Features

Hereditary nephritis has been reported in several breeds of dogs. An autosomal recessive form of the disease occurs in English Cocker Spaniels and English Springer Spaniels, whereas Bull Terriers and Dalmatians develop an autosomal dominant form.[47-51] An X-linked dominant form of HN has been described in Samoyeds and mixed-breed dogs; carrier females may have mild disease.[48] The report in Samoyeds is of a single kindred; the disease is not considered to be common in this breed. HN is characterized by proteinuria, renal hematuria, and progressive glomerular disease. Concurrent hearing and ocular abnormalities, as described in humans with HN, appear to be uncommon in affected dogs, with the exception of anterior lenticonus, which occurs in some Bull Terriers.[49]

Pathogenesis

HN is the result of a genetic mutation or deletion in type IV collagen, the primary protein constituent of the GBM.[52,53] The presence of defective collagen leads to premature deterioration of the GBM and progressive glomerular disease.

Histopathologic Characterization

Before electron micrographic studies of English Cocker Spaniels, the renal lesions were described as renal cortical hypoplasia or membranoproliferative or sclerosing GN. TEM is required to make the diagnosis of HN. Multilaminar splitting and fragmentation of the GBM are seen, often with intramembranous, electron-dense deposits.

Specific Treatment

No specific treatment is available for affected dogs. Use of a diet formulated for kidney disease and administration of angiotensin-converting enzyme (ACE) inhibitors have proved beneficial in affected dogs. Early detection of HN through screening of dogs of relevant breeds for microalbuminuria allows early therapeutic intervention, which may slow disease progression.[24]

Prognosis

The rate of progression is predictable in Samoyeds and English Cocker Spaniels, with terminal kidney disease generally developing before 2 years of age.[47] However, disease progression is more variable in Bull Terriers and Dalmatians, with some dogs surviving for as long as 10 years.[49,50]

Minimal Change Disease

Although uncommonly described in dogs and cats, minimal change disease (MCD) is a common cause of NS in humans, especially children.[11,54] Because TEM is required for diagnosis, the disease most likely is underdiagnosed in dogs and perhaps in cats. In humans this disease is sometimes referred to as nil disease, lipoid nephrosis, or idiopathic NS. There have been isolated reports of dogs that appear to have MCD. However, there is only one well-described case report of MCD in a dog presenting with NS.[54]

Clinical Features

Proteinuria is likely to be of heavy magnitude with this disease, and NS is common.

Pathogenesis

In humans, MCD is usually idiopathic, although secondary disease also occurs. Increased production of lymphokines by dysfunctional T cells is believed to be responsible for an increase in GBM permeability.[11] The primary change is loss of anionic charge in the glomerular capillary wall, leading to collapse of the podocyte foot processes. This loss of charge selectivity is the crucial event leading to proteinuria. The resultant proteinuria is highly selective; albumin is the primary protein lost.

Histopathologic Characterization

There is a lack of light microscopic lesions in the glomerulus, hence the name MCD.[10] Occasionally, slight hypercellularity is present. Some lipid droplets may be present in the renal tubules, but there should not be any evidence of tubular atrophy or interstitial fibrosis. Immunoglobulin deposition is absent when evaluated by IFM; however, there may be increased staining of vimentin, a marker for visceral glomerular epithelial cells. The diagnosis is confirmed with TEM by identification of marked foot process effacement (Figure 325-13). In a study of glomerular lesions in dogs, 28 of 115 dogs fell into the World Health Organization classification of minor glomerular abnormalities, but only one of these dogs had MCD.[19] Therefore, identification of only minor glomerular abnormalities in a dog or cat with proteinuria does not make a diagnosis of MCD.

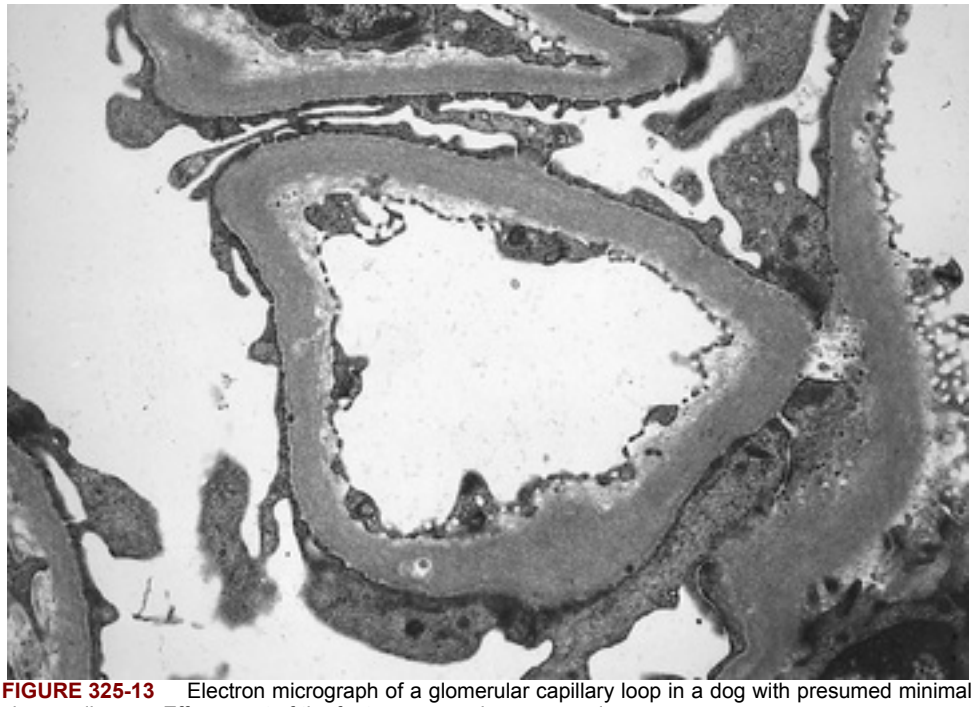


FIGURE 325-13 Electron micrograph of a glomerular capillary loop in a dog with presumed minimal change disease. Effacement of the foot processes has occurred.

Specific Treatment

An important reason to include MCD on the list of differential diagnoses for dogs with NS is the disease's seemingly exquisite response to corticosteroids; the expected response rate in humans with MCD is 80% to 90%.[11]

Prognosis

The prognosis for MCD in dogs is unknown. One or more relapses are seen in 75% to 85% of affected humans.[11]

Glomerulosclerosis

Glomerulosclerosis accounted for approximately 20% of the glomerular lesions of dogs in a large study.[4] Whereas glomerulosclerosis often develops as an end-stage lesion in response to glomerular injury, focal segmental glomerulosclerosis (FSGS) is a primary glomerular disease.[10] The prevalence of glomerulosclerosis increases with age, although the percentage of glomeruli expected to be sclerotic in dogs of advancing age groups has not been fully characterized. Glomerulosclerosis is a common finding in diabetic nephropathy of humans. Although glomerulosclerosis and proteinuria can develop in dogs with diabetes mellitus, the clinical relevance of this is unknown. Glomerulosclerosis can also develop after hypertensive renal damage.

FSGS was identified in 29% of the thoroughly evaluated biopsies in a recent study, making it one of the more common glomerular diseases (Figure 325-14).[10,19,23] FSGS is diagnosed in the proteinuric patient that has segmental glomerulosclerosis in a glomerulus that is otherwise normal, without other glomerular lesions present to explain the sclerosis. IFM evaluation should be negative in affected patients; however, nonspecific trapping of immunoglobulins and C3 can occur in sclerotic areas.

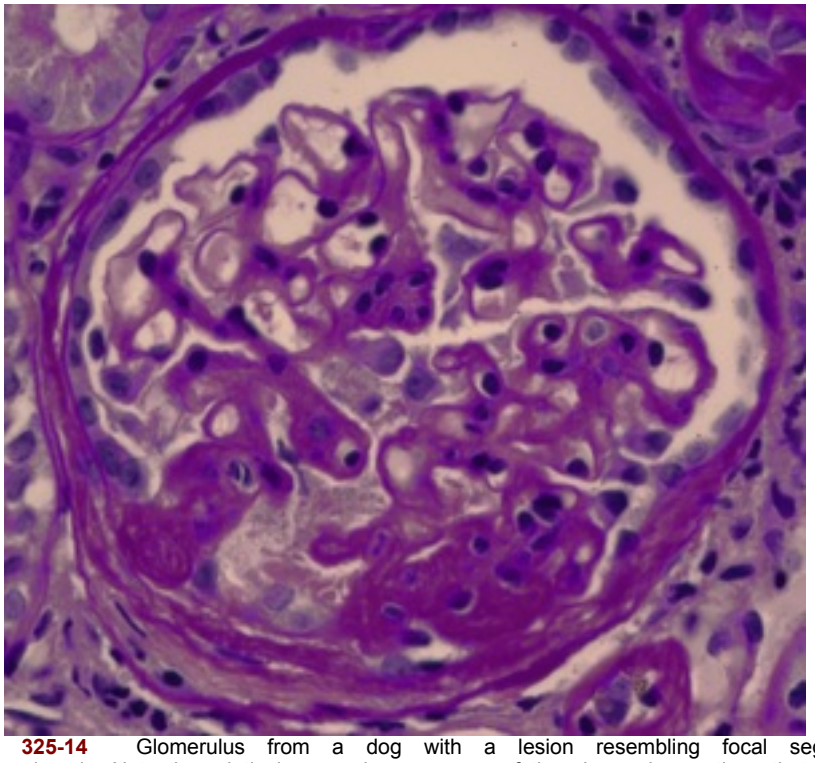


FIGURE 325-14 Glomerulus from a dog with a lesion resembling focal segmental glomerulosclerosis. Note the relatively normal appearance of the glomerular sections that are not sclerotic.

Tubulointerstitial Lesions Associated with Glomerular Disease

Proteinuria induces tubular damage, leading to progressive nephron loss.[55] Chronic proteinuria can lead to interstitial fibrosis, tubular degeneration and atrophy and peritubular capillary rarefaction. Heavy proteinuria is associated with a negative patient outcome in humans with various glomerular diseases; the urine of proteinuric humans shows mediators of renal inflammation and fibrosis, some of which are produced by renal tubules exposed to various proteins.[55] However, albumin is probably not the culprit because rats and humans with highly selective proteinuria appear to be at lower risk of eventual tubulointerstitial damage.

Protein in the tubules is resorbed by the proximal tubules; the reabsorbed proteins are cytotoxic to tubular epithelial cells.[56,57] Not only are proteins cytotoxic but they increase the workload of the tubular epithelial cells. Initially, this leads to compensatory hypertrophy of the tubular epithelial cells but eventually the cell cannot keep up with the increased workload and will die. Some damage also occurs secondary to obstruction of the tubules by protein casts.[58] Glomerular injury also results in decreased perfusion of the tubulointerstitium and additional injury. A direct link has not been established between proteinuria and

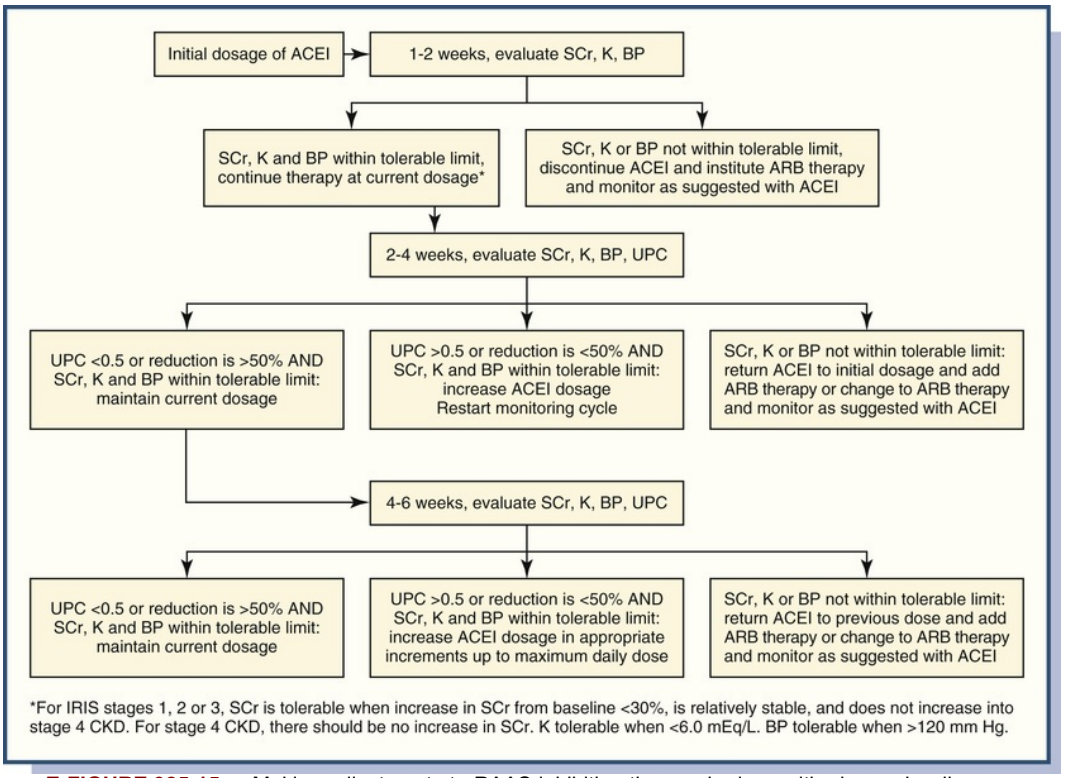
progressive renal damage in dogs, but it certainly exists to some extent. Because proteinuria may be a major factor responsible for progressive renal disease in patients with glomerular disease, aggressive management of proteinuria should be considered a cornerstone of the treatment of dogs and cats with glomerular disease.

Standard Therapy of Glomerular Disease

In addition to specific management that might be implemented with the various glomerular diseases, some therapeutic interventions are standard considerations for all dogs with glomerular disease.[6] This therapy can be divided into three major categories: (1) treatment of potential underlying diseases processes, (2) reduction of proteinuria, and (3) management of uremia and other complications of generalized kidney disease (discussed in ch. 324).

ICGN or amyloidosis develop after a strong, potentially malorganized, immune or inflammatory reaction, respectively, that has developed in response to a stimulus—often infectious, inflammatory or neoplastic. Accordingly, an underlying disease might have initiated the glomerular disease in up to 63% of affected dogs; a thorough evaluation for underlying diseases is warranted. Sometimes, the inciting agent is not obvious at first presentation because the offending disease is no longer present or is occult. Continued observation and scrutiny are necessary, because the causative disease process may become obvious in the ensuing months after presentation. The initial step in the management of a persistently proteinuric dog or cat is to treat and eliminate, if possible, any potential predisposing diseases. Animals that are seropositive for infectious diseases should be given specific anti-infective treatment immediately, even when there is not direct evidence that the infection is causing the proteinuria, and consideration should be given for immunosuppressive treatment using the same guidelines presented in the following discussion.[9] The dog should be subsequently evaluated for resolution of the proteinuria, which may occur slowly over a period of months. If proteinuria does not resolve or worsens, a renal biopsy to determine the histologic diagnosis may be warranted.

Antiproteinuric agents should be considered when the UPC is persistently above 0.5 in a dog; ACE inhibitors (e.g., enalapril, benazepril) are the drugs of choice for most affected dogs. Enalapril significantly reduced proteinuria and delayed either the onset or the progression of azotemia in dogs with GN.[59] Treatment of dogs with glomerular diseases with ACE inhibitors is now considered a standard of care.[59] ACE inhibitors may reduce proteinuria and preserve renal function by several possible mechanisms. The decreased efferent glomerular arteriolar resistance brought about by ACE inhibitors leads to decreased glomerular transcapillary hydraulic pressure and decreased proteinuria. Other proposed mechanisms include reduced loss of glomerular heparan sulfate, decreased size of the glomerular capillary endothelial pores, improved lipoprotein metabolism, slowed glomerular mesangial growth and proliferation, and inhibition of bradykinin degradation.[59] Typically enalapril or benazepril (0.5 mg/kg given orally) is administered once a day, although approximately half of the dogs may eventually need twice daily administration. The initial dosage can be gradually increased to achieve the therapeutic target of UPC <0.5 (ideal target) or >50% reduction from baseline (alternate target) (E-Figure 325-15). Serum creatinine concentration should be monitored; it is uncommon for dogs to have dose-limiting worsening of azotemia (i.e., >30% increase in serum creatinine or progression to IRIS CKD stage 4 CKD) because of ACE inhibitor administration alone. Hyperkalemia is a common side effect in dogs with glomerular disease that are treated with an ACE inhibitor and can be controlled by feeding a potassium-reduced home-prepared diet that has been formulated by a veterinary nutritionist.[60] If severe hyperkalemia develops or proteinuria is not adequately controlled with an ACE inhibitor, an angiotensin receptor blocker (ARB; telmisartan, losartan) can be substituted or added. Combination therapy with an ACE inhibitor and an ARB may lead to a greater reduction in proteinuria than monotherapy with either an ACE inhibitor or an ARB but should be used with caution and careful patient monitoring until results of controlled studies become available.[61]



E-FIGURE 325-15 Making adjustments to RAAS inhibition therapy in dogs with glomerular disease. *ACEI,* Angiotensin-converting enzyme inhibitor; *ARB,* angiotensin-receptor blocker; *BP,* blood pressure; *K,* serum or plasma potassium; *SCr,* serum creatinine; *UPC,* urine protein : creatinine ratio.

Adequate blood pressure control of hypertensive dogs (see ch. 158) may also lead to a reduction in proteinuria and slow the progression of disease (see ch. 157). Because ACE inhibitors are relatively weak antihypertensive agents, additional antihypertensive agents (e.g., amlodipine) may be needed if hypertension (i.e., systolic blood pressure greater than 160 mm Hg) persists after the initiation of ACE inhibitor therapy.

Platelets and thromboxane may play an important role in the pathogenesis of GN and thromboxane synthetase inhibitors have been shown to decrease proteinuria in dogs with experimentally induced GN.[62] Aspirin is a nonspecific cyclooxygenase inhibitor that may be used to reduce glomerular inflammation and inhibit platelet aggregation, which may have an added benefit of preventing thromboembolism. In theory, low doses of aspirin (1-5 mg/kg PO daily) may be used but the optimum aspirin protocol for platelet inhibition in dogs is unknown. Clopidogrel (Plavix, 1.1 mg/kg PO q 24 h) also may effectively reduce platelet activity in dogs, although there is no evidence that it is superior to aspirin.[63]

The IRIS consensus recommendation is to feed modified protein diets to dogs with glomerular disease (see ch. 184). Dietary protein reduction reduces proteinuria and slows progression of CKD.[64,65] Diets should not be supplemented with protein, because this may aggravate urinary protein losses. The enhanced omega-3 to -6 polyunsaturated fatty acid ratio and restriction in salt and phosphorus found in canine renal diets might also be of benefit to dogs with glomerulopathies. Omega-3 fatty acid supplementation has been shown to be renoprotective in dogs with kidney disease and mitigate hypertension and reduce serum triglyceride and cholesterol concentrations in humans with NS.[66] These positive effects are in part mediated through generation of the three-series prostaglandins. Sodium restriction is beneficial in the control of hypertension and fluid retention.

Immunosuppressive Treatment of Dogs With Glomerular Disease

The use of immunosuppressive drugs (see ch. 165) in the treatment of dogs with glomerular disease has not been fully studied and should still be considered experimental. However, consensus recommendations are to treat dogs that have severe, persistent, or progressive glomerular disease with evidence of an active immune pathogenesis based on biopsy findings.[7] Finding electron-dense deposits in subendothelial, subepithelial, intramembranous, or mesangial locations of the glomerulus by EM or demonstrating positive and unequivocal immunofluorescent staining for immunoglobulins and/or complement in an immune-complex

and antiglomerular basement membrane pattern of deposition in peripheral capillary loops or the mesangial compartment with IFM provides compelling evidence to initiate a trial of immunosuppressive therapy.[7] Probable evidence of an immunopathogenesis can be documented by LM with one of the following: red granular staining of capillary walls with Masson's Trichrome, spikes along the GBM or holes within the GBM with Jones Methenamine sliver stain. These findings would be expected in just under 50% of dogs with glomerular disease.[23] When renal biopsy results are not available it becomes more difficult to make a decision about using immunosuppressive treatment because approximately 50% of dogs with glomerular disease would be expected **not** to have an immunopathogenesis of their disease. Consensus recommendations are to consider immunosuppressive drugs in the treatment of dogs with glomerular disease when the source of proteinuria is clearly glomerular in origin, the drugs are not otherwise contraindicated, the dog breed and age of disease onset are not suggestive of a familial nephropathy, amyloidosis has been deemed unlikely and the serum creatinine is >3.0 mg/dL or progressively increasing, or the serum albumin is <2.0 g/dL.[8]

Dogs with more severe disease or rates of progression should be treated more aggressively than those with more stable disease. According to the IRIS consensus statement,[7] single agent or combination therapy for rapid onset of immunosuppression should be considered in dogs with high magnitude proteinuria with hypoalbuminemia, NS, or rapidly progressive azotemia. Mycophenolate, or cyclophosphamide, with or without short-term administration of glucocorticoids, was suggested as the first choice. Glucocorticoids should be limited to short-term therapy because proteinuria has been demonstrated in dogs with corticosteroid excess and may induce glomerular lesions and prednisolone administration was shown to reversibly increase proteinuria in dogs with hereditary nephritis.[17,67,68] Dogs with stable or more slowly progressive disease that have only partial or no response to standard therapy might be given drugs that have either a rapid or a more delayed onset of action, such as mycophenolate, chlorambucil or cyclophosphamide. Cyclosporine was also suggested as a first choice for stable or slowly progressive dogs; however, this is the only drug that has been studied prospectively in dogs with glomerular disease and was found to be of no benefit, although there were flaws in that study.[69] All dogs treated with immunosuppressive therapy for their glomerular disease should be monitored closely. Treatment should be discontinued or adjusted if adverse drug effects develop. In the absence of adverse effects, 8-12 weeks of therapy should be provided before changing the course of treatment. If the therapeutic response is suboptimal at the end of 8-12 weeks, an alternate drug protocol should be considered. However, if after 3-4 months a therapeutic response has not been achieved, consideration should be given to discontinuing immunosuppressive drug administration. If after this time, a response has been noted, the drug dose or schedule should be tapered to one that maintains the response without worsening of proteinuria, azotemia or clinical signs.[7]

Patient Monitoring

Dogs with stable glomerular disease and IRIS CKD stage 1 or 2 should be evaluated 3-14 days following changes in therapy, whereas those with unstable disease or IRIS CKD stage 3 or 4 should be evaluated 3-5 days after any change in therapy. If therapeutic changes are not being made and the dogs are seemingly stable, standard re-evaluations should be made every 3 months. The UPC, urinalysis, body weight, body condition score, systemic arterial blood pressure and serum albumin, creatinine and potassium concentrations should be included in these evaluations. Because histologic lesions do not necessarily resolve even though renal function may improve, repeat biopsies generally are not needed.

Response to therapy has historically been focused on a reduction in proteinuria. However, it is logical also to evaluate changes in serum creatinine and albumin concentrations. A complete response to therapy is defined as a reduction in UPC to <0.5, a reduction in serum creatinine to <1.4 mg/dL, or a sustained increase in serum albumin to >2.5 g/dL; whereas a partial response is defined as a >50% reduction in UPC, >25% sustained reduction in serum creatinine or >50% sustained reduction in serum albumin when compared with baseline values or an increase in serum albumin to >2.0-2.5 g/dL.[7] Day-to-day variations in the UPC occur in most dogs with glomerular proteinuria, with greater variation occurring in dogs with UPC >4.[70] Changing proteinuria is most accurately measured by assessing trends in the UPC over time. Because there is greater variation in dogs with UPC >4, consideration should be given to either averaging two to three serial UPC or measuring a UPC in urine that has been pooled from two to three collections.

Complications of Glomerular Disease

Complications of severe proteinuria include edema formation, systemic hypertension, hypercoagulability and

thromboembolism, hyperlipidemia, increased risk for infection, altered pharmacokinetics (see ch. 160), malnutrition, muscle wasting (see ch. 177), and endocrine abnormalities.[58] Edema formation, systemic hypertension, and hypercoagulability are the complications most frequently recognized in dogs, and less commonly in cats, with glomerular disease.

Edema Formation

Several factors contribute to the formation of edema in patients with NS (see ch. 18).[58] In severe forms of NS, decreases in the plasma oncotic pressure allow for transudation of fluid into the interstitial spaces. The resultant decrease in effective plasma volume leads to increased renin-angiotensin-aldosterone activity and retention of water and sodium and worsening of edema. However, most humans with NS do not have reduced blood volumes or increased plasma renin or aldosterone activities. Thus primary sodium retention must also be involved in the pathogenesis of edema in these patients. Proposed mechanisms in primary renal sodium retention include a reduced single nephron glomerular filtration rate with enhanced proximal tubular resorption and cytokine-induced modification of distal resorption, leading to resistance to natriuretic factors, including atrial natriuretic peptide. In humans, it is believed that mechanisms of primary renal sodium retention are the most important determinants of edema formation until the serum albumin concentration decreases below 2 g/dL. Below this concentration, the plasma oncotic pressure is sufficiently reduced to allow for transudation of fluid from the vascular compartment into the interstitial space.[58] Dogs may be more resistant to the formation of edema, which does not generally occur until the serum albumin concentration is below 1.5 g/dL. Plasma volume may be reduced at this point, making the use of diuretics in the management of edema relatively ineffective and also dangerous because of the increased risk of acute kidney injury and thromboembolism.[58] Dogs with glomerular disease should have careful assessment of their hydration status and vascular volume prior to and during fluid therapy. This evaluation should be based on serial body weight measurements, skin turgor, mucous membrane color and moisture, capillary refill time, temperature of the extremities, heart rate, pulse quality and systemic blood pressure. The use of diuretics should be limited to situations where ascites or pleural effusion is critically impairing organ function.[6] When indicated, furosemide may be the drug of choice for dogs with pulmonary edema or hyperkalemia and spironolactone for dogs with pleural or abdominal effusion.[6] Provision of adequate exercise also may help reduce the formation of edema or ascites.

Hypertension

Systemic hypertension has been reported in up to 80% of dogs with glomerular disease (see ch. 157). The frequency of hypertension in each form of glomerular disease has not been established fully in dogs but does vary in humans. Preliminary findings suggest a higher frequency of hypertension might be found in dogs with MPGN.[23] The primary mechanism of hypertension in association with NS is believed to be expansion of the plasma volume in association with primary renal sodium retention. However, generation of several vasoactive factors (e.g., renin, angiotensin II, endothelin) is increased in human patients with NS and may contribute to hypertension. Nitric oxide deficiency may also play an important role in the development of hypertension.[58] The blood pressure should be measured in all dogs and cats with glomerular disease, because uncontrolled hypertension is a risk factor for progressive renal injury (see ch. 157 for complete discussion of hypertension).

Thromboembolism

Thromboembolism (see ch. 256), perhaps the most serious complication of glomerular disease, was reported in 5% of dogs with GN, 14% of dogs with amyloidosis, and 13% of dogs with all forms of glomerular disease.[16,17,22] Because emboli may be difficult to detect, the prevalence of thromboembolism in dogs with glomerular disease may be higher than indicated by these studies. The risk of thromboembolism is highest in dogs with nephrotic-range proteinuria and hypoalbuminemia. Pulmonary thromboembolism is most common, but emboli may also lodge in other arteries (e.g., mesenteric, renal, iliac, brachial, coronary) or the portal vein (see ch. 243 for complete discussion of pulmonary thromboembolism).

Although urinary loss of antithrombin (AT) has gained the most attention in veterinary medicine, the pathogenesis of the hypercoagulable state is multifactorial.[58] AT is a serine protease inhibitor that modulates fibrin generation; heparin catalyzes these reactions. AT (65,000 Daltons) is similar in charge and size to

albumin (69,000 Daltons); serum AT activity closely correlates with the serum albumin concentration. Prior studies have suggested that this close correlation can be used to predict thromboembolism when the serum albumin concentration is <2 g/dL, when serum AT III activity would be expected to be less than 75% of normal.[16] A recent study of thromboelastography in dogs with glomerular disease failed to support this conclusion, demonstrating that hypercoagulability may develop before alterations in serum albumin or AT activity occur.[71] This is because the pathogenesis of hypercoagulability is complex; other factors are involved. Albumin binds to arachidonic acid, which, if unbound, would stimulate platelet aggregation through the generation of prostaglandins (i.e., thromboxane B_2); hypoalbuminemia is associated with increased platelet aggregation.[58] Hypercholesterolemia contributes to platelet hypersensitivity by influencing membrane-associated enzyme and receptor activity through alteration of the membrane composition. The role of platelet hypersensitivity in the development of hypercoagulability may be enhanced by thrombocytosis, which occurs in many animals with glomerular disease. Increased fibrinogen concentrations (i.e., above 300 mg/dL), which are often present in patients with NS, lead to increased fibrin complex formation and platelet hyperaggregation. The risk of thromboembolism may be further enhanced by increased concentrations of $alpha_2$ macroglobulin; $alpha_2$ antiplasmin; procoagulant cytokines; coagulation factors V, VII, VIII, and X; increased plasma viscosity and interstitial pressure; decreased plasma plasminogen concentrations; decreased plasma volume and blood flow; endothelial injury; and infections.[58]

Warfarin, aspirin and clopidogrel have been used in the prevention of thromboembolism in at-risk dogs. Warfarin is highly protein-bound. It is very difficult to titrate the dose adequately to prolong the prothrombin time appropriately (i.e., 150% of baseline) in dogs with hypoalbuminemia, and its use is not recommended. Alternatively, low-dose aspirin is inexpensive, easy to administer, and has the added benefit of potentially reducing proteinuria. Both aspirin and clopidogrel inhibit platelet function and there is not a clear therapeutic benefit of one agent over the other. In theory, heparin would be ineffective in dogs with reduced AT activity.

Hyperlipidemia

Hypercholesterolemia was reported in 79% of dogs with GN and 86% of dogs with amyloidosis (see ch. 182).[17,22] Cholesterol concentrations as high as 749 mg/dL have been reported, although the mean concentration was 325 mg/dL in 69 dogs with GN and 350 mg/dL in 23 dogs with amyloidosis.[16,17] Increases in total plasma cholesterol, very-low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) occur.[72] Hyperlipidemia is variably seen in humans with NS and has not been fully studied in dogs. The pathogenesis of hyperlipidemia in association with NS is complex.[72] Hypoalbuminemia stimulates hepatic protein synthesis, including the synthesis of lipoproteins, leading to hypercholesterolemia.[58] The serum albumin concentration and plasma oncotic pressure inversely correlate with the magnitude of hypercholesterolemia. It is unclear whether hypoalbuminemia or the decreased plasma oncotic pressure, or both, induce the increased synthesis. Alterations in lipid catabolism also contribute to the development of hyperlipidemia. Orosomucoid, which plays an important role in the maintenance of glomerular permselectivity, is lost in the urine of patients with glomerular disease. Urinary losses of orosomucoid exacerbate proteinuria but also contribute to hyperlipidemia by indirectly causing decreased hepatic production of heparin sulfate, a cofactor needed in normal lipoprotein lipase function.[72]

Some evidence supports the theory that uncontrolled hyperlipidemia contributes to glomerular and tubulointerstitial injury. LDL and oxidized LDL may alter mesangial cell function and increase the synthesis of mesangial matrix, thereby accelerating the formation of glomerulosclerosis.[58] Glomerular and tubulointerstitial lipoprotein deposition and lipoprotein-induced cytotoxicity also contribute to renal injury. Interestingly glomerular lesions have been identified in cats with lipoprotein lipase deficiency and Miniature Schnauzers with hyperlipidemia.[7]

Prognosis

The prognosis for dogs and cats with glomerular disease is variable and most likely based on a combination of factors including the histologic diagnosis. Although progressive disease can be expected to occur in a large percentage of animals with glomerular disease, spontaneous remission and response to specific therapy can also be expected. Furthermore, disease progression can be slow enough for the animals to lead relatively normal lives, especially when the diagnosis is established early in the disease process. In humans, azotemia, severe proteinuria, systemic hypertension, and marked tubulointerstitial lesions at presentation are the most

significant predictors of an unfavorable outcome in most forms of glomerular disease. Clinical impressions suggest that these same variables affect the prognosis in dogs and cats.

The median survival of 53 dogs with GN and amyloidosis that were not dead or euthanized shortly after presentation was only 28 days, although individual dogs survived for more than 3 years.[16] Dogs with glomerular disease and NS had a shorter median survival than those without NS (12.5 vs. 104.5 days, respectively).[20] Survival of non-azotemic dogs (serum creatinine <1.5 mg/dL) with or without NS (51 vs. 605 days, respectively) was longer.[20] More study is needed to characterize the natural history and prognosis of the various glomerular diseases in dogs and cats.

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CHAPTER 326

Renal Tubular Diseases

Marie E. Kerl

Renal tubules control body fluid balance, drug excretion, acid-base balance, and electrolyte regulation. While glomerular filtration rate (GFR) is the main determinant of renal function, the tubules determine the final composition of the urine. Glomerular ultrafiltrate contains all plasma solutes that are smaller than 69,000 Daltons; therefore all filtered glucose, amino acids, and electrolytes are delivered to the tubules via the ultrafiltrate. The bulk of filtered substances is reabsorbed. Tubular defects causing lack of function are uncommon to rare. They can occur regionally or globally in the tubules and are either congenital or acquired. Indicators from biochemical profiles, blood gas analysis, and urinalysis can be monitored to assess tubular function.

Renal tubules are described according to function and anatomic location. The proximal tubule receives ultrafiltrate from Bowman's space and reabsorbs 60% to 65% of the ultrafiltrate, a proportion that is maintained across a wide range of GFR. This property is responsible for preventing the more distal nephron segments from being overwhelmed by excessive solute delivery. Tubular absorption is accomplished by active transport of sodium (Na^+), which in turn promotes passive resorption of other solutes. The proximal tubule also actively secretes some solutes (e.g., organic anions, cations, and hydrogen ions [H+]).[1] Solutes are not reabsorbed uniformly; virtually all filtered glucose and amino acids are reabsorbed, whereas lesser amounts of bicarbonate (HCO_3^-), Na^+, and chloride are reabsorbed. The main function of the loop of Henle is to reabsorb approximately 30% of filtered sodium chloride (NaCl) against a concentration gradient to generate a concentrated medullary interstitium and create an ultrafiltrate that is hypoosmolar to plasma.[2] The distal tubule and the collecting tubule and duct are responsible for fine control of electrolytes, including Na^+, potassium, and calcium; final regulation of acid-base balance; and water resorption to produce concentrated urine.[3] Clinical manifestations of renal tubular disorders include formation of urinary calculi, metabolic acidosis, glucosuria, aminoaciduria, electrolyte disorders, and failure of urine concentration.

Cystinuria

Cystinuria is caused by inherited proximal tubular defects in which resorption of particular nonessential amino acids fails. Of these amino acids, cystine is relatively insoluble in urine, resulting in the formation of cystic calculi in acidic urine.[4-6] Many dog breeds have been reported with cystinuria, and rare reports have been made for cats.[7,8] The dog breeds reported with an increased risk of cystine urolith formation vary somewhat with geographic location, and include English Bulldog, Staffordshire Bull Terrier, Chihuahua, Newfoundland, Dachshund, Welsh Corgi, Rottweiler, Miniature Pinscher, and Jack Russell Terrier.[9-11] In one report, cystine stone diagnosis from Newfoundland dogs decreased to 38%, compared to 71% identified 10 years prior.[11] Cystine calculi identification is rare in cats.[12]

Inheritance patterns for cystinuria vary in people, and are classified as type 1 and non–type 1. Type 1 cystinuria is characterized by an autosomal recessive inheritance pattern, in which carriers have normal urine amino acid concentrations. Non–type 1 is characterized by an autosomal dominant inheritance pattern with incomplete penetrance. In non–type 1, the incidence of calculi formation is limited in carrier individuals with cystinuria. Defects in the *Slc3a1* and *Slc7a9* genes account for most of the genetic defects associated with cystinuria in people.[4,13] Similar to people, cystinuric dogs have different methods of inheritance. Newfoundland dogs and Labrador Retrievers have been identified with a severe form of type 1 cystinuria caused by a missense mutation that was identified in exon 2 of the *Slc3a1* gene.[4,13,14] More recently, Australian Cattle Dogs have been identified with an autosomal dominant form of cystinuria caused by a 6 base pair deletion removing 2 threonine molecules in the *Slc3a1* gene, and in Miniature Pinschers caused by a

missense mutation in *Slc7a9*.[15] Genetic testing has been available for the mutation in Newfoundland dogs for several years, perhaps accounting for the decreased identification of cystine calculi in this breed.[11,14] Genetic testing is also available for other affected breeds.[15]

The mean age of calculus formation is 4.9 years overall for cystine stones; however Newfoundland dogs and Labrador Retrievers typically are affected as early as 4 to 6 months of age.[4,11] The degree of cystinuria can vary among individuals, and may decrease with age.[5] Males are overrepresented for clinical cystine calculi, but cystinuria without calculi formation has been reported in females. Clinical signs associated with cystine calculi formation include stranguria, pollakiuria, and hematuria (also see ch. 331). Male dogs may develop secondary urethral obstruction. Evaluation of urine sediment reveals cystine crystalluria in some affected dogs, but a complete blood count and serum biochemical analysis do not aid diagnosis. Imaging studies may identify calculi, but the size, shape, and radiographic density of calculi vary. The radiographic opacity of cystine calculi is similar to that of struvite and silica calculi; therefore, larger cystine calculi can often be visualized on plain film radiographs. Ultrasonography and contrast cystourethrography may be diagnostic if plain film radiography is unrewarding.[16]

Treatment involves mechanical removal or medical dissolution of calculi and long-term medical management to prevent recurrence (see ch. 107 and 331). Surgical management is indicated in animals with urethral obstruction. Quantitative calculi analysis provides a definitive diagnosis. Bacterial urinary tract infection should be resolved with appropriate antibiotic therapy (see ch. 330). Dissolution and prevention strategies include exclusive feeding of protein-restricted diets. Cystine is twice as soluble at a pH of 7.8 as at 6.5; therefore, urinary alkalization is desired.[17] Some protein-restricted diets (e.g., Prescription Diet Canine u/d, Hill's Pet Nutrition, Topeka, KS) result in the formation of alkaline urine, but if dietary therapy does not maintain the urine pH at the desired level, oral potassium citrate is recommended.[16] Induction of diuresis (e.g., by feeding canned, low-protein food or adding water to dry food) is likely to be beneficial.[5,16]

Drug therapies to reduce the formation of cystine calculi include the thiol drugs D-penicillamine and 2-mercaptopropionylglycine (2-MPG) (tiopronin [Thiola, Mission Pharmaceuticals]). Cystine is formed by a disulfide bond between two cysteine molecules. Thiol drugs form a disulfide bond with cysteine to create a more soluble cystine-thiol drug complex. Although both drugs are effective, metal chelation and gastrointestinal side effects of D-penicillamine make it a less desirable choice.[6] 2-MPG (15-20 mg/kg PO q 12 h) is the treatment of choice, in combination with dietary modifications for dissolution and prevention of cystine calculi.[5,6,18]

Carnitinuria

Carnitine is a sulfur-containing nonessential amino acid that functions as an enzyme cofactor necessary to transport energy-generating fatty acids from the cytosol to the mitochondrial matrix. Continued deficiency, which has been reported in dogs with dilated cardiomyopathy (see ch. 252), may result from defective biosynthesis, defective tissue uptake or retention, or excessive renal excretion.[19,20] Carnitinuria has been reported in dogs with cystinuria.[19] Although high-fat, low-protein diets are recommended for the management of cystinuria, high-fat diets increase renal carnitine excretion in humans. Healthy dogs that consume low- and high-fat diets excrete similar amounts of carnitine; however, cystinuric dogs with altered amino acid resorption might excrete an excessive amount of carnitine if they consume a high-fat diet.[19] Chronic, excessive carnitine excretion eventually results in carnitine deficiency, leading to cardiomyopathy.

Hyperuricosuria

Hyperuricosuria is defined as an excessive quantity of uric acid, an intermediate product of protein metabolism, in the urine. The purine portions of nucleic acids undergo metabolism to form hypoxanthine and xanthine, which are oxidized to uric acid by xanthine oxidase (XO). In most mammals, uric acid is further metabolized to allantoin (a more soluble product) by hepatic uricase (see ch. 332). In healthy dogs, allantoin is the primary metabolic product that is renally excreted, while humans and higher apes excrete mostly uric acid.[21] Certain naturally occurring diseases, such as hyperadrenocorticism, cancer, and chronic kidney disease, can alter excretion patterns for these metabolites, resulting in greater excretion of xanthine or uric acid compared to allantoin.[22] Abnormal purine metabolism or excretion accounts for hyperuricosuria in dogs of certain breeds with a genetic predisposition to formation of urate calculi, or those with underlying hepatic disease. The dog breed that is most commonly affected with hyperuricosuria is the Dalmatian; however,

English Bulldogs and Black Russian Terriers have also been identified.[9,11] Dalmatians are intermediate between dogs of other breeds and humans with regard to purine metabolism, excreting approximately one half to two thirds as much allantoin as urate.[4] In humans, uric acid in circulation can precipitate into the joints to cause the clinical syndrome of gout; however Dalmatian dogs have serum uric acid levels more similar to non-Dalmatian dogs than people and do not develop gout.[23] Differences exist between Dalmatians and non-Dalmatian dogs in both hepatic and renal management of uric acid. The enzyme uricase, which converts uric acid to allantoin, is stored in hepatic peroxisomes. Uric acid must be transported into hepatocytes before conversion to allantoin can occur. Dalmatians have normal amounts of uricase compared with non-Dalmatian dogs, but Dalmatians have abnormal uric acid transport across the hepatic membrane, which limits uric acid metabolism.[24] Uric acid is secreted via glomerular filtration and reabsorbed in the proximal tubule; however Dalmatians appear to have less proximal tubular resorption than do non-Dalmatian dogs. In addition, Dalmatians have active distal tubular secretion of urates as a result of a membrane transport defect.[4,25] The defect, a missense mutation in the *Slc2a9* gene that encodes for a transporter of uric acid, is inherited as an autosomal recessive trait that all Dalmatians carry.[26] Clinical manifestations occur in 25% of male Dalmatians. This gene has also been identified as abnormal in English Bulldogs and Black Russian Terriers affected with hyperuricosuria.[27]

Dogs with primary hepatic disease have reduced conversion of uric acid to allantoin and of ammonia to urea. These metabolic defects cause hyperuricuria and hyperammonuria.[28] Portal vascular anomalies and hepatic microvascular dysplasia have been most commonly associated with urate calculi formation, although any severe hepatic dysfunction could predispose to calculi formation (see ch. 284).[29] Cats have been reported with urate urolithiasis. While some cats with urate stones have been diagnosed with portosystemic shunts, the cause is not apparent in other cats.[30,31]

Clinical signs of urate urolithiasis are consistent with lower urinary tract disease (see ch. 331). Male dogs can develop urethral obstruction (see ch. 107). Young to middle-aged dogs are more commonly affected than are older dogs.[9,11] For Dalmatians, males are more frequently diagnosed with urinary calculi than are females.[11] Dogs with primary hepatic disease have no gender predisposition for calculi formation; however, older male dogs are more clinically affected.[29] Cats that develop urate urinary calculi and are diagnosed with a hepatic vascular anomaly are generally younger (<2 years) compared to those not diagnosed with hepatic vascular anomaly (4-7 years), and are neutered.[30,31] Definitive diagnosis of cystic calculi depends on calculi retrieval and quantitative analysis. Urate calculi are radiopaque on plain film radiography, but can be visualized using abdominal ultrasonography or double-contrast cystography. Hepatic function studies (e.g., serum pre- and postprandial bile acids, blood ammonia evaluation) are appropriate for non-Dalmatian dogs and for cats. Urate calculi typically are small and smooth and vary in color from yellow to green to black.[32]

Treatment consists of calculi removal or dissolution, followed by long-term medical management to prevent recurrence. Dissolution therapy includes a calculolytic diet, medication with XO inhibitors, urine alkalization, elimination of secondary infections, and induction of isosthenuria.[32] A purine-restricted diet that is low in calculogenic minerals (e.g., Prescription Diet Canine u/d; Hill's Pet Nutrition, Topeka, KS) is recommended.[25,33,34] The synthetic XO inhibitor allopurinol is used for treating and preventing urate urolithiasis in Dalmatians because it can reduce serum and urinary uric acid concentrations by blocking metabolism of hypoxanthine and xanthine to uric acid. Allopurinol should be administered only to dogs consuming a purine-restricted diet, to avoid the formation of hypoxanthine and xanthine calculi, and the dosage should be adjusted based on reduction of uric acid concentration in the urine.[32,34,35]

Urine alkalization reduces renal tubular production of ammonia, thereby diminishing the production of urinary ammonium ions that complex with urate to form calculi. Alkalizing agents (e.g., oral sodium bicarbonate [$NaHCO_3$] or potassium citrate) should be administered at a dosage that maintains the urine pH near 7.0 to 7.5.[32,34,35] Dilute urine production is accomplished by feeding protein-restricted diets that reduce renal medullary concentrating ability.

Mechanical calculi removal should be considered in animals with urethral obstruction or in those that do not respond to dissolution therapy. The average time to dissolution of urate calculi is approximately 3.5 months (range, 1 to 18 months).[34] Dissolution sometimes occurs with definitive repair of a portovascular anomaly, but calculi do not resolve without resolution of underlying hepatic defects.[35] Because the causes of urate stones differ, allopurinol therapy is not recommended for dogs with hepatic defects, and should not be used in cats.[35]

The prognosis is fair to guarded for calculi recurrence in Dalmatians and long-term success depends on the owner's commitment to lifelong management. In dogs with underlying liver disease, the prognosis is good if definitive therapy for the liver disease exists but guarded to poor in dogs with irreparable liver disease.

Hyperxanthinuria

Xanthine calculi are rare. Xanthine is derived from dietary purines and is metabolized to uric acid by activity of XO (see ch. 332). Reduced enzymatic conversion increases urinary excretion of xanthine, which has solubility similar to that of uric acid in urine. Most dogs that form xanthine-containing calculi are receiving allopurinol, an XO inhibitor, for urate calculi; however, idiopathic xanthine calculi have been reported.[11,36] Xanthine uroliths are rare in cats, and have been reported in cats not receiving allopurinol.[36-38] Congenital xanthinuria has been reported in Cavalier King Charles Spaniels, and in one Wirehaired Dachshund.[39-41] Prevention consists of monitoring for xanthine crystalluria in dogs receiving allopurinol to prevent urate calculi, and tailoring allopurinol dosing to the patient.

Renal Glucosuria

Under normal conditions, glucose is freely filtered at the glomerulus and reabsorbed in the proximal tubules by facilitated diffusion in a cotransport mechanism with Na^+. The transport mechanism has a maximum capacity that is exceeded at a blood glucose concentration of 180 to 220 mg/dL (10-12.2 mmol/L) in dogs and 260 to 310 mg/dL (14.4-17.2 mmol/L) in cats.[42] When blood glucose concentration exceeds the renal transport maximum (e.g., hyperglycemia from stress or diabetes mellitus), glucosuria occurs. This is the most common explanation for glucosuria. Rarely, proximal tubular defects caused by tubular damage or inherited disorders can cause glucosuria in the absence of hyperglycemia.[42-45]

Primary renal glucosuria is rare but has been reported in Scottish Terriers, Basenjis, Norwegian Elkhounds, and mixed-breed dogs.[42,46,47] Persistent glucosuria typically causes polyuria and polydipsia from osmotic diuresis, although some dogs are asymptomatic. Evaluation of serial blood glucose measurements or the serum fructosamine concentration should be considered to diagnose renal glucosuria definitively by ruling out hyperglycemia as a cause for glucosuria.[48] There is no cure for primary renal glucosuria, but the long-term prognosis is good with appropriate fluid intake and control of concurrent urinary infections. In some dogs, renal glucosuria is the initial sign of Fanconi syndrome.

Fanconi Syndrome

In humans, Fanconi syndrome is an inherited proximal tubular defect that results in glucosuria, aminoaciduria, proteinuria, phosphaturia, and hypophosphatemia. Fanconi syndrome has also been reported in dogs, and Basenjis are most commonly affected.[44,45,49,50] Fanconi syndrome is inherited in 10% to 30% of all Basenjis. Genetic testing for this syndrome became available in 2011.[51] Idiopathic and inherited Fanconi syndrome has been reported rarely in other dog breeds.

Acquired Fanconi syndrome has been reported in association with a number of different causes including gentamicin administration, various toxicoses causing acute tubular necrosis, and primary hypoparathyroidism.[43,52-54] Recently, a number of cases of acquired Fanconi syndrome in dogs having consumed chicken jerky treats manufactured in China were identified.[55-59] The first documentation of acquired Fanconi syndrome in cats has been reported. Four cats being treated for alimentary lymphoma or inflammatory bowel disease were undergoing treatment with chlorambucil. Urine metabolic assays confirmed aminoaciduria and glucosuria, and glucosuria stopped in 3 of 4 cats when chlorambucil was discontinued.[60]

Fanconi syndrome causes abnormal fractional excretion of many solutes.[45] Abnormal glucose absorption, resulting in glucosuria and osmotic diuresis, is the most obvious finding. Amino acid resorptive abnormalities vary from one individual to another but generally include abnormal absorption of cystine. Abnormal absorption of bicarbonate, sodium, potassium, and urate also occur. Isosthenuria sometimes occurs prior to glucosuria and osmotic diuresis as a result of nephrogenic diabetes insipidus.[61]

The onset of clinical signs in affected Basenjis typically occurs by 4 to 8 years of age, and there is no gender predilection.[45] Clinical signs typically include polyuria, polydipsia, weight loss, poor hair coat, weakness, and dehydration. Diagnosis prior to the onset of clinical signs is possible if predisposed breeds are regularly

evaluated for glucosuria.[45] Diagnostic testing typically reveals glucosuria, euglycemia, and isosthenuria. As the disease progresses, hyperchloremic metabolic acidosis and renal failure occur. Clinically significant hypokalemia might contribute to muscle weakness. Progression is variable; some affected dogs develop renal failure within a few months of the onset of clinical signs, whereas others remain stable for years.[45]

Treatment is supportive, because there is no cure for the tubular defects. Monitoring for metabolic acidosis, urinary tract infections, and azotemia should be performed regularly. Veterinarians frequently are asked to participate in a Fanconi syndrome management protocol developed by Basenji breed enthusiasts known as the Gonto protocol.[45] This protocol involves intensive monitoring and treatment of secondary electrolyte abnormalities and metabolic acidosis. With this protocol, chronic proximal tubular bicarbonate loss that results in metabolic acidosis is managed by administration of oral sodium bicarbonate, 8-12 mg/kg PO q 12 h. This method of alkalinization will increase sodium load and result in bicarbonaturia; however, there is no information in the peer-reviewed literature of long-term effects of bicarbonate administration in dogs or cats with naturally occurring disease. Alternatively, management of chronic metabolic acidosis from renal tubular disease can be accomplished with administration of potassium citrate 40-75 mg/kg PO q 12 h. The goals of alkalization should be to maintain the serum [HCO_3^-] in a normal range (≈18-24 mEq/L), and the serum [K^+] at 4 to 6 mEq/L. Renal failure should be managed with dietary protein restriction, fluid therapy, histamine-2 receptor antagonists, and treatment of hypertension (see ch. 324). Treatment for acquired Fanconi syndrome should be directed at resolving the underlying cause of the disorder and providing supportive care. In a survey completed by owners and veterinarians of dogs affected with Fanconi syndrome to identify clinical and biochemical changes and long-term patient outcome, median survival time following diagnosis was 5.25 years (range, 7 days to 9.8 years).[45] In addition, 86% of owners reported quality of life as "excellent" to "good" during long-term management.[45] Of 29 dogs, 17 died or were euthanized for reasons unrelated to Fanconi syndrome.[45]

Renal Tubular Acidosis

The renal tubules regulate acid-base homeostasis through two processes: (1) resorption of 80% to 90% of filtered HCO_3^- in the proximal renal tubule, and (2) excretion of acids by means of titration of urinary buffers and excretion of ammonium in the distal renal tubule.[62] The term renal tubular acidosis (RTA) describes rare tubular disorders that lead to hyperchloremic metabolic acidosis. Various types of RTA have been described based on the area of the affected renal tubules. Proximal RTA (type II) occurs as a result of inability of the proximal tubules to prevent loss of HCO_3^-, and distal RTA (classic, or type I) occurs as the result of inability of the distal tubule to excrete H^+. Type IV RTA is distal RTA and hyperkalemia secondary to hypoaldosteronism or aldosterone deficiency. Unique diagnostic criteria exist for each type of RTA (Table 326-1).[63]

TABLE 326-1

Clinical Features of Proximal and Distal Renal Tubular Acidosis (RTA)[63]

FEATURE	PROXIMAL RTA	DISTAL RTA
Hypercalciuria	Yes	Yes
Hyperphosphaturia	Yes	Yes
Urinary citrate	Normal	Decreased
Bone disease	Less severe	More severe
Nephrocalcinosis	No	Possible
Nephrolithiasis	Not usually	Yes
Hypokalemia	Mild	Mild to severe
Potassium wasting	Worsened by alkali therapy	Improved by alkali therapy
Alkali required for treatment	>11 mEq/kg/day	<4 mEq/kg/day
Other defects of proximal tubular function*	Yes	No

Reductions in plasma bicarbonate (HCO_3^-)	Moderate	Variable
Fractional excretion of bicarbonate with normal serum bicarbonate	>15%	<15%
Urine pH during acidemia	<6.0	>6.0
Urine pH following administration of ammonium chloride	<6.0	>6.0

*Decreased resorption of sodium, potassium, phosphate, uric acid, glucose, and amino acids.

A defect in the basolateral membrane Na^+-HCO_3^- co-transporter, with leakage of HCO_3^- into the tubular lumen, results in proximal RTA.[64] This disorder can occur alone or as part of another tubular defect (e.g., Fanconi syndrome).[63] Ongoing loss causes a reduced plasma bicarbonate concentration, but the associated metabolic acidosis is self-limiting because of the distal tubule's ability to excrete acid. If oral sodium bicarbonate ($NaHCO_3$) is prescribed to normalize the plasma bicarbonate concentration, the amount of HCO_3^- presented to the distal tubule increases and overwhelms the distal buffering system, resulting in marked bicarbonaturia.[63]

The diagnosis of proximal RTA is based on an acidic urine pH and hyperchloremic metabolic acidosis, with a normal GFR but increased urine pH and fractional excretion of HCO_3^- (>15%) after normalization of the plasma HCO_3^- concentration with alkali administration. Identification of concurrent proximal tubular defects (e.g., euglycemic glucosuria, aminoaciduria) also helps localize proximal RTA.[63] Bicarbonate wasting makes metabolic acidosis from proximal RTA difficult to correct, and alkali therapy exacerbates potassium wasting. Potassium citrate is better suited for chronic use than is sodium bicarbonate.[63] One 540 mg tablet of potassium citrate provides 5 mEq of potassium and 1.7 mEq of citrate, and its metabolism yields 5 mEq of HCO_3^-.[17]

Distal RTA causes impairment of urinary acidification as a result of impaired H^+ secretion in the distal tubule.[62,63] Consequently, the kidneys are unable to maximally acidify urine in response to systemic metabolic acidosis. Under normal conditions, the distal tubule is able to excrete H^+ ions against a steep concentration gradient because of a hydrogen ion-adenosine triphosphatase (H^+-ATPase) pump. These tubular segments have tight junctions that resist back leak of acid, and they are able to generate ammonia to capture H^+ ions by forming ammonium ions, which are subsequently excreted.[64]

Type IV distal RTA is associated with hypoaldosteronism or aldosterone antagonism. Acidosis most likely results from loss of aldosterone stimulation of H+-ATPase and decreased distal Na^+ absorption. This syndrome has not been characterized in veterinary medicine but should be considered in animals with hyperchloremic metabolic acidosis and hypokalemia.[62,63]

Characteristics useful in the diagnosis of distal RTA include hyperchloremic metabolic acidosis with an increased urine pH (>6.0). In contrast to proximal RTA, with its relatively mild systemic metabolic acidosis, distal RTA can have a more severe metabolic acidosis because the distal tubule does not provide buffering ability. Clinical characteristics seen in humans with distal RTA include nephrolithiasis, nephrocalcinosis, bone demineralization, growth retardation, and hypokalemia.[62,64] Distal RTA has been reported in cats with pyelonephritis and in one cat with hepatic lipidosis, as well as in three dogs with immune-mediated hemolytic anemia, and one dog each with leptospirosis and receiving zonisamide therapy.[65-67] One cat with idiopathic distal RTA has been reported.[68] The diagnosis may be made by failure to acidify urine with an ammonium chloride challenge test. This test is performed by measuring the urine pH before and at hourly intervals for 6 hours after oral administration of 110 mg/kg of ammonium chloride. Normal dogs should acidify their urine to a pH of 5.0, and cats to a pH of 5.5.

Treatment for distal RTA consists of administration of an alkali source. A combination of potassium and sodium citrate, at a dosage range of 1 to 5 mEq/kg/day, orally, divided into 2 doses, may be preferred over HCO_3^- as the alkali source.

Nephrogenic Diabetes Insipidus

The term nephrogenic diabetes insipidus (NDI) describes any disorder in which the urinary concentrating mechanism is unable to respond to antidiuretic hormone (ADH) to produce concentrated urine. ADH is produced in the hypothalamus, stored in the posterior pituitary, and is released into circulation in response to

hyperosmolarity or hypovolemia.[69] Following release, ADH attaches to receptors at the basolateral membrane of the renal collecting tubules and collecting ducts, causing the tubular luminal surface to become permeable to free water, which promotes formation of urine that is more concentrated than plasma. Acquired NDI is a common cause of polyuria, because it can result from receptor interference caused by toxins (e.g., *Escherichia coli* endotoxin), drugs (e.g., glucocorticoids, chemotherapeutics), metabolic conditions (e.g., hypokalemia, hypercalcemia), tubular injury or loss (e.g., renal cystic disease, bacterial pyelonephritis), or alterations in the medullary concentration gradient (e.g., medullary washout).[70] Acquired NDI also has been identified as the initial presenting complaint that occurred 11 days prior to development of acute kidney failure from leptospirosis.[71]

Congenital NDI is a rare disease that is caused by a deficiency of ADH receptors. Clinical signs, apparent soon after birth, include severe polydipsia and polyuria, and hyposthenuric urine (specific gravity of 1.001-1.005; osmolarity <200 mOsm/kg). The diagnosis is based on failure to concentrate urine after modified water deprivation testing, failure to respond to exogenous ADH, and exclusion of more common causes of NDI.[69,72]

Treatment for acquired NDI should be directed at resolving the underlying cause. Congenital NDI therapy consists of free-choice water consumption, dietary sodium and protein restriction, and/or thiazide diuretics (chlorothiazide, 20-40 mg/kg PO q 12 h; or hydrochlorothiazide, 2 mg/kg PO q 12 h). Dietary sodium and protein restriction reduces the amount of solute presented to the kidney that must be excreted in the urine each day, further reducing obligatory water loss (see ch. 184).[72] The addition of diuretic therapy to dietary restrictions results in mild dehydration, increased fluid and sodium uptake in the proximal tubule, and 20% to 50% reduction of urine output.[72] If medical management is not an option for the client and polyuria can be tolerated, the animal can be maintained on free-choice water consumption alone. Diabetes insipidus is discussed further in ch. 296.

Evidence of Acute Tubular Injury Using Urine Biomarkers

Acute tubular injury (ATI) represents the initial phase of development of structural and functional kidney damage, and precedes development of clinically apparent acute renal failure since serum renal biomarkers are not typically above reference limits (see ch. 322). Initiation of ATI occurs from naturally occurring disease (e.g., toxic insult, renal ischemia, infectious disease) but can also occur secondary to other critical illnesses, secondary to the systemic inflammatory response, or from therapeutic intervention with nephrotoxic agents.[73,74] Early identification of ATI would allow the veterinary practitioner to alter therapy to halt ongoing renal injury, or be useful as a prognostic indicator when counseling clients. Serum biochemical findings, urinalysis, and sediment evaluations have been shown to be relatively insensitive indicators of acute tubular necrosis. The concept of urine biomarkers refers to the presence of biochemical substances in the urine that might provide an indication of tubular cell dysfunction and death.[75,76]

Examples of common urine biomarkers that are currently in use include urine glucose and albumin. Novel biomarkers currently undergoing investigation are in three categories: high molecular weight protein biomarkers from systemic circulation, low molecular weight protein biomarkers from systemic circulation or that are constitutively expressed in various renal cells, and enzyme biomarkers (also see ch. 321).[75,76] Enzyme biomarkers of greatest research interest are large (>80 kD) and are therefore only expressed in the urine from leakage of damaged tubular cells. These biomarkers may prove to have greater clinical utility because enzymes become elevated in urine prior to onset of overt dysfunction, analysis is often easier than for proteins, and the quantity or ratio to creatinine of certain enzymes may be able to predict the degree and severity of injury.[77-81] In the future, panels of biomarkers might be useful to localize the renal site of injury, determine severity, and monitor progression; however, urine biomarkers require further study to determine sensitivity and specificity for particular diseases, and assay standardization, prior to becoming available for clinical use to practicing veterinarians. Table 326-2 provides a summary of urine biomarkers studied for ATI in dogs.

TABLE 326-2

Urine Biomarkers Currently Undergoing Study to Determine Renal Dysfunction in Dogs[75,76]

BIOMARKER	NEPHRON SEGMENT	MECHANISM	COMMENTS

Intermediate/High Molecular Weight Proteins			
Albumin	G, PT	Glomerular leak, decreased reabsorption	Widely available. Not specific for location of injury (glomerular vs. proximal tubular)
Immunoglobulin A/G	G	Glomerular leak	No diagnostic advantage over monitoring urine protein: urine creatinine ratio
Low Molecular Weight Proteins			
Retinol binding protein	PT	Decreased reabsorption	Stable in acidic urine and when frozen Progressive increases with chronic kidney disease Wide intraindividual variation
Alpha-1 microglobulin	PT	Decreased reabsorption	Stable in acidic urine Decreased by hepatic disease
Beta-2 microglobulin	PT	Decreased reabsorption	Good predictor of GFR in dogs Unstable in acidic urine Not sensitive to monitor progression
Tubular Enzymes			
N-acetyl-B-D-glucosaminidase (NAG)	PT, DT	Increased release	Can measure from spot urine sample Affected by other diseases (e.g., hyperthyroidism, diabetes mellitus), pyuria, and long-term storage
Gamma-glutamyl transferase (GGT)	PT	Increased release	Can measure from spot urine sample Unstable in acidic urine Hematuria and pyuria cause assay interference
Alkaline phosphatase (intestinal variant)	PT, DT	Increased release	
Lactate dehydrogenase	PT	Increased release	
Neutrophil gelatinase-associated lipocalin	PT	Increased release	Stable with freeze-thaw cycles Hematuria and pyuria cause assay interference Malignancy, inflammation, and infection may decrease specificity

DT, Distal tubule; *G*, glomerulus; *GFR*, glomerular filtration rate; *PT*, proximal tubule.

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CHAPTER 327

Pyelonephritis

Astrid M. van Dongen

Introduction

Pyelonephritis is an inflammation involving the renal pelvis but also the renal parenchyma. In companion animals, it is usually seen in the context of a complicated urinary tract infection due to bacteria that have ascended from the lower urinary tract (see ch. 330).[1] However, different routes of infection (e.g., hematogenous) can occur, and other infectious agents such as fungi[2-4] and even nematodal renal infestations have been described.[5]

This disease is a common sequel in companion animals with predisposing conditions that compromise systemic immunity, significantly change the urinary composition, or impair the host defense mechanisms of the urinary tract (ranging from abnormalities in voiding, to pre-existing tissue abnormalities in the upper urinary tract). If left untreated, bacterial pyelonephritis will give rise to permanent and progressive damage of the involved kidney, can expand to a retroperitoneal abscess[24] or even could lead to septicemia.

Timely recognition of affected patients can be challenging because the clinical signs and diagnostic findings sometimes are deceptively mild, especially if pyelonephritis is only unilateral. Moreover, associated signs are nonspecific and can easily be overshadowed by those arising from comorbidities. Likewise, the management of these patients is demanding, usually requiring repeat assessments as complications and/or relapses are not uncommon.

Pathophysiology

Ascending infection from the urethra, via the urinary bladder and ureter to the renal pelvis and renal tissue, is considered a much more likely route in companion animals, rather than hematogenous or via the lymphatic system (e.g., in the context of bacterial endocarditis or discospondylitis). Subsequent colonization of the renal pelvis and establishment of bacterial foci in the medullary area of the kidney is not easily accomplished and usually requires additional morbidity (Box 327-1).

Box 327-1

Comorbidities Associated with Bacterial Pyelonephritis

Compromising systemic immunocompetence

- Endocrine
  - Hyperadrenocorticism (spontaneous or iatrogenic)
  - Diabetes mellitus
- Infectious
  - Feline immunodeficiency virus

Impairing local defence mechanisms

- Kidney
  - Renal scarring
  - Renal glucosuria
  - Pyelectesia (due to ureteral obstruction, nephroliths, blood clot, etc.)
- Ureter
  - Ureteral obstruction (urolith, stricture, circumjacent pressure, etc.)
  - Ectopic ureter(s)

- Bladder
  - Vesicoureteral reflux
  - Pre-existing bacterial cystitis (occult bacteruria?)

Bacterial virulence properties

- Survival in urine
- Adherence to uroepithelium
- Ability to reside intracellularly
- Formation of biofilm
- Development of antimicrobial resistance

Predisposing Factors (see Box 327-1)

Bacterial pyelonephritis is cited as a complication in patients with a systemic disease hampering their immune system, such as hyperadrenocorticism in dogs[6] or cats with feline immunodeficiency virus infection.[11] Glucosuria, either of renal origin[12] or because of diabetes mellitus[7,13] also is associated with complicated urinary tract infections. Structural changes of the kidneys,[10] accumulation of material (e.g., a blood clot or nephrolith)[8] in the renal pelvis, and pyelectasis due to ureteral obstruction, will make it easier for uropathogens to colonize the upper urinary tract. Similarly, anatomical disorders like ectopic ureters[9] or functional abnormalities as occur in vesicoureteral reflux (VUR)[14] can facilitate the further ascension of urinary tract infection. For a more detailed discussion of these comorbidities the reader is referred to chapters concerning hyperadrenocorticism (see ch. 306 and 307), diabetes mellitus (see ch. 304 and 305), chronic kidney disease (see ch. 324), urolithiasis (see ch. 331 and 332), lower urinary tract infections (see ch. 330), and disorders of micturition (see ch. 333).

Apart from these host-related factors, bacterial characteristics regarding their capacity to persist in the urine, adhere to the uroepithelium, relocate intracellularly, form a biofilm, and develop antimicrobial resistance[19] will also impact their virulence.

Sequelae

Whether or not preexisting chronic kidney disease was present, additional kidney injury is likely to occur as a consequence of pyelonephritis. Depending on the magnitude, this injury can result in additional clinical signs (e.g., polyuria/polydipsia) and metabolic changes that are more severe.

At initial diagnosis, it can be challenging or impossible to determine the proportion of azotemia that is due to acute kidney injury as opposed to preexisting chronic kidney disease (commonly referred to as acute-on-chronic kidney disease). Nevertheless, during patient management, it is important to consider and address both the chronic kidney disease and the acute kidney injury, if one exists, because remarkable clinical and biochemical improvement can still occur in one to three months following successful treatment of an acute process like pyelonephritis.

Diagnosis (Box 327-2)

Environmental factors should be considered, as these can impact exposure to pathogens. Geographical differences exist with regards to occurrence of fungal and nematodal infections, but also can be applied on a more local level, like exposure to (possibly multiresistant) uropathogens in a hospital setting.[29]

Box 327-2

Checklist for Patients Suspected of Having Pyelonephritis

Geographic differences/regional prevalences

Signalment (species, breed, sex, age-associated predispositions to comorbidities)

History

- Risk factors (travel, diet, case and family histories, medication)
- Clinical signs involving the urinary system (dysuria, polyuria, polydipsia, abnormal urine)

- Clinical signs of systemic illness (fever, vomiting)

Physical examination

- Depending on comorbidities
- Abdominal palpation (especially kidneys and adjacent area)

Urinalysis

- Specific gravity
- Dipstick (glucose, ketones)
- Microscopic examination of sediment
  - Crystals, casts, cells (epithelial, erythrocytes, leukocytes)
  - Infectious agents (bacteria, yeast, fungi, ova)
- Microbiological examination (culture and sensitivity)

Complete blood count (hematocrit, leukocyte count and differential)

Serum biochemistry profile (azotemia, electrolytes, others based on comorbidities)

Diagnostic imaging

- Abdominal ultrasound
  - Kidneys, ureters, bladder
  - Pyelocentesis
- Contrast radiography (less commonly performed when high-resolution ultrasound with skilled sonographer is available)

Others based on comorbidities

Signalment

Differences between species can be considered because urinary tract infections are reported more commonly in dogs than cats. However, for pyelonephritis, there will likely be a bigger impact from sex, age, and breed predispositions for the various comorbidities as discussed under pathophysiology, above.

History and Chief Complaint

The medical history concerning a patient with possible pyelonephritis should include questions to assess risk factors through travel, diet, previous illnesses, medication, and suggestive family histories.

Owner-observed signs associated with pyelonephritis can range from abnormal body posture suggestive of abdominal pain, and various changes in micturition including dysuria, polyuria/polydipsia, and/or macroscopically abnormal urine. These are more suggestive of pyelonephritis if they coincide with generalized signs of malaise, vomiting, and/or recurrent febrile episodes. However, none of these is specific to pyelonephritis, which even can remain subclinical.

Physical Findings

For the reasons described above, the focus of the physical exam needs to include systems and possible abnormalities associated with suspected comorbidities (see Box 327-1). In all cases, thorough and careful abdominal palpation is indicated. In cats, the kidneys are only loosely attached to the dorsal abdominal wall, allowing for adequate assessment even if the cat is hunching. Palpating both kidneys in dogs often is difficult, but an assessment still can be made by judging the response to palpation in the renal and perirenal regions. Repeatable evidence of discomfort could be indicative of renal pain and adds to justification for diagnostic imaging.

Laboratory Tests

Urinalysis (see ch. 72) not only is instrumental in the diagnosis of pyelonephritis, but it will also provide valuable information on possible comorbidities. In turn, this determines the need for additional diagnostic tests and is an important element for guiding the treatment plan. Sampling method, sample volume, and macroscopic evaluation should be noted, and will help with interpretation of final result. A routine urine examination[15] generally includes refractometer determination of specific gravity and dipstick analysis for presence of at least glucose (combined with ketones) in view of predisposing factors.

Microscopic examination will help distinguish hematuria from hemo- (myo-) globinuria and could hold clues to help with localization (casts, different epithelial cells) and underlying disease (e.g., crystals, infection). Examination of stained, air-dried sediment[16] can allow identification of white blood cells and potential causal agents (ranging from bacteria, yeasts, and fungal components to parasite ova). The magnitude of presumed renal proteinuria, which is measured by means of a urinary protein-to-creatinine ratio, is best assessed after urinary tract inflammation is addressed.[17]

When signalment and history could be indicative of hyperadrenocorticism, a home-collected voided urine sample for assessing urinary corticoid-to-creatinine ratio may be worthwhile to consider (see ch. 306).[18]

Although a definitive diagnosis of bacterial pyelonephritis can only be established if indeed a positive culture of a pyelocentesis sample is found, a cystocentesis urine sample in the context of suggestive history, physical examination and/or imaging generally is accepted. Preferably, a quantitative aerobic bacterial culture and sensitivity is performed, but more cost-effective options such as urine dipstick paddle systems can be considered.[20]

Complete Blood Count

Assessing the hematocrit has no diagnostic value for pyelonephritis itself, but it can have an impact on patient management in view of suspected comorbidities, or when findings during physical examination were suggestive of either anemia or erythrocytosis.[22] Similarly, patients with pyelonephritis can display abnormal white blood cell counts ranging from leukopenia to (predominantly neutrophilic) leukocytosis. If characterized by a left shift, leukocytosis also can be indicative of secondary bacteremia.

Serum Biochemistry Profile

Whether cause or consequence, abnormal renal function is a common feature of pyelonephritis reflected not only in urinary abnormalities but also through serum electrolyte disturbances and possible development of azotemia if both kidneys are involved. For those patients that show other comorbidities, a much wider range of parameters can become of interest; for example, in cases with glucosuria, plasma glucose levels will also be of interest.

Diagnostic Imaging

Abdominal ultrasound offers a convenient modus to assess renal morphology, including corticomedullary distinction and renal pelvic diameter (Figure 327-1).[23] It also can provide guidance for percutaneous pyelocentesis and, depending on the ureteral diameter, operator experience, and patient cooperation, even can allow visualization of the ureter downstream, identification of an obstruction, and/or assessment of the location of its inflow in the bladder.

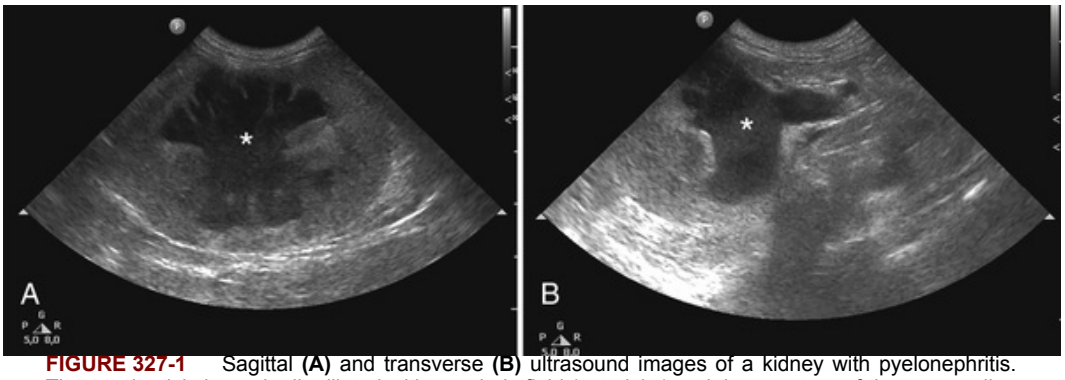

FIGURE 327-1 Sagittal **(A)** and transverse **(B)** ultrasound images of a kidney with pyelonephritis. The renal pelvis is markedly dilated with anechoic fluid (asterisks) and the structure of the surrounding renal parenchyma is distorted.

Survey radiographs provide limited information but can indicate the location of the kidneys, the location of adjacent structures, and the presence of material with abnormal radiopacity (e.g., calcifications) in the renal region and/or lower parts of the urinary tract.

With the aid of contrast fluid (administered antegrade or retrograde), radiographic imaging of the urinary

system can be greatly enhanced to identify anatomical (ectopic ureters) and functional disorders such as vesicoureteral reflux.

Computed tomography and magnetic resonance imaging can enhance specific features of the urinary tract, thus providing additional value in cases where doubt remains on the nature or degree of extension of the disease process, but such modalities generally are not needed to achieve a diagnosis of pyelonephritis.

Although renal tissue biopsies can facilitate the diagnosis of diffuse renal disease, it is far less likely that they can adequately identify very localized infiltrates that predominantly are present in the medulla. This limitation, added to the increased risks involved with biopsy of contaminated tissue, means that it is not recommended to obtain a core or wedge renal biopsy sample in cases with any urinary tract infection, including active bacterial pyelonephritis.

Patient Management (Box 327-3)

The treatment plan should be customized according to the patient's findings because pyelonephritis seldom is an isolated entity and inaccurate or incomplete treatment can give rise to serious or even life-threatening complications (from poorly addressed comorbidities, uncontrolled pyelonephritis, or both).

Box 327-3

Management of Patients with Bacterial Pyelonephritis

Stabilize if needed (fluid and electrolyte support, IV antibiotic)

Eliminate or reduce predisposing factors/comorbidities

Initiate antibiotic treatment, preferably based on culture and sensitivity (treatment duration: 3-4 weeks or longer)

Follow-up

- Check for clinical improvement (first week)?
- Check urinalysis before end of treatment
- Revaluate urinalysis for relapse of reinfection
  - 1 to 2 weeks after cessation of antibiotics
  - When clinical signs appear

Assess and monitor renal function (and other comorbidities)

The highest priority should be given to respiratory and hemodynamic stabilization if findings are indicative of severe systemic illness. This will usually require hospitalization, and combining IV fluids and electrolyte support with parenteral antibiotics. With severely ill pyelonephritis patients, antibiotic selection initially is empirical (e.g., ampicillin 20 mg/kg IV q 8 h), and is based on locally applicable antimicrobial susceptibility patterns[28] and regulations (e.g., banning use of last-resort antibiotics like fluoroquinolones and third-generation cephalosporins if not underpinned by culture and sensitivity results).

To the extent it is possible, measures to attempt eradication or at least reduction of treatable predisposing factors should be undertaken (e.g., initiation of treatment for diabetes mellitus, or initiation of measures to normalize micturition [see ch. 333]).

In patients that are more stable, it is appropriate to consider awaiting *in vitro* bacterial sensitivity results before determining which antibiotic is going to be used, or at least re-evaluating previous treatment choices and their results. This approach can both improve outcome compared to empirically chosen antibiotics, and (ideally) also contribute to halting the rise in antibiotic resistance.[21] Apart from *in vitro* sensitivity, it is worthwhile to also consider an antibiotic's capacity to penetrate into the renal tissue. Costs and potential for side-effects also should be weighed, as a prolonged treatment duration of at least 3-4 weeks or even longer routinely is appropriate in animals with complicated urinary tract infections. However, the evidence supporting these lengthy time frames is very limited and currently under scrutiny in view of the rise in antibiotic resistance patterns and occurrence.[25]

A reported alternative treatment option is ultrasound-guided percutaneous drainage with lavage,[26] where repetitive localized treatment with antiseptic solution successfully eliminated the infection in the renal pelvis. Unilateral nephrectomy[27] as treatment for pyelonephritis should be viewed as a last resort when, despite

appropriate antimicrobial treatment, relapses occur and a bacterial niche (e.g., nephrolith) in the kidney is likely. It is vital to try to ensure beforehand that the remaining kidney will have adequate function. Persistent azotemia therefore could be viewed as a contraindication because it implies that both kidneys are debilitated. In non-azotemic animals, other findings (e.g., urinalysis, renal ultrasound findings) can be helpful, but ideally renal scintigraphy should be considered for separating left from right renal function before considering nephrectomy.

Additional measures to address chronic kidney disease should be prioritized at this stage (see ch. 324); even when the patient is assumed to be clinically stable, he/she should be closely monitored to ensure adequate intake of fluid and food. If there is doubt, it is better to postpone any dietary changes that could influence this adversely, until appetite has improved satisfactorily.

Established treatment plans for pyelonephritis patients that already had preexisting chronic kidney disease could require several (temporary) adjustments until stabilization and stage are reconfirmed on follow-up, because control or elimination of pyelonephritis can play a minor to major role in disease progression depending on the severity of the condition and response to treatment.

Follow-Up

Apart from any underlying diseases, patients with pyelonephritis should be considered chronic unless proven otherwise, meaning they should have at least one, and preferably two, follow-up appointments.

Routine telephone follow-up is an easy way to ensure clinical improvement, which should be noticeable to the owner within a week if treatment is effective. This contact also can yield further substantiation for an actual follow-up visit or at least submitting a urine sample for recheck. Urinalysis to exclude persistent urinary tract infection is performed preferably before the end of treatment, and could be the best way to ensure the duration of treatment is indeed acceptable for that case. Ideally, urinalysis is also repeated after 1-2 weeks without antibiotics and at any time thereafter when clinical signs present themselves.

Microbial examination of the urine will allow for differentiation between relapse (same microorganism is present) or reinfection (different organism is present). A relapse is more indicative of a niche somewhere in the urogenital tract that allows that organism to persist and remerge even after an appropriate antibiotic, and this information has clinical importance in terms of eliminating the inciting cause.

Reinfection usually occurs in immunocompromised animals (systemic or locally in the urinary tract), and likewise, this information can focus the diagnostic and treatment plan more specifically.

Especially for those patients that were azotemic at, or before, the time of diagnosis, it is worthwhile to reassess the patient more fully by means of physical examination (including blood pressure measurement), urinalysis (preferably including urine protein-to-creatinine ratio), a complete serum biochemistry profile, and complete blood count.

An improvement in kidney function frequently occurs after treatment of an acute kidney injury like pyelonephritis. Performing rechecks at two time points after successful treatment of pyelonephritis allows the clinician to identify the presence and magnitude of such an improvement, and also determine the degree of residual function loss (i.e., staging chronic kidney disease once infection is controlled).

Frequency and extent of additional monitoring are highly dependent on the clinical picture, and should be executed more promptly in cases showing an acute exacerbation but can easily stretch to periods of one to three months in stable animals.[30] As chronic kidney disease is considered to be both at the origin of many cases of pyelonephritis, as well as a sequel to it, expanding routine urinalysis and culture with a urinary protein-to-creatinine ratio is recommended, as is monitoring the blood pressure, complete blood count, and serum biochemistry profiles as clinically indicated.[30]

Prognosis

The prognosis is highly dependent on efficacy of treatment, remaining issues that could lead to relapse/reinfection, and amount of damage that was inflicted on the renal tissue. Chronic kidney disease is considered to be both at the origin of, as well as a sequel to, pyelonephritis, but it does not necessarily carry a poor prognosis, as morbidity is quite variable and linked to the stage of disease. Patients with the earlier stage who respond well to antibacterial treatment can remain stable for extended periods of time with an excellent quality of life.

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CHAPTER 328

Familial and Congenital Renal Diseases of Cats and Dogs

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Client Information Sheet: Familial and Congenital Renal Diseases of Cats and Dogs

Introduction

Congenital diseases may result from either a genetic disorder or abnormal organ development during gestation; namely, congenital disorders are not necessarily inherited. Familial diseases are present in a relatively high prevalence in specific breeds, develop relatively early in life, and are assumed to have an inherited basis; however the latter assumption has yet to be proven. In both congenital and familial diseases, clinical signs may be present at birth or become apparent during various stages in life (i.e., a late onset). Due to their potential late onset, congenital and familial diseases should be suspected in animals that have signs of chronic kidney disease (CKD) at a relatively young age (e.g., <5 years). Congenital and familial diseases are more prevalent in dogs compared to cats and might affect different locations within the nephron (i.e., glomerulus, tubuli, interstitium). These diseases are often progressive in nature and ultimately become fatal; however, the progression rate is highly variable.

Developmental Diseases

Definitions

Renal Agenesis, Hypoplastic Kidneys

Renal agenesis is a complete absence of one or both kidneys. Bilateral agenesis has been reported, but results in death. Renal agenesis is often associated with other congenital urogenital abnormalities, such as ureteral agenesis. The etiology is unknown, but familial predisposition has been suggested in few breeds including Beagles, Doberman Pinchers and Shetland Sheepdogs.[1-3] Unilateral renal agenesis is a clinically silent condition, provided that the contralateral kidney function is normal. Hypoplastic kidneys are small, and have a reduced number of functioning nephrons. The condition is often congenital and should be differentiated from renal atrophy, which might be secondary to other congenital disorders.[4] Clinical signs and prognosis depend on the degree of hypoplasia and the overall kidney function.

Renal Dysplasia

Renal dysplasia represents a group of developmental anomalies, and is defined as an abnormal differentiation of the renal parenchyma.[5] Grossly, the kidneys are indistinguishable from those with advanced acquired CKD. Histopathologically, the most consistent finding is inappropriate differentiation (compared to the development of the host) of various nephron components. For example, one may observe immature (fetal) nephrons alongside normal nephrons. The functioning nephrons undergo compensatory hypertrophy. Fetal glomeruli and tubules are often present in radial segments, extending from the surface of the kidney to the corticomedullary junction. Additional histologic findings include persistent immature mesenchyme, persistent metanephric ducts, atypical tubular epithelial proliferation, and dysontogenic metaplasia. Secondary changes may also be present and include interstitial nephritis, fibrosis, mineralization, cystic glomerular atrophy, cortical and medullary cysts, and glomerular lipidosis. Proper assessment is often hampered by the more dominant secondary changes. Renal dysplasia has been suspected in multiple breeds. In some breeds, the disease has been extensively characterized but in other breeds, it may be limited to a

single case report or case series (Table 328-1).[5-13] Reports of congenital nephropathy in several breeds (e.g., Great Dane, Yorkshire Terrier, Keeshond) likely represented renal dysplasia.

TABLE 328-1

Congenital and Familial Kidney Diseases of Dogs and Cats

DISORDER	AFFECTED BREEDS	COMMENTS
Renal Dysplasia		
	Lhasa Apso, Shih Tzu, SCWT, CKCS, Bulldog, Standard Poodle, Bull Mastiff, Cairn Terrier, Alaskan Malamute, Golden Retriever, Chow Chow, Cocker Spaniel, Dutch Kooiker, Boxer, Finnish Harrier, Norwegian Elkhound, Miniature Schnauzer	In some breeds (e.g., Lhasa Apso, Shih Tzu) the disease is well characterized and the criteria are fully met, while in others the disease is poorly characterized, based on a single case report/series. Other breeds are likely affected.
Glomerulopathies		
Amyloidosis	Dogs: Chinese Shar-Pei, English Foxhound, Beagle Cats: Abyssinian	Possible autosomal recessive in Chinese Shar-Pei.23
Hereditary nephritis	English Cocker Spaniel, Samoyed, Dalmatian, Bull Terrier	
Podocytopathy	SCWT, Airedale Terriers	
MPGN	Bernese Mountain dog59	Deposition of immune complexes. suggested autosomal recessive inheritance.
	Brittany Spaniel60,61	Congenital deficiency of the third component of complement (C3).
Atrophic glomerulopathy	Rottweiler62	Diffuse global, atrophic membranous glomerulopathy with secondary degenerative changes. Both genders are affected and azotemia develops in the first year of life.
Other glomerulopathies	Pembroke Welsh Corgi,63 Doberman Pinscher,64 Soft Coated Wheaten Terrier, Bullmastiff,65 Newfoundland66	
Polycystic Kidney Disease		
	Dogs: Bull Terrier, Cairn Terrier, WHWT	
	Cats: Persian, Himalayan, British Blue	May be present in any cat crossbred with Persian cats.
Tubular Defects		
Primary glucosuria	Norwegian Elkhound67	
Cystinuria	Described in multiple dog breeds68,69 and in cats.70 Common dog breeds include English Bulldog, Newfoundland,71,72 Dachshund, Basset Hound, Rottweiler.73	Inherited proximal tubular defect. Classified as type 1 (autosomal recessive) and non–type 1 (autosomal dominant with incomplete penetrance). Predisposes to cystine uroliths (see ch. 331).
Hyperuricosuria	Dalmatian,68 English Bulldog, Black Russian Terrier	Membrane transport defect (autosomal recessive). Dalmatian dogs also present decreased proximal tubular resorption and active distal tubular secretion of urates.
Hyperxanthinuria	A congenital disorder reported in the Cavalier King Charles Spaniel74 and in the Wirehaired Dachshund75	
Fanconi syndrome	Basenjis55-57	

Congenital NDI	Various breeds[76]	Deficiency of antidiuretic hormone receptor in the distal nephron and collecting ducts. Affected animals present with profound polyuria and polydipsia.
Miscellaneous		
Telangiectasia	Pembroke Welsh Corgi[77]	Periodic gross hematuria typically at 2 to 8 years of age.
Reflux nephropathy with segmental hypoplasia	Boxer[78,79]	Atrophic, non-obstructive pyelonephritis due to vesico-ureteral reflux causing renal hypoplasia.
Cystadenocarcinoma	German Shepherd dogs[80]	An autosomal dominant trait. A mutation in the BHD gene has been suspected.[81] The disease has a late onset. May be associated with concurrent nodular dermatofibrosis and uterine leiomyomas.

CKCS, Cavalier King Charles Spaniel; *MPGN*, membranoproliferative glomerulonephritis; *SCWT*, Soft Coated Wheaten Terrier; *WHWT*, West Highland White Terrier.

Clinical Evaluation

Clinical and clinicopathologic findings in dogs with renal dysplasia are consistent with acquired CKD. However, some dogs with renal dysplasia have profound polyuria and polydipsia (PU/PD), perhaps due to concurrent nephrogenic diabetes insipidus (see ch. 45 and 296).[9] Ultrasonographic (US) changes are highly variable, depend on severity of disease, and are not necessarily symmetrical. These include decreased corticomedullary definition and presence of multifocal hyperechoic speckles within the renal medulla, along with generalized medullary hyperechogenicity.[14] Final diagnosis is established histologically by evaluating a large number of glomeruli, often necessitating a surgical wedge biopsy.[15]

Staging and Treatment Guidelines

Staging and treatment guidelines for dogs and cats with developmental kidney disease are similar to those recommended for acquired CKD (see ch. 324) with few modifications. Dietary protein must be closely assessed in growing animals. Animals with congenital CKD are often resilient to azotemia and may present few clinical signs even with advanced disease. However, complete staging and appropriate management should not be delayed, as one of the main therapeutic targets is to slow the disease progression rate.

Glomerular Diseases

Overview

Several familial and congenital glomerular diseases have been documented in a few breeds (see Table 328-1). The most common are hereditary nephritis and amyloidosis. Clinical signs of affected animals may be related to protein losing nephropathy (PLN) *per se*, or to azotemia (see ch. 62, 72, 324, and 325). The nephrotic syndrome (i.e., proteinuria, hypoalbuminemia, hypercholesterolemia, and edema/ascites) has been documented in a subset of dogs. Systemic hypertension (see ch. 157) and thromboembolism (see ch. 243 and 256) are also potential complications. The hallmark of glomerular disease is proteinuria; therefore, early detection requires urinalysis (see ch. 72), in the absence of genetic testing (see ch. 3 and 4).

Amyloidosis

Definitions

Amyloidosis is a heterogeneous group of diseases characterized by extracellular deposition of insoluble, fibrillary proteins with a specific beta-pleated sheet conformation.[16] Hereditary amyloidosis is caused by mutant genes encoding variant proteins whose structure makes them amyloidogenic.[17] Amyloid proteins may originate from multiple precursors and their formation may be primary or secondary (reactive).

Secondary amyloidosis is the most common form in dogs and cats.[18] Despite their diverse origins, all amyloid proteins possess similar structural, physical and chemical properties including formation of X-ray diffraction patterns characteristic of beta-sheet aggregates, uniform fibril morphology and fibril formation patterns, and specific staining with Congo-red and thioflavin T.[19] In dogs and cats, renal amyloidosis fibrils are composed of an N-terminal fragment of the acute phase protein, serum amyloid A (see ch. 325).

Familial Amyloidosis

Amyloidosis has been described in Chinese Shar-Peis (CSPs), Beagles, English Foxhounds, and in Abyssinian cats.[20-22] Amyloidosis is mostly reactive, and is relatively well characterized in CSPs.[23] Familial Shar-Pei fever, characterized by recurrent episodes of fever with concurrent swollen hocks (see ch. 203), likely predisposes to systemic reactive amyloidosis, similar to human Familial Mediterranean Fever.[24,25] Deposits are composed of the amino-terminal acute phase protein amyloid A, produced during inflammation as part of the acute phase response. The kidney is the most frequent and often the sole site of amyloid deposition. There are notable differences between amyloidosis in CSPs and other dog breeds. First, in CSPs (as in Abyssinian cats), renal medullar lesions predominate, although when advanced, renal amyloid deposition involves all parts of the nephron.[26,27] In CSPs, amyloid deposition is commonly noted in extra-renal organs: spleen, liver, adrenal glands, pancreas, gastric and intestinal submucosa, myocardium, thyroid, prostate and lymph nodes.[16,27,28]

The disease has a late clinical onset. Most dogs and cats are presented for medical care when in middle age; however, diagnosis is made in a very wide range of ages.[28] Most CSPs have severe azotemia and are not brought for veterinary care due to clinical signs associated with PLN. The nephrotic syndrome is uncommon in CSP because their amyloid deposition is predominantly medullary, which causes interstitial prior to glomerular damage.[28] Consequently, compared to other breeds, the degree of proteinuria in CSPs is lower and the degree of azotemia higher. Histology is required to confirm a diagnosis. The prognosis is poor, however survival times vary substantially, depending on the disease stage and the degree of azotemia.[28] This emphasizes the need for early diagnosis.

Hereditary Nephritis

Definitions

Hereditary nephritis, one of the most thoroughly characterized congenital kidney diseases, originates from a genetic mutation which causes abnormal formation of type IV collagen. Normally, glomerular capillary basement membranes are composed of a collagen heteromer network containing alpha-3-alpha-4-alpha-5 chains. A mutation in one of the encoding genes (COL4A3, COL4A4, COL4A5) results in improperly formed chains unable to interact with other chains to form the alpha-3-alpha-4-alpha-5 heteromers.

Mutations Demonstrated

Various mutations and modes of inheritance have been described, including X-linked, autosomal recessive, and autosomal dominant. X-linked hereditary nephritis was first reported in the Samoyed, with a single nucleotide substitution in the COL4A5 gene as the mutation origin, causing abnormal alpha-5 chains and abnormal assembly of type IV collagen. This results in splitting of the basement membrane, which can be detected via electron microscopy early in life. Proteinuria is the first diagnostic indicator of the disease and, in male dogs, can be detected at as early as 3 months of age. Azotemia in males develops and progresses over few months until death at approximately 1 year of age.[29] Carrier females develop mosaic expression of the alpha3-alpha4-alpha5 chains. As in males, their proteinuria can be detected early in life; however, azotemia progresses at a much slower rate and is apparent only after a few years of age.[30]

In English Cocker Spaniels, the disease is autosomal recessive and originates from a single nucleotide substitution in the COL4A4 gene. Due to this mode of inheritance, males and females are affected equally. Proteinuria is detected at as early as a few months of age, and azotemia progresses over the first and second years of life.[31,32] An autosomal dominant mutation has been described in Bull Terrier and Dalmatian dogs, mostly from Australia.[33-35] The underlying genetic mutation has not been fully characterized, but all affected dogs have proteinuria. The clinical presentation is highly variable and azotemia develops over a wide range of time spans, to become apparent by several months or as late as 7-8 years of age.[34,36] Consequently, dogs with subclinical disease may be bred and the disease is difficult to eradicate.

Diagnosis

Diagnosis of hereditary nephritis is based on kidney biopsy. In X-linked hereditary nephritis, light microscopy reveals morphologic features of membranoproliferative glomerulonephropathy. In the X-linked and autosomal recessive disorders, immunostaining of the glomerular basement membrane demonstrates the abnormal pattern of the type IV collagen, but in the Bull Terriers and Dalmatians, immunostaining shows a normal pattern of type IV collagen, and the diagnosis can only be made based on electron microscopic examination. For some of the hereditary nephritis disease types, genetic testing is available.[37]

Podocytopathy and Glomerulosclerosis

Protein-losing nephropathy is diagnosed in 10-15% of Soft Coated Wheaten Terriers, with a complex mode of inheritance.[38,39] Histology of kidney biopsies reveals glomerulonephritis, glomerulosclerosis and evidence of podocyte degeneration and loss. The disease has a late onset, with a mean age of 6 years.[39] Therefore, affected dogs are often bred before identified as affected. Clinical signs usually involve the intestinal tract as well as PLN. There is no biologic marker available for early identification; however, sequencing candidate genes in two Airedale Terriers revealed single nucleotide changes in the closely linked *NPHS1* and *KIRREL2* genes, which encode the slit diaphragm proteins nephrin and Neph3/filtrin, respectively.[39,40]

Polycystic Kidney Disease

Definitions and Breeds Affected

Canine

Polycystic kidney disease (PKD) has been reported in both dogs and cats. Affected dog breeds include the Bull Terrier, Cairn Terrier, and West Highland White Terrier (WHWT). A genetic mutation in the polycystin-1 (PKD1) gene[41,42] with an autosomal dominant mode of inheritance has been suggested in the Bull Terrier.[43] An autosomal recessive mode of inheritance was suggested in the Cairn Terrier and the WHWT.[44,45] Bull Terrier dogs have decreased kidney function in the first years of life, with cysts limited to the kidneys. Cairn Terriers and WHWT dogs develop clinical signs in the first months of life, with multiple cysts in both the kidneys and the liver.

Feline

PKD is the most common genetic feline disease affecting Persian cats and outcrossed breeds and is characterized by renal, hepatic and occasional pancreatic cysts. The reported prevalence in Persian cats is approximately 40%, worldwide.[46,47] The mode of inheritance is an autosomal dominant defect that originates from a single nucleotide mutation (C to A transversion) in Exon 29 of the *PKD1* gene, resulting in a premature stop codon.[48,49] No homozygous cats have been identified, supporting the suggestion that the mutation is embryonic lethal.[49] PKD has also been described in cats lacking the *PKD1* mutation and, therefore, other mutations may trigger PKD in cats.[50] Renal cysts grow slowly, resulting in a gradual decrease in the amount of the normal renal parenchyma.

Signs and Diagnosis

Clinical signs are consistent with CKD (see ch. 324). The kidneys are usually enlarged and irregular on physical examination. Early detection can be made using genetic testing tools (in cats)[51,52] and ultrasonography,[53] which demonstrates numerous cortical and medullar round or oval hypoechoic to anechoic cysts at as early as 7 weeks of age.[54] In both dogs and cats, their absence at 6 months of age is correlated with the absence of PKD.[48]

Tubular Disorders

Prevalence, Definitions

Tubular defects are uncommon in dogs and cats. Tubular disorders have been reported as an isolated condition or they may accompany other hereditary or familial renal disorders (see Table 328-1). Tubular

disorders include primary glucosuria, aminoaciduria (e.g., cystinuria), electrolyte disorders, acid base disorders (i.e., proximal and distal renal tubular acidosis), and water metabolism disorders (i.e., nephrogenic diabetes insipidus).

Fanconi Syndrome

Fanconi syndrome is a complex familial disorder in Basenji dogs, with a prevalence of at least 10% and an uncertain mode of inheritance (see ch. 326).[55-57] Renal tubular handling of glucose, phosphate, sodium, potassium, uric acid, amino acids, and bicarbonate may be impaired. On urinalysis, glucosuria, proteinuria (usually mild), and low urine specific gravity are often present. In dogs with advanced disease, azotemia, hypokalemia and variable degrees of hyperchloremic metabolic acidosis are often present. Clinical signs include polyuria and polydipsia, weight loss, and weakness. Most affected dogs are diagnosed between 4 to 8 years of age. The disease progression rate is highly variable with some dogs having normal life span.[58]

Miscellaneous Conditions

There are multiple other renal disorders that have been suggested to have genetic basis. Some of these are limited to a very small number of animals, are poorly characterized, and the genetic underlying cause is not yet determined (see Table 328-1).

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SECTION XXIV

Diseases of the Lower Urinary Tract

OUTLINE

Chapter 329 Ureteral Disorders
Chapter 330 Lower Urinary Tract Infections
Chapter 331 Lower Urinary Tract Urolithiasis in Dogs
Chapter 332 Lower Urinary Tract Urolithiasis—Feline
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CHAPTER 329

Ureteral Disorders

Larry G. Adams

Client Information Sheets:
Ectopic Ureters: Laser Correction
Ureteral Stones (Ureterolithiasis)

Anatomy and Physiology of the Ureters

The ureters are fibromuscular tubes that carry urine from the renal pelvis to the bladder via a retroperitoneal course. The ureteral wall is composed of an outer adventitial layer, a muscular layer, submucosa, and a mucosa of transitional epithelium. The muscular wall of the ureter consists of an outer longitudinal, middle circular, and inner longitudinal muscle layer except at the ureterovesicular junction (UVJ), where only longitudinal fibers are present. The maximum ureteral luminal diameter in the dog is normally less than 2.7 mm even with fluid diuresis.[1,2] The normal ureteral luminal diameter in cats is only 0.3 to 0.4 mm; therefore, even small ureteroliths or cellular debris may occlude the ureter in cats. The ureters enter the urinary bladder on the serosal surface and tunnel though the bladder wall obliquely to the mucosal surface. The oblique path of the intramural ureter results in a valve-like effect termed the vesicoureteral valve. The vesicoureteral valve, along with ureteral peristalsis and a compliant bladder, promotes unidirectional flow of urine to aid in prevention of ascending infection or urine reflux to the kidneys (vesicoureteral reflux). The intramural ureter has a j-hook conformation terminally turning from a caudal to a cranial direction before entering the bladder at the trigone. The degree of curvature of the distal ureter at the trigone depends on the degree of bladder distension with greater distention of the urinary bladder resulting in greater degree of curvature of the distal ureter. Recognition of this curvature is important for interpretation of excretory urography studies and for retrograde access to the ureters during cystoscopy (see ch. 108). Attempts to pass a urologic guidewire and ureteral catheter retrograde up the ureter via cystoscopy are impaired when the urinary bladder is overdistended.

Innervation to the ureter includes both sympathetic and parasympathetic nerves; however, the sympathetic innervation appears to be most important for neurogenically mediated ureteral contraction.[3,4] Studies have shown the presence of alpha-1, alpha-2, and beta-adrenoceptors and muscarinic cholinergic receptors in the canine ureter.[4,5] Similar studies are lacking in cats. The density of alpha-1 receptors binding sites is significantly greater than that of the other receptor types in dogs. However, ureteral innervation is not responsible for normal ureteral peristalsis, which is myogenic in origin. Ureteral peristalsis occurs when urine enters the ureter, initiating electrical impulses to be conducted between smooth muscle cells. Normally peristaltic activity is initiated in the renal pelvis and urine is propelled toward the bladder. Because normal ureteral peristalsis is myogenic in origin, ureteral peristalsis persists with transplantation. During obstruction of the ureter, spasmodic contractions occur that are mediated via sympathetic input and normal peristaltic activity is inhibited. Stimulation of the ureter with alpha-adrenergic agonists causes ureteral contraction and stimulation with beta-adrenoreceptor agonists causes ureteral relaxation.[3-5] Furthermore, alpha-1 adrenergic antagonists inhibit basal ureteral tone, peristaltic frequency and ureteral contractions.[6] Understanding of innervation of the ureter may contribute to selection of medications for management of ureteral diseases. For example, drug therapy to facilitate relaxation of the ureter for expulsion of ureteroliths might include alpha-adrenergic antagonists or selective beta-2/beta-3 agonists to relax the ureters and reduce ureteral spasm.[4,7,8]

Diagnostic Approach to Diseases of the Ureters

The reader is referred to ch. 321 for an overview of the diagnostic approach to renal disease. For dogs and cats suspected of having ureteral disease, the diagnostic evaluation should include history, physical examination, complete blood count, serum biochemistry profile, urinalysis, urine culture, and abdominal radiographs. Abdominal radiographs should include the entire urinary tract from the diaphragm to the caudal-most portion of the urethra. Abdominal ultrasonographic examination of the urogenital tract is a useful complement to abdominal radiographs when available to the practitioner.

Abdominal ultrasound examination of the urogenital tract (combined with abdominal radiographs and urethrocystoscopy) has largely replaced excretory urography for evaluation of the ureters. Contrast CT scans are also useful for evaluating ureteral disorders such as delineating the extent and location of ureteral strictures, ureteroliths, ureteral neoplasia, or extramural compressive lesions that obstruct the ureter. If ureteral obstruction is highly suspected on the basis of abdominal radiographs and ultrasound, then antegrade pyelography may be performed during interventional procedures such as placement of ureteral stent or subcutaneous ureteral bypass (see ch. 124), often eliminating the need for CT scan or other contrast studies such as excretory urography.[9]

Ureteroliths

Diagnosis of Ureteroliths

Ureteroliths result from migration of nephroliths or nephrolith fragments into the ureter. Similar to uroliths in other portions of the urinary tract, ureteroliths are diagnosed on the basis of results from radiography or ultrasonography. Radiopaque ureteroliths are often visualized in the retroperitoneal region on abdominal radiographs (Figure 329-1), but should be confirmed by other imaging modalities prior to any type of intervention. Some ureteroliths are radiolucent and some radiopaque ureteroliths are too small to be detected on abdominal radiographs. Ultrasonography is often useful for detection of ureteroliths or for detection of renal pelvic or ureteral dilation proximal to obstructive ureteroliths (Figure 329-2).[10,11] Direct visualization of the ureteroliths is often possible with ultrasonography (see Figure 329-2); however, in one study, ultrasonographic confirmation was not possible in 23% of cats with ureteroliths.[11] Although comparable information has not been published for dogs with ureteroliths, results are likely similar to results in cats. Ultrasound-guided nephropyelocentesis for antegrade pyelography via injection of contrast media into the renal pelvis is a minimally invasive option for documenting ureteral obstruction; however, the technique requires that the renal pelvis be sufficiently dilated to permit accurate needle puncture of the pelvis.[12] During nephropyelocentesis, urine is aspirated from the renal pelvis, and then iodinated contrast medium is injected into the pelvis in a volume approximately equal to one half the aspirated volume. Serial radiographs or fluoroscopy are used to monitor the passage of the contrast to document the severity and location of ureteral obstruction. Computed tomographic (CT) scans obtained before and after intravenous contrast administration may also be used for confirmation of the number and location of ureteroliths. Contrast-enhanced CT is preferred over nephropyelocentesis, especially if the renal pelvis is not sufficiently dilated. Advanced imaging such as CT is often not necessary prior to interventional procedures because antegrade pyelography is performed as the initial step in interventional procedures to document and treat ureteral obstruction (see ch. 124).[9]

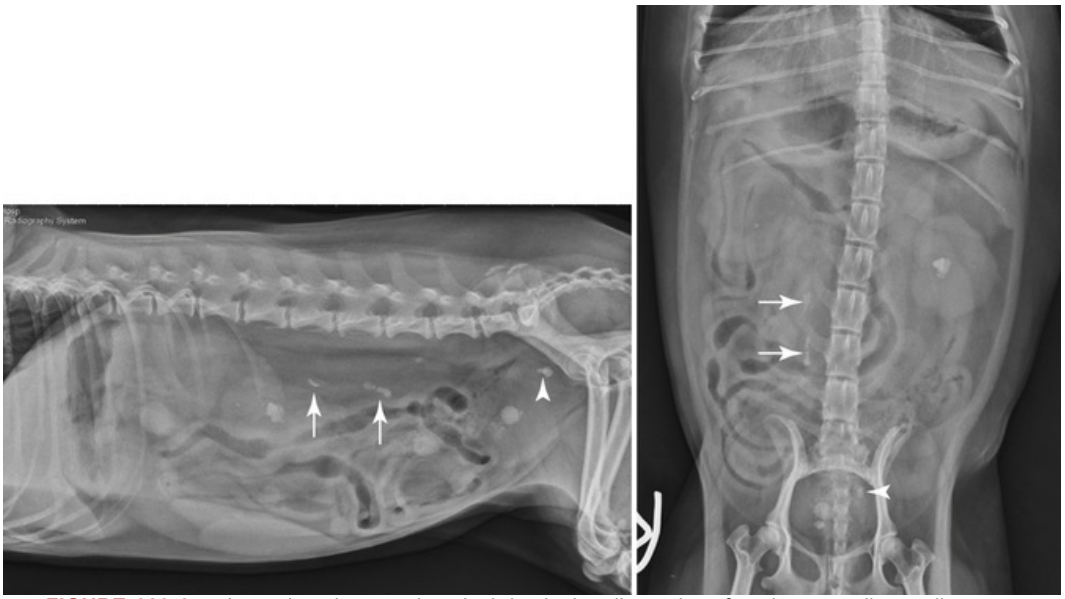

FIGURE 329-1 Lateral and ventrodorsal abdominal radiographs of a dog revealing radiopaque ureteroliths in the right ureter (arrows) and distal left ureter (arrowhead). A left nephrolith is also present and the margins of the left kidney are irregular. Ultrasonography revealed moderately severe dilatation of the right ureter and renal pelvis proximal to the ureteroliths. The distal left ureteroliths passed into the urinary bladder within 24 hours with IV fluid therapy.

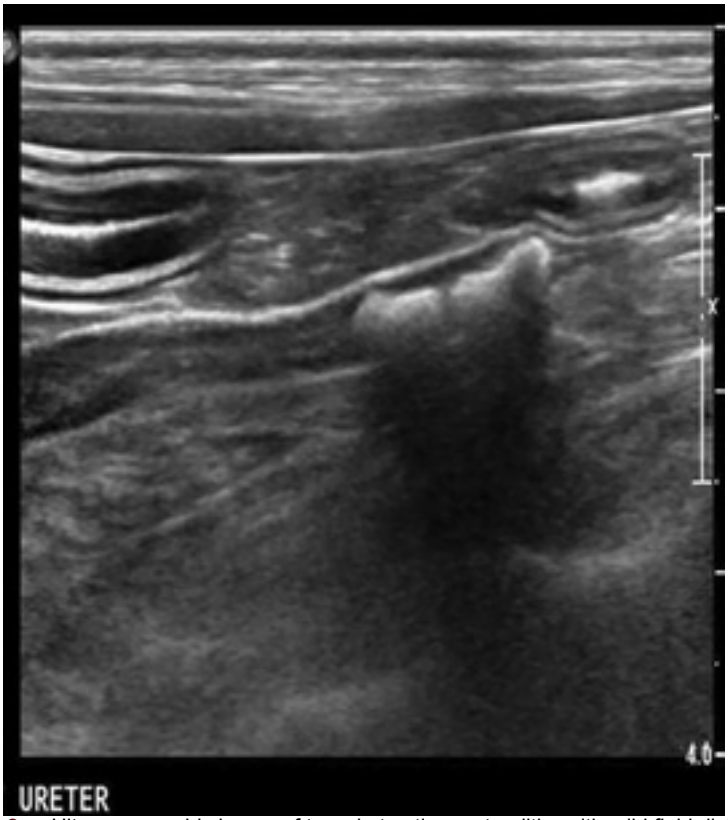

FIGURE 329-2 Ultrasonographic image of two obstructive ureteroliths with mild fluid distention of the ureter proximal to the ureterolith. Note the acoustic shadow created by the ureteroliths.

Management of Ureteroliths

Removal of ureteroliths is more difficult than removal of uroliths from the lower urinary tract. Medical dissolution of ureteroliths is not an option without placement of a ureteral stent, because ureteroliths are not continually bathed in urine. In both dogs and cats, calcium oxalate is the most common composition of ureteroliths; therefore, most ureteroliths are not amenable to dissolution. Conservative medical management by serial monitoring of ureteroliths along with administration of intravenous fluids and diuretics (e.g., mannitol) has been recommended, provided there is minimal renal functional compromise and no infection, renal colic, or progressive ureteral dilation.[13-15] Typically, dogs and cats with evidence of complete obstruction by the ureterolith, worsening azotemia, or evidence of pyelonephritis should be treated by either minimally invasive procedures, open surgical intervention, or shock wave lithotripsy (SWL; in dogs only).[9,13,16-20] Because of several factors (size of the ureter, urolith susceptibility to SWL fragmentation, differences in urolith composition), the treatment approach for dogs and cats with ureteroliths is different for each species.

Spontaneous Passage of Ureteroliths

Size and location of the ureterolith may help determine if intervention is required. In humans, 68% of ureteroliths <5 mm in diameter and 47% of ureteroliths between 5 and 10 mm will pass spontaneously.[21] The majority of ureteroliths that pass spontaneously occur within 4-6 weeks. Most human ureteroliths >10 mm require intervention with SWL or ureteroscopic laser lithotripsy for removal.[21] It is difficult to apply these specific criteria to dogs and cats because of the wide variation in body weight and ureteral diameter, but the rate of spontaneous passage of ureteroliths appears to be much less in both dogs and cats than it is in humans. In an experimental study of artificial ureteroliths in Hound dogs, solid spheres 2.8 mm in diameter or larger became firmly impacted in the ureter; however, spheres 2.3 mm in diameter passed to the urinary bladder within 1 to 24 hours.[22] However, this study may not apply to smaller dogs with spontaneous ureteroliths because of their smaller ureteral diameter. Likewise, the normal cat ureteral luminal diameter of only 0.3-0.4 mm results in inability to pass even <1-2 mm ureteroliths in most cats. In one study of cats with ureteroliths, medical management for the treatment of cats with obstructive ureteroliths was only reported to be effective in 8-13% of cases.[13] Also, recent data indicate that over 20% of ureteroliths in cats are associated with concurrent ureteral strictures; therefore, success of medical management may be limited by concurrent strictures.[17]

Medical Expulsive Therapy

Medical expulsive therapy (MET) may have a role in management of obstructive ureteroliths. Suggested METs have included IV fluid administration with diuretics (e.g., mannitol), alpha-adrenergic antagonists, calcium channel-blocking agents (nifedipine), amitriptyline, and glucagon. In humans, the criteria for utilization of MET versus interventional procedures include adequate well-controlled pain during MET, no evidence of sepsis, and adequate renal reserve.[21] The medical therapy for MET in dogs and cats that most agree on is IV fluid administration with diuretics to increase urine flow to facilitate ureterolith passage with serial monitoring of the ureterolith position by radiographs and ultrasonography, along with administration of the alpha-adrenergic antagonist prazosin.[23,24]

In humans, if a ureterolith remains in the same location for 2 weeks, progressive enlargement of the ureter or renal pelvis is observed, pain cannot be effectively managed, or renal function is impaired by the obstruction, interventional techniques are recommended over MET,[21] and this information can also be applied to dogs and cats with ureteroliths. If an animal is monitored for 2 weeks and the ureterolith is not moving distally despite MET, some type of intervention should be considered. In dogs and cats, the ureteroliths may also spontaneously move retrograde back into the renal pelvis rather than passing distally towards the urinary bladder.[25]

In humans, meta-analysis of multiple clinical studies confirmed that alpha-adrenergic antagonists facilitate passage of ureteral calculi more effectively than other medications do. The alpha-adrenergic antagonist tamsulosin showed a 29% increase in the rate of successful ureterolith passage compared to control patients.[21] In dogs and cats, use of the alpha-adrenergic antagonist prazosin has been suggested for MET as an alternative to tamsulosin, but clinical studies of efficacy of MET are lacking in these species.[24] Overall success in MET in cats is low and concurrent ureteral strictures are often present; therefore, MET should only be considered for a limited time (usually 24-48 hours) and only for cats without evidence of oliguria, severe azotemia, severe hydronephrosis, sepsis, overhydration, or hyperkalemia. In dogs and cats, non-obstructive

ureteroliths (renal pelvis < 4-5 mm) that are not associated with infection or azotemia may be managed conservatively using MET for 1-2 weeks provided renal function is stable. However, frequent monitoring for complications such as progressive enlargement of the ureter or renal pelvis, progressive azotemia, oliguria, and evidence of urinary tract infection (UTI) or sepsis, is required to prevent the potential of permanent loss of renal function of the affected kidney.

Although there are anecdotal clinical reports that glucagon facilitates passage of ureteral calculi in cats, the only clinical study of glucagon administration in cats did not demonstrate any benefits for management of obstructive ureteroliths and an unacceptably high incidence of side-effects occurred.[26] Given the unacceptable number of side-effects and lack of documented efficacy, glucagon administration is not recommended for dogs and cats with ureteroliths.

In one report, amitriptyline facilitated passage of urethral plugs in male cats with urethral obstruction.[27] Although the article title implies urethral calculi, the cats in the report all appeared to have urethral *plugs* rather than actual *uroliths.* There are no clinical reports supporting the use of amitriptyline for expulsive therapy of ureteroliths in any species; therefore, its use for this purpose is also discouraged.

Management of Struvite Ureteroliths in Dogs

While the vast majority of upper tract uroliths in cats are calcium oxalate, infection-induced struvite nephroliths and ureteroliths are the second most common type of urolith in the upper tract of dogs. Clinical findings that would support struvite nephro-ureteroliths include UTI with urease-producing organisms *(Staphylococcus, Proteus, Klebsiella, Corynebacterium* and *Mycoplasma),* alkaline urine pH, moderately radiopaque uroliths in the renal pelvis or ureter, and struvite crystalluria. While struvite uroliths in the kidney and bladder may be medically dissolved in dogs, obstruction of the ureter by the ureteroliths prevents effective medical dissolution and causes obstructive pyonephrosis, which frequently leads to urosepsis.[28] In dogs with obstructive struvite ureteroliths, the obstruction must be corrected prior to attempts at medical dissolution.[28] In humans, the recommended treatment for pyonephrosis involves emergency drainage of the infected urine along with ureteral stent placement.[21] In a recent report in dogs, obstructive pyonephrosis was successfully managed by a minimally invasive approach of retrograde lavage of the renal pelvis using an open-ended ureteral catheter combined with cystoscopic-guided ureteral stent placement.[28] Both fluoroscopy and cystoscopy are required for this approach (see ch. 124). Once the initial pyonephrosis crisis is effectively managed by drainage, ureteral stent placement and IV antibiotic therapy, then medical dissolution of the ureterolith is possible using a combination of antimicrobial therapy of the UTI (guided by urine culture results) and struvite dissolution diets such as Royal Canin Urinary SO diet, Hill's Prescription diet s/d or c/d Multicare, or Purina Veterinary diet UR Urinary Ox/St Canine diet (see ch. 331 and 332). Medical dissolution of struvite ureteroliths should not be attempted without concurrent ureteral stent placement because of the risk of obstruction, treatment failure, and sepsis. The diet and antibiotics should be continued until radiographs and ultrasound document complete dissolution of the uroliths. The author's preference is to remove the ureteral stent by cystoscopic retrieval or to consider ureteral stent exchange prior to discontinuing the antibiotics.

Interventions for Ureteroliths

If dogs and cats with obstructive ureteroliths require intervention, options include ureteral stent placement, shock-wave lithotripsy (SWL), ureterotomy to remove ureteroliths, transection of the ureter and reimplantation of the proximal ureter into the bladder (ureteroneocystostomy), and subcutaneous ureteral bypass (SUB) placement. The relative success rates, indications and complications of these techniques vary by species (see ch. 124).

Ureteral Stents

Resolution of ureteral obstruction by ureteroliths is possible by placement of ureteral stents via surgery or cystoscopy to divert the urine through the stent around the ureteral obstruction. In dogs, ureteral stents may be placed retrograde up the ureter over a urologic guidewire via cystoscopy (Figure 329-3).[9,24,28] In cats, ureteral stent placement usually requires surgery for antegrade stent placement through nephropyelocentesis, and stent placement is much more difficult compared to dogs.[17] Stents may be used temporarily or left in place long-term. In dogs and female cats, if the ureteral stent is no longer needed to bypass the ureteral obstruction, the stent can be easily extracted via cystoscopy by grasping the distal end of the ureteral stent and providing gentle traction to withdraw the stent through the ureter and urethra. In cats, ureteral stents are

usually left in the ureter long-term, although periodic stent exchange may be required in approximately 20-25% of cats.[17] Indwelling stents may develop mineral encrustation on both outside and inside the stent, resulting in occlusion of the ureter and necessitating stent removal or exchange for a new stent (Figure 329-4).[16]

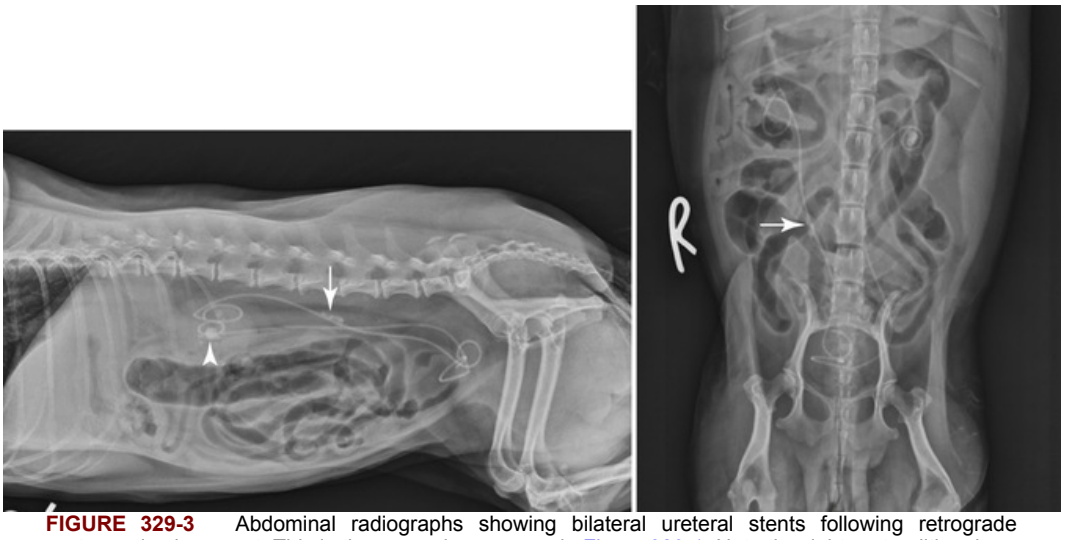

FIGURE 329-3 Abdominal radiographs showing bilateral ureteral stents following retrograde cystoscopic placement. This is the same dog as seen in Figure 329-1. Note the right ureteroliths along the outside of the right ureteral stent (arrow) and the left nephrolith (arrowhead). The dog was subsequently treated using shock-wave lithotripsy to fragment the nephrolith and ureteroliths, and then the stents and urolith fragments were removed by cystoscopy.

FIGURE 329-4 Ureteral stent removed from a dog because of encrustation with calcium oxalate deposits, which are visible on the outside of the stent. Mineral deposits inside the stent resulted in partial obstruction of the stent, requiring stent exchange.

Subcutaneous Ureteral Bypass (SUB) Devices

Surgical placement of a SUB device to provide a route for urine to bypass the obstructed ureter is a relatively new procedure. This technique has rapidly become one of the preferred options for management of ureteroliths and ureteral strictures in cats.[9] Compared to traditional ureteral surgery, SUB placement has a much lower perioperative mortality rate with 94% of cats having survived to discharge following SUB placement.[9] Long-term prognosis for cats with ureteral stents and SUBs correlates to the stage of residual CKD following relief of ureteral obstructions, with cats having stage 1-2 CKD surviving significantly longer than cats with stage 3-4 CKD.[20] See ch. 124 and references for details of interventional urology procedures such as ureteral stent and SUB placement.[9,17,19,24]

Ureteral Surgery

Open surgical ureterotomy is one option for management of ureteroliths in dogs and cats.[13,29] In the author's opinion, ureterotomy or ureteroneocystostomy are only appropriate for dogs and cats with single ureterolith without concurrent nephroliths or ureteral stricture (ureterotomy). Ureteral surgery may result in temporary obstruction of the ureteral lumen postoperatively because of mucosal swelling at the ureterotomy site; therefore, diversion of urine by a ureteral stent placement (see above) may be considered to assist with management of ureteral obstruction.[13,17,29] Because ureterotomy and ureteroneocystostomy have higher mortality and surgical complication rates than SWL and ureteral stent or SUB placement, the author prefers these minimally invasive alternatives to ureterotomy or ureteroneocystostomy.[9,13,17,19,20,29]

Shock Wave Lithotripsy for Ureteroliths

Shock wave lithotripsy is a minimally invasive option for fragmentation and removal of nephroliths and ureteroliths in dogs, but not cats.[16,30-32] In SWL, uroliths are fragmented using shock waves that are generated outside the body and targeted at the uroliths using integrated fluoroscopy or ultrasonography (see ch. 124). Approximately 80% of ureteroliths in dogs can be resolved by SWL although approximately 50% of dogs require 2 or more SWL treatments, which is a higher re-treatment rate than in dogs with nephroliths.[16,32] This is similar to observations in humans and in research models that confirm impacted ureteroliths are more difficult to fragment compared with nephroliths.[33,34] This difficulty in fragmenting ureteroliths compared to nephroliths appears to be due to the inability of cavitation bubbles to form and collapse on the surface of the ureterolith if it is surrounded by the ureteral wall rather than urine.[35,36] The advantages of SWL include that the procedure is non-invasive and complications occur in fewer than 10% of dogs, with transient ureteral obstruction by urolith fragments being the most common complication.[16,32]

Placement of ureteral stents is not essential for treatment of ureteroliths by SWL, but there are advantages of ureteral stents that facilitate SWL efficiency and patient management. Ureteral stents allow urine to bypass ureteral obstruction at the site of the ureterolith immediately and prevent additional renal damage from obstructive uropathy (see Figure 329-3). Because ureteral stents are radiopaque, they facilitate accurate targeting of ureteroliths during SWL. Ureteral stents also induce passive ureteral dilation, thus increasing the diameter of the ureter lumen by approximately 3-fold.[37] Although this has the theoretical advantage of increasing the efficiency of urolith fragmentation, ureteral stent placement is not recommended for SWL treatment of ureteroliths in humans.[30] Nonetheless, ureteral stents may be more beneficial with SWL in dogs compared to humans due to their smaller ureteral diameter. Passive dilation of the ureter also facilitates passage of nephrolith and ureterolith fragments following ureteral stent removal. Placement of a ureteral stent may also be used to prevent ureteral obstruction by ureterolith fragments following SWL treatment of larger nephroliths or ureteroliths in dogs (see Figure 329-3).[16]

Unlike dogs, SWL is *not* effective for fragmentation and removal of ureteroliths in cats.[16,32] Because of the small ureteral diameter in cats, even <1-mm fragments fail to pass down the ureter in cats, and in other species, SWL typically results in urolith fragments of 1-2 mm or larger. In addition to the smaller ureteral diameter, feline calcium oxalate uroliths are resistant to fragmentation compared to calcium oxalate uroliths from dogs.[38] In clinically normal research cats, kidney damage and reduced renal function were routinely

observed after less than 50% of the normal therapeutic shock-wave "dose" used in dogs for SWL.[32] In combination, all of these factors result in the recommendation that SWL should *not* be used for treatment of nephroliths or ureteroliths in cats.

Ureteral Obstruction

Clinical signs of ureteral obstruction may not be apparent unless bilateral obstruction or unilateral obstruction in combination with decreased function of the contralateral kidney occurs. Clinical signs of ureteral obstruction include abdominal pain or so-called ureteral colic (less consistently observed than in humans with ureteral obstruction), dysuria (especially with distal ureteral obstruction in cats), and signs of renal functional impairment such as anorexia, vomiting, and oliguria. Patients with complete, bilateral ureteral obstruction show signs of severe oliguric renal failure. Complete bilateral ureteral obstruction may be fatal within 48-72 hours. Many ureteral obstructions are partial, especially those associated with ureteroliths.

Ureteral obstruction may occur from intraluminal, intramural, or extramural causes. Intraluminal obstruction may occur as a result of ureteroliths, blood clots or other intraluminal debris. Intramural causes include ureteral stricture, ureteral stenosis, mucosal edema, and neoplasia. Extramural compression may occur from circumcaval ureters, retroperitoneal masses, retroperitoneal fibrosis, bladder neoplasia, or from accidental surgical ligation of the ureter during ovariohysterectomy. Circumcaval ureter (or retrocaval ureter) is a congenital anomaly characterized by ventral displacement (or duplication) of the caudal vena cava, which crosses over the ureter resulting in potential compression of the proximal ureter as it passes behind the vena cava. The right ureter is affected more often than the left ureter. In one recent study, circumcaval ureters were present in approximately 1/3 of cat cadavers and were not associated with obvious obstruction of the ureters.[39] However, in clinical reports of cats with ureteral obstructions, circumcaval ureters appeared to be associated with ureteral stricture formation just proximal to the location that the vena cava crossed the ureter.[40,41] The difference in these two reports may be that the presence of circumcaval ureters combined with even small ureteroliths may result in ureteral stricture formation. The clinical signs and outcomes of cats with obstruction associated with circumcaval ureters are similar to other causes of ureteral obstruction.[40] Ureteral strictures associated with circumcaval ureters may be more effectively managed by SUB placement compared to surgery or ureteral stent placement.[17,40] In humans, ureteral stenosis at the ureteropelvic junction (UPJ) is a commonly recognized disorder. Ureteral stenosis at the UPJ was recently reported in one dog.[42] The dog was successfully managed by retrograde cystoscopic ureteral stent placement. UPJ stenosis has also been reported in an adult cat resulting in severe renal failure from end-stage hydronephrosis.[43] Retroperitoneal fibrosis leading to extramural ureteral obstruction was reported in 29 of 138 (21%) of feline renal transplant recipients.[44] All 29 cats had azotemia from obstructive uropathy secondary to the retroperitoneal fibrosis. Surgery was performed to relieve the ureteral obstruction in 25 of the 29 cats, and recurrence of ureteral obstruction occurred in 6 cats (22%).[44]

The most common neoplasm resulting in ureteral obstruction in dogs is transitional cell carcinoma located in the trigone of the urinary bladder (see ch. 351). Metastatic neoplasia may also result in ureteral obstruction. Malignant ureteral obstructions can be bypassed using palliative ureteral stent placement.[45] Because it is difficult to identify the ureteral orifice via cystoscopy in dogs with extensive trigonal neoplasia, ureteral stents in these patients must be placed either percutaneous antegrade through nephropyelocentesis or via open surgery (see ch. 124).[45]

Primary ureteral neoplasia is rare in dogs and cats. Types of primary ureteral neoplasia include transitional cell carcinoma, leiomyoma, leiomyosarcoma, sarcoma, mast cell tumor, benign papillomas, and fibroepithelial polyp.[46-52] Fibroepithelial polyps are the most common type of primary ureteral neoplasia in dogs.[47,48] Ureteronephrectomy has been the most commonly reported treatment for unilateral ureteral neoplasia, but SUB or ureteral stent placement may be possible alternatives in some cases.[47,48]

Ureteral Trauma

Trauma to the ureters has rarely been reported in dogs and cats.[53,54] Ureteral injury can result from blunt abdominal trauma, penetrating wounds, or iatrogenic damage during surgery such as inadvertent ligation or transection of the ureter during ovariohysterectomy. Ureteral injury resulting from blunt trauma accounted for only 0.01% of canine hospital admissions in a one report.[53]

Rupture of the ureter results in accumulation of urine in the retroperitoneal space, post-renal azotemia,

hyperkalemia and metabolic acidosis. If the contralateral kidney and ureter are functioning normally, recognition of ureteral rupture may be delayed for several days. If the ureter ruptures near the ureterovesicular junction or if the retroperitoneum is disrupted by the trauma, uroabdomen may also occur. Ureteral rupture may also occur as an uncommon complication of ureteroliths.

The extent and location of ureteral injury and function of the contralateral kidney determine treatment of ureteral injury. Ureteronephrectomy has been reported as the most common treatment for unilateral ureteral rupture provided that the contralateral kidney and ureter are functioning normally.[53] For dogs with distal ureteral trauma, implantation of the healthy portion of the ureter above the damaged area (ureteroneocystostomy) is an alternative to ureteronephrectomy.[54] For incomplete tears of the ureter (<50% of the circumference), conservative management via urine diversion often allows for healing of the ureteral lesion. Ureteral stent placement via cystoscopy or surgery is a minimally invasive option for urinary diversion to allow for healing of partial ureteral tears (see ch. 124).

An uncommon consequence of ureteral trauma is formation of a paraureteral pseudocyst, or urinoma, which forms when urine that has leaked from a ureter into the retroperitoneum becomes encapsulated in a thick, fibrous wall.[55-57] Inadvertent ureteral transection during ovariohysterectomy was the cause of urinoma in a dog.[58] Ureteronephrectomy may be required for treatment of urinoma provided the contralateral kidney has normal function.

Anatomic Abnormalities

Congenital Ureteral Abnormalities

Congenital ureteral abnormalities include ectopic ureters, ureteroceles, ureterovesicular junction (UVJ) stenosis, ureteral agenesis and ureteral duplication. Ureteral agenesis and ureteral duplication are rare in dogs and cats.[59-61] Ureteral agenesis results from failure of development of the ureteral bud and may be complete or segmental. Ureteral agenesis is commonly associated with contralateral renal agenesis, because the ureteral bud induces the embryonic metanephric kidney to proliferate and differentiate.[60] Ureteral duplication occurs when more than one ureteral bud develops from the same mesonephric duct or from division of the ureteral bud.[59] Ureteral duplication may be associated with a duplex kidney and with ureteral ectopia.[59,61] Congenital UVJ stenosis was reported in 10 dogs; in 7 dogs the UVJ stenosis was associated with an ectopic ureteral opening.[62] Stenosis of the UVJ causes partial distal ureteral obstruction (Figure 329-5, *C*). The UVJ stenosis was corrected successfully by cystoscopic-guided laser ablation in all 10 dogs.[62]

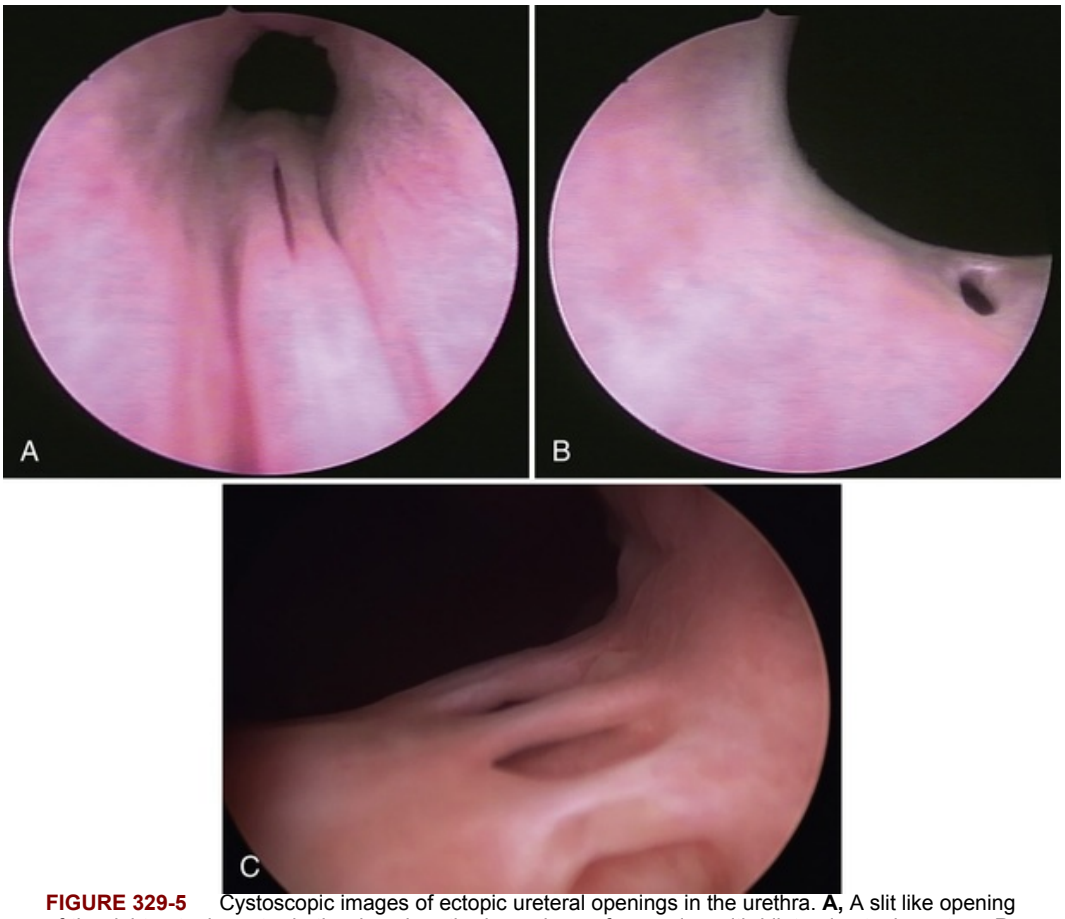

FIGURE 329-5 Cystoscopic images of ectopic ureteral openings in the urethra. **A,** A slit like opening of the right ectopic ureter in the dorsal urethral membrane from a dog with bilateral ectopic ureters. **B,** Stenotic opening of the left ectopic ureter in proximal urethra just distal to junction of the bladder and urethra (same dog as Figure 329-5, *A*). **C,** Multiple openings of an ectopic ureter in the proximal urethra of another dog.

Ectopic Ureters

Ectopic ureters are defined as ureteral openings located anywhere distal to the normal trigonal location (see ch. 336).[63] Ectopic ureters may be unilateral or bilateral and extramural or intramural. Extramural ectopic ureters bypass the urinary bladder entirely and insert at a distal location. Intramural ectopic ureters enter the serosal surface of bladder in a normal dorsolateral location; however, instead of opening in the trigone, the ureter tunnels through the submucosa of the bladder and urethra and opens in the bladder neck distal to the normal trigonal location, urethra, or vaginal vestibule. Variations of the configuration of intramural ectopic ureters include double ureteral openings, multiple fenestrated openings, two intramural ureters opening in a single orifice, and ureteral troughs (see Figure 329-5). Ectopic ureters commonly are associated with other abnormalities of the urogenital tract, including renal agenesis, renal hypoplasia, irregular shape of the kidneys, hydroureter, ureterocele, UVJ stenosis, urachal remnants, pelvic bladder, urethral abnormalities, and paramesonephric septal remnant.[62-68] Breeds reported to be at greater risk for ectopic ureters include the Siberian Husky, Labrador Retriever, Golden Retriever, Newfoundland, English Bulldog, West Highland White Terrier, Fox Terrier, Skye Terrier, Border Terrier, Griffon, Entlebucher Mountain Dog, and Miniature and Toy Poodle.[68-70] Female dogs are much more commonly affected by ectopic ureters than male dogs. Ectopic ureters are less common in cats compared to dogs. During cystoscopy or excretory urography, the ureteral openings in normal cats appear to be located in the proximal urethra and this normal anatomic location should not be confused as ectopic ureters.

While the diagnosis of ectopic ureters was historically made by excretory urography, where available, cystoscopy has become the preferred method of diagnosis (see Figure 329-5). Ultrasonography has also been advocated as a diagnostic option for detection of ectopic ureters; however, ultrasonography does not accurately detect all ectopic ureters.[71] Studies have compared the diagnostic accuracy of excretory urography,

contrast enhanced CT scans and cystoscopy for detection of ectopic ureters.[63,72] Contrast enhanced CT scans and cystoscopy were the most accurate diagnostic methods for detection of ectopic ureters.[63,72] Cystoscopy has the additional advantage that intramural ectopic ureters may be diagnosed and corrected by cystoscopic-laser ablation during the same anesthetic procedure.[73-75]

Laser ablation of the wall between the urethral lumen and the intramural ureteral lumen effectively moves the ureteral opening to the bladder lumen without open surgery (see ch. 108 and 124). Cystoscopic-guided laser ablation of intramural ectopic ureters may be performed using a holmium : YAG or diode laser.[73-75] Results appear to be similar to surgical results for correction of ectopic ureters, although there are no published studies directly comparing outcomes of surgical correction and laser ablation. Dogs with good urethral function are continent after laser correction of ectopic ureters, whereas dog with concurrent urethral incompetence continue to have urinary incontinence unless treatment of the concurrent urethral incompetence is effective.[73-75] Extramural ectopic ureters cannot be corrected by laser ablation and require surgical transection and re-implantation into the urinary bladder.

Ureterocele

A ureterocele is a cystic dilatation of the terminal portion of the ureter, which often protrudes into the bladder lumen (see ch. 336).[76-80] Ureteroceles are classified as either orthotopic (also called intravesical) if the ureter opening is in a normal trigonal location, or ectopic if the ureter opening is distal to the normal trigonal position. Ureteroceles may cause a variety of clinical signs depending on their size and whether or not the ureter is ectopic. Urinary incontinence is the most common clinical sign of ureteroceles.[76,77] Ureteroceles may place pressure on the bladder and proximal urethra, resulting in functional urinary retention or they may cause signs of dysuria, stranguria and pollakiuria. Dogs with ureteroceles may also present for recurrent UTI. Although ureteroceles are congenital abnormalities, some dogs with ureteroceles do not develop clinical signs until later in life.[76] Ureteroceles may be associated with developmental or acquired abnormalities of the upper or LUT including moderate to severe hydroureter and hydronephrosis, ectopic ureters, and urethral anomalies. Ureteroceles are diagnosed by excretory urography, cystoscopy or ultrasonography.

Treatment of ureteroceles depends on the type and extent of concurrent anomalies and whether or not the ureteral opening is ectopic. Surgical excision of the ureterocele with re-implantation of the ureter has been recommended for ectopic ureteroceles or ureteroceles associated with ureteral obstruction.[76,80] The author has successfully treated intramural ectopic ureteroceles via cystoscopic-guided laser ablation in 4 female dogs, thereby avoiding open surgery. Orthotopic ureteroceles may also be incised cystoscopically using a laser or by cystotomy; however, this often results in vesicoureteral reflux, which could contribute to pyelonephritis if UTI is also present. Effective control of UTI is therefore recommended prior to correction of ureteroceles.

Urethrorectal or Ureterovaginal Fistula

Fistulas between the urethra and the rectum or between the ureter and vagina are uncommon conditions in dogs that may be congenital or acquired (see ch. 336).[81-86] Ureterovaginal fistulas usually form as a result of ovariohysterectomy when the ureter is accidentally included in a ligature around the vaginal stump. Urethrorectal fistulas may be congenital or may be acquired after pelvic trauma. English Bulldogs are the most commonly affected breed with congenital urethrorectal fistulas.[85,86] Clinical signs of urethrorectal fistulas include passing of urine from the anus during voiding and most commonly recurrent UTI.[85,86] Urinary incontinence is the most common clinical sign of ureterovaginal fistulas in dogs.[81,82] Surgical correction of urethrorectal or ureterovaginal fistulas is recommended; however, surgical correction of urethrorectal fistulas may be difficult due to intrapelvic location and concurrent UTI. Resolution of secondary UTI is essential following surgical correction of urethrorectal fistulas and may require prolonged antimicrobial therapy.

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CHAPTER 330

Lower Urinary Tract Infections

Michael W. Wood

Client Information Sheet: Recurrent Lower Urinary Tract Infections

Introduction

The development of urinary tract infection (UTI) is multifactorial, being dependent on the interplay between the virulence of an organism and alterations in anatomic, environmental, and immunologic competency of the host. Most commonly, the microbes are uropathogenic bacteria that originate from the enteric flora and ascend from the distal urogenital tract into the proximal urethra and urinary bladder.[1-3] For many dogs with normal urinary defenses, invading bacteria are cleared within 3 days without the need for antibiotic therapy.[4] It is those with compromised defenses that are at increased risk for colonization and persistent bacteriuria (Box 330-1).

Box 330-1

Natural and Acquired Host Defenses of the Lower Urinary Tract

- Normal micturition
  - Adequate urine volume
  - Frequent voiding
  - Complete voiding
  - Urinary continence
- Anatomic structures
  - Urethral high-pressure zones
  - Surface characteristics of urothelium
  - Urethral peristalsis
  - Prostatic secretions (antibacterial fraction and immunoglobulins)
  - Length of urethra
  - Ureterovesical flap valves
  - Ureteral peristalsis
- Mucosal defense barriers
  - Antibody production
  - Surface layer of glycosaminoglycans
  - Intrinsic mucosal antimicrobial properties
  - Exfoliation of urothelial cells
  - Bacterial interference by commensal microbes of distal urogenital tract
  - Mucosal innate immunity: toll-like receptors, etc.
- Antimicrobial properties of urine
  - Extreme high and low of urine pH
  - Hyperosmolality
  - High concentration of urea
  - Organic acids
  - Low-molecular-weight carbohydrates
  - Tamm-Horsfall mucoproteins
  - Host defense peptides (e.g., defensins)

Systemic immunocompetence
  Cell-mediated immunity
  Humoral-mediated immunity

Adapted from Osborne CA, Lees GE: Bacterial infections of the canine and feline urinary tract. In Osborne CA, Finco DR, editors: *Canine and feline nephrology and urology*, Baltimore, 1995, Williams & Wilkins, pp 759-797.

Other organisms like fungi account for UTI in ≈1% of dogs and cats and will not be discussed in this chapter. Please refer to the 7th edition of this textbook, ch. 313 (Urinary Tract Infections) by Barrak Pressler for a review of nonbacterial UTI.

Characteristics of Infection

Asymptomatic Bacteriuria

Traditional UTI definitions require invading organisms to adhere, multiply, and persist within the urinary tract.[5,6] Based on recent observations in human and veterinary medicine, microbiologic documentation of bacteriuria is not equivalent to diagnosing a UTI. Not all bacteriuria is associated with clinical signs of lower urinary tract (LUT) infection such as caudal abdominal pain, pollakiuria, stranguria, hematuria, and dysuria. In human medicine, persistently bacteriuric individuals lacking LUT clinical signs are termed as having asymptomatic bacteriuria (ASB).[7] In dogs and cats, recognizing subtle signs of UTI is challenging and the term subclinical bacteriuria (SCB) may be more appropriate.[8]

In people, the treatment of ASB is not recommended in many circumstances because eradication of ASB does not prevent future urinary bladder re-colonization[9] and the presence of ASB strains is hypothesized to convey a degree of protection against urinary tract colonization with more virulent bacteria.[10] Evidence demonstrating the benefit of ASB in veterinary medicine is lacking; however, in limited veterinary studies, the prevalence of ASB has been reported to be 2.1-8.9% in dogs[11, 12] and 10-28.8% in cats,[13,14] with *E. coli* and *Enterococcus faecalis* being the most common bacteria identified.[11-13]

Fitness and Virulence Factor Roles in Infection

Whether bladder colonization causes clinical disease ultimately depends on bacterial gene expression. Bacteria contain genomic islands encoding fitness factors that promote commensalism and/or virulence factors and dictate the severity of the UTI. The amount of genetic material a bacterium can contain is limited; therefore, bacteria typically evolve by increasing fitness or virulence.[15] Hence, bacteria with high fitness, such as multiple antibiotic resistance genes, are commonly found in chronic infections that also have decreased virulence potential.[16]

Fitness and virulence genes have tremendous plasticity, and bacteria constantly adapt to changes within their microenvironment.[17] Bacteria respond to changes in nutrient availability, osmolarity, and host defenses by obtaining genetic material via horizontal gene transfer, mutating existing genes, and altering expression of virulence and antivirulence genes.[18] Many ASB strains contain unexpressed virulence genes; therefore, the current bacterial phenotype is not necessarily predictive of future pathogenicity, particularly if the urinary bladder environment is in flux.[15,19] Certain genes are more important predictors of virulence than others, including genes that encode the production of toxins such as hemolysin or the expression of urothelial adherence pili.[20]

Bacterial adhesion molecules each have different affinities for areas of the urinary tract. In uropathogenic *E. coli* (UPEC), type 1 fimbriae, encoded by *fim* genes, bind mannose targets on the urothelium[21] and are expressed by nearly 100% of bacteria that cause pyelonephritis and cystitis and 77% of ASB strains.[22] Clinically, the presence of type 1 fimbriae usually is associated with an increased severity of infection[23] and they are commonly found on the surface of UPEC during initial colonization of the urinary bladder.[24] In contrast, P fimbriae encoded by *pap* genes bind to alpha-D-galactopyranosyl-(1-4)-beta-D-galactopyranoside receptors located in the upper urinary tract.[25] These adhesion molecules are found in 78% of pyelonephritis strains, 22% of cystitis strains, and only 15% of asymptomatic strains.[22] Among other uropathogens it is largely the Gram-negative organisms that express similar adhesion molecules with high affinity for kidney

tissue[26] and hence organisms such as *Streptococcus* spp. and *Enterococcus* spp. often are not associated with pyelonephritis.[27]

Diagnosing Urinary Tract Infection

Identifying Bacteriuria

Aerobic culture remains the gold standard for identifying bacteriuria. Quantitative urine culture identifies the specific infecting organism and colony count, both of which are important when considering the bacteriuria's clinical importance. Urine culture also provides information for identifying persistent infections and reinfections, and may provide some clues as to which therapeutics may be effective based on the organism isolated. Urine culture will not distinguish between ASB and UTI; however, urine sediment examination can provide evidence of inflammation, making it useful for these two diagnostic tests to be run in parallel (see ch. 72).

When interpreting the results of urine culture and sediment examination, sample collection and storage must be considered. Both diagnostic tests are affected by time to processing, storage temperature, and storage media. Red and white blood cells as well as casts can be destroyed in hypotonic or alkaline urine left at room temperature after only a few hours. Bacteria can begin to proliferate or die if urine samples are left unrefrigerated, yielding false positive or false negative results.[28] Urine sediment examination and culture should be performed within 30 minutes of collection to reduce these confounding variables. If diagnostics must be delayed, samples should be refrigerated at 4°C and testing performed within 24 hours.[28] Alternatively, if urine culture submission is contingent on pending diagnostics, storing urine in a preservative or reducing media vial such as a Port-a-cul (BD Biosciences) or Amies transport media can extend the time that bacteria will be viable for up to 72 hours without allowing for bacterial proliferation.[29,30]

Urine sediment examination can detect bacteriuria in some instances. Rod-shaped bacteria are readily detected when colony counts exceed 10,000 colony-forming units (cfu)/mL while cocci are largely undetectable until cfu/mL reach 100,000.[31] Overall, the sensitivity and specificity for detecting bacteriuria in unstained urine sediment are 75.9% and 56.7%, respectively.[32] Bacteriuria detection can be improved by staining the sediment with new methylene blue, Gram stain, or modified Wright stain, increasing the sensitivity of bacteriuria detection to ≥83% and specificity to ≥98%.[32-35] A catalase-based point-of-care urine test such as the Accutest Uriscreen (Jant Pharmaceuticals Co) can also improve the sensitivity of bacteriuria detection to 89%; however, cross reactivity of bacteria with somatic cells such as white blood cells (WBC) and epithelial cells decreases the assay specificity to 71%.[36] Catalase-negative bacteria such as *Enterococcus* spp. and *Streptococcus* spp. may also be difficult to detect. See ch. 72 for more information.

Epidemiology of Bacteriuria

The growth of most uropathogens on culture media will be apparent within 18-24 hours of incubation; however, some organisms such as *Corynebacterium* spp. and *Mycoplasma* spp. can take 4 to 7 days, respectively. Gram-negative bacteria are most commonly isolated in dogs, comprising >60% of positive cultures. Overall, *E. coli* is isolated from 45-55% of bacteriuric dogs while other Gram-negative organisms including *Proteus* spp., *Pseudomonas aeruginosa,* and *Klebsiella* spp., and the Gram-positive bacteria *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp. are each cultured between 2-14% of the time.[37,38]

In cats, *E. coli* also is the most common cause of bacteriuria (37.3%) but Gram-negative and Gram-positive infections each occur roughly half the time, with Gram-positive *Enterococcus faecalis* present in 27% of culture-positive urine samples.[39] Overall, the incidence of bacteriuria is much lower in cats than in dogs, but in both species females and older animals are more commonly affected.[32,37,39]

Significant Bacteriuria

Upon detecting bacteriuria via urine culture or urine sediment examination, a clinician must differentiate urine contamination from colonization. In female dogs, the normal vaginal flora can harbor many uropathogenic bacterial strains. Gram-positive organisms such as *Enterococcus* spp., *Staphylococcus* spp., and *Streptococcus* spp. predominate, but *E. coli, Proteus* spp., and *Pasteurella* spp. also are common, making it essential to consider the urine collection method and colony count before diagnosing clinically significant bacteriuria.[40-42]

When significant bacteriuria is detected, finding concurrent pyuria (>3-5 WBC/high-power field) in the urine of cats or dogs is suggestive of infection even in the absence of clinical signs.[31] This is not true in people, where ASB can associated with pyuria.[7] Given the difficulty in detecting subtle clinical signs in dogs and cats, the veterinary definition for UTI errs on the side of overdiagnosis so that subtle pathogenic infections are not overlooked. Occasionally, such as in the immunocompromised individual, a virulent pathogen might colonize the urinary tract without causing clinical signs or an obvious inflammatory response (see ch. 306).[43] In these instances, the clinician must rely on his/her knowledge of the organism present to determine whether intervention is necessary.

Treatment of Urinary Tract Infection

Upon diagnosing true UTI, the use of antimicrobials remains the standard therapy. Treatment plans will vary depending on previous UTI history, concurrent diseases, neutering status, and species. However, broadly speaking, treatment strategies for UTI fall into two large categories: the treatment of uncomplicated UTI and the treatment of complicated UTI.

Uncomplicated UTI

An uncomplicated UTI, also known as a simple UTI, is defined as a bladder infection that occurs no more than once every 6 months in an otherwise healthy dog with normal urinary tract anatomy and function. Cats and intact male dogs are an exception. Infections in these patients should be considered complicated, as intact male dogs can have concurrent prostatitis and infection in cats commonly is associated with a concurrent systemic disease.[44-46]

Uncomplicated infections often are associated with severe lower urinary tract signs of dysuria, pollakiuria, and stranguria, and require therapy while awaiting urine culture results. When choosing an antibiotic for an infection of unknown bacterial susceptibility, selection should be made with consideration of local community resistance patterns, attainable urinary antibiotic concentrations, risk for adverse events, and cost. Veterinarians are encouraged to monitor antimicrobial resistance patterns within their clinic to select an antibiotic with a spectrum and efficacy against the suspected causative agent. The first-line antibiotic should have a local resistance rate of <10% for uncomplicated (not all) UTI detected in the clinic. Suggested first-line antibiotics to consider include amoxicillin, cephalexin, or trimethoprim-sulfonamide.[8]

If the patient's antimicrobial susceptibility results reveal that the colonizing bacteria are resistant to the chosen antibiotic but clinically the patient has improved, the antibiotic course should be completed as prescribed, with a follow-up urinalysis and culture performed 3-5 days after the conclusion of therapy to ensure eradication of the infection. Alternatively, if the colonizing bacteria are resistant to the chosen antibiotic and clinical signs remain, then the original antibiotic should be discontinued and an appropriate antibiotic begun.

The recommended treatment duration for uncomplicated UTI in veterinary medicine is 7-14 days.[47,48] However, short-duration (≤3 d) antibiotic therapy may be equally efficacious. Advantages of short-duration therapy include reduced patient side effects, improved compliance, reduced cost, and decreased antibiotic resistance while maintaining clinical efficacy. Recent studies have indicated that treatment of uncomplicated UTI in dogs with trimethoprim-sulfamethoxazole or high-dosage enrofloxacin for 3 days yielded similar cure rates when compared to 10 days of cephalexin or 14 days of amoxicillin-clavulanic acid.[49,50] Short-duration treatment protocols also reduce the risk of sulfonamide hypersensitivity reactions and of inducing fluoroquinolone-resistant mutants when high-dosage enrofloxacin is used.[49,51] Despite these studies, the use of second-line antibiotics such as amoxicillin-clavulanic acid, fluoroquinolones, and cefovecin is not recommended for the treatment of uncomplicated UTI when first-line antibiotics are options.

When the treatment course of an uncomplicated UTI is complete, additional monitoring or diagnostic testing usually is not required. Adjunctive therapies and preventive therapy (see below) also are not necessary.

Complicated UTI

Complicated UTI implies that an underlying anatomic, functional, or metabolic abnormality or comorbidity is present, either preventing the clearance of an infection (persistence and relapse) or allowing for reinfection. Addressing the primary reason for, and location of, bacterial colonization is important to avoid treatment

failure or recurrence of UTI.

Persistent Infection

Persistent (refractory) infections occur when appropriate antimicrobial therapy fails to sterilize the urine. Provided that the prescribed antibiotic was administered at the appropriate dosage/duration, persistent infections indicate that the infecting bacteria developed resistance, the immune system of the patient is compromised, or the mean urinary concentration (MUC) of antibiotic was unable to achieve concentrations at least four times the minimum inhibitory concentration (MIC) for bacterial growth.[47,52]

Since measuring drug concentrations in the urine is not widely available, recognizing when urinary drug excretion might be altered is necessary to prevent persistent infections. Reduced MUC of an antibiotic can occur with decreased intestinal absorption of oral medications, altered perfusion of infected tissue, altered drug metabolism, or reduced urinary concentrating ability. In short, persistent infections require screening for systemic disease, including an assessment of the function of the immune, gastrointestinal, hepatic, and renal systems. If the disorder resulting in a persistent infection cannot be corrected, then antibiotic doses should be adjusted to maximize the MUC or an alternative antibiotic should be chosen.

Over the last few decades, as the incidence of multidrug resistant (MDR) UTI has increased, there is a growing population of patients with infections not susceptible to first- or even second-line antibiotics. Alternative therapies have been proposed that are largely supported by individual case reports and anecdotal evidence. The use of high-dosage amoxicillin/clavulanic acid is one technique that uses urinary concentrating ability to treat MDR infections that otherwise appear resistant on susceptibility testing.[53] Another approach bypasses the steps of antibiotic absorption, metabolism and excretion by directly instilling aminoglycoside antibiotics into the urinary bladder.[54-56]

Occasionally, therapies that are more invasive may be indicated for the treatment of persistent infections such as encrusted cystitis. Associated primarily with *Corynebacterium urealyticum* UTI, encrusted cystitis occurs when urease-positive bacteria form mineralized plaques on the ulcerated and inflamed mucosa of the urinary tract.[57,58,58a] Suspicion of encrusted cystitis should occur when a urease-positive infection persists in combination with alkaline urine containing struvite crystals. Diagnosis can be assisted by ultrasonography and cystoscopy, and treatment frequently requires appropriate antibiotic therapy in conjunction with urine acidification and surgical debridement.[58]

Relapse

Relapse of UTI differs from a persistent infection in that, during relapse, urine can be cleared of infection but bacterial reservoirs remain allowing for urine recolonization with the same organism within a few days to weeks. Sites that can harbor bacterial colonies include the kidneys, prostate, uroliths, vagina, and possibly the urothelium.

The treatment goal for relapsing infections is to identify the site of infection so that eradication of the reservoir infection is ensured. For suspected tissue infections, bacterial sensitivities should be determined based on the achievable plasma concentrations and tissue penetration of the antibiotic and not the MUC. Therapy traditionally is prolonged, with general recommendations of treatment for 4-6 weeks. However, the optimal treatment duration to clear these infections is largely unknown. It is possible that in certain circumstances treatment duration could be safely reduced (see ch. 327, 331, 332, and 337).

Relapse due to the formation of intracellular bacterial communities is a unique example of complicated UTI of unknown clinical importance in dogs and cats. Bacteria expressing type 1 fimbriae, such as *E. coli* and *Klebsiella pneumoniae*, have been shown experimentally to rapidly move intracellularly during infection.[59-61] Small collections of intracellular bacteria can form quiescent intracellular reservoirs (QIR) that reseed the bladder weeks to months later upon exfoliation of urothelial cells.[62-64] Antibiotic therapy even with prolonged treatment duration is unable to clear QIR[65]; however, intravesicular and intraperitoneal administration of forskolin produced from the *Coleus forskohlii* plant did reduce urothelial bacterial loads in a mouse model of intraurothelial infection.[66] The clinical efficacy of forskolin treatment has never been proven and more evidence is necessary before recommending this therapy for UTI relapse.

Reinfection

Reinfection occurs when there is an alteration to host defenses that allows new bacterial strains to colonize the urinary bladder weeks to months after an initial UTI (see Box 330-1). In both reinfection and relapse, a time period exists when the patient's urine is sterile, making it challenging to differentiate between the two when

similar bacterial species are isolated in subsequent infections. Comparing antibiotic susceptibility patterns of prior and current infections is often used as a means of differentiating reinfection and relapse, but different bacterial strains can have similar susceptibility profiles and the same infecting organism can shift its antibiotic sensitivity, making this method unreliable.[67,68] Genotyping using pulse field electrophoresis provides definitive evidence of reinfection/relapse.[68] Correctly categorizing infection as reinfection or relapse is important, as the pathophysiology and necessary treatment of reinfection is different than that of relapse.

If reinfection is suspected, a complete systemic evaluation of the patient should be undertaken. When possible, an evaluation of the conformation of the external genitalia is performed, including a digital exam and voiding evaluation. Urine retention should be assessed by measuring the post-void bladder residual volume via catheterization or ultrasound estimation.[69-71] Residual volume should be low, with common estimates in the range of 0.1-0.4 mL/kg (Video 330-1).[72,73] Advanced diagnostics, including radiographs/contrast studies, ultrasound, cystoscopy, and urethral pressure profilometry, can assist with identifying alterations in host defenses, including anatomical and mechanical changes to lower urinary tract.

Treatment of reinfection requires a urine culture and sensitivity to guide therapy. In both dogs and cats, prior antibiotic administration is the leading risk factor for development of MDR infections[74,75] and therefore, patients with histories of reinfection will be at increased risk of treatment failure if antibiotics are chosen empirically. If clinical signs are mild at the time of diagnosis of the UTI, it is prudent to wait for antibiotic susceptibility results before starting therapy. In instances when treatment must be instituted immediately, a first-line antibiotic should be chosen as described for uncomplicated UTI, above. Since reinfection is caused by recolonization with a different bacterial strain each time, treatment duration is similar to the patient having numerous single infections, making long antibiotic courses usually unnecessary.

Preventive Therapies

In >25% of dogs, the defect allowing re-colonization is not identified or cannot be corrected.[76] In these patients, treatment of reinfection with antibiotics provides only transient urine sterilization.[76,77] A successful treatment plan focused on prevention of pathogenic UTI would be a superior treatment option. Unfortunately, there is little clinical evidence proving the long-term efficacy of nearly all preventive treatments. Most of the following therapies are based on theoretical ideas, *in vitro* studies, small case series, or anecdotal reports. The International Society for Companion Animal Infectious Diseases did not recommend any of the following therapies in the urinary tract infection treatment guidelines published in 2011.[8]

The first step in all preventative therapy plans begins with identifying whether a true UTI is present and then, if appropriate, eradicating the current infection. Upon sterilizing the urine, preventative protocols can be divided into therapies that allow the bacteria to remain viable and those that kill invading organisms. Successful treatment with nonantimicrobial therapies is most attractive because they do not apply bactericidal selective pressures, bacterial resistance is not induced, and the normal flora within the body remains viable. Categories of nonantimicrobial prophylaxis include adherence blockade and bacterial interference, while antimicrobial prophylaxis frequently centers on modified-dosage, long-term antimicrobial administration.

Anti-Adherence

The basis of anti-adherence therapeutics is to block the ability of bacteria to adhere to the urothelium, allowing urination to flush invading organisms from the urinary tract. One of the most widely accepted preventative therapeutics is the consumption of cranberries and cranberry extract. Proanthocyanidins (PAC) with type A-linkages isolated from cranberries have anti-biofilm properties and can prevent pyelonephritis-inducing P-fimbriated UPEC from binding to uroepithelial cells.[78-82] In veterinary patients, *in vivo* evidence demonstrating the clinical efficacy of PACs is lacking, although urine produced by PAC-consuming dogs has reduced *E. coli* adherence *in vitro*.[83] Therefore, the use of PACs might be effective in limiting the colonization of the urinary tract with certain P-fimbriated–expressing bacterial strains.

The oral administration of D-mannose is a second anti-adherence therapeutic. D-mannose aims to disrupt bacterial adhesion to the urothelium by blocking the ability of lectins on the tips of type 1 fimbriae to interact with carbohydrate moieties located on urothelial cells.[84,85] Several rodent studies have demonstrated decreased UPEC colonization after incubation of bacteria with D-mannose.[86-88] Although questions remain about whether orally administered D-mannose is capable of concentrating within the urine,[89] a recent clinical study in women suggested that regular oral consumption of D-mannose might reduce UTI recurrence.[90] Clinical evidence of efficacy in dogs and cats is lacking.

A third anti-adherence therapeutic is the use of glycosaminoglycans (GAGs). During *E. coli* UTI, virulence factors produced by bacteria can injure the protective GAG barrier overlying the urothelium.[91,92] GAG therapy contends that exogenous GAG will adhere to the urothelium or bind to invading bacteria, preventing bacteria-induced injury. In people, several independent studies have demonstrated that direct instillation of the GAG hyaluronic acid into the urinary bladder significantly reduces UTI recurrence rates[93-95]; however, in veterinary medicine, the efficacy of GAG bladder instillations to prevent UTI remains unproven.

Bacterial Interference

The use of bacteria to prevent UTI is based on the idea that established colonies of nonvirulent organisms alter the microenvironment, stopping proliferation of virulent colonizers. One form of bacterial interference involves the intravesicular instillation of nonpathogenic *E. coli.* This therapy aims to colonize the urinary bladder with an organism that will utilize local nutrients, reducing the ability of uropathogens to colonize.[96] In people with disorders of urine retention causing reinfection, instilling *E. coli* 83972 into the urinary bladder to induce ASB reduced reinfection by up to 50%.[97,98] Two studies attempting to inoculate healthy dog urinary bladders with *E. coli* 83972 were unable to consistently establish persistent colonies[99,100]; however, a defect such as urine retention might be necessary for colonization success.

A second method of altering the urinary microenvironment is with the use of probiotics. *Lactobacillus* and other lactic acid-producing bacteria are theorized to decrease vaginal pH, thereby inhibiting uropathogenic bacterial colonization.[101] Frequently, uropathogenic bacteria colonize the vaginal mucosa of women with recurrent UTI.[101,102] Oral and vaginal administration of *Lactobacillus* have been shown to effectively increase the population of lactic acid-producing bacteria within the vagina, reduce the number of uropathogenic bacteria isolated, and reduce the recurrence of UTI.[103-105] In female dogs, the importance of *Lactobacillus* as a vaginal colonizer is not known, as it sporadically colonizes the vaginal vault of both dogs with recurrent UTI and normal, spayed female dogs.[41] Orally supplementing female dogs with lactic acid-producing bacteria also failed to alter the vaginal bacterial population, suggesting that oral supplements containing lactic acid-producing bacteria are of limited utility for preventing reinfection in dogs.[106]

Miscellaneous Non-Antimicrobial Preventatives

The use of estrogens helps to prevent reinfection in women by altering the urinary microenvironment through promotion of vaginal *Lactobacillus* growth, lowering of vaginal pH, and restoration of atrophic mucosa within the urethra.[107] Vaginally applied and not orally administered estrogen supplements reduce the number of recurrent UTIs in postmenopausal women.[108] It is unknown how this treatment translates to dogs and cats, but patients with subclinical urethral sphincter mechanism incompetence may benefit from estrogen therapy (see ch. 335).

Methenamine salts are urinary antiseptics that produce formaldehyde from hexamine in an acidic urine environment. Since a urinary pH of 5.5 is required to convert methenamine to bacteriostatic concentrations of formaldehyde,[109,110] vitamin C or other urine acidifiers are co-administered to achieve this low pH. Contraindications to methenamine use include urease-positive UTI and conditions associated with metabolic acidosis such as chronic kidney disease/uremia.[111] A Cochrane review suggested that methenamine hippurate might benefit people without appreciable urinary tract abnormalities when used for a week or less. Methenamine appears ineffectual in patients with neuropathic bladders and no definitive information is known about its long-term effectiveness.[112] No veterinary recommendations for its use exist.

Additional therapies that appear promising for the future include the development of anti-bacterial antibodies using various vaccination strategies[113, 114] and the introduction of bacteriophages able to lyse UPEC.[115] Some vaccination therapies have achieved modest success in human clinical trials and may provide additional prophylactic treatment options for preventing bacterial adherence and colonization of the urothelium.

Antimicrobial Preventative Therapy

In both humans and veterinary patients, the use of long-term, modified-dosage antibiotic prophylaxis is controversial.[8,116] In human studies, active prophylaxis did reduce the recurrence of infection, and this therapy might be useful in some animals suffering from severe clinical signs.[111] This treatment will not prevent infection once the antibiotics are discontinued, and selective pressures applied to bacteria via

repeated courses of antibiotics could lead to the development of multidrug resistant uropathogenic bacterial strains and treatment failure.[74,75,117]

The basis of prophylactic antibiotic therapy is to provide ⅓ to ½ of the total daily dose of an antibiotic, usually at night after the last void of the day. Antibiotics concentrate in the urinary bladder overnight, preventing colonization of the urine. The daily treatments are continued for 6 months with monthly cultures to ensure a breakthrough infection has not occurred. After 6 months, if the urine remains sterile, the antibiotics can then be discontinued and the therapy repeated as necessary.

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CHAPTER 331

Lower Urinary Tract Urolithiasis in Dogs

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Client Information Sheet: Urinary Stones in the Bladder and Urethra of Dogs

Urolithiasis is a general term referring to the causes and effects of stones anywhere in the urinary tract. Urolithiasis should not be viewed conceptually as a single disease with a single cause but rather as a sequela of multiple interacting abnormalities. Thus, the syndrome of urolithiasis may be defined as the occurrence of familial, congenital, or acquired pathophysiological factors that in combination progressively increase the risk of precipitation of excretory metabolites in urine to form stones (i.e., uroliths; Figure 331-1).

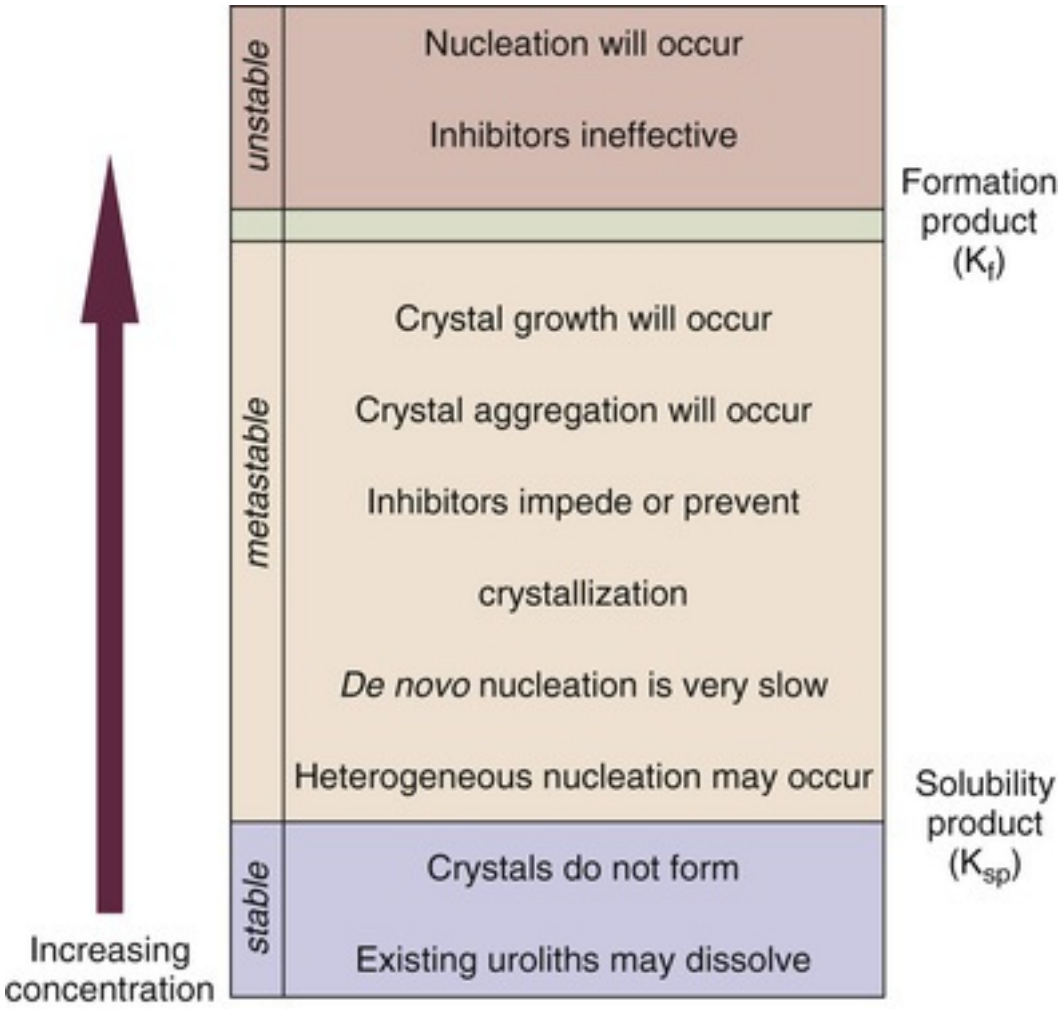

FIGURE 331-1 States of saturation related to the formation of crystals in urine.

Diagnosis

Lower urinary tract signs (see ch. 46) are a common indication to evaluate dogs for uroliths. Medical imaging is the most utilized confirmatory test.[1] When performing abdominal radiography, it is important to include the entire urinary tract to avoid overlooking the possibility that uroliths may also reside in any region within the urethra. Because small uroliths less than 2 mm in diameter and some stone types have poor radiographic opacity (e.g., urate, cystine), abdominal ultrasonography (US), contrast urethrocystography, or other more sensitive techniques should be considered before uroliths can be completely eliminated as the cause for clinical signs. These imaging modalities have also been useful in differentiating mineralized urothelial neoplasia or cystic foreign bodies from uroliths. Although palpation of the lower urinary tract is an insensitive method of diagnosis, this simple diagnostic tool should not be abandoned. In some instances, rectal palpation of the pelvic urethra has revealed uroliths that were obscured by the pelvic bones when viewed radiographically or were inaccessible by routine US.

A diagnosis of urolithiasis without predicting their composition is insufficient to optimally select effective therapy. For example, a dog with infection-induced struvite nephroliths and cystoliths cannot be adequately managed with cystotomy alone. Similarly, if urine was not cultured for aerobic bacteria prior to therapy, treating with a therapeutic diet would not be as effective as controlling the underlying infection. Review of appropriate imaging and urinalysis with a portion saved for bacterial culture is essential in all urolith cases. In addition, many require evaluating a serum biochemical profile, especially those with liver disease or urethral obstruction.

Predicting Mineral Composition

Overview

Accurately predicting mineral composition of uroliths, prior to their removal, permits developing a safe and effective therapeutic plan. For example, avoiding nonsteroidal pain medications and anesthetics that are primarily metabolized by the liver will improve patient outcomes in dogs with suspected urate uroliths caused by hepatic portovascular anomalies (see ch. 284). Likewise, some dogs with suspected cystine uroliths may benefit from castration at the time of urolith removal to minimize recurrence.[2] Crystalluria, the primary method of predicting urolith composition, is insensitive and unreliable.[3] Once stones form, crystals associated with that stone type often decrease or disappear from the urine. To more accurately predict urolith composition, survey radiography should be the first tool used, together with stone prevalence, breed, and gender (Table 331-1). This information, crystal identification, and urine pH are often sufficient to accurately predict the major component of most uroliths.

TABLE 331-1

Predicting Mineral Composition of Uroliths in Dogs

UROLITH TYPE	PREVALENCE (%)	RADIOGRAPHIC APPEARANCE	COMMON BREEDS	GENDER % (I/N)	CRYSTALLURIA	URINE PH
Calcium oxalate monohydrate	37.5	Markedly to moderately radiopaque Round, bosselated to irregular	Mixed, Mn Schnauzer, Shih Tzu, Yorkshire Terrier, Chihuahua, Bichon (59.2%)	F-22 (3.2/18.8) M-76.8 (15.4/61.4)	Dumbbells, pickets	<6.5
Calcium oxalate dihydrate	5.3	Markedly to moderately radiopaque Spiculated and star-shaped rosettes	Shih Tzu, Yorkshire Terrier, Mn Schnauzer, Bichon, Chihuahua	F-17.1 (2.3/14.8) M-81.4 (26.1/55.3)	Envelope with cross	<6.5
Struvite	36.8	Moderately to markedly radiopaque Round to faceted	Shih Tzu, Mn Schnauzer, Dachshund, Pug, Bichon	F-82.2 (15.2/67.0) M-14.4 (7.2/7.2)	Prismatic	>7
Urate salts	4.0	Radiolucent to	Dalmatian, Mixed,	F-19.2	Amorphous,	≤6.5

		marginally radiopaque Round smooth to mulberry	Yorkshire Terrier, English Bulldog, Shih Tzu, Miniature Schnauzer	(4.8/14.4) M-79.1 (25.1/54.0)	speculated globules with and without spicules	
Cystine	2.1	Radiolucent to marginally radiopaque Round smooth to mulberry	English Bulldog, Mixed, Chihuahua, Dachshund, French Bulldog, Pitbull	F-0.9 (0.4/0.5) M-97.2 (76.8/20.4)	Hexagon	≤6.5
Silica	0.4	Moderately to markedly radiopaque Star shaped with geometrically radiating low to high spikes	Mixed, Labrador Retriever, Shih Tzu, German Shepherd Dog, Chihuahua, Golden Retriever	F-6.7 (2.1/4.6) M-91.5 (37.3/54.2)		
Calcium phosphate carbonate	0.5	Moderately to markedly radiopaque. Smooth round to faceted.	Mixed, Shih Tzu, Bichon, Pug, Mn Schnauzer, Chihuahua (57.2%)	F-77.8 (11.9/55.9) M-31.3 (13.8/17.5)	Amorphous	≥7.5
Brushite	0.3	Small moderately to markedly radiopaque. Smooth round.	Shih Tzu, Mixed, Bichon, Yorkshire terrier, Papillon, Maltese (71.3%)	F-32.0 (4.6/27.4) M-66.8 (31.4/35.4)	Amorphous	>6.5
CaP apatite	0.1	Small moderately to markedly radiopaque. Smooth round.	Mixed, Shih Tzu, Pug, Labrador Retriever, Dachshund, Papillon (60.5%)	F-34.8 (4.6/30.2) M-62.8 (22.1/40.7)	Amorphous	>6.5
Xanthine	0.1	Radiolucent round to irregular	Mixed, Dalmatian, Labrador, Not reported, Cavalier KCS, Rottweiler (66.14%)	F-16.9 (7.0/16.9) M-81.7 (33.8/47.9)	Globular	
Compound	9.9	Larger stones with inner and outer layers of different radiopacity	Mixed, Shih Tzu, Mn Schnauzer, Yorkshire Terrier, Bichon, Dachshund (61.1%)	F-69.9 (13.8/56.1) M-28.7 (9.4/19.3)	Variable	
Mixed	3.2	Variable	Mixed, Shih Tzu, Mn Schnauzer, Bichon, Yorkshire Terrier, Pug (61.7%)	F-77.3 (14.3/63.0) M-21.0 (8.6/12.4)	Variable	

I/N, Intact/neutered; *Mn*, Miniature.

Urolith Prevalence

Knowing the frequency at which different mineral types of uroliths are diagnosed is of value when predicting their composition. Calcium oxalate and struvite stones accounted for about 80% of almost 70,000 canine uroliths analyzed. Calcium oxalate predominated in North America, Asia and Europe, while struvite was the most common stone in Africa, Australia (but not New Zealand), and South America.[4] In this analysis, the majority of dogs that formed calcium oxalate were male (78%) and the majority of dogs that formed struvite were female (82%).

Radiographic Appearance of Uroliths

The radiographic appearance of uroliths (radiopacity, uniformity of radiopacity, size, shape, and contour) is highly correlated with composition and is one of the most reliable tools for predicting urolith type prior to

analysis (Figure 331-2).[5] Uroliths composed of calcium oxalate, calcium phosphate, and silica are radiopaque. Struvite is moderately radiopaque, but cystine, urate, and xanthine stones are commonly radiolucent. Radiopaque uroliths <2 mm may be difficult to discern on survey radiographs, requiring US or contrast enhancement techniques to be seen. Radiolucent uroliths >5 mm may be visible on survey radiographs. A urolith whose central area has a radiopacity different from the outer layer is consistent with a compound urolith. The same radiographic generalities for noncompound uroliths apply to the layers of compound uroliths. Urinalysis is usually most consistent with the composition of the stone's outer layer.

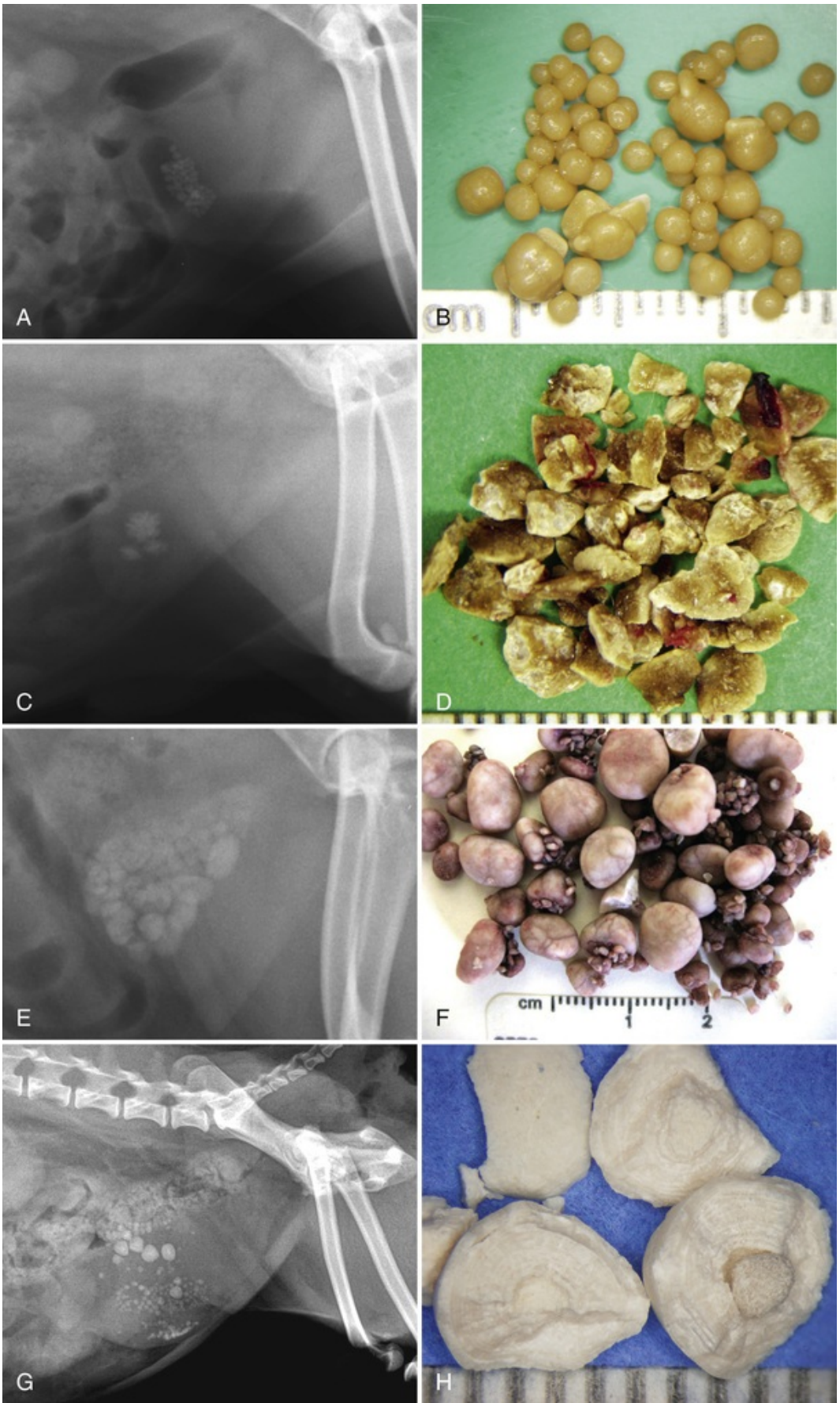

FIGURE 331-2 Calcium oxalate monohydrate uroliths before and after voiding urohydropropulsion **(A** and **B),** calcium oxalate dihydrate uroliths before and after laser lithotripsy **(C** and **D),** infection-

induced struvite uroliths before and after cystotomy **(E** and **F),** compound stones with a center of calcium oxalate and an outer layer of struvite before and after laser lithotripsy **(G** and **H).**

Breed

Breed predispositions and genetic inherited defects in the processing of calculogenic precursors support utilization of patient signalment to assist prediction of urolith composition.[2,6,7] While calcium oxalate uroliths have been identified in >100 breeds, 50% are identified in 6 breeds: Miniature Schnauzer, Shih Tzu, Yorkshire Terrier, Chihuahua, Bichon Frise, and Maltese. These and related breeds of small dogs are also overrepresented in the prevalence of other stone types (see Table 331-1). English Bulldogs are overrepresented among urate and cystine urolith formers.[8] Breed would be a more reliable predictor of urolith type if it segregated out as nicely as Dalmatians and urate uroliths: 96% of urolith-forming Dalmatians produced uroliths of salts of urate.[9]

Urinalysis

Knowing the type of urine crystals and pH can be helpful in managing dogs with urolithiasis, but such information is not perfectly sensitive or specific as a predictor of urolith composition.[3] Once stones form, it is thermodynamically more favorable for minerals to deposit on the surface of a preformed stone than to form new crystals. As a result, crystals are often absent in the urine of a pet with cystic calculi. When present, crystals may not represent urolith composition but instead form as a function of pH or factors unrelated to the urolith. This may explain why struvite crystalluria is observed in dogs with calcium oxalate uroliths as urine is therapeutically alkalinized.

Urolith Retrieval

Accurately predicting mineral composition of some uroliths may be difficult, especially those that are mixed (i.e., not composed of a primary mineral), compound, or uncommon. If uroliths are less than 3 mm, they can be collected during voiding or catheter retrieval (Video 331-1).[10] During voiding, owners can position a fine meshed cooking strainer or fishnet in the urine stream path. If urolith collection is not successful after several attempts, uroliths can be retrieved with a large-bore urinary catheter after placing a dog in left or right lateral recumbency. Local anesthetic lubricant is instilled in the urethra, but some anxious dogs are helped by sedation. Using clean technique, the tip of the urinary catheter is inserted in the distal urethra and passed forward to the trigone. Precise location can be determined by measuring distances using radiographs. A syringe should be attached to the catheter, and gentle intermittent negative pressure should be applied as the catheter tip is withdrawn from the bladder. As the tip of the urinary catheter is moved from the bladder to the urethra, urine flow will cease. Then advance the catheter toward the bladder and urine flow resumes when the tip of the catheter enters the trigone. The catheter tip can also be positioned with fluoroscopy or US guidance. While agitating the bladder, remove the remaining urine and inspect the syringe contents for small stones. If no stones are retrieved, repeat the procedure by instilling 5 mL/kg body weight (up to 50 mL when using a 60-mL syringe) of sterile isotonic solution through the catheter and agitate the bladder while emptying (Videos 331-2 and 331-3). The procedure can be repeated until stones are collected. Submit retrieved uroliths for quantitative mineral analysis.

Urolith Removal

Overview

Urolith removal has, classically, been the province of the surgeon. Less invasive procedures have been developed, and some can be performed by any veterinarian (e.g., medical dissolution and voiding urohydropropulsion). Others may require advanced training and special equipment (e.g., basket retrieval, laser lithotripsy [Figure 331-3], percutaneous cystolithotomy; see ch. 124).

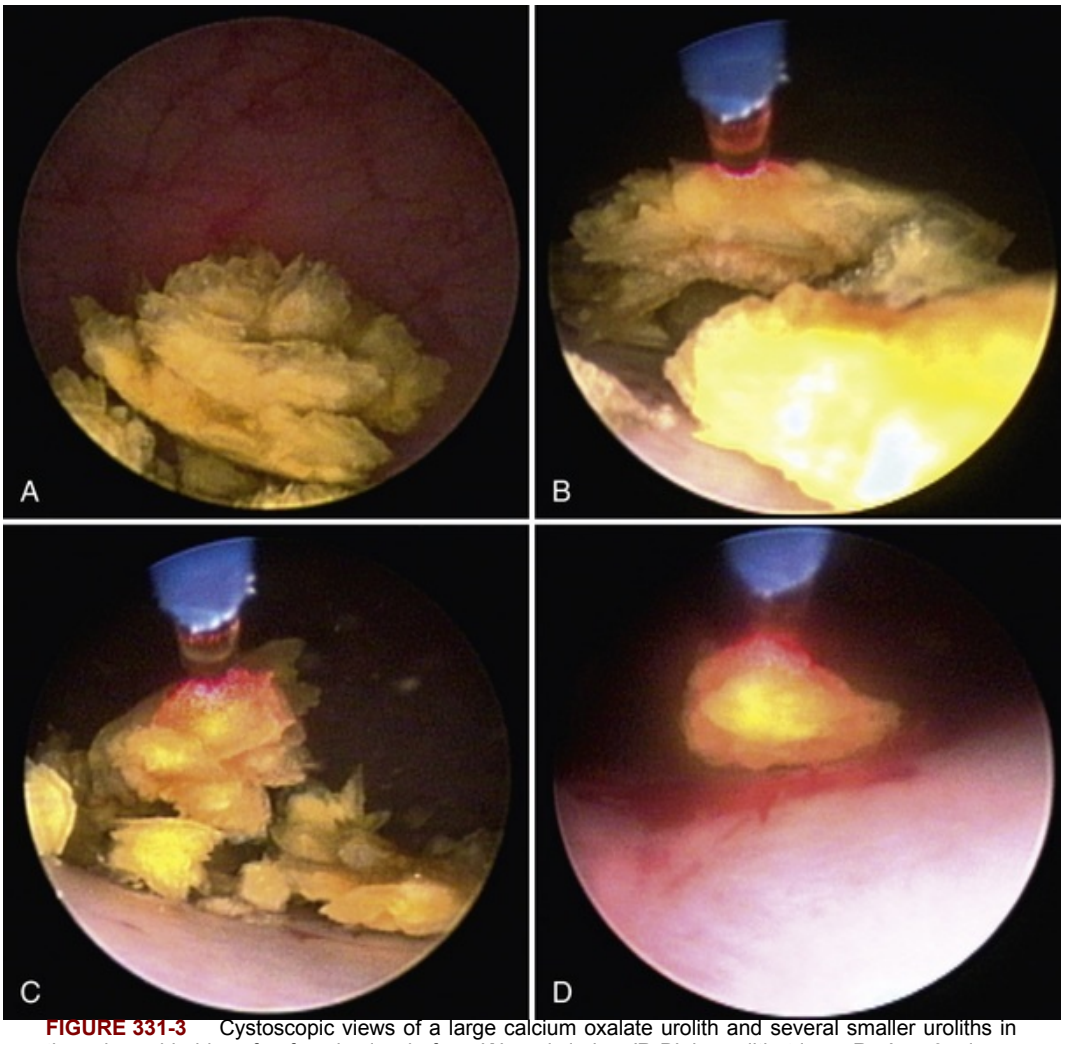

FIGURE 331-3 Cystoscopic views of a large calcium oxalate urolith and several smaller uroliths in the urinary bladder of a female dog before **(A)** and during **(B-D)** laser lithotripsy. **B,** A 550-micron diameter flexible quartz laser fiber is positioned near the surface of the urolith, which has broken into two larger fragments. Notice the red aiming beam visible on the surface of the urolith. **C,** Calcium oxalate urolith fragments after additional laser lithotripsy. **D,** Notice a small urolith fragment adjacent to the mucosa and that the laser energy fragments the urolith without damage to the adjacent mucosa. There is a minimal amount of mucosal trauma from the sharp projections of the urolith fragment. (Reprinted with permission from Adams LG, Berent AC, Moore GE, Bagley DH: Use of laser lithotripsy for fragmentation of uroliths in dogs: 73 cases [2005-2006]. *J Am Vet Med Assoc* 232:1680-1687, 2008.)

Goals

When selecting a procedure to remove uroliths, consider the following patient-centered goals:

1. Remove all stones and stone fragments. Chance of future urethral obstruction can follow failure to remove all uroliths. Failure to remove all stones may cause signs of hematuria, stranguria and dysuria to continue, and urinary tract infection will remain as well. Thus, there would be need for additional urolith extraction procedures.[11,12] Surgery has not consistently resulted in removal of all stones. In 128 dogs undergoing surgery for cystic calculi removal, only 19 (15%) had appropriate postsurgical imaging and incomplete urolith removal was identified in 8/19 (42%).[13] Efficacy of laser lithotripsy was prospectively evaluated in 100 dogs with naturally occurring uroliths and incomplete removal was identified in 18 (9 with uroliths ≥3 mm, 7 with uroliths 1-3 mm, and 3 with uroliths <1 mm).[14]
2. Minimize injury to healthy tissues. The advantage of noninvasive and minimally invasive procedures is their ability to preserve normal anatomy. Avoiding surgery or minimally disrupting tissues is likely to be associated with reduced infection, reduced pain, shorter hospitalization, faster return to function, fewer complications and less scarring.[15]

3. Select procedures less likely to contribute to urolith recurrence. Recurrence of uroliths following removal is commonly attributed to failure of medical therapy. However, when recurrent uroliths from 1733 dogs were analyzed, 163 (9.4%) were attributable to a nidus of suture.[16] These findings emphasize the risk of surgical procedures to contribute to recurrent disease that may have been avoided by minimally invasive techniques.

Methods of Removal in Asymptomatic Pets

Treatment of asymptomatic uroliths composed of struvite involves urine acidification and antibiotics.[17,18] Cystine stones are often managed with a prescription diet (Hill's u/d).[19,20] Urate stones are managed with allopurinol and prescription diet u/d.[21] Allopurinol-induced xanthine stones require stopping the allopurinol. An attempt should be made to dissolve these stones medically, unless previous attempts were ineffective or poorly tolerated. Uroliths can be monitored and removed when symptoms develop (Table 331-2). Asymptomatic uroliths small enough to pass through the urethra should be removed with voiding urohydropropulsion (see Video 331-2) or basket retrieval (Video 331-4).[14,22,23] Larger uroliths should be left alone until the patient becomes symptomatic. Owners should be advised of the clinical signs and follow-up plans in the event of a urethral obstruction. Pets in whom owner monitoring is unreliable may be best managed with urolith removal prior to the onset of clinical disease.

TABLE 331-2

Minimally Invasive Methods of Stone Removal

METHOD	SUITABLE CANDIDATES	RELATIVE CONTRAINDICATION	STRATAGEM	COMMON MISCONCEPTIONS THAT ARE NOT TRUE
Spontaneous voiding	Small uroliths (e.g., <2 to 3 mm) that can easily pass through the urethra	Symptomatic dogs with uroliths of potential size to obstruct the urethra	A small cooking strainer or fishnet placed under the dog's urine stream will allow collection of passed stones for analysis.	
Medical dissolution	Highly successful for struvite, allopurinol-induced xanthine, and cystine uroliths. Less successful for urate uroliths	Urethral obstruction A single large stone occupying almost all of the urinary bladder	For infection-induced struvite, administer antibiotics throughout the entire period of dissolution.	Dogs are at increased risk for urethral obstruction.
Voiding urohydropropulsion	Stones likely to pass through the urethra; usually smooth uroliths <4 mm, or irregular uroliths <3 mm but this is influenced by the size of the dog and its urethra. Dogs of a weight that are suitable for lifting	Urethral obstruction Recent cystotomy Urethral stricture	Avoid anesthetics that increase urethral tone (e.g., dexmedetomidine). Administer a caudal epidural (lidocaine) to ensure urethral relaxation. To further relax the urethral in anesthetized dogs, administer 1 mg/kg propofol IV just prior to bladder expression. With many irregular stones, consider basket removal	A light plane of anesthesia is sufficient to relax the urethra. A stone that becomes lodged in the urethral is difficult to flush back into the urinary bladder.

			before voiding urohydropropulsion.	
Stone basket retrieval	Stones or stone fragments likely to pass through the urethra; usually, smooth uroliths <4 mm but this is primarily influenced by the size of the dog and its urethra		Orient stones so they are lengthwise when passing through the urethra with their sharp edges pointing opposite to their direction of retraction. Use baskets that permit dislodgement of the uroliths in case uroliths become entangled in urethral lumen and need reorientation or repositioning.	
Intracorporeal laser lithotripsy	In males ≥6 kg with not more than three stones requiring lithotripsy (i.e., between 4 to 7 mm in diameter). In females, no restriction in stone size, but struvite stones should be medically dissolved. All uroliths in the urethra	Marked hematuria will markedly reduce visibility. Large stone burden, unless more than one lithotripsy session is anticipated to complete removal. Male cats and small male dogs in which the scope cannot be passed through the urethral lumen	To improve visibility initially and periodically, use an 8-Fr catheter to empty bladder, then flush repeatedly with sterile isotonic solution. Avoid anesthetics that increase urethral tone (e.g., dexmedetomidine). Administer a caudal epidural (lidocaine) to ensure urethral relaxation.	Urolith fragments will pass during spontaneous voiding and do not need to be removed.
Percutaneous cystolithotomy	Males with greater than three larger (>7 mm) stones but can be performed for all types if lithotripsy is not available. In females, most stones can be managed by lithotripsy.		Place a Foley catheter in the urethra such that the inflated cuff occludes the proximal urethra to minimize distal migration of stones.	

Methods of Removal in Symptomatic Pets

Once uroliths cause clinical signs, they are often too large to be flushed out of the urinary tract by voiding urohydropropulsion. Medical dissolution should be attempted first for those amenable to dissolution. If urethral obstruction has occurred, stones should be removed to prevent reobstruction. Strive to remove all uroliths by a combination of basket retrieval (see Video 331-4), laser lithotripsy (Videos 331-5 and 331-6) or percutaneous cystolithotomy (see ch. 124).[14,24-29] If these procedures are not available, uroliths can be removed by cystotomy after any urethroliths have been flushed back into the bladder prior to surgery. Because of the high frequency of adverse effects associated with urethral surgery (e.g., stricture, recurrent urinary tract infections, etc.), urethrotomy and urethrostomy are discouraged except in special circumstances (e.g., client inability to afford additional care with recurrent obstruction).[30]

Urolith Prevention (Table 331-3)

Calcium Oxalate (CaOx)

CaOx urolithiasis is a chronic disease with a high rate of recurrence (about 50% in 2 years).[30] Hypercalciuria appears to be the primary driving force for stone formation, but selecting effective therapy can be challenging because (1) the precise etiologic causes are poorly understood, (2) it is not known which risk factors contribute most to disease, and (3) surrogate endpoints of therapeutic efficacy such as relative supersaturation are mathematical models that may not correlate well with urolith formation, especially when evaluated in clinically healthy dogs without uroliths.[32-34] Therefore, CaOx uroliths tend to recur despite our best efforts. Current therapeutic strategies to reduce urinary quantity of Ca available to bind Ox include feeding only high-moisture foods (e.g., canned, loaf, gravies) to achieve a urine specific gravity <1.020 and avoiding foods that promote urine acidification (<pH of 6.6 to 7). Diets that promote formation of acidic urine in dogs (pH <6.6) were associated with increased Ca excretion and CaOx uroliths.[35,36] One can administer potassium citrate or other citrate salts to dogs with consistently acidic urine. Add hydrochlorothiazide diuretics (2 mg/kg PO q 12 h) to the treatment strategy in dogs with persistent CaOx crystalluria or highly recurrent disease.[37]

TABLE 331-3

Common Medications Used to Manage Uroliths in Dogs

NAME	DOSE	MECHANISM OF ACTION	ADVERSE COMPLICATIONS	ADDITIONAL INFORMATION
Allopurinol	Dissolution:15 mg/kg q 12 h Prevention: 5 to 7 mg/kg q 12 to 24 h	Allopurinol and its active metabolite, oxypurinol, inhibit xanthine oxidase, blocking the conversion of hypoxanthine and xanthine to uric acid	Xanthine uroliths Hypersensitivity Renal disease	Newer xanthine oxidase inhibitors (Febuxostat) are not purine analogs and do not require hepatic metabolism to extend duration of action.
Potassium citrate	75 mg/kg q 12-24 h titrated to achieve a urine pH between 7 and 8	Augments renal excretion of citrate which binds calcium, reduces calcium oxalate formation and their attachment to urothelium	Decreased appetite Hyperkalemia	Give with food. Most formulations inappropriately contain cranberry, which may augment urine oxalate. Most are formulated with silica dioxide, which may contribute to silica in recurrent stones.
dl-methionine	100 mg/kg q 12 h	Urinary acidifier to enhance struvite dissolution in dogs not managed with therapeutic foods	Decreased appetite Acidemia	Give with food.
Vitamin B_6	2 to 4 mg/kg q 24 to 48 h	Favors conversion of oxalate precursors to glycine, minimizing oxalate production		Only recommended for dogs consuming B_6-deficient foods.
Hydrochlorothiazide	2 mg/kg q 12 h	Reduce urine calcium excretion by enhancing renal tubular reabsorption of calcium	Hypercalcemia Mild dehydration	
Tiopronin (Thiola)	Dissolution 15 to 20 mg/kg q 12 h Prevention 5 to 15 mg/kg q 12 h	Binds to cysteine to form a more soluble complex than the cysteine dimer (i.e., cystine)	Proteinuria Thrombocytopenia Anemia Pustules	Difficult to obtain—consider consulting a compounding pharmacy.

Commercially manufactured diets have been designed to prevent CaOx recurrence, but they may not be

ideal for all pets. Hill's Prescription diet u/d has been shown to decrease Ca and Ox excretion and recurrence in dogs with CaOx urolithiasis.[37] This diet has lower levels of sodium and protein, promoting neutral to alkaline urine. Although it has passed AAFCO feeding trials, some consider the protein content too low. If this is the case, consider feeding ½ u/d and ½ of a canned moderate protein senior food that does not acidify the urine (e.g., Hill's Prescription diet g/d or Hill's Prescription diet c/d multicare). Because u/d is high in fat, dogs with hereditary hyperlipidemia (e.g., some Miniature Schnauzers) may benefit from a similar feeding mixture. Hill's Prescription diet w/d has been recommended for dogs with CaOx urolithiasis with fat/lipid intolerance or fat/lipid responsive disorders (e.g., a history of pancreatitis). Because this diet promotes formation of acidic urine, administer potassium citrate to promote a more favorable urine pH (>6.5). Royal Canin SO has been shown to decrease CaOx relative supersaturation in dogs with CaOx uroliths.[34] Because this diet promotes acidic urine, concomitant administration of potassium citrate is necessary to achieve a more favorable urine pH (>6.5).

Struvite

The majority of struvite uroliths form as a consequence of urinary tract infection (UTI) with bacteria that produce urease. Urease is responsible for converting urea to ammonia, which alkalinizes urine and favors struvite precipitation. Therefore, the most effective strategy to minimize urolith recurrence is to eliminate future urinary tract infections (see ch. 330; Figure 331-4). Sterile struvite uroliths, by contrast, are effectively prevented with therapeutic foods (Hill's Prescription diet c/d multicare, Royal Canin SO, others).

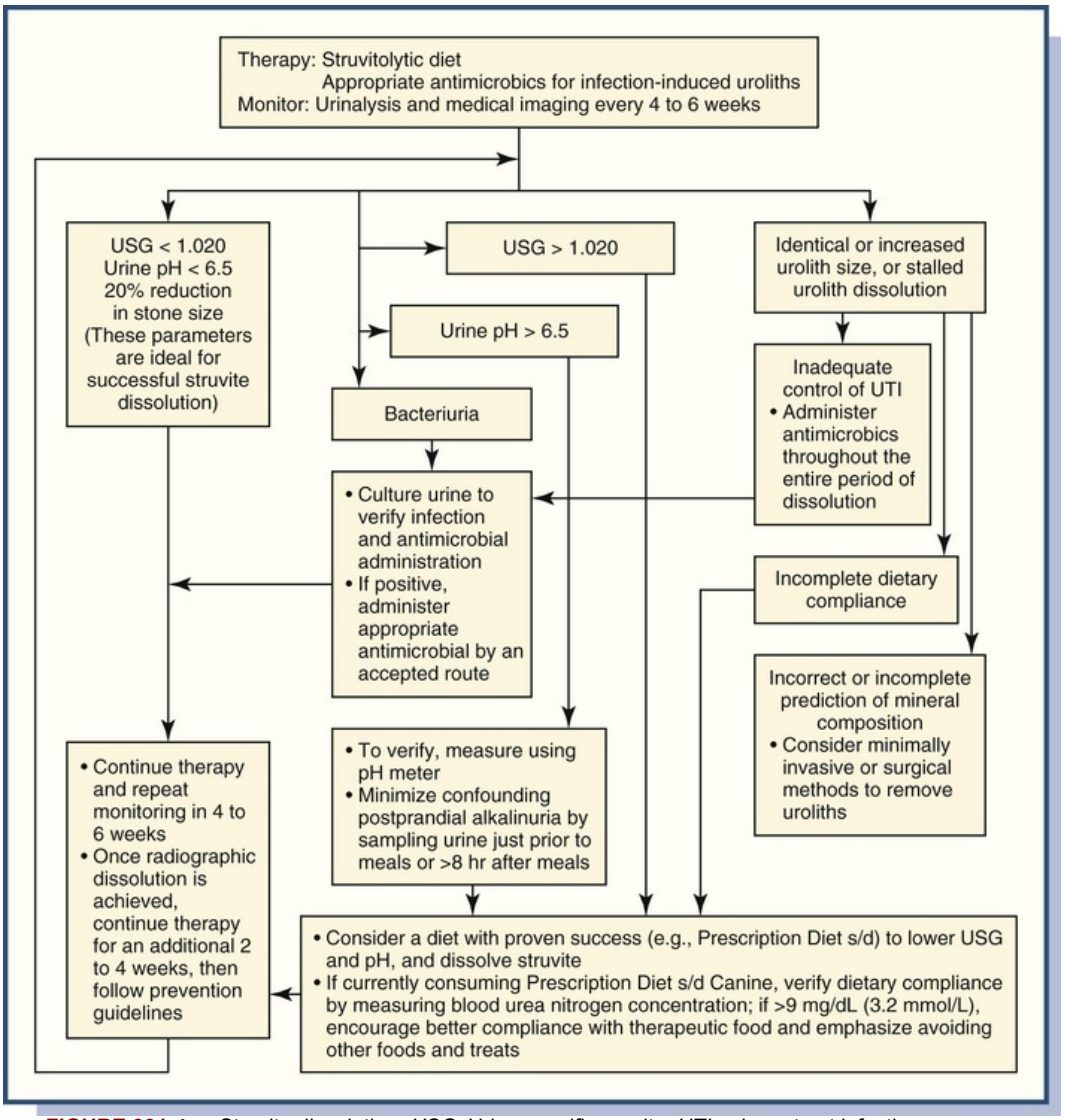

FIGURE 331-4 Struvite dissolution. *USG*, Urine specific gravity; *UTI*, urinary tract infection.

Urate Uroliths

Two distinct diseases are associated with urate urolithiasis in dogs: an inherited alteration of the urate transporter encoded by the SLC2A9 gene (Figure 331-5) and hepatic portovascular anomalies (see ch. 284).[7,38] Common to both is inefficient transport of uric acid into hepatocytes where it normally is enzymatically oxidized into the highly water-soluble end product, allantoin. Instead, high concentrations of uric acid are excreted in the urine. Minimizing urolith recurrence is achieved by decreasing hyperuricosuria (e.g., reducing dietary purine intake and blocking metabolism of urate precursors) and increasing urate solubility (i.e., increasing urine pH [7.0 to 7.5]). Several therapeutic foods have been formulated to lower purine intake (Purina HA, Royal Canin UC, and Hill's Prescription diet u/d). Feed high-moisture foods or add water to food to achieve consistently low specific gravities (<1.020). If urine pH is <7, consider potassium citrate.

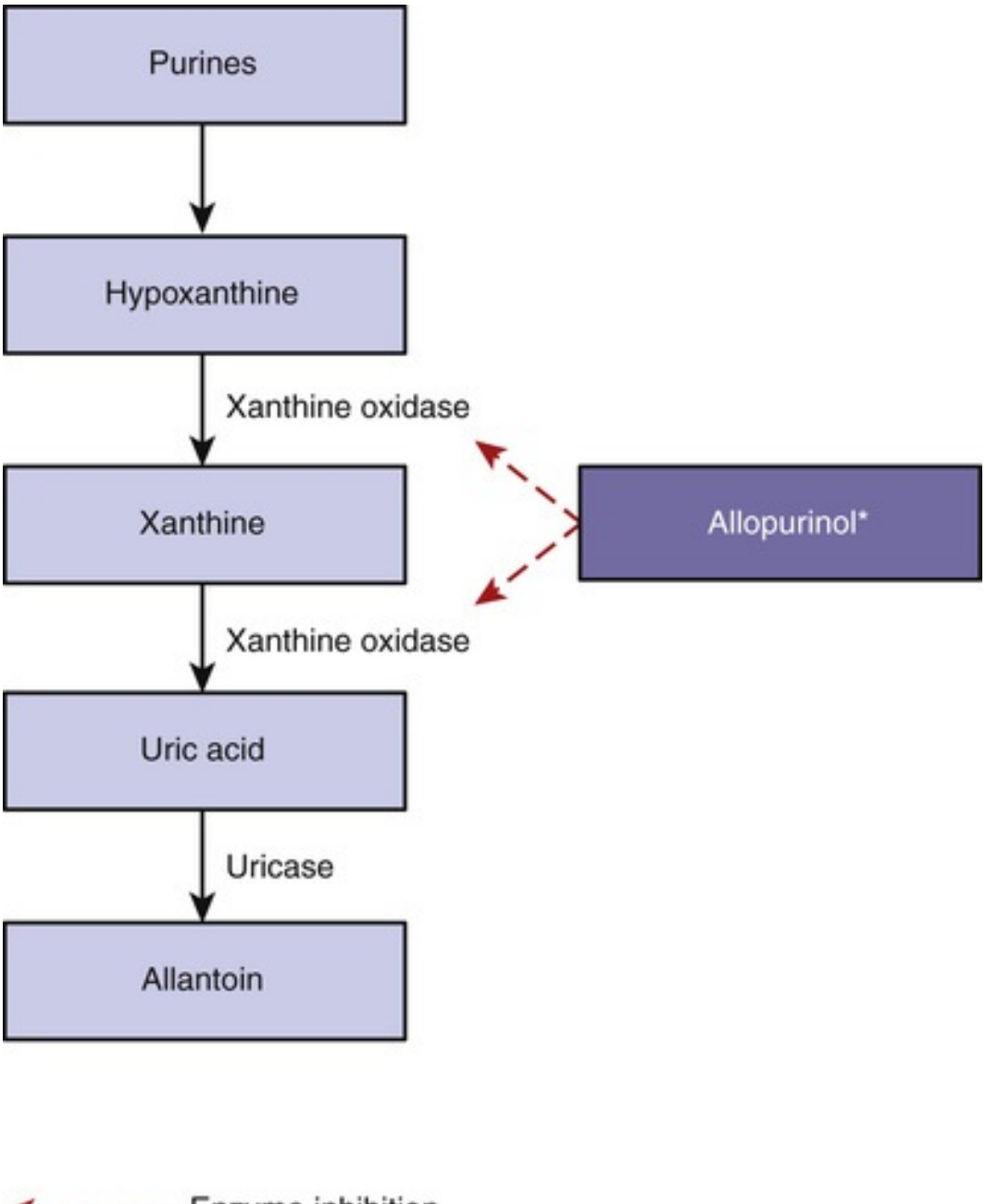

FIGURE 331-5 Metabolic pathway of purine degradation to allantoin showing site of action of allopurinol. *The major metabolite of allopurinol, oxypurinol, is also an inhibitor of xanthine oxidase.

Preventing uroliths in dogs with portovascular anomalies is complicated. Low doses of allopurinol (xanthine oxidase inhibitors) are commonly administered to dogs without liver disease (e.g., Dalmatians, Bulldogs, etc.) to minimize the conversion of purines to uric acid. However, sufficient liver function is needed to convert allopurinol to its more effective, longer-acting analog, oxypurinol. Lower purine/protein foods and vegetable proteins of lower biological value may not be ideal for dogs with liver disease. Lastly, surgical correction of the vascular anomaly is not typically sufficient to eliminate urolith recurrence. Therefore, sufficient water and urine alkalization are important.

Cystine

Cystinuria is a rare inherited disease characterized by failure of renal tubular reabsorption of cystine (a poorly soluble amino acid; see ch. 328). Affected pets have recurrent cystine urolith formation. To minimize urolith recurrence, it is best to increase fluid consumption, limit animal protein intake, limit sodium intake, and

alkalinize urine. Recurrence has been controlled with pharmacologic therapy alone (Thiola) and nutritional therapy alone (Hill's Prescription diet u/d).[19,21] In some forms of cystinuria, neutering has been associated with reductions in urine cystine concentration and prevention of recurrence. To identify which dogs can be effectively managed by neutering, measure urine cystine before and after castration. It is unknown if castration alone will promote urolith dissolution in this subset of dogs.

Compound Uroliths

The most common compound urolith is an inner layer of CaOx and an outer layer of struvite. To prevent recurrence, select nutritional therapy to manage CaOx and antimicrobial therapy to manage struvite. The second most common compound stone is an inner layer of struvite and an outer layer of calcium phosphate carbonate. Control of urinary tract infection will prevent both of these minerals from forming.

Xanthine Uroliths

Naturally occurring xanthinuria results from genetic defects in the enzymes or cofactors that catalyze the final steps of purine degradation. To minimize urolith recurrence, increase fluid consumption, limit animal purine/protein intake, and alkalinize urine. Allopurinol-induced xanthine uroliths can be controlled by eliminating or reducing allopurinol dosage at the same time that a reduction in purine/protein consumption is instituted.

Calcium Phosphate

Hydroxyapatite, calcium hydrogen phosphate dihydrate (Brushite), tricalcium orthophosphate (Whitlockite), and octacalcium phosphate uroliths are rare. Strategies to prevent these stones from forming are the same as those employed for CaOx, unless associated with hypercalcemic disorders, which, when corrected, should prevent recurrence (see ch. 69 and 297). In contrast, prevention of calcium phosphate carbonate uroliths depends on early diagnosis and eradication of urinary tract infections while avoiding nutritional strategies that promote calcium excretion (e.g., urine acidification).

Silica

The cause for silica uroliths is unknown but appears to be associated with three sources: silicon dioxide found as an inert ingredient of many tablets; consumption of whole grains, particularly rice, beet pulp, and soybeans; and using water and plant foods derived from active geothermal (volcanos, hot springs, geysers) locations. Replacing each of these sources with lower or nonsilica substitutes and encouraging high fluid consumption should reduce recurrence.

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Suggested Readings

[Genetic testing for cystine uroliths; Available at] research.vet.upenn.edu/PennGenHome/tabid/91/Default.aspx.

[Genetic testing for uric acid uroliths; Available at] vgl.ucdavis.edu/services/Hyperuricosuria.php.

[Minnesota Urolith Center for stone submission and therapeutic recommendations; Available at] urolithcenter.org.

[Select a nutritionist to help construct a homemade diet; Available at] http://www.acvn.org/directory/.

[Stone analysis laboratory; Available at] http://www.vetmed.ucdavis.edu/usal/index.cfm.

CHAPTER 332

Lower Urinary Tract Urolithiasis—Feline

Mary Anna Labato

Client Information Sheet: Lower Urinary Tract Urolithiasis—Feline

Introduction

Urolithiasis is defined as the formation of uroliths (calculi or stones) within the urinary tract. Uroliths can vary in their mineral composition.[1] Recent studies have reported that 7-28% of cats presenting for lower urinary tract signs were diagnosed with urolithiasis.[2-4] The most common feline urolith types are struvite (magnesium ammonium phosphate) and calcium oxalate (CaOx) (each >40% of uroliths).[2-8] Purine uroliths represent about 5% of cases, with about 7% being composed of other substances such as matrix, calcium phosphate, blood stones, compound stones and drug-induced.[7,9] (Figure 332-1).

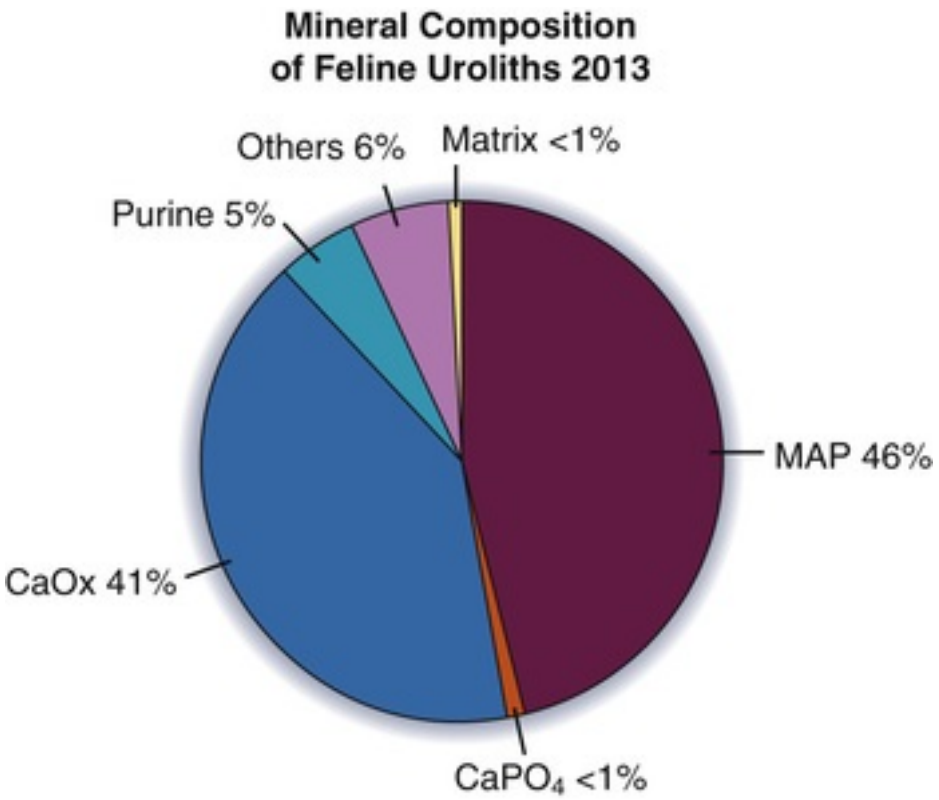

FIGURE 332-1 Mineral composition of feline uroliths—2013 data. *CaOx,* Calcium oxalate; *$CaPO_4$,* calcium phosphate; *MAP,* magnesium ammonium phosphate (struvite). (From Minnesota Urolith Center.)

Clinical Signs

Cats with cystouroliths can present with a variety of lower urinary tract signs. These include pollakiuria, stranguria, hematuria, periuria, or a combination of these signs. When a urolith becomes lodged in the urethra, the clinical signs are those related to urethral obstruction (see ch. 334 and 335). These signs are not specific for uroliths and include as differentials urinary tract infections, feline idiopathic cystitis and neoplasia. Frequently cystouroliths do not result in any clinical signs and are an incidental finding on either abdominal palpation, survey radiographs or abdominal ultrasound.

Clinical Testing

For cats presenting with clinical signs suggestive of urolithiasis, a basic diagnostic minimal database workup consists of a complete blood count and serum biochemistry profile. In most instances these will be within normal parameters but may reveal underlying conditions that could predispose to urolith formation such as diabetes mellitus, chronic kidney disease, and liver function tests, suggesting a preexisting condition such as a portosystemic shunt. In the geriatric cat, a thyroid level should be determined as well.

A urinalysis is essential (see ch. 72), although uroliths can be present without crystalluria and crystalluria may not accurately predict urolith type. Crystalluria is not a consistent feature of urinalysis in cats with uroliths. Urine specific gravity is important to determine, especially in those cats with a history of prior urolith formation. In these cases, it is important to create dilute urine so that minerals in the urine do not reach the point of saturation to result in crystal aggregation and ultimate stone formation. Urine pH affects crystal formation as well. Struvite, calcium carbonate, and calcium phosphate (apatite) are less soluble in alkaline urine. Ammonium urate, silica and cysteine are less soluble in acid urine. Urine samples should be analyzed within one hour of collection to minimize temperature and time-dependent *in vitro* crystallization.[10] Urine culture should be submitted if there is an active sediment or if the urine specific gravity is low and infection is high on the list of differentials.

Diagnostic imaging should be utilized to confirm the presence of uroliths. Survey radiographs should be positioned to include the entire urinary system. Mineralized stones that can be visualized with radiographs include CaOx, struvite, apatite and silica (Figure 332-2). Most ammonium urate and cysteine uroliths are nonmineralized and thus not visible with radiographs unless they are mixed with some mineralized stones. Contrast cystourethrography is needed to visualize these uroliths.

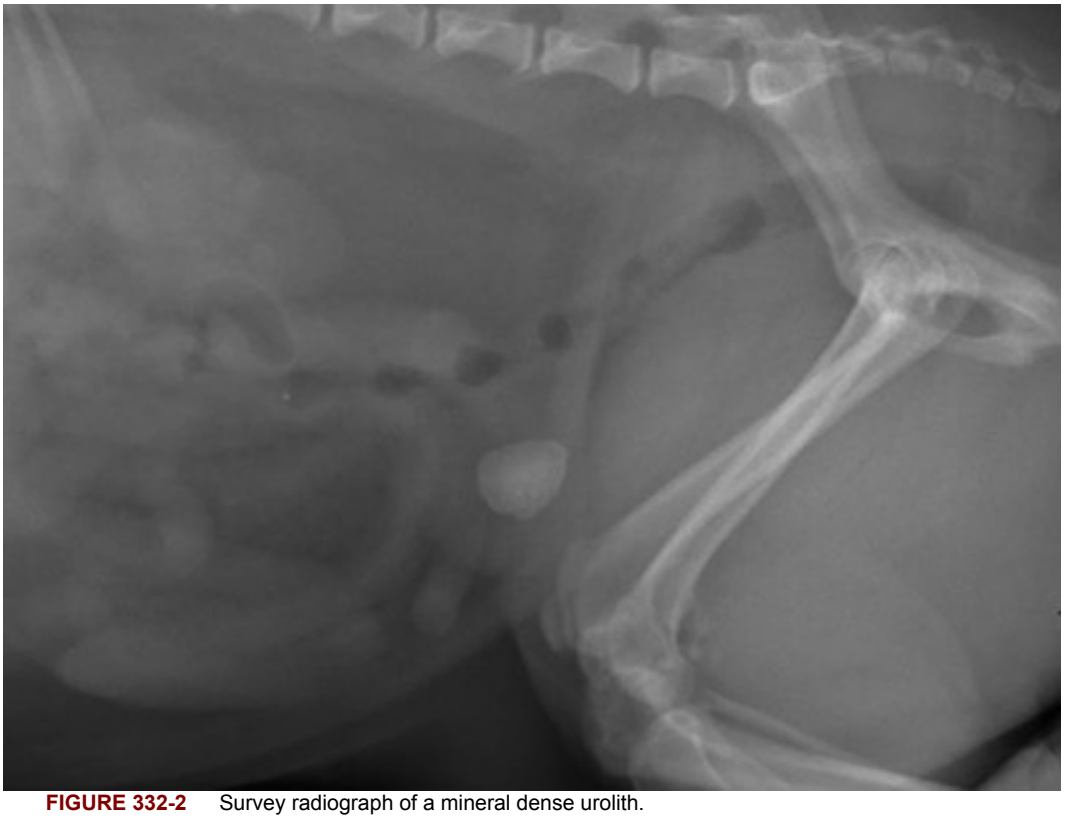

FIGURE 332-2 Survey radiograph of a mineral dense urolith.

Abdominal ultrasound is useful in identifying uroliths, both mineralized and nonmineralized varieties. As a diagnostic modality, it is able to detect large nonmineralized stones, as well as those very small uroliths that can often be successfully voided by the patients (especially female cats) (Figures 332-3 and 332-4 and Video 332-1).

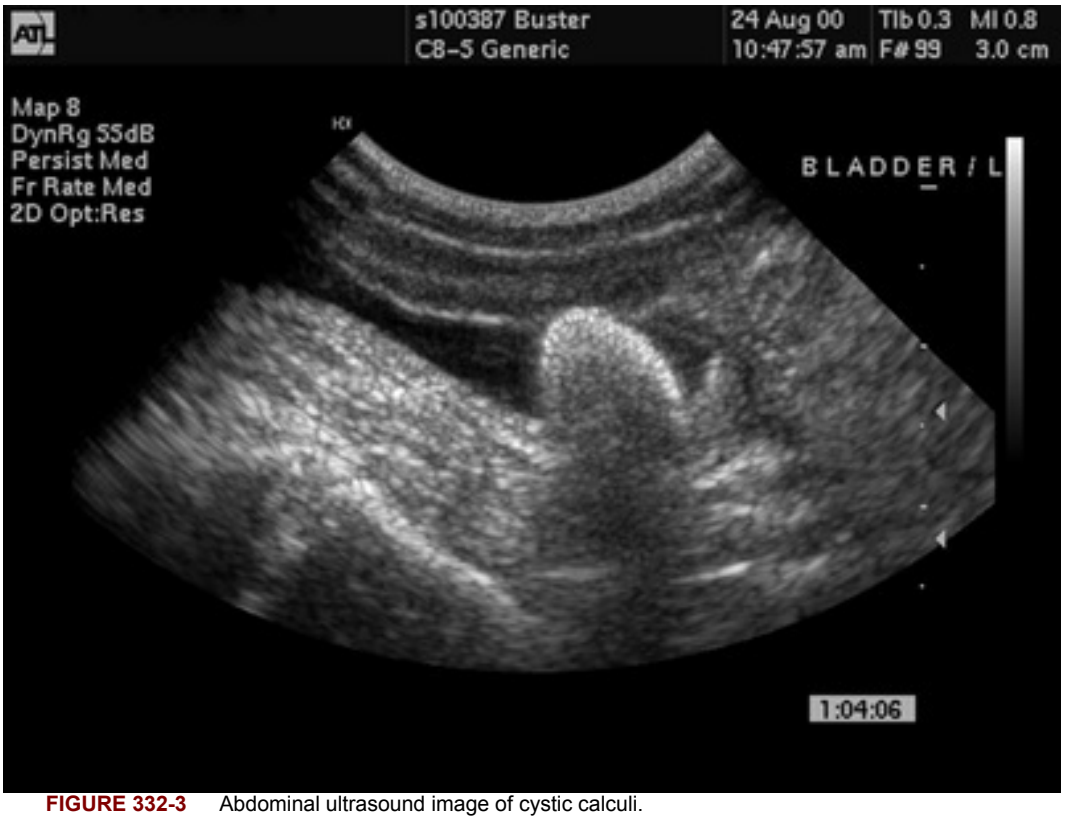

FIGURE 332-3 Abdominal ultrasound image of cystic calculi.

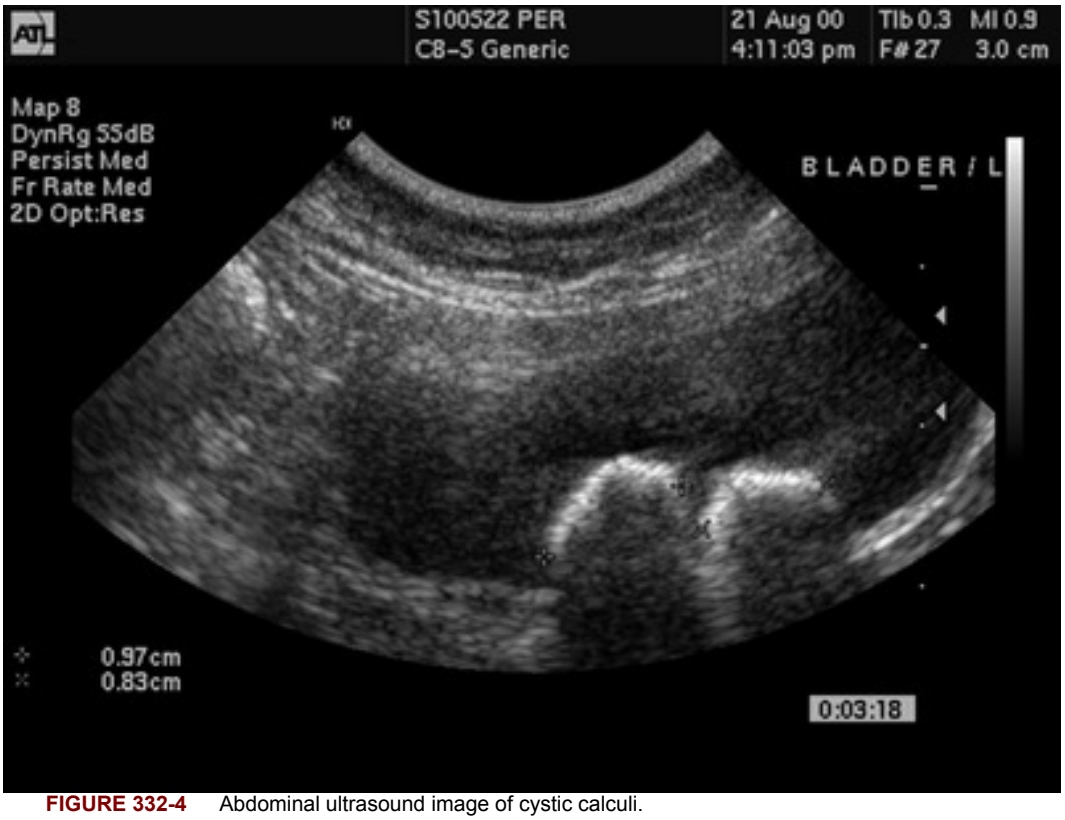

FIGURE 332-4 Abdominal ultrasound image of cystic calculi.

Principles of Stone Analysis

There is a variety of methods available to analyze stones, offered by a number of diagnostic laboratories (Box 332-1). If a stone is available for analysis, the stone should be submitted. The results will aid in management recommendations. The only time when analysis is not required is when there are mineral dense uroliths that respond to dissolution diets, which would confirm the working diagnosis of struvite urolithiasis.

Box 332-1

Diagnostic Laboratories Performing Veterinary Urinary Stone Analysis

Minnesota Urolith Center, University of Minnesota, http://www.cvm.umn.edu/depts/minnesotaurolithcenter/home.html
G.V. Ling Urinary Stone Analysis Laboratory, University of California, Davis, http://www.vetmed.ucdavis.edu/usal/index.cfm
Urolithiasis Laboratory, Houston, TX, http://urolithiasis-lab.com
Canadian Veterinary Urolith Centre, Guelph, Ontario, http://www.guelphlabservices.com
A noninclusive list—check with your diagnostic laboratory for other locations.

Management of Urolithiasis

Most cystic uroliths are removed surgically via a routine cystostomy (also referred to commonly as cystotomy); however, there are a number of alternative methods that can be employed depending upon urolith number and size. A less invasive surgical approach is to perform a laparoscopic-assisted cystostomy, but for most small cats it is essentially easier to perform just a routine cystotomy. If there are small uroliths in the 1- to 3-mm range in female cats, a noninvasive method is voiding urohydropropulsion. This requires general anesthesia and the patient should be in a deep plane of unconsciousness. An indwelling urinary catheter is aseptically placed (3- or 5-Fr catheter). The bladder is distended with sterile saline until full, but

not taut. The cat is then held vertically, allowing the uroliths to fall into the trigone and proximal urethra. The catheter is removed and the bladder expressed while the urine is collected in a container with a filter ("stone strainer") to trap the uroliths. This should not be attempted in male cats unless they have had a perineal urethrostomy. Complications with this procedure include minimally hematuria or as a significant complication, bladder rupture.[10]

Purine Urolithiasis (Urate and Xanthine)

The prevalence of purine-based uroliths has been relatively stable over the years with reports varying between 3 and 10%.[11-13] Urate uroliths are the third most frequently reported in cats. Uric acid is one of several biodegradation products of purine nucleotide metabolism. Ammonium urate is the most common form of naturally occurring purine uroliths observed in cats. There is little information available for urate uroliths in cats. The form of urate urolith most commonly identified was ammonium hydrogen urate[12] (Figure 332-5).

FIGURE 332-5 Purine metabolic pathway. *UC*, Uricase; *XDH*, xanthine dehydrogenase.

The study reported by Appel et al. examined uroliths from 10,083 cats.[11] There were 398 urate stone formers (3.9%), of which the majority were ammonium urate (385) and uric acid (13). Males represented 58% and females 41% of the stone formers. In this particular study, the prevalence of urate urolithiasis was highest in the Egyptian Maus (82%) and consistent with other reports, the Birman (27%) and Siamese (13%) breeds were also both significantly overrepresented compared with other breeds.[11]

There is also an association between urate urolithiasis and age. The mean age of urate urolithiasis is younger than for nonurate urolith stone formers. Egyptian Maus seem to be significantly younger compared with other breeds combined among all stone formers.

Predisposing conditions for the formation of urate urolithiasis include portovascular anomalies (see ch. 284), microvascular dysplasia (see ch. 284), and any form of severe hepatic dysfunction (see ch. 280). Additionally, an underlying genetic metabolic defect in certain cat breeds may exist. The presence of urate urolithiasis in cats should prompt a complete evaluation of liver function and hepatic vascular abnormalities.

Management of Urate Urolithiasis

Surgical removal of urate uroliths is still the treatment of choice until further studies are performed confirming safety and efficacy of medical dissolution in cats. A protein-restricted alkalinizing diet is recommended for the prevention of recurrence. Canned food is preferable to help increase fluid consumption. Periodic abdominal ultrasonography is recommended to assess for recurrence and is preferable to double contrast cystography because sedation or general anesthesia is typically not required.

Xanthine Urolithiasis

Xanthine urolithiasis is uncommon in felines and is usually associated with allopurinol administration.[14,15] There have been a few case reports of naturally occurring xanthine uroliths in cats.[14,16,17] Xanthine is a rarely recognized disorder characterized by a deficiency in xanthine dehydrogenase (XDH) enzyme activity observed in humans and other mammalians. XDH deficiency leads to excess urinary excretion of xanthine and hypoxanthine. Hypoxanthine is very soluble, but xanthine is extremely insoluble in urine at any pH.

Management of Xanthine Urolithiasis

No medical dissolution protocol for feline xanthine uroliths exists. The treatment of choice is surgical removal. Prevention involves feeding a protein-restricted alkalinizing diet and creation of a dilute urine by ensuring extra water intake.

Cystine Urolithiasis

Feline cystinuria was first documented in 1991.[18] Cystine uroliths are rare and represent only 0.1% of all uroliths seen in cats in the United States and Canada.[6,13,18] Cystinuria is a hereditary renal transport disorder involving cystine and the dibasic amino acids ornithine, lysine and arginine (COLA). This inborn error of metabolism leads to the formation of cystine crystals and ultimately to uroliths. Recently, feline cystinuria caused by a missense mutation in the SLC3A1 gene was identified in a young male domestic shorthair cat with cystine calculi.[1] There is a large degree of genetic heterogeneity of cystinuria in dogs and humans; mutations in the *SLC3A1* gene coding for a globular protein with a single transmembrane tail (rBAT) are observed most commonly.[19-21] The *SLC7A9* gene encodes for an intramembrane transporter protein called $b^{o,+}$ AT protein. The COLA amino acid transporter is a heterotetramer formed from 2 heterodimers of $b^{o,+}$ AT and r BAT.[22] There in fact may be other mutations responsible for cystinuria in cats that have not been identified as yet. Screening of 5 other cystinuric cats did not have this mutation.[19]

Cystine uroliths have been diagnosed in cats from 4 months to 12 years of age with a mean age of 3.6 years. There appears to be no sex or breed predisposition. Although most cats are domestic shorthairs, the Siamese seems to be slightly overrepresented.[23] Although cystine nephroliths have been identified in humans and dogs, thus far all cystine uroliths in cats have been found in the lower urinary tract.

In addition to lower urinary tract signs, cystinuric cats have been reported to have hypersalivation, lethargy and seizures. These clinical signs have been attributed to secondary hyperammonemia arising from impaired intestinal absorption and excessive renal excretion of COLAs. Arginine deficiency in cats can cause hyperammonemia. Cystinuric cats with impaired intestinal absorption and renal reabsorption of arginine will become arginine-deficient.

Management of Cystine Uroliths

Medical, dietary and surgical treatment options have been described for the management of cystine uroliths in humans and dogs but have not been described in cats. Cystine solubility increases above pH 7.5, so urinary alkalinization with potassium citrate (75 mg/kg PO q 12 h) along with ensuring adequate fluid intake are important in prevention of cystine uroliths. D-penicillamine and 2-mercaptoproprionylglycine (2-MPG) are cystine chelating agents that have been used in dogs and humans but not in cats. 2-MPG has been reported to have been used safely in cats.[23] A nonacidifying canned food, perhaps supplemented with arginine, should be fed as well.

In type III cystinuria in dogs (an androgen-dependent form), neutering of adult males seems to be curative. It is unknown if this form occurs in cats, but castration would seem to be a logical consideration.

Silica and Mixed Compound Uroliths

At one urolith analysis laboratory, silica-containing calculi accounted for approximately 0.3% of feline accessions. There did not appear to be a gender or sex predisposition. There are no dissolution diets available. Recommendations for preventing this urolith type are not well established. In dogs, a diet low in vegetable content and higher in animal protein and moisture is recommended. In cats, a similar strategy seems to make sense.

The Minnesota Urolith Center reported an incidence of 6% for mixed compound stones. If a dissolution diet is tried initially, as for struvite, and it does not appear to be successful, another mineral type may be found in the core of the urolith.

Struvite Uroliths

In cats, struvite uroliths typically form in sterile urine. This is unlike dogs and humans where struvite uroliths are most often associated with a urease-producing bacterial infection. The pathophysiology of struvite urolith formation is not completely understood but likely results from a combination of breed, sex and dietary factors. The influence of magnesium on struvite formation depends on urine pH and influence of ions, minerals, and other components in urine. Alkaluria is associated with increased risk of struvite formation. Struvite is more soluble in acidic urine (pH < 6.8). Factors that may be associated with the formation of alkaline urine such as a low animal protein diet, distal renal tubular acidosis, or family history of struvite uroliths should be considered in cats with struvite urolithiasis.[23] Increasing ionic concentrations of urinary minerals are the driving forces underlying crystal formation. Persistently alkaline urine and subsequent struvite crystalluria may be an indication to culture the urine for urease-producing microbes including

Staphylococcus sp., *Proteus* sp., and *Ureaplasma* sp., even though the urine of most cats is sterile.[24] Sterile struvite uroliths form typically in cats 1-10 years old. The Minnesota Urolith Center reported that struvite uroliths represented 46% of their submissions.

Management of Struvite Uroliths

The choice of urolith treatment method depends on clinician experience, patient factors, and client preferences. Several therapeutic foods are marketed for dissolution of struvite uroliths and are formulated to avoid excessive magnesium and phosphorus and to maintain acidic urine pH (this increases struvite solubility)[24] (Boxes 332-2 and 332-3). Therapeutic diets are formulated to avoid excessive magnesium and phosphorus and to maintain acidic urine pH, resulting in increased struvite solubility. Dissolution diets have not been associated with urethral obstruction as uroliths decrease in size. When feeding a diet formulated for dissolution, abdominal radiographs should be reevaluated 2 to 4 weeks after starting the diet. At this time the uroliths should be 33% to 100% smaller. With minimal change in size, the mineral composition of the urolith is unlikely struvite or nutritional recommendations are not being followed by the owners. After radiographic dissolution of the uroliths, the dissolution diet should be continued for an additional 2 to 4 weeks. In the rare circumstance when there is a concurrent urinary tract infection, an appropriate antibiotic should be administered throughout the entire period of dissolution.

Box 332-2

Diets Marketed for Struvite Only Dissolution and Prevention

Hill's Prescription Diet s/d can and dry—dissolution only
Iams Urinary-S Plus can and dry—prevention only
Box is not Inclusive of all dietary possibilities.

Box 332-3

Diets Marketed for Struvite Dissolution and Prevention and Calcium Oxalate Prevention

Hill's Prescription Diet c/d Multicare can and dry
Hill's Prescription Diet Metabolic + Urinary can and dry
Hill's Prescription Diet c/d Multicare Stress can and dry
Royal Canin Veterinary Diets Urinary SO can and dry
Royal Canin Veterinary Diets Moderate Calorie can and dry
Royal Canin Veterinary Diets Olfactory Attraction dry
Purina Veterinary Diet UR St/Ox Urinary Formula can and dry
Box is not inclusive of all dietary possibilities.

In female cats and males having had perineal urethrostomies, when urolith burden is low and the size is less than 4 mm, then voiding urohydropropulsion is another minimally invasive procedure (see Management of Urolithiasis, above). This technique will provide uroliths for analysis and culture, as well as providing a means of urolith removal, especially if the cat is demonstrating marked clinical signs or the owners prefer not to pursue a dissolution diet. The final management technique is a surgical intervention of either a cystostomy or a laparoscopic-assisted cystostomy.

Prevention of Struvite Uroliths

Prevention strategies for struvite uroliths include creating a dilute urine by encouraging the cat to drink water or increasing the water content of the diet. This will promote frequent voiding, thus allowing the passage of struvite crystals or small uroliths. There are several commercial diets that are produced not only for dissolution but for prevention of recurrence (see Box 332-3). There are several advantages of multipurpose foods including the ability to feed long-term as a maintenance diet, as well as the fact that they can be fed to all other healthy cats in the household and thus improve owner compliance. Typically they are relatively

palatable and there is no need to transition cats to a different food for urolith prevention.

Calcium Oxalate Uroliths

Epidemiology

Cats affected with CaOx urolithiasis typically are middle-aged to older, male, and neutered. Cat breeds at higher risk include the Persian and Himalayan.

Clinical Signs

The clinical signs have been discussed earlier in this chapter. They include pollakiuria, stranguria, hematuria, periuria, or a combination. Male cats can also present with urethral obstruction secondary to a urolith lodged in the narrow distal urethra. None of these signs are specific for uroliths and other rule-outs including idiopathic cystitis (see ch. 334), urinary tract infections (see ch. 330) and neoplasia (see ch. 351) should be considered. Cystic uroliths may also be incidental findings without the cat demonstrating any clinical signs.

Pathophysiology

The physical chemistry governing crystal formation in urine is complex, and many variables must be considered. The two major factors that affect this process are supersaturation of urine with calculogenic materials (calcium and oxalate) and the balance between substances that promote and those that inhibit CaOx formation. When urine is supersaturated with calcium and oxalate, crystal formation is more likely to occur; one measure that reflects this state is the relative supersaturation of urine (RSS). This measure is used widely to assess the risk of CaOx formation in people and is finding use in veterinary medicine as well.[8,25]

To assess supersaturation of the urine with calculogenic materials, the relative importance of urinary water content, calcium concentration, and oxalate concentration have been examined. Water content is perhaps the single most important variable affecting CaOx formation. Increased water dilutes the urine and increases urine volume, thereby reducing CaOx RSS. Hyperoxaluria also plays a role. Urinary excretion of oxalate depends on dietary intake, intestinal absorption, renal tubular secretion, and the rate of endogenous synthesis. Intestinal absorption is influenced by factors that determine the amount of free oxalate in the gut lumen. Calcium and magnesium both can bind oxalate, creating complexes that are excreted instead of absorbed. Intestinal flora such as *Oxalobacter formigenes* and lactic acid bacteria can degrade oxalate and may play a role in the pathophysiology of this disease. Hyperoxaluria due to endogenous overproduction has been found to be a primary genetic condition in people caused by metabolic defects and exists in two forms (type I and type II). A few cases of primary hyperoxaluria also have been reported in cats and appear to be most similar to the type II variant in people.[8,25,26]

Like oxalate excretion, urinary calcium excretion depends on dietary intake, intestinal absorption, and renal tubular excretion. Intestinal absorption of calcium is similar to that of oxalate in that calcium is poorly absorbed when it exists as a complex but is absorbed more readily when unbound. The appropriate level of calcium intake to minimize urinary CaOx RSS is thus intertwined with the amount of oxalate present, as well as the amount of other substances with which it may form complexes (e.g., phosphate). Hypercalciuria also can result from hypercalcemia and impaired tubular reabsorption of calcium.

Several substances have been identified as promoting or inhibiting CaOx formation in urine. Inhibitors include magnesium, citrate, and pyrophosphate, which form soluble complexes with calcium in the urine and prevent crystal formation with oxalate. Citrate also may lower the risk of CaOx formation by alkalinizing the urine. Proteins such as nephrocalcin and Tamm-Horsfall glycoprotein interfere with CaOx crystal formation and may play an additional role.

There is controversy over the importance of the role of urinary pH in the formation of CaOx formation. The absolute solubility of CaOx in urine is affected marginally over a broad pH range, but there are several reasons why a low pH may promote CaOx formation: persistent aciduria is associated with low-grade metabolic acidosis, which induces calcium resorption from bone and can increase urinary calcium excretion; acidic urine may diminish the ability of citrate and pyrophosphate to act as CaOx inhibitors; and increased reabsorption of calcium from the distal tubule occurs when the urine is alkaline. Furthermore, feeding an acidifying diet has been identified as a risk factor for CaOx formation in cats. In cats, the risk was three times higher when diets were fed producing a urinary pH of 5.99 to 6.15 compared with diets producing a pH of 6.5 to 6.9.[27] Studies also have evaluated the effect of pH specifically on CaOx RSS, but results so far have been conflicting.

Diagnosis

The initial evaluation of a cat with CaOx urolithiasis should include a thorough investigation for any underlying cause. A complete blood count, chemistry panel, urinalysis, and urine culture are considered a minimum database. Urinalysis should be evaluated ideally within 60 minutes of collection to minimize time and temperature effects on *in vitro* crystal formation.[8] The urine specific gravity should be recorded, and reasonable goals to decrease this value can be established after urolith identification. The urine pH in cats with CaOx is variable, and CaOx crystals are not always present in cats with CaOx-containing uroliths.[8] If the total calcium concentration is elevated, the ionized calcium level should be measured, and if hypercalcemia is confirmed, measurement of parathyroid hormone, parathyroid hormone–related protein, and possibly serum vitamin D levels is recommended (see ch. 297). Imaging should include both abdominal radiography and ultrasonography because in some cases stones may be missed when only one modality is used. As CaOx uroliths have a mineral opacity, they typically are easily seen with survey radiographs. However, very small uroliths may require ultrasound to detect their presence. Additionally, uroliths in the urethra are difficult to detect with ultrasound and so imaging the caudal abdomen including the pelvis requires radiography.

Management

Surgical and Interventional Management

There is no known protocol to dissolve CaOx uroliths at this time, and in many cases the only effective treatment is removal. Urolith removal can be achieved surgically, and less invasive methods are becoming increasingly available such as laparoscopic-assisted percutaneous cystostomy, cystoscopy (in females with uroliths < 3 mm in size) and voiding urohydropropulsion (in females and males with perineal urethrostomy and uroliths < 3 mm in size). If there have been prior uroliths, than radiographs or abdominal ultrasound should be performed every 2 to 3 months.

Dietary Management

CaOx uroliths occur in two common forms, CaOx monohydrate (whewellite) and CaOx dihydrate (weddellite). Management approaches for the two different forms are the same.

Perhaps the most important dietary modification that can be made is to increase water intake and urinary volume while decreasing urine specific gravity. Retrospective studies of cats with CaOx urolithiasis found a significantly lower risk of CaOx formation with higher dietary moisture content.[27] Feeding a canned diet is the best way to increase water intake, but some cats will not eat canned food. In these cases, water or broth can be added to dry food, or broth can be added to the water supply. Water fountains also may be helpful to increase water intake in cats. Appropriate targets for specific gravity are less than 1.025 in cats; achieving dilute urine can be very difficult in cats.

There are several commercially available prescription diets that have been designed to influence the RSS of CaOx and by decreasing the RSS lessen the likelihood of urolith recurrence. These diets typically have a slightly higher sodium chloride concentration and are slightly restricted in protein (see Boxes 332-3 and 332-4). Supplementation of sodium chloride has been investigated as a means of increasing water consumption but has been a point of controversy. Increased sodium consumption increases urinary calcium excretion and may increase the risk of CaOx urolithiasis. However, prospective studies have shown that increasing dietary sodium content significantly decreased the CaOx RSS in healthy and CaOx stone–forming cats.[28] The *total* daily urinary calcium excretion increased in these studies, but apparently the effect on CaOx RSS is offset by the increase in water intake and urine volume. These findings suggest a benefit to NaCl supplementation, but long-term studies still are needed. Sodium supplementation can be considered if there is an inadequate response to dietary therapy and the urine is not dilute, but patient selection must be done carefully. Short-term studies in cats have shown no adverse effects on kidney function or blood pressure, but caution is required when considering adding salt to the diets of cats with kidney disease or hypertension until longer-term studies are done. Additionally, high-sodium diets are contraindicated for animals with heart disease.[25]

Box 332-4

Diets Designed for Calcium Oxalate Prevention Only

Iams Urinary-O Plus can and dry—prevention only

Box is not Inclusive of all dietary possibilities.

Higher protein level historically has been associated with an elevated risk of CaOx formation because it can promote acidosis and hypercalciuria. However, retrospective studies in cats have found a lower risk of CaOx formation with higher dietary protein.[25,29] Overall, the exact amount and type of protein that is ideal has yet to be determined, but most diets designed to reduce CaOx urolithiasis have reduced protein levels.

Other nutrients to consider in the dietary management of CaOx uroliths include magnesium, citrate and phosphorus. Urinary magnesium and phosphate (and citrate) are thought to act as inhibitors of CaOx urolith formation and should not be restricted in the diet. Dietary phosphorus should also not be restricted because reduced serum phosphorus levels could activate the parathyroid gland, resulting in increased vitamin D_3 levels and increased intestinal absorption of calcium.

Acidifying diets have been associated with a higher risk of CaOx formation in cats, but further studies have yielded conflicting results regarding the importance of daily urinary pH in CaOx prevention. Overall, it can be said that pH generally appears to be less important in controlling CaOx stone formation than in controlling formation of other stones such as struvite. Given the available information it seems prudent to avoid significant acidification of the urine. An appropriate initial target urine pH is approximately 7.0; however, with this in mind, the target urinary pH values achieved by feeding almost all of the diets listed in Boxes 332-3 and 332-4 are acidic. This is because the goal of the Royal Canin Urinary SO formulation and Hill's Prescription Diet C/D Multicare is to prevent both CaOx *and* struvite uroliths. Since urine pH control is more important for dissolution and prevention in treating struvite stones than in treating CaOx stones, these diets target a lower pH as part of the strategy to prevent struvites. Despite causing a mildly acidic urine, all the listed diets are effective in producing urine with a low CaOx RSS. This apparent paradox exemplifies the complex nature of CaOx urolithiasis, and many factors must be considered in designing an appropriate diet. Of course, if CaOx uroliths continue to be a problem despite feeding an appropriate diet, alkalinization of the urine can be considered (see later) to potentially improve control.[25]

Medication

Pharmacologic agents can be added to the management plan for CaOx urolithiasis if dietary therapy alone is not effective in preventing urolith growth or regrowth. Potassium citrate has been used effectively in people as a urinary alkalinizing agent, and it also may enhance the inhibitory action of citrate on CaOx formation. However, no study to date has shown a clear benefit to the use of citrate in cats. Furthermore, there is no evidence for hypocitraturia as a risk factor for CaOx formation in cats. The recommended dosage of potassium citrate is 75 mg/kg q 12 h PO. If potassium citrate is used clinically for alkalinization, the starting dosage mentioned previously can be used and the dosage increased until a pH of approximately 7.0 is achieved. To avoid hyperkalemia, serum potassium levels should be monitored when this drug is used. Further studies are necessary in the cat.

Thiazide diuretics provide another medical option to reduce CaOx saturation. These drugs inhibit the sodium-chloride cotransporter in the distal tubule and by doing so stimulate calcium reabsorption and decrease urinary calcium excretion. In a study of healthy cats treated with hydrochlorothiazide at a dosage of 1 mg/kg q 12 h PO, a significant decrease in urinary CaOx RSS was found.[30] Studies of the safety and effectiveness of long-term administration are lacking.[25]

Monitoring

The probability of CaOx urolith recurrence varies among studies and has been reported to be as high as approximately 7% (this may be higher in that a recurrence of uroliths does not always prompt repeat analysis). Two studies in cats have found differing results: resubmissions of uroliths were recorded from 7.1% of over 2000 affected cats within a 5-year period (mean resubmission time, 25 months), whereas 40% of a group of cats with ureteroliths exhibited recurrence within about a year.[25,31,32] Neither study group reflects the total population at risk. If new stones are identified before they become large, less invasive therapies such as voiding urohydropulsion may be used. The size of stone that can be expelled varies depending on breed and size, but in general bladder stones smaller than 5 mm in female cats, and 1 mm in male cats are amenable to voiding urohydropropulsion. Removal of larger uroliths requires a more invasive method. Four weeks after the initial procedure, then at 3 and 6 months, and every 6 months thereafter radiography or ultrasonography is recommended immediately following a removal procedure to verify that no uroliths

remain.

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CHAPTER 333

Diseases of Abnormal Micturition

Julie K. Byron

Client Information Sheet: Diseases of Abnormal Urination

Introduction

Physiology of Micturition

The primary purpose of the lower urinary tract is to store urine and to facilitate its elimination at an appropriate time. The bladder stores urine 99% of the time and is in emptying phase only 1% of the time. Coordination of storage and emptying requires a complex interaction between the somatic and autonomic nervous systems, as well as normal function of the organs and tissues involved.

All three components of the peripheral nervous system are involved in the micturition cycle (Table 333-1). In addition, conscious voiding involves the lumbar and sacral spinal cord, as well as the brainstem and cerebral cortex.

TABLE 333-1

Peripheral Nervous System Components of Micturition

TYPE	LOCATION	NERVE	FUNCTION WHEN STIMULATED	FUNCTION WHEN BLOCKED	FUNCTION WHEN INAPPROPRIATELY STIMULATED	FUNCTION INAPPRO BLOCKEI
Parasympathetic (M3 muscarinic)	Bladder body (detrusor)	Pelvic nerve (S1-S3)	Contraction and bladder emptying	Detrusor relaxation and bladder filling	Overactive bladder	Bladder ato retentio
Sympathetic (beta-3 adrenergic)	Bladder body (detrusor)	Hypogastric nerve (L1-L4)	Detrusor relaxation and filling	Detrusor relaxation and urination	Urine retention	Decreased b compliai increase pressure
Sympathetic (alpha-1 adrenergic)	Bladder neck/urethra	Hypogastric nerve (L1-L4)	Contraction and continence	Urination	Urine retention	Open ureth incontin
Somatic (nicotinic)	Distal urethra/pelvic floor	Pudendal nerve (S1-S2)	Conscious/reflex contraction and continence	Urination	Urine retention	Open ureth incontin

During filling and storage, activation of stretch receptors in the bladder wall leads to a reflex arc increasing urethral tone and relaxing the detrusor muscle via sympathetic pathways (Figure 333-1). During initiation of micturition, stretch receptors send afferent signals along myelinated fibers of the pelvic nerve to the lumbar spinal cord and cranial to the pontine micturition center in the brain. If the situation is appropriate for urination, parasympathetic pathways are activated to stimulate bladder smooth muscle contraction and parasympathetic signals are inhibited to relax the urethra (Figure 333-2). There is also a local urethral reflex arc that causes the somatic-mediated contraction of the striated muscle surrounding the urethra in response to

a sudden increase in abdominal pressure and movement of urine into the urethra, such as during a cough or sneeze.

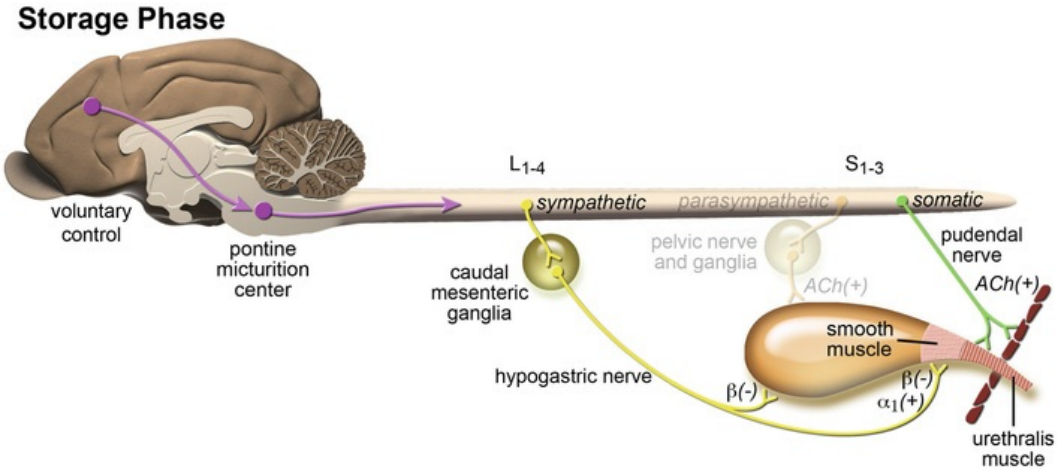

FIGURE 333-1 Innervation and signal pathways during the storage phase of the micturition cycle. *ACh,* Acetylcholine-mediated receptors; *alpha,* alpha-adrenergic receptors; *beta,* beta-adrenergic receptors; $L_{1\text{-}4}$, lumbar spinal cord segments 1-4; $S_{1\text{-}3}$, sacral spinal cord segments 1-3; *(+),* stimulation of muscular contraction; *(−),* inhibition of muscular contraction. (Drawing by Tim Vojt. Reproduced by permission of The Ohio State University.)

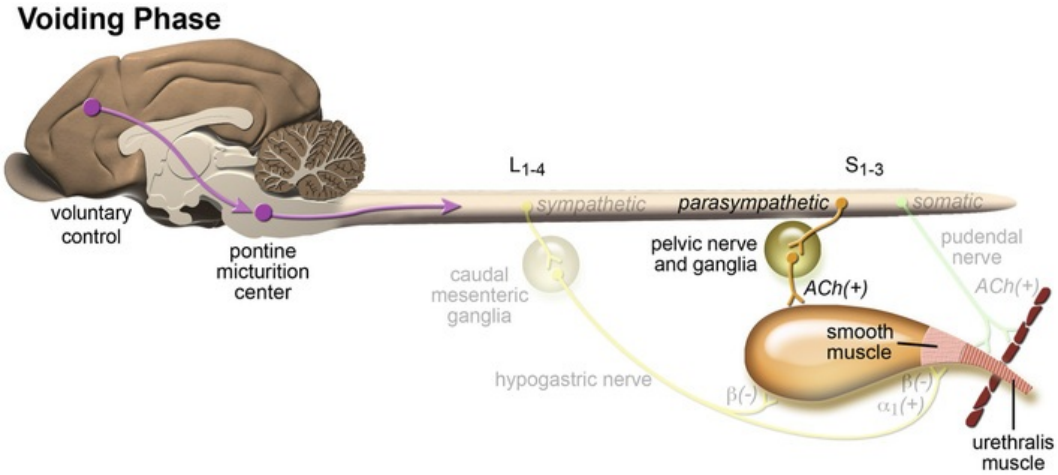

FIGURE 333-2 Innervation and signal pathways during the voiding phase of the micturition cycle. *ACh,* Acetylcholine-mediated receptors; *alpha,* alpha-adrenergic receptors; *beta,* beta-adrenergic receptors; $L_{1\text{-}4}$, lumbar spinal cord segments 1-4; $S_{1\text{-}3}$, sacral spinal cord segments 1-3; *(+),* stimulation of muscular contraction; *(−),* inhibition of muscular contraction. (Drawing by Tim Vojt. Reproduced by permission of The Ohio State University.)

In addition to normal neurologic mechanisms, several other factors are important for the normal function of the micturition cycle in dogs and cats. The integrity of the smooth muscle of the urethra, normal urethral mucosa, associated vasculature, and the support of connective tissues are also key.[1,2] In females, estrogen appears to have a significant impact on these tissues.[3,4] Its decline after neutering appears to play a role in urethral sphincter mechanism incompetence.[5,6] Prostatic hyperplasia in intact male dogs can lead to functional urethral obstruction and urinary retention.

Disorders of Storage

Storage disorders primarily occur due to an inability to maintain adequate urethral tone in the face of normal

bladder pressures. These may result from an anatomic or developmental abnormality or acquired dysfunction in the spinal cord, urinary bladder, or urethra and surrounding tissues. Congenital abnormalities (see ch. 336) such as ectopic ureters or urogenital sinus malformation can result in the unconscious loss of urine in juveniles, while acquired urinary incontinence disorders including urethral sphincter mechanism incompetence (USMI), lower motor neuron bladder (LMB), and overactive bladder (OAB) may develop later in life (see ch. 46).

Urethral Sphincter Mechanism Incompetence

Urethral sphincter mechanism incompetence is the most common urinary storage disorder in dogs.[7] The urethral sphincter mechanism involves the smooth muscle of the urethra, as well as the surrounding support tissues, submucosal vasculature, and urothelium. USMI is thought to result from the breakdown in this complex through reduced muscular responsiveness and tone and changes in the periurethral tissues. In female dogs, these changes appear to be associated with a reduction in estrogen and increases in follicle-stimulating hormone and luteinizing hormone after neutering—thus the term "hormone-responsive incontinence."[8,9] The pathophysiology of its development in neutered male dogs is poorly understood; however, increases in follicle-stimulating and luteinizing hormone levels have been documented in response to decreased testosterone.[10,11]

Urethral sphincter mechanism incompetence is most common among neutered female dogs. It is less common in neutered males and rare in intact male dogs and cats.[11] It appears to affect up to 20% of neutered females and up to 30% of large-breed dogs. Several breeds have been found to have increased risk including the Doberman Pinscher, Giant Schnauzer, Old English Sheepdog, Rottweiler, Weimaraner, and Boxer, but any breed may be affected.[12] Recent literature has demonstrated an increased risk of development of USMI in dogs neutered before 3 months of age.[13,14] Other studies have found no relationship to age at neuter,[15] and the most optimal time to neuter for prevention of USMI remains controversial (see ch. 313). It is possible that this is related to the development and sensitivity of the sphincter mechanism tissues to estrogen and other hormones; however, the mechanism is incompletely understood.

Predisposing factors such as a pelvic bladder, short urethra, or recessed vulva may also be associated with increased risk of developing USMI; however, the presence of any of these does not necessarily lead to incontinence. A reduction in pressure transmission from the abdomen to the proximal urethra has the potential to lead to urinary incontinence in animals with a short urethra or pelvic bladder by setting up a negative pressure gradient from the bladder to the urethra. The leakage of urine seen with a recessed or "juvenile" vulva may be related to pooling of urine in the vestibule during urination, which leaks out at a later time.

Clinical Presentation and Diagnosis of USMI

Incontinence due to USMI often appears within a few years of neutering but has a wide range of age of onset. Dogs with USMI usually have normal bladder capacity and are able to urinate normally, with complete emptying of the bladder. While most of these dogs are otherwise healthy, clinical signs can worsen dramatically if comorbidities develop, especially those leading to polyuria. In patients with polyuric conditions, the increased volume of urine in the bladder may lead to increased pressure on the already weakened sphincter mechanism and leakage. Lower urinary tract infection can also increase clinical signs (see ch. 330). It is suspected that USMI, and urinary incontinence of any cause, are associated with increased risk of urinary tract infection, but no studies have been conducted to fully evaluate this.

Owners often seek veterinary care when the frequency of incontinence becomes bothersome, although in the author's experience, the incontinence may have been present for months or years. It is essential to establish that the animal is passing urine unconsciously. Many owners will complain of "incontinence" when the animal is demonstrating submissive urination or is otherwise consciously urinating in inappropriate places (see ch. 9). Dogs with USMI may leak urine when recumbent, sleeping, or after exertion. Although the passage of urine is involuntary, dogs may increase grooming of the perivulvar or preputial area. USMI is an acquired condition, so questioning of the owner regarding the onset of clinical signs is important. Animals that have been incontinent from birth or prior to neutering should be assessed for congenital malformations such as ectopic ureters prior to making a diagnosis of USMI (see ch. 336).

Physical examination of these animals is often normal, with the exception of perivulvar or preputial urine staining. The conformation of the vulva and condition of perivulvar skin should be noted. The presence of perivulvar dermatitis may increase the risk of urinary tract infection. Rectal examination and palpation of the

urethra are usually normal. Urination is observed to be normal and complete, with little or no residual volume. The assessment of residual urine is essential in male dogs with urinary incontinence to differentiate USMI from detrusor urethral dyssynergia, a disorder of incomplete bladder emptying (see below).

The presence of urinary incontinence in an otherwise healthy neutered female dog that was previously continent is often adequate for presumptive diagnosis of USMI and a trial of empirical therapy. Due to its lower prevalence outside the neutered female dog population, intact female dogs, intact or neutered male dogs, and cats with similar histories and clinical signs require additional evaluation before making a diagnosis of USMI.

A urinalysis and urine culture should be performed (see ch. 72). The presence of isosthenuria or hyposthenuria may contribute to severity of incontinence and necessitates additional evaluation for an underlying cause. As noted above, the risk of urinary tract infection in animals with USMI has not been evaluated, but its presence may lead to worsening signs. Complete blood count and serum biochemistry panels are not essential for diagnosis of USMI, although they may be helpful when making treatment decisions and are important in evaluating animals with polyuria.

If anatomic abnormalities are suspected, imaging such as contrast radiography, abdominal ultrasound, or contrast computed tomography is indicated. Cystoscopic evaluation of the lower urinary tract may also be necessary to assess conformation of the lower urinary tract and vagina (see ch. 108). Advanced diagnostics such as urodynamic studies are designed to quantify the pressure produced along the urethra and the compliance and detrusor function of the urinary bladder. These are available at some referral institutions and may be indicated in patients with equivocal signs and poor response to therapy.

Medical Treatment of USMI

Medical therapy of USMI is generally considered the first line of management; only after failure or intolerance of medical therapy are surgical options considered. Medical treatment of USMI in the neutered female dog consists of increasing number and sensitivity of alpha-receptors in the urethral sphincter with estrogen, or by stimulating those receptors with an alpha-agonist (Table 333-2).

TABLE 333-2

Drugs Frequently Used to Treat Urethral Sphincter Mechanism Incompetence[38]

DRUG	CLASS	DOSE	SIDE EFFECTS	CAUTION
Phenylpropanolamine	Alpha-agonist	1-1.5 mg/kg PO q 8-12 h	Hypertension, aggression, restlessness, gastrointestinal upset, anxiety	Hypertension, hyperadrenocorticism, renal disease
Diethylstilbestrol (DES)	Estrogen	0.1-1 mg/dog PO q 24 h for 5-7 days, then weekly or as needed	Myelosuppression (rare at these dosages), attractiveness to males, mammary/vulvar swelling, behavior changes	Males (can develop prostatic metaplasia)
Conjugated estrogen	Estrogen	0.02 mg/kg PO q 24 h for 5-7 days, then q 2-4 days as needed	Same as DES	Same as DES
Estriol	Estrogen	2 mg/dog PO q 24 h × 14 days, then reduce to 1 mg q 24 h	Same as DES	Same as DES
Testosterone cypionate	Androgen	2.2 mg/kg IM q 4-8 weeks	Behavior change, aggression, perianal adenoma, prostatic hyperplasia	Cardiac disease, renal disease, hepatic disease, prostatic disease

The most commonly used estrogens are diethylstilbestrol (DES) and estriol (Incurin, Merck Animal Health, Madison, NJ). DES is not available commercially, so it must be compounded. Estriol appears to have a higher response rate among female dogs than DES (89% and 65%, respectively).[16,17] Adverse effects associated with estrogen use are dose-related and include mammary gland development, vulvar swelling, and attractiveness

to males.[16] These usually subside with dosage reduction. A more serious adverse event associated with estrogen use is irreversible bone marrow suppression (see ch. 199).[18] It is considered standard of care to monitor the complete blood count in animals receiving estrogen compounds; however, the doses associated with bone marrow suppression are much higher than those recommended to treat USMI. The author recommends performing a complete blood count before starting treatment with an estrogen compound and then rechecking it one month later.

Phenylpropanolamine (PPA, Proin, PRN Pharmacal, Pensacola, FL) is the most widely used alpha-agonist for the treatment of USMI. The dosage and frequency needed for each animal vary widely and may need to be increased over time to maintain continence. Adverse effects associated with PPA include restlessness, aggression, changes in sleeping patterns, and gastrointestinal signs. These are also usually alleviated by a reduction in dosage or frequency.[19,20] Clinical response to PPA administration ranges from 75%-90%.[20,21] Frequently, both an estrogen and PPA are used in the same patient for severe or refractory incontinence. There are anecdotal reports of greater improvement when used together, but there is little published evidence to support a synergistic effect.[22]

Phenylpropanolamine is also frequently used in male dogs and cats with USMI. In addition, neutered male dogs may be treated with testosterone cypionate as monthly injections; however, its efficacy is not well documented. Although male dogs with USMI are most responsive to PPA, it is at a rate of only 43%, much lower than in females.[11] Estrogen compounds should not be used in males due to the risk of prostatic metaplasia. They are rarely used in cats, and care should be taken to monitor the mammary glands for neoplasia in cats receiving estrogens.

Surgical Treatment of USMI

In patients that fail medical therapy, it may be necessary to consider surgical intervention. This is generally only pursued if the animal does not respond to, or cannot tolerate, medical treatment. Several surgical procedures have been used to treat USMI, many to increase abdominal pressure transmission to the proximal urethra. These include colposuspension, transobturator vaginal tape, and urethropexy. Outcomes are variable, and they are considered to have poor long-term efficacy, particularly in animals with normal bladder position.[23] The most promising and commonly performed surgical procedure for USMI is placement of an artificial urethral sphincter, which may be adjusted via a subcutaneous port (see ch. 124). Recent studies have shown a significant increase in continence in male and female dogs that had failed medical therapy for USMI.[24-26]

Historically, injectable urethral bulking agents have been used, particularly bovine cross-linked collagen, to increase resting urethral pressure in dogs with USMI. In 2009 the manufacturers of the most commonly used product removed it from the market, so at the time of writing, injectable bulking agent therapy for USMI is considered unavailable, except in some research settings.

Lower Motor Neuron Bladder

Incontinence as a disorder of storage can also occur secondary to spinal cord injury or disease. Lesions in the S1-S2 region will lead to weakness of the striated muscular sphincter. Disruption of the local reflex arc at these segments leads to an easily expressible bladder, which may empty with minor increases in abdominal pressure. Decreased anal tone and a poor perineal reflex, as well as their easily expressible bladder, identify these animals (see ch. 259). Most of these animals are unable to voluntarily void and require intermittent catheterization (see ch. 105) or manual expression by the owner. Correction of the underlying lesion may lead to some return to normal function. Because of the tendency to have incomplete emptying of the bladder with manual expression, these animals are at increased risk of developing urinary tract infection and appropriate surveillance must be in place (see ch. 330). The muscarinic agonist bethanechol has been used in these patients to increase detrusor contraction; however, the evidence for its efficacy remains controversial.[27,28]

Detrusor Hyperreflexia/Overactive Bladder

Detrusor hyperreflexia/overactive bladder (OAB), is the most common form of urinary incontinence in people, but it has been poorly characterized in companion animals. The true incidence of OAB and its importance as a cause of urinary incontinence in dogs and cats are unknown. In people, it is characterized by sudden urgency to urinate and involuntary loss of urine associated with bursts of detrusor contractions at bladder volumes far below capacity. In dogs, it may manifest as loss of bladder compliance and capacity and

thus the need to urinate more often without polyuria or inflammation of the lower urinary tract. OAB may be a cause of treatment failure in some dogs treated for presumed USMI and should be considered in these cases. Diagnosis of OAB in animals can be challenging and is only definitively made using urodynamic studies such as cystometrography. Response to therapy with antimuscarinic drugs is often used to presumptively diagnose OAB in veterinary species. The most commonly used include oxybutynin and imipramine, the latter of which also has alpha-agonist effects, potentially increasing urethral sphincter tone. Adverse effects of these medications include gastrointestinal abnormalities such as diarrhea and constipation, as well as parasympatholytic signs like tachycardia and hyposalivation.

Disorders of Emptying

The inability to completely empty the bladder during a normal void can result from either a functional or mechanical obstruction of the outflow tract and urethra, or an abnormality of the detrusor muscle, which would impair the bladder's contraction. Overflow incontinence can result from the lack of complete emptying, often when the animal is at rest. An owner may not be able to differentiate this from an animal with a storage disorder (e.g., USMI), and it is up to the clinician to determine the underlying process so that appropriate therapy can be instituted. Inability to completely empty the bladder is a risk factor for UTI, and these animals should be monitored for infection.

Detrusor Atony

Complete emptying of the urinary bladder is dependent on the normal contraction of the detrusor muscle. In the normal animal, the bladder relaxes during filling, with only small increases in intravesical pressure. As the bladder continues to fill, the pressure increases to a threshold, which triggers a detrusor contraction and emptying. Loss of adequate detrusor contraction can result from neurogenic or non-neurogenic abnormalities. Injury to the sacral spinal cord (S1–S3) or pelvic nerves can lead to bladder atony and is often associated with weakened urethral tone. These animals often have decreased perineal reflexes and easily expressed bladders (LMB). Treatment of the underlying lesion, if possible, may lead to improved voiding function. However, until normal function returns, careful management of urination must be followed. Male dogs are manually expressed or aseptically catheterized 2-4 times a day either in the hospital or at home (see ch. 105), and cats and female dogs are often manually expressed.

Direct damage to the detrusor muscle can occur from overdistension due to mechanical or functional outflow obstruction of an acute or chronic nature. The muscle fibers of the detrusor transmit action potentials, which initiate contraction via tight junctions. With overdistension, these tight junctions are interrupted, leading to an absent or ineffective contraction. The overdistension may be acute as with obstructive feline idiopathic cystitis in a male cat, or chronic, as in a dog with a functional obstruction of the urethra. Relief of the obstruction and maintenance of a small bladder volume for up to 2 weeks may allow the junctions to reestablish and the return of coordinated detrusor function. This is usually managed by either indwelling or frequent sterile catheterization of the bladder. Bethanechol may be used in these patients to enhance stimulation of the detrusor contraction since the pelvic nerve is intact. Other medications that have been shown to enhance detrusor function are cisapride and metoclopramide; however, the individual response varies widely.[29,30] It is essential that relief of any urethral obstruction, functional or mechanical, be attained before starting medical therapy to enhance detrusor contraction.

Detrusor Urethral Dyssynergy

Functional urethral obstruction, or detrusor urethral dyssynergy (DUD), arises from an abnormality in the reflex arc that normally allows the urethral sphincter to relax at the initiation of urination. The lesion is thought to be in the reticulospinal tract, Onuf's nucleus, or the caudal mesenteric ganglion, and likely involves the loss of inhibitory signals to the pudendal and hypogastric nerves.[31] It is unknown if injuries to peripheral nerves, neuromuscular junctions, or smooth or striated muscular sphincters are also involved.[32] Unlike the “upper motor neuron bladder” seen in animals with thoracolumbar intervertebral disc disease and other spinal cord lesions, these animals typically have an otherwise normal neurologic examination (see ch. 259).

The disorder affects primarily middle-aged, large and giant-breed male dogs, although female dogs and cats can be affected. One case series of 22 dogs reported a mean age of 4.9 years.[33] Clinical signs are similar to those of mechanical obstruction. The animal often postures to urinate and is able to produce a urine stream

that quickly becomes attenuated or stops completely. The animal may continue to posture to urinate or make several attempts without fully emptying the bladder (Video 333-1). The retention of large amounts of residual urine typically leads to overflow incontinence and may be mistaken for USMI. This leakage can occur because the hypertonicity of the involved sphincter is often dynamic and is triggered by the act of voiding. In chronic cases, bladder overdistension and subsequent atony may develop. Unlike animals with mechanical obstruction, these dogs are typically easy to catheterize (see ch. 105) and contrast urethrography may be normal or reveal areas of narrowing of the urethra (urethrospasm).

Presumptive diagnosis of DUD is often made by observing the dog urinate with a typical interrupted pattern, documentation of a large residual urine volume, easy passage of a urinary catheter, and ruling out of a mechanical obstruction. Normal residual urine volumes in 48 normal dogs were reported to be 0.1-3.4 mL/kg body weight with a mean of 0.2 mL/kg (see ch. 330 and Video 330-1).[34] The author uses <0.5 mL/kg as a general guideline. Ultrasonography is recommended to assess the ureters and renal pelves for dilation secondary to chronic obstruction and ureterorenal reflux of urine.

Treatment of the hypertonic urethral sphincter generally consists of alpha-adrenergic blockade with prazosin, an $alpha_1$-specific antagonist with demonstrated effects on both the internal and external urethral sphincter.[35] Tamsulosin, which is specific for the $alpha_{1A}$ subtype found in the internal urethral sphincter, has also been successful in these dogs. Some dogs will require additional therapy if the striated muscle is more significantly affected. Benzodiazepines, such as diazepam, or other skeletal muscle relaxants, including acepromazine and methocarbamol, may be more effective if the external urethral sphincter is involved. Diazepam is typically administered 30 minutes before voiding to decrease external urethral sphincter pressure. Dantrolene and baclofen have been used in the past as skeletal muscle relaxants; however, the potential for adverse effects has decreased their use in veterinary patients.[35,36] In severe and refractory cases, intermittent sterile catheterization by the owner at home may be necessary (see ch. 105). Medical therapy of associated bladder atony should only be started after adequate relief of the functional urethral obstruction has been reached (Table 333-3). Close monitoring of these patients for residual urine volume and UTI is needed to assess efficacy of treatment and prevent complications (see ch. 330).

TABLE 333-3

Drugs Frequently Used to Treat Disorders of Bladder Emptying[38]

DRUG	MECHANISM	DOSAGE	SIDE EFFECTS/CAUTION
Prazosin	Alpha-1-antagonism, smooth muscle relaxant	1 mg/animal < 15 kg; 2 mg/animal > 15 kg; q 8-12 h PO	Hypotension, weakness, syncope, gastrointestinal (GI) upset/renal disease, cardiac disease
Tamsulosin*	Alpha-1A-antagonism, smooth muscle relaxant	0.01-0.2 mg/kg PO q 24 h	Hypotension
Phenoxybenzamine	Nonspecific alpha-antagonism, smooth muscle relaxant	Dog: 0.25 mg/kg q 8-12 h, Cat: 1.25-7.5 mg/cat q 8-12 h PO	Hypotension, tachycardia, miosis/ first dose hypotension
Acepromazine	Nonspecific alpha-antagonism, smooth muscle relaxant, anxiolytic	0.5-2.2 mg/kg q 6-8 h PO	Sedation, hypotension
Diazepam	Skeletal muscle relaxant, anxiolytic	Dog: 0.5-2 mg/kg q 8 h PO or 30 min prior to voiding	Sedation, ataxia/liver dysfunction, do not use in cats
Methocarbamol	Skeletal muscle relaxant	22-44 mg/kg q 8 h PO	Sedation, weakness, hypersalivation
Baclofen*	Skeletal muscle relaxant	Dog: 1-2 mg/kg q 8 h PO	Weakness, GI upset/do not use in cats
Dantrolene	Skeletal muscle relaxant	Dog: 1-5 mg/kg q 8 h PO, Cat: 1-2 mg/kg q 8 h PO	Weakness/liver disease
Bethanechol	Parasympathomimetic	Dog: 2.5-15 mg/dog q 8 h PO, Cat: 1.25-5 mg/cat q 8 h PO	Diarrhea/GI or urethral obstruction
Cisapride	Prokinetic	Dog: 0.1-0.5 mg/kg q 8-12 h PO, Cat: 2.5-5 mg/cat q 8-12 h PO	Ataxia, GI upset/GI obstruction

*From Lane IF, Westropp JL: Urinary incontinence and micturition disorders: pharmacologic management. *Kirk's current veterinary therapy*, ed 14, St Louis, 2009, Elsevier, pp 955-959.

Prognosis for recovery of normal voiding is good, but most dogs will require lifelong therapy for DUD. Attempts to taper medications to the lowest effective dosage may be hampered by relapse of clinical signs after months of normal voiding.[33] Prognosis appears to be worse in patients with bladder atony or UTI secondary to urine retention. Anecdotally, urethral stenting may improve clinical signs (see ch. 124); however, this is considered a salvage procedure, with several potential complications, and is indicated only in the most refractory of cases.

Upper Motor Neuron Bladder

Spinal cord lesions cranial to the sacral segment generally cause neurogenic functional urethral obstruction. This leads to loss of inhibitory signals to the hypogastric and pudendal nerves that prevents sphincter relaxation upon voiding. This is the classic "upper motor neuron bladder" in which the patient is unable to urinate normally and is difficult to manually express. The most commonly affected patients are those with intervertebral disc disease and associated paresis (see ch. 266). These animals typically have additional neurologic deficits including paresis and nociceptive loss (see ch. 259). Treatment of the underlying lesion typically leads to partial or complete return to normal voiding function after days to weeks. Until normal voiding resumes, the patients are managed as for DUD with alpha-adrenergic blockade and manual expression or catheterization. Monitoring for overdistension and UTI are critical in these patients, as is nursing care, particularly since the overflow incontinence that can accompany this process may lead to skin breakdown in these recumbent animals.

Dysautonomia

Dysautonomia is a rare condition involving the degeneration of the neurons of the autonomic nervous ganglia, leading to sympathetic and parasympathetic dysfunction. It has been most commonly reported in both dogs and cats in the United Kingdom and Scandinavia, but small clusters of cases in both species have been seen in the United States.[37] Its underlying cause is unknown, but neurotoxin exposure is strongly suspected. In addition to the classic findings of unresponsive mydriasis and prolapsed nictitans, the abnormalities seen with dysautonomia can range from ileus and constipation to decreased systolic function of the heart. These dogs and cats often have significant voiding dysfunction and urine retention due to bladder atony and overflow incontinence secondary to urethral sphincter incompetence. There is no specific treatment for dysautonomia, and spontaneous remission is uncommon. The prognosis is related to the severity of the clinical signs and the specific organ functions affected.

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CHAPTER 334

Feline Idiopathic Cystitis

C.A. Tony Buffington

Client Information Sheet: Feline Idiopathic Cystitis

Introduction

Feline idiopathic (interstitial) cystitis (FIC) is the most common cause of chronic lower urinary tract signs (LUTS) in cats.[1] We coined the term feline interstitial cystitis[1] because of the similarities of FIC to interstitial cystitis (IC) in humans,[2] which used to require cystoscopic evaluation of the bladder to make the diagnosis. We use the term FIC to refer to idiopathic cystitis in this chapter since cystoscopy no longer is required to make the diagnosis in humans[3] and is rarely available (or indicated) for cats.

In addition to the "classical" chronic LUTS etiologies, I recently proposed a central nervous system cause for FIC in some cats, which I called Pandora Syndrome[4]; others have suggested a similar etiology in humans.[5-7] Additionally, periuria can represent marking behavior or be "related to primary environmental or social factors."[8] Clinicians also must consider whether they are seeing an initial episode or recurrence of a chronic disease.[9,10]

Recent Epidemiology

In 2014, the Banfield State of Pet Health[11] reported that "cystitis" (LUTS) accounted for approximately 5% of diagnoses in cats older than one year of age presented for care for a health problem, and Veterinary Pet Insurance reported that "bladder/urinary tract problems" was the most common insurance claim for cats in 2013.[12] The prevalence of diseases in cats presented for evaluation of LUTS appears to be on the order of (% of cases) FIC—55-73%, urolithiasis—10-20%, microbial infection—1[13-15]-25%[16-18] (what, if any, role viruses play in FIC remains unknown[19]), and other causes—5-20%.

A 2011 retrospective case-control study[20] reported that cats with FIC had a significantly higher body weight and body condition score; were more likely to be housed in multicat households, more nervous and fearful, more prone to hide from unknown visitors in the house, more likely to use a litter container; had lower owner-reported water intake, activity level, hunting behavior, and less access to the outside than did control cats. Of the stressful situations queried, only house move occurred with increased frequency in cats with FIC. Pyuria, hematuria, and an increased urine protein : creatinine ratio were significantly higher in obstructed males compared with nonobstructed males, and obstruction was significantly more likely in the presence versus absence of struvite crystalluria. While this finding suggested an association between struvite crystalluria and obstruction in male cats with FIC, it cannot clarify whether crystal formation occurred before, during, or after the obstructing event.

A prospective study of causes of LUTS in 119 primary care cases of cats (34 were obstructed) in Norway between 2003 and 2007 also was reported in 2011.[21] Sixty-five cats (55%) were diagnosed with FIC, 25 (21.0%) had urethral plugs, and 14 (12%) had either bacterial urinary tract infection (UTI) or urolithiasis. Seventy-three (62%) cats were having a first episode of LUTS, whereas 44 (38%) were recurrences.

A 2014 study[22] reported on 302 cats presented for care of LUTS at the Clinic of Small Animal Medicine, Ludwig Maximilian University Munich between 2000 and 2007. The most common diagnoses were FIC (55.0%), UTI (18.9%), urethral plug (10.3%), urolithiasis (7.0%), and neoplasia (3.6%). Six cats (2.0%) had severe struvite crystalluria without urethral obstruction, and nine cats were identified with neurogenic disorders (3.0%). Urethral plugs were significantly more frequent in cats with FIC than in cats with UTI, and

cats with FIC and urethral plugs had significantly higher body weights and were significantly younger (<10 years of age) than were cats with UTI or neoplasia. Males were significantly more likely than females to have FIC or a urethral plug than a UTI or neoplasia. No differences between affected and unaffected cats regarding breed distribution, living conditions, diets, outdoor access, number of cats in the household, or seasonal variation were identified.

Results of epidemiological studies must be interpreted cautiously. Significant (unintentional) selection bias, in addition to the ability to identify associations but not causations, often occurs in cases presented for care of a clinical sign from which most samples are drawn. Determining the population-level prevalence and distribution of causes of LUTS would require a population-based study, as has been done for humans with IC and related disorders.[23] Another potentially informative approach would be a prospective longitudinal study, such as the currently ongoing Bristol Cats Study.[24]

Pathophysiology

Because the presenting complaint of most owners of cats with FIC is LUTS, for many years most research focused on identification of intraluminal or intrinsic abnormalities of the bladder.[25-35] As mentioned, observation of submucosal petechial hemorrhages (glomerulations) by cystoscopy used to be required for the diagnosis of IC in humans, but these lesions are neither sensitive nor specific for IC[36] and so are no longer part of the diagnostic criteria.[37] Cystoscopy still can be used to rule out the presence of "confusable" diseases in complicated cases, however.[3,38] A variety of other abnormal bladder findings also have been reported,[32,33,35,39-42] but their role in the etiopathogenesis of FIC is unknown.

Changes in sensory nerve function occur in cats with FIC.[4,43] A modest increase in substance P (SP) immunoreactivity in sensory neurons[44] and upregulation of the neurokinin-1 receptor for SP[35] has been found in the bladder of cats with FIC and in humans with IC.[45,46] Clinical trials of SP antagonists have been disappointing, however,[47] and recent evidence[48,49] suggests that SP might limit the severity of inflammatory reactions, opening the possibility that the changes observed in patients might reflect a protective response. Abnormalities also have been identified in dorsal root ganglion cell bodies throughout the lumbosacral (L4-S3) spinal cord from cats with FIC.[50,51]

Treatments targeting bladder sensory neurons have been tested without success to date. Controlled trials of both capsaicin and resiniferatoxin in human beings with IC failed to find significant benefits over placebo.[52] In 2006, one expert concluded, "Intravesical instillation therapy has basically not changed during the last few years, although some studies have disconfirmed some regimens.[53]" This continues to be the case,[54] and in 2014[55] pentosan polysulfate (Elmiron, Janssen Scientific, Titusville, NJ) was found to be equivalent to placebo for human patients with IC, a finding reported in cats in 2009.[56]

Abnormalities of the central stress response system (SRS) also have been identified.[4] Pursuing some anomalous results obtained during experiments with a corticotropin-releasing factor receptor antagonist,[57] we identified significantly smaller zonae fasciculata and reticularis in the adrenal glands of cats with FIC compared to healthy cats.[58] The most parsimonious explanation identified to date for these findings is the occurrence of a stressful early life event that permitted maternal glucocorticoids to cross the placenta and inhibit fetal ACTH release.[59,60]

Sufficiently intense activation of the maternal SRS also can cause other changes in her offspring.[61,62] Recent research has shown how evolutionarily conserved developmental processes can interact with environmental cues, often transmitted from the mother via the placenta, to attempt to match the physiology of the developing organism to its postnatal environment. One prominent mechanism underlying these effects is epigenetic modulation of gene expression.[63,64] Once the SRS becomes sensitized, repeated activation by environmental events can adversely affect a variety of organs based on familial (genetic, epigenetic) susceptibility. In addition to abnormalities of the LUT, cats with FIC often have a variety of other health problems.[65-67] Although these health problems might result from a severe chronic bladder pain syndrome, they often *preceded* the diagnosis of FIC, making this explanation unlikely. A similar pattern has been identified in human beings.[68-70]

It is important to appreciate that the SRS can be activated either peripherally by local factors like infection or inflammation ("bottom up"),[71] or centrally by perception of an external environmental threat ("top down").[72,73] External environmental threats can be physical, psychological, or social and can be acute or

chronic. Increased SRS activity is common in cats confined in unenriched environments,[74] which can complicate clinical interpretation of diagnostic procedures by influencing the cat's temperature, heart and respiratory rates and blood pressure,[75,76] and may play a role in predisposing, precipitating, or perpetuating a variety of chronic health problems in cats.[77] Additionally, increased sensitivity of the acoustic startle response, a brainstem reflex that responds to unexpected loud stimuli,[78] has been identified both in cats with FIC[79,80] and humans with IC[81] and to be responsive to environmental enrichment (EE) in cats with FIC.[80]

Activation of the SRS can increase autonomic, particularly sympathetic outflow, which in turn can increase epithelial permeability acutely and result in epithelial damage if chronic.[82] In cats with FIC, exposure to external stressors increased circulating catecholamine concentrations,[83,84] which increased further as exposure to the stressors continued,[84] possibly due to desensitization of alpha-2 adrenergic receptors.[85,86] In contrast, plasma catecholamine concentrations decreased in healthy cats as they acclimated to the stressors.[84]

Chronic psychosocial stress also is well known to stimulate low-grade systemic inflammation,[87-89] which can result in the expression of sickness behaviors.[90] Sickness behaviors refer to variable combinations of vomiting, diarrhea, periuria, inappetence, fever, lethargy, somnolence, and enhanced painlike behaviors, as well as decreased general activity, body care activities (grooming), and social interactions. Sickness behaviors in cats can result from peripheral *or* central immune activation.[74,84,91] In cats, external stressors were associated with significant increases in sickness behaviors, most commonly manifested as decreased food intake and elimination, and increased elimination outside the litter box.[67] Thus, some of the most commonly observed abnormalities in client-owned cats, such as "finicky" eating and litter-box problems, occurred after exposure to external threats in both FIC and healthy cats, suggesting that clinicians should include the presence of environmental threat in the differential diagnosis of cats presented for care for these signs. Importantly, we also have observed resolution of these behaviors in both laboratory[67] and clinical[66] studies of cats with FIC in response to multimodal environmental modification (MEMO).

Summary

Current understanding of the etiopathogenesis of FIC has expanded from the bladder to include roles for developmental influences, probably mediated by epigenetic modulation of gene expression, and complex interactions between individuals and their environments. It remains to be determined how these systems communicate and manifest as FIC in some cats but not in others. Environmental and behavioral stressors also are associated with exacerbations of signs of FIC and can result in sickness behaviors in both healthy and affected cats. The number and variability of physiological and behavioral abnormalities identified in cats with FIC may represent different disease entities and/or different manifestations of a common underlying problem because of natural variation in the relative activation of neural, endocrine, and immune responses by the SRS. While there is still much to be learned about FIC, this perspective has led directly to refinements in diagnosis and to principles of treatment that have resulted in better clinical outcomes.

Diagnosis (see ch. 46)

Cats of any age, breed, or sex can develop FIC, although it is diagnosed most commonly in younger and middle-aged cats. The majority of cats with chronic LUTS have FIC, and most cats with FIC resolve their clinical signs in a few days without treatment,[10,20,67,92,93] so diagnostics may not be needed (but can always be offered to the owner) for young cats presented for a first episode of LUTS. Additional evaluation is indicated for cats with recurrent signs.

An abdominal radiograph that includes the entire urinary tract can identify radiopaque stones, and a contrast cystogram and urethrogram can identify radiolucent stones, mass lesions, blood clots, or strictures. Contrast studies of the bladder and urethra usually are normal, although diffuse or asymmetrical thickening of the bladder wall occurs in about 15% of cases.[34,94] Contrast studies or ultrasonographic examination are indicated in cats >10 years of age, when FIC is less likely (see ch. 332).

Abdominal ultrasound (see ch. 88) allows visualization of blood clots, polyps, neoplasia, and cystine or ammonium urate stones, which are radiolucent, but is not ideal for evaluating the urethra (e.g., it cannot be used to evaluate most of the urethra of male cats); radiography with or without contrast should always be performed to identify urethral stones or plugs if present.

Although most cats with FIC do not have a UTI, a complete urinalysis (see ch. 72) should be performed at least once in cats with chronic LUTS (see ch. 330) and as explained above, cystoscopy may be useful to

exclude alternative diagnoses even though it is not helpful for the diagnosis of FIC (see ch. 108).

Treatment

Recent treatment advances for FIC reflect the perspective that FIC often represents a problem affecting the bladder rather than a bladder problem. If these cats have a sensitized SRS, then approaches that aim to reduce activation of the SRS are more likely to be effective than those that do not. Because environmental conditions are known to affect the behavior and health of animals,[95] particularly captive animals,[96] we focused on the effects of environmental enrichment (EE) for FIC by adapting approaches used in zoos and research facilities.[97] From this perspective, EE consists of creating conditions that permit the animal to feel safe, which means to sustain a perception of control that exceeds its perception of threat. These conditions include access to species-appropriate novelty, activity, and interactions with other animals (including humans). We operationalized these concepts as MEMO,[98,99] which recently were incorporated into professional EE guidelines.[100] The prognosis for FIC depends on the cat, the housing situation, and the ability and commitment of the client to implement MEMO. In my experience with cats with severe FIC,[66,67,84] implementation of effective EE leads to recovery without the need for pharmacotherapy or any special diet in nearly all patients.

Treatment for FIC includes consideration of acute and chronic approaches to the cat, the owner, and the environment. As mentioned, clinical signs of LUTS commonly resolve in most cats within a few days. Unless a concurrent UTI is documented, antibiotics are not warranted. Analgesic therapy may be appropriate for acute management of FIC (described below). Owners of otherwise healthy cats less than 10 years of age can be told that the most common cause of their cat's signs is FIC, offered diagnostic evaluations to rule out other diagnoses if they choose to do so, and MEMO to facilitate recovery. Cage enrichment is helpful for hospitalized cats, and recent guidelines[101] and recommendations[102] are available.

Effective communication determines MEMO treatment outcome.[98,103] When owners understand that their effective implementation of MEMO can decrease the severity and frequency of LUTS and signs of comorbid disorders in their cats, the prognosis is excellent.[66,67,84] MEMO consists of owner education about cats in general, FIC, effective resource management (food, water, rest areas, litter containers, etc.), and modification of the environment to reduce perceived threats and intercat conflict in multicat households. A variety of resource materials that can be recommended to clients is provided in the client handout.

A quadratic relationship exists between the environment and health, with problems occurring both in barren and chaotic situations,[77] so forms to facilitate evaluating the cat and its surroundings are available.[104,105] In addition, I prefer to use a "coaching" (adherence) as opposed to an "expert" (compliance) approach whenever possible to help the client do the change work of EE because clients perceive it to be in their interest.[106,107] Trained technicians also can carry out this work effectively and empathically.

When changes are suggested, cats are offered choices of resources to determine their preferences for food and feeding management, water and watering, litter container and substrate,[8] space, and form of interactions with people and other animals. MEMO also provides opportunities for play and interactions that are species-appropriate for the cat. In households with more than one cat, the number and locations of resources is increased to create a "house of plenty" to decrease competition for resources that might contribute to recurrence of signs of FIC related to intercat conflict.

Some cats are especially sensitive to changes in feeding schedule, owner work schedule, addition or removal of people or pets from the household, and the owner's emotions, so disruptions in their environment should be kept to a minimum, made gradually, and tailored to the cat's needs and limitations. While beyond the scope of this chapter, detailed guidance for environmental evaluation and implementation of MEMO is available that can be used to inform recommendations.[98-100]

A variety of aspects of nutrition have been considered for incorporation into treatment plans for cats with LUTS (see ch. 185); few have been demonstrated to be effective in cats with FIC.[108] For example, dilution of the urine has been proposed to reduce the risk of recurrence of signs in cats with FIC,[109] but clinical studies of FIC have found no effect of diet moisture content,[10] and both laboratory and clinical studies of MEMO for FIC have reported large reductions in recurrence of signs without dilution of the urine,[66,67] so any salutary effect must be modest.

Some veterinary diets are marketed for FIC. Attributes of these foods include variable combinations of increases in water content to reduce the urine specific gravity and changes in the amounts of minerals,

sodium chloride, omega-3 fatty acids, antioxidants, tryptophan, and alpha-casozepine. Unfortunately, no results of controlled clinical trials of any of the diets currently sold for cats with FIC are available in the peer-reviewed scientific literature. In a 2013 manufacturer-sponsored diet study abstract,[110] the recurrence rate for cats fed a test veterinary diet was comparable to that recorded in other studies,[10,56,66,67,93] whereas the recurrence rate for cats fed a test commercial diet was higher. Recommendations for EE were offered to all owners, but no group treated with EE alone was described, nor was a "usual care" group included. Regrettably, the composition of the veterinary diet currently commercially available is different from that of the diet tested, so the results will not be clinically relevant even if they are eventually published.

Tryptophan, an essential amino acid, has been added to some diets based on the idea that it would increase central serotonin concentrations, which would then exert an anxiolytic effect. Most studies of tryptophan's effects on mood are acute feeding studies, however, with very little, if any, evidence of long-term beneficial effects.[111] Moreover, dietary tryptophan may not exert this effect on serotonin in cats,[112] and even if it did, one would still need to demonstrate that this led to the desired clinical outcome in the target population, since other constituents of the diet can influence tryptophan availability. Diets also have been supplemented with alpha-casozepine, but to my knowledge, no studies of effects of these foods on cats with FIC have appeared in the peer-reviewed scientific literature.

Recommending a diet change seems most reasonable when either the owner or the cat does not like the diet currently fed. Some owners and cats prefer dry foods and may object to forced transition to canned foods, particularly when the diets are of little demonstrable therapeutic value. Attempts to alter the urine to minimize crystalluria in cats with nonobstructive FIC are not indicated. I am not aware of any published evidence supporting the idea that the common types of crystals in cat urine damage the urothelium or worsen LUTS in cats with FIC. If a diet change seems advisable, I recommend offering the new food at mealtime next to the usual food in a separate container so the cat can express its preference. If the cat chooses the new food, the old food can be removed.

Feeding management is another aspect of nutritional care to consider, since it can provide EE. Natural feline feeding behavior includes predatory activities such as stalking and pouncing. These may be simulated by hiding small amounts of food around the house or by putting food in a feeding device from which the cat has to extract individual pieces or move to release the food pieces (if such activity appeals to the cat). Opportunities to express species-typical prey behaviors are commonly used in captive felids to provide enrichment,[113-115] and, although not yet carefully studied in domestic cats, food puzzles might benefit some cats with FIC. Most cats also seem to prefer to eat individually in a quiet location where they will not be startled by other animals, sudden movement, or activity of an air duct or appliance that may begin operation unexpectedly.

A combination of a synthetic feline facial pheromone and valerian (Feliway; Ceva Sante Animale, Libourne, France) is marketed to exert a calming effect on cats, although a recent systematic review questioned its efficacy.[116] The product seems to benefit some cats, so I offer a trial of the electric room diffuser form of it to clients. One or more diffusers can be placed where the cat may be the most stressed: windows, doors, soiled furniture, or the litter container. The product can be used during or after implementation of MEMO if EE alone is found not to control signs sufficiently.

The most effective analgesic therapy for chronic visceral pain in cats is not known. We currently treat acute episodes or flares with oral transmucosal buprenorphine at 10 to 20 mcg/kg two to four times daily for up to 7 days, often combined with acepromazine (0.25 mg IM or 2.5 mg [injectable form given orally] q 8 h), for up to 4 days. Sustained-release formulations of buprenorphine that can provide up to 72 hours of therapeutic drug levels for pain relief following a single injection are available, but I am not aware of any reports of their use for FIC. Our approach has not been tested in controlled trials; it is only our clinical impression that it provides relief to affected cats. We provide analgesic therapy for up to 5 days and recommend further diagnostic evaluations if clinical signs do not significantly improve by then. Analgesics also can be dispensed for use if clinical signs recur prior to contacting the veterinarian.

Butorphanol also has been used, but its effects are not as long-lived or potent as those of buprenorphine[117]; fentanyl patches also have been used in rare cases in which bladder pain was assessed as severe. Anecdotal reports of the use of nonsteroidal anti-inflammatory drugs (NSAIDs), especially meloxicam and ketoprofen, abound, but no published studies of safety or effectiveness of these drugs for FIC currently are available to my knowledge. NSAIDs are licensed for use in cats for preemptive pain management, usually as a single treatment before anesthesia and surgery; chronic use can risk development of acute intrinsic kidney failure, especially if the cat is dehydrated at the time of administration. The FDA recently required the following statement to be added to the label for meloxicam use in cats, "Repeated use of meloxicam in cats has been

associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats. See Contraindications, Warnings, and Precautions for detailed information." Robenacoxib, a long-acting NSAID, recently has become available for use in cats; its effectiveness for cats with FIC has yet to be reported to my knowledge. Additionally, NSAIDs do not seem to provide relief for human beings with IC.[118]

A variety of other pharmacological approaches to treatment of FIC have been tried, including drugs to alter bladder/urethral contractility, to modify the bladder lining, and to alter central neurotransmitter profiles.[109] As with analgesics, effectiveness of most of these drugs has not been tested in controlled clinical trials. Moreover, little consideration has been given to the potential negative effects of chronic forced pilling on the cat, and as mentioned, resolution of clinical signs has been repeatedly demonstrated without the use of drug therapy.[10,66,67,110,119]

Notwithstanding the occasional anecdotal report, no clinical trials of drugs to alter bladder or urethral contractility in cats with FIC have been published to my knowledge, and this class of drug is not effective for humans with IC. Studies to date also have shown no benefit of oral glucosamine[93] or pentosan polysulfate supplementation by mouth[56] or subcutaneous injection[120] over that of placebo for FIC (or IC[55]). Two tricyclic antidepressants, amitriptyline and clomipramine, have been used to treat cats with severe FIC, although neither is specifically indicated for this purpose, and should be used with caution.[10,17,109,121]

Summary

The most common cause for LUTS in cats is FIC, which unfortunately remains a diagnosis of exclusion. Converging evidence from a variety of studies suggests that most cases of FIC are more likely to be a disorder affecting the bladder than a primary bladder disorder, which led to the "Pandora Syndrome" hypothesis.[4] Because FIC can be a chronic, frustrating disease, excellent client communication in conjunction with MEMO, analgesics, and possibly other pharmacologic agents can often provide sufficient EE to permit clinical recovery in both acute and chronic cases.

Beyond therapy, however, we veterinarians take an oath to use our scientific knowledge and skills to protect animal health and welfare and to prevent and relieve animal suffering. Given the documented effects of confinement on cats,[67,102,122,123] I advocate for implementation of effective EE as preventive health care for all cats, as necessary for their health and welfare as provision of satisfactory nutrition, appropriate vaccination, and parasite control.

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CHAPTER 335

Urethral Diseases

Joseph W. Bartges

Urethral disease occurs commonly in dogs and cats, often in association with diseases of the urinary bladder. Clinical signs of urethral disease include pollakiuria, stranguria, periuria, hematuria (see ch. 47), obstruction of urine flow, or urinary incontinence (see ch. 46). Physical examination (see ch. 2) should include palpation of the perineal region, rectal examination (the pelvic urethra is palpable through the rectal wall running dorsal to the pelvic bones), and examination of the external genitalia. Urinalysis (see ch. 72) is important as it may contain evidence of infection or neoplasia. Imaging procedures such as survey abdominal radiography, contrast urethrocystography (see ch. 124), and cystoscopy (see ch. 108) may be required for diagnosis. Ultrasonographic (US) evaluation of the urethra is limited by the pelvis (see ch. 88).

Urethral Sphincter Mechanism Incompetence (USMI)

Degenerative USMI is the most common cause of urinary incontinence in dogs, occurring primarily in spayed females several years after ovariohysterectomy (see ch. 333).[1,2] Clinical signs include unconsciously leaving a puddle of urine wherever the dog lies, but while awake, urination is normal and incontinence is not present. Bacterial urinary tract infection (UTI) occurs commonly with incontinence and is often not associated with active urine sediment. UTI does worsen the urinary incontinence. Estrogenic or alpha-agonist agents, alone or in combination, are treatments typically employed. Dogs unresponsive to these medications can be managed with surgical injection of urethral bulking agents or placement of a hydraulic urethral occluder.[1,3-5]

Anatomic Congenital Urethral Disease

Ectopic Ureter

Definition

Ectopic ureters are included in this chapter because urinary incontinence is a result of their abnormal urethral or vaginal opening (see ch. 336). Normally, ureters enter the dorsolateral caudal surface of the bladder and empty into the trigone after a short intramural course. Ectopic ureter results from termination of one or both ureters at a site other than this and likely result from an embryologic abnormality of the mesonephric duct ureteral bud. Degree of ureteral bud deviation from the normal position determines the ectopic opening location. Ectopic ureters may be unilateral or bilateral, intramural or extramural. An extramural ectopic ureter bypasses insertion at the trigone and inserts distally in the urethra, vagina or vestibule in females, or ductus deferens in males. An intramural ectopic ureter inserts at the trigone but tunnels in the urethral wall to open distally. Variations of the intramural ectopic ureter include ureteral troughs, double ureteral openings, multiple fenestrated openings, and two intramural ureters opening in a single orifice.[6] Ectopic ureters may be associated with other congenital defects of the urogenital tract including agenesis, hypoplasia, or renal dysplasia; hydroureter; ureterocele; urachal remnants, pelvic bladder; vulvovaginal strictures; and persistent hymen.[7,8]

Signalment

Ectopic ureters (most often bilateral and intramural) are most commonly diagnosed in young female dogs (median age of 10 months).[8,9] Males with ectopic ureter are often slightly older (about 24 months) of age when diagnosed. It is presumed that many males are never diagnosed because they remain continent due to their urethral length and their external urethral sphincter.[9] Breeds reported to be at greater risk for ectopic ureter include the Siberian Husky, Labrador Retriever, Golden Retriever, Newfoundland, English Bulldog,

West Highland White Terrier, Fox Terrier, Skye Terrier, and Miniature and Toy Poodles.[8] A genetic basis may exist but is unproven in most cases. Cats are rarely diagnosed with ectopic ureter.

Clinical Signs and Physical Examination

Intermittent or continuous urinary incontinence since birth or weaning is the most frequently reported clinical sign in dogs with ectopic ureter. Most, however, also appear to void normally. Physical examination findings are often unremarkable, with the exception of moist or urine-stained hair in the perivulvar or preputial region. Urine scalding may cause secondary dermatitis, and owners may report frequent licking of the vulvar or preputial area. Some dogs have vulvovaginitis, a vulvovaginal stricture, or a persistent hymen that can be detected digitally or with vaginoscopy. About two-thirds of these dogs have a history of UTI.[6]

Diagnosis

Survey radiography should be performed to assess the size, shape, and location of kidneys and bladder. Excretory urography combined with pneumocystography, abdominal US, contrast urethrocystography with vesicoureteral reflux, fluoroscopy, or contrast-enhanced computed tomography (CT) may be used to diagnose ectopic ureter (Figure 335-1).[8,10] Urethrocystoscopy (see ch. 108) is excellent, especially when combined with other imaging modalities (E-Figure 335-2).[8] Dilation of the ectopic ureter is often, but not always, present.

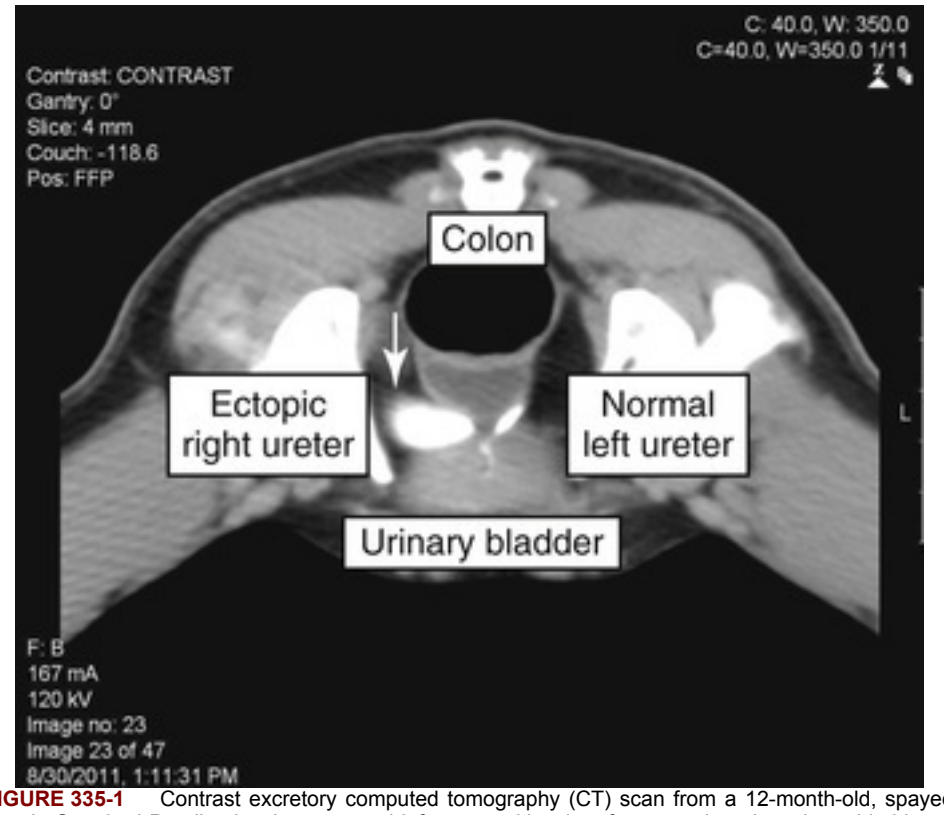
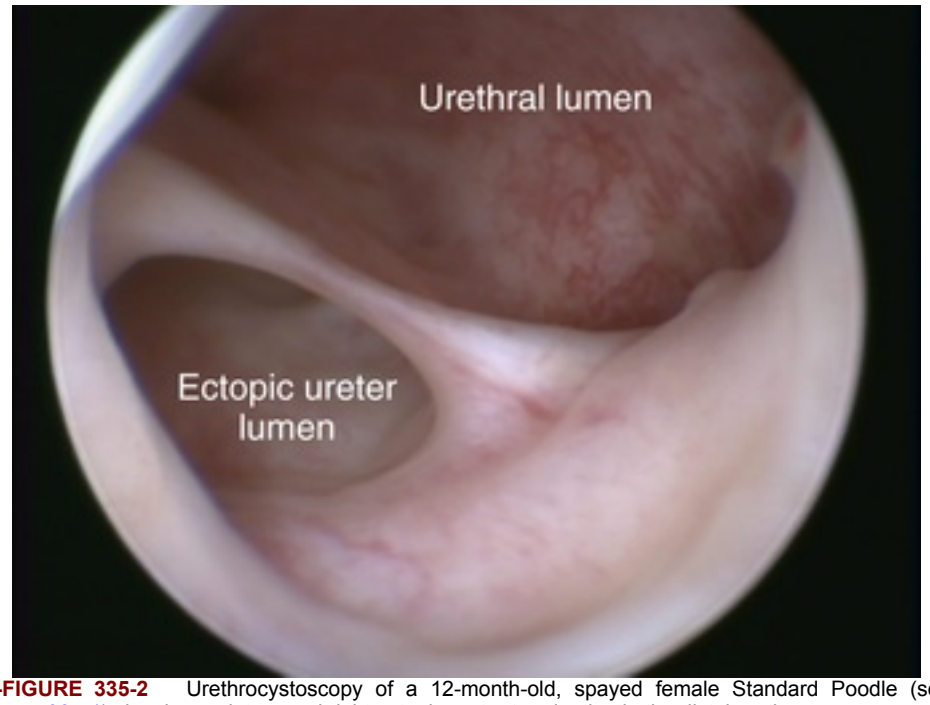


FIGURE 335-1 Contrast excretory computed tomography (CT) scan from a 12-month-old, spayed female Standard Poodle showing a normal left ureter with a jet of contrast into the urinary bladder at the trigone and a dilated right ureter that enters that urinary bladder at the trigone but tunnels distally.



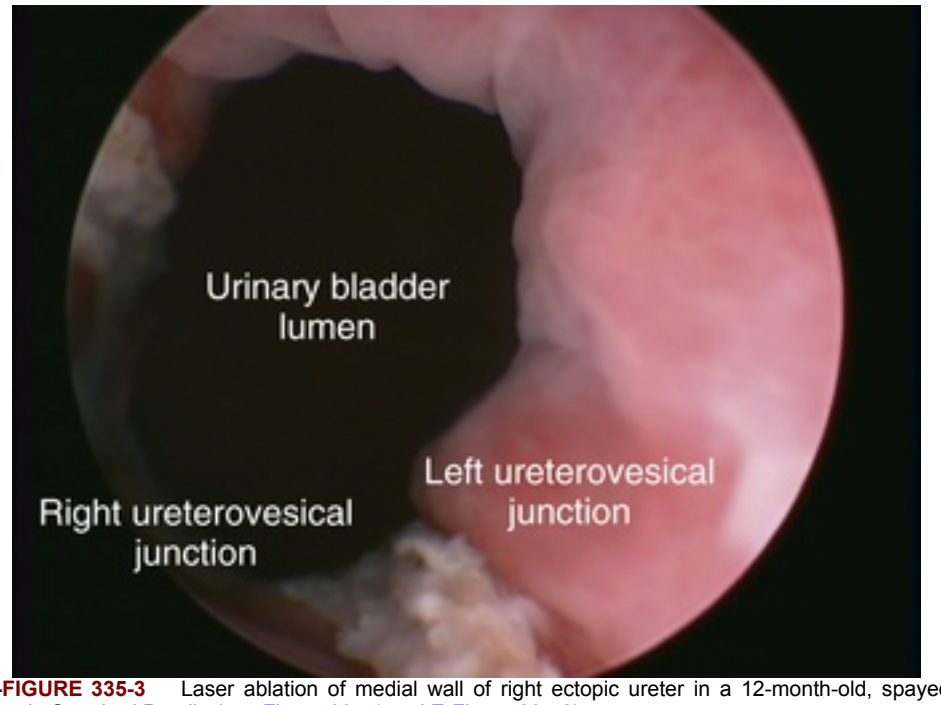
E-FIGURE 335-2 Urethrocystoscopy of a 12-month-old, spayed female Standard Poodle (see Figure 335-1) showing an intramural right ectopic ureter terminating in the distal urethra.

Treatment—Surgery

Some dogs may respond partially or completely to the drugs used for USMI. While medical management may help control urinary incontinence, surgical correction or laser ablation is preferred. An extramural ectopic ureter can be ligated at its distal end and reimplanted into the bladder between its apex and trigone (neoureterocystostomy). The bladder wall should be cultured or urine from the renal pelvis should be collected for culture at the time of surgery due to the frequency of bacterial UTI. Traditionally, intramural ectopic ureters are treated by ligation of the distal submucosal ureteral segment and creating a new ureteral opening in the trigone of the urinary bladder (neoureterostomy and urethral-trigonal reconstruction); however, incontinence persists in many (44-67%) because the intramural segment of ureter disrupts the functional anatomy of the internal urethral sphincter mechanism.[8,11,12]

Treatment—Laser

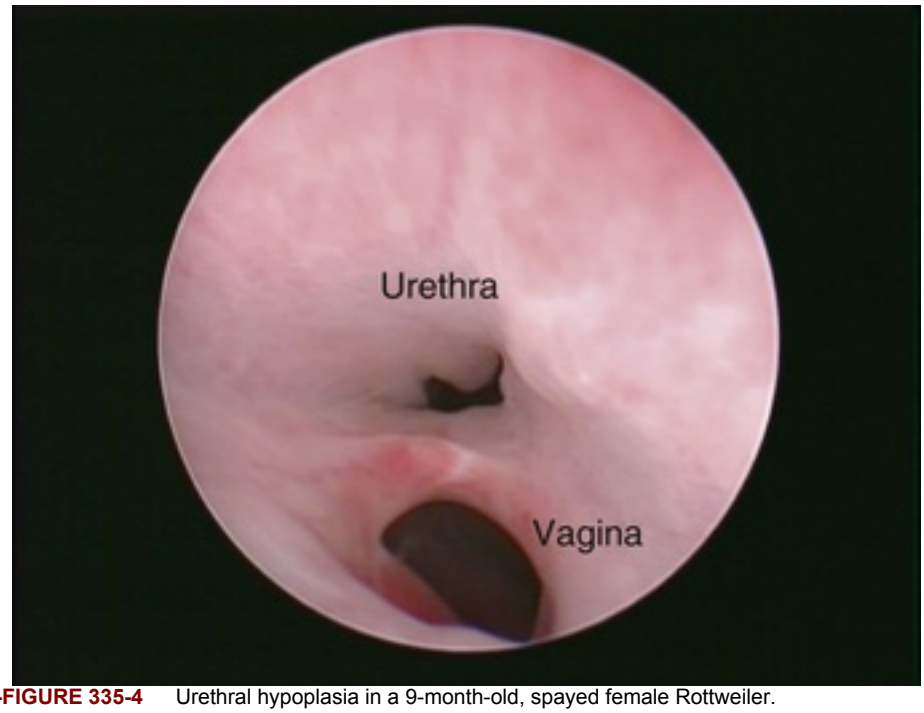
Transurethral laser ablation may be used to correct intramural ectopic ureters (see ch. 124). A rigid (in females) or flexible (in males) endoscope is inserted retrograde into the urethra; diagnostic urethrocystoscopy is performed. A catheter is inserted into the lumen of the ectopic ureter in order to protect the lateral urethral wall. A laser fiber, diode or preferably Holmium : YAG, is inserted through the operating channel of the cystoscope and used to transect the free wall of the ectopic ureter until the opening is as close as possible to the normal trigone anatomic location (E-Figure 335-3).[13-16] Incontinence may persist with intramural ectopic ureters because the proximal urethra and internal urethral sphincter mechanisms can be disrupted.[17] Following the laser procedure, it appears that dogs are more likely to be continent than after surgery. In dogs with a kidney that cannot be saved due to hydronephrosis or pyelonephritis, nephroureterectomy can be performed.



E-FIGURE 335-3 Laser ablation of medial wall of right ectopic ureter in a 12-month-old, spayed female Standard Poodle (see Figure 335-1 and E-Figure 335-2).

Urethral Aplasia and Hypoplasia

Urethral aplasia is a rare congenital anomaly characterized by complete absence of a patent urethra. Incontinence is associated with ectopic ureters.[18,19] Urethral hypoplasia has been described in immature female cats in association with juvenile-onset urinary incontinence (E-Figure 335-4).[20-22] Diagnosis is based on clinical signs and imaging studies. Radiographic features include urethral shortening and vaginal aplasia. Urethral hypoplasia may be associated with other congenital anomalies and bacterial UTI. Some dogs respond to sympathomimetic therapy. Surgical reconstruction of the bladder neck may improve or resolve clinical signs.[21,22]

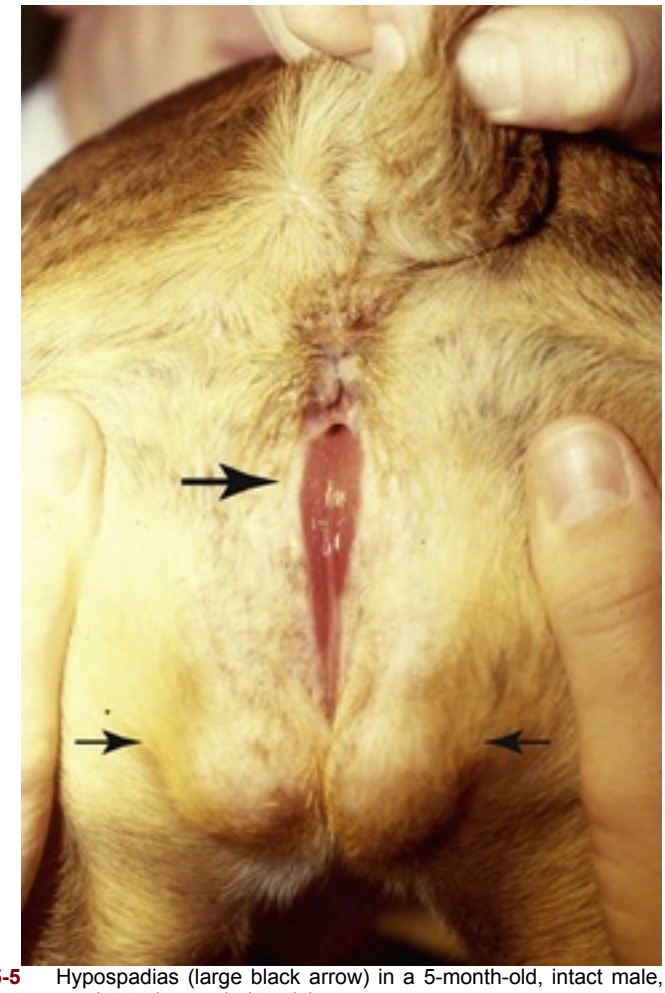


E-FIGURE 335-4 Urethral hypoplasia in a 9-month-old, spayed female Rottweiler.

Epispadias and Hypospadias

Definitions

Epispadias is a congenital defect in the dorsal aspect of the distal urethra. Hypospadias is an anomalous ventral malposition of the urethral meatus.[23] Epispadias has been associated with exstrophy of the urinary bladder in an 8-month-old, female, English Bulldog.[24] Hypospadias is most commonly seen in males. The Boston Terrier and Dalmatian have been described as having increased risk (E-Figure 335-5).[23,25] It has been described in a Himalayan cat.[26] Additionally, it has been described in an East Greenland Male Sledge Dog after potential *in utero* exposure to 320 mcg/day organochlorine (128 pg TEQ/kg/day), 32-128 times the World Health Organization (WHO) guidelines and threshold levels for teratogen and reproductive effects.[27] The condition is rare, and etiology is unclear. The types are glandular, penile, scrotal, perineal, or anal, according to urethral opening location and can be classified as mild, moderate or severe. In the severe form, underdevelopment or absence of the penis, failure of fusion of the scrotum, and failure of the urethra to close in the perineal area may be seen. Other abnormalities associated with hypospadias include retained testicles, kidney agenesis, bone or anorectal defects, umbilical hernia, hydrocephalus, urinary incontinence and ascending UTI.[23,28] Chromosome analysis can be used to differentiate hypospadias from true hermaphroditism.[25]



E-FIGURE 335-5 Hypospadias (large black arrow) in a 5-month-old, intact male, English bulldog; the small black arrows point to descended testicles.

History, Physical Findings, Diagnosis and Treatment

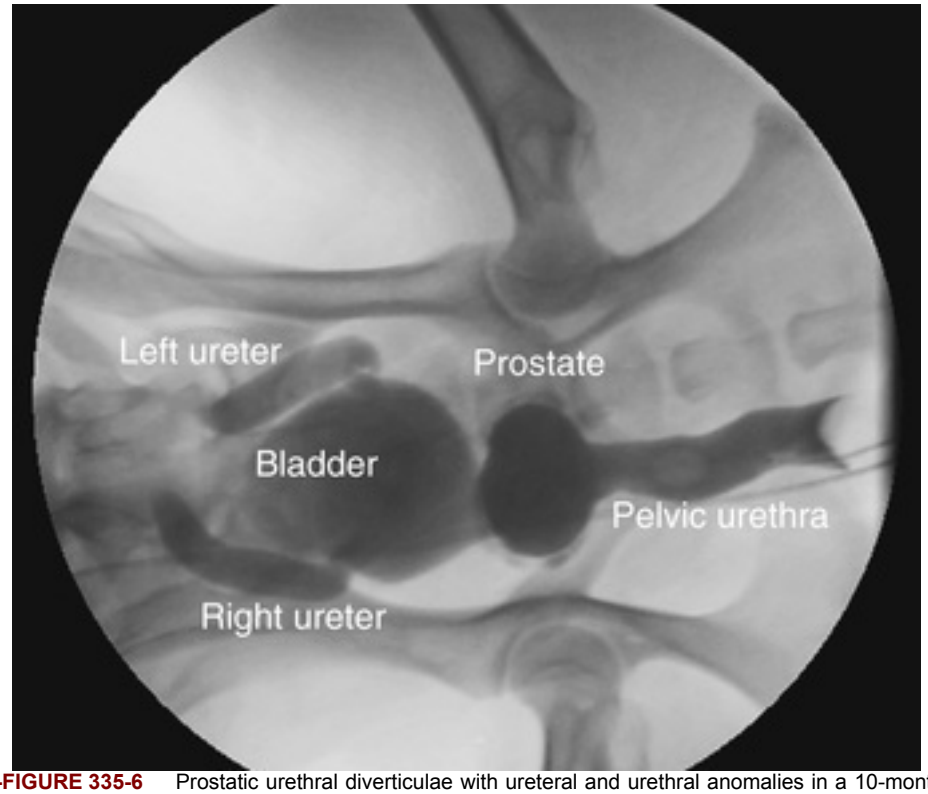
Affected dogs are diagnosed at various ages; some show no clinical signs whereas some present with urinary incontinence, periurethral dermatitis, or bacterial UTI.[28,30] Diagnosis is often based on physical examination. Affected male dogs have an abnormal ventral urethral meatus that may be located anywhere along the shaft of the penis, scrotum, or perineum, usually associated with malformation of the prepuce and/or penis.[28,29] Hypospadias has been described in female dogs in association with genetic intersex. Embryonically, hypospadias results from incomplete fusion of the urogenital fold. The presence of an *os penis* in male dogs precludes surgical reconstruction in most. Scrotal or perineal urethrostomy combined with castration and removal of vestigial preputial and penile tissues may be of cosmetic value. Shortening of the penis, amputation, and urethral reconstruction have been described.[31-34] One technique described significant reconstruction, urethrostomy, and partial penile amputation. This technique may be considered for glandular or penile hypospadias or after resecting the ventral aspect of the distal prepuce when inadequate tissue is present for a simple two-layer closure.[35]

Urethrogenital Malformations

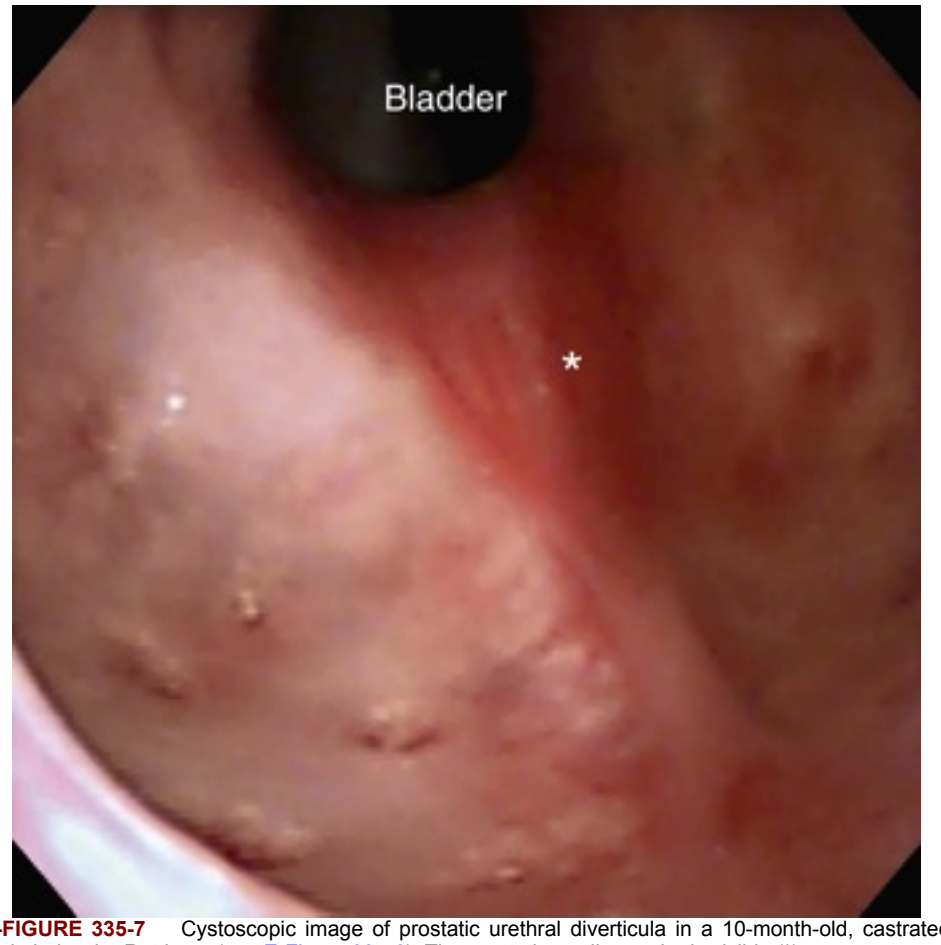
Urethrogenital malformations are seen with intersex conditions, and pseudohermaphroditism is often associated with urinary incontinence.[36] Pseudohermaphrodites have gonads of one gender and external genitalia of the other.[37] It occurs in both sexes as a result of simultaneous development of müllerian duct derivatives (oviduct, uterus, and portions of the vagina) and masculinization of the urogenital sinus. The phenotype (appearance) depends on the degree of masculinization of the urogenital sinus. Incontinence likely results from retention of urine in anomalous communications between urethra and genital tract, which then

passively leak.[38] The condition develops early in life and may be accompanied by UTI.[38] Diagnosis is based on physical signs and imaging studies. Urinary incontinence may resolve with surgical correction.[36]

Prostatic urethral diverticulae have been described in male dogs in association with abnormally short and wide intrapelvic urethra, widened urinary bladder neck, and ureteral anomalies (E-Figures 335-6 and 335-7).[39] This seems similar to a condition described in an infant with congenital obstructive posterior urethral membrane, where a membrane extended proximally from the verumontanum toward the bladder neck. While this often results in chronic renal disease, a mild degree of obstruction and protective pressure pop-off mechanisms have been reported, resulting in dilation of the prostatic utricle.[40]



E-FIGURE 335-6 Prostatic urethral diverticulae with ureteral and urethral anomalies in a 10-month-old, castrated male Labrador Retriever. Ventrodorsal contrast urethrocystogram with ureteral reflux of contrast using fluoroscopy. Bilateral hydroureter is present and the ureters enter the urinary bladder through one vesicoureteral junction. The urinary bladder neck is nonexistent and there is post-prostatic urethral dilation.



E-FIGURE 335-7 Cystoscopic image of prostatic urethral diverticula in a 10-month-old, castrated male Labrador Retriever (see E-Figure 335-6). The prostatic median raphe is visible (*).

Urethral Duplication

Urethral duplication is an uncommon congenital anomaly only described in immature dogs.[41-45] Because of close association between embryonic development of the urogenital and gastrointestinal systems, urethral duplication is almost always accompanied by other duplication anomalies. The anomalies result from abnormal sagittal midline division and subsequent parallel development of the embryonic hindgut, cloaca, rectum, or urogenital sinus.[46] Associated anomalies depend on the stage at which dysmorphogenesis occurs. Physical examination may reveal anatomic abnormalities, urinary incontinence, or clinical signs associated with secondary bacterial UTI. Diagnosis is based on physical examination, imaging, and exploratory surgery. Urethral duplication may in some cases be amenable to surgical extirpation of the duplicated structure; however, surgical reconstruction has rarely been attempted with extensive duplication.

Ectopic Urethra

Ectopic urethra is characterized by abnormal position of the external urethral orifice. Embryonically, urethral ectopia results from anomalous morphogenesis of the urogenital sinus, paramesonephric ducts (müllerian ducts), or mesonephric ducts.[47] Clinical signs depend on the site of the urethral termination and other concurrent urogenital anomalies. Lifelong urinary incontinence was the predominant clinical feature in a 21-month-old female English Bulldog with unilateral ureteral ectopia and an ectopic urethra terminating in the distal vagina.[48] In contrast, a 2-month-old, female, domestic shorthair cat with ectopic urethra terminating in the ventral rectum did not have urinary incontinence but did void urine through the anus.[49]

Urethrorectal, Urethrovaginal, and Urethroperineal Fistulas and Urethral

Diverticula

Fistulas connecting the urethral lumen with the large bowel, vagina, and perineal region have been described in dogs and cats.[44,50-57] Congenital urethrorectal fistulas occur because of failure of separation of the fetal cloaca into the anterior urethrovesical segment and the posterior rectal segment by the urorectal septum, resulting in a permanent communication between the urethra and the rectum. Micropenis and midline vestibuloperineal fistula were described in two dogs with urinary incontinence considered to be intersexes (78XX karyotype).[58] It has also been described as an acquired disease due to prostatic abscessation in a dog but may occur due to traumatic, inflammatory, or neoplastic processes.[53,59] Males appear to be affected more frequently, and English Bulldogs appear to have a predilection for urethrorectal fistula.[59] Clinical signs are due to abnormal passage of urine from the fistula during urination. Additional signs may include diarrhea, perineal dermatitis, and signs associated with secondary bacterial UTI. Fistulas have been associated with infection-induced struvite urolithiasis.[51,53,55] Diagnosis is based on clinical signs and imaging studies (Figure 335-8). Treatment is surgical correction or urinary diversion. Conservative therapy (indwelling urinary catheter, low-residue diet, and antibiotics) was successful in a dog with a urethrorectal fistula secondary to a prostatic abscess.[53]

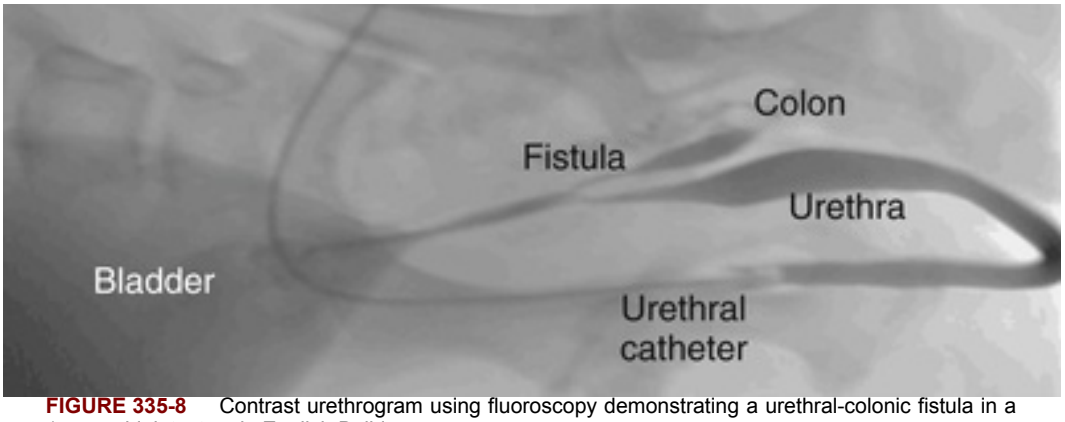


FIGURE 335-8 Contrast urethrogram using fluoroscopy demonstrating a urethral-colonic fistula in a 1-year-old, intact male English Bulldog.

Urethral Prolapse

Urethral prolapse occurs when the distal urethra protrudes through the urethral orifice of the penis. It appears as a red or purple mass at the tip of the penis and occurs in male dogs <5 years of age (Figure 335-9)[60]; English Bulldogs and Boston Terriers appear predisposed.[61-63] Urethral prolapse may not be associated with clinical signs or owners may only notice a red to purple "mass" at the tip of the penis during urination; however, it may be associated with dripping of blood, licking of the prepuce or penis, or signs of lower urinary tract disease (see ch. 44, 45, and 46). Diagnosis is based on physical examination; it must be differentiated from neoplasia. If urethral prolapse is associated with no to few signs, treatment may not be necessary.[64] Urethral prolapse is treated by attempting to manually reduce the prolapsed tissue; applying hypertonic saline may facilitate the attempt. A loose purse-string suture is then placed but recurrences are common. Surgical reduction or urethropexy are treatments of choice.[63]

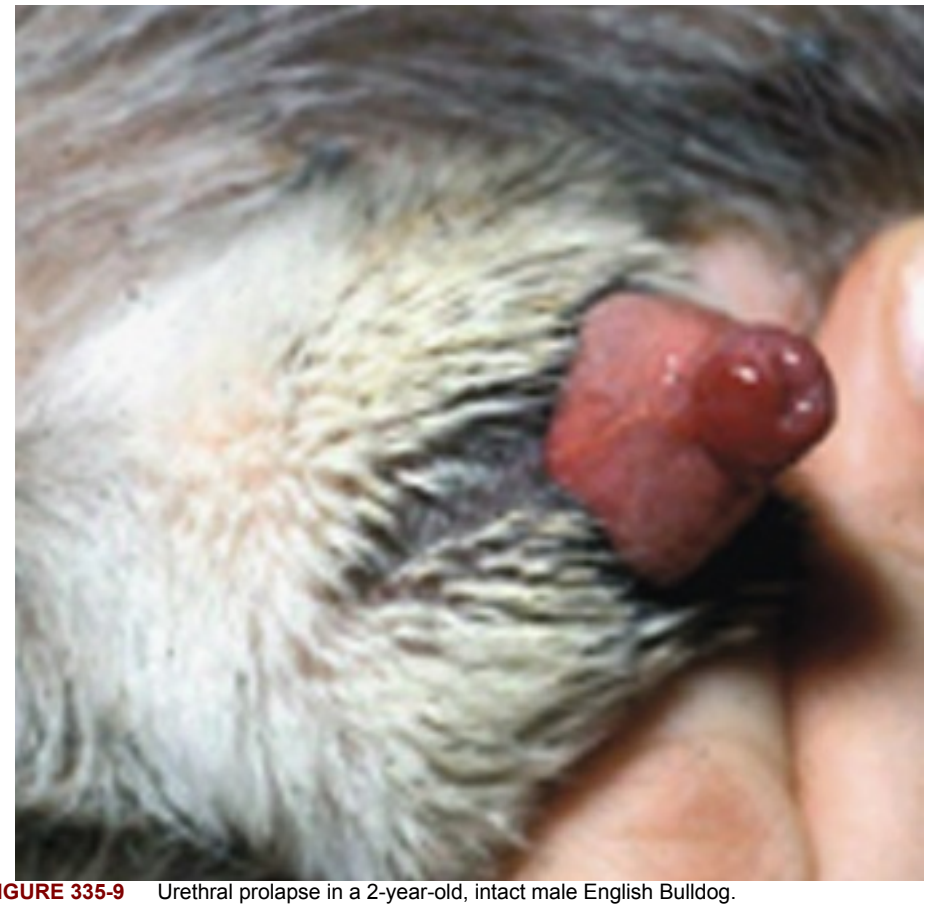


FIGURE 335-9 Urethral prolapse in a 2-year-old, intact male English Bulldog.

Urethral Stricture and Hypoplasia

Congenital urethral strictures and hypoplasia have been described in young dogs and cats.[21,65] Clinical signs relate to partial or complete urethral obstruction with stricture or urinary incontinence with hypoplasia (see ch. 44-46). Systemic signs, bladder distention or rupture, overflow incontinence, secondary bacterial UTI, or hydronephrosis can follow outflow obstruction or incontinence with urethral hypoplasia. Urinary incontinence and bilateral hydroureter and hydronephrosis were observed in an 8-month-old, male, German Shepherd Dog with congenital midurethral stricture.[65] Treatment involves surgery. If the stricture occurs in the extrapelvic urethra, urethrostomy may be performed; if it occurs in the intrapelvic or intraabdominal urethra, then urethral resection and anastomosis or prepubic urethrostomy may be indicated.[66,67] Dilation of the urethral stricture may also be attempted with balloon or bougienage catheters. Urinary incontinence secondary to urethral hypoplasia may be treated surgically or with a hydraulic urethral occluder with variable success.[21]

Congenital Urinary Incontinence

Many congenital disorders are associated with urinary incontinence. In addition to those described in the preceding sections, spinal dysraphism (cleftlike malformations of the spine and spinal cord resulting from incomplete closure of the neural tube) is associated with urinary and fecal incontinence. Congenital USMI has been described in dogs and cats associated with urethral hypoplasia[21] or due to neurogenic abnormalities in pseudohermaphrodites[38]; however, ectopic ureter is most commonly associated with juvenile urinary incontinence.[8,14,68]

Metabolic Urethral Disease—Urethrolithiasis and Feline Matrix-Crystalline Urethral Plugs and Urethral Obstruction

Definitions

Obstructive uropathy refers to abnormalities in structure or function of the urinary tract caused by impairment of normal flow of urine and the resulting local and systemic effects of that impairment.[69,70] Impairment of flow through the urethra either due to physical obstruction (E-Figures 335-10 and 335-11 and Figure 335-12) or detrusor or urethral dysfunction causes signs. Although there are many causes of urethral obstruction, urolithiasis is the most common cause in dogs (see ch. 331) and crystalline-matrix urethral plugs and uroliths are most common in cats (see ch. 332). About 10-20% of cats with lower urinary tract signs have urolithiasis or urethral plugs. Struvite and calcium oxalate are the most common uroliths reported.[71] Most urethral plugs contain large quantities of matrix (mucoprotein containing mucus and inflammatory debris) with varying quantities of mineral. Crystals become trapped in the matrix. It is thought that the mucus is secreted by urinary bladder and urethral mucosal cells in response to an irritant or inflammatory stimulus. Matrix also contains sloughed tissue or blood with or without inflammatory cells. Matrix-crystalline plugs usually occur at the tip of the penis where the urethra narrows, but they can occur anywhere in the urethra.

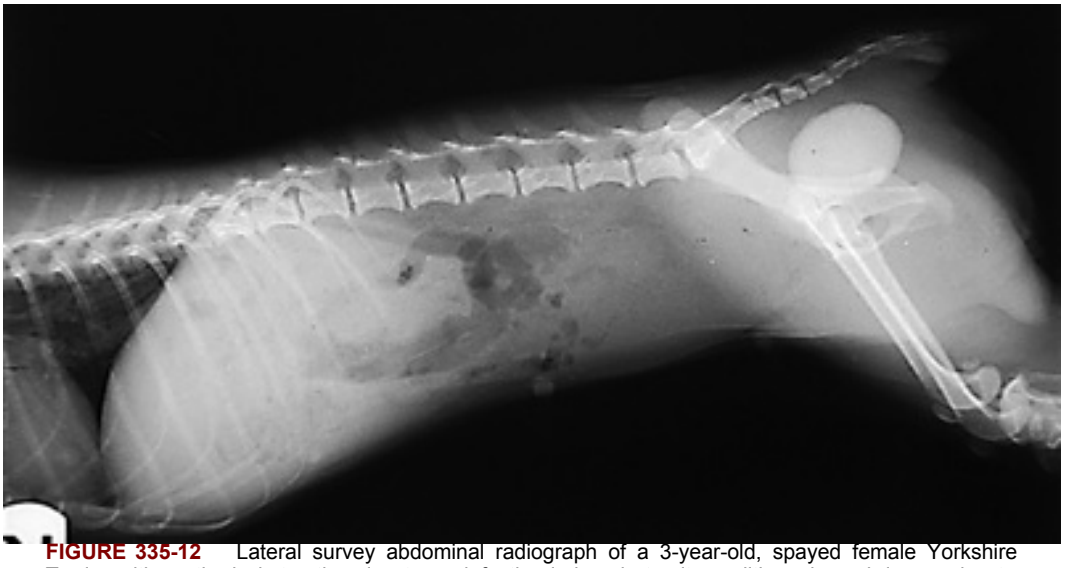
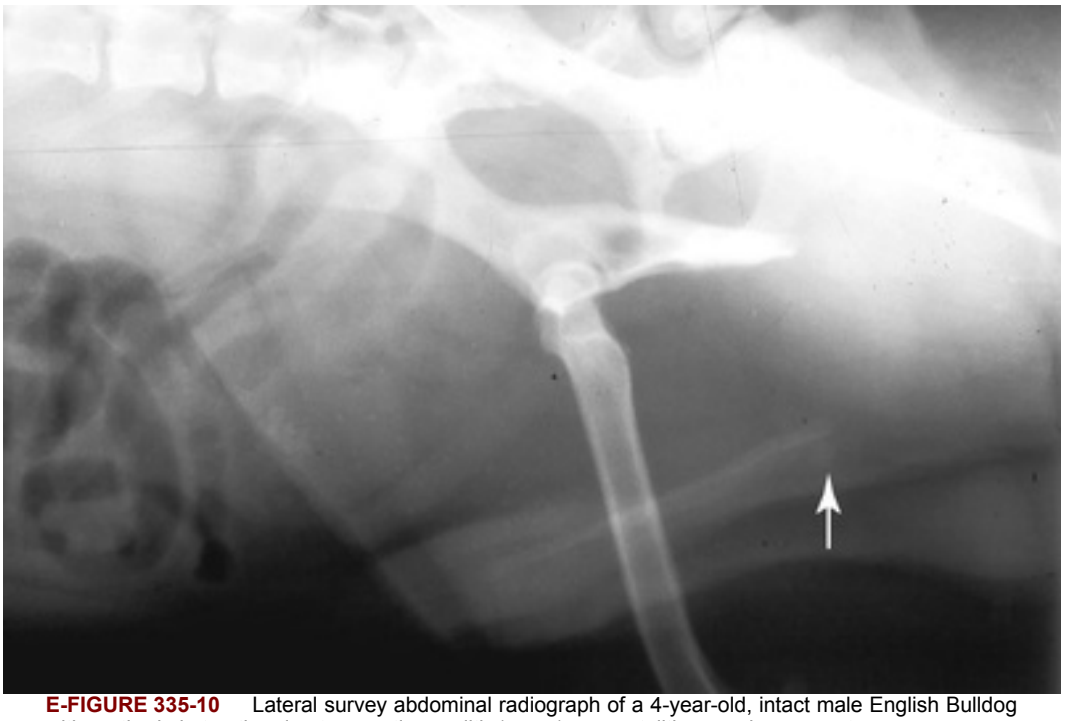
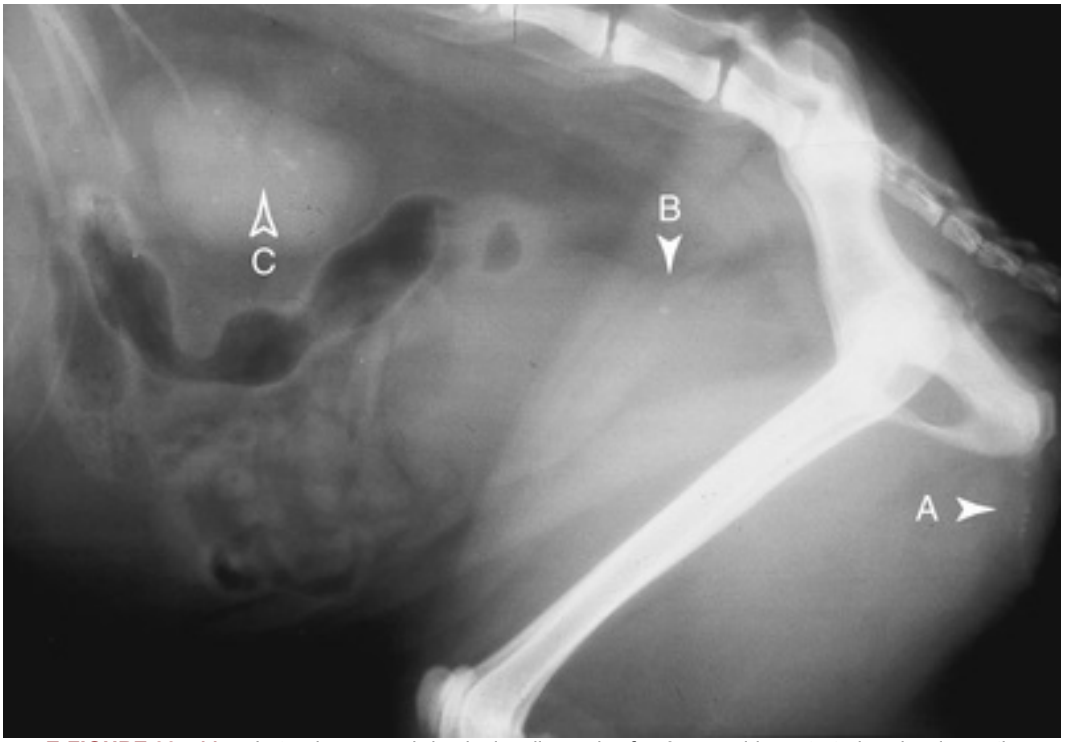


FIGURE 335-12 Lateral survey abdominal radiograph of a 3-year-old, spayed female Yorkshire Terrier with urethral obstruction due to an infection-induced struvite urolith and uroabdomen due to urinary bladder rupture.



E-FIGURE 335-10 Lateral survey abdominal radiograph of a 4-year-old, intact male English Bulldog with urethral obstruction due to a cystine urolith (arrow); urocystoliths are also present.



E-FIGURE 335-11 Lateral survey abdominal radiograph of a 9-year-old, castrated male, domestic shorthaired cat with calcium oxalate urethroliths causing obstruction **(A),** cystolith **(B),** and nephroliths **(C).**

Clinical Consequences

Clinical consequences of urethral obstruction are often, but not always, associated with signs of uremia.

Partial or early outflow obstruction may not impair renal function sufficiently to cause uremia; however, clinical signs of uremia usually occur within 24 hours of complete urethral obstruction. As functional renal mass decreases or as intravesical, ureteral, and renal pressure increases, urine concentrating ability is lost. Increased renal tubular volume of urine and increased tubular pressure occur, causing azotemia and uremia. Early detection and removal of obstruction can result in prompt resolution of uremic signs, although renal abnormalities may persist for some time. Also, urethral obstruction may lead to detrusor atony, urethral injury, urethral and bladder mucosal damage, UTI, or urethral or bladder rupture.

Clinical Signs, Physical Examination, Laboratory Test Results

Signs of obstructive uropathy vary depending on several factors: degree of urine outflow impairment, duration of disease, and presence of bacterial UTI. Patients with urethral obstruction may or may not have preceding signs of lower urinary disease. They may only exhibit clinical signs localized to the lower urinary tract, such as dysuria, hematuria, pollakiuria, inability to pass urine, or pain (see ch. 44, 45, and 46). They may, however, exhibit polysystemic signs of uremia: vomiting, anorexia, obtundation. Owners may mistake animals with urethral obstruction as being constipated or having abdominal or back pain.

Physical examination may reveal a healthy dog or one that is extremely ill. A large painful bladder may be palpable. Bradycardia, hypothermia, pale mucous membranes with prolonged capillary refill time, hyperpnea, and halitosis may be present. The tip of the penis may be dark purple and swollen, and one or more uroliths may be palpated in the urethra. Rectal examination should be performed, when possible, to rule out a pelvic urethral urolith or obstruction from neoplasia or prostatic disease. Samples for complete blood count, serum biochemical analysis, urinalysis and urine culture should be collected. Cystocentesis may be performed successfully even with urethral obstruction, if care is taken to insert the needle gently, angling the tip toward the trigone while stabilizing the bladder (see ch. 105). When the pet is stable, survey abdominal radiography should be performed. Additional imaging such as ultrasound (see ch. 88), contrast urethrocystography, or urethrocystoscopy (see ch. 108) may be considered.

Treatment—Emergency Stabilization

Priorities of treating a patient with urethral obstruction depend on degree of obstruction and the patient's general health. If the animal is extremely depressed, oxygen should be administered (see ch. 131), an IV catheter placed (see ch. 75), and blood and urine samples obtained. Management of such emergencies, including fluid therapy and correcting electrolyte abnormalities, are fully reviewed in E-Box 335-1 and ch. 127, 129, 150, and 322. Once stabilized, the pet can be sedated or anesthetized in order to relieve the urethral obstruction. If the animal is severely depressed or unconscious, relieving the urethral obstruction may be possible without sedation or anesthesia. In some male dogs, passing a urinary catheter may be performed while the dog is awake and urethroliths retropulsed into the urinary bladder without sedation or anesthesia.

E-Box 335-1

Emergency Treatment for Patients with Urethral Obstruction

Fluid Therapy (see ch. 129)

Fluid therapy should be instituted with the rate based on physiologic status of the patient. Estimate the degree of dehydration and administer an isotonic replacement electrolyte solution over 6-12 hours if minimally dehydrated, over 4 hours if moderately dehydrated, and rapidly if shock is present. Rate of fluid therapy should be assessed and adjusted based on response to therapy including heart rate, electrocardiogram, respiratory rate, and thoracic auscultation. If bradyarrhythmia is present due to hyperkalemia, it should be treated aggressively (see below).

Hyperkalemia (see Section VII and ch. 309)

Clinical and experimental studies have shown that obstructive uropathy alters sodium, potassium, magnesium, phosphorus, and calcium metabolism.[72,73] Hyperkalemia is caused by acidemia, decreased renal excretion of potassium, and tissue catabolism. Alterations in P-R interval, S-T segment, and T waves on electrocardiograms are associated frequently with hyperkalemia. Dysrhythmias may also occur, including third-degree heart block and ventricular arrhythmias. Varying degrees of neuromuscular weakness and flaccid paralysis occur as a result of impaired impulse transmission. Serum

concentration of potassium approaching 10 mEq/L may be associated with bradycardia and cardiac arrest.

Immediate life-threatening arrhythmias due to hyperkalemia should be treated first. Treatment can include calcium gluconate (50-100 mg/kg IV over 2-3 minutes, monitor ECG) to counteract effect of hyperkalemia at the sinoatrial node, or measures to decrease serum potassium concentration: bicarbonate (1-2 mEq/kg IV), 10% dextrose infusion (4-10 mL/kg IV), insulin (0.1-0.25 IU/kg IV q 2-4 h), or dextrose and insulin infusion (0.5 IU/kg regular insulin + 4 mL of 50% dextrose/IU of insulin IV).

Metabolic Acidosis (see ch. 128)

Metabolic acidosis is often present in acute urethral obstruction; however, usually it is not severe enough (pH seldom < 7.0) to warrant specific treatment.

Hypocalcemia (see ch. 69)

Ionized hypocalcemia may occur in cats with urethral obstruction and it exacerbates the effects of hyperkalemia; it is treated with calcium gluconate (see above).[74]

Many protocols are available to facilitate relief of urethral obstruction including: morphine (0.1-0.3 mg/kg IM), butorphanol (0.2-0.4 mg/kg IV or IM), propofol (2-4 mg/kg IV), short-acting barbiturate (5 mg/kg IV), isoflurane anesthesia administered by mask, and ketamine (2.5-5 mg/kg IV) mixed with diazepam (0.125-0.25 mg/kg IV) or midazolam (0.125-0.25 mg/kg IV or IM) or acepromazine (0.05-0.1 mg/kg IV). Cystocentesis, if necessary, should be performed using a 22-gauge, 1 1/2-inch needle or a 22-gauge over-the-needle catheter attached to an IV extension set and three-way stopcock, to decompress the urinary bladder and collect samples. It is important to stabilize the needle or catheter in order to avoid further bladder damage and avoid bladder rupture and uroabdomen. Urethral unobstruction should be performed as soon as possible. In male cats, a urethral crystalline-matrix plug may be dislodged by massaging the distal penis between the thumb and forefinger and applying gentle pressure to the bladder (E-Figure 335-13). If the obstruction is not relieved, retrograde hydropropulsion should be performed.

E-FIGURE 335-13 Urethral plug dislodged from a 5-year-old, castrated male, domestic shorthaired cat by massaging the penile urethra and applying gentle pressure on the urinary bladder.

Relieving Feline Matrix-Crystalline Urethral Plugs (see ch. 107)

Once stabilized, the cat is usually placed on its side or back and the penis is extended from the preputial sheath by pulling it in a caudal-dorsal direction and straightening the urethra. The end of the penis and periurethral tissues are cleansed gently, the tip of a lubricated 3.5-French (Fr) polypropylene open-ended tomcat catheter is inserted gently into the external urethral orifice, and the lumen of the penile urethra flushed with 12 mL sterile solution (Video 335-1). This is often successful in flushing the obstructing material back into the bladder. Do not flush the urethra with lidocaine as it may become absorbed and can be toxic. Rectal massage of the pelvic urethra may help dislodge the plug.

Relieving Uroliths (see ch. 107)

Retropulsing Uroliths in Obstructed Male Dogs

Uroliths that cause urethral obstruction should be retropulsed into the urinary bladder using a dilute sterile lubricant solution made by mixing 1 part sterile lubricant with 1 part sterile water.[75] One can place 15 mL sterile lubricant in a 35-mL syringe and 15-20 mL of sterile fluid in a second 35-mL syringe. Attach syringes to the 3-way stopcock, squirt the sterile solution into the lubricant, and then pass the combination back and forth from one syringe to the other, several times. Alternatively, add sterile fluid to sterile lubricant in a syringe and let stand for 5 to 10 minutes. Anesthetize or sedate the dog or cat. Insert a red rubber catheter (5.0-8.0 Fr) in dogs or a polypropylene catheter (3.5-Fr) in cats to site of obstruction. Infuse sterile lubricant-fluid solution to lubricate the urethra. Sometimes, this is adequate to retropulse urethroliths into the urinary bladder.

If needed, attach a syringe with sterile fluid to the urethral catheter. Then, occlude the urethra proximally by rectal palpation, applying digital pressure to trap the urethra against the pelvic floor. At the same time, occlude the distal penile urethra and infuse sterile fluid under pressure. When the urethra is distended, release occlusion of the pelvic urethra. Often, as uroliths are retropulsed into the bladder, there is a "popping" sensation, and the person doing the rectal can often feel the uroliths move cranially. Uroliths that are amenable to this procedure include urate and cystine because of their smooth texture, most struvite, and some calcium oxalate, because of surface texture. This procedure will not work if uroliths are embedded in the urethral mucosa or if there is a stricture proximal to the urolith in the urethra. An alternative treatment for urethroliths is lithotripsy (see ch. 124).[76-79]

Female Dogs and Cats of Either Gender

Occasionally, female dogs and cats have urethral obstruction due to urolithiasis. Urethroliths are often palpable on rectal examination and may be retropulsed into the urinary bladder using a combination of urethral catheterization and flushing and digital moving of the urolith per rectum.

Indwelling Urinary Catheters (see ch. 106)

The decision for placing an indwelling, closed-system urinary catheter depends on difficulty in relieving the urethral obstruction, stream of urine obtained, amount of crystalline and/or gelatinous debris in the urine after copious flushing of the bladder, degree of bladder overdistention, likelihood of detrusor atony, degree of systemic illness, and cause of urethral obstruction. Administration of an alpha$_2$-receptor antagonist (prazosin or phenoxybenzamine) helps to decrease urethral spasm secondary to the catheter.[80,81] Depending on the cause of the urethral obstruction, definitive treatment and appropriate preventative measures should be undertaken.[82] Antibiotics should not be administered while an indwelling urinary catheter is present. While antibiotics decrease the incidence of bacterial UTI, when infections occur they exhibit a higher degree of antimicrobial resistance.[83] In one study of induced sterile cystitis in cats with indwelling urinary catheters, some cats receiving amoxicillin developed bacterial cystitis and at necropsy had positive bacterial cultures from kidney samples.[84]

Complications

Bacterial Infection

Bacterial infection may be present before urethral obstruction or be introduced as a consequence of procedures used to relieve obstruction (see ch. 330). Alkaline urine associated with infection by urease-producing microorganisms may predispose to struvite crystalluria and urolithiasis or to struvite-matrix plug formation. Infection is difficult to eradicate while urinary stasis exists. Signs of lower urinary tract infection

may persist after urethral obstruction is relieved. Outflow obstruction predisposes the upper tract to ascending bacterial infection due to vesicoureteral reflux.

Micturition Dysfunction

After a prolonged period of retaining urine, pets may have difficulty completely emptying the bladder (see ch. 333). This may be due to decreased bladder elasticity, damage to nerves, damage to contractile elements, or urethral edema/inflammation resulting in urethral spasm.[85] Detrusor atony or urethral swelling or spasm may persist for unpredictable periods, depending on the underlying disease and the amount of irreversible damage caused by urethral obstruction, and may impact survival.

Postobstructive Diuresis

Relief of urethral obstruction is accompanied by alterations in ability to modulate water and sodium balance. This postobstructive diuresis can be profound, can affect hydration status and electrolyte balance, and may require days of IV or SC fluids to avoid dehydration (see ch. 322). Measuring urine output and body weight after relieving urethral obstruction aids in determining necessary fluid therapy to maintain hydration.

Intrinsic Renal Failure

Although postrenal azotemia occurs more commonly than renal azotemia with urethral obstruction, primary renal failure may follow (see ch. 322). Factors that may contribute to renal failure include loss of renal parenchyma due to sustained increased intrarenal pressure, cytokine production by infiltrating leukocytes into renal parenchyma, electrolyte imbalances, fibrosis of damaged renal parenchyma, and ischemia due to dehydration associated with urethral obstruction and postobstructive diuresis.[86]

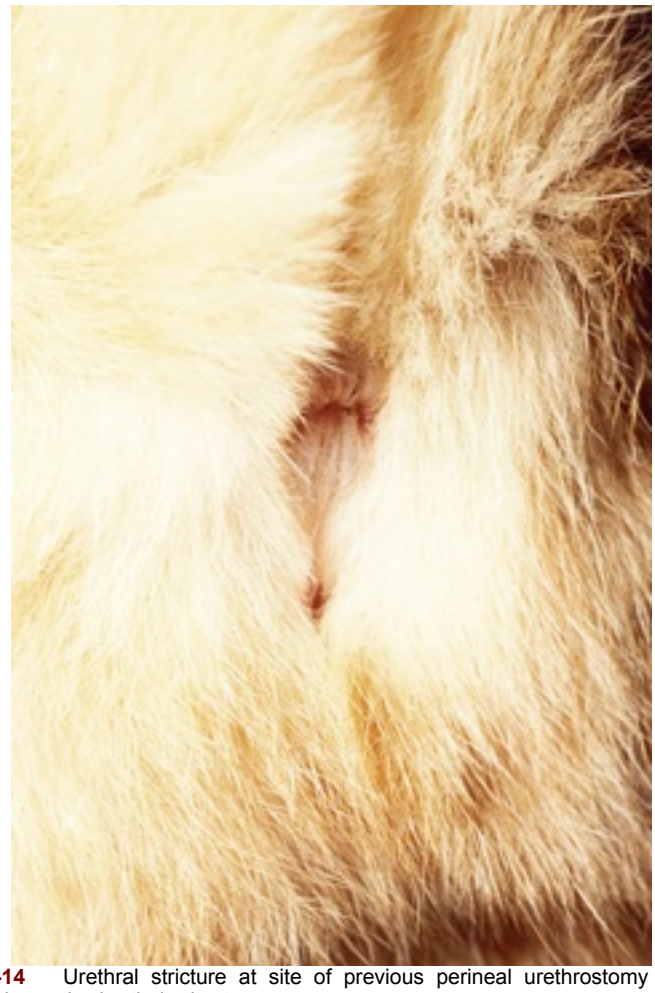
Death

Obstructive uropathy that persists for more than 24 hours usually results in postrenal uremia. The increased backpressure induced by obstruction impairs glomerular filtration, renal blood flow, and tubular function.[87] After obstructing the urethra of normal cats, death occurred in 3-6 days as a result of cardiopulmonary failure associated with fluid and electrolyte imbalances or acute oliguric/anuric renal failure.[73] Damage to the mucosal surface of the urinary bladder and presence of bacterial UTI shorten survival times.

Prognosis

Prognosis for animals with urethral obstruction is dependent upon its cause, ease with which it is relieved, and success of preventative therapy. In one study of 45 male cats with urethral obstruction, reobstruction due to uroliths or crystalline-matrix plugs occurred in about one-third, clinical signs recurred in about half, and euthanasia was performed in 20%.[88] The primary mineral component of feline matrix-crystalline urethral plugs is struvite; therefore, preventative measures should include dietary modification to prevent crystal reformation in these cats.

If the obstruction cannot be relieved, is recurrent despite appropriate treatment, or if penile trauma occurs during attempted relief of urethral obstruction, surgical urinary diversion (scrotal urethrostomy or perineal urethrostomy) should be considered.[89,90] Complications of scrotal urethrostomy in dogs are hemorrhage at time of surgery or stricture at the site afterward. Perineal urethrostomy in cats may be associated with stricture formation (E-Figure 335-14), urine leakage, or recurrent bacterial UTI.[89,91-93] For urethral obstruction due to neoplasia, urethral stents or cystostomy catheters may be used (see ch. 124).[94]



E-FIGURE 335-14 Urethral stricture at site of previous perineal urethrostomy in a 3-year-old, castrated male, domestic shorthaired cat.

Neoplastic Urethral Disease

Primary neoplasia of the urethra is uncommon in dogs and cats. Extension neoplasia into the urethra is seen with some bladder transitional cell carcinomas and some prostatic squamous cell carcinomas, but other neoplasms have been described.[95-104] Diagnosis is made by rectal palpation of the urethra, contrast urethrography, or cystoscopy (Figures 335-15 and 335-16). Treatment involves surgical removal or laser ablation and/or chemotherapy (see ch. 351); insertion of a urethral stent to relieve obstruction may also be done (Figure 335-17; see ch. 124).[105-107]

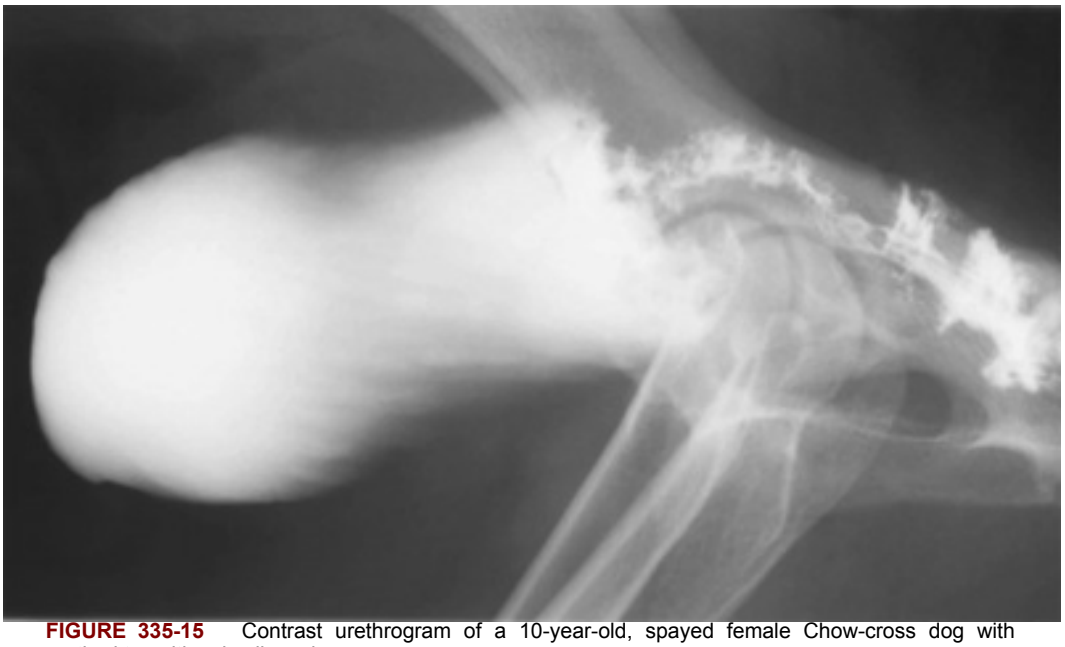


FIGURE 335-15 Contrast urethrogram of a 10-year-old, spayed female Chow-cross dog with urethral transitional cell carcinoma.

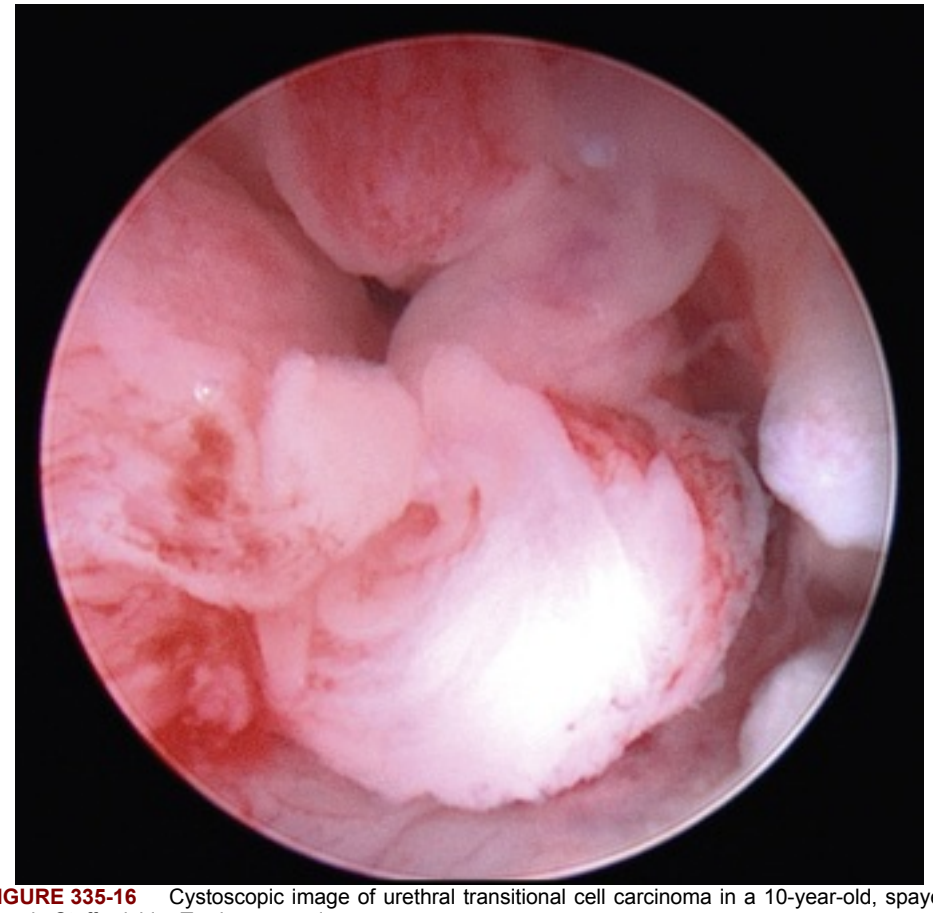


FIGURE 335-16 Cystoscopic image of urethral transitional cell carcinoma in a 10-year-old, spayed female Staffordshire Terrier–cross dog.

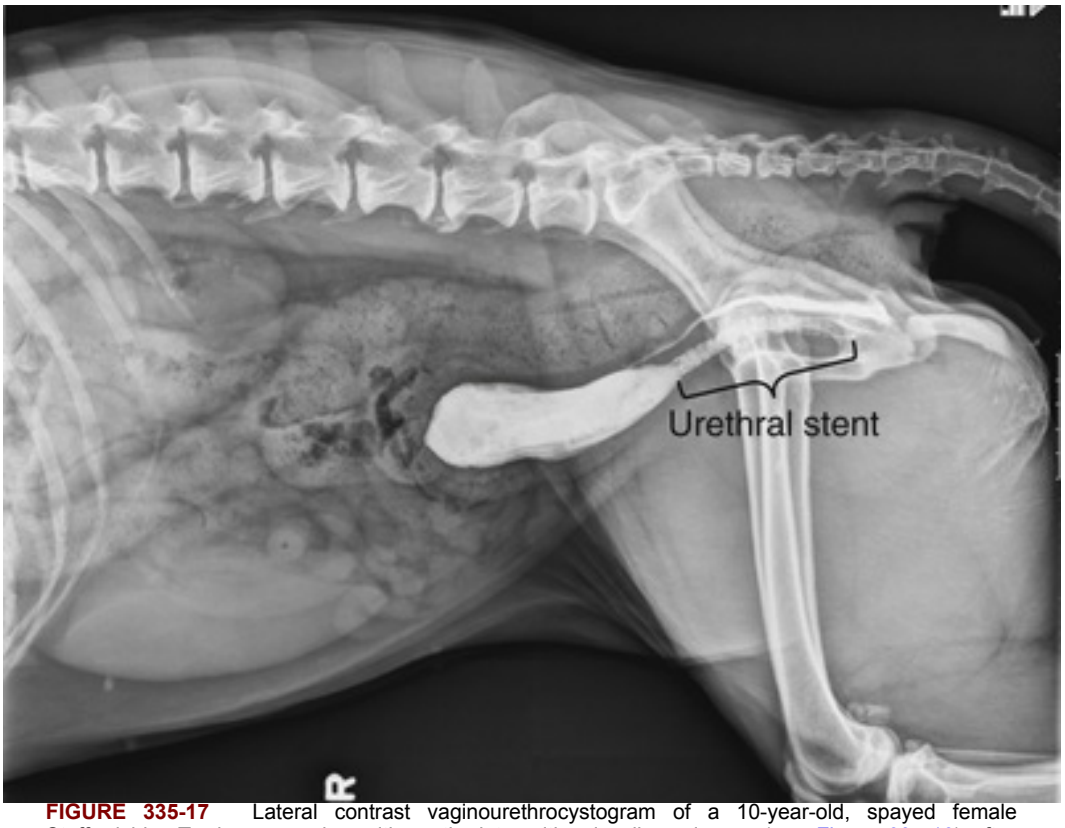


FIGURE 335-17 Lateral contrast vaginourethrocystogram of a 10-year-old, spayed female Staffordshire Terrier–cross dog with urethral transitional cell carcinoma (see Figure 335-16) after insertion of a self-expanding metallic urethral stent.

Idiopathic Urethral Disease—Reflex Dyssynergia

Definitions

During normal urine voiding, the detrusor contracts and the urethra relaxes. This results in the expulsion of urine. Reflex dyssynergia, also called *functional urethral obstruction* or *detrusor urethral dyssynergy,* occurs when there is a lack of coordinated detrusor contraction with urethral relaxation during voiding; the urethra either does not relax or it contracts before the bladder is empty (see ch. 333). Clinically, pets either attempt to urinate without success or initial urination results in a normal urine stream that stops even though the animal continues to attempt to urinate. Sometimes the normal stream will stop completely or will decrease to spurts or drips of urine. A cause for reflex dyssynergia is not identified in more than 50% of dogs. It can be associated with spinal lesions cranial to the second lumbar cord segment. Hypothesized lesions that could cause reflex dyssynergia include the reticulospinal tract, Oluf's nucleus, caudal mesenteric ganglion, or loss of inhibitor signals to the pudendal and hypogastric nerves.[108]

Signalment, Signs, Diagnosis

Reflex dyssynergia affects primarily middle-aged, large- and giant-breed male dogs, although female dogs and cats may be affected.[109-113] As mentioned, the animal postures to urinate and often produces a good initial stream that suddenly stops or becomes spurts or drips of urine despite continued attempts to urinate. Residual urinary bladder urine volume is large due to the functional urethral obstruction. Dogs should have less than 0.5 mL/kg residual urine volume after urination.[114] Urine leakage may occur after attempts to urinate cease, mimicking overflow incontinence. This occurs because the internal urethral sphincter hypertonicity is thought to be triggered by voiding. In chronic cases, bladder overdistention may result in some degree of detrusor atony resulting in large residual urine volume. Diagnosis is made by historical information and watching the animal void. Imaging studies may show a large urinary bladder after voiding, and contrast urethrography may show an inability to adequately dilate the proximal urethra or urethral spasm. Thorough neurological examination is important (see ch. 259), although most patients do not have

neurological deficits. The only clinical sign may be pain, e.g., cervical pain on manipulation.

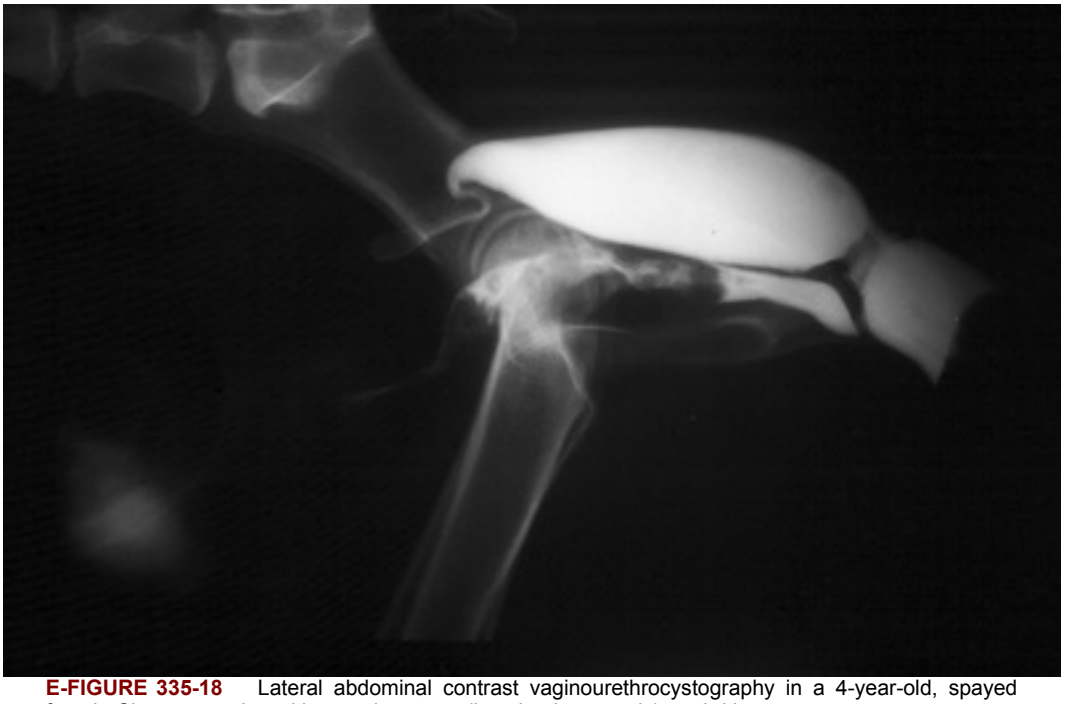
Treatment

Treatment involves urethral relaxation and, occasionally, stimulation of bladder contraction. Alpha-blockers such as prazosin, tamsulosin, and phenoxybenzamine, decrease internal urethral sphincter smooth muscle tone. Relaxing external urethral sphincter skeletal muscle may be of help, using benzodiazepines or other relaxants (acepromazine, methocarbamol, dantrolene).[114-118] Clean intermittent urinary catheterization by owners at home may be necessary (see ch. 105 and 106). A cystostomy catheter may be used to prevent urinary bladder overdistention and, in refractory cases, a urethral stent may be inserted across the part of the urethra that is narrowed or has spasms based on contrast urethrography (see ch. 124).[109] Prognosis is generally fair to good; however, patients often require lifelong therapy and relapses occur. Prognosis is worse with detrusor atony and recurrent UTI.

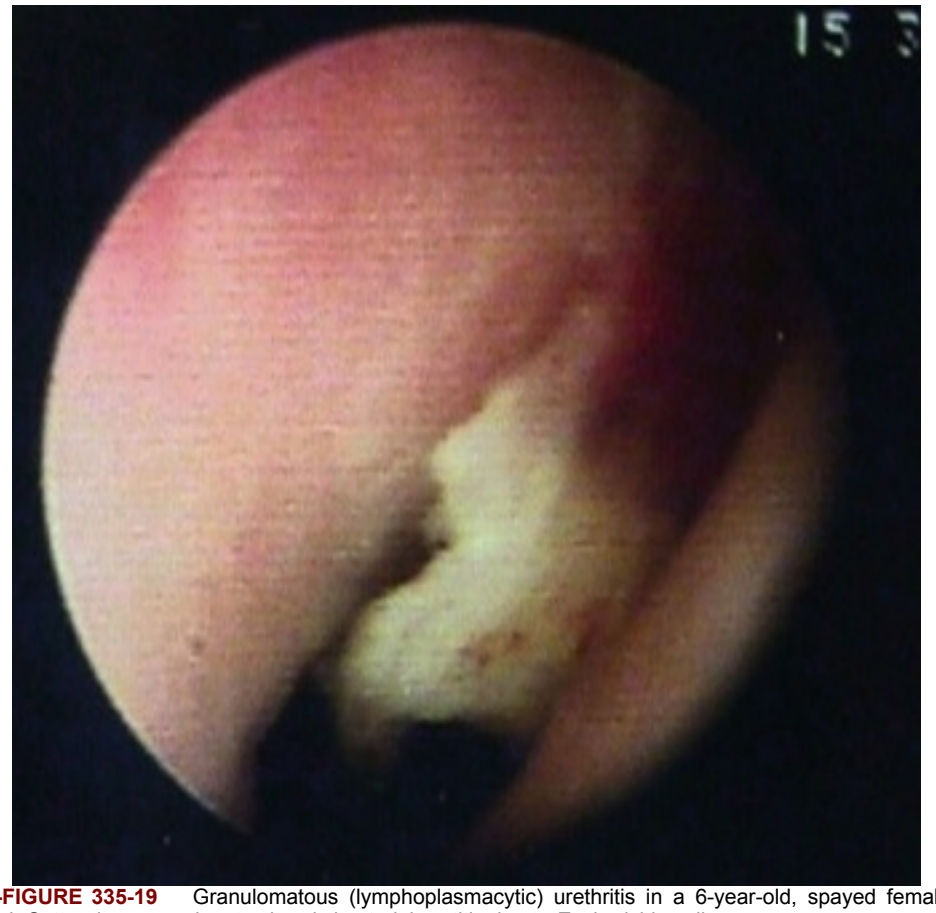
Inflammatory/Infectious Urethral Disease

Urethritis refers to inflammation of the urethra. Inflammation may be primary or secondary to other diseases including trauma, urolithiasis, or neoplasia.[96,119] Urethritis often occurs with bacterial cystitis in dogs or idiopathic cystitis in cats. Inflammation occurs due to breakdown of the urothelial lining and may result in ulceration and erosion. Proliferative urethritis may occur secondary to chronic bacterial infection or immune-mediated disease. Granulomatous or lymphoplasmacytic urethritis causes epithelial hyperplasia, lymphocyte and plasma cell infiltration, and chronic bacterial infections.[120]

Clinical signs are consistent with lower urinary tract disease (see ch. 44-47). Diagnosis is made by rectal palpation of the urethra, contrast urethrography, or cystoscopy (E-Figures 335-18 and 335-19; see ch. 108). Biopsy of the urethra confirms the inflammation. Treatment includes antimicrobial therapy and, possibly, anti-inflammatory drugs if granulomatous urethritis is present. Anti-inflammatory therapy with prednisone (1 mg/kg PO q 24 h), cyclophosphamide (2.2 mg/kg PO q 24 h for 4 days per week), or piroxicam (0.3 mg/kg PO q 24 h) may be tried. For proliferative urethritis, anti-inflammatory therapy as described or immunosuppressive therapy (azathioprine 2 mg/kg PO q 24-48 h, or prednisone 2 mg/kg PO q 24 h) with concurrent antimicrobial therapy is recommended. If urethral obstruction is present, a cystostomy catheter may be required until regression of the inflammatory infiltration and urethral obstruction.[94]



E-FIGURE 335-18 Lateral abdominal contrast vaginourethrocystography in a 4-year-old, spayed female Chow-cross dog with granulomatous (lymphoplasmacytic) urethritis.



E-FIGURE 335-19 Granulomatous (lymphoplasmacytic) urethritis in a 6-year-old, spayed female Irish Setter dog secondary to chronic bacterial cystitis due to *Escherichia coli.*

Traumatic Urethral Disease

Urethral trauma may occur from blunt or penetrating injuries, especially from traumatic urinary catheterization (Figure 335-20).[121-124] Blunt vehicular trauma may damage the urethra due to pubic or os penis fractures. Iatrogenic urethral trauma during urinary catheterization may occur, especially when using a stiff polypropylene catheter (see ch. 105 and 106). Clinical signs relate to the lower urinary tract. Urine may collect SC or into the abdomen. Hematuria may be the only clinical sign. Diagnosis is made by contrast urethrography or cystoscopy. Treatment includes placement of an indwelling urinary catheter and surgical correction or urinary diversion.[121,122,125,126] Urethrostomy may be necessary if the urethra is not salvageable.

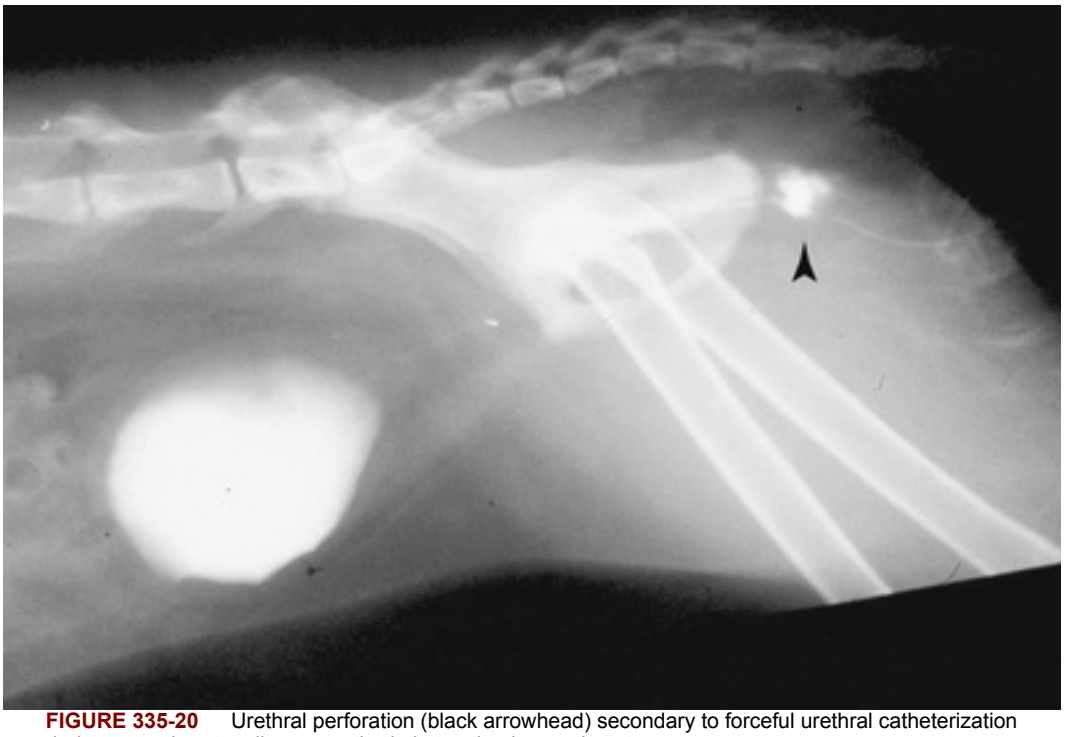


FIGURE 335-20 Urethral perforation (black arrowhead) secondary to forceful urethral catheterization during procedure to relieve a urethral obstruction in a male cat.

Urethral Stricture

Urethral stricture usually occurs secondary to urethral trauma, especially urinary catheterization in cats,[89,125] or surgery (see E-Figure 335-14).[127,128] Clinically, dogs and cats with urethral strictures strain to urinate, have hematuria, or are unable to urinate (see ch. 44-47). There is often a history of a traumatic or surgical event, although urethral stricture may occur secondary to a neoplastic process such as a transitional cell carcinoma. Diagnosis is made by visualization if the stricture is at the site of a previous urethrostomy procedure, by contrast urethrography, or cystoscopy (see ch. 108). Treatment includes surgical correction, dilation of the strictured area, or insertion of a urethral stent (see ch. 124).[89,90,106,127,129,130]

Urethral Foreign Bodies

Occasionally dogs or cats with clinical signs of lower urinary tract disease and/or urethral obstruction have a urethral foreign body. Among the foreign bodies reported are grass awns, lead pellets, a migrating popsicle stick resulting in struvite urolith formation, and a sewing needle–associated struvite urolith.[131-134] Indwelling urethral catheters may serve as a foreign body for clinical signs or obstruction (E-Figures 335-21 and 335-22) if the dog or cat chews the distal end of the catheter, resulting in retention of the proximal end within the urinary system. These may serve as a nidus for infection or encrustation (Figure 335-23 and E-Figure 335-24). Removal of the foreign body results in resolution of clinical signs as long as urethral stricture or detrusor atony has not occurred. Prevention of catheter-retained fragment foreign body involves ensuring the whole catheter is present when removed by the patient or by medical personnel.

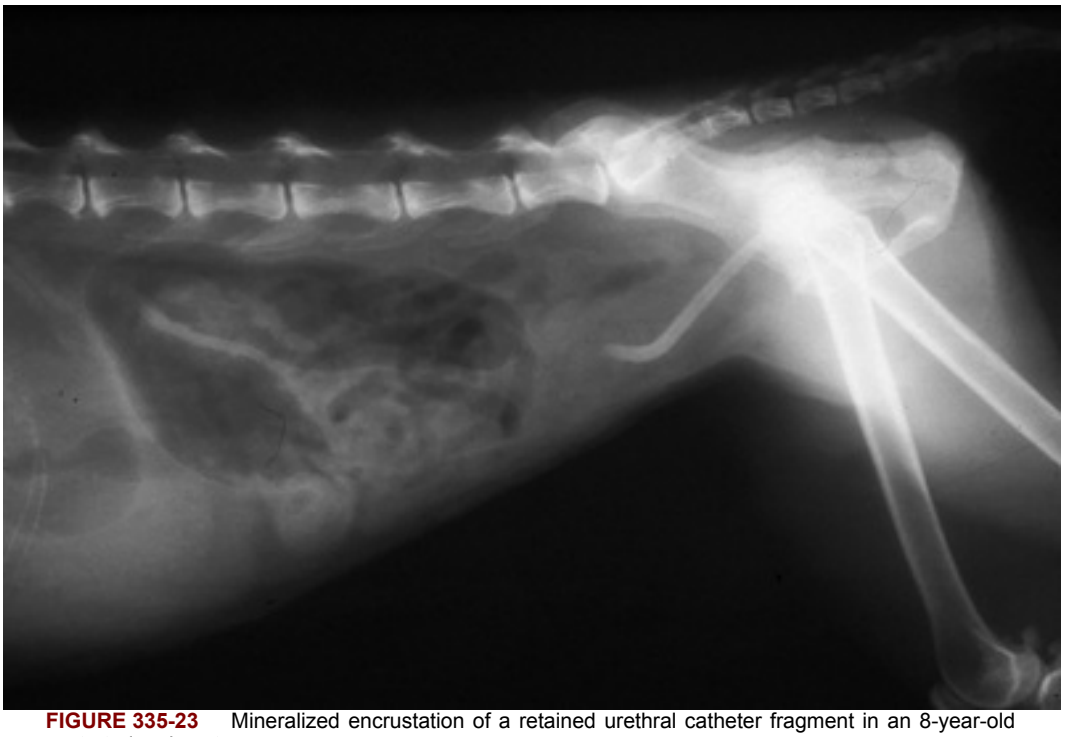
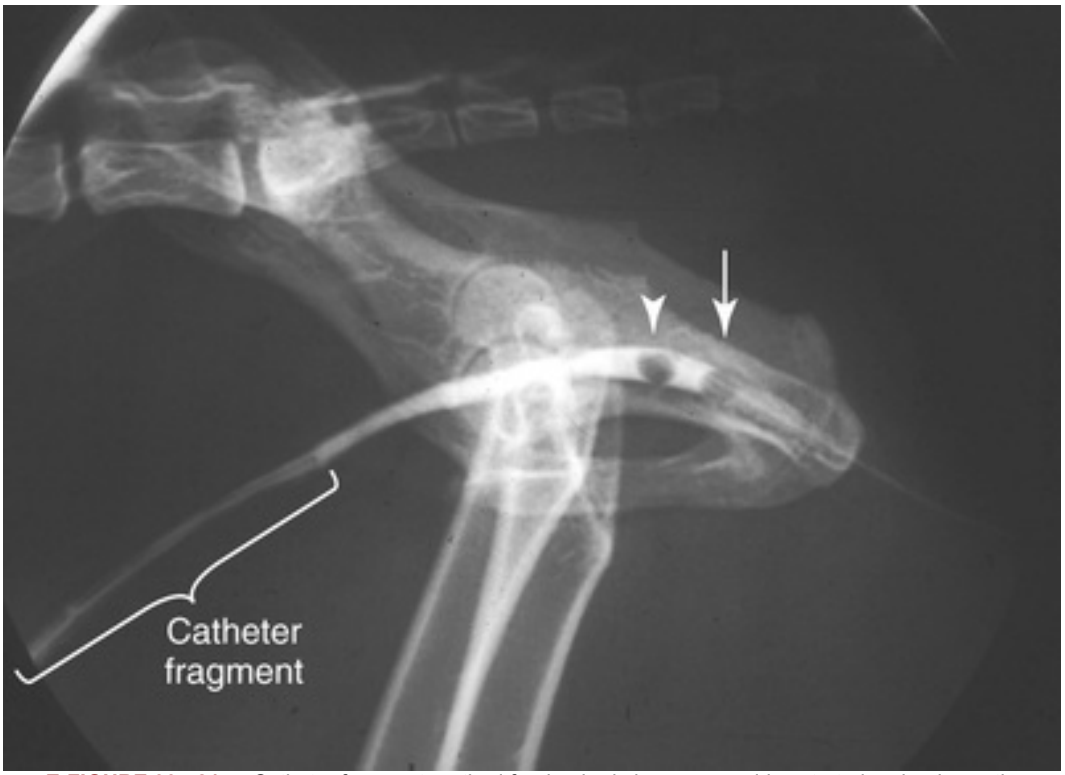


FIGURE 335-23 Mineralized encrustation of a retained urethral catheter fragment in an 8-year-old castrated male cat.



E-FIGURE 335-21 Catheter fragment urethral foreign body in a 5-year-old castrated male, domestic shorthaired cat with repeated urethral obstruction. The balloon of an angiographic catheter (white arrow) and an air bubble in the urethra (white arrowhead) are seen.

E-FIGURE 335-22 Catheter fragment foreign body from cat described in E-Figure 335-21.

E-FIGURE 335-24 Encrusted catheter fragment from patient in Figure 335-23.

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CHAPTER 336

Congenital Diseases of the Lower Urinary Tract

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Congenital urinary tract disorders occurring in young dogs and cats may result from heritable (genetic) or acquired processes that affect differentiation and growth of the developing urinary tract or from similar processes that eventually affect the structure or function of the mature urinary system. Formation of the urinary system depends on sequential and coordinated development and interaction of multiple embryonic tissues involving expression of over 400 regulatory genes.[1-6] Despite the extraordinary complexity of urinary system organogenesis, congenital anomalies of the urinary bladder and urethra are relatively infrequent causes of lower urinary tract disease.

Anomalies of the Ureterovesical Junction

Ectopic Ureters (Ureteral Ectasia)

Congenital ectopic ureters (EUs) are characterized by termination of one or both ureters at a site other than the craniolateral aspect of the bladder trigone.[7] Dysembryogenesis of the ureteral bud and failure of common excretory duct apoptosis during ureter transposition result in ectopic openings positioned along the path of ureteral migration (the so-called ectopic pathway).[8-11] EUs are classified according to the location of the anomalous opening relative to the bladder neck and the anatomic course of the anomalous ureter to its termination. *Intravesicular* EUs terminate caudal and medial to their normal position in the craniolateral aspect of the trigone but cranial to the bladder neck. *Extravesicular* EUs terminate caudal to the distal apex of the trigone in the bladder neck, urethra, uterus, or vagina.[8,9,12-14] *Intramural* EUs contact the bladder wall normally but course distally in the submucosa through the trigone before opening into the urethra or vagina (Figure 336-1).[7] Intramural EUs may also form ureteral troughs, develop multiple ureteral openings, or fail to develop a distal orifice.[15] *Extramural* EUs totally bypass the bladder before terminating in the urethra, vagina, or uterus (Figure 336-2). Female dogs appear to be affected more commonly than males; however; the prevalence of EUs in male dogs may be underestimated.[8,14,16-18] The majority of EUs in male and female dogs are intramural and bilateral.[8,9,14,19-21] EUs are considered very rare in cats. Only 31 cases of feline EU have been reported, of which 57% were males and 43% were females.[20,22-40] The vast majority of feline EUs are extramural with a similar prevalence of unilateral (55%) or bilateral (45%) malformations. The urethra is the most common site of termination in female dogs and cats. In male dogs, the majority of EUs terminate in the bladder neck or preprostatic urethra.[8] Because of the close relationship between metanephric duct system and development of the urogenital organs, EUs may be associated with other concurrent congenital anomalies such as renal ectopia, renal aplasia/hypoplasia, ureteroceles, urachal remnants, urinary bladder agenesis/hypoplasia, urethral agenesis or ectopia, urethral sphincter mechanism incompetence (see ch. 333), vestibulovaginal malformations, phimosis, and cryptorchidism.[41,42] Duplicated (double) ureters associated with ureteral ectopia, hydroureter, hydronephrosis, and urinary tract infection have also been reported in male and female dogs and in a male cat.[28,43,44]

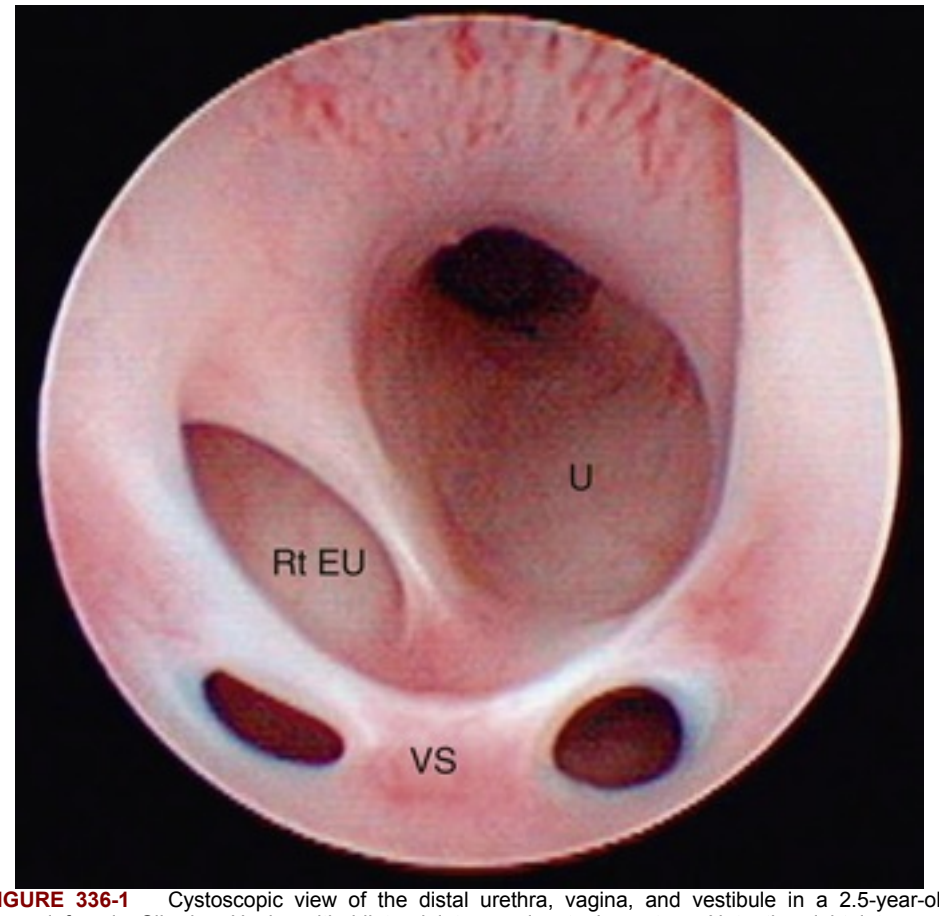

FIGURE 336-1 Cystoscopic view of the distal urethra, vagina, and vestibule in a 2.5-year-old spayed female Siberian Husky with bilateral intramural ectopic ureters. Note the right intramural ectopic ureter opening (Rt EU) in the distal urethra (U) and a persistent vaginal septum (VS).

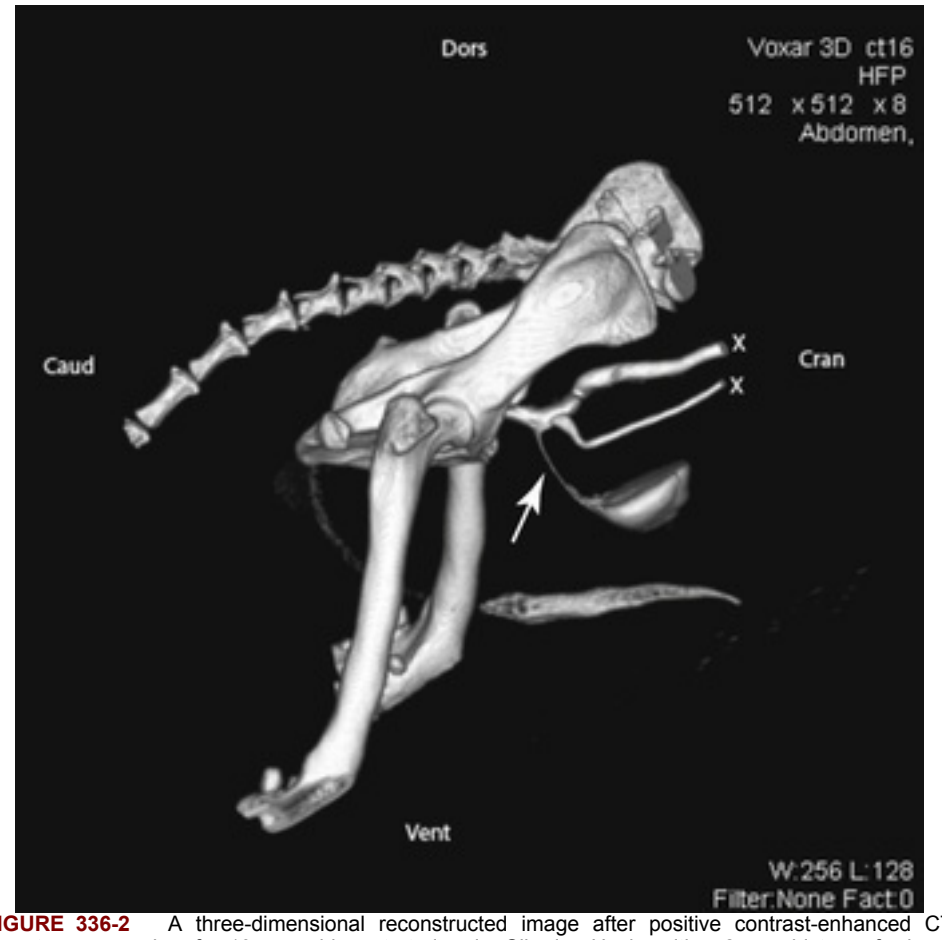

FIGURE 336-2 A three-dimensional reconstructed image after positive contrast-enhanced CT excretory urography of a 10-year-old, castrated male, Siberian Husky with a 2-year history of urinary incontinence and bilateral extramural ectopic ureters. Note dilation of the right and left extramural ectopic ureters (denoted by an X), which enter the dorsal preprostatic urethra approximately 1 cm caudal to the vesicourethral junction. The white arrow depicts contrast medium in the proximal urethra traveling from a partially distended urinary bladder.

Epidemiologic studies in North America and Europe have identified an increased prevalence of EU in Border Terriers, Briards, English Bulldogs, Entlebucher Mountain Dogs, Fox Terriers, Golden Retrievers, Griffons, Labrador Retrievers, Miniature and Toy Poodles, Newfoundland dogs, Siberian Huskies, Skye Terriers, and West Highland White Terriers.[8,12,45-48] The high predilection in these breeds, observation of EU in closely related dogs, and results of pedigree analyses strongly suggest a hereditary basis for the disorder.[12,14,45,49] Recent population genetic studies have confirmed a hereditary basis for EUs in Entlebucher Mountain Dogs.[45] However, the specific mode of inheritance and genetic mutation(s) involved in EUs in this and other dog breeds have not been reported. Familial or breed predilections have not been identified in cats with EUs.[33]

Clinical signs vary, depending on site(s) of EU termination and presence of other concurrent urogenital abnormalities. Urinary incontinence is the predominant clinical sign in affected dogs and cats (see ch. 46). In most dogs, incontinence is often recognized shortly after weaning, and its severity may vary from continuous involuntary dribbling to intermittent incontinence associated with rest, excitement, or changes in body position. However, onset of urinary incontinence may be delayed in some dogs, especially males.[8,12,14,17,18,50] In addition, some affected male and female dogs and cats may remain continent.[8,12,14,40] Other clinical signs may include abdominal distention, discoloration of the periurethral hair, perivulvar dermatitis, and other lower urinary tract signs (e.g., pollakiuria and dysuria). Ureteral ectopia is frequently complicated by concurrent urinary tract infection in dogs (see ch. 330), whereas infection appears to be less common in affected cats.[15,30]

Although urinary incontinence in juvenile animals is highly suggestive of EU, other congenital and acquired causes of incontinence should be considered (see ch. 333).[3] Survey abdominal radiography and

ultrasonography allow assessment of the size, shape, and location of the kidneys, ureters, and urinary bladder. Administration of a diuretic (furosemide 1 mg/kg IV) during color Doppler ultrasonography may improve the sensitivity of this technique and permit phenotyping dogs as normal, intravesicular ectopic, or extravesicular ectopic (Video 336-1).[45,51-53] However, definitive diagnosis requires additional diagnostic methods, or combination of methods, including excretory urography (±pneumocystography), retrograde vaginography, urethrography, contrast-enhanced computerized tomography (CT), or urethrocystoscopy (see ch. 108).[8,9,12,42,53] Contrast-enhanced CT and urethrocystoscopy appear to be the most reliable methods of establishing a diagnosis, characterizing ureteral opening morphology, and identifying other concurrent urogenital anomalies (see Figures 336-1 and 336-2). Contrast-enhanced CT may have diagnostic advantages in male dogs, whereas urethrocystoscopy is considered the gold standard in female dogs.[8,9,12,53]

Treatment of urinary incontinence associated with EU requires correction of the anomalous ureteral opening(s) and management of any contributing comorbid conditions such as urethral sphincter mechanism incompetence. Surgical strategies employed for correction of EUs include transection and reimplanatation of the ureter (neoureterocystotomy), creation of a neostoma (*in situ* neoureterostomy), or complete removal of the kidney and its ureter (nephroureterectomy).[14,20,42,54] Over the past decade, transurethral cystoscopic-guided laser ablation of intramural EU has emerged as a minimally invasive alternative to surgical correction in dogs (see ch. 124).[18,19,21,55,56] With this technique, a holmium : YAG or diode laser is used to transect the free wall of the EU that is adjacent to urethral lumen, effectively transposing the ureteral opening into the urinary bladder (Video 336-2). Regardless of approach, residual postprocedure urinary incontinence is common, especially in female dogs, with residual incontinence rates ranging from 30% to 75%.[14,21] Interestingly, surgical or laser correction of EU in male dogs may be associated with more favorable outcomes.[8,14,18] Dogs with persistent postoperative incontinence may have concurrent urinary sphincter mechanism incompetence and may benefit from pharmacologic management with alpha-adrenergic agonists, transurethral bulking agent injections, or placement of an artificial urethral hydraulic occluder (see ch. 124).[57-64]

Ureteroceles

Ureteroceles are a congenital cystic dilation of the terminal submucosal segment of the distal ureter. *Orthoptic (simple) ureteroceles* are located at the trigone of the urinary bladder with the ureteral orifice in normal position. Ureteroceles accompanying ectopic ureters are classified as *ectopic ureteroceles.* Ureteroceles may be unilateral or bilateral and are usually ectopic.[8,14,65-67] Ureteroceles have been most commonly reported in female dogs but have also been reported in male dogs and a male cat.[14,20,47,65-72] Patients with orthoptic ureteroceles may be asymptomatic or may develop lower urinary tract signs (i.e., dysuria, stranguria, pollakiuria, and hematuria).[67,72-76] Patients with ectopic ureteroceles typically develop urinary incontinence. In addition, both orthoptic and ectopic ureteroceles are frequently associated with concurrent urinary tract infection and ipsilateral hydroureter, hydronephrosis, and renal dysfunction.[65-78] A diagnosis of ureterocele is based on excretory urography, contrast-enhanced CT, ultrasonography, urethrocystoscopy, or exploratory celiotomy and cystotomy.[42,53] Treatment of ureteroceles is directed at alleviating clinical signs by transurethral laser ureterocele ablation, ureterocelectomy, neoureterocystotomy, or ureteronephrectomy.[42,77]

Anomalies of the Urinary Bladder

Urinary Bladder Agenesis and Hypoplasia

Agenesis or hypoplasia of the urinary bladder results in diminished capacity for urine storage and presents as urinary incontinence.[17,30,79-81] Complete agenesis of the urinary bladder is rare but has been reported in a 4-month-old, female, mixed-breed dog with urinary incontinence.[79,80] Hypoplasia is more common in dogs and cats and may result from embryonic bladder maldevelopment or from conditions that limit adequate bladder filling during fetal development.[82] Ureteral ectopia is frequently associated with bladder hypoplasia, which may contribute to urinary incontinence after surgical correction.[17,30,81] Bladder capacity may increase substantially over a period of several months after correction of EU.[81,83]

Pelvic Bladder

Pelvic bladder refers to urinary bladders that have a blunt-shaped trigone, which is located in an intrapelvic location and associated with a shortened urethra.[84] Although some affected dogs are continent, other dogs with pelvic bladders have refractory incontinence without any other identifiable cause.[84-87] Pelvic bladder has also been associated with other concurrent lower urinary tract disorders.[84] A diagnosis of pelvic bladder is established by contrast radiography. Since the degree of bladder distention directly affects trigone position relative to the pelvic brim, adequate distention during contrast urethrocystography is necessary to assess bladder position. If pelvic bladder is associated with urinary incontinence, pharmacologic management with alpha-adrenergic agonists may be attempted (see ch. 333).[64] If urinary incontinence is refractory to medical therapy, then surgical interventions, injections of urethral bulking agents, or placement of an artificial urethral sphincter may be considered (see ch. 124).[59-63]

Exstrophy

Exstrophy refers to eversion of the urinary bladder, and often the intestines and external genitalia, through midline defects in the ventral abdominal wall.[88] This rare disorder has been reported in an 8-month-old, female, English Bulldog with urinary incontinence and pyelonephritis and in a cat.[89,90] Treatment involves reconstructive surgery.

Urinary Bladder Duplication

Complete and partial urinary bladder duplication with and without urethral duplication has been reported in young dogs and cats.[91-93] Clinical signs may include dysuria, stranguria, urinary incontinence, and abdominal distention. Diagnosis is made by physical examination and imaging studies. Treatment involves surgical correction; however, success depends on degree of malformation and presence of additional congenital anomalies.

Urachal Anomalies

Urachal anomalies occur commonly in dogs and cats. The urachus is a fetal connection allowing urine to pass between the developing urinary bladder and the placenta. It undergoes complete atrophy at birth. However, macroscopic or microscopic urachal remnants may persist as a patent urachus or as urachal cysts or diverticula.[94,95]

A patent urachus occurs when the urachal canal remains functionally patent, resulting in inappropriate urine loss through the umbilicus.[69,96-99] A patent urachus is often accompanied by omphalitis, ventral dermatitis, and urinary tract infections. Rarely, uroabdomen may occur when a patent urachus terminates in the abdominal cavity.[100] A urachal cyst may develop if the urachal epithelium in an isolated segment of a patent urachus continues to secrete fluid.[95]

A vesicourachal diverticulum occurs when a portion of the urachus located at the bladder vertex fails to close. Urachal remnants are microscopic lumens lined by transitional epithelium that are located at the bladder vertex.[95] Approximately 40% of bladders from 80 cats had microscopic diverticula in one study.[101] Congenital microscopic diverticula are usually clinically silent; however, macroscopic diverticula may develop in cats and dogs with microscopic urachal remnants following the onset of concurrent but unrelated acquired lower urinary tract disease (e.g., urinary tract infections, urolithiasis, or idiopathic cystitis).[102-105] Many macroscopic diverticula in cats disappear within 2 to 3 weeks following treatment of the acquired disease and resolution of clinical signs.[103,104] Congenital macroscopic vesicourachal diverticula are thought to be caused by urine outflow obstruction and develop before or shortly after birth. In a necropsy study of 50 dogs without signs of urinary tract disease, 30% of dogs had macroscopic vesicourachal diverticula.[102] Persistent macroscopic diverticula increase risk of bacterial urinary tract infection and associated clinical signs of lower urinary tract disease.[106]

Vesicourachal diverticula are best visualized by positive contrast urethrocystography, ultrasonography (see ch. 88), or cystoscopy (see ch. 108). Treatment of vesicourachal diverticula depends on their size, biological behavior, and association with clinical disease. Many macroscopic diverticula associated with active lower urinary tract disease regress with successful treatment of the acquired disease.[103,104] If diverticula persist after appropriate therapy and are associated with recurrent lower urinary tract disease, then diverticulectomy may

be warranted.[105]

Trigonal (Paraureteric) Diverticulum

Congenital bladder diverticula may also arise from the region of the trigone, presumably as a result of an inherent weakness in the bladder musculature and subsequent herniation of the bladder mucosa.[107] Putative congenital trigonal diverticula have been observed in two young German Shepherd Dogs presented for hematuria, dysuria, stranguria, and urinary tract infection.[108,109] Diagnosis of trigonal diverticula is established by positive contrast cystography, ultrasonography (see ch. 88), cystoscopy (see ch. 108), or exploratory laparotomy. Diverticulectomy is indicated to eliminate urine stasis and reduce risk of infection, urolithiasis, obstruction, and malignant transformation.

Colovesical Fistula and Uterine-Bladder Communication

Rarely, the urinary bladder may communicate with the colon or uterine horn.[32,33,110,111] Clinical manifestations include abnormal urination patterns (simultaneous passage of urine from the prepuce or vulva, and from the anus), urinary incontinence, lower urinary tract signs, and urinary tract infection. Treatment is limited to surgical correction.

Primary Urinary Bladder Neoplasia

Urinary bladder neoplasms are rare in immature dogs and cats.[112] Botryoid rhabdomyosarcoma has been observed in large-breed dogs younger than 18 months but can occur in other dogs.[113-122] Botryoid rhabdomyosarcomas are embryonic mesenchymal tumors arising from pluripotent stem cells originating from primitive urogenital ridge remnants. They are infiltrating tumors that project from the trigone into the bladder lumen as botryoid (resembling a cluster of grapes) masses.[115] Tumors may be associated with lower urinary tract signs, obstructive uropathy, and hypertrophic osteoarthropathy.[114,115] Treatment includes surgery with or without additional chemotherapy.[123,124] Metastases to local tissues (lymph nodes, mesentery, omentum, prostate) and distant organs (lung, liver, kidney, spleen) have been described with this tumor.[113,120,122]

Anomalies of the Urethra

Urethral Aplasia and Hypoplasia

Urethral aplasia is a rare congenital anomaly characterized by complete absence of a patent urethra. Incontinence occurs associated with ureteral ectopia.[69,125] Urethral hypoplasia has been described in immature female cats and is associated with juvenile-onset urinary incontinence.[30,126,127] Diagnosis is based on clinical signs and imaging studies. Radiographic features include urethral shortening and absence of a vagina. Urethral hypoplasia may be associated with other congenital anomalies and urinary tract infection. Affected animals may respond to alpha-adrenergic therapy; however, surgical reconstruction of the bladder neck may be required in some cases to improve or resolve clinical signs.[126,127]

Epispadias and Hypospadias

Epispadias refers to congenital defects in the dorsal aspect of the distal urethra, and hypospadias refers to anomalous ventral malposition of the urethral meatus.[128] Epispadias has been associated with exstrophy of the urinary bladder in an 8-month-old, female English Bulldog.[89] Hypospadias occurs more commonly and usually in male dogs; Boston Terriers and Dalmatians have been described as having an increased risk.[128-130] Hypospadias has been described in a Himalayan cat.[131] In affected male dogs, an abnormal ventral urethral meatus may be located anywhere along the shaft of the penis, scrotum, or perineum. It is usually associated with malformation of the prepuce and penis.[132,133] Hypospadias has been described in female dogs in associated with concurrent disorders of intersexuality. Affected dogs present at various ages and may be asymptomatic or have clinical signs of urinary incontinence, periurethral dermatitis, or urinary tract infection.[132,133] Diagnosis is often based on physical examination. The presence of an *os penis* in male dogs

precludes surgical reconstruction in most cases. Scrotal or perineal urethrostomy combined with castration and removal of vestigial preputial and penile tissues may be of cosmetic value. Shortening of the penis, amputation, and urethral reconstruction has also been described.[134-138]

Urethral Duplication

Urethral duplication is an uncommon congenital anomaly encountered in immature male and female dogs.[139-144] Because of the close association between embryonic development of the urogenital and gastrointestinal systems, urethral duplication is often accompanied by other duplication anomalies involving the descending colon, rectum, urinary bladder, vagina, vulva or penis. Examination of affected animals may reveal anatomic abnormalities, urinary incontinence, or clinical signs associated with secondary urinary tract infection. Diagnosis is based on physical examination, imaging studies, and exploratory surgery. Urethral duplication may in some cases be amenable to surgical extirpation or cyanoacrylate glue embolization of the duplicated structure.[139,144]

Ectopic Urethra

Ectopic urethra is characterized by abnormal position of the external urethral orifice. Clinical signs depend on the site of the termination of the abnormal urethra and other concurrent urogenital anomalies. Lifelong urinary incontinence was the predominant clinical feature in a 21-month-old female English Bulldog with unilateral ureteral ectopia and an ectopic urethra terminating in the distal vagina.[145] In contrast, a 2-month-old, female, domestic shorthair cat with an ectopic urethra terminating in the ventral rectum did not have urinary incontinence but did void urine through the anus.[33]

Urethrorectal, Urethrovaginal, and Urethroperineal Fistula

Congenital fistulas connecting the urethral lumen with the large bowel, vagina, and perineum have been described in dogs and cats.[79,142,146-152] Male dogs appear to be affected more frequently and English Bulldogs appear to have a predilection for urethrorectal fistula.[153] Clinical signs are due to abnormal passage of urine through the fistula during urination and may include diarrhea, perineal dermatitis, and signs associated with secondary urinary tract infections. Fistulas have been associated with infection-induced struvite urolithiasis.[79,149,151] Diagnosis is based on clinical signs and imaging studies. Treatment involves fistulectomy, surgical urinary diversion, and eradication of secondary urinary tract infections (see ch. 330).

Urethral Stricture

Presumed congenital urethral strictures have been described in young dogs and cats.[127,154,155] Clinical signs relate to partial or complete urethral obstruction and may include stranguria, pollakiuria, prolonged urination, bladder distention, overflow incontinence, hydroureter, and hydronephrosis. Urinary incontinence and bilateral hydroureter and hydronephrosis were observed in an 8-month-old, male, German Shepherd Dog with congenital midurethral stricture.[154] Extrapelvic urethral strictures may be managed by urethrostomy, whereas intrapelvic or intraabdominal urethral strictures may require urethral resection and anastomosis or prepubic urethrostomy.[156,157] Alternatively, urethral strictures may be managed by cystoscopic or fluoroscopic-guided balloon catheter dilation.[158-160]

Congenital Urethral Sphincter Incompetence

Congenital urethral sphincter mechanism incompetence has been described in dogs and cats and is often associated with other urogenital malformations (ureteral ectopia, urethral hypoplasia or aplasia, urethral dilation, and prostatic urethral diverticula).[30,42,60,127,161] However, in some sexually intact juvenile patients, congenital sphincter mechanism incompetence may occur in the absence of other concurrent urogenital anomalies. Although urinary incontinence may lessen or resolve with pharmacologic management, many patients require additional surgical intervention, injections of urethral bulking agents, or placement of an artificial urethral sphincter (see ch. 124).[57-64]

Urethrogenital Malformations

Urethrogenital malformations associated with diseases of intersexuality, especially pseudohermaphroditism, are often associated with urinary incontinence.[162-164] Pseudohermaphrodites have gonads of one sex and external genitalia resembling those of the opposite sex.[165] It occurs in both sexes as a result of simultaneous development of müllerian duct derivatives (oviduct, uterus, and portions of the vagina) and masculinization of the urogenital sinus. Appearance of the genitalia depends on the degree of masculinization of the urogenital sinus. Incontinence develops early in life and may be accompanied by urinary tract infection and other lower urinary tract signs. Urinary incontinence likely results from retention of urine in anomalous communications between the urethra and the genital tract and subsequent passive leakage.[166] Diagnosis is based on clinical signs and imaging studies. Urinary incontinence may resolve with surgical correction.[162]

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CHAPTER 337

Prostatic Diseases

Michelle Anne Kutzler

Client Information Sheet: Prostatic Diseases

The most important prostatic diseases in dogs include benign prostatic hyperplasia (BPH), acute and chronic bacterial prostatitis, prostatic abscess, paraprostatic cysts, and prostatic neoplasia. The reported prevalence of each prostatic disease varies markedly between studies, depending on population age and neutering status. Reports likely are biased toward BPH and prostatitis in countries where dogs are seldom castrated and toward neoplasia in countries where castration is more common. Studies of dogs with clinical manifestations of prostatic disease certainly are not representative of their true prevalence, given the common occurrence of subclinical prostatic disease in dogs. A study focusing on dogs that died of diseases unrelated to the prostate indicated a 76% prevalence of subclinical prostatic disease.[1] Severe systemic manifestations suggestive of sepsis or inflammation should always raise a suspicion of acute bacterial prostatitis in intact male dogs. The possibility of prostatic disease should not be ruled out in neutered dogs, as castration increases the risk of prostatic neoplasia when compared with intact dogs.[2]

The anatomy and location of the feline prostate differs from dogs in that it lies at the cranial rim of the pelvis, midway between the root of the penis and the neck of the bladder. The prostate includes two lobes and covers the urethra only dorsally and laterally.[3] Based on this location, it seems reasonable to expect that, besides lower urinary tract signs, constipation and dyschezia could occur in toms as a result of partial large bowel obstruction by the enlarged prostate.[4]

Diseases of the prostate gland are extremely rare in cats and include chronic bacterial prostatitis, prostatic abscess, estrogen-induced squamous metaplasia, paraprostatic cysts, and neoplasia.[3,5-11] Despite the rarity of these diseases, diagnostic testing (e.g., cystocentesis for urine sediment exam and culture and sensitivity [see ch. 72], ultrasonography with fine needle aspirate or biopsy of the prostate as indicated [see ch. 88, 89, and 111]) should be performed if prostatic enlargement is identified. Prostatic disease should be included in the list of differential diagnoses for dyschezia or constipation in male cats, even in neutered animals.

Benign Prostatic Hyperplasia

Although normal prostatic growth is achieved by about 2 years of age, prostatic cells undergo ongoing hypertrophy and hyperplasia under the influence of androgens. Prostatic volume tends to increase with age and this process should be considered normal in intact male dogs. This spontaneous benign hyperplasia is observed both in dogs and in men. BPH has been reported to occur in 80% of intact dogs >5 years old and 95% of dogs >9 years old.[4,12] However, histologic evidence of BPH can be encountered as early as two years of age, with a reported prevalence of 16% at that age.[13] In addition, BPH seems to affect Scottish Terriers more severely than other breeds.[4]

Pathogenesis

Prostatic cell growth is under the influence of dihydrotestosterone (DHT) (and to a much lower extent testosterone), estradiol-17-beta, and many other local growth factors. Age-related changes in the androgen : estrogen ratio seem important for development of BPH. DHT represents the main mediator of BPH, promoting growth of stromal and glandular elements.[12,14-17] BPH can progress to cystic BPH as well as predispose dogs to chronic bacterial prostatitis that can progress to cystitis, epididymitis, and orchitis. Estradiol can induce cellular metaplasia of prostatic epithelial cells with glandular obstruction, retention of

prostatic fluid and blood, and formation of parenchymal cysts of varying size that might or might not communicate with the urethra.[18] Progressive secretory stasis and subsequent ductal occlusion result in the formation of multiple cavitary areas within the prostate gland. Parenchymal (intraprostatic) cysts typically communicate with the urethra, unlike paraprostatic cysts (see below).[15,19]

Diagnosis

Dogs with BPH have a symmetrically enlarged prostate that is moderately firm and not painful on rectal palpation. Most affected dogs show no overt clinical signs.[15,20] Prostate asymmetry can be palpated in dogs with prominent prostatic cysts, as often occurs with cystic BPH. Clinical signs occur mostly in advanced stages, when the enlarged prostate compresses the colon dorsally and dogs have problems defecating. Other signs include sanguineous discharge from the tip of the penis unrelated to urinating, hematuria, dysuria, hematospermia, and infertility. Since dogs with BPH are at increased risk of developing chronic bacterial prostatitis, clinical signs such as signs of caudal abdominal pain, stiff gait, reluctance to move, and severe systemic manifestations consistent with sepsis can dominate the clinical picture. Definitive diagnosis of BPH requires prostatic biopsy, although a presumptive diagnosis can be based on signalment, history, physical and rectal exam, and prostatic fluid examination (see ch. 111).[15] Seminal fluid from affected dogs contains blood with or without minimal mononuclear inflammation.[21] Quantitative bacterial culture should yield <100 bacteria per milliliter.[22] Abdominal ultrasound (see ch. 88) typically confirms the findings of the rectal exam and shows a mild diffuse hypo- or hyperechogenicity (Figure 337-1).[23,24] The sublumbar lymph nodes should not be enlarged in uncomplicated BPH. Fine needle aspiration (see ch. 89) and cytologic evaluation (see ch. 93) can reveal the typical characteristics of hypertrophied prostatic cells, which further increases the suspicion of BPH.[25] The suspicion of BPH can be confirmed with a therapeutic trial using androgen suppression. Options include osaterone acetate (Ypozane; available in U.S.) 0.25-0.5 mg/kg PO q 24 h for 7 days, which has been shown to decrease prostatic volume by ≈27% after 1 week and 40% after 2 weeks[26]; or medroxyprogesterone acetate (available in U.S.) 3-4 mg/kg SC single injection, which has been shown to eliminate clinical signs in 84% of dogs in 4-6 weeks, with 68% remaining free of signs for at least 10 months[27]; or deslorelin (Suprelorin; not available in U.S.) 4.7 mg/dog SC implant, which has been shown to decrease prostate size beginning after 22 days, being complete after 52 days.[28] It is difficult to justify a more invasive procedure like an aspiration or a biopsy when less invasive methods (ultrasonography and response to treatment) strongly support BPH.[15] It is important to realize that BPH is a common incidental finding in middle-aged to older dogs and this diagnosis should be interpreted with caution in dogs with moderate to severe clinical signs.

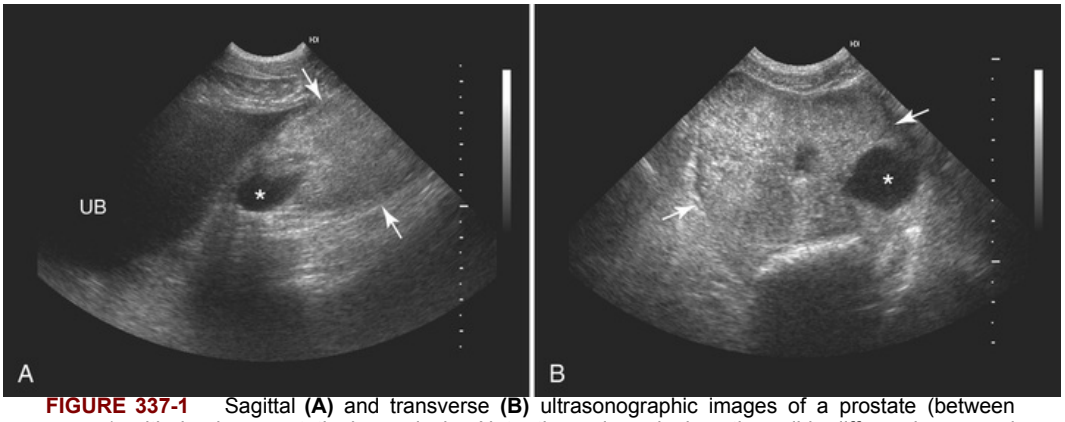


FIGURE 337-1 Sagittal **(A)** and transverse **(B)** ultrasonographic images of a prostate (between arrows) with benign prostatic hyperplasia. Note the enlarged size, the mild, diffuse, hypo- and hyperechogenicity, and the presence of an anechoic intraprostatic cyst (asterisk). The urinary bladder (UB) is to the left in the sagittal image.

Therapy

The goal of therapy for dogs with BPH is reducing prostatic size to alleviate clinical signs and to decrease the

risk of complications such as chronic bacterial prostatitis or prostatic abscess. *Castration* is the first choice treatment for most dogs. It causes rapid reduction in prostatic volume by 50% in 3 weeks and 75% in 3 months. Approximately 3 weeks after castration, involution of the prostate should be verified by rectal palpation or by ultrasound to rule out concurrent, previously masked neoplasia or abscessation. Reversible androgen suppression therapy should be considered for breeding dogs or older dogs with increased anesthetic risk. These forms of therapy are safe and practical, even for mid- to long-term treatment.

Finasteride (Proscar, Merck, 5 mg/dog [irrespective of body weight] PO q 24 h) is a 5-alpha-reductase inhibitor that blocks conversion of testosterone to its bioactive metabolite DHT. This treatment results in decrease in prostatic volume by 50-70% in 2-4 weeks via apoptosis.[29,30] Semen volume decreases without negative effect on semen quality.[31] Although DHT concentrations decrease, serum testosterone concentrations remain unchanged. Dogs, therefore, maintain libido and fertility, and they can be bred successfully.[32] Clinical signs associated with BPH begin to resolve after 1 week of therapy and most dogs have complete resolution of signs within 4 weeks.[31] The prostate will return to its enlarged BPH size within 8 weeks of discontinuing therapy. Therefore, treatment protocols either should be continuous for the remainder of the dog's reproductive life or should be used with a 6-weeks-on-and-6-weeks-off therapy schedule to be more affordable for owners. Regular physical exams including rectal palpation are recommended in these dogs.

Acute Bacterial Prostatitis

Acute prostatitis usually is a disease of mature, intact or recently-castrated dogs. It usually is the result of an ascending infection with normal aerobic urethral bacteria into a hyperplastic prostate gland,[3] although hematogenous infection can occur.[33] The most commonly identified bacterial organism in dogs is *Escherichia coli* (70%), followed by *Staphylococcus* spp., *Klebsiella* spp., *Proteus mirabilis, Mycoplasma canis, Pseudomonas aeruginosa, Enterobacter* spp., *Streptococcus* spp., *Pasteurella* spp., and *Haemophilus* spp.[12] Infections with anaerobic bacterial or fungal organisms have been reported rarely, including one dog with prostatic pythiosis.[33,34]

Diagnosis

Dogs with acute bacterial prostatitis typically present with signs of systemic disease such as depression, anorexia, vomiting, and fever, as well as more organ-specific signs including stranguria or tenesmus, signs of caudal abdominal pain, urethral/preputial discharge, and stiff or stilted gait. The prostate can feel normal in size and shape or it can be asymmetric with an irregular surface on rectal examination. The prostate almost always is painful on palpation.[23] Affected dogs often are severely ill. Blood work reflects systemic inflammation, including neutrophilia with a left shift and toxic changes. Urinalysis (see ch. 72) can be normal or show hematuria, pyuria, and bacteriuria. Urine collected by cystocentesis should be cultured, as prostatic secretions will flow retrograde into the bladder and results of urine and prostatic fluid cultures are highly correlated.[35] Imaging studies (either radiography or ultrasonography [see ch. 88]) for acute bacterial prostatitis will show prostatomegaly, which may not have been palpable per rectum. Ultrasound-guided fine needle aspiration or biopsy can provide samples of prostatic fluid or parenchyma for cytology and bacterial culture and sensitivity, but because of the risk of bacterial seeding along the needle tract, prostatic wash and brush sampling techniques are a safer alternative for obtaining these samples (see ch. 111).[15]

Therapy

The mainstay of treatment for acute bacterial prostatitis is appropriate antimicrobial therapy based on results of urine and/or prostatic fluid or parenchyma culture and sensitivity. Since the blood-prostate barrier is broken in acute bacterial prostatitis, this barrier should not be a major concern when selecting an antibiotic. However, it is recommended, when possible, to initiate therapy directly with an antibiotic that has good prostatic parenchymal penetration so that once the barrier is restored (following the acute phase of infection), antibiotics will not need to be changed.[23] The blood-prostate barrier prevents the diffusion of ionized drugs and of those with low lipid solubility or high protein binding.[16,36] Basic antibiotics with a pKa >7.0 (e.g., trimethoprim-sulfamethoxazole and chloramphenicol) diffuse easily from the blood to the prostatic parenchyma. As the pH of the normal canine prostatic fluid is typically acidic, the pH gradient between blood and prostate favors additional trapping of weakly basic drugs that are ionized in the acidic prostatic fluid.[12,37]

Fluoroquinolones are able to penetrate the prostate parenchyma well regardless of pH and are therefore a good choice for initial empirical antibiotic treatment while waiting for culture results.[38] At a dosage of 5 mg/kg PO q 12 h, enrofloxacin achieves prostatic fluid and parenchymal concentrations exceeding the minimum inhibitory concentration for most pathogens.[38] Antimicrobial therapy should continue for a prolonged period of time (i.e., 4-6 weeks) to reduce the likelihood of prostatic abscess formation. Urine and/or prostatic fluid should be re-cultured 2-3 weeks into treatment while the patient is still under therapy to confirm efficacy (culture is negative). Culture also should be repeated 1 to 3 weeks after cessation of antimicrobial therapy.

The potential impact of acute bacterial prostatitis should not be underestimated clinically since it can lead to sepsis, systemic inflammation, and multiple organ involvement (see ch. 132). Affected dogs should be monitored and treated, if needed, with intravenous (IV) fluids (see ch. 129), analgesics (see ch. 126 and 166), and supportive care. Following the acute phase of infection, castration may be performed as an adjunctive therapy in order to reduce prostatic size (and volume of infected tissue).[23] Castration is not recommended during the acute phase of infection, as scirrhous spermatic cords may form secondary to bacterial ascension.[39] Reversible androgen suppression therapy with finasteride should be used initially until the infection is controlled and a safe surgical castration is possible, or long-term (as described above) in cases of breeding males where castration is not desired.[12]

Prostatic Abscessation

Prostatic abscessation can occur secondary to acute bacterial prostatitis or following estrogen-induced squamous prostatic metaplasia from an infected cyst.[35,40,41]

Diagnosis

Clinical signs of prostatic abscessation are similar to those of acute bacterial prostatitis, including signs of systemic illness, lethargy, fever, pain on urination and defecation and caudal abdominal pain.[15] In addition to an inflammatory leukogram, affected dogs can have sepsis-induced hypoglycemia. Abscesses can be walled off and lose direct contact with the prostatic ductal system. Therefore, bacterial culture of prostatic fluid can yield false-negative results.[42] Ultrasound (see ch. 88) is important for diagnosis and it reveals one or more hypo- to anechoic cavitary lesions within the parenchyma of an enlarged, irregularly-outlined and asymmetrically-shaped prostate gland. A highly-skilled ultrasonographer can differentiate abscesses from uninfected cysts, cavitary neoplasias, or hematomas.[43] Hyperechoic focal areas suggestive of necrotic debris within an abscess can be observed.[39] Even though prostatic abscessation can present similarly to acute prostatitis clinically, it is important to make the correct diagnosis, as the treatment regimen differs.

Therapy

Prostatic abscessation requires a combination of drainage (see below) and appropriate antimicrobial treatment, as antibiotics alone will not successfully eliminate the infection. Local ischemia tends to hinder penetration of antibiotics into the abscess and, in contrast to acute bacterial prostatitis, the prostate-blood barrier commonly is intact.[39] Antibiotics that readily cross the intact prostate-blood barrier (e.g., enrofloxacin, trimethoprim-sulfonamide, chloramphenicol) should be chosen and administered for 6 weeks following drainage. The prostate should be reassessed by ultrasonography to confirm the abscess cavity is not refilling. Similar to the treatment of acute bacterial prostatitis, the prostatic fluid should be cultured both during treatment and 2-4 weeks after antimicrobial therapy is discontinued. Castration and/or reversible androgen suppression therapy should be employed to promote a more rapid resolution of bacterial infection.[44]

Abscesses must be drained either surgically or by ultrasound-guided percutaneous aspiration.[40,45] Ultrasound-guided, percutaneous drainage may be a useful alternative to surgical treatment if the cavitary lesions are well-circumscribed and neither concurrent systemic illness nor prostatic neoplasia is suspected. There is a potential risk for causing iatrogenic peritonitis during percutaneous aspiration.[39] Also, >50% of dogs that undergo aspiration of prostatic abscesses have experienced abscess recurrence.[45] Instillation of 95% ethanol into the drained abscess cavity was used successfully in a dog with recurrent disease.[40] Surgical drainage of a prostatic abscess should include omentalization or marsupialization with placement of a Penrose drain. In one study of 92 dogs with the latter technique, 22 dogs died or were euthanized in the

immediate perioperative period and only 33 dogs were reported to have good to excellent results.[46] Omentalization results in a lower rate of recurrence, lower mortality, and a lower incidence of urinary incontinence postoperatively compared with marsupialization, which is why omentalization is favored by surgeons.[39,47]

Chronic Bacterial Prostatitis

Chronic bacterial prostatic infections are more common than are acute bacterial infections. Both mainly affect mature intact dogs or those infected immediately prior to castration.[48] The prevalence of chronic bacterial prostatitis is difficult to estimate because up to 35% of dogs exhibit no clinical signs nor do they even have an inflammatory leukogram. One study reported a prevalence of 24% subclinical chronic prostatitis in dogs that died of diseases unrelated to the prostate.[1]

Diagnosis

The most common presenting complaint for chronic bacterial prostatitis is a recurrent urinary tract infection with persistence of the same pathogen in an otherwise healthy intact or recently-castrated dog. Infection persists in the prostate during short-term antimicrobial treatment and this leads to reinfection of the urinary tract once antimicrobial therapy is discontinued.[23,49] Other possible clinical signs include sanguineous urethral discharge independent of urination, as well as hematuria, hindlimb gait abnormalities, or discomfort when rising.[50] Less common owner observations are signs of testicular pain from ascending epididymitis, or infertility. Findings on rectal palpation of the prostate vary from normal for a mature, intact male dog to, less commonly, asymmetric, firm and irregular. The prostate usually is not painful on palpation and this may lead to the false assumption that prostatic disease can be excluded.[23] Prostatic fluid evaluation (see ch. 111) shows evidence of suppurative inflammation. In >70% of dogs with chronic bacterial prostatitis, prostatic fluid culture grows a single organism.[16,51] Fine needle aspirate and/or biopsy of the prostate can result in septic peritonitis (see ch. 279) secondary to needle-tract seeding, as has been reported with acute bacterial prostatitis. Radiographically, the prostate is usually normal. Mineralization can be present, but it is not specific and it is indistinguishable from neoplasia.[23] Ultrasonographic findings include a heterogeneous pattern of mixed echogenicity with a focal or diffuse increase in parenchymal echogenicity and hypo- to anechoic parenchymal cavities (Figure 337-2).[52,53] Sonographic shadowing can be seen with calcification, fibrosis, or gas.[23]

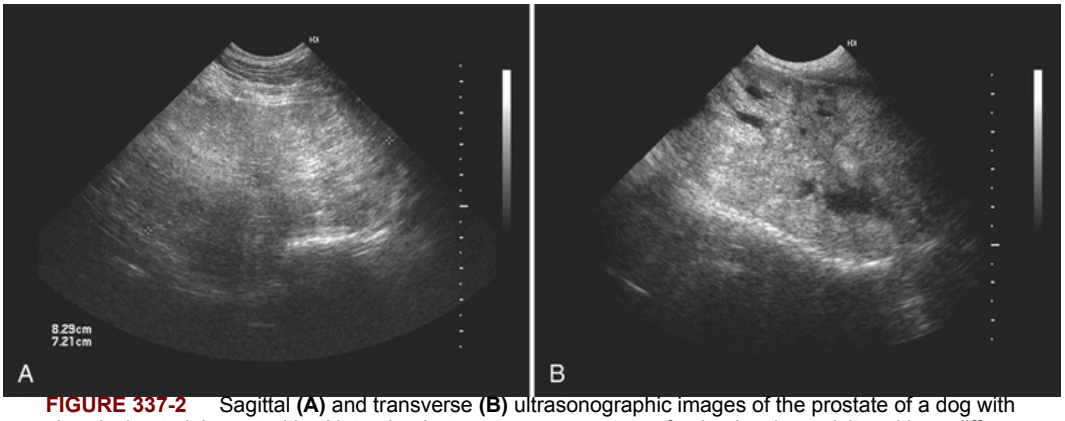


FIGURE 337-2 Sagittal **(A)** and transverse **(B)** ultrasonographic images of the prostate of a dog with chronic bacterial prostatitis. Note the heterogeneous pattern of mixed echogenicity with a diffuse increase in parenchymal echogenicity and hypo- to anechoic parenchymal cavities (intraprostatic cysts).

Therapy

Treatment of chronic bacterial prostatitis is similar to therapy for acute bacterial infections. Therefore, good antibiotic choices for chronic bacterial prostatitis include trimethoprim-sulfonamide for most aerobic bacterial

infections, fluoroquinolones against *Mycoplasma* spp., and chloramphenicol against anaerobes (see section on Acute Bacterial Prostatitis for complete explanation).[4,23,38] As with acute bacterial prostatitis, antimicrobial treatment should be based on culture and sensitivity and should be continued for a minimum of 4-6 weeks, regardless of earlier resolution of clinical signs.[36] When compared with intact control dogs, castration leads to significantly faster resolution of infection.[44,54] Antibiotics should be started 5-7 days prior to castration to reduce the risk of scirrhous cord formation.[15]

Paraprostatic Cysts

Paraprostatic cysts are fluid-filled remnants of the uterus masculinus, which, when present, are located outside the prostatic parenchyma.[55]

Diagnosis

Clinical signs are related to cyst size and can include dyschezia and dysuria from extraluminal compression on the colon or urethra, respectively. Urinary incontinence has been described in dogs where the cyst causes partial urethral obstruction with subsequent bladder overdistention.[43] Depending on their size, paraprostatic cysts may be suspected on abdominal palpation and they may be palpated as a mass within the pelvic canal on rectal exam.[55] They usually arise craniolaterally to the prostate and they tend to displace the bladder cranioventrally or dorsally and the colon and rectum dorsally on radiographs (Figure 337-3). Common histopathologic characteristics include connective or fibrous tissue wall, with or without an epithelial lining, and osseous metaplasia. Radiographic evidence of cyst mineralization is a frequent finding, occurring in 50% of dogs in one report.[55] Mineralized paraprostatic cysts have been discussed as a possible contributing factor in the development of perineal hernias in male dogs.[56] Ultrasonographically, paraprostatic cysts typically have hyperechoic rims and hypo- or anechoic contents, sometimes with septations.

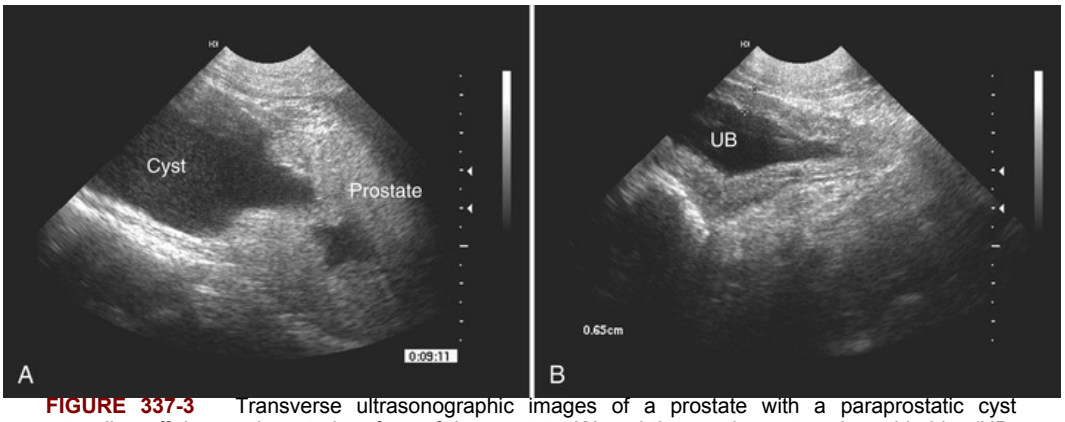


FIGURE 337-3 Transverse ultrasonographic images of a prostate with a paraprostatic cyst extending off the cranioventral surface of the prostate **(A)** and the nearly empty urinary bladder (UB; wall thickness of 0.65 cm is within normal limits for an empty bladder) present on the caudoventral surface of the prostate **(B).**

Therapy

While most paraprostatic cysts do not require any treatment because they are incidental findings, treatment for paraprostatic cysts that are causing clinical signs includes surgical debridement, omentalization, marsupialization and, if needed, placement of surgical drains.[39] Alternatives to surgical treatment include ultrasound-guided percutaneous drainage, which was associated with lower morbidity, lower costs, and improved outcome when compared to surgery in one study.[45]

Prostatic Neoplasia

Except for humans, dogs are the only species known to have a clinically significant incidence of prostatic

cancer. Both species share several similarities, and the dog serves as a model for human disease.[57,58] Adenocarcinoma is the most frequent prostatic neoplasm in dogs, but more than half exhibit intratumoral heterogeneity.[58] The tumor can arise from both glandular or ductal epithelial cells of the prostate or from the urothelium of the prostatic urethra, but in most cases, the precise cellular origin remains unknown.[59] The other common prostatic neoplasm in dogs is transitional cell carcinoma, derived from the prostatic urethra. Other tumors such as sarcomatoid carcinoma, primary and metastatic hemangiosarcoma, and lymphoma have been reported rarely[60-63] (see ch. 351).

Diagnosis

The specific diagnosis of canine prostatic neoplasms may be challenging, as many primary adenocarcinomas in the dog have morphologic and light microscopic features similar to those of transitional cell carcinoma.[59] Overall, canine prostate cancers are malignant epithelial neoplasms that often exhibit gland-like or acinar structures and are, therefore, usually classified as adenocarcinomas.[64] Most canine prostate cancers do not express androgen receptors and are hormonally independent, and, therefore, do not respond to androgen deprivation.[12,64] It is important to note that in dogs, castration significantly increases the risk of developing prostatic cancer. In a large multicenter retrospective study, the risk of developing prostatic transitional cell tumor was 8 times higher in castrated than in intact dogs, and it was 2.1 times higher for prostatic adenocarcinoma.[65] On a histologic level, it has been shown that castration leads to an increased occurrence of less-differentiated growth patterns in canine prostatic cancer.[57] Castration does not seem to initiate tumor development, but it favors tumor progression. This may be the result of supraphysiologic luteinizing hormone (LH) concentrations that persist for the dog's life following castration, as a result of the loss of testicular negative feedback. LH receptors are present within human prostatic epithelium[66] but have not been investigated in dog normal or neoplastic prostate tissue yet. Breed predispositions for prostate cancer include mixed-breed dogs, Shetland Sheepdogs, Scottish Terriers, Airedale Terriers, and Doberman Pinschers.[65]

Common clinical findings in dogs with prostatic neoplasms include dysuria, macroscopic hematuria, dyschezia, hindlimb pain, and ataxia.[64] In more advanced stages, clinical signs of paraneoplastic syndromes such as lethargy, anorexia, weight loss, and poor body condition are present. Dysuria can be due to concurrent prostatitis or to local invasion into the prostatic urethra, occasionally resulting in urethral obstruction. Pyuria and hematuria were found in 62% and 66%, respectively, of 24 dogs with prostate cancer.[67] Because of the aggressive nature of canine prostate cancer, most dogs are in advanced stages of disease when diagnosed. Often, there is extensive local invasion and widespread visceral metastases, with a prevalence up to 80% at the time of diagnosis.[67] The most common sites of metastasis are the sublumbar and iliac lymph nodes, lung, and bone (mostly the lumbar vertebrae and pelvis). Involvement of liver, kidney, spleen, and brain has been reported. The presence of neoplastic tissue in the urinary bladder is a common manifestation of local invasion by neoplastic cells, which also can be found in the prostatic lymphatics, perineural space, and pelvic musculature. In dogs, all prostate cancers are considered to be highly aggressive neoplasms with widespread metastatic tendency.

Diagnosis of prostatic neoplasia in dogs usually is based on history, clinical signs, prostatic imaging (see ch. 88), fluid analysis (see ch. 111), cytology (see ch. 93) and/or histopathology. Radiographic changes can include prostatomegaly, mineralization of the prostate, evidence of regional lymphadenomegaly, and possibly evidence of metastasis to the lungs and bones, especially to the lumbar vertebrae and pelvis. Ultrasound findings can include focal to diffuse hyperechoic areas, mineralization, and loss of normal prostatic contour (Figure 337-4).[15] Percutaneous, ultrasound-guided fine needle aspiration is a viable diagnostic tool for cytologic diagnosis of prostatic neoplasia (E-Figure 337-5).[68] However, there is a potential risk of needle-tract seeding into the abdominal wall.[69] This complication seems to be rare, but the possibility should not be neglected and the needle tract should be resected at surgery if possible. Prostatic wash is a valuable alternative to fine needle aspiration (see ch. 111).

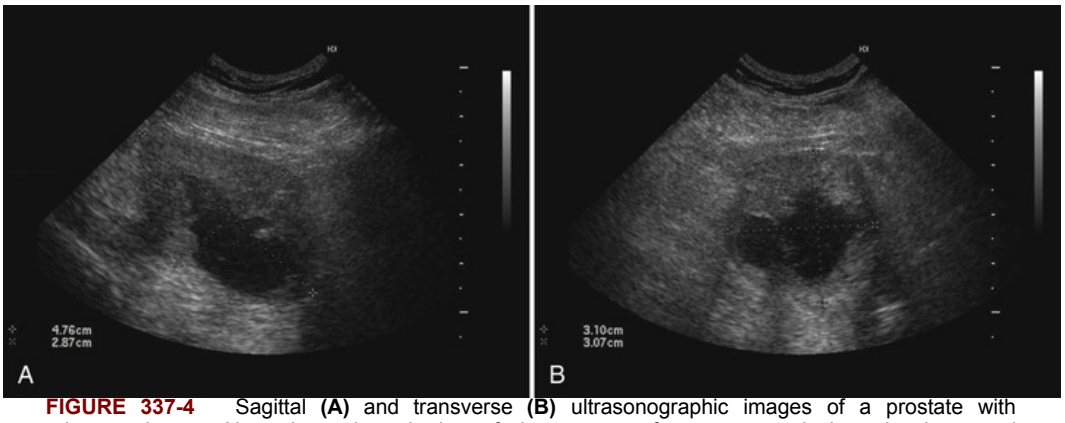
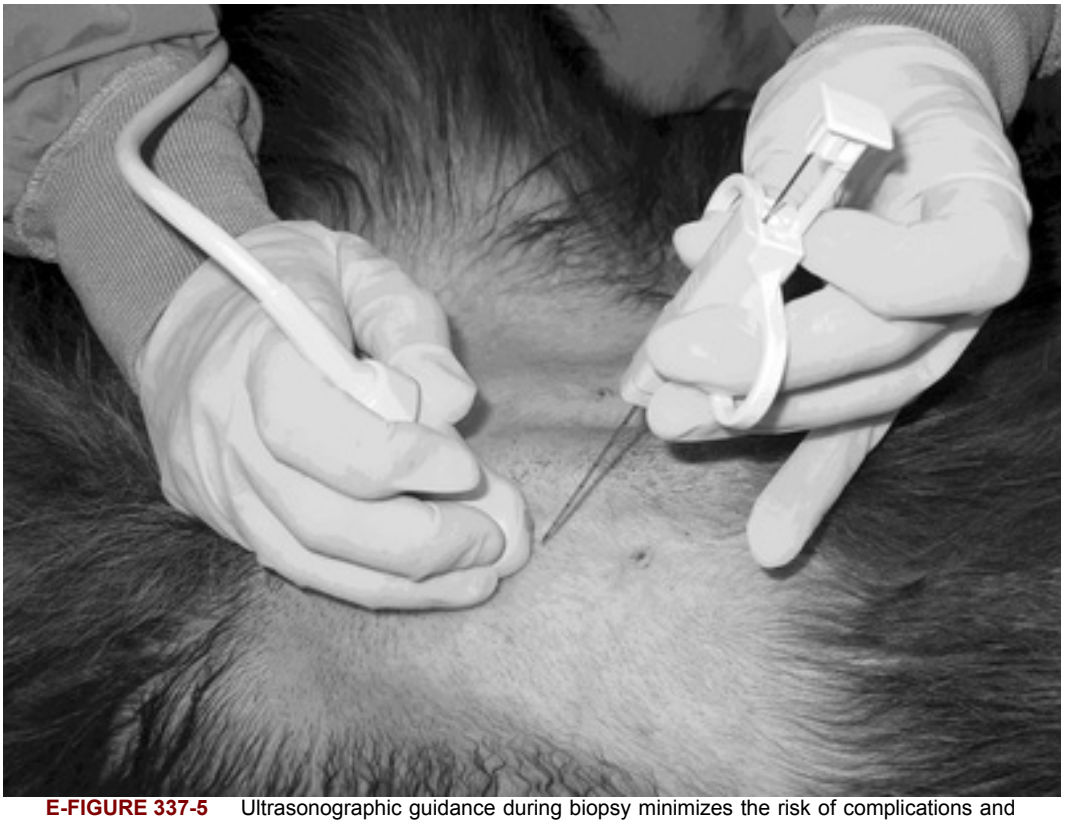


FIGURE 337-4 Sagittal **(A)** and transverse **(B)** ultrasonographic images of a prostate with adenocarcinoma. Note the enlarged size of the prostate for a castrated dog, the increased echogenicity, and presence of large, coalescing cysts with hypoechoic luminal contents. The ultrasonographic appearance of a prostatic abscess can be similar to that of a prostatic adenocarcinoma. The diagnosis should be confirmed by evaluation of a prostatic fluid sample and/or prostatic biopsy.



E-FIGURE 337-5 Ultrasonographic guidance during biopsy minimizes the risk of complications and maximizes the diagnostic value of the sample.

Therapy

In general, the survival for most dogs with clinical prostate cancer is short, often only ranging from weeks to months.[58] Since canine prostate cancer is aggressive and highly metastatic, ideally both local and systemic therapies are indicated. However, there is no widely accepted standard of care at present, and treatment options are limited and rather unrewarding.[64] Piroxicam, a nonsteroidal anti-inflammatory, can be administered at 0.3 mg/kg PO q 24 h, and has successfully reduced the size of various canine carcinomas.[70] A

combination of piroxicam with cisplatin (60 mg/m^2 IV q 21 d) has resulted in complete or partial remission in 71% of dogs with urinary bladder cancer, compared with no tumor remission with cisplatin treatment only (see ch. 351).[71] Radiation therapy did not improve survival significantly and its role in the treatment of canine prostatic neoplasia is unclear.

Other treatment options include palliative partial or total surgical prostatectomy.[72] However, such approaches are associated with serious risks of complications and they do not necessary prolong survival time.[64] Other palliative treatment options could be beneficial and include bisphosphonates to inhibit osteoclasts and help in the management of skeletal metastases (see ch. 352).[73] Inhibition of bone resorption relieves pain, reduces the risk of fracture, and controls paraneoplastic hypercalcemia.[64] Despite numerous attempts to improve treatment of prostatic cancer in dogs, the prognosis currently remains poor.

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SECTION XXV

Cancer

OUTLINE

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CHAPTER 338

The Hallmarks/Origin of Cancer

Chand Khanna, Amanda Foskett

There has been a recent explosion in our understanding of the biology of cancer that has led to a parallel explosion in our opportunities to better diagnose and treat cancer. Accordingly, it is now necessary for clinicians to have a sound understanding of the basic biology of cancer so as to best implement novel and conventional therapeutic options. It is also important to integrate this insight to appropriately consider the use of recently developed molecular tests for cancer and cancer progression.

In 2000, the Nobel laureates Hanahan and Weinberg proposed a model for understanding the complexity of cancer, referred to as the "hallmarks of cancer."[1]

An attractive component of this proposed model was a cohesive structure in which one could consider the complexity and growing number of molecular changes that have been identified in cancer cells, and how these events independently and collectively contribute to the formation of a cancer. Briefly, this model suggested that despite the large number of molecular alterations that have been associated with cancer, they all could be understood by their contribution to six critical features necessary for the development of a cancer. These critical features were described as the "hallmarks of cancer." A specific molecular alteration could contribute to cancer by providing a cell with one or more of these hallmarks; however, it is the acquisition of all of the hallmarks that yields the full cancer phenotype. The traits ("hallmarks") that the authors prioritized in the model are summarized in Figure 338-1.

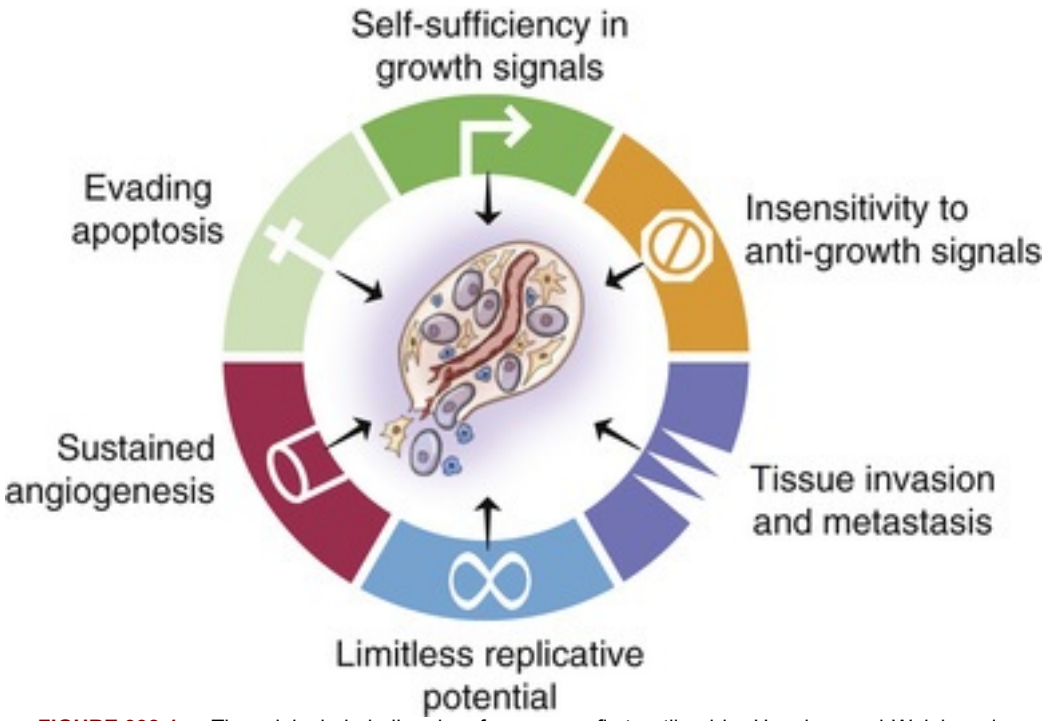

FIGURE 338-1 The original six hallmarks of cancer as first outlined by Hanahan and Weinberg in 2000. (From Hanahan D, Weinberg RA: The hallmarks of cancer. *Cell* 100[1]:57-70, 2000.)

An important clinical corollary of this model is that the effective treatment of a cancer should prioritize

cancer targets that are most needed to deliver a hallmark to a cell. In summary, this model allows the simplification of thousands of genes linked to the cancer phenotype to a simple set of six "hallmarks" that must be acquired in order to create cancer from a normal cell. Additionally, this model allows a focus on the fundamental features of cancer rather than on the specific functions of various molecular changes.

Ten years after the original publication of this model, a revision was proposed that refined the "hallmarks" through some clarity in the features of cancer progression and metastasis, and inclusion of "enabling features" of cancer.[2]

The use of this model allows the clinician to focus on the critical features of the cancer phenotype rather than a long list of genetic molecular alterations. Furthermore, it provides a simple framework to characterize the contributions made by various molecular alterations.

Cancer Is a Genetic Disease

It is clear from all points of evidence, that cancer is a genetic disease.[3,4] Indeed, related to the above discussion on the hallmarks of cancer, each of the six hallmarks required for a cancer can be delivered through alterations in genes. To say that cancer is a genetic disease does not suggest that cancer is a hereditary disease, although there are familial, and therefore hereditary, risks associated with cancer.[5]

The classical association between cancer and genetics involves a discussion of tumor promoting genes that become overactive, referred to as oncogenes, or the loss of genes that normally constrain one or more of the hallmarks of cancer, referred to as tumor suppressor genes. The activation of oncogenes occurs for a variety of reasons. Often, this involves a mutation or other structural change that activates the normal gene (a proto-oncogene) to become a cancer-associated oncogene. The gain of function seen in an oncogene is a dominant event, and therefore requires the alteration of only one of a gene's alleles.[6,7] Conversely, the loss of a tumor suppressor gene is recessive event, and therefore requires the loss of both alleles for the function of that tumor suppressor to be lost. Interestingly, it is the loss of a tumor suppressor gene, *P53,* that is believed to be the most common genetic alteration seen across human cancers. Not surprisingly, loss of P53 has also been described in a variety of veterinary cancers.[8-12] P53 is a member of a family of genes described as checkpoint genes. P53 and other checkpoint genes serve to "survey" the genetic landscape of a cell and determine if there has been sufficient DNA damage to warrant halting the division of the cell and its progress through the cell cycle (referring to a series of steps that allows the cell to undergo mitosis). Halting the division of the cell allows DNA repair mechanisms to repair the DNA damage identified in the cell. If the DNA damage is more significant, genes like P53 will not only halt the mitotic process, but will shift the cell into a pathway of programmed cell death (apoptosis). This allows elimination of this genetically altered cell, therefore preventing it from potentially contributing to a hallmark of cancer. Accordingly, the loss of P53 and its checkpoint function will eliminate the ability of cells to enter this suicide/death pathway, and therein increase the number of cells present with genetically altered landscapes. The loss of two alleles in a tumor suppressor gene which, as described, will contribute to a hallmark of cancer, often occurs as a result of a hereditary and sporadic ("second hit") event. In this scenario, the first loss of a tumor suppressor gene is a familial risk and the second loss is sporadic. The resultant loss of these two alleles, often described as "two hits," explains why there are families at increased risk for specific cancers. This was first described by Knudson in the familial and sporadic form of retinoblastoma in humans, which results from a two-hit loss of the retinoblastoma (Rb) tumor suppressor gene.[13]

Historically it was believed that the genetic alteration that results in the dysregulation of a specific gene occurred as an alteration in the nucleic acids that constitute that gene. It is now increasingly understood that these alterations in gene function can occur outside a specific change in the gene itself. This understanding is included in a large field of cancer biology referred to as epigenetics. Briefly, epigenetics largely refers to changes in the regulatory elements of a gene (namely the promoter or enhancer of the gene). Epigenetic alterations in gene function in fact can be a more common mechanism for cancer-associated gene dysregulation than structural changes in a gene (i.e., mutation). Interestingly, these epigenetic changes in gene function have been aligned closely with various environmental and other acquired risks for cancer.[14,15]

Telomerase and the Acquisition of Limitless Replicative Potential

The acquisition of limitless replicative potential is a hallmark of cancer. This hallmark has been closely associated with the telomere and telomerase. Telomeres are specialized DNA protein complexes that cap the ends of chromosomes and maintain genomic stability by preventing recombination or fusion with other

chromosomes. Each telomere consists of tandem repeats of TTAGGG and several telomere-related proteins. In normal cells, telomeres shorten with each cell division, referred to as telomeric attrition. Telomerase is a reverse transcriptase capable of making the terminal telomeric repeats, thus extending the telomere and compensating for attrition during cell division.[16] Very low levels are detected in normal somatic tissues; however, telomerase is found at high levels in germline and cancer cells, giving them long-term proliferative potential. Some cancer cells are capable of maintaining telomere length and surviving without telomerase.[17] In these instances, alternative mechanisms, referred to collectively as alternate lengthening of telomeres (ALTs), are used.[18,19] The mechanisms are not fully understood, but have uncovered novel therapeutic targets (i.e., ataxia telangiectasia and Rad3-related kinase [ATR]) that are being targeted in dogs by novel anticancer drugs.[20]

Tumor Progression and Metastasis

In order for cancer cells to spread from the primary tumor to distant secondary sites, individual cells and groups of cells must accomplish a number of discrete processes associated with the metastatic cascade. A detailed study of the metastatic cascade has now defined critical steps, which appear to be the most difficult for cancer cells to pass through successfully. These steps represent *unique periods of vulnerability* during which cellular stresses result in the death of the majority of cancer cells, and especially non-metastatic cells. These stresses appear to be highest as metastatic cells interact with the microenvironment at the secondary metastatic sites. It is only the minority of cancer cells that can adapt and survive these vulnerable states during the metastatic cascade. Indeed, the metastatic phenotype now can be defined by an ability of cells to adapt to stresses experienced during these vulnerable states.[21-23] An understanding of these stresses and the mechanisms by which cells overcome them could provide a new opportunity for the discovery and development of metastasis-specific therapies.

Metastasis is a multistep process that results in the dissemination of tumor cells from a primary site to distant secondary organs, and the eventual progression of disease at these secondary sites. Metastatic cancer cells are uniquely programmed to endure and overcome cellular stresses associated with each step in this process.

Based on studies of the metastatic phenotype of sarcoma cells in dogs, mice and humans, we believe that a common determinant of metastatic cancer cells is their ability to resist these stresses.[24] Starting with our study of the metastasis-associated protein ezrin, we have taken this cross-species (murine, canine, human) comparative approach to the study of metastasis as a means to develop an understanding of metastasis that can be translated rapidly to the clinic in the form of novel therapeutics.[24]

Recent and preliminary data now suggest the endoplasmic reticulum (ER) of highly metastatic cells as being distinct from that of low metastatic cells. Indeed, the ER response in highly metastatic cells seems to lead to a protective effect that is not seen in low metastatic cells.[25] These data suggest the ER and the ER responses in highly metastatic cells could serve as potential targets for novel antimetastatic therapy. Studies now are underway to screen and identify drugs that target the stress adaptation pathways of the ER and, in so doing, could be useful against metastatic progression.

Angiogenesis and the Tumor Microenvironment

Tumor vasculature and angiogenesis have been studied extensively, especially as a target for cancer therapy. Tumor angiogenesis refers to the formation of blood vessels within the tumor microenvironment through sprouting or intussusception of pre-existing blood vessels. This is in contrast to vasculogenesis, or formation of blood vessels *de novo*, during embryogenesis. The vasculature within and surrounding a tumor is of critical importance, as it supplies the nutrients, growth factors, metabolites, inflammatory mediators, and oxygen for primary tumor proliferation.[26] Tumor blood vessels also provide a means for tumor cells to enter the vasculature and spread to other parts of the body, and play a vital role in the metastatic cascade.

Normal angiogenesis occurs in all tissues and is of particular importance in embryogenesis and wound healing. Hypoxia is the primary physiologic stimulator in the development of vasculature. Hypoxia-sensing mechanisms in poorly perfused tissues induce new vessel formation to satisfy the metabolic requirements of cells in the hypoxic environment. Cells respond by secreting proangiogenic growth factors, including vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF) and basic fibroblast growth factor (bFGF), among others. Briefly, these factors induce endothelial cells from surrounding blood vessels to migrate towards the angiogenic stimulus and organize to form new vessels. Generation of a new blood

supply to these tissues eliminates the hypoxic stimulus, and VEGF production declines.[27]

The tumor microenvironment often does not abide by normal physiologic rules. Many cancer cells are capable of inducing angiogenesis in the absence of hypoxia. Multiple mechanisms have proven responsible for this phenomenon, including the overproduction of VEGF, and upregulation of other vascular stimulating cytokines. This phenotype has been associated with the activation of oncogenes, loss of function in a number of tumor-suppressor genes, and downregulation of angiogenic inhibiting mechanisms. The tumor microenvironment also lacks the normal barriers present in non-cancerous tissues. For example, the basement membrane and connective tissues often are compromised in malignant tissues, creating an altered tumor-vascular interface, which could influence metastatic potential, access to nutrients, and access to other mediators.[28]

In human medicine, a plethora of therapeutic agents has been developed to target various steps in the angiogenic pathway.[29,30] In veterinary medicine, small-molecular targeted therapies also have started to emerge on the market. Specifically, Palladia (toceranib) is a receptor tyrosine kinase (RTK) inhibitor developed to target c-kit in mast cell tumors. This drug also inhibits the RTKs of VEGF, and other proteins, involved in angiogenesis. Toceranib has known activity against a number of cancer types, independent of c-kit.[31] Indeed, many tumor types overexpress VEGF or PDGF, or have aberrant VEGF signaling, and reasonably could be targeted with this drug.[32]

The Cancer Stem Cell Hypothesis

It is recognized that within a cancer there is a variety of subpopulations, including those that account for the rapid recurrence of a cancer after initial response to therapy. The cancer stem cell hypothesis proposes that a small but definable population of cells within a tumor is able to self-renew and give rise to tumor cells both at the primary tumor site and sites of metastasis. Within this heterogeneous environment exists a small number of slowly dividing cells that differ from the rest of the cancer cell population that are resistant to conventional treatment. This population is proposed as the cause for recurrent disease despite initial response to treatment (e.g., chemotherapy, radiation, or surgery) or distant metastasis to other sites in the body later in disease progression.[33]

Clinically, cancer stem cells (CSCs) have become a prominent area of interest and research as a potential target for cancer treatment. CSCs were first pinpointed in acute myeloid leukemia (AML). These cells were identified by their ability to self-renew and repopulate the bone marrow of severe combined immunodeficient (SCID) mice following transplantation of human AML cells and administration of *in vivo* cytokine stimulation.[34] Later experiments identified a hierarchy among these populations, and discovered specific cell markers, present only on this small population of CSCs, that were capable of differentiating into blastic leukemic cells.[35] Various CSC markers now have been identified on a number of solid tumors including breast cancer,[36] colorectal,[37-39] pancreatic,[40] hepatocellular,[41] ovarian,[42] and prostatic cancers,[43] among many others including melanoma.[44] Specific markers identified in these tumor types have been associated with prognosis, metastatic rate, and response to treatment in human cancer patients, indicating that these CSCs could be a valid target for novel cancer therapy. Varying therapies targeting altered cellular pathways in the stem-cell population have shown promise *in vitro* and in some early clinical trials.[45,46] Immunotherapy also has been used for targeting cell surface markers unique to CSCs with varying efficacy in both the *in vitro* and *in vivo* settings[47] (see ch. 341).

Although new, targeted therapies towards CSCs are not yet common practice in veterinary medicine, this approach presents a new, exciting front that will likely benefit the veterinary patient in the future.

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CHAPTER 339

Principles and Practice of Chemotherapy

Angela E. Frimberger, Antony S. Moore

Client Information Sheet: Chemotherapy Safety for Pet Owners

Chemotherapy is the principal modality used to treat systemic cancers such as hematologic malignancies and metastatic solid tumors.

Tumor Biology in Chemotherapy

A good understanding of tumor biology, discussed in detail in ch. 338, is necessary in planning chemotherapy.

Chemotherapy works best against a small tumor burden. As tumors grow, the growth fraction decreases, the cell cycle time increases, cellular heterogeneity increases (leading to a higher level of spontaneous resistance), and areas of poor perfusion increase. Thus, it may not be possible for chemotherapy drugs to be delivered to cancer cells at cytotoxic levels. In addition, because resistance to chemotherapy can occur through spontaneous mutations that occur with each cell division at a rate intrinsic to each tumor, the likelihood that mutations resulting in drug resistance have occurred is related to the number of cell divisions that have taken place. Finally, chemotherapeutic cytotoxicity follows fractional-kill kinetics. For example, if a particular dose of drug kills 4 logs of cells, then it will reduce a tumor of 10^{12} cells to 10^{8} cells and a tumor of 10^{10} cells to 10^{6} cells—either will appear clinically as a complete response because 10^{9} cells is usually the limit of clinical detection; however, the latter scenario is obviously preferable. Therefore, it is most advantageous to begin treatment with the smallest tumor, and in general, chemotherapy will be most active either after early detection or after a cytoreductive ("debulking") procedure such as surgery or radiation therapy.

Chemotherapy Strategies

In managing chemotherapy, communication between veterinarian and owner is essential. These communications must be both frank and compassionate. All options should be presented to owners without preconceptions of the owner's preferences.

A definitive diagnosis of tumor type, clinical stage of disease, and the patient's overall health are important both in establishing a prognosis and prescribing a treatment plan. The general health screen is necessary to detect other conditions that may affect life expectancy (i.e., other systemic disease), conditions that need to be resolved prior to starting chemotherapy (e.g., subclinical urinary tract infection), or conditions that need to be taken into account in planning chemotherapy (e.g., subclinical cardiac or renal disease).

Staging and General Health Evaluation

Every patient is an individual, and the metabolism and excretion of the drugs are individual, and every cancer is also an individual. The purposes of staging are to evaluate the extent of disease and to assess the pet's general health—this is important both to evaluate fitness for therapy and to screen for unrelated or secondary conditions that may require management before starting cancer therapy or may separately impact on the pet's overall prognosis. Staging often carries prognostic significance that may help the veterinarian and client make informed, rational decisions about the type of therapy. Most staging systems are based on assessment of three major components of the malignant process: the size of the primary tumor (T), lymph node metastasis (N), and distant metastasis (M).

Goal of Treatment

It is important to establish the goal of treatment at the outset because it often determines the course of therapy. The goal of chemotherapy in human oncology is usually to cure the patient; however, in veterinary medicine, palliation may sometimes be a more appropriate goal. A continuing, open dialogue will allow an owner to make an informed decision and will ultimately create a "team" approach to treatment of the pet's cancer.

Palliative Intent Treatment

Palliation is defined as improving quality of life, and possibly extending life, but without expectation of cure. Palliative treatment is often appropriate when the prognosis is poor and significant toxicity cannot be justified when only a short duration of survival is expected. For many older veterinary patients, the diagnosis of cancer is made at a time when other diseases may limit survival to a greater extent than does the cancer. For these animals, palliative care may be most appropriate, and the choice of chemotherapy must be weighed against the risk of toxicosis. It is rarely effective to begin treatment with palliative intent and then later to switch to a more aggressive approach. However, it is common to begin treatment with curative intent and then later switch to a palliative course.

Curative Intent Treatment

Cure is defined as eradication of all tumor cells resulting in a permanent disease-free state, and is an ideal although not always realistic outcome. The restriction on chemotherapy doses to keep side effects within an acceptable range means that cures are usually only possible in a small number of veterinary patients—for example, 15% of dogs with lymphoma and 20% of dogs with osteosarcoma, given standard of care therapy. For dogs and cats that are in good health and have no concurrent illnesses and when chemotherapy holds the possibility of prolonged control of their cancer with little risk of toxicosis, chemotherapy with curative intent may be undertaken.

Chemotherapy in Combination with Other Treatment Modalities

In veterinary oncology, primary chemotherapy (chemotherapy as the sole or main treatment) is usually reserved for hematopoietic tumors (lymphoma, leukemias, multiple myeloma). For dogs with metastatic solid tumors (carcinomas and sarcomas) chemotherapy alone is rarely curative and is better considered to be palliative.

Adjuvant chemotherapy is used after resection or radiation of a primary tumor, to slow the progress of metastatic disease or possibly to provide a cure. This is done in settings when the animal is at significant risk of recurrence or metastasis, but before disease progression is clinically detectable—for example, after amputation in dogs with osteosarcoma. Adjuvant chemotherapy is effective because it is used at the earliest stages of growth. When a primary tumor is resected, micrometastatic foci of tumors cells have a high growth fraction and a low number of resistant cells. The disadvantage of adjuvant chemotherapy is that patients cured with surgery are treated unnecessarily. For tumors such as osteosarcoma and hemangiosarcoma in dogs and mammary tumors in cats, this percentage of surgical cures is small, but for animals with other tumors, the decision of whether chemotherapy will be beneficial or not may be more difficult.

Neoadjuvant chemotherapy is used before localized treatment modalities such as surgery or radiation therapy, with the objective of reducing the size of the primary tumor and reducing the scope and side effects of other definitive treatment. *Chemoradiotherapy* refers to the use of chemotherapy drugs primarily as radiation sensitizers rather than for their direct antitumor effect.

Drug Classes and Combination Chemotherapy

Many standard of care treatment protocols use chemotherapy drug combinations. Understanding combination chemotherapy requires a knowledge of the common classes of drugs in use in veterinary oncology.

Alkylating agents (Table 339-1) create cross-links in DNA, causing strand breaks. An interesting feature of this class of drugs is the apparent lack of cross-resistance between different alkylating agents or with other classes of drugs.

TABLE 339-1

Commonly Used Alkylating Agents

DRUG	FORM	POTENTIAL SIDE EFFECTS	DOSAGE/REGIMEN
Cyclophosphamide (Cytoxan)	25, 50 mg tablets; 500 mg vials	Myelosuppression Hemorrhagic cystitis	250 mg/m^2 PO q 3 wk 200 mg/m^2 IV q 3 wk 50 mg/m^2 PO q 48 h
Chlorambucil (Leukeran)	2 mg tablets (refrigerate)	Mild but cumulative myelosuppression	6-8 mg/m^2 PO q 48 h 15 mg/m^2 PO daily for 4 days q 3 wk
Melphalan (Alkeran)	2 mg tablets (refrigerate)	Myelosuppression	1.5 mg/m2 PO daily for 10 days, then a 10-day "rest"
Lomustine (CCNU; Gleostine)	5, 10, 40, and 100 mg capsules	Myelosuppression, neutropenia, and delayed thrombocytopenia in dogs; delayed neutropenia in cats Irreversible renal and liver toxicosis (uncommon)	50-90 mg/m^2 PO q 4-6 wk (dogs) 50 mg/m^2 PO q 6 wk (cats)
Mechlorethamine (Mustargen)	10 mg vials	Myelosuppression Extravasation reaction	In MOPP: 3 mg/m2 IV weekly
Procarbazine (Matulane)	50 mg capsules	Nausea, anorexia, diarrhea Myelosuppression	50 mg/m2 PO daily for 14 days (dogs); 10 mg/cat PO daily for 14 days
Dacarbazine (DTIC)	200 mg vials	Myelosuppression Anorexia, vomiting, diarrhea	800 mg/m2 q 3-4 wk (dolasetron is used prior to treatment) IV slow infusion over 5-8 hours
Ifosfamide (Ifex)	1 g with mesna 1 g vials	Myelosuppression Hemorrhagic cystitis (must be given with mesna and diuresis protocol) Renal toxicosis in cats	375 mg/m^2 IV (dogs) 900 mg/m^2 IV (cats) Given q 3 wk in 0.9% NaCl with mesna

Antitumor antibiotics (anthracyclines) (Table 339-2) act by DNA intercalation, interfering with topoisomerases, and other mechanisms. These drugs usually exhibit cross-resistance with others in their class and with drugs in some other classes, particularly mitotic inhibitors, and they are substrates for the multidrug resistance (MDR) pump.

TABLE 339-2

Commonly Used Antitumor Antibiotics

DRUG	FORM	POTENTIAL SIDE EFFECTS	DOSAGE/REGIMEN
Doxorubicin (Adriamycin)	2 mg/mL 10, 20, 50, 200 mg vials	Myelosuppression Cumulative cardiotoxicosis Anorexia, vomiting, diarrhea Allergic reaction Extravasation reaction Renal toxicosis in cats	30 mg/m^2 IV (large dogs) 25 mg/m^2 or 1 mg/kg IV (cats and small dogs) Given q 2-3 wk (infusion rate should not exceed 2 mg/min)
Mitoxantrone (Novantrone)	10, 20 mg vials	Myelosuppression GI effects (uncommon)	5.5-6 mg/m^2 IV (dogs) 6.5 mg/m^2 IV (cats)

			Given q 3 wk
Dactinomycin (actinomycin D, Cosmegen)	0.5 mg vials	Myelosuppression Extravasation reaction Diarrhea, vomiting	0.5-1 mg/m^2 IV Requires slow infusion rate (not reported used in cats to date)
Bleomycin (Blenoxane)	15 U (15 mg) vials NOTE: 1 U (USP unit) corresponds to 1000 IU (International Units) corresponds to 1 mg potency. Note 1 mg potency is defined by bioassay and is not identical to 1 mg dry weight (1 mg dry weight according to USP corresponds to 1.5 to 2 mg potency).	In humans: allergic reaction, pulmonary fibrosis	0.3-0.5 U/kg IV or SC weekly

Mitotic inhibitors (Table 339-3) act to inhibit assembly (vinca alkaloids) or disassembly (paclitaxel) of the mitotic spindle.

TABLE 339-3

Commonly Used Mitotic Inhibitors

DRUG	FORM	POTENTIAL SIDE EFFECTS	DOSAGE/REGIMEN
Vincristine (Oncovin)	1 mg/mL	Mild myelosuppression (dosage related) Anorexia in cats, rarely dogs (dosage related) Peripheral neuropathy (rare) Extravasation reaction	0.5-0.75 mg/m2 IV weekly
Vinblastine (Velban)	10 mg vials	Myelosuppression Peripheral neuropathy (very rare) Extravasation reaction	3 mg/m^2 IV q 2 wk (dogs) 1.5-2 mg/m^2 IV q 2 wk (cats)
Vinorelbine (Navelbine)	10 mg vials	Myelosuppression Peripheral neuropathy (very rare) Possible renal toxicosis in cats Extravasation reaction	15-18 mg/m^2 IV q 2 wk (dogs) 11.5 mg/m^2 IV q 1 wk (cats)

Platinum compounds (Table 339-4) create cross-links in DNA. The mechanism of action is similar to that of alkylating agents, and no cross-resistance with other classes of chemotherapeutic drugs is seen.

TABLE 339-4

Platinums Used as Chemotherapeutic Agents

DRUG	FORM	POTENTIAL SIDE EFFECTS	DOSAGE/REGIMEN
Cisplatin (Platinol)	50 mg vials	Renal toxicosis Vomiting and (less commonly) diarrhea Mildly myelosuppressive Fatal pulmonary edema in cats	50-70 mg/m^2 IV with 0.9% saline diuresis q 3-4 wk DO NOT USE IN CATS
Carboplatin (Paraplatin)	50, 150, 450, 600 mg vials	Myelosuppression	250-300 mg/m^2 IV q 3-4 wk (dogs) 210-240 mg/m^2 IV q 4 wk (cats)

Antimetabolites are analogs of normal metabolites that are incorporated into DNA where they interfere with enzyme activity, transcription, or translation. These drugs often have significant toxicity with low efficacy at veterinary dosages and are not frequently used in veterinary oncology. Gemcitabine is finding more application in veterinary medicine; for this drug, the infusion rate and time are an extremely important determinant of the efficacy and side effects, and the optimal dosage and infusion schedule are still being determined.

An important new class of chemotherapeutics is the tyrosine kinase inhibitors (TKIs). This class is rapidly expanding in human oncology and also contains the first chemotherapeutics developed specifically for dogs. The two veterinary drugs in this class are toceranib (Palladia) and masitinib (Masivet). The label dosage of toceranib (3.25 mg/kg PO q 48 h) is now considered higher than clinically appropriate (2.5-2.75 mg/kg q 48 h or 3 times per week). Although these are exciting new drugs and administered orally, the potential for adverse effects is as real with this class of drugs as with other chemotherapeutics. Scheduled monitoring, dosage adjustments, and supportive care are equally important.

Tumor resistance to individual chemotherapy drugs is common even before treatment is started. Further, tumor cells acquire resistance rapidly after drug exposure because of their high mutation rate. Combination chemotherapy may overcome some resistance problems by affecting different metabolic pathways in cells that are resistant to other drugs in the combination. Although combination chemotherapy could potentially be more toxic to normal cells, patterns of toxicity vary between drugs (Table 339-5). Judicious scheduling of chemotherapeutic agents so that their toxicities do not overlap can improve tumor cell kill without compounding toxicity.

Chemotherapy protocol design is complex and requires detailed knowledge of the drugs and their effects. Each drug included must be at least partially effective against the target tumor as a single agent. When drugs are given in combination on the same day, it may be necessary to reduce the dosage of each individual drug to achieve higher total dose intensity (see to follow); however, care must be taken not to reduce the dosage of a highly effective drug to allow administration of a second, less effective drug. The drugs are then scheduled, taking into account both the mechanism of action and the toxicity profile of each, to expose the tumor to the highest possible number of agents and maximize dose intensity while minimizing toxicoses. The safest and most effective protocols are designed by veterinary oncologists.

To reduce the development of drug resistance, it is important not to administer drugs at subtherapeutic dosages; the highest dose intensity possible should be delivered. It is also important not to modify the planned doses or schedule in anticipation of toxicosis that has not occurred. For example, a dog that became neutropenic after receiving doxorubicin is not at increased risk for myelosuppression from other chemotherapeutics such as cyclophosphamide, so doses of other drugs should only be reduced if they cause toxicosis. Supportive care such as preventative antiemesis also reduces need for chemotherapy dose reductions. On the other hand, if tumor growth occurs, it is not good practice to continue the same treatment protocol at the same dosages. Instead, an alternative regimen of non–cross-resistant but effective drugs should be used.

TABLE 339-5

Myelosuppressive Potential of Some Commonly Used Chemotherapeutic Agents

HIGHLY MYELOSUPPRESSIVE	MODERATELY MYELOSUPPRESSIVE	MILDLY MYELOSUPPRESSIVE
Doxorubicin Lomustine (CCNU) Cyclophosphamide Carboplatin Vinblastine Mitoxantrone Vinorelbine	Vincristine (0.75 mg/m^2)* Chlorambucil Melphalan Methotrexate Cisplatin Hydroxyurea 5-Fluorouracil	Corticosteroids L-asparaginase* Vincristine (0.5 mg/m^2)* Bleomycin Streptozotocin

*However, the combination of vincristine and L-asparaginase can be highly myelosuppressive.

Chemotherapy Drug Choices

Published data on tumor sensitivity to chemotherapy are changing rapidly. Although good published data are available on dogs with the most common diseases, information on other malignancies often is unavailable or is based on small case series. In contrast, for rare tumors that uncommonly metastasize, it is difficult to demonstrate adjuvant efficacy for any chemotherapy. Even when studies are completed, publication may be delayed; and the best resources for veterinarians are veterinary oncologists, the Veterinary Cancer Society (www.vetcancersociety.org), and Internet literature databases, such as Medline or PubMed.

In addition to efficacy, and possibly more important, the final choice of a drug (or protocol) depends on

toxicities, an owner's tolerance for side effects, the treatment goals, the cost, and the veterinarian's level of comfort in delivering chemotherapy and supportive care.

Timing of Chemotherapy

Although it is tempting to think of chemotherapy protocols as a "recipe" for treating cancer, in fact they should be considered as a guide. Veterinary chemotherapy protocols are often simple, consisting of one or two chemotherapy agents given at an interval that minimizes the risk of toxicosis but maintains the highest possible dose intensity. However, lymphoma protocols are often complex, with many agents scheduled in combination (see ch. 344).

Chemotherapy Dosing

Because their desired effect is cytotoxicity, many chemotherapy drugs have narrow therapeutic margins; that is, the toxic dosage is close to the effective dosage. Therefore, it is important to be as accurate as possible when calculating doses. For some drugs, dosing is based on "metabolic body size" (body surface area [BSA, m^2]) rather than weight. Although imperfect, this is based on the generalization that smaller animals have a higher metabolic rate and therefore should receive a higher dose on a body weight basis. For some drugs (e.g., doxorubicin) dosing based on BSA is imperfect, and small dogs and cats should be dosed at lower rate than larger dogs. Until further guidelines are available, veterinarians should check the dosing basis for any drug to be used and use a BSA conversion table when metabolic dosing is indicated.

In human oncology, dosing may be tailored to the individual either by monitoring drug levels or based on patient characteristics. For example, the appropriate dose of carboplatin can be calculated from a formula based on the patient's glomerular filtration rate (GFR) and the desired area under the curve (AUC). This type of calculation is not usually done in veterinary oncology; however, similar principles are recognized: in patients with reduced GFR (increased serum creatinine concentrations) carboplatin dosing should be reduced.

Evidence in both human and veterinary oncology suggests that optimal dose intensity improves the outcome for patients treated with chemotherapy. Dose intensity is defined as mg/m^2 of drug per week of therapy and can be modified by adjusting the dosage, the intertreatment interval, or both.

Route of Administration

Most chemotherapeutic agents are delivered either intravenously (IV) or orally (PO). Less commonly, they are given subcutaneously (SC) or intramuscularly (IM). Other modes of administration are sometimes used. For most intravenous chemotherapy administrations, injection through a peripherally located over-the-needle catheter is safest, reducing the risk of extravasation even when a small volume is to be administered. For longer infusions (more than 30 minutes), a through-the-needle catheter is less likely to become dislodged.

When long infusions are required, either for timed drug delivery (such as gemcitabine) or for the saline diuresis that accompanies nephrotoxic drugs (such as cisplatin or streptozocin), an infusion pump is recommended to ensure continued diuresis and/or even delivery of the drug dose. Changes in either of these factors could affect efficacy and the risk of toxicosis.

Vascular access may become a problem in small dogs and cats receiving chemotherapy. Because the risk of extravasation is greater in these animals, a subcutaneous implantable vascular access port may ease timely drug delivery and reduce stress during administration of chemotherapy. Such a port may be maintained for the duration of therapy and then removed. The implantable vascular access port must be placed surgically, in a similar manner to a tunneled catheter, with a subcutaneous pocket for positioning of the port. Ports for veterinary use are available from Norfolk Vet Products, Skokie, Illinois (www.norfolkvetproducts.com).

Most oral medications are administered as tablets or capsules. Tablet formulations should not be split for personnel safety reasons, and because distribution of the drug may not be uniform throughout the tablet, or the tablet may be enteric coated (e.g., chlorambucil). For small animals, reformulation of oral medications into smaller capsule sizes by a reputable compounding pharmacy specially equipped for handling cytotoxics can be considered.

Cisplatin and carboplatin can be delivered to dogs as an intracavitary infusion into the pleural, pericardial, or peritoneal cavities; or intravesicularly (into the urinary bladder) for bladder tumors.

Intralesional chemotherapy usually involves suspension of a chemotherapeutic agent in a vehicle. The use of cisplatin, bleomycin or 5-fluorouracil in sterile sesame oil or bovine collagen matrix has been reported. The mixture is injected into a tumor, creating high drug exposure to tumor cells. This involves minimal systemic

drug levels, avoiding the risk of systemic toxicosis. Intralesional chemotherapy is used to treat only small, easily accessible tumors. In this method, great care must be taken to avoid exposure of personnel, because spillage occurs easily and drug may leak from the injection sites.

Topical administration is available (5-fluorouracil—dogs only) but is rarely used because of drug toxicity and risk of exposure to humans who either apply the medication or interact with the dog. Certain drugs can also be administered intraarterially or intrathecally for specific treatment protocols; however, this is rarely done in veterinary medicine.

Encapsulation in liposomes can reduce or alter the toxicity of some chemotherapy drugs. Conjugation of the liposome with polyethylene glycol reduces clearance by the reticuloendothelial system, producing "stealth" liposomes with greater circulating time. A liposome-encapsulated doxorubicin formulation has been reported to be less cardiotoxic in dogs and cats, but resulted in a new cutaneous toxicosis.

Metronomic Chemotherapy

Metronomic chemotherapy uses small doses of chemotherapy frequently (usually daily or every other day), in contrast to conventional chemotherapy which uses maximum tolerated doses at intervals of weeks. This administration schedule appears to result in a shift in the mechanism of action of the drugs from cytotoxic to antiangiogenic (mainly through targeting tumor endothelial cells) and immunomodulatory (mainly through inhibition of Tregs). Chemotherapy drugs chosen for metronomic use are usually oral, such as cyclophosphamide, chlorambucil and lomustine (CCNU). Most often, cyclooxygenase inhibitors are also included in combination to further increase the antiangiogenic and immunomodulatory effect. Metronomic chemotherapy has become popular in veterinary medicine because it is usually well tolerated, but its efficacy has not been well documented in most settings. Although the treatment is generally less costly in the short term compared to conventional chemotherapy, many animals will need the commercially available drug sizes reformulated for metronomic use and this can be costly. Additionally, metronomic chemotherapy is usually continued for a much longer time (up to years) so total costs can mount up over time.

Despite its popularity, most of the published literature on metronomic chemotherapy consists of relatively small retrospective studies, often in groups of dogs with mixed types of malignancies. Thus, data are difficult to interpret and promising preliminary results have yet to be followed by more conclusive evidence of efficacy in most settings. Occasional good tumor responses are seen, but the majority of the antitumor efficacy that has been reported consists of stable disease (however, it is fair to say that there are many situations in veterinary oncology where long-term stabilization of disease is indeed a significant clinical benefit).

Although metronomic chemotherapy is generally thought of as less toxic than conventional chemotherapy, there are still risks of toxicosis and careful monitoring is still important. Metronomic cyclophosphamide poses a real risk of urothelial toxicosis, just as conventionally dosed cyclophosphamide does; the authors find that administering furosemide with each dose of cyclophosphamide reduces this risk substantially although we still see it occasionally and we still monitor carefully for microscopic hematuria. Metronomic lomustine was reported to result in a 30% rate of discontinuation of therapy for toxicosis; therefore, this treatment approach should be used with caution. The nonsteroidal anti-inflammatory drug (NSAID) component of many metronomic protocols obviously can also be associated with toxicosis as with any NSAID (see ch. 164). Metronomic cyclophosphamide also appears to be fairly safe in most cats, although again the published evidence is in a small, mixed group of cats with relatively short follow-up.

In the authors' opinion, long-term metronomic cyclophosphamide chemotherapy is probably the best chemotherapeutic option for incompletely resected soft tissue sarcomas where complete excision and/or radiation is not possible. Metronomic chemotherapy can also be considered in other settings where the pet's owners decline conventional chemotherapy, surgery and/or radiotherapy, where conventional therapy has been tried and failed, or as "maintenance" following adjuvant conventional chemotherapy for particularly high-risk tumors. However, until further evidence is available, the authors suggest that metronomic chemotherapy be considered investigational and not considered first-line therapy in most settings. Finally, client safety must be carefully considered when considering chronic use of alkylating agents at home and clients must be reminded regularly not to become complacent with safety procedures.

Chemoprotection

The administration of a second drug specifically to reduce the host organ toxicity of a chemotherapy drug is termed *chemoprotection.* Chemoprotectants in use in human and veterinary oncology include mesna and dexrazoxane. Mesna reduces the risk of cystitis associated with ifosfamide and cyclophosphamide by binding

toxic metabolites in the urine. Dexrazoxane protects against doxorubicin-associated chronic cardiotoxicosis and reduces severity of doxorubicin-associated extravasation injury when used soon thereafter.

Supporting Animals Undergoing Chemotherapy

Adverse effects of chemotherapy are discussed in detail in ch. 343. Before chemotherapy is administered, drug dosages and toxicities, as well as the administration schedule, must be reviewed with the owner. After treatment, the pet should be monitored at home for signs of toxicosis. An algorithm for interpretation of post-chemotherapy neutrophil counts is found in Figure 339-1.

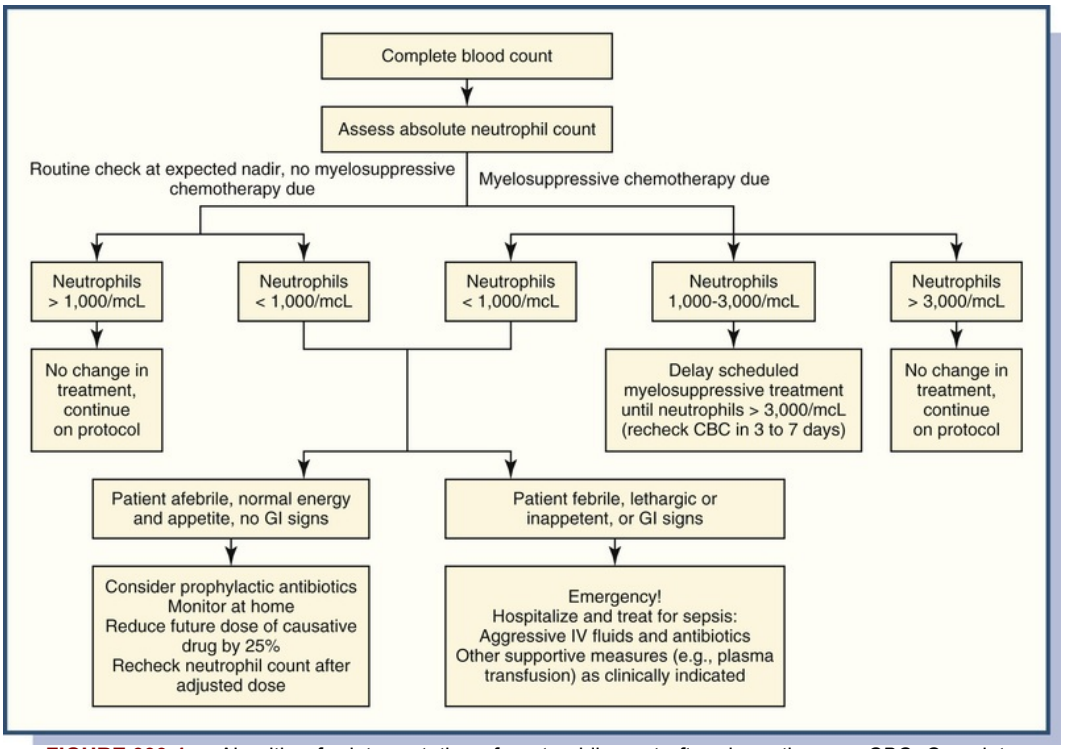


FIGURE 339-1 Algorithm for interpretation of neutrophil count after chemotherapy. *CBC*, Complete blood count; *GI*, gastrointestinal.

In order that pets maintain the highest quality of life, and that chemotherapy dosages be maintained at the highest level, the veterinarian should, whenever possible, use proactive supportive care to prevent or manage common toxicoses. Advances in the prevention and management of pain and nausea as well as organ-specific toxicoses such as cystitis will improve the veterinarian's ability to deliver adequate chemotherapy doses and provide high quality of life for pets with cancer.

Evaluating Treatment Response

To determine if a given treatment is effective, it is necessary to evaluate treatment response regularly. This is important to avoid unneeded expense, toxicosis and tumor progression that result from continuing to administer an ineffective drug. Clinicians can refer to Veterinary Cooperative Oncology Group criteria for measurement of both solid tumors and lymph nodes. The response to treatment can then be categorized as clinical remission/complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). In the literature, *overall response rate (ORR)* refers to CR and PR combined. (Another term used in more recent literature, *clinical benefit*, refers to CR, PR and SD combined; while there are many clinical settings where SD is certainly beneficial, care needs to be taken when reading reports of treatment trials not to compare ORR to clinical benefit, as they are not equivalent).

Chemotherapy Drug Resistance

Resistance to chemotherapy may be either inherent or acquired. Drugs may be physically unable to reach tumors that are in sanctuary sites such as the central nervous system or that are poorly perfused. Tumor cells may inherently lack receptors for a drug or not be susceptible to the mechanism in some other way (e.g., cells that have asparagine synthetase will be resistant to L-asparaginase). Tumor cells may develop drug resistance spontaneously through mutation. With each cell division comes the risk of a resistance mutation; therefore the larger a tumor is (i.e., the more cell divisions it has undergone), the higher the likelihood that resistance will occur. Tumor cells can also develop drug resistance specifically. Exposure to sublethal drug concentrations can result in gene amplification of detoxifying proteins.

Although combination chemotherapy may circumvent individual drug resistance, it does not avoid the problem of cross-resistance to multiple unrelated chemotherapy drugs. The transmembrane pump protein (P-glycoprotein) is present at increased levels in some tumor cells, and both the level and prevalence increase with exposure to chemotherapy. This phenomenon of multiple drug resistance (MDR) occurs between anthracyclines, mitotic inhibitors, and others. However, alkylating agents are not substrates for the P-glycoprotein pump, and so they become the mainstay of treatment in patients that have this type of drug resistance.

Safe Chemotherapy Drug Handling

Most chemotherapeutic agents are both toxic and mutagenic. Because most are effective in the active phases of the cell cycle, toxicosis from chemotherapy is most common in tissues that are renewing and is usually related to drug dose. This has implications for the patient (toxicity and efficacy), as well as pet owner and veterinary staff safety in handling the drugs during administration and patient care. Precautions should be taken when handling chemotherapy drugs during any phase of preparation, administration and disposal of drugs or waste. Alkylating agents have been associated with the highest risks to handlers. Organ damage and increased risk of fetal loss have been reported in persons handling and administering chemotherapy with inadequate attention to personal safety.

The proper administration of chemotherapy has been covered in great detail by many authors. In brief, the regulations set by the U.S. Occupational Safety and Health Administration (OSHA) should be followed, and pet owners as well as all personnel coming in contact with chemotherapeutic agents should be protected to the best of the veterinarian's abilities. Some countries, and states, now have specific legislation for administering chemotherapy in veterinary practice. It is advisable to contact the relevant authority before making a treatment plan. A chemotherapy logbook, which includes identification of animals treated and the personnel involved in the treatments, should be maintained to track exposures. Information contained in the Material Data Safety Sheet (MSDS) for each drug covers specific health hazards, including carcinogenicity, primary routes of exposure, protective equipment, treatment of personnel acutely exposed, chemical activators, solubility, stability, volatility, and specific procedures to be undertaken in case of a spill. The MSDS should be requested with the initial shipment of any chemotherapeutic agent and should be kept on file in an easily accessible location. A spill kit (commercially available) should be maintained.

Ideally a vertical laminar flow biological safety cabinet should be used to prepare all chemotherapy drugs. Closed system drug delivery devices such as Equashield and PhaSeal (Video 339-1) are now available in small quantities suitable for veterinary practices and should be routinely used in handling cytotoxic drugs. All these items are usually available through distributors of chemotherapeutic agents. During parenteral administration, Luer-Lok syringes decrease the risk of drug leakage or spills. Chemotherapy vials should be stored in zip style bags, and if syringes containing chemotherapy are carried around the hospital they should be carried in zip style bags.

Risks to Pet Owners

A pet owner information sheet on chemotherapy safety should be provided. If owners are administering drugs orally at home, gloves and waste (zip style) bag should be provided. However, the primary concern is for people who are handling the drugs (mixing and administering), with less risk to those handling the feces and urine in hospital and at home.

Clear safety guidelines for pet owners handling bodily fluids of chemotherapy patients are still not entirely clear, and tend to err on the conservative side. A period of 24 to 72 hours is therefore a “best guess” as being beyond the major excretion of metabolites from a bolus injection. Drug and metabolite excretion in bodily fluids should be treated with respect but not panic. Most pet owners avoid contact with their pet's urine and feces as part of routine hygiene anyway; however, accidental one-time contact is no cause for alarm if

followed by normal washing. For drugs that are excreted in the urine, the pet should be encouraged to urinate on soil where urine will drain quickly, and any urine in other areas should be handled and disposed of as chemotherapy. Pregnant pet owners should consult their obstetrician before making a decision about having contact with their pet on chemotherapy, and should not handle any chemotherapeutic agents.

Suggested Readings

Nguyen SM, Thamm DH, Vail DM, et al. Response evaluation criteria for solid tumours in dogs (v1.0): a Veterinary Cooperative Oncology Group (VCOG) consensus document. *Vet Comp Oncol*. 2015;13(3):176–183.

Vail DM, Michels GM, Khanna C, et al. Response evaluation criteria for peripheral nodal lymphoma in dogs (v1.0)–a Veterinary Cooperative Oncology Group (VCOG) consensus document. *Vet Comp Oncol*. 2010;8(1):28–37.

CHAPTER 340

Principles and Practice of Radiation Oncology

Jessica Lawrence

Client Information Sheet: Radiation Therapy for Pets with Cancer

Introduction

Overview

Cancer is the leading natural cause of death in cats and dogs and its prevalence may be increasing.[1-3] *Cancer* is an umbrella term encompassing many diseases with various biological behaviors, standards of care and prognoses. Veterinarians are encouraged to be knowledgeable resources for clients and their pets. Radiation therapy began in the 19th century, following Roentgen's description of x-rays in 1895 and the discovery of radium by Marie and Pierre Curie in 1898.[4-6] *Radiation oncology* refers to the medical use of ionizing radiation as an integral part of cancer treatment by killing or controlling malignant cells. Radiation therapy is available in many facilities, both public and private.[7-9]

The primary purpose of radiation therapy is to provide local and/or loco-regional tumor control, although half body or total body irradiation is occasionally prescribed. Depending on the clinical situation, the primary intent of treatment is either palliative or definitive (potentially curative) and is commonly used in conjunction with surgery and/or systemic therapy. One of the most important challenges during radiation treatment is to target tumor tissue with tumoricidal doses while sparing normal tissue. Most of the advances in radiation oncology, including intensity modulated radiation therapy (IMRT), stereotactic radiation therapy (SRT), stereotactic radiosurgery (SRS), and image-guided radiation therapy (IGRT), focus on improving the ability to localize the tumor target, administer precisely aligned radiation beams, and spare normal structures to improve overall tolerability and outcome (Box 340-1). The two potential goals of radiation therapy include definitive intent ("curative" intent) radiation therapy and palliative radiation therapy. The aim of definitive intent radiation therapy is long-term control (sometimes cure) of a tumor. The aim of palliative intent radiation therapy is to ameliorate specific symptoms caused by a tumor (such as bleeding or pain) (Box 340-2).

Box 340-1

Common Radiation Terminology

Radiation terminology can be confusing and some terms inaccurately used as synonyms. Common terminology and abbreviations are provided below to improve the reader's understanding of commonly used terms.

- **Dose**—amount of radiation absorbed by the patient (Gray = Gy = 1 Joule/kg; the older term "rad" is not utilized).
- **Fraction**—individual administration of radiation.
- **Fractionation**—radiation dose is divided into fractions over the course of several days to weeks depending on the intent of treatment.
- **Radiation prescription**—particular dose and number of fractions prescribed to a tumor for a patient.
- **External beam radiation**—radiation delivered from outside the body by a machine that focuses high-energy photons at a tumor.
- **3-D Conformal radiation therapy (3D-CRT)**—conformal radiation therapy that is image-based and

improves radiation dose distribution across the tumor volume, which can limit the normal tissue involved.

- **Intensity-modulated radiation therapy (IMRT)**—improved radiation planning and delivery in which the intensity of the radiation beams aimed at the target volume vary over the treatment in order to improve conformity of the radiation dose distribution to tumor with a rapid fall-off in radiation dose to adjacent normal structures.
- **Image-guided radiation therapy (IGRT)**—imaging that occurs immediately prior to or during treatment in order to detect errors in patient and tumor positioning. IGRT provides a level of quality assurance, verifying that radiation beams will be precisely directed to the tumor volume.
- **Stereotactic radiosurgery (SRS)**—a single treatment involving a large fraction size (15-20 Gy), usually used to treat small well-delineated tumors.
- **Stereotactic radiation therapy (SRT)**—a small number of treatments (3-8) involving a large fraction size (10-20 Gy) used to treat small well-defined lesions.
- **Plesiotherapy**—"surface" radiation with limited penetration (2-3 mm), usually delivered by a strontium-90 (^{90}Sr) probe.
- **Brachytherapy**—short-distance radiation (commonly internal radiation), usually delivered through use of radioactive seeds.

Box 340-2

Radiation Therapy (RT) Protocol Summary

Definitive Intent RT Protocols

- Generally large number of fractions
- Low dose/fraction
- Expect acute side effects
- Generally more expensive
- Intent is to achieve long-term control ("curative") while limiting late toxicity
- Low risk of clinically significant late toxicity

Palliative Intent RT Protocols

- Smaller number of fractions
- High dose/fraction
- Few acute side effects
- Generally moderate expense to owner
- Intent is to improve quality of life (improve function, decreasing pain or bleeding)
- Higher risk of clinically significant late toxicity

Stereotactic RT Protocols

- Smaller number of fractions
- High dose/fraction but overall tumoricidal dose
- Decreased acute toxicity due to minimal normal tissue in the high dose region
- Reliant on image-guided positioning verification
- Expensive
- Intent may be palliation or long-term control while limiting normal tissue toxicity
- Clinical outcome data in dogs and cats are pending

General Considerations When Choosing Veterinary Patients for Radiation Therapy

Candidacy

Dogs and cats (and occasionally other species) should be evaluated carefully to ensure that they are good candidates for radiation treatment. Once the tumor type, biological behavior and extent of disease are known, the role of radiation therapy can be determined. Radiation therapy alone or in combination with surgery may be appropriate for managing patients with local or loco-regional disease. Adjuvant chemotherapy may be administered concurrent with radiation, depending on tumor type. Prospective planning is best approached as involving a team that includes the primary clinician, surgeon, medical oncologist, radiation oncologist and the owner. These are the decision makers in determining an optimal approach to managing a tumor. A viable treatment plan for one patient may not be suitable for another, even with a similar tumor.

Staging

Staging, determining the cancer's extent, is important to understand if localized disease is present when considering definitive intent radiation therapy. Diagnostic tests typically relate to the primary tumor type and may include complete blood count (CBC), biochemical profile, urinalysis, aspiration cytology of regional lymph nodes, thoracic and/or abdominal imaging, and advanced imaging. Computed tomography (CT) is one of the most useful tools for imaging tumors and is critical for computer-assisted radiation treatment planning. Magnetic resonance imaging (MRI) may be used for planning in some situations. Advanced imaging can allow initial subjective assessments regarding extent of disease, proximity of critical tissues near or in a potential treatment field, and which therapeutic options are reasonable and applicable. CT and/or MRI may not be indicated prior to radiation therapy if results will not change the therapy.

Client Education

With clients included on the team of decision makers, they should understand expense, frequency and anticipated duration of treatments. They should also be made aware of probability of adverse events and the projected outcomes. Radiation oncologists are able to define several aspects of radiation treatment, namely: (1) the indication for radiation therapy based on existing veterinary literature, (2) the goal of radiation therapy, (3) the target of radiation therapy (usually a localized disease pre- or postsurgery), (4) the type or technique of radiation treatment, (5) the planned dose and schedule of the radiation protocol, and (6) expected acute and late adverse events.

Basic Principles of Radiation Physics

See E-Box 340-3.

E-Box 340-3

Basic Principles of Radiation Physics

Overview and Radiation Sources

Radiation physics describes the manner in which radiation interacts with matter in order to induce an effect. Electromagnetic radiation can be considered moving packets of energy, or photons.[6] The amount of energy in each photon defines its position within the electromagnetic spectrum; for example, x-rays and gamma-rays contain more energy than ultraviolet (UV) light photons and are therefore at the higher end of the spectrum. Sufficiently energetic x-ray or gamma-ray photons may completely displace an electron from its orbit surrounding an atom when they interact with matter. All matter is composed of atoms and although the model of an atom has been updated, the simple Bohr model of an atom is sufficient for understanding the interactions of photons and atoms. An atom consists of a nucleus with one or more protons and neutrons held together by strong intranuclear forces, forming the positive charge of the atom, surrounded by a cloud of electrons held in place by electrostatic forces, which forms the negative charge.

How Does Radiation Interact with Tissue?

Radiation interacts with biological material by removing an orbiting electron, a process termed *ionization*.[10] External beam radiation uses a source of photons for therapy derived from either radioactive decay (^{60}Cobalt) or from man-made devices (linear accelerator) that create photons from fast electron streams striking a target. Ionizing radiation consists of both x-rays and gamma-rays: gamma-rays occur from radioactive decay while linear accelerators generate x-rays. Ionization events occur as photons and

particles travel through tissue and deposit their energy. The *gray* (Gy) is the term applied to the radiation dose that describes the quantity of energy deposited per mass of tissue, where 1 Gy is equal to 1 joule (J) of energy deposited per kilogram of tissue. The *centigray* (cGy) is often used to describe individual doses (fractions) of radiation (100 cGy = 1 Gy). The *rad* is a historical term used to describe radiation dose (1 rad = 1 cGy) and may appear in older radiation texts or journal articles.

A *photon* is any wave of energy traveling through space at the speed of light; the energy of the photon dictates its type of physical interaction with tissue. Low-energy photons used for diagnostic purposes are absorbed differentially in tissue, proportional to the cube power of the tissue's atomic number (density). This photoelectric effect results in densities typical of fat, soft tissues, and bone seen on diagnostic radiographs. The high-energy photons used for therapeutic purposes have physical interactions with tissue that occur predominantly via Compton scattering, related to tissue electron density. It minimizes differential absorption, providing uniform radiation dose deposition across a variety of tissues. With Compton scattering, photons interact with loosely bound electrons, giving their energy to the atom. Electrons are then ejected from the atom along with a second photon emitted in a different direction; both the electron and secondary photon can interact with additional tissue. Electrons are responsible for the effects of radiation as they can directly or indirectly damage biologic targets critical for cell survival.

Current Sources and Their Application

Ionizing radiation can be used to treat cancer. Radiation can be delivered by external beam units (linear accelerators, ^{60}Cobalt teletherapy, orthovoltage, charged particle accelerators) or by brachytherapy (^{125}Iodine, ^{192}Iridium, ^{103}Palladium). Low-energy x-ray beams in the range of 50-250 kiloelectron volts (KeV) deposit energy at or just below the skin surface. High-energy x-ray beams (>1 million electron volts or MeV) are less attenuated by the skin surface and deposit most of their energy at a greater depth in the body; thus, they are “skin sparing” energies. Charged particles such as electrons, protons, and heavy particles (carbon or argon ions) can be used for radiation therapy. Electron beams are used to treat tissues or tumors that require a uniform dose distribution from skin surface to a limited superficial depth. Particle beams such as protons are used for high-precision dose delivery at a particular depth in the body but are not commonly used in veterinary radiation oncology.

Medical radiation physics plays an integral role in the discipline of clinical radiation oncology, beyond identification and characterization of radiation dose and tissue distribution. It is also used for improving radiation therapy machines, development of three-dimensional (3D) treatment planning for identification of tumor target volumes, normal tissue dose, development of intensity-modulation and image-guided radiation therapies (IMRT, IGRT), particle therapy, improvement in immobilization techniques for improved reproducibility of treatment, and advancements in brachytherapy and hyperthermia.[5] All of these radiation physics developments have focused on improving radiation dose distribution across tumor volumes while decreasing normal tissue toxicity, which theoretically should improve local tumor control.

Radiation Therapy Machines

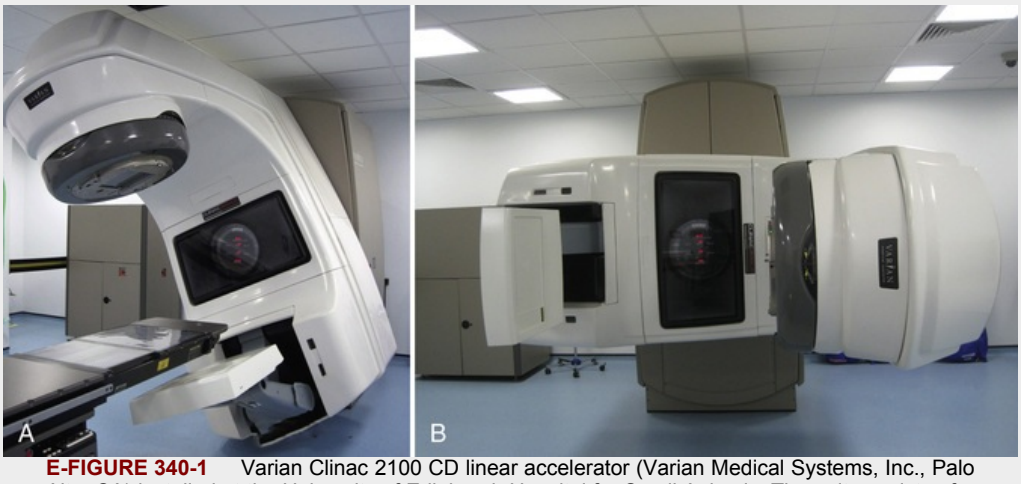
Ionizing radiation can be administered from different sources (external beam radiation therapy or teletherapy), through radioactive isotopes placed interstitially (brachytherapy), by surface therapy (plesiotherapy) or by systemic or intracavitary injection of radio-isotopes (^{131}Iodine or ^{153}Samarium). The most common form used in veterinary medicine is external beam radiation therapy. External beam units vary widely. Megavoltage external beam is most common, while orthovoltage units are used for certain conditions.

Orthovoltage machines produce lower energy (150-300 keV) x-rays and are considered relatively superficial in dose distribution. Its maximum energy is deposited at the surface of the skin with little penetration. There will be more attenuation by bone than soft tissue. Limited beam-modifiers can be used to attenuate or increase dose, such as wedges or blocks to limit normal tissue toxicity. Acute side effects with orthovoltage are often quite robust and late radiation effects administered to bone and skin may be dose-limiting.[11] Generally, orthovoltage therapy should be limited to small superficial tumors.

Megavoltage radiation has higher energy (>1 MeV), provides more uniform dose deposition within tissues, and has some skin-sparing properties. Because megavoltage machines require a specific depth of tissue (0.5 cm to 2.0 cm) to build the maximum dose, tissue-equivalent material (bolus) may be needed if the skin needs to be included in the treatment field. ^{60}Cobalt teletherapy units produce gamma-rays through radioactive decay to Nickel that have an average energy of 1.25 MeV. A ^{60}Cobalt source

measures approximately 2-3 cm so there is relatively large *penumbra* of treatment fields; the penumbra refers to the edges of the field where there is rapid dose fall-off. Because the energy produced by cobalt units is relatively low, there is only 0.5 cm of skin sparing; however, it is difficult to treat deep-seated tumors. One major disadvantage of ^{60}Cobalt teletherapy is that the radiation source is constantly decaying. This permits stable mechanics, but dose output constantly decreases and must be replaced every 5 years to avoid longer treatment times.

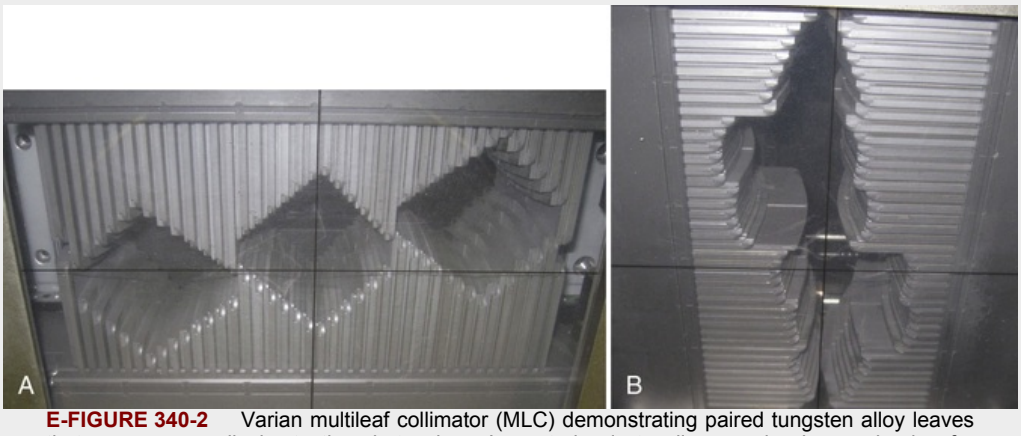
Linear accelerators are designed with various energy capabilities and produce x-rays ranging from 4-25 MeV in peak photon energies. In contrast to ^{60}Cobalt units, most linear accelerators have a high radiation output, and output can be manipulated manually if treatments need to be administered quickly. There is an even larger source-skin distance (100 cm versus 80 cm) so larger treatment fields can be used, and it affords the radiation technician more leniency when rotating the gantry (the head of the machine) around the patient. Linear accelerators have a small focal point, thus penumbra is small at the treatment field. As they are also megavoltage machines, linear accelerator degree of skin-sparing depends on the energy of the photons derived (approximately 1.5 cm for a 6 MeV photon beam). The depth of skin sparing increases with increasing photon energy. Field modifiers such as blocks, wedges, and beam spoilers may be used with both ^{60}Cobalt units and linear accelerators to improve dose distribution within the target region and reduce dose to normal tissues. Additionally, both are isocentric machines, meaning that the gantry head is capable of rotating 360 degrees around the patient to reduce patient re-positioning error and allow faster treatment delivery (E-Figure 340-1).



E-FIGURE 340-1 Varian Clinac 2100 CD linear accelerator (Varian Medical Systems, Inc., Palo Alto, CA) installed at the University of Edinburgh Hospital for Small Animals. The unit consists of a conventional multimodality linear accelerator with a retractable electronic portal imaging device (EPID) mounted perpendicular to the linear accelerator to permit assessment of patient positioning. **A,** Demonstrates the gantry head at 350 degrees to the table. **B,** Demonstrates the gantry head at 90 degrees.

Modern linear accelerators usually have multileaf collimators (MLCs), paired metal leaves that move in and out to create a desired field shape. They are ideal for complex and irregular treatment volumes (E-Figure 340-2). Although 3D conformal radiation therapy utilizes CT imaging to formulate a treatment plan, it does not always meet the needs of a particular shape unless a large number of beams are used and the target volume has a simple shape.[12,13] IMRT, by varying the MLC leaves during treatment, takes 3D conformal radiation therapy one step further by precisely shaping each beam or beamlet (subfields of each beam direction) to vary the photon fluence, therefore providing the optimal dose distribution for the radiation prescription.[12-14] Most current accelerators are also equipped with on-board imaging devices to aid with accurate patient positioning to ensure that a tumor is treated as indicated by the treatment plan. Imaging devices may vary from electronic portal imaging devices (EPIDs; see E-Figure 340-1) to mounted on-board kV CT units that allow precise registration (or image matching) of the patient's treatment position to the original optimal planning position. IGRT seeks to remove uncertainties associated with daily anatomical positioning by acquiring images of the patient immediately prior to beam delivery on the treatment machine. Images are then registered to the optimal position at planning and patient adjustments are made prior to treatment to verify the tumor position.[15-18] IGRT therefore

offers a level of quality assurance and verifies that radiation beams will be precisely directed to the target.



E-FIGURE 340-2 Varian multileaf collimator (MLC) demonstrating paired tungsten alloy leaves that move perpendicular to the photon beam's central axis to allow precise beam shaping for complex **(A)** and irregular **(B)** treatment volumes.

Many linear accelerators that are ≥6 MV are also capable of producing electrons that can be captured and used for therapy. Electrons are ideal for treating superficial tumors since they have rapid fall-off in dose with increasing depth of tissue. Electron therapy can spare critical structures deep to superficial lesions, such as an incompletely excised tumor located over the abdominal cavity. Various energy electron beams can be emitted, with the depth of tissue penetration dependent on electron energy. Because electrons scatter in air, an electron cone is used for collimation to the patient while a secondary cutout can be used to provide conformal treatment (E-Figure 340-3). Many superficial tumors in animals can be treated with electron therapy: incompletely excised soft tissue sarcoma, mast cell tumors, and injection site sarcomas.

E-FIGURE 340-3 Electron beam therapy is suitable for shallow tumors (<5 cm deep), such as tumors over the thoracic or abdominal wall. Electron cones are attached the head of the linear

accelerator and provide collimation to the animal's surface.

Biological Principles of Radiation Oncology

See E-Box 340-4.

E-Box 340-4

Biologic Principles of Radiation Oncology

Overview

High-energy photons collide with orbiting electrons of biologic molecules in tissue, which leads to the ejection of electrons. Ejected electrons can directly damage biologic targets in close proximity of the atom; more commonly, electrons interact with water, since cells are comprised of 80% water, to produce highly reactive free radicals that damage the target (indirect damage). Tumor cell DNA is classically considered to be the principal target of therapeutic photons, although damage to cell membranes and blood vessels may also contribute to tumor control.[4-6] Alternative methods of radiation-induced cellular damage involve disruption of cellular homeostasis through various means such as protein modification, induction of stress response that alters the tumor microenvironment, vascular damage (at high doses of radiation), abscopal effects (antitumor immunity that affects responses distant from the primary tumor treated with radiation), and alterations in signal transduction.[4,5] Cell survival following radiation has been correlated to the residual level of double strand breaks within DNA, thus giving credence to the notion that DNA is the principal target.[4] Other DNA damage produced by ionizing radiation includes single strand breaks, base damage, sugar damage, and cross-links between DNA-DNA or DNA-protein.[4-6]

Linear Energy Transfer and Relative Biological Effectiveness

Ionizing radiation deposits energy along a track, linear energy transfer (LET), that leads to DNA damage and subsequent cell killing. Photons and electrons are considered low LET radiation because as they interact with tissue, electrons are set in motion. Those electrons are easily deflected, creating convoluted tracks. Protons and neutrons are considered high LET radiation; they are heavier particles that are more resistant to deflection and have straighter tracks through tissue.[4,6] The relative biological effectiveness (RBE) of different types of radiation is dependent on the LET and models exist to help predict tumor cell response.[4,6,19] The RBE formula is represented by the ratio of the standard radiation dose (usually 250 kV x-rays or ^{60}Cobalt) to the dose of test radiation that produces the same biologic effect. For example, 1 Gy of photons creates the same biologic effect as 1 Gy of electrons; however, 1 Gy of protons causes substantially more biological damage than 1 Gy of photons as the LET is much higher.

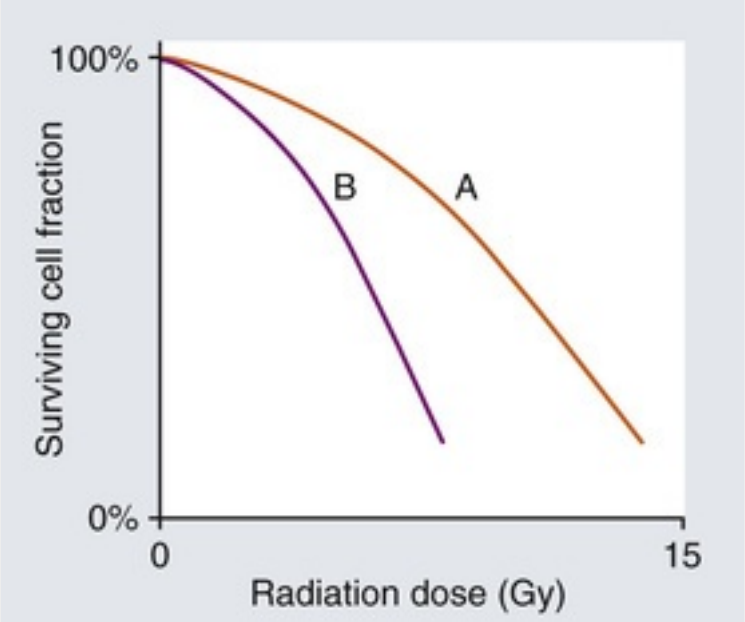
Energy deposited within tissue occurs randomly due to the nature of ionizing radiation interactions. Most ionization events do not cause DNA damage.[4,6,20,21] In most circumstances, large doses of low LET radiation (10-100 Gy) are required to significantly impact tumor cell growth and survival.[20,22] It has been estimated that approximately 10^5 ionizations can occur within the cell per Gy of absorbed low LET radiation dose, leading to approximately 1000 cross-links and base damages, 500-1000 single strand DNA breaks, and 25-50 double strand DNA breaks.[20] High LET radiation increases the number and severity of DNA lesions, which are more difficult for the cell to repair.[4]

Radiation Effects

Background

Inhibition of the continued reproductive ability of tumor cells is an important sequela of radiation treatment. Most cellular death following exposure to ionizing radiation results from chromosomal aberrations that ultimately leads to mitotic death or terminal growth arrest (similar to senescence), although lethally damaged cells may undergo senescence or interphase death (lymphocytes).[4] Many cells therefore do not demonstrate morphological evidence of radiation damage until cell division, at which time evidence of either apoptosis or necrosis may be present. The extent to which one mechanism of cell

death occurs versus another is dependent on cell type, radiation dose and the tumor microenvironment.[6] Cell survival following radiation is often described by the cell survival curve, which is an illustration of the relationship between radiation dose and cell kill (E-Figure 340-4). Radiation induces logarithmic cell kill, in which the probability of a critical target being damaged is proportional to dose. For example, a standard cell survival curve often demonstrates that a dose of 2 Gy kills approximately 50% of cells within a tumor. In a simplistic model where factors that increase or decrease cell kill are not included, the math suggests that a small tumor measuring 1 cm in diameter (containing 10^9 cells) will have 5×10^8 cells remaining after the first fraction and after 20 fractions of 2 Gy (40 Gy), 953 tumor cells would remain.[5] Radiation is therefore generally more effective on microscopic disease compared to macroscopic tumors, although there are exceptions depending on the intrinsic cell radiosensitivity (lymphoma). As most cells sustain mitotic or reproductive damage, measurable tumors often do not respond immediately but rather shrink after several weeks or months. For example, canine thyroid tumors treated with variable radiation therapy prescriptions have a time to maximal tumor reduction that varies from 6-24 months.[23-25]



E-FIGURE 340-4 A schematic of a cell survival curve following a single dose of radiation with low-LET radiation such as x-rays. Curve **A** has a wider shoulder region than curve **B,** suggesting that there is more reparable damage sustained by the cell population in **A** compared to the tumor population in **B.**

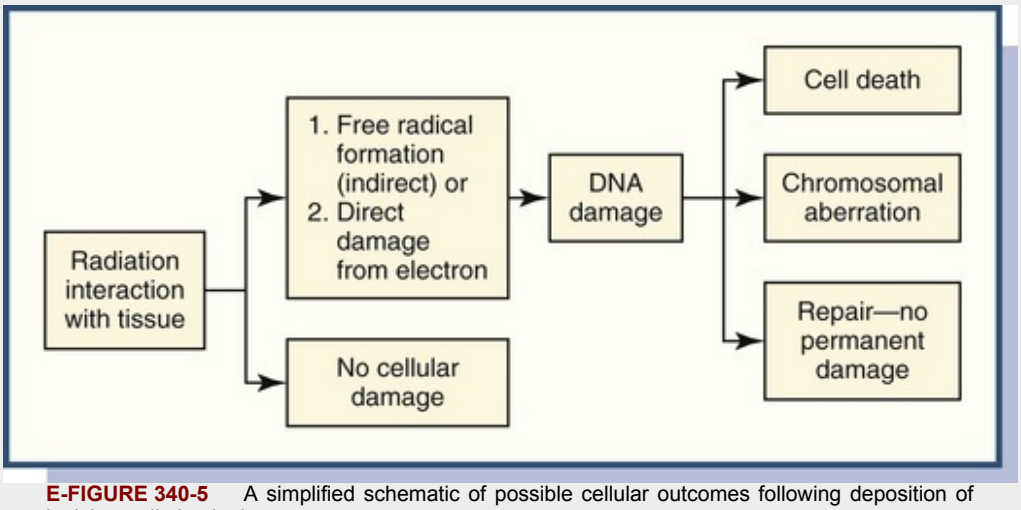
The "4 Rs"

Radiation biology is a subspecialty within radiation oncology. The focused is on tumor and normal tissue response to ionizing radiation to aid in developing safe and effective radiation protocols. The response of tumors (and normal tissue) to radiation has been predominantly characterized by factors that influence the ability of radiation to induce cell damage and each cell's ability to recover. Classically, the 4 "Rs" of radiobiology have been viewed as critical in determining the net response of tumors to radiation: repair, redistribution (reassortment), repopulation, and reoxygenation. Radiosensitivity has largely been incorporated as the fifth R as the intrinsic radiosensitivity of cells *in vitro* correlates to the responsiveness of tumors to radiation therapy in the clinic.[4,26-28] With the advent and increasing popularity of SRS and SRT, which involve one or a few large doses of radiation (8-30 Gy per fraction), respectively, researchers have re-evaluated the role of the 5 Rs of radiobiology. For most tumors, the concepts of the Rs still apply to SRS and SRT with the exception that antitumor immunity (abscopal effects) may be enhanced in some tumors by very large doses of radiation.[26,29]

Cellular Repair of Radiation Damage

Several consequences can occur within cells after DNA damage secondary to ionizing radiation. That damage is classified as lethal, sublethal, or potentially lethal, thus leading to a spectrum of tumor and

tissue responses from significant damage to no net cellular damage (E-Figure 340-5),[4,6] The repair of cellular damage between radiation doses is the major mechanism underlying observations that a larger total dose can be tolerated when the radiation dose is fractionated, or divided into smaller administrations, rather than administered all at once. The shoulder of a cell survival curve reflects the accumulation of sublethal damage that can be repaired if given adequate time (see E-Figure 340-4). Repair of sublethal damage increases cell survival before the subsequent fraction of radiation; this is important when normal tissue is within or near the radiation field. An increase in total dose to tumor is therefore required in order to provide the same degree of biological damage when a single dose of radiation is fractionated.[4] Most radiation damage is repaired within 6-24 hours of radiation administration. Double stranded DNA breaks appear to be the most challenging for repair as they are more likely to result in chromosomal or chromatid aberrations.[4,6,30,31] In mammalian cells, homologous recombination and non-homologous end joining both occur depending on the cell cycle phase.[4] Faulty repair of DNA strand breaks may lead to chromosomal aberrations which can result in cell lethality or in stable anomalies.[4,32,33]



E-FIGURE 340-5 A simplified schematic of possible cellular outcomes following deposition of ionizing radiation in tissue.

Redistribution and Cell Cycle Effects

Synthesis (S) is the cell cycle phase in which DNA synthesis occurs. The Gap 2 (G2) phase follows and mitosis (M) follows G2. Cells then enter the Gap 1 phase (G1) and can continue to S phase or enter a period in which cell division ceases (G0). The cell cycle phase at radiation influences inherent sensitivity or resistance to radiation. Cells within the late G1 to early S phase and G2 or M phases are most sensitive to radiation while cells in G1 and mid-late S phases are most resistant.[4] Cells that are not actively cycling (G0) tend to be more resistant. Cells that survive radiation tend to be synchronized in the more resistant phases of the cell cycle within a few hours; however, cells then cycle into more radiosensitive phases prior to the next fractionated dose of radiation.[4] Redistribution of cells into radiosensitive phases of the cell cycle is an important concept when considering concurrent chemotherapy treatment as drugs are typically chosen based on their ability to redistribute cells into G2 or M phase.

Repopulation

Following a dose of radiation, if surviving cells are given long intervals of time between treatments, the tumor population will increase due to replication. This process is termed *repopulation* and can affect cell survival in between fractions of radiation or over the course of a protocol. Accelerated repopulation may occur in some tumors, in which tumors appear to repopulate more rapidly than their initial growth rate.[4,30,34,35] Repopulation of tumor cells during a conventional course of fractionated radiation therapy is an important factor affecting the local control rate of rapidly growing tumors. This is the basis for the avoidance of treatment delays and for accelerated protocols in human oncology, where a prescribed radiation dose is "accelerated" and administered in a shorter period of time.

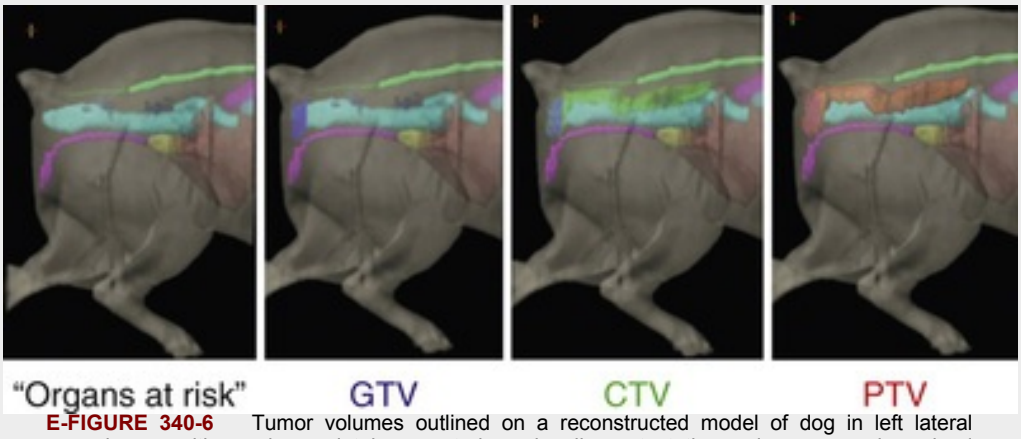
Reoxygenation

One of the most important influences the microenvironment has on tumor response to radiation is the presence or absence of oxygen at the time. Hypoxia is common in tumor tissues that grow rapidly, outgrow their blood supply, and cause abnormal angiogenesis. The biological effects of radiation on cells are enhanced by oxygen. Oxygen interacts with free radicals generated by radiation to "fix" DNA damage, resulting in damage that is very difficult to repair. For this effect, oxygen must be present at the time of radiation or within a few milliseconds.[4,33,36] Cells irradiated in the oxic conditions are approximately three times as sensitive as cells irradiated under hypoxic conditions. Chronic hypoxia, or diffusion-mediated hypoxia, develops due to the limited distance that oxygen can diffuse from a vessel before it is entirely consumed and represents a larger challenge than acute hypoxia, or transient and fluctuating hypoxia that results from intermittent tumor blood flow. Cells that are chronically hypoxic will reoxygenate only when their proximity to blood vessels increases; as tumors shrink with treatment, tumor oxygen levels increase. This is likely one of the most important advantages to fractionated radiation therapy.[26] Multiple strategies, including use of hypoxic cell sensitizers, hyperbaric oxygen, and erythropoietin, have attempted to improve oxygenation within tumor tissue. But, they have generally resulted in variable and minimal clinical improvement.[4,33,36-40]

Time, Dose, and Fractionation

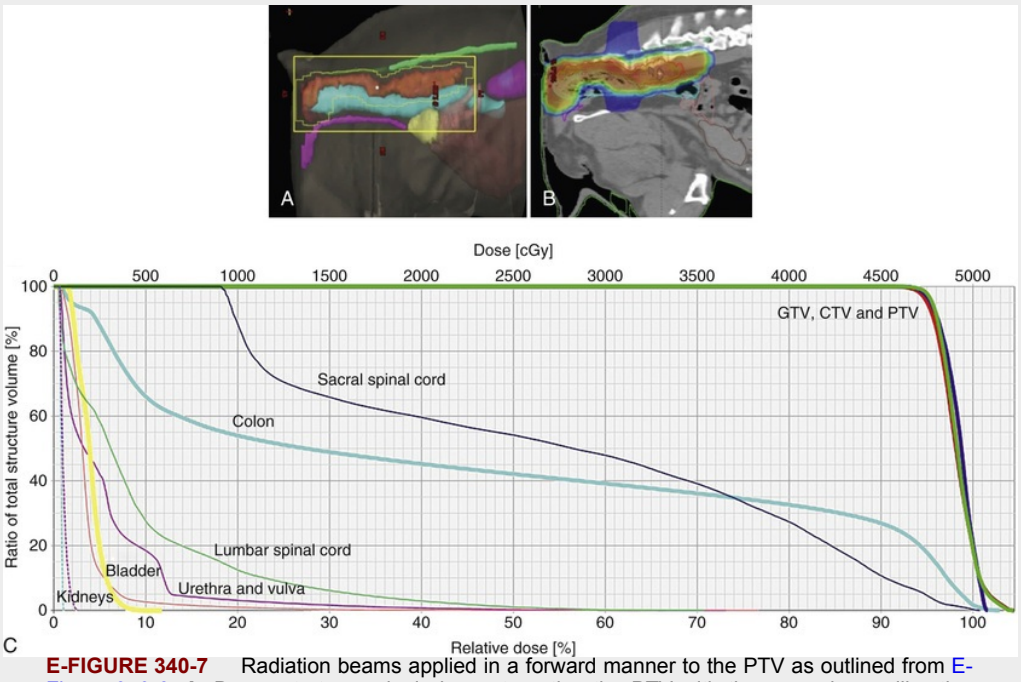
Factors that influence the effectiveness and tolerability of radiation include the overall dose of radiation prescribed, the dose given in each treatment fraction, and the time required for the protocol. Radiation oncologists recognized that higher total doses could be given to patients if the daily radiation dose was reduced into smaller fractions; this led to improved tumor response and decreased normal tissue damage. The primary goal of radiation therapy is to precisely target the tumor volume with tumoricidal doses of radiation while minimizing dose to surrounding normal structures. The overall dose and fractionation protocol is largely based on the particular tumor type and grade, adjacent normal tissue, the inherent radiosensitivity of the tumor cells, and clinical evidence (and sometimes clinical experience). Advanced imaging (often with CT alone but sometimes a registration of CT and MRI and/or positron emission tomography [PET]-CT) is commonly used for radiation treatment planning and aids in the delineation of tumor volumes and target structures for most non-extremity tumors.

Typically a radiation oncologist identifies and outlines three main tumor volumes as well as normal tissues (organs at risk [OAR]) within the data set used for planning. Tumor volumes include the gross tumor volume (GTV), the clinical target volume (CTV) that includes the GTV plus a margin to account for microscopic disease, and the planning target volume (PTV) that includes the CTV and an additional margin to account for intrinsic and extrinsic setup error (E-Figure 340-6). The radiation dose and fractionation protocol is typically prescribed to the PTV. Improved computerized treatment planning has improved ability to target tumor volume and reduce the radiation dose to normal structures (conformal radiation, E-Figure 340-7).



E-FIGURE 340-6 Tumor volumes outlined on a reconstructed model of dog in left lateral recumbency with an incompletely resected, regionally metastatic anal sac apocrine gland adenocarcinoma. Organs at risk outlined included the rectum (aqua), urethra and vulva (magenta), spleen (brown), spinal cord (green), bladder (yellow) and kidney (purple). The GTV represents the gross tumor volume, or visible tumor tissue; the CTV represents the clinical target volume that includes the GTV plus a margin to account for microscopic disease, and the PTV represents the planning target volume, which includes the CTV and a margin for intrafraction and interfraction motion. To illustrate the volumes, this dog's surgical scar was considered the GTV, while the CTV

included the GTV plus the visible draining sacral (hypogastric) and medial iliac lymph nodes. A standard margin of 3 mm was added to the CTV to create the PTV, to which radiation was prescribed.



E-FIGURE 340-7 Radiation beams applied in a forward manner to the PTV as outlined from E-Figure 340-6. **A,** Demonstrates a single beam targeting the PTV with the secondary collimation achieving conformation via the leaves of the multileaf collimator. **B,** Illustrates the dose in color wash, with the prescribed dose in orange. Lower radiation dose is represented by the cooler colors (green and blue). **C,** Illustrates a dose volume histogram, highlighting the high dose to the tumor volumes and lower dose to normal structures.

In veterinary medicine, current conventional prescriptions for definitive intent radiation therapy consists of 15-20 fractions of 2.5-4 Gy per fraction administered daily to total doses of 42-63 Gy.[8,9,30] Palliative intent radiation protocols vary but generally include higher doses per fraction (4-9 Gy) given less frequently to lower overall doses (20-32 Gy).[8,9] Fractionation was designed to exploit the Rs of radiobiology; specifically, to avoid repair and repopulation but allow reoxygenation and redistribution into sensitive phases of the cell cycle within tumor tissue over the treatment duration. Accelerated fractionation, hyperfractionation, and hypofractionation are altered schemes used in some definitive intent protocols to improve local control. The goal of accelerated fractionation is to complete radiation before tumor cells begin accelerated repopulation. The goal of hyperfractionation is to deliver smaller doses per fraction but a higher overall dose of radiation. Hyperfractionated protocols often include modest acceleration. Hypofractionation involves the administration of a larger dose per fraction but a smaller number of fractions; this is somewhat similar to a palliative protocol but with IGRT and SRT may provide good or superior tumor control for some tumor types.[33] SRT and SRS involve a small number of treatments (1-8) to a small but visible tumor target with rapid dose fall-off to adjacent structures. Both techniques require image guidance and verification to ensure proper patient and target position in order to acquire the advantage of having minimal normal tissue included in the high dose region. This allows a "conformal avoidance" approach in that ablative doses of radiation can be administered without significant concern for radiation damage to normal tissue.

Clinical Radiation Therapy

Practical Aspects of Veterinary Radiation Administration

When a veterinary patient undergoes radiation therapy, it is important that prospective planning develop an optimal therapy and determine a method for reproducible and verified patient positioning. In this manner,

radiation can be administered to the targeted tumor volume. Advanced treatment planning and administration, such as IGRT and SRT, rely on the patient being positioned properly for delivery of each radiation fraction. Decreasing margins of the PTV are successful if proper positioning is confirmed prior to each treatment.

Unlike in human radiation oncology, pets are anesthetized for treatment planning as well as for each radiation treatment in order to ensure reproducible and prolonged positioning for treatment. Most anesthesia protocols utilize rapid acting anesthetic agents to permit quick recovery. Typical radiation patients are anesthetized for 60-90 minutes for the first treatment, but only 10-15 minutes for subsequent treatments. Positioning devices, such as immobilization mattresses, face masks, bite blocks, and foam wedges, are often used to create a patient-specific setup position that can be replicated for each treatment (Figure 340-8). Not all tumors require extensive planning, but generally when normal structures are in close proximity to the target, 3D treatment planning (usually via CT for tissue density information) aids in reducing normal tissue toxicity. Tumors of the extremity, which are located away from critical tissues, rarely require 3D planning unless preoperative radiation therapy is performed or if there is concern about the postoperative tumor extent.

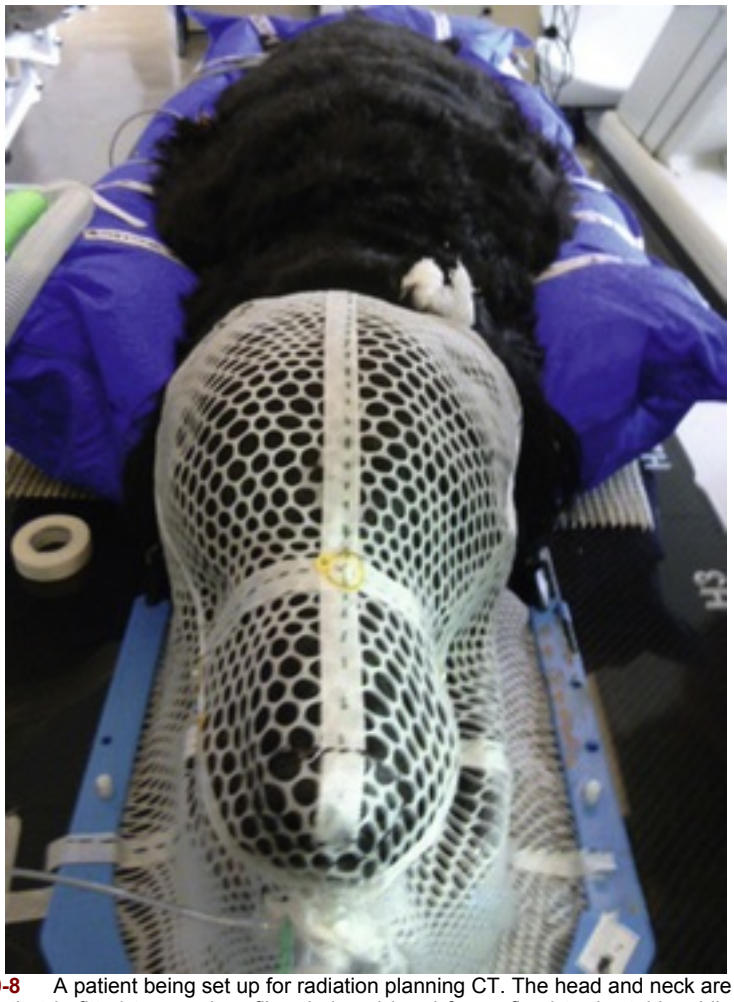


FIGURE 340-8 A patient being set up for radiation planning CT. The head and neck are resting on a plastic insert that is fitted to a carbon fiber–indexed head frame fixed to the table while the body is immobilized in a vacuum lock mattress. An acrylic face mask is used to conform to and secure the head to the head rest and frame. Laser alignment is used to aid in positioning between CT and radiation therapy.

Tissue Toxicities

Fractionating Therapy

There is often concern regarding radiation-induced toxicity within the treated volume. It is important that

thorough discussions take place among all involved prior to starting radiation therapy. Treatment toxicity depends on the fractionation schedule, time over which radiation occurs, and the type and volume of normal tissues within a radiation field. As radiation does not discriminate between cell types, both tumor and normal tissue react similarly. However, therapeutic radiation, fractionation and delivery technique employed attempt, in part, to exploit the difference in repair capabilities of normal and tumor tissues. Tumor cells typically have impaired repair mechanisms and an increased number of cells in the cell cycle by nature of their increased proliferative rates. Normal tissue in the radiation field is "dose-limiting" with respect to the maximum dose that can be safely administered. Dose per fraction, treatment schedule, and total dose affect normal tissue tolerance.

Tissue structure is important because fractionating radiation reduces toxicity to normal tissues and may improve the overall response of a tumor as compared with giving a small number of fractions but a high dose per fraction. Radiation administered once or twice a day allows normal cells to repair but does not provide enough time for repair of tumor cells. This allows cumulative damage to develop within the tumor exposed to repeated fractions.[4] The probability of tumor control is always weighted against the probability of complications. At lower doses of radiation, the probability of complications is low and provides a moderate chance of tumor control whereas increasing the dose gains a higher chance of tumor control but with a higher risk for normal tissue complications (Figure 340-9).

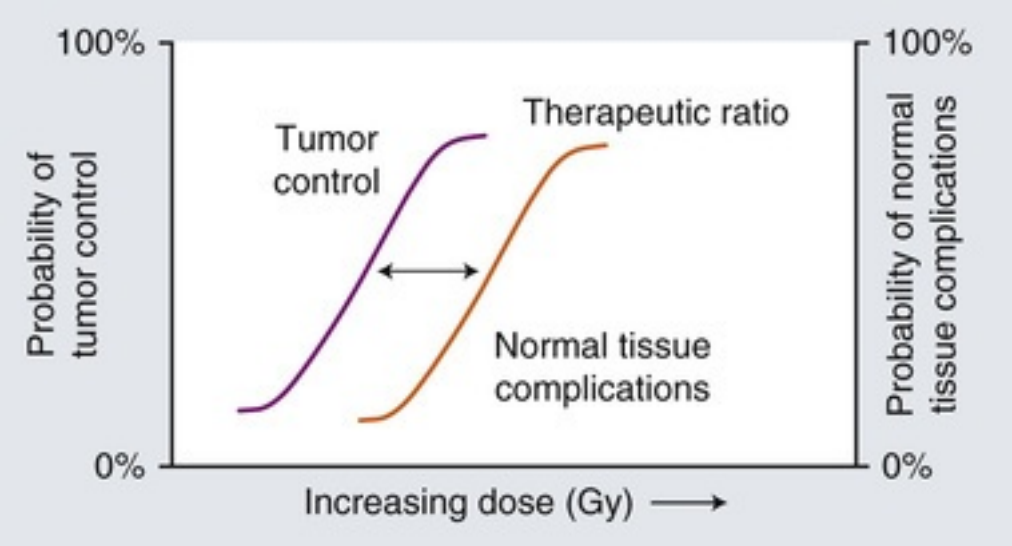


FIGURE 340-9 Therapeutic ratio described for radiation therapy, in which the probability of tumor control is weighted against the probability of normal tissue complications. At lower doses of radiation, the probability of complications is low but with a moderate probability of tumor control. Increasing the dose may gain a higher chance of tumor control but at the cost of a higher risk for normal tissue complications.

Acute Radiation Toxicity

Acute radiation toxicity is typically reversible, self-limiting, occurs during or shortly after therapy, and effects are confined to the irradiated area. Rapidly proliferating tissues such as epithelium, mucosa, and tumor are most affected acutely. Acutely affected tissues tend to heal within 2-4 weeks (Figure 340-10). Discomfort is expected in the short-term and acute toxicity is often unpleasant for both the owner and pet. Acute toxicities are predominantly dependent on the total dose of radiation administered (the higher the dose, the greater the toxicity) but also on the duration and frequency of treatment (shorter overall treatment time increases toxicity) and the fraction size (the higher the fraction size, the greater the toxicity). Concurrent chemotherapy administered in conjunction with radiation may increase acute radiation toxicity. Guidelines on culpable drugs in veterinary oncology are not available.[41] Acute effects are self-limiting and heal in most cases without medical intervention, although analgesia is important in managing radiation patients.

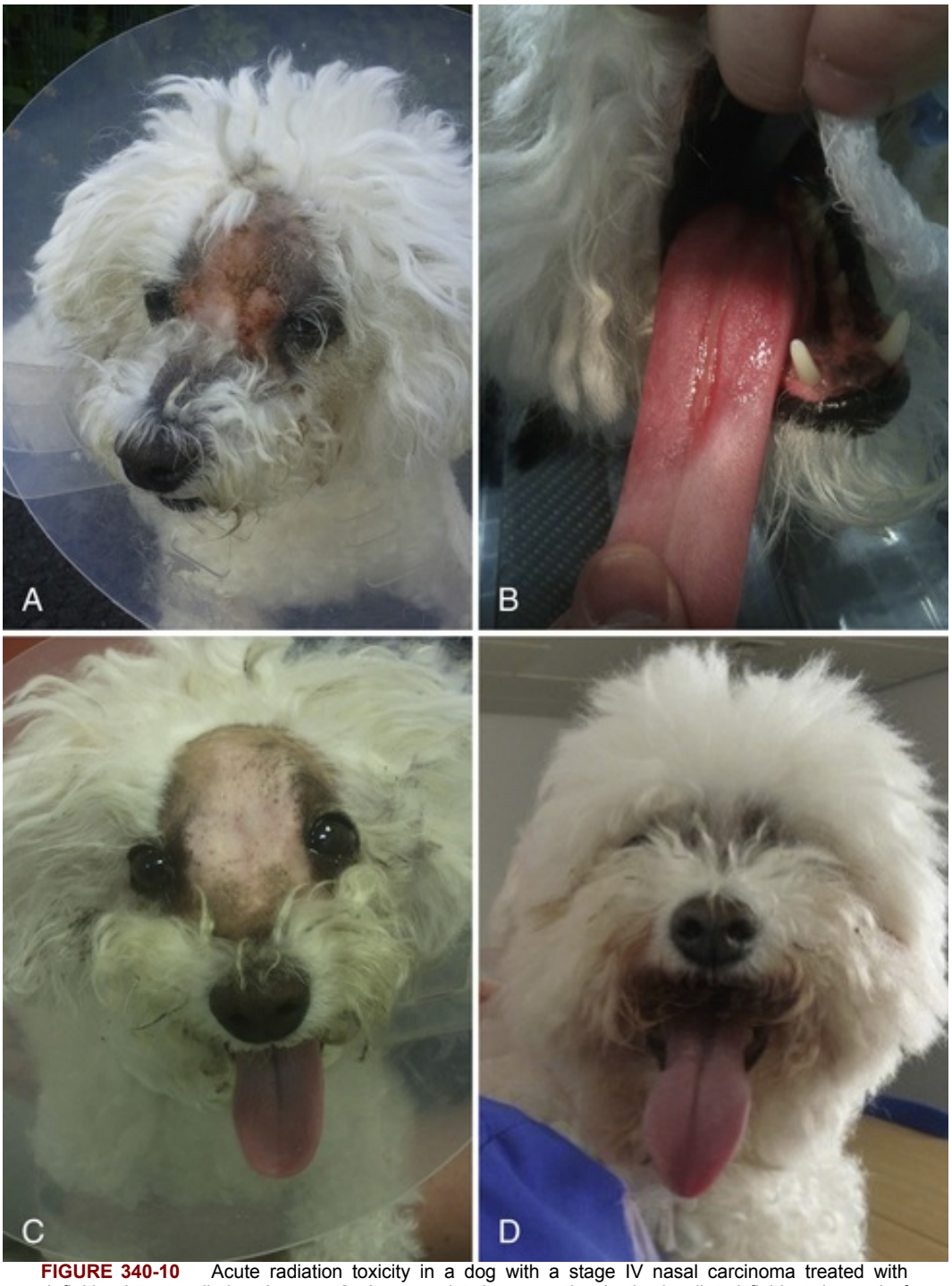


FIGURE 340-10 Acute radiation toxicity in a dog with a stage IV nasal carcinoma treated with definitive intent radiation therapy. **A,** Acute moist desquamation in the irradiated field at the end of treatment. **B,** Acute oral mucositis of the tongue, which was within the irradiated field. **C,** Healing desquamation 2 weeks post radiation therapy. **D,** Fully healed acute radiation adverse effects 16 months post radiation therapy.

For unexpected severe acute toxicity, standard surgical wound management may be used to ensure the site remains clean and protected. Little has been published regarding optimal methods to manage veterinary patients undergoing radiation therapy and there are no evidence-based consensus guidelines for radiation oncology.[42] In a survey of North American veterinary radiation facilities, about 75% used oral antibiotics and oral analgesics to manage radiation induced dermatitis. But, there were many opinions regarding treatment strategies.[42] The team must employ methods to avoid further trauma from licking, scratching or rubbing at the radiation site. For oral lesions, soft food, oral rinses and occasionally antibiotics (with oral coverage) are

used. Given our heightened awareness of antimicrobial resistance, in part due to the widespread indiscriminate use of broad-spectrum oral antibiotics, efforts should be made to determine if alternative methods are useful in the management of radiation toxicity.[43-45]

Late Adverse Effects

"Late" radiation adverse effects typically occur ≥6 months after completing therapy. Effects seen are determined by the structures within the irradiated field. Late radiation adverse effects typically develop in slowly proliferating or non-renewing tissues such as heart, lung, kidneys, nerve, bone, and muscle. Late effects, directly related to unexpected, severe, acute side effects that do not adequately recover, are also seen. These non-renewing tissues are dose-limiting. Thus, prescribed tumor dose should keep the probability of clinically relevant late effects at <5%. Late tissue damage is progressive and irreparable in most cases and results from vascular damage, chronic inflammation, fibrosis, necrosis, and loss of normal tissue stem cells. The most common late effects are cosmetic, but clinically relevant toxicity such as osteoradionecrosis or secondary tumor formation can occur if long-term survival (>3-5 years) follows radiation therapy (Figure 340-11).[11] Likelihood of late radiation effects depends on the fraction size (the greater the fraction size, the greater probability of late toxicity). The overall dose prescribed is also important. Because late radiation effects are generally irreversible, effort is made to avoid their development (Table 340-1).

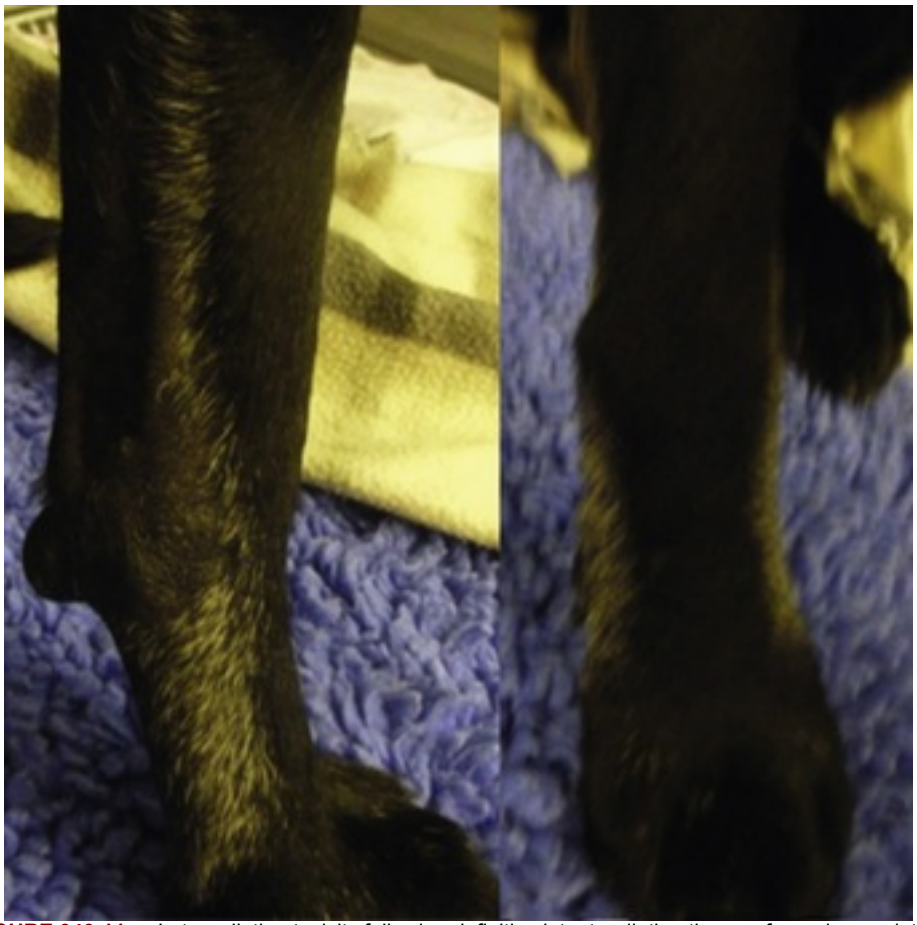


FIGURE 340-11 Late radiation toxicity following definitive intent radiation therapy for an incompletely excised soft tissue sarcoma. The radiation field is outlined along the lateral and caudal aspect of the limb by alopecia and leukotrichia, where the dorsal aspect of the distal limb was spared to permit lymphatic drainage.

TABLE 340-1

Radiation-Induced Toxicities That Can Occur in the Dog and Cat

SKIN	ACUTE RADIATION TOXICITY	LATE RADIATION TOXICITY
Skin and subcutis	Moist desquamation Alopecia	Fibrosis and contraction Non-healing ulcer Leukotrichia Alopecia Secondary tumor (sarcoma)
Extremity	Nail or pad slough	Neuropathy Muscle fibrosis and contraction
Spinal cord	Delayed "acute" transient myelopathy (rare)	Myelopathy Infarction Radiculopathy (lower motor neuron syndrome)
Cervical region	Pharyngitis Esophagitis Tracheitis	Hypothyroidism Esophageal stricture
Oral cavity	Mucositis	Periodontal disease Xerostomia (dry mouth)
Nasal cavity	Mucositis Nasal discharge	Chronic rhinitis (nasal discharge)
GI tract	Gastritis, enteritis or gastroenteritis Colitis/anusitis	Stricture
Eye	Blepharitis/blepharospasm Conjunctivitis Corneal ulceration Keratitis Uveitis	Cataract Keratoconjunctivitis sicca (KCS) Retinal changes Blindness
Brain	Encephalopathy (rare) Edema (rare) Systemic effects: lethargy, nausea, vomiting (rare)	Encephalopathy Infarction/hemorrhage
Bone		Osteoradionecrosis Secondary tumor formation (sarcoma)
Kidney	Acute nephropathy	Fibrosis leading to nephropathy

Palliative versus Definitive Protocols (see Box 340-2)

Factors dictating likelihood of late toxicity help in choosing between definitive and palliative radiation protocols. It is common to recommend definitive intent radiation protocols for pets with a good prognosis and high likelihood of survival beyond 6 months. The dose given each day in this type of protocol is lower in order to "protect" normal tissue from developing significant late toxicities that could negatively impact quality of life. Palliative protocols are typically reserved for animals with a poor prognosis. The goals of palliative therapy are to alleviate pain associated with the tumor, decrease the size of any mass causing obstruction (a laryngeal mass or compressive medial iliac lymph node), and to otherwise alleviate debilitating signs of cancer (bleeding from a large ulcerated oral mass).

Palliative radiation therapy is not intended to prolong survival, although it may do so indirectly. Rather, it is prescribed to improve quality of life. There are many different protocols for palliative radiation. They often involve radiation administered once or twice weekly for 3-4 doses or 4-5 total doses are administered daily. Because the dose of radiation is higher for each fraction, if pets do well with treatment and survive greater than 6-12 months following treatment, there is a higher likelihood of clinically relevant late toxicity (Figure 340-12). SRS and SRT utilize modest hypofractionation but the techniques involve precise delivery of a highly conformal radiation to a small target, minimizing the amount of normal tissue within the prescribed high radiation dose region.[5] Clinical data in dogs and cats are limited. Such radiation has been employed for solid tumors: brain, canine osteosarcoma, feline injection site sarcoma, and canine nasal tumors.[46-52]

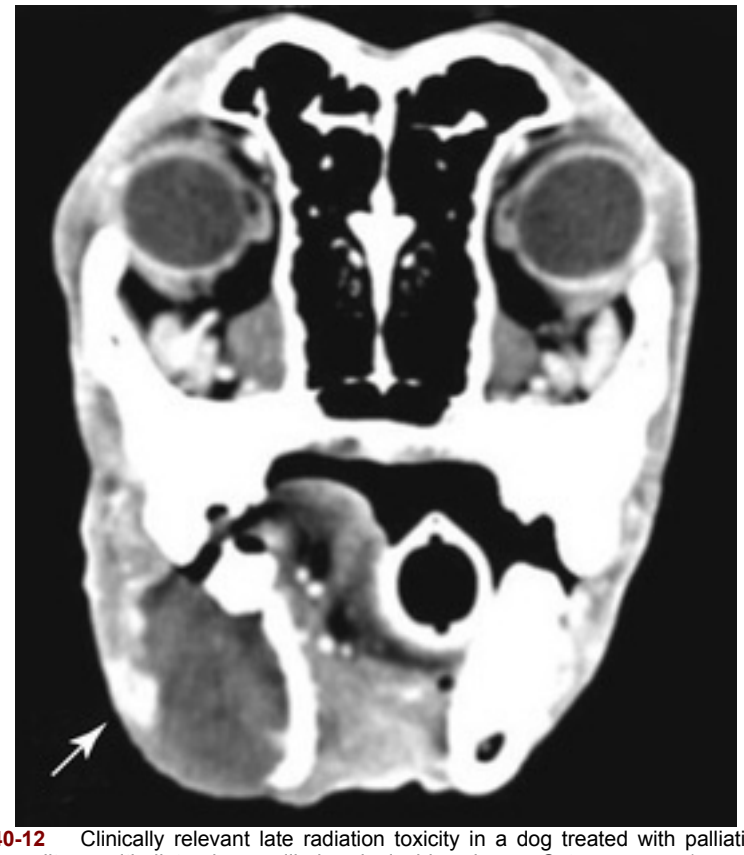


FIGURE 340-12 Clinically relevant late radiation toxicity in a dog treated with palliative radiation therapy for a solitary epitheliotropic mandibular gingival lymphoma. Osteosarcoma (arrow) developed within the radiation site 4 years following treatment for lymphoma; following mandibulectomy, there was no evidence of lymphoma in the histologic sections.

Adjuvant Radiation Therapy

Overview

Because cell killing follows exponential kinetics, larger tumors require higher doses of radiation to induce a complete response. Indeed, several studies have demonstrated an inverse relationship between the likelihood of tumor control following radiation therapy and tumor size for canine mast cell tumors, soft tissue sarcomas, pituitary tumors, and oral tumors, and feline nasal planum squamous cell carcinomas and oral squamous cell carcinomas.[53-59] Radiation tends to be most useful in microscopic disease due to the nature of solid tumor growth (Gompertzian growth) and double strand DNA breaks in tumor cells being the target of therapy. There are exceptions, but radiation therapy is considered most effective in the postoperative setting for most tumors in animals, when surgical margins are incomplete or narrow and there is risk of tumor recurrence (Figure 340-13).

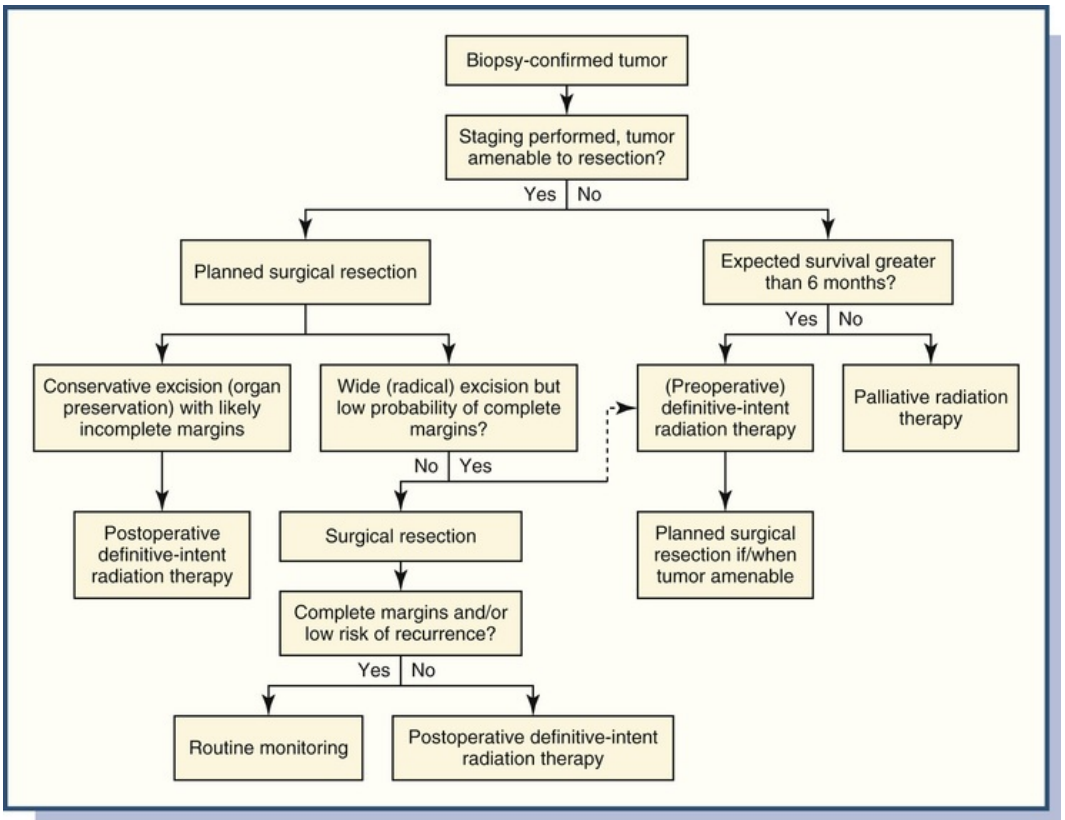


FIGURE 340-13 Algorithm for the role of radiation therapy in the management of veterinary cancer patients. Tumor histology, clinical characteristics, staging and other factors will influence the decision to pursue definitive radiation therapy. Palliative radiation is generally considered for patients with advanced cancer.

In most cases, radiation therapy begins 10-20 days after surgery, allowing tissue time to heal. The radiation field then includes all areas potentially contaminated by the surgical approach and areas likely to contain microscopic disease. Advantages of postoperative radiation therapy include: surgical staging permits tailoring of radiation target volumes and doses; radiation is most effective at achieving long-term control when targeting microscopic disease; there is no negative impact on post-surgical wound healing (although this is rare in companion animals); and there is no delay in surgery, which may have a psychological benefit for people with cancer (and potentially pet owners).

Advantages and Disadvantages of Surgery Preceding Radiation

Surgical staging is generally considered one of the best methods of determining true tumor extent, as samples are submitted for histologic evaluation after removal. The surgeon therefore has a critical role when postoperative radiation therapy is planned. Prior to surgical resection, it is often helpful to determine if placement of radiopaque clips or markers is useful to identify surgical excision borders. Use of markers can aid in postoperative tumor volume delineation (GTV and CTV) to be targeted. This improves ability to exclude normal tissue.[60] Potential disadvantages of postoperative radiation therapy include the volume of normal tissue irradiated is larger after surgery, especially if the surgical scar does not relate well to the tumor bed; there may be increased risk of tumor cell dissemination at surgery; there may be alteration in the blood supply to residual tumor cells, creating a more hypoxic and radio-resistant environment, thus necessitating higher overall dose; if there are surgical complications with wound healing, the time to start of radiation may be delayed.

Preoperative Radiation Therapy

Pre-operative radiation therapy is often recommended for large tumors when it is not known whether a tumor can be safely and completely excised, i.e., canine thyroid tumors or feline injection site sarcomas.[23-25,51,61-63] Radiation therapy is often prescribed for a 3-4 week protocol which is then followed by a 2-4 week period in which any acute toxicities are permitted to heal prior to surgery. Possible advantages of performing

preoperative radiation therapy include using less radiation, perhaps because there has been no alteration in vasculature by surgical manipulation; a smaller treatment field is treated as the tumor volume and target volumes can be better defined; there is no delay in the start of radiation; and the extent of surgery may be slightly less depending on the response to treatment.

Potential disadvantages of preoperative radiation therapy include the lack of initial surgical staging, which may limit radiation therapy planning; a potential deleterious effect on post-surgical wound healing (although this is not well recognized in veterinary medicine even in cases where surgery is performed months following radiation therapy); and hypoxic regions in measurable bulky tumors may inhibit good cellular responses to radiation. Cats with injection site sarcomas often have extensive and highly infiltrative disease at the time of presentation, thus preoperative radiation therapy plays a major role in decreasing potential late radiation effects by permitting a lower overall dose to be prescribed to a smaller treatment volume. For unresectable tumors, preoperative radiation therapy may create a smaller tumor (downstaging) more amenable to excision. The decision to undertake preoperative versus postoperative radiation therapy should be a team decision.

Chemotherapy and Radiation Therapy

Chemotherapy may be administered concurrently with radiation due to the biologic behavior of some tumors, their underlying tumor histology, or as a radio-sensitizer. The extent to which chemotherapy drugs synergize with radiation is extremely variable. In people, some interact strongly (doxorubicin) and others show no obvious synergy (cytosine arabinoside). Efforts to evaluate chemotherapy drugs such as carboplatin and gemcitabine as radiation sensitizers for dogs and cats have been disappointing.[64,65] While many animals tolerate concurrent chemotherapy and radiation therapy or tyrosine kinase inhibitors and radiation therapy, it is important to monitor for unexpected hematologic, gastrointestinal, or radiation adverse events.[41,64,66,67]

Common Tumor Types Treated with Radiation Therapy in Veterinary Oncology

Many tumors are responsive to radiation; however, the overall response tends to be variable and dependent on the signalment, tumor histology, location, grade, and/or stage of disease. It is always important to remember that normal critical structures adjacent to the radiation field limit the amount of radiation that can be administered; occasionally doses must be modified to avoid significant injury. A general guide for tumor types that are responsive to radiation is provided in E-Table 340-2. Radiation therapy may be used for other tumor types as well, such as solitary plasma cell tumors, solitary lymphoma, salivary gland tumors, distal urinary tract tumors, thymomas, and histiocytic sarcomas, depending on the clinical picture. Palliative radiation therapy can be employed for most tumors as well in an effort to improve dysfunction or pain. For tumors that have positive responses to radiation therapy, re-irradiation may be a viable option but is dependent on the initial radiation protocol, the overall dose and fractionation schedule and normal tissues in close proximity to the recurrent or progressive tumor. Given advances in therapeutic radiation technology, it is likely that the role of radiation therapy in the management of veterinary cancer patients will become increasingly important and integrated into multimodality approaches.

E-TABLE 340-2

Common Tumor Types in Dogs and Cats Treated with Radiation Therapy

TUMOR	TREATMENT TYPE	RESPONSE TO RADIATION	TOXICITIES*	OUTCOME/COMMENTS
Oral Tumors—Dogs				
Oral ameloblastoma[68,69]	Definitive intent† radiation therapy only	Excellent	*Acute:* oral mucositis, moist desquamation *Late:* leukotrichia, alopecia and lichenification of skin within the irradiated site; risk of periodontal disease, osteoradionecrosis,	Median survival: 4 years

			carcinogenesis	
Oral fibrosarcoma[54,70,71]	Definitive intent radiation therapy following incomplete resection[54,70,71]	Fair to good	*Acute:* oral mucositis (can be severe), moist desquamation *Late:* leukotrichia, alopecia and lichenification of skin within the irradiated site; risk of periodontal disease, osteoradionecrosis, carcinogenesis	Median survival: 1.5 years
	Definitive intent radiation therapy only[72]	Fair	*Acute:* oral mucositis (can be severe), moist desquamation *Late:* leukotrichia, alopecia and lichenification of skin within the irradiated site; risk of periodontal disease, osteoradionecrosis, carcinogenesis	Median survival: 11 months
	Palliative intent radiation therapy[72]	Good	*Acute:* minimal due to palliative approach *Late:* leukotrichia, alopecia and lichenification of skin within the irradiated site; risk of periodontal disease, osteoradionecrosis, carcinogenesis	Median survival: 4-10 months
Oral melanoma[54,55,65,73]	Coarse-fraction (palliative) radiation therapy with or without surgery and/or chemotherapy	Fair to good	*Acute:* minimal due to palliative type protocol *Late:* leukotrichia, alopecia and lichenification of skin within the irradiated site; moderate to high risk of periodontal disease, osteoradionecrosis and carcinogenesis if long-term survival achieved	Median survival: 7-10 months Size is prognostic for outcome. Location, stage and histologic criteria may be prognostic for outcome. Radiation offers good local control but death is often due to metastatic disease
Oral (non-tonsillar) squamous cell carcinoma[54,74,75]	Definitive intent radiation therapy only or in conjunction with surgery	Good	*Acute:* oral mucositis (can be severe), moist desquamation	Median survival: 8 months-1.2 years
			Late: leukotrichia, alopecia and lichenification of skin within the irradiated site; risk of periodontal disease, osteoradionecrosis, carcinogenesis	Size and location are prognostic for outcome.
Tonsillar oral squamous cell carcinoma[76,77]	Palliative radiation therapy often in conjunction with surgery and chemotherapy	Fair to good	*Acute:* minimal due to palliative type protocol	Median survival: 6 months Fair to good local control but death typically due to progressive lymph node or lung metastasis
			Late: leukotrichia, alopecia and lichenification of skin within the irradiated site; low risk due to short survival time	

Oral Tumors—Cats				
Oral squamous cell carcinoma[53,78-82]	Accelerated hypofractionated radiation therapy[53,78,79]	Fair	*Acute:* mucositis, moist desquamation	Median survival: 6 months Progression-free survival: 4.5 months
			Late: leukotrichia, alopecia; low risk due to short survival	Size was prognostic for outcome
	Palliative or various hypofractionated radiation therapy with or without surgery[80,81]	Poor to fair	*Acute:* mucositis, moist desquamation	Median survival: 2-6 months
			Late: low risk due to short survival	Mandibular location associated with improved outcome
	Definitive intent radiation therapy[82]	Poor to fair	*Acute:* mucositis, moist desquamation, inappetence *Late:* leukotrichia, alopecia, lichenification; low risk for significant effects due to short survival	Median survival: 3-6 months
Nasal Tumors—Dogs				
Nasal carcinomas and sarcomas[17,47,83-91]	Definitive intent radiation therapy (conformal radiation therapy and IMRT)[17,86,87,89,91]	Good	*Acute:* oral mucositis, rhinitis, moist desquamation, blepharospasm, conjunctivitis, uveitis *Late:* cataracts, keratoconjunctivitis sicca, blindness, chronic rhinitis, periodontal disease	Median survival: 8-19 months IMRT is associated with dramatically reduced radiation adverse effects. Poorly differentiated carcinomas or squamous cell carcinoma may carry worse prognosis Stage IV nasal tumors with extension through the cribriform plate carry a worse prognosis. Median survival: 6 months.
	Palliative radiation therapy (conformal radiation therapy, SRT)[47,83-85,88,90,91]	Good	*Acute:* oral mucositis, rhinitis, blepharospasm, conjunctivitis, uveitis *Late:* cataracts, keratoconjunctivitis sicca, blindness, osteoradionecrosis and fistula formation, chronic rhinitis, periodontal disease if long-term survival is achieved	Median survival: 6-10 months Epistaxis may be negatively associated with outcome. SRT may yield higher risk of late toxicity.
	Re-irradiation with palliative radiation therapy following local failure[87]	Good	*Acute:* oral mucositis, rhinitis, blepharospasm, conjunctivitis, uveitis *Late:* cataracts, keratoconjunctivitis sicca, blindness, osteoradionecrosis and fistula formation, chronic	Median progression-free survival: 9 months from reirradiation Note: high risk of late toxicity due to prolonged survival and high overall dose to normal tissues

			rhinitis, periodontal disease	
Nasal Tumors—Cats				
Nasal carcinoma92-94	Definitive intent hypofractionated radiation therapy94	Good	*Acute:* oral mucositis, rhinitis, blepharospasm, conjunctivitis, uveitis *Late:* cataracts, keratoconjunctivitis sicca, chronic rhinitis, periodontal disease	Median survival: 11 months Range in survival: 1 month-3 years
	Palliative hypofractionated radiation therapy92,94	Good	*Acute:* mucositis, moist desquamation, conjunctivitis *Late:* cataracts, keratoconjunctivitis sicca, chronic rhinitis, osteoradionecrosis, periodontal disease; higher risk of late toxicity	Median survival: 12 months
Nasal lymphoma95-97	Definitive intent radiation therapy alone96	Excellent	*Acute:* oral mucositis, rhinitis, blepharospasm, conjunctivitis, uveitis *Late:* cataracts, keratoconjunctivitis sicca, chronic rhinitis, periodontal disease	Median survival: 1.5-3 years
	Definitive intent radiation therapy with multidrug chemotherapy96,97	Excellent	(As above)	Median survival: 1.5 years
	Palliative hypofractionated radiation therapy95,96	Good	*Acute:* oral mucositis, rhinitis, blepharospasm, conjunctivitis, uveitis *Late:* cataracts, keratoconjunctivitis sicca, ocular atrophy, chronic rhinitis, secondary tumor formation, periodontal disease	Median survival: 1-1.2 years
Skin/Subcutaneous Tumors—Dogs				
Mast cell tumor58,98-104	Definitive intent radiation following incomplete resection with or without chemotherapy98-104	Excellent	*Acute:* moist desquamation, rarely ulceration *Late:* leukotrichia, alopecia, lichenification, fibrosis, osteoradionecrosis, secondary tumor formation	Median survival: 2-6.8 years Median progression-free survival: 2.7-3.4 years Survival linked to grade and stage of mast cell tumor. Chemotherapy is typically administered for tumors at high risk for metastasis.
	Definitive radiation alone58	Good	*Acute:* moist desquamation, rarely ulceration *Late:* leukotrichia, alopecia, lichenification, fibrosis	Median survival: 1.5 years Size is prognostic for outcome
Soft tissue sarcoma57,70,105-108	Definitive intent radiation therapy following incomplete	Excellent	*Acute:* moist desquamation, rarely ulceration *Late:* leukotrichia, alopecia,	Median survival: > 5.4 years 5-year survival rate: 78%

	resection70,107		lichenification, fibrosis, osteoradionecrosis, secondary tumor formation	
	Definitive intent radiation therapy alone57	Fair	*Acute:* moist desquamation, rarely ulceration *Late:* leukotrichia, alopecia, lichenification, fibrosis	1-year tumor control rate: 67% 2-year tumor control rate: 33%
	Palliative radiation therapy105,106,108	Good	*Acute:* rare due to palliative approach *Late:* leukotrichia, alopecia, lichenification, fibrosis, higher risk of osteoradionecrosis, secondary tumor formation if long-term control achieved	Response rates: 50-87%
Ceruminous gland adenocarcinoma109,110	Definitive intent following incomplete resection	Good to excellent	*Acute:* moist desquamation, rarely ulceration of the ear canal, secondary otitis externa or interna, temporary deafness *Late:* leukotrichia, alopecia, lichenification, fibrosis, chronic otitis externa and/or interna, tympanosclerosis	Mean tumor control: 3.2 years 1-year tumor control rate: 56%
Thyroid carcinoma23-25,111	Definitive intent radiation therapy only24,111	Good to excellent	*Acute:* moist desquamation, esophagitis, tracheitis, caudal oral mucositis *Late:* leukotrichia, alopecia, lichenification, fibrosis, esophageal stricture and regurgitation, tracheal stricture and/or cough, hypothyroidism, osteoradionecrosis, secondary tumor formation	Response rates: >75% Median survival: 2.1-3.8 years When considering post-radiation surgical resection, the time to maximum response can vary from 6-22 months
	Hypofractionated (palliative) radiation therapy23,25	Good	As above, with higher probability of late effects such as esophageal stricture	Median survival: 1.8 years
Anal sac apocrine gland adenocarcinoma112	Definitive intent following surgical resection to primary tumor bed and locoregional lymph nodes	Good to excellent	*Acute:* colitis, anusitis, moist desquamation of the skin *Late:* leukotrichia, alopecia, lichenification, fibrosis, rectal stricture	Median survival: 1.5 years The probability of late toxicity to pelvis is highly dependent on fraction size protocol
Skin/Subcutaneous Tumors—Cats				
Injection site sarcoma (vaccine associated sarcoma)51,61-63,113-115	Definitive intent radiation therapy following incomplete resection61,63,113,114	Good	*Acute:* moist desquamation, other effects possible depending on anatomic tumor location *Late:* leukotrichia, alopecia, lichenification, fibrosis, other effects possible depending on anatomic tumor location	Median survival: 1.9-3.5 years Disease-free interval: 1.1-1.3 years

	Preoperative definitive intent radiation therapy[62,114,115]	Good	As above but lower volume of tissue developing acute toxicity and at risk for late toxicity	Median survival: 1.6-2.1 years Median disease-free interval: 1.1-1.7 years
	Stereotactic radiation therapy (palliative)[51]	Good	*Acute:* skin erythema and dry desquamation *Late:* dependent on normal tissue irradiated	Margin status is prognostic for outcome
Brain Tumors—Dogs				
Various tumors: intra-axial, extra-axial[116-118]	Definitive intent radiation therapy[116,117]	Fair to good	*Acute:* minimal; possible skin desquamation, oral mucositis, ocular effects, acute cerebral edema, altered mentation *Late:* fibrosis, necrosis, seizures, altered behavior	Median survival: 8 months-1.9 years
	Stereotactic radiation surgery[118]		As above with fewer acute side effects	Median survival: 1.1 years
Meningioma[119,120]	Definitive intent radiation therapy following incomplete resection	Good	*Acute:* minimal; possible skin desquamation, oral mucositis, ocular effects, acute cerebral edema, altered mentation *Late:* fibrosis, necrosis, seizures, altered behavior	Median survival: 1.4 years
Pituitary tumors[56,121-123]	Definitive intent radiation therapy	Good	*Acute:* minimal; possible skin desquamation, oral mucositis, ocular effects, acute cerebral edema, altered mentation *Late:* fibrosis, necrosis, seizures, altered behavior	Median survival: 1- >2 years
Brain Tumors—Cats				
Pituitary tumors[52,124,125]	Definitive intent radiation therapy	Good to excellent	*Acute:* minimal; possible skin desquamation, oral mucositis, ocular effects, acute cerebral edema, altered mentation *Late:* fibrosis, necrosis, seizures, altered behavior	Median survival: 1.5-2.1 years Median survival for all cause mortality (tumor-related median survival not reached)
Bone Tumors—Dogs				
Osteosarcoma[48,49,126-129]	Palliative intent radiation therapy with or without systemic therapy[126-129]	Fair to good	*Acute:* erythema, dry desquamation (appendicular), mucositis (axial) *Late:* leukotrichia, alopecia, lichenification, fibrosis of soft tissues, osteoradionecrosis, fracture if prolonged survival achieved	Response rate for pain relief: 50-83% Median response duration: 1.5-2.5 months Median survival time: 4 months
	Stereotactic radiosurgery for limb-spare in conjunction with chemotherapy[48,49]	Fair to good	As above with potentially higher risk of late toxicity	Median survival: 10-12 months

*Note that acute and late toxicities are heavily dependent on the treatment site, radiation protocol and type of radiation therapy prescribed

and administered; therefore general information on potential toxicities is provided.

†Definitive intent radiation therapy was defined as radiation therapy administered with the intent of long-term control.

IMRT, Intensity-modulated radiation therapy; *SRT,* stereotactic radiation therapy.

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CHAPTER 341

Cancer Immunotherapy

Barbara J. Biller

Client Information Sheet: Cancer Immunotherapy

Introduction

Of the treatment modalities available to treat cancer, immunotherapy has the greatest potential to specifically target tumors and spare normal tissues. It is also unique in its ability to provide a long-term memory response that could prevent tumor recurrence. Much of cancer research traditionally has been focused on understanding properties of the tumor cell itself, such as aberrant cell signaling, immortalization and activation of invasion, and metastasis. More recently, there has been a growing awareness of the importance of the host and the tumor microenvironment in shaping cancer progression (see ch. 338); among the most critical of these factors are the immune system and its response to cancer.

The idea that the immune system can control cancer is not a new one. In 1909, Ehrlich suggested cancer might occur at an "overwhelming frequency" if not for the function of the patient's immune system.[1] In the 1960s, Burnet proposed that lymphocytes were constantly patrolling normal tissues and eliminating abnormal cells through a process he termed *immune surveillance.*[1,2] Burnet's theory was not widely accepted until the 1990s, when tumor-associated antigens and tumor-specific lymphocytes were first identified in human cancer patients. Now it is recognized that nearly every known innate and adaptive immune effector mechanism participates to some degree in tumor recognition and control or, conversely, in helping tumors avoid detection.

Overview of Tumor Immunology

The dual role of the immune system in protecting against tumor development and promoting tumor growth is illustrated by the phenomenon of *immunoediting.* During this process, the phenotype of neoplastic cells evolves to escape detection by the host immune system. Immunoediting can be characterized by three distinct phases. During the initial phase of immunosurveillance (also known as elimination), transformed cells are recognized and destroyed through a combination of innate and adaptive immune responses (reviewed in Box 341-1). The few cells that manage to survive enter an equilibrium phase in which there is a dynamic balance between tumor cell destruction and survival. In the final escape phase, however, constant immune pressure and the genetic instability of the tumor promote the expansion of a population of poorly immunogenic and potently immunosuppressive tumor cells that are well-equipped to evade further detection.[3]

Box 341-1

Principal Immune Cells Involved in Stimulation and/or Inhibition of Antitumor Immune Responses

Response Type

Innate

Dendritic cell (DC)

- Initiate adaptive immune responses through antigen presentation and T-cell activation; some subsets are immunosuppressive in the tumor microenvironment

Tumor-associated neutrophil (TAN)

- May recruit Treg and support tumor angiogenesis

Macrophage
- Very efficient phagocytes

M1
- Help activate T-cell mediated antitumor responses

M2
- Produce immunosuppressive cytokines and facilitate tumor evasion

Myeloid-derived suppressor cell (MDSC)
- Direct and indirect inhibition of T-cell immune responses; recruit Treg

Natural killer (NK) cell
- Perforin-dependent, direct killing of tumor cells recognized as "non-self"

Adaptive: Cellular

Cytotoxic T lymphocyte (CTL, CD8+ effector)
- Direct killing through activation and recognition of tumor antigens

CD8+ memory
- Recalled to protect against relapsing or metastatic disease

Helper T lymphocyte (T_h)
- Aid (T_h1) or inhibit (T_h2, T_h17) CTL function depending on tumor microenvironment

CD4+ T_h (T_h1, T_h2, T_h17)

Regulatory T lymphocyte (Treg)
- Indirect and direct effects; recruited to inhibit other immune effectors such as CTLs and DCs

Adaptive: Humoral

Antibody-mediated (Direct)
- Recognize tumor cells and induce apoptosis

Complement dependent (Indirect)
- Forms membrane attack complex that leads to tumor cell cytotoxicosis

Immune escape occurs through multiple complex mechanisms that can be divided into two broad categories. The first involves selection for tumor cells with features of reduced recognition (such as the absence of strong tumor antigens or loss of major histocompatibility complex molecules) and an increased ability to survive. The second mechanism is the development of an immunosuppressive tumor microenvironment dominated by the production of inhibitory cytokines (transforming growth factor-beta [TGF-beta] and interleukin [IL]-10) and the recruitment of immunoregulatory immune cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Together, these changes create a tumor microenvironment that facilitates tumor progression rather than detection.

Recognition of the impact of cancer immunoediting is leading to improvements in the efficacy of immune based therapies, many of which are likely to become more widely available to the veterinary profession over the coming years. This chapter highlights some of the most promising therapies under evaluation in veterinary clinical trials or already used in practice. The chapter reviews immune therapies that stimulate immunity in general (nonspecific tumor immunotherapy) as well as some of the tumor-specific approaches such as tumor vaccines and monoclonal antibodies (Figure 341-1).

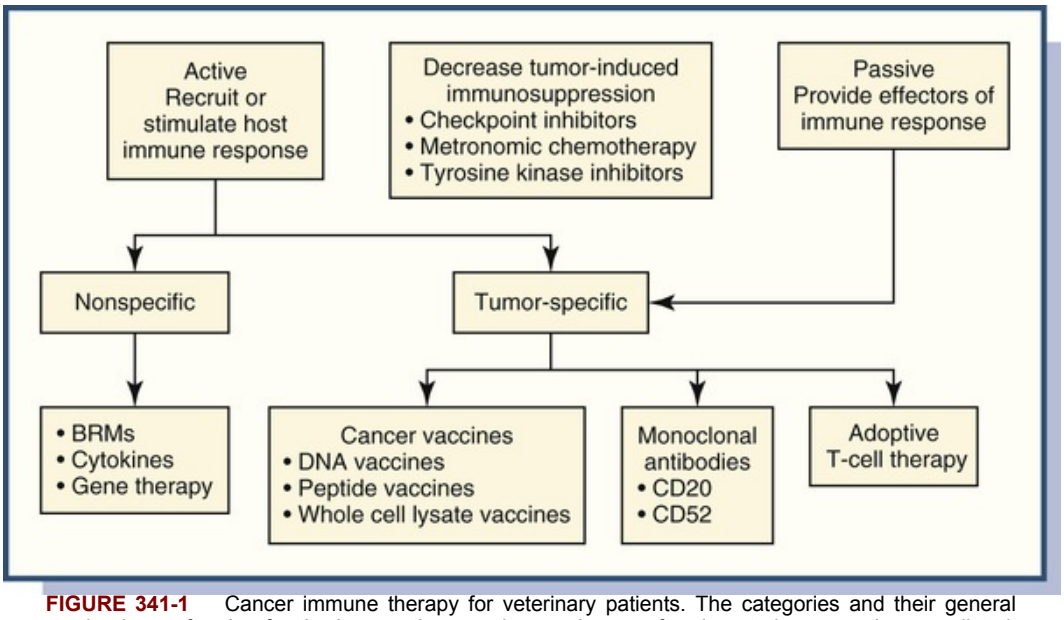

FIGURE 341-1 Cancer immune therapy for veterinary patients. The categories and their general mechanisms of action for the immunotherapeutics used most often in veterinary oncology are listed. Each is grouped according to the overall goal of therapy. *BRMs*, Biologic response modifiers.

Nonspecific Tumor Immunotherapy

The goal of nonspecific immunotherapy is to engage the innate and adaptive arms of the immune response in the recognition and destruction of neoplastic cells. In general, better stimulation of innate immunity (mediated primarily by dendritic cells and macrophages) results in more effective T- and B-cell mediated adaptive immune responses.

Bacillus of Calmette and Guérin (BCG)

One of the best-studied forms of nonspecific therapy is the biologic response modifier (BRM) known as BCG (bacillus of Calmette and Guérin), a modified strain of *Mycobacterium bovis* initially developed as a vaccine for tuberculosis in the early 20th century. Direct contact of BCG with malignant cells elicits production of multiple inflammatory cytokines including interferon (IFN)-gamma, IFN-alpha, IL-2, IL-6, IL-12 and tumor necrosis factor (TNF)-alpha.[4] This proinflammatory response attracts and activates neutrophils, macrophages, and cytotoxic T-lymphocytes, triggering destruction of tumor cells and induction of long-lived memory T-lymphocytes.[5]

Infusion of BCG into the bladder is one of the most effective forms of therapy for urogenital transitional cell carcinoma in people.[5] Although BCG has been instilled into the canine bladder and is well-tolerated at low doses, it is not effective in the treatment of canine transitional cell carcinoma (TCC), which typically presents as much more invasive disease in dogs compared to humans.[6,7] BCG has also been combined with human chorionic gonadotropin and administered subcutaneously to treat mast cell tumors in dogs, where it was found to be as effective as single-agent vinblastine chemotherapy with fewer side-effects in one randomized clinical trial.[8] Other studies evaluating the administration of BCG in dogs either alone or in combination with other therapies for mammary carcinoma, osteosarcoma, and lymphoma have not demonstrated a therapeutic benefit.[9-11]

Liposome-Encapsulated Muramyl Tripeptide (L-MTP-PE)

Muramyl dipeptide (MDP) is an immunostimulatory component of the BCG cell wall modified by addition of a peptide and incorporation into liposomal membranes to result in L-MTP-PE, a pharmaceutical product efficiently taken up by monocytes and macrophages that stimulates a cascade of innate and adaptive antitumor immune responses in the host.[12] Based on clinical studies in dogs with osteosarcoma, hemangiosarcoma, melanoma, and mammary adenocarcinoma, L-MTP-PE was moved into clinical trials in

humans (mostly children) with osteosarcoma.[13-15] A phase III prospective randomized trial showed significant reduction in the risk of death from osteosarcoma when L-MTP-PE was added to systemic chemotherapy for the treatment of localized disease.[15] Patients with metastatic or recurrent disease also had a decreased risk of further recurrence and death when L-MTP-PE was included in the treatment strategy. Also known as mifamurtide, L-MTP-PE was licensed by the European Medical Association in 2009 as an adjunct to chemotherapy in children with localized osteosarcoma. Mifamurtide has orphan drug status in the United States, but is not currently available to veterinarians. If this situation changes, it is likely that the drug initially will be cost-prohibitive but may prove to be a valuable nonspecific immunotherapeutic for dogs with osteosarcoma and other malignancies.

Cytokine and Gene Therapy

Cytokines with immunostimulatory properties, including IL-2, IL-12 and IL-15, IFN-gamma, and TNF-alpha, also are of interest as tumor-nonspecific immunotherapies. While each has been at least preliminarily assessed in veterinary patients, IL-12 appears most promising because it can be effectively targeted to tumor tissues, thus avoiding the toxicoses associated with systemic cytokine administration. In a clinical investigation of dogs with malignant melanoma, IL-12 was linked to an antibody targeting necrotic tumor regions and administered SC. This strategy resulted in minimal serious toxic effects as well as encouraging immunologic and clinical activity (about a 50% overall response rate).[16]

Another way to deliver cytokines is through gene therapy, in which host cells are transfected or transduced to express specific recombinant proteins of interest. For example, the IL-12 gene can be targeted specifically to tumor cells, triggering a locally immunostimulatory environment. This approach could be particularly useful in controlling large tumors including fibrosarcoma, squamous cell carcinoma, and malignant melanoma, as evidenced by several recent studies investigating efficacy in cats, dogs, and horses, respectively.[17-20]

Tumor-Specific Immunotherapy

Through a variety of approaches, the objective of tumor-specific immunotherapy is to elicit an antitumor immune response that results in clinical regression of a tumor or its metastases. Unlike cytotoxic chemotherapy, which induces rapid tumor cell death, clinical responses depend on the development of adaptive immune responses that can take several months or more to appear. Furthermore, it is becoming increasingly evident that a measurable cell-mediated or humoral antitumor immune response does not necessarily correlate with tumor regression. The observation of "mixed responses" is another frequent problem in assessing outcome; this phenomenon is characterized by the differential response of metastases within different tissues of the same patient. Factors such as these pose significant challenges to the design of clinical trials evaluating tumor-specific immunotherapy, especially in terms of determining efficacy and making comparisons between trials. To address some of these obstacles, specific immune-related response criteria are currently being evaluated alongside the more traditional RECIST (Response Evaluation Criteria in Solid Tumors) methods to more comprehensively capture a variety of clinical response patterns and standardize evaluation of various immunologic endpoints.[21,22] With these caveats in mind, the rest of this chapter will focus on cancer vaccines and monoclonal antibodies, two forms of tumor-specific immunotherapy with particular relevance to veterinary oncology.

Cancer Vaccines

As outlined in Figure 341-1, there are several methods by which anticancer vaccines can be generated, including those that deliver specific tumor antigens against a defined target (DNA and peptide vaccines) and those that provide exposure to a range of potential tumor-associated antigens that are usually not known (whole cell tumor lysate vaccines). While each approach has pros and cons in terms of vaccine preparation and the quality of the immune response evoked, cancer vaccines are versatile and can be engineered to boost key aspects of the immune response or to target specific tumor types or even antigens common to a spectrum of malignancies.

The only cancer vaccine currently commercially available for veterinary patients is Oncept (Merial Ltd, Duluth, MN), which is a xenogeneic nucleic acid vaccine containing the DNA sequence encoding human tyrosinase. Tyrosinase is an intracellular glycoprotein essential for melanin synthesis that is overexpressed in the majority of canine melanocytic tumors.[23,24] Early work demonstrated evidence of immunologic and clinical activity in dogs with malignant melanoma of the oral cavity and digit, leading to the vaccine's

licensure in 2010 for use in stage II and III oral canine malignant melanoma.[25-28] However, more recently, studies have reported conflicting outcomes, with some showing improved outcome in Oncept-vaccinated versus unvaccinated dogs while others have not.[29-31] Although better clarification of Oncept's effectiveness awaits investigation in larger randomized clinical trials, introduction of a cancer vaccine specifically for dogs is an exciting step towards improving the availability of immunotherapy for veterinary cancer patients.

There is a variety of other tumor vaccine strategies under clinical investigation in veterinary oncology. One of the most intriguing is the use of attenuated *Listeria monocytogenes*, genetically modified to express specific tumor antigens. When the vaccine construct is administered systemically, the *Listeria* organism infects the patient's myeloid cells, which then induces expression of the desired antigen by the neoplastic cells. This approach shows promise in mouse tumor models and is currently being explored using the tumor antigen HER2/*neu* as the target in canine osteosarcoma.[32-34]

Monoclonal Antibodies

Some of the most significant advances in the treatment of human cancers have been brought about by the use of therapeutic monoclonal antibodies (MAbs) that selectively target malignant cells. There is a growing number of MAbs that are being used to treat human patients with non-Hodgkin's lymphoma and carcinoma of the breast, prostate, and colon.[35] Many therapeutic MAbs are unconjugated and act by binding to specific targets on the surface of malignant cells to induce apoptosis. Apoptosis occurs through direct and indirect effects; the indirect effects typically are mediated by the activation of secondary immune effector mechanisms, such as antibody dependent cell-mediated cytotoxicity (ADCC) or the complement cascade. MAbs also can be linked to toxins, radioisotopes, or chemotherapy agents to induce tumor cell death or they can be used for abrogating tumor-induced immunosuppression (e.g., by blockade of CTLA-4 or PD-1, which limit T-cell mediated antitumor immune responses).

Although MAbs are not yet commercially available for use in veterinary patients, several are under investigation in clinical trials. Preliminary data showed that addition of an anti-CD20 MAb (Aratana Therapeutics) to CHOP or doxorubicin chemotherapy improved survival compared to dogs treated with chemotherapy alone.[36,37] Another MAb targeting the T-cell antigen CD52 (Aratana Therapeutics) has undergone evaluation in dogs with T-cell lymphoma; efficacy has not yet been reported. NV-01 (NexVet), a MAb that blocks nerve growth factor signaling, recently has been tested in clinical trials for dogs with osteoarthritis. In addition to its efficacy as an analgesic, NV-01 was found to decrease bone pain in dogs with osteosarcoma.[38] NV-01 appears promising for managing chronic bone and joint pain of various causes, either as a stand-alone therapy or combined with other medications. It is anticipated that these and other MAbs will be more widely available over the next couple of years.

Challenges for the Future

This chapter provides a brief overview of cancer immunotherapy, focusing on the strategies used most often for veterinary patients. There are other approaches not covered here, such as adoptive T-cell therapy or the administration of oncolytic viruses, which also hold promise and are actively being explored. No matter the approach employed, the success of cancer immunotherapy will depend on the continued development of therapies targeting tumor-induced immunosuppression. The recent U.S. Food and Drug Administration approval of the immune checkpoint inhibitors ipilimumab and nivolumab, which are MAbs targeting CTLA-4 and PD-1, respectively, illustrates the growing awareness of this need.

Investigations of the immunomodulatory properties of tyrosine kinase inhibitors (e.g., toceranib phosphate) and of metronomic chemotherapy are further examples of efforts to alleviate immunosuppression. In dogs with a variety of tumors, administration of either toceranib or low daily dosages of cyclophosphamide is associated with a reduction in circulating Treg numbers.[39,40] Similarly, liposomal preparations of the chemotherapy agent clodronate may be helpful in reducing canine MDSCs via the drug's effects on tumor-associated macrophages.[41]

Despite the challenges ahead, the potential to improve the outcome for people and animals with cancer using novel immune therapies is significant. Veterinarians are in a unique and critically important position to contribute to this effort through their work with companion animals as both cancer patients and translational models. As our understanding of the tumor microenvironment and our ability to target it rapidly improve, the use of anticancer immunotherapy in the clinic likely will become as commonplace as other modalities such as radiation therapy and chemotherapy.

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CHAPTER 342

Molecular Targeted Therapy

Cheryl London

Introduction

Advances in molecular biology, DNA sequencing and bioinformatics have resulted in a much more detailed characterization of how key cellular processes are dysregulated in cancer cells. In particular, understanding the contribution of proteins that normally play essential roles in regulating cell survival, growth, differentiation and migration to tumor biology has helped to establish a framework for the development of novel therapies to disrupt tumor growth. Targets relevant for therapeutic intervention included kinases, transcription factors, proteins that block apoptosis, heat shock proteins and regulators of nuclear export, among others. The two most common approaches for targeting aberrant cellular proteins are monoclonal antibodies and small molecule inhibitors. While antibodies primarily are directed at cell surface proteins, small molecule inhibitors can impact proteins on the cell surface, in the cytoplasm and in the nucleus. Several small molecule inhibitors have been approved for the treatment of human cancers and many more are undergoing clinical testing. In veterinary medicine, the use of small molecule inhibitors is more recent, with just two inhibitors, toceranib (Palladia) and masitinib (Kinavet) approved or conditionally approved by the U.S. Food and Drug Administration (FDA) for use in dogs.[1,2] This chapter discusses the current status of small molecule inhibitors in veterinary clinical oncology.

Toceranib (Palladia)

Toceranib phosphate is an orally bioavailable small molecule inhibitor that blocks a variety of cell surface receptor tyrosine kinases (RTKs) by acting as a reversible competitive inhibitor of adenosine triphosphate (ATP) binding, preventing phosphorylation and subsequent downstream signaling. The inhibitory profile of toceranib includes the RTKs VEGFR2, PDGFRbeta, and KIT.[2-5] Toceranib is very closely related to sunitinib (Sutent) that blocks the activity of VEGFR2/3, PDGFRalpha/beta, KIT, CSF1R, FLT-3, and RET.[6] While it was initially developed as an anti-angiogenic agent, toceranib's broad target profile results in direct anti-tumor activity as well. It is also evident that toceranib has immunomodulatory properties in dogs with cancer through modulation of regulatory T cells (Tregs) further contributing to its effects against several tumor types in dogs.

Phase 1 Clinical Trial

Toceranib initially was studied in a phase 1 clinical trial in 57 dogs with a variety of cancers.[3] Objective responses were noted in 16 dogs (6 complete responses [CR] and 10 partial responses [PR]) with stable disease (SD) in an additional 15 dogs for an overall biological activity of 54%. Based on the known involvement of KIT dysregulation in canine mast cell tumors (MCTs), the highest response rate was observed in this disease setting, with 10/11 dogs with KIT mutations exhibiting clinical benefit. The maximum tolerated dosage (MTD) was established as 3.25 mg/kg PO q 48 h and the adverse event profile was found to be primarily gastrointestinal (GI) in nature including loss of appetite, diarrhea, and less commonly vomiting.

Pivotal Field Study

A placebo-controlled randomized clinical field study of toceranib subsequently was performed in dogs with non-resectable Grade 2 and 3 MCTs.[2] The response rate for all 145 dogs that received toceranib in this trial was 42.8% (21 CR, 41 PR) with an additional 16 dogs experiencing SD for an overall biological activity of 60%. Dogs whose MCT had mutations in KIT were twice as likely to respond to toceranib as those without, and

dogs without lymph node metastasis had a higher response rate than those with involvement. These data formed the basis for the subsequent FDA approval of toceranib in 2009 for the treatment of dogs with MCTs.

Off-Label Activity

Following its approval, toceranib was used off label to treat a variety of tumors in dogs. A retrospective analysis captured this off-label use and clinical benefit (CR, PR, or SD) was observed in 63/85 (74%) of dogs with solid tumors including: anal sac adenocarcinoma (28/32; 8 PR, 20 SD), metastatic osteosarcoma (11/23; 1 PR, 10 SD), thyroid carcinoma (12/15; 4 PR, 8 SD), head and neck carcinoma (7/8; 1 CR, 5 PR, 1 SD), and nasal carcinoma (5/7; 1 CR, 4 SD).[7] The median dosage of toceranib used was 2.8 mg/kg PO; 58.7% of dogs were given drug three times a week (Monday/Wednesday/Friday [M/W/F]), and 74.6% received treatment for 4 months or longer.

Activity also has been reported in lymphangiosarcoma[8] and chronic monocytic leukemia[9] with several other anecdotal reports in individual tumor types not yet published. This indicates that toceranib could have broad anti-tumor activity in dogs.

Combination Therapies

Piroxicam, a nonsteroidal anti-inflammatory mixed cyclooxygenase (COX)-1/COX-2 inhibitor, has shown activity in the treatment of carcinomas and often is included in metronomic chemotherapy regimens. A phase 1 trial was performed in dogs with cancer to establish the safety of toceranib/piroxicam co-administration.[10] Several anti-tumor responses were observed and the combination of standard oral dosages of both drugs (toceranib 3.25 mg/kg PO q 48 h, piroxicam 0.3 mg/kg PO q 24 h) was found generally to be safe. However, the dogs were not monitored to assess whether GI side effects occurred after long-term administration. Therefore, piroxicam often is administered q 48 h alternating with the toceranib to help reduce the risk of GI toxicosis.

To assess whether vinblastine and toceranib could be combined effectively, a phase 1 clinical trial was performed in dogs with MCT.[11] The dose-limiting toxicosis for the toceranib/vinblastine combination was found to be neutropenia, and the MTD of vinblastine was 1.6 mg/m^2 every other week when administered with toceranib at 3.25 mg/kg PO q 48 h. Despite the reduction in vinblastine, the objective response rate was 71%, suggesting that there is additive or synergistic activity when the drugs are given in combination.

To determine whether the combination of radiation and toceranib would be of benefit in MCTs, dogs with non-resectable tumors received prednisone, omeprazole, diphenhydramine, and toceranib at 2.75 mg/kg on M/W/F for 1 week prior to receiving coarse fractionated radiation therapy.[12] The objective response rate was 76.4% (58.8% CR, 17.6% PR) and the median survival time was not reached with a median follow-up of 374 days and no reported enhancement of radiation toxicoses. These data indicate that combined radiation/toceranib has significant clinical benefit in dogs with non-resectable MCTs. The combination of radiation and toceranib also appears to benefit dogs with nasal carcinoma. Dogs receiving 10 fractions of radiation (total dose 42 Gy; see ch. 340) with toceranib had a median survival time of 615 days compared to 371 days for a similarly treated historical control that did not get toceranib.[13]

Immunomodulatory Properties

Low-dosage cyclophosphamide often is used in metronomic treatment regimens to alter the local microenvironment through modulation of angiogenesis and reduction in the number of immunosuppressive Tregs. To assess the effects of toceranib on immune function, dogs with cancer received drug q 48 h for 2 weeks, at which time low-dosage cyclophosphamide was added to the treatment regimen.[14] Toceranib significantly reduced the number and percentage of Tregs in the peripheral blood of treated dogs, with a concomitant increase in interferon (IFN)-gamma serum concentrations. These data indicate that toceranib can have efficacy in metronomic therapy regimens.

Toceranib in Microscopic Metastatic Disease

The activity of toceranib has been evaluated in the microscopic metastatic disease setting. In one study, dogs with appendicular osteosarcoma underwent amputation followed by carboplatin chemotherapy, then were randomized to receive either toceranib/piroxicam/cyclophosphamide or piroxicam/cyclophosphamide (controls).[15] There was no difference in progression-free survival or overall survival, and these did not differ

significantly from historical data regarding dogs that underwent amputation and were treated with carboplatin alone. In a second study, dogs with stage 1 or 2 splenic hemangiosarcoma underwent splenectomy and were treated with doxorubicin.[16] If deemed free of disease after chemotherapy, they went on to receive toceranib. When compared to a historical control group that received doxorubicin alone, there was no improvement in progression-free survival or overall survival. These data indicate that toceranib likely has no benefit in the setting of microscopic metastatic disease in the absence of a known tumor driver (i.e., mutant KIT in MCTs).

Current Dosage Recommendations

Evidence now exists that good biologic activity occurs when doses are initiated below the 3.25 mg/kg MTD and that alternative dosing schedules are effective. In a study of dogs with solid tumors, dosages of toceranib ranging from 2.4-2.9 mg/kg PO q 48 h were associated with drug exposure considered sufficient for target inhibition, resulting in modulation of a key pharmacodynamic marker consistent with VEGFR signaling inhibition.[17] Importantly, the lower dosages were associated with a substantially reduced adverse event profile compared to 3.25 mg/kg. Both PR and CR were documented and 35/40 dogs remained on toceranib for an average duration of 4 months.[17] Data generated from the retrospective analysis of toceranib use in solid tumors found that the three times a week dosing schedule may be better tolerated by some dogs, particularly when toceranib is combined with other therapeutics, such as nonsteroidal anti-inflammatory drugs.

Masitinib and Imatinib

Masitinib mesylate (Kinavet), conditionally approved in 2010, blocks the activity of KIT, PDGFR and the cytoplasmic kinase Lyn. A large placebo-controlled clinical trial was performed in >200 dogs with MCTs in which masitinib significantly improved time to progression compared to placebo, and outcome was improved in dogs with MCTs possessing KIT mutations.[1] Subsequent follow-up of patients treated with masitinib for 2 years identified an increased number of patients with long-term disease control compared to those treated with placebo (40% versus 15% alive at 2 years).[18] A retrospective analysis of dogs with MCT treated with masitinib showed a response rate of approximately 50%.[19] Although the number of dogs evaluated in this study was small and there were varying disease presentations, this study suggests that biologic activity of masitinib is likely to be higher in the setting of primary rather than relapsed disease. Masitinib has also been reported to have activity against T-cell lymphoma in dogs, although no formal clinical trials have been undertaken in this disease setting.

There have been no specific studies of imatinib mesylate (Gleevec) in veterinary medicine, although a few reports have been published regarding its use in both dogs and cats. In these, imatinib was well tolerated, and objective anti-tumor responses were observed in dogs with MCTs carrying both mutant and wild-type KIT.[20-22] Responses also have been observed in cats with MCT that have KIT mutations.[23,24]

Management of Adverse Events Associated With Toceranib and Masitinib

Nearly all small molecule inhibitors induce adverse events; as underlying co-morbidities may contribute to these effects, efforts should be made to increase the health status of dogs prior to their use. For both toceranib and masitinib, the most common side effects relate to the GI tract, including loss of appetite, diarrhea and occasionally vomiting (see ch. 343).[1-3,17,19] The administration of a gastric acid suppressant, particularly omeprazole, may be beneficial in mitigating the risk of GI ulceration, especially in the setting of MCTs. Inappetence is a relatively common side-effect and typically responds to standard anti-nausea therapies (metoclopramide, ondansetron, maropitant; see ch. 39) or low-dose prednisone. With respect to diarrhea, metronidazole and/or loperamide along with probiotics are often useful. Both protein losing nephropathy (PLN; see ch. 325) and systemic hypertension (see ch. 157) have been associated with toceranib administration. The PLN is generally mild to moderate and effectively managed with enalapril/benazepril and/or dose reduction. Similarly, the hypertension can be typically managed with amlodipine. Masitinib is reported to induce PLN, although a much more serious and sometimes fatal condition of protein loss can occur in rare cases.[19,25] Other toxicoses including hepatotoxicosis, neutropenia and anemia have been observed, although these occur infrequently. Drug holiday, dose reduction and schedule modification represent extremely useful tools for managing these toxicoses.

Additional Molecular Targets

While kinases have represented the most common target for therapeutic intervention, several other proteins are critical for cancer cell growth and survival. The heat shock protein HSP90 is responsible for folding several client proteins, many of which are oncogenes (KIT, MET, BRAF, AKT). HSP90 inhibitors block protein folding, resulting in protein degradation and tumor cell death. The HSP90 inhibitor STA-1474 showed good activity in dogs with a variety of solid tumors, particularly MCTs, in a phase 1 study.[26] A subsequent regimen-finding study in dogs with MCTs showed that 2-day consecutive dosing was most effective at inducing objective responses and providing sustained KIT downregulation (London et al, unpublished). Exportin 1 (XPO1)[27] is the sole nuclear exporter of several major tumor suppressor and growth regulatory proteins.[28,29] Its expression is upregulated in hematologic malignancies and solid tumors, often correlating with a poor prognosis. KPT-335 (verdinexor), an orally bioavailable small molecule XPO1 inhibitor, has shown activity in dogs with T and B cell lymphoma in phase 1 and 2 clinical trials.[30] Verdinexor is undergoing clinical development for treatment of canine lymphoma.

Histone deacetylase (HDAC) enzymes remove acetyl groups from histone proteins and regulate gene transcription.[31] HDAC inhibitors (HDACi) can alter the expression of epigenetically silenced genes and thereby inhibit tumor progression.[32,33] The anti-epileptic drug valproic acid is an HDACi that has activity in several tumor models.[34-36] In a phase 1 trial, valproic acid was given prior to doxorubicin in dogs with cancer.[37] Objective responses were observed and a few occurred in traditionally anthracycline-resistant tumors; importantly, the combination was safe and well tolerated. Lastly, RV1001 is a novel orally bioavailable small molecule inhibitor of phosphatidylinositol-3-kinase delta (PI3Kdelta), a cellular signaling protein known to contribute to tumor growth. RV1001 has activity against PI3Kdelta at low nanomolar concentrations, with effects on beta and gamma isoforms at low micromolar concentrations. A phase 1 clinical trial of RV1001 in dogs with naive or relapsed T or B cell lymphoma revealed excellent activity, with an objective response rate of 62% (3 CR, 10 PR).[38] Inhibition of pAKT was demonstrated in tumor samples within 2 hours of RV1001 dosing, showing rapid target modulation. RV1001 is undergoing further development for the treatment of canine lymphoma.

Summary

The development of small molecule inhibitors targeting key proteins that drive tumor growth and survival has transformed human cancer therapy. Such agents are only beginning to impact veterinary oncology with the availability of toceranib and masitinib, although more are likely to become available in the near future. The combination of small molecule inhibitors with standard chemotherapy and radiation therapy likely will markedly enhance treatment outcomes for veterinary patients in the future.

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CHAPTER 343

Complications of Anticancer Therapy

Louis-Philippe de Lorimier, Craig A. Clifford

Client Information Sheet: Side Effects and Complications of Anticancer Drugs

Introduction

Traditionally, because of the mere objective to kill as many cancer cells as possible with each dose administered, the dosage of conventional cytotoxic agents has been based on the concept of maximum tolerated dose (MTD) rather than the standard pharmokinetic/pharmodynamic (PK/PD) modeling (see ch. 160).[1] With this concept, some side effects will be expected and accepted ("tolerated" by the patient) when dosing below the MTD, and what is considered tolerated is determined based on the severity (grading) of the observed side effects.[2] When using anticancer therapy, the potential benefits should always outweigh the risks, but even with a thorough knowledge of the common side effects, it is rarely possible to accurately predict how an individual will react to a specific drug until it has been administered (i.e., the patient's own MTD is unknown). Most anticancer drugs have dosage ranges that will vary depending on the condition treated, the presence of co-morbidities, the age of the patient, the pre-treatment blood test results (organ function), the species to be treated, the breed of the patient, and the user's experience.

Most cytotoxic drugs are dosed on a mg/m^2 basis, the calculation based on body surface area (BSA) being presumably a more appropriate predictor of drug pharmacokinetics. However, the limitations of this approach have been demonstrated and dosing pets based on BSA may result in overdosing smaller patients (<10-15 kg), and possibly underdosing very large dogs.[3,4] For this reason, certain chemotherapy drugs may be best dosed on a mg/kg basis in smaller patients, such as the commonly used carboplatin and doxorubicin.

Corticosteroids are arguably the class of anticancer drugs with the most consistent side effect profile, polyuria/polydipsia (PU/PD) being the most noticeable one negatively impacting both the patients' and owners' quality of life.

New therapeutic classes of anticancer drugs are emerging (e.g., tyrosine kinase inhibitors, therapeutic vaccines, monoclonal antibodies) and the MTD concept may not be best suited to establish the appropriate dosage with these novel oncology treatments. For some of these newer drugs, *in vivo* "target inhibition" can be studied to help determine optimal dosing, which may be well below the MTD in some cases.[5] The common complications and side effects of anticancer therapy are generally classified by system, and a common terminology criteria and grading scheme has been established.[2] An expression that has long been used to describe the most common complications was "a BAG of side effects," which stood for Bone marrow (suppression), Alopecia, and Gastrointestinal. It is obvious that other systems can be affected.

Myelosuppression

Traditional cytotoxic chemotherapy agents are myelosuppressive by nature, since they affect rapidly dividing cells. The enzyme L-asparaginase is an exception amongst traditional anticancer agents, in that it is generally not myelosuppressive in and of itself. Typically, conventional chemotherapy drugs may cause various degrees of neutropenia and/or thrombocytopenia, since neutrophils and platelets have short bone marrow transit times and circulating half-lives. With red blood cells having longer bone marrow transit time and circulating half-life, a resulting anemia from chemotherapy may nevertheless happen in certain individuals, especially over the course of longer multi-agent protocols. The severity of cytopenias is graded from 1 to 4 (E-Table 343-1).[2]

E-TABLE 343-1

Grading of Cytopenias from Anticancer Therapy

ADVERSE EVENT	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Neutropenia	1.5 k/mcL to <LLN	1.0-1.499 k/mcL	0.5-0.999 k/mcL	<0.499 k/mcL
Thrombocytopenia	100 k/mcL to <LLN	50-99 k/mcL	25-49 k/mcL	<25 k/mcL
Anemia (PCV)				
Dogs	30% to <LLN	20-30%	15-20%	<15%
Cats	25% to <LLN	20-25%	15-20%	<15%

LLN, Lower limit of normal; *PCV*, packed cell volume.

Adapted from the VCOG-CTCAE grading system.[2]

With lymphoma, certain cytopenias may be encountered at diagnosis, before any therapy is started, especially anemia (often non-regenerative anemia of chronic disease) and thrombocytopenia (often with an immune-mediated component, or resulting from bone marrow infiltration). Anemia and thrombocytopenia are also common with visceral hemangiosarcoma at diagnosis; the regenerative anemia, from internal blood loss and microangiopathy, and the thrombocytopenia, resulting from consumption and destruction, both generally resolve following surgery (i.e., splenectomy) and before initiation of chemotherapy.

With high grade lymphomas and acute leukemias, myelophthisis may occur and lead to more pronounced cytopenias at diagnosis or following chemotherapy. This is a situation where L-asparaginase and corticosteroids might be best used initially, owing to their lack of myelosuppressive effects.

The nadir, or low point in the cell count following treatment, varies between chemotherapy drugs. Most often, it occurs around 6-8 days following the administration of the commonly used cytotoxic drugs including the vinca alkaloids (vincristine, vinblastine, vinorelbine), doxorubicin, mitoxantrone, and high-dose pulse alkylators (cyclophosphamide, lomustine in dogs). Carboplatin causes a nadir that manifests closer to 14 days post-treatment in dogs, and around 14 to more than 25 days in cats.[6,7] Lomustine is also unpredictable in cats, with nadirs happening between 7 to 28 days following administration, depending on the individual and the dosage used.[8]

Even though all cytotoxic agents may result in neutropenia, depending on the dosage used, the drugs most commonly associated with clinically significant neutropenias in dogs and cats include carboplatin, doxorubicin, lomustine, mitoxantrone, vinblastine, and vinorelbine. Vincristine and cyclophosphamide have often been said to be less myelosuppressive; however, both can result in severe (grade 4) neutropenia when used at the higher end of the dosage range, or in individuals that may be intrinsically more sensitive.[9] A more pronounced neutropenia may be observed when vincristine is co-administered with L-asparaginase. Importantly, dogs with the mutation of the ABCB1-1delta (MDR-1) gene are known to be at higher risk of side effects from various drugs and many chemotherapeutic agents including vinca alkaloids (vincristine, vinblastine, vinorelbine), doxorubicin, mitoxantrone, taxanes, and dactinomycin.[10,11] The breeds most commonly affected with the mutation include the Collie (rough or smooth), Australian Shepherd (miniature or standard), McNab, Silken Windhound, Long-haired Whippet, Shetland Sheepdog, and German Shepherd to name a few.[12] For complete and updated lists of breeds at risk and problem drugs, or for information on the genetic testing, visit the Washington State University Veterinary Clinical Pharmacology Laboratory website (http://vcpl.vetmed.wsu.edu/). Dogs of the previously mentioned breeds should be tested to determine their mutation status, and dose reductions of problem chemotherapy drugs are required for affected individuals. Interestingly, ABCB1-1delta mutations were recently described in cats, and may also affect chemotherapy and other drugs sensitivity in the affected feline patients.[13]

A complete blood cell (CBC) count should be performed prior to administering a pulsed dose of a cytotoxic agent to any patient. Generally speaking, a potentially myelosuppressive drug will not be administered if the neutrophil count is below 2,000/mcL or if the platelet count is below 75,000/mcL. When cytopenias are present that prevent the safe administration of chemotherapy, treatment should be delayed by 2 to 7 days, and a CBC repeated. When delays are necessary, the number of days should be based on the cell lineage in question (e.g., shorter duration with neutropenia, since the bone marrow transit time is shorter).

Because of reasons discussed above, CBCs should also be repeated 7 days and occasionally 14 days after

therapy as well, to monitor and document the nadir. An increased risk of systemic infection (neutropenic sepsis) is present with neutrophil counts below 1,000/mcL. Prophylactic oral antibacterial therapy is generally recommended in neutropenic patients that do not demonstrate clinical signs of illness (i.e., fever, lethargy), and common choices include trimethoprim/sulfamethoxazole (15-30 mg/kg PO q 12 h), amoxicillin/clavulanic acid (13-15 mg/kg PO q 12 h), and cephalexin (22-25 mg/kg PO q 12 h). Owners should be instructed to monitor their animal at home (general attitude, appetite, body temperature). In a vast majority of cases, the neutropenia will resolve within 2 to 5 days in dogs, and a rebound neutrophilic leukocytosis is often observed following marrow recovery. Episodes of neutropenia in cats may take longer to recover (7 to >14 days), especially following lomustine and carboplatin therapy. After a severe neutropenic episode (<1,000/mcL), dosage of the causative agent should be reduced by 10-20% on subsequent treatments, so as to reduce the risk of serious complications. It is important to know that neutropenia, being an indicator of the MTD being reached or approached, may be associated with a better prognosis (remission duration and survival times) in dogs and in people with lymphoma.[14] Trying to completely avoid any neutropenic episode at all cost ultimately may be detrimental to the patient and favor early resistance and relapse.

Cytotoxic drugs affecting both the gastrointestinal tract and bone marrow may be more likely to result in neutropenic septic episodes, likely because of an increased risk of bacterial translocation from the gastrointestinal tract. Two studies demonstrated that risk factors for the development of sepsis in dogs following chemotherapy included lower body weight, the diagnosis of lymphoma, and the administration of doxorubicin or vincristine.[15,16]

Severe neutropenic episodes resulting in clinical signs of illness, typically including fever, lethargy and anorexia, are to be treated aggressively with the patients hospitalized and monitored more intensively to prevent sepsis. This includes more comprehensive monitoring of blood glucose, lactate levels, electrolytes, as well as closer monitoring of patient parameters such as blood pressure (see ch. 99), temperature, etc. Supportive therapy for sepsis should be undertaken (see ch. 132). Digestive signs should be treated when present (see below), as are other findings on the biochemical profile (e.g., electrolyte imbalances) or complementary tests. Blood cultures would logically be optimal but are rarely necessary or rewarding knowing that most neutropenic septic episodes respond rapidly and completely with aggressive empirical therapy, marrow recovery being the most crucial element.

The use of colony stimulating factors (e.g., rhG-CSF) is controversial and of questionable benefit to most patients, since high endogenous levels of canine G-CSF are likely present during the neutropenic episode. Furthermore, a recent study demonstrated that dogs receiving rhG-CSF for neutropenic septic episodes were at higher risk for longer hospital stays and in-hospital mortality.[16] In most patients with uncomplicated episodes of neutropenic sepsis, the fever abates rapidly, within hours after supportive therapy is begun, and the patient released home, away from the risk of nosocomial infections. A study on 70 canine cases of chemotherapy-induced neutropenic septic episodes reported a mortality rate of 8.5%.[16]

Cats appear to develop true neutropenic sepsis much less commonly than do dogs, even though the nadirs are often prolonged in this species.

Transient thrombocytopenia often follows cytotoxic chemotherapy administration. This is most commonly observed with carboplatin, lomustine, dacarbazine, melphalan, dactinomycin, cytosine arabinoside and doxorubicin. Clinical signs are rarely observed with platelet counts above 25,000/mcL, but patients with severe thrombocytopenia should be monitored for ecchymoses, petechiae, and bleeding (gastrointestinal, gingival, epistaxis) and avoid trauma. Certain alkylating agents may cause cumulative, sometimes not completely reversible thrombocytopenia following chronic administration, including lomustine, melphalan and chlorambucil.[17] Regular CBCs should be monitored and the drug discontinued if a trend is observed or if the platelet count falls below 100,000-125,000/mcL. The use of thrombopoietic agents is controversial and poorly documented at present.

Two orally administered tyrosine kinases, toceranib phosphate (Palladia) and masitinib mesylate (Kinavet-CA1, Masivet), were developed and marketed to treat canine mast cell tumors. Even though they are not considered to be truly myelosuppressive like traditional cytotoxic agents, cytopenias may be observed with both veterinary-approved kinase inhibitors, secondary to growth signal inhibition, including neutropenia, thrombocytopenia, and anemia.[18-21] Most often, these cytopenias will be mild and reversible but may occasionally be severe enough to warrant a treatment delay (drug holiday), until the cell counts return to normal.

Dermatologic Complications

Alopecia, Changes in Pigmentation

Chemotherapy-induced alopecia is a common complication in people and, though it is a cosmetic side effect, it bears an important negative psychological impact for many patients. The loss of hair following chemotherapy is less of a problem in veterinary oncology, but certain canine breeds with continuously growing hair may shed more than usual or truly become partially or completely alopecic. More commonly affected breeds include the Maltese, Bichon Frisé, Poodles, certain Terrier breeds, Shih Tzu, and Old English Sheepdog. This side effect does not negatively impact their quality of life, and is reversible once treatment is discontinued (Figure 343-1). Cats may occasionally lose whiskers or facial hair (most typically) while undergoing chemotherapy.

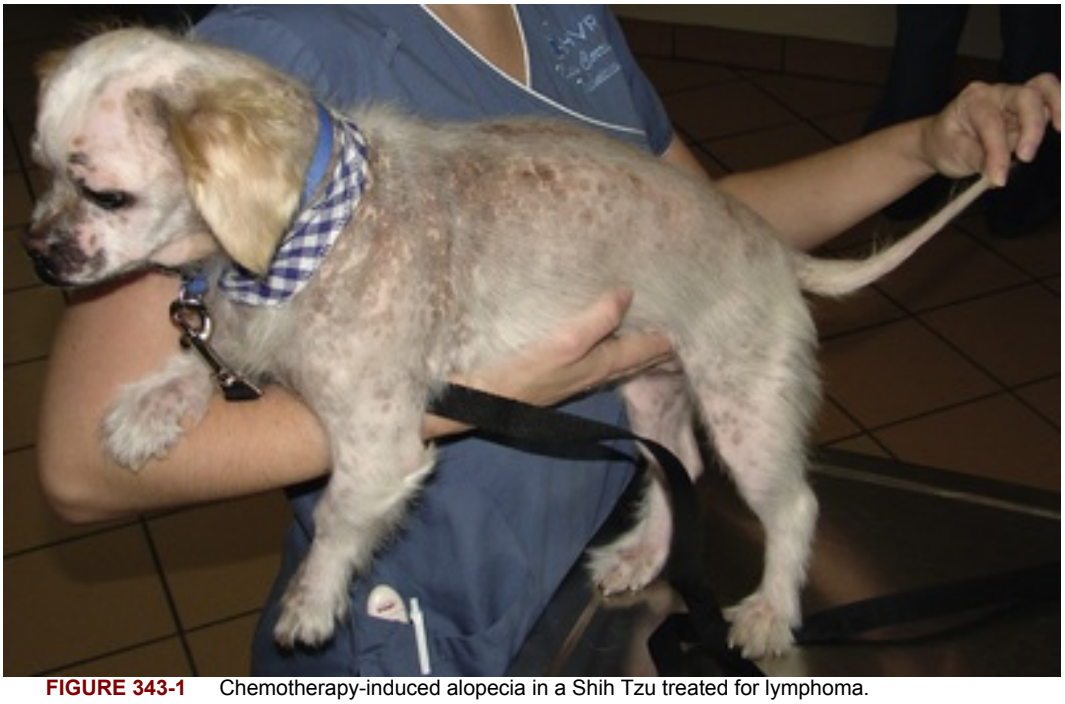

FIGURE 343-1 Chemotherapy-induced alopecia in a Shih Tzu treated for lymphoma.

Transient pigmentation alterations, most often depigmentation, have been reported in dogs treated with toceranib phosphate (Palladia), especially affecting the nose, footpads, lips, and less commonly the entire hair coat.[19] This complication, like alopecia, appears to be purely cosmetic and does not negatively impact the quality of life. It may be stem from the KIT protein inhibition, negatively impacting the skin melanocytes, and resolves upon discontinuation of the drug.

Extravasation

Certain chemotherapy drugs are irritants when administered perivenously, and include the platinum drugs (carboplatin and cisplatin), dacarbazine, mitoxantrone, and the taxanes. The local reaction with extravasation of irritants is mild to moderate and includes some degree of discomfort, erythema, crusting, and edema. True vesicants include the vinca alkaloids (vincristine, vinblastine, vinorelbine), anthracyclines (doxorubicin, epirubicin), dactinomycin, and mechlorethamine, and cause much more serious tissue damage when extravasated.

It is better to prevent extravasation injuries than to treat them after they occur. Using a vein that has not been used for >48 hours and installing a long catheter with a "clean stick" technique (see ch. 75) just before chemotherapy administration reduces the risks. Fluid pumps should be avoided, and simple gravity or manual syringe pushing favored. Minimal bandaging is recommended during chemotherapy administration, so as to see the catheter site and point of dermal entry as much as possible. If or when an extravasation of chemotherapy is observed, chemotherapy administration should be immediately discontinued, and negative pressure applied to the catheter to remove as much as possible of the agent at the site of perivenous leakage. Negative pressure should then be applied as the catheter is gently removed. Occlusive bandaging should be

avoided.

For extravasation of vinca alkaloids (vincristine, vinblastine, vinorelbine), it is recommended to apply warm compresses, for 15-20 minutes duration, four times a day, for 2-3 days. Some recommend instilling sterile saline (5-10 mL) around the site of leakage, to dilute the vesicant in local tissues. Others mention topical administration of dimethyl sulfoxide (DMSO), sometimes mixed with a corticosteroid, after heat application but these approaches are of arguable efficacy. The local infiltration of hyaluronidase has been described and may help reduce the severity of local tissue damage from vinca alkaloids, but the erratic availability of the drug makes it difficult to use consistently.[22] In general, vinca extravasation results in mild to moderate tissue damage, less commonly severe, and completely heals over 2-3 weeks without permanent consequences (Figures 343-2, *A-D*).

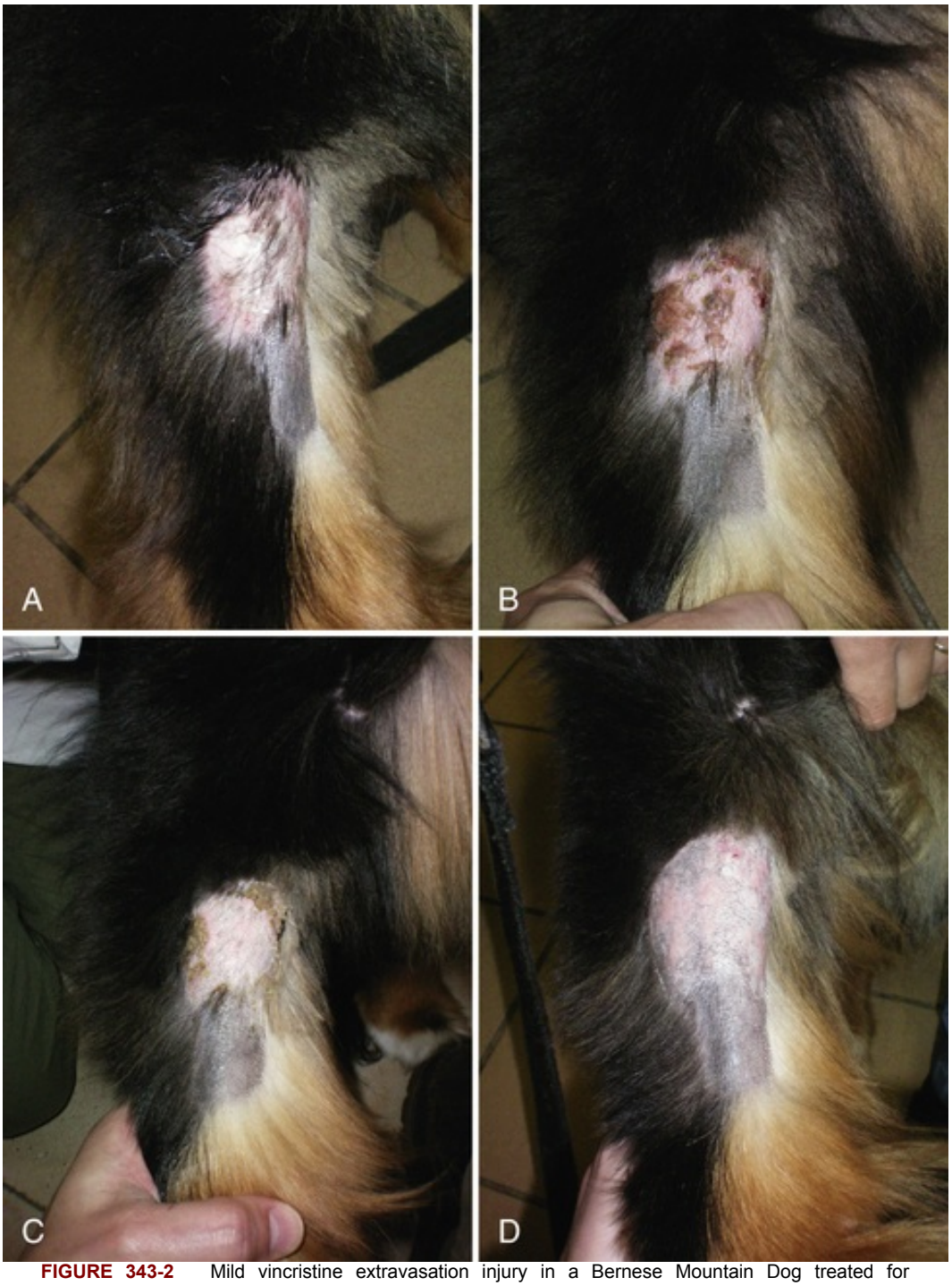

FIGURE 343-2 Mild vincristine extravasation injury in a Bernese Mountain Dog treated for

lymphoma, demonstrating progression of the lesion at days 5 **(A)** and 10 **(B),** and then improvement on days 13 **(C)** and 17 **(D).**

More serious, extravasation of doxorubicin, epirubicin or dactinomycin can result in very severe local tissue damage, sometimes progressing to dissecting necrosis in the deep tissues eventually requiring debridement surgery or, when damage appears irreversible, limb amputation (Figure 343-3). Contrary to the approach of extravasated vinca alkaloids, cold compresses on the site of injury are recommended with extravasation of these agents, for 15-20 minutes duration, four times a day, for 2-3 days. Again, the application of topical DMSO is of dubious benefit, but the timely intravenous administration of dexrazoxane, an iron chelator, may help markedly reduce and sometimes completely prevent the extent of local tissue damage.[23,24] Dexrazoxane is dosed at 10 times the dosage of doxorubicin (e.g., 300 mg/m^2 if the dog received 30 mg/m^2 of doxorubicin) and administered intravenously as soon as possible after the extravasation has occurred, and then ideally repeated 24 and 48 hours later. In rat studies, a benefit was observed when utilized within a 6-hour window of the extravasation.

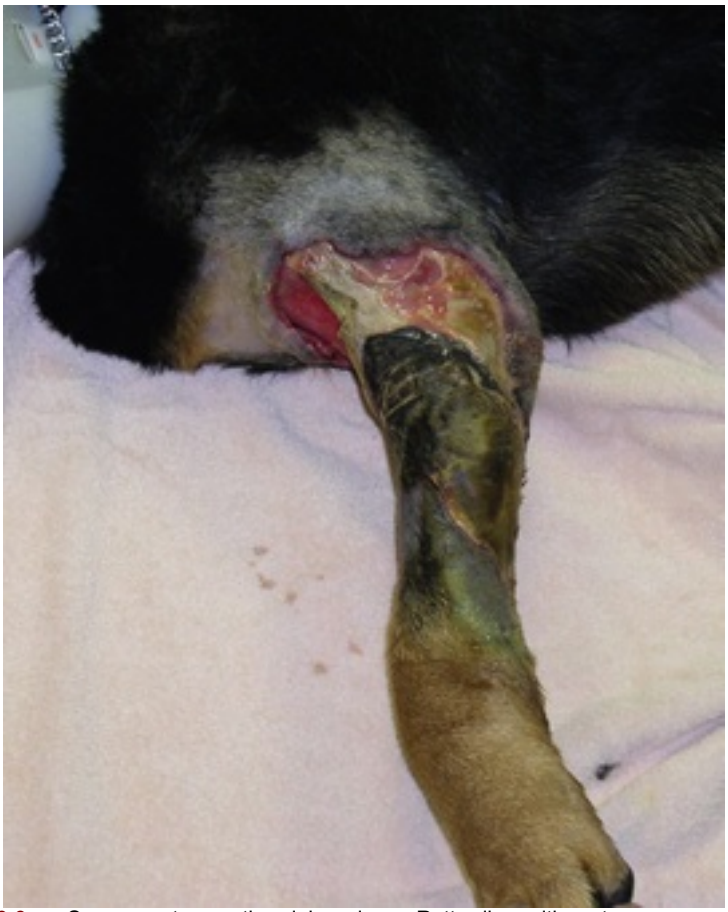

FIGURE 343-3 Severe extravasation injury in a Rottweiler with osteosarcoma treated with doxorubicin 12 days prior.

Mechlorethamine extravasations can be treated with a 2.5% solution of sodium thiosulfate, a sulfur group donor, injected directly into the tissues at the extravasation site (same volume as the volume of mechlorethamine administered).

In all cases of extravasation, adequate analgesia should be provided with nonsteroidal anti-inflammatory drugs or corticosteroids (see ch. 164), and adjuvant analgesic drugs (including antihistamines) as needed (see ch. 126 and 166). Occasionally, antibiotics may be beneficial when secondary bacterial infections are confirmed or suspected. Importantly, self-trauma should always be prevented (e.g., Elizabethan collar).

Palmar-Plantar Erythrodysesthesia (PPES)

Also known as the "hand-foot syndrome" in people, PPES is a frequent dermatologic toxicosis associated with the intravenous administration of liposomal doxorubicin in dogs and cats.[25-29] It may present as discomfort, erythema, alopecia, and ulceration in the axilla, inguinal area, and skin surrounding the footpads in dogs, and as focal alopecia on the chin and limbs in cats.[25-29] Though PPES is self-limiting, the discomfort may be severe enough to warrant treatment delays or discontinuation. The co-administration of oral pyridoxine (vitamin B_6; 50 mg PO q 8 h) markedly reduces the severity of PPES lesions in dogs.[26]

Gastrointestinal Complications

Gastrointestinal (GI) side effects from anticancer therapy are often the most feared by human cancer patients and owners of cancer-bearing pets, and for good reasons as they always negatively impact the quality of life. The toxicosis may result from direct damage to the rapidly dividing cells of the intestinal crypts, or from a stimulation of the chemoreceptor trigger zone (CTZ), in the medulla oblongata, via neurotransmitters such as serotonin and substance P binding to 5-HT_3 and NK_1 receptors, respectively. Vomiting from stimulation of the CTZ is an acute phenomenon, often occurring within 24 hours of drug administration, and the chemotherapy agents most commonly at fault include cisplatin (by far the most emetogenic), dacarbazine, streptozotocin, doxorubicin, and mechlorethamine. Anorexia, nausea, vomiting, and diarrhea caused by toxicosis affecting immature enterocytes generally occurs 1 to 5 days following administration, and the drugs most at risk of causing clinical signs include doxorubicin, epirubicin, dactinomycin, mitoxantrone, dacarbazine, vinca alkaloids, and taxanes. The tyrosine kinase inhibitors, toceranib and masitinib, may cause direct GI irritation resulting in anorexia, nausea, vomiting, diarrhea, or hematochezia. NSAIDs are commonly used in cancer-bearing pets for analgesia and for their known anticancer effects. The potential for GI irritation exists, and may be amplified when the non-selective drug piroxicam is combined with certain cytotoxic chemotherapy agents.[30,31] The severity of GI side effects is graded from 1 to 4 (E-Table 343-2).

E-TABLE 343-2

Grading of Gastrointestinal Side Effects from Anticancer Therapy

ADVERSE EVENT	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Anorexia	Coaxing or dietary changes required to maintain appetite	Oral intake altered ≤3 days w/o weight loss; appetite stimulants may be indicated	>3 days duration; significant weight loss (≥10%) or malnutrition; IV fluids, tube feeding or forcefeeding indicated	Life-threatening consequences; TPN indicated; >5 days duration
Nausea	Loss of appetite w/o alteration in eating habits	Salivation or "smacking of lips" <3 days, grade 2 anorexia	Salivation or "smacking of lips" 3-5 days, grade 3 anorexia	Salivation or "smacking of lips" >5 days, grade 4 anorexia
Vomiting	<3 episodes in 24 h, medical intervention not needed	3-10 episodes in 24 h; <5 episodes/day for ≤48 h; parenteral fluids (IV or SC) indicated ≤48 h; medications indicated	Multiple episodes >48 h and IV fluids or PPN/TPN indicated >48 h	Life threatening (e.g., hemodynamic collapse)
Diarrhea	Increase of up to 2 stools/day over baseline; no increase in frequency but consistency decreased over baseline	Increase of 3-6 stools/day over baseline; medications indicated; parenteral fluids (IV or SC) indicated ≤48 h; not interfering with ADL	Increase of >6 stools/day over baseline; incontinence >48 h; IV fluids >48 h; hospitalization; interfering with ADL	Life threatening (e.g., hemodynamic collapse)

ADL, Activities of daily living (eating, sleeping, defecating and urinating); *PPN*, partial parenteral nutrition; *TPN*, total parenteral nutrition.

Adapted from the VCOG-CTCAE grading system.[2]

Vincristine, via a neurotoxic effect on enteric motor function, may cause temporary ileus (dogs and cats)

and occasionally constipation (cats) in the days following administration. Abdominal discomfort, anorexia, nausea or vomiting may occur as a result, and patients may benefit from treatment with the prokinetic drug metoclopramide (0.3-0.5 mg/kg SC, PO q 8 h). In cancer-bearing pets not tolerating vincristine because of its effects on intestinal motility, replacing it with vinblastine may be a valid option.[31]

Chemotherapy-induced anorexia can be approached by offering more palatable foods, and pharmacologic appetite stimulation may also be used when necessary (see ch. 23). Commonly used drugs include cyproheptadine (dogs: 0.2 mg/kg PO q 12-24 h; cats: 2-4 mg PO q 12-24 h) and mirtazapine (dogs: 0.5 mg/kg PO q 24 h; cats: 0.5 mg/kg PO q 24-72 h).[33] Corticosteroids are generally not considered great choices for appetite stimulation because of their catabolic effects, but may be used at low dosage (e.g., prednisone at 0.5 mg/kg PO q 24 h, dexamethasone at 0.05 mg/kg PO q 24 h) and for short term use if not contraindicated. Oxazepam and megestrol acetate have been used on occasion for appetite stimulation in pets, the latter being a common choice in people with cancer cachexia, but are seldom recommended for this use nowadays. Low-dose intravenous propofol was shown to significantly increase food consumption in healthy dogs without causing excessive sedation, but the desired effect did not last long enough (15 minutes) to make it clinically useful.[34] A novel veterinary approved appetite stimulant, capromorelin, will soon become available as an option for anorexic pets. Nausea is a common underlying cause of anorexia, and may lead to vomiting when severe enough. Educating owners on how to recognize nausea in their pet is crucial. Signs of nausea may include loss of appetite, hypersalivation, licking the lips, turning the head when offered food, and vomiting. Offering more palatable foods to a nauseated animal may worsen the nausea and is not recommended. Treating actual or suspected nausea is crucial, even when no vomiting is reported, and may help improve the appetite. The drugs recommended to treat nausea are roughly the same as the ones used for vomiting (see below, and ch. 39).

Mild vomiting (<3 episodes/24 h) may be approached by food restriction for 12-24 hours, followed by gradual introduction of frequent small meals of a bland diet. If vomiting occurs when the stomach is empty (e.g., morning), gastric acid-suppressing drugs may be beneficial and include famotidine (0.5-1 mg/kg IV or PO q 12 h) and omeprazole (0.5-1 mg/kg PO q 24 h). With moderate vomiting, the use of antiemetics is warranted, and supportive therapy with parenteral crystalloids becomes indicated in more severe cases. The centrally acting antiemetic maropitant, a neurokinin 1 (NK_1) receptor inhibitor, is approved for use in dogs to prevent vomiting associated with cisplatin, and was also shown to be effective at reducing vomiting following doxorubicin administration.[35-37] Maropitant can be used both in dogs (1 mg/kg IV, SC q 24 h; 2 mg/kg PO q 24 h) and cats (1 mg/kg IV, SC, PO q 24 h).[35-38] Other antiemetics include metoclopramide, the $5\text{-}HT_3$ antagonists ondansetron (0.5-1 mg/kg IV, PO q 12-24 h) and dolasetron (0.5-1 mg/kg SC, IV q 12-24 h), and prochlorperazine (0.1-0.5 mg/kg IV, IM, SC q 8 h; 0.5-1 mg/kg PO q 8-12 h). Though antacids do not have direct antiemetic effects, their use may be beneficial to patients with severe nausea and vomiting. Severe vomiting requires supportive fluid therapy, and monitoring of chemistry profiles including electrolytes and acid-base status. Parenteral nutrition may also be required in more severe cases. Dosage reduction (10-20%) and a preventive approach should be implemented for subsequent administration of anticancer drugs that resulted in moderate to severe vomiting. A change of protocol may be required in more severe cases.

When treating macroscopic mast cell tumors, some of the GI clinical signs may result from hyperhistaminemia and hyperacidity following spontaneous degranulation or as a result of cytotoxic therapy.[39,40] High histamine levels, via the binding to H2-receptors on parietal cells, result in excessive secretion of hydrochloric acid, low gastric pH, and gastric irritation.

Mild diarrhea or soft stools can be approached with the feeding of a bland, highly digestible diet. With more severe chemotherapy-induced diarrhea, loperamide (0.1 mg/kg PO q 8-12 h) can be used in non-MDR-1 mutant dogs.[41,42] The antibiotics metronidazole (15 mg/kg PO q 12 h) and tylosin (10-20 mg/kg PO q 12 h) are also common choices. The use of naturally occurring clay to treat chemotherapy-induced diarrhea has also been shown to be beneficial.[43] Probiotics are now routinely used in clinics to treat acute or chronic diarrhea, and can be combined with other antidiarrheal therapies (see ch. 40, 167, and 178). A study evaluating the effect of maropitant to prevent vomiting from doxorubicin, serendipitously found that it also significantly reduced the frequency and severity of diarrhea in treated dogs, when compared to placebo.[37] Another placebo-controlled study evaluated the prophylactic use of trimethoprim-sulfadiazine (TMS) in dogs treated with doxorubicin for osteosarcoma and lymphoma.[44] The treated dogs (TMS group) had a significantly reduced hospitalization rate, and lower frequency and severity of GI toxicosis when compared to the placebo group.[44]

Mild GI toxicoses do not require dosage modifications. Moderate to severe toxicoses may require

hospitalization for supportive and symptomatic therapy, and should lead to subsequent dosage reductions of 10-25% or change in protocols, in addition to more aggressive prophylactic therapy (antiemetic, antidiarrheals).

Lethargy

Perhaps one of the most common and underreported side effects of anticancer therapy in pets, mild lethargy is generally self-limiting. Drugs most commonly associated with some degree of fatigue in the days following treatment are often also myelosuppressive and include doxorubicin, carboplatin, and lomustine, to name the most common only.

It is important to distinguish fatigue as a temporary and reversible side effect of therapy from lethargy secondary to nausea, anemia, pain, or tumor progression, as these underlying causes should be specifically addressed but chemotherapy-induced lethargy itself generally does not require intervention. Following a first dose of vincristine administered to a chemo naïve lymphoma patient, it is not rare to observe some self-limiting mild lethargy of short duration (generally 2-3 days) while billions of lymphoma cells are rapidly dying, resulting in significant energy consumption by large numbers of activated macrophages. A few weeks later, the same patient, receiving a second and identical dose of vincristine with a lymphoma that is now in partial remission (much smaller tumor burden), may not experience any fatigue.

When lethargy is moderate to severe, additional diagnostic tests should be performed to rule out cytopenias, disease progression, or concurrent disorders. Extreme lethargy in the 24-48 hours following aggressive chemotherapy administered to a chemo naïve lymphoma or lymphoblastic leukemia patient with a large disease burden could be secondary to the uncommon acute tumor lysis syndrome (ATLS; see ch. 344).

Cardiac Toxicosis

Cardiac toxicosis from chemotherapy is uncommon, but well described in pets and mainly associated with doxorubicin. Other drugs (e.g., mitoxantrone, epirubicin) were developed hoping for a similar efficacy profile but reduced risk of cardiotoxicosis. Also, it was demonstrated in dogs that a liposomal form of doxorubicin results in a much lower risk of cumulative cardiotoxicosis.[45]

There are two types of doxorubicin-induced cardiotoxicosis: acute or cumulative. Acute toxicosis presents as transient ventricular arrhythmias occurring during intravenous infusion, secondary to the spontaneous release of histamine and catecholamines, and generally does not bear clinical significance. The more serious cumulative cardiotoxicosis is the result of permanent damage to the cardiomyocytes, specifically oxidative injury to the sarcoplasmic reticulum, leading to reduced contractility, with or without arrhythmias, and to irreversible congestive heart failure (see ch. 247 and 252).

In dogs with no underlying myocardial disease, the risk of permanent cardiotoxicosis rises with cumulative doses above 180-240 mg/m^2. The risk/benefit ratio must be taken into account when treating dogs with underlying myocardial disease or with cumulative doses exceeding 240 mg/m^2. Options then include the use of a less cardiotoxic agent, or the co-administration of intravenous dexrazoxane (dosed at 10 times the doxorubicin dosage), an iron chelator known to reduce the risk of cardiotoxicosis from doxorubicin in dogs and people.[46,47]

Hepatotoxicosis

Lomustine (CCNU) is known to be hepatotoxic in dogs, and serum alanine aminotransferase (ALT), an indicator of hepatocellular damage, increases in up to 86% of treated dogs.[48-54] This hepatotoxicosis is cumulative and often irreversible. Acute liver failure may also rarely occur following a single treatment. In addition to pre-treatment CBC, the ALT should be monitored before each dose of lomustine and elevations of more than three times the upper normal limit should suffice to delay or discontinue treatment, unless the benefits of continued therapy clearly outweigh the risks. A prospective randomized clinical trial evaluated the co-administration of hepatoprotectants, combining S-adenosylmethionine and silybin, to lomustine in cancer-bearing dogs.[54] A reduced rate and severity of liver enzyme elevations was observed in dogs receiving the hepatoprotectants, when compared to dogs treated with lomustine alone.[54] In another study, dogs treated with lomustine were given the nutraceutical alpha-lipoic acid as a hepatoprotectant, but conclusions could not be made regarding the efficacy of this approach, owing to the lack of controls.[55] As a general rule, the concurrent use of hepatoprotectants is recommended in dogs receiving lomustine. Hepatotoxicosis in cats

receiving lomustine appears to be much less common.[56] The severity of liver enzyme and bilirubin elevations is graded from 1 to 4 (E-Table 343-3).

E-TABLE 343-3

Grading of Liver- and Kidney-Related Elevations from Anticancer Therapy

ALTERED SERUM BIOCHEMICAL PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
ALP				
Dogs	>ULN to 2.5 × ULN	>2.5-5.0 × ULN, transient (<2 wks)	>5-20 × ULN	>20 × ULN
Cats	>ULN to 1.25 × ULN	>1.25-1.5 × ULN, transient (<2 wks)	>1.5-2.0 × ULN	>2 × ULN
ALT				
Dogs	>ULN to 1.5 × ULN	>1.5-4.0 × ULN, transient (<2 wks)	>4.0-10 × ULN	>10 × ULN
Cats	>ULN to 1.25 × ULN	>1.25-1.5 × ULN, transient (<2 wks)	>1.5-2.0 × ULN	>2 × ULN
Bilirubin	>ULN to 1.5 × ULN	1.5-3.0 × ULN	3-10 × ULN	>10 × ULN
BUN	>1 to 1.5 × baseline; >ULN to 1.5 × ULN	>1.5 to 3 × baseline; >1.5 to 2.0 × ULN	>3 × baseline; >2.0-3 × ULN	>3 × ULN
Creatinine				

ALP, Alkaline phosphatase; *ALT*, alanine aminotransferase; *BUN*, blood urea nitrogen; *ULN*, upper limit of normal reference range.

Adapted from the VCOG-CTCAE grading system.[2]

Elevations in serum ALT are also reported to occur with the administration of streptozotocin to dogs with insulinoma.[57]

Vincristine is not hepatotoxic but, like other chemotherapy agents, is mainly eliminated via biliary excretion. In patients with marked cholestasis, as can be seen occasionally with hepatic infiltration by lymphoma, vincristine should temporarily be avoided or used at lower dosages in light of an increased risk of toxicosis resulting from a prolonged circulating half-life.

Even though they may not be considered true hepatotoxicoses, elevations of the corticosteroid-induced alkaline phosphatase and vacuolar hepatopathy are commonly associated with the use of corticosteroids in dogs, cancer-bearing or not (see ch. 285). Mild to moderate reversible liver enzyme elevations are also reported relatively commonly with the veterinary-approved tyrosine kinase inhibitors, toceranib and masitinib, and monitoring is indicated with chronic therapy.[19,58]

Neurologic Toxicosis

Neurologic toxicosis is uncommon in veterinary cancer patients when compared to people. Vincristine is known to cause GI signs in pets (ileus, constipation in cats) from its neurotoxic effect on enteric motor function, but very rarely a peripheral neuropathy similar to the dose-limiting toxicity observed in people.[59] The risk of central neurotoxicosis from vincristine, normally extremely low, may be higher in dogs homozygous for the ABCB1-1delta mutation.[60]

The antimetabolite 5-fluorouracil (5-FU) rarely causes clinically significant signs of neurotoxicosis in dogs when used at the standard dosage (150 mg/m^2 IV).[61] It is, however, extremely neurotoxic with accidental exposures to higher doses in dogs, and 5-FU is absolutely contraindicated in cats owing to a fatal neurotoxicity in this species.[62,63]

The alkylator chlorambucil, especially when used as a high-dose pulse regimen, may rarely cause reversible myoclonus and seizures in cats and dogs.[64,65] Chlorambucil is known to cause neurotoxic effects in the form of mood alterations and seizures in people as well.[66,67]

Mechlorethamine rarely causes reversible diminished hearing or hearing loss in people, and anecdotal reports of partially reversible hearing loss have been observed in cats.[68]

Urinary Tract Toxicosis

Nephrotoxicosis

Certain chemotherapy drugs are known nephrotoxicants requiring intense saline diuresis to reduce the risk of kidney disease in pets. These include cisplatin (dogs only), ifosfamide (dogs and cats), and streptozotocin (dogs).[57,69-71] Cancer-bearing pets with known or suspected kidney disease should not be treated with these drugs, owing to a high risk/benefit ratio. The close monitoring or renal parameters is advised, and their administration should be discontinued if creatinine elevations are observed. The severity of BUN and creatinine elevations is graded from 1 to 4 (see E-Table 343-3).

Doxorubicin has been described as a potential nephrotoxicant in cats, especially when administered at the dosage commonly used in dogs.[72] It has been demonstrated that the drug can be safely administered to cats at a dosage of 22-25 mg/m^2, and that the very low dosage recommended (1 mg/kg) following the initial toxicity study may have been too much of a dose reduction.[73] Renal parameters should be monitored in cats treated with doxorubicin, and prudence is recommended. In addition to the previously mentioned hepatotoxicity, lomustine (CCNU) may also be a potential nephrotoxicant in dogs, whether it is administered with a high-dose pulse or low-dose metronomic protocol.[53,74]

NSAIDs, including piroxicam and many veterinary approved molecules, are known for their nephrotoxic potential independent of their cyclooxygenase (COX)-2 selectivity. They are commonly administered to cancer-bearing pets, both for their analgesic and potential anticancer properties. Caution should be observed and regular monitoring performed, especially when combining their use to other potential nephrotoxicants, with chronic use, or when patients have questionable or decreased renal function. The combination of NSAIDs with cisplatin is simply too toxic and should be discouraged.[75-77]

The bisphosphonates are a class of drugs used in cancer patients for their inhibitory effect on osteoclasts, which is beneficial in the treatment of osteolytic bone pain and hypercalcemia. They are generally very well tolerated but both pamidronate and zoledronate, two potent and clinically useful intravenous aminobisphosphonates, showed the potential for nephrotoxicosis in preclinical toxicology studies. Clinical studies in cancer-bearing dogs showed that they could be safely administered to dogs and cats, alone or combined with other anticancer therapies.[78-85] The duration of infusion appears to play a role in their nephrotoxicity, and pamidronate (dogs: 1-2 mg/kg IV; cats: 1-1.5 mg/kg IV) should be administered over 2 hours, while zoledronate (dogs: 0.15-0.25 mg/kg; cats: 0.15-0.2 mg/kg) requires a shorter 15-minute infusion, both in 0.9% saline.[78-85]

The tyrosine kinase inhibitor masitinib mesylate has been shown to cause a protein-losing nephropathy (PLN) in up to 10% of treated pets, resulting in severe proteinuria in some cases.[20,21,86] Renal parameters, serum albumin, urinalyses and urine protein/creatinine ratios must be monitored, and the administration of the drug discontinued with progressive proteinuria. This drug-induced PLN is apparently reversible in most cases if identified early and the causative agent is removed.[20,21,86]

Carboplatin, unlike cisplatin, is not nephrotoxic at the clinically useful dosage. Studies in cats confirmed that, optimally, dosage would be individualized and based on glomerular filtration rate and area under the curve.[87-89]

Urothelial Toxicosis

Sterile hemorrhagic cystitis (SHC) is a well-recognized complication of cyclophosphamide and ifosfamide administration, direct urothelial irritation being chiefly caused by acrolein, an inactive metabolite. The risk of SHC in dogs may vary depending on the protocol of cyclophosphamide administration and cumulative doses, and the co-administration of furosemide or the thiol-based compound mesna was shown to significantly reduce this risk.[90-94] Cats may be at lower risk of developing SHC, but caution should be used when predisposing factors are present, including feline idiopathic cystitis.

If the use of mesna may not be mandatory with standard dosing of cyclophosphamide in dogs, it is recommended with ifosfamide or with high-dose (myeloablative) cyclophosphamide, as both would otherwise result in a high rate of serious SHC.[70,71,95-97] Ifosfamide, as previously mentioned, also requires saline diuresis to reduce the risk of nephrotoxicosis.

Various treatment strategies have been described anecdotally for SHC. It is imperative first and foremost to discontinue administration of the causative agent indefinitely, and to confirm SHC by ruling out other differentials (urinary tract infection, crystalluria, bladder tumor, etc.).

The signs of SHC generally tend to abate once the cause has been removed, but may take weeks or months to do so with severe cases. Early detection, when microscopic hematuria is confirmed without detectable clinical signs followed by discontinuation may improve the chances of mild, rapidly resolving SHC.

Symptomatic therapy is most typically used with SHC, and often includes the use of NSAIDs, to control discomfort and inflammation, and oxybutynin (dogs: 0.2-0.3 mg/kg PO q 8-12 h) to reduce the severity of muscle spasms. Some advocate the use of polysulfated glycosaminoglycan (Adequan) or pentosan polysulfate (Cartrophen Vet), so as to help restore the protective layer of the urinary bladder mucosa. Adjuvant analgesics may be required with more severe cases, and drugs anecdotally used to treat idiopathic cystitis (see ch. 334) may be useful, including amitriptyline (1-2 mg/kg PO q 12-24 h) and gabapentin (8-15 mg/kg PO q 8-12 h). In rare, more extreme and refractory cases, surgery may be required in the form of debridement or partial cystectomy. A medical treatment that has been described for such severe cases is the instillation of diluted formalin in the bladder, a procedure that resulted in improvement of the clinical signs in the few reported cases.[98,99]

Hypersensitivity Reactions (see ch. 137)

Hypersensitivity reactions are not common, but are well recognized with the administration of a handful of chemotherapeutic agents. A true type I, IgE-mediated anaphylactic reaction may occur following the administration of L-asparaginase, the risk being higher with increasing dose numbers. It is recommended to never administer L-asparaginase intravenously, the intramuscular or subcutaneous route being favored in dogs and cats, respectively, and to pre-treat with diphenhydramine (1-2 mg/kg IM or SC) 15 minutes prior to administration.

Doxorubicin may cause an anaphylactoid reaction, with accompanying hypotension and tachycardia, resulting from spontaneous histamine release by mast cells via a non-IgE mediated mechanism.[100] This histamine release, also a cause of cardiac arrhythmias, may be more pronounced with faster administration, hence the general recommendation to deliver as a short 15-30 minutes infusion. When following this recommendation, pre-treatment with diphenhydramine or dexamethasone may not always be required.

Finally, certain chemotherapy agents may be associated with relatively severe cutaneous hypersensitivity reactions in pets, mediated by their inert vehicles. The reactions include pruritus, flushing, urticaria, and facial swelling.[101-103] They were reported with both paclitaxel (cats and dogs) and etoposide (dogs) owing to their carriers, Cremophor EL and polysorbate-80, respectively, and the reactions occurred despite aggressive premedication.[100-103] Newer formulations or methods of administration may help minimize the risk of such reactions, including micellar incorporation of paclitaxel, or the use of the subcutaneous route.[104-106]

Specific and Uncommon Toxicoses

Cisplatin administered intravenously to cats causes severe, fatal pulmonary edema, and is therefore absolutely contraindicated, apart from the occasional low-dose intralesional use.

Pulmonary fibrosis can be a complication associated with high cumulative doses of bleomycin in dogs, but is an uncommon clinical concern in practice.[107] In cats, pulmonary hypertension and fibrosis may result from high cumulative doses of lomustine.[108] Pulmonary fibrosis may also be an uncommon complication in dogs treated with the novel chemotherapy agent rabacfosadine (VDC-1101), under evaluation to become FDA approved for the treatment of canine lymphoma.[109]

Streptozotocin is a chemotherapy agent that is especially toxic to the pancreatic beta-cells, and is used only to treat insulinoma in people and dogs. An expected potential complication is diabetes mellitus, from complete beta-cell ablation, and was observed in 42% of treated dogs in a recent prospective study.[57]

Pancreatitis has been reported to occur in a low percentage of dogs treated with toceranib phosphate.[19] The cause-effect relationship or underlying mechanism has not been established. Appropriate diagnostic tests are recommended when a dog receiving toceranib phosphate has clinical signs compatible with possible pancreatitis.

Lameness, most likely from muscular cramps, has been associated with the use of toceranib phosphate in dogs.[19] The lameness is most typically mild and weight-bearing, and resolves with a short (1-2 doses) drug holiday and an appropriate analgesic approach. Interestingly, the lameness rarely recurs upon re-initiation of

toceranib administration.

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CHAPTER 344

Hematopoietic Tumors

David M. Vail

Client Information Sheet: Hematopoietic Tumors

Lymphoma

Lymphoma is the most common hematopoietic tumor affecting dogs and cats and is defined as a proliferation of malignant lymphoid cells affecting primarily the lymph nodes or solid visceral organs, such as the liver or spleen. Lymphoma is a loose categorization of a broad and varied group of several cancer subtypes arising from lymphoid cells. Subcategorization of the various types of lymphoma in dogs and cats is becoming more generally available and ultimately may allow more accurate prognostication and more individualized therapy.

Etiology

The etiology of lymphoma in companion animals is poorly understood. Several etiologic factors have been investigated including genetic and molecular,[1-31] infectious,[32-42] environmental[43-54] and immunologic factors.[55-61] While several genetic and molecular aberrations have been documented in dogs and cats, the clinical and therapeutic relevance of these factors are currently investigational and are therefore beyond the scope of the current chapter and the interested reader is referred to original manuscripts listed. Although certain uncommon varieties of lymphoma in cats have been directly and indirectly associated with feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV), respectively, no strong evidence exists for a retroviral etiology in dogs. Impaired immune function, including immunosuppressive therapy (e.g., renal transplant therapy) has been implicated in both dogs and cats, as has the presence of chronic inflammatory disease such as atopic dermatitis and cutaneous lymphoma. Additionally, an association between gastric *Helicobacter* infection and gastric mucosa associated lymphoid tissue (MALT) lymphoma in cats[62] and perhaps the dog[34] is suggested in one study and since this is a recognized syndrome in people, warrants further investigation.

Classification

Several classification schemes for lymphoma have been evaluated, including those based on anatomic site, World Health Organization (WHO) clinical staging (Table 344-1), histologic/cytologic/immune-phenotype, and genotype.

TABLE 344-1

World Health Organization Clinical Staging for Domestic Animals with Lymphoma

STAGE	CRITERIA
I	Single lymph node
II	Multiple lymph nodes in a regional area
III	Generalized lymphadenopathy
IV	Liver and/or spleen involvement (with or without stage III)

V	Bone marrow or blood involvement and/or any nonlymphoid organ (with or without stages I to IV)
Substage a	Without clinical signs of disease
Substage b	With clinical signs of disease

World Health Organization: *TNM classification of tumors in domestic animals*, Geneva, 1980, World Health Organization.

Canine Classification

In the dog, 80% to 85% of cases are of the multicentric peripheral nodal anatomic type and present as WHO stage III or IV. Alimentary (≈7%), cutaneous (≈6%), mediastinal (≈3%) and miscellaneous extranodal sites (central nervous system [CNS], bone, heart, nasal cavity, and primary ocular locations) are less frequently encountered. As previously mentioned, lymphoma is really a catch-all term for a varied group of several cancer subtypes arising from lymphoid cells. Recent advances in flow-cytometric, histopathologic, immunophenotypic and genotypic characterizations are just now beginning to provide us with data that may subcategorize this disease into prognostically important groups that may ultimately result in more personalized treatment recommendations. The most commonly applied histologic classification scheme is the WHO scheme based on immunophenotype and histologic phenotype.[63] Most cases (≈80%) equate to intermediate or high-grade non-Hodgkin's lymphoma in humans. Most canine lymphoma is of the B-cell immunophenotype, with approximately 25% to 30% being of T-cell derivation. Applying WHO classification, Valli et al. reported the 5 most common lymphoma subtypes in dogs (representing approximately 80% of cases) in decreasing order of frequency as diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphoma not otherwise specified, nodal T-zone lymphoma, T lymphoblastic lymphoma, and marginal zone lymphoma.[64] DLBCL can be further classified into the prognostically distinct germinal center and post-germinal center subtypes by gene expression profiling.[23] Diagnosis/classification of clinical specimens by flow-cytometric and histopathologic methods for the purposes of prognoses and treatment will be discussed subsequently. Indolent forms of lymphoma (e.g., T zone, marginal zone) also exist.[63-69]

Feline Classification

Most lymphomas in cats are currently classified by anatomic site and whether they represent small cell/low grade indolent forms versus large cell/intermediate grade phenotypes. The overall prevalence of lymphoma in cats appears to be increasing and the increased prevalence appears due to an increase in the number and relative frequency of the alimentary (and in particular the intestinal) anatomic form of lymphoma in the species.[70-78] The typical signalment for cats with lymphoma cannot be uniformly stated as it varies widely based on anatomic site and FeLV status and therefore will be discussed individually under site-specific discussions and in Table 344-2.[35,79-86] In general, Siamese cats appear overrepresented and within the Siamese breed, there appears to be a predisposition for a mediastinal form that is not FeLV-associated and represents a younger population (median of 3 years).[87] Two distinct forms of lymphoma in cats bear special mention. Large granular lymphocyte lymphoma, a granulated, round cell tumor, usually involves the intestinal tract and abdominal viscera, with systemic involvement being the norm.[88-91] Affected cats are generally FeLV/FIV negative, and a preponderance of CD3+/CD8+ T-cell or NK-cell immunophenotype suggests a small intestinal intraepithelial origin. A second distinct class in cats resembling human Hodgkin's disease also has been characterized.[92-94] This form typically involves solitary or regional nodes of the head and neck and tumors are immunophenotypically classified as T-cell rich, B-cell lymphoma. Histologically, lymph nodes can be effaced by either nodular or diffuse small to blastic lymphocytes with characteristic bizarre or multinucleated cells (Reed-Sternberg-like cells). No association with FeLV or FIV has been documented.

TABLE 344-2

General Characteristics of the Most Commonly Encountered Anatomic Forms of Lymphoma in Cats*

ANATOMIC FORM†	RELATIVE FREQUENCY‡	MEDIAN AGE (YRS)	FELV ANTIGENEMIC	B-CELL	T-CELL	GENERAL PROGNOSIS
Alimentary/gastrointestinal§						
Small cell/low-grade	Common	13	Rare	Rare	Common	Good

Intermediate/large cell	Moderate	10	Rare	Common	Rare	Poor
Nasal	Uncommon	9.5	Rare	Common	Uncommon	Good
Mediastinal	Uncommon	2-4	Common	Uncommon	Common	Poor-Fair
Peripheral nodal	Uncommon	7	Uncommon	Moderate	Moderate	Fair-Poor
Laryngeal/tracheal	Uncommon	9	Rare	ID	ID	Good-Fair
Renal	Rare	9	Rare	Common	Uncommon	Poor-Fair
CNS	Rare	4-10	Rare	ID	ID	Poor
Cutaneous	Rare	10-13	Rare	Rare	Common	Fair
Hepatic (pure)	Rare	12	Rare	Uncommon	Common	Poor

*Data may include overlap or mixing of sites and represents the "post-FeLV era."

†As the primary site of presentation, rather than extension or progression.

‡Common = >50% of clinical presentations; Moderate = 20-50 % of clinical presentations; Uncommon = 5-20% of clinical presentation; Rare = <5% of clinical presentations.

§Includes those reported as "intra-abdominal" where intestinal is a documented component.

CNS, Central nervous system; *FeLV*, feline leukemia virus; *ID*, insufficient data.

Clinical Presentation and Signs

Canine Multicentric Nodal Lymphoma

Lymphoma affects primarily middle-aged to older dogs. No sex predilection is observed, and many different breeds are represented. The prevalence of certain immunophenotypes of lymphoma in dogs varies by breed.[16] Most cases present as relatively healthy dogs (substage a) with incidental generalized lymphadenopathy (Figure 344-1). In dogs with substage b disease, clinical signs are nonspecific and can include inappetence, weight loss, and lethargy. Paraneoplastic hypercalcemia (see ch. 352) may result in presentation for polyuria and polydipsia (see ch. 45). In stage V disease, if bone marrow involvement is marked, peripheral cytopenias may result in presentations reflecting neutropenic sepsis, thrombocytopenic hemorrhage, or anemia.

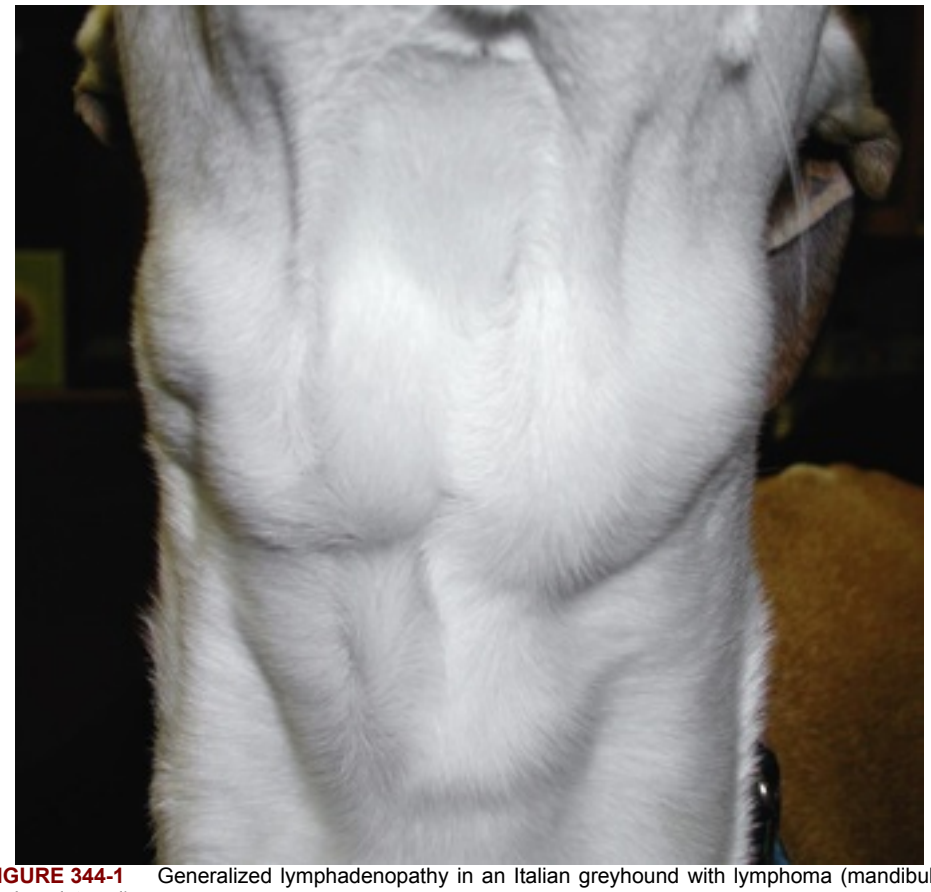

FIGURE 344-1 Generalized lymphadenopathy in an Italian greyhound with lymphoma (mandibular nodes pictured).

Canine Lymphoma of Other Sites

The presentation and associated clinical signs of lymphoma reflect the anatomic form present in each individual case. *Alimentary forms* may present with signs specific to the gastrointestinal tract (e.g., vomiting [see ch. 39], diarrhea [see ch. 40], weight loss [see ch. 19], inappetence [see ch. 23]). Mediastinal forms may present with respiratory signs (dyspnea [see ch. 28], muffled heart sounds) or with precaval syndrome characterized by pitting edema (see ch. 18) of the head, neck, and forelimbs secondary to tumor compression of the cranial vena cava (Figure 344-2). Nearly half of cases with mediastinal lymphoma are associated with paraneoplastic hypercalcemia,[95] resulting in polydipsia and polyuria as a presenting complaint.

FIGURE 344-2 Precaval syndrome in a dog with mediastinal lymphoma. Pitting edema of the head and neck are noted.

Cutaneous lymphoma has been called the "great imitator" because of its propensity to present in many varying forms. Single or multiple cutaneous lesions can occur, which may appear as mild, eczematous plaques or more impressive nodular tumors (Figure 344-3). Lesions may or may not be pruritic and can occur anywhere on the skin and in the oral cavity.

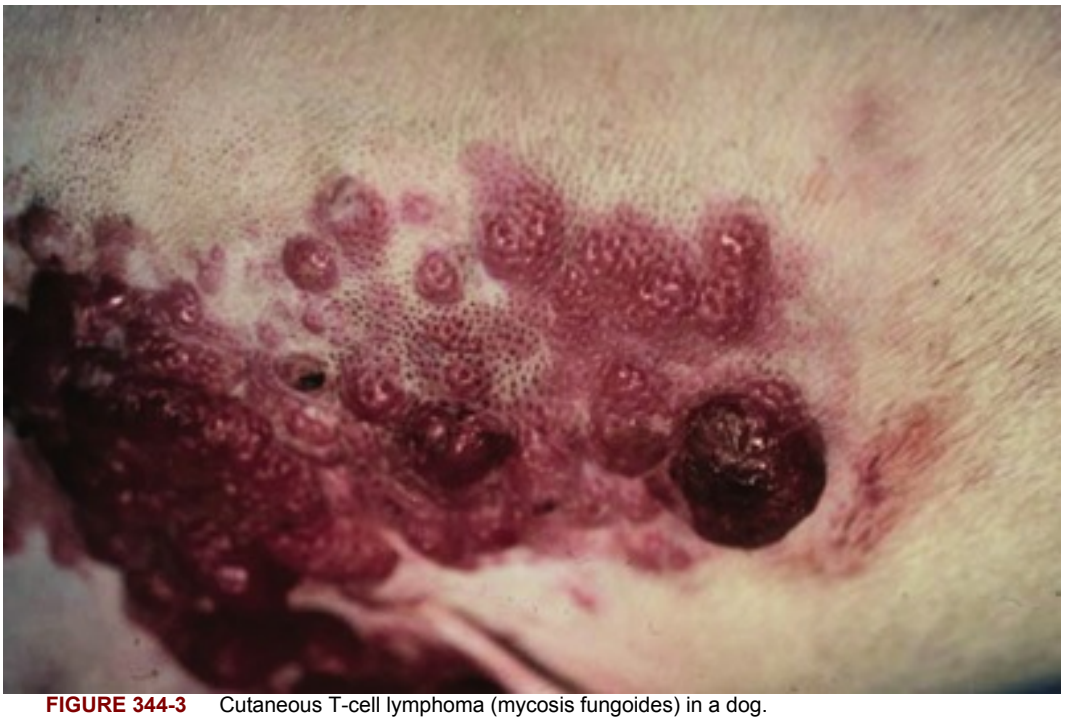

FIGURE 344-3 Cutaneous T-cell lymphoma (mycosis fungoides) in a dog.

Miscellaneous sites of lymphoma result in signs attributable to the location (i.e., lameness for bone lesions, neurologic compromise for CNS lymphoma).

Feline Lymphoma

No sex predilections have been consistently identified; however, the Siamese breed may be overrepresented.[87] In general, cats are more likely than dogs to present with clinical illness; ≥75% present with substage b signs, reflecting in part the high frequency of gastrointestinal involvement. Cats with alimentary lymphoma or large granular lymphocyte lymphoma present with varying degrees of weight loss (see ch. 19), unkempt hair coat, inappetence (see ch. 23), chronic diarrhea (see ch. 40), and vomiting (see ch. 39). Cats with mediastinal disease are often in severe respiratory distress (see ch. 139) secondary to an intrathoracic mass or the presence of significant pleural effusion (see ch. 244). Cats with renal lymphoma may present with polyuria/polydipsia secondary to renal failure. In the case of nasal lymphoma, sneezing (see ch. 27), chronic serosanguineous nasal discharge, exophthalmos, and facial deformity are common presentations. Cats with CNS lymphoma can present with constitutional signs (anorexia, lethargy) and signs referring to intracranial lesions, spinal lesions, or both. Cats with FeLV-associated lymphoma are more likely to present with anemia. Cats with Hodgkin's-like disease often present with a solitary enlarged mandibular or cervical node and are otherwise clinically healthy (substage a).

Diagnosis

For dogs suspected of having lymphoma, the diagnostic evaluation should include a thorough physical examination, complete blood count (CBC), serum biochemical profile and urinalysis. Optimally, ionized calcium should be measured. Ultimately, obtaining tissue and/or cytologic specimens for a definitive diagnosis is essential.

Physical Examination

A thorough physical examination should include palpation of all assessable lymph nodes and a digital rectal examination in the dog (see ch. 2). Mucous membranes should be evaluated for pallor or petechiae indicative of anemia or thrombocytopenia secondary to myelophthisis and for evidence of major organ failure, including the presence of icterus or uremic ulcers. Abdominal palpation may reveal organomegaly, intestinal wall thickening, or mesenteric lymphadenopathy. The presence of a mediastinal mass and/or pleural effusion may be suspected based on thoracic compression in cats and auscultation in both dogs and cats. An ophthalmic examination (see ch. 11) reveals abnormalities (e.g., uveitis, retinal hemorrhage, ocular

infiltration) in approximately one third to one half of dogs and cats with lymphoma.[96,97]

Hematologic Abnormalities

Hematologic abnormalities occur in the majority of cases. Anemia, when present, is usually normocytic, normochromic, and nonregenerative, reflecting anemia of chronic disease. Regenerative anemias may reflect concomitant blood loss or hemolysis. Cats with FeLV-associated disease may have a macrocytic anemia. If significant myelophthisis is present, the anemia may be accompanied by thrombocytopenia and leukopenia. Circulating atypical lymphocytes may be indicative of bone marrow involvement and leukemia. Hypoproteinemia is more commonly observed in animals with alimentary lymphoma.

Bone marrow aspiration cytology is recommended for staging due to the prognostic significance of marked marrow involvement (see ch. 92); it is also recommended for cases in which lymphoma is suspected but is not documented by assessment of peripheral nodes.

Serum Biochemical Abnormalities

Approximately 15% of dogs with lymphoma (40% of dogs with mediastinal involvement) are hypercalcemic (see ch. 297), often owing to the ectopic production of parathyroid hormone-related peptide (see ch. 352).[95,98] In cases of hypercalcemia of unknown origin, lymphoma should always be considered high on the differential disease list. In addition, the presence of hypercalcemia can serve as a marker for response to therapy. Elevations in blood urea nitrogen and serum creatinine may occur secondary to renal infiltration with tumor, hypercalcemic nephrosis, or dehydration. Liver-specific enzyme or bilirubin elevations may result from hepatic parenchymal infiltration. Serum globulin elevations, usually monoclonal, occur infrequently with B-cell lymphoma.

Retroviral Status

In the cat, retroviral screening (i.e., FeLV [see ch. 223] and FIV [see ch. 222]) is important from diagnostic, prognostic, and husbandry standpoints. The relative frequency of FeLV associations is presented in Table 344-2.

Imaging

Imaging (radiographic, ultrasonographic, computed tomography [CT], positron emission tomography [PET], PET/CT) may be important for diagnosis (especially in cases lacking peripheral lymphadenopathy) and to characterize treatment response. Imaging is equally important for clinical staging (i.e., determining the extent of disease), as results may significantly affect the overall prognosis and alter the caregiver's willingness to pursue therapy. Abnormalities on thoracic radiographs may include evidence of pulmonary infiltrates and thoracic lymphadenomegaly (Figure 344-4). Abdominal radiographs or ultrasound may reveal evidence of abdominal lymphadenopathy and/or spleen and liver involvement. Abdominal ultrasound (see ch. 88) is most important when intestinal lymphoma is suspected in the absence of peripheral lymphadenopathy. Additional imaging, including contrast studies of the gastrointestinal tract, CT, PET/CT, MR or myelographic studies of the CNS, and skeletal radiographic/scintigraphy surveys are reserved for cases in which involvement of the appropriate anatomic site is suspected. PET/CT represents the standard of care for staging and monitoring response in people with lymphoma; however, a lack of widespread availability precludes its routine use in veterinary oncology.[99-102] In the author's practice, unless clinical signs attributable to the abdomen exist, for typical cases of canine peripheral nodal lymphoma, imaging is limited to thoracic radiographs, as there is no prognostic difference between dogs with stage III and stage IV disease (i.e., liver/spleen involvement); however, the presence of cranial mediastinal lymphadenopathy is of prognostic significance.

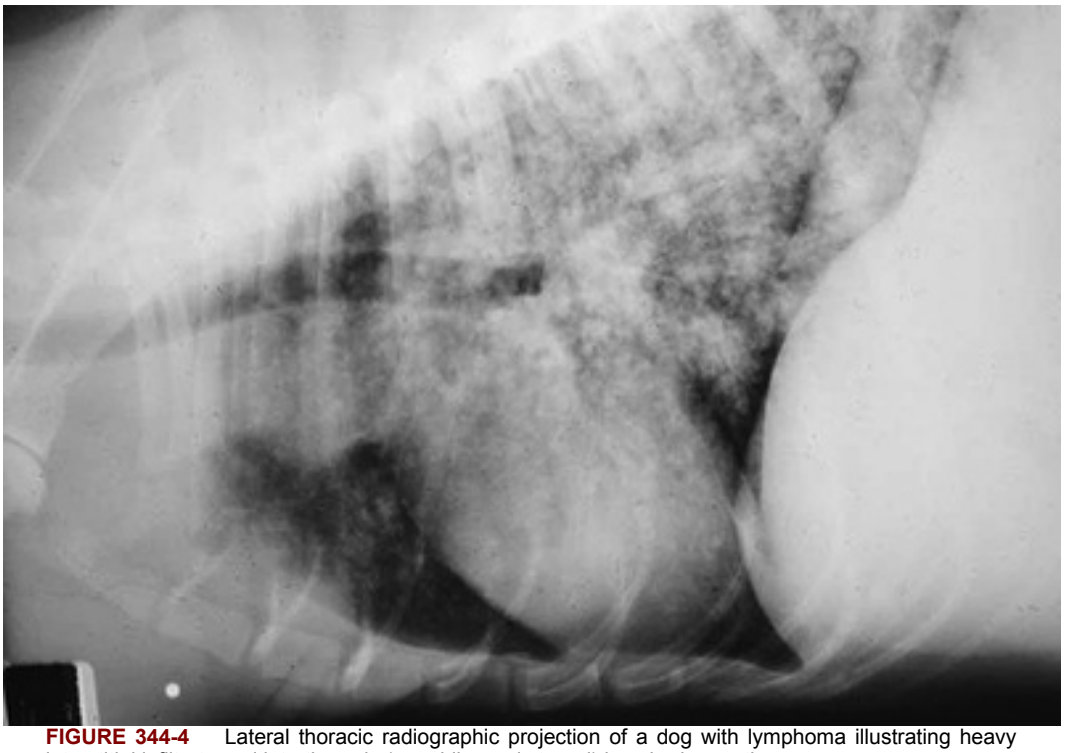

FIGURE 344-4 Lateral thoracic radiographic projection of a dog with lymphoma illustrating heavy interstitial infiltrate and intrathoracic (e.g., hilar and sternal) lymphadenopathy.

Cytologic and Histopathologic Diagnosis

In the author's opinion, a combination of histopathologic (Tru-Cut, wedge, whole node) and flow-cytometric assessment of needle aspirates should be the standard of care for diagnosis of nodal lymphoma (see ch. 95).[68,103-105] This allows accurate subtyping, provides a growing body of prognostic information and ultimately may result in treatment protocols tailored more specifically to the subtype encountered. While fine needle aspirate (FNA) cytologic assessment by a clinical pathologist is often adequate to make a diagnosis of lymphoma in dogs, clinically important subtyping is not possible with cytology alone. The predominance of a homogenous population of immature lymphoid cells is suggestive of lymphoma (Figure 344-5), although several small cell and indolent nodular variants exist and histological/immunophenotypic assessment of these less common forms is recommended.

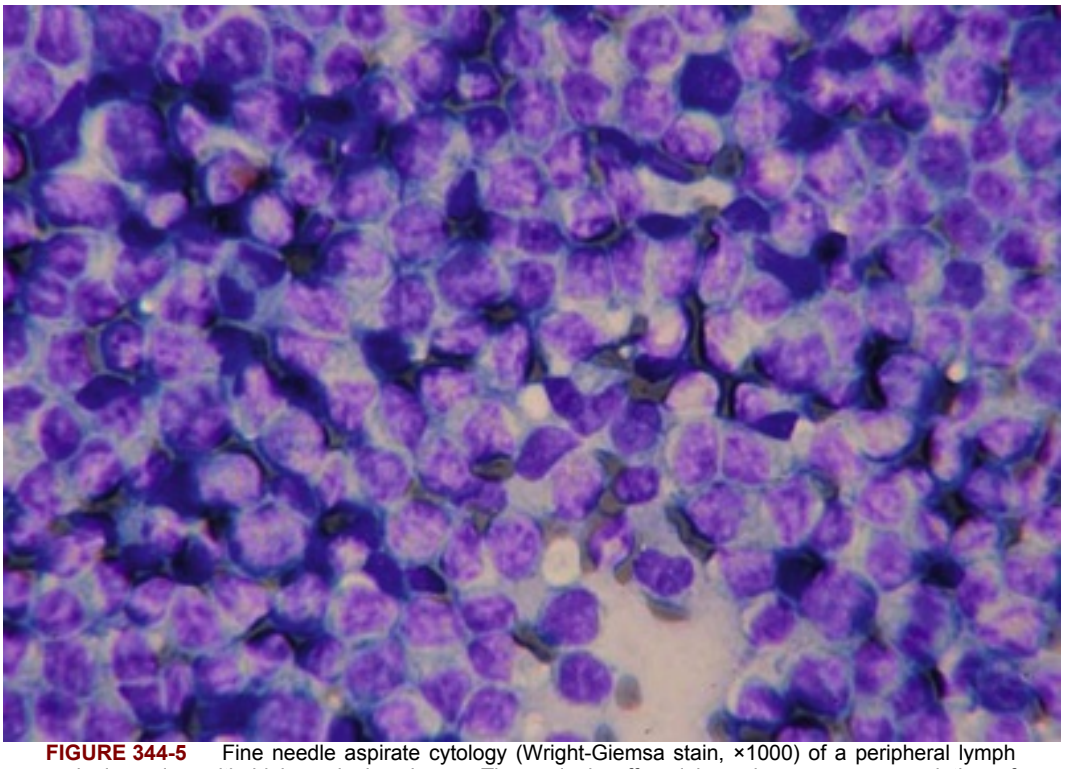

FIGURE 344-5 Fine needle aspirate cytology (Wright-Giemsa stain, ×1000) of a peripheral lymph node in a dog with high-grade lymphoma. The node is effaced by a homogenous population of immature lymphoid cells.

Additional site-specific cytologic or histologic assessments may be warranted when extranodal forms are suspected. Thoracocentesis (see ch. 102) followed by cytologic/flow-cytometric evaluation of pleural fluid is often diagnostic in cats with mediastinal lymphoma, but is less likely to be of value in dogs with effusions secondary to mediastinal involvement. Conversely, cerebrospinal fluid (CSF) analysis (see ch. 115) is more commonly helpful in dogs than cats with CNS lymphoma because the more common spinal form in cats is generally extradural.[106-108] In cats suspected of having CNS lymphoma, bone marrow (see ch. 92) and renal (see ch. 321) involvement are often present, and cytologic assessment of these organs is generally more easily attainable than from CNS sites.

For gastrointestinal lymphoma, controversy still exists as to the diagnostic sensitivity of endoscopically derived biopsy versus full thickness surgical biopsies; the former (see ch. 113) remains the gold standard; however, the latter is gaining more favor as techniques advance.[70-74,109,110] This is particularly germane for indolent gastrointestinal lymphoma which represents the most common form of lymphoma in cats but is rare in dogs. Advanced diagnostic techniques (e.g., flow cytometry, polymerase chain reaction [PCR] for antigen receptor rearrangement [PARR]) may be necessary in these instances. For cats and dogs having intermediate or high-grade gastrointestinal lymphoma, often abdominal lymphadenopathy, measurable intestinal/gastric masses or other abdominal organ involvement allows a less invasive definitive diagnostic approach whereby aspirate cytology or ultrasound guided core biopsies can be diagnostic without the need for laparotomy/laparoscopic intestinal derived biopsy.

Advanced Diagnostic Techniques

Besides their role in confirming a diagnosis of lymphoma, histologic and cytologic samples can be analyzed by various histochemical, immunohistochemical and flow-cytometric techniques to determine the immunophenotype (e.g., B, T, null cell, major histocompatibility complex [MHC] expression), cell size, tumor proliferation rate (e.g., Ki-67, proliferating cell nuclear antigen [PCNA], argyrophilic nucleolar organizer regions [AgNOR]), and subtype (high-, intermediate-, or low-grade/indolent tumors) as well as the presence or absence of an ever increasing number of molecular markers under investigation for prognostic, predictive, and therapeutic potential.[68,103-105,111-113] Several laboratories now offer routine advanced immunophenotypic analysis of samples with an ever increasing panel of immunophenotypic markers (e.g., B, T, MHC class, etc.) that provide the clinician and the client more accurate prognostic information; this author currently utilizes

Colorado State University's Clinical Immunology Laboratory for such analysis (http://csu-cvmbs.colostate.edu/academics/mip/ci-lab/Pages/default.aspx). As more samples are analyzed and correlated with outcome assessments following treatment, therapy recommendations aimed at specific lymphoma subtypes and indeed, individual patients will become available to veterinary patients, as is the standard in people.

In uncommon circumstances, routine cytologic and histologic assessments of tissues or cellular fluids are inadequate to confirm even a nonspecific diagnosis of lymphoma. When suspicious solid tissues, circulating lymphocytes, and effusive samples include a mixed-cell population or do not entirely discriminate malignant from benign reactive proliferations, assays of cellular clonality may be helpful in addition to flow-cytometric analysis.[103,114,115] Clonality is the hallmark of malignancy; that is, the malignant cell population theoretically should be derived from expansion of a single malignant clone characterized by a particular DNA region unique to that tumor. For example, in a dog with T-cell lymphoma all the malignant cells should contain the same DNA sequence for the variable region of the T-cell receptor gene. Likewise, a dog with B-cell lymphoma should have malignant cells with identical DNA sequences in the variable region of the immunoglobulin receptor gene. Conversely, in benign reactive lymphocytosis the cells are polyclonal for their antigen receptors. Polymerase chain reaction technology is used to amplify the variable regions of the T-cell and immunoglobulin receptor genes to detect clonality. Such assays are approximately 70% to 90% sensitive in the dog and less so in the cat. False-negative (e.g., null cell populations, incorrect PCR primers) and false-positive (e.g., ehrlichiosis and Lyme disease) rates of approximately 5% can occur. In these cases, a diagnosis should be made only after considering the results of all diagnostic evaluations, including histologic/cytologic evaluation, immunophenotyping, and clonality studies in conjunction with the signalment and physical findings. In general, for samples suspicious for but not diagnostic for lymphoma, flow-cytometric analysis is superior to PARR analysis; however, the performance of both may be preferable.

Molecular and proteomic analysis of DNA and serum biomarkers, respectively, are currently being investigated for their diagnostic and prognostic utility.[116-123] These molecular techniques, while helpful for diagnosis, could also have utility in defining more accurate clinical stage, determining treatment response and relapse and so-called molecular remission rates and minimal residual disease levels.

Differential Diagnosis

The differential diagnoses for lymphoma, which vary with the anatomic form of the disease, are presented in Table 344-3.

TABLE 344-3

Common Differential Diagnoses for Lymphoma

ANATOMIC FORM	DIFFERENTIAL LIST
Generalized	Disseminated infections lymphadenopathy (e.g., bacterial, viral, rickettsial, parasitic, and fungal) Immune-mediated disorders (e.g., lupus, polyarthritis, vasculitis, dermatopathy) Other hematopoietic tumors (e.g., leukemia, multiple myeloma, malignant or systemic histiocytosis) Tumors metastatic to nodes In cats, many benign reactive hyperplastic syndromes (see text)
Alimentary	Infiltrative enteritis (e.g., lymphocytic, plasmacytic enteritis) Nonlymphoid intestinal neoplasms Granulomatous enteritis Granulated round cell tumors in cats Gastrointestinal mast cell tumors in cats
Cutaneous	Infectious dermatitis (e.g., advanced pyoderma) Immune-mediated dermatitis (e.g., pemphigus) Other cutaneous neoplasms
Mediastinal	Thymoma Heart base tumor (chemodectoma) Ectopic thyroid tumor Pulmonary lymphomatoid granulomatosis Granulomatous disease (e.g., hilar lymphadenopathy)

Therapy

Untreated dogs and cats live an average of 4 to 6 weeks once a diagnosis of intermediate or high-grade lymphoma has been established, although significant variations can exist depending on location and subtype. In general, lymphoma is a systemic disease and requires a systemic approach to therapy (i.e., chemotherapy, immunotherapy). In cases of solitary nodal or extranodal lymphoma, local therapy involving either surgery or radiation may be indicated.

Systemic Chemotherapy in Dogs with Intermediate and High-Grade Lymphoma

The management of lymphoma initially is quite gratifying in both species, as response rates approach 90% in dogs and 70% in cats treated with multiagent chemotherapeutic approaches. Importantly, client perception of their pets' experiences during chemotherapy are generally positive, and the vast majority of clients feel that treatment is worthwhile and results in improvements in their companions' well-being and overall quality of life.[124-126] Unfortunately, most animals eventually succumb to relapse of chemotherapy-resistant, disseminated disease. Many chemotherapy protocols for dogs with lymphoma have been published and previously reviewed,[127,128] reflecting our inability to achieve cure in the majority of cases. Several factors should be considered and discussed with caregivers when choosing a protocol for a particular situation. These factors include the cost, time commitment, efficacy, toxicity, and experience of the clinician with the protocols in question. In general, more complex combination chemotherapy protocols are more expensive, more time-consuming (i.e., requiring repeated office visits and closer monitoring), and more likely to result in adverse events than are simpler, single agent protocols. However, as a general rule, more complex combination protocols initially result in longer remission and survival durations than do single agent protocols. Most complex combination protocols are modifications of "CHOP," a protocol initially designed for human oncologic use. The CHOP protocol represents combinations of cyclophosphamide (C), doxorubicin (hydroxydaunorubicin [H]), vincristine (Oncovin [O]), and prednisone (P). In the 1990s, large multi-institutional randomized clinical trials in people with intermediate and high-grade lymphomas established that more complex protocols or protocols did *not* result in enhanced efficacy and indeed, resulted in greater frequency of adverse events.[129] For this reason, CHOP remains the standard chemotherapy protocol for most intermediate and high-grade lymphoma in people. While large randomized trials have not been performed in dogs, it appears that regardless of which CHOP-based protocol is used, the overall median remission and survival times are approximately 8 and 12 months, respectively.[127,128] Approximately 20% to 25% of treated dogs are alive 2 years after initiation of these protocols. Response rates and the length of response vary, depending on the presence or absence of prognostic factors discussed subsequently. Historically, lymphoma treatment protocols began with an intensive induction phase, during which drugs are given weekly; this was followed by a maintenance phase, during which treatment intervals are slowly spread out and the drugs are given less frequently. More current treatment protocols have abandoned the use of a maintenance phase, as most data now show no benefit from their inclusion.[130-137] In general, shorter chemotherapy protocols are associated with similar response rates and first remission durations achieved with longer maintenance-containing protocols and have the advantage of less time on chemotherapy and less associated expense and adverse events. Additionally, overall survival lengths are not different once reinduction or rescue protocols are factored in. For peripheral nodal lymphoma, by convention, remission status is assessed according to the Veterinary Cooperative Oncology Group (VCOG) response evaluation criteria v1.0.[138] This simple and easily applied evaluation takes into account our inability to achieve true molecular complete remissions or cures and allows more accurate comparison of response following different protocols. The CHOP-based combination induction protocol used most often by the author is presented in Table 344-4.

TABLE 344-4

University of Wisconsin–Madison Combination Chemotherapy Protocol for Dogs with Lymphoma

TREATMENT WEEK	DRUG, DOSAGE, ROUTE	TREATMENT WEEK	DRUG, DOSAGE, ROUTE
1	Vincristine: 0.5-0.7 mg/m^2 IV Prednisone: 2 mg/kg PO q 24 h × 7 days	11	Vincristine: 0.5-0.7 mg/m2 IV

2	Cyclophosphamide: 250 mg/m^2 IV/PO Furosemide: 1 mg/kg IV* Prednisone: 1.5 mg/kg PO q 24 h × 7 days	12	Cyclophosphamide: 250 mg/m^2 IV/PO Furosemide: 1 mg/kg IV
3	Vincristine: 0.5-0.7 mg/m^2 IV Prednisone: 1 mg/kg PO q 24 h × 7 days	13	Vincristine: 0.5-0.7 mg/m2 IV
4	Doxorubicin: 30 mg/m^2 IV PO Prednisone: 0.5 mg/kg PO q 24 h × 7 days	14	Doxorubicin: 30 mg/m2 IV
6	Vincristine: 0.5-0.7 mg/m2 IV	16	Vincristine: 0.5-0.7 mg/m2 IV
7	Cyclophosphamide: 250 mg/m^2 IV/PO Furosemide: 1 mg/kg IV	17	Cyclophosphamide: 250 mg/m^2 IV/PO Furosemide: 1 mg/kg IV
8	Vincristine: 0.5-0.7 mg/m2 IV	18	Vincristine: 0.5-0.7 mg/m2 IV
9†	Doxorubicin: 30 mg/m2 IV	19‡	Doxorubicin: 30 mg/m2 IV

*Furosemide is given concurrently with cyclophosphamide to decrease the incidence of sterile hemorrhagic cystitis.

†If the patient is in complete remission at week 9, treatment continues to week 11.

‡If the patient is in complete remission at week 19, therapy is discontinued and the dog is rechecked monthly for recurrence.

Note: A complete blood count (CBC) should be performed before each chemotherapy treatment. If the neutrophil count is less than 2000 cells/mcL, the clinician should wait 5 to 7 days and then repeat the CBC; the drug is administered if the neutrophil count has risen above the 2000 cells/mcL cutoff.

Doxorubicin (30 mg/m^2 IV q 3 weeks for five treatments) along with oral prednisone remains the most effective and commonly used single agent cytotoxic chemotherapy protocol for dogs with lymphoma.[139-142] Approximately 70% of cases will respond, with median remission and survival durations of approximately 5 and 7 months, respectively. This single agent protocol is less time-consuming, less expensive, and requires fewer hospital visits. If clients choose to employ only oral medications, lomustine (CCNU; 70 mg/m^2 PO q 3 weeks) or cyclophosphamide (250-300 mg/m^2, PO or IV, q 2-3 weeks) and prednisone therapy can be used, although response rates and durations are less than those achieved with doxorubicin.[143]

If financial or other client concerns preclude the use of more aggressive systemic chemotherapy, prednisone therapy (2 mg/kg PO q 24 h) often results in short-lived remissions of approximately 1 to 2 months. It is advisable to inform clients that if they should decide to pursue more aggressive therapy at a later date, dogs with prior prednisone therapy are more likely to develop drug-resistant disease and to experience shorter remission and survival durations when subsequent chemotherapy protocols are attempted.[144-146] Modifications in chemotherapy dosage and/or frequency may be necessary under conditions of excess adverse events (AEs) (see ch. 343). In the absence of clinically significant AEs, in particular when a lack of expected neutrophil nadir is observed, dose increases are also warranted as this may imply inadequate dosing based on an individual patient's pharmacogenetics. Breeds at risk for abnormalities in P-glycoprotein drug transport (e.g., Collies, Shetland Sheepdogs, herding breeds) that predict risk for chemotherapy induced AEs should undergo MDR1 gene mutation analysis prior to using MDR1 substrate agents.[147]

When hypercalcemia is present, if the dog has substage a disease and is eating and drinking, ancillary therapy for hypercalcemia is usually unnecessary as chemotherapy results in normalization of serum calcium within a few days. If the animal is ill, azotemic, or showing significant signs attributable to hypercalcemia, therapy directed specifically at hypercalcemia (see ch. 69 and 297) concurrent with the initiation of systemic chemotherapy is warranted.

Systemic Chemotherapy in Cats with Intermediate and High-Grade Lymphoma

Several combination chemotherapy protocols for cats have been reported and reviewed previously.[148-150] The addition of doxorubicin to COP-based protocols (C, cyclophosphamide; O, Oncovin [vincristine]; P, prednisolone) appears superior to COP alone in the cat. However, in some studies, cats receiving COP experienced remission and survival durations comparable to cats treated with CHOP protocols.[151,152] In contrast to dogs, doxorubicin does not appear to be as effective a single agent therapy for feline lymphoma. In general, cats with intermediate or high-grade lymphoma do not enjoy as high a response rate or as long remission and survival durations as dogs with intermediate or high-grade lymphoma. Complete response

rates vary between 50% and 80%, and overall median remission and survival durations are approximately 4-6 and 6-8 months, respectively. However, a significant proportion of cats (30% to 40%) that achieve a complete response with combination chemotherapy enjoy more durable overall remission and survival times (i.e., 2 years) than that seen in dogs. The modified CHOP-based protocol preferred by the author for cats is presented in Table 344-5.

TABLE 344-5

University of Wisconsin–Madison Combination Chemotherapy Protocol for Cats with Lymphoma

TREATMENT WEEK	DRUG, DOSAGE, ROUTE	TREATMENT WEEK	DRUG, DOSAGE, ROUTE
1	Vincristine: 0.5-0.7 mg/m^2 IV L-asparaginase: 400 U/kg SC Prednisolone: 2 mg/kg PO q 24 h × 14 days	11	Vincristine: 0.5-0.7 mg/m2 IV
2	Cyclophosphamide: 200 mg/m^2 IV/PO Prednisolone: 2 mg/kg PO q 24 h (continued)	13†	Cyclophosphamide: 200 mg/m2 IV/PO
3	Vincristine: 0.5-0.7 mg/m^2 IV Prednisolone: 1 mg/kg PO q 24 h × 7 days	15	Vincristine: 0.5-0.7 mg/m2 IV
4	Doxorubicin: 25 mg/m^2 IV Prednisolone: 1 mg/kg PO q 48 h*	17	Doxorubicin: 25 mg/m2 IV
6	Vincristine: 0.5-0.7 mg/m2 IV	19	Vincristine: 0.5-0.7 mg/m2 IV
7†	Cyclophosphamide: 200 mg/m2 IV/PO	21†	Cyclophosphamide: 200 mg/m2 IV/PO
8	Vincristine: 0.5-0.7 mg/m2 IV	23	Vincristine: 0.5-0.7 mg/m2 IV
9‡	Doxorubicin: 25 mg/m2 IV	25§	Doxorubicin: 25 mg/m2 IV

*Prednisolone (1 mg/kg PO) is continued every other day from this point on.

†If renal or CNS lymphoma is present, substitute cytosine arabinoside (600 mg/m^2 SC q 12 h over 2 days) at these treatments.

‡If the patient is in complete remission at week 9, continue to week 11.

§If the patient is in complete remission at week 25, therapy is discontinued and the cat is rechecked monthly for recurrence.

Note: A complete blood count (CBC) should be performed before each chemotherapy treatment. If the neutrophil count is less than 1500 cells/mcL, the clinician should wait 5 to 7 days and then repeat the CBC; the drug is administered if the neutrophil count has risen above the 1500 cell/mcL cutoff.

Reinduction or Rescue Therapy

Ultimately, most dogs and cats with intermediate and high-grade lymphoma successfully treated with induction chemotherapy relapse with a more drug-resistant form. At the first recurrence, if >2 months has occurred between cessation of chemotherapy and relapse, it is recommended that *reinduction* be attempted by repeating the induction protocol that was initially successful. While the likelihood of a response is high at reinduction, the length of the response is generally shorter than seen with the initial therapy.[153] If reinduction fails, if the patient does not respond to initial induction, or relapses during initial induction, then so-called *rescue* agents or rescue protocols are used. These drugs or drug combinations typically are not found in the standard CHOP protocol and are withheld for use in drug-resistant cases. A number of single agent and multiagent rescue protocols have been reported and reviewed in the veterinary literature.[138,148,154,155] Overall rescue response rates of 40% to 90% are reported; however, responses are usually not durable, with median responses of 1.5 to 2.5 months being typical, regardless of the complexity of the protocol. The sequential application of several different rescue protocols can result in several months of extended survival with acceptable quality of life.

Immunotherapy for Lymphoma (also see ch. 341)

The most significant advancement in treating non-Hodgkin's lymphoma (NHL) in people in the last 2 decades

has been the development of monoclonal antibody therapies that are combined with standard CHOP protocols (e.g., R-CHOP, for rituximab-CHOP). This anti-human CD20 monoclonal antibody has significantly increased both progression free and overall survival in people with NHL when compared to CHOP alone.[156] Monoclonal antibody therapy has become the standard of care (in combination with chemotherapy) for several hematopoietic tumors in people (e.g., NHL, chronic lymphocytic leukemia, cutaneous lymphoma, gamma delta T-cell lymphoma). In veterinary oncology, national multicenter randomized trials are ongoing to determine the therapeutic efficacy of monoclonal antibody therapies against both canine B-cell (caninized anti-CD20; Aratana AT-004) and canine T-cell (caninized anti-CD52; Aratana AT-005) lymphoma that have received full USDA license approval. While safety has been established for these two agents, only preliminary (abstract form) efficacy data are available at the time of this writing and represent a reasonable but not complete expectation of anti-tumor activity. Once these trials (combining monoclonal and standard chemotherapy) have been completed and the results subject to rigorous peer review the true efficacy of these products will be known. It is hoped that these and potentially other[157] monoclonal antibody therapies in development will similarly revolutionize the treatment of NHL in dogs.

Investigations are also currently underway regarding the development of other immunologic therapies, including anti-lymphoma vaccines and bone marrow or stem cell transplant techniques following bone marrow ablative therapies.[158,159] Currently these are investigational in scope.

Radiation Therapy for Lymphoma

Radiation therapy for lymphoma is generally limited to cases where solitary anatomic sites are present without systemic involvement or in investigational trials utilizing whole or half body radiation protocols in combination with chemotherapy (see ch. 340).[160-168]

Therapy—Indolent (Low-Grade) Lymphoma

Indolent lymphomas include a varied group of tumors that are uncommon in dogs[63-69] but represent the most common form in cats (feline indolent gastrointestinal lymphoma).[70-79] Dogs with indolent lymphoma (e.g., marginal zone, mantel cell, T-zone lymphoma) generally experience prolonged survivals, often in the absence of chemotherapy. Dogs with indolent lymphoma may be devoid of clinical signs beyond nodal or splenic enlargement and despite their tumors being less responsive to chemotherapy, enjoy long-term survival. Owing to the less common nature of the indolent lymphomas in dogs, treatment recommendations are not well established. Initially, a decision is made whether to treat based on the presence of clinical signs effecting quality of life, presence of organomegaly or clinically significant cytopenias secondary to myelophthisis. In such cases, therapy usually is initiated with either single agent chlorambucil (20 mg/m^2 PO q 2 weeks) or cyclophosphamide (250 mg/m^2 PO q 2-3 weeks) with prednisone. In dogs with indolent lymphoma confined to the spleen or a solitary node, splenectomy or nodal extirpation without adjuvant chemotherapy often provides long-term control, with many living normal lifespans and dying of diseases other than their indolent lymphoma.

Cats with low-grade *small cell* alimentary lymphoma (i.e., gastrointestinal, hepatic) are best treated with a less aggressive chemotherapy protocol such as oral chlorambucil (20 mg/m^2 PO q 2 weeks) and prednisolone. Median survival times of approximately 2-3 years can be expected.

Therapy for Extranodal Lymphoma

If extranodal involvement is part of a more generalized or multicentric disease process, the systemic therapies previously discussed should be instituted. Conversely, if the extranodal site is solitary, local therapy without institution of systemic chemotherapy may be pursued. In these cases, strict adherence to staging diagnostics (i.e., bone marrow evaluation, radiographic/ultrasonographic, CT, or PET/CT imaging) is warranted to ensure localized disease. Local surgery and/or radiotherapy is often effective, and while systemic lymphoma may ultimately occur months to years later, it is the author's opinion that systemic therapy may be withheld until systemic disease has been documented.

In cases in which CNS involvement is part of a more generalized process, penetration of chemotherapeutic drugs through the blood-brain barrier (BBB) may be a concern. In standard CHOP protocols, only prednisone consistently penetrates the BBB. The addition of cytosine arabinoside, which achieves therapeutic CSF levels, to a CHOP-based protocol has been recommended; however, evidence of its activity in this setting is lacking. L-asparaginase, while not crossing the BBB, will exert its action (asparagine depletion) in the CSF. Radiation

therapy can also be effective, directed either to the entire neural axis (multifocal CNS lymphoma) or to specific CNS locations (solitary central or spinal lymphoma). Cytoreductive surgery has been attempted in a small number of cases of extradural lymphoma, with mixed results.

Cutaneous lymphoma in solitary sites may be effectively treated with local surgery or radiation therapy, but the likelihood of ultimate systemic involvement is high. Multiple cutaneous lesions are more commonly encountered (see Figure 344-3), and systemic therapy is necessary. In general, cutaneous lymphoma is less responsive to chemotherapy than multicentric lymphoma, however clinical signs can wax and wane considerably over time and long term outcomes may occur. First line therapy for dogs with cutaneous lymphoma currently includes lomustine (CCNU, 50-70 mg/m^2 PO q 3 weeks) and prednisone with response rates of approximately 80% and median response durations of 3 months.[169,170] Other chemotherapeutics with reported activity include Doxil (a liposome-encapsulated form of doxorubicin), L-asparaginase, dacarbazine, topical nitrogen mustard, and standard CHOP-based protocols. Monoclonal antibody therapy (anti-CD52) is effective in people for cutaneous T-cell lymphoma and data are currently being collected on cases treated with the caninized monoclonal (Aratana, AT-005) to determine its efficacy in dogs.

Cats with nasal lymphoma without concurrent systemic therapy can also be treated with local radiation therapy and generally enjoy long-term survival.[171-173]

Prognosis

Prognostic Factors in Dogs

A list of factors known or suspected to affect remission rates and/or remission and survival durations in dogs with lymphoma is presented in Table 344-6.[63-79,122,123,174-186] The three factors that most consistently correlate with prognosis in dogs are the immunophenotype/flow cytometric characteristics, histologic subtype and the WHO substage. Dogs with T-cell lymphoma generally have significantly shorter remission and survival durations; however, indolent T-zone lymphomas enjoy the longest survivals.

TABLE 344-6

Prognostic Factors for Lymphoma in Dogs[63-79,122,123,174-186]

FACTOR	STRONG ASSOCIATION	MODEST ASSOCIATION REQUIRING FURTHER INVESTIGATION	COMMENTS
WHO clinical stage		X	Stage I/II: favorable. Stage V with significant bone marrow involvement—unfavorable.
WHO clinical substage	X		Substage—b (clinically ill): associated with decreased survival.
Histopathology	X		High-grade/medium grade: associated with high response rate but reduced survival. The indolent lymphomas generally experience prolonged survivals, often in the absence of systemic therapy.
Immunophenotype/flow cytometric characteristics	X		T-cell phenotype associated with reduced survival. Low MHCII expression on B-cells associated with reduced survival.
Flow cytometric characteristics of peripheral blood	X		This includes combined size and immunophenotypic analysis.
Sex		X	Some studies suggest females have a favorable prognosis.
Anemia	X		
Molecular assessment of minimal residual		X	Likely to become much more important when more "curative" therapeutic approaches are developed and

disease (e.g., PARR)			instituted.
Measures of proliferation		X	Contradictory reports exist.
Prolonged steroid pretreatment	X		Most reports suggest previous steroid use shortens response durations; however, length of exposure necessary is unknown.
P-glycoprotein expression (drug resistance factors)		X	May be associated with poor response rates and shortened remissions.
Cranial mediastinal lymphadenopathy	X		Large compilation of cases reports shorter remission and survival durations.
Anatomic location	X		Leukemia, diffuse cutaneous and alimentary, hepatosplenic forms associated with unfavorable prognosis.
Chemotherapy induced hematologic toxicosis		X	Dogs experiencing grade III/IV neutropenia have prolonged first remission durations.

MHC, Major histocompatibility complex; *PARR*, polymerase chain reaction (PCR) for antigen receptor rearrangement.

Prognostic Factors in Cats

Factors most strongly associated with a more positive prognosis in cats appear to be presence of indolent lymphoma, complete response to therapy (which unfortunately cannot be determined prior to treatment), negative retroviral status, early clinical stage, anatomic site and perhaps the addition of doxorubicin to the treatment protocol.[71,75,81-83,87,88,90] In general, FeLV-negative cats that achieve a complete response on CHOP-based protocols have a high likelihood of long-term survival, with approximately 35% alive at 1.5 years after diagnosis. Cats with alimentary small cell lymphoma have the best overall prognosis with median survivals of 2 years or longer following therapy. Cats with nasal lymphoma have a fair prognosis as radiation therapy (or chemotherapy, if radiation therapy is not available) results in median survivals of 1.5 years. Little is known about the clinical course of Hodgkin's-like lymphoma in cats; following surgical extirpation of the affected node, recurrence may take months, and response to chemotherapy varies. Large granular lymphoma in cats appears to have a more aggressive and less responsive course.

Lymphoid Leukemia

Leukemia is defined as a proliferation of neoplastic cells in the bone marrow. The malignant cells may or may not be present in the peripheral blood circulation. Categorization of lymphoid leukemia into acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL) is important from a diagnostic, prognostic, and therapeutic standpoint (Figure 344-6).[103,186-193] Flow cytometric analysis of immunophenotypic markers (see earlier sections) is particularly helpful.

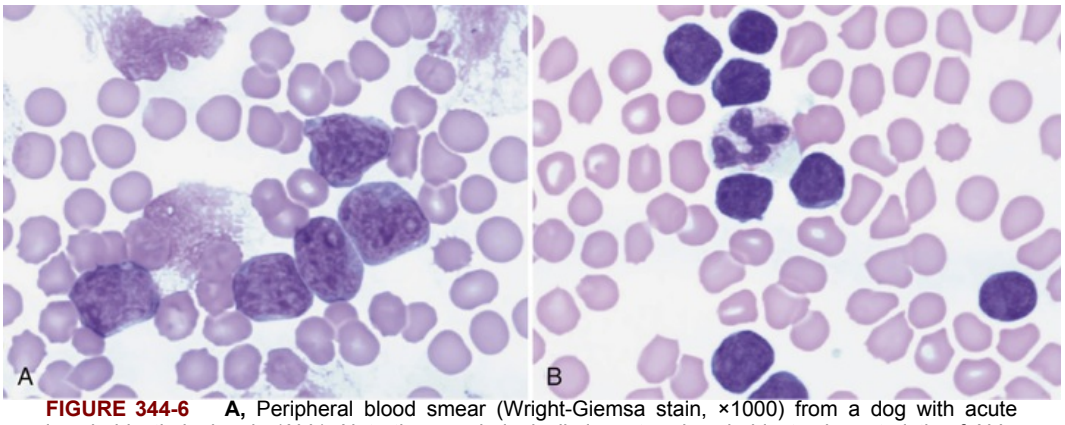

FIGURE 344-6 **A,** Peripheral blood smear (Wright-Giemsa stain, ×1000) from a dog with acute lymphoblastic leukemia (ALL). Note the morphologically immature lymphoblasts characteristic of ALL. **B,** Peripheral blood smear (Wright-Giemsa stain, ×1000) of a dog with chronic lymphocytic leukemia (CLL). Note the morphologically mature lymphocytes characteristic of CLL. (Courtesy Dr. Karen Young, University of Wisconsin-Madison.)

Acute Lymphoblastic Leukemia (ALL)

ALL is characterized by proliferations of morphologically immature lymphoblasts in the bone marrow and may be confused with multicentric stage V lymphoma (i.e., secondary bone marrow infiltration). The clinical course of ALL is rapid, progressive, and poorly responsive to therapy, although some immunophenotypic subclassifications are associated with better overall prognoses. Cats with ALL are younger and are often FeLV antigenemic. Presentations are nonspecific and may include lethargy, weight loss, intermittent pyrexia, hepatosplenomegaly, nonspecific abdominal pain, and neurologic signs. Most animals are anemic, and varying degrees of thrombocytopenia and leukopenia are present. Diagnosis is suggested by marked lymphoblast proliferation in the bone marrow or peripheral blood. Bone marrow aspirate or core biopsy (see ch. 92) and a CBC are usually all that are required for diagnosis of acute leukemia; however, immature forms can be difficult to classify beyond a blast form and flow-cytometric immunophenotype is employed to confirm. Aspiration cytology of lymph node (see ch. 95) and involved organs (see ch. 89) and confirmation of retroviral status in cats may be contributory. Approximately 10% of cases are classified as "aleukemic" leukemia because bone marrow infiltration is present but peripherally circulating lymphoblasts are absent. ALL may be further differentiated clinically from stage V multicentric lymphoma by its more rapid progression, lack of significant lymphadenopathy, poor chemo responsiveness and CD34+ immunophenotype. The prognosis is poor for dogs and cats with ALL. Remission durations are short and survival times of more than a few months are rare. It remains to be seen what role, if any, the new monoclonal antibody therapies will play in the treatment of lymphoid leukemia.

Chronic Lymphocytic Leukemia (CLL)

CLL is characterized by the proliferation of phenotypically mature lymphocytes rather than lymphoblasts. The majority of CLL cases in dogs and cats are of the T-cell lineage with dogs being primarily CD8+ T cells, many of which show a granular lymphocytic morphology.[147] CLL occurs in older dogs and cats presenting with nonspecific signs including lethargy, organomegaly, pyrexia, polyuria/polydipsia, hemorrhage (from thrombocytopenia), intermittent lameness, and collapse. However, asymptomatic lymphocytosis may be detected on routine geriatric or preanesthetic screening in some animals. Peripheral lymphocytosis can range from 10,000 to ≥300,000/mcL. Anemia, thrombocytopenia and neutropenia may be present secondary to myelophthisis. No association with FeLV infection has been documented in the cat. Unlike ALL, CLL often has a protracted course and is initially highly responsive to chemotherapy. Treatment is not initiated unless significant clinical signs, organomegaly, or peripheral cytopenias (anemia, neutropenia, thrombocytopenia) are present that affect the animal's quality of life. CLL cases have been followed for many months without the necessity for therapy. If therapy is indicated, chlorambucil (dogs: 0.2 mg/kg PO q 24 h for 10 days, then 0.1 mg/kg/day; cats: 2 mg/cat PO q 48 h: alternatively, 20 mg/m^2 PO q 2 weeks) is combined with daily or every other day prednisone. The majority of animals respond and enjoy good quality of life, with a median survival time of approximately 1 to 1.5 years. While prognosis is good in the short term, eventually CLL becomes resistant to therapy or progresses to ALL. While anti-CD52 monoclonal antibody is approved for use in people with CLL, the new canonized monoclonal antibody therapies have not been evaluated for CLL in dogs.

Nonlymphoid Leukemias and Myeloproliferative Disorders

Myeloproliferative disorders (MPDs) are defined as a group of rare nonlymphoid bone marrow cell disorders in which proliferation of one, several, or all marrow cell lines occurs. The disorders may represent preneoplastic or neoplastic conditions that may have a benign or malignant course. With few exceptions (e.g., see Polycythemia Vera, ch. 200), the veterinary literature on MPDs is sparse at best and is composed almost entirely of single case reports. MPDs are classified first on the basis of the derivation of the cell in question and second on the degree of cellular differentiation. If the proliferating cell population is phenotypically well differentiated, the disorder is classified as chronic; if immature or poorly differentiated, the disease is classified as acute. Table 344-7 lists possible MPDs variants reported in companion animal species. Because pluripotent bone marrow stem cells are involved, one MPD may evolve into another, and more than one cell line is involved in the same disorder.

TABLE 344-7

Myeloproliferative Disorders Possible in Dogs and Cats

CLASSIFICATION	CELL LINEAGE
Acute Myeloproliferative Disorders	
Acute myelogenous leukemia (AML)	Myeloblasts
Acute myelomonocytic leukemia (AMML)	Myeloblasts/monoblasts
Acute monocytic leukemia (AmoL)	Monoblasts
Acute megakaryoblastic leukemia (AmkL)	Megakaryoblasts
Erythroleukemia	Erythroblasts
Chronic Myeloproliferative Disorders	
Chronic myelogenous leukemia (CML)	Neutrophils, late precursors
Primary thrombocythemia	Platelets
Basophilic leukemia	Basophils and precursors
Eosinophilic leukemia	Eosinophils and precursors
Polycythemia vera	Erythrocytes

Animals with a chronic MPD may have no clinical signs until organ involvement or bone marrow myelophthisis results in clinical signs which are generally nonspecific and can include organomegaly, pallor, sepsis, and hemorrhage from thrombocytopenia. Most MPDs have been associated with FeLV infection in cats.

The diagnosis of MPD is based on demonstration of the proliferating cell line in the absence of nonneoplastic diseases associated with bone marrow hyperplasia or hypoplasia. Differential diagnoses therefore include chronic inflammatory diseases (e.g., ehrlichiosis), multicentric lymphoma, estrogen toxicity, lead poisoning and, in the case of essential or primary thrombocytosis, iron deficiency. Because many of the acute MPDs are poorly differentiated and/or represent combinations of cell lineages, light microscopic morphology is often insufficient and flow cytometric and histochemical analysis is ultimately necessary for precise classification. A complete listing of available tests is beyond the scope of the present chapter; these have been reviewed elsewhere.[191,193,194]

The acute MPDs are poorly responsive to single agent or combination chemotherapy protocols and the prognosis is grave. If chemotherapy is pursued, aggressive supportive therapy is necessary and to address cytopenias secondary to myelophthisis. Chronic MPDs carry a guarded prognosis; however, initial durable responses to therapy are more likely. Therapy is not required until clinical signs or significant peripheral cytopenia develops. Hydroxyurea has occasionally resulted in partial remission of several types of chronic MPD, particularly polycythemia vera, essential thrombocythemia, basophilic leukemia, and chronic myelogenous leukemia (CML). In dogs with CML, hydroxyurea is administered at an initial dosage of 20 to 25 mg/kg given PO q 12 h. This dosage is continued until the leukocyte count drops to less than 20,000 cells/mcL, at which time the dosage is reduced to 10 to 15 mg/kg q 24 h or switched to 50 mg/kg PO once every 2 to 3 weeks. A common side effect of hydroxyurea therapy in dogs is onychomadesis (sloughing of the claw or toenail). Ultimately, many of the chronic MPDs shift into a terminal phase or blast crisis, in which a fatal acute leukemic phase is observed. Tyrosine kinase receptor inhibitors (e.g., toceranib, masitinib) have not been thoroughly evaluated for the MPDs but may be considered.

Polycythemia vera (PV) (see ch. 57 and 200) is defined as an abnormal proliferation of erythroid precursors in the bone marrow; this occurs independent of erythropoietin (EP), and the cells follow a normal, orderly pattern of maturation.[150,151] The result is an abnormally elevated packed cell volume, erythroid count, and blood hemoglobin level. PV must be differentiated from so-called relative polycythemia or secondary polycythemia. Middle-aged dogs and cats are typically affected, presenting with varied signs including hyperemic mucous membranes, injected scleral and retinal vessels, weakness, exercise intolerance, frank hemorrhage (epistaxis, hematuria, melena), neurologic signs (dementia, seizures, paralysis, ataxia), and occasional splenomegaly. Cardiac or renal compromise may also be present. The majority of signs reported occur secondary to hyperviscosity syndrome, discussed in the plasma cell tumor portion of this chapter. The diagnosis is made by documentation of significant erythrocytosis (60% to 75% hematocrit) with normal to decreased serum EP levels and the absence of conditions associated with relative or secondary polycythemia. Thoracic and abdominal radiographs, thoracic and abdominal ultrasound, arterial blood gas determinations,

bone marrow aspirate testing, and serum EP levels should be procured to rule out differentials. Erythroid hyperplasia with relatively normal patterns of maturation is found on bone marrow cytology. Therapy involves reduction of red blood cell mass (phlebotomy;15 to 20 cc/kg body weight and reinfusion of the patient's plasma) and suppression of erythroid production in the bone marrow.[150,151] To suppress erythrocyte production, the use of radioactive phosphorus (^{32}P) or, more commonly available, chemotherapy (e.g., hydroxyurea, melphalan, cyclophosphamide, busulfan) have been used with mixed results.

Myeloma-Related Disorders

Myeloma-related disorders (MRD) arise when a cell of the plasma cell or immunoglobulin-producing B-lymphocyte precursor lineage transforms and proliferates to form a neoplastic population of similar cells. This population in most instances is monoclonal, producing a homogenous immunoglobulin although biclonal and polyclonal MRD neoplasms exist. MRDs include multiple myeloma (MM), IgM (Waldenstrom's) macroglobulinemia, solitary plasmacytoma (including solitary osseous plasmacytoma and extramedullary plasmacytoma [EMP]), and immunoglobulin secreting lymphomas and leukemias (including plasma cell leukemia). Multiple myeloma is the most important MRD based on incidence and severity. There exists some discordance and blurring of the distinction between MM and multicentric EMP in cats.

Multiple Myeloma

MM represents 8% of all canine hematopoietic tumors but is relatively rare in the cat.[195-202] In MM, the M-component may represent any class of immunoglobulin or only a portion of the molecule, such as the light-chain (Bence Jones protein) or heavy chain (heavy chain disease) of the molecule. Feline myeloma/MRD, while involving the bone marrow in the majority of cases, appears to involve extramedullary sites (e.g., skin, abdominal viscera) more commonly than in dogs.[198,200-202,204] The etiology of MM is for the most part unknown. Genetic predispositions, molecular alterations (e.g., TKI receptor abnormalities), viral infections, chronic immune stimulation, and exposure to carcinogens have all been suggested as contributing factors. MM has not been associated with either FeLV or FIV infection.

Pathophysiology

A wide array of pathologic abnormalities and related clinical syndromes can occur as a result of tumor infiltration of various organ systems, the presence of high levels of circulating M-component, or a combination thereof. Hyperviscosity syndrome (HVS) represents one of a constellation of clinicopathologic abnormalities resulting from increased serum viscosity. The magnitude of HVS is related to the type, size, shape, and concentration of the M-component in the blood. It is more common with IgM macroglobulinemia owing to its high molecular weight.[203] HVS can result in bleeding diathesis, neurologic signs (e.g., dementia, depression, seizure activity, coma; see ch. 260), ophthalmic abnormalities (e.g., dilated/tortuous retinal vessels, retinal hemorrhage, retinal detachment; see ch. 11), and increased cardiac workload with subsequent cardiomyopathy or congestive failure. These consequences are thought to be a result of sludging of blood in small vessels, ineffective delivery of oxygen and nutrients, and coagulation abnormalities. HVS is less common in cats.[204] Renal disease is present in 30% to 50% of dogs with MM as a result of Bence Jones (light chain) proteinuria, tumor infiltration into renal tissue, hypercalcemia, amyloidosis, diminished perfusion secondary to HVS, dehydration, or ascending urinary tract infection. Hypercalcemia occurs in 15% to 20% of dogs with MM and results primarily from the production of osteoclast-activating factor, other cytokines, or circulating N-terminal parathyroid hormone-related protein by neoplastic cells (see ch. 352). Hypercalcemia is rare in cats with MM.

Susceptibility to infection and immunodeficiency are often the ultimate causes of death in animals with MM. Normal immunoglobulin levels can be severely depressed, and leukopenias may be present secondary to marrow infiltration (myelophthisis). A normocytic, normochromic, nonregenerative anemia is encountered in approximately two thirds of dogs. This can result from myelophthisis, blood loss from coagulation disorders, anemia of chronic disease, or increased erythrocyte destruction secondary to high serum viscosity. Similar factors may lead to thrombocytopenia and leukopenia in 25% to 30% of affected dogs. Bleeding diathesis can result from one or a combination of events. M-components may interfere with coagulation including inhibition of platelet aggregation and the release of platelet factor-3, adsorption of minor clotting proteins, generation of abnormal fibrin polymerization, production of heparin-like anticoagulants, and a functional decrease in calcium.

Clinical Presentation

MM occurs in aged dogs and cats, with no breed or sex predilection. Clinical signs are variable due to the wide range of pathologic effects possible and may be present up to 1 year prior to diagnosis. In the dog, the most common clinical signs in decreasing order of frequency are lethargy and weakness, lameness as a result of bone destruction, hemorrhage (see ch. 135), polyuria/polydipsia (see ch. 45), and neurologic deficits (see ch. 259 and 260). Bleeding diathesis is usually represented by epistaxis and gingival bleeding (see ch. 29). CNS signs may include dementia, seizure activity, and deficiencies in midbrain or brainstem localizing reflexes secondary to HVS or extreme hypercalcemia. Signs reflective of transverse myelopathies secondary to vertebral column infiltration, pathologic fracture, or extradural mass compression can also occur (see ch. 267). In the cat, anorexia and weight loss are the most common clinical signs.[198,200-202,204] Lameness may be present due to bone lesions and hepatosplenomegaly is more commonly seen than in dogs. Epistaxis, pleural (see ch. 244) and peritoneal (see ch. 17) hemorrhagic effusions, retinal hemorrhage, and central neurologic signs have been reported. Polydipsia and polyuria can occur secondary to renal disease, and dehydration may develop.

Diagnosis

The diagnosis of MM usually follows demonstration of bone marrow plasmacytosis and serum or urine myeloma proteins (M-component), as well as detection of osteolytic bone lesions and/or other sites of visceral organ involvement. In the absence of osteolytic bone lesions or overt visceral organ involvement, a diagnosis can be made if marrow plasmacytosis is associated with a progressive increase in the M-component. All animals suspected of plasma cell tumors should receive a CBC, platelet count, serum biochemistry profile, and urinalysis. Serum electrophoresis and immunoelectrophoresis are performed to detect a monoclonal gammopathy (Figure 344-7) and to categorize the isotype of immunoglobulin involved. In early publications, the M-component was usually of the IgG or IgA class in nearly equal incidence in dogs,[195] however in the author's experience, the vast majority of dogs present with IgA disease.[205] In the cat, MM is usually associated with IgG elevations; only a few cases of IgA or IgM gammopathies have been reported.[198,200-202,204] Rarely, cryoglobulinemia is observed in dogs and cats with MM. Cryoglobulins are paraproteins that are insoluble at temperatures below 37° C and require blood collection and clotting to be performed at 37° C before serum separation. If Bence Jones proteinuria is suspected, heat precipitation and electrophoresis of urine are necessary, as commercial urine dipstick methods are not capable of this determination. "Nonsecretory" varieties of MM have been reported rarely in dogs.

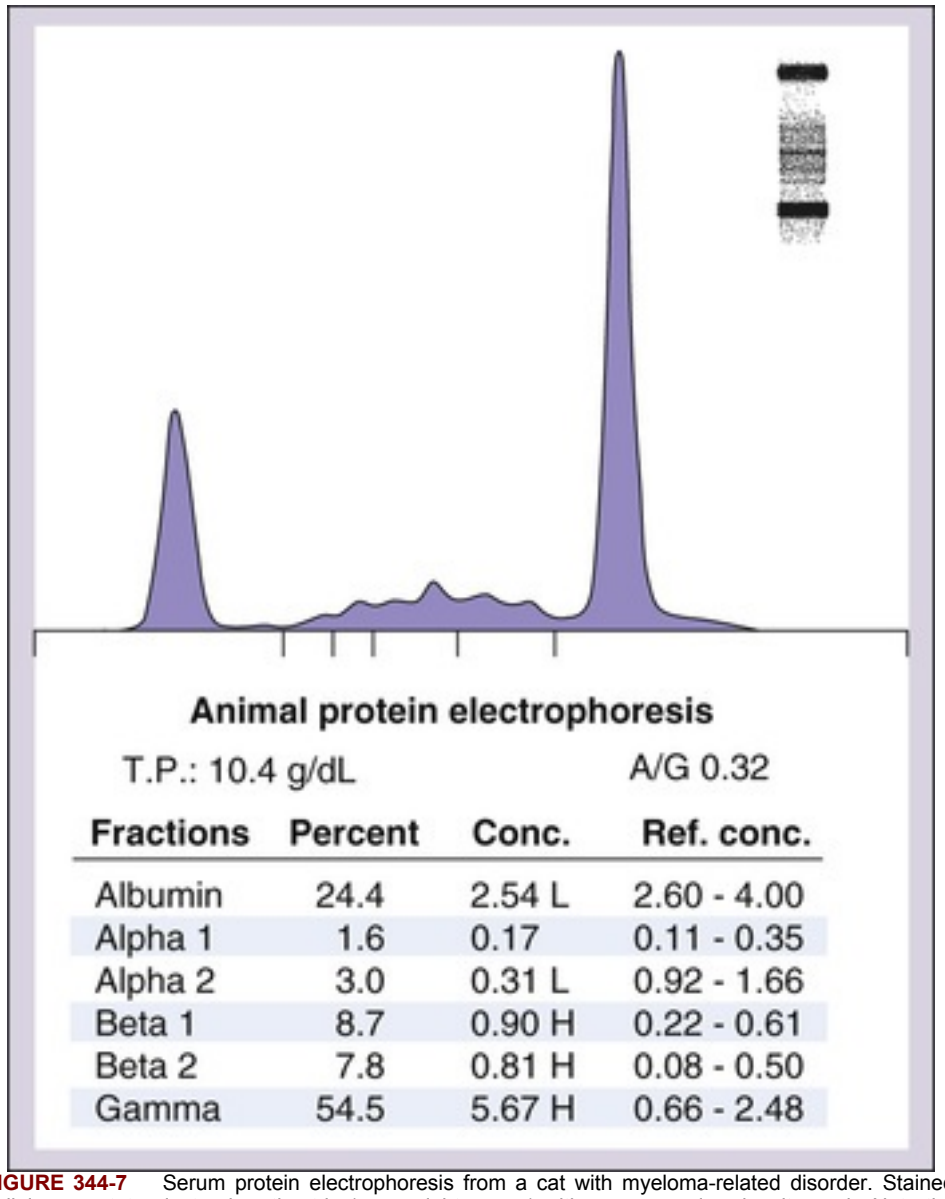

FIGURE 344-7 Serum protein electrophoresis from a cat with myeloma-related disorder. Stained cellulose acetate electrophoretic strip (upper right corner) with accompanying densitograph. Note the large M-component spike (representing an IgG monoclonal gammopathy) present in the gamma region. (Courtesy Dr. Frances Moore, Marshfield Laboratories, Marshfield, WI.)

Definitive diagnosis usually requires a bone marrow aspirate or core biopsy. Normal marrow contains less than 5% plasma cells, whereas myelomatous marrow often greatly exceeds this level. Malignant plasma cells can have a varied microscopic appearance, ranging from that of normal plasma cells to early stages of differentiation.

Skeletal survey radiographs are recommended to determine the presence and extent of osteolytic lesions, which may have diagnostic, prognostic, and therapeutic implications. Rarely, biopsy of osteolytic lesions (i.e., Jamshidi core biopsy) is necessary for diagnosis. Bone lesions may be isolated, discrete lesions (including pathologic fractures; Figure 344-8) or diffuse osteopenias.

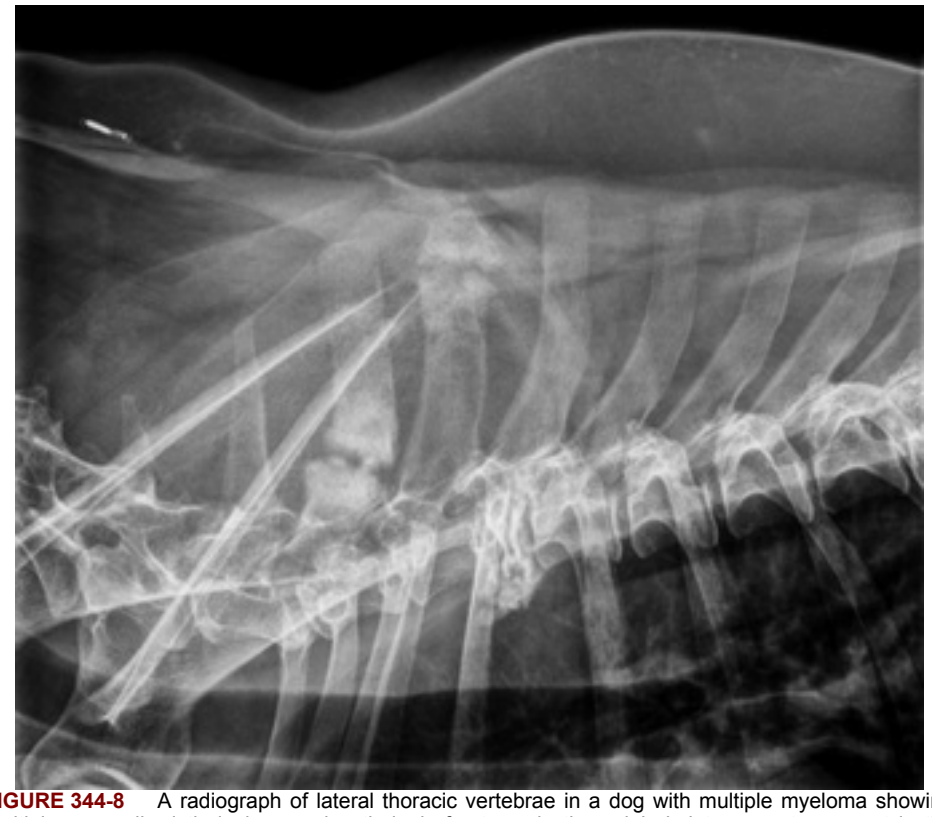

FIGURE 344-8 A radiograph of lateral thoracic vertebrae in a dog with multiple myeloma showing multiple expansile, lytic lesions and pathologic fractures in the axial skeleton, most apparent in the spinous processes of the vertebrae and in a collapse fracture of the T3 vertebral body.

Approximately 25% to 75% of dogs with MM have evidence of bony lysis or diffuse osteoporosis. Bones engaged in active hematopoiesis are more commonly affected (e.g., vertebrae, ribs, pelvis, skull, and proximal long bones). Skeletal lesions are present in as few as 8% and as many as 68% of affected cats.[198,200-202,204] In macroglobulinemia, malignant cells often infiltrate the spleen, liver, and lymphoid tissue rather than bone, although bone involvement is occasionally seen.

If clinical evidence of hemorrhage is present, coagulation assessment (e.g., platelet count, prothrombin time [PT], and partial thromboplastin time [PTT]) and serum viscosity measurements should be undertaken. Nearly half of these patients have abnormal PT and PTT values. All animals should undergo a careful funduscopic examination; abnormalities may include retinal hemorrhage, venous dilatation with sacculation and tortuosity, retinal detachment, and blindness.

Differential Diagnosis

Other disease syndromes can be associated with monoclonal gammopathies including lymphoid tumors (lymphoma, CLL, and ALL), chronic infections (e.g., ehrlichiosis, Leishmaniasis, feline infectious peritonitis [FIP]), and monoclonal gammopathy of unknown significance (MGUS). MGUS (i.e., benign, essential, or idiopathic monoclonal gammopathy) is a benign monoclonal gammopathy not associated with osteolysis, bone marrow infiltration, or Bence Jones proteinuria.

Treatment

Initial Therapy of Multiple Myeloma

Therapy is directed at both the tumor cell mass and the secondary systemic effects. Chemotherapy is highly effective at reducing the myeloma cell burden, relieving bone pain, initiating skeletal healing, and reducing levels of serum immunoglobulins. It significantly extends both the quality and length of most patients' lives. Complete elimination of neoplastic myeloma cells is rarely achieved, however, and eventual relapse is to be expected.

Melphalan in combination with prednisone is the treatment of choice. In the dog, melphalan (0.1 mg/kg PO q 24 h) is given for 10 days then reduced (0.05 mg/kg q 24 h) and continued indefinitely. Prednisone

(0.5 mg/kg PO q 24 h) for 10 days is then reduced to 0.5 mg/kg PO every other day. Therapy continues until clinical relapse occurs or myelosuppression necessitates a dose reduction. The most clinically significant toxicity of melphalan is myelosuppression, particularly thrombocytopenia. CBCs should be performed biweekly for 2 months after initiation of therapy and monthly thereafter. If significant myelosuppression occurs, reduction of the dosage or the treatment frequency may be necessary. An alternative pulse-dosing regimen for melphalan (7 mg/m^2 PO q 24 h for 5 consecutive days out of every 21 days) has been used successfully at the University of Wisconsin in a small number of cases in which myelosuppression limited more conventional continuous low-dose therapy. Melphalan and prednisone therapy has also been used in cats with MRD although results are less rewarding. A cyclophosphamide, vincristine and prednisone combination has also been used in cats.

Cyclophosphamide can be used as an alternate alkylating agent, sometimes in combination with melphalan; however, no evidence exists to suggest superiority. In the author's practice, cyclophosphamide (250 mg/m^2) is limited to cases presenting with severe hypercalcemia or widespread systemic involvement, in which a faster acting alkylating agent may be beneficial. Cyclophosphamide is given IV once at the same time as oral melphalan therapy is started. Chlorambucil (0.2 mg/kg PO q 24 h) has been used for IgM macroglobulinemia in dogs.

Evaluation of Response to Therapy

Response is based on improvement in clinical signs, clinicopathologic parameters, and radiographic improvement of skeletal lesions. Improvement in bone pain, lameness, lethargy, and anorexia should be evident within 3 to 4 weeks. Objective laboratory improvement, including a reduction in serum immunoglobulin levels or Bence Jones proteinuria, is usually noted within 3 to 8 weeks.[205] Radiographic improvement in osteolytic bone lesions may take months, and resolution may only be partial. As previously discussed, complete resolution of MM rarely occurs, and a good response is defined as a reduction in measured M-component to at least 50% of pretreatment values. For routine follow-up, quantitation of serum immunoglobulins or measurement of urine Bence Jones proteins are performed monthly until a good response is noted and then every 2 to 3 months. Repeat bone marrow aspiration is performed if warranted and PARR analysis can be used to confirm molecular remissions.[205]

Therapy Directed at Complications of Multiple Myeloma

Long-term control of complications, including hypercalcemia, HVS, bleeding diathesis, renal disease, immunosuppression, and pathologic skeletal fractures, depends on control of the tumor mass. However, therapy directed more specifically at these complications may be indicated in the short term. If hypercalcemia is marked and significant clinical signs exist, standard therapies are indicated (see ch. 69). Moderate hypercalcemia typically resolves in 2 to 3 days of initiation of chemotherapy.

HVS is best treated in the short term by plasmapheresis. Bleeding diathesis usually resolves along with HVS; however, platelet-rich transfusions may be necessary with thrombocytopenia.

Renal impairment may necessitate aggressive fluid therapy. Careful attention to secondary urinary tract infections and appropriate antimicrobial therapy is indicated. Pathologic fractures of weight-bearing long bones and vertebrae may require immediate intervention in conjunction with systemic chemotherapy. Orthopedic fracture stabilization is undertaken and may be followed with radiotherapy. Inhibition of osteoclast activity with bisphosphonate drugs have been used with mixed results to reduce incidence/severity of skeletal complications.[206,207]

Rescue Therapy

At relapse or in cases initially resistant to melphalan, rescue therapy may be attempted. A combination of doxorubicin (30 mg/m^2 IV every 21 days), vincristine (0.7 mg/m^2 IV on days 8 and 15 of the cycle), and dexamethasone sodium phosphate (0.5 mg/kg IV on days 1, 8 and 15) administered in 21-day cycles has been employed by this author. Most dogs initially respond to rescue; however, the duration tends to be short-lived. High-dose cyclophosphamide and liposome-encapsulated doxorubicin have also been used for rescue.[208] Bone marrow ablative therapy and marrow or stem-cell rescue, thalidomide (and other antiangiogenic therapies), bortezomib (a proteasome inhibitor), arsenic trioxide, the bisphosphonates, VDC-1011 and other molecular targeting therapies have been utilized; however, their use in veterinary species is limited or completely absent at present.[205] A dog with melphalan-resistant MM achieved a partial response to tyrosine kinase inhibitor therapy (toceranib) that was maintained for 6 months.[209]

Prognosis

The prognosis for dogs with MM is good for initial control and a return to good quality of life. In 60 dogs with MM, >90% achieved a complete or partial remission with melphalan and prednisone.[195] Long-term survival is the norm, with a median of 540 days reported. Hypercalcemia, Bence Jones proteinuria, and extensive bony lysis are negative prognostic factors in the dog. The long-term prognosis is poor, owing to drug-resistant recurrence.

The prognosis for multicentric MRD in the cat is not as favorable as in the dog because remission durations are generally 2-4 months; however, occasional long-term survival has been reported.[198,200-202,204]

Solitary Plasmacytoma

Solitary collections of monoclonal plasmacytic tumors can originate in bone or soft tissues and are referred to as solitary osseous plasmacytoma (SOP) and extramedullary plasmacytoma (EMP), respectively. The majority of SOPs eventually progress to systemic MM.[172,173] Solitary cutaneous EMP, including oral cavity EMP, is typically a benign disorder in dogs.[174-180] Conversely, the natural behavior of noncutaneous EMP appears more aggressive. Gastrointestinal EMPs have been reported to involve the esophagus, stomach, and small and large intestine or colon.[181-185] Metastasis to associated lymph nodes is common, although bone marrow involvement and monoclonal gammopathies are less common. Colorectal forms progress slowly and may be cured with excision.[185] Few reports exist in cats and while some are controlled with surgical excision, widespread systemic involvement is more likely.[155-158,186-191]

Clinical Signs

Clinical signs associated with solitary plasmacytoma relate to the location. SOP usually is associated with pain and lameness if the appendicular skeleton is affected or with neurologic signs if vertebral bodies are involved. Cutaneous EMP usually has a benign course, whereas gastrointestinal EMP presents with nonspecific signs that suggest alimentary involvement.

Diagnosis

The diagnosis of SOP and EMP requires cytology or tissue biopsy. Thorough staging of SOP and noncutaneous EMP with bone marrow aspirate, serum electrophoresis, and skeletal survey radiographs is important to ensure disease is confined prior to initiation of therapy. In poorly differentiated solitary plasmacytic tumors, immunohistochemical (e.g., MUM1) may be helpful in confirming a diagnosis.[190,192-194] PCR techniques can also be used to determine clonality.

Therapy

Animals with solitary plasma cell tumors may be treated with local therapy (e.g., surgery and/or radiation therapy) in the absence of systemic chemotherapy provided thorough clinical staging does not reveal systemic involvement. Dogs with noncutaneous SOP and EMP may eventually develop systemic MRD. Systemic dissemination may not occur for many months to years beyond diagnosis in humans and no benefit from initiation of systemic chemotherapy prior to the documentation of subsequent systemic involvement is observed. Long-term follow-up of patients with solitary plasmacytoma is indicated to detect both recurrence of disease and systemic spread.

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CHAPTER 345

Tumors of the Skin

Kenneth M. Rassnick

Client Information Sheet: Tumors of the Skin

The skin is the most common site of occurrence for neoplasms in the dog and the second most common site in the cat. Subcutaneous (SC) and cutaneous tumors together account for >1/3 of all canine tumors. Approximately 20% to 30% are histologically malignant.[1] Mast cell tumors, perianal (sebaceous) adenomas, lipomas, sebaceous gland adenomas, histiocytomas, trichoblastomas (formerly classified as basal cell tumors), squamous cell carcinomas, melanomas, fibrosarcomas, hemangiopericytomas, and papillomas are the most common histologic types of canine tumors.[1-4] Skin and SC tissues account for ≈1/4 of all tumors in the cat, and 50% to 65% are histologically malignant.[1,2,5] The histologic appearance of malignancy does not necessarily correlate with the tendency to metastasize. The most common skin tumors in cats include basal cell tumors, mast cell tumors, squamous cell carcinomas, fibrosarcomas, melanomas, and hemangiomas.[2,5,6]

Tumors of the skin and subcutis can be broadly classified histologically according to tissue of origin: epithelial, mesenchymal, round cell, or melanocytic (Box 345-1). They can be classified further according to cell of origin, when sufficient differentiation is present. This chapter focuses on tumors of epithelial origin, melanocytic tumors, and certain round cell tumors.

Box 345-1

Common Skin and Subcutaneous Tumors

Epithelial Tumors

Papilloma
Intracutaneous cornifying epithelioma
Squamous cell carcinoma
Basal cell tumors (basal cell epithelioma)
Trichoepithelioma
Follicular stem cell carcinoma
Pilomatricoma
Trichoblastoma
Sebaceous gland tumors
Hepatoid gland tumors (perianal gland tumors)
Sweat gland tumors (apocrine gland tumors)
Ceruminous gland tumors
Anal sac apocrine gland tumors

Mesenchymal Tumors

Soft-tissue sarcomas (see ch. 346)

Round Cell Tumors

Plasmacytoma
Mast cell tumor (see ch. 349)
Lymphoma (see ch. 344)
Histiocytoma (see ch. 350)

Transmissible venereal tumor (see ch. 351)

Melanocytic Tumors

Melanoma

General Approach

History and Physical Examination

Because lesions and masses involving the skin are easily seen, they are common reasons for owners to seek veterinary care. General history taking should include duration and rate of tumor growth, change in appearance over time, response to previous treatments, and related medical problems. Benign tumors are more likely to have a history of slow growth over months to years. In contrast, malignant tumors tend to be rapidly-growing and -changing in appearance. All tumors should be accurately reported in the medical record (location, diagrams/photographs, caliper measurements). The record also should include gross appearance (color, alopecia, ulceration), consistency (firm, soft), borders (circumscribed, infiltrative), and attachments to underlying tissues (fixed, movable). Most benign skin tumors are well-circumscribed and freely movable. In contrast, malignant skin tumors often are fixed to underlying structures and have ill-defined margins. As part of the patient's complete physical examination, lymph nodes draining a skin mass should always be thoroughly evaluated.

Diagnostics

General

The key to the appropriate management of skin tumors is a specific diagnosis. Often, diagnosis and characterization of a skin mass should be done before surgical excision, so the clinician can plan an appropriate surgical approach; make decisions about the need for adjuvant radiation therapy, chemotherapy, or immunotherapy; and discuss realistic outcomes of therapy and prognosis with clients. Figure 346-2 shows a general approach to the diagnosis of superficial masses using fine needle aspiration (FNA) and biopsy.

Routine hematologic and biochemical analyses rarely are helpful in the diagnosis of cutaneous masses; however, some skin tumors might be associated with paraneoplastic complications (see ch. 352). Screening blood tests are recommended before a definitive procedure is planned.

Radiographs of the thorax are required in the staging of malignant skin tumors, and abdominal ultrasound can be useful to assess potential sites of metastases for some tumors. For tumors that attach deeply to underlying tissues, radiographs, computed tomography (CT), or magnetic resonance imaging (MRI) can help delineate tumor borders prior to surgical excision.

Enlarged lymph nodes should always be evaluated cytologically or histologically (see ch. 95). For some tumors (mast cell tumors, melanomas), metastases might be present in lymph nodes that are palpably normal; therefore, lymph node evaluation should be a routine part of the evaluation of an animal with a cutaneous mass.

Fine Needle Aspiration

Fine needle aspiration (see ch. 86) for cytologic assessment (see ch. 87) is easy and quick to perform, and often provides information about the neoplastic cell type.[7] It is most useful in the diagnosis of round cell tumors (mast cell tumors, cutaneous lymphoma, histiocytoma) and for identifying benign skin tumors or papules, nodules, and masses that are nonneoplastic. When cytologic results are nondiagnostic, a biopsy should be performed. Likewise, when a cytologic diagnosis of neoplasia is obtained, a biopsy should always be done to confirm the diagnosis and assess important prognostic information, such as the degree of differentiation or the tumor grade, a description of vessel invasion, and an evaluation of tissue margins[8] when the biopsy is excisional.

Biopsy

A number of biopsy techniques can be used (see ch. 86). Incisional, needle core, or punch biopsies are indicated for large, infiltrative masses or for tumors in a difficult area for reconstruction, such as extremities and perineal or periocular regions. For superficial exophytic lesions, shave biopsies done with a scalpel blade might be adequate. For small, movable dermal masses, excisional biopsy can be both diagnostic and

therapeutic. Even when the diagnosis is known before biopsy, histopathologic assessment of the final specimen is essential because it might provide information for treatment planning.

For nonexcisional biopsies, the site should be in an area that can easily be included in a definitive resection or radiation field. As a general rule, all biopsy incisions on extremities should be longitudinal along the axis of the limb. Injection of local anesthetics into cutaneous and SC tumors should be avoided due to tissue distortion. The biopsy should be taken deeply enough to avoid superficial necrotic tissue and surrounding inflammation. The biopsy procedure should never disrupt tissue planes. Drain placement should be avoided, because it allows neoplastic cells in draining fluid to contact all tissues through which the drain is placed.

An ideal histologic specimen includes the junction of the tumor with adjacent normal tissue. Samples <1×1 mm usually are inadequate, but 1×5 mm needle core samples can be adequate. Samples that fall apart in formalin are often blood, mucus, or necrotic material and are usually nondiagnostic. Large biopsy samples or multiple specimens from different areas of the tumor, collected through the same incision, can improve the likelihood of an accurate diagnosis. Cautery instruments should not be used during the biopsy procedure; cautery for hemostasis can be used once the sample has been removed. Surgical diode lasers often make suboptimal samples; carbon dioxide lasers cause less thermal injury, but still might render small samples nondiagnostic.[9] Finally, formalin fixation can cause marked tissue contraction.[10] Applying India ink or other dyes to all cut surfaces of tumors before formalin fixation helps the pathologist distinguish surgical margins from preparation artifacts.

Epithelial Tumors

Papilloma

Cutaneous papillomas are benign proliferations of the epidermis and are common in the dog but relatively rare in cats. Grossly, they are whitish or gray, pedunculated or cauliflower-like masses and are often referred to as *warts* or *verrucae.* Both viral and nonviral forms exist.[11,12] Papillomaviruses are DNA viruses and are species-specific; causality was not proven in a case report of cutaneous papilloma in a cat from which a human papillomavirus was amplified.[13] Papillomaviruses can survive for >2 months at 4° to 8° C and for 6 hours at 37° C.[14] They can be transmitted by direct and indirect (e.g., fomite) contact. In general, papillomavirus infection occurs in damaged skin, and incubation times vary from 1 to 2 months.[14]

Cutaneous papillomas occur in older dogs, and single or multiple lesions can be seen. They most commonly occur on the head, eyelids, and paws and are not associated with papillomavirus. Canine oral papillomatosis is a contagious disease of viral origin that often affects young or immunocompromised dogs (see ch. 228 and 272).[15] Cutaneous inverted papillomas, cup-shaped lesions seen in young dogs, are also caused by infection with a papillomavirus. They occur on the ventral abdomen and inguinal region.[16] Rare cases of multiple, pigmented plaques, or papular papillomas, have been reported in dogs.[17] Pugs appear to be predisposed to these pigmented plaques, and the disease is related to a novel papillomavirus.[18] Finally, progression of viral papilloma into carcinoma might rarely occur in some dogs.[11,12]

In cats, most solitary cutaneous papillomas are not caused by papillomavirus. In contrast, papillomas that occur on the ventral tongue in cats are generally viral in origin, as are multiple cutaneous papillomas. These viral papillomas might be precursors to feline multicentric squamous cell carcinoma, or Bowen disease (see Feline Squamous Cell Carcinoma, below).[19]

Surgical excision of solitary cutaneous papillomas is curative. Canine oral papillomatosis usually undergoes spontaneous regression within 3 months, and the dog is then immune to reinfection.[14] Immunocompromised animals or those treated with immunosuppressive therapies, such as corticosteroids, might suffer from persistent papillomavirus infections and lesions.[15,20] Autogenous vaccines (to induce regression) have been used, and current attempts aim to create prophylactic and therapeutic recombinant vaccines.[21] Oral administration of retinoids has been reported to be effective for canine inverted papillomas.[22] Interferon or azithromycin might be effective in the treatment of severe oral or cutaneous viral papillomatosis.[23,24]

Intracutaneous Cornifying Epithelioma (Infundibular Keratinizing Acanthoma)

Intracutaneous cornifying epitheliomas (keratoacanthomas) arise from the outer portion of the hair follicle.

They usually occur in relatively young, purebred dogs. Most are solitary, but generalized forms exist. Norwegian Elkhounds and Keeshonden are predisposed to the generalized form.[25] These tumors often have a central pore filled with inspissated keratinous material. Gentle digital pressure applied to the mass results in expulsion of a gray-white keratinous material. Often, there is diagnostic disagreement among pathologists evaluating these lesions; the most common variant diagnosis for keratoacanthomas is well-differentiated squamous cell carcinoma.[26]

Intracutaneous cornifying epitheliomas are benign and do not recur after adequate surgical removal. In the generalized form, new tumors might develop throughout a dog's life. Orally administered retinoids might be useful in the treatment of multiple intracutaneous cornifying epitheliomas (5/7 complete, and 2/7 partial, remissions in one study).[23] Spontaneous regression has also been reported to occur in a dog with the generalized form.[27]

Canine Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is a common malignant neoplasm in the dog. The etiology usually is not known. Tumors that develop in unpigmented or lightly pigmented skin, such as the abdomen and inguinal areas, are believed to be induced by ultraviolet radiation (sun damage).[28] Occasionally, SCC might be caused by burns, chronic infectious or immune-mediated diseases, or progression from viral papillomas.[11,12,24] In an immunohistochemical study of 40 dogs with SCC, 100% of lesions expressed cyclooxygenase-2 (COX-2).[29] COX-2 has been implicated in the oncogenesis of various human cancers, but the mechanisms leading to upregulation of COX-2 are not known. SCC in the dog can be proliferative, ulcerative, or erosive. The clinical features and management of canine SCC are highly dependent on the anatomic location.

Canine Cutaneous Squamous Cell Carcinoma

Cutaneous SCC might first be diagnosed as a preneoplastic lesion, but it ultimately progresses to an invasive tumor. Metastasis to regional lymph nodes and the lungs is rare.[30] Canine cutaneous SCC is best managed with adequate surgical excision. Preneoplastic lesions might respond to orally administered retinoids,[28] and intralesional therapy with sustained-release cisplatin, 5-fluorouracil, or carboplatin might have a role in the management of some dogs with superficial SCC.[31] Comprehensive surgical excision is the treatment of choice for invasive cutaneous SCC. Radiation therapy for incompletely excised tumors; chemotherapy with platinum drugs, doxorubicin, or gemcitabine; or perhaps treatment with COX-2 inhibitors, can be considered for metastatic tumors, but their efficacy is unproven.

Canine Nasal Planum Squamous Cell Carcinoma

Nasal planum SCC can be treated with comprehensive surgical excision of the nasal planum and premaxilla, but the prognosis is extremely guarded. Case selection is important: in a study of six dogs treated surgically, two recurred in less than 2 months, probably because of incomplete resections.[32] Radiation therapy has been largely disappointing, with 7/7 dogs treated with radiation for incompletely excised tumors suffering recurrences in 8 to 12 weeks in one study.[32]

Canine Digital Squamous Cell Carcinoma

SCC originates from the subungual epithelium, or occasionally from other tissues of the digit, and it is the most common digital tumor in dogs. A breed predilection for large-breed, black-coated dogs—including Giant Schnauzers, Standard Poodles, Labrador Retrievers, Rottweilers, and Flat Coated Retrievers—has been reported.[33] Dachshunds with a black hair coat might be overrepresented.[33] Approximately 80% of digital SCCs invade bony tissue of the third phalanx. Metastases are uncommon initially but can be diagnosed after treatment in as many as 30% of dogs.[33-35] Rarely, dogs might develop SCC on multiple digits, either simultaneously or over time.[33,34] Wide amputation, with disarticulation of the first phalanx and metacarpal/metatarsal bone is the treatment of choice. Overall, <50% of dogs with digital SCC die as a result of their disease, so median survival cannot be determined.[34] In one study, the 1- and 2-year survival rates were 95% and 74%, respectively, for subungual epithelial SCC, and 60% and 40%, respectively, for SCC arising from other parts of the digit.[34] Chemotherapy with platinum drugs, doxorubicin, or gemcitabine, or perhaps treatment with COX-2 inhibitors, can be considered for metastatic tumors, but efficacy is unproven.

Feline Squamous Cell Carcinoma

As with dogs, SCC in cats occurs most frequently in sun-damaged skin and is usually preceded by actinic (solar) keratosis.[24] Viruses might also be underlying etiologies for feline SCC. In one study, 24% of cats infected with feline immunodeficiency virus (FIV) developed SCC.[36] It is unclear whether a direct causal relationship exists or whether the condition is due to outdoor sunlight exposure in these cats. Papillomavirus has been identified in lesions of multicentric SCC *in situ* (Bowen disease).[24,37] As in canine SCC, COX-2 immunoreactivity has been shown in all cases of feline cutaneous SCC,[38] though the mechanisms are unknown. As in dogs, SCC is the most common digital neoplasm in cats.[39] The histologic differentiation of primary digital SCC in cats can be difficult to discern from metastatic pulmonary adenocarcinoma in the digits, so thoracic radiography is recommended if a diagnosis of SCC is returned.[39,40]

Feline Cutaneous Squamous Cell Carcinoma

Cutaneous SCC in the cat usually starts as a crusted area that eventually develops into an erosive or ulcerative lesion. The most common sites are unpigmented areas exposed to sunlight, including the external nares, pinnae, eyelids, and lips. Multiple lesions occur in ≈45% of affected cats.[41] Metastases are rare.

Several treatment options exist for feline cutaneous SCC, including comprehensive surgical excision (pinnectomy, nosectomy), cryotherapy, external-beam radiation, strontium-90 plesiotherapy, photodynamic therapy, topical immunotherapy (imiquimod cream), electrochemotherapy, and intralesional chemotherapy. These treatments are most successful in small (<5 cm), superficial lesions; therefore, early diagnosis and prompt therapy are essential. Small, minimally invasive SCC lesions can be controlled for >1 year in most cats, and long-term control (2-7 years) is possible in 10% to 60%. Treatment of larger (>5 cm) or invasive tumors is disappointing, with control times generally <2 years.[41-48] In all cats, avoidance of sunlight is important to prevent additional lesions.

Feline Multicentric Squamous Cell Carcinoma *In Situ* (Bowen Disease)

Bowen disease is a condition of small, plaquelike, crusted SCC lesions that histologically do not invade the basement membrane. Unlike solar-induced SCC, multicentric SCC *in situ* is found in haired, pigmented areas and might be caused by infection with a papillomavirus.[37]

Lesions are multifocal over the head, neck, thorax, abdomen, and limbs. Occasionally, focal areas of invasive SCC or concurrent invasive SCC lesions might be present.[49,50] When possible, surgical excision is the treatment of choice. Strontium-90 plesiotherapy can be effective for small lesions (<8.5 mm in diameter); multiple overlapping fields are needed for larger lesions.[46] Due to the multicentric nature of the disease, some cats might need alternative therapies. Imiquimod is an immune-response modulator, and regression of Bowen disease lesions treated with this cream has been reported.[50] Therapy with orally administered retinoids is variably successful.[12]

Basal Cell Tumors (Basal Cell Epithelioma)

Basal cell tumors (basal cell epitheliomas) are benign neoplasms that arise from the basal cells of the epidermis. They are the most common skin tumor affecting the cat.[51] The tumor previously classified as basal cell tumor in the dog has been reclassified as trichoblastoma. Basal cell tumors usually are solitary, firm, rounded, and well-circumscribed. Occasionally, they might be cystic. Basal cell tumors often are pigmented, which can lead to a clinical misdiagnosis of melanoma. Adequate surgical excision is the treatment of choice.

Basal Cell Carcinoma

Basal cell carcinomas usually are solitary and similar to basal cell tumors; they are often pigmented brown or black. This tumor is locally invasive; therefore, clinical management should include wide surgical excision. In most cases, local excision is curative. Animals with local recurrence[52] and/or metastases rarely have been reported.[53] Adjunctive radiation therapy can be considered when adequate surgical margins cannot be achieved.

Trichoepithelioma

Trichoepitheliomas are benign neoplasms from the hair follicle sheath. They are relatively common in the dog and uncommon in the cat. Surgical excision is the treatment of choice. Malignant trichoepithelioma with lymph node and lung metastasis has rarely been reported.

Follicular Stem Cell Carcinoma

Follicular stem cell carcinoma is an uncommon epithelial tumor in the dog that has not been reported in other species.[54] Tumors previously referred to as *sebaceous carcinomas* now are named *follicular stem cell carcinomas.*[54] They show areas of apocrine or trichoepitheliomatous (hair follicle) differentiation or both. The biological behavior has not been well described, but lymphatic invasion is noted in some tumors, and metastases have been reported.[54]

Pilomatricoma

Pilomatricomas are uncommon, benign tumors that arise from the hair follicle. They usually are solitary and well circumscribed. On cut section, the tumor consists of several layers of gray-white chalky tissue. Surgical excision is the treatment of choice. Malignant pilomatricomas have been reported rarely; lymphatic invasion is seen histologically, and metastases to bone, lymph nodes, lungs, skin and the nervous system might occur.[55]

Trichoblastoma

Trichoblastomas are common benign tumors that predominately derive from primitive hair germ epithelium. This neoplasm was previously classified as basal cell tumor. Trichoblastomas are generally solitary and can be pigmented. Surgical excision is curative.

Other Follicular Tumors

Other uncommon follicular tumors (tricholemmoma, trichofolliculoma, dilated pore of Winer, and warty dyskeratoma) are benign lesions, and adequate surgical excision should be curative.

Sebaceous Gland Tumors

Sebaceous gland tumors are derived from sebocytes, produce sebum (an oily white fluid), and are among the most common skin tumors in dogs. Predisposed breeds include English Cocker Spaniel, Cocker Spaniel, Samoyed, Siberian Husky, Cock-A-Poo, Alaskan Malamute, West Highland White Terrier, Cairn Terrier, Dachshund, Miniature and Toy Poodle, and Shih Tzu. These tumors are uncommon in cats.

Histologically, sebaceous gland tumors are classified as sebaceous hyperplasia, epitheliomas, adenomas, or, rarely, carcinomas. The lesions are wartlike or cauliflower-like in appearance and can occur throughout the body, including on the eyelids. They usually are solitary, but multiple sebaceous gland tumors can occur. Tumors previously referred to as *sebaceous carcinomas* in the literature are now named *follicular stem cell carcinomas* (see above).[54]

Surgical excision is the treatment of choice for all types of sebaceous gland tumors. Local recurrence is rare, but up to 10% of dogs might develop lesions at other sites.[56] Dogs with sebaceous hyperplasia might respond to therapy with orally administered retinoids.[23] Sebaceous carcinomas appear to have a low potential for metastasis.[56]

Hepatoid Gland Tumors (Perianal Gland Tumors)

Perianal gland tumors arise from canine circumanal glands, which are nonsecretory, modified sebaceous glands.[57-60] These tumors are discussed in ch. 278.

Sweat Gland Tumors (Apocrine Gland Tumors)

Sweat gland tumors in dogs and cats commonly occur in the inguinal or axillary regions. These tumors have various clinical presentations, including solitary nodular masses or a diffuse, inflammatory, and ulcerative, plaquelike growth. Cats with a histologic diagnosis of apocrine gland carcinoma of the digit might actually

have digital metastases from a pulmonary carcinoma.

Most sweat gland tumors are histologically malignant carcinomas, and >20% might have evidence of lymphatic or vascular invasion.[61-63] Wide surgical excision is the treatment of choice. In two case series, <2% of canine sweat gland carcinomas developed distant metastases, possibly in association with vascular invasion.[61,62]

Ceruminous Gland Tumors

Ceruminous gland tumors originate from modified apocrine sweat glands in the external ear canal. Chronic otitis externa might be a predisposing factor (see ch. 237).[64] Common clinical signs associated with ear canal tumors include the presence of a mass, aural discharge, odor, pruritus, and pain. Neurologic signs, including Horner's syndrome and vestibular disease, might also be present. Radiographs of the skull and/or CT are important imaging modalities that should precede surgery. Careful evaluation of the mandibular and periauricular lymph nodes is essential.

Ceruminous gland adenomas can be managed by conservative surgical resection. For ceruminous gland carcinomas, however, comprehensive surgical excision, including ear canal ablation and lateral bulla osteotomy, is the treatment of choice. A 42-month median remission, 25% recurrence rate, and 75% 1-year survival rate are associated with such treatment, compared to a 10-month median remission, 40% recurrence rate, and a 33% 1-year survival rate with lateral ear resection alone.[65] Complete ear canal ablation with lateral bulla osteotomy in 7 dogs resulted in 0 recurrences over a 36 month follow-up, compared with recurrence within 4 months in 3/4 dogs treated with a more conservative lateral ear canal resection.[66] Radiation therapy can be used as an adjunct to incomplete resection. A median progression-free interval of 40 months and a 56% 1-year survival rate were achieved in six cats and five dogs treated with radiation therapy after incomplete resection of ceruminous gland adenocarcinoma.[67]

Anal Sac Adenocarcinoma

Anal sac adenocarcinomas arise from the apocrine glands in the ventrolateral aspects of the anus. They occur almost equally in female and male dogs but are rare in cats.[68] Up to 30% of anal sac adenocarcinomas are detected incidentally on a routine physical examination, underscoring the importance of complete rectal examination on routine exams. Twenty-five percent to 50% of anal sac adenocarcinomas produce parathyroid hormone–related protein (PTHrP), leading to hypercalcemia of malignancy[68,69] (see ch. 297 and 352); hypercalcemia generally resolves quickly after resection of the primary tumor, but supportive therapies (e.g., intravenous fluids, corticosteroids, and/or bisphosphonates) might be needed in some cases until surgery can be done or when hypercalcemia cannot be controlled with surgery alone. Metastases generally arise in the iliac lymph nodes, although distant metastases might also be seen in the liver, spleen, lungs, bones, and other sites. Occasionally, extension from the iliac lymph nodes into the lumbar vertebrae may occur.[69] The diagnosis and treatment of these tumors[70,71] are discussed further in ch. 278.

Tumor size generally is an important predictor of survival of dogs with anal sac adenocarcinoma. Dogs with small tumors (<2.5 cm diameter) and no metastases have an excellent prognosis (median survival ≈3.5 years[73]) after surgical excision. For tumors >2.5 cm in diameter, the survival time with surgical excision alone is ≈1.5 years.[73] In a study of 24 dogs with anal sac tumors ≥10 cm, survival times were <1 year.[74] The rate of local recurrence after surgical excision of anal sac adenocarcinoma is approximately 50%. It is unclear whether this correlates with incomplete histologic margins,[69,70] but adjunctive radiation therapy for dogs with incompletely resected tumors might improve the outcome.[75]

Forty percent[69] to 80%[70] of dogs with anal sac adenocarcinoma have metastases to the iliac lymph nodes at initial diagnosis, but anal saculectomy and sublumbar lymphadenectomy can still confer a median survival time of ≈2 years.[76]

It is unclear whether paraneoplastic hypercalcemia of malignancy or E-cadherin (a transmembrane protein that mediates adhesions between epithelial cells and the extracellular matrix) influences the outcome of dogs with anal sac adenocarcinoma.[67,73,74,77]

Anticancer agents most widely evaluated include cisplatin, carboplatin, doxorubicin, mitoxantrone, actinomycin, and melphalan,[70,73-75] but the exact role of chemotherapy for this disease is not known. Evidence suggests that toceranib phosphate has biologic activity against canine anal sac adenocarcinoma (see

below, and ch. 341).[78] Indications for chemotherapy and/or receptor tyrosine kinase inhibitors might include nonresectable tumors, metastatic disease, or even evidence of lymphatic invasion, and additional studies are needed to assess this.

Round Cell Tumors

Round cell tumors also may be called *discrete cell tumors.* Cytologically, they appear as individually oriented round cells that have no obvious attachments to each other. Round cell tumors include lymphoma, mast cell tumors, plasmacytomas, histiocytomas, and transmissible venereal tumors. Occasionally, melanomas and basal cell tumors might mimic round cell patterns. In some cases, the type of tumor is not readily distinguished cytologically; a biopsy of the lesion should be submitted for histopathologic analysis. If the cell lineage is still not determined, immunohistochemistry or special stains can be performed. Examples include CD3/CD4/CD8 (T-cell lymphoma), CD21/CD79a (B-cell lymphoma), CD-117/Toluidine blue/Giemsa (mast cell tumor), MUM1/RF4 (plasma cell tumor), CD 18 (histiocytoma) and Melan A/PNL2/S100 (melanoma).

Lymphoma, Mast Cell Tumor, Histiocytoma, and Transmissible Venereal Tumors

These tumor types are discussed in ch. 344, 349, 350, and 351, respectively.

Plasmacytoma

Cutaneous plasma cell tumors (cutaneous extramedullary plasmacytomas) usually are solitary, and common locations of occurrence are the digits, lips, pinnae, oral cavity, and rectum.[78,79] The majority of cutaneous plasmacytomas in the dog are benign and are unrelated to multiple myeloma (see ch. 344). The behavior of canine plasmacytomas does not seem to have any relationship to the degree of histologic atypia or pleomorphism.[79,80] Additional information is available under Myeloma-Related Disorders (ch. 344).

The treatment of choice for cutaneous plasmacytomas is surgical excision. Local recurrence might be associated with incomplete margins.[79] Radiation therapy (see ch. 340) can be considered for nonresectable tumors, but information is limited.[81,82]

Most plasma cell tumors reported in cats are systemic (myeloma-related disease), so testing is indicated as described for multiple myeloma (see ch. 344).[83] Solitary cutaneous plasmacytomas in cats should be excised. Adjunctive chemotherapy with predniso(lo)ne and alkylating drugs (i.e., melphalan, chlorambucil, or cyclophosphamide) is recommended if the disease is multicentric. As in dogs, radiation therapy can be considered for the treatment of a nonresectable cutaneous lesion.

Melanocytic Tumors

Melanoma

The etiology of cutaneous melanomas in dogs and cats is unknown, but breed predilections in dogs suggest a genetic basis. Breeds reported to be at risk include Scottish Terriers, Airedales, Boston Terriers, Cocker and Springer Spaniels, Boxers, Golden Retrievers, Standard and Miniature Schnauzers, Irish and Gordon Setters and Doberman Pinschers.[24] In dogs, lesions usually are solitary and are brown to black in appearance. Common sites include the eyelid, muzzle, trunk, interdigital skin, and subungual epithelium (nail bed). Digital melanomas are the second most common digital tumor in dogs, after SCC.[33] In cats, the most common pigmented cutaneous tumor is a basal cell tumor. However, melanomas also are black. Common sites in cats include the pinnae, nose, and neck.

The biological behavior of cutaneous melanomas can be benign or malignant. Of critical importance is the location of the tumor. As a general rule, tumors arising from haired skin are benign. Those arising from mucocutaneous junctions are malignant, the only exception being those arising on the eyelids. Melanomas of the digit can be highly malignant, and malignant melanomas commonly spread via lymphatics to draining lymph nodes and the lungs. Metastases to distant sites such as the liver, spleen, brain, heart, and bone marrow occasionally occur.

In dogs, traditional histologic criteria of malignancy appear to be appropriate for diagnosing malignancy in tumors of melanocytic origin, but no single feature or pattern of features always correlates with outcome.[84-86]

Histologic mitotic index appears to be generally predictive of biologic behavior.[84,87-89] A mitotic index of <3 per 10 high-power fields appears to be associated with benign behavior.[87,93] It is difficult to predict the biologic behavior of cutaneous melanomas in cats based on mitotic index, because 25% of malignant tumors can show no mitotic figures.[90]

The treatment of choice for cutaneous melanomas in both the dog and the cat is surgical excision. A median survival of 26 months and a 2-year tumor-related death rate of 10% occurred in 59 dogs where the mitotic index of the tumor was <3, compared to a median survival of 7.5 months and a 2-year tumor-related death rate of 73% in 26 dogs where the mitotic index was ≥3.[87] With digital melanomas in dogs, >50% metastasize.[33,35] A median survival time of 12 months has been reported for dogs treated by amputation of the affected digit.[33,34,85] Other studies have reported median survival times of 18 to 24 months.[87,88]

The prognosis for cats with cutaneous melanomas is guarded. In one study of 57 cats with these tumors, metastases were documented at initial diagnosis in 11 (19%). Forty-five cats were treated by surgical excision, and 22 of these animals developed local recurrence or metastases.[91]

Coarsely fractionated radiation therapy is useful for treating dogs with oral melanoma and might be beneficial for local control of nonresectable cutaneous melanomas in dogs and cats.[92]

Also, a clinical response to treatment with carboplatin can be seen in dogs with oral melanomas. Therefore, this might be considered as an adjunct therapy in dogs with digital melanomas or in dogs and cats with malignant or nonresectable tumors or metastatic disease.[93,94] Finally, a xenogeneic DNA canine melanoma vaccine is commercially available (Canine Melanoma Vaccine, Merial) (see ch. 341). The product immunizes with human DNA encoding tyrosinase, the enzyme essential for melanin synthesis. Long survival times have been reported in dogs in clinical stage II (tumor 2-4 cm in diameter) or stage III (tumor >4 cm in diameter or with local lymph node metastasis) oral melanoma with adequate local control (i.e., with surgery and/or radiotherapy) treated with the vaccine. However, reliability of vaccine efficacy data is severely hampered by lack of randomized clinical trials.[95-97]

A xenogeneic tyrosinase DNA vaccine was safe when used in conjunction with local and regional disease control in a group of 58 dogs with malignant digit melanoma. Overall median survival time was 476 days, with a 1-year survival rate of 63%. The xenogeneic vaccine used in the study was of murine DNA origin, unlike the commercially available product, which is of human DNA origin. However, the authors believe that the immune response and therefore response to vaccine treatment should be the same.[98] Canine melanoma vaccine might have a role in the management of malignant cutaneous melanomas, but this has yet to be determined.

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CHAPTER 346

Soft-Tissue Sarcomas*

Margaret C. McEntee

Client Information Sheet: Injection-Site Sarcomas in Cats

Introduction

Definitions

Collectively, soft-tissue sarcomas (STSs) include several histologic subcategories derived from neoplasms of mesenchymal origin (Box 346-1). Distinct biologic behaviors have been described for tumors in each of these subcategories but the collective experience of pathologists and specialists managing sarcomas in dogs has permitted development of a histologic grading scheme that describes predicted tumor behavior by the degree of differentiation rather than by specific histologic type (Table 346-1). Histologic grade of a tumor can suggest radical versus functional surgery or be used in the decision process regarding the addition of radiation therapy (RT) or chemotherapy. Tumor size and location also impact surgical options for local control.

Box 346-1

Histologic Categories of Soft-Tissue Sarcomas in Dogs and Cats

Fibrosarcoma
Peripheral nerve-sheath tumor (malignant schwannoma, neurofibrosarcoma, hemangiopericytoma)
Myxosarcoma
Malignant fibrous histiocytoma
Synovial cell sarcoma
Neurofibrosarcoma
Rhabdomyosarcoma
Leiomyosarcoma
Liposarcoma
Schwannoma
Undifferentiated sarcoma

TABLE 346-1

Proposed Grading Criteria for Canine Soft-Tissue Sarcomas

SCORE	DEGREE OF DIFFERENTIATION	MITOTIC INDEX*	NECROSIS
1	Normal appearance	0-9	None
2	Specific histologic type	10-19	<50%
3	Undifferentiated	≥20	>50%
Grade (Cumulative Score)			
1	3 or 4		
2	5 or 6		

3	7, 8, or 9		

*Number of mitotic figures/10 high-powered fields (40×).

Adapted from Kuntz CA, Dernell WS, Powers BE, et al: Prognostic factors for surgical treatment of soft-tissue sarcomas in dogs: 75 cases (1986-1996). *J Am Vet Med Assoc* 211:1147-1151, 1997.

Despite the general consensus that grade may influence success in complete tumor removal, debate continues regarding the universal applicability of histologic STS grade as a clinically meaningful predictor of response to therapy in dogs. To date, no consistent convincing evidence exists for comparison of grade with outcome for feline STSs. Cellular proliferation as measured by argyrophilic nucleolar organizing regions score, as well as intratumoral microvessel density using factor VIII–related antigen as the endothelial marker, have been investigated in canine STSs and may supplement the prognostic information provided by tumor grade.[1,2] Specific histopathologic types of tumors that have been reported in cats with injection-associated sarcomas (IAS; previously referred to as *vaccine-associated sarcomas [VAS])* include fibrosarcoma, undifferentiated sarcoma, osteosarcoma, rhabdomyosarcoma, liposarcoma, malignant fibrous histiocytoma (or myofibrosarcoma), and leiomyosarcoma. Hemangiosarcomas (see ch. 347), synovial cell sarcomas (see ch. 348), and mast cell tumors (see ch. 349) are discussed separately. Other, less common sarcomas are not included due to insufficient information to consider them in the collective terminology (e.g., rhabdomyosarcoma).

Descriptions

STSs are typically focal, solitary, palpable, soft to firm lumps found in the dermis, subcutaneous (SC) tissue, or deeper muscular and musculofascial compartments. Masses that have grown rapidly or those that are large because they have been present for a prolonged time can have ulcerated surfaces and may be painful. Most STSs are 2 to 4 cm in diameter at the time of initial examination. Tumor size can vary depending on a number of factors, including location; specifically, is the mass located superficially in the dermis or deep in a muscle? Other factors include how quickly an owner identifies a new lump and overall body condition, because masses are more easily observed on a trim pet or those with shorter hair.

STSs can develop in any location on the body but are most common on the limbs or head. Depending on tumor location, other clinical signs may include vomiting, diarrhea, and/or weight loss with gastrointestinal tumors; pain and/or lameness with peripheral nerve root tumors; and halitosis, difficulty prehending food, and other signs with oral tumors. In cats, STSs are frequently associated with sites of vaccination/injection and therefore are more commonly located on the trunk, either in the interscapular region, dorsal lumbar, or flank region, with location changing as recommendations are made regarding the best sites to vaccinate cats (see ch. 208).

Factors in Diagnosis and Management

STSs are usually painless SC masses similar to other benign or malignant nodules. Therefore, accurate diagnosis is critical for appropriate treatment planning. An incisional biopsy is recommended for all but the smallest of nodules to prevent disruption of the surrounding normal tissue prior to definitive surgical planning. Excisional biopsies should be avoided unless the mass is small (<1 to 2 cm proportional to the size of the dog or cat) and surrounded by abundant normal tissue. In addition, all biopsy procedures should be carefully planned for SC nodules to avoid inadvertent contamination of surrounding tissues. Definitive surgery requires excision of the biopsy tract and although local control is expected with complete surgical removal, local recurrence is often observed following suboptimal surgical procedures. Aggressive treatment at the first opportunity is required for successful management of STSs. The challenge of surgical planning, the improved prognosis with multimodal therapy in many instances, and the potential for metastases despite local control in high-grade sarcomas (44% rate of metastases in one report[3]) add complexity to the decision-making process. It is particularly important to meet these challenges for successful management of IAS in cats.

Etiology

Genetic, Biochemical, Radiation Exposure

The genetic or specific biochemical mechanisms responsible for development of STSs in dogs and cats remain

largely unknown.[4,5] Most STSs in dogs occur sporadically, although there is evidence that Golden Retrievers have an increased risk of tumors in general, including STSs.[6] Germline mutations or familial forms of sarcomas have been confirmed in people. Provocative anecdotal epidemiologic evidence suggests similar processes may be present in dogs. However, detailed genetic or pedigree characterization of dogs that develop STSs at a young age (<2 years), or where a breed prevalence seems likely, have not been conducted.

It is well established that exposure to radiation, viral infection (feline sarcoma virus), trauma, or chronic inflammatory conditions can be associated with development of sarcomas in dogs and cats. Conventional irradiation schedules for management of a primary cancer carries risk of a second cancer developing in <5% of cases. Radiation-induced tumors occur 3 years or more after radiation therapy (RT).[7] The benefits of primary tumor control outweigh the risk of radiation-induced second tumors. High intraoperative doses of RT given once are more likely to produce sarcomas (20% to 25%) in dogs after a median latency of 4 years.[8]

Injection-Associated Sarcomas (IAS)

Risk Factors

In a large study of risk factors associated with development of IAS in cats, no specific brand, no type of vaccine within antigen class, and no vaccine practice altered risk of developing IAS.[9] Furthermore, some long-acting injectable medications (penicillin, methylprednisolone acetate) may also be associated with sarcoma formation, thus the term injection-associated sarcoma (IAS).[9,10] There are also case reports of STSs in cats at sites of cisplatin injection, a deep nonabsorbable suture, retained surgical sponge, microchip, or SC fluid port.[11-15] Likely, a combination of local inflammatory reactions and genetic factors is involved.[16] Similarly, the development of ocular sarcomas in cats is often associated with a history of ocular trauma.[17]

Molecular and Cellular Abnormalities

The molecular development of IASs in cats is not yet fully defined. There have been several reports eliminating the most common feline viral infections (oncorna, papilloma, polyoma viruses) as causative etiologies.[18-20] Unique molecular features of IASs have been identified. Epidermal growth factor/receptor (EGFR), platelet-derived growth factor/receptor (PDGF), and transforming growth factor-beta–expressions are abundant on tumor cells and infiltrating lymphocytes in IASs. Such changes are not expressed in cells from non–injection-site feline sarcomas.[21] An overexpression of C-Jun, a protooncogene, has also been identified in feline IASs and may be the result of persistent growth-factor stimulation.[21] Fibrosarcomas at presumed sites of injection have been reported in dogs, as well as at the site of microchip implant in two dogs, but are not well documented as a distinct entity.[22-24]

P53 abnormalities have been reported in feline IASs. In one report, approximately 43% of samples from sarcomas strongly overexpressed the p53 protein and, in another, 5 of 8 tumor samples with overexpressed p53 protein contained mutated genes.[25,26] No cats from a control group of 13 IASs, without p53 protein overexpression, had gene mutations.[26] In this latter study, no surrounding tissue had p53 mutations, suggesting that abnormalities in p53 function did not exist prior to tumor development. One study demonstrated an association of germ-line polymorphisms in the p53 gene with genetic predisposition to feline IAS.[27] These data indicate that molecular and cellular abnormalities exist and suggest several hypotheses, but no specific cause has been associated with the development of feline IAS.

Abnormalities in p53 and MDM2, a gene whose product suppresses p53 expression, have been reported in canine STS.[28] Twenty percent of sarcomas had base substitutions resulting in single amino acid misreads in the p53 gene. Three of 6 tumors with mutations were malignant nerve-sheath tumors. Canine MDM2 gene amplification (threefold or greater) was identified in 5 of the 30 sarcomas. In all but one of these combined samples, there was coordination of these abnormalities, resulting in p53 disruption (mutations) or secondary p53 suppression due to MDM2 overexpression. Thus, directly or indirectly, almost one third of canine sarcomas appear to have altered p53 function and 5 of 7 malignant peripheral nerve-sheath tumors had p53 functional abnormalities.

Initial Clinical Evaluation

History, Physical Examination and Initial Assessments

Evaluation of dogs and cats should begin with a thorough history (see ch. 1) and physical examination (see

ch. 2). Tumor staging includes assessing the extent of local disease and detecting any evidence of regional and/or distant metastasis. Further, comorbidities and concurrent primary tumors should be identified via laboratory testing, thoracic radiography and abdominal ultrasound (US).[29] Thorough description and measurement of masses in three dimensions can be valuable for documenting subsequent growth if there is a delay in initiating therapy and/or documenting response to therapy. STSs, in general, have a relatively low metastatic rate, but rates increase with increasing tumor grade. The greatest concern of metastasis is with high-grade sarcomas via hematogenous routes. The most common sites for spread are lung and liver. Regional lymph nodes should be evaluated by aspiration and/or biopsy, particularly if enlarged or if the STS is a high-grade tumor, even though this is not the most likely site of spread. The incidence of metastasis for sarcomas at initial diagnosis is considered to be low, but without specific examination of regional lymph nodes or careful follow-up, the actual incidence is unknown. In cats with vaccine-associated fibrosarcomas, sites of metastasis include lung, skin, SC, regional lymph nodes, mediastinum, liver, and pelvis.

Imaging

Appropriate imaging for evaluation of the primary tumor, as well as thoracic radiographs and abdominal US (see ch. 88 and 89), should be conducted during the staging process if malignancy is confirmed. Imaging techniques may also aid in planning biopsy and treatment options. US evaluation of the primary tumor may aid in determining the best site for biopsy. US-guidance may be necessary for accurate sampling of deep-seated tumors. Imaging of STSs increasingly involves cross-sectional studies, such as computed tomography (CT) or magnetic resonance imaging (MRI).[30] CT scans, with IV contrast, can assist in delineating the extent of local disease as well as invasion into the surrounding tissues. It is highly recommended that imaging precede therapeutic intervention. Particularly for IASs in cats, the extent of invasion into surrounding tissues can be substantial and an initial excisional biopsy can impair the ability to achieve local tumor control. Tumor volume, measured from contrast-enhanced CT studies of feline sarcomas, can exceed physical measurements by 2 to 5 times. Also, attachment of the tumor to surrounding muscle and tissue can be more extensive than expected (Figure 346-1).[31]

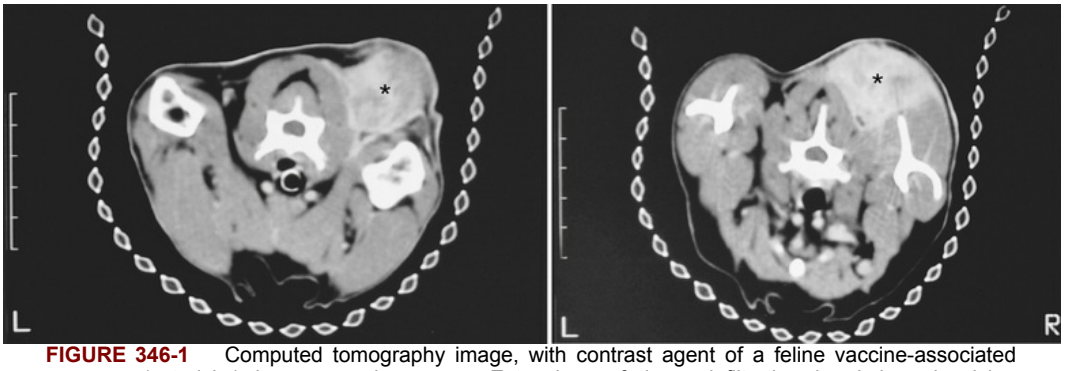

FIGURE 346-1 Computed tomography image, with contrast agent of a feline vaccine-associated sarcoma (asterisks) in prescapular space. Extensive soft-tissue infiltration is obvious involving numerous muscles adjacent to tumor tissue.

Surgery without accurate prior knowledge of tumor extent for feline injection-site sarcomas is not recommended. Furthermore, in dogs, STSs frequently occur on the extremities, where they are difficult to resect with adequate margins. An initial biopsy and imaging can provide both a diagnosis and an understanding of disease extent, with preplanning possible such that an owner can be apprised of whether combination therapy is indicated, considering its potential for increased duration of medical management and cost. Of interest is a report on surgical outcomes in 350 dogs with STSs managed in first-opinion practices. This study revealed differences in extent of staging prior to surgery and the apparent tendency for lower grade tumors to be managed at primary care, rather than at referral, practices.[32]

Diagnosis

Fine Needle Aspiration and Cytology

A definitive diagnosis is needed to determine the best treatment strategy. Aspiration cytology can provide

initial information on a dermal or SC lump that may support the diagnosis of a nonneoplastic process (see ch. 87, 89, 93, and 95). Aspiration cytology can be diagnostic for neoplasia and may suggest that a mass is most likely of round cell, epithelial, or mesenchymal origin. Cytology is not usually definitive regarding specific histologic classification. Mesenchymal tumors are less likely to exfoliate during aspiration. For STSs, aspiration cytology is performed primarily to rule out other disease processes, although some may be diagnostic for sarcoma.

Biopsy

An incisional biopsy is recommended to obtain a definitive diagnosis and to determine the specific histopathologic type and tumor grade (see ch. 86). The biopsy procedure for sarcomas should be carefully planned to obtain a representative sample of the tumor and prevent any unnecessary complications or contamination of surrounding tissue with tumor. If a cutting needle is to be used, care should be taken not to penetrate beyond the known tumor perimeter to avoid tumor seeding. Sarcomas often adhere to adjacent tissues, and extension along fascial planes can be difficult to appreciate on physical examination. Therefore, biopsy samples such as those obtained from limited incisions, punch biopsy tools, or cutting needles are preferred to excisional biopsy to minimize tissue disruption. The acquisition of a biopsy sample allows grading of the tumor based on assessment of a number of histopathologic features, although there can be discordance between the pre-treatment biopsy and the excisional biopsy results with either under- or overestimation of the tumor grade.[33]

Histology

Histologic features assessed in STSs to assign a tumor grade include degree of differentiation, percentage of necrosis, and mitotic rate (see Table 346-1, see ch. 87 and 93). Tumor grade for STSs in dogs can have prognostic significance, with a more progressive course and higher likelihood of metastasis with a high-grade tumor. Obtaining complete margins on histopathology is predictive for non-recurrence. Histologic grade has been shown to be a strong predictor for recurrence of marginally excised SC STSs in dogs, with increased likelihood of local recurrence with increasing grade.[34,35] One report on prognosis in cats after surgical excision of fibrosarcomas showed a correlation between mitotic index (sum of mitotic figures in 10 high-power fields [400× magnification]) and median survival.[36] For cats with a mitotic index <6, the median survival was 32 months, as compared to 4 months if the mitotic index was ≥6. Most studies have not shown a correlation between tumor grade and survival in cats with injection-site sarcomas, which may represent a more aggressive tumor overall.

General Treatment Considerations

Surgery versus Multi-modal Therapy

Surgical excision of any tumor without preplanning can result in incomplete removal and need for a second, more extensive surgical procedure, radiation therapy (RT), and potentially a higher complication and/or failure rate. STSs in particular are likely to be incompletely removed with close marginal excision due to tumor extension beyond visible tumor tissue or because they can appear well encapsulated. However, these are usually pseudo-capsules: compressed tumor tissue and reactive fibrovascular tissue. Higher morbidity and higher cost associated with incomplete resection justify the referral of STS pets with large or high-grade tumors for consideration of multidisciplinary evaluation and possibly multimodal therapy. Figure 346-2 represents a decision-making algorithm for soft-tissue sarcomas, or any superficial nodule, based on the initial estimation of surgical success. Pivotal decision points in this algorithm include the determination of whether curative surgery is possible; the success of surgery based on thorough evaluation of the margins; and the need for any adjuvant chemotherapy based on grade and stage.

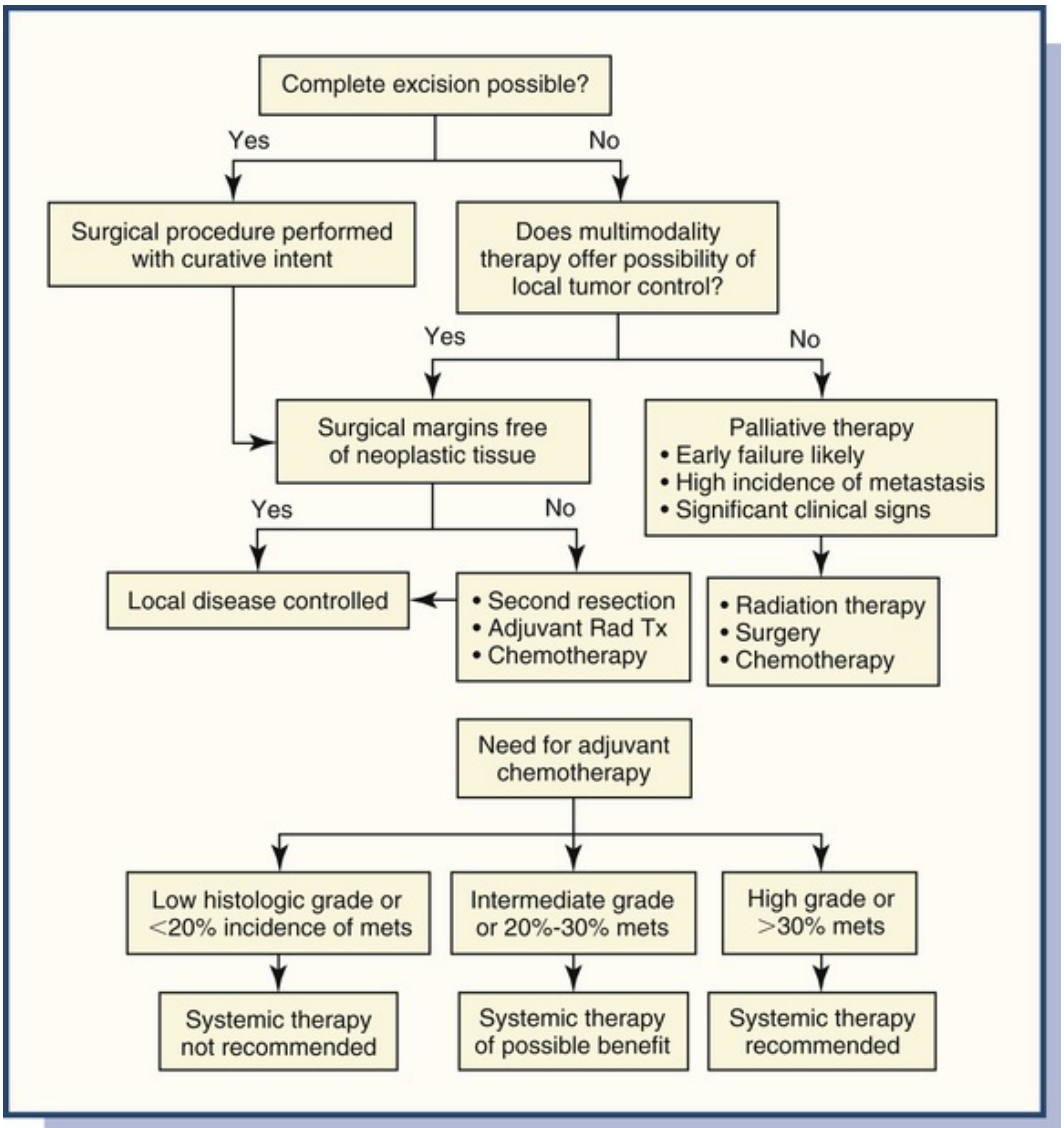

FIGURE 346-2 Treatment algorithm for peripheral solid tumor (clinical and histologic staging completed). *Mets*, Metastases; *Rad Tx*, radiation therapy.

The decision regarding surgical resection of a STS is perhaps the most critical point in the algorithm. The decision to attempt resection should be made from accurate measurement of the mass, assessment of deep tissue attachments, location, surrounding normal tissue limitations for deep resection, and the surgeon's skill. A retrospective study of 100 dogs with mast cell tumors or STS demonstrated that level of surgical training impacted success of complete excision.[37] The surgical procedure should be well planned to accomplish complete resection and reduce or prevent likelihood of inadvertent tumor seeding of the site or surrounding tissues. New and aggressive oncologic surgical techniques are being evaluated and implemented.[38-41] In a pilot study of a novel imaging system, dogs with sarcomas received an IV fluorescent probe to aid detection of residual tumor after wide surgical resection; in 9 of 10 cases histopathologic assessment of surgical margins correlated with intraoperative imaging.[42] Planned resection with a vascularized flap to close the defect facilitates timely initiation of postoperative RT, with a high success rate associated with flaps that are irradiated.[43]

Assuming the Surgical Field Is Contaminated with Tumor Cells

Following a surgical procedure, it must be assumed that the entire operating field, including the scar, is potentially contaminated. The use of appropriate technique is essential, including incision planning, avoidance of unnecessary manipulation of the tumor itself, or placement of drains with distant tissue

dissection. During the procedure, hemoclips may be used to define the deep and lateral extent of the tumor and surgical plane. This will be of benefit to determine the area of re-resection or RT, if needed.[44,45]

Examination of the lateral and deep margins for completeness of resection is of critical importance for determining local tumor control. This explains the paramount importance of submitting the entire resected specimen rather than only a portion. The histopathologic analysis of tumor margins is aided by marking the surgical margins with permanent dye and thoroughly describing the specimen orientation.[46-48] In one study, the investigators used a three-dimensional histological technique for evaluating lateral and deep surgical margins in 48 excised feline IASs; this approach has the potential to increase the accuracy of margin assessment.[49] Adequate margins around the tumor tissue can be difficult to estimate once the tissue has been processed for fixation and microscopic evaluation. Surgical margin definitions vary in the literature and include but are not limited to: incomplete (excision with tumor cells at or within 1 mm of surgical margins), narrow or close (excision with no tumor cells at surgical margin but histologically normal tissue extending <1 cm beyond histologic margins, or less than 3 mm), and wide or complete (excision with histologically normal tissue >1 cm at the surgical margin, or a minimum of 3-5 mm).[35] A minimum of 10 cell diameters between tumor and deep surface is recommended for classifying a mass as completely resected. This arbitrary designation should be carefully examined with more defined measurements of distance that could be correlated to the required margin necessary to prevent recurrence for different grades of sarcoma.

Palliative Therapy

Palliative therapy may be necessary for tumors that are not amenable to definitive approaches, such as aggressive surgery or multimodal therapy. Palliative therapy should be actively pursued, and numerous treatment options have been devised specifically for management of patients with incurable tumors or patients with significant morbidity associated with the presence of the tumor.

Management of Canine Soft-Tissue Sarcomas

Detection

There are no known risk factors that allow early detection or prediction of canine STS of clinical use. Therefore, general recommendations for cancer screening and detection (frequent physical examination, radiographs, other imaging studies) represent the only means of early STS recognition. Any mass should be characterized with measurements, appropriate imaging, and biopsy as soon as is possible. If a STS is identified, the procedures outlined above for treatment planning should be implemented.

Treatment Planning and Surgical Aggressiveness (see Figure 346-2)

Decisions regarding primary tumor management and whether chemotherapy for adjuvant treatment should be instituted following local control must be made, ideally decided by the entire veterinary and owner team. Surgical resection should be the first consideration for any STS. Concluding a mass is potentially curable with surgery should be closely scrutinized, because local recurrence represents a serious complication of inadequate surgery and will impact future treatment options.[50] The importance of the type of surgery performed is demonstrated in a report of 56 dogs with liposarcoma in which the median survival was 1188, 649, and 183 days, respectively, if they had a wide excision, marginal excision, or incisional biopsy.[51]

A report on the results of marginal excision of low-grade spindle cell sarcomas of the canine extremities documented a low local recurrence rate (10.8%) with a mean survival time of 703.5 days (median was not reached yet).[52] Wide local excision (2 cm lateral margin, and 1 fascial plane deep) of STSs in 31 dogs (primary excision in 21; scar revision after incomplete resection in 10) with tumors involving the distal limb demonstrated excellent long-term local control; the majority of wounds healed completely by second intention (median time of 53 days, range 25-179 days).[53] The majority of STSs of the digit, the third most common digital tumor, are controlled by amputation of the digit.[54] Referral for more extensive tumor evaluation and aggressive management is warranted for STS in areas of complex musculofascial anatomy, because adequate normal tissue removal around the sarcoma improves local control.[55] Multimodal therapy is an appropriate consideration for tumors not easily resectable, with preplanning of paramount importance.

Radiation Therapy (RT)

RT has been shown to be of significant benefit for local control of STS not completely resectable (see ch. 340). The use of preoperative or postoperative definitive RT can be considered, although ideally the schedule for application of RT should be made before initiating treatment.[56] Furthermore, there are specific considerations to bear in mind when combining surgery and RT, such as the impact of preoperative irradiation on wound healing.[57] Several studies have demonstrated that RT results in long-term control of STSs in dogs.[58,59] Local relapse-free survival has been estimated at 75% to 85% for 3 or more years, and this combination should be recommended for all incompletely excised canine STS. Hypofractionated radiation protocols have been applied in the microscopic disease setting and are associated with long-term control in the majority of dogs.[60,61] Intentional marginal excision of canine STS on an extremity followed by hypofractionated RT (8-9 Gy/fraction, weekly, 32-36 Gy total dose) potentially reduces surgical complications but may be associated with increased late radiation side effects when using a large dose per fraction.[60] Current treatment schedules and technology make RT of tumor sites less likely to result in limiting side effects.[62] However, STSs can arise in any tissue, and adjacent normal structures can be difficult to avoid without compromising tumor control.

Chemotherapy

There are several indications for chemotherapy in STS (see ch. 339): when patients have an inoperable STS but a measurable reduction might allow function-preserving resection; for patients with recurrent STS not amenable to second surgical procedures; in dogs with high-grade STS, to reduce or delay metastatic nodules; and in dogs with STS that have an inherently greater likelihood of metastasis.[63,64] Doxorubicin has been considered the most active single agent for canine STS, but based on one study, it has not been shown to improve outcome in dogs with high-grade sarcomas.[3] Other options include platinum-containing agents and ifosfamide. Intraoperative cisplatin has been used in the treatment of canine STS to increase local drug concentrations while reducing systemic toxicosis, but an unacceptable 16 of 19 dogs had local complications.[65] There may be a role for the use of metronomic chemotherapy for high-grade STS or incompletely excised STS with the goal of inhibiting angiogenesis as opposed to direct cytotoxicity associated with full dose chemotherapy, as well as modulation of the immune system.[64,66-68] Metronomic chemotherapy with cyclophosphamide and piroxicam significantly delayed tumor recurrence in 30 dogs with incompletely excised STSs as compared to 55 control dogs; but 40% developed usually mild treatment-related adverse effects.[67] Although no definitive evidence exists to make adjuvant chemotherapy a general recommendation for dogs with high-grade STS, many specialists feel that the chance (≈40%) for distant metastasis, even with local control, warrants a recommendation of treatment with chemotherapy.[3,55]

Palliative Therapy

Palliative therapy is available for dogs with significant functional abnormalities directly related to the tumor mass. Irradiation schedules for palliative management are designed to deliver a significant dose to the tumor without debilitating side-effects and with minimal hospitalization; these can be effective in the short term.[69] Tumors causing pain, dysphagia, dyspnea, dyschezia, or dysuria, and those that are assumed to be incurable with surgery, should be considered for palliative RT. Palliative chemotherapy may also be offered in hopes of reducing the mass causing debilitating clinical signs. Palliative surgical procedures designed specifically for improved quality of life in patients with extensive disease include resolution of ulceration and management of secondary infection.

Canine Soft-Tissue Sarcomas With Unique Clinical Features

Overview

Most STSs (see Box 346-1) can be managed with the principles described above after considering the histologic grade and the likelihood of local control. Special consideration should be given to select sarcomas due to unique presentations or tumor biology, e.g., the retroperitoneal location for soft-tissue sarcomas, although rare, is associated with a high rate of local recurrence and metastasis with a short survival time (median 37.5 days).[70] Synovial cell sarcoma (see ch. 348), and hemangiosarcoma (see ch. 347) are discussed in their respective chapters.

Leiomyosarcoma/Gastrointestinal (GI) Stromal Tumors

Sarcomas of smooth muscle occur most often in the GI tract and require special management considerations related to their site of origin. After reclassifying canine GI smooth-muscle tumors, gastrointestinal stromal tumors (GISTs) are considered distinct from leiomyomas and leiomyosarcomas.[71-74] GISTs express c-kit as detected by immunohistochemistry (IHC), and many have activating mutations that are thought to drive oncogenesis.[75] GISTs may be responsive to receptor tyrosine kinase inhibitors that target KIT.[76-78] More recently, DOG1 (discovered on GI stromal tumors protein 1) has been shown to be a sensitive and specific marker for the diagnosis of canine gastrointestinal stromal tumors.[79] It has been recommended that both DOG1 and KIT IHC be included in diagnostic panels to improve the diagnostic accuracy of canine GISTs.

Since second surgeries are unlikely, it is recommended that GI tumors be resected widely, and any lymph nodes or other sites of concern in the abdomen also be resected to aid in staging. Several reviews reported clinical outcomes of approximately 100 dogs with intestinal leiomyosarcoma.[80-82] In addition, data describing the site or origin and metastases of 158 dogs and 22 cats with leiomyosarcomas have been summarized.[83] Leiomyosarcomas are most often located in the stomach, small intestine, spleen, or urogenital tract. GISTs appeared to develop more frequently in the cecum and large intestine, although in one study they occurred mainly in the small intestine.[71,84] Feline leiomyosarcomas are uncommon but occur in the GI tract more often than other sites. If complete surgical resection can be accomplished, median survival times are about 18 to 37 months. Many dogs die from causes other than recurrence or metastasis. Reports vary on whether there is a difference in survival depending on whether it is a GIST or a leiomyosarcoma, with one report indicating a shorter median survival for leiomyosarcomas.[71] Metastatic lesions are reported in 15-30% of dogs with leiomyosarcomas and are most likely to be found in the mesentery, spleen, or liver. Metastases may be slow to develop (1 to 2 years) and relatively slow to progress. Information on response to chemotherapy is limited.[71]

Management of Feline Sarcomas

Investigations are being carried out to determine the optimal treatment approach for IAS. Best success lies in early detection and aggressive management. Ideally, development of IAS can be prevented.[110] Analysis of alterations in p53 may be of utility in both directing therapy for individual cats that are at increased risk of recurrence, and in the future, for use in molecular targeting of mutant p53.[96,111]

Surgery

Need for Wide Margins

Surgical excision of soft-tissue sarcomas in cats represents the best chance of effecting local tumor control.[31,85-88] An initial biopsy of a suspected STS in a cat together with cross-sectional imaging (CT or MRI) will provide the most accurate assessment of tumor extent and assists in treatment planning.[89,90] An excisional biopsy of an IAS is rarely complete, is likely to result in local recurrence, and a second, more difficult surgery will be necessary. Tumor recurrence has been documented to occur as early as 2 weeks after surgery, but will typically occur within 6 months of incomplete resection.[91] An aggressive surgical resection is necessary to effect local control, and this can entail resection of the tumor with 3- to 5-cm margins, removal of associated bone (e.g., dorsal spinous processes, partial scapulectomy), and at least one fascial plane deep to involved tissues.

There has not been consistency between studies in terms of prognostic factors identified for cats with soft-tissue sarcomas. In a group of 42 cats with a variety of different STSs treated with surgery alone, median survival time was longer in cats with tumors <2 cm in diameter and in cats with fibrosarcomas or nerve-sheath tumors, compared to cats with a malignant fibrous histiocytoma; median survival time for all cats was 608 days.[92] In a report of 91 cats treated by radical excision with 5-cm margins around the palpable tumor and deep margins, including 2 muscle planes or bone deep to the tumor without adjunctive treatment, the overall median survival time was 901 days despite not performing preoperative cross-sectional imaging.[93] Radical surgery was complete in 88 of 91 cats and the local recurrence rate of 14% is lower than previously reported with surgery alone or in combination with adjuvant therapy. Major complications occurred in 10 cats (7 with incisional dehiscence).[93]

Recurrence and Metastasis

Tumor recurrence and metastasis were significantly associated with survival time. Median survival of cats with (n = 13; 14%) and without recurrence was 499 and 1461 days, respectively. Median survival of cats with (n = 18; 20%) and without metastasis was 388 and 1528 days, respectively. In a retrospective study of 49 cats that underwent wide excision (3 cm margin based on contrast-enhanced CT imaging) of IAS on the trunk, duration of surgery was related to the complexity of the procedure. Length of surgery was identified as the best predictor of wound healing complications; 19 cats (major in 8 cats; minor in 11 cats).[94] Although some pathologists consider all IAS to be high-grade based on their biologic behavior, in one study cats with high-grade IAS were more likely to develop metastasis (IASs were graded low, medium and high), which was associated with significantly shorter (165 versus 929 days) median survival times.[95] There appears to be a strong association of somatic deletion in the conserved region of the p53 gene with postsurgical recurrence and decreased survival.[96]

Tumor Location and Use of Multimodal Therapies

IASs have commonly occurred in the interscapular space, a difficult location for surgery that requires removal of dorsal spinous processes and the surrounding musculature. For this reason, the Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) recommends vaccinating with rabies and feline leukemia virus (FeLV) in the distal hindlimb (right and left hindlimb, respectively), such that amputation is possible, should IAS develop (see ch. 208). Even with amputation or hemipelvectomy, it may not be possible to completely excise an IAS.

It is often necessary to use a multimodal approach, combining radiation therapy (RT) and surgery. For instance, preoperative irradiation of a proximal limb sarcoma may be necessary prior to amputation. The use of RT preoperatively often reduces tumor size and, theoretically, sterilizes peripheral tumor components that could otherwise result in incomplete resection and the potential for rapid tumor regrowth (see ch. 240).[56,97] RT with stereotactic body radiation therapy (24-32.5 Gy delivered in 3-5 fractions) employed to treat 11 cats with IAS documented a partial response in 5 and complete response in 3 cats. The median progression-free interval was 242 days and overall survival was 301 days.[98] This approach is an option for palliation of tumors, but requires additional study to determine its role in combination therapy. In a retrospective study of 79 cats with STSs treated with preoperative (n = 24) or postoperative (n = 55) RT, the overall median survival was 520 days.[99] The median survival of cats treated with preoperative RT (310 days) was significantly shorter than cats irradiated postoperatively (705 days), but this may have been due to selection bias because the cats with larger tumors were irradiated preoperatively. Of note, anemia was determined to be a negative prognostic factor with a median survival of 308 days for cats with a PCV <25%, and 760 days for cats with a PCV ≥25%.[99]

Chemotherapy

Chemotherapy may be used in the management of IAS as adjuvant therapy to address potential metastatic disease, as neoadjuvant therapy to reduce the tumor in size prior to surgical resection, or as palliative therapy for nonresectable tumors. Combining doxorubicin and cyclophosphamide for 12 cats with nonresectable tumors had a 50% overall response rate.[100] The median survival time was significantly longer in those cats that responded (242 days) than in those that did not respond (83 days). In a study of 69 cats, no significant difference in survival or disease-free interval was reported among cats that had surgery alone versus those who had surgery and received doxorubicin.[101] Twenty-one cats with IAS received 3 cycles of neoadjuvant chemotherapy with epirubicin prior to surgical resection, followed by 3 additional cycles in the adjuvant setting.[102] Chemotherapy was well tolerated, and their mean survival time was 2014 days. Cats treated for gross disease with ifosfamide had a 70 day median duration of response.[103] Cats with IAS dosed with carboplatin based on glomerular filtration rate may improve responses.[104,105] In a Phase I/II prospective trial of 28 cats with IAS treated with lomustine, their overall response rate was 25% with a median response duration of 82.5 days.[106]

Combining Surgery, Radiation Therapy, and Chemotherapy

A combination of surgery, radiation therapy, and chemotherapy may result in the greatest potential for long-term tumor control. In 92 cats given preoperative RT for IAS, their median time from the start of treatment to local recurrence, metastasis, or date of death or euthanasia was significantly longer (986 days, n = 59 cats) if complete resection was accomplished when compared with those who had incomplete resection (292 days, n

= 28 cats).[97] There was a trend toward improved survival with the addition of chemotherapy (carboplatin, other) with a median time to first event of 1059 days (n = 33 cats) in cats that received chemotherapy, versus 584 days (n = 59 cats) in cats treated only with RT and surgery. The overall rate of metastasis was about 20%, although complete follow-up was not available for all cats. In 71 cats, concurrent doxorubicin extended the disease-free interval in cats undergoing postoperative RT (median disease-free interval of 15.4 versus 5.7 months) but did not significantly impact survival.[107] Ten cats with advanced STSs were treated with concomitant liposomal doxorubicin and palliative 5-7 daily fractions of RT with a median total dose of 20 Gy (range 20-31.5 Gy).[108] One dose of liposomal doxorubicin was administered at the beginning of RT and 7 cats received further free or liposomal doxorubicin after completion of the liposomal doxorubicin/RT protocol. Five of the 10 cats achieved a partial response and 2 had a complete response; median response duration was 237 days. The median progression-free interval (PFI) was 117 days and median overall survival time was 324 days. Concomitant liposomal radiochemotherapy was overall well tolerated.

A retrospective study of 73 cats treated with definitive RT (n = 46, majority with clean margins; 1 cat also received chemotherapy), or coarse fractionated RT (n = 27, majority with macroscopic disease or incomplete margins) showed that both approaches are options for the treatment of IAS.[109] Cats treated with postoperative definitive RT had a median survival of 43 months and a median PFI of 37 months. In the group treated with coarsely fractionated RT, median survival was 24 months and median PFI 10 months. In this latter group predictors of a better outcome included lack of a visible mass (n = 10) as opposed to macroscopic disease (n = 17, survival 30 versus 7 months); adjuvant chemotherapy for gross disease (n = 5/17, survival 29 versus 5 months), and a small number of surgeries prior to RT.

Prevention

The etiology of most canine STS is unknown; therefore, it is not feasible to develop strategies for prevention. However, for cats it may be possible to decrease risk of developing STS. Considerations include limiting the number of vaccinations administered to cats to only those necessary to maintain health (see ch. 208). Also, one should follow recommendations provided by the VAFSTF: limit to one vaccine per site and document the location of each vaccine (right hindlimb for rabies, left hindlimb for FeLV, and right-lateral scapular region for feline viral rhinotracheitis, calicivirus, panleukopenia vaccine). These recommendations have been further refined by the American Association of Feline Practitioners to vaccinate cats distal to the elbow joint or below the stifle joint specifying each vaccine and its appropriate location.[112] In this way, even if a tumor is to develop, owners can be informed where and what to look at when checking for a possible tumor.

A pilot study has shown that tail vaccination is well tolerated, with similar serological responses when compared to vaccination in the distal limbs.[113] Vaccines have been developed that do not appear to result in a local inflammatory response and may therefore translate into a decreased risk of tumor development at that site. However, a study of the prevalence of feline IASs submissions from 1992 to 2010 showed no decrease in prevalence or increase in age of affected cats despite changes instituted in vaccine formulation or recommended changes in vaccination protocols.[114] Furthermore, although a study of 392 cats with IAS demonstrated that veterinarians are partially complying with recommendations, more attention needs to be paid to vaccinating as distally as possible on a limb.[115] There have been isolated reports of tumors developing in cats at sites not associated with vaccination, but rather due to some other inciting event that has resulted in a local inflammatory response. Increased awareness of the variable inciting causes of feline sarcomas will likely aid early detection as well as potential avoidance of these products when feasible.

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CHAPTER 347

Hemangiosarcoma

Craig A. Clifford, Louis-Philippe de Lorimier

Client Information Sheet: Canine Hemangiosarcoma

General Features, Pathology, and Biologic Behavior

Hemangiosarcoma (HSA; angiosarcoma, malignant hemangioendothelioma) is a highly malignant tumor with an aggressive biologic behavior.[1-5] It was long thought this disease had an endothelial ontogeny; however, recent data suggest that these tumors arise from bone marrow progenitor cells with differentiation arrest at the angioblast or hemangioblast stage and subsequent transit to peripheral vascular sites.[6,7] HSA is diagnosed more frequently in dogs than in any other domestic species and it accounts for ≈2 % of all canine tumors.[1-5,8,9] HSA tends to affect older dogs of either sex (although several reports have suggested a male predominance) with a median age of 10 years at diagnosis.[1-5,9,10] While dogs of any breed can develop HSA, German Shepherds, Golden Retrievers, and other large or giant breeds appear to be predisposed.[1-5,9,10]

Primary HSA has been reported in many sites in dogs. However, the spleen, heart (right atrium or auricle), skin or subcutaneous tissues, and liver are the four most common primary sites (Figure 347-1). Other reported primary sites include kidney, retroperitoneal space, muscle, bone, oral/nasal cavity, urinary bladder, and lungs.[2-5,9,11-15] The biologic behavior varies depending on primary tumor location, with certain sites, such as the skin, being associated with a more favorable prognosis in comparison to others. Generally, local infiltration and metastatic dissemination occur early in the course of disease, either hematogenously or via local seeding following tumor rupture and subsequent intra-abdominal implantation (Figure 347-2). Metastasis can occur at any site; the liver, omentum, and lungs are the most frequent sites of dissemination.[1-5] Sometimes, it is difficult to discern the true site of origin because of the multifocal nature of the disease. Interestingly, HSA is the most common sarcoma to metastasize to the central nervous system (CNS).[16,17]

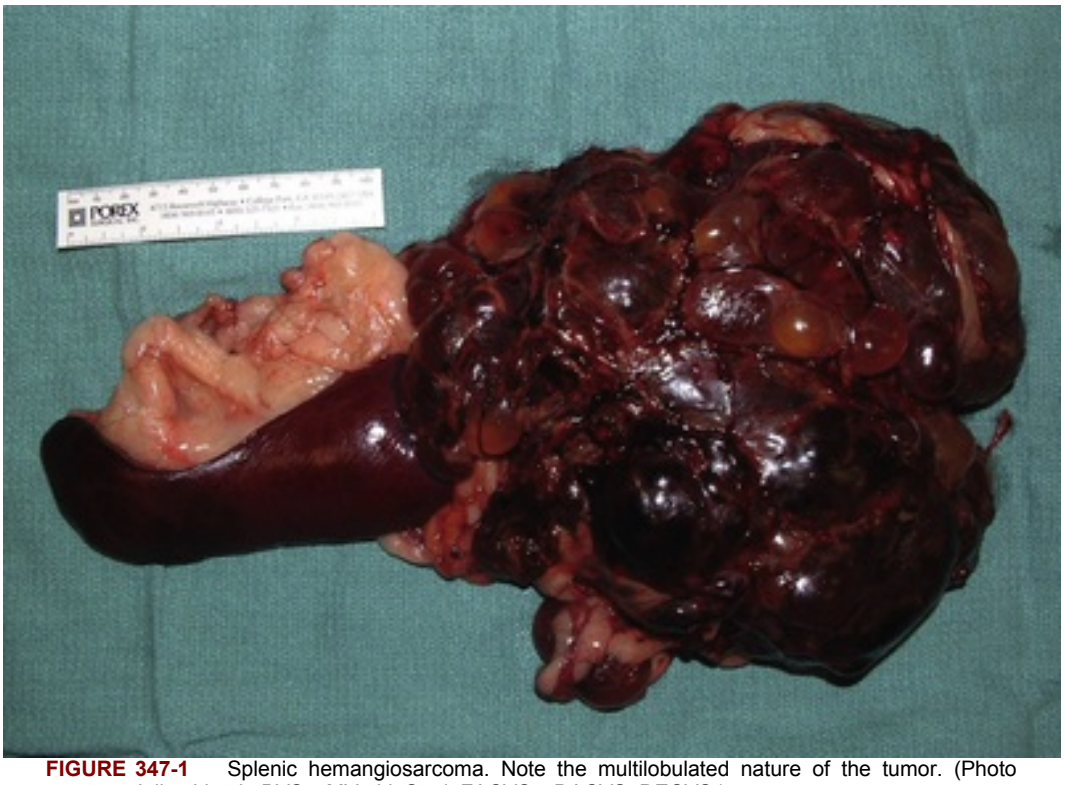

FIGURE 347-1 Splenic hemangiosarcoma. Note the multilobulated nature of the tumor. (Photo courtesy Julius Liptak, BVSc, MVetLinStud, FACVSc, DACVS, DECVS.)

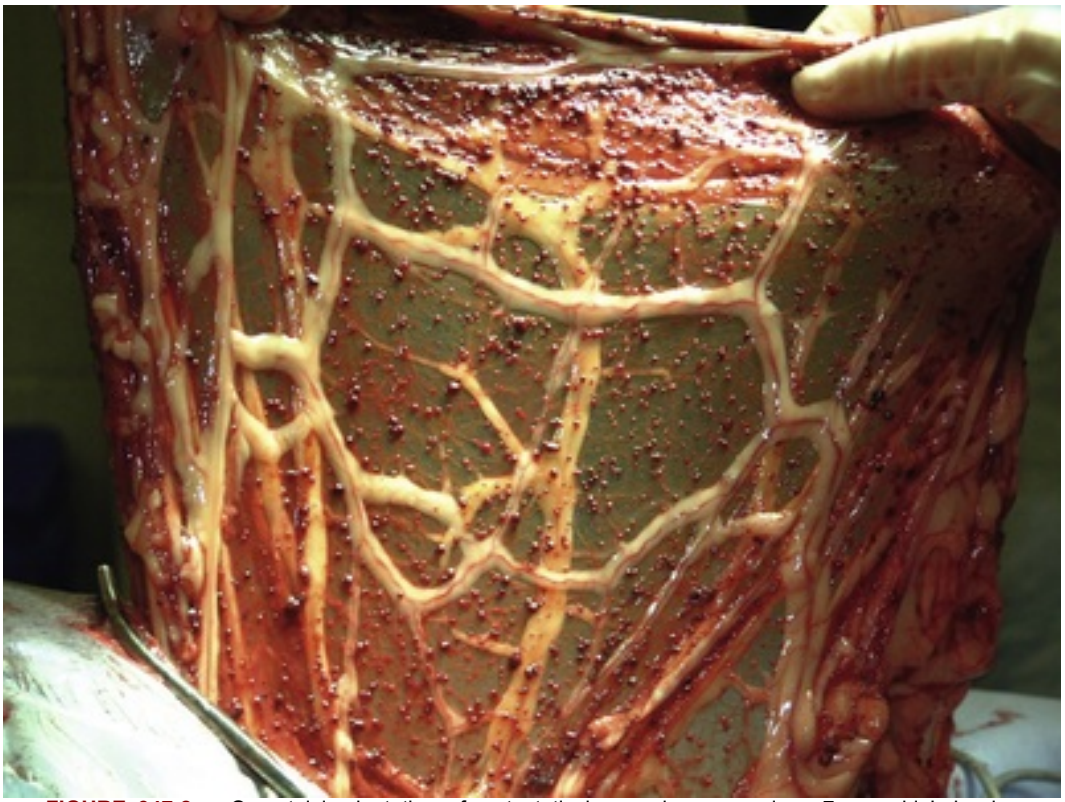

FIGURE 347-2 Omental implantation of metastatic hemangiosarcoma in a 7-year-old Labrador Retriever. (Photo courtesy Julius Liptak, BVSc, MVetLinStud, FACVSc, DACVS, DECVS.)

The spleen is the most commonly affected primary organ in dogs, and based on a number of pathology

studies, the "rule of two thirds" was informally established. The summary of these findings suggested that approximately two thirds of dogs with a splenic mass have a malignancy, and, as such, one third are not malignant. Of the two thirds with malignant splenic tumors, approximately two thirds are HSA.[8,10] Two other large pathology studies evaluating canine spleens noted that closer to 50% had malignant disease, with 50-74% of those malignancies being HSA.[18,19] More recent retrospective studies evaluating patients presenting with a non-traumatic hemoabdomen noted that 68-80% were secondary to visceral neoplasia, with 63-70% of all dogs confirmed to have HSA.[20-22] Although there is some discrepancy in the exact prevalence of splenic HSA, it is undoubtedly the most common primary splenic neoplasm in dogs. However, the differential diagnosis for a splenic mass also should include other neoplasms, such as malignant fibrous histiocytoma, leiomyosarcoma, fibrosarcoma, anaplastic/undifferentiated sarcomas, and lymphoma. Common non-neoplastic diagnoses include nodular hyperplasia, extramedullary hematopoiesis, and splenic hematoma.[8,18,19] Grossly, intra-abdominal HSA can present as a solitary mass or it can be characterized by multifocal lesions that appear soft with a dark red appearance and could be oozing blood constituents.

The heart is another common primary site for HSA in dogs, and HSA represents the most common primary tumor of the canine heart. Specifically, the tumor most commonly originates on the right atrium/auricle; however, other cardiac sites have been reported (see ch. 254).[5,23-27] It was previously reported that ≈25% of dogs with splenic HSA also have a second primary HSA in the heart, consistent with synchronous or metachronous disease.[28] More recent data suggest this phenomenon is less common (8.7%).[29] The kidneys, although an uncommon site for primary HSA, can be associated with a more prolonged clinical history, generally smaller lesions, less-advanced disease at diagnosis, and a more favorable prognosis compared to other internal presentations of HSA.[12] HSA represents the most common tumor type affecting the retroperitoneal space, and it is associated with a high metastatic and recurrence rate, with very short survival times (<40 days) when originating in this location.[13]

Data are lacking regarding the true incidence of HSA in cats. However, it appears to occur much less commonly than it does in dogs, and likely represents <0.5% of all feline tumors. Generally, HSA occurs in older cats with no sex predisposition noted. The spleen, liver, gastrointestinal tract, cutaneous/subcutaneous tissue, and mesentery are the most common primary sites. Hemangiosarcoma uncommonly has been reported as a variant of feline injection site sarcoma (see ch. 346). Although HSA occurs less commonly than it does in dogs, its biologic behavior appears to be similar, with common metastatic sites including lungs, liver, and omentum.[30-37] A study evaluating spontaneous hemoperitoneum in 65 cats noted that 30/65 (46%) had abdominal neoplasia, and 54% had non-neoplastic conditions. Sixty percent (18/30) of the cats with a neoplastic etiology had HSA, and the spleen was the most common site of origin for neoplasia (11/30; 37%).[38] Another study evaluating 26 cats with visceral hemangiosarcoma reported pulmonary metastasis and multifocal disease in 33% and 77% of cats, respectively.[34]

Etiology and Pathobiology

The definitive etiology of canine HSA remains unclear; however, several associated risk factors have been reported, including UV light exposure and radiation therapy.[39-41] Chronic UV light exposure with superficial (dermal) HSA along the ventral abdomen and conjunctival locations are noted in lightly pigmented, short haired breeds such as Salukis, Whippets, Italian Greyhounds, and Greyhounds.[40] Development of HSA lesions at previous radiation therapy sites has been reported, but the actual risk is considered quite low. Exposure to toxins such as vinyl chloride, dioxides, radiation, and arsenicals has been reported to be associated with angiosarcoma and HSA in humans,[42-44] but no such data exist in companion animals.

A few studies have suggested a hormonal link with HSA related to neutering (see ch. 313). Specifically, in a study assessing tumors of cardiac origin, cardiac HSA in spayed females was four times more common than in intact females.[23] A study evaluating splenic HSA similarly noted that spayed females had greater than two times the prevalence compared to intact females.[1] More recently, a study evaluating the effects of early neutering in Golden Retrievers noted that the percentage of HSA in "late-neutered" females was four times that of intact or early-neutered dogs.[45] It is important to note that the number of affected dogs in these studies was low; however, this is an active area of interest from both veterinary and public health perspectives.

With the advent of platforms enabling evaluation of genome-wide gene expression, we are beginning to elucidate specific genes associated with HSA. A recent study using such techniques identified three distinct tumor subtypes in dogs with primary hemangiosarcoma. Specifically, these were associated with

angiogenesis, inflammation, and adipogenesis.[46] These findings suggest that tumors either can arise from single multipotent progenitor cells that differentiate down multiple lineages as part of an adaptive process, or that multiple progenitor lineages might contribute to tumor formation, with one progenitor giving rise to endothelial-like and adipogenic-like cells and another progenitor giving rise to myeloid-like cells. Further research using multi-parameter flow cytometry has demonstrated that canine HSA originates from hematopoietic precursor with commitment to the endothelial lineage.[7,47] These data similarly refute the long held belief that HSA represents malignant transformation of mature endothelial cells in the peripheral vasculature. Furthermore, it is conceivable that this modality, which can assess the expression patterns of cell surface markers observed in those multipotential bone marrow–derived stem cells, can aid in confirming the early diagnosis of HSA and possibly be useful in the monitoring of minimal residual disease.[7,47,48]

Differences between malignant and non-malignant endothelial cells have been documented in regards to increased expression of genes involved in inflammation, angiogenesis, adhesion, invasion, metabolism, cell cycle, signaling, and patterning in neoplastic cells. Interestingly, this "signature" has reflected not only a cancer-associated angiogenic phenotype, but has distinguished HSA from other cancers.[49] Furthermore, specific abnormalities in oncogenes and tumor suppressor genes have been identified in HSA, both of which can play a role in tumor formation.[50,51] This explosion of research has identified several cancer "driver" genes associated with aberrant cellular signaling pathways. It is interesting to note that several of these pathways are associated with angiogenesis,[46,49] a process that often is dysregulated in neoplasia. Multiple angiogenic factors and their associated receptors are overexpressed in HSA and increased levels of angiogenic factors are present in the blood of dogs with HSA (also see ch. 338).[52-57]

History and Clinical Signs

Clinical presentation, history, and associated clinical signs are based on tumor location; however, the majority of patients with HSA arising in the spleen, liver, and heart present for urgent veterinary attention secondary to tumor rupture and internal hemorrhage (see ch. 135 and 143). In some cases, this can lead to collapse (see ch. 127) and sudden death. Patients with intra-abdominal or intrathoracic HSA commonly have a history of acute weakness, collapse, and pale mucous membranes secondary to blood loss anemia. Oftentimes, the emergent presentation might not be the first time that similar, albeit less severe, signs have occurred and a thorough history can reveal previous episodes. For splenic or hepatic HSA, it is likely that upon cessation of acute bleeding and resorption of blood from the affected cavity, patients recover and seemingly appear to be clinically normal until subsequent bleeding occurs. Other historical findings include anorexia, weight loss, lethargy, abdominal distension, vomiting, dyspnea, and vocalization.[4,5,20-22,26,27] Similar clinical signs are noted with renal HSA, sometimes with hematuria.[12] Patients with cardiac HSA might require even more rapid attention due to the development of life-threatening cardiac tamponade (see ch. 254). On physical examination, clinical signs in such patients similar to that of right heart failure are present secondary to the pericardial effusion. Specifically, muffled heart sounds and secondary arrhythmias are commonly noted in patients with pericardial effusions.[25-27] Although clinical stage affects prognosis, a delay in complete clinical staging might be necessary to allow for emergency intervention, with subsequent staging performed only once the patient is clinically stable. Clinical presentation with central nervous system (CNS) HSA can vary widely depending on tumor location, with seizures and mentation changes being the most common (see ch. 260).[16,17]

Cutaneous HSA presentations vary depending on whether the lesion is primarily dermal or subcutaneous (also see ch. 10 and 345). Dermal HSAs are typically small, discrete, blood blister–like lesions, while subcutaneous HSAs are deeper, often larger, and more mass-like, with associated bruising. Intramuscular HSAs typically are large masses or "mass effects" with associated distal swelling and lameness when occurring on or near a limb.[39,40,58-62] Metastasis to external and/or internal sites is much more common with subcutaneous and intramuscular HSA compared to the dermal presentation.[59-62]

Diagnosis and Staging

Although histopathologic evaluation of tissue is the gold standard for diagnosis of this tumor, a presumptive diagnosis of HSA often is made based on the history, signalment, and physical examination. Therefore, many times, complete clinical staging is performed even before a histologic diagnosis is achieved if the clinical presentation is suggestive of HSA. Complete staging includes standard laboratory work (complete blood

count, serum biochemistry profile, urinalysis, and coagulation profiles), three-view thoracic radiographs, abdominal ultrasound (see ch. 88), and if applicable and available, multiple image-plane echocardiography (see ch. 104). There also could be a role for the use of advanced imaging and novel biomarkers in the diagnosis and staging of this disease. The results of clinical staging allow accurate assessment of the patient's stage of disease (Box 347-1), information that helps inform prognosis and guide therapy.

Box 347-1

Canine Hemangiosarcoma TNM Clinical Staging System

T = Tumor (Primary Tumor)

T0 = No evidence of tumor
T1 = Tumor confined to primary site and/or dermis and <5 cm in diameter
T2 = Tumor invading SC tissues and/or ≥5 cm in diameter
T3 = Any T1 or T2 with tumor invading adjacent structures and/or muscle

N = Node (Regional Lymph Nodes)

N0 = No evidence of regional lymph node involvement
N1 = Regional lymph node involvement
N2 = Distant lymph node involvement

M = Metastasis (Distant)

M0 = No evidence of distant metastasis
M1 = Distant metastasis

TNM Stages

I = T0 or T1, N0, M0
II = T1 or T2, N0 or N1
III = T2 or T3, N0 or N1 or N2, M1

Pathologic Evaluation

Depending on the specific lesion and clinical presentation, tissue can be evaluated histologically via submission of an entire affected organ after surgical removal, excision of a localized external (i.e., dermal/subcutaneous/intramuscular) mass, or a simple diagnostic (i.e., incisional, wedge, core needle/"Tru-Cut") biopsy of either internal or external lesions, if deemed clinically safe. Histologically, HSA is composed of irregular, anastomosing vascular channels lined by pleomorphic spindle cells with large multifocal cavities filled with blood. Areas of necrosis commonly are noted within the tumor. Marked anisokaryosis and anisocytosis are common, and often a high mitotic index is noted[1,2,9,18,19,26,39,40,58] (Figure 347-3). A classic cause of clinician and owner frustration is related to discordant clinical and histopathologic results. Often, this situation can be associated with the submission of small or wedge sections from a large splenic mass to conserve finances due to high costs of shipping large amounts of formalin or where a large formalin container is not available. In such cases, the sample can be sectioned serially ("bread-loafed") to allow for full fixation by formalin overnight, with removal from formalin and submission in formalin-wetted towels the following day. Additionally, although cytologic analysis is a non-invasive and clinically valuable technique for the diagnosis of cancer in general, the diagnostic yield for HSA is reportedly low.[5,63,64] However, in some cases of subcutaneous or intramuscular tumors, cytologic evaluation of smears may provide a diagnosis in lieu of histopathologic analysis (Figure 347-4).

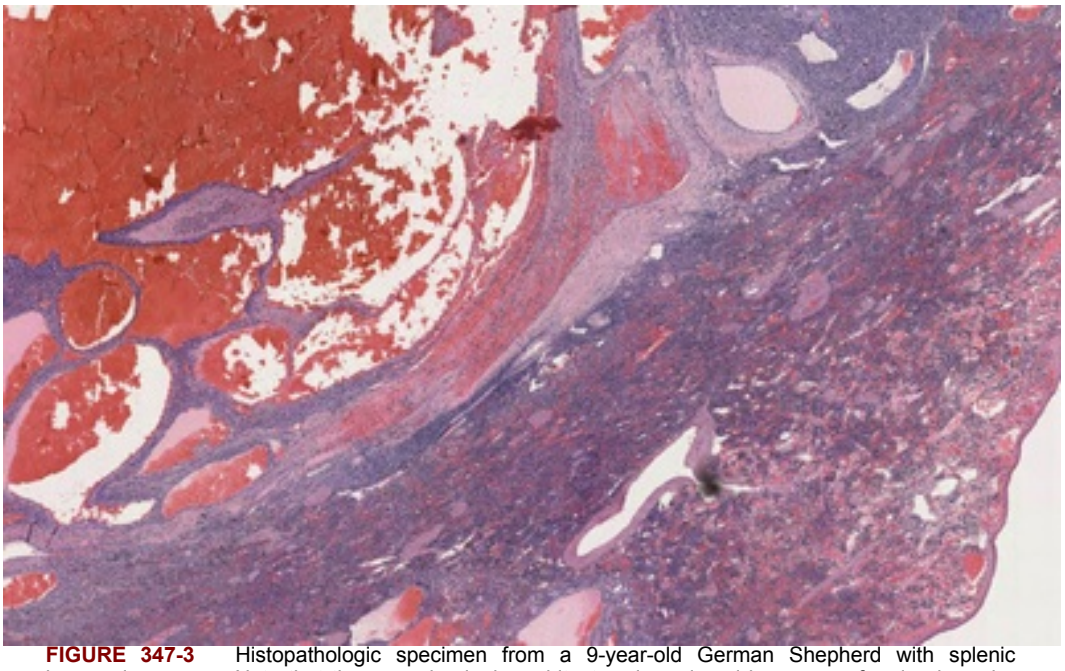

FIGURE 347-3 Histopathologic specimen from a 9-year-old German Shepherd with splenic hemangiosarcoma. Note that the normal splenic architecture is replaced by a mass forming irregular anastomosing vascular channels lined by pleomorphic spindle cells with large multifocal cavities filled with blood. Spindle cells have indistinct cell borders, little eosinophilic cytoplasm and large, irregular, oval, hyperchromatic or stippled nuclei with inconspicuous nucleoli. Anisokaryosis and anisocytosis are moderate to marked, and atypical mitotic figures are common. (Image and description courtesy Danielle Reel, DVM, DACVP, Eastern VetPath.)

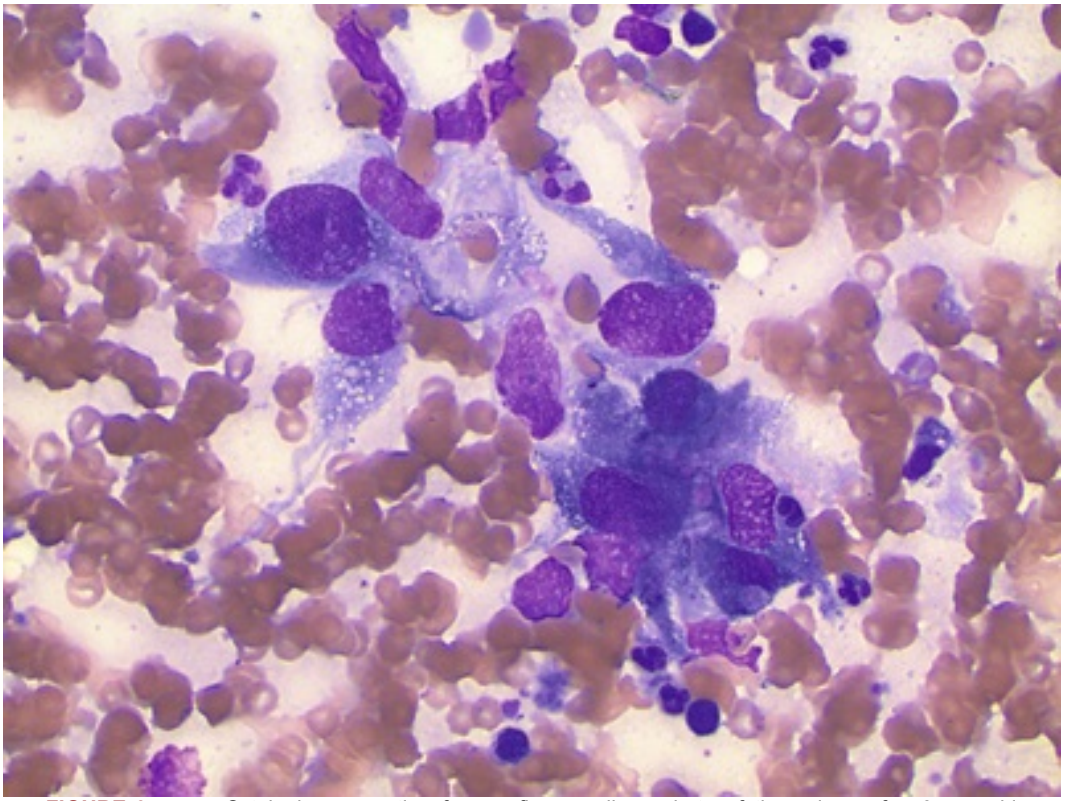

FIGURE 347-4 Cytologic preparation from a fine needle aspirate of the spleen of a 6-year-old neutered male Golden Retriever with splenic hemangiosarcoma and pulmonary metastasis. An aggregate of spindle- to irregularly-shaped cells with wispy basophilic cytoplasm with few punctate vacuoles is seen. The nuclei are oval to irregularly-shaped and exhibit moderate anisokaryosis. 50×

objective/500× magnification. (Image and description courtesy Casey J. LeBlanc, DVM, PhD, DACVP, Eastern VetPath.)

In addition to histopathologic findings, there are several surgical points that are worthy of comment. Given the highly metastatic nature of visceral HSA and the effect of stage on prognosis, any suspicious lesions noted at the time of surgery should be sampled and examined histologically. A recent retrospective study in 79 dogs evaluated the association between macroscopic appearance of hepatic lesions and the corresponding histologic findings in dogs undergoing laparotomy for splenic HSA. All HSA-positive samples were obtained from grossly abnormal livers; however, 59% of histologically benign lesions also were obtained from grossly abnormal livers. Furthermore, only 50% of grossly abnormal livers had HSA metastasis; diagnoses reported in the other 50% of cases included nodular hyperplasia, hepatic vacuolar degeneration, lipogranulomas, extramedullary hematopoiesis, and hemosiderosis.[65] Livers that had multiple nodules and/or dark red or black lesions were more likely to be consistent with HSA (Figure 347-5). Therefore, the presence of gross hepatic abnormalities was associated with a high sensitivity (100%) but low specificity and PPV (41% and 48%, respectively) for HSA, reaffirming the importance of histologic confirmation prior to clinical decision-making. Furthermore, although it cannot be overemphasized that the definitive diagnosis of HSA can only be made via histologic examination, a recent study evaluating 65 dogs that underwent splenectomy, including 30 dogs (46%) with HSA, noted that larger splenic masses, determined by a higher ratio of mass to splenic volume, and heavier spleens (as a percentage of body weight), were more likely to be benign and less likely to be HSA.[66] Although these results do suggest that mass-to-splenic volume ratio and splenic weight as a percentage of body weight could be useful in differentiating between hemangiosarcoma and benign lesions in dogs with splenic masses, no attempts were made to determine sensitivity or specificity of these variables or to identify optimal cut-offs in the referenced study.

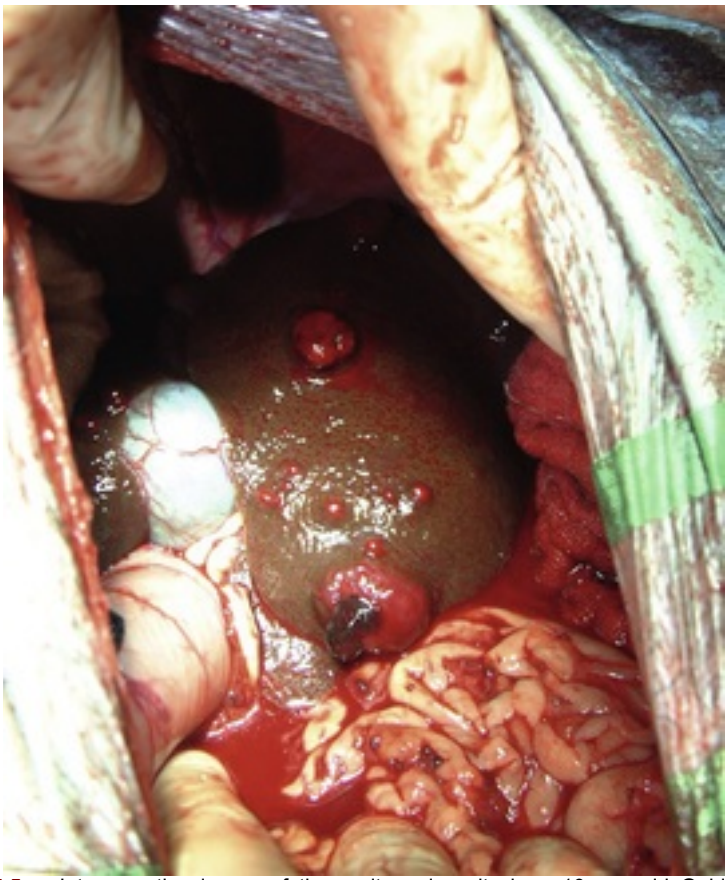

FIGURE 347-5 Intraoperative image of the peritoneal cavity in a 10-year-old Golden Retriever presenting with hemoabdomen secondary to hemangiosarcoma. Note the multiple, raised, red-purple lesions along the liver, some of which were actively bleeding. (Image courtesy Julius Liptak, BVSc, MVetLinStud, FACVSc, DACVS, DECVS.)

Laboratory Evaluation

Several abnormalities on the complete blood cell count can be present in patients with HSA, the most common being anemia. The anemia is generally regenerative and schistocytes, acanthocytes, and nucleated red blood cells often are noted, consistent with microangiopathic-related damage secondary to vasculitis, hepatic insufficiency, deficient reticuloendothelial system, and acute hemorrhage.[67-71] Neutrophilic leukocytosis is another common hematologic abnormality and has been postulated to be a result of a paraneoplastic syndrome and/or necrosis that occurs in large tumors and rapidly growing tumors.[27,72] More recent research suggests that this tumor-associated neutrophilia (and often a monocytosis) could be partially composed of myeloid derived suppressor cells (MDSCs), a subset of granulocytes responsible for suppressing innate anti-tumor immunity and associated with a poor prognosis in some cancers.[73-76] Thrombocytopenia is noted in up to 75% of dogs with HSA and it can be a result of tumor hemorrhage, destruction via fibrin crosslinks within the tumor vasculature, or secondary consumptive coagulopathies such as disseminated intravascular coagulation (DIC; see ch. 197), which has been reported in up to 50% of dogs with hemangiosarcoma.[27,70,71] As a result of DIC, abnormalities can be present on coagulation profiles (prothrombin time, partial thromboplastin time, fibrin[ogen] degradation products, fibrinogen, d-dimers; see ch. 196). The serum biochemistry profile and urinalysis rarely aid in the diagnosis of HSA given their lack of specificity, although in one study, 53% of cats with visceral HSA had increased aspartate aminotransferase (AST) levels.[38]

Other more novel ancillary diagnostic tests could aid in early detection of HSA, since most patients likely have microscopic metastatic dissemination at the time of histologic diagnosis. Early work with flow cytometry has shown the ability to identify cells of specific lineage that co-express certain cell surface markers that are detected in higher numbers in the peripheral blood of dogs with HSA compared to that of healthy control dogs or dogs that are free of measurable HSA following surgical excision.[6]

Diagnostic Imaging

Three-view thoracic radiographs consisting of right and left lateral and ventrodorsal views typically are performed for detection of metastatic disease. The typical radiographic appearance of measurable pulmonary metastatic disease is that of a coalescing miliary pattern; however, either nodular or generalized miliary interstitial patterns also can be observed (Figure 347-6). In one study in which thoracic radiographic and postmortem findings were compared in dogs with histologically confirmed HSA, the radiographic sensitivity was 78% and the negative predictive value was 74% for metastatic pulmonary HSA.[77]

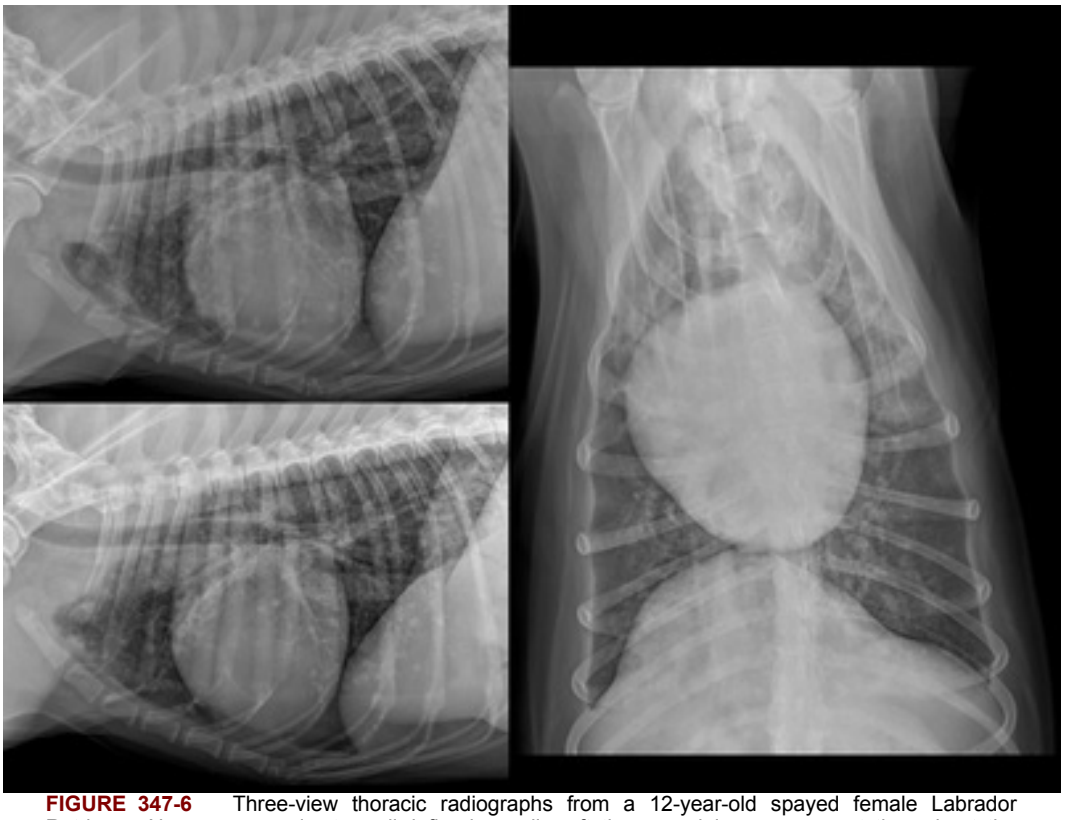

FIGURE 347-6 Three-view thoracic radiographs from a 12-year-old spayed female Labrador Retriever. Numerous poorly- to well-defined, small, soft tissue nodules are present throughout the lungs, consistent with metastatic hemangiosarcoma. (Images and description courtesy Chris Ryan, VMD, DABVP, DACVR.)

Abdominal ultrasonography is one of the most commonly utilized imaging modalities in veterinary medicine and it is readily able to identify effusions, hepatic and splenic lesions, as well as metastatic omental lesions, depending upon the skill level of the operator. Hemangiosarcoma can take on many different echogenic characteristics (anechoic to hypoechoic to mixed) and it often has areas of cavitation (Figure 347-7).[78] More advanced techniques such as contrast harmonic ultrasonography, which can evaluate tissue perfusion dynamics, could hold promise.[79,80] One study demonstrated improved diagnostic yield for hepatic HSA via detection of nodules not seen during traditional gray-scale ultrasound examination.[80] Multiple studies evaluating splenic lesions demonstrated that hypoechogenicity of the splenic lesion during the early and late vascular phases was highly associated with malignancy.[81-83]

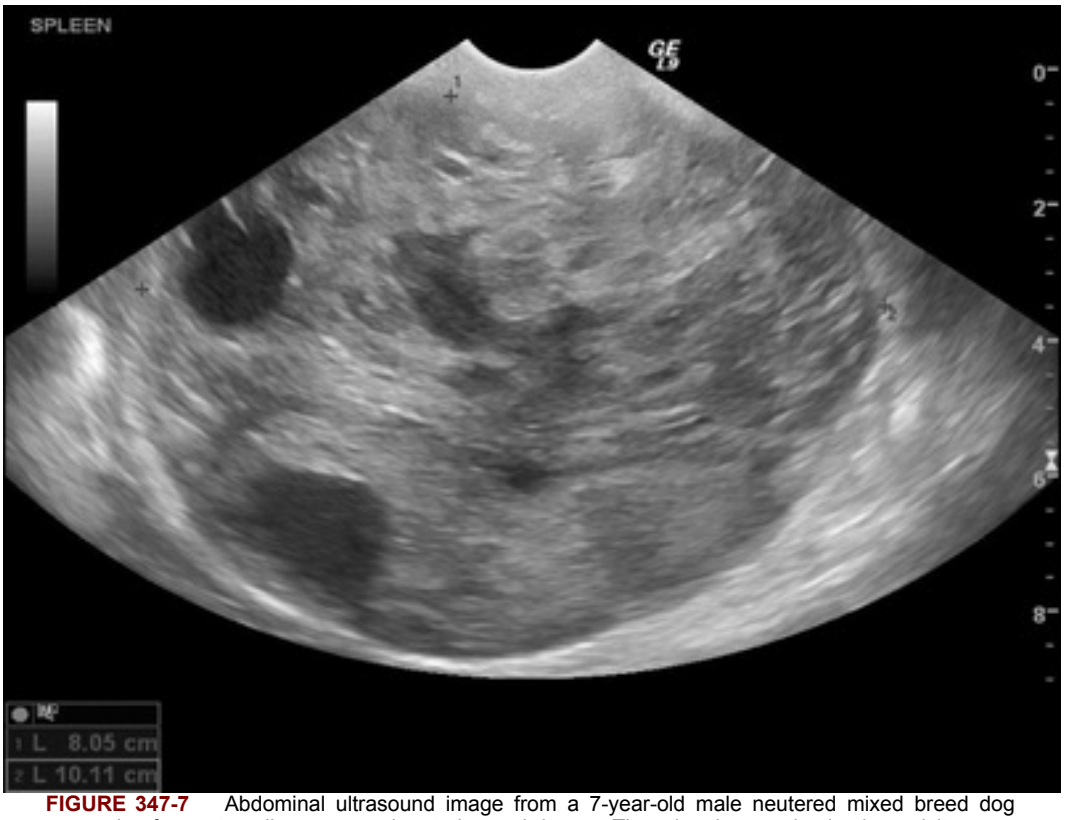

FIGURE 347-7 Abdominal ultrasound image from a 7-year-old male neutered mixed breed dog presenting for acute collapse secondary to hemoabdomen. There is a large, mixed-echogenicity mass with multiple central cavitations effacing the normal splenic architecture and occupying most of the image. (Images and description courtesy Chris Ryan, VMD, DABVP, DACVR.)

Undoubtedly, the presence of acute hemoabdomen (see ch. 143) along with ultrasound findings of a splenic mass are highly suggestive of HSA. In one study evaluating 39 dogs with acute non-traumatic hemoabdomen, 80% were secondary to visceral neoplasia, of which 70% were confirmed as HSA.[20] In a second study evaluating a similar population of 60 dogs, HSA was confirmed in 63% of dogs.[22] Although these data can be considered compelling, it is these authors' belief that no patient with hemoabdomen should be euthanized based on splenic or hepatic lesions that are "consistent with HSA" because many nonmalignant splenic lesions, such as hematomas, appear similar on ultrasound and carry a very good to excellent prognosis with splenectomy alone.[8,18,19] As noted above, a recent study evaluating hepatic abnormalities found at the time of splenectomy for splenic HSA showed that only 50% of dogs with grossly abnormal livers had histologic evidence of hepatic metastasis.[65]

Some groups are investigating combinations of clinical and laboratory parameters in conjunction with ultrasound findings in an effort to increase the confidence of a diagnosis of HSA prior to surgery. One such study evaluated the prevalence of splenic HSA in 71 anemic dogs with a splenic mass and hemoperitoneum in order to identify factors that could differentiate between dogs with HSA versus other splenic masses at the time of hospital admission. Malignant splenic neoplasia was identified in 76% of dogs, of which 92.6% had HSA, and a diagnosis of HSA was significantly associated with a low serum total solids concentration and thrombocytopenia.[21]

Echocardiography remains the modality of choice to identify cardiac (right atrial/auricular) tumors and the presence of pericardial effusion improves the detection of such masses (see ch. 254 and Video 347-1).[84,85] Its use in routine staging for HSA that is first identified in other locations is considered controversial since the overall detection of concurrent lesions is low.[29] However, echocardiography also can be utilized as a screening tool prior to the initiation of doxorubicin chemotherapy to assess heart function in breeds at risk for dilated cardiomyopathy; therefore, its value for such HSA patients can be two-fold.[86] Also, from a cardiac standpoint, perioperative ventricular arrhythmias have been documented in up to 44% of dogs undergoing splenectomy for HSA.[25,87-89] Ventricular arrhythmias in dogs with splenic masses are thought to develop as a result of compromised venous return to the heart, micrometastasis to the heart, and/or DIC, and have been

associated significantly with tumor rupture and anemia. Many dogs experiencing pre- and post-operative cardiac arrhythmias might not be directly clinically affected by these abnormalities and often, their treatment can consist of controlling triggers for the arrhythmias (e.g., treating anemia with blood transfusions, or correcting serum electrolyte imbalances) rather than antiarrhythmic therapy (see ch. 248). In one study, dogs that developed intra-operative arrhythmias had an odds ratio of death that was greater than twice that of dogs that did not experience intra-operative arrhythmias.[89] Resolution of perioperative arrhythmias should be confirmed prior to patient discharge and subsequent adjuvant treatments, as in a small number of cases they could represent underlying organic cardiac dysfunction, a strong contraindication to doxorubicin chemotherapy.[90]

With increased access to more advanced imaging techniques, both computed tomography (CT) and magnetic resonance imaging (MRI) can be utilized for evaluation of subcutaneous, intramuscular, cardiac, splenic, and hepatic HSA. CT and MRI can aid in determining the exact anatomic origin and extent and invasiveness of disease, thereby assisting in the planning of surgical resection and/or radiation therapy.[91] Furthermore, both MRI and CT carry a high sensitivity and specificity in discriminating benign from malignant splenic and hepatic lesions (Figure 347-8).[92,93] An increased sensitivity of thoracic CT for early pulmonary metastasis detection also has been documented.[94,95] As costs for such modalities decrease, they soon could become commonplace in the routine staging of dogs with HSA.

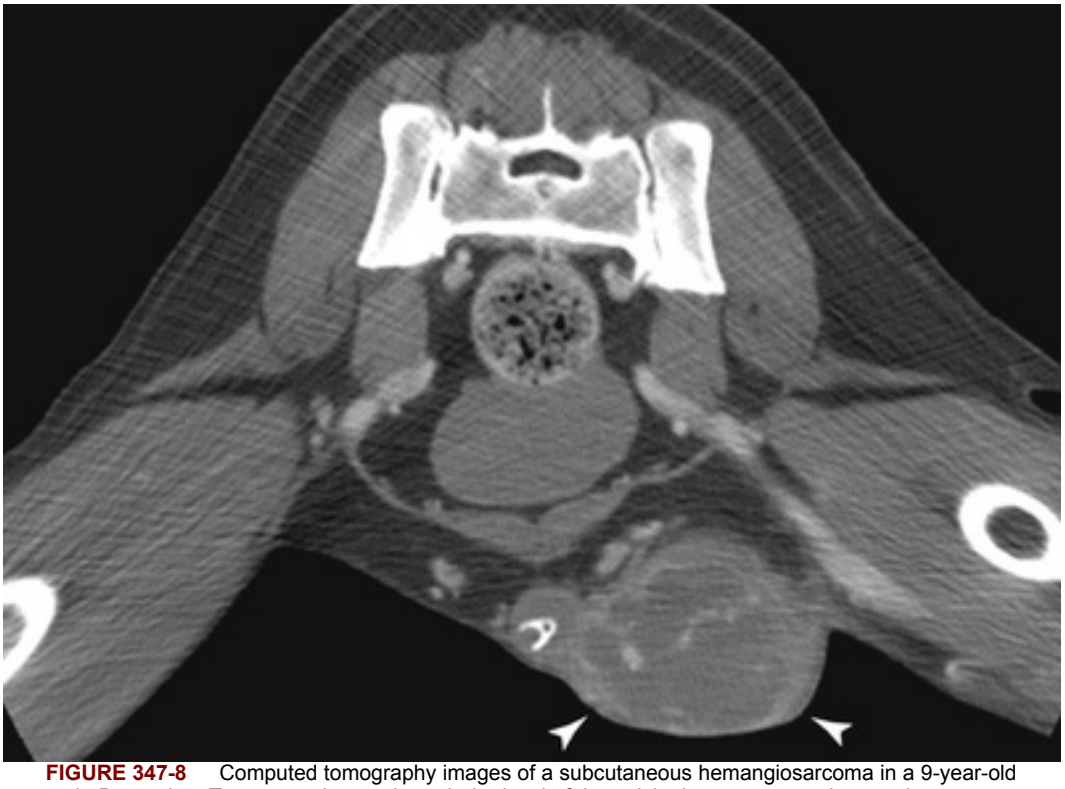

FIGURE 347-8 Computed tomography images of a subcutaneous hemangiosarcoma in a 9-year-old male Boxer dog. Transverse image through the level of the pelvis demonstrates a large subcutaneous mass in the left inguinal region (white arrowheads). The mass is heterogeneously contrast-enhancing at the periphery, non-enhancing centrally, and has multiple thick, irregular, contrast-enhancing septae. (Images and description courtesy Chris Ryan VMD, DABVP, DACVR.)

Biomarkers

The use of HSA-specific biomarkers could be clinically useful not only to enable early detection and intervention but also to monitor the patient's disease status during and after treatment. Several recent studies have evaluated such markers in both the blood and effusions of dogs with HSA. Cardiac troponin I (cTnI) has proven to be a highly specific and sensitive marker for cardiomyocyte damage (see ch. 246).[96,97] A recent study showed that the median plasma cTnI concentration in dogs with cardiac HSA was significantly higher

than the median concentration in dogs with hemangiosarcoma at other sites, dogs with other neoplasms, and dogs with pericardial effusion not caused by hemangiosarcoma (see ch. 254). Specifically, increased cTnI concentrations could identify cardiac involvement in dogs with HSA at any site (sensitivity, 78%; specificity, 71%) as well as identify cardiac HSA in dogs with pericardial effusion (sensitivity, 81%; specificity, 100%).[96] Similarly, serum collagen XXVII peptide concentration was measured in the serum of dogs with hemangiosarcoma and levels in dogs with large metastatic burdens were found to be 9.5-fold higher than those in healthy dogs.[97] It has been proposed that elevations could be related to protein cleavage or degradation in surrounding tissue, or be associated with invasive behavior or angiogenic processes. Interestingly, collagen XXVII peptide concentrations for dogs with other forms of neoplasia (osteosarcoma, lymphoma, carcinomas) and inflammatory disease also were increased, but the values consistently were lower than those for HSA. Reductions in collagen XXVII peptide levels after surgical resection of HSA and subsequent increases with tumor recurrence demonstrate that this peptide could serve as a useful HSA biomarker.[97] Another marker evaluated in dogs with HSA is the cytosolic enzyme thymidine kinase (TK1), the activity of which is closely correlated with DNA synthesis and expression restricted to proliferating cells.[99] A recent study demonstrated that serum TK1 activity was significantly higher in archived serum of dogs with HSA compared to that of healthy dogs. Serum TK1 then was prospectively evaluated in 62 dogs with hemoabdomen secondary to either a benign splenic mass or HSA. Statistically, there was no difference in mean TK1 activity level, but differentiation of the two groups became possible when a specific two-tiered cut-off system was implemented.[99]

Treatment and Prognosis

Localized Therapies

Surgery

Surgery still is the mainstay of therapy for HSA, and splenectomy, liver lobectomy, nephrectomy, excision of dermal, subcutaneous, intramuscular or retroperitoneal masses, and right auriculectomy all have been reported. Such surgeries are performed to remove all macroscopic tumors and prevent further risk of acute hemorrhage, establishment of DIC, and death. The postoperative prognosis associated with HSA is highly dependent on tumor location, stage, completeness of excision, and use of adjuvant therapies.

Specifically, cutaneous HSA that is limited to the dermis without hypodermal invasion (as opposed to subcutaneous/intramuscular lesions) has a lower metastatic rate and often can be controlled with surgery alone. Median survival times (MSTs) of 780-987 days have been reported for dogs after excision of dermal HSA.[58,59] In one study of 94 dogs, predisposed breeds with ventral tumor location and histologic solar changes had even longer survivals. Tumors with subcutaneous invasion were more likely to develop metastasis. Interestingly, even though long-term survival was reported in that study, locoregional recurrence occurred in 77% of dogs.[59] These survival data are in stark contrast to those reported for tumors with subcutaneous or intramuscular involvement, where MSTs of 172 and 307 days have been reported, respectively.[58] For subcutaneous or intramuscular HSA, surgical excision should be as thorough as possible in order to achieve wide margins. Sometimes, this necessitates limb amputation or the use of adjuvant radiation therapy in the event of incomplete or narrow excision, as the local recurrence rate for inadequately excised HSA is substantial.[59,60,62] Furthermore, because of the higher risk of associated and poor long-term survival associated with subcutaneous/intramuscular HSA, adjuvant systemic therapy also is warranted for this particular tumor presentation. Cats with cutaneous HSA treated via surgical excision have been reported to have MSTs of ≈9 months to 4 years.[35,36] Similar to the situation in dogs, feline HSA with subcutaneous involvement was associated with incomplete excision, higher metastatic rate, and tumor-associated euthanasia.[35,36]

Because of the high risk for metastasis, surgery for visceral (most commonly primary splenic) HSA is considered palliative and is associated with a median survival time (MST) of only 19 to 86 days for dogs undergoing splenectomy alone, and 77 days for cats undergoing laparotomy.[1-5,34,100] Therefore, adjuvant chemotherapy, discussed below, is recommended following surgery for essentially all forms of visceral HSA.

For dogs with cardiac HSA, surgical tumor excision typically either is impossible due to the difficult location or is declined due to risks and/or the expected poor to grave prognosis. However, a few case reports and case series exist that describe long-term survival after tumor excision.[101-106] Pericardiectomy via thoracotomy or thoracoscopy is performed more commonly and it can alleviate life-threatening cardiac

tamponade, but alone it is unlikely to significantly prolong survival (see ch. 254).[107]

Although an uncommon variant, primary renal HSA without evidence of hemoperitoneum or metastasis could carry a more favorable prognosis with surgery alone. In a study of 14 dogs with renal HSA, most patients had localized disease on presentation and ten were treated with surgery alone. An MST of 286 days was noted in dogs treated with surgery alone (n = 10), but 10/14 dogs still died of effects secondary to HSA.[12] HSA is the most common histologic diagnosis for retroperitoneal sarcomas in dogs and is extremely aggressive locally, carries a high rate of local invasion and metastasis, and as such, is associated with a poor survival time even when treated with multimodality therapy.[13]

Radiation Therapy

Due to HSA's predilection for inaccessible anatomic sites, its frequently acute presentation, and its high metastatic rate, the use of radiation therapy for HSA has been limited. A study of 20 dogs with measurable, histologically confirmed non-splenic HSA treated with palliative RT showed subjective reduction in tumor size in 14 dogs (70%), with four complete responses and an MST of 95 days.[108] These results are encouraging, and further validation with combination protocols consisting of RT and systemic chemotherapy is needed. Furthermore, although not yet formally evaluated or reported, there also could be a role for the application of strontium-90 plesiotherapy for small and superficial dermal HSA, because it has been shown to provide a high rate of complete response and long-term tumor control in other superficial tumor types.[109]

Systemic Therapies

Conventional Chemotherapy

Doxorubicin (DOX) appears to be the most active agent and has provided the best extension of post-splenectomy survival times to date. Common protocols include single agent DOX; combination DOX and cyclophosphamide (AC protocol); combination vincristine, DOX, and cyclophosphamide (VAC protocol); and combination DOX and ifosfamide.[110-114] Median survival times are related to stage of disease and typically are in the 5-7 month range with the aforementioned DOX-based protocols. In a recent prospective study comparing an AC and DOX/DTIC protocol in 27 dogs with HSA of various locations (20/27 splenic), an overall MST of 142 days was reported for 18 dogs treated with an AC protocol, while the MST for 9 dogs treated with DOX/DTIC was >550 days.[115] However, the small number of dogs in the DOX/DTIC group raises the question about the true significance of these results. An older study evaluating liposome-encapsulated muramyl tripeptide phosphatidylethanolamine (L-MTP-PE), an immunomodulator derived from mycobacterial cell walls that increases monocyte tumoricidal activity, together with DOX, reported the longest survivals to date, where all dogs receiving DOX/L-MTP-PE survived a median of 277 days, with clinical Stage I dogs receiving the combination living a median of 425 days.[116] Unfortunately, L-MTP-PE is no longer clinically available. Therefore, in the absence of L-MTP-PE, it is unclear whether any of the remaining DOX-based protocols is truly superior to the others (Table 347-1).

TABLE 347-1

Selected Median Survival Times with Various Therapies for Canine HSA

TUMOR LOCATION	TREATMENT	MST* (DAYS)	REFERENCES
Spleen	Splenectomy	19-86	1, 2, 10, 100
	Splenectomy + VAC	140-145	10, 113, 126
	Splenectomy + AC	140‡-180	112, 115, 116
	Splenectomy + AC + L-MTP-PE	277	116
	Splenectomy + LDC	178	127
	Splenectomy + EPI	144	120
	Splenectomy + A	172-210†	117, 118
	Splenectomy + A + VAX	182	145

	Splenectomy + A/DER	150	111
	Splenectomy + DOXIL (IV)	166	118
	Splenectomy + DOXIL (IP)	131	119
	Splenectomy + IFOS	147	121
	Splenectomy + A/IFOS	123	114
	Splenectomy + A/DTIC	>550§	115
	Splenectomy + A + TOC	172	151
	Splenectomy + PSP	117-199	154
Heart	Pericardectomy + tumor resection	42-120	25, 122
	Pericardectomy + tumor resection + A	175	122
	A‖	139.5	123
	A	116	124
Kidney	Nephrectomy ± chemotherapy	278	12
Retroperitoneal	Various	37.5¶	13
Cutaneous	Tumor resection	780-987	58,59
Subcutaneous (SC)	Surgery	172	58
	Surgery + A ± RT	1189	60
	A	140.5	61
Intramuscular (IM)	Tumor resection	302	58
	Tumor resection + A ± RT	272.5	60
Miscellaneous			
SC/IM combined	Variable	172	62
	Tumor resection + chemo ± RT	246	62
Various (non-splenic)	RT	89	108
Various (including splenic)	Tumor resection + A	60-172	110
	Tumor resection + AC	202	112
	Tumor resection + AC + MINO	170	134
Various advanced stage (metastatic and/or inoperable)	VAC ± tumor resection	195	126
	DAV	125	125

*Not separated by stage of disease.

†Data for stage II splenic only.

‡Only 15/18 dogs had splenic HSA.

§Only 5/9 dogs had splenic HSA.

‖Various DOX-based protocols.

¶Only 9/14 dogs had HSA.

A, Adriamycin; *C,* cyclophosphamide; *DER,* deracoxib; *doxil,* pegylated liposomal encapsulated doxorubicin; *DTIC,* dacarbazine; *epi,* epirubicin; *HSA,* hemangiosarcoma; *IFOS,* ifosfamide; *L-MTP-PE,* liposomal muramyl tripeptide phosphatidylethanolamine; *LDC,* low dose chemotherapy (cyclophosphamide, etoposide, piroxicam); *MST,* median survival time; *PSP,* polysaccharopeptide *(Coriolus versicolor); ref,* references; *RT,* radiation therapy; *TOC,* toceranib phosphate; *V,* vincristine; *VAX,* tumor lysate vaccine.

Attempts to improve on reported MSTs have been made through the use of dosage-intensified single agent DOX protocols along with both intravenous (IV) and intraperitoneal (IP) administration of the liposome-encapsulated form of DOX (Doxil), but have not resulted in significant survival benefit.[117-119] However, interestingly, the IP-treated dogs had fewer serosal, mesenteric, and omental metastases than historical controls treated with systemic doxorubicin.[119]

Epirubicin, a stereoisomer of doxorubicin, was developed in an effort to decrease cardiotoxicosis in people and has been evaluated in dogs. In a study of 18 dogs receiving epirubicin following splenectomy, an MST of 144 days was noted.[120] Epirubicin was associated with a higher rate of gastrointestinal side effects, often necessitating hospitalization, than the rate of such side effects commonly seen with monotherapy DOX. Regardless, this agent could be an attractive alternative for patients with pre-existing cardiomyopathy. Additionally, in a small study, ifosfamide was administered to six dogs following splenectomy for HSA, resulting in a comparable MST of 147 days.[121]

For dogs with subcutaneous or intramuscular HSA, chemotherapy generally is used in the postoperative setting in order to address the considerable metastatic rate. According to multiple studies, dogs with lower stage disease and with tumors that are less locally invasive appear to have a better prognosis.[58,60,62] Interestingly, the results of two recent retrospective studies evaluating dogs undergoing local therapy followed by adjuvant doxorubicin were quite disparate. In the first study, a median survival time of 1189 days was reported for dogs undergoing surgery and adjuvant doxorubicin ± radiation therapy for non-metastatic subcutaneous HSA (n = 17) and 272.5 days for dogs receiving similar therapy for non-metastatic intramuscular HSA (n = 4).[60] The second study evaluating 71 dogs (subcutaneous HSA n = 55, intramuscular HSA n = 16) reported an overall survival time of 246 days for those dogs having adequate local tumor control of smaller (<4 cm) tumors without metastasis.[62] Possibilities to explain this discrepancy might involve the terminology used for cutaneous and subcutaneous HSA (in the first study, dogs with primary cutaneous HSA with subcutaneous extension might have been included, whereas the second study included only those dogs with tumors arising from the subcutaneous space and excluded those with primary cutaneous HSA) and the small number of dogs in each group.

The MST for dogs with cardiac HSA (see ch. 254) remains notably lower than those achieved for the splenic presentation, likely due to the difficulty in obtaining local control for a cardiac tumor as compared with HSA arising from other anatomic sites. However, when surgical excision is feasible and is combined with adjuvant chemotherapy, survival times comparable to those achieved with splenectomy and chemotherapy might be possible. Specifically, a recent study evaluating 23 dogs with cardiac HSA reported an MST of 42 days for dogs treated with surgery alone versus 175 days for dogs receiving adjuvant chemotherapy.[122] When surgical biopsy is not possible, the diagnosis of cardiac HSA becomes only presumptive. Only recently have some data become available regarding the outcomes of patients undergoing chemotherapy for macroscopic presumed cardiac HSA. A small study of 16 dogs with right atrial masses that received DOX either alone or in combination with cyclophosphamide, ifosfamide, or dacarbazine, documented an MST of 140 days.[123] A second, larger retrospective study evaluated 64 dogs treated with a standardized protocol of single-agent DOX. The objective response rate was 41% and the biologic response rate (measureable responses plus stable disease), or "clinical benefit," was 68%. The MST for treated dogs was 116 days and was significantly improved compared to the MST of 12 days for the 76 untreated contemporary control dogs.[124]

Patients presenting with non-resectable and/or higher stage HSA represent a therapeutic challenge and little information exists regarding treatment of these patients in large number. Due to a perceived poor prognosis, patients often are not treated; however, data exist to suggest that a subset can respond to therapy. A study of 18 dogs receiving DOX-based chemotherapy for non-resectable subcutaneous HSA reported a response rate of 38% for a median duration of only 53 days.[66] Thus, this approach could represent a more palliative therapy or a possible neoadjuvant therapy to downsize tumors to improve resectability. A more drug-intensive protocol combining dacarbazine, DOX, and vincristine (DAV protocol) was evaluated in 24 dogs with advanced stage inoperable HSA and a response rate of 47.4% was reported, including five complete and four partial responses.[125] The median time to tumor progression was 101 days in this study. Another retrospective study evaluated 67 dogs with stage III (n = 25) or stage I/II (n = 42) treated with a VAC chemotherapy protocol.[126] Of the 25 stage III dogs, primary tumor location varied, but a predilection was noted for the spleen (n = 11), subcutaneous tissue (n = 5), and right atrium (n = 4). The overall MST for the 67 dogs was 189 days and interestingly, there was no significant difference between MST for the stage III (195 days) and stage I/II dogs (189 days). Response data were available for 28 dogs and the overall objective response rate for these patients was 86%.[126]

Metronomic Chemotherapy

A shift in the paradigm of chemotherapy administration currently is underway. Specifically, the use of metronomic (low dosage, continuous) chemotherapy is becoming more commonplace and has been evaluated in canine HSA.[127] Conventional chemotherapy typically involves the use of cycles ("pulses" or "bursts") of

chemotherapy given at the maximally tolerated dose (MTD) with long breaks to allow normal cells to recover from damage. Conversely, metronomic chemotherapy utilizes continuous (typically once daily) administration of chemotherapeutics at a dosage well below the MTD, without prolonged drug-free breaks.[127-131] A key feature of metronomic chemotherapy is compression of the drug administration schedule with the cumulative dose being significantly less than with MTD-based chemotherapy, the result of which should be a favorable toxicity profile and the potential for long-term administration without interruption. Unlike MTD chemotherapy, where the tumor cells are the primary targets of therapy, metronomic therapy appears to target cells of the tumor microenvironment including the endothelial cells that support and nourish the tumor. In this context, the chemotherapeutics may act as anti-angiogenic agents.[127-131] The mechanisms of action include direct apoptosis for dividing endothelial cells, suppression of the mobilization of circulating endothelial progenitor cells (CEPs) from the bone marrow, and increasing production of the body's own natural angiogenesis inhibitors.[127-131] Furthermore, metronomic chemotherapy has been shown to selectively inhibit and deplete T-regulatory (Tregs) lymphocytes, thereby decreasing immune tolerance.[127-131] A pilot study evaluated a metronomic protocol consisting of cyclophosphamide, etoposide, and piroxicam in nine splenectomized dogs with stage II HSA. The MST of 178 days compared favorably to an MST of 133 days in 24 dogs with stage II HSA treated with splenectomy and five doses of adjuvant DOX.[127] No severe adverse effects were noted in the dogs treated with the metronomic chemotherapy protocol. Furthermore, dogs with macroscopic primary and metastatic hemangiosarcoma treated with metronomic lomustine (CCNU) had a median survival of 120 days, with no actual measureable responses documented.[132] In another study, low-dosage administration of chlorambucil resulted in stable disease in 3 of 5 dogs with macroscopic HSA.[133] Finally, minocycline is an antibiotic with mild antiangiogenic activity that has been found to be safe in combination with adjuvant AC chemotherapy in dogs with HSA. However no improvement in survival was noted in comparison to controls.[134]

Cyclooxygenase Inhibitors

Cyclooxygenases (COXs) catalyze the initial rate-limiting steps in the conversion of arachidonic acid to prostaglandins and thromboxanes. Two isoforms of this enzyme have been identified: COX-1 and COX-2. Research has shown that COX-2 plays a significant role in the development and progression of cancer, and as such, it represents a novel antineoplastic therapeutic target.[135-139] COX-2 inhibitors are commonplace as part of metronomic protocols and they have documented activity as single agents for certain cancers, specifically carcinomas.[138-142] Unlike most canine carcinomas surveyed so far, canine HSA typically does not appear to overexpress COX-2.[143] However, because COX-2-inhibiting nonsteroidal anti-inflammatory drugs have shown clinical efficacy against other tumors that do not overexpress COX-2, it is reasonable to use them both as part of metronomic chemotherapy[127] and in combination with conventional chemotherapy for HSA. In fact, the addition of a selective COX-2 inhibitor, deracoxib, has been evaluated as part of a protocol for dogs with HSA treated with standard DOX therapy.[111] An overall median survival of 150 days was noted and the dogs with stage III disease had a median survival of 149 days, which is longer than previously reported for dogs with this more advanced presentation of disease.[111]

Novel Therapies

Immunotherapy

Immunotherapy has long been a field of active research in human cancer medicine and more recently it has become of increasing interest in veterinary oncology (see ch. 341). Immunotherapy strategies include biologic response modifiers, recombinant cytokines, and tumor vaccines.[144] A small number of studies investigating immunotherapies in canine HSA have been published. For example, the use of a novel tumor vaccine was evaluated in conjunction with DOX in 28 dogs with various presentations of HSA. The vaccine consisted of lysates from an allogeneic canine HSA cell line mixed with an adjuvant composed of liposome DNA complex. Vaccinated dogs were found to mount strong antibody responses against canine HSA cells, but this response did not translate into improved survival, as the median survival time of 13 dogs with stage II splenic HSA that received the tumor vaccine plus DOX chemotherapy was 182 days.[145] The combination of the AC protocol and the immunomodulator L-MTP-PE resulted in a significant increase in disease free survival and overall survival time (277 days) compared to dogs receiving chemotherapy with placebo liposomes.[116] This improvement was most evident in dogs that presented with Stage I HSA, while dogs with Stage II HSA did

not appear to derive significant additional survival benefit beyond that achieved with DOX-based chemotherapy alone.[116] As noted above, L-MTP-PE currently is not commercially available, thus limiting its clinical use.

Molecular Targeted Therapy

Understandably, given the failure of chemotherapeutic and immunotherapeutic approaches to significantly improve outcomes of dogs with visceral HSA, the potential for the use of more targeted therapies provides a new area of investigation for this disease (see ch. 342). Exploiting the angiogenic nature of this cancer is one such avenue, and analysis of canine HSA cell lines, tumor samples, and blood/effusion samples from dogs with the disease demonstrate active angiogenic pathways.[6,7,46,48] Furthermore, expression of receptor tyrosine kinases including stem cell factor receptor (KIT), platelet derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR) family members has been documented.[52-57] Targeted small molecule inhibitors such as masitinib, which blocks the function of KIT and PDGFR, demonstrated growth inhibition and the ability to induce apoptosis in canine HSA cell lines *in vitro*.[146,147] The challenge, as with many agents initially evaluated in the *in vitro* setting, is that the drug concentrations required for this effect are unlikely to be achieved *in vivo* without significant toxicosis. Two other small molecule inhibitors—imatinib, which blocks KIT and PDGFR, and dasatinib which blocks KIT, PDGFR, and SRC—also have demonstrated activity against HSA cell lines *in vitro*.[54] Furthermore, imatinib demonstrated significant growth inhibition of canine HSA xenografts in mice. Toceranib phosphate (Palladia) is another small molecule inhibitor that blocks signaling of KIT, PDGFR, and VEGFR family members. Toceranib has demonstrated activity against multiple tumor types, including mast cell tumor, anal sac adenocarcinoma, metastatic osteosarcoma, nasal carcinoma, thyroid carcinoma, and oral squamous cell carcinoma.[148-150] A recent prospective study evaluated the impact of toceranib administration on progression-free survival in 31 dogs with stage I or II HSA following splenectomy and single agent DOX treatment. Disappointingly, there was no significant improvement in median disease free interval (DFI = 161 days) or overall survival (MST = 172 days) for dogs receiving maintenance toceranib.[151]

Natural Products

Alternative therapies using natural products have become a novel source of investigation in HSA. Yunnan Baiyao is a Chinese herbal medicine that, anecdotally, was utilized to control bleeding in dogs with HSA. An *in vitro* study evaluated the effects of Yunnan Baiyao in three canine HSA cell lines and documented a dose- and time-dependent cell death via caspase-mediated apoptosis.[152] Polysaccharopeptide (PSP), the bioactive agent from the mushroom *Coriolus versicolor*, has putative *in vitro* and *in vivo* antitumor effects.[153] In a recent double-blind, randomized, multi-dosage pilot study, high-dose PSP significantly delayed the progression of metastases and improved survival times for canine HSA patients when compared with historical control data of dogs undergoing surgery alone.[154] Although this study's results were promising, it is important to point out that each group contained only five dogs.

Summary

As discussed above, there is variation in the presentation and associated prognoses with the different anatomic forms of HSA. Regardless, HSA remains one of the most aggressive and lethal cancers in companion animals. Certainly, surgical tumor removal followed by adjuvant DOX chemotherapy, as is the current treatment of choice for splenic HSA, remains the approach that is most likely to provide the longest survival benefit for any anatomic presentation of this neoplasm. However, the emergence of more novel therapies could hold promise for potential improvements in historically stagnant survival times associated with this cancer.

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CHAPTER 348

Bone and Joint Tumors

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Canine Appendicular Osteosarcoma

The four primary bone tumors are osteosarcoma (OSA), chondrosarcoma (CSA), fibrosarcoma (FSA), and hemangiosarcoma (HSA).[1] Liposarcoma, rhabdomyosarcoma, plasma cell tumors (solitary plasmacytoma and multiple myeloma), and lymphoma also can involve bone, but more typically as a secondary process.[1] OSA is the most common primary bone tumor, accounting for more than 85% to 98% of all appendicular bone tumors.[1,2] OSA can also occur primarily in the axial skeleton and extraskeletal tissues, including visceral organs, skin, and mammary glands.

OSA is a tumor of unknown cause. Repetitive injury to the physis has been proposed, due to the high incidence of OSA in the metaphyseal region of large-breed dogs with late-closing physes. However, published evidence fails to support this theory.[1,3] Other potential causes include viral transmission and a genetic predisposition.[1,4] OSA has been reported in association with previous fractures and/or implants, particularly in the femoral diaphysis, and in other bone diseases such as infarcts and bone cysts.[4] An association between tibial plateau leveling osteotomy (TPLO) and proximal tibial OSA has been proposed, but this is more likely due to the mechanisms associated with fracture-associated sarcomas than to the TPLO procedure specifically.[5,6] Radiation-induced OSA also has been documented and could be associated with protocols involving radiation doses >3.5 Gy per fraction (see ch. 340).[1]

Signalment

Appendicular OSA usually is a disease of large to giant breeds of dogs.[1] OSA also affects smaller breeds, but they are 20 times less likely to develop OSA.[7] Breed predispositions have been reported; however, size, and particularly height, are more important risk factors than breed.[1,8] Neutered dogs, regardless of sex, have a twofold greater risk of developing OSA compared with sexually intact dogs.[8] The age distribution at diagnosis is bimodal, with most dogs between 7 and 9 years of age and a smaller population between 1 and 2 years of age.[1,8]

Diagnosis

Lameness and localized limb swelling are the most common signs.[1] Pain and lameness are caused by microfractures, disruption of the periosteum with tumor extension, and pathologic fracture.[1] Appendicular OSA occurs in the metaphyseal region of long bones. The thoracic limb is involved 1.7 times more frequently than the pelvic limb.[1,9] The distal radius (23.1% of OSA cases) and proximal humerus (18.5%) are the two most common sites for OSA.[1,9] In the hindlimb, OSA occurs in the tibia and femur with equal frequency. The femur is the most common site in dogs weighing <15 kg.[7]

An orthopedic examination (see ch. 353) is necessary to localize the source of lameness and differentiate metaphyseal pain from other common diseases (e.g., osteoarthritis, cranial cruciate ligament rupture, hip dysplasia). Physical examination and a minimum database consisting of a complete blood count, serum biochemistry profile, and urinalysis are important to evaluate general health status and ability to tolerate surgery and chemotherapy.

Regional radiographs are recommended to establish a tentative diagnosis and differentiate primary bone tumors from other orthopedic diseases. Three basic types of OSA exist: endosteal, periosteal, and

parosteal.[1,10] Periosteal and parosteal OSA are rare and arise from the surface of long bones.[1,10] Endosteal OSA is far more common.[1] The radiographic appearance of endosteal OSA can range from lytic to blastic, and it is usually a mixture of both patterns.[1,10] Other characteristic radiographic signs of primary bone tumors include cortical lysis; periosteal proliferation; palisading new bone formation perpendicular to the axis of cortical bone (sunburst effect); periosteal lifting due to subperiosteal hemorrhage (Codman's triangle); loss of the fine, trabecular pattern in metaphyseal bone; and pathologic fracture with metaphyseal collapse.[1,10] Appendicular FSA and CSA have a similar radiographic appearance to OSA and cannot be differentiated radiographically. However, classic signalment and radiographic findings are often sufficient for the diagnosis of a primary bone tumor.[1,10]

Differential diagnoses for primary bone tumors include fungal osteomyelitis, especially *Coccidioides immitis* (see ch. 232) and *Blastomyces dermatitidis* (see ch. 233).[1,10] A thorough history is necessary to determine whether the dog lives in or has traveled through an area where fungal disease is endemic. Dogs with fungal osteomyelitis often have systemic illness and polyostotic bone disease.[1,10] Conversely, dogs with primary bone tumors rarely show signs of systemic illness, and bone involvement usually is confined to one site.[1,10] Bacterial osteomyelitis, atypical bone cysts, and metastatic neoplasia are other potential differential diagnoses.

Bone biopsy can be performed to confirm the diagnosis using closed (see ch. 92) or open techniques.[11-16] Fine needle aspiration (FNA; see ch. 93), with or without ultrasound guidance, is a useful, minimally invasive technique to diagnose sarcoma and differentiate primary bone tumors from metastatic disease and fungal osteomyelitis.[11-14] Core aspirate cytology using a bone marrow biopsy needle has a 95% success rate for the diagnosis of OSA in dogs compared to 85% for FNA cytology.[13] The use of alkaline phosphatase (ALP) staining following either FNA or core aspirate cytology has had a 100% sensitivity for the diagnosis of OSA.[12,13] Closed-needle core biopsy, using either a Jamshidi needle or a Michele trephine, is invasive and requires general anesthesia.[1] Biopsies should be planned and performed meticulously, preferably by the primary surgeon, so the biopsy does not compromise surgical options.[1] The biopsy should be performed to ensure that the biopsy tract can be excised en bloc with the tumor and that unaffected tissues are not contaminated during the biopsy procedure or by postbiopsy hematoma formation.[1] Large core samples can be obtained with a Michele trephine, resulting in a diagnostic accuracy rate of 94%, but the larger bone defect also increases the risk of pathologic fracture.[1,15] Bone biopsies procured with a Jamshidi needle have an accuracy rate of 82%, and the smaller-gauge needle decreases the risk of complications and creates a much smaller biopsy tract.[16] Two to four biopsy samples should be collected from the center and periphery of the lesion through a single stab incision in the skin. The risk of pathologic fracture increases if the biopsy needle penetrates both the near and far cortices.[1] Multiple specimens increase diagnostic accuracy, because small samples can be misdiagnosed due to the heterogeneity of OSA.[1] Central bone biopsies are recommended, because the peripheral aspects of bone tumors often contain reactive bone.[1] After definitive surgery, the entire tumor should be submitted for histologic analysis to confirm the diagnosis.

Appendicular OSA is a highly aggressive tumor. More than 60% of dogs will eventually die because of metastatic disease; however, <15% of dogs have clinically detectable metastasis at the time of initial diagnosis.[1] Metastasis occurs primarily hematogenously, particularly to the lungs and other bone, although metastasis to regional lymph nodes is reported in 4.4% of dogs with OSA.[17,18] Palpation of regional lymph nodes, thoracic radiographs, and nuclear scintigraphy are essential tools for thorough staging of dogs with a suspected primary bone tumor (Figure 348-1). The presence of detectable metastatic disease markedly influences the management options for dogs with OSA.[1,19-21] High-detail, three-view inspiratory thoracic radiographs, including right and left lateral and ventrodorsal or dorsoventral projections, are required for the diagnosis of pulmonary metastases.[1,10] Lesions ≥7 mm in diameter can be detected with good-quality radiographs.[1,22] Computed tomography (CT) provides greater sensitivity to detect metastatic lesions, but has been associated with false-positive diagnoses of metastases.[1,19,22-24] Pulmonary metastatic lesions are detected significantly more frequently with thoracic CT scans (28%-64%) compared to three-view thoracic radiographs (5%-52%).[23,24] However, while the number of metastatic nodules has a significant influence on survival time, the presence of pulmonary metastatic lesions on CT scan has not been significantly associated with survival time.[23] Whole-body bone scintigraphy, using radiolabeled technetium pertechnetate, is highly sensitive for the detection of concurrent skeletal abnormalities, including both primary and metastatic

tumors, but it is not specific for the diagnosis of neoplasia.[1,20,21] In one study, a second asymptomatic bone lesion, consistent with metastatic disease, was identified in 7.8% of 399 dogs with OSA.[21] If a suspicious lesion is identified, fine-detail radiographs of the region should be obtained. Bone biopsy may be performed for confirmation if radiographic results are equivocal. Alternatively, survey radiographs of the skeleton, consisting of lateral radiographs of long bones and ventrodorsal radiographs of the pelvis, can screen for bone metastases if scintigraphy is unavailable.[25] When present, metastatic skeletal disease is a negative prognostic indicator. This becomes extremely important when limb amputation is planned, because occult skeletal metastases may become clinically symptomatic after surgery, rendering the dog nonambulatory.

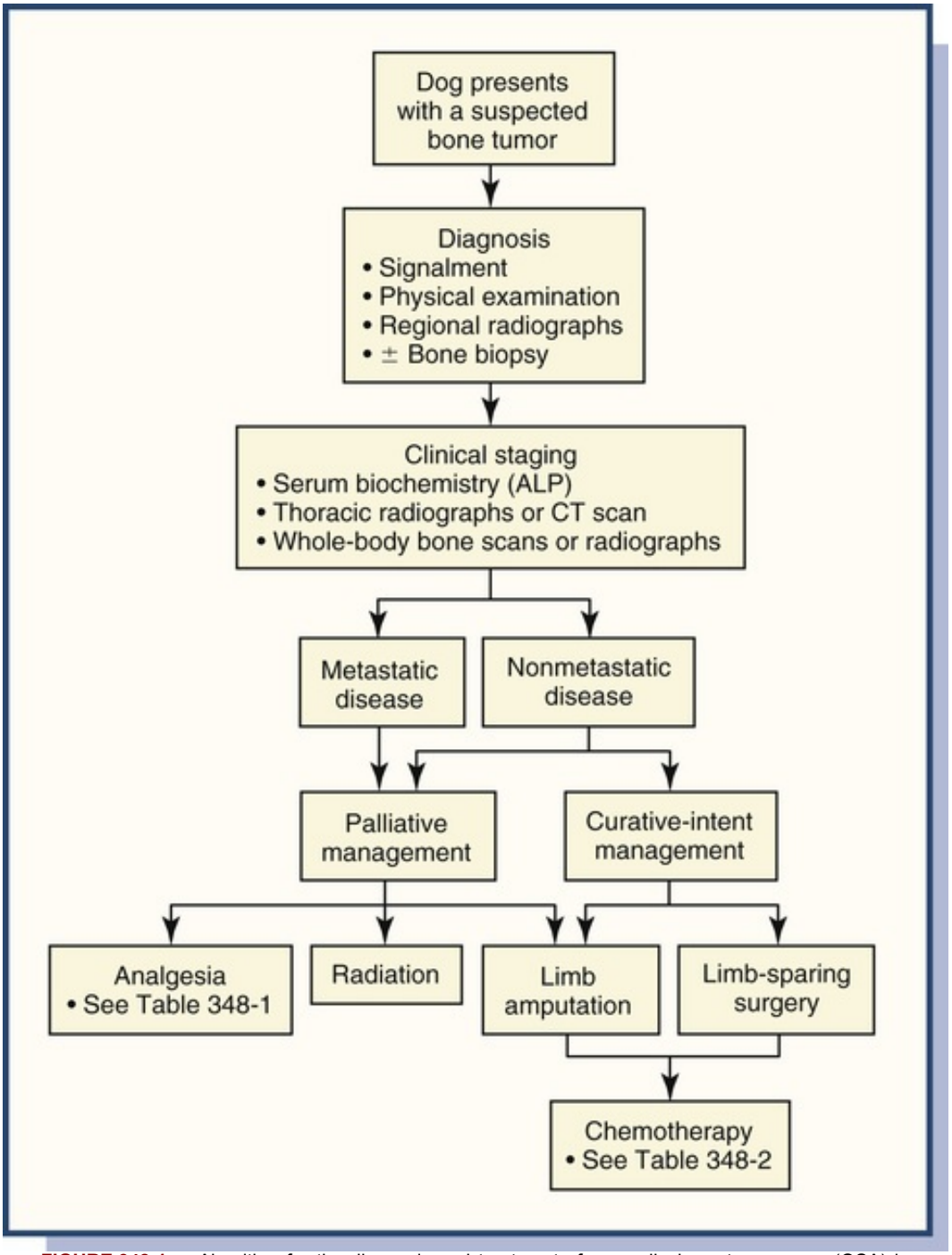


FIGURE 348-1 Algorithm for the diagnosis and treatment of appendicular osteosarcoma (OSA) in dogs. This algorithm would not be correct for non-OSA long bone tumors. *ALP*, Alkaline phosphatase; *CT*, computed tomography.

Treatment

Palliative Management: General

Management options for dogs with appendicular OSA can be classified into two pathways: palliative-intent or curative-intent (E-Figure 348-2). Palliation is indicated for dogs with metastatic disease, or when owners do not want to pursue more intensive treatment options. Palliative therapy is geared toward management of pain and lameness associated with the primary bone tumor but does not improve survival time. Analgesia is the cornerstone for such treatment (Table 348-1).[26] Nonsteroidal antiinflammatory drugs (NSAIDs) may initially be sufficient to manage pain and improve quality of life (see ch. 164). Cyclooxygenase-1-sparing NSAIDs are preferred, as adverse effects are reduced.[26] More potent analgesic drugs, or combinations of drugs, often are required for effective pain relief (see Table 348-1 and ch. 356).[26] Bisphosphonate drugs such as pamidronate have been shown to be safe in dogs and effective in achieving analgesia for >4 months in 28% of dogs, with a 231-day median duration of analgesia when combined with an NSAID.[27,28] Multiple-drug combinations are most efficacious for refractory pain, creating an additive or synergistic analgesic effect. The median survival time (MST) for dogs with appendicular OSA treated with analgesic drugs alone has not been reported, although anecdotal evidence suggests that 1 to 3 months is a reasonable expectation.

TABLE 348-1

Oral and Transdermal Analgesic Drugs Used for the Palliation of Dogs with Appendicular Osteosarcoma[26-28]

ANALGESIC DRUG	DOSAGE	INTERVAL	COMMENTS
NSAIDs			
Carprofen	2.2 mg/kg	12 h	Idiosyncratic hepatic failure, gastric ulceration, kidney injury, and lethargy
Deracoxib	1-2 mg/kg	24 h	Gastric ulceration, kidney injury
Etodolac	10-15 mg/kg	24 h	Gastric ulceration, kidney injury
Meloxicam	0.05-0.1 mg/kg	24 h	Gastric ulceration, kidney injury
Ketoprofen	0.5-1 mg/kg	24 h	Gastric ulceration, kidney injury, and platelet aggregation inhibition
Piroxicam	0.3 mg/kg	48 h	Gastric ulceration, kidney injury
Partial Agonists			
Butorphanol	0.55 mg/kg	1-2 h	Controlled substance; short duration of activity, ceiling effect of analgesia, sedation, and respiratory depression
Opioids			
Morphine	0.5-1 mg/kg	8-12 h	Controlled substance; sedation, euphoria, bradycardia, vomiting, urine retention, and constipation
Fentanyl patch	50 mcg/h (10-20 kg)	72 h	Controlled substance; variable serum concentration due to application site, skin blood flow and temperature, and hydration; correct disposal required, as residual dose can be lethal to humans
	75 mcg/h (20-30 kg)	72 h	
	100 mcg/h (>30 kg)	72 h	
Miscellaneous			
Pamidronate	1-2 mg/kg	28 days	Bisphosphonate drug with antiosteoclastic and possible antineoplastic activity; analgesic effect best when combined with an NSAID; contraindicated with kidney disease

Tramadol	2-5 mg/kg	8-12 h	Constipation with chronic use, lethargy at high doses
Codeine-acetaminophen	0.5-2 mg/kg	6-8 h	Controlled substance, anemia
Amantadine	3 mg/kg	24 h	NMDA antagonist
Prednisone	0.5-1 mg/kg	12-24 h	Anti-inflammatory, synergistic activity with opiates, contraindicated with NSAIDs
Amitriptyline	1-2 mg/kg	12-24 h	Tricyclic antidepressant, alters serotonin and norepinephrine activity

NMDA, N-methyl-D-aspartate; *NSAIDs*, nonsteroidal anti-inflammatory drugs.

E-FIGURE 348-2 A photograph of a dog 6 months after forequarter amputation for a proximal humeral osteosarcoma. Quality of life is often excellent following limb amputation in large-breed dogs, despite their size and body weight and frequent preexisting osteoarthritis.

Palliative Radiation Therapy

Radiation therapy (see ch. 240) is effective for palliation of dogs with primary bone tumors. Many different protocols have been described, most commonly 4 to 10 Gy administered on a 0-7-21–day or monthly protocol.[29-36] These protocols are relatively inexpensive and do not require prolonged hospitalization. Radiation reduces local inflammation, minimizes pain, slows progression of metastatic lesions, and improves quality of life in dogs with primary and metastatic lesions.[29-36] A 50% to 92% response rate has been reported, with the median onset of response 11 to 14 days after initiation of radiation therapy and median duration of response lasting 53 to 130 days.[29-36] The duration of response is significantly improved when <50% of bone length is affected by tumor. Primary bone tumors located in the proximal humerus[32,33] and distal radius[35] have been reported to have better responses. Higher cumulative doses, higher intensity of treatment, and the addition of chemotherapy to palliative radiation protocols have been reported to improve rate and duration of response.[31-33,36] Palliative radiation therapy is not associated with acute effects and does not negatively influence quality of life.[29-36] The MST for dogs with appendicular OSA treated with palliative radiation is 122 to 313 days.[29-36] Radiopharmaceuticals, such as samarium, have been used for the palliation of primary and metastatic bone lesions, but they are expensive and are not widely available in veterinary medicine.[37-39] The

combination of palliative radiation and pamidronate has been recommended, but one study showed a significantly decreased MST in dogs receiving this treatment (122 days) compared to palliative radiation therapy alone or combined with chemotherapy (307 days).[36]

Limb Amputation

Limb amputation can be used as palliative therapy and as part of the curative-intent treatment in dogs with primary bone tumors.[1,17,40,41] Amputation is an effective means of pain control, particularly in dogs with pathologic fracture and lameness unresponsive to analgesic drugs or radiation therapy. Osteoarthritis, neurologic disease, obesity, and large body size have been cited as relative contraindications.[1,40,41] Experience has shown that osteoarthritis, weight, and body size are rarely problematic. Most dogs with OSA are middle-aged to older, large-breed dogs with moderate preexisting osteoarthritis. They rarely have difficulties following amputation (see E-Figure 348-2 and ch. 355).[41] Dogs with neurologic disease or severe signs of osteoarthritis are exceptions, and palliative management or limb-sparing techniques should be considered in these dogs.

When the thoracic limb is amputated, the scapula should be removed, because tumor control is better, particularly for dogs with proximal humeral OSA, and cosmetic appearance is improved.[1] In the pelvic limb, coxofemoral disarticulation should be performed for dogs with OSA distal to the proximal femur, whereas dogs with proximal femoral OSA should be treated with either en bloc acetabulectomy or subtotal hemipelvectomy to achieve adequate tumor control and minimize the risk of local recurrence.

Most dogs are able to ambulate unassisted within 12 to 24 hours after limb amputation. Amputees should be encouraged by the owners to ambulate at home after discharge to speed recovery. Studies have shown that most dogs fully adapt to amputation by 4 weeks after surgery. If the dog was significantly lame from the tumor prior to surgery, full recovery often occurs more quickly than 4 weeks. In addition, a positive attitude by the owners shortens the time to adaptation after amputation.[41] Body weight and thoracic or pelvic limb amputation do not have a significant influence on the time to adaptation after amputation; however, early in the postoperative period, dogs with thoracic limb amputation have greater difficulty in balancing.[41] Behavioral changes, such as increased anxiety and loss of dominance, have also been observed but are relatively uncommon.[41] Complications associated with limb amputation are rare. Intraoperative complications can include hemorrhage, air embolism, and inadvertent thoracotomy (during forequarter amputations). Possible postoperative complications include infection, seroma formation, and stump recurrence. The survival time of dogs treated with amputation alone is significantly better than with the use of analgesic drugs or palliative radiation therapy.[14] The MST for dogs with OSA treated with limb amputation alone is 103 to 175 days with a 6-month survival rate of 47% to 52%, a 12-month survival rate of 11% to 21%, and a 24-month survival rate of 0% to 4%.[17,42-45] The MST of 257 days is longer for small breed dogs with appendicular OSA treated with amputation alone.[46]

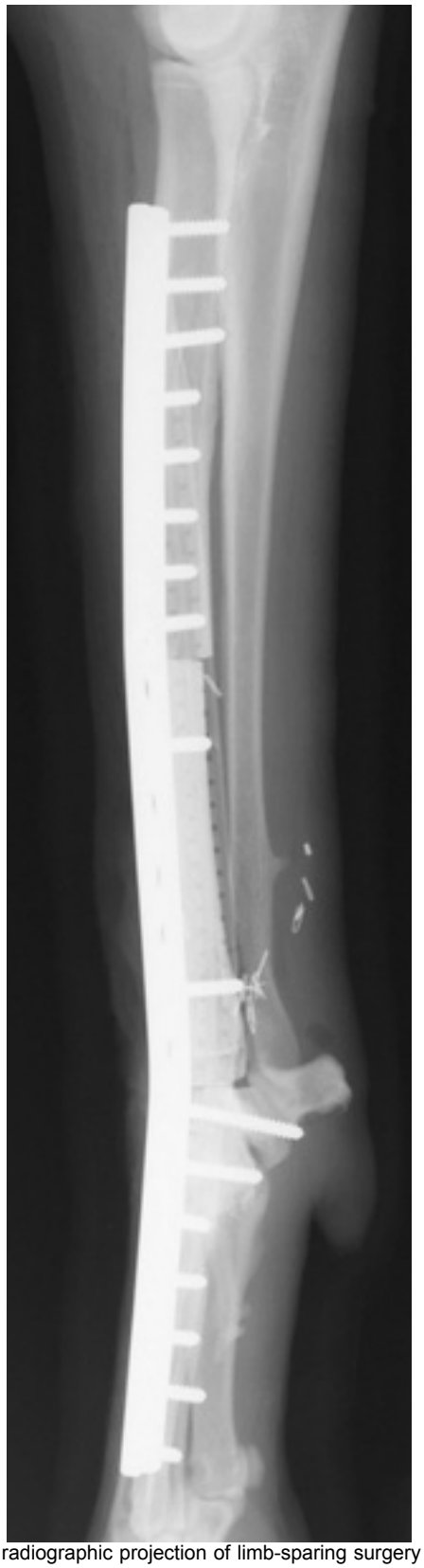
Limb-Sparing Surgery

Limb-sparing techniques are more common despite the success of limb amputation in dogs with primary bone tumors.[1,40,47-61] The most common reason for limb sparing in dogs with OSA is owner reluctance to proceed with amputation. Medical indications for limb sparing include previous amputation of another limb, severe concurrent osteoarthritis, or neurologic disease.[1,40]

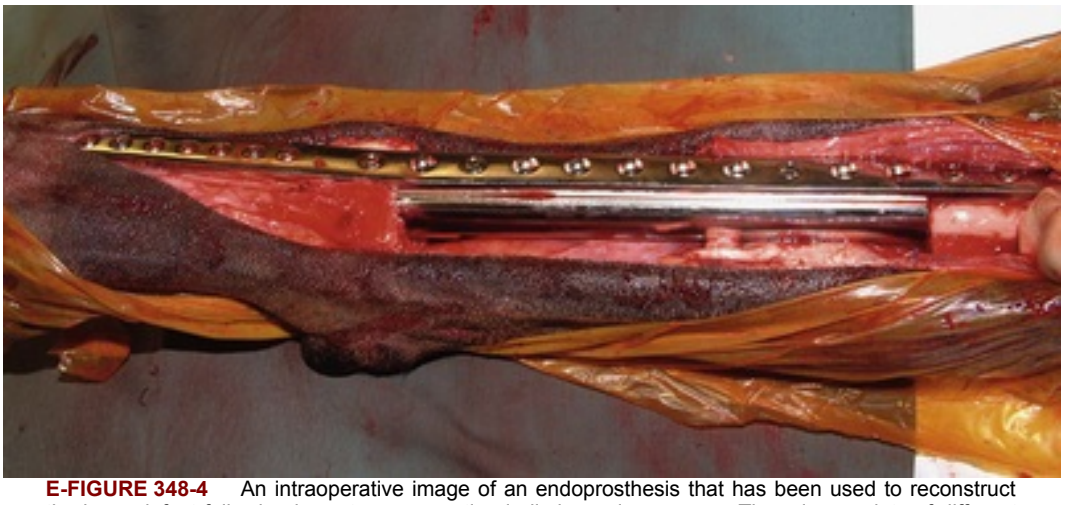
Limb-sparing surgery is most successful for dogs with primary bone tumors in the distal radius and ulna.[40,47-58] Limb-sparing surgery for other anatomic locations is often associated with a high complication rate and poor postoperative limb function.[55-58] Candidates for limb-sparing surgery include dogs with tumors confined to the bone, minimal extension into adjacent soft tissue, and involvement of <50% of the bone length.[1,40] The extent of bone involvement is most accurately determined using CT scans;[62] bone involvement is overestimated by radiographs, nuclear scintigraphy, and magnetic resonance imaging (MRI).[62-64] Pathologic fractures are a relative contraindication due to local contamination via hemorrhage and hematoma, although the risk of local tumor recurrence can be reduced by preoperative chemotherapy or radiation therapy.[40]

Many surgical techniques have been reported to preserve limb function.[1,40,47-58] After marginal resection of the soft-tissue component of the bone tumor, the osseous defect is filled with a massive cortical allograft (E-Figure 348-3), endoprosthesis (E-Figure 348-4), vascularized ulnar graft, pasteurized or irradiated autograft,

or segmental bone transport osteogenesis.[1,40,47-58] Arthrodesis of the adjacent joint often is required;[1,40] pancarpal arthrodesis is well tolerated in dogs, but arthrodesis of the shoulder, stifle, or tarsal joint results in poor limb function. Joint preservation is possible with OSA of the ulna or diaphysis of any other long bone,[65] and joint-preserving limb-salvage options may become more popular as total joint arthroplasties are adapted for oncologic applications.[66] Weight-bearing and range-of-motion exercises can be started immediately postoperatively, but activity should be restricted to leashed walks for the first 4 weeks.[1,40] Exercise is important to prevent flexure contracture of the digits and to minimize swelling of the paw and digits (see ch. 355). Good to excellent limb use is achieved in >75% of dogs.[1,40,47-49]



E-FIGURE 348-3 Lateral radiographic projection of limb-sparing surgery of the distal radius using a cortical allograft.



E-FIGURE 348-4 An intraoperative image of an endoprosthesis that has been used to reconstruct the bone defect following bone tumor resection in limb-sparing surgery. There is a variety of different limb-sparing techniques, and this procedure is becoming more common in the treatment of dogs with distal radial bone tumors.

The most commonly reported complications with limb-sparing surgery are implant failure, local tumor recurrence, and infection.[1,40,47-59] Implant failure occurs in up to 40% of cases, and techniques exist for reducing the risk of this complication.[49] Local tumor recurrence is caused by incomplete resection or, more commonly, by residual neoplastic cells remaining in the soft tissue adjacent to the tumor capsule.[1,40] Local recurrence has either no effect[49] or a negative influence on survival time,[57] depending on the study cited. Infection is the most significant postoperative complication encountered with limb-sparing surgery, occurring in up to 70% of limb-spare cases where reconstruction is performed with nonautogenous techniques.[1,40,47-61,68] Several different bacteria have been cultured.[61] Initially, infections are treated with appropriate antibiotics based on sensitivity results, isotonic saline lavages, and wet-to-dry bandages.[1,61] Further options include implantation of antibiotic-impregnated methylmethacrylate beads for persistent infection, or limb amputation for uncontrollable infection.[1,59,61]

A variation on limb-sparing surgery is internal or external fixation of pathologic fractures. In a study of 16 dogs, limb use immediately after surgery was good to very good in all but 2 dogs.[69]

Radiation Therapy

Radiation therapy (see ch. 340) most commonly is used for palliation, but it can be used for control of the primary bone tumor in dogs where surgical options are either not indicated or refused.[70-72] Stereotactic radiation has been used successfully for appendicular OSA in a variety of locations.[70] A steep-dose gradient of radiation is administered locally, with the center of the lesion receiving 45 to 60 Gy and the periphery 30 to 35 Gy.[70] Full-course external-beam radiation therapy has been investigated,[71,72] with total doses ranging between 24 to 54 Gy.[71,72] Complications following both stereotactic and full-course radiation include moist desquamation, alopecia, depigmentation, bone marrow suppression, and pathologic fracture.[70-72] The MST for dogs with OSA treated with stereotactic and curative-intent radiation therapy and adjuvant chemotherapy is 363 days and 7 months, respectively.[70-72] Fracture following stereotactic radiation is a relatively common complication and can be treated with internal fixation.[73]

Chemotherapy

Definitive management of dogs with appendicular OSA requires treatment of both the local bone tumor and micrometastatic disease. The efficacy of chemotherapy in other types of primary bone tumors is less clear. Surgery, unless combined with chemotherapy, is considered palliative.[42-45] Conversely, chemotherapy without surgery does not provide a survival benefit over other palliative techniques, although improved MSTs have been reported with the combination of palliative radiation therapy and chemotherapy.[74,75] In most oncology practices, chemotherapy is initiated at the time of suture removal, but this can vary from prior to surgery, perioperatively, to up to 21 days after surgery.[76] Current chemotherapy protocols include the use

of cisplatin, carboplatin, doxorubicin, and gemcitabine, either as a single agent or in combination (Table 348-2).[1,42-45,76-88] Studies have not shown differences in survival times among the different protocols using single or multiple agents[86,87]; however, carboplatin alone had a significantly longer disease-free interval (DFI) than alternating carboplatin-doxorubicin protocols in one study[86] and was associated with significantly fewer adverse effects in another study.[87] Practically speaking, protocol selection often depends on drug cost, adverse effects, and intensity of treatment. While these chemotherapy agents are administered IV, a single SC infusion of carboplatin has been reported in 17 dogs with appendicular OSA following limb amputation with a MST of 365 days.[89] If cisplatin is used, saline diuresis is necessary to minimize the risk of nephrotoxicosis (Table 348-3).[1] Nephrotoxicosis can also be reduced by using carboplatin instead of cisplatin or concurrently administering amifostine.[1,81-83,90] Doxorubicin has been associated with myocardial toxicosis, particularly with cumulative doses greater than 180 mg/m^2. Therefore, a cardiac evaluation (echocardiogram, serum cardiac troponin-I level, or both) is recommended prior to starting chemotherapy, especially in high-risk breeds.[1,90a,90b]

TABLE 348-2

Chemotherapy Protocols Used in the Management of Dogs with Appendicular Osteosarcoma[42-45,76-88]

AGENT(S)	DOSAGE	INTERVAL	NUMBER	COMMENTS
Cisplatin	70 mg/m2	3 weeks	5	Vomiting during administration, nephrotoxicosis, gastrointestinal toxicosis, mild myelosuppression; nadir at 10 days; MST 262-413 days
Carboplatin	300 mg/m2	3 weeks	4	Myelosuppression, gastrointestinal toxicosis; nadir at 11-14 days; MST 321-366 days
Doxorubicin	30 mg/m2	2-3 weeks	5	Anaphylaxis during administration, gastrointestinal toxicosis, myocardial toxicosis, myelosuppression, nadir at 10 days; MST 366 days
Cisplatin Doxorubicin	50 mg/m^2 15 mg/m^2	3 weeks	4	Cisplatin administered on day 1, doxorubicin on day 2; MST 300-540 days
Carboplatin Doxorubicin	300 mg/m^2 30 mg/m^2	3 weeks	6	Carboplatin and doxorubicin administered alternately every 3 weeks for 3 doses each, for a total of 6 doses; MST 388 days

MST, Median survival time.

TABLE 348-3

Saline Diuresis Protocols Used to Minimize Cisplatin-Associated Nephrotoxicosis[1]

PROTOCOL	PHASE I	PHASE II	PHASE III
6-h	Saline, 18.3 mL/kg/h, 4 h	Cisplatin for 20 min	Saline, 18.3 mL/kg/h, 2 h
24-h	Saline, 3.75 mL/kg/h, 16 h	Cisplatin for 16 h	Saline, 3.75 mL/kg/h, 6 h

After administration of chemotherapy, especially after the first dose, dogs should be discharged with antibiotics and antiemetics for palliation of gastrointestinal disease and nausea if needed at home (see ch. 343). A complete blood count should be performed at the time of leukocyte nadir, generally 7 to 10 days after chemotherapy, and immediately before subsequent chemotherapy doses, to assess for myelosuppression. Chemotherapy administration should be delayed, or the dose decreased, if the neutrophil count is <2000/mcL, or platelet count is <100,000/mcL.[1] The MST for dogs treated with surgery and chemotherapy is 235-366 days (12-month survival, 33-65%; 24-month survival, 16-28%).[42-45,76-88] The MST for small breed dogs with appendicular OSA treated with curative intent is 415 days.[46]

The combination of full course chemotherapy and metronomic chemotherapy has been investigated because continuous metronomic chemotherapy might improve outcomes in dogs with OSA. In 30 dogs with

appendicular OSA, metronomic chemotherapy (piroxicam and low-dosage cyclophosphamide) was well-tolerated when combined with either carboplatin alone or alternating carboplatin and doxorubicin, but there were significantly more grade 3 and 4 toxicoses when combined with carboplatin alone.[91]

The role of immunotherapy (see ch. 341) is undefined. A significantly longer DFI and survival time have been reported in dogs treated with a nonspecific immunostimulant, muramyl tripeptide phosphatidylethanolamine.[92,93] The antimicrobial drug suramin plus doxorubicin after amputation for appendicular OSA in 47 dogs was well tolerated, with a MST of 369 days.[88] Increased immune stimulation also is suspected in the prolonged survival times of dogs with infected limb-sparing surgery and four dogs with spontaneous regression of OSA lesions.[49,68,94,95]

Metastasis

Metastatic disease is the most common cause of death or euthanasia in dogs with appendicular OSA after definitive treatment.[1] Pulmonary (Figure 348-5) and skeletal sites are most frequently involved; other metastatic sites include SC tissue, mediastinum, myocardium, diaphragm, kidneys, spleen, small intestine, spinal cord and brain, and lymph nodes.[1,14,17] Interestingly, metastatic disease rarely occurs in dogs undergoing palliative, nonsurgical treatment, but it is the major cause of death in dogs treated with surgery alone, despite the minimal difference in survival time. A recent study, using a mouse OSA model, showed that primary tumor resection enhanced systemic angiogenesis, resulting in progression of distant metastatic lesions.[96] The distribution of metastatic lesions depends on the type of treatment. Pulmonary metastases are more common when only the local tumor is ablated, whereas skeletal metastases are more prevalent when chemotherapy is added to the treatment regimen. Pulmonary metastasis accounts for 61% of all metastatic lesions in dogs treated with amputation alone and 26% when treated with amputation and cisplatin.[17,78] In comparison, skeletal metastases develop in up to 47% of dogs after surgery and postoperative cisplatin.[97]

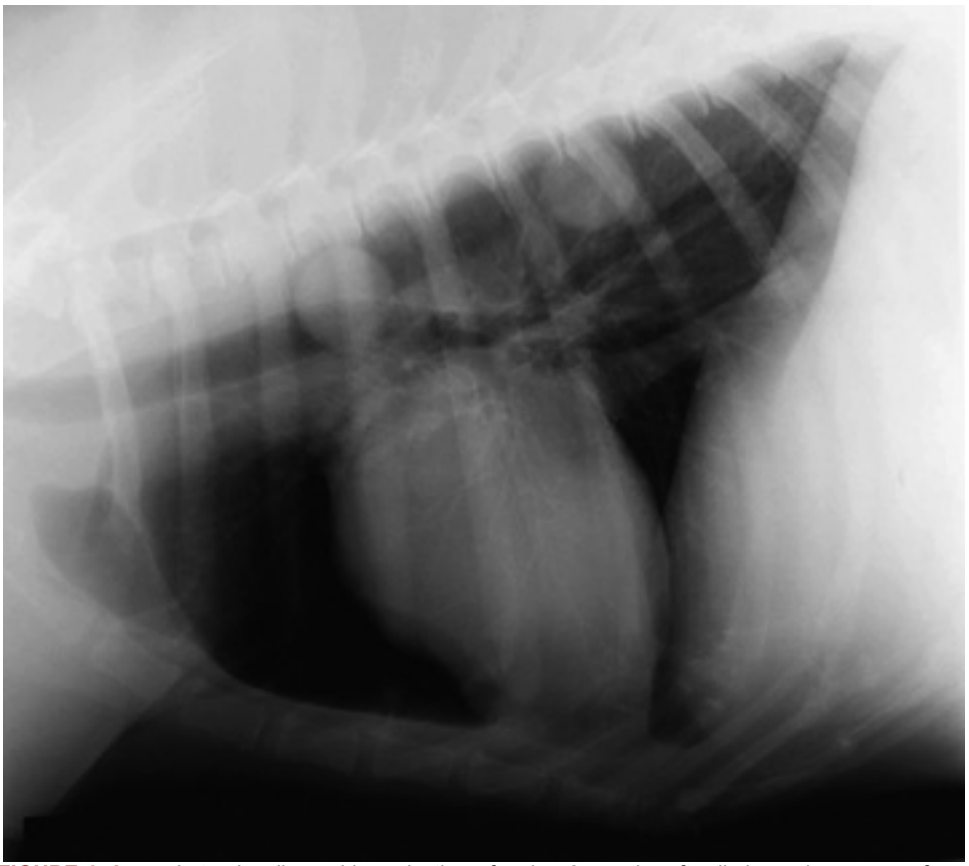


FIGURE 348-5 Lateral radiographic projection of a dog 8 months after limb-sparing surgery for a distal radial osteosarcoma. Two metastatic lesions are seen in the dorsal lung fields.

Generalized malaise is the most common sign in dogs with pulmonary metastasis. Respiratory signs are usually a late development. Occasionally, hypertrophic osteopathy can be the first indication of pulmonary metastasis. Chemotherapy using platinum and antibiotic agents is ineffective in prolonging survival time in dogs with measurable pulmonary metastasis.[97,98] Surgical resection of metastatic lesions, by either subpleural resection or partial lung lobectomy, can significantly improve survival time in select cases (Figure 348-6).[99,100] Candidates for pulmonary metastatectomy include dogs that develop pulmonary metastasis >300 days after initial diagnosis of appendicular OSA, have ≤3 radiographically evident metastatic lesions, have lesions that do not double in size, and have no new lesions develop in a 4-week period.[99] The MST for dogs with metastasis to the lungs is 61 to 95 days when treated with chemotherapy[97,98] and 176 days after metastatectomy.[99] Pulmonary metastatectomy is also recommended for dogs with hypertrophic osteopathy, regardless of the time after diagnosis, as surgical excision of a metastatic lesion can result in immediate resolution of clinical signs.[100]

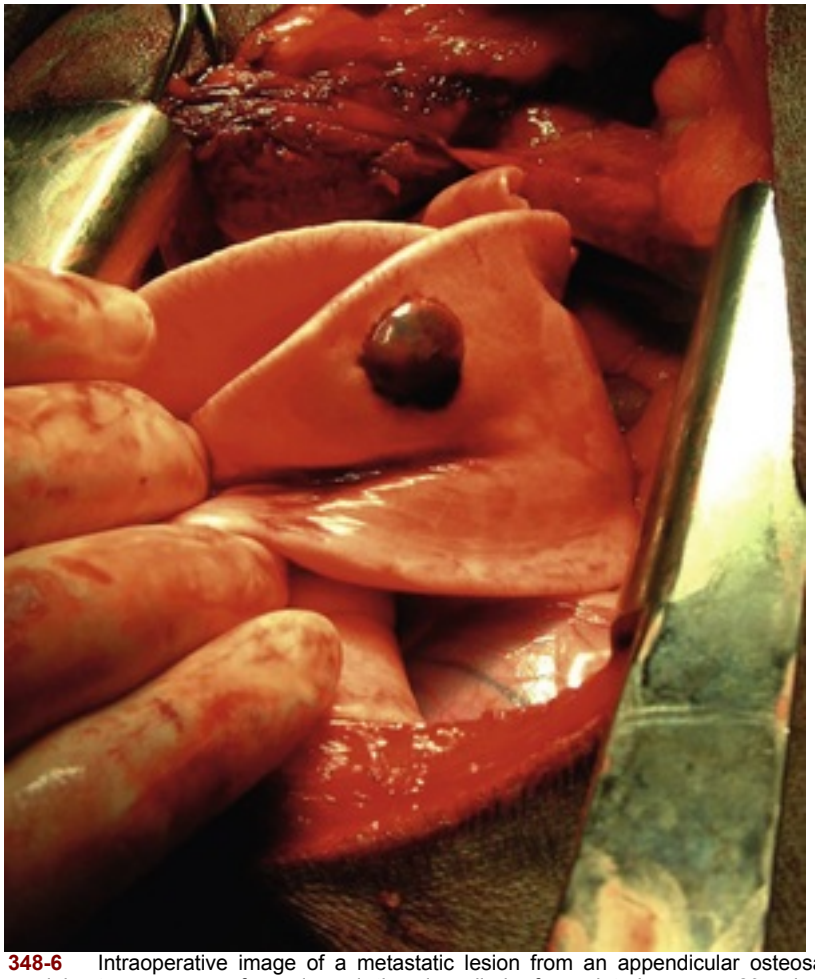


FIGURE 348-6 Intraoperative image of a metastatic lesion from an appendicular osteosarcoma. Partial lung lobectomy was performed, and the dog died of unrelated causes 294 days after metastatectomy.

Management options for dogs with skeletal metastasis include pain control with analgesic drugs, bisphosphonates, and palliative radiation therapy. Bisphosphonates block osteoclast activity, minimizing the risk of pathologic fracture.[27,28,101,102] Dogs with skeletal metastases treated with palliative radiation and chemotherapy have a significantly longer MST (130 days) compared to other palliative treatment modalities and combinations.[103] The combination of pamidronate and an NSAID also can palliate dogs with tumor-related bone pain, with up to 28% of dogs experiencing an analgesic effect for >4 months (median: 231 days).[28] Limb-sparing surgery and curative-intent radiation therapy have been used for treating metastatic skeletal lesions for select cases but are not routinely recommended.[103]

Prognostic Factors

Poor prognostic factors in dogs with OSA include age <7 years or >10 years, body weight >40 kg, large tumor volume, proximal humeral location, increased preoperative total and bone-specific serum alkaline phosphatase (ALP) activity that fails to normalize within 40 days of surgical removal of the tumor, high tumor grade, and presence of metastases.[1,77,84,86,104-107] Dogs with proximal humeral OSA have a significantly shorter DFI and MST than other appendicular OSA sites; however, this could be a function of tumor volume rather than site.[77,86,106,107] The MST for dogs with normal and elevated total serum ALP is 12.5 and 5.5 months, respectively.[105] The MST for dogs with normal and elevated bone-specific serum ALP is 16.6 and 9.5 months.[105] For both bone-specific and total serum ALP, each increase of 100 IU/L increases the risk of death due to OSA by 25%.[104,105] Dogs with limb-sparing-related infection have significantly longer MSTs (685 days) compared to dogs without surgical infections (289 days).[49,68,94] OSA can be histologically subclassified as osteoblastic, chondroblastic, fibroblastic, telangiectatic, and undifferentiated, but histologic subtype has not been shown to be prognostic in dogs or humans.[1]

Canine Appendicular Chondrosarcoma

CSA is the second most common primary bone tumor in dogs.[1] Appendicular CSA accounts for 9-17% of all canine CSA cases.[108-111] The cause is unknown, although CSA has been reported to arise from osteochondroma or sites of previous trauma. Golden Retrievers, German Shepherds, and Boxers are overrepresented. The median age at presentation is 6.0-8.7 years.[108-115] Clinical findings are similar to dogs with appendicular OSA, and biopsy is required to differentiate tumor types. The femur is most commonly involved, and CSA may have a more lytic radiographic appearance than OSA.[110,111] Limb amputation and limb-salvage procedures can be used for managing the local tumor. Metastatic disease is reported in up to 31% of dogs with CSA and is dependent on histologic grade, with distant metastasis reported in 0%, 31% and 50% of dogs with grade I, II and III CSA, respectively.[108-112,115] Chemotherapy does not provide a survival benefit in humans with CSA, and a similar situation probably exists in dogs.[112,113]

The MST for dogs with untreated CSA is 46 days, compared with 540 days to >2618 days for dogs treated with limb amputation alone.[111,112,115] Prognostic criteria in dogs include tumor location and histologic grade.[110,112,114,115] The MSTs for dogs with grade I, II and III appendicular CSA treated with amputation alone are 6.0, 2.7, and 0.9 years, respectively.[115]

Canine Appendicular Fibrosarcoma

FSA is the third most common skeletal neoplasm in dogs and it occurs more commonly in axial than appendicular sites.[109] Two distinct appendicular FSAs exist: central and parosteal.[116] A palpable mass often is present in dogs with parosteal but not central FSA. Parosteal FSA may represent a tumor of soft-tissue origin with secondary invasion into bone.[109,116] The radiographic features of appendicular FSA are similar to OSA, although lytic lesions and pathologic fracture are reported in up to 50% of dogs with FSA.[116] Amputation and limb salvage are the main surgical treatment options. The role of chemotherapy is unknown. Appendicular FSA metastasizes late in the course of disease, often to sites other than the lungs, such as myocardium, pericardium, skin, and other bones.[116] Survival times are difficult to interpret, because >50% of fibroblastic OSAs are misdiagnosed as FSAs.[1,116] The 12-month survival rate for dogs with appendicular FSA treated with limb amputation alone is 66%.[116]

Canine Appendicular Hemangiosarcoma

Skeletal HSA is rare, accounting for 3.6% of all primary bone tumors (see also ch. 347). German Shepherd, Great Dane, and Boxer dogs are overrepresented, with a mean age at presentation of 6.2 to 8.2 years. This is a younger age at presentation than what is reported with most other primary bone tumors.[109] Distribution between appendicular and axial sites is similar, with 43% of cases occurring in the appendicular skeleton.[109,117] The proximal humerus is the most common appendicular site.[117] Skeletal HSA has a different biologic behavior than other primary bone tumors: Most appendicular HSAs have a lytic radiographic appearance, and cortical and periosteal changes may be minimal.[109,117] Polyostotic disease, soft-tissue

extension, and pathologic fractures are common.[109,117] In dogs with appendicular HSA, abdominal ultrasonography and echocardiography are recommended in addition to the other standard staging tests, because 82% of dogs are reported to have extraosseous disease or metastasis.[117] The value of local and systemic treatment is uncertain, because most dogs develop metastases before 6 months, and the 12-month survival rate is <10%.[109,117] However, limb amputation and doxorubicin protocols may be indicated for dogs with nonmetastatic monostotic appendicular HSA.[118] Palliative radiation therapy may be used in dogs with polyostotic disease.

Canine Axial Skeletal Tumors

OSA of the axial skeleton accounts for 25% of all OSA and 59% of OSA in dogs weighing <15 kg.[7,119] However, medium- to large-breed dogs are commonly affected.[118,120] Boxers may be overrepresented, and a female predisposition is reported for all axial sites except the ribs and vertebrae.[119,120] The most common sites of axial OSA are mandible (27% of axial OSA), maxilla (16-22%), vertebrae (7-15%), scapula (13%), skull (11-12%), ribs (10-11%), nasal and paranasal sinuses (9%), and pelvis (4-5%).[119,120] OSA of the hard palate and patella also have been reported.[121,122]

Advanced imaging techniques, particularly CT, are useful for staging and surgical planning. Surgical resection is recommended, although radiation therapy also can be used for local tumor control.[119,120,123] Local recurrence is reported in up to 80% of dogs, and is the most common cause of death. The metastatic rate is 11-46%.[119,120,123-125] The role of chemotherapy is unclear.[119,120,123-130]

The MST for dogs with axial OSA is 120-154 days, with 12- and 24-month survival rates of 26.3% and 18.4%, respectively.[119,120,123] Prognostic factors include anatomic site, body size, breed, increased total serum ALP, and surgical margins.[120,123-130] Smaller-breed dogs have a significantly better survival rate than large-breed dogs.[120] The MST of Golden Retrievers with axial OSA is 100 days, compared with 182 days in purebred dogs and 264 days in mixed-breed dogs.[123] Mandibular OSA has a better prognosis than OSA of the ribs, scapulae, and skull,[120] and in another study, scapular OSA was associated with a 2.8-times increased risk of tumor-related death compared to other non-calvarial axial OSA sites.[131] For dogs with OSA of the mandible, maxilla, or skull, the MST with surgical excision (329 days) is significantly better than with radiation therapy (132 days).[125] Incomplete surgical resection significantly increases the risk of both local recurrence and metastasis.[125-130] The MST after palliative and curative-intent radiation therapy of axial OSA in large-breed dogs is 79 and 265 days respectively,[123] while samarium-153 has been shown to confer a subjective improvement in 4 of 25 dogs with skull tumors.[39]

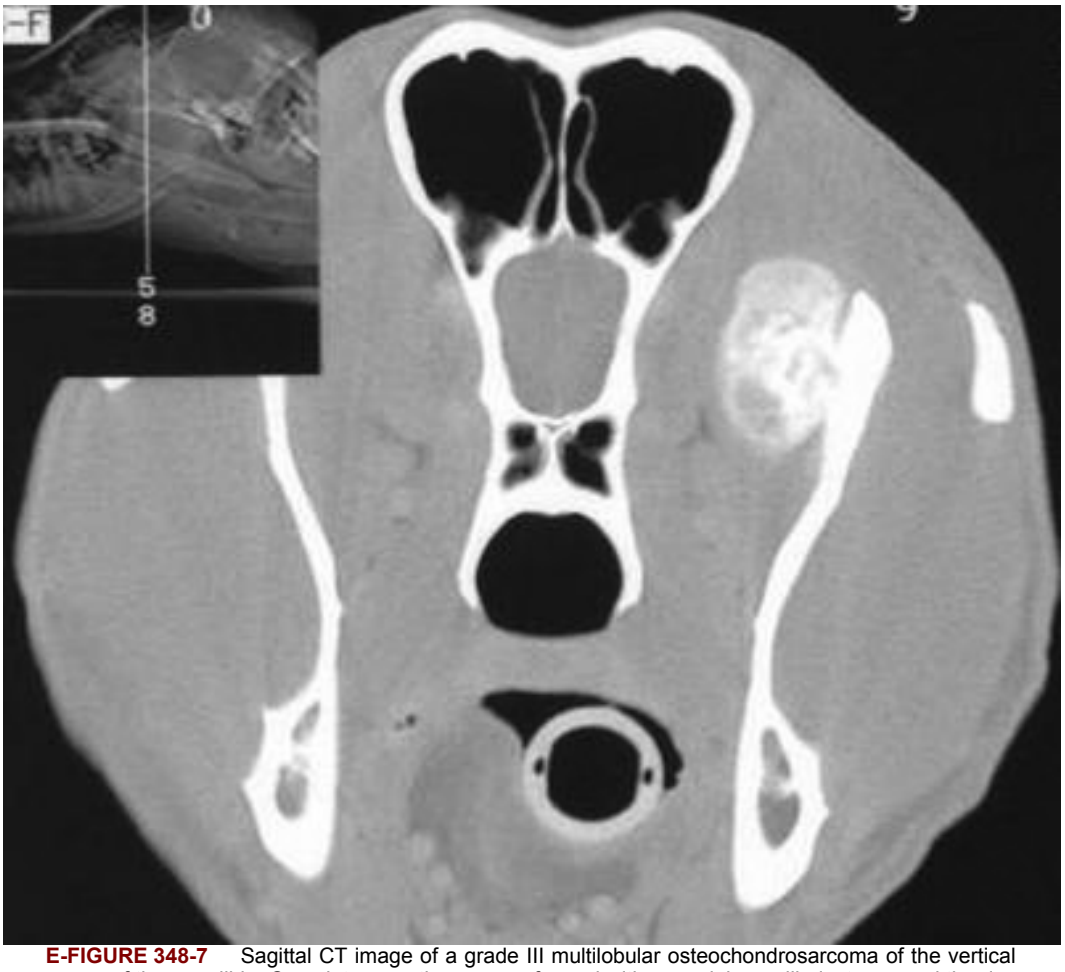
Skull Tumors

OSA of the skull can involve the calvarium, nasal and paranasal sinuses, maxilla, and mandible. Calvarial OSA accounts for 11-12% of axial OSA.[119,120] Signs include a visible external mass and neurologic signs due to extradural compression of the brain; direct invasion of the brain is rare.[1] Surgical resection is recommended after CT imaging. Perioperative complications can include cerebral edema, brain herniation, pneumomeningocele, aspiration pneumonia, and death.

Axial OSA may also involve the maxilla and mandible; however, it is less common than the other tumors affecting these bones. The most common canine oral tumors are malignant melanoma, squamous cell carcinoma, FSA, OSA, and benign epulides, and these are discussed in ch. 272.[126-130]

The most common cause of death in dogs with axial OSA is local tumor recurrence rather than metastasis. Metastasis is reported in up to 30% of skull OSA. The MST for mandibular OSA treated with mandibulectomy is 7-18 months, with a 12-month survival rate of up to 71%.[124,126-128] Postoperative chemotherapy significantly improves survival time in dogs with mandibular OSA.[124] Histologic grade and score are predictive of survival in dogs with mandibular OSA.[124,128] In contrast, the MST for maxillary OSA treated with maxillectomy is 4.5-10 months, with a 12-month survival rate of 17% to 27%.[129,130] Comprehensive surgical excision with complete histologic margins significantly improves local recurrence and survival rates.[125] Postoperative radiation therapy and chemotherapy have not been shown to improve survival, even in dogs with incomplete tumor resection.[123,125] Similarly, samarium-153 has minimal benefit as sole treatment

for canine calvarial OSA or multilobular osteochondrosarcoma (E-Figure 348-7).[39]



E-FIGURE 348-7 Sagittal CT image of a grade III multilobular osteochondrosarcoma of the vertical ramus of the mandible. Complete resection was performed with a caudal mandibulectomy, and the dog was alive and disease-free at the last follow-up 308 days later.

Scapular Tumors

Scapular OSA accounts for up to 13% of all axial OSA.[109,120,121,123] CSA, FSA, HSA, histiocytic sarcoma, and soft tissue sarcoma also have involved the scapula.[110,132-136] Lameness is the most common clinical sign.[136] Radiographic changes are consistent with appendicular OSA, typically with a mixed pattern of lytic and productive changes.[132] However, due to positioning difficulties and superimposition of the body wall, the extent of disease may be difficult to determine with plain radiographs. CT imaging is helpful to determine the location and extent of involvement (Figure 348-8). Partial or total scapulectomy is recommended, with good to excellent limb function after resection of up to 90% of the scapula.[132-136] A high metastatic rate has been reported in dogs with scapular OSA, and postoperative chemotherapy is recommended.[120,121,136]

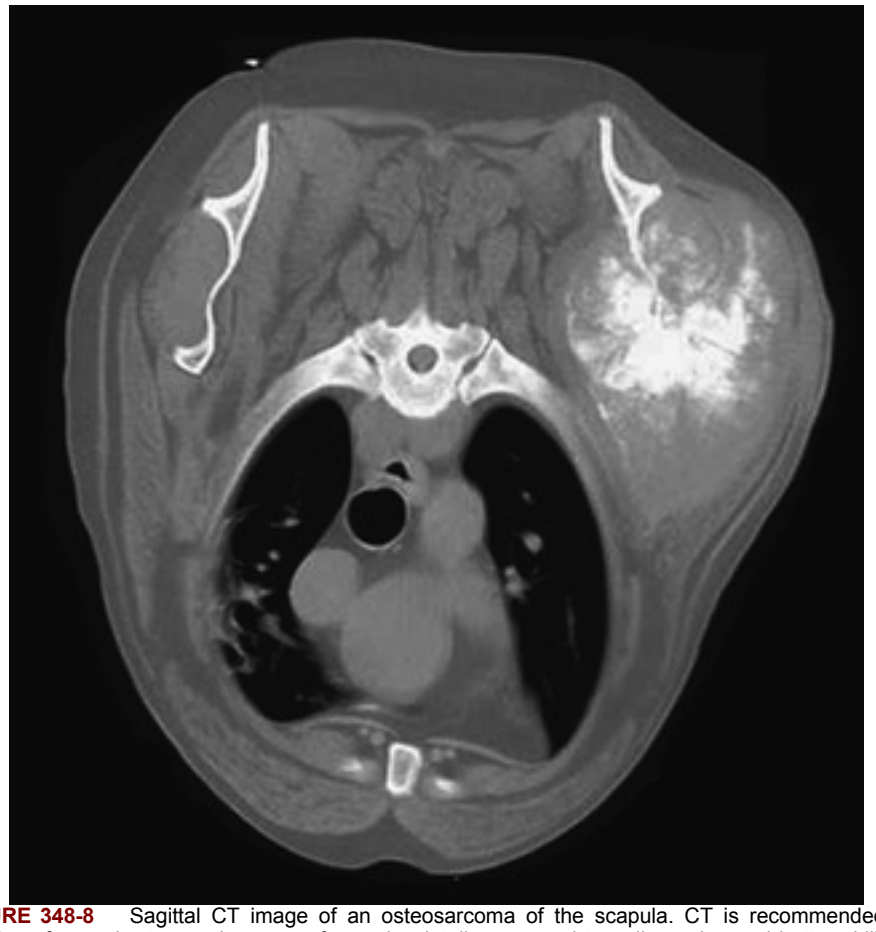


FIGURE 348-8 Sagittal CT image of an osteosarcoma of the scapula. CT is recommended for imaging of scapular tumors because of superior detail, compared to radiographs, and better ability to determine the location and extent of the tumor for surgical planning and the presence of pulmonary metastasis.

Tumors of the Pelvis

OSA of the pelvic bones accounts for 4-6% of axial OSA.[109,119,120] Pelvic FSA, CSA, and OSA occur at similar frequencies.[109,110,111,137,138] Boxer dogs may be predisposed to pelvic CSA.[108] Lameness is common, although tenesmus, due to compression of the rectum, and neurologic deficits, as a result of peripheral nerve compression, have also been observed.[138] Radiographic abnormalities are similar to those of appendicular OSA (Figure 348-9). CT imaging is helpful for local staging and surgical planning.[138] Either subtotal or total hemipelvectomy is the recommended treatment for dogs with pelvic tumors.[137-139] If necessary, the lateral third of the sacrum, lateral to the dorsal sacral foramina, can be resected en bloc with the affected pelvis.[138,139] Limb salvage is possible if the weight-bearing axis can be preserved by internal hemipelvectomy.[139] Chemotherapy should be considered for dogs with pelvic OSA, because the biologic behavior may be similar to that of appendicular OSA.[137,138] In one study, 11/28 dogs treated with hemipelvectomy for pelvic OSA developed metastases and 15 dogs died of tumor-related reasons.[138] The MST for these dogs with pelvic OSA was 533 days with 1- and 2-year survival rates of 51% and 35%, respectively.[138] The MST for dogs with pelvic CSA was 1232 days with a 1-year survival rate of 87%, while the MST for dogs with pelvic and parapelvic soft tissue sarcoma was 373 days, with 1- and 2-year survival rates of 47% and 38%, respectively.[138]

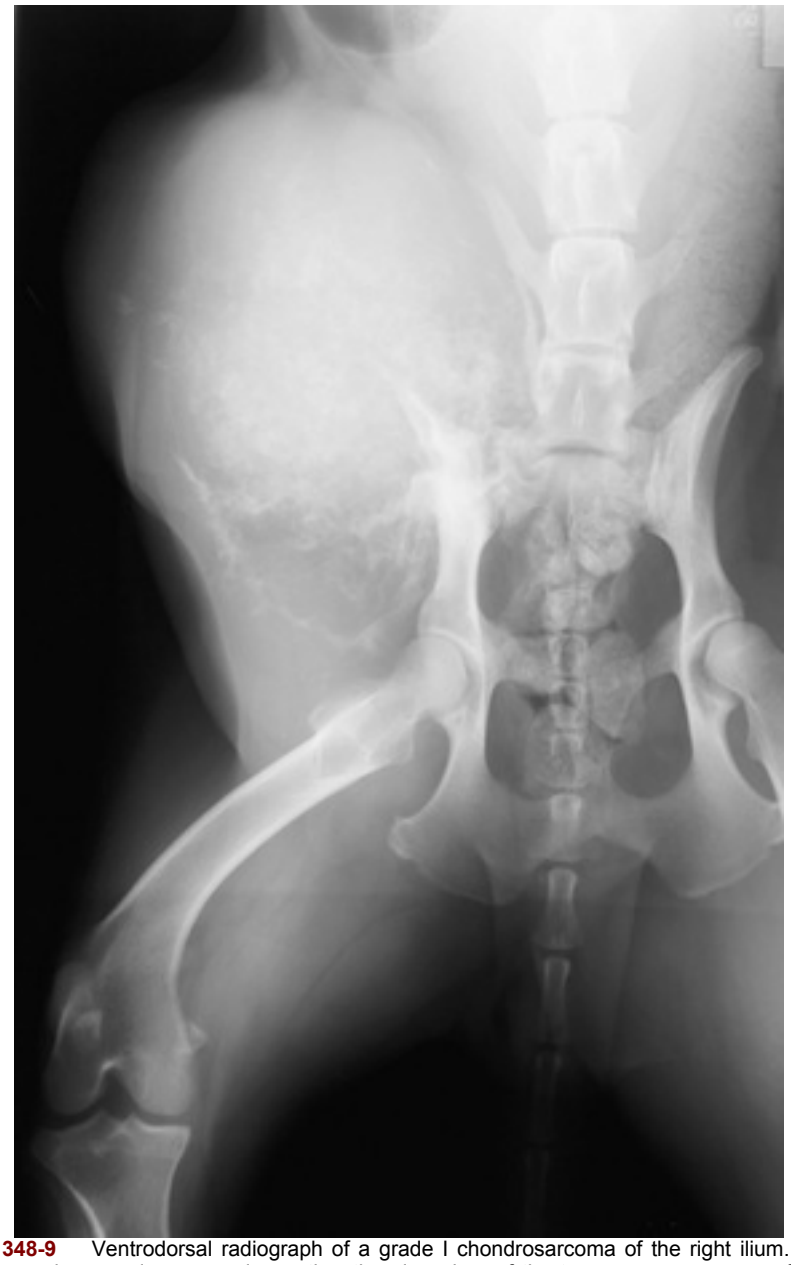


FIGURE 348-9 Ventrodorsal radiograph of a grade I chondrosarcoma of the right ilium. Note the large tumor volume and compression, rather than invasion, of the transverse processes of the sixth and seventh lumbar vertebra. Hemipelvectomy was performed, and the dog was alive and disease-free at the last follow-up 640 days later.

Rib Tumors

Rib tumors are uncommon, and reported tumor types include OSA, CSA, FSA, HSA, multilobular osteochondrosarcoma (MLO; see below), and mast cell tumor (see ch. 349).[1,119,120,123,140-143] OSA is the most common rib tumor, accounting for 73% of rib tumors and 11% of axial OSA.[119,120,140-143] No breed or sex predispositions have been reported, but rib tumors may occur in younger, large-breed dogs with a mean age of 4.5 to 6 years.[119,120,123,140-143]

Rib tumors usually occur in the distal third of the rib, near the costochondral junction.[140-142] A palpable, firm, and fixed mass is the most common clinical sign, although pain and dyspnea are also reported.[143] Radiographic changes include lysis, sclerosis, or a mixture of lytic and blastic patterns, with displacement of adjacent ribs and intrathoracic structures such as the heart and lungs, and medial displacement of the parietal pleura resulting in an extrapleural sign (Figure 348-10).[140-143] Intrathoracic extension and invasion of

pericardium and lung lobes are fairly common.[143] CT is recommended for determining the location and extent of the tumor, potential invasion into adjacent structures, and presence of metastases (E-Figures 348-11 and 348-12). Pulmonary metastasis is common (especially telangiectatic OSA), and up to 45% of dogs with rib OSA have metastases at diagnosis.[140,141] Metastasis was detected in 100% of dogs with rib OSA, 53% to 57% with CSA, 67% with HSA, and 100% of dogs with rib FSA at the time of death.[140,141] Due to the similar biologic behavior of rib and appendicular OSA, rib OSA should be treated with rib resection and postoperative chemotherapy.[141,143] The role of chemotherapy in other tumor types is undefined but warrants consideration due to the high metastatic rate.

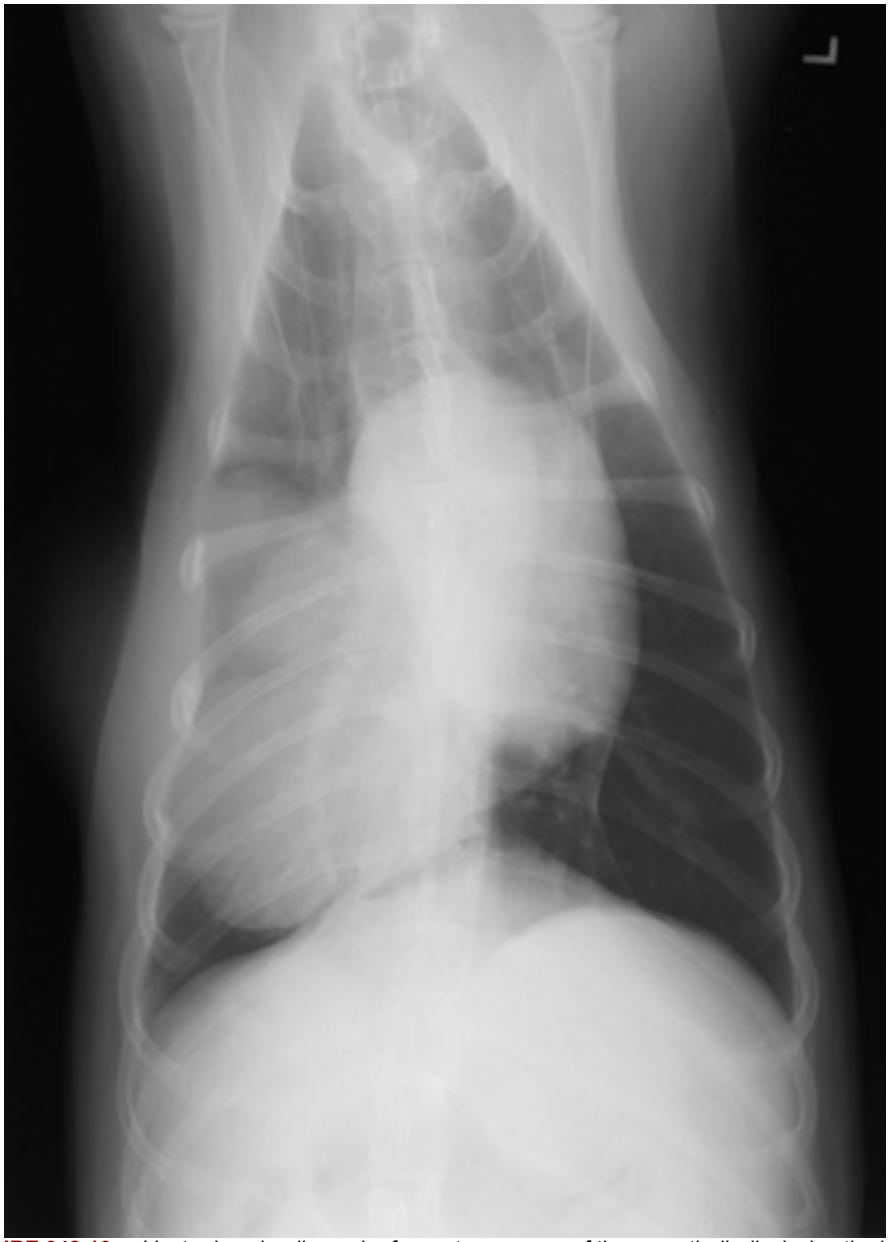
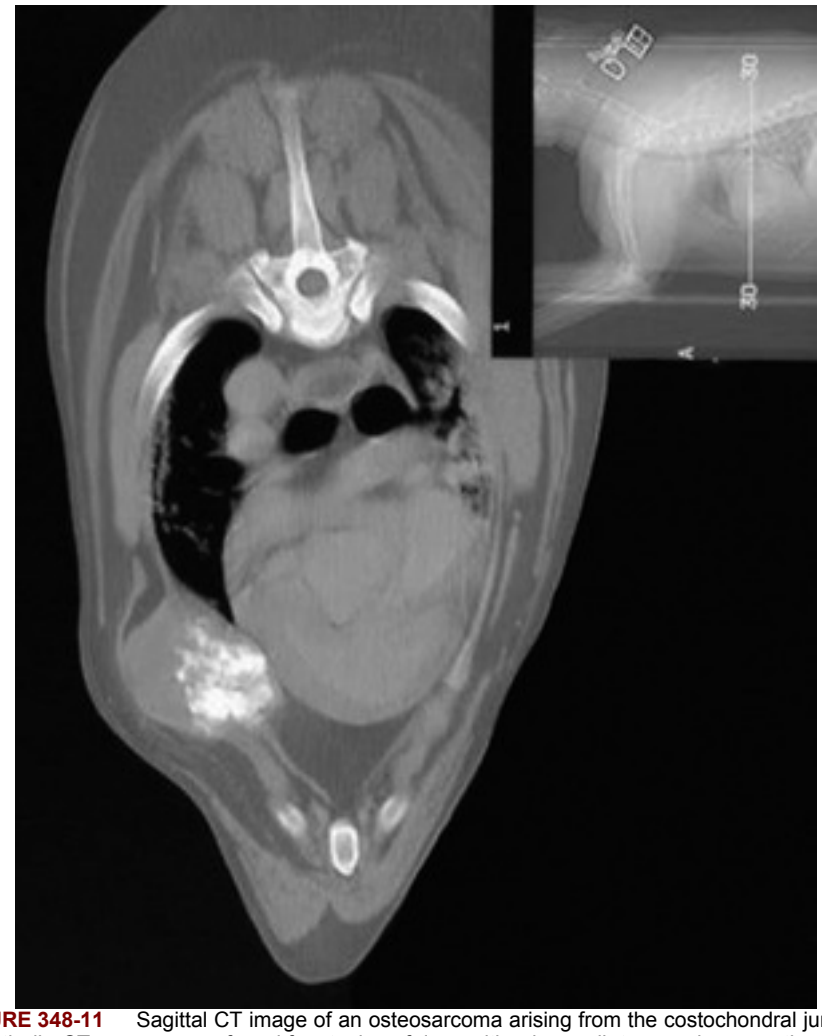
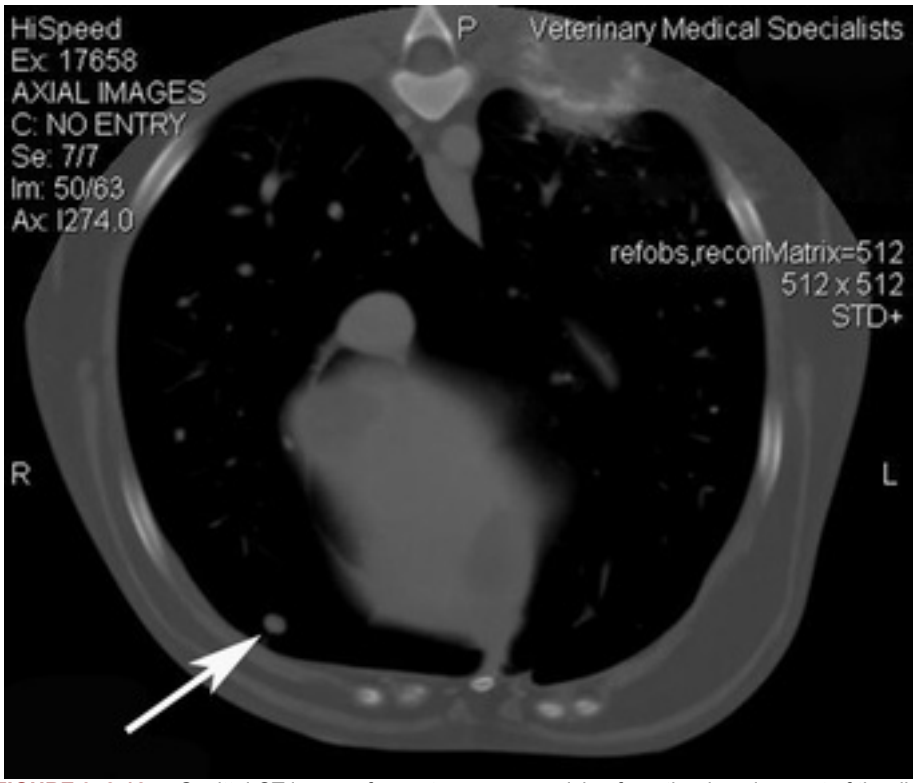


FIGURE 348-10 Ventrodorsal radiograph of an osteosarcoma of the seventh rib displacing the heart and caudal lung lobes to the left side, causing medial displacement of the parietal pleura and resulting in an extrapleural sign.



E-FIGURE 348-11 Sagittal CT image of an osteosarcoma arising from the costochondral junction of the fourth rib. CT scans are preferred for staging of dogs with primary rib tumors, because they provide superior information on the location and extent of the tumor, possible invasion into adjacent pericardium and lungs, and pulmonary metastasis.



E-FIGURE 348-12 Sagittal CT image of an osteosarcoma arising from the dorsal aspect of the rib. A metastatic lesion is visible (arrow). Breath-hold helical CT scans are significantly more sensitive for the detection of metastatic pulmonary nodules, compared to high detail radiographs. This dog also had evidence of tumor invasion into the lung lobe on other CT images.

The MST after rib resection alone for OSA is 90 days; it varies from 1080 days to >1750-3820 days for dogs with CSA.[112,140-143] Most dogs with primary rib CSA can be cured with surgery alone.[112,143] For dogs with primary rib OSA, prognostic factors include preoperative serum total ALP activity and the administration of postoperative chemotherapy. High total serum ALP activity significantly decreases MST, from 675 to 210 days.[143] Postoperative chemotherapy significantly extends MST in dogs with primary rib OSA, to 240-290 days.[141,143] Dogs with incomplete surgical excision are up to 6.7 times more likely to develop local recurrence and possibly metastatic disease.[141,143]

Vertebral Tumors

OSA is the most common extradural tumor of the nervous system and it accounts for up to 16% of axial OSA.[119,120,144,145] Other vertebral tumors include CSA, FSA, HSA, multiple cartilaginous exostoses, lymphoma, liposarcoma, giant cell tumor, plasma cell tumors—either as solitary plasmacytoma or multiple myeloma—and metastatic carcinomas and sarcomas.[144,145] A breed predisposition has not been reported, although German Shepherds, Labrador Retrievers, and Standard Poodles were overrepresented in one study.[144] Large breeds are commonly affected; only 5% of dogs with vertebral tumors weigh <20 kg.[144,145]

Primary vertebral tumors tend to occur in a younger subset of dogs than do metastatic tumors of the vertebrae. The median age for dogs with primary vertebral tumors is 6-8 years, and 8-9 years for secondary tumors.[145] A thorough physical examination (see ch. 2) should be performed to identify possible occult primary tumors. Carcinomas of the mammary and thyroid glands, bladder, and prostate, and visceral HSAs, are known to metastasize to the vertebrae. Thoracic and lumbar vertebrae are most commonly involved.[144] Soft-tissue tumors, particularly histiocytic sarcomas (see ch. 350), can secondarily involve the vertebrae.

Pain and neurologic deficits (see ch. 259) are the two most common signs in dogs with vertebral tumors.[144,145] Neurologic deficits are caused by compression of the nerve roots or spinal cord (see ch. 267).[144,145] Neurologic signs are typically slowly progressive, but pathologic fracture can cause an acute deterioration. A neurologic scoring system has been devised and is prognostic for outcome and survival.[145]

A spectrum of radiographic changes is observed in dogs with vertebral tumors. These changes can be difficult to detect due to inconsistent vertebral shape and superimposition of overlying ribs and soft tissue.[144] Cortical lysis with vertebral body collapse is a characteristic finding in primary vertebral tumors but a late event in metastatic tumors.[144,145] Skip and multiple tumors are reported in up to 25% of dogs with vertebral OSA and can be difficult to differentiate from metastatic tumors.[144] Osteochondromas are well-circumscribed, benign lesions that frequently involve the dorsal lamina and spinous process rather than the vertebral body.[146]

Imaging techniques include myelography, CT, MRI, and nuclear scintigraphy.[147] Nuclear scintigraphy can identify the location of single and multiple lesions but cannot differentiate multifocal OSA from multiple metastatic lesions. Furthermore, most plasma cell tumors are photopenic due to marked osteolysis and minimal new bone production. Myelographic changes include collapse of the subarachnoid space and unilateral or asymmetric cord displacement (Figure 348-13).[144] Advanced imaging is best for evaluating vertebral involvement (Figure 348-14), but differentiating intradural and extradural involvement can be difficult.[147] Surgical resection with vertebrectomy is rarely feasible, although dorsal decompression can provide meaningful palliation in dogs with localized dorsal tumors.[145,148] Radiation therapy, either with palliative or curative intent, can be beneficial in dogs with vertebral tumors.[145] The role of chemotherapy is unknown, even in dogs with vertebral OSA, because most dogs are euthanized due to the local tumor rather than metastatic disease.[145]

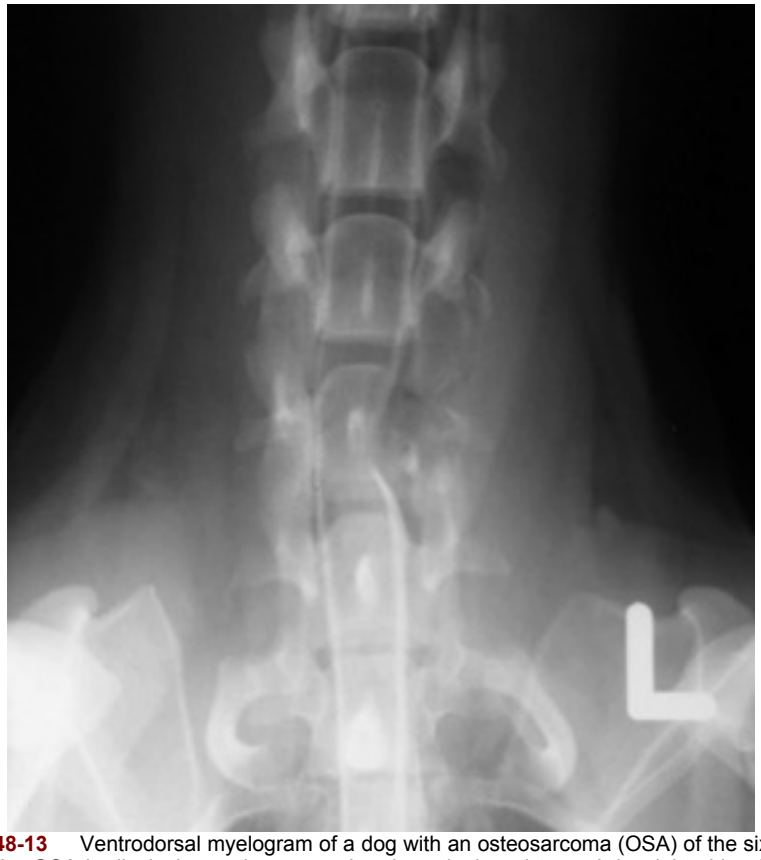


FIGURE 348-13 Ventrodorsal myelogram of a dog with an osteosarcoma (OSA) of the sixth cervical vertebra. The OSA is displacing and compressing the spinal cord toward the right side of the spinal canal.

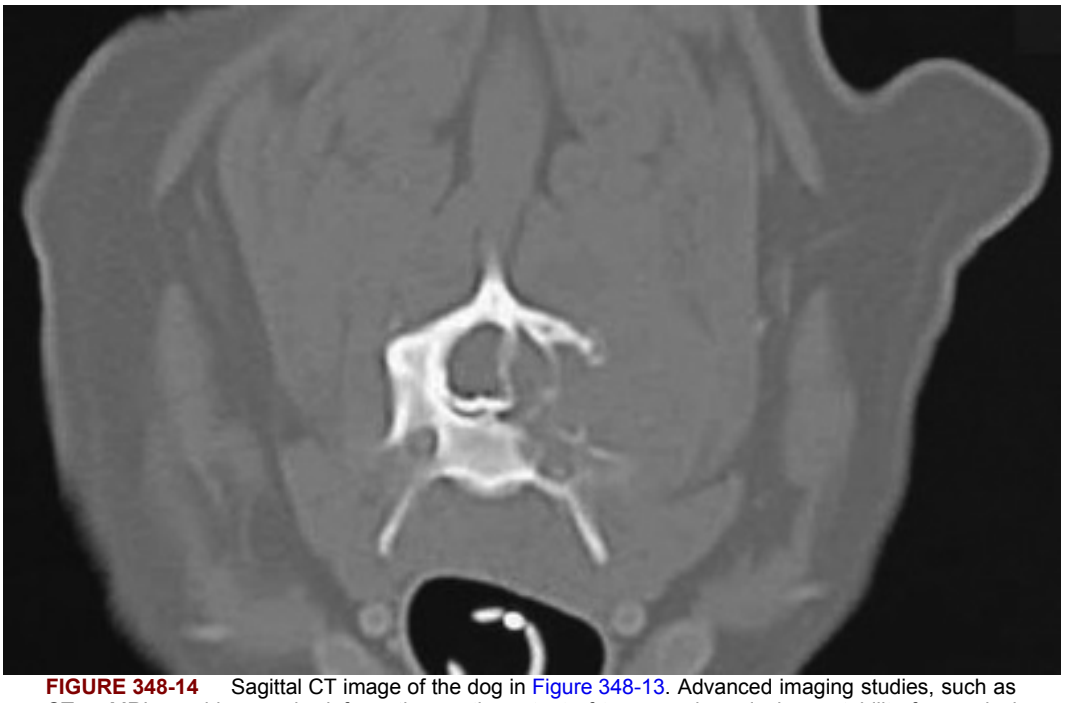


FIGURE 348-14 Sagittal CT image of the dog in Figure 348-13. Advanced imaging studies, such as CT or MRI, provide superior information on the extent of tumor and surgical resectability for surgical and/or radiation planning.

The MST for dogs with malignant vertebral tumors is 135 days.[145] Survival time is not significantly influenced by preoperative neurologic score, tumor type (OSA or FSA), primary or metastatic disease, anatomic location (cervical, thoracic, or lumbar), chemotherapy, or radiation therapy.[145] Although not significant, neurologic score can provide useful information, as dogs with a preoperative score of 1 had a survival time of 330 days, compared with 120 days if the neurologic score was greater than 1.[145] Furthermore, dogs with a posttreatment neurologic score of 1 or 2 were 12 times more likely to survive than dogs with a posttreatment score of 3 or 4.[145] Curative-intent radiation therapy provides a significant improvement in survival time compared to palliative radiation, with survival times of 150 and 15 days, respectively.[145]

Multilobular Osteochondrosarcoma (MLO)

MLO is an uncommon tumor arising from the periosteum of bones formed by intramembranous ossification.[149,150] The skull is most commonly involved, including the calvarium, orbit, zygomatic arch, mandible, and maxilla.[149,150] Other sites include the pelvis, ribs, and hard palate. Cats have also been reported with MLO.

MLO usually is a disease of middle-aged, large-breed dogs.[149,150] No known sex or breed predisposition exists. Clinical signs are dependent on tumor location and include a palpable firm and fixed mass, neurologic signs with calvarial MLO, pain on opening of the jaw with mandibular and zygomatic arch MLO, exophthalmos with orbital MLO, and dyspnea with MLO of the tympanic bulla.[149,150] The imaging changes associated with MLO are characteristic, with the tumor described as having a "popcorn" appearance with well-defined borders and a lobulated pattern on both radiographs and CT scans.[149-152] Advanced imaging is indicated for surgical planning of calvarial MLO, because the extent of intracranial involvement can be extensive (Figure 348-15).[149,150]

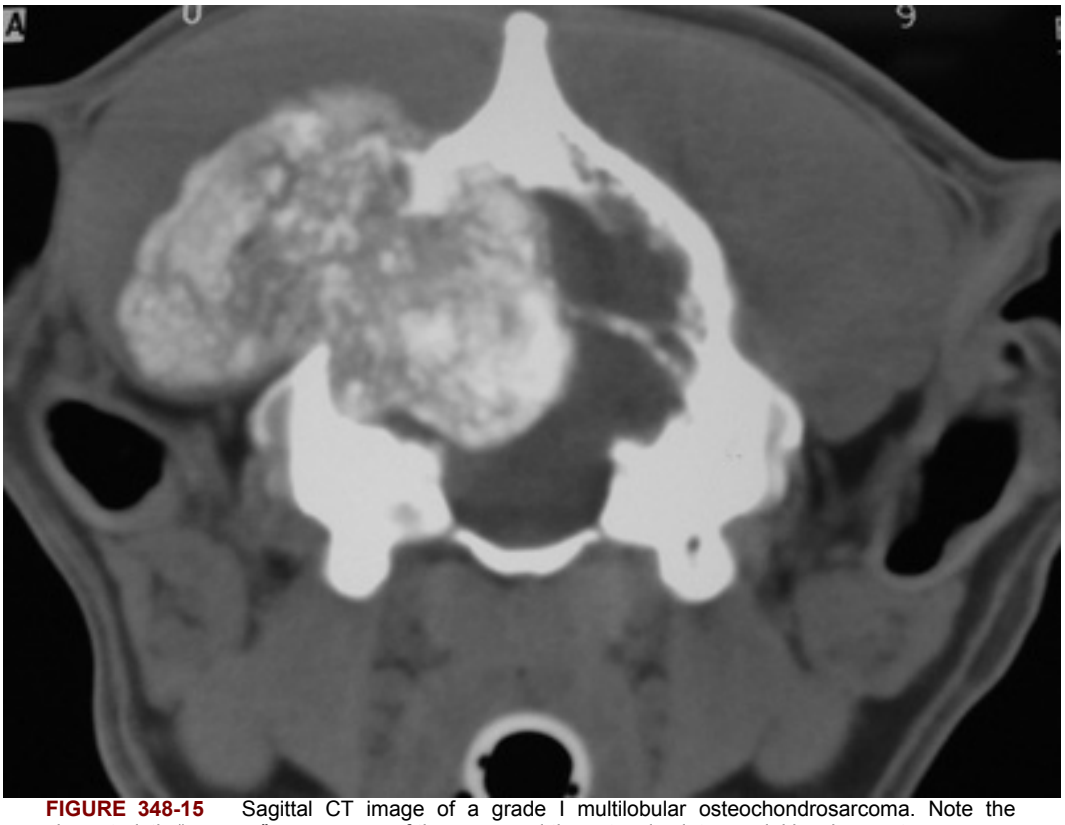


FIGURE 348-15 Sagittal CT image of a grade I multilobular osteochondrosarcoma. Note the characteristic "popcorn" appearance of the mass and the extensive intracranial involvement.

Treatment options include surgical resection and radiation therapy.[149,150] Cranioplasty has been described after calvarial resection but may not be necessary. Neurologic recovery, particularly with marked intracranial involvement, can be prolonged, although most dogs return to normal function within 2 weeks. MLOs grow slowly, usually resulting in a relative resistance and poor response to radiation therapy. Variable preliminary responses have been reported using external-beam radiation therapy and radiopharmaceuticals.[39,150]

A histologic grading scheme for MLO is prognostic for local recurrence and metastasis.[120] Other prognostic factors include site and completeness of surgical resection.[149,150] The rate of local recurrence is 47-58%, with a median DFI of 426-797 days, depending on histologic grade.[149,150] The local recurrence rate for grade I MLO is 30%, with grade II it is 47%, and with grade III, 78%.[149,150] A comprehensive surgical approach is recommended, because incomplete resection significantly increases the risk of local recurrence. The median DFI after incomplete resection is 330 days, but median DFI was not reached and was greater than 1332 days with completely resected MLO.[149,150]

The MST for untreated MLO is 24 days, compared with 669 to 797 days for surgically resected MLO.[149,150] Tumor site is prognostic, with mandibular MLO having a significantly better MST than other sites: 1487 days for mandibular MLO and 528 days for nonmandibular MLO.[150] The MST for grade I MLO is greater than 897 days, whereas the MST for grades II and III MLO is 520 and 405 days, respectively.[150]

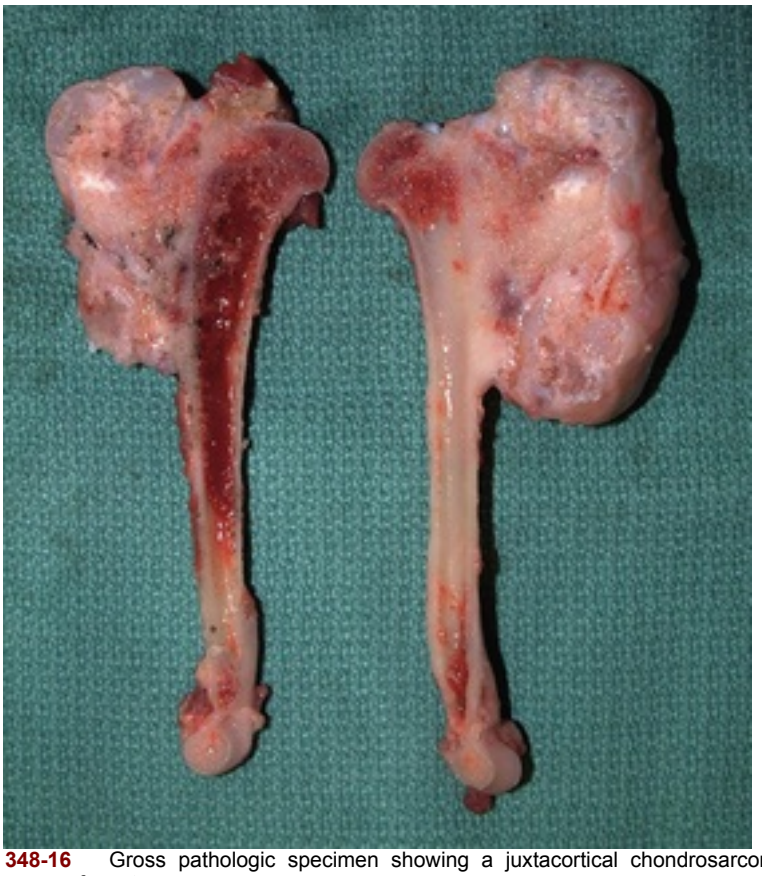
Feline Appendicular Osteosarcoma

Primary bone tumors are uncommon in cats.[153-158] Unlike dogs, 10-33% of primary bone tumors in cats are benign.[154] OSA accounts for 70-80% of all feline bone tumors, whereas FSA, CSA, HSA, and rhabdomyosarcoma have also been reported.[153-155,159] The mean age at diagnosis of appendicular OSA is 10-11 years, and males are overrepresented, with a male-to-female ratio of 1.5-1.7 : 1.[154,157] Several differences exist in the presentation and biologic behavior of OSA in cats versus dogs.[157] In feline OSA, bones of the pelvic limb are involved 1.6 times more frequently than those of the thoracic limb.[154] The digits and proximal humerus are the most common sites, closely followed by the distal femur and proximal tibia.[153-158] Radiographic features are similar in cats and dogs, although lytic and juxtacortical lesions are more

common.[153-157] Metastasis is uncommon (<10% of cats with OSA).[153-158] Metastatic sites include lungs, brain, liver, kidneys, and spleen. Due to the infrequency of metastatic disease, limb amputation without chemotherapy is recommended for the treatment of cats with appendicular OSA. The MST after limb amputation alone is reported to be 11.8-49.2 months.[153-158]

Other Feline Appendicular Tumors

FSA and CSA have a similar biologic behavior to OSA (E-Figure 348-16). Limb amputation may be curative, although metastatic disease has been reported for both tumor types.[153,154]



E-FIGURE 348-16 Gross pathologic specimen showing a juxtacortical chondrosarcoma of the proximal humerus of a cat.

Feline Axial Tumors

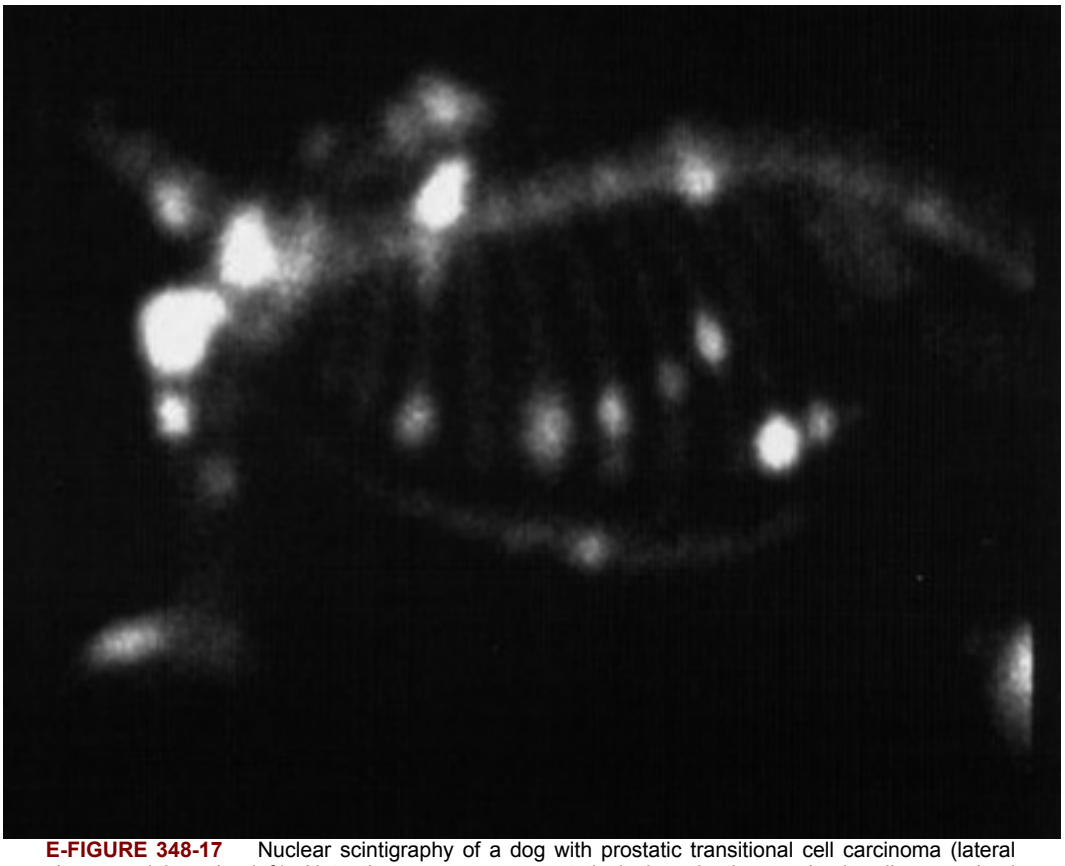
OSA is the most common tumor of the feline axial skeleton.[153,157] FSA and CSA also are reported to involve the axial skeleton.[153,154] The mean age at presentation for cats with axial OSA is 10.4 years, which is significantly older than cats with appendicular OSA.[157] The skull and pelvis frequently are affected; other sites include ribs, vertebrae, and scapulae.[153-157] Presenting signs, radiographic features, and treatment recommendations are similar to malignant canine axial tumors. Periosteal new bone formation and juxtacortical tumors are more common in cats with axial OSA.[153,157] Complete surgical resection is complicated by tumor location, resulting in incomplete resection and poor tumor control. The MST for cats with axial OSA is 5.5 to 6.1 months, with most euthanized due to local recurrence rather than metastatic disease.[156,157]

Metastatic Bone Tumors

Metastatic bone tumors are infrequently diagnosed in cats and dogs. Metastasis usually occurs

hematogenously. In dogs, urogenital carcinomas, particularly of the bladder and prostate, are the most common primary tumors to metastasize to bone.[7,160] Skeletal metastasis also is reported in dogs with OSA, mammary carcinoma, thyroid carcinoma, pulmonary carcinoma, nasal carcinoma, apocrine gland anal sac adenocarcinoma, and renal tumors.[1,7,160-163] Metastatic lesions represent 24% of all bone tumors in dogs weighing <15 kg and only 5% in large-breed dogs.[1,7,162] The most common metastatic sites are the axial and proximal appendicular skeleton, with <11% of dogs having metastatic lesions distal to the elbow or stifle.[160] In contrast, acrometastasis involving one or more digits is the most common presentation for cats with metastatic pulmonary carcinoma ("lung-digit syndrome").[161-164]

Nuclear scintigraphy is recommended for the identification of multiple bone lesions (E-Figure 348-17). Treatment options for skeletal metastasis include surgery, radiation therapy, and pharmaceuticals.[28,61] Surgical curettage and stabilization of metastatic lesions is uncommonly performed in veterinary medicine but may provide a meaningful response in select cases. Radiation therapy is indicated for management of pain and inflammation.[33]



E-FIGURE 348-17 Nuclear scintigraphy of a dog with prostatic transitional cell carcinoma (lateral view, cranial to the left). Note the numerous metastatic lesions in the proximal radius, proximal humerus, cervical and thoracic vertebrae, ribs, and sternum.

Canine Joint Tumors

Joint tumors usually are primary and malignant.[165-169] Previously, synovial cell sarcoma was considered the most common tumor of the canine joint.[165,166] However, recent evidence suggests that other soft-tissue sarcomas of periarticular tissue are more prevalent. Immunohistochemistry (IHC) is required to differentiate these tumor types.[167,168] Other reported joint tumors include histiocytic sarcoma and malignant fibrous histiocytoma, synovial myxoma and myxosarcoma, OSA, FSA, CSA, HSA, liposarcoma, rhabdomyosarcoma, and undifferentiated sarcoma.[1,167-171] An association between histiocytic sarcoma and pre-existing joint disease has been identified in Bernese Mountain Dogs (see ch. 350).[170]

Synovial cell sarcomas are malignant tumors arising from mesenchymal cells in tenosynovial tissue of joints, bursae, and tendon sheaths.[165] The stifle, elbow, shoulder, carpal, tarsal, and hip joints are most commonly involved, in decreasing order of frequency.[1,165] The mean age at presentation is 6 to 8 years.[165-169] Males are overrepresented, and Flat Coated Retrievers are predisposed.[165-169] Metastasis to the regional lymph nodes and lungs is reported in up to 32% of dogs at diagnosis and in 41% to 54% of dogs during the course of disease.[165-169]

Typically, affected dogs have lameness, signs of joint pain, and synovial effusion. Dogs with suspected joint tumors should be staged with palpation of regional lymph nodes and regional and three-view thoracic radiographs. Regional radiographs often reveal a soft-tissue opacity adjacent to the affected joint. Mineralization of the soft-tissue mass occasionally is seen in humans but rarely in dogs. Bone involvement is observed in 11-100% of cases and can either be smooth and well delineated, due to pressure necrosis from the expansile mass, or permeative to punctate lytic as a result of bony invasion.[165-169]

Biopsy is required for a definitive diagnosis. Synovial fluid analysis usually is consistent with chronic, low-grade inflammation, and neoplastic cells rarely are identified. Large core biopsies, using either a Jamshidi needle or open wedge, can establish the diagnosis and histologic grade.

Synovial cell sarcomas have two distinct populations of cells: epithelioid and spindle.[1,165] Based on histologic features, synovial cell sarcomas are subclassified as either monophasic, with one cell type, or biphasic, with both cell types.[165] However, this histologic appearance is not adequate to differentiate synovial cell sarcoma from other soft-tissue sarcomas. IHC stains have been used for differentiating joint tumors: synovial cell sarcomas stain positively with cytokeratin antibody AE1/AE3, histiocytic sarcomas stain positively with CD18 antibody, and malignant fibrous histiocytomas stain positively with smooth muscle actin.[168]

Limb amputation is the recommended treatment for dogs with a histologically confirmed joint tumor.[165-169] Local recurrence is common after conservative excision and has also been reported with relative frequency in the stump of the amputation site.[165] The role of radiation therapy and chemotherapy is unknown, but chemotherapy does not improve survival time in humans with synovial cell sarcoma.[172] However, a doxorubicin-based chemotherapy protocol is recommended for high-grade synovial cell sarcoma due to their high metastatic potential.

Several prognostic factors have been identified in dogs with synovial cell sarcoma, including clinical stage, treatment, histologic grade, and IHC staining.[165-169] Synovial cell sarcoma is locally staged as well-defined, with no evidence of invasion into regional structures (T_1), or with invasion into the soft tissue (T_2) or bone and joints (T_3).[165] Local staging is not prognostic; however, dogs with metastases to regional lymph nodes or lungs have MSTs of <6 months. Comprehensive surgical resection is important in prolonging both DFI and survival time. Local tumor control is poor after conservative local excision, with a median DFI of 4.5 months compared with 30 months after limb amputation.[165,169] Furthermore, survival time is significantly improved with more extensive local treatment regimens: 93 days with no treatment, 455 days with conservative resection, and 840 days with limb amputation.[169] Histologic grade is also prognostic, because the MST for dogs with grade I synovial cell sarcoma is >48 months; with grade II, 36 months; and with grade III, 7 months.[165]

Clinical staging and surgical recommendations (limb amputation) are the same for dogs with histiocytic sarcoma (see ch. 350). Dogs with periarticular histiocytic sarcoma have a better prognosis than dogs with non-periarticular locations with MSTs of 391 days and 128 days, respectively.[169] However, despite the better prognosis, 68% of dogs with periarticular histiocytic sarcoma present with metastases. Dogs without metastases at diagnosis had a significantly better MST (980 days) than dogs with metastases (253 days).[169] Postoperative CCNU is recommended in dogs with periarticular histiocytic sarcoma because of this high metastatic risk.[173]

Feline Joint Tumors

Synovial cell sarcoma is rarely diagnosed in cats. Based on individual case reports, biologic behavior may be more benign than in dogs.[174,175] However, two cats have been reported with metastatic synovial cell sarcoma (regional lymph nodes in both, and pulmonary 12 months postoperatively in one).[176] Limb amputation is recommended for local management because, similar to dogs, local recurrence has been reported after

conservative excision.[174,175]

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CHAPTER 349

Mast Cell Disease

Douglas H. Thamm

Client Information Sheet: Mast Cell Tumors

Canine Mast Cell Tumors

Introduction

Prevalence

Mast cell tumors (MCTs) represent the most common cutaneous malignancy in the dog, accounting for between 16 and 21% of all cutaneous tumors (see ch. 10 and 345).[1] Several breeds are at increased risk for MCTs, including brachycephalic breeds (Boxer, Boston Terrier, English Bulldog, Pug), retrievers, Cocker Spaniels, Schnauzers, Staffordshire Terriers, Beagles, Rhodesian Ridgebacks, Weimaraners, and Shar-Pei.[1-3] While brachycephalic breeds are at higher risk for MCT development, MCTs in these dogs are more likely to be low grade.[1,4] In contrast, anecdotal evidence suggests that Shar-Pei may develop more biologically aggressive MCTs.

Pathophysiology

Perhaps the best-described molecular abnormality in canine MCT involves the receptor tyrosine kinase (RTK) KIT. KIT is expressed normally on a variety of cells including hematopoietic stem cells, melanocytes, and mast cells.[5,6] The ligand for KIT, stem cell factor (SCF), induces KIT dimerization, phosphorylation, and generation of intracellular signaling promoting proliferation, differentiation, and maturation of normal mast cells.[5,6] KIT expression has been demonstrated on canine MCTs and aberrant cytoplasmic localization of KIT in MCTs may be associated with dysregulated KIT function.[7-9] Furthermore, 25-30% of intermediate- and high-grade canine MCTs possess mutations in the *c-kit* gene, which result in constitutive, SCF-independent activation of KIT.[10-13] The presence of an activating *c-kit* mutation is linked to increased risk of local recurrence, metastasis, and a worse prognosis.[10,12,14-16]

History and Clinical Signs

Most MCTs in dogs occur in the dermis and subcutaneous (SC) tissues. Most are solitary, although 11-14% of dogs have multiple lesions.[17-21] A visceral form of MCT has also been described.[22,23] Cutaneous MCTs have an extremely varied range of clinical appearances and are sometimes inadvertently mistaken for non-neoplastic lesions. The history and clinical signs of dogs with MCT may occasionally be complicated by signs attributable to release of histamine, heparin and other vasoactive amines from mast cell granules, such as erythema and edema in surrounding tissues, pruritus, or changes in tumor size. Dogs with substantial tumor burdens (i.e., large tumors, metastatic disease) are more likely to have systemic signs related to the release of mast cell mediators. These may include vomiting, diarrhea, fever, melena, and peripheral edema. Collapse is a rare event. Histamine released from MCT granules is thought to act on gastric parietal cells via H2 receptors, resulting in increased hydrochloric acid secretion.

Diagnosis, Staging, Prognosis

Fine-Needle Aspiration

Most MCTs are readily diagnosed on the basis of fine-needle aspiration (FNA) cytology (see ch. 86 and 87).

Mast cells appear as small to medium-sized round cells with abundant, small, uniform cytoplasmic granules that usually stain purplish red (metachromatic), while a small number do not stain readily.[1,24] In these cases, a Wright-Giemsa or toluidine blue stain will often reveal granules; however, histologic assessment of a biopsy sample may be necessary. Highly anaplastic, agranular MCTs can be challenging to diagnose by routine light microscopy. CD117 (KIT) immunohistochemistry is often used to differentiate anaplastic MCTs from other round cell tumors.[7]

Patient Assessment

Complete staging includes a minimum database (complete blood count [CBC], serum biochemistry profile), cytologic assessment of regional lymph node(s) (see ch. 95), abdominal ultrasound (US; see ch. 88) with cytologic assessment of spleen or liver if warranted (see ch. 89 and 93), and thoracic radiographs. It is likely that extensive staging is not necessary for dogs with node-negative MCTs and no negative prognostic factors (see below; Figure 349-1). If the MCT is in a location amenable to wide surgical excision and no negative prognostic indicators are present, then no further tests other than minimum database and cytology of the regional lymph nodes (even if normal in size) are necessary. If the tumor presents at a site that is not amenable to wide surgical excision or if negative prognostic factors exist, additional diagnostics are recommended prior to definitive therapy. These include abdominal US, FNA cytology of abnormal organs, and thoracic radiographs.[25,26] Incisional biopsy may be performed to determine histologic grade if needed for the owner's decision to pursue therapy.

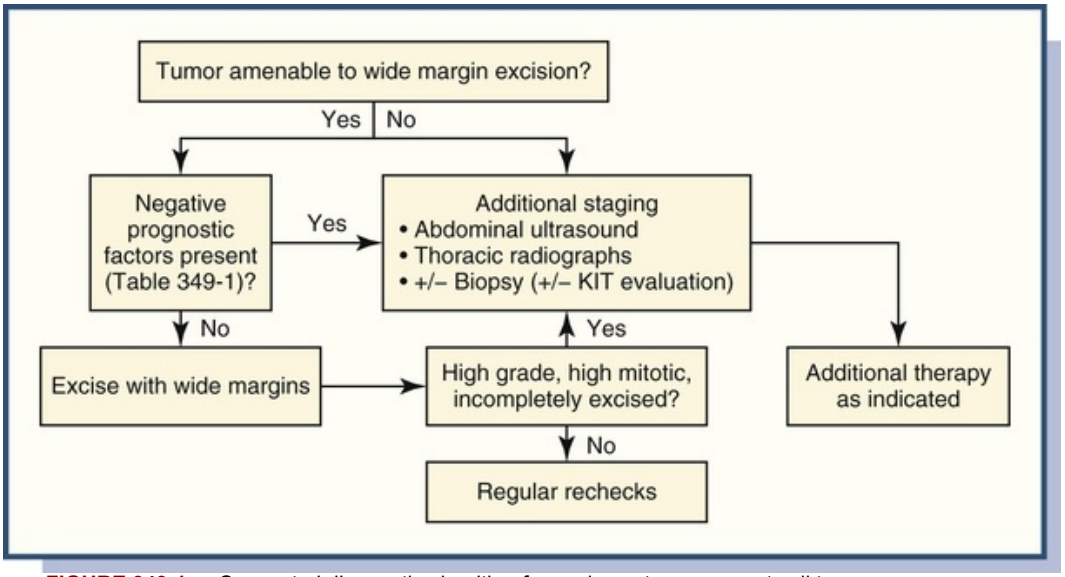

FIGURE 349-1 Suggested diagnostic algorithm for canine cutaneous mast cell tumors.

With respect to cytologic evaluation of lymph nodes, an occasional solitary mast cell is not necessarily indicative of metastasis; rather, clustering and aggregates are more worrisome.[27] Disease in the regional node, but not beyond, should not be considered a reason to avoid surgery; rather, the node should be excised and submitted for histopathology at the time of primary tumor resection. Histologic assessment may be necessary to accurately determine whether mast cells in a lymph node represent metastatic disease. A grading scheme has been proposed to better quantify the degree of lymph node infiltration in canine MCT.[28] With the exception of the extremely rare primary mastocytic leukemia, involvement of marrow or peripheral blood in the absence of disease in regional lymph node or abdominal viscera is unlikely.[29] Therefore, buffy coat smears and bone marrow aspiration cytology are rarely necessary.

Prognostic Factors

The major prognostic factors for dogs with MCTs should be reviewed (Table 349-1). It is important to note that no one factor is entirely predictive of biologic behavior and as such, all prognostic indicators should be taken into consideration when evaluating a patient.

TABLE 349-1

Prognostic Factors for Canine Mast Cell Tumors

FACTOR	COMMENT	REFERENCES
Histologic grade	High grade tumors have an increased risk of both local recurrence and metastasis.	2, 35, 91-93
Clinical stage	Some studies suggest that regional node involvement is a negative prognostic factor. The effect of multiple tumors on outcome is questionable.	17, 18, 20, 21, 27, 36, 41, 48, 50, 53, 55, 92, 94, 95
Location	Subungual, oral, and other mucous membrane sites are associated with more high grade tumors and worse prognosis. Visceral tumors have a very poor prognosis. Subcutaneous tumors are generally associated with a good prognosis.	22, 23, 47, 96-98
Cell proliferation rate	Mitotic index, relative frequency of argyrophilic nucleolar organizer regions (AgNORs), and percent proliferating cell nuclear antigen (PCNA) or Ki-67 immunopositivity, are predictive of post-surgical outcome.	15, 37, 91, 93, 94, 98-107
Recurrence	Local recurrence following surgical excision may carry a more guarded prognosis.	36
Systemic signs	The presence of systemic illness (e.g., anorexia, vomiting, melena, gastrointestinal ulceration) may be associated with a higher stage of disease.	18, 23
Breed	Mast cell tumors (MCTs) in Boxers (and potentially other brachycephalic breeds) tend to be of low or intermediate grade and are thus associated with a better prognosis. MCTs in the Shar-Pei may be higher grade.	1, 4
c-kit mutation	The presence of an activating mutation in the *c-kit* gene is associated with a worse prognosis.	10, 14, 15
KIT protein localization	Predominantly aberrant (cytoplasmic) KIT localization is associated with a worse prognosis.	108

Treatment

"Low Risk" Mast Cell Disease

Surgery

Treatment decisions are predicated on the presence or absence of negative prognostic factors and on the clinical stage of disease. In tumors localized to the skin in areas amenable to wide excision, surgery is the treatment of choice. Surgical excision should include a 3 cm margin of surrounding normal tissue. However, some evidence suggests that 1-2 cm lateral margins and one uninvolved deep fascial plane may be sufficient for complete excision of many MCTs, particularly those that are small and lower grade.[30-33] Surgical margins should be evaluated histologically for completeness of excision. Routine use of neoadjuvant corticosteroids to facilitate surgical resection is not recommended, except in cases where marginal excision is not possible due to location or extent of disease.

Incomplete Surgical Removal

For cases where margins are incomplete, additional local therapy is warranted to prevent recurrence[34-36]; however, not all MCTs with surgically incomplete margins will recur.[37,38] Re-excision of the surgical scar with additional wide margins should be performed if possible. If additional surgery is not possible, adjuvant radiation therapy (RT) can be quite effective (see ch. 240). Two-year control rates of 85-95% can be expected following RT for incompletely resected tumors of low or intermediate grade.[39-41] A less optimal alternative is a combination of surgery and chemotherapy (discussed below).[42,43] For tumors where marginal excision is not possible, RT alone,[41,44,45] RT plus toceranib,[46] or medical therapy alone (see below) may be considered.

Monitoring

Regardless of the local therapy chosen, dogs with low and intermediate grade tumors should be reevaluated

regularly for local recurrence ± metastasis. Local site and regional lymph node evaluation, complete physical examination and aspiration of any new cutaneous masses or enlarged lymph nodes should be considered. More complete staging, including abdominal US, should be included if a dog has had a MCT with high risk for metastasis.

"High-Risk" Mast Cell Disease

Overview

The treatment of "high-risk" MCT remains challenging. This category includes dogs with high grade tumors, intermediate grade tumors with regional or distant metastasis, or high proliferative activity as assessed by mitotic index or special stains. Also included are MCTs arising from a mucous membrane or mucocutaneous junction. Some studies suggest that low/intermediate grade tumors have a better prognosis if there is only regional node involvement than that for high grade tumors. The author recommends, however, that such tumors be treated as if they have a high capacity for metastasis.[47-50] In addition to appropriate local therapy as above, adjuvant medical therapy should be offered for dogs with high-risk MCT in an attempt to delay or prevent further metastasis. Corticosteroids have been reported to be of some benefit[45,51,52]; however, most responses are incomplete and transient. Corticosteroid-induced reduction of peritumoral edema/inflammation may interfere with response assessment.

Use of Chemotherapy

Several studies have evaluated response rates of measurable canine MCT to various cytotoxic chemotherapy protocols.[36,53-59] Response rates as high as 64% have been reported, and multi-agent protocols may confer a higher response rate than single-agent therapy.[36,53,55,57,58] The most commonly employed first-line agents, vinblastine (VBL) and lomustine, are often given with corticosteroids.[36,54,57,59] Importantly, in most instances, the response of a bulky MCT to any chemotherapy protocol tends to be short-lived, stressing the need for local control of disease if at all possible prior to the institution of medical therapy. A few single-arm retrospective studies have evaluated efficacy of post-surgical chemotherapy with vinblastine or lomustine for "high-risk" MCT. Dogs receiving chemotherapy tended to have longer disease-free and overall survival times than surgery alone, with median survival times exceeding 2 years in most studies.[15,48,55,57,60]

Toceranib

Oral tyrosine kinase inhibitors (TKIs) have been developed that inhibit signaling through KIT. The two veterinary-approved TKIs in this class are toceranib (Palladia, Zoetis) and masitinib (Masivet/Kinavet, AB Science). Some studies have also been conducted with the human KIT inhibitor imatinib (Gleevec, Novartis).[61] Following encouraging early-phase clinical trials, a multi-center, placebo-controlled, double-blind, randomized study of toceranib was performed in dogs with recurrent or metastatic intermediate or high grade MCT.[13,62] The objective response rate in toceranib-treated dogs was 37.2% (7 complete, 25 partial) versus 7.9% (all partial) in placebo-treated dogs. The median duration of response and time to tumor progression were 12.0 and 18.1 weeks, respectively. Dogs whose MCT harbored *c-kit* gene activating mutations had objective response rates higher than those with wild-type *c-kit* (69% vs. 37%). Gastrointestinal toxicity (inappetence, weight loss, diarrhea, and occasionally vomiting or melena) were the most common adverse effects, and were generally manageable with symptomatic therapy, drug "holidays" and dose reductions. Other adverse effects include mild to moderate leukopenia and occasional muscle pain.[62] Clinical experience with toceranib suggests that equivalent antitumor activity and reduced adverse effects may be observed if dosages lower than the label dosage are employed. A dosage of 2.4-2.75 mg/kg every other day or 3 days per week (Monday, Wednesday, Friday) is currently utilized by many.[46,63]

Masitinib

A clinical trial of similar design was conducted with masitinib in dogs with recurrent or unresectable MCT, demonstrating improved time to progression in masitinib-treated versus placebo-treated dogs, and again, outcome was improved in dogs with MCT harboring activating *c-kit* mutations and those treated in the first-line setting.[64] Subsequent follow-up of dogs treated with long-term masitinib identified an increased number with long-term disease control compared to those treated with placebo (40% vs. 15% alive at 2 years).[65] Gastrointestinal adverse effects (vomiting or diarrhea) were most common but were usually mild and self-limiting. Mild myelosuppression was also observed. A small percentage of dogs developed protein-losing

nephropathy and edema. Increases in blood urea nitrogen (BUN) and creatinine were observed in some dogs. Hemolytic anemia was also observed rarely.[64]

Combining TKIs and Other Therapies

There are a few studies evaluating combination KIT inhibitors and standard forms of therapy such as RT or cytotoxic chemotherapy, but evidence of benefit when used postoperatively has yet to be demonstrated. One recent clinical trial evaluated a combination of toceranib and vinblastine in dogs with measurable MCT. Significant reductions in vinblastine dosage and frequency were necessary owing to additive myelosuppression.[66] Nevertheless, encouraging clinical activity (71% objective response rate) was observed despite the necessary dosage reductions. Another study investigated the combination of toceranib, prednisone and hypofractionated RT in dogs with non-resectable and/or metastatic MCT.[46] The overall response rate was about 76%, with almost 60% of dogs achieving complete remission (CR) and another 17% having partial remission. The overall median progression free interval was 10.5 months.

Palliative Therapy

Ancillary palliative therapy to address the systemic effects of mast cell mediators is sometimes warranted using both H1 and H2 blockers (e.g., diphenhydramine, famotidine). The proton pump inhibitor omeprazole may be more effective for diminishing gastric acid secretion, particularly in the setting of bulky mast cell disease. These agents are particularly useful in cases where (1) systemic signs are present; (2) the tumor is likely to be extensively manipulated at surgery (i.e., cytoreductive surgery, incisional biopsy); or (3) treatment is undertaken in the context of gross disease (e.g., RT or medical therapy for tumors that are not cytoreduced). There is no clinical evidence that H1/H2 blockers or omeprazole have any antineoplastic effects.

Feline Mast Cell Tumors

Unlike MCTs in the dog, which are primarily cutaneous or SC, MCTs in cats typically occur in three distinct syndromes: cutaneous, splenic/visceral and intestinal. In one study, 67% of cutaneous and splenic/visceral MCT had *c-kit* activating mutations.[67]

Feline Cutaneous Mast Cell Tumors

Definitions

MCTs are the second most common cutaneous tumor in cats, accounting for about 20%.[68,69] The typical feline cutaneous MCT is a solitary, raised, firm, well-circumscribed, hairless, dermal nodule between 0.5 and 3 cm in diameter. Approximately 20% are multiple, although one series reported multiple lesions in most cases.[1] Two distinct types of cutaneous MCT in the cat have been reported: the more typical mastocytic MCT, which is histologically similar to MCT in dogs, and the less common histiocytic MCT. The histiocytic MCT has morphologic features characteristic of histiocytic mast cells, and may regress spontaneously over 4 to 24 months.[70,71] Siamese cats appear to be predisposed to both types.[68-72] The mastocytic form can be subdivided on histologic appearance into two categories: compact (50-90% of all cases) and diffuse (anaplastic).[68,70,73] Well-differentiated compact tumors tend to behave in a benign manner and metastasis is uncommon, while anaplastic tumors may have a high mitotic index, marked cellular and nuclear pleomorphism, and SC infiltration. Clinical behavior of these anaplastic tumors is variable according to the literature.[71,72,74-76]

Diagnosis

Most feline MCTs are easily diagnosed by cytologic examination of FNAs (see ch. 86 and 87). Cats with cutaneous MCTs should be evaluated for evidence of additional tumors, as well as potential splenic involvement by abdominal US (see ch. 88). One study suggested some cats with multiple cutaneous MCTs also had splenic disease.[74] A minimum database is recommended, along with careful examination of local lymph nodes. The histologic grading system described for canine MCTs has provided no prognostic information for the cat and is not used. Tumors with a high mitotic index appear to be at greatest risk for local recurrence and metastasis.[71,72,76,77]

Treatment

The recommended treatment for most cutaneous feline MCTs is surgical excision. Reports have demonstrated

local recurrence rates following excision between 0 and 24%,[68,71,72,74-76] and metastatic rates from 0 to 22%.[71,72,74-76] Histologically anaplastic tumors or those with a high mitotic index may be best managed with systemic therapy as for canine MCT, although statistics regarding efficacy are lacking.[76,78] After biopsy confirmation, conservative resection or active surveillance may be taken with the histiocytic form. Some may spontaneously regress.[68-70] RT may be considered for tumors that are incompletely excised (see ch. 240).[79] Limited information exists concerning the utility of chemotherapy in cats with MCT. Objective responses to lomustine (CCNU) have been reported in cats.[80,81] Anecdotally, prednisone/vinblastine, as used in dogs, appears to be associated with antitumor activity in some cats. Administration of imatinib has been associated with partial responses in cats with MCT expressing activating mutations in *c-kit*.[67,82,83] Neither masitinib nor toceranib has been formally evaluated in cats with MCT.

Feline Splenic/Visceral Mast Cell Tumors

Prevalence and Signs

MCT represents the most common differential for splenic disease in cats, accounting for 15% of submissions in one series.[84] Most cats with splenic MCT do not have a history of cutaneous MCT, although recent evidence suggests that some cats with multiple cutaneous MCTs may also have splenic involvement.[74] While the spleen is the primary site affected by this disease, other organs may also be involved.[68,85] Peripheral blood mastocytosis has been reported in the majority of cases, with peripheral mast cell counts as high as 32,000 cells/mcL reported.[68,86] Cats with splenic MCT may have signs of systemic illness including vomiting, inappetence, and weight loss.[68,85] Clinical signs associated with degranulation, such as GI ulceration, hemorrhage, hypotensive shock and labored breathing may also be noted. Abdominal palpation usually reveals marked cranial organomegaly. Cats with suspected splenic MCT should undergo a standard work-up including minimum database, abdominal US (see ch. 88) and thoracic radiographs. US-guided FNA cytology (see ch. 89 and 93) or cytologic evaluation of effusions is usually diagnostic for splenic MCT.

Treatment

Splenectomy is the treatment of choice for cats with splenic MCT, even if other organ involvement is noted. Long-term survival with good quality of life is common following splenectomy. Even in cats with significant bone marrow and peripheral blood involvement, median survival times are 12 to 19 months.[68,85,87] As with high-risk feline cutaneous MCT, the utility of adjuvant medical therapy is unknown.

Feline Intestinal Mast Cell Tumors

Intestinal MCT is the third most common primary intestinal tumor in cats after lymphoma and adenocarcinoma.[68] Most cats have a history of vomiting, diarrhea and inappetence. A palpable abdominal mass is often evident.[68,88] Enlarged mesenteric lymph nodes and/or hepatomegaly may be noted on physical examination. Peritoneal effusion containing mast cells and eosinophils may be present. Diagnosis is usually made by FNA of the mass or involved organs. Cats with intestinal MCT should be staged with a minimum database, thoracic radiographs and abdominal US. Intestinal MCT in cats carries a poor prognosis, as metastasis is common at the time of diagnosis.[68,88-90] Surgery is the treatment of choice and wide surgical margins are necessary (5-10 cm) as the tumor typically extends histologically well beyond the obvious gross disease.[68,88] Limited information exists regarding the use of medical therapy for feline intestinal MCT.

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CHAPTER 350

Canine and Feline Histiocytic Diseases

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Histiocytic diseases represent a diverse and potentially confusing spectrum of syndromes ranging from solitary lesions that spontaneously regress (histiocytoma) to highly malignant tumors involving multiple sites in the body (disseminated histiocytic sarcoma). Also included in this category are reactive conditions associated with underlying immune dysregulation (cutaneous histiocytosis, systemic histiocytosis). The aim of this chapter is to characterize the origin, behavior, clinical presentation and treatment of these various conditions.

Cell Origin and Development

Histiocytes develop from CD34+ bone marrow stem cells, migrate from the bone marrow to the blood as monocytes, and enter various tissues, where they undergo differentiation into macrophages and dendritic cells (DCs). Under the influence of monocyte/macrophage-colony stimulating factor, blood monocytes differentiate into macrophages, while granulocyte-macrophage colony stimulating factor, interleukin-4 and tumor necrosis factor-alpha lead to various DC lineages, including interstitial DC and Langerhans cells (LCs), the latter of which are critically dependent on transforming growth factor-beta1 stimulation.[1-3] Interstitial DCs occur in perivascular locations in many organs, while LCs are predominantly in the epidermis with more recently identified populations identified in lymph nodes and other locations.[4,5]

Histiocytes play a key role in the immune system through phagocytosis (macrophages) and antigen processing and presentation (DCs, LCs). DCs represent the most potent antigen-presenting cells (APCs) for inducing immune responses in naïve T cells. Cells are defined by their expression of molecules essential to their function as APCs (Table 350-1). Canine- and feline-specific monoclonal antibodies for these functionally important molecules aid identification of macrophages, DCs, and LCs in tissues, and can be useful in distinguishing among histiocytic diseases. For this reason, collection of fresh, snap-frozen tissue often is recommended in addition to more routine sample collection for cytologic and histopathologic evaluation.

TABLE 350-1

Characterization of Histiocytic Diseases of Dogs and Cats[8]

DISEASE	SPECIES	CELL OF ORIGIN	IMMUNOPHENOTYPE
Histiocytoma	Dog	LC	CD1a, CD11c/CD18, E-cadherin
Cutaneous Langerhans cell histiocytosis	Dog	LC	CD1a, CD11c/CD18, E-cadherin
Pulmonary Langerhans cell histiocytosis	Cat	LC	CD1a,* CD18, E-cadherin
Cutaneous histiocytosis	Dog	DC	CD1a, CD4, CD11c/CD18, CD90
Systemic histiocytosis	Dog	DC	CD1a, CD4, CD11c/CD18, CD90
Histiocytic sarcoma	Dog, cat	DC	CD1a, CD11c/CD18
Hemophagocytic histiocytic sarcoma	Dog, cat	Macrophage	CD1a (low), CD11d/CD18 (dog)
Feline progressive histiocytosis	Cat	DC	CD1a, CD11†/CD18, CD5 (50%)

*CD1a expected, not assessed to date.

†CD11c expected but not currently assessable in cats.

DC, Dendritic cell; *LC*, Langerhans cell.

Histiocytic Diseases

Canine Histiocytoma

Canine histiocytoma is a common, benign skin tumor originating from LCs. Usually occurring in young dogs, the incidence drops after 3 years of age. In a retrospective study of histologic tumor diagnoses in dogs < 1 year of age in the United Kingdom, cutaneous histiocytoma was the most common diagnosis, representing 89% of the total.[6]

Lesions typically are solitary and they present as hairless dome- or button-shaped masses on the skin surface. The head is a frequent site, although lesions can develop anywhere on the body. Diagnosis requires cytologic evaluation. Cytologic features vary, but typically consist of a population of round cells with benign nuclear features, abundant cytoplasm, and often a high mitotic index.

Histiocytomas usually undergo spontaneous regression, typically within 3 months, and recurrence is uncommon. Regression is mediated by CD8+ T-cells and progressive lymphocyte infiltration is evident within tumors over time.[7] Surgical or medical treatment generally is not needed, but may be considered for lesions that are persistent, recurrent, or problematic for the animal.

Canine Cutaneous Langerhans Cell Histiocytosis

The presence of multiple histiocytomas in dogs is uncommon and may be best considered in the spectrum of cutaneous Langerhans cell histiocytosis (LCH), since the skin is consistently involved and is considered the site of origin.[8] Lesions may be limited to the skin or extend to involve regional lymph nodes and rarely, internal organs. Diagnosis requires cytologic examination with consideration of histopathologic evaluation and immunophenotyping for definitive diagnosis. Lymph node evaluation, thoracic radiographs, and an abdominal sonogram are helpful in determining extent of disease.

Spontaneous regression of lesions can occur and may be delayed, with lesions persisting several months prior to regression. Unfortunately, lack of regression and the challenging management of extensive ulcerated lesions often ultimately lead to euthanasia. Limited information exists on effective treatments, although one case report described transient improvement following administration of CCNU chemotherapy.[9]

Feline Pulmonary Langerhans Cell Histiocytosis

Proliferative disorders of LCs are rare in cats. One report describes 3 cats with primarily pulmonary proliferative disease of LC origin.[10] The cats in this series were older (10-15 years) and presented with signs of respiratory disease and distress ranging from 5 days to 7 months' duration. Thoracic radiographs identified a severe, diffuse, bronchointerstitial pattern in all 3 cats with diffuse miliary to nodular opacities noted in 2 cats. Glucocorticoid therapy in 2 cats did not improve clinical signs. Euthanasia was elected in each case due to progressive respiratory signs. The diagnosis of LCH was made postmortem through histopathologic, immunohistochemical and electron microscopic evaluations. Postmortem evaluation identified metastasis to sites including pancreas, liver, kidneys and visceral lymph nodes.

Canine Reactive Histiocytosis (Cutaneous Histiocytosis, Systemic Histiocytosis)

Reactive histiocytosis consists of a group of non-neoplastic diseases of DC origin. Lesions in affected dogs either can be confined to skin, subcutaneous tissue and draining lymph nodes (cutaneous histiocytosis), or can involve skin and varied other sites including lymph node, liver, spleen, lung, bone marrow, eye, and mucous membranes (systemic histiocytosis). Cutaneous lesions are similar in both forms, and progression from cutaneous to systemic histiocytosis is possible. The exact etiology and pathogenesis are unknown, but dysregulation of immune response mechanisms has been proposed.

Cutaneous Histiocytosis

Cutaneous histiocytosis tends to occur in younger dogs. In a retrospective study of 32 dogs, median age was 4 years (range, 1-8 years).[11] Duration of signs prior to diagnosis is variable, with a median of 1.75 months and

range of 0-30 months reported in this same study.[11] Lesions present as multifocal nodules, plaques, and crusts within the skin and subcutaneous tissues. Ulceration of overlying skin is common.

Diagnosis requires histopathologic assessment and consideration of immunophenotyping. Lesions are characterized by histiocytic infiltrate, with variable angiocentricity, within the dermis and subcutaneous tissues. Lymphoid infiltration is common, comprising up to 50% of dermal infiltrates.[11,12] Histiocyte antigen expression patterns are consistent with DC origin.[12] Lymph node evaluation (see ch. 95), thoracic radiographs, and an abdominal sonogram (see ch. 88) are helpful in distinguishing cutaneous versus systemic forms of disease.

The disease course can be punctuated by remissions and relapses, especially early in the course of the disease. Given its diffuse nature, surgery generally is of limited use. Instead, treatment typically involves administration of systemic immunomodulatory drugs (see ch. 165). Variable responses were seen with systemic administration of corticosteroids in 7 dogs in one study.[12] In another series, complete resolution of dermatologic lesions was reported in dogs receiving a variety of immunomodulatory drugs within a median of 45 days (range, 14-162 days).[11] Immunomodulatory drugs included prednisone alone or in combination with tetracycline/niacinamide or azathioprine, tetracycline/niacinamide alone, and cyclosporine.

Long-term maintenance therapy or repeated treatment courses may be needed. In the report describing complete resolution of lesions, 30% of dogs developed recurrence and each of these dogs responded to further treatment.[11] At the conclusion of the study, with a median follow-up of 25 months, 26 of 32 (81%) dogs were alive with no lesions. The other 6 dogs were deceased with no signs of cutaneous histiocytosis.

Systemic Histiocytosis

Systemic histiocytosis was initially reported in a group of closely related Bernese Mountain Dogs, suggesting a genetic predisposition in this breed.[13] A predilection in Rottweilers, Golden Retrievers and Labrador Retrievers also has been suggested.[12] Systemic histiocytosis predominantly affects middle-aged dogs (median 5 years; range, 1-9 years).[12,13]

Presenting signs often are nonspecific and include depression, anorexia, and weight loss, and vary according to the distribution and extent of lesions. Cutaneous and subcutaneous lesions are similar, though possibly more widespread, to those seen with cutaneous histiocytosis. Involvement of lymph nodes, liver, spleen, lung, bone marrow, eye (conjunctiva, sclera, orbit, third eyelid), and mucous membranes (gingiva, nasal cavity) are variably present.[12,14]

Diagnosis requires histopathologic evaluation and consideration of immunophenotyping. Lesions are identical to those described for cutaneous histiocytosis with the notation that angiocentric infiltration with vascular invasion may be more consistently seen with the systemic form of disease.[12] Lymph node evaluation (see ch. 95), thoracic radiographs, and abdominal sonography (see ch. 88) are helpful in determining extent of disease. These collective features also are helpful in distinguishing systemic histiocytosis from malignant histiocytic and non-histiocytic diseases.

As with cutaneous histiocytosis, the disease course can be punctuated by remissions and relapses. Systemic medications that have shown some efficacy include prednisone, cyclosporine, leflunomide, experimental bovine thymosin fraction 5, and the chemotherapy drug doxorubicin.[12,13] The clinical course can be prolonged, although subsequent relapses often are associated with increased severity of signs and diminishing response to treatment.

A waxing and waning disease course and occasional spontaneous remission complicate the assessment of treatment efficacy. Nonetheless, repeatable responses to immunomodulatory agents capable of inhibiting T-cell activation support the theory that reactive histiocytosis is the result of disordered immune regulation arising from abnormal DC/T-cell interactions and not a neoplastic process.

Feline Progressive Histiocytosis

Histiocytic proliferative diseases are uncommon in cats. One characterized syndrome is feline progressive histiocytosis, a disease of DC origin. Affected cats typically are older, with a median age of 10 years (range, 2-17 years).[15] Cats present with intradermal papules and nodules in the skin that are occasionally solitary, but more often multiple. Similar to reactive histiocytosis in dogs, lesions wax and wane in size, although unlike canine histiocytosis, complete spontaneous regression was not seen in one series of 30 cats.[15]

Diagnosis requires histopathologic examination and consideration of immunophenotyping. Microscopic lesions consist of diffuse dermal histiocytic infiltrates, which may extend into the subcutis. Some lesions

manifest epitheliotropism. Cellular atypia and extension deep into the subcutis are more notable in late-stage lesions.[8,15] Histiocyte antigen expression patterns are consistent with DC origin.[8,15]

Nodules progress in size over time, with some coalescing to form larger plaques that can become ulcerated and painful. In the majority of cats, lesions remain confined to the skin for extended periods. Occasionally, internal involvement is present at the time of diagnosis, as was the case in 4 of 22 (18%) cats in the series noted above.[15] Lymph node evaluation, thoracic radiographs, and abdominal sonography are helpful in determining whether internal sites of disease are present. The disease usually is progressive over months to years (median 13.4 months) and in the advanced disease setting, spread to internal sites becomes more common, as reported in 4 of 18 (22%) cats.[15]

Given its diffuse nature, surgery is of limited benefit and should be reserved for lesions that are particularly bothersome or causing morbidity. In the study cited above, surgery was performed in 8 cats.[15] Local tumor recurrence was seen in 4 cats and all 8 cats developed additional lesions distant from the surgery site. Medical therapy including corticosteroids, chemotherapy agents (L-asparaginase, vincristine, vinblastine, cyclophosphamide, nitrogen mustard) and immune modulating agents (corticosteroids, cyclosporine, leflunomide, interferon-gamma, retinoids) have met with disappointing results.

Feline progressive histiocytosis is characterized by multiple cutaneous nodules and a slowly progressive disease course. Lesions may wax and wane and disease may stay confined to the skin for long periods of time. The etiology is unknown. While certain features are similar to canine reactive histiocytosis, the lack of spontaneous remissions and non-responsiveness to immunomodulatory drugs makes an etiology linked to immune dysregulation unlikely. Instead it appears that feline progressive histiocytosis represents a neoplastic process, initially indolent and ultimately more aggressive.

Histiocytic Sarcoma Complex

Malignant disease of histiocytic origin was first reported in dogs in the late 1970s.[16] One early report described histiocytic sarcoma (HS) in 11 Bernese Mountain Dogs, 9 of whom were closely related, suggesting a genetic predisposition in this breed.[17] Flat-Coated Retrievers, Rottweilers, Golden Retrievers, and Labrador Retrievers also appear to be overrepresented.[18,19] While not considered an at-risk breed for HS in other body regions, Pembroke Welsh Corgis are overrepresented in cases originating within the central nervous system (CNS), comprising 47% of the study population in one report.[20,21] Affected dogs are typically middle-aged.

While classification continues to evolve, *histiocytic sarcoma* has become the preferred term for this group of malignancies, with two forms described: localized HS and disseminated HS (formerly referred to as malignant histiocytosis). Both arise from DCs, with characteristic positive staining for CD11c and CD18 antibodies. While microarray analyses have identified variation in gene expression between localized and disseminated HS,[22] they are morphologically and immunophenotypically identical and are distinguished on the basis of clinical presentation. Localized HS arises from a single organ while disseminated HS is a multisystem disease. Hemophagocytic HS represents another subtype, unique in its macrophage origin, and characterized by positive CD11d and CD18 antibody staining.

Localized Histiocytic Sarcoma

Localized HS most commonly affects the skin and subcutis, most often of the limbs and periarticular tissues, although other reported sites include spleen, lung, brain, spinal cord, nasal cavity, bone, and bone marrow.[18-21,23-26] Periarticular and CNS forms of disease have been described as unique subsets of localized HS.[20,21,23,26] Periarticular HS might be more common in Rottweilers.[23] Lameness and/or periarticular soft tissue swelling are the most common presenting clinical signs, reported in 79% and 68% of dogs, respectively, in one study.[26] The stifle appears to be the most common location, reported in 37-61% of dogs.[23,26] Interestingly, 55% of dogs in one study had a history of cranial cruciate ligament (CCL) rupture in the same joint later developing HS.[23] Inflamed synovium from dogs with CCL rupture contains numerous DCs, although a relationship between inflammation and subsequent tumor development has not been well defined.[27] Radiographs are indicated for dogs with suspected periarticular HS. Sixty percent of dogs in one study had radiographic evidence of osteolysis or proliferation at the tumor site.[26] HS of the CNS can be localized, confined to a single site within the brain or spinal cord, or multifocal (see ch. 260 and 267). Presenting signs reflect neuroanatomic location (see ch. 259) and include seizures, altered mentation or behavioral changes, postural reaction deficits, and paresis.[20,21] Metastasis is present in 15-70% of dogs with localized HS at the time of diagnosis and 50-90% of

dogs eventually develop metastatic disease to lymph nodes, lung, and abdominal viscera.[18,21,23,24,26]

Disseminated Histiocytic Sarcoma

Disseminated HS involves multiple organ systems, suggesting either progression and metastasis from the localized form of disease or a primary multicentric disease with tumors arising simultaneously in multiple locations. Lungs, spleen, liver, lymph nodes, and/or bone marrow are most commonly affected.[18] Diagnosis of HS requires cytologic (see ch. 93) or histopathologic evaluation and consideration of immunophenotyping. With any diagnosis of HS, staging evaluation including lymph node aspiration for cytologic assessment (see ch. 95; or biopsy for histopathologic evaluation), thoracic radiographs, an abdominal sonogram (see ch. 88) ± cytologic assessment of bone marrow (or bone marrow biopsy; see ch. 92) is indicated to characterize extent of disease.

Treatment of Histiocytic Sarcoma

Limited reports document outcome after surgical excision of localized HS. One study reported a median survival time of 6 months in 5 dogs with synovial HS treated with amputation alone.[23] Chemotherapy should always be considered, either as adjuvant therapy for localized HS or for treatment of metastatic or disseminated HS. CCNU appears to be the most effective chemotherapeutic agent for treating HS in dogs. Overall response rates of 29-46% have been reported when CCNU is used for treating gross measurable disease, with a median response duration of 90 days (range, 29-805 days).[28,29] An improved outcome can be achieved for localized HS when local therapy is combined with adjuvant CCNU chemotherapy. In one series, 16 dogs with localized HS and no evidence of distant metastatic disease were treated with intensive local therapy (surgery and/or radiation therapy) and CCNU chemotherapy.[30] Metastatic regional lymph nodes, identified in 4 of 16 (25%) dogs at the time of diagnosis, were resected at the time of primary tumor removal. Median disease-free interval was 8 months and overall median survival time was 18.6 months in this study.[30]

A more favorable outcome has been suggested for dogs with periarticular HS. One study reported a median survival of 391 days (range, 48-980 days) for dogs treated in a variety of ways, including local therapy combined with chemotherapy (47%), chemotherapy alone (42%) or local therapy alone (11%). This outcome was achieved despite an overall metastatic rate of 68% at the time of diagnosis.[26]

Combination chemotherapy may be superior to single-agent therapy, although ideal agents and combinations have yet to be determined. There is limited information regarding other effective chemotherapy drugs, although doxorubicin, paclitaxel, and vinorelbine have shown some promise.[26,31-33] A study reporting the use of alternating doxorubicin and CCNU described an overall response rate of 58% and median time to progression of 185 days (range, 59-268) in dogs with measurable gross disease.[34]

Another area of study has focused on the potential role of the bisphosphonate clodronate, which kills osteoclasts and other macrophages via induction of apoptosis. When clodronate is incorporated within liposomes, uptake by phagocytic cells is greatly enhanced, resulting in selective targeting of macrophages. Susceptibility of HS cells to this approach has been demonstrated *in vitro*.[35] A pilot study of liposomal clodronate demonstrated regression of lesions in 2 of 5 dogs (40%) with HS.[35] Combining bisphosphonates with chemotherapy may prove beneficial. In vitro data suggest an increase in HS cytotoxicity when selected bisphosphonates are combined with either vincristine or doxorubicin.[36]

Hemophagocytic Histiocytic Sarcoma

While DC origin is a common element among other histiocytic diseases, the neoplastic histiocytes in hemophagocytic HS are of macrophage origin. Cells express a distinctive surface antigen profile consistent with their origin within the splenic red pulp and bone marrow. Hemophagocytic HS appears to be more common in certain breeds, including Bernese Mountain Dogs, Golden Retrievers, and Rottweilers.[37]

Its clinicopathologic features also are unique, perhaps the most striking of which is marked erythrophagocytosis by neoplastic histiocytes, resulting in a moderate to marked regenerative hemolytic anemia. Ninety-four percent of dogs in one study presented with regenerative anemia (median Hct 22.6%, range 10.1-37).[37] Other common findings include thrombocytopenia (88%), hypoalbuminemia (94%), and hypocholesterolemia (69%).[37] Splenomegaly with diffuse, ill-defined nodular change is consistently present. Liver, bone marrow, and lungs frequently are diffusely infiltrated and spread occurs via insidious intravascular invasion with minimal mass formation.

Diagnosis is made cytologically or histopathologically, with consideration of immunophenotyping. There

appears to be marked variation in the cytologic characteristics of neoplastic histiocytes, although marked erythrophagocytosis accompanied by foci of extramedullary hematopoiesis is a consistent feature.[37] Not to be confused with immune-mediated hemolytic anemia and thrombocytopenia (Evans syndrome; see ch. 198 and 201), dogs with hemophagocytic HS are Coombs-negative. Staging evaluation including lymph node evaluation (see ch. 95), thoracic radiographs, abdominal sonography (see ch. 88) and bone marrow aspiration (see ch. 92) for cytologic assessment (or biopsy) is indicated to characterize the extent of disease.

Hemophagocytic HS carries a poor prognosis, and reports on durable effective treatments are lacking. In one study of 17 dogs, all dogs died or were euthanized, with a median time from initial onset of clinical signs to death or euthanasia reported as 4 weeks (range 2-32 weeks)[37]; information on attempted treatments was not provided. Given reported activity against other forms of HS, CCNU may be a reasonable consideration. Unfortunately, in one study reporting the use of CCNU, while not specifically characterized as hemophagocytic HS, dogs with anemia, thrombocytopenia, hypoalbuminemia and splenic involvement were significantly less likely to respond to treatment. Further, thrombocytopenia and hypoalbuminemia were associated with a significantly decreased median survival of 28 days or less, compared with 163 days or longer in the absence of these signs.[28]

HS rarely has been reported in cats. In one series of 3 cats, the disease closely resembled hemophagocytic HS in dogs.[38] Age at presentation was variable (1, 4, and 9 years). Anemia (packed cell volume, 9-15%) and thrombocytopenia (31,000-94,000 cells/mcL) were identified in all 3 cats. All cats were euthanized shortly after the diagnosis. Postmortem evaluation identified malignant histiocytic cells exhibiting erythrophagocytosis in the liver, spleen, and bone marrow in each cat. Other sites of disease included lymph node, lung, kidney, brain and urinary bladder.

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CHAPTER 351

Urogenital and Mammary Gland Tumors

Juan F. Borrego

Client Information Sheet: Canine Mammary Gland Tumors

Urinary Bladder and Urethra

Prevalence and Risk Factors

Tumors of the urinary bladder are uncommon in dogs and rare in cats but their prevalence appears to be increasing over the last 30 years.[14] Most bladder and urethral tumors are epithelial and malignant. Intermediate to high-grade invasive transitional cell carcinoma (TCC) is by far the most common diagnosis in both species.[1] Other differentials include squamous cell carcinoma, adenocarcinoma, rhabdomyosarcoma, lymphoma, and other mesenchymal tumors.[15] A trigonal location with urethral and prostatic involvement is frequent with this type of tumor, often leading to urinary tract obstruction (Figure 351-1; see ch. 335).[15] Metastatic disease is detected in 10-20% of dogs at time of diagnosis and in up to 58% at necropsy.[16] Common metastatic sites of canine TCC include lymph nodes, lung, bone, and skin.[1,17,18] Feline TCC is uncommon, affects geriatric cats, metastasis is rare, and the majority do not involve the bladder trigone.[19,20]

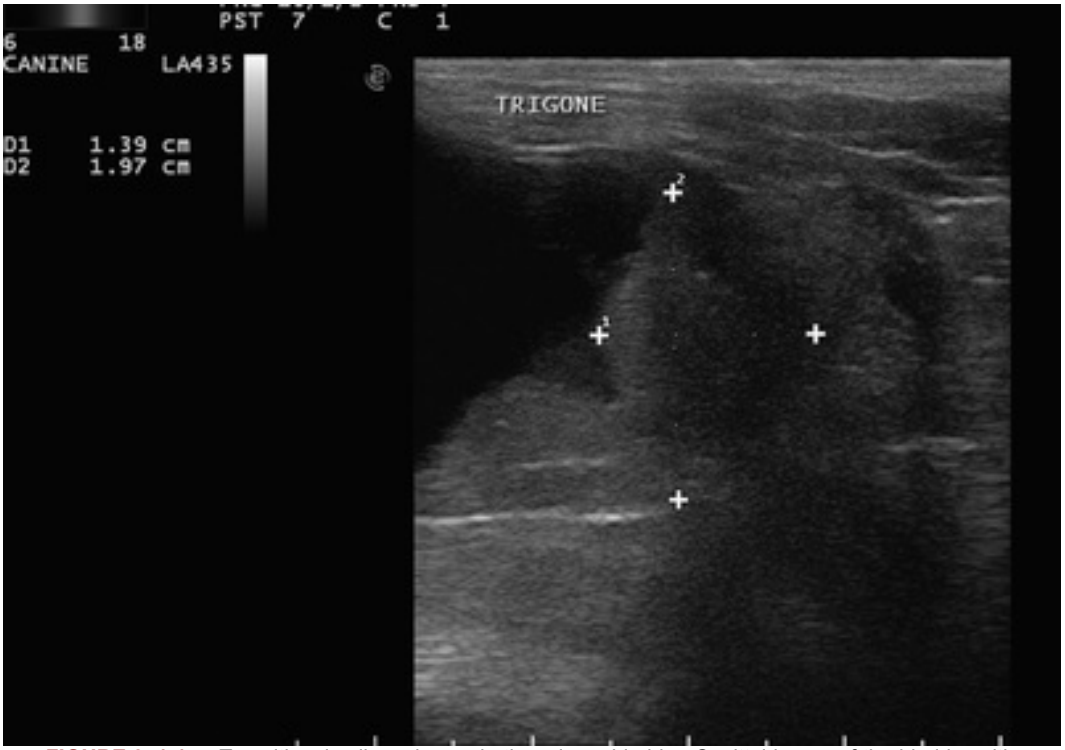


FIGURE 351-1 Transitional cell carcinoma in the urinary bladder. Sagittal image of the bladder with a lobulated mass in the trigone.

Several risk factors have been described for TCC in dogs. Older (9-11 years) female dogs seem to be predisposed and small breeds, such as Scottish Terriers, are up to 21 times more likely to have TCC. West Highland White Terriers, Shetland Sheepdogs, and Beagles are three to five times more likely to have TCC than are mixed-breed dogs.[14,17,21] Other potential factors include obesity, neutering status, and cyclophosphamide therapy. Exposure to older-generation flea control products and lawn chemicals have been associated with TCC, while newer spot-on flea control products, such as fipronil, appear safer.[21-23] Vegetable consumption has been reported to reduce the risk of TCC in Scottish Terriers.[24]

Signs and Diagnosis

Common clinical signs caused by neoplasia within the bladder or urethra mimic bacterial cystitis or urolithiasis and are typical of lower urinary tract infection (UTI) or inflammation: stranguria, pollakiuria (see ch. 46), hematuria (see ch. 47), dysuria, urinary incontinence (see ch. 46), or any combination thereof. Antibiotic treatment may temporarily resolve signs, since concurrent infections are documented in about 25% of cases at diagnosis.[25] If clinical signs do not completely resolve with antibiotic treatment or if they reoccur, the presence of stones or cancer should be investigated, especially in predisposed breeds (Figure 351-2). In advanced cases, a mass is palpable in the caudal abdomen; abnormalities such as a thickened urethra or enlarged sublumbar or intrapelvic lymph nodes may be identified on rectal examination. Less commonly, dogs can have lameness caused by pain due to bone metastasis. Skin metastases can appear as erythematous, ulcerated, or proliferative lesions.[18]

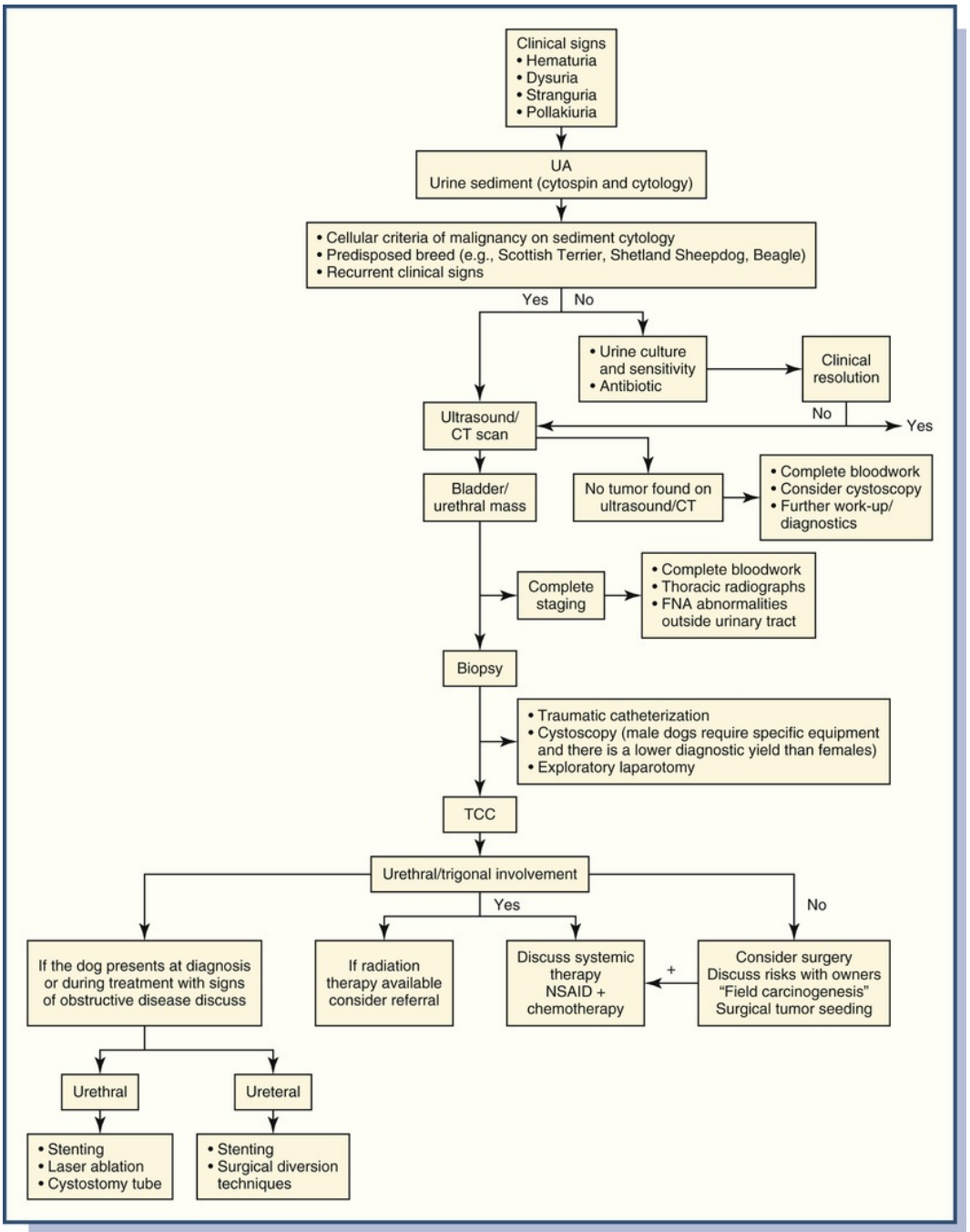


FIGURE 351-2 Algorithm for the evaluation of bladder and urethral tumors. *CT,* Computed tomography; *TCC,* transitional cell carcinoma; *NSAID,* nonsteroidal anti-inflammatory drug; *UA,* urinalysis.

Following a thorough physical examination (see ch. 2), a complete blood count (CBC), serum chemistry profile and urinalysis (UA) should be performed. Due to the high rate of UTI, urine culture and sensitivity tests should be included in the initial evaluation and periodically during treatment.[25] Urine from these patients should be obtained by free catch or catheterization. If cystocentesis is needed, ultrasound guidance should be employed to avoid penetrating the tumor mass. The presence of abnormal epithelial cells in the urine sediment of pets with a bladder mass or thickened wall is suggestive of TCC; however, other inflammatory conditions have "reactive" epithelial cells (Figure 351-3). Thoracic radiography should be performed to assess for lung metastasis. Abdominal ultrasound is preferred for assessing location and extent of disease (E-Figure 351-4). Ultrasonography should not be the only method of assessment due to inter- and intraoperator variability.[26,27] Histological examination of cytology or tissue samples obtained via traumatic catheter (Videos 351-1 and 351-2), surgical, or cystoscopic biopsy often provides a definitive diagnosis (see

ch. 93). Ultrasound-guided aspiration or biopsy is not recommended, as seeding of the biopsy tract with viable tumor cells is a possible complication.[28,29] Cystoscopic biopsy is an effective method to obtain biopsy samples in dogs with TCC of the bladder and urethra. Cystoscopy (see ch. 108) is more likely to produce a diagnostic-quality biopsy sample in female dogs with TCC (96%) than in male dogs with TCC (65%).[30]

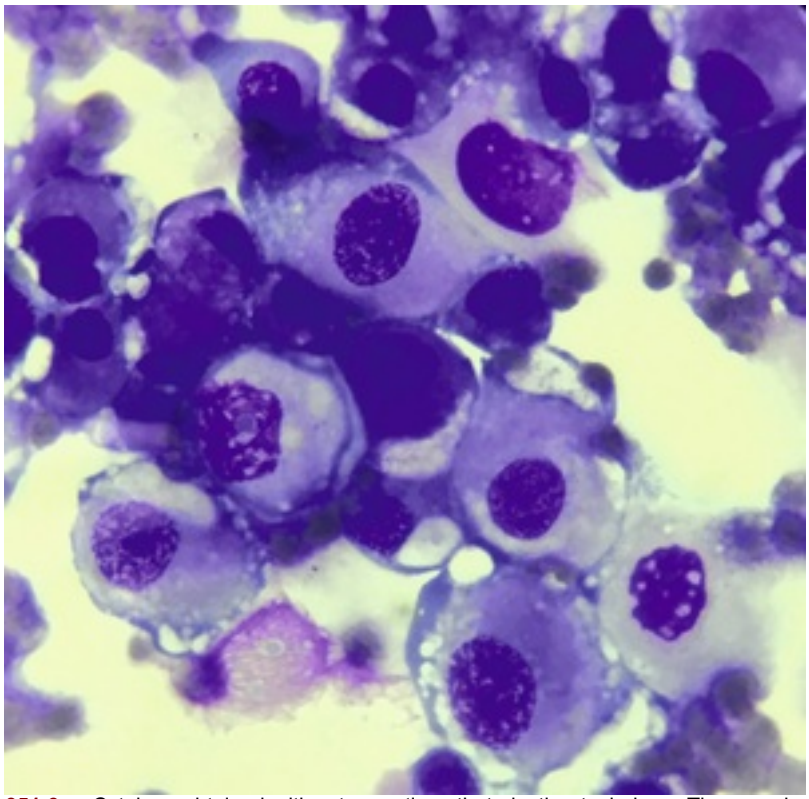
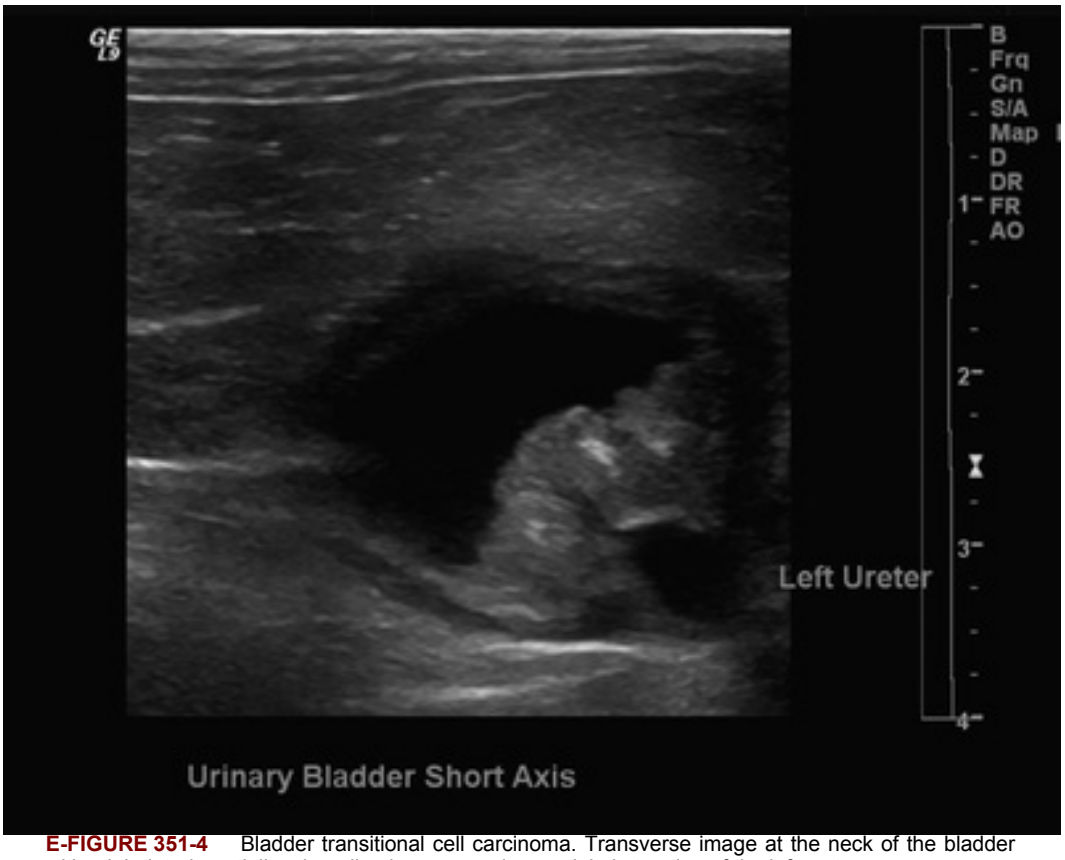


FIGURE 351-3 Cytology obtained with a traumatic catheterization technique. The sample contains dense clusters of round to polygonal cells. There are several criteria of malignancy including moderate anisocytosis and anisokaryosis, variable nuclear-cytoplasmic ratio and prominent nucleoli.



E-FIGURE 351-4 Bladder transitional cell carcinoma. Transverse image at the neck of the bladder with a lobulated, partially mineralized mass causing partial obstruction of the left ureter.

Treatment

Most dogs with TCC are managed with drug therapy and, less commonly, radiation or surgery. Surgery should be considered for tumors located cranially in the bladder; however, because the trigone region is usually involved, complete resection with acceptable postoperative function is rarely feasible. TCC has also been reported in the abdominal wall, most likely due to its highly exfoliative nature. Abdominal wall TCC is likely to have been implanted during procedures such as surgery to obtain biopsy specimens, tumor removal, tumor debulking, cystotomy tube placement or fine-needle aspiration (FNA) of TCC in the urinary bladder, urethra, and prostate.[31] TCC located in the abdominal wall carries a worse prognosis, so caution is warranted to avoid seeding the tumor into the abdomen or along the surgery site during those procedures, especially surgery (Figure 351-5).[31] After handling the mass, new gloves and clean sterilized instruments should be used to close the abdomen.

FIGURE 351-5 Abdominal wall transitional cell carcinoma tumor seeding after a subtotal cystectomy to remove the primary bladder tumor. Transitional cell carcinomas located in the abdominal wall carry a worse prognosis than those in the urinary tract.

Chemotherapy, cyclooxygenase (COX) inhibitors, and combinations thereof are the mainstay of treatment for TCC in dogs. Remission rates are typically less than 20% with single-agent therapy (nonsteroidal anti-inflammatory drug [NSAID] or chemotherapy), and 35-50% with combined chemotherapy including a COX inhibitor.[15,16] Platinum agents appear to be the most active in canine TCC, especially when combined with a COX inhibitor,[32] although combinations of cisplatin and piroxicam should be avoided, due to high rates of nephrotoxicosis and kidney failure.[33,34] Some of the other chemotherapy drugs most often used as single agents include mitoxantrone, doxorubicin, vinblastine, and gemcitabine.[14] Median survival times in dogs with TCC are typically between 130 and 195 days after single-agent drug treatment and >250 days after combination drug treatment.[16] The current treatment recommendations for single-agent therapy are a non-selective COX inhibitor such as piroxicam (0.3 mg/kg PO q 24 h)[16] or a more selective COX inhibitor such as deracoxib or firocoxib.[33,35] In case of combination therapy, a COX inhibitor and a chemotherapy drug with known antitumor activity in this disease should be used, using response to therapy every 4-8 weeks as a guideline for continued treatment.[16] One emerging treatment strategy is metronomic chemotherapy using orally administered chlorambucil, which has had good results, including 67% of patients with stable disease and 3% with partial remissions.[36]

Because TCC in cats is often located in the cranial bladder, surgery is an option to be considered. COX inhibitors (piroxicam and meloxicam) used alone or in combination protocols may have a role in the palliative management of TCC in the urinary bladder of the cat with reported survival times of 261 to 311 days.[19,20]

Newer state-of-the-art radiation therapy equipment enabling the administration of a highly conformal dose of radiation to a select target has made it possible to treat TCC as part of a combination protocol with medical therapy with a much lower risk of damage to surrounding tissues.[37,38] The advantages of this technique are that it is non-invasive, urinary continence is retained, and local control can be achieved. The disadvantages are related to the cost and availability of such radiation facilities.

Palliative Procedures and Prognosis

Most dogs with TCC die from complications secondary to urinary tract obstruction prior to the development of substantial metastatic disease. Several surgical techniques have been described to palliate TCC obstructing the urethra (see ch. 124); however, they are not commonly performed due to morbidity and cost. Uretero-

colonic anastomosis is not recommended because it is associated with neurologic and gastrointestinal complications secondary to hyperammonemia, metabolic acidosis, uremia, and chronic pyelonephritis. Other techniques with better outcomes include total cystectomy and removal of the bladder neck and trigone.[39,40] For neoplasia confined to the urethra, vaginourethroplasty and transurethral resection have been described.[16,41,42]

Cystostomy tubes have been used as a much simpler and better-tolerated procedure to bypass urinary obstructions that allows pets to survive an additional average of 3 months.[43,44] Techniques for placing a cystostomy tube include open approaches to the caudal abdomen, minimally invasive approaches to the abdomen, laparoscopic approaches, or use of fluoroscopy and a self-retaining, pig-tail catheter. Complications are frequent but easily managed, the most common being inadvertent tube removal and UTIs.

Another palliative option is urethral stent placement via interventional radiography (see ch. 124).[45,46] With the caveat of urinary incontinence in 26-39% of dogs, urethral stents are well tolerated and solve urinary tract obstructions in 97% of cases.[45,46] Despite the good short-term urinary tract obstruction resolution rate, this technique remains palliative with short median survival times.[45-47] Another palliative option is ultrasound-guided endoscopic laser and carbon dioxide laser ablations to debulk and remove obstructive or potentially obstructive TCC lesions. The main risk of this procedure is bladder perforation.[48]

Kidney Tumors

See E-Box 351-1.

E-Box 351-1

Kidney Tumors

Primary renal neoplasia is uncommon, estimated to account for 0.3-1.5% of all canine neoplasms.[1] Epithelial tumors and, in particular, renal cell carcinomas are the most common primary tumor of the canine kidney and must be differentiated from other primary epithelial neoplasms, including renal adenomas, renal oncocytomas, nephroblastomas, transitional cell carcinomas, lymphoma and sarcomas.[1-3] The average age of dogs with renal tumors is around 9 years, and males are overrepresented with a reported male/female ratio of 1.2-1.6 : 1.[2,4] An unusual syndrome in female German Shepherds includes the presence of cystadenocarcinoma with concurrent nodular dermatofibrosis and uterine tumors.[5]

The most common renal tumor in cats is lymphoma. In contrast with older reports, most affected cats in the post–feline leukemia virus (FeLV) era are not concurrently infected with the virus; the median age is 9 years, with no breed or sex predilection.[6] Other primary tumors affecting the kidneys in cats include adenoma, adenocarcinoma, transitional cell carcinoma, hemangiosarcoma, nephroblastoma, and squamous cell carcinoma.[1,7]

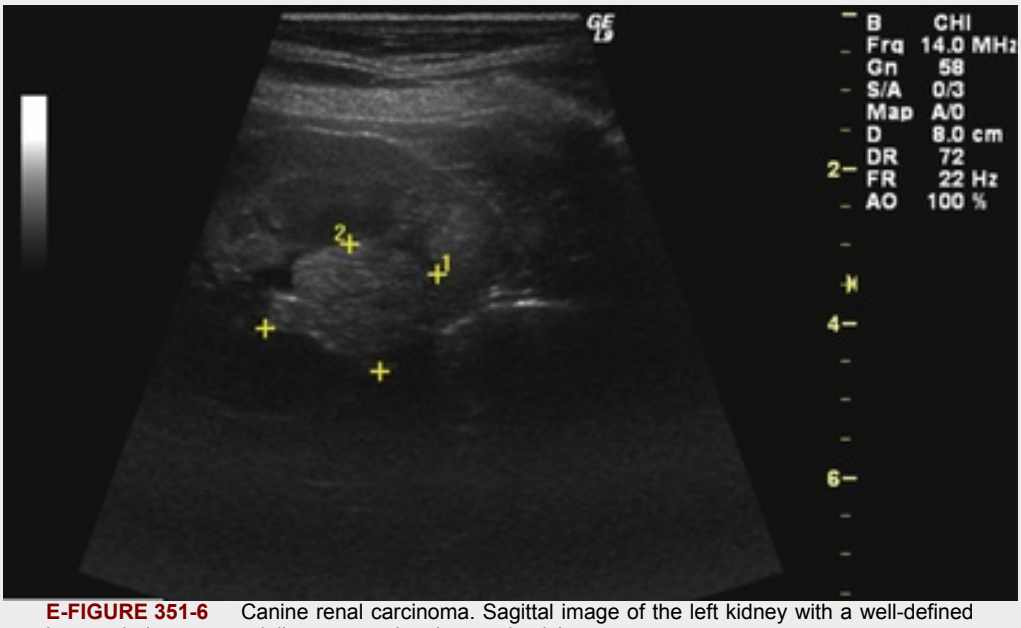
Animals can present with any combination of nonspecific signs, such as inappetence, weight loss, lethargy, vomiting, or hematuria. Physical examination may reveal unilaterally or bilaterally enlarged kidneys, which may be painful on palpation. Renal cystadenocarcinoma may be associated with firm, nodular dermal lesions and benign uterine growths in German Shepherds.

Histopathological examination is required for diagnosis, although ultrasound-guided cytology (see ch. 89) could be diagnostic in the majority of lymphoma cases.[3,6] Tumor tissue can be obtained by ultrasound-guided percutaneous biopsy or at surgery (see ch. 89). Ancillary tests such as a complete blood count (CBC), serum chemistry profile, and urinalysis (UA; see ch. 72) could detect anemia or erythrocytosis secondary to decreased or increased erythropoietin production, nonspecific serum biochemical changes such as azotemia or hypoalbuminemia, and, potentially, certain rarer paraneoplastic syndromes associated with renal tumors, such as neutrophilic leukocytosis.[8]

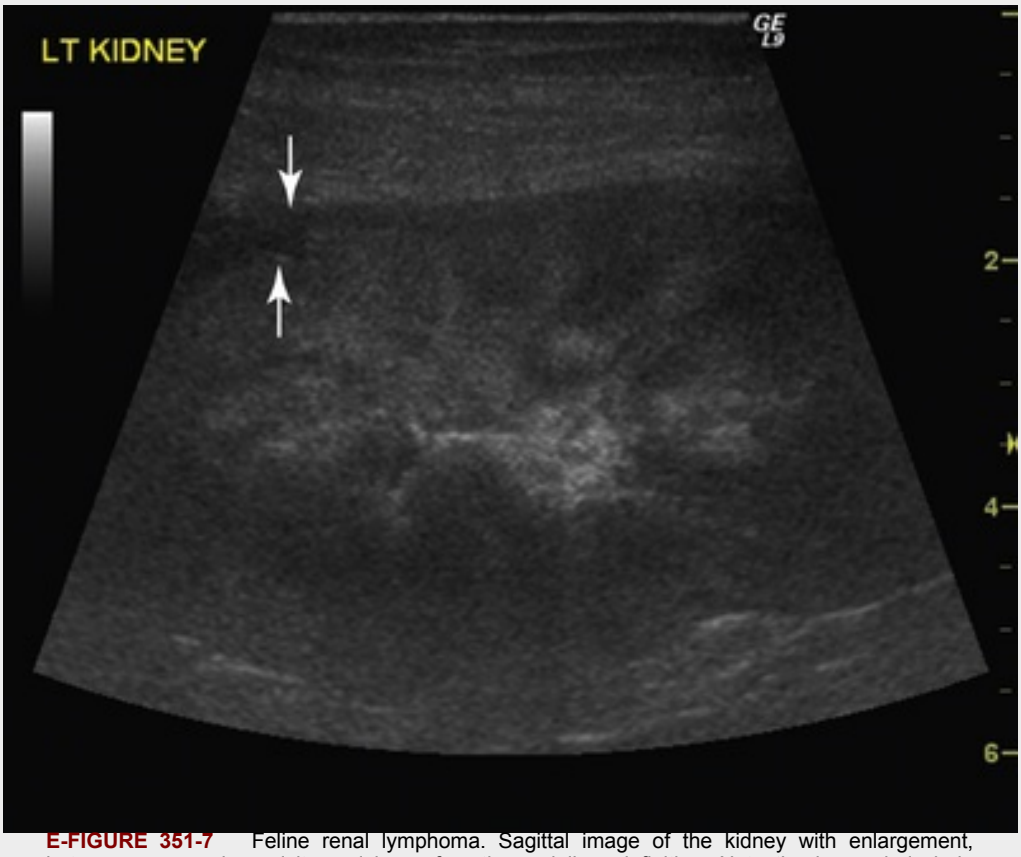
Thoracic radiographs are part of clinical staging since dogs and cats with epithelial renal tumors can develop pulmonary metastases; indeed, this has been reported in as many as half of dogs with primary tumors.[9] Newer studies[3,4] show lower pulmonary metastatic rates at diagnosis in renal cell carcinoma (RCC; 11-18%), probably because dogs today live in an era of increased clinical detection of disease.

In terms of imaging techniques, abdominal ultrasonography (E-Figure 351-6; see ch. 88) is preferred to abdominal radiographs, as it helps with the staging of the patient by enabling examination of regional

lymph nodes and other intra-abdominal structures and guides the fine-needle aspiration (FNA) of these organs.[10] The combination of renomegaly, hypoechoic focal lesions, and bilateral involvement seems to be a common ultrasonographic characteristic in canine lymphoma. Bilateral involvement is common for lymphoma but is rare in patients with carcinoma.[3,10,11] Renal lymphoma imaging in cats usually reveals bilateral (>80%), irregular renomegaly with hypoechoic subcapsular thickening[12] (E-Figure 351-7), as well as the involvement of other organs.



E-FIGURE 351-6 Canine renal carcinoma. Sagittal image of the left kidney with a well-defined hyperechoic mass partially compressing the renal pelvis.



E-FIGURE 351-7 Feline renal lymphoma. Sagittal image of the kidney with enlargement, heterogeneous echogenicity and loss of corticomedullary definition. Note the hypoechoic halo around the kidney (arrows). (Courtesy Ricardo Guillem Gallach, Penn Vet Radiology, University of Pennsylvania, Philadelphia, USA.)

Surgical planning should evaluate renal function. Some of the available tests for doing so include excretory urography, computed tomography (CT), and evaluation of the glomerular filtration rate (GFR) via scintigraphy. Caval invasion by RCC is an uncommon finding; however, it should be assessed by ultrasonography or CT prior to surgery.[4]

With regard to surgery, nephrectomy is the most effective treatment for dogs with unilateral tumors, with median survival times of 16-24 months for carcinomas, 9 months for hemangiosarcomas, and 6 months for nephroblastomas.[3,4,13] A mitotic index >30 seems to be associated with a worse outcome in RCC following surgery.[4] The role of adjunctive therapy in canine renal tumors remains unclear, with some studies suggesting no benefit.[4] Treatment with chemotherapy is indicated for cats or dogs with renal lymphoma (see ch. 344). In addition to being bilateral, the disease is typically systemic, and on rare occasions primary.[10] Extension to the central nervous system (CNS) is frequent in cats (40-50%). Multidrug protocols are more commonly used with the addition of drugs that reach the CNS (e.g., cytosine arabinoside). With treatment, the average survival time is 3-6 months.[6,13] Surgery is the treatment of choice for cats with other renal tumors. Renal cystadenocarcinomas in German Shepherds, although malignant and metastatic, progress more slowly than other renal malignancies, and survival times may be longer.

Prostatic Tumors

Prevalence, Risk Factors, and Signs

Prostatic tumors are rare in dogs, with a prevalence of less than 1% (see ch. 337). Median age at diagnosis is 10 years. Neutered dogs, Shetland Sheepdogs and Scottish Terriers have an increased risk.[49-51] The majority are carcinomas and may arise from the glandular epithelium, prostatic ducts, or prostatic urethra. Other conditions to be included in the differential diagnosis for prostatomegaly, especially in intact male dogs, are

chronic prostatitis, prostatic abscessation, benign prostatic hyperplasia (BPH), and prostatic cysts.[52] Due to rapid growth and high risk for metastasis (up to 80% in necropsy studies),[53] dogs may be seen late in the course of the disease, when clinical signs are representative of metastatic disease (weight loss, rear limb lameness, pain or neurological signs) rather than a primary urogenital disease (stranguria, hematuria, pollakiuria). Skeletal metastases are documented in as many as 40% of dogs at the time of diagnosis, causing pain, gait abnormalities or lameness. Other clinical signs caused by the enlarged prostate or metastases to local lymph nodes include dyschezia, tenesmus, constipation, or ribbon-like stools.

Diagnosis

Rectal examination usually reveals an asymmetric, fixed, and firm prostate. Continuing careful rectal palpation, one may also be able to detect enlarged intrapelvic lymph nodes. A CBC and serum chemistry profile may show non-regenerative anemia, leukocytosis, azotemia due to obstructive disease, and/or paraneoplastic hypercalcemia (see ch. 352). Bacteriuria is often detected on UA because UTI is common in these dogs. Neoplastic cells may be seen in urine sediment, although differentiation between reactive and neoplastic epithelial cells may not be possible.[53] Due to the high percentage of distant metastatic disease at diagnosis, three-view thoracic radiographs are recommended. Abdominal ultrasound (see ch. 88) is preferred over abdominal radiography to determine locoregional lymph node metastasis, bladder/ureter involvement, and other potentially affected intra-abdominal organs (E-Figure 351-8). Mineralization of the prostate on abdominal radiographs or ultrasound is not pathognomonic for prostatic carcinoma, because other benign processes cause mineralization; however. this finding is highly suggestive of neoplasia.[54] While bone metastasis that appears as lytic, proliferative, or mixed lesions on radiography can occur anywhere, lumbar vertebrae are the most common location, followed by the pelvis and femur (Figure 351-9).

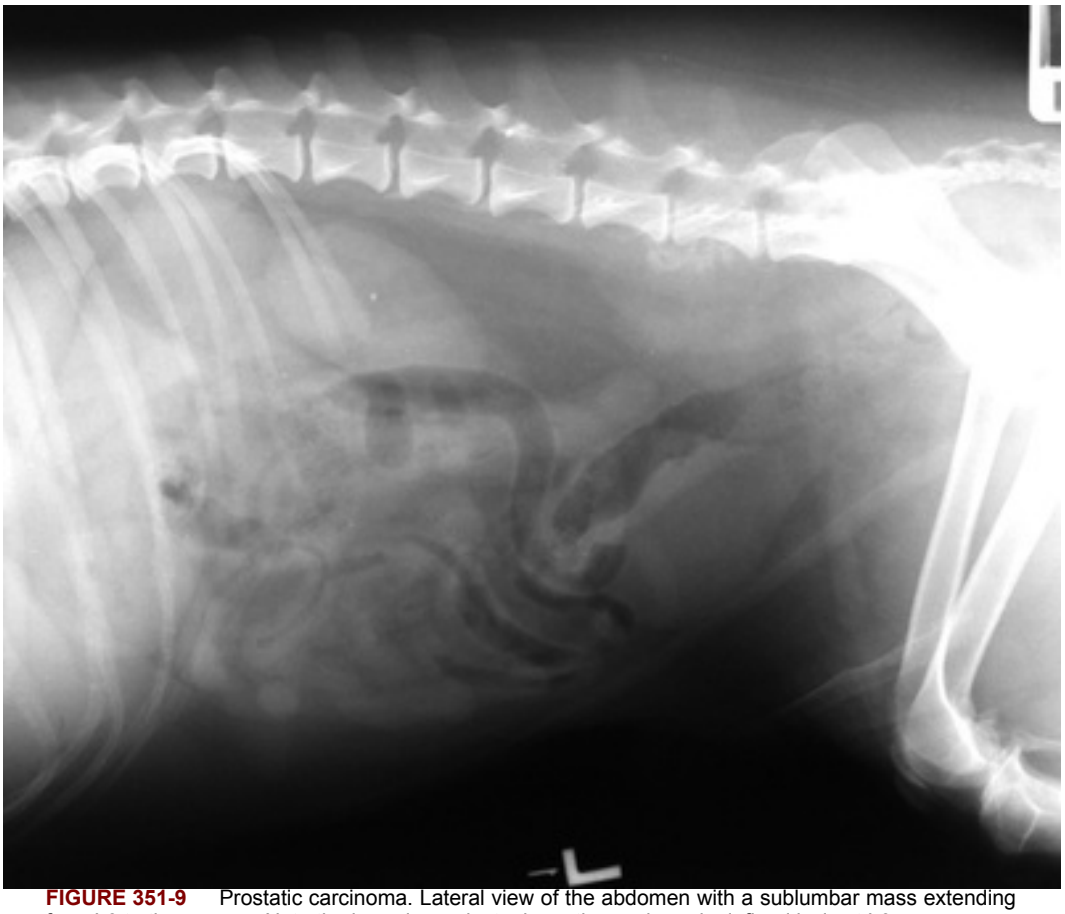
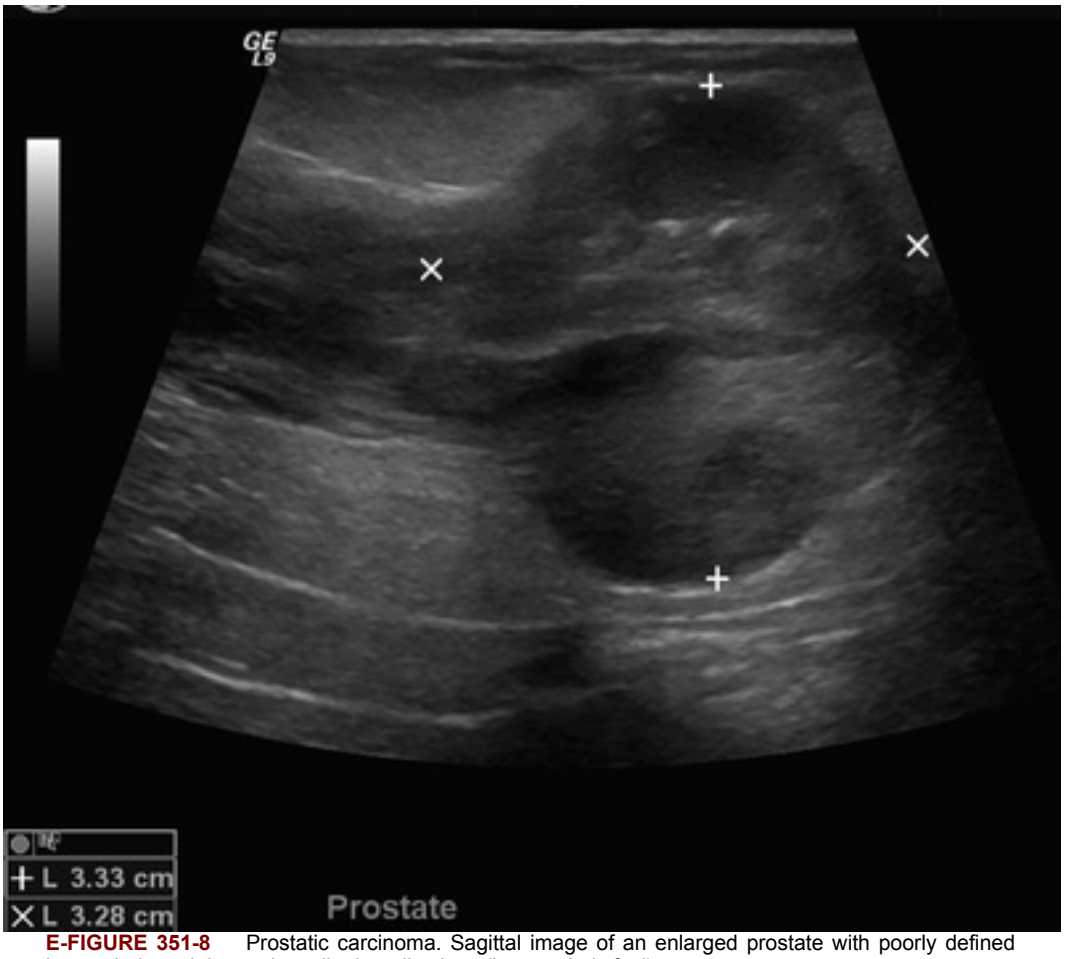


FIGURE 351-9 Prostatic carcinoma. Lateral view of the abdomen with a sublumbar mass extending from L6 to the sacrum. Note the irregular periosteal reaction and poorly defined lysis at L6.



E-FIGURE 351-8 Prostatic carcinoma. Sagittal image of an enlarged prostate with poorly defined hypoechoic nodules and small mineralizations (hyperechoic foci).

Histologic examination remains the gold standard for diagnosis of prostatic cancer. Despite common secondary infections and inflammation, agreement between cytological and histological findings is high for prostatic carcinoma.[52,55] Samples for cytologic examination (see ch. 93) can be collected via traumatic catheterization (see ch. 111), prostatic wash (see ch. 111), or ultrasound-guided needle aspiration (see ch. 89). Cytology or histology of any other suspected metastatic lesions (e.g., lymph node, bone) may aid with diagnosis and staging. Ultrasound-guided aspiration and biopsies should be performed carefully due to the possibility of seeding the tumor. However, only one case of tumor seeding has been published with prostatic tumors.[28] Prostatic adenocarcinoma is the most common tumor, followed by TCC.[53] Immunohistochemistry can be performed to further delineate cell of origin; however, canine prostatic carcinomas express markers of both urothelial and ductal origin, making the differentiation between adenocarcinoma and TCC problematic.

Treatment and Prognosis

Several histological subtypes have been reported, without changing prognosis.[53,56,57] Because the majority of dogs with prostate cancer are diagnosed with advanced disease, the overall prognosis is poor. Therapy is considered largely palliative, focusing on controlling local and distant metastatic disease. Several surgical techniques have been described to achieve local control; however, they are typically associated with high morbidity and poor outcomes (<3-4 months). Subtotal intracapsular prostatectomy could be considered in dogs with early stage disease, since it can immediately palliate local clinical signs and is associated with a lower rate of postoperative complications than total prostatectomy.[58]

Urethral obstructions can be managed with tube cystostomy or urethral stenting (see ch. 124). Palliative stenting can immediately alleviate obstructions in most dogs with a low complication rate. Incontinence and stent dislodgement are the common complications.[47] There is no consensus on standard-of-care systemic therapy to treat prostatic carcinoma, and the role of chemotherapy is still under investigation. However, most

of the treatment options include a COX-2 inhibitor. The use of piroxicam or carprofen was associated with an increased survival rate in treated patients compared to an untreated group. Image-guided intensity-modulated radiation therapy (IMRT) has shown promising results in treating local disease with few side effects and should be considered if there is evidence of distant metastatic disease.[37]

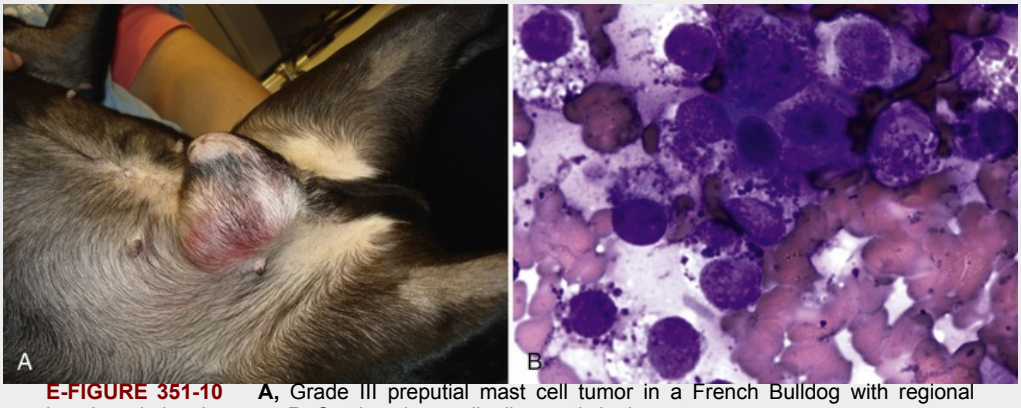
Penile, Preputial and Scrotal Tumors

See E-Box 351-2.

E-Box 351-2

Penile, Preputial, and Scrotal Tumors

Most tumors of the penile area have a soft-tissue origin and do not originate from the penile bone, with the most common type being the transmissible venereal tumor (TVT). Nevertheless, some tumors do occasionally arise from the penile bone, such as ossifying fibroma, chondrosarcoma, osteosarcoma or multilobular osteochondrosarcoma. The prepuce and scrotum could be affected by any cutaneous tumor occurring elsewhere on the skin (E-Figure 351-10). In one recent study, mast cell tumors (see ch. 349) accounted for more than 50% of scrotal tumors, followed by mesenchymal and melanocytic tumors.[59]



E-FIGURE 351-10 **A,** Grade III preputial mast cell tumor in a French Bulldog with regional lymph node involvement. **B,** Cytology is usually diagnostic in these tumors.

Complete staging including a minimum database (CBC, serum chemistry profile, urinalysis) and regional lymph node evaluation (palpation, aspiration or biopsy, and ultrasonography) is recommended prior to surgery. General recommendations for the treatment of penile tumors depend on the tumor site and involve either a partial penile amputation or ablation of the external genitalia with the creation of a urethrostomy in the scrotal area if necessary.[60] Scrotal and preputial mast cell tumors are associated with worse outcomes compared to other locations requiring a multimodal approach that should include local (surgery/radiation therapy) and systemic (chemotherapy/tyrosine kinase inhibitors) treatment.[61,62]

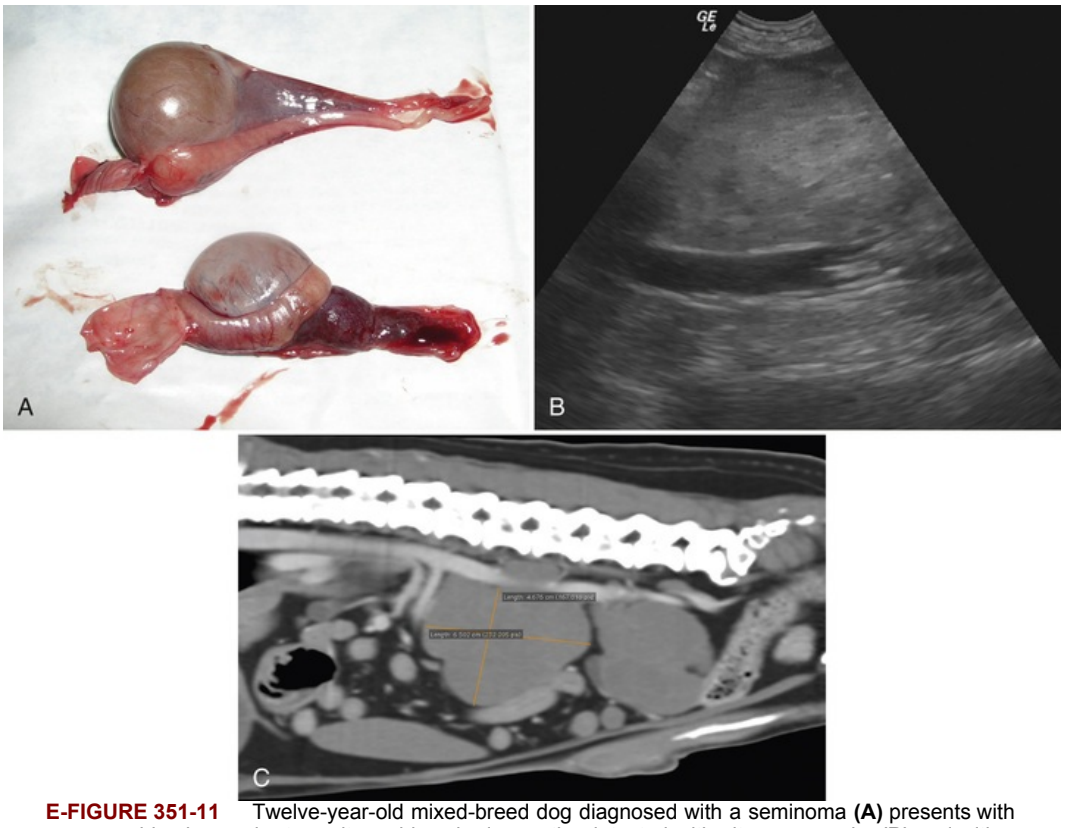
TVT rarely metastasizes, is readily diagnosed via cytology, and is usually curable with vincristine (0.5-0.7 mg/m^2 IV weekly).[63] The involution of the lesions is gradual, with complete remission in 90% of treated cases taking 2 to 8 injections. Therapy should be continued for 1 to 2 doses beyond complete visible resolution. Lesions that are resistant to vincristine may be successfully treated with doxorubicin or radiation therapy.

TESTICULAR Tumors

Prevalence, Diagnosis, Staging

The second most common tumor in intact male dogs (middle-aged to geriatric) is testicular, with three common histologic types: interstitial (Leydig) cell tumor, seminoma, and Sertoli cell tumor. Recent studies suggest a lower prevalence of Sertoli cell tumors (8-16%) and higher incidence of interstitial cell tumors and

seminomas.[64,65] Cryptorchid dogs have a higher risk of developing right-sided Sertoli cell tumors or seminomas, more commonly in testicles in the inguinal area than abdominal, and at a younger age than intact males.[65] Most testicular tumors do not metastasize. If Sertoli cell tumors or seminomas spread (<15%), it is usually to regional lymph nodes (E-Figure 351-11). Although most testicular tumors are incidentally noted on physical examination, clinical signs may include decreased libido, signs of prostatomegaly (stranguria, tenesmus), and inappetence and/or weakness secondary to anemia. Asymmetric testicles, scrotal or inguinal swellings and prostatomegaly secondary to estrogen-induced squamous metaplasia may be noted on physical and rectal examinations. Signs of hyperestrogenism including alopecia, gynecomastia, a pendulous prepuce, and a poor haircoat may be seen in as many as 50% of dogs with Sertoli cell tumors. Feminization signs are rare in seminomas and Leydig tumors. About 20% of dogs diagnosed with one testicular tumor, actually have two. Therefore, it is essential to always palpate both to compare size, shape, and firmness.[66]



E-FIGURE 351-11 Twelve-year-old mixed-breed dog diagnosed with a seminoma **(A)** presents with severe sublumbar and retroperitoneal lymphadenopathy detected with ultrasonography **(B)** and with a CT scan **(C)**.

Complete staging of these patients should include a CBC, abdominal ultrasound to evaluate regional lymph node size and to aid in identifying cryptorchid testicles, and three-view thoracic radiographs. Testicular ultrasound may aid in ruling out non-neoplastic processes such as orchitis or testicular torsion. Histology provides the final diagnosis; however, a diagnosis could also be obtained via FNA and cytology (see ch. 93).[67] Bone-marrow suppression is a rare but well-documented complication of hyperestrogenism, characterized initially by neutrophilic leukocytosis, which ultimately progresses into pancytopenia (see ch. 57, 92, and 199).

Treatment and Prognosis

Bilateral orchiectomy with scrotal ablation is preferred surgery and is curative in most (Figure 351-12). If lymph node metastasis is present, an excisional biopsy should be performed. The role of adjunctive chemotherapy, radiation therapy or novel targeted therapies in dogs with metastatic disease is unknown, with only a few reports showing some degree of efficacy.[68,69] If estrogen-induced myelosuppression has occurred, the prognosis is guarded-to-grave, requiring months of hematologic support and antibiotics.

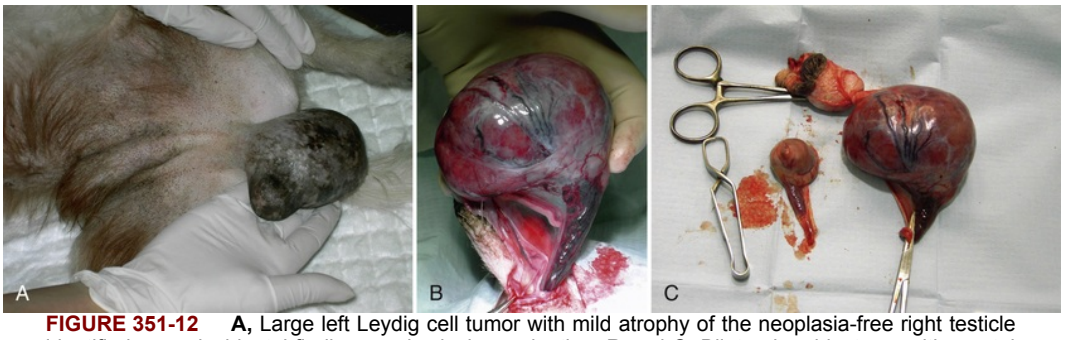


FIGURE 351-12 **A,** Large left Leydig cell tumor with mild atrophy of the neoplasia-free right testicle identified as an incidental finding on physical examination. **B** and **C,** Bilateral orchiectomy with scrotal ablation was performed.

Vaginal and Vulvar Tumors

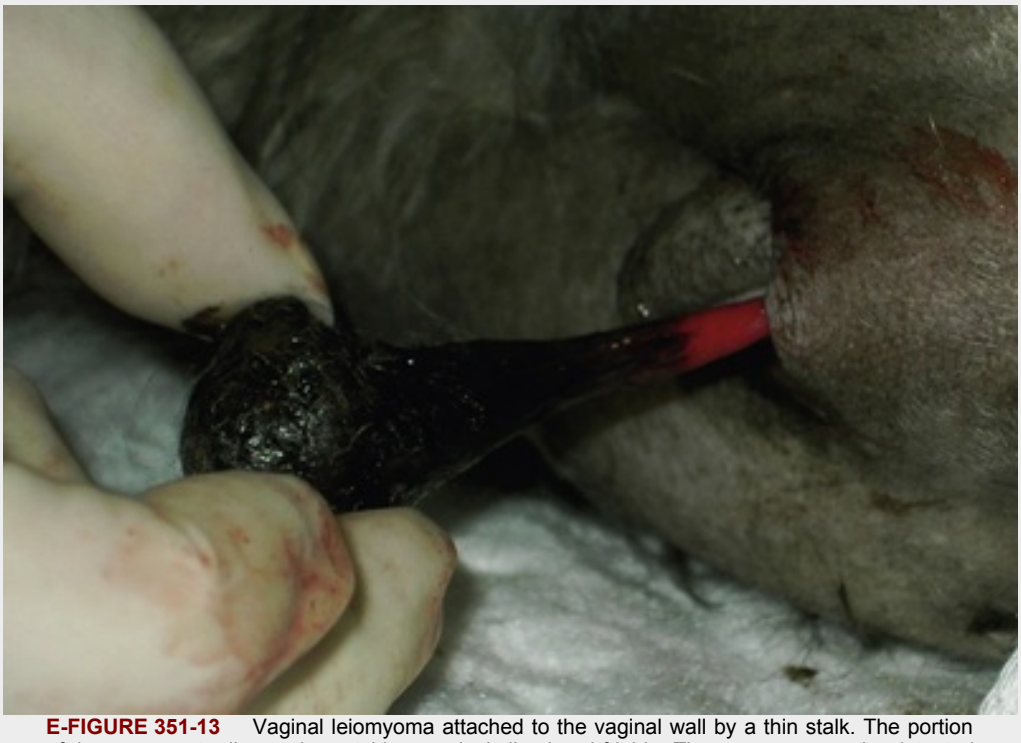
See E-Box 351-3.

E-Box 351-3

Vaginal and Vulvar Tumors

Tumors of the vagina and vulva most commonly affect older intact nulliparous bitches and are rare in cats. Most are benign smooth muscle tumors. Leiomyoma is the predominant histologic type; polyps and fibromas are also frequently described in histopathology reports.[70] Other benign tumors have been reported in this area, including lipomas and hemangiomas, some of which can be associated with vaginal hemorrhage.[71] The most common malignant tumor is leiomyosarcoma, but other malignant tumors arising on the labia of the vulva have been described (melanoma, TVT, mast cell tumors). Other less frequent tumors in the area include adenocarcinoma affecting the clitoris and the extension of urethral tumors into the urethral papilla.[72]

Tumors may be intraluminal or extraluminal. Intraluminal tumors are often associated with stranguria; owners may see the mass protrude during urination or defecation. These are usually solitary, measure up to several centimeters in diameter, and are attached to the vaginal wall by a thin stalk (E-Figure 351-13). Other possible clinical signs include bleeding, discharge, dysuria, and vulvar licking. Extraluminal tumors appear as slow-growing perineal masses (E-Figure 351-14). Diagnostic evaluation should include vaginal and rectal palpation and a vaginoscopic examination. Fine-needle aspiration of the mass can help in the diagnosis, although histopathology is required. Complete staging with thoracic radiographs and abdominal ultrasound to evaluate for lymph node involvement should be considered in those cases of non-pedunculated masses. Diagnosis of pedunculated intraluminal tumors usually requires excisional biopsy transecting the pedicle, and local recurrence is rare in most cases. For benign, hormonally-responsive tumors, ovariohysterectomy (OHE) performed at the time of tumor removal reduces the risk of recurrence even further and is usually curative.



E-FIGURE 351-13 Vaginal leiomyoma attached to the vaginal wall by a thin stalk. The portion of the mass protruding to the outside was devitalized and friable. These masses can be detected by owners when the mass protrudes during micturition or defecation.

E-FIGURE 351-14 **A–C,** Extraluminal leiomyosarcoma in a 10-year-old intact female Great Dane. Malignant vaginal masses tend to be broad-based and infiltrative, often requiring more extensive surgical resection.

Unlike benign tumors, malignant vaginal masses tend to be broad-based and infiltrative, often requiring more extensive surgical resection. Episiotomy alone, ventral median celiotomy, a combination of ventral median celiotomy with episiotomy and pubic osteotomy, and ostectomy have been reported. More recently, a subtotal vaginectomy technique has been described for invasive benign and malignant vaginal neoplasia or extensive vaginal disease with few complications and good outcomes.[73] Radiation and/or chemotherapy may be discussed for the rare, malignant masses. Based on a small study, the prognosis for cats with vulvar adenocarcinoma appears to be poor; the cats were euthanized for progressive local disease or reoccurrence.[74]

Uterine Neoplasia

Tumors of the uterus, including horn, body and cervix, are relatively rare in dogs and cats, with leiomyomas (85-90%) and leiomyosarcomas (10%) accounting for the vast majority. Other mesenchymal tumors

(fibroadenomas, adenocarcinomas, lipomas, lymphomas and mast cell tumors) are less frequent. Spayed females could develop tumors arising from their uterine stump.[75] Adenocarcinoma is the most common uterine tumor in cats, affecting middle-aged to older animals with occasional reports of cats <1 year of age.[76-78] Some German Shepherd Dogs have a syndrome, with a hereditary component, characterized by renal cystadenocarcinomas, nodular dermatofibrosis, and uterine leiomyomas.[79] Most uterine tumors in dogs are slow-growing, non-invasive, and non-metastatic. In cats, uterine tumors usually are aggressive and widespread metastases are present at time of diagnosis.[76]

Uterine tumors in dogs are rarely associated with clinical signs, although uterine enlargement, abdominal distension, vaginal discharge, and urinary symptoms have been described. Cats may also have signs related to metastatic disease. Laboratory testing and thoracic radiographs should be included in the evaluation, even though abnormalities are not often identified. Abdominal radiographs may confirm the presence of a soft-tissue mass in the caudal aspect of the abdomen. Ultrasound may be more effective in mass identification and in determining the likely tissue involved (uterine body or cervical tumors). Ultrasound appearance of uterine tumors in dogs is variable. Definitive diagnosis is made by histologic examination of surgically excised specimens (Figure 351-15).[80] Ovariohysterectomy (OHE) is often curative for dogs. In cats, however, the aggressive biological behavior of uterine tumors prevents OHE from being curative and this form of neoplasia carries a guarded prognosis. The efficacy of chemotherapy in both dogs and cats is largely unknown.

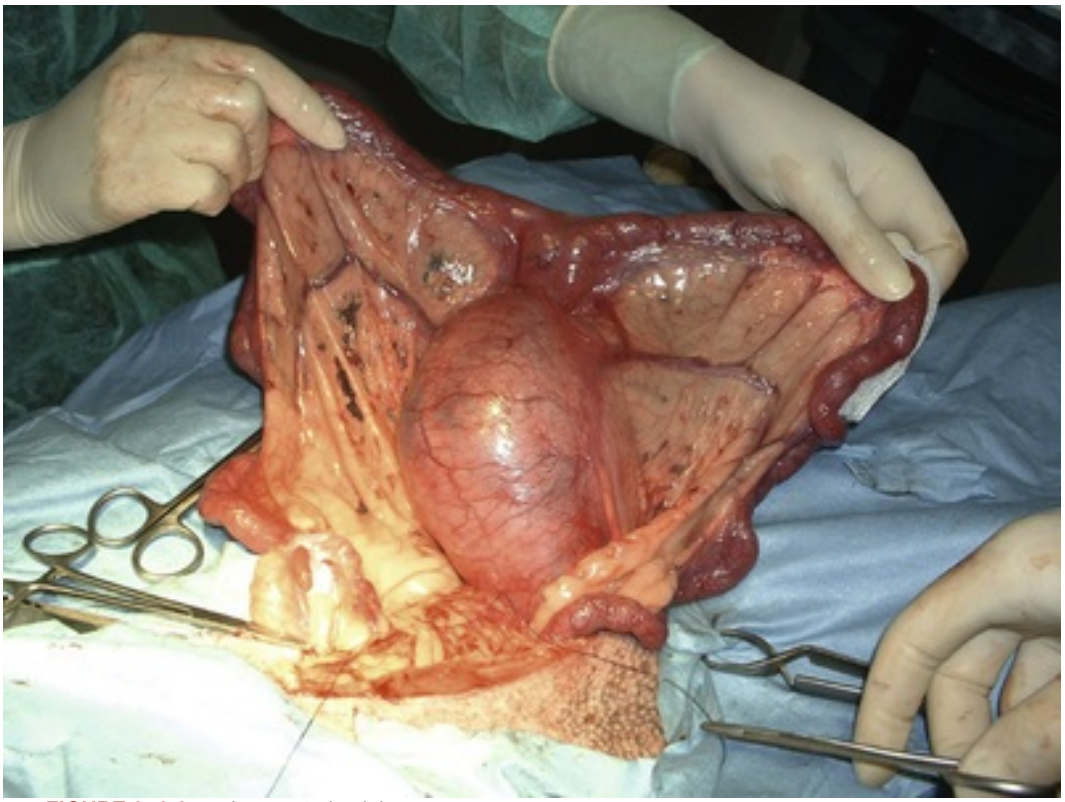


FIGURE 351-15 Large uterine leiomyosarcoma.

Ovarian Tumors

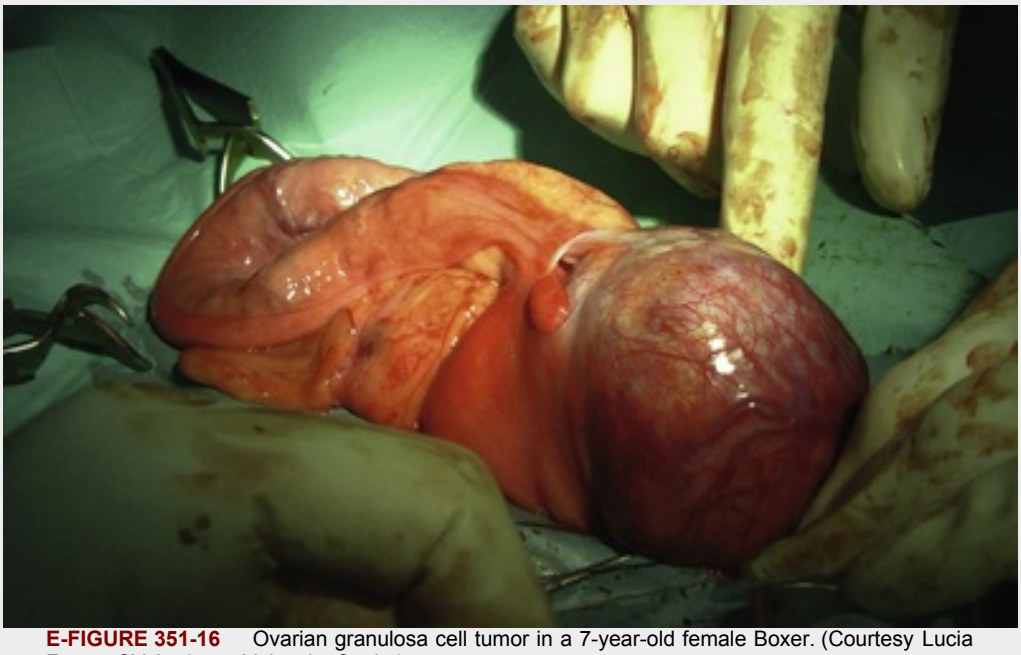
See E-Box 351-4.

E-Box 351-4

Ovarian Tumors

Ovarian neoplasms are rare, probably because a large portion of the canine population is neutered at an early age. The prevalence in intact females is 6.25%, and they affect older dogs, with a median age of 10 to 12 years.[70] Asymptomatic ovarian tumors are most commonly found during routine ovariohysterectomy (OHE) in older animals (E-Figure 351-16); however, other differentials in this situation should be considered, including ovarian cysts, which require histopathologic analysis. Other tumors may attain a larger size prior to detection, presenting clinical signs associated with a space-occupying abdominal mass including a palpable mass or signs of ascites. Rarely, they present with systemic effects of hormone production. Tumors of the ovary are classified based on the human World Health Organization (WHO) classification into epithelial tumors of Mullerian origin, sex cord-stromal tumors, germ cell tumors, and mesenchymal tumors.[81] Most are either epithelial or sex cord-stromal tumors, which account for 80-90% of ovarian tumors.[82] The malignant forms may metastasize to the peritoneum and can cause a malignant effusion; metastases are also seen in the lymph nodes, liver, and lungs.

Feline ovarian tumor types are similar to those of dogs with the exception of mesenchymal tumors, which have not been reported to date. Epithelial ovarian tumors include the histologic diagnoses of papillary adenoma, cystadenoma, papillary adenocarcinoma, and undifferentiated adenocarcinoma. These tumors are typically unilateral, rarely bilateral, usually non-functional, and have a metastatic rate of approximately 50%.[82] Epithelial tumors are rare in cats.



E-FIGURE 351-16 Ovarian granulosa cell tumor in a 7-year-old female Boxer. (Courtesy Lucia Fayos, CV Assisvet, Valencia, Spain.)

Germ cell tumors arise from primordial cells in the ovary and include dysgerminomas, teratomas, and malignant teratomas (teratocarcinomas), making up roughly 10% of ovarian neoplasms in dogs. Dysgerminomas (ovarian seminomas) arise from undifferentiated germ cells, are usually unilateral, and have a low reported metastatic rate (10-30%).[82] Teratomas are made up of more than one germ cell layer (ectoderm, mesoderm, and/or endoderm), and most are well differentiated. Teratocarcinomas have differentiated and undifferentiated components, and metastasis is noted in up to 50% of cases.[82] In cats, approximately 15% of ovarian tumors are dysgerminomas with a similar metastatic rate to that found in dogs.[70]

The granulosa cell tumor is the most common sex cord-stromal tumor and the only tumor in this category that can metastasize, followed by less common histologies, including Sertoli-Leydig tumors, thecomas, and luteomas. They are rarely bilateral, are functional in approximately 50% of cases, and have a metastatic rate of less than 20%.[82] These tumors can produce estrogen and progesterone with clinical signs related to estrogenic effects such as vulvar enlargement, vaginal discharge, and cystic

endometrial hyperplasia. In cats, sex cord-stromal tumors make up roughly 50% of ovarian tumors, and more than 50% are malignant. The most common histologic type in cats is granulosa cell tumors, and hyperestrogenism is commonly seen.

Residual ovarian tissue can become neoplastic in dogs; in one recent study, the incidence proved to be higher (26.3%) than in intact ovaries. All but one of the neoplasms of the ovarian fragment were granulosa cell tumors; a single case was a cystadenoma.[83] Diagnostic evaluation of dogs or cats with ovarian tumors should include a minimum database, thoracic radiographs, and abdominal ultrasound. If ascites is present, cytologic examination of the fluid may be diagnostic for malignancy. Ultrasound-guided FNA has also been described with a high correlation (94%) between cytologic and histopathologic diagnosis.[84,85] The risk of tumor seeding and tumor spillage, especially in malignant cystic tumors has not been evaluated. The ultrasonographic characteristics of ovarian tumors in dogs have been reported, with the tumors ranging from solid to cystic in appearance. Uterine changes, findings consistent with cystic endometrial hyperplasia, and pyometra are commonly found with sex cord-stromal tumors.[86]

Treatment of ovarian tumors relies primarily on OHE and carries an overall good prognosis for benign or localized malignant tumors. Metastatic disease carries a poor prognosis, and the role of conventional therapies such as chemotherapy or radiation therapy has not been widely investigated. In the rare cases of peritoneal metastases or malignant ascites, intracavitary chemotherapy with platinum agents may be of benefit.[87]

Mammary Gland Tumors

Prevalence and Risk Factors

Mammary gland tumors (MGTs) are the most common tumor in intact female dogs and the third most common tumor overall in cats.[88] The incidence of mammary tumors varies greatly between countries, likely due to different attitudes regarding neutering. Older females of either species are more likely to develop a mammary tumor and those with benign tumors are slightly younger than dogs with malignant tumors. Malignant mammary tumors in dogs <5 years of age are rare.[89] Dog breeds at risk include Poodles, English Cocker Spaniels, Brittany Spaniels, English Setters, and German Shepherd Dogs. Siamese cats also have an increased risk. Exposure to ovarian hormones during the first 2 years of life is a well-recognized risk factor for the development of tumors, and OHE greatly decreases the risk of MGT in both species.[90,91] Dogs spayed before their first estrus have a risk of 0.5%; after their first estrus it is about 8% and after their second it rises to 26%. After the third estrous cycle or about 4 years of age, OHE provides only modest protection. There is decreased risk of developing additional mammary tumors if OHE is performed when the first tumor is removed, suggesting a continuous effect of hormones.[92]

Neutering before the first estrus in cats reduces risk by 91%; before the second, it is 86% and before the third, it provides only an 11% risk reduction.[93] After the age of 2 years in cats, there is no benefit associated with OHE. Exogenous hormone exposure also increases risk of benign tumor development. Estrogen and progesterone receptors have been identified in dog and cat MGTs, although there is less expression in poorly differentiated tumors. Although the hormonal association is accepted, male dogs and cats can develop MGTs. In dogs they are usually benign but in cats they are highly malignant.[94-96] Obesity when young and high-fat diets have been linked to increased risk of MGT in dogs, and their tumors are usually a higher grade and are diagnosed at a younger age.[97-99]

Physical Examination and Diagnosis

On physical examination, animals may have single or multiple nodules (>50% of cases) within the mammary gland (E-Figure 351-17). Benign tumors tend to be small, well circumscribed, and firm on palpation. The caudal mammary glands are the most often involved in dogs (Figure 351-18), whereas feline tumors occur with equal frequency in all glands.[89] MGTs may be freely movable, adherent to skin, or abdominal wall. They may be ulcerated, inflamed and edematous, or associated with discharge from the nipple (E-Figure 351-19). Inflammatory mammary carcinomas (IMCs) are rapidly growing tumors with signs of pain, inflammation, and, occasionally, edema of the extremities (Figure 351-20). Differentials for MGT include dermatologic neoplasms, mastitis, lobular hyperplasia, and fibroepithelial hyperplasia in cats.

FIGURE 351-18 Large inguinal mammary gland tumor. Clinical presentation characteristics are prognostic, including the growth pattern, fixation and ulceration.

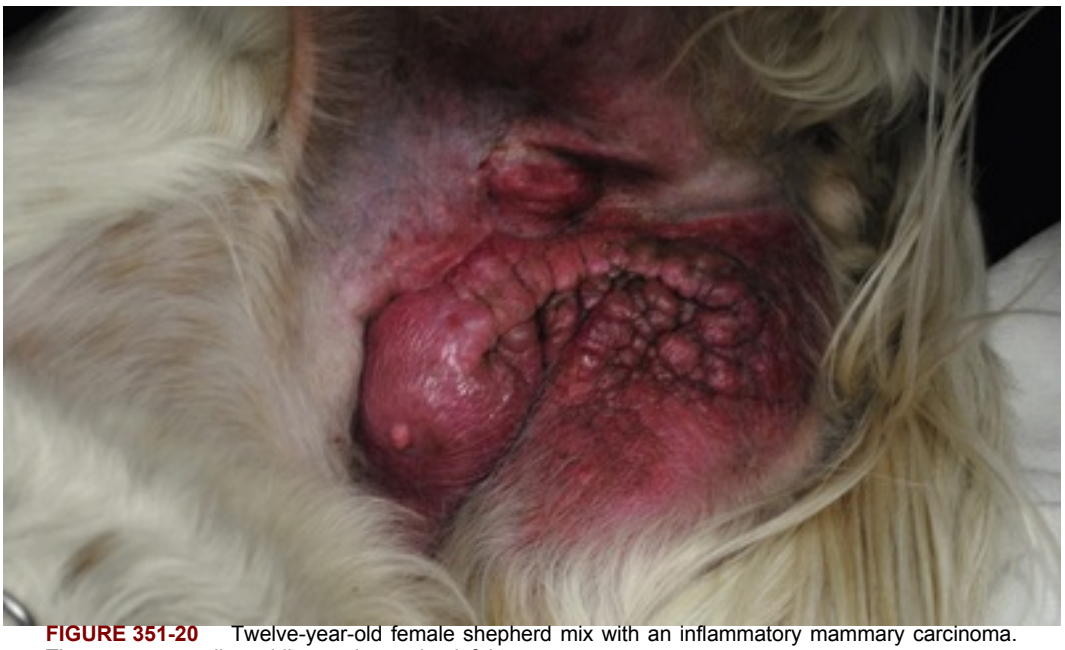
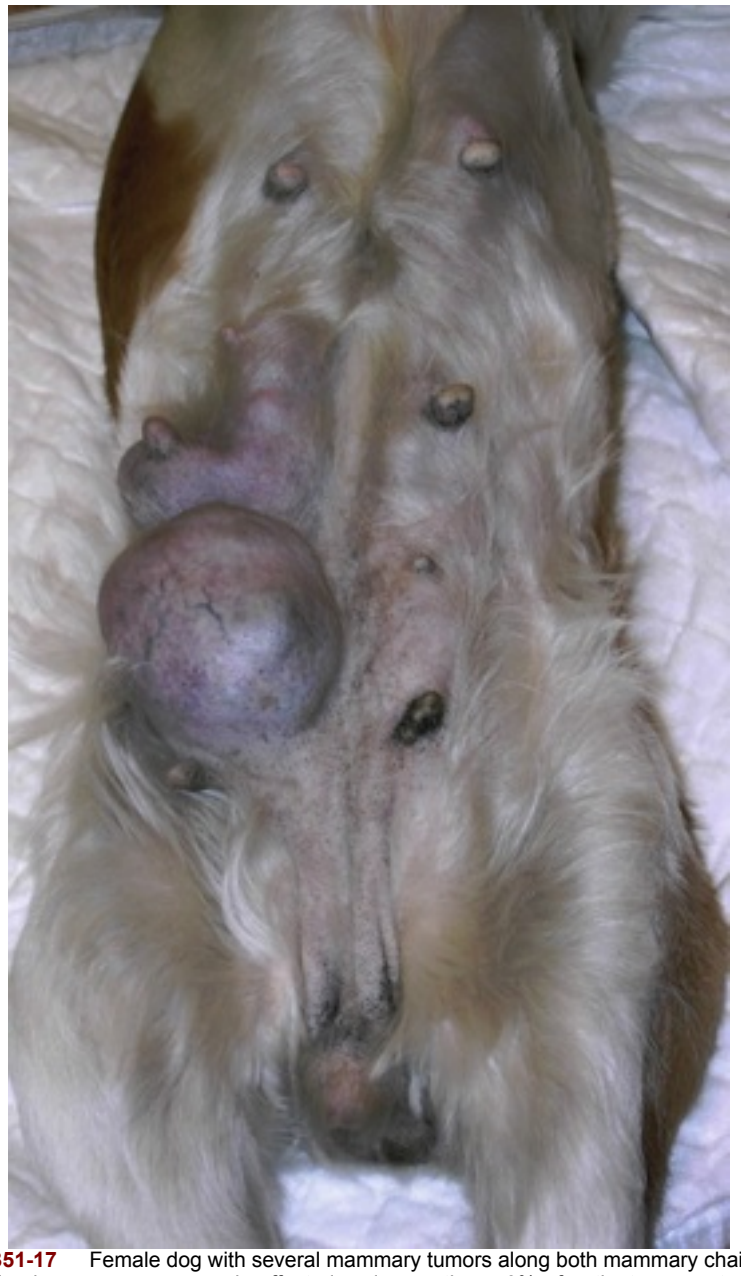
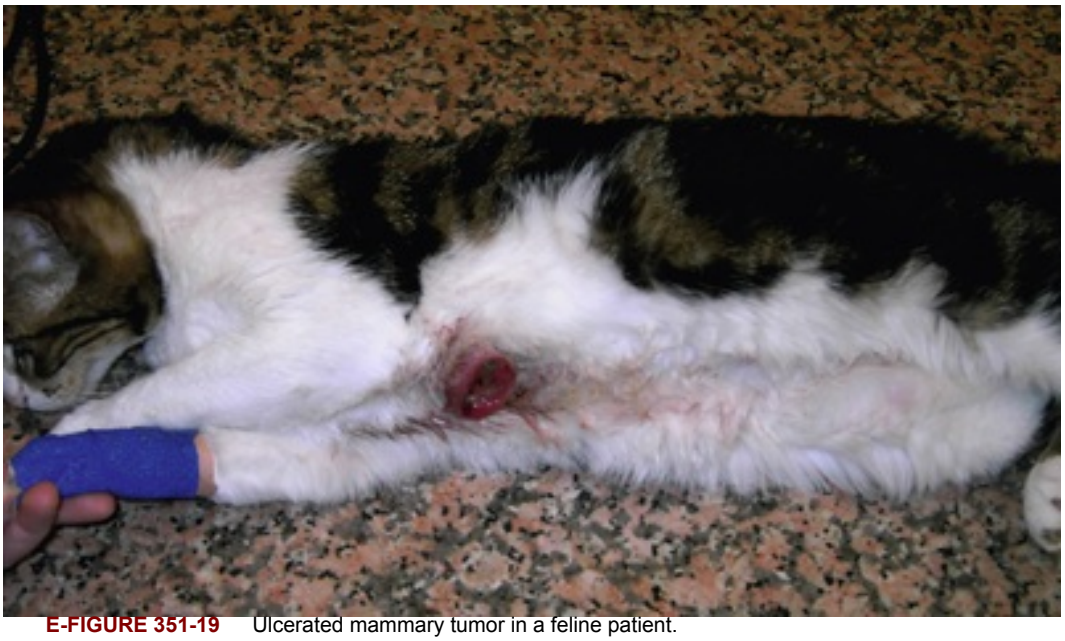


FIGURE 351-20 Twelve-year-old female shepherd mix with an inflammatory mammary carcinoma. These are generally rapidly growing and painful tumors.



E-FIGURE 351-17 Female dog with several mammary tumors along both mammary chains. Inguinal mammary glands are more commonly affected and more than 50% of patients present with multiple masses at diagnosis. These masses are not usually of a single histological tumor type.



E-FIGURE 351-19 Ulcerated mammary tumor in a feline patient.

Diagnostic evaluation of animals with mammary neoplasia should include a CBC, chemistry profile, and UA. Histological examination of the excised mass is considered the gold standard for the diagnosis of canine mammary tumors. Cytological evaluation of the mass is usually performed (see ch. 87) and may help to distinguish benign from malignant lesions; however, histopathology is still required due to possible underestimation of the tumor's malignant potential. Cytology is most helpful in ruling out other differentials, detecting locoregional lymph node metastasis, and in those cases where dermal extension is suspected (aggressive MGT or IMC; Figure 351-21). Metastatic spread in malignant MGTs occurs via lymphatic vessels to the regional lymph nodes or hematogenously to the lungs.[97] Lymph node histology is required to definitively diagnose metastasis/micrometastasis.[100] Thoracic radiographs are important to evaluate for pulmonary metastatic disease or pleural effusion (common in cats). Abdominal ultrasound should be a component of thorough staging in order to assess locoregional (superficial inguinal, axillary lymph node) or intra-abdominal metastatic lymphadenopathy, especially in those cases where mammary tumors are localized in the caudal mammary glands. Ultrasound-based suspicion of metastasis should be confirmed by cytological analysis of FNAs. Ultrasonography of mammary masses has been reported; however, correlation with histology and recognition of malignancy varies among studies.[101,102]

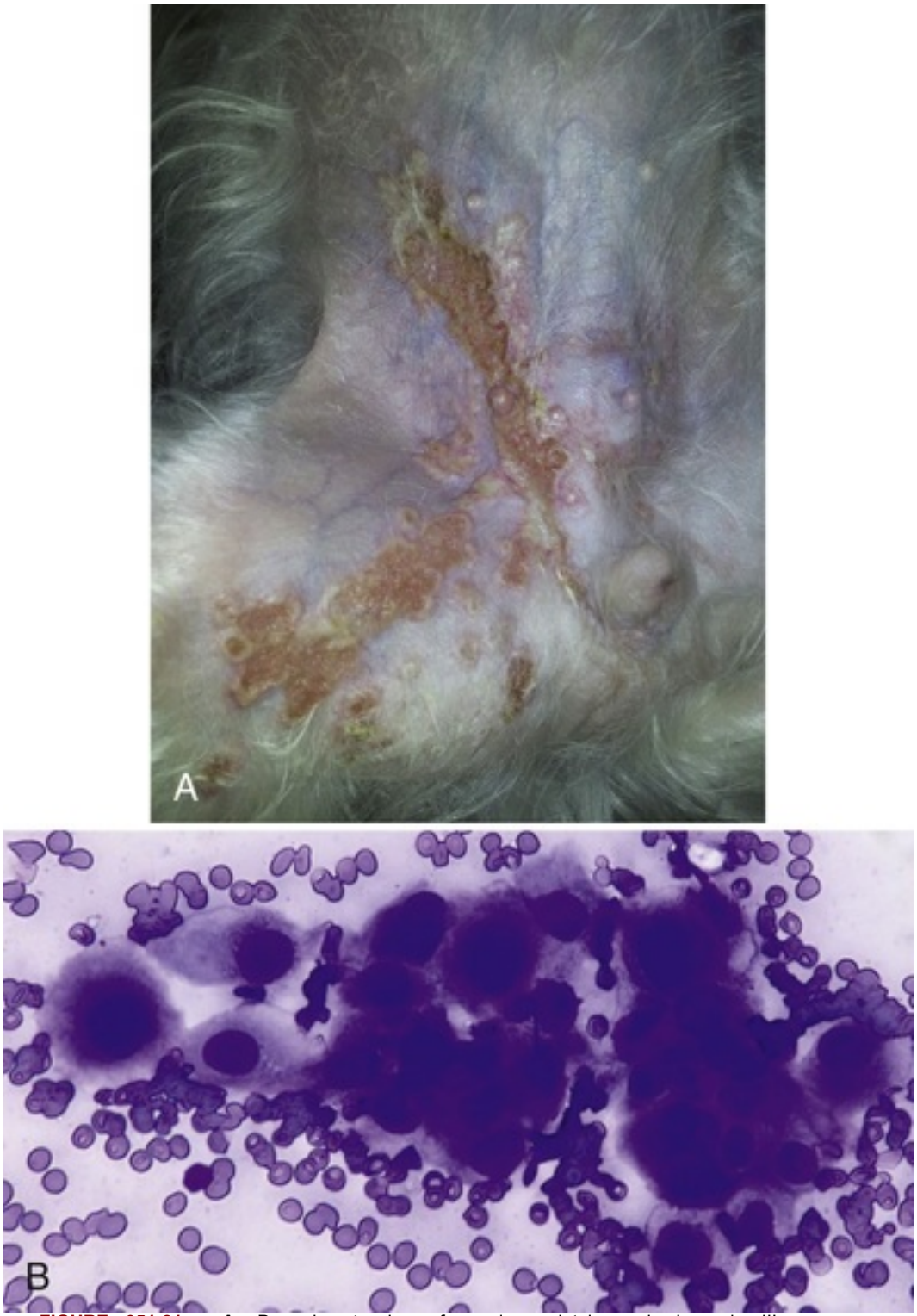


FIGURE 351-21 **A,** Dermal extension of an incompletely excised grade III mammary adenocarcinoma. **B,** Cytologic analysis of cutaneous lesions revealed pleomorphic glandular epithelial cell clusters with several criteria of malignancy (anisokaryosis, anisocytosis, macrokaryosis, and macronucleoli).

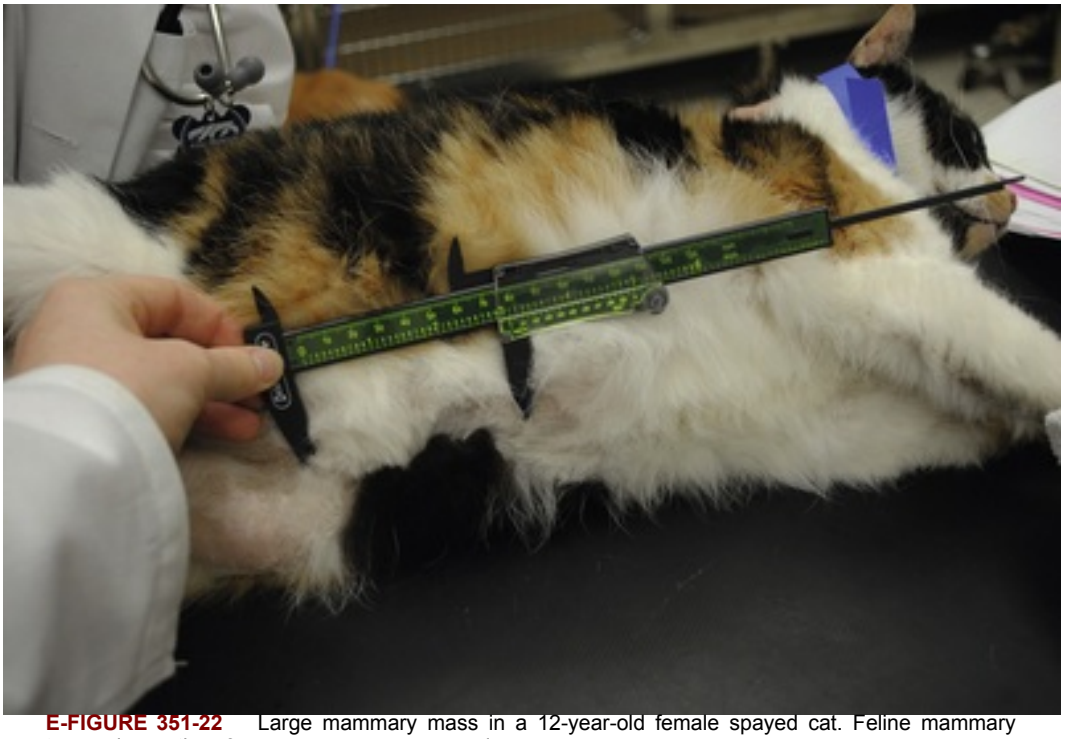
Canine Mammary Tumors

In dogs, almost 60% of MGTs are benign, most often fibroadenomas (benign mixed tumors).[103] The most common types of malignancies in dogs are solid carcinomas or tubular adenocarcinomas. Only about 3-5%

are sarcomas and 1% are IMCs. Of the malignant tumors, 50% will recur or metastasize following the first surgical resection.[104] Factors associated with shorter survival in dogs with MGTs include histologic type (poorly differentiated tumors, sarcoma, and inflammatory carcinomas have a worse prognosis), histological grade, stage, tumor size greater than 3 cm, lymph node involvement, histologic evidence of lymphatic or vascular invasion, OHE status, lymphocytic infiltrate intensity, expression of hormone receptors (ER and PR), COX-2 expression, microvessel density, proliferation markers, clinical behavior (growth pattern, fixation, ulceration) and distant metastases.[105-108]

Feline Mammary Tumors

The majority (80-90%) of feline MGTs are malignant adenocarcinomas.[109] IMCs have also been reported in cats, in whom they are biologically aggressive with a high metastatic rate. Survival times vary significantly. Tumor size, disease stage, histological grading, and the extent of surgical intervention have been shown to influence prognosis.[110-112] Tumors >3 cm are associated with survival times of only 4-12 months (E-Figure 351-22).[113,114] Type of surgery and completeness of resection have been shown to be prognostic for the disease-free interval but not for survival time.[109] Histologic grading using the Elston and Ellis system and a revised novel grading system have shown significant correlation with survival.[115]



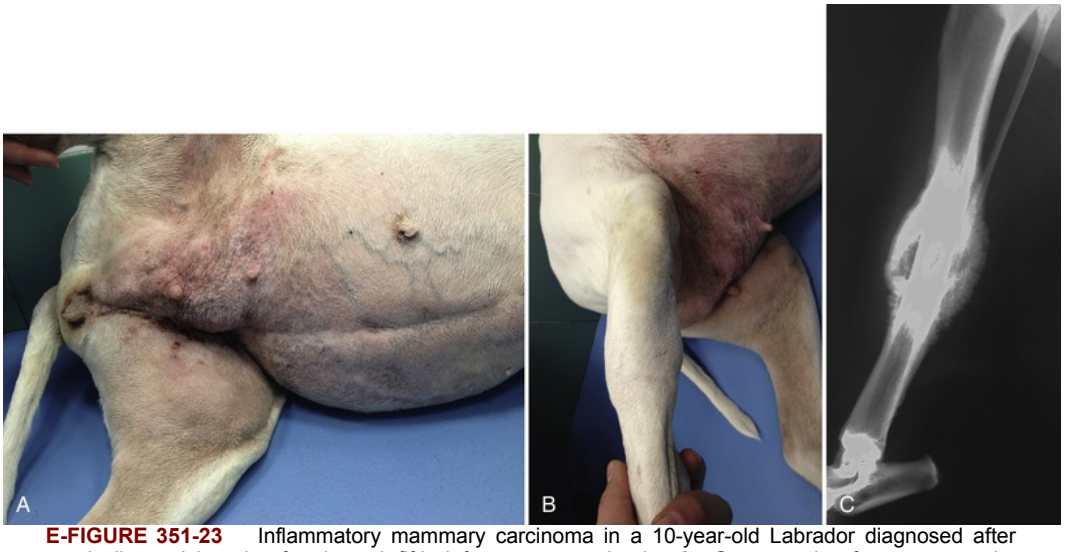
E-FIGURE 351-22 Large mammary mass in a 12-year-old female spayed cat. Feline mammary tumors larger than 3 cm carry a worse prognosis.

Treatment

Surgery

Surgery remains the gold-standard treatment for mammary tumors in dogs and cats. A major contraindication to surgery are the IMCs associated with high rates of early regional and distant metastases and a high incidence of locoregional recurrence (E-Figure 351-23). IMC should be considered a systemic disease, even if metastases are not identified.[116] In dogs with other MGTs, the goal of surgery is to remove the entire tumor by the simplest procedure possible. For example, a lumpectomy is acceptable for small (≈1 cm) superficial mammary nodules since they are most likely benign. Masses 1 to 2 cm in diameter may require a mammectomy. If masses are present in multiple glands, they may be resected individually or in a chain. Again, the surgery chosen should be the easiest for removing all abnormal tissue. Lymphatic drainage of the

affected glands is a consideration.



E-FIGURE 351-23 Inflammatory mammary carcinoma in a 10-year-old Labrador diagnosed after surgically excising the fourth and fifth left mammary glands. **A,** One month after surgery, the contralateral mammary glands were affected. **B** and **C,** An aggressive bone metastatic lesion on the diaphysis of the right tibia was also detected.

OHE should be recommended at the time of mastectomy to prevent future ovarian or uterine disease and to reduce future mammary tumor development risk.[90,92,105] Prophylactic mastectomies of normal mammary tissues, especially when a tumor is located in a caudal gland, could be considered to prevent new mammary tumors. Dogs that undergo removal of a single mammary tumor are likely to develop new tumors ipsilaterally in up to 60% of cases.[104] The majority of canine MGTs are cured with surgery alone. In cats, because of the possible lymphatic connections between individual glands and between sides, complete unilateral or bilateral mastectomies, including the underlying fascia "en bloc," are recommended (Figure 351-24). For staged bilateral mastectomies, a minimum 2-week interval is recommended. The inguinal lymph node should always be removed with the caudal mammary gland, while the axillary lymph node should only be removed if enlarged.

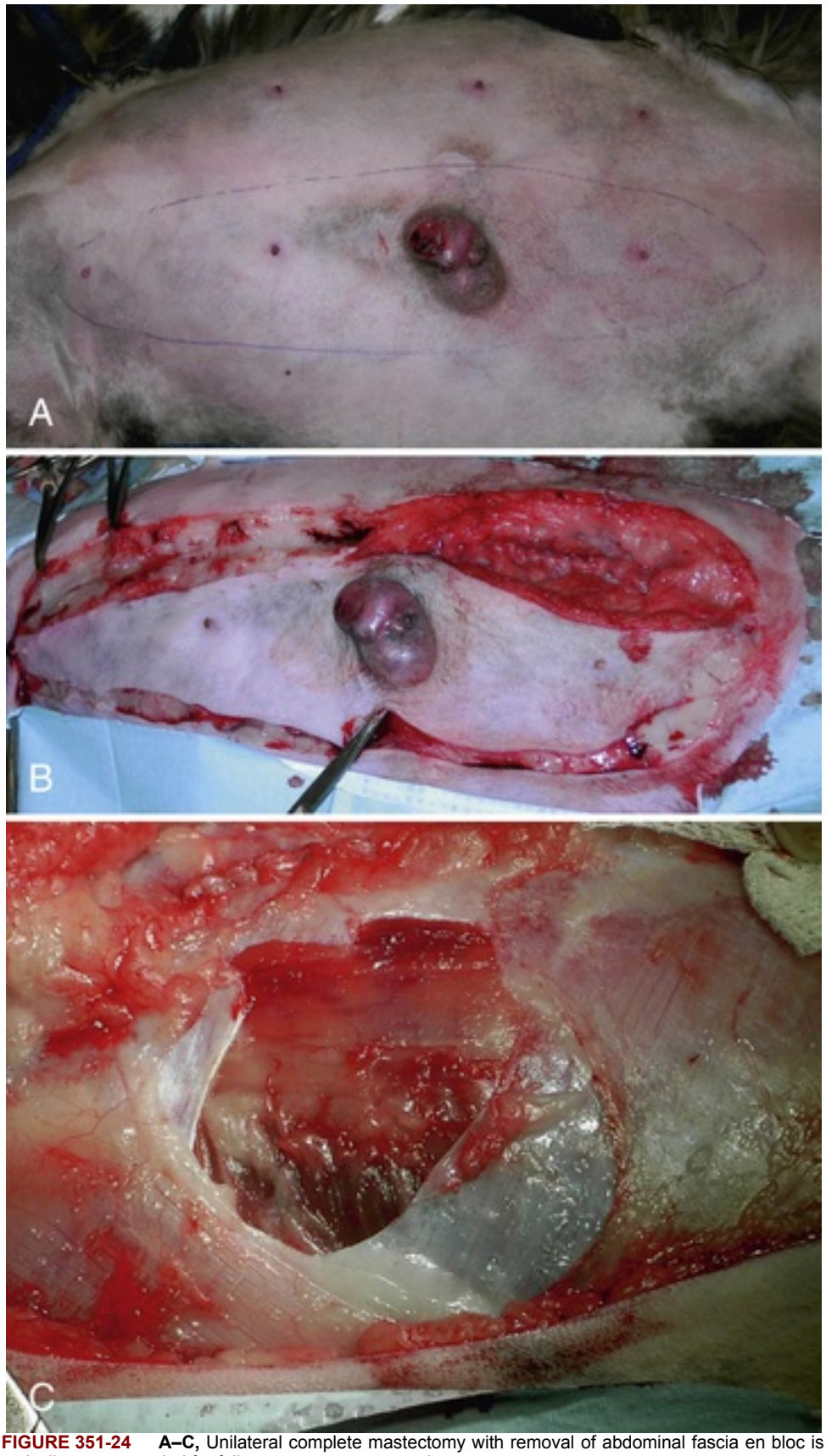


FIGURE 351-24 **A–C,** Unilateral complete mastectomy with removal of abdominal fascia en bloc is typically recommended for feline mammary tumor patients.

Radiation and Medical Treatments

Radiation therapy is not routinely used for this disease in dogs or cats. Despite mammary tumors being common, little information is available regarding the efficacy of chemotherapy for canine or feline MGTs. Most medical treatments are considered experimental, especially those in the adjuvant setting after surgery. In dogs with malignant mammary tumors and additional poor prognostic factors, locally advanced or metastatic disease, or a biologically aggressive histological type, adjuvant treatment such as chemotherapy or antiangiogenic therapy may be beneficial. Several drugs have been used as single agents or in combination protocols in the macroscopic setting with modest results and response rates around 20%, the most common being doxorubicin, carboplatin, mitoxantrone, 5-fluorouracil, and cyclophosphamide.[108] New formulations of paclitaxel, a drug active against mammary neoplasia, are associated with fewer allergic reactions and moderate response rates.[117]

Little information is available regarding the role of chemotherapy in the adjuvant setting after surgery. COX-2 expression is increased in malignant MGTs compared with benign MGTs or normal mammary tissue and is associated with a worse prognosis.[118,119] COX-2 inhibitors have only been described in cases of IMC as part of a multi-therapy treatment to improve quality of life and increase survival rate over chemotherapy alone.[120] Further studies in other canine mammary tumors are needed before the use of COX-2 inhibitors can be routinely recommended as an adjuvant therapy.

Despite the guarded prognosis in pets with IMC (1 to 2 months), medical treatment may improve outcome.[116,120] Administration of 1 mcg/kg desmopressin IV 30 min presurgically and 24 h postsurgically increased disease-free survival and overall survival in a group of dogs with MGTs.[121] Antiangiogenic therapies with toceranib phosphate have shown efficacy against canine and feline MGTs in the macroscopic setting, encouraging further research on its adjuvant role in MGTs.[122,123] Postoperative chemotherapy is usually recommended in feline patients. Doxorubicin is commonly used in feline patients although conflicting reports exist regarding its role in prolonging survival.[113,114,124] Recently, adjunctive carboplatin and mitoxantrone chemotherapy have been reported; however, these studies included few cases, and the role of adjunctive chemotherapy remains largely unknown in this type of tumor in cats.[125,126]

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CHAPTER 352

Paraneoplastic Syndromes

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Client Information Sheet: Paraneoplastic Syndromes

Paraneoplastic syndromes (PNSs) are signs arising from the indirect effects of tumors' production and release of biologically active substances. While some oncologists ascribe the term *paraneoplastic syndrome* only to those instances when the compound released by the tumor is not normally produced by the tumor cell of origin, this stringent definition would exclude many commonly cited PNSs including hypoglycemia secondary to pancreatic insulinoma. The signs of PNSs typically arise at sites distant to the tumor location and may be the first evidence of neoplastic disease. These signs often resolve with the successful treatment of the underlying neoplastic process. A recrudescence of these signs may occur prior to grossly detectable recurrence or relapse of the inciting neoplastic process; therefore, the continued monitoring for these signs is important.

Endocrine-Related Paraneoplastic Syndromes

Hypercalcemia of Malignancy

Cancer is the most common cause of hypercalcemia in dogs, whereas non-neoplastic conditions predominate in cats.[1-3] Perturbations in calcium regulation may be caused by a wide variety of non-neoplastic diseases and the diagnostic approach to hypercalcemia is discussed in detail in ch. 69. Hypercalcemia of malignancy (HM) accounts for up to two-thirds and one-third of hypercalcemia in dogs and cats, respectively.[2,3] The primary mechanism of HM is promotion of bone resorption by osteoclasts and the subsequent release of calcium into the bloodstream. Factors released from neoplastic cells may also affect the kidney and intestinal tract's ability to modulate calcium concentrations. The most common of these substances is parathyroid hormone–related peptide (PTHrP).[4,5] Other factors produced and released by neoplastic cells that have been shown to contribute to HM include receptor activator of nuclear factor kappa-B ligand (RAN-kappa-L), transforming growth factor-beta, interleukin-6 (IL-6), and tumor necrosis factor.[6]

Lymphoma, anal sac gland adenocarcinoma, and multiple myeloma are the malignancies most commonly associated with HM in dogs.[7] While this list is not exhaustive, other tumor types associated with HM include mammary gland tumors, melanoma, chronic lymphocytic leukemia, and thymoma.[8-11] In anal sac gland adenocarcinoma, a linear correlation exists between serum calcium and PTHrP concentration, whereas no such correlation exists in canine lymphoma.[12] This suggests other factors contribute to HM in canine lymphoma.

HM in cats is most frequently reported with squamous cell carcinoma and lymphoma, though it is reported in cats with multiple myeloma, osteosarcoma, and bronchogenic adenocarcinoma.[3,13,14] Similar to dogs, PTHrP is considered to be a main culprit of HM in cats.

The serum ionized calcium concentration should normalize rapidly with successful treatment of the inciting tumor. Assessment of serum ionized calcium should be included with follow-up monitoring of any patient with HM. For patients in which the inciting tumor is not amenable to complete removal or refractory to treatment, other supportive measures for managing hypercalcemia (see ch. 69 and 297) should be attempted, though the success of these measures are often short-lived.

Hypoglycemia

Paraneoplastic hypoglycemia should be on the list of differential diagnoses for hypoglycemic animals (see ch.

61). This PNS is most commonly associated with tumors of the pancreatic beta-islet cells (insulinomas).[15] Other non-insulinoma tumors that have been associated with hypoglycemia include hepatocellular carcinoma, hemangiosarcoma, mammary tumors, oral melanoma, multiple myeloma, plasma cell tumors, renal tumors, salivary gland tumors, and smooth muscle tumors (leiomyoma and leiomyosarcoma).[16-20]

Hypoglycemia associated with an insulinoma is due to the overproduction of insulin by the primary tumor. In contrast, hypoglycemia of the extra-pancreatic tumors has been associated with low insulin concentrations and is caused by insulin-like growth factors I and II, and somatomedins.[16] Other potential causes of paraneoplastic hypoglycemia include the increased expression of insulin receptors or glucose utilization by neoplastic cells, or decreased hepatic glycogenolysis or gluconeogenesis, and binding of insulin by M proteins in multiple myeloma.

Paraneoplastic hypoglycemia is optimally treated by the surgical removal of the neoplasm. However, it may be necessary to symptomatically treat the hypoglycemia before surgery, or medically manage the hypoglycemia (see ch. 61 and 303) if surgery is not feasible.

Ectopic Adrenocorticotropic Hormone Syndrome

The ectopic production of adrenocorticotropic hormone (ACTH) or ACTH-like substances by malignancies in animals is extremely rare. Case reports exist describing such a syndrome in dogs with primary lung tumors, an abdominal neuroendocrine tumor, and a hepatic carcinoid.[21-23]

Hyperestrogenism

The most common neoplastic cause of hyperestrogenism is the Sertoli cell tumor.[24] Sertoli cell tumors that arise in the cryptorchid testicle are more likely to produce excess estrogen relative to Sertoli cell tumors in descended testicles.[25,26] Overall, 30-50% of dogs with a Sertoli cell tumor will display signs of hyperestrogenemia.[25,26] Not all dogs with clinical signs of hyperestrogenemia will have detectably high estrogen concentration. The increased production of inhibin-alpha reduces testosterone production, ultimately reducing the testosterone : estrogen ratio, which likely contributes to clinical signs.[27] Clinical signs of hyperestrogenism include bilateral symmetrical alopecia, cutaneous hyperpigmentation, epidermal thinning, gynecomastia, galactorrhea, attraction of other males, preputial atrophy, and atrophy of the non-neoplastic testicle.[27] A pancytopenia may be present on the complete blood count (CBC) of affected animals and bone marrow evaluation (see ch. 92) will reveal a hypocellular marrow.[24] Severely pancytopenic animals may demonstrate lethargy, bleeding secondary to thrombocytopenia, petechiae, and pale mucous membranes.[24]

The successful treatment of paraneoplastic hyperestrogenism is dependent upon the surgical excision of the Sertoli cell tumor. Recurrence of feminization has been documented in a dog with delayed-onset metastatic disease.[28] Pancytopenic animals may require pre-operative care including the administration of broad-spectrum antibiotics and blood or red cell transfusions. Bone marrow recovery may take weeks to months following tumor removal.

Hematologic Paraneoplastic Syndromes

Anemia

Anemia is one of the most common PNSs in dogs and cats. Cancer-related anemia is one of the most frequent causes of anemia in dogs.[29] The majority of paraneoplastic anemias are likely secondary to anemia of chronic disease (ACD), immune-mediated hemolytic anemia, microangiopathic hemolytic anemia, or blood loss anemia. For blood loss anemia to be considered a PNS, the blood loss must occur at a site distant to the primary tumor. Examples of this would include blood loss due to gastrointestinal ulceration secondary to excessive histamine secretion from mast cell tumors (MCTs) or excessive gastrin production by gastrinomas.

ACD is the most common form of anemia seen in cancer patients. ACD arises secondary to impaired iron storage and metabolism resulting in a suppression of erythroid progenitor cell differentiation, decreased erythropoietin production, and decreased survival of erythrocytes. ACD is generally characterized by a mild/moderate, normocytic, normochromic and non-regenerative anemia. This type of anemia is slowly progressive and rarely requires supportive measures.

Paraneoplastic immune-mediated hemolytic anemia (IMHA) is most commonly associated with

hematopoietic tumors, but it has been reported in association with solid tumors. The PNS is considered a secondary IMHA, as the antibodies against tumor cell-membrane antigens cross-react with erythrocytes resulting in their destruction. Clinical signs commonly associated with IMHA are lethargy, weakness, tachycardia, pallor, icterus, hepatosplenomegaly, hemoglobinuria, and anorexia. Diagnostic tests for secondary IMHA are further discussed in ch. 198.

As with most PNSs, the treatment of choice for the paraneoplastic IMHA is removal of the underlying tumor; however, this may not be immediately feasible. Therefore, immunosuppressive dosages of prednisone are frequently used in the treatment of secondary IMHA. Additional immunosuppressive medications including azathioprine, cyclosporine, and cyclophosphamide may be necessary for IMHA cases refractory to prednisone, though the efficacy in treating secondary IMHA with these drugs is poorly defined.[30,31]

Microangiopathic hemolytic anemia is most often associated with the microvascular solid tumors, such as hemangiosarcoma (HSA; see ch. 347), though it may occur with any tumor, including hematopoietic tumors, associated with disseminated intravascular coagulation (DIC; see ch. 197).[32] The fragmentation of erythrocytes may occur as red blood cells pass through intravascular fibrin formed in DIC, or secondary to abnormal vascularity within the tumor, pulmonary intraluminal tumor emboli, or the narrowing of pulmonary arterioles.[32] Successful treatment of the underlying malignancy is considered the only effective therapy for paraneoplastic microangiopathic hemolytic anemia.

Erythrocytosis

Erythrocytosis, or polycythemia, is an uncommon PNS in animals that is most often associated with primary or secondary tumors of the kidney.[33-38] Other neoplasms that have been reported to cause erythrocytosis include lymphoma, schwannoma, nasal fibrosarcoma, transmissible venereal tumor, bronchioalveolar carcinoma, and cecal leiomyosarcoma.[38-43]

Paraneoplastic erythrocytosis is a form of secondary erythrocytosis (see ch. 200), as the underlying mechanism is an increased level of erythropoietin. Clinical findings with polycythemia may include erythema of mucous membranes, polydipsia, and neurologic signs such as disorientation, ataxia, and seizures secondary to hyperviscosity or hypervolemia.

Neutrophilic and Eosinophilic Leukocytosis

The presence of an increased number of mature neutrophils in the absence of infection or leukemia defines a paraneoplastic neutrophilic leukocytosis. Renal carcinomas (transitional cell and tubular), lymphoma, metastatic fibrosarcoma, pulmonary carcinoma, and rectal adenomatous polyps have been associated with this syndrome.[44-50] Neutrophilic leukocytosis is also common in dogs with paraneoplastic hypertrophic osteopathy.[51] This PNS is driven by tumor production of granulocyte colony-stimulating factors (G-CSFs) in cats and both G-CSF and granulocyte-monocyte (GM)-CSF in dogs.[47,49,52] This PNS is most commonly an incidental finding and resolves with successful treatment of the underlying tumor.

Paraneoplastic eosinophilia is rare in dogs and cats. There are case reports of this condition in dogs with pericardial leiomyosarcoma, intestinal T-cell lymphoma, rectal polyps, mammary carcinoma, and oral fibrosarcoma.[48,53-56] Paraneoplastic eosinophilia has been reported in cats with MCTs, intestinal T-cell lymphoma, acute leukemia and transitional cell carcinoma of the bladder.[57-61] Eosinophilia as a PNS is generally an incidental finding.

Thrombocytopenia

Paraneoplastic thrombocytopenia (see ch. 201) has been associated with lymphoma, melanoma, HSA, osteosarcoma (OSA), MCT, histiocytic malignancies, and various carcinomas.[62-64] In one study, up to 36% of dogs with untreated malignancies had thrombocytopenia on CBC.[30] The mechanisms underlying this PNS are common to any causes of thrombocytopenia. Decreased platelet production may occur secondary to myelophthisis induced by marrow-infiltrating malignancies or arise due to estrogen-secreting testicular or ovarian tumors.[65-67] Thrombocytopenia secondary to sequestration may occur with splenic malignancies.[67] Increased platelet destruction may occur through immune-mediated processes and has been associated with lymphoma or multiple myeloma. Thrombocytopenia secondary to consumption may occur with tumors that induce hemorrhage (HSA or MCTs) or coagulopathies such as DIC (multiple metastatic tumors and

HSA).[62,68]

Clinical signs of thrombocytopenia, including petechiation, are not typically evident until the platelet count decreases below 30 × 10^9/L. The treatment of PNS thrombocytopenia depends on the mechanism inciting the thrombocytopenia, although resolution of the primary tumor is the optimal treatment. Fresh whole blood may be indicated prior to tumor resection (see ch. 201).

Thrombocytosis

Thrombocytosis as a PNS is recognized less frequently than thrombocytopenia. In retrospective studies assessing cats and dogs with thrombocytosis, neoplasia was the most commonly diagnosed concurrent illness.[70,71] Thrombocytosis has been described in animals with OSA, gingival carcinoma, chronic myeloid leukemia, bronchoalveolar carcinoma, metastatic squamous cell carcinoma, and in those undergoing chemotherapy.[70-74]

Paraneoplastic thrombocytosis is a diagnosis of exclusion. Causes of thrombocytosis include vinca alkaloid administration, splenectomy, iron deficiency, and myeloproliferative disorders. Resolution occurs with successful treatment of the underlying malignancy.

Platelet Hyperaggregability, Hypercoagulability, and Disseminated Intravascular Coagulation

Changes in platelet function have been demonstrated in dogs with cancer.[75-78] Both platelet hyperaggregation and hypercoagulability were found to be common hemostatic abnormalities in canine cancer patients.[75,78] The assessment and management of bleeding disorders is covered in ch. 197.

DIC is a complex syndrome characterized by the excessive activation of the coagulation cascade, resulting in widespread microthrombosis and multiorgan failure. As a PNS, DIC has been associated with tumors of the vasculature and solid tumors, with a reported incidence of 9.6%.[79] DIC may be present in up to 50% of HSA cases on initial evaluation.[79,80] Along with the mechanisms of DIC common to other diseases, tissue factor (TF) is expressed on cancer cells and complexes with factor VIIa to stimulate thrombin formation and activation of factors IX and X. Patients with paraneoplastic DIC generally have a poor prognosis.

Hyperglobulinemia

Hyperglobulinemia is a PNS most commonly associated with multiple myeloma, although it has also been noted with lymphoma, chronic lymphocytic leukemia, and plasmacytoma.[81-83] Hyperglobulinemia arises due to excess production of immunoglobulins by plasma cells or lymphocytes.[83,84] Most animals with multiple myeloma have an IgG or IgA monoclonal gammopathy. Clinical signs relate to the hyperviscosity secondary to excess globulins in circulation. In addition to hypertension and tissue hypoxia, the decreased production of normal immunoglobulins may result in infections. The hyperviscosity may result in cardiomegaly, renal failure, ocular disorders including retinopathies, and neurologic abnormalities.[85-88] Bleeding tendencies are common with hyperglobulinemia and relate to decreased adhesion of platelets to damaged endothelial surfaces, coating of platelets with immunoglobulins, and release of platelet factor III. Confirmation of hyperglobulinemia is via serum electrophoresis.[104] Treatment of animals with paraneoplastic hyperglobulinemia is dependent upon successful treatment of the inciting tumor, usually with chemotherapy. Cases in which the inciting neoplasia is not amenable to a quick resolution may require plasmapheresis.[88]

Cutaneous ParaneopLastic Syndromes

Feline Paraneoplastic Alopecia

A unique PNS of alopecia occurs in some cats with pancreatic and biliary carcinoma (see ch. 10 and 280).[89-93] Acute, progressive, non-pruritic symmetrical alopecia occurs, with lesions characterized by easily epilated hair and smooth, shiny skin underneath.[89-93] Palliation may be possible with resection of the primary tumor.

Superficial Necrolytic Dermatitis

Superficial necrolytic dermatitis (see ch. 285) is a rare PNS most commonly associated with glucagon-

secreting tumors in dogs. Superficial necrolytic dermatitis as a PNS has also been reported in a cat with a glucagon-producing neuroendocrine carcinoma (hepatic carcinoid).[94] Hypoaminoacidemia is a characteristic feature and may be central to the etiology of this syndrome. The erythema, crusting, exudation, ulceration, and non-pruritic alopecia is characterized histologically by epidermal parakeratosis with laminar hydropic degeneration of the stratum spinosum, hyperbasophilia of the deep epidermis, and hyperplasia of the stratum basale.[95] Resolution of superficial necrolytic dermatitis has been noted with surgical removal of pancreatic tumors and somatostatin therapy.[96,97]

Nodular Dermatofibrosis

Nodular dermatofibrosis is associated with renal cystadenoma or cystadenocarcinoma and rarely with uterine leiomyoma and ovarian adenoma.[97-101] This PNS is commonly associated with German Shepherd Dogs and linked to mutations in the chromosomal region overlapping the Birt-Hogg-Dubé locus.[97-100]

Gastrointestinal Paraneoplastic Syndromes

Cancer Cachexia

Weight loss and metabolic alterations observed in cancer patients despite adequate nutritional intake are termed *cancer cachexia.* In people this has been associated with negative effects on strength, immune function, wound healing, and survival.[102] Similarly, poor body condition has been associated with shortened survival times in feline cancer patients.[103] Cachexia is further reviewed in ch. 177.

Gastrointestinal Ulceration

Paraneoplastic gastrointestinal (GI) ulceration most commonly is secondary to excessive histamine release from mast cell disease. The excessive histamine stimulates gastric H2 receptors, leading to increased secretion of gastric acid. Studies have demonstrated that up 75% of dogs with macroscopic MCT have increased plasma histamine concentration, with approximately 30% demonstrating clinical signs of GI hyperacidity.[104,105] Nonspecific supportive therapies such as proton pump inhibitors, H2 blockers, misoprostol, and sucralfate may benefit patients affected by GI ulceration; however, resolution of the paraneoplastic GI ulceration is expected only for cases in which the primary tumor is adequately controlled. In addition to MCTs, gastrinomas have also been associated with GI ulceration as a PNS.[106,107]

Neurologic Paraneoplastic Syndromes

Myasthenia Gravis

Myasthenia gravis (MG) as a PNS most often occurs with thymoma, but it has been described in association with cholangiocarcinoma, lymphoma, OSA, and an oral sarcoma.[11,108-110] Antibodies against the nicotinic acetylcholine receptors are produced by the tumor, resulting in the failure of synaptic transmission. Clinical signs of MG include weakness, dysphagia, regurgitation, and aspiration pneumonia secondary to megaesophagus. Additional information on diagnostic testing and management of MG is provided in ch. 117 and 269. Removal of the primary tumor is recommended; however, MG may not resolve despite removal of the inciting cause.

Peripheral Neuropathy

Paraneoplastic peripheral neuropathy (see ch. 268) has been reported in dogs and cats with HSA, primary lung tumors, leiomyosarcoma, mammary tumors, multiple myeloma, lymphoma, insulinoma and undifferentiated sarcoma.[111-114] Paraneoplastic peripheral neuropathy is likely secondary to the production of antibodies targeting antigens shared between the primary tumor and peripheral nerves. Removal of the tumor is the only effective treatment for this PNS.

Renal PARANEOPLASTIC SYNDROMES

Glomerulonephritis and Nephropathies

The deposition of tumor-related immune complexes in the renal glomeruli may result in glomerular disorders of cancer-bearing patients. Although the prevalence of paraneoplastic glomerulonephritis is unknown in veterinary medicine, there is a report of immune complex glomerulonephritis in a dog with lymphocytic leukemia.[115] Nephropathy in dogs and cats with neoplasia may occur secondary to paraneoplastic hypercalcemia, resulting in mineralization of the basement membrane. Therapy for paraneoplastic glomerulonephritis and nephropathy should be aimed at removal of the inciting tumor (see ch. 325).

Miscellaneous Paraneoplastic Syndromes

Hypertrophic Osteopathy

Hypertrophic osteopathy (HO) is a well-characterized PNS most often associated with primary intrathoracic masses. Renal, adrenal, metastatic Sertoli cell tumors and urinary bladder tumors have also been associated with this PNS.[51,116-121] Hypertrophic osteopathy is characterized by periosteal proliferation along the shafts of long bones, typically in the distal extremities, and associated soft tissue swelling of the limbs. The syndrome oftentimes affects all four limbs, starting distally and moves proximally. While HO is most commonly associated with neoplastic conditions, it has been associated with infectious/inflammatory pulmonary diseases, *Spirocerca lupi* esophageal granuloma, and bacterial endocarditis.[51,122-124] Dogs and cats affected by HO often present with shifting-leg lameness and/or a reluctance to move. Typically, the distal extremities are warm and swollen on palpation. A diagnosis of HO is aided by radiography of the affected bones and subsequent radiographic evaluation of the thorax. If thorax radiographs are negative for intrathoracic disease, additional diagnostics to evaluate for infectious/inflammatory causes should be pursued.

The stimulation of afferent nerves is thought to be involved with HO, resulting in increased blood flow to the extremities and periosteal proliferation. The resolution of signs in some patients following vagotomy supports this belief. Successful treatment of the primary mass will result in resolution of HO.[51] Efforts to manage the pain associated with HO should be attempted using anti-inflammatory doses of steroids or nonsteroidal anti-inflammatory drugs (NSAIDs).

Fever

Paraneoplastic fever occurs secondary to elaboration of pyrogenic cytokines by either the tumor or by the host immune response to the tumor. These pyrogens include IL-1, IL-6, interferons, and tumor necrosis factor-alpha, which act on the thermoregulatory center of the anterior hypothalamus. In addition to pyrogen-induced fever, neoplastic infiltration into the hypothalamus may result in fever. Therapy is dependent upon the underlying cause of the fever, although symptomatic therapy with NSAIDs may provide some palliation if the underlying cancer cannot be eliminated.

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SECTION XXVI

Musculoskeletal Diseases

OUTLINE

Chapter 353 Skeletal Disorders in Companion Animals
Chapter 354 Muscular Disorders
Chapter 355 Physical Therapy and Rehabilitation
Chapter 356 Chronic Pain Pathophysiology, Identification and General Management

CHAPTER 353

Skeletal Disorders in Companion Animals

Denis J. Marcellin-Little

Client Information Sheet: Osteoarthritis in Dogs

Skeletal disorders in dogs and cats interfere with pain-free movement and mobility; they negatively impact quality of life; and they may require surgery or may lead to euthanasia. Orthopedic problems result from orthopedic injuries or from skeletal disorders. Orthopedic injuries affect all musculoskeletal tissues: bone, ligaments, muscles, and tendons. Because dogs and cats sustain a wide range of trauma, the onset and severity of orthopedic injuries is unpredictable. The diagnosis and management of orthopedic trauma is described elsewhere.[1,2] Skeletal disorders, by comparison, have a much more predictable onset and progression. Skeletal disorders are most often triggered by the presence of faulty genes, of improper nutrition, of infection, by metabolic disorders, or by the presence of developmental disorders affecting bones or joints. Despite these widely ranging causes and pathophysiology, skeletal disorders have common consequences on skeletal health and mobility. The purpose of this chapter is to review the causes and pathophysiology of skeletal disorders in dogs and cats, their clinical impact, their diagnosis, and their treatment options with a focus on medical management.

Causes of Skeletal Disorders

Skeletal disorders in companion animals often have a genetic basis.[3] Orthopedic disorders can result from a single faulty gene or from multiple faulty genes (multigenic diseases). Often, a genetic cause is suspected based on population data but specific genetic links are not identified.[4-6] For example, chondrodystrophy in dogs can result from one of several genetic disorders but little is known about the specific genetic mutations causing these disorders.[7] In humans, dwarfism (achondroplasia) is an autosomal dominant disease resulting from a mutation of the fibroblast growth factor receptor 3 (FGFR3) gene. In dogs, various forms of dwarfism (see ch. 295) lead to having short or deformed long bones and affect limbs (Basset Hound or Dachshund) or the skull (brachycephaly in Boxer dogs).[8-10] Dwarfism is also present in cats (see ch. 294).[10] Dwarfism in cats is generally linked to metabolic diseases, including congenital hypothyroidism (see ch. 300), mucopolysaccharidosis (see ch. 260), and congenital hyposomatotropism (see ch. 294).[11-13] Cats can have a classic chondrodystrophic morphology (Munchkin cats) in the absence of metabolic disorders. Genetic and genomic tests to detect markers of orthopedic disease are in their early stages.[14] The identification of specific genes responsible for developmental orthopedic diseases is challenging and only few genetic markers are in use in orthopedics. For example, the SERPINH1/HSP47 mutation is responsible for osteogenesis imperfecta in the Dachshund.[15] Genomic selection rather than marker-based selection has been suggested as strategy for reduction of canine hip dysplasia[16] and other orthopedic disorders.[17]

Nutrition can impact skeletal disorders directly by causing these disorders, or indirectly by promoting the expression of faulty genes or by accelerating the progression of orthopedic diseases. Nutritional imbalance can cause skeletal disorders (see ch. 192).[18] The most common nutritional imbalance is nutritional secondary hyperparathyroidism (see ch. 171, 172, 174, 187, and 297). Dogs and cats that eat an all-meat diet ingest a low-calcium high-phosphorus diet (see ch. 192) that triggers an increase in parathyroid hormone. That increase promotes a loss of calcium from bones. Affected patients have a loss of bone stiffness that leads to increased bone elasticity (*rubber jaw* syndrome; see ch. 324) or fractures. Bone healing is not negatively impacted. Other nutritional disorders affecting bones and joints include hypervitaminosis A and osteopetrosis (excessive bone density).[19-21] Nutrition has a direct impact on bone growth.[22] Growth rates for bone mineral content, fat, and

lean tissue are influenced by nutrition.[23] The calcium and phosphorus concentrations in the diet of young puppies are reflected in their bones until 5 to 6 months of age.[23] Excess energy (see ch. 171 and 187) in the diet and excess calcium intake negatively impact bone growth (by accelerating it) and appear to promote the expression of genes linked to developmental orthopedic diseases.[22,24]

Infections can affect joints and bones.[25] Tick-borne diseases, particularly Lyme disease (*Borrelia burgdorferi*; see ch. 211), can lead to fibrinopurulent arthritis after several months of incubation.[26] Ehrlichiosis (see ch. 218) can also lead to polyarthritis[27] (see ch. 203). In neonates, omphalophlebitis can lead to bacterial embolization of growth plates (septic physitis), joints (septic arthritis), or bones (osteomyelitis). Septic physitis leads to impaired physeal growth and often results in a severe bone deformity because the physeal problem occurs very early in life. Septic arthritis, if left undiagnosed or untreated, will lead to cartilage damage and osteoarthritis. *Escherichia coli* bacteremia has been found in association with hypertrophic osteodystrophy.[28] In humans, arthritis can result from inflammation associated with bacterial infection, a syndrome described as spondyloarthritis that includes reactive arthritis, psoriatic arthritis, and ankylosing spondylitis (see ch. 15 and 203).[29]

Skeletal fungal infections are uncommon and are generally secondary: Histoplasmosis (see ch. 233) generally involves a primary intestinal lesion, aspergillosis (see ch. 234 and 235) generally involves a sinonasal lesion, and blastomycosis (see ch. 233) and coccidioidomycosis (see ch. 232) generally involve a primary pulmonary lesion.[30-32] Bone or joint lesions associated with fungal disease are not uncommon. Focal inoculations of blastomycosis and coccidioidomycosis have been reported.[33] Paecilomycosis (see ch. 336) of the distal radial epiphysis was reported in one dog.[34] Viral osteomyelitis in dogs has been described.[35] Distemper virus (see ch. 228) has been implicated in the pathogenesis of several proliferative bone diseases: hypertrophic osteodystrophy and panosteitis in dogs and Paget's disease, a proliferative bone disease of the skull, in humans.[36-38] Several parasites can lead to orthopedic problems. Leishmaniasis (see ch. 221) has been associated with polyarthritis.[39-41] Arthritis in dogs with leishmaniasis may be linked to the presence of a *Bartonella* infection (see ch. 215).[42] *Dirofilaria immitis* larvae have been found in joint fluid (see ch. 255).[43,44] In regions with an increased prevalence of *Toxocara canis*, seroprevalence has been associated with rheumatoid arthritis in dogs.[45]

Even if the relevant scientific literature is scant,[46] several orthopedic problems are seemingly linked to metabolic disorders: hyperadrenocorticism (see ch. 306), hypothyroidism (see ch. 299), diabetes (see ch. 304 and 305), and high estrogen and progesterone concentration (in female dogs during the whelping period; see ch. 315). Orthopedic problems in dogs with metabolic diseases include rupture of the cranial cruciate ligament, rupture of the common calcanean tendon, rupture of the palmar fibrocartilage and secondary carpal hyperextension, rupture of the plantar fascia, rupture of the tendon of insertion of the triceps brachii muscle. They appear to result from the loss of collagen strength associated with *negative nitrogen balance.* Growth hormone excess (acromegaly; see ch. 294 and 295) or deficit (proportional dwarfism; see ch. 294 and 295) has consequences on bone development.

Developmental orthopedic diseases are multifactorial diseases that are reportedly influenced by genetics, nutrition, growth, and the mechanical environment of joints. The genetic basis of developmental orthopedic diseases is often suspected, based on breed predisposition. The risk for 10 common developmental orthopedic diseases was evaluated in one study.[47] The most common developmental orthopedic diseases are hip dysplasia, elbow dysplasia, patellar luxation, and osteochondritis dissecans. Less common developmental orthopedic diseases include panosteitis, hypertrophic osteodystrophy, craniomandibular osteopathy, Legg-Perthes disease, and incomplete ossification of the humeral condyle.

Canine hip dysplasia is a ubiquitous disease affecting most if not all dog breeds. It is reportedly the most common canine developmental orthopedic disease and patients with hip dysplasia represented 10% of orthopedic patients in one large survey of dogs treated in veterinary teaching hospitals.[48] In two scientific reports, hip dysplasia was present in more than 40% of Golden Retrievers, Labrador Retrievers, and Rottweilers.[49,50] Hip dysplasia is an inherited developmental condition involving joint laxity and a lack of fit between the femoral head and acetabulum leading to osteoarthritis.[51] When present, hip dysplasia is most often bilateral. Accelerated growth resulting from high caloric intake increases the severity of hip dysplasia (see ch. 187).[52] Cats have hip dysplasia but little is known about the disease in this species. In one study involving 78 cats, there was a weak association between hip dysplasia and patellar luxation: Cats were three times more likely to have hip dysplasia and patellar luxation than to have either disease alone.[53]

Elbow dysplasia is common in dogs. According to statistics provided by the Orthopedic Foundation for Animals for the 50 most affected breeds, elbow dysplasia has been present in 16% of the 180,000 dogs that have been tested. There is a clear lack of awareness among veterinarians, breeders, and owners with regard to elbow dysplasia. It is by far the most common source of pain in growing dogs with a forelimb lameness and the most common source of osteoarthritis affecting the elbow joint. Several pathophysiologic processes have been proposed to explain elbow dysplasia. Most agree that the disease is mechanical in origin and is a consequence of abnormal growth of the radius relative to the ulna or the humeral condyle whilst some think there is humero-ulnar curvature mismatch between the humeral condyle and the ulnar trochlear notch. Impaired longitudinal growth of the radius relative to the ulna can create a transient or permanent humero-radial subluxation that leads to cartilage damage in the elbow within weeks.[54] Similarly, chondrodystrophic dogs often have early elbow osteoarthritis as a result of their impaired antebrachial growth. One key reason for the lack of the early diagnosis of elbow dysplasia in the young dog and of elbow subluxation secondary to dwarfism is that they are difficult to visualize on radiographs. Many patients with elbow dysplasia do not have a problem that can be predictably seen on radiographs of the elbow joint. While ununited anconeal process and osteochondritis dissecans of the humeral condyle can predictably be seen on radiographs, they only affect a minority of patients with elbow dysplasia.[55] However, mild joint incongruity (distal humero-ulnar subluxation or distal humero-radial subluxation) or the presence of an abnormal medial coronoid process are present in a large majority of cases with elbow dysplasia. These cannot be readily seen on radiographs.[56] Advanced imaging (computed tomography, magnetic resonance imaging) and arthroscopy (see ch. 94) greatly increase the detection of these problems but these methods have limited availability and are costly, compared to radiographs.

Patellar luxation is one of the most common orthopedic problems in dogs, reportedly being the cause of 6% of orthopedic referrals.[48] Patellar luxation may be the most common orthopedic problem in small dogs.[48] Patellar luxations are defined as complete dislodgement of the patella medial or lateral to the trochlear groove. Luxations are categorized as grade 1 luxations when they can be manually elicited through digital pressure and are reduced as soon as pressure is released, grade 2 luxations when they are elicited through digital pressure but are not reduced when the pressure is released, grade 3 luxations when they are luxated most of the time but can be reduced through digital pressure, and grade 4 luxations when they are always luxated (and therefore cannot be reduced through digital pressure). Medial luxation is more common than lateral luxation. Some dogs may have medial and lateral luxations, most likely as a result of soft tissue laxity (e.g., Basset Hounds). Traumatic patellar luxations can occur but are rare. In most instances, patellar luxations are a secondary sign of a primary orthopedic problem. In general terms, the *mechanical* axis of the pelvic limb (a virtual line joining the center of the femoral head to the metatarsal pad) is abnormal. The center of the stifle joint may be axially (medially) or abaxially (laterally) displaced compared to the mechanical axis of the limb. In more specific terms, patellar luxations are generally the consequence of an array of geometric problems affecting the femur and tibia, including having abnormal angulation or torsion of the proximal or distal portion of the femur, abnormal tibial angulation or torsion, an abnormally high (generally described as *patella alta*) or low patella *(patella baja),* and abnormal torsional laxity of the stifle joint (Figure 353-1). These abnormalities often coexist. They may be present in dogs with conformation disorders that include bow-legged and knock-kneed stances.

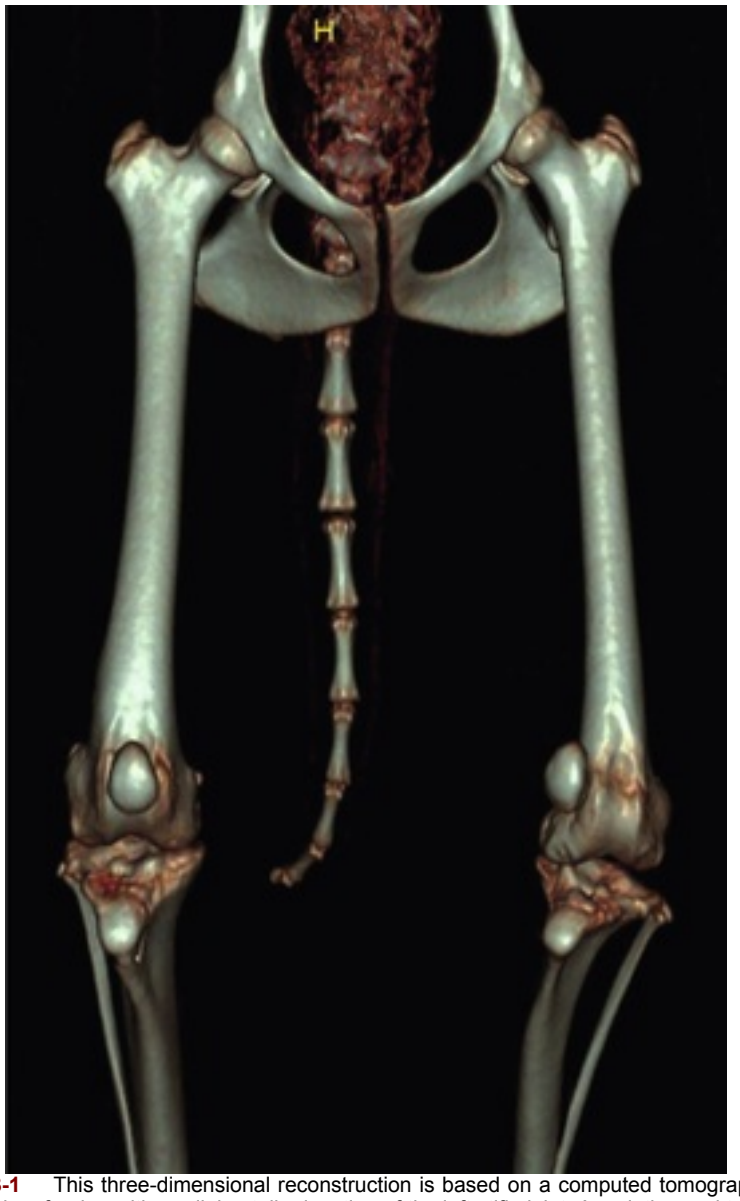

FIGURE 353-1 This three-dimensional reconstruction is based on a computed tomography scan of the pelvic limbs of a dog with medial patellar luxation of the left stifle joint. Angulation and torsion of the femur and tibia, the shape of the trochlea and femoral condyle, and the position of the patella are assessed for both pelvic limbs by manipulating the rendering.

If a patellar luxation occurs early in life while bones and joints are developing, additional abnormalities are likely to develop, including a shallow or absent trochlear groove, and a medially displaced tibial crest. Often, a pattern that includes varus and internal rotation of the distal portion of the femur is the root cause of medial patellar luxation. Sometimes, an underdeveloped lateral femoral condyle and resulting valgus orientation of the tibia is the root cause of lateral patellar luxation.[57,58] In patients with patellae that are severely displaced medially and caudally, a lack of stifle joint extension may result from the fact that the quadriceps femoris ceases to function as extensor muscle of the stifle when the tension generated by muscle contractions is directed along a line that is no longer cranial to the femur (Figure 353-2). Over time, as the femur grows, the caudomedially-displaced quadriceps lacks length and acts as tether, limiting stifle extension. Stifle extension is painful in these dogs, complicating the implementation of manual or exercise-based stretching programs (see ch. 355). Femoral shape, tibial shape, torsional laxity, and stifle extension must be evaluated when assessing dogs with a patellar luxation. The initial evaluation is done when the dog is standing and walking slowly. The clinician should assess limb conformation by asking: Are the pelvic limbs straight, bow-legged, or knock-kneed? Are the paws pointing forward or are they internally or externally rotated? Are stifle joints appropriately held or are they excessively flexed or extended? Limbs are also evaluated with the dog lying in lateral recumbency. The luxation is graded from 1 to 4 and the proximodistal position of the patella is

recorded (high [alta], normal, or low [baja] patella). The presence of angulation (varus or valgus) and limb torsion (internal or external) is assessed with the hip relaxed (not extended nor flexed) and the stifle held in extension. Bone shape is confirmed by making orthogonal radiographs of the femur and tibia. If the dog is sufficiently small, a single craniocaudal radiograph that includes the femur, tibia, and pes is made and used to assess the mechanical axis of the limb. In large dogs, this can be accomplished by making two craniocaudal horizontal beam radiographs of the proximal and distal portions of the limb, respectively, that are made by translating the x-ray source without changing the limb position. Three-dimensional reconstructions based on a computed tomographic scan of the limb allow for more rapid and accurate assessment of bone shape than radiographs (see Figure 353-1). Rotational laxity of the stifle joint is assessed with the joint held at a neutral (≈90-degree) angle. Normal tibio-femoral rotation is approximately 20 degrees. Some patients have 60 to 90 degrees of tibio-femoral rotation, potentially as a result of the torque placed on the tibia by the quadriceps femoris. Palpation of the stifle joint should also observe for joint effusion, crepitus, cranial drawer, and pain response to palpation. Joint effusion, palpable immediately caudal to the patellar ligament on the medial aspect of the stifle, is unusual in dogs with patellar luxation. The presence of effusion should make clinicians suspect the presence of a problem beyond patellar luxation, most commonly a rupture of the cranial cruciate ligament. With a traumatic patellar luxation, stifle joint effusion could result from a tear of the medial or lateral parapatellar fibrocartilage. Crepitus is unusual in dogs with a patellar luxation. Most often, crepitus may result from full-thickness cartilage damage to the patella and the ridge of the trochlea where the patella is luxating. Cranial drawer may be present if a dog has concurrent patellar luxation and cranial cruciate ligament injury. The presence of a patellar luxation seemingly predisposes dogs to cranial cruciate ligament injuries, potentially because of the change in forces sustained by the ligament due to the displacement of quadriceps femoris muscle or due to the displacement of the tibia in relation to the femur. Overall, pain response to palpation of the stifle or to reduction of a luxated patella in dogs with patellar luxation is unusual. However, when pain is present, it can be very pronounced. Pain response to palpation is most often present in dogs with a lack of stifle joint extension (because of tightness in the quadriceps, as described above), in dogs with cruciate ligament rupture (because of the severe joint inflammation resulting from the cruciate ligament rupture), in dogs with *tight* patellae that require significant effort to reduce their patellae, in dogs with patella alta that have bone resorption at the proximal aspect of the trochlea, and in dogs with osteoarthritis.

FIGURE 353-2 This 11-month-old miniature Poodle stands with flexed stifle joints. The dog has grade 4 medial patellar luxation in both hindlimbs. Approximately 60 degrees of extension in both stifle joints is lost because internal rotation of the tibia is so severe that the quadriceps femoris no longer functions as an extensor muscle of the stifle joint.

Osteochondrosis is an abnormal development of the articular surface with delayed focal ossification of the subchondral bone, potentially leading to the formation of a flap of articular cartilage, a problem named **osteochondritis dissecans** (OCD). In dogs, OCD affects the caudal aspect of the humeral head, the medial aspect of the humeral condyle, the distal aspect of the medial and lateral femoral condyles, and the proximal aspect of the medial and lateral ridges of the trochlea of the talus. The pathogenesis of osteochondrosis has two competing theories (mechanical and vascular), both plausible. The mechanical OCD theory is based on the fact that subchondral bone of rapidly growing dogs is coarse and mechanically weak, predisposing to fracture in areas resisting high loads.[22] The vascular OCD theory is based on the loss of blood supply to the epiphysis as a result of cartilage canal vessel degeneration.[59] From a population genetic perspective, OCD of the humeral condyle and fragmentation of the medial process appear to be distinct genetic disases.[4] OCD of the humeral condyle, femoral condyles, and talar trochlea is highly inflammatory to affected joints (with severe, palpable joint effusion) and often triggers the rapid development of osteoarthritic changes. Conversely, OCD of the humeral head appears unlikely to trigger rapid osteoarthritic changes in the shoulder joint.

Several inflammatory bone diseases affect growing dogs. They may affect the shaft of long bones (panosteitis), the metaphyseal regions of long bones (hypertrophic osteodystrophy) or the skull (craniomandibular osteopathy). Panosteitis affects long bones (radius, ulna, humerus, femur) most often in large-breed dogs. It generally affects a single site but can affect several sites in succession, leading to the name of *shifting leg lameness.* The radiographic appearance of panosteitis varies with each phase. Acutely, there is a loss of trabecular pattern in the affected area (the bone looks blurry). After a few weeks, the affected area becomes radiopaque, potentially because new bone is apposed during remodeling of dead trabecular bone. In severe situations, a focal, smooth periosteal reaction centered on the lesion may be visible. The cause of **panosteitis** is not known; some have suggested an infectious cause. Viral genome from canine distemper virus has been linked with bone lesions resembling panosteitis, similar to hypertrophic osteodystrophy (described below).[38,60] Panosteitis is self-limiting; lesions subside after a few weeks.

Hypertrophic osteodystrophy is an inflammatory bone disease that affects the metaphyseal regions of long bones. It is also named metaphyseal osteopathy. The cause of hypertrophic osteodystrophy is not known; (distemper) viral RNA has been identified in osteoblasts of the metaphyseal region of long bones in affected dogs and metaphyseal lesions have been identified in distemper-infected dogs.[37,38] Modified live vaccination has been reported to be a trigger for hypertrophic osteodystrophy.[61] *E. coli* bacteremia has been reported in a pup with hypertrophic osteodystrophy.[28] It is unclear whether bacteremia preceded or followed hypertrophic osteodystrophy. Rapid growth caused by increased food intake has been suggested to increase the likelihood of hypertrophic osteodystrophy.[62,63] In mild cases of hypertrophic osteodystrophy, lesions are generally limited to the distal portion of the radius, ulna, and tibia. In severe cases, lesions often can affect the proximal and distal metaphyses of all long bones. Severe hypertrophic osteodystrophy triggers a thick periosteal reaction around the metaphyseal region of the distal portion of the radius and ulna. That periosteal reaction is often associated with a severe caudal angulation (cranial bowing) of the radius.[64] Hypertrophic osteodystrophy is a self-limiting disease that subsides in the majority of patients (85%, in one study)[65] by the time of physeal closure. However, angulation resulting from severe forms of hypertrophic osteodystrophy persists. Hypertrophic osteodystrophy has been reported in cats.[66]

Retained cartilaginous cores are radiographically visible lesions affecting the metaphyseal regions of long bones, particularly the distal ulna.[67] These cores have been reported in combination with hypertrophic osteodystrophy.[68] While retained cartilaginous cores (in the ulna, and to a lesser extent, in the radius) are often associated with impaired longitudinal growth and the formation of bilateral multiapical valgus and caudal angular deformity of the radius, causation is unclear. In other words, the retained cartilaginous cores and the angular deformities could both be consequences of the same growth disturbance rather than growth disturbance being the consequence of retained cartilaginous cores. Large-breed pups sometimes present with bilateral valgus deformities of the radius and yet they may have a retained cartilaginous core visible in a single limb, suggesting that the retained cartilaginous core is a consequence of the impaired longitudinal growth rather than its cause.

Craniomandibular osteopathy is a proliferative bone disease affecting the mandible and maxilla in skeletally immature dogs.[69,70] The disease is most often associated with West Highland White Terriers but it has been reported in other breeds, including Boxers, Great Danes, and Doberman Pinschers. Craniomandibular osteopathy is also self-limiting.

Legg-Perthes disease is a degenerative disease of the femoral head and neck that occurs in growing small-breed dogs. The disease is often unilateral but may affect both hips. Little is known about the pathophysiology of Legg-Perthes disease. Femoral head remodeling and collapse is thought to be the result of collapse of the vessels supplying the femoral head.[71] Fractures across the proximal femoral physis (also named capital physis fractures, slipped capital physes, femoral head fractures, or epiphysiolysis) occurring in the absence of known trauma have been reported in dogs and cats.[72,73] In two cats, these proximal femoral physeal fractures were the result of multicentric epiphyseal dysplasia.[74] Osteonecrosis of the radial carpal bone similar to Legg-Perthes was reported in one dog.[75]

Incomplete ossification occurs in dog bones, often in subchondral regions of small bones (near to articular surfaces). Incomplete ossification may be due to abnormal forces placed on growing bones as a result of chondrodystrophy or other growth impairment (Figure 353-3).[76-78] Breed predisposition has been reported with some forms of incomplete ossification, suggesting the presence of genetic triggers. For example, ununited anconeal process occurs in German Shepherd Dogs, incomplete ossification of the humeral condyle occurs in spaniel breeds, and incomplete ossification of the radial carpal bone occurs in Boxer dogs.[76,79-81] The articular surface overlying the incompletely ossified bone may be discontinuous, allowing fluid exchange between joint and subchondral bone. Incomplete ossification leads to osteoarthritis potentially because of a step in the articular surface, joint instability, or fluid exchange between joint and subchondral bone.[76] Also, incomplete ossification can act a stress riser, triggering the catastrophic mechanical failure of a long bone, as has been reported in the humeral condyle.[76] In addition to incomplete ossification of the anconeal process, humeral condyle, and radial carpal bone, incomplete ossification of the caudal aspect of the glenoid and the atlas have been reported.[82,83] Delayed ossification of the proximal aspect of the tibia has been reported in Greyhounds and other large-breed dogs.[84,85]

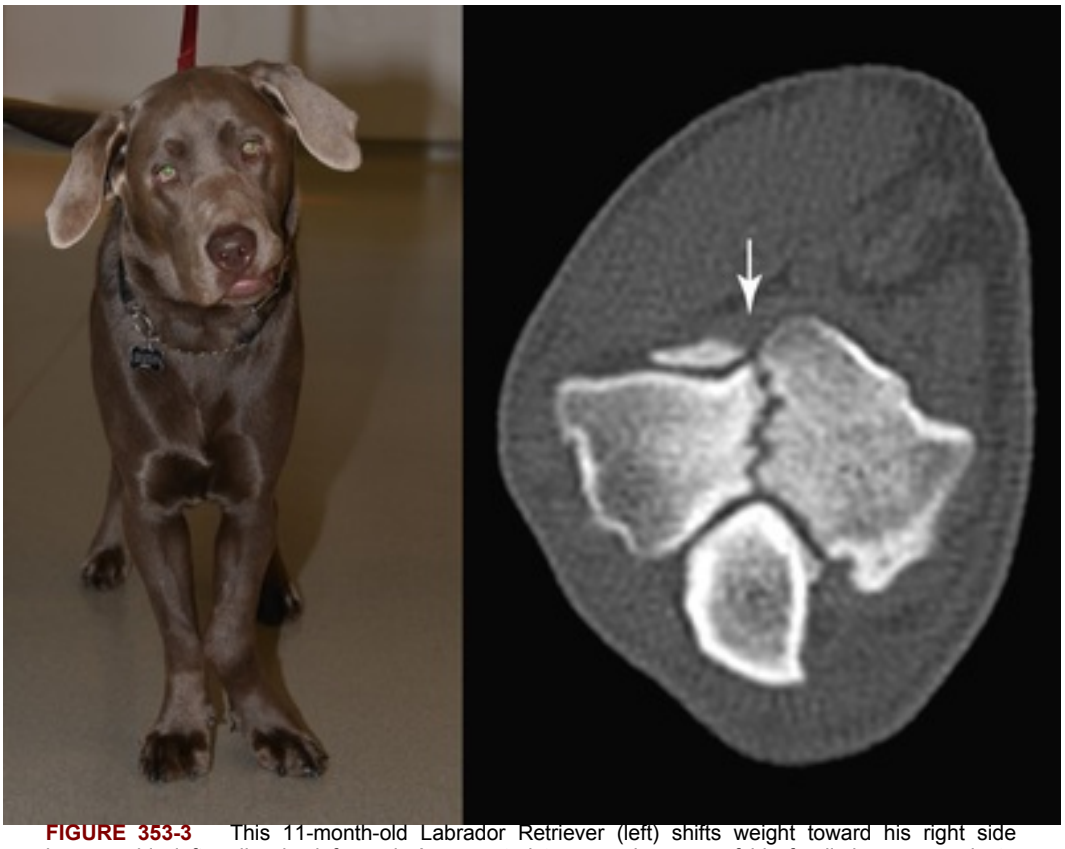

FIGURE 353-3 This 11-month-old Labrador Retriever (left) shifts weight toward his right side because his left radius is deformed. A computed tomography scan of his forelimbs was made to assess the geometry of his deformity. The dog had incomplete ossification of the left and right humeral condyles. The non-ossified region within the right condyle was complete (arrow) and the non-ossified region within the left condyle was partial. The condyles were stabilized with the placement of transcondylar bone screws.

Bone disorders also include **bone cysts.** Large cysts in bones are rare. Cysts can predispose to fracture.[86,87] Cysts can form as a result of arterio-venous fistulae (see ch. 250 and 257).[88] Small subchondral bone cysts are common as a consequence of chronic osteoarthritis.[89] A subchondral cyst of the ulnar notch has been reported in one dog.[90]

Hypertrophic osteoarthropathy, named Marie's disease in humans, is a proliferative bone disease where a slightly irregular diffuse periosteal proliferation occurs in the distal portions of limbs. The disease is caused by the presence of a mass or mass-effect in the chest or abdomen, most commonly lung tumors.[91] Hypertrophic osteoarthropathy also has been reported in dogs and cats as a consequence of pneumonia, bronchitis, megaesophagus, endocarditis, intra-abdominal (renal, liver, bladder) tumors, and spirocercosis.[92-95] Hypertrophic osteoarthropathy has been associated with pregnancy in the horse[96] and in humans. The periosteal proliferation is considered to be most likely the consequence of increased blood flow resulting from a paraphysiologic afferent vagal reflex, but other theories have been proposed.[94,97]

Cranial cruciate ligament (CCL) injuries are among the most common orthopedic problems in dogs. In one large survey, CCL injuries represented 8% of patients.[48] While a minority of CCL injuries results from direct trauma, most CCL injuries result from skeletal disorders. Often, CCL injuries are diagnosed when a veterinarian evaluates a chronic weight-bearing lameness of a pelvic limb in a middle-aged large-breed dog without history of trauma. In one study involving more than 1.2 million dogs treated during a 40-year period, nine breeds were at increased risk of CCL injuries; the breeds at highest risk were the Newfoundland and the Rottweiler.[98] Scientific consensus regarding the chain of events leading to CCL injuries is lacking. CCL injuries are clearly multifactorial. Patellar luxation is a predisposing factor for CCL injury.[99] Some favor a mechanical chain of events as trigger for CCL disease that may include the tibial plateau slope, femoral anteversion angle, width of the trochlear notch, and extensor moment at the hock joint.[100,101] Others favor a biologic chain of events that includes immune-mediated disease, fibrocartilaginous metaplasia, and matrix

degradation as triggers of CCL injury.[102,103] Bacterial DNA has been identified in stifle joints with osteoarthritis.[104] Obesity (see ch. 176) predisposes dogs to CCL injury.[105] Castration and ovariohysterectomy are associated with an increased risk of CCL injury,[106,107] but a causal relationship has not been demonstrated. Rupture of the opposite CCL is common after CCL injury. Median survival of the opposite ligament has been reported to be 947 days.[108] Meniscal injuries are common consequences of CCL injuries, particularly when the CCL is completely ruptured, when dogs are large, and when treatment is delayed.[109,110]

Neoplasia affects bones and joints. The most common tumor affecting bone is osteosarcoma (see ch. 348). Other tumors affect bones and joints, including chondrosarcoma, fibrosarcoma, and malignant melanoma. Multiple cartilaginous exostoses have been reported in dogs[111] and have been found in littermates and across generations.[112,113] In addition to osteosarcoma, melanoma, and hemangiopericytoma, several tumor types specifically affect the digits in dogs, including squamous cell carcinoma in dark-haired dogs, metastatic lung carcinoma, and papilloma.[114-118] Long bone tumors have been reported in association with multifocal bone medullary infarction, such as in Schnauzers with hyperlipidemia, and in association with focal medullary infarction secondary to total hip replacement.[119-121]

Orthopedic disorders include pathologic fractures, fractures that occur in bones weakened by preexisting disease. The most common pathologic fractures are fatigue fractures, also known as stress fractures, defined as fractures induced by normal forces applied to abnormal bone, by comparison with conventional fractures, that are induced by abnormal forces placed on normal bone.[122] Fatigue fractures have only been reported in racing Greyhounds, who can fracture their central tarsal bone, metacarpal and metatarsal bones, and acetabulum.[122-125] Pathologic fractures also occur as a result of bone loss secondary to periodontal disease,[126] osteosarcoma,[127,128] or bone cysts.[86,87] Pathologic fractures also occur in dogs and cats with osteogenesis imperfecta (see ch. 187).[129,130]

General Consequences of Skeletal Disorders

Pain

The clinical signs of orthopedic disorders most often result from **pain** arising from joints, bones, or other musculoskeletal tissues (see ch. 126). Subjectively, joint pain and bone pain have a more severe clinical impact than pain arising from ligaments, muscles, or tendons. Limb use does not appear to be particularly compromised in dogs that have muscle tears. For example, a racing Greyhound that tears its gracilis muscle would be expected to slow down by a few lengths during a race, a slowdown of approximately 3% (1 second over a 35-second race). Similarly, tendonitis is rarely diagnosed as a source of lameness in dogs (presumably because tendonitis does not induce lameness) but when a tendon courses through a joint, gets inflamed, and causes synovitis in the joint that it crosses, clinical signs can be very severe. For example, when the tendon of origin of the biceps brachii muscle becomes inflamed, a tendon that travels through the shoulder joint, clinical signs are often very severe.[131]

The dominant cause of joint pain in dogs is osteoarthritis. Joint pain can also result from immune-mediated joint disease, septic arthritis, joint tumors (synovial cell sarcoma), incomplete ossification, the presence of osteochondral flaps or fragments, or from other causes. Subjectively, one could estimate joint pain secondary to osteoarthritis to be the cause of 99% of joint-related pain because osteoarthritis is common in dogs and other causes of joint pain are rare. Joint disease can be acute or chronic. It can be inflammatory or degenerative. Acute joint pain is generally caused by synovitis. Lameness from synovitis is so predictable that urate crystal-induced synovitis is used as experimental model of transient lameness.[132-134] Synovitis can result from the presence of an osteochondral fragment in the joint (e.g., OCD flap, fragmented medial coronoid process), from full-thickness cartilage damage (hip dysplasia, elbow dysplasia), from fluid exchange between joint and subchondral bone (OCD flap, incomplete ossification), or from the presence of torn collagen fibers in the joint (CCL injury, biceps brachii tendon injury). Intra-articular bleeding induces synovitis[135] and damages cartilage, particularly immature cartilage.[136] Also, subchondral bone exposed to joint fluid becomes inflamed.[137] Acute, inflammatory disease results in pain but it is not associated with structural changes to the joint. In that situation, lameness is present but the range of motion is within normal limits. The pain response to acute inflammatory joint problems is managed like acute pain induced by injury or surgery (see ch. 126 and 166). If joint inflammation persists, over time joint disease becomes chronic: The joint capsule thickens and joint motion is decreased. Local pain amplification (peripheral primary

sensitization) and spinal (central) sensitization are likely. Loss of joint motion is unpredictable. It varies between joints and it varies with different joint motions. For example, with chronic hip dysplasia, Labrador Retrievers lose extension but they do not lose flexion.[138] Chronic joint disease is managed like chronic pain (see below).

Clinical signs can also be caused by bone pain. Overall, bone pain is much less common than joint pain in dogs. In the United States, one can estimate that millions of dogs are suffering from joint pain whereas thousands of dogs are suffering from bone pain.[48,98,139] The two most common causes of bone pain are iatrogenic: failure of fixation after an orthopedic procedure and osteomyelitis. Other causes of bone pain, in decreasing order of frequency, include juvenile inflammatory bone diseases (panosteitis, hypertrophic osteodystrophy, and craniomandibular osteopathy), neoplasia (osteosarcoma chondrosarcoma, metastatic carcinoma, and others), hypertrophic osteoarthropathy, and pathologic fractures. Failure of fixation is a source of bone pain because the first stage of fracture healing is inflammatory. That inflammatory stage persists and increases in intensity in fractures managed without surgery and after failure of fixation. Severe, chronic inflammation is the likely mechanism leading to pain associated with osteomyelitis.[140] Intramedullary edema has been implicated as a factor leading to pain in dogs with inflammatory bone diseases.[141] Excessive osteoclastic activity is a critical factor in the pain resulting from osteosarcoma.[142]

Abnormal Gait

Having an abnormal gait is a common consequence of orthopedic disorders because bones may be abnormally angled or short or because of joint instability resulting from focal or systemic connective tissue problems. Focal connective tissue problems include hyperextension of the carpus or tarsus. Carpal hyperextension is most often reported in large-breed growing dogs, particularly in German Shepherd Dogs (Figure 353-4), in dogs with metabolic disorders, particularly hyperadrenocorticism, and in dogs with immune-mediated joint disease (Figure 353-5; see ch. 203). Abnormal gait also results from the presence of lameness. Lameness can be defined as a voluntary alteration of gait to minimize the pain perceived during locomotion. Lameness varies in dogs based on the nature, severity, and chronicity of orthopedic problems, patient size and behavior (patient "personality"), and other factors.

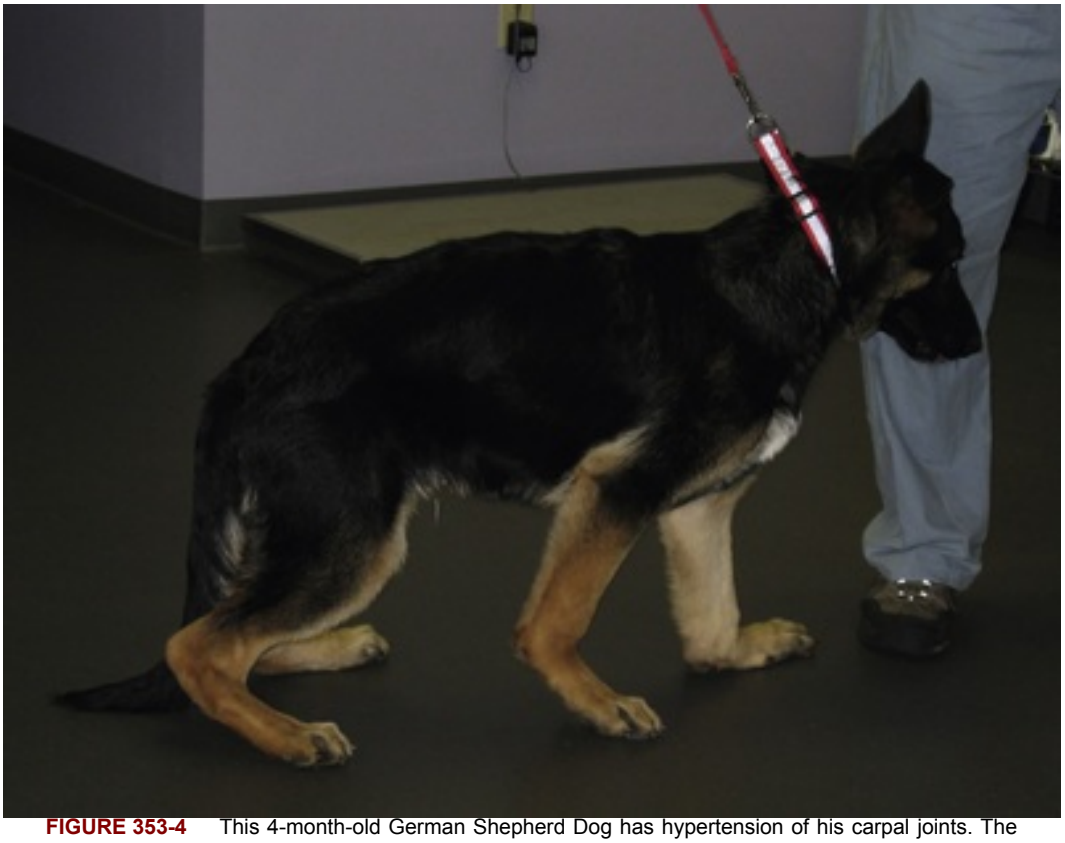

FIGURE 353-4 This 4-month-old German Shepherd Dog has hypertension of his carpal joints. The

dog is palmigrade. Laxity between the calcaneus and fourth tarsal bone is also present.

FIGURE 353-5 This mixed-breed dog has carpal hyperextension because of a low-grade nonerosive polyarthritis. While carpi and tarsi are often affected in dogs with immune-mediated polyarthritis, carpal hyperextension is generally visible earlier and is more severe than tarsal hyperextension.

Clinical Signs

The consequences of skeletal disorders range widely, from no detectable lameness to non–weight-bearing lameness, where a limb is not used and is held in a flexed position. Owners, clinicians, and researchers use different parameters to judge the severity of orthopedic problems and the response to therapy. Owners generally look at whether their pets are "happy" (a fairly subjective outcome measure), whether they are able to perform their activities of daily living (walking in and out of the house, climbing steps and stairs in and around the house, getting in and out of a vehicle), whether they vocalize in response to pain, and whether they are playful. Owners routinely assess lameness, for example to evaluate disease progression or response to therapy. Little is known about the accuracy of owner assessment of lameness. Owners tend to underestimate the severity of lameness increases over time.[143] Clinicians judge the severity of orthopedic disorders based on the severity of lameness, usually through the use of simple qualitative scales such as mild, moderate, severe weight-bearing or non–weight-bearing lameness.[144-146] Clinicians sometimes attempt to document orthopedic problems more specifically than simple qualitative lameness scores, such as when they perform physical rehabilitation (see ch. 355).[147] Specific orthopedic assessments may include joint effusion, crepitus, the pain response to palpation, and joint motion assessed subjectively or measured objectively using a plastic goniometer (Figure 353-6).[148,149]

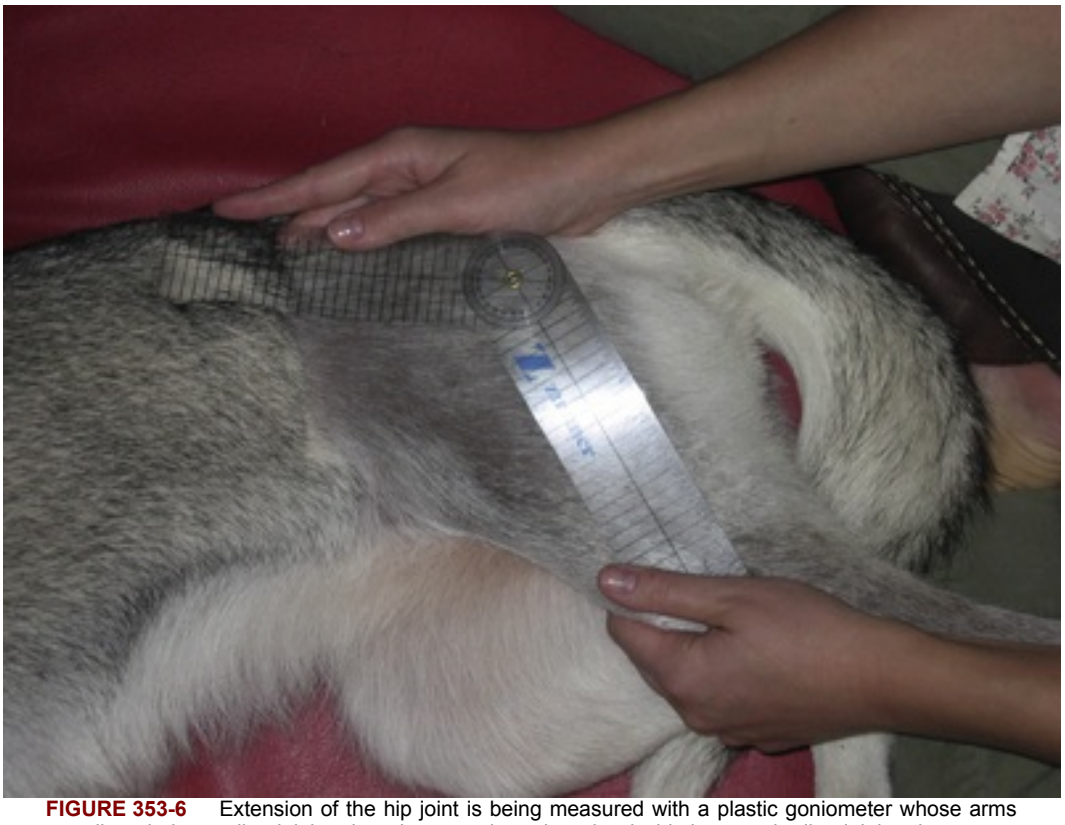

FIGURE 353-6 Extension of the hip joint is being measured with a plastic goniometer whose arms are aligned along a line joining the tuber sacrale to the tuber ischiaticum and a line joining the greater trochanter to the craniocaudal midpoint between the patella and lateral fabella, respectively. Normal hip extension in dogs is approximately 160 degrees. In this dog that had undergone a femoral head ostectomy, hip extension was 123 degrees.

Limb Disuse

Limb disuse is a common consequence of severe orthopedic disorders that are responsible for sustained chronic pain (Figure 353-7). With limb disuse, dogs are toe touching or non–weight-bearing (Figure 353-8) when standing and walking. Dogs with limb disuse shift weight away from their affected leg or legs. Dogs with disuse in a single limb shift weight side-to-side onto the opposite side (Figure 353-9 and Video 353-1). Dogs with disuse in two limbs shift weight away from these limbs: forward, if hind limbs are affected (Figure 353-10) or backward, if forelimbs are affected. By doing so, dogs modify the angles of their spine and limb joints (Figure 353-11). These changes in posture become deeply rooted over time and are hard to eliminate, even when the original orthopedic disorder is successfully managed. Physiologically, limb disuse leads to a loss of bone mass, a loss of muscle mass, a loss of cartilage thickness and stiffness, and a loss of ligament strength. Most of these changes are slowly reversible once the cause of limb disuse is treated.

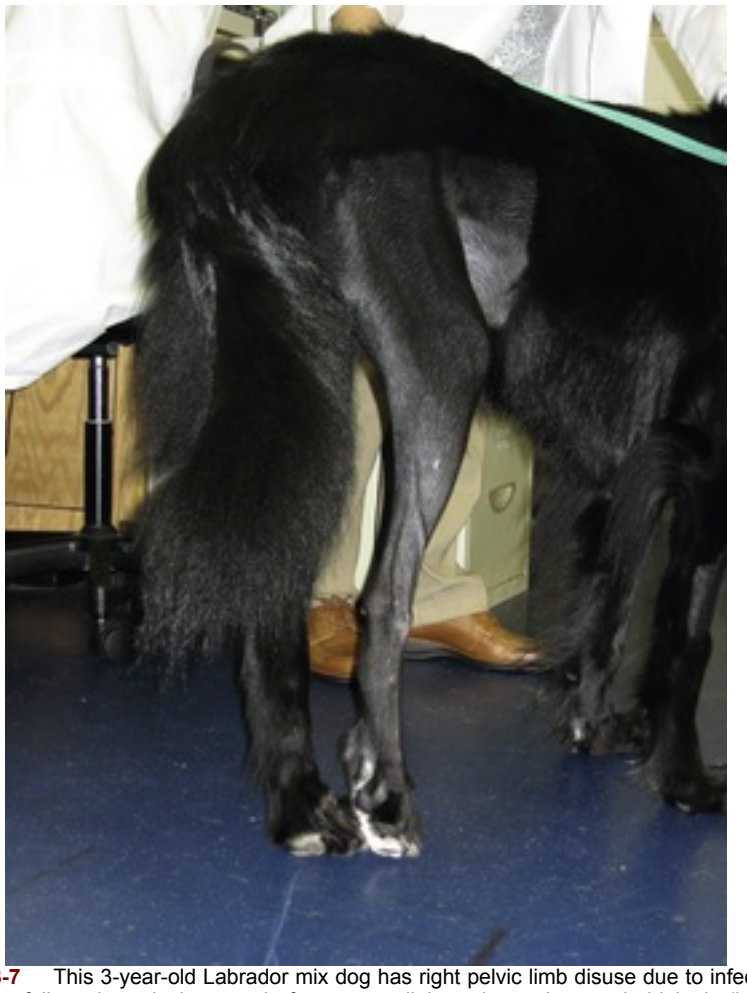

FIGURE 353-7 This 3-year-old Labrador mix dog has right pelvic limb disuse due to infection of the stifle joint that followed surgical removal of a torn medial meniscus. Iatrogenic biologic (infection) or mechanical problems (failure of fixation of a surgical repair) are common causes of limb disuse.

FIGURE 353-8 This 4-month-old Yorkshire Terrier is non–weight-bearing in his left pelvic limb because of a grade 4 medial patellar luxation. The tibia is internally rotated in relation to the femur. Patellar luxation is the most common cause of limb disuse in growing dogs.

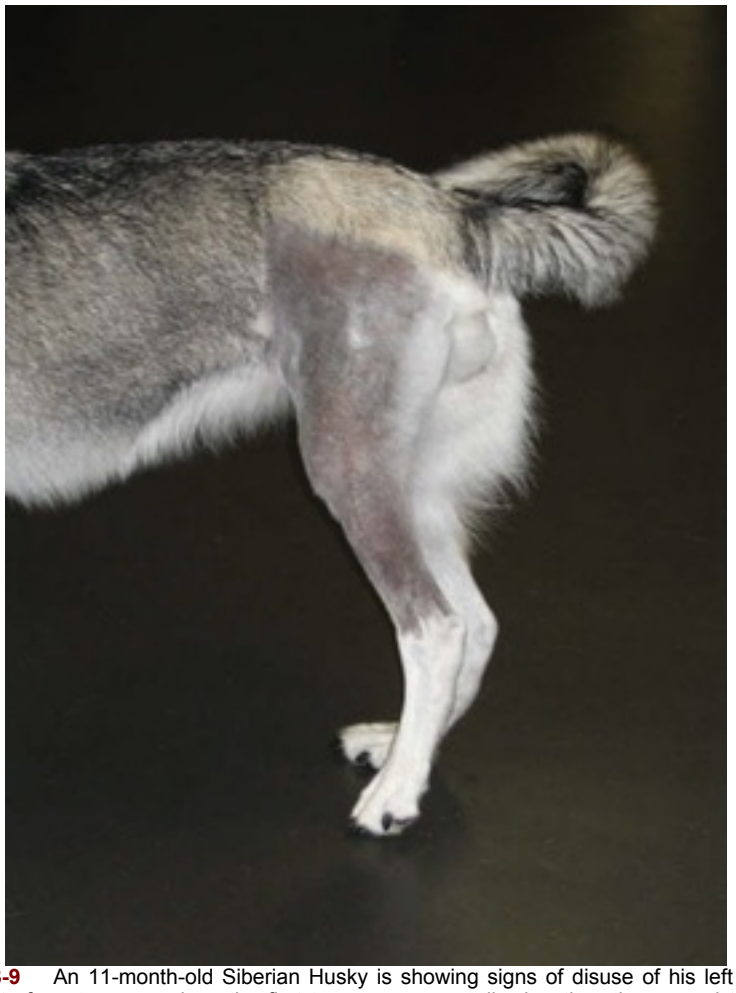

FIGURE 353-9 An 11-month-old Siberian Husky is showing signs of disuse of his left pelvic limb. Disuse results from two surgeries—the first to manage a patellar luxation, the second to perform a femoral head ostectomy to manage hip dysplasia. A severe pain response to hip extension was identified during palpation. Hip extension was 123 degrees, a loss of approximately 40 degrees (see Figure 353-6).

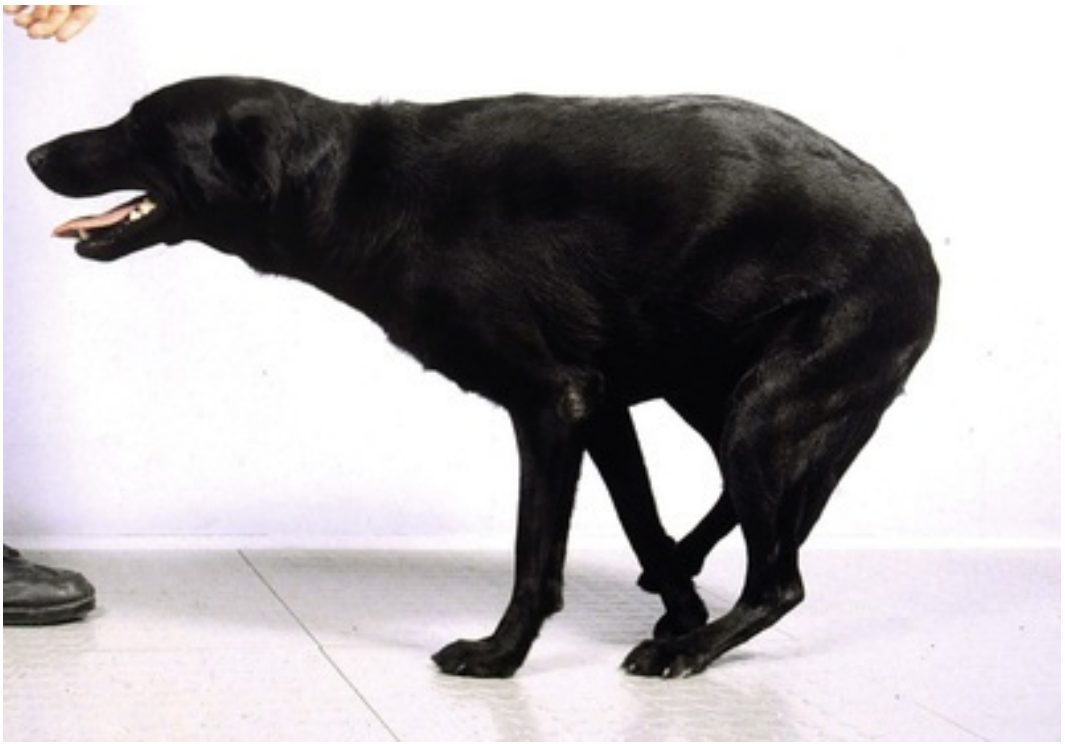

FIGURE 353-10 This Labrador Retriever has a partial tear of his cranial cruciate ligament in both stifle joints. While this dog shifts most of his weight toward his forelimbs, weight shifts are often more subtle.

FIGURE 353-11 This 11-month-old male St. Bernard shifts weight forward and has hyperextended talocrural joints. Tarsal hyperextension resulting from a weight shift is most often seen in young dogs of large and giant breeds that shift weight forward because of hip pain caused by hip subluxation. These

dogs are reluctant to extend their hip joint when they stand and walk and, instead, stretch their talocrural joints toward hyperextension.

The radiographic appearance or progression of osteoarthritis is often used as outcome measure of the progression of orthopedic problems. However, information on the relationship between functional impairment, pain, and radiographic changes is lacking. That relationship was assessed in cats with osteoarthritis, and the findings from joint palpation and radiographic changes correlated poorly.[150,151] In the dog stifle, the progression of osteoarthritis after surgery to manage CCL injury[152-155] and surgical stabilization of patellar luxation[156] have been reported. In the dog elbow joint, the progression of osteoarthritis after surgery to remove fragmented medial coronoid processes[157,158] and as result of being overweight[159] have been reported. In the dog hip joint, the progression of osteoarthritis as a result of being overweight (see ch. 176) has been reported.[50,159] In an unrelated study, the severity of osteoarthritis in Labrador Retrievers with hip dysplasia did not appear to be associated with the severity of lameness.[138] Advanced imaging, including computed tomography, magnetic resonance imaging, or bone scintigraphy, is sometimes used as assessment tool. Computed tomography is widely used to assess the elbow joint, and its findings correlate with findings of arthroscopy.[160] Researchers also judge the severity of orthopedic disorders based on objective kinetic measures (force plate or pressure-sensitive walkway measurements), on objective kinematic measures (2-D or 3-D kinematic analysis), on serum biomarkers, or on histology.

The clinical signs in dogs and cats with specific orthopedic disorders are rarely described with precision and are rarely investigated. Logically, most of the information available in the literature relates to the most common orthopedic disorders: hip dysplasia, elbow dysplasia, and CCL injuries. The clinical signs of hip dysplasia are most often described as acute in skeletally immature or young adult dogs and chronic in older dogs. Acute clinical signs reflect acute pain: a generally severe and often unilateral lameness. Acute signs generally appear during rapid skeletal growth, between 4 and 8 months of age. Affected dogs may show a reluctance to perform propulsive activities, including jumping, climbing steps or stairs, galloping, walking for extended periods of time, or may exhibit behavioral changes including reluctance to play, introversion, or exhibiting aggressive behavior. The chronic clinical signs of hip dysplasia reflect chronic pain and, as a consequence, loss of strength. These signs include exercise intolerance, a reluctance to jump up and climb steps or stairs, and a bunny-hopping gait anomaly at a gallop. Surprisingly, little has been written about the physiologic changes present in dogs with chronic hip dysplasia.[138,161-164] Dogs with hip dysplasia have pain arising from their femoral and acetabular joint surfaces and hip joint capsule, particularly when moving at higher speed and during extension of the hip joints. Over time, dysplastic dogs may lose hip extension but do not appear to lose hip flexion. In a study evaluating a cohort of 60 Labrador Retrievers with hip dysplasia, a statistical model indicated a loss of 1 degree of hip extension per year.[138] Dysplastic hip joints may lose extension because of joint capsule fibrosis or the development of large osteophytes or enthesiophytes on the caudal and ventral aspects of the acetabulum and on the femoral neck and caudal aspect of the greater trochanter, or because of changes in periarticular tissues or regional muscles. Pain response during hip joint flexion, subjectively, is very unusual and may be the consequence of other problems such as a septic arthritis, a bone tumor, or another problem. Most dysplastic dogs lose muscle mass in their pelvic limbs. Some may displace their center of gravity forward by flexing their spine, shoulder, and elbow joints. The clinical signs of hip dysplasia vary widely among affected dogs. Many dogs have very discrete signs that may appear after long periods of exercise or after strenuous exercise[138]; others are severely disabled and may be unable to trot, gallop, or jump. Little is known about the relationship of specific aspects of hip joint disease (dorsal subluxation, dorsal luxation, cartilage wear, dorsal rim wear, joint capsule thickening, osteophytes production, the presence of joint mice) and the type and severity of clinical signs. For the Labrador Retriever cohort mentioned above, 94% of the dogs had no lameness or had a lameness that was deemed mild or moderate and 6% had a severe lameness.[138] Two factors increased the severity of lameness: the presence of hip luxation (compared to hip subluxation and to no luxation nor subluxation) and exercising <20 minutes per day (compared to exercising >60 minutes per day). In that study, the size and location of osteophytes did not correlate well with the clinical signs of hip dysplasia.

Clinical signs appear to be linked to dog size but scientific data confirming the association of size and lameness or assessing factors influencing clinical signs (demeanor, training, human animal bond, etc.) are lacking.

Subjectively, clinicians often state that large dogs may be less likely to be non–weight-bearing or to present with severe limb disuse compared to smaller dogs. This trend seemingly applies to all skeletal problems.

Larger dogs may be less likely to have a toe-touching or a non–weight-bearing lameness than smaller dogs, possibly because it is harder for large dogs than small dogs to stand or ambulate on three limbs.

Hip dysplasia is also common in cats.[150,165] However, little is known about the clinical signs of hip dysplasia in cats. The low correlation between radiographic signs of osteoarthritis, cartilage damage, and abnormal findings during an orthopedic examination complicates the detection of joint disease in cats.[151]

The clinical signs of elbow dysplasia have been described[79] but the relationship of features of elbow dysplasia and clinical signs has only been reported in one study that involved 55 Rottweiler pups.[166] These clinical signs may include a forelimb lameness that can be intermittent or constant, joint effusion, loss of range of motion in flexion and (to a lesser extent) extension, and abnormal posture when resting in a sternal position (flexion of the carpus and supination of the antebrachium; Figure 353-12).[77]

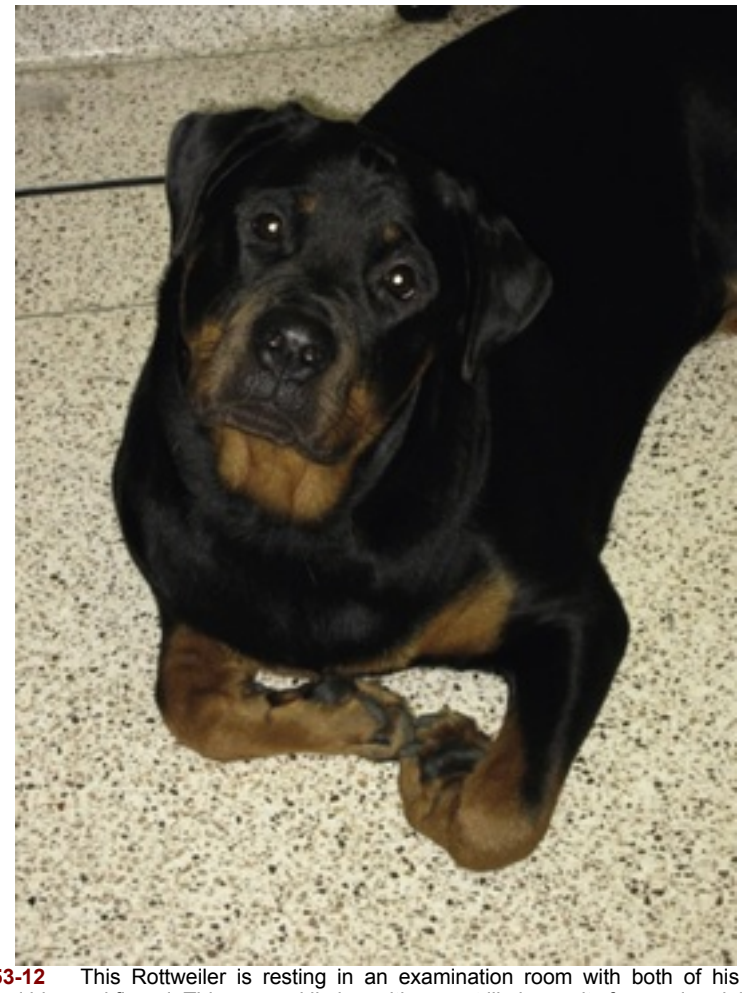

FIGURE 353-12 This Rottweiler is resting in an examination room with both of his antebrachia supinated and his carpi flexed. This unusual limb position most likely results from pain originating in the elbow joints. Pain response to manipulation of his elbow joints was detected during palpation. The dog has bilateral elbow dysplasia.

The clinical signs of CCL injuries have been reported,[167] but the relationship of features of CCL injuries and lameness has not been evaluated. Palpation of the patellar ligament appears to be the most sensitive sign for the detection of CCL injury.[167] The presence of a meniscal click is a strongly suggestive of the presence of a meniscal tear in dogs with CCL injury.[109,168] The clinical consequences of patellar luxation vary widely from no clinical sign to the lack of ability to ambulate. Little is known about factors influencing these clinical signs. Subjectively, dogs with *loose* patellae tolerate patellar luxation well. Dogs with *tight* patellae show signs of lameness. Lameness is also present in dogs with patella alta (these may show signs of bone resorption proximal to the femoral trochlea) and in dogs with loss of stifle joint extension as a result of severe displacement of the patella.

Patient Assessment

The assessment of orthopedic disorders includes the collection of a medical history, the observation of the patient, limb palpation, and imaging.

Medical History

Most owners are knowledgeable regarding the onset and impact of orthopedic disorders on their pet's activities of daily living but these thoughts are rarely organized. The goal of history is to accurately discuss and record information that will identify orthopedic disorders and gauge their severity and progression (see ch. 1). The medical history also aims to detect the presence of clinical signs affecting other organ systems, particularly neurologic signs because manifestations of orthopedic and neurologic problems resemble each other. The medical history is also used to discriminate between orthopedic injuries from non-traumatic orthopedic disorders and to assess the chronicity and the progression of the problem. Questions regarding activities of daily living *(Is the dog able to void independently, to climb steps, and to go on a walk?)* and questions regarding playfulness provide information on the impact of an orthopedic disorder on quality of life. Exercise intolerance reported by owners may be the consequence of a lack of ability or a lack of willingness. Lack of ability may result from loss of strength, loss of joint motion, lack of fitness (rarely) or the presence of a neurologic compromise. Lack of willingness generally results from pain. The duration of an orthopedic disorder is most often underestimated because owners tend to think that the lameness started when they discovered it. That is rarely true. Also, orthopedic disorders are often chronic and it is hard to recall the date of onset of an event that took place months or years in the past. It may be helpful to ask owners whether the patient was already lame at the time of a specific holiday or event (e.g., *Was your dog already limping on the 4th of July?*).

Patient Observation

Patient observation provides valuable information for clinicians (see ch. 2). Dogs react to orthopedic pain in a predictable fashion and the information that follows refers to examining dogs. Observation of the patient starts in a resting position. Dogs are more relaxed before their limbs are palpated and, therefore, assessment of their posture at rest and when getting up, standing, walking, and trotting should occur before palpation. The dog can be observed when resting in a waiting room and when getting up to walk into an examination room. If lameness is difficult to ascertain, it is helpful to have the owner take the dog outside as if they were leaving a clinic and accompany dog and owner. The dog may be more relaxed and lameness may become obvious. It is important to make sure that any lameness that is observed corresponds to the owners' perceived lameness. While most owners are objective, some overestimate the severity of lameness and others underestimate it. Dogs intended for conformation *(show dogs)* sometimes are presented because they pace rather than trot. Pacing is unacceptable during conformation events. Some dogs pace because of chronic orthopedic problems; other dogs pace in the absence of any orthopedic problem. A solid knowledge of gait patterns is helpful to differentiate normal from abnormal gaits. A digital camera, particularly one that can record or show gait in slow motion, is helpful to observe and record lameness.

Dogs adopt the stance that provides the best compromise between pain perceived and energy expanded. When standing, lame dogs often shift weight away from painful limbs. If a single limb hurts, dogs shift weight to the opposite side. Side-to-side weight shifts do not require a large effort.

If both pelvic limbs hurt, dogs shift weight forward by flexing their thoracic spine, shoulders, and elbows, and widening the stance of their forelimbs. Conversely, if both thoracic limbs hurt, dogs shift weight backward by flexing their lumbar spine, hips and stifles and widening the stance of their pelvic limbs. The most classic weight shift is forward, in response to severe bilateral hip dysplasia or bilateral CCL injuries. Dogs with chronic forward weight shift have wide rib cages, abducted elbows, and internally rotated antebrachia (like a Bulldog). Forward or backward weight shifts require a large effort. While the dog is still standing, weight shifts can be appreciated when paws are lifted off the ground. Dogs that shift weight may pant or their limbs may have tremors because of that effort and because of the pain perceived. Tarsal hyperextension may result from a forward weight shift (see Figure 353-11). Forward weight shift in dogs with conformational abnormalities of the pelvic limbs (genu valgum or other) may lead to torsional laxity of the intertarsal joints.[169]

Dogs lift a painful limb from the ground only if the pain perceived decreases when that limb is elevated and when the effort of lifting that limb is offset by the decrease in pain perceived. Because the effort of lifting the limbs is lesser in small dogs than large dogs, small dogs are more often non–weight-bearing than large- and giant-breed dogs. When multiple limbs are involved (for example, after vehicular trauma, immune-

mediated polyarthritis, or a multifocal inflammatory bone disease), dogs become recumbent.

When dogs are sitting, they must hyperflex the stifle and tarsal joints. Dogs with painful stifle joints, most often after CCL injury, are reluctant to sit straight and prefer extending their painful leg or legs to the side. When they stand up, they shift their weight to the front of their body to avoid having to push on their pelvic limbs (see Figure 353-10).

Lameness

Lameness is generally assessed at a walk and trot. It is important to differentiate lameness from a gait abnormality that could be secondary to a problem that interferes with locomotion but is not an active orthopedic disorder—for example, chondrodystrophic dwarfism, a growth deformity secondary to physeal injury, a fracture malunion, or neurologic disease. Dogs with gait abnormalities may or may not have painful limbs. With forelimb lameness, a head bob is present. The head moves up when the sore limb strikes the ground and moves down when the sound leg strikes the ground. Similarly, with pelvic limb lameness the tail base moves up and down. With hip pain, a dog may avoid flexing the hip joint when moving a leg forward, and, instead, will shift the pelvis from side to side. This leads to an oscillating movement of the base of the tail, when the dog is seen from the back. Some orthopedic problems may be more easily detected at a stance; other problems may be more easily detected at a walk, trot, or gallop. Stance should be assessed for lack of joint motion or excessive joint motion. Some orthopedic disorders are more visible at faster gaits. For example, problems associated with joint subluxation, like hip dysplasia, lead to bunny hopping at a gallop. If the lameness is unclear when the dog is walking, it is often useful to observe the dog while trotting or galloping. Head tilts are often more pronounced when trotting than when walking. Most pups with hip dysplasia will have a characteristic bunny-hop when galloping. It may be useful to watch a dog jump up or down, or climb stairs. For example, dogs with contracture of their semimembranosus muscle will have an abnormal gait at a trot and (hunting) dogs with fibrotic contracture of the infraspinatus muscle will have a characteristic circumduction of the forelimb when climbing steps. As a whole, cats are more difficult to observe than dogs. While some cats are easy to examine as they walk around an examination room, many cats are reluctant to walk during an examination (see Video 2-24). They may prefer staying in a cat carrier, crouching in place, or fleeing to hide.

Palpation

Palpation should include the neck, shoulders, trunk, and all limbs. Optimally, palpation should start with the dog standing, facilitating a comparison between the left and right sides of the body. Muscle atrophy of a forelimb often leads to a more prominent spine of the scapula, because of supraspinatus and infraspinatus muscle atrophy. In the hindlimb, muscle atrophy is most readily identified through atrophy of the biceps femoris muscle. That difference can be determined by comparing the circumference of both thighs, using a (calibrated) tape measure. Conscious proprioception of all four limbs should be evaluated. If it is decreased, a full neurologic examination of the dog should be performed. In trauma patients, especially non-ambulatory patients, the neurological examination should include anal tone, panniculus reflex, withdrawal reflex, and deep pain sensation.

Limb palpation is best conducted while the dog is lying down with the feet toward the examiner. If the dog is fractious or nervous, starting with the limb where the lameness originates may be preferable. Otherwise, collecting information on (presumably) non-painful limbs before a painful limb is palpated may be preferable. Information collected during palpation should be compared between left and right sides of the body. It is best to conduct palpation using a consistent method to avoid omissions and maximize efficacy (see ch. 2). Palpation of the forelimb includes digits, metacarpal bones, carpus, radius and ulna, elbow, humeral condyles and greater tubercle, and shoulder joint. Palpation of the hindlimb includes digits, metatarsal bones, tarsus, tibia, stifle, femoral condyles and greater trochanter, and hip joint. When palpating joints, crepitus, range of motion, effusion (or swelling), pain response to palpation and instability should be evaluated. The first letters of these parameters form the acronym CREPI, the first letters of crepitus. These parameters are evaluated simultaneously: While one hand moves the joint throughout its range of motion, the other hand feels crepitus, effusion or instability, and the examiner looks for a pain response. The evaluation of the range of motion is the most critical part of the palpation because in many instances periarticular inflammation or fibrosis will limit the movement of the joint, especially in smaller, more intricate joints. *When palpating bones, crepitus (when a fracture is present), abnormal shape, and pain response are evaluated.* Some joints require specific tests. For example, the Ortolani sign of the hip joint can be evaluated in immature dogs and is a reflection of the degree of subluxation of the joint. Other hip-specific signs include the Barlow sign and Bardens sign (described below) and the palpation of the triangle formed by the tuber sacrale, tuber ischiaticum, and greater

trochanter. The shape of that triangle changes when dogs have a hip luxation. In the stifle, the cranial drawer sign is the craniocaudal translational instability present after rupture of the cranial cruciate ligament. By the end of the orthopedic palpation, the clinician should know which limb or limbs is/are affected and which changes are present in affected joints.

Decision Making for Management of Orthopedic Disorders

Orthopedic disorders may be managed conservatively (i.e., non-surgically) or may be managed by use of surgery. Surgery is the unequivocal choice when stabilizing fractures, particularly fractures involving articular surfaces and growth plates. Few fractures are managed conservatively: some pelvic fractures with minor displacement or pelvic canal collapse, some long bone fractures with minor displacement, and other fractures.[84,170,171] Because so few publications concentrate on conservative fracture management, the outcome of fractures managed conservatively is generally not known scientifically speaking, and appears to be poor based on clinical experience and a few publications. When managing orthopedic disorders, the benefits of surgery are often less obvious.[138,172] Many orthopedic disorders are managed conservatively, including hip dysplasia, elbow dysplasia, limb deformities, patellar luxation, and cranial cruciate injuries.[173-175]

Surgical Management of Orthopedic Disorders

While the technical description of the surgical management of orthopedic disorders is beyond the scope of this chapter, the principles of surgical management are relevant and are described here. Several surgical procedures are performed with the intent to **alter bone growth.** The juvenile pubic symphysiodesis is a surgical procedure where the parasagittal pubic growth plates are heated (or mechanically removed) at a young age to decrease the longitudinal growth of the pubis. The decrease in pubic length leads to a more horizontal position of the acetabulum and an increase in tolerance of hip subluxation.[176,177] The juvenile pubic symphysiodesis is generally performed at 16 weeks of age, after hip laxity has been measured. Hip laxity can be measured objectively using the PennHIP method.[178] In dogs with premature closure of the distal ulnar physis, segmental ulnar ostectomies can be used to avoid the interference of the ulna with radial growth.[179] Bone growth of the proximal aspect of the tibia can be altered with the intent to decrease the slope of the tibial plateau. This surgery has been proposed in young dogs with cranial cruciate ligament injuries.[180] Surgical procedures are also performed to **change the shape of bones**—for example, to manage limb deformities. Deformity correction can be done with an acute, intraoperative correction or with a progressive correction that relies on bone formation within a distraction gap, a process named distraction osteogenesis.[181]

Surgical procedures are performed to **change the relative positions of bones within joints** to improve joint health. Segmental ulnar ostectomies are also performed with the intent to improve load distributions within the elbow joint.[182] Surgical procedures are performed to **increase the stability of joints** and positively impact joint mechanics. Increasing joint stability may be done by arthrodesis, the fusion of joints across an articulation. Arthrodeses of distal joints (particularly intercarpal, carpometacarpal, intertarsal, and tarsometatarsal) are performed more routinely and yield a better functional outcome than arthrodeses of proximal joints.

Non-Surgical Management of Orthopedic Disorders

Many orthopedic disorders are managed without surgery. Also, many orthopedic disorders managed surgically require non-surgical management beyond surgery. The non-surgical management of orthopedic disorders includes orthopedic screening, optimization of musculoskeletal development, pain relief, weight management, and optimization of activity and exercise. Non-surgical management may include more specific goals including strengthening (in weak patients), stretching (in patients lacking joint motion), or ambulation assistance (in patients with impaired mobility). These specific goals are often part of a physical rehabilitation (i.e., physical therapy, physiotherapy) program. While a physical rehabilitation environment is not necessary to manage orthopedic problems (and is generally not available), the fact that there is so much overlap between physical rehabilitation and the long-term management of orthopedic problems makes rehabilitation a very logical environment to develop, implement, and oversee the management of orthopedic disorders (see ch. 355). Braces, also known as orthoses, can also be used to manage specific skeletal disorders (Figure 353-13). Bracing is a growing field that potentially can be part of the management of several orthopedic disorders. The successful use of braces relies on a specific orthopedic assessment, brace design, fabrication, fitting, and

adjustments, and patient and owner training. Bracing is described elsewhere.[183]

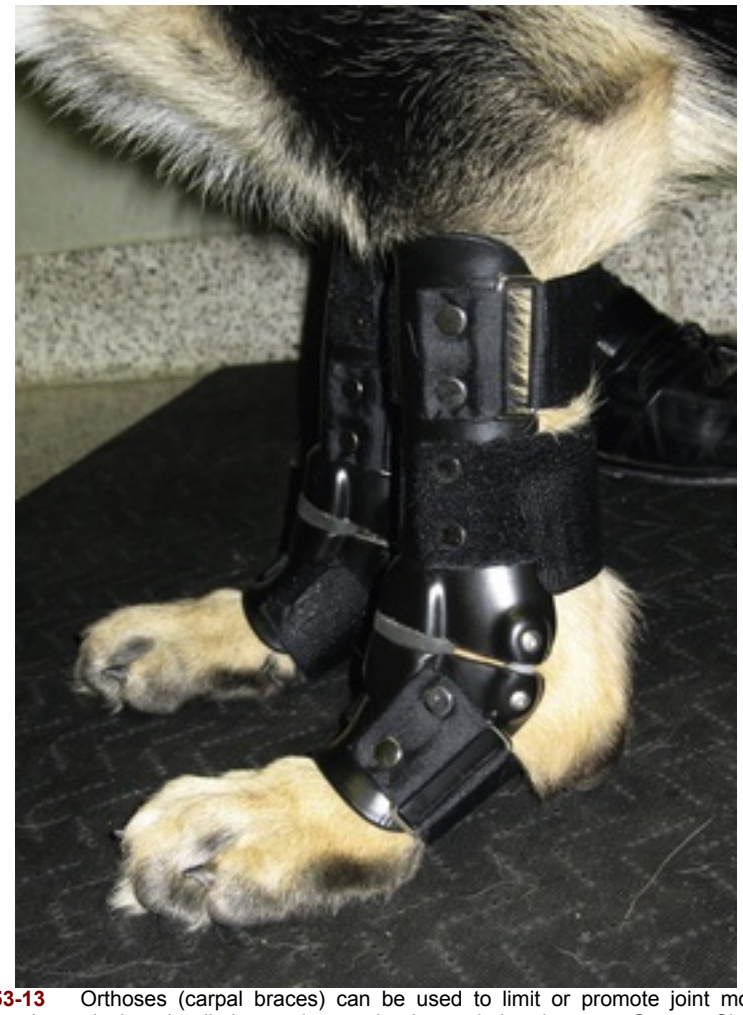

FIGURE 353-13 Orthoses (carpal braces) can be used to limit or promote joint motion. These orthoses have been designed to limit carpal extension in a palmigrade young German Shepherd Dog. The orthoses are hinged to allow carpal flexion. The thickness of the soft rubber on the cranial aspect of the carpus can be modified to control the endpoint of carpal extension.

Early Screening

Because many dogs with orthopedic disorders show mild signs that are often undetected by owners or are accounted for as clumsiness or having an "odd" or "funny" gait or posture, orthopedic screening must be initiated by the clinicians rather than by the owner. Orthopedic screening can be done at any point in life but is particularly relevant in the first few months of life, when developmental orthopedic diseases develop and before damage to joints or changes in posture occur. The hip joint, for example, can be evaluated by use of the PennHIP or Orthopedic Foundation for Animals methods after 4 months of age. Screening starts by asking owners specific questions related to the animal's posture, gait, and ability to perform activities of daily living. Screening should include an observation of the pup's resting position, transitioning between body positions (e.g., getting up, squatting down), walking, and trotting. Screening should also include an orthopedic examination. This examination is performed without sedation in most instances. Palpation of skeletally immature patients requires patience and a gentle demeanor. Even though puppies have limited training and a short attention span, a clinician should be able to detect a repeatable pain response to the palpation of major joints, particularly flexion and extension of the elbow joints, stifle joint extension, and hip extension.

Because of the high prevalence of hip dysplasia in many breeds, particularly in large breeds with thick subcutaneous tissue and relatively modest muscle development (St. Bernards, Bernese Mountain Dogs, Mastiffs, Welsh Corgis), hip screening is commonly performed. Hip subluxation is the early manifestation of

hip dysplasia and hip joints should be screened for the presence of hip subluxation at a young age. Hip subluxation may be detected at approximately 4 months of age—16 weeks of age using palpation. Palpation may be performed awake or under sedation. On palpation, generally performed with the patient in lateral recumbency with the hip joint held in a position similar to a standing position, a flat hand may be placed on the proximal and medial aspect of the thigh and with abaxial pressure (elevation of the thigh in relation to the pelvis), abaxial translation of the femur in relation to the pelvis is palpated by feeling the relative position of the greater trochanter and the ischial tuberosity (Figure 353-14 and Video 353-2). This translation is named the *Bardens* sign. Palpation of the reduction of a previously subluxated femoral head into the acetabulum as a result of abduction of the femur can be performed (Figure 353-15 and Video 353-3). This palpation is most conveniently done with the dog held in dorsal recumbency by holding the hip joints in a position matching a standing position with the stifle joint flexed and slowly abducting the stifle joint. Each vertically held femur corresponds to an angle of 0 degrees. Positive angles correspond to abduction and negative angles correspond to adduction past midline. The Ortolani maneuver can also be performed with the dog in lateral recumbency, but, subjectively, the pelvis is more mobile and it is harder to control the orientation of the pelvis when measuring reduction and subluxation angles. If the hip joint is initially subluxated, a clunking sound, named *Ortolani* sign, can be felt or heard as the femoral head relocates into the acetabulum. The angle at which the Ortolani sign occurs is a reflection of potential wear of the dorsal acetabular rim: Larger angles correspond to more severe wear. The *feel* of the Ortolani also matters; a smooth and crisp Ortolani sign suggests that the dorsal acetabular rim is normal or near normal but a subtle Ortolani sign or an Ortolani sign with crepitus indicates significant loss of articular cartilage and damage to the dorsal acetabular rim and femoral head. When the femur is slowly adducted toward a standing position, a discreet translation is felt as the femoral head subluxates again. This subluxation is named *Barlow* sign. As for reduction angles, higher subluxation angles indicate more severe dorsal rim damage. The difference between the angles of reduction and subluxation often ranges between 20 and 40 degrees. Dogs with hip laxity without dorsal rim damage often have angles of reduction of 10 to 20 degrees and angles of subluxation approximately −10 to −20 degrees. Dogs with severe dorsal rim damage often have angles of reduction around 45 degrees and angles of subluxation around 20 degrees. Subjectively, it appears that higher reduction and subluxation angles result from dorsal rim wear rather than pure joint laxity. Dogs with small reduction angles and negative subluxation angles may be able to maintain their hip joint reduced or intermittently reduce their hip joint during locomotion by slightly abducting their femur, just like dogs with patellar luxation may relocate their patella by extending their stifle joint. This may be observed at a walk or trot. With time, most dogs with hip subluxation will develop dorsal rim wear and the positive Ortolani sign will disappear because of permanent dorsal hip subluxation. The frequency and age at which the Ortolani signs disappear in dysplastic dogs has not been scientifically assessed, to our knowledge. Clinically, most Ortolani signs disappear by 18 months of age. Most dogs with positive Ortolani signs will develop hip dysplasia during the first few years of their adult life.

FIGURE 353-14 Hip laxity is palpated by placing a hand medial to the thigh with fingers running along the shaft of the femur, stabilizing the femur with the thumb, and lateralizing the femur in relation to the pelvis while the other thumb detects the translation of the greater trochanter relative to the tuber ischiadicum. This maneuver is named the *Bardens* sign. The Bardens maneuver induces discomfort so it is performed under sedation.

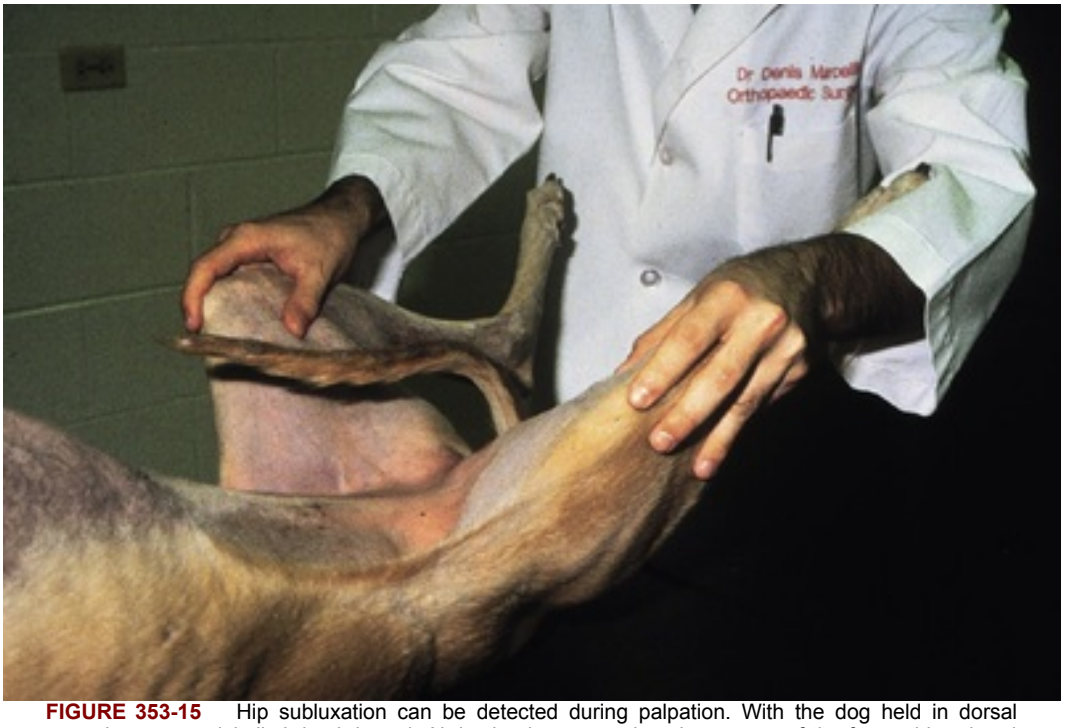

FIGURE 353-15 Hip subluxation can be detected during palpation. With the dog held in dorsal recumbency, a pelvic limb is abducted. Abduction increases dorsal coverage of the femoral head and can lead to the reduction of a subluxated joint. Hip reduction resulting from abduction is referred to as the *Ortolani* sign. The angle of reduction can be measured.

The radiographic assessment of joints in young dogs is often unrewarding, particularly if one solely bases the diagnosis of a developmental joint disease on the presence of osteophytes, because it may take weeks, months, or years to have detectable osteophytes in a joint with a developmental orthopedic disease. Specialized radiographic views are used for the early detection of joint disease. They include the well-established PennHIP method for the screening of hip subluxation. PennHIP evaluations are performed under sedation. While multiple radiographic assessment methods exist, the PennHIP method is the most accurate method used to assess the presence of hip laxity. A PennHIP evaluation includes a distraction view that quantifies the degree of abaxial displacement of the femoral head in relation to the acetabulum during a maneuver resembling the Barden's sign. Reliable hip distraction is achieved using foam-covered adjustable acrylic tubes. The distraction index (DI) is the distance separating the centers of the acetabulum and femoral head during distraction divided by the radius of the femoral head. Dogs with low DI (<0.30) are very unlikely to develop hip dysplasia. Dogs with higher DI (>0.70) are very likely to develop hip dysplasia. Some dog breeds are more laxity tolerant than other breeds. For example, in a study involving 3,729 German Shepherd Dogs and 6,278 Labrador Retrievers older than 24 months, the likelihood of having hip osteoarthritis (OA) in dogs with a distraction index of 0.6 was approximately 58% for German Shepherds compared to approximately 16% for Labrador Retrievers. This shows that joint laxity is not the sole factor leading to the development of hip arthritis, and suggests that differences in anatomy and joint mechanics play an important role in the development of hip dysplasia.[184] In a report assessing 459 clinically normal dogs, palpation was at best moderately correlated with radiographic measures of joint laxity, indicating the need to combine palpation with stress radiography when screening dogs for hip laxity.[185] An oblique view named the distomedial-proximolateral oblique view has been shown to enhance the detection of fragmented medial coronoid process in the elbow joint of dogs.[56]

Optimization of Musculoskeletal Development

The optimization of musculoskeletal development is a critical aspect of the management of orthopedic disorders because many disorders impact patients during growth and because the expression of faulty genes is increased when growth is accelerated. In dogs, growth acceleration results from excessive energy intake (eating too much carbohydrates) or calcium supplementation (see ch. 189).

Dogs that eat as much as they want grow very rapidly. A modest food intake restriction of 25% compared to unlimited *(ad libitum)* feeding dramatically slows growth. For example in growing male Great Danes, a 25% restriction leads to a mean weight of 26 kg at 6 months of age compared to a mean weight of 52 kg for dogs fed *ad libitum*.[22] Dogs with restricted food intake reach the same adult size as dogs fed *ad libitum* but have fewer orthopedic problems. Owners should be instructed to restrict the food intake of growing dogs, particularly large-breed dogs and dogs from breeds predisposed to developmental orthopedic diseases. The protein content of the diet does not influence growth rate and therefore growing dogs should eat a diet with appropriately high protein content. Growing dogs should not receive calcium supplementation, beyond the calcium included in their balanced diet.

Pain Management

Pain is often the key consequence of orthopedic disorders and therefore minimizing pain is the major aspect of the conservative management of orthopedic disorders. Minimizing pain is achieved by optimizing the living conditions of patients, tailoring their activities, encouraging weight loss (see ch. 176), giving pain medications (see ch. 126, 164, and 166), and food supplementation.

While little is known about the impact of living conditions on the clinical signs of orthopedic disorders in dogs, it seems logical to adapt living conditions of dogs to minimize the challenges associated with living in a home and exercising regularly. Changes in temperature (cold wave), humidity, and barometric pressure (decrease in pressure) have been reported to influence the pain perceived from arthritic joints in humans. To minimize the potential impact of weather conditions on arthritic dogs, it may be beneficial to make sure that they are housed in a weather-controlled environment. Minimizing slipping and falling may benefit them as well, and may be achieved by improving the traction of walking surfaces and by avoiding activities requiring sudden changes in direction or speed.

In humans, the signs of joint disease (e.g., osteoarthritis) fluctuate over time. There are periods of relative comfort and periods of sudden exacerbation of signs named flare-ups or flares. With time, flares become more frequent, more severe, last longer, and are more difficult to control. Similarly, in dogs with joint disease, flares

can result from excessive activity in unfit dogs (weekend warrior syndrome) or from events that place excessive stress on abnormal joints, like jumping or stepping in a hole. Flares may last a few hours or may last several weeks. Determining whether or not an abnormal joint has flared is an important part of the initial assessment because treatment methods and management goals differ. Flares are likely in dogs whose clinical signs are significantly more severe than they were in preceding weeks. Patients with joint disease are often in the middle of a flare at the time of first evaluation because owners seek veterinary care due to the sudden increase in clinical signs. A sudden loss of performance (inability to climb steps or climb into a motor vehicle, exercise intolerance) generally results from a flare, can result from a chronic, progressive loss of strength and fitness secondary to OA combined with aging, or can result from a change in the status of an arthritic joint (a subluxated hip joint becomes luxated). Irreversible decisions such as surgery or euthanasia should not be made during flares because patients may appear overly affected and can have a dramatic loss of mobility or independence that will subside when the flare subsides. Instead, focus should be on comprehensive pain management and on rest. Between flares, owners should avoid strenuous activities that trigger flares and lead to an increase in clinical signs. Strenuous activities that can trigger flares include jumping up, chasing, retrieving, and playing with other dogs. Unfortunately, owners often select these activities because dogs love them, because they are easy to perform, and because they require minimal owner participation.

In dogs with severe orthopedic disorders, ambulation assistance may be provided by a step-in sling or harness. Neoprene harnesses with hook-and-loop fasteners are popular because they are ergonomic, relatively soft, durable, and washable. For large, heavy, or independent dogs with locomotion difficulties, an ambulation cart may provide effective ambulation assistance. In most instances, when pain and weakness are limited to the pelvic region, a 2-wheel cart is used. When dogs have problems involving all four limbs, a 4-wheel (quad) cart may be considered. The cart supports the pelvic region during outdoor activity. Carts are much more convenient for small dogs than large dogs. Some dogs learn to negotiate doorframes and may use their cart indoors, while others cannot. Subjectively, neoprene slings may work better than a rigid platform (foam-covered metal rings) for carts in patients with orthopedic disorders, because they have normal motor function during activity, compared to paralyzed dogs, that may function better when using carts with rigid platforms.

Without appropriate pain relief, maintaining joint mobility or regaining lost strength is rarely achievable. Pain relief is achieved by interfering with the peripheral (tissue inflammation and damage) and central (neuropathic; involving the central nervous system) aspects of pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the cornerstone of pharmacologic management of peripheral musculoskeletal pain (see ch. 126, 164, and 166).[186] NSAID administration in dogs with joint disease may lead to dramatic improvement in limb use and overall function. Several scientific reports, often used as supporting studies for drug approval, have shown that NSAID administration has led to an increase in the peak vertical force and vertical impulse placed on the pelvic limbs of arthritic dogs.[186] There are no peer-reviewed studies that compared commercially available NSAIDs using blinded, prospective, randomized, crossover designs. Also, the relative occurrence and seriousness of side effects after administration of various NSAIDs in dogs has not been scientifically evaluated. All NSAIDs have infrequent but potentially serious side effects (see ch. 169) and should be used cautiously in dogs, particularly in patients with compromised liver or renal function, hypovolemic patients, and in patients with gastrointestinal disease. This is particularly relevant since many arthritic dogs show an increase in clinical signs later in life when liver, renal, and gastrointestinal problems are more likely to be present. Periodic enzymatic and liver function screening is recommended in dogs receiving NSAIDs. While there is no consensus on the frequency of these screenings, it seems reasonable to perform them before the administration of NSAIDs, after a few weeks of NSAID administration, and if clinical signs arise. The risk of side effects of NSAIDs does not appear to increase when NSAIDs are administered over longer periods of time.[187]

As in all forms of chronic pain, peripheral sensitization and spinal cord wind-up occur with chronic hip dysplasia (see ch. 356). Multimodal drug and non-drug therapy has been recommended to manage this chronic pain. This includes the off-label use of pain medications that are adjunctive or alternative to NSAIDs. Adjunctive drugs may be considered for NSAID-intolerant dogs or for dogs whose clinical signs are only partially improved during NSAID therapy. The scientific information supporting these alternative medications is scant but clinical research in that area is active. Tramadol, a synthetic morphine analogue is seemingly the most commonly used adjunctive drug for chronic hip pain. Other emerging drugs used in the multimodal drug management of OA include the gamma-aminobutyric acid analogue drug gabapentin and the antiviral drug amantadine.[188] Subjectively, dogs with severe arthritic flares may benefit from continuous rate intravenous infusion of a combination of an alpha-2 adrenergic agonist (medetomidine), a sodium

channel blocker (lidocaine), and an N-methyl D-aspartate receptor antagonist (ketamine). Twice-weekly injection of polysulfated glycosaminoglycans between 6 weeks and 8 months of age led to less subluxation and indicated a trend toward less cartilage damage for pups predisposed to the development of hip dysplasia in one prospective study.[189]

Nutritional supplementation has long been used to potentially decrease arthritic pain in humans, most often through the use of compounded herbs and vegetables, such as in traditional Chinese medicine and Indian Ayurvedic medicine. More than 30 herbs or compounds have shown some level of pain relief in prospective randomized trials involving humans with OA. In Western medicine, the attention has mainly focused on the use of glucosamine, chondroitin sulphate, and polyunsaturated (omega-3) fatty acids for the management of arthritic joint pain with several well-structured studies documenting their benefits. By comparison, little is known about the benefits of nutritional supplements in arthritic dogs. However, several clinical trials documented the benefits of a diet containing glucosamine, chondroitin, and eicosapentaenoic acid (EPA), an omega-3 fatty acid, on the clinical signs of hip dysplasia in dogs. Several reports have documented the anti-inflammatory or anti-catabolic effects of omega-3 fatty acids, glucosamine, or chondroitin on human and canine chondrocytes *in vitro*. Increasing the nutritional intake of EPA has been shown to decrease osteoarthritic pain, probably by decreasing arachidonic acid concentrations and increasing EPA concentrations in the cell membranes of canine chondrocytes. Green-lipped mussel supplements also appear to alleviate the clinical signs of osteoarthritis in dogs.[190] Our current body of knowledge suggests that the most reasonable drug administration and nutritional plans for arthritic dogs would be to keep them free of clinical signs by using NSAIDs, omega-3 fatty acids, glucosamine, and chondroitin sulphate, and by potentially adding adjunctive drugs, if deemed necessary based on the clinical signs or as an alternative to NSAIDs if clinical signs of intolerance are present.

There are numerous nonpharmacologic anti-inflammatory options for peripheral pain management, including cold therapy, also known as cryotherapy or icing, and massage. Icing provides direct pain relief by decreasing nerve conduction velocity. It also provides secondary pain relief by decreasing edema (itself a source of pain) and decreasing the overactivity of catabolic enzymes in osteoarthritic cartilage for a few hours after application. Icing is a consideration for osteoarthritic pets with flares. Icing may also help after a period of exercise or before bedtime. Ice cubes or frozen vegetables are not recommended because they have air pockets that decrease cold conduction. Ice bags filled with ice chips or crushed ice or cold packs provide more effective cold delivery. Most cold packs reach therapeutic temperatures after 2 hours in a freezer. For longhaired patients, one approach is to place and hold an ice bag or cold pack directly on the pet's arthritic joint or joints and secure it with a self-adhesive band. A pillowcase may be used between the cold pack or bag and the skin in patients with short or no hair. Some cold packs have a built-in self-adhesive band. A neoprene sleeve may also be used to secure a cold pack or bag. Icing may last for 10 to 15 minutes. Most patients tolerate the treatment. The person applying the ice should make sure the patient is not uncomfortable and that the skin surface feels cold to the touch after icing is complete. The short- and long-term effects of massage in companion animals are not known. Massage may decrease myofascial pain and muscle tension. Nonpharmacologic options for central pain management include low-level heating, massage, and possibly acupuncture, acupressure, and electro-acupuncture. These methods primarily stimulate A-beta sensory fibers with conduction velocities that are more rapid (30 to 70 m/sec) than A-delta (12 to 30 m/sec) and C fibers (0.5 to 3 m/sec). Heat is widely considered to positively impact painful osteoarthritis patients. The use of heat is two-fold. Low-level heat (elevation of tissue temperature by 1° to 2°C) relieves pain through the stimulation of non-nociceptive A-beta sensory fibers, as well as the vasodilation and normalization of blood flow. Tissue relaxation may be achieved by keeping osteoarthritic patients in relatively dry and warm temperatures throughout the day (sleeping in heated indoor environments or providing heated beds). More intense heat (elevation of tissue temperature by 3° to 4°C) is used to increase the effectiveness of stretching while minimizing tissue damage. Intense heating is most often applied by a healthcare professional using a hot pack that is heated by a hydrocollator or microwave oven. Four layers of dry towels are generally placed between a hot pack and the skin, and heat is generally applied for 15 to 20 minutes. Caution must be used when placing a hot pack on a dog because burns can occur. Initially, the packs may not appear excessively hot to the touch, but they can induce thermal damage after several minutes of contact. It is therefore important to check for excessive redness, skin swelling, or blistering every few minutes during intense-heat therapy.

Maintaining Fitness and Limb Strength

The lifelong benefits of having a lighter body weight on osteoarthritis and longevity have been clearly documented in a Labrador Retriever lifelong study.[50] In that study, compared to their overweight

counterparts, the lighter dogs lived 1.8 years longer. For both groups, however, lack of mobility late in life due to OA was the dominant cause of euthanasia.[191] This study proved that OA progressed more slowly and was more easily controlled in lighter dogs. Adult patients with musculoskeletal disorders routinely carry excessive body weight. Excess weight has a clear negative impact and loss of excess weight has a clear positive impact on patients with skeletal disorders.[192,193] In one study, a subjective decrease in lameness detected using a numerical rating scale was observed once weight loss was larger than 6.1% and an objective decrease in lameness detected by use of a force plate was observed once weight loss was larger than 8.5%.[194] Weekly weight loss rates of 1 to 2% body weight are recommended for overweight dogs. This loss may be achieved by feeding an amount approximately equivalent to 60% of the calories needed to maintain body weight. Weight loss in dogs with osteoarthritis does not appear to be associated with an increase in spontaneous activity.[195]

Muscle strength has been shown to decrease in humans with OA and that loss of strength is both quantitative (due to a loss of muscle mass) and qualitative (due to a loss of muscle performance) potentially as a result of limb disuse and the reflex inhibition of the contraction of muscles adjacent to arthritic joints. Loss of muscle mass is commonly observed in dogs with chronic skeletal disorders. However, the extent of loss of strength has not been assessed in dogs with various chronic skeletal disorders and little research has focused on specific strategies to protect against loss of strength or to regain strength. With few exceptions, the maintenance of muscle strength is achieved through active exercises. These exceptions include neuromuscular electrical stimulation and active range of motion therapy. Neuromuscular electrical stimulation may be considered in arthritic dogs with severe loss of muscle strength where successful exercise is not possible because of severe pain or limb disuse. As a general rule, it is simplest and most effective to use therapeutic exercises than other strategies to strengthen patients (Table 353-1).

TABLE 353-1

Therapeutic Exercises Potentially Included in the Management of Canine Hip Dysplasia

PURPOSE	THERAPEUTIC EXERCISES
Increasing limb strength	Daily walk or trot longer than 10 minutes; tunnel-walk repetitions; sit-to-stand and stand-to-sit repetitions
Increasing core strength	Daily walk or trot longer than 10 minutes; swimming
Increasing cardiovascular fitness	Daily walk or trot longer than 10 minutes
Stretching pelvic limbs	Climbing up slopes, hills, and stairs; low jumps
Increasing proprioception	Daily walk or trot longer than 10 minutes; walk on soft surfaces: sand, mulch, gravel, leaves, grass; teeter-totter; pole weaving

Cardiovascular fitness and muscle endurance have been poorly described in dogs. Because chronic skeletal disorders are likely to negatively impact mobility, muscle endurance, and cardiovascular fitness, it is logical to promote regular aerobic physical activities in dogs with skeletal disorders (see ch. 359).

Increasing muscle endurance requires repeated movements over a period of several minutes. Such endurance building is unlikely to be achieved through self-driven activities in areas with limited space, such as a dog being left unattended in an average fenced-in backyard. Instead, dogs should be exercised with purpose on a regular basis. In humans, skeletal disorders and aging contribute to a loss of proprioception. Little is known about the negative impact of naturally occurring osteoarthritis on proprioception in dogs. However, there is clear evidence that osteoarthritis progresses rapidly in patients with joint injuries that have sensory deficits. In older humans with decreased proprioception, balance exercises readily improve proprioception. In dogs with osteoarthritis, a portion of exercise programs should focus on exercises that train proprioception, such as exercises requiring rapid and unpredictable side-to-side weight shifts and, to a lesser extent, front-to-back and back-to-front weight shifts. These exercises include walking on soft or irregular surfaces and gentle agility exercises, including pole weaving and walking on a teeter-totter, dog walk, or over low rails (see ch. 355).

Little is known about the impact of hip arthritis on joint motion. As mentioned above, dysplastic hip joints seemingly lose extension but not flexion. A loss of hip extension of 30 degrees or more likely leads to the dog's inability to gallop, trot, jump up, or climb steps or stairs. It appears beneficial, therefore, to assess joint

motion in dogs with chronic hip dysplasia. Since it is much easier to maintain joint motion than to regain it once lost, it seems reasonable to recommend intermittent physical activities that increase hip joint extension without creating significant clinical signs. These activities may include walking uphill or dancing backward. If regaining joint motion is deemed important, a stretching program may be implemented. Stretching is more effective when tissues are heated immediately prior to and during the stretching session. Empirically and based on techniques used in humans, performing ten to fifteen 20- to 40-second-long sustained stretches during each session can be considered. Sessions may be performed two or three times per day. With chronic loss of motion, a gain of 3 to 5 degrees of joint motion per week is anticipated as a result of a sustained stretching regimen.

Dogs with skeletal disorders with minor locomotion problems have a management program focused on decreasing pain, maintaining limb and core strength, stretching affected joints, and stimulating proprioception. Pain management is generally achieved with simple pharmacologic steps, rest, and exercise. Pharmacologic and other forms of pain relief may be intermittent as long as dogs adhere to a long-term exercise program. For dogs with skeletal disorders with major locomotion problems, it is critically important to implement several support strategies to decrease the impact of the disease on the dogs' well-being and mobility. These strategies can include rest, multimodal pharmacologic management, ice, heat, massage, acupuncture, acupressure, electroacupuncture, or transcutaneous electrical nerve stimulation. Once pain is managed, it is important to initiate a progressive exercise program. Patients with severe osteoarthritis may need temporary or permanent ambulation assistance. Slings are the most common and cost-effective ambulation assistance devices. Severely impaired dogs may benefit from an ambulation cart. Overall, a management program for companion animals with osteoarthritis should be simple and logical: Managing pain is the first priority. The program must then address the most critical aspects of each patient's unique situation and, over time, improve the patient's mobility, strength, proprioception and, above all, quality of life.

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CHAPTER 354

Muscular Disorders

G. Diane Shelton

Clinical Overview

Muscle diseases (myopathies) can be diagnostic challenges, as there are many different diseases (Figure 354-1) that share relatively few clinical signs. Recognition of the myopathic phenotype is the important first step (see ch. 2, 31-35 and 259). Clinical signs of muscle disease include variable degrees of muscle weakness, stiffness, myalgia, and muscle atrophy or hypertrophy. Clinical signs can involve just the limb muscles or affect special muscle groups, such as the laryngeal muscles, pharyngeal muscles, masticatory muscles, tongue, and heart. The breed, age of onset, and clinical progression should aid in the differential diagnosis.

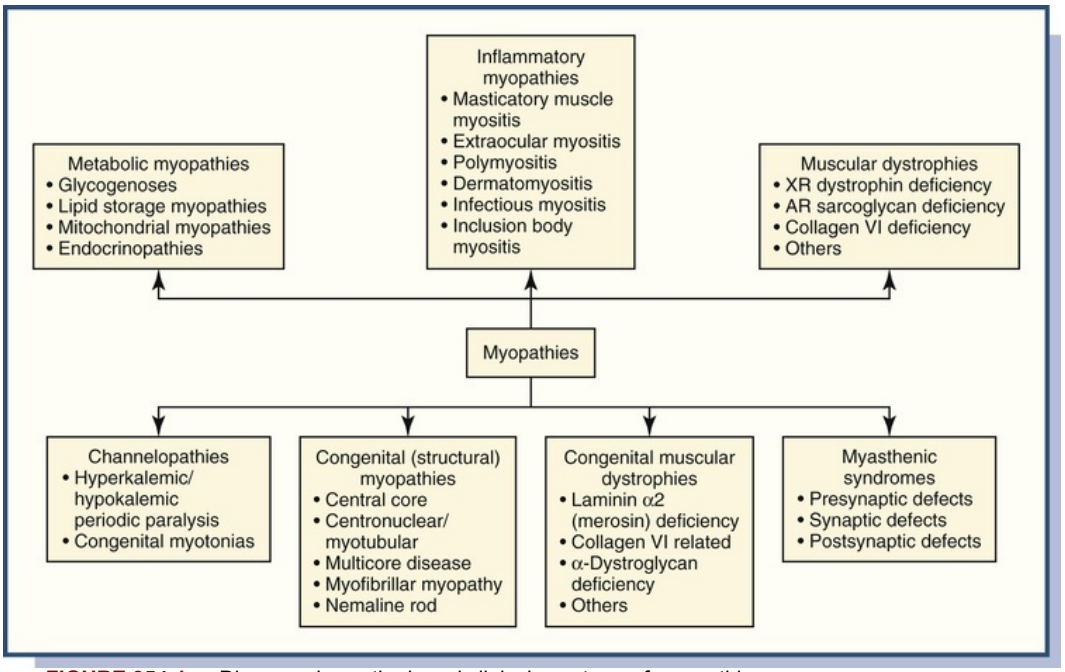


FIGURE 354-1 Diagram shows the broad clinical spectrum of myopathies.

Routine laboratory screening including a complete blood count, serum biochemical profile, and urinalysis can identify some of the most common systemic abnormalities that cause muscle weakness and myalgia (see ch. 12 and 21).[1] Serum creatine kinase (CK) activity (see ch. 66) and thyroid evaluation (see ch. 299) should be included in every neuromuscular minimum database. Even if only mildly elevated, a persistently elevated CK activity would be an indication for further investigation of a muscle disease. At the time of initial diagnosis of hypothyroidism in people, up to 80% report problems attributable to skeletal muscle dysfunction, and nearly 40% have clinical evidence of muscle weakness.[2] Similarly, muscle stiffness and myalgia may be an early indicator of hypothyroidism in dogs without obvious classical clinical signs. Identification of hypothyroid myopathy can prevent unnecessary diagnostic expenses if confirmed by routine diagnostic testing.

Since autoimmune myasthenia gravis (see ch. 269) can mimic any neuromuscular disease, testing for acetylcholine receptor (AChR) antibodies should be included in the minimum database for dogs or cats with acquired clinical signs of weakness, and in particular, in dogs with acquired megaesophagus. The AChR

antibody test remains the gold standard for the diagnosis of acquired myasthenia gravis and confirms an autoimmune response against nicotinic AChRs.[1,3]

The single most important test for the diagnosis of a muscle disease is the muscle biopsy (see ch. 116). This procedure is minimally invasive and does not require extensive surgical training. Muscle biopsies should be evaluated in frozen sections by a laboratory with expertise in the examination of muscle. Unless the myopathy is inflammatory or neoplastic in nature, a formalin-fixed biopsy evaluated in paraffin sections will be of limited diagnostic value and many myopathies will be missed. Fixed muscle specimens are of value for ultrastructural examination of congenital myopathies following a presumptive diagnosis in frozen biopsy sections. An accurate diagnosis is critical given the emergence of genetic testing for inherited muscle diseases and development of new DNA-based tests.

The field of muscle disease is a rapidly expanding one in both human and veterinary medicine.[4] This topic cannot be covered entirely in the limited space devoted to this chapter. Thus, the most common clinical disorders will be covered with references cited to those myopathies less frequently encountered.

Inflammatory Myopathies

Masticatory Muscle Myositis

Masticatory muscle myositis (MMM) is a relatively common, focal, autoimmune muscle disease, primarily affecting dogs[5] and rarely cats. All breeds can be affected and at any age. A particularly severe form of MMM occurs in puppies at 2-3 months of age, notably in Cavalier King Charles Spaniels.[6] Clinical signs are restricted to the muscles of mastication and can vary from an acute onset of swelling of the masticatory muscles with restricted jaw mobility and jaw pain, to slowly progressive atrophy of the masticatory muscles with or without jaw pain or restricted jaw mobility. A retrobulbar abscess and disorders of the temporomandibular joint should be ruled out (see ch. 272). The serum assay for detection of autoantibodies against masticatory muscle type 2M fibers is useful for the diagnosis of MMM.[5,7-9] For most accurate results, serum should be collected prior to administration of corticosteroids. A temporalis muscle biopsy also is useful for the diagnosis of MMM and for prognosis (see ch. 116). It is important to not biopsy the frontalis muscle that overlies the temporalis muscle, as this biopsy will produce a false-negative result.[5]

Response to therapy should be good if MMM is treated early and appropriately.[5] Immunosuppressive dosages of corticosteroids should be used until jaw mobility returns to normal and jaw pain is no longer evident. The dosage should be gradually decreased until the lowest alternate day dosage is reached that will keep the dog free of clinical signs. Low-dosage therapy should be continued for 6-8 months with monitoring of jaw mobility. Relapses are common if treatment is stopped too soon. For end-stage or severe MMM, response to therapy may only be partial. A muscle biopsy is particularly useful in these cases.

Extraocular Muscle Myositis

Extraocular muscle myositis (EOM) is a focal inflammatory myopathy that selectively affects the extraocular muscles while sparing the masticatory and limb muscles. The clinical presentation is exophthalmos in the acute stage while enopthalmos and restrictive strabismus may occur in the chronic stage.[10,11] The serum CK activity usually is normal. The serum 2M antibody titer is negative. The diagnosis of EOM is best made by orbital ultrasound or imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI). Response to corticosteroid therapy is usually good in the acute stage and treatment is similar to that of MMM (see above).

Immune-Mediated Polymyositis

Immune-mediated polymyositis (PM) is a generalized inflammatory myopathy in which multiple skeletal muscle groups are invaded by nonsuppurative mixed mononuclear cell infiltrations.[12,13] The clinical presentation can vary depending on which muscle groups are affected, and can include generalized weakness (see ch. 21) with a stiff and stilted gait, megaesophagus (see ch. 273), dysphagia (see ch. 38), myocarditis (see ch. 252 and 253), and glossitis.[14-18] While PM can occur in all breeds, genetic predispositions have been identified in Newfoundland[14] and Vizsla[19,20] dogs. PM also can occur as part of a polyarthritis/PM syndrome[21] or as a paraneoplastic disorder (see ch. 352).[22] PM is uncommon in cats and can be associated with thymoma, myasthenia gravis, lymphoma, or concurrent neuritis.[23]

The serum CK activity in PM can be variable, with mild to moderate increases (2000-20,000 U/L) depending on the severity of myofiber damage.[1] A normal or minimally elevated CK activity should not rule out a diagnosis of PM, nor should a markedly elevated CK activity confirm the diagnosis of PM. Markedly elevated CK activities (>20,000 U/L) usually are found in the necrotizing myopathies[24,25] and muscular dystrophies.[26-28] Evaluation of muscle biopsy specimens is the most direct way to distinguish among the inflammatory, necrotizing or dystrophic myopathies (Figure 354-2). Demonstration of antibodies against unidentified sarcolemmal proteins has been useful in the diagnosis of PM in Boxers and Newfoundland dogs.[29] Infectious causes of myositis (see below) should be ruled out before corticosteroid or other immunosuppressant therapy is initiated. Corticosteroid therapy as for MMM and EOM is commonly used. Expression of major histocompatibility complex (MHC) I and MHC II antigens has proven to be diagnostically useful in biopsies taken from areas remote from inflammation[30-32] (E-Figure 354-3). Treatment should be initiated early and appropriately to prevent irreversible muscle fiber loss, fibrosis, and contractures.

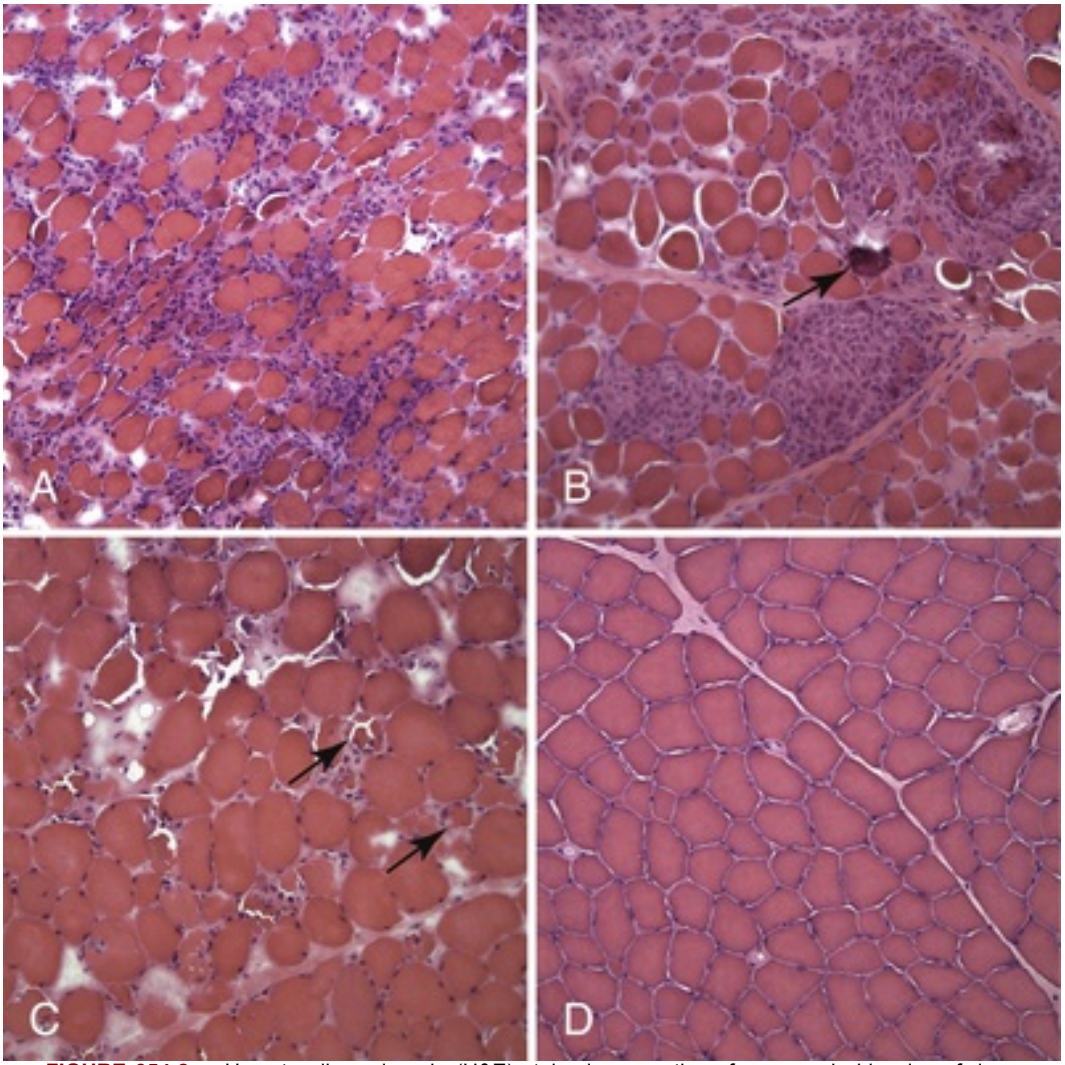
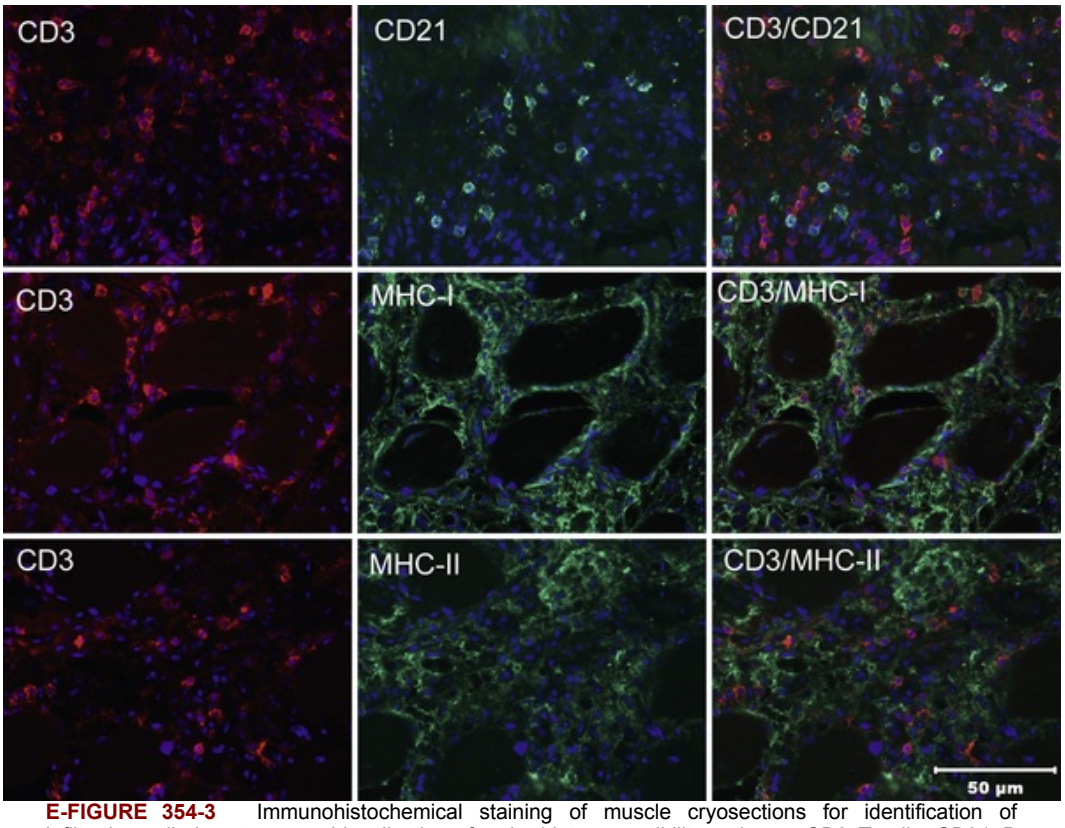


FIGURE 354-2 Hematoxylin and eosin (H&E) stained cryosections from muscle biopsies of dogs with inflammatory myopathy **(A),** muscular dystrophy (**B,** arrow points to calcific muscle fiber), necrotizing myopathy (**C,** arrows point to necrotic muscle fibers) and for comparison from normal dog muscle **(D).** Magnification ×20 for all images.



E-FIGURE 354-3 Immunohistochemical staining of muscle cryosections for identification of infiltrating cell phenotypes and localization of major histocompatibility antigens. *CD3,* T cells; *CD21,* B cells; *MHC-1,* major histocompatibility antigen type 1; *MHC-II,* major histocompatibility antigen type 2.

Dermatomyositis

Dermatomyositis (also see ch. 10) is an immune-mediated inflammatory disease of striated muscles, skin, and vasculature. In dogs, the skin lesions predominate, with less obvious myopathic features. A familial form of dermatomyositis has been described in Collies,[33] Shetland Sheepdogs[34] and occasionally in other breeds.[35] Treatment includes prednisone, pentoxifylline, and vitamin E.

Inclusion Body Myositis

Sporadic inclusion body myositis is the most common myopathy in people over the age of 50 years and it also occurs in older dogs.[36] The clinical presentation is of chronic and progressive muscle weakness and atrophy. The diagnosis is made by muscle biopsy, with demonstration of degenerative changes such as vacuoles and Congo–red-positive amyloid deposits, and inflammation. While no specific treatments are available, supplements including L-carnitine and antioxidants may be of some benefit.

Infectious Myositis

Protozoal myositis is caused by *Toxoplasma gondii, Neospora caninum, Hepatozoon canis, Babesia canis, Leishmania,* or *Trypanosoma* organisms (see ch. 221).[37] While thought to be an incidental finding in muscle biopsies, severe cases of myositis associated with *Sarcocystis* spp. infection recently were identified in 2 dogs.[38] Although myositis in general is rare in cats, feline immunodeficiency virus has been reported to cause a subclinical myopathy.[39]

Necrotizing Myopathy

Necrotizing myopathies are characterized histologically by necrosis and phagocytosis without lymphocytic infiltration.[24,25] A necrotizing myopathy should be considered in every case with an acute onset of markedly

elevated CK activity, rhabdomyolysis, and myoglobinuria, or in cases with episodic CK elevations and sporadic myoglobinuria. Etiologies include drug reactions and toxic exposure, bites from venomous insects, electrolyte disorders and infectious diseases. Unfortunately the cause of these disorders is rarely found.[25] Ventilatory support and intensive fluid therapy should result in recovery. Corticosteroid therapy might worsen clinical signs.[40,41] In recurrent cases, metabolic disorders of glycogen and lipid metabolism should be considered. A muscle biopsy is helpful to identify storage products and direct further diagnostics.

Congenital (Structural) Myopathies

Congenital myopathies are a group of genetic muscle disorders characterized clinically by weakness, hyporeflexia, and hypotonia, usually from birth.[42] The congenital myopathies are classified histopathologically on the basis of characteristic morphological features seen on muscle biopsy (Figure 354-4) and include rods (nemaline myopathy),[43,44] cores (central core disease and multiminicore disease),[45] central nuclei (centronuclear[46-49] and myotubular myopathy),[50-52] selective hypotrophy of type 1 fibers (congenital myofiber disproportion)[53] and myofibrillar myopathy.[54] The muscle biopsy (see ch. 116) and analysis of muscle histology, histochemistry, immunohistochemistry and ultrastructure by light and electron microscopy are necessary for reaching the diagnosis of a congenital myopathy.[42]

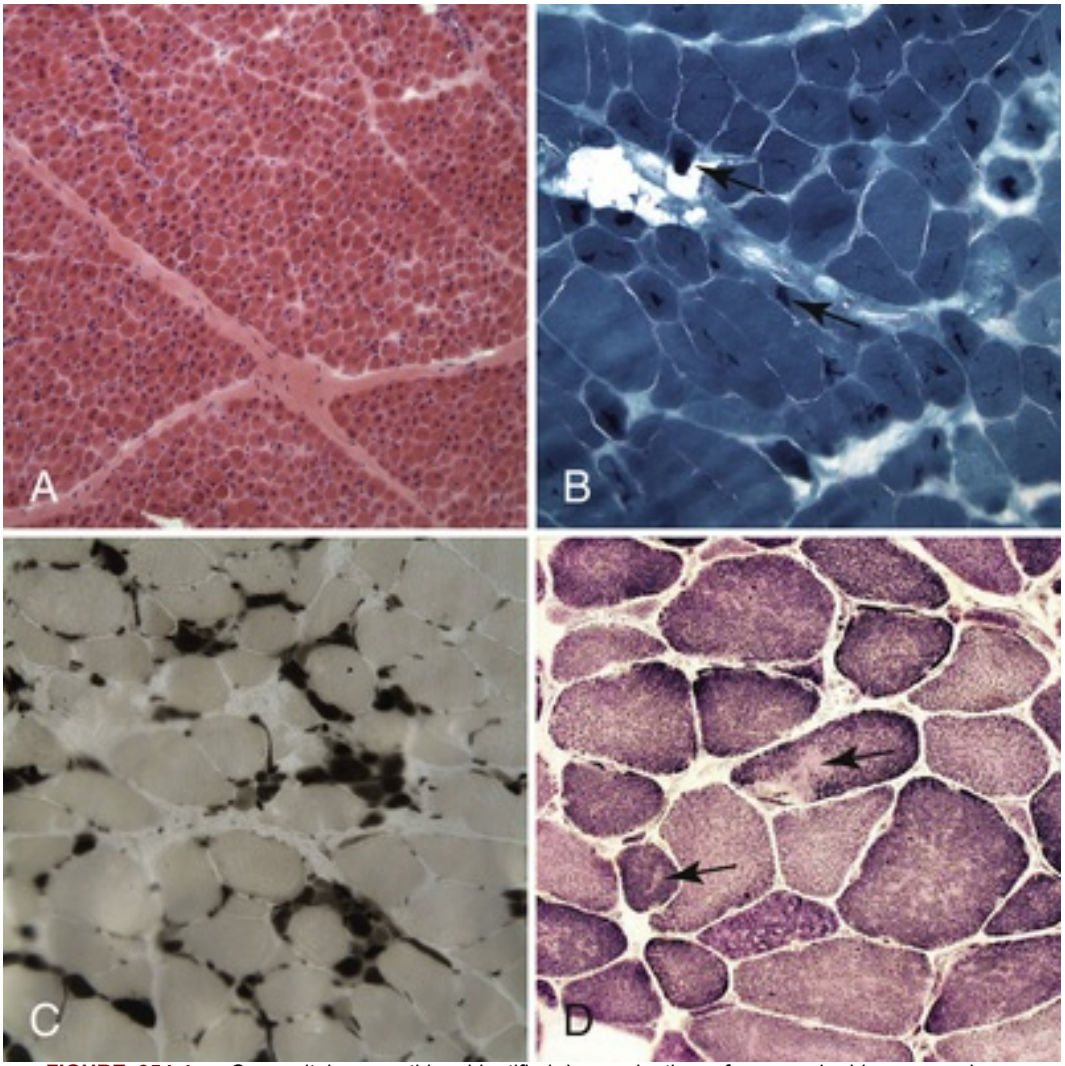


FIGURE 354-4 Congenital myopathies identified by evaluation of a muscle biopsy specimen including the following: **A,** X-linked myotubular myopathy (H&E stain). **B,** Nemaline rod myopathy (modified Gomori trichrome stain; arrows = clumps of rod bodies). **C,** Congenital fiber type disproportion (myofibrillar ATPase reaction at pH 4.3, type 1 fibers are dark). **D,** Multi-minicore disease (NADH-TR reaction; arrows point to areas devoid of oxidative enzyme activity consistent with cores or

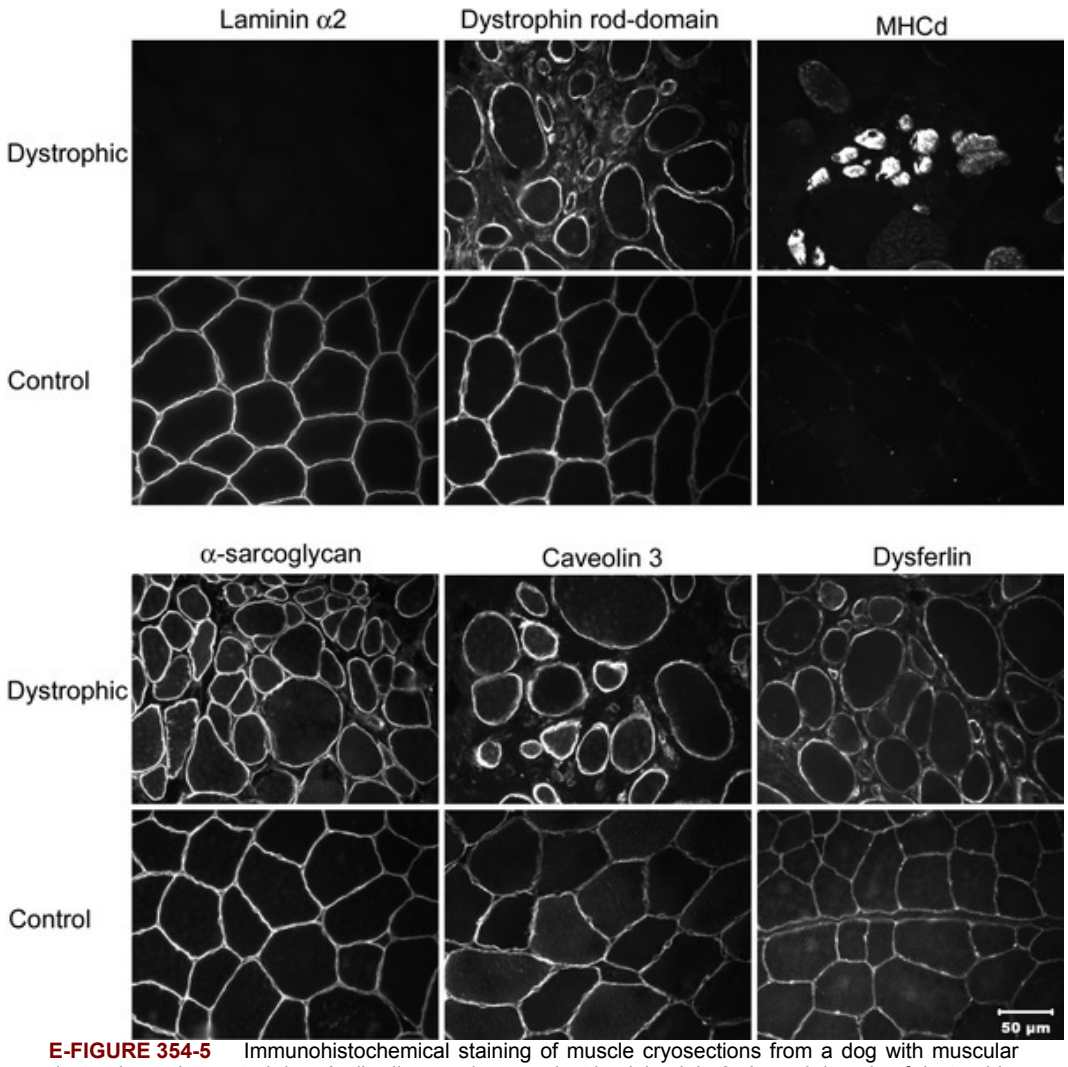
minicores). Magnification ×20 for all images.

Following identification of a structural abnormality, a targeted search for a gene mutation can be initiated. DNA testing is now available for a growing number of neurologic diseases[55] and the list of tests available for inherited myopathies is also increasing. Genetic heterogeneity can occur in the congenital myopathies, with mutations in more than one gene causing a specific myopathy. For example, there are at least eight different genetic loci that can result in nemaline rod myopathy.[42] Different breeds of dogs affected with X-linked myotubular myopathy can have mutations in different loci of the *MTM1* gene, as has been shown for the Labrador Retriever,[50] Rottweiler[52] and Siberian Husky (Shelton, unpublished). No specific therapies for these disorders are clinically available but prevention of the disease with altered breeding strategies should be effective because these myopathies, for the most part, occur early in life.

The centronuclear myopathies (CNMs) have been in the Labrador Retriever and Great Dane population for many years but have been known under various names. Centronuclear myopathy in Labrador Retrievers has been called type 2 fiber deficiency,[56] autosomal recessive muscular dystrophy[57] and inherited myopathy of Labrador Retrievers.[58] In the Great Dane, CNM previously has been referred to as central core myopathy.[59] With the identification of specific mutations in genes associated with the CNMs, these myopathies can now be correctly defined in line with classifications used in human medicine.

Muscular Dystrophies

Muscular dystrophies (MDs) are a heterogeneous group of over 40 different genetic diseases that result in progressive muscle degeneration, repeated cycles of regeneration, and progressive weakness. The most common MDs involve mutations in the gene that encodes the cytoskeletal protein dystrophin[60] and in the dystrophin-associated complex (DAC),[61] which links the extracellular matrix with the actin cytoskeleton, stabilizing the muscle membrane during contraction. Mutations in the dystrophin gene results in X-linked Duchenne- and Becker-type muscular dystrophies in humans.[62] Mutations in other genes of the DAC such as the sarcoglycans result in the group of dystrophies referred to as limb-girdle MDs, which have autosomal dominant or autosomal recessive modes of inheritance.[63] Muscle biopsies (see ch. 116)are an important component of the diagnosis of MD (see Figure 354-1) and immunohistochemistry is an essential component in identification of a specific form of MD (E-Figure 354-5).[64]



E-FIGURE 354-5 Immunohistochemical staining of muscle cryosections from a dog with muscular dystrophy and a control dog. Antibodies used are against laminin alpha2, the rod domain of dystrophin, developmental myosin heavy chain for regenerating fibers, sarcoglycan-alpha, caveolin 3 and dysferlin. The absence of staining with the antibody against laminin alpha2 confirmed a laminin alpha2-deficient congenital muscular dystrophy.

X-Linked (Dystrophin-Deficient) Muscular Dystrophy

Dystrophin-deficient MD is the most common form of MD in dogs[65] and mutations in the dystrophin gene have been identified in several breeds, including the Golden Retriever,[66] Rottweiler,[67] German Shorthaired Pointer,[68] Cavalier King Charles Spaniel,[69] Pembroke Welsh Corgi,[70] Cocker Spaniel, Tibetan Terrier, and Labrador Retriever.[71] Affected dogs have a severe and progressive myopathic phenotype, including gradual loss of muscle mass and development of contractures. Tongue hypertrophy and pharyngeal and esophageal dysfunction result in drooling, dysphagia, and regurgitation. The serum CK activity is persistently and dramatically elevated, which can be detected at a few weeks of age. No specific therapies are currently available. Early death can occur from cardiomyopathy, complications of dysphagia and esophageal dysfunction, or respiratory impairment from a greatly thickened diaphragm. A family of dystrophin-deficient Labrador Retrievers has been identified, with no or very minimal clinical signs of muscular dystrophy but markedly and persistently elevated CK activities.[72] Clinical signs of feline dystrophin deficiency can vary from muscle hypertrophy to atrophy, diaphragmatic thickening, megaesophagus, and an enlarged tongue with white plaques.[73,74] The serum CK activity is markedly and persistently elevated. The prognosis for recovery is poor. Mutations in the feline dystrophin gene have been identified.[74]

Autosomal Sarcoglycan-Deficient Muscular Dystrophy

Sarcoglycans are components of the DAC and, in striated muscle, are composed of alpha, beta, gamma, and delta subunits. Mutations in genes encoding the sarcoglycans result in the diverse group classified in humans as limb-girdle MDs.[63] Sarcoglycan-deficient MDs have been described in Boston Terriers,[75] a Cocker Spaniel,[76] a female Doberman dog,[77] and a domestic shorthair cat.[78] Sarcoglycan deficiency with a mutation in the gene encoding delta-sarcoglycan has been identified in Boston Terriers (Shelton, unpublished). The clinical presentation of a sarcoglycanopathy is similar to that of a dystrophinopathy, and muscle biopsies show the degenerative and regenerative dystrophic phenotype. Immunostaining for sarcoglycan proteins is necessary to distinguish this form of MD from dystrophin deficiency.

Laminin alpha2–Deficient Congenital Muscular Dystrophy

Laminins are large glycoproteins that contribute to the basement membrane in muscle and are connected to the sarcolemma via the DAC.[79] Laminin alpha2–deficient MD has been reported in cats[80,81] and in a Springer Spaniel cross-breed dog.[82] Clinical signs varied from generalized muscle weakness and atrophy to progressive stiffness with limited range of motion of the limb joints and limited opening of the jaw. Laminin alpha2 also is found in the Schwann cell basement membrane.[83,84] A demyelinating neuropathy was evident in one of the dystrophic cats where peripheral nerve was studied.[80] One or more mutation(s) in the laminin alpha2 gene has/have not yet been identified.

Collagen VI–Deficient Muscular Dystrophy

Progressive gait abnormality and multiple joint deformities were described in a young Labrador Retriever with collagen VI deficiency.[85] A mutation in the collagen VI gene has been identified (Shelton, unpublished). This case demonstrates the importance of considering a form of congenital MD in young animals presenting primarily for limb contractures.

Congenital Myasthenic Syndromes

Congenital myasthenic syndromes (CMSs) are heterogeneous disorders in which the safety margin for neuromuscular transmission is compromised by defects in proteins residing at the presynaptic, synaptic, or post-synaptic regions of the neuromuscular junction (NMJ) (see ch. 269).[86] CMSs usually occur in animals between 6-12 weeks of age, are familial, and are characterized by severe, generalized muscle weakness. Affected animals were never clinically normal. To date, CMSs have been reported in the Jack Russell Terrier,[87,88] Smooth Fox Terrier,[89] Springer Spaniel,[90] Smooth-haired Dachshund,[91] and Old Danish Pointing Dog.[92] A mutation in the choline acetyltransferase gene *(CHAT)* has been identified in CMS affecting the Old Danish Pointing Dogs.[93] Recently, an endplate acetylcholinesterase (AChE) deficiency resulting from a mutation in *COLQ*, the gene encoding the collagenous tail of AChE, was identified in a family of young Labrador Retrievers.[94] A mutation in *CHRNE*, the gene encoding the epsilon subunit of the muscle nicotinic AChR, recently has been identified in Jack Russell Terriers (Shelton, unpublished). A CMS also occurs in young Golden Retriever puppies, although the molecular defect has not yet been identified.

In general, the prognosis for CMSs in dogs is poor, since clinical signs usually are severe and desensitization to medications such as pyridostigmine can occur. Drugs that benefit one type of CMS can be ineffective or harmful in another type.[95] In Labrador Retriever dogs with a *COLQ* mutation, an AChE inhibitor resulted in worsening of muscle weakness. Conversely, AChE inhibitors in the Jack Russell Terriers with a mutation in *CHRNE* resulted in an increase in muscle strength. The adrenergic agonists salbutamol and ephedrine were empirically effective in CMS in people caused by a mutation in *COLQ*.[95]

Metabolic and Endocrine Disorders

Compared to the frequency of inflammatory and congenital myopathies in the companion dog and cat population, metabolic disorders involving glycogen, lipid, or mitochondrial metabolism are relatively uncommon.

Glycogen Storage Disorders

Glycogen storage diseases (GSDs) are a group of autosomal recessive disorders of glycogen metabolism that result in glycogen accumulation in tissue and that disrupt glucose homeostasis (also see ch. 260). The clinical phenotype begins early in life and can vary depending on severity of the enzyme defect and specific tissues in which the enzyme is normally expressed. A myopathic phenotype can be found with GSD type II (deficiency of lysosomal acid alpha-glucosidase, Pompe disease) in Finnish and Swedish Lapphund dogs,[96] GSD III (deficiency of glycogen debranching enzyme) in German Shepherd Dogs[97,98] and Curly-Coated Retrievers,[99] and type VII (phosphofructokinase, PFK deficiency) in English Springer Spaniels,[100] American Cocker Spaniels,[101] Whippets,[102] and Wachtelhund[103] dogs. Unlike in humans, where exertional myopathy is the more common presentation of PFK deficiency, hemolytic crisis is the predominant clinical manifestation in dogs. Glycogen storage disease type IV has been identified in Norwegian Forest cats.[104]

Mitochondrial Myopathies and Lipid Storage Disorders

The clinical recognition of mitochondrial disease is often challenging. In addition to a predominantly myopathic or encephalomyopathic presentation, multi-organ system manifestations can occur, in which muscle involvement is only a part. Mitochondrial disorders can present at any age. Organs with a high energy demand typically are affected, including skeletal and cardiac muscle, endocrine organs, kidney, non-mucosal components of the intestinal tract, retina, and the central nervous system.[105]

A mutation in the pyruvate dehydrogenase phosphatase 1 gene *(PDP1)* has been identified in Clumber and Sussex Spaniels having very limited exercise capacity beginning within the first year of life.[106] Markedly elevated resting and post-exercise plasma lactate and pyruvate concentrations with a lactate-to-pyruvate ratio <10 supported a mitochondrial disorder. A high-fat, low-carbohydrate diet and supplementation with L-carnitine, coenzyme Q_{10}, and a B-complex vitamin results in improved exercise tolerance, although the lifespan is shortened. A mitochondrial myopathy associated with altered cytochrome C oxidase activity has been reported in Old English Sheepdog littermates.[107]

Lipid storage myopathies are associated with primary or secondary disorders of carnitine metabolism or disorders of fatty acid beta-oxidation.[108,109] Clinical signs include progressive generalized weakness and prominent myalgia. The diagnosis can only be made by demonstration of excessive and large intramyofiber lipid droplets in type 1 muscle fibers using a stain for neutral triglycerides. Lactic acidemia can be a concurrent finding. Therapy usually is successful, using a combination of L-carnitine, antioxidants, and a B-complex vitamin.

Myopathies Associated with Endocrine Disorders

Myalgia, stiffness, and muscle atrophy or hypertrophy are common findings in senior dogs with endocrine disorders, most notably hypothyroidism (see ch. 299) and Cushing's syndrome (see ch. 306). Neuromuscular signs can occur without the classical clinical signs of an endocrinopathy.[110] Pathologic changes in muscle, such as type 2 fiber atrophy and type 1 fiber predominance, can be the first indication of an endocrine-associated myopathy.[111] With hypothyroidism, the response to thyroid supplementation should be excellent. Muscle weakness in cats with hyperthyroidism has a good response to therapy (see ch. 301). In chronic and untreated Cushing's syndrome, a pseudomyotonia may develop (see Video 306-2) that is poorly responsive to specific therapy for hyperadrenocorticism. Muscle cramping has been reported in hypoadrenocorticism in dogs (see ch. 309).[112]

Channelopathies

Congenital Myotonia and Periodic Paralysis

Congenital myotonias are caused by dysfunction of sarcolemmal ion channels, resulting in abnormal myofiber excitability. Clinical signs occur before 6 months of age and include marked muscle hypertonicity, hypertrophy, and visible percussion dimpling when affected muscles are struck with a reflex hammer. Hypertrophy of the tongue is prominent in cats. Electromyographic examination (see ch. 117) with demonstration of dive bomber potentials is diagnostic. Specific mutations have been identified in Miniature Schnauzers,[113] Australian Cattle Dogs[114] and domestic cats,[115] and DNA screening tests are available.

Membrane-stabilizing agents such as procainamide and mexiletine are considered the most effective treatments.

The periodic paralyses are rarely described in veterinary medicine. Episodic weakness resulting from hypokalemia has been described in Burmese kittens.[116] Oral potassium supplementation prevents episodes. A mutation has been identified and a genetic test is available.[117] Hyperkalemic periodic paralysis responsive to acetazolamide has been reported in a single American Pit Bull Terrier.[118]

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CHAPTER 355

Physical Therapy and Rehabilitation

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Client Information Sheet: Physical Therapy and Rehabilitation

Physical therapy is a profession with an established scientific basis in humans and companion animals. It has numerous clinical applications in the restoration, maintenance, and promotion of optimal physical function.

In providing physical therapy and rehabilitation, the goal is to restore, maintain, and promote optimal function, fitness, wellness, and quality of life as they relate to movement disorders and overall health.[1-7] In dogs, this may include treating patients during their recovery from orthopedic surgical procedures, such as fracture repair and cruciate surgery, monitoring weight loss programs (see ch. 176), providing overall rehabilitation after neurological injuries such as intervertebral disc disease (see ch. 266), and helping to manage chronic conditions, such as osteoarthritis (see ch. 353), or progressive conditions, such as degenerative myelopathy (see ch. 266).[8-14] A major emphasis is to prevent or minimize the onset, clinical signs, and progression of impairments, functional limitations, and disabilities that may result from diseases, disorders, conditions, and injuries.

Physical therapy and rehabilitation in small animal practice is becoming increasingly common and will likely continue to emerge as an essential aspect of veterinary medicine as the scientific literature continues to expand. In many orthopedic and neurologic conditions, physical rehabilitation is becoming routine as a means to enhance recovery, as in human medicine. Wellness and preventive medicine (e.g., weight reduction, maintenance of muscle strength and function, improving cardiorespiratory fitness, and sport specific conditioning) is also a growing trend in rehabilitation and sports medicine. In the human and canine literature, rehabilitation therapy has been shown to be effective in numerous areas related to internal medicine including pain management, cardiorespiratory function, musculoskeletal and neurological recovery and function, and oncology, to name a few.[15-24]

In 2012, the American College of Veterinary Sports Medicine and Rehabilitation (ACVSMR) was approved as a board-certified specialty under the American Veterinary Medical Association's American Board of Veterinary Specialties (ABVS). This newly formed college is aimed at veterinary practitioners who specialize and excel in sports medicine and rehabilitation. Certificate programs in canine rehabilitation are also available and require on-line and live coursework, externships, and examination processes.

Rehabilitation is a time-intensive specialty and has traditionally employed a collaborative approach that engages multiple professions to maximize outcomes including veterinarians, veterinary technicians, physical therapists, orthotists and prosthetists, behaviorists, trainers, and of course owners.

Physical Therapy/Rehabilitation Evaluation

The physical therapy/rehabilitation process begins with a diagnosis from the veterinarian and a careful physical therapy evaluation. The physical therapy evaluation differs from a medical evaluation in that function is paramount. Range of motion, strength, gait, pain, balance, endurance, and other functional factors are all documented, and a plan for rehabilitation is developed, in conjunction with the owner (Appendix 355-1). The plan of care must be unique to the patient and must take into account all abnormal findings and other factors, including the severity of the condition, the age and disposition of the dog, the expectations for future function and performance, the urgency of the recovery, the available equipment and technical skills of the therapist, and the financial constraints of the owner. The plan of care is then continually modified as needed, based on frequent assessments. A qualified rehabilitation practitioner may or may not be found locally, so home programs are sometimes a necessity. A list of practitioners is available at http://ccrp.utvetce.com/practitioners.asp.

It is important to determine the expectations of the owner during the evaluation to help determine the type and length of program necessary to meet the goals. In most cases, owners are realistic about expectations, especially for pets with chronic, severe conditions in which improved mobility and pain control are desired. Occasionally, an owner will have unrealistic goals, and it is important to discuss the realities of the underlying condition(s) and whether or not the desired objectives are likely to be achieved.

Assessment Techniques

Assessing the outcome of treatments in physical therapy and rehabilitation is essential to determine how an animal is progressing and to assess the effectiveness of the treatment. These techniques should consist of objective data whenever possible because subjectively owners and veterinarians often believe a patient is doing better than the data suggest. In addition, documentation of progress is important to provide incentives for owners to continue rehabilitation and justify continued treatment. Numerous measurements are useful for assessing outcomes, including the ability to perform functional activities of daily living, gait analysis, joint motion and function (Figure 355-1), muscle mass and strength, body composition and weight changes, pain assessment, activity levels, and functional scales.[25-37]

FIGURE 355-1 A 6-month-old Labrador Retriever is recovering from extracapsular stabilization of his left stifle joint after avulsion of his cranial cruciate ligament. The dog is undergoing static weight shifting exercises **(A),** walking in an underwater treadmill **(B),** trotting on a treadmill **(C),** and walking with an elastic band eliminating the external rotation present in his right pelvic limb during the recovery period **(D).** (From Millis DL, Levine D: *Canine rehabilitation and physical therapy*, ed 2, St Louis, 2014, Saunders.)

Common Interventions in Physical Therapy/Rehabilitation

Thermotherapy and Cryotherapy

Superficial heat (thermotherapy) and cold (cryotherapy) have been used therapeutically for centuries on soft tissues and joints. Cryotherapy is commonly used after tissue trauma whether accidental (sprains, strains, etc.) or intentional (surgery, intense exercise), with the goals of decreasing inflammation, swelling, and pain and improving function.[38] Heating connective tissues using superficial heat such as hot packs and

compresses typically is used for chronic conditions, such as arthritis and other disease processes causing stiffness, and helps to increase connective tissue extensibility. Thermotherapy may also be used to decrease pain and facilitate healing.[39] Both of these treatments are easily taught to owners and can be administered at home.

Therapeutic Ultrasound

Therapeutic ultrasound (TUS) is primarily used as a deep heating agent (up to 5 cm) and is used in small animal practice for heating joints, muscles, and tendons, commonly before stretching. It is also used for tissue healing and repair and to enhance the transdermal administration of drugs (phonophoresis). Only two frequencies are used in TUS (in comparison with diagnostic ultrasound), 1 MHz for treating tissues between 3 and 5 cm in depth and 3 MHz for treating tissues 1 to 2 cm in depth.[40-42]

Electrical Stimulation

Electrical stimulation (ES) is a commonly used modality in physical therapy and can be effective for many purposes, including increasing muscle strength and decreasing pain.[14,43-47] These devices work by stimulating motor nerves to cause a muscle contraction and by stimulating sensory nerves to help decrease pain. Many dogs tolerate ES well, but some dogs may dislike the sensation and care must be used when attempting this modality.

Therapeutic LASER

LASER is an acronym for light amplification by stimulated emission of radiation. The concept of the use of light for therapeutic purposes, called phototherapy, originated from the belief that the sun and other sources of light have therapeutic benefits. Therapeutic lasers have become increasingly popular in veterinary rehabilitation for a variety of conditions. The lasers used in rehabilitation are thought to help modulate cellular functions, a process known as photobiomodulation (PBM). PBM has been reported to modulate various biologic processes, such as mitochondrial respiration and adenosine triphosphate (ATP) synthesis, to accelerate wound and joint healing and promote muscle regeneration.[48-58] It is also commonly used for pain control, and some studies have found it to be an effective adjunct in the treatment of musculoskeletal pain. Therapeutic lasers are typically Class IIIb (5 to 500 mW) or Class IV (>500 mW) and possess appropriate infrared wavelengths to penetrate to various tissue depths (Figure 355-2).

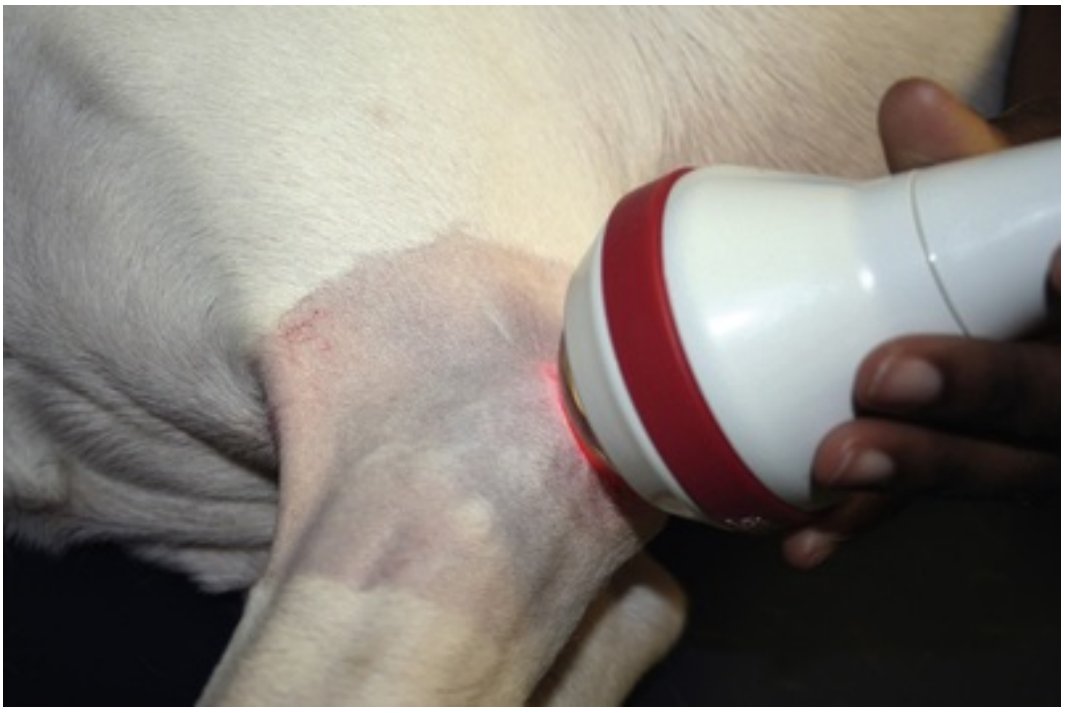


FIGURE 355-2 Treatment of an arthritic joint with a therapeutic laser.

Range of Motion and Stretching

Range of motion (ROM) and stretching exercises are extremely important to achieve improved motion of joints after acute injury or surgery (articular fractures) or in patients afflicted with chronic conditions (osteoarthritis). They are also important to help increase flexibility, prevent adhesions between soft tissues and bones, remodel periarticular fibrosis, and improve muscle and other soft tissue extensibility to help prevent further injury.[59] Joint motion may be measured using goniometry, which has been validated in dogs and cats (Figure 355-3).[60,61] These exercises can also be performed at home if the owner has been carefully instructed.

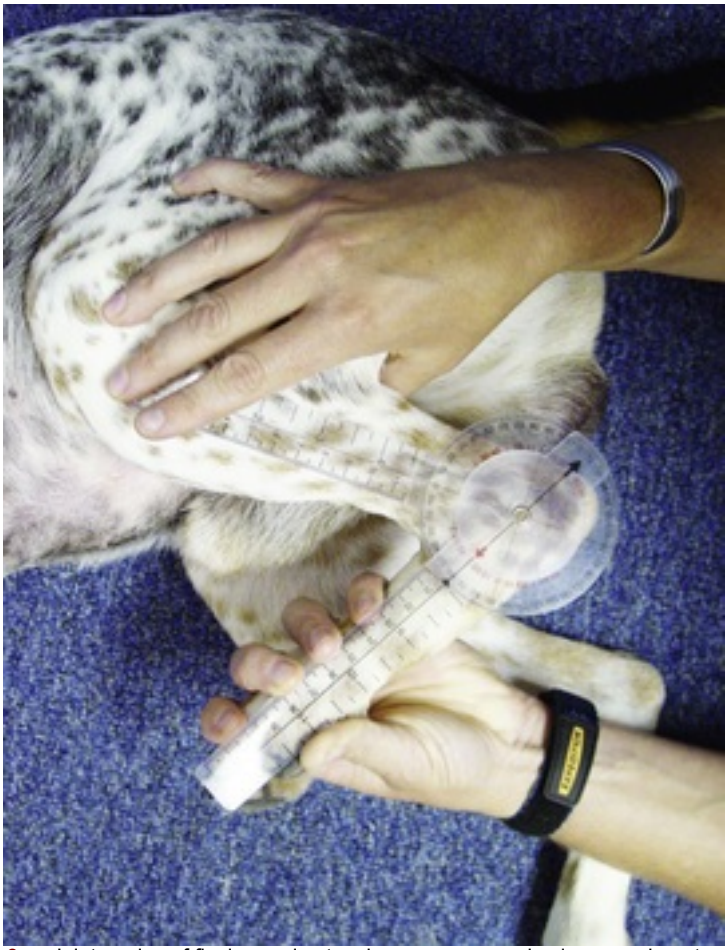


FIGURE 355-3 Joint angles of flexion and extension are measured using a goniometer.

Massage

Massage has many forms and is employed by many practitioners of various backgrounds. One common definition is that massage is the scientific and systematic manipulation of the soft tissues of the body. The use of massage in humans is common for relaxation, pain control, recovery from injury, and improving flexibility[62-66] and is becoming more accepted and commonplace in veterinary practice. In some states (but not all) massage therapists are licensed and regulated, but for small animal practice this is not common. Continuing education courses and schools that teach massage are available.

Therapeutic Exercise

See Videos 355-1, 355-2, 355-3, 355-4, 355-5, 355-6, 355-7, 355-8, 355-9, 355-10, 355-11, 355-12, 355-13, 355-14, 355-15, 355-16, 355-17, 355-18, and 355-19.

Therapeutic exercise is very likely the most common and most valuable modality used in physical therapy and rehabilitation. Therapeutic exercise is an important method to return the animal to the optimal level of independence and function.[13,14,67,68] Some of the common goals of exercises are to improve active range of motion, flexibility, muscle mass and muscle strength, balance, endurance, and performance of activities of daily living.[11,59,68-74] Therapeutic exercise programs designed for the home environment also provide an opportunity for owners to become actively involved in their pet's rehabilitation (Figures 355-4 to 355-8).

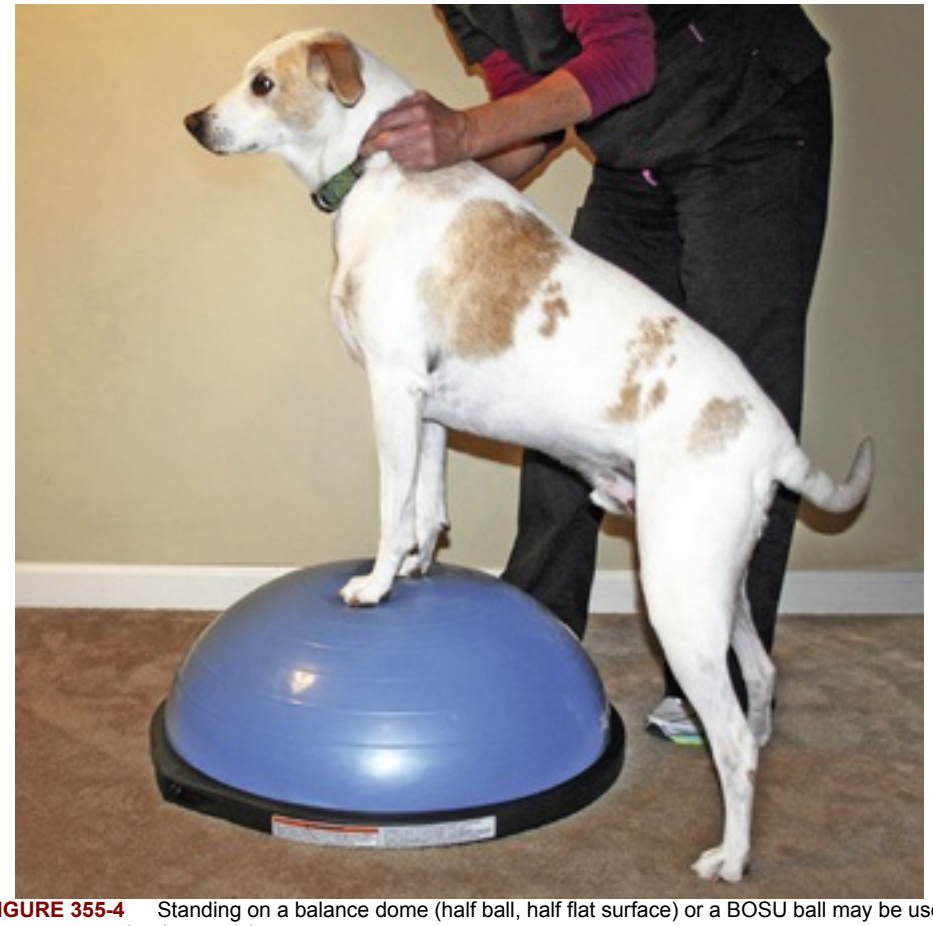


FIGURE 355-4 Standing on a balance dome (half ball, half flat surface) or a BOSU ball may be used for core strengthening exercises.

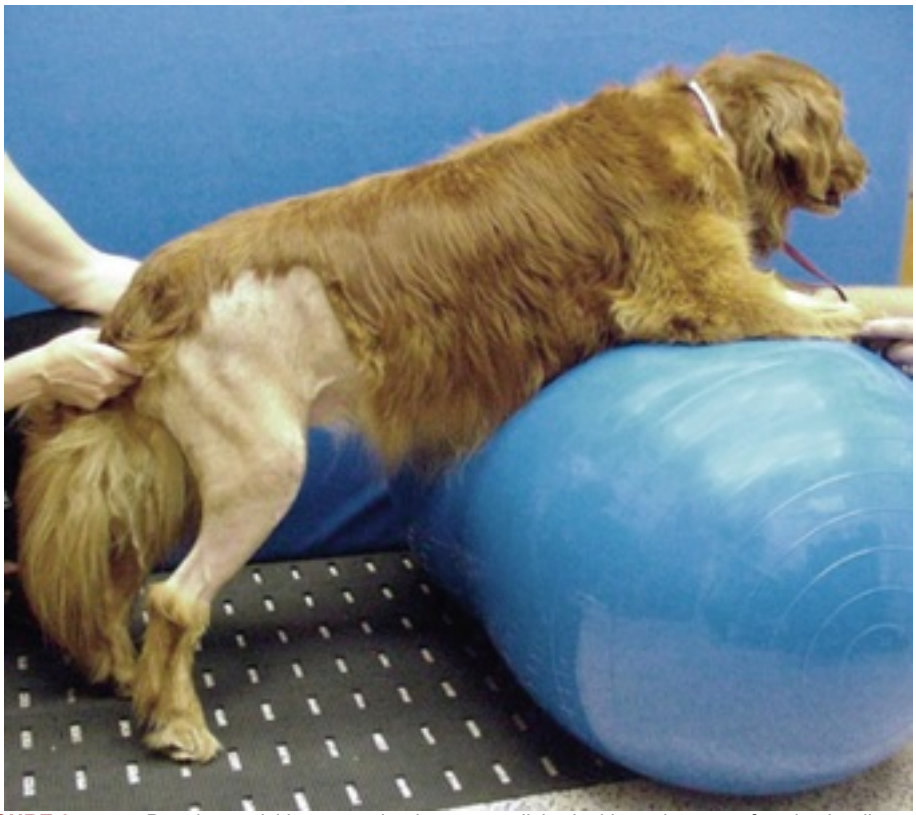


FIGURE 355-5 Dancing activities may also be accomplished with assistance of a physioroll or egg ball. The patient places the front limbs on the roll or ball, and the therapist slowly rolls the ball toward or away from the patient forcing the patient to move the hindlimbs backward or forward.

FIGURE 355-6 Tetraparesis or other conditions causing weakness in multiple limbs. **A,** Use of a sling to help provide support for standing. **B,** As the patient begins to fatigue and attempts to sit, the therapist lifts the dog back into a standing position.

FIGURE 355-7 Walking over cavaletti rails helps dogs learn how to negotiate obstacles and walk over them by lifting their limbs to the appropriate height.

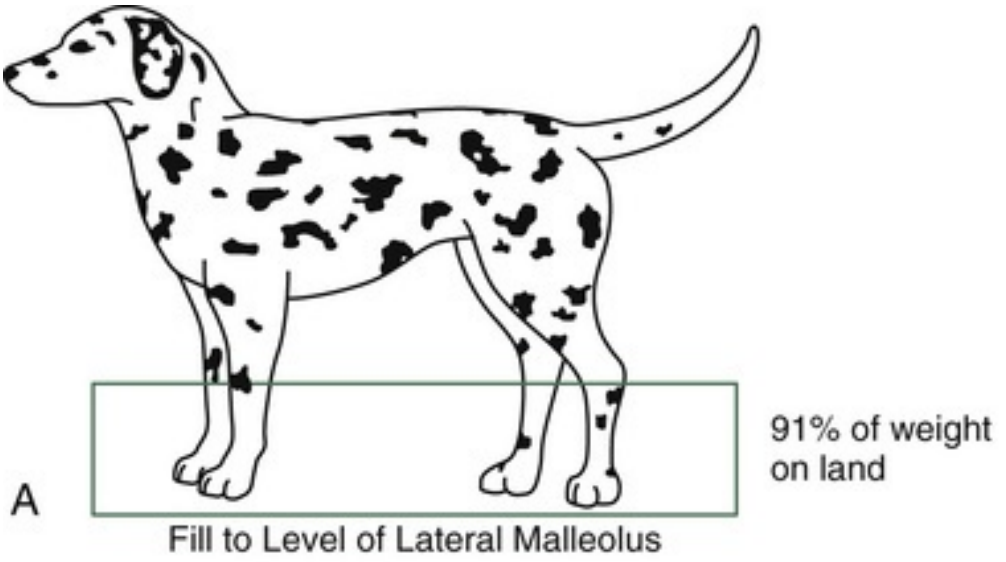
FIGURE 355-8 Standing or walking on foam rubber, mattresses, air mattresses, or trampolines alters the texture of the ground and challenges the animal's functional balance and proprioceptive ability.

Aquatic Therapy

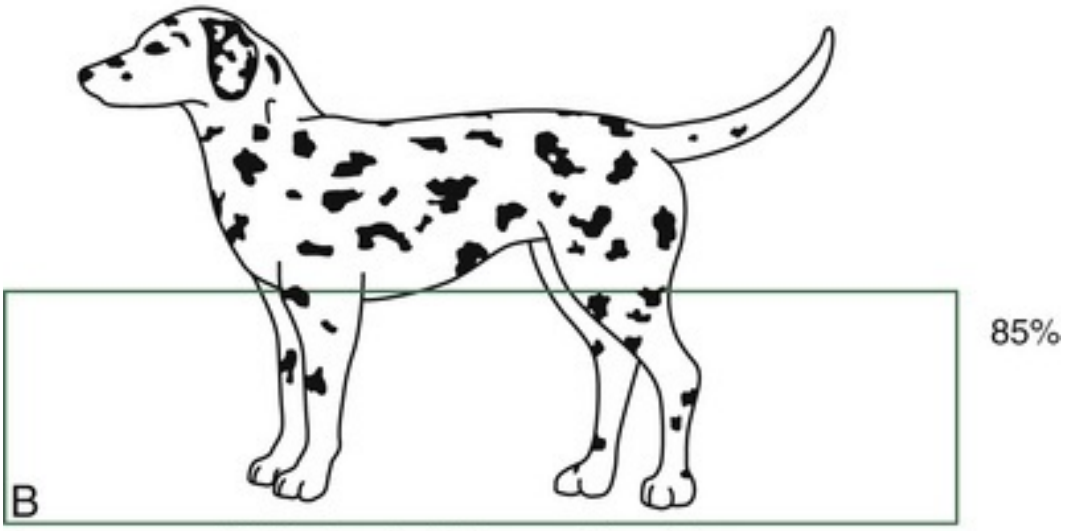
Aquatic therapy has become a very valuable component of veterinary physical therapy and rehabilitation. Underwater treadmills (UWTMs) and pools have become commonplace in veterinary rehabilitation facilities (Figures 355-1, *B* and 355-9). A major benefit of using a UWTM is buoyancy, which decreases the load on the joints during exercise.[12,14,75,76]

FIGURE 355-9 Plastic bumpers in an underwater treadmill to prevent standing on its nonmoving sides. (From Levine D, Millis DL, Flocker J, et al: Aquatic therapy. In Millis DL, Levine D, Taylor RA, editors: *Canine rehabilitation and physical therapy,* St Louis, 2014, Saunders, p 532; with permission.)

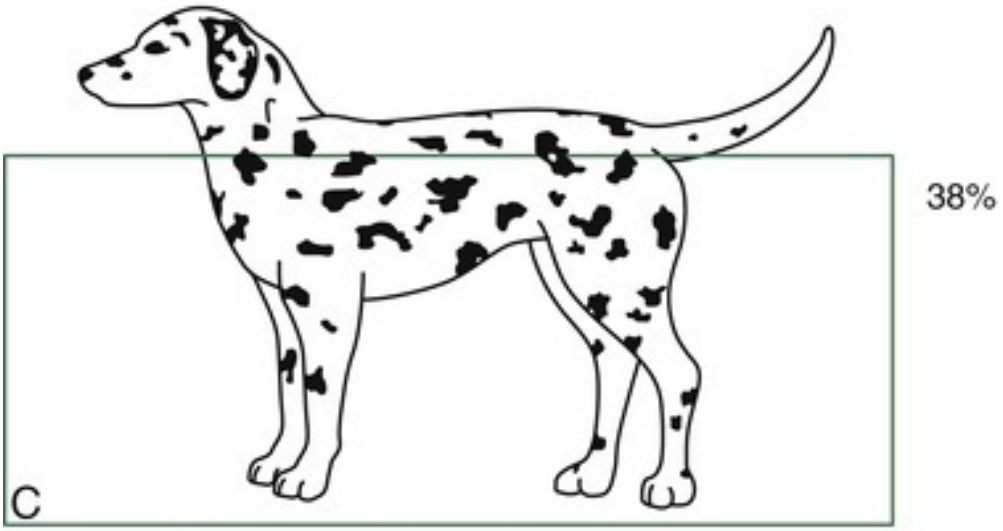
In a study performed on dogs, the amount of body weight borne when the dog was immersed in water (as a percentage of body weight on dry ground) was approximately 91% when the water was at the level of the lateral malleolus of the tibia, 85% at the level of the lateral condyle of the femur, and 38% at the level of the greater trochanter of the femur.[75] This information may be particularly useful when treating patients with conditions such as arthritis because joints may be unloaded as a result of the buoyant properties of water (Figure 355-10, *A-C*). The use of UWTMs is favored for enhancing function such as gait. It also encourages joint motion in a more normal gait pattern compared with swimming. Swimming tends to increase flexion and overall range of motion of the limbs, but joint extension is less compared with UWTW walking. Swimming is a much more difficult activity from an endurance and cardiovascular perspective, though, and just a minute or two can be exhausting, especially for dogs that are in poor condition. Flotation devices are also helpful to allow for greater buoyancy and ease of exercise.



Fill to Level of Lateral Malleolus



Fill to Level of Femoral Condyles



Fill to Level of Greater Trochanter

FIGURE 355-10 **A,** Dog in water to the level of the lateral malleolus. **B,** Dog in water to the level of the lateral epicondyle. **C,** Dog in water to the level of the greater trochanter. (Data from Levine D, Marcellin DJ, Millis DL, et al: Effects of partial immersion in water on vertical ground reaction forces and weight distribution in dogs. *Am J Vet Res* 71:1413-1416, 2010.)

Aquatic therapy such as UWTMs and swimming comes naturally to many patients, which is especially beneficial because exercises in animal patients must be in a form that they naturally perform or can be easily trained to do. It is also an exercise owners can perform with their dogs at home if they have the facilities.

Assistive Devices in Rehabilitation (Carts, Slings, Harnesses, Supports, Orthotics, and Prosthetics)

Numerous assistive devices are used in rehabilitation to assist animals with gait and function (Figures 355-11 and 355-12). These range from adaptive equipment and inexpensive harnesses and supports, to carts and wheelchairs that may be customized to the patient (Figure 355-13). Many of these supports help provide an ergonomic benefit for the owner and provide comfort and safety for the dog.[77,78] Orthotics is the evaluation, fabrication, and custom fitting of braces, known as orthoses. Prosthetics is the evaluation, fabrication, and custom fitting of artificial limbs, known as prostheses (Figure 355-14). Practices offering rehabilitation services have knowledgeable staff regarding obtaining this equipment and training owners in its use.

FIGURE 355-11 An assistive device, such as an abdominal sling, can be used to help a thoracolumbar patient stand and ambulate. (From Millis DL, Levine D: *Canine Rehabilitation and Physical therapy,* ed 2, St Louis, 2014, Saunders.)

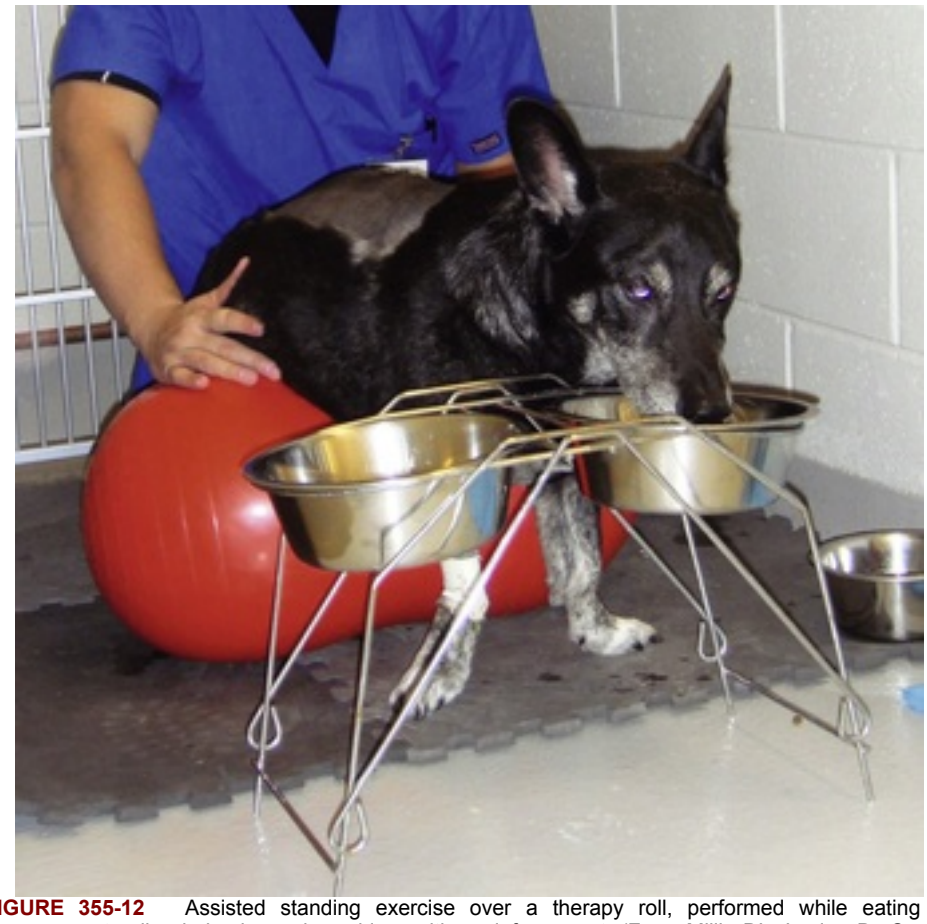


FIGURE 355-12 Assisted standing exercise over a therapy roll, performed while eating to encourage standing behavior and provide positive reinforcement. (From Millis DL, Levine D: *Canine rehabilitation and physical therapy,* ed 2, St Louis, 2014, Saunders.)

FIGURE 355-13 An assistive device, such as a cart, can be used to help a thoracolumbar patient

stand and ambulate. (From Millis DL, Levine D: *Canine rehabilitation and physical therapy,* ed 2, St Louis, 2014, Saunders.)

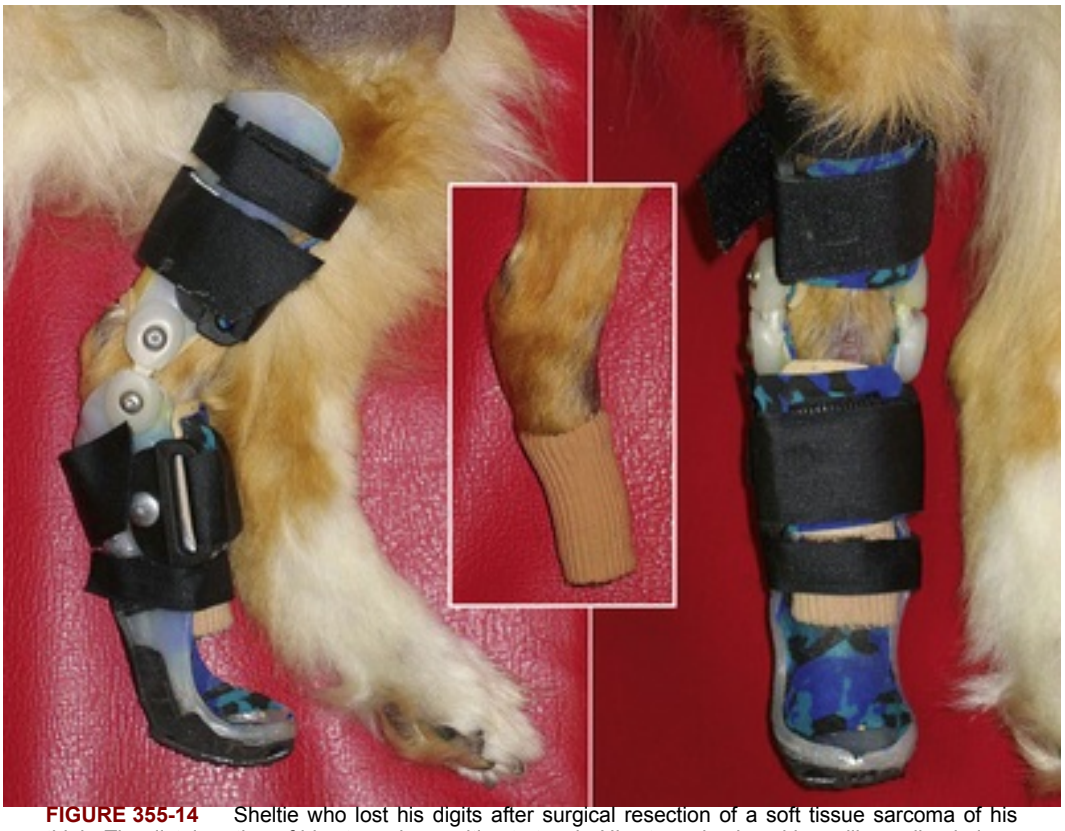


FIGURE 355-14 Sheltie who lost his digits after surgical resection of a soft tissue sarcoma of his thigh. The distal portion of his stump is sensitive to touch. His stump is placed in a silicone-lined glove finger and fitted in a hinged prosthesis held in place with four hook-and-loop fasteners.

Appendix 355-1

PHYSICAL THERAPY INITIAL EVALUATION

Patient's name:	
Date:	

PHYSICAL EXAMINATION:

Skin/incisions:		Color/temp:	
Heart rate:		Respirations:	

POSTURE/GAIT:

General observation:				
Preop/injury lameness:	Walk:		Trot:	
Postop/injury lameness:	Walk:		Trot:	
Standing limb position:		Sitting limb position:		

Circumference (cm):	70% femur	80% humerus	Joint line	Other
Affected:				
Unaffected:				
Other:				

RANGE OF MOTION:

Joint(s): Aff/Unaff	Flexion	Extension	AB/adduction	Varus/Valgus	Other
Hip:					
Stifle:					
Hock:					
Shoulder:					
Elbow:					
Carpus:					
Other:					

PALPATION:

Forelimb	
Hind limb	
Spine	
Other	

SPECIAL TESTS:

Neurologic:	
Orthopedic:	
Functional:	
Other:	

TREATMENT:

Modalities:	Manual:	Therex:
Interferential current ☐	Massage ☐	Gait training ☐
Neuro-muscular electrical stimulation ☐	Joint mobilization ☐	Aquatic ☐
	Passive range of motion ☐	Functional ☐
		Swiss ball ☐
Other stim ☐		Foam roll ☐
Ultrasound ☐	Other:	Owner education ☐
Ice ☐		Protocol review ☐
Heat ☐		Other:
Other ☐		

ASSESSMENT/GOALS:

Decrease pain	
Decrease edema	
Increase weight-bearing	
Independent home exercise program	
Return to previous function	
Other	

PLAN:

Return visit	
Call for follow-up	
Call DVM	
Other	

DVM Signature _____

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CHAPTER 356

Chronic Pain

Pathophysiology, Identification and General Management

Lisa Moses

Chronic pain is an enigmatic and intricate problem in veterinary medicine. The maladaptive nature of chronic pain and animals' inability to self-report add to the complexity of management. Pet owners' concerns about chronic pain are not surprising given the prevalence of this problem in people. Chronic pain in adults is considered a global public health crisis, affecting one in five adults for a median duration of 7 years.[1] Chronic pain syndromes that are sufficiently significant to impact quality of life are often a consequence of sustained management of chronic diseases and longer-lived companion animals. The clinical challenge of chronic pain will grow in importance as dogs' and cats' longevity increases. The existence of this new chapter recognizes that management of chronic pain is an integral part of veterinary internal medicine.

Diagnosing and effectively treating chronic pain in patients who cannot self-report is done by proxy. This can feel uncomfortable compared with the general practice of medicine in which a diagnosis is made on the basis of objective data and progress is gauged on seemingly concrete outcome measures. Consequently, chronic pain remains markedly underdiagnosed and undertreated in companion animals, despite evidence of its frequent occurrence.[2,3]

All types of pain are subjective experiences, defined in both sensory and emotional terms. Although veterinarians and clients assume that pain would be fairly easy to assess in verbal patients compared to animals, an "objective" measure of pain in people currently is the subject of intense research. Even physicians are doubtful about the reliability of the gold-standard of self-reporting.[4] For now, the diagnosis of chronic pain depends on functional behavioral changes and response to treatment. Chronic pain states can be inferred from historical and physical examination data and managed in the same way, without posing substantial risk to the patient. Although the problem of underrecognition can be reduced by changing the approach to patients with likely chronic pain, data on effective treatment strategies for animals are still sparse and practice is dependent on extrapolation from adult and pediatric chronic pain medicine.

Chronic Pain: Pathophysiology

A clear distinction exists between the physiology of pain and the pathophysiology of chronic pain. Pain can be a physiologic process meant to protect tissues from potential damage or further injury (nociceptive and acute pain, respectively; see ch. 126) or it can be a maladaptive disease syndrome with no known function (chronic pain).[5,6] Many "definitions" of chronic pain exist in the literature, but none conveys the complexity or totality of this disease. Even Greene's concise and precise definition, "… aberrant somatosensory processing in the periphery or central nervous system (CNS) that is sustained beyond the normal expected time course relative to the stimulus" is acknowleged to be partial.[6] From a pathophysiologic and clinical standpoint, chronic pain is a disease state of the CNS, rather than a clinical sign of long-lasting tissue damage.[7] The clinical marks of chronic pain are altered responses to nociceptive stimulation via allodynia (pain provoked by normally non-noxious stimuli), hyperalgesia (increased sensitivity to noxious stimuli), and sensitization (increase responsiveness by neurons to noxious stimuli).[8] Chronic pain can also be generated spontaneously from CNS activity without tissue damage, or it can persist after tissue healing.[8] These characteristics are clinically very confusing since a structural lesion that explains the pain might seem minor, could have resolved, or might be nonexistent. In chronic pain states, the perception and experience of pain is disconnected from the peripheral lesion.[9]

Chronic pain is caused by both structural and functional changes in pain pathways. Neuronal mechanisms include disinhibition, descending pathway facilitation, and long-term potentiation in the spinal cord and cortex.[10] A main contributor to the generation of chronic pain is the sensitization of the pain signaling system. Central sensitization is a type of CNS plasticity that has been best characterized as a process in the dorsal horn of the spinal cord, importantly involving N-methyl-D-aspartate (NMDA) receptor recruitment.[7] Contemporary research suggests that a similar process of sensitization likely occurs at other CNS sites.[11] Neuronal, immune, and glial-related triggers of central sensitization all appear to be important, besides the frequently mentioned NMDA receptor mechanisms.[8] Both sensitization and tonic activation (another key element) are stimulated by mediators released at all levels of the pain nervous system.[11]

Non-neuronal elements such as glia and immune cells are integral to the transition from acute pain to chronic pain.[8] In fact, recent research has posited that chronic pain is a "gliopathy," or dysregulation of glial function in the nervous system.[10] Activation of glia and neuro-glial interaction involving three types of glial cells (astrocytes, microglia, and satellite glia) are emerging as key processes in the transition to, and maintenance of, chronic pain states.[10-12]

Gene expression in nociceptors is significantly altered in persistent pain (epigenetic change), as is cortical activity as measured by functional magnetic resonance imaging studies.[11] Other contributors to chronic pain mechanisms are genetic or gender differences and bacteria in chronic infections (which can directly stimulate nociceptors).[8]

Chronic pain is not inevitable after acute or even persistent pain. Susceptibility to chronic pain is a complex equation of genetic predisposition and environmental factors. Current research is attempting to link brain imaging techniques with genetic phenotypes or biomarkers in order to better characterize the biological basis for chronic pain.[13,14]

An important functional aspect of pain physiology is the existence of an endogenous pain inhibitory (analgesic) system.[15] The ability of the nervous system to reduce pain appears to be achieved via net inhibition from multiple, interacting, opioid-sensitive circuits at all levels of the nervous system that produce descending modulation of pain signals.[7,15] This system is responsible for the actions of most analgesic drugs and many nonpharmacological methods of producing analgesia including the placebo effect, acupuncture, and exercise.[7,14-16] Many analgesic drugs utilize this circuitry by mimicking the effect of endogenous opiates.[15]

Identification of Chronic Pain and Assessment of Response to Treatment

In contrast to the human species, there is little information about the incidence of chronic pain in veterinary species.[17,18] Recognition of chronic pain in the clinical setting arguably is more difficult than identification of acute pain. Surveys of veterinarians in several cultures have reported the challenge of identification as an obstacle to treatment of chronic pain.[19-21] Although there is widespread acknowledgment of the significance of chronic pain in these surveys, there is also large variation in frequency, duration, and type of treatment provided.

Knowledge of the signs of chronic pain is integral to identification. It is important to bear in mind that some patients show *no* observable signs of chronic pain and some actively hide clues. Important signs of chronic pain in dogs include abnormal postures and movements, changes in willingness to engage in social behaviors, deviations from usual demeanor, trembling, panting, different vocalizations, changes in overall activity level, biting or licking painful areas or forelimbs, and decreased appetite.[22-24] Important signs of chronic pain in cats include changes in jumping up or down, changes in elimination behaviors, lower activity levels, decreased grooming, and social self-isolation.[25,26]

Efforts have been made to identify objective measures of changes due to (primarily) musculoskeletal pain. Physical examination and imaging techniques could yield supportive information in the diagnosis of chronic pain, but their significance is uncertain without a context of functional and/or behavioral changes. Observation methods of lameness scoring and physical exam findings (e.g., joint range of motion) have poor interobserver variability and have not been validated.[22,27] As with assessment of acute pain, measures of homeostasis and physiologic responses to pain are not specific to chronic pain. Radiographic indices of osteoarthritis do not always correlate well with pain levels, particularly in cats.[28-30] Methods that evaluate ground reaction forces like force plate analysis are considered to be the gold standard for assessing lameness even though there are substantial limitations on the clinical utility of this technique.[27,31] Using force plate

analysis as a pain measurement is based on the assumption that lameness equates with pain, but the relationship between pain and lameness is inconsistent and individually variable. Monitors of physical activity have shown promise in some studies, but not others, as indicators of pain relief and have been used clinically in dogs and cats.[26,32-34]

Chronic pain in humans is recognized as a complex and individual experience that cannot be described fully using simple scales that only assess severity (unidimensional).[35] Chronic pain in animals is assumed to be similar given than the "machinery" of pain experience is the same between species.[22] Most authors agree that chronic pain can be identified via changes in behavior, demeanor, and function as observed by veterinarians and caregivers.[26,36,37] The situation could be more complicated in cats, however. Lameness is not the most consistent or reported sign of musculoskeletal pain in cats, and owners might be less able to recognize pain behaviors in cats than in dogs.[28,38] Evidence suggests that veterinarians might not see many of these changes during a routine office visit or even during a thorough physical examination. The most obvious limitation is a lack of self-reporting, but other factors contribute. These include masking of pain signs by release of stress hormones during examination, the inconstant nature of chronic pain, and that chronic neuropathic or visceral pain often is not elicited during palpation of a lesion. Fortunately, caregivers can be accurate reporters of changes in locomotion, behavior, and demeanor even if they do not realize that pain is the cause of the changes.[39-41] Therefore, education of caregivers about pain behaviors is crucial to their understanding of their pet's pain. For example, many owners will attribute signs of pain to normal aging processes.

Validated, multidimensional scoring tools have been developed to assess chronic pain due to osteoarthritis in both dogs and cats and bone tumors in dogs, as well as to measure the effects of chronic pain and cancer on health-related quality of life in dogs.[26,42-44] Health-related quality of life measurement instruments are used in human health care to assess the adverse impact of pain (or other health problems) on health and well-being in a more global way than unidimensional scales.[35] This approach might better describe how patients experience chronic pain and can be used for treatment decision making.

Veterinary tools have also been used to assess response to surgery and medical management of chronic pain and to compare outcome with and without surgery.[25,26,37,40,43,45] Examples of some of these tools can be downloaded from www.vetmed.helsinki.fi/english/animalpain/hcpi and www.CanineBPI.com.

Response to analgesic therapy and withdrawal of analgesia is a valid method of assessing chronic pain, particularly in patients who mask signs or whose owners have difficulty gauging chronic pain levels in pets.[39] Trials with and without analgesics must be coupled with patient-specific outcome measures to be useful.

In assessment of chronic pain or response to treatment, caregiver "placebo" effect is a frequent source of bias and must be considered when evaluating results of assessments.[33,46] The bias can originate from anyone making an assessment (veterinarian or owner). Although this is not a true placebo effect (i.e., the patient does not have a therapeutic effect from the sham treatment), it does impact therapeutic decision making and must be considered when evaluating a patient.

General Approach to the Chronic Pain Patient

Treatment of chronic pain is frequently frustrating to the veterinarian and client (and, probably, the patient). Some of the frustration stems from the limits of approaching this complex clinical problem as a succession of acute events rather than a true chronic illness. Much of the frustration can be generated from unrealistic expectation of clients. Pet owners, like chronic pain patients, frequently seek a simple medical intervention that will fix the problem and its attendant negative impacts on their quality of life. While veterinarians and physicians know this is rarely likely, they can be perceived as ineffective or uncaring when they cannot deliver immediate relief. Since chronic pain is often incurable and progressive, client education and the setting of shared goals and expectations are imperative to outcome success. Changing the paradigm of patients seeking simple symptom relief to that of shared goal setting and responsibility toward longer-term solutions is described as "goal-directed health care."[47] This approach is being used to better treat chronic pain in people and can be helpful for veterinary patients as well. The goals are identified by evaluating the impact of chronic pain on the patient and the caregiver's daily life, their relationship, and the loss of functions that are integral to the patient's well-being. Contextualizing chronic pain as part of daily life can help pinpoint what is most important to try and restore. Client questionnaires simplify the process of assessing the toll taken on daily life and the recognition of realistic goals. An example of the author's client survey can be accessed for use and adaptation at www.angell.org/painsurvey and www.angell.org/catpainsurvey (adapted

from Taylor et al.[48]). For animals with suspected chronic pain, those with chronic illnesses that may cause chronic pain, or geriatric patients, prefilled questionnaires describing functional and social behavior can improve visit efficiency and identify more chronic pain patients.

General Approach to Management of Chronic Pain

Due to the differences between distinct types of chronic pain and the importance of individual genetic phenotype and epigenetics in pain processing, there cannot be a standard formula for treatment. Effective management depends on thorough investigation of all sources of pain, since many comorbidities impact pain states.

Identification of client- and patient-specific outcome measures, derived from initial surveys and visits, are key to gauging progress or lack thereof. Having owners keep a "pain diary" or "comfort journal" consisting of four to five simple, personalized questions can be useful, particularly for those clients who have difficulty identifying changes. It can be especially useful to incorporate the personalized outcome measures in the diary (e.g., "did your pet get on their favorite chair without assistance today?"), to instruct clients to answer the questions once daily at about the same time, and to tell clients not to review the diary for several weeks at a time for best utility.

Recheck examinations, rather than phone or email updates, can identify subtle changes and allow for more accurate management plan adjustments. Accurate pain assessment is improved by having frequent reevaluations by the same observer. Recheck visits also help solidify the partnership between the caregiver and the veterinarian in the goal-directed health care approach.

Multimodal treatment plans and the use of nontraditional analgesics and nonpharmacologic therapies are generally required for successful treatment of significant chronic pain.[5,41,49] Identifying the type(s) and/or source of pain can allow for more precise matching of appropriate treatment strategies.[50] The clinician should recognize that chronic pain states often consist of several types of pain and as disease progresses, the source of pain can change.

The pathophysiology and management of degenerative joint disease has rightly received a great deal of attention, as it is probably the most common cause of chronic pain in veterinary patients.[30,41,51] The reader is referred to ch. 353 and 355 for additional information on this important subject.

Chronic pain can be categorized as inflammatory somatic pain, visceral pain, and neuropathic pain.[52] While inflammatory somatic pain, like pain associated with degenerative joint disease and chronic otitis externa, are familiar and often easily appreciated, visceral and neuropathic pain can be more nebulous. Visceral or neuropathic pain is often episodic and spontaneous, and its signs might not be elicited on palpation.[52] Visceral pain feels diffuse and is difficult to localize even when self-reported.[53] Referred pain is visceral pain that is felt at a somatic location near or distant from the source. Visceral pain, referred or not, can correlate poorly with visceral injury.[53] Chronic visceral and neuropathic pain can be challenging to diagnose and treat, but attention to them can improve outcome in chronic illness that fails to response to therapies only aimed at curing the inciting cause.

Cancer pain etiology is different and often more complex than other types of pain. The specific sources and mechanisms of pain generation morph during the course of cancer proliferation, invasion and metastasis; accordingly, pain management must be adjusted while the disease course is changing.[54] Within the cancer microenvironment, mediators are released that directly stimulate primary nociceptors and indirectly cause increased release of nociceptive mediators. Some of these algogenic (pain-inducing) substances affect both cancer cells and nociceptors. This leads to profound changes in the peripheral nervous system and the CNS due to peripheral and central sensitization. In addition to the changes in the cancer microenvironment, tissue-level and systemic changes occur during invasion and metastasis.[54,55] Therefore, cancer pain can be inflammatory pain, neuropathic pain, and can occur centrally. Pain management plans must address all sources to be effective.

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SECTION XXVII

Comorbidities

OUTLINE

Chapter 357 Heart Disease and Kidney Disease
Chapter 358 Diabetes Mellitus and Corticosteroid-Responsive Disease
Chapter 359 Comorbidities Associated with Obesity
Chapter 360 Concurrent Infection and Immune Suppression

CHAPTER 357

Heart Disease and Kidney Disease

Mark A. Oyama, Shelly L. Vaden, Clarke Atkins

Overview

Cardiovascular disease and kidney disease are highly prevalent in geriatric dogs and cats. Both organ systems are closely involved in the regulation of vasomotor tone and fluid balance. In both health and disease, interaction between systems is critical in determining blood pressure and blood volume. Due to this interdependence, the diagnosis, therapy, and monitoring of animals suffering from concomitant cardiovascular and kidney disease can be challenging. In humans, the term *cardiorenal syndrome* is used to describe conditions in which dysfunction of one system leads to injury and dysfunction of the other.[1] An important facet of the cardiorenal syndrome is the "if and how": whether the close interrelationship between the two organ systems, through common pathophysiological mechanisms, impacts outcome. In people, there is increasing evidence that the "cardiorenal axis" contributes to morbidity and mortality in many types of primary cardiovascular and kidney diseases.[2-4] In 2014, The Cardiorenal Consensus Study Group brought together a group of veterinary heart and kidney specialists to develop a summary statement regarding the definition, epidemiology, pathophysiology, diagnosis, and management of cardiovascular-renal disorders (CvRDs) in veterinary patients. The content of this chapter is based largely on the deliberations and conclusions of that group.[5]

Epidemiology

CvRDs are defined as disease-, toxin-, or drug-induced structural and/or functional damage to the cardiovascular system and/or kidneys leading to disruption of normal interactions between the systems, to the ongoing detriment of one or both. CvRD includes instances wherein primary disease of one organ system is believed to injure the other (e.g., systemic hypertension injuring the glomerulus), as well as instances wherein primary disease coexists in both organ systems (e.g., a cat with hypertrophic cardiomyopathy and tubulointerstitial fibrosis), complicating treatment of either condition. One should not only consider the presence of disease in either system, but the directionality of injury from the primary organ to the "bystander" organ (Box 357-1). Pathophysiological mechanisms likely important in CvRD include hemodynamic alterations, neurohormonal activation, and reactive oxygen species (Figure 357-1); however, the exact nature and existence of CvRD in veterinary patients is largely theoretical and understudied. Accordingly, a key goal of the cardiologists and nephrologists in The Cardiorenal Study Group was to foster collaborative research, based on hemodynamic homeostasis being dependent on the cooperative actions of the cardiovascular and renal systems.

Box 357-1

Potential Etiologies of Cardiovascular Renal Disorders in Dogs and Cats

Primary Cardiovascular Disease Causing Kidney Injury

- Systemic hypertension causing glomerular disease
- Systemic arterial thromboembolism causing infarction of the renal arteries
- Heartworm infection or caval disease causing glomerulonephritis
- Passive congestion of the renal vein during congestive heart failure causing worsening renal function

Primary Kidney Disease Causing Cardiac Injury

- Kidney-mediated systemic hypertension leading to increased afterload, left ventricular hypertrophy, worsening mitral or aortic insufficiency, arrhythmias, vasculopathy, or retinopathy
- Volume overload leading to congestion or systemic hypertension
- Hypokalemia or hyperkalemia leading to cardiac arrhythmias
- Reduced renal clearance of drugs (e.g., digoxin) leading to toxicosis
- Uremic hypodipsia, anorexia, or emesis leading to volume depletion and reduced cardiac output and perfusion
- Uremic pericarditis
- Activation of the renin-angiotensin-aldosterone axis leading to sodium and water retention, cardiac and vascular remodeling, or congestion
- Anemia secondary to chronic kidney disease leading to volume overload, reduced cardiac tissue oxygenation

Systemic Conditions Causing Both Cardiovascular and Kidney Injury

- Septic or neoplastic emboli leading to renal and cardiac infarction
- Gastric dilation and volvulus leading to cardiac arrhythmias and azotemia
- Infectious disease (e.g., *Trypanosoma cruzi*)
- Glycogen storage disease leading to glycogen deposition in the kidneys and heart
- Amyloidosis leading to amyloid deposition in the kidney and cardiac tissues

Adapted from Pouchelon JL, Atkins CE, Bussadori C, et al: Cardiovascular-renal axis disorders in the domestic dog and cat: a veterinary consensus statement. *J Small Anim Pract* 56(9):537-552, 2015.

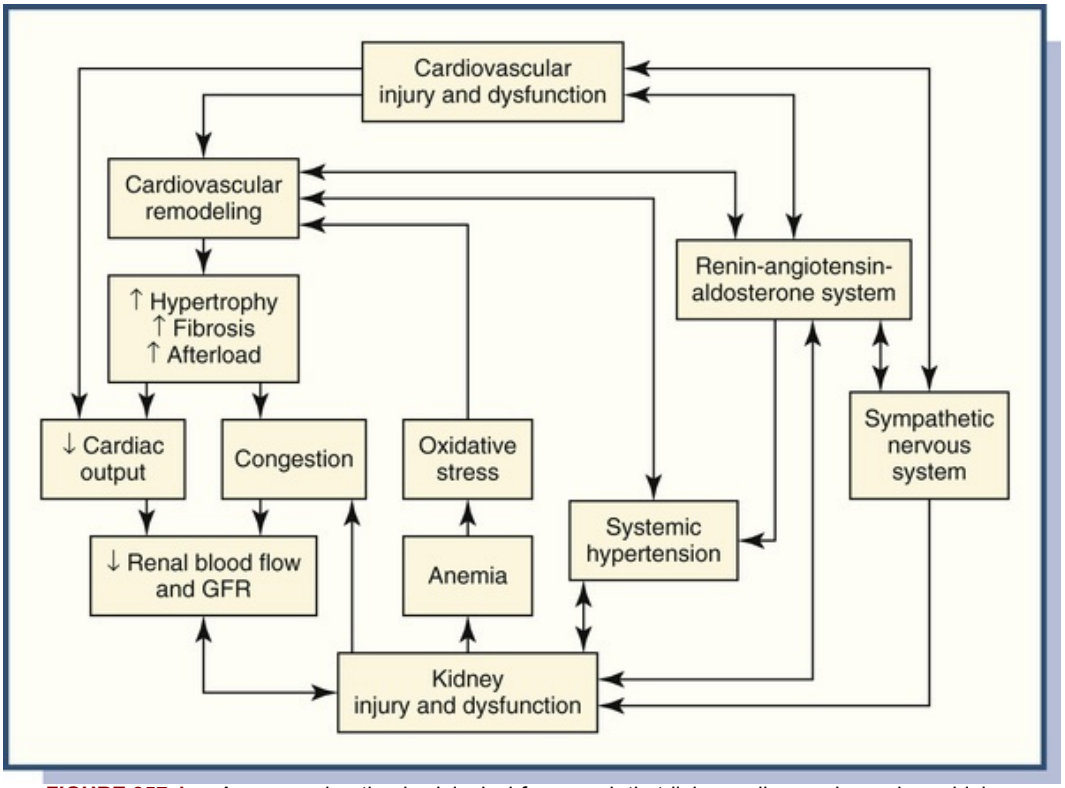

FIGURE 357-1 A proposed pathophysiological framework that links cardiovascular and renal injury and dysfunction in dogs and cats. Injury to the cardiovascular system, kidney, or both potentially causes activation of neurohormonal systems, pathological cardiac remodeling, decreased cardiac function and output, congestion, poor renal blood flow, oxidative stress, and dysregulation of vascular tone. Ultimately, progressive deterioration of either or both systems results. These interconnected and complex series of events require careful consideration when treating disease of each organ system. *GFR,* Glomerular filtration rate. (Adapted from Pouchelon JL, Atkins CE, Bussadori C, et al:

Pathophysiology

There exist both known and suspected adverse effects of kidney disease on the cardiovascular system. These involve electrolyte abnormalities (e.g., hyperkalemia [hyperK]), toxicoses involving drugs primarily cleared by the kidneys (e.g., digoxin, enalapril), volume depletion, volume overload, and systemic hypertension. Likewise, known and suspected adverse effects of cardiovascular disease on kidney function include decreased renal perfusion, activation of neurohormonal systems such as the renin-angiotensin-aldosterone (RAAS) and sympathetic nervous systems, generation of reactive oxygen species by injured endothelial tissue, and passive venous congestion of the kidneys. Some of these effects can be further heightened by administration of diuretics used to treat congestive heart failure (CHF; see ch. 247). For instance, mild acute kidney injury (AKI; see ch. 322), defined as a creatinine concentration >1.6 g/dL (>1.7 to 2.5 [>141 mcmol/L; 142 to 220]) is commonly documented in dogs or cats treated for CHF.[6] Many clinicians, when managing CHF, disregard these elevations as clinically insignificant, yet, regardless of whether transient or permanent, mild AKI may lead to permanent structural damage to the kidneys and worsen outcome. In addition to primary disease of the heart or kidney, CvRD also encompasses conditions outside these systems. Examples of conditions that can cause arrhythmias and/or compromised renal perfusion include sepsis, infectious disease, and gastric dilatation/volvulus.

Management of Heart and Kidney Disease

Heart

Clinical diagnosis, staging, and management of CHF, AKI, and chronic kidney disease (CKD), as separate entities, have been extensively described.[7-9] In brief, heart failure is the condition wherein the diseased heart fails to provide adequate cardiac output or can only do so in the presence of elevated venous filling pressures and risk of congestion (see ch. 246). Treatment involves the use of diuretics, such as furosemide; vasodilators, including angiotensin-converting enzyme inhibitors (ACEIs) such as enalapril or benazepril, and agents such as amlodipine, nitroglycerin, and nitroprusside; neurohormonal blocking agents, including ACEIs, spironolactone, and beta-adrenergic blockers; and positive inotropes such as digoxin, dobutamine, and pimobendan.

Kidneys

AKI (see ch. 322) and CKD (see ch. 324) are conditions wherein diseased kidneys fail to adequately excrete waste products or maintain fluid volume and electrolyte balance. The resulting azotemia, volume alterations, electrolyte abnormalities, and clinical signs of uremia ensue as failure progresses. Treatment may involve the use of parenteral fluids, arterial vasodilators, ACEIs, gastrointestinal protectants, alkalizing and erythropoiesis-stimulating agents, phosphate binders, and dietary modification. Diuretics may be indicated when there is oliguria, volume overload, or hyperK. Relative to this discussion, once disease is present and therapy started, assessment of organ function can be complicated by azotemia that can develop in animals given diuretics or ACEI, as well as those with heart disease and CHF when given fluids.

Treatment of Concomitant Conditions

Overview

A critical aspect of treating either cardiovascular or kidney disease is the requirement to restore and maintain normal fluid homeostasis. AKI and CKD require adequate intravascular volume and pressure for sufficient renal perfusion while avoiding fluid overload and electrolyte imbalances. CHF requires reduction of intravascular volume and hydrostatic pressure through use of diuretics and other preload-reducing therapies. Treatment of CvRD is quite challenging because dogs or cats with advanced kidney disease commonly require fluid replacement therapy to restore perfusion while animals with CHF commonly need diuretic therapy to alleviate congestion (i.e., pulmonary edema or third space effusions). Reduction in vascular volume in cases of CHF or an increase in vascular volume in cases of oliguric kidney disease can lead to adverse effects in the other organ system. Evidence-based guidelines for the recognition and treatment of

CvRD are lacking. The study group's management recommendations are based, primarily, on theory and expert opinion.

Management of Cardiovascular Disease in Consideration of the Kidney

In patients with CHF, relief of congestion should be performed using the lowest necessary dosage of diuretics, particularly after the acute rescue phase. Overzealous diuresis can lead to volume depletion and adverse effects on renal perfusion and function. Strategies to lower incidence of kidney injury include reducing the daily dose of diuretics while augmenting forward cardiac output with inotropic drugs such as pimobendan or dobutamine. A minority of clinicians elect to delay administration of ACEI in acute CHF, due to perceived risk of ACEI-mediated renal injury in the presence of aggressive parenteral diuretic use. One potential strategy, considered by the study group, is to introduce ACEI at the lower end of the recommended dosage range and titrate upwards as kidney function and hydration status permits. Most clinicians recommend *ad libitum* availability of water during diuresis for CHF, as restriction can lead to overly severe volume contraction. In instances of severe volume depletion following diuretic therapy, careful rehydration with attention to sodium (Na) and potassium (K) concentrations using IV, SC, or orogastric fluids is considered. The use of feeding tubes (see ch. 82) should be considered in anorexic animals to provide both nutrition and Na-reduced hydration (see ch. 177 and 189).

Management of Kidney Disease in Consideration of the Heart

AKI, CKD, or a combination typically requires correction of abnormal fluid and electrolyte balance to improve renal function but increases risk of heart failure in animals with preexisting cardiac disease. Fluid therapy, diuretics, and antihypertensive agents should be administered based on hydration status and systemic blood pressure. The goals are to restore and maintain normal fluid balance and blood pressure while avoiding Na or fluid overload. In animals with significant volume depletion and no evidence of CHF, parenteral fluid replacement is commonly given to restore fluid and electrolyte homeostasis and to increase urine production. Patients with AKI and oligoanuria are often prescribed diuretics, despite no evidence of any reduction in morbidity or mortality. A cautious and stepwise approach to fluid replacement and maintenance fluid therapy is recommended for dogs and cats with or at risk for congestion. Low-Na fluids, such as Normosol M or 0.18% NaCl in 1.5% or 4% dextrose, are administered while monitoring body weight, respiratory rate and effort, and arterial blood pressure, as well as being observant for jugular venous distension and/or ascites.

Fluid and drug needs must be continually assessed in order to avoid congestion. Even in the absence of clinical signs of CHF, fluid supplementation should be closely monitored and discontinued if weight gain becomes excessive. In instances where signs of overhydration and congestion occur, fluid administration should be discontinued and diuretic therapy considered. Resting or sleeping (i.e., nonpanting) respiratory rates >40 breaths per minute are a sensitive indicator of early pulmonary edema. In patients with preexisting cardiac disease or in those receiving large doses of fluids, volume expansion puts additional stress on the cardiovascular system and heightens risk of congestion. Except in cases of systemic hypotension, dopamine is not indicated for management of patients with kidney disease because of the lack of proven efficacy and potential for adverse cardiac side effects, such as arrhythmias and sinus tachycardia. Renal replacement therapies, such as hemodialysis (see ch. 110), allow for better control of blood volume. Their role in the management of patients with CvRD warrants study.

General Considerations for Management of CvRD

Systemic Hypertension

Systemic hypertension, by virtue of its ability to cause both cardiac and kidney injury, is a leading cause of cardiorenal disorders in humans and is an important and likely underdiagnosed problem in dogs and cats. The detection and management of systemic hypertension is the subject of several comprehensive reviews,[10-12] as well as chapters in this textbook (see ch. 99, 157, and 158). In brief, accurate measurement of systolic blood pressure requires close attention to equipment and technique. Chronic treatment typically involves calcium-channel blockers (i.e., amlodipine) and ACEI (i.e., benazepril, enalapril) as first-line agents in cats and dogs, respectively. Other antihypertensive drugs, such as diuretics and beta-adrenergic blockers, are used as needed. The authors commonly recommend that cats with systemic hypertension receive combination therapy with both amlodipine and ACEI. In dogs and cats with CvRD, the goal is to maintain normal systolic

blood pressure between 120 and 160 mm Hg, preventing or minimizing hypertensive target organ damage. Typical target organs include the eyes, brain, vasculature, heart, and kidneys. As blood pressure increases above 160 mm Hg, potential for target organ damage increases and antihypertensive treatment is recommended, regardless of evidence for target organ damage. In both dogs and cats, moderate dietary Na restriction is recommended along with concurrent pharmacological therapy (see ch. 183 and 184).

Fluids, Diuretics, Cardiac, and Other Drugs

Animals with CvRD are less likely to be tolerant of extreme changes to volume status (see ch. 129). As such, dosages of diuretics, ACEI, inotropes and/or fluids should be carefully tailored to the needs of the patient, particularly considering body weight, each drug's elimination method, and relative severity of renal and cardiac function. Change in diuretics or fluids (type or dosage) are performed in a stepwise manner, with concurrent monitoring of hydration status, body weight, renal function, blood pressure, and resting heart and respiratory rates. When pets with AKI or CKD require volume expansion, fluid administration should be performed with caution. Low-Na parenteral fluids or Na-reduced enteral hydration via feeding tube should be used. However, any fluid type can precipitate CHF or a hypertensive crisis if saline content is high, if the fluids are administered too rapidly or if excessive volumes are given.

During treatment, the veterinary team members and/or owners should monitor the animals' renal function, respiratory rate and effort, food and water intake, body weight, and urine output. Ideally, within the first 3 to 5 days following any dosage adjustment, renal function, body weight, hydration, electrolyte status, and systemic blood pressure should be reassessed. Change in any parameter may signal changing disease status but could also indicate a change in hydration status and need for medication adjustment. In instances of severe CvRD, in which treatment balance is difficult to achieve, referral to a secondary or tertiary hospital should be considered. Ideally, a cardiologist and internist/nephrologist would jointly formulate diagnostic and treatment plans in patients with CvRD.

Drug Pharmacokinetics and Pharmacodynamics

Drug pharmacokinetic and pharmacodynamic properties can be altered in patients with impaired heart or kidney function. For example, decreased renal perfusion and/or tubular injury decrease active secretion of furosemide across proximal renal tubule cells, thereby decreasing furosemide concentration in the tubular lumen, binding to Na/Cl co-transporters, and expected diuretic response. Many commonly prescribed cardiovascular drugs, such as digoxin, enalapril and atenolol, are primarily excreted by the kidneys and may require dosage reduction in animals with AKI or CKD. Patients with CvRD may have metabolic acidosis or hypoalbuminemia. Dosages of drugs that are highly protein bound (e.g., pimobendan or digoxin) or altered by decreased pH may need to be adjusted. In animals with persistent third-space effusions, presence of ascites or pleural effusion will alter the volume of drug distribution, and drug dosing must then be performed on estimates of lean body weight to avoid overdosing.

Nutritional Support

Ensuring proper nutrition is an important component of managing CvRD (see ch. 183, and 184). The appetite and nutritional needs of the patient should be monitored, with consideration given to feeding a reduced Na and phosphate (PO_4) diet, while providing appropriate protein and caloric intake. Severe protein restriction, occasionally prescribed in animals with severe kidney disease, can contribute to cardiac cachexia in patients with coexisting heart disease (see ch. 177). The development of cardiac cachexia often necessitates a reduction in dosage, as the drug's volume of distribution or protein binding may be altered. Diets that are moderately Na-restricted are appropriate for animals with either kidney or cardiovascular disease. Severe Na restriction can lead to poor caloric intake due to decreased diet palatability or can contribute to dilutional hyponatremia in animals with severe heart failure. Animals with kidney disease may benefit from additional changes in nutrient content including, but not limited to, altering PO_4 and fatty acid content. As previously mentioned, dogs with end-stage heart disease typically lose muscle mass and body condition. Therefore, maintaining adequate protein and caloric intake is an important nutritional goal, and in animals with CvRD, these needs must be weighted against protein and PO_4 intake contributing to azotemia, progressive kidney injury, and clinical signs of uremia. Careful dietary planning, potentially in consultation with a veterinary nutritionist, is recommended.

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CHAPTER 358

Diabetes Mellitus and Corticosteroid-Responsive Disease

Lucy J. Davison

Client Information Sheet: Diabetes Mellitus and Corticosteroid-Responsive Disease

The Dilemma

Corticosteroids have a wide range of indications for use in veterinary medicine (Table 358-1). Dogs (see ch. 304) and cats (see ch. 305) affected with diabetes mellitus (DM) commonly suffer from concurrent diseases, which might benefit from corticosteroid treatment; however, this situation leaves the clinician with a dilemma: Anticipated benefits of corticosteroid treatment must be carefully weighed against their potential detrimental effects on glycemic control such as profound insulin resistance. Further, an asymptomatic pre-diabetic pet may develop overt DM once treated with corticosteroids. This chapter reviews the topic of corticosteroid treatment in pre-diabetic and diabetic patients, including discussion of the associated risks and side effects, clinical decision making and potential alternative options for specific indications.

TABLE 358-1

Common Indications for Steroid Therapy and Possible Steroid Alternative or Steroid-Sparing Treatments That May Be Considered

SPECIALTY	CONDITION	USUAL INITIAL DOSAGE	CHRONICITY	POTENTIAL ALTERNATIVE TO ORAL STEROIDS OR POSSIBLE ADDITIONAL STEROID-SPARING MEDICATION
Dermatology	Urticaria (C, D)	Anti-inflammatory	Days	Antihistamines, topical steroid if localized
	Atopic dermatitis (C, D)	Anti-inflammatory	Weeks to months, possibly permanent	Cyclosporine,70 essential fatty acids,71 oclacitinib,70,72 immunotherapy
	Autoimmune diseases (e.g., pemphigus) (C, D)	Immunosuppressive	Weeks to months, possibly permanent	Cyclosporine73 ± azathioprine74 (D only), topical tacrolimus (D)75
Endocrinology	Primary hypoadrenocorticism (C, D)	Physiologic	Permanent	None but use lowest possible daily dose. Consider desoxycorticosterone plus a glucocorticoid76 if fludrocortisone impacting glycemic control via its glucocorticoid action.
	Atypical hypoadrenocorticism (cortisol deficiency) (C, D)	Physiologic	Permanent	None but use lowest possible daily dose
	Hypoadrenocorticism	Physiologic	Permanent	None but use lowest possible daily dose

	secondary to pituitary surgery (C, D)			
Gastroenterology	Inflammatory bowel disease (C, D)	Anti-inflammatory	Weeks to months, possibly permanent	Cyclosporine,77 dietary management, azathioprine (D only), chlorambucil78,79), budesonide,7 metronidazole
	Immune-mediated cholangitis, cholangiohepatitis or hepatitis (C, D)	Immunosuppressive	Weeks to months, possibly permanent	Cyclosporine, chlorambucil, budesonide, metronidazole
	Chronic pancreatitis (C)	Anti-inflammatory	Days	Dietary management, supportive care, antiemetics, antibiotics and analgesia64
Hematology	Immune-mediated hemolytic anemia (C, D)	Immunosuppressive	Weeks to months, possibly permanent	Intravenous gamma globulin and leflunomide80 (D only), cyclosporine, mycophenolate mofetil,81 splenectomy82
	Immune-mediated thrombocytopenia (mostly D)	Immunosuppressive	Weeks to months, possibly permanent	Intravenous gamma globulin and leflunomide80 (D only), cyclosporine
Orthopedic disease	Immune-mediated polyarthritis (mostly D)	Immunosuppressive	Weeks to months, possibly permanent	Cyclosporine (± nonsteroidal anti-inflammatories) or use of a second immunosuppressive to minimize steroid dose or leflunomide83
Cardiovascular system	Vasculitis (C, D)	Immunosuppressive	Weeks to months, possibly permanent	Alternative or steroid-sparing immunosuppressive drugs84 (e.g., cyclosporine85)
Neurologic system	Steroid-responsive meningitis and arteritis (mostly D)	Immunosuppressive	Weeks to months, possibly permanent	Low-dose nonsteroidal anti-inflammatory drug may be appropriate in mild cases86
	Brain neoplasia (C, D)	Anti-inflammatory	Potentially permanent if tolerated	Low-dose steroid may be preferable to surgery or euthanasia
Respiratory system	Asthma (C)	Anti-inflammatory	Weeks to months, possibly permanent	Inhaled steroids (e.g., budesonide,9 fluticasone), bronchodilators, cyclosporine87
	Eosinophilic bronchopneumopathy (D)	Anti-inflammatory	Weeks to months, possibly permanent	Inhaled steroid therapy8 (e.g., fluticasone)
	Secondary complications of parasitic disease (mostly D)	Anti-inflammatory	Days to weeks	Low-dose steroid may be preferable to the inflammation associated with severe parasitic disease
	Allergic rhinitis (mostly D)	Anti-inflammatory	Weeks to months, possibly permanent	Inhaled, nebulized or nasal drop steroids, or nonsteroidal anti-inflammatory with doxycycline88 (D)
	Chronic bronchitis (mostly D)	Anti-inflammatory	Weeks to months, possibly permanent	Inhaled steroid,8 bronchodilators

Ophthalmology	Uveitis (C, D)	Anti-inflammatory	Days to weeks	Topical steroid drops or consider systemic immunosuppression if appropriate
Renal	Glomerulonephritis (C, D)	Immunosuppressive	Weeks to months, possibly permanent	Mycophenolate mofetil,89 cyclosporine
Immunology	Anaphylaxis (C, D)	Anti-inflammatory	Days	Steroid treatment may be required as a lifesaving measure ± epinephrine
	Drug allergy (C, D)	Anti-inflammatory	Days	Dependent on the drug that has triggered the reaction, nonsteroidal anti-inflammatory or antihistamine may be appropriate in milder cases
	Chronic gingivostomatitis syndrome (C)	Anti-inflammatory or immunosuppressive	Months	Recombinant interferon omega90
Oncology	Chemotherapy protocols (C, D)	Anti-inflammatory	Permanent if tolerated in some cases	Steroid-sparing or steroid-free protocols (e.g., single agent doxorubicin for lymphoma91 [D]), Lomustine,92 or exclusion of prednisolone from the protocol

C, Cat; *D*, dog.

Corticosteroid Medications

Actions

Corticosteroids are synthetic analogues of the natural adrenocortical hormones (e.g., cortisol) and can have both glucocorticoid and mineralocorticoid activities.[1] *Glucocorticoid actions* include effects on carbohydrate, protein, and fat metabolism; insulin antagonism; and dose-dependent anti-inflammatory, immunosuppressive, vasoconstrictive and antineoplastic properties (see ch. 164 and 165). *Mineralocorticoid activity* mimics naturally occurring aldosterone and impacts electrolyte and water balance in the renal tubules, primarily leading to sodium and water retention with potassium loss (see ch. 67 and 68).

When treating DM, it is often the glucocorticoid-associated insulin antagonism that is most challenging to overcome because of its impact on glycemic control and appetite. Glucocorticoid receptors are widely expressed in the cytosol, and steroid therapy affects many body systems.[2] Glucocorticoids alter the expression of many anti-inflammatory and pro-inflammatory genes. Their overall effect is to reduce inflammatory and immune responses, making them the treatment of choice in many immune-mediated and inflammatory conditions (see ch. 198 and 201-204).[3] In addition to their effects on the immune system, corticosteroids also affect metabolism with a net effect of raising blood glucose concentration.[4,5] Glucocorticoids stimulate gluconeogenesis in the liver by increasing the expression of the enzymes involved in generating glucose from amino acids and glycerol.[4,6] They promote lipolysis, stimulate amino acid mobilization from tissues, and antagonize effects of insulin, inhibiting uptake of glucose into cells. In a healthy animal corticosteroid-induced, reduced peripheral insulin sensitivity is balanced by increased beta cell function. Hyperglycemia occurs if this compensation is not fully effective but this may be particularly problematic in diabetic or pre-diabetic patients.[2]

Compounds

Corticosteroid compounds have variable glucocorticoid to mineralocorticoid activity ratios, side effects, potencies and durations of action (Table 358-2). Some are predominantly glucocorticoid and others predominantly mineralocorticoid.[6]

TABLE 358-2

Comparison of Glucocorticoid and Mineralocorticoid Activities of Different Corticosteroid Drugs

DRUG	GLUCOCORTICOID PROPERTIES	MINERALOCORTICOID PROPERTIES	GENERAL THERAPEUTIC INDICATION
Glucocorticoids			
Hydrocortisone (S)	1	1	Relatively high mineralocorticoid activity makes it unsuitable for long-term use.
Cortisone (S)	0.8	0.8	Similar to hydrocortisone.
Prednisolone (I)	4	0.8	High glucocorticoid activity makes it useful for long-term treatment and as an anti-inflammatory and immunosuppressant.
Methylprednisolone (I)	5	Minimal	Anti-inflammatory and immunosuppressive.
Dexamethasone (L)	30	Minimal	Anti-inflammatory and immunosuppressive, used especially when water retention is undesirable as it has insignificant mineralocorticoid activity. Long duration of action makes it useful in some conditions.
Betamethasone (L)	30	Negligible	Anti-inflammatory and immunosuppressive, used especially when water retention is undesirable as it has insignificant mineralocorticoid activity. Long duration of action makes it useful in some conditions.
Mineralocorticoids			
Aldosterone	None	500	Useful in mineralocorticoid deficiency. No glucocorticoid activity, so not useful as anti-inflammatory or immunosuppressant.
Fludrocortisone	15	150	Useful in mineralocorticoid deficiency. Very low glucocorticoid activity, so not useful as anti-inflammatory or immunosuppressant.

I, Intermediate acting, biological half-life 18-36 hours; *L*, long acting, biological half-life 36-54 hours; *S*, short acting, biological half-life 8-12 hours.

Adapted from http://cks.nice.org.uk/corticosteroids-oral#!scenario.

Topical and Inhaled

In addition to parenteral formulations, some topical (eye, ear, skin) and inhalant medications contain anti-inflammatory doses of glucocorticoid. Since corticosteroids are generally metabolized by the hepatic p450 system, topical application bypasses the liver and its first pass effect, minimizing doses required and associated side effects.[6] Other steroid preparations include budesonide, a glucocorticoid designed for humans with Crohn's disease, which undergoes extensive first-pass hepatic metabolism resulting in local intestinal effects and, theoretically, avoiding systemic effects.[7] Fluticasone and budesonide may be used as inhaled forms for some respiratory diseases, but systemic effects have been demonstrated in cats and people, potentially having negative impact on glycemic control (see ch. 241).[8-11]

Oral and Injectable

Prednisolone is commonly used because of its high glucocorticoid to mineralocorticoid activity ratio. Prednisone is similar to prednisolone but less well absorbed orally in cats.[12] Dexamethasone has a similar glucocorticoid/mineralocorticoid ratio to prednisolone but is more potent, can be given orally or parenterally, and has a longer duration of activity. Cortisone and hydrocortisone are less potent glucocorticoids, although their relatively high mineralocorticoid activity can be of benefit in treating hypoadrenocorticism. The most commonly used oral mineralocorticoid drug is fludrocortisone, which is prescribed for hypoadrenocorticism. Although high dosages may result in signs of glucocorticoid excess, hyperglycemia is rare. The other major side effect of mineralocorticoid drugs (including desoxycorticosterone pivalate, which does not have any glucocorticoid activity) is potassium wasting. Therefore, it is important that electrolytes be monitored, especially in DM, where insulin may also reduce serum potassium.

Side Effects and Risks of Steroid Therapy in Diabetes Mellitus

Prior to making any recommendations regarding corticosteroid treatment in diabetic dogs and cats, it is necessary to review the pathogenesis of diabetes in these species and the side effects of steroid therapy (see ch. 304 and 305).

Canine Diabetes and Its Management

In dogs, DM (see ch. 304) is almost always a disease of total insulin deficiency and hence an insulin-dependent condition, with some similarities in its management to human type 1 DM.[13] DM is most commonly diagnosed in dogs older than 7 years of age, and most patients respond best to twice-daily insulin injections combined with a careful feeding and exercise routine to achieve glycemic control.[14] Unlike cats, diabetic dogs do not tend to have periods of diabetic remission, nor is there convincing evidence that obesity contributes to DM risk, although it can contribute to insulin resistance.[15-17] The underlying causes of insulin deficiency are heterogeneous in dogs, including exocrine pancreatic inflammation (acute or chronic pancreatitis), islet exhaustion as a result of chronic insulin resistance (e.g., hyperadrenocorticism, diestrus DM in females), and possible autoimmunity.[18,19] Reversible canine DM may occur in specific situations in which a syndrome of insulin resistance (such as pyometra) can be treated by ovariohysterectomy in a timely manner.[20] In general, however, DM in dogs is irreversible. Risk factors for DM in dogs include genetic factors, demonstrated by an increased prevalence in certain breeds (e.g., Samoyed, Tibetan Terrier, Miniature Poodle), as well as a greater risk in dogs with a history of pancreatitis, entire females, pregnant females and dogs with hyperadrenocorticism.[14,21-24] It may be prudent to avoid corticosteroid therapy in dogs with known DM risk factors, as they may already be pre-diabetic.

Feline Diabetes and Its Management

Feline DM (see ch. 305) shares many features with human type 2 DM, which is usually characterized by insulin resistance rather than deficiency.[13] In addition to breed-related risk factors (e.g., Burmese cats), obesity and inactivity increase risk of feline DM.[25] Most cats with acromegaly[26] (excess growth hormone secretion from a pituitary macroadenoma) and most with hyperadrenocorticism[27] have DM. Cats with acute or chronic pancreatitis are at increased risk of developing DM. Unlike dogs, there is no evidence for autoimmune DM in cats. Diabetic cats also often have some pancreatic beta cell function at the time of diagnosis.[25] The choice of therapy depends on blood glucose, clinical signs and underlying cause of insulin resistance. In some cases, mild disease can be managed with weight loss, a reduced carbohydrate diet and/or oral hypoglycemic medication. Increasingly, insulin therapy is employed early in the course of disease to try to achieve a period of DM remission.[28,29] Remission is possible in many cats with DM, even those with a history of diabetic ketoacidosis or pancreatitis at the time of diagnosis, but is less likely in cats with acromegaly or hyperadrenocorticism, particularly without specific treatment of the underlying condition.[30] Clinicians should avoid steroid use in normoglycemic cats with a history of DM, since they are likely to have reduced insulin sensitivity. Similarly, it is wise to avoid corticosteroid therapy where possible in non-diabetic cats with known risk factors, especially obesity and/or inactivity, since they may already be pre-diabetic.[31]

General Side Effects of Steroid Therapy

Corticosteroid therapy is associated with a range of potential side effects, even in healthy pets. The risk of side effects increases with dose and duration of treatment, and side effects are highly variable among individual patients receiving similar dosages, possibly due to variability in numbers of glucocorticoid receptors.[3] Dogs appear to suffer more steroid side effects than do cats. Cats may be more tolerant of higher dosages, although risk of DM being induced by corticosteroids may be higher in cats. It is also likely that very young and very old patients may be more susceptible to steroid side effects. Certain medications may also interact with glucocorticoids (e.g., ketoconazole [may decrease glucocorticoid metabolism], digoxin [may result in hypokalemia if given with prednisolone]), and thus concurrent treatments may increase risk of detrimental effects from corticosteroid therapy.

With long-term glucocorticoid use, especially at high dosages, dogs and cats may develop classic clinical signs of hyperadrenocorticism: abdominal enlargement, muscle wasting, polyphagia, bilaterally symmetric alopecia, polyuria, and polydipsia. Other potential side effects in addition to insulin resistance–induced

hyperglycemia include osteoporosis, destabilization of cardiovascular disease, hypertension, hyperlipidemia, muscle wasting, proteinuria, a hypercoagulable state and increased susceptibility to opportunistic infections (especially bacterial, fungal and yeast infections).[32]

Side Effects of Steroid Therapy in Patients with Diabetes Mellitus

Virtually all the steroid side effects discussed earlier are undesirable in DM, especially insulin resistance. Indeed, there is potential for certain steroid side effects to be more common or severe in DM, for several reasons. Firstly, the majority of DM dogs[22] and cats[33] are middle-aged or older, so they are more likely to have preexisting conditions (e.g., renal or cardiac disease that may be exacerbated by steroid therapy). Secondly, there is also considerable overlap in the clinical signs of DM and the side effects of steroid therapy (e.g., polyuria, polydipsia, polyphagia, liver enlargement, panting, weakness), some of which may be exacerbated by steroid treatment (e.g., polydipsia). In addition, since diabetic pets are at increased risk of infection[22,34] due to persistent hyperglycemia, employing steroids will exacerbate this risk via immune suppression. Furthermore, the insulin resistance as a consequence of infection may complicate things further. Although some effects of initiating corticosteroid treatment may be predictable and dose-dependent, the response of the DM patient depends on a range of individual factors, including presence of preexisting insulin resistance syndromes (e.g., acromegaly in cats; diestrus in dogs), the presence of infection or inflammatory disease and the current degree of glycemic control.[3] Corticosteroid-induced insulin resistance without adequate adjustments in insulin therapy may have catastrophic consequences, including the development of diabetic ketoacidosis or nonketotic hyperosmolar syndrome (see ch. 142). Conversely, overzealous increases in insulin dosage anticipating insulin resistance due to corticosteroid treatment may lead to dangerous hypoglycemic episodes and must also be avoided.

Decision Making in Treating Corticosteroid-Responsive Disease in Diabetic Patients

Overview

The decision to use corticosteroid-based medications in DM patients is challenging. Risks must be weighed against benefits (Figure 358-1). Corticosteroids are preferred to other drugs in many allergic, inflammatory and autoimmune conditions because of their effectiveness; their rapid action; and clinician familiarity with these drugs.[3] However, DM is a complex disease to manage and if any alternative is available, it should be considered. There are some situations where no alternative to steroid therapy exists, e.g., cortisol deficiency associated with hypoadrenocorticism (see ch. 309), where a daily physiological dose of corticosteroid is vital. Topical or local (e.g., inhaled) therapy may be preferable if appropriate, since this may limit systemic side effects (see Table 358-1).

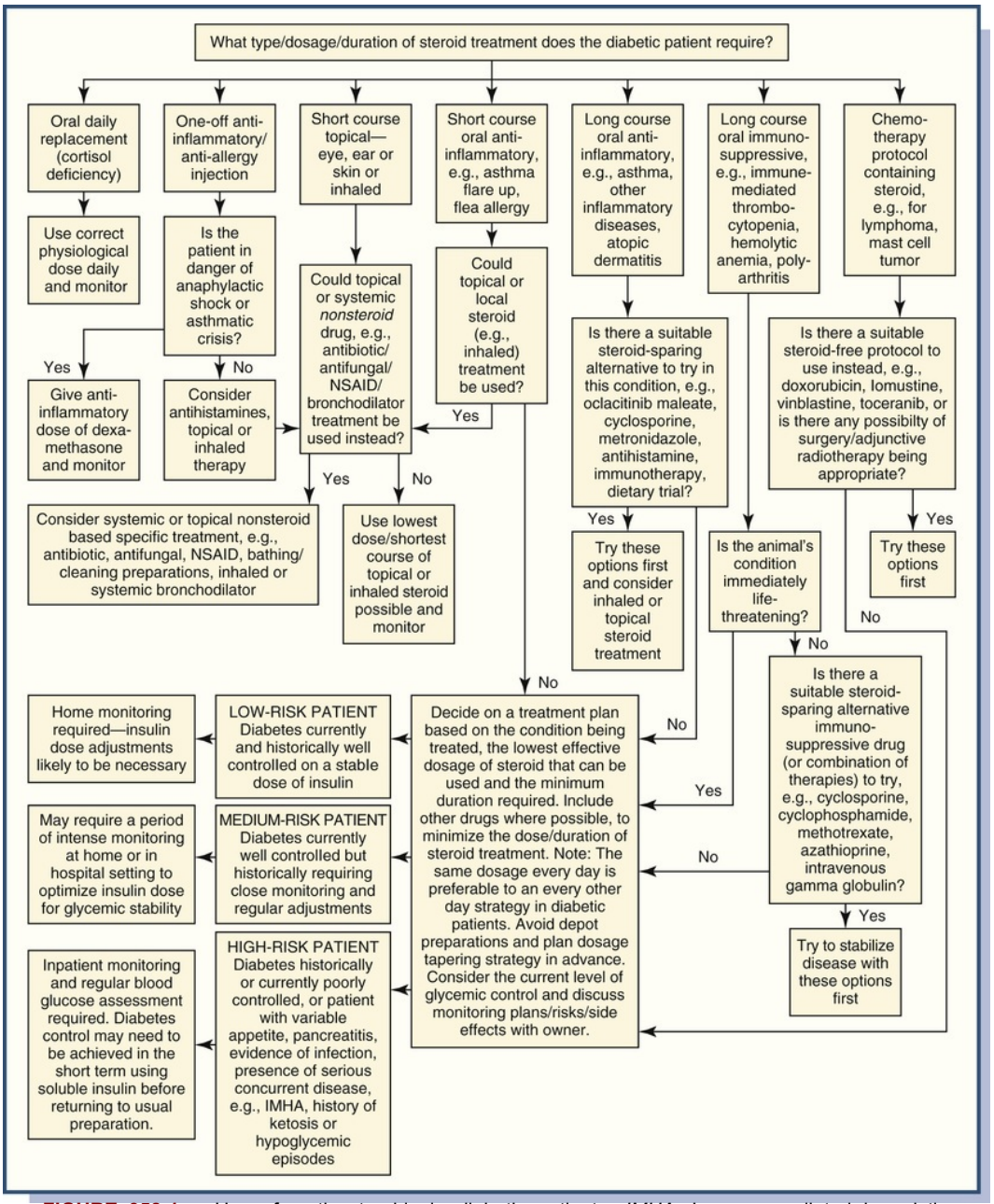

FIGURE 358-1 Use of corticosteroids in diabetic patients. *IMHA*, Immune-mediated hemolytic anemia; *NSAID*, nonsteroidal anti-inflammatory drug.

Steroid Treatment of Diabetic Humans

For type 1 and type 2 human DM patients, guidelines have been developed regarding treatment for common concurrent steroid-responsive diseases (e.g., asthma, inflammatory bowel disease or autoimmune diseases).[35] The most recent statements by the American Diabetes Association and the European Association for the Study of Diabetes emphasize the need for close monitoring and treatment targets individualized to each patient.[36] Various pre-emptive treatments may be used to stabilize blood glucose, tailored to the pharmacodynamics of the glucocorticoid employed.[37,38] No consensus on "best practice" has been developed, highlighting the difficulty in managing DM and a concurrent "steroid-responsive" condition.[39] Although there are likely to be species-specific differences between dogs, cats and humans, it is still beneficial to review the broad principles behind the human guidelines.

The effects of dexamethasone administration on blood glucose in humans occur within a few hours of administration and are dose dependent, with high-dose therapy increasing insulin resistance, characterized

by depressed peripheral utilization of glucose and impaired glucose transport in both preexisting and new-onset DM.[40,41] People with DM receiving steroid therapy more than once daily tend to be hyperglycemic throughout the day. Those receiving prednisolone only once daily, each morning, usually experience hyperglycemia in the afternoon and evening. Plasma prednisolone levels peak at 2-3 hours and return to baseline within 12 hours.[35,42] Adaptation in beta cell function to dexamethasone-induced insulin resistance is lacking in humans with low inherent insulin sensitivity.[43,44] Although dexamethasone-induced hyperinsulinemia is usually accompanied by normoglycemia at rest, the dynamic dysregulation of glucose homeostasis by steroids is emphasized by the presence of postprandial hyperglycemia in some individuals.[45] This effect of poor compensation can also be seen in obese rodent models and may be relevant to the use of corticosteroids in obese cats.[46] Such cats are already likely to have decreased insulin sensitivity and may therefore be at high risk of steroid-induced hyperglycemia and diabetes.[13]

Ulcerative colitis serves as an example of the individualized approach recommended with regard to steroid treatment of diabetic people. This first involves assessment of the DM and then assessment of risks and benefits of steroid therapy for the concurrent disease. In ulcerative colitis, decisions regarding treatment are based on activity and location of the disease.[47,48] In severe illness, the patient with *well-controlled* DM should be treated with corticosteroids. However, initiating corticosteroid treatment requires intense monitoring of blood glucose, evaluation for potential sepsis and ketoacidosis, as well as careful electrolyte control. If the ulcerative colitis patient has *unstable* DM, risk of steroid treatment is considered too high and alternative drugs are used (cyclosporine, monoclonal antibody therapy).[49] In more moderate ulcerative colitis with concurrent DM, to avoid systemic steroids, topical or oral mesalazine and topical steroid such as beclamethasone are recommended.

Evidence of Corticosteroid Impact on Glycemic Control in Cats

Immunosuppressive steroid treatment given to healthy cats resulted in significant increases in serum albumin, glucose, triglycerides and cholesterol after 56 days.[50] In a similar study, investigating the diabetogenic potential of prednisolone and dexamethasone, 14 healthy cats received daily prednisolone (4.4 mg/kg) or dexamethasone (0.55 mg/kg) for 56 days, followed by evaluation of urine glucose and serum fructosamine and glucose tolerance. At study completion, several cats were glycosuric and fructosamine concentrations were elevated. There was also a trend toward dexamethasone having more impact on blood glucose than prednisolone at "equipotent" doses.[5] In a separate study, healthy cats were treated with methylprednisolone by injection, resulting in a substantial increase in serum glucose concentration 3 to 6 days later. Variables only returned to baseline 16 to 24 days after treatment, with response kinetics varying between individuals.[51,52]

Evidence of Corticosteroid Impact on Glycemic Control in Dogs

The potential for corticosteroid therapy to impact blood glucose is illustrated clinically by two case reports of dogs with transient DM by prednisolone therapy.[53,54] Experimentally, in healthy dogs, methylprednisolone significantly enhanced gluconeogenesis and hyperglycemia induced by norepinephrine. This effect was most marked if the glucocorticoid had been given for at least 2 consecutive days prior to the epinephrine challenge, suggesting *de novo* synthesis of gluconeogenic enzymes, as well as more immediate effects.[4] Topical treatment with glucocorticoid has also been shown to impact blood glucose in dogs. Two topical dexamethasone applications (dermal and ototopical) were each associated with an exaggerated rise in insulin in beagles, despite maintenance of normal serum glucose levels.[55] Upon drug withdrawal, it took a week for insulin secretion to return to baseline. Similarly, in atopic dogs treated with prednisolone, serum fructosamine and glucose concentrations were not affected but serum insulin concentrations increased, emphasizing need for functioning and responsive beta cells to maintain euglycemia.[56] Effects of endogenous cortisol on glucose metabolism were examined in a canine DM model using an IV glucose challenge, demonstrating a tendency for glucose tolerance and insulin sensitivity to decrease after 60 minutes.[57] This emphasizes the relatively immediate impact of steroid treatment on glycemic control.

Use of Corticosteroids in Diabetic Dogs and Cats

In managing comorbidities, the optimal approach to treating combined disorders is not always the same as the sum of optimal treatments for the two disorders managed separately.[38] There is also a key difference

between canine and feline DM to consider: the question of insulin sensitivity and secretion. Diabetic dogs usually have no functional beta cells. Diabetic cats may have retained a significant number of functioning beta cells and it is important to preserve or even enhance their survival and function.[13] In some situations—life-threatening anaphylaxis as an example—immediate and short-term use of steroids takes priority over the potential impact on DM management.[3] However, in chronic immune-mediated or neoplastic diseases, consideration can be given to use of alternative immunosuppressive or chemotherapeutic drugs (see Table 358-1).[3] Alternative drugs may be used alone or in combination with lower steroid dosages to minimize impact on glycemic control. Local-acting steroid preparations may control some inflammatory conditions with fewer side effects, e.g., respiratory and inflammatory bowel diseases.[7,8]

Use of Alternatives to Corticosteroids

Importantly, some of the alternative immunosuppressive drugs also have the potential to negatively impact glycemic control or pancreatic function. For example, cyclosporine, an immunosuppressive drug used commonly in atopic disease, can increase glucose and fructosamine concentrations in dogs because of its negative effect on insulin secretion.[58] Arguably, cyclosporine has the potential to precipitate DM in dogs with impaired glucose tolerance.[59-61] It is unlikely, however, for the drug to significantly impact glycemic control of dogs already suffering from DM, as they have no functional islets. Similarly, the immunosuppressive drug azathioprine[62] (which is not recommended for cats) has been linked to the development of pancreatitis in dogs, a disease which is likely to complicate glycemic control.

Indeed, the relationship between corticosteroid treatment and pancreatitis is complex and not well characterized in either dogs or cats, although the disease is commonly associated with DM in both species (see ch. 290).[63] Some clinicians have successfully used anti-inflammatory doses of prednisolone to treat chronic pancreatitis in cats (see ch. 291), while *ex vivo* experimental evidence suggests that corticosteroids may actually have a detrimental effect on pancreas function in dogs.[65] Another option when using corticosteroids in DM, particularly cats, may be to consider the use of oral hypoglycemic drugs or insulin sensitizers such as pioglitazone, which appear to hold some promise in obese cats.[66,67] There is also potential benefit in chromium supplementation in cats with impaired glucose tolerance.[68]

Summary: Important Points When Considering Corticosteroids for Diabetic Dogs or Cats

Once the decision has been made to treat a diabetic dog or cat with corticosteroids, it is recommended that the following guidelines be considered:

1. Oral or parenteral corticosteroids should only be used where a firm diagnosis has been reached and only under careful supervision. The lowest effective dosage should be used, for the minimum period possible, avoiding the use of long-acting depot preparations.
2. The individual patient should be assessed for risk of disease exacerbation by steroid treatment. Clinicians should consider age, other comorbidities (especially infection and insulin resistance syndromes), other drug treatments (e.g., nonsteroidal anti-inflammatories) and the condition being treated.
3. The type and dose of glucocorticoid should be selected carefully and used to inform initial adjustments to the insulin regimen. Short-acting preparations are preferable.[37]
4. Although the diurnal variation in cortisol varies in dogs and little is published on the subject in cats, many veterinarians recommend dosing cats with steroids in the evening and dogs in the morning to minimize adrenal suppression.[69] Regardless of time and frequency chosen, it is important that these dosing times be adhered to in diabetic patients. This will minimize wide fluctuation in steroid concentrations and wide fluctuation in glycemic control. Once-daily dosing may be preferable to every other day protocols to make maintaining glycemic control easier (although this may lead to more adrenal suppression). In patients receiving twice-daily insulin, some clinicians elect to administer the steroid with the evening dose of insulin to minimize issues of postprandial hyperglycemia, since less food is generally consumed overnight than during the day. Alternatively, some clinicians may choose to split the daily steroid dose in two so that in each 12-hour period the patient receives the same food, the same dose of steroid and the same dose of insulin.
5. The clinician should recognize that for long-term steroid use, the insulin dosage is likely to require titration to suit the needs of the individual. Conversely, once steroid therapy is tapered, careful adjustment in insulin dosage must be made to avoid hypoglycemia.

6. Close monitoring of the patient is necessary. For low-dose steroid therapy in a stable diabetic animal, home glucose or urine monitoring to avoid profound hyperglycemia or ketosis may be appropriate, but for more severe disease or in previously unstable diabetic patients, monitoring in a hospital environment may be necessary. Close attention to blood glucose, electrolytes, pancreatitis, infection or destabilization of other diseases is required.
7. Where very high dosages of steroid are required, the patient has a poor appetite, pancreatitis or infection, consideration should be given to switching to a short-acting soluble insulin preparation during the initial phase of steroid therapy. This can be titrated more accurately according to blood glucose and appetite.
8. It is useful to provide the owner of the pet receiving treatment with a steroid information sheet (an example accompanies this chapter) to advise him or her about adverse effects and to ensure that treatment is tapered rather than stopped abruptly.

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CHAPTER 359

Comorbidities Associated with Obesity

Angela L. Witzel

Obesity rates among human beings have risen dramatically in the past 30 years and are currently at epidemic proportions.[1] While adipose tissue was once considered a metabolically inactive energy storage depot, we now know a myriad of hormones, cytokines, and inflammatory mediators are produced and disseminated from fat tissue.[2] The combinations of excess mass exerting pressure and force on the body, low-grade inflammation causing oxidative damage, and hormonal alterations leading to metabolic disruption result in obesity being associated with and progressing to a variety of diseases. This chapter reviews the veterinary and applicable human literature to discuss the conditions in which obesity plays a prominent role in disease development or progression.

Being overweight can indirectly contribute to the development of some diseases because overall health assessments are more difficult in the obese patient. For example, abdominal palpation, thoracic auscultation, blood collection, cystocentesis, palpation of peripheral lymph nodes, and diagnostic imaging are all more challenging when thick layers of fat are present.[3] As a result, diagnosis of serious diseases like cancer, chronic kidney disease, and heart valve disorders may be delayed or missed. Obesity (see ch. 176) can also increase the risks and complications associated with anesthetic procedures. Excess adipose tissue can potentially lead to reduced cardiovascular reserves, increase the risk for respiratory compromise, and slow the recovery following inhalation anesthesia due to greater drug deposition in fat tissue.[4] Consequently, the odds of anesthetic death in cats weighing more than 6 kg are nearly three times higher than the odds in cats who weigh between 2 and 6 kg.[5]

Obesity's Impact on Respiratory Disease

It has been well documented in humans that obesity negatively impacts respiratory function. The average respiratory rate of obese patients (body mass index ≥ 40 kg/m^2) is 15 to 21 compared with 10 to 12 breaths per minute in normal-weight individuals.[6] Obese patients also tend to have reduced tidal and lung volumes. Possible mechanisms for the reduction in lung volume are that abdominal fat displaces the diaphragm into the abdomen or excess fat within the chest wall compresses the thoracic cage.[7] Compliance of the respiratory system is also reduced in obese humans due to a combination of limited chest wall and lung compliance. Mild hypoxemia is a common occurrence as well and may result from microatelectasis in the lungs. Weight reduction typically reverses these respiratory changes.[6]

There is only a handful of studies evaluating obesity's contribution to respiratory disease in veterinary patients. One study documented that obese cats have reductions in tidal and minute volume and decreased peak inspiratory and expiratory flows when compared with normal-weight cats.[8] Respiratory tidal volume is also reduced in obese dogs.[9] One notable difference between dogs and cats is the effect of obesity on resting respiratory rate. Obese dogs had their mean respiratory rates increase threefold (11.41 ± 0.94 vs. 33.80 ± 7.89).[9] In contrast, the resting respiratory rates of obese cats did not differ from those in lean cats.[8] Another characteristic respiratory change in obese dogs is increased bronchoreactivity.[9] This may contribute to bronchospasm and is closely associated with asthma and chronic obstructive pulmonary disease in humans.[10]

Anecdotal reports suggest obesity contributes to the severity of certain upper airway diseases such as laryngeal paralysis and tracheal collapse in dogs and asthma in cats (see ch. 241).[11] In humans, obesity is a risk factor for obstructive sleep apnea (OSA), which is the result of pharyngeal dilator muscle relaxation and collapse of the upper airway during inspiration (see ch. 238).[12] The English Bulldog is considered a potential model for OSA.[13] While OSA can lead to hypoventilation and hypercapnia in either asleep or conscious

humans,[14] changes in $PaCO_2$ were not detected in obese dogs under heavy sedation before or after weight loss.[15] While only a few studies have evaluated the connection between obesity and respiratory disease in veterinary medicine, a strong relationship has been established in humans and obese dogs and cats are likely to have similar respiratory consequences. More research is needed to further explore the impact of obesity on respiratory diseases like asthma, OSA, laryngeal paralysis, and tracheal collapse in veterinary patients (see ch. 176, 238, 239, and 241).

Obesity's Impact on Cardiovascular Disease

The link between obesity and cardiovascular disease in humans is well established and focuses primarily on the development of ischemic heart disease and hypertension.[16,17] Obesity appears to have some influence on the development of hypertension in dogs, but the changes attributed to weight gain are mild (5 to 20 mm Hg) and unlikely to have pathologic consequences.[18-20] A consensus statement by the American College of Veterinary Internal Medicine concluded that obesity has minimal impact on the pathogenesis of canine and feline hypertension.[21]

Atherosclerosis is rare in dogs and cats and does not appear connected to obesity.[20] While obese dogs will have elevations in serum total cholesterol and triglycerides, the concentrations remain below levels expected to be atherogenic.[20,22,23] In a study comparing chronically obese cats with lean cats, total cholesterol levels were not different but triglyceride concentrations doubled (21 vs. 48 mg/dL).[24] Dogs and cats have key differences from humans that may protect them from developing atherosclerosis and myocardial infarctions. First, they have high concentrations of high-density lipoprotein (HDL) cholesterol. HDL cholesterol is important for reverse cholesterol transport, which moves cholesterol from arteries and peripheral tissues to the HDL molecules for disposal by the liver.[25] Dogs and cats also appear to lack the enzyme cholesterol ester transfer protein (CETP), which aids in reverse cholesterol transport.[26] CETP has the potential to be atherogenic by increasing the number of very-low and low-density lipoprotein (VLDL and LDL) cholesterol molecules.[25]

Although obese dogs may not have clinically significant risks of ischemic heart disease or hypertension, there are documented structural changes to the heart. Left ventricular (LV) hypertrophy occurs in obese dogs and can be corrected with weight loss.[27-29] In humans, obesity-associated LV hypertrophy is thought to be the result of mild elevations in blood pressure or secondary to chronic hypoxemia from OSA.[30]

In humans, being overweight or moderately obese is associated with increased survival rates in patients with heart failure (the "obesity paradox"; see ch. 177).[31] However, this relationship is less evident in dogs and cats. In a study of 101 cats with heart failure secondary to cardiomyopathy, there was a U-shaped association between body weight and survival time where the lightest and heaviest cats had shorter survivals compared with cats in the center of the curve.[32] While there was no significant relationship between body condition score (BCS; see ch. 2, 170, and 177) and survival, the body weight findings could suggest that cats who are mildly to moderately overweight may benefit from a protective factor.[32] In a similar study evaluating dogs with heart failure, survival time was also not correlated to BCS.[33] While there are several theories explaining why overweight humans are more likely to live longer with heart failure than lean individuals, the fact that myocardial infarctions and ischemic heart disease are the most common causes of heart failure in human means extrapolations to dogs and cats are unreliable.[31] In summary, the cardiovascular consequences of obesity in dogs and cats are not as apparent as in humans.

Obesity's Impact on Musculoskeletal and Intervertebral Disk Disease

In humans, obesity is a well-recognized risk factor for the development of knee osteoarthritis (OA).[34] The combination of increased joint load and changes in the direction of joint forces secondary to instability account for increased risk of OA development with obesity.[35] While changes in biomechanical forces contribute to OA in the knee, there are also associations between obesity and OA in non-weight-bearing joints such as the hand.[36] It is well established that obesity leads to a state of chronic low-grade inflammation. Increases in reactive oxygen species, inflammatory mediators, advanced glycosylated end products, and hormones like leptin may also contribute to the development and/or progression of OA.[37]

Results from a series of projects utilizing data from a now classic lifetime study on canine obesity have shown a direct impact of being overweight on the development and severity of osteoarthritis (see ch. 187 and

353).[38-40] Forty-eight Labrador puppies were evaluated for radiographic evidence of osteoarthritis at various time points throughout their lives. Half the puppies in the study were fed *ad libitum* for the first 3 years of life (control group), and the other half were fed 75% of the food consumed by controls (restricted group). The control group dogs had higher BCS throughout life (6.7/9 vs. 4.6/9 at age 12).[41] The dogs who were restricted in their calorie intake had a reduced prevalence and later onset of hip osteoarthritis when compared with controls (12 vs. 6 years of age).[40] Overweight dogs in the study also had increased radiographic severity of elbow and shoulder arthritis.[38,39] While the results of these studies provide clear evidence that being overweight impacts the development and progression of OA, the dogs in these studies were only mildly overweight with average body condition scores of 6.7/9 at age 12. The results would likely be more dramatic in a population of obese or morbidly obese dogs. In addition to studies showing that being overweight contributes to OA in dogs, there is also evidence that weight reduction can improve clinical signs of arthritis. Weight reduction of just over 6% resulted in decreased lameness in a study of 14 obese client-owned dogs with OA.[42]

Obesity not only affects the development of OA but is also a major contributor to other orthopedic diseases in dogs. Obese dogs are four times more likely to have a single cranial cruciate ligament rupture, and overweight dogs are almost twice as likely to have bilateral tears.[43,44] Hip dysplasia is also less likely in lean compared with overweight Labrador Retrievers.[45] The risk of developing intervertebral disk extrusion (IVDE; see ch. 266) is also increased in obese dogs of various breeds and sizes.[46] For example, Miniature Dachshunds with body conditions scores of 9/9 are about 4 times as likely to have IVDE compared with lean Dachshunds.[46]

Compared with dogs, the research connecting obesity to musculoskeletal disease in cats is sparse. In an epidemiologic study of almost 1500 cats, overweight cats were almost 5 times more likely to require veterinary care for lameness compared with ideal weight cats.[47] In a separate study of approximately 8000 cats, overweight cats had slightly higher rates of arthritis (0.4% vs. 0.3%) and obese cats had higher rates of musculoskeletal disease (0.8% vs. 0.7%) compared with ideal weight cats.[48] A prospective study of evaluating the rate of osteoarthritis in 100 cats greater than 6 years of age found no correlations between OA and BCS. However, only 14 cats in the study had a BCS greater than 6 on a 9-point scale, and none of those cats were scored a 9.[49] It is clear that more research is needed to understand the impact of being overweight or obese on musculoskeletal disease in cats.

Urinary Disease

Obesity is a systemic disease with inflammatory mediators, cytokines, and hormones that affect almost every organ, including the kidneys. In humans, obesity has been linked with higher rates of proteinuria, renal insufficiency, chronic renal failure, and mortality among dialysis patients.[50] Obese patients have higher renal plasma flow, filtration fractions, and glomerular filtration rates when compared with nonobese individuals.[51,52] In addition, renal mass and the diameter of the glomeruli also increase with weight gain.[53] Increased glomerular size without concurrent expansion of podocytes supporting the glomerular basement membrane could lead to gaps and loss in protein filtration selectivity.[50] If podocytes detach or are unable to cover the basement membrane, these areas can become denuded with subsequent glomerulosclerosis.[54] Obesity also stimulates the renin-angiotensin-aldosterone system (RAAS), leading to glomerular hypertension.[50]

In a study evaluating the incidence of proteinuria in overweight and obese dogs, there was no significant difference between dogs with body condition scores greater than or less than 6 on a 9-point scale.[55] In humans, being obese is more likely to result in renal changes than being overweight and while the data were suggestive, this study did not have enough obese dogs (n = 6 out of total n = 44) to detect significant differences in an obese subgroup.[55,56] When obese dogs were enrolled in a weight loss program, multiple markers of early renal disease improved including urine protein-creatinine ratio, urine albumin corrected by creatinine, urine specific gravity, homocysteine, cystatin C, and clusterin.[57] With the high rates of obesity and kidney disease in dogs and cats, characterizing the relationship between these diseases may lead to better treatment and prevention of chronic kidney disease.

In humans, it is well established that obesity increases the risk of kidney stone development.[58] Calcium stones make up the majority of kidney stones in humans, and obesity appears to increase oxalate and reduce calcium oxalate stone inhibitors like magnesium and citrate in the urine.[59] Associations between urinary

bladder stones and obesity in humans have not been determined, and little data are also available for dogs or cats. A recent study evaluating risk factors for calcium oxalate bladder stone development did not find dogs with higher BCS to be at increased risk.[60] An older epidemiologic study found that about 29% of dogs with urolithiasis were also overweight.[61] However, the rate of obesity in the general study population was not provided. While there is some evidence that obesity could contribute to the development of urinary tract stones in dogs, more data are needed to determine if obesity is a significant factor in disease development.

While urinary disease is abundant in felids, there are almost no data evaluating the role of obesity in renal or lower urinary tract disease in cats. Obesity appears to increase the risk of feline idiopathic cystitis (FIC) (see ch. 334).[62] However, some risk factors for FIC also predispose to obesity. For example, indoor cats are more likely to be inactive and gain weight and the lack of environmental enrichment is also thought to contribute to stress-induced cystitis.[62] A study looking for risk factors associated with the diagnosis of chronic kidney disease (CKD) in cats found an inverse relationship between BCS and disease development.[63] This study evaluated cats that were already diagnosed with CKD, and weight loss is often a manifestation of the disease. Therefore, it is difficult to determine if being overweight or obese lowers the risk of disease development, or if being thinner is just a disease sequela. In a separate study, the prevalence of urinary disease was approximately 1.5 times higher in obese and overweight cats compared with normal and underweight cats.[64] Given the clear associations between obesity and urinary disease in humans, more work needs to be done in dogs and cats to determine if epidemiologic associations translate to causative factors.

Cancer

Increased adiposity is estimated to cause approximately 20% to 35% of all human cancers.[65] In 2007, the World Cancer Research Fund found that obesity was associated with increased rates of renal carcinomas, colorectal cancer, and postmenopausal breast cancer.[66] Other meta-analyses also showed relationships between obesity and prostate, endometrial, and esophageal cancers; hematologic malignancies; malignant melanoma; and large B-cell lymphomas.[67-74] As adipose tissue expands, the adipocytes move further from the vasculature and local hypoxia of the tissue occurs.[74] This hypoxia results in low-grade, chronic inflammation as proinflammatory cytokines, such as TNF-alpha, interleukin 6, monocyte chemotactic protein, leptin, and plasminogen activator inhibitor type 1, are released.[75,76] In addition to inflammatory cytokines, the adipose stromal/stem cells (ASCs) can increase proliferation and metastasis of cancer cells. ASCs can differentiate into mesenchymal tissue and are immune privileged since they do not express MHC class II molecules. ASCs can also be recruited to tumor sites and, as in the case of breast cancer, increase the release of tumor-promoting factors.[74] The mechanisms behind obesity and cancer development are also tumor specific. For example, alterations in reproductive hormones are important factors for breast and endometrial cancers while increased insulin production is more likely to affect colon and prostate cancers.[65,77] Many other cancer types may develop secondary to inflammatory conditions.[65]

Another area of concern regarding obesity and cancer is the effect of excess body weight on chemotherapy dosage. Fears of overdosing obese patients using their current weight instead of a more ideal weight are generally considered to be unfounded in human medicine. A consensus article by the American Society of Clinical Oncology recommends dosing chemotherapeutics on current body weight or using a fixed dosage, regardless of body mass index.[78]

While there is clear evidence that obesity contributes to the development and progression of multiple cancer types in humans, there is far less evidence in dogs and cats. Overweight and obese dogs appear to have a greater risk of bladder and mammary cancers.[79-81] There are likely connections between adiposity and other tumor types in dogs and cats, but more research is needed to determine if such relationships exist.

Endocrine Disease

Since the discovery of the adipose hormone leptin in 1996, thousands of investigators have confirmed that fat tissue is an active endocrine organ. However, the goal of this section is to discuss obesity's role in the development or management of clinical endocrine disease. The quintessential obesity-related endocrine disease is type 2 diabetes mellitus (see ch. 304 and 305). It is well established that obese individuals are less sensitive to the effects of insulin in peripheral tissues like muscle, liver, and adipose. As excess free fatty acids are deposited into tissues, they disrupt insulin signaling, insulin-mediated glucose uptake, and glycogen synthesis.[82,83] As a result, glucose accumulates in the bloodstream. Prolonged hyperglycemia damages

pancreatic beta cells that secrete insulin. This damage likely results from a combination of ever-increasing insulin production and the accumulation of reactive oxygen species. Eventually beta cells become "exhausted" and hypoinsulinemia occurs.[84] Once insulin production is unable to keep up with circulating glucose levels, diabetes mellitus occurs.

Numerous studies have confirmed a direct association between obesity and type 2 diabetes mellitus in cats (see ch. 305).[85-89] Appleton et al. demonstrated that weight gain of just under 2 kg reduced insulin sensitivity by approximately 50%.[85] Obese cats are also almost four times more likely to develop diabetes mellitus compared with ideal weight cats.[47]

The association between obesity and diabetes is less clear in dogs (see ch. 304). While obesity has been shown to induce insulin resistance in dogs,[23] this does not appear to progress to type 2 diabetes, and type I diabetes is far more common.[90] There are notable differences between species that develop type 2 diabetes (humans and cats) and dogs. First, dogs do not spontaneously form aggregates of islet amyloid in their pancreas. Islet-amyloid polypeptide (IAPP) (a.k.a. amylin) is cosecreted with insulin. As insulin and IAPP production increase to combat hyperglycemia, toxic intracellular oligomers of IAPP and extracellular amyloid are deposited in the pancreas of humans and cats, but not dogs.[90] Another potentially key difference between humans, cats, and dogs is the first-phase insulin response. Despite years of obesity and documented insulin resistance, dogs still manage to secrete adequate amounts of insulin immediately following a glucose challenge.[91] Blunting of the initial insulin response to glucose in humans is considered an important marker of beta cell damage in humans.[92]

While the impairment of insulin sensitivity that accompanies obese dogs can potentially make regulation of type 1 diabetes more difficult, obesity is probably not a critical factor in disease development. With that being said, obese dogs are at a slightly higher risk of developing pancreatitis and have a higher prevalence of diabetes mellitus compared with lean dogs (0.7% vs. 0.3%).[48,93]

The relationship between obesity and other common endocrine disorders besides diabetes mellitus in dogs is also unclear. While obesity can be a side effect of hypothyroidism (see ch. 299) and hyperadrenocorticism (see ch. 306), it does not appear to be a causative factor. In humans, thyroid-stimulating hormone negatively correlates with resting energy requirements, even when serum thyroid-stimulating hormone (TSH) concentrations are within normal limits.[94] In a study evaluating hormonal function of obese dogs with no clinical signs of endocrine disease, TSH levels were elevated (>0.5 ng/mL) in 15 out of 31 dogs. Eleven out of the 15 dogs with elevated TSH also had low free T4 values. Of the 20 obese dogs that did not have a classic pattern of hypothyroidism on test results, only 13 had both normal free T4 and TSH.[95] The implications of this study are that obesity may interfere with thyroid function, but it could also be that subclinically low thyroid levels contributed to the development of obesity (see ch. 299 and 300).

Central adiposity is a hallmark of hypoadrenocorticism or Cushing's disease in both humans and dogs.[96] Treatment of the disease typically results in a loss of abdominal fat. There is little information regarding the role of obesity in the development of Cushing's disease in dogs, and excess adiposity is seen more as a side effect than a comorbidity.

Exercise-Limiting Disorders

The benefits of exercise in maintaining both physical and mental health in humans are well-established.[97] Anxiety, depression, muscle strength and flexibility, cancer, cardiovascular health, and chronic health conditions are all improved with regular physical activity.[97-100] In addition, moderate exercise and physical fitness reduce mortality rates. For example, one study showed runners with low to moderate intensity running habits had a 30% lower risk of all-cause and a 45% lower risk of cardiovascular mortality with an increased life expectancy of 3 years.[101] The Centers for Disease Control and Prevention currently recommend adults receive about 2½ hours of moderate aerobic activity combined with 2 days of weight training per week.[102]

Little work has been done in veterinary medicine to establish the health benefits and optimum levels of exercise in dogs and cats. However, studies in dogs suggest exercise can reduce noise sensitivity and separation anxiety behaviors, improve the quality of life for patients with chronic mitral valve disease, and lower body weight and BCSs.[103-106] Most of the work related to cats and exercise has focused on the negative relationship between physical activity (indoor vs. outdoor lifestyle) and BCS.[107,108]

One's ability to exercise consistently can be affected by many diseases including obesity, heart disease, respiratory disease, orthopedic pain, neurologic abnormalities, and systemic illnesses, which result in lethargy and malaise. The benefits of exercise go beyond weight management, and physical activity should be encouraged in all our veterinary patients. In addition, veterinarians should be cognizant of the barriers to exercise in our patients and help facilitate more activity. Examples include pain control for patients with orthopedic disease and weight reduction for obese animals. Given the results in humans, even low-intensity exercise is likely to provide health improvements in dogs and cats.[109,110]

Summary

Obesity is the most common form of malnutrition in dogs and cats and with prevalence rates of greater than 35%. It is one of the most common diseases found in companion animals.[48,64,111-113] The physiologic consequences of obesity are numerous and stem from combinations of inflammatory, hormonal, and mechanical changes in the body. The impact of obesity on overall health can be demonstrated by its effect on mortality. In a lifetime study of overweight dogs versus lean dogs, the leaner dogs lived almost 2 years longer on average.[114] Obesity management is critical for preventing or treating conditions related to respiratory, cardiac, urinary, musculoskeletal, and endocrine systems. Obesity also appears to influence the outcomes of several types of cancer. In addition, physical activity is likely to improve the mental and physical health of dogs and cats. The inability to exercise should be considered a comorbidity to conditions which preclude regular physical activity such as obesity, arthritis, cardiac, and respiratory disease.

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CHAPTER 360

Concurrent Infection and Immune Suppression

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Client Information Sheet: Infections in Pets with a Suppressed Immune System

A functional immune system protects against pathogens and emergence of neoplasia while preventing adverse responses to self-antigens and harmless commensal, environmental, and food antigens. Whenever the immune system is compromised, there is a risk of infection. Immune compromise occurs due to use of immunosuppressive drugs (ID), congenital immunodeficiency, or acquired immunodeficiency states (which include pathogen damage to host tissues and pathogen subversion of the immune response). Hence, clinicians are frequently required to prevent, diagnose, and treat infection in the face of immunosuppression. This comorbidity presents numerous challenges. Some infections are only seen in immunocompromised patients (e.g., *Pneumocystis jirovecii* pneumonia), and awareness of such unusual pathogens might be low. Some clinical signs attributed to common infections in immunocompetent individuals are the result of immune activation and associated inflammatory responses, which can be impaired or absent in immunosuppressed individuals. Heightened vigilance is required in such patients and sometimes active surveillance and monitoring by laboratory testing for infection. Commercial assays to interrogate many components of the immune response are not available. Therefore, some immunodeficiency states may be suspected or inferred from patterns or infection but are difficult to diagnose definitively without access to a research laboratory.

Infection and Immunosuppressive Drug Use

Infection and Treatment of Immune-Mediated Disease

Autoimmunity in the absence of an identifiable trigger is referred to as primary (idiopathic) autoimmunity. When an infection provokes an immune response against host tissues, this is secondary autoimmunity. However, some infections mimic autoimmunity and it is likely that some conditions currently regarded as primary autoimmunity may be recognized as infectious disorders in the future. A notable recent example of this shift is histiocytic ulcerative colitis in Boxers, which was long considered to be an idiopathic, immune-mediated disease, but recent studies have shown that it is caused by adherent and invasive *E. coli* and responds to appropriate antibiotics (see ch. 277).[1] Infections triggering secondary autoimmunity or mimicking primary autoimmunity sometimes may only be unmasked following weeks or months of ID therapy (e.g., bacterial endocarditis), so constant vigilance and monitoring are appropriate. Immunosuppressive therapy frequently needs to be commenced at short notice, but before prescribing it, the veterinarian should perform an appraisal of previous and ongoing disease states that may confer an increased risk of infection, in order to fully inform the owners, address treatable comorbidities, and plan any supplementary therapy and monitoring. Examples of such considerations are listed in Table 360-1.

TABLE 360-1

Guidelines on Prescribing Immunosuppressant Drugs—Pretreatment Considerations That Influence Risk of Infectious Complications

PREEXISTING FACTOR OR COMORBID CONDITION AND EXAMPLES	INFECTIOUS COMPLICATION THAT COULD BE PRECIPITATED OR WORSENED BY IMMUNOSUPPRESSANT DRUG USE	COMMENT

Latent infection		
Feline calicivirus (see ch. 229) Feline herpesvirus (see ch. 229) Canine herpesvirus (see ch. 228) *Toxoplasma gondii* (see ch. 221)	Reactivation of latent infection and virus shedding	Most cases of *Toxoplasma* reactivation have been associated with cyclosporine therapy
Surgical implants		
Orthopedic—prosthetic hip Cardiac—pacemaker generator and lead (see ch. 249)	Infected implant/osteomyelitis	
	Infected unit/lead/endocarditis	
Urinary tract—urethral and ureteral stents, ureteral bypass devices (see ch. 124)	Urinary tract infection	Urinary tract implants are still relatively new to veterinary medicine; consequently, best practice recommendations for infection surveillance and management are still evolving
Intravenous catheters		
Jugular catheter (see ch. 76)	Local phlebitis, infected thrombus	Potential for embolization of infected material from catheter
Feeding tubes		
Esophagostomy (see ch. 82) Percutaneous endoscopic gastrotomy (see ch. 82)	Bacterial or fungal infections of the skin or stoma, local abscessation	Many immunosuppressants impede wound healing, compromising formation of stable adhesions between the skin and the esophageal or gastric lumen
Body surface inflammation/infection		
Gingivitis/periodontal disease (see ch. 272) Pyoderma Otitis externa (see ch. 237)	Bacteremia	
Severe osteoarthritis		
Legacy of elbow osteochondritis in aged Labrador Retriever (see ch. 353)	Septic arthritis	Blood flow and lymphatic drainage are compromised around severely arthritic joints
Prolonged recumbency		
Pressure sores Reduced clearance of airway secretions	Local pyoderma, abcessation, bacteremia, pneumonia, rhinitis	
Airway compromise		
Laryngeal paralysis (LP) (see ch. 239)	Aspiration pneumonia	Risk still applies following surgical correction. LP often is the first manifestation of a more generalized neuropathy
Dysphagia		
Megaesophagus (see ch. 273)	Aspiration pneumonia	Particular care is required when glucocorticoids are prescribed, as they can exacerbate muscular weakness
Congenital cardiac defect		
Severe subaortic stenosis (see ch. 250)	Bacterial endocarditis	Disease association has been described mainly with subaortic stenosis but may also apply to other

		congenital defects

Many autoimmune diseases are ultimately life-threatening and have a tendency to relapse; therefore, high-dosage, long-duration, generalized (nontargeted) immunosuppressive therapy has been the norm. There is considerable scope for refinement and reduction of current ID use by careful choice of ID, dosage, duration, and monitoring, which should reduce all complications, including infection. See ch. 165 and Box 360-1 for further information.

Box 360-1

Guidelines on Refinement and Reduction of Immunosuppressive Drug Use to Reduce Risk of Infection

1. **Does the disease require ID use?** Not all autoimmune diseases do. For example, canine acquired myasthenia gravis has the potential for spontaneous remission with appropriate supportive care and anticholinesterase therapy.[2]
2. **Consult the latest literature on the disease in question.** Some good-quality, prospective, and often placebo-controlled studies are emerging, improving the level of evidence available to guide prescribing practices. For example, sequential studies on canine immune-mediated thrombocytopenia showed that vincristine in combination with glucocorticoid therapy reduced time for platelet count to increase, resulting in shorter hospitalization times, and that vincristine was as effective as IV human immunoglobulin in this role.[3-5]
3. **Make the best use of available monitoring options**—In dogs with idiopathic immune-mediated polyarthropathy, serial measurements of C-reactive protein (CRP) and interleukin-6 correlate well with levels of disease activity and synovial inflammation, providing objective information to guide weaning of immunosuppressive drugs while reducing the need for serial arthrocentesis[6] (reducing risk of morbidity). Commercial CRP assays are widely available.
4. **Use short-acting, oral, injectable, or topical glucocorticoids,** rather than long-acting or depot preparations, such that immunosuppression is likely to rapidly subside on discontinuing the agent. Consider dosing prednisolone on a body surface area (BSA) basis for larger dogs, rather than dosing based on body weight. Suggested maximum immunosuppressive dose: 50 mg/m^2/24 h (Trepanier L, personal communication, April 8, 2015).
5. **Pharmacogenomics**—Be aware of the potential for individual or breed-related variations in the ability to metabolize or transport drugs in and out of cells. Examples include variation in levels of thiopurine methyltransferase (the enzyme that metabolises azathioprine) and mutations influencing the expression of the drug efflux transporter molecule p-glycoprotein. Some chemotherapeutic agents (doxorubicin, vincristine, vinblastine) are substrates of p-glycoprotein.[8]
6. **Drug interactions**—For example, cyclosporine has numerous potential drug interactions due to its metabolism by cytochrome P450.[9]
7. **Consider monitoring blood levels of the drug** (e.g., there are commercial assays for cyclosporine and leflunomide) to ensure adequate blood levels are achieved as quickly as possible while avoiding overdosage with the associated increase in risk of infection. For cyclosporine, pharmacodynamic monitoring is also available (measurement of activated T-cell mRNA for interleukin 2 and interferon gamma) for further refinement of drug dosing in individual dogs.[10] It is likely that further assays of drug levels and effect will become available in the future.
8. **Scan the horizon**—New drug agents will allow better targeting of specific immune response pathways implicated in specific disease conditions, for which a more potent drug causing more generalized immunosuppression would have been used in the past. Examples include the Janus Kinase inhibitor oclacitinib, approved for use in canine atopic dermatitis[11] and emergent "caninized" monoclonal antibody therapy.[12]

Managing Infection in Patients Being Treated with Immunosuppressive Drugs for IMD

The countless permutations of this comorbidity make it impossible to design a universal algorithm to guide the clinician through every scenario. In some cases, decision making is straightforward. The following case scenarios are typical examples:

- Asymptomatic urinary tract infection with a bacterium that is sensitive to a wide range of antibiotics is documented on routine monitoring in a dog that is being weaned off glucocorticoid therapy. In the first instance, a 7- to 10-day course of bactericidal antibiotics is prescribed, followed by repeat urine culture 7 days after completion of the antibiotic course.
- Mild upper respiratory tract signs consistent with reactivation of latent herpesvirus develop in a cat that is being treated with glucocorticoids and cyclosporine for idiopathic immune-mediated hemolytic anemia, which has just gone into remission. Provided the upper respiratory signs remain mild and nondebilitating, no treatment adjustments are required. If the signs become debilitating, the clinician will need to provide an augmented level of supportive care and consider reducing the dosage of one of the IDs sooner than originally planned. Antiviral therapy could also be instituted.

In other cases, typically those in which life-threatening infection develops in a patient with autoimmunity that is itself either debilitating or life-threatening, decision making will be considerably more challenging. Here, answers are often based on professional opinion born from experience, anecdote, or weak levels of published evidence. This should not detract from the importance of asking these questions, making prompt decisions and frequent observations to determine the effect of the decision on patient status. Table 360-2 lists decisions that need to be made and questions that should be asked to make the best decisions in such cases. The following detailed example demonstrates the application of several of these broad principles to difficult decision points during treatment of concurrent immune-mediated disease and an infectious complication.

TABLE 360-2

Aid to Decision-Making When Life Threatening Infection Develops in a Patient Receiving Immunosuppressive Drugs for Autoimmunity

TYPE OF DECISION AND OPTIONS	RELEVANT QUESTIONS BEFORE MAKING THE DECISION	COMMENTS
Decisions on the Infection		
Whether to treat the infection Yes/No	• Can the infection be treated? • Are there reports of successful treatment of this type of infection in patients receiving IDs? • Is there only one infection? • Any zoonotic implications?	Patient welfare, owner wishes, finances, and prognosis are paramount. Some infections (e.g., aortic valve endocarditis) carry a poor prognosis even in the absence of immunosuppressive drug therapy.
When to treat the infection Immediately or later	**What will kill the patient first—infection or autoimmunity?**	Typically, antimicrobial therapy is commenced immediately, but surgical management of infection might require ID dosage adjustment.
How to treat the infection Medical or surgical management, or both?	• Is the infection localized or generalized? • If surgery may offer a better prognosis, can the patient be made stable for surgery?	Poorly controlled autoimmunity may preclude anesthesia (neuromuscular disease, severe anemia) or surgery (severe thrombocytopenia).
Decisions on the Immunosuppressant Drugs		
Whether to change ID dosage/regime Yes/No	• Is the autoimmune disease under control? • Is this infection exacerbating the autoimmunity? • Has the infection arisen because of drug-induced	Severe infection often exacerbates autoimmunity (numerous mechanisms, predominantly associated with the increase in inflammatory cytokines), but also can suppress immune responses. Therefore, ID dose may need to be increased or decreased. This should be assessed on an individual patient basis.

	immunosuppression? • Is myelosuppression or any other drug toxicosis present? • Are drug interactions likely when antimicrobials are started?	
When to change ID dosage/regime Immediately or later	**What will kill the patient first—infection or autoimmunity?**	
How to change ID dosage/regime • Increase dosage • Start additional drug • No change • Short-term reduction • Accelerated weaning • Complete cessation	See questions relating to whether to change ID dosage. Also consider: Is this the first episode or autoimmunity or a relapse?	Relapsing autoimmunity requires more gradual weaning of immunosuppressants or lifelong therapy, compared with the first bout of autoimmunity.

Example: Management of Concurrent Myasthenia Gravis and Aspiration Pneumonitis/Pneumonia

Acquired myasthenia gravis (AMG) is an immune-mediated disease with varying clinical presentations (see ch. 269). Approximately 85% of cases have megaesophagus, and aspiration pneumonia (see ch. 242) is the leading cause of death in AMG patients. Use of IDs in AMG is destined to remain controversial for the foreseeable future because it is difficult to perform meaningful, controlled studies of a low-prevalence disease with the potential for spontaneous remission. When aspiration pneumonia is present, an additional layer of complexity is added to the decision-making process. Successful management of these two comorbidities and similar pairs of comorbidities requires (1) a good understanding of mechanisms of the comorbid diseases and of the complications associated with their interactions; (2) appropriate selection of IDs; (3) appropriate selection of antibiotics and other essential supportive measures; and (4) monitoring and treatment modification.

1. Reasons that AMG patients develop and succumb to aspiration pneumonia
   - AMG-associated, autoimmune-mediated attack of nicotinic acetylcholine receptors (AChRs) can cause esophageal dysfunction and megaesophagus.
   - Risk of aspiration increases further with weakness of the pharyngeal and laryngeal muscles.
   - AMG patients are frequently recumbent, and some have respiratory muscle weakness, impairing normal airway clearance mechanisms.
   - Other immune-mediated diseases that can affect neuromuscular function sometimes accompany AMG, which, if not recognized and managed promptly, can exacerbate dysphagia. These include hypoadrenocorticism, hypothyroidism, and polymyositis. AMG also occurs as a paraneoplastic phenomenon, mainly secondary to thymoma.
   - The anticholinesterase drugs (pyridostigmine and sometimes neostigmine) that constitute standard therapy for AMG have a narrow therapeutic index and can cause salivation and vomiting, increasing risk of further aspiration. Cholinergic side effects can be reduced by concurrent administration of atropine or giving the drug with food.
2. Indications for, and choice of, immunosuppressive drugs in AMG

   Indications:
   - Dogs with repeatably increased AChR antibody titers that persist despite the passage of time and provision of supportive care.

- Dogs not responding well to anticholinesterase therapy, or where such drugs are causing unacceptable side effects. Dogs with positive AChR antibody titers but negative edrophonium challenge tests might be predicted to respond poorly to other anticholinesterase drugs and thus be candidates for early ID treatment.
- Surgical removal of neoplastic tissue, if possible, is indicated in paraneoplastic AMG, in preference to ID therapy (i.e., elimination of underlying cause).
- Dogma regarding AMG states that IDs should not be commenced until infection is controlled. However, if a patient is experiencing life-threatening pneumonia resulting from frequent and ongoing aspiration events and anticholinesterase therapy is not improving neuromuscular transmission sufficiently to stop these events, rapid-onset immunosuppressive therapy to control the immune-mediated neuromuscular dysfunction could be the only hope of preventing further aspiration events. The pragmatic clinician will realize that in such dire situations, there is little to lose by commencing ID therapy in the face of infection.

Choice of drug:

- Glucocorticoids, if used, can be started at a low dosage (e.g., prednisolone 0.5 mg/kg q 24 to 48 h PO or via feeding tube, or use equipotent dose of an injectable glucocorticoid) and increased every 2 to 4 days. While this can be beneficial, and injectable glucocorticoids are easy to administer, reasons often cited for avoiding glucocorticoids include:
  - Exacerbation in muscle weakness (effects on excitation-coupling and altered ion channel of AChR)
  - Increased thirst and appetite, making regurgitation more likely
  - Increased panting
  - Global immunosuppression, including the innate immune response (neutrophil and macrophage function), worsening pneumonia
  - High-dosage IV methylprednisolone sodium succinate has been suggested for fulminant AMG since it does not exacerbate muscle weakness
- Nonglucocorticoid or "steroid-sparing" options include azathioprine, mycophenolate mofetil, and cyclosporine, which are more lymphocyte selective with fewer effects on innate immune responses (see ch. 165).
  - Azathioprine acts slowly, but in very ill patients, a rapid response is desirable. Myelosuppressive and sometimes hepatotoxic.
  - Cyclosporine—veterinary-approved formulations exist. Injectable formulations exist. Acts within days. Pharmacokinetic and pharmacodynamic monitoring available. A significant proportion (approx. 25%) of cases have transient gastrointestinal upset in the first few days of therapy.
  - Mycophenolate mofetil—rapid acting. Tablet, oral suspension, and intravenous preparations exist. Less myelosuppressive than azathioprine, but high cumulative doses can cause hemorrhagic gastroenteritis. Long-term benefit unproven but may be useful as rescue treatment in severe generalized AMG.

3. Antibiotic choice and other supportive measures
   - The material aspirated into the lungs in AMG may be a combination of oropharyngeal, esophageal and gastric contents and is likely to have substantial bacterial contamination.
   - Ideally, antibiotic therapy is guided by results of lower respiratory tract sampling (see ch. 101), especially if previous therapy has failed or risk factors are present for multiple drug resistance. However, morbidity associated with sedation or anesthesia for such sampling procedures and studies showing that most patients with aspiration pneumonia yield multiple bacterial isolates mandate the use of very broad-spectrum antibiotic therapy for initial empiric treatment.
   - Several antibiotics have the potential to worsen neuromuscular blockade (aminoglycosides, ampicillin, ciprofloxacin, erythromycin, imipenem) and should be avoided.
   - As for other megaesophagus patients, offering food and water from an elevated position is essential (see ch. 273). If unsuccessful, use of oral medications is also likely to be ineffective, and parenterally administered drugs should be given or placement of a percutaneous endoscopic gastrostomy (PEG) tube should be performed (see ch. 82). Since PEG tube placement requires general anaesthesia, the opportunity for concurrent lower airway sampling should be exploited if patient status permits. NOTE: Glucocorticoid therapy will impede formation of a stable adhesion between a newly placed PEG tube and the body wall, probably more so than other immunosuppressive drugs.
   - Oxygen therapy and saline nebulization may also be beneficial if tolerated (see ch. 97 and 131).
   - Coupage should be used with caution in patients with megaesophagus.

4. Monitoring
   - Improvement in respiratory status and pulmonary infiltrates on radiographs indicates improvement in aspiration pneumonia. Antibiotic therapy should be continued for at least a week beyond clinical resolution.
   - Serial AChR antibody titers often correlate well with disease activity in AMG. While a decreasing titer in response to immunosuppressive drugs is encouraging, it should not be interpreted as full remission of the disease until the IDs have been completely weaned with AChR antibody titer remaining below the normal level of 0.6 nmol/L.
   - If AChR titer remains increased, therapy should be continued even if clinical signs have resolved.

See E-Case Study 360-1 (online) for a "real-world" example of managing life-threatening autoimmunity and infection in a dog with immune-mediated hemolytic anemia and infective endocarditis.

Infection and Cancer Chemotherapy (See Ch. 343)

Cytotoxic (myelosuppressive) IDs form the mainstay of many cancer chemotherapy regimens. Once the tumor burden has been reduced from a macroscopic to a microscopic level, a reduction in blood neutrophil count to <3000 cells/mcL has been used as a surrogate marker of likely drug efficacy. It has been suggested that optimal dosage intensity is defined by giving doses of myelosuppressive drugs that deliver a neutrophil nadir between 1000 and 1500 cells/mcL and to consider increasing drug dosage for the next cycle if this is not achieved.[13] If this goal is adopted, it is essential that the logic behind this practice is understood by the patient's owner and all clinicians involved and that hematological monitoring establishes the neutrophil nadir for each myelosuppressive drug. However, with severe neutropenia being the most common dose-limiting toxicosis of these drugs, it is the author's observation that few veterinary oncologists are prepared to sail so close to the wind, with most settling for a nadir approaching, or just below, 3000 cells/mcL. Neutrophil and platelet counts should always be checked before any further myelosuppressive agent is given, with administration postponed until neutrophil count exceeds 3000 cells/mcL. A neutrophil count of <1000 cells/mcL, or long duration of neutropenia regardless of severity, should prompt reduction of all subsequent doses of that myelosuppressive drug, typically by 20% to 30%. Most veterinary oncologists believe that a neutrophil count >1000 cells/mcL is adequate to fight infection and that neutrophil counts at this level still confer a low risk of infection.[14] The risk of sepsis increases markedly at neutrophil counts <500 cells/mcL. Risk factors for chemotherapy-induced severe neutropenia include low body weight, hematological tumors, drug used, and being in the induction phase.[15] Therefore, vigilance is required from the owner and veterinarian regarding any clinical signs that could suggest neutropenia-related infection and an understanding that infections still occur in nonneutropenic chemotherapy patients. The requirement for prophylactic or therapeutic antibiotic use in chemotherapy patients depends on presence or absence of clinical signs, especially fever, and the absolute blood neutrophil count. It should be noted that neutropenia itself does not cause clinical signs.

Management of Asymptomatic Neutropenic Patients

If the neutrophil count is between 1000 and 3000 cells/mcL, antibiotics are not required unless other independent risk factors for infection are present (see Table 360-1). When the neutrophil count is <1000 cells/mcL, prophylactic oral antibiotics are indicated and the neutrophil count should be reassessed in 3 to 7 days. The choice of antibiotic might be restricted by institutional prescribing guidelines. Since sepsis in neutropenic patients is thought most likely to result from gastrointestinal translocation of Gram-negative aerobic bacteria and anaerobic bacteria prevent overgrowth of aerobes in the gut, consideration should be given to prescribing agents with minimal anaerobic spectrum.[15] Although hospitalization is not typically required, close observation is essential and any change in vital signs or demeanor, a reduced appetite, or gastrointestinal signs at home should trigger urgent reassessment by the veterinarian for evidence of infection/sepsis.

Management of Symptomatic Neutropenic Patients

Deterioration in physical status of a neutropenic patient should prompt immediate intervention to prevent or address septicemia. While onset of fever is of particular concern, its presence should not be relied on as an obligatory marker of sepsis (especially in cats), since some septic patients have such severe immune dysfunction they cannot release sufficient quantities of cytokines to generate a fever.[16] Following standard measures appropriate for any patient with serious illness (meticulous physical examination, complete blood

count, serum, biochemistry profile, and urinalysis), the clinician should not allow exhaustive attempts to identify the source of infection to take priority over establishing IV access (using meticulous aseptic technique) and instituting parenteral antibiotic therapy along with appropriate IV fluid therapy and hemodynamic monitoring. Any additional supportive measures that are necessary (e.g., antiemetics, analgesia, blood products) can then be started. Generally, very broad-spectrum (four-quadrant) antibiotic coverage is appropriate initially, unless there is strong initial evidence to implicate a specific organ system and class of bacteria in the illness. Antibiotics may need to be used at the high end of recommended dosages to offset reduced organ perfusion in sepsis.[17] Antibiotic therapy may be refined when culture results become available and in light of case progression, being mindful of the increasing problem of antibiotic resistance in human and veterinary medicine. Most symptomatic neutropenic chemotherapy patients respond to appropriate supportive care within the first 24 hours. Recombinant granulocyte colony stimulating factor (G-CSF) could be considered for use in patients that have received an inadvertent overdose with a myelosuppressive drug or when profound neutropenia persists for over 1 week. However, routine use of G-CSF should be discouraged because neutropenic dogs should have high endogenous G-CSF concentrations and therapy with the human recombinant product carries the risk of cross-reacting antibody formation.[18]

By comparison, management of human patients with fever and neutropenia is governed by stratified risk assessments, based on a larger evidence base and body of expert opinion than is available in veterinary medicine. Algorithms are being developed that encompass empirical or preemptive use of antifungal and antiviral therapy in addition to antibiotics in some subsets of patients. High-risk patients are those with anticipated prolonged (>7 days) and profound (<100 cells/mcL) neutropenia and/or significant comorbid conditions, including hypotension, pneumonia, new-onset abdominal pain, or neurologic changes. Low-risk patients are those with a neutropenia that is anticipated to be brief (<7 days), with no or few comorbid conditions, and these patients are managed with oral antibiotic prophylaxis.[19]

Infection in Organ Transplantation (See Ch. 323)

Renal transplantation is available for cats suffering from irreversible kidney disease at a few centers in North America and one in Australia. Recipients receive lifelong immunosuppressive therapy, typically including glucocorticoids and cyclosporine. Posttransplant infection is a common cause of graft deterioration, morbidity, and mortality. It also can be responsible for delayed discharge and multiple and often prolonged admissions. In the largest published study on infections in cats after renal transplantation, infection accounted for death in 14% of recipients and was second only to graft rejection as a cause of death.[20] Half of the infections developed within 2.5 months of transplantation, when immunosuppression was greatest. Cats with diabetes mellitus were at significantly increased risk of infection. Bacterial infections were most common including those associated with the urinary tract, feeding tubes, *Mycobacterium* spp. and *Nocardia* spp. Viral infections (predominantly affecting the upper respiratory tract) were next most common, followed by fungal and protozoal infections.[20]

Preoperative donor and recipient screening is thorough (see ch. 323). Urinary tract infections must have been successfully treated, with two negative post-treatment cultures. A cyclosporine challenge may be performed if pyelonephritis is suspected, with urine resubmitted for culture after 7 days of cyclosporine administration. One institution has accepted cats with chronic viral upper respiratory tract disease for transplantation if the disease was well managed at the time of assessment and clinical signs did not worsen on a cyclosporine trial.[21] Disseminated toxoplasmosis has been diagnosed in feline and canine renal transplant recipients.[22] As a result, some institutions place cats that are seropositive for *T. gondii* on life-long clindamycin treatment to prevent recrudescence. It is worthy of note that in a small, short-term study performed as part of a cyclosporine licensing application, healthy experimental cats that were seronegative for *T. gondii* and receiving cyclosporine, then challenged with *T. gondii,* suffered more severe disease than cats that were already seropositive when cyclosporine therapy commenced.[23]

When infection occurs in a renal transplant recipient, alongside appropriate antimicrobial therapy, it is imperative that the clinician check that immunosuppression is optimized. Blood cyclosporine levels should not be abnormally high, which would suggest excessive immunosuppression, yet not abnormally low, which could jeopardize the graft. As with other immunocompromised patients, antimicrobial therapy may need to be given for significantly longer and at higher dosages than would routinely be used.

Renal transplantation in dogs is currently beset with challenges that often prove insurmountable, notably high morbidity and mortality rates from infection associated with the substantially more aggressive immunosuppressive drug regimens that are required to prevent graft rejection.[24-26]

Use of Glucocorticoids in the Management of Infectious Disease

Contrary to dogma, there is no absolute contraindication to the use of immunosuppressive drugs in the presence of infection. There are select clinical scenarios where short-term use of anti-inflammatory or immunosuppressive agents (predominantly glucocorticoids) is of great benefit to the patient. However, since there are few veterinary studies evaluating the safety and efficacy of combined immunosuppressive and antimicrobial therapy, clinicians should continuously evaluate the risks versus the benefits of this practice on an individual patient basis. Empirical use of glucocorticoids in all patients with a given infection is not appropriate, but neither is blanket avoidance of their use in the presence of infection.

Infections That Cause Secondary Autoimmunity

Many infections can trigger secondary immune-mediated processes that have an adverse effect on the host, including formation of antibodies against erythrocytes, platelets, megakaryocytes and neutrophils and formation of immune complexes.[27] While numerous viral, bacterial, protozoal and helminth infections can be involved, vector-borne infections are most frequently and increasingly incriminated. The burgeoning literature on vector-borne disease (VBD), changes in taxonomy, identification of new agents and coinfections,[28] and sometimes protracted and expensive testing required for diagnosing VBD all contribute to the significant challenge that the clinician faces in identifying and managing this particular comorbidity, in which the boundaries between primary and secondary autoimmunity can be hard to define. If results of tests for infection are pending but patient status dictates that treatment is commenced, empirical antimicrobial therapy appropriate for the agent suspected should be started before or at the same time as glucocorticoid therapy. Glucocorticoid therapy will not be required for all cases, and prompt antimicrobial therapy increases the chances of spontaneous resolution of secondary autoimmunity without glucocorticoid use. If suspicion of infection lingers, despite negative test results, the clinician should remain skeptical about the longevity of any clinical improvement that follows initial glucocorticoid therapy and be vigilant for subtle signs that could reflect worsening of the infection. Repeat testing should be considered, especially for conditions where culture is appropriate, since glucocorticoid therapy can increase the likelihood of identifying the infection. Examples of pathogens incriminated in immune reactions against self-tissue are shown in E-Box 360-2. One of the few published studies relating to secondary autoimmunity describes experimentally induced Rocky Mountain spotted fever. Dogs treated with doxycycline and immunosuppressive dosages of glucocorticoids did not have more severe disease than dogs treated with doxycycline alone[29]. However, others report relapse of parasitemia when dogs that had recovered from rickettsial infections following doxycycline treatment were subsequently treated with immunosuppressive doses of glucocorticoids.[30] It has also been suggested that glucocorticoid therapy might be beneficial in feline leukemia (FeLV)-associated cyclic cytopenias, FeLV-associated anemias where an autodestructive component is involved or coinfection with hemotropic mycoplasmas exists, and for short-term use in babesiosis. Pure red cell aplasia in cats with FeLV infection has been suggested to benefit from glucocorticoid and cyclosporine therapy.[30]

E-Box 360-2

Examples of Pathogens Incriminated in Immune Reactions Against Self-Tissue (Secondary Autoimmunity)

Viruses

Feline leukemia virus (C)
Feline immunodeficiency virus (C)
Feline infectious peritonitis (C)

Bacteria

Ehrlichia canis (D)
Anaplasma phagocytophilum (D)
Anaplasma platys (D)
Leptospira spp. (D)
Hemotropic mycoplasmas (C)

Protozoa

Babesia canis (D)
Babesia rossi (D)
Babesia gibsonii (D)
Cytauxzoon felis (C)
Leishmania infantum (D)

Helminths

Dirofilaria immitis (D)
Angiostrongylus vasorum (D)
C, Cats; *D*, dogs.

E-Box 360-3

Chapters Containing Additional Information Pertinent to Infection and Immune Suppression

This box directs readers to other chapters containing more detailed information about specific complaints, diseases and drugs relevant to this chapter.

General Relevance

Fever (see ch. 48)
Sepsis and the Systemic Inflammatory Response Syndrome (see ch. 132)
The Endocrine Response to Critical Illness (see ch. 133)
Diseases of the Trachea and Small Airways (see ch. 241)
Inflammatory, Infectious, and Other Multifocal Brain Diseases (see ch. 261)
Spinal Cord Diseases: Congenital (Developmental), Inflammatory, and Degenerative Disorders (see ch. 266)
Neuromuscular Junction Disorders (see ch. 269)
Diseases of the Stomach (see ch. 275)
Diseases of the Small Intestine (see ch. 276)
Diseases of the Large Intestine (see ch. 277)
Canine Inflammatory/Infectious Hepatic Disease (see ch. 282)
Feline Inflammatory/Infectious Hepatic Disease (see ch. 283)
Glomerular Diseases (see ch. 325)
Muscular Disorders (see ch. 354)

Immune-Mediated Diseases

Immunologic and Hematologic Diseases: Introduction and Drug Therapy (see ch. 195)
Immune-Mediated Hemolytic Anemias and Other Regenerative Anemias (see ch. 198)
Immune-Mediated Thrombocytopenia, von Willebrand Disease, and Other Platelet Disorders (see ch. 201)
Immune-Mediated and Other Nonneoplastic White Blood Cell Disorders (see ch. 202)
Immune-Mediated Polyarthritis and Other Polyarthritides (see ch. 203)
Immune-Mediated Dermatologic Disorders (see ch. 204)
Systemic Lupus Erythematosus (see ch. 205)

Infectious Disease

Laboratory Diagnosis of Infectious Disease (see ch. 207)
Antimicrobial Resistance, Surveillance, and Nosocomial Infections (see ch. 209)
Bacterial diseases (see ch. 211-220)
Protozoal diseases (see ch. 221)
Viral diseases (see ch. 222-230)
Fungal diseases (see ch. 231-236)

Drug Therapy

Principles of Drug Disposition and Pharmacokinetics (see ch. 160)
Antibacterial Drug Therapy (see ch. 161)
Antifungal and Antiviral Therapy (see ch. 162)

Antiparasitic Therapy (see ch. 163)
Immunosuppressive Therapy (see ch. 165)
Principles and Practice of Chemotherapy (see ch. 339)
Complications of Anticancer Therapy (see ch. 343)

Infections That Cause Debilitating or Life-Threatening Inflammation

In some infections, inflammation secondary to cellular damage, adverse immune response to pathogen antigens, and further release of inflammatory mediators on death/lysis of the pathogen during treatment become more dangerous than the tissue destruction caused by the pathogen itself. This is especially pertinent in infections involving the lung, eye, or central nervous system. A recent meta-analysis offers fascinating insight into the potential benefits and harms of giving systemic glucocorticoids in combination with disease-appropriate antimicrobials in treating infections in humans.[31] Infections were categorized into groups according to whether glucocorticoids were considered to improve survival (e.g., bacterial or tuberculous meningitis, severe tetanus, *Pneumocystis* pneumonia), reduce long-term disability (bacterial arthritis), significantly relieve symptoms (chronic middle ear effusion, acute laryngotracheobronchitis, cellulitis), or be of uncertain benefit or harmful (viral hepatitis).[31] Duration of therapy was generally short term (<14 days), and glucocorticoid dosage varied widely between studies.

In veterinary medicine, anti-inflammatory glucocorticoid use has been suggested to be of benefit if managing life-threatening pneumonitis induced by treatment of systemic mycoses, heartworm disease, or severe leptospirosis; for protracted cough in dogs with infectious tracheobronchitis; for reducing inflammation in feline infectious peritonitis; and for feline calicivirus-associated ulceroproliferative stomatitis (sometimes with cyclosporine).[30,32] Immunosuppressive dosages of glucocorticoids are considered appropriate for juvenile cellulitis ("puppy strangles").[32]

A retrospective study on concurrent systemic antifungal and glucocorticoid use (prednisolone 0.7 mg/kg/day PO for a mean duration of 3 months) for treatment of ocular blastomycosis in 12 dogs concluded that steroids did not adversely affect survival rate.[33] A brief report comparing glucocorticoid therapy with nonsteroidal anti-inflammatory therapy when combined with antifungal therapy for severe pulmonary blastomycosis in dogs found no difference in outcome.[34] Another study on use of prednisolone or prednisone (2 to 4 mg/kg/day PO) with or without systemic antifungals led to more rapid resolution of hilar lymphadenopathy caused by chronic histoplasmosis than antifungal therapy alone, again without dissemination of the disease; cases were carefully screened to rule out acute histoplasmosis.[35]

Glucocorticoids in Septic Shock

Some practitioners favor use of low-dosage glucocorticoid (hydrocortisone) replacement therapy in volume-loaded vasopressor-refractory hypotension associated with septic shock and related conditions (see ch. 132). Controversies surrounding optimal diagnostic and therapeutic strategies for this phenomenon, termed critical illness–related corticosteroid insufficiency, have recently been reviewed[36] and are discussed in ch. 133.

Immunodeficiency States Not Induced by Immunosuppressive Drugs

Naturally occurring immunodeficiency states may be divided into primary (congenital, usually hereditary) and secondary (acquired) immunodeficiencies. Key features consistent with immunodeficiency include:

- Recurrent or chronic infections (especially respiratory, skin, gastrointestinal, or urinary), often with incomplete response to antimicrobials
- Opportunistic infection with normally harmless or commensal organisms or unusual pathogens, often with severe disease manifestations
- Adverse response to modified live vaccines
- Ill thrift/fading neonates

Primary immunodeficiencies are uncommon in dogs and rare in cats. Knowledge of the more prevalent disorders and affected breeds, or the foresight to consult a list of such disorders when presented with a patient with suggestive clinical features, is central to reaching a diagnosis. Specific disorders have been reviewed elsewhere.[37] Prognosis varies according to the nature of the deficit, with many of the severe immunodeficiencies proving fatal.[38]

Secondary immunodeficiency states are common in dogs and cats and comprise a large, heterogeneous group of disorders that affect animals that are born with all components of the immune system intact but that develop transient or permanent immune impairment due to life stage, a disease state, or exposure to specific drugs, infections, or toxins. Broad categories of secondary immunodeficiency include age-related (e.g., colostrum deprivation), organ dysfunction (especially endocrinopathies), barrier damage (e.g., burns, catheters), nutritional disorders, and immunosuppressive coinfections. In many secondary immunodeficiencies, the underlying disorder either is transient or can be corrected or controlled, maximizing the potential for control of any resultant infection. For example, bacterial urinary tract infections are common in patients suffering from diabetes mellitus or hyperadrenocorticism. Tight control of the endocrinopathy should reduce frequency and severity of urinary infections but does not remove the need for routine surveillance (urine cultures) in diabetics.

Immunosuppression Caused by Infection

Successful pathogens, by definition, must breach physical barriers and suppress or subvert host immune responses to facilitate their own survival and propagation. Thus, infection begets immunosuppression, which begets further infection. Mechanisms of pathogen-induced immunosuppression are as numerous and varied as the pathogens themselves, with the arm of the immune system that is compromised directly influencing the type of secondary infections that occur. Damage to physical barriers and impairment of granulocyte function facilitate bacterial and sometimes fungal invasion. Impaired cell-mediated immunity can allow opportunistic pathogens (e.g., *Nocardia* spp., *Toxoplasma gondii*) to become established,[39] and compromised humoral immunity favors pyogenic bacteria. The archetypal immunosuppressive infection is feline immunodeficiency virus, which has complex effects on the immune system,[40] with depletion of $CD4^+$ T cells (T-helper cells) and activation of regulatory T-cells being key events.[40,41] Several other major pathogens infect cells of the immune system (FeLV, canine distemper, *Ehrlichia canis, Anaplasma phagocytophilum,* and *Leishmania*). Canine and feline parvoviruses have a tropism for rapidly dividing cells, causing the devastating combination of massive barrier damage (loss of intestinal epithelial crypt cells) with associated neutrophil sequestration, and myelosuppression. Other pathogens have downstream effects on immune cells (the glucuronylxylomannan capsule on *Cryptococcus* sp. inhibits phagocytosis, leukocyte migration, complement and Th1 responses) or direct effects on barrier function (*Bordetella bronchiseptica* paralyzes respiratory cilia).[39]

Such is the diversity of pathogen effects on the immune system and other target tissues that coinfections and secondary infections are inevitable. Recognition, management, and avoidance of these secondary infections require not only the ability to diagnose the primary infection but a detailed understanding of the pathogen's effects and survival strategy. Additional information relevant to infection and immune suppression is found online in E-Box 360-3.

E-Case Study 360-1

Immune-Mediated Hemolytic Anemia and Bacterial Endocarditis in a Dog

A "real-world" example of managing life-threatening autoimmunity and infection, with commentary.

Reference ranges used throughout this case:

PCV 37-55
Neutrophils 3000 to 11,500/mcL
Bands 0 to 300/mcL
ALT 0 to 40 U/L
ALKP 0 to 50 U/L
Bilirubin 0 to 0.53 mg/dL
Urea 5.6 to 25.2 mg/dL

Signalment: 4.5 year-old female intact Lhasa Apso, 10 kg

Vaccination and worming were current and appropriate for the geographic area. The dog had not been in an area with a high prevalence of vector-borne disease, and there was no history of flea or tick exposure.

Clinical Scenario: The dog presented with a 12-hour history of dark urine, reduced appetite, and lethargy. Physical examination revealed pallor and fever (39.4°C) and a grade 2/6 systolic murmur. A diagnosis of **idiopathic immune-mediated hemolytic anemia** (IMHA) was made based on a severe,

highly regenerative anemia (PCV = 14%) accompanied by spherocytosis, autoagglutination, moderate icterus, and marked bilirubinuria. Platelet count was normal. Neutrophilia was present (24,400/mcL with bands 300/mcL). Elevations were noted in baseline serum alkaline phosphatase (ALKP) = 170 U/L, alanine aminotransferase (ALT) = 98 U/L, and bilirubin = 2.76 mg/dL. Prothrombin and activated partial thromboplastin times were normal. Abdominal ultrasound and thoracic and abdominal radiographs were normal. Urine culture was negative. Heart valves were echocardiographically normal, suggesting that the murmur was hemic.

Management and progress days 1-9:

The dog remained hospitalized in first-opinion practice following initial diagnostic testing, and the following oral therapy was instituted:

- Prednisolone 1 mg/kg q 12 h
- Aspirin 1 mg/kg q 24 h
- Clopidogrel 25 mg/dog q 24 h
- Omeprazole 1 mg/kg q 24 h

After 24 hours, the dog developed hemorrhagic diarrhea and occasional vomiting, the PCV declined, and tachycardia developed. An indwelling right jugular vein catheter was placed (Seldinger technique), and additional therapy commenced consisting of:

- Intravenous infusion of polymerized bovine hemoglobin (Oxyglobin) over 36 hours with concurrent crystalloids. Ongoing balanced crystalloid therapy when Oxyglobin finished.
- Metoclopramide (IV), maropitant (SC), metronidazole (PO)—these therapies were all withdrawn by Day 6 when gastrointestinal signs had resolved.

Day 5: PCV = 16%, ALT was normal, ALKP = 1565 U/L, bilirubin = 3.51 mg/dL.

Day 6: PCV = 19%. The jugular catheter had become permanently occluded and was removed. The dog was progressively brighter.

Day 7: PCV = 19%, occasional spherocytes present. Azathioprine (25 mg PO q 24 h) commenced.

Day 8: The dog was discharged receiving unchanged dosages of prednisolone, aspirin, clopidogrel, omeprazole and azathioprine.

Commentary: *Gastrointestinal signs are common in IMHA and can also be precipitated by glucocorticoids. Oxyglobin therapy is a convenient, valid alternative to canine packed red cells but causes short-term interference with colorimetric tests on blood and urine. IMHA cases are hypercoagulable, but the optimal anticoagulant regimen is yet to be determined. The rising ALKP is likely to be glucocorticoid associated. Up to this point, this is an unremarkable case of IMHA.*

Management and progress days 9-14:

Day 9: PCV = 18%, spherocytosis, anisocytosis, polychromasia, nucleated erythrocytes, neutrophilia (29,800/mcL) bands (1800/mcL), toxic change. ALKP = 3780 U/L, ALT = 1163 U/L, bilirubin = 9.65 mg/dL, in-saline agglutination negative. The dog showed lethargy, fever, tachycardia, icterus, and cranial abdominal pain. It had vomited bile once. A canine pancreatic lipase immunoreactivity value was normal. Thoracic radiographs were normal. Abdominal ultrasound showed hyperechoic fat/mesentery in the region of the pancreas. Liver parenchyma was normal. A mild abdominal effusion was present, provisionally classified as an exudate containing a predominance of nondegenerate neutrophils, with some macrophages and mesothelial cells. Ascitic fluid and urine samples were submitted for culture. Heart valves were normal on ultrasound. Changes to therapy on Day 9:

- Azathioprine discontinued (prednisolone, aspirin and omeprazole ongoing)
- Parenteral antibiotic therapy started (amoxicillin-clavulanate and enrofloxacin)
- Intravenous crystalloids and oral sucralfate started
- Methadone analgesia, changed on Day 10 to a morphine-ketamine combination

Day 12: PCV 21%, neutrophil count = 56,000/mcL with bands = 7000 mcL. ALKP = 9030 U/L, ALT = 363 U/L, bilirubin = 0.64 mg/dL. Culture results: urine and ascitic fluid yielded coagulase-positive *Staphylococcus.* In addition, the ascitic fluid yielded a lactose-fermenting coliform. Both organisms were sensitive to the antibiotics instituted on Day 9. The dog was more comfortable and the amount of effusion reduced, but ultrasound now showed a 2 × 3 cm area of hypoechoic nodular change in the left medial liver lobe. Fine-needle aspirates of this area showed marked suppurative hepatitis with rare intralesional bacilli.

Day 14: PCV = 22%, spherocytes present, neutrophils = 44,000/mcL, bands = 1900/mcL. Abdominal ultrasound showed the liver lesion unchanged, but thickening and hyperechogenicity of the gallbladder wall. The primary care provider was concerned that the dog might require cholecystectomy and elected

referral to a multidisciplinary specialist practice.

Commentary: *On Day 9, IMHA was incompletely controlled and new cranial abdominal disease was apparent. While the rise in bilirubin and ALT could in part have been related to worsening/exacerbation of IMHA, the fever, toxic left shift in the neutrophil line, and presence of a neutrophilic abdominal exudate could have been explained by pancreatitis, sterile or septic thrombosis affecting the liver or pancreas, septicemia, or emergence of abdominal neoplasia. Septicemia itself can cause icterus due to effects of inflammatory cytokines on bilirubin uptake and intrahepatic processing and by causing intrahepatic cholestasis. The suspicion of infection was confirmed by the results of cultures of the urine and ascitic fluid, and the suspicion of liver involvement was confirmed by the emergence of new ultrasound changes and cytologic evidence of suppurative hepatitis. While azathioprine can cause hepatopathy and pancreatitis, since only 2 days of therapy with this drug had been given it was considered unlikely to have been implicated in the clinical deterioration. The mild increase in PCV seen during this time despite the presence of spherocytes validated the decision not to reduce or discontinue prednisolone treatment. In addition to immunosuppressive drug therapy, there were at least three possible explanations for development of infection in the liver:*

- *Ascending cholangiohepatitis/cholangitis*
- *Increase in bacterial content of portal blood during the hemorrhagic gastroenteritis that occurred in the first week of illness*
- *Liver localization following bacteremia/septicemia (supported by concurrent positive urine culture), which could have developed from infection of the indwelling jugular vein catheter (the catheter was problematic and isolation of Staphylococcus could suggest skin origin)*

Management and progress days 14-20:

At the referral center on Day 14, a grade 3/6 systolic murmur localized to the mitral area was present. There was bruising around the left jugular vein. The right jugular vein could not be located. Echocardiography revealed a vegetative mass lesion on the posterior mitral valve leaflet causing mitral insufficiency. The left atrium was moderately enlarged, with left atrial : aortic ratio of 2 : 1 (normal <1.3 : 1). E-wave velocity indicated significantly increased left atrial pressures. Systolic indices were normal. Blood cultures were submitted. Abdominal ultrasound findings were similar to those reported at the first-opinion practice. Prothrombin time and activated partial thromboplastin times were normal. ALKP = 11,676 U/L, ALT = 420 U/L. Bilirubin = 0.58 mg/dL, PCV = 22%, spherocytes ++, anisocytosis +++, polychromasia +.

The owner was advised that the findings were consistent with recent development of **bacterial endocarditis,** carrying a very poor long-term prognosis, especially in view of the incompletely controlled immune-mediated disease and the need for ongoing immunosuppressive therapy. Despite this, the dog was relatively bright and the owner elected to continue treatment. Medication regimen:

- Prednisolone, aspirin, clopidogrel, omeprazole and sucralfate as before
- Intravenous marbofloxacin and amoxicillin-clavulanate
- Oral clindamycin

Day 15: PCV = 26, ascites almost fully resolved on ultrasound, but liver and gallbladder changes static. New lesion on anterior mitral valve leaflet.

Day 16: PCV = 28, spherocytes absent, neutrophils = 23,600/mcL, bands = 1400/mcL, liver enzymes and bilirubin static.

Day 19: Signs of local peritonitis resolved on ultrasound despite liver and gallbladder changes remaining. Mitral valve lesions enlarging.

Day 20: PC 36%. Dog discharged receiving all above medications orally.

Commentary: *Since initial bacterial colonization of the heart valve endothelium may not be detected on echocardiography, it is difficult to be certain whether bacterial endocarditis caused septic embolization to the liver, or whether hepatobiliary infection was the initiating event that led to bacterial endocarditis. Suppurative hepatitis in isolation is a treatable lesion, which should not imply a poor prognosis in the face of an immune-mediated disease that is responding to treatment. However, superimposed bacterial endocarditis, with valvular lesions that progressed during the days following diagnosis, and with significant volume overload at the time of recognition, was a development that immediately downgraded the prognosis to extremely poor. The risks of congestive heart failure, thromboembolic disease, and ongoing infection were significant. In such circumstances, the very mild mineralocorticoid (sodium loading) effect of prednisolone has to be considered. Despite persistent ultrasound changes in the gallbladder wall and profound elevations in ALKP, hard evidence for imminent or actual biliary tract rupture was lacking, and therefore, cholecystectomy was not indicated. The resolution of the ascitic fluid, subjectively bright demeanor of the patient, and progressive improvements in PCV and neutrophil count with*

disappearance of spherocytes from the blood all added support to the conservative management path. Blood cultures were reported as being negative for growth after 2 weeks' incubation.

Management and progress days 21-60 (first-opinion practice):

Day 23: PCV = 36%. Prednisolone dose reduced from 1 mg/kg q 12 h to 1 mg/kg in a.m., 0.5 mg/kg in p.m. (i.e., a 25% dose reduction).

Day 30: PCV = 30%. Prednisolone dose returned to 1 mg/kg q 12 h. Mitral valve appearance and left atrial size unchanged. Dog bright.

Days 37 and 43: PCV = 30%. Spherocytes absent. Normal reticulocyte count indicating nonregenerative anemia.

Day 57: PCV = 32%. Left atrium unchanged. Owner concerned regarding muscle wasting and other signs of glucocorticoid excess. Prednisolone reduced again to 1 mg/kg in a.m., 0.5 mg/kg in p.m.

Day 59: Dog presented with signs consistent with left-sided congestive heart failure (tachypnea, tachycardia, pale membranes, normothermic), 10.25 kg. PCV 28%, neutrophils = 30,000/mcL, urea = 36.7 mg/dL. Responded well to intravenous furosemide, with resolution of tachycardia and tachypnea after 24 hours. 9.9 kg.

Day 60: Dog discharged receiving the following oral medications:

- Prednisolone 1 mg/kg in a.m. 0.5 mg/kg in p.m., aspirin, clopidogrel, omeprazole, and sucralfate as before
- Marbofloxacin 2 mg/kg q 24 h, amoxicillin-clavulanate 20 mg/kg q 24 h and clindamycin 7 mg/kg q 12 h
- Furosemide 2 mg/kg PO q 12 h, benazepril 0.25 mg/kg q 24 h, pimobendan 0.25 mg/kg q 12 h

Commentary: *The glucocorticoid dosage reduction on Day 23 would normally have been considered premature (PCV was not in the normal range), but the risk of congestive heart failure/thromboembolic disease was considered such that this compromise was acceptable under the circumstances. The reduction was reversed following the decline in PCV 1 week later. The subsequent static PCV and then slowly rising PCV in the absence of spherocytes allowed a further attempt at dosage reduction on Day 57. The dog's nonimmunologic problems gave ample justification for a component of "anemia of chronic disease." Unfortunately, congestive heart failure manifested on Day 59.*

Management and progress days 61-112:

Day 61: Hypokalemia present (furosemide associated)—oral potassium supplementation commenced.

Day 76: PCV = 34%. ALKP = 7000 U/L, ALT = 1403 U/L. Prednisolone dosage reduced to 0.5 mg/kg q 12 h. All other medications unchanged.

Day 84: Prednisolone reduced to 0.25 mg/kg q 12 h. ALKP and ALT unchanged. Ultrasound showed generalized hepatomegaly with hyperechogenicity. The nodular hepatic lesions had resolved. Gallbladder wall changes persisted. Oral S-adenosylmethionine supplementation commenced.

Day 106: PCV 39%. ALKP and ALT elevations unchanged. Prednisolone dose reduced to 0.25 mg/kg q 12 h.

Day 112: Acute onset vomiting, diarrhea, abdominal pain, tachycardia. Abdominal ultrasound revealed mild ascites, small uroliths, evidence of a previous infarct in the right kidney, a mineralized mass at the iliac bifurcation of the aorta causing turbulent blood flow but not impeding femoral pulses. Opioid analgesia was administered before dog suffered cardiopulmonary arrest. Resuscitation was not attempted.

Commentary: *It seems very likely that this dog had ongoing hepatic and biliary tract disease based on the liver enzyme elevations that persisted in the face of reducing doses of prednisolone. Control of IMHA appeared good during this time period, and endocarditis-related congestive heart failure also responded well to treatment. The cause of the signs immediately preceding the dog's demise was not defined, but it seems likely that the dog eventually succumbed to either recurrent infection, thromboembolic disease, or both.*

NOTE: While the case notes shown earlier might not exemplify perfect case management, they represent what could practically be achieved over a significant period of time in order to illustrate some of the challenges and compromises discussed in the main chapter text. The author is very grateful to Jon Camilleri and Theresa McCann for their assistance in case management.

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Conversion to Systeme International (SI) Units

Hormone Assays

Measurement	SI Unit	Common Unit	Common → SI*	SI → Common*
Aldosterone	pmol/L	ng/dL	27.7	0.036
Corticotropin (ACTH)	pmol/L	pg/mL	0.220	4.51
Cortisol	nmol/L	μg/dL	27.59	0.036
C-peptide	nmol/L	ng/mL	0.331	3.02
β-Endorphin	pmol/L	pg/mL	0.292	3.43
Epinephrine	pmol/L	pg/mL	5.46	0.183
Estrogen (estradiol)	pmol/L	pg/mL	3.67	0.273
Gastrin	ng/L	pg/mL	1.00	1.00
Gastrointestinal polypeptide	pmol/L	pg/mL	0.201	4.98
Glucagon	ng/L	pg/mL	1.00	1.00
Growth hormone	μg/L	ng/mL	1.00	1.00
Insulin	pmol/L	μU/mL	7.18	0.139
Metanephrine	pmol/L	pg/mL	5.07	0.197
αMSH	pmol/L	pg/mL	0.601	1.66
Norepinephrine	pmol/L	pg/mL	5.91	0.169
Normetanephrine	pmol/L	pg/mL	5.46	0.183
Pancreatic polypeptide	mmol/L	mg/dL	0.239	4.18
Parathyroid hormone (PTH)	pmol/L	pg/mL	0.11	9.1
Progesterone	nmol/L	ng/mL	3.18	0.315
Prolactin	μg/L	ng/mL	1.00	1.00
Renin	ng/L/s	ng/mL/h	0.278	3.60
Somatostatin	pmol/L	pg/mL	0.611	1.64
Testosterone	nmol/L	ng/mL	3.47	0.288
Thyroxine (T_4)	nmol/L	μg/dL	12.87	0.078
Free thyroxine (fT_4)	pmol/L	ng/dL	12.87	0.078
Triiodothyronine (T_3)	nmol/L	μg/dL	0.0154	64.9
Vasoactive intestinal polypeptide	pmol/L	pg/mL	0.301	3.33

*Factor to multiply to convert from one unit to other.

From Feldman EC, Nelson RW, Reusch CE: *Canine & feline endocrinology,* ed 4, St Louis, 2015, Elsevier.

Common Serum Chemistry Data

Measurement	SI Unit	Common Unit	Common → SI*	SI → Common*

Albumin	g/L	g/dL	10.0	0.100
Bile acids	μmol/L	mg/L	2.55	0.392
Bilirubin	μmol/L	mg/dL	17.10	0.058
Calcium	mmol/L	mg/dL	0.250	4.00
Carbon dioxide content	mmol/L	mEq/L	1.00	1.00
Chloride	mmol/L	mEq/L	1.00	1.00
Cholesterol	mmol/L	mg/dL	0.026	38.7
Creatinine	μmol/L	mg/dL	88.40	0.011
Creatinine clearance	mL/s	mL/min	0.017	60.0
Glucose	mmol/L	mg/dL	0.056	18.0
Inorganic phosphorus	nmol/L	mg/dL	0.323	3.10
Magnesium	mmol/L	mg/dL	0.41	2.44
Osmolality	nmol/kg	mOsm/kg	1.00	1.00
Potassium	mmol/L	mEq/L	1.00	1.00
Protein, total	g/L	g/dL	10.0	0.100
Sodium	mmol/L	mEq/L	1.00	1.00
Triglycerides	mmol/L	mg/dL	0.011	88.3
Urea nitrogen	mmol/L	mg/dL	0.357	2.8

*Factor to multiply to convert from one unit to other.

From Feldman EC, Nelson RW, Reusch CE: *Canine & feline endocrinology,* ed 4, St Louis, 2015, Elsevier.

Body Weight–to–Body Surface Area (BSA) Correlation

Dogs

Weight, kg *(lb)*	BSA (m^2)
0.5 *(1)*	0.06
1 *(2)*	0.1
2 *(4.5)*	0.15
3 *(6.5)*	0.2
4 *(9)*	0.25
5 *(11)*	0.29
6 *(13)*	0.33
7 *(15.5)*	0.36
8 *(17.5)*	0.40
9 *(20)*	0.43
10 *(22)*	0.46
11 *(24.5)*	0.49
12 *(26.5)*	0.52
13 *(28.5)*	0.55
14 *(31)*	0.58
15 *(33)*	0.6
16 *(35)*	0.63
17 *(37.5)*	0.66
18 *(39.5)*	0.69
19 *(42)*	0.71
20 *(44)*	0.74
21 *(46)*	0.76
22 *(48.5)*	0.78
23 *(50.5)*	0.81
24 *(53)*	0.83
25 *(55)*	0.85
26 *(57)*	0.88
27 *(59.5)*	0.9
28 *(61.5)*	0.92
29 *(64)*	0.94
30 *(66)*	0.96

31 *(68)*	0.99
32 *(70.5)*	1.01
33 *(72.5)*	1.03
34 *(75)*	1.05
35 *(77)*	1.07
36 *(79)*	1.09
37 *(81.5)*	1.11
38 *(83.5)*	1.13
39 *(86)*	1.15
40 *(88)*	1.17
41 *(90)*	1.19
42 *(92.5)*	1.21
43 *(94.5)*	1.23
44 *(97)*	1.25
45 *(99)*	1.26
46 *(101)*	1.28
47 *(103.5)*	1.3
48 *(105.5)*	1.32
49 *(108)*	1.34
50 *(110)*	1.36
51 *(112)*	1.39
52 *(114.5)*	1.41
53 *(116.5)*	1.43
54 *(119)*	1.44
55 *(121)*	1.46
56 *(123)*	1.48
57 *(125.5)*	1.5
58 *(127.5)*	1.51
59 *(130)*	1.53
60 *(132)*	1.55
61 *(134)*	1.57
62 *(136.5)*	1.58
63 *(138.5)*	1.6
64 *(141)*	1.62
65 *(143)*	1.64
66 *(145)*	1.65
67 *(147.5)*	1.67
68 *(149.5)*	1.68
69 *(152)*	1.7
70 *(154)*	1.72
71 *(156)*	1.74
72 *(158.5)*	1.75
73 *(160.5)*	1.77

74 *(163)*	1.78
75 *(165)*	1.8
76 *(167)*	1.81
77 *(169.5)*	1.83
78 *(171.5)*	1.84
79 *(174)*	1.86
80 *(176.5)*	1.88

Cats

Weight, kg *(lb)*	BSA (m^2)
2 *(4.5)*	0.159
2.5 *(5.5)*	0.184
3 *(6.5)*	0.208
3.5 *(7.75)*	0.231
4 *(8.75)*	0.252
4.5 *(10)*	0.273
5 *(11)*	0.292
5.5 *(12.25)*	0.311
6 *(13.25)*	0.33
6.5 *(14.25)*	0.348
7 *(15.5)*	0.366
7.5 *(16.5)*	0.383
8 *(17.5)*	0.4
8.5 *(18.75)*	0.416
9 *(19.75)*	0.432
9.5 *(21)*	0.449
10 *(22)*	0.464

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